

Advanced Organic Chemistry

Part B: Reactions and Synthesis

Fifth Edition

Francis A. Carey
Richard J. Sundberg

 Springer

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PART A: Structure and Mechanisms

PART B: Reactions and Synthesis

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Library of Congress Control Number: 2006939782

ISBN-13: 978-0-387-68350-8 (hard cover) e-ISBN-13: 978-0-387-44899-2
ISBN-13: 978-0-387-68354-6 (soft cover)

Printed on acid-free paper.

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9 8 7 6 5 4 3 2 (corrected 2nd printing, 2008)

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Preface

The methods of organic synthesis have continued to advance rapidly and we have made an effort to reflect those advances in this Fifth Edition. Among the broad areas that have seen major developments are enantioselective reactions and transition metal catalysis. Computational chemistry is having an expanding impact on synthetic chemistry by evaluating the energy profiles of mechanisms and providing structural representation of unobservable intermediates and transition states.

The organization of Part B is similar to that in the earlier editions, but a few changes have been made. The section on introduction and removal of protecting groups has been moved forward to Chapter 3 to facilitate consideration of protecting groups throughout the remainder of the text. Enolate conjugate addition has been moved from Chapter 1 to Chapter 2, where it follows the discussion of the generalized aldol reaction. Several new sections have been added, including one on hydroalumination, carboalumination, and hydrozirconation in Chapter 4, another on the olefin metathesis reactions in Chapter 8, and an expanded discussion of the carbonyl-ene reaction in Chapter 10.

Chapters 1 and 2 focus on enolates and other carbon nucleophiles in synthesis. Chapter 1 discusses enolate formation and alkylation. Chapter 2 broadens the discussion to other carbon nucleophiles in the context of the generalized aldol reaction, which includes the Wittig, Peterson, and Julia olefination reactions. The chapter considers the stereochemistry of the aldol reaction in some detail, including the use of chiral auxiliaries and enantioselective catalysts.

Chapters 3 to 5 focus on some fundamental functional group modification reactions. Chapter 3 discusses common functional group interconversions, including nucleophilic substitution, ester and amide formation, and protecting group manipulations. Chapter 4 deals with electrophilic additions to double bonds, including the use of hydroboration to introduce functional groups. Chapter 5 considers reductions by hydrogenation, hydride donors, hydrogen atom donors, and metals and metal ions.

Chapter 6 looks at concerted pericyclic reactions, including the Diels-Alder reaction, 1,3-dipolar cycloaddition, [3,3]- and [2,3]-sigmatropic rearrangements, and thermal elimination reactions. The carbon-carbon bond-forming reactions are emphasized and the stereoselectivity of the reactions is discussed in detail.

Chapters 7 to 9 deal with organometallic reagents and catalysts. Chapter 7 considers Grignard and organolithium reagents. The discussion of organozinc reagents emphasizes their potential for enantioselective addition to aldehydes. Chapter 8 discusses reactions involving transition metals, with emphasis on copper- and palladium-mediated reactions. Chapter 9 considers the use of boranes, silanes, and stannanes in carbon–carbon bond formation. These three chapters focus on reactions such as nucleophilic addition to carbonyl groups, the Heck reaction, palladium-catalyzed cross-coupling, olefin metathesis, and allyl- boration, silation, and stannylation. These organometallic reactions currently are among the more important for construction of complex carbon structures.

Chapter 10 considers the role of reactive intermediates—carbocations, carbenes, and radicals—in synthesis. The carbocation reactions covered include the carbonyl-ene reaction, polyolefin cyclization, and carbocation rearrangements. In the carbene section, addition (cyclopropanation) and insertion reactions are emphasized. Catalysts that provide both selectivity and enantioselectivity are discussed. The section on radicals considers both intermolecular and intramolecular (cyclization) addition reactions of radicals are dealt with. The use of atom transfer steps and tandem sequences in synthesis is also illustrated.

Chapter 11 focuses on aromatic substitution, including electrophilic aromatic substitution, reactions of diazonium ions, and palladium-catalyzed nucleophilic aromatic substitution. Chapter 12 discusses oxidation reactions and is organized on the basis of functional group transformations. Oxidants are subdivided as transition metals, oxygen and peroxides, and other oxidants.

Chapter 13 illustrates applications of synthetic methodology by multistep synthesis and perhaps provides some sense of the evolution of synthetic capabilities. Several syntheses of two relatively simple molecules, juvabione and longifolene, illustrate some classic methods for ring formation and functional group transformations and, in the case of longifolene, also illustrate the potential for identification of relatively simple starting materials by retrosynthetic analysis. The syntheses of Prelog-Djerassi lactone highlight the methods for control of multiple stereocenters, and those of the Taxol precursor Baccatin III show how synthesis of that densely functionalized tricyclic structure has been accomplished. The synthesis of epothilone A illustrates both control of acyclic stereochemistry and macrocyclization methods, including olefin metathesis. The syntheses of (+)-discodermolide have been added, illustrating several methods for acyclic stereoselectivity and demonstrating the virtues of convergency. The chapter ends with a discussion of solid phase synthesis and its application to syntheses of polypeptides and oligonucleotides, as well as in combinatorial synthesis.

There is increased emphasis throughout Part B on the representation of transition structures to clarify stereoselectivity, including representation by computational models. The current practice of organic synthesis requires a thorough knowledge of molecular architecture and an understanding of how the components of a structure can be assembled. Structures of enantioselective reagents and catalysts are provided to help students appreciate the three-dimensional aspects of the interactions that occur in reactions.

A new feature of this edition is a brief section of commentary on the reactions in most of the schemes, which may point out a specific methodology or application. Instructors who want to emphasize the broad aspects of reactions, as opposed to specific examples, may wish to advise students to concentrate on the main flow of the text, reserving the schemes and commentary for future reference. As mentioned in the

Acknowledgment and Personal Statement, the selection of material in the examples and schemes does not reflect priority, importance, or generality. It was beyond our capacity to systematically survey the many examples that exist for most reaction types, and the examples included are those that came to our attention through literature searches and reviews.

Several computational studies have been abstracted and manipulable three-dimensional images of reactants, transition structures, intermediates, and products provided. This material provides the opportunity for detailed consideration of these representations and illustrates how computational chemistry can be applied to the mechanistic and structural interpretation of reactivity. This material is available in the Digital Resource at springer.com/carey-sundberg.

As in previous editions, the problems are drawn from the literature and references are given. In this addition, brief answers to each problem have been provided and are available at the publishers website.

Acknowledgment and Personal Statement

The revision and updating of *Advanced Organic Chemistry* that appears as the Fifth Edition spanned the period September 2002 through December 2006. Each chapter was reworked and updated and some reorganization was done, as described in the Prefaces to Parts A and B. This period began at the point of conversion of library resources to electronic form. Our university library terminated paper subscriptions to the journals of the American Chemical Society and other journals that are available electronically as of the end of 2002. Shortly thereafter, an excavation mishap at an adjacent construction project led to structural damage and closure of our departmental library. It remained closed through June 2007, but thanks to the efforts of Carol Hunter, Beth Blanton-Kent, Christine Wiedman, Robert Burnett, and Wynne Stuart, I was able to maintain access to a few key print journals including the *Journal of the American Chemical Society*, *Journal of Organic Chemistry*, *Organic Letters*, *Tetrahedron*, and *Tetrahedron Letters*. These circumstances largely completed an evolution in the source for specific examples and data. In the earlier editions, these were primarily the result of direct print encounter or search of printed *Chemical Abstracts* indices. The current edition relies mainly on electronic keyword and structure searches. Neither the former nor the latter method is entirely systematic or comprehensive, so there is a considerable element of circumstance in the inclusion of specific material. There is no intent that specific examples reflect either priority of discovery or relative importance. Rather, they are interesting examples that illustrate the point in question.

Several reviewers provided many helpful corrections and suggestions, collated by Kenneth Howell and the editorial staff of Springer. Several colleagues provided valuable contributions. Carl Trindle offered suggestions and material from his course on computational chemistry. Jim Marshall reviewed and provided helpful comments on several sections. Michal Sabat, director of the Molecular Structure Laboratory, provided a number of the graphic images. My co-author, Francis A. Carey, retired in 2000 to devote his full attention to his text, *Organic Chemistry*, but continued to provide valuable comments and insights during the preparation of this edition. Various users of prior editions have provided error lists, and, hopefully, these corrections have

been made. Shirley Fuller and Cindy Knight provided assistance with many aspects of the preparation of the manuscript.

This Fifth Edition is supplemented by the *Digital Resource* that is available at springer.com/carey-sundberg. The *Digital Resource* summarizes the results of several computational studies and presents three-dimensional images, comments, and exercises based on the results. These were developed with financial support from the Teaching Technology Initiative of the University of Virginia. Technical support was provided by Michal Sabat, William Rourk, Jeffrey Hollier, and David Newman. Several students made major contributions to this effort. Sara Higgins Fitzgerald and Victoria Landry created the prototypes of many of the sites. Scott Geyer developed the dynamic representations using IRC computations. Tanmaya Patel created several sites and developed the measurement tool. I also gratefully acknowledge the cooperation of the original authors of these studies in making their output available. *Problem Responses* have been provided and I want to acknowledge the assistance of R. Bruce Martin, David Metcalf, and Daniel McCauley in helping work out some of the specific kinetic problems and in providing the attendant graphs.

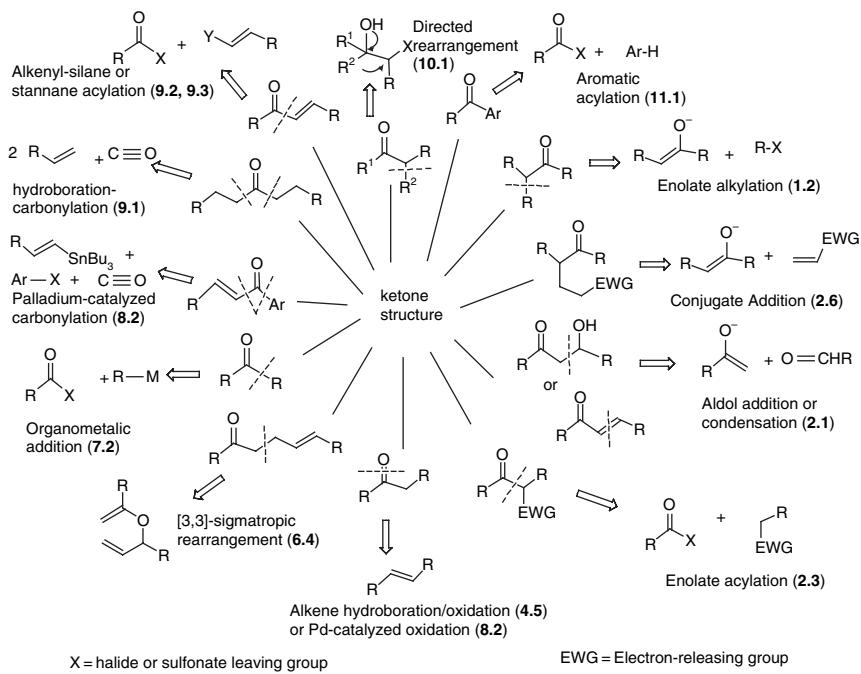
It is my hope that the text, problems, and other material will assist new students to develop a knowledge and appreciation of structure, mechanism, reactions, and synthesis in organic chemistry. It is gratifying to know that some 200,000 students have used earlier editions, hopefully to their benefit.

Richard J. Sundberg
Charlottesville, Virginia
June 2007

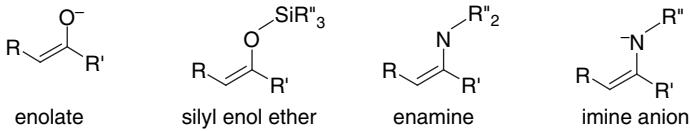
Introduction

The focus of Part B is on the closely interrelated topics of *reactions* and *synthesis*. In each of the first twelve chapters, we consider a group of related reactions that have been chosen for discussion primarily on the basis of their usefulness in synthesis. For each reaction we present an outline of the mechanism, its regio- and stereochemical characteristics, and information on typical reaction conditions. For the more commonly used reactions, the schemes contain several examples, which may include examples of the reaction in relatively simple molecules and in more complex structures. The goal of these chapters is to develop a fundamental base of knowledge about organic reactions in the context of synthesis. We want to be able to answer questions such as: What transformation does a reaction achieve? What is the mechanism of the reaction? What reagents and reaction conditions are typically used? What substances can catalyze the reaction? How sensitive is the reaction to other functional groups and the steric environment? What factors control the stereoselectivity of the reaction? Under what conditions is the reaction enantioselective?

Synthesis is the application of one or more reactions to the preparation of a particular target compound, and can pertain to a single-step transformation or to a number of sequential steps. The selection of a reaction or series of reactions for a synthesis involves making a judgment about the most effective possibility among the available options. There may be a number of possibilities for the synthesis of a particular compound. For example, in the course of learning about the reactions in Chapter 1 to 12, we will encounter a number of ways of making ketones, as outlined in the scheme that follows.

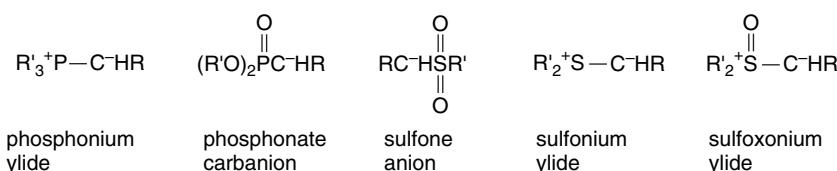


The focus of Chapters 1 and 2 is enolates and related carbon nucleophiles such as silyl enol ethers, enamines, and imine anions, which can be referred to as *enolate equivalents*.



Chapter 1 deals with alkylation of carbon nucleophiles by alkyl halides and tosylates. We discuss the major factors affecting stereoselectivity in both cyclic and acyclic compounds and consider intramolecular alkylation and the use of chiral auxiliaries.

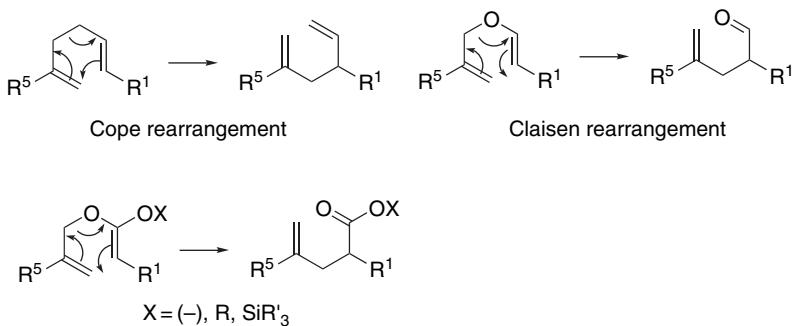
Aldol addition and related reactions of enolates and enolate equivalents are the subject of the first part of Chapter 2. These reactions provide powerful methods for controlling the stereochemistry in reactions that form hydroxyl- and methyl-substituted structures, such as those found in many antibiotics. We will see how the choice of the nucleophile, the other reagents (such as Lewis acids), and adjustment of reaction conditions can be used to control stereochemistry. We discuss the role of open, cyclic, and chelated transition structures in determining stereochemistry, and will also see how chiral auxiliaries and chiral catalysts can control the enantioselectivity of these reactions. Intramolecular aldol reactions, including the Robinson annulation are discussed. Other reactions included in Chapter 2 include Mannich, carbon acylation, and olefination reactions. The reactivity of other carbon nucleophiles including phosphonium ylides, phosphonate carbanions, sulfone anions, sulfonium ylides, and sulfoxonium ylides are also considered.



Among the olefination reactions, those of phosphonium ylides, phosphonate anions, silylmethyl anions, and sulfone anions are discussed. This chapter also includes a section on conjugate addition of carbon nucleophiles to α,β -unsaturated carbonyl compounds. The reactions in this chapter are among the most important and general of the carbon-carbon bond-forming reactions.

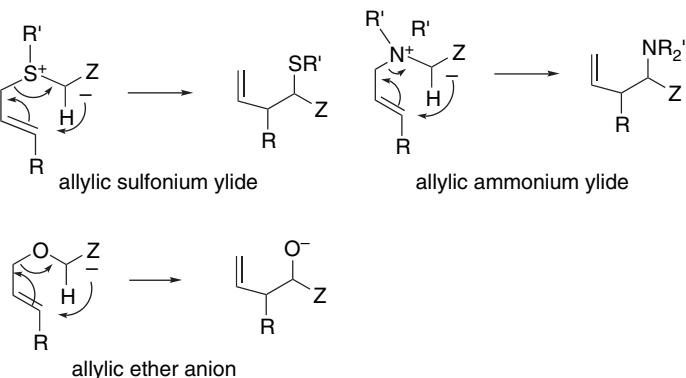
Chapters 3 to 5 deal mainly with introduction and interconversion of functional groups. In Chapter 3, the conversion of alcohols to halides and sulfonates and their subsequent reactions with nucleophiles are considered. Such reactions can be used to introduce functional groups, invert configuration, or cleave ethers. The main methods of interconversion of carboxylic acid derivatives, including acyl halides, anhydrides, esters, and amides, are reviewed. Chapter 4 discusses electrophilic additions to alkenes, including reactions with protic acids, oxymercuration, halogenation, sulfenylation, and selenylation. In addition to introducing functional groups, these reagents can be used to effect cyclization reactions, such as iodolactonization. The chapter also includes the fundamental hydroboration reactions and their use in the synthesis of alcohols, aldehydes, ketones, carboxylic acids, amines, and halides. Chapter 5 discusses reduction reactions at carbon-carbon multiple bonds, carbonyl groups, and certain other functional groups. The introduction of hydrogen by hydrogenation frequently establishes important stereochemical relationships. Both heterogeneous and homogeneous catalysts are discussed, including examples of enantioselective catalysts. The reduction of carbonyl groups also often has important stereochemical consequences because a new stereocenter is generated. The fundamental hydride transfer reagents NaBH_4 and LiAlH_4 and their derivatives are considered. Examples of both enantioselective reagents and catalysts are discussed, as well as synthetic applications of several other kinds of reducing agents, including hydrogen atom donors and metals.

In Chapter 6 the focus returns to carbon-carbon bond formation through cycloadditions and sigmatropic rearrangements. The Diels-Alder reaction and 1,3-dipolar cycloaddition are the most important of the former group. The predictable regiochemistry and stereochemistry of these reactions make them very valuable for ring formation. Intramolecular versions of these cycloadditions can create at least two new rings, often with excellent stereochemical control. Although not as broad in scope, [2 + 2] cycloadditions, such as the reactions of ketenes and photocycloaddition reactions of enones, also have important synthetic applications. The [3,3]- and [2,3]-sigmatropic rearrangements also proceed through cyclic transition structures and usually provide predictable stereochemical control. Examples of [3,3]-sigmatropic rearrangements include the Cope rearrangement of 1,5-dienes, the Claisen rearrangement of allyl vinyl ethers, and the corresponding reactions of ester enolate equivalents.



Claisen-type rearrangements of
ester enolates, ketene acetals,
and silyl ketene acetals

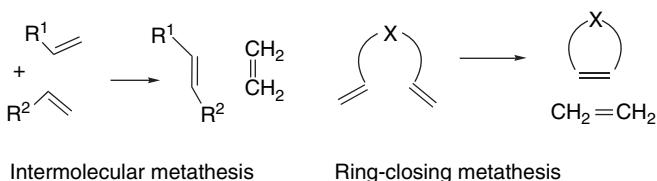
Synthetically valuable [2,3]-sigmatropic rearrangements include those of allyl sulfonium and ammonium ylides and α' -carbanions of allyl vinyl ethers.



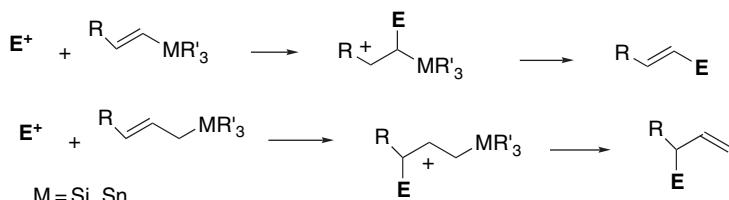
This chapter also discusses several β -elimination reactions that proceed through cyclic transition structures.

In Chapters 7, 8, and 9, the focus is on organometallic reagents. Chapter 7 considers the Group I and II metals, emphasizing organolithium, -magnesium, and -zinc reagents, which can deliver saturated, unsaturated, and aromatic groups as nucleophiles. Carbonyl compounds are the most common co-reactants, but imines and nitriles are also reactive. Important features of the zinc reagents are their adaptability to enantioselective catalysis and their compatibility with many functional groups. Chapter 8 discusses the role of transition metals in organic synthesis, with the emphasis on copper and palladium. The former provides powerful nucleophiles that can react by displacement, epoxide ring opening, and conjugate addition, while organopalladium compounds are usually involved in catalytic processes. Among the important applications are allylic substitution, coupling of aryl and vinyl halides with alkenes (Heck reaction), and cross coupling with various organometallic reagents including magnesium, zinc, tin, and boron derivatives. Palladium catalysts can also effect addition of organic groups to carbon monoxide (carbonylation) to give ketones, esters, or amides. Olefin metathesis reactions, also discussed in this chapter, involve ruthenium or molybdenum catalysts.

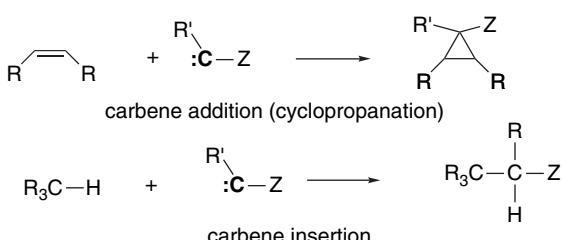
and both intermolecular and ring-closing metathesis have recently found applications in synthesis.



Chapter 9 discusses carbon–carbon bond-forming reactions of boranes, silanes, and stannanes. The borane reactions usually involve B → C migrations and can be used to synthesize alcohols, aldehydes, ketones, carboxylic acids, and amines. There are also stereoselective alkene syntheses based on organoborane intermediates. Allylic boranes and boronates provide stereospecific and enantioselective addition reactions of allylic groups to aldehydes. These reactions proceed through cyclic transition structures and provide a valuable complement to the aldol reaction for stereochemical control of acyclic systems. The most important reactions of silanes and stannanes involve vinyl and allyl derivatives. These reagents are subject to electrophilic attack, which is usually followed by demetallation, resulting in net substitution by the electrophile, with double-bond transposition in the allylic case. Both these reactions are under the regiochemical control of the β-carbocation–stabilizing ability of the silyl and stannylyl groups.

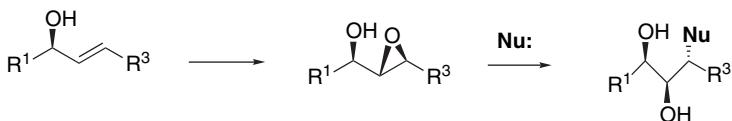


In Chapter 10, the emphasis is on synthetic application of carbocations, carbenes, and radicals in synthesis. These intermediates generally have high reactivity and short lifetimes, and successful application in synthesis requires taking this factor into account. Examples of reactions involving carbocations are the carbonyl-ene reaction, polyene cyclization, and directed rearrangements and fragmentations. The unique divalent character of the carbenes and related intermediates called carbenoids can be exploited in synthesis. Both addition (cyclopropanation) and insertion are characteristic reactions. Several zinc-based reagents are excellent for cyclopropanation, and rhodium catalysts have been developed that offer a degree of selectivity between addition and insertion reactions.



Radical reactions used in synthesis include additions to double bonds, ring closure, and atom transfer reactions. Several sequences of tandem reactions have been developed that can close a series of rings, followed by introduction of a substituent. Allylic stannanes are prominent in reactions of this type.

Chapter 11 reviews aromatic substitution reactions including electrophilic aromatic substitution, substitution via diazonium ions, and metal-catalyzed nucleophilic substitution. The scope of the latter reactions has been greatly expanded in recent years by the development of various copper and palladium catalysts. Chapter 12 discusses oxidation reactions. For the most part, these reactions are used for functional group transformations. A wide variety of reagents are available and we classify them as based on metals, oxygen and peroxides, and other oxidants. Epoxidation reactions have special significance in synthesis. The introduction of the epoxide ring can set the stage for subsequent nucleophilic ring opening to introduce a new group or extend the carbon chain. The epoxidation of allylic alcohols can be done enantioselectively, so epoxidation followed by ring opening can control the configuration of three contiguous stereocenters.



The methods available for synthesis have advanced dramatically in the past half-century. Improvements have been made in selectivity of conditions, versatility of transformations, stereochemical control, and the efficiency of synthetic processes. The range of available reagents has expanded. Many reactions involve compounds of boron, silicon, sulfur, selenium, phosphorus, and tin. Catalysis, particularly by transition metal complexes, has also become a key part of organic synthesis. The mechanisms of catalytic reactions are characterized by *catalytic cycles* and require an understanding not only of the ultimate bond-forming and bond-breaking steps, but also of the mechanism for regeneration of the active catalytic species and the effect of products, by-products, and other reaction components in the catalytic cycle.

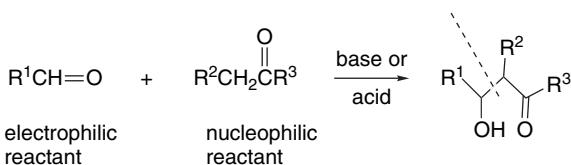
Over the past decade enantioselectivity has become a key concern in reactivity and synthesis. Use of *chiral auxiliaries* and/or *enantioselective catalysts* to control configuration is often a crucial part of synthesis. The analysis and interpretation of enantioselectivity depend on consideration of diastereomeric intermediates and transition structures on the reaction pathway. Often the differences in free energy of competing reaction pathways are on the order of 1 kcal, reflecting small and subtle differences in structure. We provide a number of examples of the structural basis for enantioselectivity, but a good deal of unpredictability remains concerning the degree of enantioselectivity. Small changes in solvent, additives, catalyst structure, etc., can make large differences in the observed enantioselectivity.

Mechanistic insight is a key to both discovery of new reactions and to their successful utilization in specific applications. Use of reactions in a synthetic context often entails optimization of reaction conditions based on mechanistic interpretations. Part A of this text provides fundamental information about the reactions discussed here. Although these mechanistic concepts may be recapitulated briefly in Part B, the details may not be included; where appropriate, reference is made to relevant sections in Part A. In addition to experimental mechanistic studies, many reactions of

synthetic interest are now within the range of computational analysis. Intermediates and transition structures on competing or alternative reaction pathways can be modeled and compared on the basis of MO and/or DFT calculations. Such computations can provide intricate structural details and may lead to mechanistic insight. A number of such studies are discussed in the course of the text.

A key skill in the practice of organic synthesis is the ability to recognize important aspects of molecular structure. Recognition of all aspects of stereochemistry, including conformation, ring geometry, and configuration are crucial to understanding reactivity and applying reactions to synthesis. We consider the stereochemical aspects of each reaction. For most reactions, good information is available on the structure of key intermediates and the transition structure. Students should make a particular effort to understand the consequences of intermediates and transition structures for reactivity.

Applying the range of reactions to synthesis involves planning and foreseeing the outcome of a particular sequence of reactions. Planning is best done on the basis of *retrosynthetic analysis*, the identification of key subunits of the target molecule that can be assembled by feasible reactions. The structure of the molecule is studied to identify bonds that are amenable to formation. For example, a molecule containing a carbon-carbon double bond might be disconnected at that bond, since there are numerous ways to form a double bond from two separate components. β -Hydroxy carbonyl units suggest the application of the aldol addition reaction, which assembles this functionality from two separate carbonyl compounds.

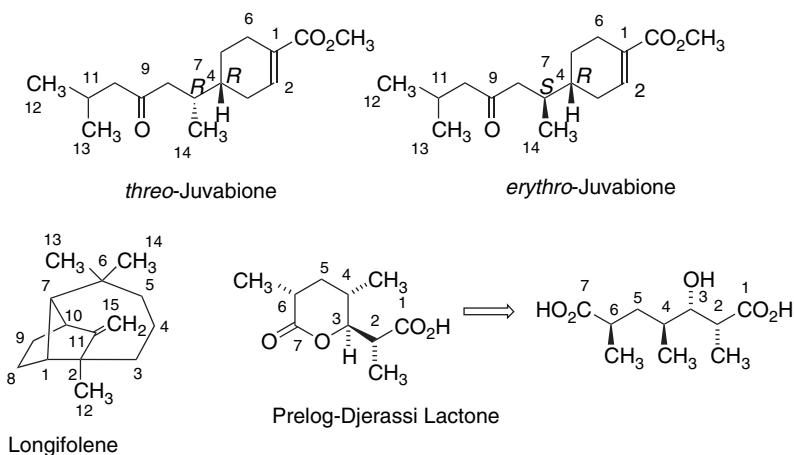


The construction of the overall molecular skeleton, that is, the carbon-carbon and other bonds that constitute the framework of the molecule, is the primary challenge. Molecules also typically contain a number of functional groups and they must be compatible with the projected reactivity at each step in the synthesis. This means that it may be necessary to modify or protect functional groups at certain points. Generally speaking, the protection and interconversion of functional groups is a less fundamental challenge than construction of the molecular framework because there are numerous methods for functional group interconversion.

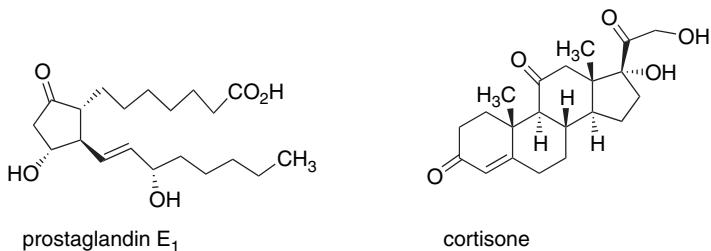
As the reactions discussed in Chapters 1 to 12 illustrate, the methodology of organic synthesis is highly developed. There are many possible means for introduction and interconversion of functional groups and for carbon-carbon bond formation, but putting them together in a multistep synthesis requires more than knowledge of the reactions. A plan that orchestrates the sequence of reactions toward the final goal is necessary.

In Chapter 13, we discuss some of the generalizations of multistep synthesis. Retrosynthetic analysis identifies bonds that can be broken and key intermediates. Various methods of stereochemical control, including intramolecular interactions. Chiral auxiliaries, and enantioselective catalysts, can be used. Protective groups can be utilized to prevent functional group interferences. Ingenuity in synthetic planning can lead to efficient construction of molecules. We take a retrospective look at the synthesis of six molecules of differing complexity. Juvabione is an oxidized terpene

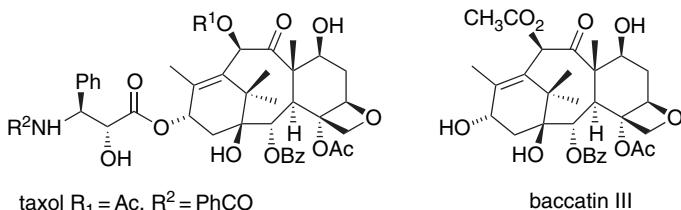
with one ring and two stereocenters. Successful syntheses date from the late 1960s to the present. Longifolene is a tricyclic sesquiterpene and its synthesis poses the problem of ring construction. The Prelog-Djerassi lactone, the lactone of $(2R,3S,4R,6R)$ -3-hydroxy-2,4,6-trimethylheptanedioic acid, is a degradation product isolated from various antibiotics. Its alternating methyl and hydroxy groups are typical of structural features found in many antibiotics and other natural substances biosynthetically derived from polypropionate units. Its synthesis illustrates methods of acyclic stereochemical control.



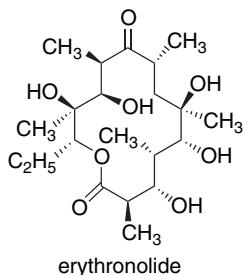
Synthetic methodology is applied to molecules with important biological activity such as the prostaglandins and steroids. Generally speaking, the stereochemistry of these molecules can be controlled by relationships to the ring structure.



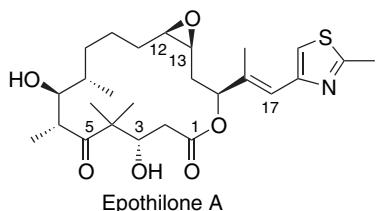
A somewhat more complex molecule, both in terms of the nature of the rings and the density of functionality is Baccatin III, a precursor of the antitumor agent Taxol®. We summarize syntheses of Baccatin III that involve sequences of 40–50 reactions. Baccatin III is a highly oxygenated diterpene and these syntheses provide examples of ring construction and functional group manipulations. Despite its complexity, the syntheses of Baccatin III, for the most part, also depend on achieving formation of rings and use of the ring structure to control stereochemistry.



Macrocyclic antibiotics such as the erythronolide present an additional challenge.

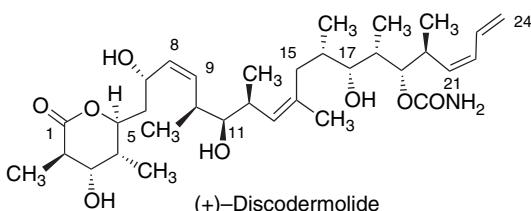


These molecules contain many stereogenic centers and they are generally constructed from acyclic segments, so the ability to control configuration in acyclic systems is necessary. Solutions to this problem developed beginning in the 1960s are based on analysis of transition structures and the concepts of cyclic transition structure and facial selectivity. The effect of nearby stereogenic centers has been studied carefully and resulted in concepts such as the Felkin model for carbonyl addition reactions and Cram's model of chelation control. In Chapter 13, several syntheses of epothilone A, a 16-membered lactone that has antitumor activity, are summarized. The syntheses illustrate methods for both acyclic stereochemical control and macrocyclization, including the application of the olefin metathesis reaction.



We also discuss the synthesis of (+)-discodermolide, a potent antitumor agent isolated from a deep-water sponge in the Caribbean Sea. The first synthesis was reported in the mid-1990s, and synthetic activity is ongoing. Discodermolide is a good example of the capability of current synthetic methodology to produce complex molecules. The molecule contains a 24-carbon chain with a single lactone ring connecting C(1) and C(5). There are eight methyl substituents and six oxygen substituents, one of which is carbamoylated. The chain ends with a diene unit. By combining and refining elements of several earlier syntheses, it was possible to carry

out a 39-step synthesis. The early stages were done on a kilogram scale and the entire effort provided 60 grams of the final product for preliminary clinical evaluation.



There is no synthetic path that is uniquely “correct,” but there may be factors that recommend particular pathways. The design of a synthesis involves applying one’s knowledge about reactions. Is the reaction applicable to the particular steric and electronic environment under consideration? Is the reaction compatible with other functional groups and structures that are present elsewhere in the molecule? Will the reaction meet the regio- and stereochemical requirements that apply? Chemists rely on mechanistic considerations and the precedent of related reactions to make these judgments. Other considerations may come into play as well, such as availability and/or cost of starting materials, and safety and environmental issues might make one reaction preferable to another. These are critical concerns in synthesis on a production scale.

Certain types of molecules, especially polypeptides and polynucleotides, lend themselves to synthesis on solid supports. In such syntheses, the starting material is attached to a small particle (bead) or a surface and the molecule remains attached during the course of the synthetic sequence. Solid phase synthesis also plays a key role in creation of combinatorial libraries, that is, collections of many molecules synthesized by a sequence of reactions in which the subunits are systematically varied to create a range of structures (*molecular diversity*).

There is a vast amount of knowledge about reactions and how to use them in synthesis. The primary source for this information is the published chemical literature that is available in numerous journals, and additional information can be found in patents, theses and dissertations, and technical reports of industrial and governmental organizations. There are several means of gaining access to information about specific reactions. The series *Organic Syntheses* provides examples of specific transformations with detailed experimental procedures. Another series, *Organic Reactions*, provides fundamental information about the scope and mechanism as well as comprehensive literature references to many examples of a specific reaction type. Various review journals, including *Accounts of Chemical Research* and *Chemical Reviews*, provide overviews of particular reactions. A traditional system of organization is based on *named reactions*. Many important reactions bear well-recognized names of the chemists involved in their discovery or development. Other names such as dehydration, epoxidation, enolate alkylation, etc., are succinct descriptions of the structural changes associated with the reaction. This vocabulary is an important tool for accessing information about organic reactions. There are large computerized databases of organic reactions, most notably those of *Chemical Abstracts* and *Beilstein*. Chemical structures can be uniquely described and these databases can be searched for complete or partial structures. Systematic ways of searching for reactions are also incorporated into the databases. Another database, *Science Citation Index*, allows search for subsequent citations of published work.

A major purpose of organic synthesis at the current time is the discovery, understanding, and application of biological activity. Pharmaceutical laboratories, research foundations, and government and academic institutions throughout the world are engaged in this research. Many new compounds are synthesized to discover useful biological activity, and when activity is discovered, related compounds are synthesized to improve it. Syntheses suitable for production of drug candidate molecules are developed. Other compounds are synthesized to explore the mechanisms of biological processes. The ultimate goal is to apply this knowledge about biological activity for treatment and prevention of disease. Another major application of synthesis is in agriculture for control of insects and weeds. Organic synthesis also plays a part in the development of many consumer products, such as fragrances.

The unique power of synthesis is the ability to create new molecules and materials with valuable properties. This capacity can be used to interact with the natural world, as in the treatment of disease or the production of food, but it can also produce compounds and materials beyond the capacity of living systems. Our present world uses vast amounts of synthetic polymers, mainly derived from petroleum by synthesis. The development of nanotechnology, which envisions the application of properties at the molecular level to catalysis, energy transfer, and information management has focused attention on multimolecular arrays and systems capable of self-assembly. We can expect that in the future synthesis will bring into existence new substances with unique properties that will have impacts as profound as those resulting from syntheses of therapeutics and polymeric materials.

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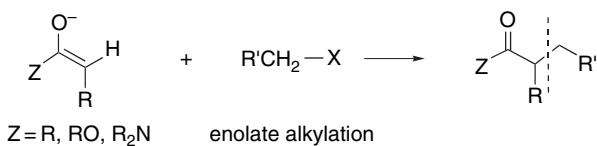
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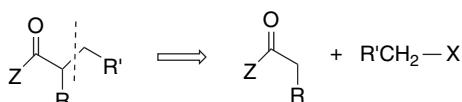
Alkylation of Enolates and Other Carbon Nucleophiles

Introduction

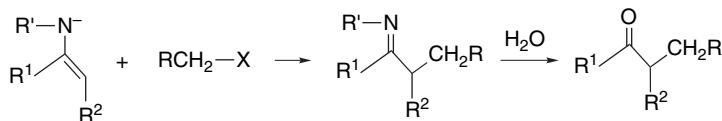
Carbon-carbon bond formation is the basis for the construction of the molecular framework of organic molecules by synthesis. One of the fundamental processes for carbon-carbon bond formation is a reaction between a nucleophilic and an electrophilic carbon. The focus in this chapter is on *enolates*, *imine anions*, and *enamines*, which are carbon nucleophiles, and their reactions with *alkylating agents*. Mechanistically, these are usually S_N2 reactions in which the carbon nucleophile displaces a halide or other leaving group with inversion of configuration at the alkylating group. Efficient carbon-carbon bond formation requires that the S_N2 alkylation be the dominant reaction. The crucial factors that must be considered include: (1) the conditions for generation of the carbon nucleophile; (2) the effect of the reaction conditions on the structure and reactivity of the nucleophile; and (3) the regio- and stereo-selectivity of the alkylation reaction. The reaction can be applied to various carbonyl compounds, including ketones, esters, and amides.



These reactions introduce a new substituent α to the carbonyl group and constitute an important method for this transformation. In the retrosynthetic sense, the disconnection is between the α -carbon and a potential alkylating agent.



There are similar reactions involving nitrogen analogs called *imine anions*. The alkylated imines can be hydrolyzed to the corresponding ketone, and this reaction is discussed in Section 1.3.



Either enolate or imine anions can be used to introduce alkyl α -substituents to a carbonyl group. Because the reaction involves a nucleophilic substitution, primary groups are the best alkylating agents, with methyl, allyl, and benzyl compounds being particularly reactive. Secondary groups are less reactive and are likely to give lower yields because of competing elimination. Tertiary and aryl groups cannot be introduced by an S_N2 mechanism.

1.1. Generation and Properties of Enolates and Other Stabilized Carbanions

1.1.1. Generation of Enolates by Deprotonation

The fundamental aspects of the structure and stability of carbanions were discussed in Chapter 6 of Part A. In the present chapter we relate the properties and reactivity of carbanions stabilized by carbonyl and other EWG substituents to their application as nucleophiles in synthesis. As discussed in Section 6.3 of Part A, there is a fundamental relationship between the stabilizing functional group and the acidity of the C–H groups, as illustrated by the pK data summarized in Table 6.7 in Part A. These pK data provide a basis for assessing the stability and reactivity of carbanions. The acidity of the reactant determines which bases can be used for generation of the anion. Another crucial factor is the distinction between *kinetic or thermodynamic control of enolate formation by deprotonation* (Part A, Section 6.3), which determines the enolate composition. Fundamental mechanisms of S_N2 alkylation reactions of carbanions are discussed in Section 6.5 of Part A. A review of this material may prove helpful.

A primary consideration in the generation of an enolate or other stabilized carbanion by deprotonation is the choice of base. In general, reactions can be carried out under conditions in which the enolate is *in equilibrium* with its conjugate acid or under which the reactant is *completely converted* to its conjugate base. The key determinant is the amount and strength of the base. For complete conversion, the base must be derived from a substantially weaker acid than the reactant. Stated another way, the reagent must be a stronger base than the anion of the reactant. Most current procedures for alkylation of enolates and other carbanions involve complete conversion to the anion. Such procedures are generally more amenable to both regiochemical and stereochemical control than those in which there is only a small equilibrium concentration of the enolate. The solvent and other coordinating or chelating additives also have strong effects on the structure and reactivity of carbanions formed by

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and Other
Stabilized Carbanions

deprotonation. The nature of the solvent determines the degree of ion pairing and aggregation, which in turn affect reactivity.

Table 1.1 gives approximate pK data for various functional groups and some of the commonly used bases. The strongest acids appear at the top of the table and the strongest bases at the bottom. The values listed as pK_{ROH} are referenced to water and are appropriate for hydroxylic solvents. Also included in the table are pK values determined in dimethyl sulfoxide (pK_{DMSO}). The range of acidities that can be measured directly in DMSO is greater than that in protic media, thereby allowing direct comparisons between weakly acidic compounds to be made more confidently. The pK values in DMSO are normally larger than in water because water stabilizes anions more effectively, by hydrogen bonding, than does DMSO. Stated another way, many anions are more strongly basic in DMSO than in water. This relationship is particularly apparent for the oxy anion bases, such as acetate, hydroxide, and the alkoxides, which are much more basic in DMSO than in protic solvents. At the present time, the pK_{DMSO} scale includes the widest variety of structural types of synthetic interest.¹ The pK values collected in Table 1.1 provide an ordering of some important

Table 1.1. Approximate pK Values from Some Compounds with Carbanion Stabilizing Groups and Some Common Bases^a

Compound	pK_{ROH}	pK_{DMSO}	Base	pK_{ROH}	pK_{DMSO}
O ₂ NCH ₂ NO ₂	3.6		CH ₃ CO ₂ ⁻	4.2	11.6
CH ₃ COCH ₂ NO ₂	5.1				
CH ₃ CH ₂ NO ₂	8.6	16.7	HCO ₃ ⁻	6.5	
CH ₃ COCH ₂ COCH ₃	9				
PhCOCH ₂ COCH ₃	9.6		PhO ⁻	9.9	16.4
CH ₃ NO ₂	10.2	17.2			
CH ₃ COCH ₂ CO ₂ C ₂ H ₅	10.7	14.2	CO ₃ ²⁻	10.2	
NCCH ₂ CN	11.2	11.0	(C ₂ H ₅) ₃ N	10.7	
PhCH ₂ NO ₂		12.3	(CH ₃ CH ₂) ₂ NH	11	
CH ₂ (SO ₂ CH ₃) ₂	12.2	14.4			
CH ₂ (CO ₂ C ₂ H ₅) ₂	12.7	16.4			
Cyclopentadiene	15		CH ₃ O ⁻	15.5	29.0
PhSCH ₂ COCH ₃		18.7	HO ⁻	15.7	31.4
CH ₃ CH ₂ CH(CO ₂ C ₂ H ₅) ₂	15		C ₂ H ₅ O ⁻	15.9	29.8
PhSCH ₂ CN		20.8	(CH ₃) ₂ CHO ⁻	30.3	
(PhCH ₂) ₂ SO ₂		23.9	(CH ₃) ₃ CO ⁻	19	32.2
PhCOCH ₃	15.8	24.7			
PhCH ₂ COCH ₃	19.9				
CH ₃ COCH ₃	20	26.5			
CH ₃ CH ₂ COCH ₂ CH ₃		27.1			
Fluorene	20.5	22.6			
PhSO ₂ CH ₃		29.0			
PhCH ₂ SOCH ₃	29.0		[(CH ₃) ₃ Si] ₂ N ⁻	30 ^b	
CH ₃ CN	25	31.3			
Ph ₂ CH ₂		32.2			
Ph ₃ CH	33	30.6	NH ₂ ⁻	35	41
			CH ₃ SOCH ₂ ⁻	35	35.1
PhCH ₃		43	(CH ₃ CH ₂) ₂ N ⁻	36	
CH ₄		56			

a. From F. G. Bordwell, *Acc. Chem. Res.*, **21**, 456 (1988).

b. In THF; R. R. Fraser and T. S. Mansour, *J. Org. Chem.*, **49**, 3442 (1984).

¹. F. G. Bordwell, *Acc. Chem. Res.*, **21**, 456 (1988).

substituents with respect to their ability to stabilize carbanions. The order indicated is $\text{NO}_2 > \text{COR} > \text{CN} \sim \text{CO}_2\text{R} > \text{SO}_2\text{R} > \text{SOR} > \text{Ph} \sim \text{SR} > \text{H} > \text{R}$. Familiarity with the relative acidity and approximate pK values is important for an understanding of the reactions discussed in this chapter.

There is something of an historical division in synthetic procedures involving carbanions as nucleophiles in alkylation reactions.² As can be seen from Table 1.1, β -diketones, β -ketoesters, malonates, and other compounds with two stabilizing groups have pK values slightly below ethanol and the other common alcohols. As a result, these compounds can be converted completely to enolates by sodium or potassium alkoxides. These compounds were the usual reactants in carbanion alkylation reactions until about 1960. Often, the second EWG is extraneous to the overall purpose of the synthesis and its removal requires an extra step. After 1960, procedures using aprotic solvents, especially THF, and amide bases, such as lithium di-isopropylamide (LDA) were developed. The dialkylamines have a pK around 35. These conditions permit the conversion of monofunctional compounds with $pK > 20$, especially ketones, esters, and amides, completely to their enolates. Other bases that are commonly used are the anions of hexaalkyldisilylamines, especially hexamethyldisilazane.³ The lithium, sodium, and potassium salts are abbreviated LiHMDS, NaHMDS, and KHMDS. The disilylamines have a pK around 30.⁴ The basicity of both dialkylamides and hexaalkyldisilylamides tends to increase with branching in the alkyl groups. The more branched amides also exhibit greater steric discrimination. An example is lithium tetramethylpiperidide, LiTMP, which is sometimes used as a base for deprotonation.⁵ Other strong bases, such as amide anion ($-\text{NH}_2^-$), the conjugate base of DMSO (sometimes referred to as the “dimsyl” anion),⁶ and triphenylmethyl anion, are capable of effecting essentially complete conversion of a ketone to its enolate. Sodium hydride and potassium hydride can also be used to prepare enolates from ketones, although the reactivity of the metal hydrides is somewhat dependent on the means of preparation and purification of the hydride.⁷

By comparing the approximate pK values of the bases with those of the carbon acid of interest, it is possible to estimate the position of the acid-base equilibrium for a given reactant-base combination. For a carbon acid C–H and a base B–H,

$$K_{a_{(\text{C}-\text{H})}} = \frac{[\text{C}^-][\text{H}^+]}{[\text{C}-\text{H}]} \quad \text{and} \quad K_{a_{(\text{B}-\text{H})}} = \frac{[\text{B}^-][\text{H}^+]}{[\text{B}-\text{H}]}$$

at equilibrium

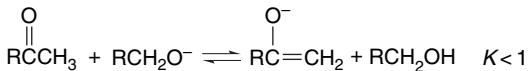
$$\frac{K_{a_{(\text{C}-\text{H})}} [\text{C}-\text{H}]}{[\text{C}^-]} = \frac{K_{a_{(\text{B}-\text{H})}} [\text{B}-\text{H}]}{[\text{B}^-]}$$

for the reaction

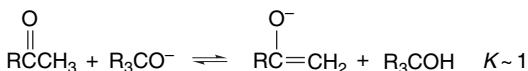


- ² D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **27**, 1624 (1988).
- ³ E. H. Amonoco-Neizer, R. A. Shaw, D. O. Skovlin, and B. C. Smith, *J. Chem. Soc.*, 2997 (1965); C. R. Kruger and E. G. Rochow, *J. Organomet. Chem.*, **1**, 476 (1964).
- ⁴ R. R. Fraser and T. S. Mansour, *J. Org. Chem.*, **49**, 3442 (1984).
- ⁵ M. W. Rathke and R. Kow, *J. Am. Chem. Soc.*, **94**, 6854 (1972); R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.*, **95**, 581, 582 (1973).
- ⁶ E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).
- ⁷ C. A. Brown, *J. Org. Chem.*, **39**, 1324 (1974); R. Pi, T. Friedl, P. v. R. Schleyer, P. Klusener, and L. Brandsma, *J. Org. Chem.*, **52**, 4299 (1987); T. L. Macdonald, K. J. Natalie, Jr., G. Prasad, and J. S. Sawyer, *J. Org. Chem.*, **51**, 1124 (1986).

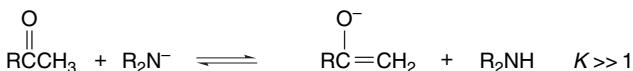
If we consider the case of a simple alkyl ketone in a protic solvent, for example, we see that hydroxide ion or primary alkoxide ions will convert only a fraction of a ketone to its anion.



The slightly more basic tertiary alkoxides are comparable to the enolates in basicity, and a more favorable equilibrium will be established with such bases.



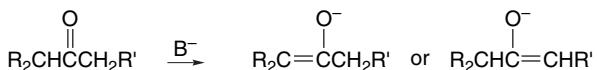
Note also that dialkyl ketones such as acetone and 3-pentanone are slightly *more acidic* than the simple alcohols in DMSO. Use of alkoxide bases in DMSO favors enolate formation. For the amide bases, $K_{a(\text{B}-\text{H})} << K_{a(\text{C}-\text{H})}$, and complete formation of the enolate occurs.



It is important to keep the position of the equilibria in mind as we consider reactions of carbanions. The base and solvent used determine the extent of deprotonation. Another important physical characteristic that has to be kept in mind is the degree of aggregation of the carbanion. Both the solvent and the cation influence the state of aggregation. This topic is discussed further in Section 1.1.3.

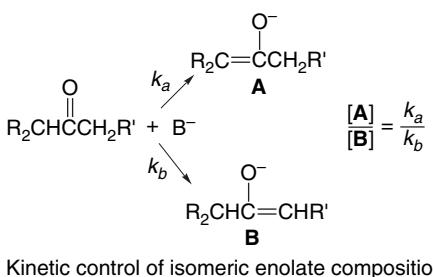
1.1.2. Regioselectivity and Stereoselectivity in Enolate Formation from Ketones and Esters

Deprotonation of the corresponding carbonyl compound is a fundamental method for the generation of enolates, and we discuss it here for ketones and esters. An unsymmetrical dialkyl ketone can form two *regiosomeric* enolates on deprotonation.



Full exploitation of the synthetic potential of enolates requires control over the regioselectivity of their formation. Although it may not be possible to direct deprotonation so as to form one enolate to the exclusion of the other, experimental conditions can often be chosen to favor one of the regiosomers. The composition of an enolate mixture can be governed by kinetic or thermodynamic factors. The enolate ratio is governed

by *kinetic control* when the product composition is determined by the *relative rates of the competing proton abstraction reactions*.



Kinetic control of isomeric enolate composition

By adjusting the conditions of enolate formation, it is possible to establish either kinetic or thermodynamic control. *Conditions for kinetic control of enolate formation are those in which deprotonation is rapid, quantitative, and irreversible.*⁸ This requirement is met experimentally by using a very strong base such as LDA or LiHMDS in an aprotic solvent in the absence of excess ketone. Lithium is a better counterion than sodium or potassium for regioselective generation of the kinetic enolate, as it maintains a tighter coordination at oxygen and reduces the rate of proton exchange. Use of an aprotic solvent is essential because protic solvents permit enolate equilibration by reversible protonation-deprotonation, which gives rise to the thermodynamically controlled enolate composition. Excess ketone also catalyzes the equilibration by proton exchange.

Scheme 1.1 shows data for the regioselectivity of enolate formation for several ketones under various reaction conditions. A consistent relationship is found in these and related data. *Conditions of kinetic control usually favor formation of the less-substituted enolate*, especially for methyl ketones. The main reason for this result is that removal of a less hindered hydrogen is faster, for steric reasons, than removal of a more hindered hydrogen. Steric factors in ketone deprotonation are accentuated by using bulky bases. The most widely used bases are LDA, LiHMDS, and NaHMDS. Still more hindered disilylamides such as hexaethyldisilylamine⁹ and *bis*-(dimethylphenylsilyl)amide¹⁰ may be useful for specific cases.

The equilibrium ratios of enolates for several ketone-enolate systems are also shown in Scheme 1.1. Equilibrium among the various enolates of a ketone can be established by the presence of an excess of ketone, which permits reversible proton transfer. Equilibration is also favored by the presence of dissociating additives such as HMPA. The composition of the equilibrium enolate mixture is usually more closely balanced than for kinetically controlled conditions. In general, the more highly substituted enolate is the preferred isomer, but if the alkyl groups are sufficiently branched as to interfere with solvation, there can be exceptions. This factor, along with CH_3/CH_3 steric repulsion, presumably accounts for the stability of the less-substituted enolate from 3-methyl-2-butanone (Entry 3).

⁸. For reviews, see J. d'Angelo, *Tetrahedron*, **32**, 2979 (1976); C. H. Heathcock, *Modern Synthetic Methods*, **6**, 1 (1992).

⁹. S. Masamune, J. W. Ellingboe, and W. Choy, *J. Am. Chem. Soc.*, **104**, 5526 (1982).

¹⁰. S. R. Angle, J. M. Fevig, S. D. Knight, R. W. Marquis, Jr., and L. E. Overman, *J. Am. Chem. Soc.*, **115**, 3966 (1993).

Scheme 1.1. Composition of Enolate Mixtures Formed under Kinetic and Thermodynamic Control^a

				SECTION 1.1
				<i>Generation and Properties of Enolates and Other Stabilized Carbanions</i>
1	 Kinetic, (LDA 0°C)	 71%	 13%	 16%
2	 Kinetic (LDA -78°C) Thermodynamic (KH, 20°C)	 100%	 0%	 0%
3	 Kinetic (KHMDS, -78°C) Thermodynamic (KH)	 99%	 1%	 12%
4 ^b	 Kinetic LDA LTMP LHMDS LiNHC6H2Cl3	 40%	 60%	 0%
5	 Kinetic (LDA 0°C) Thermodynamic (NaH)	 14%	 86%	 98%
6	 Kinetic (LDA, 0°C) Thermodynamic (NaH)	 99%	 1%	 74%

(Continued)

Scheme 1.1. (Continued)

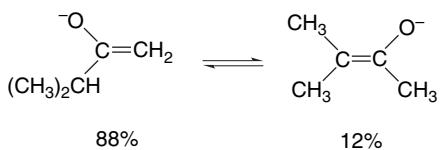
CHAPTER 1

*Alkylation of Enolates
and Other Carbon
Nucleophiles*

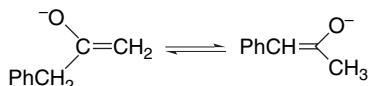
7			
	Kinetic (Ph ₃ CLi)	100%	0%
	Thermodynamic (Ph ₃ CK)	35%	65%
8			
	Kinetic (Ph ₃ CLi)	82%	18%
	Thermodynamic (Ph ₃ CK)	52%	48%
9			
	Kinetic (LDA)	98%	2%
	Thermodynamic (NaH)	50%	50%

a. Selected from a more complete compilation by D. Caine, in *Carbon-Carbon Bond Formation*, R. L. Augustine, ed., Marcel Dekker, New York, 1979.

b. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980); L. Xie, K. Vanlandeghem, K. M. Isenberger, and C. Bernier, *J. Org. Chem.* **68**, 641 (2003).



The acidifying effect of an adjacent phenyl group outweighs steric effects in the case of 1-phenyl-2-propanone, and as a result the conjugated enolate is favored by both kinetic and thermodynamic conditions (Entry 5).



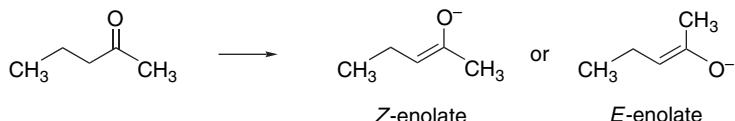
For cyclic ketones conformational factors also come into play in determining enolate composition. 2-Substituted cyclohexanones are kinetically deprotonated at the C(6) methylene group, whereas the more-substituted C(2) enolate is slightly favored

SECTION 1.1

Generation and Properties of Enolates and Other Stabilized Carbanions

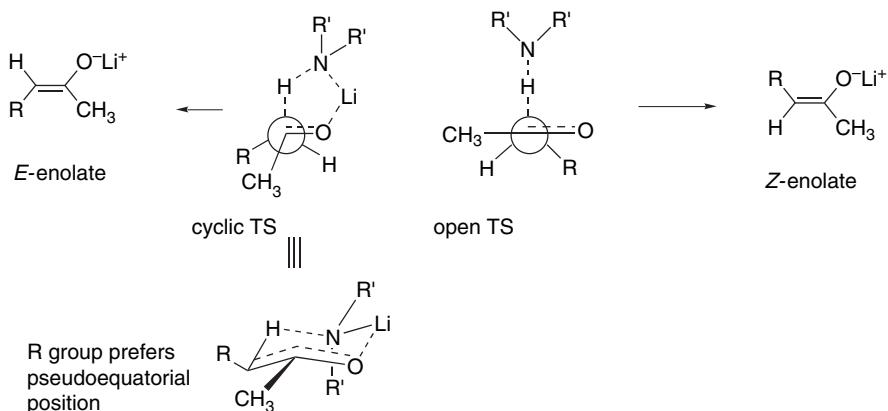
at equilibrium (Entries 6 and 7). A 3-methyl group has a significant effect on the regiochemistry of kinetic deprotonation but very little effect on the thermodynamic stability of the isomeric enolates (Entry 8).

Many enolates can exist as both *E*- and *Z*-isomers.¹¹ The synthetic importance of LDA and HMDS deprotonation has led to studies of enolate stereochemistry under various conditions. In particular, the stereochemistry of some enolate reactions depends on whether the *E*- or *Z*-isomer is involved. Deprotonation of 2-pentanone was examined with LDA in THF, with and without HMPA. C(1) deprotonation is favored under both conditions, but the *Z*:*E* ratio for C(3) deprotonation is sensitive to the presence of HMPA.¹² More *Z*-enolate is formed when HMPA is present.



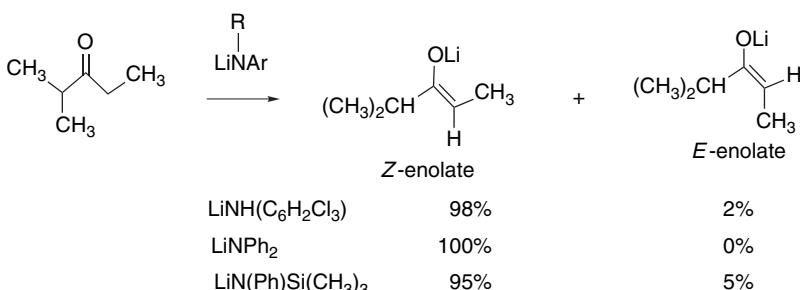
Ratio C(1):C(3) deprotonation	Ratio <i>Z</i> : <i>E</i> for C(3) deprotonation
0° C, THF alone	7.9
−60° C, THF alone	7.1
0° C, THF-HMPA	8.0
−60° C, THF-HMPA	5.6
	0.20
	0.15
	1.0
	3.1

These and other related enolate ratios are interpreted in terms of a tight, reactant-like cyclic TS in THF and a looser TS in the presence of HMPA. The cyclic TS favors the *E*-enolate, whereas the open TS favors the *Z*-enolate. The effect of the HMPA is to solvate the Li⁺ ion, reducing the importance of Li⁺ coordination with the carbonyl oxygen.¹³



11. The enolate oxygen is always taken as a high-priority substituent in assigning the *E*- or *Z*-configuration.
12. L. Xie and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **113**, 3123 (1991).
13. R. E. Ireland and A. K. Willard, *Tetrahedron Lett.*, 3975 (1975); R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1972); R. E. Ireland, P. Wipf, and J. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).

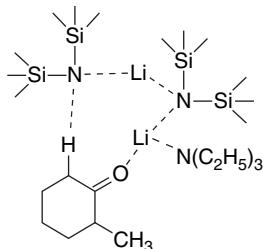
In contrast to LDA, LiHMDS favors the *Z*-enolate.¹⁴ Certain other bases show a preference for formation of the *Z*-enolate. For example, lithium 2,4,6-trichloroanilide, lithium diphenylamide, and lithium trimethylsilylanilide show nearly complete *Z*-selectivity with 2-methyl-3-pentanone.¹⁵



The *Z*-selectivity seems to be associated primarily with reduced basicity of the amide anion. It is postulated that the shift to *Z*-stereoselectivity is the result of a looser TS, in which the steric effects of the chair TS are reduced.

Strong effects owing to the presence of lithium halides have been noted. With 3-pentanone, the *E*:*Z* ratio can be improved from 10:1 to 60:1 by addition of one equivalent of LiBr in deprotonation by LiTMP.¹⁶ (Note a similar effect for 2-methyl-3-pentanone in Table 1.2) NMR studies show that the addition of the halides leads to formation of mixed 1:1 aggregates, but precisely how this leads to the change in stereoselectivity has not been unraveled. A crystal structure has been determined for a 2:1:4:1 complex of the enolate of methyl *t*-butyl ketone, with an HMDS anion, four lithium cations, and one bromide.¹⁷ This structure, reproduced in Figure 1.1, shows that the lithium ions are clustered around the single bromide, with the enolate oxygens bridging between two lithium ions. The amide base also bridges between lithium ions.

Very significant acceleration in the rate of deprotonation of 2-methylcyclohexanone was observed when triethylamine was included in enolate-forming reactions in toluene. The rate enhancement is attributed to a TS containing LiHMDS dimer and triethylamine. Steric effects in the amine are crucial in selective stabilization of the TS and the extent of acceleration that is observed.¹⁸



- ¹⁴. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).
- ¹⁵. L. Xie, K. M. Isenberger, G. Held, and L. M. Dahl, *J. Org. Chem.*, **62**, 7516 (1997); L. Xie, K. Vanlandeghem, K. M. Isenberger, and C. Bernier, *J. Org. Chem.*, **68**, 641 (2003).
- ¹⁶. P. L. Hall, J. H. Gilchrist, and D. B. Collum, *J. Am. Chem. Soc.*, **113**, 9571 (1991); P. L. Hall, J. H. Gilchrist, A. T. Harrison, D. J. Fuller, and D. B. Collum, **113**, 9575 (1991).
- ¹⁷. K. W. Henderson, A. E. Dorigo, P. G. W. Williard, and P. R. Bernstein, *Angew. Chem. Int. Ed. Engl.*, **35**, 1322 (1996).
- ¹⁸. P. Zhao and D. B. Collum, *J. Am. Chem. Soc.*, **125**, 4008, 14411 (2003).

SECTION 1.1

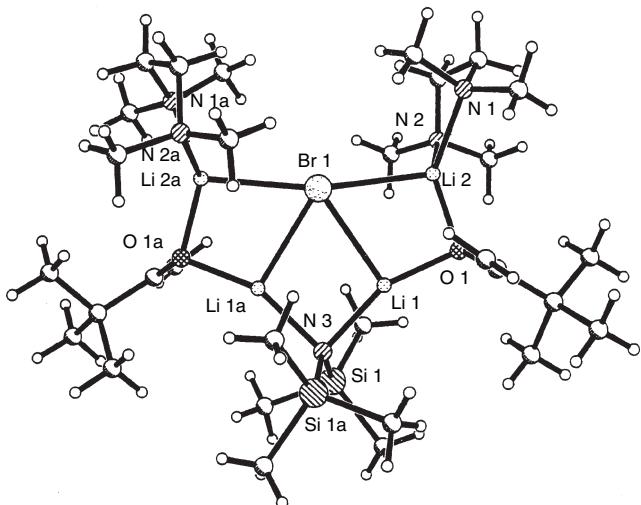
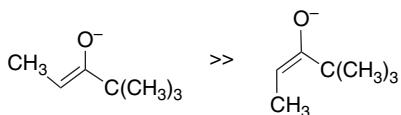
Generation and
Properties of Enolates
and Other
Stabilized Carbanions

Fig. 1.1. Crystal structure of lithium enolate of methyl *t*-butyl ketone in a structure containing four Li^+ , two enolates, and one HMDA anions, one bromide ion, and two TMEDA ligands. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **35**, 1322 (1996), by permission of Wiley-VCH.

These effects of LiBr and triethylamine indicate that there is still much to be learned about deprotonation and that there is potential for further improvement in regio- and stereoselectivity.

Some data on the stereoselectivity of enolate formation from both esters and ketones is given in Table 1.2. The switch from *E* to *Z* in the presence of HMPA is particularly prominent for ester enolates. There are several important factors in determining regio- and stereoselectivity in enolate formation, including the strength of the base, the identity of the cation, and the nature of the solvent and additives. In favorable cases such as 2-methyl-3-pentanone and ethyl propanoate, good selectivity is possible for both stereoisomers. In other cases, such as 2,2-dimethyl-3-pentanone, the inherent stability difference between the enolates favors a single enolate, regardless of conditions.



Chelation affects the stereochemistry of enolate formation. For example, the formation of the enolates from α -siloxyesters is *Z* for LiHMDS, but *E* for LiTMP.¹⁹

¹⁹. K. Hattori and H. Yamamoto, *J. Org. Chem.*, **58**, 5301 (1993); K. Hattori and H. Yamamoto, *Tetrahedron*, **50**, 3099 (1994).

Table 1.2. Stereoselectivity of Enolate Formation^a

CHAPTER 1	Reactant	Base	THF (hexane) (Z:E)	THF (23% HMPA) (Z:E)
<i>Alkylation of Enolates and Other Carbon Nucleophiles</i>				
Ketones				
CH ₃ CH ₂ COCH ₂ CH ₃ ^{b,c}	LDA	30:70	92:8	
CH ₃ CH ₂ COCH ₂ CH ₃ ^b	LiTMP	20:80		
CH ₃ CH ₂ COCH ₂ CH ₃ ^b	LiHMDS	34:66		
CH ₃ CH ₂ COCH(CH ₃) ₂ ^b	LDA	56:44		
CH ₃ CH ₂ COCH(CH ₃) ₂ ^b	LiHMDS	> 98:2		
CH ₃ CH ₂ COCH(CH ₃) ₂ ^d	LiNPh ₂	100:0		
CH ₃ CH ₂ COCH(CH ₃) ₂ ^e	LiTMP.LiBr	4:96		
CH ₃ CH ₂ COC(CH ₃) ₃ ^b	LDA	< 2:98		
CH ₃ CH ₂ COPh ^b	LDA	> 97:3		
Esters				
CH ₃ CH ₂ CO ₂ CH ₂ CH ₃ ^f	LDA	6:94	88:15	
CH ₃ CO ₂ C(CH ₃) ₃ ^g	LDA	5:95	77:23	
CH ₃ (CH ₂) ₃ CO ₂ CH ₃ ^g	LDA	9:91	84:16	
PhCH ₂ CO ₂ CH ₃ ^h	LDA	19:81	91:9	
Amides				
CH ₃ CH ₂ CON(C ₂ H ₅) ₂ ⁱ	LDA ⁱ	> 97:3		
CH ₃ CH ₂ CON(CH ₂) ₄ ⁱ	LDA	> 97:3		

a. From a more extensive compilation given by C. H. Heathcock, *Modern Synthetic Methods*, **6**, 1 (1992).

b. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).

c. Z. A. Fataftah, I. E. Kopka, and M. W. Rathke, *J. Am. Chem. Soc.*, **102**, 3959 (1980).

d. L. Xie, K. Vanlandeghem, K. M. Isenberger, and C. Bernier, *J. Org. Chem.*, **68**, 641 (2003).

e. P. L. Hall, J. H. Gilchrist, and D. B. Collum, *J. Am. Chem. Soc.*, **113**, 9571 (1991).

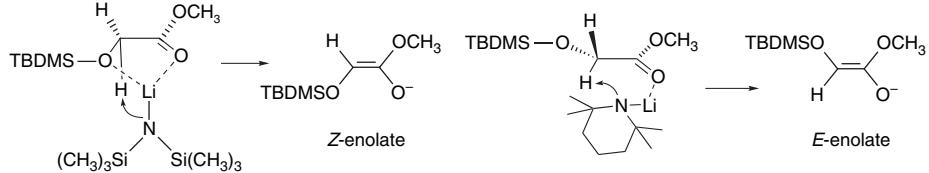
f. R. E. Ireland, P. Wipf, and J. D. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).

g. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).

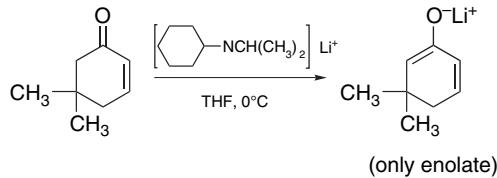
h. F. Tanaka and K. Fuji, *Tetrahedron Lett.*, **33**, 7885 (1992).

i. J. M. Takacs, Ph. D. Thesis, California Institute of Technology, 1981.

It has been suggested that this stereoselectivity might arise from a chelated TS in the case of the less basic LiHMDS.



Kinetically controlled deprotonation of α,β -unsaturated ketones usually occurs preferentially at the α' -carbon adjacent to the carbonyl group. The polar effect of the carbonyl group is probably responsible for the faster deprotonation at this position.

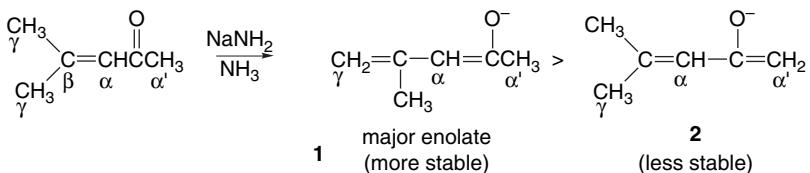


Ref. 20

²⁰. R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, *Tetrahedron Lett.*, 965 (1973).

SECTION 1.1

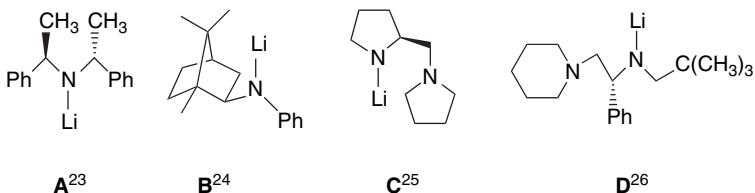
Generation and Properties of Enolates and Other Stabilized Carbanions



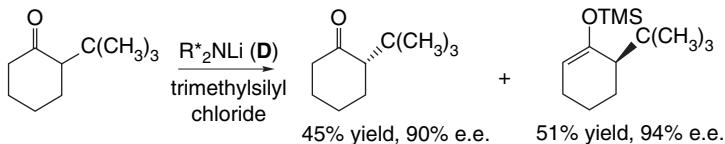
Ref. 21

Under conditions of thermodynamic control, however, it is the enolate corresponding to deprotonation of the γ -carbon that is present in the greater amount.

It is also possible to achieve *enantioselective enolate formation* by using chiral bases. Enantioselective deprotonation requires discrimination between two enantiotopic hydrogens, such as in *cis*-2,6-dimethylcyclohexanone or 4-(*t*-butyl)cyclohexanone. Among the bases that have been studied are chiral lithium amides such as **A** to **D**.²²



Enantioselective enolate formation can also be achieved by *kinetic resolution* through preferential reaction of one of the enantiomers of a racemic chiral ketone such as 2-(*t*-butyl)cyclohexanone (see Section 2.1.8 of Part A to review the principles of kinetic resolution).



Ref. 25a

²¹ G. Buchi and H. Wuest, *J. Am. Chem. Soc.*, **96**, 7573 (1974).

²² P. O'Brien, *J. Chem. Soc., Perkin Trans. I*, 1439 (1998); H. J. Geis, *Methods of Organic Chemistry*, Vol. E21a, Houben-Weyl, G. Thieme Stuttgart, 1996, p. 589.

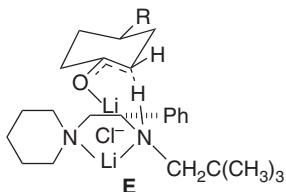
²³ P. J. Cox and N. S. Simpkins, *Tetrahedron: Asymmetry*, **2**, 1 (1991); N. S. Simpkins, *Pure Appl. Chem.*, **68**, 691 (1996); B. J. Bunn and N. S. Simpkins, *J. Org. Chem.*, **58**, 533 (1993).

²⁴ C. M. Cain, R. P. C. Cousins, G. Coumbarides, and N. S. Simpkins, *Tetrahedron*, **46**, 523 (1990).

²⁵ (a) D. Sato, H. Kawasaki, T. Shimada, Y. Arata, K. Okamura, T. Date, and K. Koga, *J. Am. Chem. Soc.*, **114**, 761 (1992); (b) T. Yamashita, D. Sato, T. Kiyoto, A. Kumar, and K. Koga, *Tetrahedron Lett.*, **37**, 8195 (1996); (c) H. Chatani, M. Nakajima, H. Kawasaki, and K. Koga, *Heterocycles*, **46**, 53 (1997); (d) R. Shirai, D. Sato, K. Aoki, M. Tanaka, H. Kawasaki, and K. Koga, *Tetrahedron*, **53**, 5963 (1997).

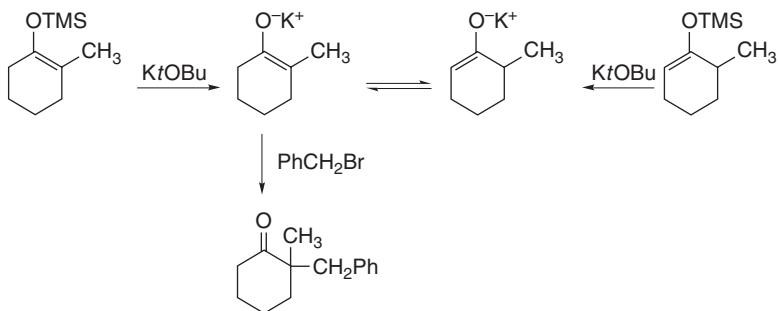
²⁶ M. Asami, *Bull. Chem. Soc. Jpn.*, **63**, 721 (1996).

Such enantioselective deprotonations depend upon kinetic selection between prochiral or enantiomeric hydrogens and the chiral base, resulting from differences in diastereomeric TSs.²⁷ For example, transition structure **E** has been proposed for deprotonation of 4-substituted cyclohexanones by base **D**.²⁸ This structure includes a chloride generated from trimethylsilyl chloride.



1.1.3. Other Means of Generating Enolates

Reactions other than deprotonation can be used to generate specific enolates under conditions in which lithium enolates do not equilibrate with regio- and stereoisomers. Several methods are shown in Scheme 1.2. Cleavage of trimethylsilyl enol ethers or enol acetates by methylolithium (Entries 1 and 3), depends on the availability of these materials in high purity. Alkoxides can also be used to cleave silyl enol ethers and enol acetates.²⁹ When KO-*t*-Bu is used for the cleavage, subsequent alkylation occurs at the more-substituted position, regardless of which regioisomeric silyl enol ether is used.³⁰ Evidently under these conditions, the potassium enolates equilibrate and the more highly substituted enolate is more reactive.



Trimethylsilyl enol ethers can also be cleaved by tetraalkylammonium fluoride (Entry 2). The driving force for this reaction is the formation of the very strong Si–F bond, which has a bond energy of 142 kcal/mol.³¹ These conditions, too, lead to enolate equilibration.

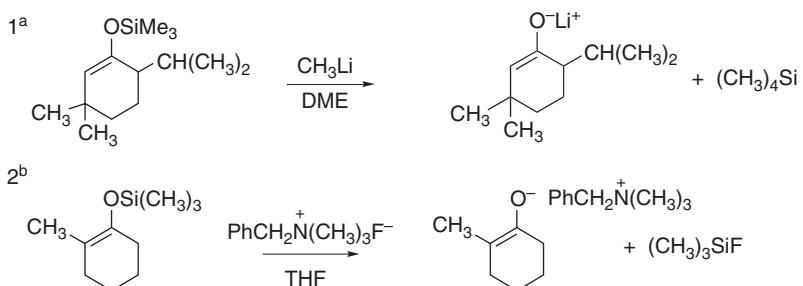
- ²⁷. A. Corruble, J.-Y. Valnot, J. Maddaluno, Y. Prigent, D. Davoust, and P. Duhamel, *J. Am. Chem. Soc.*, **119**, 10042 (1997); D. Sato, H. Kawasaki, and K. Koga, *Chem. Pharm. Bull.*, **45**, 1399 (1997); K. Sugasawa, M. Shindo, H. Noguchi, and K. Koga, *Tetrahedron Lett.*, **37**, 7377 (1996).
- ²⁸. M. Toriyama, K. Sugasawa, M. Shindo, N. Tokutake, and K. Koga, *Tetrahedron Lett.*, **38**, 567 (1997).
- ²⁹. D. Cahard and P. Duhamel, *Eur. J. Org. Chem.*, 1023 (2001).
- ³⁰. P. Duhamel, D. Cahard, Y. Quesnel, and J.-M. Poirier, *J. Org. Chem.*, **61**, 2232 (1996); Y. Quesnel, L. Bidois-Sery, J.-M. Poirier, and L. Duhamel, *Synlett*, 413 (1998).
- ³¹. For reviews of the chemistry of O-silyl enol ethers, see J. K. Rasmussen, *Synthesis*, 91 (1977); P. Brownbridge, *Synthesis*, 1, 85 (1983); I. Kuwajima and E. Nakamura, *Acc. Chem. Res.*, **18**, 181 (1985).

Scheme 1.2. Other Means of Generating Specific Enolates

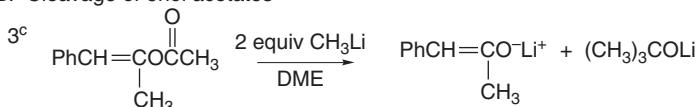
SECTION 1.1

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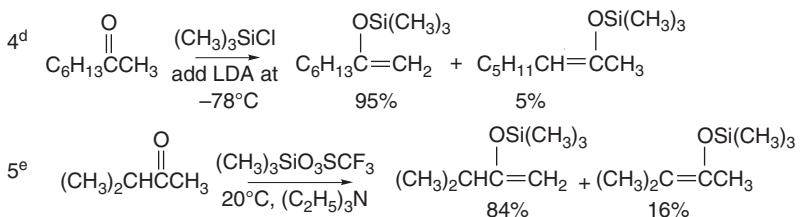
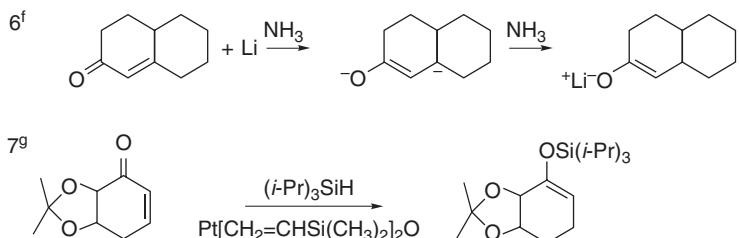
A. Cleavage of trimethylsilyl ethers



B. Cleavage of enol acetates



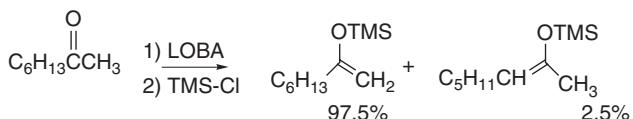
C. Regioselective silylation of ketones by in situ enolate trapping

D. Reduction of α,β -unsaturated ketones

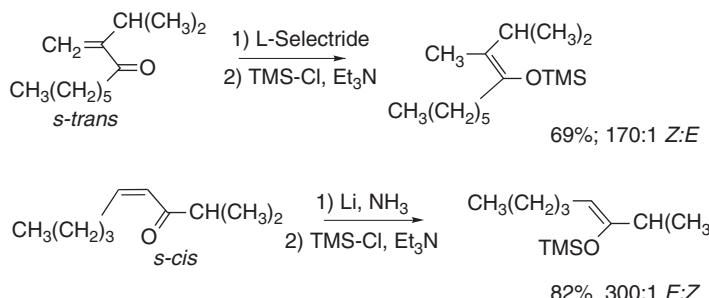
- a. G. Stork and P. Hudrik, *J. Am. Chem. Soc.*, **90**, 4464 (1968); H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).
- b. I. Kuwajima and E. Nakamura, *J. Am. Chem. Soc.*, **97**, 3258 (1975).
- c. G. Stork and S. R. Dowd, *Org. Synth.*, **55**, 46 (1976); see also H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).
- d. E. J. Corey and A. W. Gross, *Tetrahedron Lett.*, **25**, 495 (1984).
- e. E. Emde, A. Goetz, K. Hofmann, and G. Simchen, *Justus Liebigs Ann. Chem.*, 1643 (1981).
- f. G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965).
- g. C. R. Johnson and R. K. Raheja, *J. Org. Chem.*, **59**, 2287 (1994).

The composition of the trimethylsilyl enol ethers prepared from an enolate mixture reflects the enolate composition. If the enolate formation can be done with high regioselection, the corresponding trimethylsilyl enol ether can be obtained in high purity. If not, the silyl enol ether mixture must be separated. Trimethylsilyl enol ethers can be prepared directly from ketones. One procedure involves reaction with trimethylsilyl

chloride and a tertiary amine.³² This procedure gives the regioisomers in a ratio favoring the thermodynamically more stable enol ether. Use of *t*-butyldimethylsilyl chloride with potassium hydride as the base also seems to favor the thermodynamic product.³³ Trimethylsilyl trifluoromethanesulfonate (TMS-OTf), which is more reactive, gives primarily the less-substituted trimethylsilyl enol ether.³⁴ Higher ratios of the less-substituted enol ether are obtained by treating a mixture of ketone and trimethylsilyl chloride with LDA at -78°C.³⁵ Under these conditions the kinetically preferred enolate is immediately trapped by reaction with trimethylsilyl chloride. Even greater preferences for the less-substituted silyl enol ether can be obtained by using the more hindered lithium amide from *t*-octyl-*t*-butylamine (LOBA).



Lithium-ammonia reduction of α , β -unsaturated ketones (Entry 6) provides a very useful method for generating specific enolates.³⁶ The starting enones are often readily available and the position of the double bond in the enone determines the structure of the resulting enolate. For acyclic enones, the TMS-Cl trapping of enolates generated by conjugate reduction gives a silyl enol ether having a composition that reflects the conformation of the enone.³⁷ (See Section 2.2.1 of Part A to review enone conformation.)

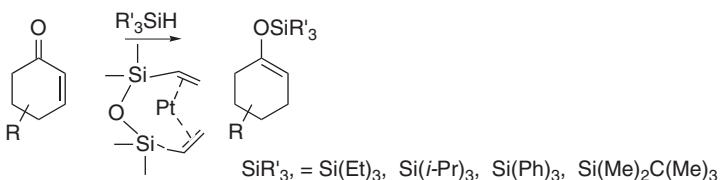


Trimethylsilyl enol ethers can also be prepared by 1,4-reduction of enones using silanes as reductants. Several effective catalysts have been found,³⁸ of which the most versatile appears to be a Pt complex of divinyltetramethyldisiloxane.³⁹ This catalyst gives good yields of substituted silyl enol ethers (e.g., Scheme 1.2, Entry 7).

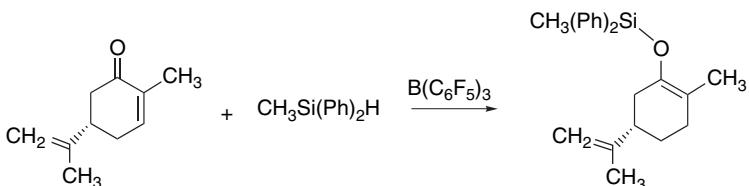
32. H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969); R. D. Miller and D. R. McKean, *Synthesis*, 730 (1979).
 33. J. Orban, J. V. Turner, and B. Twitchin, *Tetrahedron Lett.*, **25**, 5099 (1984).
 34. H. Emde, A. Goetz, K. Hofmann, and G. Simchen, *Liebigs Ann. Chem.*, 1643 (1981); see also E. J. Corey, H. Cho, C. Ruecker, and D. Hua, *Tetrahedron Lett.*, 3455 (1981).
 35. E. J. Corey and A. W. Gross, *Tetrahedron Lett.*, **25**, 495 (1984).
 36. For a review of α , β -enone reduction, see D. Caine, *Org. React.*, **23**, 1 (1976).
 37. A. R. Chamberlin and S. H. Reich, *J. Am. Chem. Soc.*, **107**, 1440 (1985).
 38. I. Ojima and T. Kogure, *Organometallics*, **1**, 1390 (1982); T. H. Chan and G. Z. Zheng, *Tetrahedron Lett.*, **34**, 3095 (1993); D. E. Cane and M. Tandon, *Tetrahedron Lett.*, **35**, 5351 (1994).
 39. C. R. Johnson and R. K. Raheja, *J. Org. Chem.*, **59**, 2287 (1994).

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Generation and Properties of Enolates and Other Stabilized Carbanions

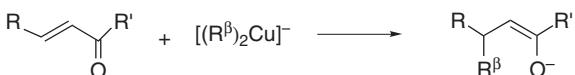


Excellent yields of silyl enol have also been obtained from enones using $\text{B}(\text{C}_6\text{F}_5)_3$ as a catalyst.⁴⁰ *t*-Butyldimethylsilyl, triethylsilyl, and other silyl enol ethers can also be made under these conditions.



These and other reductive methods for generating enolates from enones are discussed more fully in Chapter 5.

Another very important method for specific enolate generation is the conjugate addition of organometallic reagents to enones. This reaction, which not only generates a specific enolate, but also adds a carbon substituent, is discussed in Section 8.1.2.3.



1.1.4. Solvent Effects on Enolate Structure and Reactivity

The rate of alkylation of enolate ions is strongly dependent on the solvent in which the reaction is carried out.⁴¹ The relative rates of reaction of the sodium enolate of diethyl *n*-butylmalonate with *n*-butyl bromide are shown in Table 1.3. Dimethyl sulfoxide (DMSO) and *N,N*-dimethylformamide (DMF) are particularly effective in enhancing the reactivity of enolate ions. Both of these are *polar aprotic solvents*. Other

Table 1.3. Relative Alkylation Rates of Sodium Diethyl *n*-Butylmalonate in Various Solvents^a

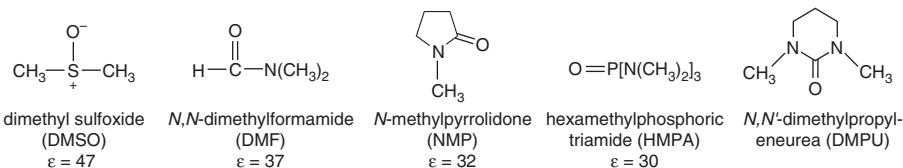
Solvent	Dielectric constant ϵ	Relative rate
Benzene	2.3	1
Tetrahydrofuran	7.3	14
Dimethoxyethane	6.8	80
<i>N,N</i> -Dimethylformamide	37	970
Dimethyl sulfoxide	47	1420

a. From H. E. Zaugg, *J. Am. Chem. Soc.*, **83**, 837 (1961).

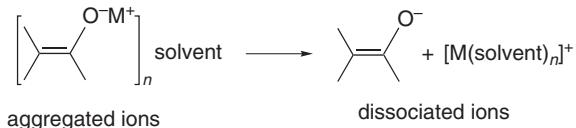
⁴⁰ J. M. Blackwell, D. J. Morrison, and W. E. Piers, *Tetrahedron*, **58**, 8247 (2002).

⁴¹ For reviews, see (a) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969); (b) L. M. Jackmann and B. C. Lange, *Tetrahedron*, **33**, 2737 (1977).

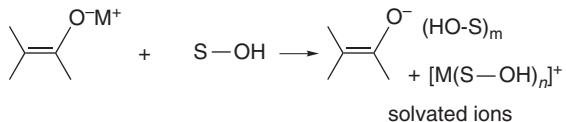
compounds that are used as cosolvents in reactions between enolates and alkyl halides include *N*-methylpyrrolidone (NMP), hexamethylphosphoric triamide (HMPA) and *N,N'*-dimethylpropyleneurea (DMPU).⁴² Polar aprotic solvents, as the name indicates, are materials that have high dielectric constants but lack hydroxy or other hydrogen-bonding groups. Polar aprotic solvents possess excellent metal cation coordination ability, so they can solvate and dissociate enolates and other carbanions from ion pairs and clusters.



The reactivity of alkali metal (Li^+ , Na^+ , K^+) enolates is very sensitive to the state of aggregation, which is, in turn, influenced by the reaction medium. The highest level of reactivity, which can be approached but not achieved in solution, is that of the “bare” unsolvated enolate anion. For an enolate-metal ion pair in solution, the maximum reactivity is expected when the cation is strongly solvated and the enolate is very weakly solvated. Polar aprotic solvents are good cation solvators and poor anion solvators. Each one has a negatively polarized oxygen available for coordination to the metal cation. Coordination to the enolate anion is less effective because the positively polarized atoms of these molecules are not nearly as exposed as the oxygen. Thus, these solvents provide a medium in which enolate-metal ion aggregates are dissociated to give a less encumbered, more reactive enolate.



Polar protic solvents such as water and alcohols also possess a pronounced ability to separate ion aggregates, but are less favorable as solvents in enolate alkylation reactions because they can coordinate to both the metal cation and the enolate anion. Solvation of the enolate anion occurs through hydrogen bonding. The solvated enolate is relatively less reactive because the hydrogen bonding must be disrupted during alkylation. Enolates generated in polar protic solvents such as water, alcohols, or ammonia are therefore less reactive than the same enolate in a polar aprotic solvent such as DMSO. Of course, hydroxylic solvents also impose limits on the basicity of enolates that are stable.



⁴². T. Mukhopadhyay and D. Seebach, *Helv. Chim. Acta*, **65**, 385 (1982).

SECTION 1.1

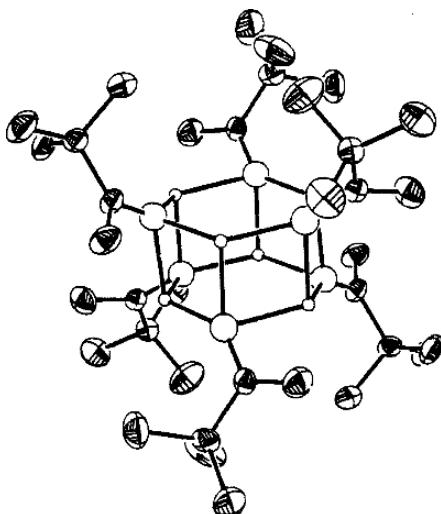
Generation and Properties of Enolates and Other Stabilized Carbanions

Fig. 1.2. Unsolvated hexameric aggregate of lithium enolate of methyl *t*-butyl ketone; the open circles represent oxygen and the small circles are lithium. Reproduced from *J. Am. Chem. Soc.*, **108**, 462 (1986), by permission of the American Chemical Society.

Tetrahydrofuran (THF) and dimethoxyethane (DME) are slightly polar solvents that are moderately good cation solvators. Coordination to the metal cation involves the oxygen unshared electron pairs. These solvents, because of their lower dielectric constants, are less effective at separating ion pairs and higher aggregates than are the polar aprotic solvents. The structures of the lithium and potassium enolates of methyl *t*-butyl ketone have been determined by X-ray crystallography. The structures are shown in Figures 1.2 and 1.3.⁴³ Whereas these represent the solid state structures,

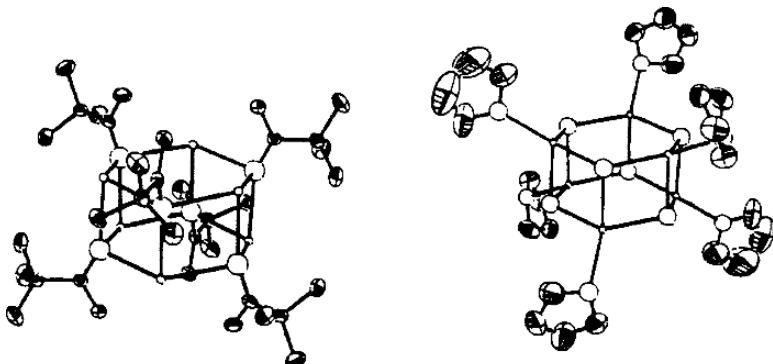


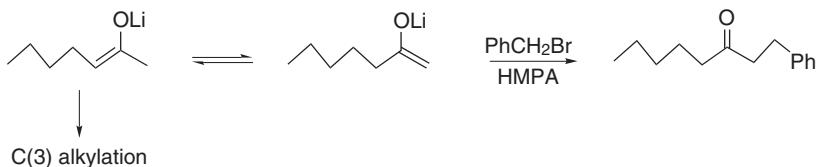
Fig. 1.3. Potassium enolate of methyl *t*-butyl ketone; open circles are oxygen and small circles are potassium. (a) left panel shows only the enolate structures; (b) right panel shows only the solvating THF molecules. The actual structure is the superposition of both panels. Reproduced from *J. Am. Chem. Soc.*, **108**, 462 (1986), by permission of the American Chemical Society.

⁴³ P. G. Williard and G. B. Carpenter, *J. Am. Chem. Soc.*, **108**, 462 (1986).

the hexameric clusters are a good indication of the nature of the enolates in relatively weakly coordinating solvents. In both structures, series of alternating metal cations and enolate oxygens are assembled in two offset hexagons. The cluster is considerably tighter with Li^+ than with K^+ . The $\text{M}-\text{O}$ bonds are about 1.9 Å for Li^+ and 2.6 Å for K^+ . The enolate C–O bond is longer (1.34 Å) for Li^+ than for K^+ (1.31 Å), whereas the C=C bond is shorter for Li^+ (1.33 Å) than for K^+ (1.35 Å). Thus, the Li^+ enolate has somewhat more of oxy-anion character and is expected to be a “harder” than the potassium enolate.

Despite the somewhat reduced reactivity of aggregated enolates, THF and DME are the most commonly used solvents for synthetic reactions involving enolate alkylation. They are the most suitable solvents for *kinetic enolate generation* and also have advantages in terms of product workup and purification over the polar aprotic solvents. Enolate reactivity in these solvents can often be enhanced by adding a reagent that can bind alkali metal cations more strongly. Popular choices are HMPA, DMPU, tetramethylethylenediamine (TMEDA), and the crown ethers. TMEDA chelates metal ions through the electron pairs on nitrogen. The crown ethers encapsulate the metal ions through coordination with the ether oxygens. The 18-crown-6 structure is of such a size as to allow sodium or potassium ions to fit in the cavity. The smaller 12-crown-4 binds Li^+ preferentially. The cation complexing agents lower the degree of aggregation of the enolate and metal cations, which results in enhanced reactivity.

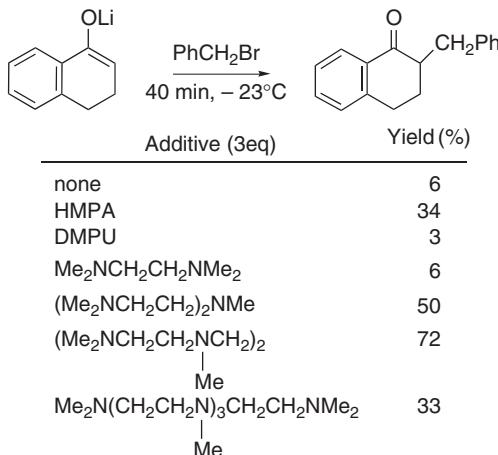
The effect of HMPA on the reactivity of cyclopentanone enolate has been examined.⁴⁴ This enolate is primarily a dimer, even in the presence of excess HMPA, but the reactivity increases by a factor of 7500 for a tenfold excess of HMPA at –50° C. The kinetics of the reaction with CH_3I are consistent with the dimer being the active nucleophile. It should be kept in mind that the reactivity of regio- and stereoisomeric enolates may be different and the alkylation product ratio may not reflect the enolate composition. This issue was studied with 2-heptanone.⁴⁵ Although kinetic deprotonation in THF favors the 1-enolate, a nearly equal mixture of C(1) and C(3) alkylation was observed. The inclusion of HMPA improved the C(1) selectivity to 11:1 and also markedly accelerated the rate of the reaction. These results are presumably due to increased reactivity and less competition from enolate isomerization in the presence of HMPA.



The effect of chelating polyamines on the rate and yield of benzylation of the lithium enolate of 1-tetralone was compared with HMPA and DMPU. The triamine

⁴⁴. M. Suzuki, H. Koyama, and R. Noyori, *Bull. Chem. Soc. Jpn.*, **77**, 259 (2004); M. Suzuki, H. Koyama, and R. Noyori, *Tetrahedron*, **60**, 1571 (2004).

⁴⁵. C. L. Liotta and T. C. Caruso, *Tetrahedron Lett.*, **26**, 1599 (1985).



The reactivity of enolates is also affected by the metal counterion. For the most commonly used ions the order of reactivity is $Mg^{2+} < Li^+ < Na^+ < K^+$. The factors that are responsible for this order are closely related to those described for solvents. The smaller, harder Mg^{2+} and Li^+ cations are more tightly associated with the enolate than are the Na^+ and K^+ ions. The tighter coordination decreases the reactivity of the enolate and gives rise to more highly associated species.

1.2. Alkylation of Enolates⁴⁷

1.2.1. Alkylation of Highly Stabilized Enolates

Relatively acidic compounds such as malonate esters and β -ketoesters were the first class of compounds for which reliable conditions for carbanion alkylation were developed. The alkylation of these relatively acidic compounds can be carried out in alcohols as solvents using metal alkoxides as bases. The presence of two electron-withdrawing substituents facilitates formation of the resulting enolate. Alkylation occurs by an S_N2 process, so the alkylating agent must be reactive toward nucleophilic displacement. Primary halides and sulfonates, especially allylic and benzylic ones, are the most reactive alkylating agents. Secondary systems react more slowly and often give only moderate yields because of competing elimination. Tertiary halides give only elimination products. Methylene groups can be dialkylated if sufficient base and alkylating agent are used. Dialkylation can be an undesirable side reaction if the monoalkyl derivative is the desired product. Sequential dialkylation using two different alkyl groups is possible. Use of dihaloalkanes as alkylating reagents leads to ring formation. The relative rates of cyclization for ω -haloalkyl malonate esters

⁴⁶. M. Goto, K. Akimoto, K. Aoki, M. Shindo, and K. Koga, *Chem. Pharm. Bull.*, **48**, 1529 (2000).

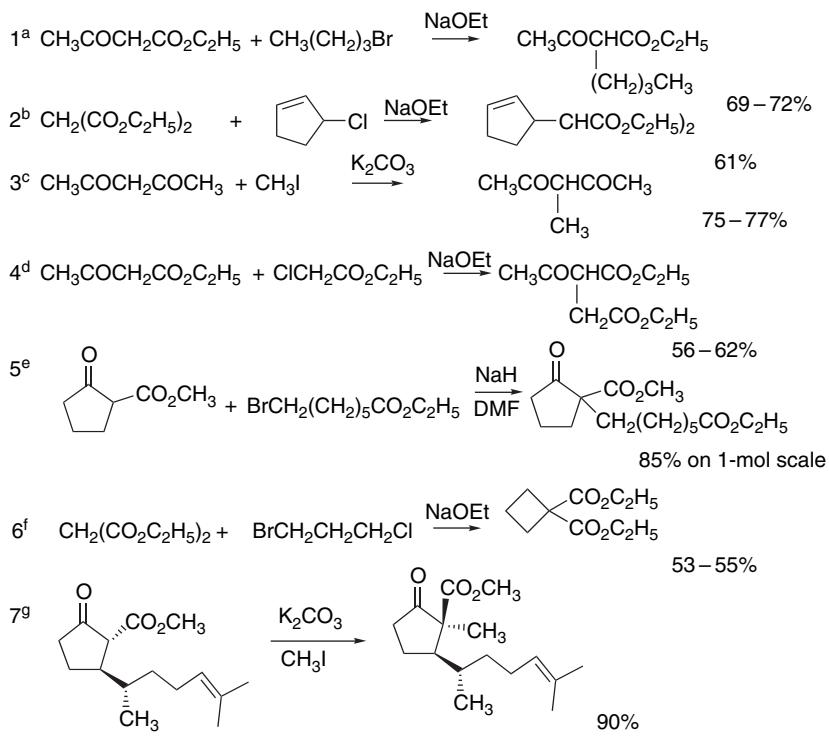
⁴⁷. For general reviews of enolate alkylation, see D. Caine, in *Carbon-Carbon Bond Formation*, Vol. 1, R. L. Augustine, ed., Marcel Dekker, New York, 1979, Chap. 2; C. H. Heathcock, *Modern Synthetic Methods*, **6**, 1 (1992).

are 650,000:1:6500:5 for formation of three-, four-, five-, and six-membered rings, respectively.⁴⁸ (See Section 4.3 of Part A to review the effect of ring size on S_N2 reactions.)

Some examples of alkylation reactions involving relatively acidic carbon acids are shown in Scheme 1.3. Entries 1 to 4 are typical examples using sodium ethoxide as the base. Entry 5 is similar, but employs sodium hydride as the base. The synthesis of diethyl cyclobutanedicarboxylate in Entry 6 illustrates ring formation by *intramolecular alkylation reactions*. Additional examples of intramolecular alkylation are considered in Section 1.2.5. Note also the stereoselectivity in Entry 7, where the existing branched substituent leads to a *trans* orientation of the methyl group.

The 2-substituted β -ketoesters (Entries 1, 4, 5, and 7) and malonic ester (Entries 2 and 6) prepared by the methods illustrated in Scheme 1.3 are useful for the synthesis

Scheme 1.3. Alkylation of Enolates Stabilized by Two Functional Groups



a. C. S. Marvel and F. D. Hager, *Org. Synth.*, **I**, 248 (1941).

b. R. B. Moffett, *Org. Synth.*, **IV**, 291 (1963).

c. A. W. Johnson, E. Markham, and R. Price, *Org. Synth.*, **42**, 75 (1962).

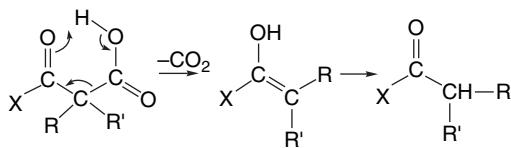
d. H. Adkins, N. Isbell, and B. Wojciek, *Org. Synth.*, **II**, 262 (1943).

e. K. F. Bernhardy, J. F. Poletto, J. Nocera, P. Miranda, R. E. Schaub, and M. J. Weiss, *J. Org. Chem.*, **45**, 4702 (1980).

f. R. P. Mariella and R. Raube, *Org. Synth.*, **IV**, 288 (1963).

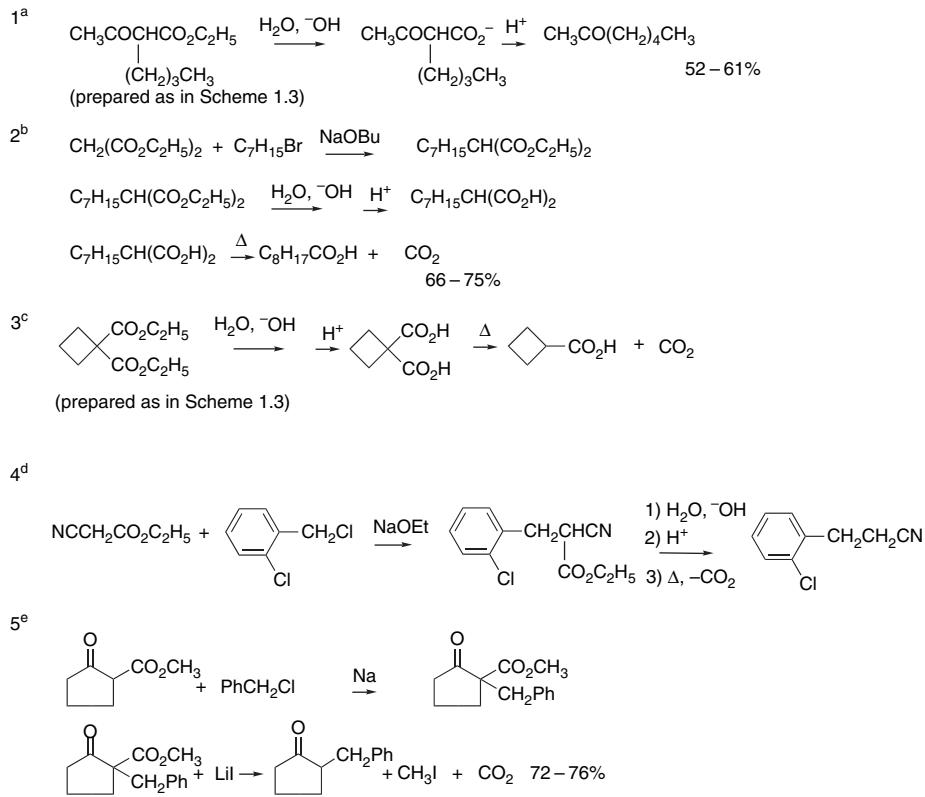
g. D. F. Taber and S. C. Malcom, *J. Org. Chem.*, **66**, 944 (2001).

⁴⁸ A. C. Knipe and C. J. Stirling, *J. Chem. Soc. B*, 67 (1968); For a discussion of factors that affect intramolecular alkylation of enolates, see J. Janjatovic and Z. Majerski, *J. Org. Chem.*, **45**, 4892 (1980).



Examples of this approach to the synthesis of ketones and carboxylic acids are presented in Scheme 1.4. In these procedures, an ester group is removed by hydrolysis and decarboxylation after the alkylation step. The malonate and acetoacetate carbanions are the *synthetic equivalents* of the simpler carbanions that lack the additional ester substituent. In the preparation of 2-heptanone (Entry 1), for example, ethyl acetoacetate functions

Scheme 1.4. Synthesis by Decarboxylation of Malonates and other β -Dicarbonyl Compounds



a. J. R. Johnson and F. D. Hager, *Org. Synth.*, **I**, 351 (1941).

b. E. E. Reid and J. R. Ruhoff, *Org. Synth.*, **II**, 474 (1943).

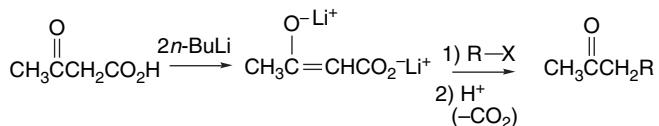
c. G. B. Heisig and F. H. Stodola, *Org. Synth.*, **III**, 213 (1955).

d. J. A. Skorcz and F. E. Kaminski, *Org. Synth.*, **48**, 53 (1968).

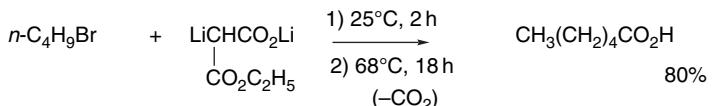
e. F. Elsinger, *Org. Synth.*, **V**, 76 (1973).

as the synthetic equivalent of acetone. Entries 2 and 3 show synthesis of carboxylic acids via the malonate ester route. Entry 4 is an example of a nitrile synthesis, starting with ethyl cyanoacetate as the carbon nucleophile. The cyano group also facilitates decarboxylation. Entry 5 illustrates an alternative decarboxylation procedure in which lithium iodide is used to cleave the β -ketoester by nucleophilic demethylation.

It is also possible to use the dilithium derivative of acetoacetic acid as the synthetic equivalent of acetone enolate.⁴⁹ In this case, the hydrolysis step is unnecessary and decarboxylation can be done directly on the alkylation product.



Similarly, the dilithium dianion of monoethyl malonate is easily alkylated and the product decarboxylates after acidification.⁵⁰



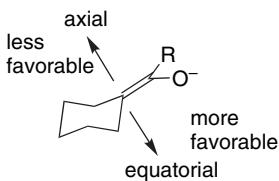
1.2.2. Alkylation of Ketone Enolates

The preparation of ketones and ester from β -dicarbonyl enolates has largely been supplanted by procedures based on selective enolate formation. These procedures permit direct alkylation of ketone and ester enolates and avoid the hydrolysis and decarboxylation of keto ester intermediates. The development of conditions for stoichiometric formation of both kinetically and thermodynamically controlled enolates has permitted the extensive use of enolate alkylation reactions in multistep synthesis of complex molecules. One aspect of the alkylation reaction that is crucial in many cases is the stereoselectivity. The alkylation has a stereoelectronic preference for approach of the electrophile perpendicular to the plane of the enolate, because the π electrons are involved in bond formation. A major factor in determining the stereoselectivity of ketone enolate alkylations is the difference in steric hindrance on the two faces of the enolate. The electrophile approaches from the less hindered of the two faces and the degree of stereoselectivity depends on the steric differentiation. Numerous examples of such effects have been observed.⁵¹ In ketone and ester enolates that are exocyclic to a conformationally biased cyclohexane ring there is a small preference for

⁴⁹. R. A. Kjonaas and D. D. Patel, *Tetrahedron Lett.*, **25**, 5467 (1984).

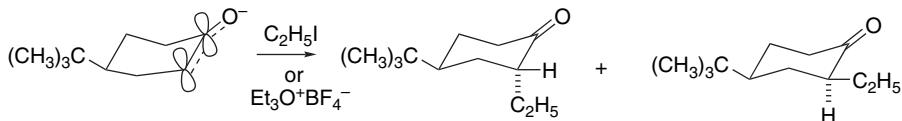
⁵⁰. J. E. McMurry and J. H. Musser, *J. Org. Chem.*, **40**, 2556 (1975).

⁵¹. For reviews, see D. A. Evans, in *Asymmetric Synthesis*, Vol. 3, J. D. Morrison, ed., Academic Press, New York, 1984, Chap. 1; D. Caine, in *Carbon-Carbon Bond Formation*, R. L. Augustine, ed., Marcel Dekker, New York, 1979, Chap. 2.



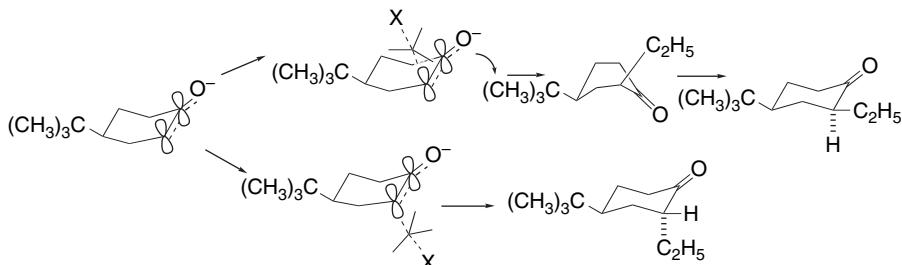
the electrophile to approach from the equatorial direction.⁵² If the axial face is further hindered by addition of a substituent, the selectivity is increased.

For simple, conformationally biased cyclohexanone enolates such as that from 4-*t*-butylcyclohexanone, there is little steric differentiation. The alkylation product is a nearly 1:1 mixture of the *cis* and *trans* isomers.

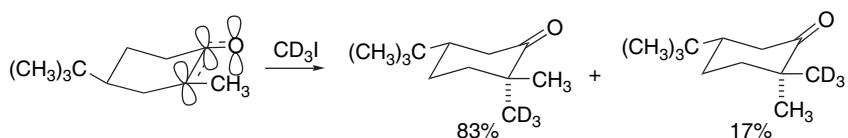


Ref. 53

The *cis* product must be formed through a TS with a twistlike conformation to adhere to the requirements of stereoelectronic control. The fact that this pathway is not disfavored is consistent with other evidence that the TS in enolate alkylations occurs *early* and reflects primarily the structural features of the reactant, not the product. A late TS would disfavor the formation of the *cis* isomer because of the strain associated with the nonchair conformation of the product.



The introduction of an alkyl substituent at the α -carbon in the enolate enhances stereoselectivity somewhat. This is attributed to a steric effect in the enolate. To minimize steric interaction with the solvated oxygen, the alkyl group is distorted somewhat from coplanarity, which biases the enolate toward attack from the axial direction. The alternate approach from the upper face increases the steric interaction by forcing the alkyl group to become eclipsed with the enolate oxygen.⁵⁴

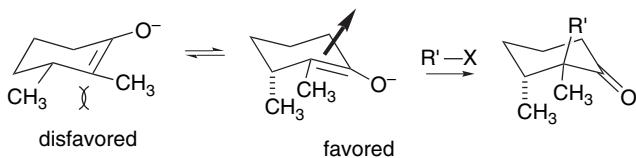


⁵² A. P. Krapcho and E. A. Dundulis, *J. Org. Chem.*, **45**, 3236 (1980); H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).

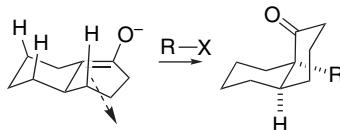
⁵³ H. O. House, B. A. Terfertiller, and H. D. Olmstead, *J. Org. Chem.*, **33**, 935 (1968).

⁵⁴ H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 1000 (1973).

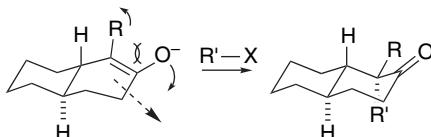
When an additional methyl substituent is placed at C(3), there is a strong preference for alkylation *anti* to the 3-methyl group. This is attributed to the conformation of the enolate, which places the C(3) methyl in a pseudoaxial orientation because of allylic strain (see Part A, Section 2.2.1). The axial C(3) methyl then shields the lower face of the enolate.⁵⁵



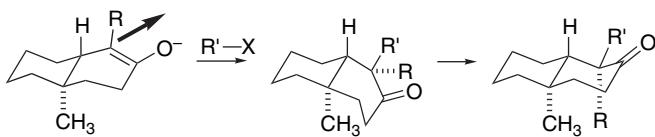
The enolates of 1- and 2-decalone derivatives provide further insight into the factors governing stereoselectivity in enolate alkylations. The 1(9)-enolate of 1-decalone shows a preference for alkylation to give the *cis* ring juncture, and this is believed to be due primarily a steric effect. The upper face of the enolate presents three hydrogens in a 1,3-diaxial relationship to the approaching electrophile. The corresponding hydrogens on the lower face are equatorial.⁵⁶



The 2(1)-enolate of *trans*-2-decalone is preferentially alkylated by an axial approach of the electrophile.



The stereoselectivity is enhanced if there is an alkyl substituent at C(1). The factors operating in this case are similar to those described for 4-*t*-butylcyclohexanone. The *trans*-decalone framework is conformationally rigid. Axial attack from the lower face leads directly to the chair conformation of the product. The 1-alkyl group enhances this stereoselectivity because a steric interaction with the solvated enolate oxygen distorts the enolate to favor the axial attack.⁵⁷ The placement of an axial methyl group at C(10) in a 2(1)-decalone enolate introduces a 1,3-diaxial interaction with the approaching electrophile. The preferred alkylation product results from approach on the opposite side of the enolate.

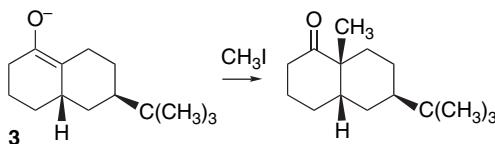


⁵⁵ R. K. Boeckman, Jr., *J. Org. Chem.*, **38**, 4450 (1973).

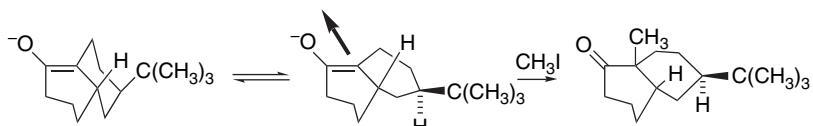
⁵⁶ H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).

⁵⁷ R. S. Mathews, S. S. Grigenti, and E. A. Folkers, *J. Chem. Soc., Chem. Commun.*, 708 (1970); P. Lansbury and G. E. DuBois, *Tetrahedron Lett.*, 3305 (1972).

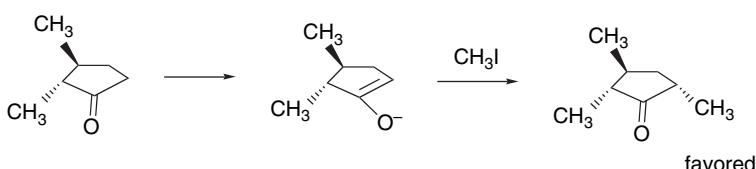
The prediction and interpretation of alkylation stereochemistry requires consideration of conformational effects in the enolate. The decalone enolate **3** was found to have a strong preference for alkylation to give the *cis* ring junction, with alkylation occurring *cis* to the *t*-butyl substituent.⁵⁸



According to molecular mechanics (MM) calculations, the minimum energy conformation of the enolate is a twist-boat (because the chair leads to an axial orientation of the *t*-butyl group). The enolate is convex in shape with the second ring shielding the bottom face of the enolate, so alkylation occurs from the top.



Houk and co-workers examined the role of torsional effects in the stereoselectivity of enolate alkylation in five-membered rings, and their interpretation can explain the preference for C(5) alkylation *syn* to the 2-methyl group in *trans*-2,3-dimethylcyclopentanone.⁵⁹



The *syn* TS is favored by about 1 kcal/mol, owing to reduced eclipsing, as illustrated in Figure 1.4. An experimental study using the kinetic enolate of 3-(*t*-butyl)-2-methylcyclopentanone in an alkylation reaction with benzyl iodide gave an 85:15 preference for the predicted *cis*-2,5-dimethyl derivative.

In acyclic systems, the enolate conformation comes into play. β,β -Disubstituted enolates prefer a conformation with the hydrogen eclipsed with the enolate double bond. In unfunctionalized enolates, alkylation usually takes place *anti* to the larger substituent, but with very modest stereoselectivity.

⁵⁸. H. O. House, W. V. Phillips, and D. Van Derveer, *J. Org. Chem.*, **44**, 2400 (1979).

⁵⁹. K. Ando, N. S. Green, Y. Li, and K. N. Houk, *J. Am. Chem. Soc.*, **121**, 5334 (1999).

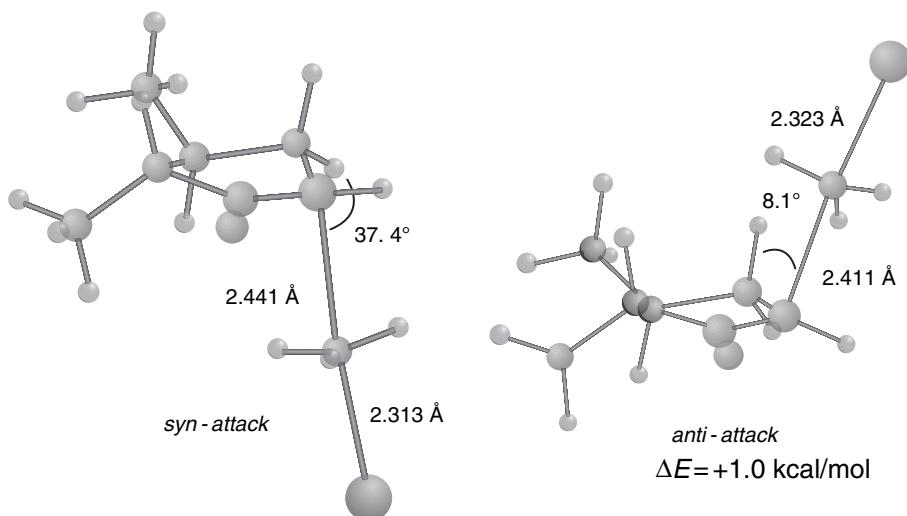
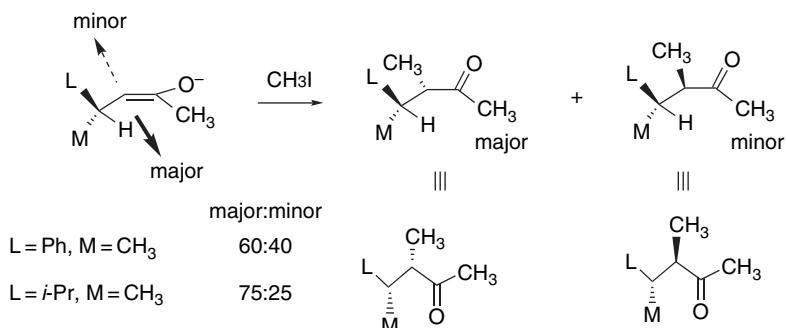


Fig. 1.4. Transition structures for *syn* and *anti* attack on the kinetic enolate of *trans*-2,3-dimethylcyclopentanone showing the staggered versus eclipsed nature of the newly forming bond. Reproduced from *J. Am. Chem. Soc.*, **121**, 5334 (1999), by permission of the American Chemical Society.



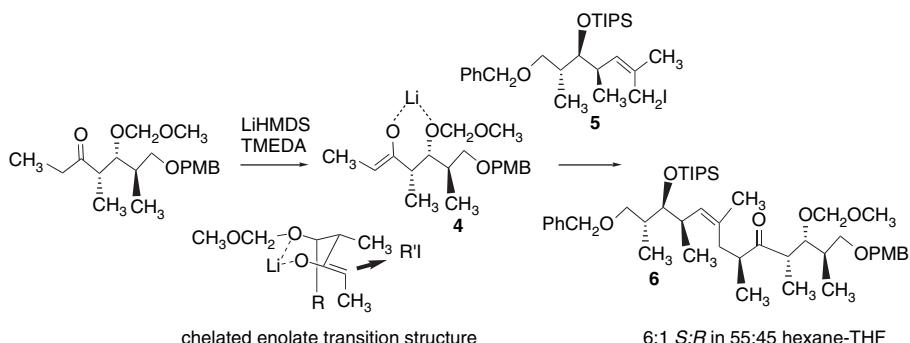
Ref. 60

These examples illustrate the issues that must be considered in analyzing the stereoselectivity of enolate alkylation. *The major factors are the conformation of the enolate, the stereoelectronic requirement for an approximately perpendicular trajectory, the steric preference for the least hindered path of approach, and minimization of torsional strain.* In cyclic systems the ring geometry and positioning of substituents are often the dominant factors. For acyclic enolates, the conformation and the degree of steric discrimination govern the stereoselectivity.

For enolates with additional functional groups, chelation may influence stereoselectivity. Chelation-controlled alkylation has been examined in the context of the synthesis of a polyol lactone (-)-discodermolide. The lithium enolate **4** reacts with the allylic iodide **5** in a hexane:THF solvent mixture to give a 6:1 ratio favoring the desired stereoisomer. Use of the sodium enolate gives the opposite stereoselectivity, presumably because of the loss of chelation.⁶¹ The solvent seems to be quite important in promoting chelation control.

⁶⁰ I. Fleming and J. J. Lewis, *J. Chem. Soc., Perkin Trans. 1*, 3257 (1992).

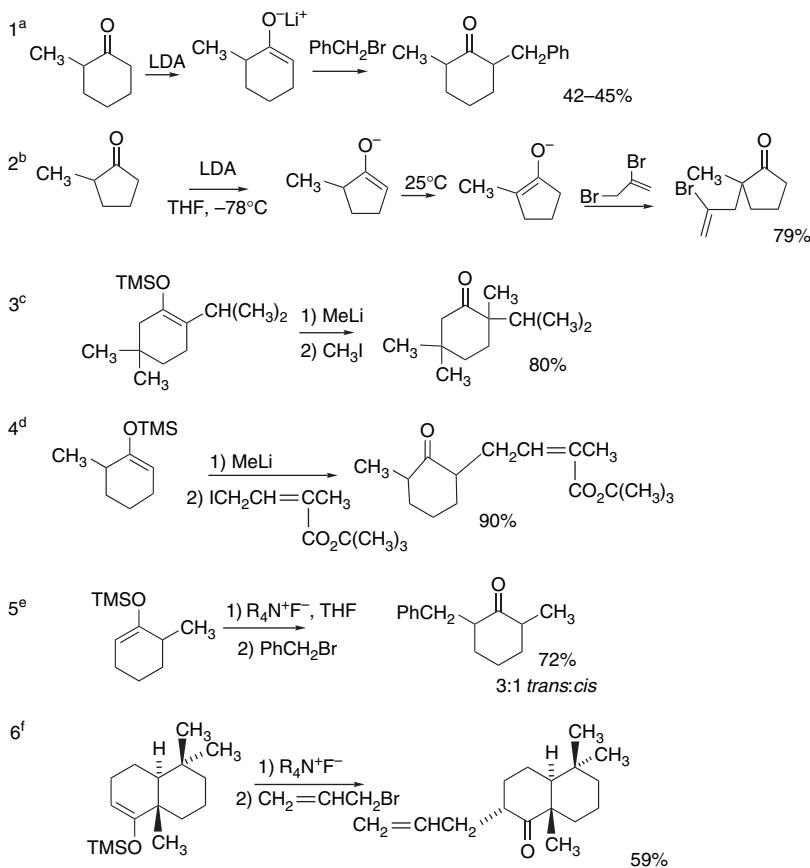
⁶¹ S. S. Harried, G. Yang, M. A. Strawn, and D. C. Myles, *J. Org. Chem.*, **62**, 6098 (1997).



Previous studies with related enolates having different protecting groups also gave products with the opposite C(16)-R configuration.⁶²

Scheme 1.5 gives some examples of alkylation of ketone enolates. Entries 1 and 2 involve formation of the enolates by deprotonation with LDA. In Entry 2, equilibration

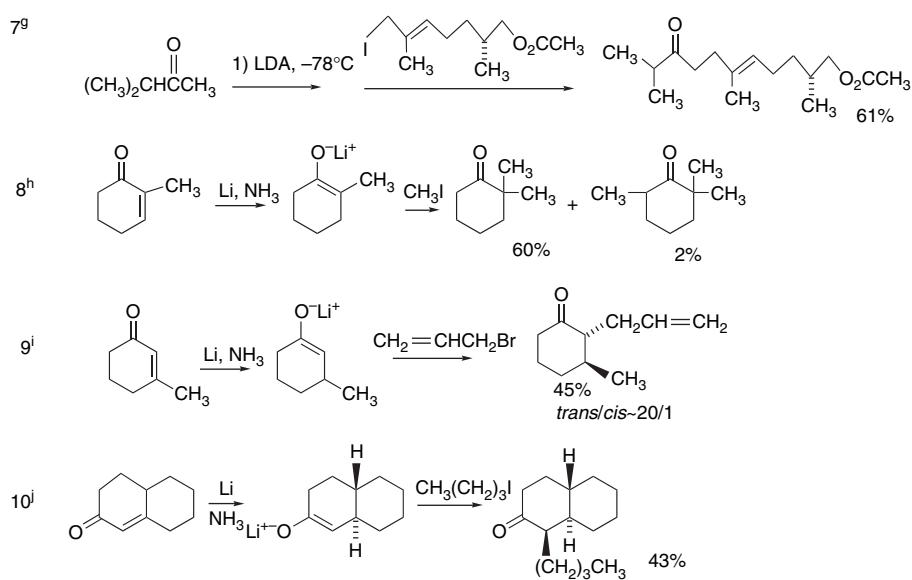
Scheme 1.5. Alkylation of Ketone Enolates



(Continued)

⁶². D. T. Hung, J. B. Nerenberg, and S. L. Schreiber, *J. Am. Chem. Soc.*, **118**, 11054 (1996); D. L. Clark and C. H. Heathcock, *J. Org. Chem.*, **58**, 5878 (1993).

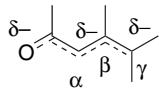
Scheme 1.5. (Continued)



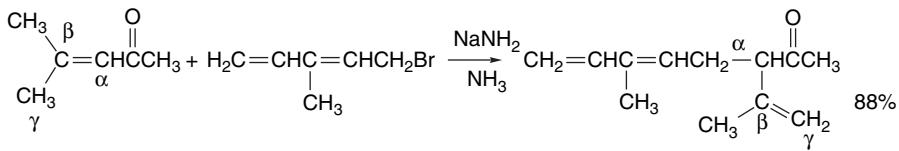
- a. M. Gall and H. O. House, *Org. Synth.*, **52**, 39 (1972).
 b. S. C. Welch and S. Chayabunjonglerd, *J. Am. Chem. Soc.*, **101**, 6768 (1979).
 c. G. Stork and P. F. Hudrik, *J. Am. Chem. Soc.*, **90**, 4464 (1968).
 d. P. L. Stotter and K. A. Hill, *J. Am. Chem. Soc.*, **96**, 6524 (1974).
 e. I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **104**, 1025 (1982).
 f. A. B. Smith, III, and R. Mewshaw, *J. Org. Chem.*, **49**, 3685 (1984).
 g. Y. Li, C. Huang, W. Li, and Y. Li, *Synth. Commun.*, **27**, 4341 (1997).
 h. H. A. Smith, B. J. L. Huff, W. J. Powers, III, and D. Caine, *J. Org. Chem.*, **32**, 2851 (1967).
 i. D. Caine, S. T. Chao, and H. A. Smith, *Org. Synth.*, **56**, 52 (1977).
 j. G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsujii, *J. Am. Chem. Soc.*, **87**, 275 (1965).

to the more-substituted enolate precedes alkylation. Entries 3 and 4 show regiospecific generation of enolates by reaction of silyl enol ethers with methylolithium. Alkylation can also be carried out using silyl enol ethers by generating the enolate by fluoride ion.⁶³ Anhydrous tetraalkylammonium fluoride salts in anhydrous are normally the fluoride ion source.⁶⁴ Entries 5 and 6 illustrate this method. Entry 7 shows the kinetic deprotonation of 3-methylbutanone, followed by alkylation with a functionalized allylic iodide. Entries 8, 9, and 10 are examples of alkylation of enolates generated by reduction of enones. Entry 10 illustrates the preference for axial alkylation of the 2-(1-decalone) enolate.

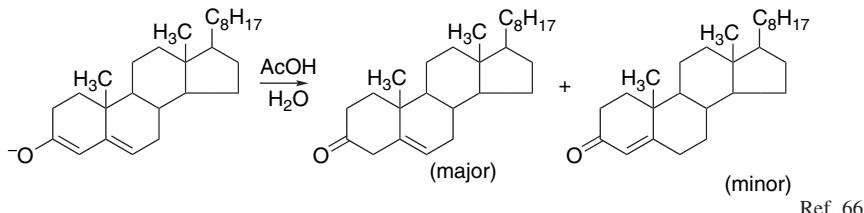
In enolates formed by proton abstraction from α,β -unsaturated ketones, there are three potential sites for attack by electrophiles: the oxygen, the α -carbon, and the γ -carbon. The kinetically preferred site for both protonation and alkylation is the α -carbon.⁶⁵



- ⁶³. I. Kuwajima, E. Nakamura, and M. Shimizu, *J. Am. Chem. Soc.*, **104**, 1025 (1982).
⁶⁴. A. B. Smith, III, and R. Mewshaw, *J. Org. Chem.*, **49**, 3685 (1984).
⁶⁵. R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, *Tetrahedron Lett.*, 965 (1973); J. A. Katzenellenbogen and A. L. Crumrine, *J. Am. Chem. Soc.*, **96**, 5662 (1974).

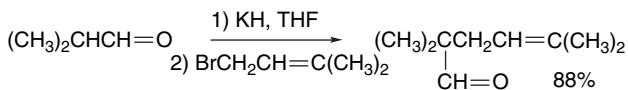


Protonation of the enolate provides a method for converting α,β -unsaturated ketones and esters to the less stable β,γ -unsaturated isomers.



1.2.3. Alkylation of Aldehydes, Esters, Carboxylic Acids, Amides, and Nitriles

Among the compounds capable of forming enolates, the alkylation of ketones has been most widely studied and applied synthetically. Similar reactions of esters, amides, and nitriles have also been developed. Alkylation of aldehyde enolates is not very common. One reason is that aldehydes are rapidly converted to aldol addition products by base. (See Chapter 2 for a discussion of this reaction.) Only when the enolate can be rapidly and quantitatively formed is aldol formation avoided. Success has been reported using potassium amide in liquid ammonia⁶⁷ and potassium hydride in tetrahydrofuran.⁶⁸ Alkylation via enamines or enamine anions provides a more general method for alkylation of aldehydes. These reactions are discussed in Section 1.3.

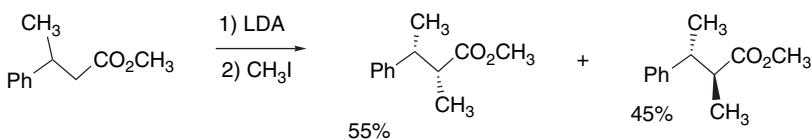


Ref. 68

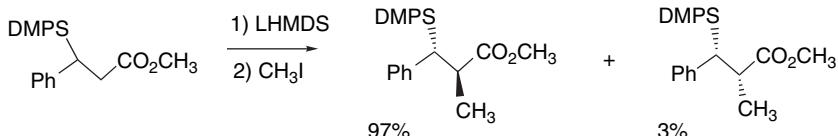
Ester enolates are somewhat less stable than ketone enolates because of the potential for elimination of alkoxide. The sodium and potassium enolates are rather unstable, but Rathke and co-workers found that the lithium enolates can be generated at -78°C .⁶⁹ Alkylations of simple esters require a strong base because relatively weak bases such as alkoxides promote condensation reactions (see Section 2.3.1). The successful formation of ester enolates typically involves an amide base, usually LDA or LiHMDS, at low temperature.⁷⁰ The resulting enolates can be successfully alkylated with alkyl bromides or iodides. HMPA is sometimes added to accelerate the alkylation reaction.

- ^{66.} H. J. Ringold and S. K. Malhotra, *Tetrahedron Lett.*, 669 (1962); S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1538 (1963).
- ^{67.} S. A. G. De Graaf, P. E. R. Oosterhof, and A. van der Gen, *Tetrahedron Lett.*, 1653 (1974).
- ^{68.} P. Groenewegen, H. Kallenberg, and A. van der Gen, *Tetrahedron Lett.*, 491 (1978).
- ^{69.} M. W. Rathke, *J. Am. Chem. Soc.*, **92**, 3222 (1970); M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050 (1973).
- ^{70.} (a) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2318 (1971); (b) R. J. Cregge, J. L. Herrmann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 2425 (1973); (c) J. L. Herrmann and R. H. Schlessinger, *J. Chem. Soc., Chem. Commun.*, 711 (1973).

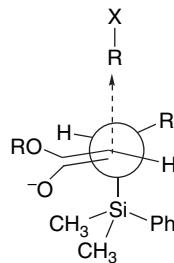
In acyclic systems, the stereochemistry of alkylation depends on steric factors. Stereoselectivity is low for small substituents.⁷¹



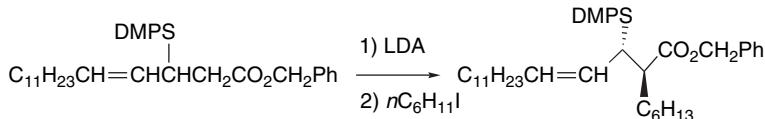
When a larger substituent is present, the reaction becomes much more selective. For example, a β -dimethylphenylsilyl substituent leads to more than 95:5 *anti* alkylation in ester enolates.⁷²



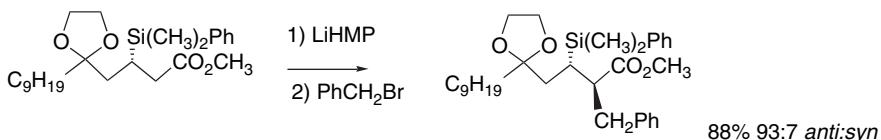
This stereoselectivity is the result of the conformation of the enolate and steric shielding by the silyl substituent.



This directive effect has been employed in stereoselective synthesis.



Ref. 72



Ref. 73

A careful study of the alkylation of several enolates of dialkyl malate esters has been reported.⁷⁴ These esters form dianions resulting from deprotonation of the hydroxy

⁷¹. R. A. N. C. Crump, I. Fleming, J. H. M. Hill, D. Parker, N. L. Reddy, and D. Waterson, *J. Chem. Soc., Perkin Trans. 1*, 3277 (1992).

⁷². I. Fleming and N. J. Lawrence, *J. Chem. Soc., Perkin Trans. 1*, 2679 (1998).

⁷³. R. Verma and S.K. Ghosh, *J. Chem. Soc., Perkin Trans. 2*, 265(1999).

⁷⁴. M. Sefkow, A. Koch, and E. Kleinpeter, *Helv. Chim. Acta*, **85**, 4216 (2002).

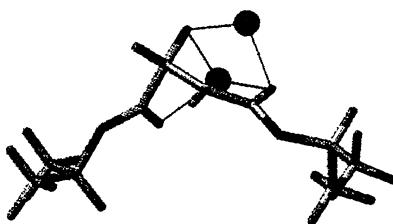
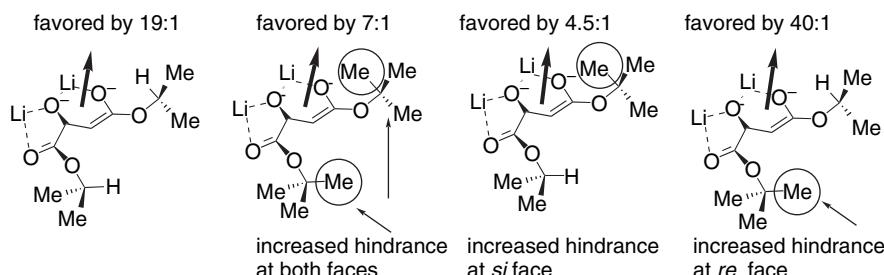
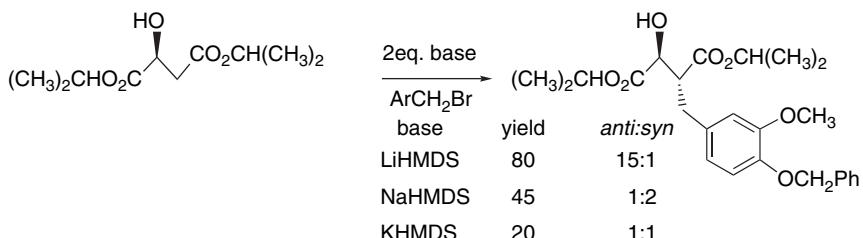


Fig. 1.5. Minimum energy structure of dilithium derivative of di-*iso*-propyl malate. Reproduced from *Helv. Chim. Acta*, **85**, 4216 (2002), by permission of Wiley-VCH.

group as well as the C(3). HF/6-31G* computations indicate that tricoordinate structures are formed, such as that shown for the di-*iso*-propyl ester in Figure 1.5. Curiously, the highest diastereoselectivity (19:1) is seen with the di-*iso*-propyl ester. For the dimethyl, diethyl, and di-*t*-butyl esters, the ratios are about 8:1. The diastereoselectivity is even higher (40:1) with the mixed *t*-butyl-*iso*-propyl ester. This result can be understood by considering the differences in the *si* and *re* faces of the enolates. In the di-*t*-butyl ester, both faces are hindered and selectivity is low. The di-*iso*-propyl ester has more hindrance to the *re* face, and this is accentuated in the mixed ester.



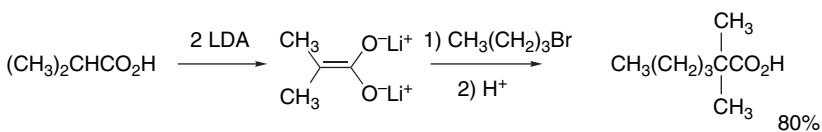
Alkylations of this type also proved to be sensitive to the cation. Good stereo-selectivity (15:1) was observed for the lithium enolate, but the sodium and potassium enolates were much less selective.⁷⁵ This probably reflects the weaker coordination of the latter metals.



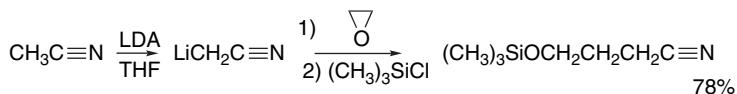
Carboxylic acids can be directly alkylated by conversion to dianions with two equivalents of LDA. The dianions are alkylated at the α -carbon, as would be expected, because the enolate carbon is more strongly nucleophilic than the carboxylate anion.⁷⁶

⁷⁵. M. Sefkow, *J. Org. Chem.*, **66**, 2343 (2001).

⁷⁶. P. L. Creger, *J. Org. Chem.*, **37**, 1907 (1972); P. L. Creger, *J. Am. Chem. Soc.*, **89**, 2500 (1967); P. L. Creger, *Org. Synth.*, **50**, 58 (1970).

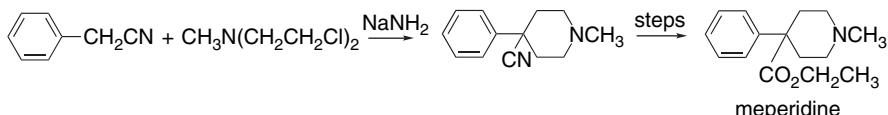


Nitriles can also be converted to anions and alkylated. Acetonitrile ($\text{pK}_{\text{DMSO}} = 31.3$) can be deprotonated, provided a strong nonnucleophilic base such as LDA is used.



Ref. 77

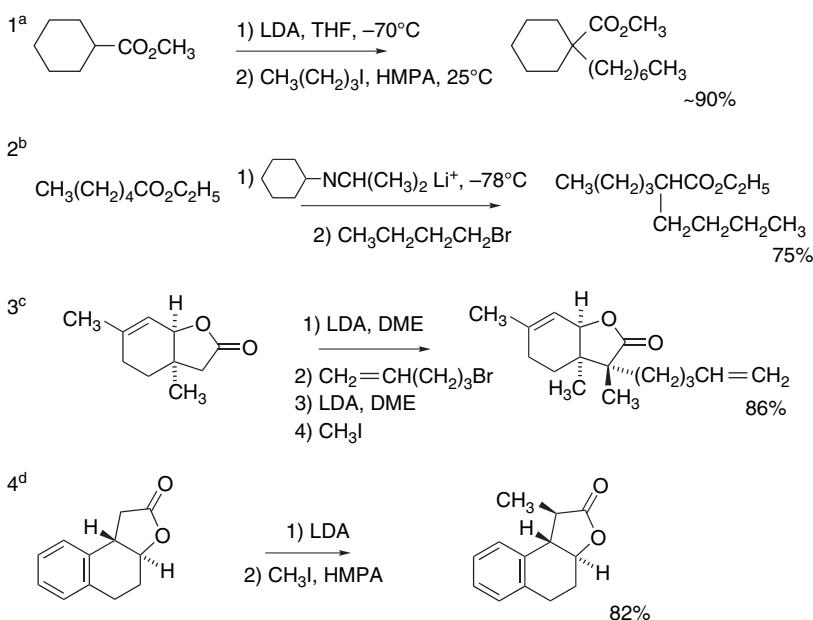
Phenylacetonitrile ($\text{pK}_{\text{DMSO}} = 21.9$) is considerably more acidic than acetonitrile. Dialkylation has been used in the synthesis of meperidine, an analgesic substance.⁷⁸



We will see in Section 1.2.6 that the enolates of *imides* are very useful in synthesis. Particularly important are the enolates of chiral *N*-acyloxazolidinones.

Scheme 1.6 gives some examples of alkylation of esters, amides, and nitriles. Entries 1 and 2 are representative ester alkylations involving low-temperature

Scheme 1.6. Alkylation of Esters, Amides, and Nitriles



(Continued)

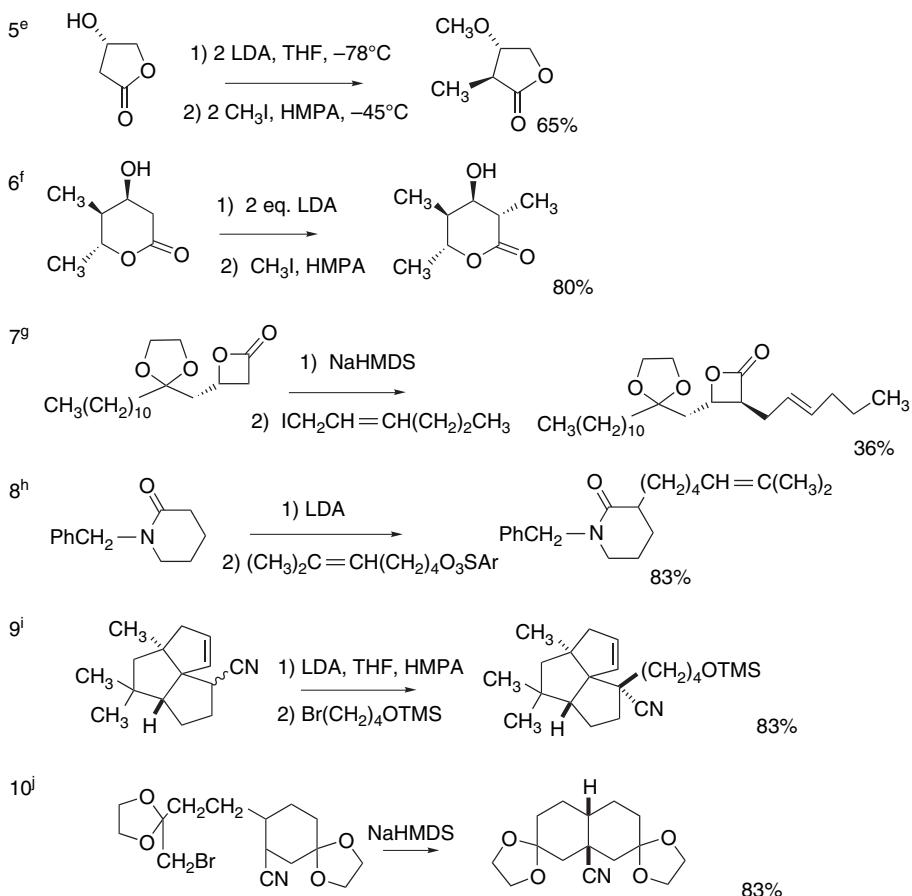
⁷⁷. S. Murata and I. Matsuda, *Synthesis*, 221 (1978).

⁷⁸. O. Eisleb, *Ber.*, **74**, 1433 (1941); cited in H. Kagi and K. Miescher, *Helv. Chim. Acta*, **32**, 2489 (1949).

Scheme 1.6. (Continued)

SECTION 1.2

Alkylation of Enolates

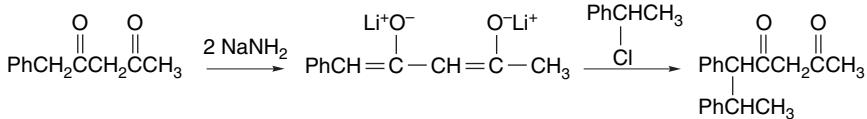


- a. T. R. Williams and L. M. Sirvio, *J. Org. Chem.*, **45**, 5082 (1980).
- b. M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2320 (1971).
- c. S. C. Welch, A. S. C. Prakasa Rao, G. G. Gibbs, and R. Y. Wong, *J. Org. Chem.*, **45**, 4077 (1980).
- d. W. H. Pirkle and P. E. Adams, *J. Org. Chem.*, **45**, 4111 (1980).
- e. H.-M. Shieh and G. D. Prestwich, *J. Org. Chem.*, **46**, 4319 (1981).
- f. J. Tholander and E. M. Carriera, *Helv. Chim. Acta*, **84**, 613 (2001).
- g. P. J. Parsons and J. K. Cowell, *Synlett*, 107 (2000).
- h. D. Kim, H. S. Kim, and J. Y. Yoo, *Tetrahedron Lett.*, **32**, 1577 (1991).
- i. L. A. Paquette, M. E. Okazaki, and J.-C. Caille, *J. Org. Chem.*, **53**, 477 (1988).
- j. G. Stork, J. O. Gardner, R. K. Boeckman, Jr., and K. A. Parker, *J. Am. Chem. Soc.*, **95**, 2014 (1973).

deprotonation by hindered lithium amides. Entries 3 to 7 are lactone alkylations. Entry 3 involves two successive alkylation steps, with the second group being added from the more open face of the enolate. Entry 4 also illustrates stereoselectivity based on a steric effect. Entry 5 shows alkylation at both the enolate and a hydroxy group. Entry 6 is a step in the synthesis of the C(33)–C(37) fragment of the antibiotic amphotericin B. Note that in this case although the hydroxy group is deprotonated it is not methylated under the reaction conditions being used. Entry 7 is a challenging alkylation of a sensitive β-lactone. Although the corresponding saturated halide was not reactive enough, the allylic iodide gave a workable yield. Entry 8 is an alkylation of a lactam. Entries 9 and 10 are nitrile alkylations, the latter being intramolecular.

1.2.4. Generation and Alkylation of Dianions

In the presence of a very strong base, such as an alkylolithium, sodium or potassium hydride, sodium or potassium amide, or LDA, 1,3-dicarbonyl compounds can be converted to their *dianions* by two sequential deprotonations.⁷⁹ For example, reaction of benzoylacetone with sodium amide leads first to the enolate generated by deprotonation at the more acidic methylene group between the two carbonyl groups. A second equivalent of base deprotonates the benzyl methylene group to give a dienediolate.



Ref. 80

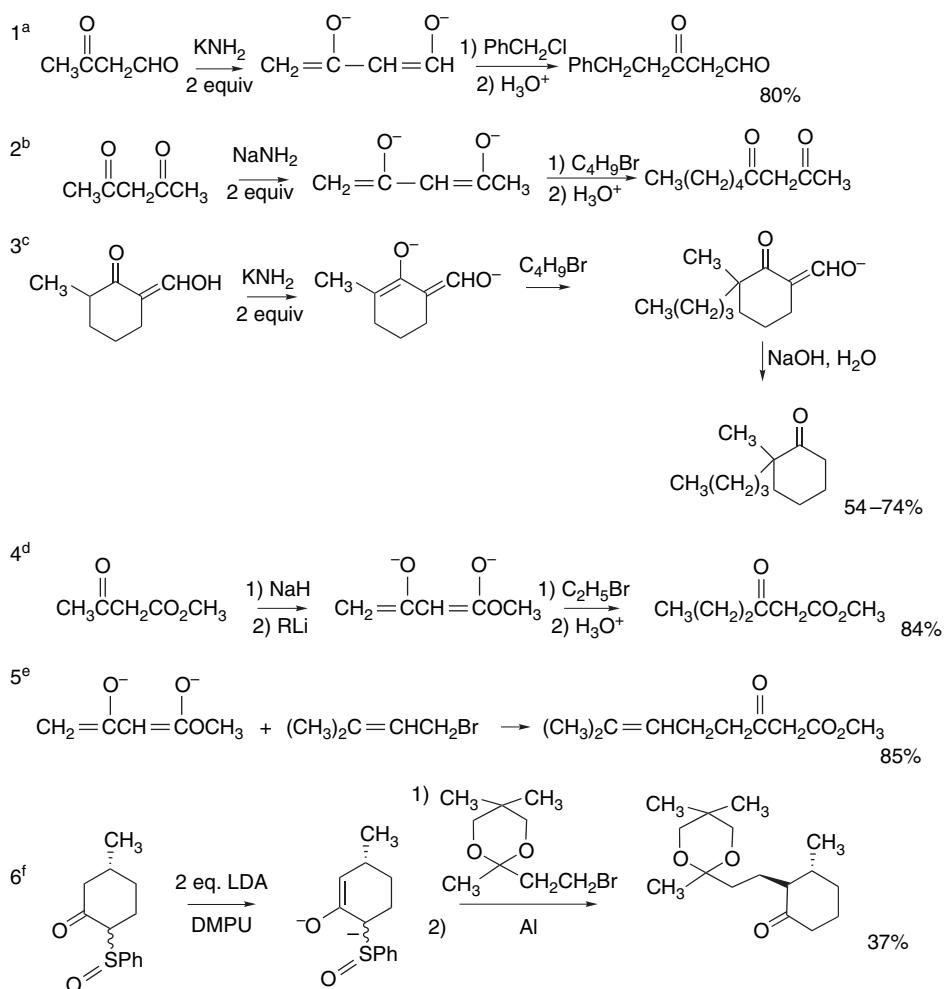
Alkylation of dianions occurs at the *more basic carbon*. This technique permits alkylation of 1,3-dicarbonyl compounds to be carried out cleanly at the less acidic position. Since, as discussed earlier, alkylation of the monoanion occurs at the carbon between the two carbonyl groups, the site of monoalkylation can be controlled by choice of the amount and nature of the base. A few examples of the formation and alkylation of dianions are collected in Scheme 1.7. In each case, alkylation occurs at the less stabilized anionic carbon. In Entry 3, the α -formyl substituent, which is removed after the alkylation, serves to direct the alkylation to the methyl-substituted carbon. Entry 6 is a step in the synthesis of artemisinin, an antimalarial component of a Chinese herbal medicine. The sulfoxide serves as an anion-stabilizing group and the dianion is alkylated at the less acidic α -position. Note that this reaction is also stereoselective for the *trans* isomer. The phenylsulfinyl group is removed reductively by aluminum. (See Section 5.6.2 for a discussion of this reaction.)

1.2.5. Intramolecular Alkylation of Enolates

There are many examples of formation of three- through seven-membered rings by intramolecular enolate alkylation. The reactions depend on attainment of a TS having an approximately linear arrangement of the nucleophilic carbon, the electrophilic carbon, and the leaving group. Since the HOMO of the enolate (ψ_2) is involved, the approach must be approximately perpendicular to the enolate.⁸¹ In intramolecular alkylation, these stereochemical restrictions on the direction of approach of the electrophile to the enolate become important. Baldwin has summarized the general principles that govern the energetics of intramolecular ring-closure reactions.⁸² Analysis of the stereochemistry of intramolecular enolate alkylation requires consideration of both the direction of approach and enolate conformation. The intramolecular alkylation reaction of **7** gives exclusively **8**, having the *cis* ring juncture.⁸³ The alkylation probably occurs through a TS like **F**. The TS geometry permits the π electrons of the enolate to achieve an approximately colinear alignment with the sulfonate leaving group. The TS **G** for

- ⁷⁹ For reviews, see (a) T. M. Harris and C. M. Harris, *Org. React.*, **17**, 155 (1969); E. M. Kaiser, J. D. Petty, and P. L. A. Knutson, *Synthesis*, 509 (1977); C. M. Thompson and D. L. C. Green, *Tetrahedron*, **47**, 4223 (1991); C. M. Thompson, *Dianion Chemistry in Organic Synthesis*, CRC Press, Boca Raton, FL, 1994.
- ⁸⁰ D. M. von Schriltz, K. G. Hampton, and C. R. Hauser, *J. Org. Chem.*, **34**, 2509 (1969).
- ⁸¹ J. E. Baldwin and L. I. Kruse, *J. Chem. Soc., Chem. Commun.*, 233 (1977).
- ⁸² J. E. Baldwin, R. C. Thomas, L. I. Kruse, and L. Silberman, *J. Org. Chem.*, **42**, 3846 (1977).
- ⁸³ J. M. Conia and F. Rouessac, *Tetrahedron*, **16**, 45 (1961).

Scheme 1.7. Generation and Alkylation of Dianions



a. T. M. Harris, S. Boatman, and C. R. Hauser, *J. Am. Chem. Soc.*, **85**, 3273 (1963); S. Boatman, T. M. Harris, and C. R. Hauser, *J. Am. Chem. Soc.*, **87**, 82 (1965); K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **28**, 1946 (1963).

b. K. G. Hampton, T. M. Harris, and C. R. Hauser, *Org. Synth.*, **47**, 92 (1967).

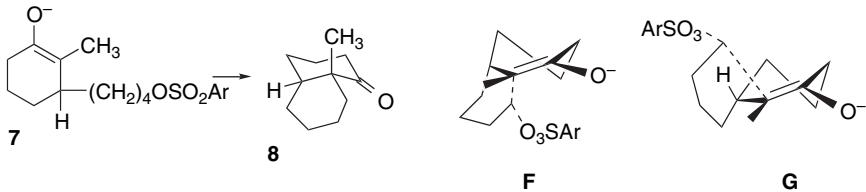
c. S. Boatman, T. M. Harris, and C. R. Hauser, *Org. Synth.*, **48**, 40 (1968).

d. S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.*, **96**, 1082 (1974).

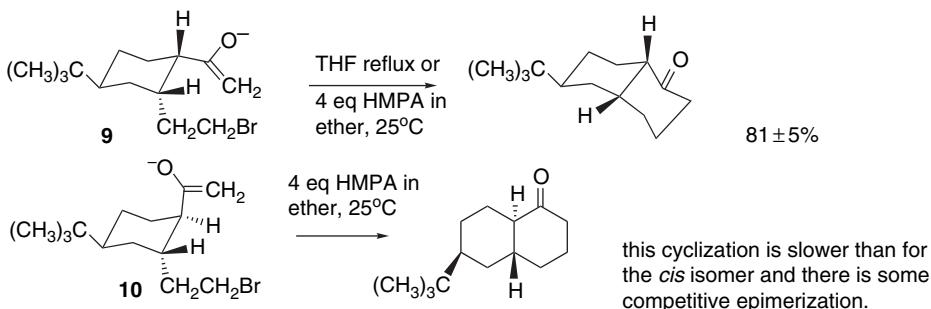
e. F. W. Sum and L. Weiler, *J. Am. Chem. Soc.*, **101**, 4401 (1979).

f. M. A. Avery, W. K. M. Chong, and C. Jennings-White, *J. Am. Chem. Soc.*, **114**, 974 (1992).

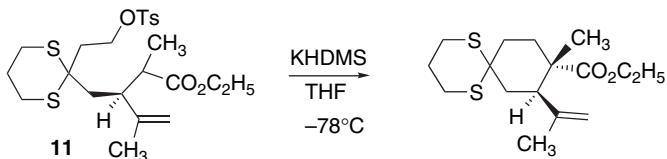
formation of the *trans* ring junction would be more strained because of the necessity to span the distance to the opposite face of the enolate π system.



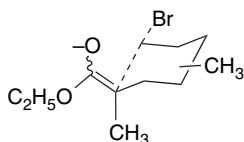
Geometric factors in the TS are also responsible for differences in the case of cyclization of enolates **9** and **10**.⁸⁴



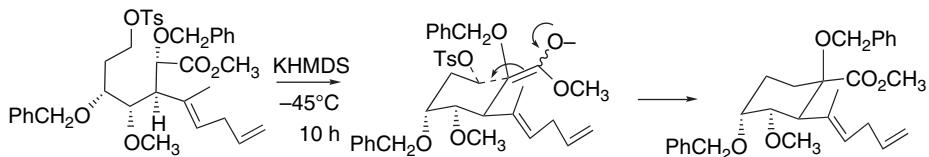
A number of examples of good stereoselectivity based on substituent control of reactant conformation have been identified. For example, **11** gives more than 96% stereoselectivity for the isomer in which the methyl and 2-propenyl groups are *cis*.⁸⁵



Similar *cis* stereoselectivity was observed in formation of four- and five-membered rings.⁸⁶ The origin of this stereoselectivity was probed systematically by a study in which a methyl substituent was placed at the C(3), C(4), C(5), and C(6) positions of ethyl 7-bromoheptanoate. Good (>93%) stereoselectivity was noted for all but the C(5) derivative.⁸⁷ These results are consistent with a chairlike TS with the enolate in an equatorial-like position. In each case the additional methyl group can occupy an equatorial position. The reduced selectivity of the 5-methyl isomer may be due to the fact that the methyl group is farther from the reaction site than in the other cases.



An intramolecular alkylation following this stereochemical pattern was used in the synthesis of (-)-fumagillol, with the alkadienyl substituent exerting the dominant conformational effect.⁸⁸

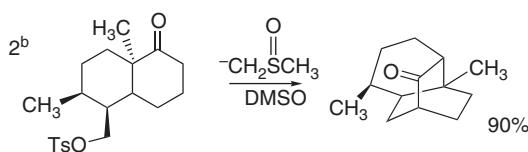
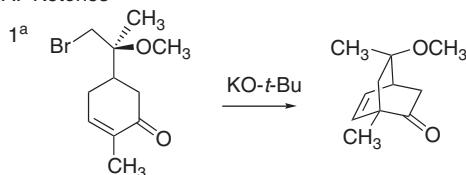


84. H. O. House and W. V. Phillips, *J. Org. Chem.*, **43**, 3851 (1978).
 85. D. Kim and H. S. Kim, *J. Org. Chem.*, **52**, 4633 (1987).
 86. D. Kim, Y. M. Jang, I. O. Kim, and S. W. Park, *J. Chem. Soc., Chem. Commun.*, 760 (1988).
 87. T. Tokoroyama and H. Kusaka, *Can. J. Chem.*, **74**, 2487 (1996).
 88. D. Kim, S. K. Ahn, H. Bae, W. J. Choi, and H. S. Kim, *Tetrahedron Lett.*, **38**, 4437 (1997).

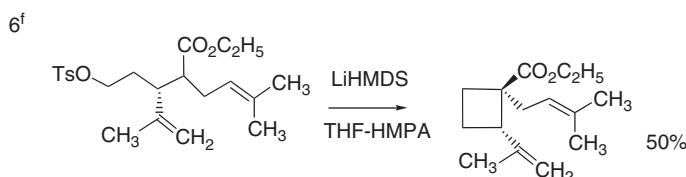
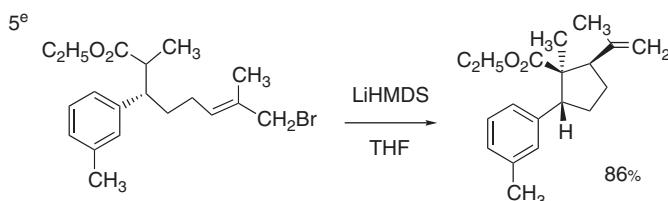
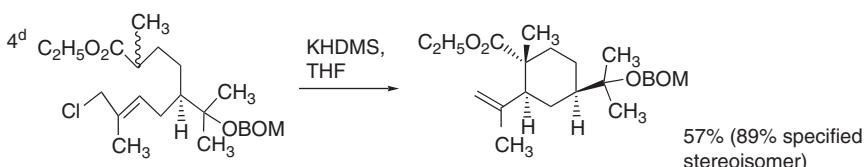
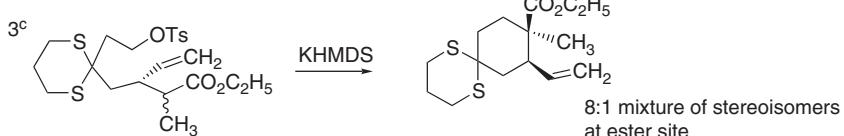
Scheme 1.8 shows some intramolecular enolate alkylations. The reactions in Section A involve alkylation of ketone enolates. Entry 1 is a case of α -alkylation of a conjugated dienolate. In this case, the α -alkylation is also favored by ring strain effects because γ -alkylation would lead to a four-membered ring. The intramolecular alkylation in Entry 2 was used in the synthesis of the terpene seychellene.

Scheme 1.8. Intramolecular Enolate Alkylation

A. Ketones

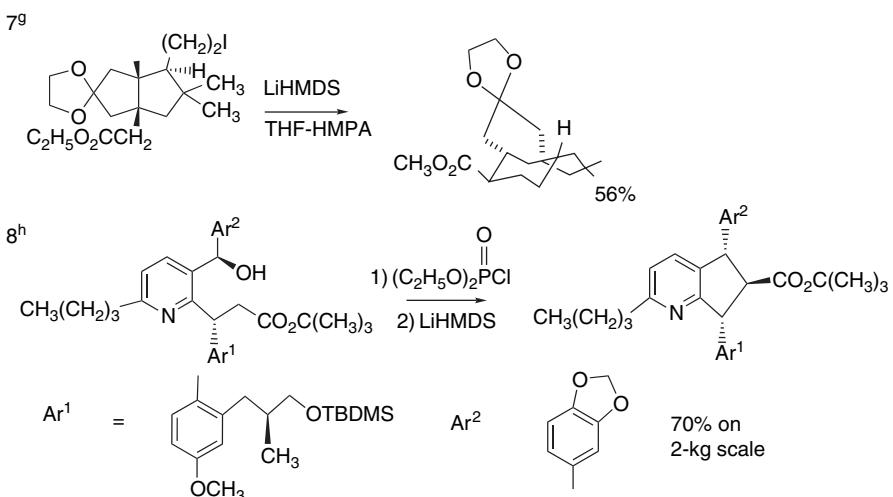


B. Esters



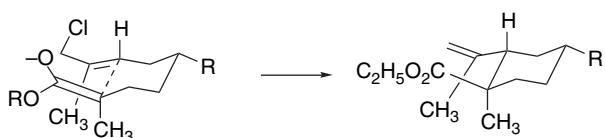
(Continued)

Scheme 1.8. (Continued)



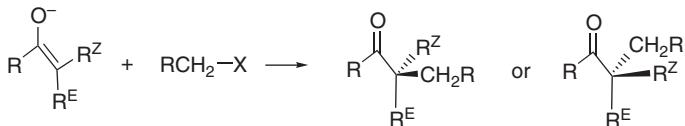
- a. A. Srikrishna, G. V. R. Sharma, S. Danielloss, and P. Hemamalini, *J. Chem. Soc., Perkin Trans. 1*, 1305 (1996).
 b. E. Piers, W. de Waal, and R. W. Britton, *J. Am. Chem. Soc.*, **93**, 5113 (1971).
 c. D. Kim, S. Kim, J.-J. Lee, and H. S. Kim, *Tetrahedron Lett.*, **31**, 4027 (1990).
 d. D. Kim, J. I. Lim, K. J. Shin, and H. S. Kim, *Tetrahedron Lett.*, **34**, 6557 (1993).
 e. J. Lee and J. Hong, *J. Org. Chem.*, **69**, 6433 (2004).
 f. F.-D. Boyer and P.-H. Ducrot, *Eur. J. Org. Chem.*, 1201 (1999).
 g. S. Danishefsky, K. Vaughan, R. C. Gadwood, and K. Tsuzuki, *J. Am. Chem. Soc.*, **102**, 4262 (1980).
 h. Z. J. Song, M. Zhao, R. Desmond, P. Devine, D. M. Tschaen, R. Tilley, L. Frey, R. Heid, F. Xu, B. Foster, J. Li, R. Reamer, R. Volante, E. J. Grabowski, U. H. Dolling, P. J. Reider, S. Okada, Y. Kato and E. Mano, *J. Org. Chem.*, **64**, 9658 (1999).

Entries 3 to 6 are examples of ester enolate alkylations. These reactions show stereoselectivity consistent with cyclic TSs in which the hydrogen is eclipsed with the enolate and the larger substituent is pseudoequatorial. Entries 4 and 5 involve S_N2' substitutions of allylic halides. The formation of the six- and five-membered rings, respectively, is the result of ring size preferences with $5 > 7$ and $6 > 8$. In Entry 4, reaction occurs through a chairlike TS with the tertiary C(5) substituent controlling the conformation. The cyclic TS results in a *trans* relationship between the ester and vinylic substituents.

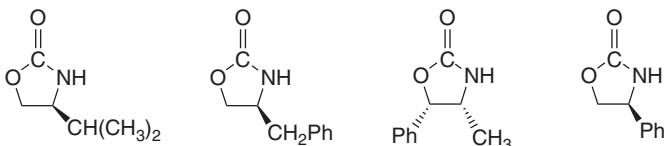


Entry 6 results in the formation of a four-membered ring and shows good stereo-selectivity. Entry 7 is a step in the synthesis of a tetracyclic lactone, quadrone, that is isolated from a microorganism. Entry 8 is a step in a multikilo synthesis of an endothelin receptor antagonist called cyclopentapyridine I. The phosphate group was chosen as a leaving group because sulfonates were too reactive at the diaryl carbinol site. The reaction was shown to go with inversion of configuration.

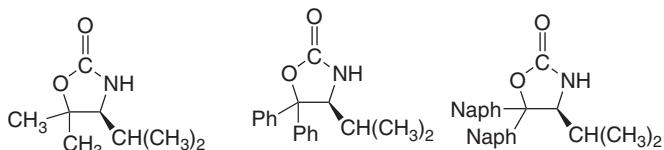
The alkylation of an enolate creates a new stereogenic center when the α -substituents are nonidentical. In enantioselective synthesis, it is necessary to control the direction of approach and thus the configuration of the new stereocenter.



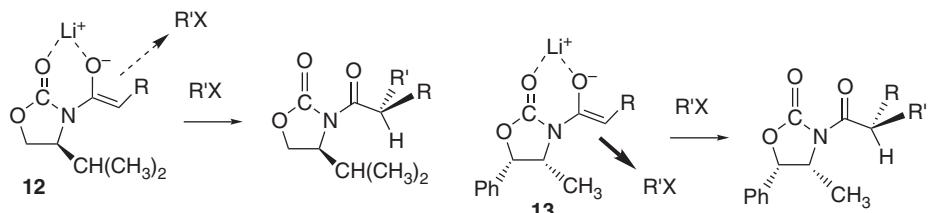
Enantioselective enolate alkylation can be done using chiral auxiliaries. (See Section 2.6 of Part A to review the role of chiral auxiliaries in control of reaction stereochemistry.) The most frequently used are the *N*-acyloxazolidinones.⁸⁹ The 4-isopropyl and 4-benzyl derivatives, which can be obtained from valine and phenylalanine, respectively, and the *cis*-4-methyl-5-phenyl derivatives are readily available. Another useful auxiliary is the 4-phenyl derivative.⁹⁰



Several other oxazolidinones have been developed for use as chiral auxiliaries. The 4-isopropyl-5,5-dimethyl derivative gives excellent enantioselectivity.⁹¹ 5,5-Diaryl derivatives are also quite promising.⁹²



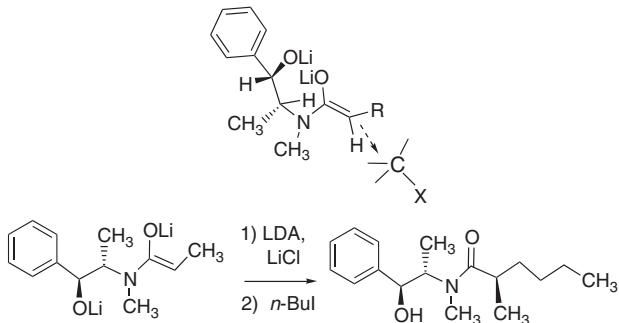
The reactants are usually *N*-acyl derivatives. The lithium enolates form chelate structures with *Z*-stereochemistry at the double bond. The ring substituents then govern the preferred direction of approach.



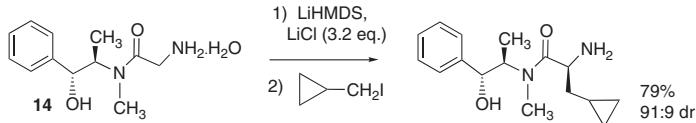
- ^{89.} D. A. Evans, M. D. Ennis, and D. J. Mathre, *J. Am. Chem. Soc.*, **104**, 1737 (1982); D. J. Ager, I. Prakash, and D. R. Schaad, *Chem. Rev.*, **96**, 835 (1996); D. J. Ager, I. Prakash, and D. R. Schaad, *Aldrichimica Acta*, **30**, 3 (1997).
- ^{90.} E. Nicolas, K. C. Russell, and V. J. Hruby, *J. Org. Chem.*, **58**, 766 (1993).
- ^{91.} S. D. Bull, S. G. Davies, S. Jones, and H. J. Sangane, *J. Chem. Soc., Perkin Trans. 1*, 387 (1999); S. G. Davies and H. J. Sangane, *Tetrahedron: Asymmetry*, **6**, 671 (1995); S. D. Bull, S. G. Davies, R. L. Nicholson, H. J. Sangane, and A. D. Smith, *Org. Biomol. Chem.*, **1**, 2886 (2003).
- ^{92.} T. Hintermann and D. Seebach, *Helv. Chim. Acta*, **81**, 2093 (1998); C. L. Gibson, K. Gillon, and S. Cook, *Tetrahedron Lett.*, **39**, 6733 (1998).

In **12** the upper face is shielded by the isopropyl group, whereas in **13** the lower face is shielded by the methyl and phenyl groups. As a result, alkylation of the two derivatives gives products of the opposite configuration. The initial alkylation product ratios are typically 95:5 in favor of the major isomer. Since these products are diastereomeric mixtures, they can be separated and purified. Subsequent hydrolysis or alcoholysis provides acids or esters in enantiomerically enriched form. Alternatively, the acyl imides can be reduced to alcohols or aldehydes. The final products can often be obtained in greater than 99% enantiomeric purity.

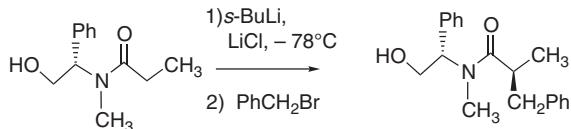
A number of other types of chiral auxiliaries have been employed in enolate alkylation. Excellent results are obtained using amides of pseudoephedrine. Alkylation occurs *anti* to the α -oxybenzyl group.⁹³ The reactions involve the *Z*-enolate and there is likely bridging between the two lithium cations, perhaps by di-(isopropyl)amine.⁹⁴



Both enantiomers of the auxiliary are available, so either enantiomeric product can be obtained. This methodology has been applied to a number of enantioselective syntheses.⁹⁵ For example, the glycine derivative **14** can be used to prepare α -amino acid analogs.⁹⁶



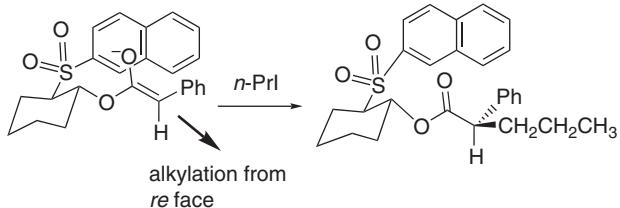
Enolates of phenylglycinol amides also exhibit good diastereoselectivity.⁹⁷ A chelating interaction with the deprotonated hydroxy group is probably involved here as well.



The *trans*-2-naphthyl cyclohexyl sulfone **15** can be prepared readily in either enantiomeric form. The corresponding ester enolates can be alkylated in good yield and diastereoselectivity.⁹⁸ In this case, the steric shielding is provided by the naphthyl

- ^{93.} A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, and J. L. Gleason, *J. Am. Chem. Soc.*, **119**, 6496 (1997); A. G. Myers, M. Siu, and F. Ren, *J. Am. Chem. Soc.*, **124**, 4230 (2002).
- ^{94.} J. L. Vicario, D. Badia, E. Dominguez, and L. Carrillo, *J. Org. Chem.*, **64**, 4610 (1999).
- ^{95.} S. Karlsson and E. Hedenstrom, *Acta Chem. Scand.*, **53**, 620 (1999).
- ^{96.} A. G. Myers, P. S. Schnider, S. Kwon, and D. W. Kung, *J. Org. Chem.*, **64**, 3322 (1999).
- ^{97.} V. Jullian, J.-C. Quirion, and H.-P. Husson, *Synthesis*, 1091 (1997).
- ^{98.} G. Sarakinos and E. J. Corey, *Org. Lett.*, **1**, 1741 (1999).

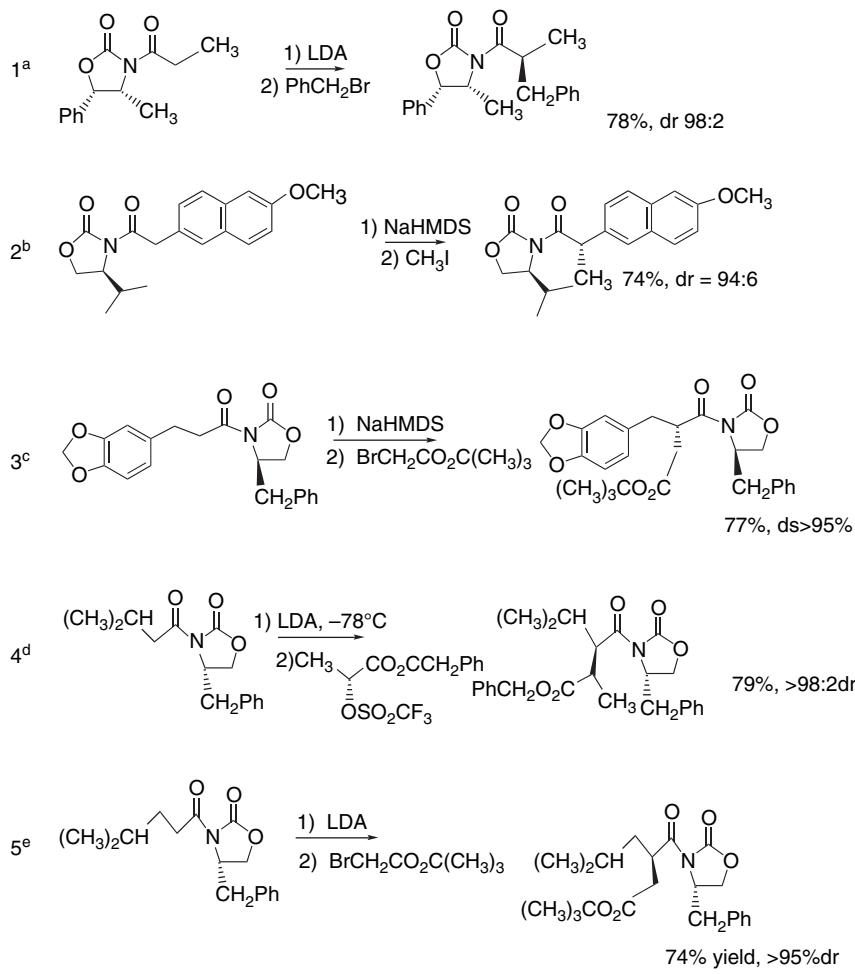
group and there is probably also a $\pi - \pi$ interaction between the naphthalene ring and the enolate.



As with the acyl oxazolidinone auxiliaries, each of these systems permits hydrolytic removal and recovery of the chiral auxiliary.

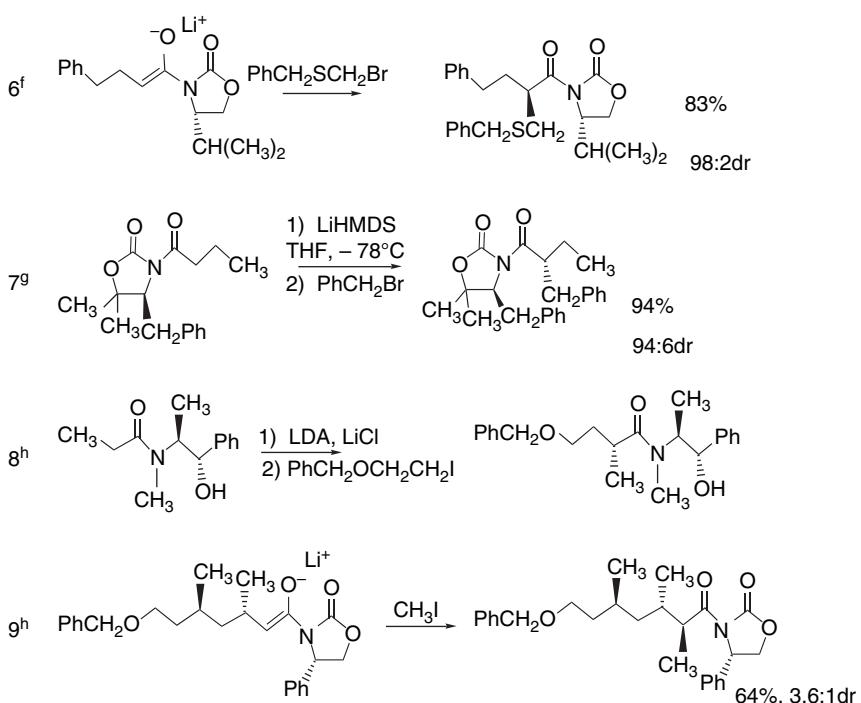
Scheme 1.9 gives some examples of diastereoselective enolate alkylations. Entries 1 to 6 show the use of various *N*-acyloxazolidinones and demonstrate the

Scheme 1.9. Diastereoselective Enolate Alkylation Using Chiral Auxiliaries



(Continued)

CHAPTER 1

Alkylation of Enolates
and Other Carbon
Nucleophiles

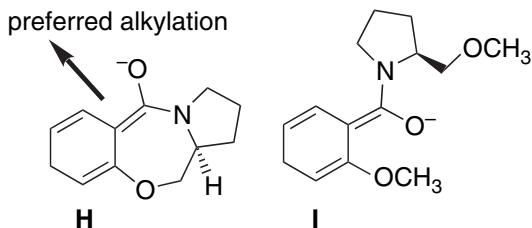
- a. D. A. Evans, M. D. Ennis, and D. J. Mathre, *J. Am. Chem. Soc.*, **104**, 1737 (1982).
- b. A. Fadel, *Synlett*, 48 (1992).
- c. J. L. Charlton and G-L. Chee, *Can. J. Chem.*, **75**, 1076 (1997).
- d. C. P. Decicco, D. J. Nelson, B. L. Corbett, and J. C. Dreabit, *J. Org. Chem.*, **60**, 4782 (1995).
- e. R. P. Beckett, M. J. Crimmin, M. H. Davis, and Z. Spavold, *Synlett*, 137 (1993).
- f. D. A. Evans, D. J. Mathre, and W. L. Scott, *J. Org. Chem.*, **50**, 1830 (1985).
- g. S. D. Bull, S. G. Davies, R. L. Nicholson, H. J. Sangane, and A. D. Smith, *Organic and Biomol. Chem.*, **1**, 2886 (2003).
- h. J. D. White, C.-S. Lee and Q. Xu, *Chem. Commun.* 2012 (2003).

stereochemical control by the auxiliary ring substituent. Entry 2 demonstrated the feasibility of enantioselective synthesis of α -aryl acetic acids such as the structure found in naproxen. Entries 3 to 6 include ester groups in the alkylating agent. In the case of Entry 4, it was shown that inversion occurs in the alkylating reagent. Entry 7 is an example of the use of one of the more highly substituted oxazolidinone derivatives. Entries 8 and 9 are from the synthesis of a neurotoxin isolated from a saltwater bacterium. The pseudoephedrine auxiliary shown in Entry 8 was used early in the synthesis and the 4-phenyloxazolidinone auxiliary was used later, as shown in Entry 9.

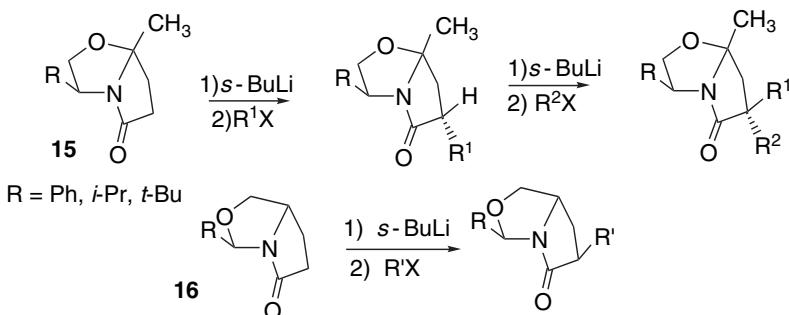
The facial selectivity of a number of more specialized enolates has also been explored, sometimes with surprising results. Schultz and co-workers compared the cyclic enolate **H** with **I**.⁹⁹ Enolate **H** presents a fairly straightforward picture. Groups such as methyl, allyl, and benzyl all give selective β -alkylation, and this is attributed to steric factors. Enolate **I** can give either α - or β -alkylation, depending on the conditions. The presence of NH_3 or use of LDA favors α -alkylation, whereas the use

⁹⁹. A. G. Schultz, M. Macielag, P. Sudararaman, A. G. Taveras, and M. Welch, *J. Am. Chem. Soc.*, **110**, 7828 (1988).

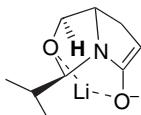
of *n*-butyllithium as the base favors β -alkylation. Other changes in conditions also affect the stereoselectivity. This is believed to be due to alternative aggregated forms of the enolate.



The compact bicyclic lactams **15** and **16** are examples of chiral systems that show high facial selectivity. Interestingly, **15** is alkylated from the convex face. When two successive alkylations are done, both groups are added from the *endo* face, so the configuration of the newly formed quaternary center can be controlled. The closely related **16** shows *exo* stereoselectivity.¹⁰⁰



Crystal structure determination and computational studies indicate substantial pyramidalization of both enolates with the higher HOMO density being on the *endo* face for both **15** and **16**. However, the TS energy [MP3/6-31G+(*d*)] correlates with experiment, favoring the *endo* TS for **15** (by 1.3 kcal/mol) and *exo* for **16** (by 0.9 kcal/mol). A B3LYP/6-31G(*d*) computational study has also addressed the stereoselectivity of **16**.¹⁰¹ As with the ab initio calculation, the Li⁺ is found in the *endo* position with an association with the heterocyclic oxygen. The *exo* TS is favored but the energy difference is very sensitive to the solvent model. The differences between the two systems seems to be due to the *endo* C(4) hydrogen that is present in **16** but not in **15**.

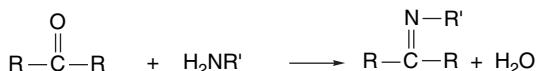


¹⁰⁰. A. I. Meyers, M. A. Seefeld, B. A. Lefker, J. F. Blake, and P. G. Williard, *J. Am. Chem. Soc.*, **120**, 7429 (1998).

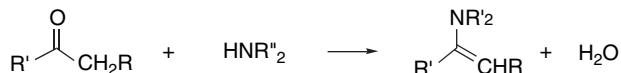
¹⁰¹. Y. Ikuta and S. Tomoda, *Org. Lett.*, **6**, 189 (2004).

1.3. The Nitrogen Analogs of Enols and Enolates: Enamines and Imine Anions

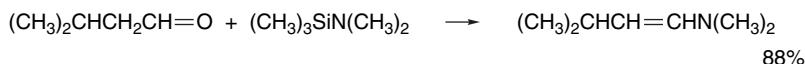
The nitrogen analogs of ketones and aldehydes are called imines, azomethines, or Schiff bases, but *imine* is the preferred name and we use it here. These compounds can be prepared by condensation of primary amines with ketones or aldehydes.¹⁰² The equilibrium constants are unfavorable, so the reaction is usually driven forward by removal of water.



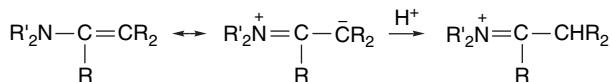
When secondary amines are heated with ketones or aldehydes in the presence of an acidic catalyst, a related reaction occurs, and the product is a substituted vinylamine or *enamine*.



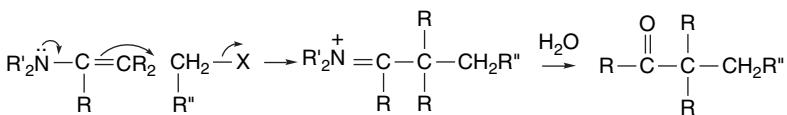
There are other methods for preparing enamines from ketones that utilize strong chemical dehydrating reagents. For example, mixing carbonyl compounds and secondary amines followed by addition of titanium tetrachloride rapidly gives enamines. This method is especially applicable to hindered amines.¹⁰³ Triethoxysilane can also be used.¹⁰⁴ Another procedure involves converting the secondary amine to its *N*-trimethylsilyl derivative. Owing to the higher affinity of silicon for oxygen than nitrogen, enamine formation is favored and takes place under mild conditions.¹⁰⁵



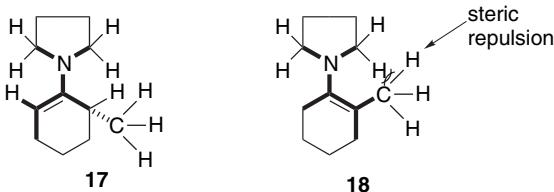
The β -carbon atom of an enamine is a nucleophilic site because of conjugation with the nitrogen atom. Protonation of enamines takes place at the β -carbon, giving an iminium ion.



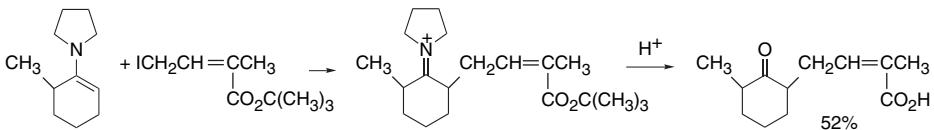
- ¹⁰². For general reviews of imines and enamines, see P. Y. Sollenberger and R. B. Martin, in *Chemistry of the Amino Group*, S. Patai, ed., Interscience, New York, 1968, Chap. 7; G. Pitacco and E. Valentin, in *Chemistry of Amino, Nitroso and Nitro Groups and Their Derivatives*, Part 1, S. Patai, ed., Interscience, New York, 1982, Chap. 15; P. W. Hickmott, *Tetrahedron*, **38**, 3363 (1982); A. G. Cook, ed., *Enamines, Synthesis, Structure and Reactions*, Marcel Dekker, New York, 1988.
- ¹⁰³. W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967); R. Carlson, R. Phan-Tan-Luu, D. Mathieu, F. S. Ahounde, A. Babadjamian, and J. Metzger, *Acta Chem. Scand.*, **B32**, 335 (1978); R. Carlson, A. Nilsson, and M. Stromqvist, *Acta Chem. Scand.*, **B37**, 7 (1983); R. Carlson and A. Nilsson, *Acta Chem. Scand.*, **B38**, 49 (1984); S. Schubert, P. Renaud, P.-A. Carrupt, and K. Schenk, *Helv. Chim. Acta*, **76**, 2473 (1993).
- ¹⁰⁴. B. E. Love and J. Ren, *J. Org. Chem.*, **58**, 5556 (1993).
- ¹⁰⁵. R. Comi, R. W. Franck, M. Reitano, and S. M. Weinreb, *Tetrahedron Lett.*, 3107 (1973).



The enamines derived from cyclohexanones are of particular interest. The pyrrolidine enamine is most frequently used for synthetic applications. The enamine mixture formed from pyrrolidine and 2-methylcyclohexanone is predominantly isomer **17**.¹⁰⁶ A steric effect is responsible for this preference. Conjugation between the nitrogen atom and the π orbitals of the double bond favors coplanarity of the bonds that are darkened in the structures. In isomer **17** the methyl group adopts a quasi-axial conformation to avoid steric interaction with the amine substituents.¹⁰⁷ A serious nonbonded repulsion ($A^{1,3}$ strain) in **18** destabilizes this isomer.



Owing to the predominance of the less-substituted enamine, alkylations occur primarily at the less-substituted α -carbon. Synthetic advantage can be taken of this selectivity to prepare 2,6-disubstituted cyclohexanones. The iminium ions resulting from C-alkylation are hydrolyzed in the workup procedure.



Ref. 108

Alkylation of enamines requires relatively reactive alkylating agents for good results. Methyl iodide, allyl and benzyl halides, α -halo esters, α -halo ethers, and α -halo ketones are the most successful alkylating agents. The use of enamines for selective alkylation has largely been supplanted by the methods for kinetic enolate formation described in Section 1.2.

Some enamine alkylation reactions are shown in Scheme 1.10. Entries 1 and 2 are typical alkylations using reactive halides. In Entries 3 and 4, the halides are secondary with α -carbonyl substituents. Entry 5 involves an unactivated primary bromide and the yield is modest. The reaction in Entry 6 involves introduction of two groups. This

¹⁰⁶ W. D. Gurowitz and M. A. Joseph, *J. Org. Chem.*, **32**, 3289 (1967).

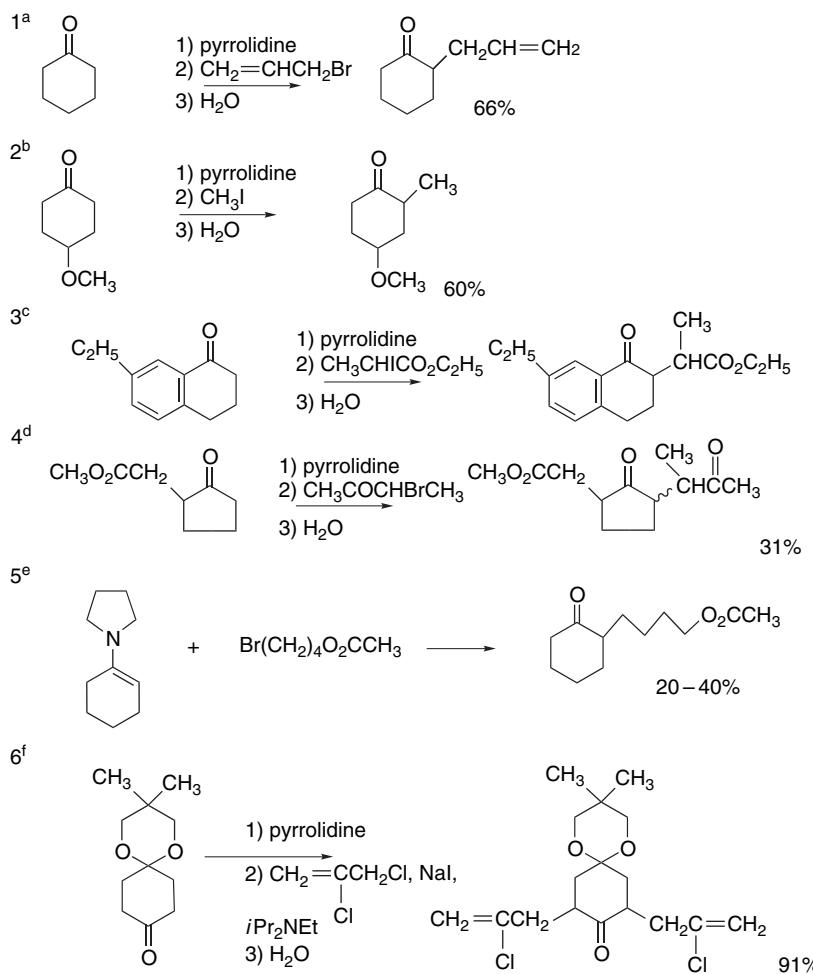
¹⁰⁷ F. Johnson, L. G. Duquette, A. Whitehead, and L. C. Dorman, *Tetrahedron*, **30**, 3241 (1974); K. Muller, F. Previdoli, and H. Desilvestro, *Helv. Chim. Acta*, **64**, 2497 (1981); J. E. Anderson, D. Casarini, and L. Lunazzi, *Tetrahedron Lett.*, **25**, 3141 (1988).

¹⁰⁸ P. L. Stotter and K. A. Hill, *J. Am. Chem. Soc.*, **96**, 6524 (1974).

Scheme 1.10. Alkylation of Enamines

CHAPTER 1

Alkylation of Enolates
and Other Carbon
Nucleophiles



a. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

b. G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 1761 (1964).

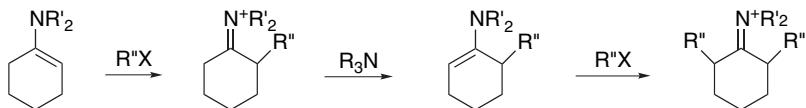
c. D. M. Locke and S. W. Pelletier, *J. Am. Chem. Soc.*, **80**, 2588 (1958).

d. K. Sisido, S. Kurozumi, and K. Utimoto, *J. Org. Chem.*, **34**, 2661 (1969).

e. I. J. Borowitz, G. J. Williams, L. Gross, and R. Rapp, *J. Org. Chem.*, **33**, 2013 (1968).

f. J. A. Marshall and D. A. Flynn, *J. Org. Chem.*, **44**, 1391 (1979).

was done by carrying out the reaction in the presence of an amine, which deprotonates the iminium ion and permits the second alkylation to occur.



Imines can be deprotonated at the α -carbon by strong bases to give the nitrogen analogs of enolates. Originally, Grignard reagents were used for deprotonation but lithium amides are now usually employed. These anions, referred to as *imine anions*

SECTION 1.3

The Nitrogen Analogs of
Enols and Enolates:
Enamines
and Imine Anions

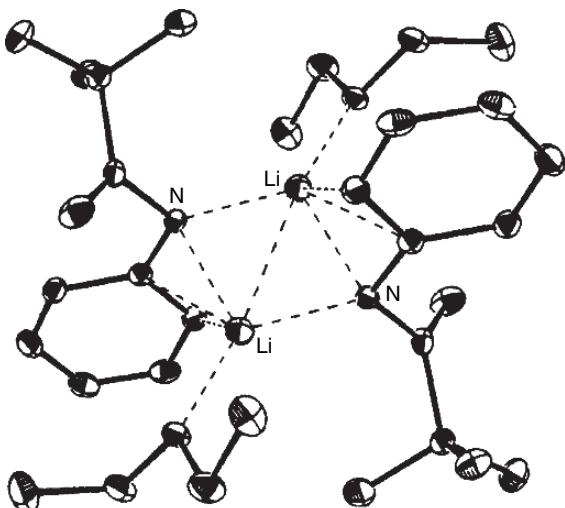
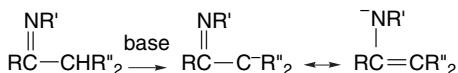


Fig. 1.6. Crystal structure of dimer of lithium salt of *N*-phenylimine of methyl *t*-butyl ketone. Two molecules of diethyl ether are present. Reproduced from *J. Am. Chem. Soc.*, **108**, 2462 (1986), by permission of the American Chemical Society.

or *metalloenamines*,¹⁰⁹ are isoelectronic and structurally analogous to both enolates and allyl anions; they can also be called *azaallyl anions*.



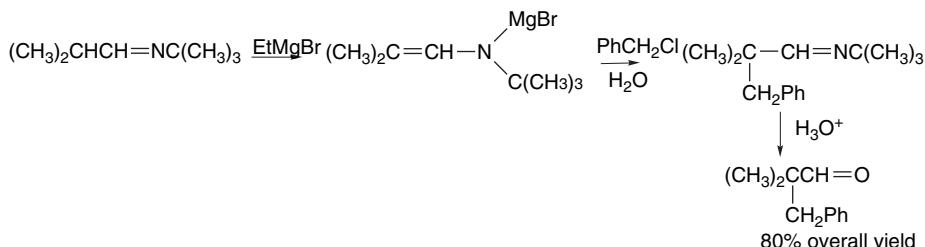
Spectroscopic investigations of the lithium derivatives of cyclohexanone *N*-phenylimine indicate that it exists as a dimer in toluene and that as a better donor solvent, THF, is added, equilibrium with a monomeric structure is established. The monomer is favored at high THF concentrations.¹¹⁰ A crystal structure determination was done on the lithiated *N*-phenylimine of methyl *t*-butyl ketone, and it was found to be a dimeric structure with the lithium cation positioned above the nitrogen and closer to the phenyl ring than to the β -carbon of the imine anion.¹¹¹ The structure, which indicates substantial ionic character, is shown in Figure 1.6.

Just as enamines are more nucleophilic than enol ethers, imine anions are more nucleophilic than enolates and react efficiently with alkyl halides. One application of imine anions is for the alkylation of aldehydes.

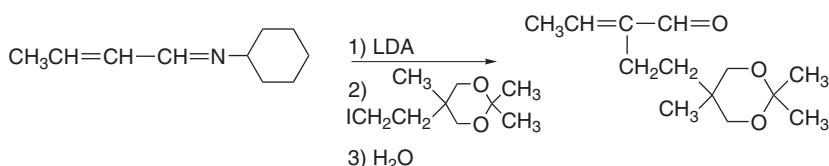
¹⁰⁹. For a general review of imine anions, see J. K. Whitesell and M. A. Whitesell, *Synthesis*, 517 (1983).

¹¹⁰. N. Kallman and D. B. Collum, *J. Am. Chem. Soc.*, **109**, 7466 (1987).

¹¹¹. H. Dietrich, W. Mahdi, and R. Knorr, *J. Am. Chem. Soc.*, **108**, 2462 (1986); P. Knorr, H. Dietrich, and W. Mahdi, *Chem. Ber.*, **124**, 2057 (1991).

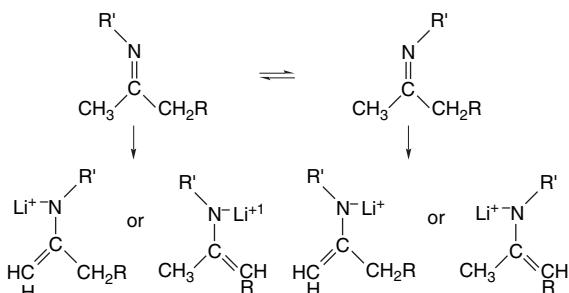


Ref. 112

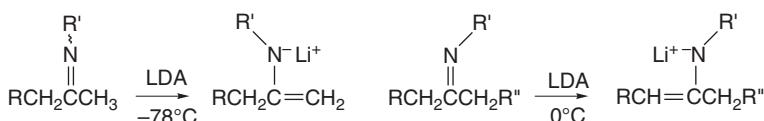


Ref. 113

Ketone imine anions can also be alkylated. The prediction of the regioselectivity of lithioenamine formation is somewhat more complex than for the case of kinetic ketone enolate formation. One of the complicating factors is that there are two imine stereoisomers, each of which can give rise to two regiosomeric imine anions. The isomers in which the nitrogen substituent R' is *syn* to the double bond are the more stable.¹¹⁴



For methyl ketimines good regiochemical control in favor of methyl deprotonation, regardless of imine stereochemistry, is observed using LDA at -78°C . With larger N-substituents, deprotonation at 25°C occurs *anti* to the nitrogen substituent.¹¹⁵

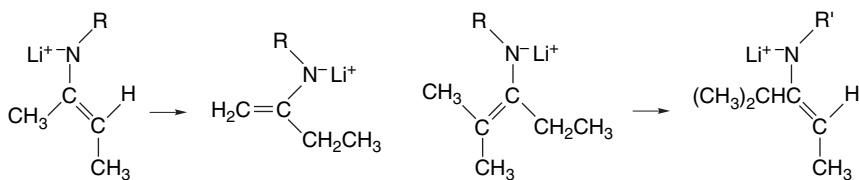


¹¹². G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).

¹¹³. T. Kometani, Y. Suzuki, H. Furuyama, and T. Honda, *J. Org. Chem.*, **48**, 31 (1983).

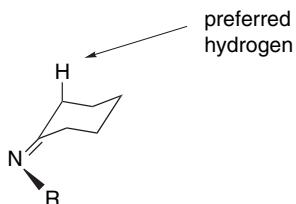
¹¹⁴. K. N. Houk, R. W. Stozier, N. G. Rondan, R. R. Frazier, and N. Chauqui-Ottermans, *J. Am. Chem. Soc.*, **102**, 1426 (1980).

¹¹⁵. J. K. Smith, M. Newcomb, D. E. Bergbreiter, D. R. Williams, and A. I. Meyer, *Tetrahedron Lett.*, **24**, 3559 (1983); J. K. Smith, D. E. Bergbreiter, and M. Newcomb, *J. Am. Chem. Soc.*, **105**, 4396 (1983); A. Hosomi, Y. Araki, and H. Sakurai, *J. Am. Chem. Soc.*, **104**, 2081 (1982).



The complete interpretation of regiochemistry and stereochemistry of imine deprotonation also requires consideration of the state of aggregation and solvation of the base.¹¹⁶

A thorough study of the factors affecting the rates of formation of lithiated imines from cyclohexanone imines has been carried out.¹¹⁷ Lithiation occurs preferentially *anti* to the *N*-substituent and with a preference for abstraction of an axial hydrogen.



If the amine carries a chelating substituent, as for 2-methoxyethylamine, the rate of deprotonation is accelerated. For any specific imine, ring substituents also influence the imine conformation and rate of deprotonation. These relationships reflect steric, stereoelectronic, and chelation influences, and sorting out each contribution can be challenging.

One of the potentially most useful aspects of the imine anions is that they can be prepared from enantiomerically pure amines. When imines derived from chiral amines are alkylated, the new carbon-carbon bond is formed with a bias for one of the two possible stereochemical configurations. Hydrolysis of the imine then leads to enantiomerically enriched ketone. Table 1.4 lists some examples that have been reported.¹¹⁸

The interpretation and prediction of the relationship between the configuration of the newly formed chiral center and the configuration of the amine is usually based on steric differentiation of the two faces of the imine anion. Most imine anions that show high stereoselectivity incorporate a substituent that can engage the metal cation in a

¹¹⁶. M. P. Bernstein and D. B. Collum, *J. Am. Chem. Soc.*, **115**, 8008 (1993).

¹¹⁷. S. Liao and D. B. Collum, *J. Am. Chem. Soc.*, **125**, 15114 (2003).

¹¹⁸. For a review, see D. E. Bergbreiter and M. Newcomb, in *Asymmetric Synthesis*, Vol. 2, J. D. Morrison, ed., Academic Press, New York, 1983, Chap. 9.

Table 1.4. Enantioselective Alkylation of Ketimines

CHAPTER 1

Alkylation of Enolates and Other Carbon Nucleophiles

	Amine	Ketone	Alkyl group	Yield%	e.e.
1 ^a	(CH ₃) ₃ C (CH ₃) ₃ CO ₂ C NH ₂	Cyclohexanone	CH ₂ =CHCH ₂ Br	75	84
2 ^b	PhCH ₂ H CH ₂ OCH ₃ H ₂ N	Cyclohexanone	CH ₂ =CHCH ₂ Br	80	>99
3 ^c	(CH ₃) ₃ CH (CH ₃) ₃ CO ₂ C NH ₂	2-Carbomethoxy- cyclohexanone	CH ₃ I	57	>99
4 ^d		3-pentanone	CH ₃ CH ₂ CH ₂ I	57	97
5 ^e	PhCH ₂ H CH ₂ OCH ₃ H ₂ N	5-Nonanone	CH ₂ =CHCH ₂ Br	80	94

a. S. Hashimoto and K. Koga, *Tetrahedron Lett.*, 573 (1978).

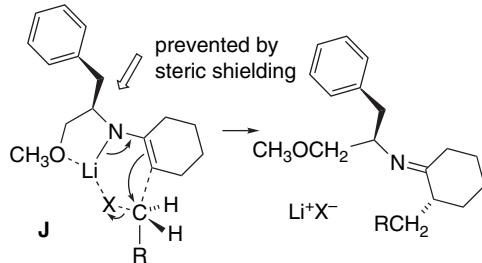
b. A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, and M. Druelinger, *J. Am. Chem. Soc.*, **103**, 3081 (1981).

c. K. Tomioka, K. Ando, Y. Takemasa, and K. Koga, *J. Am. Chem. Soc.*, **106**, 1718 (1984).

d. D. Enders, H. Kipphardt, and P. Fey, *Org. Synth.*, **65**, 183 (1987).

e. A. I. Meyers, D. R. Williams, S. White, and G. W. Erickson, *J. Am. Chem. Soc.*, **103**, 3088 (1981).

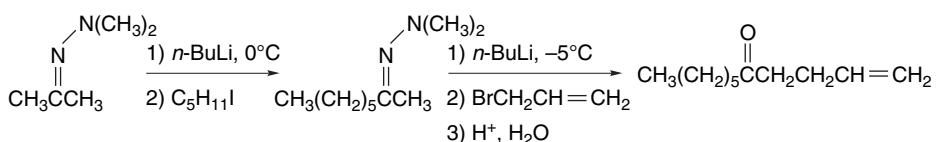
compact TS by chelation. In the case of Entry 2 in Table 1.4, for example, the TS **J** rationalizes the observed enantioselectivity.



The important features of this transition structure are: (1) the chelation of the methoxy group with the lithium ion, which establishes a rigid structure; (2) the interaction of the lithium ion with the bromide leaving group, and (3) the steric effect of the benzyl group, which makes the underside the preferred direction of approach for the alkylating agent.

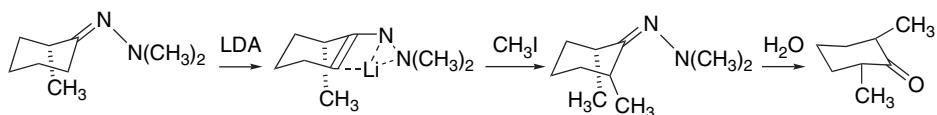
Hydrazones can also be deprotonated to give lithium salts that are reactive toward alkylation at the β -carbon. Hydrazones are more stable than alkylimines and therefore have some advantages in synthesis.¹¹⁹ The *N,N*-dimethylhydrazones of methyl ketones are kinetically deprotonated at the methyl group. This regioselectivity is independent

¹¹⁹. D. Enders, in *Asymmetric Synthesis*, J. D. Morrison, ed., Academic Press, Orlando, FL, 1984.

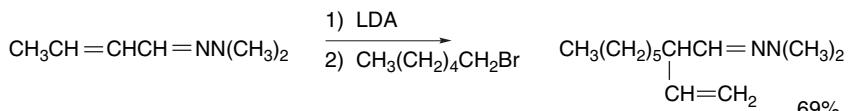


Ref. 121

The anion of cyclohexanone *N,N*-dimethylhydrazone shows a strong preference for axial alkylation.¹²² 2-Methylcyclohexanone *N,N*-dimethylhydrazone is alkylated by methyl iodide to give *cis*-2,6-dimethylcyclohexanone. The 2-methyl group in the hydrazone occupies a pseudoaxial orientation. Alkylation apparently occurs *anti* to the lithium cation, which is on the face opposite the 2-methyl substituent.



The *N,N*-dimethylhydrazones of α,β -unsaturated aldehydes give α -alkylation, similarly to the enolates of enones.¹²³



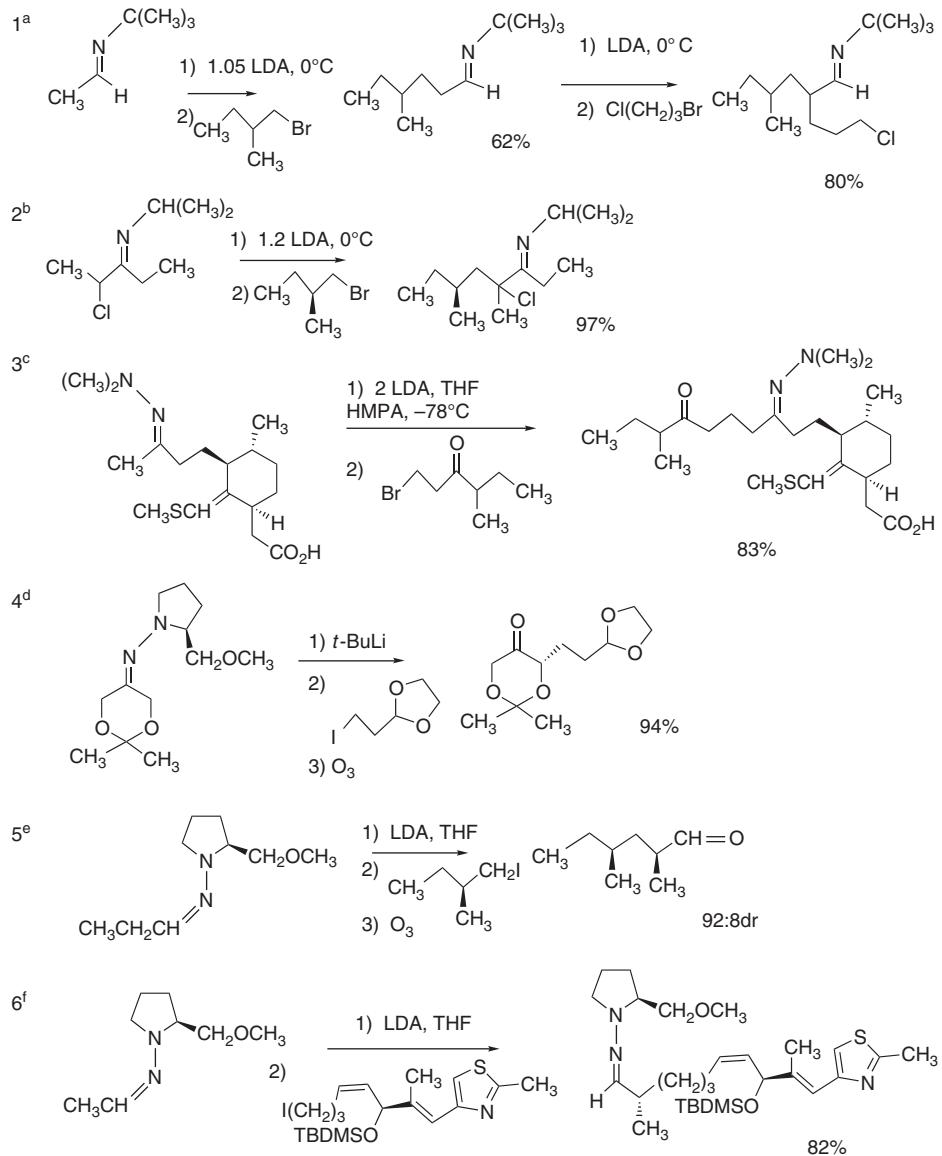
Chiral hydrazones have also been developed for enantioselective alkylation of ketones. The hydrazones are converted to the lithium salt, alkylated, and then hydrolyzed to give alkylated ketone in good chemical yield and with high diastereoselective¹²⁴ (see Table 1.4, Entry 4). Several procedures have been developed for conversion of the hydrazones back to ketones.¹²⁵ Mild conditions are necessary to maintain the configuration at the enolizable position adjacent to the carbonyl group. The most frequently used hydrazones are those derived from *N*-amino-2-methoxymethylpyrrolidine, known as SAMP. The (*R*)-enantiomer is called RAMP. The crystal structure of the lithium anion of the SAMP hydrazone from 2-acetylnaphthalene has been determined¹²⁶ (Figure 1.7). The lithium cation is chelated by the exocyclic nitrogen and the methoxy group.

- ^{120.} D. E. Bergbreiter and M. Newcomb, *Tetrahedron Lett.*, 4145 (1979); M. E. Jung, T. J. Shaw, R. R. Fraser, J. Banville, and K. Taymaz, *Tetrahedron Lett.*, 4149 (1979).
- ^{121.} M. Yamashita, K. Matsumiya, M. Tanabe, and R. Suetmitsu, *Bull. Chem. Soc. Jpn.*, **58**, 407 (1985).
- ^{122.} D. B. Collum, D. Kahne, S. A. Gut, R. T. DePue, F. Mohamadi, R. A. Wanat, J. Clardy, and G. Van Duyne, *J. Am. Chem. Soc.*, **106**, 4865 (1984); R. A. Wanat and D. B. Collum, *J. Am. Chem. Soc.*, **107**, 2078 (1985).
- ^{123.} M. Yamashita, K. Matsumiya, and K. Nakano, *Bull. Chem. Soc. Jpn.*, **60**, 1759 (1993).
- ^{124.} D. Enders, H. Eichenauer, U. Baus, H. Schubert, and K. A. M. Kremer, *Tetrahedron*, **40**, 1345 (1984); D. Enders, H. Kipphardt, and P. Fey, *Org. Synth.*, **65**, 183 (1987); D. Enders and M. Klatt, *Synthesis*, 1403 (1996).
- ^{125.} D. Enders, L. Wortmann, and R. Peters, *Acc. Chem. Res.*, **33**, 157 (2000).
- ^{126.} D. Enders, G. Bachstadtler, K. A. M. Kremer, M. Marsch, K. Hans, and G. Boche, *Angew. Chem. Int. Ed. Engl.*, **27**, 1522 (1988).

Scheme 1.11. Alkylation of Imine and Hydrazone Anions

CHAPTER 1

Alkylation of Enolates
and Other Carbon
Nucleophiles



- a. C. Stevens and N. De Kimpe, *J. Org. Chem.*, **58**, 132 (1993).
- b. N. De Kimpe and W. Aelterman, *Tetrahedron*, **52**, 12815 (1996).
- c. M. A. Avery, S. Mehrotra, J. D. Bonk, J. A. Vroman, D. K. Goins, and R. Miller, *J. Med. Chem.*, **39**, 2900 (1996).
- d. M. Majewski and P. Nowak, *Tetrahedron Asymmetry*, **9**, 2611 (1998).
- e. K. C. Nicolaou, E. W. Yue, S. LaGreca, A. Nadin, Z. Yang, J. E. Leresche, T. Tsuri, Y. Naniwa, and F. De Riccardis, *Chem. Eur. J.*, **1**, 467 (1995).
- f. K. C. Nicolaou, F. Sarabia, S. Ninkovic, M. Ray, V. Finlay, and C. N. C. Body, *Angew. Chem. Int. Ed. Engl.*, **37**, 81 (1998).

Scheme 1.11 provides some examples of alkylation of imine and hydrazone anions. Entries 1 and 2 involve alkylation of anions derived from *N*-alkylimines. In Entry 1, two successive alkyl groups are added. In Entry 2, complete regioselectivity

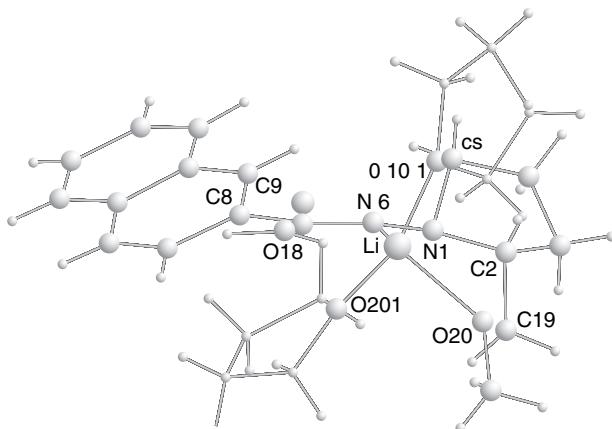


Fig. 1.7. Crystal structure of lithium salt of SAMP hydrazone of 2-acetylnaphthalene. Two molecules of THF are present. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **27**, 1522 (1988), by permission of Wiley-VCH.

for the chloro-substituted group is observed. This reaction was used in the synthesis of an ant alarm pheromone called (*S*)-manicone. Entry 3 is an alkylation of a methyl group in an *N,N*-dimethylhydrazone. This reaction was used to synthesize analogs of the antimalarial substance arteminsinin. Entries 4 to 6 take advantage of the SAMP group to achieve enantioselective alkylations in the synthesis of natural products. Note that in Entries 4 and 5 the hydrazone was cleaved by ozonolysis. The reaction in Entry 6 was done in the course of synthesis of epothilone analogs. (See Section 13.2.5. for several epothilone syntheses.) In this case, the hydrazone was first converted to a nitrile by reaction with magnesium monoperoxyphthalate and then reduced to the aldehyde using DiBALH.¹²⁷

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- D. Caine, in *Carbon-Carbon Bond Formation*, Vol. 1, R. L. Augustine, ed., Marcel Dekker, New York, 1979, Chap. 2.
- A. G. Cook, ed., *Enamines: Synthesis, Structure and Reactions*, 2d Edition, Marcel Dekker, New York, 1988
- C. H. Heathcock, *Modern Synthetic Methods*, **6**, 1 (1992).
- V. Snieckus, ed., *Advances in Carbanion Chemistry*, Vol. 1, JAI Press, Greenwich, CT, 1992.
- J. C. Stowell, *Carbanions in Organic Synthesis*, Wiley-Interscience, New York, 1979.

¹²⁷ D. Enders, D. Backhaus, and J. Runsink, *Tetrahedron*, **52**, 1503 (1996).

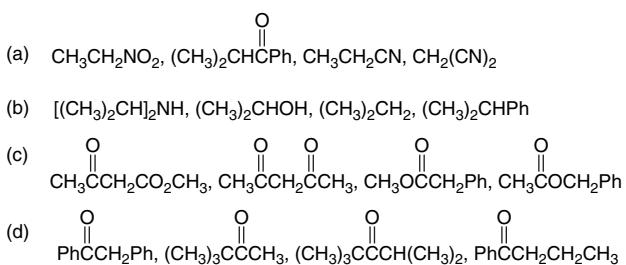
Problems

CHAPTER 1

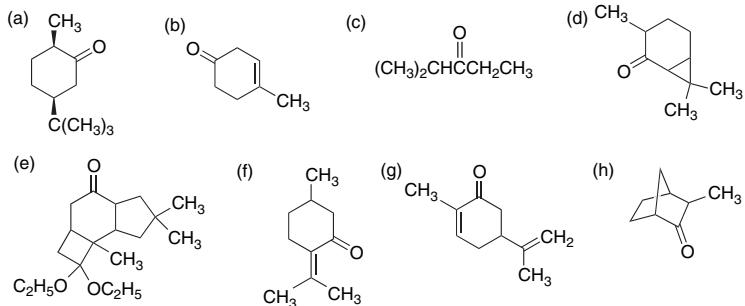
Alkylation of Enolates
and Other Carbon
Nucleophiles

(References for these problems will be found on page 1271.)

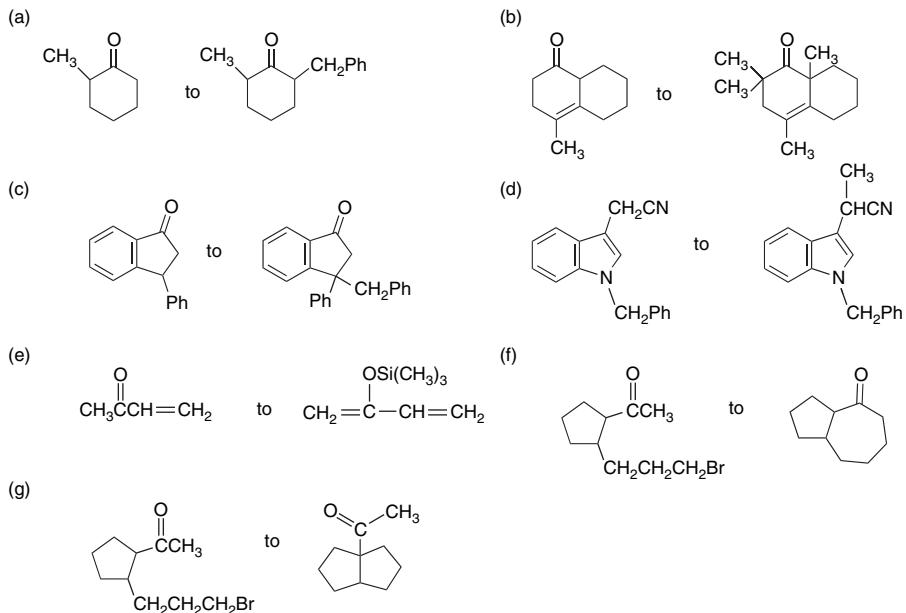
- 1.1. Arrange each series of compounds in order of decreasing acidity.



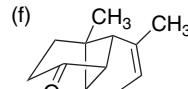
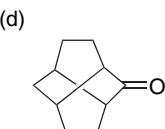
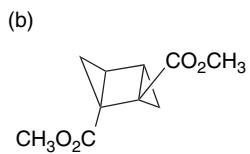
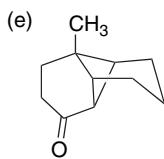
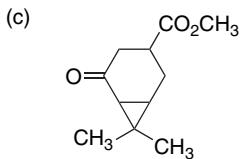
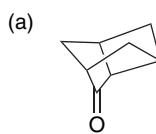
- 1.2. Write the structures of all possible enolates for each ketone. Indicate which you expect to be favored in a kinetically controlled deprotonation. Indicate which you would expect to be the most stable enolate.



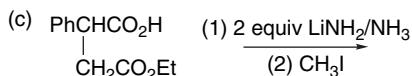
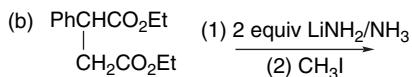
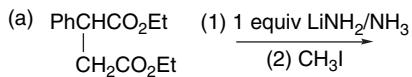
- 1.3. Suggest reagents and reaction conditions that would be suitable for effecting each of the following conversions.



1.4. Intramolecular alkylation of enolates can be used to synthesize bi- and tricyclic compounds. Identify all the bonds in the following compounds that could be formed by intramolecular enolate alkylation. Select the one that you think is most likely to succeed and suggest reasonable reactants and reaction conditions for cyclization.

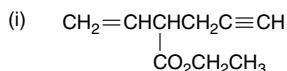
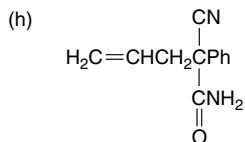
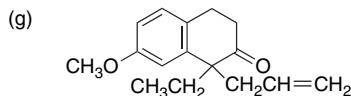
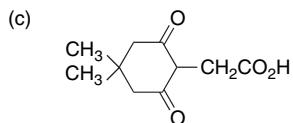
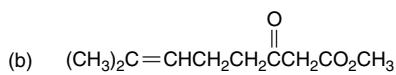
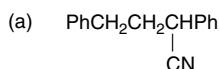


1.5. Predict the major product of each of the following reactions:

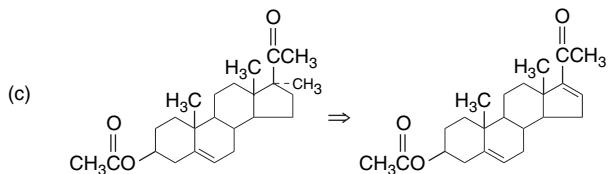
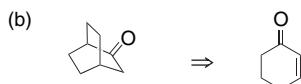
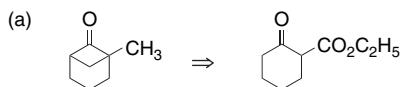


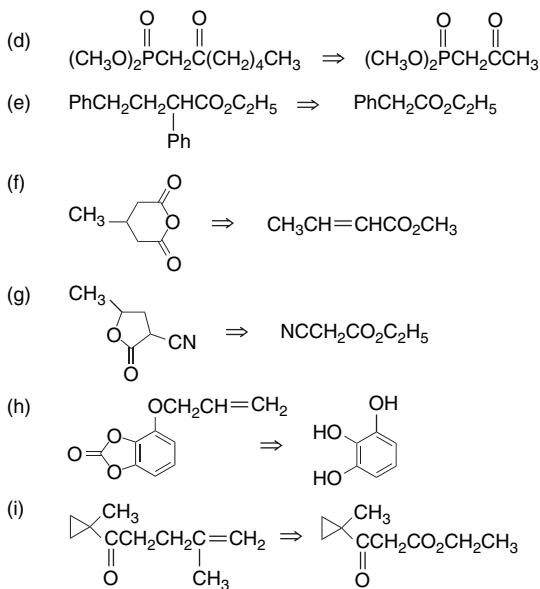
1.6. Treatment of 2,3,3-triphenylpropanonitrile with one equivalent of KNH_2 in liquid ammonia, followed by addition of benzyl chloride, gives 2-benzyl-2,3,3-triphenylpropanonitrile in 97% yield. Use of two equivalents of KNH_2 gives an 80% yield of 2,3,3,4-tetraphenylbutanonitrile under the same reaction conditions. Explain.

1.7. Suggest readily available starting materials and reaction conditions suitable for obtaining each of the following compounds by a procedure involving alkylation of a carbon nucleophile.

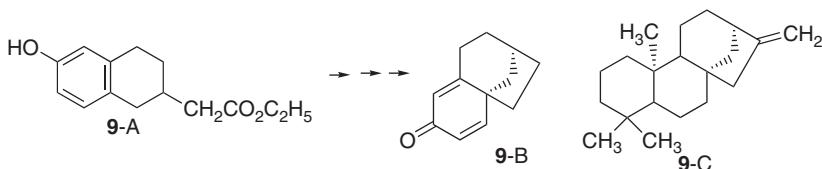


1.8. Perform a retrosynthetic dissection of each of the following compounds to the suggested starting material using reactions that involve alkylation of an enolate or an enolate equivalent. Then suggest a sequence of reactions that you think would succeed in converting the suggested starting material to the desired product.

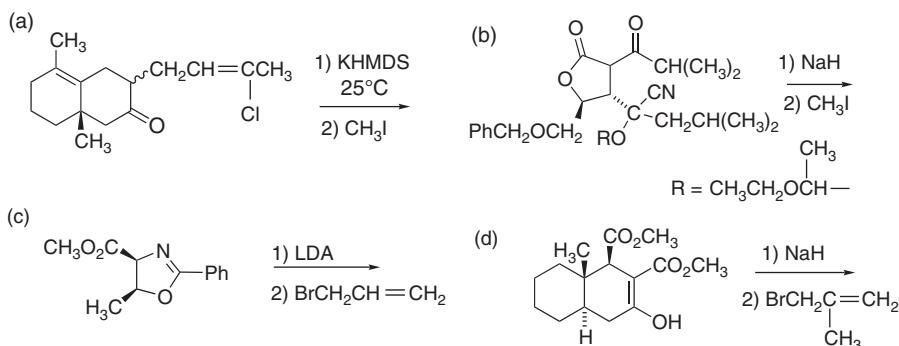


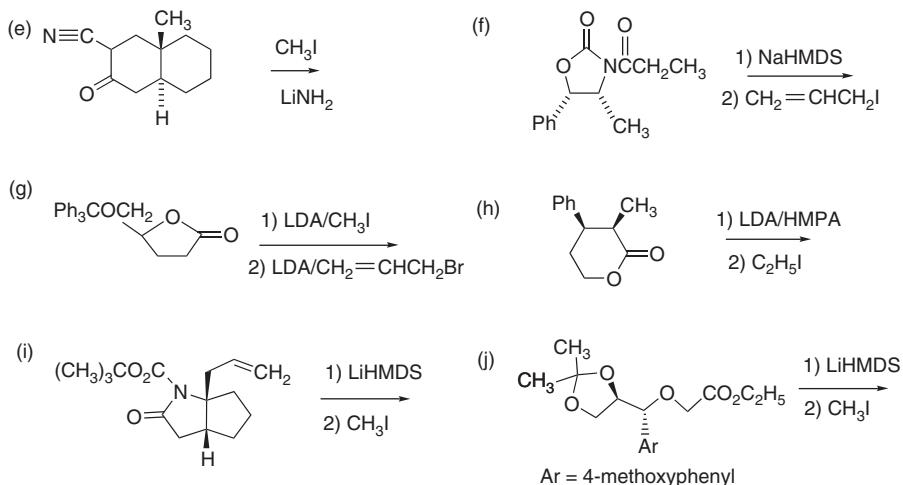


1.9. The carbon skeleton in structure **9-B** is found in certain natural substances, such as **9-C**. Outline a strategy to synthesize **9-B** from **9-A**.

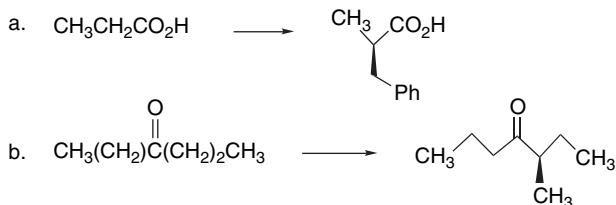


1.10. Analyze the factors that you expect to control the stereochemistry of the following reactions:

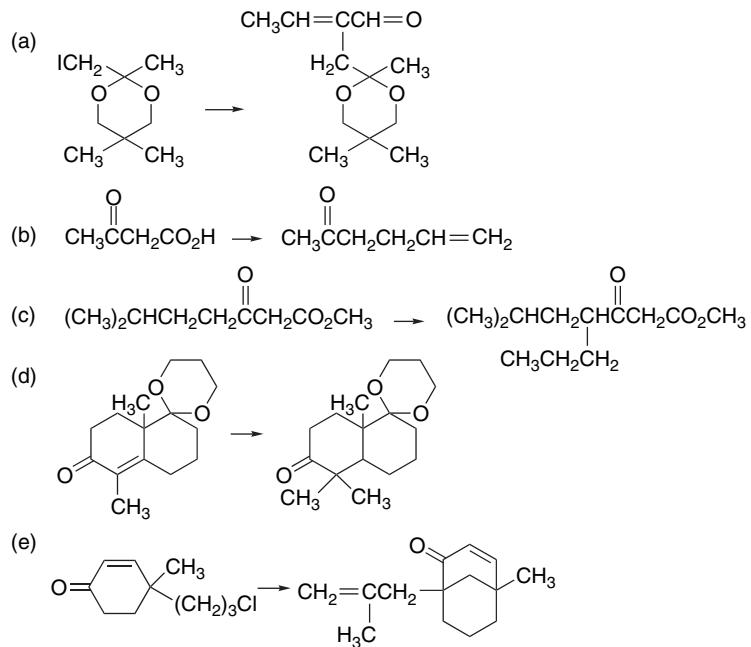




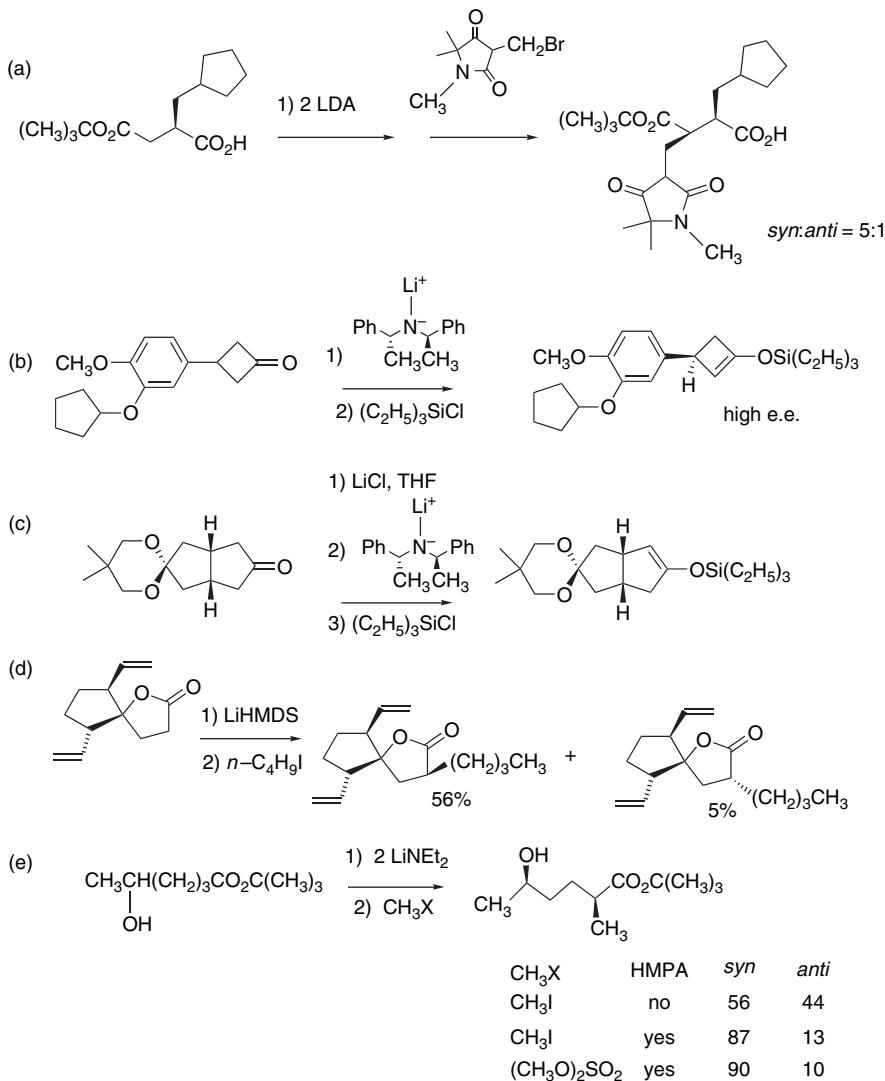
1.11. Suggest methodology for carrying out the following transformations in a way that high enantioselectivity could be achieved.



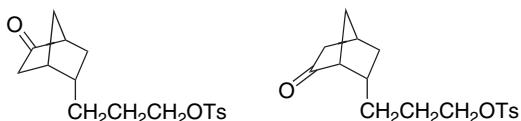
1.12. Indicate reagents and approximate reaction conditions that could be used to effect the following transformations. More than one step may be required.



- 1.13. The observed stereoselectivity of each of the following reactions is somewhat enigmatic. Discuss factors that could contribute to stereoselectivity in these reactions.

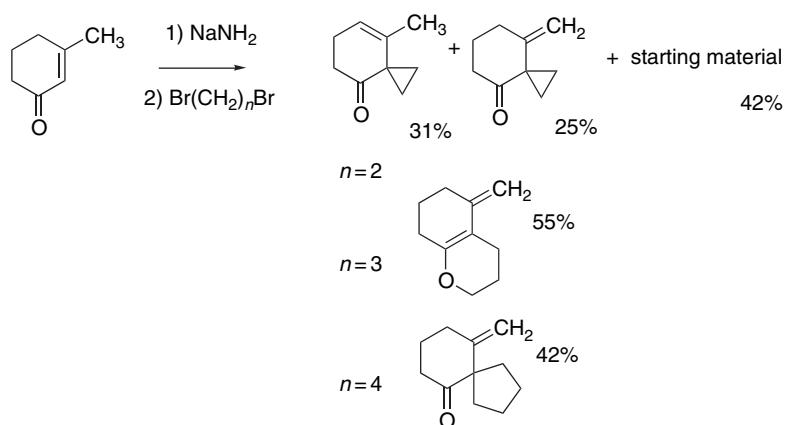


- 1.14. One of the compounds shown below undergoes intramolecular cyclization to give a tricyclic ketone on being treated with NaHMDS, but the other does not cyclize. Indicate which compound will cyclize more readily and offer an explanation.

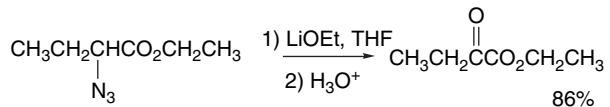


- 1.15. The alkylation of the enolate of 3-methyl-2-cyclohexenone with several different dibromides led to the products shown below. Discuss the course

of each reaction and offer an explanation for the dependence of the product structure on the chain length of the dihalide.



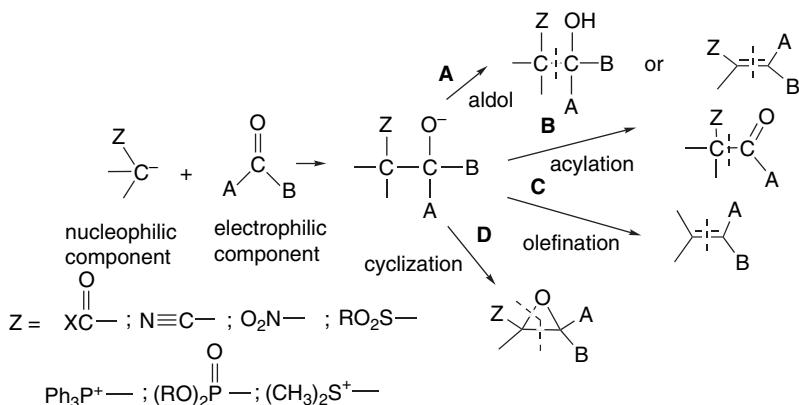
- 1.16. Treatment of ethyl 2-azidobutanoate with a catalytic amount of lithium ethoxide in THF leads to evolution of nitrogen. Quenching the resulting solution with 3 *N* HCl gives ethyl 2-oxobutanoate in 86% yield. Suggest a mechanism for this process.



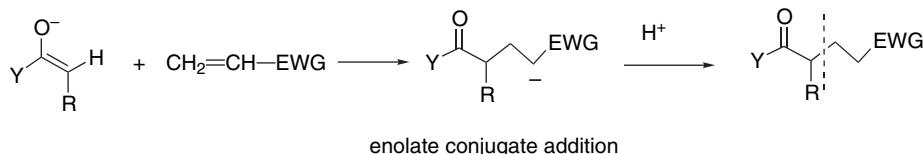
Reactions of Carbon Nucleophiles with Carbonyl Compounds

Introduction

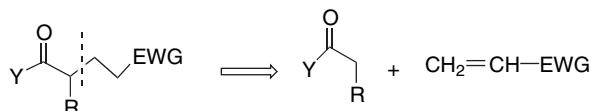
The reactions described in this chapter include some of the most useful methods for carbon-carbon bond formation: *the aldol reaction*, the *Robinson annulation*, the *Claisen condensation* and other *carbon acylation* methods, and the *Wittig reaction* and other *olefination methods*. All of these reactions begin with the addition of a stabilized carbon nucleophile to a carbonyl group. The product that is isolated depends on the nature of the stabilizing substituent (Z) on the carbon nucleophile, the substituents (A and B) at the carbonyl group, and the ways in which A, B, and Z interact to complete the reaction pathway from the addition intermediate to the product. Four fundamental processes are outlined below. Aldol addition and condensation lead to β -hydroxyalkyl or α -alkyldene derivatives of the carbon nucleophile (Pathway A). The acylation reactions follow Pathway B, in which a group leaves from the carbonyl electrophile. In the Wittig and related olefination reactions, the oxygen in the adduct reacts with the group Z to give an elimination product (Pathway C). Finally, if the enolate has an α -substituent that is a leaving group, cyclization can occur, as in Pathway D. This is observed, for example, with enolates of α -haloesters. The fundamental mechanistic concepts underlying these reactions were introduced in Chapter 7 of Part A. Here we emphasize the scope, stereochemistry, and synthetic utility of these reactions.



A second important reaction type considered in this chapter is *conjugate addition*, which involves addition of nucleophiles to electrophilic double or triple bonds. A crucial requirement for this reaction is an electron-withdrawing group (EWG) that can stabilize the negative charge on the intermediate. We focus on reactions between enolates and α,β -unsaturated carbonyl compounds and other electrophilic alkenes such as nitroalkenes.



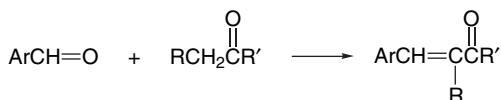
The retrosynthetic dissection is at a bond that is α to a carbonyl and β to an anion-stabilizing group.



2.1. Aldol Addition and Condensation Reactions

2.1.1. The General Mechanism

The general mechanistic features of the aldol addition and condensation reactions of aldehydes and ketones were discussed in Section 7.7 of Part A, where these general mechanisms can be reviewed. That mechanistic discussion pertains to reactions occurring in *hydroxylic solvents* and under *thermodynamic control*. These conditions are useful for the preparation of aldehyde dimers (aldols) and certain α,β -unsaturated aldehydes and ketones. For example, the mixed condensation of aromatic aldehydes with aliphatic aldehydes and ketones is often done under these conditions. The conjugation in the β -aryl enones provides a driving force for the elimination step.



The aldol reaction is also important in the synthesis of more complex molecules and in these cases control of both regiochemistry and stereochemistry is required. In most cases, this is accomplished under conditions of *kinetic control*. In the sections that follow, we discuss how variations of the basic mechanism and selection of specific reagents and reaction conditions can be used to control product structure and stereochemistry.

The addition reaction of enolates and enols with carbonyl compounds is of broad scope and of great synthetic importance. Essentially all of the stabilized carbanions mentioned in Section 1.1 are capable of adding to carbonyl groups, in what is known as the *generalized aldol reaction*. Enolates of aldehydes, ketones, esters, and amides, the carbanions of nitriles and nitro compounds, as well as phosphorus- and sulfur-stabilized carbanions and ylides undergo this reaction. In the next section we emphasize the fundamental regiochemical and stereochemical aspects of the reactions of ketones and aldehydes.

2.1.2. Control of Regio- and Stereoselectivity of Aldol Reactions of Aldehydes and Ketones

The synthetic utility of the aldol reaction depends on both the versatility of the reactants and the control of the regio- and stereochemistry. The term *directed aldol addition* is applied to reactions that are designed to achieve specific regio- and stereochemical outcomes.¹ Control of product structure requires that one reactant act exclusively as the *nucleophile* and the other exclusively as the *electrophile*. This requirement can be met by pre-forming the nucleophilic enolate by deprotonation, as described in Section 1.1. The enolate that is to serve as the nucleophile is generated stoichiometrically, usually with lithium as the counterion in an aprotic solvent at low temperature. Under these conditions, the kinetic enolate does not equilibrate with the other regio- or stereoisomeric enolates that can be formed from the ketone. The enolate gives a specific adduct, provided that the addition step is fast relative to proton exchange between the nucleophilic and electrophilic reactants. The reaction is under *kinetic control*, at both the stage of formation of the enolate and the addition step.

Under other reaction conditions, the product can result from *thermodynamic control*. Aldol reactions can be effected for many compounds using less than a stoichiometric amount of base. In these circumstances, the aldol reaction is reversible and the product ratio is determined by the relative stability of the various possible products. Thermodynamic conditions also permit equilibration among the enolates of the nucleophile. The conditions that lead to equilibration include higher reaction temperatures, protic or polar dissociating solvents, and the use of weakly coordinating cations. Thermodynamic conditions can be used to enrich the composition in the *most stable* of the isomeric products.

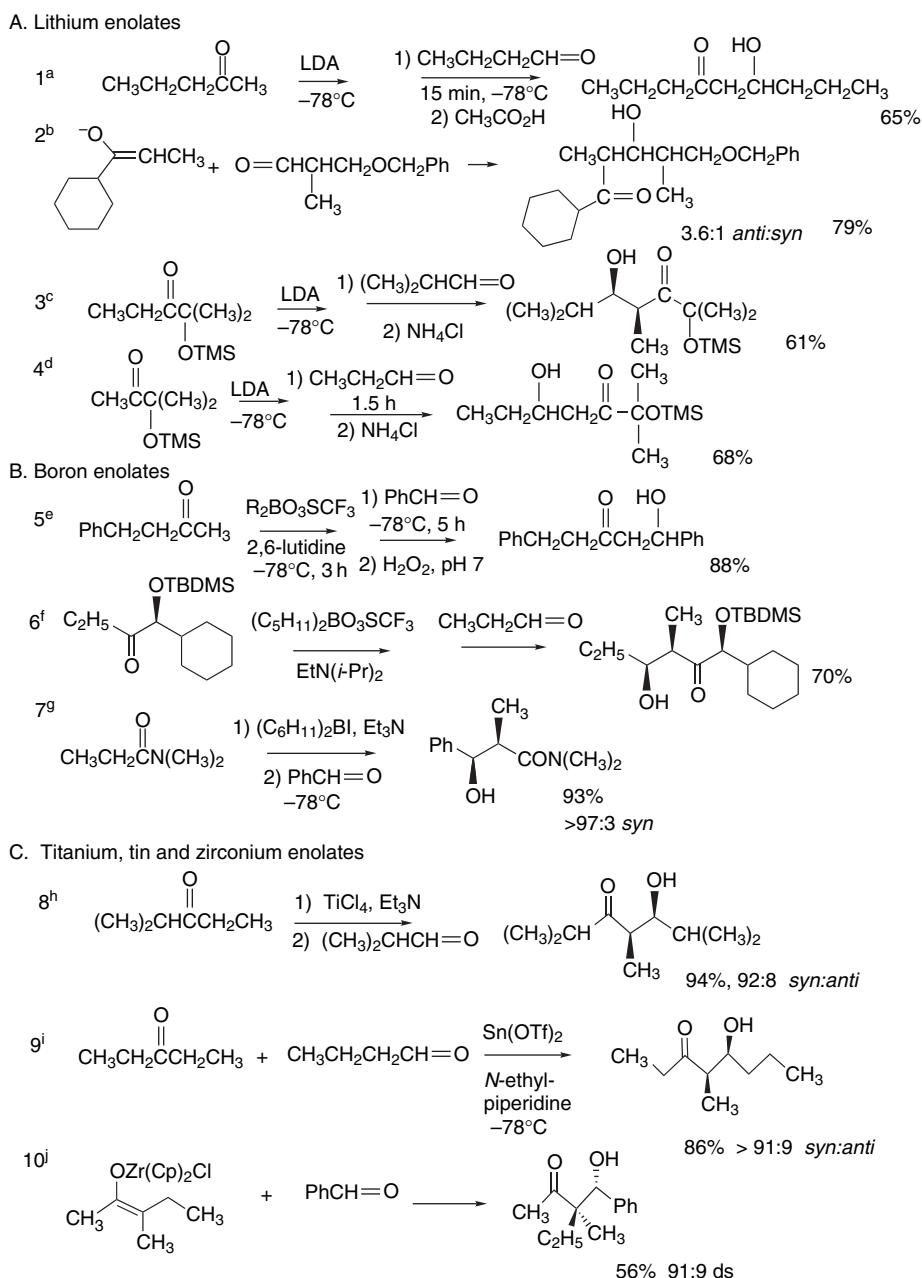
Reaction conditions that involve other enolate derivatives as nucleophiles have been developed, including boron enolates and enolates with titanium, tin, or zirconium as the metal. These systems are discussed in detail in the sections that follow, and in Section 2.1.2.5, we discuss reactions that involve *covalent enolate equivalents*, particularly silyl enol ethers. Scheme 2.1 illustrates some of the procedures that have been developed. A variety of carbon nucleophiles are represented in Scheme 2.1, including lithium and boron enolates, as well as titanium and tin derivatives, but in

¹. T. Mukaiyama, *Org. React.*, **28**, 203 (1982).

Scheme 2.1. Examples of Directed Aldol Reactions

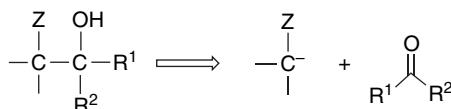
CHAPTER 2

Reactions of Carbon
Nucleophiles with
Carbonyl Compounds



- a. G. Stork, G. A. Kraus, and G. A. Garcia, *J. Org. Chem.*, **39**, 3459 (1974).
 b. S. Masamune, J. W. Ellingboe, and W. Choy, *J. Am. Chem. Soc.*, **104**, 5526 (1982).
 c. R. Bal, C. T. Buse, K. Smith, and C. Heathcock, *Org. Synth.*, **63**, 89 (1984).
 d. P. J. Jerris and A. B. Smith, III, *J. Org. Chem.*, **46**, 577 (1981).
 e. T. Inoue, T. Uchimaru, and T. Mukaiyama, *Chem. Lett.*, 153 (1977).
 f. S. Masamune, W. Choy, F. A. J. Kerdesky, and B. Imperiali, *J. Am. Chem. Soc.*, **103**, 1566 (1981).
 g. K. Ganeshan and H. C. Brown, *J. Org. Chem.*, **59**, 7346 (1994).
 h. D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991).
 i. T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, *Tetrahedron*, **40**, 1381 (1984).
 j. S. Yamago, D. Machii, and E. Nakamura, *J. Org. Chem.*, **56**, 2098 (1991).

each case the electrophile is an aldehyde. Pay particular attention to the retrosynthetic relationship between the products and the reactants, which corresponds in each case to Path A (p. 64). We see that the aldol addition reaction provides β -hydroxy carbonyl compounds or, more generally, adducts with a hydroxy group β to the stabilizing group Z of the carbon nucleophile.



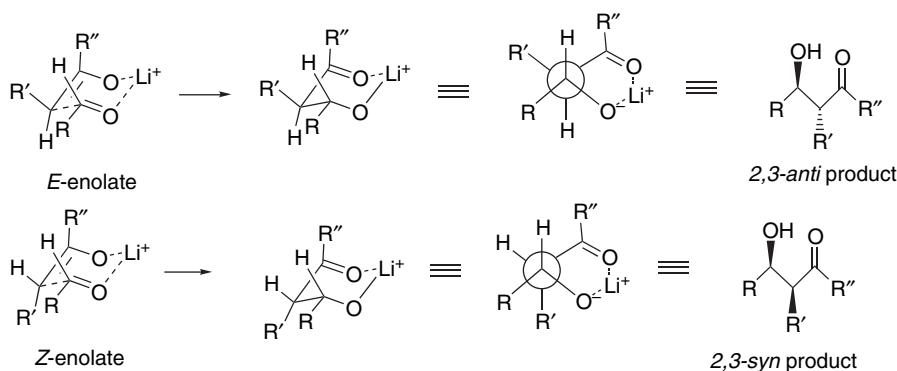
Note also the stereochemistry. In some cases, two new stereogenic centers are formed. The hydroxy group and any C(2) substituent on the enolate can be in a *syn* or *anti* relationship. For many aldol addition reactions, the stereochemical outcome of the reaction can be predicted and analyzed on the basis of the detailed mechanism of the reaction. Entry 1 is a mixed ketone-aldehyde aldol addition carried out by kinetic formation of the less-substituted ketone enolate. Entries 2 to 4 are similar reactions but with more highly substituted reactants. Entries 5 and 6 involve boron enolates, which are discussed in Section 2.1.2.2. Entry 7 shows the formation of a boron enolate of an amide; reactions of this type are considered in Section 2.1.3. Entries 8 to 10 show titanium, tin, and zirconium enolates and are discussed in Section 2.1.2.3.

2.1.2.1. Aldol Reactions of Lithium Enolates. Entries 1 to 4 in Scheme 2.1 represent cases in which the nucleophilic component is a lithium enolate formed by kinetically controlled deprotonation, as discussed in Section 1.1. Lithium enolates are usually highly reactive toward aldehydes and addition occurs rapidly when the aldehyde is added, even at low temperature. The low temperature ensures kinetic control and enhances selectivity. When the addition step is complete, the reaction is stopped by neutralization and the product is isolated.

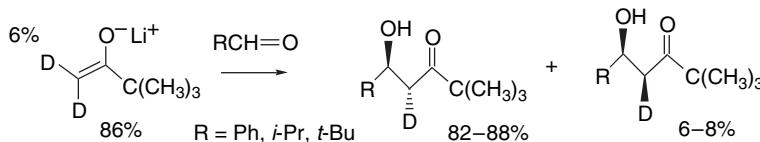
The fundamental mechanistic concept for diastereoselectivity of aldol reactions of lithium enolates is based on a cyclic TS in which both the carbonyl and enolate oxygen are coordinated to the lithium cation.² The Lewis acid character of the lithium ion promotes reaction by increasing the carbonyl group electrophilicity and by bringing the reactants together in the TS. Other metal cations and electrophilic atoms can play the role of the Lewis acid, as we will see when we discuss reactions of boron and other metal enolates. The fundamental concept is that the aldol addition normally occurs through a chairlike TS. It is assumed that the structure of the TS is sufficiently similar to a chair cyclohexane that the conformational concepts developed for cyclohexane rings can be applied. In the structures that follow, the reacting aldehyde is shown with R rather than H in the equatorial-like position, which avoids a 1,3-diaxial interaction with the enolate C(1) substituent. A consequence of this mechanism is that the reaction

². (a) H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, **79**, 1920 (1957); (b) P. Fellman and J. E. Dubois, *Tetrahedron*, **34**, 1349 (1978); (c) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).

is stereospecific with respect to the E- or Z-configuration of the enolate. The E-enolate gives the *anti* aldol product, whereas the Z-enolate gives the *syn*-aldol.³

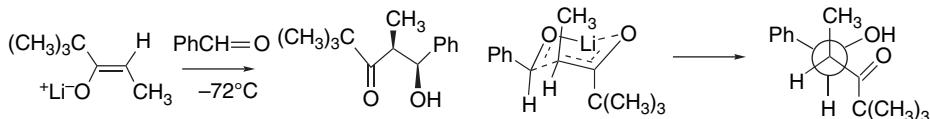


The preference for chairlike TSs has been confirmed by using deuterium-labeled enolates prepared from the corresponding silyl enol ethers. The ratio of the locations of the deuterium corresponds closely to the ratio of the stereoisomeric enolates for several aldehydes.⁴



Provided that the reaction occurs through a chairlike TS, the $E \rightarrow anti/Z \rightarrow syn$ relationship will hold. There are three cases that can lead to departure from this relationship. These include a nonchair TS, that can involve either an open TS or a nonchair cyclic TS. Internal chelation of the aldehyde or enolate can also cause a change in TS structure.

The first element of stereocontrol in aldol addition reactions of ketone enolates is the enolate structure. Most enolates can exist as two stereoisomers. In Section 1.1.2, we discussed the factors that influence enolate composition. The enolate formed from 2,2-dimethyl-3-pentanone under kinetically controlled conditions is the *Z*-isomer.⁵ When it reacts with benzaldehyde only the *syn* aldol is formed.⁴ The product stereochemistry is correctly predicted if the TS has a conformation with the phenyl substituent in an equatorial position.

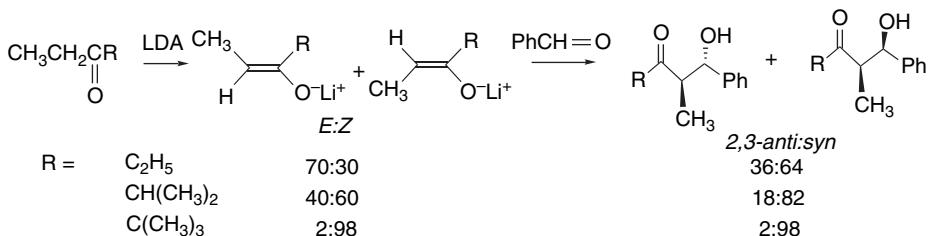


3. For consistency in designating the relative configuration the carbonyl group is numbered (1). The newly formed bond is labeled 2,3- and successive carbons are numbered accordingly. The carbons derived from the enolate are numbered 2',3', etc., starting with the α' -carbon.

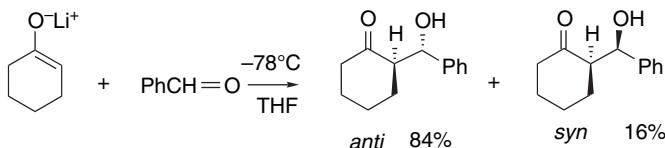
⁴ C. M. Liu, W. J. Smith, III, D. J. Gustin, and W. R. Roush, *J. Am. Chem. Soc.*, **127**, 5770 (2005).

5. To avoid potential uncertainties in the application of the Cahn-Ingold-Prelog priority rules, by convention the enolate oxygen is assigned the higher priority.

A similar preference for formation of the *syn* aldol is found for other *Z*-enolates derived from ketones in which one of the carbonyl substituents is bulky. Ketone enolates with less bulky substituents show a decreasing stereoselectivity in the order *t*-butyl > *i*-propyl > ethyl.^{2c} This trend parallels a decreasing preference for stereoselective formation of the *Z*-enolate.



The enolates derived from cyclic ketones are necessarily *E*-isomers. The enolate of cyclohexanone reacts with benzaldehyde to give both possible stereoisomeric products. The stereoselectivity is about 5:1 in favor of the *anti* isomer under optimum conditions.⁶



From these and many related examples the following generalizations can be made about kinetic stereoselection in aldol additions of lithium enolates. (1) The chair TS model provides a basis for analyzing the stereoselectivity observed in aldol reactions of ketone enolates having one bulky substituent. The preference is *Z*-enolate \rightarrow *syn* aldol; *E*-enolate \rightarrow *anti* aldol. (2) When the enolate has no bulky substituent, stereoselectivity is low. (3) *Z*-Enolates are more stereoselective than *E*-enolates. Table 2.1 gives some illustrative data.

The requirement that an enolate have at least one bulky substituent restricts the types of compounds that give highly stereoselective aldol additions via the lithium enolate method. Furthermore, only the enolate formed by kinetic deprotonation is directly available. Whereas ketones with one tertiary alkyl substituent give mainly the *Z*-enolate, less highly substituted ketones usually give mixtures of *E*- and *Z*-enolates.⁷ (Review the data in Scheme 1.1.) Therefore efforts aimed at increasing the stereoselectivity of aldol additions have been directed at two facets of the problem: (1) better control of enolate stereochemistry, and (2) enhancement of the degree of stereoselectivity in the addition step, which is discussed in Section 2.1.2.2.

The *E:Z* ratio can be modified by the precise conditions for formation of the enolate. For example, the *E:Z* ratio for 3-pentanone and 2-methyl-3-pentanone can be increased by use of a 1:1 lithium tetramethylpiperidide(LiTMP)-LiBr mixture for

⁶ M. Majewski and D. M. Gleave, *Tetrahedron Lett.*, **30**, 5681 (1989).

⁷ R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976); W. A. Kleschick, C. T. Buse, and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 247 (1977); Z. A. Fataftah, I. E. Kopka, and M. W. Rathke, *J. Am. Chem. Soc.*, **102**, 3959 (1980).

Table 2.1. Diastereoselectivity of Addition of Lithium Enolates to Benzaldehyde

<i>R</i> ¹	Z:E ratio	<i>syn:anti</i> ratio	
H	100:0	50:50	
H	0:100	65:35	
C ₂ H ₅	30:70	64:36	
C ₂ H ₅	66:34	77:23	
(CH ₃) ₂ CH	>98:2	90:10	
(CH ₃) ₂ CH	0:100	45:55	
(CH ₃) ₃ C	>98:2	>98:2	
1-Adamantyl	>98:2	>98:2	
C ₆ H ₅	>98:2	88:12	
Mesityl	8:92	8:92	
Mesityl	87:13	88:12	

a. From C. H. Heathcock, in *Asymmetric Synthesis*, Vol. 3, J. D. Morrison, ed., Academic Press, New York, 1984, Chap. 2.

kinetic enolization.⁸ The precise mechanism of this effect is still a matter of investigation, but it is probably due to an aggregate species containing bromide acting as the base (see Section 1.1.1).⁹

	E:Z Stereoselectivity		
	LDA	LiTMP	LiTMP + LiBr
	3.3:1	5:1	50:1
	1.7:1	2:1	21:1
	1: >50	1: >20	1:>20

Other changes in deprotonation conditions can influence enolate composition. Relatively weakly basic lithium anilides, specifically lithium 2,4,6-trichloroanilide and lithium diphenylamide, give high *Z:E* ratios.¹⁰ Lithio 1,1,3,3-tetramethyl-1,3-diphenyldisilylamide is also reported to favor the *Z*-enolate.¹¹ On the other hand, lithium *N*-trimethylsilyl-*iso*-propylamide and lithium *N*-trimethylsilyl-*tert*-butylamide give selectivity for the *E*-enolate¹² (see Scheme 1.1).

⁸. P. L. Hall, J. H. Gilchrist, and D. B. Collum, *J. Am. Chem. Soc.*, **113**, 9571 (1991).

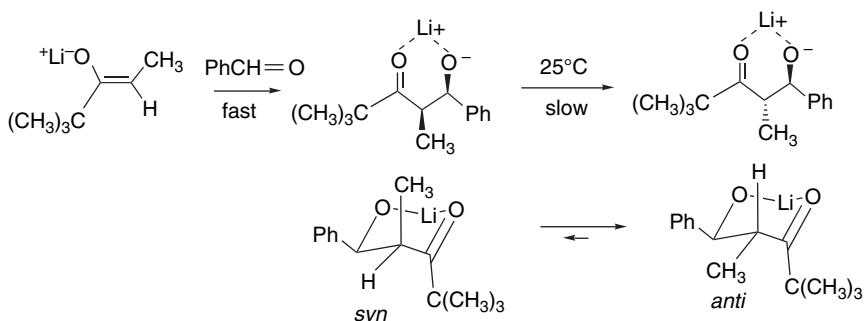
⁹. F. S. Mair, W. Clegg, and P. A. O'Neil, *J. Am. Chem. Soc.*, **115**, 3388 (1993).

¹⁰. L. Xie, K. Vanlandeghem, K. M. Isenberger, and C. Bernier, *J. Org. Chem.*, **68**, 641 (2003).

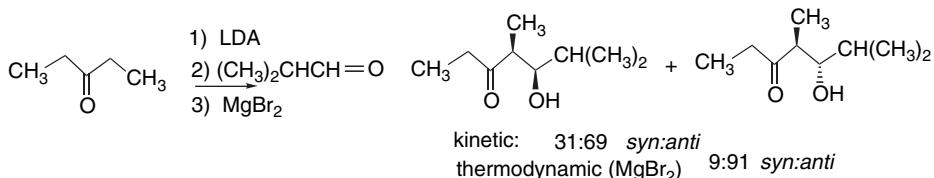
¹¹. S. Masamune, J. W. Ellingboe, and W. Choy, *J. Am. Chem. Soc.*, **104**, 5526 (1982).

¹². L. Xie, K. M. Isenberger, G. Held, and L. M. Dahl, *J. Org. Chem.*, **62**, 7516 (1997).

When aldol addition is carried out under thermodynamic conditions, the product stereoselectivity is usually not as high as under kinetic conditions. All the regio- and stereoisomeric enolates can participate as nucleophiles. The adducts can return to reactants, so the difference in *stability* of the stereoisomeric *anti* and *syn* products determines the product composition. In the case of lithium enolates, the adducts can be equilibrated by keeping the reaction mixture at room temperature. This has been done, for example, with the product from the reaction of the enolate of 2,2-dimethyl-3-pentanone and benzaldehyde. The greater stability of the *anti* isomer is attributed to the pseudoequatorial position of the methyl group in the chairlike product chelate. With larger substituent groups, the thermodynamic preference for the *anti* isomer is still greater.¹³



For synthetic efficiency, it is useful to add $MgBr_2$, which accelerates the equilibration.



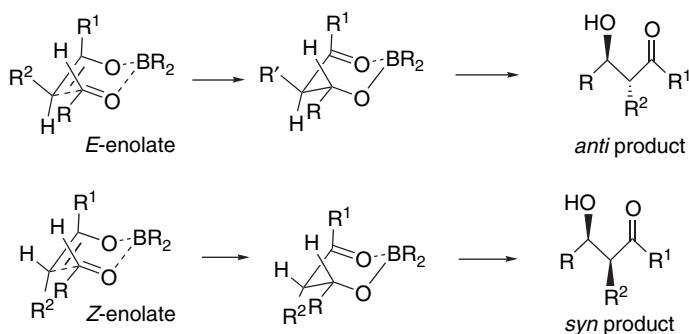
Ref. 14

2.1.2.2. Aldol Reactions of Boron Enolates. The matter of increasing stereoselectivity in the addition step can be addressed by using other reactants. One important version of the aldol reaction involves the use of boron enolates.¹⁵ A cyclic TS similar to that for lithium enolates is involved, and the same relationship exists between enolate configuration and product stereochemistry. In general, the stereoselectivity is higher than for lithium enolates. The O–B bond distances are shorter than for lithium enolates, and this leads to a more compact structure for the TS and magnifies the steric interactions that control stereoselectivity.

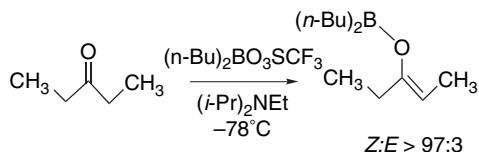
¹³. C. H. Heathcock and J. Lampe, *J. Org. Chem.*, **48**, 4330 (1983).

¹⁴. K. A. Swiss, W.-B. Choi, D. C. Liotta, A. F. Abdel-Magid, and C. A. Maryanoff, *J. Org. Chem.*, **56**, 5978 (1991).

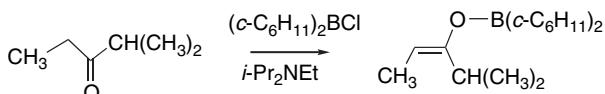
¹⁵. C. J. Cowden and I. A. Paterson, *Org. React.*, **51**, 1 (1997); E. Tagliavini, C. Trombini, and A. Umani-Ronchi, *Adv. Carbanion Chem.*, **2**, 111 (1996).



Boron enolates can be prepared by reaction of the ketone with a dialkylboron trifluoromethanesulfonate (triflate) and a tertiary amine.¹⁶ Use of boron triflates and a bulky amine favors the *Z*-enolate. The resulting aldol products are predominantly the *syn* stereoisomers.



The *E*-boron enolates of some ketones can be preferentially obtained by using dialkylboron chlorides.¹⁷



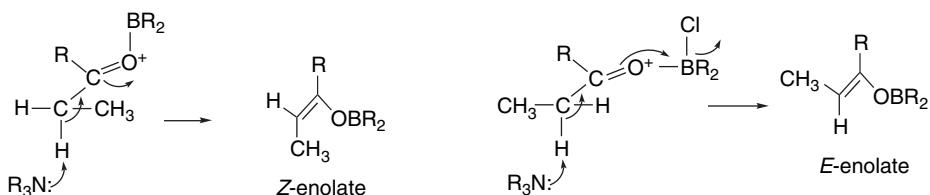
The contrasting stereoselectivity of the boron triflates and chlorides has been discussed in terms of reactant conformation and the stereoelectronic requirement for alignment of the hydrogen being removed with the carbonyl group π orbital.¹⁸ With the triflate reagents, the boron is *anti* to the enolizable group. With the bulkier dicyclohexylboron chloride, the boron favors a conformation *cis* to the enolizable group. A computational study of the reaction also indicates that the size of the boron ligand and the resulting conformational changes are the dominant factors in determining stereoselectivity.¹⁹ There may also be a distinction between the two types of borylation reagents in the extent of dissociation of the leaving group. The triflate is probably an ion pair, whereas with the less reactive chloride, the deprotonation may be a concerted (E2-like) process.^{18b} The two proposed TSs are shown below.

¹⁶ D. A. Evans, E. Vogel, and J. V. Nelson, *J. Am. Chem. Soc.*, **101**, 6120 (1979); D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, *J. Am. Chem. Soc.*, **103**, 3099 (1981).

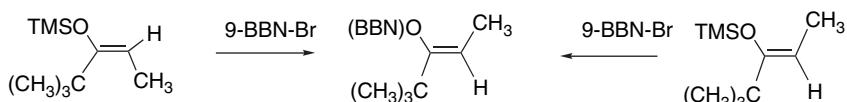
¹⁷ H. C. Brown, R. K. Dhar, R. K. Bakshi, P. K. Pandiarajan, and B. Singaram, *J. Am. Chem. Soc.*, **111**, 3441 (1989); H. C. Brown, R. K. Dhar, K. Ganesan, and B. Singaram, *J. Org. Chem.*, **57**, 499 (1992); H. C. Brown, R. K. Dhar, K. Ganesan, and B. Singaram, *J. Org. Chem.*, **57**, 2716 (1992); H. C. Brown, K. Ganesan, and R. K. Dhar, *J. Org. Chem.*, **58**, 147 (1993); K. Ganesan and H. C. Brown, *J. Org. Chem.*, **58**, 7162 (1993).

¹⁸ (a) J. M. Goodman and I. Paterson, *Tetrahedron Lett.*, **33**, 7223 (1992); (b) E. J. Corey and S. S. Kim, *J. Am. Chem. Soc.*, **112**, 4976 (1990).

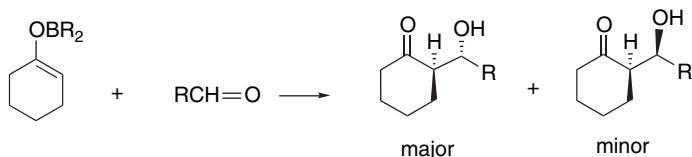
¹⁹ J. Murga, E. Falomir, M. Carda, and J. A. Marco, *Tetrahedron*, **57**, 6239 (2001).



Z-Boron enolates can also be obtained from silyl enol ethers by reaction with the bromoborane derived from 9-BBN (9-borabicyclo[3.3.1]nonane). This method is necessary for ketones such as 2,2-dimethyl-3-pentanone, which give *E*-boron enolates by other methods. The *Z*-stereoisomer is formed from either the *Z*- or *E*-silyl enol ether.²⁰



The *E*-boron enolate from cyclohexanone shows a preference for the *anti* aldol product. The ratio depends on the boron alkyl groups and is modest (2:1) with di-*n*-butylboron but greater than 20:1 for cyclopentyl-*n*-hexylboron.¹⁶



The general trend is that boron enolates *parallel* lithium enolates in their stereoselectivity but show *enhanced stereoselectivity*. There also are some advantages in terms of access to both stereoisomeric enol derivatives. Another important characteristic of boron enolates is that they are not subject to internal chelation. The tetracoordinate dialkylboron in the cyclic TS is not able to accept additional ligands, so there is no tendency to form a chelated TS when the aldehyde or enolate carries a donor substituent. Table 2.2 gives some typical data for boron enolates and shows the strong correspondence between enolate configuration and product stereochemistry.

2.1.2.3. Aldol Reactions of Titanium, Tin, and Zirconium Enolates. Metals such as Ti, Sn, and Zr give enolates that are intermediate in character between the ionic Li^+ enolates and covalent boron enolates. The Ti, Sn, or Zr enolates can accommodate additional ligands. Tetra-, penta-, and hexacoordinate structures are possible. This permits the formation of chelated TSs when there are nearby donor groups in the enolate or electrophile. If the number of anionic ligands exceeds the oxidation state of the metal, the complex has a formal negative charge on the metal and is called an “ate” complex. Such structures enhance the nucleophilicity of enolate ligands. Depending on the nature of the metal ligands, either a cyclic or an acyclic TS can be involved. As we will see in Section 2.1.3.5, the variability in the degree and nature of coordination provides an additional factor in analysis and control of stereoselectivity.

²⁰ J. L. Duffy, T. P. Yoon, and D. A. Evans, *Tetrahedron Lett.*, **36**, 9245 (1993).

Table 2.2. Diastereoselectivity of Boron Enolates toward Aldehydes^a

R^1	L	X	R^2	$Z:E$	<i>syn:anti</i>
$C_2H_5^b$	$n-C_4H_9$	OTf	Ph	>97:3	>97:3
$C_2H_5^b$	$n-C_4H_9$	OTf	Ph	69:31	72:28
$C_2H_5^b$	$n-C_4H_9$	OTf	$n-C_3H_7$	>97:3	>97:3
$C_2H_5^b$	$n-C_4H_9$	OTf	$t-C_4H_9$	>97:3	>97:3
$C_2H_5^b$	$n-C_4H_9$	OTf	$CH_2=CHCH_3$	>97:3	92:8
$C_2H_5^b$	$n-C_4H_9$	OTf	$E-C_4H_7$	>97:3	93:7
$i-C_3H_7^b$	$n-C_4H_9$	OTf	Ph	45:55	44:56
$i-C_4H_9^b$	$n-C_4H_9$	OTf	Ph	>99:1	>97:3
$t-C_4H_9^b$	$n-C_4H_9$	OTf	Ph	>99:1	>97:3
$n-C_5H_{11}^c$	$n-C_4H_9$	OTf	Ph	95:5	94:6
$n-C_9H_{19}^c$	$n-C_4H_9$	OTf	Ph	91:9	91:9
$c-C_6H_{11}^c$	$n-C_4H_9$	OTf	Ph	95:5	94:6
$PhCH_2^c$	$n-C_4H_9$	OTf	Ph	98:2	>99:1
Ph^b	$n-C_4H_9$	OTf	Ph	96:4	95:5
$C_2H_5^d$	$c-C_6H_{11}$	Cl	Ph		21:79
$i-C_3H_7^d$	$c-C_6H_{11}$	Cl	Ph		<3:97
$c-C_6H_{11}^d$	$c-C_6H_{11}$	Cl	Ph		<1:99
$t-C_4H_9^d$	$c-C_6H_{11}$	Cl	Ph		<3:97

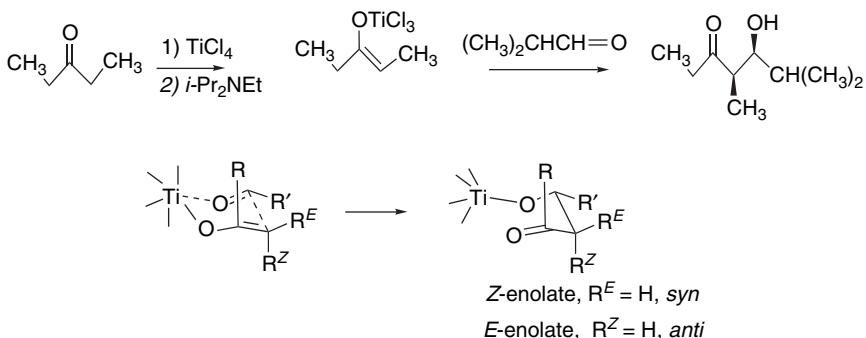
a. From a more complete compilation, see C. H. Heathcock, in *Asymmetric Synthesis*, Vol. 3, J. D. Morrison, ed., Academic Press, New York, 1984, Chap. 3.

b. D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, *J. Am. Chem. Soc.*, **103**, 3099 (1981).

c. I. Kuwajima, M. Kato, and A. Mori, *Tetrahedron Lett.*, **21**, 4291 (1980).

d. H. C. Brown, R. K. Dhar, R. K. Bakshi, P. K. Pandiarajan, and P. Singaram, *J. Am. Chem. Soc.*, **111**, 3441 (1989); H. C. Brown, K. Ganeshan, and R. K. Dhar, *J. Org. Chem.*, **58**, 147 (1993).

Titanium enolates can be prepared from lithium enolates by reaction with trialkoxytitanium(IV) chloride, such as *tris*-(isopropoxy)titanium chloride.²¹ Titanium enolates are usually prepared directly from ketones by reaction with $TiCl_4$ and a tertiary amine.²² Under these conditions, the *Z*-enolate is formed and the aldol adducts have *syn* stereochemistry. The addition step proceeds through a cyclic TS assembled around titanium.



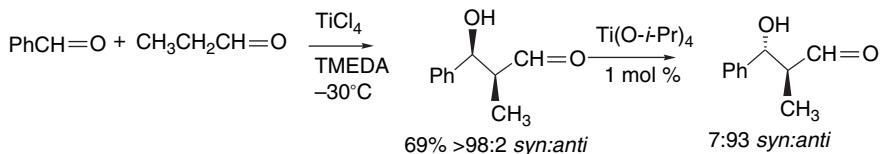
Entry 8 in Scheme 2.1 is an example of this method. Titanium enolates are frequently employed in the synthesis of complex molecules and with other carbonyl derivatives,

²¹. C. Siegel and E. R. Thornton, *J. Am. Chem. Soc.*, **111**, 5722 (1989).

²². D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991).

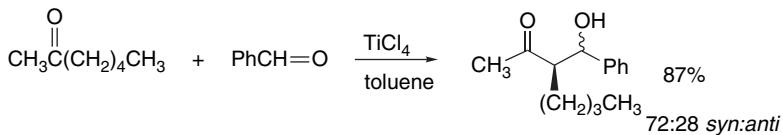
such as the *N*-acyloxazolidinones that serve as chiral auxiliaries (see Section 2.1.3.4).

Mixed aldehyde-aldehyde additions have been carried out using TiCl_4 and TMEDA. The reaction gives *syn* adducts, presumably through a cyclic TS. Treatment of the *syn* adducts with 1 mol % $\text{Ti}(\text{O}-i\text{-Pr})_4$ leads to equilibration to the more stable *anti* isomer.²³



The equilibration in this case is believed to involve oxidation-reduction at the alcohol center, rather than reversal of the addition. (See Section 5.3.2 for a discussion of $\text{Ti}(\text{O}-i\text{-Pr})_4$ as an oxidation-reduction catalyst.)

Ketone-aldehyde additions have been effected using TiCl_4 in toluene.²⁴ These reactions exhibit the same stereoselectivity trends as other titanium-mediated additions. With unsymmetrical ketones, this procedure gives the product from the more-substituted enolate.²⁵



Titanium enolates can also be used under conditions in which the titanium exists as an “ate” species. Crossed aldehyde-aldehyde additions have been accomplished starting with trimethylsilyl enol ethers, which are converted to lithium enolates and then to “ate” species by addition of $\text{Ti}(\text{O}-n\text{-Bu})_4$.²⁶ These conditions show only modest stereoselectivity.

Silyl enol ether	R	<i>syn:anti</i>
Z	C_2H_5	28:72
Z	$(\text{CH}_3)_2\text{CH}$	20:80
Z	$(\text{CH}_3)_3\text{C}$	10:90
Z	Ph	54:46
E	$(\text{CH}_3)_2\text{CH}$	47:53
E	$(\text{CH}_3)_3\text{C}$	28:72

Titanium “ate” species have also been used to add aldehyde enolates to ketones. This reaction is inherently difficult because of the greater reactivity of aldehyde

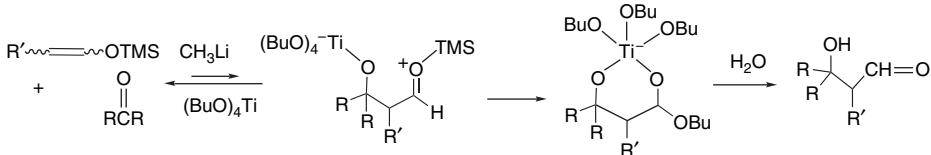
²³ R. Mahrwald, B. Costisella, and B. Gundogan, *Synthesis*, 262 (1998).

²⁴ R. Mahrwald, *Chem. Ber.*, **128**, 919 (1995).

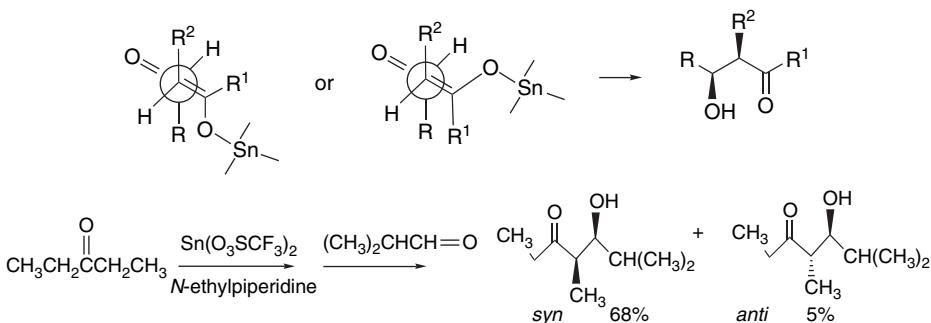
²⁵ R. Mahrwald and B. Gundogan, *J. Am. Chem. Soc.*, **120**, 413 (1998).

²⁶ K. Yachi, H. Shinokubo, and K. Oshima, *J. Am. Chem. Soc.*, **121**, 9465 (1999).

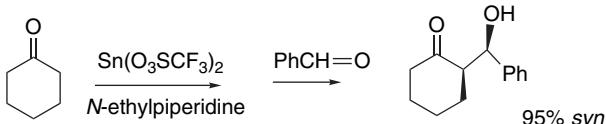
carbonyls over ketone carbonyls. The reaction works best with ketones having EWG substituents such as alkynones and α -haloketones. The reaction is thought to proceed through a cyclic intermediate that is stable until hydrolysis. This cyclic intermediate may be necessary to drive the normally unfavorable equilibrium of the addition step.



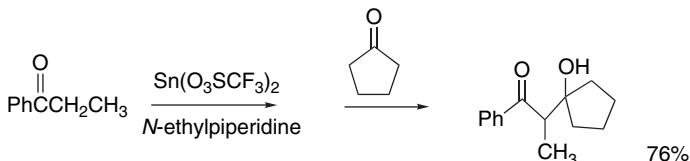
Tin enolates are also used in aldol reactions.²⁷ Both the Sn(II) and Sn(IV) oxidation states are reactive. Tin(II) enolates can be generated from ketones and $\text{Sn}(\text{II})(\text{O}_3\text{SCF}_3)_2$ in the presence of tertiary amines.²⁸ The subsequent aldol addition is *syn* selective and independent of enolate configuration.²⁹ This preference arises from avoidance of *gauche* interaction of the aldehyde group and the enolate β -substituent. The *syn* stereoselectivity indicates that reaction occurs through an open TS.



Even cyclohexanone gives the *syn* product.



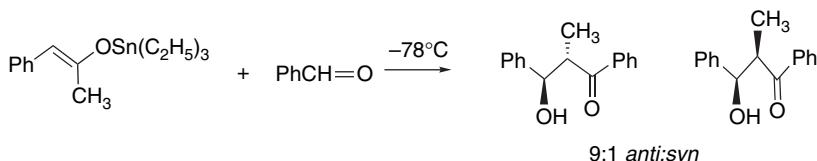
Entry 9 of Scheme 2.1 is an example of application of these conditions. Tin(II) enolates prepared in this way also show good reactivity toward ketones as the electrophilic component.



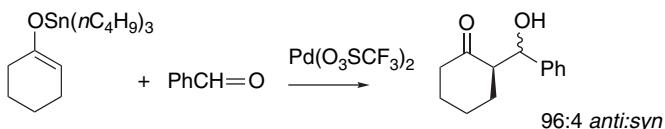
Ref. 30

- ²⁷. T. Mukaiyama and S. Kobayashi, *Org. React.*, **46**, 1 (1994).
- ²⁸. T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, *Tetrahedron*, **40**, 1381 (1984); I. Shibata and A. Babu, *Org. Prep. Proc. Int.*, **26**, 85 (1994).
- ²⁹. T. Mukaiyama, R. W. Stevens, and N. Iwasawa, *Chem. Lett.*, 353 (1982).
- ³⁰. R. W. Stevens, N. Iwasawa, and T. Mukaiyama, *Chem. Lett.*, 1459 (1982).

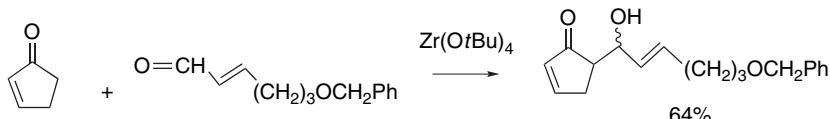
Trialkylstannyl enolates can be prepared from enol acetates by reaction with trialkyltin alkoxides and are sufficiently reactive to add to aldehydes. Uncatalyzed addition of trialkylstannyl enolates to benzaldehyde shows *anti* stereoselectivity.³¹



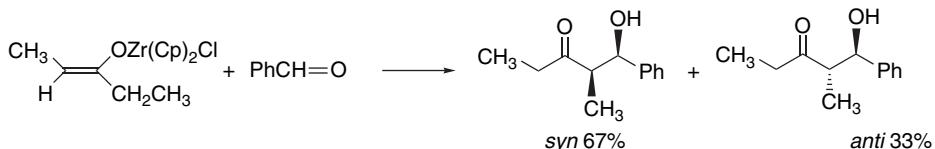
Isolated tri-*n*-butylstannyl enolates react with benzaldehyde under the influence of metal salts including $\text{Pd}(\text{O}_3\text{SCF}_3)_2$, $\text{Zn}(\text{O}_3\text{SCF}_3)_2$, and $\text{Cu}(\text{O}_3\text{SCF}_3)_2$.³² The tri-*n*-butylstannyl enol derivative of cyclohexanone gives mainly *anti* product. The *anti:syn* ratio depends on the catalyst, with $\text{Pd}(\text{O}_3\text{SCF}_3)_2$ giving the highest ratio.



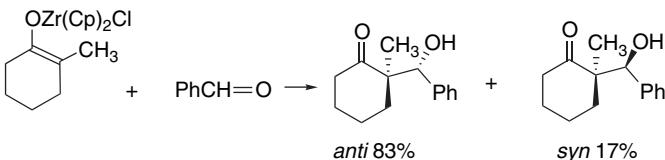
Zirconium *tetra-t*-butoxide is a mildly basic reagent that has occasionally been used to effect aldol addition.³³



Zirconium enolates can also be prepared by reaction of lithium enolates with $(\text{Cp})_2\text{ZrCl}_2$, and they act as nucleophiles in aldol addition reactions.³⁴



Ref. 34d



Ref. 34d

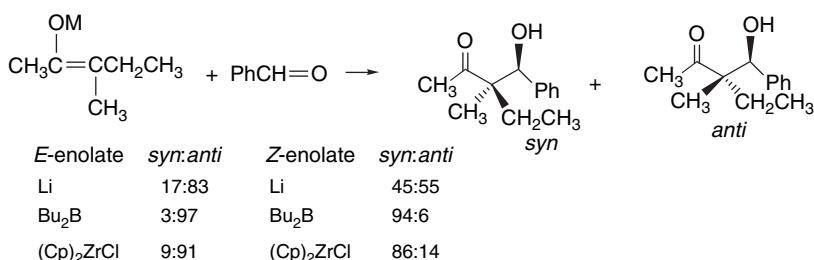
³¹ S. S. Labadie and J. K. Stille, *Tetrahedron*, **40**, 2329 (1984).

³² A. Yanagisawa, K. Kimura, Y. Nakatsuka, and M. Yamamoto, *Synlett*, 958 (1998).

³³ H. Sasai, Y. Kirio, and M. Shibasaki, *J. Org. Chem.*, **55**, 5306 (1990).

³⁴ (a) D. A. Evans and L. R. McGee, *Tetrahedron Lett.*, **21**, 3975 (1980); (b) Y. Yamamoto and K. Maruyama, *Tetrahedron Lett.*, **21**, 4607 (1980); (c) M. Braun and H. Sacha, *Angew. Chem. Int. Ed. Engl.*, **30**, 1318 (1991); (d) S. Yamago, D. Machii, and E. Nakamura, *J. Org. Chem.*, **56**, 2098 (1991).

A comparison of the *anti:syn* diastereoselectivity of the lithium, dibutylboron, and $(Cp)_2Zr$ enolates of 3-methyl-2-hexanone with benzaldehyde has been reported.^{34d} The order of stereoselectivity is $Bu_2B > (Cp)_2Zr > Li$. These results suggest that the reactions of the zirconium enolates proceed through a cyclic TS.



2.1.2.4. Summary of the Relationship between Diastereoselectivity and the Transition Structure. In this section we considered *simple diastereoselection* in aldol reactions of ketone enolates. Numerous observations on the reactions of enolates of ketones and related compounds are consistent with the general concept of a chairlike TS.³⁵ These reactions show a consistent $E \rightarrow anti : Z \rightarrow syn$ relationship. Noncyclic TSs have more variable diastereoselectivity. The prediction or interpretation of the specific ratio of *syn* and *anti* product from any given reaction requires assessment of several variables: (1) What is the stereochemical composition of the enolate? (2) Does the Lewis acid promote tight coordination with both the carbonyl and enolate oxygen atoms and thereby favor a cyclic TS? (3) Does the TS have a chairlike conformation? (4) Are there additional Lewis base coordination sites in either reactant that can lead to reaction through a chelated TS? Another factor comes into play if either the aldehyde or the enolate, or both, are chiral. In that case, facial selectivity becomes an issue and this is considered in Section 2.1.5.

2.1.3. Aldol Addition Reactions of Enolates of Esters and Other Carbonyl Derivatives

The enolates of other carbonyl compounds can be used in mixed aldol reactions. Extensive use has been made of the enolates of esters, thiol esters, amides, and imides, including several that serve as chiral auxiliaries. The methods for formation of these enolates are similar to those for ketones. Lithium, boron, titanium, and tin derivatives have all been widely used. The silyl ethers of ester enolates, which are called *silyl ketene acetals*, show reactivity that is analogous to silyl enol ethers and are covalent equivalents of ester enolates. The silyl thioketene acetal derivatives of thiol esters are also useful. The reactions of these enolate equivalents are discussed in Section 2.1.4.

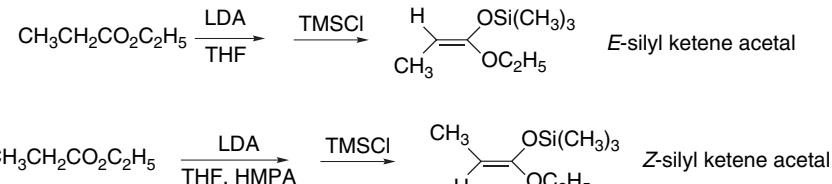
Because of their usefulness in aldol additions and other synthetic methods (see especially Section 6.4.2.3), there has been a good deal of interest in the factors that

³⁵ C. H. Heathcock, *Modern Synthetic Methods*, **6**, 1 (1992); C. H. Heathcock, in *Asymmetric Syntheses*, Vol. 3, J. D. Morrison, ed., 1984, Chap. 2, Academic Press; C. H. Heathcock, in *Comprehensive Carbanion Chemistry*, Part B, E. Bunzel and T. Durst, ed., Elsevier, Amsterdam, 1984, Chap. 4; D. A. Evans, J. V. Nelson, and T. R. Taber, *Top. Stereochem.*, **13**, 1 (1982); A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968); R. Mahrwald, ed., *Modern Aldol Reactions*, Wiley-VCH (2004).

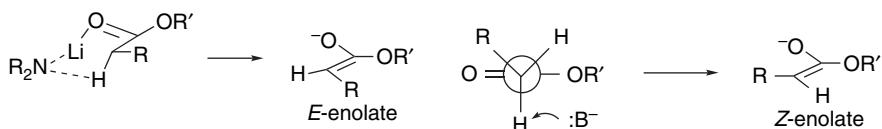
SECTION 2.1

Aldol Addition and Condensation Reactions

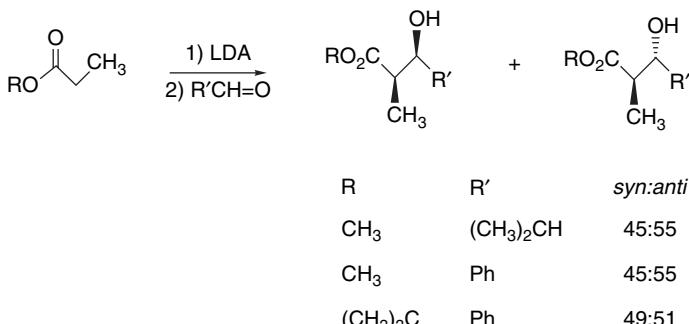
control the stereoselectivity of enolate formation from esters such as ethyl propanoate, the *E*-enolate is preferred under kinetic conditions using a strong base such as LDA in THF solution. Inclusion of a strong cation-solvating cosolvent, such as HMPA or DMPU, favors the *Z*-enolate.³⁶ These enolates can be trapped and analyzed as the corresponding silyl ketene acetals. The relationships are similar to those discussed for formation of ketone enolates in Section 1.1.2.



These observations are explained in terms of a chairlike TS for the LDA/THF conditions and a more open TS in the presence of an aprotic dipolar solvent.



Despite the ability to control ester enolate geometry, the aldol addition reactions of unhindered ester enolate are not very stereoselective.³⁷

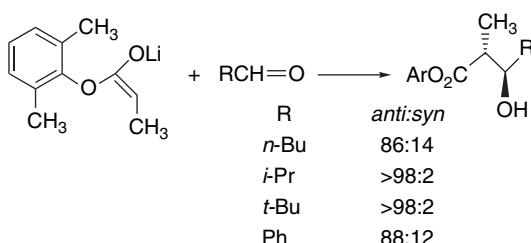


This stereoselectivity can be improved by use of a very bulky group. 2,6-Dimethylphenyl esters give *E*-enolates and *anti* aldol adducts.³⁸

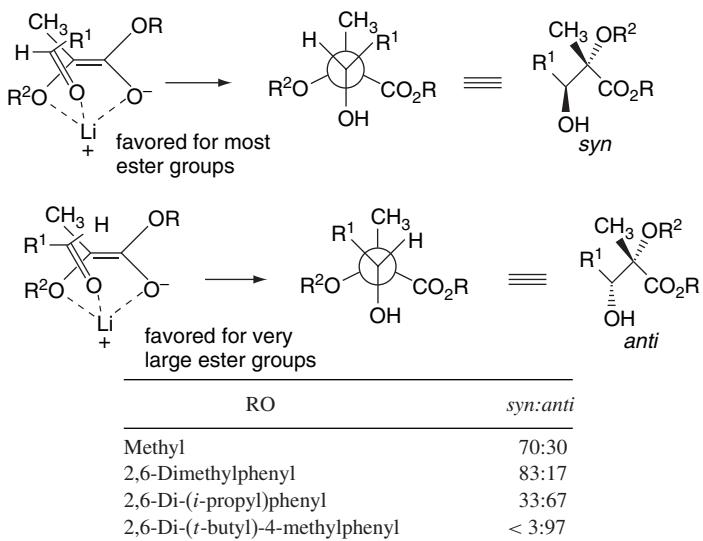
³⁶ R. E. Ireland and A. K. Willard, *Tetrahedron Lett.*, 3975 (1975); R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976); R. E. Ireland, P. Wipf, and J. D. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).

³⁷ A. I. Meyers and P. J. Reider, *J. Am. Chem. Soc.*, **101**, 2501 (1979); C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, *J. Org. Chem.*, **45**, 1066 (1980).

³⁸ M. C. Pirrung and C. H. Heathcock, *J. Org. Chem.*, **45**, 1728 (1980).

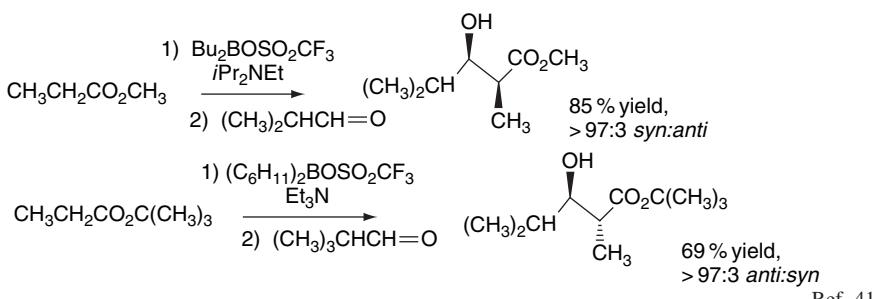


The lithium enolates of α -alkoxy esters exhibit high stereoselectivity, which is consistent with involvement of a chelated enolate.^{37a,39} The chelated ester enolate is approached by the aldehyde in such a manner that the aldehyde R group avoids being between the α -alkoxy and methyl groups in the ester enolate. A syn product is favored for most ester groups, but this shifts to *anti* with extremely bulky groups.

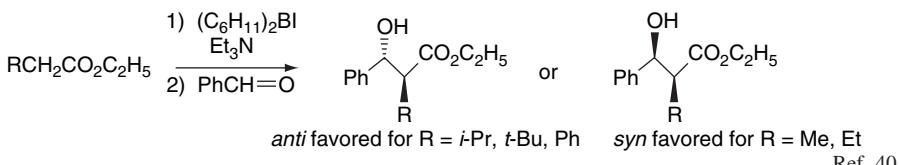


Boron enolates can be obtained from esters^{40,41} and amides⁴² by methods that are similar to those used for ketones. Various combinations of borylating reagents and amines have been used and the E:Z ratios are dependent on the reagents and conditions. In most cases esters give Z-enolates, which lead to *syn* adducts, but there are exceptions. Use of branched-chain alcohols increases the amount of *anti* enolate, and with *t*-butyl esters the product ratio is higher than 97:3.

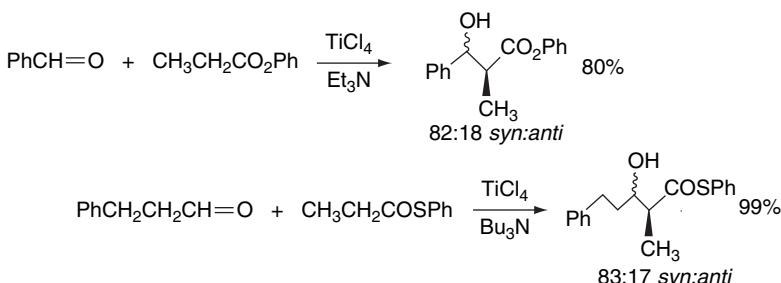
- ³⁹. C. H. Heathcock, M. C. Pirrung, S. D. Young, J. P. Hagen, E. T. Jarvi, U. Badertscher, H.-P. Marki, and S. H. Montgomery, *J. Am. Chem. Soc.*, **106**, 8161 (1984).
- ⁴⁰. K. Ganesan and H. C. Brown, *J. Org. Chem.*, **59**, 2336 (1994).
- ⁴¹. A. Abiko, J.-F. Liu, and S. Masamune, *J. Org. Chem.*, **61**, 2590 (1996); T. Inoue, J.-F. Liu, D. C. Buske, and A. Abiko, *J. Org. Chem.*, **67**, 5250 (2002).
- ⁴². K. Ganesan and H. C. Brown, *J. Org. Chem.*, **59**, 7346 (1994).



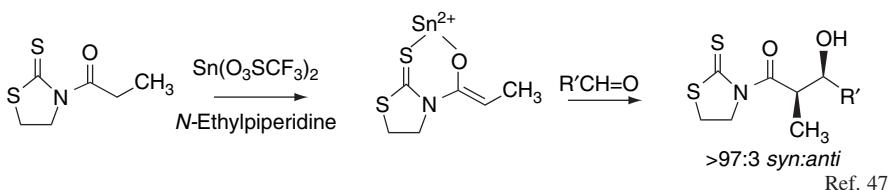
Branched-chain esters also give mainly *anti* adducts when the enolates are formed using dicyclohexyl iodoborane.



Phenyl and phenylthio esters have proven to be advantageous in $TiCl_4$ -mediated additions, perhaps because they are slightly more acidic than the alkyl analogs. The reactions show *syn* diastereoselectivity, indicating that *Z*-enolates are formed.⁴³



Among the most useful carbonyl derivatives are *N*-acyloxazolidinones, and as we shall see in Section 2.3.4, they provide facial selectivity in aldol addition reactions. 1,3-Thiazoline-2-thiones constitute another useful type of chiral auxiliary, and they can be used in conjunction with $Bu_2BO_3SCF_3$,⁴⁴ $Sn(O_3SCF_3)_2$,⁴⁵ or $TiCl_4$ ⁴⁶ for generation of enolates. The stereoselectivity of the reactions is consistent with formation of a *Z*-enolate and reaction through a cyclic TS.



⁴³. Y. Tanabe, N. Matsumoto, S. Funakoshi, and N. Manta, *Synlett*, 1959 (2001).

⁴⁴. C.-N. Hsiao, L. Liu, and M. J. Miller, *J. Org. Chem.*, **52**, 2201 (1987).

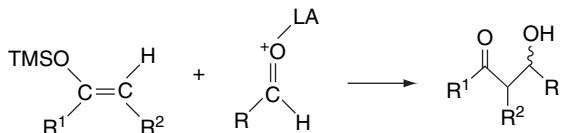
⁴⁵. Y. Nagao, Y. Hagiwara, T. Kumagai, M. Ochiai, T. Inoue, K. Hashimoto, and E. Fujita, *J. Org. Chem.*, **51**, 2391 (1986); Y. Nagao, Y. Nagase, T. Kumagai, H. Matsunaga, T. Abe, O. Shimada, T. Hayashi, and Y. Inoue, *J. Org. Chem.*, **57**, 4243 (1992).

⁴⁶. D. A. Evans, S. J. Miller, M. D. Ennis, and P. L. Ornstein, *J. Org. Chem.*, **57**, 1067 (1992).

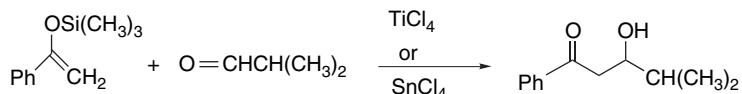
⁴⁷. T. Mukaiyama and N. Isawa, *Chem. Lett.*, 1903 (1982); N. Isawa, H. Huang, and T. Mukaiyama, *Chem. Lett.*, 1045 (1985).

2.1.4. The Mukaiyama Aldol Reaction

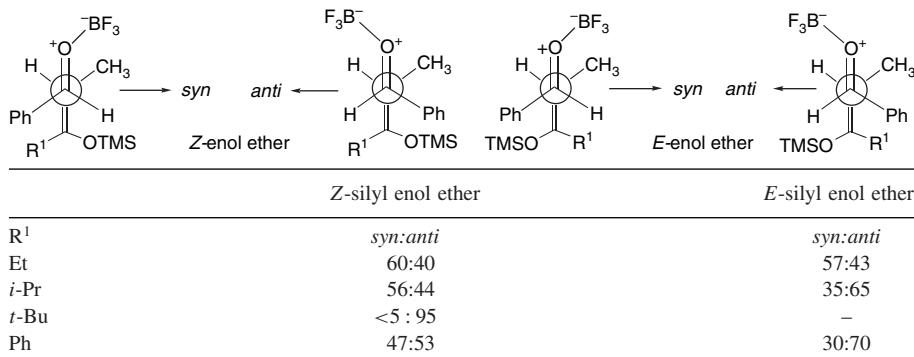
The *Mukaiyama aldol reaction* refers to Lewis acid–catalyzed aldol addition reactions of silyl enol ethers, silyl ketene acetals, and similar *enolate equivalents*.⁴⁸ Silyl enol ethers are not sufficiently nucleophilic to react directly with aldehydes or ketones. However, Lewis acids cause reaction to occur by coordination at the carbonyl oxygen, activating the carbonyl group to nucleophilic attack.



Lewis acids such as TiCl_4 and SnCl_4 induce addition of both silyl enol ethers and ketene silyl acetals to aldehydes.⁴⁹



If there is no other interaction, the reaction proceeds through an acyclic TS and steric factors determine the amount of *syn* versus *anti* addition. This is the case with BF_3 , where the tetracoordinate boron-aldehyde adduct does not offer any free coordination sites for formation of a cyclic TS. Stereoselectivity increases with the steric bulk of the silyl enol ether substituent R^1 .⁵⁰



Quite a number of other Lewis acids can catalyze the Mukaiyama aldol reaction, including $\text{Bu}_2\text{Sn}(\text{O}_3\text{SCF}_3)_2$,⁵¹ $\text{Bu}_3\text{SnClO}_4$,⁵² $\text{Sn}(\text{O}_3\text{SCF}_3)_2$,⁵³ $\text{Zn}(\text{O}_3\text{SCF}_3)_2$,⁵⁴ and

⁴⁸ R. Mahrwald, *Chem. Rev.*, **99**, 1095 (1999).

⁴⁹ T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).

⁵⁰ C. H. Heathcock, K. T. Hug, and L. A. Flippin, *Tetrahedron Lett.*, **25**, 5973 (1984).

⁵¹ T. Sato, J. Otera, and H. Nozaki, *J. Am. Chem. Soc.*, **112**, 901 (1990).

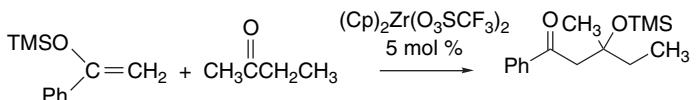
⁵² J. Otera and J. Chen, *Synlett*, 321 (1996).

⁵³ T. Oriyama, K. Iwanami, Y. Miyauchi, and G. Koga, *Bull. Chem. Soc. Jpn.*, **63**, 3716 (1990).

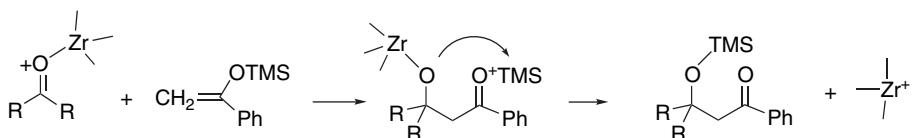
⁵⁴ M. Chini, P. Crotti, C. Gardelli, F. Minutolo, and M. Pineschi, *Gazz. Chim. Ital.*, **123**, 673 (1993).

LiClO_4 .⁵⁵ Cerium, samarium, and other lanthanide halides promote addition of silyl ketene acetals to aldehydes.⁵⁶ Triaryl perchlorate salts are also very active catalysts.⁵⁷ In general terms, there are at least three possible mechanisms for catalysis. One is through Lewis acid activation of the electrophilic carbonyl component, similar to that discussed for BF_3 , TiCl_4 , and SnCl_4 . Another is by exchange with the enolate equivalent to generate a more nucleophilic species. A third is activation of a catalytic cycle that generates trimethylsilyl cation as the active catalysts.

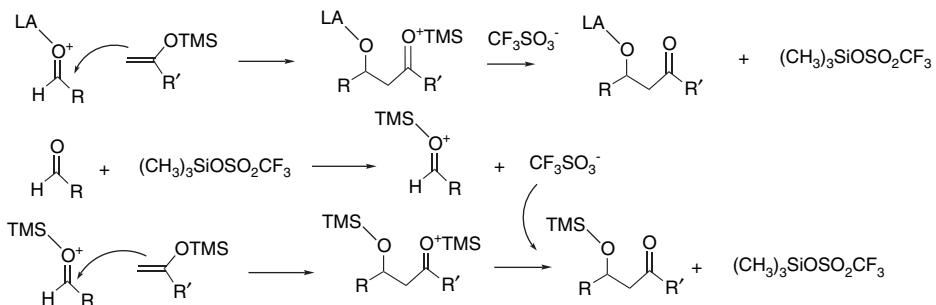
Aldol additions of silyl enol ethers and silyl ketene acetals can be catalyzed by $(\text{Cp})_2\text{Zr}^{2+}$ species including $[(\text{Cp})_2\text{ZrO}-t\text{-Bu}]^+$ and $(\text{Cp})_2\text{Zr}(\text{O}_3\text{SCF}_3)_2$.⁵⁸



The catalytic cycle involves transfer of the silyl group to the adduct.



Trialkylsilyl cations may play a key role in other Lewis acid–catalyzed reactions.⁵⁹ For example, trimethylsilyl triflate can be formed by intermolecular transfer of the silyl group. When this occurs, the trimethylsilyl triflate can initiate a catalytic cycle that does not directly involve the Lewis acid.



⁵⁵ M. T. Reetz and D. N. A. Fox, *Tetrahedron Lett.*, **34**, 1119 (1993).

⁵⁶ P. Van de Weghe and J. Colin, *Tetrahedron Lett.*, **34**, 3881 (1993); A. E. Vougioukas and H. B. Kagan, *Tetrahedron Lett.*, **28**, 5513 (1987).

⁵⁷ T. Mukaiyama, S. Kobayashi, and M. Murakami, *Chem. Lett.*, 447 (1985); T. Mukaiyama, S. Kobayashi, and M. Murakami, *Chem. Lett.*, 1759 (1984); S. E. Denmark and C.-T. Chen, *Tetrahedron Lett.*, **35**, 4327 (1994).

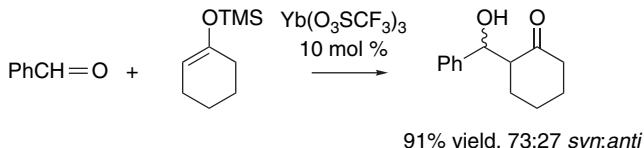
⁵⁸ (a) T. K. Hollis, N. P. Robinson, and B. Bosnich, *Tetrahedron Lett.*, **33**, 6423 (1992); (b) Y. Hong, D. J. Norris, and S. Collins, *J. Org. Chem.*, **58**, 3591 (1993).

⁵⁹ E. M. Carreira and R. A. Singer, *Tetrahedron Lett.*, **35**, 4323 (1994); T. K. Hollis and B. Bosnich, *J. Am. Chem. Soc.*, **117**, 4570 (1995).

Hindered *bis*-phenoxyaluminum derivatives are powerful cocatalysts for reactions mediated by TMS triflate and are believed to act by promoting formation of trimethylsilyl cations by sequestering the triflate anion.⁶⁰

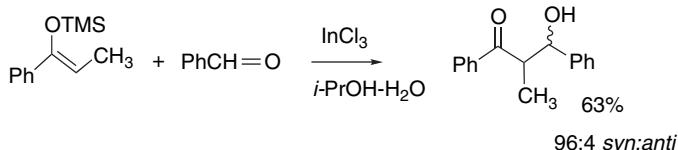


The lanthanide salts are unique among Lewis acids in that they can be effective as catalysts in aqueous solution.⁶¹ Silyl enol ethers react with formaldehyde and benzaldehyde in water-THF mixtures using lanthanide triflates such as $\text{Yb}(\text{O}_3\text{SCF}_3)_3$. The catalysis reflects the strong affinity of lanthanides for carbonyl oxygen, even in aqueous solution.



Ref. 62

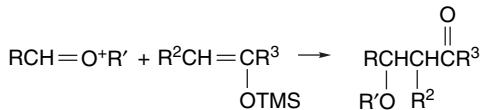
Certain other metal ions also exhibit catalysis in aqueous solution. Two important criteria are rate of ligand exchange and the acidity of the metal hydrate. Metal hydrates that are too acidic lead to hydrolysis of the silyl enol ether, whereas slow exchange limits the ability of catalysis to compete with other processes. Indium(III) chloride is a borderline catalysts by these criteria, but nevertheless is effective. The optimum solvent is 95:5 isopropanol-water. Under these conditions, the reaction is *syn* selective, suggesting a cyclic TS.⁶³



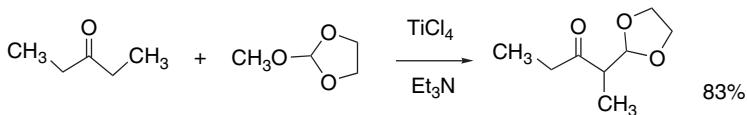
In addition to aldehydes, acetals can serve as electrophiles in Mukaiyama aldol reactions.⁶⁴ Effective catalysts include TiCl_4 ,⁶⁵ SnCl_4 ,⁶⁶ $(\text{CH}_3)_3\text{SiO}_3\text{SCF}_3$,⁶⁷ and

- ⁶⁰. M. Oishi, S. Aratake, and H. Yamamoto, *J. Am. Chem. Soc.*, **120**, 8271 (1998).
- ⁶¹. S. Kobayashi and K. Manabe, *Acc. Chem. Res.*, **35**, 209 (2002).
- ⁶². S. Kobayashi and I. Hachiya, *J. Org. Chem.*, **59**, 3590 (1994).
- ⁶³. O. Munoz-Muniz, M. Quintanar-Audelo, and E. Juaristi, *J. Org. Chem.*, **68**, 1622 (2003).
- ⁶⁴. Y. Yamamoto, H. Yatagai, Y. Naruta, and K. Maruyama, *J. Am. Chem. Soc.*, **102**, 7107 (1980); T. Mukaiyama and M. Murakami, *Synthesis*, 1043 (1987).
- ⁶⁵. T. Mukaiyama and M. Hayashi, *Chem. Lett.*, 15 (1974).
- ⁶⁶. R. C. Cambie, D. S. Larsen, C. E. F. Rickard, P. S. Rutledge, and P. D. Woodgate, *Austr. J. Chem.*, **39**, 487 (1986).
- ⁶⁷. S. Murata, M. Suzuki, and R. Noyori, *Tetrahedron*, **44**, 4259 (1988).

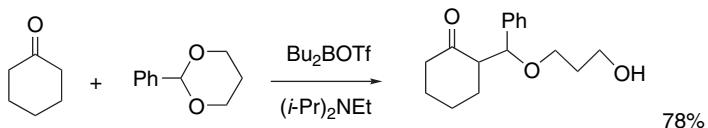
$\text{Bu}_2\text{Sn}(\text{O}_3\text{SCF}_3)_2$.⁶⁸ The Lewis acids promote ionization of the acetal to an oxonium ion that acts as the electrophile. The products are β -alkoxy ketones.



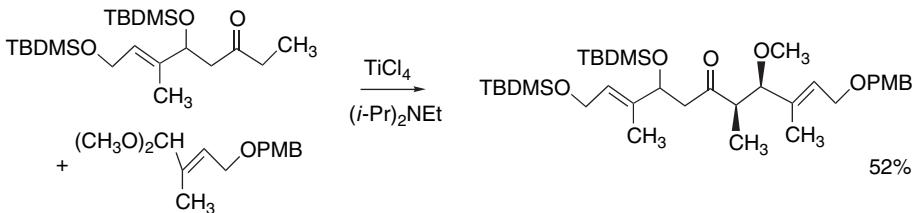
In some cases, the enolate can be formed directly in the presence of the acetal with the Lewis acid also activating the acetal.⁶⁹



Dibutylboron triflate promotes both enol borinate formation and addition.⁷⁰



Reactions with acetals can serve to introduce β -alkoxy groups into complex molecules, as in the following reaction.⁷¹



It has been proposed that there may be a single electron transfer mechanism for the Mukaiyama reaction under certain conditions.⁷² For example, photolysis of benzaldehyde dimethylacetal and 1-trimethylsilyloxyhexene in the presence of a

⁶⁸. T. Sato, J. Otera, and H. Nozaki, *J. Am. Chem. Soc.*, **112**, 901 (1990).

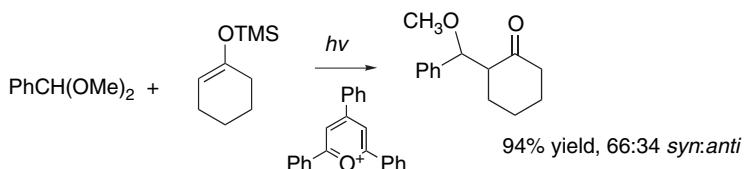
⁶⁹. D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark, and M. T. Bilodeau, *J. Am. Chem. Soc.*, **112**, 8215 (1990).

⁷⁰. L.-S. Li, S. Das, and S. C. Sinha, *Org. Lett.*, **6**, 127 (2004).

⁷¹. G. E. Keck, C. A. Wager, T. T. Wager, K. A. Savin, J. A. Covell, M. D. McLaws, D. Krishnamurthy, and V. J. Cee, *Angew. Chem. Int. Ed. Engl.*, **40**, 231 (2001).

⁷². T. Miura and Y. Masaki, *J. Chem. Soc., Perkin Trans. 1*, 1659 (1994); T. Miura and Y. Masaki, *J. Chem. Soc., Perkin Trans. 1*, 2155 (1995); J. Otera, Y. Fujita, N. Sakuta, M. Fujita, and S. Fukuzumi, *J. Org. Chem.*, **61**, 2951 (1996).

typical photoelectron acceptor, triphenylpyrylium cation, gives an excellent yield of the addition product.



Ref. 73

These reactions may operate by providing a source of trimethylsilyl cations, which serve as the active catalyst by a cycle similar to that for Lewis acids.

The Mukaiyama aldol reaction can provide access to a variety of β -hydroxy carbonyl compounds and use of acetals as reactants can provide β -alkoxy derivatives. The issues of stereoselectivity are the same as those in the aldol addition reaction, but the tendency toward acyclic rather than cyclic TSs reduces the influence of the *E*- or *Z*-configuration of the enolate equivalent on the stereoselectivity.

Scheme 2.2 illustrates several examples of the Mukaiyama aldol reaction. Entries 1 to 3 are cases of addition reactions with silyl enol ethers as the nucleophile and TiCl_4 as the Lewis acid. Entry 2 demonstrates steric approach control with respect to the silyl enol ether, but in this case the relative configuration of the hydroxy group was not assigned. Entry 4 shows a fully substituted silyl enol ether. The favored product places the larger C(2) substituent *syn* to the hydroxy group. Entry 5 uses a silyl ketene thioacetal. This reaction proceeds through an open TS and favors the *anti* product.

Entries 6 to 9 involve reactions conducted under catalytic conditions. Entry 6 uses an yttrium catalyst that is active in aqueous solution. Entries 7 and 8 are examples of the use of $(\text{Cp})_2\text{Ti}(\text{O}_3\text{SCF}_3)_2$ as a Lewis acid. Entry 9 illustrates the TMS triflate-MABR catalytic combination.

Entries 10 to 14 show reactions involving acetals. Interestingly, Entry 10 shows much-reduced stereoselectivity compared to the corresponding reaction of the aldehyde (The BF_3 -catalyzed reaction of the aldehyde is reported to be 24:1 in favor of the *anti* product; ref. 80, p. 91). There are no stereochemical issues in Entries 11 or 12. Entry 13, involving two cyclic reactants, gave a 2:1 mixture of stereoisomers. Entry 14 is a step in a synthesis directed toward the taxane group of diterpenes. Four stereoisomeric products were produced, including the *Z:E* isomers at the new enone double bond.

2.1.5. Control of Facial Selectivity in Aldol and Mukaiyama Aldol Reactions

In the discussion of the stereochemistry of aldol and Mukaiyama reactions, the most important factors in determining the *syn* or *anti* diastereoselectivity were identified as the nature of the TS (cyclic, open, or chelated) and the configuration (*E* or *Z*) of the enolate. If either the aldehyde or enolate is chiral, an additional factor enters the picture. The aldehyde or enolate then has two nonidentical faces and the stereochemical outcome will depend on *facial selectivity*. In principle, this applies to any stereocenter in the molecule, but the strongest and most studied effects are those of α - and β -substituents. If the aldehyde is chiral, particularly when the stereogenic center is adjacent to the carbonyl group, the competition between the two diastereotopic faces of the carbonyl group determines the stereochemical outcome of the reaction.

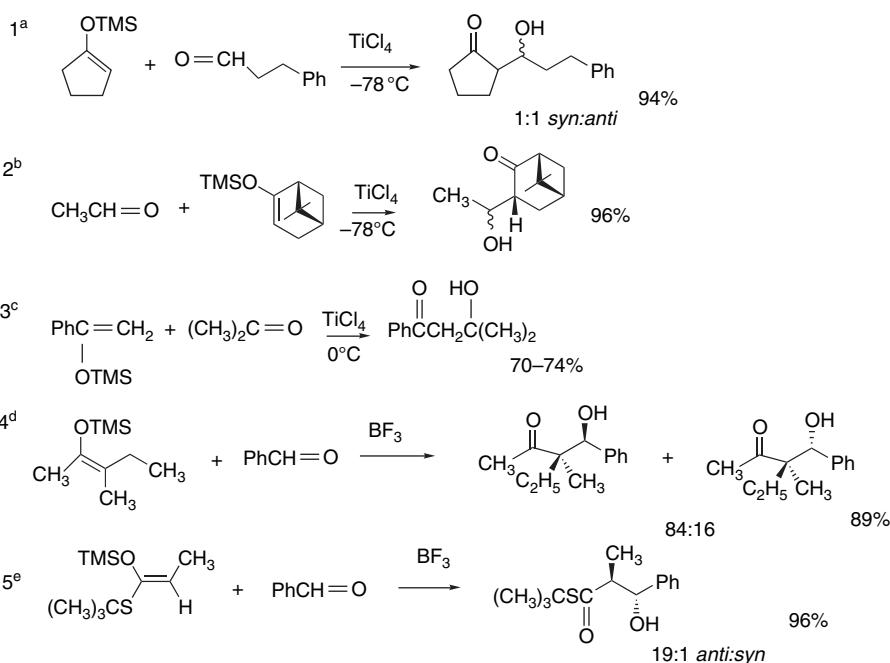
⁷³ M. Kamata, S. Nagai, M. Kato, and E. Hasegawa, *Tetrahedron Lett.*, **37**, 7779 (1996).

Scheme 2.2. The Mukaiyama Aldol Reaction

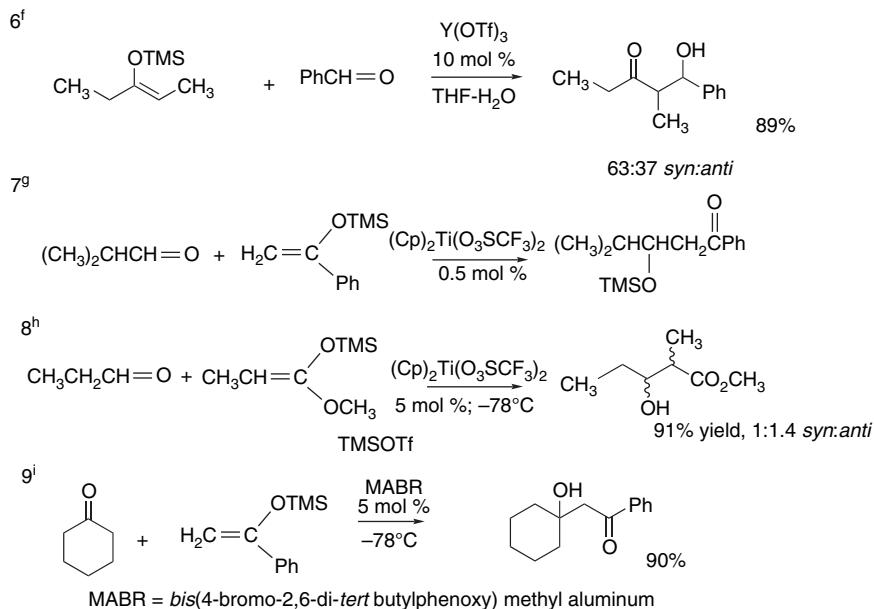
SECTION 2.1

Aldol Addition and Condensation Reactions

A. Reactions of silyl ene ethers with aldehydes and ketones



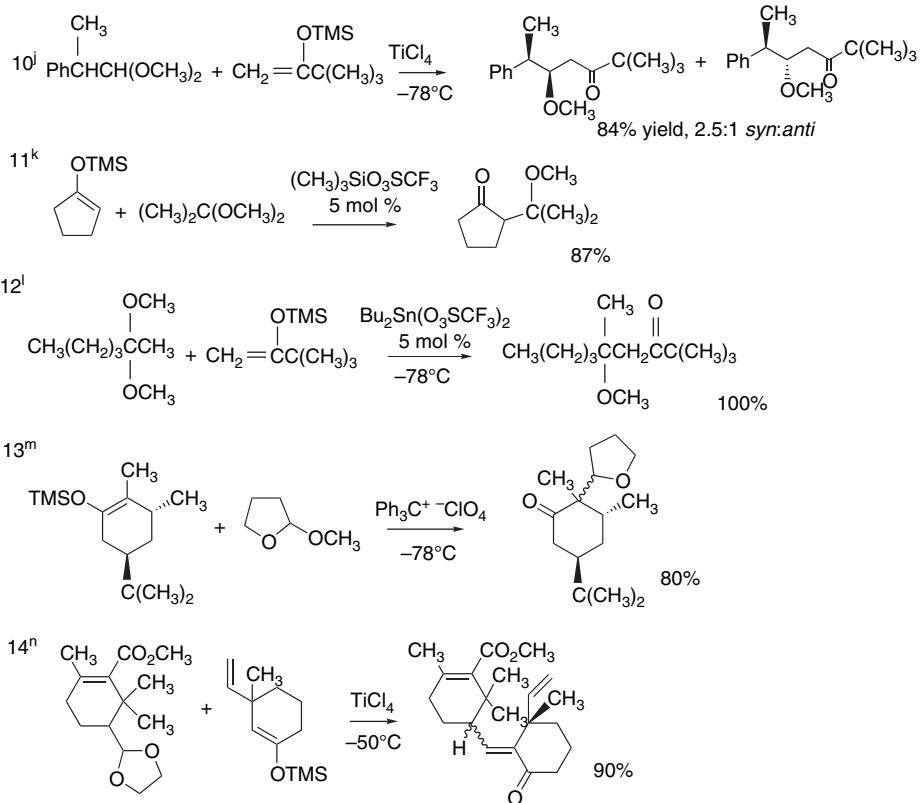
B. Catalytic Mukaiyama Reactions

MABR = bis(4-bromo-2,6-di-*tert* butylphenoxy) methyl aluminum

(Continued)

Scheme 2.2. (Continued)

C. Reactions with acetals



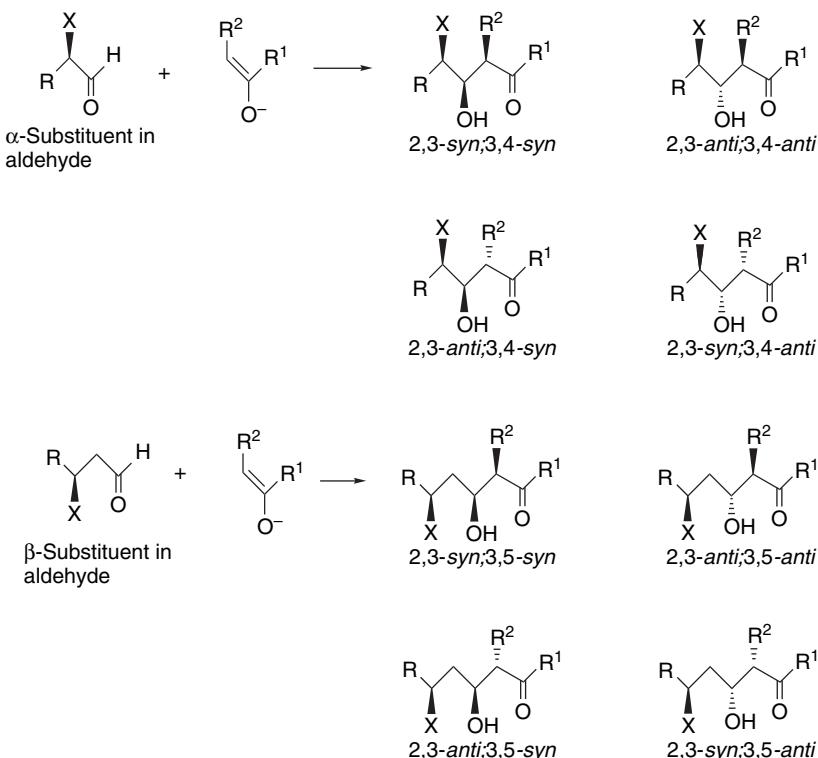
- a. T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974).
- b. T. Yanami, M. Miyashita, and A. Yoshikoshi, *J. Org. Chem.*, **45**, 607 (1980).
- c. T. Mukaiyama and K. Narasaka, *Org. Synth.*, **65**, 6 (1987).
- d. S. Yamago, D. Machii, and E. Nakamura, *J. Org. Chem.*, **56**, 2098 (1991).
- e. C. Gennari, A. Bernardi, S. Cardani, and C. Scolastico, *Tetrahedron Lett.*, **26**, 797 (1985).
- f. S. Kobayashi and I. Hachiya, *J. Org. Chem.*, **59**, 3590 (1994).
- g. T. K. Hollis, N. Robinson, and B. Bosnich, *Tetrahedron Lett.*, **33**, 6423 (1992).
- h. Y. Hong, D. J. Norris, and S. Collins, *J. Org. Chem.*, **58**, 3591 (1993).
- i. M. Oishi, S. Aratake, and H. Yamamoto, *J. Am. Chem. Soc.*, **120**, 8271 (1998).
- j. I. Mori, K. Ishihara, L. A. Flippin, K. Nozaki, H. Yamamoto, P. A. Bartlett, and C. H. Heathcock, *J. Org. Chem.*, **55**, 6107 (1990).
- k. S. Murata, M. Suzuki, and R. Noyori, *Tetrahedron*, **44**, 4259 (1998).
- l. T. Satay, J. Otera, and H. N. Zaki, *J. Am. Chem. Soc.*, **112**, 901 (1990).
- m. T. M. Meulemans, G. A. Stork, B. J. M. Jansen, and A. de Groot, *Tetrahedron Lett.*, **39**, 6565 (1998).
- n. A. S. Kende, S. Johnson, P. Sanfilippo, J. C. Hodges, and L. N. Jungheim, *J. Am. Chem. Soc.*, **108**, 3513 (1986).

Similarly, there will be a degree of selectivity between the two faces of the enolate if it contains a stereocenter.

The stereogenic centers may be integral parts of the reactants, but chiral auxiliaries can also be used to impart facial diastereoselectivity and permit eventual isolation of enantiomerically enriched product. Alternatively, use of chiral Lewis acids as catalysts can also achieve facial selectivity. Although the general principles of control of the stereochemistry of aldol addition reactions have been well developed for simple molecules, the application of the principles to more complex molecules and the

selection of the optimum enolate system requires analyses of the individual cases.⁷⁴ Often, one of the available reactant systems proves to be superior.⁷⁵ Sometimes a remote structural feature strongly influences the stereoselectivity.⁷⁶ The issues that have to be addressed in specific cases include the structure of the reactants, including its configuration and potential sites for chelation; the organization of the TS (cyclic, open, or chelated); and the steric, electronic, and polar factors affecting the facial selectivity.

2.1.5.1. Stereochemical Control by the Aldehyde. A chiral center in an aldehyde can influence the direction of approach by an enolate or other nucleophile. This facial selectivity is in addition to the simple *syn*, *anti* diastereoselectivity so that if either the aldehyde or enolate contains a stereocenter, four stereoisomers are possible. There are four possible chairlike TSs, of which two lead to *syn* product from the *Z*-enolate and two to *anti* product from the *E*-enolate. The two members of each pair differ in the facial approach to the aldehyde and give products of opposite configuration at *both of the newly formed stereocenters*. If the substituted aldehyde is racemic, the enantiomeric products will be formed, making a total of eight stereoisomers possible.

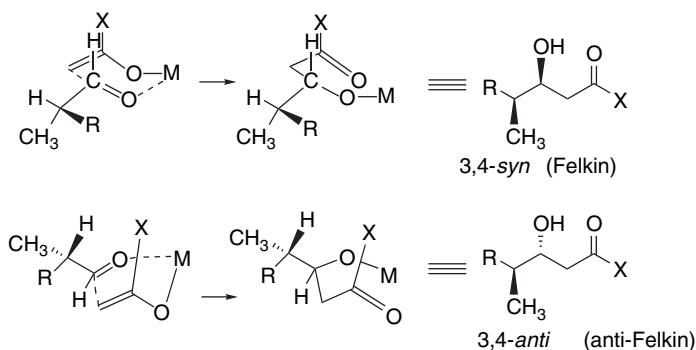


⁷⁴ (a) W. R. Roush, *J. Org. Chem.*, **56**, 4151 (1991); (b) C. Gennari, S. Vieth, A. Comotti, A. Vulpetti, J. M. Goodman, and I. Paterson, *Tetrahedron*, **48**, 4439 (1992); (c) D. A. Evans, M. J. Dart, J. L. Duffy, and M. G. Yang, *J. Am. Chem. Soc.*, **118**, 4322 (1996); (d) A. S. Franklin and I. Paterson, *Contemp. Org. Synth.*, **1**, 317 (1994).

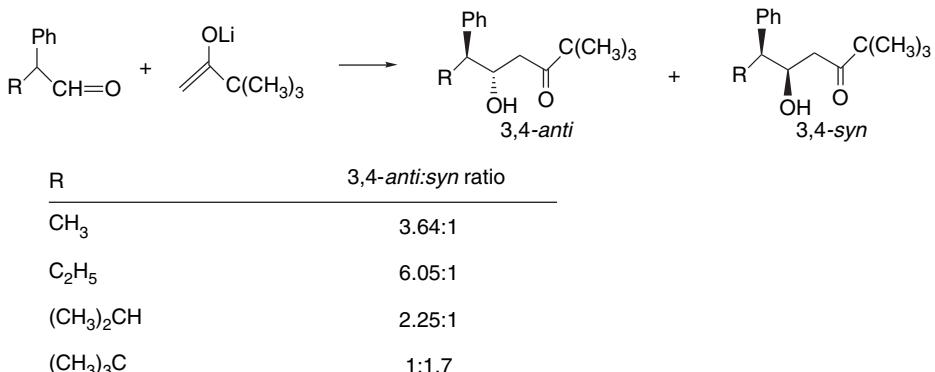
⁷⁵ E. J. Corey, G. A. Reichard, and R. Kania, *Tetrahedron Lett.*, **34**, 6977 (1993).

⁷⁶ A. Balog, C. Harris, K. Savin, X.-G. Zhang, T. C. Chou, and S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.*, **37**, 2675 (1998).

If the substituents are nonpolar, such as an alkyl or aryl group, the control is exerted mainly by steric effects. In particular, for α -substituted aldehydes, the Felkin TS model can be taken as the starting point for analysis, in combination with the cyclic TS. (See Section 2.4.1.3, Part A to review the Felkin model.) The analysis and prediction of the direction of the preferred reaction depends on the same principles as for simple diastereoselectivity and are done by consideration of the attractive and repulsive interactions in the presumed TS. In the Felkin model for nucleophilic addition to carbonyl centers the larger α -substituent is aligned *anti* to the approaching enolate and yields the 3,4-*syn* product. If reaction occurs by an alternative approach, the stereochemistry is reversed, and this is called an anti-Felkin approach.



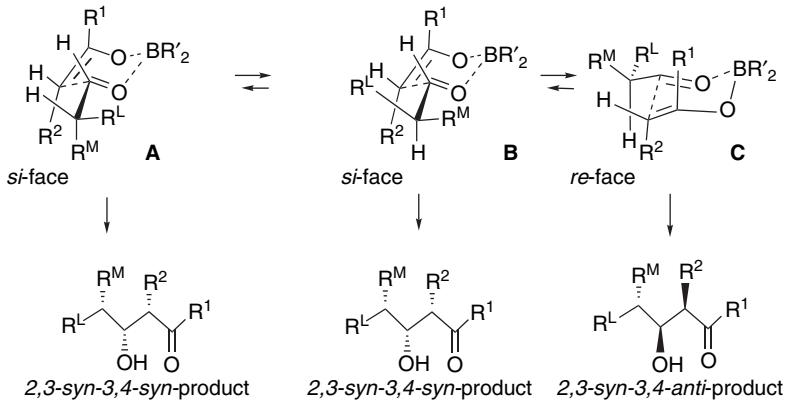
A study of the lithium enolate of pinacolone with several α -phenyl aldehydes gave results generally consistent with the Felkin model. Steric, rather than electronic, effects determine the conformational equilibria.⁷⁷ If the alkyl group is branched, it occupies the “large” position. Thus, the *t*-butyl group occupies the “large” position, not the phenyl.



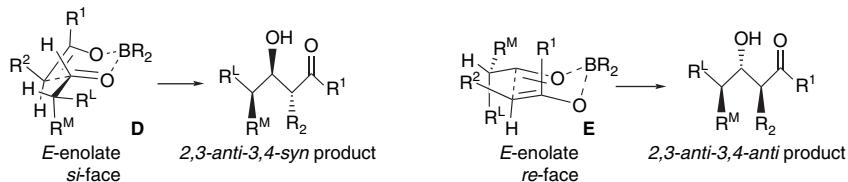
The situation encounters another factor with enolates having a C(2) substituent. The case of steric control has been examined carefully. The stereoselectivity depends on the orientation of the stereocenter relative to the remainder of the TS. The Felkin TS is **A**. TS **B** represents a non-Felkin conformer, but with the same facial approach as **A**. The preferred TS for the Z-enolate is believed to be structure **C**. This TS is preferred to **A** because of the interaction between the R^M group and the R² group of the enolate

⁷⁷ E. P. Lodge and C. H. Heathcock, *J. Am. Chem. Soc.*, **109**, 3353 (1987).

in **A**.⁷⁸ This *double-gauche* interaction is analogous to the 1,3-diaxial relationship in chair cyclohexane. TS **C** results in the anti-Felkin approach. The relative energy of TS **B** and TS **C** depends on the size of R^L, with larger R groups favoring TS **C** because of an increased R²/R^L interaction.

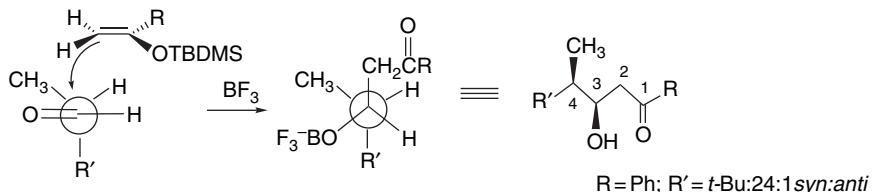


For *E*-enolates the Felkin TS is preferred, the enolate approaches opposite the largest aldehyde substituent, and the preferred product is 2,3-*anti*-3,4-*syn*. TS **D** is preferred for *E*-enolates because of the *gauche* interaction between R² and R^L in TS **E**.



The qualitative application of these models depends on evaluating the magnitude of the steric interactions among the various groups. In this regard, phenyl and vinyl groups seem to be smaller than alkyl groups, perhaps because of their ability to rotate into conformations in which the π dimension minimizes steric repulsions. These concepts have been quantitatively explored using force field models. For nonpolar substituents, steric interactions are the controlling factor in the stereoselectivity, but there is considerable flexibility for adjustment of the TS geometry in response to the specific interactions.⁷⁹

Mukaiyama reactions of α -methyl aldehydes proceed through an open TS and show a preference for the 3,4-*syn* stereoisomer, which is consistent with a Felkin TS.⁸⁰



⁷⁸ W. R. Roush, *J. Org. Chem.*, **56**, 4151 (1991).

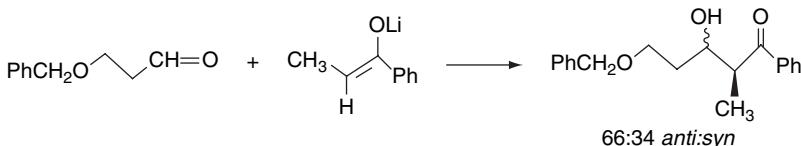
⁷⁹ C. Gennari, S. Vieth, A. Comotti, A. Vulpetti, J. M. Goodman, and I. Paterson, *Tetrahedron*, **48**, 4439 (1992).

⁸⁰ C. H. Heathcock and L. A. Flippin, *J. Am. Chem. Soc.*, **105**, 1667 (1983); D. A. Evans and J. R. Gage, *Tetrahedron Lett.*, **31**, 6129 (1990).

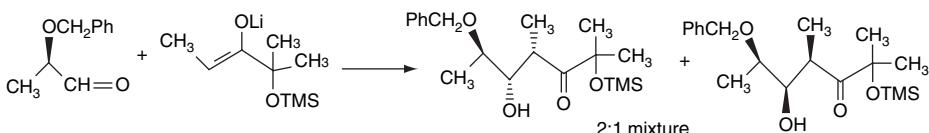
The stereoselectivity of aldol addition is also affected by chelation.⁸¹ α - and β -Alkoxy aldehydes can react through chelated structures with Li^+ and other Lewis acids that can accommodate two donor groups.



The potential for coordination depends on the oxy substituents.⁸² Alkoxy substituents are usually chelated, whereas highly hindered silyloxy groups usually do not chelate. Trimethylsiloxy groups are intermediate in chelating ability. The extent of chelation also depends on the Lewis acid. Studies with α -alkoxy and β -alkoxy aldehydes with lithium enolates found only modest diastereoselectivity.⁸³

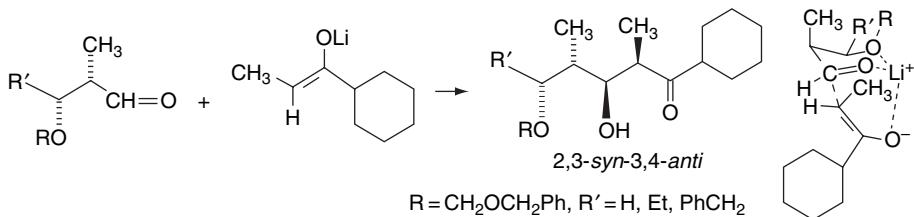


Ref. 84



Ref. 83b

Several α -methyl- β -alkoxyaldehydes show a preference for 2,3-*syn*-3,4-*anti* products on reaction with *Z*-enolates. A chelated TS can account for the observed stereochemistry.⁸⁵ The chelated aldehyde is most easily approached from the face opposite the methyl and R' substituents.



Dialkylboron enolates cannot accommodate an additional aldehyde ligand group and chelated TSs are not expected. When BF_3 is used as the Lewis acid, chelation is

⁸¹ M. T. Reetz, *Angew. Chem. Int. Ed. Engl.*, **23**, 556 (1984); R. Mahrwald, *Chem. Rev.*, **99**, 105 (1999).

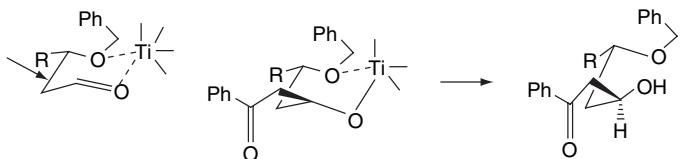
⁸² X. Chen, E. R. Hortelano, E. L. Eliel, and S. V. Frye, *J. Am. Chem. Soc.*, **114**, 1778 (1992).

⁸³ (a) C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, and D. Van Derveer, *J. Org. Chem.*, **45**, 3846 (1980); (b) C. H. Heathcock, M. C. Pirrung, J. Lampe, C. T. Buse, and S. D. Young, *J. Org. Chem.*, **46**, 2290 (1981).

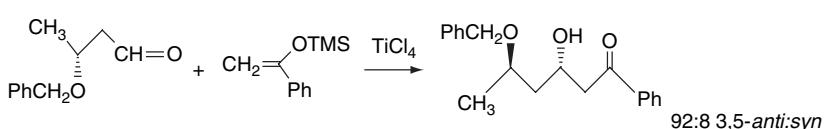
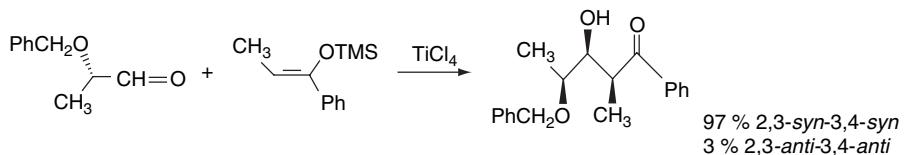
⁸⁴ M. T. Reetz, K. Kesseler, and A. Jung, *Tetrahedron*, **40**, 4327 (1984).

⁸⁵ S. Masamune, J. W. Ellingboe, and W. Choy, *J. Am. Chem. Soc.*, **104**, 5526 (1982).

also precluded in Mukaiyama reactions. Chelation control does occur in the Mukaiyama reaction using other Lewis acids. Both α - and β -alkoxy aldehydes give chelation-controlled products with SnCl_4 and TiCl_4 , but not with BF_3 .⁸⁶ If there is an additional substituent on the aldehyde, the chelate establishes a facial preference for the approach of the nucleophile.⁸⁷



In each instance, the silyl enol ether approaches *anti* to the methyl substituent on the chelate. This results in a 3,4-*syn* relationship between the hydroxy and alkoxy groups for α -alkoxy aldehydes and a 3,5-*anti* relationship for β -alkoxy aldehydes with the main chain in the extended conformation.



A crystal structure is available for the SnCl_4 complex of 2-benzyloxy-3-pentanone.⁸⁹ The steric shielding by the methyl group with respect to the C=O is evident in this structure (Figure 2.1). NMR studies indicate that the reaction involves

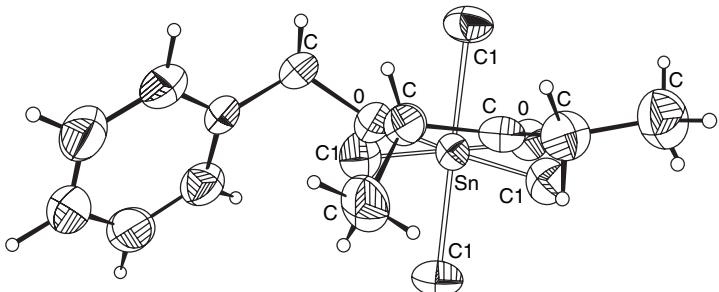
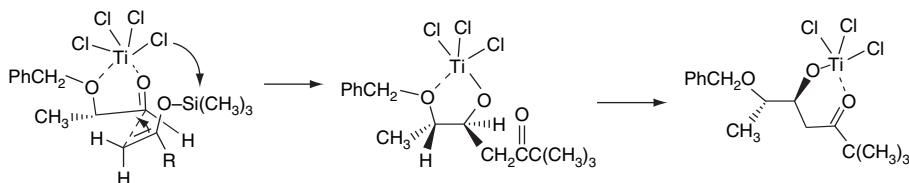


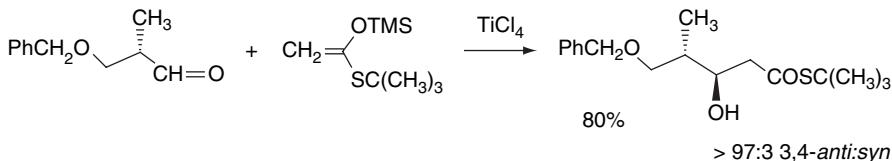
Fig. 2.1. Structure of the SnCl_4 complex of 2-benzyloxy-3-pentanone. Reproduced from *Acc. Chem. Res.*, **26**, 462 (1993) by permission of the American Chemical Society.

- ⁸⁶ C. H. Heathcock, S. K. Davidsen, K. T. Hug, and L. A. Flippin, *J. Org. Chem.*, **51**, 3027 (1986).
- ⁸⁷ M. T. Reetz and A. Jung, *J. Am. Chem. Soc.*, **105**, 4833 (1983); C. H. Heathcock, S. Kiyooka, and T. A. Blumenkopf, *J. Org. Chem.*, **51**, 4214 (1984).
- ⁸⁸ M. T. Reetz, K. Kesseler, S. Schmidtberger, B. Wenderoth, and P. Steinbach, *Angew. Chem. Int. Ed. Engl.*, **22**, 989 (1983).
- ⁸⁹ M. T. Reetz, K. Harms, and W. Reif, *Tetrahedron Lett.*, **29**, 5881 (1988).

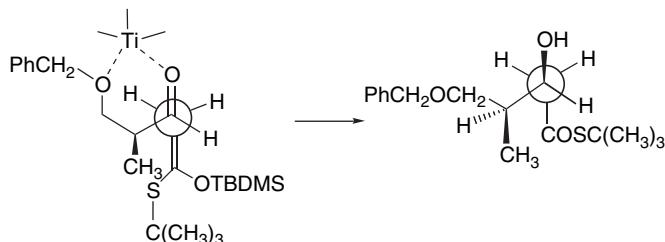
formation of trimethylsilyl chloride from the chelated intermediate. This step is followed by conversion to the more stable aldol chelate.⁹⁰



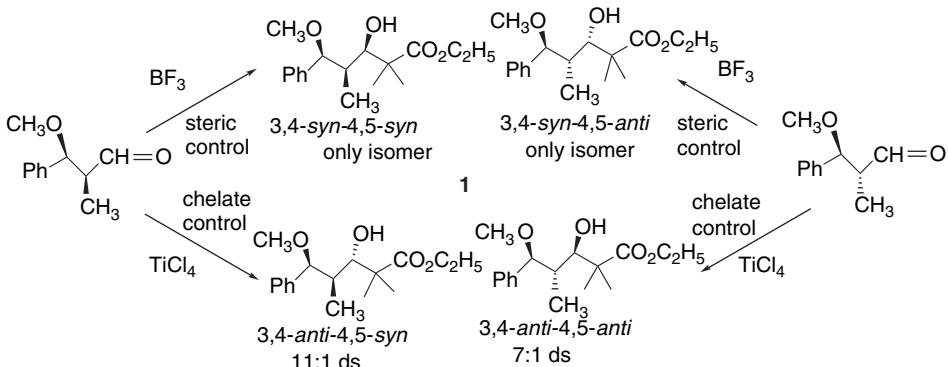
With α - and β -benzyloxyaldehydes, the *t*-butylthio ketene acetals also gave chelation-controlled addition.⁹¹



This reaction occurs through a TS in which the aldehyde is chelated, but the silyl thioketene acetal is not coordinated to the Ti (open TS).



The choice of Lewis acid can determine if a chelated or open TS is involved. For example, all four possible stereoisomers of **1** were obtained by variation of the Lewis acid and the stereochemistry in the reactant.⁹² The BF_3 -catalyzed reactions occur through an open TS, whereas the TiCl_4 reactions are chelation controlled.

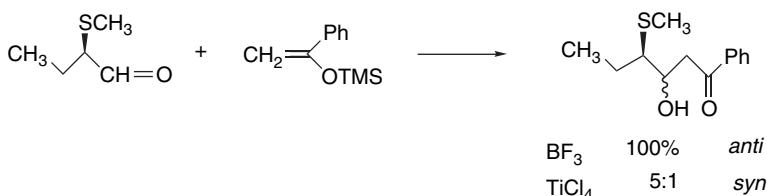


⁹⁰ M. T. Reetz, B. Raguse, C. F. Marth, H. M. Hügel, T. Bach, and D. N. A. Fox, *Tetrahedron*, **48**, 5731 (1992); M. T. Reetz, *Acc. Chem. Res.*, **26**, 462 (1993).

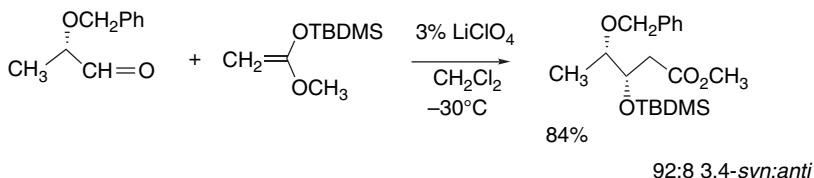
⁹¹ C. Gennari and P. G. Cozzi, *Tetrahedron*, **44**, 5965 (1988).

⁹² S. Kiyooka, M. Shiinoki, K. Nakata, and F. Goto, *Tetrahedron Lett.*, **43**, 5377 (2002).

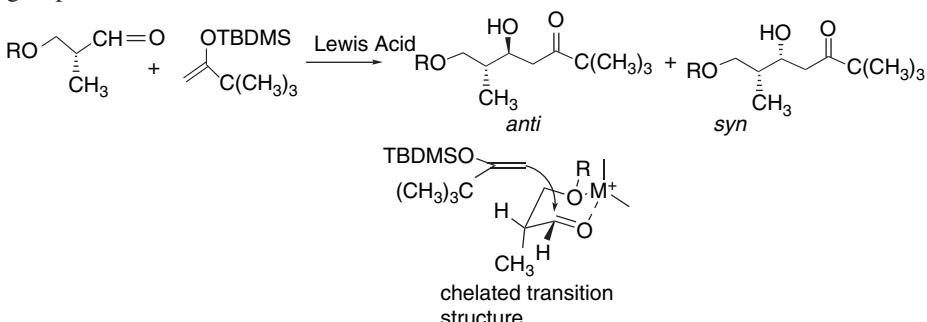
In the reaction of α -methylthiobutanal, where the methylthio group has the potential for chelation, BF_3 gave 100% of *anti* product, whereas TiCl_4 gave a 5:1 *syn:anti* ratio.⁹³



Chelation-controlled product is formed from reaction of α -benzyloxypropanal and the TBDMS silyl ketene acetal derived from ethyl acetate using 3% LiClO_4 as catalyst.⁹⁴



Recently, $(\text{CH}_3)_2\text{AlCl}$ and CH_3AlCl_2 have been shown to have excellent chelation capacity. These catalysts effect chelation control with both 3-benzyloxy- and 3-(*t*-butyldimethylsilyloxy)-2-methylpropanal, whereas BF_3 leads to mainly *syn* product.⁹⁵ The reaction is believed to occur through a cationic complex, with the chloride ion associated with a second aluminum as $[(\text{CH}_3)_2\text{AlCl}_2]^-$. Interestingly, although TiCl_4 induced chelation control with the benzyloxy group, it did not do so with the TBDMS group.



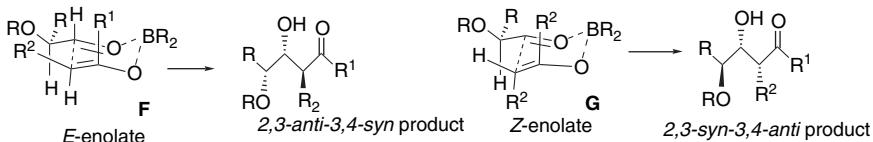
Lewis acid	$R = \text{CH}_2\text{Ph}$	$R = \text{OTBDMS}$
	<i>anti:syn</i>	<i>anti:syn</i>
BF_3	26:74	9:91
SnCl_4	50:50	7:93
TiCl_4	97:3	7:93
$(\text{CH}_3)_2\text{AlCl}$	90:10	97:3
CH_3AlCl_2	78:22	77:23

⁹³ R. Annuziata, M. Cinquini, F. Cozzi, P. G. Cozzi, and E. Consolandì, *J. Org. Chem.*, **57**, 456 (1992).

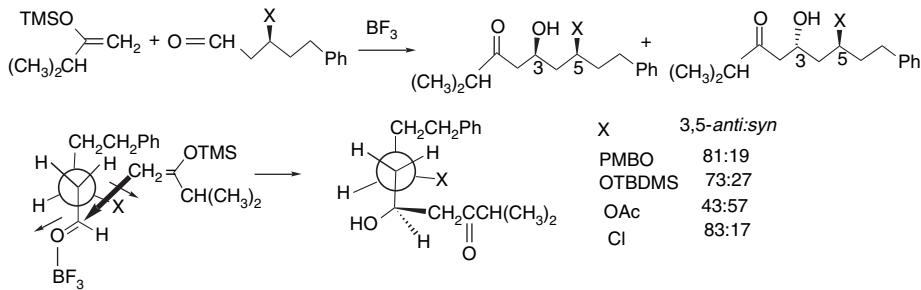
⁹⁴ M. T. Reetz and D. N. A. Fox, *Tetrahedron Lett.*, **34**, 1119 (1993).

⁹⁵ D. A. Evans, B. D. Allison, and M. G. Yang, *Tetrahedron Lett.*, **40**, 4457 (1999); D. A. Evans, B. D. Allison, M. G. Yang, and C. E. Masse, *J. Am. Chem. Soc.*, **123**, 10840 (2001).

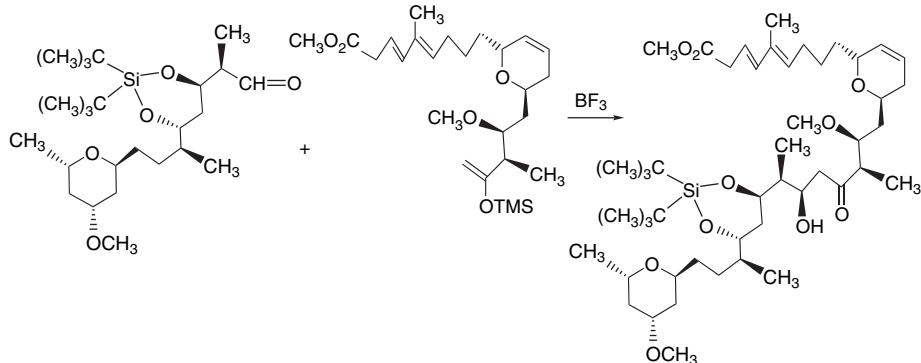
Heteroatom substituents also introduce polar effects. In the case of α -alkoxy aldehydes the preferred TS appears to be **F** and **G** for the *E*- and *Z*-enolates, respectively. These differ from the normal Felkin TS for nucleophilic addition. The reactant conformation is believed to be determined by minimization of dipolar repulsion between the alkoxy substituent and the carbonyl group.⁹⁶ This model predicts higher 3,4-*anti* ratios for *Z*-enolates, and this is observed.



Dipole-dipole interactions may also be important in determining the stereoselectivity of Mukaiyama aldol reactions proceeding through an open TS. A BF_3 -catalyzed reaction was found to be 3,5-*anti* selective for several β -substituted 5-phenylpentanals. This result can be rationalized by a TS that avoids an unfavorable alignment of the C=O and C–X dipoles.⁹⁷



The same stereoselectivity was observed with a more complex pair of reactants in which the β -substituent is a cyclic siloxy oxygen.⁹⁸

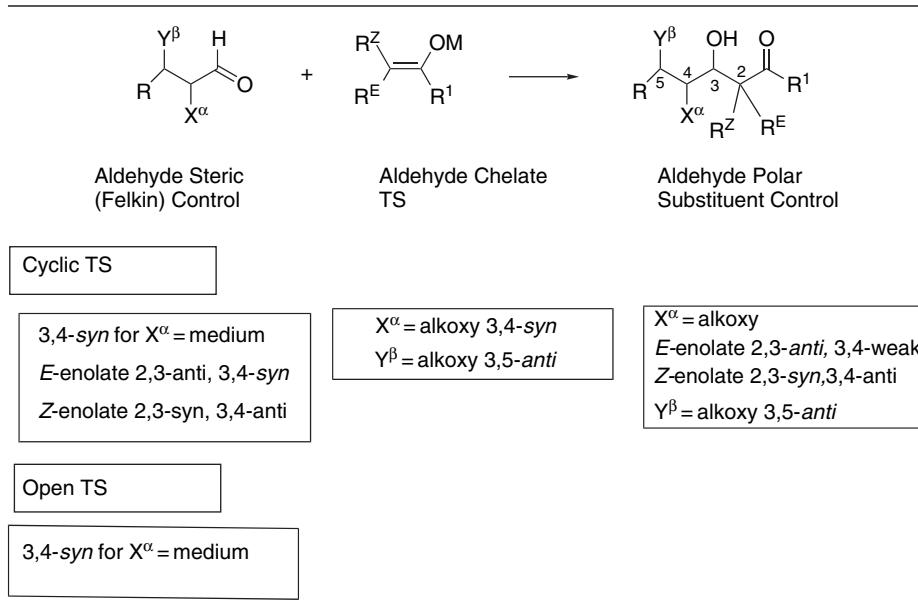


Thus we see that steric effects, chelation, and the polar effects of α - and β -substituents can influence the facial selectivity in aldol additions to aldehydes. These relationships provide a starting point for prediction and analysis of stereoselectivity.

⁹⁶ D. A. Evans, S. J. Siska, and V. J. Cee, *Angew. Chem. Int. Ed. Engl.*, **42**, 1761 (2003).

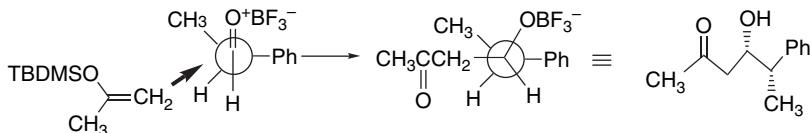
⁹⁷ D. A. Evans, M. J. Dart, J. L. Duffy, and M. G. Yang, *J. Am. Chem. Soc.*, **118**, 4322 (1996).

⁹⁸ I. Paterson, R. A. Ward, J. D. Smith, J. G. Cumming, and K.-S. Yeung, *Tetrahedron*, **51**, 9437 (1995).

Table 2.3. Summary of Stereoselectivity for Aldol Addition Reactions

based on structural effects in the reactant aldehyde. These general principles have been applied to the synthesis of a number of more complex molecules. Table 2.3 summarizes the relationships discussed in this section.

Scheme 2.3 shows reactions of several substituted aldehydes of varying complexity that illustrate aldehyde facial diastereoselectivity in the aldol and Mukaiyama reactions. The stereoselectivity of the new bond formation depends on the effect that reactant substituents have on the detailed structure of the TS. The 3,4-*syn* stereoselectivity of Entry 1 derives from a Felkin-type acyclic TS.

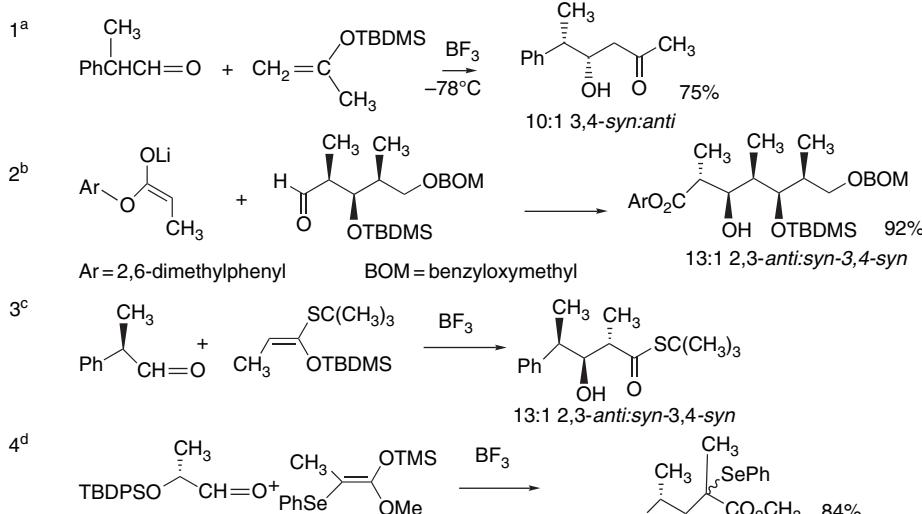


Entry 2 shows an *E*-enolate of a hindered ester reacting with an aldehyde having both an α -methyl and β -methoxy group. The reaction shows a 13:1 preference for the Felkin approach product (3,4-*syn*) and is controlled by the steric effect of the α -methyl substituent. Another example of steric control with an ester enolate is found in a step in the synthesis of (+)-discodermolide.⁹⁹ The *E*-enolate of a hindered aryl ester was generated using LiTMP and LiBr. Reaction through a Felkin TS resulted in *syn* diastereoselectivity for the hydroxy and ester groups at the new bond.

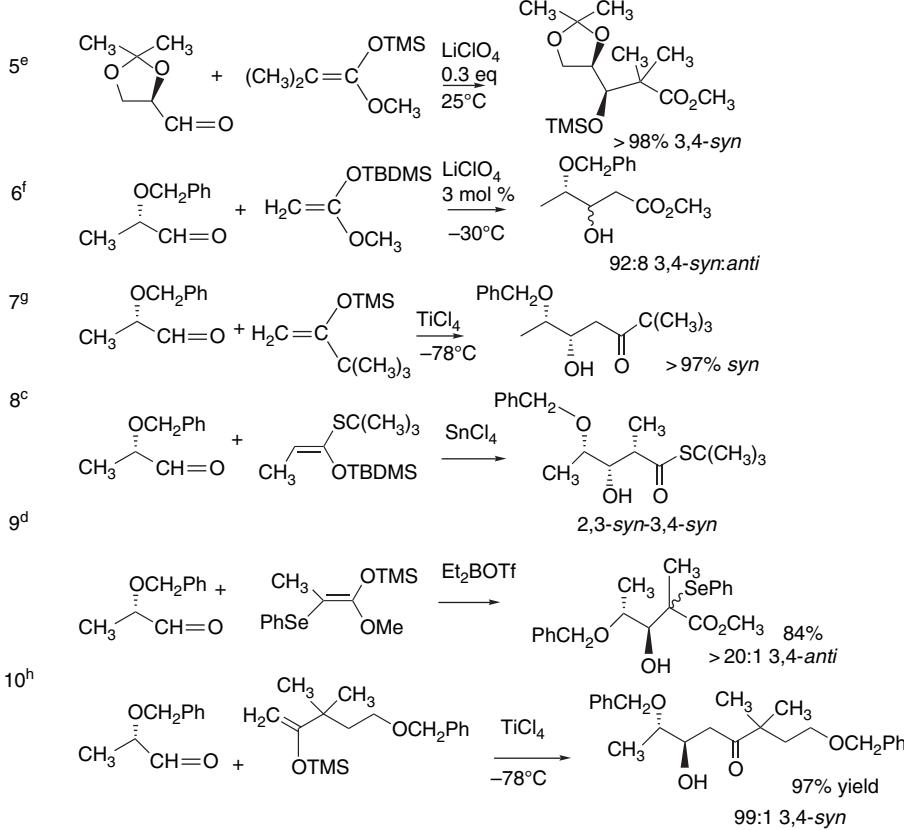
⁹⁹. I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, and N. Sereinig, *J. Am. Chem. Soc.*, **123**, 9535 (2001).

Scheme 2.3. Examples of Aldol and Mukaiyama Reactions with Stereoselectivity Based on Aldehyde Structure

A. Steric Control

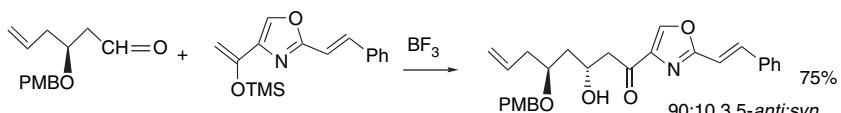
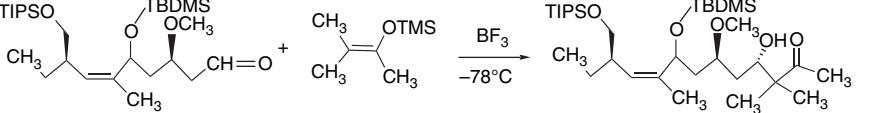
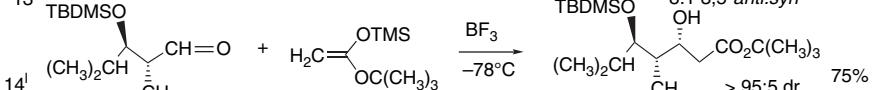
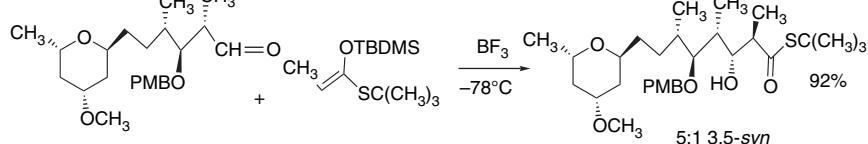
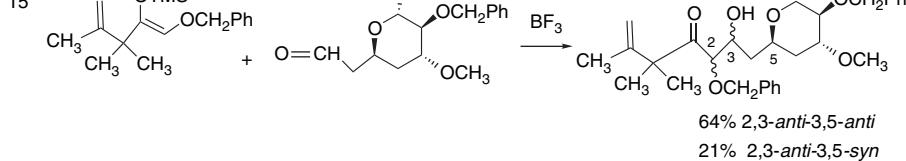


B. Chelation Control



(Continued)

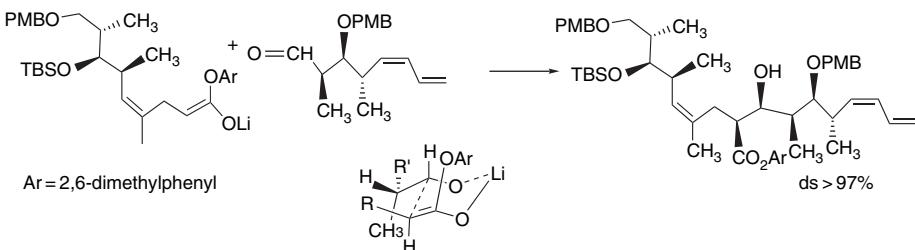
Scheme 2.3. (Continued)

C. Polar Control
11ⁱ12^j13^k14^l15^m

SECTION 2.1

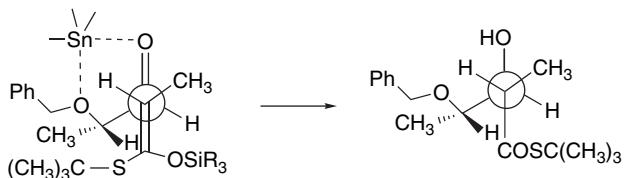
Aldol Addition and Condensation Reactions

- a. C. H. Heathcock and L. A. Flippin, *J. Am. Chem. Soc.*, **105**, 1667 (1983).
 b. I. Paterson, *Tetrahedron Lett.*, **24**, 1311 (1983).
 c. C. Gennari, M. G. Beretta, A. Bernardi, G. Moro, C. Scolastico, and R. Todeschini, *Tetrahedron*, **42**, 893 (1986).
 d. Y. Guindon, M. Prevost, P. Mochirian, and B. Guerin, *Org. Lett.*, **4**, 1019 (2002).
 e. J. Ipaktschi and A. Heydari, *Chem. Ber.*, **126**, 1905 (1993).
 f. M. T. Reetz and D. N. A. Fox, *Tetrahedron Lett.*, **34**, 1119 (1993).
 g. M. T. Reetz, B. Raguse, C. F. Marth, H. M. Hügel, T. Bach, and D. N. A. Fox, *Tetrahedron*, **48**, 5731 (1992).
 h. C. Q. Wei, X. R. Jiang, and Y. Ding, *Tetrahedron*, **54**, 12623 (1998).
 i. F. Yokokawa, T. Asano, and T. Shioiri, *Tetrahedron*, **57**, 6311 (2001).
 j. R. E. Taylor and M. Jin, *Org. Lett.*, **5**, 4959 (2003).
 k. L. C. Dias, L. J. Steil and V. de A. Vasconcelos, *Tetrahedron: Asymmetry*, **15**, 147 (2004).
 l. G. E. Keck and G. D. Lundquist, *J. Org. Chem.*, **64**, 4482 (1999).
 m. D. W. Engers, M. J. Bassindale, and B. L. Pagenkopf, *Org. Lett.*, **6**, 663 (2004).

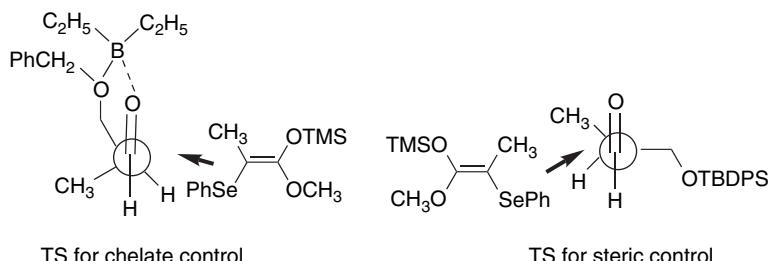


Entries 3 and 8 show additions of a silyl thioketene acetal to α -substituted aldehydes. Entry 3 is under steric control and gives an 13:1 2,3-anti-syn ratio. The reaction proceeds through an open TS with respect to the nucleophile and both the

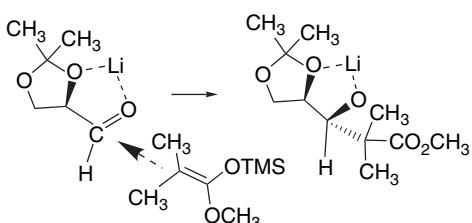
E- and *Z*-silyl thioketene acetals give the 2,3-*anti* product. The 3,4-*syn* ratio is 50:1, and is consistent with the Felkin model. When this nucleophile reacts with 2-benzyloxypropanal (Entry 8), a chelation product results. The facial selectivity with respect to the methyl group is now reversed. Both isomers of the silyl thioketene acetal give mainly the 2,3-*syn*-3,4-*syn* product. The ratio is higher than 30:1 for the *Z*-enolate but only 3:1 for the *E*-enolate.



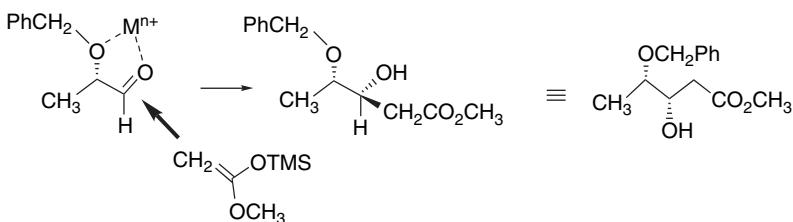
Entries 4 and 9 are closely related structures that illustrate the ability to control stereochemistry by choice of the Lewis acid. In Entry 4, the Lewis acid is BF_3 and the β -oxygen is protected as a *t*-butyldiphenylsilyl derivative. This leads to reaction through an open TS, and the reaction is under steric control, resulting in the 3,4-*syn* product. In Entry 9, the enolate is formed using di-*n*-butylboron triflate (1.2 equiv.), which permits the aldehyde to form a chelate. The chelated aldehyde then reacts via an open TS with respect to the silyl ketene acetal, and the 3,4-*anti* isomer dominates by more than 20:1.



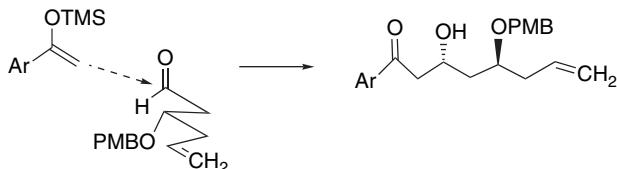
Entry 5 is an example of LiClO_4 catalysis and results in very high stereoselectivity, consistent with a chelated structure for the aldehyde.



Entries 6 and 7 are examples of reactions of α -benzyloxypropanal. In both cases, the product stereochemistry is consistent with a chelated TS.

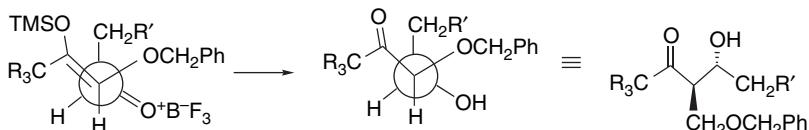


Entry 10 is an example of the application of chelate-controlled stereoselectivity using TiCl_4 . Entry 11 also involves stereodirection by a β -(*p*-methoxybenzyloxy) substituent. In this case, the BF_3 -catalyzed reaction should proceed through an open TS and the β -polar effect described on p. 96 prevails, resulting in the *anti*-3,5-isomer.

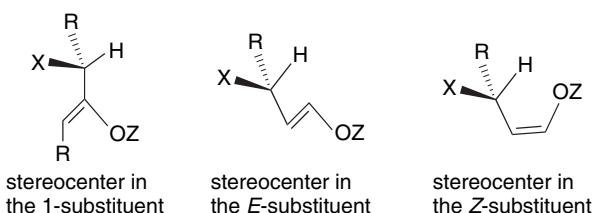


The β -methoxy group in Entry 12 has a similar effect. The aldehydes in Entries 13 and 14 have α -methyl- β -oxy substitution and the reactions in these cases are with a silyl ketene acetal and silyl thioketene acetal, respectively, resulting in a 3,4-*syn* relationship between the newly formed hydroxy and α -methyl substituents.

Entry 15 involves a benzyloxy group at C(2) and is consistent with control by a β -oxy substituent, which in this instance is part of a ring. The *anti* relationship between the C(2) and the C(3) groups results from steric control by the branched substituent in the silyl enol ether. The stereogenic center in the ring has only a modest effect.

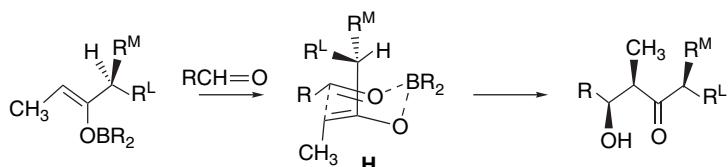


2.1.5.2. Stereochemical Control by the Enolate or Enolate Equivalent. The facial selectivity of aldol addition reactions can also be controlled by stereogenic centers in the nucleophile. A stereocenter can be located at any of the adjacent positions on an enolate or enolate equivalent. The configuration of the substituent can influence the direction of approach of the aldehyde.

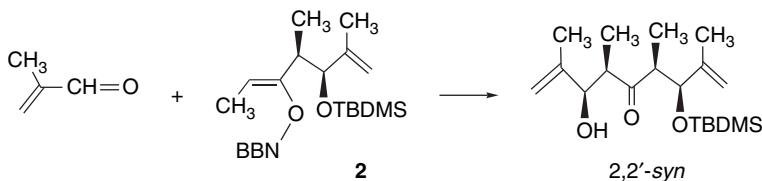


When there is a nonchelating stereocenter at the 1-position of the enolate, the two new stereocenters usually adopt a 2,2'-*syn* relationship to the M substituent. This

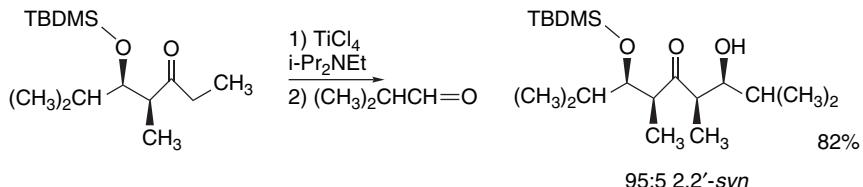
result is consistent with a cyclic TS having a conformation of the chiral group with the hydrogen pointed toward the boron and the approach to the aldehyde from the smaller of the other two substituents as in TS **H**.¹⁰⁰



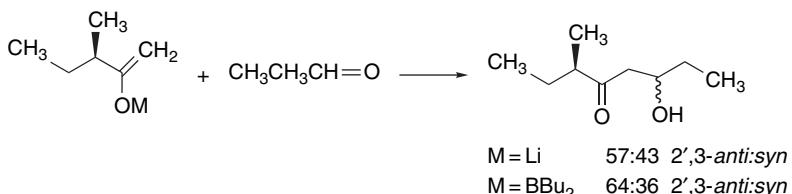
This stereoselectivity, for example, was noted with enolate **2**.¹⁰¹



The same effects are operative with titanium enolates.^{100a}



Little steric differentiation is observed with either the lithium or boron enolates of 2-methyl-2-pentanone.¹⁰²



α -Oxygenated enolates show a strong dependency on the nature of the oxygenated substituent. TBDMS derivatives are highly selective for 2, 2'-*syn*-2,3-*syn* product, but benzyloxy substituents are much less selective. This is attributed to involvement of two competing chelated TSs in the case of benzyloxy, but of a nonchelated TS for the siloxy substituent.¹⁰³ The contrast between the oxy substituents is consistent with the tendency for alkoxy groups to be better donors toward Ti(IV) than siloxy groups.

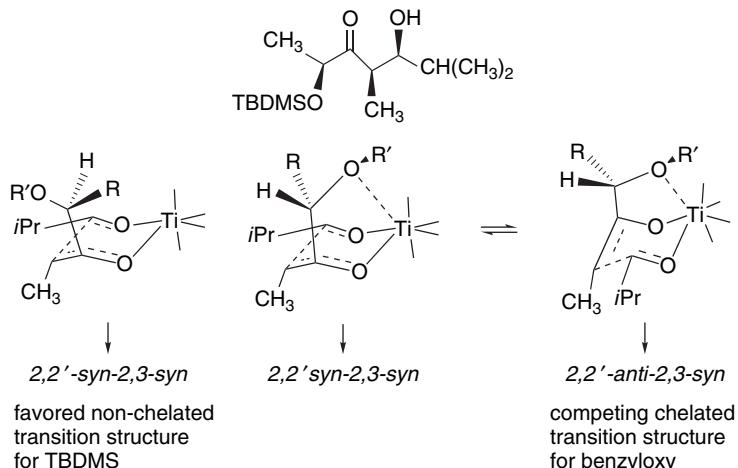
^{100.} (a) D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991); (b) A. Bernardi, A. M. Capelli, A. Comotti, C. Gennari, M. Gardner, J. M. Goodman, and I. Paterson, *Tetrahedron*, **47**, 3471 (1991).

^{101.} I. Paterson and A. N. Hulme, *J. Org. Chem.*, **60**, 3288 (1995).

^{102.} D. Seebach, V. Ehrig, and M. Teschner, *Liebigs Ann. Chem.*, 1357 (1976); D. A. Evans, J. V. Nelson, E. Vogel, and T. R. Taber, *J. Am. Chem. Soc.*, **103**, 3099 (1981).

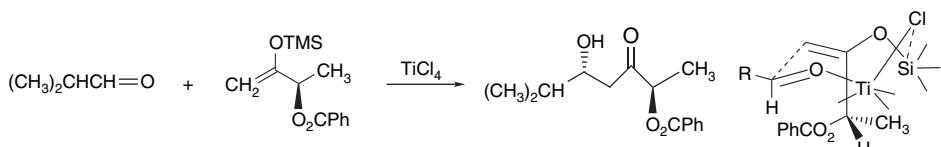
^{103.} S. Figueras, R. Martin, P. Romea, F. Urpi, and J. Vilarrasa, *Tetrahedron Lett.*, **38**, 1637 (1997).

Oxy substituent	R	2, 2'- <i>syn</i> -2,3- <i>syn</i> :2,2'- <i>anti</i> -2,3- <i>syn</i>
TBDMS	CH ₃	30:1
TBDMS	PhCH ₂	35:1
TBDMS	(CH ₃) ₂ CH	> 95:1
PhCH ₂	CH ₃	5:1
PhCH ₂	PhCH ₂	4:1
PhCH ₂	(CH ₃) ₂ CH	1:1



The stereoselectivity of this reaction also depends on the titanium reagent used to prepare the enolate.¹⁰⁴ When the substituent is benzyloxy, the 2, 2'-*anti*-2,3-*syn* product is preferred when $(i\text{-PrO})\text{TiCl}_3$ is used as the reagent, as would be expected for a chelated TS. However, when TiCl_4 is used, the 2, 2'-*syn*-2,3-*syn* product is formed. A detailed explanation for this observation has not been established, but it is expected that the benzyloxy derivative would still react through a chelated TS. The reversal on use of TiCl_4 indicates that the identity of the titanium ligands is also an important factor.

High facial selectivity attributable to chelation was observed with the TMS silyl ethers of 3-acyloxy-2-butanone.¹⁰⁵

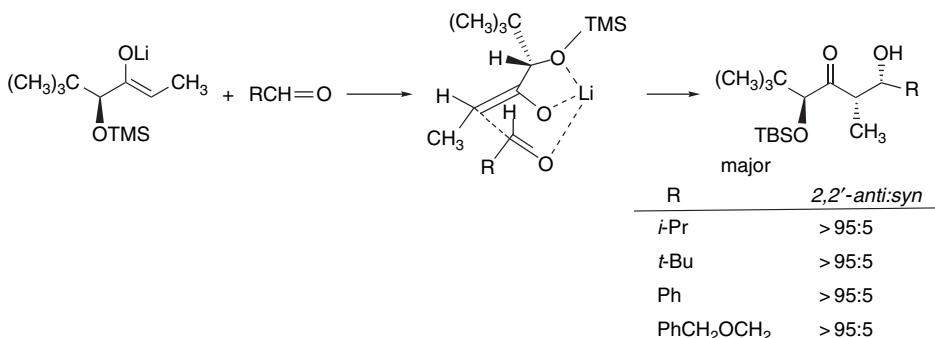


Several enolates of 4,4-dimethyl-3-(trimethylsiloxy)-2-pentanone have been investigated.¹⁰⁶ The lithium enolate reacts through a chelated TS with high 2,2'-*anti* stereoselectivity, based on the steric differentiation by the *t*-butyl group.

¹⁰⁴ J. G. Solsona, P. Romea, F. Urpi, and J. Villarrasa, *Org. Lett.*, **5**, 519 (2003).

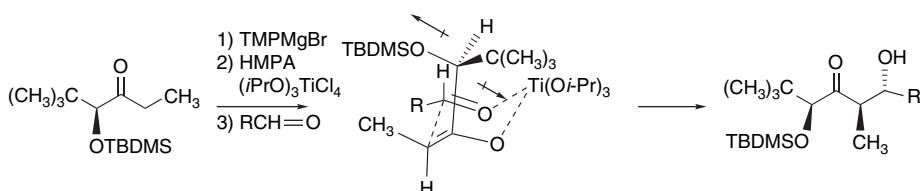
¹⁰⁵ B. M. Trost and H. Urabe, *J. Org. Chem.*, **55**, 3982 (1990).

¹⁰⁶ C. H. Heathcock and S. Arseniyadis, *Tetrahedron Lett.*, **26**, 6009 (1985) and Erratum *Tetrahedron Lett.*, **27**, 770 (1986); N. A. Van Draanen, S. Arseniyadis, M. T. Crimmins, and C. H. Heathcock, *J. Org. Chem.*, **56**, 2499 (1991).

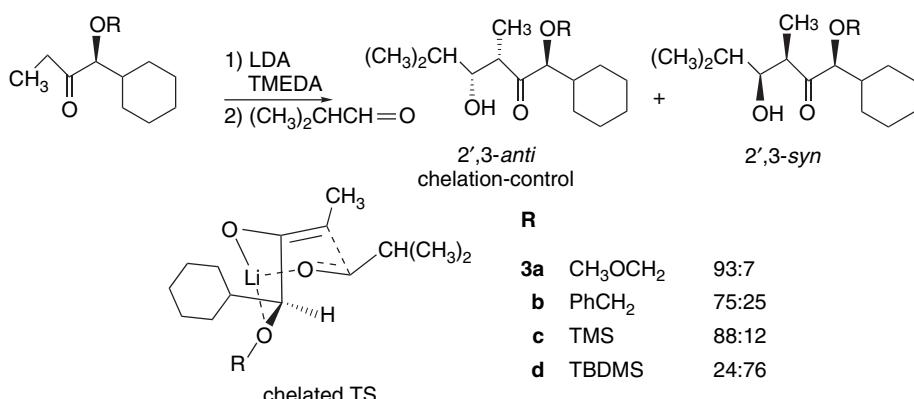


The corresponding di-*n*-butylboron enolate gives the 2,2'-*syn* adduct. The nonchelating boron is thought to react through a TS in which the conformation of the substituent is controlled by a dipolar effect.

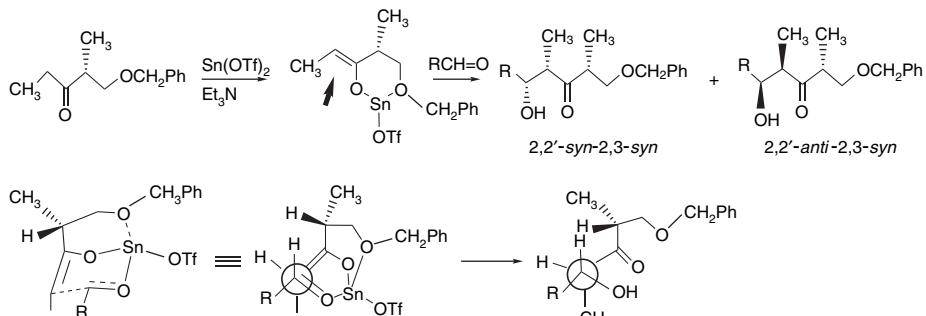
The *E*-titanium enolate was prepared by deprotonation with TMP-MgBr, followed by reaction with $(i\text{-PrO})_3\text{TiCl}$ in the presence of HMPA. The TS for addition is also dominated by a polar effect and gives and 2,2'-*anti* product.



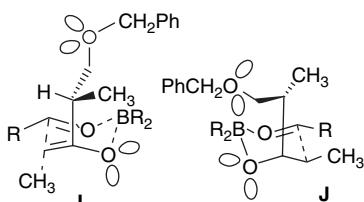
An indication of the relative effectiveness of oxygen substituent in promoting chelation of lithium enolates is found in the enolates **3a-d**. The order of preference for the chelation-controlled product is $\text{CH}_3\text{OCH}_2\text{O} > \text{TMSO} > \text{PhCH}_2\text{O} > \text{TBDMsO}$, with the nonchelation product favored for TBDMsO.¹⁰⁷



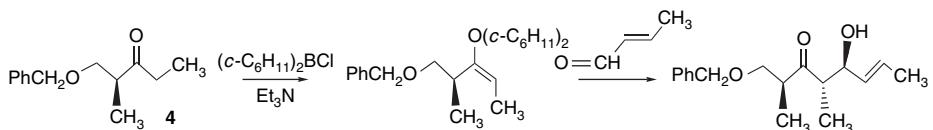
¹⁰⁷ C. Siegel and E. R. Thornton, *Tetrahedron Lett.*, **27**, 457 (1986); A Choudhury and E. R. Thornton, *Tetrahedron Lett.*, **34**, 2221 (1993).



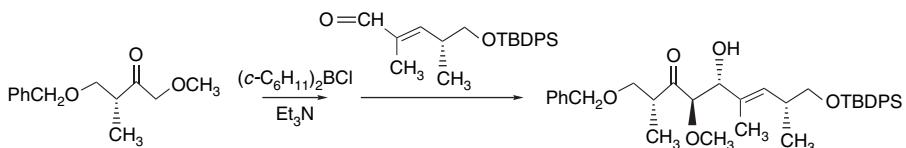
Polar effects appear to be important for 3'-alkoxy substituents in enolates. 3-Benzyl groups enhance the facial selectivity of *E*-boron enolates, and this is attributed to a TS **I** in which the benzyloxy group faces toward the approaching aldehyde. This structure is thought to be preferable to an alternate conformation **J**, which may be destabilized by electron pair repulsions between the benzyloxy oxygen and the enolate oxygen.¹⁰⁹



This effect is seen in the case of ketone **4**, where the stereoselectivity of the benzyloxy derivative is much higher than the compound lacking the benzyloxy group.¹¹⁰



The same β -alkoxy effect appears to be operative in a 2'-methoxy substituted system.¹¹¹



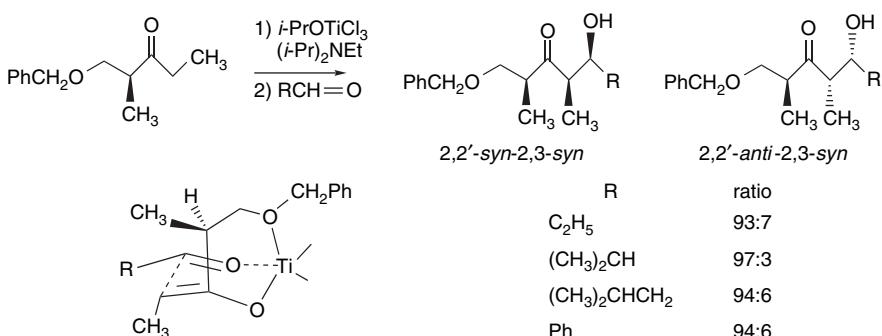
^{108.} I. Paterson and R. D. Tillyer, *Tetrahedron Lett.*, **33**, 4233 (1992).

^{109.} A. Bernardi, C. Gennari, J. M. Goodman, and I. Paterson, *Tetrahedron: Asymmetry*, **6**, 2613 (1995).

^{110.} I. Paterson, J. M. Goodman, and M. Isaka, *Tetrahedron Lett.*, **30**, 7121 (1989).

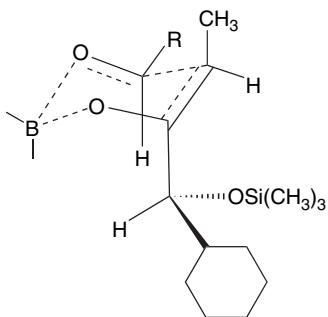
^{111.} I. Paterson and R. D. Tillyer, *J. Org. Chem.*, **58**, 4182 (1993).

A 3'-benzyloxy ketone gives preferential 2,2'-*syn* stereochemistry through a chelated TS for several titanium enolates. The best results were obtained using isopropoxytitanium trichloride.¹¹² The corresponding *E*-boron enolate gives the 2,2'-*anti*-2,3-*anti* isomer as the main product through a nonchelated TS.¹¹⁰

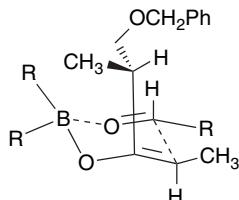


In summary, the same factors that operate in the electrophile, namely steric, chelation, and polar effects, govern facial selectivity for enolates. The choice of the Lewis acid can determine if the enolate reacts via a chelate. The final outcome depends upon the relative importance of these factors within the particular TS.

Scheme 2.4 provides some specific examples of facial selectivity of enolates. Entry 1 is a case of steric control with Felkin-like TS with approach *anti* to the cyclohexyl group.



Entry 2 is an example of the polar β -oxy directing effect. Entries 3 and 4 involve formation of *E*-enolates using dicyclohexylboron chloride. The stereoselectivity is consistent with a cyclic TS in which a polar effect orients the benzyloxy group away from the enolate oxygen.

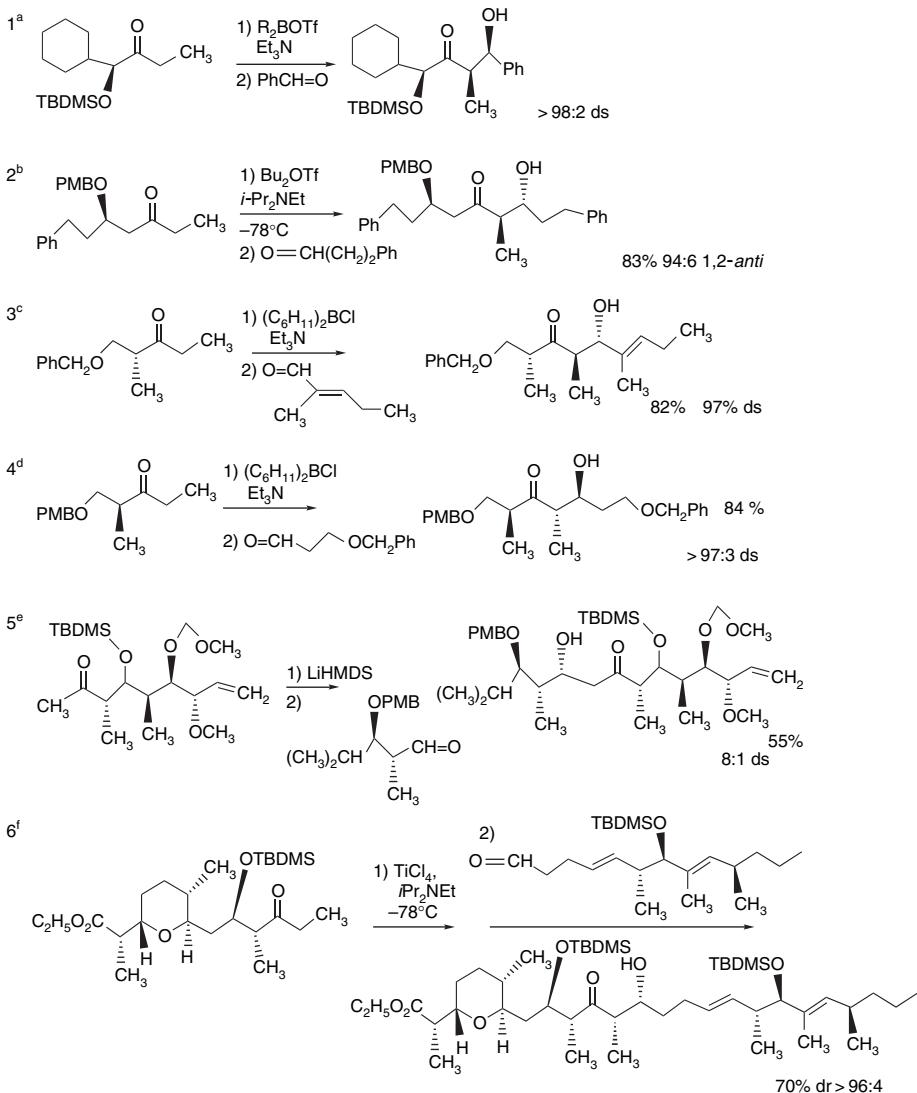


¹¹². J. G. Solsona, J. Nebot, P. Romea, and F. Urpi, *J. Org. Chem.*, **70**, 6533 (2005).

Scheme 2.4. Examples of Facial Selectivity in Aldol and Mukaiyama Reactions Based on Enolate Structure

SECTION 2.1

Aldol Addition and Condensation Reactions



a. D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991).

b. D. A. Evans, P. J. Coleman, and B. Cote, *J. Org. Chem.*, **62**, 788 (1997).

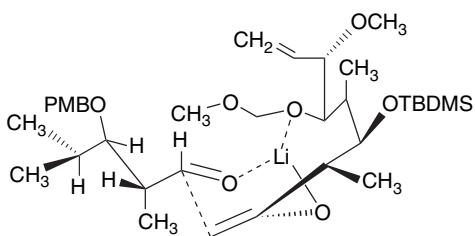
c. I. Paterson and M. V. Perkins, *Tetrahedron*, **52**, 1811 (1996).

d. I. Paterson and I. Lyothier, *J. Org. Chem.*, **70**, 5454 (2005).

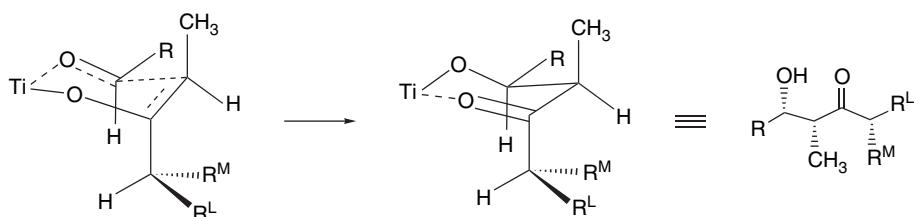
e. W. R. Roush, T. D. Bannister, M. D. Wendt, J. A. Jablonski, and K. A. Scheidt, *J. Org. Chem.*, **67**, 4275 (2002).

f. M. Defosseux, N. Blanchard, C. Meyer, and J. Cossy, *J. Org. Chem.*, **69**, 4626 (2004).

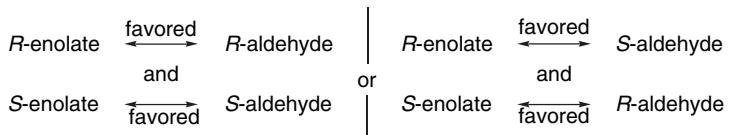
Entry 5, where the same stereochemical issues are involved was used in the synthesis of (+)-discodermolide. (See Section 13.5.6 for a more detailed discussion of this synthesis.) There is a suggestion that this entry involves a chelated lithium enolate and there are two stereogenic centers in the aldehyde. In the next section, we discuss how the presence of stereogenic centers in both reactants affects stereoselectivity.



Entry 6 involves a titanium enolate of an ethyl ketone. The aldehyde has no nearby stereocenters. Systems with this substitution pattern have been shown to lead to a 2,2'-*syn* relationship between the methyl groups flanking the ketone, and in this case, the β -siloxy substituent has little effect on the stereoselectivity. The configuration (*Z*) and conformation of the enolate determines the 2,3-*syn* stereochemistry.¹¹³



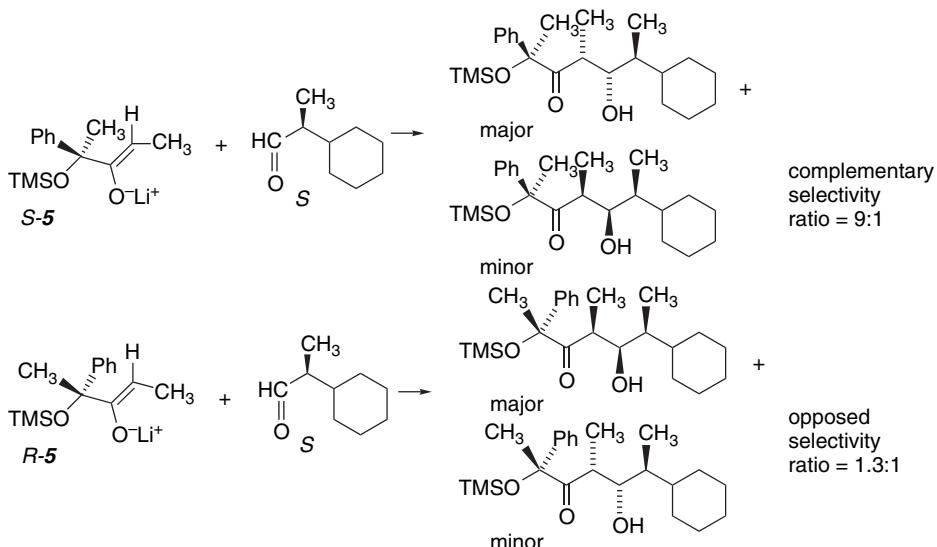
2.1.5.3. Complementary/Competitive Control: Double Stereodifferentiation. If both the aldehyde and the enolate in an aldol addition are chiral, mutual combinations of stereoselectivity come into play. The chirality in the aldehyde and enolate each impose a bias toward one absolute configuration. The structure of the chairlike TS imposes a bias toward the relative configuration (*syn* or *anti*) of the newly formed stereocenters as described in Section 2.1.2. One combination of configurations, e.g., (*R*)-aldehyde/(*S*)-enolate, provides complementary, reinforcing stereoselection, whereas the alternative combination results in opposing preferences and leads to diminished overall stereoselectivity. The combined interaction of stereocenters in both the aldehyde and the enolate component is called *double stereodifferentiation*.¹¹⁴ The reinforcing combination is called *matched* and the opposing combination is called *mismatched*.



¹¹³ D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991).

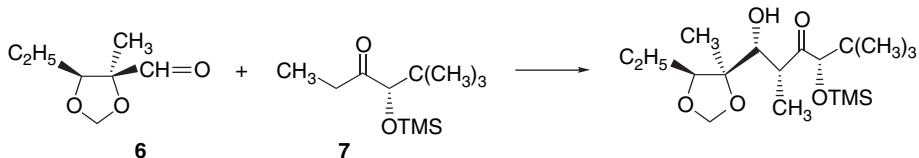
¹¹⁴ S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem. Int. Ed. Engl.*, **24**, 1 (1985).

For example the aldol addition of (*S*)-2-cyclohexylpropanal is more stereoselective with the enolate (*S*)-**5** than with the enantiomer (*R*)-**5**. The stereoselectivity of these cases derives from relative steric interactions in the matched and mismatched cases.



Ref. 115

Chelation can also be involved in double stereodifferentiation. The lithium enolate of the ketone **7** reacts selectively with the chiral aldehyde **6** to give a single stereoisomer.¹¹⁶ The enolate is thought to be chelated, blocking one face and leading to the observed product.

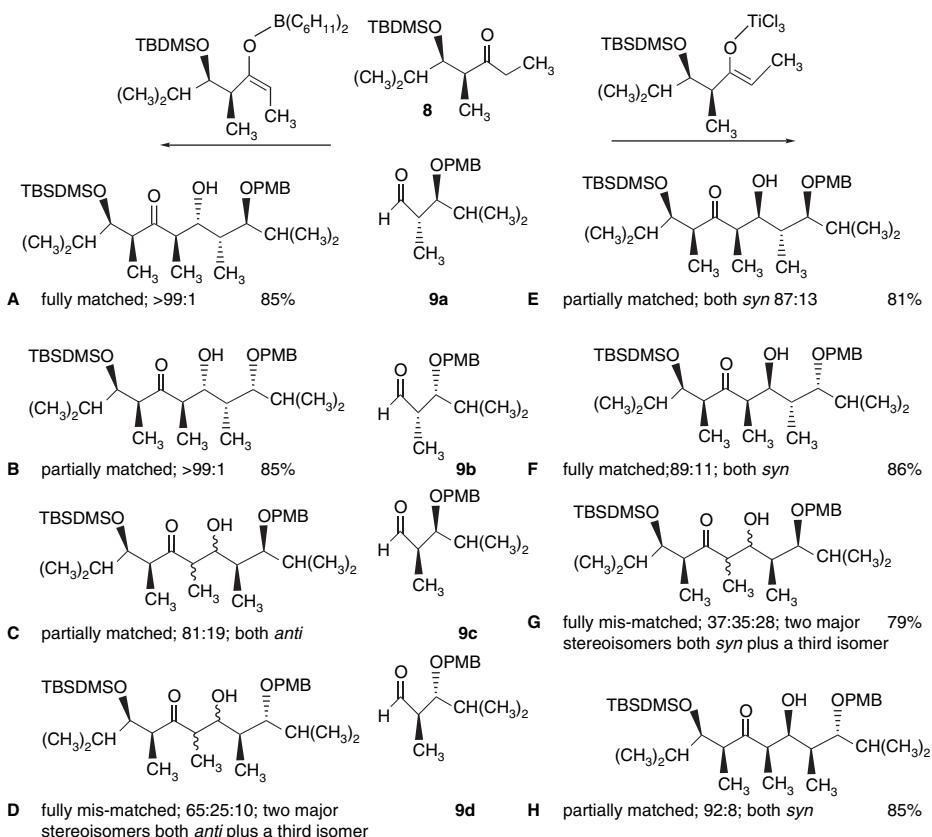


There can be more than two stereocenters, in which case there are additional combinations. For example with three stereocenters, there will be one fully matched set, one fully mismatched set, and two partially matched sets. In the latter two, one of the factors may dominate the others. For example, the ketone **8** and the four stereoisomers of the aldehyde **9** have been examined.¹¹⁷ Both the *E*-boron and the *Z*-titanium enolates were studied. The results are shown below.

¹¹⁵ S. Masamune, S. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem. Int. Ed. Engl.*, **19**, 557 (1980).

¹¹⁶ C. H. Heathcock, M. C. Pirrung, C. T. Buse, J. P. Hagen, S. D. Young, and J. E. Sohn, *J. Am. Chem. Soc.*, **101**, 7077 (1979).

¹¹⁷ D. A. Evans, M. J. Dart, J. L. Duffy, and D. L. Rieger, *J. Am. Chem. Soc.*, **117**, 9073 (1995).

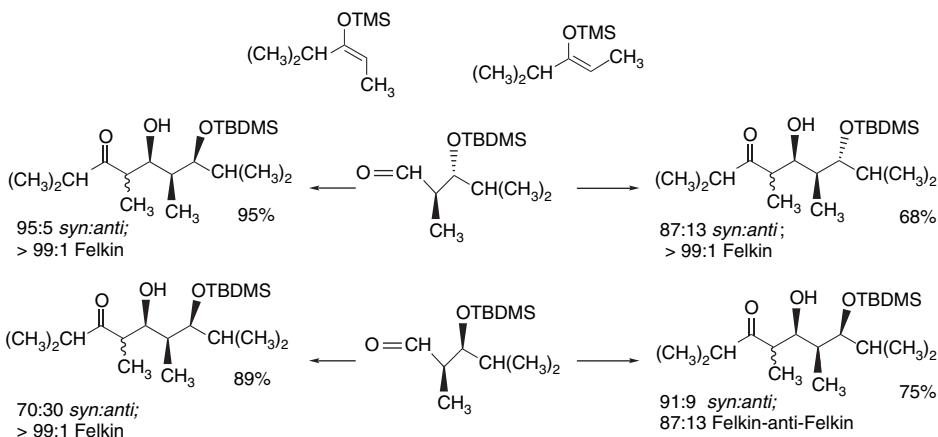


The results for the boron enolates show that when the aldehyde and enolate centers are matched the diastereoselectivity is high (Cases **A** and **B**). In Case **C**, the enolate is matched with respect to the β -alkoxy group but mismatched with the α -methyl group. The result is an 81:19 dominance of the anti-Felkin product. For the titanium enolates, Cases **E** and **F** correspond to a matched relationship with the α -stereocenter. Case **G** is fully mismatched and shows little selectivity. In Case **H**, the matched relationship between the enolate and the β -alkoxy group overrides the α -methyl effect and a 2,3-*syn* (Felkin) product is formed. The corresponding selectivity ratios have also been determined for the lithium enolates.¹¹⁸ Comparison with the boron enolates shows that although the stereoselectivity of the fully matched system is higher with the boron enolate, in the mismatched cases for the lithium enolate, the aldehyde bias overrides the enolate bias and gives modest selectivity for the alternative *anti* isomer.

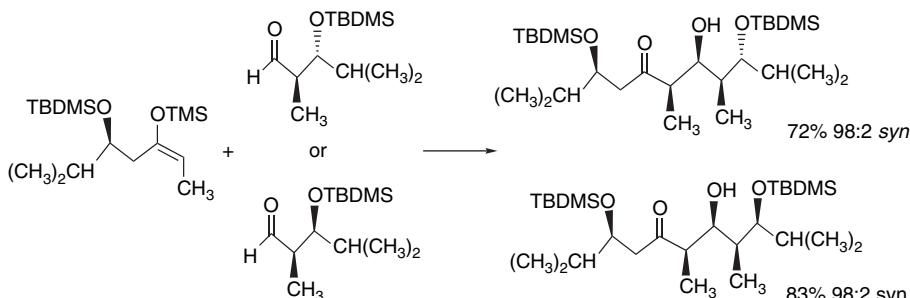
In general, BF_3 -catalyzed Mukaiyama reactions lack a cyclic organization because of the maximum coordination of four for boron. In these circumstances, the reactions show a preference for the Felkin type of approach and exhibit a preference for *syn* stereoselectivity that is independent of silyl enol ether structure.¹¹⁹

¹¹⁸. D. A. Evans, M. G. Yang, M. J. Dart, and J. L. Duffy, *Tetrahedron Lett.*, **37**, 1957 (1996).

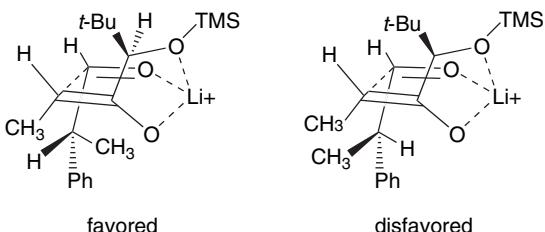
¹¹⁹. D. A. Evans, M. G. Yang, M. J. Dart, J. L. Duffy, and A. S. Kim, *J. Am. Chem. Soc.*, **117**, 9598 (1995).



When there is also a stereogenic center in the silyl enol ether, it can enhance or detract from the underlying stereochemical preferences. The two reactions shown below possess reinforcing structures with regard to the aldehyde α -methyl and the enolate TBDMOSO groups and lead to high stereoselectivity. The stereochemistry of the β -TBDMOSO group in the aldehyde has little effect on the stereoselectivity.

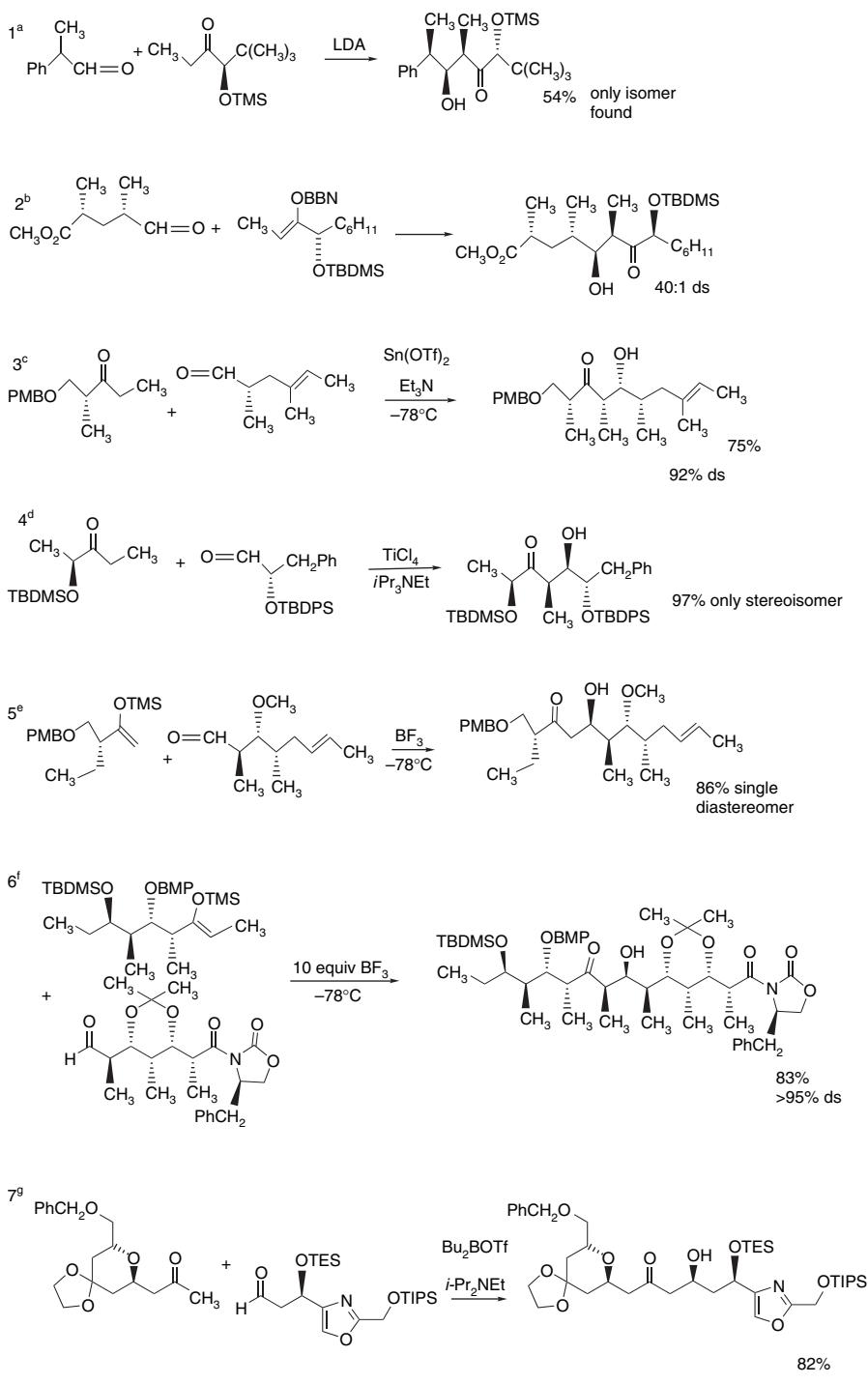


Scheme 2.5 gives some additional examples of double stereodifferentiation. Entry 1 combines the steric (Felkin) facial selectivity of the aldehyde with the facial selectivity of the enolate, which is derived from chelation. In reaction with the racemic aldehyde, the (*R*)-enantiomer is preferred.



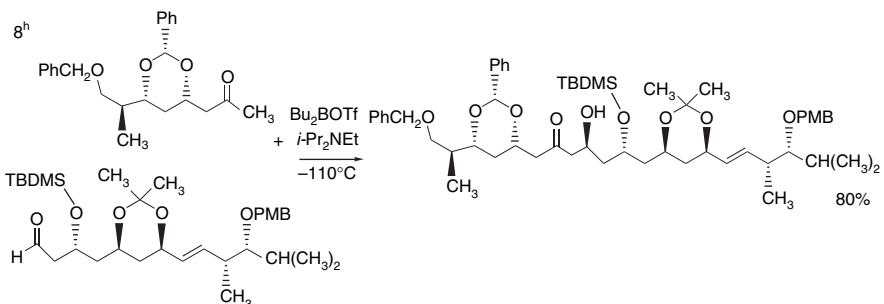
Entry 2 involves the use of a sterically biased enol boronate with an α -substituted aldehyde. The reaction, which gives 40:1 facial selectivity, was used in the synthesis of 6-deoxyerythronolide B and was one of the early demonstrations of the power of double diastereoselection in synthesis. In Entry 3, the *syn* selectivity is the result of a chelated TS, in which the β -*p*-methoxybenzyl substituent interacts with the tin ion.¹²⁰

¹²⁰ I. Paterson and R. D. Tillyer, *Tetrahedron Lett.*, **33**, 4233 (1992).

Scheme 2.5. Examples of Double Stereodifferentiation in Aldol and Mukaiyama Reactions

(Continued)

Scheme 2.5. (Continued)

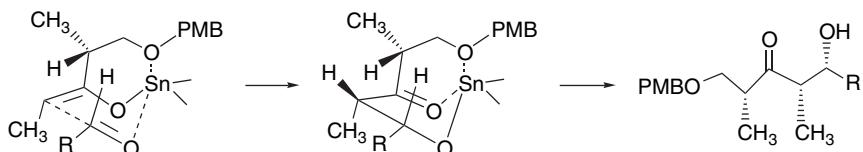


SECTION 2.1

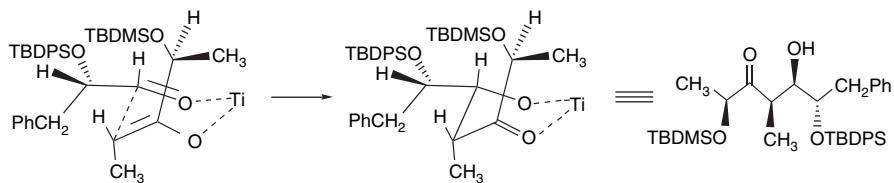
Aldol Addition and Condensation Reactions

- a. C. H. Heathcock, M. C. Purrung, J. Lampe, C. T. Buse, and S. D. Young, *J. Org. Chem.*, **46**, 2290 (1981).
 b. S. Masamune, M. Hirama, S. Mori, S. A. Ali, and D. S. Garvey, *J. Am. Chem. Soc.*, **103**, 1568 (1981).
 c. I. R. Correa, Jr., and R. A. Pilli, *Angew. Chem. Int. Ed. Engl.*, **42**, 3017 (2003).
 d. C. Esteve, M. Ferrero, P. Romea, F. Urpi, and J. Vilarrasa, *Tetrahedron Lett.*, **40**, 5083 (1999).
 e. G. E. Keck, C. E. Knutson, and S. A. Wiles, *Org. Lett.*, **3**, 707 (2001).
 f. D. A. Evans, A. S. Kim, R. Metternich, and V. J. Novack, *J. Am. Chem. Soc.*, **120**, 5921 (1998).
 g. D. A. Evans, D. M. Fitch, T. E. Smith, and V. J. Cee, *J. Am. Chem. Soc.*, **122**, 10033 (2000).
 h. D. A. Evans, B. Cote, P. J. Coleman, and B. T. Connell, *J. Am. Chem. Soc.*, **125**, 10893 (2003).

The aldehyde α -methyl substituent determines the facial selectivity with respect to the aldehyde.



Entry 4 has siloxy substituents in both the (titanium) enolate and the aldehyde. The TBDSO group in the aldehyde is in the “large” Felkin position, that is, perpendicular to the carbonyl group.¹²¹ The TBDMS group in the enolate is nonchelated but exerts a steric effect that governs facial selectivity.¹²² In this particular case, the two effects are matched and a single stereoisomer is observed.

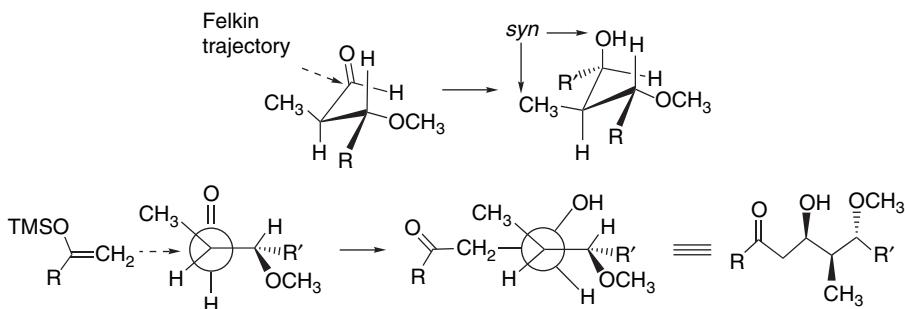


Entry 5 is a case in which the α - and β -substituents reinforce the stereoselectivity, as shown below. The largest substituent is perpendicular to the carbonyl, as in the Felkin model. When this conformation is incorporated into the TS, with the α -methyl

¹²¹ C. Esteve, M. Ferrero, P. Romea, F. Urpi, and J. Vilarrasa, *Tetrahedron Lett.*, **40**, 5079 (1999).

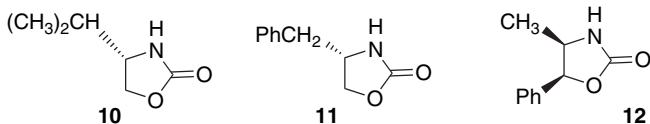
¹²² S. Figueras, R. Martin, P. Romea, F. Urpi, and J. Vilarrasa, *Tetrahedron Lett.*, **38**, 1637 (1997).

group in the “medium position,” the predicted approach leads to the observed 3,4-*syn* stereochemistry.

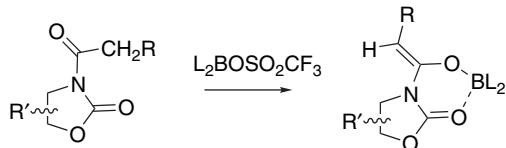


Entry 6 is an example of the methodology incorporated into a synthesis of 6-deoxyerythronolide.¹²³ Entries 7 and 8 illustrates the operation of the β -alkoxy group in cyclic structures. The reaction in Entry 7 was used in the synthesis of phorboxazole B.

2.1.5.4. Stereochemical Control Through Chiral Auxiliaries. Another approach to control of stereochemistry is installation of a *chiral auxiliary*, which can achieve a high degree of facial selectivity.¹²⁴ A very useful method for enantioselective aldol reactions is based on the oxazolidinones **10**, **11**, and **12**. These compounds are available in enantiomerically pure form and can be used to obtain either enantiomer of the desired product.

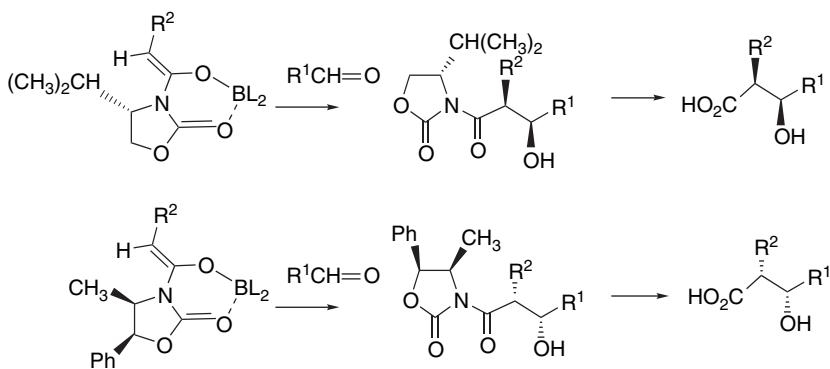


These oxazolidinones can be acylated and converted to the lithium, boron, tin, or titanium enolates by the same methods applicable to ketones and esters. For example, when they are converted to boron enolates using di-*n*-butylboron triflate and triethylamine, the enolates are the *Z*-stereoisomers.¹²⁵

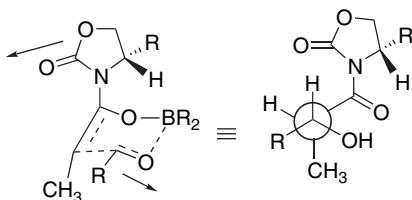


The substituents direct the approach of the aldehyde. The acyl oxazolidinones can be solvolyzed in water or alcohols to give the enantiomeric β -hydroxy acid or ester. Alternatively, they can be reduced to aldehydes or alcohols.

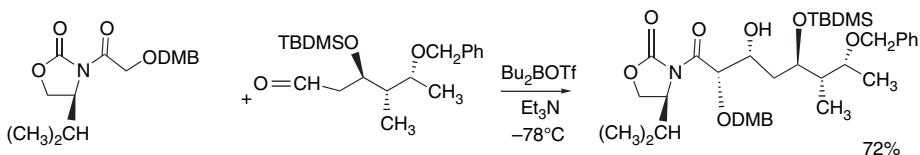
- ¹²³ D. A. Evans, A. S. Kim, R. Metternich, and V. J. Novack, *J. Am. Chem. Soc.*, **120**, 5921 (1998).
- ¹²⁴ M. Braun and H. Sacha, *J. Prakt. Chem.*, **335**, 653 (1993); S. G. Nelson, *Tetrahedron: Asymmetry*, **9**, 357 (1998); E. Carreira, in *Catalytic Asymmetric Synthesis*, 2nd Edition, I. Ojima, ed., Wiley-VCH, 2000, pp. 513–541; F. Velazquez and H. F. Olivo, *Curr. Org. Chem.*, **6**, 303 (2002).
- ¹²⁵ D. A. Evans, J. Bartoli, and T. L. Shih, *J. Am. Chem. Soc.*, **103**, 2127 (1981).



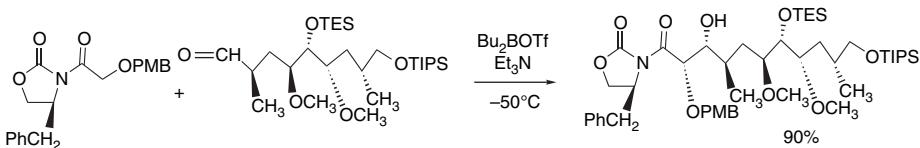
The reacting aldehyde displaces the oxazolidinone oxygen at the tetravalent boron in the reactive TS. The conformation of the addition TS for boron enolates is believed to have the oxazolidinone ring oriented with opposed dipoles of the ring and the aldehyde carbonyl groups.



The chiral auxiliary methodology using boron enolates has been successfully applied to many complex structures (see also Scheme 2.6).



Ref. 126

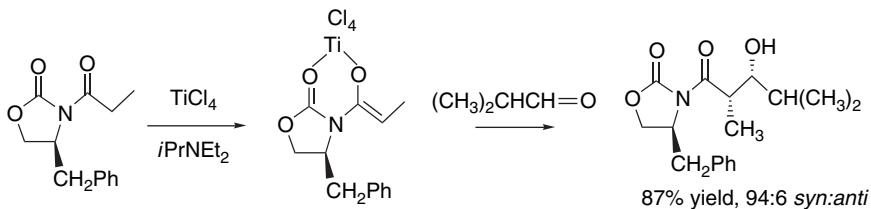


Ref. 127

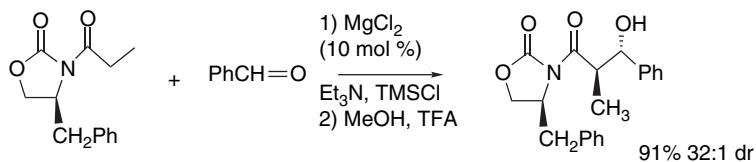
¹²⁶ W. R. Roush, T. G. Marron, and L. A. Pfeifer, *J. Org. Chem.*, **62**, 474 (1997).

¹²⁷ T. K. Jones, R. A. Reamer, R. Desmond, and S. G. Mills, *J. Am. Chem. Soc.*, **112**, 2998 (1990).

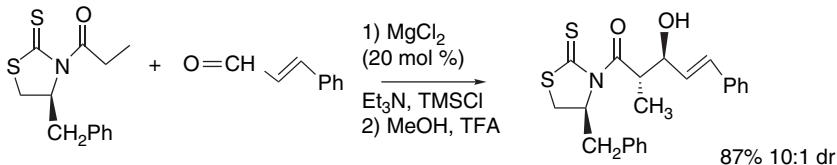
Titanium enolates also can be prepared from *N*-acyloxazolidinones. These Z-enolates, which are chelated with the oxazolidinone carbonyl oxygen,¹²⁸ show *syn* stereoselectivity, and the oxazolidinone substituent exerts facial selectivity.



The *N*-acyloxazolidinones give *anti* products when addition is effected by a catalytic amount of $MgCl_2$ in the presence of a tertiary amine and trimethylsilyl chloride. Under these conditions the adduct is formed as the trimethylsilyl ether.¹²⁹



Under similar conditions, the corresponding thiazolidinethione derivatives give *anti* product of the *opposite absolute configuration*, at least for cinnamaldehyde.



The mechanistic basis for the stereoselectivity of these conditions remains to be determined. The choice of reactant and conditions can be used to exert a substantial degree of control of the stereoselectivity.

Recently several other molecules have been developed as chiral auxiliaries. These include derivatives of ephedrine and pseudoephedrine. The *N*-methylephedrine [(*1R,2S*)-2-dimethylamino-1-phenyl-1-propanol] chiral auxiliary **13** has been examined with both the (*S*)- and (*R*)-enantiomers of 2-benzyloxy-2-methylpropanal.¹³⁰ The two enantiomers reacted quite differently. The (*R*)-enantiomer gave a 60% yield of a pure enantiomer with a *syn* configuration at the new bond. The (*S*)-enantiomer gave a combined 22% yield of two diastereomeric products in a 1.3:1 ratio. The aldehyde is known from NMR studies to form a chelated complex with $TiCl_4$,¹³¹ and presumably reacts through a chelated TS. The TS **J** from the (*R*)-enantiomer has the methyl groups from both the chiral auxiliary and the silyl enol ether in favorable environments (matched pair). The products from the (*S*)-enantiomer arise from TS **K** and

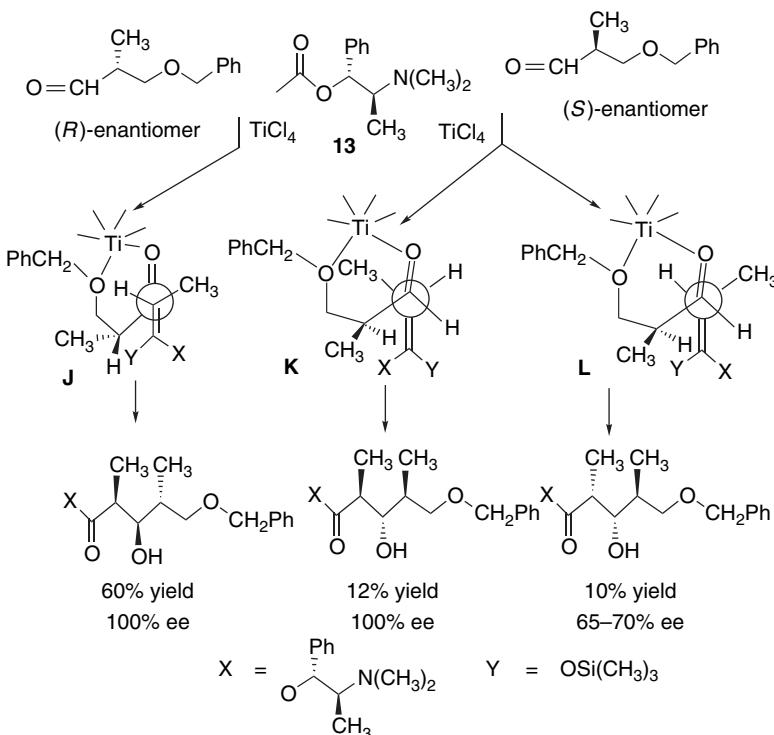
¹²⁸ D. A. Evans, D. L. Rieger, M. T. Bilodeau, and F. Urpi, *J. Am. Chem. Soc.*, **113**, 1047 (1991).

¹²⁹ D. A. Evans, J. S. Tedrow, J. T. Shaw, and C. W. Downey, *J. Am. Chem. Soc.*, **124**, 392 (2002).

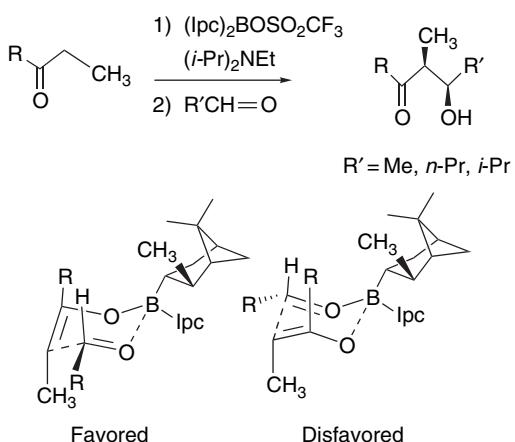
¹³⁰ G. Gennari, L. Colombo, G. Bertolini, and G. Schimperna, *J. Org. Chem.*, **52**, 2754 (1987).

¹³¹ G. E. Keck and S. Castellino, *J. Am. Chem. Soc.*, **108**, 3847 (1986).

TS L, each of which has one of the methyl groups in an unfavorable environment. (mismatched pairs).

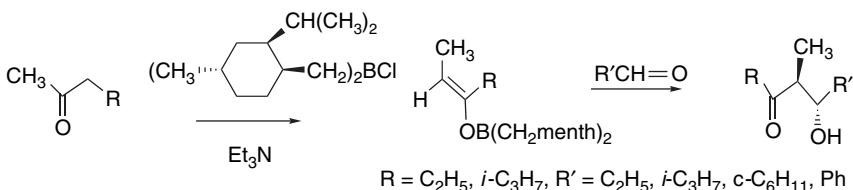


Enantioselectivity can also be induced by use of chiral boron enolates. Both the (+) and (−) enantiomers of diisopinocampheylboron triflate have been used to generate *syn* addition through a cyclic TS.¹³² The enantioselectivity was greater than 80% for most cases that were examined. Z-Boron enolates are formed under these conditions and the products are 2,3-*syn*.

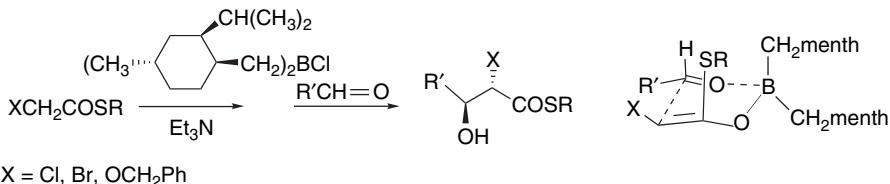


¹³² I. Paterson, J. M. Goodman, M. A. Lister, R. C. Schumann, C. K. McClure, and R. D. Norcross, *Tetrahedron*, **46**, 4663 (1990).

Another promising boron enolate is derived from $(-)$ -menthone.¹³³ It yields *E*-boron enolates that give good enantioselectivity in the formation of *anti* products.¹³⁴

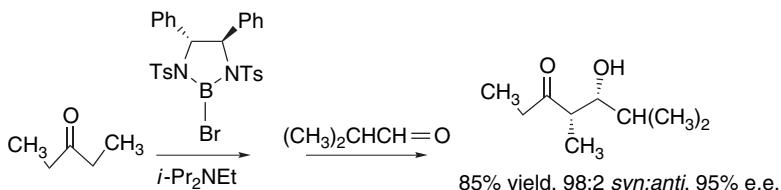
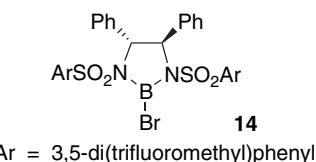


The boron enolates of α -substituted thiol esters also give excellent facial selectivity.¹³⁵



The facial selectivity in these chiral boron enolates has its origin in the steric effects of the boron substituents.

Several chiral heterocyclic borylating agents have been found useful for enantioselective aldol additions. The diazaborolidine **14** is an example.¹³⁶



Derivatives with various substituted sulfonamides have been developed and used to form enolates from esters and thioesters.¹³⁷ An additional feature of this chiral auxiliary is the ability to select for *syn* or *anti* products, depending upon choice of reagents and reaction conditions. The reactions proceed through an acyclic TS, and diastereoselectivity is determined by whether the *E*- or *Z*-enolate is formed.¹³⁸ *t*-Butyl esters give *E*-enolates and *anti* adducts, whereas phenylthiol esters give *syn* adducts.¹³⁶

¹³³ C. Gennari, *Pure Appl. Chem.*, **69**, 507 (1997).

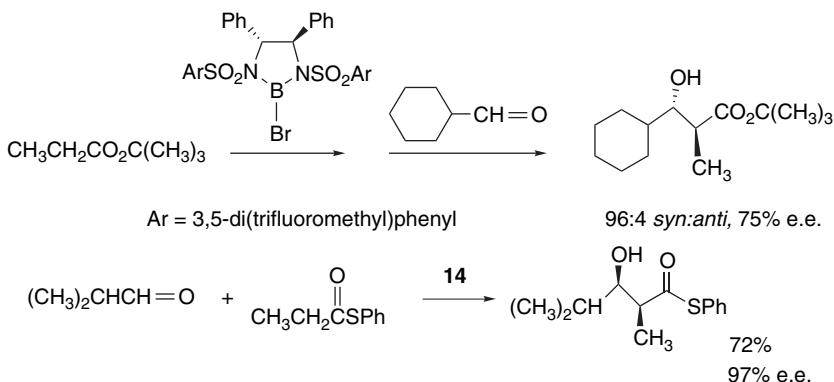
¹³⁴ G. Gennari, C. T. Hewkin, F. Molinari, A. Bernardi, A. Comotti, J. M. Goodman, and I. Paterson, *J. Org. Chem.*, **57**, 5173 (1992).

¹³⁵ C. Gennari, A. Vulpetti, and G. Pain, *Tetrahedron*, **53**, 5909 (1997).

¹³⁶ E. J. Corey, R. Imwinkelried, S. Pikul, and Y. B. Xiang, *J. Am. Chem. Soc.*, **111**, 5493 (1989).

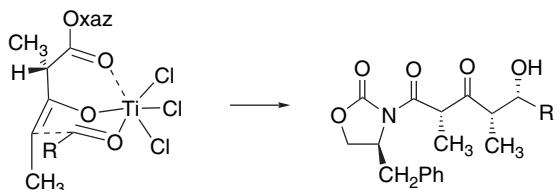
¹³⁷ E. J. Corey and S. S. Kim, *J. Am. Chem. Soc.*, **112**, 4976 (1990).

¹³⁸ E. J. Corey and D. H. Lee, *Tetrahedron Lett.*, **34**, 1737 (1993).



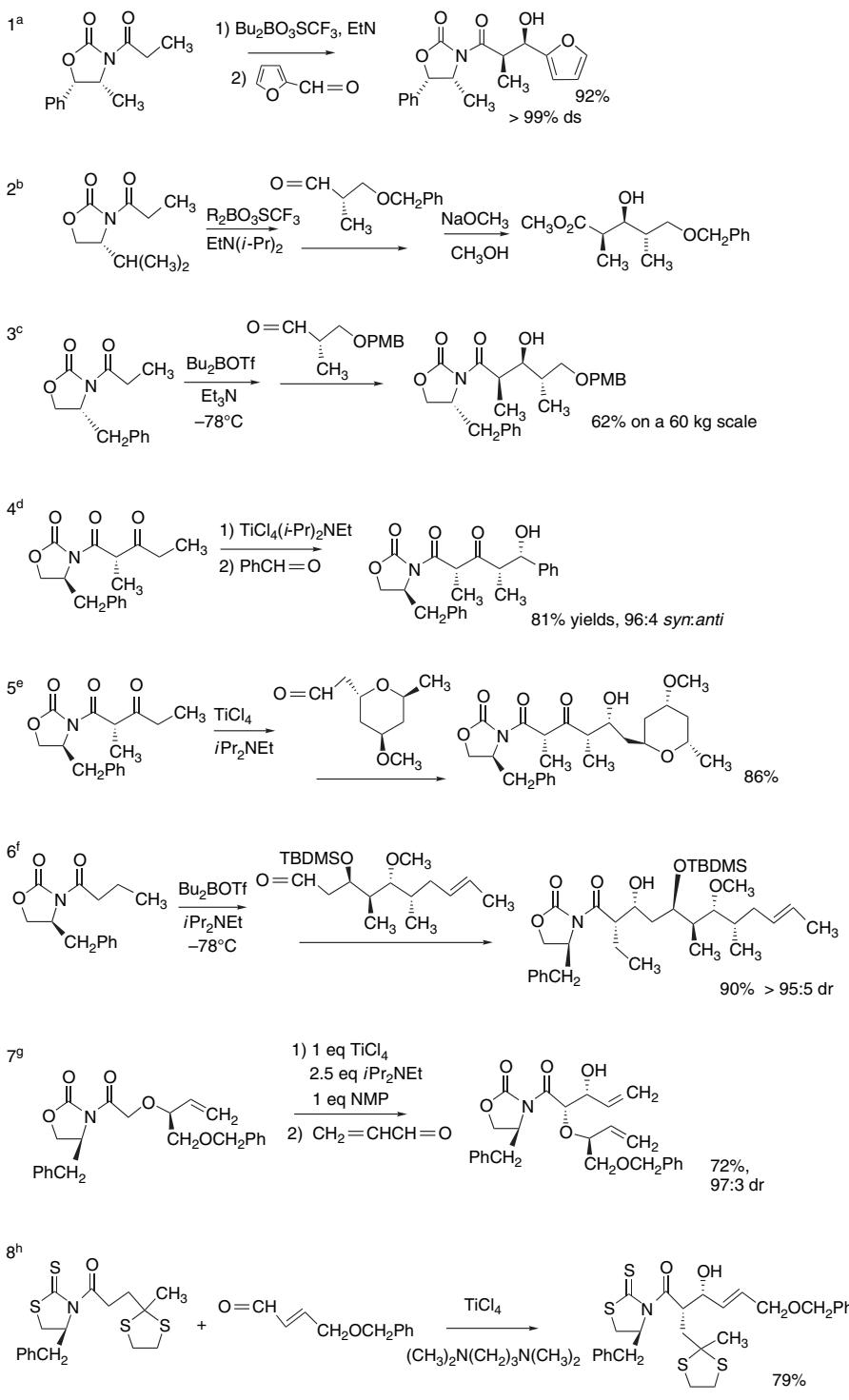
Scheme 2.6 shows some examples of the use of chiral auxiliaries in the aldol and Mukaiyama reactions. The reaction in Entry 1 involves an achiral aldehyde and the chiral auxiliary is the only influence on the reaction diastereoselectivity, which is very high. The *Z*-boron enolate results in *syn* diastereoselectivity. Entry 2 has both an α -methyl and a β -benzyloxy substituent in the aldehyde reactant. The 2,3-*syn* relationship arises from the *Z*-configuration of the enolate, and the 3,4-*anti* stereochemistry is determined by the stereocenters in the aldehyde. The product was isolated as an ester after methanolysis. Entry 3, which is very similar to Entry 2, was done on a 60-kg scale in a process development investigation for the potential antitumor agent (+)-discodermolide (see page 1244).

Entries 4 and 5 are cases in which the oxazolidinone substituent is a β -ketoacyl group. The α -hydrogen (between the carbonyls) does not react as rapidly as the γ -hydrogen, evidently owing to steric restrictions to optimal alignment. The all-*syn* stereochemistry is consistent with a TS in which the exocyclic carbonyl is chelated to titanium.



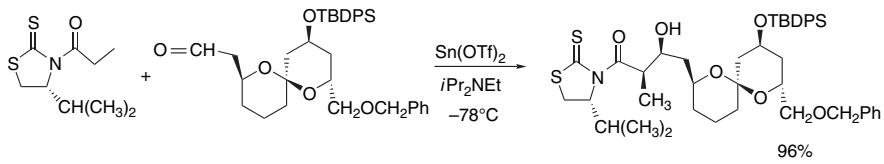
In Entry 5, the aldehyde is also chiral and double stereodifferentiation comes into play. Entry 6 illustrates the use of an oxazolidinone auxiliary with another highly substituted aldehyde. Entry 7 employs conditions that were found effective for α -alkoxyacyl oxazolidinones. Entries 8 and 9 are examples of the application of the thiazolidine-2-thione auxiliary and provide the 2,3-*syn* isomers with diastereofacial control by the chiral auxiliary.

2.1.5.5. Stereochemical Control Through Reaction Conditions. In the early 1990s it was found that the stereochemistry of reactions of boron enolates of *N*-acyloxazolidinones can be altered by using a Lewis acid complex of the aldehyde or an excess of the Lewis acid. These reactions are considered to take place through an open TS, with the stereoselectivity dependent on the steric demands of the Lewis acid. With various aldehydes, TiCl₄ gave a *syn* isomer, whereas the reaction was

Scheme 2.6. Control of Stereochemistry of Aldol and Mukaiyama Aldol Reactions Using Chiral Auxiliaries

(Continued)

Scheme 2.6. (Continued)

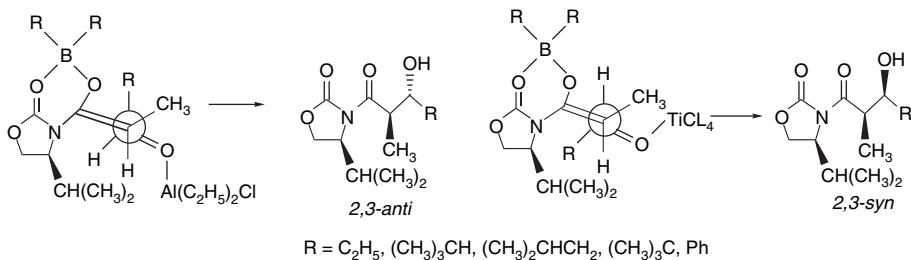
9ⁱ

SECTION 2.1

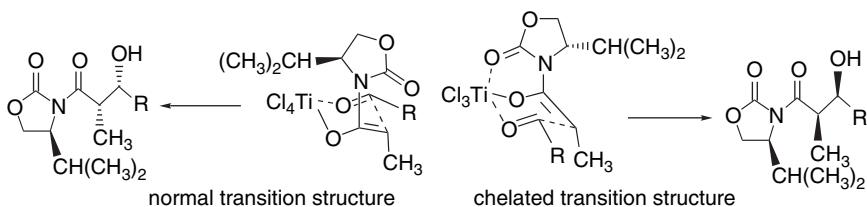
Aldol Addition and Condensation Reactions

- a. S. F. Martin and D. E. Guinn, *J. Org. Chem.*, **52**, 5588 (1987).
- b. D. Seebach, H.-F. Chow, R. F. W. Jackson, K. Lawson, M. A. Sutter, S. Thaisrivongs, and J. Zimmerman, *J. Am. Chem. Soc.*, **107**, 5292 (1985).
- c. S. J. Mickel, G. H. Sedelmeier, D. Niererer, R. Daeffler, A. Osmani, K. Schreiner, M. Seeger-Weibel, B. Berod, K. Schaer, R. Gamboni, S. Chen, W. Chen, C. T. Jagoe, F. Kinder, M. Low, K. Prasad, O. Repic, W. C. Shieh, R. M. Wang, L. Wakole, D. Xu, and S. Xue, *Org. Proc. Res. Dev.*, **8**, 92 (2004).
- d. D. A. Evans, J. S. Clark, R. Metternich, V. J. Novack, and G. S. Sheppard, *J. Am. Chem. Soc.*, **112**, 866 (1990).
- e. G. E. Keck and G. D. Lundquist, *J. Org. Chem.*, **64**, 4482 (1999).
- f. L. C. Dias, L. G. de Oliveira, and M. A. De Sousa, *Org. Lett.*, **5**, 265 (2003).
- g. M. T. Crimmins and J. She, *Synlett*, 1371 (2004).
- h. J. Wu, X. Shen, Y.-Q. Yang, Q. Hu, and J.-H. Huang, *J. Org. Chem.*, **69**, 3857 (2004).
- i. D. Zuev and L. A. Paquette, *Org. Lett.*, **2**, 679 (2000).

anti selective using $(C_2H_5)_2AlCl$.¹³⁹ The *anti* selectivity is proposed to arise as a result of the greater size requirement for the complexed aldehyde with $(C_2H_5)_2AlCl$. These reactions both give a different stereoisomer than the reaction done *without the additional Lewis acid*. The chiral auxiliary is the source of facial selectivity.



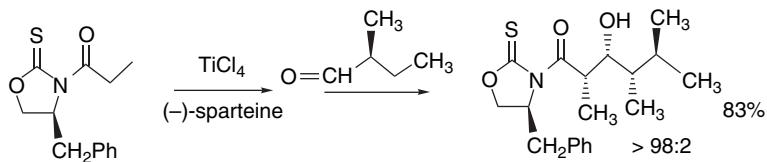
With titanium enolates it was found that use of excess (3 equiv.) of the titanium reagent reversed facial selectivity of oxazolidinone enolates.¹⁴⁰ This was attributed to generation of a chelated TS in the presence of the excess Lewis acid. The chelation rotates the oxazolidinone ring and reverses the facial preference, while retaining the *Z*-configuration *syn* diastereoselectivity.



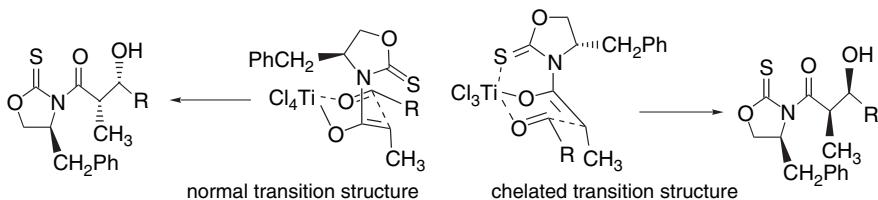
¹³⁹. M. A. Walker and C. H. Heathcock, *J. Org. Chem.*, **56**, 5747 (1991).

¹⁴⁰. M. Nerz-Stormes and E. R. Thornton, *Tetrahedron Lett.*, **27**, 897 (1986); M. Nerz-Stormes and E. R. Thornton, *J. Org. Chem.*, **56**, 2489 (1991).

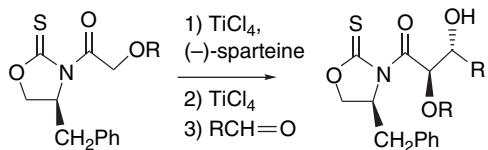
Crimmins and co-workers have developed *N*-acyloxazolidinethiones as chiral auxiliaries. These reagents show excellent 2,3-*syn* diastereoselectivity and enantioselectivity in additions to aldehydes. The titanium enolates are prepared using TiCl_4 , with (–)-sparteine being a particularly effective base.¹⁴¹



The facial selectivity of these compounds is also dependent on the amount of TiCl_4 that is used. With two equivalents, the facial selectivity is reversed. This reversal is also achieved by adding AgSbF_6 . It was suggested that the excess reagent or the silver salt removes a Cl^- from the titanium coordination sphere and promotes chelation with the thione sulfur.¹⁴² This changes the facial selectivity of the enolate by causing a reorientation of the oxazolidinethione ring. The greater affinity of titanium for sulfur over oxygen makes the oxazolidinethiones particularly effective in these circumstances. The increased tendency for chelation has been observed with other chiral auxiliaries having thione groups.¹⁴³



A related effect is noted with α -alkoxyacyl derivatives. These compounds give mainly the *anti* adducts when a second equivalent of TiCl_4 is added prior to the aldehyde.¹⁴⁴ The *anti* addition is believed to occur through a TS in which the alkoxy oxygen is chelated. In the absence of excess TiCl_4 , a nonchelated cyclic TS accounts for the observed *syn* selectivity.

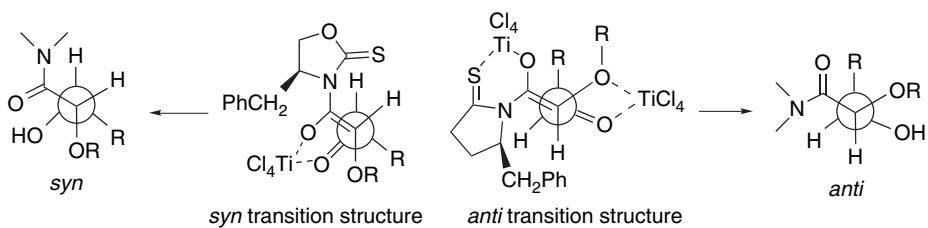


¹⁴¹ M. T. Crimmins and B. W. King, *J. Am. Chem. Soc.*, **120**, 9084 (1998); M. T. Crimmins, B. W. King, E. A. Tabet, and C. Chaudhary, *J. Org. Chem.*, **66**, 894 (2001); M. T. Crimmins and J. She, *Synlett*, 1371 (2004).

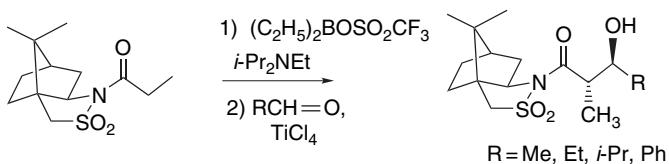
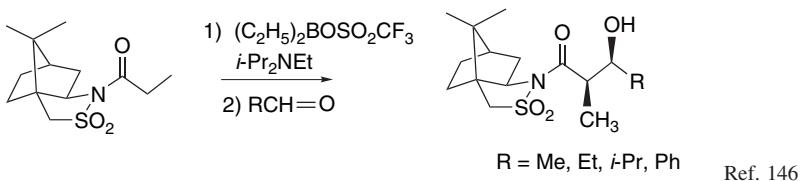
¹⁴² M. T. Crimmins, B. W. King, and E. A. Tabet, *J. Am. Chem. Soc.*, **119**, 7883 (1997).

¹⁴³ T. H. Yan, C. W. Tan, H. C. Lee, H. C. Lo, and T. Y. Huang, *J. Am. Chem. Soc.*, **115**, 2613 (1993).

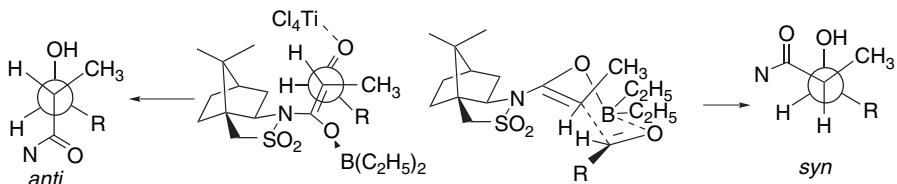
¹⁴⁴ M. T. Crimmins and P. J. McDougall, *Org. Lett.*, **5**, 591 (2003).



Camphor-derived sulfonamide can also permit control of enantioselectivity by use of additional Lewis acid. These chiral auxiliaries can be used under conditions in which either cyclic or noncyclic TSs are involved. This frequently allows control of the *syn* or *anti* stereoselectivity.¹⁴³ The boron enolates give *syn* products, but inclusion of SnCl_4 or TiCl_4 gave excellent selectivity for *anti* products and high enantioselectivity for a range of aldehydes.¹⁴⁵



In the case of boron enolates of the camphor sulfonamides, the TiCl_4 -mediated reaction is believed to proceed through an open TS, whereas in its absence, the reaction proceeds through a cyclic TS.



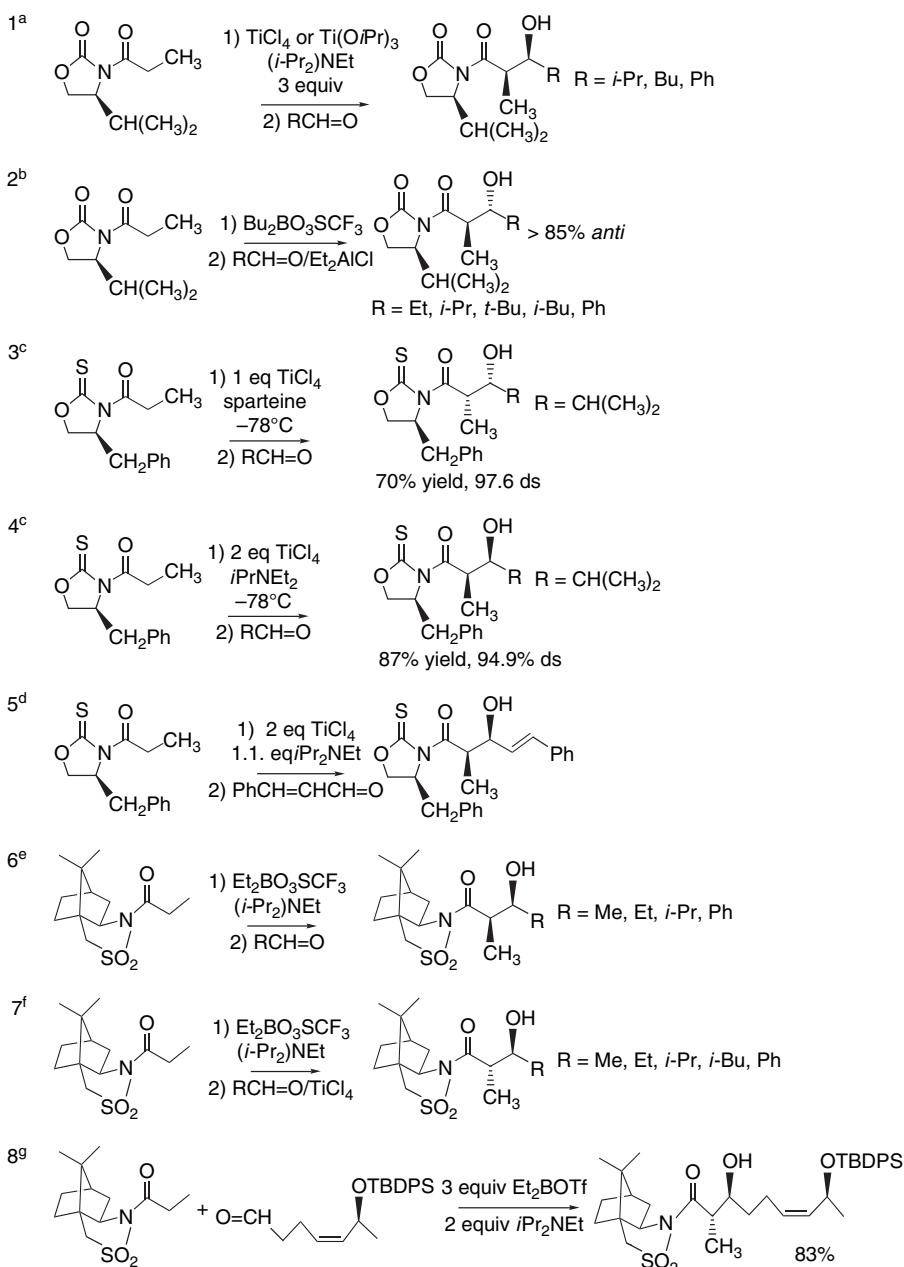
Scheme 2.7 gives some examples of the control of stereoselectivity by use of additional Lewis acid and related methods. Entry 1 shows the effect of the use of excess TiCl_4 . Entry 2 demonstrates the ability of $(\text{C}_2\text{H}_5)_2\text{AlCl}$ to shift the boron enolate toward formation of the 2,3-*anti* diastereomer. Entries 3 and 4 compare the use of one versus two equivalents of TiCl_4 with an oxazolidine-2-thione auxiliary. There is a nearly complete shift of facial selectivity. Entry 5 shows a subsequent application of this methodology. Entries 6 and 7 show the effect of complexation of the aldehyde

¹⁴⁵ Y.-C. Wang, A.-W. Hung, C.-S. Chang, and T.-H. Yan, *J. Org. Chem.*, **61**, 2038 (1996).

¹⁴⁶ W. Oppolzer, J. Blagg, I. Rodriguez, and E. Walther, *J. Am. Chem. Soc.*, **112**, 2767 (1990).

¹⁴⁷ W. Oppolzer and P. Lienhard, *Tetrahedron Lett.*, **34**, 4321 (1993).

Scheme 2.7. Examples of Control of Stereoselectivity by Use of Additional Lewis Acid



a. M. Nerz-Stormes and E. R. Thornton, *J. Org. Chem.*, **56**, 2489 (1991).

b. M. A. Walker and C. H. Heathcock, *J. Org. Chem.*, **56**, 5747 (1991).

c. M. T. Crimmins, B. W. King, and E. A. Tabet, *J. Am. Chem. Soc.*, **119**, 7883 (1997).

d. T. K. Chakraborty, S. Jayaprakash, and P. Laxman, *Tetrahedron*, **57**, 9461 (2001).

e. W. Oppolzer, J. Blagg, I. Rodriguez, and E. Walther, *J. Am. Chem. Soc.*, **112**, 2767 (1990).

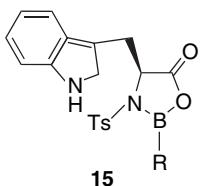
f. W. Oppolzer and P. Lienhard, *Tetrahedron Lett.*, **34**, 4321 (1993).

g. B. Fraser and P. Perlmutter, *J. Chem. Soc., Perkin Trans. 1*, 2896 (2002).

with TiCl_4 using the camphor sultam auxiliary. Entry 8 is an example of the use of excess diethylboron triflate to obtain the *anti* stereoisomer in a step in the synthesis of epothilone.

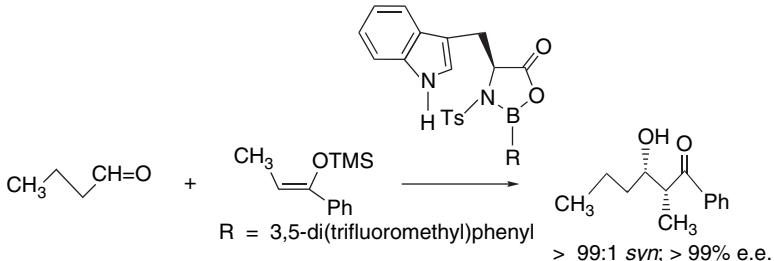
These examples and those in Scheme 2.6 illustrate the key variables that determine the stereochemical outcome of aldol addition reactions using chiral auxiliaries. The first element that has to be taken into account is the configuration of the ring system that is used to establish steric differentiation. Then the nature of the TS, whether it is acyclic, cyclic, or chelated must be considered. Generally for boron enolates, reaction proceeds through a cyclic but nonchelated TS. With boron enolates, excess Lewis acid can favor an acyclic TS by coordination with the carbonyl electrophile. Titanium enolates appear to be somewhat variable but can be shifted to chelated TSs by use of excess reagent and by auxiliaries such as oxazolidine-2-thiones that enhance the tendency to chelation. Ultimately, all of the factors play a role in determining which TS is favored.

2.1.5.6. Enantioselective Catalysis of the Aldol Addition Reaction. There are also several catalysts that can effect enantioselective aldol addition. The reactions generally involve enolate equivalents, such as silyl enol ethers, that are unreactive toward the carbonyl component alone, but can react when activated by a Lewis acid. The tryptophan-based oxazaborolidinone **15** has proven to be a useful catalyst.¹⁴⁸



This catalyst induces preferential *re* facial attack on simple aldehydes, as indicated in Figure 2.2. The enantioselectivity appears to involve the shielding of the *si* face by the indole ring through a π -stacking interaction.

The *B*-3,5-bis-(trifluoromethyl)phenyl derivative was found to be a very effective catalyst.¹⁴⁹



¹⁴⁸. E. J. Corey, C. L. Cywin, and T. D. Roper, *Tetrahedron Lett.*, **33**, 6907 (1992); E. J. Corey, T.-P. Loh, T. D. Roper, M. D. Azimioara, and M. C. Noe, *J. Am. Chem. Soc.*, **114**, 8290 (1992); S. G. Nelson, *Tetrahedron: Asymmetry*, **9**, 357 (1998).

¹⁴⁹. K. Ishihara, S. Kondo, and H. Yamamoto, *J. Org. Chem.*, **65**, 9125 (2000).

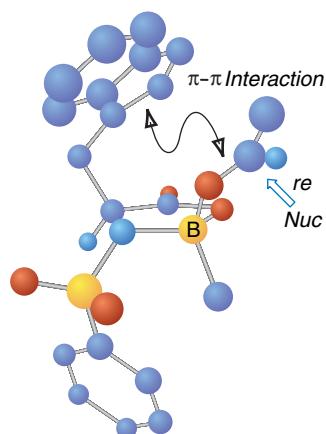
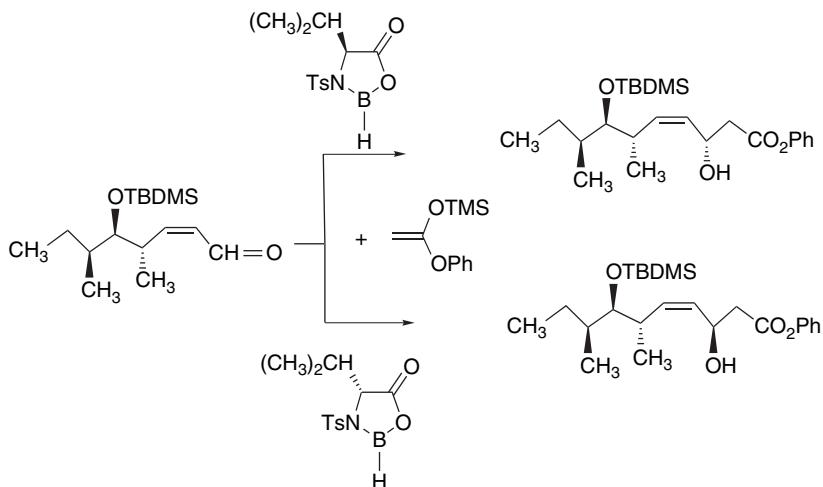


Fig. 2.2. Origin of facial selectivity in indolylmethylloxazaborolidinone structure. Reproduced from *Tetrahedron: Asymmetry*, **9**, 357 (1998), by permission of Elsevier. (See also color insert.)

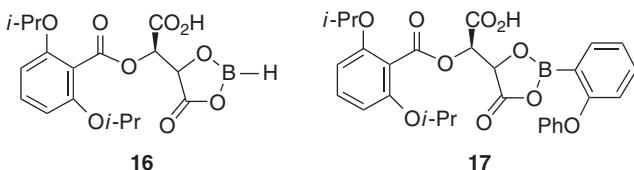
An oxazaborolidinone derived from valine is also an effective catalyst. In one case, the two enantiomeric catalysts were completely enantioselective for the newly formed center.¹⁵⁰



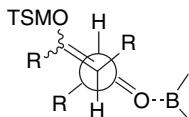
Another group of catalysts consist of cyclic borinates derived from tartaric acid. These compounds give good reactivity and enantioselectivity in Mukaiyama aldol reactions. Several structural variations such as **16** and **17** have been explored.¹⁵¹

¹⁵⁰. S. Kiyooka, K. A. Shahid, F. Goto, M. Okazaki, and Y. Shuto, *J. Org. Chem.*, **68**, 7967 (2003).

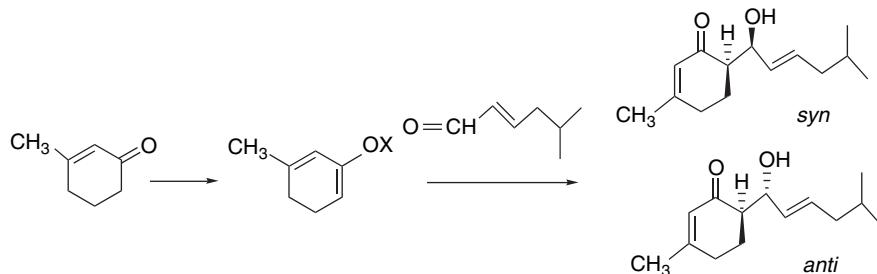
¹⁵¹. K. Ishihara, T. Maruyama, M. Mourai, Q. Gao, K. Furuta, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **66**, 3483 (1993).



These catalysts are believed to function through an acyclic TS. In addition to the normal steric effects of the open TS, the facial selectivity is probably influenced by π stacking with the aryl ring and possibly hydrogen bonding by the formyl hydrogen.¹⁵²



An interesting example of the use of this type of catalysis is a case in which the addition reaction of 3-methylcyclohex-2-enone to 5-methyl-2-hexenal was explored over a range of conditions. The reaction was investigated using both the lithium enolate and the trimethylsilyl enol ether. The yield and stereoselectivity are given for several sets of conditions.¹⁵³ Whereas the lithium enolate and achiral Lewis acids $TiCl_4$ and BF_3 gave moderate *anti* diastereoselectivity, the catalyst **17** induces good *syn* selectivity, as well as high enantioselectivity.



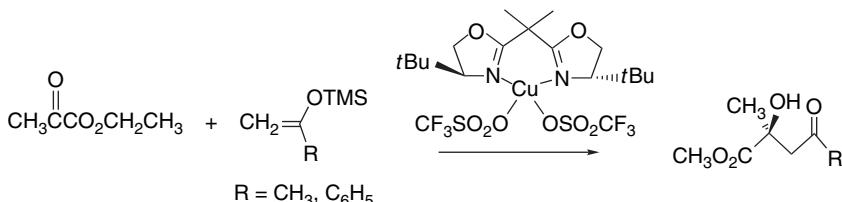
X	Conditions	Yield	<i>syn</i>	<i>anti</i>	e.e.
Li	(kinetic)	63	18	82	—
Li	(thermo)	66	55	45	—
TMS	$TiCl_4$	53	15	85	—
TMS	BF_3	68	25	75	—
TMS	Cat 16	51	42	58	24(<i>R</i>)
TMS	Cat 17	94	91	9	99(<i>R</i>)

The lesson from this case is that reactions that are quite unselective under simple Lewis acid catalysis can become very selective with chiral catalysts. Moreover, as this particular case also shows, they can be very dependent on the specific structure of the catalyst.

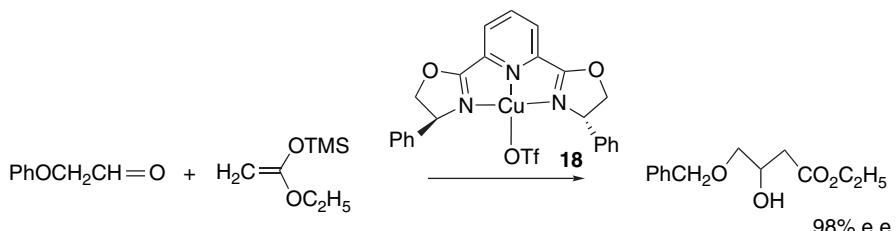
¹⁵² K. Furuta, T. Maruyama, and H. Yamamoto, *J. Am. Chem. Soc.*, **113**, 1041 (1991); K. Ishihara, Q. Gao, and H. Yamamoto, *J. Am. Chem. Soc.*, **115**, 10412 (1993).

¹⁵³ K. Takao, T. Tsujita, M. Hara, and K. Tadano, *J. Org. Chem.*, **67**, 6690 (2002).

Another effective group of catalysts is composed of copper *bis*-oxazolines.¹⁵⁴ The chirality is derived from the 4-substituents on the ring.

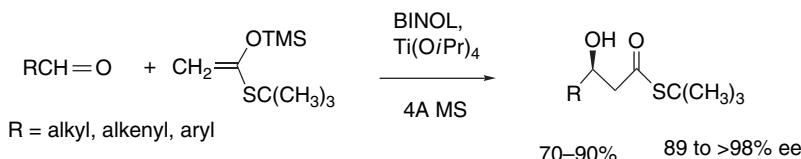


This and similar catalysts are effective with silyl ketene acetals and silyl thioketene acetals.¹⁵⁵ One of the examples is the tridentate pyridine-BOX-type catalyst **18**. The reactivity of this catalyst has been explored using α - and β -oxy substituted aldehydes.¹⁵⁴ α -Benzoyloxyacetaldehyde was highly enantioselective and the α -trimethylsiloxy derivative was weakly so (56% e.e.). Nonchelating aldehydes such as benzaldehyde and 3-phenylpropanal gave racemic product. 3-Benzoyloxypropanal also gave racemic product, indicating that the β -oxy aldehydes do not chelate with this catalyst.



The Cu-BOX catalysts function as Lewis acids at the carbonyl oxygen. The chiral ligands promote facial selectivity, as shown in Figure 2.3.

Several catalysts based on Ti(IV) and BINOL have shown excellent enantioselectivity in Mukaiyama aldol reactions.¹⁵⁶ A catalyst prepared from a 1:1 mixture of BINOL and Ti(O-*i*-Pr)₄ gives good results with silyl thioketene acetals in ether, but is very solvent sensitive.¹⁵⁷



The structure of the active catalyst and the mechanism of catalysis have not been completely defined. Several solid state complexes of BINOL and Ti(O-*i*-Pr)₄ have been characterized by X-ray crystallography.¹⁵⁸ Figure 2.4 shows the structures of complexes having the composition (BINOLate)Ti₂(O-*i*-Pr)₆ and (BINOLate)Ti₃(O-*i*-Pr)₁₀.

¹⁵⁴ D. A. Evans, J. A. Murry, and M. C. Kozlowski, *J. Am. Chem. Soc.*, **118**, 5814 (1996).

¹⁵⁵ D. A. Evans, D. W. C. MacMillan, and K. R. Campos, *J. Am. Chem. Soc.*, **119**, 10859 (1997); D. A. Evans, M. C. Kozlowski, C. S. Burgey, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **119**, 7893 (1997).

¹⁵⁶ S. Matsukawa and K. Mikami, *Tetrahedron: Asymmetry*, **6**, 2571 (1995); H. Matsunaga, Y. Yamada, T. Ide, T. Ishizuka, and T. Kunieda, *Tetrahedron: Asymmetry*, **10**, 3095 (1999).

¹⁵⁷ G. E. Keck and D. Krishnamurthy, *J. Am. Chem. Soc.*, **117**, 2363 (1995).

¹⁵⁸ T. J. Davis, J. Balsells, P. J. Carroll, and P. J. Walsh, *Org. Lett.*, **3**, 699 (2001).

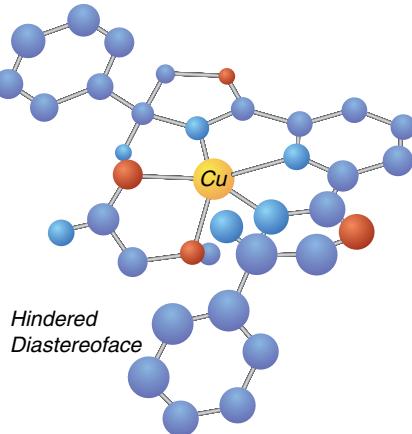


Fig. 2.3. Origin of facial selectivity of bis-oxazoline catalyst. Reproduced from *Tetrahedron: Asymmetry*, 9, 357 (1998), by permission of Elsevier. (See also color insert.)

Halogenated BINOL derivatives of $Zr(O-t\text{-}Bu)_4$ such as **19** also give good yields and enantioselectivity.¹⁵⁹

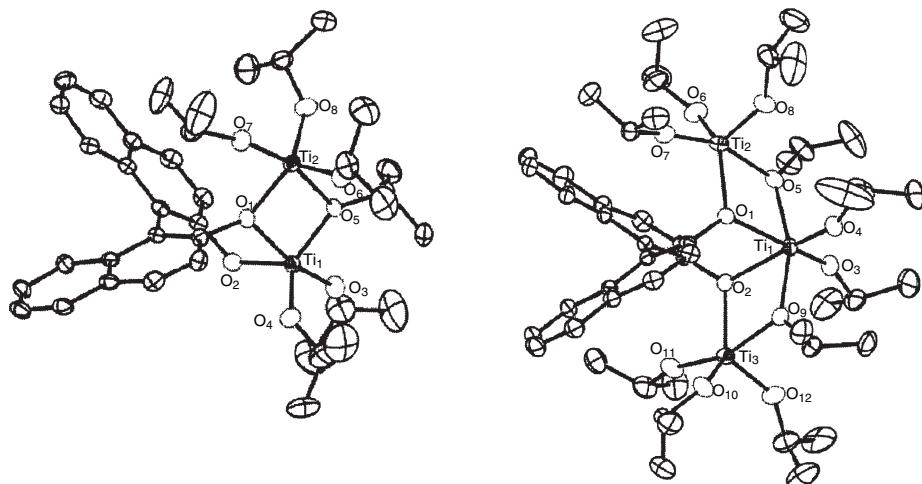
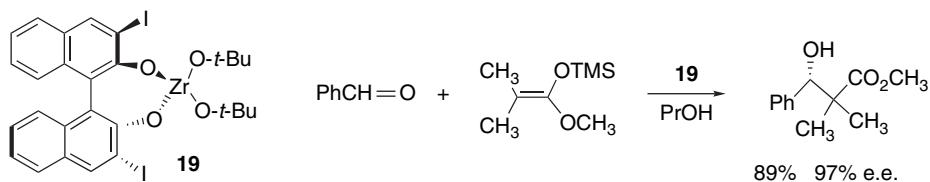
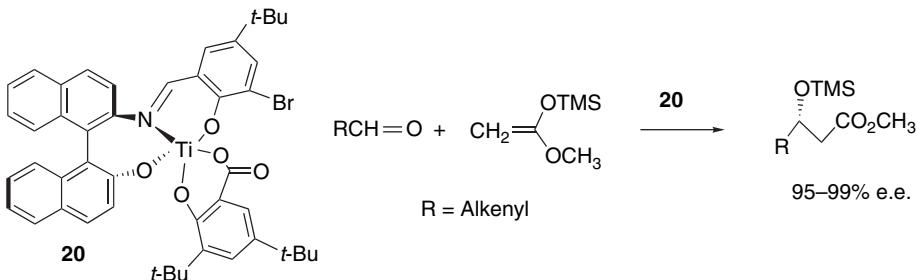


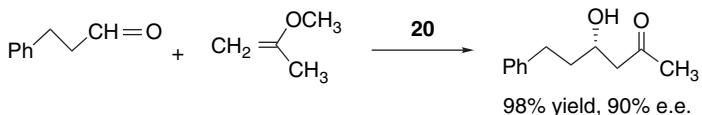
Fig. 2.4. Left: dinuclear complex of composition (BINOLate) $Ti_2(O-i-Pr)_6$. Right: trinuclear complex of composition (BINOLate) $Ti_3(O-i-Pr)_{10}$. Reproduced from *Org. Lett.*, **3**, 699 (2001), by permission of the American Chemical Society.

¹⁵⁹. S. Kobayashi, H. Ishitani, Y. Yamashita, M. Ueno, and H. Shimizu, *Tetrahedron*, **57**, 861 (2001).

A titanium catalyst **20** that incorporates binaphthyl chirality along with imine and phenolic (salen) donors is highly active in addition of silyl ketene acetals to aldehydes.¹⁶⁰

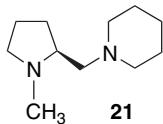


This catalyst is also active toward the simple enol ether 2-methoxypropene.¹⁶¹



Entry 6 in Scheme 2.9 is an example of the use of this catalyst in a multistep synthesis.

The enantioselectivity of Sn(II) enolate reactions can be controlled by chiral diamine additives. These reagents are particularly effective for silyl thioketene acetals.¹⁶² Several diamines derived from proline have been explored and 1-methyl-2-(1-piperidinomethyl)pyrrolidine **21** is an example. Even higher enantioselectivity can be achieved by attachment of bicyclic amines to the pyrrolidinomethyl group.¹⁶³



These reactions have been applied to α -benzyloxy and α -(*t*-butyldimethylsiloxy)-thioacetate esters.¹⁶⁴ The benzyloxy derivatives are *anti* selective, whereas the siloxy derivatives are *syn* selective. These differences are attributed to a chelated structure in the case of the benzyloxy derivative and an open TS for the siloxy system.

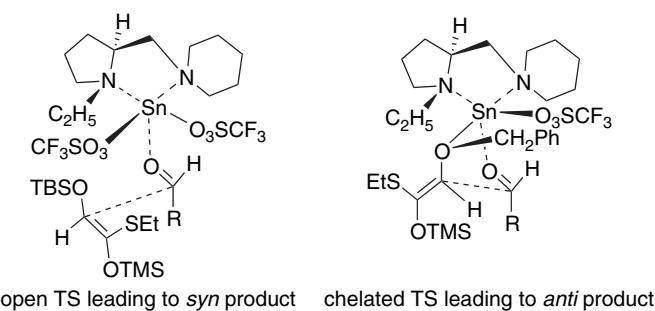
¹⁶⁰ E. M. Carreira, R. A. Singer, and W. Lee, *J. Am. Chem. Soc.*, **116**, 8837 (1994).

¹⁶¹ E. M. Carreira, W. Lee, and R. A. Singer, *J. Am. Chem. Soc.*, **117**, 3649 (1995).

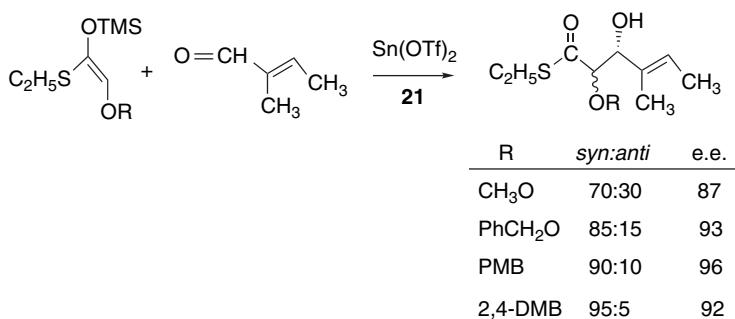
¹⁶² S. Kobayashi, H. Uchiyo, Y. Fujishita, I. Shiina, and T. Mukaiyama, *J. Am. Chem. Soc.*, **113**, 4247 (1991); S. Kobayashi, H. Uchiyo, I. Shiina, and T. Mukaiyama, *Tetrahedron*, **49**, 1761 (1993).

¹⁶³ S. Kobayashi, M. Horibe, and M. Matsumura, *Synlett*, 675 (1995); S. Kobayashi and M. Horibe, *Chem. Eur. J.*, **3**, 1472 (1997).

¹⁶⁴ T. Mukaiyama, I. Shiina, H. Uchiyo, and S. Kobayashi, *Bull. Chem. Soc. Jpn.*, **67**, 1708 (1994).



White and Deerberg explored this reaction system in connection with the synthesis of a portion of the structure of rapamycin.¹⁶⁵ Better yields were observed from benzyloxy than for a methoxy substituent, and there was a slight enhancement of stereoselectivity with the addition of ERG substituents to the benzyloxy group.



Scheme 2.8 gives some examples of chiral Lewis acids that have been used to catalyze aldol and Mukaiyama reactions.

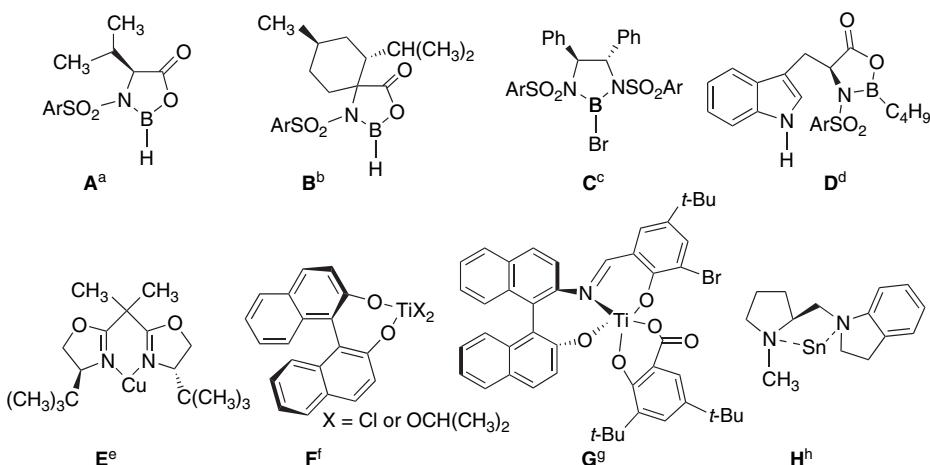
Scheme 2.9 gives some examples of use of enantioselective catalysts. Entries 1 to 4 are cases of the use of the oxazaborolidinone-type of catalyst with silyl enol ethers and silyl ketene acetals. Entries 5 and 6 are examples of the use of BINOL-titanium catalysts, and Entry 7 illustrates the use of Sn(OTf)₂ in conjunction with a chiral amine ligand. The enantioselectivity in each of these cases is determined entirely by the catalyst because there are no stereocenters adjacent to the reaction sites in the reactants.

A different type of catalysis is observed using proline as a catalyst.¹⁶⁶ Proline promotes addition of acetone to aromatic aldehydes with 65–77% enantioselectivity. It has been suggested that the carboxylic acid functions as an intramolecular proton donor and promotes reaction through an enamine intermediate.

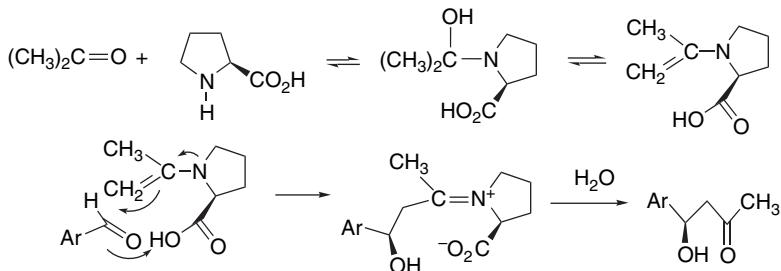
¹⁶⁵ J. D. White and J. Deerberg, *Chem. Commun.*, 1919 (1997).

¹⁶⁶ B. List, R. A. Lerner, and C. F. Barbas, III, *J. Am. Chem. Soc.*, **122**, 2395 (2000); B. List, L. Hoang, and H. J. Martin, *Proc. Natl. Acad. Sci., USA*, **101**, 5839 (2004).

Scheme 2.8. Chiral Catalysts for the Mukaiyama Aldol Reactions



- a. S. Kiyooka, Y. Kaneko, M. Komura, H. Matsuo, and M. Nakano, *J. Org. Chem.*, **56**, 2276 (1991).
b. E. R. Parmee, O. Tempkin, S. Masamune, and A. Abiko, *J. Am. Chem. Soc.*, **113**, 9365 (1991).
c. E. J. Corey, R. Imwinkelried, S. Pakul, and Y. B. Xiang, *J. Am. Chem. Soc.*, **111**, 5493 (1989).
d. E. J. Corey, C. L. Cywin, and T. D. Roper, *Tetrahedron Lett.*, **33**, 6907 (1992); E. J. Corey, D. Barnes-Seeman, and T. W. Lee, *Tetrahedron Lett.*, **38**, 1699 (1997).
e. D. A. Evans, J. A. Murry, and M. C. Koslowski, *J. Am. Chem. Soc.*, **118**, 5814 (1996); D. A. Evans, M. C. Koslowski, C. S. Burgey, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **119**, 7893 (1997); D. A. Evans, D. W. C. MacMillan, and K. R. Campos, *J. Am. Chem. Soc.*, **119**, 10859 (1997).
f. K. Mitami and S. Matsukawa, *J. Am. Chem. Soc.*, **115**, 7039 (1993); K. Mitami and S. Matsukawa, *J. Am. Chem. Soc.*, **116**, 4077 (1994); G. E. Keck and D. Krishnamurthy, *J. Am. Chem. Soc.*, **117**, 2363 (1995); G. E. Keck, X.-Y. Li, and D. Krishnamurthy, *J. Org. Chem.*, **60**, 5998 (1995).
g. E. M. Carreira, R. A. Singer, and W. Lee, *J. Am. Chem. Soc.*, **116**, 8837 (1994).
h. S. Kobayashi and M. Horibe, *Chem. Eur. J.*, **3**, 1472 (1997).



A DFT study found a corresponding TS to be the lowest energy.¹⁶⁷ This study also points to the importance of the solvent, DMSO, in stabilizing the charge buildup that occurs. A further computational study analyzed the stereoselectivity of the proline-catalyzed aldol addition reactions of cyclohexanone with acetaldehyde, isobutyraldehyde, and benzaldehyde on the basis of a similar TS.¹⁶⁸ Another study, which explored the role of proline in intramolecular aldol reactions, is discussed in the next section.¹⁶⁹

¹⁶⁷. K. N. Rankin, J. W. Gauld, and R. J. Boyd, *J. Phys. Chem. A*, **106**, 5155 (2002).

¹⁶⁸. S. Bahmanyar, K. N. Houk, H. J. Martin, and B. List, *J. Am. Chem. Soc.*, **125**, 2475 (2003).

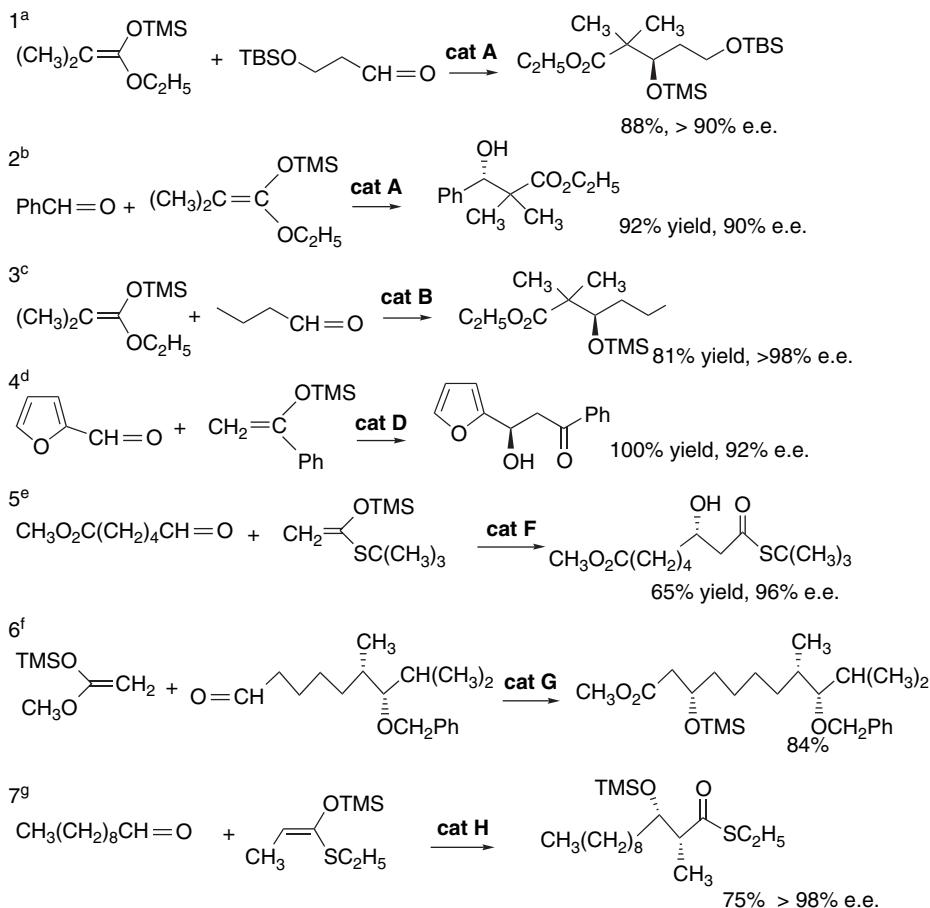
¹⁶⁹. S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, **123**, 12911 (2001).

Scheme 2.9. Enantioselective Catalysis of Aldol and Mukaiyama Aldol Reactions

133

SECTION 2.1

Aldol Addition and Condensation Reactions



a. J. Mulzer, A. J. Mantouidis, and E. Ohler, *Tetrahedron Lett.*, **39**, 8633 (1998).

b. S. Kiyooka, Y. Kaneko, and K. Kume, *Tetrahedron Lett.*, **33**, 4927 (1992).

c. E. J. Corey, C. L. Cywin, and T. D. Roper, *Tetrahedron Lett.*, **33**, 6907 (1992).

d. E. R. Parmee, O. Tempkin, S. Masamune, and A. Abiko, *J. Am. Chem. Soc.*, **113**, 9365 (1991).

e. R. Zimmer, A. Peritz, R. Czerwonka, L. Schefzig, and H.-U. Reissig, *Eur. J. Org. Chem.*, 3419 (2002).

f. S. D. Rychnovsky, U. R. Khire, and G. Yang, *J. Am. Chem. Soc.*, **119**, 2058 (1997).

g. S. Kobayashi, H. Uchiyo, I. Shiina, and T. Mukaiyama, *Tetrahedron*, **49**, 1761 (1993).

Visual models, additional information and exercises on Proline-Catalyzed Aldol Reactions can be found in the Digital Resource available at: Springer.com/carey-sundberg.

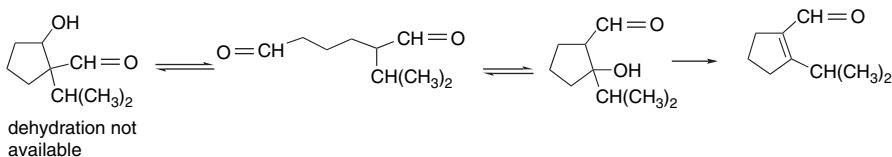
2.1.5.7. Summary of Facial Stereoselectivity in Aldol and Mukaiyama Reactions. The examples provided in this section show that there are several approaches to controlling the facial selectivity of aldol additions and related reactions. The *E*- or *Z*-configuration of the enolate and the open, cyclic, or chelated nature of the TS are the departure points for prediction and analysis of stereoselectivity. The Lewis acid catalyst and the donor strength of potentially chelating ligands affect the structure of the TS. Whereas dialkyl boron enolates and BF_3 complexes are tetracoordinate, titanium and tin can be

hexacoordinate. If the reactants are chiral, facial selectivity must be taken into account. Examples of steric, chelation, and polar effects on TS structure have been described. Chiral auxiliaries can influence facial selectivity not only by their inherent steric effects, but also on the basis of the conformation of their Lewis acid complexes. This can be controlled by the choice of the enolate metal and reaction conditions. Dialkylboron enolates react through a cyclic TS that cannot accommodate additional coordination. Titanium and tin enolates of oxazolidinones are chelated under normal conditions, but the use of excess Lewis acid can modify the TS structure and reverse facial selectivity. Chiral catalysts require that additional stereochemical features be taken into account, and the issue becomes the fit of the reactants within the chiral environment. Although most catalysts rely primarily on steric factors for facial selectivity, hydrogen bonding and π stacking can also come into play.

2.1.6. Intramolecular Aldol Reactions and the Robinson Annulation

The aldol reaction can be applied to dicarbonyl compounds in which the two groups are favorably disposed for intramolecular reaction. Kinetic studies on cyclization of 5-oxohexanal, 2,5-hexanedione, and 2,6-heptanedione indicate that formation of five-membered rings is thermodynamically somewhat more favorable than formation of six-membered rings, but that the latter is several thousand times faster.¹⁷⁰ A catalytic amount of acid or base is frequently satisfactory for formation of five- and six-membered rings, but with more complex structures, the techniques required for directed aldol condensations are used.

Scheme 2.10 illustrates intramolecular aldol condensations. Entries 1 and 2 are cases of formation of five-membered rings, with aldehyde groups serving as the electrophilic center. The regioselectivity in Entry 1 is due to the potential for dehydration of only one of the cyclic aldol adducts.



In Entry 2, the more reactive aldehyde group serves as the electrophilic component in preference to the ketone. Entries 3 to 6 are examples of construction of new rings in preexisting cyclic systems. The structure and stereochemistry of the products of these reactions are dictated by ring geometry and the proximity of reactive groups. Entry 5 is interesting in that it results in the formation of a bridgehead double bond. Entries 7 to 9 are intramolecular Mukaiyama reactions, using acetals as the precursor of the electrophilic center. Entry 9, which is a key step in the synthesis of jatrophones, involves formation of an eleven-membered ring. From a retrosynthetic perspective, bonds between a carbinol (or equivalent) carbon and a carbon that is α to a carbonyl carbon are candidates for formation by intramolecular aldol additions.

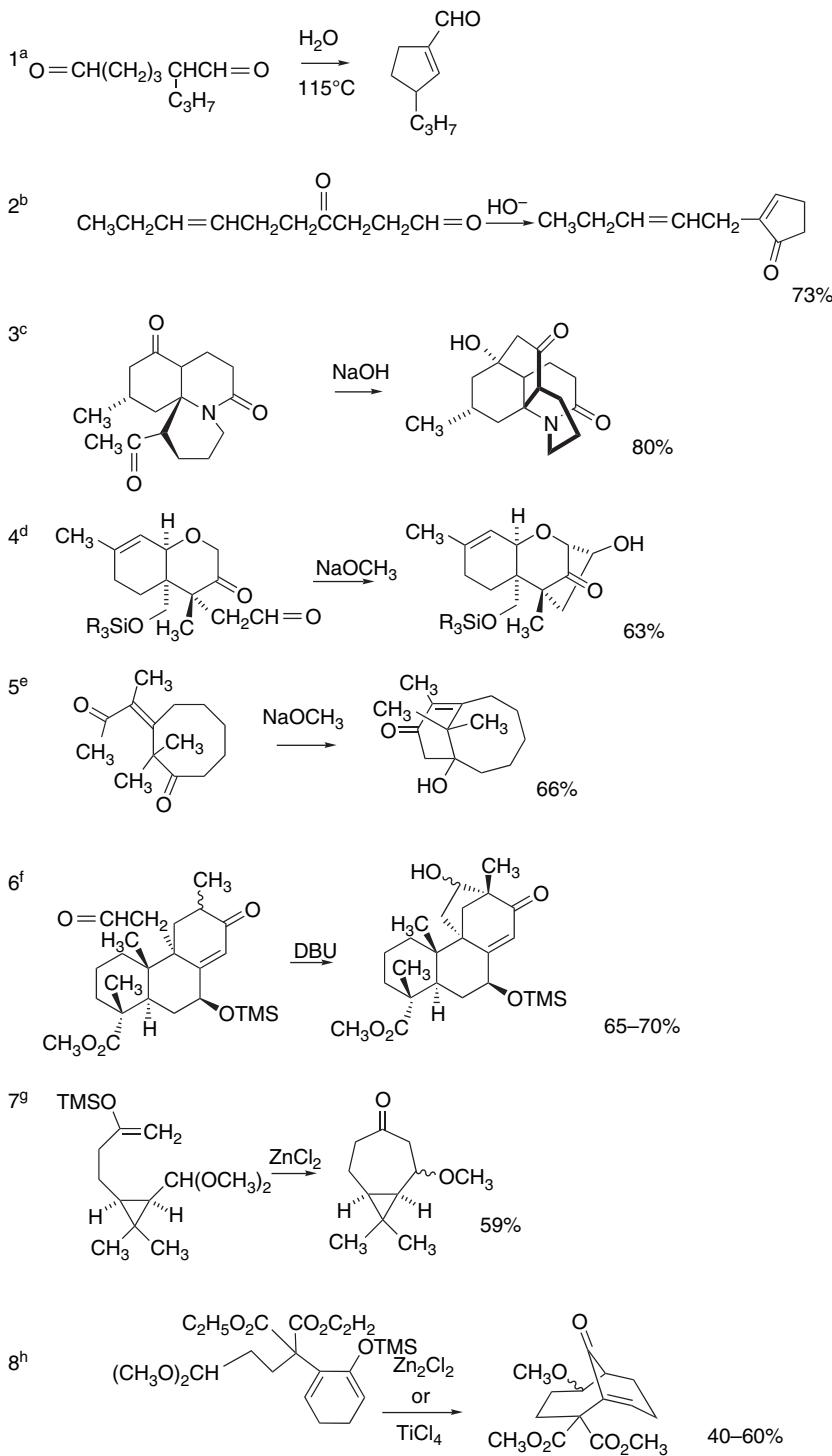
A particularly important example of the intramolecular aldol reaction is the *Robinson annulation*, a procedure that constructs a new six-membered ring from a ketone.¹⁷¹ The reaction sequence starts with conjugate addition of the enolate to methyl

¹⁷⁰ J. P. Guthrie and J. Guo, *J. Am. Chem. Soc.*, **118**, 11472 (1996).

Scheme 2.10. Intramolecular Aldol and Mukaiyama Aldol Reactions

SECTION 2.1

Aldol Addition and Condensation Reactions

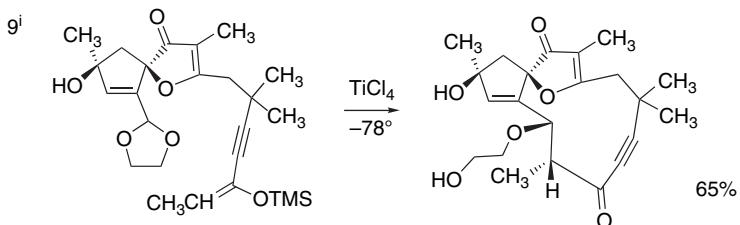


(Continued)

Scheme 2.10. (Continued)

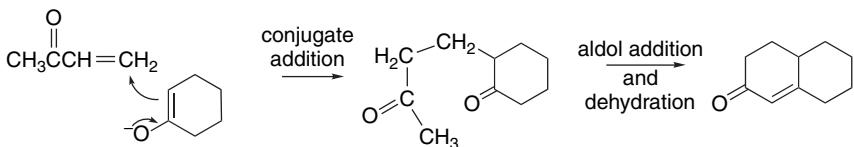
CHAPTER 2

Reactions of Carbon Nucleophiles with Carbonyl Compounds



- a. J. English and G. W. Barber, *J. Am. Chem. Soc.*, **71**, 3310 (1949).
- b. A. I. Meyers and N. Nazarenko, *J. Org. Chem.*, **38**, 175 (1973).
- c. K. Wiesner, V. Musil, and K. J. Wiesner, *Tetrahedron Lett.*, 5643 (1968).
- d. G. A. Kraus, B. Roth, K. Frazier, and M. Shimagaki, *J. Am. Chem. Soc.*, **104**, 1114 (1982).
- e. K. Yamada, H. Iwadare, and T. Mukaiyama, *Chem. Pharm. Bull.*, **45**, 1898 (1997).
- f. J. K. Tagat, M. S. Puar, and S. W. McCombie, *Tetrahedron Lett.*, **37**, 8463 (1996).
- g. M. D. Taylor, G. Minaskanian, K. N. Winzenberg, P. Santone, and A. B. Smith, III, *J. Org. Chem.*, **47**, 3960 (1962).
- h. A. Armstrong, T. J. Critchley, M. E. Gourdel-Martin, R. D. Kelsey, and A. A. Mortlock, *J. Chem. Soc., Perkin Trans. 1*, 1344 (2002).
- i. A. B. Smith, III, A. T. Lupo, Jr., M. Ohba, and K. Chen, *J. Am. Chem. Soc.*, **111**, 6648 (1989).

vinyl ketone or a similar enone. This is followed by cyclization by an intramolecular aldol addition. Dehydration usually occurs to give a cyclohexenone derivative.



Other α,β -unsaturated enones can be used, but the reaction is somewhat sensitive to substitution at the β -carbon and adjustment of the reaction conditions is necessary.¹⁷²

Scheme 2.11 shows some examples of Robinson annulation reactions. Entries 1 and 2 show annulation reactions of relatively acidic dicarbonyl compounds. Entry 3 is an example of use of 4-(trimethylammonio)-2-butanone as a precursor of methyl vinyl ketone. This compound generates methyl vinyl ketone *in situ* by β -elimination. The original conditions developed for the Robinson annulation reaction are such that the ketone enolate composition is under thermodynamic control. This usually results in the formation of product from the more stable enolate, as in Entry 3. The C(1) enolate is preferred because of the conjugation with the aromatic ring. For monosubstituted cyclohexanones, the cyclization usually occurs at the more-substituted position in hydroxylic solvents. The alternative regiochemistry can be achieved by using an enamine. Entry 4 is an example. As discussed in Section 1.9, the less-substituted enamine is favored, so addition occurs at the less-substituted position.

Conditions for kinetic control of enolate formation can be applied to the Robinson annulation to control the regiochemistry of the reaction. Entries 5 and 6 of Scheme 2.11 are cases in which the reaction is carried out on a preformed enolate. Kinetic

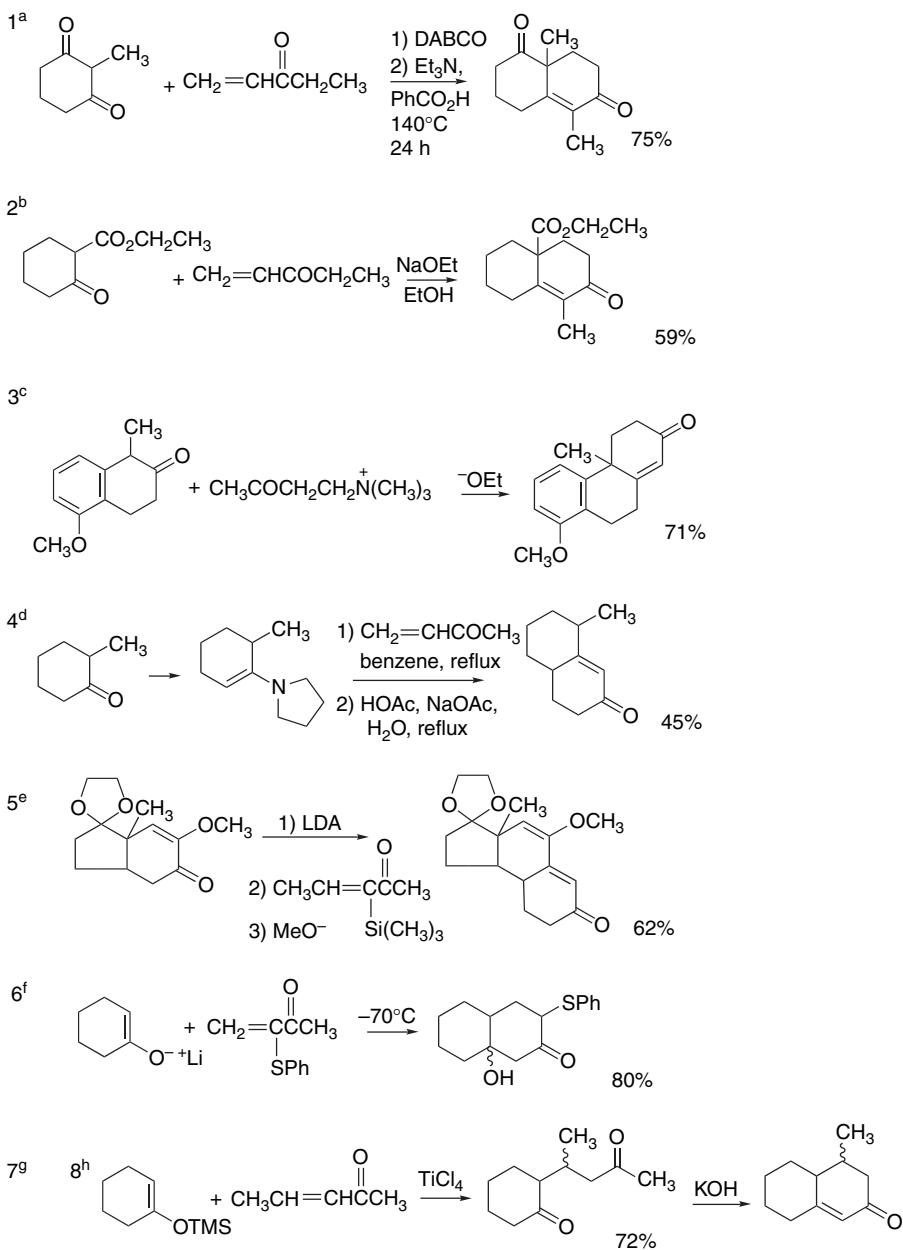
¹⁷¹ E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React.*, **10**, 179 (1950); J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949); R. Gawley, *Synthesis*, 777 (1976); M. E. Jung, *Tetrahedron*, **32**, 3 (1976); B. P. Mundy, *J. Chem. Ed.*, **50**, 110 (1973).

¹⁷² C. J. V. Scanio and R. M. Starrett, *J. Am. Chem. Soc.*, **93**, 1539 (1971).

Scheme 2.11. The Robinson Annulation Reaction

SECTION 2.1

Aldol Addition and Condensation Reactions



a. F. E. Ziegler, K.-J. Hwang, J. F. Kadow, S. I. Klein, U. K. Pati, and T.-F. Wang, *J. Org. Chem.*, **51**, 4573 (1986).

b. D. L. Snitman, R. J. Himmelsbach, and D. S. Watt, *J. Org. Chem.*, **43**, 4578 (1978).

c. J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).

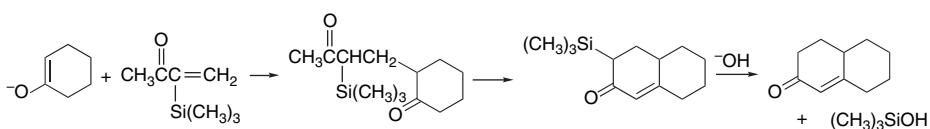
d. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

e. G. Stork, J. D. Winkler, and C. S. Shiner, *J. Am. Chem. Soc.*, **104**, 3767 (1982).

f. K. Takaki, M. Okada, M. Yamada, and K. Negoro, *J. Org. Chem.*, **47**, 1200 (1982).

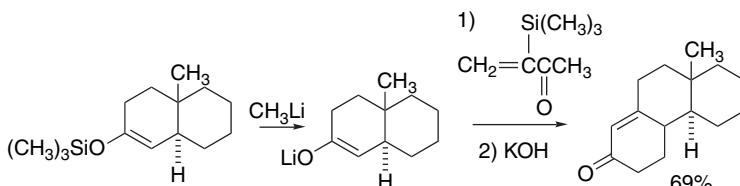
g. J. W. Huffman, S. M. Potnis, and A. V. Smith, *J. Org. Chem.*, **50**, 4266 (1985).

control is facilitated by use of somewhat more activated enones, such as methyl 1-(trimethylsilyl)vinyl ketone.



Ref. 173

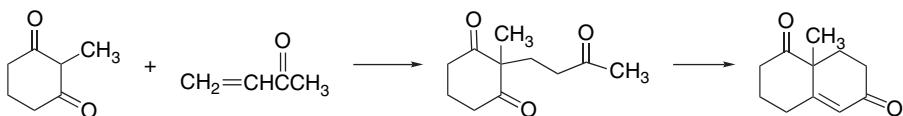
The role of the trimethylsilyl group is to stabilize the enolate formed in the conjugate addition. The silyl group is then removed during the dehydration step. Methyl 1-trimethylsilylvinyl ketone can be used under aprotic conditions that are compatible with regiospecific methods for enolate generation. The direction of annulation of unsymmetrical ketones can therefore be controlled by the method of enolate formation.



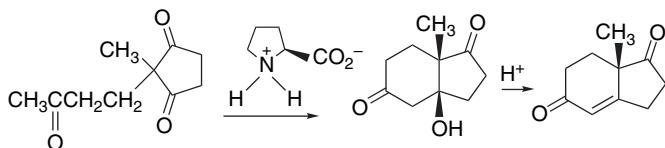
Ref. 174

Methyl 1-phenylthiovinyl ketones can also be used as enones in kinetically controlled Robinson annulation reactions, as illustrated by Entry 6. Entry 7 shows a annulation using silyl enol ether as the enolate equivalent. These reactions are called *Mukaiyama-Michael reactions* (see Section 2.6.3).

The Robinson annulation is a valuable method for preparing bicyclic and tricyclic structures that can serve as starting materials for the preparation of steroids and terpenes.¹⁷⁵ Reaction with 2-methylcyclohexan-1,3-dione gives a compound called the *Wieland-Miescher ketone*.



A similar reaction occurs with 2-methylcyclopentane-1,3-dione,¹⁷⁶ and can be done enantioselectively by using the amino acid L-proline to form an enamine intermediate. The (*S*)-enantiomer of the product is obtained in high enantiomeric excess.¹⁷⁷



¹⁷³ G. Stork and B. Ganem, *J. Am. Chem. Soc.*, **95**, 6152 (1973); G. Stork and J. Singh, *J. Am. Chem. Soc.*, **96**, 6181 (1974).

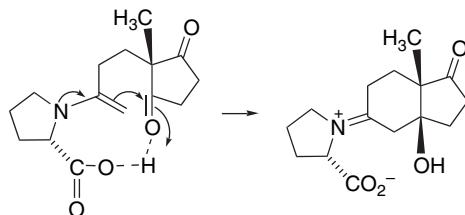
¹⁷⁴ R. K. Boeckman, Jr., *J. Am. Chem. Soc.*, **96**, 6179 (1974).

¹⁷⁵ N. Cohen, *Acc. Chem. Res.*, **9**, 412 (1976).

¹⁷⁶ Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **39**, 1615 (1974); U. Eder, G. Sauer, and R. Wiechert, *Angew. Chem. Int. Ed. Engl.*, **10**, 496 (1971); Z. G. Hajos and D. R. Parrish, *Org. Synth.*, **63**, 26 (1985).

¹⁷⁷ J. Gutzwiler, P. Buchshacher, and A. Furst, *Synthesis*, 167 (1977); P. Buchshacher and A. Furst, *Org. Synth.*, **63**, 37 (1984); T. Bui and C. F. Barbas, III, *Tetrahedron Lett.*, **41**, 6951 (2000).

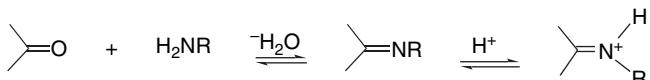
The detailed mechanism of this enantioselective transformation remains under investigation.¹⁷⁸ It is known that the acidic carboxylic group is crucial, and the cyclization is believed to occur via the enamine derived from the catalyst and the exocyclic ketone. A computational study suggested that the proton transfer occurs through a TS very similar to that described for the proline-catalyzed aldol reaction (see page 132).¹⁷⁹



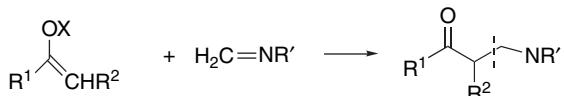
Visual models, additional information and exercises on Proline-Catalyzed Aldol Reactions can be found in the Digital Resource available at: Springer.com/carey-sundberg.

2.2. Addition Reactions of Imines and Iminium Ions

Imines and iminium ions are nitrogen analogs of carbonyl compounds and they undergo nucleophilic additions like those involved in aldol reactions. The reactivity order is $\text{C}=\text{NR} < \text{C}=\text{O} < [\text{C}=\text{NR}_2]^+ < [\text{C}=\text{OH}]^+$. Because iminium ions are more reactive than imines, the reactions are frequently run under mildly acidic conditions. Under some circumstances, the iminium ion can be the reactive species, even though it is a minor constituent in equilibrium with the amine, carbonyl compound, and unprotonated imine.



Addition of enols, enolates, or enolate equivalents to imines or iminium ions provides an important route to β -amino ketones.

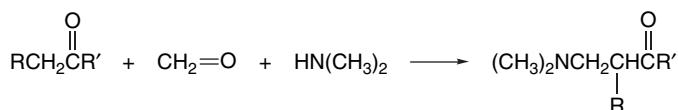


¹⁷⁸. P. Buchschacher, J.-M. Cassal, A. Furst, and W. Meier, *Helv. Chim. Acta*, **60**, 2747 (1977); K. L. Brown, L. Damm, J. D. Dunitz, A. Eschenmoser, R. Hobi, and C. Kratky, *Helv. Chim. Acta*, **61**, 3108 (1978); C. Agami, F. Meynier, C. Puchot, J. Guilhem, and C. Pascard, *Tetrahedron*, **40**, 1031 (1984); C. Agami, J. Levisalles, and C. Puchot, *J. Chem. Soc., Chem. Commun.*, 441 (1985); C. Agami, *Bull. Soc. Chim. Fr.*, 499 (1988).

¹⁷⁹. S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, **123**, 12911 (2001).

2.2.1. The Mannich Reaction

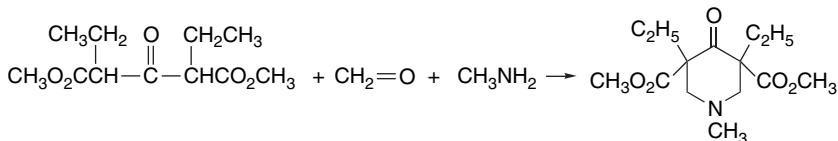
The *Mannich reaction* is the condensation of an enolizable carbonyl compound with an iminium ion.¹⁸⁰ It is usually done using formaldehyde and introduces an α -dialkylaminomethyl substituent.



The electrophile is often generated *in situ* from the amine and formaldehyde.



The reaction is normally limited to secondary amines, because dialkylation can occur with primary amines. The dialkylation reaction can be used to advantage in ring closures.



Ref. 181

Scheme 2.12 shows some representative Mannich reactions. Entries 1 and 2 show the preparation of typical “Mannich bases” from a ketone, formaldehyde, and a dialkylamine following the classical procedure. Alternatively, formaldehyde equivalents may be used, such as *bis*-(dimethylamino)methane in Entry 3. On treatment with trifluoroacetic acid, this aminal generates the iminium trifluoroacetate as a reactive electrophile. *N,N*-(Dimethyl)methylene ammonium iodide is commercially available and is known as *Eschenmoser’s salt*.¹⁸² This compound is sufficiently electrophilic to react directly with silyl enol ethers in neutral solution.¹⁸³ The reagent can be added to a solution of an enolate or enolate precursor, which permits the reaction to be carried out under nonacidic conditions. Entries 4 and 5 illustrate the preparation of Mannich bases using Eschenmoser’s salt in reactions with preformed enolates.

The dialkylaminomethyl ketones formed in the Mannich reaction are useful synthetic intermediates.¹⁸⁴ Thermal elimination of the amines or the derived quaternary salts provides α -methylene carbonyl compounds.

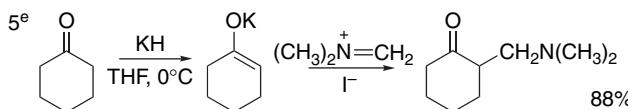
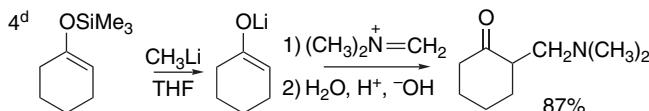
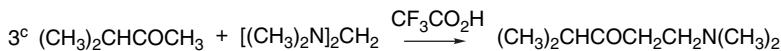
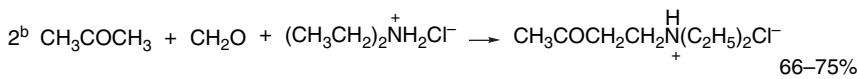
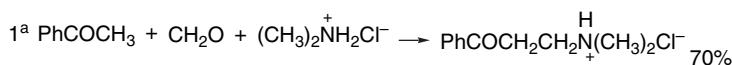
- ¹⁸⁰ F. F. Blicke, *Org. React.*, **1**, 303 (1942); J. H. Brewster and E. L. Eliel, *Org. React.*, **7**, 99 (1953); M. Tramontini and L. Angiolini, *Tetrahedron*, **46**, 1791 (1990); M. Tramontini and L. Angiolini, *Mannich Bases: Chemistry and Uses*, CRC Press, Boca Raton, FL, 1994; M. Ahrend, B. Westerman, and N. Risch, *Angew. Chem. Int. Ed. Engl.*, **37**, 1045 (1998).
- ¹⁸¹ C. Mannich and P. Schumann, *Chem. Ber.*, **69**, 2299 (1936).
- ¹⁸² J. Schreiber, H. Maag, N. Hashimoto, and A. Eschenmoser, *Angew. Chem. Int. Ed. Engl.*, **10**, 330 (1971).
- ¹⁸³ S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Am. Chem. Soc.*, **98**, 6715 (1976).
- ¹⁸⁴ G. A. Gevorgyan, A. G. Agababyan, and O. L. Mndzhoyan, *Russ. Chem. Rev. (Engl. Transl.)*, **54**, 495 (1985).

Scheme 2.12. Synthesis and Utilization of Mannich Bases

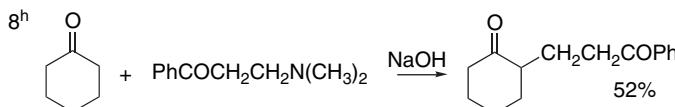
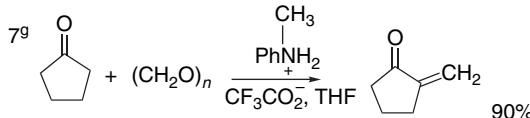
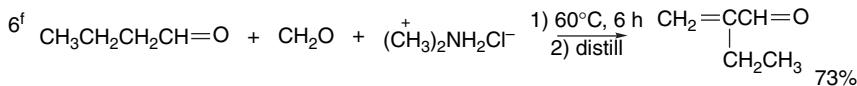
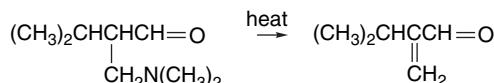
SECTION 2.2

Addition Reactions of
Imines and Iminium Ions

A. Aminomethylation Using the Mannich Reaction



B. Reactions Involving Secondary Transformations of Aminomethylation Products.

a. C. E. Maxwell, *Org. Synth.*, **III**, 305 (1955).b. A. L. Wilds, R. M. Novak, and K. E. McCaleb, *Org. Synth.*, **IV**, 281 (1963).c. M. Gaudry, Y. Jasor, and T. B. Khac, *Org. Synth.*, **59**, 153 (1979).d. S. Danishefsky, T. Kitahara, R. McKee, and P. F. Schuda, *J. Am. Chem. Soc.*, **98**, 6715 (1976).e. J. L. Roberts, P. S. Borromeo, and C. D. Poulter, *Tetrahedron Lett.*, 1621 (1977).f. C. S. Marvel, R. L. Myers, and J. H. Saunders, *J. Am. Chem. Soc.*, **70**, 1694 (1948).g. J. L. Gras, *Tetrahedron Lett.*, 2111, 2955 (1978).h. A. C. Cope and E. C. Hermann, *J. Am. Chem. Soc.*, **72**, 3405 (1950).i. E. B. Knott, *J. Chem. Soc.*, 1190 (1947).

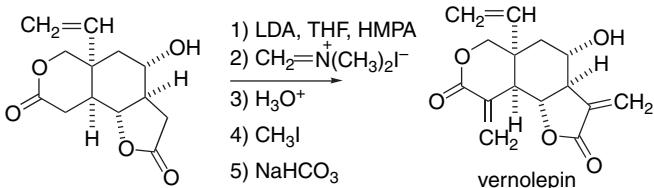
Ref. 185

These α,β -unsaturated ketones and aldehydes are used as reactants in conjugate additions (Section 2.6), Robinson annulations (Section 2.1.4), and in a number of other reactions that we will encounter later. Entries 8 and 9 in Scheme 2.12 illustrate

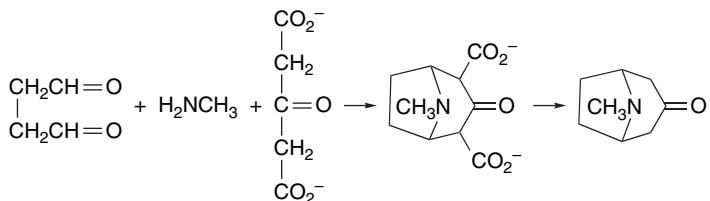
185. C. S. Marvel, R. L. Myers, and J. H. Saunders, *J. Am. Chem. Soc.*, **70**, 1694 (1948).

conjugate addition reactions carried out by *in situ* generation of α,β -unsaturated carbonyl compounds from Mannich bases.

α -Methylenelactones are present in a number of natural products.¹⁸⁶ The reaction of ester enolates with *N,N*-(dimethyl)methyleneammonium trifluoroacetate,¹⁸⁷ or Eschenmoser's salt,¹⁸⁸ has been used for introduction of the α -methylene group in the synthesis of vernolepin, a compound with antileukemic activity.^{189,190}



Mannich reactions, or a mechanistic analog, are important in the biosynthesis of many nitrogen-containing natural products. As a result, the Mannich reaction has played an important role in the synthesis of such compounds, especially in syntheses patterned after the biosynthesis, i.e., *biomimetic synthesis*. The earliest example of the use of the Mannich reaction in this way was Sir Robert Robinson's successful synthesis of tropinone, a derivative of the alkaloid tropine, in 1917.



Ref. 191

As with aldol and Mukaiyama addition reactions, the Mannich reaction is subject to enantioselective catalysis.¹⁹² A catalyst consisting of Ag^+ and the chiral imino aryl phosphine **22** achieves high levels of enantioselectivity with a range of *N*-(2-methoxyphenyl)imines.¹⁹³ The 2-methoxyphenyl group is evidently involved in an interaction with the catalyst and enhances enantioselectivity relative to other *N*-aryl substituents. The isopropanol serves as a proton source and as the ultimate acceptor of the trimethylsilyl group.

¹⁸⁶ S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).

¹⁸⁷ N. L. Holy and Y. F. Wang, *J. Am. Chem. Soc.*, **99**, 499 (1977).

¹⁸⁸ J. L. Roberts, P. S. Borromes, and C. D. Poulter, *Tetrahedron Lett.*, 1621 (1977).

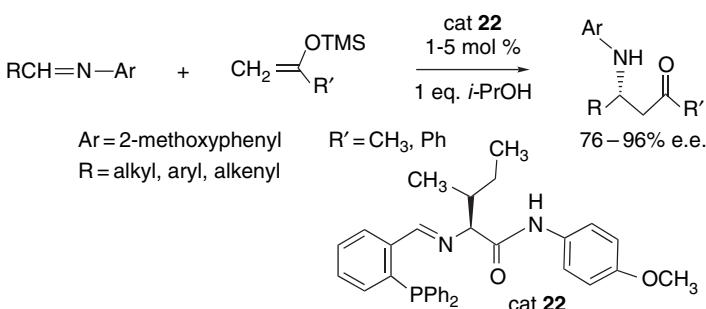
¹⁸⁹ S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, *J. Am. Chem. Soc.*, **99**, 6066 (1977).

¹⁹⁰ For reviews of methods for the synthesis of α -methylene lactones, see R. B. Gammill, C. A. Wilson, and T. A. Bryson, *Synth. Comm.*, **5**, 245 (1975); J. C. Sarma and R. P. Sharma, *Heterocycles*, **24**, 441 (1986); N. Petragnani, H. M. C. Ferraz, and G. V. J. Silva, *Synthesis*, 157 (1986).

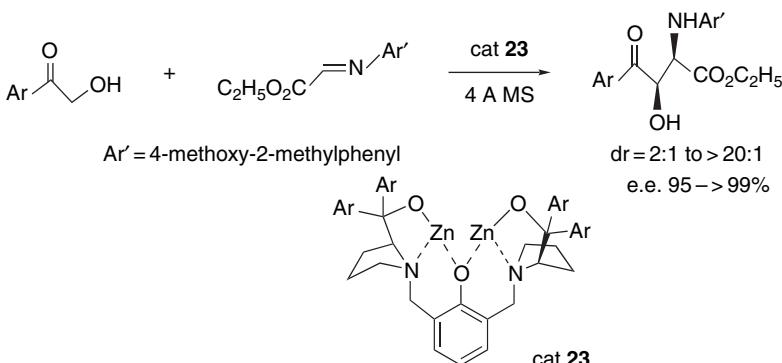
¹⁹¹ R. Robinson, *J. Chem. Soc.*, 762 (1917).

¹⁹² A. Cordova, *Acc. Chem. Res.*, **37**, 102 (2004).

¹⁹³ N. S. Josephsohn, M. L. Snapper, and A. H. Hoveyda, *J. Am. Chem. Soc.*, **126**, 3734 (2004).

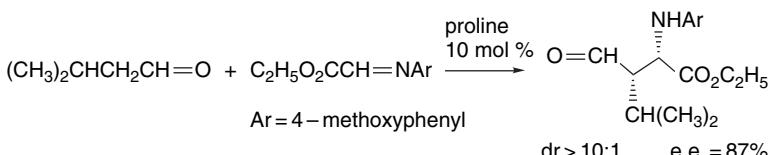


A zinc catalyst **23** was found effective for aryl hydroxymethyl ketones in reactions with glyoxylic imines. In this case, the 4-methoxy-2-methylphenylimines gave the best results.¹⁹⁴ Interestingly, the 2-methoxyphenyl ketone gave substantially enhanced 2,3-diastereoselectivity (20:1) compared to about 10:1 for most other aryl groups, suggesting that the *o*-methoxy group may introduce an additional interaction with the catalyst. All the compounds gave e.e. > 95%.



Other types of catalysts that are active in Mannich reactions include the Cu-*bis*-oxazolines.¹⁹⁵ Most of the cases examined to date are for relatively reactive imines, such as those derived from glyoxylate or pyruvate esters.

As already discussed for aldol and Robinson annulation reactions, proline is also a catalyst for enantioselective Mannich reactions. Proline effectively catalyzes the reactions of aldehydes such as 3-methylbutanal and hexanal with *N*-arylimines of ethyl glyoxalate.¹⁹⁶ These reactions show 2,3-*syn* selectivity, although the products with small alkyl groups tend to isomerize to the *anti* isomer.



¹⁹⁴ B. M. Trost and L. M. Terrell, *J. Am. Chem. Soc.*, **125**, 338 (2003).

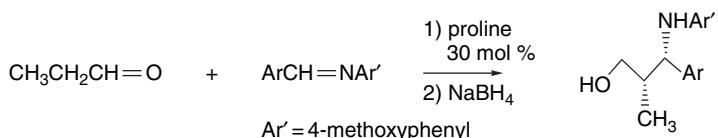
¹⁹⁵ K. Juhl and K. A. Jorgensen, *J. Am. Chem. Soc.*, **124**, 2420 (2002); M. Marigo, A. Kjaersgaard, K. Juhl, N. Gathergood, and K. A. Jorgensen, *Chem. Eur. J.*, **9**, 2359 (2003).

¹⁹⁶ W. Notz, F. Tanaka, S. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, and C. F. Barbas, III, *J. Org. Chem.*, **68**, 9624 (2003).

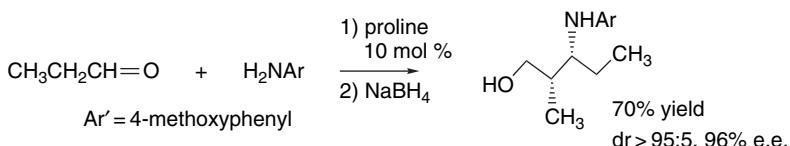
With aromatic aldehydes, d.r. ranged up to more than 10:1 for propanal.

CHAPTER 2

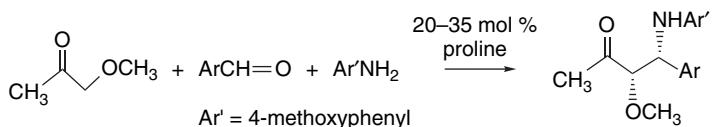
Reactions of Carbon Nucleophiles with Carbonyl Compounds



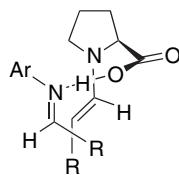
The proline-catalyzed reaction has been extended to the reaction of propanal, butanal, and pentanal with a number of aromatic aldehydes and proceeds with high *syn* selectivity.¹⁹⁷ The reaction can also be carried out under conditions in which the imine is formed in situ. Under these conditions, the conjugative stabilization of the aryl imines leads to the preference for the aryl imine to act as the electrophile. A good yield of the expected β -aminoalcohol was obtained with propanal serving as both the nucleophilic and the electrophilic component. The product was isolated as a γ -amino alcohol after reduction with NaBH_4 .



Ketones such as acetone, hydroxyacetone, and methoxyacetone can be condensed with both aromatic and aliphatic aldehydes.¹⁹⁸



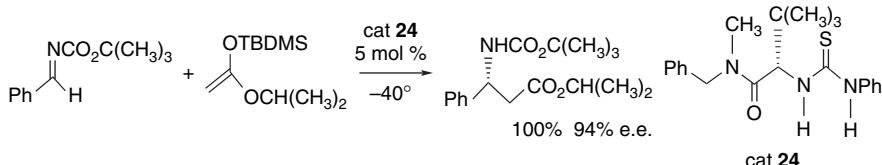
The TS proposed for these proline-catalyzed reactions is very similar to that for the proline-catalyzed aldol addition (see p. 132). In the case of imines, however, the aldehyde substituent is directed *toward* the enamine double bond because of the dominant steric effect of the *N*-aryl substituent. This leads to formation of *syn* isomers, whereas the aldol reaction leads to *anti* isomers. This is the TS found to be the most stable by B3LYP/6-31G* computations.¹⁹⁹ The proton transfer is essentially complete at the TS. As with the aldol addition TS, the enamine is oriented *anti* to the proline carboxy group in the most stable TS.



¹⁹⁷. Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, and K. Sakai, *Angew. Chem. Int. Ed. Engl.*, **42**, 3677 (2003).

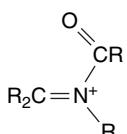
¹⁹⁸. B. List, P. Pojarliev, W. T. Biller, and H. J. Martin, *J. Am. Chem. Soc.*, **124**, 827 (2002).

¹⁹⁹. S. Bahmanyar and K. N. Houk, *Org. Lett.*, **5**, 1249 (2003).

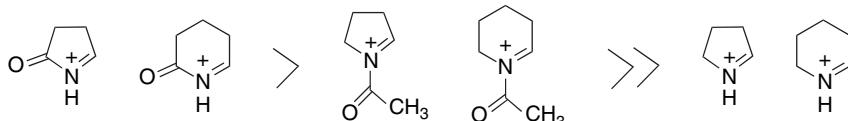


2.2.2. Additions to *N*-Acyl Iminium Ions

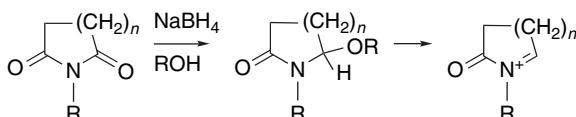
Even more reactive C=N bonds are present in *N*-acyliminium ions.²⁰²



Gas phase reactivity toward allyltrimethylsilane was used to compare the reactivity of several cyclic *N*-acyliminium ions and related iminium ions.²⁰³ Compounds with endocyclic acyl groups were found to be more reactive than compounds with exocyclic acyl substituents. Five-membered ring compounds are somewhat more reactive than six-membered ones. The higher reactivity of the endocyclic acyl derivatives is believed to be due to geometric constraints that maximize the polar effect of the carbonyl group.



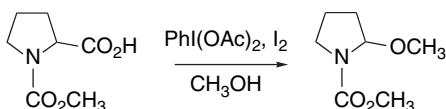
N-Acyliminium ions are usually prepared *in situ* in the presence of a potential nucleophile. There are several ways of generating acyliminium ions. Cyclic examples can be generated by partial reduction of imides.²⁰⁴



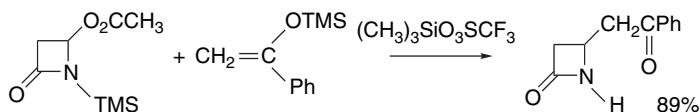
Various oxidations of amides or carbamates can also generate acyliminium ions. An electrochemical oxidation forms α -alkoxy amides and lactams, which then generate

- ²⁰⁰. P. Vachal and E. N. Jacobsen, *J. Am. Chem. Soc.*, **124**, 10012 (2002).
- ²⁰¹. A. G. Wenzel, M. P. Lalonde, and E. N. Jacobsen, *Synlett*, 1919 (2003).
- ²⁰². H. Hiemstra and W. N. Speckamp, in *Comprehensive Organic Synthesis*, Vol. 2, B. Trost and I. Fleming, eds., 1991, pp. 1047–1082; W. N. Speckamp and M. J. Moolenaar, *Tetrahedron*, **56**, 3817 (2000); B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, and C. A. Maryanoff, *Chem. Rev.*, **104**, 1431 (2004).
- ²⁰³. M. G. M. D’Oca, L. A. B. Moraes, R. A. Pilli, and M. N. Eberlin, *J. Org. Chem.*, **66**, 3854 (2001).
- ²⁰⁴. J. C. Hubert, J. B. P. A. Wijnberg, and W. Speckamp, *Tetrahedron*, **31**, 1437 (1975); H. Hiemstra, W. J. Klaver, and W. N. Speckamp, *J. Org. Chem.*, **49**, 1149 (1984); P. A. Pilli, L. C. Dias, and A. O. Maldaner, *J. Org. Chem.*, **60**, 717 (1995).

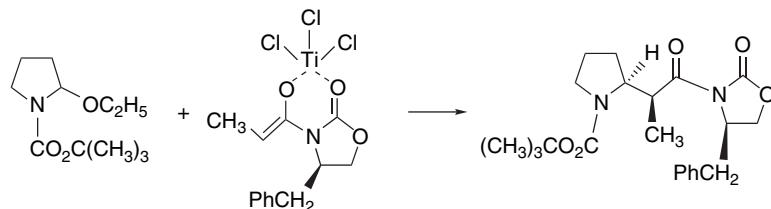
acyliminium ions.²⁰⁵ *N*-Acyliminium ions can also be obtained by oxidative decarboxylation of *N*-acyl- α -amino acids such as *N*-acyl proline derivatives.²⁰⁶



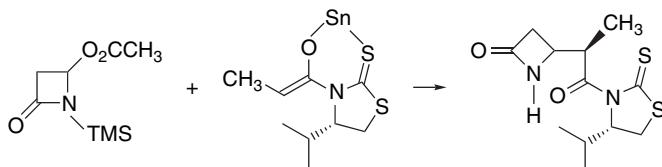
Acyliminium ions are sufficiently electrophilic to react with enolate equivalents such as silyl enol ethers²⁰⁷ and isopropenyl acetate.²⁰⁸



Acyliminium ions can be used in enantioselective additions with enolates having chiral auxiliaries, such as *N*-acyloxazolidinones or *N*-acylthiazolidinethiones.



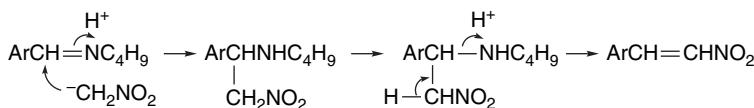
Ref. 209



Ref. 210

- ²⁰⁵ T. Shono, H. Hamaguchi, and Y. Matsumura, *J. Am. Chem. Soc.*, **97**, 4264 (1975); T. Shono, Y. Matsumura, K. Tsubata, Y. Sugihara, S. Yamane, T. Kanazawa, and T. Aoki, *J. Am. Chem. Soc.*, **104**, 6697 (1982); T. Shono, *Tetrahedron*, **40**, 811 (1984).
- ²⁰⁶ A. Boto, R. Hernandez, and E. Suarez, *J. Org. Chem.*, **65**, 4930 (2000).
- ²⁰⁷ R. P. Attrill, A. G. M. Barrett, P. Quayle, J. van der Westhuizen, and M. J. Betts, *J. Org. Chem.*, **49**, 1679 (1984); K. T. Wanner, A. Kartner, and E. Wadenstorfer, *Heterocycles*, **27**, 2549 (1988); M. A. Ciufolini, C. W. Hermann, K. H. Whitmire, and N. E. Byrne, *J. Am. Chem. Soc.*, **111**, 3473 (1989); D. S. Brown, M. J. Earle, R. A. Fairhurst, H. Heaney, G. Papageorgiou, R. F. Wilkins, and S. C. Eyley, *Synlett*, 619 (1990).
- ²⁰⁸ T. Shono, Y. Matsumura, and K. Tsubata, *J. Am. Chem. Soc.*, **103**, 1172 (1981).
- ²⁰⁹ R. A. Pilli and D. Russowsky, *J. Org. Chem.*, **61**, 3187 (1996); R. A. Pilli, C. de F. Alves, M. A. Boeckelmann, Y. P. Mascarenhas, J. G. Nery, and I. Vencato, *Tetrahedron Lett.*, **40**, 2891 (1999).
- ²¹⁰ Y. Nagao, T. Kumagi, S. Tamai, T. Abe, Y. Kuramoto, T. Taga, S. Aoyagi, Y. Nagase, M. Ochiai, Y. Inoue, and E. Fujita, *J. Am. Chem. Soc.*, **108**, 4673 (1986); T. Nagao, W.-M. Dai, M. Ochiai, S. Tsukagoshi, and E. Fujita, *J. Org. Chem.*, **55**, 1148 (1990).

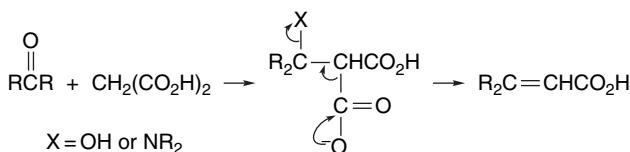
Iminium ions are intermediates in a group of reactions that form α,β -unsaturated compounds having structures corresponding to those formed by mixed aldol addition followed by dehydration. These reactions are catalyzed by amines or buffer systems containing an amine and an acid and are referred to as *Knoevenagel condensations*.²¹¹ The reactive electrophile is probably the protonated form of the imine, since it is a more reactive electrophile than the corresponding carbonyl compound.²¹²



The carbon nucleophiles in amine-catalyzed reaction conditions are usually rather acidic compounds containing two EWG substituents. Malonate esters, cyanoacetate esters, and cyanoacetamide are examples of compounds that undergo condensation reactions under Knoevenagel conditions.²¹³ Nitroalkanes are also effective as nucleophilic reactants. The single nitro group activates the α -hydrogens enough to permit deprotonation under the weakly basic conditions. A relatively acidic proton in the nucleophile is important for two reasons. First, it permits weak bases, such as amines, to provide a sufficient concentration of the enolate for reaction. An acidic proton also facilitates the elimination step that drives the reaction to completion. Usually the product that is isolated is the α,β -unsaturated derivative of the original adduct.



Malonic acid or cyanoacetic acid can also be used as the nucleophile. With malonic acid or cyanoacetic acid as reactants, the products usually undergo decarboxylation. This may occur as a concerted fragmentation of the adduct.²¹⁴



Decarboxylative condensations of this type are sometimes carried out in pyridine, which cannot form an imine intermediate, but has been shown to catalyze the decarboxylation of arylidene malonic acids.²¹⁵ The decarboxylation occurs by concerted decomposition of the adduct of pyridine to the α,β -unsaturated diacid.

²¹¹ G. Jones, *Org. React.*, **15**, 204 (1967); R. L. Reeves, in *The Chemistry of the Carbonyl Group*, S. Patai, ed., Interscience, New York, 1966, pp. 593–599.

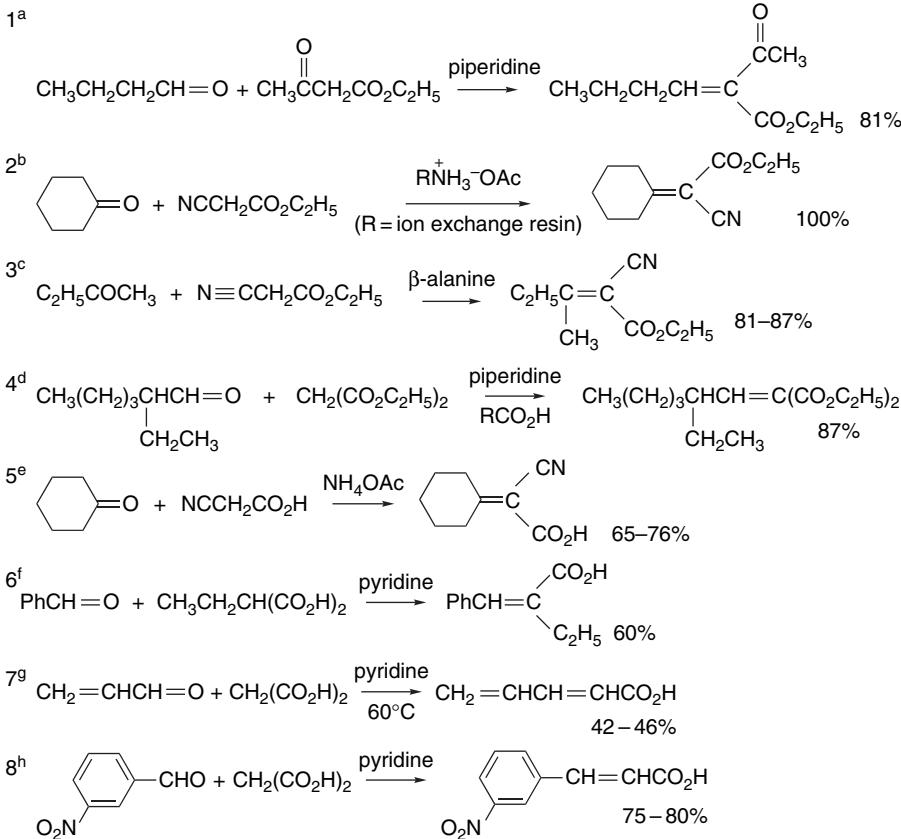
²¹² T. I. Crowell and D. W. Peck, *J. Am. Chem. Soc.*, **75**, 1075 (1953).

²¹³ A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

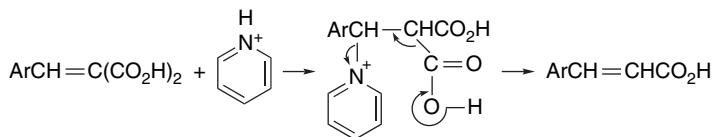
²¹⁴ E. J. Corey, *J. Am. Chem. Soc.*, **74**, 5897 (1952).

²¹⁵ E. J. Corey and G. Fraenkel, *J. Am. Chem. Soc.*, **75**, 1168 (1953).

Scheme 2.13. Amine-Catalyzed Condensation Reactions of the Knoevenagel Type



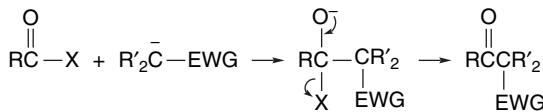
- a. A. C. Cope and C. M. Hofmann, *J. Am. Chem. Soc.*, **63**, 3456 (1941).
 b. R. W. Hein, M. J. Astle, and J. R. Shelton, *J. Org. Chem.*, **26**, 4874 (1961).
 c. F. S. Prout, R. J. Harman, E. P.-Y. Huang, C. J. Korpics, and G. R. Tichelaar, *Org. Synth.*, **IV**, 93 (1963).
 d. E. F. Pratt and E. Werbie, *J. Am. Chem. Soc.*, **72**, 4638 (1950).
 e. A. C. Cope, A. A. D'Addieco, D. E. Whyte, and S. A. Glickman, *Org. Synth.*, **IV**, 234 (1963).
 f. W. J. Gensler and E. Berman, *J. Am. Chem. Soc.*, **80**, 4949 (1958).
 g. P. J. Jessup, C. B. Petty, J. Roos, and L. E. Overman, *Org. Synth.*, **59**, 1 (1979).
 h. R. H. Wiley and N. R. Smith, *Org. Synth.*, **IV**, 731 (1963).



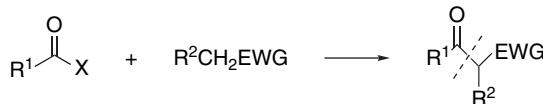
Scheme 2.13 gives some examples of Knoevenagel condensation reactions.

2.3. Acylation of Carbon Nucleophiles

The reactions that are discussed in this section involve addition of carbon nucleophiles to carbonyl centers having a potential leaving group. The tetrahedral intermediate formed in the addition step reacts by expulsion of the leaving group. The overall

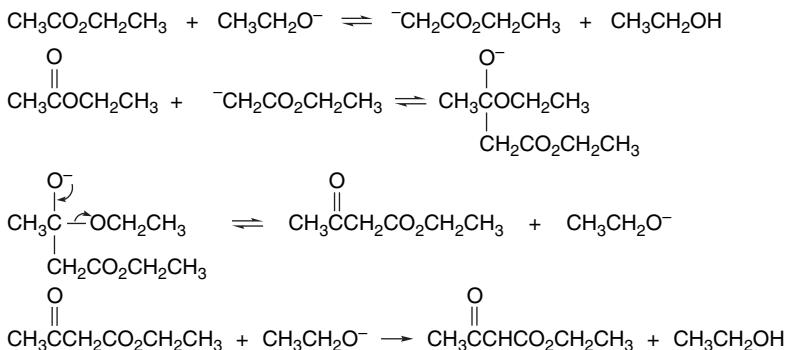


The reaction pattern can be used for the synthesis of 1,3-dicarbonyl compounds and other systems in which an acyl group is β to an anion-stabilizing group.



2.3.1. Claisen and Dieckmann Condensation Reactions

An important group of acylation reactions involves esters, in which case the leaving group is alkoxy or aryloxy. The self-condensation of esters is known as the *Claisen condensation*.²¹⁶ Ethyl acetoacetate, for example, is prepared by Claisen condensation of ethyl acetate. All of the steps in the mechanism are reversible, and a full equivalent of base is needed to bring the reaction to completion. Ethyl acetoacetate is more acidic than any of the other species present and is converted to its conjugate base in the final step. The β -ketoester product is obtained after neutralization.



As a practical matter, the alkoxide used as the base must be the same as the alcohol portion of the ester to prevent product mixtures resulting from ester interchange. Sodium hydride with a small amount of alcohol is frequently used as the base for ester condensation. The reactive base is the sodium alkoxide formed by reaction of sodium hydride with the alcohol released in the condensation.

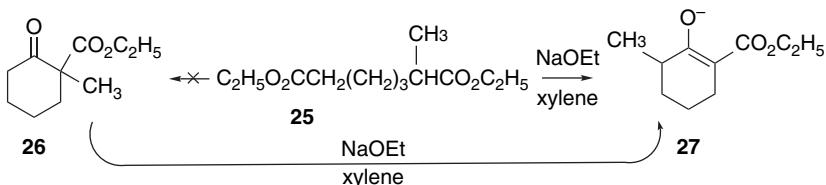


As the final proton transfer cannot occur when α -substituted esters are used, such compounds do not condense under the normal reaction conditions, but this limitation

²¹⁶ C. R. Hauser and B. E. Hudson, Jr., *Org. React.*, **1**, 266 (1942).

can be overcome by use of a very strong base that converts the reactant ester completely to its enolate. Entry 2 of Scheme 2.14 illustrates the use of triphenylmethylsodium for this purpose. The sodium alkoxide is also the active catalyst in procedures that use sodium metal, such as in Entry 3 in Scheme 2.14. The alkoxide is formed by reaction of the alcohol that is formed as the reaction proceeds.

The intramolecular version of ester condensation is called the *Dieckmann condensation*.²¹⁷ It is an important method for the formation of five- and six-membered rings and has occasionally been used for formation of larger rings. As ester condensation is reversible, product structure is governed by thermodynamic control, and in situations where more than one product can be formed, the product is derived from the most stable enolate. An example of this effect is the cyclization of the diester **25**.²¹⁸ Only **27** is formed, because **26** cannot be converted to a stable enolate. If **26**, synthesized by another method, is subjected to the conditions of the cyclization, it is isomerized to **27** by the reversible condensation mechanism.



Entries 3 to 8 in Scheme 2.14 are examples of Dieckmann condensations. Entry 6 is a Dieckmann reaction carried out under conventional conditions, followed by decarboxylation. The product is a starting material for the synthesis of a number of sarpagine-type indole alkaloids and can be carried out on a 100-g scale. The combination of a Lewis acid, such as $MgCl_2$, with an amine can also promote Dieckmann cyclization.²¹⁹ Entry 7, which shows an application of these conditions, is a step in the synthesis of a potential drug. These conditions were chosen to avoid the use of $TiCl_4$ in a scale-up synthesis and can be done on a 60-kg scale. The 14-membered ring formation in Entry 8 was carried out under high dilution by slowly adding the reactant to the solution of the NaHMDS base. The product is a mixture of both possible regioisomers (both the 5- and 7-carbomethoxy derivatives are formed) but a single product is obtained after decarboxylation.

Mixed condensations of esters are subject to the same general restrictions as outlined for mixed aldol reactions (Section 2.1.2). One reactant must act preferentially as the acceptor and another as the nucleophile for good yields to be obtained. Combinations that work best involve one ester that cannot form an enolate but is relatively reactive as an electrophile. Esters of aromatic acids, formic acid, and oxalic acid are especially useful. Some examples of mixed ester condensations are shown in Section C of Scheme 2.14. Entries 9 and 10 show diethyl oxalate as the acceptor, and aromatic esters function as acceptors in Entries 11 and 12.

2.3.2. Acylation of Enolates and Other Carbon Nucleophiles

Acylation of carbon nucleophiles can also be carried out with more reactive acylating agents such as acid anhydrides and acyl chlorides. These reactions must

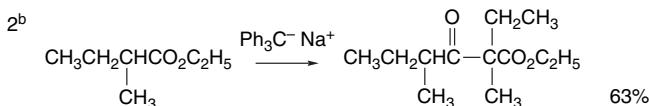
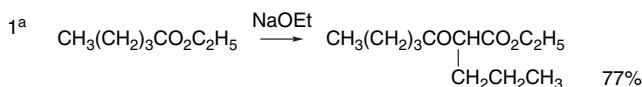
²¹⁷ J. P. Schaefer and J. J. Bloomfield, *Org. React.*, **15**, 1 (1967).

²¹⁸ N. S. Vul'fson and V. I. Zaretskii, *J. Gen. Chem. USSR*, **29**, 2704 (1959).

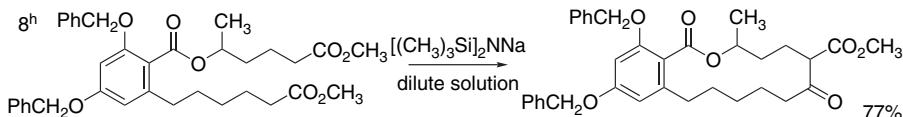
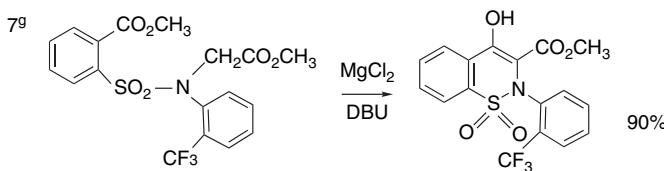
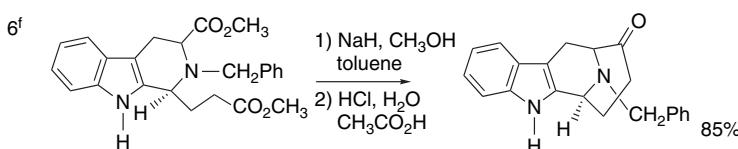
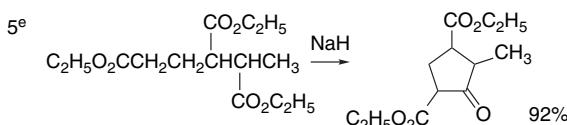
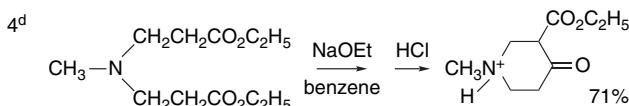
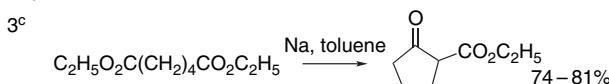
²¹⁹ S. Tamai, H. Ushitoguchi, S. Sano, and Y. Nagao, *Chem. Lett.*, 295 (1995).

A. Intermolecular ester condensations

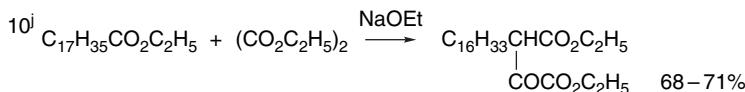
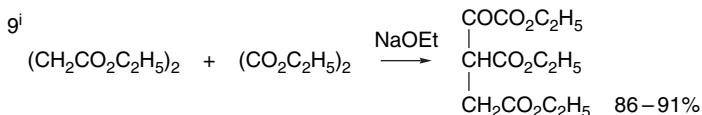
A. Intermolecular ester condensations



B. Cyclization of diesters



C. Mixed ester condensations

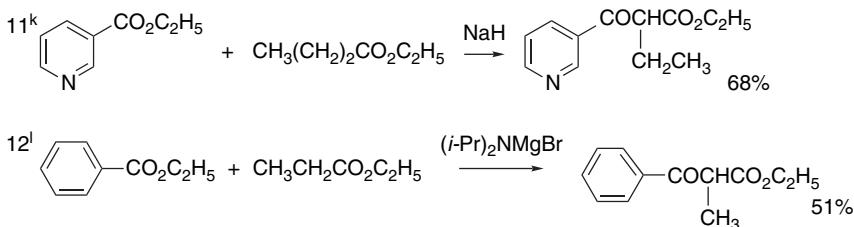


(Continued)

Scheme 2.14. (Continued)

CHAPTER 2

Reactions of Carbon Nucleophiles with Carbonyl Compounds



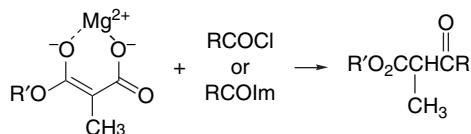
- a. R. R. Briese and S. M. McElvain, *J. Am. Chem. Soc.*, **55**, 1697 (1933).
- b. B. E. Hudson, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **63**, 3156 (1941).
- c. P. S. Pinkney, *Org. Synth.*, **II**, 116 (1943).
- d. E. A. Prill and S. M. McElvain, *J. Am. Chem. Soc.*, **55**, 1233 (1933).
- e. M. S. Newman and J. L. McPherson, *J. Org. Chem.*, **19**, 1717 (1954).
- f. J. Yu, T. Wang, X. Liu, J. Deschamps, J. Flippin-Anderson, X. Liao, and J. M. Cook, *J. Org. Chem.*, **68**, 7565 (2003); P. Yu, T. Wang, J. Li, and J. M. Cook, *J. Org. Chem.*, **65**, 3173 (2000).
- g. T. E. Jacks, D. T. Belmont, C. A. Briggs, N. M. Horne, G. D. Kanter, G. L. Kerrick, J. L. Krikke, R. J. McCabe, J. G. Mustakis, T. N. Nanninga, G. S. Risedorph, R. E. Seamans, R. Skeean, D. D. Winkle, and T. M. Zennie, *Org. Proc. Res. Develop.*, **8**, 201 (2004).
- h. R. N. Hurd and D. H. Shah, *J. Org. Chem.*, **38**, 390 (1973).
- i. E. M. Bottorff and L. L. Moore, *Org. Synth.*, **44**, 67 (1964).
- j. F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.*, **72**, 1352 (1950).
- k. D. E. Floyd and S. E. Miller, *Org. Synth.*, **IV**, 141 (1963).
- l. E. E. Royals and D. G. Turpin, *J. Am. Chem. Soc.*, **76**, 5452 (1954).

be done in nonnucleophilic solvents to avoid solvolysis of the acylating agent. The use of these reactive acylating agents can be complicated by competing O-acylation. Magnesium enolates play a prominent role in these C-acylation reactions. The magnesium enolate of diethyl malonate, for example, can be prepared by reaction with magnesium metal in ethanol. It is soluble in ether and undergoes C-acylation by acid anhydrides and acyl chlorides. The preparation of diethyl benzoylmalonate (Entry 1, Scheme 2.15) is an example of the use of an acid anhydride. Entries 2 to 5 illustrate the use of acyl chlorides. Entry 3 is carried out in basic aqueous solution and results in deacylation of the initial product.

Monoalkyl esters of malonic acid react with Grignard reagents to give a chelated enolate of the malonate monoanion.



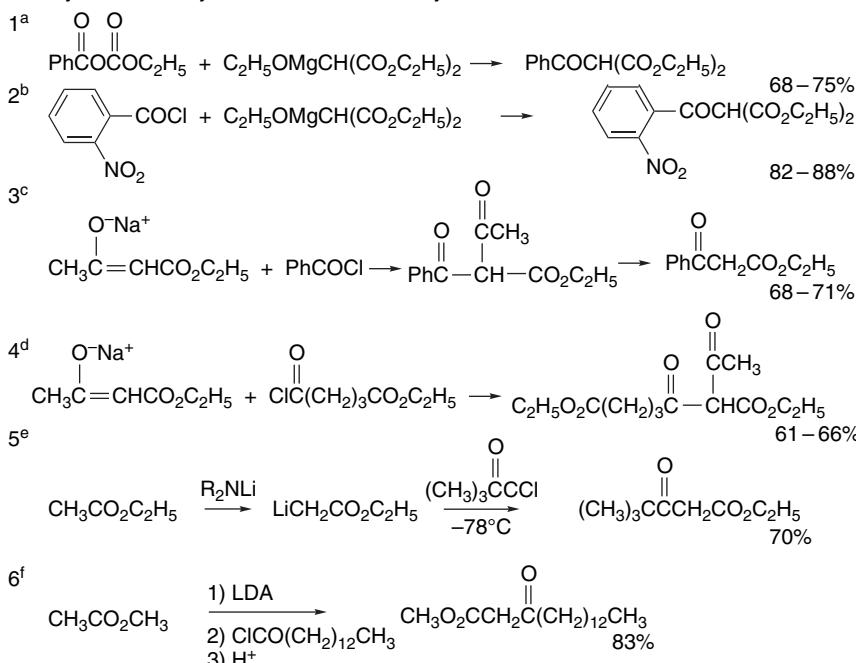
These carbon nucleophiles react with acyl chlorides²²⁰ or acyl imidazolides.²²¹ The initial products decarboxylate readily so the isolated products are β -ketoesters.



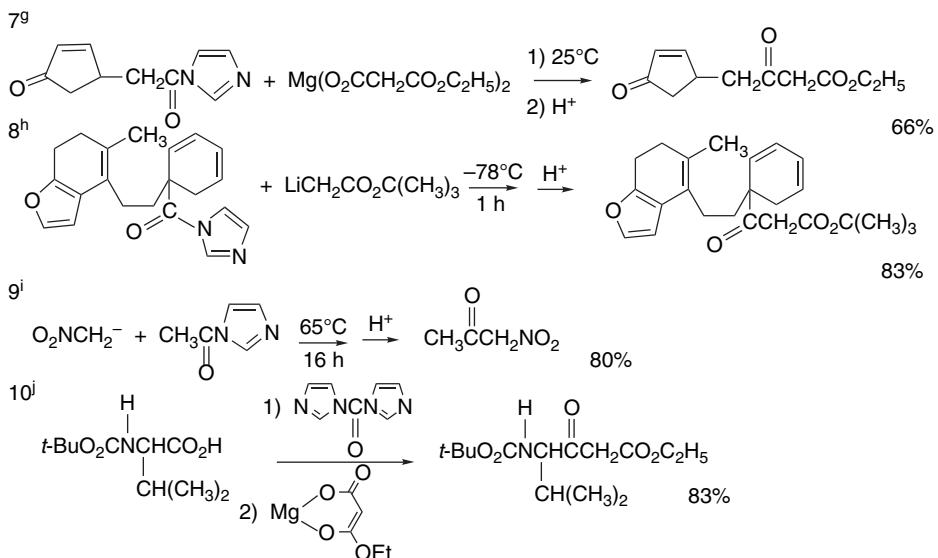
²²⁰ R. E. Ireland and J. A. Marshall, *J. Am. Chem. Soc.*, **81**, 2907 (1959).

²²¹ J. Maibaum and D. H. Rich, *J. Org. Chem.*, **53**, 869 (1988); W. H. Moos, R. D. Gless, and H. Rapoport, *J. Org. Chem.*, **46**, 5064 (1981); D. W. Brooks, L. D.-L. Lu, and S. Masamune, *Angew. Chem. Int. Ed. Engl.*, **18**, 72 (1979).

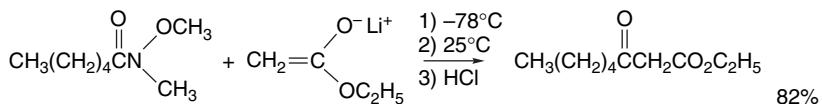
A. Acylation with acyl halides and mixed anhydrides



B. Acylation with imidazolides

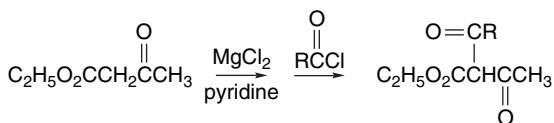
a. J. A. Price and D. S. Tarbell, *Org. Synth.*, **IV**, 285 (1963).b. G. A. Reynolds and C. R. Hauser, *Org. Synth.*, **IV**, 708 (1963).c. J. M. Straley and A. C. Adams, *Org. Synth.*, **IV**, 415 (1963).d. M. Guha and D. Nasipuri, *Org. Synth.*, **V**, 384 (1973).e. M. W. Rathke and J. Deitch, *Tetrahedron Lett.*, 2953 (1971).f. D. F. Taber, P. B. Dekker, H. M. Fales, T. H. Jones, and H. A. Lloyd, *J. Org. Chem.*, **53**, 2968 (1988).g. A. Barco, S. Bennetti, G. P. Pollini, P. G. Baraldi, and C. Gandolfi, *J. Org. Chem.*, **45**, 4776 (1980).h. E. J. Corey, G. Wess, Y. B. Xiang, and A. K. Singh, *J. Am. Chem. Soc.*, **109**, 4717 (1987).i. M. E. Jung, D. D. Grove, and S. I. Khan, *J. Org. Chem.*, **52**, 4570 (1987).j. J. Maibaum and D. H. Rich, *J. Org. Chem.*, **53**, 869 (1988).

Acyl imidazolides are more reactive than esters but not as reactive as acyl halides. Entry 7 is an example of formation of a β -ketoesters by reaction of magnesium enolate monoalkyl malonate ester by an imidazolide. Acyl imidazolides also are used for acylation of ester enolates and nitromethane anion, as illustrated by Entries 8, 9, and 10. *N*-Methoxy-*N*-methylamides are also useful for acylation of ester enolates.



Ref. 222

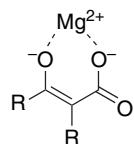
Both diethyl malonate and ethyl acetoacetate can be acylated by acyl chlorides using magnesium chloride and pyridine or triethylamine.²²³



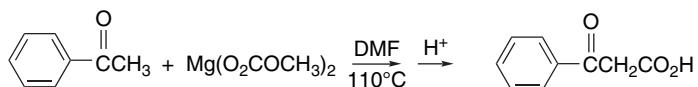
Rather similar conditions can be used to convert ketones to β -keto acids by carboxylation.²²⁴



These reactions presumably involve formation of a magnesium chelate of the keto acid. The β -ketoacid is liberated when the reaction mixture is acidified during workup.



Carboxylation of ketones and esters can also be achieved by using the magnesium salt of monomethyl carbonate.



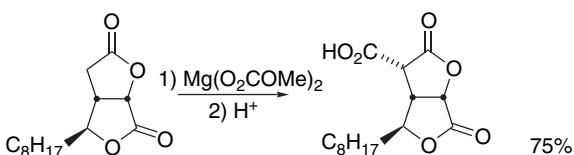
Ref. 225

²²². J. A. Turner and W. S. Jacks, *J. Org. Chem.*, **54**, 4229 (1989).

²²³. M. W. Rathke and P. J. Cowan, *J. Org. Chem.*, **50**, 2622 (1985).

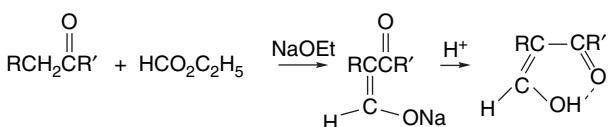
²²⁴. R. E. Tirpak, R. S. Olsen, and M. W. Rathke, *J. Org. Chem.*, **50**, 4877 (1985).

²²⁵. M. Stiles, *J. Am. Chem. Soc.*, **81**, 2598 (1959).

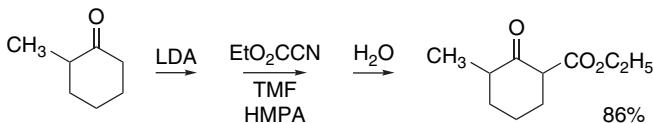


Ref. 226

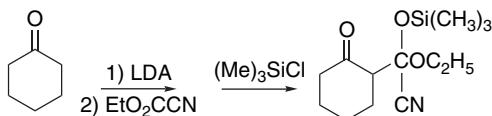
The enolates of ketones can be acylated by esters and other acylating agents. The products of these reactions are β -dicarbonyl compounds, which are rather acidic and can be alkylated by the procedures described in Section 1.2. Reaction of ketone enolates with formate esters gives a β -ketoaldehyde. As these compounds exist in the enol form, they are referred to as *hydroxymethylene derivatives*. Entries 1 and 2 in Scheme 2.16 are examples. Product formation is under thermodynamic control so the structure of the product can be predicted on the basis of the stability of the various possible product anions.



Ketones are converted to β -ketoesters by acylation with diethyl carbonate or diethyl oxalate, as illustrated by Entries 4 and 5 in Scheme 2.16. Alkyl cyanoformate can be used as the acylating reagent under conditions where a ketone enolate has been formed under kinetic control.²²⁷

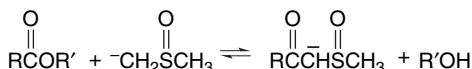


When this type of reaction is quenched with trimethylsilyl chloride, rather than by neutralization, a trimethylsilyl ether of the adduct is isolated. This result shows that the tetrahedral adduct is stable until the reaction mixture is hydrolyzed.



Ref. 228

β -Keto sulfoxides can be prepared by acylation of dimethyl sulfoxide anion with esters.²²⁹



²²⁶ W. L. Parker and F. Johnson, *J. Org. Chem.*, **38**, 2489 (1973).

²²⁷ L. N. Mander and S. P. Sethi, *Tetrahedron Lett.*, **24**, 5425 (1983).

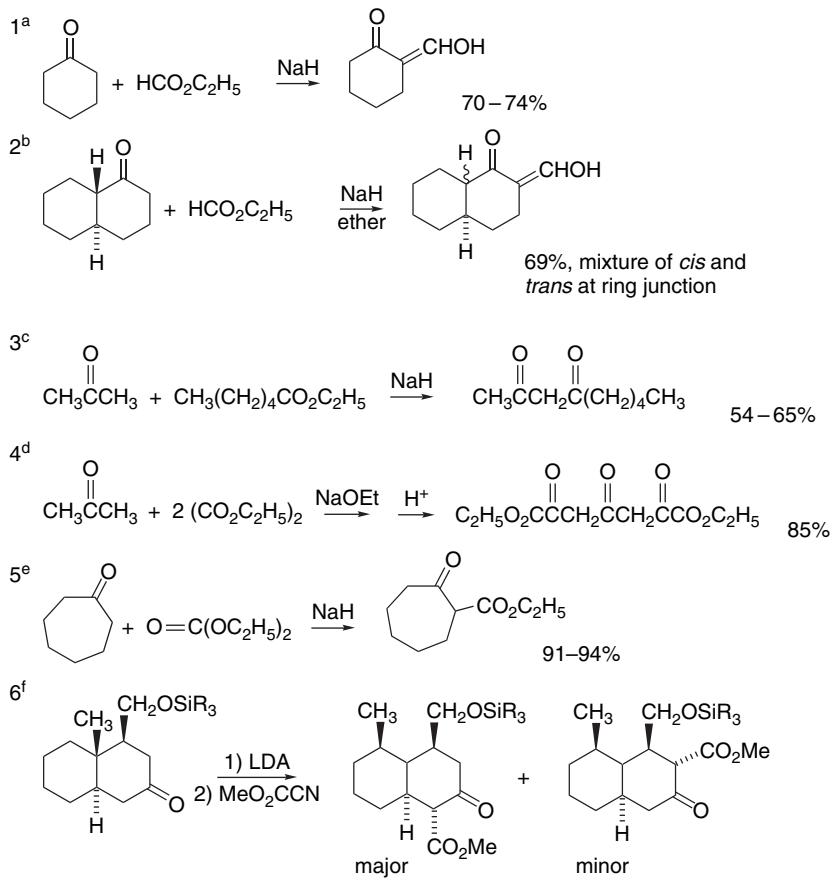
²²⁸ F. E. Ziegler and T.-F. Wang, *Tetrahedron Lett.*, **26**, 2291 (1985).

²²⁹ E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965); H. D. Becker, G. J. Mikol, and G. A. Russell, *J. Am. Chem. Soc.*, **85**, 3410 (1963).

Scheme 2.16. Acylation of Ketones by Esters

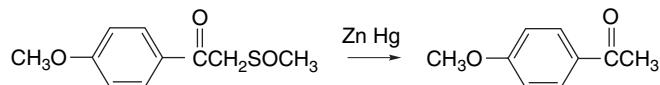
CHAPTER 2

Reactions of Carbon
Nucleophiles with
Carbonyl Compounds



- a. C. Ainsworth, *Org. Synth.*, **IV**, 536 (1963).
 b. P. H. Lewis, S. Middleton, M. J. Rosser, and L. E. Stock, *Aust. J. Chem.*, **32**, 1123 (1979).
 c. N. Green and F. B. La Forge, *J. Am. Chem. Soc.*, **70**, 2287 (1948); F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.*, **72**, 1352 (1950).
 d. E. R. Riegel and F. Zwilgmeyer, *Org. Synth.*, **II**, 126 (1943).
 e. A. P. Krapcho, J. Diamanti, C. Cayen, and R. Bingham, *Org. Synth.*, **47**, 20 (1967).
 f. F. E. Ziegler, S. I. Klein, U. K. Pati, and T.-F. Wang, *J. Am. Chem. Soc.*, **107**, 2730 (1985).

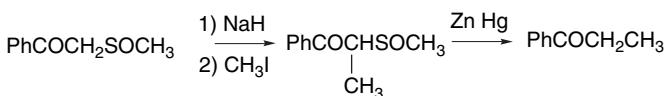
Mechanistically, this reaction is similar to ketone acylation. The β -keto sulfoxides have several synthetic applications. The sulfoxide substituent can be removed reductively, which leads to methyl ketones.



Ref. 230

The β -keto sulfoxides can be alkylated via their anions. Inclusion of an alkylation step prior to the reduction provides a route to ketones with longer chains.

²³⁰ G. A. Russell and G. J. Mikol, *J. Am. Chem. Soc.*, **88**, 5498 (1966).

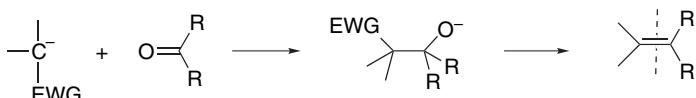


Ref. 231

These reactions accomplish the same overall synthetic transformation as the acylation of ester enolates, but use desulfurization rather than decarboxylation to remove the anion-stabilizing group. Dimethyl sulfone can be subjected to similar reaction sequences.²³²

2.4. Olefination Reactions of Stabilized Carbon Nucleophiles

This section deals with reactions that correspond to Pathway C, defined earlier (p. 64), that lead to formation of alkenes. The reactions discussed include those of phosphorus-stabilized nucleophiles (Wittig and related reactions), α -silyl (Peterson reaction) and α -sulfonyl carbanions (Julia olefination) with aldehydes and ketones. These important reactions can be used to convert a carbonyl group to an alkene by reaction with a carbon nucleophile. In each case, the addition step is followed by an elimination.



A crucial issue for these reactions is the stereoselectivity for formation of *E*- or *Z*-alkene. This is determined by the mechanisms of the reactions and, as we will see, can be controlled in some cases by the choice of particular reagents and reaction conditions.

2.4.1. The Wittig and Related Reactions of Phosphorus-Stabilized Carbon Nucleophiles

The *Wittig reaction* involves *phosphonium ylides* as the nucleophilic carbon species.²³³ An ylide is a molecule that has a contributing resonance structure with opposite charges on adjacent atoms, each of which has an octet of electrons. Although this definition includes other classes of compounds, the discussion here is limited to ylides having the negative charge on the carbon. Phosphonium ylides are stable, but quite reactive, compounds. They can be represented by two limiting resonance structures, which are referred to as the ylide and ylene forms.



²³¹ P. G. Gassman and G. D. Richmond, *J. Org. Chem.*, **31**, 2355 (1966).

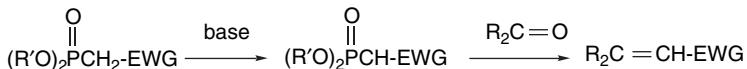
²³² H. O. House and J. K. Larson, *J. Org. Chem.*, **33**, 61 (1968).

²³³ For general reviews of the Wittig reaction, see A. Maercker, *Org. React.*, **14**, 270 (1965); I. Gosney and A. G. Rowley, in *Organophosphorus Reagents in Organic Synthesis*, J. I. G. Cadogan, ed., Academic Press, London, 1979, pp. 17–153; B. A. Maryanoff and A. B. Reitz, *Chem. Rev.*, **89**, 863 (1989); A. W. Johnson, *Ylates and Imines of Phosphorus*, John Wiley, New York, 1993; N. J. Lawrence, in *Preparation of Alkenes*, Oxford University Press, Oxford, 1996, pp. 19–58; K. C. Nicolaou, M. W. Harter, J. L. Gunzer, and A. Nadin, *Liebigs Ann. Chem.*, 1283 (1997).

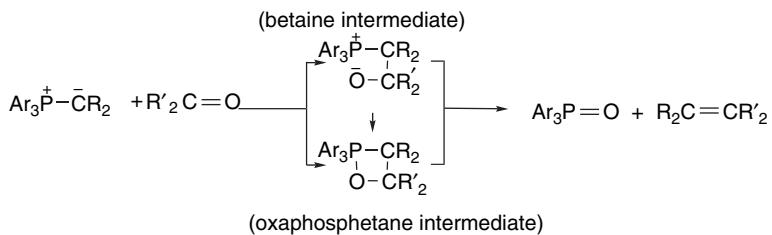
NMR spectroscopic studies (^1H , ^{13}C , and ^{31}P) are consistent with the dipolar ylide structure and suggest only a minor contribution from the ylene structure.²³⁴ Theoretical calculations support this view.²³⁵ The phosphonium ylides react with carbonyl compounds to give olefins and the phosphine oxide.



There are related reactions involving phosphonate esters or phosphines oxides. These reactions differ from the Wittig reaction in that they involve *carbanions* formed by deprotonation. In the case of the phosphonate esters, a second EWG substituent is usually present.

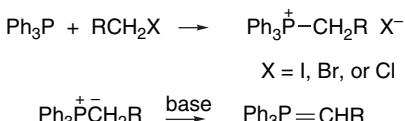


2.4.1.1. Olefination Reactions Involving Phosphonium Ylides. The synthetic potential of phosphonium ylides was developed initially by G. Wittig and his associates at the University of Heidelberg. The reaction of a phosphonium ylide with an aldehyde or ketone introduces a carbon-carbon double bond in place of the carbonyl bond. The mechanism originally proposed involves an addition of the nucleophilic ylide carbon to the carbonyl group to form a dipolar intermediate (a *betaine*), followed by elimination of a phosphine oxide. The elimination is presumed to occur after formation of a four-membered *oxaphosphetane* intermediate. An alternative mechanism proposes direct formation of the oxaphosphetane by a cycloaddition reaction.²³⁶ There have been several computational studies that find the oxaphosphetane structure to be an intermediate.²³⁷ Oxaphosphetane intermediates have been observed by NMR studies at low temperature.²³⁸ Betaine intermediates have been observed only under special conditions that retard the cyclization and elimination steps.²³⁹



- ²³⁴ H. Schmidbaur, W. Bucher, and D. Schentzow, *Chem. Ber.*, **106**, 1251 (1973).
- ²³⁵ A. Streitwieser, Jr., A. Rajca, R. S. McDowell, and R. Glaser, *J. Am. Chem. Soc.*, **109**, 4184 (1987); S. M. Bachrach, *J. Org. Chem.*, **57**, 4367 (1992); D. G. Gilheany, *Chem. Rev.*, **94**, 1339 (1994).
- ²³⁶ E. Vedejs and K. A. J. Snoble, *J. Am. Chem. Soc.*, **95**, 5778 (1973); E. Vedejs and C. F. Marth, *J. Am. Chem. Soc.*, **112**, 3905 (1990).
- ²³⁷ R. Holler and H. Lischka, *J. Am. Chem. Soc.*, **102**, 4632 (1980); F. Volatron and O. Eisenstein, *J. Am. Chem. Soc.*, **106**, 6117 (1984); F. Mari, P. M. Lahti, and W. E. McEwen, *J. Am. Chem. Soc.*, **114**, 813 (1992); A. A. Restrepocossio, C. A. Gonzalez, and F. Mari, *J. Phys. Chem. A*, **102**, 6993 (1998); H. Yamataka and S. Nagase, *J. Am. Chem. Soc.*, **120**, 7530 (1998).
- ²³⁸ E. Vedejs, G. P. Meier, and K. A. J. Snoble, *J. Am. Chem. Soc.*, **103**, 2823 (1981); B. E. Maryanoff, A. B. Reitz, M. S. Mutter, R. R. Inners, H. R. Almond, Jr., R. R. Whittle, and R. A. Olofson, *J. Am. Chem. Soc.*, **108**, 7684 (1986).
- ²³⁹ R. A. Neumann and S. Berger, *Eur. J. Org. Chem.*, 1085 (1998).

SECTION 2.4

*Olefination Reactions of
Stabilized Carbon
Nucleophiles*

Alkyltriphenylphosphonium halides are only weakly acidic, and a strong base must be used for deprotonation. Possibilities include organolithium reagents, the anion of dimethyl sulfoxide, and amide ion or substituted amide anions, such as LDA or NaHMDS. The ylides are not normally isolated, so the reaction is carried out either with the carbonyl compound present or with it added immediately after ylide formation. Ylides with nonpolar substituents, e.g., R = H, alkyl, aryl, are quite reactive toward both ketones and aldehydes. Ylides having an α -EWG substituent, such as alkoxy carbonyl or acyl, are less reactive and are called *stabilized ylides*.

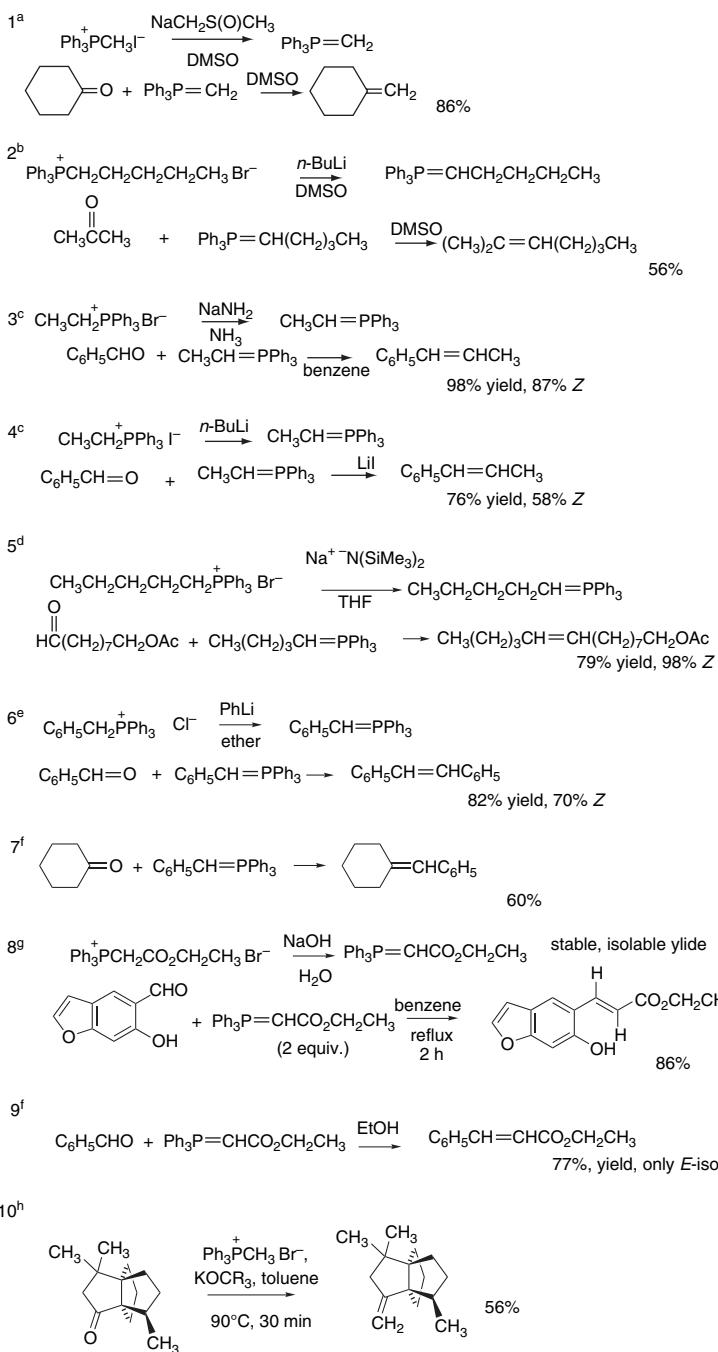
The stereoselectivity of the Wittig reaction is believed to be the result of steric effects that develop as the ylide and carbonyl compound approach one another. The three phenyl substituents on phosphorus impose large steric demands that govern the formation of the diastereomeric adducts.²⁴⁰ Reactions of unstabilized phosphoranes are believed to proceed through an early TS, and steric factors usually make these reactions selective for the *cis*-alkene.²⁴¹ Ultimately, however, the precise stereoselectivity is dependent on a number of variables, including reactant structure, the base used for ylide formation, the presence of other ions, solvent, and temperature.²⁴²

Scheme 2.17 gives some examples of Wittig reactions. Entries 1 to 5 are typical examples of using ylides without any functional group stabilization. The stereoselectivity depends strongly on both the structure of the ylide and the reaction conditions. Use of sodium amide or NaHMDS as bases gives higher selectivity for *Z*-alkenes than do ylides prepared with alkyl lithium reagents as base (see Entries 3 to 6). Benzylidenetriphenylphosphorane (Entry 6) gives a mixture of both *cis*- and *trans*-stilbene on reaction with benzaldehyde. The diminished stereoselectivity is attributed to complexes involving the lithium halide salt that are present when alkyl lithium reagents are used as bases.

β -Ketophosphonium salts are considerably more acidic than alkylphosphonium salts and can be converted to ylides by relatively weak bases. The resulting ylides, which are stabilized by the carbonyl group, are substantially less reactive than unfunctionalized ylides. More vigorous conditions are required to bring about reactions with ketones. Stabilized ylides such as (carboethoxymethylidene)triphenylphosphorane (Entries 8 and 9) react with aldehydes to give exclusively *trans* double bonds.

- ^{240.} M. Schlosser, *Top. Stereochem.*, **5**, 1 (1970); M. Schlosser and B. Schaub, *J. Am. Chem. Soc.*, **104**, 5821 (1982); H. J. Bestmann and O. Vostrowsky, *Top. Curr. Chem.*, **109**, 85 (1983); E. Vedejs, T. Fleck, and S. Hara, *J. Org. Chem.*, **52**, 4637 (1987).
- ^{241.} E. Vedejs, C. F. Marth, and P. Ruggeri, *J. Am. Chem. Soc.*, **110**, 3940 (1988); E. Vedejs and C. F. Marth, *J. Am. Chem. Soc.*, **110**, 3948 (1988); E. Vedejs and C. F. Marth, *J. Am. Chem. Soc.*, **112**, 3905 (1990).
- ^{242.} A. B. Reitz, S. O. Nortey, A. D. Jordan, Jr., M. S. Mutter, and B. E. Maryanoff, *J. Org. Chem.*, **51**, 3302 (1986); B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, **89**, 863 (1989); E. Vedejs and M. J. Peterson, *Adv. Carbanion Chem.*, **2**, 1 (1996); E. Vedejs and M. J. Peterson, *Top. Stereochem.*, **21**, 1 (1994).

Scheme 2.17. The Wittig Reaction

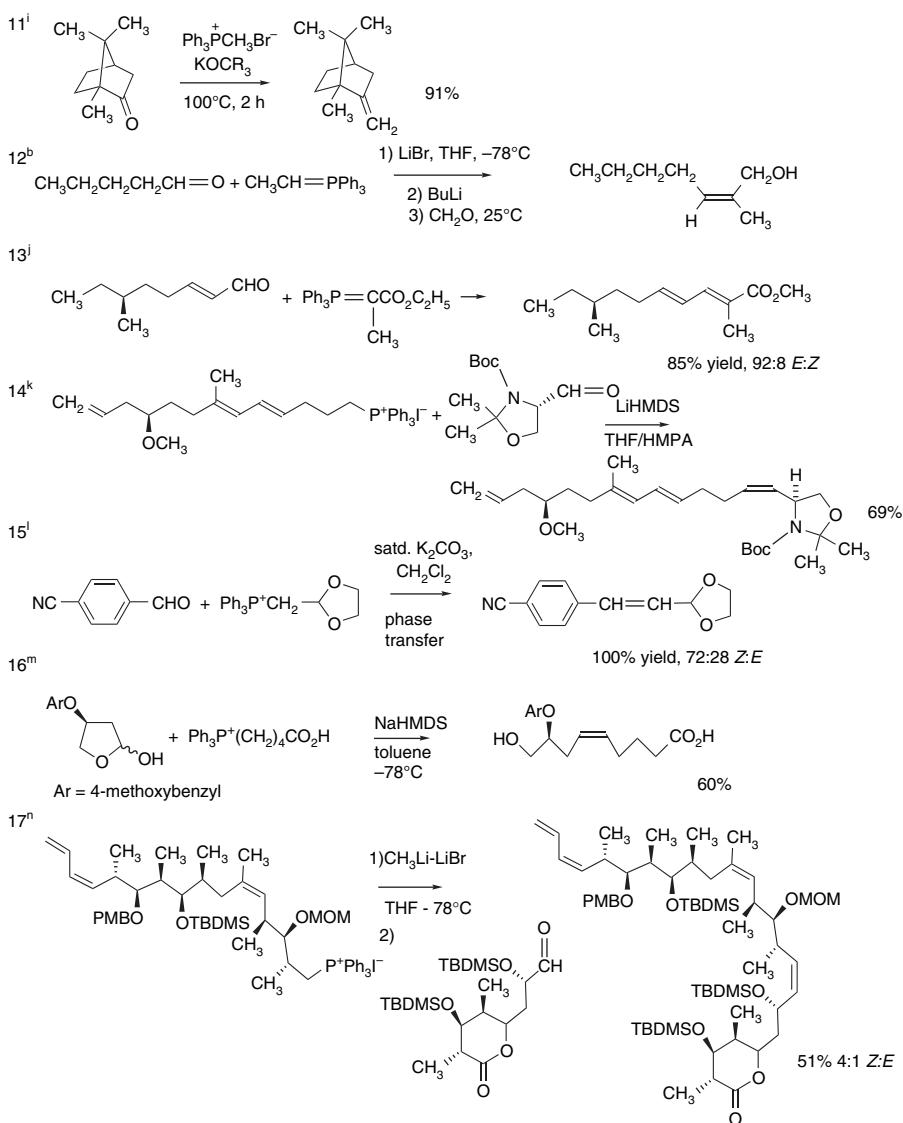


(Continued)

Scheme 2.17. (Continued)

SECTION 2.4

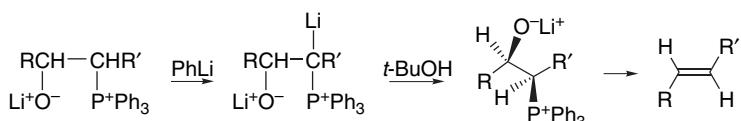
Olefination Reactions of
Stabilized Carbon
Nucleophiles



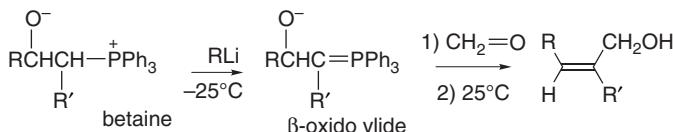
- a. R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).
- b. U. T. Bhalerao and H. Rapoport, *J. Am. Chem. Soc.*, **93**, 4835 (1971).
- c. M. Schlosser and K. F. Christmann, *Liebigs Ann. Chem.*, **708**, 1 (1967).
- d. H. J. Bestmann, K. H. Koschatzky, and O. Vostrowsky, *Chem. Ber.*, **112**, 1923 (1979).
- e. G. Wittig and U. Schollkopf, *Chem. Ber.*, **87**, 1318 (1954).
- f. G. Wittig and W. Haag, *Chem. Ber.*, **88**, 1654 (1955).
- g. Y. Y. Liu, E. Thom, and A. A. Liebman, *J. Heterocycl. Chem.*, **16**, 799 (1979).
- h. A. B. Smith, III, and P. J. Jerris, *J. Org. Chem.*, **47**, 1845 (1982).
- i. L. Fitjer and U. Quabeck, *Synth. Commun.*, **15**, 855 (1985).
- j. J. D. White, T. S. Kim, and M. Nambu, *J. Am. Chem. Soc.*, **119**, 103 (1997).
- k. N. Daubresse, C. Francesch, and G. Rolando, *Tetrahedron*, **54**, 10761 (1998).
- l. A. G. M. Barrett, M. Pena, and J. A. Willardsen, *J. Org. Chem.*, **61**, 1082 (1996).
- m. D. Critcher, S. Connell, and M. Wills, *J. Org. Chem.*, **62**, 6638 (1997).
- n. A. B. Smith, III, B. S. Freeze, I. Brouard, and T. Hirose, *Org. Lett.*, **5**, 4405 (2003).

When a hindered ketone is to be converted to a methylene derivative, the best results are obtained if potassium *t*-alkoxide is used as the base in a hydrocarbon solvent. Under these conditions the reaction can be carried out at elevated temperatures.²⁴³ Entries 10 and 11 illustrate this procedure.

The reaction of nonstabilized ylides with aldehydes can be induced to yield *E*-alkenes with high stereoselectivity by a procedure known as the *Schlosser modification* of the Wittig reaction.²⁴⁴ In this procedure, the ylide is generated as a lithium halide complex and allowed to react with an aldehyde at low temperature, presumably forming a mixture of diastereomeric betaine-lithium halide complexes. At the temperature at which the addition is carried out, there is no fragmentation to an alkene and triphenylphosphine oxide. This complex is then treated with an equivalent of strong base such as phenyllithium to form a β -*oxido ylide*. Addition of one equivalent of *t*-butyl alcohol protonates the β -*oxido ylide* stereoselectively to give the *syn*-betaine as a lithium halide complex. Warming the solution causes the *syn*-betaine-lithium halide complex to give *trans*-alkene by a *syn* elimination.

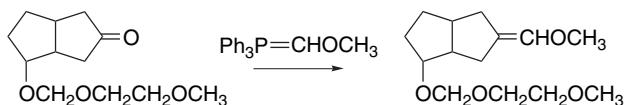


An extension of this method can be used to prepare allylic alcohols. Instead of being protonated, the β -*oxido ylide* is allowed to react with formaldehyde. The β -*oxido ylide* and formaldehyde react to give, on warming, an allylic alcohol. Entry 12 is an example of this reaction. The reaction is valuable for the stereoselective synthesis of *Z*-allylic alcohols from aldehydes.²⁴⁵



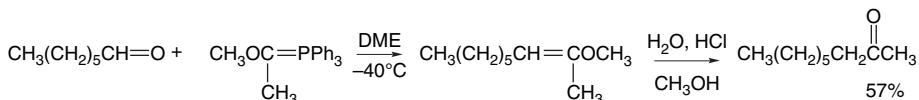
The Wittig reaction can be applied to various functionalized ylides.²⁴⁶ Methoxymethylene and phenoxyethylene ylides lead to vinyl ethers, which can be hydrolyzed to aldehydes.²⁴⁷

- ²⁴³ J. M. Conia and J. C. Limasset, *Bull. Soc. Chim. France*, 1936 (1967); J. Provin, F. Leyendecker, and J. M. Conia, *Tetrahedron Lett.*, 4053 (1975); S. R. Schow and T. C. Morris, *J. Org. Chem.*, **44**, 3760 (1979).
- ²⁴⁴ M. Schlosser and K.-F. Christmann, *Liebigs Ann. Chem.*, **708**, 1 (1967); M. Schlosser, K.-F. Christmann, and A. Piskala, *Chem. Ber.*, **103**, 2814 (1970).
- ²⁴⁵ E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 226 (1970); E. J. Corey, H. Yamamoto, D. K. Herron, and K. Achiwa, *J. Am. Chem. Soc.*, **92**, 6635 (1970); E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 6636 (1970); E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 6637 (1970); E. J. Corey, J. I. Shulman, and H. Yamamoto, *Tetrahedron Lett.*, 447 (1970).
- ²⁴⁶ S. Warren, *Chem. Ind. (London)*, 824 (1980).
- ²⁴⁷ S. G. Levine, *J. Am. Chem. Soc.*, **80**, 6150 (1958); G. Wittig, W. Boll, and K. H. Kruck, *Chem. Ber.*, **95**, 2514 (1962).



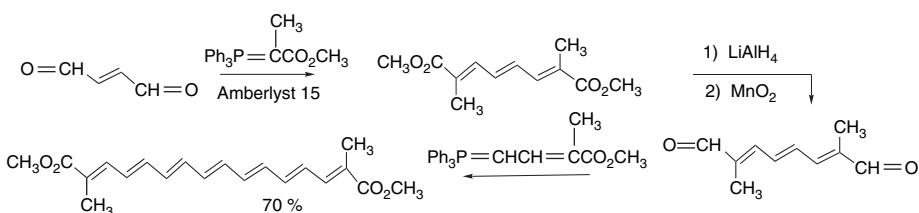
Ref. 248

2-(1,3-Dioxolanyl)methyl ylides can be used for the introduction of α, β -unsaturated aldehydes (see Entry 15, Scheme 2.17). Methyl ketones can be prepared by a reaction using the α -methoxyethylidene phosphorane.

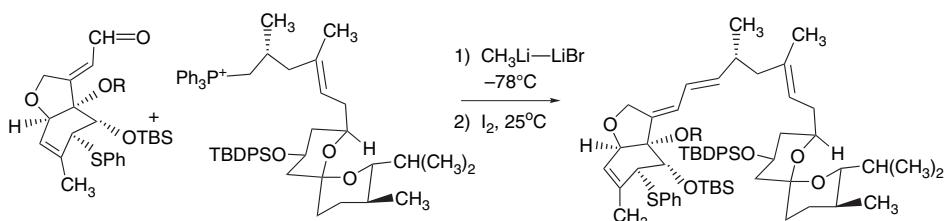


Ref. 249

There have been many applications of the Wittig reaction in multistep syntheses. The reaction can be used to prepare extended conjugated systems, such as crocetin dimethyl ester, which has seven conjugated double bonds. In this case, two cycles of Wittig reactions using stabilized ylides provided the seven double bonds. Note the use of a conjugated stabilized ylide in the second step.²⁵⁰



In several cases of syntheses of highly functionalized molecules, use of $\text{CH}_3\text{Li}-\text{Br}$ for ylide formation has been found to be advantageous. For example, in the synthesis of milbemycin D, Crimmins and co-workers obtained an 84% yield with 10:1 *Z:E* selectivity.²⁵¹ In this case, the more stable *E*-isomer was required and it was obtained by I_2 -catalyzed isomerization.



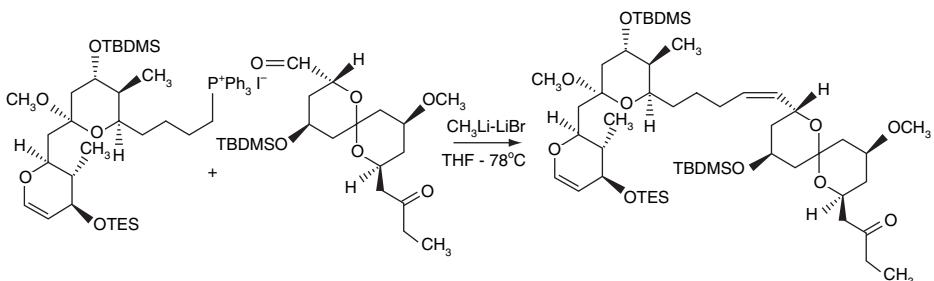
²⁴⁸. M. Yamazaki, M. Shibasaki, and S. Ikegami, *J. Org. Chem.*, **48**, 4402 (1983).

²⁴⁹. D. R. Coulsen, *Tetrahedron Lett.*, 3323 (1964).

²⁵⁰. D. Frederico, P. M. Donate, M. G. Constantino, E. S. Bronze, and M. I. Sairre, *J. Org. Chem.*, **68**, 9126 (2003).

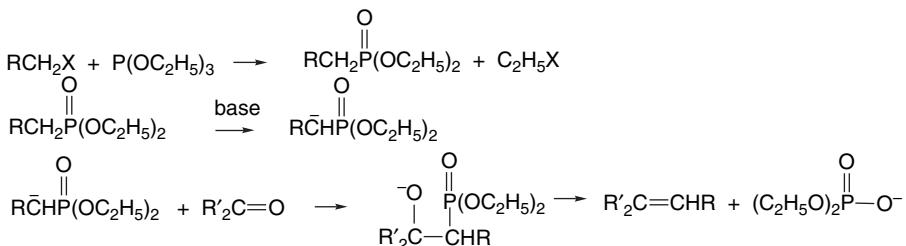
²⁵¹. M. T. Crimmins, R. S. Al-awar, I. M. Vallin, W. G. Hollis, Jr., R. O'Mahony, J. G. Lever, and D. M. Bankaitis-Davis, *J. Am. Chem. Soc.*, **118**, 7513 (1996).

This methodology was also used in the connecting of two major fragments in the synthesis of spongistatins.²⁵²

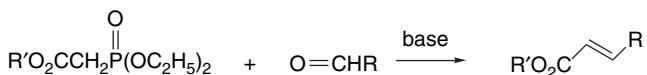


These conditions were also employed for a late stage of the synthesis of (+)-discodermolide (see Entry 17, Scheme 2.17).

2.4.1.2. Olefination Reactions Involving Phosphonate Anions. An important complement to the Wittig reaction involves the reaction of phosphonate carbanions with carbonyl compounds.²⁵³ The alkylphosphonic acid esters are made by the reaction of an alkyl halide, preferably primary, with a phosphite ester. Phosphonate carbanions are generated by treating alkylphosphonate esters with a base such as sodium hydride, *n*-butyllithium, or sodium ethoxide. Alumina coated with KF or KOH has also found use as the base.²⁵⁴



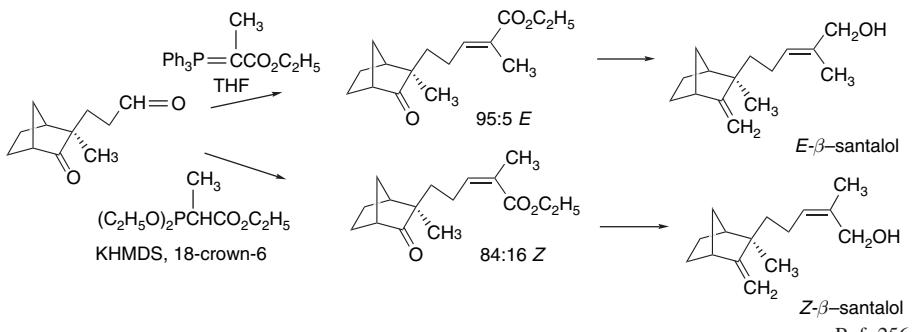
Reactions with phosphonoacetate esters are used frequently to prepare α,β -unsaturated esters. This reaction is known as the *Wadsworth-Emmons reaction* and usually leads to the *E*-isomer.



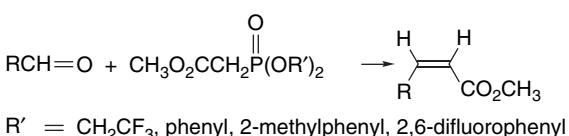
The conditions can be modified to favor the *Z*-isomer. Use of KHMDS with 18-crown-6 favors the *Z*-product.²⁵⁵ This method was used, for example, to control the

- ²⁵². M. T. Crimmins, J. D. Katz, D. G. Washburn, S. P. Allwein, and L. F. McAtee, *J. Am. Chem. Soc.*, **124**, 5661 (2002); see also C. H. Heathcock, M. McLaughlin, J. Medina, J. L. Hubbs, G. A. Wallace, R. Scott, M. M. Claffey, C. J. Hayes, and G. R. Ott, *J. Am. Chem. Soc.*, **125**, 12844 (2003).
- ²⁵³. For reviews of reactions of phosphonate carbanions with carbonyl compounds, see J. Boutagy and R. Thomas, *Chem. Rev.*, **74**, 87 (1974); W. S. Wadsworth, Jr., *Org. React.*, **25**, 73 (1977); H. Gross and I. Keitels, *Z. Chem.*, **22**, 117 (1982).
- ²⁵⁴. F. Texier-Boulet, D. Villemain, M. Ricard, H. Moison, and A. Foucaud, *Tetrahedron*, **41**, 1259 (1985); M. Mikolajczyk and R. Zurawinski, *J. Org. Chem.*, **63**, 8894 (1998).
- ²⁵⁵. W. C. Still and C. Gennari, *Tetrahedron Lett.*, **24**, 4405 (1983).

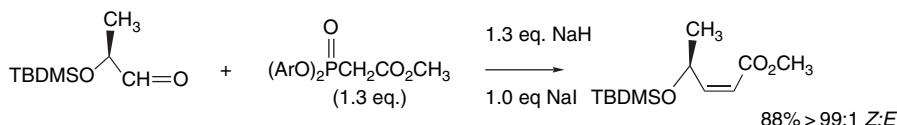
stereochemistry in the synthesis of the *Z*- and *E*-isomers of β -santalol, a fragrance that is a component of sandalwood oil.



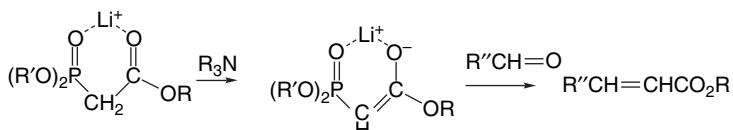
Several modified phosphonoacetate esters show selectivity for the *Z*-enoate product. Trifluoroethyl,²⁵⁶ phenyl,²⁵⁷ 2-methylphenyl,²⁵⁸ and 2,6-difluorophenyl²⁵⁹ esters give good *Z*-stereoselectivity with aldehydes. The trifluoroethyl esters also give *Z*-selectivity with ketones.²⁶⁰



Several other methodologies have been developed for control of the stereoselectivity of Wadsworth-Emmons reactions. For example, K_2CO_3 in chlorobenzene with a catalytic amount of 18-crown-6 is reported to give excellent *Z*-selectivity.²⁶¹ Another group found that use of excess Na^+ , added as NaI , improved *Z*-selectivity for 2-methylphenyl esters.



An alternative procedure for effecting the condensation of phosphonoacetates is to carry out the reaction in the presence of lithium chloride and an amine such as diisopropylethylamine. The lithium chelate of the substituted phosphonate is sufficiently acidic to be deprotonated by the amine.²⁶²



²⁵⁶ A. Krotz and G. Helmchen, *Liebigs Ann. Chem.*, 601 (1994).

²⁵⁷ K. Ando, *Tetrahedron Lett.*, **36**, 4105 (1995); K. Ando, *J. Org. Chem.*, **63**, 8411 (1998).

²⁵⁸ K. Ando, *J. Org. Chem.*, **62**, 1934 (1997); K. Ando, T. Oishi, M. Hirama, H. Ohno, and T. Ibuka, *J. Org. Chem.*, **65**, 4745 (2000).

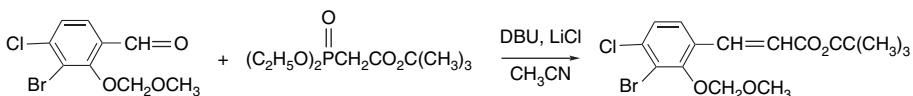
²⁵⁹ K. Kokin, J. Motoyoshiya, S. Hayashi, and H. Aoyama, *Synth. Commun.*, **27**, 2387 (1997).

²⁶⁰ S. Sano, K. Yokoyama, M. Shiro, and Y. Nagao, *Chem. Pharm. Bull.*, **50**, 706 (2002).

²⁶¹ F. P. Touchard, *Tetrahedron Lett.*, **45**, 5519 (2004).

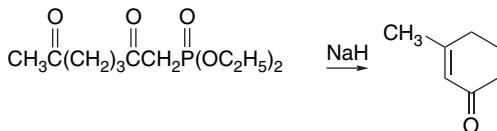
²⁶² M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, and T. Sakai, *Tetrahedron Lett.*, **25**, 2183 (1984).

This version of the Wadsworth-Emmons reaction has been used in the scaled-up syntheses of drugs and drug-candidate molecules. For example, it is used to prepare a cinnamate ester that is a starting material for pilot plant synthesis of a potential integrin antagonist.²⁶³



Entries 10 and 11 of Scheme 2.18 also illustrate this procedure.

Scheme 2.18 gives some representative olefination reactions of phosphonate anions. Entry 1 represents a typical preparative procedure. Entry 2 involves formation of a 2,4-dienoate ester using an α,β -unsaturated aldehyde. Diethyl benzylphosphonate can be used in the Wadsworth-Emmons reaction, as illustrated by Entry 3. Entries 4 to 6 show other anion-stabilizing groups. Intramolecular reactions can be used to prepare cycloalkenes.²⁶⁴



Ref. 265

Intramolecular condensation of phosphonate carbanions with carbonyl groups carried out under conditions of high dilution have been utilized in macrocycle syntheses. Entries 7 and 8 show macrocyclizations involving the Wadsworth-Emmons reaction. Entries 9 to 11 illustrate the construction of new double bonds in the course of a multistage synthesis. The LiCl/amine conditions are used in Entries 9 and 10.

The stereoselectivity of the reactions of stabilized phosphonate anions is usually considered to be the result of reversible adduct formation, followed by rate/product-controlling elimination that favors the *E*-isomer. This matter has been investigated by computation. The Wadsworth-Emmons reaction between lithio methyl dimethylphosphonoacetate and acetaldehyde has been modeled at the HF/6-31G* level. Energies were also calculated at the B3LYP/6-31G* level.²⁶⁶ The energy profile for the intermediates and TSs are shown in Figure 2.5. In agreement with the prevailing experimental interpretation, the highest barrier is for formation of the oxaphosphetane and the addition step is reversible. The stereochemistry, then, is determined by the relative ease of formation of the stereoisomeric oxaphosphetanes. The oxaphosphetane species is of marginal stability and proceeds rapidly to product. At the B3LYP/6-31 + G* level, TS_{2,trans} is 2.2 kcal/mol more stable than TS_{2,cis}. The path to the *cis* product encounters two additional small barriers associated with slightly stable stereoisomeric

²⁶³. J. D. Clark, G. A. Weisenburger, D. K. Anderson, P.-J. Colson, A. D. Edney, D. J. Gallagher, H. P. Kleine, C. M. Knable, M. K. Lantz, C. M. V. Moore, J. B. Murphy, T. E. Rogers, P. G. Ruminski, A. S. Shah, N. Storer, and B. E. Wise, *Org. Process Res. Devel.*, **8**, 51 (2004).

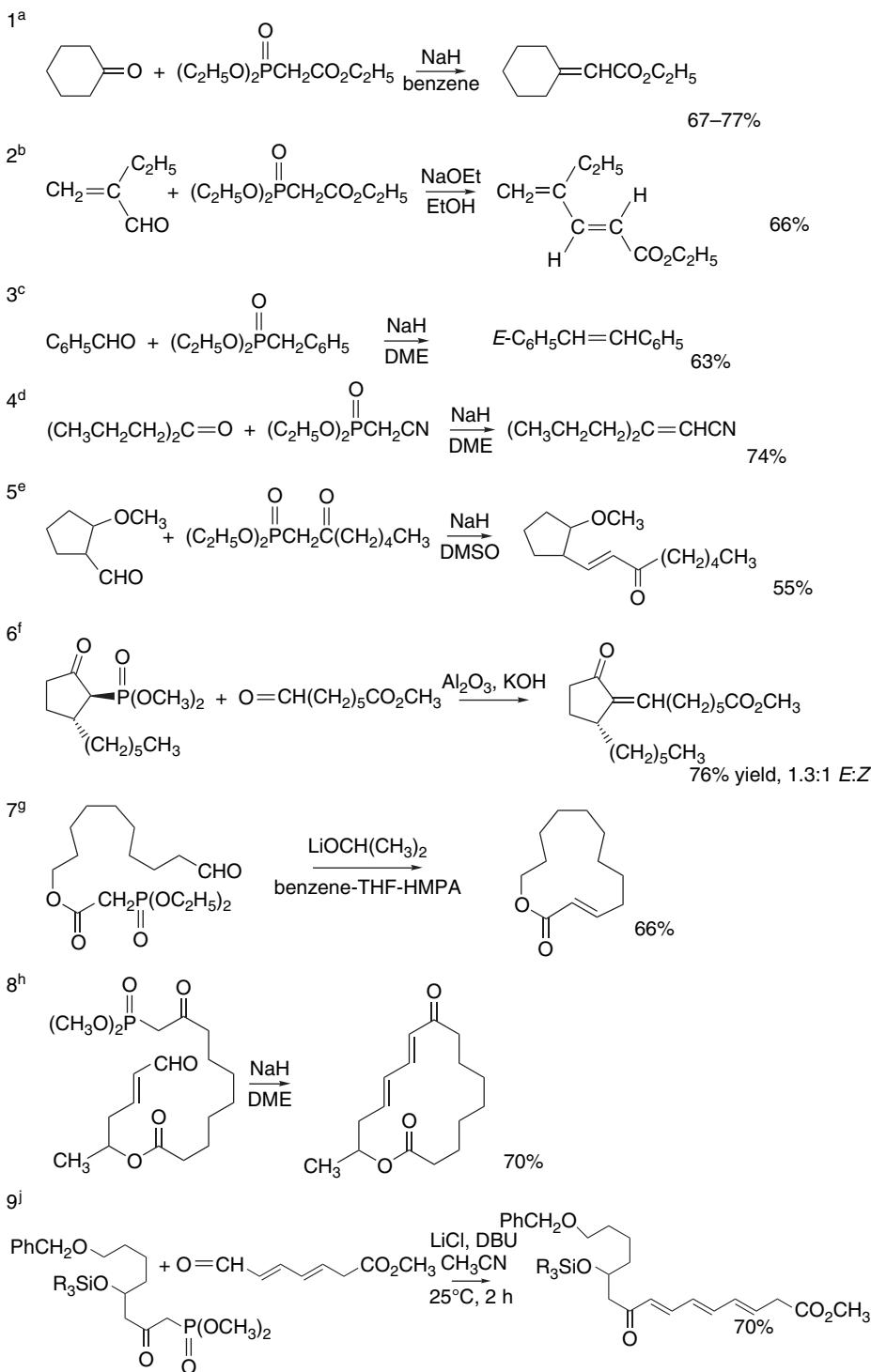
²⁶⁴. K. B. Becker, *Tetrahedron*, **36**, 1717 (1980).

²⁶⁵. P. A. Grieco and C. S. Pogonowski, *Synthesis*, 425 (1973).

²⁶⁶. K. Ando, *J. Org. Chem.*, **64**, 6815 (1999).

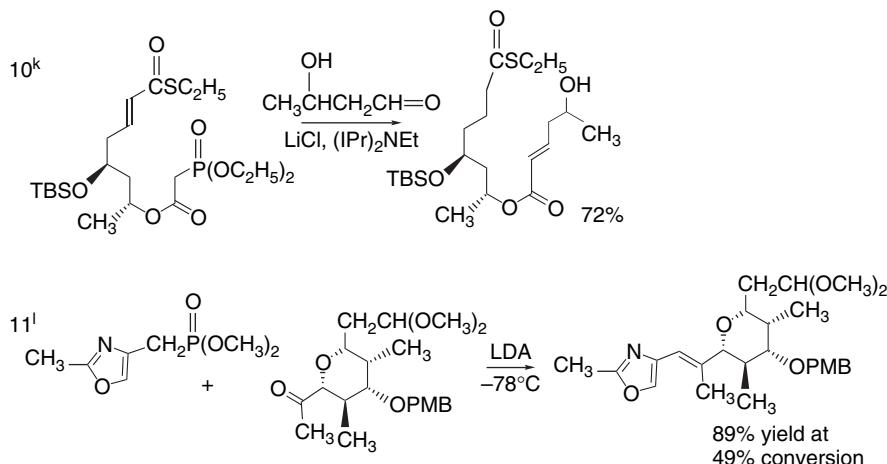
SECTION 2.4

Olefination Reactions of
Stabilized Carbon
Nucleophiles



(Continued)

Scheme 2.18. (Continued)



- a. W. S. Wadsworth, Jr., and W. D. Emmons, *Org. Synth.*, **45**, 44 (1965).
- b. R. J. Sundberg, P. A. Bukowick, and F. O. Holcombe, *J. Org. Chem.*, **32**, 2938 (1967).
- c. W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).
- d. J. A. Marshall, C. P. Hagan, and G. A. Flynn, *J. Org. Chem.*, **40**, 1162 (1975).
- e. N. Finch, J. J. Pitt, and I. H. S. Hsu, *J. Org. Chem.*, **40**, 206 (1975).
- f. M. Mikolajczyk and R. Zurawski, *J. Org. Chem.*, **63**, 8894 (1998).
- g. G. M. Stork and E. Nakamura, *J. Org. Chem.*, **44**, 4010 (1979).
- h. K. C. Nicolaou, S. P. Seitz, M. R. Pavia, and N. A. Petasis, *J. Org. Chem.*, **44**, 4010 (1979).
- i. M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, and T. Sakai, *Tetrahedron Lett.*, **25**, 2183 (1984).
- j. G. E. Keck and J. A. Murry, *J. Org. Chem.*, **56**, 6606 (1991).
- k. G. Pattenden, M. A. Gonzalez, P. B. Little, D. S. Millan, A. T. Plowright, J. A. Tornos, and T. Ye, *Org. Biomol. Chem.*, **1**, 4173 (2003).

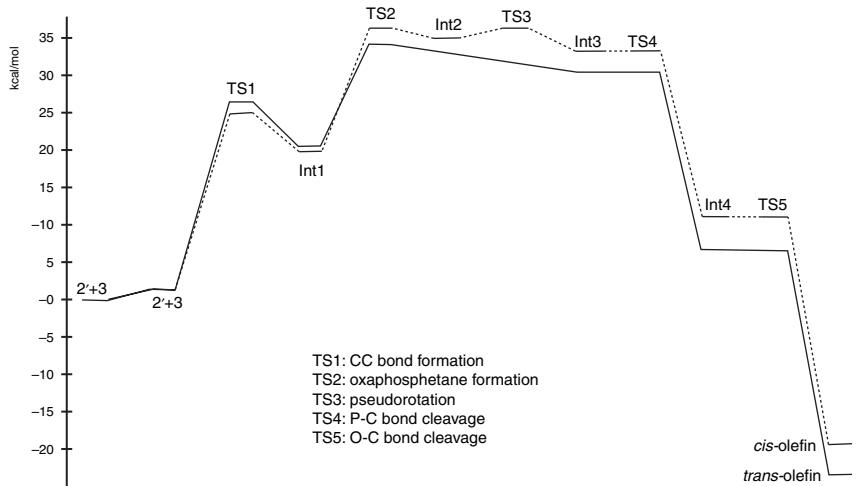
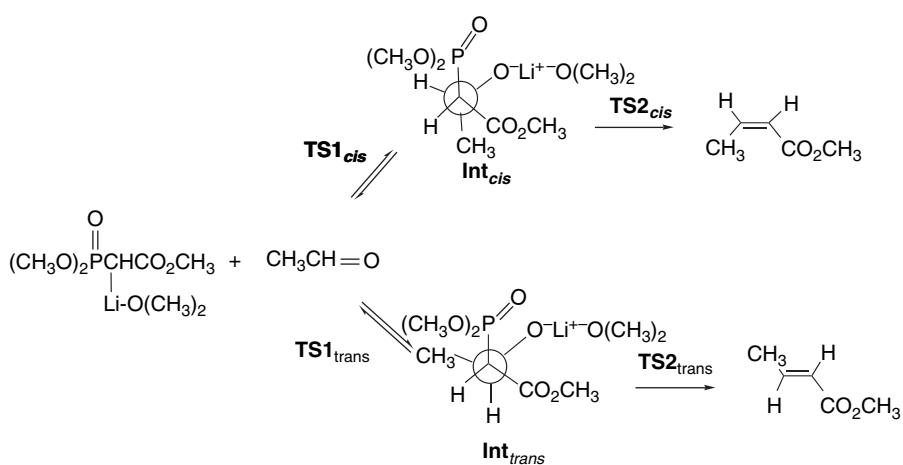


Fig. 2.5. Comparison of energy profile (ΔG) for pathways to *E*- and *Z*-product from the reaction of lithio methyl dimethylphosphonoacetate and acetaldehyde. One molecule of dimethyl ether is coordinated to the lithium ion. Reproduced from *J. Org. Chem.*, **64**, 6815 (1999), by permission of the American Chemical Society.

oxaphosphetane intermediates. The oxaphosphatane is not a stable intermediate on the path to *trans* product.



Visual models, additional information and exercises on the Wadsworth-Emmons Reaction can be found in the Digital Resource available at: Springer.com/carey-sundberg.

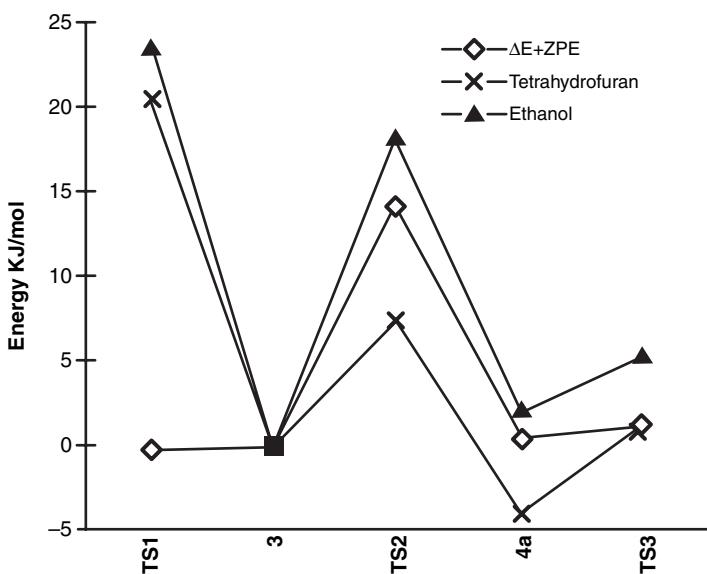
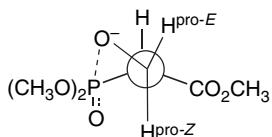
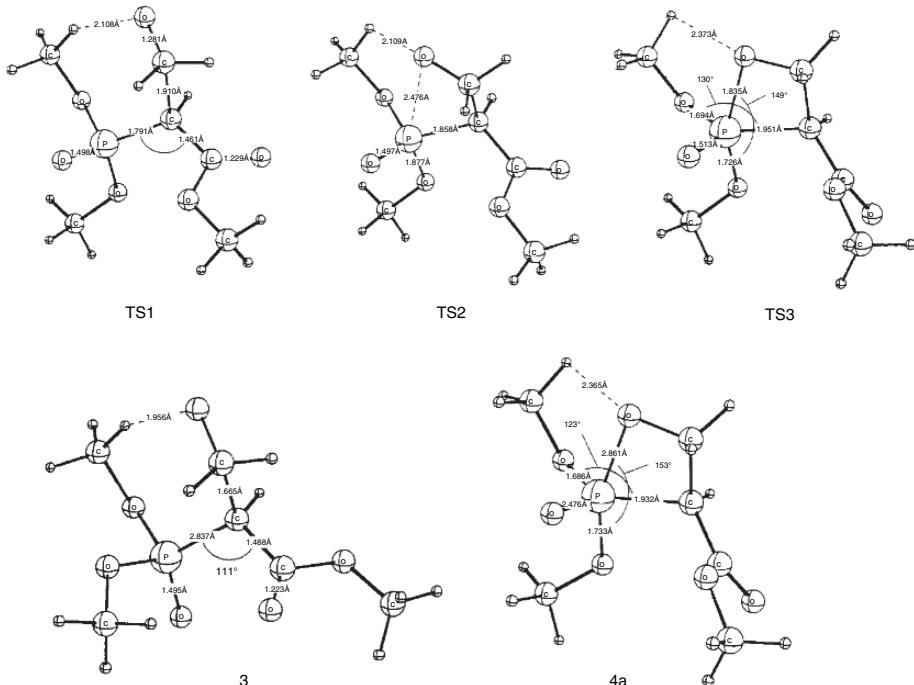


Fig. 2.6. Free-energy profile (B3LYP/6-31 + G* with ZPE correction) for intermediates and transition structures for Wadsworth-Emmons reactions between the lithium enolate of trimethyl phosphonoacetate anion and formaldehyde in the gas phase and in tetrahydrofuran or ethanol. Adapted from *J. Org. Chem.*, **63**, 1280 (1998), by permission of the American Chemical Society.

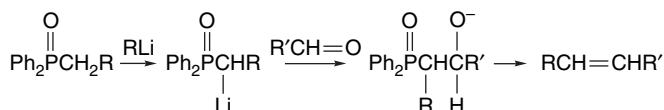
Another computational study included a solvation model.²⁶⁷ Solvation strongly stabilized the oxyanion adduct, suggesting that its formation may be rate and product determining under certain circumstances. When this is true, analysis of stereoselectivity must focus on the addition TS. Figure 2.6 shows the computed energy profile for the TSs and intermediates. TS1 is the structure leading to the oxyanion intermediate. According to the energy profile, its formation is irreversible in solution and therefore determines the product stereochemistry. The structure shows a rather small (30° – 35°) dihedral angle and suggests that steric compression would arise with a Z-substituent.



Structure **3** is the intermediate oxyanion adduct. TS2 is the structure leading to cyclization of the oxyanion to the oxaphosphetane. Structure **4a** is the oxaphosphetane, and the computation shows only a small barrier for its conversion to product.



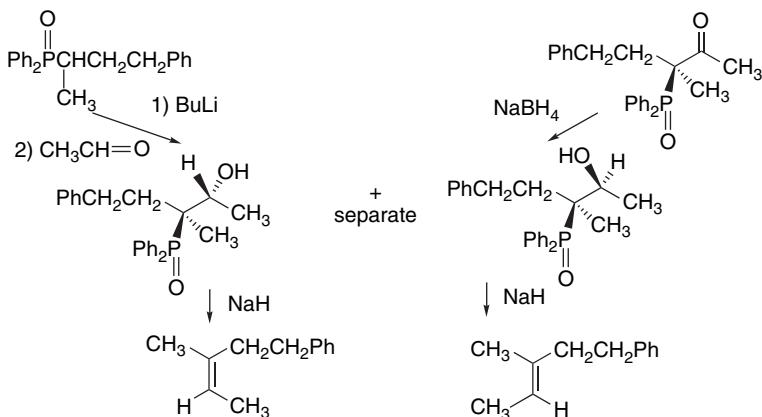
Carbanions derived from phosphine oxides also add to carbonyl compounds. The adducts are stable but undergo elimination to form alkene on heating with a base such as sodium hydride. This reaction is known as the *Horner-Wittig* reaction.²⁶⁸



²⁶⁷ P. Brandt, P.-O. Norrby, I. Martin, and T. Rein, *J. Org. Chem.*, **63**, 1280 (1998).

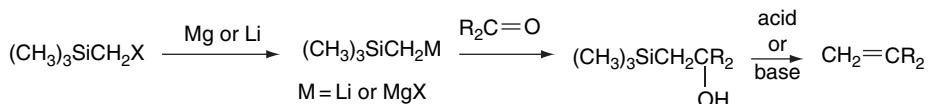
²⁶⁸ For a review, see J. Clayden and S. Warren, *Angew. Chem. Int. Ed. Engl.*, **35**, 241 (1996).

The unique feature of the Horner-Wittig reaction is that the addition intermediate can be isolated and purified, which provides a means for control of the reaction's stereochemistry. It is possible to separate the two diastereomeric adducts in order to prepare the pure alkenes. The elimination process is *syn*, so the stereochemistry of the alkene that is formed depends on the stereochemistry of the adduct. Usually the *anti* adduct is the major product, so it is the *Z*-alkene that is favored. The *syn* adduct is most easily obtained by reduction of β -ketophosphine oxides.²⁶⁹

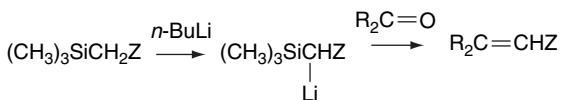


2.4.2. Reactions of α -Trimethylsilylcarbanions with Carbonyl Compounds

Trialkylsilyl groups have a modest stabilizing effect on adjacent carbanions (see Part A, Section 3.4.2). Reaction of the carbanions with carbonyl compounds gives β -hydroxyalkylsilanes. β -Hydroxyalkylsilanes are converted to alkenes by either acid or base.²⁷⁰ These eliminations provide the basis for a synthesis of alkenes. The reaction is sometimes called the *Peterson reaction*.²⁷¹ For example, the Grignard reagent derived from chloromethyltrimethylsilane adds to an aldehyde or ketone and the intermediate can be converted to a terminal alkene by acid or base.²⁷²



Alternatively, organolithium reagents of the type $(\text{CH}_3)_3\text{SiCH}(\text{Li})\text{Z}$, where Z is a carbanion-stabilizing substituent, can be prepared by deprotonation of $(\text{CH}_3)_3\text{SiCH}_2\text{Z}$ with *n*-butyllithium.



²⁶⁹ A. D. Buss and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 2307 (1985).

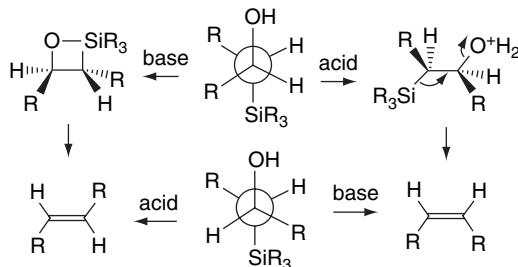
²⁷⁰ P. F. Hudrik and D. Peterson, *J. Am. Chem. Soc.*, **97**, 1464 (1975).

²⁷¹ For reviews, see D. J. Ager, *Org. React.*, **38**, 1 (1990); D. J. Ager, *Synthesis*, 384 (1984); A. G. M. Barrett, J. M. Hill, E. M. Wallace, and J. A. Flygare, *Synlett*, 764 (1991).

²⁷² D. J. Peterson, *J. Org. Chem.*, **33**, 780 (1968).

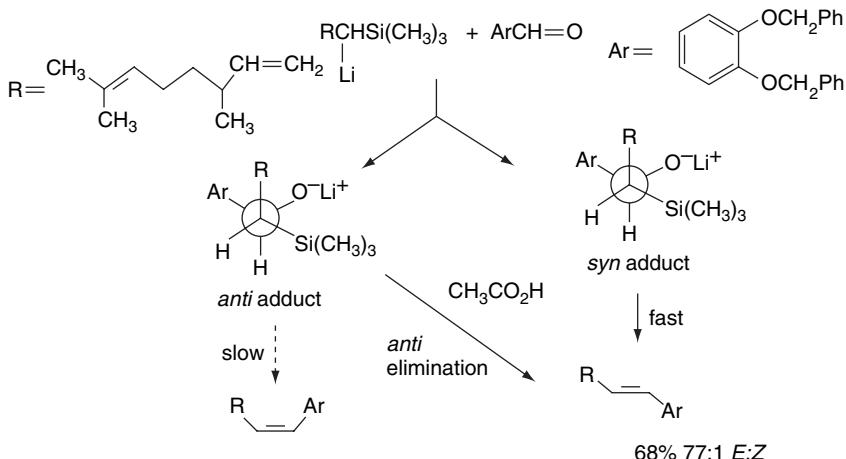
These reagents usually react with aldehydes and ketones to give substituted alkenes directly. No separate elimination step is necessary because fragmentation of the intermediate occurs spontaneously under the reaction conditions.

In general, the elimination reactions are *anti* under acidic conditions and *syn* under basic conditions. This stereoselectivity is the result of a cyclic mechanism under basic conditions, whereas under acidic conditions an acyclic β -elimination occurs.



The *anti* elimination can also be achieved by converting the β -silyl alcohols to trifluoroacetate esters.²⁷³ The stereoselectivity of the Peterson olefination depends on the generation of pure *syn* or *anti* β -silylalcohols, so several strategies have been developed for their stereoselective preparation.²⁷⁴

There can be significant differences in the rates of elimination of the stereoisomeric β -hydroxysilanes. Van Vranken and co-workers took advantage of such a situation to achieve a highly stereoselective synthesis of a styryl terpene. (The lithiated reactant is prepared by reductive lithiation; see p. 625). The *syn* adduct decomposes rapidly at -78°C but because of steric effects, the *anti* isomer remains unreacted. Acidification then promotes *anti* elimination to the desired *E*-isomer.²⁷⁵



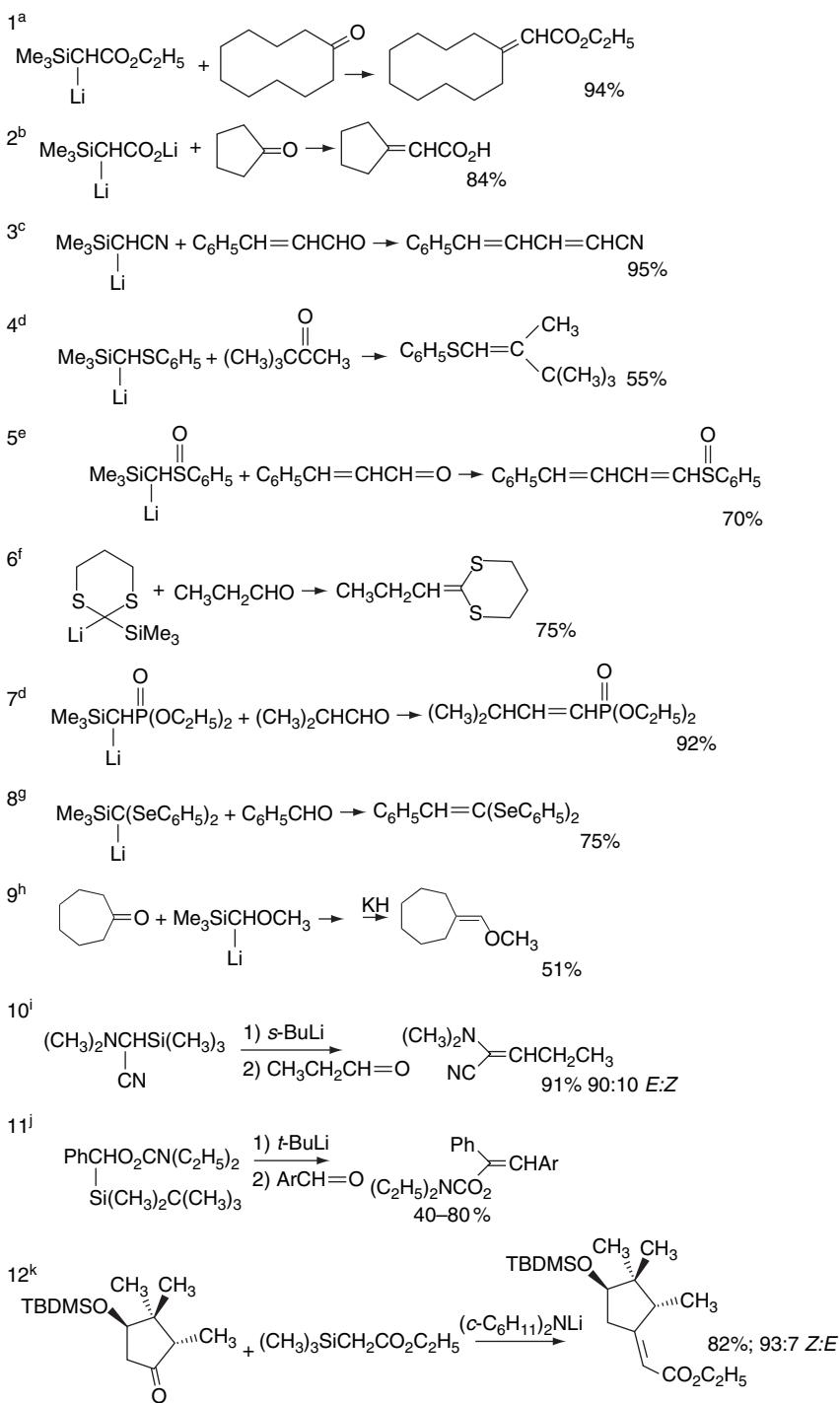
Scheme 2.19 provides some examples of the Peterson olefination. The Peterson olefination has not been used as widely in synthesis as the Wittig and Wadsworth-Emmons reactions, but it has been used advantageously in the preparation of relatively

²⁷³ M. F. Connil, B. Jousseaume, N. Noiret, and A. Saux, *J. Org. Chem.*, **59**, 1925 (1994).

²⁷⁴ A. G. M. Barrett and J. A. Flygare, *J. Org. Chem.*, **56**, 638 (1991); L. Duhamel, J. Gralak, and A. Bouyanzer, *J. Chem. Soc., Chem. Commun.*, 1763 (1993).

²⁷⁵ J. B. Perales, N. F. Makino, and D. L. Van Vranken, *J. Org. Chem.*, **67**, 6711 (2002).

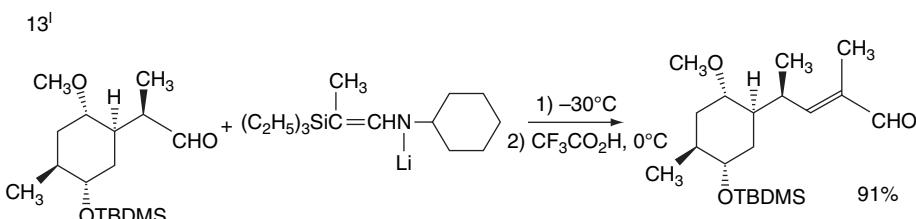
Scheme 2.19. Carbonyl Olefination Using Trimethylsilyl-Substituted Organo-lithium Reagents



(Continued)

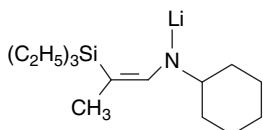
CHAPTER 2

Reactions of Carbon Nucleophiles with Carbonyl Compounds



- a. K. Shimoji, H. Taguchi, H. Yamamoto, K. Oshima, and H. Hozaki, *J. Am. Chem. Soc.*, **96**, 1620 (1974).
 b. P. A. Grieco, C. L. J. Wang, and S. D. Burke, *J. Chem. Soc. Chem. Commun.*, 537 (1975).
 c. I. Matsuda, S. Murata, and Y. Ishii, *J. Chem. Soc., Perkin Trans. 1*, 26 (1979).
 d. F. A. Carey and A. S. Court, *J. Org. Chem.*, **37**, 939 (1972).
 e. F. A. Carey and O. Hernandez, *J. Org. Chem.*, **38**, 2670 (1973).
 f. D. Seebach, M. Kolb, and B.-T. Grobel, *Chem. Ber.*, **106**, 2277 (1973).
 g. B. T. Grobel and D. Seebach, *Chem. Ber.*, **110**, 852 (1977).
 h. P. Magnus and G. Roy, *Organometallics*, **1**, 553 (1982).
 i. W. Adam and C. M. Ortega-Schulte, *Synlett*, 414 (2003).
 j. L. F. van Staden, B. Bartels-Rahm, J. S. Field, and N. D. Emslie, *Tetrahedron*, **54**, 3255 (1998).
 k. J.-M. Galano, G. Audran, and H. Monti, *Tetrahedron Lett.*, **42**, 6125 (2001).
 l. S. F. Martin, J. A. Dodge, L. E. Burgess, and M. Hartmann, *J. Org. Chem.*, **57**, 1070 (1992).

unstable olefins. Entries 1 to 8 show the use of lithio silanes having a range of anion-stabilizing groups. The anions are prepared using alkyllithium reagents or lithium amides. Entries 9 to 11 illustrate the utility of the reaction to prepare relatively unstable substituted alkenes. The silyl anions are typically more reactive than stabilized Wittig ylides, and in the case of Entry 12 good results were obtained while the triphenylphosphonium ylide was unreactive. Entry 13 shows the use of Peterson olefination for chain extension with an α -methyl- α , β -unsaturated aldehyde. The preferred reagent for this transformation is a lithio β -trialkylsilylenamine.²⁷⁶



2.4.3. The Julia Olefination Reaction

The *Julia olefination* involves the addition of a sulfonyl-stabilized carbanion to a carbonyl compound, followed by elimination to form an alkene.²⁷⁷ In the initial versions of the reaction, the elimination was done under *reductive conditions*. More recently, a modified version that avoids this step was developed. The former version is sometimes referred to as the *Julia-Lythgoe olefination*, whereas the latter is called the *Julia-Kocienski olefination*. In the reductive variant, the adduct is usually acylated and then treated with a reducing agent, such as sodium amalgam or samarium diiodide.²⁷⁸

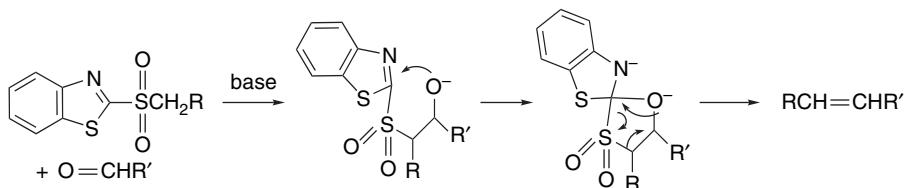
²⁷⁶. R. Desmond, S. G. Mills, R. P. Volante, and I. Shinkai, *Tetrahedron Lett.*, **29**, 3895 (1988).

²⁷⁷. P. R. Blakemore, *J. Chem. Soc., Perkin Trans. 1*, 2563 (2002).

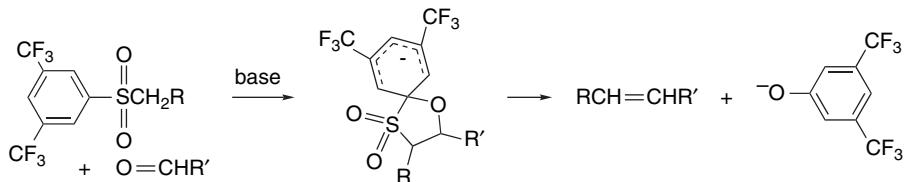
²⁷⁸. A. S. Kende and J. Mendoza, *Tetrahedron Lett.*, **31**, 7105 (1990); G. E. Keck, K. A. Savin, and M. A. Weglarz, *J. Org. Chem.*, **60**, 3194 (1995); K. Fukumoto, M. Ihara, S. Suzuki, T. Taniguchi, and Y. Yokunaga, *Synlett*, 895 (1994); I. E. Marko, F. Murphy, and S. Dolan, *Tetrahedron Lett.*, **37**, 2089 (1996); I. E. Marko, F. Murphy, L. Kumps, A. Ates, R. Touillaux, D. Craig, S. Carballares, and S. Dolan, *Tetrahedron*, **57**, 2609 (2001).



In the modified procedure one of several heteroaromatic sulfones is used. The crucial role of the heterocyclic ring is to provide a nonreductive mechanism for the elimination step, which occurs by an addition-elimination mechanism that results in fragmentation to the alkene. The original example used a benzothiazole ring,²⁷⁹ but more recently tetrazoles have been developed for this purpose.²⁸⁰



Other aryl sulfones that can accommodate the nucleophilic addition step also react in the same way. For example, excellent results have been obtained using 3,5-bis-(trifluoromethyl)phenyl sulfones.²⁸¹



As is the case with the Wittig and Peterson olefinations, there is more than one point at which the stereoselectivity of the reaction can be determined, depending on the details of the mechanism. Adduct formation can be product determining or reversible. Furthermore, in the reductive mechanism, there is the potential for stereorandomization if radical intermediates are involved. As a result, there is a degree of variability in the stereoselectivity. Fortunately, the modified version using tetrazolyl sulfones usually gives a predominance of the *E*-isomer.

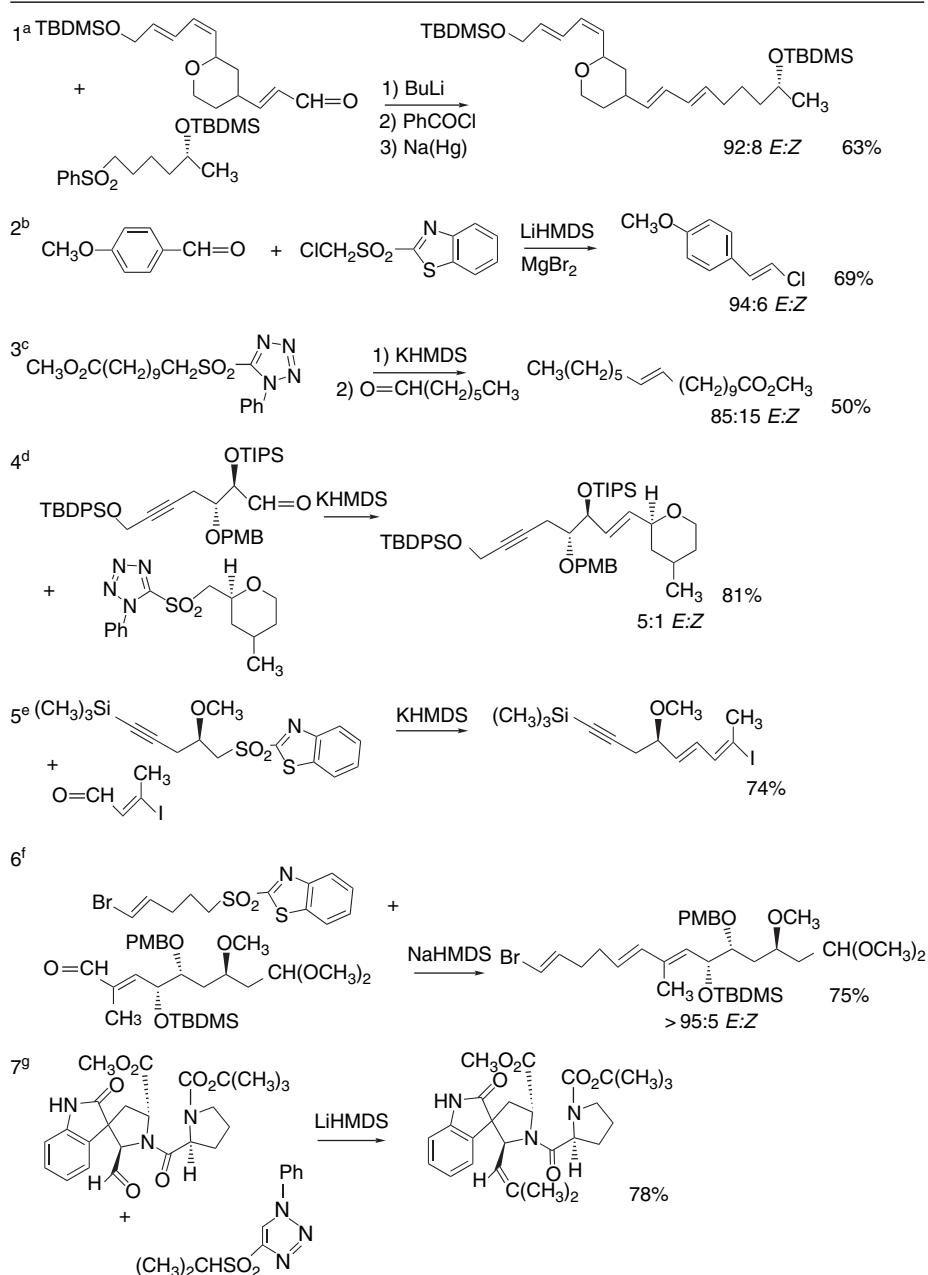
Scheme 2.20 gives some examples of the application of the Julia olefination in synthesis. Entry 1 demonstrates the reductive elimination conditions. This reaction gave a good *E*:*Z* ratio under the conditions shown. Entry 2 is an example of the use of the modified reaction that gave a good *E*:*Z* ratio in the synthesis of vinyl chlorides. Entry 3 uses the tetrazole version of the reaction in the synthesis of a long-chain ester. Entries 4 to 7 illustrate the use of modified conditions for the synthesis of polyfunctional molecules.

²⁷⁹ J. B. Baudin, G. Hareau, S. A. Julia, and O. Ruel, *Tetrahedron Lett.*, **32**, 1175 (1991).

²⁸⁰ P. R. Blakemore, W. J. Cole, P. J. Kocienski, and A. Morley, *Synlett*, 26 (1998); P. J. Kocienski, A. Bell, and P. R. Blakemore, *Synlett*, 365 (2000).

²⁸¹ D.A. Alonso, M. Fuensanta, C. Najera, and M. Varea, *J. Org. Chem.*, **70**, 6404 (2005).

Scheme 2.20. Julia Olefination Reactions



a. J. P. Marino, M. S. McClure, D. P. Holub, J. V. Comasseto, and F. C. Tucci, *J. Am. Chem. Soc.*, **124**, 1664 (2002).

b. M.-E. Lebrun, P. Le Marquand, and C. Berthelette, *J. Org. Chem.*, **71**, 2009 (2006).

c. P. E. Duffy, S. M. Quinn, H. M. Roche, and P. Evans, *Tetrahedron*, **62**, 4838 (2006).

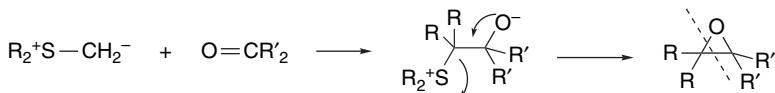
d. A. Sivaramakrishnan, G. T. Nadolski, I. A. McAlexander, and B. S. Davidson, *Tetrahedron Lett.*, **43**, 2132 (2002).

e. G. Pattenden, A. T. Plowright, J. A. Tornos, and T. Ye, *Tetrahedron Lett.*, **39**, 6099 (1998).

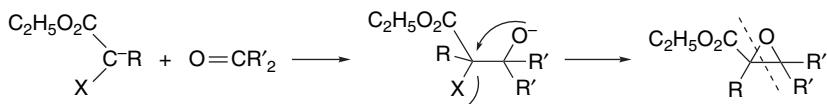
f. D. A. Evans, V. J. Cee, T. E. Smith, D. M. Fitch, and P. S. Cho, *Angew. Chem. Int. Ed. Engl.*, **39**, 2533 (2000).

g. C. Marti and E. M. Carreira, *J. Am. Chem. Soc.*, **127**, 11505 (2005).

The reactions in this section correspond to the general Pathway **D** discussed earlier (p. 64), in which the carbon nucleophile contains a potential leaving group. This group can be the same or a different group from the anion-stabilizing group. One group of reagents that reacts according to this pattern are the sulfonyl ylides, which react with carbonyl compounds to give epoxides.

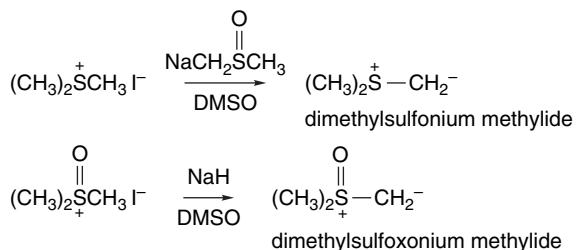


There are related reactions in which the sulfur is at the sulfoxide or sulfilimine oxidation level. Another example of the addition-cyclization route involves α -haloesters, which react to form epoxides by displacement of the halide ion.

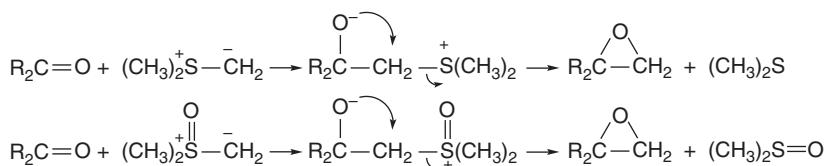


2.5.1. Sulfur Ylides and Related Nucleophiles

Sulfur ylides have several applications as reagents in synthesis.²⁸² Dimethylsulfonium methylide and dimethylsulfoxonium methylide are particularly useful.²⁸³ These sulfur ylides are prepared by deprotonation of the corresponding sulfonium salts, both of which are commercially available.



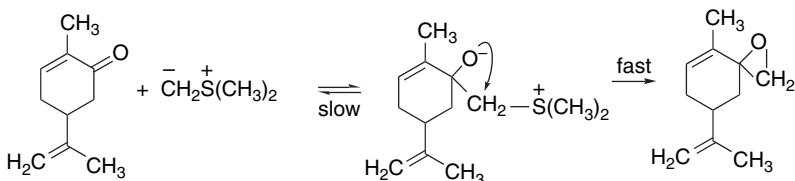
Whereas phosphonium ylides normally react with carbonyl compounds to give alkenes, dimethylsulfonium methylide and dimethylsulfoxonium methylide yield epoxides. Instead of a four-center elimination, the adducts from the sulfur ylides undergo intramolecular displacement of the sulfur substituent by oxygen. In this reaction, the sulfur substituent serves both to promote anion formation and as the leaving group.



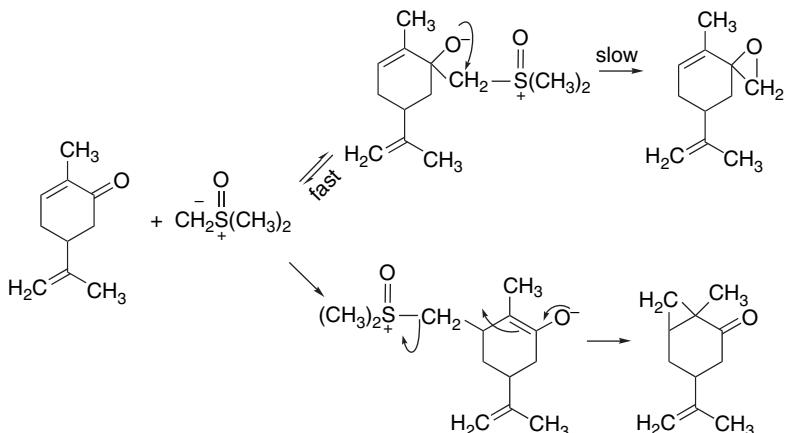
²⁸² B. M. Trost and L. S. Melvin, Jr., *Sulfur Ylides*, Academic Press, New York, 1975; E. Block, *Reactions of Organosulfur Compounds*, Academic Press, New York, 1978.

²⁸³ E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

Dimethylsulfonium methylide is both more reactive and less stable than dimethylsulfoxonium methylide, so it is generated and used at a lower temperature. A sharp distinction between the two ylides emerges in their reactions with α, β -unsaturated carbonyl compounds. Dimethylsulfonium methylide yields epoxides, whereas dimethylsulfoxonium methylide reacts by conjugate addition and gives cyclopropanes (compare Entries 5 and 6 in Scheme 2.21). It appears that the reason for the difference lies in the relative rates of the two reactions available to the betaine intermediate: (a) reversal to starting materials, or (b) intramolecular nucleophilic displacement.²⁸⁴ Presumably both reagents react most rapidly at the carbonyl group. In the case of dimethylsulfonium methylide the intramolecular displacement step is faster than the reverse of the addition, and epoxide formation takes place.

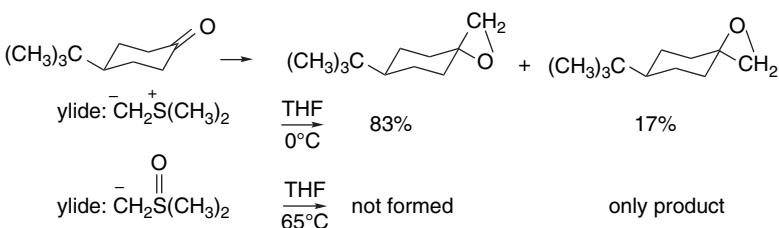


With the more stable dimethylsulfoxonium methylide, the reversal is relatively more rapid and product formation takes place only after conjugate addition.



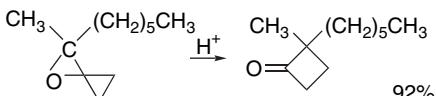
Another difference between dimethylsulfonium methylide and dimethylsulfoxonium methylide concerns the stereoselectivity in formation of epoxides from cyclohexanones. Dimethylsulfonium methylide usually adds from the axial direction whereas dimethylsulfoxonium methylide favors the equatorial direction. This result may also be due to reversibility of addition in the case of the sulfoxonium methylide.⁹² The product from the sulfonium ylide is the result the kinetic preference for axial addition by small nucleophiles (see Part A, Section 2.4.1.2). In the case of reversible addition of the sulfoxonium ylide, product structure is determined by the rate of displacement and this may be faster for the more stable epoxide.

²⁸⁴ C. R. Johnson, C. W. Schroeck, and J. R. Shanklin, *J. Am. Chem. Soc.*, **95**, 7424 (1973).

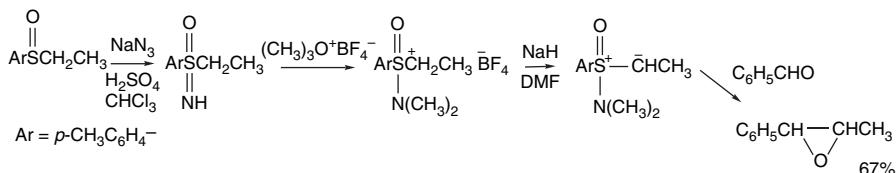


Examples of the use of dimethylsulfonium methylide and dimethylsulfoxonium methylide are listed in Scheme 2.21. Entries 1 to 5 are conversions of carbonyl compounds to epoxides. Entry 6 is an example of cyclopropanation with dimethyl sulfoxonium methylide. Entry 7 compares the stereochemistry of addition of dimethylsulfonium methylide to dimethylsulfoxonium methylide for norborn-5-en-2-one. The product in Entry 8 was used in a synthesis of α -tocopherol (vitamin E).

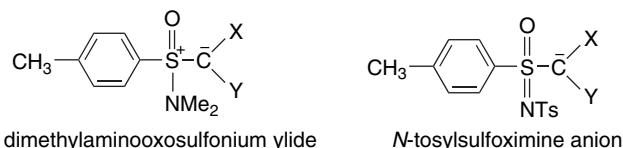
Sulfur ylides can also transfer substituted methylene units, such as isopropylidene (Entries 10 and 11) or cyclopropylidene (Entries 12 and 13). The oxaspiropentanes formed by reaction of aldehydes and ketones with diphenylsulfonium cyclopropylide are useful intermediates in a number of transformations such as acid-catalyzed rearrangement to cyclobutanones.²⁸⁵



Aside from the methylide and cyclopropylide reagents, the sulfonium ylides are not very stable. A related group of reagents derived from sulfoximines offers greater versatility in alkylidene transfer reactions.²⁸⁶ The preparation and use of this class of ylides is illustrated below.



A similar pattern of reactivity has been demonstrated for the anions formed by deprotonation of *S*-alkyl-*N*-*p*-toluenesulfoximines (see Entry 14 in Scheme 2.21).²⁸⁷



The sulfoximine group provides anion-stabilizing capacity in a chiral environment and a number of synthetic applications have been developed based on these properties.²⁸⁸

²⁸⁵ B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **95**, 5321 (1973).

²⁸⁶ C. R. Johnson, *Acc. Chem. Res.*, **6**, 341 (1973); C. R. Johnson, *Aldrichimica Acta*, **18**, 3 (1985).

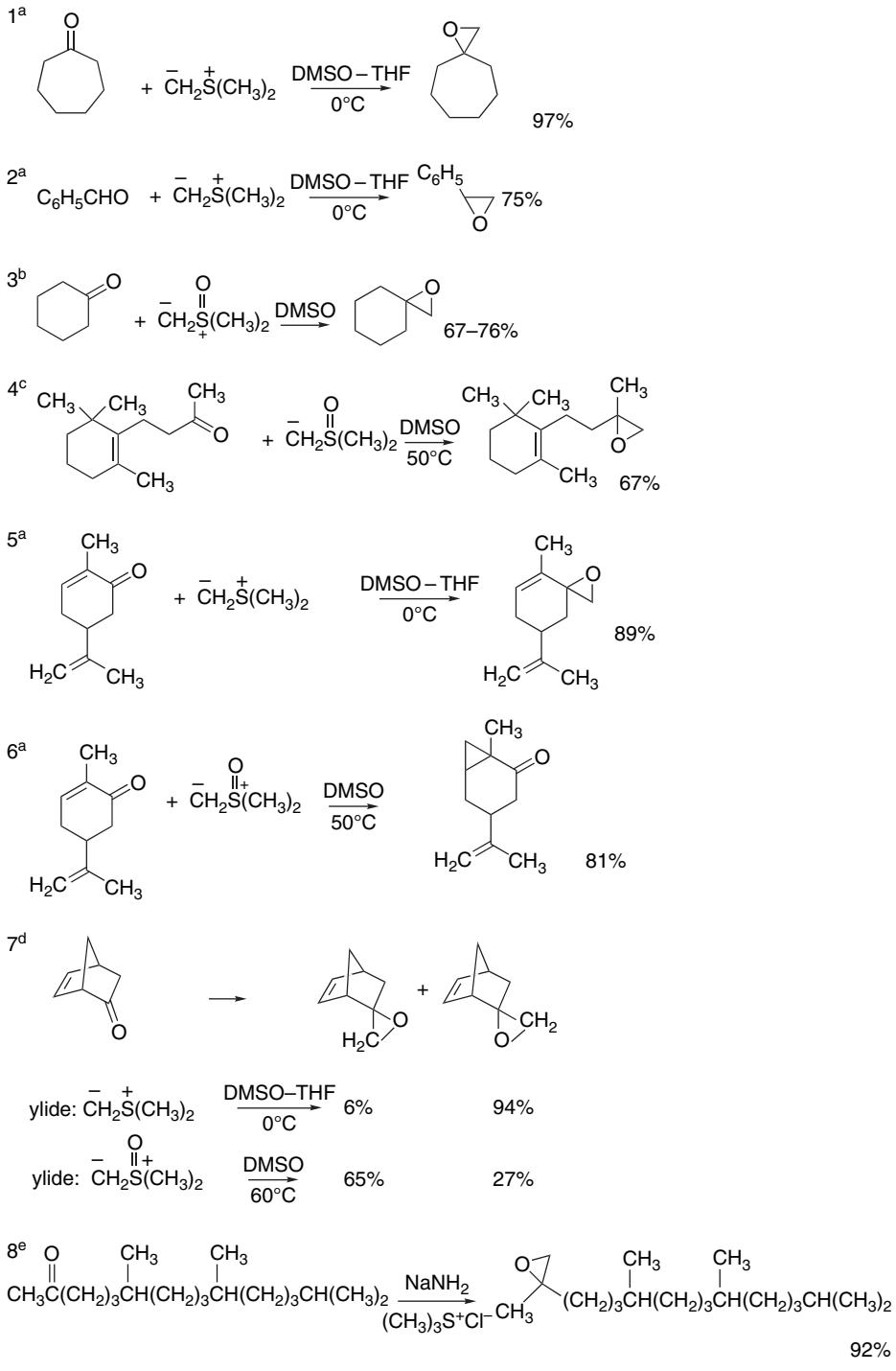
²⁸⁷ C. R. Johnson, R. A. Kirchoff, R. J. Reischer, and G. F. Katekar, *J. Am. Chem. Soc.*, **95**, 4287 (1973).

²⁸⁸ M. Reggelin and C. Zur, *Synthesis*, 1 (2000).

Scheme 2.21. Reactions of Sulfur Ylides

CHAPTER 2

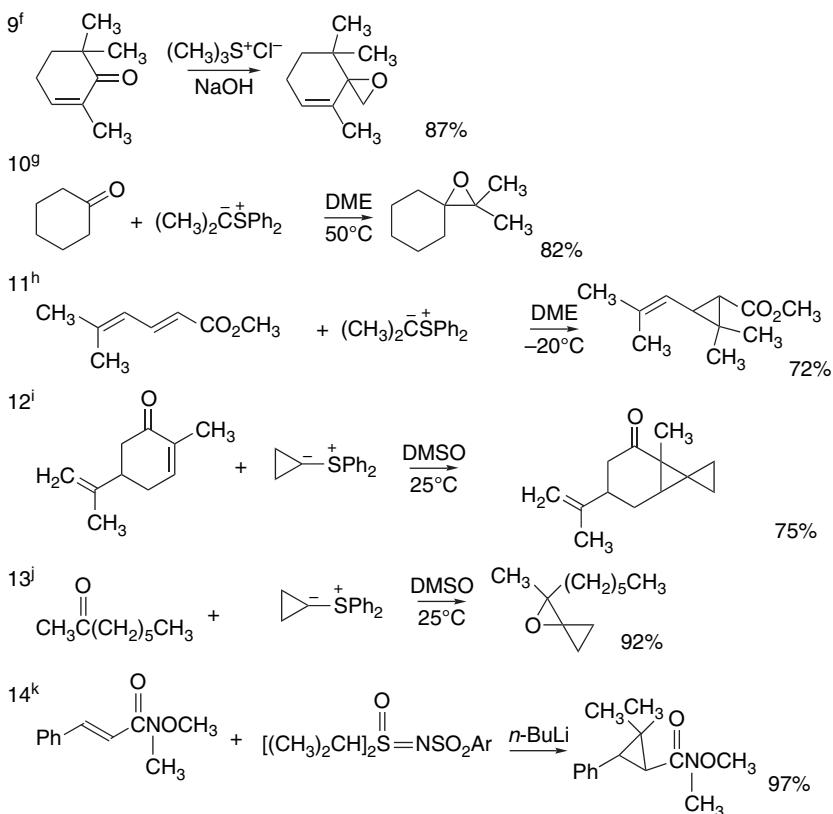
Reactions of Carbon Nucleophiles with Carbonyl Compounds



(Continued)

Scheme 2.21. (Continued)

SECTION 2.5

Reactions Proceeding by
Addition-Cyclization

- a. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
 b. E. J. Corey and M. Chaykovsky, *Org. Synth.*, **49**, 78 (1969).
 c. M. G. Fracheboud, O. Shimomura, R. K. Hill, and F. H. Johnson, *Tetrahedron Lett.*, 3951 (1969).
 d. R. S. Bly, C. M. DuBose, Jr., and G. B. Konizer, *J. Org. Chem.*, **33**, 2188 (1968).
 e. G. L. Olson, H.-C. Cheung, K. Morgan, and G. Saucy, *J. Org. Chem.*, **45**, 803 (1980).
 f. M. Rosenberger, W. Jackson, and G. Saucy, *Helv. Chim. Acta*, **63**, 1665 (1980).
 g. E. J. Corey, M. Jautelat, and W. Oppolzer, *Tetrahedron Lett.*, 2325 (1967).
 h. E. J. Corey and M. Jautelat, *J. Am. Chem. Soc.*, **89**, 3112 (1967).
 i. B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **95**, 5307 (1973).
 j. B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **95**, 5311 (1973).
 k. K. E. Rodrigues, *Tetrahedron Lett.*, **32**, 1275 (1991).

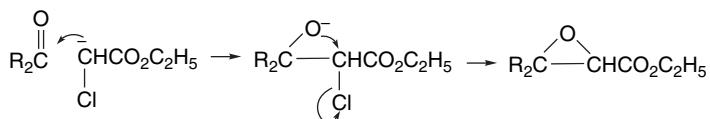
Dimethylsulfonium methylide reacts with reactive alkylating reagents such as allylic and benzylic bromides to give terminal alkenes. A similar reaction occurs with primary alkyl bromides in the presence of LiI. The reaction probably involves alkylation of the ylide, followed by elimination.²⁸⁹



²⁸⁹. L. Alcaraz, J. J. Harnett, C. Mioskowski, J. P. Martel, T. LeGall, D.-S. Shin, and J. R. Falck, *Tetrahedron Lett.*, **35**, 5453 (1994).

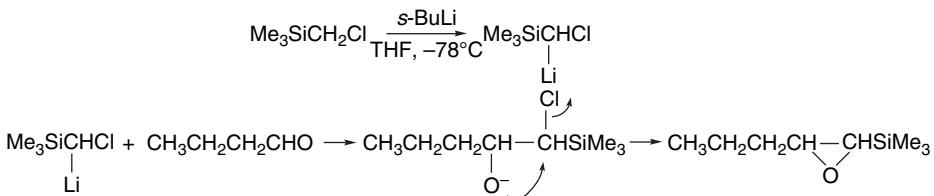
2.5.2. Nucleophilic Addition-Cyclization of α -Haloesters

The pattern of nucleophilic addition at a carbonyl group followed by intramolecular nucleophilic displacement of a leaving group present in the nucleophile can also be recognized in a much older synthetic technique, the *Darzens reaction*.²⁹⁰ The first step in this reaction is addition of the enolate of the α -haloester to the carbonyl compound. The alkoxide oxygen formed in the addition then effects nucleophilic attack, displacing the halide and forming an α,β -epoxy ester (also called a glycidic ester).

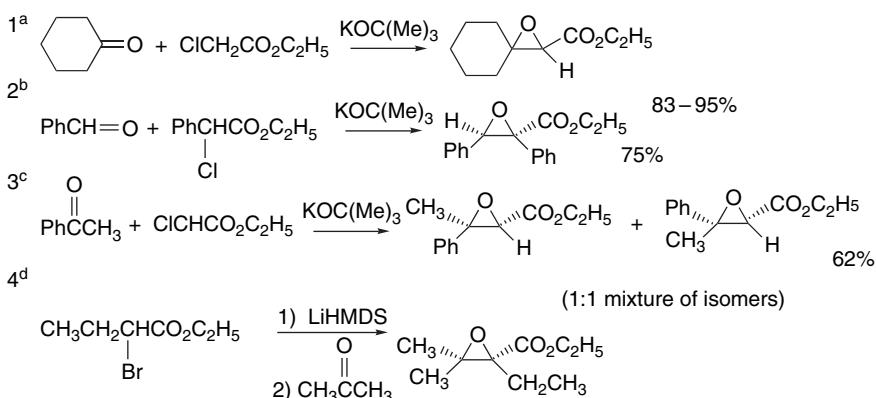


Scheme 2.22 shows some examples of the Darzens reaction.

Trimethylsilyl epoxides can be prepared by an addition-cyclization process. Reaction of chloromethyltrimethylsilane with *sec*-butyllithium at very low temperature gives an α -chloro lithium reagent that leads to an epoxide on reaction with an aldehyde or ketone.²⁹¹



Scheme 2.22. Darzens Condensation Reaction



a. R. H. Hunt, L. J. Chinn, and W. S. Johnson, *Org. Synth.*, **IV**, 459 (1963).

b. H. E. Zimmerman and L. Ahramjian, *J. Am. Chem. Soc.*, **82**, 5459 (1960).

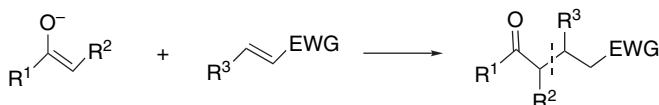
c. F. W. Bachelor and R. K. Bansal, *J. Org. Chem.*, **34**, 3600 (1969).

d. R. F. Borch, *Tetrahedron Lett.*, 3761 (1972).

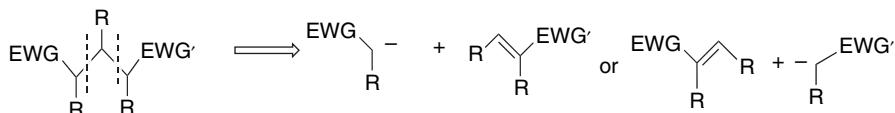
²⁹⁰ M. S. Newman and B. J. Magerlein, *Org. React.*, **5**, 413 (1951).

²⁹¹ C. Burford, F. Cooke, E. Ehlinger, and P. D. Magnus, *J. Am. Chem. Soc.*, **99**, 4536 (1977).

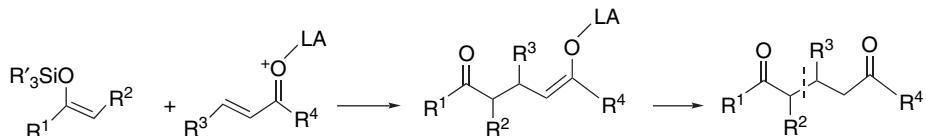
The previous sections dealt with reactions in which the new carbon-carbon bond is formed by addition of the nucleophile to a carbonyl group. Another important method for alkylation of carbon nucleophiles involves addition to an electrophilic multiple bond. The electrophilic reaction partner is typically an α,β -unsaturated ketone, aldehyde, or ester, but other electron-withdrawing substituents such as nitro, cyano, or sulfonyl also activate carbon-carbon double and triple bonds to nucleophilic attack. The reaction is called *conjugate addition* or the *Michael reaction*.



More generally, many combinations of EWG substituents can serve as the anion-stabilizing and alkene-activating groups. Conjugate addition has the potential to form a bond α to one group and β to the other to form a α,γ -disubstituted system.



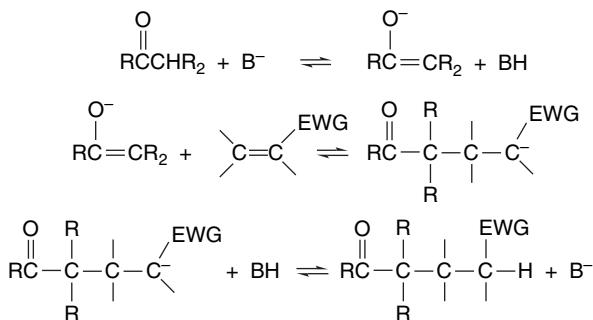
The scope of the conjugate addition reaction can be further expanded by use of Lewis acids in conjunction with enolate equivalents, especially silyl enol ethers and silyl ketene acetals. The adduct is stabilized by a new bond to the Lewis acid and products are formed from the adduct.



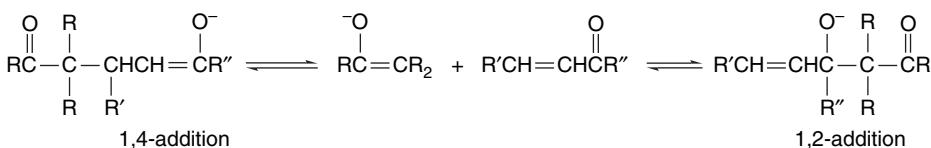
Other kinds of nucleophiles such as amines, alkoxides, and sulfide anions also react with electrophilic alkenes, but we focus on the carbon-carbon bond forming reactions.

2.6.1. Conjugate Addition of Enolates

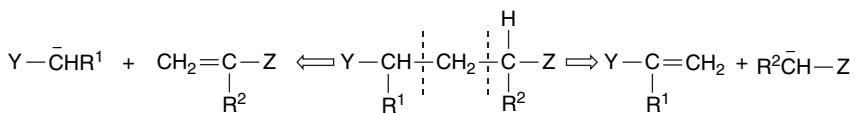
Conjugate addition of enolates under some circumstances can be carried out with a catalytic amount of base. All the steps are reversible.



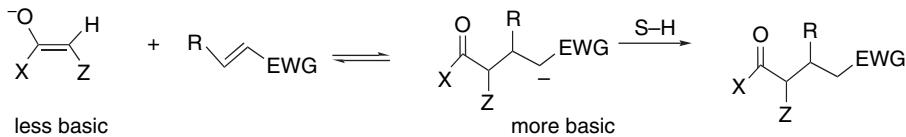
When the EWG is a carbonyl group, there can be competition with 1,2-addition, which is especially likely for aldehydes but can also occur with ketones. With successively less reactive carbonyl groups, 1,4-addition becomes more favorable. Highly reactive, hard nucleophiles tend to favor 1,2-addition and the reaction is irreversible if the nucleophile is a poor leaving group. For example with organometallic reagents, 1,2-addition is usually observed and it is irreversible because there is no tendency to expel an alkyl anion. Section 2.6.5 considers some exceptions in which organometallic reagents are added in the 1,4-manner. With less basic nucleophiles, the 1,2-addition is more easily reversible and the 1,4-addition product is usually more stable.



Retrosynthetically, there are inherently two possible approaches to the products of conjugate addition as represented below, where Y and Z represent two different anion-stabilizing groups.



When a catalytic amount of base is used, the most effective nucleophiles are enolates derived from relatively acidic compounds such as β -ketoesters or malonate esters. The adduct anions are more basic than the nucleophile and are protonated under the reaction conditions.

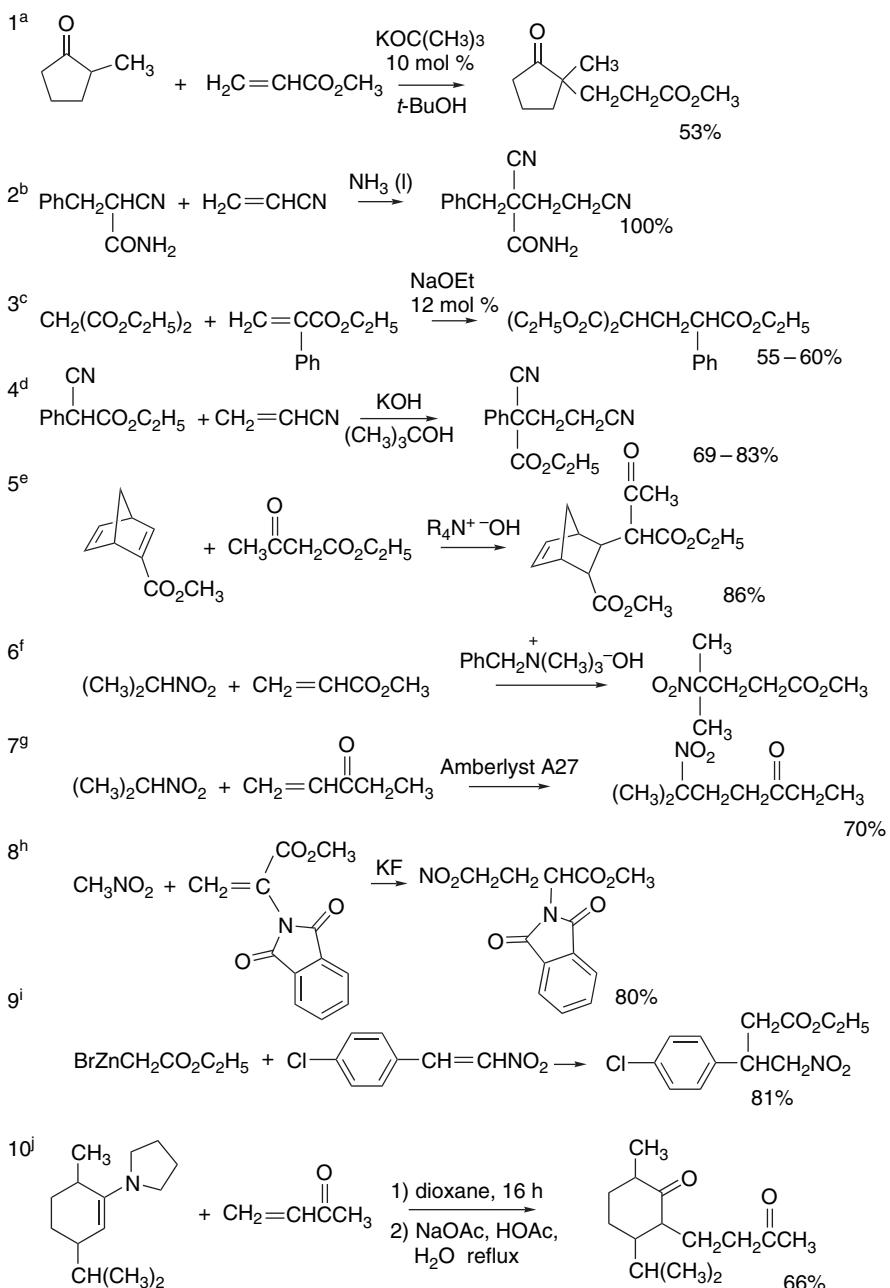


Scheme 2.23 provides some examples of conjugate addition reactions. Entry 1 illustrates the tendency for reaction to proceed through the more stable enolate. Entries 2 to 5 are typical examples of addition of doubly stabilized enolates to electrophilic alkenes. Entries 6 to 8 are cases of addition of nitroalkanes. Nitroalkanes are comparable in acidity to β -ketoesters (see Table 1.1) and are often excellent nucleophiles for conjugate addition. Note that in Entry 8 fluoride ion is used as the base. Entry 9 is a case of adding a zinc enolate (Reformatsky reagent) to a nitroalkene. Entry 10 shows an enamine as the carbon nucleophile. All of these reactions were done under equilibrating conditions.

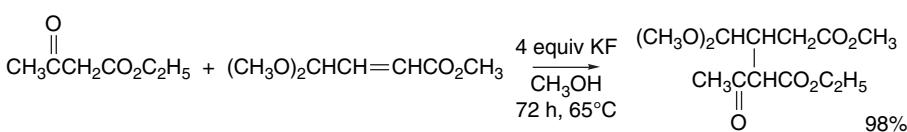
The fluoride ion is an effective catalyst for conjugate additions involving relatively acidic carbon nucleophiles.²⁹² The reactions can be done in the presence of excess

²⁹² J. H. Clark, *Chem. Rev.*, **80**, 429 (1980).

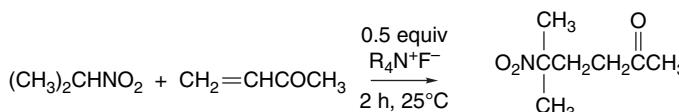
Scheme 2.23. Conjugate Addition by Carbon Nucleophiles

a. H. O. House, W. L. Roelofs, and B. M. Trost, *J. Org. Chem.*, **31**, 646 (1966).b. S. Wakamatsu, *J. Org. Chem.*, **27**, 1285 (1962).c. E. M. Kaiser, C. L. Mao, C. F. Hauser, and C. R. Hauser, *J. Org. Chem.*, **35**, 410 (1970).d. E. C. Horning and A. F. Finelli, *Org. Synth.*, IV, 776 (1963).e. K. Alder, H. Wirtz, and H. Koppelberg, *Liebigs Ann. Chem.*, **601**, 138 (1956).f. R. B. Moffett, *Org. Synth.*, IV, 652 (1963).g. R. Ballini, P. Marziali, and A. Mozzicafreddo, *J. Org. Chem.*, **61**, 3209 (1996).h. M. J. Crossley, Y. M. Fung, J. J. Potter, and A. W. Stamford, *J. Chem. Soc., Perkin Trans. 2*, 1113 (1998).i. R. Menicagli and S. Samaritani, *Tetrahedron*, **52**, 1425 (1996).j. K. D. Croft, E. L. Ghisalberti, P. R. Jefferies, and A. D. Stuart, *Aust. J. Chem.*, **32**, 2079 (1979).

fluoride, where the formation of the $[F-H-F^-]$ ion occurs, or by use of a tetralkylammonium fluoride in an aprotic solvent.



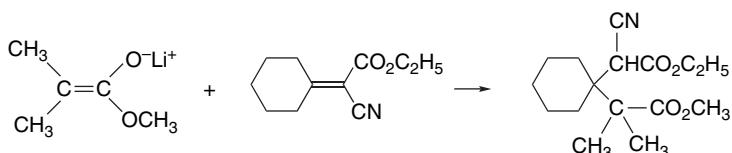
Ref 293



Ref. 294

As in the case of aldol addition, the scope of conjugate addition reactions can be extended by the use of techniques for regio- and stereospecific preparation of enolates and enolate equivalents. If the reaction is carried out with a stoichiometrically formed enolate in the absence of a proton source, the initial product is the enolate of the adduct. The replacement of a π bond by a σ bond ensures a favorable ΔH .

Among Michael acceptors that have been shown to react with ketone and ester enolates under kinetic conditions are methyl α -trimethylsilylvinyl ketone,²⁹⁵ methyl α -methylthioacrylate,²⁹⁶ methyl methylthiovinyloxide,²⁹⁷ and ethyl α -cyanoacrylate.²⁹⁸ Each of these acceptors benefits from a second anion-stabilizing substituent. The latter class of acceptors has been found to be capable of generating contiguous quaternary carbon centers.



Ref. 298

Several examples of conjugate addition of carbanions carried out under aprotic conditions are given in Scheme 2.24. The reactions are typically quenched by addition of a proton source to neutralize the enolate. It is also possible to trap the adduct by silylation or, as we will see in Section 2.6.2, to carry out a tandem alkylation. Lithium enolates preformed by reaction with LDA in THF react with enones to give 1,4-diketones (Entries 1 and 2). Entries 3 and 4 involve addition of ester enolates to enones. The reaction in Entry 3 gives the 1,2-addition product at -78°C but isomerizes to the 1,4-product at 25°C . Esters of 1,5-dicarboxylic acids are obtained by addition of ester enolates to α,β -unsaturated esters (Entry 5). Entries 6 to 8 show cases of

²⁹³ S. Tori, H. Tanaka, and Y. Kobayashi, *J. Org. Chem.*, **42**, 3473 (1977).

²⁹⁴ J. H. Clark, J. M. Miller, and K.-H. So, *J. Chem. Soc. Perkin Trans. I*, 941 (1978).

²⁹⁵ G. Stork and B. Ganem, *J. Am. Chem. Soc.*, **95**, 6152 (1973).

²⁹⁶ R. J. Gregoire, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Lett.*, 2603 (1973).

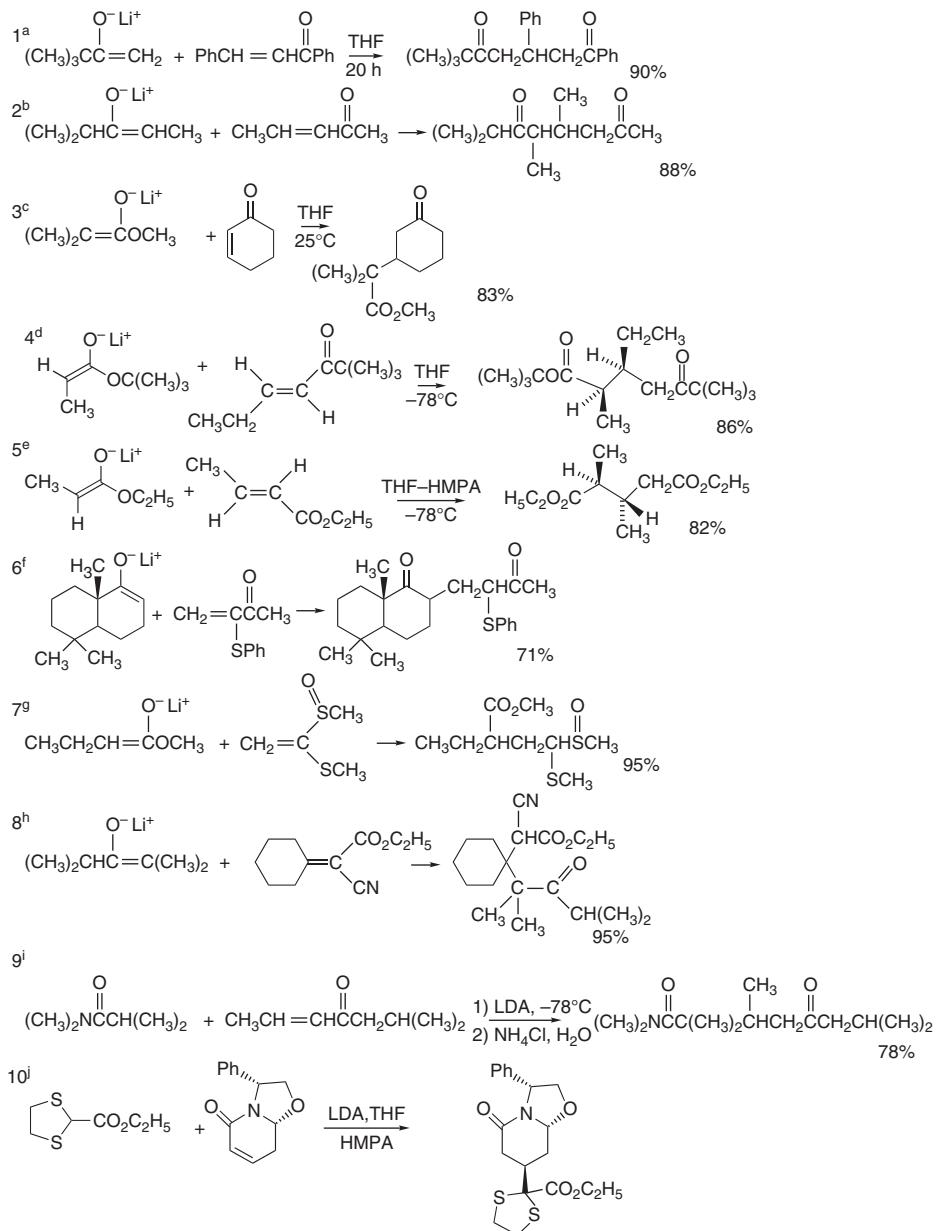
^{297.} J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, P. J. Wepple, and R. H. Schlessinger, *Tetrahedron Lett.*, 4711 (1973).

²⁹⁸ R. A. Holton, A. D. Williams, and B. M. Kennedy, *J. Org. Chem.*, **51**, 5480 (1986).

Scheme 2.24. Conjugate Addition under Aprotic Conditions

SECTION 2.6

Conjugate Addition by Carbon Nucleophiles



a. J. Bertrand, L. Gorrivon, and P. Maroni, *Tetrahedron*, **40**, 4127 (1984).

b. D. A. Oare and C. H. Heathcock, *Tetrahedron Lett.*, **27**, 6169 (1986).

c. A. G. Schultz and Y. K. Yee, *J. Org. Chem.*, **41**, 4044 (1976).

d. C. H. Heathcock and D. A. Oare, *J. Org. Chem.*, **50**, 3022 (1985).

e. M. Yamaguchi, M. Tsukamoto, S. Tanaka, and I. Hirao, *Tetrahedron Lett.*, **25**, 5661 (1984).

f. K. Takaki, M. Ohsguri, M. Okada, M. Yasumura, and K. Negoro, *J. Chem. Soc., Perkin Trans. 1*, 741 (1984).

g. J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, P. J. Wepplo, and R. H. Schlessinger, *Tetrahedron Lett.*, 4711 (1973).

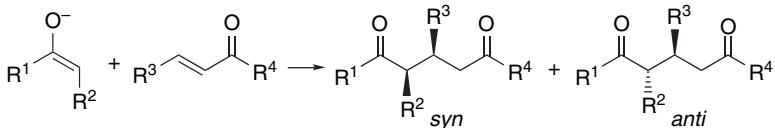
h. R. A. Holton, A. D. Williams, and R. M. Kennedy, *J. Org. Chem.*, **51**, 5480 (1986).

i. D. A. Oare, M. A. Henderson, M. A. Sanner, and C. H. Heathcock, *J. Org. Chem.*, **55**, 132 (1990).

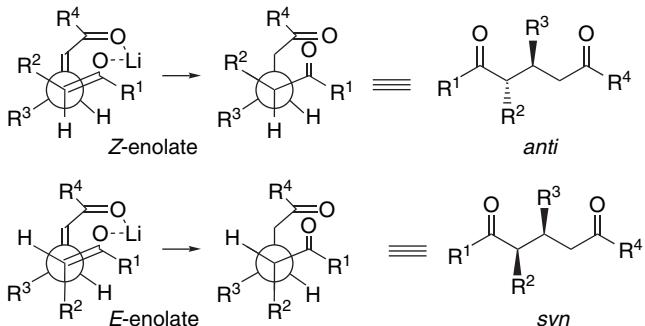
j. M. Amat, M. Perez, N. Llor, and J. Bosch, *Org. Lett.*, **4**, 2787 (2002).

enolate addition to acceptors with two anion-stabilizing groups. Entry 8 is noteworthy in that it creates two contiguous quaternary carbons. Entry 9 shows an addition of an amide anion. Entry 10 is a case of an enolate stabilized by both the dithiane ring and ester substituent. The acceptor, an α,β -unsaturated lactam, is relatively unreactive but the addition is driven forward by formation of a new σ bond. The chiral moiety incorporated into the five-membered ring promotes enantioselective formation of the new stereocenter.

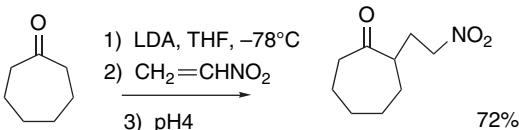
There have been several studies of the stereochemistry of conjugate addition reactions. If there are substituents on both the nucleophilic enolate and the acceptor, either *syn* or *anti* adducts can be formed.



The reaction shows a dependence on the *E*- or *Z*-stereochemistry of the enolate. *Z*-enolates favor *anti* adducts and *E*-enolates favor *syn* adducts. These tendencies can be understood in terms of an eight-membered chelated TS.²⁹⁹ The enone in this TS is in an *s-cis* conformation. The stereochemistry is influenced by the *s-cis/s-trans* equilibria. Bulky R⁴ groups favor the *s-cis* conformer and enhance the stereo-selectivity of the reaction. A computational study on the reaction also suggested an eight-membered TS.³⁰⁰



The carbonyl functional groups are the most common both as activating EWG substituents in the acceptor and as the anion-stabilizing group in the enolate, but several other EWGs also undergo conjugate addition reactions. Nitroalkenes are excellent acceptors. The nitro group is a strong EWG and there is usually no competition from nucleophilic attack on the nitro group.



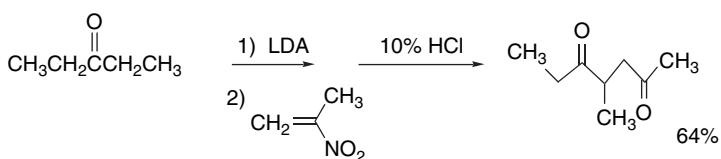
Ref. 301

²⁹⁹ D. Oare and C. H. Heathcock, *J. Org. Chem.*, **55**, 157 (1990); D. A. Oare and C. H. Heathcock, *Top. Stereochem.*, **19**, 227 (1989); A. Bernardi, *Gazz. Chim. Ital.*, **125**, 539 (1995).

³⁰⁰ A. Bernardi, A. M. Capelli, A. Cassinari, A. Comotti, C. Gennari, and C. Scolastico, *J. Org. Chem.*, **57**, 7029 (1992).

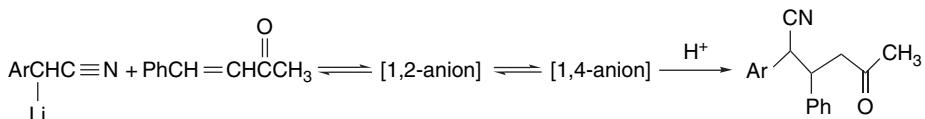
³⁰¹ R. J. Flintoft, J. C. Buzby, and J. A. Tucker, *Tetrahedron Lett.*, **40**, 4485 (1999).

The nitro group can be converted to a ketone by hydrolysis of the nitronate anion, permitting the synthesis of 1,4-dicarbonyl compounds.

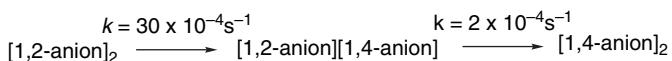


Ref. 302

Anions derived from nitriles can act as nucleophiles in conjugate addition reactions. A range of substituted phenylacetonitriles undergoes conjugate addition to 4-phenylbut-3-en-2-one.



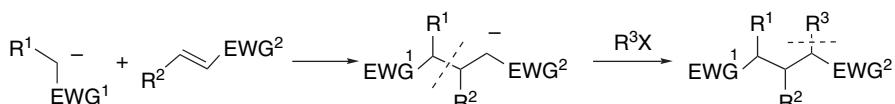
The reaction occurs via the 1,2-adduct, which isomerizes to the 1,4-adduct,³⁰³ and there is an energy difference of about 5 kcal/mol in favor of the 1,4-adduct. With the parent compound in THF, the isomerization reaction has been followed kinetically and appears to occur in two phases. The first part of the reaction occurs with a half-life of a few minutes, and the second with a half-life of about an hour. A possible explanation is the involvement of dimeric species, with the homodimer being more reactive than the heterodimer.



A very important extension of the conjugate addition reaction is discussed in Chapter 8. Organocopper reagents have a strong preference for conjugate addition. Organocopper nucleophiles do not require anion-stabilizing substituents, and they allow conjugate addition of alkyl, alkenyl, and aryl groups to electrophilic alkenes.

2.6.2. Conjugate Addition with Tandem Alkylation

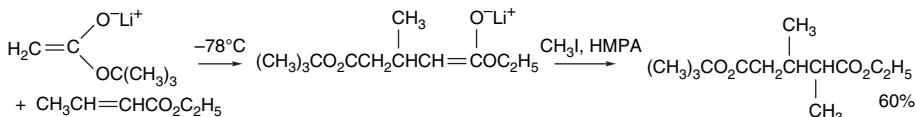
When conjugate addition is carried out under aprotic conditions with stoichiometric formation of the enolate, the adduct is present as an enolate until the reaction mixture is quenched with a proton source. It is therefore possible to effect a second reaction of the enolate by addition of an alkyl halide or sulfonate to the solution of the adduct enolate, which results in an alkylation. This reaction sequence permits the formation of two new C–C bonds.



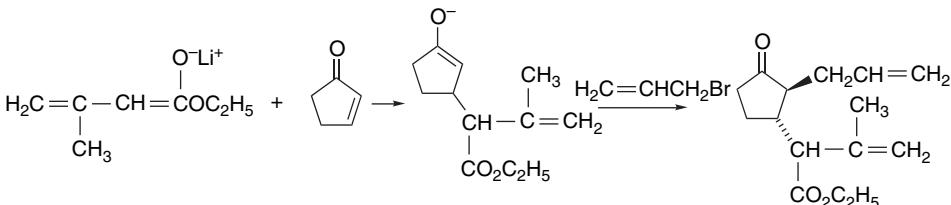
³⁰² M. Miyashita, B. Z. Awen, and A. Yoshikoshi, *Synthesis*, 563 (1990).

³⁰³ H. J. Reich, M. M. Biddle, and R. J. Edmonston, *J. Org. Chem.*, **70**, 3375 (2005).

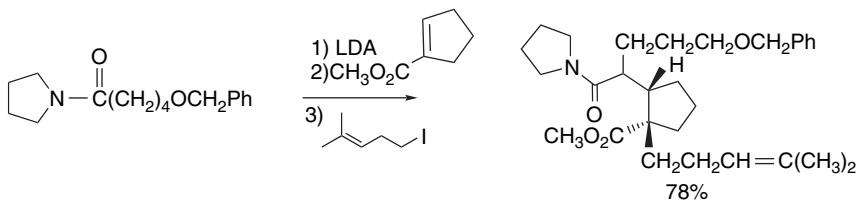
Several examples of tandem conjugate addition-alkylation follow.



Ref. 304



Ref. 305

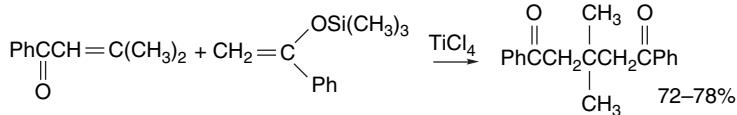


Ref. 306

Tandem conjugate addition-alkylation has proven to be an efficient means of introducing groups at both α - and β -positions at enones.³⁰⁷ As with simple conjugate addition, organocupper reagents are particularly important in this application, and they are discussed further in Section 8.1.2.3.

2.6.3. Conjugate Addition by Enolate Equivalents

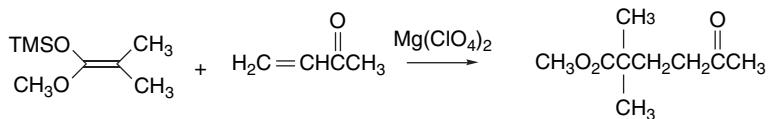
Conditions for effecting conjugate addition of neutral enolate equivalents such as silyl enol ethers in the presence of Lewis acids have been developed and are called *Mukaiyama-Michael reactions*. Trimethylsilyl enol ethers can be caused to react with electrophilic alkenes by use of TiCl_4 . These reactions proceed rapidly even at -78°C .³⁰⁸



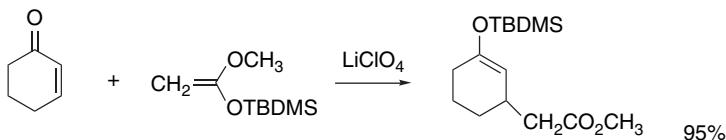
Ref. 309

- ³⁰⁴ M. Yamaguchi, M. Tsukamoto, and I. Hirao, *Tetrahedron Lett.*, **26**, 1723 (1985).
- ³⁰⁵ W. Oppolzer, R. P. Helou, G. Bernardinelli, and K. Baettig, *Tetrahedron Lett.*, **24**, 4975 (1983).
- ³⁰⁶ C. H. Heathcock, M. M. Hansen, R. B. Ruggeri, and J. C. Kath, *J. Org. Chem.*, **57**, 2544 (1992).
- ³⁰⁷ For additional examples, see M. C. Chapdelaine and M. Hulce, *Org. React.*, **38**, 225 (1990); E. V. Gorobets, M. S. Miftakhov, and F. A. Valeev, *Russ. Chem. Rev.*, **69**, 1001 (2000).
- ³⁰⁸ K. Narasaka, K. Soai, Y. Aikawa, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **49**, 779 (1976).
- ³⁰⁹ K. Narasaka, *Org. Synth.*, **65**, 12 (1987).

Silyl ketene acetals also undergo conjugate addition. For example, $Mg(ClO_4)_2$ and $LiClO_4$ catalyze addition of silyl ketene acetals to enones.

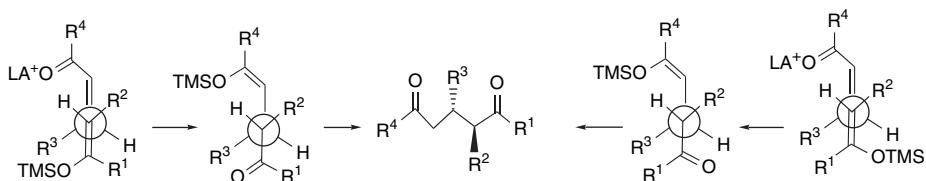


Ref. 310

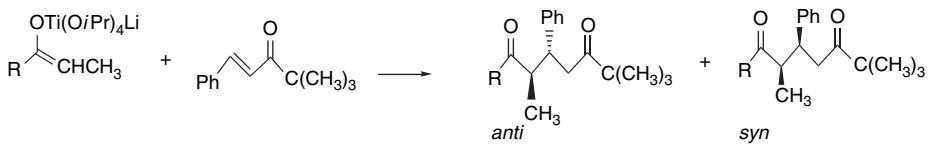


Ref. 311

Initial stereochemical studies suggested that the Mukaiyama-Michael reaction proceeds through an open TS, since there was a tendency to favor *anti* diastereoselectivity, regardless of the silyl enol ether configuration.³¹²



The stereoselectivity can be enhanced by addition of $Ti(O-i-Pr)_4$. The active nucleophile under these conditions is expected to be an “ate” complex in which a much larger $Ti(O-i-Pr)_4$ group replaces Li^+ as the Lewis acid.³¹³ Under these conditions, the *syn:anti* ratio is dependent on the stereochemistry of the enolate.



R	Configuration	<i>anti:syn</i>	Yield(%)
Et	Z	95:5	69
Ph	Z	> 92:8	85
<i>i</i> -Pr	Z	> 97:3	65
<i>i</i> -Pr	E	17:83	91

Silyl acetals of thiol esters have also been studied. With $TiCl_4$ as the Lewis acid, there is correspondence between the configuration of the silyl thioketene acetal and the adduct stereochemistry.³¹⁴ *E*-Isomers show high *anti* selectivity, whereas *Z*-isomers are less selective.

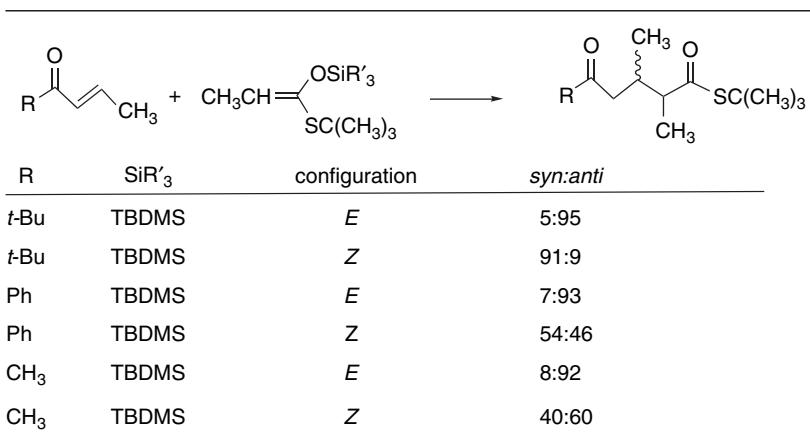
^{310.} S. Fukuzumi, T. Okamoto, K. Yasui, T. Suenobu, S. Itoh, and J. Otera, *Chem. Lett.*, 667 (1997).

^{311.} P. A. Grieco, R. J. Cooke, K. J. Henry, and J. M. Vander Roest, *Tetrahedron Lett.*, **32**, 4665 (1991).

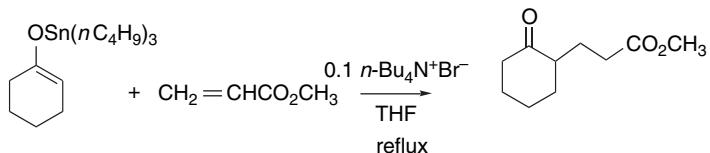
^{312.} C. H. Heathcock, M. H. Norman, and D. E. Uehling, *J. Am. Chem. Soc.*, **107**, 2797 (1985).

^{313.} A. Bernardi, P. Dotti, G. Poli, and C. Scolastico, *Tetrahedron*, **48**, 5597 (1992); A. Bernardi, M. Cavicchioi, and C. Scolastico, *Tetrahedron*, **49**, 10913 (1993).

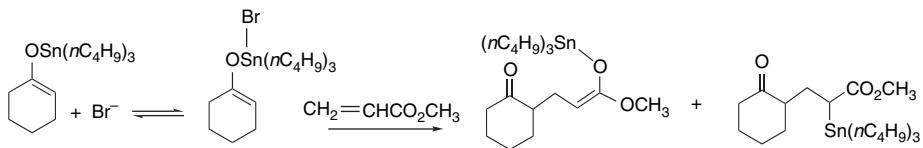
^{314.} Y. Fujita, J. Otera, and S. Fukuzumi, *Tetrahedron*, **52**, 9419 (1996).



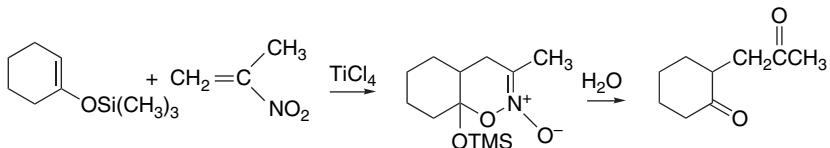
Stannyl enolates give good addition yields in the presence of a catalytic amount of $n\text{-}(\text{C}_4\text{H}_9)_4\text{N}^+\text{Br}^-$.³¹⁵ The bromide ion plays an active role in this reaction by forming a more reactive species via coordination at the tin atom.



It is believed that this reaction involves the formation of the α -stannyl ester. Metals such as lithium that form ionic enolates would be more likely to reverse the addition step.



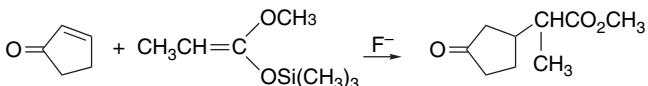
Nitroalkenes are also reactive Michael acceptors under Lewis acid-catalyzed conditions. Titanium tetrachloride or stannic tetrachloride can induce addition of silyl enol ethers. The initial adduct is trapped in a cyclic form by trimethylsilylation.³¹⁶ Hydrolysis of this intermediate regenerates the carbonyl group and also converts the *aci*-nitro group to a carbonyl.³¹⁷



³¹⁵ M. Yasuda, N. Ohigashi, I. Shibata, and A. Baba, *J. Org. Chem.*, **64**, 2180 (1999).

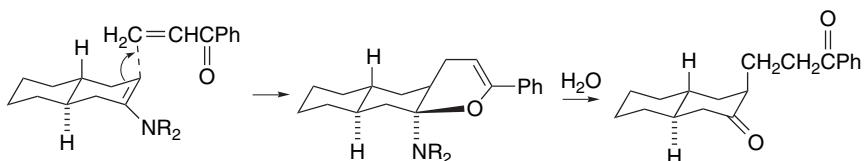
³¹⁶ A. F. Mateos and J. A. de la Fuente Blanco, *J. Org. Chem.*, **55**, 1349 (1990).

³¹⁷ M. Miyashita, T. Yanami, T. Kumazawa, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **106**, 2149 (1984).



Ref. 318

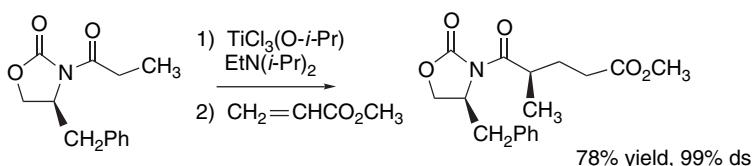
Enamines also react with electrophilic alkenes to give conjugate addition products. The addition reactions of enamines of cyclohexanones show a strong preference for attack from the axial direction.³¹⁹ This is anticipated on stereochemical grounds because the π orbital of the enamine is the site of nucleophilicity.



Scheme 2.25 shows some examples of additions of enolate equivalents. A range of Lewis acid catalysts has been used in addition to TiCl_4 and SnCl_4 . Entry 1 shows uses of a lanthanide catalyst. Entry 2 employs LiClO_4 as the catalyst. The reaction in Entry 3 includes a chiral auxiliary that controls the stereoselectivity; the chiral auxiliary is released by a cyclization using *N*-methylhydroxylamine. Entries 4 and 5 use the triphenylmethyl cation as a catalyst and Entries 6 and 7 use trimethylsilyl triflate and an enantioselective catalyst, respectively.

2.6.4. Control of Facial Selectivity in Conjugate Addition Reactions

As is the case for aldol addition, chiral auxiliaries and catalysts can be used to control stereoselectivity in conjugate addition reactions. Oxazolidinone chiral auxiliaries have been used in both the nucleophilic and electrophilic components under Lewis acid-catalyzed conditions. *N*-Acyloxazolidinones can be converted to nucleophilic titanium enolates with $\text{TiCl}_3(\text{O}-i\text{-Pr})$.³²⁰



³¹⁸ T. V. Rajan Babu, *J. Org. Chem.*, **49**, 2083 (1984).

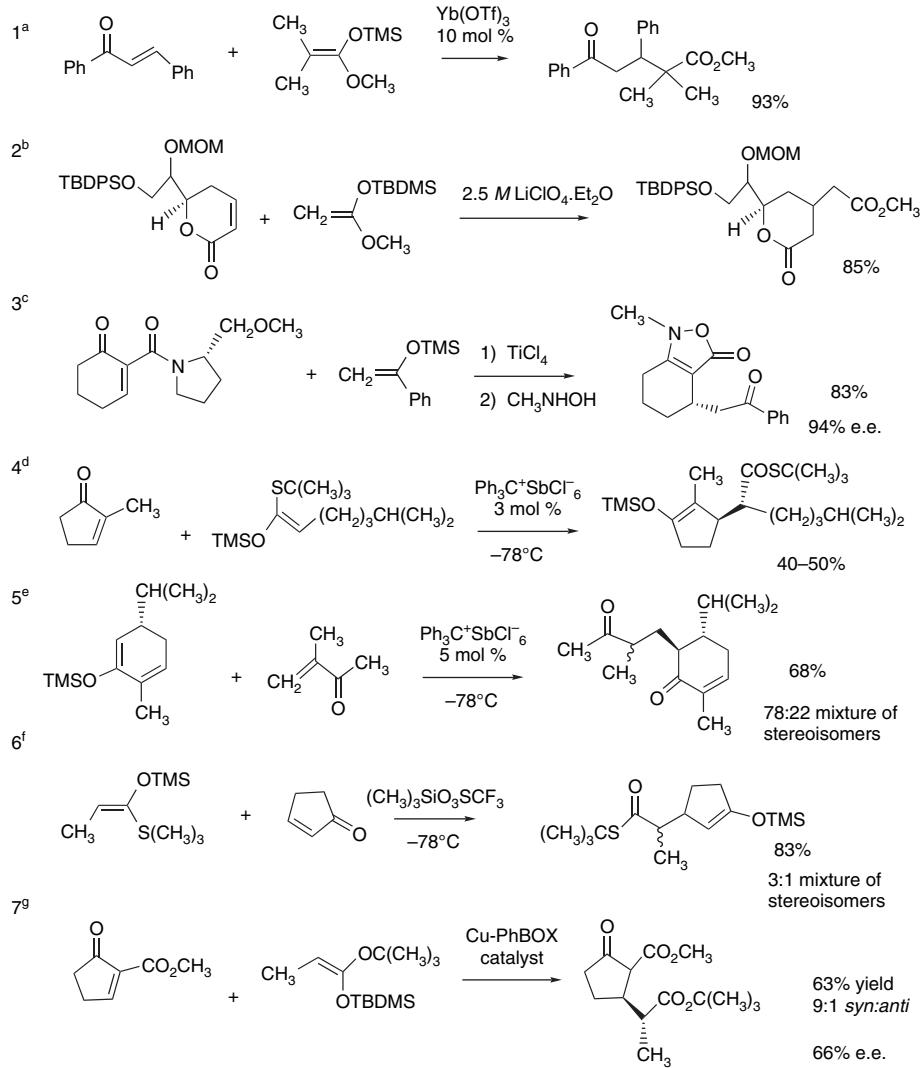
³¹⁹ E. Valentin, G. Pitacco, F. P. Colonna, and A. Risalti, *Tetrahedron*, **30**, 2741 (1974); M. Forchiassin, A. Risalti, C. Russo, M. Calligaris, and G. Pitacco, *J. Chem. Soc.*, 660 (1974).

³²⁰ D. A. Evans, M. T. Bilodeau, T. C. Somers, J. Clardy, D. Cherry, and Y. Kato, *J. Org. Chem.*, **56**, 5750 (1991).

Scheme 2.25. Conjugate Addition of Enolate Equivalents

CHAPTER 2

Reactions of Carbon
Nucleophiles with
Carbonyl Compounds



a. S. Kobayashi, I. Hachiya, T. Takahori, M. Araki, and H. Ishitani, *Tetrahedron Lett.*, **33**, 6815 (1992).

b. P. A. Grieco, R. J. Cooke, K. J. Henry, and J. M. Vander Roest, *Tetrahedron Lett.*, **32**, 4665 (1991).

c. A. G. Schultz and H. Lee, *Tetrahedron Lett.*, **33**, 4397 (1992).

d. P. Grzywacz, S. Marczał, and J. Wicha, *J. Org. Chem.*, **62**, 5293 (1997).

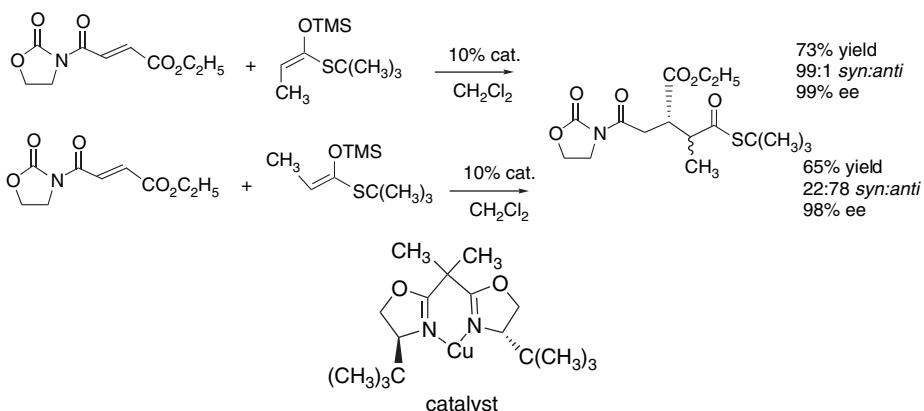
e. A. V. Baranovsky, B. J. M. Jansen, T. M. Meulemans, and A. de Groot, *Tetrahedron*, **54**, 5623 (1998).

f. K. Michalak and J. Wicha, *Polish J. Chem.*, **78**, 205 (2004).

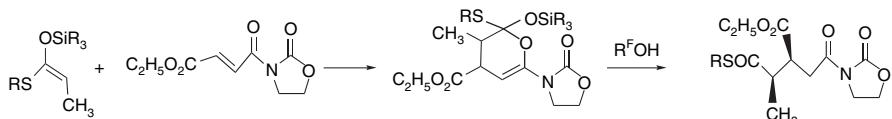
g. A. Bernardi, G. Colombo and C. Scolastico, *Tetrahedron Lett.*, **37**, 8921 (1996).

Unsaturated acyl derivatives of oxazolidinones can be used as acceptors, and these reactions are enantioselective in the presence of chiral *bis*-oxazoline catalysts.³²¹ Silyl ketene acetals of thiol esters are good reactants and the stereochemistry depends on the ketene acetal configuration. The *Z*-isomer gives higher diastereoselectivity than the *E*-isomer.

³²¹ D. A. Evans, K. A. Scheidt, J. N. Johnston, and M. C. Willis, *J. Am. Chem. Soc.*, **123**, 4480 (2001).

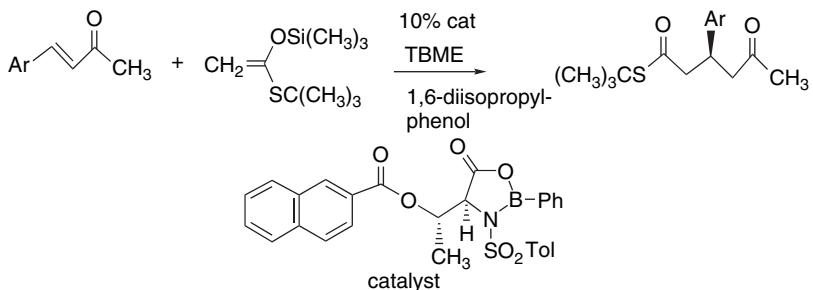


The above examples contain an ester group that acts as a second activating group. The reactions are also accelerated by including one equivalent of $(CF_3)_2CHOH$. This alcohol functions by promoting solvolysis of a dihydropyran intermediate that otherwise inhibits the catalyst.



Alkylidenemalonate esters are also good acceptors in reactions with silyl ketene acetals or thiol esters under very similar conditions.³²²

A number of other chiral catalysts can promote enantioselective conjugate additions of silyl enol ethers, silyl ketene acetals, and related compounds. For example, an oxazaborolidinone derived from allothreonine achieves high enantioselectivity in additions of silyl thioketene acetals.³²³ The optimal conditions for this reaction also include a hindered phenol and an ether additive.



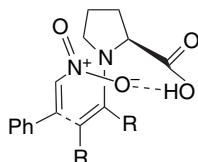
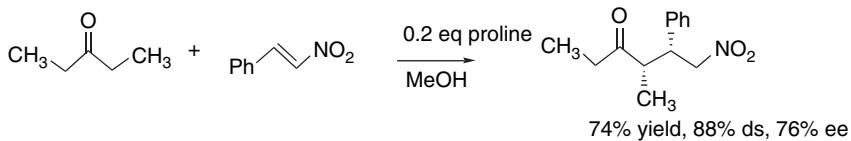
Enantioselectivity has been observed for acyclic ketones, using proline as a catalyst. Under optimum conditions, ds > 80% and e.e. > 70% were observed.³²⁴ These

³²² D. A. Evans, T. Rovis, M. C. Kozlowski, C. W. Downey, and J. S. Tedrow, *J. Am. Chem. Soc.*, **122**, 9134 (2000).

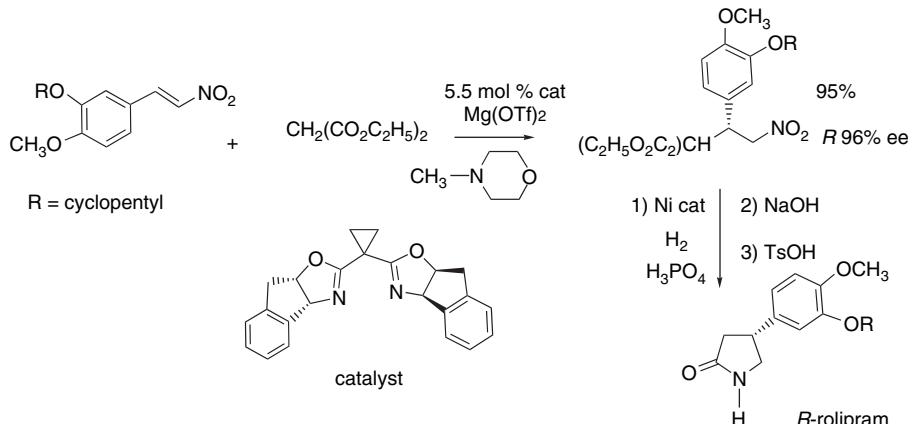
³²³ X. Wang, S. Adachi, H. Iwai, H. Takatsuki, K. Fujita, M. Kubo, A. Oku, and T. Harada, *J. Org. Chem.*, **68**, 10046 (2003).

³²⁴ D. Enders and A. Seki, *Synlett*, 26 (2002).

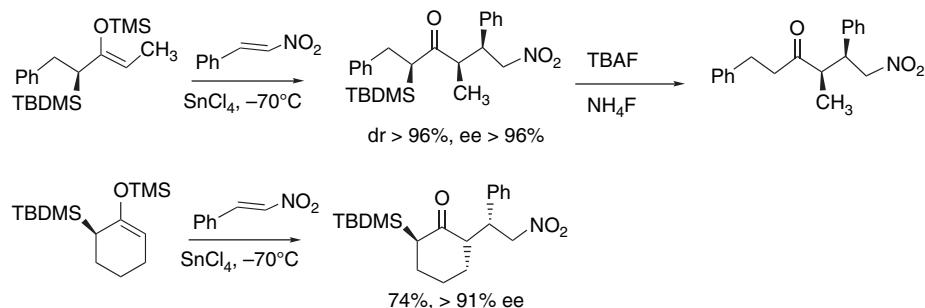
reactions presumably involve the proline-derived enamine. (See Section 2.1.5.6 for a discussion of enantioselective reactions of proline enamines.)



Enantioselective additions of β -dicarbonyl compounds to β -nitrostyrenes have been achieved using *bis*-oxazolidine catalysts. This method was used in an enantioselective synthesis of the antidepressant drug rolipram.³²⁵



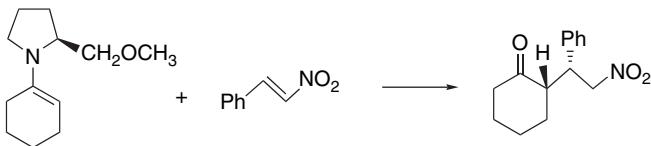
Enantioselectivity can also be based on structural features present in the reactants. A silyl substituent has been used to control stereochemistry in both cyclic and acyclic systems. The silyl substituent can then be removed by TBAF.³²⁶ As with enolate alkylation (see p. 32), the steric effect of the silyl substituent directs the approach of the acceptor to the opposite face.



³²⁵ D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, and J. Zhang, *J. Am. Chem. Soc.*, **124**, 13097 (2002).

³²⁶ D. Enders and T. Otten, *Synlett*, 747 (1999).

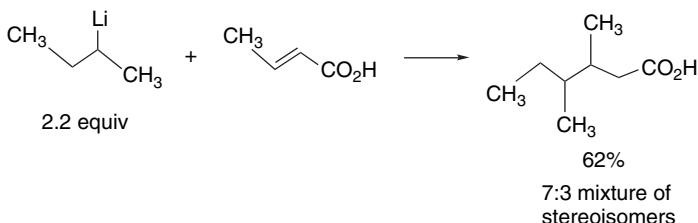
High stereoselectivity is also observed in the addition of an enamine using 2-methoxymethylpyrrolidine as the amine.³²⁷



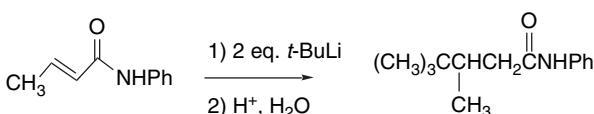
2.6.5. Conjugate Addition of Organometallic Reagents

There are relatively few examples of organolithium compounds acting as nucleophiles in conjugate addition. Usually, organolithium compounds react at the carbonyl group, to give 1,2-addition products. Here, we consider a few cases of organometallic reagents that give conjugate addition products. There are a very large number of copper-mediated conjugate additions, and we discuss these reactions in Section 8.1.2.3.

Alkyl and aryllithium compounds have been found to undergo 1,4-addition with the salts of α, β -unsaturated acids.³²⁸ This result reflects the much reduced reactivity of the carboxylate carbonyl group as an electrophile.

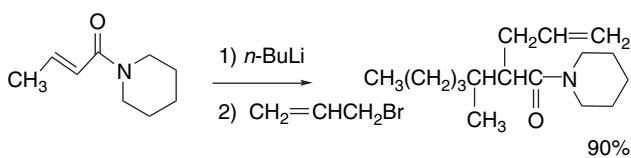


α, β -Unsaturated amides have been found to be good reactants toward organometallic reagents. These reactions involve the deprotonated amide ion, which is less susceptible to 1,2-addition than ketones and esters.



Ref. 329

Similar reactions have also been observed with tertiary amides and the adducts can be alkylated by tandem S_N2 reactions.



Ref. 330

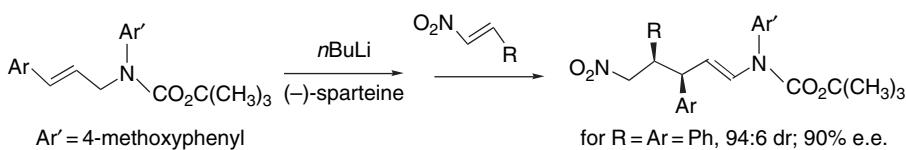
³²⁷ S. J. Blarer, W. B. Schweizer, and D. Seebach, *Helv. Chim. Acta*, **65**, 1637 (1982); S. J. Blarer and D. Seebach, *Chem. Ber.*, **116**, 2250 (1983).

³²⁸ B. Plunian, M. Vaultier, and J. Mortier, *Chem. Commun.*, 81 (1998).

³²⁹ J. E. Baldwin and W. A. Dupont, *Tetrahedron Lett.*, **21**, 1881 (1980).

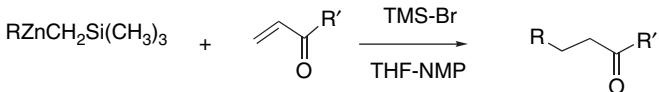
³³⁰ G. B. Mpango, K. K. Mahalanabis, S. Mahdavi-Damghani, and V. Snieckus, *Tetrahedron Lett.*, **21**, 4823 (1980).

Lithiated *N*-allylcarambates add to nitroalkenes. In the presence of (−)-sparteine, this reaction is both diastereoselective (*anti*) and enantioselective.³³¹

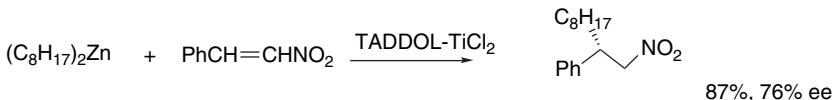


The enantioselectivity is due to the retention of the chiral sparteine in the lithiated reagent. The adducts have been used to synthesize a number of pyrrolidine and piperidine derivatives.

Several mixed organozinc reagents having a trimethylsilylmethyl group as the nonreacting substituent add to enones under the influence of TMS-Br.³³² The types of groups that can be added include alkyl, aryl, heteroaryl, and certain functionalized alkyl groups, including 5-pivaloyloxypropyl and 3-ethoxycarbonylpropyl.

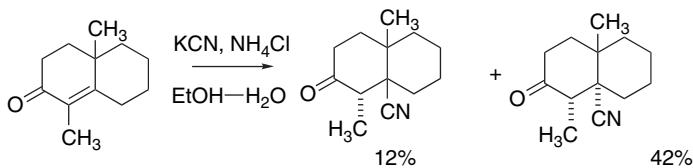


α,β -Unsaturated aldehydes and esters, as well as nitroalkenes, can also function as acceptors under these conditions. Dialkylzinc reagents add to β -nitrostyrene in the presence of TADDOL-TiCl₂.³³³



2.6.6. Conjugate Addition of Cyanide Ion

Cyanide ion acts as a carbon nucleophile in the conjugate addition reaction. The *pK* of HCN is 9.3, so addition in hydroxylic solvents is feasible. An alcoholic solution of potassium or sodium cyanide is suitable for simple compounds.



Ref. 334

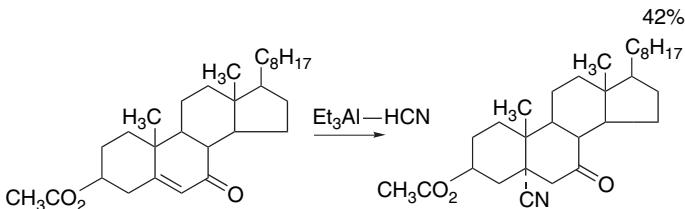
Cyanide addition has also been done under Lewis acid catalysis. Triethylaluminum-hydrogen cyanide and diethylaluminum cyanide are useful reagents for conjugate

³³¹ T. A. Johnson, D. O. Jang, B. W. Slafer, M. D. Curtis, and P. Beak, *J. Am. Chem. Soc.*, **124**, 11689 (2002).

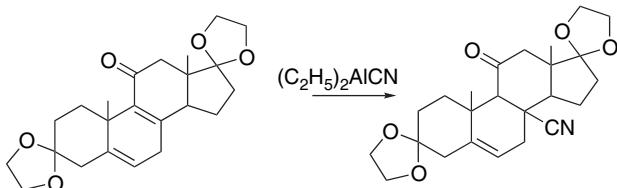
³³² P. Jones, C. K. Reddy, and P. Knochel, *Tetrahedron*, **54**, 1471 (1998).

³³³ H. Schaefer and D. Seebach, *Tetrahedron*, **51**, 2305 (1995).

³³⁴ O. R. Rodig and N. J. Johnston, *J. Org. Chem.*, **34**, 1942 (1969).

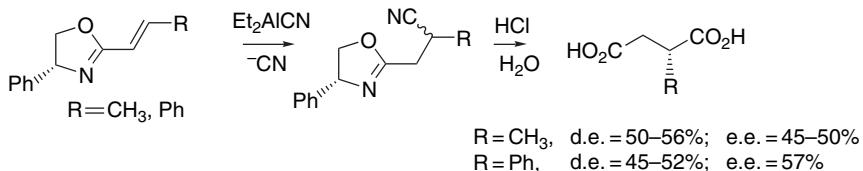


Ref. 335



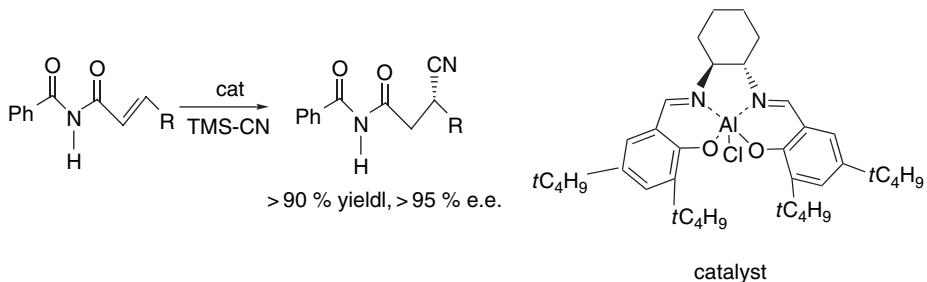
Ref. 336

Diethylaluminum cyanide mediates conjugate addition of cyanide to α,β -unsaturated oxazolines. With a chiral oxazoline, 30–50% diastereomeric excess can be achieved. Hydrolysis gives partially resolved α -substituted succinic acids. The rather low enantioselectivity presumably reflects the small size of the cyanide ion.



Ref. 337

A chiral aluminum-salen catalyst gives good enantioselectivity in the addition of cyanide (from TMS-CN) to unsaturated acyl imides.³³⁸



³³⁵ W. Nagata and M. Yoshioka, *Org. Synth.*, **52**, 100 (1972).

³³⁶ W. Nagata, M. Yoshioka, and S. Hirai, *J. Am. Chem. Soc.*, **94**, 4635 (1972).

³³⁷ M. Dahuuron and N. Langlois, *Synlett*, 51 (1996).

³³⁸ G. M. Sammis and E. N. Jacobsen, *J. Am. Chem. Soc.*, **125**, 4442 (2003).

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CHAPTER 2

Reactions of Carbon Nucleophiles with Carbonyl Compounds

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 A. S. Franklin and I. Paterson, *Contemp. Org. Synth.*, **1**, 317 (1994).
 C. H. Heathcock, in *Comprehensive Carbanion Chemistry*, E. Bunzel and T. Durst, ed., Elsevier, Amsterdam, 1984.
 C. H. Heathcock, in *Asymmetric Synthesis*, Vol. 3, J. D. Morrison, ed., Academic Press, New York, 1984.
 R. Mahrwald, ed. *Modern Aldol Reactions*, Wiley-VCH, 2004.
 S. Masamune, W. Choy, J. S. Petersen, and L. R. Sita, *Angew. Chem. Int. Ed. Engl.*, **24**, 1 (1985).
 T. Mukaiyama, *Org. React.*, **28**, 203 (1982).
 A. T. Nielsen and W. T. Houlihan, *Org. React.*, **16**, 1 (1968).

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- R. E. Gawley, *Synthesis*, 777 (1976).
 M. E. Jung, *Tetrahedron*, **32**, 3 (1976).

Mannich Reactions

- F. F. Blicke, *Org. React.*, **1**, 303 (1942).
 H. Bohme and M. Heake, in *Iminium Salts in Organic Chemistry*, H. Bohmne and H. G. Viehe, ed., Wiley-Interscience, New York, 1976, pp. 107–223.
 M. Tramontini and L. Angiolini, *Mannich Bases: Chemistry and Uses*, CRC Press, Boca Raton, FL, 1994.

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 A. W. Johnson, *Ylides and Imines of Phosphorus*, John Wiley, New York, 1993.
 A. Maercker, *Org. React.*, **14**, 270 (1965).
 W. S. Wadsworth, Jr., *Org. React.*, **25**, 73 (1977).

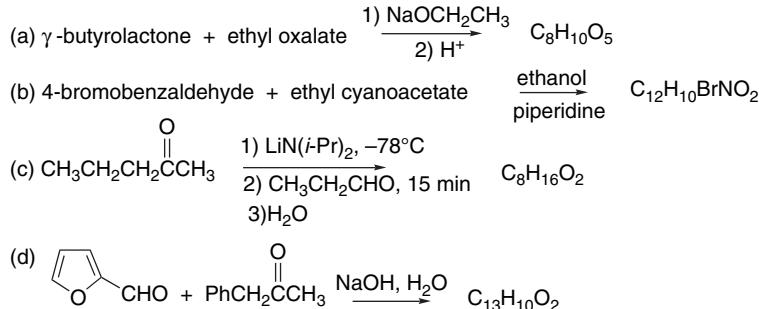
Conjugate Addition Reactions

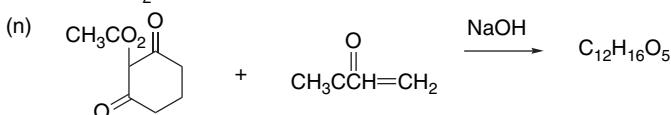
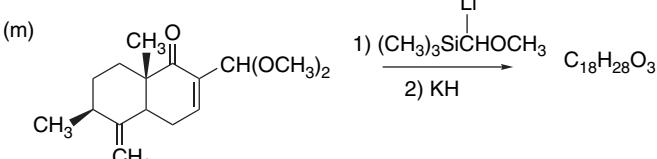
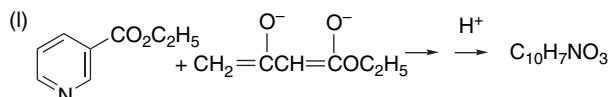
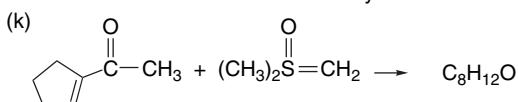
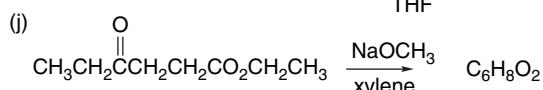
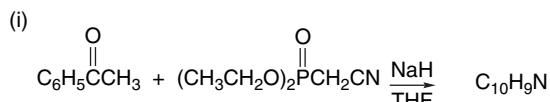
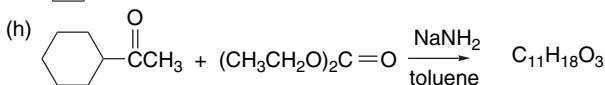
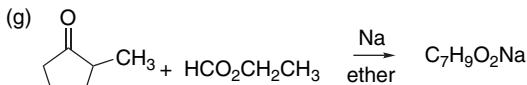
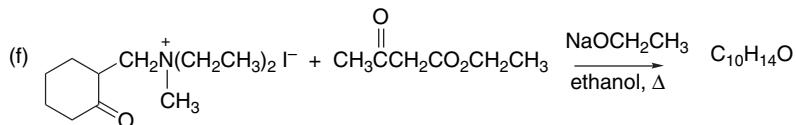
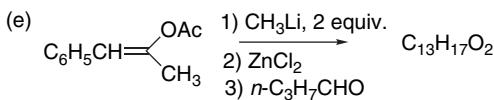
- P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Permagon Press, New York, 1992.

Problems

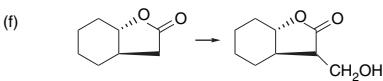
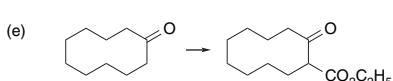
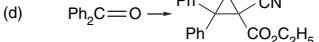
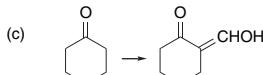
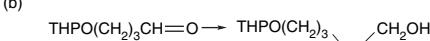
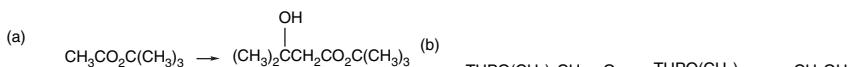
(References for these problems will be found on page 1272.)

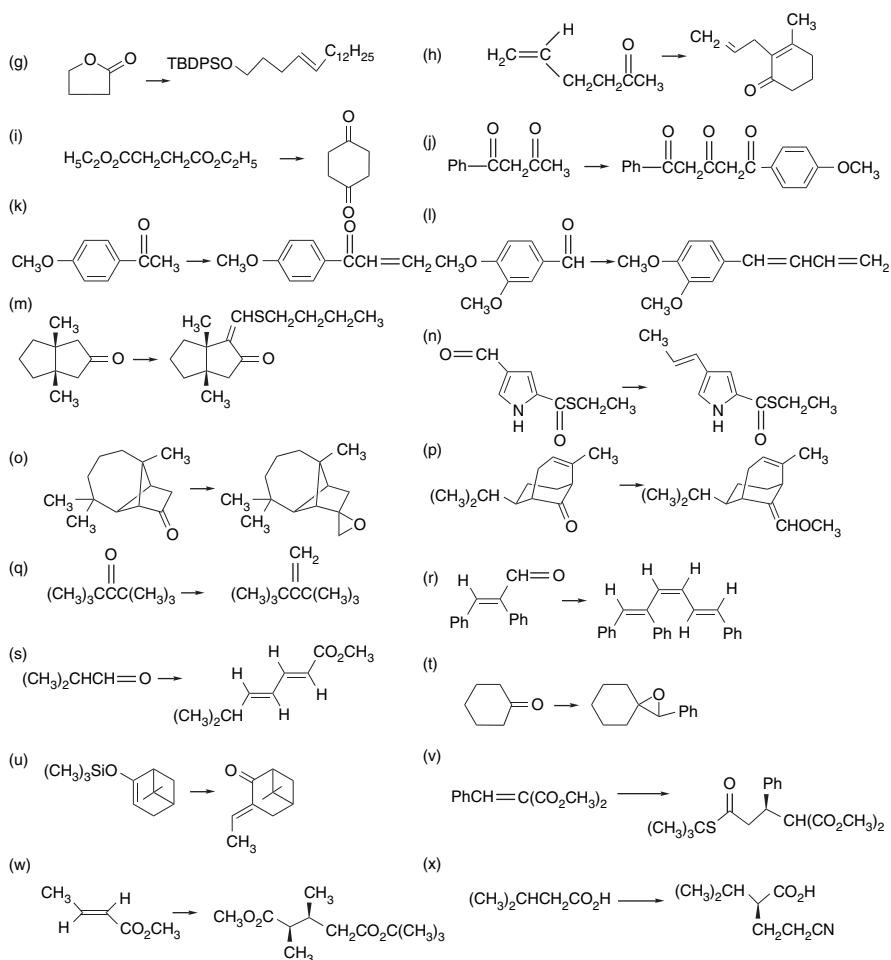
2.1 Predict the product formed in each of the following reactions:



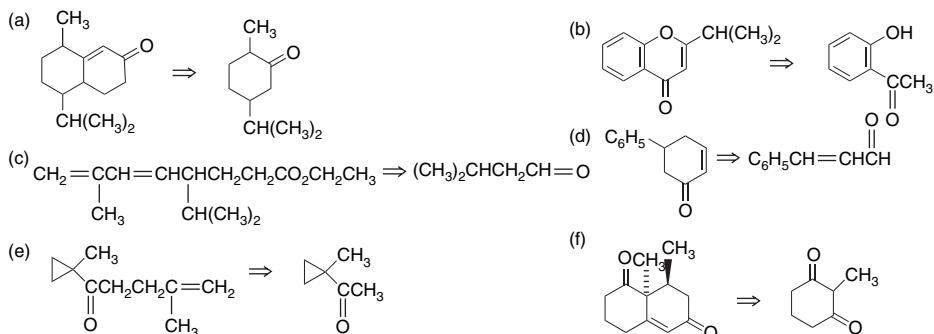


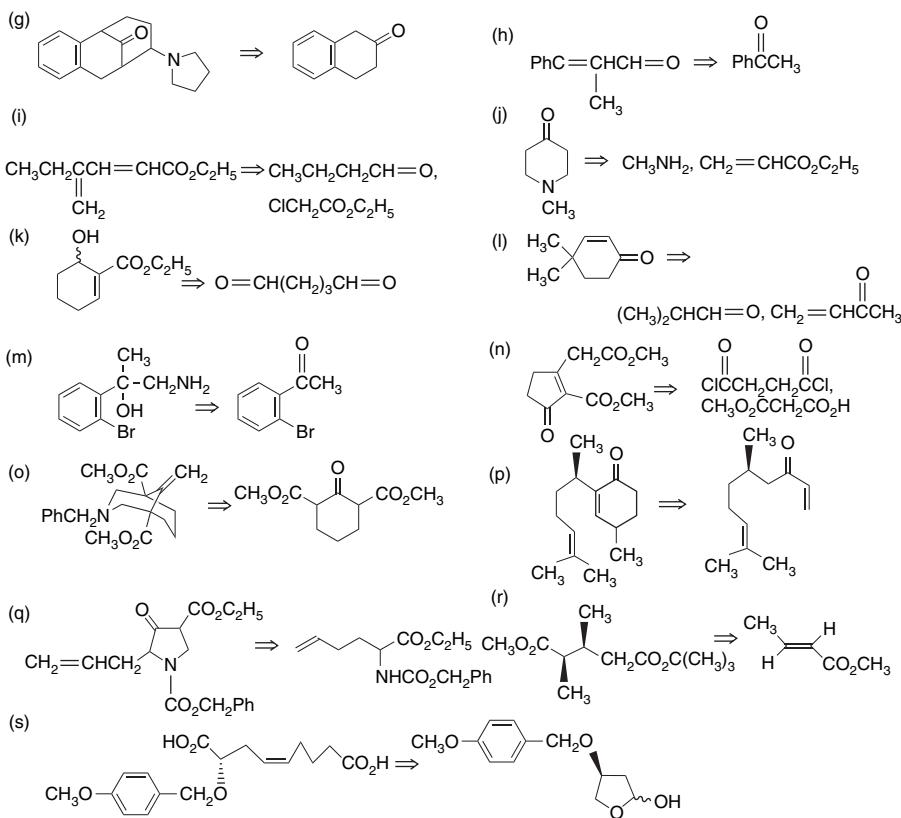
2.2. Indicate reaction conditions or a series of reactions that could effect each of the following synthetic conversions:



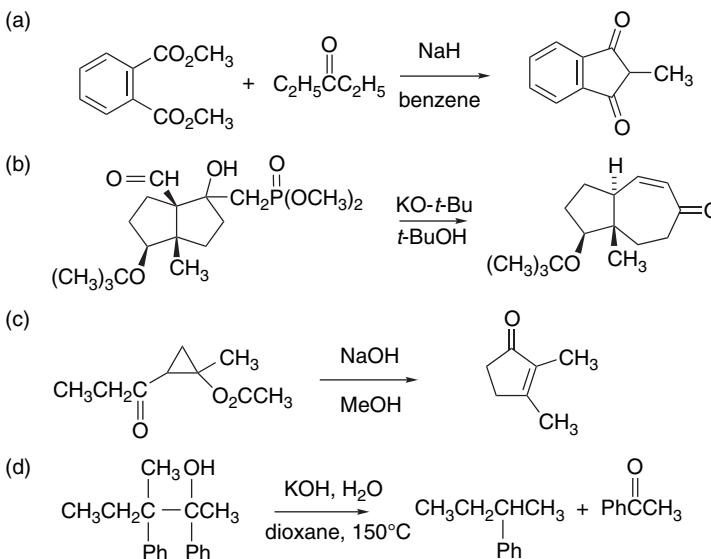


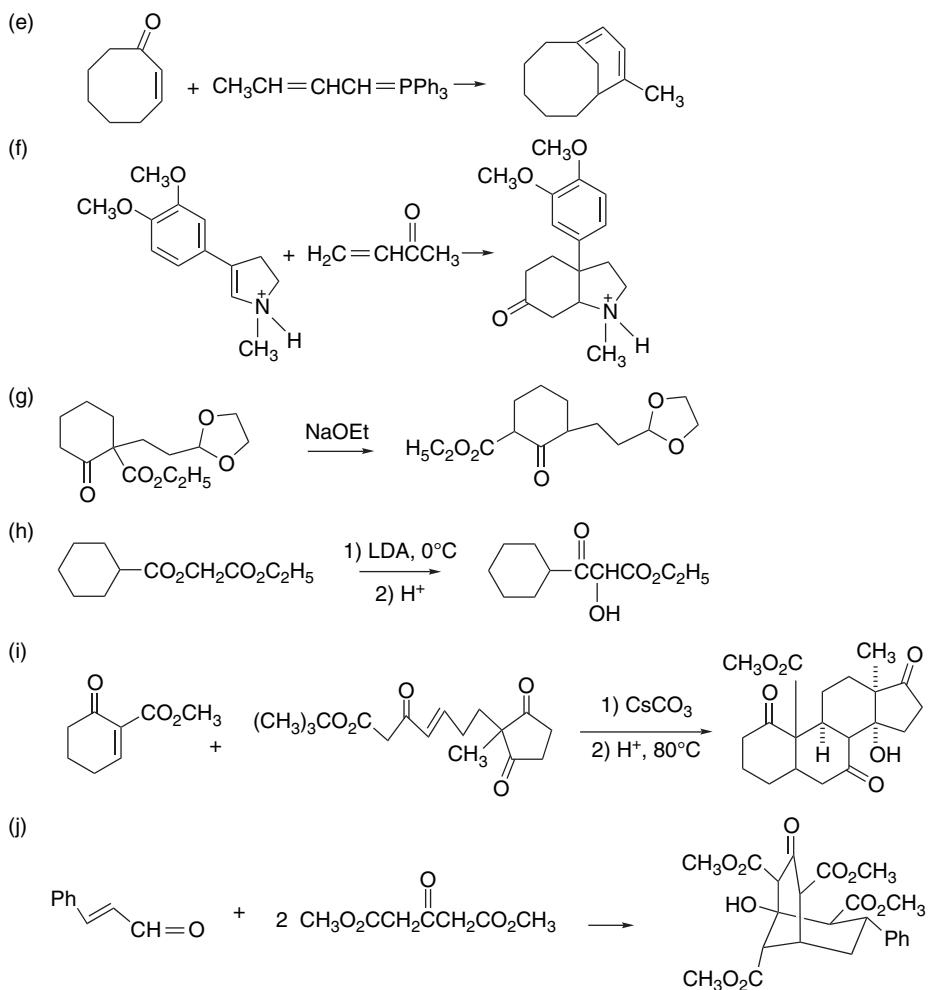
2.3. Step-by-step retrosynthetic analysis of each of the target molecules reveals that they can be efficiently prepared in a few steps from the starting material shown on the right. Do a retrosynthetic analysis and suggest reagents and reaction conditions for carrying out the desired synthesis.



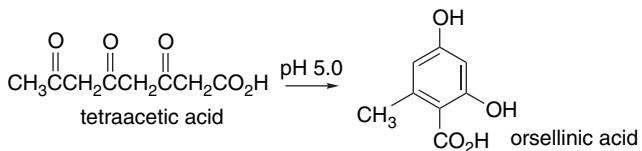


2.4. Offer a mechanism for each of the following reactions:





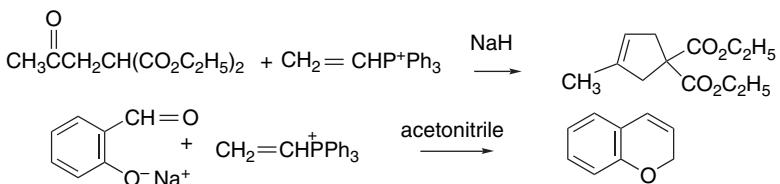
2.5. Tetraacetic acid (or a biological equivalent) is suggested as an intermediate in the biosynthesis of phenolic natural products. In the laboratory, it can be readily converted to orsellinic acid. Suggest a mechanism for this reaction under the conditions specified.



2.6. a. A stereospecific method for deoxygenating epoxides to alkenes involves reaction of the epoxide with the diphenylphosphide ion, followed by methyl iodide. The method results in overall inversion of alkene stereochemistry. Thus, *cis*-cyclooctene epoxide gives *trans*-cyclooctene. Propose a mechanism for this reaction and discuss its relationship to the Wittig reaction.

- b. Reaction of the epoxide of *E*-4-octene (*trans*-2,3-dipropylloxirane) with potassium trimethylsilanide gives *Z*-4-octene as the only alkene product in 93% yield. Suggest a reasonable mechanism for this reaction.

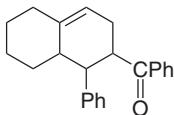
- 2.7. a. A fairly general method for ring closure has been developed that involves vinyltriphenylphosphonium halides as reactants. Indicate the mechanism of this reaction, as applied to the two examples shown below. Suggest two other types of rings that could be synthesized using vinyltriphenylphosphonium salts.



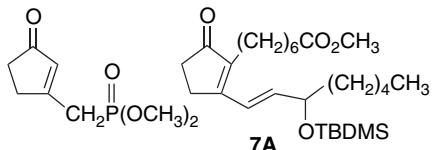
- b. Allylphosphonium salts were used as a synthon in the synthesis of cyclohexadienes. Suggest an appropriate co-reactant and other reagents that would be expected to lead to cyclohexadienes.



- c. The product shown below is formed by the reaction of vinyltriphenylphosphonium bromide, the lithium enolate of cyclohexanone, and 1,3-diphenyl-2-propen-1-one. Formulate a mechanism.

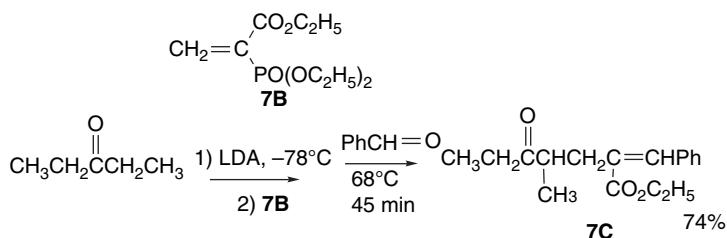


- d. The dimethoxy phosphonylmethylcyclopentenone shown below has been used as a starting material for the synthesis of prostaglandin analogs such as **7A**. The reaction involves formation of the anion, reaction with an alkyl halide, and a Wadsworth-Emmons reaction. What reactivity of the anion makes this approach feasible?

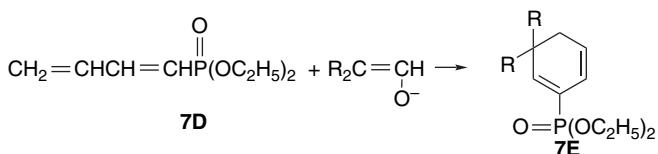


- e. The reagent **7B** has found use in the expeditious construction of more complex molecules from simple starting materials. For example, the enolate of 3-pentanone when treated first with **7B** and then with benzaldehyde gives **7C**

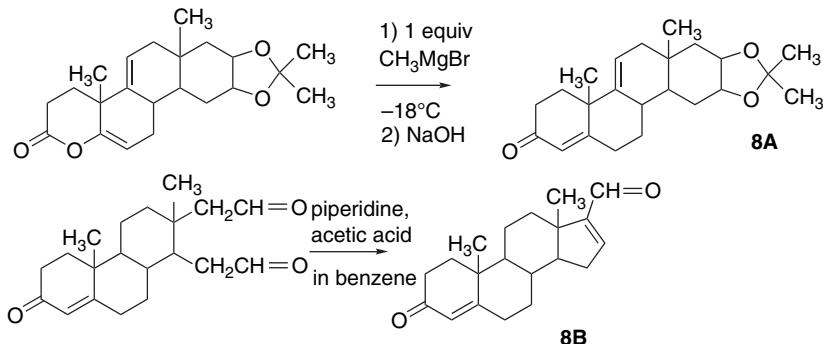
as a 2:1 mixture of stereoisomers. Explain the mechanism by which this reaction occurs.



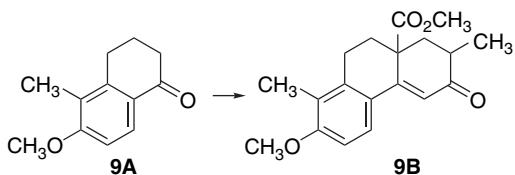
- f. The reagent **7D** converts enolates of aldehydes into cyclohexadienyl phosphonates **7E**. Write a mechanism for this reaction. What alternative products might have been observed?



- 2.8. Compounds **8A** and **8B** were key intermediates in an early total synthesis of cholesterol. Rationalize their formation by the routes shown.

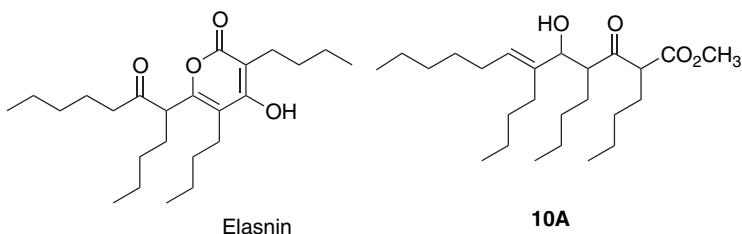


- 2.9. The first few steps in a synthesis of the alkaloid conessine produce **9B**, starting from **9A**. Suggest a sequence of reactions for effecting this conversion.

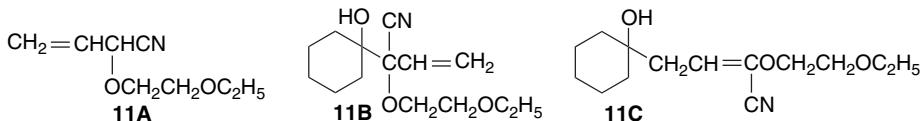


- 2.10. A substance known as elastase is involved in various inflammatory diseases such as arthritis, pulmonary emphysema, and pancreatitis. Elastase activity can be inhibited by a compound known as elasmin, obtained from a microorganism.

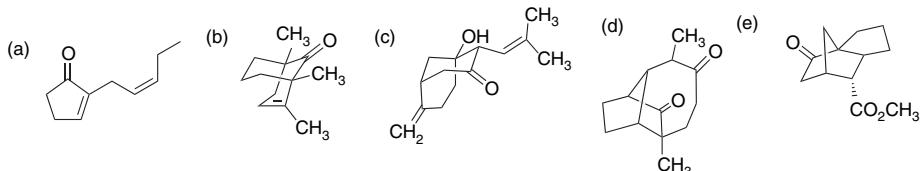
A synthesis of elasnin has been reported that utilizes compound **10A** as a key intermediate. Suggest a synthesis of **10A** from methyl hexanoate and hexanal.



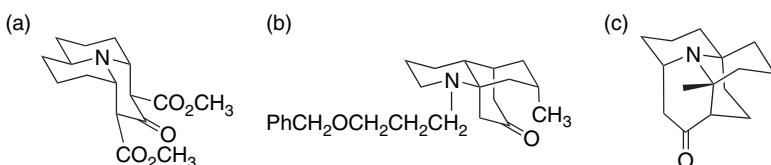
- 2.11. Treatment of compound **11A** with LDA followed by cyclohexanone can give either **11B** or **11C**. Compound **11B** is formed when the aldehyde is added at -78°C , whereas **11C** is formed if the aldehyde is added at 0°C . Treatment of **11B** with LDA at 0°C gives **11C**. Explain these results.



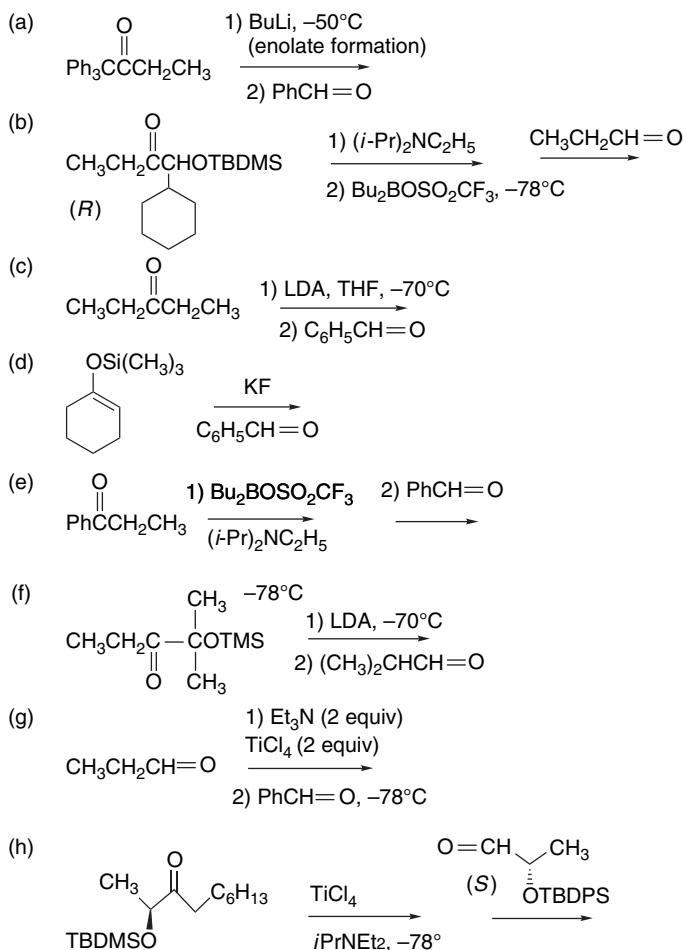
- 2.12. Dissect the following molecules into potential precursors by locating all bonds that could be made by intramolecular aldol or conjugate addition reactions. Suggest possible starting materials and conditions for performing the desired reactions.



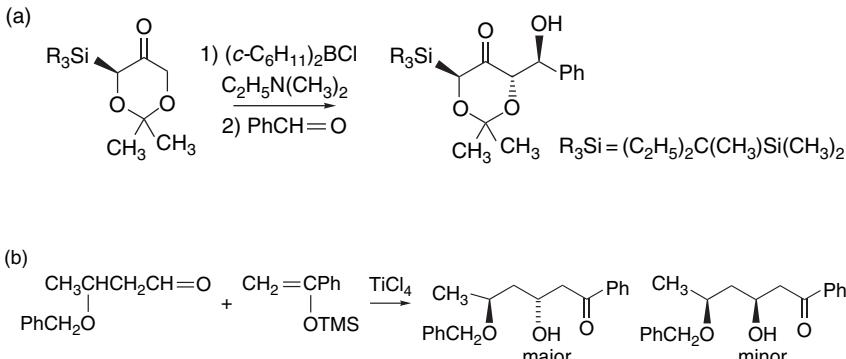
- 2.13. Mannich condensations permit one-step reactions to form the following substances from substantially less complex starting materials. Identify a potential starting material that would give rise to the product shown in a single step under Mannich reaction conditions.



- 2.14. Indicate whether or not the aldol reactions shown below would be expected to exhibit high stereoselectivity. Show the stereochemistry of the expected product(s).

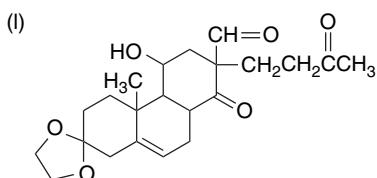
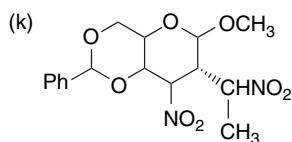
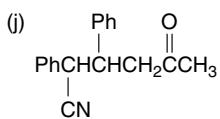
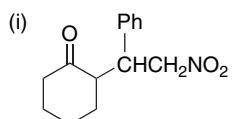
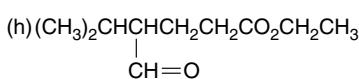
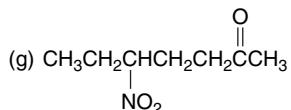
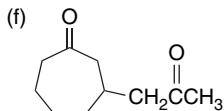
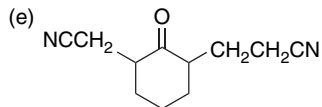


2.15. Suggest transition structures that would account for the observed stereoselectivity of the following reactions.

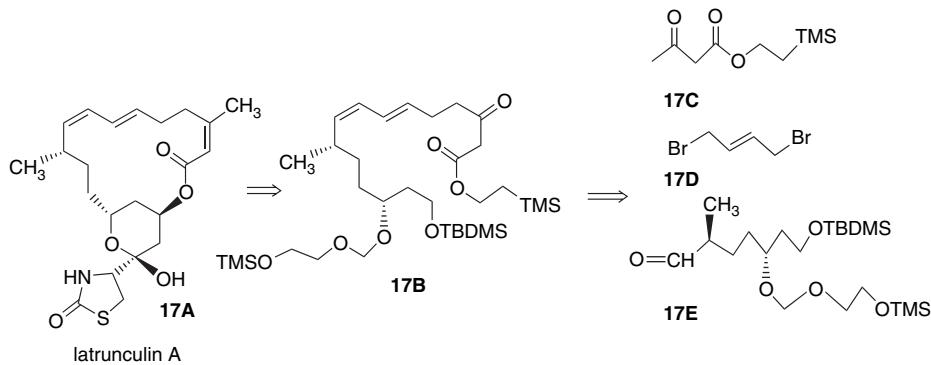


2.16. Suggest starting materials and reaction conditions suitable for obtaining each of the following compounds by a procedure involving conjugate addition.

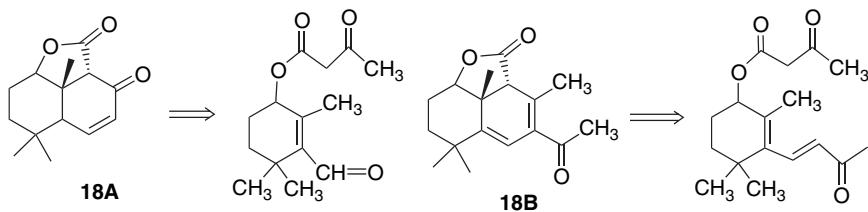
- (a) 4,4-dimethyl-5-nitropentan-2-one
 (b) diethyl 2,3-diphenylglutarate
 (c) ethyl 2-benzoyl-4-(2-pyridyl)butanoate
 (d) 2-phenyl-3-oxocyclohexaneacetic acid



- 2.17. In the synthesis of a macrolide **17A**, known as latrunculin A, the intermediate **17B** was assembled from components **17C**, **17D**, and **17E** in a “one-pot” tandem process. By a retrosynthetic analysis, show how the synthesis could occur and identify a sequence of reactions and corresponding reagents.

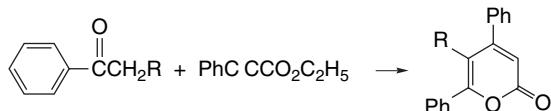


- 2.18. The tricyclic substance **18A** and **18B** are both potential synthetic intermediates for synthesis of the biologically active diterpene forskolin. These intermediates can be prepared from the monocyclic precursors shown. Indicate the nature of the reactions involved in these transformations.

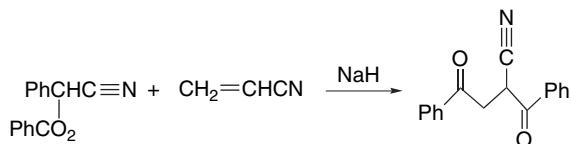


2.19. Account for the course of the following reactions:

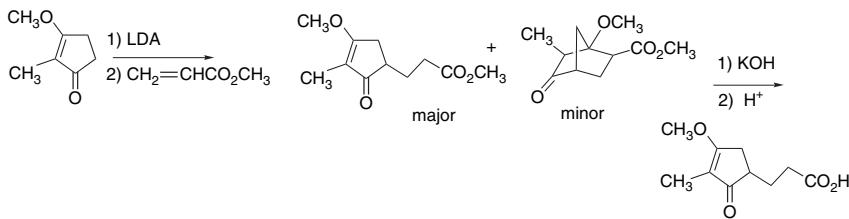
- a. Substituted acetophenones react with ethyl phenylpropionate under basic conditions to give pyrones. Formulate a mechanism for this reaction.



- b. The reaction of simple ketones such as 2-butanone or 1-phenyl-2-propanone with α,β -unsaturated ketones gives cyclohexanone on heating with methanol containing potassium methoxide. Indicate how the cyclohexanones could be formed. Can more than one isomeric cyclohexanone be formed? Can you suggest a means for distinguishing between possible cyclohexanones?
- c. α -Benzoyloxyphenylacetonitrile reacts with acrylonitrile in the presence of NaH to give 2-cyano-1,4-diphenylbutane-2,4-dione.

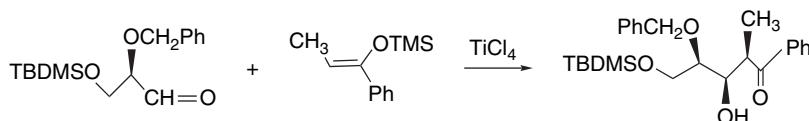


- d. Reaction of the lithium anion of 3-methoxy-2-methylcyclopentanone with methyl acrylate gives the two products shown as an 82:18 mixture. Alkaline hydrolysis of the mixture gives a single pure product. How is the minor product formed and how is it converted to the hydrolysis product?

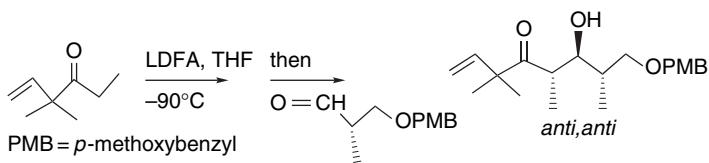


2.20. Explain the stereochemical outcome of the following reactions.

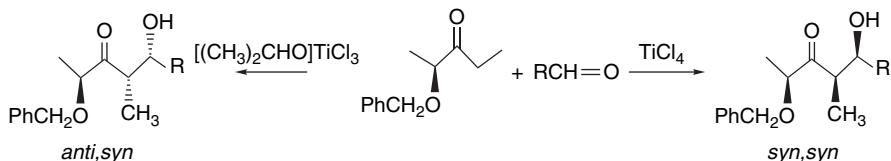
a.



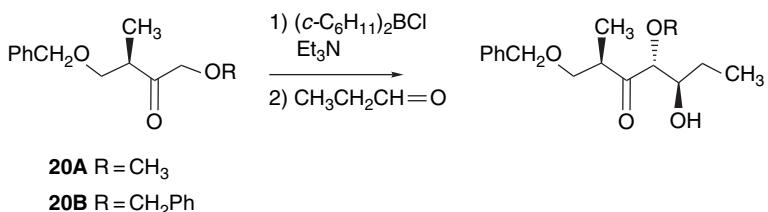
b.



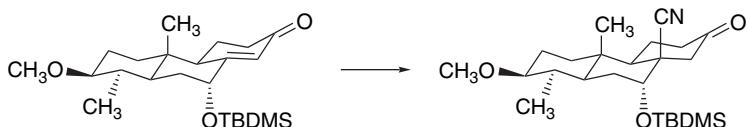
- c. The facial selectivity of 2-benzyloxy-3-pentanone toward typical alkyl, alkenyl, and aryl aldehydes is reversed by a change of catalyst from TiCl_4 to $[(\text{CH}_3)_2\text{CHO}]\text{TiCl}_3$.



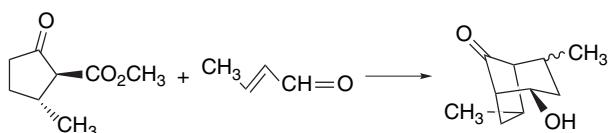
- d. The boron enolates generated from ketones **20A** and **20B** give more than 95% selectivity for the *anti,anti* diastereomer.



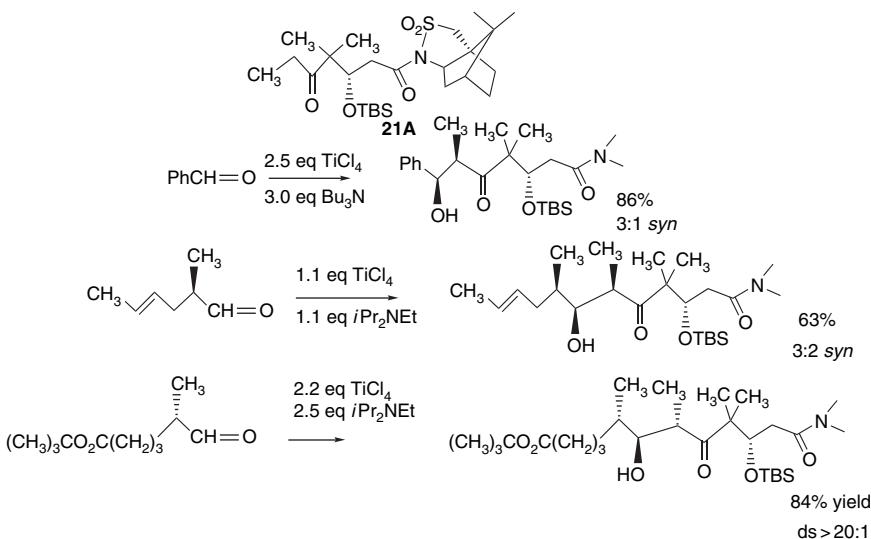
e.



f.



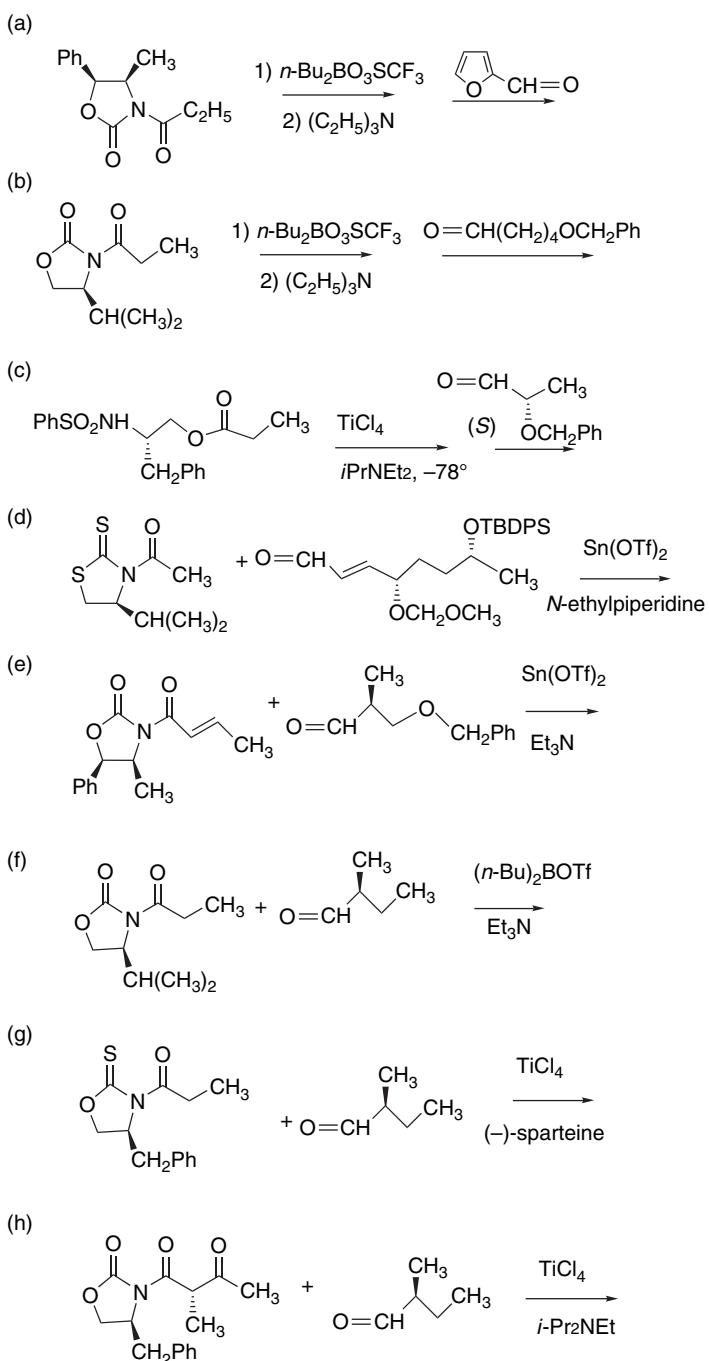
- 2.21. The camphor sultam derivative **21A** was used in a synthesis of epothilone. The stereoselectivity of the aldol addition was examined with several different aldehydes. Discuss the factors that lead to the variable stereoselectivity in the three cases shown.



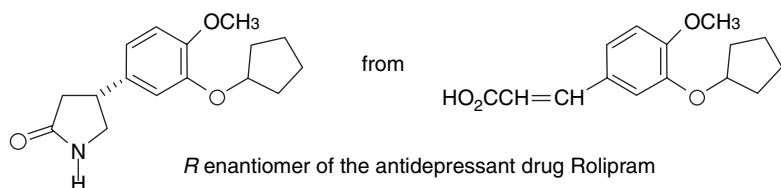
2.22. The facial selectivity of the aldehydes **22A** and **22B** is dependent on both the configuration at the β -center and the nature of the enolate as indicated by the data below. Consider possible transition structures for these reactions and offer a rationale for the observed facial selectivity.

22A	enolate	R ⁴	3,4- <i>syn:anti</i> ratio	22B	enolate	R ⁴	3,4- <i>syn:anti</i> ratio
	Li	MOM	97:3		Li	TES	66:34
	TiCl ₄	MOM	84:16		TiCl ₄	TES	60:40
	Bu ₂ B	MOM	63:38		Bu ₂ B	TES	<5:95
	(C ₅ H ₁₁) ₂ B	MOM	52:48		(C ₅ H ₁₁) ₂ B	TES	14:86
	Li	MOM	15:85		Li	TES	7:93
	TiCl ₄	MOM	62:38		TiCl ₄	TES	27:73
	Bu ₂ B	MOM	81:39		Bu ₂ B	TES	45:55
	(C ₅ H ₁₁) ₂ B	MOM	50:50		(C ₅ H ₁₁) ₂ B	TES	52:48

2.23. Predict the stereochemical outcome of the following aldol addition reactions involving chiral auxiliaries.



2.24. Suggest an enantioselective synthetic route to the antidepressant drug rolipram from the suggested reactant.



- 2.25. Figure 2.P25 shows the calculated [B3LYP/6-31G(*d,p*)] reaction energy profile for the aldol addition of benzaldehyde and cyclohexanone catalyzed by alanine. The best TSs leading to (*S,R*); (*R,S*); (*S,S*); and (*R,R*) products are given. What factors favor the observed (*R,S*) product?

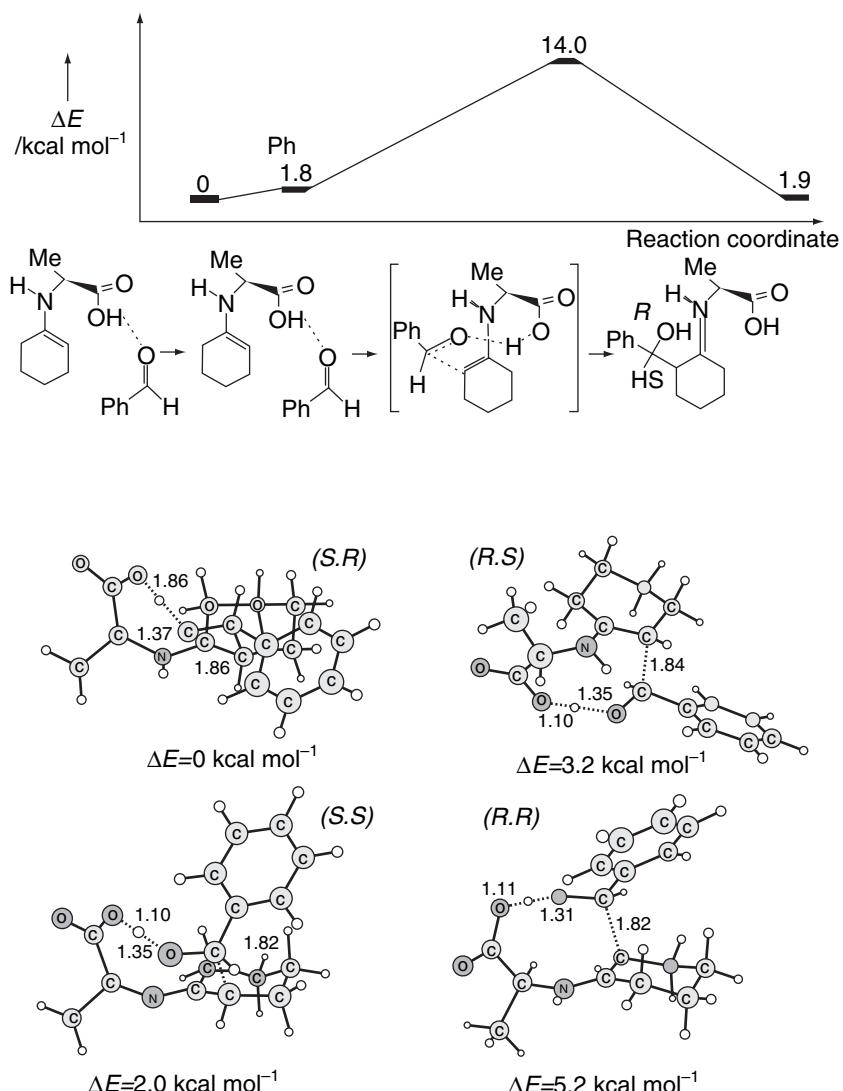


Fig. 2.P25. Top: Reaction energy profile for alanine-catalyzed aldol reaction of benzaldehyde and cyclohexanone. Bottom: Diastereomeric transition structures. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **44**, 7028 (2005), by permission of Wiley-VCH

Functional Group Interconversion by Substitution, Including Protection and Deprotection

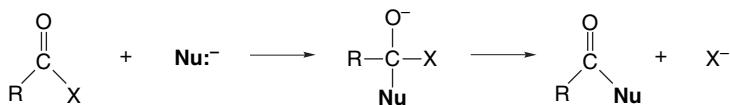
Introduction

Chapters 1 and 2 dealt with formation of new carbon-carbon bonds by reactions in which one carbon acts as the nucleophile and another as the electrophile. In this chapter we turn our attention to noncarbon nucleophiles. Nucleophilic substitution is used in a variety of interconversions of functional groups. We discuss substitution at both sp^3 carbon and carbonyl groups. Substitution at saturated carbon usually involves the S_N2 mechanism, whereas substitution at carbonyl groups usually occurs by addition-elimination.

Substitution at saturated carbons



Substitution at carbonyl groups



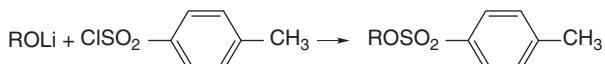
The mechanistic aspects of nucleophilic substitutions at saturated carbon and carbonyl centers were considered in Part A, Chapters 4 and 7, respectively. In this chapter we discuss some of the important synthetic transformations that involve these types of

reactions. Section 3.1 considers conversion of alcohols to reactive alkylating agents and Section 3.2 discusses the use of S_N2 reactions for various functional group transformations. Substitution reactions can also be used to *break* bonds for synthetic purposes, and Section 3.3 deals with cleavage of C–O bonds in ethers and esters by S_N2 and S_N1 reactions. The carbonyl substitution reactions that interconvert the acyl halides, acid anhydrides, esters, and carboxamides are discussed in Section 3.4. Often, manipulation of protecting groups also involves nucleophilic substitution and carbonyl exchange reactions. We discuss protection and deprotection of the most common functional groups in Section 3.5.

3.1. Conversion of Alcohols to Alkylating Agents

3.1.1. Sulfonate Esters

Alcohols are a very important compounds for synthesis. However, because the hydroxide ion is a very poor leaving group, alcohols are not reactive as alkylating agents. They can be activated to substitution by O-protonation, but the acidity that is required is incompatible with most nucleophiles except those, such as the halides, that are anions of strong acids. The preparation of sulfonate esters from alcohols is an effective way of installing a reactive leaving group on an alkyl chain. The reaction is very general and complications arise only if the resulting sulfonate ester is sufficiently reactive to require special precautions. *p*-Toluenesulfonate (*tosylate*) and methanesulfonate (*mesylate*) esters are used most frequently for preparative work, but the very reactive trifluoromethanesulfonates (*triflates*) are useful when an especially good leaving group is required. The usual method for introducing tosyl or mesyl groups is to allow the alcohol to react with the sulfonyl chloride in pyridine at 0°–25° C.¹ An alternative method is to convert the alcohol to a lithium salt, which is then allowed to react with the sulfonyl chloride.²



Trifluoromethanesulfonates of alkyl and allylic alcohols can be prepared by reaction with trifluoromethanesulfonic anhydride in halogenated solvents in the presence of pyridine.³ Since the preparation of sulfonate esters does not disturb the C–O bond, problems of rearrangement or racemization do not arise in the ester formation step. However, sensitive sulfonate esters, such as allylic systems, may be subject to reversible ionization reactions, so appropriate precautions must be taken to ensure structural and stereochemical integrity. Tertiary alkyl sulfonates are neither as easily prepared nor as stable as those from primary and secondary alcohols. Under the standard preparative conditions, tertiary alcohols are likely to be converted to the corresponding alkene.

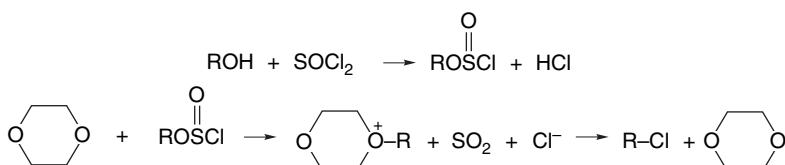
¹. R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944); G. W. Kabalka, M. Varma, R. S. Varma, P. C. Srivastava, and F. F. Knapp, Jr., *J. Org. Chem.*, **51**, 2386 (1986).

². H. C. Brown, R. Bernheimer, C. J. Kim, and S. E. Scheppelle, *J. Am. Chem. Soc.*, **89**, 370 (1967).

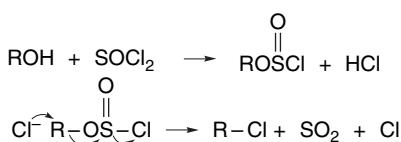
³. C. D. Beard, K. Baum, and V. Grakauskas, *J. Org. Chem.*, **38**, 3673 (1973).

The prominent role of alkyl halides in the formation of carbon-carbon bonds by enolate alkylation was evident in Chapter 1. The most common precursors for alkyl halides are the corresponding alcohols and a variety of procedures have been developed for this transformation. The choice of an appropriate reagent is usually dictated by the sensitivity of the alcohol and any other functional groups present in the molecule. In some cases, the hydrogen halides can be used. Unsubstituted primary alcohols can be converted to bromides with hot concentrated hydrobromic acid.⁴ Alkyl chlorides can be prepared by reaction of primary alcohols with hydrochloric acid-zinc chloride.⁵ Owing to the harsh conditions, these procedures are only applicable to very acid-stable molecules. These reactions proceed by the S_N2 mechanism and elimination, and rearrangements are not a problem for primary alcohols. Reactions of hydrogen halides with tertiary alcohols proceed by the S_N1 mechanism, so these reactions are preparatively useful only when the carbocation intermediate is unlikely to give rise to rearranged product.⁶ In general, these methods are suitable only for simple, unfunctionalized alcohols.

Another general method for converting alcohols to halides involves reactions with halides of certain nonmetallic elements. Thionyl chloride, phosphorus trichloride, and phosphorus tribromide are the most common examples of this group of reagents. These reagents are suitable for alcohols that are neither acid sensitive nor prone to structural rearrangement. The reaction of alcohols with thionyl chloride initially results in the formation of a chlorosulfite ester. There are two mechanisms by which the chlorosulfite can be converted to a chloride. In aprotic nucleophilic solvents, such as dioxane, solvent participation can lead to overall retention of configuration.⁷



In the absence of solvent participation, chloride attack on the chlorosulfite ester leads to product with inversion of configuration.



Primary and secondary alcohols are rapidly converted to chlorides by a 1:1 mixture of SOCl_2 and benzotriazole in an inert solvent such as CH_2Cl_2 .⁸

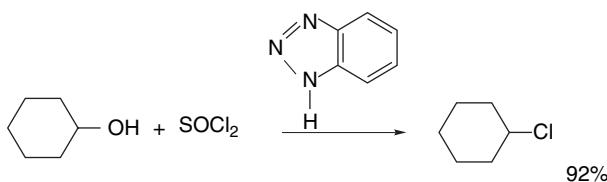
⁴ E. E. Reid, J. R. Ruhoff, and R. E. Burnett, *Org. Synth.*, **II**, 246 (1943).

⁵ J. E. Copenhaver and A. M. Wharley, *Org. Synth.*, **I**, 142 (1941).

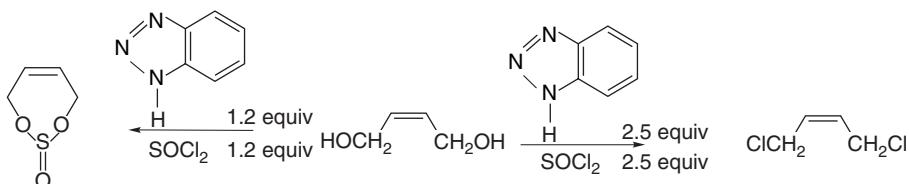
⁶ J. F. Norris and A. W. Olmsted, *Org. Synth.*, **I**, 144 (1941); H. C. Brown and M. H. Rei, *J. Org. Chem.*, **31**, 1090 (1966).

⁷ E. S. Lewis and C. E. Boozer, *J. Am. Chem. Soc.*, **74**, 308 (1952).

⁸ S. S. Chaudhari and K. G. Akamanchi, *Synlett*, 1763 (1999).

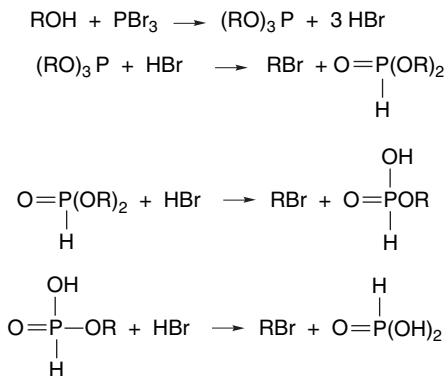


This reagent combination also converts carboxylic acids to acyl chlorides (see Section 3.4.1). The mechanistic basis for the special effectiveness of benzotriazole has not yet been determined, but it seems likely that nucleophilic catalysis is involved. Sulfinyl ester intermediates may be involved, because *Z*-2-butene-1,4-diol gives a cyclic sulfite ester with one equivalent of reagent but the dichloride with two equivalents.



Reaction with the hindered secondary alcohol menthol stops at the dialkyl sulfite ester. The examples reported do not establish the stereochemistry of the reaction.

The mechanism for the reactions of alcohols with phosphorus halides can be illustrated using phosphorus tribromide. Initial reaction between the alcohol and phosphorus tribromide leads to a trialkyl phosphite ester by successive displacements of bromide. The reaction stops at this stage if it is run in the presence of an amine, which neutralizes the hydrogen bromide that is formed.⁹ If the hydrogen bromide is not neutralized, the phosphite ester is protonated and each alkyl group is converted to the halide by nucleophilic substitution by bromide ion. The driving force for cleavage of the C–O bond is the formation of a strong phosphoryl double bond.



As C–Br bond formation occurs by back-side attack, inversion of the configuration at carbon is anticipated. However, both racemization and rearrangement are observed as competing processes.¹⁰ For example, conversion of 2-butanol to 2-butyl bromide with PBr_3 is accompanied by 10–13% racemization and a small

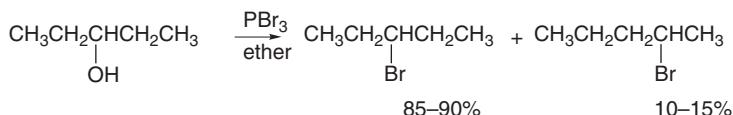
⁹. A. H. Ford-Moore and B. J. Perry, *Org. Synth.*, **IV**, 955 (1963).

¹⁰. H. R. Hudson, *Synthesis*, 112 (1969).

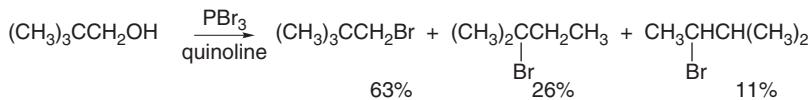
SECTION 3.1

*Conversion of Alcohols
to Alkylating Agents*

amount of *t*-butyl bromide is also formed.¹¹ The extent of rearrangement increases with increasing chain length and branching.

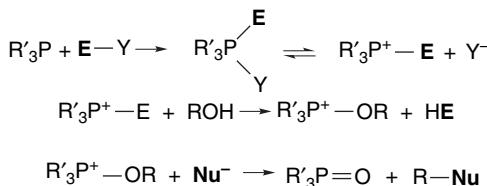


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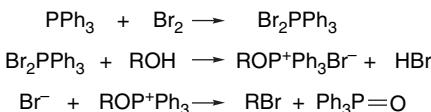


Ref. 13

Owing to the acidic conditions, these methods are limited to acid-stable molecules. Milder reagents are necessary for many functionally substituted alcohols. A very general and important method for activating alcohols toward nucleophiles is by converting them to *alkoxyphosphonium ions*.¹⁴ The trivalent phosphorus reagents are activated by reaction with a halogen or related electrophile, and the alkoxyphosphonium ions are very reactive toward nucleophilic attack, with the driving force for substitution being formation of the strong phosphoryl bond.



A variety of reagents can function as the electrophile E^+ in the general mechanism. The most useful synthetic procedures for preparation of halides are based on the halogens, positive halogens sources, and diethyl azodicarboxylate. A 1:1 adduct formed from triphenylphosphine and bromine converts alcohols to bromides.¹⁵ The alcohol displaces bromide ion from the pentavalent adduct, giving an alkoxyphosphonium intermediate. The phosphonium ion intermediate then undergoes nucleophilic attack by bromide ion, forming triphenylphosphine oxide.



The alkoxy phosphonium intermediate is formed by a reaction that does not break the C—O bond and the second step proceeds by back-side displacement on carbon, so the stereochemistry of the overall process is inversion.

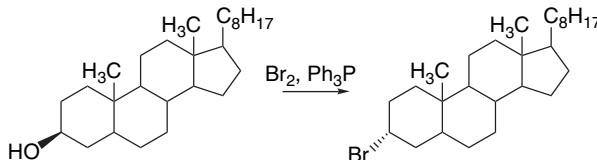
¹¹ D. G. Goodwin and H. R. Hudson, *J. Chem. Soc. B*, 1333 (1968); E. J. Coulson, W. Gerrard, and H. R. Hudson, *J. Chem. Soc.*, 2364 (1965).

¹² J. Cason and J. S. Correia, *J. Org. Chem.*, **26**, 3645 (1961).

¹³ H. R. Hudson, *J. Chem. Soc.*, 664 (1968).

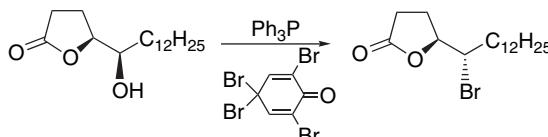
¹⁴ B. P. Castro, *Org. React.*, **29**, 1 (1983).

¹⁵ G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Am. Chem. Soc.*, **86**, 964 (1964).



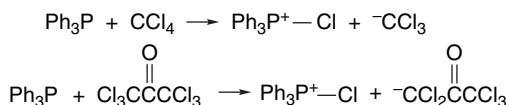
Ref. 16

2,4,4,6-Tetrabromocyclohexa-2,5-dienone is also a useful bromine source.

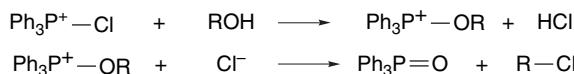


Ref. 17

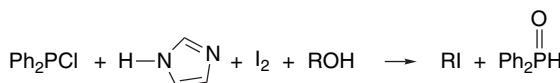
Triphenylphosphine dichloride exhibits similar reactivity and can be used to prepare chlorides.¹⁸ The most convenient methods for converting alcohols to chlorides are based on *in situ* generation of chlorophosphonium ions¹⁹ by reaction of triphenylphosphine with various chlorine compounds such as carbon tetrachloride²⁰ or hexachloroacetone.²¹ These reactions involve formation of chlorophosphonium ions.



The chlorophosphonium ion then reacts with the alcohol to give an alkoxyphosphonium ion that is converted to the chloride.

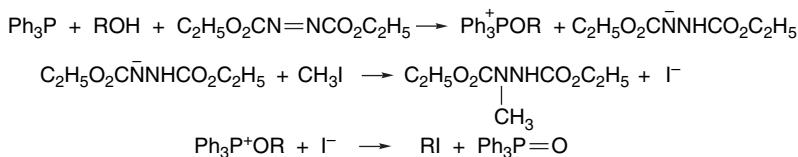


Several modifications of procedures based on halophosphonium ion have been developed. Triphenylphosphine and imidazole in combination with iodine or bromine gives good conversion of alcohols to iodides or bromides.²² An even more reactive system consists of chlorodiphenylphosphine, imidazole, and the halogen,²³ and has the further advantage that the resulting phosphorus by-product diphenylphosphinic acid, can be extracted with base during product workup.



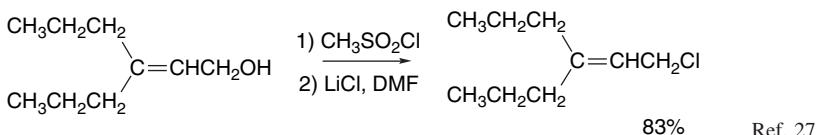
A very mild procedure for converting alcohols to iodides uses triphenylphosphine, diethyl azodicarboxylate (DEAD), and methyl iodide.²⁴ This reaction occurs

- ^{16.} D. Levy and R. Stevenson, *J. Org. Chem.*, **30**, 2635 (1965).
- ^{17.} A. Tanaka and T. Oritani, *Tetrahedron Lett.*, **38**, 1955 (1997).
- ^{18.} L. Horner, H. Oediger, and H. Hoffmann, *Justus Liebigs Ann. Chem.*, **626**, 26 (1959).
- ^{19.} R. Appel, *Angew. Chem. Int. Ed. Engl.*, **14**, 801 (1975).
- ^{20.} J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966).
- ^{21.} R. M. Magid, O. S. Fruchey, W. L. Johnson, and T. G. Allen, *J. Org. Chem.*, **44**, 359 (1979).
- ^{22.} P. J. Garegg, R. Johansson, C. Ortega, and B. Samuelsson, *J. Chem. Soc., Perkin Trans.*, **1**, 681 (1982).
- ^{23.} B. Classon, Z. Liu, and B. Samuelsson, *J. Org. Chem.*, **53**, 6126 (1988).
- ^{24.} O. Mitsunobu, *Synthesis*, 1 (1981).

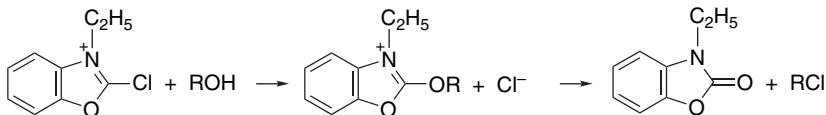


The role of the DEAD is to activate the triphenylphosphine toward nucleophilic attack by the alcohol. In the course of the reaction the N=N double bond is reduced. As is discussed later, this method is applicable for activation of alcohols to substitution by other nucleophiles in addition to halide ions. The activation of alcohols to nucleophilic attack by the triphenylphosphine-DEAD combination is called the *Mitsunobu reaction*.²⁶

A very mild method that is useful for compounds that are prone to allylic rearrangement involves prior conversion of the alcohol to a sulfonate, followed by nucleophilic displacement with halide ion.



Another very mild procedure involves reaction of the alcohol with the heterocyclic 2-chloro-3-ethylbenzoxazolium cation.²⁸ The alcohol adds to the electrophilic heterocyclic ring, displacing chloride. The alkoxy group is thereby activated toward a nucleophilic substitution that forms a stable product, 3-ethylbenzoxazolinone.



The reaction can be used for making either chlorides or bromides by using the appropriate tetraalkylammonium salt as a halide source.

Scheme 3.1 gives some examples of the various alcohol to halide conversions that have been discussed. Entries 1 and 2 are examples of synthesis of primary bromides using PBr_3 . Entry 3 is an example of synthesis of a chloride using $\text{Ph}_3\text{P}-\text{Cl}_2$. The reactant, neopentyl alcohol, is often resistant to nucleophilic substitution and prone to rearrangement, but reacts well under these conditions. Entries 4 and 5 illustrate the use of halogenated solvents as chlorine sources in Ph_3P -mediated reactions. The reactions in Entries 6 and 7 involve synthesis of bromides by nucleophilic substitution on tosylates. The reactant in Entry 7 is prone to rearrangement via ring expansion,

²⁵ H. Loibner and E. Zbiral, *Helv. Chim. Acta*, **59**, 2100 (1976).

²⁶ D. L. Hughes, *Org. React.*, **42**, 335 (1992).

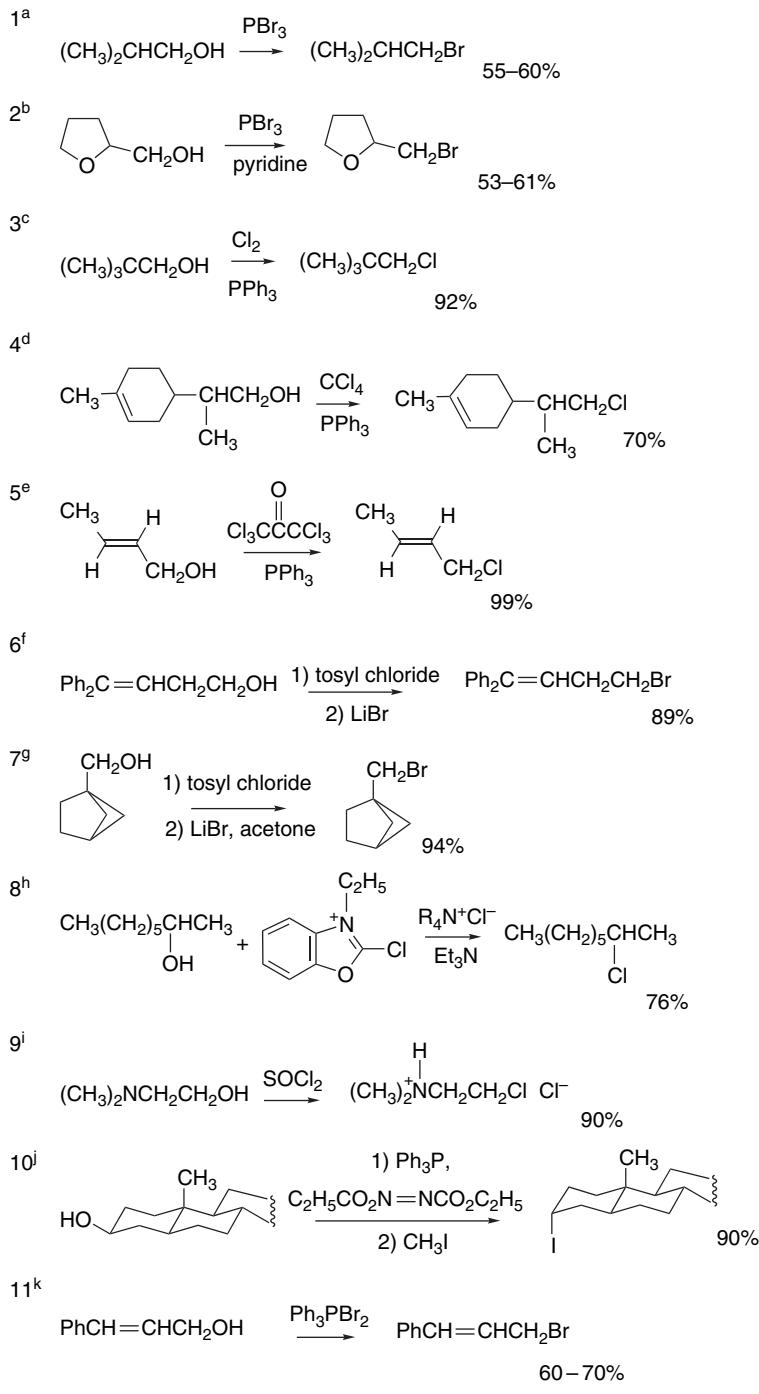
²⁷ E. W. Collington and A. I. Meyers, *J. Org. Chem.*, **36**, 3044 (1971).

²⁸ T. Mukaiyama, S. Shoda, and Y. Watanabe, *Chem. Lett.*, 383 (1977); T. Mukaiyama, *Angew. Chem. Int. Ed. Engl.*, **18**, 707 (1979).

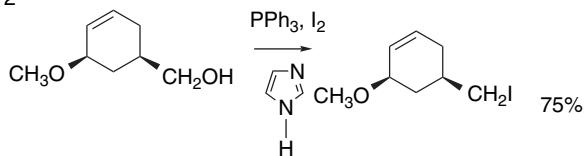
Scheme 3.1. Preparation of Alkyl Halides

CHAPTER 3

*Functional Group
Interconversion
by Substitution,
Including Protection and
Deprotection*

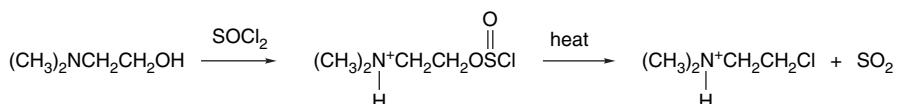


(Continued)

12^l

- a. C. R. Noller and R. Dinsomore, *Org. Synth.*, **II**, 358 (1943).
- b. L. H. Smith, *Org. Synth.*, **III**, 793 (1955).
- c. G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Am. Chem. Soc.*, **86**, 964 (1964).
- d. D. B. MacKenzie, M. M. Angelo, and J. Wolinsky, *J. Org. Chem.*, **44**, 4042 (1979).
- e. R. M. Magid, O. S. Fruchy, W. L. Johnson, and T. G. Allen, *J. Org. Chem.*, **44**, 359 (1979).
- f. M. E. H. Howden, A. Maerker, J. Burdon, and J. D. Roberts, *J. Am. Chem. Soc.*, **88**, 1732 (1966).
- g. K. B. Wiberg and B. R. Lowry, *J. Am. Chem. Soc.*, **85**, 3188 (1963).
- h. T. Mukaiyama, S. Shoda, and Y. Watanabe, *Chem. Lett.*, 383 (1977).
- i. L. A. R. Hall, V. C. Stephens, and J. H. Burkhalter, *Org. Synth.*, **IV**, 333 (1963).
- j. H. Loibner and E. Zviral, *Helv. Chim. Acta*, **59**, 2100 (1976).
- k. J. P. Schaefer, J. G. Higgins, and P. K. Shenoy, *Org. Synth.*, **V**, 249 (1973).
- l. R. G. Linde II, M. Egbertson, R. S. Coleman, A. B. Jones, and S. J. Danishefsky, *J. Org. Chem.*, **55**, 2771 (1990).

but no rearrangement was observed under these conditions. Entry 8 illustrates the use of a chlorobenzoxazolium cation for conversion of a secondary alcohol to a chloride. This reaction was shown to proceed with inversion of configuration. Entry 9 involves conversion of a primary alcohol to a chloride using SOCl_2 . In this particular example, the tertiary amino group captures the HCl that is formed by the reaction of the alcohol with SOCl_2 . There is also some suggestion from the procedure that much of the reaction proceeds through a chlorosulfite intermediate. After the reactants are mixed (exothermic reaction), the material is heated in ethanol, during which time gas evolution occurs. This suggests that much of the chlorosulfite ester survives until the heating stage.



Entry 10 illustrates the application of the Mitsunobu reaction to synthesis of a steroidal iodide and demonstrates that inversion occurs. Entry 11 shows the use of the isolated $\text{Ph}_3\text{P}-\text{Br}_2$ complex. The reaction in Entry 12 involves the preparation of a primary iodide using the $\text{Ph}_3\text{P}-\text{I}_2$ -imidazole reagent combination.

3.2. Introduction of Functional Groups by Nucleophilic Substitution at Saturated Carbon

The mechanistic aspects of nucleophilic substitution reactions were treated in detail in Chapter 4 of Part A. That mechanistic understanding has contributed to the development of nucleophilic substitution reactions as important synthetic processes. Owing to its stereospecificity and avoidance of carbocation intermediates, the S_N2 mechanism is advantageous from a synthetic point of view. In this section we discuss

the role of S_N2 reactions in the preparation of several classes of compounds. First, however, it is desirable to review the important role that solvent plays in S_N2 reactions. The knowledgeable manipulation of solvent and related medium effects has led to significant improvement of many synthetic procedures that proceed by the S_N2 mechanism.

3.2.1. General Solvent Effects

The objective in selecting the reaction conditions for a preparative nucleophilic substitution is to enhance the mutual reactivity of the leaving group and nucleophile so that the desired substitution occurs at a convenient rate and with minimal competition from other possible reactions. The generalized order of leaving-group reactivity $RSO_3^- \sim I^- > Br^- > Cl^-$ pertains for most S_N2 processes. (See Section 4.2.3 of Part A for more complete data.) Mesylates, tosylates, iodides, and bromides are all widely used in synthesis. Chlorides usually react rather slowly, except in especially reactive systems, such as allyl and benzyl.

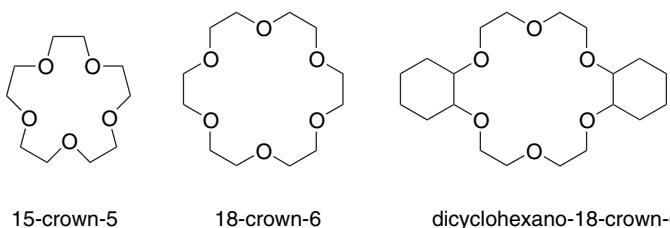
The overall synthetic objective normally governs the choice of the nucleophile. Optimization of reactivity therefore must be achieved by selection of the reaction conditions, particularly the solvent. Several generalizations about solvents can be made. Hydrocarbons, halogenated hydrocarbons, and ethers are usually unsuitable solvents for reactions involving ionic metal salts. Acetone and acetonitrile are somewhat more polar, but the solubility of most ionic compounds in these solvents is low. Solubility can be considerably improved by use of salts of cations having substantial hydrophobic character, such as those containing tetraalkylammonium ions. Alcohols are reasonably good solvents for salts, but the nucleophilicity of hard anions is relatively low in alcohols because of extensive solvation. The polar aprotic solvents, particularly dimethylformamide (DMF) and dimethylsulfoxide (DMSO), are good solvents for salts and, by virtue of selective cation solvation, anions usually show enhanced nucleophilicity in these solvents. Hexamethylphosphoric triamide (HMPA), *N,N*-dimethylacetamide, and *N*-methylpyrrolidinone are other examples of polar aprotic solvents.²⁹ The high water solubility of these solvents and their high boiling points can sometimes cause problems in product separation and purification. Furthermore, HMPA is toxic. In addition to enhancing reactivity, polar aprotic solvents also affect the order of reactivity of nucleophilic anions. In DMF the halides are all of comparable nucleophilicity,³⁰ whereas in hydroxylic solvents the order is $I^- > Br^- > Cl^-$ and the differences in reactivity are much greater.³¹

There are two other approaches to enhancing reactivity in nucleophilic substitutions by exploiting solvation effects on reactivity: the use of *crown ethers* as catalysts and the utilization of *phase transfer conditions*. The crown ethers are a family of cyclic polyethers, three examples of which are shown below.

²⁹. A. F. Sowinski and G. M. Whitesides, *J. Org. Chem.*, **44**, 2369 (1979).

³⁰. W. M. Weaver and J. D. Hutchinson, *J. Am. Chem. Soc.*, **86**, 261 (1964).

³¹. R. G. Pearson and J. Songstad, *J. Org. Chem.*, **32**, 2899 (1967).



15-crown-5

18-crown-6

dicyclohexano-18-crown-6

The first number designates the ring size and the second the number of oxygen atoms in the ring. By complexing the cation in the cavity of the crown ether, these compounds can solubilize salts in nonpolar solvents. In solution, the anions are more reactive as nucleophiles because they are weakly solvated. Tight ion pairing is also precluded by the complexation of the cation by the nonpolar crown ether. As a result, nucleophilicity approaches or exceeds that observed in aprotic polar solvents,³² but the crown ethers do present some hazards. They are toxic and also have the potential to transport toxic anions, such as cyanide, through the skin.

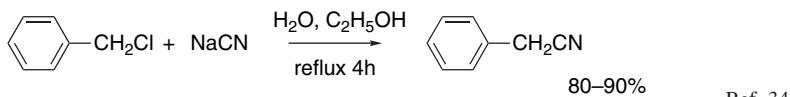
Another method of accelerating nucleophilic substitution is to use phase transfer catalysts,³³ which are ionic substances, usually quaternary ammonium or phosphonium salts, in which the hydrocarbon groups in the cation are large enough to convey good solubility in nonpolar solvents. In other words, the cations are highly *lipophilic*. Phase transfer catalysis usually is done in a two-phase system. The reagent is dissolved in a water-insoluble solvent such as a hydrocarbon or halogenated hydrocarbon. The salt of the nucleophile is dissolved in water. Even with vigorous mixing, such systems show little tendency to react, because the nucleophile and reactant remain separated in the water and organic phases, respectively. When a phase transfer catalyst is added, the lipophilic cations are transferred to the nonpolar phase and anions are attracted from the water to the organic phase to maintain electrical neutrality. The anions are weakly solvated in the organic phase and therefore exhibit enhanced nucleophilicity. As a result, the substitution reactions proceed under relatively mild conditions. The salts of the nucleophile are often used in high concentration in the aqueous solution and in some procedures the solid salts are used.

3.2.2. Nitriles

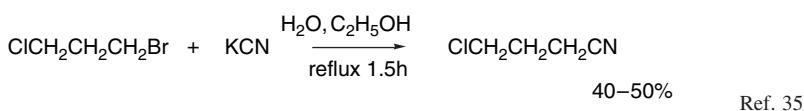
The replacement of a halide or sulfonate by cyanide ion, extending the carbon chain by one atom and providing an entry to carboxylic acid derivatives, has been a reaction of synthetic importance since the early days of organic chemistry. The classical conditions for preparing nitriles involve heating a halide with a cyanide salt in aqueous alcohol solution.

³². M. Hiraoka, *Crown Compounds: Their Characteristics and Application*, Elsevier, Amsterdam, 1982.

³³. E. V. Dehmlow and S. S. Dehmlow, *Phase Transfer Catalysis*, 3rd Edition, Verlag Chemie, Weinheim 1992; W. P. Weber and G. W. Gokel, *Phase Transfer Catalysis in Organic Synthesis*, Springer Verlag, New York, 1977; C. M. Stark, C. Liotta, and M. Halpern, *Phase Transfer Catalysis: Fundamentals, Applications and Industrial Perspective*, Chapman and Hall, New York, 1994.



Ref. 34



Ref. 35

These reactions proceed more rapidly in polar aprotic solvents. In DMSO, for example, primary alkyl chlorides are converted to nitriles in 1 h or less at temperatures of 120°–140°C.³⁶ Phase transfer catalysis by hexadecyltributylphosphonium bromide permits conversion of 1-chlorooctane to octyl cyanide in 95% yield in 2 h at 105°C.³⁷



Catalysis by 18-crown-6 of the reaction of solid potassium cyanide with a variety of chlorides and bromides has been demonstrated.³⁸ With primary bromides, yields are high and reaction times are 15–30 h at reflux in acetonitrile (83°C). Interestingly, the chlorides are more reactive and require reaction times of only about 2 h. Secondary halides react more slowly and yields drop because of competing elimination. Tertiary halides do not react satisfactorily because elimination dominates.

3.2.3. Oxygen Nucleophiles

The oxygen nucleophiles that are of primary interest in synthesis are the hydroxide ion (or water), alkoxide ions, and carboxylate anions, which lead, respectively, to alcohols, ethers, and esters. Since each of these nucleophiles can also act as a base, reaction conditions are selected to favor substitution over elimination. Usually, a given alcohol is more easily obtained than the corresponding halide so the halide-to-alcohol transformation is not used extensively for synthesis. The hydrolysis of benzyl halides to the corresponding alcohols proceeds in good yield. This can be a useful synthetic transformation because benzyl halides are available either by side chain halogenation or by the chloromethylation reaction (Section 11.1.3).

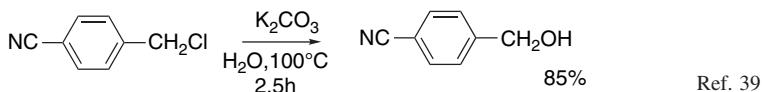
³⁴ R. Adams and A. F. Thal, *Org. Synth.*, **I**, 101 (1932).

³⁵ C. F. H. Allen, *Org. Synth.*, **I**, 150 (1932).

³⁶ L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 877 (1960); R. A. Smiley and C. Arnold, *J. Org. Chem.*, **25**, 257 (1960).

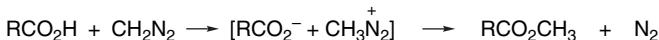
³⁷ C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971); C. M. Starks and R. M. Owens, *J. Am. Chem. Soc.*, **95**, 3613 (1973).

³⁸ F. L. Cook, C. W. Bowers, and C. L. Liotta, *J. Org. Chem.*, **39**, 3416 (1974).



Ether formation from alkoxides and alkylating reagents is a reaction of wide synthetic importance. The conversion of phenols to methoxyaromatics, for example, is a very common reaction. Methyl iodide, methyl tosylate, or dimethyl sulfate can be used as the alkylating agents. The reaction proceeds in the presence of a weak base, such as Na_2CO_3 or K_2CO_3 , which deprotonates the phenol. The conjugate bases of alcohols are considerably more basic than phenoxides, so β -elimination can be a problem. Phase transfer conditions can be used in troublesome cases.⁴⁰ Fortunately, the most useful and commonly encountered ethers are methyl and benzyl ethers, where elimination is not a problem and the corresponding halides are especially reactive toward substitution.

Two methods for converting carboxylic acids to esters fall into the mechanistic group under discussion: the reaction of carboxylic acids with diazo compounds, especially diazomethane and alkylation of carboxylate anions by halides or sulfonates. The esterification of carboxylic acids with diazomethane is a very fast and clean reaction.⁴¹ The alkylating agent is the extremely reactive methyldiazonium ion, which is generated by proton transfer from the carboxylic acid to diazomethane. The collapse of the resulting ion pair with loss of nitrogen is extremely rapid.



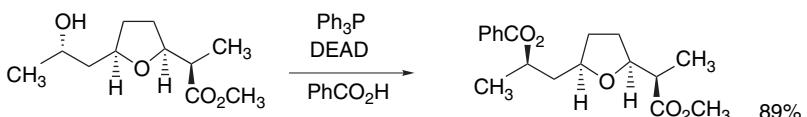
The main drawback to this reaction is the toxicity of diazomethane and some of its precursors. Diazomethane is also potentially explosive. Trimethylsilyldiazomethane is an alternative reagent,⁴² which is safer and frequently used in preparation of methyl esters from carboxylic acids.⁴³ Trimethylsilyldiazomethane also O-methylates alcohols.⁴⁴ The latter reactions occur in the presence of fluoroboric acid in dichloromethane.

Especially for large-scale work, esters may be more safely and efficiently prepared by reaction of carboxylate salts with alkyl halides or tosylates. Carboxylate anions are not very reactive nucleophiles so the best results are obtained in polar aprotic solvents⁴⁵ or with crown ether catalysts.⁴⁶ The reactivity order for carboxylate salts is $\text{Na}^+ < \text{K}^+ < \text{Rb}^+ < \text{Cs}^+$. Cesium carboxylates are especially useful in polar aprotic solvents. The enhanced reactivity of the cesium salts is due to both high solubility and minimal ion pairing with the anion.⁴⁷ Acetone is a good solvent for reaction of carboxylate anions with alkyl iodides.⁴⁸ Cesium fluoride in DMF is another useful

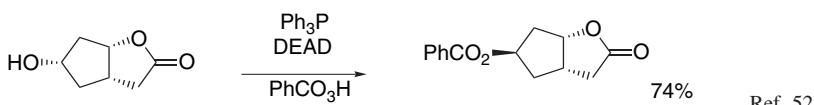
- ^{39.} J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newbery, and A. D. Self, *J. Chem. Soc.*, 103 (1942).
- ^{40.} F. Lopez-Calhorra, B. Ballart, F. Hombrados, and J. Marti, *Synth. Commun.*, **28**, 795 (1998).
- ^{41.} T. H. Black, *Aldrichimia Acta*, **16**, 3 (1983).
- ^{42.} N. Hashimoto, T. Aoyama, and T. Shiori, *Chem. Pharm. Bull.*, **29**, 1475 (1981).
- ^{43.} T. Shioiri and T. Aoyama, *Adv. Use Synthons Org. Chem.*, **1**, 51 (1993); A. Presser and A. Huefner, *Monatsh. Chem.*, **135**, 1015 (2004).
- ^{44.} T. Aoyama and T. Shiori, *Tetrahedron Lett.*, **31**, 5507 (1990).
- ^{45.} P. E. Pfeffer, T. A. Foglia, P. A. Barr, I. Schmeltz, and L. S. Silbert, *Tetrahedron Lett.*, 4063 (1972); J. E. Shaw, D. C. Kunerth, and J. J. Sherry, *Tetrahedron Lett.*, 689 (1973); J. Grundy, B. G. James, and G. Pattenden, *Tetrahedron Lett.*, 757 (1972).
- ^{46.} C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez, and K. Smith, *Tetrahedron Lett.*, 2417 (1974).
- ^{47.} G. Dijkstra, W. H. Kruizinga, and R. M. Kellogg, *J. Org. Chem.*, **52**, 4230 (1987).
- ^{48.} G. G. Moore, T. A. Foglia, and T. J. McGahan, *J. Org. Chem.*, **44**, 2425 (1979).

combination.⁴⁹ Carboxylate alkylation procedures are particularly advantageous for preparation of hindered esters, which can be relatively difficult to prepare by the acid-catalyzed esterification method (Fisher esterification), which we discuss in Section 3.4.

During the course of synthesis, it is sometimes necessary to invert the configuration at an oxygen-substituted center. One of the best ways of doing this is to activate the hydroxy group to substitution by a carboxylate anion. The activation is frequently done using the Mitsunobu reaction.⁵⁰ Hydrolysis of the resulting ester give the alcohol of inverted configuration.



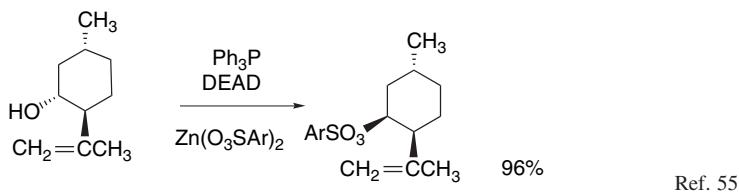
Ref. 51



Ref. 52

Carboxylate anions derived from somewhat stronger acids, such as *p*-nitrobenzoic acid and chloroacetic acid, seem to be particularly useful in this Mitsunobu inversion reaction.⁵³ Inversion can also be carried out on sulfonate esters using cesium carboxylates and DMAP as a catalyst in toluene.⁵⁴ The effect of the DMAP seems to involve complexation and solubilization of the cesium salts.

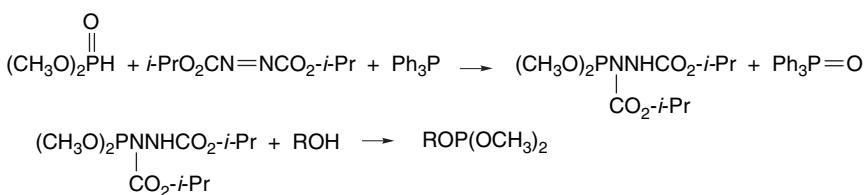
Sulfonate esters also can be prepared under Mitsunobu conditions. Use of zinc tosylate in place of the carboxylic acid gives a tosylate of inverted configuration.



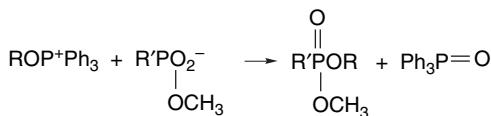
Ref. 55

The Mitsunobu conditions also can be used to effect a variety of other important and useful nucleophilic substitution reactions, such as conversion of alcohols to mixed phosphite esters.⁵⁶ The active phosphitylating agent is believed to be a mixed phosphoramidite.

- ⁴⁹. T. Sato, J. Otera, and H. Nozaki, *J. Org. Chem.*, **57**, 2166 (1992).
- ⁵⁰. D. L. Hughes, *Org. React.*, **42**, 335 (1992); D. L. Hughes, *Org. Prep. Proc. Intl.*, **28**, 127 (1996).
- ⁵¹. M. J. Arco, M. H. Trammel, and J. D. White, *J. Org. Chem.*, **41**, 2075 (1976).
- ⁵². C.-T. Hsu, N.-Y. Wang, L. H. Latimer, and C. J. Sih, *J. Am. Chem. Soc.*, **105**, 593 (1983).
- ⁵³. J. A. Dodge, J. I. Tujillo, and M. Presnell, *J. Org. Chem.*, **59**, 234 (1994); M. Saiah, M. Bessodes, and K. Antonakis, *Tetrahedron Lett.*, **33**, 4317 (1992); S. F. Martin and J. A. Dodge, *Tetrahedron Lett.*, **32**, 3017 (1991); P. J. Harvey, M. von Itzstein, and I. D. Jenkins, *Tetrahedron*, **53**, 3933 (1997).
- ⁵⁴. N. A. Hawryluk and B. B. Snider, *J. Org. Chem.*, **65**, 8379 (2000).
- ⁵⁵. I. Galynker and W. C. Still, *Tetrahedron Lett.*, 4461 (1982).
- ⁵⁶. I. D. Grice, P. J. Harvey, I. D. Jenkins, M. J. Gallagher, and M. G. Ranasinghe, *Tetrahedron Lett.*, **37**, 1087 (1996).

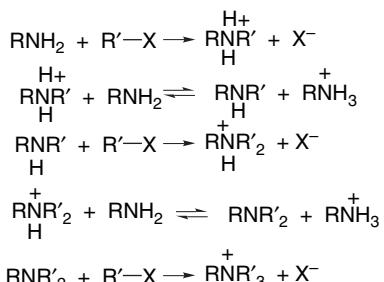


Mixed phosphonate acid esters can also be prepared from alkylphosphonate monoesters, although here the activation is believed occur at the alcohol.⁵⁷



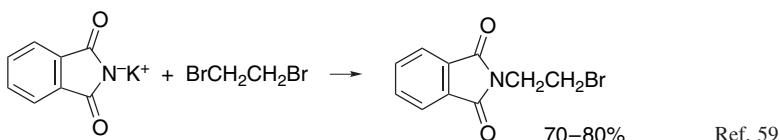
3.2.4. Nitrogen Nucleophiles

The alkylation of neutral amines by halides is complicated from a synthetic point of view by the possibility of multiple alkylation that can proceed to the quaternary ammonium salt in the presence of excess alkyl halide.



Even with a limited amount of the alkylating agent, the equilibria between protonated product and the neutral starting amine are sufficiently fast that a mixture of products may be obtained. For this reason, when monoalkylation of an amine is desired, the reaction is usually best carried out by *reductive amination*, a reaction that is discussed in Chapter 5. If complete alkylation to the quaternary salt is desired, use of excess alkylating agent and a base to neutralize the liberated acid normally results in complete reaction.

Amides are weakly nucleophilic and react only slowly with alkyl halides. The anions of amides are substantially more reactive. The classical Gabriel procedure for synthesis of amines from phthalimide is illustrative.⁵⁸

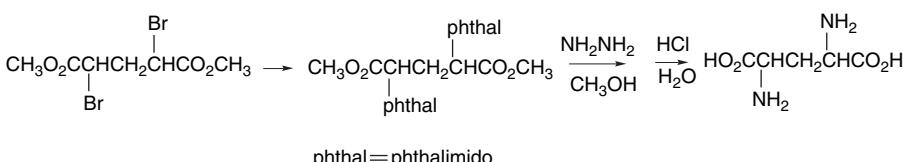


⁵⁷ D. A. Campbell, *J. Org. Chem.*, **57**, 6331 (1992); D. A. Campbell and J. C. Bermak, *J. Org. Chem.*, **59**, 658 (1994).

⁵⁸ M. S. Gibson and R. N. Bradshaw, *Angew. Chem. Int. Ed. Engl.*, **7**, 919 (1968).

⁵⁹ P. L. Salzberg and J. V. Supniewski, *Org. Synth.*, **I**, 119 (1932).

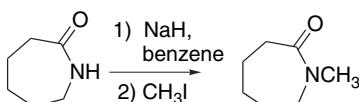
The enhanced acidity of the NH group in phthalimide permits formation of the anion, which is readily alkylated by alkyl halides or tosylates. The amine can then be liberated by reaction of the substituted phthalimide with hydrazine.



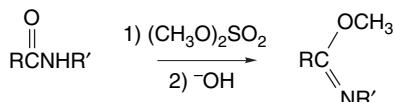
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It has been found that the deprotection phase of the Gabriel synthesis is accelerated by inclusion of NaOH.⁶¹

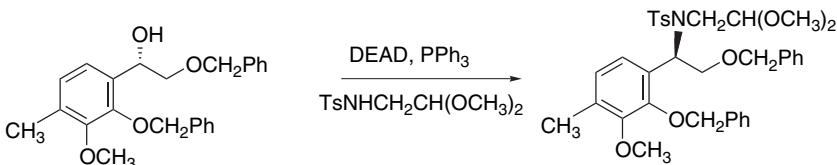
Secondary amides can be alkylated on nitrogen by using sodium hydride for deprotonation, followed by reaction with an alkyl halide.⁶²



Neutral tertiary and secondary amides react with very reactive alkylating agents, such as triethyloxonium tetrafluoroborate, to give O-alkylation.⁶³ The same reaction occurs, but more slowly, with tosylates and dimethyl sulfate. Neutralization of the resulting salt provides iminoethers.



Sulfonamides are relatively acidic and their anions can serve as nitrogen nucleophiles.⁶⁴ Sulfonamido groups can be introduced at benzylic positions with a high level of inversion under Mitsunobu conditions.⁶⁵



60. J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2786 (1950).

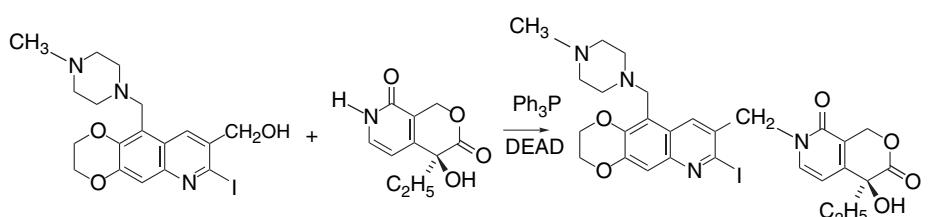
61. A. Ariffin, M. N. Khan, L. C. Lan, F. Y. May, and C. S. Yun, *Synth. Commun.*, **34**, 4439 (2004); M. N. Khan, *J. Org. Chem.*, **61**, 8063 (1996).

62. W. S. Fones, *J. Org. Chem.*, **14**, 1099 (1949); R. M. Moriarty, *J. Org. Chem.*, **29**, 2748 (1964).

63. L. Weintraub, S. R. Oles, and N. Kalish, *J. Org. Chem.*, **33**, 1679 (1968); H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.*, **154**, 83 (1939).

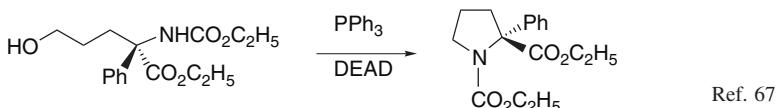
64. D. Papaioannou, C. Athanassopoulos, V. Magafa, N. Karamanos, G. Stavropoulos, A. Napoli, G. Sindona, D. W. Aksnes, and G. W. Francis, *Acta Chem. Scand.*, **48**, 324 (1994).

65. T. S. Kaufman, *Tetrahedron Lett.*, **37**, 5329 (1996).



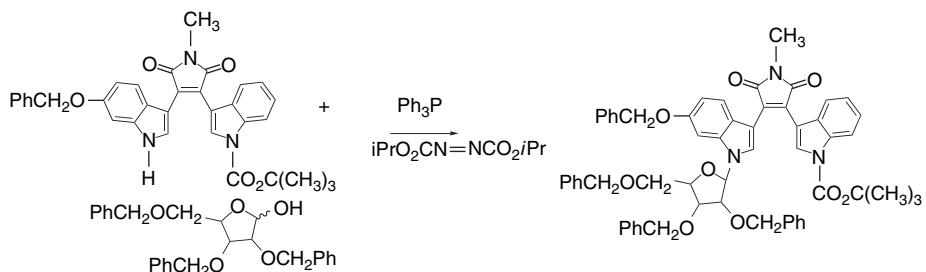
Ref. 66

Proline analogs can be obtained by cyclization of δ -hydroxyalkylamino acid carbamates.



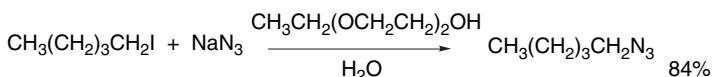
Ref. 67

Mitsunobu conditions are effective for glycosylation of weak nitrogen nucleophiles, such as indoles. This reaction has been used in the synthesis of antitumor compounds.



Ref. 68

Azides are useful intermediates for synthesis of various nitrogen-containing compounds. They can also be easily reduced to primary amines and undergo cycloaddition reactions, as is discussed in Section 6.2. Azido groups are usually introduced into aliphatic compounds by nucleophilic substitution.⁶⁹ The most reliable procedures involve heating an appropriate halide with sodium azide in DMSO ⁷⁰ or DMF .⁷¹ Alkyl azides can also be prepared by reaction in high-boiling alcohols.⁷²



⁶⁶ F. G. Fang, D. D. Bankston, E. M. Huie, M. R. Johnson, M.-C. Kang, C. S. LeHoullier, G. C. Lewis, T. C. Lovelace, M. W. Lowery, D. L. McDougald, C. A. Meerholz, J. J. Partridge, M. J. Sharp, and S. Xie, *Tetrahedron*, **53**, 10953 (1997).

⁶⁷ J. van Betsbrugge, D. Tourwe, B. Kaptein, H. Kierkals, and R. Broxterman, *Tetrahedron*, **53**, 9233 (1997).

⁶⁸ M. Ohkubo, T. Nishimura, H. Jona, T. Honma, S. Ito, and H. Morishima, *Tetrahedron*, **53**, 5937 (1997).

⁶⁹ M. E. C. Biffin, J. Miller, and D. B. Paul, in *The Chemistry of the Azido Group*, S. Patai, ed., Interscience, New York, 1971, Chap. 2.

⁷⁰ R. Goutarel, A. Cave, L. Tan, and M. Leboeuf, *Bull. Soc. Chim. France*, 646 (1962).

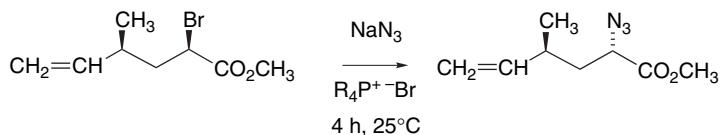
⁷¹ E. J. Reist, R. R. Spencer, B. R. Baker, and L. Goodman, *Chem. Ind. (London)*, 1794 (1962).

⁷² E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.*, **22**, 238 (1957); H. Lehmkuhl, F. Rabet, and K. Hauschild, *Synthesis*, 184 (1977).

Phase transfer conditions are used as well for the preparation of azides.⁷³

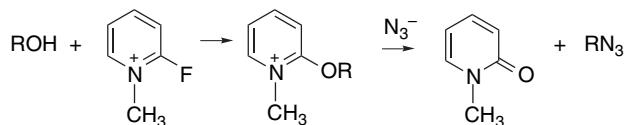
CHAPTER 3

*Functional Group
Interconversion
by Substitution,
Including Protection and
Deprotection*

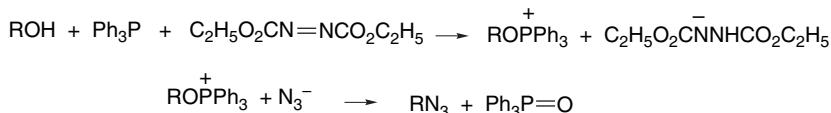


Tetramethylguanidinium azide, an azide salt that is readily soluble in halogenated solvents, is a useful source of azide ions in the preparation of azides from reactive halides such as α -haloketones, α -haloamides, and glycosyl halides.⁷⁴

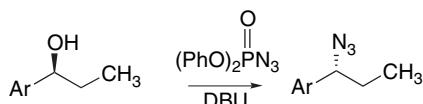
There are also useful procedures for preparation of azides directly from alcohols. Reaction of alcohols with 2-fluoro-1-methylpyridinium iodide followed by reaction with lithium azide gives good yields of alkyl azides.⁷⁵



Diphenylphosphoryl azide reacts with alcohols in the presence of triphenylphosphine and DEAD.⁷⁶ Hydrazoic acid, HN_3 , can also serve as the azide ion source under these conditions.⁷⁷ These reactions are examples of the Mitsunobu reaction.



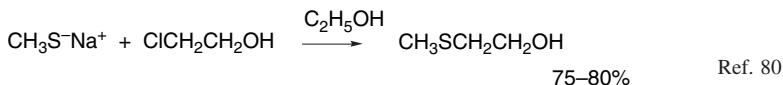
Diphenylphosphoryl azide also gives good conversion of primary alkyl and secondary benzylic alcohols to azides in the presence of the strong organic base diazabicyclicoundecane (DBU). These reactions proceed by O-phosphorylation followed by S_N2 displacement.⁷⁸



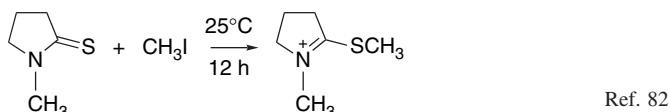
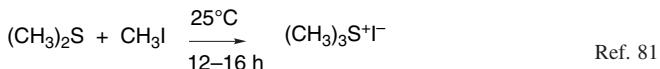
This reaction can be extended to secondary alcohols with the more reactive *bis*-(4-nitrophenyl)phosphorazidate.⁷⁹

73. W. P. Reeves and M. L. Bahr, *Synthesis*, 823 (1976); B. B. Snider and J. V. Duncia, *J. Org. Chem.*, **46**, 3223 (1981).
74. Y. Pan, R. L. Merriman, L. R. Tanzer, and P. L. Fuchs, *Biomed. Chem. Lett.*, **2**, 967 (1992); C. Li, T.-L. Shih, J. U. Jeong, A. Arasappan, and P. L. Fuchs, *Tetrahedron Lett.*, **35**, 2645 (1994); C. Li, A. Arasappan, and P. L. Fuchs, *Tetrahedron Lett.*, **34**, 3535 (1993); D. A. Evans, T. C. Britton, J. A. Ellman, and R. L. Dorow, *J. Am. Chem. Soc.*, **112**, 4011 (1990).
75. K. Hojo, S. Kobayashi, K. Soai, S. Ikeda, and T. Mukaiyama, *Chem. Lett.*, 635 (1977).
76. B. Lal, B. N. Pramanik, M. S. Manhas, and A. K. Bose, *Tetrahedron Lett.*, 1977 (1977).
77. J. Schweng and E. Zbiral, *Justus Liebigs Ann. Chem.*, 1089 (1978); M. S. Hadley, F. D. King, B. McRitchie, D. H. Turner, and E. A. Watts, *J. Med. Chem.*, **28**, 1843 (1985).
78. A. S. Thompson, G. R. Humphrey, A. M. DeMarco, D. J. Mathre, and E. J. J. Grabowski, *J. Org. Chem.*, **58**, 5886 (1993).
79. M. Mizuno and T. Shioiri, *J. Chem. Soc., Chem. Commun.*, **22**, 2165 (1997).

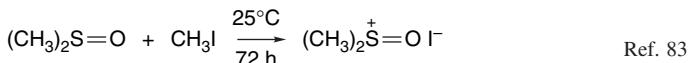
Anions derived from thiols are strong nucleophiles and are easily alkylated by halides.



Neutral sulfur compounds are also good nucleophiles. Sulfides and thioamides readily form salts with methyl iodide, for example.

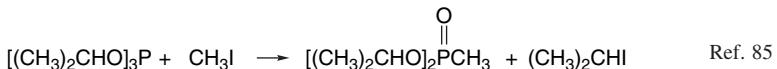
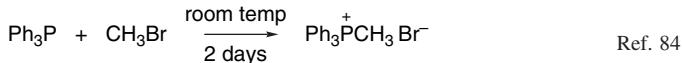


Even sulfoxides, in which nucleophilicity is decreased by the additional oxygen, can be alkylated by methyl iodide. These sulfoxonium salts have useful synthetic applications as discussed in Section 2.5.1.

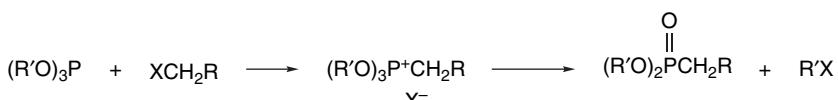


3.2.6. Phosphorus Nucleophiles

Both neutral and anionic phosphorus compounds are good nucleophiles toward alkyl halides. We encountered examples of these reactions in Chapter 2 in connection with the preparation of the valuable phosphorane and phosphonate intermediates used for Wittig reactions.



The reaction with phosphite esters is known as the *Michaelis-Arbuzov reaction* and proceeds through an unstable trialkoxyphosphonium intermediate. The second stage is another example of the great tendency of alkoxyphosphonium ions to react with nucleophiles to break the O–C bond, resulting in formation of a phosphoryl P–O bond.



⁸⁰ W. Windus and P. R. Shildneck, *Org. Synth.*, **II**, 345 (1943).

⁸¹ E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

⁸² R. Gompper and W. Elser, *Org. Synth.*, **V**, 780 (1973).

⁸³ R. Kuhn and H. Trischmann, *Justus Liebigs Ann. Chem.*, **611**, 117 (1958).

⁸⁴ G. Wittig and U. Schoellkopf, *Org. Synth.*, **V**, 751 (1973).

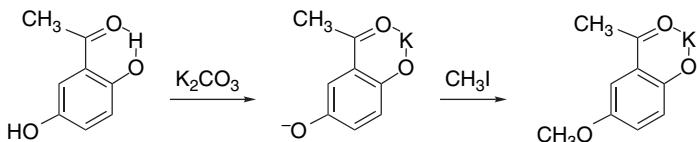
⁸⁵ A. H. Ford-Moore and B. J. Perry, *Org. Synth.*, **IV**, 325 (1963).

3.2.7. Summary of Nucleophilic Substitution at Saturated Carbon

Some of the nucleophilic substitution reactions at sp^3 carbon that are most valuable for synthesis were outlined in the preceding sections, and they all fit into the general mechanistic patterns that were discussed in Chapter 4 of Part A. The order of reactivity of alkylating groups is benzyl \sim allyl $>$ methyl $>$ primary $>$ secondary. Tertiary halides and sulfonates are generally not satisfactory because of the preference for elimination over S_N2 substitution. Owing to their high reactivity toward nucleophilic substitution, α -haloesters, α -haloketones, and α -halonitriles are usually favorable reactants for substitution reactions. The reactivity of leaving groups is sulfonate \sim iodide $>$ bromide $>$ chloride. Steric hindrance decreases the rate of nucleophilic substitution. Thus projected synthetic steps involving nucleophilic substitution must be evaluated for potential steric problems.

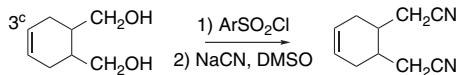
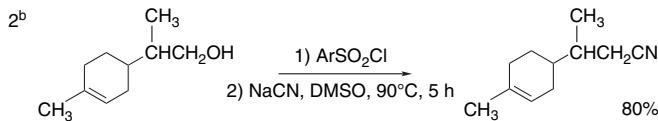
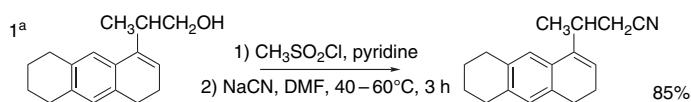
Scheme 3.2 gives some representative examples of nucleophilic substitution processes drawn from *Organic Syntheses* and from other synthetic efforts. Entries 1 to 3 involve introduction of cyano groups via tosylates and were all conducted in polar aprotic solvents. Entries 4 to 8 are examples of introduction of the azido functional group by substitution. The reaction in Entry 4 was done under phase transfer conditions. A concentrated aqueous solution of NaN_3 was heated with the alkyl bromide and 5 mol % methyltriocetylammonium chloride. Entries 5 to 7 involve introduction of the azido group at secondary carbons with inversion of configuration in each case. The reactions in Entries 7 and 8 involve formation of phosphoryl esters as intermediates. These conditions were found preferable to the Mitsunobu conditions for the reaction in Entry 7. The electron-rich benzylic reactant gave both racemization and elimination via a carbocation intermediate under the Mitsunobu conditions. Entries 9 and 10 are cases of controlled alkylation of amines. In the reaction in Entry 9, the pyrrolidine was used in twofold excess. The ester EWGs have a rate-retarding effect that slows further alkylation to the quaternary salt. In the reaction in Entry 10, the monohydrochloride of piperazine is used as the reactant. The reaction was conducted in ethanol, and the dihydrochloride salt of the product precipitates as reaction proceeds, which helps minimize quaternization or N,N' -dialkylation. The yield of the dihydrochloride is 97–99%, and that of the amine is 65–75% after neutralization of the salt and distillation. The reaction in Entry 11 is the O-alkylation of an amide. The reaction was done in refluxing benzene, and the product was obtained by distillation after the neutralization.

Sections D through H of Scheme 3.2 involve oxygen nucleophiles. The hydrolysis reactions in Entries 12 and 13 both involve benzylic positions. The reaction site in Entry 13 is further activated by the ERG substituents on the ring. Entries 14 to 17 are examples of base-catalyzed ether formation. The selectivity of the reaction in Entry 17 for the *meta*-hydroxy group is an example of a fairly common observation in aromatic systems. The *ortho*-hydroxy group is more acidic and probably also stabilized by chelation, making it less reactive.

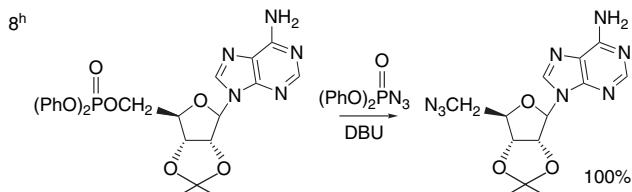
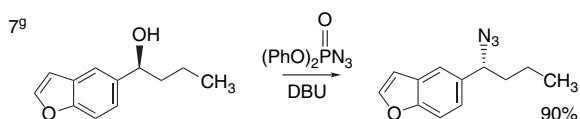
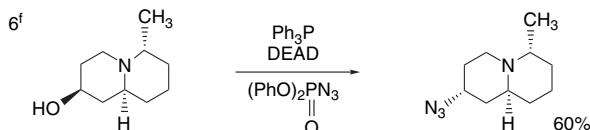
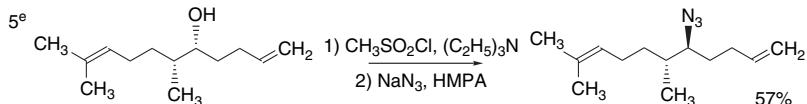
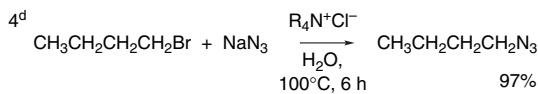


Dialkylation occurs if a stronger base ($NaOH$) and dimethyl sulfate is used. Entry 18 is a typical diazomethane methylation of a carboxylic acid. The toxicity of diazomethane

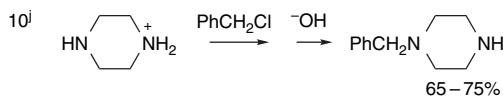
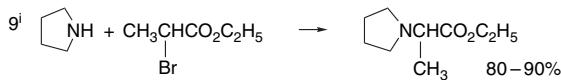
A. Nitriles



B. Azides



C. Amines and amides

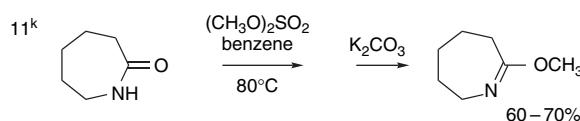


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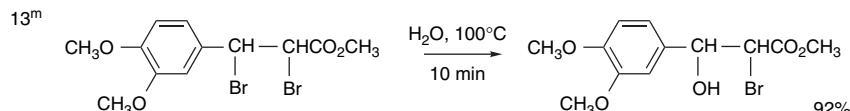
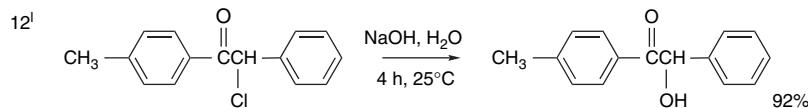
Scheme 3.2. (Continued)

CHAPTER 3

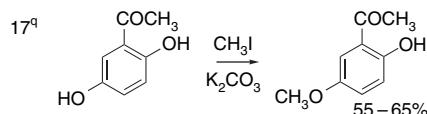
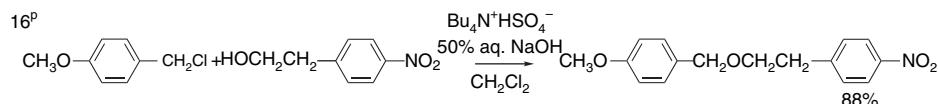
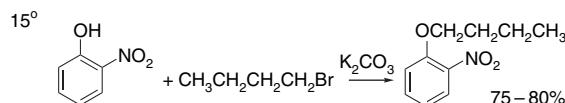
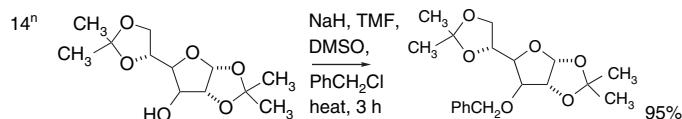
*Functional Group
Interconversion
by Substitution,
Including Protection and
Deprotection*



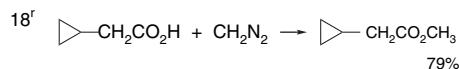
D. Hydrolysis by alkyl halides



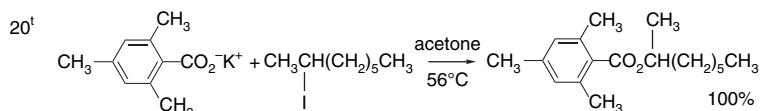
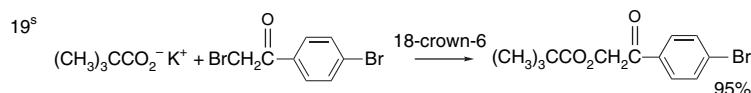
E. Ethers by base – catalyzed alkylation



F. Esterification by diazoalkanes

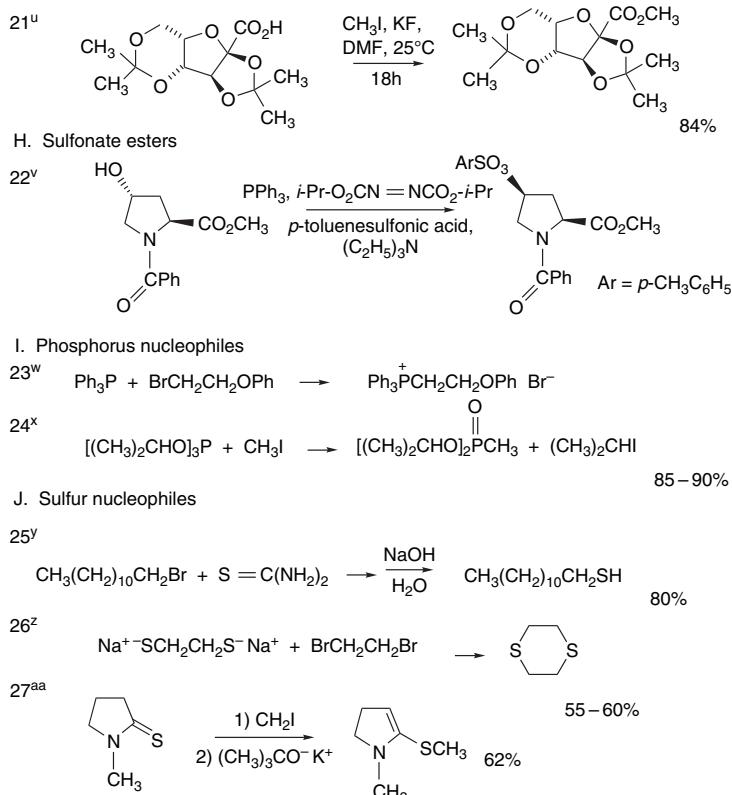


G. Esterification by nucleophilic substitution with carboxylate salts



(Continued)

Scheme 3.2. (Continued)



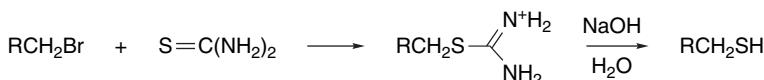
SECTION 3.2

Introduction of
Functional Groups by
Nucleophilic Substitution
at Saturated Carbon

- a. M. S. Newman and S. Otsuka, *J. Org. Chem.*, **23**, 797 (1958).
- b. B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy, *J. Am. Chem. Soc.*, **92**, 336 (1970).
- c. J. J. Bloomfield and P. V. Fennessey, *Tetrahedron Lett.*, 2273 (1964).
- d. W. P. Reeves and M. L. Bahr, *Synthesis*, 823 (1976).
- e. D. F. Taber, M. Rahimizadeh, and K. K. You, *J. Org. Chem.*, **60**, 529 (1995).
- f. M. S. Hadley, F. D. King, B. McRitchie, D. H. Turner, and E. A. Watts, *J. Med. Chem.*, **28**, 1843 (1985).
- g. A. S. Thompson, G. G. Humphrey, A. M. De Marco, D. J. Mathre, and E. J. J. Grabowski, *J. Org. Chem.*, **58**, 5886 (1993).
- h. P. Liu and D. J. Austin, *Tetrahedron Lett.*, **42**, 3153 (2001).
- i. R. B. Moffett, *Org. Synth.*, **IV**, 466 (1963).
- j. J. C. Craig and R. J. Young, *Org. Synth.*, **V**, 88 (1973).
- k. R. E. Benson and T. L. Cairns, *Org. Synth.*, **IV**, 588 (1963).
- l. R. N. McDonald and P. A. Schwab, *J. Am. Chem. Soc.*, **85**, 4004 (1963).
- m. C. H. Heathcock, C. T. White, J. J. Morrison, and D. Van Derveer, *J. Org. Chem.*, **46**, 1296 (1981).
- n. E. Adler and K. J. Bjorkquist, *Acta Chem. Scand.*, **5**, 241 (1951).
- o. E. S. West and R. F. Holden, *Org. Synth.*, **III**, 800 (1955).
- p. F. Lopez-Calahorra, B. Ballart, F. Hombrados, and J. Marti, *Synth. Commun.*, **28**, 795 (1998).
- q. G. N. Vyas and M. N. Shah, *Org. Synth.*, **IV**, 836 (1963).
- r. L. I. Smity and S. McKenzie, Jr., *J. Org. Chem.*, **15**, 74 (1950); A. I. Vogel, *Practical Organic Chemistry*, 3rd Edition, Wiley, 1956, p. 973.
- s. H. D. Durst, *Tetrahedron Lett.*, 2421 (1974).
- t. G. G. Moore, T. A. Foglia, and T. J. McGahan, *J. Org. Chem.*, **44**, 2425 (1979).
- u. C. H. Heathcock, C.-T. White, J. Morrison, and D. VanDerveer, *J. Org. Chem.*, **46**, 1296 (1981).
- v. N. G. Anderson, D. A. Lust, K. A. Colapret, J. H. Simpson, M. F. Malley, and J. Z. Gougoutas, *J. Org. Chem.*, **61**, 7955 (1996).
- w. E. E. Schweizer and R. D. Bach, *Org. Synth.*, **V**, 1145 (1973).
- x. A. H. Ford-Moore and B. J. Perry, *Org. Synth.*, **IV**, 325 (1963).
- y. G. G. Urquhart, J. W. Gates, Jr., and P. Conor, *Org. Synth.*, **III**, 363 (1965).
- z. R. G. Gillis and A. B. Lacey, *Org. Synth.*, **IV**, 396 (1963).
- aa. R. Gompper and W. Elser, *Org. Synth.*, **V**, 780 (1973).

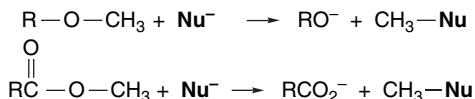
and its precursors, as well as the explosion hazard of diazomethane, requires that all recommended safety precautions be taken. Entries 19 to 21 involve formation of esters by alkylation of carboxylate salts. The reaction in Entry 19 was done in the presence of 5 mol % 18-crown-6. A number of carboxylic acids, including pivalic acid as shown in the example, were alkylated in high yield under these conditions. Entry 20 shows the alkylation of the rather hindered mesitoic acid by a secondary iodide. These conditions also gave high yields for unhindered acids and iodides. Entry 21 involves formation of a methyl ester using CH_3I and KF as the base in DMF. Entry 22 involves formation of a sulfonate ester under Mitsunobu conditions with clean inversion of configuration. The conditions reported represent the optimization of the reaction as part of the synthesis of an antihypertensive drug, fosinopril.

Sections I and J of Scheme 3.2 show reactions with sulfur and phosphorus nucleophiles. The reaction in Entry 25 is a useful method for introducing thiol groups. The solid thiourea is a convenient source of sulfur. A thiuronium ion is formed and this avoids competition from formation of a dialkyl sulfide. The intermediate is readily hydrolyzed by base.



3.3. Cleavage of Carbon-Oxygen Bonds in Ethers and Esters

The cleavage of carbon-oxygen bonds in ethers or esters by nucleophilic substitution is frequently a useful synthetic transformation.



The alkoxide group is a poor leaving group and carboxy is only slightly better. As a result, these reactions usually require assistance from a protic or Lewis acid. The classical ether cleavage conditions involving concentrated hydrogen halides are much too strenuous for most polyfunctional molecules, so several milder reagents have been developed,⁸⁶ including boron tribromide,⁸⁷ dimethylboron bromide,⁸⁸ trimethylsilyl iodide,⁸⁹ and boron trifluoride in the presence of thiols.⁹⁰ The mechanism for ether cleavage with boron tribromide involves attack of bromide ion on an adduct formed

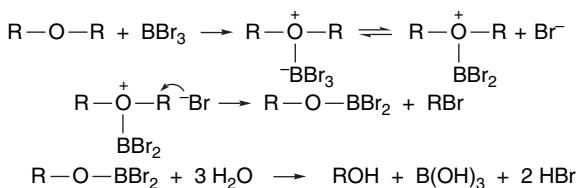
⁸⁶. M. V. Bhatt and S. U. Kulkarni, *Synthesis*, 249 (1983).

⁸⁷. J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).

⁸⁸. Y. Guindon, M. Therien, Y. Girard, and C. Yoakim, *J. Org. Chem.*, **52**, 1680 (1987).

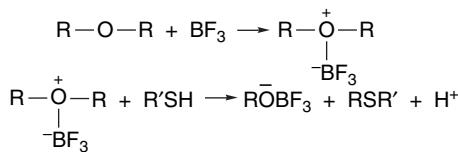
⁸⁹. M. E. Jung and M. A. Lyster, *J. Org. Chem.*, **42**, 3761 (1977).

⁹⁰. (a) M. Node, H. Hori, and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 2237 (1976); (b) K. Fuji, K. Ichikawa, M. Node, and E. Fujita, *J. Org. Chem.*, **44**, 1661 (1979).

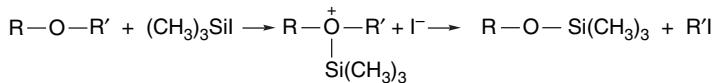


Good yields are generally observed, especially for methyl ethers. The combination of boron tribromide with dimethyl sulfide has been found to be particularly effective for cleaving aryl methyl ethers.⁹¹

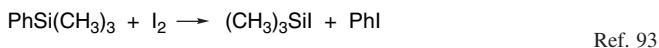
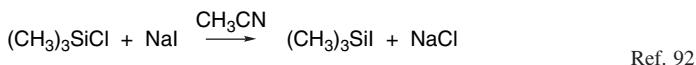
The boron trifluoride–alkyl thiol reagent combination also operates on the basis of nucleophilic attack on an oxonium ion generated by reaction of the ether with boron trifluoride.⁹⁰



Trimethylsilyl iodide (TMSI) cleaves methyl ethers in a period of a few hours at room temperature.⁸⁹ Benzyl and *t*-butyl systems are cleaved very rapidly, whereas secondary systems require longer times. The reaction presumably proceeds via an initially formed silyl oxonium ion.



The direction of cleavage in unsymmetrical ethers is determined by the relative ease of O–R bond breaking by either *S_N2* (methyl, benzyl) or *S_N1* (*t*-butyl) processes. As trimethylsilyl iodide is rather expensive, alternative procedures that generate the reagent *in situ* have been devised.



⁹¹ P. G. Williard and C. R. Fryhle, *Tetrahedron Lett.*, **21**, 3731 (1980).

⁹² T. Morita, Y. Okamoto, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 874 (1978); G. A. Olah, S. C. Narang, B. G. B. Gupta, and R. Malhotra, *Synthesis*, 61 (1979).

⁹³ T. L. Ho and G. A. Olah, *Synthesis*, 417 (1977); A. Benkeser, E. C. Mozdzen, and C. L. Muth, *J. Org. Chem.*, **44**, 2185 (1979).

CHAPTER 3

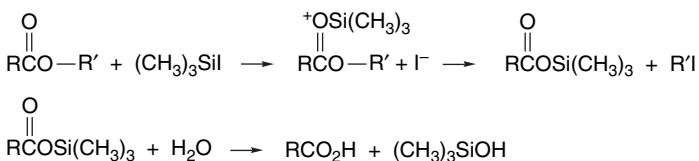
*Functional Group
Interconversion
by Substitution,
Including Protection and
Deprotection*



Ref. 94

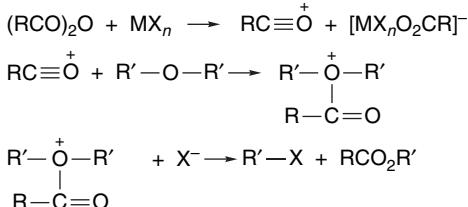
Diiiodosilane, SiH_2I_2 , is an especially effective reagent for cleaving secondary alkyl ethers.⁹⁵

TMSI also effects rapid cleavage of esters. The cleavage step involves iodide attack on the O-silylated ester. The first products formed are trimethylsilyl esters, but these are hydrolyzed rapidly on exposure to water.⁹⁶



Benzyl, methyl, and *t*-butyl esters are rapidly cleaved, but secondary esters react more slowly. In the case of *t*-butyl esters, the initial silylation is followed by a rapid ionization to the *t*-butyl cation.

Ether cleavage can also be effected by reaction with acetic anhydride and Lewis acids such as BF_3 , FeCl_3 , and MgBr_2 .⁹⁷ Mechanistic investigations point to acylium ions generated from the anhydride and Lewis acid as the reactive electrophile.



Scheme 3.3 gives some specific examples of ether and ester cleavage reactions. Entries 1 and 2 illustrate the use of boron tribromide for ether cleavage. The reactions are conducted at dry ice-acetone temperature and the exposure to water on workup hydrolyzes residual O–B bonds. In the case of Entry 2, the primary hydroxy group that is deprotected lactonizes spontaneously. The reaction in Entry 3 uses HBr in acetic acid to cleave a methyl aryl ether. This reaction was part of a scale-up of the synthesis of a drug candidate molecule. Entries 4 to 6 are examples of the cleavage of ethers and esters using TMSI. The selectivity exhibited in Entry 6 for

⁹⁴ A. Kamal, E. Laxman, and N. V. Rao, *Tetrahedron Lett.*, **40**, 371 (1999).

⁹⁵ E. Keinan and D. Perez, *J. Org. Chem.*, **52**, 4846 (1987).

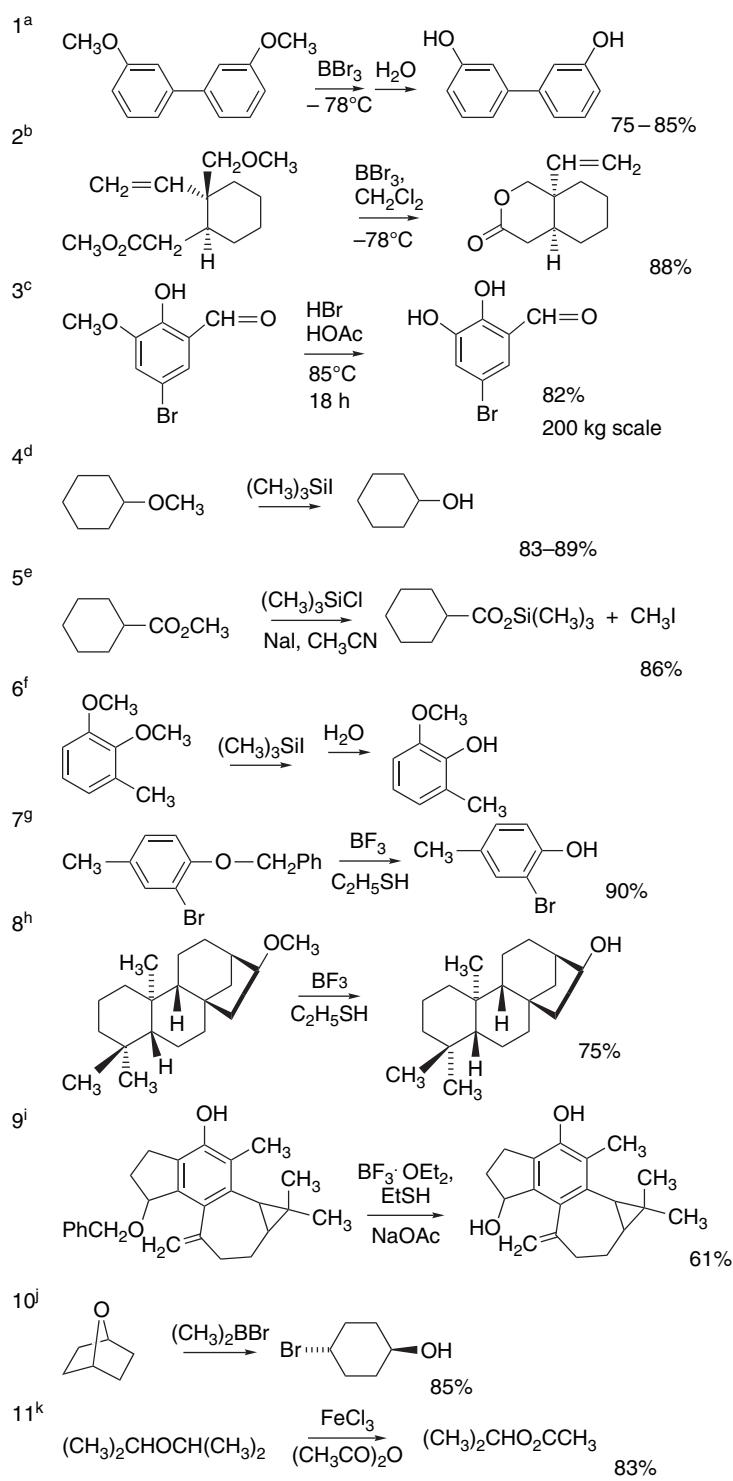
⁹⁶ T. L. Ho and G. A. Olah, *Angew. Chem. Int. Ed. Engl.*, **15**, 774 (1976); M. E. Jung and M. A. Lyster, *J. Am. Chem. Soc.*, **99**, 968 (1977).

⁹⁷ C. R. Narayanan and K. N. Iyer, *J. Org. Chem.*, **30**, 1734 (1965); B. Ganem and V. R. Small, Jr., *J. Org. Chem.*, **39**, 3728 (1974); D. J. Goldsmith, E. Kennedy, and R. G. Campbell, *J. Org. Chem.*, **40**, 3571 (1975).

Scheme 3.3. Cleavage of Ethers and Esters

SECTION 3.3

Cleavage of
Carbon-Oxygen Bonds
in Ethers and Esters



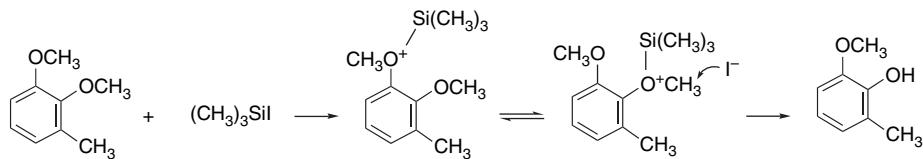
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CHAPTER 3

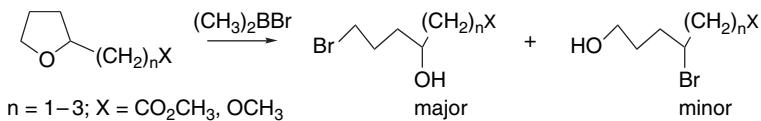
Functional Group
Interconversion
by Substitution,
Including Protection and
Deprotection

- a. J. F. W. McOmie and D. E. West, *Org. Synth.*, **V**, 412 (1973).
 b. P. A. Grieco, K. Hiroi, J. J. Reap, and J. A. Noguez, *J. Org. Chem.*, **40**, 1450 (1975).
 c. T. E. Jacks, D. T. Belmont, C. A. Briggs, N. M. Horne, G. D. Kanter, G. L. Karrick, J. J. Krikke, R. J. McCabe, J. G. Mustakis, T. N. Nanninga, G. S. Risendorph, R. E. Seamans, R. Skeean, D. D. Winkle, and T. M. Zennie, *Org. Proc. Res. Dev.*, **8**, 201 (2004).
 d. M. E. Jung and M. A. Lyster, *Org. Synth.*, **59**, 35 (1980).
 e. T. Morita, Y. Okamoto, and H. Sakurai, *J. Chem. Soc., Chem. Commun.*, 874 (1978).
 f. E. H. Vickery, L. F. Pahler, and E. J. Eisenbraun, *J. Org. Chem.*, **44**, 4444 (1979).
 g. K. Fuji, K. Ichikawa, M. Node, and E. Fujita, *J. Org. Chem.*, **44**, 1661 (1979).
 h. M. Nobe, H. Hori, and E. Fujita, *J. Chem. Soc. Perkin Trans.*, **1**, 2237 (1976).
 i. A. B. Smith, III, N. J. Liverton, N. J. Hrib, H. Sivaramakrishnan, and K. Winzenberg, *J. Am. Chem. Soc.*, **108**, 3040 (1986).
 j. Y. Guidon, M. Therien, Y. Girard, and C. Yoakim, *J. Org. Chem.*, **52**, 1680 (1987).
 k. B. Ganem and V. R. Small, Jr., *J. Org. Chem.*, **39**, 3728 (1974).

cleavage of the more hindered of the two ether groups may reflect a steric acceleration of the nucleophilic displacement step.



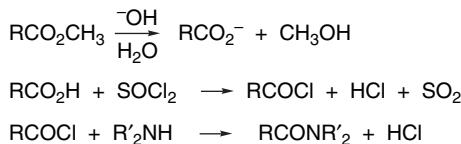
Entries 7 to 9 illustrate the use of the $\text{BF}_3\text{-EtSH}$ reagent combination. The reaction in Entry 9 was described as “troublesome in the extreme.” The problem is that the ether is both a primary benzylic ether and a secondary one, the latter associated with a ring having several ERG substituents. Electrophilic conditions lead to preferential cleavage of the secondary benzylic bond and formation of elimination products. The reaction was done successfully in the presence of excess NaOAc , which presumably allows the nucleophilic S_N2 cleavage of the primary benzyl bond to dominate by reducing the reactivity of the electrophilic species that are present. The cleavage of the cyclic ether shown in Entry 10 occurs with inversion of configuration at the reaction site, as demonstrated by the *trans* stereochemistry of the product. When applied to 2-substituted tetrahydrofurans, the reaction gives mainly cleavage of the $\text{C}(5)\text{-O}$ bond, indicating that steric access of the nucleophilic component of the reaction is dominant in determining regioselectivity.



Entry 11 illustrates a cleavage reaction using an acylating agent in conjunction with a Lewis acid.

3.4. Interconversion of Carboxylic Acid Derivatives

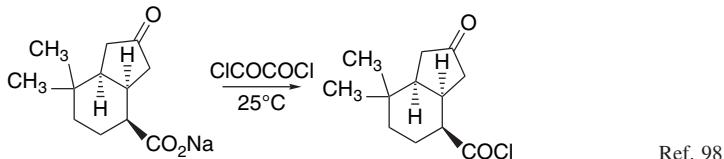
The classes of compounds that are conveniently considered together as derivatives of carboxylic acids include the acyl chlorides, carboxylic acid anhydrides, esters, and amides. In the case of simple aliphatic and aromatic acids, synthetic transformations



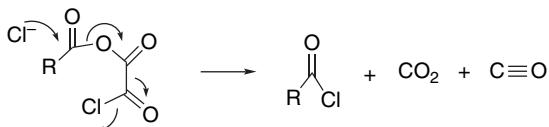
When a multistep synthesis is being undertaken with other sensitive functional groups present in the molecule, milder reagents and reaction conditions may be necessary. As a result, many alternative methods for effecting interconversion of the carboxylic acid derivatives have been developed and some of the most useful reactions are considered in the succeeding sections.

3.4.1. Acylation of Alcohols

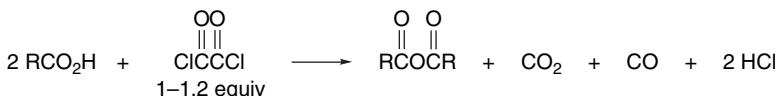
The traditional method for transforming carboxylic acids into reactive acylating agents capable of converting alcohols to esters or amines to amides is by formation of the acyl chloride. Molecules devoid of acid-sensitive functional groups can be converted to acyl chlorides with thionyl chloride or phosphorus pentachloride. When milder conditions are necessary, the reaction of the acid or its sodium salt with oxalyl chloride provides the acyl chloride. When a salt is used, the reaction solution remains essentially neutral.



This reaction involves formation of a mixed anhydride-chloride of oxalic acid, which then decomposes, generating both CO_2 and CO .



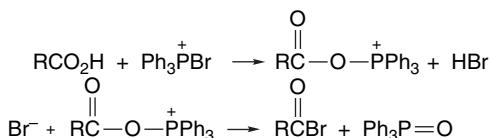
Treatment of carboxylic acids with half an equivalent of oxalyl chloride can generate anhydrides.⁹⁹



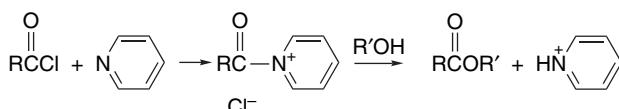
⁹⁸. M. Miyano and C. R. Dorn, *J. Org. Chem.*, **37**, 268 (1972).

⁹⁹. R. Adams and L. H. Urich, *J. Am. Chem. Soc.*, **42**, 599 (1920).

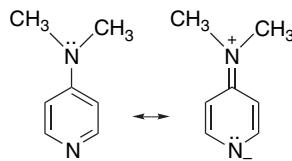
Carboxylic acids can be converted to acyl chlorides and bromides by a combination of triphenylphosphine and a halogen source. Triphenylphosphine and carbon tetrachloride convert acids to the corresponding acyl chloride.¹⁰⁰ Similarly, carboxylic acids react with the triphenyl phosphine-bromine adduct to give acyl bromides.¹⁰¹ Triphenylphosphine-*N*-bromosuccinimide also generates acyl bromide *in situ*.¹⁰² All these reactions involve acyloxyphosphonium ions and are mechanistically analogous to the alcohol-to-halide conversions that are discussed in Section 3.1.2.



Acyl chlorides are highly reactive acylating agents and react very rapidly with alcohols and other nucleophiles. Preparative procedures often call for use of pyridine as a catalyst. Pyridine catalysis involves initial formation of an acyl pyridinium ion, which then reacts with the alcohol. Pyridine is a better nucleophile than the neutral alcohol, but the acyl pyridinium ion reacts more rapidly with the alcohol than the acyl chloride.¹⁰³



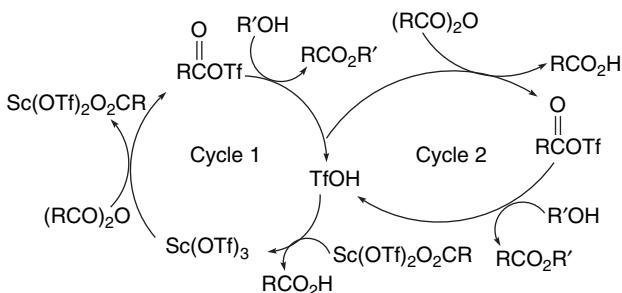
An even stronger catalytic effect is obtained when 4-dimethylaminopyridine (DMAP) is used.¹⁰⁴ The dimethylamino group acts as an electron donor, increasing both the nucleophilicity and basicity of the pyridine nitrogen.



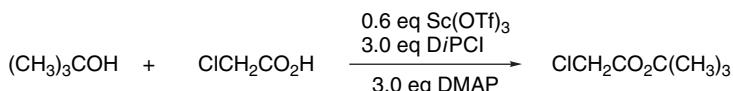
The inclusion of DMAP to the extent of 5–20 mol % in acylations by acid anhydrides and acyl chlorides increases acylation rates by up to four orders of magnitude and permits successful acylation of tertiary and other hindered alcohols. The reagent combination of an acid anhydride with MgBr₂ and a hindered tertiary amine, e.g., (i-Pr)₂NC₂H₅ or 1,2,2,6,6,-pentamethylpiperidine, gives an even more reactive acylation system, which is useful for hindered and sensitive alcohols.¹⁰⁵

- ¹⁰⁰. J. B. Lee, *J. Am. Chem. Soc.*, **88**, 3440 (1966).
- ¹⁰¹. H. J. Bestmann and L. Mott, *Justus Liebigs Ann. Chem.*, **693**, 132 (1966).
- ¹⁰². K. Sucheta, G. S. R. Reddy, D. Ravi, and N. Rama Rao, *Tetrahedron Lett.*, **35**, 4415 (1994).
- ¹⁰³. A. R. Fersht and W. P. Jencks, *J. Am. Chem. Soc.*, **92**, 5432, 5442 (1970).
- ¹⁰⁴. G. Hoefle, W. Steglich, and H. Vorbruggen, *Angew. Chem. Int. Ed. Engl.*, **17**, 569 (1978); E. F. V. Scriven, *Chem. Soc. Rev.*, **12**, 129 (1983); R. Murugan and E. F. V. Scriven, *Aldrichimica Acta*, **36**, 21 (2003).
- ¹⁰⁵. E. Vedejs and O. Daugulis, *J. Org. Chem.*, **61**, 5702 (1996).

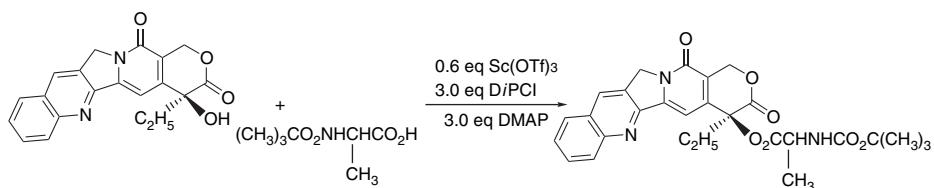
Another efficient catalyst for acylation is $\text{Sc}(\text{O}_3\text{SCF}_3)_3$, which can be used in combination with anhydrides¹⁰⁶ and other reactive acylating agents¹⁰⁷ and is a mild reagent for acylation of tertiary alcohols. Mechanistic investigation of $\text{Sc}(\text{O}_3\text{SCF}_3)_3$ -catalyzed acylation indicates that triflic acid is involved. Acylation is stopped by the presence of a sterically hindered base such as 2,6-di-(*t*-butyl)-4-methylpyridine. The active acylating agent appears to be the acyl triflate. Two catalytic cycles operate. Cycle 2 requires only triflic acid, whereas Cycle 1 involves both the scandium salt and triflic acid.¹⁰⁸



The acylation of tertiary alcohols can be effected by use of $\text{Sc}(\text{O}_3\text{SCF}_3)_3$ with diisopropylcarbodiimide (D-*i*-PCI) and DMAP.¹⁰⁹



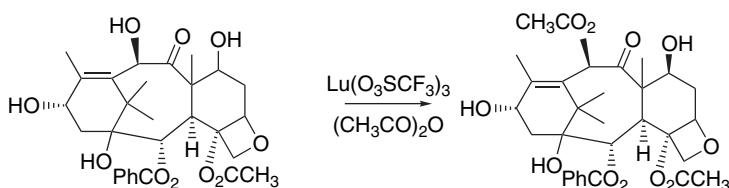
This method was effective for acylation of a hindered tertiary alcohol in the anticancer agent camptothecin by protected amino acids.



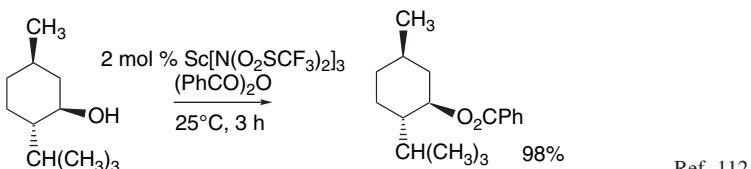
Ref. 110

Lanthanide triflates have similar catalytic effects. $\text{Yb}(\text{O}_3\text{SCF}_3)_3$ and $\text{Lu}(\text{O}_3\text{SCF}_3)_3$, for example, were used in selective acylation of 10-deacetylbaicatin III, an important intermediate for preparation of the antitumor agent paclitaxel.¹¹¹

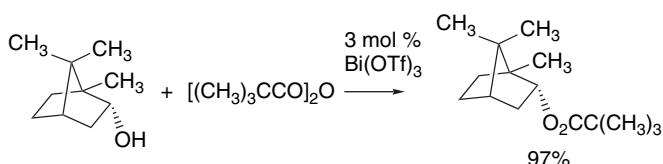
- ^{106.} K. Ishihara, M. Kubota, H. Kurihara, and H. Yamamoto, *J. Org. Chem.*, **61**, 4560 (1996); A. G. M. Barrett and D. C. Braddock, *J. Chem. Soc., Chem. Commun.*, 351 (1997).
- ^{107.} H. Zhao, A. Pendri, and R. B. Greenwald, *J. Org. Chem.*, **63**, 7559 (1998).
- ^{108.} R. Dummeunier and I. E. Marko, *Tetrahedron Lett.*, **45**, 825 (2004).
- ^{109.} H. Zhao, A. Pendri, and R. B. Greenwald, *J. Org. Chem.*, **63**, 7559 (1998).
- ^{110.} R. R. Greenwald, A. Pendri, and H. Zhao, *Tetrahedron: Asymmetry*, **9**, 915 (1998).
- ^{111.} E. W. P. Damen, L. Braamer, and H. W. Scheeren, *Tetrahedron Lett.*, **39**, 6081 (1998).



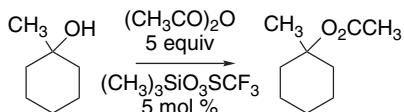
Scandium triflimidate, $\text{Sc}[\text{N}(\text{SO}_2\text{CF}_3)_2]_3$, is also a very active acylation catalyst.



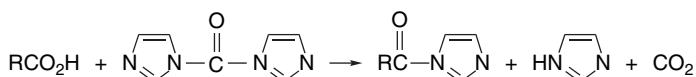
Bismuth(III) triflate is also a powerful acylation catalyst that catalyzes reactions with acetic anhydride and other less reactive anhydrides such as benzoic and pivalic anhydrides.¹¹³ Good results are achieved with tertiary and hindered secondary alcohols, as well as with alcohols containing acid- and base-sensitive functional groups.



Trimethylsilyl triflate is also a powerful catalyst for acylation by anhydrides. Reactions of alcohols with a modest excess (1.5 equiv) of anhydride proceed in inert solvents at 0°C. Even tertiary alcohols react rapidly.¹¹⁴ The active acylation reagent is presumably generated by O-silylation of the anhydride.



In addition to acyl halides and acid anhydrides, there are a number of milder and more selective acylating agents that can be readily prepared from carboxylic acids. Imidazolides, the *N*-acyl derivatives of imidazole, are examples.¹¹⁵ Imidazolides are isolable substances and can be prepared directly from the carboxylic acid by reaction with carbonyldiimidazole.



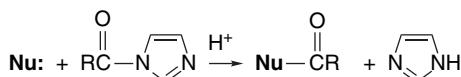
¹¹². K. Ishihara, M. Kubota, and H. Yamamoto, *Synlett*, 265 (1996).

¹¹³. A. Orita, C. Tanahashi, A. Kakuda, and J. Otera, *J. Org. Chem.*, **66**, 8926 (2001).

¹¹⁴. P. A. Procopiou, S. P. D. Baugh, S. S. Flack, and G. G. A. Inglis, *J. Org. Chem.*, **63**, 2342 (1998).

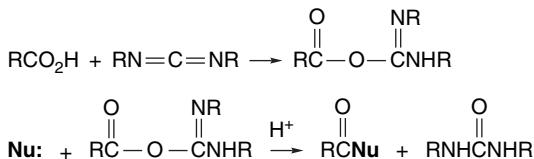
¹¹⁵. H. A. Staab and W. Rohr, *Newer Methods Prep. Org. Chem.*, **5**, 61 (1968).

Two factors are responsible for the reactivity of the imidazolides as acylating reagents. One is the relative weakness of the “amide” bond. Owing to the aromatic character of imidazole nitrogens, there is little of the $\text{N} \rightarrow \text{C}=\text{O}$ delocalization that stabilizes normal amides. The reactivity of the imidazolides is also enhanced by protonation of the other imidazole nitrogen, which makes the imidazole ring a better leaving group.

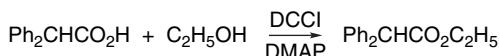


Imidazolides can also be activated by N-alkylation with methyl triflate.¹¹⁶ Imidazolides react with alcohols on heating to give esters and react at room temperature with amines to give amides. Imidazolides are particularly appropriate for acylation of acid-sensitive materials.

Dicyclohexylcarbodiimide (DCCI) is an example of a reagent that converts carboxylic acids to reactive acylating agents. This compound has been widely applied in the acylation step in the synthesis of polypeptides from amino acids¹¹⁷ (see also Section 13.3.1). The reactive species is an *O*-acyl isourea. The acyl group is highly reactive because the nitrogen is susceptible to protonation and the cleavage of the acyl-oxygen bond converts the carbon-nitrogen double bond of the isourea to a more stable carbonyl group.¹¹⁸



The combination of carboxyl activation by DCCI and catalysis by DMAP provides a useful method for *in situ* activation of carboxylic acids for reaction with alcohols. The reaction proceeds at room temperature.¹¹⁹



2-Chloropyridinium¹²⁰ and 3-chloroisoxazolium¹²¹ cations also activate carboxy groups toward nucleophilic attack. In each instance the halide is displaced from the heterocycle by the carboxylate via an addition-elimination mechanism. Nucleophilic attack on the activated carbonyl group results in elimination of the heterocyclic ring, with the departing oxygen being converted to an amidelike structure. The positive

¹¹⁶ G. Ulibarri, N. Choret, and D. C. H. Bigg, *Synthesis*, 1286 (1996).

¹¹⁷ F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, **67**, 107 (1967).

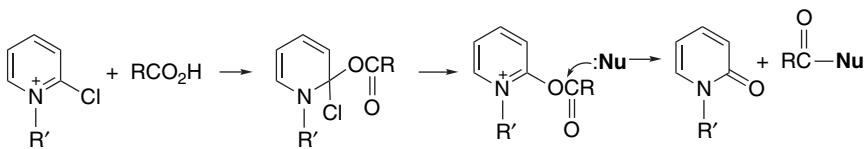
¹¹⁸ D. F. DeTar and R. Silverstein, *J. Am. Chem. Soc.*, **88**, 1013, 1020 (1966); D. F. DeTar, R. Silverstein, and F. F. Rogers, Jr., *J. Am. Chem. Soc.*, **88**, 1024 (1966).

¹¹⁹ A. Hassner and V. Alexanian, *Tetrahedron Lett.*, 4475 (1978); B. Neises and W. Steglich, *Angew. Chem. Int. Ed. Engl.*, **17**, 522 (1978).

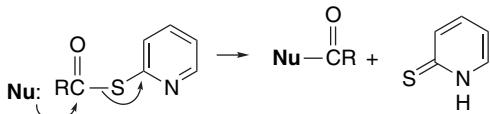
¹²⁰ T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, *Chem. Lett.*, 1045 (1975).

¹²¹ K. Tomita, S. Sugai, T. Kobayashi, and T. Murakami, *Chem. Pharm. Bull.*, **27**, 2398 (1979).

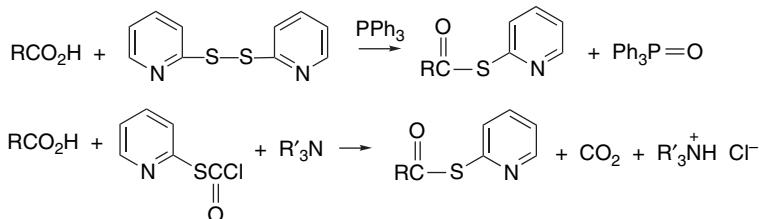
charge on the heterocyclic ring accelerates both the initial addition step and the subsequent elimination of the heterocycle.



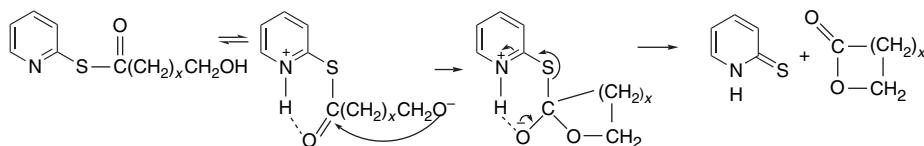
Carboxylic acid esters of thiols are considerably more reactive as acylating reagents than the esters of alcohols. Particularly reactive are esters of pyridine-2-thiol because there is an additional driving force in the formation of the more stable pyridine-2-thione tautomer.



Additional acceleration of acylation can be obtained by inclusion of cupric salts, which coordinate at the pyridine nitrogen. This modification is useful for the preparation of highly hindered esters.¹²² Pyridine-2-thiol esters can be prepared by reaction of the carboxylic acid with 2,2'-dipyridyl disulfide and triphenylphosphine¹²³ or directly from the acid and 2-pyridyl thiochloroformate.¹²⁴



The 2-pyridyl and related 2-imidazolyl disulfides have found special use in the closure of large lactone rings.¹²⁵ Structures of this type are encountered in a number of antibiotics and other natural products and require mild conditions for cyclization because numerous other sensitive functional groups are present. It has been suggested that the pyridyl and imidazoyl thioesters function by a mechanism in which the heterocyclic nitrogen acts as a base, deprotonating the alcohol group. This proton transfer provides a cyclic TS in which hydrogen bonding can enhance the reactivity of the carbonyl group.¹²⁶



¹²². S. Kim and J. I. Lee, *J. Org. Chem.*, **49**, 1712 (1984).

¹²³. T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, 1901 (1970).

¹²⁴. E. J. Corey and D. A. Clark, *Tetrahedron Lett.*, 2875 (1979).

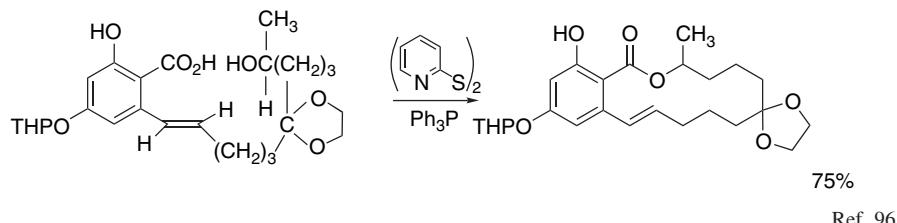
¹²⁵. E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974); K. C. Nicolaou, *Tetrahedron*, **33**, 683 (1977).

¹²⁶. E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., *J. Am. Chem. Soc.*, **97**, 654 (1975); E. J. Corey, D. J. Brunelle, and P. J. Stork, *Tetrahedron Lett.*, 3405 (1976).

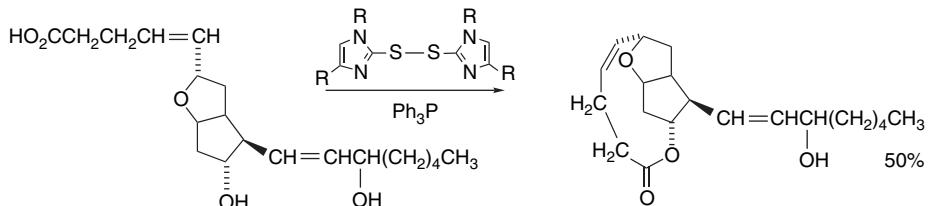
Good yields of large ring lactones are achieved by this method.

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SECTION 3.4
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Carboxylic Acid
Derivatives

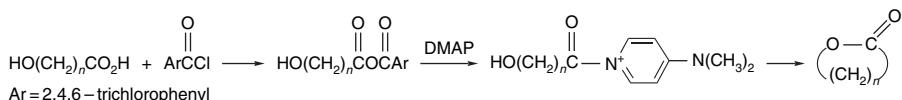


Ref. 96

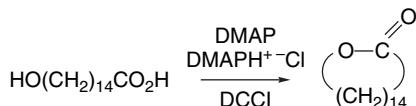


Ref. 127

Use of 2,4,6-trichlorobenzoyl chloride, Et_3N , and DMAP, known as the *Yamaguchi method*,¹²⁸ is frequently used to effect macrolactonization. The reaction is believed to involve formation of the mixed anhydride with the aryl chloride, which then forms an acyl pyridinium ion on reaction with DMAP.¹²⁹



Intramolecular lactonization can also be carried out with DCCI and DMAP. As with most other macrolactonizations, the reactions must be carried out in rather dilute solution to promote the intramolecular cyclization in competition with intermolecular reaction, which leads to dimers or higher oligomers. A study with 15-hydroxypentadecanoic acid demonstrated that a proton source is beneficial under these conditions and found the hydrochloride of DMAP to be convenient.¹³⁰



Scheme 3.4 gives some typical examples of the preparation and use of active acylating agents from carboxylic acids. Entries 1 and 2 show generation of acyl chlorides by reaction of carboxylic acids or salts with oxalyl chloride. Entry 3 shows a convenient preparation of 2-pyridylthio esters, which are themselves potential acylating agents (see p. 248). Entries 4 to 6 employ various coupling agents to form esters. Entries 7 and 8 illustrate acylations catalyzed by DMAP. Entries 9 to 13 are

¹²⁷ E. J. Corey, H. L. Pearce, I. Szekely, and M. Ishiguro, *Tetrahedron Lett.*, 1023 (1978).

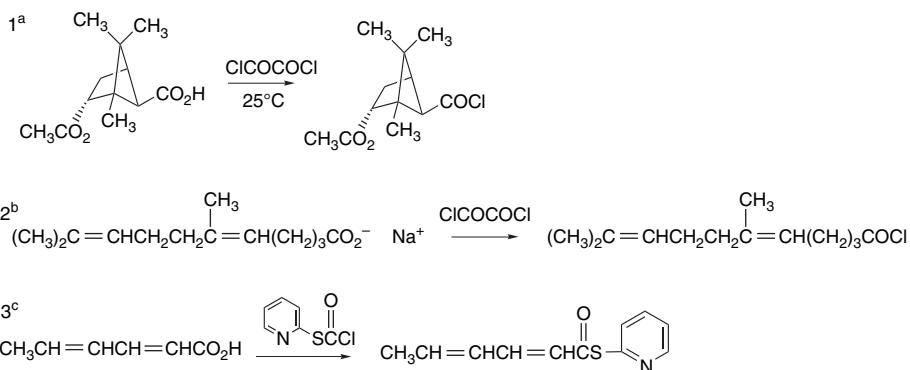
¹²⁸ H. Saiki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).

¹²⁹ M. Hikota, H. Tone, K. Horita, and O. Yonemitsu, *J. Org. Chem.*, **55**, 7 (1990).

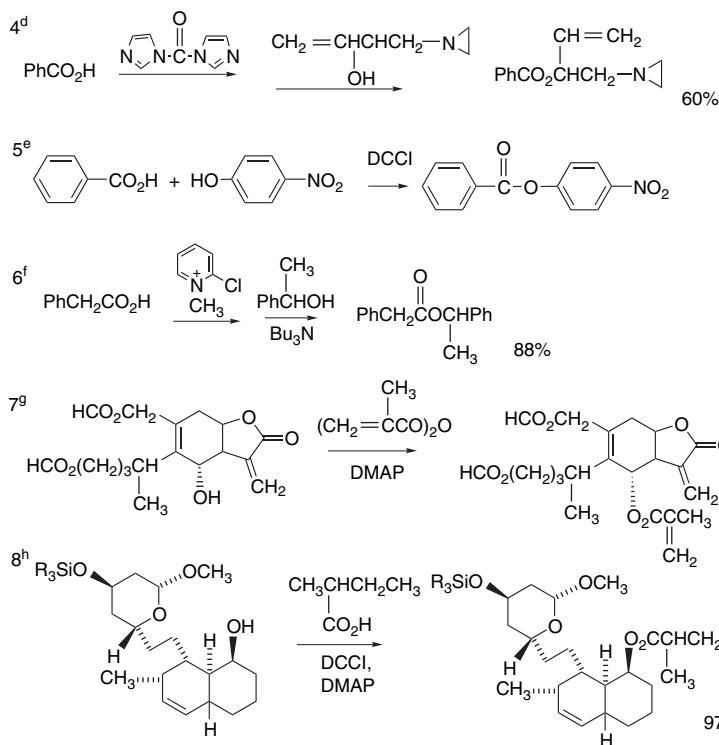
¹³⁰ E. P. Boden and G. E. Keck, *J. Org. Chem.*, **50**, 2394 (1985).

Scheme 3.4. Preparation and Reactions of Active Acylating Agents

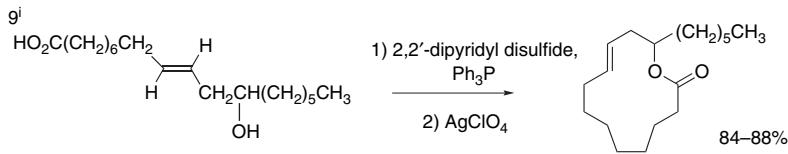
A. Generation of acylation reagents



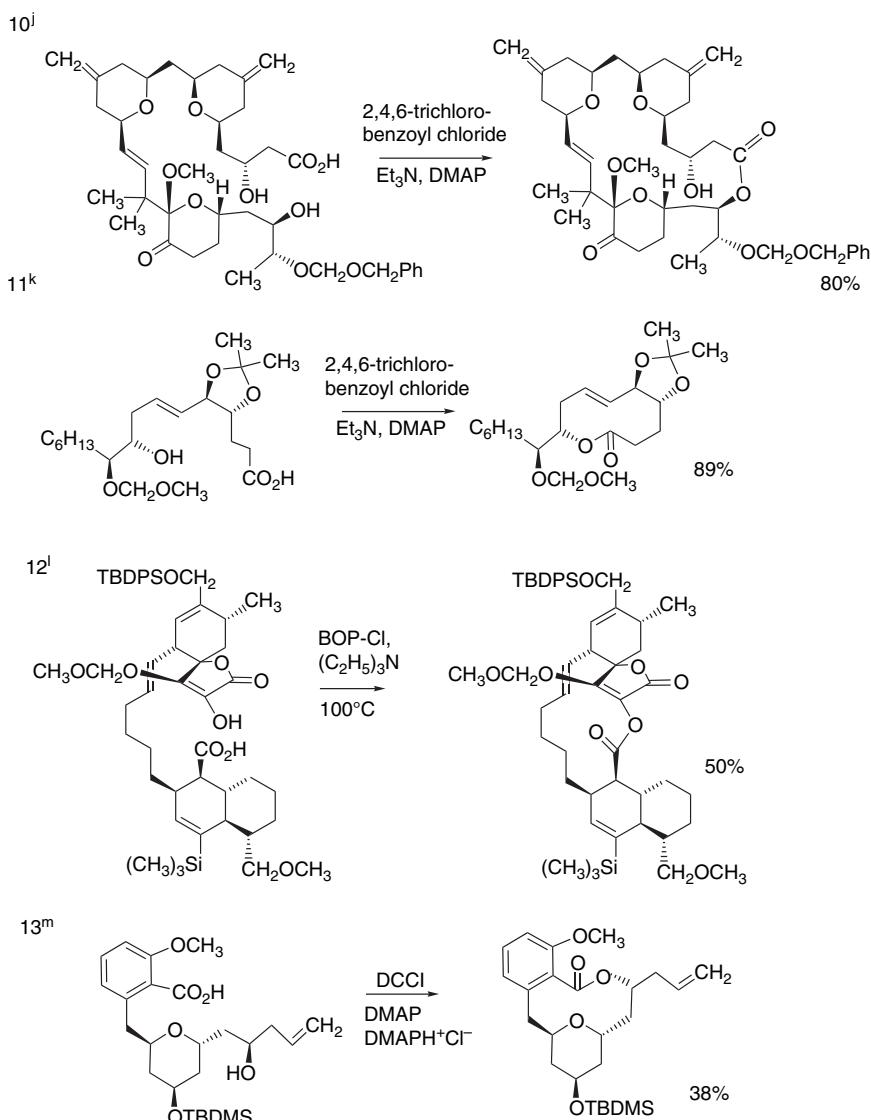
B. Esterification.



C. Macrolactonization



(Continued)

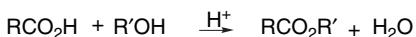


- a. J. Meinwald, J. C. Shelton, G. L. Buchanan, and A. Courtain, *J. Org. Chem.*, **33**, 99 (1968).
 b. U. T. Bhalerao, J. J. Plattner, and H. Rapoport, *J. Am. Chem. Soc.*, **92**, 3429 (1970).
 c. E. J. Corey and D. A. Clark, *Tetrahedron Lett.*, 2875 (1979).
 d. H. A. Staab and Rohr, *Chem. Ber.*, **95**, 1298 (1962).
 e. S. Neeklakantan, R. Padmasani, and T. R. Seshadri, *Tetrahedron*, **21**, 3531 (1965).
 f. T. Mukaiyama, M. Usui, E. Shimada, and K. Saigo, *Chem. Lett.*, 1045 (1970).
 g. P. A. Grieco, T. Oguri, S. Gilman, and G. DeTitta, *J. Am. Chem. Soc.*, **100**, 1616 (1978).
 h. Y.-L. Yang, S. Manna, and J. R. Falck, *J. Am. Chem. Soc.*, **106**, 3811 (1984).
 i. A. Thalman, K. Oertle, and H. Gerlach, *Org. Synth.*, **63**, 192 (1984).
 j. G. E. Keck and A. P. Troung, *Org. Lett.*, **7**, 2153 (2005).
 k. P. Kumar and S. V. Naidu, *J. Org. Chem.*, **70**, 4207 (2005).
 l. W. R. Roush and R. J. Sciotti, *J. Am. Chem. Soc.*, **120**, 7411 (1998).
 m. A. Lewis, I. Stefanuti, S. A. Swain, S. A. Smith, and R. J. K. Taylor, *Org. Biomol. Chem.*, **1**, 81 (2003)

examples of macrocyclizations. Entry 9 uses the di-2-pyridyl disulfide- Ph_3P method. The cyclization was done in approximately 0.02 M acetonitrile by dropwise addition of the disulfide. Entries 10 and 11 are examples of application of the Yamaguchi macrolactonization procedure via the mixed anhydride with 2,4,6-trichlorobenzoyl chloride. The reaction in Entry 12 uses BOP-Cl as the coupling reagent. This particular reagent gave the best results among the several alternatives that were explored. Further discussion of this reagent can be found in Section 13.3.1. Entry 13 is an example of the use of the DCCI-DMAP reagent combination.

3.4.2. Fischer Esterification

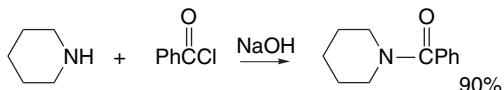
As noted in the preceding section, one of the most general methods of synthesis of esters is by reaction of alcohols with an acyl chloride or other activated carboxylic acid derivative. Section 3.2.5 dealt with two other important methods, namely, reactions with diazoalkanes and reactions of carboxylate salts with alkyl halides or sulfonate esters. There is also the acid-catalyzed reaction of carboxylic acids with alcohols, which is called the *Fischer esterification*.



This is an equilibrium process and two techniques are used to drive the reaction to completion. One is to use a large excess of the alcohol, which is feasible for simple and inexpensive alcohols. The second method is to drive the reaction forward by irreversible removal of water, and azeotropic distillation is one way to accomplish this. Entries 1 to 4 in Scheme 3.5 are examples of acid-catalyzed esterifications. Entry 5 is the preparation of a diester starting with an anhydride. The initial opening of the anhydride ring is followed by an acid-catalyzed esterification.

3.4.3. Preparation of Amides

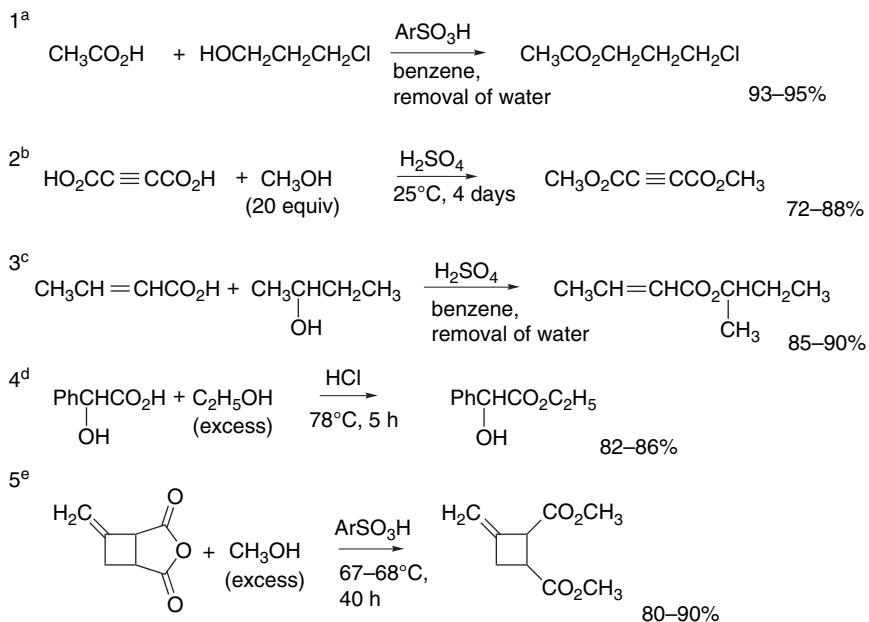
The most common method for preparation of amides is the reaction of ammonia or a primary or secondary amine with one of the reactive acylating reagents described in Section 3.4.1. Acid anhydrides give rapid acylation of most amines and are convenient if available. However, only one of the two acyl groups is converted to an amide. When acyl halides are used, some provision for neutralizing the hydrogen halide that is formed is necessary because it will react with the amine to form the corresponding salt. The *Schotten-Baumann conditions*, which involve shaking an amine with excess anhydride or acyl chloride and an alkaline aqueous solution, provide a very satisfactory method for preparation of simple amides.



Ref. 131

A great deal of work has been done on the *in situ* activation of carboxylic acids toward nucleophilic substitution by amines. This type of reaction is fundamental for synthesis of polypeptides (see also Section 13.3.1). Dicyclohexylcarbodiimide

¹³¹ C. S. Marvel and W. A. Lazier, *Org. Synth.*, I, 99 (1941).

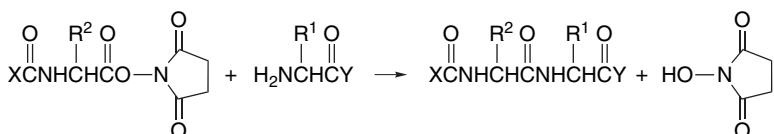


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Carboxylic Acid
Derivatives

- a. C. F. H. Allen and F. W. Spangler, *Org. Synth.*, **III**, 203 (1955).
 b. E. H. Huntress, T. E. Lesslie, and J. Bornstein, *Org. Synth.*, **IV**, 329 (1963).
 c. J. Munch-Petersen, *Org. Synth.*, **V**, 762 (1973).
 d. E. L. Eliel, M. T. Fisk, and T. Prosser, *Org. Synth.*, **IV**, 169 (1963).
 e. H. B. Stevenson, H. N. Cripps, and J. K. Williams, *Org. Synth.*, **V**, 459 (1973).

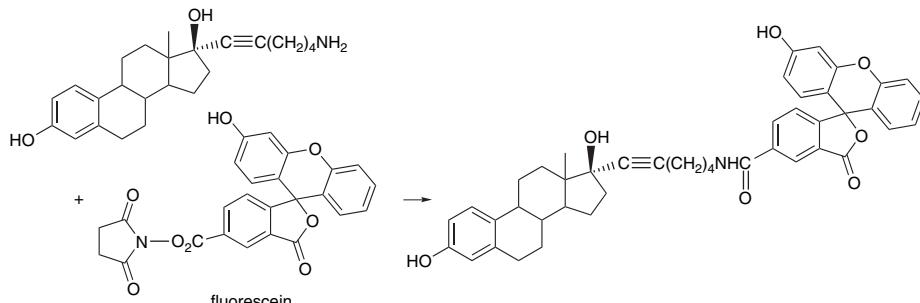
(DCCI) is often used for coupling carboxylic acids and amines to give amides. Since amines are better nucleophiles than alcohols, the leaving group in the acylation reagent need not be as reactive as is necessary for alcohols. The *p*-nitrophenyl¹³² and 2,4,5-trichlorophenyl¹³³ esters of amino acids are sufficiently reactive toward amines to be useful in amide synthesis. Acyl derivatives of *N*-hydroxysuccinimide are also useful for synthesis of peptides and other types of amides.^{134,135} Like the *p*-nitrophenyl esters, the acylated *N*-hydroxysuccinimides can be isolated and purified, but react rapidly with free amino groups.



The *N*-hydroxysuccinimide that is liberated is easily removed because of its solubility in dilute base. The relative stability of the anion of *N*-hydroxysuccinimide is also responsible for the acyl derivative being reactive toward nucleophilic attack by an

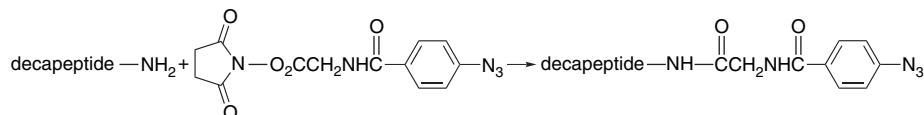
- ¹³². M. Bodanszky and V. DuVigneaud, *J. Am. Chem. Soc.*, **81**, 5688 (1959).
¹³³. J. Pless and R. A. Boissonnas, *Helv. Chim. Acta*, **46**, 1609 (1963).
¹³⁴. G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Am. Chem. Soc.*, **86**, 1839 (1964).
¹³⁵. E. Wunsch and F. Drees, *Chem. Ber.*, **99**, 110 (1966); E. Wunsch, A. Zwick, and G. Wendlberger, *Chem. Ber.*, **100**, 173 (1967).

amino group. Esters of *N*-hydroxysuccinimide are also used to carry out chemical modification of peptides, proteins, and other biological molecules by acylation of nucleophilic groups in these molecules. For example, detection of estradiol antibodies can be accomplished using an estradiol analog to which a fluorescent label has been attached.

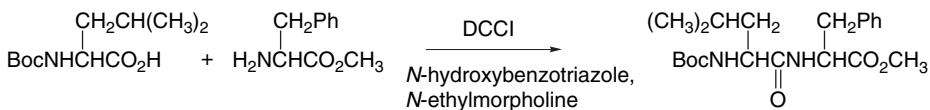


Ref. 136

Similarly, photolabels, such as 4-azidobenzoylglycine can be attached to peptides and used to detect binding sites in proteins.¹³⁷



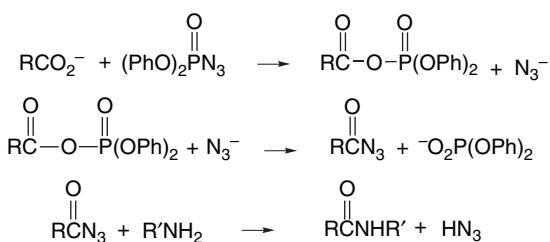
1-Hydroxybenzotriazole is also useful in conjunction with DCCI.¹³⁸ For example, Boc-protected leucine and the methyl ester of phenylalanine can be coupled in 88% yield with these reagents.



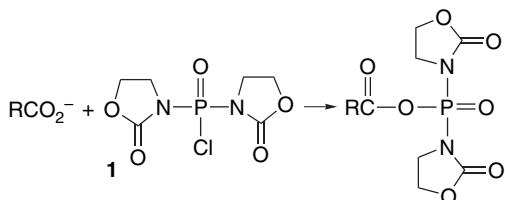
Ref. 139

Carboxylic acids can also be activated by the formation of mixed anhydrides with various phosphoric acid derivatives. Diphenyl phosphoryl azide, for example, is an effective reagent for conversion of amines to amides.¹⁴⁰ The proposed mechanism involves formation of the acyl azide as a reactive intermediate.

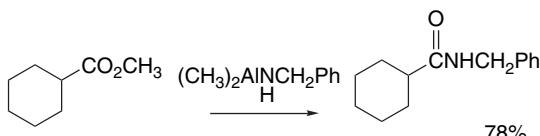
- ^{136.} M. Adamczyk, Y.-Y. Chen, J. A. Moore, and P. G. Mattingly, *Biorg. Med. Chem. Lett.*, **8**, 1281 (1998); M. Adamczyk, J. R. Fishpaugh, and K. J. Heuser, *Bioconjugate Chem.*, **8**, 253 (1997).
- ^{137.} G. C. Kundu, I. Ji, D. J. McCormick, and T. H. Ji, *J. Biol. Chem.*, **271**, 11063 (1996).
- ^{138.} W. Konig and R. Geiger, *Chem. Ber.*, **103**, 788 (1970).
- ^{139.} M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*, 2nd Edition, Springer-Verlag, Berlin, 1994, pp. 119–120.
- ^{140.} T. Shioiri and S. Yamada, *Chem. Pharm. Bull.*, **22**, 849 (1974); T. Shioiri and S. Yamada, *Chem. Pharm. Bull.*, **22**, 855 (1974); T. Shioiri and S. Yamada, *Chem. Pharm. Bull.*, **22**, 859 (1974).



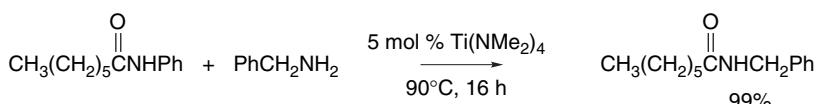
Another useful reagent for amide formation is compound **1**, known as BOP-Cl,¹⁴¹ which also proceeds by formation of a mixed carboxylic phosphoric anhydride.



Another method for converting esters to amides involves aluminum amides, which can be prepared from trimethylaluminum and the amine. These reagents convert esters directly to amides at room temperature.¹⁴²



The driving force for this reaction is the strength of the aluminum-oxygen bond relative to the aluminum-nitrogen bond. This reaction provides a good way of making synthetically useful amides of *N*-methoxy-*N*-methylamine.¹⁴³ Trialkylaminotin and *bis*-(hexamethyldisilylamido)tin amides, as well as *tetrakis*-(dimethylamino)titanium, show similar reactivity.¹⁴⁴ These reagents can also catalyze exchange reactions between amines and amides under moderate conditions.¹⁴⁵ For example, whereas exchange of benzylamine into *N*-phenylheptanamide occurs very slowly at 90°C in the absence of catalyst (> months), the conversion is effected in 16 h by $\text{Ti}[\text{N}(\text{CH}_3)_2]_4$.



¹⁴¹ J. Diago-Mesequer, A. L. Palomo-Coll, J. R. Fernandez-Lizarbe, and A. Zugaza-Bilbao, *Synthesis*, 547 (1980); R. D. Tung, M. K. Dhaon, and D. H. Rich, *J. Org. Chem.*, **51**, 3350 (1986); W. J. Collucci, R. D. Tung, J. A. Petri, and D. H. Rich, *J. Org. Chem.*, **55**, 2895 (1990); J. Jiang, W. R. Li, R. M. Przeslawski, and M. M. Joullie, *Tetrahedron Lett.*, **34**, 6705 (1993).

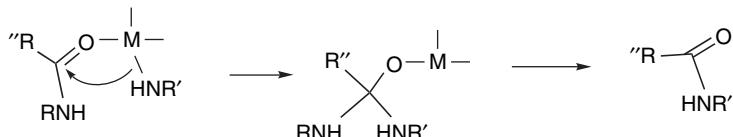
¹⁴² A. Basha, M. Lipton, and S. M. Weinreb, *Tetrahedron Lett.*, 4171 (1977); A. Solladie-Cavallo and M. Bencheqrone, *J. Org. Chem.*, **57**, 5831 (1992).

¹⁴³ J. I. Levin, E. Turos, and S. M. Weinreb, *Synth. Commun.*, **12**, 989 (1982); T. Shimizu, K. Osako, and T. Nakata, *Tetrahedron Lett.*, **38**, 2685 (1997).

¹⁴⁴ G. Chandra, T. A. George, and M. F. Lappert, *J. Chem. Soc. C*, 2565 (1969); W.-B. Wang and E. J. Roskamp, *J. Org. Chem.*, **57**, 6101 (1992); W.-B. Wang, J. A. Restituyo, and E. J. Roskamp, *Tetrahedron Lett.*, **34**, 7217 (1993).

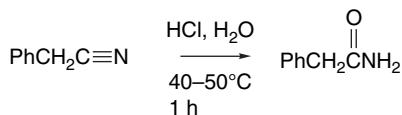
¹⁴⁵ S. E. Eldred, D. A. Stone, S. M. Gellman, and S. S. Stahl, *J. Am. Chem. Soc.*, **125**, 3423 (2003).

Tris-(dimethylamino)aluminum also promotes similar exchange reactions. The catalysis by titanium and aluminum amides may involve bifunctional catalysis in which the metal center acts as a Lewis acid while also delivering the nucleophilic amide.



Interestingly, $\text{Sc}(\text{O}_3\text{SCF}_3)_3$ is also an active catalyst for these exchange reactions.

The cyano group is at the carboxylic acid oxidation level, so nitriles are potential precursors of primary amides. Partial hydrolysis is sometimes possible.¹⁴⁶



A milder procedure involves the reaction of a nitrile with an alkaline solution of hydrogen peroxide.¹⁴⁷ The strongly nucleophilic hydrogen peroxide adds to the nitrile and the resulting adduct gives the amide. There are several possible mechanisms for the subsequent decomposition of the peroxycarboximidic adduct.¹⁴⁸



In all the mechanisms, the hydrogen peroxide is converted to oxygen and water, leaving the organic substrate hydrolyzed, but at the same oxidation level.

Scheme 3.6 illustrates some of the means of preparation of amides. Entries 1 and 2 are cases of preparation of simple amides by conversion of the carboxylic acid to an acyl chloride using SOCl_2 . Entry 3 is the acetylation of glycine by acetic anhydride. The reaction is done in concentrated aqueous solution ($\sim 3\text{ M}$) using a twofold excess of the anhydride. The reaction is exothermic and the product crystallizes from the reaction mixture when it is cooled. Entries 4 and 5 are ester aminolysis reactions. The cyano group is an activating group for the ester in Entry 4, and this reaction occurs at room temperature in concentrated ammonia solution. The reaction in Entry 5 involves a less nucleophilic and more hindered amine, but involves a relatively reactive aryl ester. A much higher temperature is required for this reaction. Entries 6 to 8 illustrate the use of several of the coupling reagents for preparation of amides. Entries 9 and 10 show preparation of primary amides by hydrolysis of nitriles. The first reaction involves partial hydrolysis, whereas the second is an example of peroxide-accelerated hydrolysis.

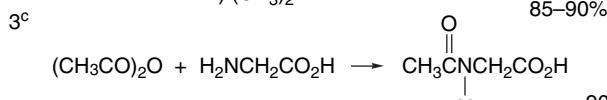
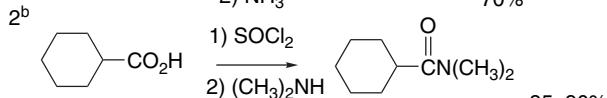
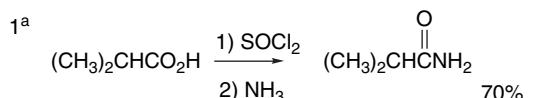
¹⁴⁶ W. Wenner, *Org. Synth.*, **IV**, 760 (1963).

¹⁴⁷ C. R. Noller, *Org. Synth.*, **II**, 586 (1943); J. S. Buck and W. S. Ide, *Org. Synth.*, **II**, 44 (1943).

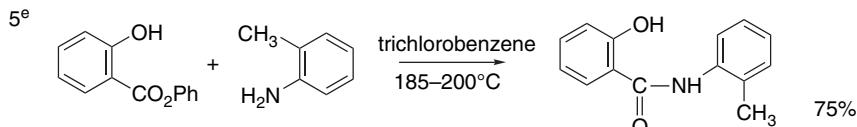
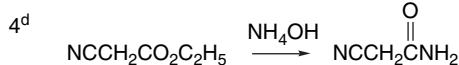
¹⁴⁸ K. B. Wiberg, *J. Am. Chem. Soc.*, **75**, 3961 (1953); *J. Am. Chem. Soc.*, **77**, 2519 (1955); J. E. McIsaac, Jr., R. E. Ball, and E. J. Behrman, *J. Org. Chem.*, **36**, 3048 (1971).

Scheme 3.6. Synthesis of Amides

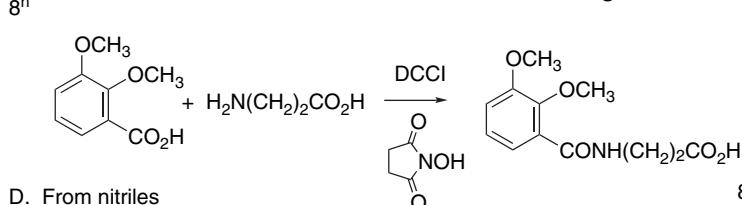
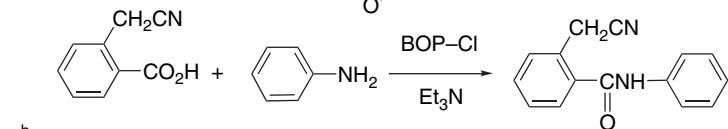
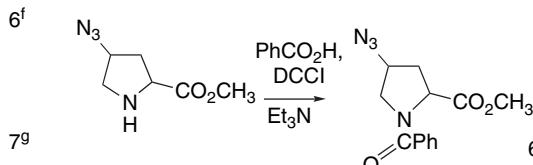
A. From acyl chlorides and anhydrides



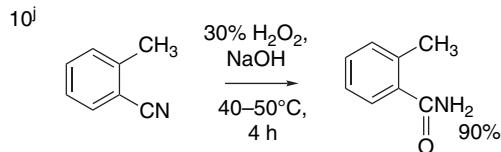
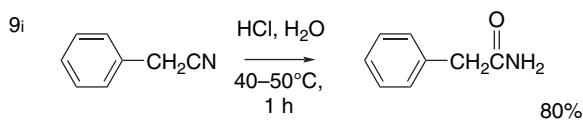
B. From esters



C. From carboxylic acids



D. From nitriles



(Continued)

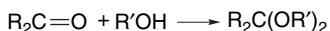
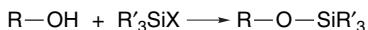
CHAPTER 3

*Functional Group
Interconversion
by Substitution,
Including Protection and
Deprotection*

- a. R. E. Kent and S. M. McElvain, *Org. Synth.*, **III**, 490 (1955).
- b. A. C. Cope and E. Ciganek, *Org. Synth.*, **IV**, 339 (1963).
- c. R. M. Herbst and D. Shemin, *Org. Synth.*, **II**, 11 (1943).
- d. B. B. Corson, R. W. Scott, and C. E. Vose, *Org. Synth.*, **I**, 179 (1941).
- e. C. F. H. Allen and J. Van Allen, *Org. Synth.*, **III**, 765 (1955).
- f. D. J. Abraham, M. Mokotoff, L. Sheh, and J. E. Simmons, *J. Med. Chem.*, **26**, 549 (1983).
- g. J. Diago-Mesenguer, A. L. Palamo-Coll, J. R. Fernandez-Lizarbe, and A. Zugaza-Bilbao, *Synthesis*, 547 (1980).
- h. R. J. Bergeron, S. J. Kline, N. J. Stolowich, K. A. McGovern, and P. S. Burton, *J. Org. Chem.*, **46**, 4524 (1981).
- i. W. Wenner, *Org. Synth.*, **IV**, 760 (1963).
- j. C. R. Noller, *Org. Synth.*, **II**, 586 (1943).

3.5. Installation and Removal of Protective Groups

Protective groups play a key role in multistep synthesis. When the synthetic target is a relatively complex molecule, a sequence of reactions that would be expected to lead to the desired product must be devised. At the present time, syntheses requiring 15–20 steps are common and many that are even longer have been completed. In the planning and execution of such multistep syntheses, an important consideration is the compatibility of the functional groups that are already present with the reaction conditions required for subsequent steps. It is frequently necessary to modify a functional group in order to prevent interference with some reaction in the synthetic sequence. A protective group can be put in place and then subsequently removed in order to prevent an undesired reaction or other adverse influence. For example, alcohols are often protected as trisubstituted silyl ethers and carbonyl groups as acetals. The silyl group masks both the acidity and nucleophilicity of the hydroxy group. An acetal group can prevent both unwanted nucleophilic additions or enolate formation at a carbonyl group.



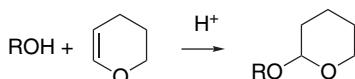
Three considerations are important in choosing an appropriate protective group: (1) the nature of the group requiring protection; (2) the reaction conditions under which the protective group must be stable; and (3) the conditions that can be tolerated for removal of the protecting group. No universal protective groups exist. The state of the art has been developed to a high level, however, and the many mutually complementary protective groups provide a great degree of flexibility in the design of syntheses of complex molecules.¹⁴⁹ Protective groups play a passive role in synthesis, but each operation of introduction and removal of a protective group adds steps to the synthetic sequence. It is thus desirable to minimize the number of such operations. Fortunately, the methods for protective group installation and removal have been highly developed and the yields are usually excellent.

3.5.1. Hydroxy-Protecting Groups

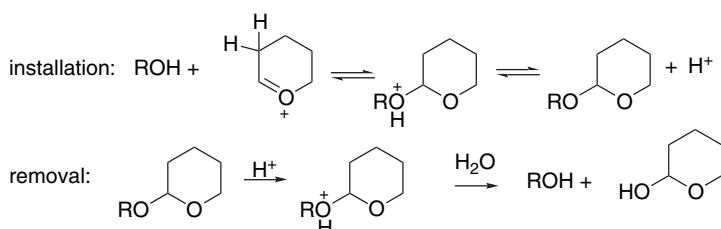
3.5.1.1. Acetals as Protective Groups. A common requirement in synthesis is that a hydroxy group be masked as a derivative lacking the proton. Examples of this requirement are reactions involving Grignard or other strongly basic organometallic

¹⁴⁹. T. W. Green and P. G. Wuts, *Protective Groups in Organic Synthesis*, 3rd Edition, Wiley, New York, 1999; P. J. Kocienski, *Protective Groups*, Thieme, New York, 2000.

reagents. The acidic proton of a hydroxy group will destroy one equivalent of a strongly basic organometallic reagent and possibly adversely affect the reaction in other ways. In some cases, protection of the hydroxy group also improves the solubility of alcohols in nonpolar solvents. The choice of the most appropriate group is largely dictated by the conditions that can be tolerated in subsequent removal of the protecting group. The tetrahydropyranyl ether (THP) is applicable when mildly acidic hydrolysis is an appropriate method for deprotection.¹⁵⁰ The THP group, like other acetals and ketals, is inert to basic and nucleophilic reagents and is unchanged under such conditions as hydride reduction, organometallic reactions, or base-catalyzed reactions in aqueous solution. It also protects the hydroxy group against oxidation. The THP group is introduced by an acid-catalyzed addition of the alcohol to the vinyl ether moiety in dihydropyran. *p*-Toluenesulfonic acid or its pyridinium salt are frequently used as the catalyst,¹⁵¹ although other catalysts are advantageous in special cases.



The THP group can be removed by dilute aqueous acid. The chemistry involved in both the introduction and deprotection stages is the reversible acid-catalyzed formation and hydrolysis of an acetal (see Part A, Section 7.1).



Various Lewis acids also promote hydrolysis of THP groups. Treatment with five equivalents of LiCl and ten equivalents of H₂O in DMSO removes THP groups in high yield.¹⁵² PdCl₂(CH₃CN)₂ smoothly removes THP groups from primary alcohols.¹⁵³ CuCl₂ is also reported to catalyze hydrolysis of the THP group.¹⁵⁴ These procedures may involve generation of protons by interaction of water with the metal cations.

A disadvantage of the THP group is the fact that a new stereogenic center is produced at C(2) of the tetrahydropyran ring. This presents no difficulties if the alcohol is achiral, since a racemic mixture results. However, if the alcohol is chiral, the reaction gives a mixture of diastereomers, which may complicate purification and/or characterization. One way of avoiding this problem is to use methyl 2-propenyl ether in place of dihydropyran (abbreviated MOP, for methoxypropyl). No new chiral center

¹⁵⁰ W. E. Parham and E. L. Anderson, *J. Am. Chem. Soc.*, **70**, 4187 (1948).

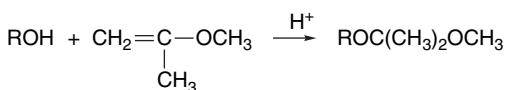
¹⁵¹ J. H. van Boom, J. D. M. Herscheid, and C. B. Reese, *Synthesis*, 169 (1973); M. Miyashita, A. Yoshikoshi, and P. A. Grieco, *J. Org. Chem.*, **42**, 3772 (1977).

¹⁵² G. Maiti and S. C. Roy, *J. Org. Chem.*, **61**, 6038 (1996).

¹⁵³ Y.-G. Wang, X.-X. Wu, and S.-Y. Jiang, *Tetrahedron Lett.*, **45**, 2973 (2004).

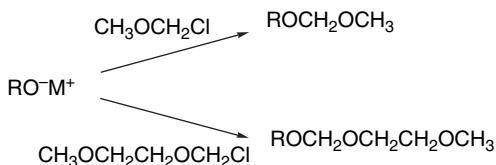
¹⁵⁴ J. K. Davis, U. T. Bhalerao, and B. V. Rao, *Ind. J. Chem. B*, **39B**, 860 (2000); J. Wang, C. Zhang, Z. Qu, Y. Hou, B. Chen, and P. Wu, *J. Chem. Res. Syn.*, 294 (1999).

is introduced, and this acetal offers the further advantage of being hydrolyzed under somewhat milder conditions than those required for THP ethers.¹⁵⁵

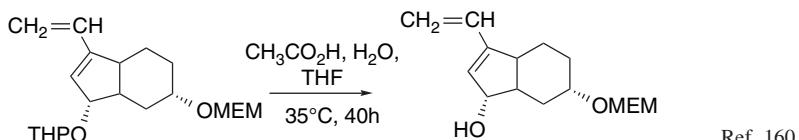


Ethyl vinyl ether is also useful for hydroxy group protection. The resulting derivative (1-ethoxyethyl ether) is abbreviated as the EE group.¹⁵⁶ As with the THP group, the EE group introduces an additional stereogenic center.

The methoxymethyl (MOM) and β -methoxyethoxymethyl (MEM) groups are used to protect alcohols and phenols as formaldehyde acetals. These groups are normally introduced by reaction of an alkali metal salt of the alcohol with methoxymethyl chloride or β -methoxyethoxymethyl chloride.¹⁵⁷



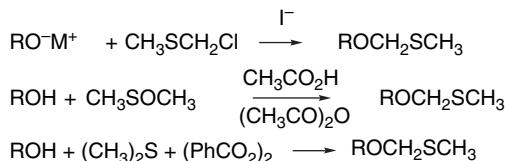
The MOM and MEM groups can be cleaved by pyridinium tosylate in moist organic solvents.¹⁵⁸ An attractive feature of the MEM group is the ease with which it can be removed under nonaqueous conditions. Reagents such as zinc bromide, magnesium bromide, titanium tetrachloride, dimethylboron bromide, or trimethylsilyl iodide permit its removal.¹⁵⁹ The MEM group is cleaved in preference to the MOM or THP groups under these conditions. Conversely, the MEM group is more stable to acidic aqueous hydrolysis than the THP group. These relative reactivity relationships allow the THP and MEM groups to be used in a complementary fashion when two hydroxy groups must be deprotected at different points in a synthetic sequence.



The methylthiomethyl (MTM) group is a related alcohol-protecting group. There are several methods for introducing the MTM group. Alkylation of an alcoholate by

- ¹⁵⁵. A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 7827 (1972).
- ¹⁵⁶. H. J. Sims, H. B. Parseghian, and P. L. DeBenneville, *J. Org. Chem.*, **23**, 724 (1958).
- ¹⁵⁷. G. Stork and T. Takahashi, *J. Am. Chem. Soc.*, **99**, 1275 (1977); R. J. Linderman, M. Jaber, and B. D. Griedel, *J. Org. Chem.*, **59**, 6499 (1994); P. Kumar, S. V. N. Raju, R. S. Reddy, and B. Pandey, *Tetrahedron Lett.*, **35**, 1289 (1994).
- ¹⁵⁸. H. Monti, G. Leandri, M. Klos-Ringuet, and C. Corriol, *Synth. Commun.*, **13**, 1021 (1983); M. A. Tius and A. M. Fauq, *J. Am. Chem. Soc.*, **108**, 1035 (1986).
- ¹⁵⁹. E. J. Corey, J.-L. Gras, and P. Ulrich, *Tetrahedron Lett.*, 809 (1976); Y. Quindon, H. E. Morton, and C. Yoakim, *Tetrahedron Lett.*, **24**, 3969 (1983); J. H. Rigby and J. Z. Wilson, *Tetrahedron Lett.*, **25**, 1429 (1984); S. Kim, Y. H. Park, and I. S. Kee, *Tetrahedron Lett.*, **32**, 3099 (1991).
- ¹⁶⁰. E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.*, **100**, 8031 (1978).

methylthiomethyl chloride is efficient if catalyzed by iodide ion.¹⁶¹ Alcohols are also converted to MTM ethers by reaction with dimethyl sulfoxide in the presence of acetic acid and acetic anhydride,¹⁶² or with benzoyl peroxide and dimethyl sulfide.¹⁶³ The latter two methods involve the generation of the methylthiomethyl lithium ion by ionization of an acyloxysulfonium ion (Pummerer reaction).

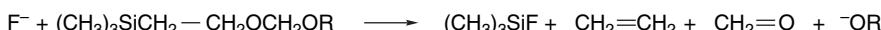


The MTM group is selectively removed under nonacidic conditions in aqueous solutions containing Ag^+ or Hg^{2+} salts. The THP and MOM groups are stable under these conditions.¹⁶¹ The MTM group can also be removed by reaction with methyl iodide, followed by hydrolysis of the resulting sulfonium salt in moist acetone.¹⁶²

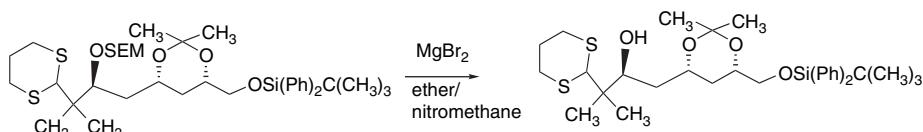
Two substituted alkoxymethoxy groups are designed for cleavage involving β -elimination. The 2,2,2-trichloroethoxymethyl groups can be cleaved by reducing agents, including zinc, samarium diiodide, and sodium amalgam.¹⁶⁴ The β -elimination results in the formation of a formaldehyde hemiacetal, which decomposes easily.



The 2-(trimethylsilyl)ethoxymethyl group (SEM) can be removed by various fluoride sources, including TBAF, pyridinium fluoride, and HF.¹⁶⁵ This deprotection involves nucleophilic attack at silicon, which triggers β -elimination.



The SEM group can also be cleaved by MgBr_2 . A noteworthy aspect of this method is that trisubstituted silyl ethers (see below) can survive.



Ref. 166

¹⁶¹ E. J. Corey and M. G. Bock, *Tetrahedron Lett.*, 3269 (1975).

¹⁶² P. M. Pojer and S. J. Angyal, *Tetrahedron Lett.*, 3067 (1976).

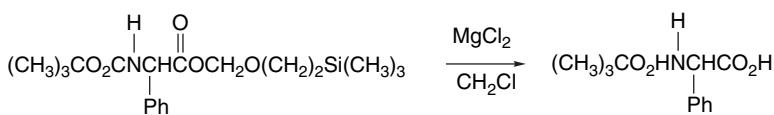
¹⁶³ J. C. Modina, M. Salomon, and K. S. Kyler, *Tetrahedron Lett.*, **29**, 3773 (1988).

¹⁶⁴ R. M. Jacobson and J. W. Clader, *Synth. Commun.*, **9**, 57 (1979); D. A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy, and T. J. Stout, *J. Am. Chem. Soc.*, **112**, 7001 (1990).

¹⁶⁵ B. H. Lipshutz and J. J. Pegram, *Tetrahedron Lett.*, **21**, 3343 (1980); B. H. Lipshutz and T. A. Miller, *Tetrahedron Lett.*, **30**, 7149 (1989); T. Kan, M. Hashimoto, M. Yanagiya, and H. Shirahama, *Tetrahedron Lett.*, **29**, 5417 (1988); J. D. White and M. Kawasaki, *J. Am. Chem. Soc.*, **112**, 4991 (1990); K. Sugita, K. Shigeno, C. F. Neville, H. Sasai, and M. Shibasaki, *Synlett*, 325 (1994).

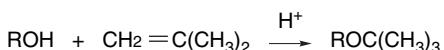
¹⁶⁶ A. Vakalopoulos and H. M. R. Hoffmann, *Org. Lett.*, **2**, 1447 (2000).

MgBr₂ removal of SEM groups is also useful for deprotection of carboxy groups in N-protected amino acids.



Ref. 167

3.5.1.2. Ethers as Protective Groups. The simple alkyl groups are generally not very useful for protection of alcohols as ethers. Although they can be introduced readily by alkylation, subsequent cleavage requires strongly electrophilic reagents such as boron tribromide (see Section 3.3). The *t*-butyl group is an exception and has found some use as a hydroxy-protecting group. Owing to the stability of the *t*-butyl cation, *t*-butyl ethers can be cleaved under moderately acidic conditions. Trifluoroacetic acid in an inert solvent is frequently used.¹⁶⁸ *t*-Butyl ethers can also be cleaved by acetic anhydride–FeCl₃ in ether.¹⁶⁹ The *t*-butyl group is normally introduced by reaction of the alcohol with isobutylene in the presence of an acid catalyst.¹⁷⁰ Acidic ion exchange resins are effective catalysts.¹⁷¹

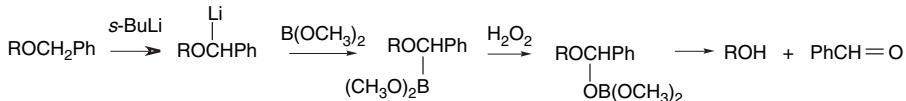


The triphenylmethyl (trityl, abbreviated Tr) group is removed under even milder conditions than the *t*-butyl group and is an important hydroxy-protecting group, especially in carbohydrate chemistry.¹⁷² This group is introduced by reaction of the alcohol with triphenylmethyl chloride via an S_N1 substitution. Owing to their steric bulk, triarylmethyl groups are usually introduced only at primary hydroxy groups. Reactions at secondary hydroxy groups can be achieved using stronger organic bases such as DBU.¹⁷³ Hot aqueous acetic acid suffices to remove the trityl group. The ease of removal can be increased by addition of ERG substituents. The *p*-methoxy (PMTr) and *p,p'*-dimethoxy (DMTr) derivatives are used in this way.¹⁷⁴ Trityl groups can also be removed oxidatively using Ce(NH₃)₆(NO₃)₃ (CAN) on silica.¹⁷⁵ This method involves a single-electron oxidation and, as expected, the rate of reaction is DMTr > PMTr > Tr. The DMTr group is especially important in the protection of primary hydroxy groups in nucleotide synthesis (see Section 13.3.2).

The benzyl group can serve as a hydroxy-protecting group if acidic conditions for ether cleavage cannot be tolerated. The benzyl C–O bond is cleaved by catalytic hydrogenolysis,¹⁷⁶ or by electron-transfer reduction using sodium in liquid ammonia or

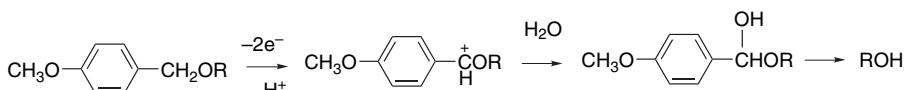
- ^{167.} W.-C. Chen, M. D. Vera, and M. M. Joullie, *Tetrahedron Lett.*, **38**, 4025 (1997).
- ^{168.} H. C. Beyerman and G. J. Heiszwolf, *J. Chem. Soc.*, 755 (1963).
- ^{169.} B. Ganem and V. R. Small, Jr., *J. Org. Chem.*, **39**, 3728 (1974).
- ^{170.} J. L. Holcombe and T. Livinghouse, *J. Org. Chem.*, **51**, 111 (1986).
- ^{171.} A. Alexakis, M. Gardette, and S. Colin, *Tetrahedron Lett.*, **29**, 2951 (1988).
- ^{172.} O. Hernandez, S. K. Chaudhary, R. H. Cox, and J. Porter, *Tetrahedron Lett.*, **22**, 1491 (1981); S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, **20**, 95 (1979).
- ^{173.} S. Colin-Messager, J.-P. Girard, and J.-C. Rossi, *Tetrahedron Lett.*, **33**, 2689 (1992).
- ^{174.} M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 430 (1962).
- ^{175.} J. R. Hwu, M. L. Jain, F.-Y. Tsai, S.-C. Tsay, A. Balakumar, and G. H. Hakimelahi, *J. Org. Chem.*, **65**, 5077 (2000).
- ^{176.} W. H. Hartung and R. Simonoff, *Org. React.*, **7**, 263 (1953).

aromatic radical anions.¹⁷⁷ Benzyl ethers can also be cleaved using formic acid, cyclohexene, or cyclohexadiene as hydrogen sources in transfer hydrogenolysis catalyzed by platinum or palladium.¹⁷⁸ Several nonreductive methods for cleavage of benzyl ether groups have also been developed. Treatment with *s*-butyllithium, followed by reaction with trimethyl borate and then hydrogen peroxide liberates the alcohol.¹⁷⁹ The lithiated ether forms an alkyl boronate, which is oxidized as discussed in Section 4.5.2.



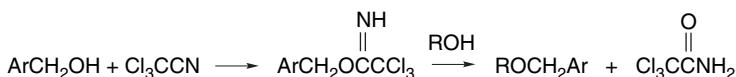
Lewis acids such as FeCl_3 and SnCl_4 also cleave benzyl ethers.¹⁸⁰

Benzyl groups having 4-methoxy (PMB) or 3,5-dimethoxy (DMB) substituents can be removed oxidatively by dichlorodicyanoquinone (DDQ).¹⁸¹ These reactions presumably proceed through a benzylic cation and the methoxy substituent is necessary to facilitate the oxidation.



These reaction conditions do not affect most of the other common hydroxy-protecting groups and the methoxybenzyl group is therefore useful in synthetic sequences that require selective deprotection of different hydroxy groups. 4-Methoxybenzyl ethers can also be selectively cleaved by dimethylboron bromide.¹⁸²

Benzyl groups are usually introduced by the Williamson reaction (Section 3.2.3). They can also be prepared under nonbasic conditions if necessary. Benzyl alcohols are converted to trichloroacetimidates by reaction with trichloroacetonitrile. These then react with an alcohol to transfer the benzyl group.¹⁸³



Phenyldiazomethane can also be used to introduce benzyl groups.¹⁸⁴

- ¹⁷⁷ E. J. Reist, V. J. Bartuska, and L. Goodman, *J. Org. Chem.*, **29**, 3725 (1964); R. E. Ireland, D. W. Norbeck, G. S. Mandel, and N. S. Mandel, *J. Am. Chem. Soc.*, **107**, 3285 (1985); R. E. Ireland and M. G. Smith, *J. Am. Chem. Soc.*, **110**, 854 (1988); H.-J. Liu, J. Yip, and K.-S. Shia, *Tetrahedron Lett.*, **38**, 2253 (1997).
- ¹⁷⁸ B. El Amin, G. M. Anatharamaiah, G. P. Royer, and G. E. Means, *J. Org. Chem.*, **44**, 3442 (1979); A. M. Felix, E. P. Heimer, T. J. Lambros, C. Tzougraki, and J. Meienhofer, *J. Org. Chem.*, **43**, 4194 (1978); A. E. Jackson and R. A. W. Johnstone, *Synthesis*, 685 (1976); G. M. Anatharamaiah and K. M. Sivandaiah, *J. Chem. Soc., Perkin Trans.*, **I**, 490 (1977).
- ¹⁷⁹ D. A. Evans, C. E. Sacks, W. A. Kleschick, and T. R. Taber, *J. Am. Chem. Soc.*, **101**, 6789 (1979).
- ¹⁸⁰ M. H. Park, R. Takeda, and K. Nakanishi, *Tetrahedron Lett.*, **28**, 3823 (1987).
- ¹⁸¹ Y. Oikawa, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, **23**, 885 (1982); Y. Oikawa, T. Tanaka, K. Horita, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, **25**, 5393 (1984); N. Nakajima, T. Hamada, T. Tanaka, Y. Oikawa, and O. Yonemitsu, *J. Am. Chem. Soc.*, **108**, 4645 (1986).
- ¹⁸² N. Hebert, A. Beck, R. B. Lennox, and G. Just, *J. Org. Chem.*, **57**, 1777 (1992).
- ¹⁸³ H.-P. Wessel, T. Iverson, and D. R. Bundle, *J. Chem. Soc., Perkin Trans.*, **I**, 2247 (1985); N. Nakajima, K. Horita, R. Abe, and O. Yonemitsu, *Tetrahedron Lett.*, **29**, 4139 (1988); S. J. Danishefsky, S. DeNinno, and P. Lartey, *J. Am. Chem. Soc.*, **109**, 2082 (1987).
- ¹⁸⁴ L. J. Liotta and B. Ganem, *Tetrahedron Lett.*, **30**, 4759 (1989).

4-Methoxyphenyl (PMP) ethers find occasional use as hydroxy protecting groups. Unlike benzylic groups, they cannot be made directly from the alcohol. Instead, the phenoxy group must be introduced by a nucleophilic substitution.¹⁸⁵ Mitsunobu conditions are frequently used.¹⁸⁶ The PMP group can be cleaved by oxidation with CAN.

Allyl ethers can be removed by conversion to propenyl ethers, followed by acidic hydrolysis of the resulting enol ether.



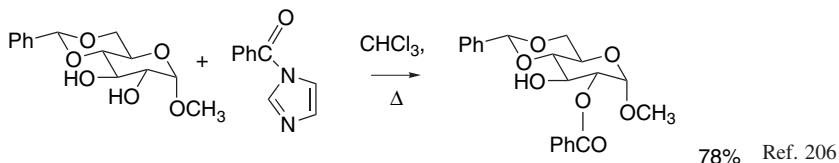
The isomerization of an allyl ether to a propenyl ether can be achieved either by treatment with potassium *t*-butoxide in dimethyl sulfoxide¹⁸⁷ or by catalysts such as Rh(PPh₃)₃Cl¹⁸⁸ or RhH(PPh₃)₄.¹⁸⁹ Heating allyl ethers with Pd-C in acidic methanol can also effect cleavage of allyl ethers.¹⁹⁰ This reaction, too, is believed to involve isomerization to the 1-propenyl ether. Other very mild conditions for allyl group cleavage include Wacker oxidation conditions¹⁹¹ (see Section 8.2.1) and DiBAIH with catalytic NiCl₂(dppp).¹⁹²

3.5.1.3. Silyl Ethers as Protective Groups. Silyl ethers play a very important role as hydroxy-protecting groups.¹⁹³ Alcohols can be easily converted to trimethylsilyl (TMS) ethers by reaction with trimethylsilyl chloride in the presence of an amine or by heating with hexamethyldisilazane. Trimethylsilyl groups are easily removed by hydrolysis or by exposure to fluoride ions. *t*-Butyldimethylsilyl (TBDMS) ethers are also very useful. The increased steric bulk of the TBDMS group improves the stability of the group toward such reactions as hydride reduction and Cr(VI) oxidation. The TBDMS group is normally introduced using a tertiary amine as a catalyst in the reaction of the alcohol with *t*-butyldimethylsilyl chloride or triflate. Cleavage of the TBDMS group is slow under hydrolytic conditions, but anhydrous tetra-*n*-butylammonium fluoride (TBAF),¹⁹⁴ methanolic NH₄F,¹⁹⁵ aqueous HF,¹⁹⁶ BF₃,¹⁹⁷ or SiF₄¹⁹⁸ can be used for its removal. Other highly substituted silyl groups, such as dimethyl(1,2,2-trimethylpropyl)silyl¹⁹⁹ and *tris*-isopropylsilyl,²⁰⁰ (TIPS) are even more

- ^{185.} Y. Masaki, K. Yoshizawa, and A. Itoh, *Tetrahedron Lett.*, **37**, 9321 (1996); S. Takano, M. Moriya, M. Suzuki, Y. Iwabuchi, T. Sugihara, and K. Ogasawara, *Heterocycles*, **31**, 1555 (1990).
- ^{186.} T. Fukuyama, A. A. Laird, and L. M. Hotchkiss, *Tetrahedron Lett.*, **26**, 6291 (1985); M. Petitou, P. Duchaussy, and J. Choay, *Tetrahedron Lett.*, **29**, 1389 (1988).
- ^{187.} R. Griggs and C. D. Warren, *J. Chem. Soc. C*, 1903 (1968).
- ^{188.} E. J. Corey and J. W. Suggs, *J. Org. Chem.*, **38**, 3224 (1973).
- ^{189.} F. E. Ziegler, E. G. Brown, and S. B. Sobolov, *J. Org. Chem.*, **55**, 3691 (1990).
- ^{190.} R. Boss and R Scheffold, *Angew. Chem. Int. Ed. Engl.*, **15**, 558 (1976).
- ^{191.} H. B. Mereyala and S. Guntha, *Tetrahedron Lett.*, **34**, 6929 (1993).
- ^{192.} T. Taniguchi and K. Ogasawara, *Angew. Chem. Int. Ed. Engl.*, **37**, 1136 (1998).
- ^{193.} J. F. Klebe, in *Advances in Organic Chemistry: Methods and Results*, Vol. 8, E. C. Taylor, ed., Wiley-Interscience, New York, 1972, pp. 97–178; A. E. Pierce, *Silylation of Organic Compounds*, Pierce Chemical Company, Rockford, IL, 1968.
- ^{194.} E. J. Corey and A. Venkataswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
- ^{195.} W. Zhang and M. J. Robins, *Tetrahedron Lett.*, **33**, 1177 (1992).
- ^{196.} R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, and S. M. Roberts, *Tetrahedron Lett.*, 3981 (1979).
- ^{197.} D. R. Kelly, S. M. Roberts, and R. F. Newton, *Synth. Commun.*, **9**, 295 (1979).
- ^{198.} E. J. Corey and K. Y. Yi, *Tetrahedron Lett.*, **32**, 2289 (1992).
- ^{199.} H. Wetter and K. Oertle, *Tetrahedron Lett.*, **26**, 5515 (1985).
- ^{200.} R. F. Cunico and L. Bedell, *J. Org. Chem.*, **45**, 4797 (1980).

sterically hindered than the TBDMS group and can be used when added stability is required. The triphenylsilyl (TPS) and *t*-butyldiphenylsilyl (TBDPS) groups are also used.²⁰¹ The hydrolytic stability of the various silyl protecting groups is in the order TMS < TBDMS < TIPS < TBDPS.²⁰² All the groups are also susceptible to TBAF cleavage, but the TPS and TBDPS groups are cleaved more slowly than the trialkylsilyl groups.²⁰³ Bromine in methanol readily cleaves TBDMS and TBDPS groups.²⁰⁴

3.5.1.4. Esters as Protective Groups. Protection of an alcohol function by esterification sometimes offers advantages over use of acetal or ether groups. Generally, esters are stable under acidic conditions, and they are especially useful in protection during oxidations. Acetates, benzoates, and pivalates, which are the most commonly used derivatives, can be conveniently prepared by reaction of unhindered alcohols with acetic anhydride, benzoyl chloride, or pivaloyl chloride, respectively, in the presence of pyridine or other tertiary amines. 4-Dimethylaminopyridine (DMAP) is often used as a catalyst. The use of *N*-acylimidazolides (see Section 3.4.1) allows the acylation reaction to be carried out in the absence of added base.²⁰⁵ Imidazolides are less reactive than the corresponding acyl chloride and can exhibit a higher degree of selectivity in reactions with a molecule possessing several hydroxy groups.



Hindered hydroxy groups may require special acylation procedures. One approach is to increase the reactivity of the hydroxy group by converting it to an alkoxide ion with strong base (e.g., *n*-BuLi or KH). When this conversion is not feasible, a more reactive acylating reagent is used. Highly reactive acylating agents are generated *in situ* when carboxylic acids are mixed with trifluoroacetic anhydride. The mixed anhydride exhibits increased reactivity because of the high reactivity of the trifluoroacetate ion as a leaving group.²⁰⁷ Dicyclohexylcarbodiimide is another reagent that serves to activate carboxy groups.

Ester groups can be removed readily by base-catalyzed hydrolysis. When basic hydrolysis is inappropriate, special acyl groups are required. Trichloroethyl carbonate esters, for example, can be reductively removed with zinc.²⁰⁸



- ²⁰¹ S. Hanessian and P. Lavalée, *Can. J. Chem.*, **53**, 2975 (1975); S. A. Hardinger and N. Wijaya, *Tetrahedron Lett.*, **34**, 3821 (1993).
- ²⁰² J. S. Davies, C. L. Higginbotham, E. J. Tremeer, C. Brown, and R. S. Treadgold, *J. Chem. Soc., Perkin Trans.*, **1**, 3043 (1992).
- ²⁰³ J. W. Gillard, R. Fortin, H. E. Morton, C. Yoakim, C. A. Quesnelle, S. Daigault, and Y. Guindon, *J. Org. Chem.*, **53**, 2602 (1988).
- ²⁰⁴ M. T. Barros, C. D. Maycock, and C. Thomassigny, *Synlett*, 1146 (2001).
- ²⁰⁵ H. A. Staab, *Angew. Chem.*, **74**, 407 (1962).
- ²⁰⁶ F. A. Carey and K. O. Hodgson, *Carbohydr. Res.*, **12**, 463 (1970).
- ²⁰⁷ R. C. Parish and L. M. Stock, *J. Org. Chem.*, **30**, 927 (1965); J. M. Tedder, *Chem. Rev.*, **55**, 787 (1955).
- ²⁰⁸ T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, 2555 (1967).

Allyl carbonate esters are also useful hydroxy-protecting groups and are introduced using allyl chloroformate. A number of Pd-based catalysts for allylic deprotection have been developed.²⁰⁹ They are based on a catalytic cycle in which Pd⁰ reacts by oxidative addition and activates the allylic bond to nucleophilic substitution. Various nucleophiles are effective, including dimedone,²¹⁰ pentane-2,4-dione,²¹¹ and amines.²¹²

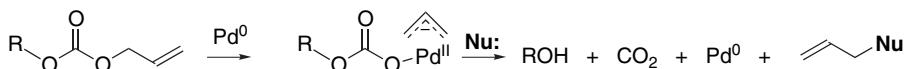
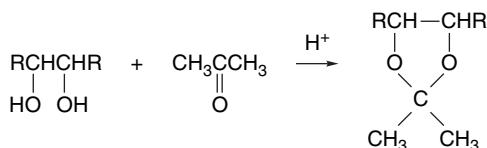
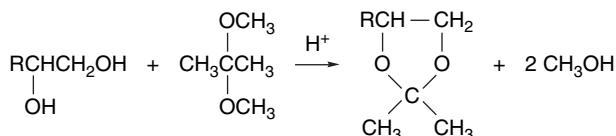


Table 3.1 gives the structure and common abbreviation of some of the most frequently used hydroxy-protecting groups.

3.5.1.5. Protective Groups for Diols. Diols represent a special case in terms of applicable protecting groups. 1,2- and 1,3-diols easily form cyclic acetals with aldehydes and ketones, unless cyclization is precluded by molecular geometry. The isopropylidene derivatives (also called acetonides) formed by reaction with acetone are a common example.



The isopropylidene group can also be introduced by acid-catalyzed exchange with 2,2-dimethoxypropane.²¹³



This acetal protective group is resistant to basic and nucleophilic reagents, but is readily removed by aqueous acid. Formaldehyde, acetaldehyde, and benzaldehyde are also used as the carbonyl component in the formation of cyclic acetals, and they function in the same manner as acetone. A disadvantage in the case of acetaldehyde and benzaldehyde is the possibility of forming a mixture of diastereomers, because of the new stereogenic center at the acetal carbon. Owing to the multiple hydroxy groups present in carbohydrates, the use of cyclic acetal protecting groups is common.

²⁰⁹ F. Guibe, *Tetrahedron*, **53**, 13509 (1997).

²¹⁰ H. Kunz and H. Waldmann, *Angew. Chem. Int. Ed. Engl.*, **23**, 71 (1984).

²¹¹ A. De Mesmaeker, P. Hoffmann, and B. Ernst, *Tetrahedron Lett.*, **30**, 3773 (1989).

²¹² H. Kunz, H. Waldmann, and H. Klinkhammer, *Helv. Chim. Acta*, **71**, 1868 (1988); S. Friedrich-Bochtnitschek, H. Waldman, and H. Kunz, *J. Org. Chem.*, **54**, 751 (1989); J. P. Genet, E. Blart, M. Savignac, S. Lemeune, and J.-M. Paris, *Tetrahedron Lett.*, **34**, 4189 (1993).

²¹³ M. Tanabe and B. Bigley, *J. Am. Chem. Soc.*, **83**, 756 (1961).

Table 3.1. Common Hydroxy-Protecting Groups

Structure	Name	Abbreviation	SECTION 3.5 <i>Installation and Removal of Protective Groups</i>
A. Ethers			
	Benzyl	Bn	
	<i>p</i> -Methoxybenzyl	PMB	
$\text{CH}_2=\text{CHCH}_2\text{OR}$ Ph_3COR	Allyl Triphenylmethyl (trityl)	Tr	
	<i>p</i> -Methoxyphenyl	PMP	
B. Acetals			
	Tetrahydropyranyl	THP	
$\text{CH}_3\text{OCH}_2\text{OR}$	Methoxymethyl	MOM	
$\text{CH}_3\text{CH}_2\text{OCHOR}$ $\quad \quad \quad $ $\quad \quad \quad \text{CH}_3$	1-Ethoxyethyl	EE	
$(\text{CH}_3)_2\text{COR}$ $\quad \quad \quad $ $\quad \quad \quad \text{OCH}_3$	2-Methoxy-2-propyl	MOP	
$\text{Cl}_3\text{CCH}_2\text{OCH}_2\text{OR}$ $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_2\text{OR}$ $(\text{CH}_3)_3\text{SiCH}_2\text{CH}_2\text{OCH}_2\text{OR}$ $\text{CH}_3\text{SCH}_2\text{OR}$	2,2,2-Trichloroethoxymethyl 2-Methoxyethoxymethyl 2-Trimethylsilylethoxymethyl Methylthiomethyl	MEM SEM MTM	
C. Silyl ethers			
$(\text{CH}_3)_3\text{SiOR}$ $(\text{C}_2\text{H}_5)_3\text{SiOR}$ $[(\text{CH}_3)_2\text{CH}]_3\text{OR}$ Ph_3SiOR $(\text{CH}_3)_3\text{CSi}(\text{CH}_3)_2\text{SiOR}$ $(\text{CH}_3)_3\text{CSi}(\text{Ph})_2\text{SiOR}$	Trimethylsilyl Triethylsilyl Tri- <i>i</i> -propylsilyl Triphenylsilyl <i>t</i> -Butyldimethylsilyl <i>t</i> -Butyldiphenylsilyl	TMS TES TIPS TPS TBDMS TBDPS	
D. Esters			
$\text{CH}_3\text{CO}_2\text{R}$ PhCO_2R $(\text{CH}_3)_3\text{CO}_2\text{R}$ $\text{CH}_2=\text{CHCH}_2\text{O}_2\text{COR}$ $\text{Cl}_3\text{CCH}_2\text{O}_2\text{COR}$ $(\text{CH}_3)_3\text{SiCH}_2\text{CH}_2\text{O}_2\text{COR}$	Acetate Benzoate Pivalate Allyl carbonate 2,2,2-Trichloroethyl carbonate 2-Trimethylsilylethyl carbonate	Ac Bz Piv Troc	

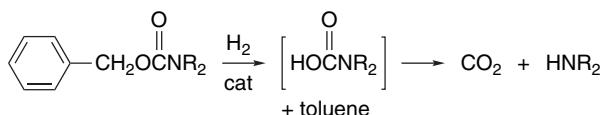
Cyclic carbonate esters are easily prepared from 1,2- and 1,3-diols. These are commonly prepared by reaction with *N,N'*-carbonyldiimidazole²¹⁴ or by transesterification with diethyl carbonate.

3.5.2. Amino-Protecting Groups

Amines are nucleophilic and easily oxidized. Primary and secondary amino groups are also sufficiently acidic that they are deprotonated by many organometallic reagents. If these types of reactivity are problematic, the amino group must be protected. The

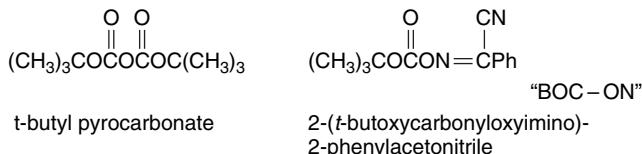
²¹⁴ J. P. Kutney and A. H. Ratcliffe, *Synth. Commun.*, 547 (1975).

most general way of masking nucleophilicity is by acylations, and carbamates are particularly useful. A most effective group for this purpose is the carbobenzyloxy (Cbz) group,²¹⁵ which is introduced by acylation of the amino group using benzyl chloroformate. The amine can be regenerated from a Cbz derivative by hydrogenolysis of the benzyl C–O bond, which is accompanied by spontaneous decarboxylation of the resulting carbamic acid.



In addition to standard catalytic hydrogenolysis, methods for transfer hydrogenolysis using hydrogen donors such as ammonium formate or formic acid with Pd-C catalyst are available.²¹⁶ The Cbz group also can be removed by a combination of a Lewis acid and a nucleophile: for example, boron trifluoride in conjunction with dimethyl sulfide or ethyl sulfide.²¹⁷

The *t*-butyloxycarbonyl (*t*Boc) group is another valuable amino-protecting group. The removal in this case is done with an acid such as trifluoroacetic acid or *p*-toluenesulfonic acid.²¹⁸ *t*-Butoxycarbonyl groups are introduced by reaction of amines with *t*-butyldipropanoate or a mixed carbonate-imide ester known as “BOC-ON.”²¹⁹

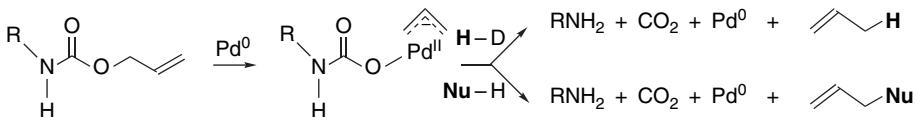


Another carbamate protecting group is 2,2,2-trichloroethoxy carbonyl, known as Troc. 2,2,2-Trichloroethyl carbamates can be reductively cleaved by zinc.²²⁰

Allyl carbamates also can serve as amino-protecting groups. The allyloxy group is removed by Pd-catalyzed reduction or nucleophilic substitution. These reactions involve formation of the carbamic acid by oxidative addition to the palladium. The allyl-palladium species is reductively cleaved by stannanes,²²¹ phenylsilane,²²² formic acid,²²³ and NaBH₄,²²⁴ which convert the allyl group to propene. Reagents

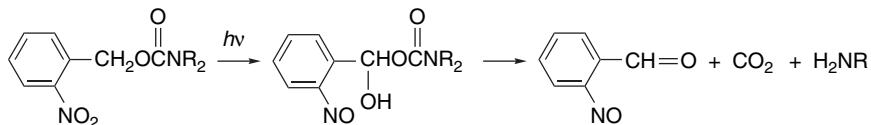
- ²¹⁵. W. H. Hartung and R. Simonoff, *Org. React.*, **7**, 263 (1953).
- ²¹⁶. S. Ram and L. D. Spicer, *Tetrahedron Lett.*, **28**, 515 (1987); B. El Amin, G. Anantharamaiah, G. Royer, and G. Means, *J. Org. Chem.*, **44**, 3442 (1979).
- ²¹⁷. I. M. Sanchez, F. J. Lopez, J. J. Soria, M. I. Larraza, and H. J. Flores, *J. Am. Chem. Soc.*, **105**, 7640 (1983); D. S. Bose and D. E. Thurston, *Tetrahedron Lett.*, **31**, 6903 (1990).
- ²¹⁸. E. Wunsch, *Methoden der Organischen Chemie*, Vol. 15, 4th Edition, Thieme, Stuttgart, 1975.
- ²¹⁹. O. Keller, W. Keller, G. van Look, and G. Wersin, *Org. Synth.*, **63**, 160 (1984); W. J. Paleveda, F. W. Holly, and D. F. Weber, *Org. Synth.*, **63**, 171 (1984).
- ²²⁰. G. Just and K. Grozinger, *Synthesis*, 457 (1976).
- ²²¹. O. Dangles, F. Guibe, G. Balavoine, S. Lavielle, and A. Marquet, *J. Org. Chem.*, **52**, 4984 (1987).
- ²²². M. Dessolin, M.-G. Guillerez, N. T. Thieriet, F. Guibe, and A. Loffet, *Tetrahedron Lett.*, **36**, 5741 (1995).
- ²²³. I. Minami, Y. Ohashi, I. Shimizu, and J. Tsuji, *Tetrahedron Lett.*, **26**, 2449 (1985); Y. Hayakawa, S. Wakabashi, H. Kato, and R. Noyori, *J. Am. Chem. Soc.*, **112**, 1691 (1990).
- ²²⁴. R. Beugelmans, L. Neville, M. Bois-Choussy, J. Chastanet, and J. Zhu, *Tetrahedron Lett.*, **36**, 3129 (1995).

used for nucleophilic cleavage include *N,N'*-dimethylbarbituric acid,²²⁵ and silylating agents, including TMS-N₃/NH₄F,²²⁶ TMSN(Me)₂,²²⁷ and TMSN(CH₃)COCF₃.²¹⁹ The silylated nucleophiles trap the deallylated product prior to hydrolytic workup.

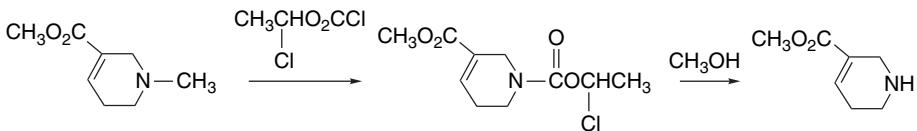


Allyl groups attached directly to amine or amide nitrogen can be removed by isomerization and hydrolysis.²²⁸ These reactions are analogous to those used to cleave allylic ethers (see p. 266). Catalysts that have been found to be effective include Wilkinson's catalyst,²²⁹ other rhodium catalysts,²³⁰ and iron pentacarbonyl.⁴⁵ Treatment of *N*-allyl amines with Pd(PPh₃)₄ and *N,N'*-dimethylbarbituric acid also cleaves the allyl group.²³¹

Sometimes it is useful to be able to remove a protecting group by photolysis. 2-Nitrobenzyl carbamates meet this requirement. The photoexcited nitro group abstracts a hydrogen from the benzylic position, which is then converted to a α -hydroxybenzyl carbamate that readily hydrolyzes.²³²



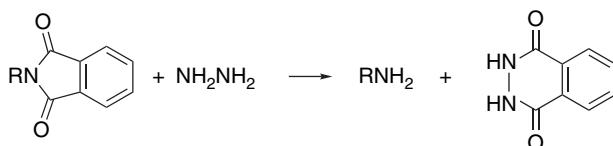
N-Benzyl groups can be removed from tertiary amines by reaction with chloroformates. This can be a useful method for protective group manipulation if the resulting carbamate is also easily cleaved. A particularly effective reagent is α -chloroethyl chloroformate, which can be removed by subsequent solvolysis,²³³ and it has been used to remove methyl and ethyl groups. These reactions are related to ether cleavage by acylation reagents (see Section 3.3).



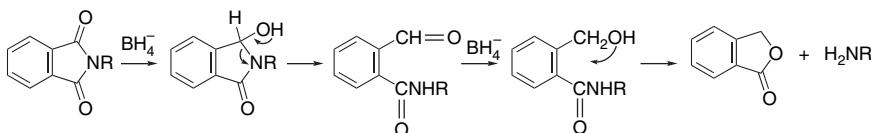
Simple amides are satisfactory protecting groups only if the rest of the molecule can resist the vigorous acidic or alkaline hydrolysis necessary for removal. For this

- ²²⁵ P. Braun, H. Waldmann, W. Vogt, and H. Kunz, *Synlett*, 105 (1990).
- ²²⁶ G. Shapiro and D. Buechler, *Tetrahedron Lett.*, **35**, 5421 (1994).
- ²²⁷ A. Merzouk, F. Guibe, and A. Loffet, *Tetrahedron Lett.*, **33**, 477 (1992).
- ²²⁸ I. Minami, M. Yuhara, and J. Tsuji, *Tetrahedron Lett.*, **28**, 2737 (1987); M. Sakaitani, N. Kurokawa, and Y. Ohfune, *Tetrahedron Lett.*, **27**, 3753 (1986).
- ²²⁹ B. C. Laguzza and B. Ganem, *Tetrahedron Lett.*, **22**, 1483 (1981).
- ²³⁰ J. K. Stille and Y. Becker, *J. Org. Chem.*, **45**, 2139 (1980); R. J. Sundberg, G. S. Hamilton, and J. P. Laurino, *J. Org. Chem.*, **53**, 976 (1988).
- ²³¹ F. Garro-Helion, A. Merzouk, and F. Guibe, *J. Org. Chem.*, **52**, 6109 (1993).
- ²³² J. F. Cameron and J. M. J. Frechet, *J. Am. Chem. Soc.*, **113**, 4303 (1991).
- ²³³ R. A. Olofson, J. T. Martz, J.-P. Senet, M. Piteau, and T. Malfroot, *J. Org. Chem.*, **49**, 2081 (1984).

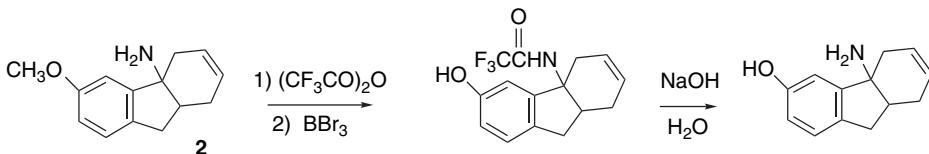
reason, only amides that can be removed under mild conditions are useful as amino-protecting groups. Phthalimides, which are used to protect primary amino groups, can be cleaved by treatment with hydrazine, as in the Gabriel synthesis of amines (see Section 3.2.4). This reaction proceeds by initial nucleophilic addition at an imide carbonyl, followed by an intramolecular acyl transfer.



A similar sequence that takes place under milder conditions uses 4-nitrophthalimides as the protecting group and *N*-methylhydrazine for deprotection.²³⁴ Reduction by NaBH₄ in aqueous ethanol is an alternative method for deprotection of phthalimides. This reaction involves formation of an *o*-(hydroxymethyl)benzamide in the reduction step. Intramolecular displacement of the amino group follows.²³⁵

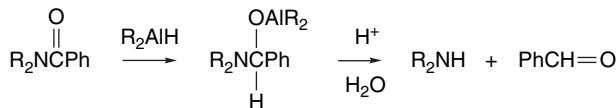


Owing to the strong EWG effect of the trifluoromethyl group, trifluoroacetamides are subject to hydrolysis under mild conditions. This has permitted trifluoroacetyl groups to be used as amino-protecting groups in some situations. For example, the amino group was protected by trifluoroacetylation during BBr₃ demethylation of **2**.



Ref. 236

Amides can also be deacylated by partial reduction. If the reduction proceeds only to the carbinolamine stage, hydrolysis can liberate the deprotected amine. Trichloroacetamides are readily cleaved by sodium borohydride in alcohols by this mechanism.²³⁷ Benzamides, and probably other simple amides, can be removed by careful partial reduction with diisobutylaluminum hydride (see Section 5.3.1.1).²³⁸



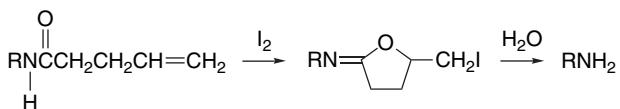
²³⁴ H. Tsubouchi, K. Tsuji, and H. Ishikawa, *Synlett*, 63 (1994).

²³⁵ J. O. Osborn, M. G. Martin, and B. Ganem, *Tetrahedron Lett.*, **25**, 2093 (1984).

²³⁶ Y.-P. Pang and A. P. Kozikowski, *J. Org. Chem.*, **56**, 4499 (1991).

²³⁷ F. Weygand and E. Frauendorfer, *Chem. Ber.*, **103**, 2437 (1970).

²³⁸ J. Gutzwiler and M. Uskokovic, *J. Am. Chem. Soc.*, **92**, 204 (1970); K. Psotta and A. Wiechers, *Tetrahedron*, **35**, 255 (1979).



Sulfonamides are very difficult to hydrolyze. However, a photoactivated reductive method for desulfonylation has been developed.²⁴⁰ Sodium borohydride is used in conjunction with 1,2- or 1,4-dimethoxybenzene or 1,5-dimethoxynaphthalene. The photoexcited aromatic serves as an electron donor toward the sulfonyl group, which then fragments to give the deprotected amine. The NaBH₄ reduces the radical cation and the sulfonyl radical.

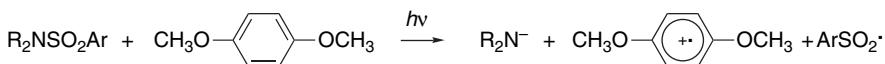
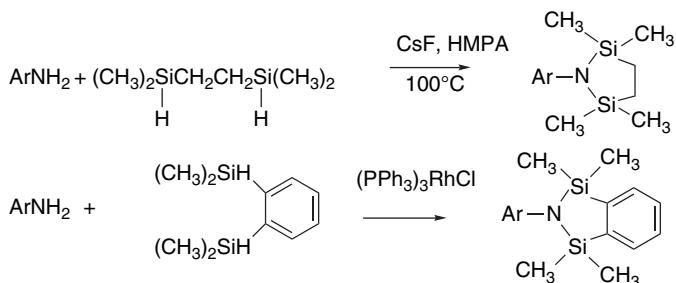


Table 3.2 summarizes the common amine-protecting groups. Reagents that permit protection of primary amino groups as cyclic *bis*-silyl derivatives have been developed. Anilines, for example, can be converted to disilazolidines.²⁴¹ These groups are stable to a number of reaction conditions, including generation and reaction of organometallic reagents.²⁴² They are readily removed by hydrolysis.



Amide nitrogens can be protected by 4-methoxy or 2,4-dimethoxyphenyl groups. The protecting group can be removed by oxidation with ceric ammonium nitrate.²⁴³ 2,4-Dimethoxybenzyl groups can be removed using anhydrous trifluoroacetic acid.²⁴⁴

- ^{239.} R. Madsen, C. Roberts, and B. Fraser-Reid, *J. Org. Chem.*, **60**, 7920 (1995).
- ^{240.} T. Hamada, A. Nishida, and O. Yonemitsu, *Heterocycles*, **12**, 647 (1979); T. Hamada, A. Nishida, Y. Matsumoto, and O. Yonemitsu, *J. Am. Chem. Soc.*, **102**, 3978 (1980).
- ^{241.} R. P. Bonar-Law, A. P. Davis, and B. J. Dorgan, *Tetrahedron Lett.*, **31**, 6721 (1990); R. P. Bonar-Law, A. P. Davis, B. J. Dorgan, M. T. Reetz, and A. Wehrsig, *Tetrahedron Lett.*, **31**, 6725 (1990); S. Djuric, J. Venit, and P. Magnus, *Tetrahedron Lett.*, **22**, 1787 (1981); T. L. Guggenheim, *Tetrahedron Lett.*, **25**, 1253 (1984); A. P. Davis and P. J. Gallagher, *Tetrahedron Lett.*, **36**, 3269 (1995).
- ^{242.} R. P. Bonar-Law, A. P. Davis, and J. P. Dorgan, *Tetrahedron*, **49**, 9855 (1993); K. C. Grega, M. R. Barbachyn, S. J. Brickner, and S. A. Miszak, *J. Org. Chem.*, **60**, 5255 (1995).
- ^{243.} M. Yamaura, T. Suzuki, H. Hashimoto, J. Yoshimura, T. Okamoto, and C. Shin, *Bull. Chem. Soc. Jpn.*, **58**, 1413 (1985); R. M. Williams, R. W. Armstrong, and J.-S. Dung, *J. Med. Chem.*, **28**, 733 (1985).
- ^{244.} R. H. Schlessinger, G. R. Bebernitz, P. Lin, and A. J. Pos, *J. Am. Chem. Soc.*, **107**, 1777 (1985); P. DeShong, S. Ramesh, V. Elango, and J. J. Perez, *J. Am. Chem. Soc.*, **107**, 5219 (1985).

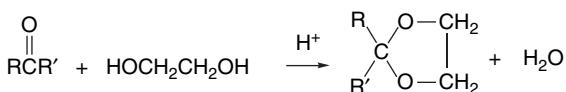
Table 3.2. Common Amine-Protecting Groups

Structure	Name	Abbreviation
A. Carbamates		
	Carbobenzyloxy (Benzylloxycarbonyl)	Cbz
	<i>t</i> -Butoxycarbonyl	<i>t</i> -Boc
	Allyloxycarbonyl	
	Trichloroethoxycarbonyl	Troc
B. <i>N</i>-Substituents		
	Benzyl	Bn
	Allyl	
	2,4-Dimethoxybenzyl	DMB
C. Amides and Imides		
	Phthaloyl	Phthal
	Trifluoroacetyl	
	4-Pentenoyl	

3.5.3. Carbonyl-Protecting Groups

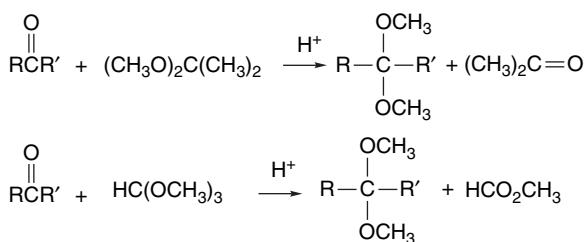
Conversion to acetals is a very general method for protecting aldehydes and ketones against nucleophilic addition or reduction.²⁴⁵ Ethylene glycol, which gives a cyclic dioxolane derivative, is frequently employed for this purpose. The dioxolanes are usually prepared by heating a carbonyl compound with ethylene glycol in the presence of an acid catalyst, with provision for azeotropic removal of water.

²⁴⁵ A. R. Hajipour, S. Khoei, and A. E. Ruoho, *Org. Prep. Proced. Int.*, **35**, 527 (2003).

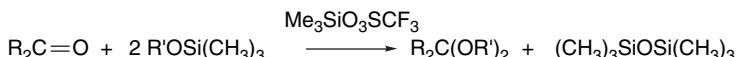


Scandium triflate is also an effective catalyst for dioxolane formation.²⁴⁶

Dimethyl or diethyl acetals can be prepared by acid-catalyzed exchange with an acetal such as 2,2-dimethoxypropane or an orthoester.²⁴⁷

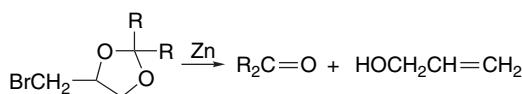


Acetals can be prepared under very mild conditions by reaction of the carbonyl compound with a trimethylsilyl ether, using trimethylsilyl trifluoromethylsulfonate as the catalyst.²⁴⁸



The carbonyl group can be deprotected by acid-catalyzed hydrolysis by the general mechanism for acetal hydrolysis (see Part A, Section 7.1). A number of Lewis acids have also been used to remove acetal protective groups. Hydrolysis is promoted by LiBF₄ in acetonitrile.²⁴⁹ Bismuth triflate promotes hydrolysis of dimethoxy, diethoxy, and dioxolane acetals.²⁵⁰ The dimethyl and diethyl acetals are cleaved by 0.1–1.0 mol % of catalyst in aqueous THF at room temperature, whereas dioxolanes require reflux. Bismuth nitrate also catalyzes acetal hydrolysis.²⁵¹

If the carbonyl group must be regenerated under nonhydrolytic conditions, β-halo alcohols such as 3-bromopropane-1,2-diol or 2,2,2-trichloroethanol can be used for acetal formation. These groups can be removed by reduction with zinc, which leads to β-elimination.



Ref. 252

²⁴⁶ K. Ishihara, Y. Karumi, M. Kubota, and H. Yamamoto, *Synlett*, 839 (1996).

²⁴⁷ C. A. MacKenzie and J. H. Stocker, *J. Org. Chem.*, **20**, 1695 (1955); E. C. Taylor and C. S. Chiang, *Synthesis*, 467 (1977).

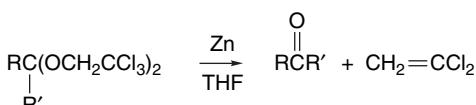
²⁴⁸ T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, **21**, 1357 (1980).

²⁴⁹ B. H. Lipshutz and D. F. Harvey, *Synth. Commun.*, **12**, 267 (1982).

²⁵⁰ M. D. Carrigan, D. Sarapa, R. C. Smith, L. C. Wieland, and R. S. Mohan, *J. Org. Chem.*, **67**, 1027 (2002).

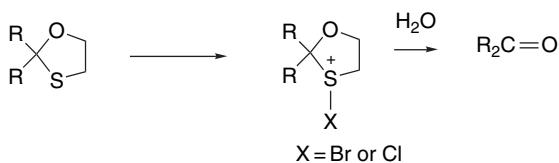
²⁵¹ N. Srivasta, S. K. Dasgupta, and B. K. Banik, *Tetrahedron Lett.*, **44**, 1191 (2003).

²⁵² E. J. Corey and R. A. Ruden, *J. Org. Chem.*, **38**, 834 (1973).

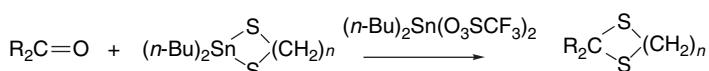


Ref. 253

Another carbonyl-protecting group is the 1,3-oxathiolane derivative, which can be prepared by reaction with mercaptoethanol in the presence of a number of Lewis acids including BF_3 ,²⁵⁴ and $\text{In}(\text{OTf})_3$,²⁵⁵ or by heating with an acid catalyst with azeotropic removal of water.²⁵⁶ The 1,3-oxathiolanes are particularly useful when nonacidic conditions are required for deprotection. The 1,3-oxathiolane group can be removed by treatment with Raney nickel in alcohol, even under slightly alkaline conditions.²⁵⁷ Deprotection can also be accomplished by treating with a mild halogenating agent, such as NBS,²⁵⁸ tetrabutylammonium tribromide,²⁵⁹ or chloramine-T.²⁶⁰ These reagents oxidize the sulfur to a halosulfonium salt and activate the ring to hydrolytic cleavage.

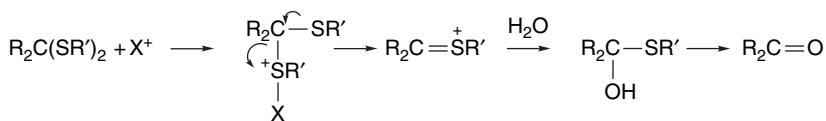


Dithioketals, especially the cyclic dithiolanes and dithianes, are also useful carbonyl-protecting groups.²⁶¹ These can be formed from the corresponding dithiols by Lewis acid-catalyzed reactions. The catalysts that are used include BF_3 , $\text{Mg}(\text{O}_3\text{SCF}_3)_2$, $\text{Zn}(\text{O}_3\text{SCF}_3)_2$, and LaCl_3 .²⁶² *S*-Trimethylsilyl ethers of thiols and dithiols also react with ketones to form dithioketals.²⁶³ Bis-trimethylsilyl sulfate in the presence of silica also promotes formation of dithiolanes.²⁶⁴ Di-*n*-butylstannyl dithiolates also serve as sources of dithiolanes and dithianes. These reactions are catalyzed by di-*n*-butylstannyl ditriflate.²⁶⁵



The regeneration of carbonyl compounds from dithioacetals and dithiolanes is often done with reagents that oxidize or otherwise activate the sulfur as a leaving

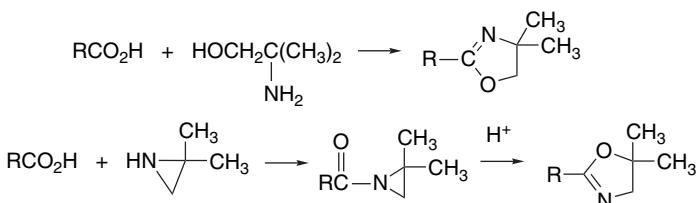
- ^{253.} J. L. Isidor and R. M. Carlson, *J. Org. Chem.*, **38**, 544 (1973).
- ^{254.} G. E. Wilson, Jr., M. G. Huang, and W. W. Scholman, Jr., *J. Org. Chem.*, **33**, 2133 (1968).
- ^{255.} K. Kazahaya, N. Hamada, S. Ito, and T. Sato, *Synlett*, 1535 (2002).
- ^{256.} C. Djerassi and M. Gorman, *J. Am. Chem. Soc.*, **75**, 3704 (1953).
- ^{257.} C. Djerassi, E. Bates, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.*, **74**, 3634 (1952).
- ^{258.} B. Karimi, H. Seradj, and M. H. Tabaei, *Synlett*, 1798 (2000).
- ^{259.} E. Mondal, P. R. Sahu, G. Bose, and A. T. Khan, *Tetrahedron Lett.*, **43**, 2843 (2002).
- ^{260.} D. W. Emerson and H. Wynberg, *Tetrahedron Lett.*, 3445 (1971).
- ^{261.} A. K. Banerjee and M. S. Laya, *Russ. Chem. Rev.*, **69**, 947 (2000).
- ^{262.} L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954); E. J. Corey and K. Shimoji, *Tetrahedron Lett.*, **24**, 169 (1983); L. Garlaschelli and G. Vidari, *Tetrahedron Lett.*, **31**, 5815 (1990); A. T. Khan, E. Mondal, P. R. Sahu, and S. Islam, *Tetrahedron Lett.*, **44**, 919 (2003).
- ^{263.} D. A. Evans, L. K. Truesdale, K. G. Grimm, and S. L. Nesbitt, *J. Am. Chem. Soc.*, **99**, 5009 (1977).
- ^{264.} H. K. Patney, *Tetrahedron Lett.*, **34**, 7127 (1993).
- ^{265.} T. Sato, J. Otero, and H. Nozaki, *J. Org. Chem.*, **58**, 4971 (1993).



3.5.4. Carboxylic Acid-Protecting Groups

If only the O–H, as opposed to the carbonyl, of a carboxyl group has to be masked, it can be readily accomplished by esterification. Alkaline hydrolysis is the usual way for regenerating the acid. *t*-Butyl esters, which are readily cleaved by acid, can be used if alkaline conditions must be avoided. 2,2,2-Trichloroethyl esters, which can be reductively cleaved with zinc, are another possibility.²⁶⁷ Some esters can be cleaved by treatment with anhydrous TBAF. These reactions proceed best for esters of relatively acidic alcohols, such as 4-nitrobenzyl, 2,2,2-trichloroethyl, and cyanoethyl.²⁶⁸

The more difficult problem of protecting the carbonyl group can be accomplished by conversion to an oxazoline derivative. One example is the 4,4-dimethyl derivative, which can be prepared from the acid by reaction with 2-amino-2-methylpropanol or with 2,2-dimethylaziridine.²⁶⁹



The heterocyclic derivative successfully protects the acid from attack by Grignard or hydride-transfer reagents. The carboxylic acid group can be regenerated by acidic hydrolysis or converted to an ester by acid-catalyzed reaction with the appropriate alcohol.

Carboxylic acids can also be protected as orthoesters. Orthoesters derived from simple alcohols are very easily hydrolyzed, and the 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane structure is a more useful orthoester protecting group. These

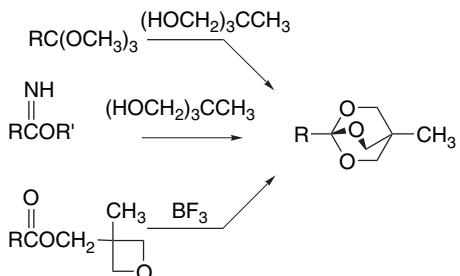
²⁶⁶ M. T. M. El-Wassimy, K. A. Jorgensen, and S. O. Lawesson, *J. Chem. Soc., Perkin Trans. I*, 2201 (1983); J. Lucchetti and A. Krief, *Synth. Commun.*, **13**, 1153 (1983); G. Stork and K. Zhao, *Tetrahedron Lett.*, **30**, 287 (1989); L. Mathew and S. Sankararaman, *J. Org. Chem.*, **58**, 7576 (1993); J. M. G. Fernandez, C. O. Mellet, A. M. Marin, and J. Fuentes, *Carbohydrate Res.*, **274**, 263 (1995); K. Tanemura, H. Dohya, M. Imamura, T. Suzuki, and T. Horaguchi, *J. Chem. Soc., Perkin Trans. I*, 453 (1996); M. Kamata, H. Otogawa, and E. Hasegawa, *Tetrahedron Lett.*, **32**, 7421 (1991); T. Ichige, A. Miyake, N. Kanoh, and M. Nakata, *Synlett*, 1686 (2004).

²⁶⁷ R. B. Woodward, K. Heusler, J. Gostelli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, *J. Am. Chem. Soc.*, **88**, 852 (1966).

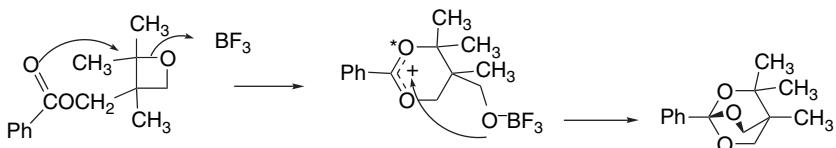
²⁶⁸ M. Namikoshi, B. Kundu, and K. L. Rinehart, *J. Org. Chem.*, **56**, 5464 (1991); Y. Kita, H. Maeda, F. Takahashi, S. Fukui, and T. Ogawa, *Chem. Pharm. Bull.*, **42**, 147 (1994).

²⁶⁹ A. I. Meyers, D. L. Temple, D. Haidukewych, and E. Mihelich, *J. Org. Chem.*, **39**, 2787 (1974).

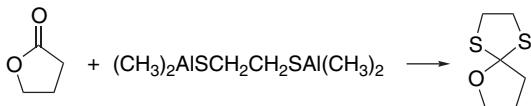
derivatives can be prepared by exchange with other orthoesters,²⁷⁰ by reaction with iminoethers,²⁷¹ or by rearrangement of the ester derived from 3-hydroxymethyl-3-methyloxetane.²⁷²



The latter method is improved by use of the 2,2-dimethyl derivative.²⁷³ The rearrangement is faster and the stability of the orthoester to hydrolysis is better. Isotopic labeling showed that the rearrangement occurs by ionization at the tertiary position.

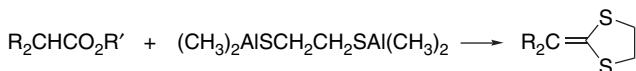


Lactones can be protected as dithiolane derivatives using a method that is analogous to ketone protection. The required reagent is readily prepared from trimethylaluminum and ethanedithiol.



Ref. 274

Acyclic esters react with this reagent to give ketene dithio acetals.



In general, the methods for protection and deprotection of carboxylic acids and esters are not as convenient as for alcohols, aldehydes, and ketones. It is therefore common to carry potential carboxylic acids through synthetic schemes in the form of protected primary alcohols or aldehydes. The carboxylic acid can then be formed at a late stage in the synthesis by an appropriate oxidation. This strategy allows one to utilize the wider variety of alcohol and aldehyde protective groups indirectly for carboxylic acid protection.

²⁷⁰ M. P. Atkins, B. T. Golding, D. A. Howe, and P. J. Sellers, *J. Chem. Soc., Chem. Commun.*, 207 (1980).

²⁷¹ E. J. Corey and K. Shimoji, *J. Am. Chem. Soc.*, **105**, 1662 (1983).

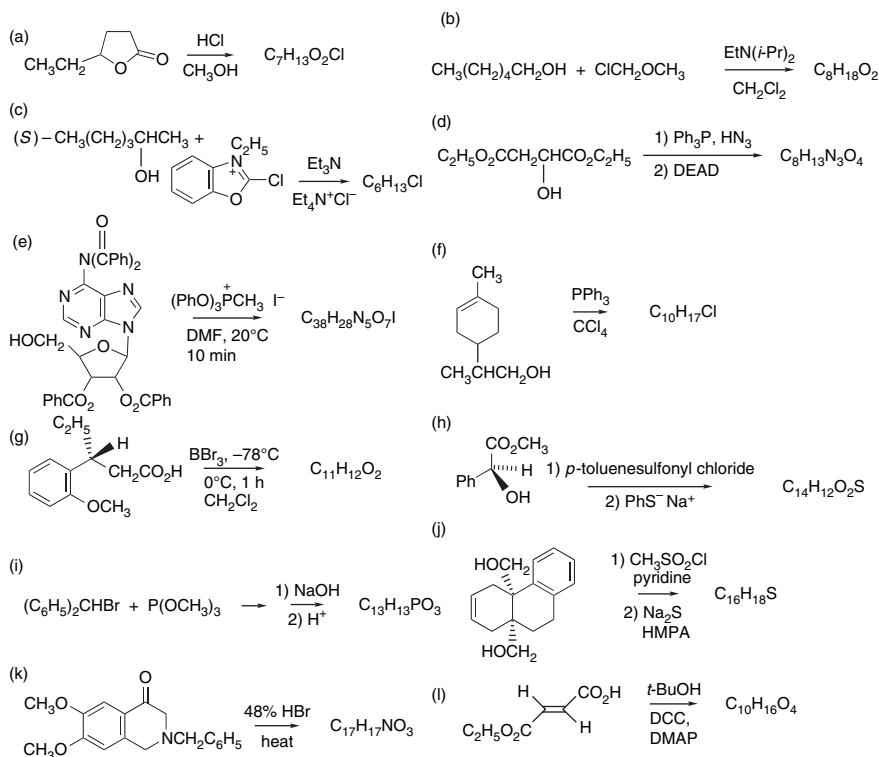
²⁷² E. J. Corey and N. Raju, *Tetrahedron Lett.*, **24**, 5571 (1983).

²⁷³ J.-L. Griner, *Org. Lett.*, **7**, 499 (2005).

²⁷⁴ E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, **95**, 5829 (1973).

(References for these problems will be found on page 1275.)

3.1. Give the products that would be expected to be formed under the specified reaction conditions. Be sure to specify all aspects of the stereochemistry.



3.2. When (R)-(-)-5-hexen-2-ol was treated with Ph₃P in refluxing, CCl₄, (+)-5-chloro-1-hexene was obtained. Conversion of (R)-(-)-5-hexen-2-ol to its 4-bromobenzenesulfonate ester and subsequent reaction with LiCl gave (+)-5-chloro-1-hexene. Reaction of (S)-(+)5-hexen-2-ol with PCl₅ in ether gave (-)-5-chloro-1-hexene.

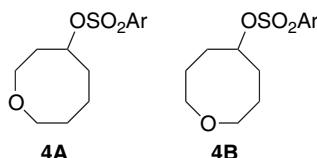
- Write chemical equations for each of these reactions and specify whether each occurs with net retention or inversion of configuration.
- What is the sign of rotation of (R)-5-chloro-1-hexene?

3.3. A careful investigation of the extent of isomeric products formed by reaction of several alcohols with thionyl chloride has been reported. The product compositions for several of the alcohols are given below. Identify the structural features that promote isomerization and show how each of the rearranged products is formed.

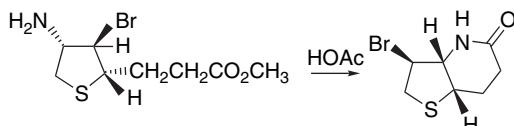
R	Percent unrearranged RCI	ROH $\xrightarrow[100^\circ\text{C}]{\text{SOCl}_2}$ RCI			Structure and amount of rearranged RCI
		ROH	SOCl_2	RCI	
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2-$	100				
$(\text{CH}_3)_2\text{CHCH}_2-$	99.7				$(\text{CH}_3)_2\text{CHCH}_3$
$(\text{CH}_3)_2\text{CHCH}_2\text{CH}_2-$	100				$\begin{array}{c} \text{Cl} \\ \\ (\text{CH}_3)_2\text{CHCH}_3 \end{array}$ 0.3%
$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CHCH}_2- \\ \\ \text{CH}_3 \end{array}$	78	$\begin{array}{c} \text{CH}_3\text{CHCH}_2\text{CH}_2\text{CH}_3, \\ \\ \text{Cl} \end{array}$ 1%	$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CHCH}_2\text{CH}_3, \\ \\ \text{Cl} \end{array}$ 11%	$\begin{array}{c} \text{CH}_3\text{CH}_2\text{C}(\text{CH}_3)_2 \\ \\ \text{Cl} \end{array}$ 10%	
$(\text{CH}_3)_3\text{CCH}_2-$	2				$\begin{array}{c} \text{CH}_3\text{CH}_2\text{C}(\text{CH}_3)_2 \\ \\ \text{Cl} \end{array}$ 98%
$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CH}_2\text{CHCH}_3 \\ \end{array}$	98				$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \\ \\ \text{Cl} \end{array}$ 2%
$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CHCH}_2\text{CH}_3 \\ \end{array}$	90				$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CH}_2\text{CHCH}_3 \\ \\ \text{Cl} \end{array}$ 10%
$\begin{array}{c} (\text{CH}_3)_2\text{CHCHCH}_3 \\ \end{array}$	5				$\begin{array}{c} \text{CH}_3\text{CH}_2\text{C}(\text{CH}_3)_2 \\ \\ \text{Cl} \end{array}$ 95%

3.4. Give a reaction mechanism that would explain the following observations and reactions.

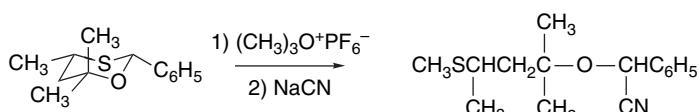
- a. Kinetic measurements reveal that solvolytic displacement of sulfonate is about 5×10^5 faster for **4B** than for **4A**.



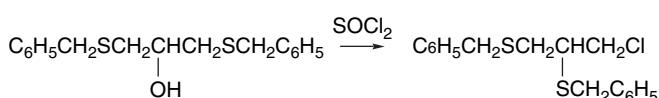
b.



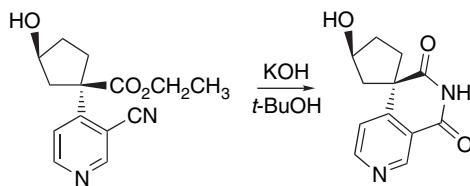
c.



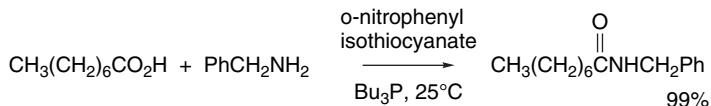
d.



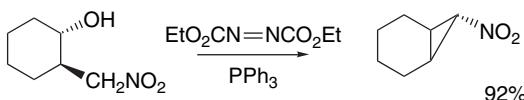
e.



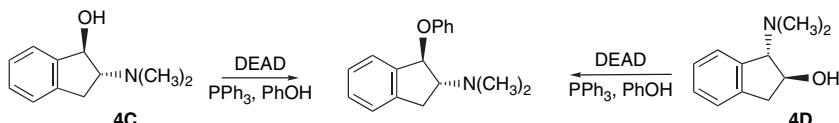
f.



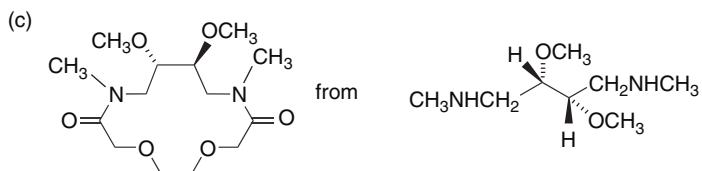
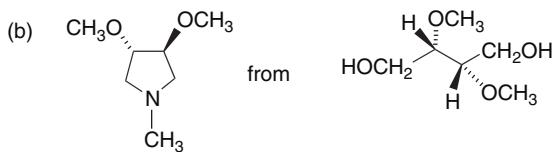
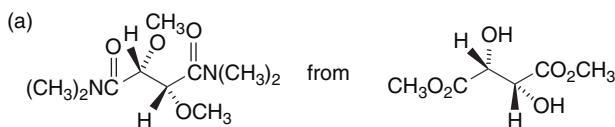
g.

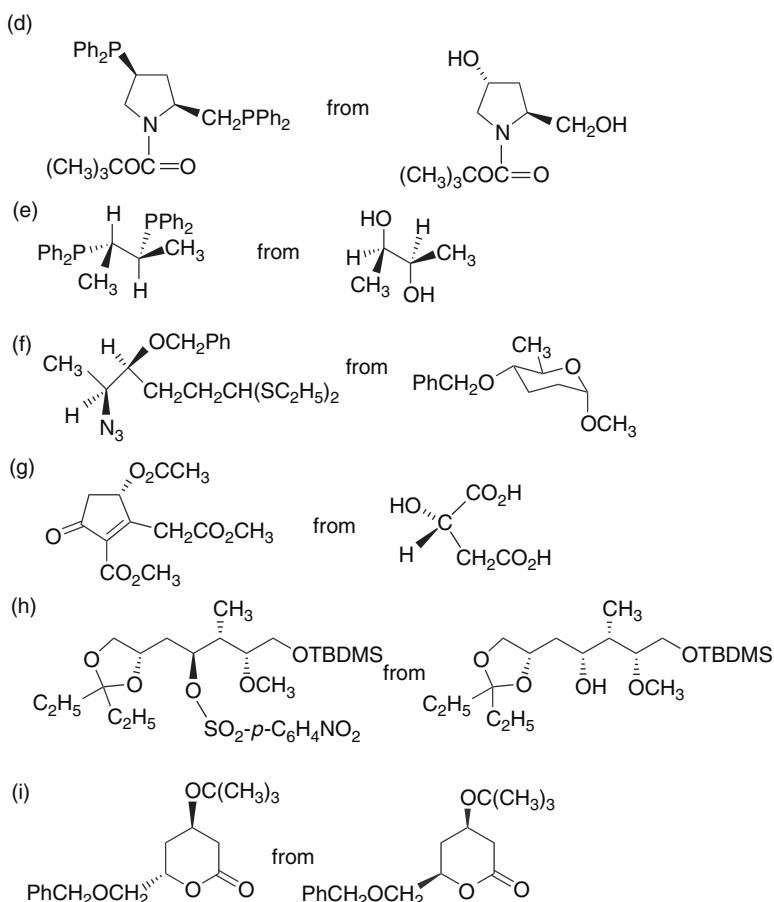


h. Both **4C** and **4D** gave the same product when subjected to Mitsunobu conditions with phenol as the nucleophile.

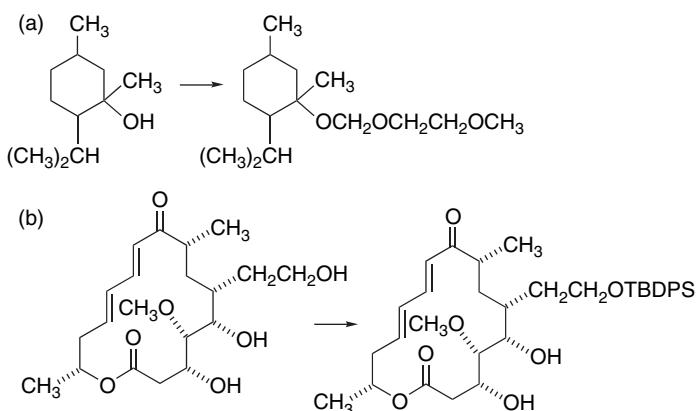


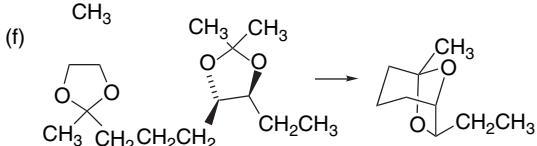
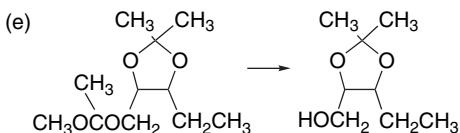
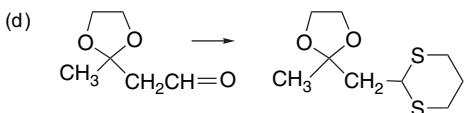
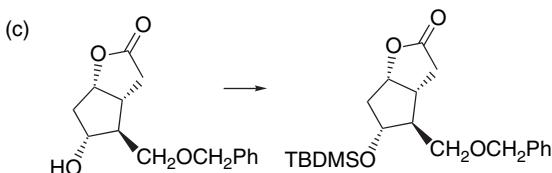
3.5. Substances such as carbohydrates and amino acids as well as other small molecules available from natural sources are valuable starting materials in enantiospecific syntheses. Suggest reagents that could effect the following transformations, taking particular care to ensure that the product will be enantiomerically pure.



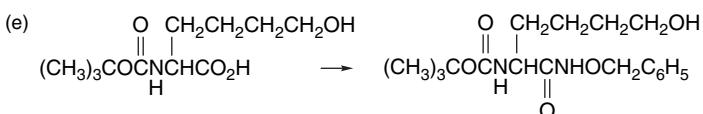
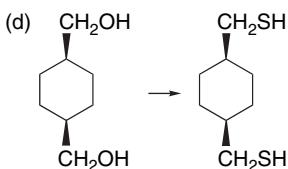
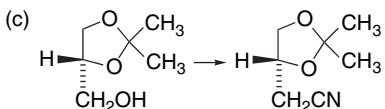
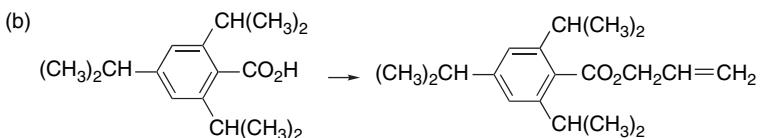
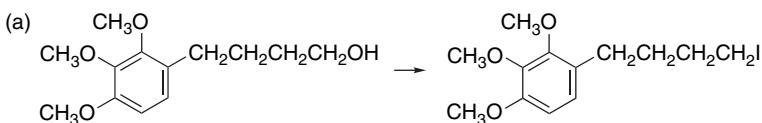


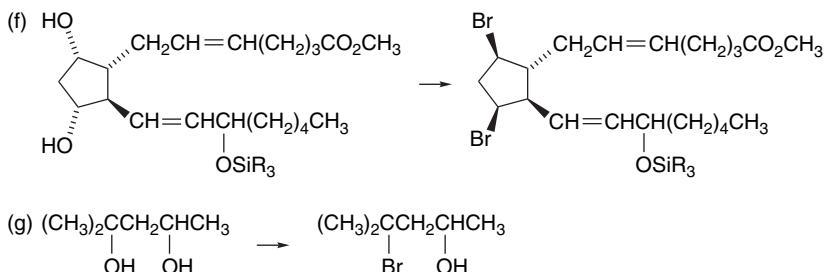
3.6. Indicate conditions that would be appropriate for the following transformations involving introduction or removal of protective groups:





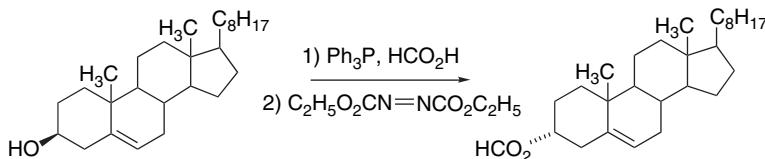
3.7. Suggest reagents and approximate reaction conditions that would effect the following conversions. Note any special features of the reactant that should be taken into account in choosing a reagent system.



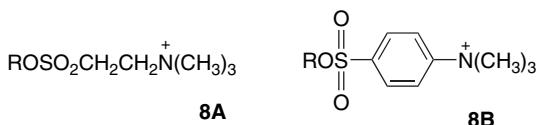


3.8. Provide a mechanistic interpretation of the following reactions and observations.

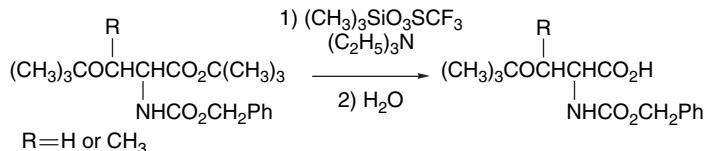
- a. Show the mechanism for inversion of a hydroxyl site under the Mitsunobu conditions, as illustrated by the reaction of cholesterol.



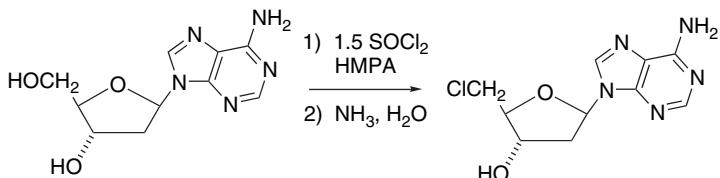
- b. Triphenylphosphine oxide reacts with trifluoromethylsulfonic anhydride to give an ionic substance having the composition of a 1:1 adduct. When this substance is added to a solution containing a carboxylic acid, followed by addition of an amine, amides are formed in good yield. Similarly, esters are formed on reaction with alcohols. What is the structure of the adduct and how does it activate the carboxylic acids to nucleophilic substitution?
- c. Sulfonate esters having quaternary nitrogen substituents, such as **8A** and **8B**, show high reactivity toward nucleophilic substitution. Sulfonates **8A** are comparable in reactivity to 2,2,2-trifluoroethylsulfonate in homogeneous solution and are even more reactive in two-phase solvent mixtures.



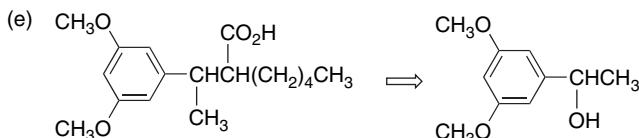
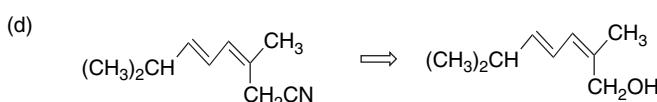
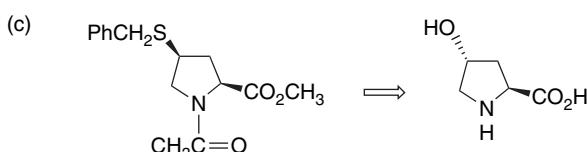
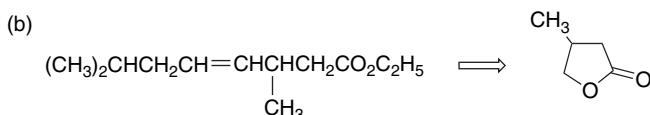
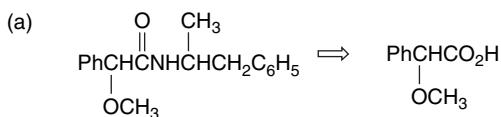
- d. Alcohols react with hexachloroacetone in the presence of DMF to give alkyl trichloroacetates in good yield. Primary alcohols react faster than secondary alcohols, but tertiary alcohols are unreactive under these conditions.
- e. The β -hydroxy- α -amino acids serine and threonine can be converted to their respective *bis*-*O*-*t*-butyl derivatives on reaction with isobutene and H_2SO_4 . Subsequent treatment with one equivalent of trimethylsilyl triflate and then water cleaves the ester group, but not the ether group. What is the basis for this selectivity?



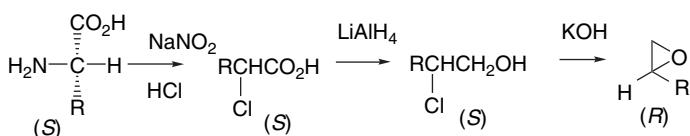
f. 2'-Deoxyadenosine can be cleanly converted to its 5'-chloro analog by reaction with 1.5 equivalent of SOCl_2 in HMPA. The reaction proceeds through an intermediate of composition $\text{C}_{20}\text{H}_{22}\text{N}_{10}\text{Cl}_2\text{O}_5\text{S}$, which is converted to the product on exposure to aqueous ammonia. With larger amounts of SOCl_2 , the 3'5'-dichloro derivative is formed.



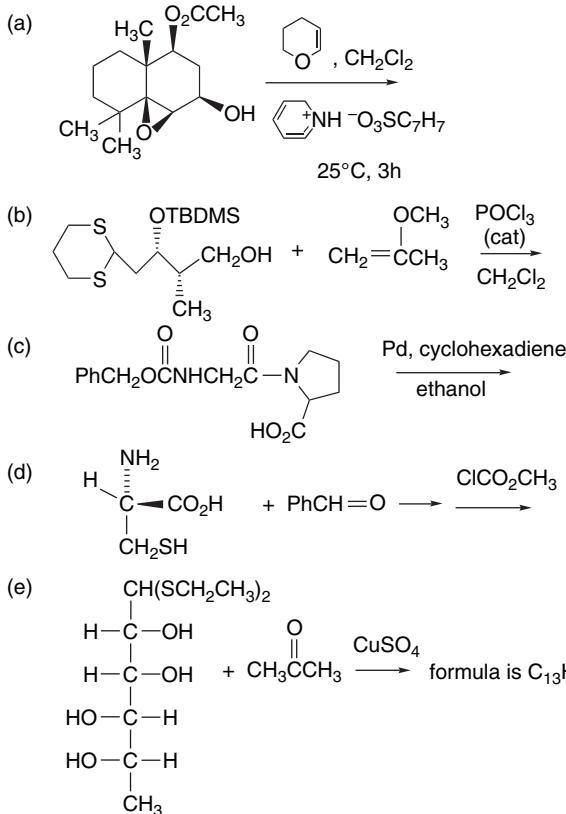
3.9. Short synthetic sequences have been used to obtain the material on the left from the starting material on the right. Suggest an appropriate method. No more than three steps should be required.



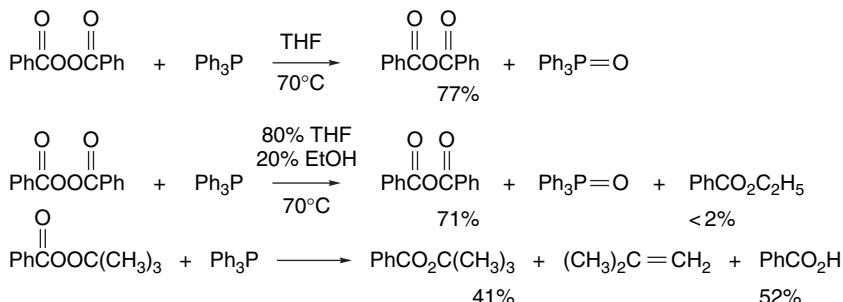
3.10. Amino acids can be converted to epoxides of high enantiomeric purity by the reaction sequence below. Analyze the stereochemistry of each step of the reaction sequence.



3.11. Indicate the product to be expected under the following reaction conditions:



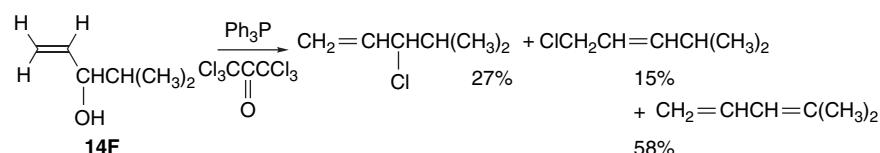
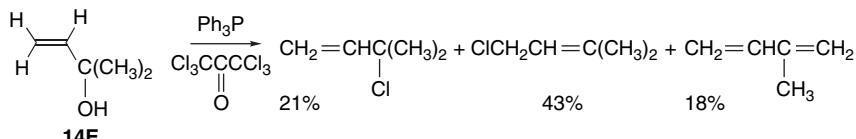
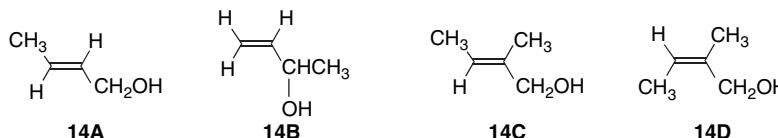
- 3.12. A reagent that can introduce benzyloxycarbonyl protecting groups on amino groups in nucleosides is prepared by allowing benzyl chloroformate to react first with imidazole and then with trimethylxonium tetrafluoroborate. What is the structure of the resulting reagent (a salt) and why is it an especially reactive acylating agent?
- 3.13. Triphenylphosphine reacts with peroxides to give intermediates that are related to those formed in the Mitsunobu reaction. The following reactions are examples:



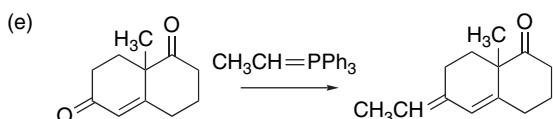
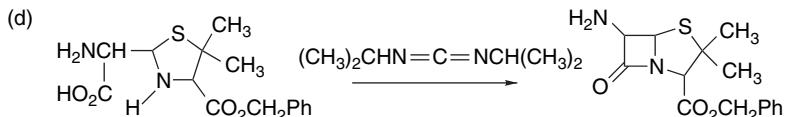
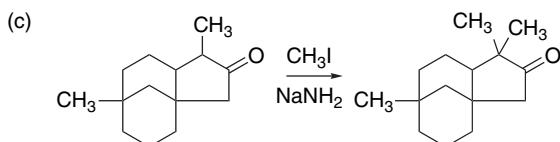
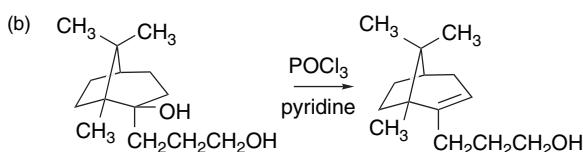
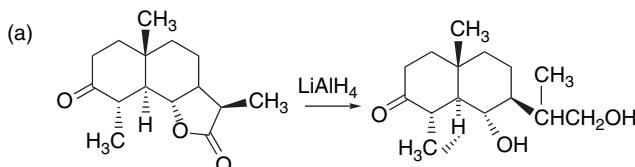
What properties of the intermediates in the Mitsunobu reaction are suggested by these reactions?

- 3.14. The scope of the reaction of $\text{Ph}_3\text{P}-\text{Cl}_3\text{CCOCl}_3$ with allylic alcohols has been studied. Primary and some secondary alcohols, such as **14A** and **14B**, give good

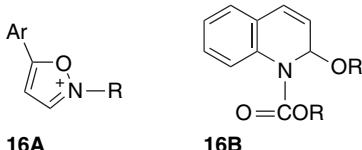
yields of unarranged allylic chlorides. The reaction also exhibits retention of *E,Z*-configuration at the allylic double bonds (**14C** and **14D**). Certain other alcohols, such as **14E** and **14F**, give more complex mixtures. What structural features determine how cleanly the alcohol is converted to chloride? How are these structural features related to the mechanism of the reaction?



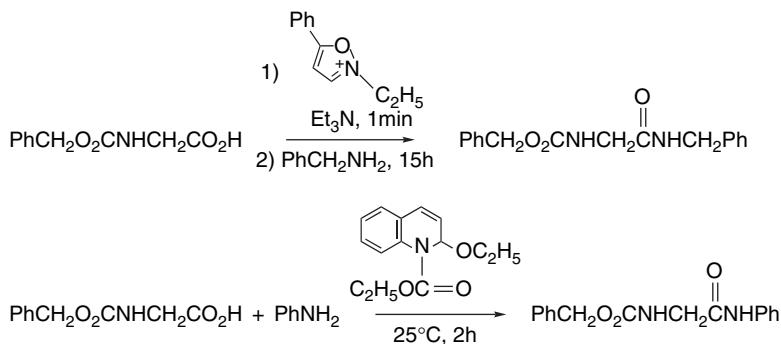
- 3.15. In each of the synthetic transformations shown, the reagents are appropriate for the desired transformation but the reaction would not succeed as written. Suggest a protective group strategy that would permit each transformation to be carried out to give the desired product.



- 3.16. Two heterocyclic ring systems that have found some use in the formation of amides under mild conditions are *N*-alkyl-5-arylisoxazolium salts (**16A**) and *N*-acyloxy-2-alkoxydihydroquinolines (**16B**).

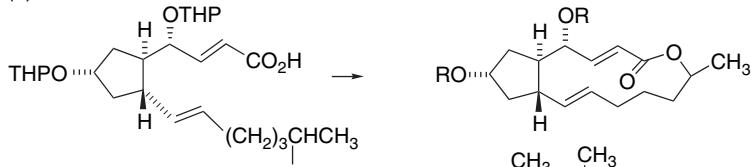


Typical reaction conditions for these reagents are shown below. Propose mechanisms by which these heterocyclic molecules can function to activate carboxy groups under these conditions.

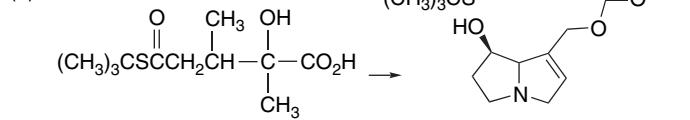


- 3.17. Either because of potential interference with other functional groups present in the molecule or because of special structural features, the following reactions require careful selection of reagents and reaction conditions. Identify the special requirements in each reactant and suggest appropriate reagents and reaction conditions for each transformation.

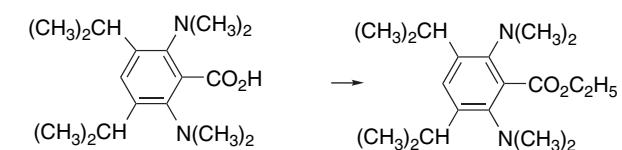
(a)



(b)

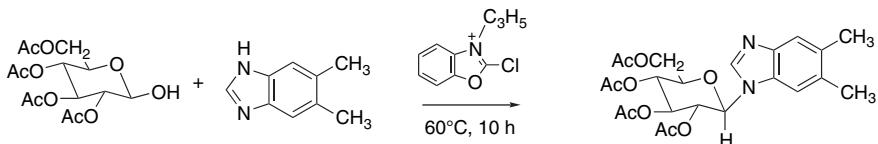


(c)

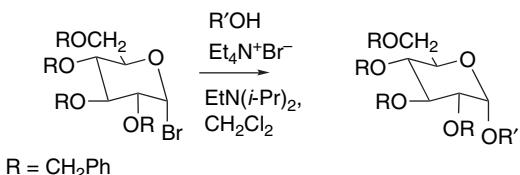


- 3.18. The preparation of nucleosides by reaction between carbohydrates and heterocyclic bases is fundamental to the study of the important biological activity

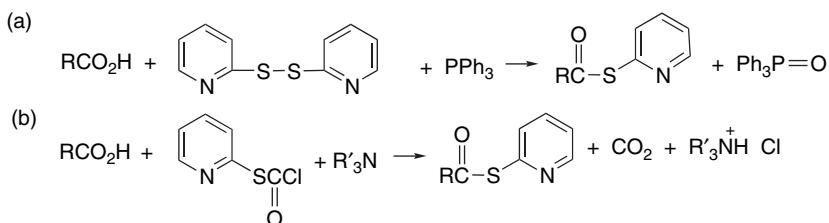
of these substances. Several methods exist for forming the nucleoside bonds. Application of 2-chloro-3-ethylbenzoxazolium chloride to this reaction was investigated using 2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranose. Good yields were observed and the reaction was stereospecific for the β -nucleoside. Suggest a mechanism to explain the retention of configuration.



- 3.19. A route to α -glycosides involves treatment of a 2,3,4,6-tetra-*O*-benzyl- α -D-glucopyranosyl bromide with an alcohol, tetraethylammonium bromide, and diisopropylethylamine in CH_2Cl_2 . Explain the stereoselectivity of this reaction.



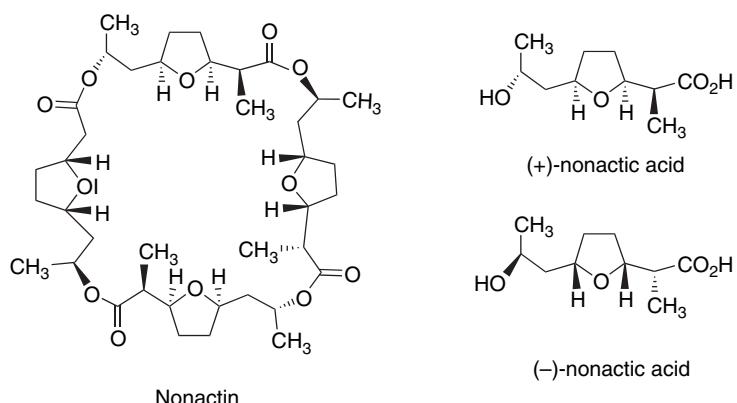
- 3.20. Write mechanisms for formation of 2-pyridylthio esters by the following methods:



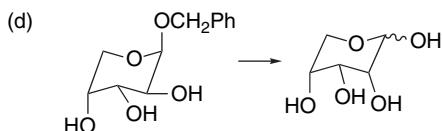
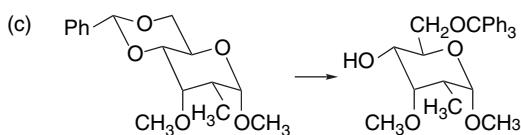
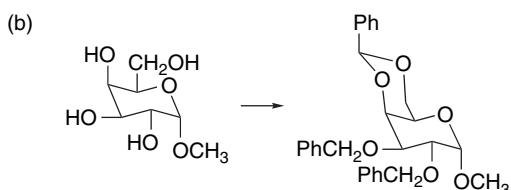
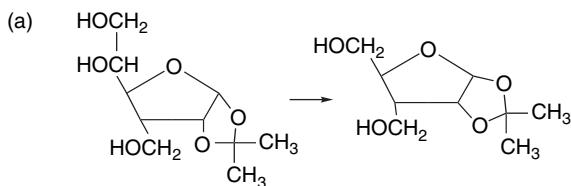
- 3.21. The ionophoric antibiotic nonactin is a 32-membered macrocycle that contains two units of ($-$)-nonactic acid and two units of ($+$)-nonactic acid in an alternating sequence.

- a. Assuming that you have access to both ($+$)- and ($-$)-nonactic acid, devise a strategy and protecting group sequence that could provide the natural macro-molecule in high stereochemical purity.

- b. Suppose you had access to (+)-nonactic acid and the C(8) epimer of (-)-nonactic acid, how could you obtain nonactin?



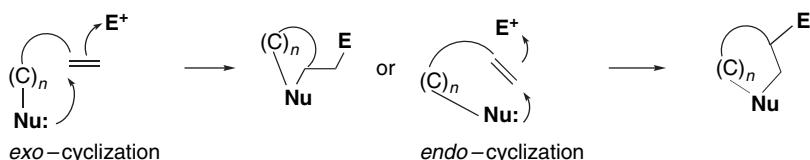
- 3.22. Because they are readily available from natural sources in enantiomerically pure form, carbohydrates are very useful starting materials for the synthesis of other enantiomerically pure substances. However, the high number of similar functional groups present in the carbohydrates requires versatile techniques for protection and deprotection. Show how appropriate manipulation of protecting groups and other selective reactions could be employed to effect the following transformations.



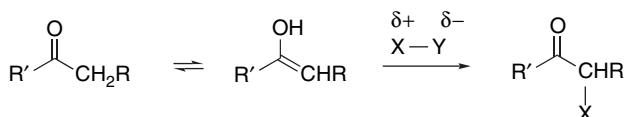
Electrophilic Additions to Carbon-Carbon Multiple Bonds

Introduction

Addition of electrophilic reagents is one of the most general and useful reactions of alkenes and alkynes. This chapter focuses on reactions that proceed through polar intermediates or transition structures. We discuss the fundamental mechanistic characteristics of this class of reactions in Chapter 5 of Part A, including proton-catalyzed additions of water and alcohols and the addition of hydrogen halides. Other electrophilic reagents that we consider there are the halogens and positive halogen compounds, electrophilic sulfur and selenium reagents, and mercuric salts. Hydroboration is another important type of electrophilic addition to alkenes. In the present chapter, we emphasize synthetic application of these reactions. For the most part, electrophilic additions are used to introduce functionality at double and triple bonds. When the nucleophile addition step is intramolecular, a new heterocyclic ring is formed, and this is a very useful synthetic method.



Carbonyl compounds can react with electrophiles via their enol isomers or equivalents, and these reactions result in α -substitution.

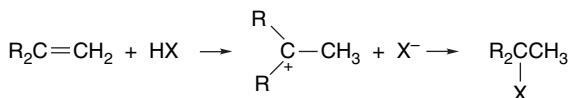


Several other types of addition reactions of alkenes are also of importance and these are discussed elsewhere. Nucleophilic additions to electrophilic alkenes are covered in Section 2.6 and cycloadditions involving concerted mechanisms are encountered in Sections 6.1 to 6.3. Free radical addition reaction are considered in Chapter 11.

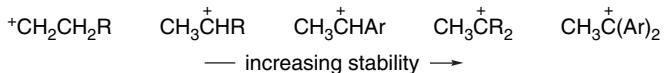
4.1. Electrophilic Addition to Alkenes

4.1.1. Addition of Hydrogen Halides

Hydrogen chloride and hydrogen bromide react with alkenes to give addition products. In early work, it was observed that addition usually takes place to give the product with the halogen atom attached to the more-substituted carbon of the double bond. This behavior is sufficiently general that the name *Markovnikov's rule* was given to the statement describing this mode of addition. The term *regioselective* is used to describe addition reactions that proceed selectively in one direction with unsymmetrical alkenes.¹ A rudimentary picture of the reaction mechanism indicates the basis of Markovnikov's rule. The addition involves either protonation or a partial transfer of a proton to the double bond. The relative stability of the two possible carbocations from an unsymmetrical alkene favors formation of the more-substituted intermediate. Addition is completed when the carbocation reacts with a halide anion.



Markovnikov's rule describes a specific case of regioselectivity that is based on the stabilizing effect of alkyl and aryl substituents on carbocations.



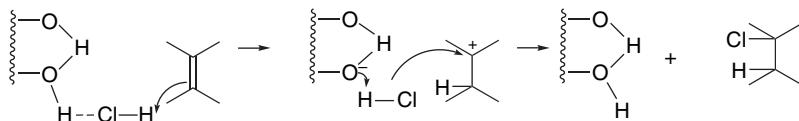
A more complete discussion of the mechanism of addition of hydrogen halides to alkenes is given in Chapter 6 of Part A. In particular, the question of whether or not discrete carbocations are involved is considered there. Even when a carbocation is not involved, the regioselectivity of electrophilic addition is the result of attack of the electrophile at the more *electron-rich* carbon of the double bond. Alkyl substituents increase the electron density of the terminal carbon by hyperconjugation (see Part A, Section 1.1.8).

Terminal and disubstituted internal alkenes react rather slowly with HCl in nonpolar solvents. The rate is greatly accelerated in the presence of silica or alumina in noncoordinating solvents such as dichloromethane or chloroform. Preparatively convenient conditions have been developed in which HCl is generated *in situ* from SOCl_2 or $(\text{ClCO})_2$.² These heterogeneous reaction systems also give a Markovnikov orientation.

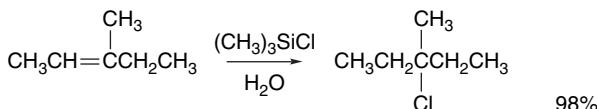
¹ A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

² P. J. Kropp, K. A. Daus, M. W. Tubergen, K. D. Kepler, V. P. Wilson, S. L. Craig, M. M. Baillargeon, and G. W. Breton, *J. Am. Chem. Soc.*, **115**, 3071 (1993).

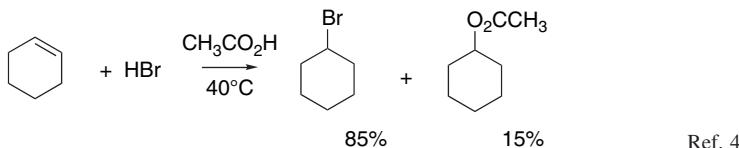
The mechanism is thought to involve an interaction of the silica or alumina surface with HCl that facilitates proton transfer.



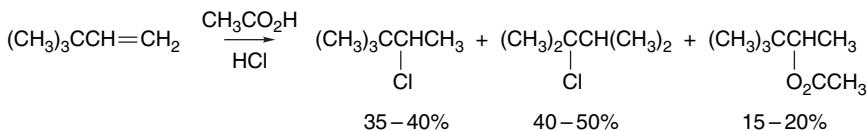
Another convenient procedure for hydrochlorination involves adding trimethylsilyl chloride to a mixture of an alkene and water. Good yields of HCl addition products (Markovnikov orientation) are formed.³ These conditions presumably involve generation of HCl by hydrolysis of the silyl chloride, but it is uncertain if the silicon plays any further role in the reaction.



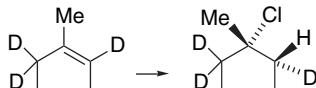
In nucleophilic solvents, products that arise from reaction of the solvent with the cationic intermediate may be formed. For example, reaction of cyclohexene with hydrogen bromide in acetic acid gives cyclohexyl acetate as well as cyclohexyl bromide. This occurs because acetic acid acts as a nucleophile in competition with the bromide ion.



When carbocations are involved as intermediates, carbon skeleton rearrangement can occur during electrophilic addition reactions. Reaction of *t*-butylethylene with hydrogen chloride in acetic acid gives both rearranged and unarranged chloride.⁵



The stereochemistry of addition of hydrogen halides to alkenes depends on the structure of the alkene and also on the reaction conditions. Addition of hydrogen bromide to cyclohexene and to *E*- and *Z*-2-butene is *anti*.⁶ The addition of hydrogen chloride to 1-methylcyclopentene is entirely *anti* when carried out at 25°C in nitromethane.⁷



³. P. Boudjouk, B.-K. Kim, and B.-H. Han, *Synth. Commun.*, **26**, 3479 (1996); P. Boudjouk, B.-K. Kim, and B.-H. Han, *J. Chem. Ed.*, **74**, 1223 (1997).

⁴. R. C. Fahey and R. A. Smith, *J. Am. Chem. Soc.*, **86**, 5035 (1964).

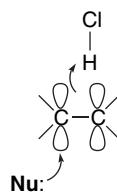
⁵. R. C. Fahey and C. A. McPherson, *J. Am. Chem. Soc.*, **91**, 3865 (1969).

⁶. D. J. Pasto, G. R. Meyer, and S. Kang, *J. Am. Chem. Soc.*, **91**, 4205 (1969).

⁷. Y. Pocker and K. D. Stevens, *J. Am. Chem. Soc.*, **91**, 4205 (1969).

1,2-Dimethylcyclohexene is an example of an alkene for which the stereochemistry of hydrogen chloride addition is dependent on the solvent and temperature. At -78°C in dichloromethane, 88% of the product is the result of *syn* addition, whereas at 0°C in ether, 95% of the product results from *anti* addition.⁸ *Syn* addition is particularly common with alkenes having an aryl substituent. Table 4.1 lists several alkenes for which the stereochemistry of addition of hydrogen chloride or hydrogen bromide has been studied.

The stereochemistry of addition depends on the details of the mechanism. The addition can proceed through an ion pair intermediate formed by an initial protonation step. Most alkenes, however, react via a complex that involves the alkene, hydrogen halide, and a third species that delivers the nucleophilic halide. This termolecular mechanism is generally pictured as a nucleophilic attack on an alkene-hydrogen halide complex. This mechanism bypasses a discrete carbocation and exhibits a preference for *anti* addition.



The major factor in determining which mechanism is followed is the stability of the carbocation intermediate. Alkenes that can give rise to a particularly stable carbocation

Table 4.1. Stereochemistry of Addition of Hydrogen Halides to Alkenes

Alkene	Hydrogen halide	Stereochemistry
1,2-Dimethylcyclohexene ^a	HBr	<i>anti</i>
1,2-Dimethylcyclohexene ^a	HCl	Solvent and temperature dependent
Cyclohexene ^b	HBr	<i>anti</i>
Z-2-Butene ^c	D ₂ Br	<i>anti</i>
E-2-Butene ^c	D ₂ Br	<i>anti</i>
1-Methylcyclopentene ^d	HCl	<i>anti</i>
1,2-Dimethylcyclopentene ^e	HBr	<i>anti</i>
Norbornene ^f	HBr	<i>syn</i> and rearrangement
Norbornene ^g	HCl	<i>syn</i> and rearrangement
E-1-Phenylpropene ^h	HBr	<i>syn</i> (9:1)
Z-1-Phenylpropene ^h	HBr	<i>syn</i> (8:1)
Bicyclo[3.1.0]hex-2-ene ⁱ	DCl	<i>syn</i>
1-Phenyl-4-(<i>t</i> -butyl)cyclohexene ^j	DCl	<i>syn</i>

a. G. S. Hammond and T. D. Nevitt, *J. Am. Chem. Soc.*, **76**, 4121 (1954); R. C. Fahey and C. A. McPherson, *J. Am. Chem. Soc.*, **93**, 2445 (1971); K. B. Becker and C. A. Grob, *Synthesis*, 789 (1973).

b. R. C. Fahey and R. A. Smith, *J. Am. Chem. Soc.*, **86**, 5035 (1964).

c. D. J. Pasto, G. R. Meyer, and B. Lepeska, *J. Am. Chem. Soc.*, **96**, 1858 (1974).

d. Y. Pocker and K. D. Stevens, *J. Am. Chem. Soc.*, **91**, 4205 (1969).

e. G. S. Hammond and C. H. Collins, *J. Am. Chem. Soc.*, **82**, 4323 (1960).

f. H. Kwart and J. L. Nyce, *J. Am. Chem. Soc.*, **86**, 2601 (1964).

g. J. K. Stille, F. M. Sonnenberg, and T. H. Kinistle, *J. Am. Chem. Soc.*, **88**, 4922 (1966).

h. M. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.*, **85**, 3645 (1963).

i. P. K. Freeman, F. A. Raymond, and M. F. Groat, *J. Org. Chem.*, **32**, 24 (1967).

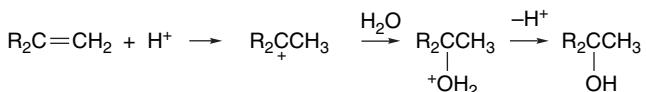
j. K. D. Berlin, R. O. Lyerla, D. E. Gibbs, and J. P. Devlin, *J. Chem. Soc., Chem. Commun.*, 1246 (1970).

⁸. K. B. Becker and C. A. Grob, *Synthesis*, 789 (1973).

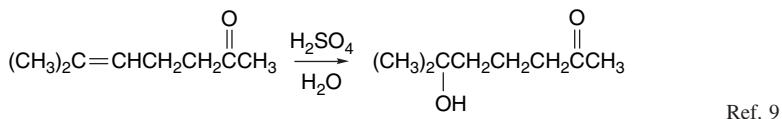
are likely to react via the ion pair mechanism, which is not necessarily stereospecific, as the carbocation intermediate permits loss of stereochemistry relative to the reactant alkene. It might be expected that the ion pair mechanism would lead to a preference for *syn* addition, since at the instant of formation of the ion pair, the halide is on the same side of the alkene as the proton being added. Rapid collapse of the ion pair intermediate would lead to *syn* addition. If the lifetime of the ion pair is longer and the ion pair dissociates, a mixture of *syn* and *anti* addition products can be formed. The termolecular mechanism is expected to give *anti* addition because the nucleophilic attack occurs on the opposite side of the double bond from proton addition. Further discussion of the structural features that affect the competition between the two possible mechanisms can be found in Section 6.1 of Part A.

4.1.2. Hydration and Other Acid-Catalyzed Additions of Oxygen Nucleophiles

Oxygen nucleophiles can be added to double bonds under strongly acidic conditions. A fundamental example is the hydration of alkenes in acidic aqueous solution.

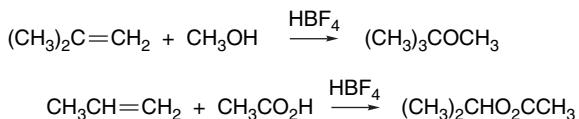


Addition of a proton occurs to give the more-substituted carbocation, so addition is regioselective and in accord with Markovnikov's rule. A more detailed discussion of the reaction mechanism is given in Section 6.2 of Part A. Owing to the strongly acidic and rather vigorous conditions required to effect hydration of most alkenes, these conditions are applicable only to molecules that have no acid-sensitive functional groups. The reaction is occasionally applied to the synthesis of tertiary alcohols.



Moreover, because of the involvement of cationic intermediates, rearrangements can occur in systems in which a more stable cation can result by aryl, alkyl, or hydrogen migration. *Oxymercuration-reduction*, a much milder and more general procedure for alkene hydration, is discussed in the next section.

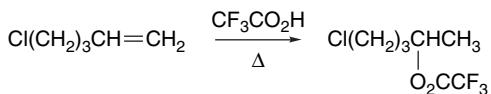
Addition of nucleophilic solvents such as alcohols and carboxylic acids can be effected by using strong acids as catalysts.¹⁰



⁹. J. Meinwald, *J. Am. Chem. Soc.*, **77**, 1617 (1955).

¹⁰. R. D. Morin and A. E. Bearse, *Ind. Eng. Chem.*, **43**, 1596 (1951); D. T. Dalgleish, D. C. Nonhebel, and P. L. Pauson, *J. Chem. Soc. C*, 1174 (1971).

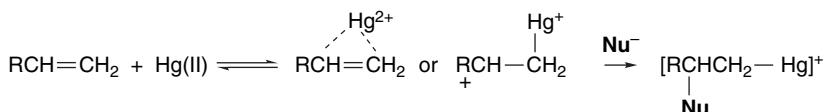
Trifluoroacetic acid (TFA) is strong enough to react with alkenes under relatively mild conditions.¹¹ The addition is regioselective in the direction predicted by Markovnikov's rule.



Ring strain enhances alkene reactivity. Norbornene, for example, undergoes rapid addition of TFA at 0° C.¹²

4.1.3. Oxymercuration-Reduction

The addition reactions discussed in Sections 4.1.1 and 4.1.2 are initiated by the interaction of a proton with the alkene. Electron density is drawn toward the proton and this causes nucleophilic attack on the double bond. The role of the electrophile can also be played by metal cations, and the mercuric ion is the electrophile in several synthetically valuable procedures.¹³ The most commonly used reagent is mercuric acetate, but the trifluoroacetate, trifluoromethanesulfonate, or nitrate salts are more reactive and preferable in some applications. A general mechanism depicts a *mercurinium ion* as an intermediate.¹⁴ Such species can be detected by physical measurements when alkenes react with mercuric ions in nonnucleophilic solvents.¹⁵ The cation may be predominantly bridged or open, depending on the structure of the particular alkene. The addition is completed by attack of a nucleophile at the more-substituted carbon. The nucleophilic capture is usually the rate- and product-controlling step.^{13,16}



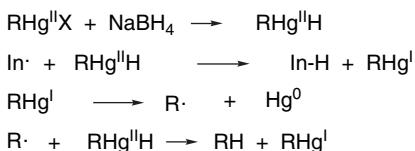
The nucleophiles that are used for synthetic purposes include water, alcohols, carboxylate ions, hydroperoxides, amines, and nitriles. After the addition step is complete, the mercury is usually reductively removed by sodium borohydride, the net result being the addition of hydrogen and the nucleophile to the alkene. The regioselectivity is excellent and is in the same sense as is observed for proton-initiated additions.¹⁷

- ¹¹. P. E. Peterson, R. J. Bopp, D. M. Chevli, E. L. Curran, D. E. Dillard, and R. J. Kamat, *J. Am. Chem. Soc.*, **89**, 5902 (1967).
- ¹². H. C. Brown, J. H. Kawakami, and K.-T. Liu, *J. Am. Chem. Soc.*, **92**, 5536 (1970).
- ¹³. (a) R. C. Larock, *Angew. Chem. Int. Ed. Engl.*, **17**, 27 (1978); (b) W. Kitching, *Organomet. Chem. Rev.*, **3**, 61 (1968).
- ¹⁴. S. J. Cristol, J. S. Perry, Jr., and R. S. Beckley, *J. Org. Chem.*, **41**, 1912 (1976); D. J. Pasto and J. A. Gontarz, *J. Am. Chem. Soc.*, **93**, 6902 (1971).
- ¹⁵. G. A. Olah and P. R. Clifford, *J. Am. Chem. Soc.*, **95**, 6067 (1973); G. A. Olah and S. H. Yu, *J. Org. Chem.*, **40**, 3638 (1975).
- ¹⁶. W. L. Waters, W. S. Linn, and M. C. Caserio, *J. Am. Chem. Soc.*, **90**, 6741 (1968).
- ¹⁷. H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **35**, 1844 (1970); H. C. Brown, J. T. Kurek, M.-H. Rei, and K. L. Thompson, *J. Org. Chem.*, **49**, 2511 (1984); H. C. Brown, J. T. Kurek, M.-H. Rei, and K. L. Thompson, *J. Org. Chem.*, **50**, 1171 (1985).

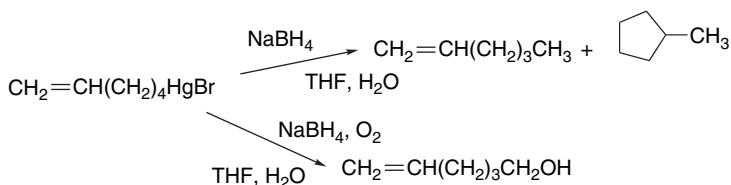
The reductive replacement of mercury using sodium borohydride is a free radical chain reaction involving a mercuric hydride intermediate.¹⁸

SECTION 4.1

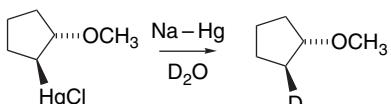
Electrophilic Addition to Alkenes



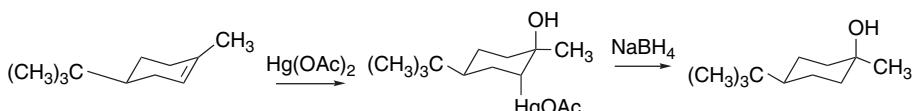
The evidence for the free radical mechanism includes the fact that the course of the reaction can be diverted by oxygen, an efficient radical scavenger. In the presence of oxygen, the mercury is replaced by a hydroxy group. Also consistent with a free radical intermediate is the formation of cyclic products when 5-hexenylmercury compounds are reduced with sodium borohydride.¹⁹ This cyclization reaction is highly characteristic of reactions involving 5-hexenyl radicals (see Part A, Section 11.2.3.3). In the presence of oxygen, no cyclic product is formed, indicating that O₂ traps the radical faster than cyclization occurs.



Tri-*n*-butyltin hydride can also be used for reductive demercuration.²⁰ An alternative reagent for demercuration is sodium amalgam in a protic solvent. Here the evidence is that free radicals are not involved and the mercury is replaced with retention of configuration.²¹



The stereochemistry of oxymercurcation has been examined in a number of systems. Conformationally biased cyclic alkenes such as 4-*t*-butylcyclohexene and 4-*t*-butyl-1-methylcyclohexene give exclusively the product of *anti* addition, which is consistent with a mercurinium ion intermediate.^{17,22}



¹⁸. C. L. Hill and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 870 (1974).

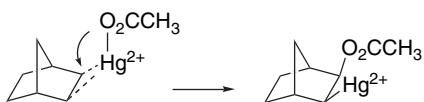
¹⁹. R. P. Quirk and R. E. Lea, *J. Am. Chem. Soc.*, **98**, 5973 (1976).

²⁰. G. M. Whiteside and J. San Fillipo, Jr., *J. Am. Chem. Soc.*, **92**, 6611 (1970).

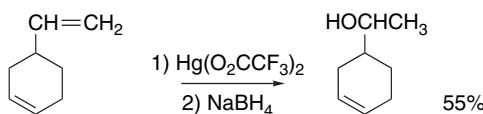
²¹. F. R. Jensen, J. J. Miller, S. J. Cristol, and R. S. Beckley, *J. Org. Chem.*, **37**, 434 (1972); R. P. Quirk, *J. Org. Chem.*, **37**, 3554 (1972); W. Kitching, A. R. Atkins, G. Wickham, and V. Alberts, *J. Org. Chem.*, **46**, 563 (1981).

²². H. C. Brown, G. J. Lynch, W. J. Hammar, and L. C. Liu, *J. Org. Chem.*, **44**, 1910 (1979).

Norbornene, in contrast reacts by *syn* addition.²³ This is believed to occur by internal transfer of the nucleophile.

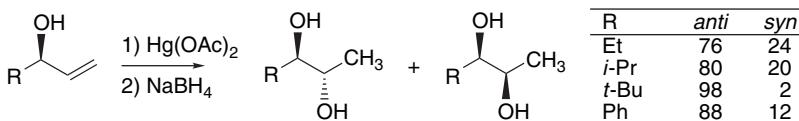


The reactivity of different alkenes toward mercuration spans a considerable range and is governed by a combination of steric and electronic factors.²⁴ Terminal double bonds are more reactive than internal ones. Disubstituted terminal alkenes, however, are more reactive than monosubstituted cases, as would be expected for electrophilic attack. (See Part A, Table 5.6 for comparative rate data.) The differences in relative reactivities are large enough that selectivity can be achieved with certain dienes.

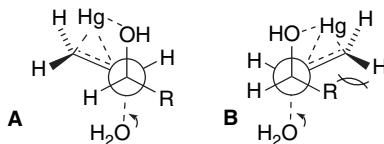


Ref. 24

Diastereoselectivity has been observed in oxymercuration of alkenes having nearby oxygen substituents. Terminal allylic alcohols show a preference for formation of the *anti* 2,3-diols.



This result can be explained in terms of a steric preference for conformation **A** over **B**. The approach of the mercuric ion is directed by the hydroxy group. The selectivity increases with the size of the substituent R.²⁵



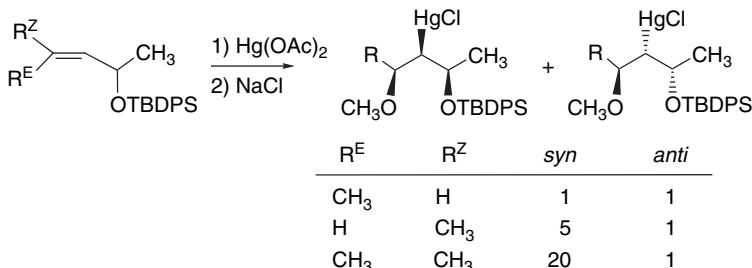
The directive effect of allylic silyoxy groups has also been examined. The reactions are completely regioselective for 1,3-oxygen substitution. The reaction of

²³ T. G. Traylor and A. W. Baker, *J. Am. Chem. Soc.*, **85**, 2746 (1963); H. C. Brown and J. H. Kawakami, *J. Am. Chem. Soc.*, **95**, 8665 (1973).

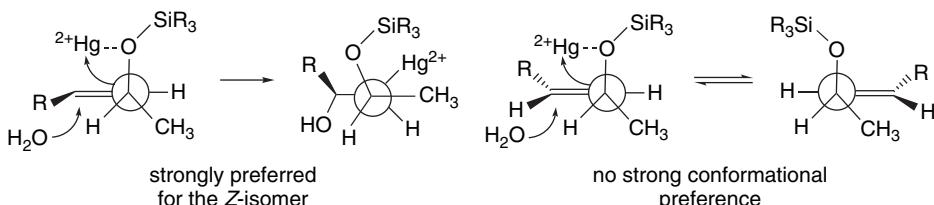
²⁴ H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **37**, 1937 (1972); H. C. Brown, P. J. Geoghegan, Jr., G. J. Lynch, and J. T. Kurek, *J. Org. Chem.*, **37**, 1941 (1972); H. C. Brown, P. J. Geoghegan, Jr., and J. T. Kurek, *J. Org. Chem.*, **46**, 3810 (1981).

²⁵ B. Giese and D. Bartmann, *Tetrahedron Lett.*, **26**, 1197 (1985).

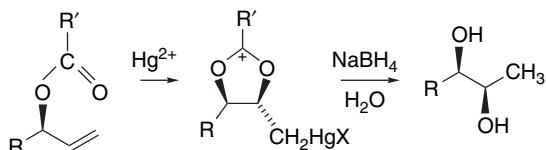
Z-isomers of 2-pentenyoxy ethers show modest stereoselectivity, but the *E*-ethers show no stereoselectivity.²⁶ Trisubstituted allylic TBDPS ethers show good stereoselectivity.²⁷



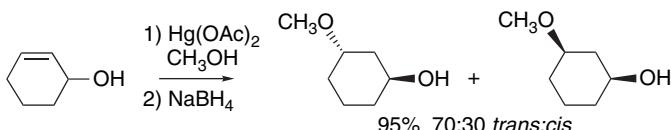
These results are consistent with a directive effect by the silyloxy substituent through the sterically favored conformation of the reactant.



With acetoxy derivatives, the 2,3-*syn* isomer is preferred as a result of direct nucleophilic participation by the carbonyl oxygen.



Polar substituents can exert a directing effect. Cyclohexenol, for example, gives high regioselectivity but low stereoselectivity.²⁸ This indicates that some factor other than hydroxy coordination is involved.



A computational study of remote directing effects was undertaken in substituted norbornenes.²⁹ It was concluded that polar effects of EWGs favors mercuration at the

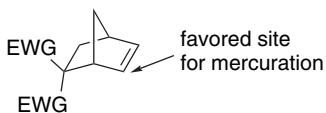
²⁶ R. Cormick, J. Loefstedt, P. Perlmutter, and G. Westman, *Tetrahedron Lett.*, **38**, 2737 (1997).

²⁷ R. Cormick, P. Perlmutter, W. Selajarern, and H. Zhang, *Tetrahedron Lett.*, **41**, 3713 (2000).

²⁸ Y. Senda, S. Takayanagi, T. Sudo, and H. Itoh, *J. Chem. Soc., Perkin Trans. 1*, 270 (2001).

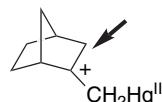
²⁹ P. Mayo, G. Orlova, J. D. Goddard, and W. Tam, *J. Org. Chem.*, **66**, 5182 (2001).

carbon that is closer to the substituent, which is attributed to a favorable polar effect that stabilizes the negative charge on the mercurated carbon.



Visual models, additional information and exercises on Oxymercuration can be found in the Digital Resource available at: Springer.com/carey-sundberg.

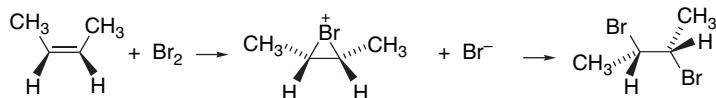
Scheme 4.1 includes examples of oxymercuration reactions. Entries 1 and 2 illustrate the Markovnikov orientation under typical reaction conditions. The high *exo* selectivity in Entry 3 is consistent with steric approach control on a weakly bridged (or open) mercurinium ion. There is no rearrangement, indicating that the intermediate is a localized cation.



Entries 4 and 5 involve formation of ethers using alcohols as solvents, whereas the reaction in Entry 6 forms an amide in acetonitrile. Entries 7 and 8 show use of other nucleophiles to capture the mercurinium ion.

4.1.4. Addition of Halogens to Alkenes

The addition of chlorine or bromine to an alkene is a very general reaction. Section 6.3 of Part A provides a discussion of the reaction mechanism. Bromination of simple alkenes is extremely fast. Some specific rate data are tabulated and discussed in Section 6.3 of Part A. As halogenation involves electrophilic attack, substituents on the double bond that increase electron density increase the rate of reaction, whereas EWG substituents have the opposite effect. Considerable insight into the mechanism of halogen addition has come from studies of the stereochemistry of the reaction. Most simple alkenes add bromine in a stereospecific manner, giving the product of *anti* addition. Among the alkenes that give *anti* addition products are *Z*-2-butene, *E*-2-butene, maleic and fumaric acid, and a number of cycloalkenes.³⁰ Cyclic, positively charged bromonium ion intermediates provide an explanation for the observed *anti* stereospecificity.



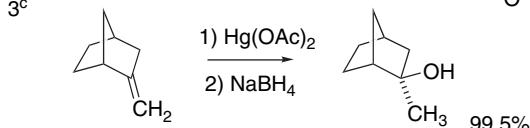
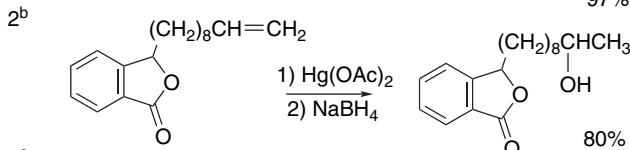
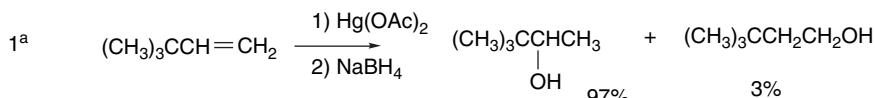
³⁰. J. H. Rolston and K. Yates, *J. Am. Chem. Soc.*, **91**, 1469, 1477 (1969).

Scheme 4.1. Addition via Mercuration Reactions

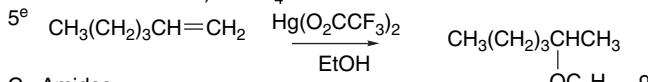
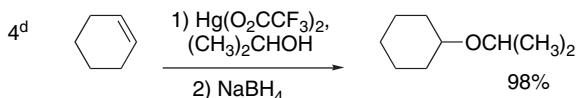
SECTION 4.1

Electrophilic Addition to
Alkenes

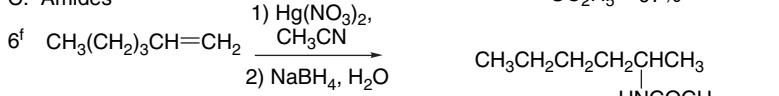
A. Alcohols



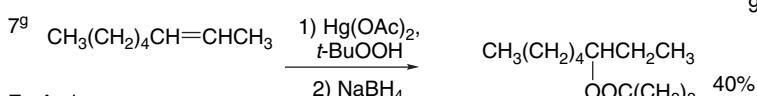
B. Ethers



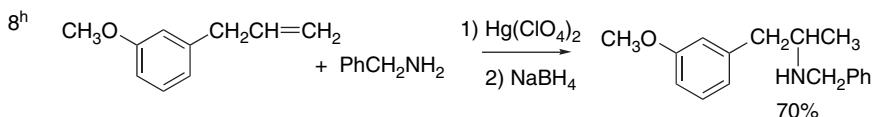
C. Amides



D. Peroxides



E. Amines

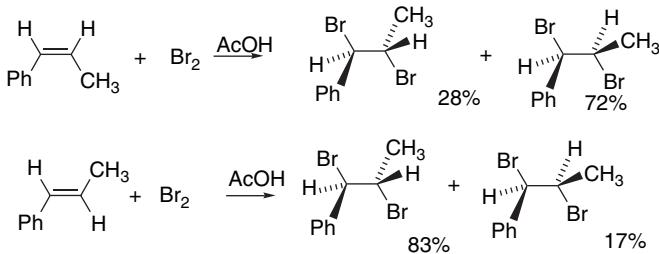
a. H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **35**, 1844 (1970).b. H. L. Wehrmeister and D. E. Robertson, *J. Org. Chem.*, **33**, 4173 (1968).c. H. C. Brown and W. J. Hammar, *J. Am. Chem. Soc.*, **89**, 1524 (1967).d. H. C. Brown and M.-H. Rei, *J. Am. Chem. Soc.*, **91**, 5646 (1969).e. H. C. Brown, J. T. Kurek, M.-H. Rei, and K. L. Thompson, *J. Org. Chem.*, **50**, 1171 (1985).f. H. C. Brown and J. T. Kurek, *J. Am. Chem. Soc.*, **91**, 5647 (1969).g. D. H. Ballard and A. J. Bloodworth, *J. Chem. Soc. C*, 945 (1971).h. R. C. Griffith, R. J. Gentile, T. A. Davidson, and F. L. Scott, *J. Org. Chem.*, **44**, 3580 (1979).

The bridging by bromine prevents rotation about the remaining bond and back-side nucleophilic opening of the bromonium ion by bromide ion leads to the observed *anti* addition. Direct evidence for the existence of bromonium ions has been obtained from NMR measurements.³¹ A bromonium ion salt (with Br_3^- as the counterion) has been isolated from the reaction of bromine with the very hindered alkene adamantylideneadamantane.³²

³¹. G. A. Olah, J. M. Bollinger, and J. Brinich, *J. Am. Chem. Soc.*, **90**, 2587 (1968); G. A. Olah, P. Schilling, P. W. Westerman, and H. C. Lin, *J. Am. Chem. Soc.*, **96**, 3581 (1974).

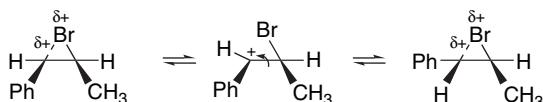
³². J. Strating, J. H. Wierenga, and H. Wynberg, *J. Chem. Soc., Chem. Commun.*, 907 (1969).

A substantial amount of *syn* addition is observed for *Z*-1-phenylpropene (27–80% *syn* addition), *E*-1-phenylpropene (17–29% *syn* addition), and *cis*-stilbene (up to 90% *syn* addition in polar solvents).



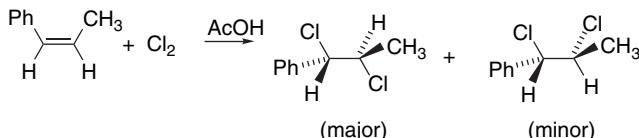
Ref. 30

A common feature of the compounds that give extensive *syn* addition is the presence of a phenyl substituent on the double bond. The presence of a phenyl substituent diminishes the strength of bromine bridging by stabilizing the cationic center. A weakly bridged structure in equilibrium with an open benzylic cation can account for the loss in stereospecificity.



The diminished stereospecificity is similar to that noted for hydrogen halide addition to phenyl-substituted alkenes.

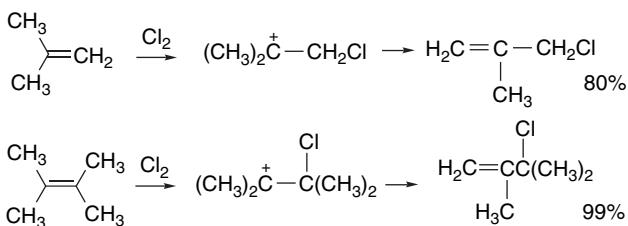
Although chlorination of aliphatic alkenes usually gives *anti* addition, *syn* addition is often dominant for phenyl-substituted alkenes.³³



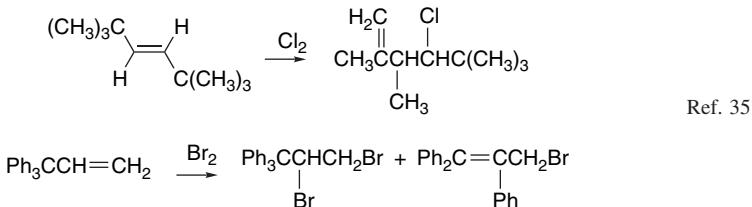
These results, too, reflect a difference in the extent of bridging in the intermediates. With unconjugated alkenes, there is strong bridging and high *anti* stereospecificity. Phenyl substitution leads to cationic character at the benzylic site, and there is more *syn* addition. Because of its smaller size and lesser polarizability, chlorine is not as effective as bromine in bridging for any particular alkene. Bromination therefore generally gives a higher degree of *anti* addition than chlorination, all other factors being the same.³⁴

³³. M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 2161, 2172 (1965); R. C. Fahey, *J. Am. Chem. Soc.*, **88**, 4681 (1966); R. C. Fahey and C. Shubert, *J. Am. Chem. Soc.*, **87**, 5172 (1965).

³⁴. R. J. Abraham and J. R. Monasterios, *J. Chem. Soc., Perkin Trans. I*, 1446 (1973).

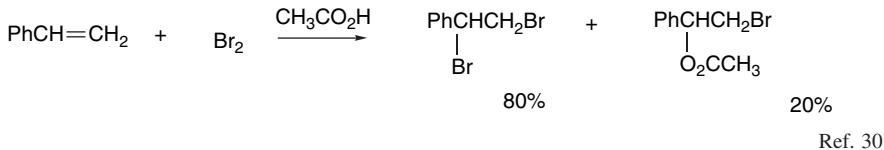


Skeletal rearrangements are observed in systems that are prone toward migration.

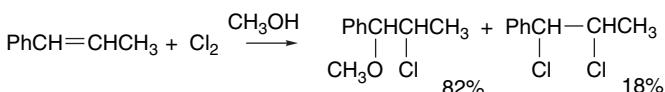


Ref. 36

Nucleophilic solvents can compete with halide ion for the cationic intermediate. For example, the bromination of styrene in acetic acid leads to significant amounts of the acetoxybromo derivative.



The acetoxy group is introduced exclusively at the benzylic carbon. This is in accord with the intermediate being a weakly bridged species or a benzylic cation. The addition of bromide salts to the reaction mixture diminishes the amount of acetoxy compound formed by shifting the competition for the electrophile in favor of the bromide ion. Chlorination in nucleophilic solvents can also lead to solvent incorporation, as, for example, in the chlorination of 1-phenylpropene in methanol.³⁷



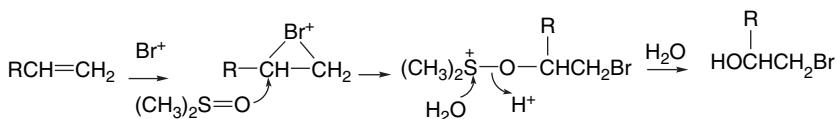
From a synthetic point of view, the participation of water in brominations, leading to bromohydrins, is the most important example of nucleophilic capture of the intermediate by solvent. To favor introduction of water, it is desirable to keep the concentration

³⁵. M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 4285 (1965).

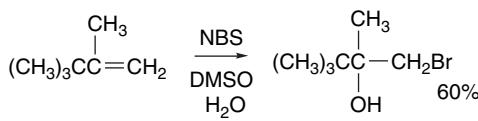
³⁶. R. O. C. Norman and C. B. Thomas, *J. Chem. Soc. B*, 598 (1967).

³⁷. M. L. Poutsma and J. L. Kartch, *J. Am. Chem. Soc.*, **89**, 6595 (1967).

of the bromide ion as low as possible. One method for accomplishing this is to use *N*-bromosuccinimide (NBS) as the brominating reagent.^{38,39} High yields of bromohydrins are obtained by using NBS in aqueous DMSO. The reaction is a stereospecific *anti* addition. As in bromination, a bromonium ion intermediate can explain the *anti* stereospecificity. It has been shown that the reactions in DMSO involve nucleophilic attack by the sulfoxide oxygen. The resulting alkoxy sulfonium ion intermediate reacts with water to give the bromohydrin.



In accord with the Markovnikov rule, the hydroxy group is introduced at the carbon best able to support positive charge.

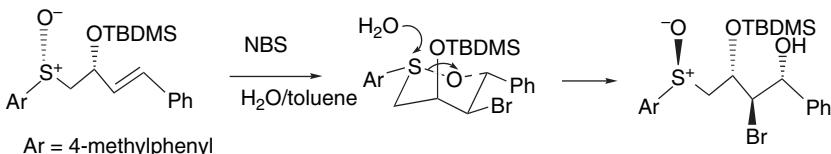


Ref. 40



Ref. 41

The participation of sulfoxide groups can be used to control the stereochemistry in acyclic systems. In the reaction shown below, the internal sulfoxide captures the bromonium ion and then undergoes inversion at sulfur in the hydrolytic step.



Ref. 42

A procedure that is useful for the preparation of both bromohydrins and iodohydrins involves *in situ* generation of the hypohalous acid from NaBrO₃ or NaIO₄ by reduction with bisulfite.⁴³

³⁸ A. J. Sisti and M. Meyers, *J. Org. Chem.*, **38**, 4431 (1973).

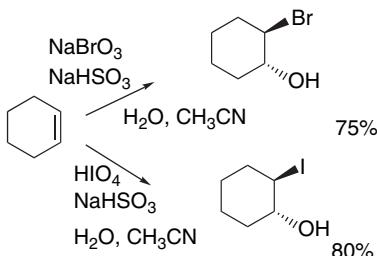
³⁹ C. O. Guss and R. Rosenthal, *J. Am. Chem. Soc.*, **77**, 2549 (1965).

⁴⁰ D. R. Dalton, V. P. Dutta, and D. C. Jones, *J. Am. Chem. Soc.*, **90**, 5498 (1968).

⁴¹ A. W. Langman and D. R. Dalton, *Org. Synth.*, **59**, 16 (1979).

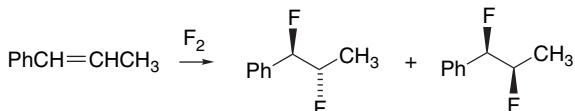
⁴² S. Raghavan and M. A. Rasheed, *Tetrahedron*, **59**, 10307 (2003).

⁴³ H. Masuda, K. Takase, M. Nishio, A. Hasegawa, Y. Nishiyama, and Y. Ishii, *J. Org. Chem.*, **59**, 5550 (1994).

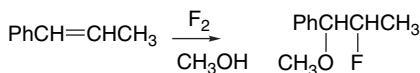


These reactions show the same regioselectivity and stereoselectivity as other reactions that proceed through halonium ion intermediates.

Because of its high reactivity, special precautions must be taken with reactions of fluorine and its use is somewhat specialized.⁴⁴ Nevertheless, there is some basis for comparison with the less reactive halogens. Addition of fluorine to *Z*- and *E*-1-propenylbenzene is not stereospecific, but *syn* addition is somewhat favored.⁴⁵ This result is consistent with formation of a cationic intermediate.

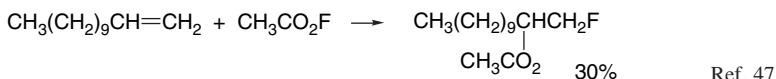
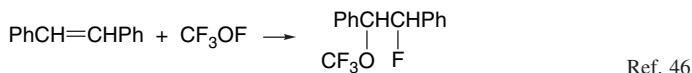


In methanol, the solvent incorporation product is formed, as would be expected for a cationic intermediate.



These results are consistent with the expectation that fluorine would not be an effective bridging atom.

There are other reagents, such as CF_3OF and $\text{CH}_3\text{CO}_2\text{F}$, that transfer an electrophilic fluorine to double bonds. These reactions probably involve an ion pair that collapses to an addition product.



The stability of hypofluorites is improved in derivatives having electron-withdrawing substituents, such as 2,2-dichloropropanoyl hypofluorite.⁴⁸ Various other fluorinating agents have been developed and used, including *N*-fluoropyridinium salts such as the

⁴⁴ H. Vypel, *Chimia*, **39**, 305 (1985).

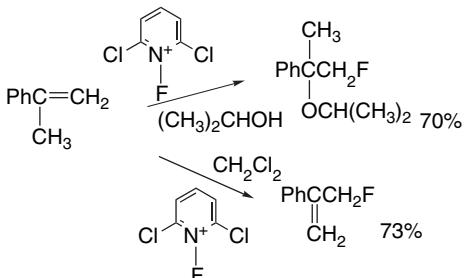
⁴⁵ R. F. Merritt, *J. Am. Chem. Soc.*, **89**, 609 (1967).

⁴⁶ D. H. R. Barton, R. H. Hesse, G. P. Jackman, L. Ogunkoya, and M. M. Pechet, *J. Chem. Soc., Perkin Trans. 1*, 739 (1974).

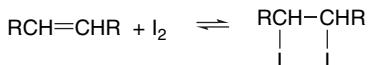
⁴⁷ S. Rozen, O. Lerman, M. Kol, and D. Hebel, *J. Org. Chem.*, **50**, 4753 (1985).

⁴⁸ S. Rozen and D. Hebel, *J. Org. Chem.*, **55**, 2621 (1990).

triflate⁴⁹ and heptafluorodiborate.⁵⁰ The reactivity of these reagents can be “tuned” by varying the pyridine ring substituents. In contrast to the hypofluorites, these reagents are storables.⁵¹ In nucleophilic solvents such as acetic acid or alcohols, the reagents give addition products, whereas in nonnucleophilic solvents, alkenes give substitution products resulting from deprotonation of a carbocation intermediate.

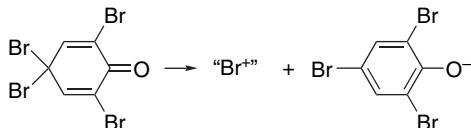


Addition of iodine to alkenes can be accomplished by a photochemically initiated reaction. Elimination of iodine is catalyzed by excess iodine, but the diido compounds can be obtained if unreacted iodine is removed.⁵²



The diido compounds are very sensitive to light and are seldom used in syntheses.

The elemental halogens are not the only sources of electrophilic halogen, and for some synthetic purposes other “positive halogen” compounds may be preferable as electrophiles. The utility of *N*-bromosuccinimide in formation of bromohydrins was mentioned earlier. Both *N*-chlorosuccinimide and *N*-bromosuccinimide transfer electrophilic halogen with the succinimide anion acting as the leaving group. As this anion is subsequently protonated to give the weak nucleophile succinimide, these reagents favor nucleophilic additions by solvent and cyclization reactions because there is no competition from a halide anion. Other compounds that are useful for specific purposes are indicated in Table 4.2. Pyridinium hydrotribromide (pyridinium hydrobromide perbromide), benzyltrimethyl ammonium tribromide, and dioxane-bromine are examples of complexes of bromine in which its reactivity is somewhat attenuated, resulting in increased selectivity. In 2,4,4,6-tetrabromocyclohexadienone is a very mild and selective source of electrophilic bromine; the leaving group is 2,4,6-tribromophenoxy ion.



⁴⁹. T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, and K. Tomita, *J. Am. Chem. Soc.*, **112**, 8563 (1990).

⁵⁰. A. J. Poss, M. Van Der Puy, D. Nalewajek, G. A. Shia, W. J. Wagner, and R. L. Frenette, *J. Org. Chem.*, **56**, 5962 (1991).

⁵¹. T. Umemoto, K. Tomita, and K. Kawada, *Org. Synth.*, **69**, 129 (1990).

⁵². P. S. Skell and R. R. Pavlis, *J. Am. Chem. Soc.*, **86**, 2956 (1964); R. L. Ayres, C. J. Michejda, and E. P. Rack, *J. Am. Chem. Soc.*, **93**, 1389 (1971).

Table 4.2. Other Sources of Electrophilic Halogen

Reagents	Synthetic applications ^a	SECTION 4.1 <i>Electrophilic Addition to Alkenes</i>
A. Chlorinating agents		
Sodium hypochlorite solution	Formation of chlorohydrins from alkenes	
<i>N</i> -Chlorosuccinimide	Chlorination with solvent participation and cyclization	
Chloramine-T ^b	Formation of chlorohydrins in acidic aqueous solution.	
B. Brominating agents		
Pyridinium hydrotribromide (pyridinium hydrobromide perbromide)	Mild and selective substitute for bromine	
Dioxane bromine complex	Same as for pyridinium hydrotribromide	
<i>N</i> -Bromosuccinimide	Used in place of bromine when low bromide concentration is required.	
2,4,4,6-Tetrabromocyclohexadienone ^c	Selective bromination of alkenes and carbonyl compounds	
Quaternary ammonium tribromides ^d	Similar to pyridinium hydrotribromide	
C. Iodinating agents		
<i>bis</i> -(Pyridinium)iodonium ^e tetrafluoroborate	Selective iodination and iodocyclization.	

a. For specific examples, consult M. Fieser and L. F. Fieser, *Reagents for Organic Synthesis*, John Wiley & Sons, New York.

b. B. Damin, J. Garapon, and B. Sillion, *Synthesis*, 362 (1981).

c. F. Calo, F. Cimina, L. Lopez, and P. E. Todesco, *J. Chem. Soc., C*, 3652 (1971); Y. Kitahara, T. Kato, and I. Ichinose, *Chem. Lett.*, 283 (1976).

d. S. Kaigashi and T. Kakinami, *Ind. Chem. Libr.*, 7, 29 (1985); G. Bellucci, C. Chiappe, and F. Marioni, *J. Am. Chem. Soc.*, 109, 515 (1987).

e. J. Barluenga, J. M. Gonzalez, M. A. Garcia-Martin, P. J. Campos, and G. Asensio, *J. Org. Chem.*, 58, 2058 (1993).

Electrophilic iodine reagents are extensively employed in iodocyclization (see Section 4.2.1). Several salts of pyridine complexes with I⁺ such as *bis*-(pyridinium)iodonium tetrafluoroborate and *bis*-(collidine)iodonium hexafluorophosphate have proven especially effective.⁵³

4.1.5. Addition of Other Electrophilic Reagents

Many other halogen-containing compounds react with alkenes to give addition products by mechanisms similar to halogenation. A complex is generated and the halogen is transferred to the alkene to generate a bridged cationic intermediate. This may be a symmetrical halonium ion or an unsymmetrically bridged species, depending on the ability of the reacting carbon atoms to accommodate positive charge. The direction of opening of the bridged intermediate is usually governed by electronic factors. That is, the addition is completed by attack of the nucleophile at the more positive carbon atom of the bridged intermediate. The regiochemistry of addition therefore follows Markovnikov's rule. The stereochemistry of addition is usually *anti*, because of the involvement of a bridged halonium intermediate.⁵⁴ Several reagents of this type are listed in Entries 1 to 6 of Scheme 4.2. The nucleophilic anions include isocyanate, azide, thiocyanate, and nitrate.

Entries 7 to 9 involve other reagents that react by similar mechanisms. In the case of thiocyanogen chloride and thiocyanogen, the formal electrophile is [NCS]⁺. The presumed intermediate is a cyanothiairanium ion. The thiocyanate anion is an

⁵³. Y. Brunel and G. Rousseau, *J. Org. Chem.*, 61, 5793 (1996).

⁵⁴. A. Hassner and C. Heathcock, *J. Org. Chem.*, 30, 1748 (1965).

Scheme 4.2. Addition Reactions of Other Electrophilic Reagents

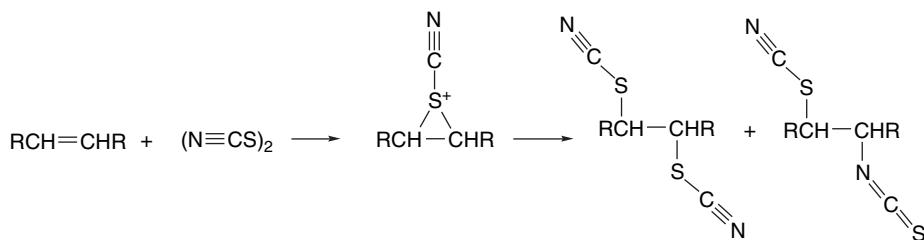
CHAPTER 4

*Electrophilic Additions
to Carbon-Carbon
Multiple Bonds*

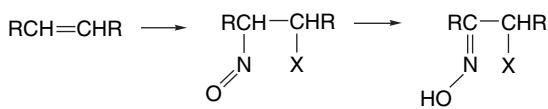
Reagent	Preparation	Product
1 ^a I—N=C=O	AgCNO, I ₂	RCH—CHR I NCO
2 ^b Br—N=N ⁺ =N ⁻	HN ₃ , Br ₂	RCH—CHR Br N ₃
3 ^c I—N=N ⁺ =N ⁻	NaN ₃ , ICl	RCH—CHR I N ₃
4 ^d I—S=C≡N	(NCS) ₂ , I ₂	RCH—CHR I S—C≡N
5 ^e I—ONO ₂	AgNO ₃ , ICl	RCH—CHR I ONO ₂
6 ^f Cl—SCN	Pb(SCN) ₂ , Cl ₂	RCH—CHR Cl SCN
7 ^g N≡CS—SC≡N	Pb(SCN) ₂ , Br ₂	RCH—CHR RCH—CHR N≡CS SC≡N and N≡CS N=C=S
8 ^h O=N—Cl		RC—CHR HON Cl
9 ⁱ O=N—O ₂ CH	C ₅ H ₁₁ ONO HCO ₂ H	RC—CHR HON O ₂ CH

- a. A. Hassner, R. P. Hoblitt, C. Heathcock, J. E. Kropp, and M. Lorber, *J. Am. Chem. Soc.*, **92**, 1326 (1970); A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967).
- b. A. Hassner, F. P. Boerwinkle, and A. B. Levy, *J. Am. Chem. Soc.*, **92**, 4879 (1970).
- c. F. W. Fowler, A. Hassner, and L. A. Levy, *J. Am. Chem. Soc.*, **89**, 2077 (1967).
- d. R. J. Maxwell and L. S. Silbert, *Tetrahedron Lett.*, 4991 (1978).
- e. J. W. Lown and A. V. Joshua, *J. Chem. Soc., Perkin Trans. 1*, 2680 (1973).
- f. R. G. Guy and I. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 281 (1973); *J. Chem. Soc., Perkin Trans. 2*, 1359 (1973).
- g. R. Bonnett, R. G. Guy, and D. Lanigan, *Tetrahedron*, **32**, 2439 (1976); R. J. Maxwell, L. S. Silbert, and J. R. Russell, *J. Org. Chem.*, **42**, 1510 (1977).
- h. J. Meinwald, Y. C. Meinwald, and T. N. Baker, III, *J. Am. Chem. Soc.*, **86**, 4074 (1964).
- i. H. C. Hamann and D. Swern, *J. Am. Chem. Soc.*, **90**, 6481 (1968).

ambident nucleophile and both carbon-sulfur and carbon-nitrogen bond formation can be observed, depending upon the reaction conditions (see Entry 7 in Scheme 4.2).

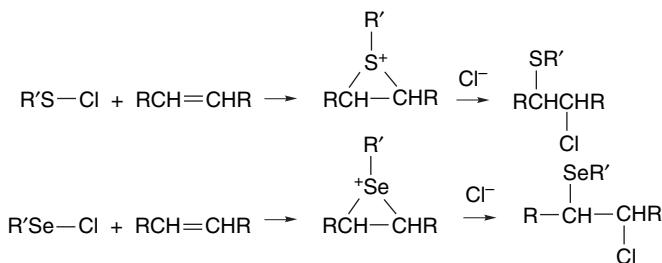


For nitrosyl chloride (Entry 8) and nitrosyl formate (Entry 9), the electrophile is the nitrosonium ion NO⁺. The initially formed nitroso compounds can dimerize or isomerize to the more stable oximes.



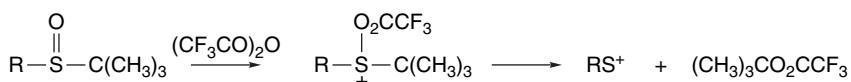
4.1.6. Addition Reactions with Electrophilic Sulfur and Selenium Reagents

Compounds having divalent sulfur and selenium atoms bound to more electronegative elements react with alkenes to give addition products. The mechanism is similar to that in halogenation and involves of bridged cationic intermediates.



In many synthetic applications, the sulfur or selenium substituent is subsequently removed by elimination, as is discussed in Chapter 6.

A variety of electrophilic reagents have been employed and several examples are given in Scheme 4.3. The sulfonylation reagents are listed in Section A. Both aryl and alkyl sulfonyl chlorides are reactive (Entries 1 and 2). Dimethyl(methylthio)sulfonium fluoroborate (Entry 3) uses dimethyl sulfide as a leaving group and can be utilized to effect capture of hydroxylic solvents and anionic nucleophiles, such as acetate and cyanide. Entries 4 and 5 are examples of *sulfenamides*, which normally require a Lewis acid catalyst to react with alkenes. Entry 6 represents application of the *Pummerer rearrangement* for in situ generation of a sulfonylation reagent. Sulfoxides react with acid anhydrides to generate sulfonium salts. When a *t*-alkyl group is present, fragmentation occurs and a sulfonylium ion is generated.⁵⁵ TFAA is the preferred anhydride in this application.



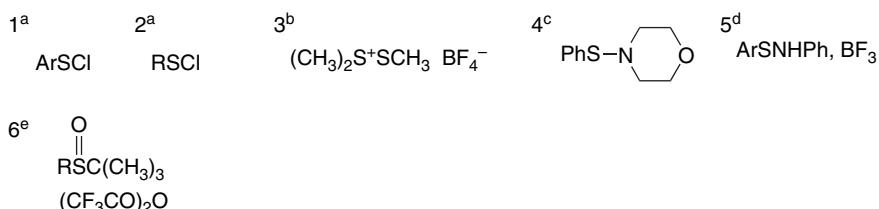
The selenylation reagents include the arylselenenyl chlorides and bromides (Entries 7 and 8), selenylium salts with nonnucleophilic counterions (Entry 9), and selenenyl trifluoroacetates, sulfates, and sulfonates (Entries 10 to 13). Diphenyl-diselenide reacts with several oxidation reagents to transfer electrophilic phenylselenenyl ions (Entries 14 to 16). *N*-Phenylselenenylphthalimide is a useful synthetic reagent that has the advantage of the nonnucleophilicity of the phthalimido leaving group (Entry 18). The hindered selenenyl bromide in Entry 19 is useful for selenylcyclizations (see Section 4.2.2).

Selenylation can also be done under conditions in which another nucleophilic component of the reaction captures the selenium-bridged ion. For

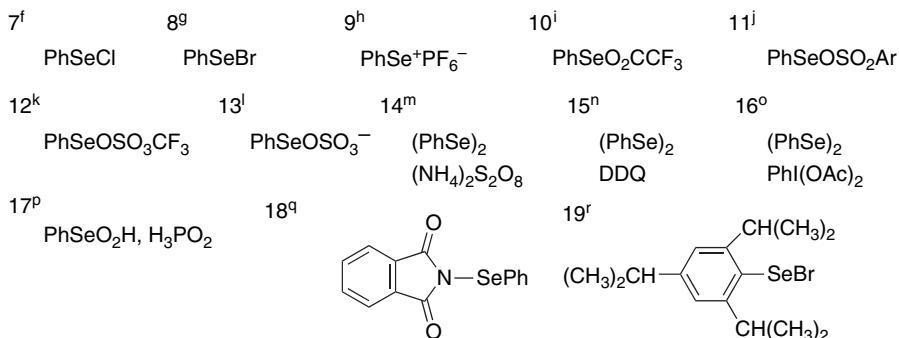
⁵⁵ M.-H. Brichard, M. Musick, Z. Janousek, and H. G. Viehe, *Synth. Commun.*, **20**, 2379 (1990).

Scheme 4.3. Sulfur and Selenium Reagents for Electrophilic Addition Reactions

A. Sulfenylation reagents

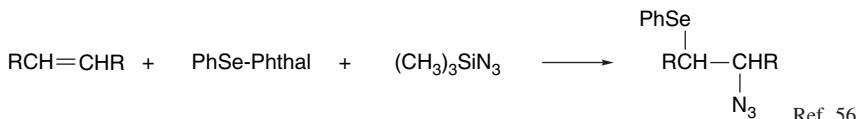


B. Selenenylation reagents



- a. G. Capozzi, G. Modena, and L. Pasquato in *The Chemistry of Sulphenic Acids and Their Derivatives*, S. Patai, ed., Wiley, Chichester, 1990, Chap. 10.
- b. B. M. Trost, T. Shibata, and S. J. Martin, *J. Am. Chem. Soc.*, **104**, 3228 (1982).
- c. P. Brownbridge, *Tetrahedron Lett.*, **25**, 3759 (1984); P. Brownbridge, *J. Chem. Soc. Chem. Commun.*, 1280 (1987); N. S. Zefirov, N. V. Zyuk, A. G. Kutateldze, and S. I. Kolbasenko, *Zh. Org. Khim.*, **23**, 227 (1987).
- d. L. Benati, P. C. Montevercchi, and P. Spagnolo, *J. Chem. Soc., Perkin Trans. I*, 1691 (1990).
- e. M.-H. Brichard, M. Musick, Z. Janousek, and H. G. Viehe, *Synth. Commun.*, **20**, 2378 (1990).
- f. K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **39**, 429 (1974).
- g. T. G. Back, *The Chemistry of Organic Selenenyl and Tellurium Compounds*, S. Patai, ed., Wiley, 1987, pp. 91–312.
- h. W. P. Jackson, S. V. Ley, and A. J. Whittle, *J. Chem. Soc.* 1173 (1980).
- i. H. J. Reich, *J. Org. Chem.*, **39**, 428 (1974).
- j. T. G. Back and K. R. Muralidharan, *J. Org. Chem.*, **56**, 2781 (1991).
- k. S. Murata and T. Suzuki, *Tetrahedron Lett.*, **28**, 4297, 4415 (1987).
- l. M. Tiecco, L. Testaferri, M. Tingoli, L. Bagnoli, and F. Marini, *J. Chem. Soc., Perkin Trans. I*, 1989 (1993).
- m. M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli, and D. Bartoli, *Tetrahedron Lett.*, **30**, 1417 (1989).
- n. M. Tiecco, L. Testaferri, A. Temperini, L. Bagnoli, F. Marini, and C. Santi, *Synlett*, 1767 (2001).
- o. M. Tingoli, M. Tiecco, L. Testaferri, and Temperini, *Synth. Commun.*, **28**, 1769 (1998).
- p. D. Labar, A. Krief, and L. Hevesi, *Tetrahedron Lett.*, 3967 (1978).
- q. K. C. Nicolaou, N. A. Petasis, and D. A. Claremon, *Tetrahedron*, **41**, 4835 (1985).
- r. B. H. Lipshutz and T. Gross, *J. Org. Chem.*, **60**, 3572 (1995).

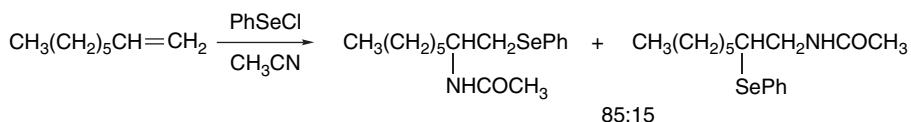
example, the combination phenylselenylphthalimide and trimethylsilyl azide generates β -azido selenides and phenylselenyl chloride used with AgBF_4 and ethyl carbamate give β -carbamido selenides.



⁵⁶. A. Hassner and A. S. Amarasekara, *Tetrahedron Lett.*, **28**, 5185 (1987); R. M. Giuliano and F. Duarte, *Synlett*, 419 (1992).

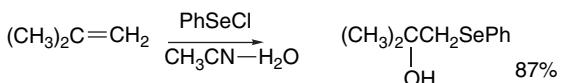
Ref. 57

In the absence of better nucleophiles, solvent can be captured, as in selenenylamidation, which occurs in acetonitrile.

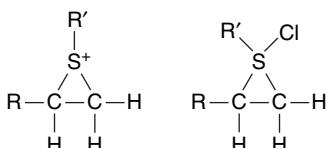


Ref. 58

When reactions with phenylselenenyl chloride are carried out in aqueous acetonitrile solution, β -hydroxyselenides are formed as the result of solvolysis of the chloride.⁵⁹

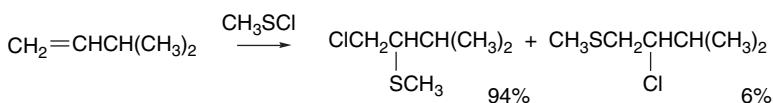


Mechanistic studies have been most thorough with the sulphenyl halides.⁶⁰ The reactions show moderate sensitivity to alkene structure, with ERGs on the alkene accelerating the reaction. The addition can occur in either the Markovnikov or anti-Markovnikov sense.⁶¹ The variation in regioselectivity can be understood by focusing attention on the sulfur-bridged intermediate, which may range from being a sulfonium ion to a less electrophilic chlorosulfurane.

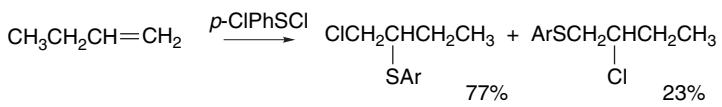


Compared to a bromonium ion, the C–S bonds are stronger and the TS for nucleophilic addition is reached later. This is especially true for the sulfurane structures. Steric interactions that influence access by the nucleophile are a more important factor in determining the direction of addition. For reactions involving phenylselenenyl chloride or methylsulphenyl chloride, the intermediate is a fairly stable species and ease of approach by the nucleophile is the major factor in determining the direction of ring opening. In these cases, the product has the anti-Markovnikov orientation.⁶²

- ⁵⁷. C. G. Francisco, E. I. Leon, J. A. Salazar, and E. Suarez, *Tetrahedron Lett.*, **27**, 2513 (1986).
- ⁵⁸. A. Toshimitsu, T. Aoai, H. Owada, S. Uemura, and M. Okano, *J. Org. Chem.*, **46**, 4727 (1981).
- ⁵⁹. A. Toshimitsu, T. Aoai, H. Owada, S. Uemura, and M. Okano, *Tetrahedron*, **41**, 5301 (1985).
- ⁶⁰. W. A. Smit, N. S. Zefirov, I. V. Bodrikov, and M. Z. Krimer, *Acc. Chem. Res.*, **12**, 282 (1979); G. H. Schmid and D. G. Garratt, *The Chemistry of Double-Bonded Functional Groups*, S. Patai, ed., Wiley-Interscience, New York, 1977, Chap. 9; G. A. Jones, C. J. M. Stirling, and N. G. Bromby, *J. Chem. Soc., Perkin Trans.*, **2**, 385 (1983).
- ⁶¹. W. H. Mueller and P. E. Butler, *J. Am. Chem. Soc.*, **90**, 2075 (1968); G. H. Schmid and D. I. Macdonald, *Tetrahedron Lett.*, **25**, 157 (1984).
- ⁶². G. H. Schmid, M. Strukelj, S. Dalipi, and M. D. Ryan, *J. Org. Chem.*, **52**, 2403 (1987).

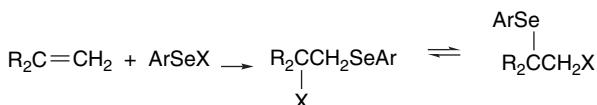


Ref. 61a



Ref. 63

Terminal alkenes react with selenenyl halides with Markovnikov regioselectivity.⁶⁴ However, the β -selenenyl halide addition products readily rearrange to the isomeric products.⁶⁵



4.2. Electrophilic Cyclization

When unsaturated reactants contain substituents that can participate as nucleophiles, electrophilic reagents frequently bring about cyclizations. Groups that can act as internal nucleophiles include carboxy and carboxylate, hydroxy, amino and amido, as well as carbonyl oxygen. There have been numerous examples of synthetic application of these electrophilic cyclizations.⁶⁶ The ring-size preference is usually $5 > 6 > 3 > 4$, but there are exceptions. Both the ring-size preference and the stereoselectivity reactions can usually be traced to structural and conformational features of the cyclization TS. Baldwin called attention to the role of stereoelectronic factors in cyclization reactions.⁶⁷ He classified cyclization reactions as *exo* and *endo* and as *tet*, *trig*, and *dig*, according to the hybridization at the cyclization center. The cyclizations are also designated by the size of the ring being formed. For any given separation ($n = 1, 2, 3$, etc.) of the electrophilic and nucleophilic centers, either an *exo* or *endo* mode of cyclization is usually preferred. The preferences for cyclization at trigonal centers are *5-endo* $>>$ *4-exo* for $n = 2$; *5-exo* $>$ *6-endo* for $n = 3$; and *6-exo* $>>$ *7-endo* for $n = 4$. These relationships are determined by the preferred trajectory of the nucleophile to the electrophilic center. Substituents can affect the TS structure by establishing a preferred conformation and by electronic or steric effects.

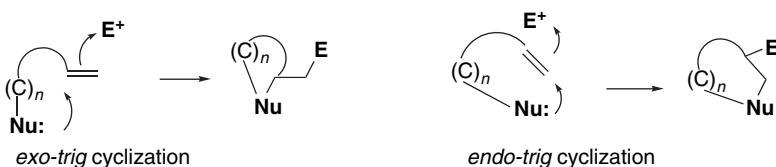
⁶³. G. H. Schmid, C. L. Dean, and D. G. Garratt, *Can. J. Chem.*, **54**, 1253 (1976).

⁶⁴. D. Liotta and G. Zima, *Tetrahedron Lett.*, 4977 (1978); P. T. Ho and R. J. Holt, *Can. J. Chem.*, **60**, 663 (1982).

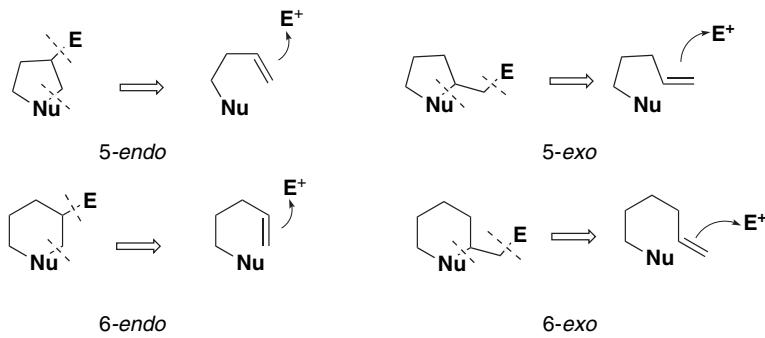
⁶⁵. S. Raucher, *J. Org. Chem.*, **42**, 2950 (1977).

⁶⁶. M. Frederickson and R. Grigg, *Org. Prep. Proced. Int.*, **29**, 63 (1997).

⁶⁷. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734, 738 (1976).



Electrophilic cyclizations are useful for closure of a variety of oxygen-, nitrogen-, and sulfur-containing rings. The product structure depends on the ring size and the *exo*-*endo* selectivity. The most common cases are formation of five- and six-membered rings.



4.2.1. Halocyclization

Brominating and iodinating reagents effect cyclization of alkenes that have a nucleophilic group situated to permit formation of five-, six-, and, in some cases, seven-membered rings. Hydroxy and carboxylate groups are the most common nucleophiles, but the reaction is feasible for any nucleophilic group that is compatible with the electrophilic halogen source. Amides and carbamates can react at either oxygen or nitrogen, depending on the relative proximity. Sulfonamides are also potential nitrogen nucleophiles. Carbonyl oxygens can act as nucleophiles and give stable products by α -deprotonation.

Intramolecular reactions usually dominate intermolecular addition for favorable ring sizes. Semiempirical (AM1) calculations found the intramolecular TS favorable to a comparable intermolecular reaction.⁶⁸ (See Figure 4.1) The intramolecular TS, which is nearly 4 kcal/mol more stable, is quite productlike with a C–O bond distance of 1.6 Å, and a bond order of 0.62. The bromonium ion bridging is unsymmetrical and fairly weak. The bond parameters for the intra- and intermolecular TSs are quite similar.

In general, cyclization can be expected in compounds having the potential for formation of five- or six-membered rings. In addition to the more typical bromination reagents, such as those listed in Table 4.2, the combination of trimethylsilyl bromide, a tertiary amine, and DMSO can effect bromolactonization.

⁶⁸ J. Sperka and D. C. Liotta, *Heterocycles*, **35**, 701 (1993).

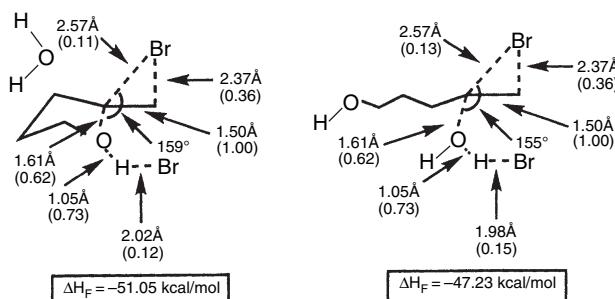
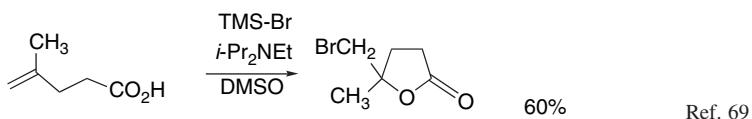
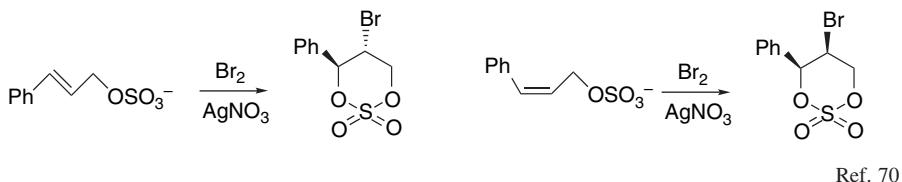


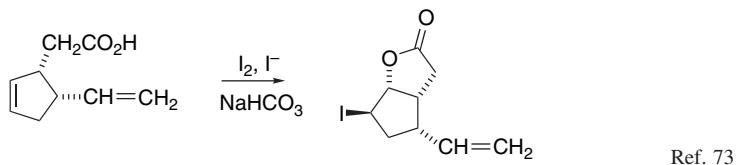
Fig. 4.1. Comparison of intramolecular and intermolecular transition structures for reaction of Br^+ , H_2O and 4-penten-1-ol. The numbers in parentheses are bond orders. From *Heterocycles*, **35**, 701 (1993)



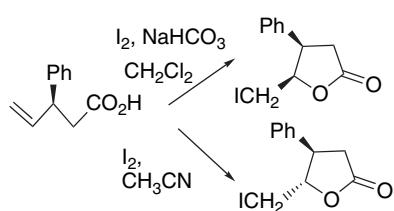
3-Phenylprop-2-enyl sulfates are cyclized stereospecifically and with Markovnikov regiochemical control. These are 6-*endo* cyclizations.



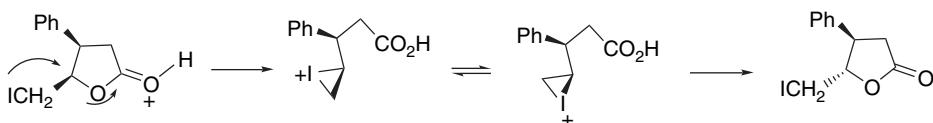
Iodine is a very good electrophile for effecting intramolecular nucleophilic addition to alkenes, as exemplified by the *iodolactonization reaction*.⁷¹ Reaction of iodine with carboxylic acids having carbon-carbon double bonds placed to permit intramolecular reaction results in formation of iodolactones. The reaction shows a preference for formation of five- over six-membered⁷² rings and is a stereospecific *anti* addition when carried out under basic conditions.



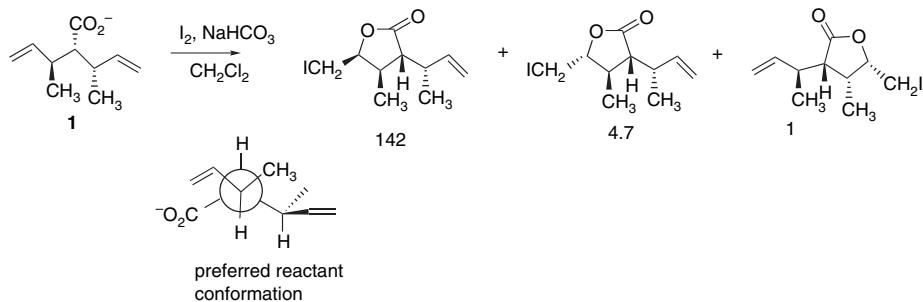
- ⁶⁹ R. Iwata, A. Tanaka, H. Mizuno, and K. Miyashita, *Heterocycles*, **31**, 987 (1990).
- ⁷⁰ J. G. Steinmann, J. H. Phillips, W. J. Sanders, and L. L. Kiessling, *Org. Lett.*, **3**, 3557 (2001).
- ⁷¹ M. D. Dowle and D. I. Davies, *Chem. Soc. Rev.*, **8**, 171 (1979); G. Cardillo and M. Orena, *Tetrahedron*, **46**, 3321 (1990); S. Robin and G. Rousseau, *Tetrahedron*, **54**, 13681 (1998); S. Ranganathan, K. M. Muraleedharan, N. K. Vaish, and N. Jayaraman, *Tetrahedron*, **60**, 5273 (2004).
- ⁷² S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *Tetrahedron*, **33**, 807 (1977); C. V. Ramana, K. R. Reddy, and M. Nagarajan, *Ind. J. Chem. B*, **35**, 534 (1996).
- ⁷³ L. A. Paquette, G. D. Crouse, and A. K. Sharma, *J. Am. Chem. Soc.*, **102**, 3972 (1980).



Ref. 75



Under kinetic conditions, iodolactonization reflects reactant conformation. Several cases illustrate how the stereoselectivity of iodolactonization can be related to reactant conformation. For example, the high stereoselectivity of **1** corresponds to proximity of the carboxylate group to one of the two double bonds in the preferred reactant conformation.⁷⁶



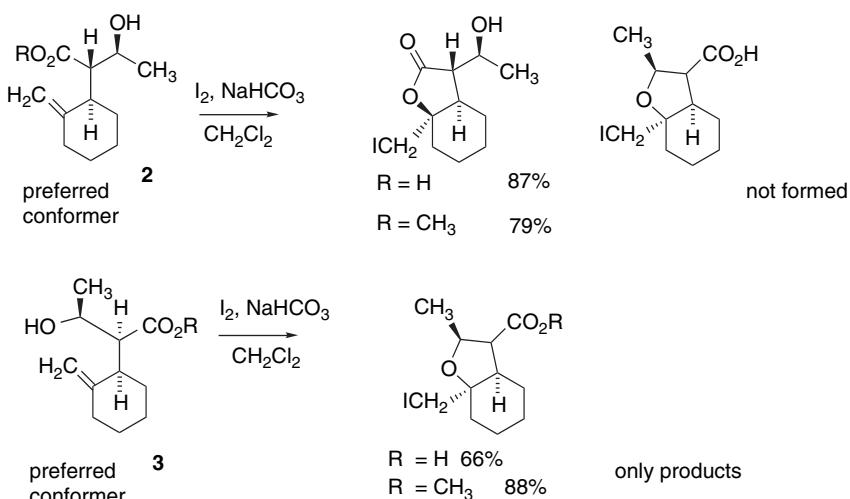
Similarly, with reactants **2** and **3** conformational preference dominates in the selectivity between CO_2^- and CH_2OH as the internal nucleophile. This conformational preference even extends to CO_2CH_3 , which can cyclize in preference to CH_2OH when it is in the conformationally preferred position.⁷⁷

⁷⁴. P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, **100**, 3950 (1978).

⁷⁵. F. R. Gonzalez and P. A. Bartlett, *Org. Synth.*, **64**, 175 (1984).

⁷⁶. M. J. Kurth and E. G. Brown, *J. Am. Chem. Soc.*, **109**, 6844 (1987).

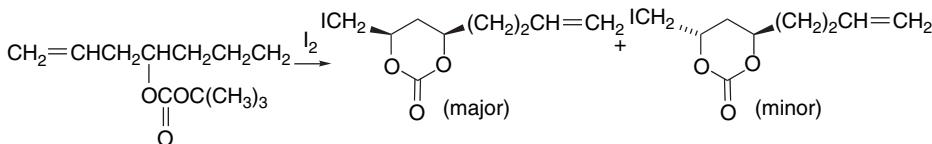
⁷⁷. M. J. Kurth, R. L. Beard, M. Olmstead, and J. G. Macmillan, *J. Am. Chem. Soc.*, **111**, 3712 (1989).



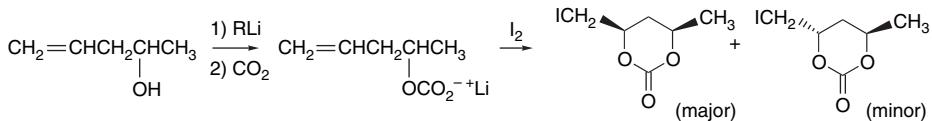
On the other hand, when the competition is between a monosubstituted and a disubstituted double bond, the inherent reactivity difference between the two double bonds overcomes reactant conformational preferences.⁷⁸



Several other nucleophilic functional groups can be induced to participate in iodocyclization reactions. *t*-Butyl carbonate esters cyclize to diol carbonates.⁷⁹



Lithium salts of carbonate monoesters can also be cyclized.⁸⁰



Enhanced stereoselectivity has been found using IBr , which reacts at a lower temperature.⁸¹ (Compare Entries 6 and 7 in Scheme 4.4.) Other reagent systems that generate electrophilic iodine, such as $\text{KI} + \text{KHSO}_5$,⁸² can be used for iodocyclization.

⁷⁸ M. J. Kurth, E. G. Brown, E. J. Lewis, and J. C. McKew, *Tetrahedron Lett.*, **29**, 1517 (1988).

⁷⁹ P. A. Bartlett, J. D. Meadows, E. G. Brown, A. Morimoto, and K. K. Jernstedt, *J. Org. Chem.*, **47**, 4013 (1982).

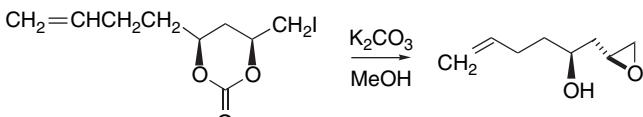
⁸⁰ A. Bogini, G. Cardillo, M. Orena, G. Ponzi, and S. Sandri, *J. Org. Chem.*, **47**, 4626 (1982).

⁸¹ J. J.-W. Duan and A. B. Smith, III, *J. Org. Chem.*, **58**, 3703 (1993).

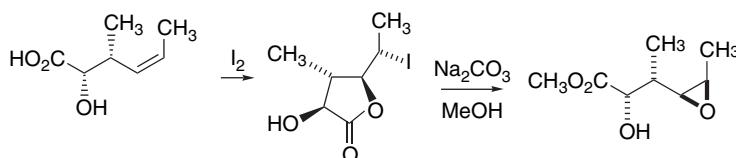
⁸² M. Curini, F. Epifano, M. C. Marcotullio, and F. Montanari, *Synlett*, 368 (2004).

Analogous cyclization reactions are induced by brominating reagents but they tend to be less selective than the iodocyclizations.⁸³ The bromonium ion intermediates are much more reactive and less selective.

The iodocyclization products have a potentially nucleophilic oxygen substituent β to the iodide, which makes them useful in stereospecific syntheses of epoxides and diols.

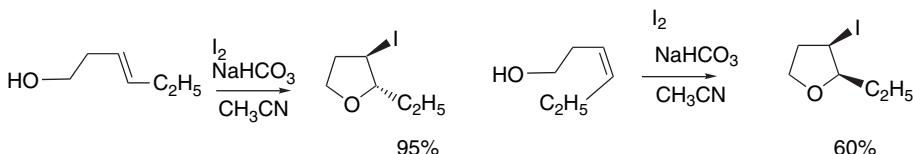


Ref. 79

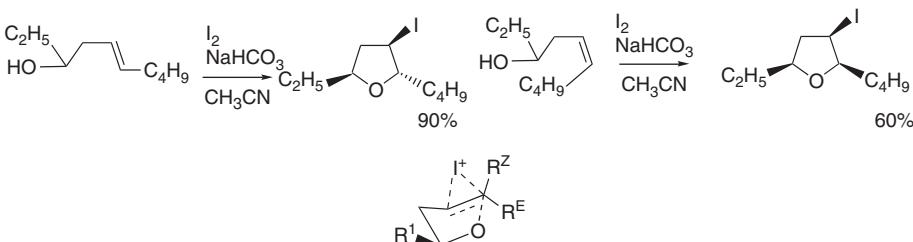


Ref. 84

Positive halogen reagents can cyclize γ - and δ -hydroxyalkenes to tetrahydrofuran and tetrahydropyran derivatives, respectively.⁸⁵ Iodocyclization of homoallylic alcohols generates 3-iodotetrahydrofurans when conducted in anhydrous acetonitrile.⁸⁶ The reactions are stereospecific, with the *E*-alcohols generating the *trans* and the *Z*-isomer the *cis* product. These are 5-*endo* cyclizations, which are preferred to 4-*exo* reactions.



With the corresponding secondary alcohols, the preferred cyclization is via a conformation with a pseudoequatorial conformation.



⁸³. B. B. Snider and M. I. Johnston, *Tetrahedron Lett.*, **26**, 5497 (1985).

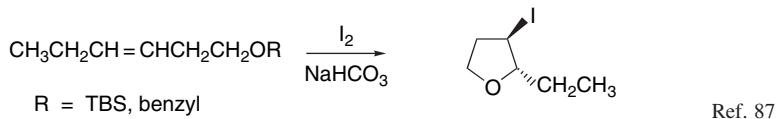
⁸⁴. C. Neukome, D. P. Richardson, J. H. Myerson, and P. A. Bartlett, *J. Am. Chem. Soc.*, **108**, 5559 (1986).

⁸⁵. A. B. Reitz, S. O. Nortey, B. E. Maryanoff, D. Liotta, and R. Monahan, III, *J. Org. Chem.*, **52**, 4191 (1981).

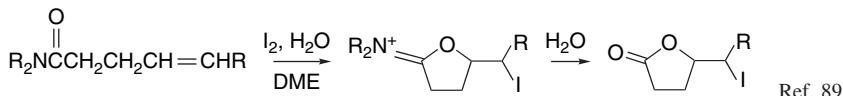
⁸⁶. J. M. Banks, D. W. Knight, C. J. Seaman, and G. G. Weingarten, *Tetrahedron Lett.*, **35**, 7259 (1994); S. B. Bedford, K. E. Bell, F. Bennett, C. J. Hayes, D. W. Knight, and D. E. Shaw, *J. Chem. Soc., Perkin Trans. I*, 2143 (1999).

CHAPTER 4

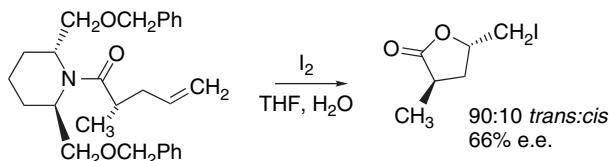
*Electrophilic Additions
to Carbon-Carbon
Multiple Bonds*



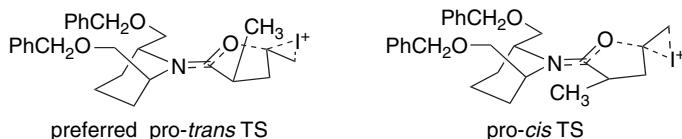
Other nucleophilic functional groups can participate in iodocyclization. Amides usually react at oxygen, generating imino lactones that are hydrolyzed to lactones.⁸⁸



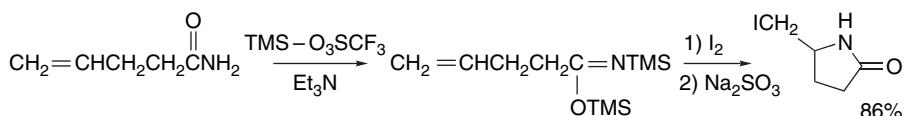
Use of a chiral amide can promote enantioselective cyclization.⁹⁰



The TS preference is influenced by avoidance of A^{1,3} strain between the α -methyl group and the piperidine ring.



Lactams can be obtained by cyclization of *O,N*-trimethylsilyl imidates.⁹¹



As compared with amides, where oxygen is the most nucleophilic atom, the silyl imidates are more nucleophilic at nitrogen.

Examples of halolactonization and related halocyclizations can be found in Scheme 4.4. The first entry, which involves NBS as the electrophile, demonstrates the *anti* stereospecificity of the reaction, as well as the preference for five-membered rings.

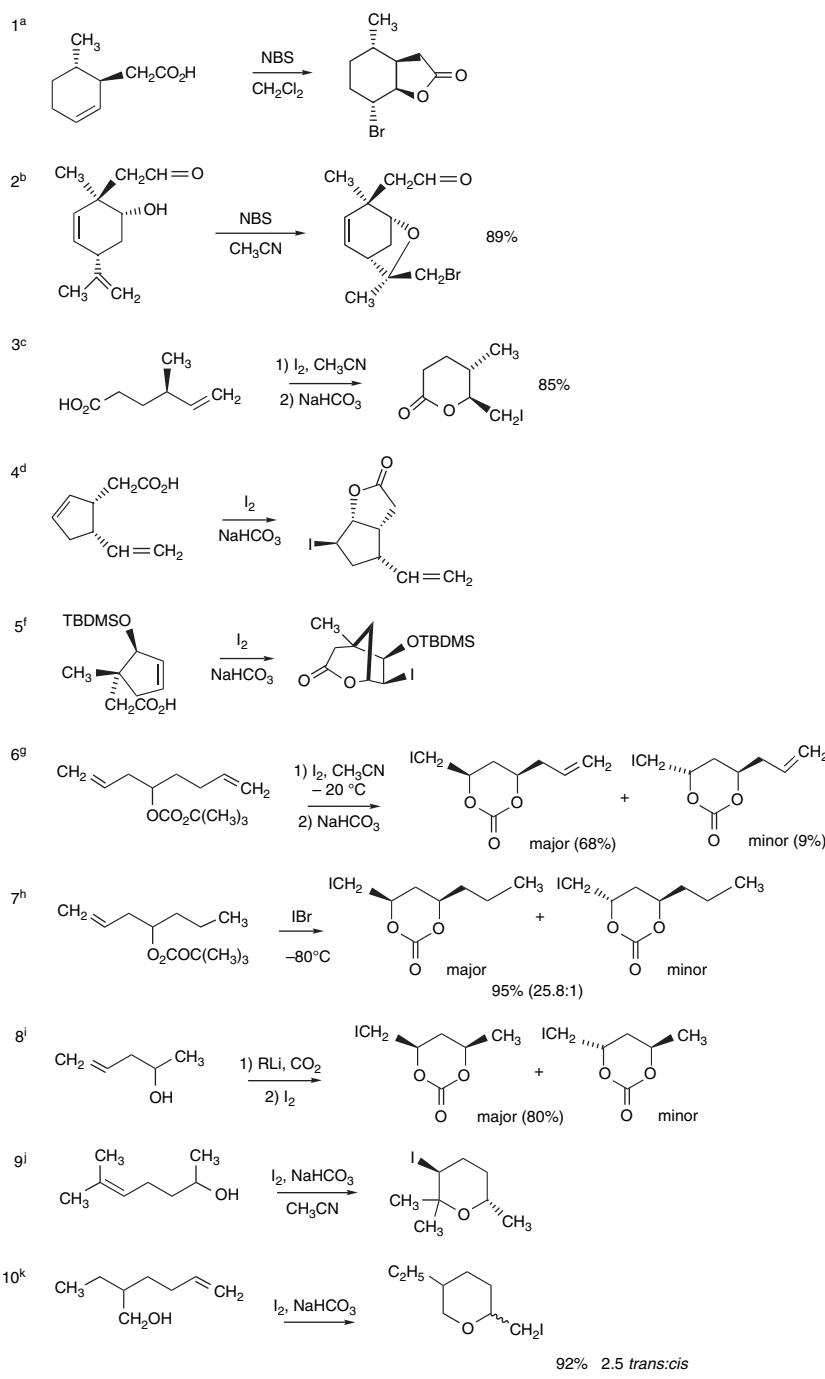
⁸⁷. S. P. Bew, J. M. Barks, D. W. Knight, and R. J. Middleton, *Tetrahedron Lett.*, **41**, 4447 (2000).

⁸⁸. S. Robin and G. Rousseau, *Tetrahedron*, **54**, 13681 (1998).

⁸⁹. Y. Tamaru, M. Mizutani, Y. Furukawa, S. Kawamura, Z. Yoshida, K. Yanagi, and M. Minobe, *J. Am. Chem. Soc.*, **106**, 1079 (1984).

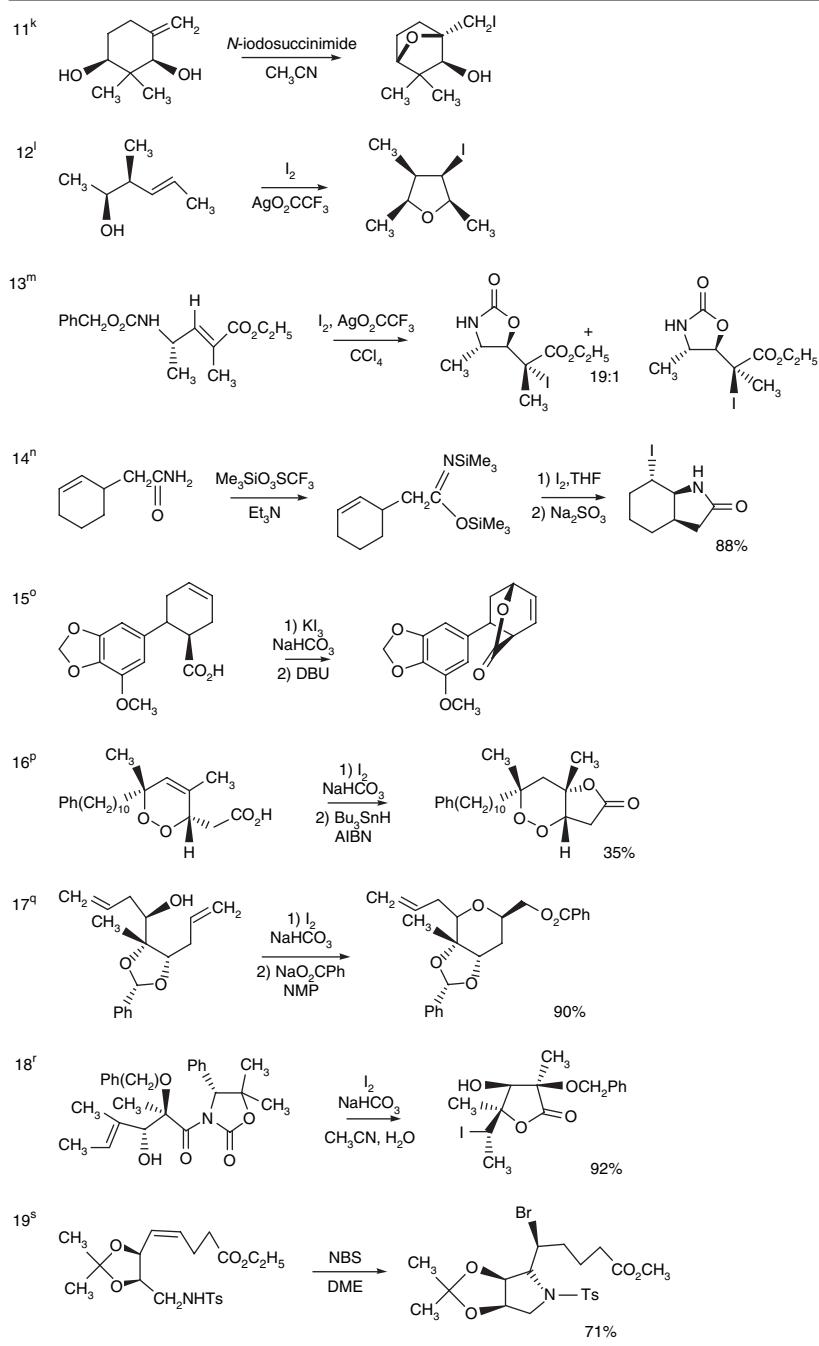
⁹⁰. S. Najdi, D. Reichlin, and M. J. Kurth, *J. Org. Chem.*, **55**, 6241 (1990).

⁹¹. S. Knapp, K. E. Rodriguez, A. T. Levorse, and R. M. Ornat, *Tetrahedron Lett.*, **26**, 1803 (1985).



(Continued)

Scheme 4.4. (Continued)

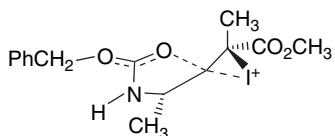


(Continued)

- a. M. F. Semmelhack, W. R. Epa, A. W. H. Cheung, Y. Gu, C. Kim, N. Zhang, and W. Lew, *J. Am. Chem. Soc.*, **116**, 7455 (1994).
 b. M. Miyashita, T. Suzuki, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **111**, 3728 (1989).
 c. A. G. M. Barrett, R. A. E. Carr, S. V. Atwood, G. Richardson, and N. D. A. Walshe, *J. Org. Chem.*, **51**, 4840 (1986).
 d. L. A. Paquette, G. D. Crouse, and A. K. Sharma, *J. Am. Chem. Soc.*, **102**, 3972 (1980).
 e. A. J. Pearson and S.-Y. Hsu, *J. Org. Chem.*, **51**, 2505 (1986).
 f. P. A. Bartlett, J. D. Meadows, E. G. Brown, A. Morimoto, and K. K. Jernstedt, *J. Org. Chem.*, **47**, 4013 (1982).
 g. J. J.-W. Duan and A. B. Smith, III, *J. Org. Chem.*, **58**, 3703 (1993).
 h. L. F. Tietze and C. Schneider, *J. Org. Chem.*, **56**, 2476 (1991).
 i. G. L. Edwards and K. A. Walker, *Tetrahedron Lett.*, **33**, 1779 (1992).
 j. A. Bongini, G. Cardillo, M. Orena, G. Porzi, and S. Sandri, *J. Org. Chem.*, **47**, 4626 (1982).
 k. A. Murai, N. Tanimoto, N. Sakamoto, and T. Masamune, *J. Am. Chem. Soc.*, **110**, 1985 (1988).
 l. B. F. Lipshutz and J. C. Barton, *J. Am. Chem. Soc.*, **114**, 1084 (1992).
 m. Y. Guindon, A. Slăssie, E. Ghiro, G. Bantle, and G. Jung, *Tetrahedron Lett.*, **33**, 4257 (1992).
 n. S. Knapp and A. T. Levorse, *J. Org. Chem.*, **53**, 4006 (1988).
 o. S. Kim, H. Ko, E. Kim, and D. Kim, *Org. Lett.*, **4**, 1343 (2002).
 p. M. Jung, J. Han, and J. Song, *Org. Lett.*, **4**, 2763 (2002).
 q. S. H. Kang, S. Y. Kang, H. Choi, C. M. Kim, H.-S. Jun, and J.-H. Youn, *Synthesis*, 1102 (2004).
 r. Y. Murata, T. Kamino, T. Aoki, S. Hosokawa, and S. Kobayashi, *Angew. Chem. Int. Ed. Engl.*, **43**, 3175 (2004).
 s. Y. G. Kim and J. K. Cha, *Tetrahedron Lett.*, **30**, 5721 (1989).

Entry 2 is a *5-exo* bromocyclization. The reaction in Entry 3 involves formation of a δ -lactone in an acyclic system. This reaction was carried out under conditions that lead to the thermodynamically favored *trans* isomer. Entry 4 shows typical iodolactonization conditions and illustrates both the *anti* stereoselectivity and preference for formation of five-membered rings. In Entry 5, a six-membered lactone is formed, again with *anti* stereospecificity. Entry 6 is a cyclization of a *t*-butyl carbonate ester. The selectivity between the two double bonds is the result of the relative proximity of the nucleophilic group. Entry 7 is a closely related reaction, but carried out at a much lower temperature by the use of IBr. The *cis:trans* ratio was improved to nearly 26:1. The ratio was also solvent dependent, with toluene being the best solvent. Entry 8 is a variation using a lithium carbonate as the nucleophile. Entries 9 and 10 involve hydroxy groups as nucleophiles. Entry 9 is a *6-endo* iodocyclization. In Entry 10, a primary hydroxy group serves as the nucleophile. Entry 11 is another cyclization involving a hydroxy group, in this case forming a 7-oxabicyclo[2.2.1]heptane structure. Entry 12 is a rather unusual *5-endo* cyclization.

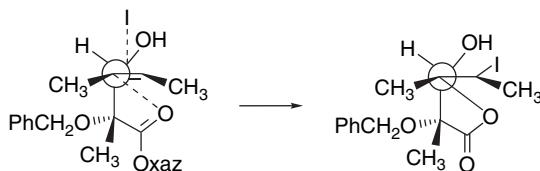
Entry 13 shows cyclization with concomitant loss of the benzyloxycarbonyl group. The TS for this reaction is *5-exo* with conformation determined by the pseudoequatorial position of the methyl group.



Entry 14 involves formation of a lactam by cyclization of a *bis*-trimethylsilylimidate. The stereoselectivity parallels that of iodolactonization.

Entries 15 to 18 are examples of use of iodocyclization in multistep syntheses. In Entry 15, iodolactonization was followed by elimination of HI from the bicyclic lactone. In Entry 16, a cyclic peroxide group remained unaffected by the standard iodolactonization and subsequent Bu_3SnH reductive deiodination. (See Section 5.5 for

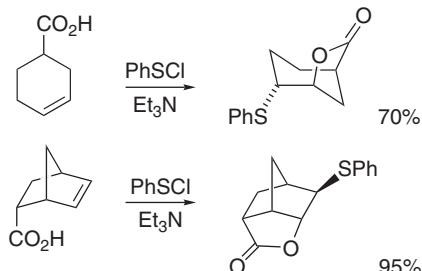
a discussion of this reaction.) In Entry 17, the primary iodo substituent was replaced by a benzoate group. In Entry 18, the reactant was prepared with high *anti* selectivity by an auxiliary-directed aldol reaction. The acyloxazolidinone auxiliary then participated in the iodocyclization and was cleaved in the process.



The reaction in Entry 19 was effected using NBS.

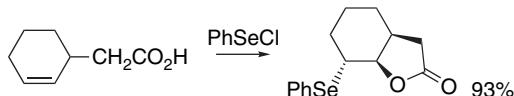
4.2.2. Sulfenylation and Selenenylation

Reactants with internal nucleophiles are also subject to cyclization by electrophilic sulfur reagents, a reaction known as *sulfenylation*.⁹² As for iodolactonization, unsaturated carboxylic acids give products that result from *anti* addition.⁹³



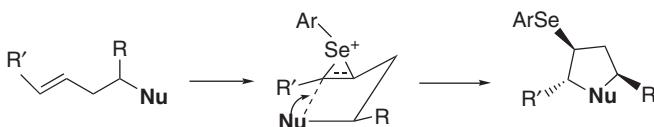
Similarly, alcohols undergo cyclization to ethers.

The corresponding reactions using selenium electrophiles are called selenenylation.^{94,95} Carboxylate (selenylactonization), hydroxy (selenyletherification), and nitrogen (selenylamidation) groups can all be captured in appropriate cases.

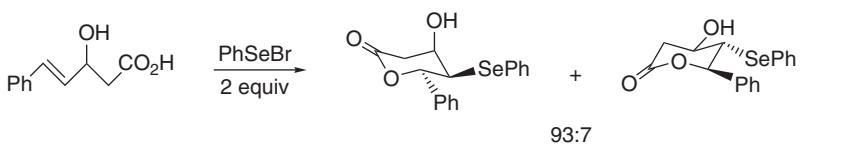
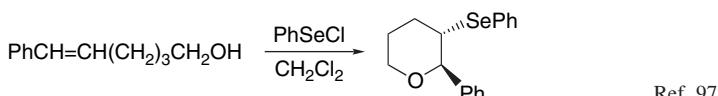


Internal nucleophilic capture of seleniranium ion is governed by general principles similar to those of other electrophilic cyclizations.⁹⁶ The stereochemistry of cyclization can usually be predicted on the basis of a cyclic TS with favored pseudoequatorial orientation of the substituents.

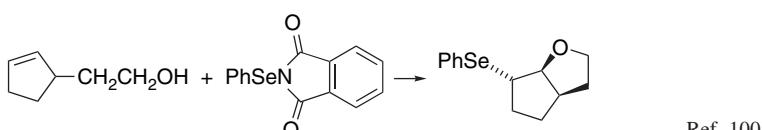
- ⁹². G. Capozzi, G. Modena, and L. Pasquato, in *The Chemistry of Sulphenic Acids and Their Derivatives*, S. Patai, ed., Wiley, Chichester, 1990, pp. 446–460.
- ⁹³. K. C. Nicolaou, S. P. Seitz, W. T. Sipio, and J. F. Blount, *J. Am. Chem. Soc.*, **101**, 3884 (1979).
- ⁹⁴. K. Fujita, *Rev. Heteroatom. Chem.*, **16**, 101 (1997).
- ⁹⁵. K. C. Nicolaou, S. P. Seitz, W. J. Sipio, and J. F. Blount, *J. Am. Chem. Soc.*, **101**, 3884 (1979); M. Tiecco, *Topics Curr. Chem.*, **208**, 7 (2000); S. Raganathan, K. M. Muraleedharan, N. K. Vaish, and N. Jayaraman, *Tetrahedron*, **60**, 5273 (2004).
- ⁹⁶. N. Petragnani, H. A. Stefani, and C. J. Valduga, *Tetrahedron*, **57**, 1411 (2001).



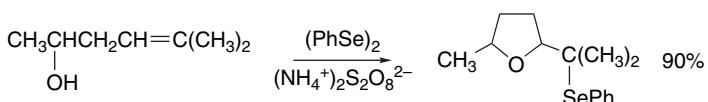
Although *exo* cyclization is usually preferred, there is no strong prohibition of *endo* cyclization and aryl-controlled regioselectivity can override the *exo* preference.



Various electrophilic selenium reagents such as those described in Scheme 4.3 can be used. *N*-Phenylselenylphthalimide is an excellent reagent for this process and permits the formation of large ring lactones.⁹⁹ The advantage of the reagent in this particular application is the low nucleophilicity of phthalimide, which does not compete with the remote internal nucleophile. The reaction of phenylselenenyln chloride or *N*-phenylselenenylnphthalimide with unsaturated alcohols leads to formation of β -phenylselenenyln ethers.



Another useful reagent for selenenylcyclization is phenylselenenyln triflate. This reagent is capable of cyclizing unsaturated acids¹⁰¹ and alcohols.¹⁰² Phenylselenenyln sulfate can be prepared in situ by oxidation of diphenyl diselenide with ammonium peroxydisulfate.¹⁰³

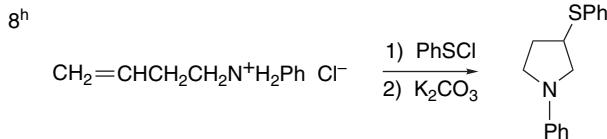
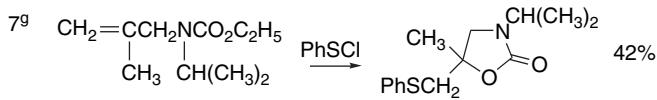
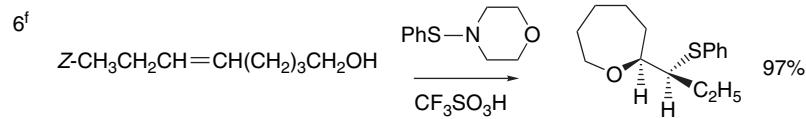
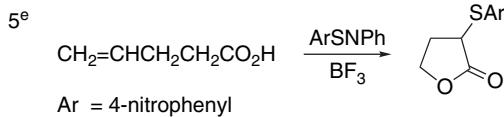
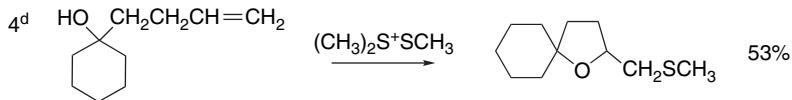
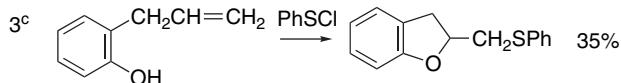
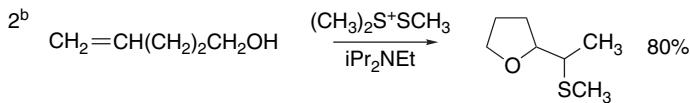
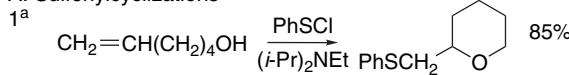


Several examples of sulfenylcyclization are given in Section A of Scheme 4.5. Entry 1 is a *6-exo* sulfenoetherification induced by phenylsulfenyln chloride. Entry 2

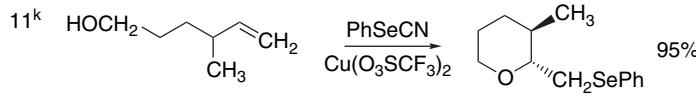
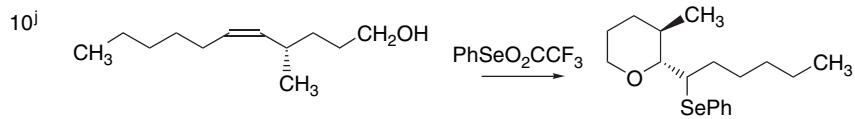
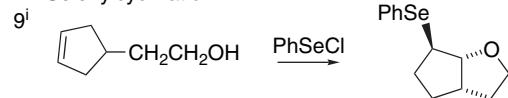
- 97. M. A. Brimble, G. S. Pavia, and R. J. Stevenson, *Tetrahedron Lett.*, **43**, 1735 (2002).
- 98. M. Gruttaduria, C. Aprile, and R. Noto, *Tetrahedron Lett.*, **43**, 1669 (2002).
- 99. K. C. Nicolaou, D. A. Claremon, W. E. Barnette, and S. P. Seitz, *J. Am. Chem. Soc.*, **101**, 3704 (1979).
- 100. K. C. Nicolaou, R. L. Magolda, W. J. Sipio, W. E. Barnette, Z. Lysenko, and M. M. Joullie, *J. Am. Chem. Soc.*, **102**, 3784 (1980).
- 101. S. Murata and T. Suzuki, *Chem. Lett.*, 849 (1987).
- 102. A. G. Kutateladze, J. L. Kice, T. G. Kutateladze, N. S. Zefirov, and N. V. Zyk, *Tetrahedron Lett.*, **33**, 1949 (1992).
- 103. M. Tiecco, L. Testaferri, M. Tingoli, D. Bartoli, and R. Balducci, *J. Org. Chem.*, **55**, 429 (1990).

Scheme 4.5. Sulphenyl- and Selenenylycyclization Reactions

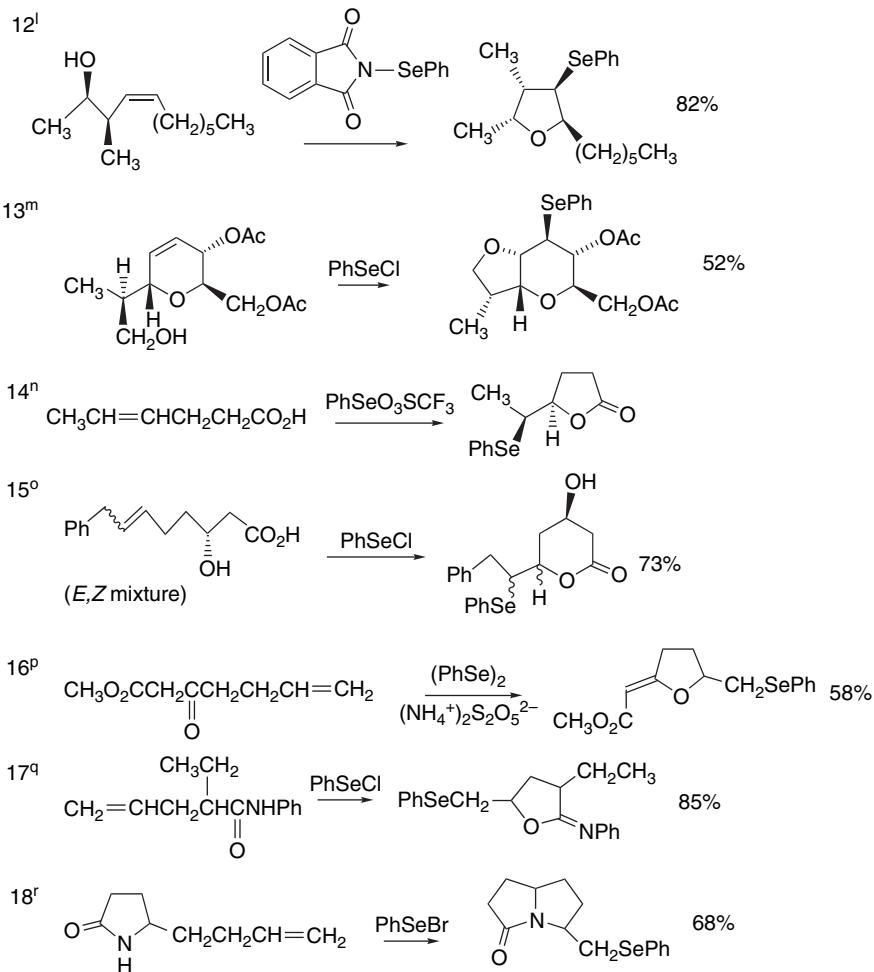
A. Sulphenylcyclizations



B. Selenenylycyclization



(Continued)

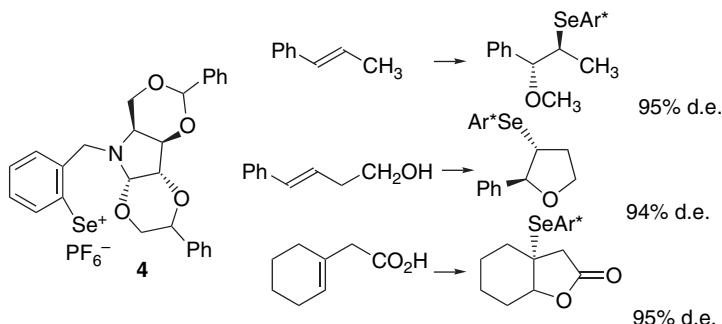


- a. S. M. Tuladhar and A. G. Fallis, *Can. J. Chem.*, **65**, 1833 (1987).
 b. G. J. O'Malley and M. P. Cava, *Tetrahedron Lett.*, **26**, 6159 (1985).
 c. M. Muehlstaedt, C. Shubert, and E. Kleinpeter, *J. Prakt. Chem.*, **327**, 270 (1985).
 d. G. Capozzi, S. Menichetti, M. Nicastro, and M. Taddei, *Heterocycles*, **29**, 1703 (1987).
 e. L. Benati, L. Capella, P. C. Monteverchi, and P. Spagnolo, *Tetrahedron*, **50**, 12395 (1994).
 f. P. Brownbridge, *J. Chem. Soc., Chem. Commun.*, 1280 (1980).
 g. M. Muehlstaedt, R. Widera, and B. Olk, *J. Prakt. Chem.*, **324**, 362 (1982).
 h. T. Ohsawa, M. Ihara, K. Fukumoto, and T. Kametani, *J. Org. Chem.*, **48**, 3644 (1983).
 i. D. L. J. Clive, G. Chittattu, and C. K. Wong, *Can. J. Chem.*, **55**, 3894 (1987).
 j. G. Li and W. C. Still, *J. Org. Chem.*, **56**, 6964 (1991).
 k. H. Inoue and S. Murata, *Heterocycles*, **45**, 847 (1997).
 l. E. D. Mihelich and G. A. Hite, *J. Am. Chem. Soc.*, **114**, 7318 (1992).
 m. S. J. Danishefsky, S. DeNinno, and P. Lartey, *J. Am. Chem. Soc.*, **109**, 2082 (1987).
 n. S. Murata and T. Suzuki, *Chem. Lett.*, 849 (1987).
 o. F. Bennett, D. W. Knight, and G. Fenton, *J. Chem. Soc., Perkin Trans. I*, 519 (1991).
 p. M. Tiecco, L. Testaferri, M. Tingoli, D. Bartoli, and R. Balducci, *J. Org. Chem.*, **55**, 429 (1990).
 q. A. Toshimitsu, K. Terao, and S. Uemura, *J. Org. Chem.*, **52**, 2018 (1987).
 r. A. Toshimitsu, K. Terao, and S. Uemura, *J. Org. Chem.*, **51**, 1724 (1986).

is mediated by dimethyl(methylthio)sulfonium tetrafluoroborate. Entries 3 and 4 are other examples of 5-*exo* cyclizations. Entries 5 and 6 involve use of sulfenamides as the electrophiles. Entry 7 shows the cyclization of a carbamate involving the carbonyl oxygen. Entry 8 is an 5-*endo* aminocyclization.

Part B of Scheme 4.5 gives some examples of cyclizations induced by selenium electrophiles. Entries 9 to 13 are various selenyletherifications. All exhibit *anti* stereochemistry. Entries 14 and 15 are selenyllactonizations. Entries 17 and 18 involve amido groups as the internal nucleophile. Entry 17 is an 5-*exo* cyclization in which the amido oxygen is the more reactive nucleophilic site, leading to an iminolactone. Geometric factors favor N-cyclization in the latter case.

Chiral selenenylating reagents have been developed and shown to be capable of effecting enantioselective additions and cyclizations. The reagent **4**, for example, achieves more than 90% enantioselectivity in typical reactions.¹⁰⁴

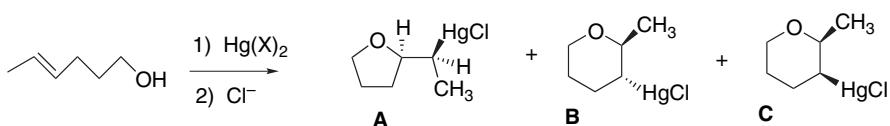


4.2.3. Cyclization by Mercuric Ion

Electrophilic attack by mercuric ion can effect cyclization by intramolecular capture of a nucleophilic functional group. A variety of oxygen and nitrogen nucleophiles can participate in cyclization reactions, and there have been numerous synthetic applications of the reaction. Mechanistic studies have been carried out on several alkenol systems. The ring-size preference for cyclization of 4-hexenol depends on the mercury reagent that is used. The more reactive mercuric salts favor 6-*endo* addition. It is proposed that reversal of formation of the kinetic *exo* product is responsible.¹⁰⁵ Equilibration to favor the thermodynamic addition products occurs using $\text{Hg}(\text{O}_3\text{SCF}_3)_2$ and $\text{Hg}(\text{NO}_3)_2$. The equilibration does not seem to be dependent on acid catalysis, since the thermodynamically favored product is also formed in the presence of the acid-scavenger TMU.

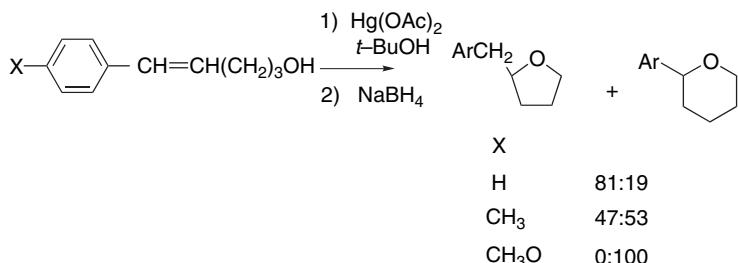
¹⁰⁴. K. Fujita, K. Murata, M. Iwaoka, and S. Tomoda, *Tetrahedron*, **53**, 2029 (1997); K. Fujita, *Rev. Heteroatom Chem.*, **16**, 101 (1997); T. Wirth, *Tetrahedron*, **55**, 1 (1999).

¹⁰⁵. M. Nishizawa, T. Kashima, M. Sakakibara, A. Wakabayashi, K. Takahasi, H. Takao, H. Imagawa, and T. Sugihara, *Heterocycles*, **54**, 629 (2001).

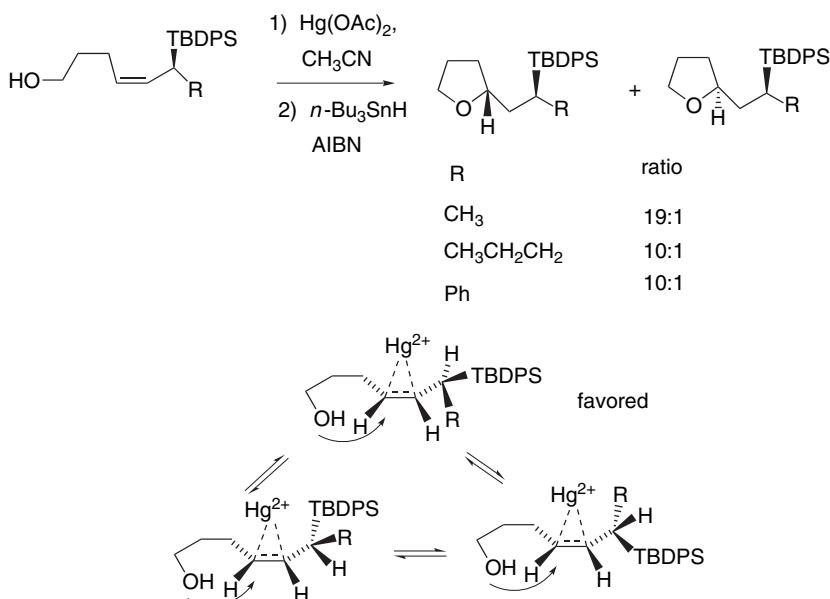


X	A	B	C
O_2CCH_3	92	8	0
O_2CCF_3	13	87	0
O_3SCF_3	0	88	12
O_3SCF_3 (TMU)	0	100	0
NO_3	0	100	0

In 5-aryl-4-hexenols with ERG substituents, electronic factors outweigh the *exo* preference.¹⁰⁶ The ERG substituents increase the cationic character at C(5).



Cyclization of δ , ϵ -enols is controlled by a conformation-dependent strain in the *exo* TS.¹⁰⁷ The C(5)–C(6) bond is rotated to minimize A^{1,3} strain.

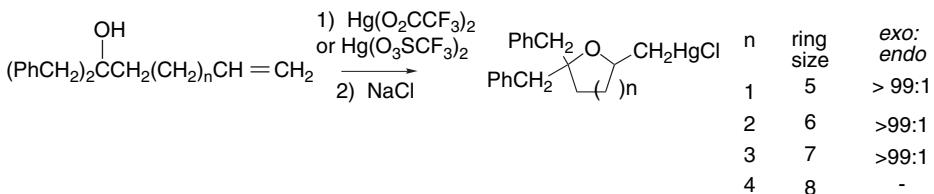


¹⁰⁶ Y. Senda, H. Kanto, and H. Itoh, *J. Chem. Soc., Perkin Trans. 2*, 1143 (1997).

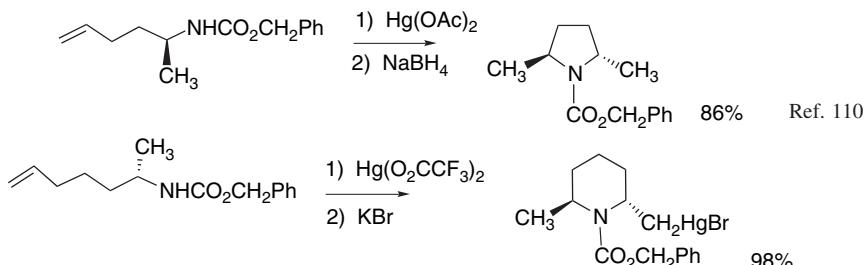
¹⁰⁷ K. Bratt, A. Garavelas, P. Perlmutter, and G. Westman, *J. Org. Chem.*, **61**, 2109 (1996).

In the corresponding *E*-alkene, where this factor is not present, the cyclization is much less stereoselective. A stabilizing interaction between the siloxy oxygen and the Hg^{2+} center has also been suggested.¹⁰⁸

Reaction of $\text{Hg}(\text{O}_2\text{CCF}_3)_2$ or $\text{Hg}(\text{O}_3\text{SCF}_3)_2$ with a series of dibenzylcarbinols gave *exo* cyclization for formation of five-, six-, and seven-, but not eight-membered rings.¹⁰⁹

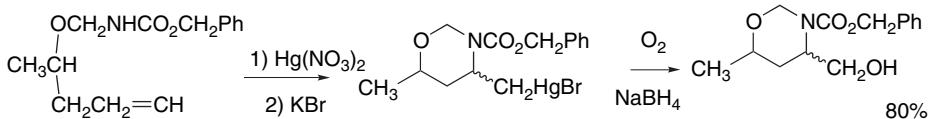


Benzyl carbamates have been used to form both five- and six-membered nitrogen-containing rings. The selectivity for N over O nucleophilicity in these cases is the result of the nitrogen being able to form a better ring size (5 or 6 versus 7 or 8) than the carbonyl oxygen.



Ref. 111

The trapping of the radical intermediate in demercuration by oxygen can be exploited as a method for introduction of a hydroxy substituent (see p. 295). The example below and Entries 3 and 4 in Scheme 4.6 illustrate this reaction.



Ref. 112

Cyclization induced by mercuric ion is often used in multistep syntheses to form five- and six-membered heterocyclic rings, as illustrated in Scheme 4.6. The reactions in Entries 1 to 3 involve acyclic reactants that cyclize to give *5-exo* products. Entry 4 is an *6-exo* cyclization. In Entries 1 and 2, the mercury is removed reductively, but in Entries 3 and 4 a hydroxy group is introduced in the presence of oxygen. Inclusion of triethylboron in the reduction has been found to improve yields (Entry 1).¹¹³

^{108.} A. Garavelas, I. Mavropoulos, P. Perlmutter, and G. Westman, *Tetrahedron Lett.*, **36**, 463 (1995).

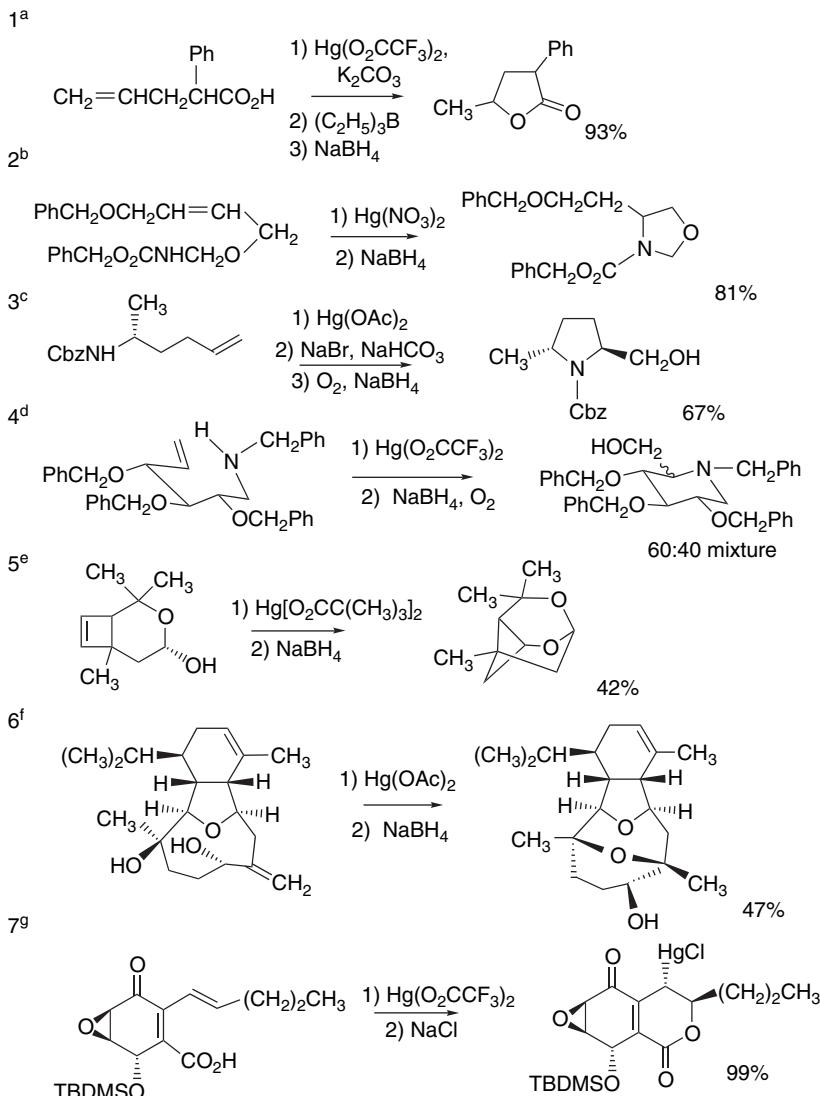
^{109.} H. Imagawa, T. Shigaraki, T. Suzuki, H. Takao, H. Yamada, T. Sugihara, and M. Nishizawa, *Chem. Pharm. Bull.*, **46**, 1341 (1998).

^{110.} T. Yamakazi, R. Gimi, and J. T. Welch, *Synlett*, 573 (1991).

¹¹¹. H. Takahata, H. Bandoh, and T. Momose, *Tetrahedron*, **49**, 11205 (1993).

^{112.} K. E. Harding, T. H. Marman, and D.-H. Nam, *Tetrahedron Lett.*, **29**, 1627 (1988).

^{113.} S. H. Kang, J. H. Lee, and S. B. Lee, *Tetrahedron Lett.*, **39**, 59 (1998).



a. S. H. Kang, J. H. Lee, and S. B. Lee, *Tetrahedron Lett.*, **39**, 59 (1998).

b. K. E. Harding and D. R. Hollingsworth, *Tetrahedron Lett.*, **29**, 3789 (1988).

c. H. Takahata, H. Bandoh, and T. Momose, *J. Org. Chem.*, **57**, 4401 (1992).

d. R. C. Bernotas and B. Ganem, *Tetrahedron Lett.*, **26**, 1123 (1985).

e. J. D. White, M. A. Avery and J. P. Carter, *J. Am. Chem. Soc.*, **104**, 5486 (1986).

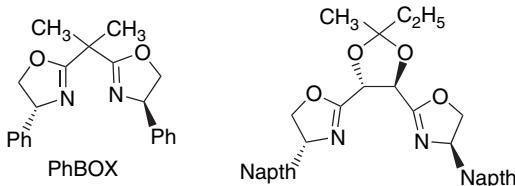
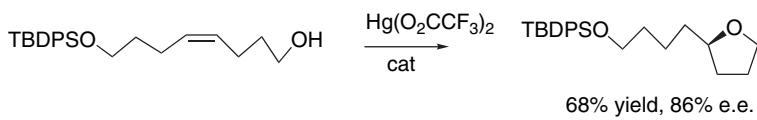
f. D. W. C. MacMillan, L. E. Overman, and L. D. Pennington, *J. Am. Chem. Soc.*, **123**, 9033 (2001).

g. M. Shoji, T. Uno, and Y. Hayashi, *Org. Lett.*, **6**, 4535 (2004).

The reaction in Entry 5 was used in the syntheses of linetin, which is an aggregation pheromone of the ambrosia beetle. In Entry 6, a transannular 5-*exo* cyclization occurs. Entry 7 is an example of formation of a lactone by carboxylate capture. In this case, the product was isolated as the mercurochloride.

Some progress has been made toward achieving enantioselectivity in mercuration-induced cyclization. Several *bis*-oxazoline (BOX) ligands have been investigated. The

diphenyl BOX ligand, in conjunction with $\text{Hg}(\text{O}_2\text{CCF}_3)_2$, results in formation of tetrahydrofuran rings with 80% e.e. Other *bis*-oxazoline ligands derived from tartaric acid were screened and the best results were obtained with a 2-naphthyl ligand, which gave more than 90% e.e. in several cases.

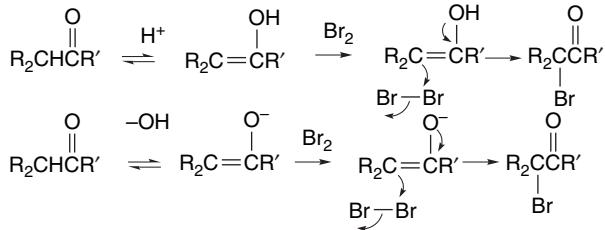


Ref. 114

4.3. Electrophilic Substitution α to Carbonyl Groups

4.3.1. Halogenation α to Carbonyl Groups

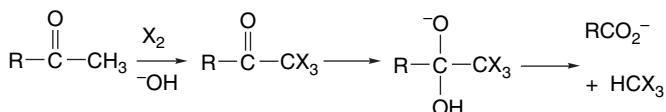
Although the reaction of ketones and other carbonyl compounds with electrophiles such as bromine leads to substitution rather than addition, the mechanism of the reaction is closely related to electrophilic additions to alkenes. An enol, enolate, or enolate equivalent derived from the carbonyl compound is the nucleophile, and the electrophilic attack by the halogen is analogous to that on alkenes. The reaction is completed by restoration of the carbonyl bond, rather than by addition of a nucleophile. The acid- and base-catalyzed halogenation of ketones, which is discussed briefly in Section 6.4 of Part A, provide the most-studied examples of the reaction from a mechanistic perspective.



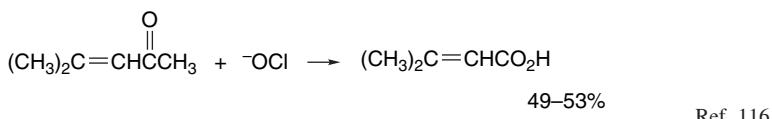
The reactions involving bromine or chlorine generate hydrogen halide and are autocatalytic. Reactions with *N*-bromosuccinimide or tetrabromocyclohexadienone do not form any hydrogen bromide and may therefore be preferable reagents in the case of acid-sensitive compounds. Under some conditions halogenation is faster than enolization. When this is true, the position of substitution in unsymmetrical ketones is governed by the relative rates of formation of the isomeric enols. In general, mixtures are formed with unsymmetrical ketones. The presence of a halogen substituent

¹¹⁴. S. H. Kang and M. Kim, *J. Am. Chem. Soc.*, **125**, 4684 (2003).

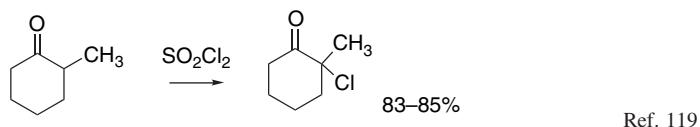
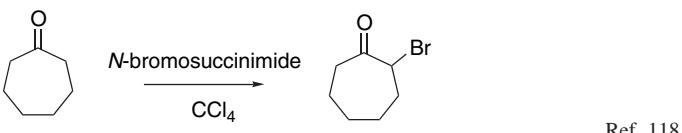
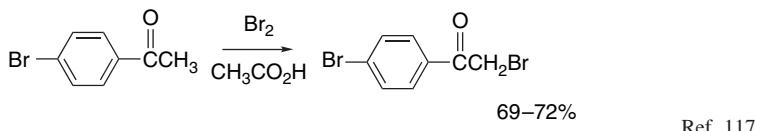
decreases the rate of acid-catalyzed enolization and thus retards the introduction of a second halogen at the same site, so monohalogenation can usually be carried out satisfactorily. In contrast, in basic solution halogenation tends to proceed to polyhalogenated products because the polar effect of a halogen accelerates base-catalyzed enolization. With methyl ketones, base-catalyzed reaction with iodine or bromine leads ultimately to cleavage to a carboxylic acid.¹¹⁵ These reactions proceed to the trihalomethyl ketones, which are susceptible to base-induced cleavage.



The reaction can also be effected with hypochlorite ion, and this constitutes a useful method for converting methyl ketones to carboxylic acids.



The most common preparative procedures involve use of the halogen, usually bromine, in acetic acid. Other suitable halogenating agents include *N*-bromosuccinimide, tetrabromocyclohexadienone, and sulfonyl chloride.



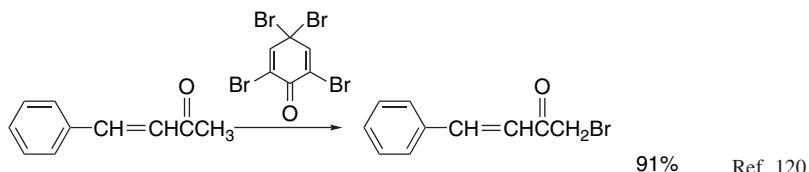
¹¹⁵. S. J. Chakabarty, in *Oxidations in Organic Chemistry*, Part C, W. Trahanovsky, ed., Academic Press, New York, 1978, Chap. V.

¹¹⁶. L. J. Smith, W. W. Prichard, and L. J. Spillane, *Org. Synth.*, **III**, 302 (1955).

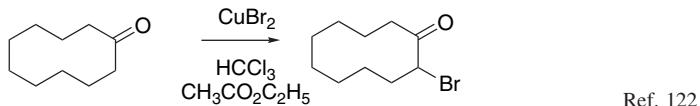
¹¹⁷. W. D. Langley, *Org. Synth.*, **1**, 122 (1932).

¹¹⁸. E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1954).

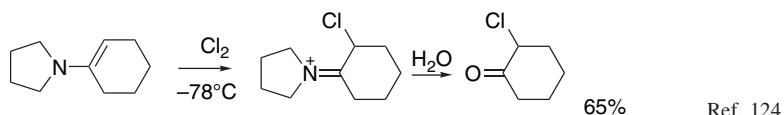
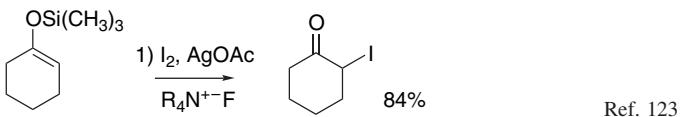
¹¹⁹. E. W. Warnhoff, D. G. Martin, and W. S. Johnson, *Org. Synth.*, **IV**, 162 (1963).



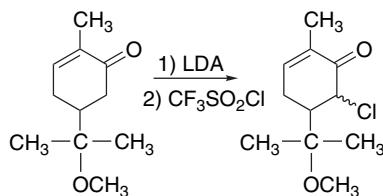
Another preparatively useful procedure for monohalogenation of ketones involves reaction with cupric chloride or cupric bromide.¹²¹



Instead of direct halogenation of ketones, reactions with more reactive derivatives such as silyl enol ethers and enamines have advantages in certain cases.



There are also procedures in which the enolate is generated quantitatively and allowed to react with a halogenating agent. Regioselectivity can then be controlled by the direction of enolate formation. Among the sources of halogen that have been used under these conditions are bromine,¹²⁵ *N*-chlorosuccinimide,¹²⁶ trifluoromethanesulfonyl chloride,¹²⁷ and hexachloroethane.¹²⁸



¹²⁰. V. Calo, L. Lopez, G. Pesce, and P. E. Todesco, *Tetrahedron*, **29**, 1625 (1973).

¹²¹. E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963); E. M. Kosower and G.-S. Wu, *J. Org. Chem.*, **28**, 633 (1963).

¹²². D. P. Bauer and R. S. Macomber, *J. Org. Chem.*, **40**, 1990 (1975).

¹²³. G. M. Rubottom and R. C. Mott, *J. Org. Chem.*, **44**, 1731 (1979); G. A. Olah, L. Ohannesian, M. Arvanaghi, and G. K. S. Prakash, *J. Org. Chem.*, **49**, 2032 (1984).

¹²⁴. W. Seufert and F. Effenberger, *Chem. Ber.*, **112**, 1670 (1979).

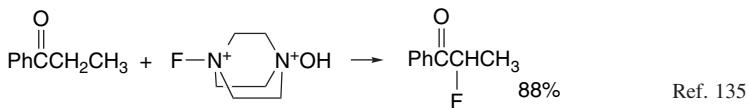
¹²⁵. T. Woolf, A. Trevor, T. Baille, and N. Castagnoli, Jr., *J. Org. Chem.*, **49**, 3305 (1984).

¹²⁶. A. D. N. Vaz and G. Schoellmann, *J. Org. Chem.*, **49**, 1286 (1984).

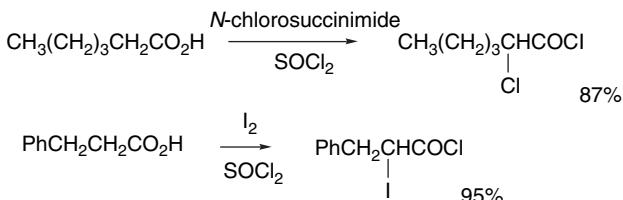
¹²⁷. P. A. Wender and D. A. Holt, *J. Am. Chem. Soc.*, **107**, 7771 (1985).

¹²⁸. M. B. Glinski, J. C. Freed, and T. Durst, *J. Org. Chem.*, **52**, 2749 (1987).

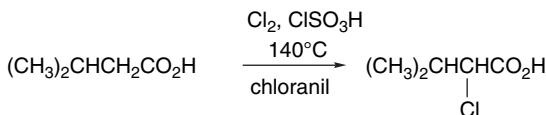
α -Fluoroketones are made primarily by reactions of enol acetates or silyl enol ethers with fluorinating agents such as CF_3OF ¹²⁹, XeF_2 ,¹³⁰ or dilute F_2 .¹³¹ Other fluorinating reagents that can be used include *N*-fluoropyridinium salts,¹³² 1-fluoro-4-hydroxy-1,4-diazabicyclo[2.2.2]octane,¹³³ and 1,4-difluoro-1,4-diazabicyclo[2.2.2]octane.¹³⁴ These reagents fluorinate readily enolizable carbonyl compounds and silyl enol ethers.



The α -halogenation of acid chlorides also has synthetic utility. The mechanism is presumed to be similar to ketone halogenation and to proceed through an enol. The reaction can be effected in thionyl chloride as solvent to give α -chloro, α -bromo, or α -iodo acyl chlorides, using, respectively, *N*-chlorosuccinimide, *N*-bromosuccinimide, or molecular iodine as the halogenating agent.¹³⁶ Since thionyl chloride rapidly converts carboxylic acids to acyl chlorides, the acid can be used as the starting material.



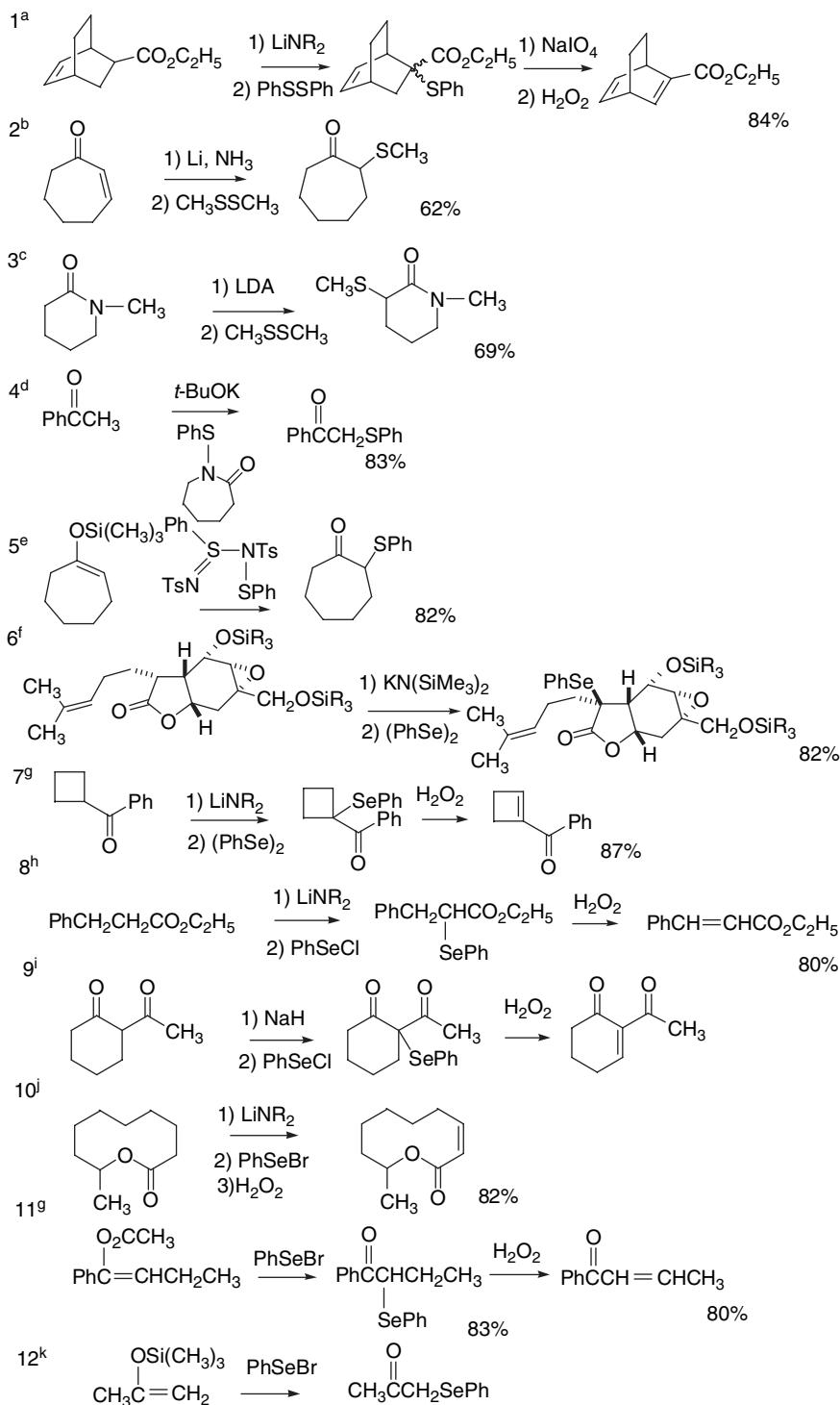
Direct chlorination can be carried out in the presence of ClSO_3H , which acts as a strong acid catalyst. These procedures use various compounds including 1,3-dinitrobenzene, chloranil, and TCNQ to inhibit competing radical chain halogenation.¹³⁷



4.3.2. Sulfenylation and Selenenylation α to Carbonyl Groups

The α -sulfonylation¹³⁸ and α -selenenylation¹³⁹ of carbonyl compounds are synthetically important reactions, particularly in connection with the introduction of

- ^{129.} W. J. Middleton and E. M. Bingham, *J. Am. Chem. Soc.*, **102**, 4845 (1980).
- ^{130.} B. Zajac and M. Zupan, *J. Chem. Soc., Chem. Commun.*, 759 (1980).
- ^{131.} S. Rozen and Y. Menahem, *Tetrahedron Lett.*, 725 (1979).
- ^{132.} T. Umemoto, M. Nagayoshi, K. Adachi, and G. Tomizawa, *J. Org. Chem.*, **63**, 3379 (1998).
- ^{133.} S. Stavber, M. Zupan, A. J. Poss, and G. A. Shia, *Tetrahedron Lett.*, **36**, 6769 (1995).
- ^{134.} T. Umemoto and M. Nagayoshi, *Bull. Chem. Soc. Jpn.*, **69**, 2287 (1996).
- ^{135.} S. Stavber and M. Zupan, *Tetrahedron Lett.*, **37**, 3591 (1996).
- ^{136.} D. N. Harpp, L. Q. Bao, C. J. Black, J. G. Gleason, and R. A. Smith, *J. Org. Chem.*, **40**, 3420 (1975); Y. Ogata, K. Adachi, and F.-C. Chen, *J. Org. Chem.*, **48**, 4147 (1983).
- ^{137.} Y. Ogata, T. Harada, K. Matsuyama, and T. Ikejiri, *J. Org. Chem.*, **40**, 2960 (1975); R. J. Crawford, *J. Org. Chem.*, **48**, 1364 (1983).
- ^{138.} B. M. Trost, *Chem. Rev.*, **78**, 363 (1978).
- ^{139.} H. J. Reich, *Acc. Chem. Res.*, **12**, 22 (1979); H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).

Scheme 4.7. α -Sulfonylation and α -Selenenylation of Carbonyl Compounds

(Continued)

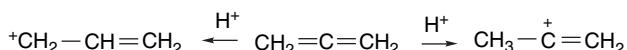
- a. B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976).
 b. P. G. Gassman, D. P. Gilbert, and S. M. Cole, *J. Org. Chem.*, **42**, 3233 (1977).
 c. P. G. Gassman and R. J. Balchunis, *J. Org. Chem.*, **42**, 3236 (1977).
 d. G. Foray, A. Penevory, and A. Rossi, *Tetrahedron Lett.*, **38**, 2035 (1997).
 e. P. Magnus and P. Rigollier, *Tetrahedron Lett.*, **33**, 6111 (1992).
 f. A. B. Smith, III, and R. E. Richmond, *J. Am. Chem. Soc.*, **105**, 575 (1983).
 g. H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).
 h. J. M. Renga and H. J. Reich, *Org. Synth.*, **59**, 58 (1979).
 i. T. Wakamatsu, K. Akasaka, and Y. Ban, *J. Org. Chem.*, **44**, 2008 (1979).
 j. H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973).
 k. I. Ryu, S. Murai, I. Niwa, and N. Sonoda, *Synthesis*, 874 (1977).

unsaturation. The products can subsequently be oxidized to sulfoxides and selenoxides that readily undergo elimination (see Section 6.8.3), generating the corresponding α,β -unsaturated carbonyl compound. Sulphenylations and selenenylation are usually carried out under conditions in which the enolate of the carbonyl compound is the reactive species. If a regiospecific enolate is generated by one of the methods described in Chapter 1, the position of sulphenylation or selenenylation can be controlled.¹⁴⁰ Disulfides are the most common sulphenylation reagents, whereas diselenides or selenenyl halides are used for selenenylation.

Scheme 4.7 gives some specific examples of these types of reactions. Entry 1 shows the use of sulphenylation followed by oxidation to introduce a conjugated double bond. Entries 2 and 3 are α -sulphenylations of a ketone and lactam, respectively, using dimethyl disulfide as the sulphenylating reagent. Entries 4 and 5 illustrate the use of alternative sulphenylating reagents. Entry 4 uses *N*-phenylsulphenylcaprolactam, which is commercially available. The reagent in Entry 5 is generated by reaction of diphenyldisulfide with chloramine-T. Entries 6 to 10 are examples of reactions of preformed enolates with diphenyl diselenide or phenylselenenyl chloride. As Entries 11 and 12 indicate, the selenenylation of ketones can also be effected by reactions of enol acetates or enol silyl ethers.

4.4. Additions to Allenes and Alkynes

Both allenes¹⁴¹ and alkynes¹⁴² require special consideration with regard to mechanisms of electrophilic addition. The attack by a proton on allene might conceivably lead to the allyl cation or the 2-propenyl cation.



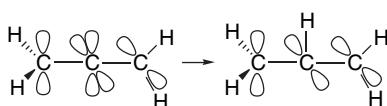
An immediate presumption that the more stable allyl ion will be formed overlooks the stereoelectronic facets of the reaction. Protonation at the center carbon without rotation of one of the terminal methylene groups leads to a primary carbocation

¹⁴⁰ P. G. Gassman, D. P. Gilbert, and S. M. Cole, *J. Org. Chem.*, **42**, 3233 (1977).

¹⁴¹ H. F. Schuster and G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, 1984; W. Smadja, *Chem. Rev.*, **83**, 263 (1983); S. Ma, in *Modern Allene Chemistry*, N. Krause and A. S. K. Hashmi, eds., Wiley-VCH, Weinheim, 2004, pp. 595–699.

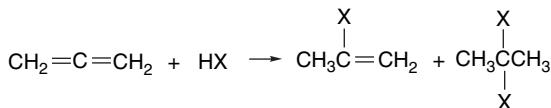
¹⁴² W. Drenth, in *The Chemistry of Triple Bonded Functional Groups*, Supplement C2, Vol. 2, S. Patai, ed., John Wiley & Sons, New York, 1994, pp. 873–915.

that is not stabilized by resonance, because the adjacent π bond is orthogonal to the empty p orbital.

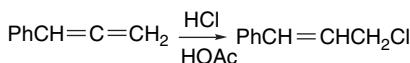


As a result, protonation both in solution¹⁴³ and gas phase¹⁴⁴ occurs at a terminal carbon to give the 2-propenyl cation, not the allylic cation.

The addition of HCl, HBr, and HI to allene has been studied in some detail.¹⁴⁵ In each case a 2-halopropene is formed, corresponding to protonation at a terminal carbon. The initial product can undergo a second addition, giving rise to 2,2-dihalopropanes. The regiochemistry reflects the donor effect of the halogen. Dimers are also formed, but we have not considered them.



The presence of a phenyl group results in the formation of products from protonation at the center carbon.¹⁴⁶

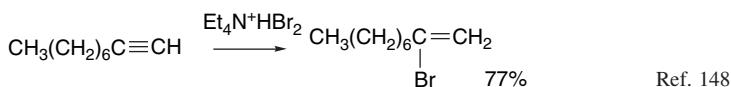


Two alkyl substituents, as in 1,1-dimethylallene, also lead to protonation at the center carbon.¹⁴⁷



These substituent effects are due to the stabilization of the carbocations that result from protonation at the center carbon. Even if allylic conjugation is not important, the aryl and alkyl substituents make the terminal carbocation more stable than the alternative, a secondary vinyl cation.

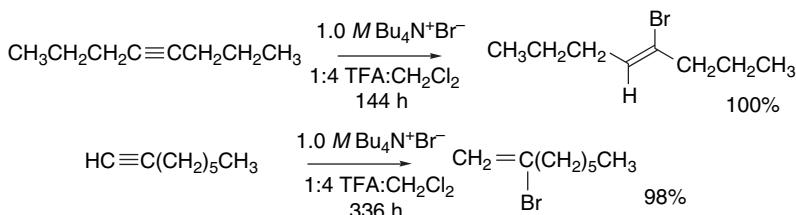
Acid-catalyzed additions to terminal alkynes follow the Markovnikov rule.



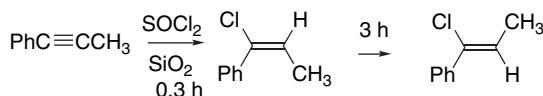
The rate and selectivity of the reaction can be considerably enhanced by using an added quaternary bromide salt in 1:1 TFA:CH₂Cl₂. Note that the reactions are quite

- ¹⁴³. P. Cramer and T. T. Tidwell, *J. Org. Chem.*, **46**, 2683 (1981).
- ¹⁴⁴. M. T. Bowers, L. Shuying, P. Kemper, R. Stradling, H. Webb, D. H. Aue, J. R. Gilbert, and K. R. Jennings, *J. Am. Chem. Soc.*, **102**, 4830 (1980); S. Fornarini, M. Speranza, M. Attina, F. Cacace, and P. Giacomello, *J. Am. Chem. Soc.*, **106**, 2498 (1984).
- ¹⁴⁵. K. Griesbaum, W. Naegele, and G. G. Wanless, *J. Am. Chem. Soc.*, **87**, 3151 (1965).
- ¹⁴⁶. T. Okuyama, K. Izawa, and T. Fueno, *J. Am. Chem. Soc.*, **95**, 6749 (1973).
- ¹⁴⁷. T. L. Jacobs and R. N. Johnson, *J. Am. Chem. Soc.*, **82**, 6397 (1960).
- ¹⁴⁸. J. Cousseau, *Synthesis*, 805 (1980).

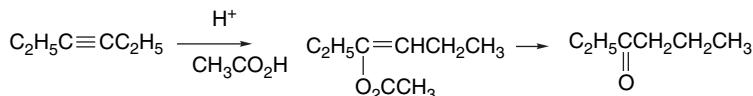
slow, even under these favorable conditions, but there is clean formation of the *anti* addition product.¹⁴⁹



Surface-mediated addition of HCl or HBr can be carried out in the presence of silica or alumina.¹⁵⁰ The hydrogen halides can be generated from thionyl chloride, oxalyl chloride, oxalyl bromide, phosphorus tribromide, or acetyl bromide. The kinetic products from HCl and 1-phenylpropane result from *syn* addition, but isomerization to the more stable *Z*-isomer occurs upon continued exposure to the acidic conditions.

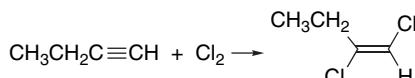


The initial addition products to alkynes are not always stable. Addition of acetic acid, for example, results in the formation of enol acetates, which are converted to the corresponding ketone under the reaction conditions.¹⁵¹



The most synthetically valuable method for converting alkynes to ketones is by mercuric ion-catalyzed hydration. Terminal alkynes give methyl ketones, in accordance with the Markovnikov rule. Internal alkynes give mixtures of ketones unless some structural feature promotes regioselectivity. Reactions with Hg(OAc)_2 in other nucleophilic solvents such as acetic acid or methanol proceed to β -acetoxy- or β -methoxyalkenylmercury intermediates,¹⁵² which can be reduced or solvolyzed to ketones. The regiochemistry is indicative of a mercurinium ion intermediate that is opened by nucleophilic attack at the more positive carbon, that is, the additions follow the Markovnikov rule. Scheme 4.8 gives some examples of alkyne hydration reactions.

Addition of chlorine to 1-butyne is slow in the absence of light. When addition is initiated by light, the major product is *E*-1,2-dichlorobutene if butyne is present in large excess.¹⁵³



¹⁴⁹ H. M. Weiss and K. M. Touchette, *J. Chem. Soc., Perkin Trans. 2*, 1523 (1998).

¹⁵⁰ P. J. Kropp and S. D. Crawford, *J. Org. Chem.*, **59**, 3102 (1994).

¹⁵¹ R. C. Fahey and D.-J. Lee, *J. Am. Chem. Soc.*, **90**, 2124 (1968).

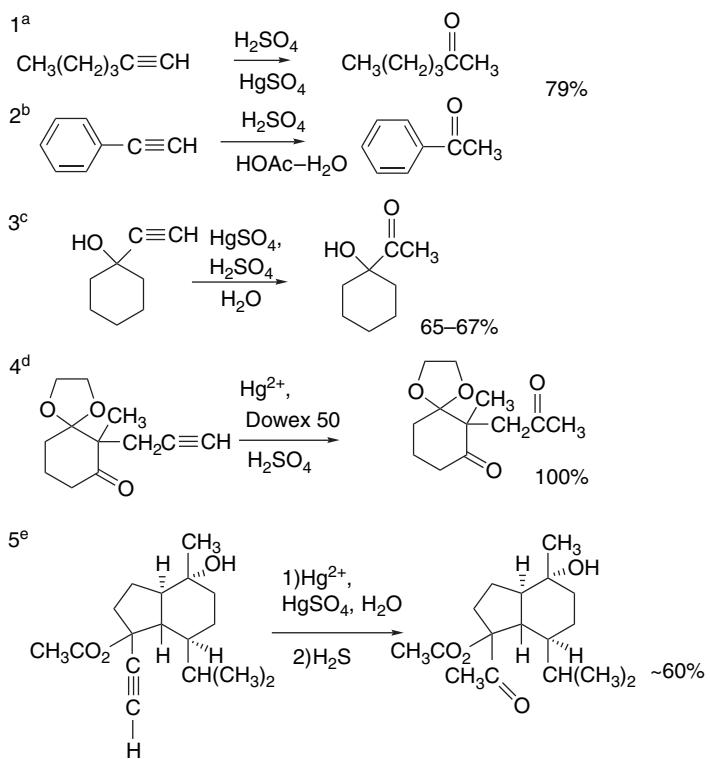
¹⁵² M. Uemura, H. Miyoshi, and M. Okano, *J. Chem. Soc., Perkin Trans. 1*, 1098 (1980); R. D. Bach, R. A. Woodward, T. J. Anderson, and M. D. Glick, *J. Org. Chem.*, **47**, 3707 (1982); M. Bassetti, B. Floris, and G. Spadafora, *J. Org. Chem.*, **54**, 5934 (1989).

¹⁵³ M. L. Poutsma and J. L. Kartch, *Tetrahedron*, **22**, 2167 (1966).

Scheme 4.8. Ketones by Hydration of Alkynes

CHAPTER 4

*Electrophilic Additions
to Carbon-Carbon
Multiple Bonds*



a. R. J. Thomas, K. N. Campbell, and G. F. Hennion, *J. Am. Chem. Soc.*, **60**, 718 (1938).

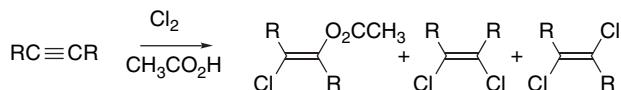
b. R. W. Bott, C. Eaborn, and D. R. M. Walton, *J. Chem. Soc.*, 384 (1965).

c. G. N. Stacy and R. A. Mikulec, *Org. Synth.*, **IV**, 13 (1963).

d. W. G. Dauben and D. J. Hart, *J. Org. Chem.*, **42**, 3787 (1977).

e. D. Caine and F. N. Tuller, *J. Org. Chem.*, **38**, 3663 (1973).

In acetic acid, both 1-pentyne and 1-hexyne give the *syn* addition product. With 2-butyne and 3-hexyne, the major products are β -chlorovinyl acetates of *E*-configuration.¹⁵⁴ Some of the dichloro compounds are also formed, with more of the *E*- than the *Z*-isomer being observed.

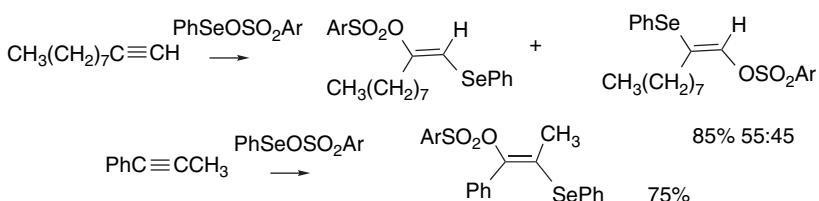


The reactions of the internal alkynes are considered to involve a cyclic halonium ion intermediate, whereas the terminal alkynes seem to react by a rapid collapse of a vinyl cation.

Alkynes react with electrophilic selenium reagents such as phenylselenenyl tosylate.¹⁵⁵ The reaction occurs with *anti* stereoselectivity. Aryl-substituted alkynes are regioselective, but alkyl-substituted alkynes are not.

¹⁵⁴. K. Yates and T. A. Go, *J. Org. Chem.*, **45**, 2385 (1980).

¹⁵⁵. T. G. Back and K. R. Muralidharan, *J. Org. Chem.*, **56**, 2781 (1991).

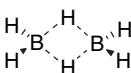


Some of the most synthetically useful addition reactions of alkynes are with organometallic reagents, and these reactions, which can lead to carbon-carbon bond formation, are discussed in Chapter 8.

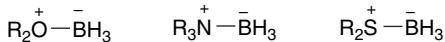
4.5. Addition at Double Bonds via Organoborane Intermediates

4.5.1. Hydroboration

Borane, BH_3 , having only six valence electrons on boron, is an avid electron pair acceptor. Pure borane exists as a dimer in which two hydrogens bridge the borons.



In aprotic solvents that can act as electron pair donors such as ethers, tertiary amines, and sulfides, borane forms Lewis acid-base adducts.



Borane dissolved in THF or dimethyl sulfide undergoes addition reactions rapidly with most alkenes. This reaction, which is known as *hydroboration*, has been extensively studied and a variety of useful synthetic processes have been developed, largely through the work of H. C. Brown and his associates.

Hydroboration is highly *regioselective* and *stereospecific*. The boron becomes bonded primarily to the *less-substituted* carbon atom of the alkene. A combination of steric and electronic effects works to favor this orientation. Borane is an electrophilic reagent. The reaction with substituted styrenes exhibits a weakly negative ρ value (-0.5).¹⁵⁶ Compared with bromination ($\rho^+ = -4.3$),¹⁵⁷ this is a small substituent effect, but it does favor addition of the electrophilic boron at the less-substituted end of the double bond. In contrast to the case of addition of protic acids to alkenes, it is the *boron, not the hydrogen, that is the more electrophilic atom*. This electronic effect is reinforced by steric factors. Hydroboration is usually done under conditions in which the borane eventually reacts with three alkene molecules to give a trialkylborane. The

¹⁵⁶ L. C. Vishwakarma and A. Fry, *J. Org. Chem.*, **45**, 5306 (1980).

¹⁵⁷ J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 2944 (1970).

second and third alkyl groups would increase steric repulsion if the boron were added at the internal carbon.

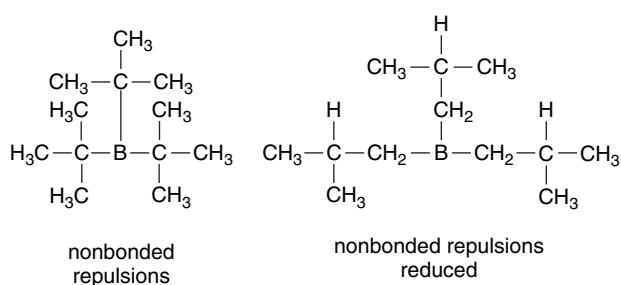


Table 4.3 provides some data on the regioselectivity of addition of diborane and several of its derivatives to representative alkenes. Table 4.3 includes data for some mono- and dialkylboranes that show even higher regioselectivity than diborane itself. These derivatives are widely used in synthesis and are frequently referred to by the shortened names shown with the structures.

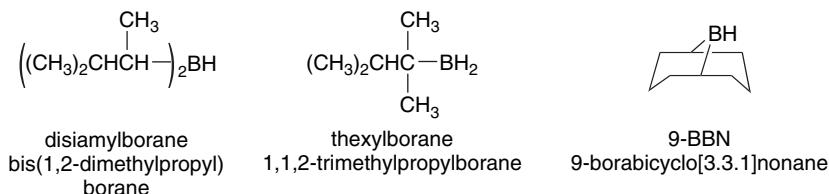


Table 4.3. Regioselectivity of Diborane and Alkylboranes toward Some Alkenes

Hydroborating agent	Percent boron at less substituted carbon			
	1-Hexene	2-Methyl-1-butene	4-Methyl-2-pentene	Styrene
Diborane ^a	94	99	57	80
Chloroborane-dimethyl sulfide ^b	99	99.5	—	98
Disiamylborane ^a	99	—	97	98
Thexyloborane-dimethyl sulfide ^c	94	—	66	95
Thexylichloroborane-dimethyl sulfide	99	99	97	99
9-Borabicyclo[3.3.1]borane	99.9	99.8 ^f	99.3	98.5

a. G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

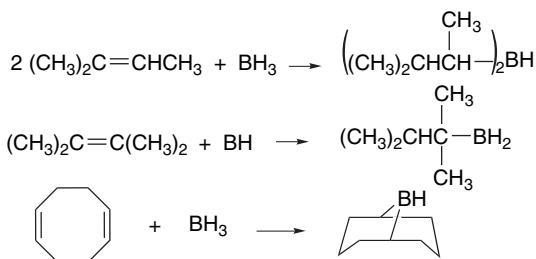
b. H. C. Brown, N. Ravindran, and S. U. Kulkarni, *J. Org. Chem.*, **44**, 2417 (1969); H. C. Brown and U. S. Racherla, *J. Org. Chem.*, **51**, 895 (1986).

c. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 4708 (1960).

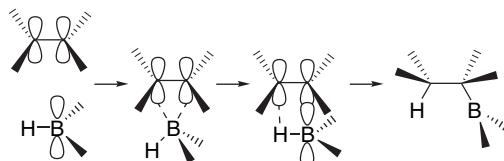
d. H. C. Brown, J. A. Sikorski, S. U. Kulkarni, and H. D. Lee, *J. Org. Chem.*, **45**, 4540 (1980).

e. H. C. Brown, E. F. Knight, and C. G. Scouten, *J. Am. Chem. Soc.*, **96**, 7765 (1974).

f. Data for 2-methyl-1-pentene.



Hydroboration is a stereospecific *syn* addition that occurs through a four-center TS with simultaneous bonding to boron and hydrogen. The new C–B and C–H bonds are thus both formed from the same face of the double bond. In molecular orbital terms, the addition is viewed as taking place by interaction of the filled alkene π orbital with the empty p orbital on boron, accompanied by concerted C–H bond formation.¹⁵⁸



As is true for most reagents, there is a preference for approach of the borane from the less hindered face of the alkene. Because diborane itself is a relatively small molecule, the stereoselectivity is not high for unhindered alkenes. Table 4.4 gives some data comparing the direction of approach for three cyclic alkenes. The products in all cases result from *syn* addition, but the mixtures result from both the low regioselectivity and from addition to both faces of the double bond. Even 7,7-dimethylnorbornene shows only modest preference for *endo* addition with diborane. The selectivity is enhanced with the bulkier reagent 9-BBN.

Table 4.4. Stereoselectivity of Hydroboration of Cyclic Alkenes^a

	Product composition ^b								
	3-Methyl cyclopentene			4-Methyl cyclohexene			7,7-Dimethylbi-cyclo[2.2.1]heptene		
	<i>trans</i> -2	<i>cis</i> -3	<i>trans</i> -3	<i>cis</i> -2	<i>trans</i> -2	<i>cis</i> -3	<i>trans</i> -3	<i>exo</i>	<i>endo</i>
Diborane	45	55		16	34	18	32	22	78 ^c
Disiamylborane	40	60		18	30	27	25	—	—
9-BBN	25	50	25	0	20	40	40	3	97

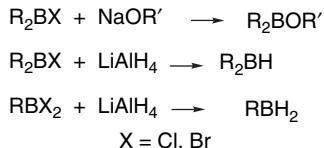
a. Data from H. C. Brown, R. Liotta, and L. Brener, *J. Am. Chem. Soc.*, **99**, 3427 (1977), except where otherwise noted.

b. Product composition refers to methylcycloalkanols formed by oxidation.

c. H. C. Brown, J. H. Kawakami, and K.-T. Liu, *J. Am. Chem. Soc.*, **95**, 2209 (1973).

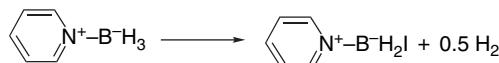
¹⁵⁸ D. J. Pasto, B. Lepeska, and T.-C. Cheng, *J. Am. Chem. Soc.*, **94**, 6083 (1972); P. R. Jones, *J. Org. Chem.*, **37**, 1886 (1972); S. Nagase, K. N. Ray, and K. Morokuma, *J. Am. Chem. Soc.*, **102**, 4536 (1980); X. Wang, Y. Li, Y.-D. Wu, M. N. Paddon-Row, N. G. Rondan, and K. N. Houk, *J. Org. Chem.*, **55**, 2601 (1990); N. J. R. van Eikema Hommes and P. v. R. Schleyer, *J. Org. Chem.*, **56**, 4074 (1991).

The haloboranes BH_2Cl , BH_2Br , BHCl_2 , and BHBBr_2 are also useful hydroborating reagents.¹⁵⁹ These compounds are somewhat more regioselective than borane itself, but otherwise show similar reactivity. A useful aspect of the chemistry of the haloboranes is the potential for sequential introduction of substituents at boron. The halogens can be replaced by alkoxide or by hydride. When halogen is replaced by hydride, a second hydroboration step can be carried out.

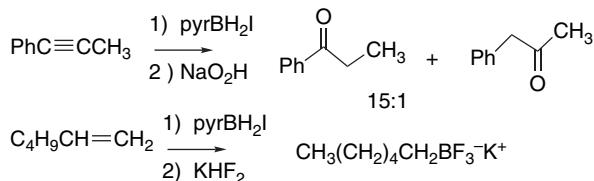


Examples of these transformations are discussed in Chapter 9, where carbon-carbon bond-forming reactions of organoboranes are covered.

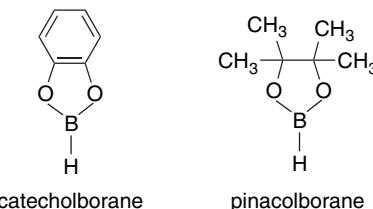
Amine-borane complexes are not very reactive toward hydroboration, but the pyridine complex of borane can be activated by reaction with iodine.¹⁶⁰ The active reagent is thought to be the pyridine complex of iodosoborane.



The resulting boranes can be subjected to oxidation or isolated as potassium trifluoroborates.



Catecholborane and pinacolborane, in which the boron has two oxygen substituents, are much less reactive hydroborating reagents than alkyl or haloboranes because the boron electron deficiency is attenuated by the oxygen atoms. Nevertheless, they are useful reagents for certain applications.¹⁶¹ The reactivity of catecholborane has been found to be substantially enhanced by addition of 10–20% of *N,N*-dimethylacetamide to CH_2Cl_2 .¹⁶²

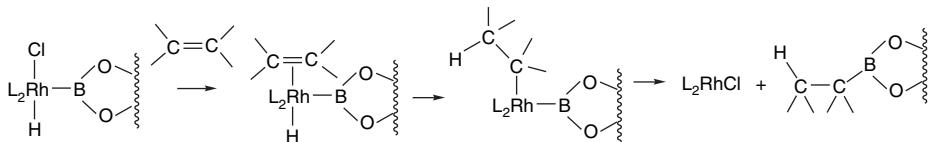


¹⁵⁹ H. C. Brown and S. U. Kulkarni, *J. Organomet. Chem.*, **239**, 23 (1982).

¹⁶⁰ J. M. Clay and E. Vedejs, *J. Am. Chem. Soc.*, **127**, 5766 (2005).

¹⁶¹ C. E. Tucker, J. Davidson, and P. Knockel, *J. Org. Chem.*, **57**, 3482 (1992).

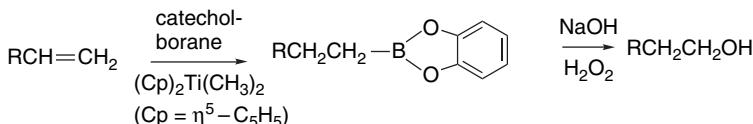
¹⁶² C. E. Garrett and G. C. Fu, *J. Org. Chem.*, **61**, 3224 (1996).



Variation in catalyst and ligand can lead to changes in both regio- and enantioselectivity. For example, the hydroboration of vinyl arenes such as styrene and 6-methoxy-2-vinylnaphthalene can be directed to the internal secondary borane by use of $\text{Rh}(\text{COD})_2\text{BF}_4$ as a catalyst.¹⁶⁶ These reactions are enantioselective in the presence of a chiral phosphorus ligand.

$\text{ArCH}=\text{CH}_2$		5 mol % $\text{Rh}(\text{COD})_2\text{BF}_4$	5 mol % Josiphos	$\text{Ar}-\underset{\substack{ \\ \text{OH}}}{\text{CH}}-\text{CH}_3$	$\text{ArCH}_2\text{CH}_2\text{OH}$	ratio	yield	e.e.
				Phenyl		83:17	87%	84%
				6-Methoxynaphthyl		95:5	83%	88%

On the other hand, iridium catalysts give very high selectivity for formation of the primary borane.¹⁶⁷ Several other catalysts have been described, including, for example, dimethyltitanocene.¹⁶⁸



Catalyzed hydroboration has proven to be valuable in controlling the stereoselectivity of hydroboration of functionalized alkenes.¹⁶⁹ For example, allylic alcohols

¹⁶³ I. Beletskaya and A. Pelter, *Tetrahedron*, **53**, 4957 (1997); H. Wadepohl, *Angew. Chem. Int. Ed. Engl.*, **36**, 2441 (1997); K. Burgess and M. J. Ohlmeyer, *Chem. Rev.*, **91**, 1179 (1991); C. M. Cradden and D. Edwards, *Eur. J. Org. Chem.*, 4695 (2003).

¹⁶⁴ D. A. Evans, G. C. Fu, and A. H. Hoveyda, *J. Am. Chem. Soc.*, **110**, 6917 (1988); D. Maenning and H. Noeth, *Angew. Chem. Int. Ed. Engl.*, **24**, 878 (1985).

¹⁶⁵ D. A. Evans, G. C. Fu, and B. A. Anderson, *J. Am. Chem. Soc.*, **114**, 6679 (1992).

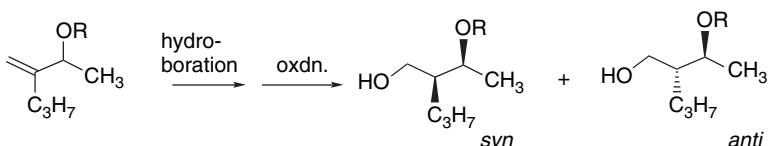
¹⁶⁶ C. M. Cradden, Y. B. Hleba, and A. C. Chen, *J. Am. Chem. Soc.*, **126**, 9200 (2004).

¹⁶⁷ Y. Yamamoto, R. Fujikawa, T. Unemoto, and N. Miyaura, *Tetrahedron*, **60**, 10695 (2004).

¹⁶⁸ X. He and J. F. Hartwig, *J. Am. Chem. Soc.*, **118**, 1696 (1996).

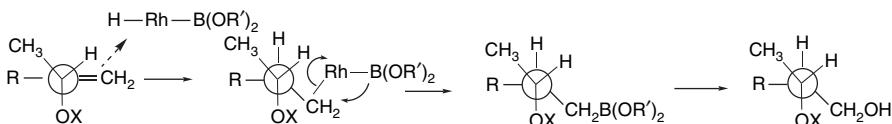
¹⁶⁹ D. A. Evans, G. C. Fu, and A. H. Hoveyda, *J. Am. Chem. Soc.*, **114**, 6671 (1992).

and ethers give mainly *syn* product when catalyzed by $\text{Rh}(\text{PPh}_3)_3\text{Cl}$, whereas direct hydroboration with 9-BBN gives mainly *anti* product.

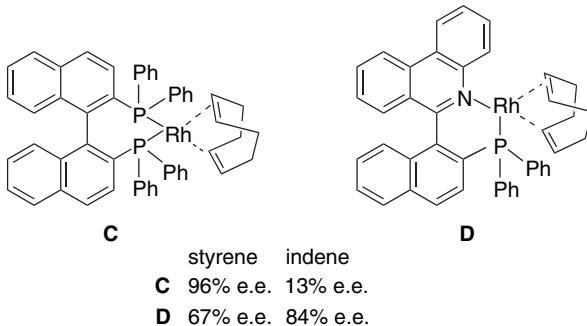


R	9-BBN		catecholborane 3 mol % $\text{Rh}(\text{PPh}_3)_3\text{Cl}$	
	yield	<i>syn:anti</i>	yield	<i>syn:anti</i>
H	91	17:83	79	81:19
PhCH ₂	82	25:75	63	80:20
TBDMS	85	13:87	79	93:7

The stereoselectivity of the catalyzed reaction appears to be associated with the complexation step, which is product determining. The preferred orientation of approach of the complex is *anti* to the oxygen substituent, which acts as an electron acceptor and more electronegative groups enhance reactivity. The preferred conformation of the alkene has the hydrogen oriented toward the double bond and this leads to a *syn* relationship between the alkyl and oxygen substituents.¹⁷⁰



The use of chiral ligands in catalysts can lead to enantioselective hydroboration. Rh-BINAP¹⁷¹ **C** and the related structure **D**¹⁷² have shown good stereoselectivity in the hydroboration of styrene and related compounds (see also Section 4.5.3).

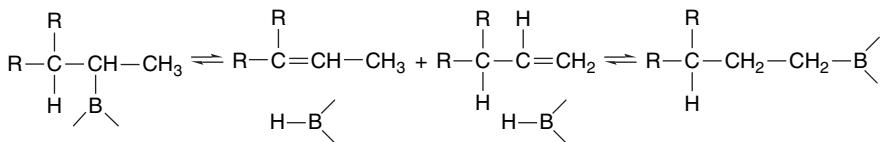


Hydroboration is thermally reversible. B—H moieties are eliminated from alkylboranes at 160° C and above, but the equilibrium still favors of the addition products.

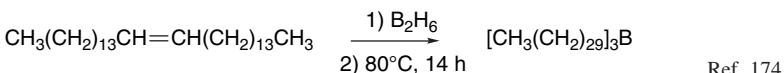
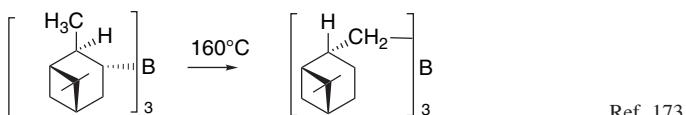
¹⁷⁰. K. Burgess, W. A. van der Donk, M. B. Jarstfer, and M. J. Ohlmeyer, *J. Am. Chem. Soc.*, **113**, 6139 (1991).

¹⁷¹. T. Hayashi and Y. Matsumoto, *Tetrahedron: Asymmetry*, **2**, 601 (1991).

¹⁷². J. M. Valk, G. A. Whitlock, T. P. Layzell, and J. M. Brown, *Tetrahedron: Asymmetry*, **6**, 2593 (1995).

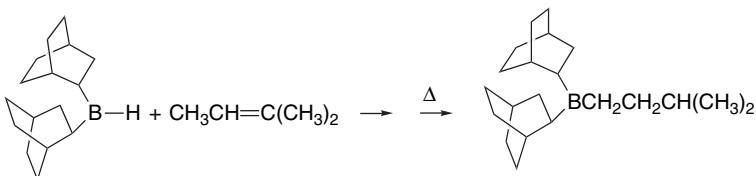


Migration cannot occur past a quaternary carbon, however, since the required elimination is blocked. At equilibrium the major trialkyl borane is the least-substituted terminal isomer that is accessible, since this isomer minimizes unfavorable steric interactions.



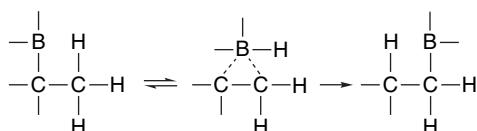
Ref. 174

Migrations are more facile for *tetra*-substituted alkenes and occur at 50°–60° C.¹⁷⁵ Bulky substituents on boron facilitate the migration. *bis*-Bicyclo[2.2.2]octanylboranes, in which there are no complications from migrations in the bicyclic substituent, were found to be particularly useful.



Ref. 176

There is evidence that boron migration occurs intramolecularly.¹⁷⁷ A TS involving an electron-deficient π complex about 20–25 kcal above the trialkylborane that describes the migration has been located computationally.¹⁷⁸



¹⁷³. G. Zweifel and H. C. Brown, *J. Am. Chem. Soc.*, **86**, 393 (1964).

¹⁷⁴. K. Maruyama, K. Terada, and Y. Yamamoto, *J. Org. Chem.*, **45**, 737 (1980).

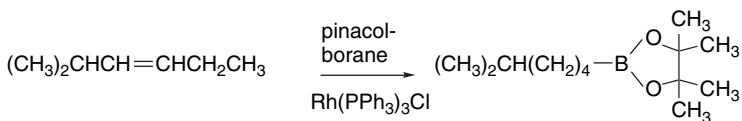
¹⁷⁵. L. O. Bromm, H. Laaziri, F. Lhermitte, K. Harms, and P. Knochel, *J. Am. Chem. Soc.*, **122**, 10218 (2000).

¹⁷⁶. H. C. Brown and U. S. Racherla, *J. Am. Chem. Soc.*, **105**, 6506 (1983).

¹⁷⁷. S. E. Wood and B. Rickborn, *J. Org. Chem.*, **48**, 555 (1983).

¹⁷⁸. N. J. R. van Eikema Hommes and P. v. R. Schleyer, *J. Org. Chem.*, **56**, 4074 (1991).

Migration of boron to terminal positions is observed under much milder conditions in the presence of transition metal catalysts. For example, hydroboration of 2-methyl-3-hexene by pinacolborane in the presence of $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ leads to the terminal boronate ester.

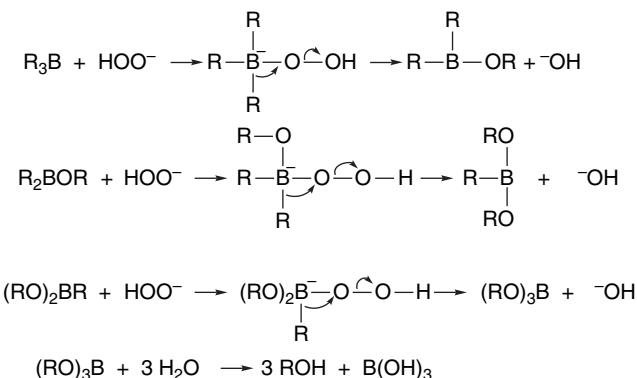


Ref. 179

4.5.2. Reactions of Organoboranes

The organoboranes have proven to be very useful intermediates in organic synthesis. In this section we discuss methods by which the boron atom can be replaced by hydroxy, carbonyl, amino, or halogen groups. There are also important processes that use alkylboranes in the formation of new carbon-carbon bonds. These reactions are discussed in Section 9.1.

The most widely used reaction of organoboranes is the oxidation to alcohols, and alkaline hydrogen peroxide is the reagent usually employed to effect the oxidation. The mechanism, which is outlined below, involves a series of B to O migrations of the alkyl groups. The R—O—B bonds are hydrolyzed in the alkaline aqueous solution, generating the alcohol.

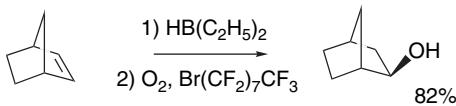


The stereochemical outcome is replacement of the C—B bond by a C—O bond with *retention of configuration*. In combination with stereospecific *syn* hydroboration, this allows the structure and stereochemistry of the alcohols to be predicted with confidence. The preference for hydroboration at the least-substituted carbon of a double bond results in the alcohol being formed with regiochemistry that is complementary to that observed by direct hydration or oxymercuration, that is, anti-Markovnikov.

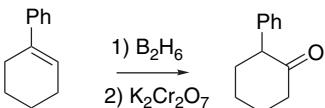
Several other oxidants can be used to effect the borane to alcohol conversion. Oxone® ($2\text{K}_2\text{SO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$) has been recommended for oxidations done on a

¹⁷⁹ S. Pereira and M. Srebnik, *J. Am. Chem. Soc.*, **118**, 909 (1996); S. Pereira and M. Srebnik, *Tetrahedron Lett.*, **37**, 3283 (1996).

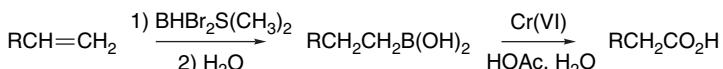
large scale.¹⁸⁰ Conditions that permit oxidation of organoboranes to alcohols using molecular oxygen,¹⁸¹ sodium peroxy carbonate¹⁸² or amine oxides¹⁸³ as oxidants have also been developed. The reaction with molecular oxygen is particularly effective in perfluoroalkane solvents.¹⁸⁴



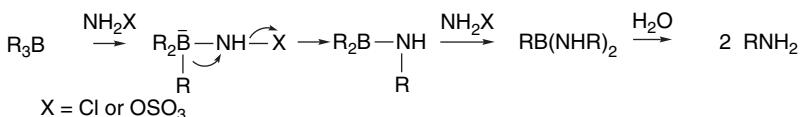
More vigorous oxidants such as Cr(VI) reagents effect replacement of boron and oxidation to the carbonyl level.¹⁸⁵



An alternative procedure for oxidation to ketones involves treatment of the alkylborane with a quaternary ammonium perruthenate salt and an amine oxide¹⁸⁶ (see Entry 6 in Scheme 4.9). Use of dibromoborane-dimethyl sulfide for hydroboration of terminal alkenes, followed by hydrolysis and Cr(VI) oxidation gives carboxylic acids.¹⁸⁷

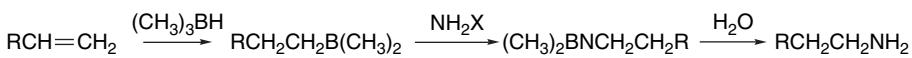


The boron atom can also be replaced by an amino group.¹⁸⁸ The reagents that effect this conversion are chloramine or hydroxylamine-*O*-sulfonic acid, and the mechanism of these reactions is very similar to that of the hydrogen peroxide oxidation of organoboranes. The nitrogen-containing reagent initially reacts as a nucleophile by adding at boron and a B to N rearrangement with expulsion of chloride or sulfate ion follows. Usually only two of the three alkyl groups migrate. As in the oxidation, the migration step occurs with retention of configuration. The amine is freed by hydrolysis.

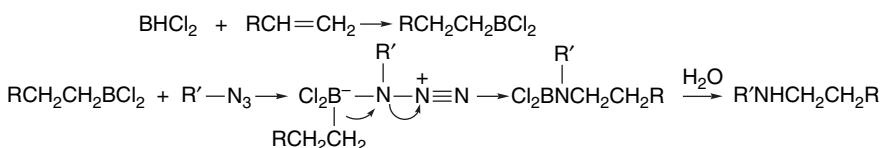


- ¹⁸⁰ D. H. B. Ripin, W. Cai, and S. T. Brenek, *Tetrahedron Lett.*, **41**, 5817 (2000).
- ¹⁸¹ H. C. Brown, M. M. Midland, and G. W. Kabalka, *J. Am. Chem. Soc.*, **93**, 1024 (1971).
- ¹⁸² G. W. Kabalka, P. P. Wadgaonkar, and T. M. Shoup, *Tetrahedron Lett.*, **30**, 5103 (1989).
- ¹⁸³ G. W. Kabalka and H. C. Hedgecock, Jr., *J. Org. Chem.*, **40**, 1776 (1975); R. Koster and Y. Monta, *Liebigs Ann. Chem.*, **704**, 70 (1967).
- ¹⁸⁴ I. Klement and P. Knochel, *Synlett*, 1004 (1996).
- ¹⁸⁵ H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2951 (1961); H. C. Brown, C. Rao, and S. Kulkarni, *J. Organomet. Chem.*, **172**, C20 (1979).
- ¹⁸⁶ M. H. Yates, *Tetrahedron Lett.*, **38**, 2813 (1997).
- ¹⁸⁷ H. C. Brown, S. V. Kulkarni, V. V. Khanna, V. D. Patil, and U. S. Racherla, *J. Org. Chem.*, **57**, 6173 (1992).
- ¹⁸⁸ M. W. Rathke, N. Inoue, K. R. Varma, and H. C. Brown, *J. Am. Chem. Soc.*, **88**, 2870 (1966); G. W. Kabalka, K. A. R. Sastry, G. W. McCollum, and H. Yoshioka, *J. Org. Chem.*, **46**, 4296 (1981).

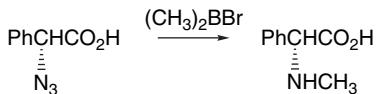
The alkene can be used more efficiently if the hydroboration is done with dimethylborane.¹⁸⁹



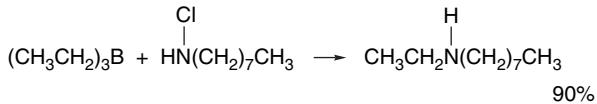
Secondary amines are formed by reaction of trisubstituted boranes with alkyl or aryl azides. The most efficient borane intermediates are monoalkyldichloroboranes, which are generated by reaction of an alkene with $\text{BHCl}_2 \cdot \text{Et}_2\text{O}$.¹⁹⁰ The entire sequence of steps and the mechanism of the final stages are summarized by the equation below.



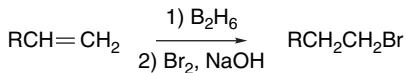
This reaction has been used to prepare α -*N*-methylamino acids using $(\text{CH}_3)_2\text{BBr}$.¹⁹¹



Secondary amines can also be made using the *N*-chloro derivatives of primary amines.¹⁹²



Organoborane intermediates can also be used to synthesize alkyl halides. Replacement of boron by iodine is rapid in the presence of base.¹⁹³ The best yields are obtained using sodium methoxide in methanol.¹⁹⁴ If less basic conditions are desirable, the use of iodine monochloride and sodium acetate gives good yields.¹⁹⁵ As is the case in hydroboration-oxidation, the regioselectivity of hydroboration-halogenation is opposite to that observed by direct ionic addition of hydrogen halides to alkenes. Terminal alkenes give primary halides.



^{189.} H. C. Brown, K.-W. Kim, M. Srebnik, and B. Singaram, *Tetrahedron*, **43**, 4071 (1987).

^{190.} H. C. Brown, M. M. Midland, and A. B. Levy, *J. Am. Chem. Soc.*, **95**, 2394 (1973).

^{191.} R. L. Dorow and D. E. Gingrich, *J. Org. Chem.*, **60**, 4986 (1995).

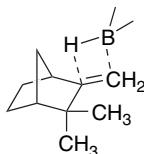
^{192.} G. W. Kabalka, G. W. McCollum, and S. A. Kunda, *J. Org. Chem.*, **49**, 1656 (1984).

^{193.} H. C. Brown, M. W. Rathke, and M. M. Rogic, *J. Am. Chem. Soc.*, **90**, 5038 (1968).

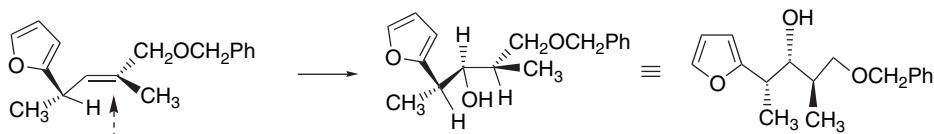
^{194.} N. R. De Lue and H. C. Brown, *Synthesis*, 114 (1976).

^{195.} G. W. Kabalka and E. E. Gooch, III, *J. Org. Chem.*, **45**, 3578 (1980).

Scheme 4.9 gives some examples of the use of boranes in syntheses of alcohols, aldehydes, ketones, amines, and halides. Entry 1 demonstrates both the regioselectivity and stereospecificity of hydroboration, resulting in the formation of *trans*-2-methylcyclohexanol. Entry 2 illustrates the facial selectivity, with the borane adding *anti* to the *endo* methyl group.



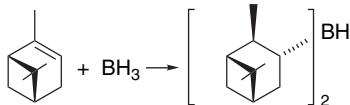
Entry 3 illustrates all aspects of the regio- and stereoselectivity, with *syn* addition occurring *anti* to the dimethyl bridge in the pinene structure. The stereoselectivity in Entry 4 is the result of the preferred conformation of the alkene and approach *syn* to the smaller methyl group, rather than the 2-furyl group.



Entries 5 to 7 are examples of oxidation of boranes to the carbonyl level. In Entry 5, chromic acid was used to obtain a ketone. Entry 6 shows 5 mol % tetrapropylammonium perruthenate with *N*-methylmorpholine-*N*-oxide as the stoichiometric oxidant converting the borane directly to a ketone. Aldehydes were obtained from terminal alkenes using this reagent combination. Pyridinium chlorochromate (Entry 7) can also be used to obtain aldehydes. Entries 8 and 9 illustrate methods for amination of alkenes via boranes. Entries 10 and 11 illustrate the preparation of halides.

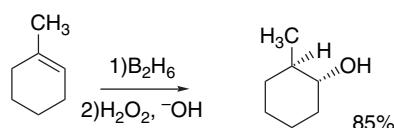
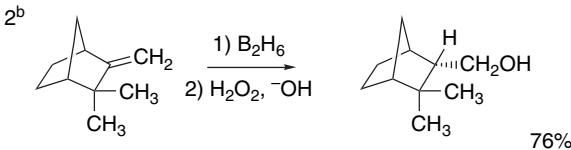
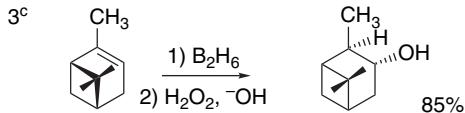
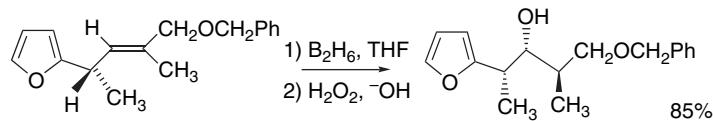
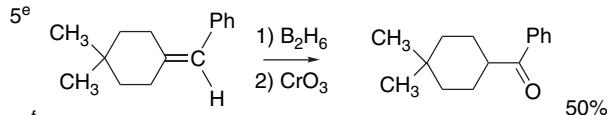
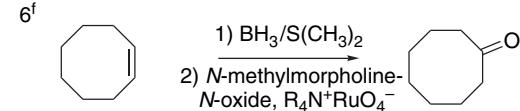
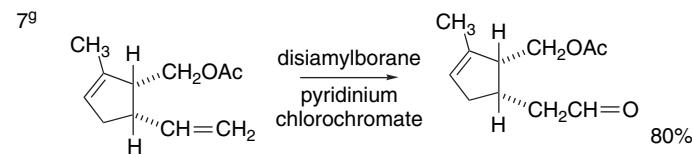
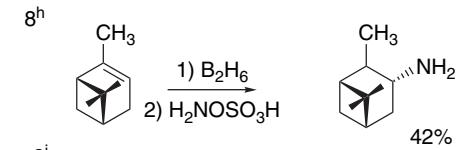
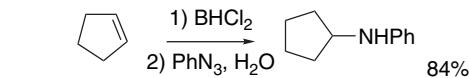
4.5.3. Enantioselective Hydroboration

Several alkylboranes are available in enantiomerically enriched or pure form and can be used to prepare enantiomerically enriched alcohols and other compounds available via organoborane intermediates.¹⁹⁶ One route to enantiopure boranes is by hydroboration of readily available terpenes that occur naturally in enantiomerically enriched or pure form. The most thoroughly investigated of these is *bis*-(isopinocampheyl)borane; (*Ipc*)₂BH, which can be prepared in 100% enantiomeric purity from the readily available terpene α -pinene.¹⁹⁷ Both enantiomers are available.



¹⁹⁶ H. C. Brown and B. Singaram, *Acc. Chem. Res.*, **21**, 287 (1988); D. S. Matteson, *Acc. Chem. Res.*, **21**, 294 (1988).

¹⁹⁷ H. C. Brown, P. K. Jadhav, and A. K. Mandal, *Tetrahedron*, **37**, 3547 (1981); H. C. Brown and P. K. Jadhav, in *Asymmetric Synthesis*, Vol. 2, J. D. Morrison, ed., Academic Press, New York, 1983, Chap. 1.

Scheme 4.9. Synthesis of Alcohols, Aldehydes, Ketones, and Amines from Organoboranes**A. Alcohols**1^a2^b3^c4^d**B. Ketones and aldehydes**5^e6^f7^g**C. Amines**8^h9ⁱ

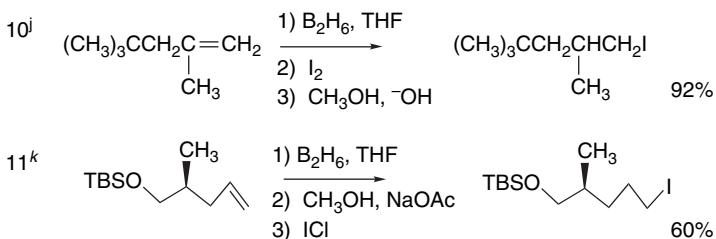
(Continued)

Scheme 4.9. (Continued)

SECTION 4.5

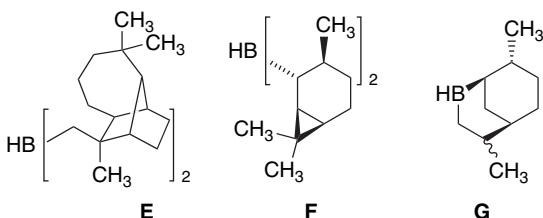
Addition at Double Bonds via Organoborane Intermediates

D. Halides

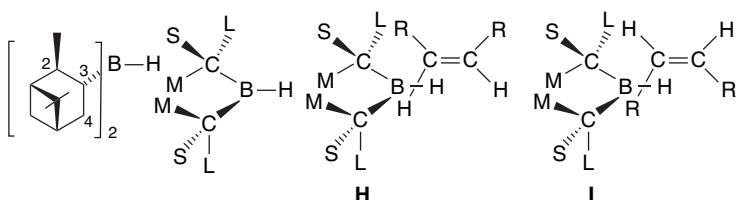


- a. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2544 (1961).
- b. R. Dulou, Y. Chretien-Bessiere, *Bull. Soc. Chim. Fr.*, 1362 (1959).
- c. G. Zweifel and H. C. Brown, *Org. Synth.*, **52**, 59 (1972).
- d. G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.*, **101**, 259 (1979).
- e. W. B. Farnham, *J. Am. Chem. Soc.*, **94**, 6857 (1972).
- f. M. H. Yates, *Tetrahedron Lett.*, **38**, 2813 (1997).
- g. H. C. Brown, S. U. Kulkarni, and C. G. Rao, *Synthesis*, 151 (1980); T. H. Jones and M. S. Blum, *Tetrahedron Lett.*, **22**, 4373 (1981).
- h. M. W. Rathke and A. A. Millard, *Org. Synth.*, **58**, 32 (1978).
- i. H. C. Brown, M. M. Midland, and A. B. Levy, *J. Am. Chem. Soc.*, **95**, 2394 (1973).
- j. H. C. Brown, M. W. Rathke, M. M. Rogic, and N. R. DeLue, *Tetrahedron*, **44**, 2751 (1988).
- k. D. Schinzer, A. Bauer, and J. Schreiber, *Chem. Eur. J.*, **5**, 2492 (1999).

Other examples of chiral organoboranes derived from terpenes are **E**, **F**, and **G**, which are derived from longifolene,¹⁹⁸ 2-carene,¹⁹⁹ and limonene,²⁰⁰ respectively.



$(\text{Ipc})_2\text{BH}$ adopts a conformation that minimizes steric interactions. This conformation can be represented schematically as in **H** and **I**, where the S, M, and L substituents are, respectively, the 3-H, 4- CH_2 , and 2- CHCH_3 groups of the carbocyclic structure. The steric environment at boron in this conformation is such that *Z*-alkenes encounter less steric encumbrance in **TS I** than in **H**.



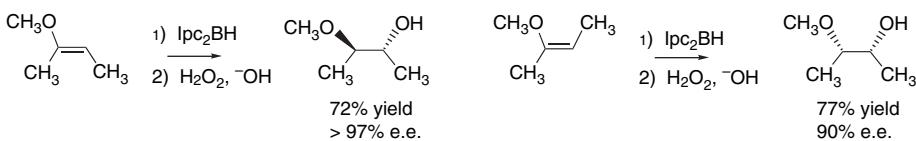
The degree of enantioselectivity of $(\text{Ipc})_2\text{BH}$ is not high for all simple alkenes. *Z*-Disubstituted alkenes give good enantioselectivity (75–90%) but *E*-alkenes and

¹⁹⁸ P. K. Jadhav and H. C. Brown, *J. Org. Chem.*, **46**, 2988 (1981).

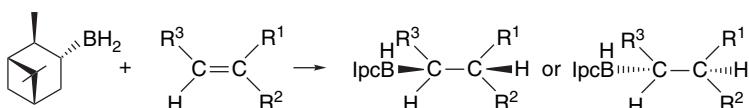
¹⁹⁹ H. C. Brown, J. V. N. Vara Prasad, and M. Zajdlewicz, *J. Org. Chem.*, **53**, 2911 (1988).

²⁰⁰ P. K. Jadhav and S. U. Kulkarni, *Heterocycles*, **18**, 169 (1982).

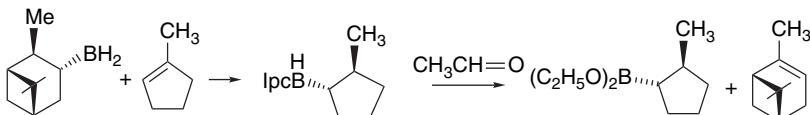
simple cycloalkenes give low enantioselectivity (5–30%). Interestingly, vinyl ethers exhibit good enantioselectivity for both the *E*- and *Z*-isomers.²⁰¹



Monoisocampheylborane (IpcBH_2) can be prepared in enantiomerically pure form by separation of a TMEDA adduct.²⁰² When this monoalkylborane reacts with a prochiral alkene, one of the diastereomeric products is normally formed in excess and can be obtained in high enantiomeric purity by an appropriate separation.²⁰³ Oxidation of the borane then provides the corresponding alcohol having the enantiomeric purity achieved for the borane.



As oxidation also converts the original chiral terpene-derived group to an alcohol, it is not directly reusable as a chiral auxiliary. Although this is not a problem with inexpensive materials, the overall efficiency of generation of enantiomerically pure product is improved by procedures that can regenerate the original terpene. This can be done by heating the dialkylborane intermediate with acetaldehyde. The α -pinene is released and a diethoxyborane is produced.²⁰⁴



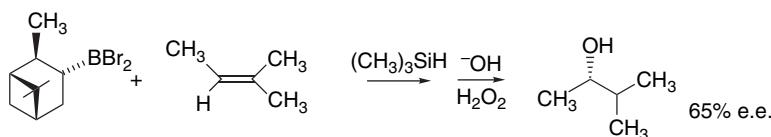
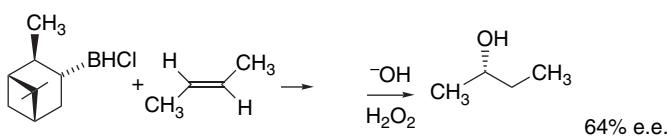
The usual oxidation conditions then convert this boronate ester to an alcohol.²⁰⁵

The corresponding haloboranes are also useful for enantioselective hydroboration. Isopinocampheylchloroborane can achieve 45–80% e.e. with representative alkenes.²⁰⁶ The corresponding bromoborane achieves 65–85% enantioselectivity with simple alkenes when used at -78°C .²⁰⁷

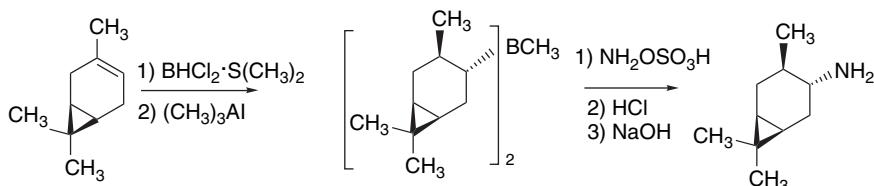
- ²⁰¹ D. Murali, B. Singaram, and H. C. Brown, *Tetrahedron: Asymmetry*, **11**, 4831 (2000).
- ²⁰² H. C. Brown, J. R. Schwier, and B. Singaram, *J. Org. Chem.*, **43**, 4395 (1978); H. C. Brown, A. K. Mandal, N. M. Yoon, B. Singaram, J. R. Schwier, and P. K. Jadhav, *J. Org. Chem.*, **47**, 5069 (1982).
- ²⁰³ H. C. Brown and B. Singaram, *J. Am. Chem. Soc.*, **106**, 1797 (1984); H. C. Brown, P. K. Jadhav, and A. K. Mandal, *J. Org. Chem.*, **47**, 5074 (1982).
- ²⁰⁴ H. C. Brown, B. Singaram, and T. E. Cole, *J. Am. Chem. Soc.*, **107**, 460 (1985); H. C. Brown, T. Imai, M. C. Desai, and B. Singaram, *J. Am. Chem. Soc.*, **107**, 4980 (1985).
- ²⁰⁵ D. S. Matteson and K. M. Sadhu, *J. Am. Chem. Soc.*, **105**, 2077 (1983).
- ²⁰⁶ U. P. Dhokte, S. V. Kulkarni, and H. C. Brown, *J. Org. Chem.*, **61**, 5140 (1996).
- ²⁰⁷ U. P. Dhokte and H. C. Brown, *Tetrahedron Lett.*, **37**, 9021 (1996).

SECTION 4.5

Addition at Double Bonds via Organoborane Intermediates

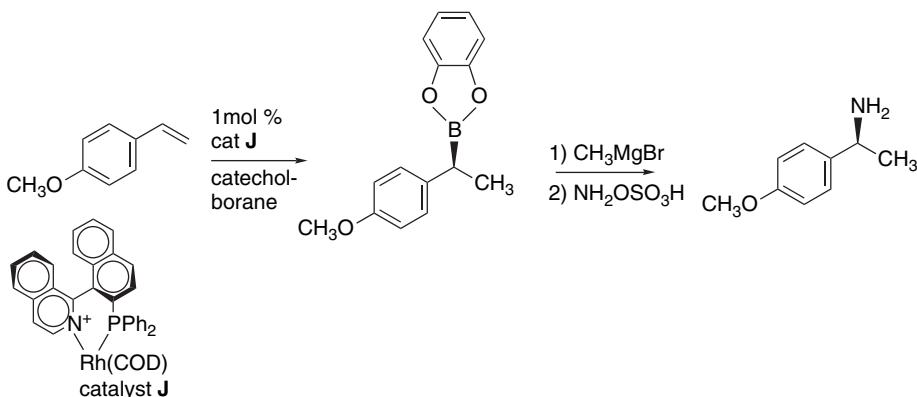


Procedures for synthesis of chiral amines²⁰⁸ and halides²⁰⁹ based on chiral alkylboranes involve applying the methods discussed earlier to the enantiomerically enriched organoborane intermediates. For example, enantiomerically pure terpenes can be converted to trialkylboranes and then aminated with hydroxylaminesulfonic acid.



Ref. 210

Combining catalytic enantioselective hydroboration (see p. 342) with amination has provided certain amines with good enantioselectivity. In this procedure the catechol group is replaced by methyl prior to the amination step.

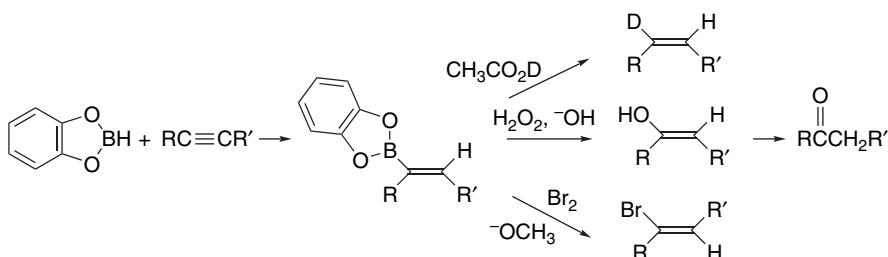


Ref. 211

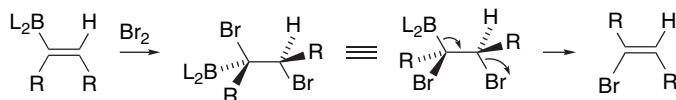
- ²⁰⁸ L. Verbit and P. J. Heffron, *J. Org. Chem.*, **32**, 3199 (1967); H. C. Brown, K.-W. Kim, T. E. Cole, and B. Singaram, *J. Am. Chem. Soc.*, **108**, 6761 (1986); H. C. Brown, A. M. Sahinke, and B. Singaram, *J. Org. Chem.*, **56**, 1170 (1991).
- ²⁰⁹ H. C. Brown, N. R. De Lue, G. W. Kabalka, and H. C. Hedgecock, Jr., *J. Am. Chem. Soc.*, **98**, 1290 (1976).
- ²¹⁰ H. C. Brown, S. V. Malhotra, and P. V. Ramachandran, *Tetrahedron: Asymmetry*, **7**, 3527 (1996).
- ²¹¹ E. Fernandez, M. W. Hooper, F. I. Knight, and J. M. Brown, *J. Chem. Soc., Chem. Commun.*, 173 (1997).

4.5.4. Hydroboration of Alkynes

Alkynes are reactive toward hydroboration reagents. The most useful procedures involve addition of a disubstituted borane to the alkyne, which avoids complications that occur with borane and lead to polymeric structures. Catechol borane is a particularly useful reagent for hydroboration of alkynes.²¹² Protonolysis of the adduct with acetic acid results in reduction of the alkyne to the corresponding *cis*-alkene. Oxidative workup with hydrogen peroxide gives ketones via enol intermediates.

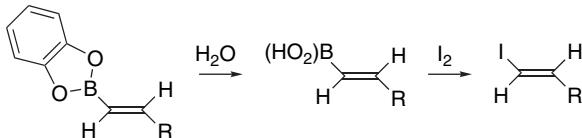


Treatment of the vinylborane with bromine and base leads to vinyl bromides. The reaction occurs with net *anti* addition, and the stereoselectivity is explained on the basis of *anti* addition of bromine followed by a second *anti* elimination of bromide and boron.

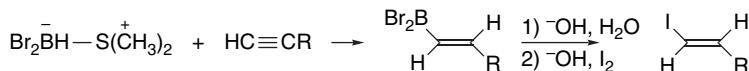


Exceptions to this stereoselectivity have been noted.²¹³

The adducts derived from catechol borane are hydrolyzed by water to vinylboronic acids. These materials are useful intermediates for the preparation of terminal vinyl iodides. Since the hydroboration is a *syn* addition and the iodinolysis occurs with retention of the alkene geometry, the iodides have the *E*-configuration.²¹⁴

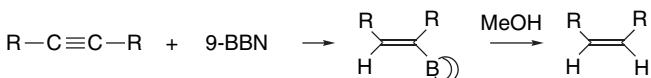


The dimethyl sulfide complex of dibromoborane²¹⁵ and pinacolborane²¹⁶ are also useful for synthesis of *E*-vinyl iodides from terminal alkynes.



- ²¹². H. C. Brown, T. Hamaoka, and N. Ravindran, *J. Am. Chem. Soc.*, **95**, 6456 (1973); C. F. Lane and G. W. Kabalka, *Tetrahedron*, **32**, 981 (1976).
- ²¹³. J. R. Wiersig, N. Waespe-Sarcevic, and C. Djerassi, *J. Org. Chem.*, **44**, 3374 (1979).
- ²¹⁴. H. C. Brown, T. Hamaoka, and N. Ravindran, *J. Am. Chem. Soc.*, **95**, 5786 (1973).
- ²¹⁵. H. C. Brown and J. B. Campbell, Jr., *J. Org. Chem.*, **45**, 389 (1980); H. C. Brown, T. Hamaoka, N. Ravindran, C. Subrahmanyam, V. Somayaji, and N. G. Bhat, *J. Org. Chem.*, **54**, 6075 (1989).
- ²¹⁶. C. E. Tucker, J. Davidson, and P. Knochel, *J. Org. Chem.*, **57**, 3482 (1992).

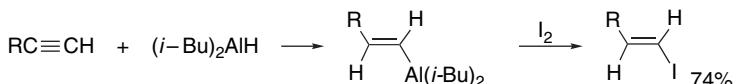
Other disubstituted boranes have also been used for selective hydroboration of alkynes. 9-BBN can be used to hydroborate internal alkynes. Protonolysis can be carried out with methanol and this provides a convenient method for formation of a disubstituted *Z*-alkene.²¹⁷



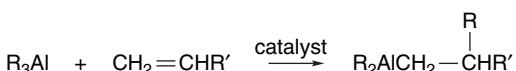
A large number of procedures that involve carbon-carbon bond formation have been developed based on organoboranes. These reactions are considered in Chapter 9.

4.6. Hydroalumination, Carboalumination, Hydrozirconation, and Related Reactions

Aluminum is the immediate congener of boron, and dialkyl and trialkyl aluminum compounds, which are commercially available, have important industrial applications. They also have some similarities with organoboranes that can be exploited for synthetic purposes. Aluminum is considerably less electronegative than boron and as a result the reagents also share characteristics with the common organometallic reagents such as organomagnesium and organolithium compounds. The addition reactions of alkenes and dialkylaluminum reagents occur much less easily than hydroboration. Only terminal or strained alkenes react readily at room temperature.²¹⁸ With internal and branched alkenes, the addition does not go to completion. Addition of dialkylalanes to alkynes occurs more readily, and the regiochemistry and stereochemistry are analogous to hydroboration. The resulting vinylalanes react with halogens with *retention of configuration* at the double bond.²¹⁹



With trialkylaluminum compounds, the addition reaction is called *carboalumination*. As discussed below, this reaction requires a catalyst to proceed.



Computational studies of both hydroalumination and carboalumination have indicated a four-center TS for the addition.²²⁰ The aluminum reagents, however, have more nucleophilic character than do boranes. Whereas the TS for hydroboration is primarily electrophilic and resembles that for attack of CH_3^+ on a double bond, the

²¹⁷ H. C. Brown and G. A. Molander, *J. Org. Chem.*, **51**, 4512 (1986); H. C. Brown and K. K. Wang, *J. Org. Chem.*, **51**, 4514 (1986).

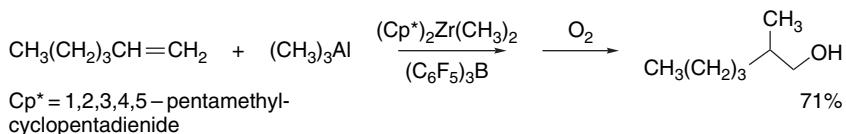
²¹⁸ F. Ansinger, B. Fell, and F. Thiessen, *Chem. Ber.*, **100**, 937 (1967); R. Schimpf and P. Heimbach, *Chem. Ber.*, **103**, 2122 (1970).

²¹⁹ G. Zweifel and C. C. Whitney, *J. Am. Chem. Soc.*, **89**, 2753 (1967).

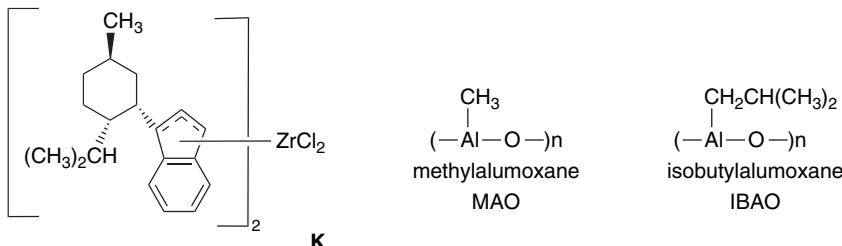
²²⁰ J. W. Bunders and M. M. Franci, *Organometallics*, **12**, 1608 (1993); J. W. Bunders, J. Yudenfreund, and M. M. Franci, *Organometallics*, **18**, 3913 (1999).

reaction with CH_3AlH_2 has a closer resemblance to reaction of CH_3^- with ethene and the strongest interaction is with the ethene LUMO. This interpretation is consistent with relative reactivity trends in which the reactivity of alkenes decreases with increasing alkyl substitution and alkynes are more reactive than alkenes.

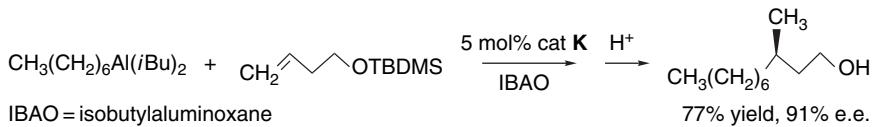
Effective catalysts have recently been developed for the addition of trialkyl-aluminum reagents to alkenes (carboalumination). *bis*-(Pentamethylcyclopentadienyl) zirconium dimethylide activated by *tris*-(pentafluorophenyl)boron promotes the addition of trimethylaluminum to terminal alkenes.²²¹



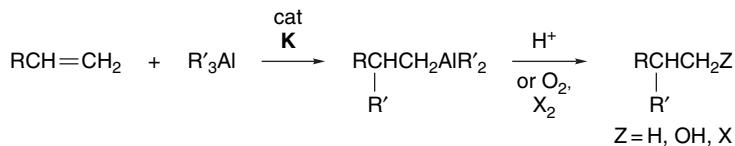
A chiral indene derivative, structure **K**, has been most commonly used.²²² The catalyst interacts with the trialkylaluminum to generate a bimetallic species that is the active catalyst.



The detailed mechanism of the catalysis is not known, but it is believed that the Lewis acid character of the zirconium is critical.²²³ The reaction is further accelerated by inclusion of partially hydrolyzed trialkylaluminum reagents known as alumoxanes.²²⁴



The adducts can be protonolyzed or converted to halides or alcohols.

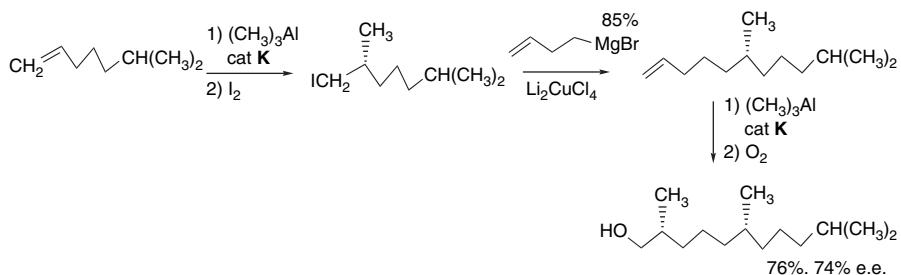


²²¹ K. H. Shaughnessy and R. M. Waymouth, *J. Am. Chem. Soc.*, **117**, 5873 (1995).

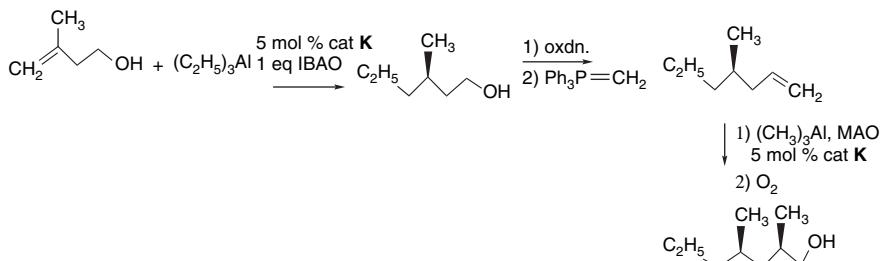
²²² D. Y. Kondakov and E. Negishi, *J. Am. Chem. Soc.*, **118**, 1577 (1996); K. H. Shaughnessy and R. M. Waymouth, *Organometallics*, **17**, 5738 (1998).

²²³ E. Negishi, D. Y. Kondakov, D. Choueiry, K. Kasai, and T. Takahashi, *J. Am. Chem. Soc.*, **118**, 9577 (1996); E. Negishi, *Chem. Eur. J.*, **5**, 411 (1999).

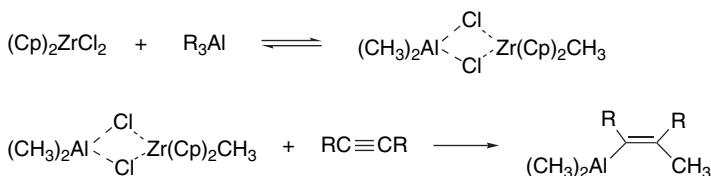
²²⁴ S. Huo, J. Shi, and E. Negishi, *Angew. Chem. Int. Ed. Engl.*, **41**, 2141 (2002).



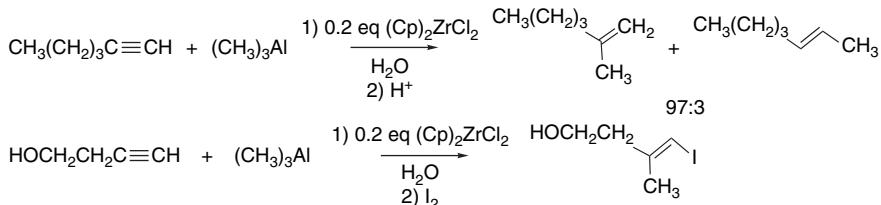
By converting the primary alcohol group to an alkene by oxidation and a Wittig reaction, the reaction can be carried out in iterative fashion to introduce several methyl groups.²²⁶



At this point in time carboalumination of alkynes has been more widely applied in synthesis. The most frequently used catalyst is $(\text{Cp})_2\text{ZrCl}_2$. It is believed that a bimetallic species is formed.²²⁷



Small amounts of water accelerate carboalumination of alkynes.²²⁸ This acceleration may be the result of formation of aluminoxanes.



²²⁵ S. Huo and E. Negishi, *Org. Lett.*, **3**, 3253 (2001).

²²⁶ E. Negishi, Z. Tan, B. Liang, and T. Novak, *Proc. Natl. Acad. Sci. USA*, **101**, 5782 (2004); M. Magnin-Lachaux, Z. Tan, B. Liang, and E. Negishi, *Org. Lett.*, **6**, 1425 (2004).

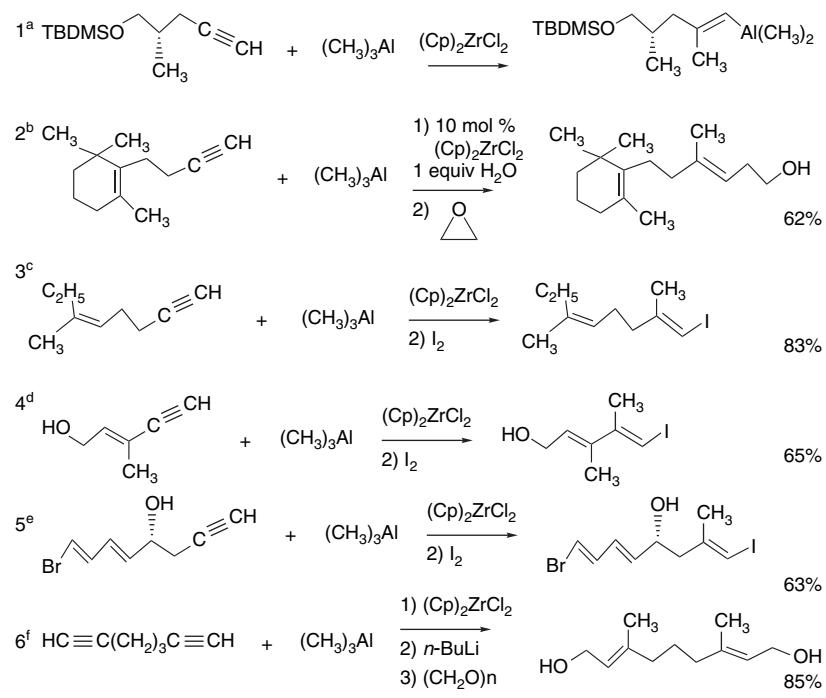
²²⁷ E. Negishi and D. Y. Kondakov, *Chem. Soc. Rev.*, **25**, 417 (1996).

²²⁸ P. Wipf and S. Lim, *Angew. Chem. Int. Ed. Engl.*, **32**, 1068 (1993).

Scheme 4.10. Carbomethylations of Alkynes

CHAPTER 4

Electrophilic Additions
to Carbon-Carbon
Multiple Bonds



a. R. E. Irelan, L. Liu, and T. D. Roper, *Tetrahedron*, **53**, 13221 (1997).

b. A. Pommier, V. Stephanenko, K. Jarowicki, and P. J. Kocienski, *J. Org. Chem.*, **68**, 4008 (2003).

c. K. Mori and N. Murata, *Liebigs Ann.*, 2089 (1995).

d. T. K. Chakraborty and D. Thippeswamy, *Synlett*, 150 (1999).

e. M. Romero-Ortega, D. A. Colby, and H. F. Olivo, *Tetrahedron Lett.*, **47**, 6439 (2002).

f. G. Hidalgo-Del Vecchio and A. C. Oehlschlager, *J. Org. Chem.*, **59**, 4853 (1994).

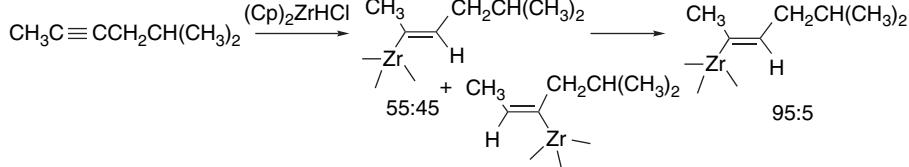
As indicated by the mechanism, carboalumination is a *syn* addition. The resulting vinylalanes react with electrophiles with net retention of configuration. The electrophiles that have been used successfully include iodine, epoxides, formaldehyde, and ethyl chloroformate.²²⁹ We will also see in Chapter 8 that the vinylalanes can undergo exchange reactions with transition metals, opening routes for formation of carbon-carbon bonds.

Scheme 4.10 gives some examples of application of alkyne carboalumination in synthesis. The reaction in Entry 1 was carried out as part of a synthesis of the immunosuppressant drug FK-506. The vinyl alane was subsequently transmetallated to a cuprate reagent (see Chapter 8). In Entry 2, the vinyl alane was used as a nucleophile for opening an epoxide ring and extending the carbon chain by two atoms. In Entries 3 to 5, the vinyl alane adducts were converted to vinyl iodides. In Entry 6, the vinyl alane was converted to an “ate” reagent prior to reaction with formaldehyde.

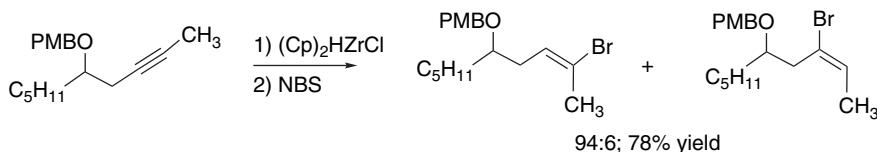
Derivatives of zirconium with a Zr–H bond also can add to alkenes and alkynes. This reaction is known as *hydrozirconation*.²³⁰ The reagent that is used most frequently

²²⁹ N. Okukado and E. Negishi, *Tetrahedron Lett.*, 2357 (1978); M. Kobayashi, L. F. Valente, E. Negishi, W. Patterson, and A. Silveira, Jr., *Synthesis*, 1034 (1980); C. L. Rand, D. E. Van Horn, M. W. Moore, and E. Negishi, *J. Org. Chem.*, **46**, 4093 (1981).

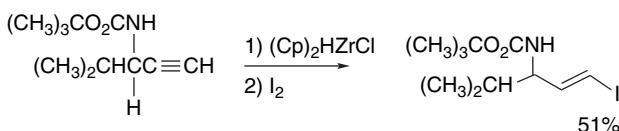
²³⁰ P. Wipf and H. Jahn, *Tetrahedron*, **52**, 1283 (1996); P. Wipf and C. Kendall, *Topics Organometallic Chem.*, **8**, 1 (2004).



The adducts react with electrophiles such as NCS, NBS, and I₂ to give vinyl halides.

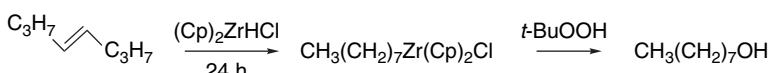


Ref. 234



Ref. 235

Alkenes are less reactive and reactivity decreases with increasing substitution. The adducts from internal alkenes undergo isomerization to terminal derivatives.²³⁶



Carbon–carbon bond formation from alkyl and alkenyl zirconium reagents usually involves transmetallation reactions and are discussed in Chapter 8.

²³¹ D. W. Hart, T. F. Blackburn, and J. Schwartz, *J. Am. Chem. Soc.*, **97**, 679 (1975); J. Schwartz and J. A. Labinger, *Angew. Chem. Int. Ed. Engl.*, **15**, 333 (1976).

²³² S. L. Buchwald, S. J. La Maire, R. B. Nielsen, B. T. Watson, and S. M. King, *Tetrahedron Lett.*, **28**, 3895 (1987).

²³³ B. H. Lipshutz, R. Kell, and E. L. Ellsworth, *Tetrahedron Lett.*, **31**, 7257 (1990).

²³⁴ A. B. Smith, III, S. S.-Y. Chen, F. C. Nelson, J. M. Reichert, and B. A. Salvatore, *J. Am. Chem. Soc.*, **119**, 10935 (1997).

²³⁵ J. R. Hauske, P. Dorff, S. Julin, J. Di Brino, R. Spencer, and R. Williams, *J. Med. Chem.*, **35**, 4284 (1992).

²³⁶ D. W. Hart and J. Schwartz, *J. Am. Chem. Soc.*, **96**, 8115 (1974); T. Gibson, *Tetrahedron Lett.*, **23**, 157 (1982).

General References

CHAPTER 4

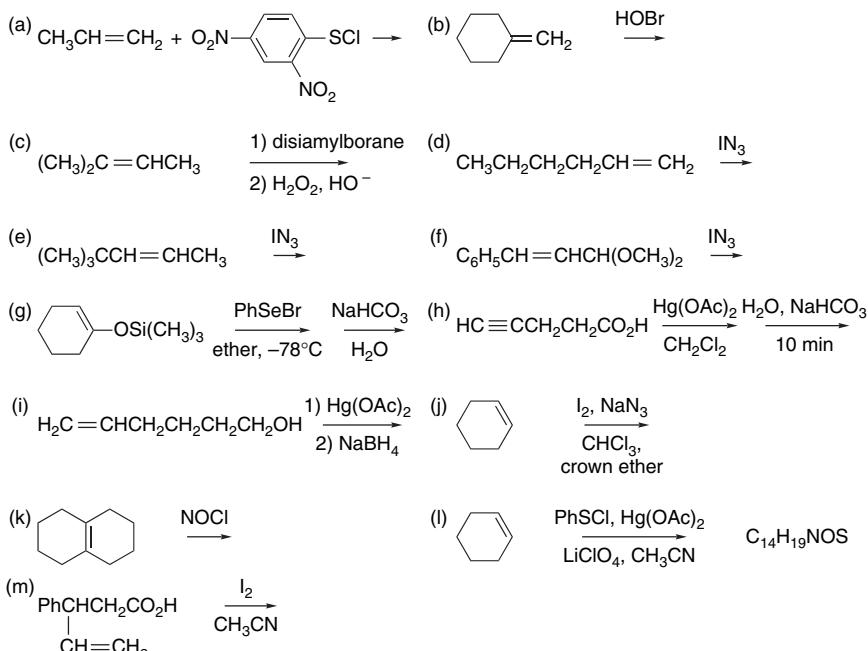
Electrophilic Additions to Carbon-Carbon Multiple Bonds

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- N. Krause and A. S. K. Hashmi, eds., *Modern Allene Chemistry*, Wiley-VCH, Weinheim, 2004.
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- P. J. Stang and F. Diederich, eds., *Modern Acetylene Chemistry*, VCH Publishers, Weinheim, 1995.

Problems

(References for these problems will be found on page 1277.)

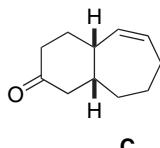
- 4.1. Predict the products, including regio- and stereochemistry, for the following reactions:



- 4.2. Bromination of 4-*t*-butylcyclohexene in methanol gives a 45:55 mixture of two compounds, each of composition $\text{C}_{11}\text{H}_{21}\text{BrO}$. Predict the structure and stereochemistry of these two products. How would you confirm your prediction?

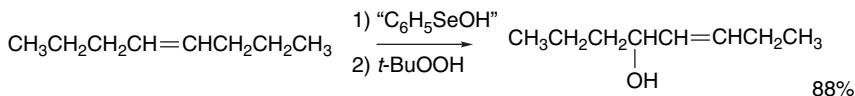
4.3. Oxymercuration of 4-*t*-butylcyclohexene, followed by NaBH₄ reduction, gives *cis*-4-*t*-butylcyclohexanol and *trans*-3-*t*-butylcyclohexanol in approximately equal amounts. 1-Methyl-4-*t*-butylcyclohexanol under similar conditions gives only *cis*-4-*t*-butyl-1-methylcyclohexanol. Formulate an explanation for these observations.

4.4. Treatment of compound C with *N*-bromosuccinimide in acetic acid containing sodium acetate gives a product C₁₃H₁₉BrO₃. Propose a structure, including stereochemistry, and explain the basis for your proposal.

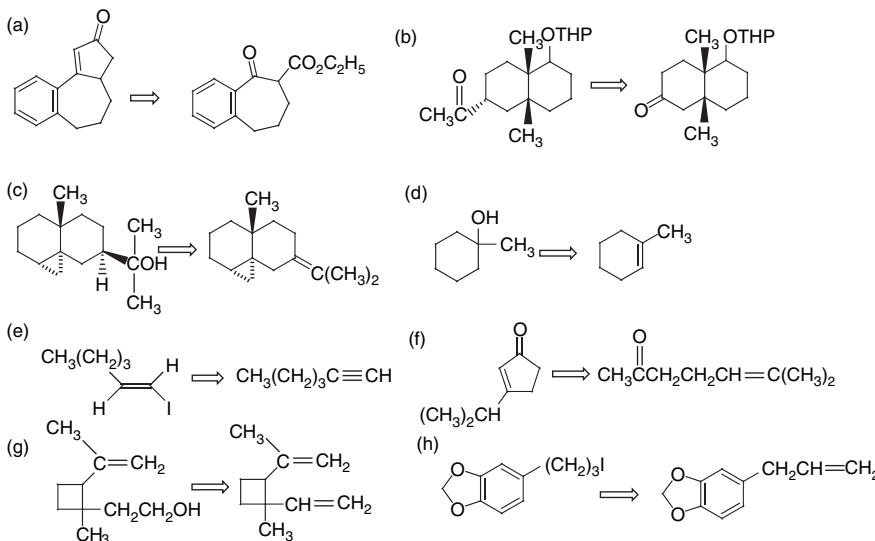


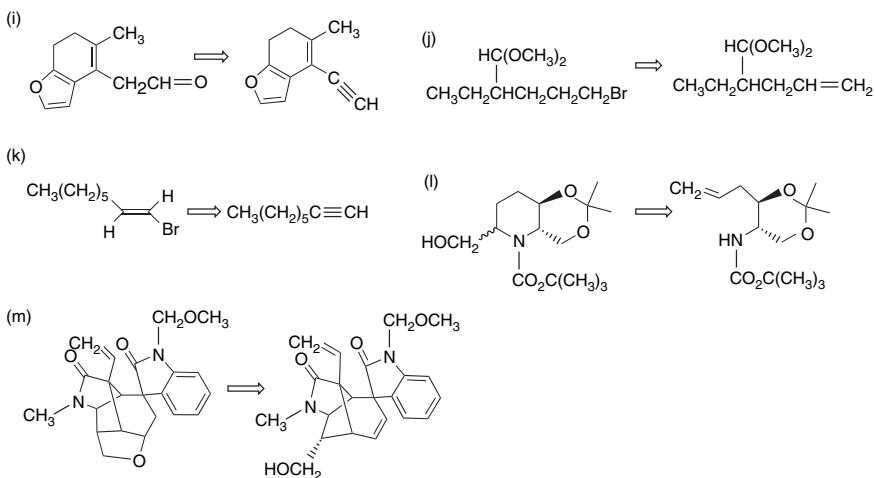
4.5. The hydration of 5-undecyn-2-one with HgSO₄ and H₂SO₄ in methanol is regioselective, giving 2,5-undecadione in 85% yield. Suggest an explanation for the high regioselectivity of this internal alkyne.

4.6. A procedure for the preparation of allylic alcohols uses the equivalent of phenylselenenic acid and an alkene. The reaction product is then treated with *t*-butylhydroperoxide. Suggest a mechanistic rationale for this process.

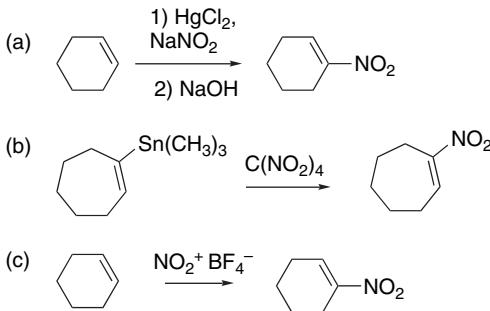


4.7. Suggest reaction conditions or short synthetic sequences that could provide the desired compound from the suggested starting material.



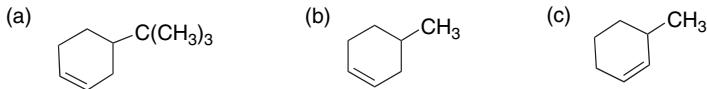


4.8. Three methods for the preparation of nitroalkenes are outlined below. Describe the mechanism by which each of these transformations occurs.

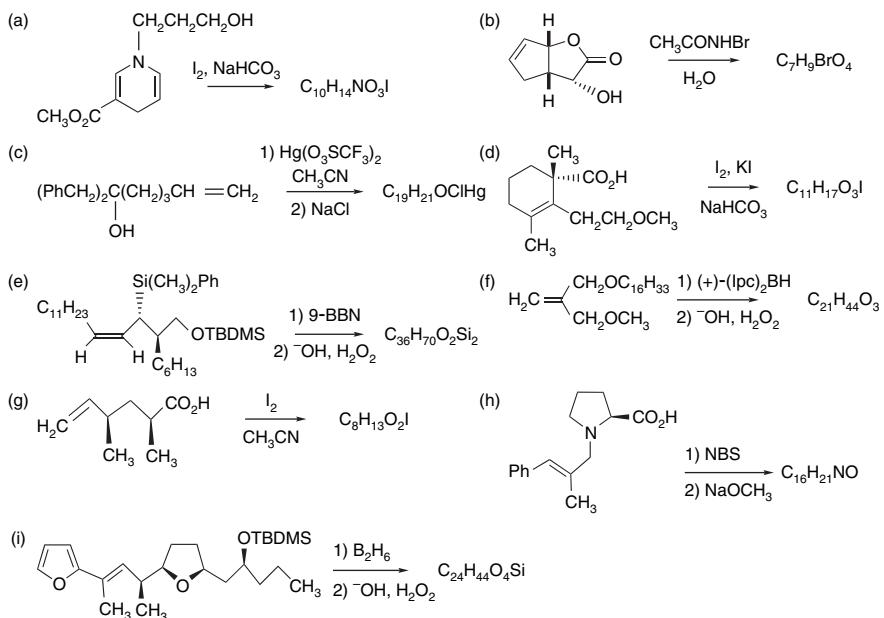


4.9. Hydroboration-oxidation of 1,4-di-*t*-butylcyclohexene gave three alcohols: **9-A** (77%), **9-B** (20%), and **9-C** (3%). Oxidation of **9-A** gave a ketone **9-D** that was readily converted by either acid or base to an isomeric ketone **9-E**. Ketone **9-E** was the only oxidation product of alcohols **9-B** and **9-C**. What are the structures of compounds **9A–9E**?

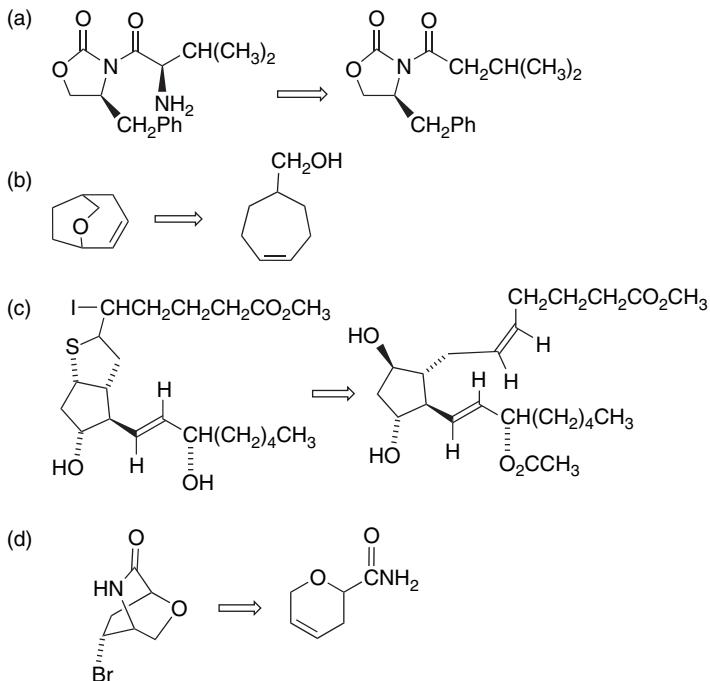
- 4.10. Show how by using regioselective enolate chemistry and organoselenium reagents, you could convert 2-phenylcyclohexanone to either 2-phenyl-2-cyclohexen-1-one or 6-phenyl-2-cyclohexen-1-one.
- 4.11. On the basis of the mechanistic pattern for oxymercuration-demercuration, predict the structure and stereochemistry of the alcohol(s) to be expected by application of the reaction to each of the following substituted cyclohexenes.

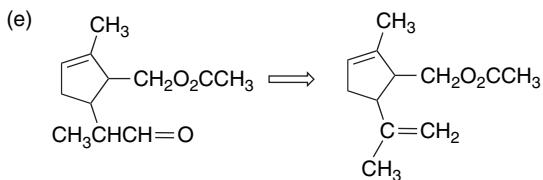


- 4.12. Give the structure, including stereochemistry, of the expected products of the following reactions. Identify the critical factors that determine the regio- and stereochemistry of the reaction.

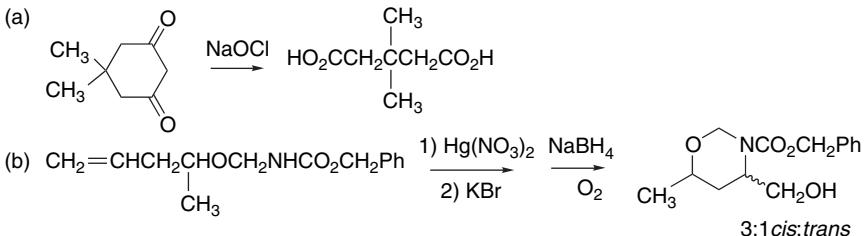


4.13. Some synthetic transformations are shown in the retrosynthetic format. Propose a short series of reactions (no more than three steps should be necessary) that could effect each conversion.

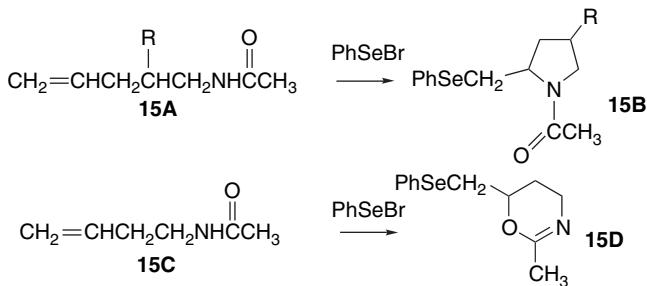




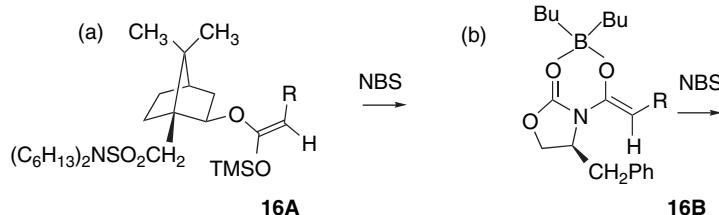
4.14. Write mechanisms for the following reactions:



4.15. 4-Pentenyl amides such as **15A** cyclize to lactams **15B** on reaction with phenyl selenenyl bromide. The 3-butenyl compound **15C**, on the other hand, cyclizes to an imino ether **15D**. What is the basis for the differing reactions?

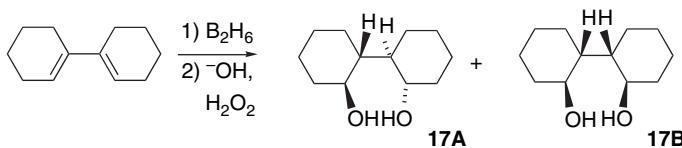


4.16. Procedures for enantioselective preparation of α -bromo acids based on reaction of NBS with enol derivatives **16A** and **16B** have been developed. Predict the absolute configuration of the halogenated compounds produced from both **16A** and **16B**. Explain the basis of your prediction.

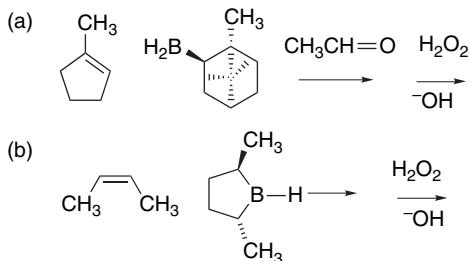


4.17. The stereochemical outcome of the hydroboration-oxidation of 1,1'-bicyclohexenyl depends on the amount of diborane used. When 1.1 equivalent

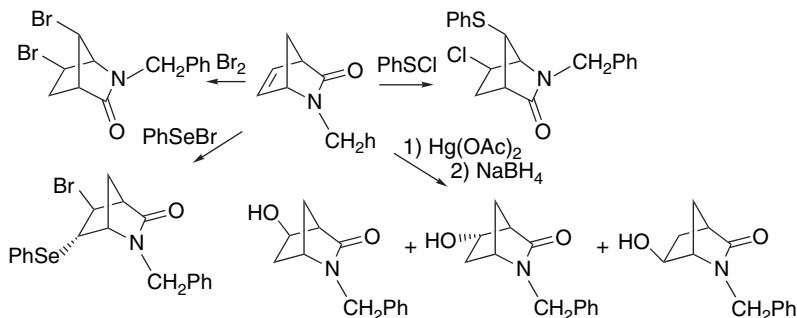
is used, the product is a 3:1 mixture of **17A** and **17B**. When 2.1 equivalent is used, **17A** is formed nearly exclusively. Offer an explanation of these results.



4.18. Predict the absolute configuration of the products obtained from the following enantioselective hydroborations.

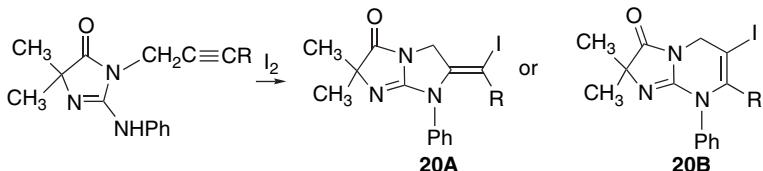


4.19. The regioselectivity and stereoselectivity of electrophilic additions to 2-benzyl-3-azabicyclo[2.2.1]hept-5-en-3-one are quite dependent on the specific electrophile. Discuss the factors that could influence the differing selectivity patterns that are observed.



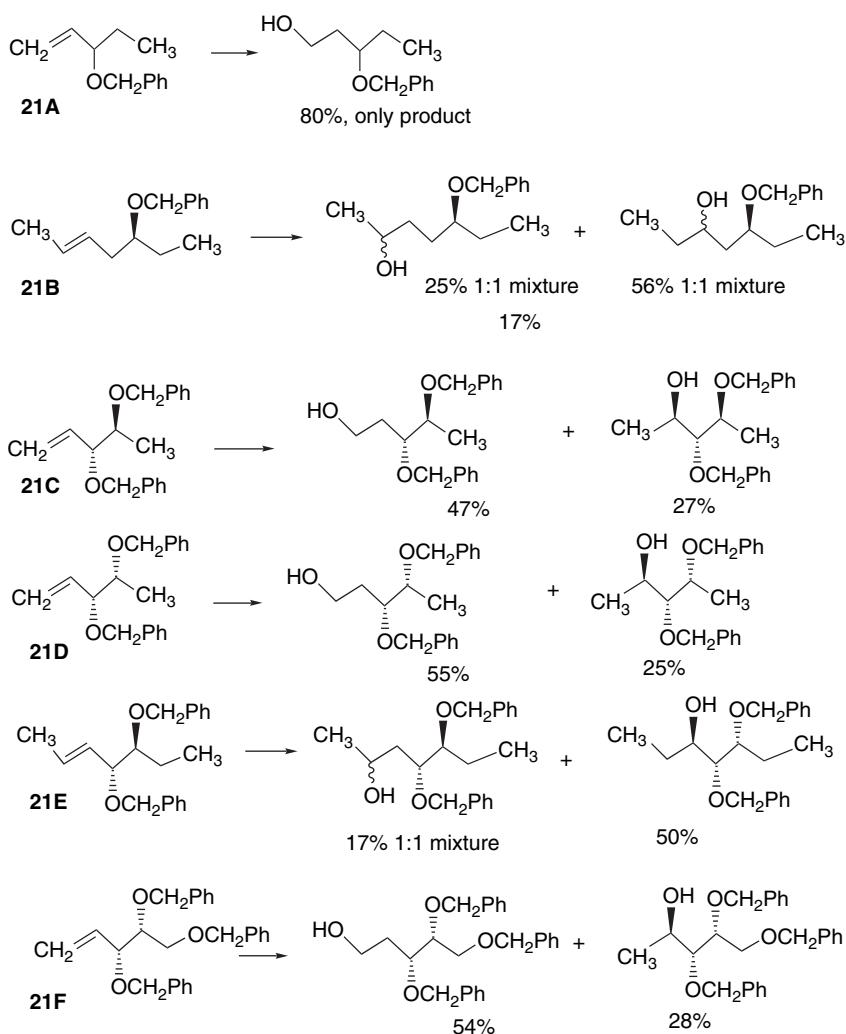
4.20. Offer mechanistic explanations of the following observations:

a. In the cyclization reactions shown below, **20A** is the preferred product for R = H, but **20B** is the preferred product for R = methyl or phenyl.

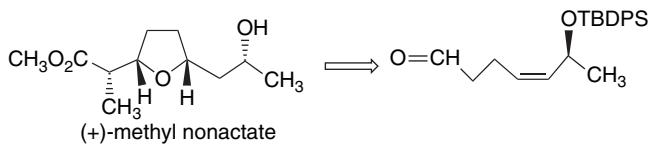


b. The pent-4-enoyl group has been developed as a protecting group for primary and secondary amines. The conditions for cleavage involve treatment with iodine and a aqueous solution with either THF or acetonitrile as the cosolvent. Account for the mild deprotection under these conditions.

- 4.21. Analyze the data below concerning the effect of allylic and homoallylic benzyloxy substituents on the regio- and stereoselectivity of hydroboration-oxidation. Propose a TS that is consistent with the results.

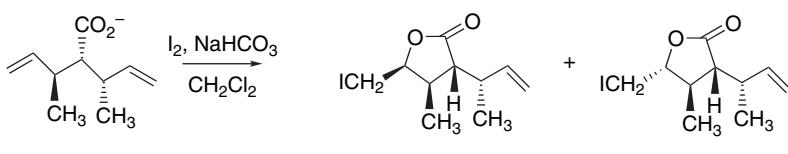


- 4.22. Propose an enantioselective synthesis of (+) methyl nonactate from the aldehyde shown.

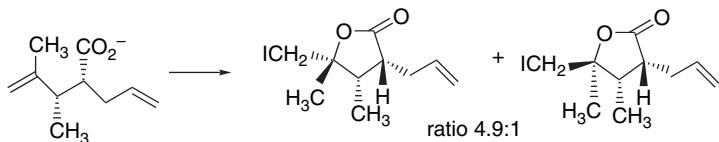


- 4.23. On page 313, the effect of methyl substitution on the stereoselectivity of α,α -diallylcroboxylic acids under iodolactonization conditions was discussed. Consider the two compounds shown and construct a reaction energy profile for

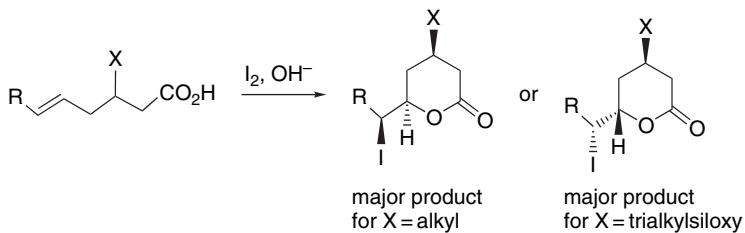
each compound that illustrates the role of conformational equilibrium, facial selectivity, and substituent effects on ΔG^\ddagger on the stereochemical outcome.



ratio 30:1



- 4.24. It has been found that when δ,ϵ -enolates bearing β -siloxy substituents are subject to iodolactonization, the substituent directs the stereochemistry of cyclization in a manner opposite to an alkyl substituent. Suggest a TS structure that would account for this difference.

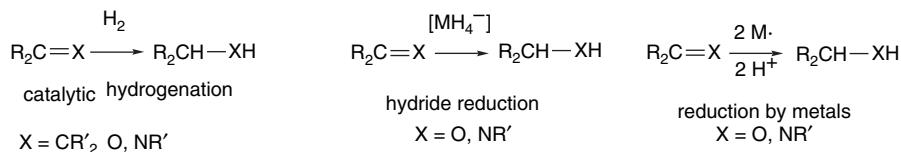


Reduction of Carbon-Carbon Multiple Bonds, Carbonyl Groups, and Other Functional Groups

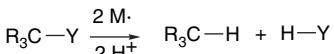
Introduction

The subject of this chapter is reduction reactions that are especially important in synthesis. Reduction can be accomplished by several broad methods including addition of hydrogen and/or electrons to a molecule or by removal of oxygen or other electronegative substituents. The most widely used reducing agents from a synthetic point of view are molecular hydrogen and hydride derivatives of boron and aluminum, and these reactions are discussed in Sections 5.1 through 5.3. A smaller group of reactions transfers hydride from silicon or carbon, and these are the topic of Section 5.4. Certain reductions involving a free radical mechanism use silanes or stannanes as hydrogen atom donors, and these reactions are considered in Section 5.5. Other important procedures use metals such as lithium, sodium, or zinc as electron donors. Reduction by metals can be applied to carbonyl compounds and aromatic rings and can also remove certain functional groups.

Addition of Hydrogen

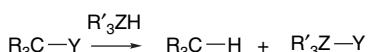


Reductive Removal of Functional Groups



dissolving metals

Y = halogen, oxygen substituents,
 α -to carbonyl groups

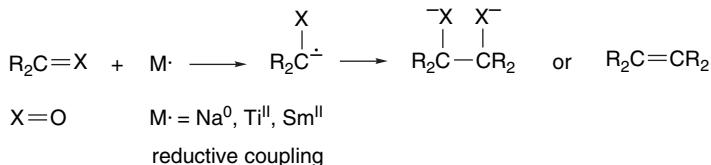


hydrogen atom donors

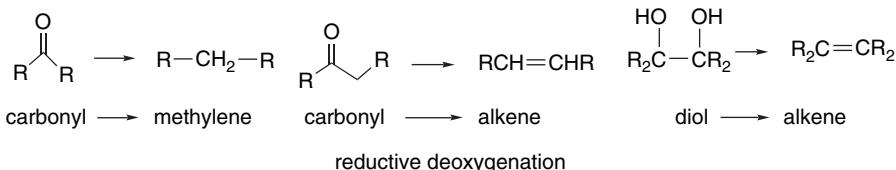
$\text{Y} = \text{halogen, thio ester}$

Z = Sn, Si

There are also procedures that form carbon-carbon bonds. Most of these reactions begin with an electron transfer that generates a radical intermediate, which then undergoes a coupling or addition reaction. These reactions are discussed in Section 5.6.

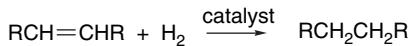


Reductive removal of oxygen from functional groups such as ketones and aldehydes, alcohols, α -oxy ketones, and diols are also important in synthesis. These reactions, which provide important methods for interconversion of functional groups, are considered in Section 5.7



5.1. Addition of Hydrogen at Carbon-Carbon Multiple Bonds

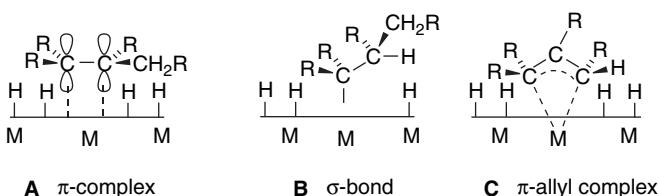
The most widely used method for adding the elements of hydrogen to carbon-carbon double bonds is catalytic hydrogenation. Except for very sterically hindered alkenes, this reaction usually proceeds rapidly and cleanly. The most common catalysts are various forms of transition metals, particularly platinum, palladium, rhodium, ruthenium, and nickel. Both the metals as finely dispersed solids or adsorbed on inert supports such as carbon or alumina (*heterogeneous catalysts*) and certain soluble complexes of these metals (*homogeneous catalysts*) exhibit catalytic activity. Depending upon conditions and catalyst, other functional groups are also subject to reduction under these conditions.



5.1.1. Hydrogenation Using Heterogeneous Catalysts

The mechanistic description of catalytic hydrogenation of alkene is somewhat imprecise, partly because the reactive sites on the metal surface are not as well

described as small-molecule reagents in solution. As understanding of the chemistry of soluble hydrogenation catalysts developed, it became possible to extrapolate the mechanistic concepts to heterogeneous catalysts. It is known that hydrogen is adsorbed onto the metal surface, forming metal hydrogen bonds similar to those in transition metal hydrides. Alkenes are also adsorbed on the catalyst surface and at least three types of intermediates have been implicated in hydrogenation. The initially formed intermediate is pictured as attached at both carbon atoms of the double bond by π -type bonding, as shown in **A**. The bonding involves an interaction between the alkene π and π^* orbitals with corresponding acceptor and donor orbitals of the metal. A hydride can be added to the adsorbed group, leading to **B**, which involves a σ -type carbon-metal bond. This species can react with another hydrogen to give the alkane, which is desorbed from the surface. A third intermediate species, shown as **C**, accounts for double-bond isomerization and the exchange of hydrogen that sometimes accompanies hydrogenation. This intermediate is equivalent to an allyl group bound to the metal surface by π bonds. It can be formed from adsorbed alkene by abstraction of an allylic hydrogen atom by the metal. The reactions of transition metals with organic compounds are discussed in Chapter 8. There are well-characterized examples of structures corresponding to each of the intermediates **A**, **B**, and **C** that are involved in hydrogenation. However, one issue that is left unresolved by this mechanism is whether there is cooperation between adjacent metal atoms, or if the reactions occur at a single metal center, which is usually the case with soluble catalysts.



Catalytic hydrogenations are usually very clean reactions with little by-product formation, unless reduction of other groups is competitive, but careful study reveals that sometimes double-bond migration takes place in competition with reduction. For example, hydrogenation of 1-pentene over Raney nickel is accompanied by some isomerization to both *E*- and *Z*-2-pentene.¹ The isomerized products are converted to pentane, but at a slower rate than 1-pentene. Exchange of hydrogen atoms between the reactant and adsorbed hydrogen can be detected by isotopic exchange. Allylic positions undergo such exchange particularly rapidly.² Both the isomerization and allylic hydrogen exchange can be explained by the intervention of the π -allyl intermediate **C** in the general mechanism for hydrogenation. If hydrogen is added at the alternative end of the allyl system, an isomeric alkene is formed. Hydrogen exchange occurs if a hydrogen from the metal surface, rather than the original hydrogen, is transferred prior to desorption.

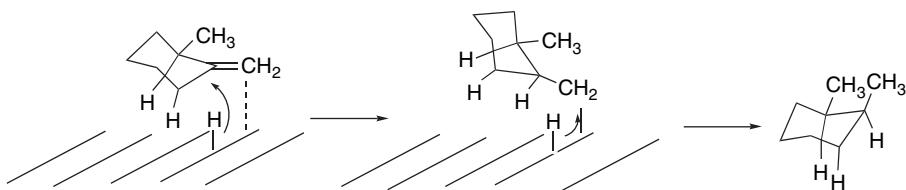
In most cases, both hydrogen atoms are added to the same face of the double bond (*syn* addition). If hydrogenation occurs by addition of hydrogen in two steps, as

¹. H. C. Brown and C. A. Brown, *J. Am. Chem. Soc.*, **85**, 1005 (1963).

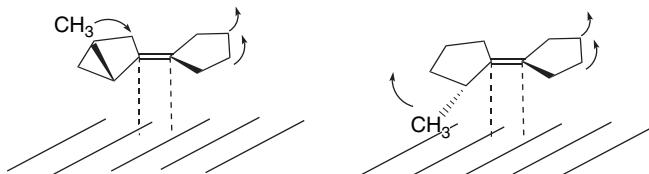
². G. V. Smith and J. R. Swoap, *J. Org. Chem.*, **31**, 3904 (1966).

implied by the above mechanism, the intermediate must remain bonded to the metal surface in such a way that the stereochemical relationship is maintained. Adsorption to the catalyst surface normally involves the less sterically congested side of the double bond, and as a result hydrogen is added from the less hindered face of the double bond. There are many hydrogenations in which hydrogen addition is not entirely *syn*, and independent corroboration of the stereochemistry is normally necessary.

Scheme 5.1 illustrates some hydrogenations in which the *syn* addition from the less hindered side is observed. Some exceptions are also included. Entry 1 shows the hydrogenation of an exocyclic methylene group. This reaction was studied at various H₂ pressures and over both Pt and Pd catalysts. 4-Methyl- and 4-*t*-butylmethylenecyclohexane also give mainly the *cis* product.³ These results are consistent with a favored (2.3:1) equatorial delivery of hydrogen.



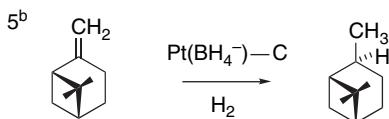
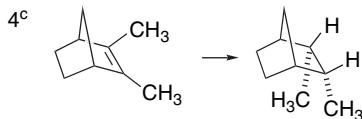
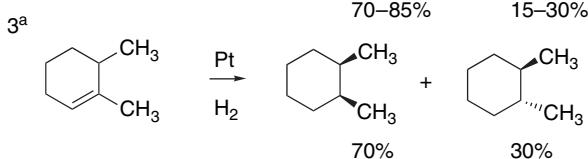
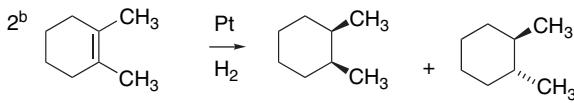
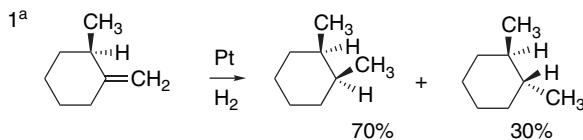
The Entry 2 reactant, 1,2-dimethylcyclohexene, was also studied by several groups and a 2:1–4:1 preference for *syn* addition was noted, depending on the catalyst and conditions. In the reference cited, the catalyst was prepared by reduction of a Pt salt with NaBH₄. A higher ratio of the *cis* product was noted at 0°C (5.2:1) than at 25°C (2.5:1). In Entry 3, the 2,6-dimethylcyclohexene gives mainly *cis* product with a Pt catalyst but *trans* product dominates with a Pd catalyst. These three cases indicate that stereoselectivity for unhindered alkenes is modest and dependent on reaction conditions. Entries 4 and 5 involve more rigid and sterically demanding alkenes. In both cases, *syn* addition of hydrogen occurs from the less hindered face of the molecule. Entries 6 to 8 are cases in which hydrogen is added from the more-substituted face of the double bond. The compound in Entry 6 gives mainly *trans* product at high H₂ pressure, where the effects of alkene isomerization are minimized. This result indicates that the primary adsorption must be from the methyl-substituted face of the molecule. This may result from structural changes that occur on bonding to the catalyst surface. In the *cis* approach, the methyl substituent moves away from the cyclopentane ring as rehybridization of the double bond occurs. In the *trans* approach, the methyl group must move closer to the adjacent cyclopentane ring.



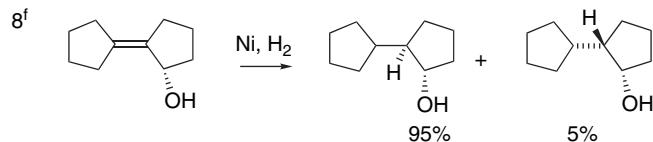
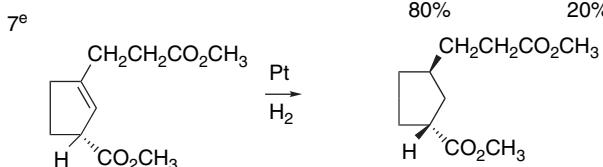
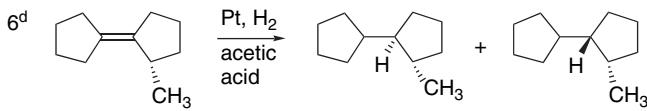
The preference for addition from the more hindered of the substituents in Entries 7 and 8 can be attributed to functional group interactions with the catalyst. Polar

³ J.-F. Sauvage, R. H. Baker, and A. S. Hussey, *J. Am. Chem. Soc.*, **82**, 6090 (1960).

Scheme 5.1. Stereochemistry of Hydrogenation of Some Alkenes

A. Examples of preferential *syn* addition from less hindered side

B. Exceptions



a. S. Siegel and G. V. Smith, *J. Am. Chem. Soc.*, **82**, 6082, 6087 (1960).

b. C. A. Brown, *J. Am. Chem. Soc.*, **91**, 5901 (1969).

c. K. Alder and W. Roth, *Chem. Ber.*, **87**, 161 (1954).

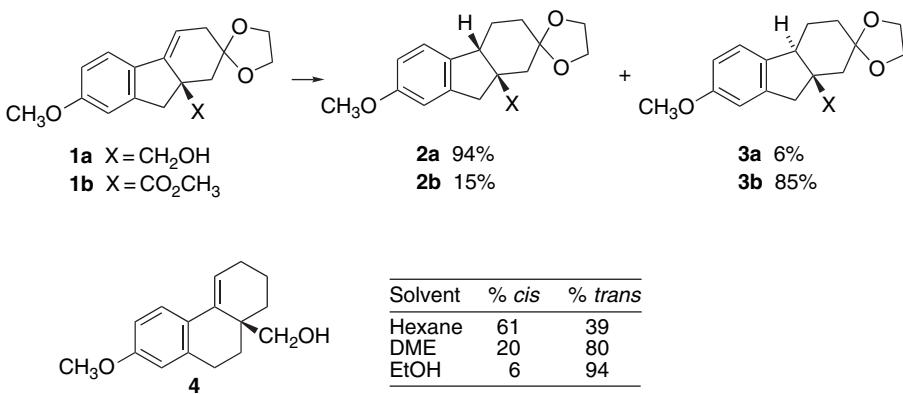
d. S. Siegel and J. R. Cozort, *J. Org. Chem.*, **40**, 3594 (1975).

e. J. P. Ferris and N. C. Miller, *J. Am. Chem. Soc.*, **88**, 3522 (1966).

f. S. Mitsui, Y. Senda, and H. Saito, *Bull. Chem. Soc. Jpn.*, **39**, 694 (1966).

groups sometimes favor *cis* addition of hydrogen, relative to the substituent. This is a very common observation for hydroxy groups, but less so for esters (*vide infra*).

The facial stereoselectivity of hydrogenation is affected by the presence of polar functional groups that can govern the mode of adsorption to the catalyst surface. For instance, there are many of examples of hydrogen being introduced from the face of the molecule occupied by the hydroxy group, which indicates that the hydroxy group interacts with the catalyst surface. This behavior can be illustrated with the alcohol **1a** and the ester **1b**.⁴ Although the overall shapes of the two molecules are similar, the alcohol gives mainly the product with a *cis* ring juncture (**2a**), whereas the ester gives a product with *trans* stereochemistry (**3b**). The stereoselectivity of hydroxy-directed hydrogenation is a function of solvent and catalyst. The *cis*-directing effect is strongest in nonpolar solvents such as hexane. This is illustrated by the results from compound **4**. In ethanol, the competing interaction of the solvent molecules evidently swamps out the effect of the hydroxymethyl group.



Thompson and co-workers have explored the range of substituents that can exert directive effects using polycyclic systems. For ring system **1**, hydroxymethyl and formyl showed strong directive effects; cyano, oximino, and carboxylate were moderate; and carboxy, ester, amide, and acetyl groups were not directive (see Table 5.1).^{4,5} As with **4**, the directive effects were shown to be solvent dependent. Strong donor solvents, such as ethanol and DMF, minimized the substituent-directing effect. Similar studies were carried out with ring system **5**.⁶ The results are given in Table 5.1. It would be expected that the overall shape of the reactant molecule would influence the effectiveness of the directive effect. The trends in ring systems **1** and **5** are similar, although ring system **5** appears to be somewhat less susceptible to directive effects. These hydrogenations were carried out in hydroxylic solvents and it would be expected that the directive effects would be enhanced in less polar solvents.

⁴. (a) H. W. Thompson, *J. Org. Chem.*, **36**, 2577 (1971); (b) H. W. Thompson, E. McPherson, and B. L. Lences, *J. Org. Chem.*, **41**, 2903 (1976).

⁵. H. W. Thompson and R. E. Naipawer, *J. Am. Chem. Soc.*, **95**, 6379 (1973).

⁶. H. W. Thompson and S. Y. Rashid, *J. Org. Chem.*, **67**, 2813 (2002).

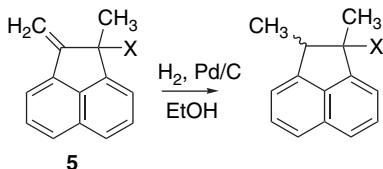
Table 5.1. Substituent Directive Effects for Ring Systems 1 and 5

Substituent X	Ring system 1^a		Ring system 5^b		SECTION 5.1 <i>Addition of Hydrogen at Carbon-Carbon Multiple Bonds</i>
	% cis (Directive)	% trans (Nondirective)	% cis (Directive)	% trans (Nondirective)	
CH ₂ NH ₂			87	13	
CH ₂ N(CH ₃) ₂			62	38	
CH ₂ OH	95	5	48	52	
CH=O	93	7	42	58	
CN	75	25	20	80	
CH=NOH	65	35	45	55	
CH ₂ OCH ₃			44	56	
CH ₂ NHCOCH ₃			33	67	
CO ₂ Na (or K)	55	45	30	70	
CO ₂ H	18	82	17	83	
CO ₂ CH ₃	15	85	16	84	
CONH ₂	10	90	33	67	
COCH ₃	14	86	22	78	

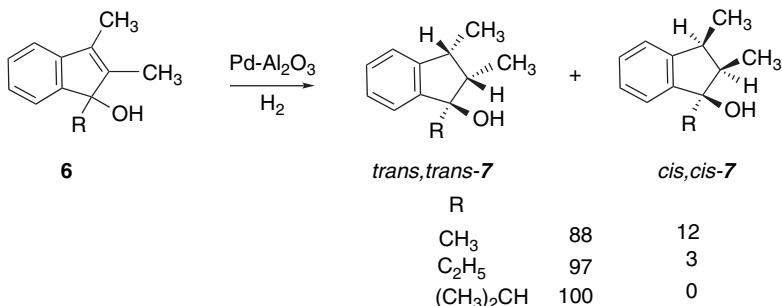
a. In methoxyethanol.

b. In ethanol.

The general ordering of aminomethyl > hydroxymethyl > CH=O > ester suggests that Lewis basicity is the dominant factor in the directive effect. Problem 5.2 involves considering the ordering of the various acyl substituents in more detail.



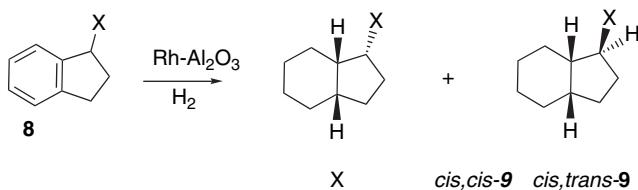
Substituted indenes provide other examples of substituent directive effects. Over Pd-alumina, the indenols **6a-c** show both *cis* stereoselectivity and a *syn* directive effect. The directive effect is reinforced by steric effects as the alkyl group becomes larger.⁷



Several indanes (**8**) were reduced to hexahydroindanes over Rh-Al₂O₃. The stereochemistry of the ring junction is established at the stage of the reduction of the tetrasubstituted double bonds. Only the amino group shows a strong directive effect.⁸

⁷. K. Borszky, T. Mallat, and A. Baiker, *J. Catalysis*, **188**, 413 (1999).

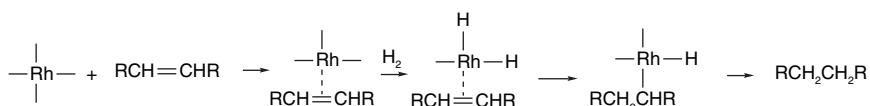
⁸. V. S. Ranade, G. Consiglio, and R. Prins, *J. Org. Chem.*, **65**, 1132 (2000); V. S. Ranade, G. Consiglio, and R. Prins, *J. Org. Chem.*, **64**, 8862 (1999).



OH	67	33
CH ₂ OH	52	48
NH ₂	1.5	98.5
CH ₃	64	36
OCH ₃	88	12
CO ₂ CH ₃	85	15
CONH ₂	81	19

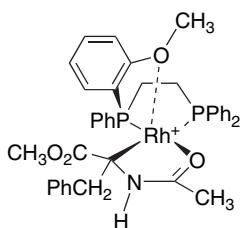
5.1.2. Hydrogenation Using Homogeneous Catalysts

In addition to solid transition metals, numerous soluble transition metal complexes are active hydrogenation catalysts.⁹ One of the first to be used was *tris*-(triphenylphosphine)rhodium chloride, known as *Wilkinson's catalyst*.¹⁰ Hydrogenation by homogeneous catalysts is believed to take place by initial formation of a π complex. The addition of hydrogen to the metal occurs by *oxidative addition* and increases the formal oxidation state of the metal by two. This is followed by transfer of hydrogen from rhodium to carbon to form an alkylrhodium intermediate. The final step is a second migration of hydrogen to carbon, leading to elimination of the saturated product (reductive elimination) and regeneration of active catalyst.

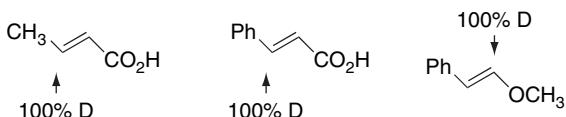


In some cases an alternative sequence involving addition of hydrogen at rhodium prior to complexation of the alkene may operate.¹¹ The phosphine ligands serve both to provide a stable soluble complex and to adjust the reactivity at the metal center. The σ -bonded intermediates have been observed for Wilkinson's catalyst¹² and for several other related catalysts.¹³ For example, a partially hydrogenated structure has been isolated from methyl α -acetamidocinnamate.¹⁴

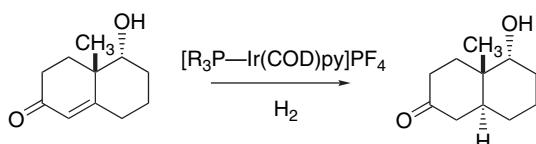
9. A. J. Birch and D. H. Williamson, *Org. React.*, **24**, 1 (1976); B. R. Jones, *Homogeneous Hydrogenation*, Wiley, New York, 1973.
10. J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).
11. I. D. Gridnev and T. Imamoto, *Acc. Chem. Res.*, **37**, 633 (2004).
12. D. Evans, J. A. Osborn and G. Wilkinson, *J. Chem. Soc. A*, 3133 (1968); V. S. Petrosyan, A. B. Permin, V. I. Bogdaskina, and D. P. Krutko, *J. Orgmet. Chem.*, **292**, 303 (1985).
13. H. Heinrich, R. Giernoth, J. Bargon, and J. M. Brown, *Chem. Commun.*, 1296 (2001); I. D. Gridnev, N. Higashi and T. Imamoto, *Organometallics*, **20**, 4542, (2001).
14. J. A. Ramsden, T. D. Claridge and J. M. Brown, *J. Chem. Soc., Chem. Commun.*, 2469 (1995).



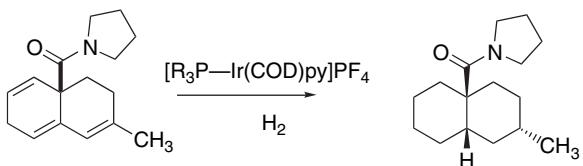
The regioselectivity of the hydride addition step has been probed by searching for deuterium exchange into isomerized alkenes that have undergone *partial* reduction.¹⁵ The results suggest that Rh is electrophilic in the addition step and that the hydride transfer is nucleophilic.



The stereochemistry of reduction by homogeneous catalysts is often controlled by functional groups in the reactant. Delivery of hydrogen occurs *cis* to a polar functional group. This behavior has been found to be particularly characteristic of an iridium-based catalyst that contains cyclooctadiene, pyridine, and tricyclohexylphosphine as ligands, known as the *Crabtree catalyst*.¹⁶ Homogeneous iridium catalysts have been found to be influenced not only by hydroxy groups, but also by amide, ester, and ether substituents.¹⁷



Ref. 18



Ref. 19

¹⁵ J. Yu and J. B. Spencer, *J. Am. Chem. Soc.*, **119**, 5257 (1997); J. Yu and J. B. Spencer, *Tetrahedron*, **54**, 15821 (1998).

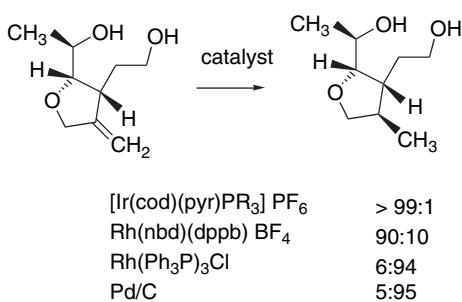
¹⁶ R. Crabtree, *Acc. Chem. Res.*, **12**, 331 (1979).

¹⁷ R. H. Crabtree and M. W. Davis, *J. Org. Chem.*, **51**, 2655 (1986); P. J. McCloskey and A. G. Schultz, *J. Org. Chem.*, **53**, 1380 (1988).

¹⁸ G. Stork and D. E. Kahne, *J. Am. Chem. Soc.*, **105**, 1072 (1983).

¹⁹ A. G. Schultz and P. J. McCloskey, *J. Org. Chem.*, **50**, 5905 (1985).

The Crabtree catalyst also exhibited superior stereoselectivity in comparison with other catalysts in reduction of an exocyclic methylene group.²⁰



Presumably, the stereoselectivity in these cases is the result of coordination of iridium by the functional group. The crucial property required for a catalyst to be stereodirective is that it be able to coordinate with both the directive group and the double bond and still accommodate the metal hydride bonds necessary for hydrogenation. In the iridium catalyst illustrated above, the cyclooctadiene ligand (COD) in the catalysts is released by hydrogenation, permitting coordination of the reactant and reaction with hydrogen.

Scheme 5.2 gives some examples of hydrogenations carried out with homogeneous catalysts. Entry 1 is an addition of deuterium that demonstrates net *syn* addition with the Wilkinson catalyst. The reaction in Entry 2 proceeds with high stereoselectivity and is directed by steric approach control, rather than a substituent-directing effect. One potential advantage of homogeneous catalysts is the ability to achieve a high degree of selectivity among different functional groups. Entries 3 and 4 are examples that show selective reduction of the unconjugated double bond. Similarly in Entry 5, reduction of the double bond occurs without reduction of the nitro group, which is usually rapidly reduced by heterogeneous hydrogenation. Entries 6 and 7 are cases of substituent-directed hydrogenation using the iridium (Crabtree) catalyst. The catalyst used in Entry 8 is related to the Wilkinson catalyst, but on hydrogenation of norbornadiene (NBD) has two open coordination positions. This catalyst exhibits a strong hydroxy-directing effect. The Crabtree catalyst gave excellent results in the hydrogenation of 3-methylpentadeca-4-enone to *R*-muscone. (Entry 9) A number of heterogeneous catalysts led to 5–15% racemization (by allylic exchange).

5.1.3. Enantioselective Hydrogenation

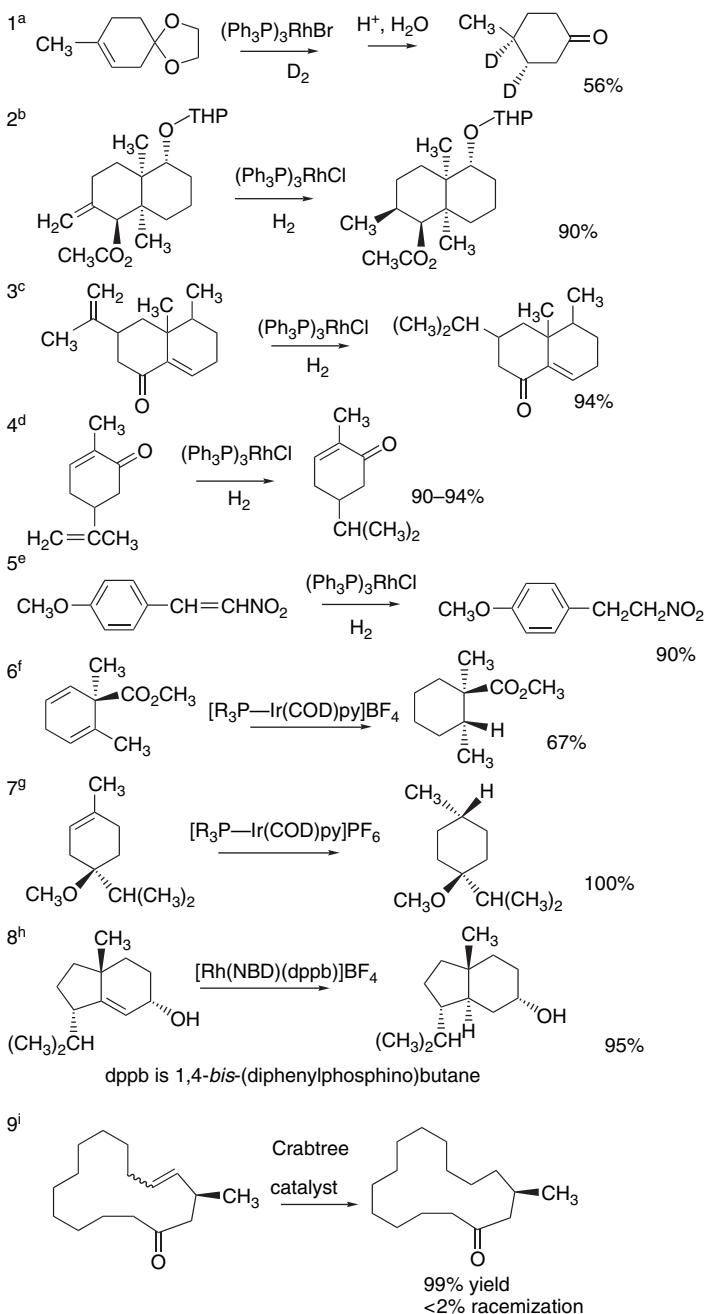
The fundamental concepts of enantioselective hydrogenation were introduced in Section 2.5.1 of Part A, and examples of reactions of acrylic acids and the important case of α -acetamido acrylate esters were discussed. The chirality of enantioselective hydrogenation catalysts is usually derived from phosphine ligands. A number of chiral phosphines have been explored in the development of enantioselective hydrogenation catalysts,²¹ and it has been found that some of the most successful catalysts are derived from chiral 1,1'-binaphthyldiphosphines, such as BINAP.²²

- ²⁰. J. M. Bueno, J. M. Coterón, J. L. Chiara, A. Fernandez-Mayoralas, J. M. Fiandor, and N. Valle, *Tetrahedron Lett.*, **41**, 4379 (2000).
- ²¹. B. Bosnich and M. D. Fryzuk, *Top. Stereochem.*, **12**, 119 (1981); W. S. Knowles, W. S. Chrisopfel, K. E. Koenig, and C. F. Hobbs, *Adv. Chem. Ser.*, **196**, 325 (1982); W. S. Knowles, *Acc. Chem. Res.*, **16**, 106 (1983).
- ²². R. Noyori and H. Takaya, *Acc. Chem. Res.*, **23**, 345 (1990).

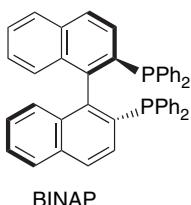
Scheme 5.2. Homogeneous Catalytic Hydrogenation

SECTION 5.1

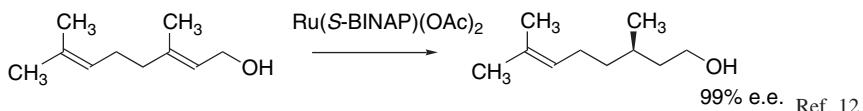
Addition of Hydrogen at
Carbon-Carbon Multiple
Bonds



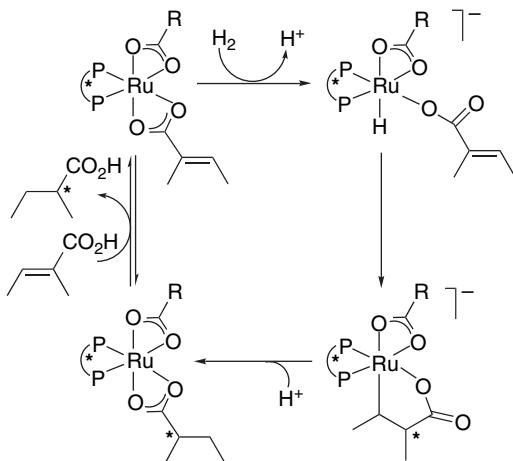
- a. W. C. Agosta and W. L. Shreiber, *J. Am. Chem. Soc.*, **93**, 3947 (1971).
 b. E. Piers, W. de Waal, and R. W. Britton, *J. Am. Chem. Soc.*, **93**, 5113 (1971).
 c. M. Brown and L. W. Piszkiewicz, *J. Org. Chem.*, **32**, 2013 (1967).
 d. R. E. Ireland and P. Bey, *Org. Synth.*, **53**, 63 (1973).
 e. R. E. Harmon, J. L. Parsons, D. W. Cooke, S. K. Gupta, and J. Schoolenberg, *J. Org. Chem.*, **34**, 3684 (1969).
 f. A. G. Schultz and P. J. McCloskey, *J. Org. Chem.*, **50**, 5905 (1985).
 g. R. H. Crabtree and M. W. Davies, *J. Org. Chem.*, **51**, 2655 (1986).
 h. D. A. Evans and M. M. Morrissey, *J. Am. Chem. Soc.*, **106**, 3866 (1984).
 i. C. Fehr, J. Galindo, I. Farris, and A. Cuenna, *Helv. Chim. Acta*, **87**, 1737 (2004).



Ruthenium complexes containing this ligand are able to reduce a variety of double bonds with e.e. above 95%. In order to achieve high enantioselectivity, the reactant must show a strong preference for a specific orientation when complexed with the catalyst. This ordinarily requires the presence of a functional group that can coordinate with the metal. The ruthenium-BINAP catalyst has been used successfully with unsaturated amides,²³ allylic and homoallylic alcohols,²⁴ and unsaturated carboxylic acids.²⁵



The mechanism of such reactions using unsaturated carboxylic acids and Ru(BINAP)(O₂CCH₃)₂ is consistent with the idea that coordination of the carboxy group establishes the geometry at the metal ion.²⁶ The configuration of the new stereocenter is then established by the hydride transfer. In this particular mechanism, the second hydrogen is introduced by protonolysis, but in other cases a second hydride transfer step occurs.



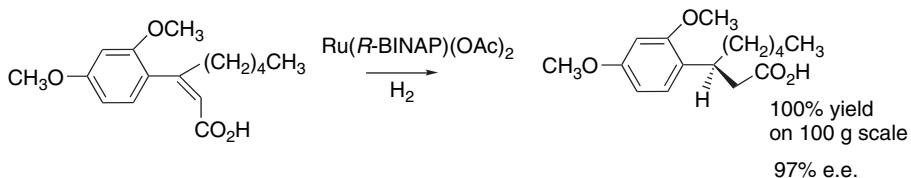
²³. R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta, and H. Takaya, *J. Am. Chem. Soc.*, **108**, 7117 (1986).

²⁴. H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S. Inoue, I. Kasahara, and R. Noyori, *J. Am. Chem. Soc.*, **109**, 1596 (1987).

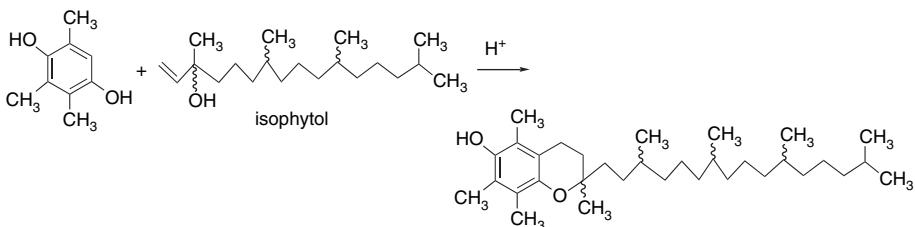
²⁵. T. Ohta, H. Takaya, M. Kitamura, K. Nagai, and R. Noyori, *J. Org. Chem.*, **52**, 3174 (1987).

²⁶. M. T. Ashby and J. T. Halpern, *J. Am. Chem. Soc.*, **113**, 589 (1991).

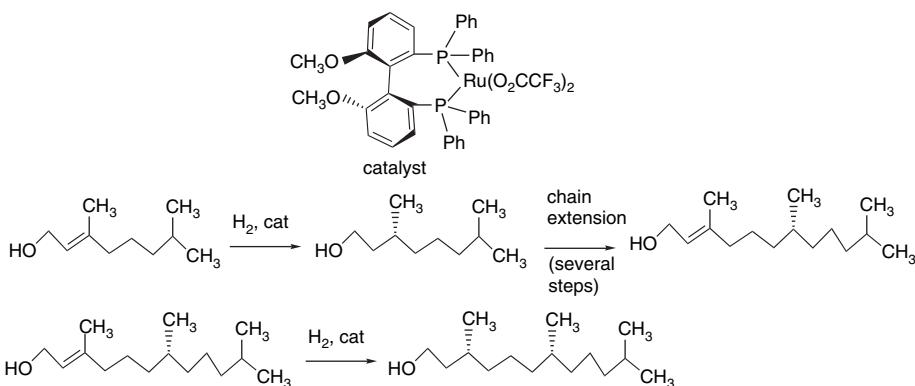
This reaction has been used in the large-scale preparation of an intermediate in the synthesis of a cholesterol acyl-transferase inhibitor.²⁷



An enantioselective hydrogenation of this type is also of interest in the production of α -tocopherol (vitamin E). Totally synthetic α -tocopherol can be made in racemic form from 2,3,5-trimethylhydroquinone and racemic isophytol. The product made in this way is a mixture of all eight possible stereoisomers.



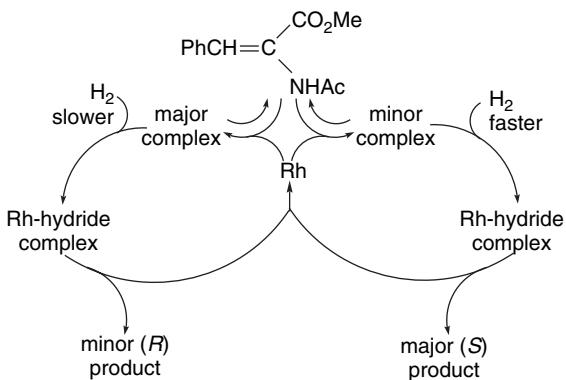
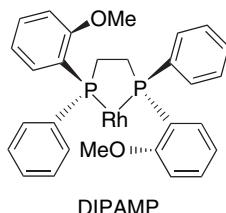
Tocopherol can be produced as the pure *2R,4'R,8'R* stereoisomer from natural vegetable oils. This is the most biologically active of the stereoisomers. The correct side-chain stereochemistry can be obtained using a process that involves two successive enantioselective hydrogenations.²⁸ The optimum catalyst contains a 6,6'-dimethoxybiphenyl phosphine ligand. This reaction has not yet been applied to the enantioselective synthesis of α -tocopherol because the cyclization step with the phenol is not enantiospecific.



²⁷. M. Murakami, K. Kobayashi, and K. Hirai, *Chem. Pharm. Bull.*, **48**, 1567 (2000).

²⁸. T. Netscher, M. Scalione, and R. Schmid, in *Asymmetric Catalysis on an Industrial Scale: Challenges, Approaches and Solutions*, H. U. Blaser and E. Schmidt, eds., Wiley-VCH, Weinheim, 2004, pp. 71–89.

An especially important case is the enantioselective hydrogenation of α -amidoacrylic acids, which leads to α -aminoacids.²⁹ A particularly detailed study has been carried out on the mechanism of reduction of methyl Z- α -acetamidocinnamate by a rhodium catalyst with a chiral diphosphine ligand DIPAMP.³⁰ It has been concluded that the reactant can bind reversibly to the catalyst to give either of two complexes. Addition of hydrogen at rhodium then leads to a reactive rhodium hydride and eventually to product. Interestingly, the addition of hydrogen occurs most rapidly in the minor isomeric complex, and the enantioselectivity is due to this kinetic preference.



A thorough computational study of this process has been carried out using B3LYP/ONIOM calculations.³¹ The rate-determining step is found to be the formation of the rhodium hydride intermediate. The barrier for this step is smaller for the minor complex than for the major one. Additional details on this study can be found at:

Visual models and additional information on Asymmetric Hydrogenation can be found in the Digital Resource available at: Springer.com/carey-sundberg.

²⁹. J. Halpern, in *Asymmetric Synthesis*, Vol. 5, J. D. Morrison, ed., Academic Press, Orlando, FL, 1985; A. Pfaltz and J. M. Brown, in *Stereoselective Synthesis*, G. Helmchen, R. W. Hoffmann, J. Mulzer, and E. Schauman, eds., Thieme, New York, 1996, Part D, Sect. 2.5.1.2; U. Nagel and J. Albrecht, *Catalysis Lett.*, **5**, 3 (1998).

³⁰. C. R. Landis and J. Halpern, *J. Am. Chem. Soc.*, **109**, 1746 (1987).

³¹. S. Feldgus and C. R. Landis, *J. Am. Chem. Soc.*, **122**, 12714 (2000).

Another mechanistic study, carried out using *S*-BINAP-ruthenium(II) diacetate catalyst, concluded that the mechanism shown in Figure 5.1 was operating.³² The rate-determining step is the hydrogenolysis of intermediate **13**, which has an E_a of about 19 kcal/mol. This step also determines the enantioselectivity and proceeds with retention of configuration. The prior steps are reversible and the relative stability of **13_R** > **13_S** determines the preference for the *S*-enantiomer. The energy relationships are summarized in Figure 5.2. The major difference between the major and minor pathways is in the precursors **12_{re}** (favored) and **12_{si}** (disfavored). There is a greater steric repulsion between the carboxylate substituent and the BINAP ligand in **12_{si}** than in **12_{re}** (Figure 5.3.).

A related study with a similar ruthenium catalyst led to the structural and NMR characterization of an intermediate that has the crucial Ru–C bond in place and also shares other features with the BINAP-ruthenium diacetate mechanism.³³ This mechanism, as summarized in Figure 5.4, shows the formation of a metal hydride prior to the complexation of the reactant. In contrast to the mechanism for acrylic acids shown on p. 378, the creation of the new stereocenter occurs at the stage of the addition of the second hydrogen.

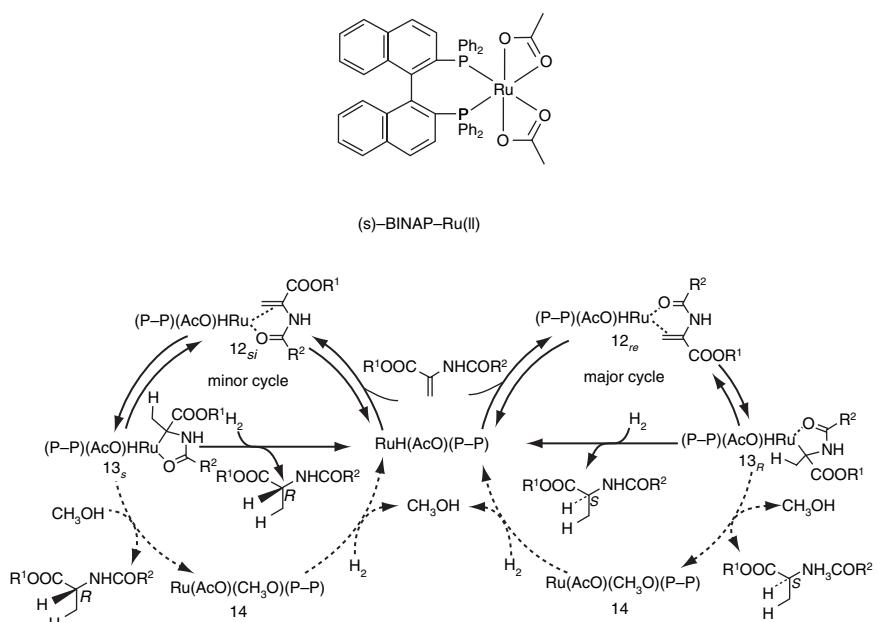


Fig. 5.1. Mechanism of ruthenium catalyzed enantioselective hydrogenation of α -acetamidoacrylate esters. Reproduced from *J. Am. Chem. Soc.*, **124**, 6649 (2002), by permission of the American Chemical Society.

³² M. Kitamura, M. Tsukamoto, Y. Bessho, M. Yoshimura, U. Kobs, M. Widhalm, and R. Noyori, *J. Am. Chem. Soc.*, **124**, 6649 (2002).

³³ J. A. Wiles and S. H. Bergens, *Organometallics*, **17**, 2228 (1998); J. A. Wiles and S. H. Bergens, *Organometallics*, **18**, 3709 (1999).

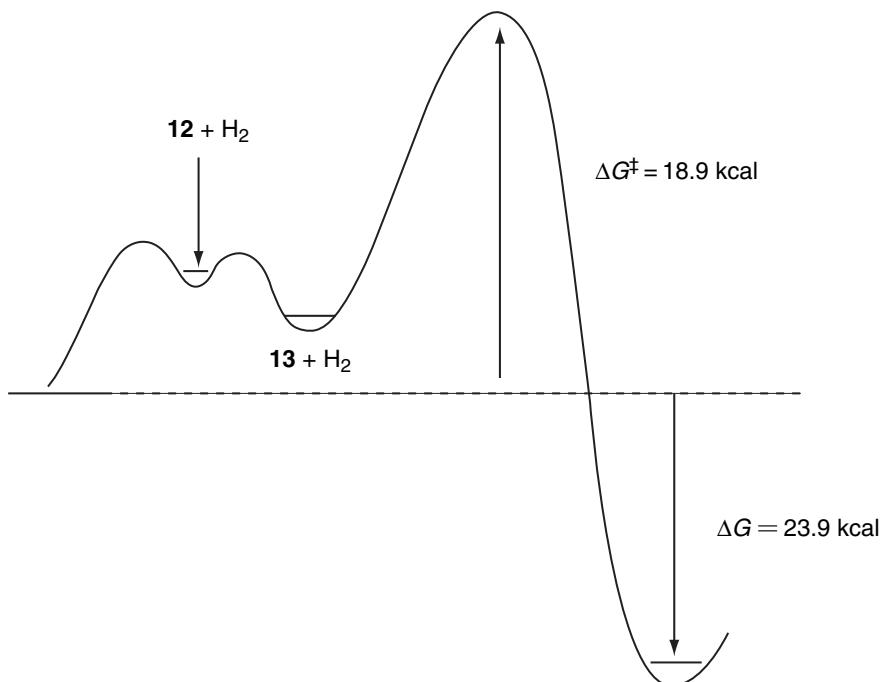


Fig. 5.2. Summary energy diagram for enantioselective ruthenium-catalyzed hydrogenation of α -acetamidoacrylate esters. Reproduced from *J. Am. Chem. Soc.*, **124**, 6649 (2002), by permission of the American Chemical Society.

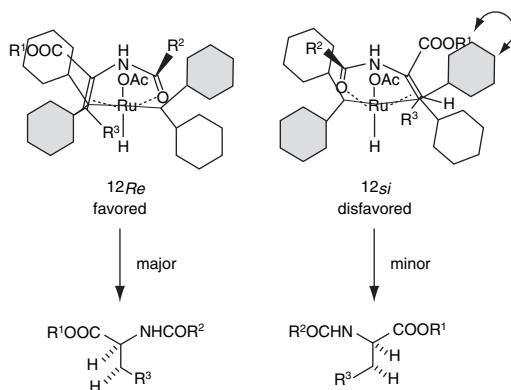


Fig. 5.3. (a) View of (*S*)-BINAP-ruthenium complex showing the chiral environment. (b) Relationship of reactant to chiral environment showing preferred orientation. The binaphthyl rings are omitted for clarity. Adapted from *J. Am. Chem. Soc.*, **124**, 6649 (2002), by permission of the American Chemical Society.

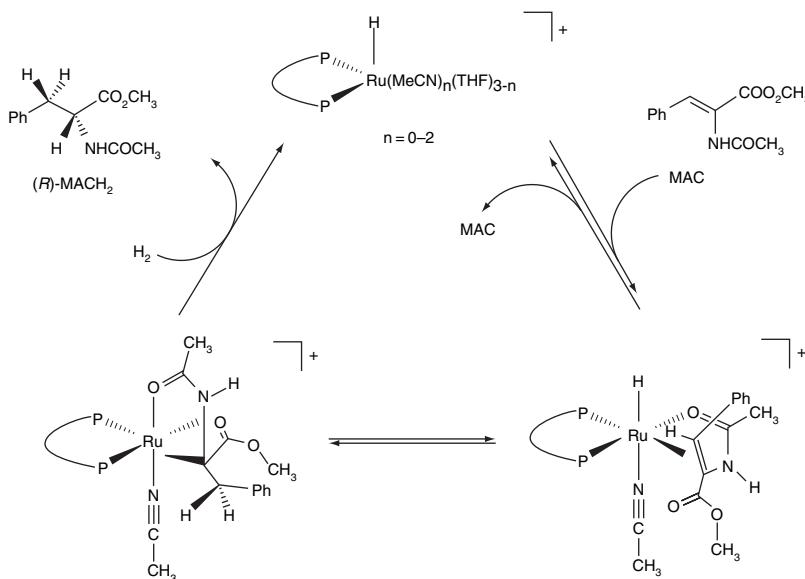
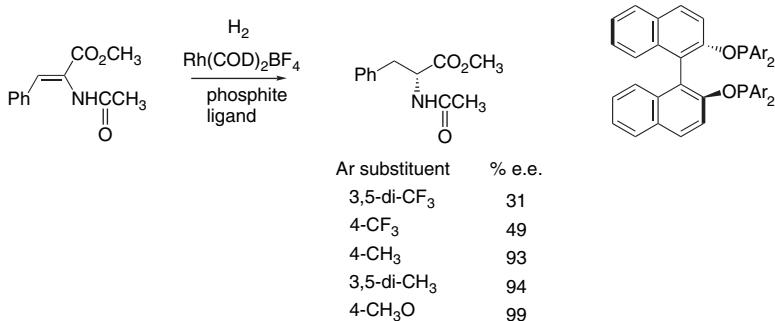


Fig. 5.4. Schematic mechanism for enantioselective hydrogenation of methyl acetamidocinnamate (MAC) over a cationic ruthenium catalyst. Reproduced from *Organometallics*, **18**, 3709 (1999), by permission of the American Chemical Society.

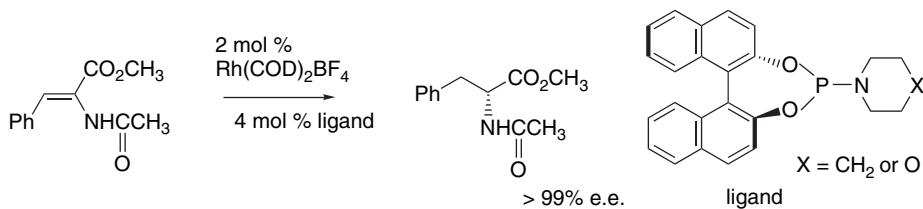
Catalyst reactivity and enantioselectivity can be affected by substituents on ligands. In the Rh-catalyzed hydrogenation of methyl *Z*- α -acetamidocinnamate, for example, BINOL phosphites with ERGs give much higher enantioselectivity than those with EWGs. The ligand substituents modify the electron density at the metal center and change the energy balance between the competing pathways. This example demonstrates the potential for fine-tuning of the catalysts by changes that are relatively remote from the catalytic site.³⁴



Many other catalysts and ligands have been examined for the enantioselective reduction of α -acetamidoacrylates and related substrates. Phosphoramidites derived from BINOL and the cyclic amines piperidine and morpholine give excellent results.³⁵

³⁴ I. Gergely, C. Hegedus, A. Szollosy, A. Monsees, T. Riermeier, and J. Bakos, *Tetrahedron Lett.*, **44**, 9025 (2003).

³⁵ H. Bernsmann, M. van der Berg, R. Hoen, A. J. Minnaard, G. Mehler, M. T. Reetz, J. G. De Vries, and B. L. Feringa, *J. Org. Chem.*, **70**, 943 (2005).

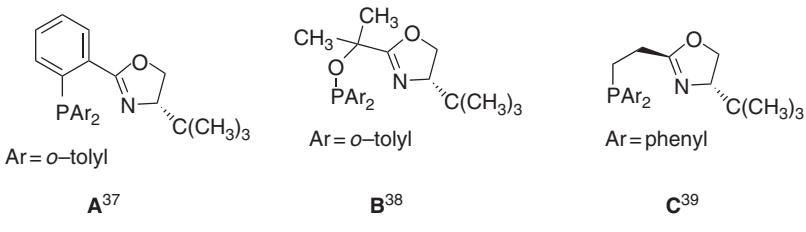


These ligands also give excellent results with dimethyl itaconate and α -arylenamides.

Scheme 5.3 shows the enantioselectivity of some hydrogenations of unsaturated acids and amides. Entries 1 to 5 are examples of hydrogenations of α -acetamidoacrylate and α -acetamidocinnamate esters. The catalyst in Entries 1 and 2 uses chiraphos as the chiral phosphine ligand and norbornadiene as the removable ligand. The catalyst in Entry 3 uses DIPAMP as the chiral ligand. BINAP is the ligand in Entry 4. The ligand in Entry 5, known as EtDuPHOS, gave highly selective reduction of the α,β -double bond in the conjugated system. Entries 6 and 7 show reduction of acrylate esters having other types of substituents that give good results with the DIPAMP catalyst. Entries 8 to 10 show examples of several alkylidene succinate half-esters.

There can be significant differences in the detailed structure and mechanism of these catalysts. For example, the geometry of the phosphine ligands may affect the reactivity at the metal ion, but the basic elements of the mechanism of enantioselection are similar. The phosphine ligands establish a chiral environment and provide an appropriate balance of reactivity and stability for the metal center. The reactants bind to the metal through the double bond and at least one other functional group, and mutual interaction with the chiral environment is the basis for enantioselectivity. The new stereocenters are established under the influence of the chiral environment.

The enantioselective hydrogenation of unfunctionalized alkenes presents special challenges. Functionalized reactants such as acrylate esters can coordinate with the metal in the catalyst and this point of contact can serve to favor a specific orientation and promote enantioselectivity. Unfunctionalized alkenes do not have such coordination sites and enantioselectivity is based on steric factors. A number of iridium-based catalysts have been developed. One successful type of catalyst incorporates phosphine or phosphite groups and a chiral oxazoline ring as donors.³⁶ The catalysts also incorporate cyclooctadiene as a removable ligand. These catalysts are extremely sensitive to even weakly coordinating anions and the preferred anion for alkene hydrogenation is *tetrakis*-[(3,5-trifluoromethyl)phenyl]borate. Most of the examples to date have been with aryl-substituted double bonds.



³⁶ G. Helmchen and A. Pfaltz, *Acc. Chem. Res.*, **33**, 336 (2000).

³⁷ F. Menges, M. Neuburger, and A. Pfaltz, *Org. Lett.*, **4**, 4713 (2002).

³⁸ S. P. Smidt, F. Menges, and A. Pfaltz, *Org. Lett.*, **6**, 2023 (2004).

³⁹ D. R. Hou, J. Reibenspies, T. J. Colacot, and K. Burgess, *Chem. Eur. J.*, **7**, 5391 (2001).

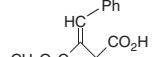
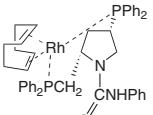
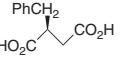
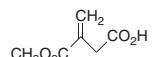
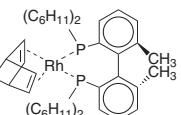
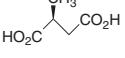
Addition of Hydrogen at
Carbon-Carbon Multiple
Bonds

Scheme 5.3. Enantioselectivity for Catalytic Hydrogenation of Substituted Acrylic Acids

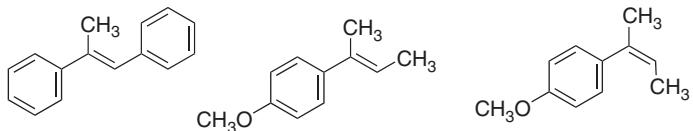
Reactant	Catalyst	Product	Configuration	% e.e.
1 ^a 			R	90
2 ^a 	Same as above		S	95
3 ^b 			R	94
4 ^c 			S	100
5 ^d 			R	99.2
6 ^b 			S	90
7 ^e 			R	88
8 ^f 			R	99

(Continued)

Scheme 5.3. (Continued)

Reactant	Catalyst	Product	Configuration	% e.e.
9 ^g 			S	>95
10 ^h 			S	96

- a. M. D. Fryzuk and B. Bosnich, *J. Am. Chem. Soc.*, **99**, 6262 (1977).
 b. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, and D. J. Weinkauf, *J. Am. Chem. Soc.*, **99**, 5946 (1977).
 c. A. Miyashita, H. Takaya, T. Souchi, and R. Noyori, *Tetrahedron*, **40**, 1245 (1984).
 d. M. J. Burk, J. G. Allen, and W. F. Kiesman, *J. Am. Chem. Soc.*, **120**, 657 (1998).
 e. W. C. Christopfel and B. D. Vineyard, *J. Am. Chem. Soc.*, **101**, 4406 (1979).
 f. M. J. Burk, F. Bienewald, M. Harris, and A. Zanotti-Gerosa, *Angew. Chem. Int. Ed. Engl.*, **37**, 1931 (1998).
 g. H. Jendralla, *Tetrahedron Lett.*, **32**, 3671 (1991).
 h. T. Chiba, A. Miyashita, H. Nohira, and H. Takaya, *Tetrahedron Lett.*, **32**, 4745 (1991).



Catalyst	Percent e.e.		
A	98	81	63
B	98	91	66
C	89	86	75

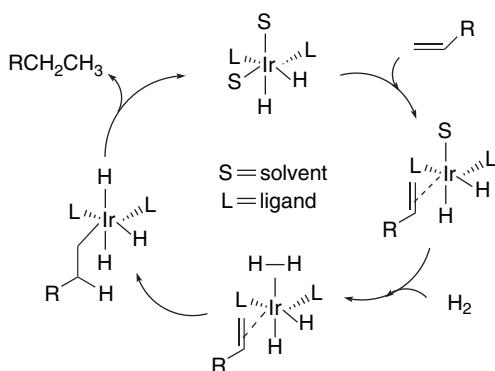
These catalysts also provide excellent results with acrylate esters and allylic alcohols.

Catalyst	Percent e.e.	
A	84	96
B	94	97

These catalysts are activated by hydrogenation of the cyclooctadiene ligand, which releases cyclooctane and opens two coordination sites at iridium. The mechanism has been probed by computational studies.⁴⁰ It is suggested that the catalytic cycle involves

⁴⁰ P. Brandt, C. Hedberg, and P. G. Andersson, *Chem. Eur. J.*, **9**, 339 (2003).

the addition of two hydrogens to the alkene-catalyst complex, followed by formation of an alkyliridium intermediate and reductive elimination.



The enantioselectivity is thought to result from both steric blocking by the *t*-butyl substituent on the oxazoline ring and an attractive van der Waals interaction of an aryl ring and the oxazoline ring, as shown in Figure 5.5.

5.1.4. Partial Reduction of Alkynes

Partial reduction of alkynes to *Z*-alkenes is an important synthetic application of selective hydrogenation catalysts. The transformation can be carried out under heterogeneous or homogeneous conditions. Among heterogeneous catalysts, the one that

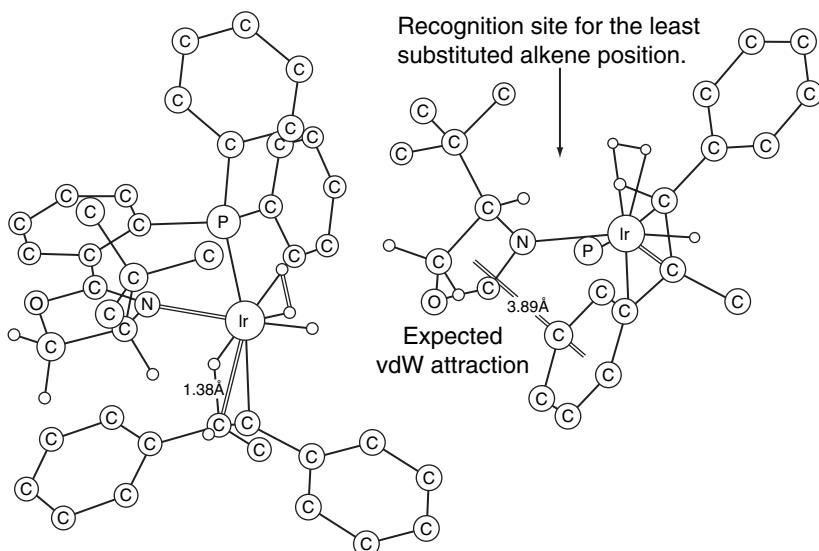
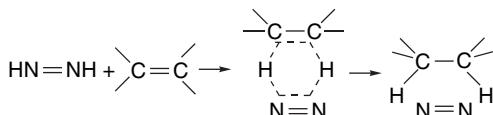


Fig. 5.5. Suggested basis of enantioselectivity in hydrogenation of α -methylstilbene by a phosphinoaryl oxazoline–iridium catalyst. Reproduced from *Chem. Eur. J.*, **9**, 339 (2003), by permission of Wiley-VCH.

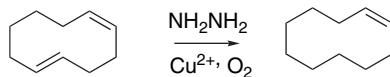
is most successful is *Lindlar's catalyst*, a lead-modified palladium- CaCO_3 catalyst.⁴¹ A nickel-boride catalyst prepared by reduction of nickel salts with sodium hydride is also useful.⁴² Rhodium catalysts have also been reported to show good selectivity.⁴³

5.1.5. Hydrogen Transfer from Diimide

Catalytic hydrogenation transfers the elements of molecular hydrogen through a series of complexes and intermediates. Diimide, $\text{HN}=\text{NH}$, an unstable hydrogen donor that can be generated in situ, finds specialized application in the reduction of carbon-carbon double bonds. Simple alkenes are reduced efficiently by diimide, but other easily reduced functional groups, such as nitro and cyano are unaffected. The mechanism of the reaction is pictured as a concerted transfer of hydrogen via a nonpolar cyclic TS.



In agreement with this mechanism is the fact that the stereochemistry of addition is *syn*.⁴⁴ The rate of reaction with diimide is influenced by torsional and angle strain in the alkene. More strained double bonds react at accelerated rates.⁴⁵ For example, the more strained *trans* double bond is selectively reduced in *Z,E*-1,5-cyclodecadiene.



Ref. 46

Diimide selectively reduces terminal over internal double bonds in polyunsaturated systems.⁴⁷

Reduction by diimide can be advantageous when compounds contain functional groups that would be reduced by other methods or when they are unstable to hydrogenation catalysts. There are several methods for generation of diimide and they are illustrated in Scheme 5.4. The method in Entry 1 is probably the one used most frequently in synthetic work and involves the generation and spontaneous decarboxylation of azodicarboxylic acid. Entry 2, which illustrates another convenient method, thermal decomposition of *p*-toluenesulfonylhydrazide, is interesting in that it

⁴¹ H. Lindlar and R. Dubuis, *Org. Synth.*, **V**, 880 (1973).

⁴² H. C. Brown and C. A. Brown, *J. Am. Chem. Soc.*, **85**, 1005 (1963); E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **91**, 4318 (1969).

⁴³ R. R. Schrock and J. A. Osborn, *J. Am. Chem. Soc.*, **98**, 2143 (1976); J. M. Tour, S. L. Pendalwar, C. M. Kafka, and J. P. Cooper, *J. Org. Chem.*, **57**, 4786 (1992).

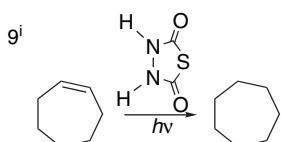
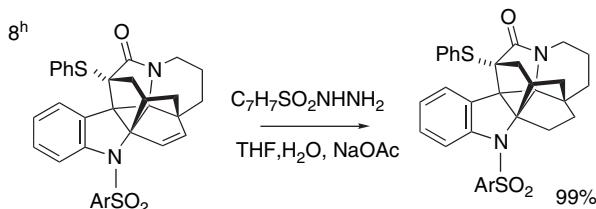
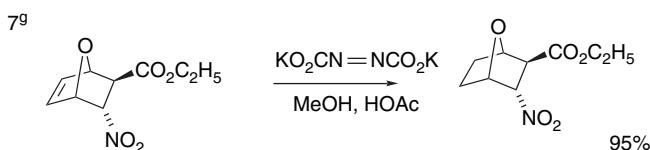
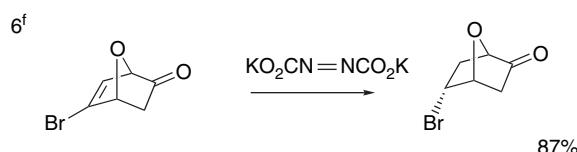
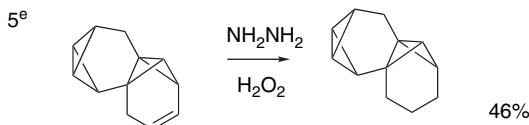
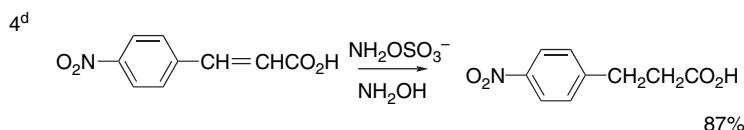
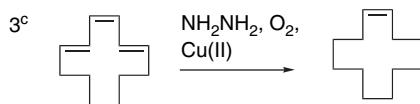
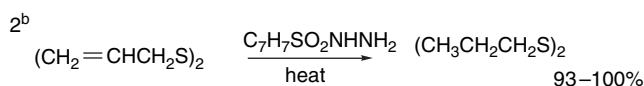
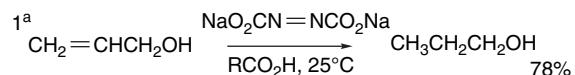
⁴⁴ E. J. Corey, D. J. Pasto, and W. L. Mock, *J. Am. Chem. Soc.*, **83**, 2957 (1961).

⁴⁵ E. W. Garbisch, Jr., S. M. Schildcrout, D. B. Patterson, and C. M. Sprecher, *J. Am. Chem. Soc.*, **87**, 2932 (1965).

⁴⁶ J. G. Traynham, G. R. Franzen, G. A. Kresel, and D. J. Northington, Jr., *J. Org. Chem.*, **32**, 3285 (1967).

⁴⁷ E. J. Corey, H. Yamamoto, D. K. Herron, and K. Achiwa, *J. Am. Chem. Soc.*, **92**, 6635 (1970); E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92**, 6636, 6637 (1970).

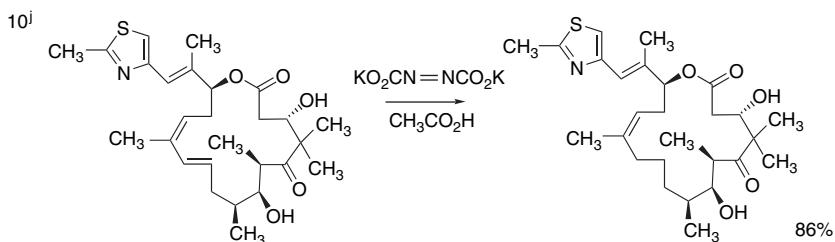
Scheme 5.4. Reductions with Diimide



(Continued)

CHAPTER 5

*Reduction of
Carbon-Carbon Multiple
Bonds, Carbonyl
Groups, and Other
Functional Groups*



- a. E. E. van Tamelen, R. S. Dewey, and R. J. Timmons, *J. Am. Chem. Soc.*, **83**, 3725 (1961).
- b. E. E. van Tamelen, R. S. Dewey, M. F. Lease, and W. H. Pirkle, *J. Am. Chem. Soc.*, **83**, 4302 (1961).
- c. M Ohno, and M. Okamoto, *Org. Synth.*, **49**, 30 (1969).
- d. W. Durckheimer, *Liebigs Ann. Chem.*, **712**, 240 (1969).
- e. L. A. Paquette, A. R. Browne, E. Chamot, and J. F. Blount, *J. Am. Chem. Soc.*, **102**, 643 (1980).
- f. J.-M. Durgnat and P. Vogel, *Helv. Chim. Acta*, **76**, 222 (1993).
- g. P. A. Grieco, R. Lis, R. E. Zelle, and J. Finn, *J. Am. Chem. Soc.*, **108**, 5908 (1986).
- h. P. Magnus, T. Gallagher, P. Brown, and J. C. Huffman, *J. Am. Chem. Soc.*, **106**, 2105 (1984).
- i. M. Squillacote, J. DeFelippis, and Y. L. Lai, *Tetrahedron Lett.*, **34**, 4137 (1993).
- j. K. Biswas, H. Lin, J. T. Njgardson, M. D. Chappell, T.-C. Chou, Y. Guan, W. P. Tong, L. He, S. B. Horwitz, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **124**, 9825 (2002).

demonstrates that the very easily reduced disulfide bond is unaffected by diimide. Entry 3 involves generation of diimide by oxidation of hydrazine and also illustrates the selective reduction of *trans* double bonds in a medium-sized ring. Entry 4 shows that nitro groups are unaffected by diimide. Entries 5 to 7 involve sensitive molecules in which double bonds are reduced successfully. Entry 8, part of a synthesis of the kopsane group of alkaloids, successfully retains a sulfur substituent. Entry 9 illustrates a more recently developed diimide source, photolysis of 1,3,4-thiadiazolin-2,5-dione. Entry 10 is a selective reduction of a *trans* double bond in a macrocyclic lactone and was used in the synthesis of epothilone analogs.⁴⁸

5.2. Catalytic Hydrogenation of Carbonyl and Other Functional Groups

Many other functional groups are also reactive under conditions of catalytic hydrogenation. Ketones, aldehydes, and esters can all be reduced to alcohols, but in most cases these reactions are slower than alkene reductions. For most synthetic applications, the hydride transfer reagents, discussed in Section 5.3, are used for reduction of carbonyl groups. The reduction of nitro compounds to amines, usually proceeds very rapidly. Amides, imines, and also nitriles can be reduced to amines. Hydrogenation of amides requires extreme conditions and is seldom used in synthesis, but reductions of imines and nitriles are quite useful. Table 5.2 gives a summary of the approximate conditions for catalytic hydrogenation of some common functional groups.

⁴⁸. For another example, see J. D. White, R. G. Carter, and K. F. Sundermann, *J. Org. Chem.*, **64**, 684 (1999).

Table 5.2. Conditions for Catalytic Reduction of Various Functional Groups^a

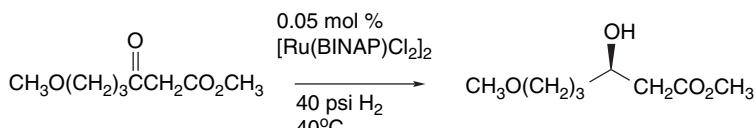
Reactant	Product	Catalyst	Conditions	SECTION 5.2 <i>Catalytic Hydrogenation of Carbonyl and Other Functional Groups</i>
		Pd, Pt, Ni, Ru, Rh	Rapid at room temperature (R.T.) and 1 atm except for highly substituted or hindered cases	
		Lindlar	R. T. and low pressure, quinoline or lead added to deactivate catalyst	
		Rh, Pt	Moderate pressure (5–10 atm), 50–100°C	
		Ni, Pd	High pressure (100–200 atm), 100–200°C	
		Pt, Ru	Moderate rate at R. T. and 1–4 atm. acid-catalyzed	
		Cu–Cr, Ni	High pressure, 50–100°C	
		Pd	R. T., 1–4 atm. acid-catalyzed	
		Pd, Ni	50–100°C, 1–4 atm	
		Pd	R. T., 1 atm. quinoline or other catalyst moderator used	
		Pd, Ni, Ru	Very strenuous conditions required	
		Cu–Cr, Ni	200°C, high pressure	
		Ni, Rh	50–100°C, usually high pressure, NH3 added to increase yield of primary amine	
		Cu–Cr	Very strenuous conditions required	
		Pd, Ni, Pt	R. T., 1–4 atm	
		Pd, Pt	R. T., 4–100 atm	
		Pd	Order of reactivity: I > Br > Cl > F, bases promote reactions for R = alkyl	
		Pt, Pd	Proceeds slowly at R. T., 1–4 atm, acid-catalyzed	

a. General References: M. Freifelder, *Catalytic Hydrogenation in Organic Synthesis: Procedures and Commentary*, John Wiley & Sons, New York, 1978; P. N. Rylander, *Hydrogenation Methods*, Academic Press, Orlando FL, 1985.

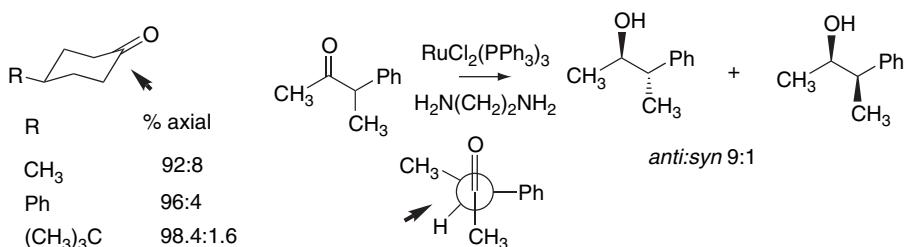
Many enantioselective catalysts have been developed for reduction of functional groups, particularly ketones. BINAP complexes of Ru(II)Cl₂ or Ru(II)Br₂ give good enantioselectivity in reduction of β-ketoesters.⁴⁹ This catalyst system has been shown to be subject to acid catalysis.⁵⁰ Thus in the presence of 0.1 mol % HCl, reduction proceeds smoothly at 40 psi of H₂ at 40°C.

⁴⁹. R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, and S. Akutagawa, *J. Am. Chem. Soc.*, **109**, 5856 (1987).

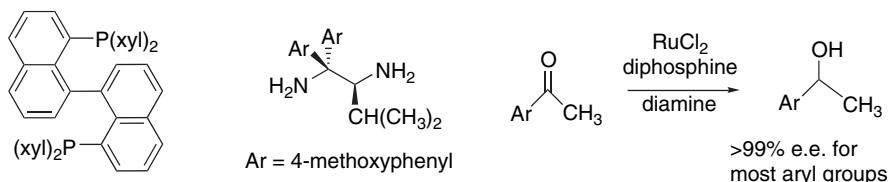
⁵⁰. S. A. King, A. S. Thompson, A. O. King, and T. R. Verhoeven, *J. Org. Chem.*, **57**, 6689 (1992).



For reduction of monofunctional ketones, the most effective catalysts include diamine ligands. The diamine catalysts exhibit strong selectivity for carbonyl groups over carbon-carbon double and triple bonds. These catalysts have a preference for equatorial approach in the reduction of cyclohexanones and for steric approach control in the reduction of acyclic ketones.⁵¹



Related catalysts include both a chiral BINAP-type phosphine and a chiral diamine ligand. A wide range of aryl ketones gave more than 95% enantioselectivity when substituted-1,1'-binaphthyl and ethylene diamines were used.⁵²



xyl = 3,5-dimethylphenyl

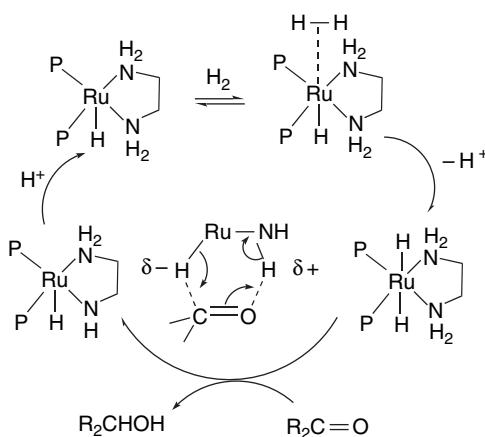
Cyclic and α,β -unsaturated ketones also gave high e.e. but straight-chain alkyl ketones did not.

The suggested catalytic cycle for the diamine catalysts indicates that the NH group of the diamine plays a direct role in the hydride transfer through a six-membered TS.⁵³ A feature of this mechanism is the absence of direct contact between the ketone and the metal. Rather, the reaction is pictured as a nucleophilic delivery of hydride from ruthenium, concerted with a proton transfer from nitrogen.

⁵¹. T. Ohkuma, H. Ooka, M. Yamakawa, T. Ikariya, and R. Noyori, *J. Org. Chem.*, **61**, 4872 (1996).

⁵². T. Ohkuma, M. Koizuma, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, and R. Noyori, *J. Am. Chem. Soc.*, **120**, 13529 (1998).

⁵³. C. A. Sandoval, T. Ohkuma, Z. Muniz, and R. Noyori, *J. Am. Chem. Soc.*, **125**, 13490 (2003).



The catalyst used for these mechanistic studies has been characterized by X-ray crystallography, as shown in Figure 5.6. It is obtained as a hydrido ruthenium(II) species that is also coordinated by a $[\text{BH}_4]^-$ anion. The catalyst is prepared by exposing the DINAP-diamine RuCl_2 complex to excess NaBH_4 .⁵⁴

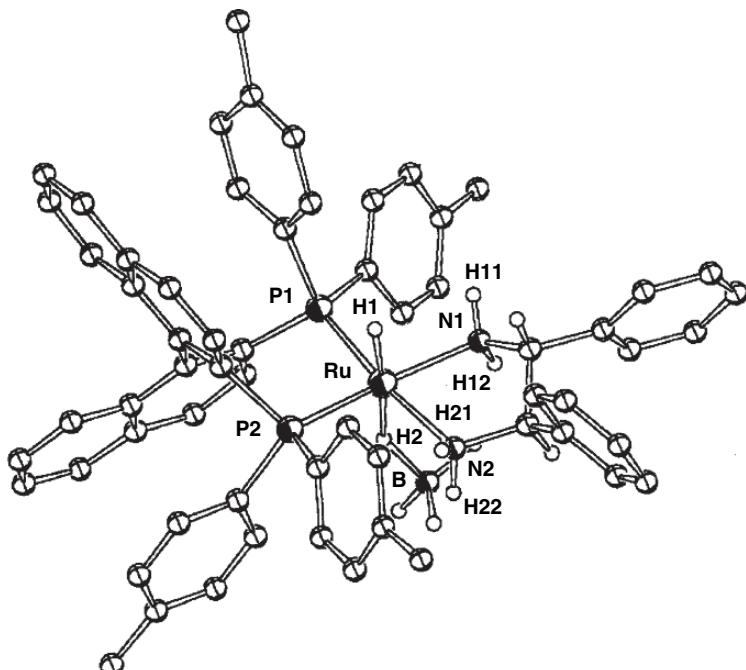
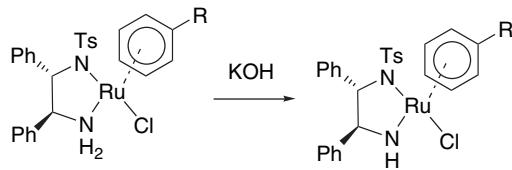


Fig. 5.6. Crystal structure of *tetrakis-P,P,P'-P'-(4-methylphenyl)-1,1'-binaphthylidiphosphine-1,2-diphenyl-1,2-ethanediamine ruthenium borohydride catalyst*. Reproduced from *J. Am. Chem. Soc.*, **124**, 6508 (2002), by permission of the American Chemical Society.

⁵⁴. T. Ohkuma, M. Koizumi, K. Muniz, G. Hilt, C. Kabuto, and R. Noyori, *J. Am. Chem. Soc.*, **124**, 6508 (2002).

Several other versions of these catalysts have been developed. Arene complexes of monotosyl-1,2-diphenylethylenediamine ruthenium chloride give good results with α,β -ynones.⁵⁵ The active catalysts are generated by KOH. These catalysts also function by hydrogen transfer, with isopropanol serving as the hydrogen source. Entries 6 to 8 in Scheme 5.3 are examples.

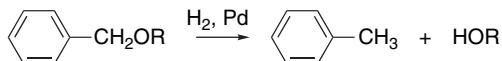


Catalyst D: Arene = mesitylene

Catalyst E: Arene = *p*-cymene

Scheme 5.5 gives some examples of the application of these Ru(II)-diphosphine and diamine catalysts. Entries 1 and 2 are examples of the hydrogenation of β -dicarbonyl compounds with Ru(BINAP)Cl₂. Excellent enantioselectivity is observed, although elevated hydrogen pressure is required. Entry 3 proceeds in fair yield and enantioselectivity, and without reduction of the conjugated carbon-carbon double bond. Entry 4 uses the cymene complex catalyst E under hydrogen transfer conditions. Entry 5 involves tandem 1,4- and 1,2-reduction and was done under hydrogen transfer conditions, using formic acid as the hydride donor. Entries 6 to 8 show good yields and enantioselectivity for several alkynyl ketones of increasing structural complexity. In the latter two cases, only a single stereoisomer was observed.

Certain functional groups can be entirely removed and replaced by hydrogen, a reaction known as *hydrogenolysis*. For example, aromatic halogen substituents are frequently removed by hydrogenation over transition metal catalysts. Aliphatic halogens are somewhat less reactive but hydrogenolysis is promoted by base.⁵⁶ The most useful type of hydrogenolysis reaction involves removal of oxygen functional groups at benzylic and allylic positions.⁵⁷



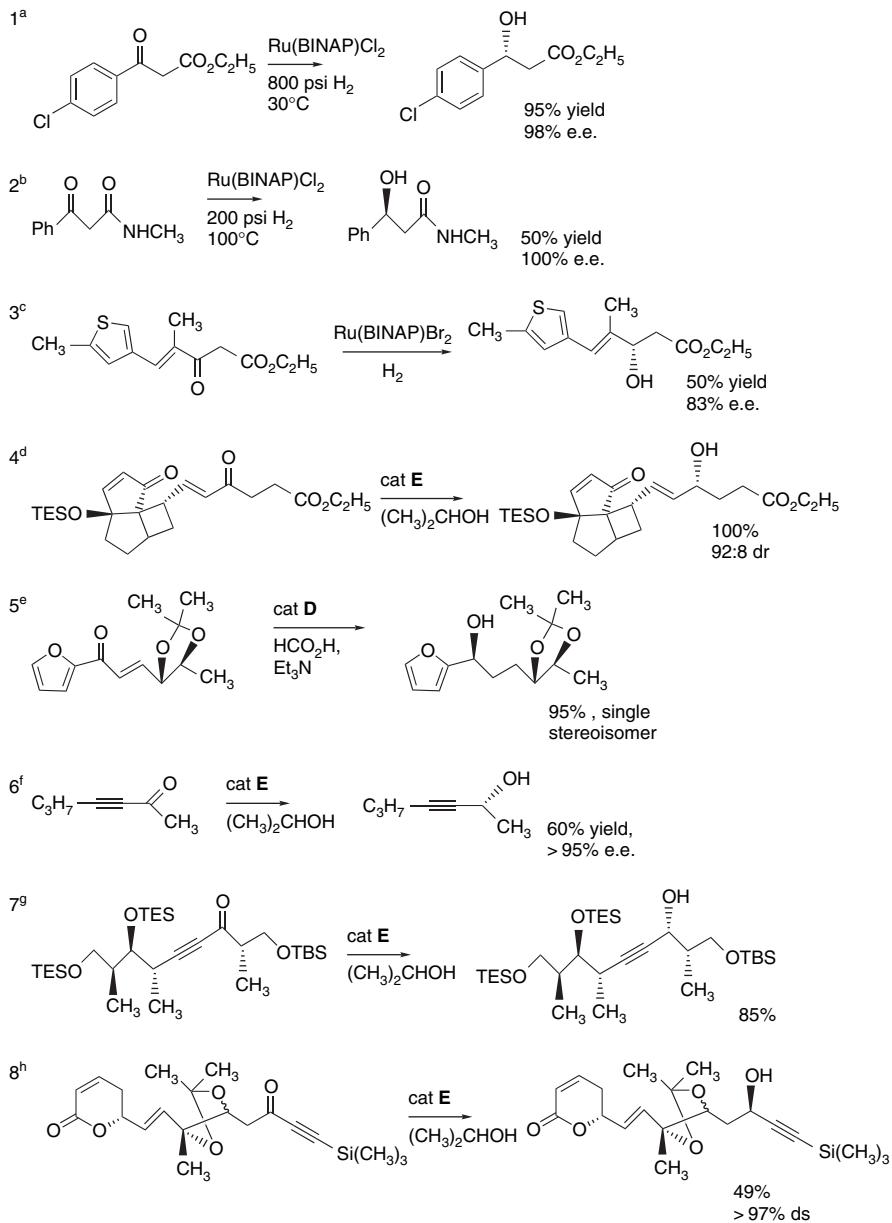
Hydrogenolysis of halides and benzylic groups presumably involves intermediates formed by *oxidative addition* to the active metal catalyst to generate intermediates similar to those involved in hydrogenation. The hydrogenolysis is completed by reductive elimination.⁵⁸ Many other examples of this pattern of reactivity are discussed in Chapter 8.

⁵⁵. K. Matsumura, S. Hashiguchi, T. Ikariya, and R. Noyori, *J. Am. Chem. Soc.*, **119**, 8738 (1997).

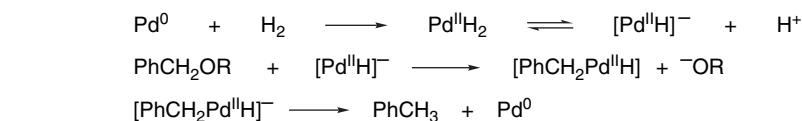
⁵⁶. A. R. Pinder, *Synthesis*, 425 (1980).

⁵⁷. W. H. Hartung and R. Simonoff, *Org. React.*, **7**, 263 (1953); P. N. Rylander, *Catalytic Hydrogenation over Platinum Metals*, Academic Press, New York, 1967, Chap. 25; P. N. Rylander, *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, New York, 1979, Chap. 15; P. N. Rylander, *Hydrogenation Methods*, Academic Press, Orlando, FL, 1985, Chap. 13.

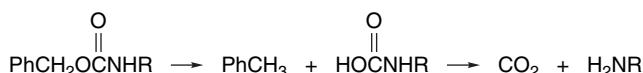
⁵⁸. The mechanism of benzylic hydrogenolysis has not been definitively established. For other possibilities, see R. B. Grossman, *The Art of Writing Reasonable Organic Mechanisms*, 2nd Edition, Springer, New York, 2003, pp. 309–310.



- a. V. V. Thakur, M. D. Nikalje, and A. Sudalai, *Tetrahedron: Asymmetry*, **14**, 581 (2003).
 - b. H.-L. Huang, L. T. Liu, S.-F. Chen, and H. Ku, *Tetrahedron:Asymmetry*, **9**, 1637 (1998).
 - c. E. A. Reiff, S. K. Nair, B. S. N. Reddy, J. Inagaki, J. T. Henri, J. F. Greiner, and G. I. Georg, *Tetrahedron Lett.*, **45**, 5845 (2004).
 - d. H. Ito, M. Hasegawa, Y. Takenaka, T. Kobayashi, and K. Iguchi, *J. Am. Chem. Soc.*, **126**, 4520 (2004).
 - e. M. Li and G. O'Doherty, *Tetrahedron Lett.*, **45**, 6407 (2004).
 - f. N. Petry, A. Parenty, and J.-M. Campagne, *Tetrahedron: Asymmetry*, **15**, 1199 (2004).
 - g. J. A. Marshall and M. P. Bourbeau, *Org. Lett.*, **5**, 3197 (2003).
 - h. K. Fujii, K. Maki, M. Kanai, and M. Shibasaki, *Org. Lett.*, **5**, 733 (2003).



The facile cleavage of the benzyl-oxygen bond has made the benzyl group a useful protecting group in multistep syntheses. A particularly important example is the use of the carbobenzyloxy group in peptide synthesis. The protecting group is removed by hydrogenolysis. The substituted carbamic acid generated by the hydrogenolysis decarboxylates spontaneously to provide the amine (see Section 3.5.2).

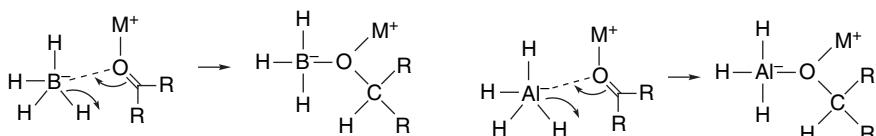


5.3. Group III Hydride-Donor Reagents

5.3.1. Comparative Reactivity of Common Hydride Donor Reagents

Most reductions of carbonyl compounds are done with reagents that transfer a hydride from boron or aluminum. The various reagents of this type that are available provide a considerable degree of chemo- and stereoselectivity. Sodium borohydride and lithium aluminum hydride are the most widely used of these reagents. Sodium borohydride is a mild reducing agent that reacts rapidly with aldehydes and ketones but only slowly with esters. It is moderately stable in hydroxylic solvents and can be used in water or alcoholic solutions. Lithium aluminum hydride is a much more powerful hydride donor, and it rapidly reduces esters, acids, nitriles, and amides, as well as aldehydes and ketones. Lithium aluminum hydride is strongly basic and reacts very rapidly (*violently*) with water or alcohols to release hydrogen. It must be used in anhydrous solvents, usually ether or tetrahydrofuran. The difference in the reactivity of these two compounds is due to properties of both the cations and the anions. Lithium is a stronger Lewis acid than sodium and AlH_4^- is a more reactive hydride donor than BH_4^- . Neither sodium borohydride nor lithium aluminum hydride reacts with isolated carbon-carbon double bonds. The reactivity of these reagents and some related reducing reagents is summarized in Table 5.3.

The mechanism by which the Group III hydrides effect reduction involves activation of the carbonyl group by coordination with a metal cation and nucleophilic transfer of hydride to the carbonyl group. Hydroxylic solvents also participate in the reaction,⁵⁹ and as reduction proceeds and hydride is transferred, the Lewis acid character of boron and aluminum becomes a factor.



⁵⁹ D. C. Wigfield and R. W. Gowland, *J. Org. Chem.*, **42**, 1108 (1977).

Table 5.3. Reactivity of Hydride-Donor Reducing Agents

	Reactant					
	Iminium ion	Acyl chloride	Aldehyde or ketone	Ester	Amide	Carboxylate salt
	Most reactive →				Least reactive	
Hydride donor	Product ^a					
LiAlH ₄ ^b	Amine	Alcohol	Alcohol	Alcohol	Amine	Alcohol
Red-Al ^c		Alcohol	Alcohol	Alcohol	Amine	Alcohol
LiAlH(OtBu) ₃ ^d		Aldehyde ^e	Alcohol	Alcohol	Aldehyde ^f	
NaBH ₄ ^b	Amine		Alcohol	Alcohol ^f		
NaBH ₃ CN ^g	Amine					
B ₂ H ₆ ^h			Alcohol		Amine	Alcohol ⁱ
AlH ₃ ^j		Alcohol	Alcohol	Alcohol	Amine	Alcohol
Disiamylborane ^k			Alcohol		Aldehyde ^e	
DIBAlH			Alcohol	Aldehyde ^e	Aldehyde ^e	Alcohol

a. Products shown are the usual products of synthetic operations. Where no entry is given, the combination has not been studied or is not of major synthetic utility.

b. J. Seyden-Penne, *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, VCH Publishers, New York, 1991.

c. J. Malek, *Org. React.*, **34**, 1 (1985); **36**, 249 (1989).

d. H. C. Brown and R. F. McFarlin, *J. Am. Chem. Soc.*, **78**, 752 (1956); **80**, 5372 (1958); H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **80**, 5377 (1958); H. C. Brown and A. Tsukamoto, *J. Am. Chem. Soc.*, **86**, 1089 (1964).

e. Reaction must be controlled by use of a stoichiometric amount of reagent and low temperature.

f. Reaction occurs slowly.

g. C. F. Lane, *Synthesis*, 135 (1975).

h. H. C. Brown, P. Heim, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 1637 (1970); N. M. Yoon, C. S. Park, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973); H. C. Brown and P. Heim, *J. Org. Chem.*, **38**, 912 (1973).

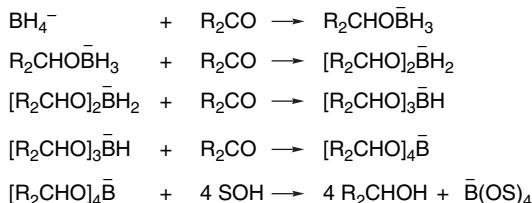
i. Reaction occurs through an acyloxyborane.

j. H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc.*, **88**, 1464 (1966).

k. H. C. Brown, D. B. Bigley, S. K. Arora, and N. M. Yoon, *J. Am. Chem. Soc.*, **92**, 7161 (1970); H. C. Brown and V. Varma, *J. Org. Chem.*, **39**, 1631 (1974).

l. E. Winterfeldt, *Synthesis*, 617 (1975); H. Reinheckel, K. Haage, and D. Jahnke, *Organomet. Chem. Res.*, **4**, 47 (1969); N. M. Yoon and Y. S. Gyoung, *J. Org. Chem.*, **50**, 2443 (1985).

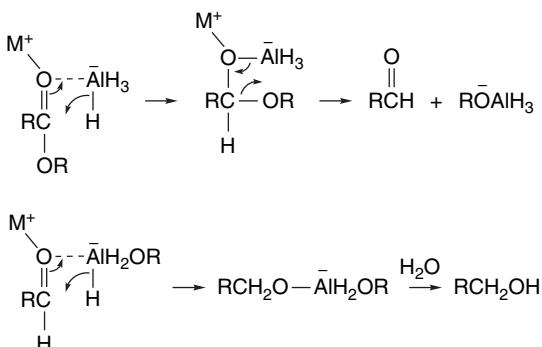
As all four of the hydrides can eventually be transferred, there are actually several distinct reducing agents functioning during the course of the reaction.⁶⁰ Although this somewhat complicates interpretation of rates and stereoselectivity, it does not detract from the synthetic utility of these reagents. Reduction with NaBH₄ is usually done in aqueous or alcoholic solution and the alkoxyboranes formed as intermediates are rapidly solvolyzed.



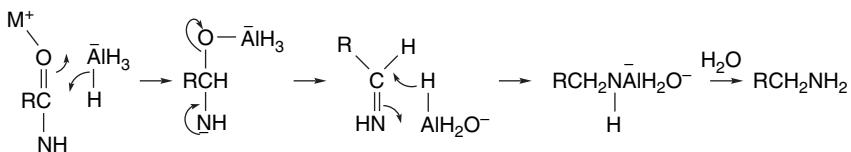
The mechanism for reduction by LiAlH₄ is very similar. However, since LiAlH₄ reacts very rapidly with protic solvents to form molecular hydrogen, reductions with this reagent must be carried out in aprotic solvents, usually ether or tetrahydrofuran.

⁶⁰. B. Rickborn and M. T. Wuesthoff, *J. Am. Chem. Soc.*, **92**, 6894 (1970).

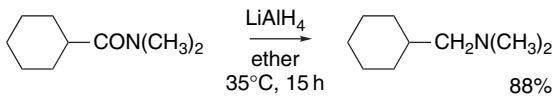
The products are liberated by hydrolysis of the aluminum alkoxide at the end of the reaction. Lithium aluminum hydride reduction of esters to alcohols involves an elimination step in addition to hydride transfers.



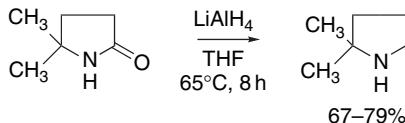
Amides are reduced to amines because the nitrogen is a poorer leaving group than oxygen at the intermediate stage of the reduction. Primary and secondary amides are rapidly deprotonated by the strongly basic LiAlH_4 , so the addition step involves the conjugate base.



Reduction of amides by LiAlH_4 is an important method for the synthesis of amines.



Ref. 61



Ref. 62

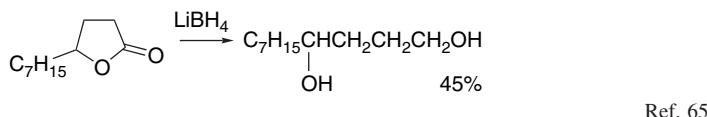
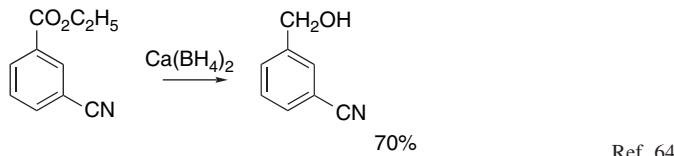
Several factors affect the reactivity of the boron and aluminum hydrides, including the metal cation present and the ligands, in addition to hydride, in the complex hydride. Some of these effects can be illustrated by considering the reactivity of ketones and aldehydes toward various hydride transfer reagents. Comparison of LiAlH_4 and NaAlH_4 has shown the former to be more reactive,⁶³ which is attributed to the greater

⁶¹ A. C. Cope and E. Ciganek, *Org. Synth.*, **IV**, 339 (1963).

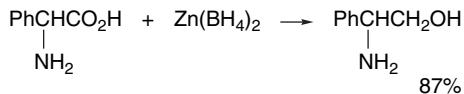
⁶² R. B. Moffett, *Org. Synth.*, **IV**, 354 (1963).

⁶³ E. C. Ashby and J. R. Boone, *J. Am. Chem. Soc.*, **98**, 5524 (1976); J. S. Cha and H. C. Brown, *J. Org. Chem.*, **58**, 4727 (1993).

Lewis acid strength and hardness of the lithium cation. Both LiBH_4 and $\text{Ca}(\text{BH}_4)_2$ are more reactive than sodium borohydride. This enhanced reactivity is due to the greater Lewis acid strength of Li^+ and Ca^{2+} , compared with Na^+ . Both of these reagents can reduce esters and lactones efficiently.



Zinc borohydride, which is also a useful reagent,⁶⁶ is prepared by reaction of ZnCl_2 with NaBH_4 in THF. Owing to the stronger Lewis acid character of Zn^{2+} , $\text{Zn}(\text{BH}_4)_2$ is more reactive than NaBH_4 toward esters and amides and reduces them to alcohols and amines, respectively.⁶⁷ $\text{Zn}(\text{BH}_4)_2$ reduces carboxylic acids to primary alcohols.⁶⁸ The reagent also smoothly reduces α -aminoacids to β -aminoalcohols.⁶⁹



Sodium borohydride is sometimes used in conjunction with CeCl_3 (*Luche's reagent*).⁷⁰ The active reductants under these conditions are thought to be alkoxyborohydrides. Sodium cyanoborohydride is a useful derivative of sodium borohydride.⁷¹ The electron-attracting cyano substituent reduces reactivity and only iminium groups are rapidly reduced by this reagent.

Alkylborohydrides are also used as reducing agents. These compounds have greater steric demands than the borohydride ion and therefore are more stereoselective in situations in which steric factors come into play.⁷² These compounds are prepared by reaction of trialkylboranes with lithium, sodium, or potassium hydride.⁷³ Several of the compounds are available commercially under the trade name Selectrides®.⁷⁴

⁶⁴ H. C. Brown, S. Narasimhan, and Y. M. Choi, *J. Org. Chem.*

⁶⁵ K. Soai and S. Ookawa, *J. Org. Chem.*, **51**, 4000 (1986).

⁶⁶ S. Narasimhan and R. Balakumar, *Aldrichimica Acta*, **31**, 19 (1998).

⁶⁷ S. Narasimhan, S. Madhavan, R. Balakumar, and S. Swamalakshmi, *Synth. Commun.*, **27**, 391 (1997).

⁶⁸ S. Narasimhan, S. Madhavan, and K. G. Prasad, *J. Org. Chem.*, **60**, 5314 (1995); B. C. Ranue and A. R. Das, *J. Chem. Soc., Perkin Trans. I*, 1561 (1992).

⁶⁹ S. Narasimhan, S. Madhavan, and K. G. Prasad, *Synth. Commun.*, **26**, 703 (1996).

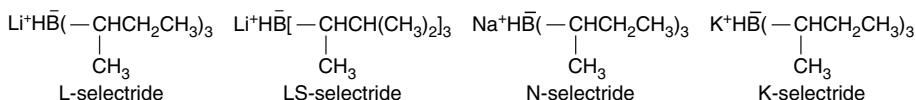
⁷⁰ A. C. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, **103**, 5454 (1981).

⁷¹ C. F. Lane, *Synthesis*, 135 (1975).

⁷² H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972); S. Krishnamurthy and H. C. Brown, *J. Am. Chem. Soc.*, **98**, 3383 (1976).

⁷³ H. C. Brown, S. Krishnamurthy, and J. L. Hubbard, *J. Am. Chem. Soc.*, **100**, 3343 (1978).

⁷⁴ Selectride is a trade name of the Aldrich Chemical Company.

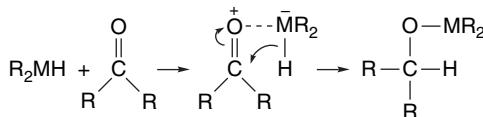


Derivatives of aluminum hydrides in which one or more of the hydrides is replaced by an alkoxide ion can be prepared by addition of the calculated amount of the appropriate alcohol.



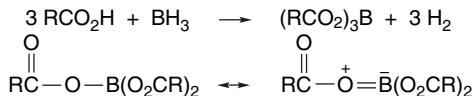
These reagents generally show increased solubility in organic solvents, particularly at low temperatures, and are useful in certain selective reductions.⁷⁵ Lithium tri-*t*-butoxyaluminum hydride and sodium *bis*-(2-methoxyethoxy)aluminum hydride (Red-Al)⁷⁶ are examples of these types of reagents that have synthetic use. Their reactivity toward carbonyl groups is summarized in Table 5.3.

Closely related to, but distinct from, the anionic boron and aluminum hydrides are the neutral boron (borane, BH_3) and aluminum (alane, AlH_3) hydrides. These molecules also contain hydrogen that can be transferred as hydride. Borane and alane differ from the anionic hydrides in being electrophilic species by virtue of the vacant *p* orbital and are Lewis acids. Reduction by these molecules occurs by an intramolecular hydride transfer in a Lewis acid-base complex of the reactant and reductant.



Alkyl derivatives of boron and alane can function as reducing reagents in a similar fashion. Two reagents of this type, disiamylborane and diisobutylaluminum hydride (DiBALH) are included in Table 5.3. The latter is an especially useful reagent.

Diborane also has a useful pattern of selectivity. It reduces carboxylic acids to primary alcohols under mild conditions that leave esters unchanged.⁷⁷ Nitro and cyano groups are relatively unreactive toward diborane. The rapid reaction between carboxylic acids and diborane is the result of formation of a triacyloxyborane intermediate by protonolysis of the B–H bonds. The resulting compound is essentially a mixed anhydride of the carboxylic acid and boric acid in which the carbonyl groups have enhanced reactivity toward borane or acetoxyborane.



Diborane also reduces amides to amines (see Section 5.3.1.2).

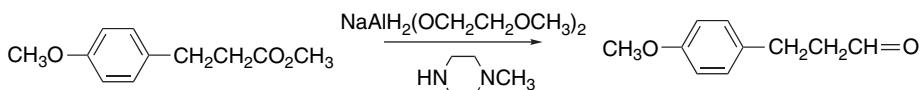
⁷⁵ J. Malek and M. Cerny, *Synthesis*, 217 (1972); J. Malek, *Org. React.*, **34**, 1 (1985).

⁷⁶ Red-Al is a trademark of the Aldrich Chemical Company.

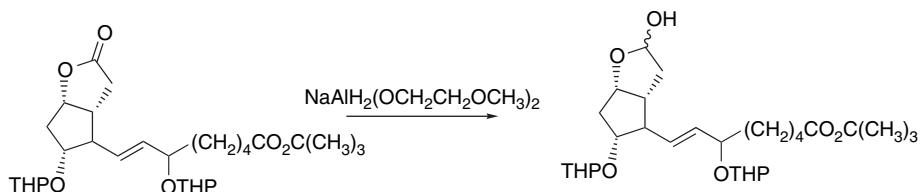
⁷⁷ N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, and T. P. Stocky, *J. Org. Chem.*, **38**, 2786 (1973).

In synthesis, the principal factors that affect the choice of a reducing agent are selectivity among functional groups (chemoselectivity) and stereoselectivity. Chemoselectivity can involve two issues. One may wish to effect a *partial reduction* of a particular functional group or it may be necessary to *reduce one group in preference to another*.⁷⁸ In the sections that follow, we consider some synthetically useful partial and selective reductions.

5.3.1.1. Partial Reduction of Carboxylic Acid Derivatives. One of the more difficult partial reductions is the conversion of a carboxylic acid derivative to an aldehyde without overreduction to the alcohol. Aldehydes are inherently more reactive than acids or esters, so the challenge is to stop the reduction at the aldehyde stage. Several approaches have been used to achieve this objective. One is to replace some of the hydrogens in the hydride with more bulky groups, thus modifying reactivity by steric factors. Lithium tri-*t*-butoxyaluminum hydride is an example of this approach.⁷⁹ Sodium tri-*t*-butoxyaluminum hydride can be used to reduce acid chlorides to aldehydes without overreduction to the alcohol.⁸⁰ The excellent solubility of sodium *bis*-(2-methoxyethoxy)aluminum hydride (Red-Al) makes it a useful reagent for selective reductions. The reagent is soluble in toluene even at -70°C, and selectivity is enhanced by the low temperature. It is possible to reduce esters to aldehydes and lactones to lactols with this reagent.



Ref. 81



Ref. 82

The most widely used reagent for partial reduction of esters and lactones at the present time is diisobutylaluminum hydride (DiBAIH).⁸³ By use of a controlled amount of the reagent at low temperature, partial reduction can be reliably achieved. The selectivity results from the relative stability of the hemiacetal intermediate that is formed. The aldehyde is not liberated until the hydrolytic workup and is therefore not

⁷⁸ For more complete discussion of functional group selectivity of hydride reducing agents, see E. R. H. Walter, *Chem. Soc. Rev.*, **5**, 23 (1976).

⁷⁹ H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **80**, 5377 (1958).

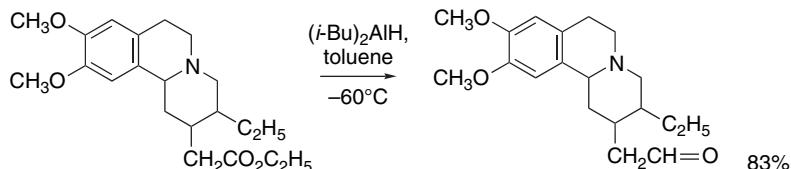
⁸⁰ J. S. Cha and H. C. Brown, *J. Org. Chem.*, **58**, 4732 (1993).

⁸¹ R. Kanazawa and T. Tokoroyama, *Synthesis*, 526 (1976).

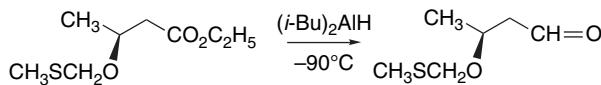
⁸² H. Disselkoetter, F. Lieb, H. Oediger, and D. Wendisch, *Liebigs Ann. Chem.*, 150 (1982).

⁸³ F. Winterfeldt, *Synthesis*, 617 (1975); N. M. Yoon and Y. G. Gyoung, *J. Org. Chem.*, **50**, 2443 (1985).

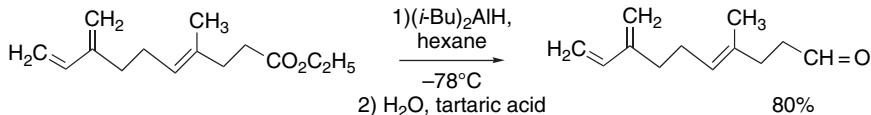
subject to overreduction. At higher temperatures, where the intermediate undergoes elimination, diisobutylaluminum hydride reduces esters to primary alcohols.



Ref. 84

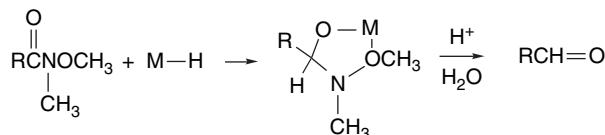


Ref. 85

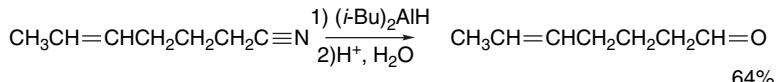


Ref. 86

Selective reduction to aldehydes can also be achieved using *N*-methoxy-*N*-methylamides.⁸⁷ LiAlH₄ and DiBAIH have both been used as the hydride donor. The partial reduction is again the result of the stability of the initial reduction product. The *N*-methoxy substituent leads to a chelated structure that is stable until acid hydrolysis occurs during workup.



Another useful approach to aldehydes is by partial reduction of nitriles to imines. The reduction stops at the imine stage because of the low electrophilicity of the deprotonated imine intermediate. The imines are then hydrolyzed to the aldehyde. Diisobutylaluminum hydride seems to be the best reagent for this purpose.^{88,89}



⁸⁴ C. Szantay, L. Toke, and P. Kolonits, *J. Org. Chem.*, **31**, 1447 (1966).

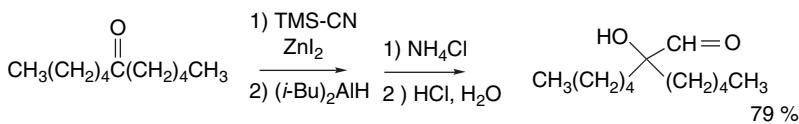
⁸⁵ G. E. Keck, E. P. Boden, and M. R. Wiley, *J. Org. Chem.*, **54**, 896 (1989).

⁸⁶ P. Baeckstrom, L. Li, M. Wickramaratne, and T. Norin, *Synth. Commun.*, **20**, 423 (1990).

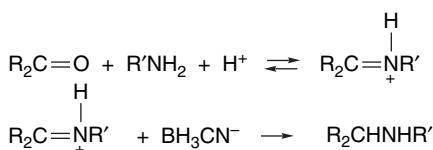
⁸⁷ S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, **22**, 3815 (1981).

⁸⁸ N. A. LeBel, M. E. Post, and J. J. Wang, *J. Am. Chem. Soc.*, **86**, 3759 (1964).

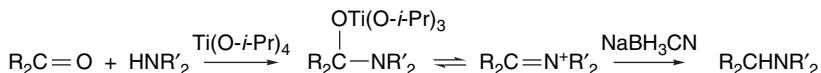
⁸⁹ R. V. Stevens and J. T. Lai, *J. Org. Chem.*, **37**, 2138 (1972); S. Trofimenko, *J. Org. Chem.*, **29**, 3046 (1964).



5.3.1.2. Reduction of Imines and Amides to Amines. A second type of chemoselectivity arises in the context of the need to reduce one functional group in the presence of another. If the group to be reduced is more reactive than the one to be left unchanged, it is simply a matter of choosing a reducing reagent with the appropriate level of reactivity. Sodium borohydride, for example, is very useful in this respect since it reduces ketones and aldehydes much more rapidly than esters. Sodium cyanoborohydride is used to reduce imines to amines, but this reagent is only reactive toward iminium ions. At pH 6–7, NaBH_3CN is essentially unreactive toward carbonyl groups. When an amine and ketone are mixed together, equilibrium is established with the imine. At mildly acidic pH only the protonated imine is reactive toward NaBH_3CN .⁹¹ This process is called *reductive amination*.



Reductive amination by NaBH_3CN can also be carried out in the presence of Ti(O-i-Pr)_4 . These conditions are especially useful for situations in which it is not practical to use the amine in excess (as is typically done under the acid-catalyzed conditions) or for acid-sensitive compounds. The Ti(O-i-Pr)_4 may act as a Lewis acid in generation of a tetrahedral adduct, which then may be reduced directly or via a transient iminium intermediate.⁹²



Sodium triacetoxyborohydride is an alternative to NaBH_3CN for reductive amination. This reagent can be used with a wide variety of aldehydes or ketones with primary and secondary amines, including aniline derivatives.⁹³ This reagent has been used successfully to alkylate amino acid esters.⁹⁴

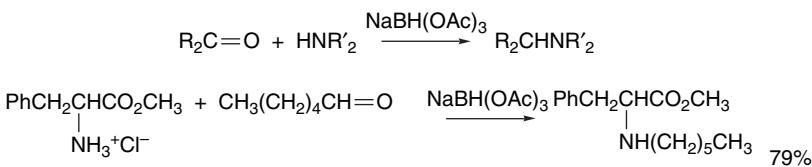
⁹⁰ M. Hayashi, T. Yoshiga, and N. Oguni, *Synlett*, 479 (1991).

⁹¹ R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, **93**, 2897 (1971).

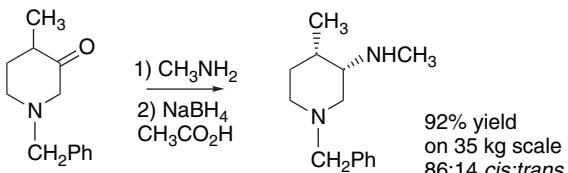
⁹² R. J. Mattson, K. M. Pham, D. J. Leuck, and K. A. Cowen, *J. Org. Chem.*, **55**, 2552 (1990).

⁹³ A. F. Abdel-Magid, K. G. Carson, B. H. Harris, C. A. Maryanoff, and R. D. Shah, *J. Org. Chem.*, **61**, 3849 (1996).

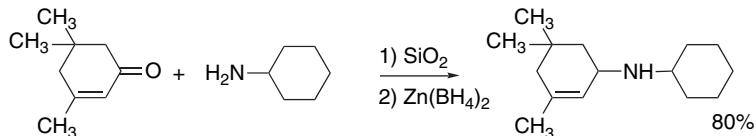
⁹⁴ J. M. Ramanjulu and M. M. Joullie, *Synth. Commun.*, **26**, 1379 (1996).



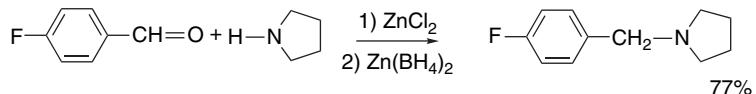
This method was used in a large-scale synthesis of 1-benzyl-3-methylamino-4-methylpiperidine.⁹⁵



Zinc borohydride has been found to effect very efficient reductive amination in the presence of silica. The amine and carbonyl compound are mixed with silica and the powder is then treated with a solution of $\text{Zn}(\text{BH}_4)_2$. Excellent yields are also obtained for unsaturated aldehydes and ketones.⁹⁶



Aromatic aldehydes can be reductively aminated with the combination $\text{Zn}(\text{BH}_4)_2\text{-ZnCl}_2$,⁹⁷ and the ZnCl_2 assists in imine formation.



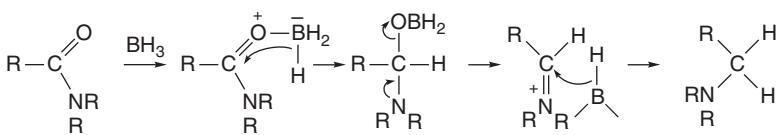
Amides are usually reduced to amines using LiAlH_4 . Amides require vigorous reaction conditions for reduction by LiAlH_4 , so that little selectivity can be achieved with this reagent. Diborane is also a useful reagent for reducing amides. Tertiary and secondary amides are easily reduced, but primary amides react only slowly.⁹⁸ The electrophilicity of borane is involved in the reduction of amides. The boron complexes at the carbonyl oxygen, enhancing the reactivity of the carbonyl center.

⁹⁵ D. H. B. Ripin, S. Abele, W. Cai, T. Blumenkopf, J. M. Casavant, J. L. Doty, M. Flanagan, C. Koecher, K. W. Laue, K. McCarthy, C. Meltz, M. Munchoff, K. Pouwer, B. Shah, J. Sun, J. Teixeira, T. Vries, D. A. Whipple, and G. Wilcox, *Org. Proc. Res. Dev.*, **7**, 115 (2003).

96. B. C. Ranu, A. Majee, and A. Sarkar, *J. Org. Chem.*, **63**, 370 (1998).

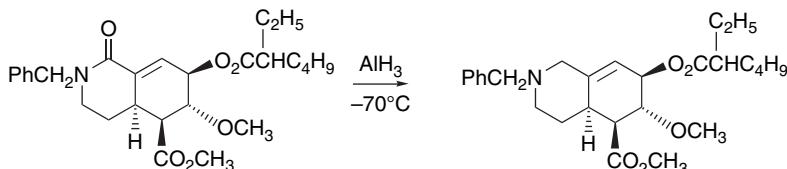
97. S. Bhattacharyya, A. Chatterjee, and J. S. Williamson, *Synth. Commun.*, **27**, 4265 (1997).

⁹⁸. H. C. Brown and P. Heim, *J. Org. Chem.*, **38**, 912 (1973).



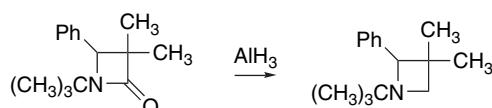
Diborane permits the selective reduction of amides in the presence of ester and nitro groups.

Alane is also a useful group for reducing amides and it, too, can be used to reduce amides to amines in the presence of ester groups.



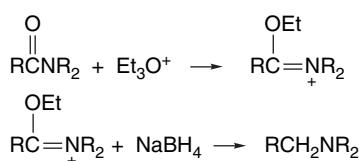
Ref. 99

The electrophilicity of alane is the basis for its selective reaction with the amide group. Alane is also useful for reducing azetidinones to azetidines. Most nucleophilic hydride reducing agents lead to ring-opened products. DiBAIH, AlH₂Cl, and AlHCl₂ can also reduce azetinones to azetidines.¹⁰⁰



Ref. 101

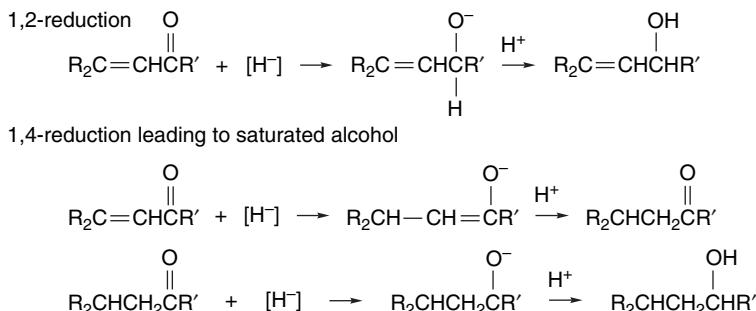
Another approach to reduction of an amide group in the presence of other groups that are more easily reduced is to convert the amide to a more reactive species. One such method is conversion of the amide to an O-alkyl derivative with a positive charge on nitrogen.¹⁰² This method has proven successful for tertiary and secondary, but not primary, amides.



Other compounds that can be readily derived from amides that are more reactive toward hydride reducing agents are α -alkylthioimmonium ions¹⁰³ and α -chloroimmonium ions.¹⁰⁴

- ^{99.} S. F. Martin, H. Rueger, S. A. Williamson, and S. Grzejszczak, *J. Am. Chem. Soc.*, **109**, 6124 (1987).
- ^{100.} I. Ojima, M. Zhao, T. Yamamoto, K. Nakanishi, M. Yamashita, and R. Abe, *J. Org. Chem.*, **56**, 5263 (1991).
- ^{101.} M. B. Jackson, L. N. Mander, and T. M. Spotswood, *Aust. J. Chem.*, **36**, 779 (1983).
- ^{102.} R. F. Borch, *Tetrahedron Lett.*, 61 (1968).
- ^{103.} S. Raucher and P. Klein, *Tetrahedron Lett.*, 4061 (1980); R. J. Sundberg, C. P. Walters, and J. D. Bloom, *J. Org. Chem.*, **46**, 3730 (1981).
- ^{104.} M. E. Kuehne and P. J. Shannon, *J. Org. Chem.*, **42**, 2082 (1972).

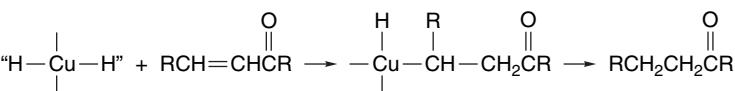
5.3.1.3. Reduction of α,β -Unsaturated Carbonyl Compounds. An important case of chemoselectivity arises in the reduction of α,β -unsaturated carbonyl compounds. Reaction can occur at the carbonyl group, giving an allylic alcohol or at the double bond giving a saturated ketone. These alternative reaction modes are called 1,2- and 1,4-reduction, respectively. If hydride is added at the carbonyl group, the allylic alcohol is usually not susceptible to further reduction. If a hydride is added at the β -position, the initial product is an enolate. In protic solvents this leads to the ketone, which can be reduced to the saturated alcohol. Both NaBH_4 and LiAlH_4 have been observed to give both types of product, although the extent of reduction to saturated alcohol is usually greater with NaBH_4 .¹⁰⁵



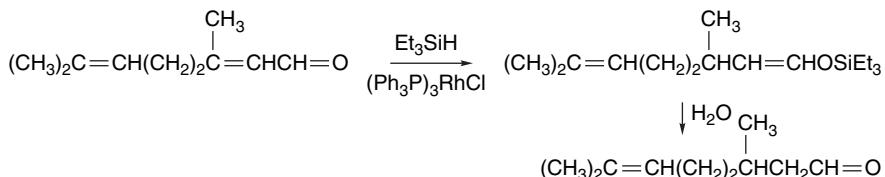
Several reagents have been developed that lead to exclusive 1,2- or 1,4-reduction. Use of NaBH_4 in combination with cerium chloride (*Luche reagent*) results in clean 1,2-reduction.¹⁰⁶ DiBAIH¹⁰⁷ and the dialkylborane 9-BBN¹⁰⁸ also give exclusive carbonyl reduction. In each case the reactivity of the carbonyl group is enhanced by a Lewis acid complexation at oxygen.

Selective reduction of the carbon-carbon double bond can usually be achieved by catalytic hydrogenation. A series of reagents prepared from a hydride reducing agent and copper salts also gives primarily the saturated ketone.¹⁰⁹ Similar reagents have been shown to reduce α,β -unsaturated esters¹¹⁰ and nitriles¹¹¹ to the corresponding saturated compounds. The mechanistic details are not known with certainty, but it is likely that “copper hydrides” are the active reducing agents and that they form an organocupper intermediate by conjugate addition.

- ¹⁰⁵ M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970); W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965).
- ¹⁰⁶ J.-L. Luche, *J. Am. Chem. Soc.*, **100**, 2226 (1978); J.-L. Luche, L. Rodriguez-Hahn, and P. Crabbe, *J. Chem. Soc., Chem. Commun.*, 601 (1978).
- ¹⁰⁷ K. E. Wilson, R. T. Seidner, and S. Masamune, *J. Chem. Soc., Chem. Commun.*, 213 (1970).
- ¹⁰⁸ K. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **42**, 1197 (1977).
- ¹⁰⁹ S. Masamune, G. S. Bates, and P. E. Georghiou, *J. Am. Chem. Soc.*, **96**, 3686 (1974); E. C. Ashby, J.-J. Lin, and R. Kovar, *J. Org. Chem.*, **41**, 1939 (1976); E. C. Ashby, J.-J. Lin, and A. B. Goel, *J. Org. Chem.*, **43**, 183 (1978); W. S. Mahoney, D. M. Brestensky, and J. M. Stryker, *J. Am. Chem. Soc.*, **110**, 291 (1988); D. M. Brestensky, D. E. Huseland, C. McGettigan, and J. M. Stryker, *Tetrahedron Lett.*, **29**, 3749 (1988); T. M. Koenig, J. F. Daeuble, D. M. Brestensky, and J. M. Stryker, *Tetrahedron Lett.*, **31**, 3237 (1990).
- ¹¹⁰ M. F. Semmelhack, R. D. Stauffer, and A. Yamashita, *J. Org. Chem.*, **42**, 3180 (1977).
- ¹¹¹ M. E. Osborn, J. F. Pegues, and L. A. Paquette, *J. Org. Chem.*, **45**, 167 (1980).

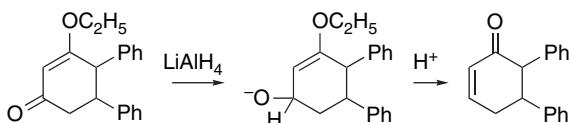


Combined use of $\text{Co}(\text{acac})_2$ and DiBALH also gives selective reduction for α,β -unsaturated ketones, esters, and amides.¹¹² Another reagent combination that selectively reduces the carbon-carbon double bond is Wilkinson's catalyst and triethylsilane. The initial product is the enol silyl ether.¹¹³



Unconjugated double bonds are unaffected by this reducing system.¹¹⁴

The enol ethers of β -dicarbonyl compounds are reduced to α,β -unsaturated ketones by LiAlH_4 , followed by hydrolysis.¹¹⁵ Reduction stops at the allylic alcohol, but subsequent acid hydrolysis of the enol ether and dehydration leads to the isolated product. This reaction is a useful method for synthesis of substituted cyclohexenones.



5.3.2. Stereoselectivity of Hydride Reduction

5.3.2.1. Cyclic Ketones. Stereoselectivity is a very important aspect of reductions by hydride transfer reagents. The stereoselectivity of the reduction of carbonyl groups is affected by the same combination of steric and stereochemical factors that control the addition of other nucleophiles, such as enolates and organometallic reagents to carbonyl groups. A general discussion of these factors is given in Section 2.4.1 of Part A. The stereochemistry of hydride reduction has been thoroughly studied with conformationally biased cyclohexanones. Some reagents give predominantly axial cyclohexanols, whereas others give the equatorial isomer. Axial alcohols are most likely to be formed when the reducing agent is a sterically hindered hydride donor because the equatorial direction of approach is more open and is preferred by bulky reagents. This is called *steric approach control*.¹¹⁶

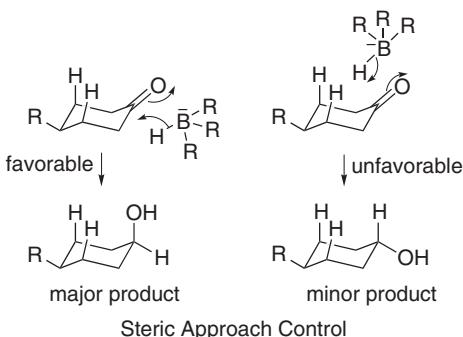
¹¹² T. Ikeno, T. Kimura, Y. Ohtsuka, and T. Yamada, *Synlett*, 96 (1999).

¹¹³ I. Ojima, T. Kogure, and Y. Nagai, *Tetrahedron Lett.*, 5035 (1972); I. Ojima, M. Nihonyanagi, T. Kogure, M. Kumagai, S. Horiuchi, K. Nakatsugawa, and Y. Nogai, *J. Organomet. Chem.*, **94**, 449 (1973).

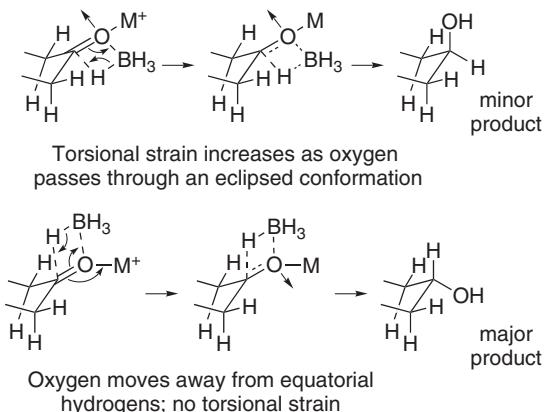
¹¹⁴ H.-J. Liu and E. N. C. Browne, *Can. J. Chem.*, **59**, 601 (1981); T. Rosen and C. H. Heathcock, *J. Am. Chem. Soc.*, **107**, 3731 (1985).

¹¹⁵ H. E. Zimmerman and D. I. Schuster, *J. Am. Chem. Soc.*, **84**, 4527 (1962); W. F. Gannon and H. O. House, *Org. Synth.*, **40**, 14 (1960).

¹¹⁶ W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).



With less hindered hydride donors, particularly NaBH_4 and LiAlH_4 , conformationally biased cyclohexanones give predominantly the equatorial alcohol, which is normally the more stable of the two isomers. However, hydride reductions are exothermic reactions with low activation energies. The TS should resemble starting ketone, so product stability should not control the stereoselectivity. A major factor in the preference for the equatorial isomer is the torsional strain that develops in the formation of the axial alcohol.¹¹⁷



An alternative interpretation is that the carbonyl group π -antibonding orbital, which acts as the LUMO in the reaction, has a greater density on the axial face.¹¹⁸ At the present time the importance of such orbital effects is not entirely clear. Most of the stereoselectivities that have been reported can be reconciled with torsional and steric effects being dominant.¹¹⁹

A large amount of data has been accumulated on the stereoselectivity of reduction of cyclic ketones.¹²⁰ Table 5.4 compares the stereoselectivity of reduction of several ketones by hydride donors of increasing steric bulk. The trends in the table illustrate

¹¹⁷. M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2205 (1968); M. Cherest and H. Felkin, *Tetrahedron Lett.*, 383 (1971).

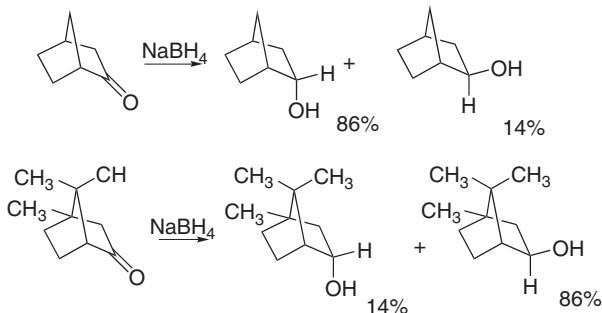
¹¹⁸. J. Klein, *Tetrahedron Lett.*, 4307 (1973); N. T. Ahn, O. Eisenstein, J.-M. Lefour, and M. E. Tran Huu Dau, *J. Am. Chem. Soc.*, **95**, 6146 (1973).

¹¹⁹. W. T. Wipke and P. Gund, *J. Am. Chem. Soc.*, **98**, 8107 (1976); J.-C. Perlberger and P. Mueller, *J. Am. Chem. Soc.*, **99**, 6316 (1977); D. Mukherjee, Y.-D. Wu, F. R. Fronczek, and K. N. Houk, *J. Am. Chem. Soc.*, **110**, 3328 (1988).

¹²⁰. D. C. Wigfield, *Tetrahedron*, **35**, 449 (1979); D. C. Wigfield and D. J. Phelps, *J. Org. Chem.*, **41**, 2396 (1976).

the increasing importance of steric approach control as both the hydride reagent and the ketone become more highly substituted. The alkyl borohydrides have especially high selectivity for the least hindered direction of approach.

When a ketone is relatively hindered, as, for example, in the bicyclo[2.2.1]heptan-2-one system, steric approach control governs stereoselectivity even for small hydride donors.



The $\text{NaBH}_4\text{-CeCl}_3$ reagent has been observed to give hydride delivery from the more hindered face of certain bicyclic ketones.¹²¹

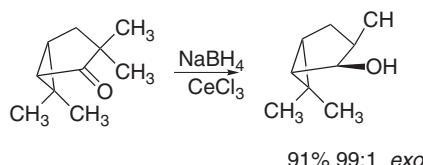


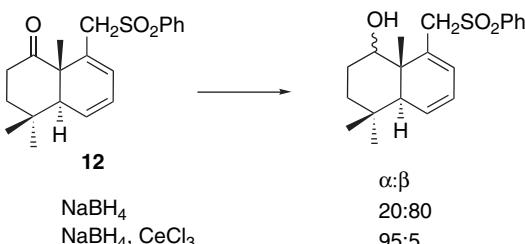
Table 5.4. Stereoselectivity of Hydride Reducing Agent

Reducing agent	(CH ₃) ₃ C	O	O	O	O
	% axial	% axial	% axial	% endo	% exo
NaBH_4	20 ^b	25 ^c	58 ^c	86 ^d	86 ^d
LiAlH_4	8	24	83	89	92
$\text{LiAl}(\text{OMe})_3\text{H}$	9	69	95	98	99
$\text{LiAl}(\text{OtBu})_3\text{H}$	9	35 ^f	99.8 ^g	94 ^f	94 ^f
L-Selectride	93 ^g	98 ^g		99.6 ^g	99.6 ^g
LS-Selectride	>99 ^h	>99 ^h		>99 ^h	NR ^h

- a. Except where noted otherwise, data are from H. C. Brown and W. D. Dickason, *J. Am. Chem. Soc.*, **92**, 709 (1970). Data for many other cyclic ketones and other reducing agents are given by A. V. Kameritzky and A. A. Akhrem, *Tetrahedron*, **18**, 705 (1962) and W. T. Wipke and P. Gund, *J. Am. Chem. Soc.*, **98**, 8107 (1976).
- b. P. T. Lansbury, and R. E. MacLeay, *J. Org. Chem.*, **28**, 1940 (1963).
- c. B. Rickborn and W. T. Wuesthoff, *J. Am. Chem. Soc.*, **92**, 6894 (1970).
- d. H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.*, **88**, 2811 (1966).
- e. J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Lett.*, 6127 (1968).
- f. E. C. Ashby, J. P. Sevenair, and F. R. Dobbs, *J. Org. Chem.*, **36**, 197 (1971).
- g. H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972).
- h. S. Krishnamurthy and H. C. Brown, *J. Am. Chem. Soc.*, **98**, 3383 (1976).

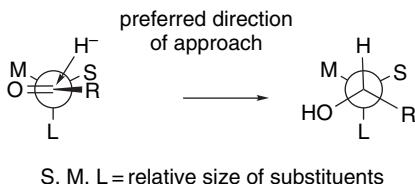
¹²¹ A. Krief and D. Surleraux, *Synlett*, 273 (1991).

Similarly, $\text{NaBH}_4\text{-CeCl}_3$ reverses the stereochemistry relative to NaBH_4 in the bicyclic ketone **12**.¹²²

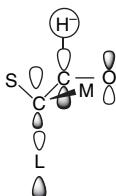


Thus, $\text{NaBH}_4\text{-CeCl}_3$ tends to give the *more stable* alcohol, but the origin of this stereoselectivity does not seem to have been established. It is thought that these reductions proceed through alkoxyborohydrides.¹²³ It is likely that equilibration occurs by reversible hydride transfer.

5.3.2.2. Acyclic Ketones. The stereochemistry of the reduction of acyclic aldehydes and ketones is a function of the substitution on the adjacent carbon atom and can be predicted on the basis of the Felkin conformational model of the TS,⁶³ which is based on a combination of steric and stereoelectronic effects.



From a purely steric standpoint, minimal interaction with the groups L and M by approaching from the direction of the smallest substituent is favorable. The stereoelectronic effect involves the interaction between the approaching hydride ion and the LUMO of the carbonyl group. This orbital, which accepts the electrons of the incoming nucleophile, is stabilized when the group L is perpendicular to the plane of the carbonyl group.¹²⁴ This conformation permits a favorable interaction between the LUMO and the antibonding σ^* orbital associated with the C–L bond.



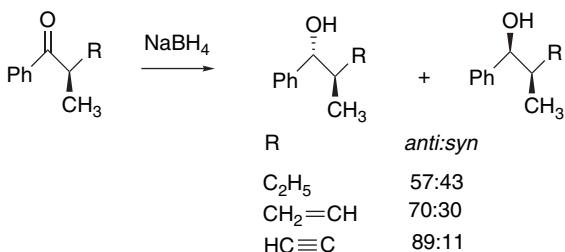
In the case of α -substituted phenyl ketones, the order of stereoselectivity is $\text{C}\equiv\text{CH} > \text{CH}=\text{CH}_2 > \text{CH}_2\text{CH}_3$.¹²⁵ These results indicate a stereoelectronic as well as a steric

¹²² M. Leclaire and P. Jean, *Bull. Soc. Chim. Fr.*, **133**, 801 (1996).

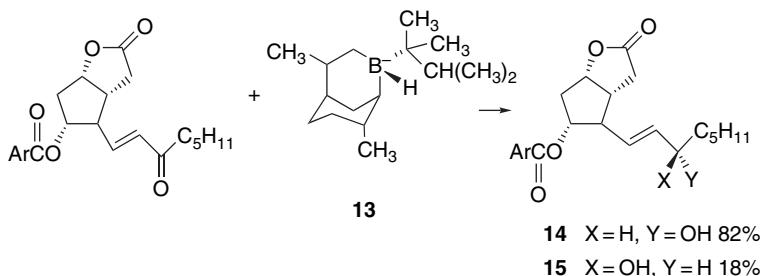
¹²³ A. C. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, **103**, 5454 (1981).

¹²⁴ N. T. Ahn, *Top. Current Chem.*, **88**, 145 (1980).

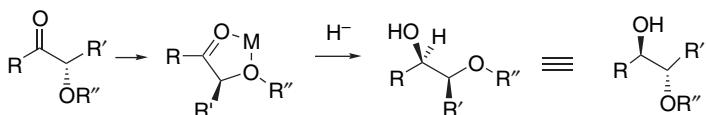
¹²⁵ M. Fujita, S. Akimoto, and K. Ogura, *Tetrahedron Lett.*, **34**, 5139 (1993).



Steric factors arising from groups that are more remote from the center undergoing reduction can also influence the stereochemical course of reduction. Such steric factors are magnified by use of bulky reducing agents. For example, a 4.5:1 preference for stereoisomer **14** over **15** is achieved by using the trialkylborohydride **13** as the reducing agent in the reduction of a prostaglandin intermediate.¹²⁶



5.3.2.3. Chelation Control. The stereoselectivity of reduction of carbonyl groups can be controlled by chelation when there is a nearby donor substituent. In the presence of such a group, specific complexation among the substituent, the carbonyl oxygen, and the Lewis acid can establish a preferred conformation for the reactant. Usually hydride is then delivered from the less sterically hindered face of the chelate so the hydroxy group is *anti* to the chelating substituent.



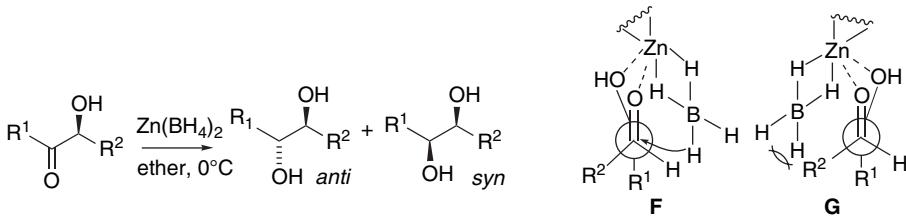
α -Hydroxy¹²⁷ and α -alkoxyketones¹²⁸ are reduced to *anti* 1,2-diols by $\text{Zn}(\text{BH}_4)_2$ through a chelated TS. This stereoselectivity is consistent with the preference for TS F

¹²⁶. E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Am. Chem. Soc.*, **93**, 1491 (1971).

¹²⁷. T. Nakata, T. Tanaka, and T. Oishi, *Tetrahedron Lett.*, **24**, 2653 (1983).

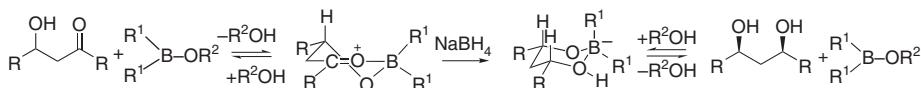
¹²⁸. G. J. McGarvey and M. Kimura, *J. Org. Chem.*, **47**, 5420 (1982).

over **G**. The stereoselectivity increases with the bulk of substituent R². LiAlH₄ shows the same trend, but is not as stereoselective.

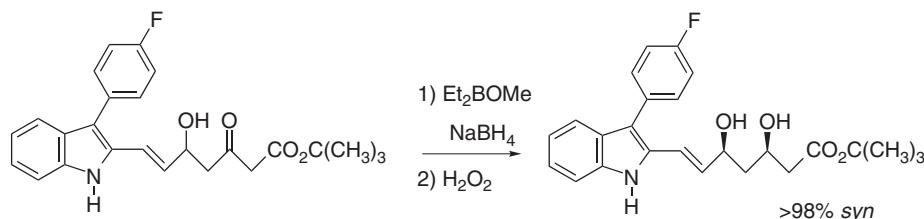


R ¹	R ²	Zn(BH ₄) ₂ <i>anti:syn</i>	LiAlH ₄ <i>anti:syn</i>
n-C ₅ H ₁₁	CH ₃	77:23	64:36
CH ₃	n-C ₅ H ₁₁	85:15	70:30
i-C ₃ H ₇	CH ₃	85:15	58:42
CH ₃	i-C ₃ H ₇	96:4	73:27
Ph	CH ₃	98:2	87:13
CH ₃	Ph	90:10	80:20

Reduction of β -hydroxy ketones through chelated TSs favors *syn*-1,3-diols. Boron chelates have been exploited to achieve this stereoselectivity.¹²⁹ One procedure involves *in situ* generation of diethylmethoxyboron, which then forms a chelate with the β -hydroxyketone. Reduction with NaBH₄ leads to the *syn*-diol.¹³⁰



This procedure was used in the synthesis of the cholesterol-reducing drug lescol.¹³¹ The diethylmethoxyboron can be prepared *in situ* from triethylboron and one equivalent of methanol.



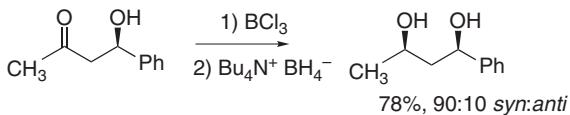
Syn-1,3-diols can be obtained from β -hydroxyketones using LiI-LiAlH₄ at low temperatures.¹³² β -Hydroxyketones also give primarily *syn*-1,3-diols when

¹²⁹ K. Narasaka and F.-C. Pai, *Tetrahedron*, **40**, 2233 (1984); K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repic, and M. J. Shapiro, *Tetrahedron Lett.*, **28**, 155 (1987).

¹³⁰ K.-M. Chen, K. G. Gunderson, G. E. Hardtmann, K. Prasad, O. Repic, and M. J. Shapiro, *Chem. Lett.*, 1923 (1987).

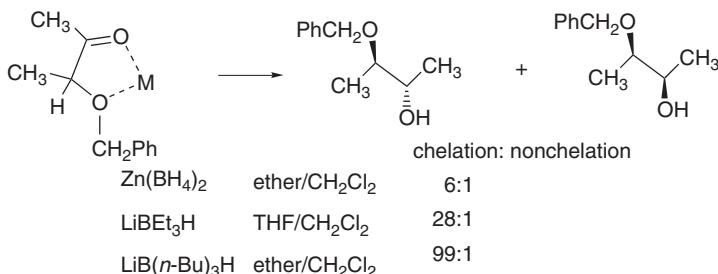
¹³¹ O. Repic, K. Prasad, and G. T. Lee, *Org. Proc. Res. Dev.*, **5**, 519 (2001).

¹³² Y. Mori, A. Takeuchi, H. Kageyama, and M. Suzuki, *Tetrahedron Lett.*, **29**, 5423 (1988).

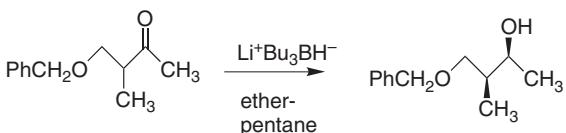


Similar results are obtained with β -methoxyketones using $TiCl_4$ as the chelating reagent.¹³⁴

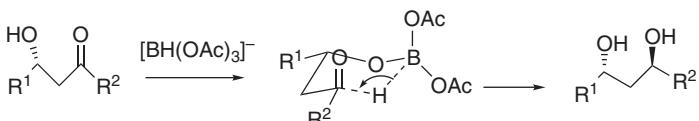
The effect of the steric bulk of the hydride reducing agent has been examined in the case of 3-benzyloxy-2-butanone.¹³⁵ The ratio of chelation-controlled product increased with the steric bulk of the reductant. This is presumably due to amplification of the steric effect of the methyl group in the chelated TS as the reductant becomes more sterically demanding. In these reactions, the degree of chelation control was also enhanced by use of CH_2Cl_2 as a cosolvent.



A survey of several of alkylborohydrides found that $LiBu_3BH$ in ether-pentane gave the best ratio of chelation-controlled reduction products from α - and β -alkoxy ketones.¹³⁴ In this case, the Li^+ cation acts as the Lewis acid. The alkylborohydrides provide an added increment of steric discrimination.



Tetramethylammonium triacetoxyborohydride gives *anti*-1,3-diols from β -hydroxy ketones.¹³⁶ These reactions are thought to occur by a rapid exchange that introduces the hydroxy group as a boron ligand.



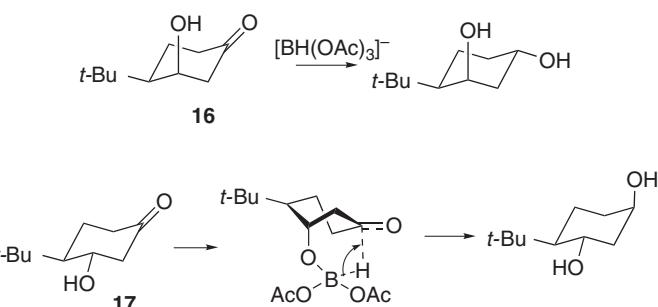
¹³³. C. R. Sarko, S. E. Collibee, A. L. Knorr, and M. DiMare, *J. Org. Chem.*, **61**, 868 (1996).

¹³⁴. C. R. Sarko, I. C. Guch, and M. DiMare, *J. Org. Chem.*, **59**, 705 (1994); G. Bartoli, M. C. Bellucci, M. Bosco, R. Dalpozzo, E. Marcantoni, and L. Sambri, *Tetrahedron Lett.*, **40**, 2845 (1999).

¹³⁵. A.-M. Faucher, C. Brochu, S. R. Landry, I. Duchesne, S. Hantos, A. Roy, A. Myles, and C. Legault, *Tetrahedron Lett.*, **39**, 8425 (1998).

¹³⁶. D. A. Evans, K. T. Chapman, and E. M. Carreira, *J. Am. Chem. Soc.*, **110**, 3560 (1988).

Similarly, cyclic ketones **16** and **17** both give the *trans*-diol, as anticipated for intramolecular delivery of hydride. In the case of the equatorial alcohol, the reaction must occur through a nonchair conformer.



In 2-hydroxy-2,4-dimethylcyclohexanone there is a strong preference for equatorial attack by LiAlH_4 , NaBH_4 , and $\text{Zn}(\text{BH}_4)_2$.¹³⁷ In the case of the less conformationally biased 2-hydroxy-2-methylcyclohexanone, stereoselectivity is much weaker for these reductants, but is high for $\text{NaB}(\text{OAc})_3\text{H}$. These results are attributed to prior complexation of the hydride at the hydroxy group with intramolecular delivery of hydride, leading to *anti*-diol. A 3-hydroxy substituent had a much weaker effect, except with $\text{NaB}(\text{OAc})_3\text{H}$. This reagent presumably reacts more rapidly with hydroxy groups because of the greater lability of the acetoxy substituents, and in this case the reagent becomes a better hydride donor by replacing acetoxy with an alkoxide.

	% anti-diol		% anti-diol
NaBH_4	100	NaBH_4	57
LiAlH_4	100	LiAlH_4	74
$\text{Zn}(\text{BH}_4)_2$	100	$\text{Zn}(\text{BH}_4)_2$	75
$\text{NaB}(\text{OAc})_3\text{H}$	100	$\text{NaB}(\text{OAc})_3\text{H}$	97

Similar studies were carried out with methoxycyclohexanones.¹³⁸ 3-Methoxy groups showed no evidence of chelation effects with these reagents and the 2-methoxy group showed an effect only with $\text{Zn}(\text{BH}_4)_2$. This supports the suggestion that the effect of the hydroxy groups operates through deprotonated alkoxide complexes.

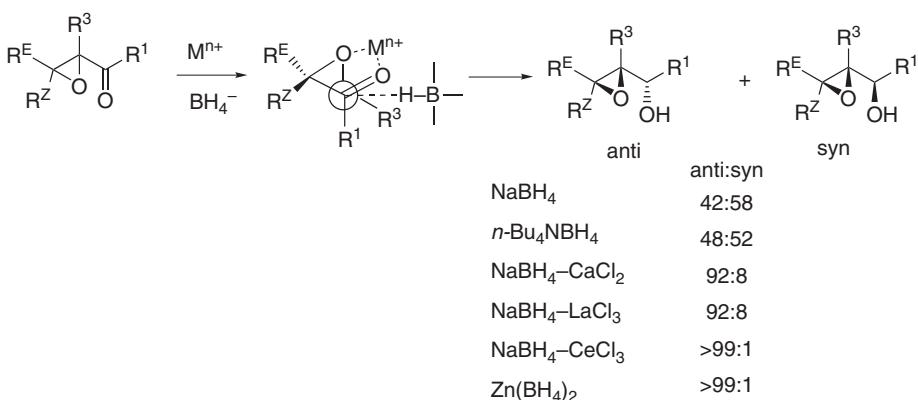
Chelation effects also come into play in the reduction of α,β -epoxyketones. Both CaCl_2 and LaCl_3 lead to enhanced *anti* stereoselectivity.¹³⁹ The same stereoselectivity is observed with CeCl_3 and with $\text{Zn}(\text{BH}_4)_2$.¹⁴⁰

¹³⁷ Y. Senda, N. Kikuchi, A. Inui, and H. Itoh, *Bull. Chem. Soc. Jpn.*, **73**, 237 (2000).

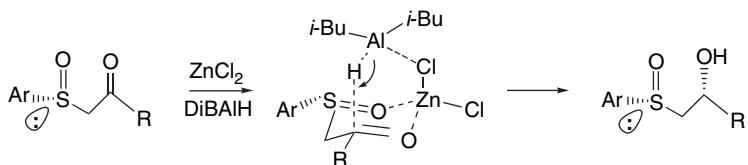
¹³⁸ Y. Senda, H. Sakurai, S. Nakano, and H. Itoh, *Bull. Chem. Soc. Jpn.*, **69**, 3297 (1996).

¹³⁹ M. Taniguchi, H. Fujii, K. Oshima, and K. Utimoto, *Tetrahedron*, **51**, 679 (1995).

¹⁴⁰ K. Li, L. G. Hamann, and M. Koreeda, *Tetrahedron Lett.*, **33**, 6569 (1992).

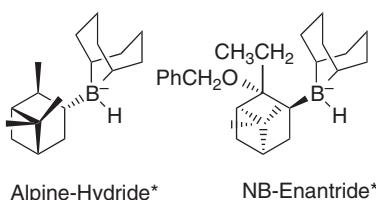


β -Ketosulfoxides are subject to chelation control when reduced by DiBAIH in the presence of $ZnCl_2$.¹⁴¹ This allows the use of chirality of the sulfoxide group to control the stereochemistry at the ketone carbonyl.



5.3.3. Enantioselective Reduction of Carbonyl Compounds

5.3.3.1. Reduction with Chiral Boranes. The reduction of an unsymmetrical ketone creates a new stereogenic center. Owing to the importance of hydroxy groups both in synthesis and in the properties of molecules, including biological activity, there has been a great deal of effort directed toward enantioselective reduction of ketones. One approach is to use chiral borohydride reagents.¹⁴² Boranes derived from chiral alkenes can be converted to alkylborohydrides, and several such reagents are commercially available.¹⁴³



Chloroboranes have also been found useful for enantioselective reduction. Di-(isopinocampheyl)chloroborane,¹⁴⁴ $(Ipc)_2BCl$, and *t*-butyl(isopinocampheyl)

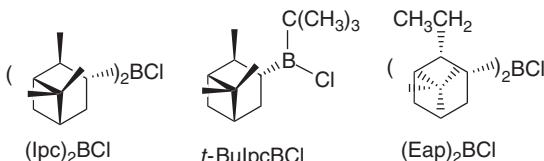
¹⁴¹ A. Solladie-Cavallo, J. Suffert, A. Adib, and G. Solladie, *Tetrahedron Lett.*, **31**, 6649 (1990).

¹⁴² M. M. Midland, *Chem. Rev.*, **89**, 1553 (1989).

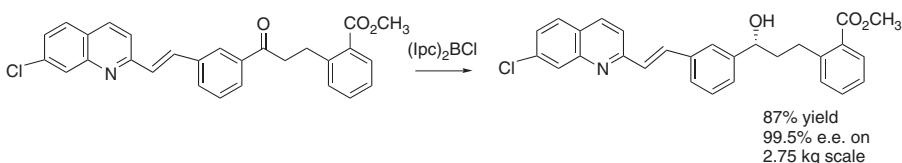
¹⁴³ Alpine-Hydride and NB-Enantride are trademarks of the Sigma-Aldrich Corporation.

¹⁴⁴ H. C. Brown, J. Chandrasekharan, and P. V. Ramachandran, *J. Am. Chem. Soc.*, **110**, 1539 (1988); M. Zhao, A. O. King, R. D. Larsen, T. R. Verhoeven, and P. J. Reider, *Tetrahedron Lett.*, **38**, 2641 (1997); N. N. Joshi, C. Pyun, V. K. Mahindroo, B. Singaram, and H. C. Brown, *J. Org. Chem.*, **57**, 504 (1992).

chloroborane¹⁴⁵ achieve high enantioselectivity for aryl and branched dialkyl ketones. Di-(iso-2-ethylapopinocampheyl)chloroborane,¹⁴⁶ (Eap)₂BCl, shows good enantioselectivity for a wider range of alcohols.



For example, (Ipc)₂BCl was found to be an advantageous in the enantioselective reduction in the large-scale preparation of L-699,392, a specific leukotriene antagonist of interest in the treatment of asthma.¹⁴⁷



These reagents react through cyclic TSs and regenerate an alkene.

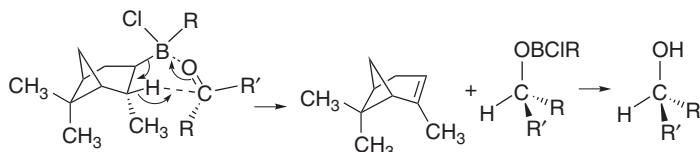
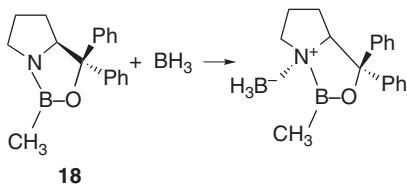


Table 5.5 gives some typical results for enantioselective reduction of ketones by alkylborohydrides and chloroboranes.

5.3.3.2. Catalytic Enantioselective Reduction of Ketones. An even more efficient approach to enantioselective reduction is to use a chiral catalyst. One of the most developed is the oxazaborolidine **18**, which is derived from the amino acid proline.¹⁴⁸ The enantiomer is also available. These catalysts are called the *CBS-oxazaborolidines*.



A catalytic amount (5–20 mol %) of the reagent, along with BH₃ as the reductant, can reduce ketones such as acetophenone and pinacolone in more than 95% e.e. An adduct of borane and **18** is the active reductant. This adduct can be prepared, stored,

¹⁴⁵ H. C. Brown, M. Srebnik, and P. V. Ramachandran, *J. Org. Chem.*, **54**, 1577 (1989).

¹⁴⁶ H. C. Brown, P. V. Ramachandran, A. V. Teodorovic, and S. Swaminathan, *Tetrahedron Lett.*, **32**, 6691 (1991).

¹⁴⁷ A. O. King, E. G. Corley, R. K. Anderson, R. D. Larsen, T. R. Verhoeven, P. J. Reider, Y. B. Xiang, M. Belley, Y. Leblanc, M. Labelle, P. Prasit, and R. J. Zamboni, *J. Org. Chem.*, **58**, 3731 (1993).

¹⁴⁸ E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen, and V. K. Singh, *J. Am. Chem. Soc.*, **109**, 7925 (1987); E. J. Corey and C. J. Helal, *Angew. Chem. Int. Ed. Engl.*, **37**, 1987 (1998); V. A. Glushkov and A. G. Tolstikov, *Russ. Chem. Rev.*, **73**, 581 (2004).

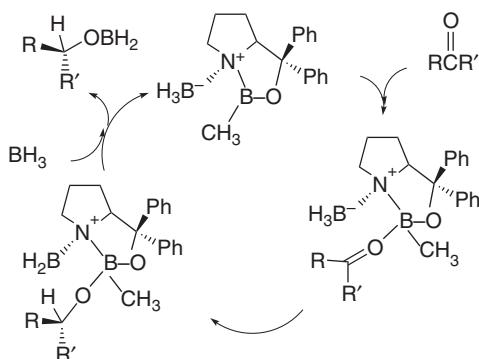
Table 5.5. Enantioselective Reduction of Ketones by Borohydrides and Chloroboranes

Reagent	Ketone	% e.e.	Configuration
Alpine-Hydride ^{a,b}	3-methyl-2-butanone	62	S
NB-Enantride ^{a,c}	2-octanone	79	S
(Ipc) ₂ BCl ^d	2-acetyl naphthalene	94	S
(tBu)(Ipc)BCl ^e	acetophenone	96	R
(Ipc) ₂ BCl ^f	2,2-dimethylcyclohexanone	91	S
(Eap) ₂ BCl ^g	3-methyl-2-butanone	95	R

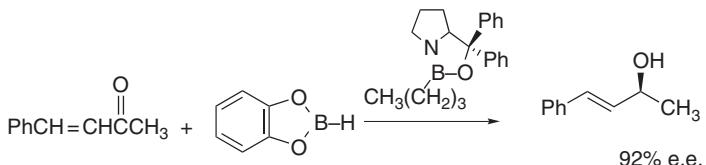
a. Trademark of Sigma-Aldrich Corporation.

b. H. C. Brown and G. G. Pai, *J. Org. Chem.*, **50**, 1384 (1985).c. M. M. Midland and A. Kozubski, *J. Org. Chem.*, **47**, 2495 (1982).d. M. Zhao, A. O. King, R. D. Larsen, T. R. Verhoeven, and A. J. Reider, *Tetrahedron Lett.*, **38**, 2641 (1997).e. H. C. Brown, M. Srebnik, and P. V. Ramachandran, *J. Org. Chem.*, **54**, 1577 (1989).f. H. C. Brown, J. Chandrasekharan, and P. V. Ramachandran, *J. Am. Chem. Soc.*, **110**, 1539 (1988).g. H. C. Brown, P. V. Ramachandran, A. V. Teodorovic, and S. Swaminathan, *Tetrahedron Lett.*, **32**, 6691 (1991).

and used as a stoichiometric reagent if so desired.¹⁴⁹ The catalytic cycle depends on dissociation of the reduced product.



The corresponding *N*-butyloxazaborolidine is also frequently used as a catalyst. The enantioselectivity and reactivity of these catalysts can be modified by changes in substituent groups to optimize selectivity toward a particular ketone.¹⁵⁰ Catecholborane can also be used as the reductant.¹⁵¹



Both mechanistic and computational studies have been used to explore the catalytic process. A crystal structure of the catalysts is available (Figure 5.7).¹⁵² The

¹⁴⁹. D. J. Mahre, A. S. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley, and E. J. J. Grabowski, *J. Org. Chem.*, **58**, 2880 (1993).

¹⁵⁰. A. W. Douglas, D. M. Tschaen, R. A. Reamer, and Y.-J. Shi, *Tetrahedron: Asymmetry*, **7**, 1303 (1996).

¹⁵¹. E. J. Corey and R. K. Bakshi, *Tetrahedron Lett.*, **31**, 611 (1990).

¹⁵². E. J. Corey, M. Azimiaora, and S. Sarshar, *Tetrahedron Lett.*, **33**, 3429 (1992).

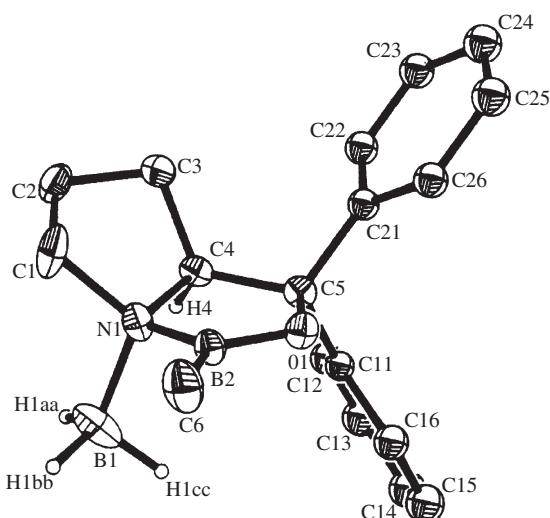
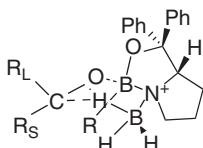


Fig. 5.7. Crystal structure of borane complex of α,α -diphenylprolinol oxazaborolidine catalysts. Reproduced from *Tetrahedron Lett.*, **33**, 3429 (1992), by permission of Elsevier.

orientation of the ketone is dictated by the phenyl groups and the relatively rigid geometry of the ring system. The enantioselectivity in these reductions is proposed to arise from a chairlike TS in which the governing steric interaction is with the alkyl substituent on boron.^{153,154} There are experimental data indicating that the steric demand of the boron substituent influences enantioselectivity.¹⁵⁴



There have been ab initio studies of the transition structure using several model catalysts and calculations at the HF/3-21G, HF/6-31G(*d*), and MP2/6-31G(*d*) levels.¹⁵⁵ The enantioselectivity is attributed to the preference for an *exo* rather than an *endo* approach of the ketone, as shown in Figure 5.8.

According to B3LYP/6-31G* computations of the intermediates and TSs, there are no large barriers to the reaction and it is strongly exothermic.¹⁵⁶ Measured E_a values are around 10 kcal/mol.¹⁵⁷ The complexation of borane to the catalyst shifts electron density from nitrogen to boron and enhances the nucleophilicity of the hydride. The

- ^{153.} D. K. Jones, D. C. Liotta, I. Shikai, and D. J. Mathre, *J. Org. Chem.*, **58**, 799 (1993).
- ^{154.} T. K. Jones, J. J. Mohan, L. C. Xavier, T. J. Blacklock, D. J. Mathre, P. Sohar, E. T. T. Jones, R. A. Beaner, F. E. Roberts, and E. J. J. Grabowski, *J. Org. Chem.*, **56**, 763 (1991).
- ^{155.} G. J. Quallich, J. F. Blake, and T. M. Woodall, *J. Am. Chem. Soc.*, **116**, 8516 (1994).
- ^{156.} G. Alagona, C. Ghio, M. Persico, and S. Tomas, *J. Am. Chem. Soc.*, **125**, 10027 (2003).
- ^{157.} H. Jockel, R. Schmidt, H. Jope, and H. G. Schmalz, *J. Chem. Soc., Perkin Trans. 2*, 69 (2000).

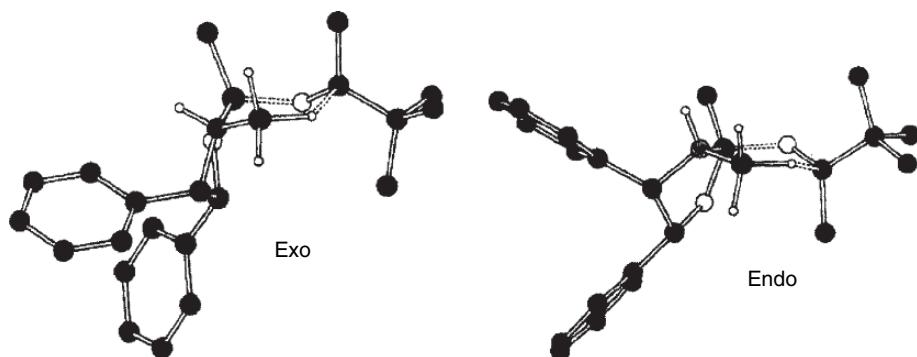
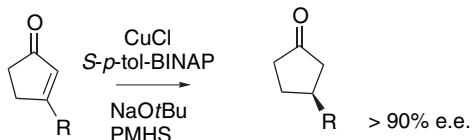


Fig. 5.8. Optimized (HF/3-21G) structures of the *exo* and *endo* transition states for reduction of *t*-butyl methyl ketone by model catalyst. The *exo* structure is favored by 2.1 kcal, in accord with an experimental e.e. of 88%. Reproduced from *J. Am. Chem. Soc.*, **116**, 8516 (1994), by permission of the American Chemical Society.

complexation also diminishes the N–B delocalization present in the oxazaborolidine ring, with the bond length increasing from 1.410 to 1.498 Å, according to the computations. The computed structural parameters are close to those found by crystallography.

Scheme 5.6 shows some examples of enantioselective reduction of ketones using CBS-oxazaborolidine catalysts. The reaction in Entry 1 was carried out in the course of synthesis of a potential drug candidate. Entry 2 employs the catalyst to achieve stereoselective reduction at the C(15) center in a prostaglandin precursor. Entries 3 and 4 report high enantioselectivity in the reduction of cyclic ketones. Entries 5 and 6 are cases of acyclic ketones with adjacent functionality and are reduced with high enantioselectivity. Entries 7 and 8 are applications of the reaction to aromatic ketones done on a relatively large scale in the course of drug development. Entry 7 used an indane-derived aminoalcohol as the oxazaborolidine precursor, whereas the procedure in Entry 8 involves *in situ* generation of the CBS catalyst. Entries 9 to 14 show other examples of the reaction that were carried out in the course of multistage syntheses of complex molecules.

Enantioselective 1,4-reduction of enones can be done using a copper-BINAP catalyst in conjunction with silicon hydride donors.¹⁵⁸ Polymethylhydrosilane (PMHS) is one reductants that is used.

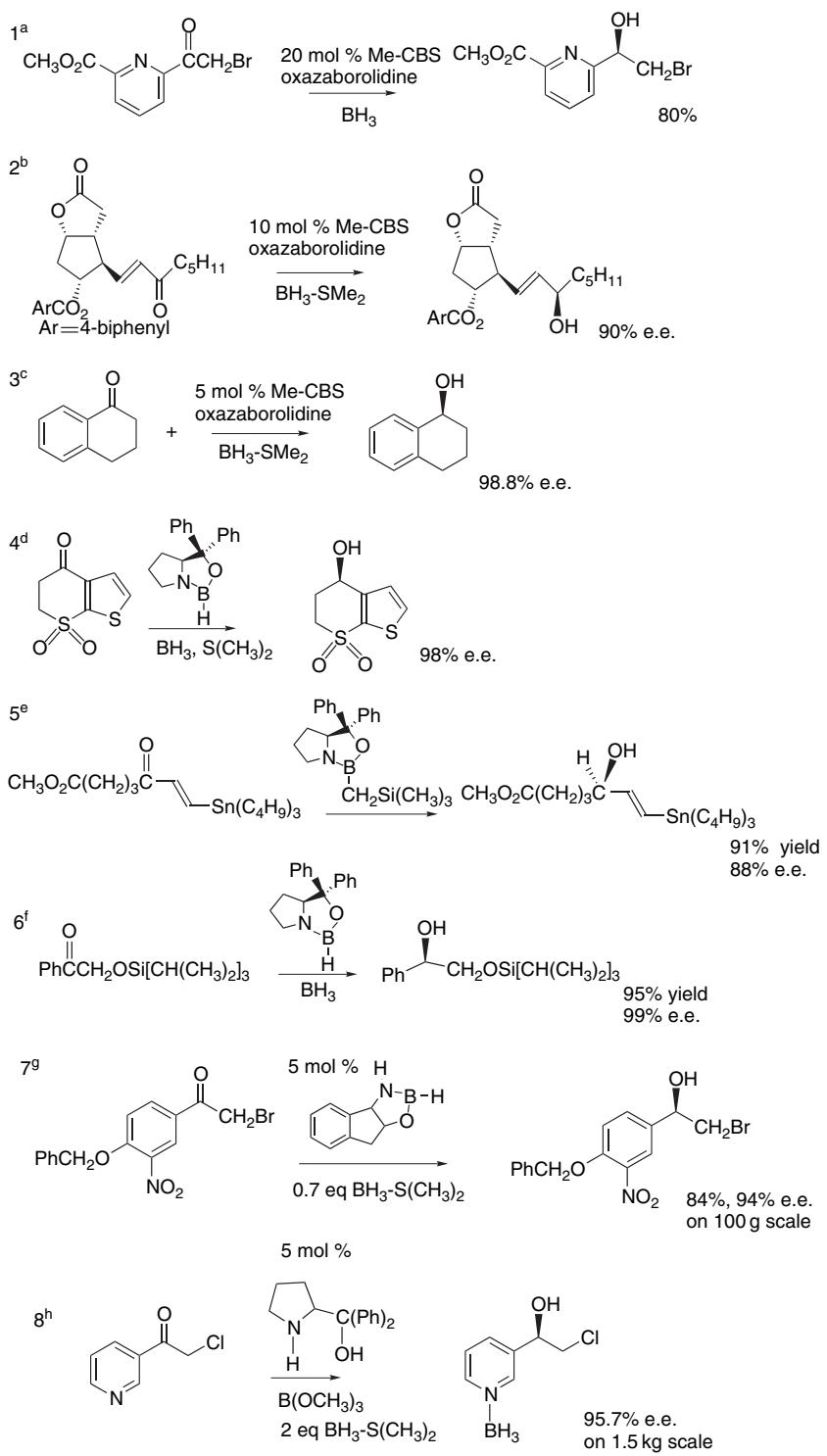


The reduction can also be effected with diphenylsilane and the intermediate silyl enol ethers can be alkylated in a tandem process.¹⁵⁹

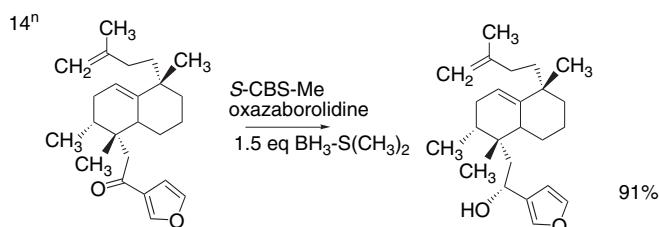
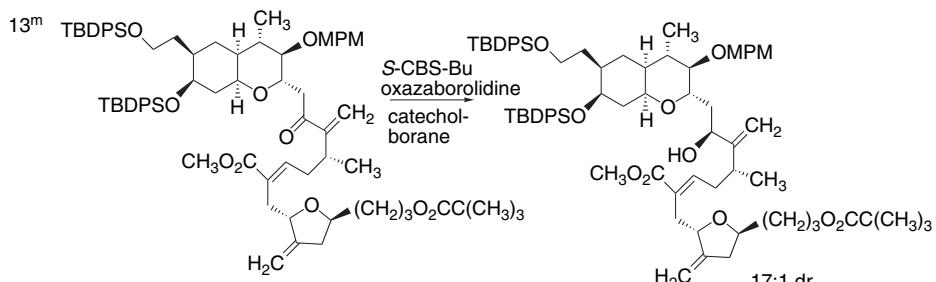
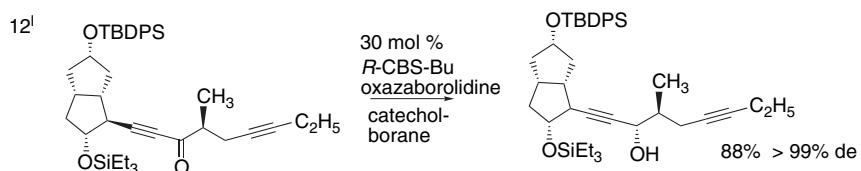
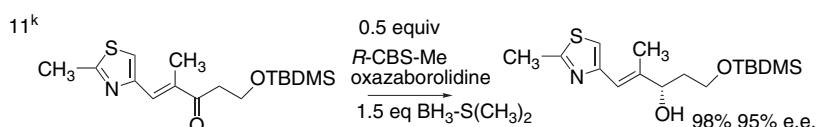
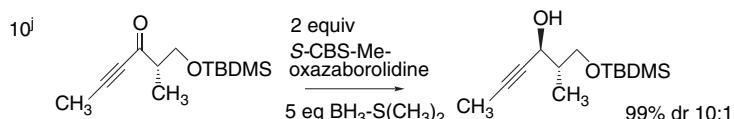
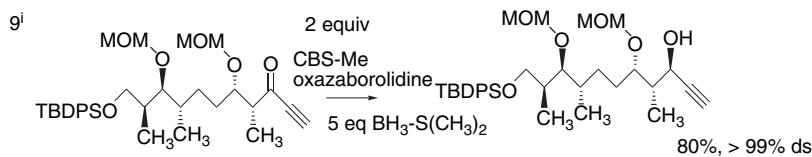
¹⁵⁸. Y. Moritani, D. H. Appella, V. Jurkauskas, and S. L. Buchwald, *J. Am. Chem. Soc.*, **122**, 6797 (2000).

¹⁵⁹. J. Yun and S. L. Buchwald, *Org. Lett.*, **3**, 1129 (2001).

Scheme 5.6. Enantioselective Reduction of Ketones Using CBS-Oxazaborolidine Catalysts



(Continued)



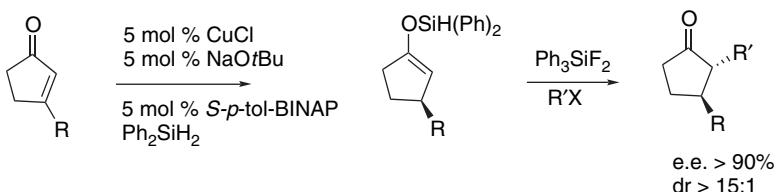
(Continued)

Scheme 5.6. (Continued)

CHAPTER 5

Reduction of
Carbon-Carbon Multiple
Bonds, Carbonyl
Groups, and Other
Functional Groups

- a. K. G. Hull, M. Visnick, W. Tautz, and A. Sheffron, *Tetrahedron*, **53**, 12405 (1997).
 b. E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, and V. K. Singh, *J. Am. Chem. Soc.*, **109**, 7925 (1987).
 c. D. J. Mathre, A. S. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley, and E. J. J. Grabowski, *J. Org. Chem.*, **58**, 2880 (1993).
 d. T. K. Jones, J. J. Mohan, L. C. Xavier, T. J. Blacklock, D. J. Mathre, P. Sohar, E. T. T. Jones, R. A. Reamer, F. E. Roberts, and E. J. J. Grabowski, *J. Org. Chem.*, **56**, 763 (1991).
 e. E. J. Corey, A. Guzman-Perez, and S. E. Lazerwith, *J. Am. Chem. Soc.*, **119**, 11769 (1997).
 f. B. T. Cho and Y. S. Chun, *J. Org. Chem.*, **63**, 5280 (1998).
 g. R. Hett, Q. K. Fang, Y. Gao, S. A. Wald, and C. H. Senanayake, *Org. Proc. Res. Dev.*, **2**, 96 (1998).
 h. J. Duquette, M. Zhang, L. Zhu, and R. S. Reeves, *Org. Proc. Res. Dev.*, **7**, 285 (2003).
 i. L. Bialy and H. Waldmann, *Chem. Eur. J.*, **10**, 2759 (2004).
 j. B. M. Trost, J. L. Guzner, O. Dirat, and Y. H. Rhee, *J. Am. Chem. Soc.*, **124**, 10396 (2002).
 k. E. A. Reiff, S. K. Nair, B. S. N. Reddy, J. Imagaki, J. T. Henri, J. F. Greiner, and G. I. Georg, *Tetrahedron Lett.*, **45**, 5845 (2004).
 l. M. Lerm, H.-J. Gais, K. Cheng, and C. Vermeeren, *J. Am. Chem. Soc.*, **125**, 9653 (2003).
 m. D. P. Stamos, S. S. Chen, and Y. Kishi, *J. Org. Chem.*, **62**, 7552 (1997).
 n. E. J. Corey and B. E. Roberts, *J. Am. Chem. Soc.*, **119**, 12425 (1997).



When necessary, the *trans:cis* ratio can be improved by base-catalyzed equilibration.

5.3.4. Reduction of Other Functional Groups by Hydride Donors

Although reductions of the common carbonyl and carboxylic acid derivatives are the most prevalent uses of hydride donors, these reagents can reduce a number of other groups in ways that are of synthetic utility. Halogen and sulfonate leaving groups can undergo replacement by hydride. Both aluminum and boron hydrides exhibit this reactivity, and lithium trialkylborohydrides are especially reactive.¹⁶⁰ The reduction is particularly rapid and efficient in polar aprotic solvents such as DMSO, DMF, and HMPA. Table 5.6 gives some indication of the reaction conditions. The normal factors in susceptibility to nucleophilic attack govern reactivity with I > Br > Cl being the order in terms of the leaving group and benzyl ~ allyl > primary > secondary > tertiary in terms of the substitution site.¹⁶¹ For primary alkyl groups, it is likely that the reaction proceeds by an S_N2 mechanism. However, the range of halides that can be reduced includes aryl halides and bridgehead halides, which cannot react by the S_N2 mechanism.¹⁶² The loss of stereochemical integrity in the reduction of vinyl halides suggests the involvement of radical intermediates.¹⁶³ Formation and subsequent

¹⁶⁰. S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **45**, 849 (1980).

¹⁶¹. S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **47**, 276 (1982).

¹⁶². C. W. Jefford, D. Kirkpatrick, and F. Delay, *J. Am. Chem. Soc.*, **94**, 8905 (1972).

¹⁶³. S. K. Chung, *J. Org. Chem.*, **45**, 3513 (1980).

Table 5.6. Reaction Conditions for Reductive Replacement of Halogen and Sulfonate Groups by Hydride Donors

SECTION 5.3

Group III

Hydride-Donor Reagents

Hydride donor	Approximate conditions for complete reduction	
	Halides	Sulfonates
NaBH ₃ CN ^a	C ₁₂ H ₂₃ I, HMPA, 25°C, 4 h	C ₁₂ H ₂₃ O ₃ SC ₇ H ₇ , HMPA, 70°C, 8 h
NaBH ₄ ^b	C ₁₂ H ₂₃ Br, DMSO, 85°C, 1.5 h	C ₁₂ H ₂₃ O ₃ SC ₇ H ₇ , DMSO, 85°C, 2 h
LiAlH ₄ ^{c,d}	C ₈ H ₁₇ Br, THF, 25°C, 1 h	C ₈ H ₁₇ O ₃ SC ₇ H ₇ , DME, 25°C, 6 h
LiB(C ₂ H ₅) ₃ H ^c	C ₈ H ₁₇ Br, THF, 25°C, 3 h	

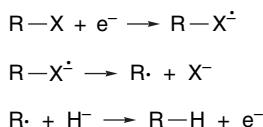
a. R. O. Hutchins, D. Kandasamy, C. A. Maryanoff, D. Masielmani, and B. E. Maryanoff, *J. Org. Chem.*, **42**, 82 (1977).

b. R. O. Hutchins, D. Kandasamy, F. Dux, III, C. A. Maryanoff, D. Rotstein, B. Goldsmith, W. Burgoine, F. Cistone, J. Dalessandro, and J. Puglis, *J. Org. Chem.*, **43**, 2259 (1978).

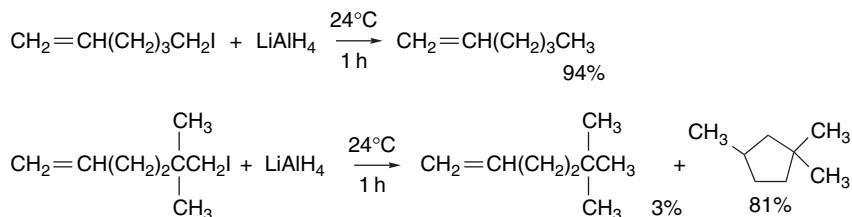
c. S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **45**, 849 (1980).

d. S. Krishnamurthy, *J. Org. Chem.*, **45**, 2550 (1980).

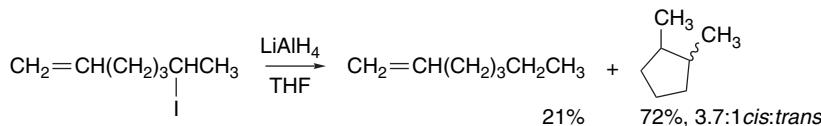
dissociation of a radical anion by one-electron transfer is a likely mechanism for reductive dehalogenation of compounds that cannot react by an S_N2 mechanism.



One experimental test for the involvement of radical intermediates is to study 5-hexenyl systems and look for the characteristic cyclization to cyclopentane derivatives (see Part A, Section 11.2.3). When 5-hexenyl bromide or iodide reacts with LiAlH₄, no cyclization products are observed. However, the more hindered 2,2-dimethyl-5-hexenyl iodide gives mainly cyclic product.¹⁶⁴



Some cyclization also occurs with the bromide, but not with the chloride or the tosylate. The secondary iodide, 6-iodo-1-heptene, gives a mixture of cyclic and acyclic product in THF.¹⁶⁵



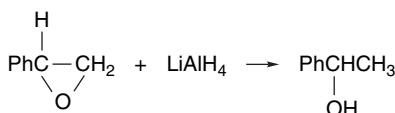
¹⁶⁴. E. C. Ashby, R. N. DePriest, A. B. Goel, B. Wenderoth, and T. N. Pham, *J. Org. Chem.*, **49**, 3545 (1984).

¹⁶⁵. E. C. Ashby, T. N. Pham, and A. Amrollah-Madjadabadi, *J. Org. Chem.*, **56**, 1596 (1991).

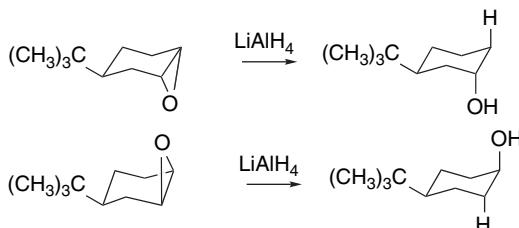
The occurrence of a radical intermediate is also indicated in the reduction of 2-octyl iodide by LiAlD_4 since, in contrast to the chloride or bromide, extensive racemization accompanies reduction.

The presence of transition metal ions has a catalytic effect on reduction of halides and tosylates by LiAlH_4 .¹⁶⁶ Various “copper hydride” reducing agents are effective for removal of halide and tosylate groups.¹⁶⁷ The primary synthetic value of these reductions is for the removal of a hydroxy function after conversion to a halide or tosylate.

Epoxides are converted to alcohols by LiAlH_4 in a reaction that occurs by nucleophilic attack, and hydride addition at the less hindered carbon of the epoxide is usually observed.



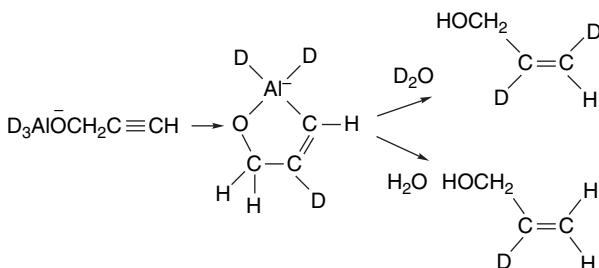
Cyclohexene epoxides are preferentially reduced by an axial approach by the nucleophile.¹⁶⁸



Lithium triethylborohydride is a superior reagent for the reduction of epoxides that are relatively unreactive or prone to rearrangement.¹⁶⁹

Alkynes are reduced to *E*-alkenes by LiAlH_4 .¹⁷⁰ This stereochemistry is complementary to that of partial hydrogenation, which gives *Z*-isomers. Alkyne reduction by LiAlH_4 is greatly accelerated by a nearby hydroxy group. Typically, propargylic alcohols react in ether or tetrahydrofuran over a period of several hours,¹⁷¹ whereas forcing conditions are required for isolated triple bonds.¹⁷² This is presumably the result of coordination of the hydroxy group at aluminum and formation of a cyclic intermediate. The involvement of intramolecular Al–H addition has been demonstrated by use of LiAlD_4 as the reductant. When reduction by LiAlD_4 is followed by quenching with normal water, propargylic alcohol gives *Z*-3-²H-prop-2-enol. Quenching with D_2O gives 2-²H-3-²H-prop-2-enol.¹⁷³

- ^{166.} E. C. Ashby and J. J. Lin, *J. Org. Chem.*, **43**, 1263 (1978).
- ^{167.} S. Masamune, G. S. Bates, and P. E. Georghiou, *J. Am. Chem. Soc.*, **96**, 3686 (1974); E. C. Ashby, J. J. Lin, and A. B. Goel, *J. Org. Chem.*, **43**, 183 (1978).
- ^{168.} B. Rickborn and J. Quartucci, *J. Org. Chem.*, **29**, 3185 (1964); B. Rickborn and W. E. Lamke, II, *J. Org. Chem.*, **32**, 537 (1967); D. K. Murphy, R. L. Alumbaugh, and B. Rickborn, *J. Am. Chem. Soc.*, **91**, 2649 (1969).
- ^{169.} H. C. Brown, S. C. Kim, and S. Krishnamurthy, *J. Org. Chem.*, **45**, 1 (1980); H. C. Brown, S. Narasimhan, and V. Somayaji, *J. Org. Chem.*, **48**, 3091 (1983).
- ^{170.} E. F. Magoon and L. H. Slaugh, *Tetrahedron*, **23**, 4509 (1967).
- ^{171.} N. A. Porter, C. B. Ziegler, Jr., F. F. Khouri, and D. H. Roberts, *J. Org. Chem.*, **50**, 2252 (1985).
- ^{172.} H. C. Huang, J. K. Rehmann, and G. R. Gray, *J. Org. Chem.*, **47**, 4018 (1982).
- ^{173.} J. E. Baldwin and K. A. Black, *J. Org. Chem.*, **48**, 2778 (1983).



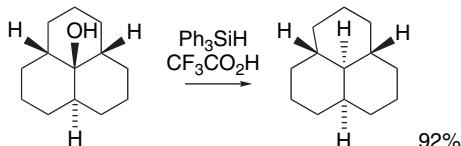
The efficiency and stereospecificity of reduction is improved by using a 1:2 mixture of $\text{LiAlH}_4\text{-NaOCH}_3$ as the reducing agent.¹⁷⁴ The mechanistic basis of this effect has not been explored in detail.

Scheme 5.7 illustrates these and other applications of the hydride donors. Entries 1 and 2 are examples of reduction of alkyl halides, whereas Entry 3 shows removal of an aromatic halogen. Entries 4 to 6 are sulfonate displacements, with the last example using a copper hydride reagent. Entry 7 is an epoxide ring opening. Entries 8 and 9 illustrate the difference in ease of reduction of alkynes with and without hydroxy participation.

5.4. Group IV Hydride Donors

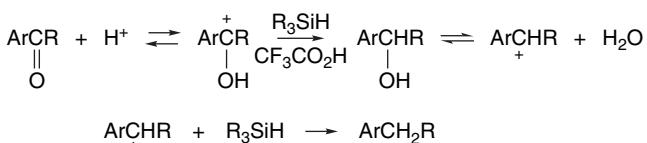
5.4.1. Reactions Involving Silicon Hydrides

Both Si–H and C–H compounds can function as hydride donors under certain circumstances. The silicon-hydrogen bond is capable of transferring a hydride to carbocations. Alcohols that can be ionized in trifluoroacetic acid are reduced to hydrocarbons in the presence of a silane.



Ref. 175

Aromatic aldehydes and ketones are reduced to alkylaromatics under similar conditions through reactions involving benzylic cations.¹⁷⁶



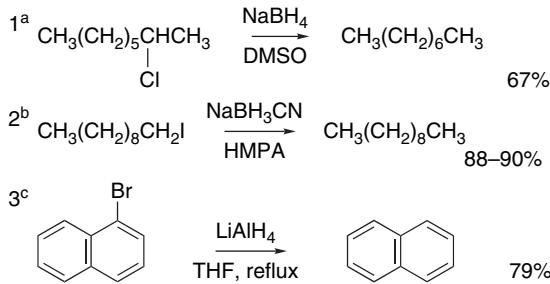
¹⁷⁴ E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 4245 (1967); B. B. Molloy and K. L. Hauser, *J. Chem. Soc., Chem. Commun.*, 1017 (1968).

¹⁷⁵ F. A. Carey and H. S. Tremper, *J. Org. Chem.*, **36**, 758 (1971).

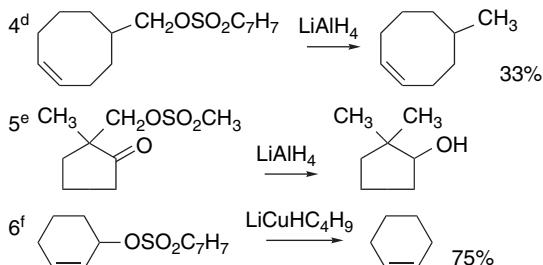
¹⁷⁶ C. T. West, S. J. Donnelly, D. A. Kooistra, and M. P. Doyle, *J. Org. Chem.*, **38**, 2675 (1973); M. P. Doyle, D. J. DeBruyn, and D. A. Kooistra, *J. Am. Chem. Soc.*, **94**, 3659 (1972); M. P. Doyle and C. T. West, *J. Org. Chem.*, **40**, 3821 (1975).

Scheme 5.7. Reduction of Other Functional Groups by Hydride Donors

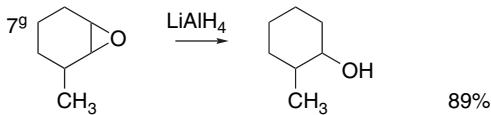
Halides



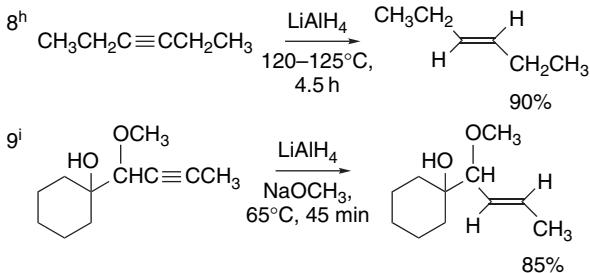
Sulfonates



Epoxides



Acetylenes



a. R. O. Hutchins, D. Hoke, J. Keogh, and D. Koharski, *Tetrahedron Lett.*, 3495 (1969); H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, **34**, 3923 (1969).

b. R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *Org. Synth.*, **53**, 107 (1973).

c. H. C. Brown and S. Krishnamurthy, *J. Org. Chem.*, **34**, 3918 (1969).

d. A. C. Cope and G. L. Woo, *J. Am. Chem. Soc.*, **85**, 3601 (1963).

e. A. Eshenmoser and A. Frey, *Helv. Chim. Acta*, **35**, 1660 (1952).

f. S. Masamune, G. S. Bates, and P. E. Geoghiou, *J. Am. Chem. Soc.*, **96**, 3686 (1974).

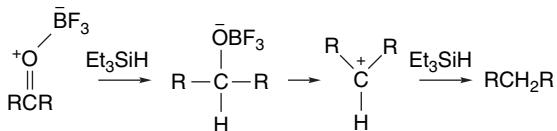
g. B. Rickborn and W. E. Lamke, II, *J. Org. Chem.*, **32**, 537 (1967).

h. E. F. Magoon and L. H. Slaugh, *Tetrahedron*, **23**, 4509 (1967).

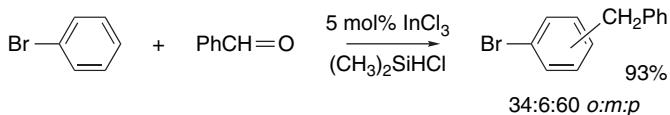
i. D. A. Evans and J. V. Nelson, *J. Am. Chem. Soc.*, **102**, 774 (1980).



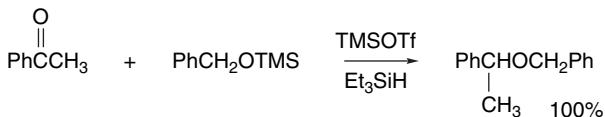
Aliphatic ketones can be reduced to hydrocarbons by triethylsilane and gaseous BF_3 .¹⁷⁸ The BF_3 is a sufficiently strong Lewis acid to promote formation of a carbocation from the intermediate alcohol.



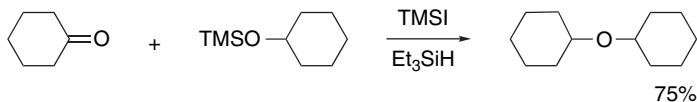
A combination of Friedel-Crafts alkylation and reduction can be achieved using InCl_3 and chlorodimethylsilane. The Lewis acid presumably promotes both the Friedel-Crafts reaction and the subsequent reduction.¹⁷⁹



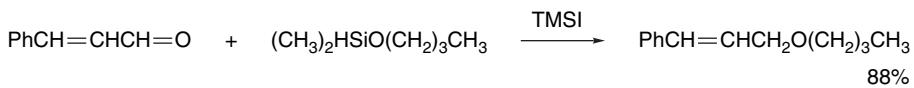
There are several procedures for reductive condensation of silyl ethers with carbonyl compounds to form ethers. One method uses TMSOTf as the catalyst.¹⁸⁰



A number of related procedures have been developed. For example, TMSI can be used.¹⁸¹



The trimethylsilyl group can be replaced by a dialkylsilyloxy group, in which case the silyl ether serves as the hydride donor.



Ref. 182

^{177.} M. Yato, K. Homma, and A. Ishida, *Heterocycles*, **49**, 233 (1998).

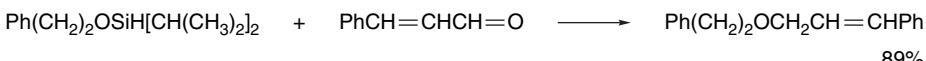
^{178.} J. L. Frey, M. Orfanopoulos, M. G. Adlington, W. R. Dittman, Jr., and S. B. Silverman, *J. Org. Chem.*, **43**, 374 (1978).

^{179.} T. Miyai, Y. Onishi, and A. Baba, *Tetrahedron Lett.*, **39**, 6291 (1998).

^{180.} S. Hatakeyama, H. Mori, K. Kitano, H. Yamada, and M. Nishizawa, *Tetrahedron Lett.*, **35**, 4367 (1994).

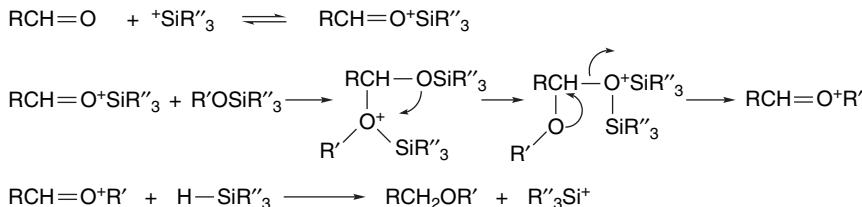
^{181.} M. B. Sassaman, K. D. Kotian, G. K. S. Prakash, and G. Olah, *J. Org. Chem.*, **52**, 4314 (1987).

^{182.} K. Miura, K. Ootsuka, S. Suda, H. Nishikori, and A. Hosomi, *Synlett*, 313 (2002).

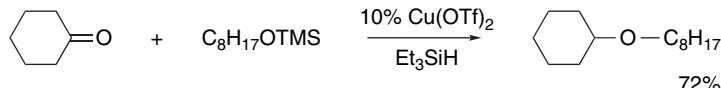


Ref. 183

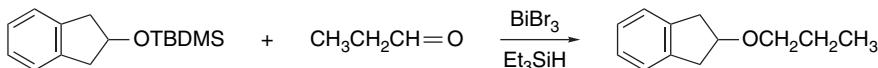
These reactions presumably proceed by catalytic cycles in which the carbonyl component is silylated. The silyl ether can then act as a nucleophile, and an oxonium ion is generated by elimination of a disilyl ether. The reduction of the oxonium ion regenerates the silyl cation, which can continue the catalytic cycle.



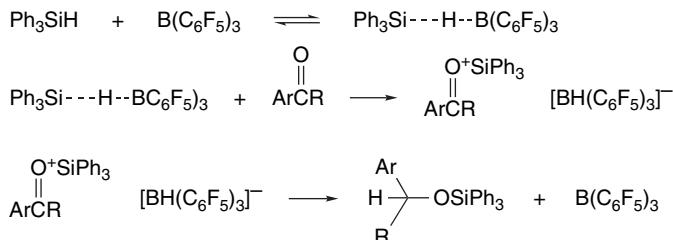
Various other kinds of Lewis acids can also promote the reaction. For example, $\text{Cu}(\text{OTf})_2$ and Et_3SiH have been used to prepare a number of benzyl and alkyl ethers.¹⁸⁴



The reductive condensation can also be carried out using BiBr_3 and Et_3SiH . The active catalyst under these conditions is Et_3SiBr , which is generated in situ.¹⁸⁵



Reduction of ketones to triphenylsilyl ethers is effected by the unique Lewis acid perfluorotriphenylborane. Mechanistic and kinetic studies have provided considerable insight into the mechanism of this reaction.¹⁸⁶ The salient conclusion is that the hydride is delivered from a borohydride ion, not directly from the silane. Although the borane forms a Lewis acid-base complex with the ketone, its key function is in delivery of the hydride.

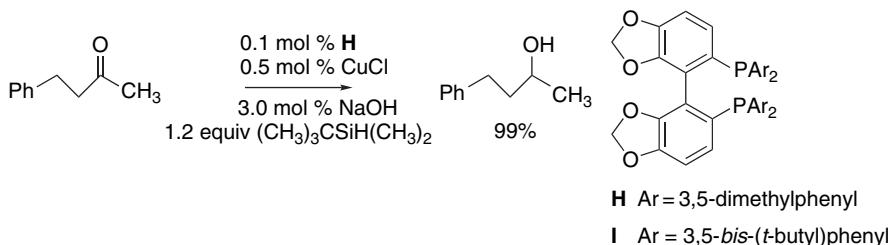


¹⁸³. X. Jiang, J. S. Bajwa, J. Slade, K. Prasad, O. Repic, and T. J. Blacklock, *Tetrahedron Lett.*, **43**, 9225 (2002).

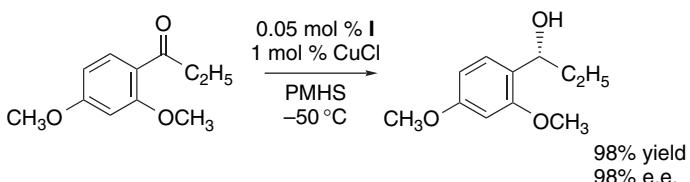
¹⁸⁴. W.-C. Yang, X.-A. Lu, S. S. Kulkarni, and S.-C. Huang, *Tetrahedron Lett.*, **44**, 7837 (2003).

¹⁸⁵. N. Komatsu, J. Ishida, and H. Suzuki, *Tetrahedron Lett.*, **38**, 7219 (1997).

¹⁸⁶. D. J. Parks, J. M. Blackwell, and W. E. Piers, *J. Org. Chem.*, **65**, 3090 (2000).

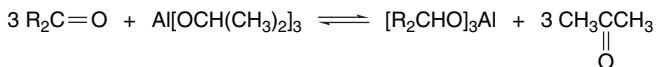


The reactions proceed with an e.e. of about 80% when the enantiopure ligand is used. Similar conditions using poly[oxy(methylsilylene)] (PMHS) as the hydride donor lead to reduction of aryl ketones with up to 98% e.e.¹⁸⁸



5.4.2. Hydride Transfer from Carbon

There are also reactions in which hydride is transferred from carbon. The carbon–hydrogen bond has little intrinsic tendency to act as a hydride donor, so especially favorable circumstances are required to promote this reactivity. Frequently these reactions proceed through a cyclic TS in which a new C–H bond is formed simultaneously with the C–H cleavage. Hydride transfer is facilitated by high electron density at the carbon atom. Aluminum alkoxides catalyze transfer of hydride from an alcohol to a ketone. This is generally an equilibrium process and the reaction can be driven to completion if the ketone is removed from the system, by, e.g., distillation, in a process known as the *Meerwein-Ponndorf-Verley reduction*.¹⁸⁹ The reverse reaction in which the ketone is used in excess is called the *Oppenauer oxidation*.



The reaction proceeds via a cyclic TS involving coordination of both the alcohol and ketone oxygens to the aluminum. Computational (DFT) and isotope effect studies are consistent with the cyclic mechanism.¹⁹⁰ Hydride donation usually takes place from

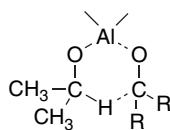
¹⁸⁷ B. H. Lipshutz, C. C. Caires, P. Kuipers, and W. Chrisman, *Org. Lett.*, **5**, 3085 (2003).

¹⁸⁸ B. H. Lipshutz, K. Noson, W. Chrisman, and A. Lower, *J. Am. Chem. Soc.*, **125**, 8779 (2003).

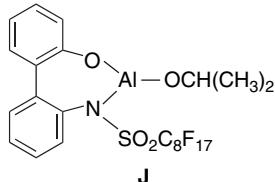
¹⁸⁹ A. L. Wilds, *Org. React.*, **2**, 178 (1944); C. F. de Graauw, J. A. Peters, H. van Bekkum, and J. Huskens, *Synthesis*, 1007 (1994).

¹⁹⁰ R. Cohen, C. R. Graves, S. T. Nguyen, J. M. L. Martin, and M. A. Ratner, *J. Am. Chem. Soc.*, **126**, 14796 (2004).

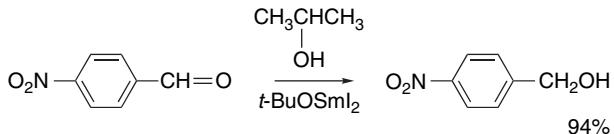
the less hindered face of the carbonyl group.¹⁹¹ However, these conditions frequently promote equilibration of the alcohol stereoisomers.



Recently, enantioselective procedures involving chiral catalysts have been developed. The combination of BINOL and $\text{Al}(\text{CH}_3)_3$ can achieve 80% e.e. in the reduction of acetophenone.¹⁹² Compound **J** is also an effective catalyst.¹⁹³

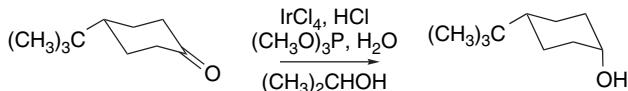


Certain lanthanide alkoxides, such as $t\text{-BuOSmI}_2$, have also been found to catalyze hydride exchange between alcohols and ketones.¹⁹⁴ Isopropanol can serve as the reducing agent for aldehydes and ketones that are thermodynamically better hydride acceptors than acetone.



Samarium metal in isopropanol also achieves reduction.¹⁹⁵ Like the Meerwein-Ponndorf-Verley procedure, these conditions are believed to be under thermodynamic control and the more stable stereoisomer is the main product.¹⁹⁶

Another reduction process, catalyzed by iridium chloride, is characterized by very high axial:equatorial product ratios for cyclohexanones and apparently involves hydride transfer from isopropanol.¹⁹⁷



Formic acid can also act as a donor of hydrogen, and the driving force in this case is the formation of carbon dioxide. A useful application is the Clark-Eschweiler

¹⁹¹ F. Nerdel, D. Frank, and G. Barth, *Chem. Ber.*, **102**, 395 (1969).

¹⁹² E. J. Campbell, H. Zhou, and S. T. Nguyen, *Angew. Chem. Int. Ed. Engl.*, **41**, 1020 (2002).

¹⁹³ T. Ooi, H. Ichikawa, and K. Maruoka, *Angew. Chem. Int. Ed. Engl.*, **40**, 3610 (2001).

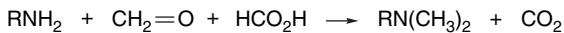
¹⁹⁴ J. L. Namy, J. Souuppe, J. Collin, and H. B. Kagan, *J. Org. Chem.*, **49**, 2045 (1984).

¹⁹⁵ S. Fukuzawa, N. Nakano, and T. Saitoh, *Eur. J. Org. Chem.*, 2863 (2004).

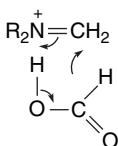
¹⁹⁶ D.A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy, and T. J. Stout, *J. Am. Chem. Soc.*, **112**, 7001 (1990).

¹⁹⁷ E. L. Eliel, T. W. Doyle, R. O. Hutchins, and E. C. Gilbert, *Org. Synth.*, **50**, 13 (1970).

reductive methylation of amines, in which heating a primary or secondary amine with formaldehyde and formic acid results in complete methylation to the tertiary amine.¹⁹⁸



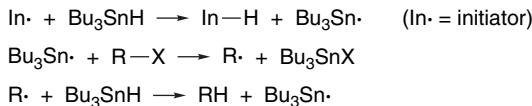
The hydride acceptor is the iminium ion that results from condensation of the amine with formaldehyde.



5.5. Reduction Reactions Involving Hydrogen Atom Donors

Reduction by hydrogen atom donors involves free radical intermediates and usually proceeds by chain mechanisms. Tri-*n*-butylstannane is the most prominent example of this type of reducing agent. Other synthetically useful hydrogen atom donors include hypophosphorous acid, dialkyl phosphites, and *tris*-(trimethylsilyl)silane. The processes that have found most synthetic application are reductive replacement of halogen and various types of thiono esters.

Tri-*n*-butylstannane is able to reductively replace halogen by hydrogen. Mechanistic studies indicate a free radical chain mechanism.¹⁹⁹ The order of reactivity for the halides is RI > RBr > RCl > RF, which reflects the relative ease of the halogen atom abstraction.²⁰⁰



Scheme 5.8 gives several examples of dehalogenation using tri-*n*-butylstannane. Entries 1 and 2 are examples from the early studies of this method. Entries 3 and 4 illustrate selective dehalogenation of polyhalogenated compounds. The stabilizing effect of the remaining halogen on the radical intermediate facilitates partial dehalogenation. These reactions also demonstrate stereoselectivity. In Entry 3, the stereochemical preference is for hydrogen abstraction from the more accessible face of the radical intermediate. Entry 4 shows retention of configuration at the fluorocyclopropyl carbon. (The stereoisomeric compound also reacts with retention of configuration.) This result indicates that hydrogen abstraction is faster than inversion for these cyclopropyl radicals (see Part A, Section 11.1.5).

A procedure that is catalytic in Bu₃SnH and uses NaBH₄ as the stoichiometric reagent has been developed.²⁰¹ This method has advantages in the isolation and purification of product. Entry 5 is an example of this procedure. The reaction was carried

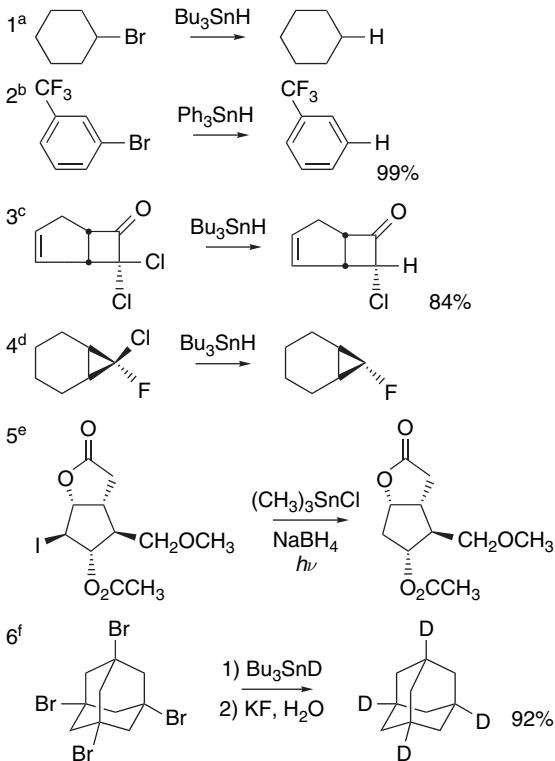
¹⁹⁸ M. L. Moore, *Org. React.*, **5**, 301 (1949); S. H. Pine and B. L. Sanchez, *J. Org. Chem.*, **36**, 829 (1971).

¹⁹⁹ L. W. Menapace and H. G. Kuivila, *J. Am. Chem. Soc.*, **86**, 3047 (1964).

²⁰⁰ H. G. Kuivila and L. W. Menapace, *J. Org. Chem.*, **28**, 2165 (1963).

²⁰¹ E. J. Corey and J. W. Suggs, *J. Org. Chem.*, **40**, 2554 (1975).

Scheme 5.8. Dehalogenation with Stannanes



a. H. G. Kuivila, L. W. Menapace, and C. R. Warner, *J. Am. Chem. Soc.*, **84**, 3584 (1962).

b. D. H. Lorenz, P. Shapiro, A. Stern, and E. J. Becker, *J. Org. Chem.*, **28**, 2332 (1963).

c. W. T. Brady and E. F. Hoff, Jr., *J. Org. Chem.*, **35**, 3733 (1970).

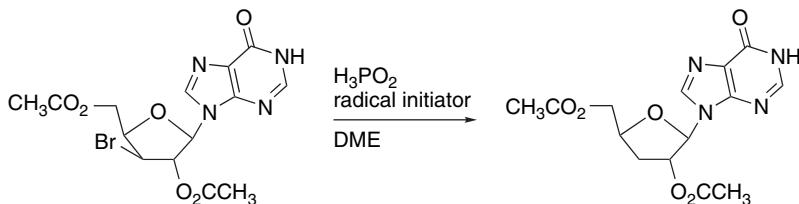
d. T. Ando, F. Namigata, H. Yamanaka, and W. Funasaka, *J. Am. Chem. Soc.*, **89**, 5719 (1967).

e. E. J. Corey and J. W. Suggs, *J. Org. Chem.*, **40**, 2554 (1975).

f. J. E. Leibner and J. Jacobson, *J. Org. Chem.*, **44**, 449 (1979).

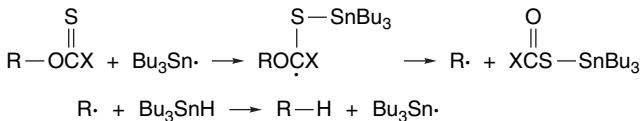
out under illumination to provide for chain initiation, and the reactant was prepared by an iodolactonization reaction. The sequence iodolactonization-dehalogenation is frequently used in the synthesis of five-membered lactones. Entry 6 illustrates the use of dehalogenation with deuterium incorporation. The addition of the fluoride salt facilitates workup by precipitation of tin by-products.

Hypophosphorous acid has been used as a hydrogen atom donor in the dehalogenation of nucleosides.²⁰²



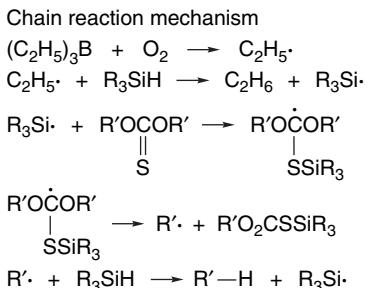
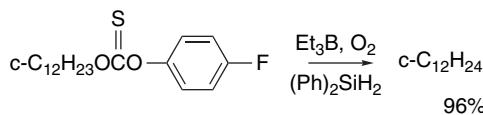
²⁰² S. Takamatsu, S. Katayama, N. Hirose, M. Naito, and K. Izawa, *Tetrahedron Lett.*, **42**, 7605 (2001).

Tri-*n*-butyltin hydride also serves as a hydrogen atom donor in radical-mediated methods for reductive deoxygenation of alcohols via thiono esters.²⁰³ The alcohol is converted to a thiocarbonyl derivative. These thiono esters undergo a radical reaction with tri-*n*-butyltin hydride. The resulting radicals fragment to give the alkyl radical, and the chain is propagated by hydrogen atom abstraction.



This procedure gives good yields from secondary alcohols and by appropriate adjustment of conditions can also be adapted to primary alcohols.²⁰⁴

Owing to the expense, toxicity, and purification problems associated with use of stoichiometric amounts of tin hydrides, there has been interest in finding other hydrogen atom donors.²⁰⁵ The trialkylboron-oxygen system for radical generation (see Part A, Section 11.1.4) has been used with *tris*-(trimethylsilyl)silane or diphenylsilane as a hydrogen donor.²⁰⁶



The alcohol derivatives that have been successfully deoxygenated include thionocarbonates and xanthates.²⁰⁷ Peroxides can be used as initiators.

Scheme 5.9 illustrates some of the conditions that have been developed for the reductive deoxygenation of alcohols. Entries 1 to 4 illustrate the most commonly used methods for generation of thiono esters and their reduction by tri-*n*-butylstannane. These include formation of thiono carbonates (Entry 1), xanthates (Entry 2), and thiono imidazolides (Entries 3 and 4). Entry 5 is an example of use of dimethyl phosphite as the hydrogen donor. Entry 6 uses *tris*-(trimethylsilyl)silane as the hydrogen atom donor.

²⁰³ D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. I*, 1574 (1975). For reviews of this method, see W. Hartwig, *Tetrahedron*, **39**, 2609 (1983); D. Crich and L. Quintero, *Chem. Rev.*, **89**, 1413 (1989).

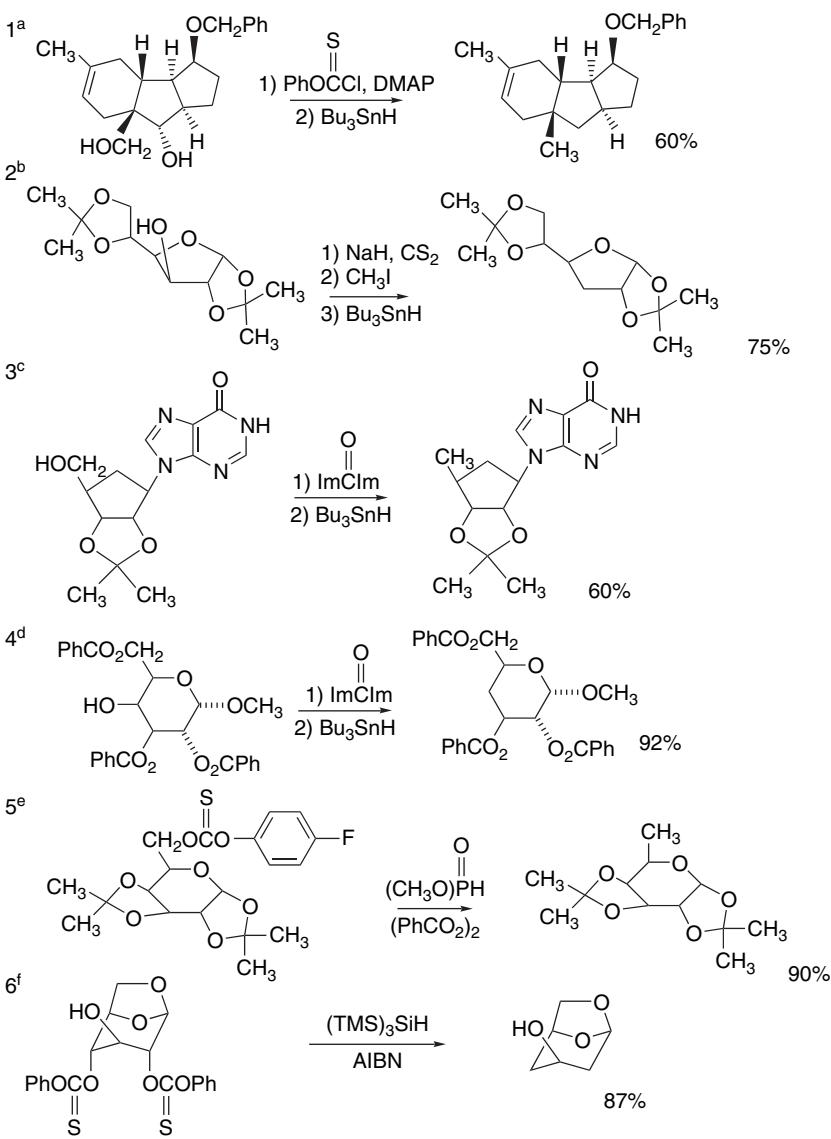
²⁰⁴ D. H. R. Barton, W. B. Motherwell, and A. Stange, *Synthesis*, 743 (1981).

²⁰⁵ A. Studer and S. Amrein, *Synthesis*, 835 (2002).

²⁰⁶ D. H. R. Barton, D. O. Jang, and J. C. Jaszerenyi, *Tetrahedron Lett.*, **31**, 4681 (1990).

²⁰⁷ J. N. Kirwan, B. P. Roberts, and C. R. Willis, *Tetrahedron Lett.*, **31**, 5093 (1990).

²⁰⁸ D. H. Barton, D. O. Jang, and J. C. Jaszerenyi, *Tetrahedron Lett.*, **33**, 7187 (1991).

Scheme 5.9. Deoxygenation of Alcohols via Thiono Esters and Related Derivatives

a. H. J. Liu and M. G. Kulkarni, *Tetrahedron Lett.*, **26**, 4847 (1985).

b. S. Iacono and J. R. Rasmussen, *Org. Synth.*, **64**, 57 (1985).

c. O. Miyashita, F. Kasahara, T. Kusaka, and R. Marumoto, *J. Antibiot.*, **38**, 98 (1985).

d. J. R. Rasmussen, C. J. Slinger, R. J. Kordish, and D. D. Newman-Evans, *J. Org. Chem.*, **46**, 4843 (1981).

e. D. H. R. Barton, D. O. Jang, and J. C. Jaszerberenyi, *Tetrahedron Lett.*, **33**, 2311 (1992).

f. D. H. R. Barton, D. O. Jang, and J. C. Jaszerberenyi, *Tetrahedron Lett.*, **33**, 6629 (1992).

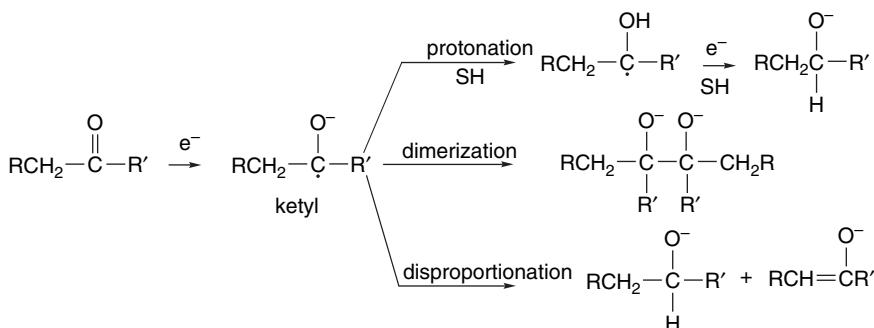
5.6. Dissolving-Metal Reductions

Another group of synthetically useful reductions employs a metal as the reducing agent. The organic reactant under these conditions accepts one or more electrons from the metal. The subsequent course of the reaction depends on the structure of the

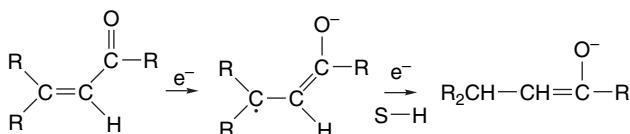
reactant and reaction conditions. Three broad types of reactions can be recognized and these are discussed separately. They include reactions in which the overall change involves: (a) net addition of hydrogen, (b) reductive removal of a functional group, and (c) formation of carbon–carbon bonds.

5.6.1. Addition of Hydrogen

5.6.1.1. Reduction of Ketones and Enones. Although the method has been supplanted for synthetic purposes by hydride donors, the reduction of ketones to alcohols in ammonia or alcohols provides mechanistic insight into dissolving-metal reductions. The outcome of the reaction of ketones with metal reductants is determined by the fate of the initial ketyl radical formed by a single-electron transfer. The radical intermediate, depending on its structure and the reaction medium, may be protonated, disproportionate, or dimerize.²⁰⁹ In hydroxyllic solvents such as liquid ammonia or in the presence of an alcohol, the protonation process dominates over dimerization. Net reduction can also occur by a disproportionation process. As is discussed in Section 5.6.3, dimerization can become the dominant process under conditions in which protonation does not occur rapidly.



α,β -Unsaturated carbonyl compounds are cleanly reduced to the enolate of the corresponding saturated ketone on reduction with lithium in ammonia.²¹⁰ Usually an alcohol is added to the reduction solution to serve as the proton source.

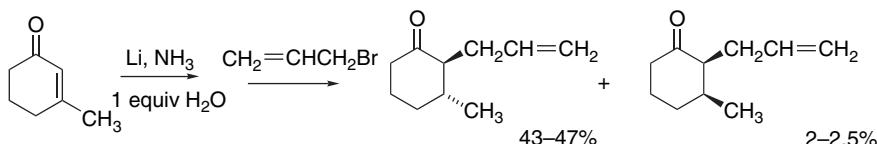


As noted in Chapter 1, this is one of the best methods for generating a specific enolate of a ketone. The enolate generated by conjugate reduction can undergo the characteristic alkylation and addition reactions that are discussed in Chapters 1 and 2. When this is the objective of the reduction, it is important to use only one equivalent of the proton donor. Ammonia, being a weaker acid than an aliphatic ketone, does

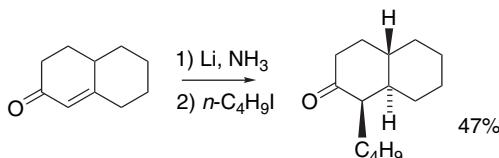
²⁰⁹ V. Rautenstrauch and M. Geoffroy, *J. Am. Chem. Soc.*, **99**, 6280 (1977); J. W. Huffman and W. W. McWhorter, *J. Org. Chem.*, **44**, 594 (1979); J. W. Huffman, P. C. Desai, and J. E. LaPrade, *J. Org. Chem.*, **48**, 1474 (1983).

²¹⁰ D. Caine, *Org. React.*, **23**, 1 (1976).

not act as a proton donor toward an enolate, and the enolate remains available for subsequent reaction, as in the tandem alkylations shown below. If the saturated ketone is the desired product, the enolate is protonated either by use of excess proton donor during the reduction or on workup.

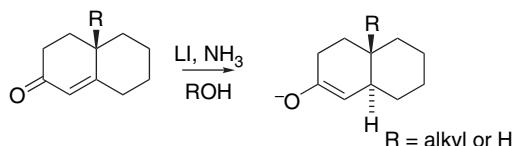


Ref. 211



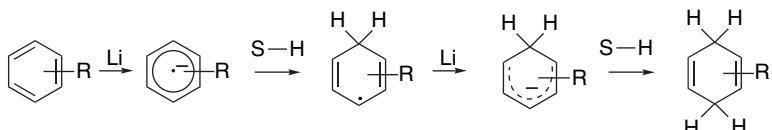
Ref. 212

The stereochemistry of conjugate reduction is established by the proton transfer to the β -carbon. In the well-studied case of $\Delta^{1,9}$ -2-octalones, the ring junction is usually *trans*.²¹³



The stereochemistry is controlled by a stereoelectronic preference for protonation perpendicular to the enolate system and, given that this requirement is met, the stereochemistry normally corresponds to protonation of the most stable conformation of the dianion intermediate from its least hindered side.

5.6.1.2. Dissolving-Metal Reduction of Aromatic Compounds and Alkynes. Dissolving-metal systems constitute the most general method for partial reduction of aromatic rings. The reaction is called the *Birch reduction*,²¹⁴ and the usual reducing medium is lithium or sodium in liquid ammonia. An alcohol is usually added to serve as a proton source. The reaction occurs by two successive electron transfer/protonation steps.



²¹¹ D. Caine, S. T. Chao, and H. A. Smith, *Org. Synth.*, **56**, 52 (1977).

²¹² G. Stork, P. Rosen, and N. L. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961).

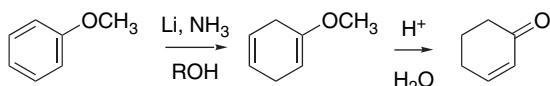
²¹³ G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965); M. J. T. Robinson, *Tetrahedron*, **21**, 2475 (1965).

²¹⁴ A. J. Birch and G. Subba Rao, *Adv. Org. Chem.*, **8**, 1 (1972); R. G. Harvey, *Synthesis*, 161 (1980); J. M. Hook and L. N. Mander, *Nat. Prod. Rep.*, **3**, 35 (1986); P. W. Rabideau, *Tetrahedron*, **45**, 1599 (1989); A. J. Birch, *Pure Appl. Chem.*, **68**, 553 (1996).

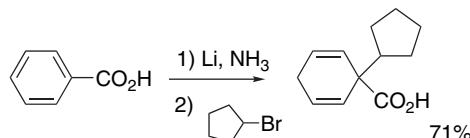
The isolated double bonds in the dihydro product are much less easily reduced than the conjugated ring, so the reduction stops at the dihydro stage. Alkyl and alkoxy aromatics, phenols, and benzoate anions are the most useful reactants for Birch reduction. In aromatic ketones and nitro compounds, the substituents are reduced in preference to the aromatic ring. Substituents also govern the position of protonation. Alkyl and alkoxy aromatics normally give the 2,5-dihydro derivative. Benzoate anions give 1,4-dihydro derivatives.



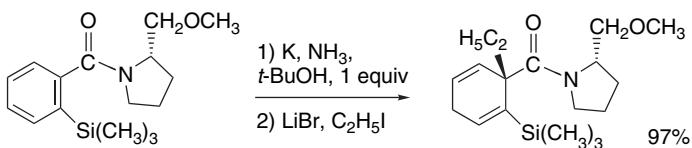
The structure of the products is determined by the site of protonation of the radical anion intermediate formed after the first electron transfer step. In general, ERG substituents favor protonation at the *ortho* position, whereas EWGs favor protonation at the *para* position.²¹⁵ Addition of a second electron gives a pentadienyl anion, which is protonated at the center carbon. As a result, 2,5-dihydro products are formed with alkyl or alkoxy substituents and 1,4-products are formed from EWG substituents. The preference for protonation of the central carbon of the pentadienyl anion is believed to be the result of the greater 1,2 and 4,5 bond order and a higher concentration of negative charge at C(3).²¹⁶ The reduction of methoxybenzenes is of importance in the synthesis of cyclohexenones via hydrolysis of the intermediate enol ethers.



The anionic intermediates formed in Birch reductions can be used in tandem alkylation reactions.



Ref. 217



Ref. 218

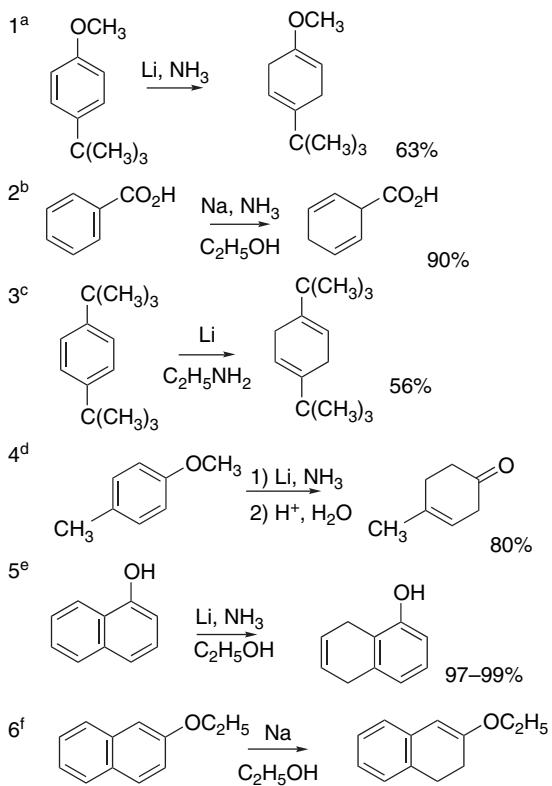
²¹⁵ A. J. Birch, A. L. Hinde, and L. Radom, *J. Am. Chem. Soc.*, **102**, 2370 (1980); H. E. Zimmerman and P. A. Wang, *J. Am. Chem. Soc.*, **112**, 1280 (1990).

²¹⁶ P. W. Rabideau and D. L. Huser, *J. Org. Chem.*, **48**, 4266 (1983); H. E. Zimmerman and P. A. Wang, *J. Am. Chem. Soc.*, **115**, 2205 (1993).

²¹⁷ P. A. Baguley and J. C. Walton, *J. Chem. Soc., Perkin Trans. 1*, 2073 (1998).

²¹⁸ A. G. Schultz and L. Pettus, *J. Org. Chem.*, **62**, 6855 (1997).

Scheme 5.10. Birch Reduction of Aromatic Rings

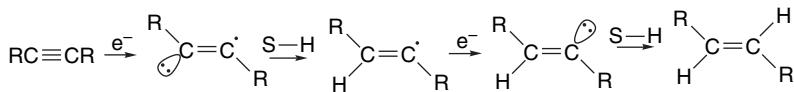


- a. D. A. Bolon, *J. Org. Chem.*, **35**, 715 (1970).
 b. M. E. Kuehne and B. F. Lambert, *Org. Synth.*, **V**, 400 (1973).
 c. H. Kwart and R. A. Conley, *J. Org. Chem.*, **38**, 2011 (1973).
 d. E. A. Braude, A. A. Webb, and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3328 (1958); W. C. Agosta and W. L. Schreiber, *J. Am. Chem. Soc.*, **93**, 3947 (1971).
 e. C. D. Gutsche and H. H. Peter, *Org. Synth.*, **IV**, 887 (1963).
 f. M. D. Soffer, M. P. Bellis, H. E. Gellerson, and R. A. Stewart, *Org. Synth.*, **IV**, 903 (1963).

Scheme 5.10 lists some examples of the use of the Birch reduction. Entries 1 and 2 illustrate the usual regioselectivity for alkoxy aromatics and for benzoic acid. Entry 3 uses an alkylamine as the solvent. In the case cited, the yield was much better than that obtained using ammonia. Entry 4 illustrates the preparation of a cyclohex-3-enone via the Birch reduction route. Entries 5 and 6 show an interesting contrast in the regioselectivity of naphthalene derivatives. The selective reduction of the unsubstituted ring may reflect the more difficult reduction of the ring having a deprotonated oxy substituent. On the other hand, empirical evidence indicates that ERG substituents in the 2-position direct reduction to the substituted ring.²¹⁹ The basis of this directive effect does not seem to have been developed in modern electronic terms.

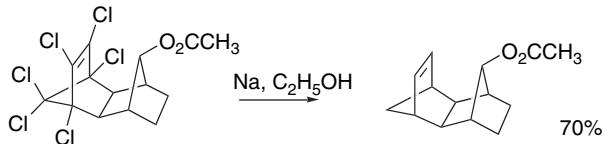
²¹⁹. M. D. Soffer, R. A. Stewart, J. C. Cavagnol, H. E. Gellerson, and E. A. Bowler, *J. Am. Chem. Soc.*, **72**, 3704 (1950).

Reduction of acetylenes can be done with sodium in ammonia,²²⁰ lithium in low molecular weight amines,²²¹ or sodium in HMPA containing *t*-butanol as a proton source,²²² all of which lead to the *E*-alkene. The reaction is assumed to involve successive electron transfer and protonation steps.



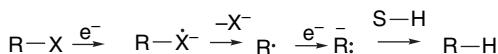
5.6.2. Reductive Removal of Functional Groups

The reductive removal of halogen can be accomplished with lithium or sodium. Tetrahydrofuran containing *t*-butanol is a useful reaction medium. Good results have also been achieved with polyhalogenated compounds by using sodium in ethanol.

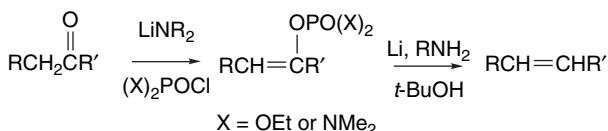


Ref. 223

An important synthetic application of this reaction is in dehalogenation of dichloro- and dibromocyclopropanes. The dihalocyclopropanes are accessible via carbene addition reactions (see Section 10.2.3). Reductive dehalogenation can also be used to introduce deuterium at a specific site. The mechanism of the reaction involves electron transfer to form a radical anion, which then fragments with loss of a halide ion. The resulting radical is reduced to a carbanion by a second electron transfer and subsequently protonated.



Phosphate groups can also be removed by dissolving-metal reduction. Reductive removal of vinyl phosphate groups is one method for conversion of a carbonyl compound to an alkene.²²⁴ (See Section 5.7.2 for other methods.) The required vinyl phosphate esters are obtained by phosphorylation of the enolate with diethyl phosphorochloridate or *N,N,N',N'*-tetramethyldiamidophosphorochloridate.²²⁵



²²⁰ K. N. Campbell and T. L. Eby, *J. Am. Chem. Soc.*, **63**, 216, 2683 (1941); A. L. Henne and K. W. Greenlee, *J. Am. Chem. Soc.*, **65**, 2020 (1943).

²²¹ R. A. Benkeser, G. Schroll, and D. M. Sauve, *J. Am. Chem. Soc.*, **77**, 3378 (1955).

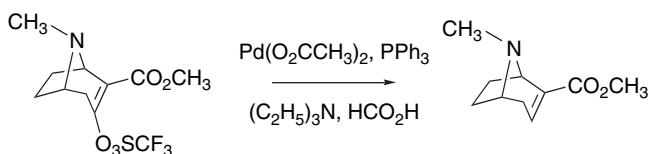
²²² H. O. House and E. F. Kinloch, *J. Org. Chem.*, **39**, 747 (1974).

²²³ B. V. Lap and M. N. Paddon-Row, *J. Org. Chem.*, **44**, 4979 (1979).

²²⁴ R. E. Ireland and G. Pfister, *Tetrahedron Lett.*, 2145 (1969).

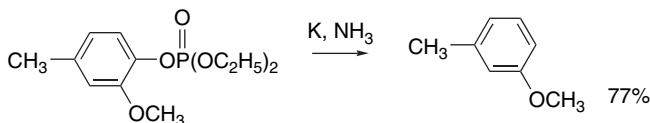
²²⁵ R. E. Ireland, D. C. Muchmore, and U. Hengartner, *J. Am. Chem. Soc.*, **94**, 5098 (1972).

Ketones can also be reduced to alkenes via enol triflates. The use of $\text{Pd}(\text{OAc})_2$ and triphenylphosphine as the catalyst and tertiary amines as the hydrogen donors is effective.²²⁶



Ref. 227

Reductive removal of oxygen from aromatic rings can also be achieved by reductive cleavage of aryl diethyl phosphate esters.



Ref. 228

There are also examples in which phosphate esters of saturated alcohols are reductively deoxygenated.²²⁹ Mechanistic studies of the cleavage of aryl dialkyl phosphates have indicated that the crucial C–O bond cleavage occurs after transfer of two electrons.²³⁰

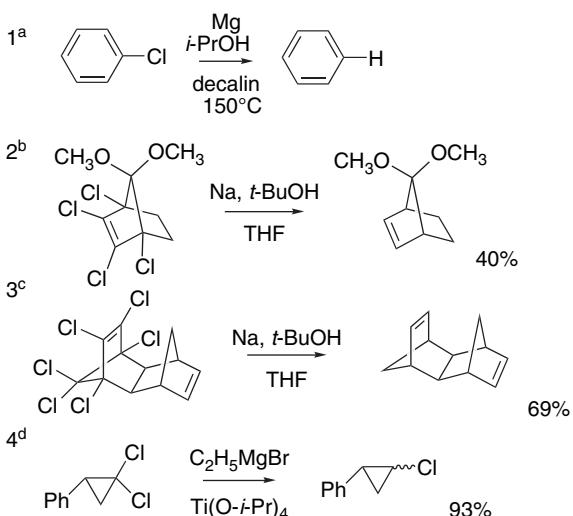


For preparative purposes, titanium metal can be used in place of sodium or lithium in liquid ammonia for both the vinyl phosphate²³¹ and aryl phosphate²³² cleavages. The titanium metal is generated in situ from TiCl_3 by reduction with potassium metal in tetrahydrofuran.

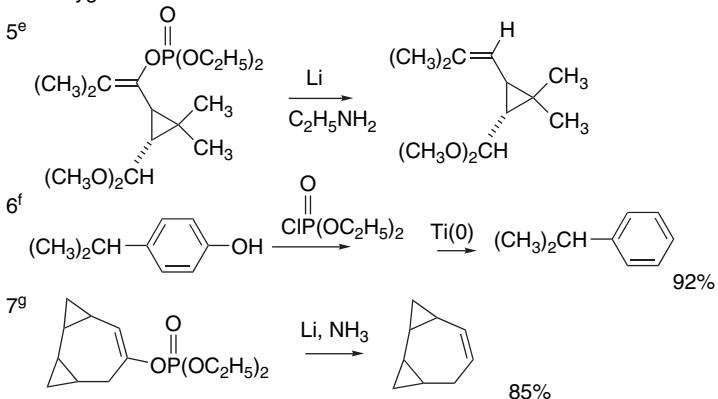
Scheme 5.11 shows some examples of these reductive reactions. Entry 1 is an example of conditions that have been applied to both alkyl and aryl halides. The reaction presumably proceeds through formation of a Grignard reagent, which then undergoes protonolysis. Entries 2 and 3 are cases of the dehalogenation of polyhalogenated compounds by sodium in *t*-butanol. Entry 4 illustrates conditions that were found useful for monodehalogenation of dibromo- and dichlorocyclopropanes. This method is not very stereoselective. In the example given, the ratio of *cis:trans* product was 1.2:1. Entries 5 to 7 are cases of dissolving-metal reduction of vinyl and aryl phosphates.

- ²²⁶ W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, **108**, 3033 (1986); L. A. Paquette, P. G. Meister, D. Friedrich, and D. R. Sauer, *J. Am. Chem. Soc.*, **115**, 49 (1993).
- ²²⁷ K. I. Keverline, P. Abraham, A. H. Lewin, and F. I. Carroll, *Tetrahedron Lett.*, **36**, 3099 (1995).
- ²²⁸ R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 2314 (1973).
- ²²⁹ R. R. Muccino and C. Djerasi, *J. Am. Chem. Soc.*, **96**, 556 (1974).
- ²³⁰ S. J. Shafer, W. D. Closson, J. M. F. van Dijk, O. Piepers, and H. M. Buck, *J. Am. Chem. Soc.*, **99**, 5118 (1977).
- ²³¹ S. C. Welch and M. E. Walters, *J. Org. Chem.*, **43**, 2715 (1978).
- ²³² S. C. Welch and M. E. Walters, *J. Org. Chem.*, **43**, 4797 (1978).

A. Dehalogenation

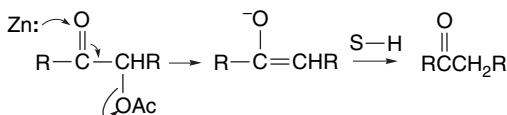


B. Deoxygenation

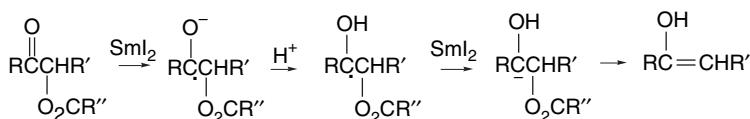


- a. D. Bryce-Smith and B. J. Wakefield, *Org. Synth.*, **47**, 103 (1967).
 b. P. G. Gassman and J. L. Marshall, *Org. Synth.*, **48**, 68 (1968).
 c. B. V. Lap and M. N. Paddon-Row, *J. Org. Chem.*, **44**, 4979 (1979).
 d. J. R. Al Duyayymi, M. S. Baird, I. G. Bolesov, V. Tversovsky, and M. Rubin, *Tetrahedron Lett.*, **37**, 8933 (1996).
 e. S. C. Welch and T. A. Valdes, *J. Org. Chem.*, **42**, 2108 (1977).
 f. S. C. Welch and M. E. Walter, *J. Org. Chem.*, **43**, 4797 (1978).
 g. M. R. Detty and L. A. Paquette, *J. Org. Chem.*, **42**, 821 (1977).

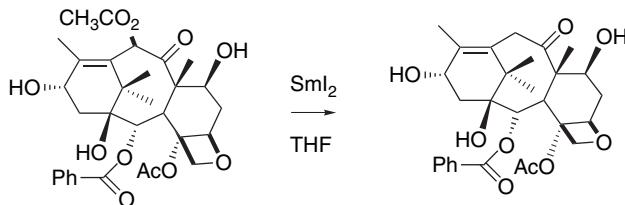
Both metallic zinc and aluminum amalgam are milder reducing agents than the alkali metals. These reductants selectively remove oxygen and sulfur functional groups α to carbonyl groups. The mechanistic picture that seems most generally applicable is a net two-electron reduction with expulsion of the oxygen or sulfur substituent as an anion. The reaction must be a concerted process, because the isolated functional groups are not reduced under these conditions.



Another useful reagent for reduction of α -acetoxyketones and similar compounds is samarium diiodide.²³³ SmI₂ is a strong one-electron reducing agent, and it is believed that the reductive elimination occurs after a net two-electron reduction of the carbonyl group.



These conditions were used, for example, in the preparation of the anticancer compound 10-deacetoxytaxol.



Ref. 234

Scheme 5.12 gives some examples of the reductive removal of functional groups adjacent to carbonyl groups. Entry 1 is an application of this reaction as it was used in an early steroid synthesis. The reaction in Entry 2 utilizes calcium in ammonia for the reduction. The reaction in Entry 3 converts the acyloin derived from dimethyl decanedicarboxylate into cyclodecanone. In the reaction in Entry 4, a sulfonate group is removed. In Entry 5 an epoxide is opened using aluminum amalgam, and in Entry 6 a lactone ring is opened. The latter reaction was part of a synthetic sequence in which the lactone intermediate was used to establish the stereochemistry of the acyclic product. The reaction in Entry 7 removes a sulfinyl group. Keto sulfoxides can be obtained by acylation of the anion of dimethylsulfoxide, so this reaction constitutes a general route to ketones (see Section 2.3.2). The reaction in Entry 8 is a *vinylogous* version of the reduction. The reductant in Entries 9 and 10 is SmI₂. In Entry 9, the 2-phenylcyclohexyloxy group that is removed was used earlier in the synthesis as a chiral auxiliary. Samarium diiodide is useful for deacetoxylation or dehydroxylation of α -oxygenated lactones derived from carbohydrates (Entry 10).²³⁵ The reaction is also applicable to protected hydroxy groups, such as in acetonides. The reactions in Scheme 5.12 include quite a broad range of reductable groups, including some (e.g., ether) that are modest leaving groups.

²³³ G. A. Molander and G. Hahn, *J. Org. Chem.*, **51**, 1135 (1986).

²³⁴ R. A. Holton, C. Somoza, and K.-B. Chai, *Tetrahedron Lett.*, **35**, 1665 (1994).

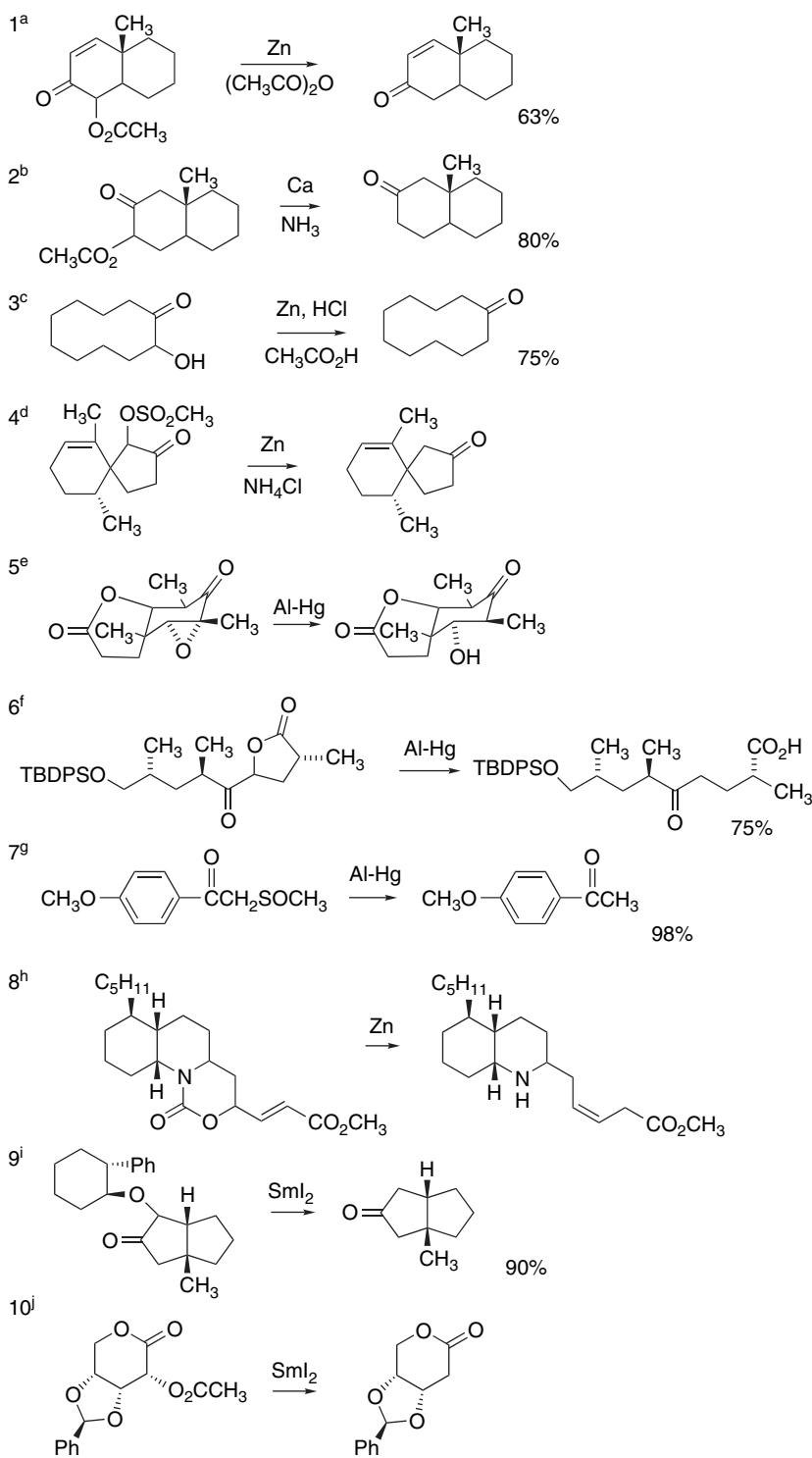
²³⁵ S. Hanessian, C. Girard, and J. L. Chiara, *Tetrahedron Lett.*, **33**, 573 (1992).

Scheme 5.12. Reductive Removal of Functional Groups from α -Substituted Carbonyl Compounds

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SECTION 5.6

Dissolving-Metal Reductions



(Continued)

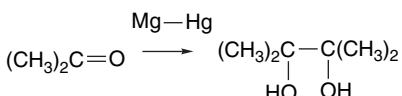
CHAPTER 5

Reduction of
Carbon-Carbon Multiple
Bonds, Carbonyl
Groups, and Other
Functional Groups

- a. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and M. W. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).
 b. J. A. Marshall and H. Roebke, *J. Org. Chem.*, **34**, 4188 (1969).
 c. A. C. Cope, J. W. Barthel, and R. D. Smith, *Org. Synth.*, **IV**, 218 (1963).
 d. T. Ibuka, K. Hayashi, H. Minakata, and Y. Inubushi, *Tetrahedron Lett.*, 159 (1979).
 e. E. J. Corey, E. J. Trybulski, L. S. Melvin, Jr., K. C. Nicolaou, J. A. Sechrist, R. Lett, P. W. Sheldrake, J. R. Falck, D. J. Brunelle, M. F. Haslanger, S. Kim, and S. Yoo, *J. Am. Chem. Soc.*, **100**, 4618 (1978).
 f. P. A. Grieco, E. Williams, H. Tanaka, and S. Gilman, *J. Org. Chem.*, **45**, 3537 (1980).
 g. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **86**, 1639 (1964).
 h. L. E. Overman and C. Fukaya, *J. Am. Chem. Soc.*, **102**, 1454 (1980).
 i. J. Castro, H. Sorensen, A. Riera, C. Morin, A. Moyano, M. A. Pericas, and A. E. Greene, *J. Am. Chem. Soc.*, **112**, 9388 (1990).
 j. S. Hanessian, C. Girard, and J. L. Chiara, *Tetrahedron Lett.*, **33**, 573 (1992).

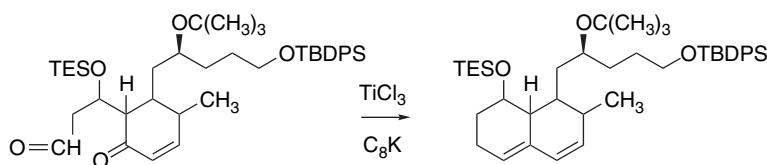
5.6.3. Reductive Coupling of Carbonyl Compounds

As reductions by metals often occur by one-electron transfers, radicals are involved as intermediates. When the reaction conditions are adjusted so that coupling competes favorably with other processes, the formation of a carbon-carbon bond can occur. The reductive coupling of acetone to 2,3-dimethylbutane-2,3-diol (pinacol) is an example of such a reaction.



Ref. 236

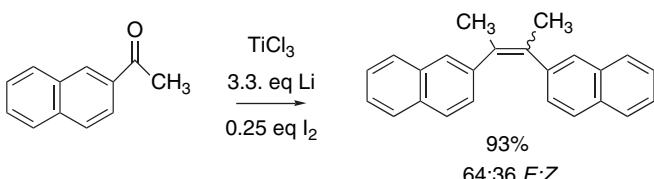
Reduced forms of titanium are currently the most versatile and dependable reagents for reductive coupling of carbonyl compounds. These reagents are collectively referred to as *low-valent titanium*. Either diols or alkenes can be formed, depending on the conditions.²³⁷ Several different procedures have evolved for titanium-mediated coupling. One procedure involves prereduction of TiCl_3 with strong reducing agents such as LiAlH_4 ,²³⁸ potassium on graphite (C_8K),²³⁹ or Na-naphthalenide.^{240b} The reductant prepared in this way is quite effective at coupling reactants with several oxygen substituents.



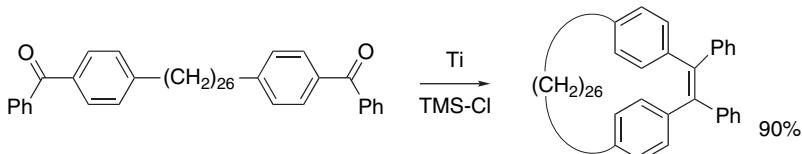
Ref. 240

- ²³⁶ R. Adams and E. W. Adams, *Org. Synth.*, **I**, 448 (1932).
²³⁷ J. E. McMurry, *Chem. Rev.*, **89**, 1513 (1989).
²³⁸ J. E. McMurry and M. P. Fleming, *J. Org. Chem.*, **41**, 896 (1976); J. E. McMurry and L. R. Krepski, *J. Org. Chem.*, **41**, 3929 (1976); J. E. McMurry, M. P. Fleming, K. L. Kees, and L. R. Krepski, *J. Org. Chem.*, **43**, 3255 (1978); J. E. McMurry, *Acc. Chem. Res.*, **16**, 405 (1983).
²³⁹ (a) A. Fürstner and H. Weidmann, *Synthesis*, 1071 (1987); (b) D. L. J. Clive, C. Zhang, K. S. K. Murthy, W. D. Hayward, and S. Daigneault, *J. Org. Chem.*, **56**, 6447 (1991).
²⁴⁰ D. L. J. Clive, K. S. K. Murthy, A. G. H. Wee, J. S. Prasad, G. V. J. Da Silva, M. Majewski, P. C. Anderson, C. F. Evans, R. D. Haugen, L. D. Heerze, and J. R. Barrie, *J. Am. Chem. Soc.*, **112**, 3018 (1990).

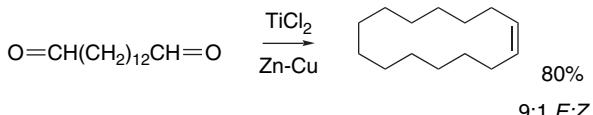
Another particularly reactive form of titanium is generated by including 0.25 equivalent of I₂. This reagent permits low-temperature reductive deoxygenation to alkenes.²⁴¹



Titanium metal is also activated by TMS-Cl.²⁴² These conditions were used in a number of dimerizations and cyclizations, including the formation of a 36-membered ring.

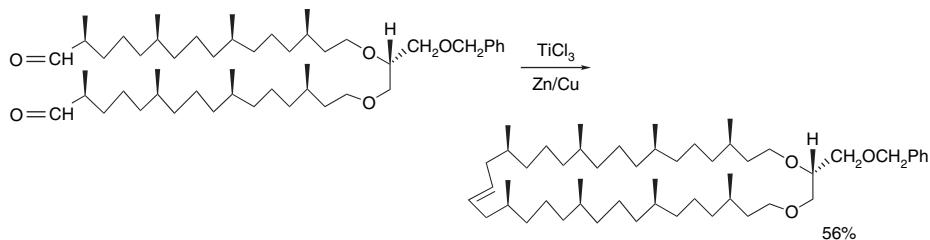


Another process that is widely used involves reduction by Zn-Cu couple. This reagent is especially reliable when prepared from TiCl₃ purified as a DME complex,²⁴³ and is capable of forming normal, medium, and large rings with comparable efficiency.



Ref. 244

The macrocyclization has proven useful in the formation of a number of natural products.²⁴⁵ These conditions have been used to prepare 36- and 72-membered rings.



Ref. 246

²⁴¹ S. Talukadar, S. K. Nayak, and A. Banerji, *J. Org. Chem.*, **63**, 4925 (1998).

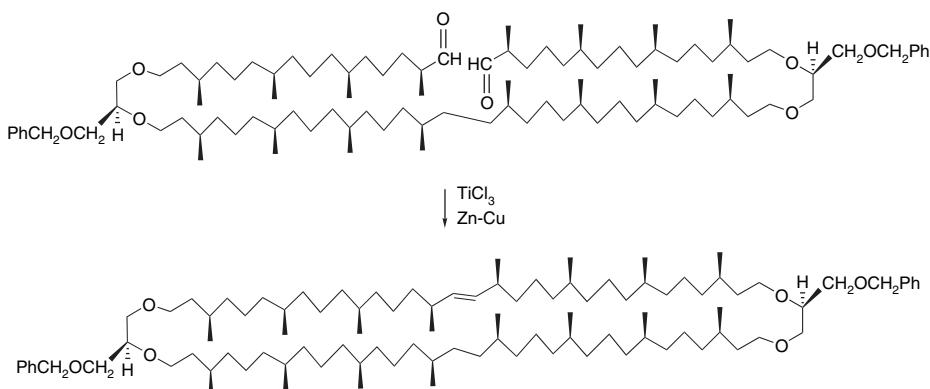
²⁴² A. Furstner and A. Hupperts, *J. Am. Chem. Soc.*, **117**, 4468 (1995).

²⁴³ J. E. McMurry, T. Lectka, and J. G. Rico, *J. Org. Chem.*, **54**, 3748 (1989).

²⁴⁴ J. E. McMurry, J. R. Matz, K. L. Kees, and P. A. Bock, *Tetrahedron Lett.*, **23**, 1777 (1982).

²⁴⁵ J. E. McMurry, J. G. Rico, and Y. Shih, *Tetrahedron Lett.*, **30**, 1173 (1989); J. E. McMurry and R. G. Dushin, *J. Am. Chem. Soc.*, **112**, 6942 (1990).

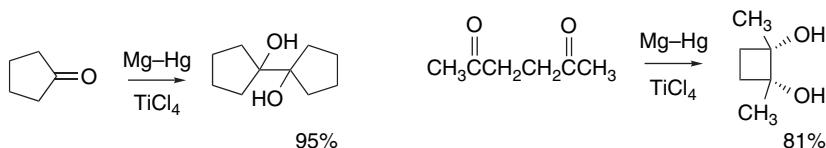
²⁴⁶ T. Eguchi, K. Arakawa, T. Terachi, and K. Kakinuma, *J. Org. Chem.*, **62**, 1924 (1997).



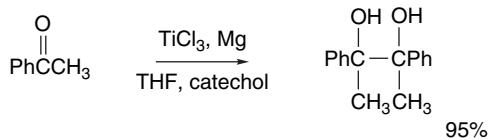
Ref. 247

The double bonds were reduced to give the saturated compounds, so the double-bond configuration was not an immediate issue. It appears, however, that the *E*-double bonds are formed. The debenzylated derivatives of propan-1,2,3-triol occur as lipid components in various prokaryotes (archaeabacteria) that grow under extreme thermal conditions.

Under other conditions, reduction leads to diols. Reductive coupling to diols can be done using magnesium amalgam²⁴⁸ or zinc dust.²⁴⁹



The most general procedures are based on low-valent titanium. Good yields of diols are obtained from aromatic aldehydes and ketones by adding catechol to the $\text{TiCl}_3\text{-Mg}$ reagent prior to coupling.²⁵⁰



Both unsymmetrical alkenes and diols can be prepared by applying these methods to mixtures of two different carbonyl compounds. An excess of one component can be used to achieve a high conversion of the more valuable reactant. A mixed reductive

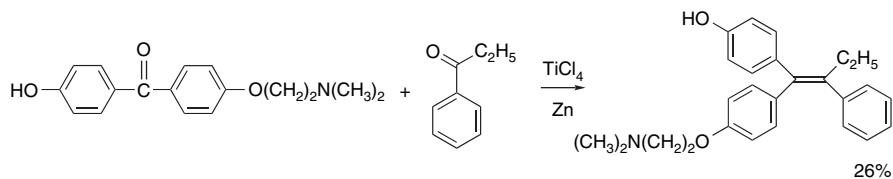
²⁴⁷ T. Eguchi, K. Ibaragi, and K. Kakinuma, *J. Org. Chem.*, **63**, 2689 (1998).

²⁴⁸ E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *J. Org. Chem.*, **41**, 260 (1976).

²⁴⁹ A. Furstner, A. Hupperts, A. Ptock, and E. Janssen, *J. Org. Chem.*, **59**, 5215 (1994).

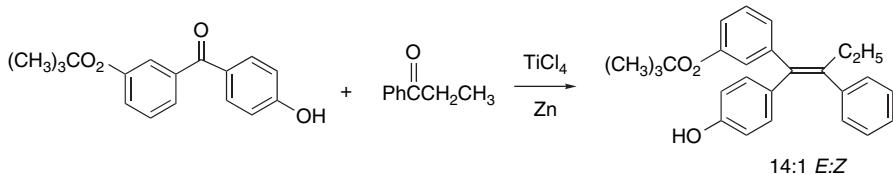
²⁵⁰ N. Balu, S. K. Nayak, and A. Banerji, *J. Am. Chem. Soc.*, **118**, 5932 (1996).

deoxygenation with $\text{TiCl}_4\text{-Zn}$ was used to prepare 4-hydroxytamoxifen, the active antiestrogenic metabolite of tamoxifen.



Ref. 251

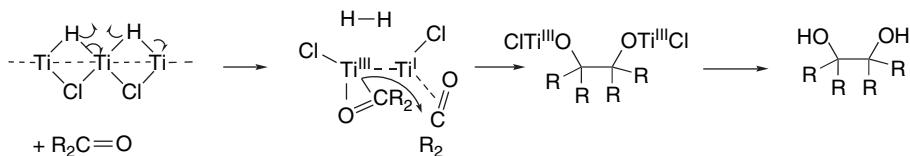
Stereoselectivity has been observed in some coupling reactions of this type. For example, coupling with 4-hydroxy-3'-pivaloyoxybenzophenone was stereoselective for the *E*-isomer.



Ref. 252

It is not clear at this time what factors determine stereoselectivity.

Titanium-mediated reductive couplings are normally heterogeneous, and it was originally thought that the reactions take place at the metal surface.²⁵³ However, mechanistic study has suggested that $\text{Ti}(\text{II})$ may be the active species. Hydride reducing agents generate a solid having the composition $(\text{HTi}^{\text{II}}\text{Cl})_n$ that effects reductive couplings. This species is believed to react with carbonyl compounds with elimination of hydrogen to generate a complexed form of the carbonyl compound. The ketone in this complex is considered to be analogous to a “ketone dianion”²⁵⁴ and is strongly nucleophilic. This mechanism accounts for the characteristic “template effect” of the titanium reagents in promoting ring formation because it involves cooperating titanium ions.



It has been suggested that a similar mechanism operates under some conditions in which the reductant is generated *in situ* by a $\text{Zn}\text{-Cu}$ couple.²⁵⁵ The key intermediate in this mechanism is a complex of the carbonyl compound with TiCl_2 . The formation

^{251.} S. Gauthier, J. Mailhot, and F. Labrie, *J. Org. Chem.*, **61**, 3890 (1996).

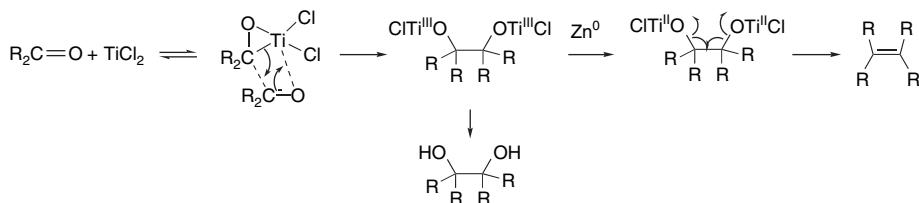
^{252.} S. Gauthier, J.-Y. Sanceau, J. Mailhot, B. Caron, and J. Cloutier, *Tetrahedron*, **56**, 703 (2000).

^{253.} R. Dams, M. Malinowski, I. Westdrop, and H. Y. Geise, *J. Org. Chem.*, **47**, 248 (1982).

^{254.} B. Bogdanovic, C. Kruger, and B. Wermeckes, *Angew. Chem. Int. Ed. Engl.*, **19**, 817 (1980).

^{255.} A. Furstner and B. Bogdanovic, *Angew. Chem. Int. Ed. Engl.*, **35**, 2442 (1996).

of alkene involves a second reduction step, which can occur at elevated temperature in the presence of excess reactant.

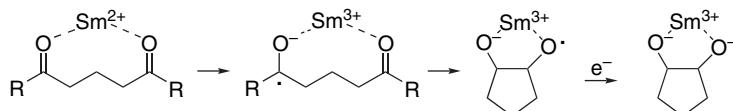


According to a DFT computational study, this mechanism is plausible.²⁵⁶

Samarium diiodide is another powerful one-electron reducing agent that can effect carbon-carbon bond formation under appropriate conditions.²⁵⁷ Aromatic aldehydes and aliphatic aldehydes and ketones undergo pinacol-type coupling with SmI_2 or SmBr_2 .

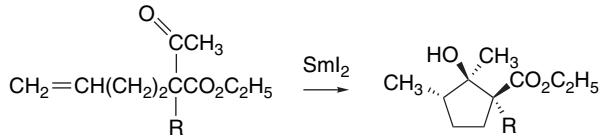


δ -Ketoaldehydes and 1,5-diketones are reduced to *cis*-cyclopentanediols.²⁵⁸ 1,6-Diketo compounds can be cyclized to cyclohexanediols, again with a preference for *cis*-diols.²⁵⁹ These reactions are believed to occur through successive one-electron transfer, radical cyclization, and a second electron transfer with Sm^{2+} serving as a tether and Lewis acid, as well as being the reductant.



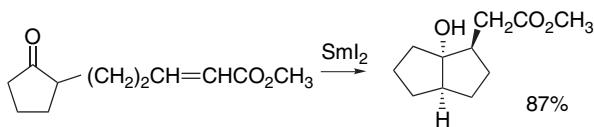
Many of the compounds used have additional functional groups, including ester, amide, ether, and acetal. These groups may be involved in coordination to samarium and thereby influence the stereoselectivity of the reaction.

The ketyl intermediates in SmI_2 reductions can be trapped by carbon-carbon double bonds, leading, for example, to cyclization of δ,ϵ -enones to cyclopentanols.



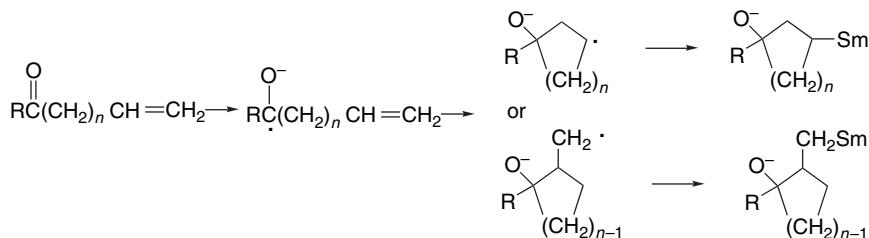
Ref. 260

- ²⁵⁶ M. Stahl, U. Pidun, and G. Frenking, *Angew. Chem. Int. Ed. Engl.*, **36**, 2234 (1997).
- ²⁵⁷ G.A. Molander, *Org. React.*, **46**, 211 (1994); J. L. Namy, J. Souuppe, and H. B. Kagan, *Tetrahedron Lett.*, **24**, 765 (1983); A. Lebrun, J.-L. Namy, and H. B. Kagan, *Tetrahedron Lett.*, **34**, 2311 (1993); H. Akane, T. Hatano, H. Kusui, Y. Nishiyama, and Y. Ishii, *J. Org. Chem.*, **59**, 7902 (1994).
- ²⁵⁸ G. A. Molander and C. Kemp, *J. Am. Chem. Soc.*, **111**, 8236 (1989); J. Uenishi, S. Masuda, and S. Wakabashi, *Tetrahedron Lett.*, **32**, 5097 (1991).
- ²⁵⁹ J. L. Chiara, W. Cabri, and S. Hanessian, *Tetrahedron Lett.*, **32**, 1125 (1991); J. P. Guidot, T. Le Gall, and C. Mioskowski, *Tetrahedron Lett.*, **35**, 6671 (1994).
- ²⁶⁰ G. Molander and C. Kenny, *J. Am. Chem. Soc.*, **111**, 8236 (1989).

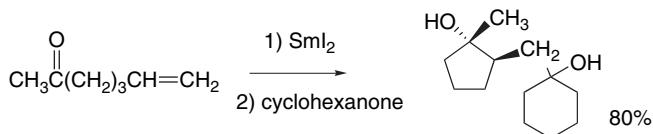


Ref. 261

SmI_2 has also been used to form cyclooctanols by cyclization of 7,8-enones.²⁶² These alkene addition reactions presumably proceed by addition of the ketyl radical to the double bond, followed by a second electron transfer.

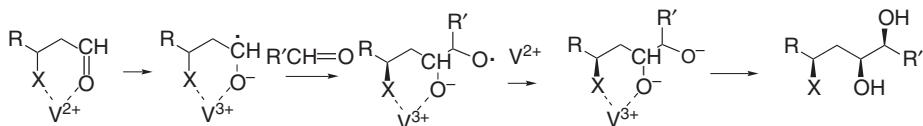


The initial products of such additions under aprotic conditions are organosamarium reagents and further (tandem) transformations are possible, including addition to ketones, anhydrides, or carbon dioxide.



Ref. 263

Another reagent that has found use in pinacolic coupling is prepared from VCl_3 and zinc dust.²⁶⁴ This reagent is selective for aldehydes that can form chelated intermediates, such as β -formylamides, α -amidoaldehydes, α -phosphinoylaldehydes,²⁶⁵ and δ -ketoaldehydes.²⁶⁶ The vanadium reagent can be used for both homodimerization and heterodimerization. In the latter case, the reactive aldehyde is added to an excess of the second aldehyde. Under these conditions, the ketyl intermediate formed from the chelated aldehyde reacts with the second aldehyde.



The $\text{VCl}_3\text{-Zn}$ reagent has also been used in cyclization reactions, as in Entries 4 and 5 in Scheme 5.13.

^{261.} E. J. Enholm and A. Trivellas, *Tetrahedron Lett.*, **30**, 1063 (1989).

^{262.} G. A. Molander and J. A. McKie, *J. Org. Chem.*, **59**, 3186 (1994).

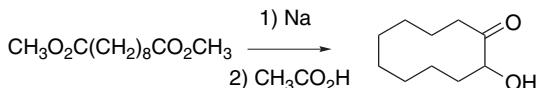
^{263.} G. A. Molander and J. A. McKie, *J. Org. Chem.*, **57**, 3132 (1992).

^{264.} J. H. Freudenberg, A. W. Konradi, and S. F. Pedersen, *J. Am. Chem. Soc.*, **111**, 8014 (1989).

^{265.} J. Park and S. F. Pedersen, *J. Org. Chem.*, **55**, 5924 (1990).

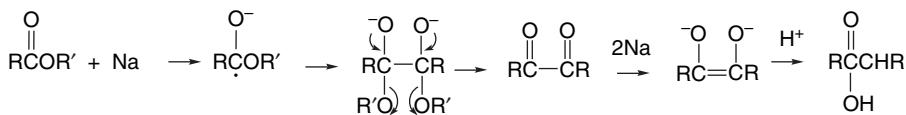
^{266.} A. S. Raw and S. F. Pedersen, *J. Org. Chem.*, **56**, 830 (1991).

Another important reductive coupling is the conversion of esters to α -hydroxyketones (*acyloin condensation*).²⁶⁷ This reaction is usually carried out with sodium metal in an inert solvent. Good results have also been obtained for sodium metal dispersed on solid supports.²⁶⁸ Diesters undergo intramolecular reactions and this is also an important method for the preparation of medium and large carbocyclic rings.

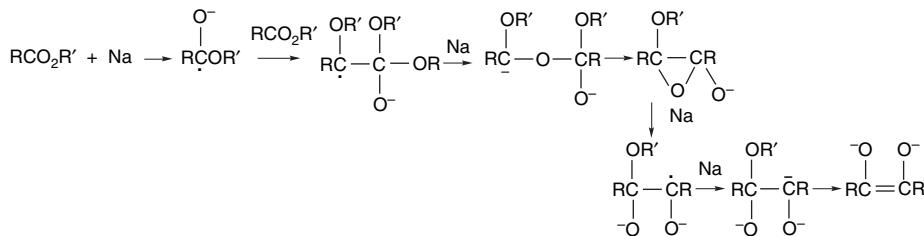


Ref. 269

There has been considerable discussion of the mechanism of the acyloin condensation. One formulation of the reaction envisages coupling of radicals generated by one-electron transfer.



An alternative mechanism bypasses the postulated α -diketone intermediate because its involvement is doubtful.²⁷⁰



Regardless of the details of the mechanism, the product prior to neutralization is the dianion of an α -hydroxy ketone, namely an enediolate. It has been found that the overall yields are greatly improved if trimethylsilyl chloride is present during the reduction to trap these dianions as trimethylsilyl ethers.²⁷¹ The silylated derivatives are much more stable to the reaction conditions than the enediolates. Hydrolysis during workup gives the acyloin product. This modified version of the reaction has been applied to cyclizations leading to small, medium, and large rings, as well as to intermolecular couplings.

Scheme 5.13 provides several examples of reductive carbon-carbon bond formation, including formation of diols, alkenes, and acyloins. Entry 1 uses magnesium amalgam in the presence of dichlorodimethylsilane. The role of the silane may be to

²⁶⁷ J. J. Bloomfield, D. C. Owsley, and J. M. Nelke, *Org. React.*, **23**, 259 (1976).

²⁶⁸ M. Makosza and K. Grela, *Synlett*, 267 (1997); M. Makosza, P. Nieczypor, and K. Grela, *Tetrahedron*, **54**, 10827 (1998).

²⁶⁹ N. Allinger, *Org. Synth.*, **IV**, 840 (1963).

²⁷⁰ J. J. Bloomfield, D. C. Owsley, C. Ainsworth, and R. E. Robertson, *J. Org. Chem.*, **40**, 393 (1975).

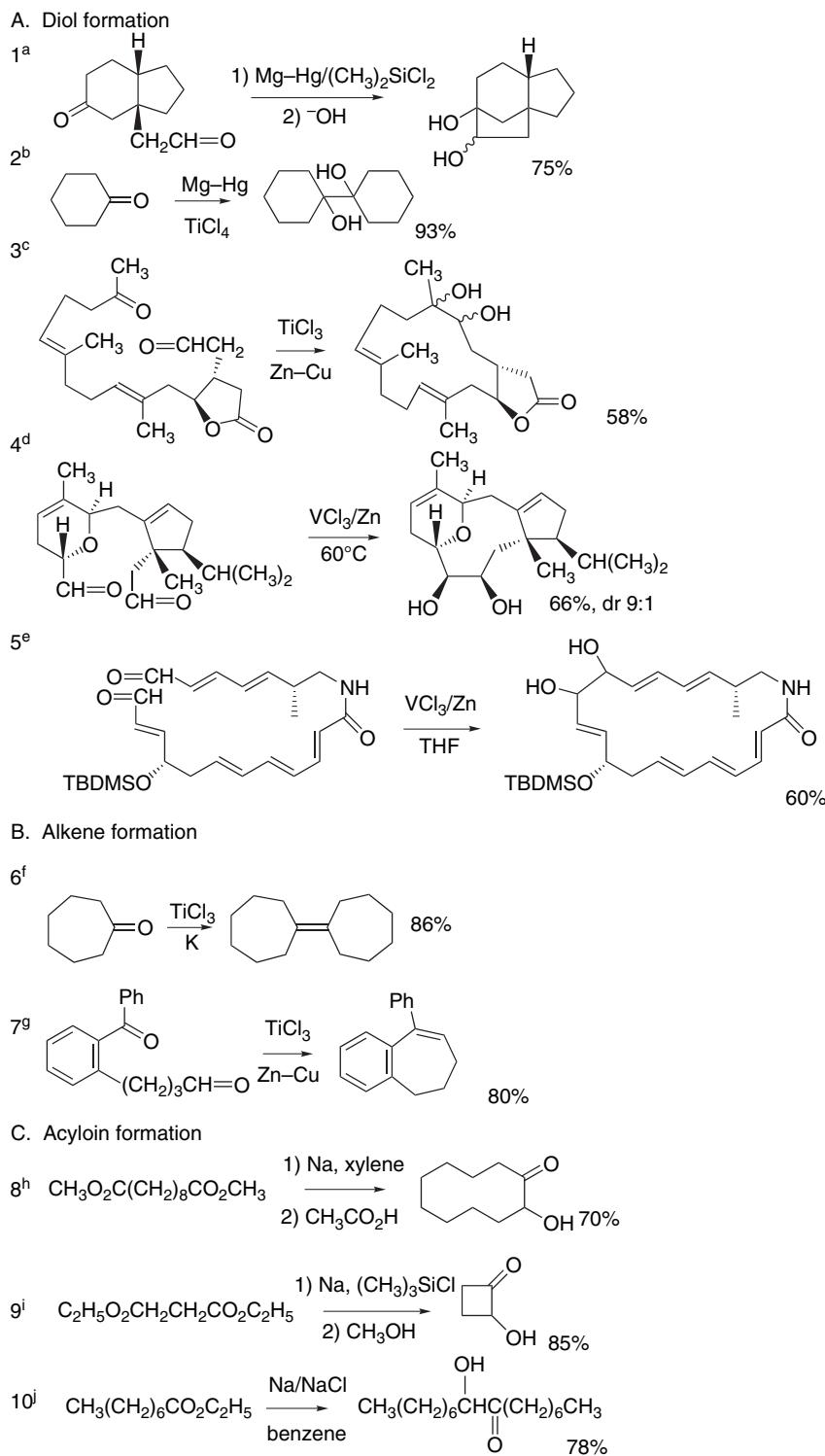
²⁷¹ K. Ruhlmann, *Synthesis*, 236 (1971).

Scheme 5.13. Reductive Coupling of Carbonyl Compound

451

SECTION 5.6

Dissolving-Metal Reductions



(Continued)

CHAPTER 5

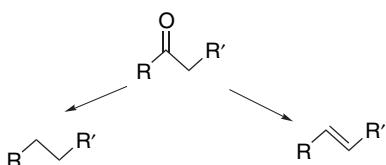
Reduction of
Carbon-Carbon Multiple
Bonds, Carbonyl
Groups, and Other
Functional Groups

- a. E. J. Corey and R. L. Carney, *J. Am. Chem. Soc.*, **93**, 7318 (1971).
- b. E. J. Corey, R. L. Danheiser, and S. Chandrasekaran, *J. Org. Chem.*, **41**, 260 (1976).
- c. J. E. McMurry and R. G. Dushin, *J. Am. Chem. Soc.*, **112**, 6942 (1990).
- d. D. R. Williams and R. W. Heidebrecht, Jr., *J. Am. Chem. Soc.*, **125**, 1843 (2003).
- e. M. Nazare and H. Waldmann, *Chem. Eur. J.*, **7**, 3363 (2001).
- f. J. E. McMurry, M. P. Fleming, K. L. Kees, and L. R. Krepski, *J. Org. Chem.*, **43**, 3255 (1978).
- g. C. B. Jackson and G. Pattenden, *Tetrahedron Lett.*, **26**, 3393 (1985).
- h. N. L. Allinger, *Org. Synth.*, **IV**, 340 (1963).
- i. J. J. Bloomfield and J. M. Nelke, *Org. Synth.*, **57**, 1 (1977).
- j. M. Makosza and K. Grela, *Synlett*, 267 (1997).

trap the pinacol as a cyclic siloxane. The reaction in Entry 2 is thought to involve Ti(II) as the active reductant and to proceed by a mechanism of the type described on p. 447. These conditions were also successful for the reaction shown in Entry 1. Entry 3 involves formation of a 14-membered ring using a low-valent titanium reagent. The product is a mixture of all four possible diastereomeric diols in yields ranging from 7 to 21%. Entry 4 is an example of a pinacol reduction using a vanadium reagent prepared *in situ* from VCl₃ and Zn, which tends to give a high proportion of *cis*-diol as a result of chelation with vanadium. Entry 5 shows the synthesis of a sensitive polyunsaturated lactam. The *cis*-diol was formed in 60% yield. In this particular case, various low-valent titanium reagents were unsuccessful. Entries 6 and 7 describe conditions that lead to alkene formation. Entries 8 to 10 are acyloin condensations. The reaction in Entry 8 illustrates the classical conditions. Entry 9 is an example of the reaction conducted in the presence of TMS-Cl to trap the enediol intermediate and make the reaction applicable to formation of a four-membered ring. The example in Entry 10 uses sodium in the form of a solid deposit on an inert material. This is an alternative to the procedures that require dispersion of molten sodium in the reaction vessel (Entries 8 and 9).

5.7. Reductive Deoxygenation of Carbonyl Groups

Several methods are available for reductive removal of carbonyl groups from organic compounds. Reduction to methylene groups or conversion to alkenes can be achieved.

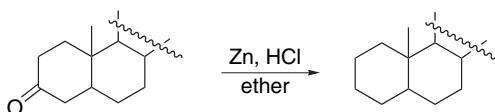


5.7.1. Reductive Deoxygenation of Carbonyl Groups to Methylenes

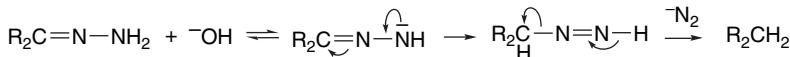
Zinc and hydrochloric acid form a classical reagent combination for conversion of carbonyl groups to methylene groups, a reaction known as the *Clemmensen reduction*.²⁷² The corresponding alcohols are not reduced under the conditions of the

²⁷² E. Vedejs, *Org. React.*, **22**, 401 (1975).

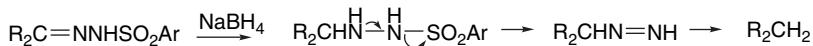
reaction, so they are evidently not intermediates. The Clemmensen reaction works best for aryl ketones and is less reliable with unconjugated ketones. The mechanism is not known in detail but may involve formation of carbon-zinc bonds at the metal surface.²⁷³ The reaction is commonly carried out in hot concentrated hydrochloric acid with ethanol as a cosolvent. These conditions preclude the presence of acid-sensitive or hydrolyzable functional groups. A modification in which the reaction is run in ether saturated with dry hydrogen chloride gave good results in the reduction of steroid ketones.²⁷⁴



The *Wolff-Kishner reaction*²⁷⁵ is the reduction of carbonyl groups to methylene groups by base-catalyzed decomposition of the hydrazone of the carbonyl compound. It is thought that alkylidimides are formed and then collapse with loss of nitrogen.²⁷⁶

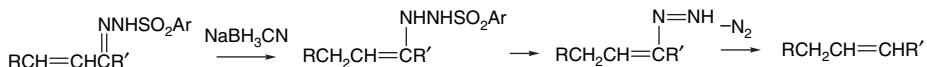


The reduction of tosylhydrazones by LiAlH_4 or NaBH_4 also converts carbonyl groups to methylene.²⁷⁷ It is believed that a diimide is involved, as in the Wolff-Kishner reaction.



Excellent yields can also be obtained using NaBH_3CN as the reducing agent.²⁷⁸ The NaBH_3CN can be added to a mixture of the carbonyl compound and *p*-toluenesulfonylhydrazide. Hydrazone formation is faster than reduction of the carbonyl group by NaBH_3CN and the tosylhydrazone is reduced as it is formed. Another reagent that can reduce tosylhydrazones to give methylene groups is $\text{CuBH}_4(\text{PPh}_3)_2$.²⁷⁹

Reduction of tosylhydrazones of α, β -unsaturated ketones by NaBH_3CN gives alkenes with the double bond located between the former carbonyl carbon and the α -carbon.²⁸⁰ This reaction is believed to proceed by an initial conjugate reduction, followed by decomposition of the resulting vinylhydrazine to a vinylidimide.



²⁷³ M. L. Di Vona and V. Rosnatti, *J. Org. Chem.*, **56**, 4269 (1991).

²⁷⁴ M. Toda, M. Hayashi, Y. Hirata, and S. Yamamura, *Bull. Chem. Soc. Jpn.*, **45**, 264 (1972).

²⁷⁵ D. Todd, *Org. React.*, **4**, 378 (1948); Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

²⁷⁶ T. Tsuji and E. M. Kosower, *J. Am. Chem. Soc.*, **93**, 1992 (1971). Alkyldimides are also converted to hydrocarbons by a free radical mechanism; A. G. Myers, M. Movassaghi and B. Zheng, *Tetrahedron Lett.*, **38**, 6569 (1997).

²⁷⁷ L. Caglioti, *Tetrahedron*, **22**, 487 (1966).

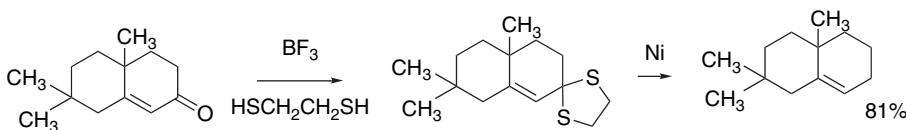
²⁷⁸ R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).

²⁷⁹ B. Milenkov and M. Hesse, *Helv. Chim. Acta*, **69**, 1323 (1986).

²⁸⁰ R. O. Hutchins, M. Kacher, and L. Rua, *J. Org. Chem.*, **40**, 923 (1975).

Catecholborane or sodium borohydride in acetic acid can also be used as a reducing reagent in this reaction.²⁸¹

Carbonyl groups can be converted to methylene groups by desulfurization of thioketals. The cyclic thioketal from ethanedithiol is commonly used. Reaction with excess Raney nickel causes hydrogenolysis of both C–S bonds.



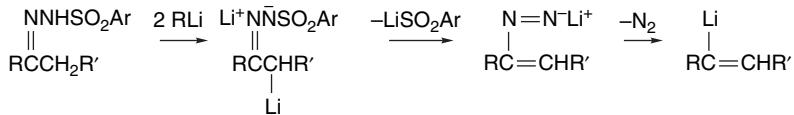
Ref. 282

Other reactive forms of nickel including nickel boride²⁸³ and nickel alkoxide complexes²⁸⁴ can also be used for desulfurization. Tri-*n*-butyltin hydride is an alternative reagent for desulfurization.²⁸⁵

Scheme 5.14 illustrates some representative carbonyl deoxygenations. Entries 1 and 2 are Clemmensen reductions of acyl phenols. Entry 3 is an example of the Wolff-Kishner reaction. Entry 4 describes modified conditions for the Wolff-Kishner reaction that take advantage of the strong basicity of the $\text{KO}t\text{Bu}-\text{DMSO}$ combination. Entries 5 to 7 are examples of conversion of sulfonylhydrazones to methylene groups (Caglioti reaction). In addition to LiAlH_4 , which was used in the original procedure, NaBH_3CN (Entry 6) and catecholborane (Entry 7) can be used as reducing agents. Entries 8 and 9 are thioketal desulfurizations.

5.7.2. Reduction of Carbonyl Compounds to Alkenes

Ketone *p*-toluenesulfonylhydrazones are converted to alkenes on treatment with strong bases such as an alkyl lithium or lithium dialkylamide.²⁸⁶ Known as the *Shapiro reaction*,²⁸⁷ this proceeds through the anion of a vinyldiimide, which decomposes to a vinyl lithium reagent. Treatment of this intermediate with a proton source gives the alkene.



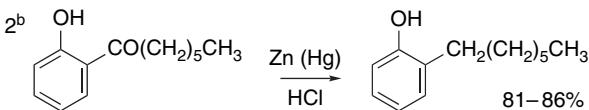
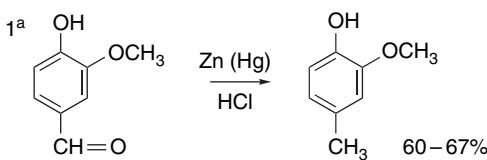
The Shapiro reaction has been particularly useful for cyclic ketones, but its scope includes acyclic systems as well. In the case of unsymmetrical acyclic ketones,

- ²⁸¹ G. W. Kabalka, D. T. C. Yang, and J. D. Baker, Jr., *J. Org. Chem.*, **41**, 574 (1976); R. O. Hutchins and N. R. Natale, *J. Org. Chem.*, **43**, 2299 (1978).
- ²⁸² F. Sondheimer and S. Wolfe, *Can. J. Chem.*, **37**, 1870 (1959).
- ²⁸³ W. E. Truce and F. M. Perry, *J. Org. Chem.*, **30**, 1316 (1965).
- ²⁸⁴ S. Becker, Y. Fort, and P. Caubere, *J. Org. Chem.*, **55**, 6194 (1990).
- ²⁸⁵ C. G. Gutierrez, R. A. Stringham, T. Nitashaka, and K. G. Glasscock, *J. Org. Chem.*, **45**, 3393 (1980).
- ²⁸⁶ R. H. Shapiro and M. J. Heath, *J. Am. Chem. Soc.*, **89**, 5734 (1967).
- ²⁸⁷ R. H. Shapiro, *Org. React.*, **23**, 405 (1976); R. M. Adington and A. G. M. Barrett, *Acc. Chem. Res.*, **16**, 53 (1983); A. R. Chamberlin and S. H. Bloom, *Org. React.*, **39**, 1 (1990).

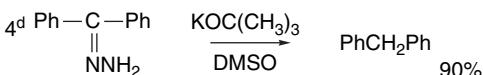
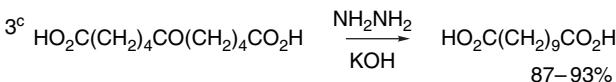
SECTION 5.7

*Reductive Deoxygenation
of Carbonyl Groups*

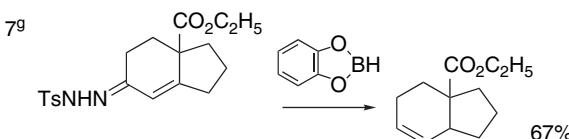
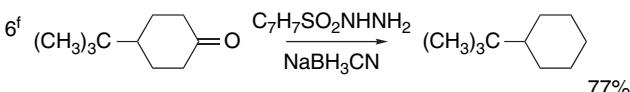
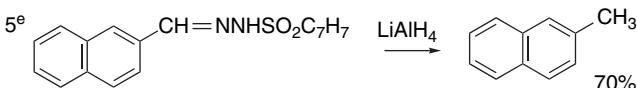
A. Clemmensen



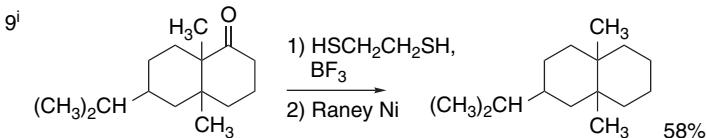
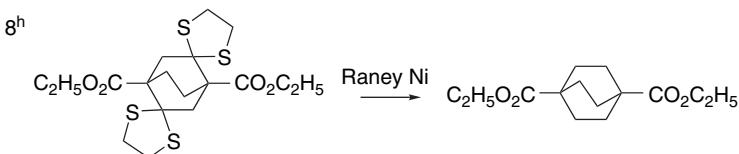
B. Wolff–Kishner



C. Tosylhydrazone reduction



D. Thioketal desulfurization



a. R. Schwarz and H. Hering, *Org. Synth.*, **IV**, 203 (1963).

b. R. R. Read and J. Wood, Jr., *Org. Synth.*, **III**, 444 (1955).

c. L. J. Durham, D. J. McLeod, and J. Cason, *Org. Synth.*, **IV**, 510 (1963).

d. D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Am. Chem. Soc.*, **84**, 1734 (1962).

e. L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963).

f. R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *J. Am. Chem. Soc.*, **93**, 1793 (1971).

g. M. N. Greco and B. E. Maryanoff, *Tetrahedron Lett.*, **33**, 5009 (1992).

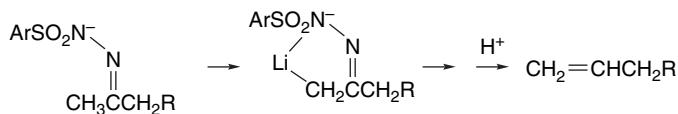
h. J. D. Roberts and W. T. Moreland, Jr., *J. Am. Chem. Soc.*, **75**, 2167 (1953).

i. P. N. Rao, *J. Org. Chem.*, **36**, 2426 (1971).

questions of both regiochemistry and stereochemistry arise. 1-Octene is the exclusive product from 2-octanone.²⁸⁸

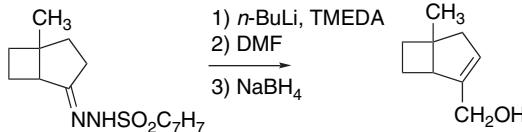


This regiospecificity has been shown to depend on the stereochemistry of the C=N bond in the starting hydrazone. There is evidently a strong preference for abstracting the proton *syn* to the arenesulfonyl group, probably because this permits chelation with the lithium ion.

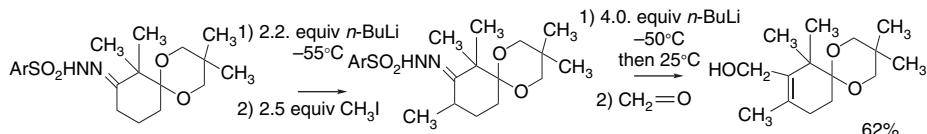


The Shapiro reaction converts the *p*-toluenesulfonylhydrazone of α,β -unsaturated ketones to dienes (see Entries 3 to 5 in Scheme 5.15).²⁸⁹

The vinyl lithium reagents generated in the Shapiro reaction can be used in tandem reactions. In the reaction shown below, a hydroxymethyl group was added by formylation followed by reduction.



In another example, a sequence of methylation-elimination-hydroxymethylation was used to install the functionality pattern found in the A-ring of taxol. The hydrazone dianion was generated and methylated at low temperature. The hydrazone was then deprotonated again using excess *n*-butyllithium and allowed to warm to room temperature, at which point formation of the vinylolithium occurred. Reaction with paraformaldehyde generated the desired product.²⁹⁰



Ar = 2,4,6-trimethylphenyl

Scheme 5.15 shows some examples of the Shapiro reaction. Entry 1 is an example of the standard procedure, as documented in *Organic Syntheses*. Entry 2 illustrates the preference for the formation of the less-substituted double bond. Entries 3, 4, and 5 involve tosylhydrazone of α,β -unsaturated ketones. The reactions proceed by α' -deprotonation. Entry 6 illustrates the applicability of the reaction to a highly strained system.

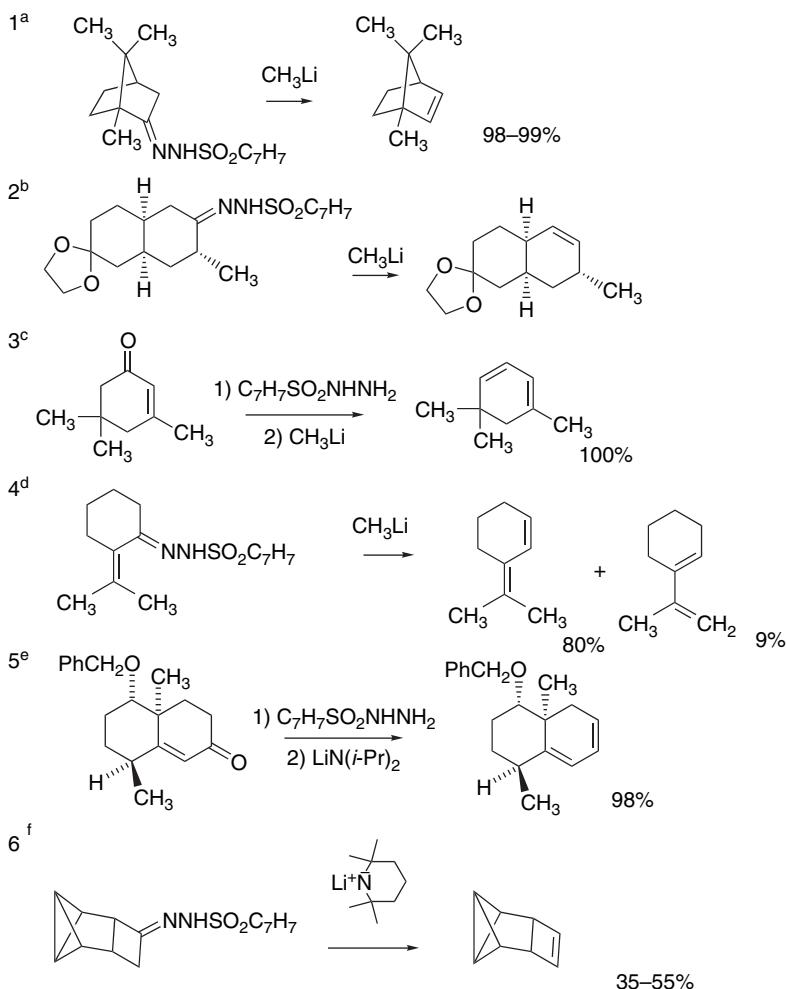
²⁸⁸ K. J. Kolonko and R. H. Shapiro, *J. Org. Chem.*, **43**, 1404 (1978).

²⁸⁹ W. G. Dauben, G. T. Rivers, and W. T. Zimmerman, *J. Am. Chem. Soc.*, **99**, 3414 (1977).

²⁹⁰ O. P. Tormakangas, R. J. Toivola, E. K. Karvinen, and A. M. P. Koskinen, *Tetrahedron*, **58**, 2175 (2002).

Scheme 5.15. Conversion of Ketones to Alkenes via Sulfonylhydrazones

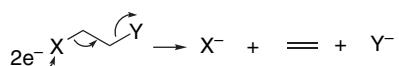
SECTION 5.8

Reductive Elimination
and Fragmentation

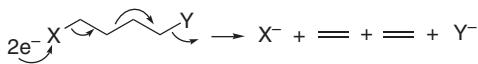
- a. R. H. Shapiro and J. H. Duncan, *Org. Synth.*, **51**, 66 (1971).
- b. W. L. Scott and D. A. Evans, *J. Am. Chem. Soc.*, **94**, 4779 (1972).
- c. W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, and K. Tomer, *J. Am. Chem. Soc.*, **90**, 4762 (1968).
- d. W. G. Dauben, G. T. Rivers, and W. T. Zimmerman, *J. Am. Chem. Soc.*, **99**, 3414 (1977).
- e. P. A. Grieco, T. Oguri, C.-L. J. Wang, and E. Williams, *J. Org. Chem.*, **42**, 4113 (1977).
- f. L. R. Smith, G. R. Gream, and J. Meinwald, *J. Org. Chem.*, **42**, 927 (1977).

5.8. Reductive Elimination and Fragmentation

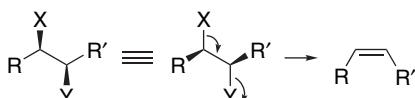
The presence of a potential leaving group β to the site of carbanionic character usually leads to β -elimination. In some useful synthetic procedures, the carbanionic character is generated by a reductive process.



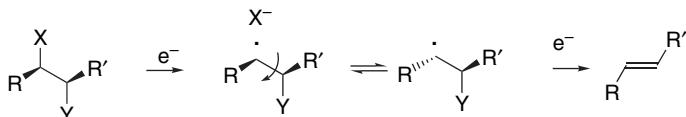
Similarly, carbanionic character δ to a leaving group can lead to β , γ -fragmentation.



A classical example of the β -elimination reaction is the reductive debromination of vicinal dibromides. Zinc metal is the traditional reducing agent.²⁹¹ A multitude of other reducing agents have been found to give this and similar reductive eliminations. Some examples are given in Table 5.7. Some of the reagents exhibit *anti* stereospecificity, whereas others do not. A stringent test for *anti* stereospecificity is the extent of *Z*-alkene formed from a *syn* precursor.



Anti stereospecificity is associated with a concerted reductive elimination, whereas single-electron transfer fragmentation leads to loss of stereospecificity and formation of the more stable *E*-stereoisomer.



As vicinal dibromides are usually made by bromination of alkenes, their utility for synthesis is limited, except for temporary masking of a double bond. Much more frequently it is desirable to convert a diol to an alkene, and several useful procedures have been developed. The reductive deoxygenation of diols via thiono carbonates was

Table 5.7. Reagents for Reductive Dehalogenation

Reagent	<i>Anti</i> stereoselectivity
Zn, cat TiCl ₄ ^a	Yes
Zn, H ₂ NSNH ₂ ^b	?
SnCl ₂ , DiBAIH ^c	?
Sm, CH ₃ OH ^d	No
Fe, graphite ^e	Yes
C ₂ H ₅ MgBr, cat Ni(dppe)Cl ₂ ^f	No

a. F. Sato, T. Akiyama, K. Ida, and M. Sato, *Synthesis*, 1025 (1982).

b. R. N. Majumdar and H. J. Harwood, *Synth. Commun.*, **11**, 901 (1981).

c. T. Oriyama and T. Mukaiyama, *Chem. Lett.*, 2069 (1984).

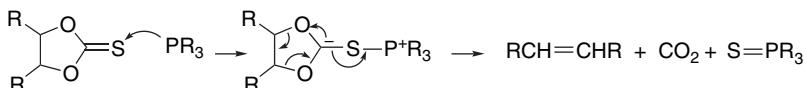
d. R. Yanada, N. Negoro, K. Yanada, and T. Fujita, *Tetrahedron Lett.*, **37**, 9313 (1996).

e. D. Savoia, E. Tagliavini, C. Trombini, and A. Umani-Ronchi, *J. Org. Chem.*, **47**, 876 (1982).

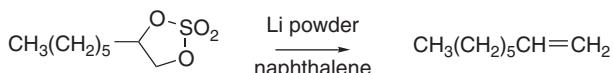
f. C. Malanga, L. A. Aronica, and L. Lardicci, *Tetrahedron Lett.*, **36**, 9189 (1995).

²⁹¹ J. C. Sauer, *Org. Synth.*, **IV**, 268 (1965).

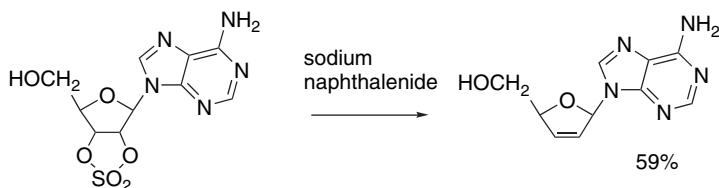
developed by Corey and co-workers.²⁹² Triethyl phosphite is useful for many cases, but the more reactive 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine can be used when milder conditions are required.²⁹³ The reaction presumably occurs by initial P–S bonding followed by a concerted elimination of carbon dioxide and the thiophosphoryl compound.



Diols can also be deoxygenated via *bis*-sulfonate esters using sodium naphthalenide.²⁹⁴ Cyclic sulfate esters are also cleanly reduced by lithium naphthalenide.²⁹⁵

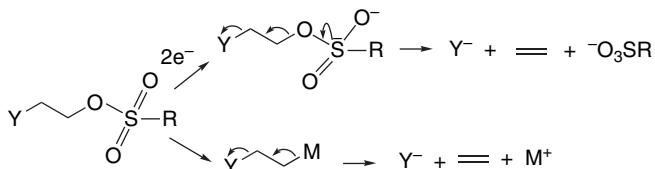


This reaction, using sodium naphthalenide, has been used to prepare unsaturated nucleosides.



Ref. 296

It is not entirely clear whether these reactions involve a redox reaction at sulfur or if they proceed by organometallic intermediates.



Iodination reagents combined with aryl phosphines and imidazole can also effect reductive conversion of diols to alkenes. One such combination is 2,4,5-triiodoimidazole, imidazole, and triphenylphosphine.²⁹⁷ These reagent combinations

²⁹² E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, **85**, 2677 (1963); E. J. Corey, F. A. Carey, and R. A. E. Winter, *J. Am. Chem. Soc.*, **87**, 934 (1965).

²⁹³ E. J. Corey and P. B. Hopkins, *Tetrahedron Lett.*, **23**, 1979 (1982).

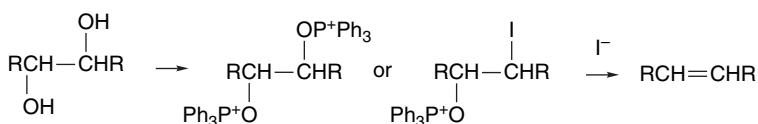
²⁹⁴ J. C. Carnahan, Jr., and W. D. Closson, *Tetrahedron Lett.*, 3447 (1972); R. J. Sundberg and R. J. Cherney, *J. Org. Chem.*, **55**, 6028 (1990).

²⁹⁵ D. Guijarro, B. Mancheno, and M. Yus, *Tetrahedron Lett.*, **33**, 5597 (1992).

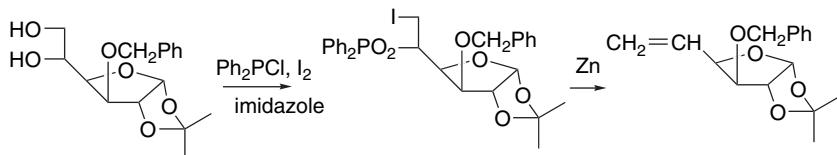
²⁹⁶ M. J. Robins, E. Lewandowska, and S. F. Wnuk, *J. Org. Chem.*, **63**, 7375 (1998).

²⁹⁷ P. J. Garegg and B. Samuelsson, *Synthesis*, 813 (1979); Y. Watanabe, M. Mitani, and S. Ozaki, *Chem. Lett.*, 123 (1987).

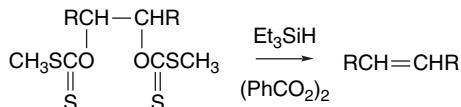
are believed to give oxyphosphonium intermediates, which then can serve as leaving groups, forming triphenylphosphine oxide as in the Mitsunobu reaction (see Section 3.2.3). The iodide serves as both a nucleophile and reductant.



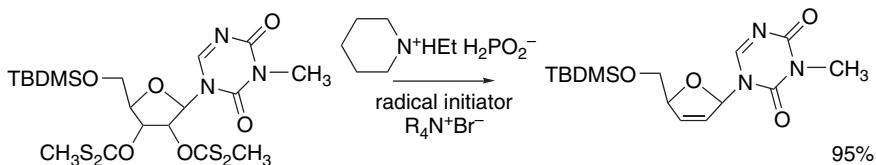
In a related procedure, chlorodiphenylphosphine, imidazole, iodine, and zinc cause reductive elimination of diols.²⁹⁸ β -Iodophosphinate esters can be shown to be intermediates in some cases.



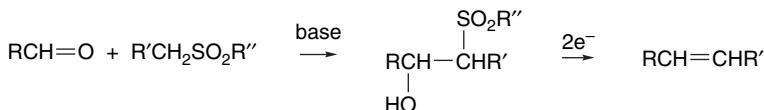
Another alternative for conversion of diols to alkenes is the use of the Barton radical fragmentation conditions (see Section 5.5) with a silane hydrogen atom donor.²⁹⁹



N-Ethylpiperidinium hypophosphite has been used as a reductant in deoxygenation of nucleoside diol xanthates in aqueous solution.³⁰⁰



The reductive elimination of β -hydroxysulfones is the final step in the *Julia-Lythgoe alkene synthesis* (see Section 2.4.3).³⁰¹ The β -hydroxysulfones are normally obtained by an aldol addition.



²⁹⁸ Z. Liu, B. Classon, and B. Samuelsson, *J. Org. Chem.*, **55**, 4273 (1990).

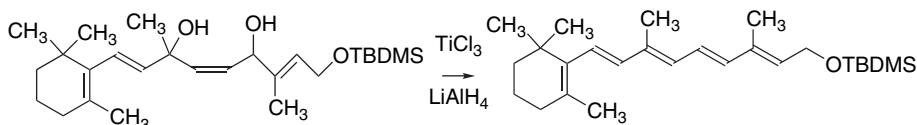
²⁹⁹ D. H. R. Barton, D. O. Jang, and J. C. Jaszberenyi, *Tetrahedron Lett.*, **32**, 2569 (1991); D. H. R. Barton, D. O. Jang, and J. C. Jaszberenyi, *Tetrahedron Lett.*, **32**, 7187 (1991).

³⁰⁰ D. O. Jang and D. H. Cho, *Tetrahedron Lett.*, **43**, 5921 (2002).

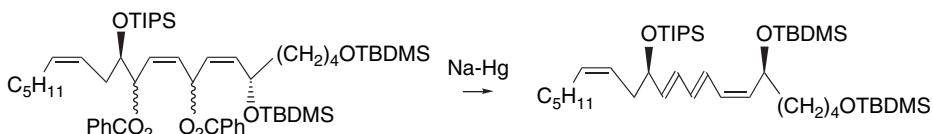
³⁰¹ P. Kocienski, *Phosphorus and Sulfur*, **24**, 97 (1985).

Several reducing agents have been used for the elimination, including sodium amalgam³⁰² and samarium diiodide.³⁰³ The elimination can also be done by converting the hydroxy group to a xanthate or thiocarbonate and using radical fragmentation.³⁰⁴

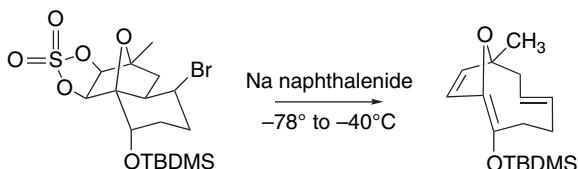
Reductive elimination from 2-en-1,4-diol derivatives has been used to generate 1,3-dienes. Low-valent titanium generated from $TiCl_3-LiAlH_4$ can be used directly with the diols. This reaction has been used successfully to create extended polyene conjugation.³⁰⁵



Benzoate esters of 2-en-1,4-diols undergo reductive elimination with sodium amalgam.³⁰⁶



The β,γ -fragmentation is known as Grob fragmentation. Its synthetic application is usually in the construction of medium-sized rings by fragmentation of fused-ring systems. The reaction below results in both a reductive fragmentation and deoxygenation via a cyclic sulfate.



Ref. 307

- ^{302.} P. J. Kocienski, B. Lythgoe, and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1045 (1980); A. Armstrong, S. V. Ley, A. Madin, and S. Mukherjee, *Synlett*, 328 (1990); M. Kagayama, T. Tamura, M. H. Nantz, J. C. Roberts, P. Somfai, D. C. Whritenour, and S. Masamune, *J. Am. Chem. Soc.*, **112**, 7407 (1990).
- ^{303.} A. S. Kende and J. S. Mendoza, *Tetrahedron Lett.*, **31**, 7105 (1990); I. E. Marko, F. Murphy, and S. Dolan, *Tetrahedron Lett.*, **37**, 2089 (1996); G. E. Keck, K. A. Savin, and M. A. Weglarz, *J. Org. Chem.*, **60**, 3194 (1995).
- ^{304.} D. H. R. Barton, J. C. Jasberenyi, and C. Tachdjian, *Tetrahedron Lett.*, **32**, 2703 (1991).
- ^{305.} G. Solladie, A. Givardin, and G. Lang, *J. Org. Chem.*, **54**, 2620 (1989); G. Solladie and V. Berl, *Tetrahedron Lett.*, **33**, 3477 (1992).
- ^{306.} G. Solladie, A. Urbano, and G. B. Stone, *Tetrahedron Lett.*, **34**, 6489 (1993).
- ^{307.} W. B. Wang and E. J. Roskamp, *Tetrahedron Lett.*, **33**, 7631 (1992).

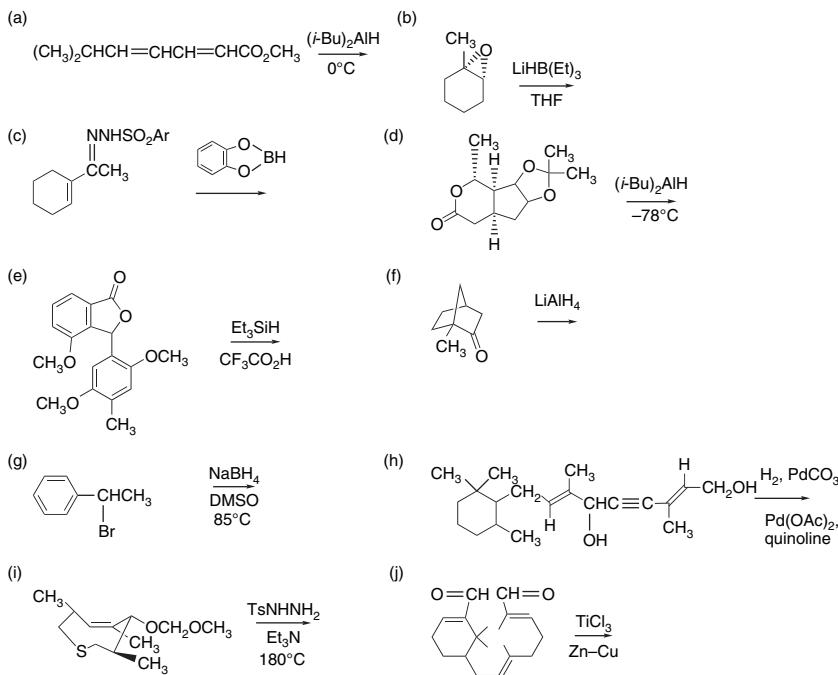
Problems

CHAPTER 5

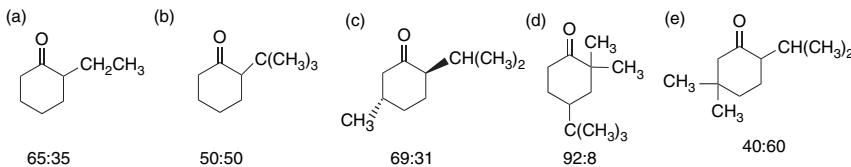
*Reduction of
Carbon-Carbon Multiple
Bonds, Carbonyl
Groups, and Other
Functional Groups*

(References for these problems will be found on page 1278.)

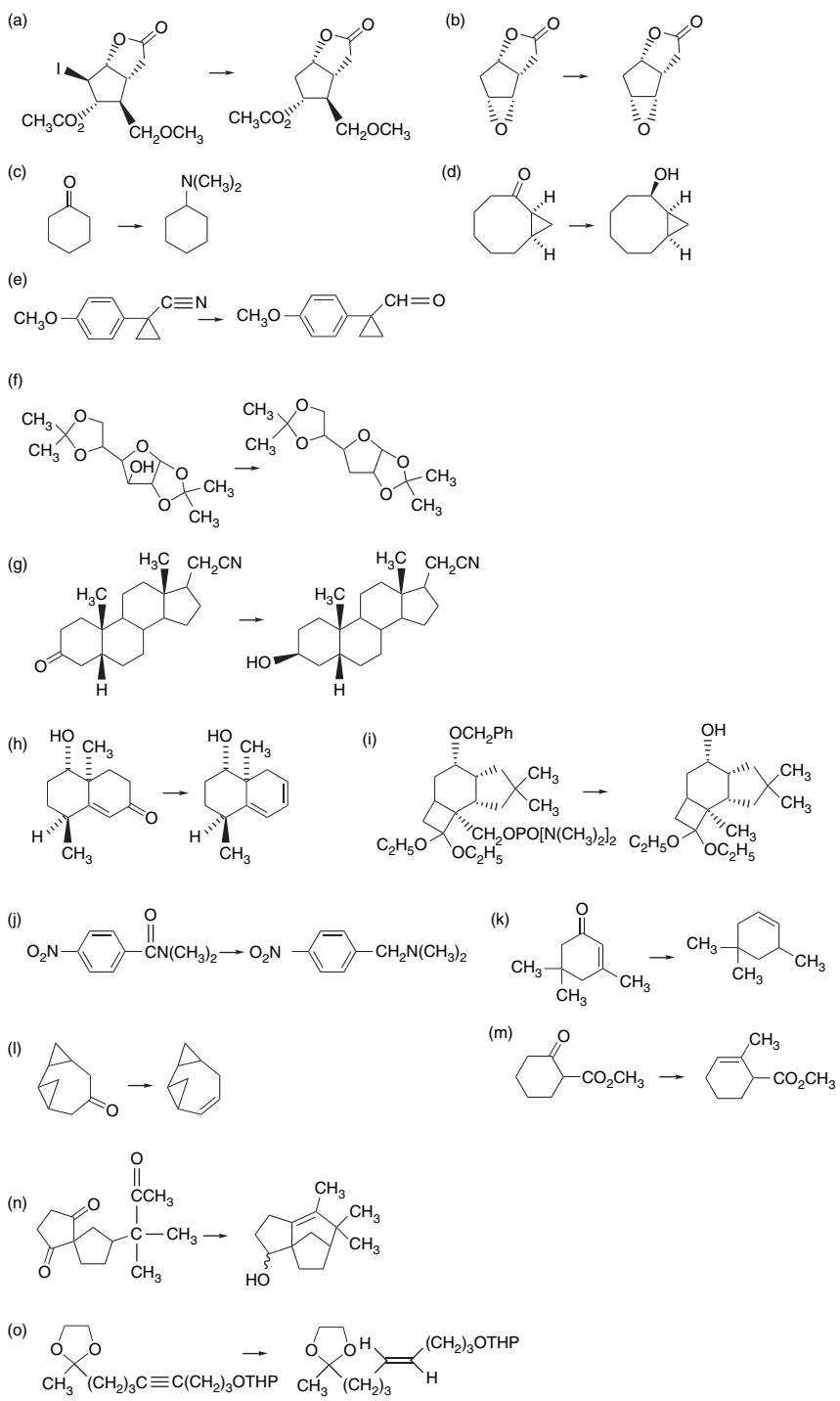
- 5.1. Give the product(s) to be expected from the following reactions. Be sure to specify all facets of stereochemistry.



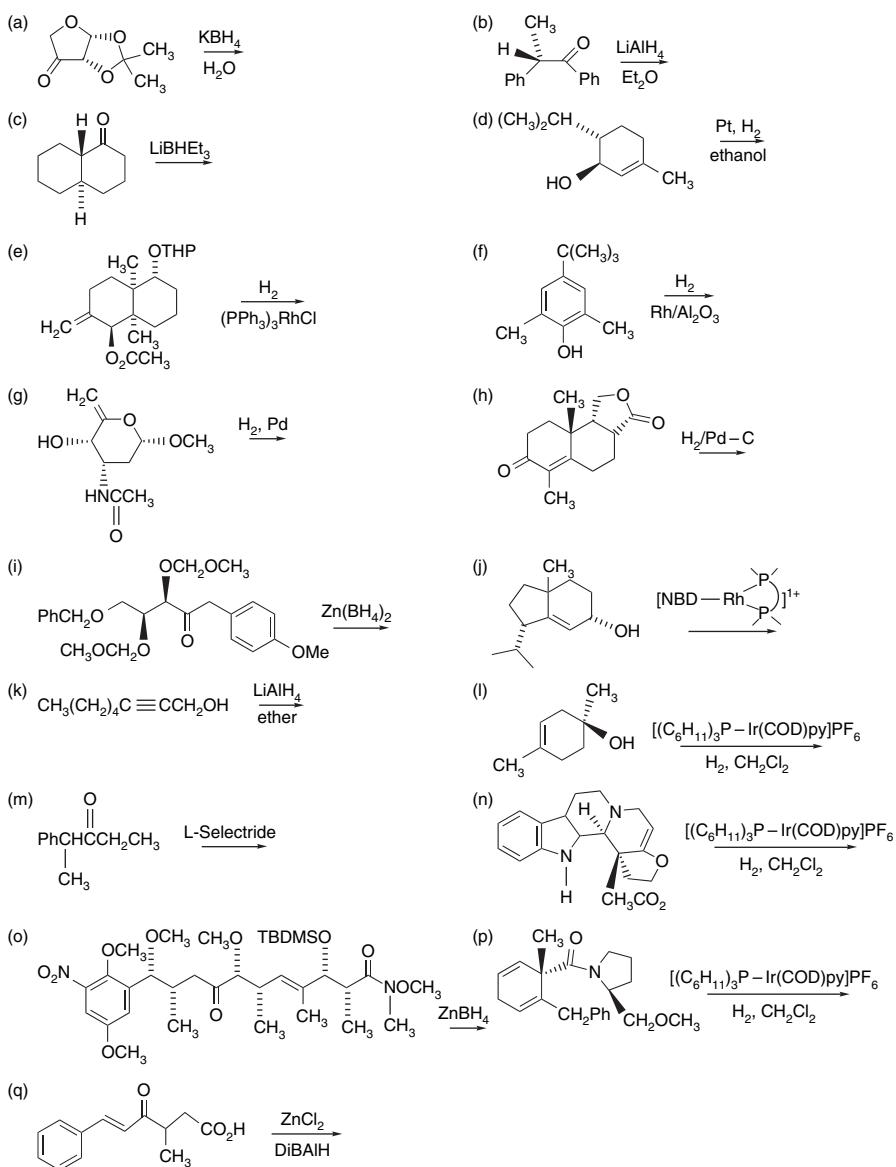
- 5.2. The data below give the ratio of equatorial:axial alcohol by NaBH_4 reduction of each cyclohexanone derivative under conditions in which 4-*t*-butylcyclohexanone gives an approximately 85:15 ratio. Analyze the effect of the substituents in each case.



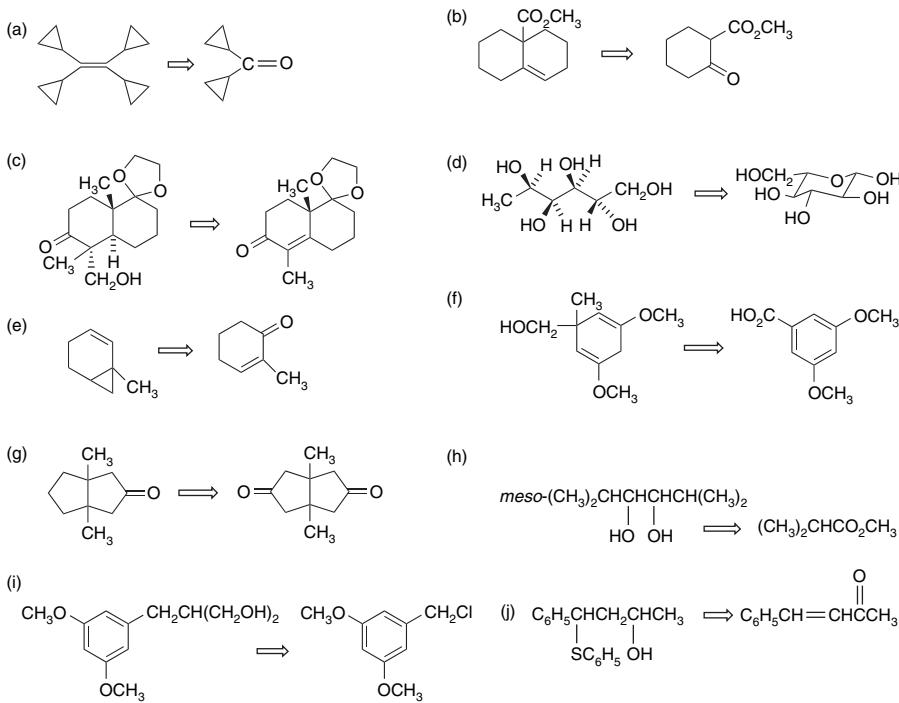
- 5.3. Indicate reaction conditions that would accomplish each of the following transformations in a single step:



5.4. Predict the stereochemistry of the products from the following reactions and justify your prediction.



5.5. Suggest a convenient method for carrying out the following syntheses. The compound on the left is to be made from the one on the right (retrosynthetic notation). No more than three steps should be necessary.

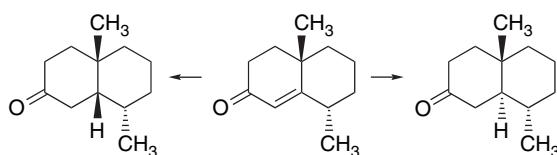


5.6. Offer an explanation to account for the observed differences in the rate of the following reactions:

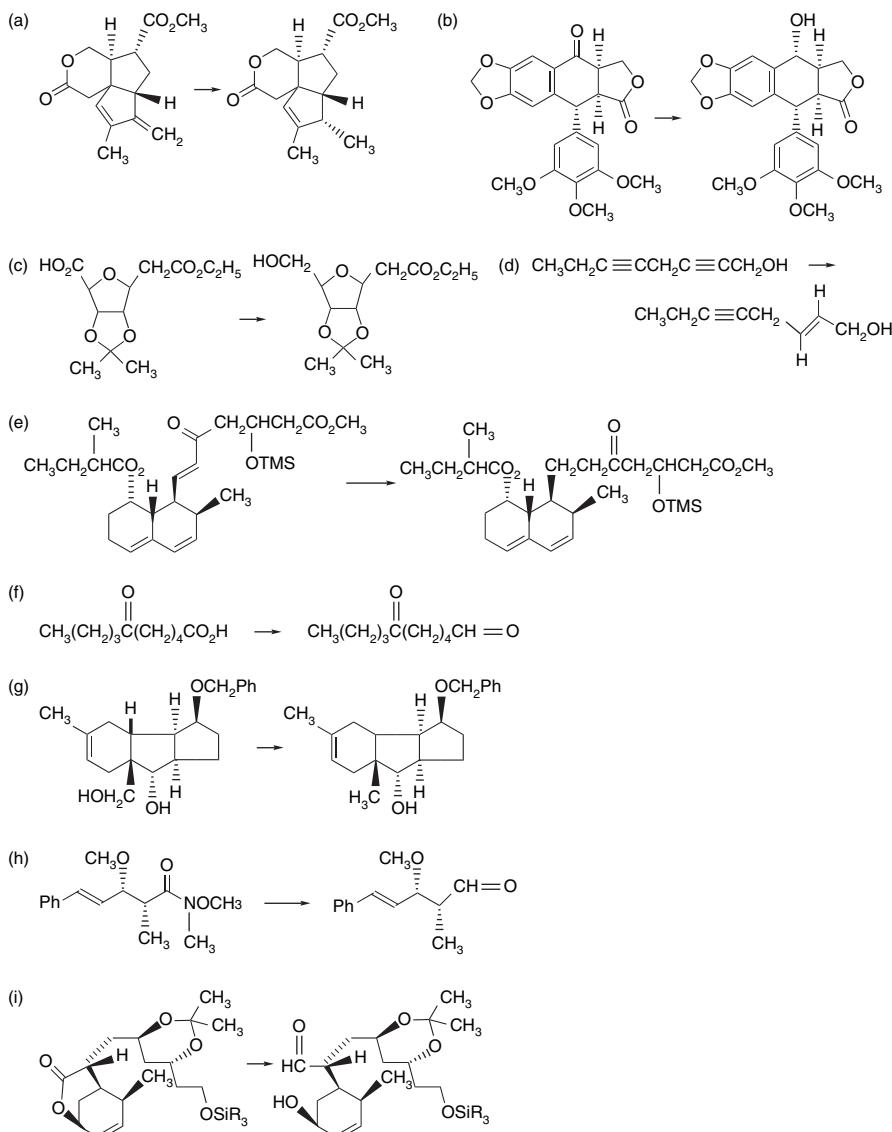
- LiAlH_4 reduces camphor about 30 times faster than does NaAlH_4 .
- The rate of reduction of camphor by LiAlH_4 is decreased by a factor of about 4 when a crown ether is added to the reaction mixture.
- For reduction of cyclohexanones by $\text{LiAlH}(t\text{-OBu})_3$, the addition of one methyl group at C(3) has little effect, but a second group on the same carbon has a large effect. The addition of a third methyl group at C(5) has no effect and the addition of a second methyl at C(5) has only a small effect.

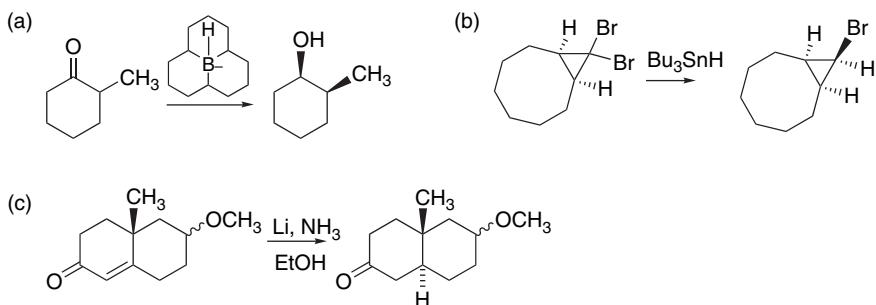
Ketone	Rel. rate
Cyclohexanone	439
3-Methylcyclohexanone	280
3,3-Dimethylcyclohexanone	17.5
3,3,5-Trimethylcyclohexanone	17.4
3,3,5,5-Tetramethylcyclohexanone	8.9

5.7. Suggest reaction conditions appropriate for stereoselective conversion of the octalone shown to each of the diastereomeric decalones.

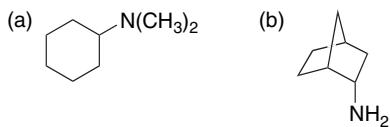


- 5.8. The fruit of a shrub that grows in Sierra Leone is very toxic and has been used as a rat poison. The toxic principal has been identified as Z-18-fluoro-9-octadecenoic acid. Suggest a synthesis from 8-fluorooctanol, 1-chloro-7-iodoheptane, acetylene, and any other necessary organic or inorganic reagents.
- 5.9. Each of the following compounds contains more than one potentially reducible group. Indicate a reducing agent that will be suitable for effecting the desired reduction. Explain the basis for the expected selectivity.

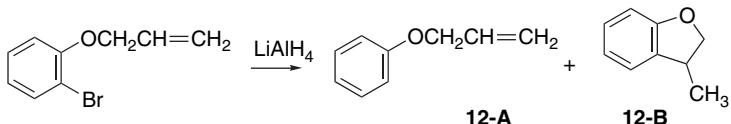




5.11. A valuable application of sodium cyanoborohydride is in the synthesis of amines by reductive amination. What combination of carbonyl and amine components would give the following amines by this method?

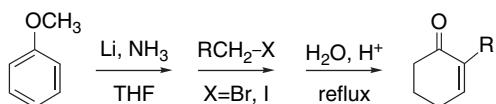


5.12. The reduction of allyl *o*-bromophenyl ether by LiAlH₄ has been studied in several solvents. In ether, two products **12-A** and **12-B** are formed. The ratio **12-A**:**12-B** increases with increasing LiAlH₄ concentration. When LiAlD₄ is used as the reductant, about half of product **12-B** is monodeuterated. Provide a mechanistic rationale for these results. What is the predicted location of the deuterium in the **12-B**? Why is the product not completely deuterated?

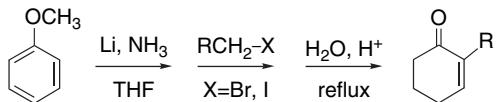


5.13. Each of the following parts describes a synthetic sequence in which Birch reduction is employed to convert aromatic rings to partially saturated products.

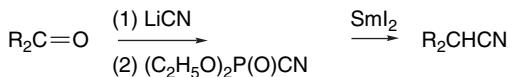
- a. A simple synthesis of 2-substituted cyclohexenones from 2-methoxybenzoic acid has been developed. The reaction sequence entails Birch reduction, tandem alkylation, and acid hydrolysis. Although the yields are only 25–30%, it can be carried out as a one-pot process using the sequence of reactions shown below. Explain the mechanistic basis of this synthesis and identify the intermediate present after each stage of the sequence.



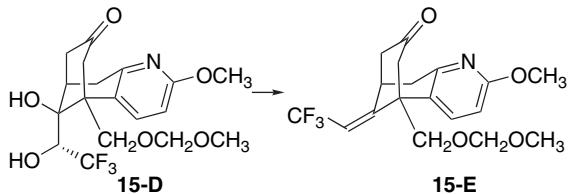
- b. Birch reduction of 3,4,5-trimethoxybenzoic acid gives a dihydrobenzoic acid in 94% yield, but it has only *two* methoxy substituents. Suggest a plausible structure for this product based on the mechanism of the Birch reduction.
- c. The cyclohexenone **13-C** has been prepared in a one-pot process starting with 4-methylpent-3-en-2-one. The reagents that are added in succession are 4-methoxyphenyllithium, Li, and NH₃, followed by acidic workup. Show the intermediates that are involved in the process.



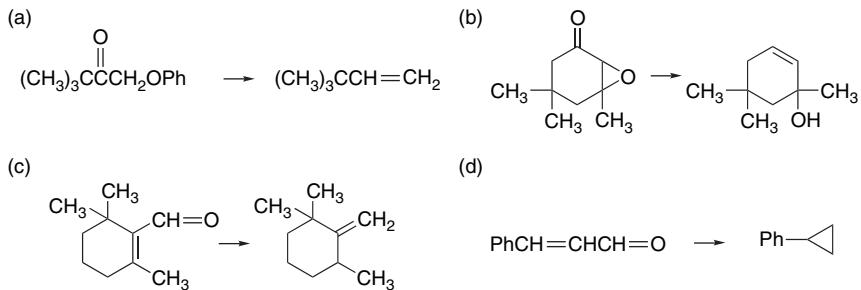
- 5.14. Ketones can be converted to nitriles by the following sequence of reagents. Indicate the intermediate stages of the reaction.



- 5.15. In the synthesis of fluorinated analogs of the acetylcholinesterase inhibitor, huperzine A, it was necessary to accomplish reductive elimination of the diol **15-D** to **15-E**. Of the methods for diol reduction, which seems most compatible with the other functional groups in this compound?



- 5.16. Wolff-Kishner reduction of ketones bearing other functional groups sometimes gives products other than the expected methylene reduction product. Several examples are given below. Indicate a mechanism for each reaction.



- 5.17. Suggest reagents and reaction conditions that would be suitable for each of the following selective or partial reductions:

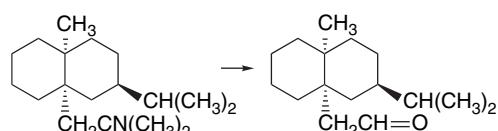
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PROBLEMS

(a)



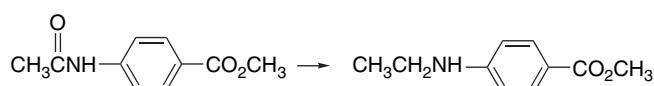
(b)



(c)



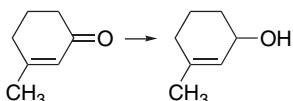
(d)



(e)



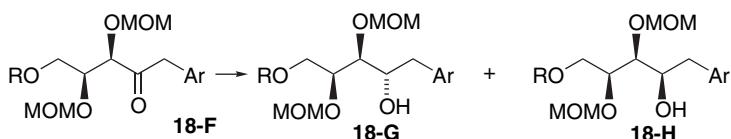
(f)



(g)



- 5.18. The reduction of the ketone **18-F** gives product **18-G** in preference to **18-H** with increasing stereoselectivity in the order $\text{NaBH}_4 < \text{LiAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2 < \text{Zn}(\text{BH}_4)_2$. With L-Selectride, however, **18-H** is favored. Account for the dependence of the stereoselectivity on the various reducing agents.

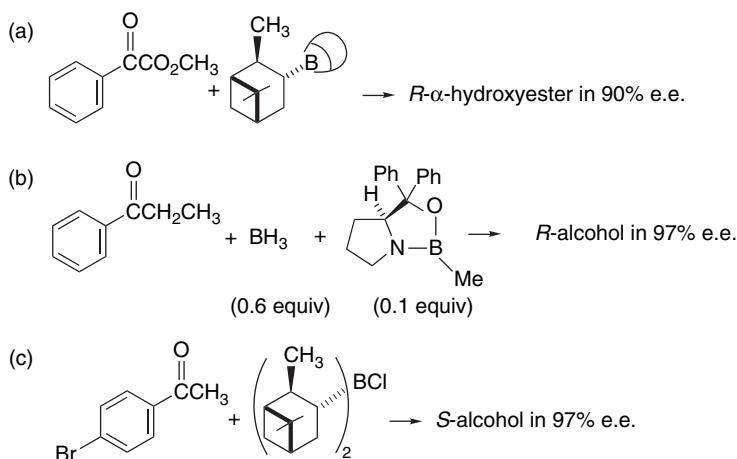


$\text{Ar} = 4\text{-methoxyphenyl}$

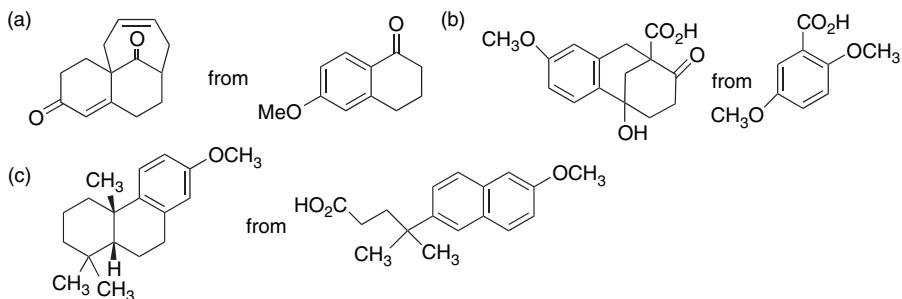
$\text{R} = \text{benzyl}$

$\text{MOM} = \text{methoxymethyl}$

- 5.19. The following reducing agents effect enantioselective reduction of ketones. Propose a transition structure that is in accord with the observed enantioselectivity.



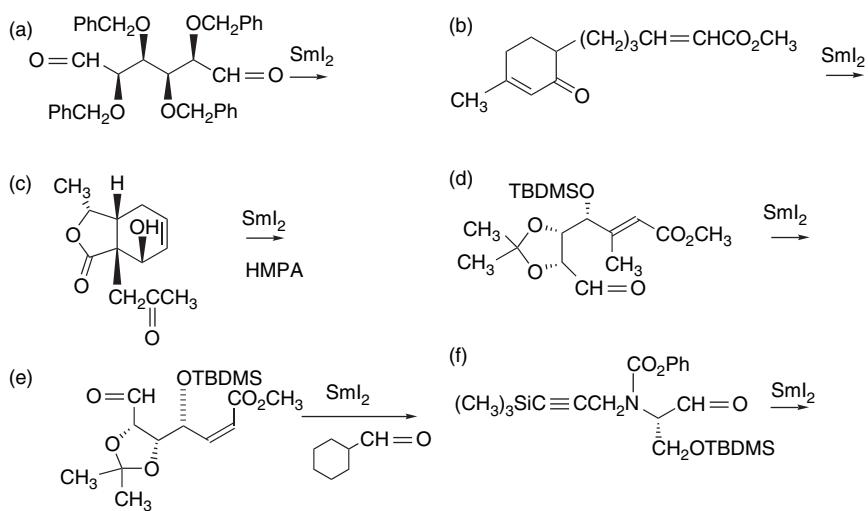
5.20. By retrosynthetic analysis, devise a sequence of reactions that would accomplish the following transformations:



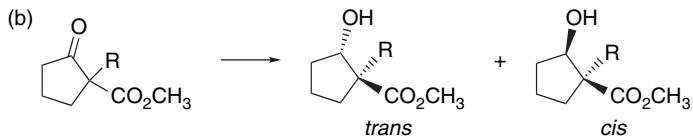
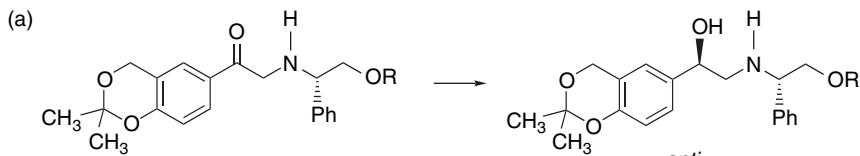
5.21. A group of topologically unique molecules called “betweenanenes” has been synthesized. Successful synthesis of such molecules depends on effective means of closing large rings. Suggest an overall strategy (details not required) to synthesize such molecules. Suggest types of reactions that might be considered for formation of the large rings.



5.22. Give the products expected from the following reactions with Sm(II) reagents.



5.23. Provide an explanation based on a transition structure for the trends in stereoselectivity revealed by the following data.



Concerted Cycloadditions, Unimolecular Rearrangements, and Thermal Eliminations

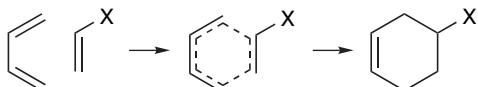
Introduction

Most of the reactions described in the preceding chapters involve polar or polarizable reactants and proceed through polar intermediates and/or transition structures. One reactant can be identified as nucleophilic and the other as electrophilic. Carbanion alkylations, nucleophilic additions to carbonyl groups, and electrophilic additions to alkenes are examples of such reactions. The reactions to be examined in this chapter, on the other hand, occur via a reorganization of electrons through transition structures that may not be much more polar than the reactants. These reactions proceed through cyclic transition structures. The activation energy can be provided by thermal or photochemical excitation of the reactant(s) and often no other reagents are involved. Most of the transformations fall into the category of *concerted pericyclic reactions*, in which there are no intermediates and the transition structures are stabilized by favorable orbital interactions, as discussed in Chapter 10 of Part A. These reactions can be classified into three broad types: cycloadditions, unimolecular rearrangements, and eliminations. We also discuss some reactions that effect closely related transformations, but which on mechanistic scrutiny are found to proceed through discrete intermediates.

6.1. Diels-Alder Reactions

6.1.1. The Diels-Alder Reaction: General Features

Cycloaddition reactions result in the formation of a new ring from two reactants. A concerted mechanism requires that a single transition state, and therefore no intermediate, lie on the reaction path between reactants and adduct. The most important example of cycloaddition is the *Diels-Alder (D-A) reaction*. The cycloaddition of alkenes and dienes is a very useful method for forming substituted cyclohexenes.¹



A clear understanding of concerted cycloaddition reactions developed as a result of the formulation of the mechanisms within the framework of molecular orbital theory. Consideration of the MOs of reactants and products reveals that in many cases a smooth transformation of the orbitals of the reactants to those of products is possible. In other cases, reactions that might appear feasible if no consideration is given to the symmetry and spatial orientation of the orbitals are found to require high-energy TSs when the orbitals are considered in detail. (Review Section 10.1 of Part A for a discussion of the orbital symmetry analysis of cycloaddition reactions.) The relationships between reactants and TS orbitals permit description of potential cycloaddition reactions as “allowed” or “forbidden” and indicate whether specific reactions are likely to be energetically favorable. The same orbital symmetry relationships that are informative as to the feasibility of a reaction are often predictive of the regiochemistry and stereochemistry. This predictability is an important feature for synthetic purposes. Another attractive aspect of the D-A reaction is the fact that *two new carbon-carbon bonds* are formed in a single reaction.

In the terminology of orbital symmetry classification, the Diels-Alder reaction is a $[4\pi_s + 2\pi_s]$ cycloaddition, an allowed process. There have been a large number of computational studies of the D-A reaction, and as it is a fundamental example of a concerted reaction, it has frequently been the subject of advanced calculations.² These studies support a concerted mechanism, which is also supported by good agreement between experimental and calculated (B3LYP/6-31G*) kinetic isotope effects.³ The TS for a concerted reaction requires that the diene adopt the *s-cis* conformation. The diene and substituted alkene (called the *dienophile*) approach each other in approximately parallel planes. The symmetry properties of the π orbitals permit stabilizing interactions between C(1) and C(4) of the diene and the dienophile. Usually, the strongest bonding

1. L. W. Butz and A. W. Rytina, *Org. React.*, **5**, 136 (1949); M. C. Kloetzel, *Org. React.*, **4**, 1 (1948); A. Wasserman, *Diels-Alder Reactions*, Elsevier, New York (1965); F. Fringuelli and A. Tatacchi, *Diels-Alder Reactions: Selected Practical Methods*, Wiley, New York, 2001.
2. P. D. Karadakov, D. L. Cooper, and J. Gerratt, *J. Am. Chem. Soc.*, **120**, 3975 (1998); H. Lischka, E. Ventura, and M. Dallows, *Chem. Phys. Phys. Chem.*, **5**, 1365 (2004); E. Kraka, A. Wu, and D. Cremer, *J. Phys. Chem. A*, **107**, 9008 (2003); S. Berski, J. Andres, B. Silvi, and L. R. Domingo, *J. Phys. Chem. A*, **107**, 6014 (2003); H. I. Sobe, Y. Takano, Y. Kitagawa, T. Kawakami, S. Yamanaka, K. Yamagushi, and K. N. Houk, *J. Phys. Chem. A*, **107**, 682 (2003).
3. E. Goldstein, B. Beno, and K. N. Houk, *J. Am. Chem. Soc.*, **118**, 6036 (1996); D. R. Singleton, S. R. Merrigan, B. R. Beno, and K. N. Houk, *Tetrahedron Lett.*, **40**, 5817 (1999).

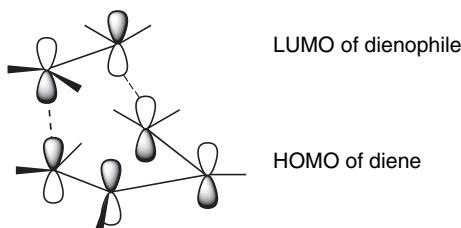
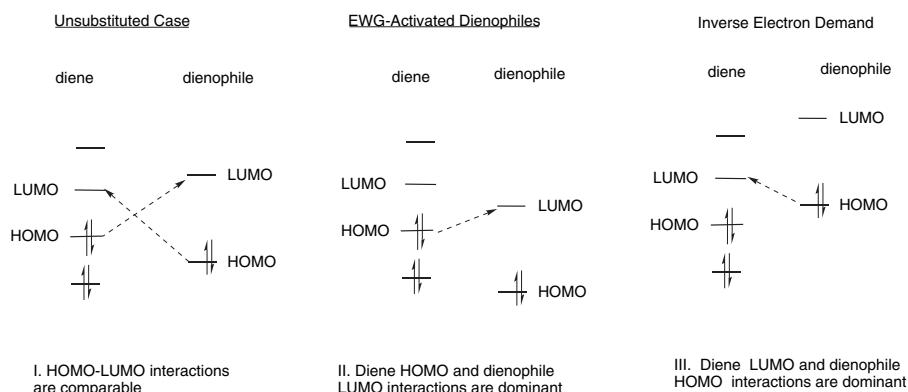


Fig. 6.1. Interaction between LUMO of dienophile and HOMO of diene in the Diels-Alder reaction.

interaction is between the HOMO of the diene and the LUMO of the dienophile. The interaction between the frontier orbitals is depicted in Figure 6.1.

6.1.2. Substituent Effects on the Diels-Alder Reaction

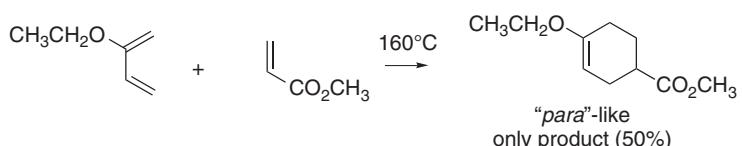
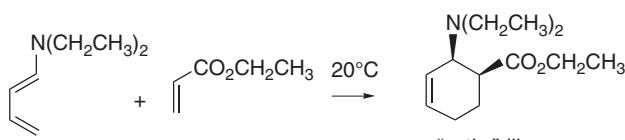
There is a strong electronic substituent effect on the D-A reaction. The most reactive dienophiles for simple dienes are those having electron-attracting groups. Thus, quinones, maleic anhydride, and nitroalkenes are among the most reactive dienophiles. α,β -Unsaturated aldehydes, esters, ketones, and nitriles are also effective dienophiles. It is significant that if an electron-poor diene is utilized, the preference is reversed and electron-rich alkenes, such as vinyl ethers, are the best dienophiles. Such reactions are called *inverse electron demand Diels-Alder reactions*, and the relationships involved are readily understood in terms of frontier orbital theory. Electron-rich dienes have high-energy HOMOs and interact strongly with the LUMOs of electron-poor dienophiles. When the substituent pattern is reversed and the diene is electron-poor, the strongest interaction is between the dienophile HOMO and the diene LUMO.



Frontier orbital theory can also explain the regioselectivity observed when both the diene and alkene are unsymmetrically substituted.⁴ Generally, there is a preference

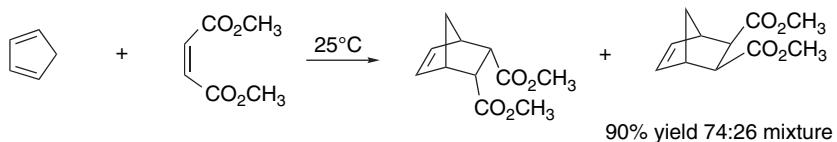
⁴. K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975); I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley-Interscience, New York, 1976; O. Eisenstein, J. M. LeFour, N. T. Anh, and R. F. Hudson, *Tetrahedron*, **33**, 523 (1977).

for the “*ortho*” product when the diene has a donor (ERG) substituent at C(1) and for “*para*” product when the diene has an ERG at C(2), as in the examples shown.⁵

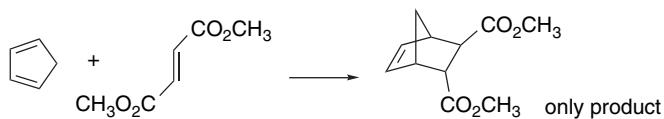


When the dienophile bears an EWG substituent and the diene an ERG, the strongest interaction is between the HOMO of the diene and the LUMO of the dienophile. The reactants are oriented so that the carbons having the highest coefficients of these two frontier orbitals can begin the bonding process, and this leads to the observed regiochemical preference as summarized in Figure 6.2.

Diels-Alder reactions are *stereospecific* with respect to the *E*- and *Z*-relationships in both the dienophile and the diene. For example, addition of dimethyl fumarate and dimethyl maleate with cyclopentadiene is completely stereospecific with respect to the *cis* or *trans* orientation of the ester substituents.

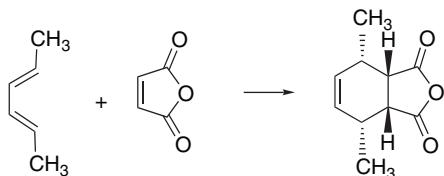


Ref. 6



Ref. 7

Similarly, *E,E*-2,4-hexadiene gives a product that is stereospecific with respect to the diene methyl groups.



Ref. 8

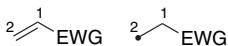
⁵. J. Sauer, *Angew. Chem. Int. Ed. Engl.*, **6**, 16 (1967).

⁶. W. Kirmse, U. Mrotzke, and R. Siegfried, *Chem. Ber.*, **124**, 238 (1991).

⁷. C. Girard and R. Bloch, *Tetrahedron Lett.*, **23**, 3683 (1982).

⁸. G. Berube and P. Deslongchamps, *Bull. Soc. Chim. Fr.*, 103 (1987).

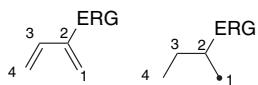
a) Coefficient at C(2) is higher than at C(1) in the LUMO of a dienophile bearing and electron-withdrawing substituent.



(b) Coefficient at C(4) is higher than at C(1) in HOMO of a diene bearing an electron-releasing substituent at C(1).



(c) Coefficient at C(1) is higher than at C(4) in HOMO of a diene bearing an electron-releasing substituent at C(1).



(d) The regioselectivity of the Diels-Alder reaction corresponds to matching the carbon atoms having the largest coefficients of the frontier orbitals.

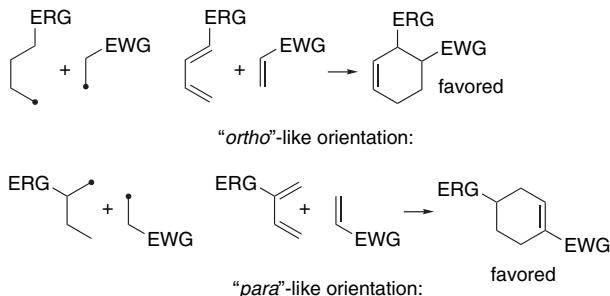
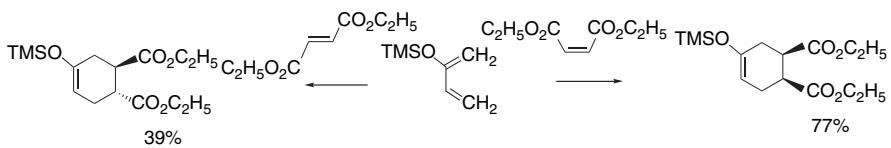


Fig. 6.2. HOMO-LUMO interactions rationalize regioselectivity of Diels-Alder reactions.

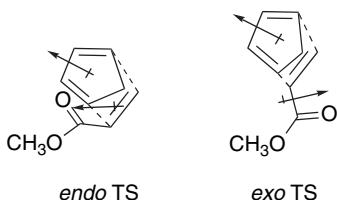
Stereospecificity also is exhibited for dienes having stronger electron-releasing groups, such as trimethylsiloxy.



Ref. 9

⁹. M. E. Jung and C. A. McCombs, *Org. Synth.*, **58**, 163 (1978); M. E. Jung and C. A. McCombs, *Tetrahedron Lett.*, 2935 (1976).

For an unsymmetrical dienophile there are two possible stereochemical orientations with respect to the diene, *endo* and *exo*, as illustrated in Figure 6.3. In the *endo* TS the reference substituent on the dienophile is oriented toward the π orbitals of the diene. In the *exo* TS the substituent is oriented away from the π system. For many substituted butadiene derivatives, the TSs lead to two different stereoisomeric products. The *endo* mode of addition is usually preferred when an electron-attracting substituent such as a carbonyl group is present on the dienophile. The empirical statement that describes this preference is called the *Alder rule*. Frequently a mixture of both stereoisomers is formed and sometimes the *exo* product predominates, but the Alder rule is a useful initial guide to prediction of the stereochemistry of a D-A reaction. The *endo* product is often the more sterically congested. The preference for the *endo* TS is strongest for relatively rigid dienophiles such as maleic anhydride and benzoquinone. For methyl acrylate, methyl methacrylate, and methyl crotonate the selectivity ratios are not high.¹⁰ The preference for the *endo* TS increases somewhat with increasing solvent polarity.¹¹ This has been attributed to a higher polarity of the *endo* TS, resulting from alignment of the dipoles.



The preference for the *endo* TS is considered to be the result of interaction between the dienophile substituent and the π electrons of the diene. These are called *secondary orbital interactions*. Dipolar attractions and van der Waals attractions may also be involved.¹² Some *exo-endo* ratios for thermal D-A reactions of cyclopentadiene are

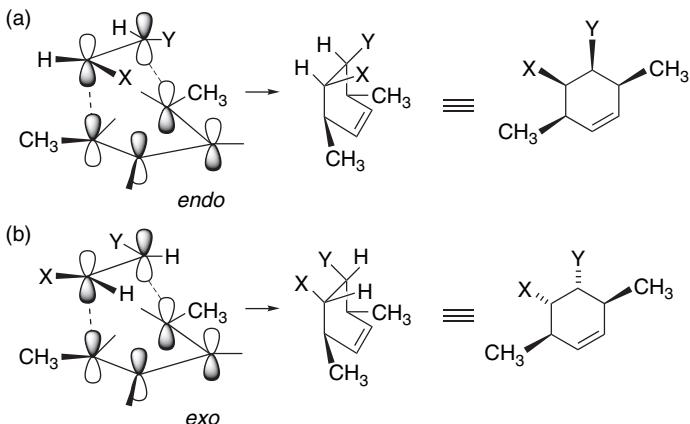


Fig. 6.3. *Endo* (a) and *exo* (b) stereochemistry in Diels-Alder reactions.

¹⁰. K. N. Houk and L. J. Lusku, *J. Am. Chem. Soc.*, **93**, 4606 (1971).

¹¹. J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Am. Chem. Soc.*, **84**, 297 (1962).

¹². Y. Kobuke, T. Sugimoto, J. Furukawa, and T. Funeo, *J. Am. Chem. Soc.*, **94**, 3633 (1972); K. L. Williamson and Y.-F. L. Hsu, *J. Am. Chem. Soc.*, **92**, 7385 (1970).

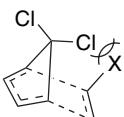
Table 6.1. *Endo:Exo* Stereoselectivity toward Cyclopentadiene

Dienophile	<i>Endo:exo</i> ratio
CH ₂ =CHCH=O ^a	80:20
CH ₂ =CHCOCH ₃ ^a	82:18
CH ₂ =CHCO ₂ CH ₃	73:27
CH ₂ =C(CH ₃)CO ₂ CH ₃ ^b	30:70
CH ₃ CH=CHCO ₂ CH ₃ ^b	52:48
CH ₂ =CHSO ₂ CH ₃ ^c	75:25
CH ₂ =CHPO(OCH ₃) ₂ ^d	55:45
CH ₂ =CHCN ^e	58:42
CH ₂ =C(CH ₃)CN ^e	12:88
CH ₃ CH=CHCN ^e	34:66

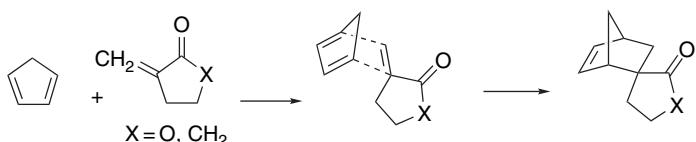
- a. O. F. Guner, R. M. Ottenbrite and D. D. Shillady, *J. Org. Chem.*, **53**, 5348 (1988).
 b. K. N. Houk and L. J. Lusku, *J. Am. Chem. Soc.*, **93**, 4606 (1971).
 c. J. C. Philips and M. Oku, *J. Org. Chem.*, **37**, 4479 (1972).
 d. H. J. Callot and C. Berezra, *J. Chem. Soc., Chem. Commun.*, 485 (1970).
 e. A. I. Konovalov and G. I. Kamashova, *Russ. J. Org. Chem. (Engl. Trans.)*, **8**, 1879 (1972)

given in Table 6.1. Most of the data pertain to dienophiles with carbonyl substituents. Note that tetrahedral noncarbonyl EWGs such as sulfonyl and phosphonyl also exhibit a small preference for the *endo* TS. The cyano group shows little *endo:exo* preference. Both α - and β -methyl groups result in more *exo* product, as seen for the methyl-substituted esters and nitriles. As we will see shortly, the use of Lewis acid catalysts usually increases the preference for the *endo* TS.

Steric effects play a dominant role with more highly substituted dienes. Hexachlorocyclopentadiene, for example, shows a higher *endo* preference than cyclopentadiene because the 5-chlorine causes steric interference with *exo* substituents.¹³



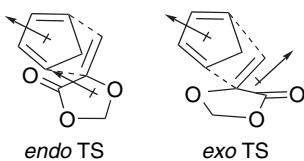
Cyclic α -methylene ketones and lactones, in which the *syn* conformation is enforced, give predominantly *exo* adducts.¹⁴



¹³. K. L. Williamson, Y.-F. L. Hsu, R. Lacko, and C. H. Youn, *J. Am. Chem. Soc.*, **91**, 6129 (1969).

¹⁴. F. Fotiadu, F. Michel, and G. Buono, *Tetrahedron Lett.*, **31**, 4863 (1990); J. Mattay, J. Mertes, and G. Maas, *Chem. Ber.*, **122**, 327 (1989).

It has been suggested that this is due to a more favorable alignment of dipoles in the *exo* TS.¹⁵



Computational studies predict a preference for the *endo* TS.¹⁶ There have been several computational efforts to dissect the various factors that contribute to the differences between the *exo* and *endo* TS.¹⁷ These generally are in agreement with the experimental preference for the *endo* TS, but there is no consensus on the dominant factors in this preference.¹⁸

Diels-Alder cycloadditions are sensitive to steric effects of two major types in the diene. Bulky substituents on the termini of the diene hinder approach of the two components to each other and decrease the rate of reaction. This effect can be seen in the relative reactivity of 1-substituted butadienes toward maleic anhydride.¹⁹

	R	$k_{\text{rel}} (25^\circ\text{C})$
	-H	1
	-CH ₃	4.2
	-C(CH ₃) ₃	< 0.05

Substitution of hydrogen by methyl results in a slight rate *increase* as a result of the electron-releasing effect of the methyl group. A *t*-butyl substituent produces a large rate *decrease* because the steric effect is dominant.

Another type of steric effect results from interactions between diene substituents. Adoption of the *s-cis* conformation of the diene in the TS brings the *cis*-oriented 1- and 4-substituents on a diene close together. *E*-1,3-Pentadiene is 10³ times more reactive than 4-methyl-1,3-pentadiene toward the very reactive dienophile tetracyanoethylene. This is because the unfavorable interaction between the additional methyl substituent and the C(1) hydrogen in the *s-cis* conformation raises the energy of the TS.²⁰

	R	k_{rel}
	-H	1
	-CH ₃	10 ⁻³

Relatively small substituents at C(2) and C(3) of the diene exert little steric influence on the rate of D-A addition. 2,3-Dimethylbutadiene reacts with maleic anhydride about ten times faster than butadiene owing to the electronic effect of the methyl

¹⁵ W. R. Roush and B. B. Brown, *J. Org. Chem.*, **57**, 3380 (1992).

¹⁶ (a) R. J. Loncharich, T. R. Schwartz, and K. N. Houk, *J. Am. Chem. Soc.*, **109**, 14 (1987);

(b) R. J. Loncharich, T. R. Schwartz, and K. N. Houk, *J. Org. Chem.*, **54**, 1129 (1989);

(c) D. M. Birney and K. N. Houk, *J. Am. Chem. Soc.*, **112**, 4127 (1990); (d) J. I. Garcia, V. Martinez-Merino, J. A. Mayoral, and L. Salvatella, *J. Am. Chem. Soc.*, **120**, 2415 (1998).

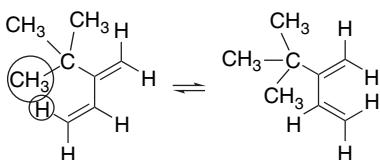
¹⁷ W. L. Jorgensen, D. Lim, and J. F. Blake, *J. Am. Chem. Soc.*, **115**, 2936 (1993); A. Arrieta, F. P. Cossio, and B. Lecea, *J. Org. Chem.*, **66**, 6178 (2001); J. I. Garcia, J. A. Mayoral, and L. Salvatella, *Eur. J. Org. Chem.*, 85, (2004).

¹⁸ J. I. Garcia, J. A. Mayoral, and L. Salvatella, *Acc. Chem. Res.*, **33**, 658 (2000).

¹⁹ D. Craig, J. J. Shipman, and R. B. Fowler, *J. Am. Chem. Soc.*, **83**, 2885 (1961).

²⁰ C. A. Stewart, Jr., *J. Org. Chem.*, **28**, 3320 (1963).

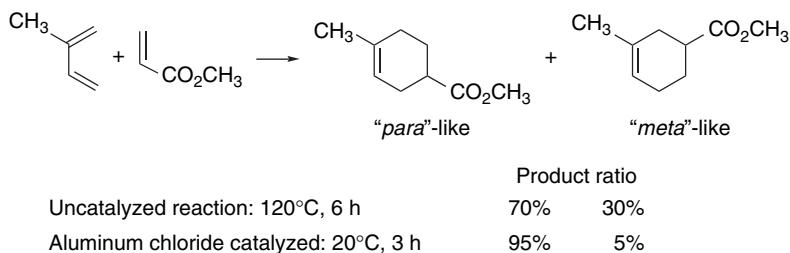
groups. 2-*t*-Butyl-1,3-butadiene is 27 times more reactive than butadiene. The *t*-butyl substituent favors the *s-cis* conformation because of steric repulsions in the *s-trans* conformation.



The presence of a *t*-butyl substituent on *both* C(2) and C(3), however, prevents attainment of the *s-cis* conformation, and D-A reactions of 2,3-di-(*t*-butyl)-1,3-butadiene have not been observed.²¹

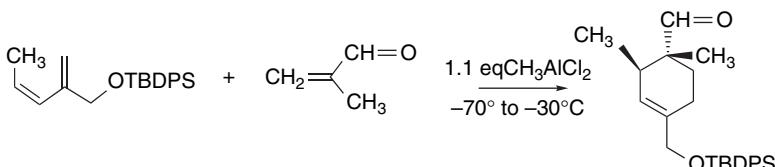
6.1.3. Lewis Acid Catalysis of the Diels-Alder Reaction

Lewis acids such as zinc chloride, boron trifluoride, tin tetrachloride, aluminum chloride, methylaluminum dichloride, and diethylaluminum chloride catalyze Diels-Alder reactions.²² The catalytic effect is the result of coordination of the Lewis acid with the dienophile. The complexed dienophile is more electrophilic and more reactive toward electron-rich dienes. The mechanism of the addition is believed to be concerted and enhanced regio- and stereoselectivity is often observed.²³



Ref. 24

Among the catalysts currently in use, CH_3AlCl_2 was the most effective when employed with *Z*-dienes, which often exhibit low reactivity.



Ref. 22g

²¹ H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **58**, 643 (1939).

²² (a) P. Yates and P. Eaton, *J. Am. Chem. Soc.*, **82**, 4436 (1960); (b) T. Inukai and M. Kasai, *J. Org. Chem.*, **30**, 3567 (1965); (c) T. Inukai and T. Kojima, *J. Org. Chem.*, **31**, 2032 (1966); (d) T. Inukai and T. Kojima, *J. Org. Chem.*, **32**, 869, 872 (1967); (e) F. Fringuelli, F. Pizzo, A. Taticchi, and E. Wenkert, *J. Org. Chem.*, **48**, 2802 (1983); (f) F. K. Brown, K. N. Houk, D. J. Burnell, and Z. Valenta, *J. Org. Chem.*, **52**, 3050 (1987); (g) W. R. Roush and D. A. Barda, *J. Am. Chem. Soc.*, **119**, 7402 (1997).

²³ K. N. Houk, *J. Am. Chem. Soc.*, **95**, 4094 (1973).

²⁴ T. Inukai and Kojima, *J. Org. Chem.*, **31**, 1121 (1966).

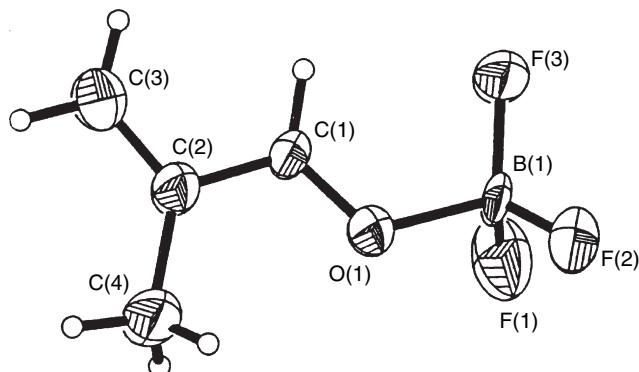


Fig. 6.4. Structure of the BF_3 -2-methylpropenal complex. Reproduced from *Tetrahedron Lett.*, **33**, 6945 (1992), by permission of Elsevier.

The stereoselectivity of any particular reaction depends on the details of the structure of the TS. The structures of several enone-Lewis acid complexes have been determined by X-ray crystallography.²⁵ The site of complexation is the carbonyl oxygen, which maintains a trigonal geometry, but with somewhat expanded angles (130° – 140°). The Lewis acid is normally *anti* to the larger carbonyl substituent. Boron trifluoride complexes are tetrahedral, but Sn(IV) and Ti(IV) complexes can be tetrahedral, bipyramidal or octahedral. The structure of the 2-methylpropenal- BF_3 complex in Figure 6.4 is illustrative.²⁶ Chelation can favor a particular structure. For example, *O*-acryloyl lactates adopt a chelated hexacoordinate structure with TiCl_4 , as shown in Figure 6.5.²⁷

Computational studies have explored the differences between thermal and Lewis acid-catalyzed D-A reactions. Ab initio calculations (HF/6-31G*) have been used to compare the energy of four possible TSs for the D-A reaction of the BF_3 complex of propenal with 1,3-butadiene.^{16d} The TSs are designated *endo* and *exo* and *s-cis* and *s-trans*. The latter designations refer to the dienophile conformation. The results are summarized in Figure 6.6. In the thermal reaction, the *endo-cis* and *exo-cis* TSs are nearly equal in total and activation energies. In the BF_3 -catalyzed reaction, the

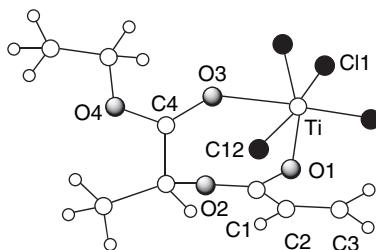
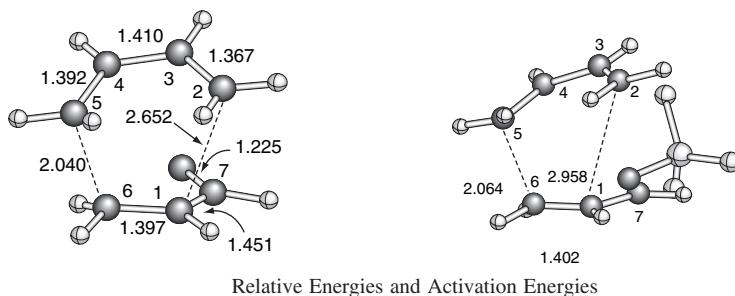


Fig. 6.5. Structure of the TiCl_4 complex of *O*-acryloyl ethyl lactate. Reproduced from *Angew. Chem. Int. Ed. Engl.*, **24**, 112 (1985), by permission of Wiley-VCH.

²⁵ S. Shambayati, W. E. Crowe, and S. L. Schreiber, *Angew. Chem. Int. Ed. Engl.*, **29**, 256 (1990).

²⁶ E. J. Corey, T.-P. Loh, S. Sarshar, and M. Azimioara, *Tetrahedron Lett.*, **33**, 6945 (1992).

²⁷ T. Poll, J. O. Metter, and G. Helmchen, *Angew. Chem. Int. Ed. Engl.*, **24**, 112 (1985).



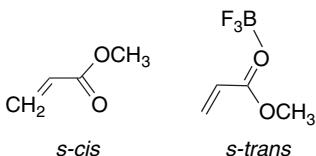
Relative Energies and Activation Energies

Thermal	$\Delta\Delta E_{298}$	ΔG^*_{298}	BF_3 -catalyzed	$\Delta\Delta E_{298}$	ΔG^*_{298}
<i>Endo-cis</i>	0.00	32.7	<i>Endo-cis</i>	0.00	23.2
<i>Endo-trans</i>	1.24	33.9	<i>Endo-trans</i>	2.25	25.7
<i>Exo-cis</i>	0.06	32.7	<i>Exo-cis</i>	1.72	24.3
<i>Exo-trans</i>	1.93	34.5	<i>Exo-trans</i>	5.61	28.3

Fig. 6.6. Relative energies of four possible transition structures for Diels-Alder reaction of 1,3-butadiene and propenal, with and without BF_3 catalyst. Geometric parameters of the most stable transition structures (*endo-cis*) are shown. Adapted from *J. Am. Chem. Soc.*, **120**, 2415 (1998), by permission of the American Chemical Society.

endo-cis TS is favored by 1.7 kcal/mol. The calculated ΔG^* is reduced by nearly 10 kcal/mol for the catalyzed reaction, relative to the thermal reaction. The catalyzed reaction shows significantly greater asynchronicity than the thermal reaction. In the BF_3 -catalyzed reaction, the forming bond distances are 2.06 and 2.96 Å, whereas in the thermal reaction they are 2.04 and 2.65 Å. (See Topic 10.1 of Part A for discussion of asynchronicity.)

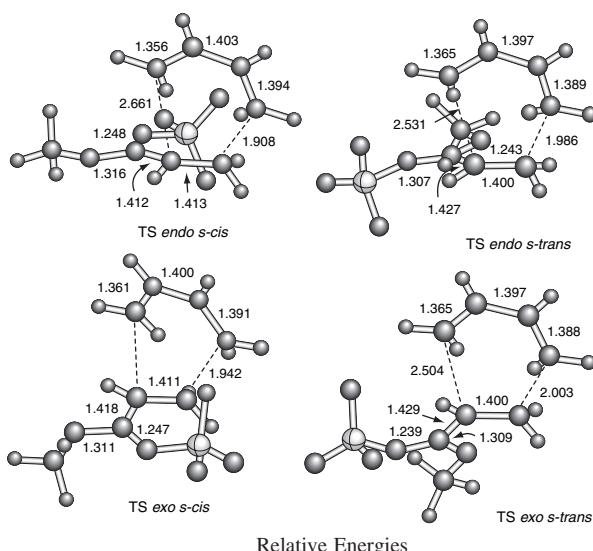
A similar study was done with methyl acrylate as the dienophile.²⁸ The uncatalyzed and catalyzed TSs are shown in Figure 6.7. As with propenal, the catalyzed reaction is quite asynchronous with C(2)–C(3) bonding running ahead of C(1)–C(6) bonding. In this system, there is a shift from favoring the *exo-s-cis* TS in the thermal reaction to the *endo-s-trans* TS in the catalyzed reaction. A large component in this difference is the relative stability of the free and complexed dienophile. The free dienophile favors the *s-cis* conformation, whereas the BF_3 complex favors the *s-trans* conformation.



Visual models, additional information and exercises on the Diels-Alder Reaction can be found in the Digital Resource available at: Springer.com/carey-sundberg.

In terms of both the effect of substituents and Lewis acid catalysis, the rates of D-A reactions *increase as the donor-acceptor character of the reactive*

²⁸. J. I. Garcia, J. A. Mayoral, and L. Salvatella, *Tetrahedron*, **53**, 6057 (1997).

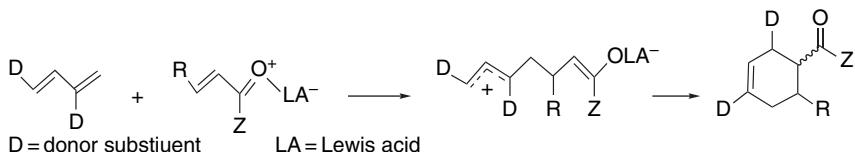


Relative Energies

Thermal	$\Delta\Delta E_{298}$	BF_3 -catalyzed	$\Delta\Delta E_{298}$
<i>Endo-cis</i>	0.38	<i>Endo-cis</i>	2.23
<i>Endo-trans</i>	1.65	<i>Endo-trans</i>	0.00
<i>Exo-cis</i>	0.00	<i>Exo-cis</i>	0.82
<i>Exo-trans</i>	1.44	<i>Exo-trans</i>	0.83

Fig. 6.7. Transition structures for the reaction between 1,3-butadiene and the methyl acrylate– BF_3 complex calculated at the ab initio HF/6-31G* level. Relative energies are in kcal/mol. Adapted from *Tetrahedron*, **53**, 6057 (1997), by permission of Elsevier.

complex increases. That is, the better the donor substituents in the diene and the stronger the acceptor substituents in the dienophile, the faster the reaction. Similarly, the more electrophilic the Lewis acid, the faster the reaction. In extreme cases, cycloaddition may become stepwise.



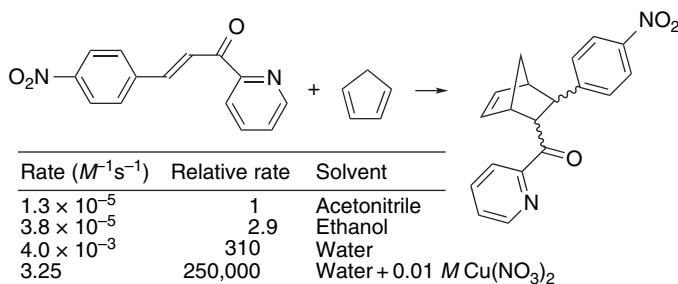
Such a stepwise reaction would not be expected to change the regiochemistry of cycloaddition, but it could lead to loss of stereospecificity if the zwitterionic intermediate has a long enough lifetime. In most reactions where only carbon–carbon bonds are being formed, the D–A reaction remains stereospecific.

In one study, the mechanisms of the reaction of methyl cinnamate and cyclopentadiene with BF_3 , AlCl_3 , and catecholborane bromide as catalysts were compared.²⁹ According to these computations (B3LYP/6-31G*), the uncatalyzed and BF_3 - and AlCl_3 -catalyzed reactions proceed by asynchronous concerted mechanisms, but a

²⁹ C. N. Alves, F. F. Camilo, J. Gruber, and A. B. F. da Silva, *Chem. Phys.*, **306**, 35 (2004).

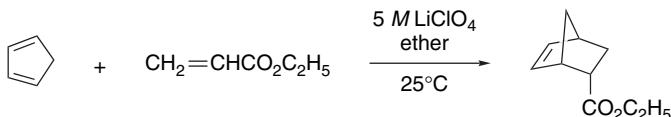
stepwise mechanism is found with catecholborane bromide. Experimentally, this is the only catalyst that is effective for this reaction.³⁰

Metal cations can catalyze reactions of certain dienophiles. For example, Cu²⁺ strongly catalyzes addition reactions of 2-pyridyl styryl ketones, presumably through a chelate involving the carbonyl oxygen and pyridine nitrogen.³¹



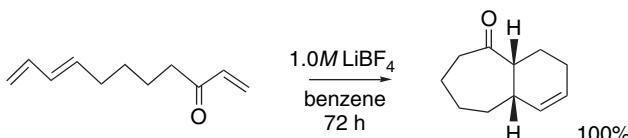
This reaction has been studied computationally with Zn²⁺ as the metal cation.³² The calculations indicate that a stepwise reaction occurs, beginning with electrophilic attack of the complexed dienophile on the diene.

Some D-A reactions are catalyzed by high concentrations of LiClO₄ in ether,³³ a catalysis that involves Lewis acid complexation of Li⁺ with the dienophile.³⁴



The LiClO₄-diethyl ether system shows a considerable dependency on concentration, with the maximal effect around 5 M, which may be due to the detailed structure of LiClO₄ in ether. The optimum reactivity may be associated with a monosolvate. Dilute solutions have more of the dietherate, whereas in more concentrated solution LiClO₄ may form less reactive aggregates.³⁵ LiN(SO₂SCF₃)₂ has been recommended as an alternative to avoid the use of a perchlorate salt.³⁶

Lithium *tetrakis*-(3,5-difluoromethyl)borate, which provides an unsolvated lithium cation in noncoordinating solvents, exhibits a several thousandfold catalysis of the reaction of cyclopentadiene and methyl vinyl ketone.³⁷ Lithium tetrafluoroborate is also an effective catalyst and in some instances has worked when LiClO₄ has failed, such as in the intramolecular reaction shown below.³⁸



³⁰ F. Camilo and J. Gruber, *Quim. Nova*, **22**, 382 (1999).

³¹ S. Otto and J. B. F. N. Engberts, *Tetrahedron Lett.*, **36**, 2645 (1995).

³² L. R. Domingo, J. Andres, and C. N. Alves, *Eur. J. Org. Chem.*, **15**, 2557 (2002).

³³ P. A. Grieco, J. J. Nunes, and M. D. Gaul, *J. Am. Chem. Soc.*, **112**, 4595 (1990).

³⁴ M. A. Forman and W. P. Dailey, *J. Am. Chem. Soc.*, **113**, 2761 (1991).

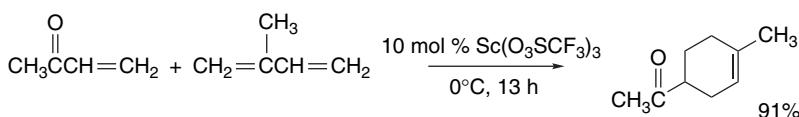
³⁵ A. Kumar and S. S. Pawar, *J. Org. Chem.*, **66**, 7646 (2001).

³⁶ S. T. Handy, P. A. Grieco, C. Mineur, and L. Ghosez, *Synlett*, 565 (1995).

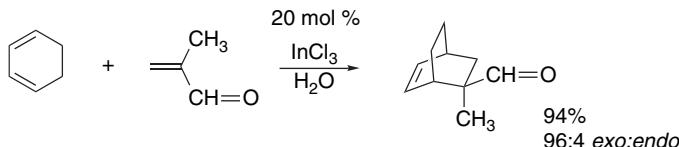
³⁷ K. Fujiki, S.-Y. Ikeda, H. Kobayashi, M. Hiroshi, A. Nagira, J. Nie, T. Sonoda, and Y. Yagupolskii, *Chem. Lett.*, 62 (2000).

³⁸ D. A. Smith and K. N. Houk, *Tetrahedron Lett.*, **32**, 1549 (1991).

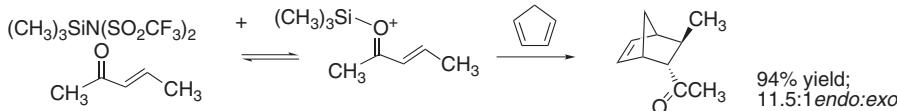
Scandium triflate has been found to catalyze D-A reactions.³⁹ For example, with 10 mol % $\text{Sc}(\text{O}_3\text{SCF}_3)_3$ present, isoprene and methyl vinyl ketone react to give the expected adduct in 91% yield after 13 h at 0°C.



Among the unique features of $\text{Sc}(\text{O}_3\text{SCF}_3)_3$ is its ability to function as a catalyst in hydroxylic solvents. Other dienophiles, including *N*-acryloyloxazolidinones, also are subject to catalysis by $\text{Sc}(\text{O}_3\text{SCF}_3)_3$. Indium trichloride is another Lewis acid that can act as a catalyst in aqueous solution.⁴⁰



Reversible O-silylation also enhances the electrophilicity of carbonyl dienophiles. For example, 10 mol % *N*-trimethylsilyl triflimide catalyzes the reaction of pent-3-en-2-one with cyclopentadiene. A hindered base, such as 2,6-bis-*t*-butyl-4-methylpyridine improves the yield in cases in which the catalyst causes the occurrence of reactant degradation.



Ref. 41

The solvent also has an important effect on the rate of D-A reactions. The traditional solvents were nonpolar organic solvents such as aromatic hydrocarbons. However, water and other highly polar solvents, such as ethylene glycol and formamide, accelerate a number of D-A reactions.⁴² The accelerating effect of water is attributed to “enforced hydrophobic interactions.” That is, the strong hydrogen-bonding network in water tends to exclude nonpolar solutes and force them together, resulting in higher effective concentrations and relative stabilization of the developing TS.⁴³ More specific hydrogen bonding with the TS also contributes to the rate acceleration.⁴⁴

- ³⁹. S. Kobayashi, I. Hachiya, M. Araki, and H. Ishitami, *Tetrahedron Lett.*, **34**, 3755 (1993); S. Kobayashi, H. Ishitani, M. Araki, and I. Hachiya, *Tetrahedron Lett.*, **35**, 6325, (1994); S. Kobayashi, *Eur. J. Org. Chem.*, 15 (1999).
- ⁴⁰. T.-P. Loh, J. Pei, and M. Lin, *Chem. Commun.*, 2315 (1995); 505 (1996).
- ⁴¹. B. Mathieu and L. Ghosez, *Tetrahedron*, **58**, 8219 (2002).
- ⁴². D. Rideout and R. Breslow, *J. Am. Chem. Soc.*, **102**, 7816 (1980); R. Breslow and T. Guo, *J. Am. Chem. Soc.*, **110**, 5613 (1988); T. Dunams, W. Hoekstra, M. Pentaleri, and D. Liotta, *Tetrahedron Lett.*, **29**, 3745 (1988).
- ⁴³. R. Breslow and C. J. Rizzo, *J. Am. Chem. Soc.*, **113**, 4340 (1991).
- ⁴⁴. W. Blokzijl, M. J. Blandamer, and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **113**, 4241 (1991); W. Blokzijl and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **114**, 5440 (1992); S. Otto, W. Blokzijl, and J. B. F. N. Engberts, *J. Org. Chem.*, **59**, 5372 (1994); A. Meijer, S. Otto, and J. B. F. N. Engberts, *J. Org. Chem.*, **65**, 8989 (1998).

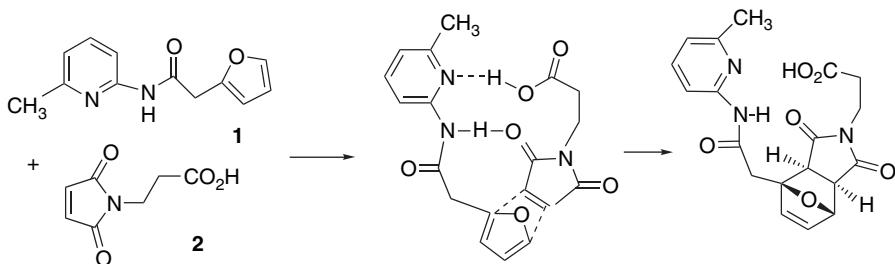


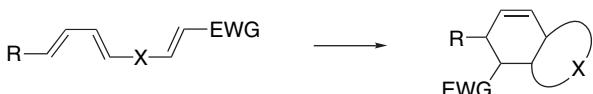
Fig. 6.8. Proposed hydrogen bonding in TS for addition of **1** and **2**. Reproduced from *Tetrahedron Lett.*, **45**, 4777 (2004), by permission of Elsevier.

Hydrogen-bonding interactions can be designed into reaction systems. For example, the reactants **1** and **2** were found to react much more rapidly than the corresponding ester and to give exclusively the *exo* product.⁴⁵ Molecular mechanics and spectroscopic studies indicate that the hydrogen-bonding pattern shown in Figure 6.8 is responsible.

To summarize the key points, D-A reactions are usually concerted processes. The regio- and stereoselectivity can be predicted by applying FMO analysis. The reaction between electron donor dienes and electron acceptor dienophiles is facilitated by Lewis acids, polar solvents, and favorable hydrogen-bonding interactions. The D-A reaction is quite sensitive to steric factors, which can retard the reaction and also influence the stereoselectivity with respect to *exo* or *endo* approach.

6.1.4. The Scope and Synthetic Applications of the Diels-Alder Reaction

Schemes 10.1 and 10.4 of Part A, respectively, give the structure of a number of typical dienophiles and show representative D-A reactions involving relatively simple reactants. The D-A reaction is frequently used in synthesis and can either be utilized early in a process to construct basic ring structures or to bring together two subunits in a convergent synthesis. The intramolecular version, which will be discussed in section 6.1.7, can be used to construct two new rings.

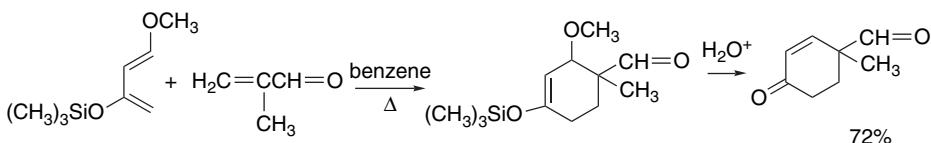


The virtues of the D-A reaction include its ability to create a cyclohexene ring by formation of *two new bonds with predictable regiochemistry*. The reaction can also create as many as four contiguous stereogenic centers. The stereoselectivity is also often predictable on the basis of the *supra-supra* stereospecificity and considerations of the preference for the *endo* or *exo* TS.

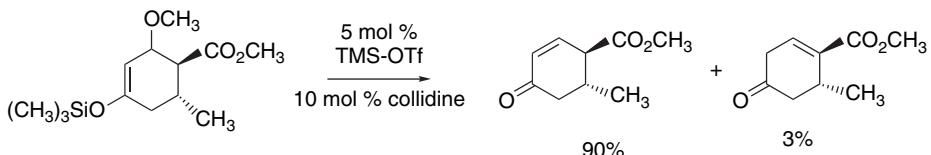
6.1.4.1. Examples of Dienes and Dienophiles. The synthetic value of D-A reactions can be enhanced in various ways. In addition to hydrocarbon dienes, substituted dienes can be used to introduce functional groups into the products. One example that illustrates the versatility of such reagents is 1-methoxy-3-trimethylsiloxy-1,3-butadiene

⁴⁵ R. J. Pearson, E. Kassianidis, and D. Philip, *Tetrahedron Lett.*, **45**, 4777 (2004).

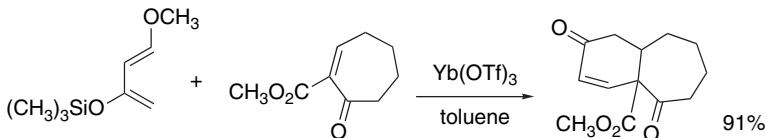
(Danishefsky's diene).⁴⁶ The two donor substituents provide strong regiochemical control. The D-A adducts are trimethylsilyl enol ethers that can be readily hydrolyzed to ketones. The β -methoxy group is often eliminated during hydrolysis, resulting in formation of cyclohexenones.



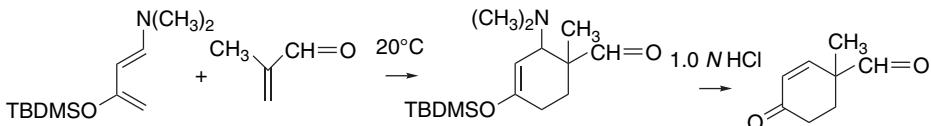
A milder protocol for the conversion to enones involves use of a catalytic amount of TMSOTf and a pyridine base.⁴⁷



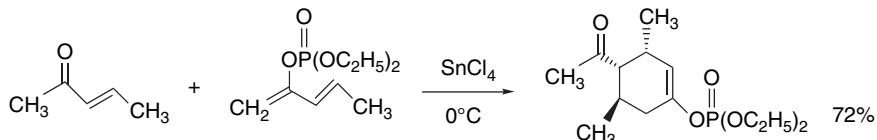
The desilylation is also promoted by various Lewis acids, $\text{Yb}(\text{OTf})_3$ being among the most effective. This catalyst can be used in a one-pot sequence in which it promotes both the cycloaddition and subsequent elimination.⁴⁸



An analogous silyoxydienamine shows a similar reactivity pattern.⁴⁹



2-(Diethoxyphosphoryloxy)-1,3-butadiene and 2-(diethoxyphosphoryloxy)-1,3-pentadiene are good dienes and are compatible with Lewis acid catalysts.⁵⁰ They exhibit the regioselectivity expected for a donor substituent and show a preference for *endo* addition with enones.



⁴⁶ S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974).

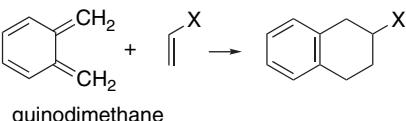
⁴⁷ P. E. Vorndam, *J. Org. Chem.*, **55**, 3693 (1990).

⁴⁸ T. Inokuchi, M. Okano, T. Miyamoto, H. B. Madon, and M. Takagi, *Synlett*, 1549 (2000); T. Inokuchi, M. Okano, and T. Miyamoto, *J. Org. Chem.*, **66**, 8059 (2001).

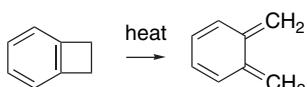
⁴⁹ S. A. Kozmin and V. H. Rawal, *J. Org. Chem.*, **62**, 5252 (1997).

⁵⁰ H.-J. Liu, W. M. Feng, J. B. Kim, and E. N. C. Browne, *Can. J. Chem.*, **72**, 2163 (1994).

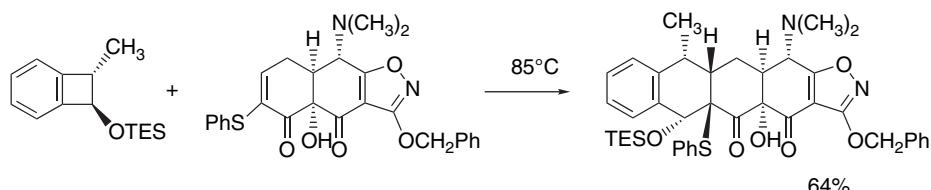
Unstable dienes can be generated *in situ* in the presence of a dienophile. Among the most useful examples are the *ortho*-quinodimethanes. These compounds are exceedingly reactive as dienes because the cycloaddition reestablishes a benzenoid ring and results in aromatic stabilization.⁵¹



There are several general routes to quinodimethanes. One is pyrolysis of benzocyclobutenes.⁵²

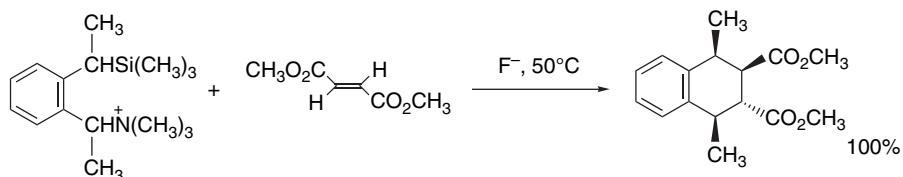


This reaction can be applied to substituted benzocyclobutenes. For example, the reaction has been used to form an array of five linear rings containing most of the functionality for the antibiotic tetracycline.



Ref. 53

1,4-Eliminations from α,α' -*ortho*-disubstituted benzenes can be carried out with various potential leaving groups. Benzylic silyl substituents can serve as the carbanion precursors.



Ref. 54

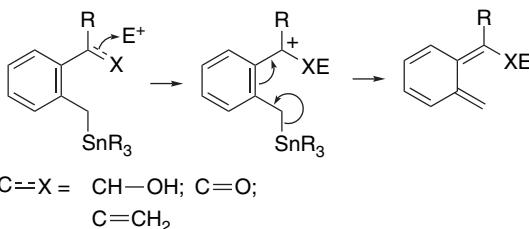
⁵¹ W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **16**, 10 (1977); T. Kametani and K. Fukumoto, *Heterocycles*, **3**, 29 (1975); J. J. McCullough, *Acc. Chem. Res.*, **13**, 270 (1980); W. Oppolzer, *Synthesis*, 793 (1978); J. L. Charlton and M. M. Alauddin, *Tetrahedron*, **43**, 2873 (1987); H. N. C. Wong, K.-L. Lau, and K. F. Tam, *Top. Curr. Chem.*, **133**, 85 (1986); P. Y. Michelllys, H. Pellissier, and M. Santelli, *Org. Prep. Proced. Int.*, **28**, 545 (1996).

⁵² M. P. Cava and M. J. Mitchell, *Cyclobutadiene and Related Compounds*, Academic Press, New York, 1967, Chap. 6; I. L. Klundt, *Chem. Rev.*, **70**, 471 (1970); R. P. Thummel, *Acc. Chem. Res.*, **13**, 70 (1980).

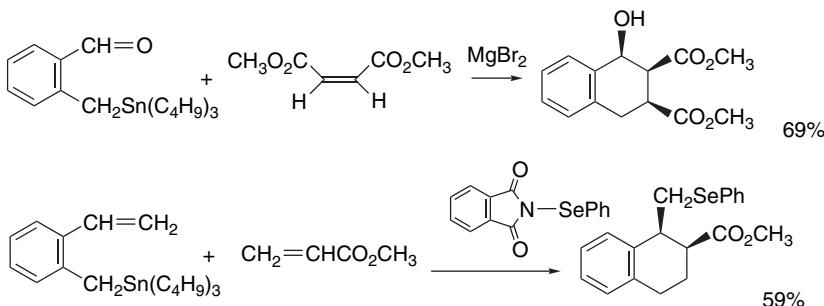
⁵³ M. G. Charest, D. R. Siegel, and A. G. Myers, *J. Am. Chem. Soc.*, **127**, 8292 (2005).

⁵⁴ Y. Ito, M. Nakatsuka, and T. Saegusa, *J. Am. Chem. Soc.*, **104**, 7609 (1982).

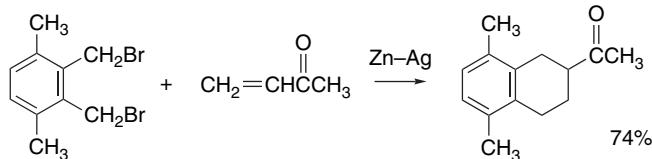
Several procedures have been developed for obtaining quinodimethane intermediates from *o*-substituted benzylstannanes. The reactions occur by generating an electrophilic center at the adjacent benzylic position, which triggers a 1,4-elimination.



Specific examples include treatment of *o*-stannylnyl benzyl alcohols with TFA,⁵⁵ reactions of ketones and aldehydes with Lewis acids,⁵⁶ and electrophilic selenation of styrenes.⁵⁷



o-bis-(Bromomethyl)benzenes can be converted to quinodimethanes with reductants such as zinc, nickel, chromous ion, and tri-*n*-butylstannide.⁵⁸



Quinodimethanes have been especially useful in intramolecular D-A reactions, as is illustrated in Section 6.1.7.

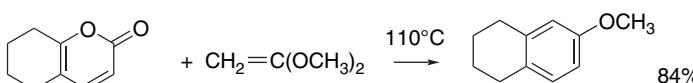
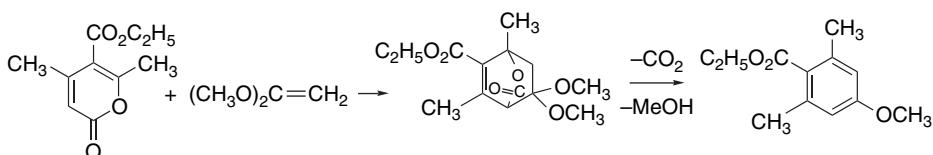
Pyrones are useful dienes, although they are not particularly reactive. The adducts have the potential for elimination of carbon dioxide, resulting in the formation of an aromatic ring. Pyrones react best with electron-rich dienophiles. Vinyl ethers are frequently used as dienophiles with pyrones. The regiochemical preference places the dienophile donor *ortho* to the pyrone carbonyl.

⁵⁵. H. Sans, H. Ohtsuka, and T. Migita, *J. Am. Chem. Soc.*, **110**, 2014 (1988).

⁵⁶. S. H. Woo, *Tetrahedron Lett.*, **35**, 3975 (1994).

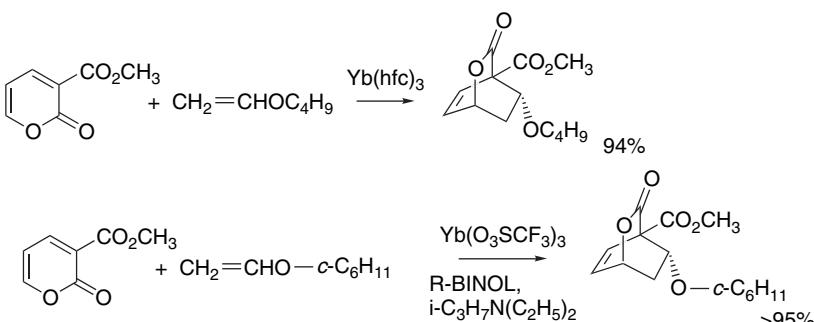
⁵⁷. S. H. Woo, *Tetrahedron Lett.*, **34**, 7587 (1993).

⁵⁸. G. M. Rubottom and J. E. Wey, *Synth. Commun.*, **14**, 507 (1984); S. Inaba, R. M. Wehmeyer, M. W. Forkner, and R. D. Rieke, *J. Org. Chem.*, **53**, 339 (1988); D. Stephan, A. Gorques, and A. LeCoq, *Tetrahedron Lett.*, **25**, 5649 (1984); H. Sato, N. Isono, K. Okamura, T. Date, and M. Mori, *Tetrahedron Lett.*, **35**, 2035 (1994).



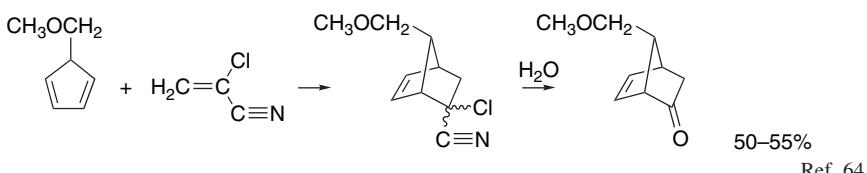
Ref. 60

These reactions can be catalyzed by Lewis acids such as *bis*-alkoxytitanium dichlorides⁶¹ and lanthanide salts.⁶²



Another type of special diene, the polyaza benzene heterocyclics, such as triazines and tetrazines, is discussed in Section 6.6.2.

The synthetic utility of the D-A reaction can be expanded by the use of dienophiles that contain *masked functionality* and are the *synthetic equivalents* of unreactive or inaccessible compounds. (See Section 13.1.2 for a more complete discussion of the concept of synthetic equivalents.) For example, α -chloroacrylonitrile shows satisfactory reactivity as a dienophile. The α -chloronitrile functionality in the adduct can be hydrolyzed to a carbonyl group. Thus, α -chloroacrylonitrile can function as the equivalent of ketene, $\text{CH}_2=\text{C}=\text{O}$,⁶³ which is not a suitable dienophile because it has a tendency to react with dienes by [2 + 2] cycloaddition, rather than the desired [4 + 2] fashion.



^{59.} M. E. Jung and J. A. Hagenah, *J. Org. Chem.*, **52**, 1889 (1987).

^{60.} D. L. Boger and M. D. Mullican, *Org. Synth.*, **65**, 98 (1987).

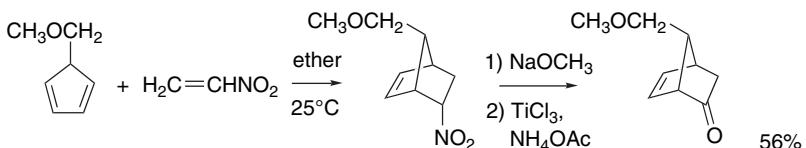
^{61.} G. H. Posner, J.-C. Carry, J. K. Lee, D. S. Bull, and H. Dai, *Tetrahedron Lett.*, **35**, 1321 (1994); G. H. Posner, H. Dai, D. S. Bull, J.-K. Lee, F. Eydoux, Y. Ishihara, W. Welsh, N. Pryor, and S. Petr, Jr., *J. Org. Chem.*, **61**, 671 (1996).

^{62.} G. H. Posner, J.-C. Carry, T. E. N. Anjeh, and A. N. French, *J. Org. Chem.*, **57**, 7012 (1992).

^{63.} V. K. Aggarwal, A. Ali, and M. P. Coogan, *Tetrahedron*, **55**, 293 (1999).

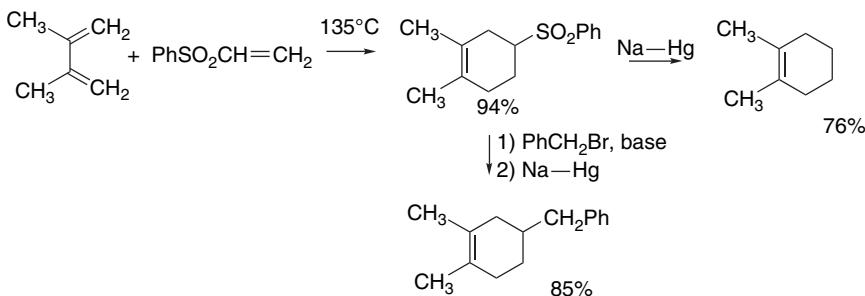
^{64.} E. J. Corey, N. M. Weinshenker, T. K. Schaff, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).

Nitroalkenes are good dienophiles and the variety of transformations available for nitro groups makes them versatile intermediates.⁶⁵ Nitro groups can be converted to carbonyl groups by reductive hydrolysis, so nitroethylene can be used as a ketene equivalent.⁶⁶

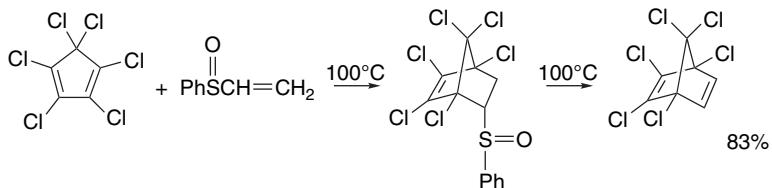


Ref. 67

Vinyl sulfones are reactive as dienophiles. The sulfonyl group can be removed reductively with sodium amalgam (see Section 5.6.2). In this two-step reaction sequence, the vinyl sulfone functions as an ethylene equivalent. The sulfonyl group also permits alkylation of the adduct, via the carbanion. This three-step sequence permits the vinyl sulfone to serve as the synthetic equivalent of a terminal alkene.⁶⁸



Phenyl vinyl sulfoxide can serve as an acetylene equivalent. Its D-A adducts can undergo thermal elimination of benzenesulfenic acid.



Ref. 69

⁶⁵. D. Ranganathan, C. B. Rao, S. Ranganathan, A. K. Mehrotra, and R. Iyengar, *J. Org. Chem.*, **45**, 1185 (1980).

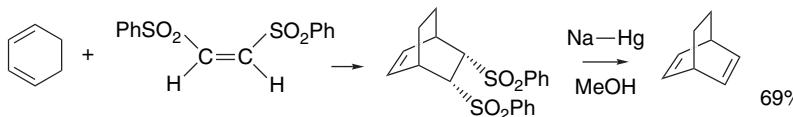
⁶⁶. For a review of ketene equivalents, see S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *Synthesis*, 289 (1977).

⁶⁷. S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, *J. Am. Chem. Soc.*, **96**, 5261 (1974).

⁶⁸. R. V. C. Carr and L. A. Paquette, *J. Am. Chem. Soc.*, **102**, 853 (1980); R. V. C. Carr, R. V. Williams, and L. A. Paquette, *J. Org. Chem.*, **48**, 4976 (1983); W. A. Kinney, G. O. Crouse, and L. A. Paquette, *J. Org. Chem.*, **48**, 4986 (1983).

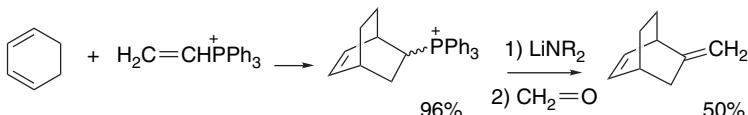
⁶⁹. L. A. Paquette, R. E. Moerck, B. Harirchian, and P. D. Magnus, *J. Am. Chem. Soc.*, **100**, 1597 (1978).

Cis- and *trans*-bis-benzenesulfonylethene are also acetylene equivalents. The two sulfonyl groups undergo reductive elimination on reaction with sodium amalgam.

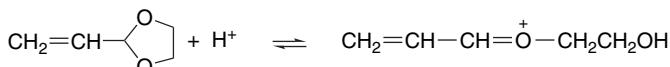


Ref. 70

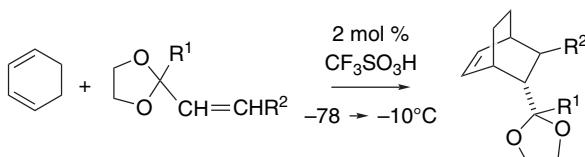
Vinylphosphonium salts are reactive as dienophiles as a result of the EWG character of the phosphonium substituent. The D-A adducts can be deprotonated to give ylides that undergo the Wittig reaction to introduce an exocyclic double bond. This sequence of reactions corresponds to a D-A reaction employing allene as the dienophile.⁷¹



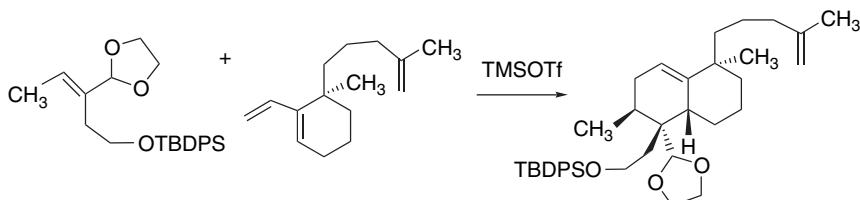
The use of 2-vinyldioxolane, the ethylene glycol acetal of acrolein, as a dienophile illustrates application of the masked functionality concept in a different way. The acetal itself would not be expected to be a reactive dienophile, but in the presence of a catalytic amount of acid the acetal is in equilibrium with the electrophilic oxonium ion.



Diels-Alder addition occurs through this cationic intermediate at room temperature.⁷² Similar reactions occur with substituted alkenyldioxolanes.



This reaction has been used to construct the carbon skeleton found in dysidiolide, a cell cycle inhibitor isolated from a marine sponge.⁷³ In this case, the reactive oxonium ion intermediate was generated by O-silylation.



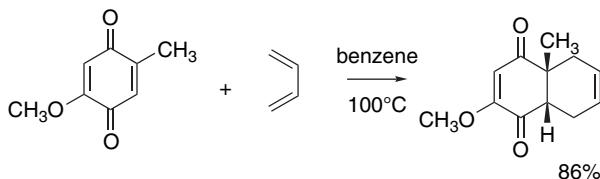
⁷⁰. O. DeLucchi, V. Lucchini, L. Pasquato, and G. Modena, *J. Org. Chem.*, **49**, 596 (1984).

⁷¹. R. Bonjouklian and R. A. Ruden, *J. Org. Chem.*, **42**, 4095 (1977).

⁷². P. G. Gassman, D. A. Singleton, J. J. Wilwerding, and S. P. Chavan, *J. Am. Chem. Soc.*, **109**, 2182 (1987).

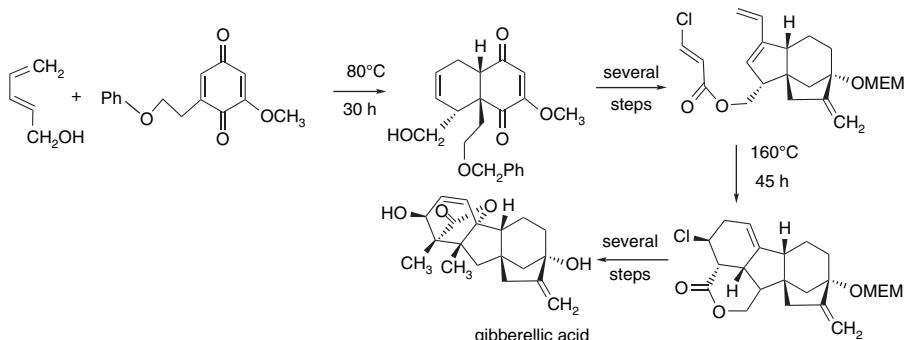
⁷³. S. R. Magnuson, L. Sepp-Lorenzino, N. Rosen, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **120**, 1615 (1998).

6.1.4.2. Synthetic Applications of the Diels-Alder Reaction. Diels-Alder reactions have long played an important role in synthetic organic chemistry.⁷⁴ The reaction of a substituted benzoquinone and 1,3-butadiene, for example, was the first step in one of the early syntheses of steroids. The angular methyl group was introduced by the methyl group on the quinone and the other functional groups were used for further elaboration.



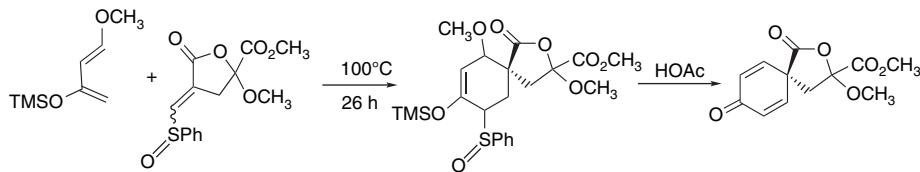
Ref. 75

In a synthesis of gibberellic acid, a diene and quinone, both with oxygen-substituted side chains, gave the initial intermediate. Later in the synthesis, an intramolecular D-A reaction was used to construct the A-ring.



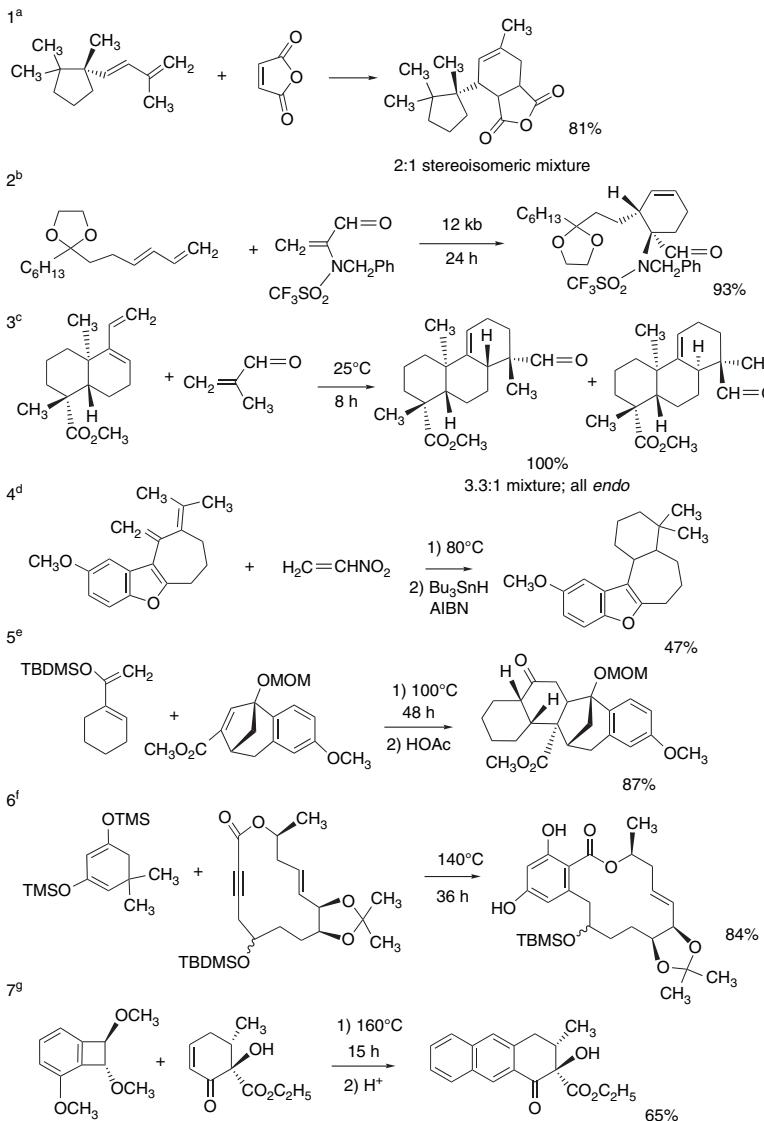
Ref. 76

Functionality can be built into either the diene or dienophile for purposes of subsequent transformations. For example, in the synthesis of prephenic acid, the diene has the capacity to generate an enone. The dienophile contains a sulfoxide substituent that is subsequently used to introduce a second double bond by elimination.



Ref. 77

- ⁷⁴. K. C. Nicolaou, S. A. Snyder, T. Montagnon, and G. Vassilikogiannakis, *Angew. Chem. Int. Ed. Engl.*, **41**, 1668 (2002).
- ⁷⁵. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).
- ⁷⁶. E. J. Corey, R. L. Danheiser, S. Chandrasekaran, P. Siret, G. E. Keck, and J.-L. Gras, *J. Am. Chem. Soc.*, **100**, 8031 (1978); E. J. Corey, R. L. Danheiser, S. Chandrasekaran, G. E. Keck, B. Gopalan, S. D. Larsen, P. Siret, and J.-L. Gras, *J. Am. Chem. Soc.*, **100**, 8034 (1978).
- ⁷⁷. S. J. Danishefsky, M. Hirama, N. Fitsch, and J. Clardy, *J. Am. Chem. Soc.*, **101**, 7013 (1979).



a. A. Nayek and S. Ghosh, *Tetrahedron Lett.*, **43**, 1313 (2002).

b. J.-H. Maeng and R. L. Funk, *Org. Lett.*, **4**, 331 (2002).

c. T. Ling, B. A. Kramer, M. A. Palladino, and E. A. Theodorakis, *Org. Lett.*, **2**, 2073 (2000).

d. M. Inoue, M. W. Carson, A. J. Frontier, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **123**, 1878 (2001).

e. P. D. O'Connor, L. N. Mander, and M. W. McLachlan, *Org. Lett.*, **6**, 703 (2004).

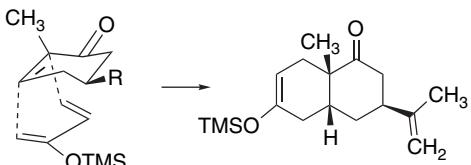
f. X. Geng and S. J. Danishefsky, *Org. Lett.*, **6**, 413 (2004).

g. K. Yamamoto, M. F. Hentemann, J. G. Allen, and S. J. Danishefsky, *Chem. Eur. J.*, **9**, 3242 (2003).

Scheme 6.1 gives some additional examples of application of thermal D-A reactions in syntheses. The reaction in Entry 1 was eventually used to construct an aromatic ring by decarboxylation and aromatization. The reaction did not exhibit much facial selectivity, but this was irrelevant for the particular application. Entry

2 illustrates the use of high pressure to accelerate reaction. This reaction gives only an *endo* product, since both the electronic effect of the formyl group and the steric effect of the sulfonamido group favor this orientation. The reaction in Entry 3 involves a typical diene and dienophiles. The reaction is completely regiospecific in the direction expected [donor alkyl groups at C(1) and C(3) of the diene unit] and is also completely *endo* selective. The facial selectivity with respect to the diene, however, is only 3.3:1. Entry 4 is an example of the use of nitroethene as an ethene equivalent. The nitro group was removed by reduction with Bu_3SnH . The reaction in Entry 5 involves a diene unit activated by a 2-siloxy substituent. On exposure to acid, this provides the product as a ketone. The reaction is evidently completely regio- and stereoselective. Entry 6 involves a doubly activated diene. The aromatic ring is formed by extrusion of isobutylene from a bicyclic intermediate. Entry 7 involves the ring opening of a benzocyclobutene to a quinodimethane. In this case, aromatization occurs as the result of the loss of two methoxy groups.

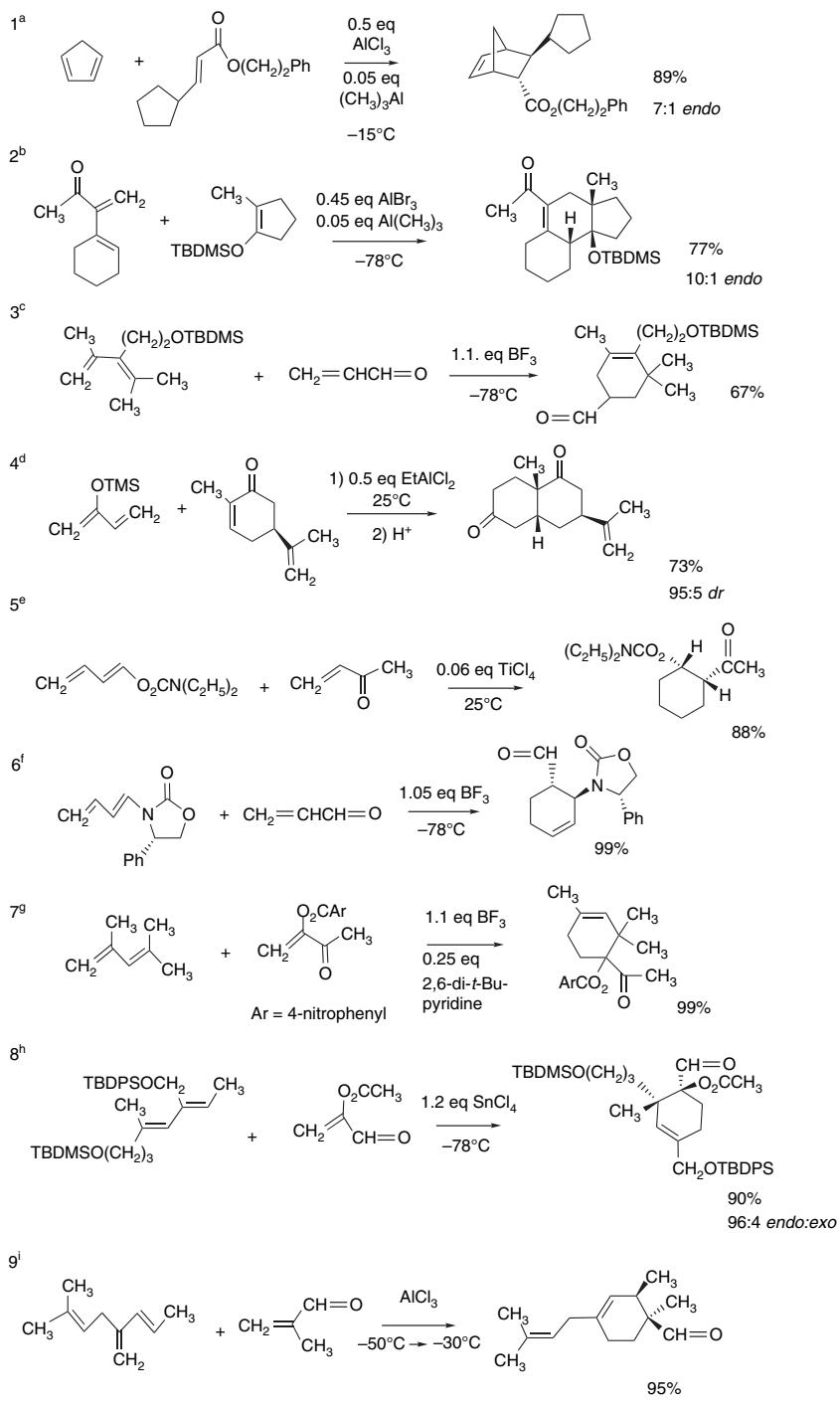
Owing to their advantages in terms of the lower temperature required and the higher regio- and stereoselectivity, Lewis acid–catalyzed D-A reactions are often preferable to the corresponding thermal version. Scheme 6.2 gives some examples of D-A reactions catalyzed by Lewis acids. Entries 1 and 2 are cases with substituent groups on the reacting bonds. Systems of this type are often relatively unreactive in thermal D-A reactions. The reaction in Entry 2 is an inverse electron demand case, and the catalyst activates the *diene* rather than the dienophile. Entry 3 involves a relatively highly substituted diene. The reaction was used to create a structure corresponding to the A-ring of the antitumor substance taxol. Entries 4, 5, and 6 involve dienes that have donor substituents that impart regioselectivity. The products of each of the reactions result from *endo* addition. The reaction in Entry 4 involves a cyclohexenone dienophile. 5-Substituted cyclohexenones have a strong preference for *anti* approach relative to the substituent.⁷⁸ The isopropenyl substituent establishes a conformational preference and the diene approaches from the *anti* direction.



Entries 5 and 6 exhibit the “ortho” regioselectivity expected for a 1-ERG on the diene. These dienes also present the possibility for competing Lewis acid coordination sites in the diene that would be expected to be *deactivating*. In Entry 6, the phenyl substituent on the oxazolidinone ring establishes a facial preference. The dienophiles in Entries 7 and 8 have both ERG and EWG substituents (sometimes called *capto-dative* dienophiles). The regiochemistry is consistent with the acceptor substituent having the dominant influence.⁷⁹ Entry 9 illustrates the excellent regio- and stereoselectivity often seen for Lewis acid–catalyzed reactions. Only a single product was found.

⁷⁸. F. Fringuelli, L. Minuti, F. Pizzo, and A. Taticchi, *Acta Chem. Scand.*, **47**, 255 (1993).

⁷⁹. R. Herrera, H. A. Jiminez-Vazquez, A. Modelli, D. Jones, B. C. Soderberg, and J. Tamariz, *Eur. J. Org. Chem.*, 4657 (2001).

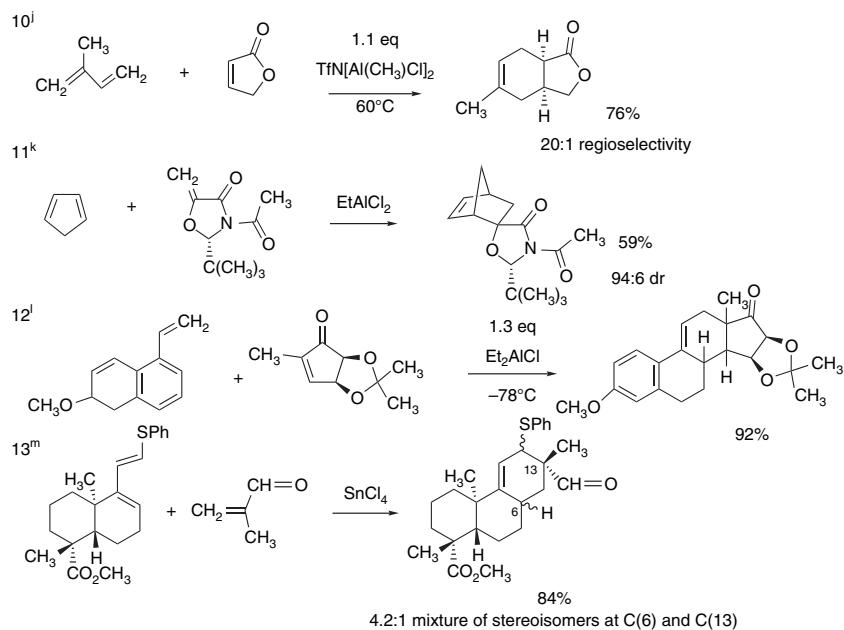


(Continued)

Scheme 6.2. (Continued)

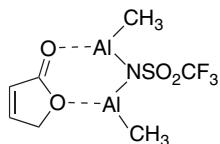
CHAPTER 6

*Concerted
Cycloadditions,
Unimolecular
Rearrangements, and
Thermal Eliminations*

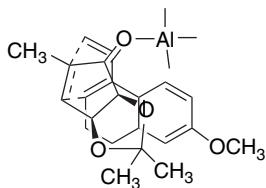


- a. R. D. Hubbard and B. L. Miller, *J. Org. Chem.*, **63**, 4143 (1998).
- b. M. E. Jung and P. Davidov, *Angew. Chem. Int. Ed. Engl.*, **41**, 4125 (2002).
- c. M. W. Tjepkema, P. D. Wilson, H. Audrain, and A. G. Fallis, *Can. J. Chem.*, **75**, 1215 (1997).
- d. A. A. Haaksma, B. J. M. Jansen, and A. de Groot, *Tetrahedron*, **48**, 3121 (1992).
- e. P. F. De Cusati and R. A. Olofson, *Tetrahedron Lett.*, **31**, 1409 (1990).
- f. D. A. Vosburg, S. Weiler, and E. J. Sorensen, *Chirality*, **15**, 156 (2003).
- g. J. D. Dudones and P. Sampson, *J. Org. Chem.*, **62**, 7508 (1997).
- h. W. R. Roush and D. A. Barda, *J. Am. Chem. Soc.*, **119**, 7402 (1997).
- i. G. Frater, U. Mueller, and F. Schroeder, *Tetrahedron: Asymmetry*, **15**, 3967 (2004).
- j. A. Saito, H. Yanai, and T. Taguchi, *Tetrahedron Lett.*, **45**, 9439 (2004).
- k. W. R. Roush, A. P. Essenfeld, J. S. Warmus, and B. B. Brown, *Tetrahedron Lett.*, **30**, 7305 (1989).
- l. K. Tanaka, H. Nakashima, T. Taniguchi, and K. Ogasawara, *Org. Lett.*, **2**, 1915 (2000).
- m. T. Ling, B. A. Kramer, M. A. Palladino, and E. A. Theodorakis, *Org. Lett.*, **2**, 2073 (2000).

Entries 10 and 11 involve lactones and lactams, respectively. The catalyst used in Entry 10 is thought to be capable of interaction with both the carbonyl and ether oxygens.



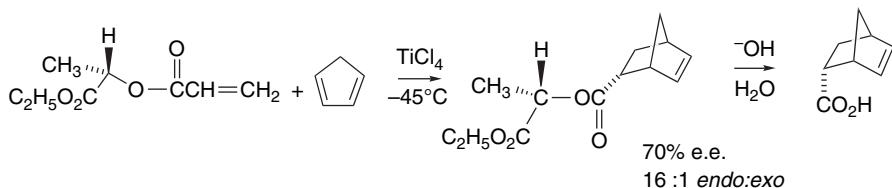
In Entry 11 the dienophile is an α -methylene lactam. As noted for this class of dienophiles, the stereoselectivity results from preferred *exo* addition (see p. 471). The reaction in Entry 12 was used in an enantiospecific synthesis of estrone. The dienophile was used in enantiomerically pure form and the dioxolane ring imparts a high facial selectivity to the dienophile. The reaction occurs through an *endo* TS.



The reaction in Entry 13 is completely regioselective and both stereoisomers are formed through an *endo* TS. The two stereoisomers result from competing facial approaches to the diene.

6.1.5. Diastereoselective Diels-Alder Reactions Using Chiral Auxiliaries

The highly ordered cyclic TS of the D-A reaction permits design of diastereo- or enantioselective reactions. (See Section 2.4 of Part A to review the principles of diastereoselectivity and enantioselectivity.) One way to achieve this is to install a chiral auxiliary.⁸⁰ The cycloaddition proceeds to give two diastereomeric products that can be separated and purified. Because of the lower temperature required and the greater stereoselectivity observed in Lewis acid-catalyzed reactions, the best diastereoselectivity is observed in catalyzed reactions. Several chiral auxiliaries that are capable of high levels of diastereoselectivity have been developed. Chiral esters and amides of acrylic acid are particularly useful because the auxiliary can be recovered by hydrolysis of the purified adduct to give the enantiomerically pure carboxylic acid. Early examples involved acryloyl esters of chiral alcohols, including lactates and mandelates. Esters of the lactone of 2,4-dihydroxy-3,3-dimethylbutanoic acid (pantolactone) have also proven useful.



Ref. 81

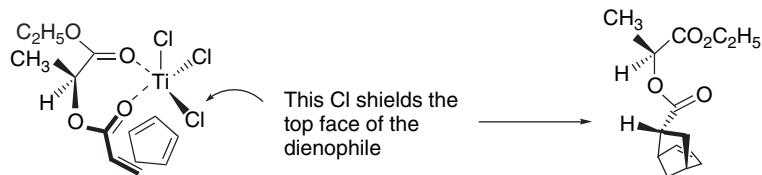
Prediction and analysis of diastereoselectivity are based on steric, stereoelectronic, and complexing interactions in the TS.⁸² In the case of the lactic acid auxiliary, a chelated structure promotes facial selectivity. In the $TiCl_4$ complex of *O*-acryloyl ethyl lactate,

⁸⁰. W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **23**, 876 (1984); M. J. Tascher, in *Organic Synthesis: Theory and Applications*, Vol. 1, T. Hudlicky, ed., JAI Press, Greenwich, CT, 1989, pp. 1–101; H. B. Kagan and O. Riant, *Chem. Rev.*, **92**, 1007 (1992); K. Narasaka, *Synthesis*, **16** (1991).

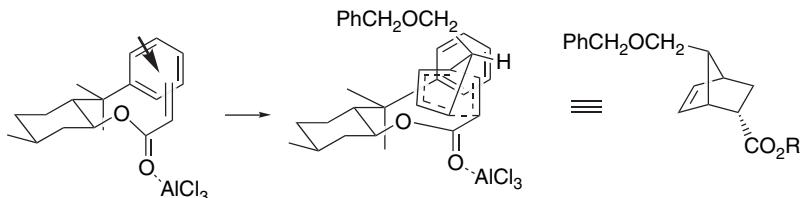
⁸¹. T. Poll, G. Helmchen, and B. Bauer, *Tetrahedron Lett.*, **25**, 2191 (1984).

⁸². For example, see T. Poll, A. Sobczak, H. Hartmann, and G. Helmchen, *Tetrahedron Lett.*, **26**, 3095 (1985).

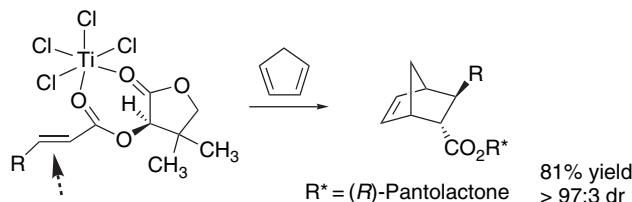
one of the chlorines attached to titanium shields one face of the double bond (see also Figure 6.5).



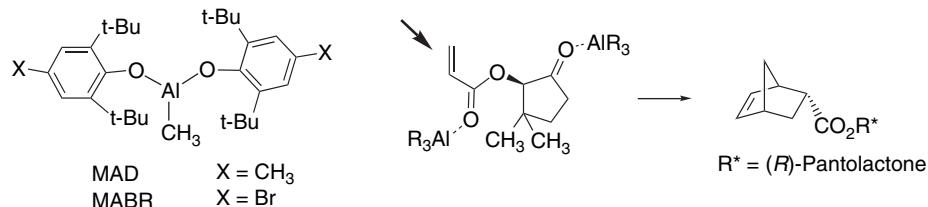
An 8-phenylmenthol ester was employed as the chiral auxiliary to achieve enantioselectivity in the synthesis of prostaglandin precursors.⁸³ The crucial features of the TS are the *anti* disposition of the Lewis acid relative to the alcohol moiety and a π stacking with the phenyl ring that provides both stabilization and steric shielding of the α -face.



The cyclic α -hydroxylactone, pantolactone, has been used extensively as a chiral auxiliary in D-A reactions.⁸⁴ Reactions involving $TiCl_4$ and $SnCl_4$ occur through chelated TSs.⁸⁵



Several other Lewis acids including BF_3 , Et_2AlCl , and $EtAlCl_2$ gave somewhat reduced levels of diastereoselectivity, but still favored the chelation-controlled product.⁸⁶ However, use of two equivalents of a highly hindered monodentate Lewis acid of the MAD type favored the other diastereoisomer. These reactions are thought to proceed through an open 2:1 complex exhibiting the opposite facial selectivity.



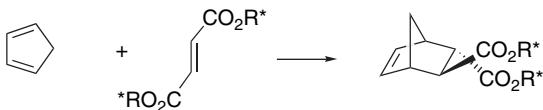
⁸³. E. J. Corey, T. K. Schaaf, W. Huber, H. Koelliker, and N. M. Weinshenker, *J. Am. Chem. Soc.*, **92**, 397 (1970).

⁸⁴. P. Campos and D. Munoz-Torreno, *Curr. Org. Chem.*, **8**, 1339 (2004).

⁸⁵. T. Poll, A. F. Abdel Hady, R. Karge, G. Linz, J. Weetman, and G. Helmchen, *Tetrahedron Lett.*, **30**, 5595 (1989).

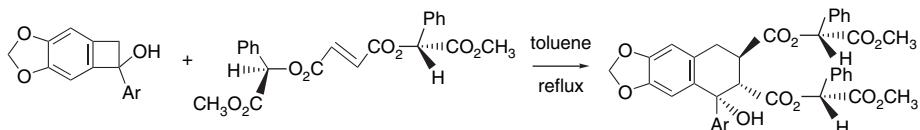
⁸⁶. R. Maruoka, M. Oishi, and H. Yamamoto, *Synlett*, 683 (1993).

For the diester of fumaric acid, EtAlCl_2 was the most effective catalyst and the reaction proceeded with more than 90% diastereoselectivity.⁸⁷

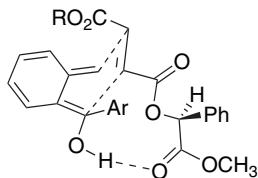


$\text{R}^* = (\text{R})\text{-Pantolactone}$

Mandelate and lactate esters have been found to generate diastereoselectivity in reactions of hydroxy-substituted quinodimethanes generated by thermolysis of benzocyclobutenols.⁸⁸ The reactions are thought to proceed by an *exo* TS with a crucial hydrogen bond between the hydroxy group and a dienophile carbonyl. The phenyl (or methyl in the case of lactate) group promotes facial selectivity.

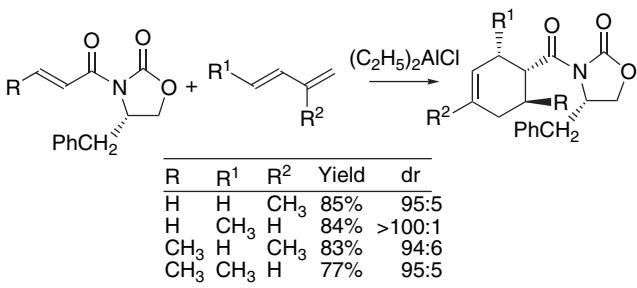


$\text{Ar} = 3,4,5\text{-trimethoxyphenyl}$



Several aspects of this reaction are intriguing. Despite the relatively high temperature (105°C), the nine-membered ring seems to have a strong influence on the stereoselectivity. The tendency for planarity at the ester bond may also contribute to the stability of the TS.

α,β -Unsaturated derivatives of chiral oxazolidinones have proven to be especially useful chiral auxiliaries for D-A additions. Reaction occurs at low temperatures in the presence of Lewis acids. The most effective catalyst for this system is $(\text{C}_2\text{H}_5)_2\text{AlCl}$.⁸⁹

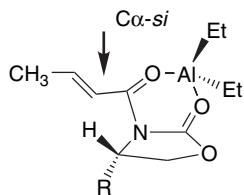


⁸⁷. G. Helmchen, A. F. A. Hady, H. Hartmann, R. Karge, A. Krotz, K. Sartor, and M. Urmann, *Pure Appl. Chem.*, **61**, 409 (1989).

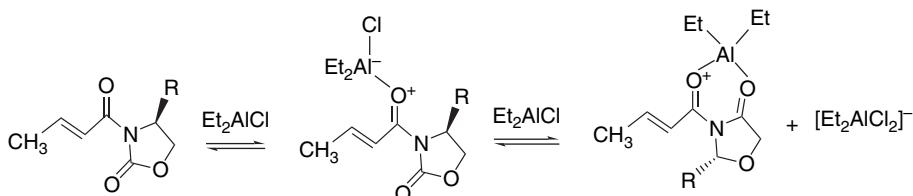
⁸⁸. D. E. Bogucki and J. L. Charlton, *J. Org. Chem.*, **60**, 588 (1995); J. L. Charlton and S. Maddaford, *Can. J. Chem.*, **71**, 827 (1993).

⁸⁹. D. A. Evans, K. T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.*, **110**, 1238 (1988).

The highest level of enantioselectivity is obtained using 1.5–2.0 equivalents of $(C_2H_5)_2AlCl$. Under these conditions the reactions are thought to proceed through a chelated TS having the vinyl substituent in the *s-cis*-conformation. For oxazolidinones having *S*-configuration at C(4) of the ring, this structure exposes the *si* face at the α -carbon of the dienophile.

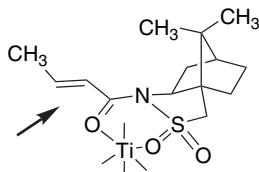


This complex is formed with more than 1.0 equivalents of $(C_2H_5)_2AlCl$ with concomitant formation of $[Et_2AlCl_2]^-$. The open and chelated structures have been characterized by NMR.⁹⁰ The chelated structure is substantially *more reactive* than the open complex, which accounts for the increase in enantioselectivity with more than 1.0 equivalents of catalyst.



Chelation alone, however, is not sufficient to induce high enantioselectivity since other Lewis acids capable of chelation, such as $SnCl_4$ and $TiCl_4$, give lower enantioselectivity.

Scheme 6.3 gives some other examples of use of chiral auxiliaries in D-A reactions.⁹¹ Entries 1 and 2 show two chiral auxiliaries developed from terpene precursors. The acrylate shown in Entry 1 gave excellent enantioselectivity with cyclopentadiene and 1,3-butadiene, but introduction of a methyl substituent on the dienophile (crotonyl derivative) resulted in a very slow reaction owing to steric problems. The sulfonamide auxiliary shown in Entry 2 has been exploited in other contexts (see, e.g., p. 123). The acyl derivatives give very good facial selectivity and are thought to react through a chelated TS. The carbocyclic ring establishes facial selectivity.



⁹⁰ S. Castellino and W. J. Dwight, *J. Am. Chem. Soc.*, **115**, 2986 (1993).

⁹¹ For additional examples, see W. Oppolzer, *Tetrahedron*, **43**, 1969, 4057 (1987).

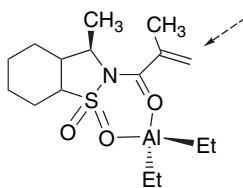
Scheme 6.3. Diels-Alder Reactions with Chiral Auxiliaries

SECTION 6.1
Diels-Alder Reactions

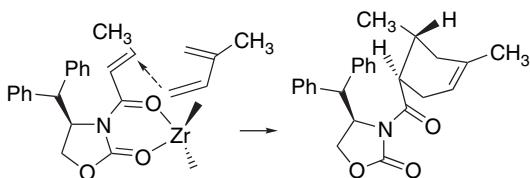
Entry	Dienophile	Diene	Catalyst, temperature	Yield (%)	dr
1 ^a			TiCl₂(i-OPr)₂, -20°C 1.5 equiv	90	>99:1
2 ^b			TiCl₄, -78°C 0.5 equiv	88	99:1
3 ^c			(C₂H₅)₂AlCl, -40°C	94	98:2
4 ^d			SnCl₄, -78°C 2 equiv	93	96:4
5 ^e			ZrCl₄, -78°C	86	>99:1
6 ^f			(C₂H₅)₂AlCl, 78°C 1.1 equiv	62	97:3
7 ^g			TiCl₄, -55° to -20°C	79	96:2

- a. W. Oppolzer, C. Chapuis, D. Dupuis, and M. Guo, *Helv. Chim. Acta*, **68**, 2100 (1985).
 b. W. Oppolzer, C. Chapuis, and G. Bernardinelli, *Helv. Chim. Acta*, **67**, 1397 (1984); M. Vanderwalle, J. Van der Eycken, W. Oppolzer, and C. Vulliod, *Tetrahedron*, **42**, 4035 (1986).
 c. W. Oppolzer, B. M. Seletsky, and G. Bernardinelli, *Tetrahedron Lett.*, **35**, 3509 (1994).
 d. R. Nougier, J.-L. Gras, B. Giraud, and A. Virgilli, *Tetrahedron Lett.*, **32**, 5529 (1991).
 e. M. P. Sibi, P. K. Deshpande, and J. Ji, *Tetrahedron Lett.*, **36**, 8965 (1995).
 f. M. Ikota, *Chem. Pharm. Bull.*, **37**, 2219 (1989).
 g. K. Miyaji, Y. Ohara, Y. Takahashi, T. Tsuruda, and K. Arai, *Tetrahedron Lett.*, **32**, 4557 (1991).

Entry 3 involves another sultam auxiliary. The chirality of the product is consistent with approach of the diene from the *re* face of a conformation in which the carbonyl oxygen is *syn* to the sulfonyl group.

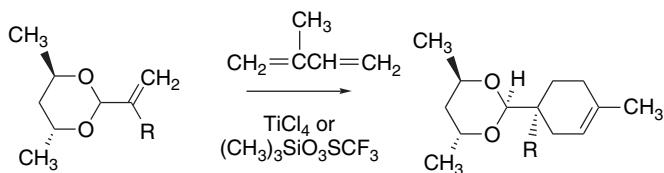


Entry 4 shows a carbohydrate-derived auxiliary with SnCl_4 as the Lewis acid. This dienophile also gives good enantioselectivity using TiCl_4 as the Lewis acid. Entry 5 is a proline-derived oxazolidinone auxiliary used in conjunction with ZrCl_4 . The observed diastereoselectivity is consistent with a chelated TS having an *s-cis* conformation at the carbonyl group.



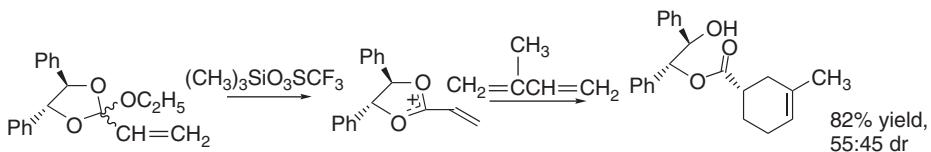
Entry 6 uses a chiral auxiliary derived from pyroglutamic acid. Entry 7 is an example of the use of pantolactone as a chiral auxiliary to form a prostaglandin precursor.

The alkenyl oxonium ion dienophiles generated from dioxolanes can be made diastereoselective by use of chiral diols. For example, acetals derived from *anti*-pentane-2,4-diol react under the influence of $\text{TiCl}_4/\text{Ti}(i\text{-OPr})_4$ with stereoselectivity ranging from 3:1 to 15:1.



Ref. 92

Dioxolanes derived from *syn*-1,2-diphenylethane-1,2-diol react with dienes such as cyclopentadiene and isoprene, but in most cases the diastereoselectivity is low.

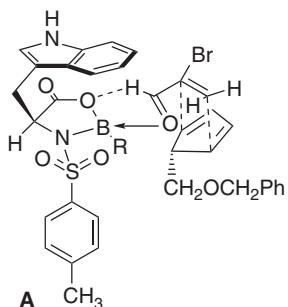
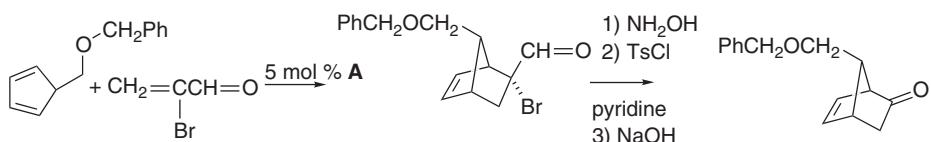


Ref. 93

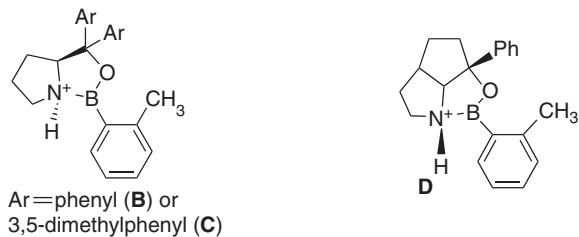
92. T. Sammakia and M. A. Berliner, *J. Org. Chem.*, **59**, 6890 (1994).

93. A. Haudrechy, W. Picoul, and Y. Langlois, *Tetrahedron: Asymmetry*, **8**, 129 (1997).

Enantioselectivity can also be achieved with chiral catalysts. The chiral oxazaborolidinones introduced in Section 2.1.5.6 as enantioselective aldol addition catalysts have been found to be useful in D-A reactions. The tryptophan-derived catalyst **A** can achieve 99% enantioselectivity in the cycloaddition between 5-benzyloxymethyl-1,3-cyclopentadiene and 2-bromopropenal. The indole ring provides π stacking and steric shielding. There is also believed to be a *formyl hydrogen bond* to the ring oxygen. A significant feature of this reaction is that the product is *exo* with respect to the formyl group. The adduct can be converted to an important intermediate for the synthesis of prostaglandins.⁹⁴



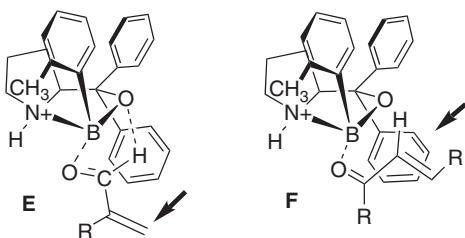
The oxazaborolidines **B** and **C** derived from proline are also effective catalysts. The protonated forms of these catalysts, generated using triflic acid or triflimide, are very active catalysts,⁹⁵ and the triflimide version is more stable above 0°C. Another protonated catalyst **D** is derived from 2-cyclopentenylacetic acid.



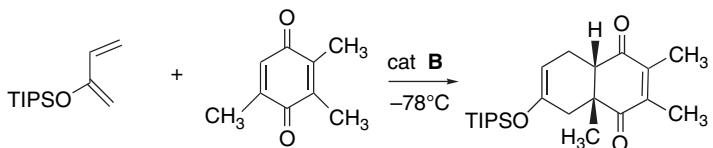
⁹⁴. E. J. Corey and T. P. Loh, *J. Am. Chem. Soc.*, **113**, 8966 (1991).

⁹⁵. E. J. Corey, T. Shibata, and T. W. Lee, *J. Am. Chem. Soc.*, **124**, 3808 (2002); D. H. Ryu and E. J. Corey, *J. Am. Chem. Soc.*, **125**, 6388 (2003); E. J. Corey, *Angew. Chem. Int. Ed.*, **41**, 1650 (2002).

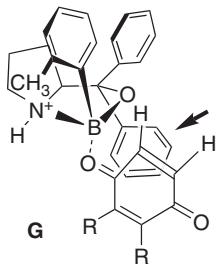
α,β -Unsaturated aldehydes react via TS **E**, whereas α,β -unsaturated ketones and esters react via TS **F**.



With trisubstituted benzoquinones and use of the cationic oxazaborolidinium catalyst **B**, 2-[*tris*-(isopropyl)silyloxy]-1,3-butadiene reacts at the monosubstituted quinone double bond. The reactions exhibit high regioselectivity and more than 95% e.e. With 2-mono- and 2,3-disubstituted quinones, reaction occurs at the unsubstituted double bond. The regiochemistry is directed by coordination to the catalyst at the more basic carbonyl oxygen.

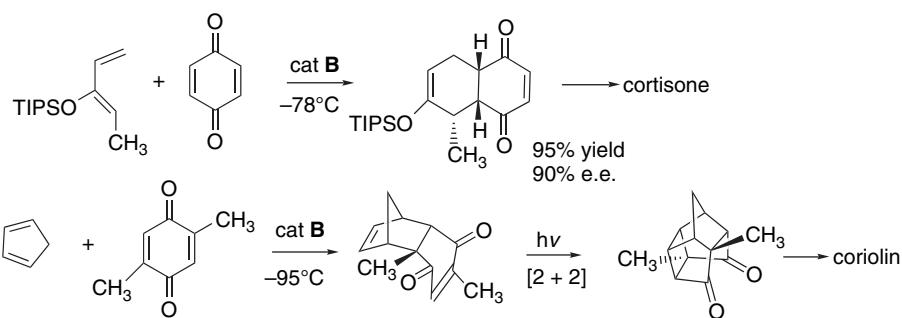


The enantioselectivity is consistent with a TS in which the less-substituted double bond of the quinone is oriented toward the catalyst, as in TS **G**.

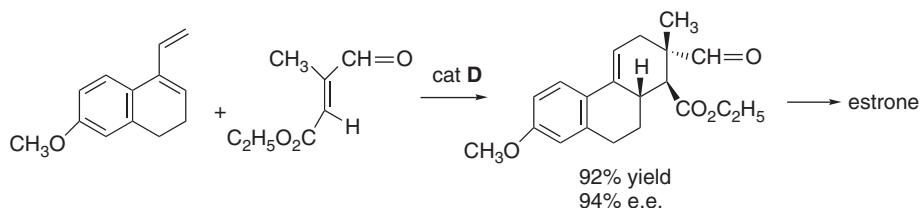


These catalysts have been applied to D-A reactions that are parts of several important synthetic routes, thereby making them enantioselective.⁹⁶ For example, key intermediates in the synthesis of cortisone and coriolin were prepared in enantiomerically pure form using catalyst **B**.

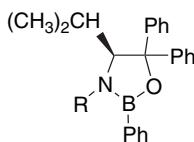
⁹⁶ Q.-Y. Hu, G. Zhou, and E. J. Corey, *J. Am. Chem. Soc.*, **126**, 13708 (2004).



Similarly, an enantioselective synthesis of estrone is based on catalyst **D**.⁹⁷



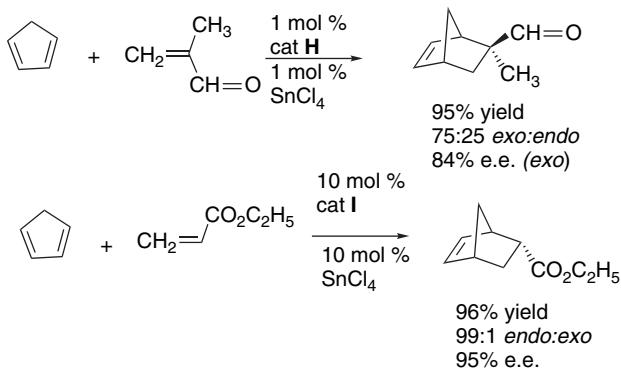
A valine-derived oxazaborolidine derivative has been found to be subject to activation by Lewis acids, with SnCl_4 being particularly effective.⁹⁸ This catalyst combination also has reduced sensitivity to water and other Lewis bases.



H R = *n*-octyl

I R = 1-naphthylmethyl

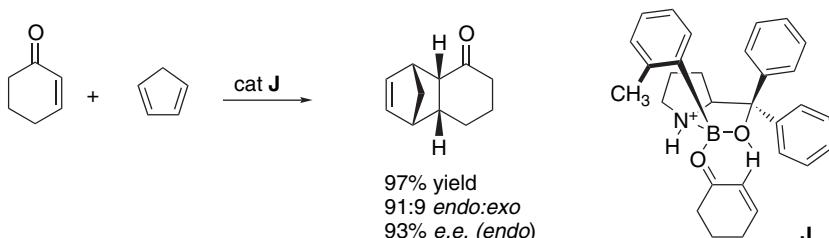
Catalyst **H** and the corresponding *N*-(1-naphthylmethyl) derivative **I** give high e.e. and good *endo* stereoselectivity for several typical dienophiles with cyclopentadiene.



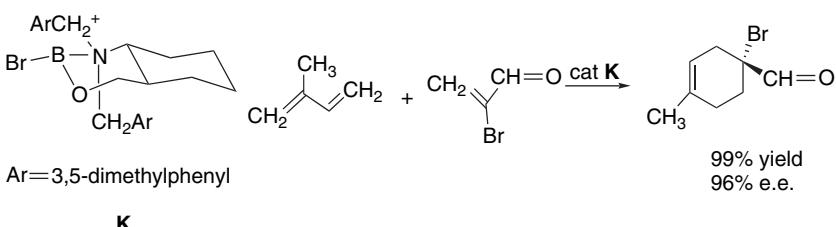
⁹⁷ Q.-Y. Hu, P. D. Rege, and E. J. Corey, *J. Am. Chem. Soc.*, **126**, 5984 (2004).

⁹⁸ K. Futatsugi and H. Yamamoto, *Angew. Chem. Int. Ed. Engl.*, **44**, 1484 (2005).

Cationic oxazaborolidines derived from α,α -diphenylpyrrolidine-2-methanol have been examined and shown to considerably extend the range of dienophiles that are responsive to the catalysts.⁹⁹ The best proton source for activation of these catalysts is triflimide, $(CF_3SO_2)_2NH$.¹⁰⁰ For example, cyclohexenone and cyclopentadiene react with 93% enantioselectivity using catalyst **J**.



Another cyclic boron catalyst **K**, derived from *trans*-2-aminocyclohexane-methanol, can be prepared with a quaternary nitrogen that enhances activity.¹⁰¹ This particular catalyst is not very stable, but it is highly active.



Another useful group of catalysts for D-A reactions is made up of Cu^{2+} chelates of *bis*-oxazolines.¹⁰² The copper salts are the most effective of the first transition metal series because they offer both strong Lewis acid activation and fast ligand exchange. The anion is also important and must be noncoordinating. The triflates can be used, but the hexafluoroantimonates are even more active.¹⁰³ These catalysts have been applied to dienophiles with two donor sites, in particular *N*-acyloxazolidinones. The chelated structures provide strong facial differentiation, as shown in Figure 6.9.¹⁰⁴ Installing chirality into the oxazolidinone results in matched and mismatched combinations. In addition to the *t*-butyl derivative, the 4-isopropyl-5,5-phenyl derivatives have also been explored.¹⁰⁵ The *bis*-oxazolines derived from *cis*-2-aminoindanol have also proven to be effective catalysts.¹⁰⁶ Various solid-supported forms of these BOX catalysts have been developed.¹⁰⁷

- ⁹⁹ E. J. Corey, T. Shibata, and T. W. Lee, *J. Am. Chem. Soc.*, **124**, 3808 (2002); D. H. Ryu, T. W. Lee, and E. J. Corey, *J. Am. Chem. Soc.*, **124**, 9992 (2002).
- ¹⁰⁰ D. H. Ryu and E. J. Corey, *J. Am. Chem. Soc.*, **125**, 6388 (2003).
- ¹⁰¹ Y. Hayashi, J. J. Rohde, and E. J. Corey, *J. Am. Chem. Soc.*, **118**, 5502 (1996).
- ¹⁰² J. J. Johnson and D. A. Evans, *Acc. Chem. Res.*, **33**, 325 (2000).
- ¹⁰³ D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy, and K. R. Campos, *J. Am. Chem. Soc.*, **121**, 7582 (1999).
- ¹⁰⁴ D. A. Evans, S. J. Miller, T. Lectka, and P. von Matt, *J. Am. Chem. Soc.*, **121**, 7559 (1999).
- ¹⁰⁵ T. Hintermann and D. Seebach, *Helv. Chim. Acta*, **81**, 2093 (1998).
- ¹⁰⁶ A. K. Ghosh, S. Fidanze, and C. H. Senanayake, *Synthesis*, 937 (1998); C. H. Senanayake, *Aldrichimica Acta*, **31**, 3 (1998).
- ¹⁰⁷ D. Rechavi and M. Lemaine, *Chem. Rev.*, **102**, 3467 (2002).

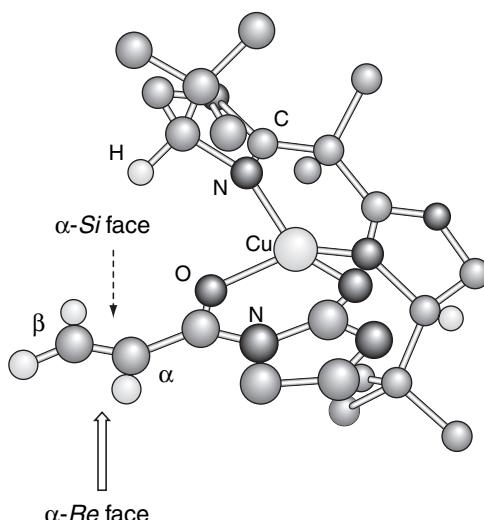
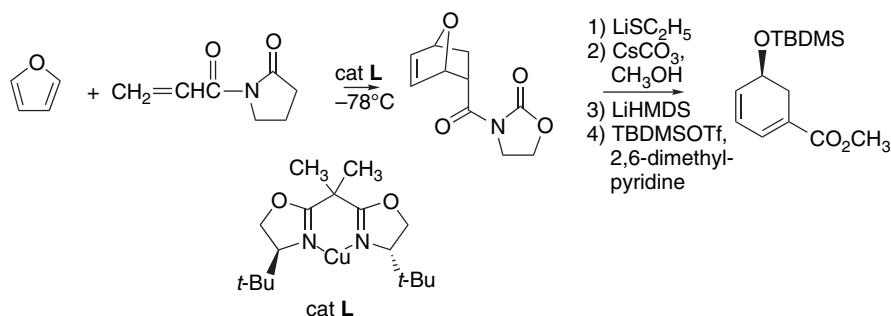


Fig. 6.9. Model of $\text{Cu}(S,S\text{-}t\text{-BuBOX})$ catalyst with N -acryloyloxazolidinone showing facial stereodifferentiation. Reproduced from *J. Am. Chem. Soc.*, **121**, 7559 (1999), by permission of the American Chemical Society.



Ref. 108

The related PyBOX ligands incorporate a pyridine ring that provides an additional coordination site and are tridentate. The Sc^{3+} and lanthanide ions with the PyBOX ligand can accommodate seven to nine donors. In these complexes, the enantioselectivity is influenced by the number and identity of the coordinating species.¹⁰⁹ Figure 6.10 shows examples of a monohydrated Sc^{3+} triflate¹¹⁰ having seven contacts and a tetrahydrated lanthanide cation with a total of nine contacts, including two triflate anions.¹¹¹

The basis of the enantioselectivity of the BOX catalysts has been probed using B3LYP/6-31G* calculations.¹¹² It has been proposed that in the case of the *t*-butyl

¹⁰⁸ D. A. Evans and D. M. Barnes, *Tetrahedron Lett.*, **38**, 57 (1997).

¹⁰⁹ G. Desimoni, G. Faita, M. Gualà, and C. Pratelli, *J. Org. Chem.*, **68**, 7862 (2003).

¹¹⁰ D. A. Evans, Z. K. Sweeney, T. Rovis, and J. S. Tedrow, *J. Am. Chem. Soc.*, **123**, 12095 (2001).

¹¹¹ G. Desimoni, G. Faita, S. Filippone, M. Mella, M. G. Zampori, and M. Zema, *Tetrahedron*, **57**, 10203 (2001).

¹¹² J. DeChancie, O. Acevedo, and J. D. Evanseck, *J. Am. Chem. Soc.*, **126**, 6043 (2004).

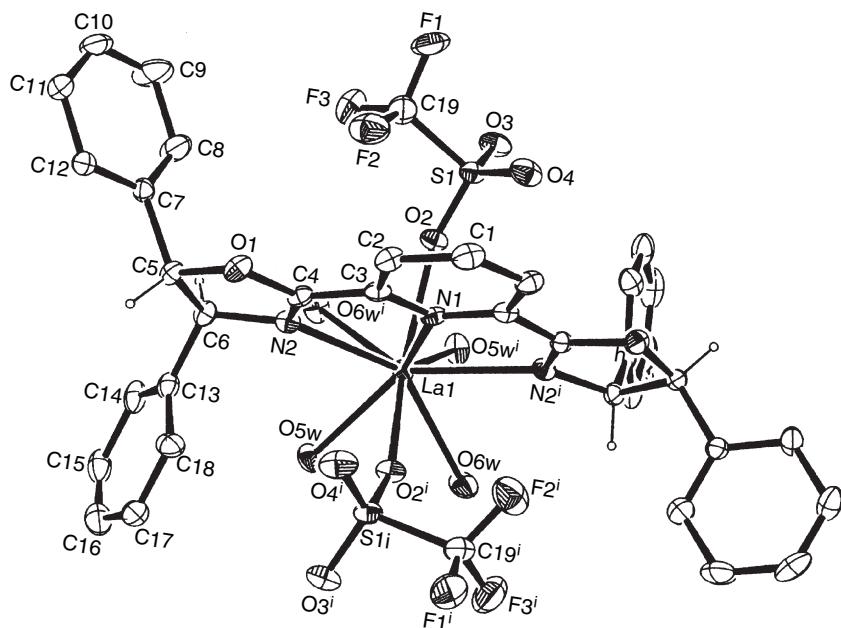
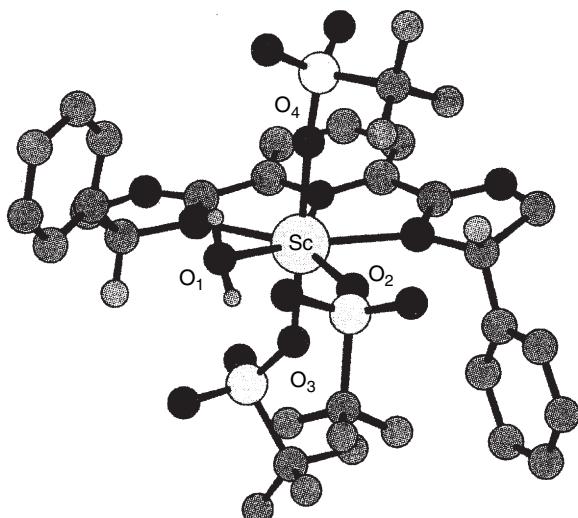
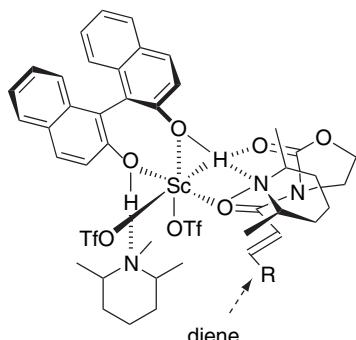


Fig. 6.10. (top) Scandium[S,S-phenylPyBOX(H₂O)(CF₃SO₃⁻)₃]. Reproduced from *J. Am. Chem. Soc.*, **123**, 12095 (2001), by permission of the American Chemical Society. (bottom) Lanthanum[R,R-phenylPyBOX(H₂O)₄(CF₃SO₃⁻)₂ cation. Reproduced from *Tetrahedron*, **57**, 10203 (2001), by permission of Elsevier.

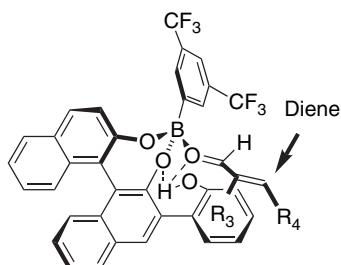
derivatives, catalyst activity and enantioselectivity are governed by the degree to which solvent or anions can approach the copper ion. The most active catalysts are those in which nucleophilic coordination is restricted by a *t*-butyl group.

Several catalysts for enantioselective D-A reactions are based on BINOL. For example, additions of *N*-acryloyloxazolidinones can be made enantioselective using

$\text{Sc}(\text{O}_3\text{SCF}_3)_3$ in the presence of a BINOL ligand.¹¹³ Optimized conditions involved use of 5–20 mol % of the catalyst along with a hindered amine such as *cis*-1,2,6-trimethylpiperidine. A hexacoordinate TS in which the amine is hydrogen bonded to the BINOL has been proposed.



Enantioselective D-A reactions of acrolein are also catalyzed by 3-(2-hydroxyphenyl) derivatives of BINOL in the presence of an aromatic boronic acid. The optimum boronic acid is 3,5-di-(trifluoromethyl)benzeneboronic acid, with which more than 95% e.e. can be achieved. The TS is believed to involve Lewis acid complexation of the boronic acid at the carbonyl oxygen and hydrogen bonding with the hydroxy substituent. In this TS π - π interactions between the dienophile and the hydroxybiphenyl substituent can also help to align the dienophile.¹¹⁴



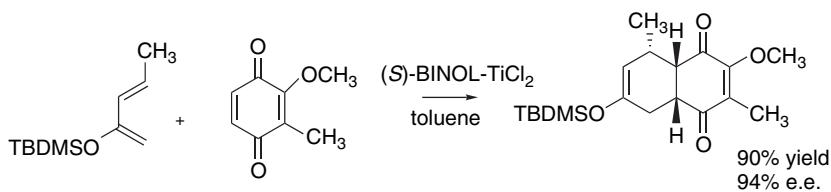
Dienophile	Yield (%)	<i>exo</i> : <i>endo</i>	e.e. (%)
$\text{CH}_2=\text{CHCH=O}$	84	3:97	95
$\text{CH}_2=\text{CCH=O}$	99	90:10	>99
$E\text{-CH}_2\text{CH}=\text{CHCH=O}$	94	10:90	95
$E\text{-PhCH=CHCH=O}$	94	26:74	80

BINOL has also been used in conjunction with Ti(IV). (*S*)-BINOL-TiCl₂ provided an enantiomerically enriched starting material in the synthesis of (−)colombiasin A.¹¹⁵

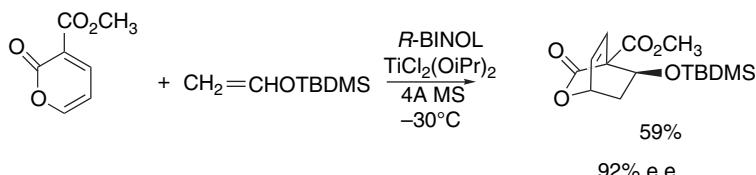
¹¹³ S. Kobayashi, M. Araki, and I. Hachiya, *J. Org. Chem.*, **59**, 3758 (1994).

¹¹⁴ K. Ishihara, H. Kurihara, M. Matsumoto, and H. Yamamoto, *J. Am. Chem. Soc.*, **120**, 6920 (1995).

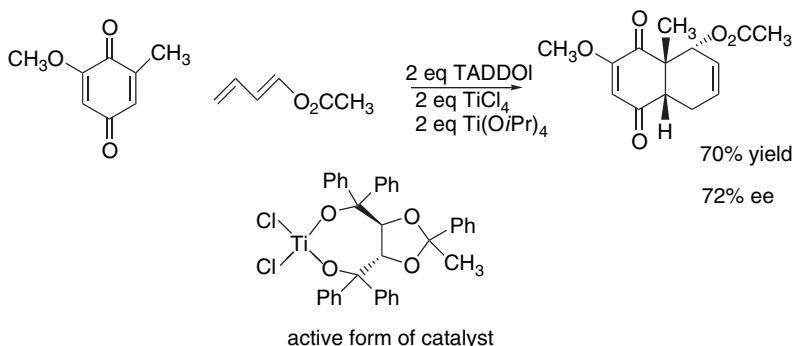
¹¹⁵ K. C. Nicolaou, G. Vassilikogiannakis, W. Magerlein, and R. Kranich, *Angew. Chem. Int. Ed. Engl.*, **40**, 2482 (2001); K. C. Nicolaou, G. Vassilikogiannakis, W. Magerlein, and R. Kranich, *Chem. Eur. J.*, **7**, 5359 (2001).



BINOL in conjunction with $\text{TiCl}_2(\text{O}-i\text{-Pr})_2$ gives good enantioselectivity in a D-A reaction with a pyrone as the diene.¹¹⁶ This is a case of an inverse electron demand reaction and the catalysts would be complexed to the diene.



The $\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) chiral ligands have also been the basis of enantioselective catalysis of the D-A reaction. In a study using 2-methoxy-6-methylquinone as the dienophile, evidence was found that the chloride-ligated form of the catalysts was more active than the dimeric oxy-bridged form.¹¹⁷



A computational study [B3LYP/3-21G(d)] examined a related aspect of the mechanism of TADDOL- TiCl_2 catalysis of reactions with *N*-acryloyloxazolidinone.¹¹⁸ The TS model does not address the steric shielding provided by the ligand substituents but rather the role of the coordination geometry at Ti. The results of this study suggest that the reaction may proceed through a *nonminimum energy complex*. Three different TSs corresponding to different coordination geometries of the ligands were characterized, as shown in Figure 6.11. Although complex MA is lowest in energy, MB has the lowest LUMO. This structure places the exocyclic carbonyl *trans* to a chloride. The authors suggest that it may therefore be the *most reactive* complex. This issue

¹¹⁶ G. H. Posner, H. Dai, D. S. Bull, J.-K. Lee, F. Eydoux, Y. Ishihara, W. Welsh, N. Pryor, and S. Peter, Jr., *J. Org. Chem.*, **61**, 671 (1996).

¹¹⁷ S. M. Moharram, G. Hirai, K. Koyama, H. Oguri, and M. Hirama, *Tetrahedron Lett.*, **41**, 6669 (2000).

¹¹⁸ J. I. Garcia, V. Martinez-Merino, and J. A. Mayoral, *J. Org. Chem.*, **63**, 2321 (1998).

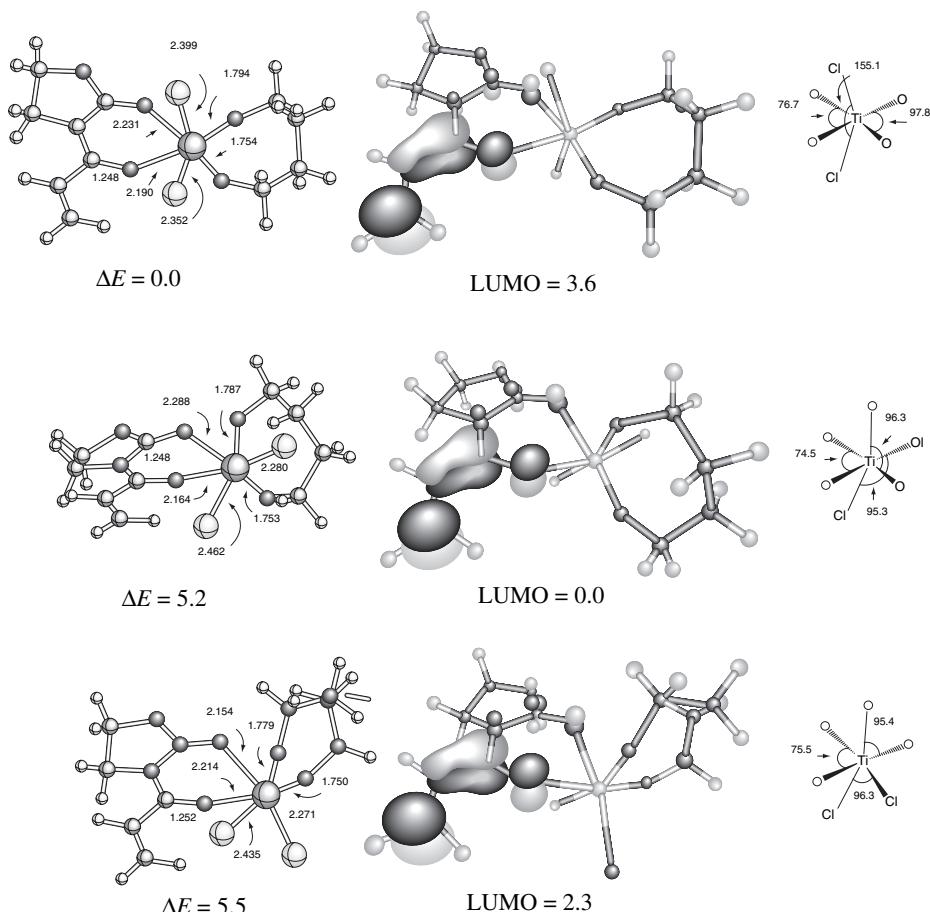


Fig. 6.11. Representation of transition structure and the LUMO orbitals for three stereoisomeric complexes of *N*-acryloyloxazolidinone with a TADDOL model, $\text{Ti}[\text{O}(\text{CH}_2)_4\text{O}]_{\text{Cl}_2}$. The LUMO energies (B3LYP/6-3111+G(d)) in kcal/mol. Reproduced from *J. Org. Chem.*, **63**, 2321 (1998), by permission of the American Chemical Society.

has not been resolved, but there is some experimental evidence that the reaction may proceed through a minor complex.¹¹⁹

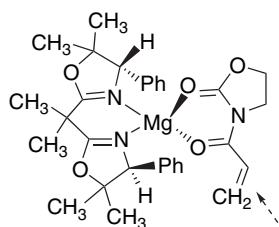
Visual models and additional information on Asymmetric Diels-Alder Reactions can be found in the Digital Resource available at: Springer.com/carey-sundberg.

These examples serve to illustrate several general points about use of chiral catalysts for D-A reactions. A cationic metal center is present in nearly all of the catalysts developed to date and has several functions. It is the anchor for the chiral ligands and also serves as a Lewis acid with respect to the dienophile. The chiral ligands establish the facial selectivity of the complexed dienophile. There are several indications of the importance of the anions to catalytic activity. Anions, in general,

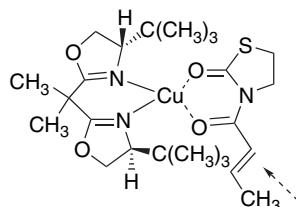
¹¹⁹ D. Seebach, R. Dahinden, R. E. Marti, A. K. Beck, D. A. Plattner, and F. N. M. Kuhnle, *J. Org. Chem.*, **60**, 1788 (1995); D. Seebach, R. E. Marti, and T. Hinterman, *Helv. Chim. Acta*, **79**, 710 (1996); C. Haase, C. R. Sarko, and M. Di Mare, *J. Org. Chem.*, **60**, 1777 (1995).

can compete for the ligand binding sites on the metal so that catalytic activity is improved with weakly coordinating anions. Finally, there are some indications in the TADDOL-type catalysts that the anions may exert electronic effects and serve to distinguish between reactivity of dienophiles in *cis* or *trans* positions in the octahedral coordination complex.

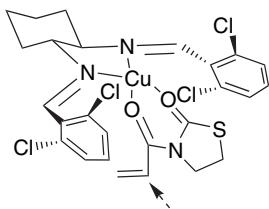
Several examples of catalytic enantioselective D-A reactions are given in Scheme 6.4. Entries 1 to 6 involve *N*-acyloxazolidinones and *N*-acylthiazolidinones as dienophiles. Note that there are no stereogenic centers in the reactants, so racemic mixtures would result from reaction in the absence of a chiral catalyst. The metal ions used in these reactions can accommodate two additional ligands in addition to those present in the catalyst. The reactions are believed to involve a chelated TS similar to those involved when chiral oxazolidinone are used (see p. 509). The catalyst in Entry 1 has a BOX-type ligand. The phenyl substituents and the tetrahedral coordination geometry at magnesium give rise to a well-defined geometry. Note that the catalyst has c_2 symmetry. The phenyl substituents cause differential facial shielding.



The enantioselectivity of this catalyst, which is prepared as the iodide salt, is somewhat dependent on the anion that is present. If $AgSbF_6$ is used as a cocatalyst, the iodide is removed by precipitation and the e.e. increases from 81 to 91%. These results indicate that the absence of a coordinating anion improved enantioselectivity. Entry 2 shows the extensively investigated *t*-BuBOX ligand with an *N*-acryloylthiazolidinone dienophile. With Cu^{2+} as the metal, the coordination geometry is square planar. The complex exposes the *re* face of the dienophile.



Entry 3 involves a catalyst derived from *(R,R)*-*trans*-cyclohexane-1,2-diamine. The square planar Cu^{2+} complex exposes the *re* face of the dienophile. As with the BOX catalysts, this catalyst has c_2 symmetry.



Scheme 6.4. Catalytic Enantioselective Diels-Alder Reactions

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SECTION 6.1

Diels-Alder Reactions

Entry	Dienophile	Diene	Catalyst	Amount	Product	Yield (%)	e.e.
1 ^a				Ph 10 mol %		82	95
2 ^b				t-Bu 10 mol %		79	94
3 ^c				ArCH=N=CHAR 9 mol % Ar = 2,6-dichlorophenyl		86	91
4 ^d				10 mol %		88	84
5 ^e				2 equiv		93	92
6 ^f				Ar = 2,6-dimethylphenyl 20 mol %		92	93
7 ^g						94	80
8 ^h				Ar = 3,5-dimethylphenyl 1 equiv CH ₃ 20 mol %		98	93
9 ⁱ				Ar = 3-indolyl 5 mol %		>99.5	
10 ^j				20 mol %		97%	91%

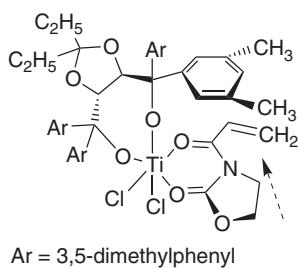
(Continued)

Scheme 6.4. (Continued)

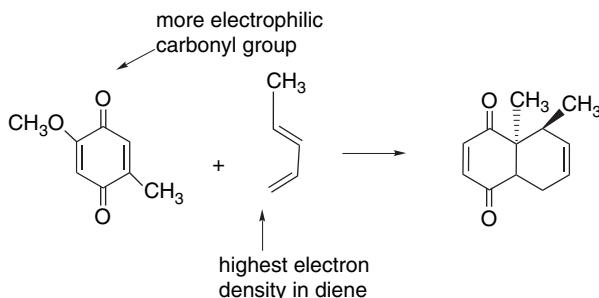
Entry	Dienophile	Diene	Catalyst	Amount	Product	Yield (%)	e.e.
11 ^k				10 mol %		81 > 99:1	99 <i>exo</i>
12 ^l				20 mol %		78	85
13 ^m				5 mol %		86	> 95:5 <i>endo</i>
14 ⁿ				1 equiv v		88	72
15 ^o				0.5 equiv v		85	> 98 <i>endo</i>

- R = *E,E*-Farnesyl Ar = 3-indolyl
- a. E. J. Corey and K. Ishihara, *Tetrahedron Lett.*, **33**, 6807 (1992).
 - b. D. A. Evans, S. J. Miller, and T. Lectka, *J. Am. Chem. Soc.*, **115**, 6460 (1993).
 - c. D. A. Evans, T. Lectka, and S. J. Miller, *Tetrahedron Lett.*, **34**, 7027 (1993).
 - d. A. K. Ghosh, H. Cho, and J. Cappiello, *Tetrahedron: Asymmetry*, **9**, 3687 (1998).
 - e. K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, and J. Sugimori, *J. Am. Chem. Soc.*, **111**, 5340 (1989).
 - f. E. J. Corey and Y. Matsumura, *Tetrahedron Lett.*, **32**, 6289 (1991).
 - g. T. A. Engler, M. A. Letavic, K. O. Lynch, Jr., and F. Takusagawa, *J. Org. Chem.*, **59**, 1179 (1994).
 - h. E. J. Corey, S. Sarshar, and D.-H. Lee, *J. Am. Chem. Soc.*, **116**, 12089 (1994).
 - i. E. J. Corey, T.-P. Loh, T. D. Roper, M. D. Azimioara, and M. C. Noe, *J. Am. Chem. Soc.*, **114**, 8290 (1992).
 - j. D. H. Ryu and E. J. Corey, *J. Am. Chem. Soc.*, **125**, 6388 (2003).
 - k. E. J. Corey, A. Guzman-Perez, and T.-P. Loh, *J. Am. Chem. Soc.*, **116**, 3611 (1994).
 - l. G. Quinkert, A. Del Gross, A. Doering, and W. Doering, R. I. Schenkel, M. Bauch, G. T. Dambacher, J. W. Bats, G. Zimmerman, and G. Durrer, *Helv. Chim. Acta*, **78**, 1345 (1995).
 - m. D. A. Evans, D. M. Barnes, J. S. Johnson, T. Lectka, P. von Matt, S. J. Miller, J. A. Murry, R. D. Norcross, E. A. Shaughnessy and K. R. Campos, *J. Am. Chem. Soc.*, **121**, 7582 (1999).
 - n. J. A. Marshall and S. Xie, *J. Org. Chem.*, **57**, 2987 (1992).
 - o. T. W. Lee and E. J. Corey, *J. Am. Chem. Soc.*, **123**, 1872 (2001).

Entry 4 is a BOX-type catalyst derived from *cis*-1-aminoindan-2-ol. This is a somewhat more rigid ligand than the monocyclic BOX ligands. The chiral ligands in Entries 5 to 7 are TADDOLS (see p. 512) derived from tartaric acid. In Entry 5 the catalyst is prepared from $\text{TiCl}_2(\text{O}-i\text{-Pr})_2$ and 4A molecular sieves. About 0.10 equivalent of the catalyst is used. In Entry 6, the catalyst was prepared using $\text{Ti}(\text{O}-i\text{-Pr})_4$ and SiCl_4 . In this catalyst, the aryl groups carry 3,5-dimethyl groups. The 3,5-di- CF_3 and 3,5-di-Cl derivatives, which were also studied, gave high *exo*:*endo* ratios, but much reduced enantioselectivity. This is thought to be due to the reduced π donor character of the rings with EWG substituents. As mentioned on p. 513, the presence of chlorides at the Ti center is also probably an important factor in the reactivity of the catalyst.

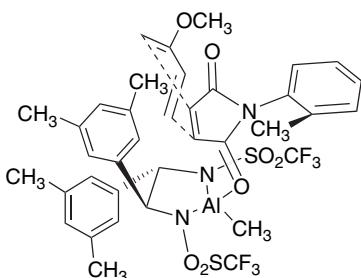


Entry 7 features a quinone dienophile. The reaction exhibits the expected selectivity for the more electrophilic quinone double bond (see p. 506). The reaction is also regioselective with respect to the diene, with the methyl group acting as a donor substituent. The enantioselectivity is 80%.



In this case, the catalyst was formed by premixing $\text{Ti}(\text{O}-i\text{-Pr})_4$ and TiCl_4 and adding the TADDOL ligand. These conditions also gave good regioselectivity with isoprene, although the e.e. was not as high.

Entry 8 uses a *bis*-trifluoromethanesulfonamido chelate of methylaluminum as the catalyst. As in Entry 6, the use of a 3,5-dimethylphenyl group in place of phenyl improved enantioselectivity. The *ortho*-methylphenyl substituent on the maleimide dienophile restricts the potential coordination sites at the metal center. NMR characterization of the reactant-catalyst complex suggests that reaction occurs through the TS shown below.



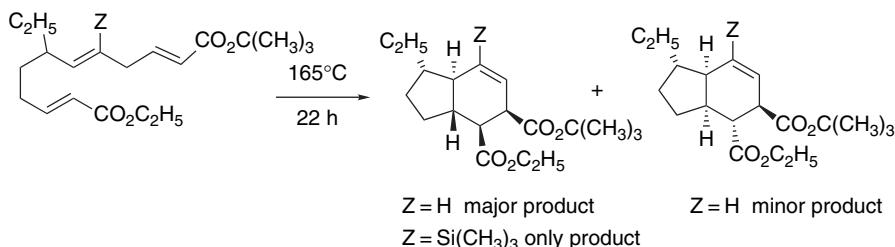
Entry 9 uses the oxaborazolidine catalysts discussed on p. 505 with 2-bromopropenal as the dienophile. The aldehyde adopts the *exo* position in each case, which is consistent with the proposed TS model. Entry 10 illustrates the use of a cationic oxaborazolidine catalyst. The chirality is derived from *trans*-1,2-diaminocyclohexane. Entry 12 shows the use of a TADDOL catalyst in the construction of the steroid skeleton. Entry 13 is an intramolecular D-A reaction catalyzed by a Cu-*bis*-oxazoline. Entries 14 and 15 show the use of the oxazaborolidinone catalyst with more complex dienes.

6.1.7. Intramolecular Diels-Alder Reactions

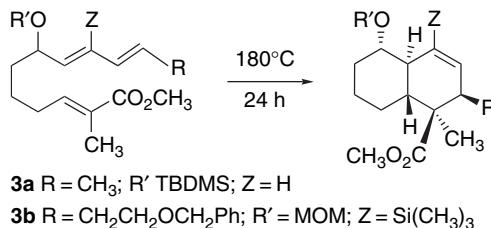
Intramolecular Diels-Alder (IMDA) reactions are very useful in the synthesis of polycyclic compounds.¹²⁰ The stereoselectivity of a number of IMDA reactions has been analyzed and conformational factors in the TS often play the dominant role in determining product structure.¹²¹ It has also been noted in certain systems that the stereoselectivity is influenced by the activating substituent on the dienophile double bond, both for thermal and Lewis acid-catalyzed reactions.¹²² The general trends in regioselectivity are in agreement with frontier orbital concepts, with conformational effects being the main factors in determining stereoselectivity. Since the conformational interactions depend on the substituent pattern in the specific case, no general rules for stereoselectivity can be put forward. Molecular modeling can frequently identify the controlling structural features.¹²³

It is possible to introduce substituents that can influence the conformational equilibria to favor a particular product. In the reactions shown below, the addition of the trimethylsilyl substituent leads to a single stereoisomer in 85% yield, whereas in the unsubstituted system two stereoisomers are formed in ratios from 4:1 to 8:1.¹²⁴

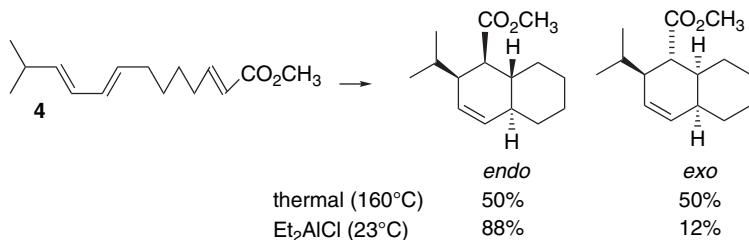
- ¹²⁰ W. Oppolzer, *Angew. Chem. Int. Ed. Engl.*, **16**, 10 (1977); G. Brieger and J. N. Bennett, *Chem. Rev.*, **80**, 63 (1980); E. Ciganek, *Org. React.*, **32**, 1 (1984); D. F. Taber, *Intramolecular Diels-Alder and Alder Ene Reactions*, Springer-Verlag, Berlin, 1984.
- ¹²¹ W. R. Roush, A. I. Ko, and H. R. Gillis, *J. Org. Chem.*, **45**, 4264 (1980); R. K. Boeckman, Jr., and S. K. Ko, *J. Am. Chem. Soc.*, **102**, 7146 (1980); W. R. Roush and S. E. Hall, *J. Am. Chem. Soc.*, **103**, 5200 (1981); K. A. Parker and T. Iqbal, *J. Org. Chem.*, **52**, 4369 (1987).
- ¹²² J. A. Marshall, J. E. Audia, and J. Grote, *J. Org. Chem.*, **49**, 5277 (1984); W. R. Roush, A. P. Essenfeld, and J. S. Warmus, *Tetrahedron Lett.*, **28**, 2447 (1987); T.-C. Wu and K. N. Houk, *Tetrahedron Lett.*, **26**, 2293 (1985).
- ¹²³ K. J. Shea, L. D. Burke, and W. P. England, *J. Am. Chem. Soc.*, **110**, 860 (1988); L. Raimondi, F. K. Brown, J. Gonzalez, and K. N. Houk, *J. Am. Chem. Soc.*, **114**, 4796 (1992); D. P. Dolata and L. M. Harwood, *J. Am. Chem. Soc.*, **114**, 10738 (1992); F. K. Brown, U. C. Singh, P. A. Kollman, L. Raimondi, K. N. Houk, and C. W. Bock, *J. Org. Chem.*, **57**, 4862 (1992); J. D. Winkler, H. S. Kim, S. Kim, K. Ando, and K. N. Houk, *J. Org. Chem.*, **62**, 2957 (1997).
- ¹²⁴ R. K. Boeckman, Jr., and T. E. Barta, *J. Org. Chem.*, **50**, 3421 (1985).



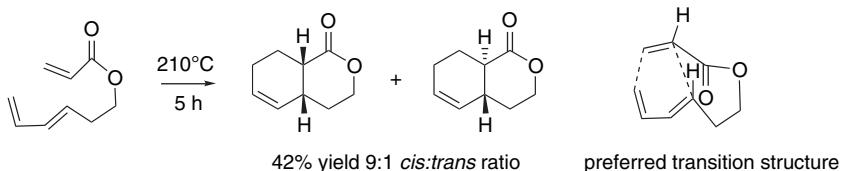
Similarly, the 2,8,10-triene **3a** gives a mixture of four isomers, but introduction of a TMS group as in **3b** gives a single stereoisomer in 89% yield. The reason for the improved stereoselectivity is that the steric effect introduced by the TMS substituent favors a single conformer.



Lewis acid catalysis usually substantially improves the stereoselectivity of IMDA reactions, just as it does in intermolecular cases. For example, the thermal cyclization of **4** at 160°C gives a 50:50 mixture of two stereoisomers, but the use of $(\text{C}_2\text{H}_5)_2\text{AlCl}$ as a catalyst permits the reaction to proceed at room temperature and *endo* addition is favored by 7:1.¹²⁵



There has been quite thorough study of 3,5-hexadienyl acrylates, where the ester functions both as part of the link and an activating substituent. The reaction tends to be quite slow, even though at first glance it would appear to encounter little strain. The *cis* ring juncture is favored by 9:1.

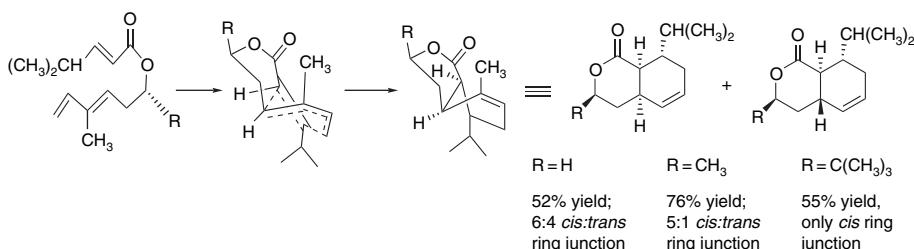


Ref. 126

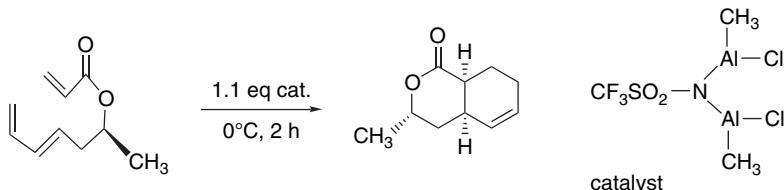
¹²⁵ W. R. Roush and H. R. Gillis, *J. Org. Chem.*, **47**, 4825 (1982).

¹²⁶ S. F. Martin, S. A. Williamson, R. P. Gist, and K. M. Smith, *J. Org. Chem.*, **48**, 5170 (1983).

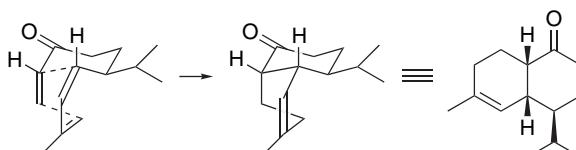
One factor that is believed to contribute to the sluggishness of the reaction is that a chairlike arrangement of the linking group causes a twist in the ester group from the preferred planarity. The TS also requires that the ester alkyl group be in an *anti* relationship to the carbonyl group, rather than the preferred *syn* conformation. Several substituted systems have been studied and they react primarily through a boatlike *endo* TS.¹²⁷ The size of the α -substituent R controls the degree of preference for the TS.



This system has been studied computationally at the B3LYP/6-31 + G* level.¹²⁸ In agreement with the experimental results, the *endo* boat TS was found to be the most stable. The *endo* chair and *exo* boat were about 1.3 kcal/mol higher in energy, and the *exo* chair still higher. This study confirmed that the boatlike TS allows the ester group to stay closer to planarity. Eclipsing interactions also contribute to the higher energy of the chairlike TS. In accordance with the idea that a bidentate Lewis acid might both effect Lewis acid catalysis and promote a planar geometry at the ester group, it was found that the reaction could be effectively catalyzed by a bidentate Lewis acid.¹²⁹ Use of one equivalent of the catalyst gave 95% yield after 2 h at 0°C. The catalyst is believed to be coordinated with both the carbonyl and the ester oxygens.



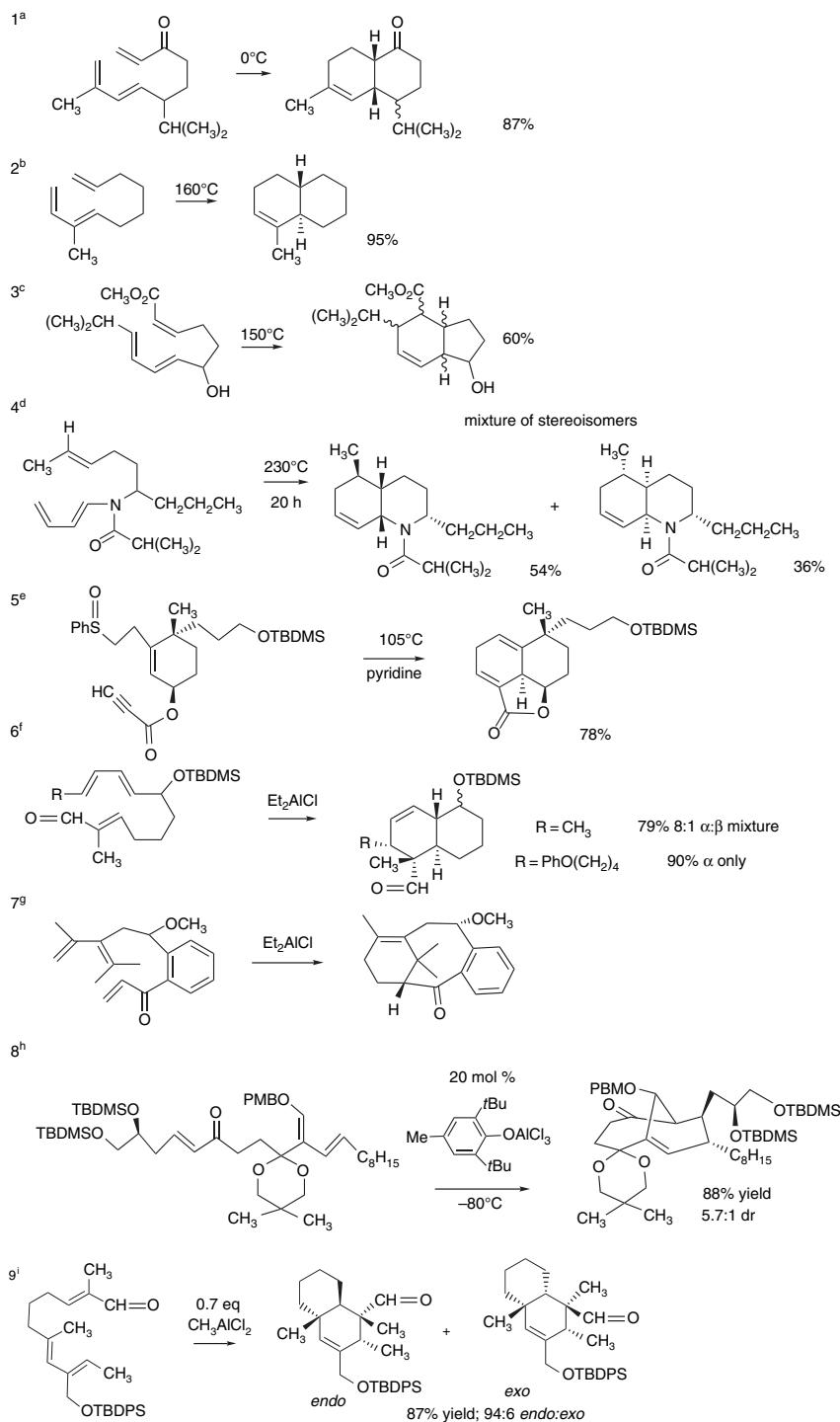
Some examples of IMDA reactions are given in Scheme 6.5. In Entry 1 the dienophilic portion bears a carbonyl substituent and cycloaddition occurs easily. Two stereoisomeric products are formed, but both have the *cis* ring fusion, which is the stereochemistry expected for an *endo* TS, with the major diastereomer being formed from the TS with an equatorial isopropyl group.



¹²⁷ M. E. Jung, A. Huang, and T. W. Johnson, *Org. Lett.*, **2**, 1835 (2000); P. Kim, M. H. Nantz, M. J. Kurth, and M. M. Olmstead, *Org. Lett.*, **2**, 1831 (2000).

¹²⁸ D. J. Tantillo, K. N. Houk, and M. E. Jung, *J. Org. Chem.*, **66**, 1938 (2001).

¹²⁹ A. Saito, H. Ito, and T. Taguchi, *Org. Lett.*, **4**, 4619 (2002).

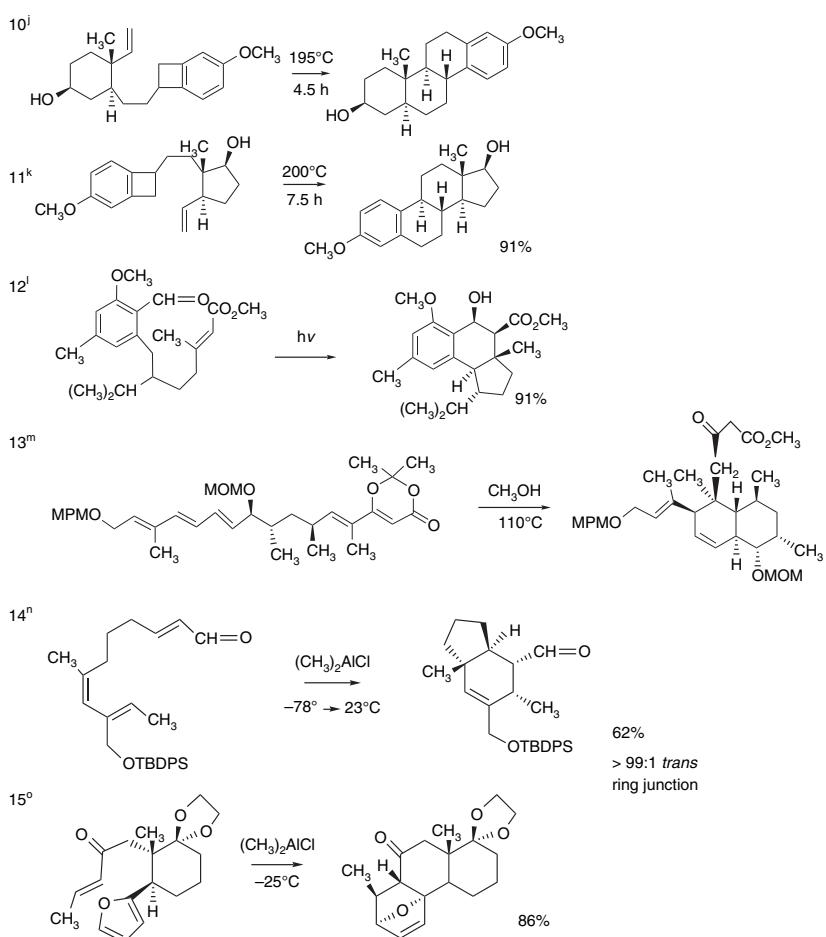


(Continued)

Scheme 6.5. (continued)

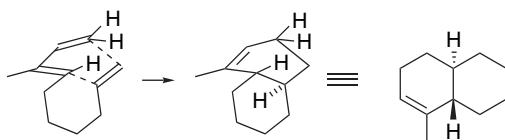
CHAPTER 6

*Concerted
Cycloadditions,
Unimolecular
Rearrangements, and
Thermal Eliminations*



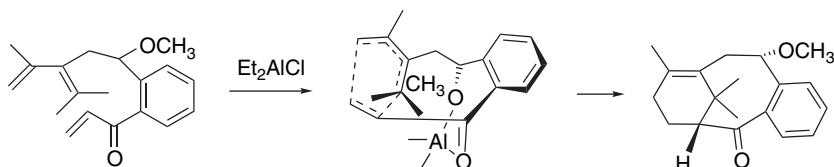
- a. D. F. Taber and B. P. Gunn, *J. Am. Chem. Soc.*, **101**, 3992 (1979).
 b. S. R. Wilson and D. T. Mao, *J. Am. Chem. Soc.*, **100**, 6289 (1978).
 c. W. R. Roush, *J. Am. Chem. Soc.*, **102**, 1390 (1980).
 d. W. Oppolzer and E. Flaskamp, *Helv. Chim. Acta*, **60**, 204 (1977); W. Oppolzer, E. Flaskamp, and L. W. Bieber, *Helv. Chim. Acta*, **84**, 141 (2001).
 e. H. Miyaoka, Y. Kajiwara, and Y. Yamada, *Tetrahedron Lett.*, **41**, 911 (2000).
 f. J. A. Marshall, J. E. Audia, and J. Grote, *J. Org. Chem.*, **49**, 5277 (1984).
 g. D. V. Smil, A. Laurent, N. S. Spassova, and A. G. Fallis, *Tetrahedron Lett.*, **44**, 5129 (2003).
 h. K. C. Nicolaou, J. Jung, W. H. Yoon, K. C. Fong, H.-S. Choi, Y. He, Y.-L. Zhong, and P. S. Baran, *J. Am. Chem. Soc.*, **124**, 2183 (2002).
 i. N. A. Yakelis and W. R. Roush, *Org. Lett.*, **3**, 957 (2001).
 j. T. Kametani, K. Suzuki, and H. Nemoto, *J. Org. Chem.*, **45**, 2204 (1980); *J. Am. Chem. Soc.*, **103**, 2890 (1981).
 k. P. A. Grieco, T. Takigawa, and W. J. Schillinger, *J. Org. Chem.*, **45**, 2247 (1980).
 l. K. C. Nicolaou, D. Gray, and J. Tae, *Angew. Chem. Int. Ed. Engl.*, **40**, 3679 (2001); K. C. Nicolaou, D. L. F. Gray, and J. Tae, *J. Am. Chem. Soc.*, **126**, 613 (2004).
 m. R. K. Boeckman, Jr., T. E. Barta, and S. G. Nelson, *Tetrahedron Lett.*, **32**, 4091 (1991).
 n. N. A. Yakelis and W. R. Roush, *Org. Lett.*, **3**, 957 (2001).
 o. S. Claeys, D. Van Haver, P. J. De Clerc, M. Milanesio, and D. Viterbo, *Eur. J. Org. Chem.*, 1051 (2002).

In Entry 2 a similar triene that lacks the activating carbonyl group undergoes reaction but a much higher temperature is required. In this case the ring junction is *trans*, which corresponds to an *exo* TS and may reflect the absence of secondary orbital interaction between the diene and dienophile.

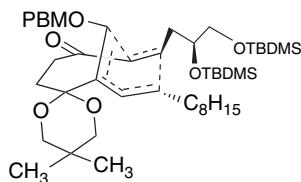


In Entry 3 the dienophilic double bond bears an EWG substituent, but a higher temperature is required than for Entry 1 because the connecting chain contains one less methylene group, which leads to a more strained TS. A mixture of stereoisomers is formed, reflecting a conflict between the Alder rule, which favors *endo* addition, and conformational factors, which favor the *exo* TS. The reaction in Entry 4 was carried out as a key step in the synthesis of the frog neurotoxin, pumiliotoxin C. The isolated double bond has no activating substituents and the reaction requires forcing conditions. Nevertheless, the yield is excellent and both products are formed with a *cis* ring juncture, but there is minimal facial selectivity. In Entry 5, the diene system is generated *in situ* by thermal elimination of the sulfoxide group and then reacts with the acetylenic dienophile.

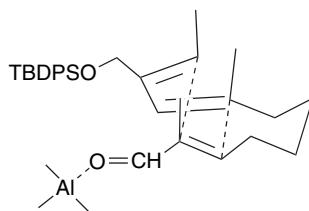
Entry 6 shows a stereoselective formation of a highly substituted *trans*-decalin system. The reaction in Entry 7 establishes a taxanelike structure. The stereochemistry is consistent with a TS in which both the carbonyl oxygen and the methoxy group are coordinated to aluminum.



The reaction in Entry 8 was used in the synthesis of members of the phomoidrides. The cyclohexene ring that is constructed creates a bicyclo[4.3.1]skeleton containing seven- and nine-membered rings.

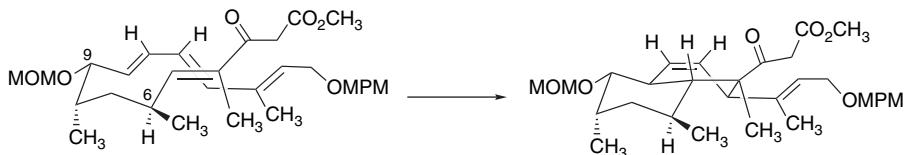


Entry 9 is a Lewis acid-catalyzed example, and the major stereoisomer is formed through a TS having an *endo* orientation of the complexed formyl group. Interestingly, the thermal version of this reaction favors the *exo* stereoisomer.

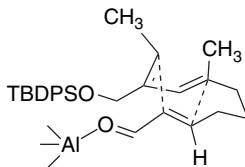


Entries 10 and 11 are examples of reactions involving thermal generation of quinodimethanes. In Entry 12 a quinodimethane is generated by photoenolization and used in conjunction with an IMDA reaction to create the carbon skeleton found in the hamigerans, which are marine natural products having antiviral activity.

In Entry 13, the dioxinone ring undergoes thermal decomposition to an acyl ketene that is trapped by the solvent methanol. The resulting β -keto- γ,δ -enoate ester then undergoes stereoselective cyclization. The stereoselectivity is controlled by the preference for pseudoequatorial conformations of the C(6) and C(9) substituents.



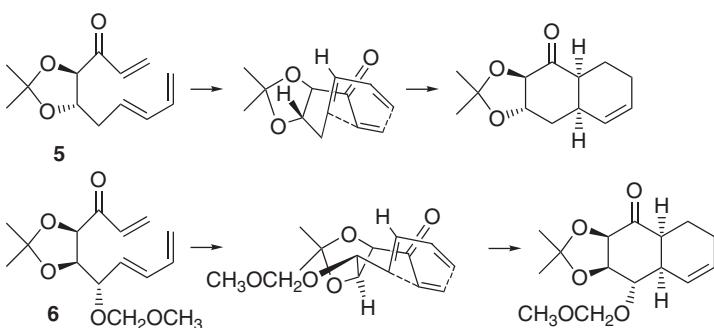
Entry 14 forms a *trans* ring juncture with greater than 99:1 selectivity. In contrast, the thermal reaction in this case shows a 2:1 preference for the *cis* ring juncture. Evidently the Lewis acid changes the structure of the TS sufficiently that the steric effects that control the thermal reaction are diminished.



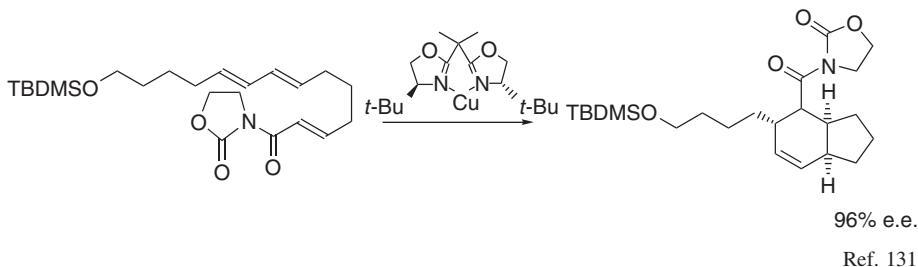
Entry 15 creates a portion of the steroid skeleton and also illustrates the use of a furan ring as a diene.

As in intermolecular reactions, enantioselectivity can be achieved in IMDA additions by use of chiral components. For example, the dioxolane ring in **5** and **6** results in TS structures that lead to enantioselective reactions.¹³⁰ The chirality in the dioxolane ring is reflected in the respective TSs, both of which have an *endo* orientation of the carbonyl group.

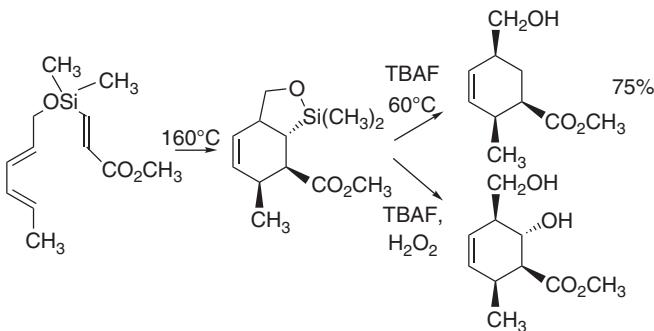
¹³⁰ T. Wong, P. D. Wilson, S. Woo, and A. G. Fallis, *Tetrahedron Lett.*, **40**, 7045 (1997).



Chiral catalysts (see Section 6.1.6) can also achieve enantioselectivity in IMDA reactions.



The kinetic advantages of IMDA additions can be exploited by installing temporary links (tethers) between the diene and dienophile components.¹³² After the addition reaction, the tether can be broken. Siloxy derivatives have been used in this way, since silicon-oxygen bonds can be readily cleaved by solvolysis or by fluoride ion.¹³³ The silyl group can also be used to introduce a hydroxy function by oxidation.

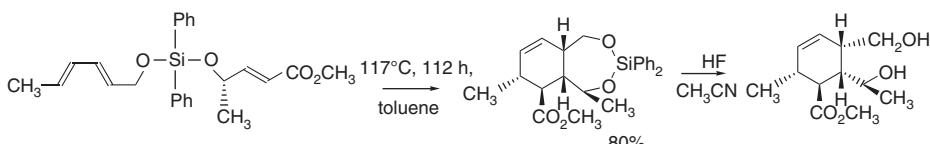


Ref. 133a

¹³¹ D. A. Evans and J. S. Johnson, *J. Org. Chem.*, **62**, 786 (1997).

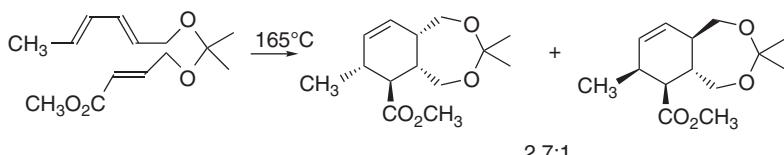
¹³² L. Fensterbank, M. Malacria, and S. McN. Sieburth, *Synthesis*, 813 (1997); M. Bols and T. Skrydstrup, *Chem. Rev.*, **95**, 1253 (1995).

¹³³ (a) G. Stork, T. Y. Chan, and G. A. Breault, *J. Am. Chem. Soc.*, **114**, 7578 (1992); (b) S. McN. Sieburth and L. Fensterbank, *J. Org. Chem.*, **57**, 5279 (1992); (c) J. W. Gillard, R. Fortin, E. L. Grimm, M. Maillard, M. Tjepkema, M. A. Bernstein, and R. Glaser, *Tetrahedron Lett.*, **32**, 1145 (1991); (d) D. Craig and J. C. Reader, *Tetrahedron Lett.*, **33**, 4073 (1992).



Ref. 133d

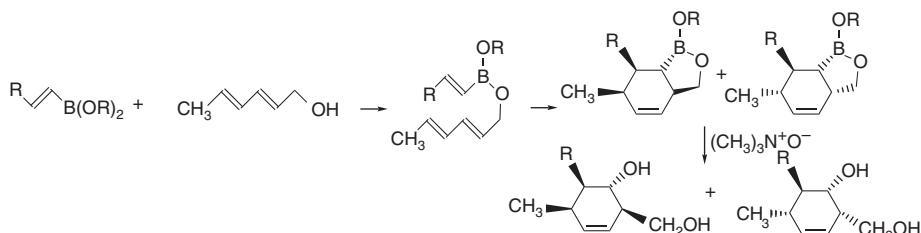
Acetals have also been used as removable tethers.



2.7:1

Ref. 134

The activating capacity of boronate groups can be combined with the ability for facile transesterification at boron to permit intramolecular reactions between vinyl-boronates and 2,4-dienols.



Ref. 135

6.2. 1,3-Dipolar Cycloaddition Reactions

In Chapter 10 of Part A, the mechanistic classification of *1,3-dipolar cycloadditions* as concerted cycloadditions was developed. Dipolar cycloaddition reactions are useful both for syntheses of heterocyclic compounds and for carbon-carbon bond formation. Table 6.2 lists some of the types of molecules that are capable of dipolar cycloaddition. These molecules, which are called *1,3-dipoles*, have π electron systems that are isoelectronic with allyl or propargyl anions, consisting of two filled and one empty orbital. Each molecule has at least one charge-separated resonance structure with opposite charges in a 1,3-relationship, and it is this structural feature that leads to the name 1,3-dipolar cycloadditions for this class of reactions.¹³⁶

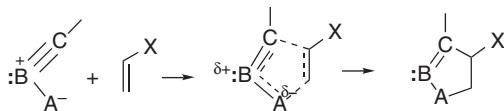
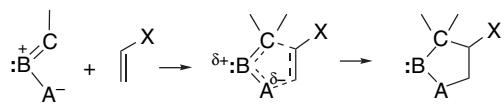
¹³⁴. P. J. Ainsworth, D. Craig, A. J. P. White, and D. J. Williams, *Tetrahedron*, **52**, 8937 (1996).

¹³⁵. R. A. Batey, A. N. Thadani, and A. J. Lough, *J. Am. Chem. Soc.*, **121**, 450 (1999).

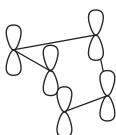
¹³⁶. For comprehensive reviews of 1,3-dipolar cycloaddition reactions, see R. Huisgen, R. Grashey and J. Sauer in *The Chemistry of Alkenes*, S. Patai, ed., Interscience London, 1965, pp. 806–878; G. Bianchi, C. DeMicheli, and R. Gandolfi, in *The Chemistry of Double Bonded Functional Groups*, Part I, Supplement A, S. Patai, ed., Wiley-Interscience, New York, 1977, pp. 369–532; A. Padwa, ed., *1,3-Dipolar Cycloaddition Chemistry*, Wiley, New York, 1984.

Table 6.2. 1,3-Dipolar Compounds

			SECTION 6.2
			1,3-Dipolar Cycloaddition Reactions
$\text{:N}^+ = \ddot{\text{N}} - \bar{\text{C}}\text{R}_2$	\leftrightarrow	$\text{:N} \equiv \text{N}^+ - \bar{\text{C}}\text{R}_2$	Diazoalkane
$\text{:N}^+ = \ddot{\text{N}} - \bar{\text{N}}\text{R}$	\leftrightarrow	$\text{:N} \equiv \text{N}^+ - \bar{\text{N}}\text{R}$	Azide
$\text{RC}^+ = \ddot{\text{N}} - \bar{\text{C}}\text{R}_2$	\leftrightarrow	$\text{RC} \equiv \text{N}^+ - \bar{\text{C}}\text{R}_2$	Nitrile ylide
$\text{RC}^+ = \ddot{\text{N}} - \bar{\text{N}}\text{R}$	\leftrightarrow	$\text{RC} \equiv \text{N}^+ - \bar{\text{N}}\text{R}$	Nitrile imine
$\text{RC}^+ = \ddot{\text{N}} - \bar{\text{O}}:$	\leftrightarrow	$\text{RC} \equiv \text{N}^+ - \bar{\text{O}}:$	Nitrile oxide
$\text{R}_2\text{C}^+ - \ddot{\text{N}} - \bar{\text{C}}\text{R}_2$	\leftrightarrow	$\text{R}_2\text{C}^+ = \ddot{\text{N}} - \bar{\text{C}}\text{R}_2$	Azomethine ylide
$\text{R}_2\text{C}^+ - \ddot{\text{N}} - \bar{\text{O}}:$	\leftrightarrow	$\text{R}_2\text{C}^+ = \ddot{\text{N}} - \bar{\text{O}}:$	Nitronate
$\text{R}_2\text{C}^+ - \ddot{\text{O}} - \bar{\text{O}}^-$	\leftrightarrow	$\text{R}_2\text{C}^+ = \ddot{\text{O}} - \bar{\text{O}}^-$	Carbonyl oxide



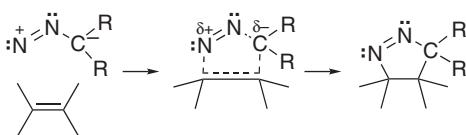
The other reactant in a dipolar cycloaddition, usually an alkene or alkyne, is referred to as the *dipolarophile*. Other multiply bonded functional groups such as imine, azo, and nitroso can also act as dipolarophiles. The 1,3-dipolar cycloadditions involve four π electrons from the 1,3-dipole and two from the dipolarophile. As in the D-A reaction, the reactants approach one another in parallel planes to permit interaction between the π and π^* orbitals.



Mechanistic studies have shown that the TSs for 1,3-dipolar cycloadditions (1,3-DCA) are not very polar, the rate of reaction is not strongly sensitive to solvent polarity, and in most cases the reaction is a concerted $[2\pi_s + 4\pi_s]$ cycloaddition.¹³⁷ The destruction of charge separation that is implied is more apparent than real because

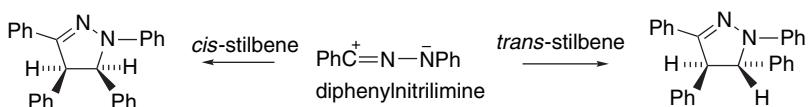
¹³⁷ P. K. Kadaba, *Tetrahedron*, **25**, 3053 (1969); R. Huisgen, G. Szeimes, and L. Möbius, *Chem. Ber.*, **100**, 2494 (1967); P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Am. Chem. Soc.*, **87**, 306 (1965).

most 1,3-dipolar compounds are not highly polar. The polarity implied by any single structure is balanced by other contributing structures.

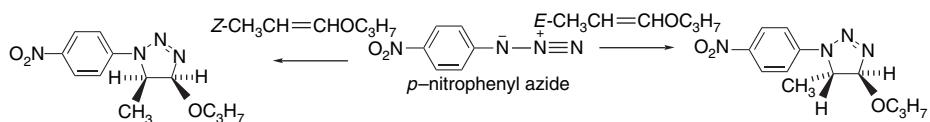


6.2.1. Regioselectivity and Stereochemistry

Two issues are essential for predicting the structure of 1,3-DCA products: (1) What is the regiochemistry? and (2) What is the stereochemistry? Many specific examples demonstrate that 1,3-dipolar cycloaddition is a stereospecific *syn* addition with respect to the dipolarophile, as expected for a concerted process.

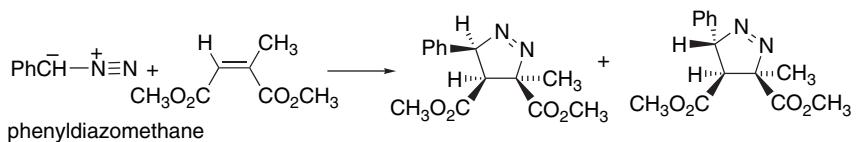


Ref. 138



Ref. 139

With some 1,3-dipoles, two possible stereoisomers can be formed by *syn* addition. These result from two differing orientations of the reacting molecules that are analogous to the *endo* and *exo* TS in D-A reactions. Phenyl diazomethane, for example, can add to unsymmetrical dipolarophiles to give two diastereomers.



Ref. 140

Each 1,3-dipole exhibits a characteristic regioselectivity toward different types of dipolarophiles. The dipolarophiles can be grouped, as were dienophiles, depending upon whether they have ERG or EWG substituents. The regioselectivity can be

¹³⁸ R. Huisgen, M. Seidel, G. Wallabillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1965).

¹³⁹ R. Huisgen and G. Szeimies, *Chem. Ber.*, **98**, 1153 (1965).

¹⁴⁰ R. Huisgen and P. Eberhard, *Tetrahedron Lett.*, 4343 (1971).

interpreted in terms of frontier orbital theory. Depending on the relative orbital energies in the 1,3-dipole and dipolarophile, the strongest interaction may be between the HOMO of the dipole and the LUMO of the dipolarophile or vice versa. Usually for dipolarophiles with EWGs the dipole-HOMO/dipolarophile-LUMO interaction is dominant. The reverse is true for dipolarophiles with ERG substituents. In some circumstances the magnitudes of the two interactions may be comparable.¹⁴¹ When HOMO-LUMO interactions control regioselectivity, the reaction is said to be under *electronic control*. If steric effects are dominant, the reaction is under *steric control*.

The prediction of regiochemistry requires estimation or calculation of the energies of the orbitals that are involved, which permits identification of the frontier orbitals. The energies and orbital coefficients for the most common dipoles and dipolarophiles have been summarized.¹⁴¹ Figure 10.15 of Part A gives the orbital coefficients of some representative 1,3-dipoles. Regioselectivity is determined by the preference for the orientation that results in bond formation between the atoms having the largest coefficients in the two frontier orbitals. This analysis is illustrated in Figure 6.12.

Apart from the role of substituents in determining regioselectivity, several other structural features affect the reactivity of dipolarophiles. Strain increases reactivity; norbornene, for example, is consistently more reactive than cyclohexene in 1,3-DCA reactions. Conjugated functional groups usually increase reactivity. This increased reactivity has most often been demonstrated with electron-attracting substituents, but for some 1,3-dipoles, enol ethers, enamines, and other alkenes with donor substituents are also quite reactive. Some reactivity data for a series of alkenes with several 1,3-dipoles are given in Table 10.6 of Part A. Additional discussion of these reactivity trends can be found in Section 10.3.1 of Part A.

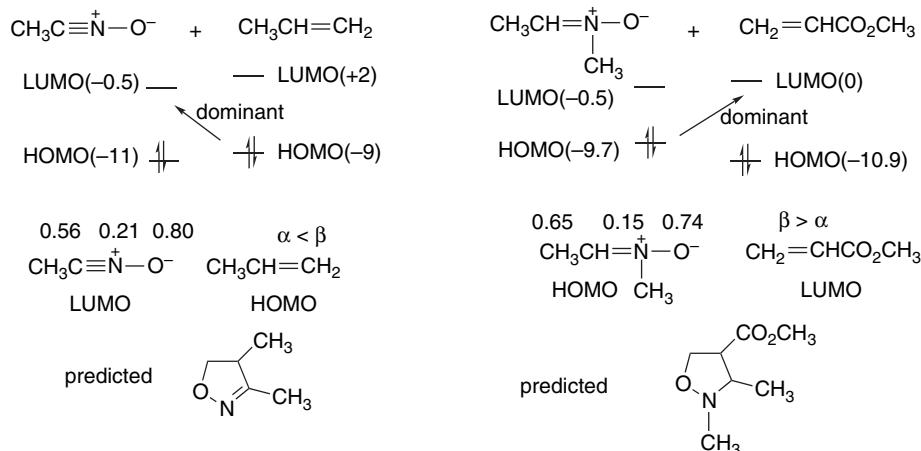
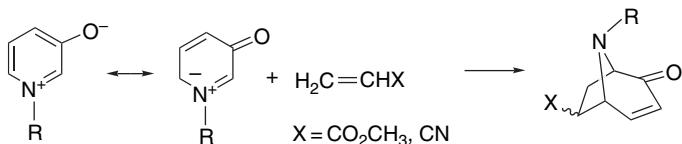


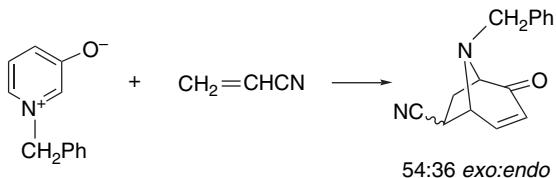
Fig. 6.12. Prediction of regioselectivity of 1,3-dipolar cycloaddition on the basis of FMO theory. The energies of the HOMO and LUMO of the reactants (in eV) are indicated in parentheses.

¹⁴¹ K. N. Houk, J. Sims, B. E. Duke, Jr., R. W. Strozier, and J. K. George, *J. Am. Chem. Soc.*, **95**, 7287 (1973); I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, New York, 1977; K. N. Houk, in *Pericyclic Reactions*, Vol. II, A. P. Marchand and R. E. Lehr, eds., Academic Press, New York, 1977, pp. 181–271.

1,3-Dipoles can be embedded in heterocyclic structures, just as diene units are present in pyrones and other ring structures (see p. 491). N-Substituted pyridinium-3-ols can be deprotonated to give 3-oxidopyridinium betaines that have 1,3-dipolar character.¹⁴²



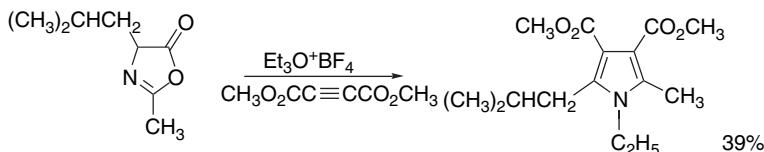
A reaction of this type was used to prepare an intermediate in the synthesis of a natural compound with antiglaucoma activity.¹⁴³



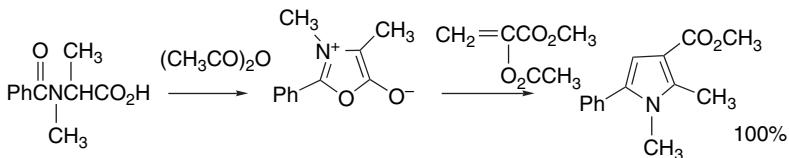
Oxazolium oxides, which can be generated by cyclization of α -amido acids, give pyrroles on reaction with acetylenic dipolarophiles.¹⁴⁴ These reactions proceed by formation of oxazolium oxide intermediates. The bicyclic adduct can then undergo a concerted (retro 4 + 2) decarboxylation.



Oxazolium oxides can also be made by *N*-alkylation of oxazolinones.¹⁴⁵



Pyrroles are also formed from dipolarophiles such as α -acetoxy esters and α -chloroacrylonitrile that have potential leaving groups.

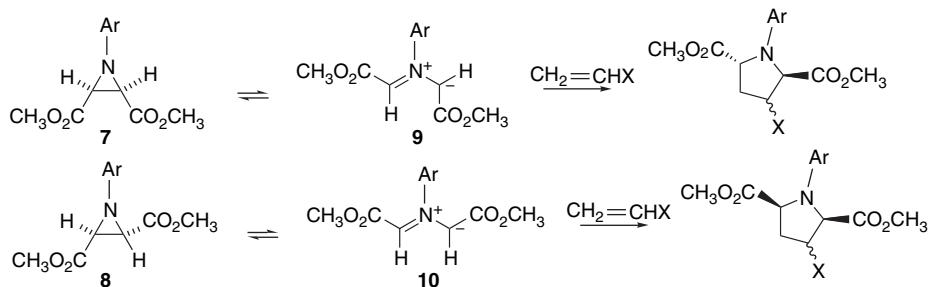


Ref. 146

- ¹⁴². N. Dennis, A. R. Katritzky, and Y. Takeuchi, *Angew. Chem. Int. Ed. Engl.*, **15**, 1 (1976).
- ¹⁴³. M. E. Jung, Z. Longmei, P. Tangsheng, Z. Huiyan, L. Yan, and S. Jingyu, *J. Org. Chem.*, **57**, 3528 (1992).
- ¹⁴⁴. H. Gotthardt, R. Huisgen, and H. O. Bayer, *J. Am. Chem. Soc.*, **92**, 4340 (1970).
- ¹⁴⁵. F. M. Hershenson and M. R. Pavia, *Synthesis*, 999 (1988).
- ¹⁴⁶. G. Grassi, F. Foti, F. Risitano, and D. Zona, *Tetrahedron Lett.*, **46**, 1061 (2005).

Ref. 147

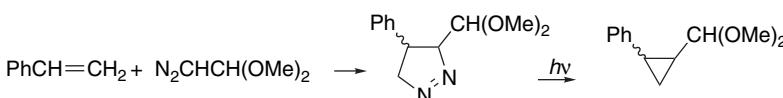
Another interesting variation of the 1,3-dipolar cycloaddition involves generation of 1,3-dipoles from three-membered rings. As an example, aziridines **7** and **8** give adducts derived from apparent formation of 1,3-dipoles **9** and **10**, respectively.¹⁴⁸



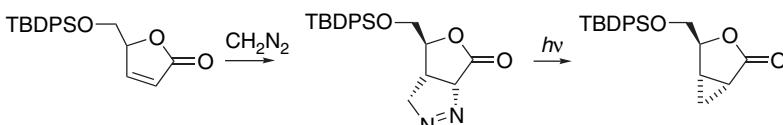
The evidence for the involvement of 1,3-dipoles as discrete intermediates includes the observation that the reaction rates are independent of dipolarophile concentration. This fact indicates that the ring opening is the rate-determining step in the reaction. Ring opening is most facile for aziridines that have an electron-attracting substituent to stabilize the carbanion center in the dipole.

6.2.2. Synthetic Applications of Dipolar Cycloadditions

1,3-DCA reactions are an important means of synthesis of a wide variety of heterocyclic molecules, some of which are useful intermediates in multistage syntheses. Pyrazolines, which are formed from alkenes and diazo compounds, for example, can be pyrolyzed or photolyzed to give cyclopropanes.



Ref. 149



Ref. 150

¹⁴⁷ I. A. Benages and S. M. Albonico, *J. Org. Chem.*, **43**, 4273 (1978).

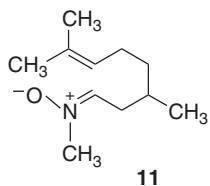
¹⁴⁸ R. Huisgen and H. Mader, *J. Am. Chem. Soc.*, **93**, 1777 (1971).

¹⁴⁹ P. Carrie, *Heterocycles*, **14**, 1529 (1980).

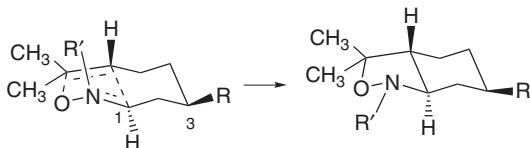
¹⁵⁰ M. Martin-Villa, N. Hanafi, J. M. Jiminez, A. Alvarez-Larena, J. F. Piniella, V. Branchadell, A. Oliva, and R. M. Ortuno, *J. Org. Chem.*, **63**, 3581 (1998).

Scheme 6.6 gives some examples of 1,3-DCA reactions. Entry 1 is an addition of an aryl azide to norbornene. The EWG nitro group is rate enhancing and the reaction occurs with a rate constant of $6.3 \times 10^{-3} M^{-1} s^{-1}$ at $25^\circ C$. Owing to steric approach control, the product is the *exo* stereoisomer. Entry 2 involves an acetylenic dipolarophile and gives an aromatic triazole as the product. Entry 3 is an addition of diazomethane to the dioxolane derivative of acrolein. The reaction is carried out in a closed vessel at room temperature. Entry 4 involves a nitrone as the 1,3-dipole. Nitrone cycloadditions are particularly useful in synthesis because a new carbon-carbon bond is formed and the adducts can be reduced to β -amino alcohols. Nitrile oxides, which are formed by dehydration of nitroalkanes or by oxidation of oximes with hypochlorite,¹⁵¹ are also useful 1,3-dipoles. They are highly reactive, must be generated *in situ*,¹⁵² and react with both alkenes and alkynes. The product in Entry 5 is an example in an isoxazole that was eventually converted to a prostaglandin derivative.

Intramolecular 1,3-dipolar cycloadditions have proven to be especially useful in synthesis.¹⁵³ The products of nitrone-alkene cycloadditions are isoxazolines and the oxygen-nitrogen bond can be cleaved by reduction, leaving both an amino and hydroxy function in place. A number of imaginative syntheses have employed this strategy. Entry 6 shows the formation of a new six-membered carbocyclic ring. The nitrone **11** is generated by condensation of the aldehyde group with *N*-methylhydroxylamine and then goes on to product by intramolecular cycloaddition.



These reactions are highly stereoselective, provided a substituent is present at C(3). The stereochemistry is consistent with a chairlike TS having the 3-substituent in an equatorial position.

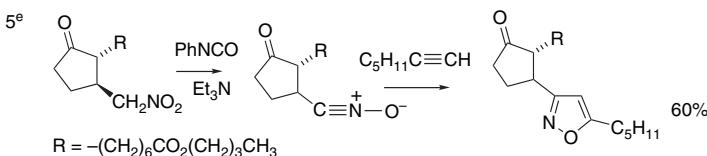
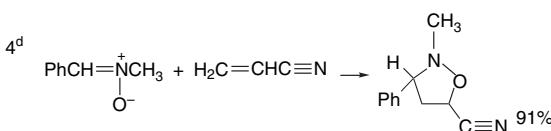
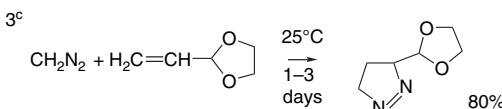
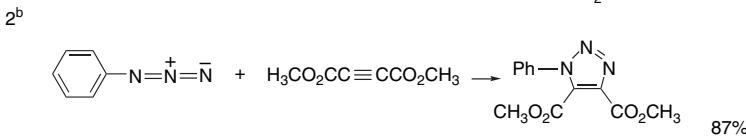
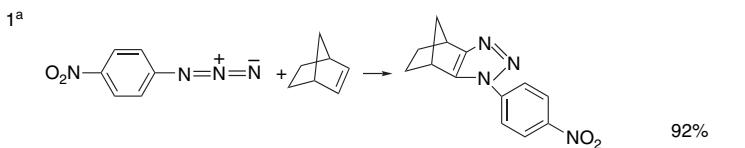


¹⁵¹ G. A. Lee, *Synthesis*, 508 (1982).

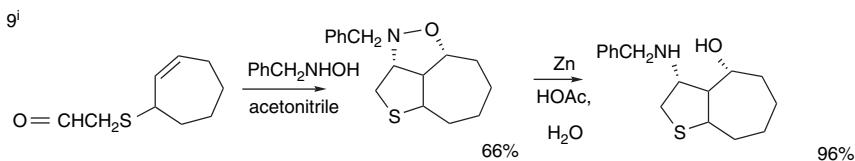
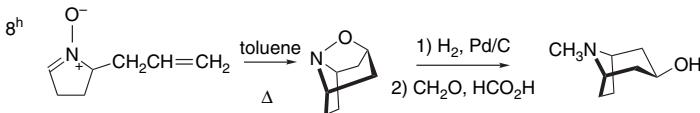
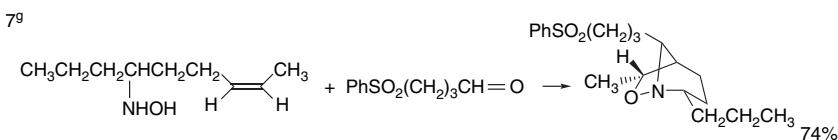
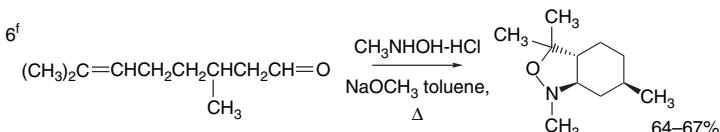
¹⁵² K. Torssell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, VCH Publishers, New York, 1988.

¹⁵³ For reviews of nitrone cycloadditions, see D. St. C. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, 205 (1975); J. J. Tufariello, *Acc. Chem. Res.*, **12**, 396 (1979); P. N. Confalone and E. M. Huie, *Org. React.*, **36**, 1 (1988); K. V. Gothelf and K. A. Jorgensen, *Chem. Rev.*, **98**, 863 (1998).

A. Intermolecular cycloaddition

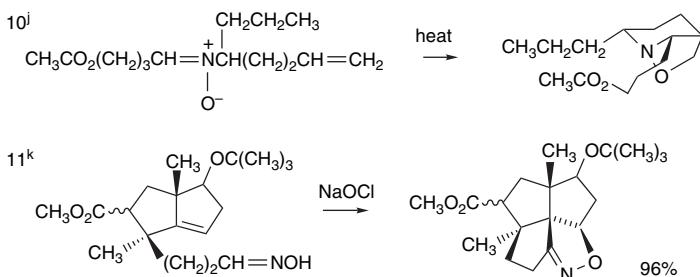


B. Intramolecular cycloaddition



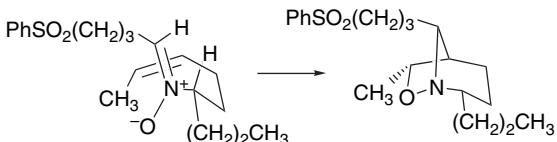
(Continued)

Scheme 6.6. (Continued)

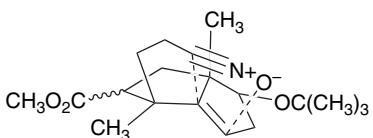


- a. P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Am. Chem. Soc.*, **87**, 306 (1965).
- b. R. Huisgen, R. Knorr, L. Möbius, and G. Szeimies, *Chem. Ber.*, **98**, 4014 (1965).
- c. J. M. Stewart, C. Carlisle, K. Kem, and G. Lee, *J. Org. Chem.*, **35**, 2040 (1970).
- d. R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968).
- e. A. Barco, S. Benetti, G. P. Pollini, P. G. Baraldi, M. Guarneri, D. Simoni, and C. Gandolfi, *J. Org. Chem.*, **46**, 4518 (1981).
- f. N. A. LeBel and D. Hwang, *Org. Synth.*, **58**, 106 (1978); N. A. LeBel, M. E. Post, and J. J. Whang, *J. Am. Chem. Soc.*, **86**, 3759 (1964).
- g. N. A. LeBel and N. Balasubramanian, *J. Am. Chem. Soc.*, **111**, 3363 (1989).
- h. J. J. Tufariello, G. B. Mullen, J. J. Tegeler, E. J. Trybulski, S. C. Wong, and S. A. Ali, *J. Am. Chem. Soc.*, **101**, 2435 (1979).
- i. P. N. Confalone, G. Pizzolato, D. I. Confalone, and M. R. Uskokovic, *J. Am. Chem. Soc.*, **102**, 1954 (1980).
- j. A. L. Smith, S. F. Williams, A. B. Holmes, L. R. Hughes, Z. Lidert, and C. Switzenbank, *J. Am. Chem. Soc.*, **110**, 8696 (1988).
- k. M. Ihara, Y. Tokunaga, N. Taniguchi, K. Fukumoto, and C. Kabuto, *J. Org. Chem.*, **56**, 5281 (1991).

Entry 7 is another intramolecular nitrone cycloaddition, but in this case the hydroxyl-amine function is present in the alkene.



The product of the reaction in Entry 8 was used in the synthesis of the alkaloid pseudotropine. The proper stereochemical orientation of the hydroxy group is determined by the structure of the oxazoline ring formed in the cycloaddition. Entry 9 portrays the early stages of synthesis of the biologically important molecule biotin. The reaction in Entry 10 was used to establish the carbocyclic skeleton and stereochemistry of a group of toxic indolizidine alkaloids found in dart poisons from frogs. Entry 11 involves generation of a nitrile oxide. Three other stereoisomers are possible. The observed isomer corresponds to approach from the less hindered convex face of the molecule.

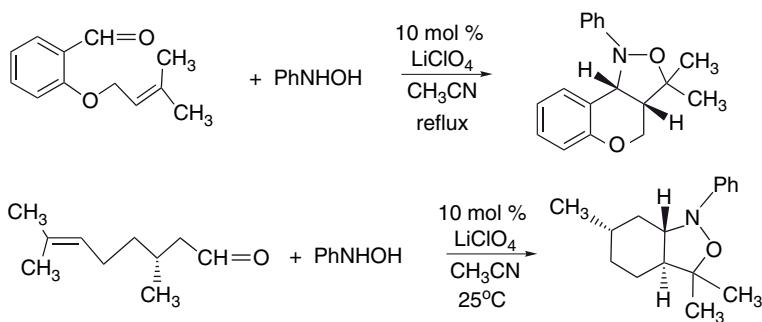


The role of Lewis acid catalysts in 1,3-DCA reactions is similar to that in D-A reactions. The catalysis results from a lowering of the LUMO energy of the dipolarophile, which is analogous to the Lewis acid catalysis of D-A reactions. The more organized TS, incorporating the metal ion and associated ligands, then enforces a preferred orientation of the reagents. In contrast to the D-A reaction involving hydrocarbon dienes, 1,3-DCA reactions may encounter competing complexation at the 1,3-dipole. Lewis acid interaction with the 1,3-dipole is likely to be detrimental if the dipole is the more nucleophilic component of the reaction. For example, with nitrones and enones, formation of a Lewis acid adduct with the nitrone in competition with the enone is detrimental. One approach to the need for selectivity is to use highly substituted catalysts that are selective for the less-substituted reactant. Bulky aryloxylaluminum compounds are excellent catalysts for nitrone cycloaddition and also enhance regioselectivity. The reaction of diphenylnitroso with enones is usually subject to steric regiochemical control. With the catalyst **L** high *electronic regiochemical control* is achieved and reactivity is greatly enhanced. The catalyst does not, however, strongly affect the *exo:endo* selectivity, which is 23:77 for propenal.

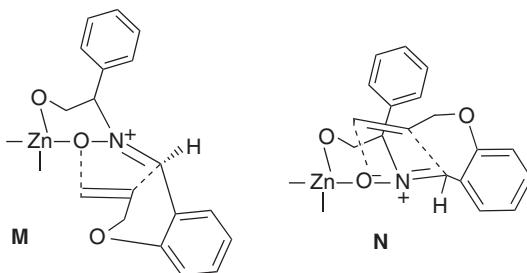
R ¹	R ²	R ³	catalyst	Yield (%)	A:B ratio	
H	H	H	no	5	20:80	electronically-controlled product
			yes	100	>99:1	
CH ₃	H	H	no	7	8:92	sterically-controlled product
			yes	82	100:0	
H	CH ₃	H	no	5	0:100	
			yes	100	91:9	
H	H	CH ₃	no	2	100:0	catalyst L
			yes	100	100:0	

Lithium perchlorate and lithium triflate in acetonitrile catalyze intramolecular cycloaddition reactions of nitrones of allyloxybenzaldehydes and unsaturated aldehydes.¹⁵⁴

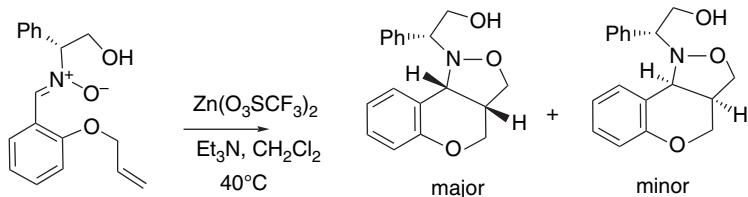
¹⁵⁴ J. S. Yadav, B. V. S. Reddy, D. Narsimhaswamy, K. Narsimulu, and A. C. Kumar, *Tetrahedron Lett.*, **44**, 3697 (2003).



A series of similar reactions was examined in the course of synthesis of substituted chromanes.¹⁵⁵ The reactions are thought to proceed through TS M in preference to N because of steric interactions with the phenyl ring on the chiral hydroxylamine.



The best Lewis acid found was $Zn(OTf)_2$, which improved stereoselectivity from 6:1 to 22:1.



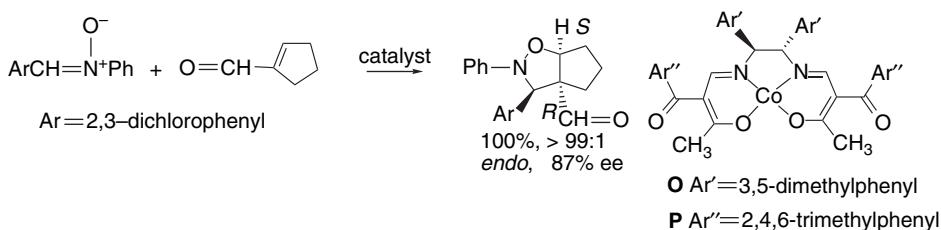
Interestingly, the reactions were modestly *slower* in the presence of the Lewis acid. It is suggested that the catalyst inverts the HOMO-LUMO relationships, making the complexed nitrone the electrophilic reactant. In agreement with this interpretation, the reaction is favored by EWGs on the aromatic ring.

As with D-A reactions, it is possible to achieve enantioselective cycloaddition in the presence of chiral catalysts.¹⁵⁶ Many of the catalysts are similar to those used in enantioselective D-A reactions. The catalysis usually results from a lowering of the LUMO energy of the dipolarophile, which is analogous to the Lewis acid catalysis of D-A reactions. The more organized TS, incorporating a metal ion and associated

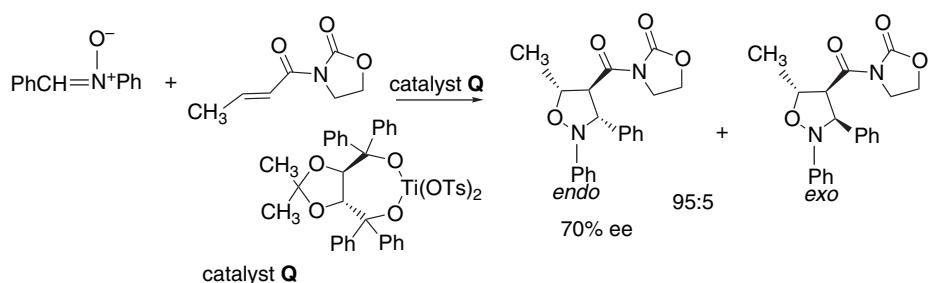
¹⁵⁵. Q. Zhao, F. Han, and D. L. Romero, *J. Org. Chem.*, **67**, 3317 (2002).

¹⁵⁶. K. V. Gothelf and K. A. Jorgensen, *Chem. Rev.*, **98**, 863 (1998); M. Frederickson, *Tetrahedron*, **53**, 503 (1997).

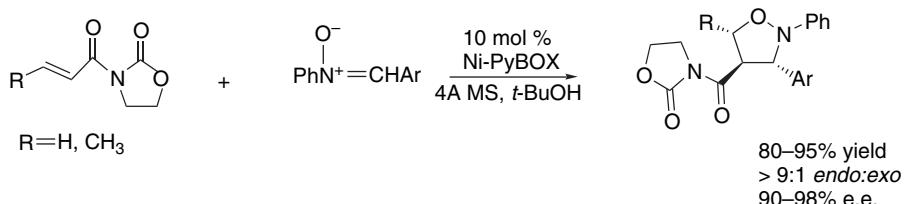
ligands, then enforces a preferred orientation of the reagents. For example, the bulky aryl groups in the catalysts **O** and **P** favor one direction of approach of the nitrone reactant.¹⁵⁷



The Ti(IV) TADDOL catalyst **Q** leads to moderate enantioselectivity in nitrone-alkene cycloaddition.¹⁵⁸



Favorable results have also been achieved using PyBOX type catalysts. Acryloyl and crotonoyloxazolidinones gave 80–95% yields, 90–98% e.e., and more than 9:1 *endo*-diastereoselectivity in reactions with *N*-phenylbenzylidene nitrone.¹⁵⁹



Other effective enantioselective catalysts include Yb(OTf)₃ with BINOL,¹⁶⁰ Mg²⁺-bis-oxazolines,¹⁶¹ and oxazaborolidinones.¹⁶²

¹⁵⁷ T. Mita, N. Ohtsuki, T. Ikeno, and T. Yamada, *Org. Lett.*, **4**, 2457 (2002).

¹⁵⁸ K. V. Gothelf and K. A. Jorgensen, *Acta Chem. Scand.*, **50**, 652 (1996); K. B. Jensen, K. V. Gothelf, R. G. Hazell, and K. A. Jorgensen, *J. Org. Chem.*, **62**, 2471 (1997); K. B. Jensen, K. V. Gothelf, and K. A. Jorgensen, *Helv. Chim. Acta*, **80**, 2039 (1997).

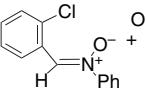
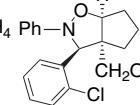
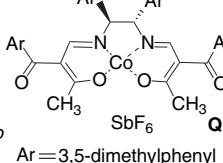
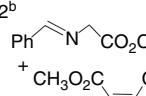
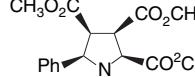
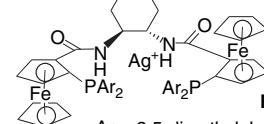
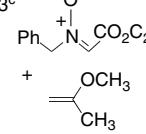
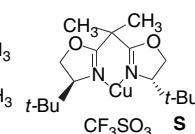
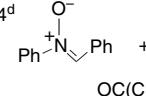
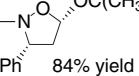
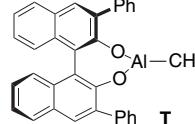
¹⁵⁹ S. Iwasa, H. Maeda, K. Nishiyama, S. Tsushima, Y. Tsukamoto, and H. Nishiyama, *Tetrahedron*, **58**, 8281 (2002).

¹⁶⁰ M. Kawamura and S. Kobayashi, *Tetrahedron Lett.*, **40**, 3213 (1999).

¹⁶¹ G. Desimoni, G. Faita, A. Mortoni, and P. Righetti, *Tetrahedron Lett.*, **40**, 2001 (1999); K. V. Gothelf, R. G. Hazell, and K. A. Jorgensen, *J. Org. Chem.*, **63**, 5483 (1998).

¹⁶² J. P. G. Seerden, M. M. M. Boeren, and H. W. Scheeren, *Tetrahedron*, **53**, 11843 (1997).

Scheme 6.7. Catalytic Enantioselective 1,3-Dipolar Cycloaddition Reactions

Entry	Reactants	Conditions	Product	Catalyst
1 ^a		5 mol % catalyst Q –40°C NaBH ₄	 96% yield, > 99% endo 80% ee	 Ar = 3,5-dimethylphenyl
2 ^b		3 mol % catalyst R	 87% yield, 87% ee	 Ar = 3,5-dimethylphenyl
3 ^c		25 mol % catalyst S C ₂ H ₅ O ₂ C- 90% ee	 exo:endo = 31:69 94% ee	
4 ^d		10 mol % catalyst T	 84% yield > 95% exo, 89% ee	

- a. T. Mitra, N. Ohtsuki, T. Ikeno, and T. Yamada. *Org. Lett.*, **4**, 2457 (2002).
 b. J. M. Longmire, B. Wang, and X. M. Zhang, *J. Am. Chem. Soc.*, **124**, 13400 (2002).
 c. K. B. Jensen, R. G. Hazell, and K. A. Jorgensen, *J. Org. Chem.*, **64**, 2353 (1999).
 d. K. B. Simonsen, B. Bayon, R. G. Hazell, D. V. Gothelf, and K. A. Jorgensen, *J. Am. Chem. Soc.*, **121**, 3845 (1999).

Scheme 6.7 shows some other examples of enantioselective catalysts. Entry 1 illustrates the use of a Co(III) complex, with the chirality derived from the diamine ligand. Entry 2 is a silver-catalyzed cycloaddition involving generation of an azomethine ylide. The ferrocenylphosphine groups provide a chiral environment by coordination of the catalytic Ag⁺ ion. Entries 3 and 4 show typical Lewis acid catalysts in reactions in which nitrones are the electrophilic component.

6.3. [2 + 2] Cycloadditions and Related Reactions Leading to Cyclobutanes

As discussed in Section 10.4 of Part A, concerted suprafacial [2π + 2π] cycloadditions are forbidden by orbital symmetry rules. Two types of [2 + 2] cycloadditions are of synthetic value: addition reactions of ketenes and photochemical additions. The latter group includes reactions of alkenes, dienes, enones, and carbonyl compounds, and these additions are discussed in the sections that follow.

[2 + 2] Cycloadditions of ketenes and alkenes have synthetic utility for the preparation of cyclobutanones.¹⁶³ The stereoselectivity of ketene-alkene cycloaddition can be analyzed in terms of the Woodward-Hoffmann rules.¹⁶⁴ To be an allowed process, the [2π_s + 2π_a] cycloaddition must be suprafacial in one component and antarafacial in the other. An alternative description of the TS is a 2π_s + (2π_s + 2π_a) addition.¹⁶⁵ Figure 6.13 illustrates these combinations. Note that both representations predict formation of the *cis*-substituted cyclobutanone.

Ketenes are especially reactive in [2 + 2] cycloadditions and an important reason is that they offer a low degree of steric interaction in the TS. Another reason is the electrophilic character of the ketene LUMO. As discussed in Section 10.4 of Part A, there is a large net charge transfer from the alkene to the ketene, with bond formation at the ketene *sp* carbon running ahead of that at the *sp*² carbon. The stereoselectivity of ketene cycloadditions is the result of steric effects in the TS. Minimization of interaction between the substituents R and R' leads to a cyclobutanone in which these substituents are *cis*, which is the stereochemistry usually observed in these reactions.

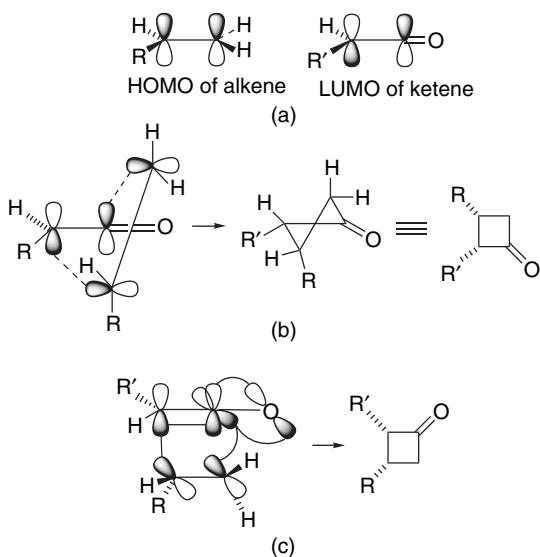
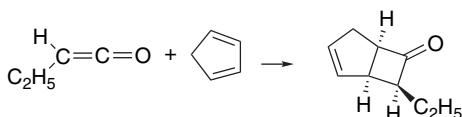


Fig. 6.13. HOMO-LUMO interactions in the [2 + 2] cycloadditions of an alkene and a ketene: (a) frontier orbitals of the alkene and ketene; (b) [2π_s + 2π_a] representation of suprafacial addition to the alkene and antarafacial addition to the ketene; (c) [2π_s + (2π_s + 2π_a)] alignment of orbitals.

¹⁶³ For reviews, see W. T. Brady, in *The Chemistry of Ketenes, Allenes, and Related Compounds*, S. Patai, ed., Wiley-Interscience, New York, 1980, Chap. 8; W. T. Brady, *Tetrahedron*, **37**, 2949 (1981); J. Hyatt and R. W. Reynolds, *Org. React.*, **45**, 159 (1994); T. T. Tidwell, *Ketenes*, Wiley, New York, 1995.

¹⁶⁴ R. B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **8**, 781 (1969).

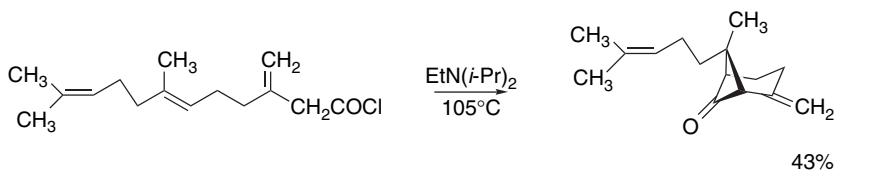
¹⁶⁵ D. J. Pasto, *J. Am. Chem. Soc.*, **101**, 37 (1979); E. Valenti, M. A. Pericas, and A. Moyano, *J. Org. Chem.*, **55**, 3582 (1990).



Ref. 166

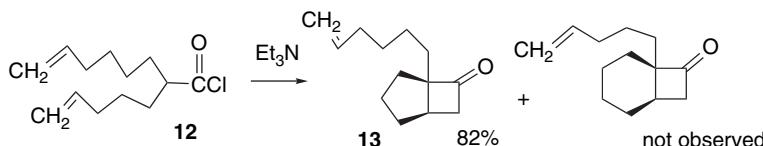
The best yields are obtained when the ketene has an electronegative substituent, such as halogen. Simple ketenes are not very stable and must usually be generated in situ. The most common method for generating ketenes for synthesis is by dehydrohalogenation of acyl chlorides. This is usually done with an amine such as triethylamine.¹⁶⁷ Other activated carboxylic acid derivatives, such as acyloxypyridinium ions, have also been used as ketene precursors.¹⁶⁸ Ketene itself and certain alkyl derivatives can be generated by pyrolysis of carboxylic anhydrides.¹⁶⁹

Intramolecular ketene cycloadditions are possible if the ketene and alkene functionalities can achieve an appropriate orientation.¹⁷⁰

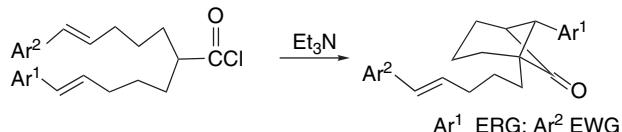


Ref. 171

Some trends in relative reactivity for intramolecular ketene cycloadditions have been examined by internal competitions.¹⁷² For example, **12** gives exclusively **13**, pointing to a preference for five-membered rings over six-membered ones.

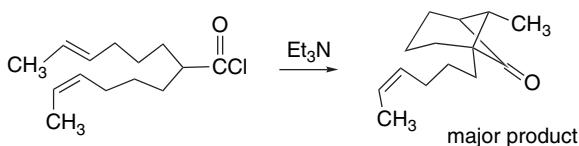


When two different aryl substituents are compared, the double bond with an ERG substituent is more reactive, as would be expected if the alkene acts primarily as an electron donor.

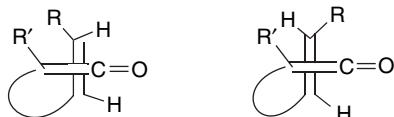


- ¹⁶⁶ M. Rey, S. M. Roberts, A. S. Dreiding, A. Roussel, H. Vanlierde, S. Toppert, and L. Ghosez, *Helv. Chim. Acta*, **65**, 703 (1982).
- ¹⁶⁷ K. Shishido, T. Azuma, and M. Shibuya, *Tetrahedron Lett.*, **31**, 219 (1990).
- ¹⁶⁸ R. L. Funk, P. M. Novak, and M. M. Abelman, *Tetrahedron Lett.*, **29**, 1493 (1988).
- ¹⁶⁹ G. J. Fisher, A. F. MacLean, and A. W. Schnizer, *J. Org. Chem.*, **18**, 1055 (1953).
- ¹⁷⁰ B. B. Snider, *Chem. Rev.*, **88**, 793 (1988).
- ¹⁷¹ E. J. Corey and M. C. Desai, *Tetrahedron Lett.*, **26**, 3535 (1985).
- ¹⁷² G. Belanger, F. Levesque, J. Paquet, and G. Barbe, *J. Org. Chem.*, **70**, 291 (2005).

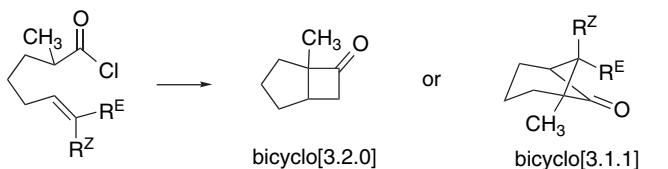
Comparison of *E*- and *Z*-double bonds indicates that the former are about 30 times more reactive.¹⁷³



This relative reactivity results from larger steric interactions in the TS for the *Z*-double bond.

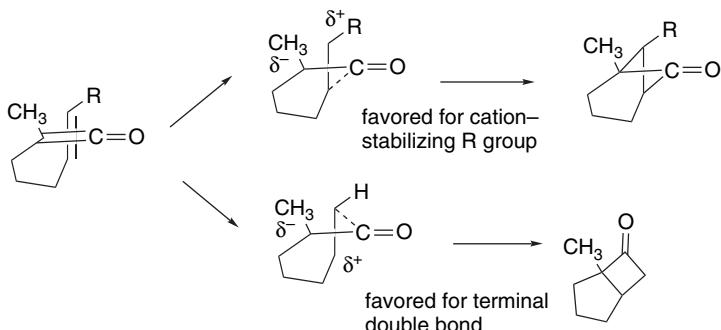


The competition between formation of bicyclo[3.2.0] and bicyclo[3.1.1] products is determined by substitution on the alkene.



R^E	R^Z	
H	H	45% (only product)
CH_3	H	23% (only product)
CH_3	CH_3	45% (only product)

Initial bond formation occurs between the ketene carbonyl and the more nucleophilic end of the alkene double bond. This is related to the charge separation in the TS and results in the second bond being formed between the terminal ketene carbon and the carbon that is best able to support positive character.¹⁷⁴

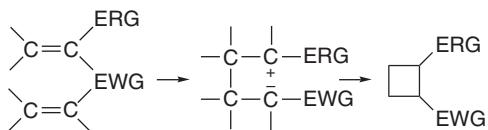


¹⁷³. B. B. Snider, A. J. Allentoff, and M. B. Walner, *Tetrahedron*, **46**, 8031 (1990).

¹⁷⁴. B. B. Snider, R. A. H. F. Hui, and Y. S. Kulkarni, *J. Am. Chem. Soc.*, **107**, 2194 (1985).

Scheme 6.8 gives some examples of ketene-alkene cycloadditions. In Entry 1, dimethylketene was generated by pyrolysis of the dimer, 2,2,4,4-tetramethylcyclobutane-1,3-dione and passed into a solution of the alkene maintained at 70°C. Entries 2 and 3 involve generation of chloromethylketene by dehydrohalogenation of α -chloropropanoyl chloride. Entry 4 involves formation of dichloroketene. Entry 5 is an intramolecular addition, with the ketene being generated from a 2-pyridyl ester. Entries 6, 7, and 8 are other examples of intramolecular ketene additions.

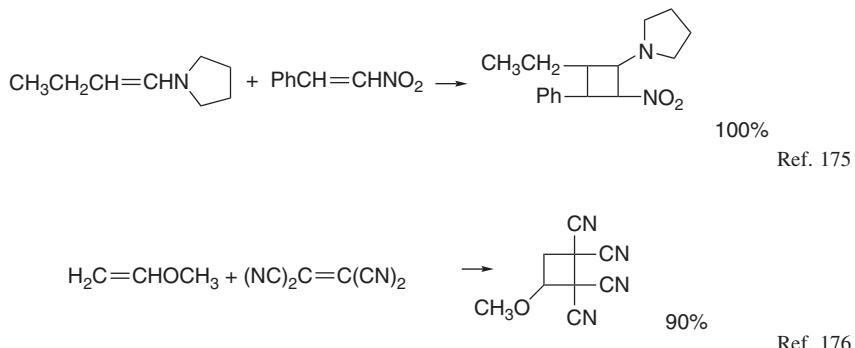
Cyclobutanes can also be formed by nonconcerted processes involving zwitterionic intermediates. The combination of an electron-rich alkene (enamine, enol ether) and an electrophilic one (nitro- or polycyanoalkene) is required for such processes.



ERG = electron releasing group ($-\text{OR}$, $-\text{NR}_2$)

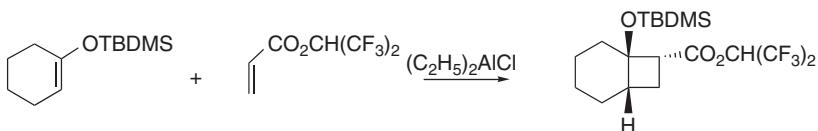
EWG = electron withdrawing group ($-\text{NO}_2$, $-\text{C}\equiv\text{N}$)

Two examples of this reaction type are shown below.



The stereochemistry of these reactions depends on the lifetime of the dipolar intermediate, which, in turn, is influenced by the polarity of the solvent. In the reactions of enol ethers with tetracyanoethylene, the stereochemistry of the enol ether is retained in nonpolar solvents. In polar solvents, cycloaddition is nonstereospecific, as a result of a longer lifetime for the zwitterionic intermediate.¹⁷⁷

Lewis acid catalysis has been used to promote stepwise [2 + 2] cycloaddition of silyl enol ethers and unsaturated esters.¹⁷⁸ The best catalyst is $(\text{C}_2\text{H}_5)_2\text{AlCl}$ and polyfluoroalkyl esters give the highest stereoselectivity. The reactions give the more stable *trans* products.



¹⁷⁵ M. E. Kuehne and L. Foley, *J. Org. Chem.*, **30**, 4280 (1965).

¹⁷⁶ J. K. Williams, D. W. Wiley, and B. C. McKusick, *J. Am. Chem. Soc.*, **84**, 2210 (1962).

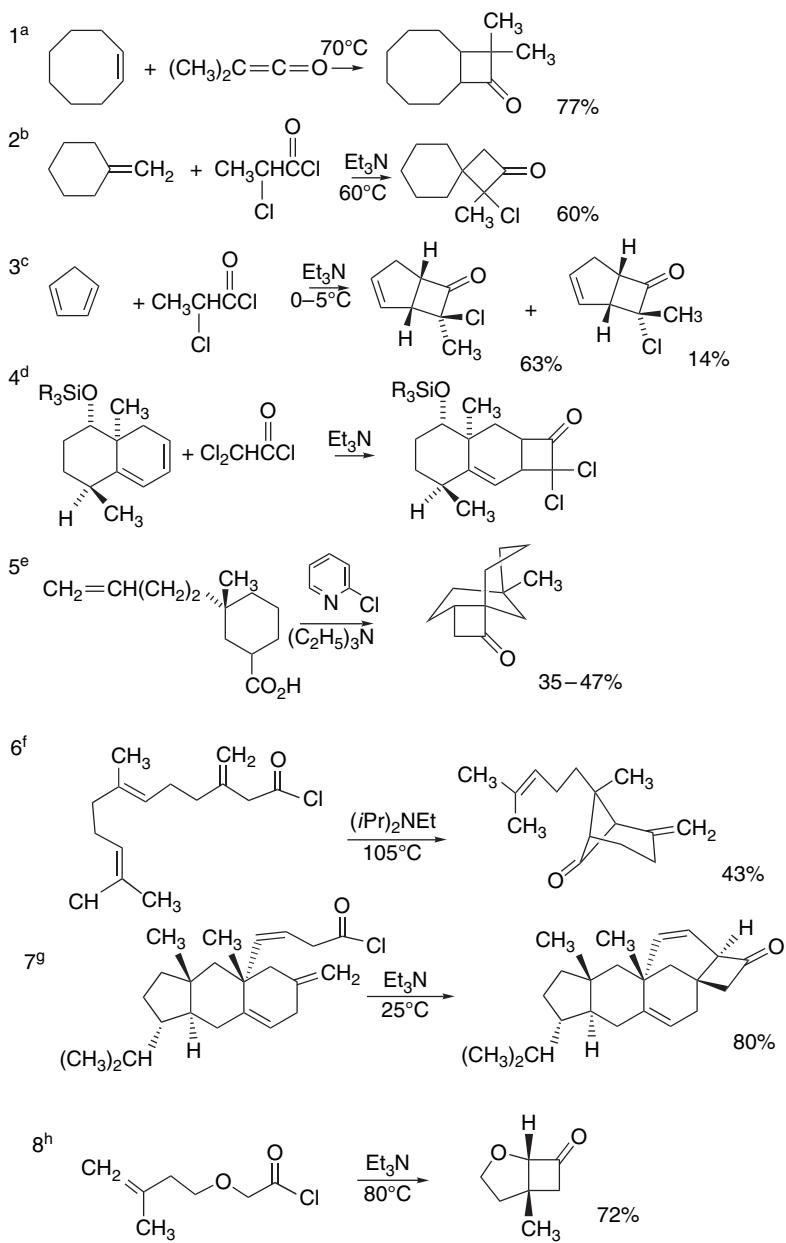
¹⁷⁷ R. Huisgen, *Acc. Chem. Res.*, **10**, 117, 199 (1977).

¹⁷⁸ K. Takasu, M. Ueno, K. Inanaga, and M. Ihara, *J. Org. Chem.*, **69**, 517 (2004).

Scheme 6.8. [2 + 2] Cycloadditions of Ketenes

SECTION 6.3

[2 + 2] Cycloadditions
and Related Reactions
Leading to Cyclobutanes



a. A. P. Krapcho and J. H. Lesser, *J. Org. Chem.*, **31**, 2030 (1966).

b. W. T. Brady and A. D. Patel, *J. Org. Chem.*, **38**, 4106 (1973).

c. W. T. Brady and R. Roe, *J. Am. Chem. Soc.*, **93**, 1662 (1971).

d. P. A. Grieco, T. Oguri, and S. Gilman, *J. Am. Chem. Soc.*, **102**, 5886 (1980).

e. R. L. Funk, P. M. Novak, and M. M. Abraham, *Tetrahedron Lett.*, **29**, 1493 (1988).

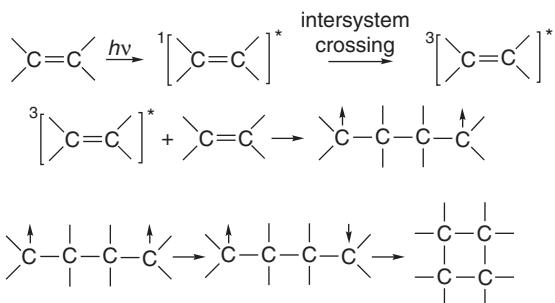
f. E. J. Corey and M. C. Desai, *Tetrahedron Lett.*, **26**, 3535 (1985).

g. E. J. Corey, M. C. Desai, and T. A. Engler, *J. Am. Chem. Soc.*, **107**, 4339 (1985).

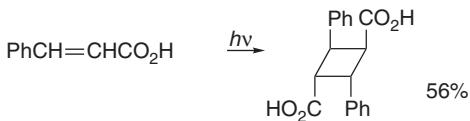
h. B. B. Snider, R. A. H. F. Hui, and Y. S. Kulkarni, *J. Am. Chem. Soc.*, **107**, 2194 (1985).

6.3.2. Photochemical Cycloaddition Reactions

6.3.2.1. Photocycloaddition of Alkenes and Dienes. Photochemical cycloadditions provide a method that is often complementary to thermal cycloadditions with regard to the types of compounds that can be prepared. The theoretical basis for this complementary relationship between thermal and photochemical modes of reaction lies in orbital symmetry relationships, as discussed in Chapter 10 of Part A. The reaction types permitted by photochemical excitation that are particularly useful for synthesis are [2 + 2] additions between two carbon-carbon double bonds and [2 + 2] additions of alkenes and carbonyl groups to form oxetanes. Photochemical cycloadditions are often not concerted processes because in many cases the reactive excited state is a triplet. The initial adduct is a triplet 1,4-diradical that must undergo spin inversion before product formation is complete. Stereospecificity is lost if the intermediate 1,4-diradical undergoes bond rotation faster than ring closure.



Intermolecular photocycloadditions of alkenes can be carried out by photosensitization with mercury or directly with short-wavelength light.¹⁷⁹ Relatively little preparative use has been made of this reaction for simple alkenes. Dienes can be photosensitized using benzophenone, butane-2,3-dione, and acetophenone.¹⁸⁰ The photodimerization of derivatives of cinnamic acid was among the earliest photochemical reactions to be studied.¹⁸¹ Good yields of dimers are obtained when irradiation is carried out in the crystalline state. In solution, *cis-trans* isomerization is the dominant reaction.



The presence of Cu(I) salts promotes intermolecular photocycloaddition of simple alkenes. Copper(I) triflate is especially effective.¹⁸² It is believed that the photoreactive species is a 2:1 alkene:Cu(I) complex in which the two alkene molecules are brought together prior to photoexcitation.¹⁸³

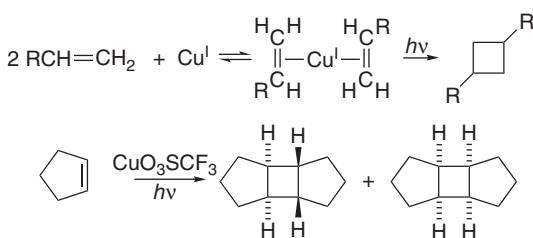
¹⁷⁹. H. Yamazaki and R. J. Cvetanovic, *J. Am. Chem. Soc.*, **91**, 520 (1969).

¹⁸⁰. G. S. Hammond, N. J. Turro, and R. S. H. Liu, *J. Org. Chem.*, **28**, 3297 (1963).

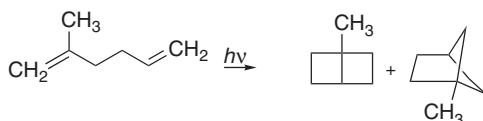
¹⁸¹. A. Mustafa, *Chem. Rev.*, **51**, 1 (1962).

¹⁸². R. G. Salomon, *Tetrahedron*, **39**, 485 (1983); R. G. Salomon and S. Ghosh, *Org. Synth.*, **62**, 125 (1984).

¹⁸³. R. G. Salomon, K. Folking, W. E. Streib, and J. K. Kochi, *J. Am. Chem. Soc.*, **96**, 1145 (1974).

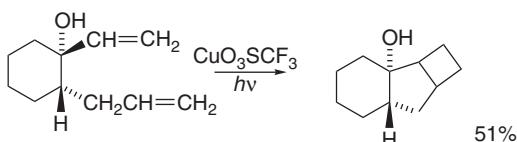


Intramolecular [2 + 2] photocycloadditions of alkenes is an important method of formation of compounds containing four-membered rings.¹⁸⁴ Direct irradiation of simple nonconjugated dienes leads to cyclobutanes.¹⁸⁵ Strain makes the reaction unfavorable for 1,4-dienes but when the alkene units are separated by at least two carbon atoms cycloaddition becomes possible.



Ref. 186

Copper(I) triflate can facilitate these intramolecular additions, as is the case for intermolecular reactions.



Ref. 187

The most widely exploited photochemical cycloadditions involve irradiation of dienes in which the two double bonds are fairly close and result in formation of polycyclic cage compounds. Some examples of alkene photocyclizations are given in Scheme 6.9. Entry 1 is a transannular cyclization. The preference for the observed product over tricyclo[4.2.0.0^{2,5}]octane does not seem to have been analyzed in detail. Entries 2, 3, and 4 involve photolysis in the presence of CuO_3SCF_3 . Entries 5 and 6 are cases in which the double bonds are in close proximity and can cyclize to caged structures.

6.3.2.2. Photocycloaddition Reactions of Enones. Cyclic α,β -unsaturated ketones are another class of molecules that undergo photochemical cycloadditions.¹⁸⁸ The reactive

¹⁸⁴ P. de Mayo, *Acc. Chem. Res.*, **4**, 41 (1971).

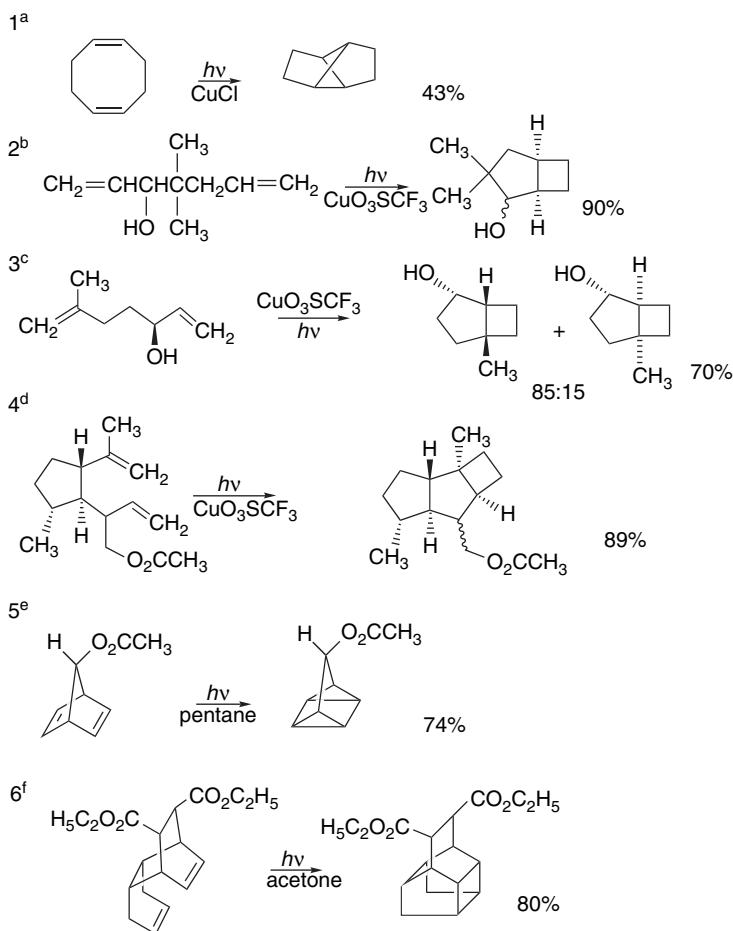
¹⁸⁵ R. Srinivasan, *J. Am. Chem. Soc.*, **84**, 4141 (1962); *J. Am. Chem. Soc.*, **90**, 4498 (1968).

¹⁸⁶ J. Meinwald and G. W. Smith, *J. Am. Chem. Soc.*, **89**, 4923 (1967); R. Srinivasan and K. H. Carlough, *J. Am. Chem. Soc.*, **89**, 4932 (1967).

¹⁸⁷ K. Avasthi and R. G. Salomon, *J. Org. Chem.*, **51**, 2556 (1986).

¹⁸⁸ A. C. Weedon, in *Synthetic Organic Photochemistry*, W. M. Horspool, ed., Plenum Press, New York, 1984, Chap. 2; D. I. Schuster, G. Lem, and N. A. Kaprindis, *Chem. Rev.*, **93**, 3 (1993); M. T. Crimmins and T. L. Reinhold, *Org. React.*, **44**, 297 (1993); D. I. Schuster, in *CRC Handbook of Organic Photochemistry and Photobiology*, W. Horspool and F. Lanci, eds., CRC Press, Boca Raton, FL, 2002, pp. 72-1–72-24.

Scheme 6.9. Intramolecular [2 + 2] Photocycloadditions of Dienes



a. P. Srinivasan, *J. Am. Chem. Soc.*, **86**, 3318 (1964); *Org. Photochem. Synth.*, **1**, 101 (1971).

b. R. G. Salomon and S. Ghosh, *Org. Synth.*, **62**, 125 (1984).

c. K. Lange and J. Mattay, *J. Org. Chem.*, **60**, 7256 (1995).

d. T. Bach and A. Spiegel, *Synlett*, 1305 (2002).

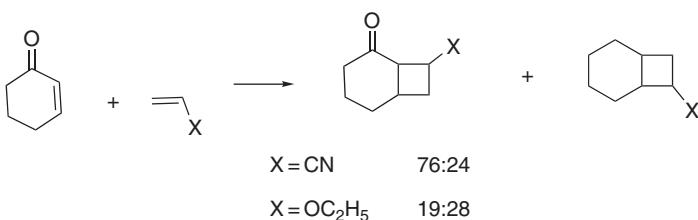
e. P. G. Gassman and D. S. Patton, *J. Am. Chem. Soc.*, **90**, 7276 (1968).

f. B. M. Jacobson, *J. Am. Chem. Soc.*, **95**, 2579 (1973).

excited state is a $\pi-\pi^*$ triplet of the enone. The reaction is most successful with cyclopentenones and cyclohexenones. The excited states of acyclic enones and larger ring compounds are rapidly deactivated by *cis-trans* isomerization and do not readily add to alkenes. Photoexcited enones can also add to alkynes.¹⁸⁹ Unsymmetrical alkenes can undergo two regiosomeric modes of addition. It is generally observed that alkenes with donor groups are oriented such that the substituted carbon becomes bound to the β -carbon, whereas with acceptor substituents the other orientation is preferred.¹⁹⁰

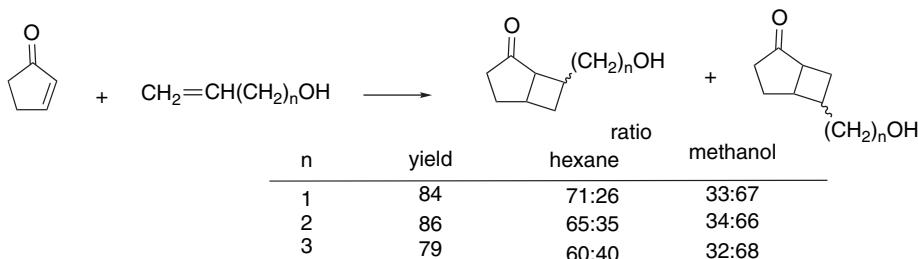
¹⁸⁹. R. L. Cargill, T. Y. King, A. B. Sears, and M. R. Willcott, *J. Org. Chem.*, **36**, 1423 (1971); W. C. Agosta and W. W. Lowrance, *J. Org. Chem.*, **35**, 3851 (1970).

¹⁹⁰. E. J. Corey, J. D. Bass, R. Le Mahieu, and R. B. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1984); T. Suishu, T. Shimo, and K. Somekawa, *Tetrahedron*, **53**, 3545 (1997).

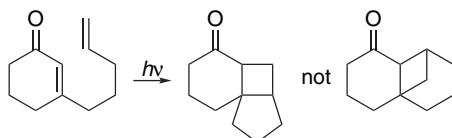


The photoadditions proceed through 1,4-diradical intermediates. Trapping experiments with hydrogen atom donors indicate that the initial bond formation can take place at either the α - or β -carbon of the enone. The excited enone has its highest nucleophilic character at the β -carbon. The initial bond formation occurs at the β -carbon for electron-poor alkenes but at the α -carbon for electron-rich alkenes.¹⁹¹ Selectivity is low for alkenes without strong donor or acceptor substituents.¹⁹² The final product ratio also reflects the rate and efficiency of ring closure relative to fragmentation of the biradical.¹⁹³

Other structural factors can influence regioselectivity. Comparison of 2-propenol, 3-butanol, and 4-pentenol in various solvents suggests that hydrogen bonding can orient the reactants.¹⁹⁴ The reversal of regioselectivity between hexane and methanol suggests that the hydrogen bonding effects are swamped in the hydroxylic solvent methanol.



Intramolecular enone-alkene cycloadditions are also possible. In the case of β -(5-pentenyl) substituents, there is a general preference for *exo*-type cyclization to form a five-membered ring.¹⁹⁵ This is consistent with the general pattern for radical cyclizations and implies initial bonding at the β -carbon of the enone.



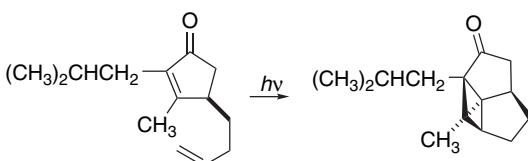
¹⁹¹ J. L. Broecker, J. E. Eksterowicz, A. J. Belk, and K. N. Houk, *J. Am. Chem. Soc.*, **117**, 1847 (1995).

¹⁹² J. D. White and D. N. Gupta, *J. Am. Chem. Soc.*, **88**, 5364 (1966); P. E. Eaton, *Acc. Chem. Res.*, **1**, 50 (1968).

¹⁹³ D. I. Schuster, G. E. Heibel, P. B. Brown, N. J. Turro, and C. V. Kumar, *J. Am. Chem. Soc.*, **110**, 8261 (1988); N. A. Kaprinidis, G. Lem, S. H. Courtney, and D. I. Schuster, *J. Am. Chem. Soc.*, **115**, 3324 (1993); D. Andrew, D. J. Hastings, and A. C. Weedon, *J. Am. Chem. Soc.*, **116**, 10870 (1994).

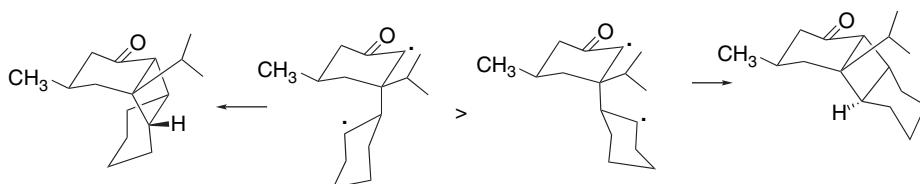
¹⁹⁴ L. K. Syudnes, K. I. Hansen, D. L. Oldroyd, A. C. Weedon, and E. Jorgensen, *Acta Chem. Scand.*, **47**, 916 (1993).

¹⁹⁵ (a) W. C. Agosta and S. Wolff, *J. Org. Chem.*, **45**, 3139 (1980); (b) M. C. Pirrung, *J. Am. Chem. Soc.*, **103**, 82 (1981); (c) P. J. Connolly and C. H. Heathcock, *J. Org. Chem.*, **50**, 4135 (1985).

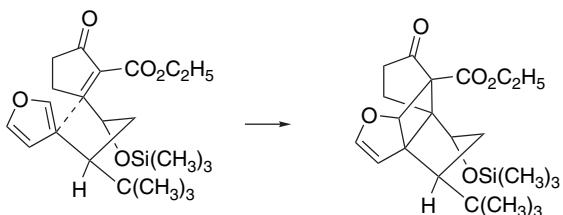


Ref. 195c

Scheme 6.10 gives some examples of enone cycloaddition reactions. The reaction in Entry 1 was done by direct irradiation ($\lambda > 290\text{ nm}$) in benzene. No regiochemical issues arise and the cyano group does not change the course of the reaction. The reaction in Entry 2 was used to construct [4.2.2]propellane, and was done at low temperature. The reaction in Entry 3 presumably occurs by initial bonding at the β -carbon. The preference for the *syn* orientation of the cyclohexane ring appears to be due to a steric interaction with the isopropyl group. The closure of the cyclobutane ring shows little stereoselectivity, resulting in a 2:1 mixture of stereoisomers.



The stereochemistry of the adduct formed in Entry 4 is evidently *cis* at the cyclopentane ring but it is not clear if the cyclobutane ring is *syn* or *anti*. The reaction in Entry 6 gave a mixture of stereoisomers that was subjected to reductive elimination of the vicinal dichloride. The reaction in Entry 7 exhibited complete facial stereoselectivity based on the convex shape of the ring and the presence of the methyl group on the concave face. Entries 8 to 13 are intramolecular additions that generate polycyclic rings. The reaction in Entry 8 was used in the synthesis of longifolene, a tricyclic terpene. Entry 9 gave a single stereoisomer that was used in the synthesis of a sesquiterpene, isocomene. Entry 10 was part of a synthetic route to [5.5.5.4]fenestrane. The fenestrans are tetracyclic compounds that share a central carbon. The reaction in Entry 11 was used in the synthesis of a nitrogenous terpene, incarvilline. In Entry 12, a furan ring is involved in the photocyclization. The stereochemistry seems to be determined by the reactant conformation. Other conformations of the reactant have more destabilizing steric interactions.



6.3.2.3. Photocycloaddition Reactions of Carbonyl Compounds and Alkenes. Photocycloaddition of ketones and aldehydes with alkenes can result in formation of four-membered cyclic ethers (oxetanes), a process often referred to as the *Paterno-Buchi reaction*.¹⁹⁶

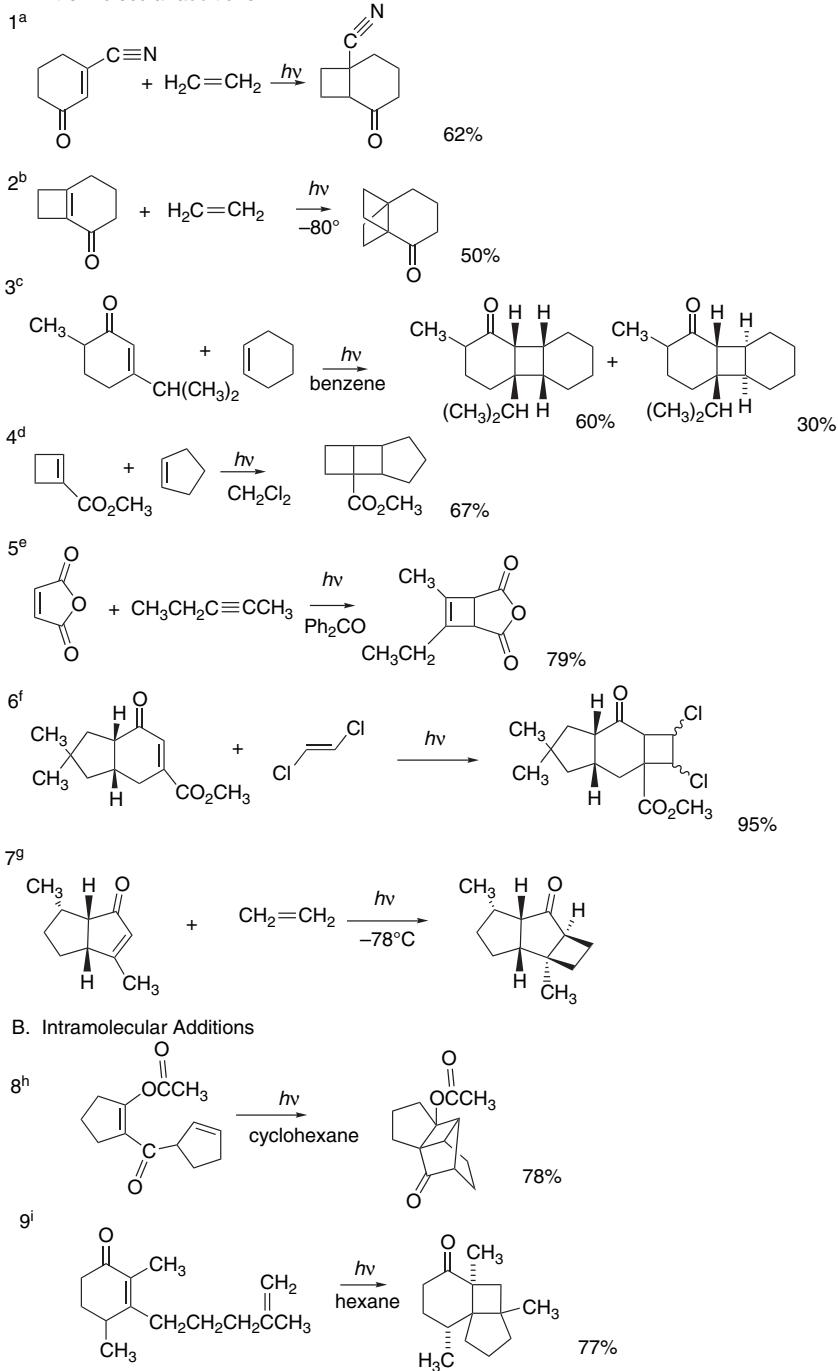
¹⁹⁶ D. R. Arnold, *Adv. Photochem.*, **6**, 301 (1968); H. A. J. Carless, in *Synthetic Organic Photochemistry*, W. M. Horspool, ed., Plenum Press, New York, 1984, Chap. 8; T. Bach, *Synthesis*, 683 (1998).

Scheme 6.10. Photocycloadditions of Enones with Alkenes and Alkynes

SECTION 6.3

[2 + 2] Cycloadditions
and Related Reactions
Leading to Cyclobutanes

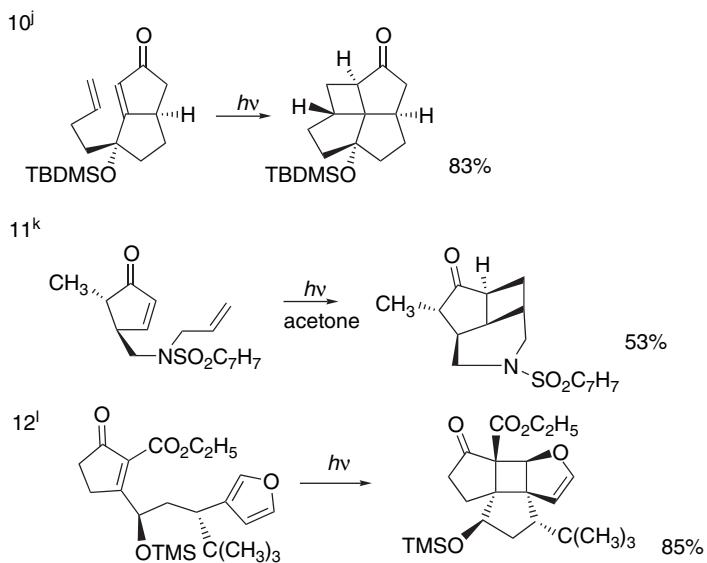
A. Intramolecular additions



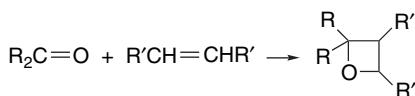
(Continued)

CHAPTER 6

*Concerted
Cycloadditions,
Unimolecular
Rearrangements, and
Thermal Eliminations*



- a. W. C. Agosta and W. W. Lowrance, Jr., *J. Org. Chem.*, **35**, 3851 (1970).
 b. P. E. Eaton and K. Nyi, *J. Am. Chem. Soc.*, **93**, 2786 (1971).
 c. P. Singh, *J. Org. Chem.*, **36**, 3334 (1971).
 d. P. A. Wender and J. C. Lechleiter, *J. Am. Chem. Soc.*, **99**, 267 (1977).
 e. R. M. Scarborough, Jr., B. H. Toder, and A. B. Smith, III, *J. Am. Chem. Soc.*, **102**, 3904 (1980).
 f. G. Mehta and K. Sreenivas, *Tetrahedron Lett.*, **43**, 703 (2002).
 g. E. Piers and A. Orellana, *Synthesis*, 2138 (2001).
 h. W. Oppolzer and T. Godel, *J. Am. Chem. Soc.*, **100**, 2583 (1978).
 i. M. C. Pirrung, *J. Am. Chem. Soc.*, **103**, 82 (1981).
 j. M. Thommen and R. Keese, *Synlett*, 231 (1997).
 k. M. Ichikawa, S. Aoyagi, and C. Kibayashi, *Tetrahedron Lett.*, **46**, 2327 (2005).
 l. M. T. Crimmins, J. M. Pace, P. G. Naternet, A. S. Kim-Meade, J. B. Thomas, S. H. Watterson, and A. S. Wagman, *J. Am. Chem. Soc.*, **122**, 8453 (2000).

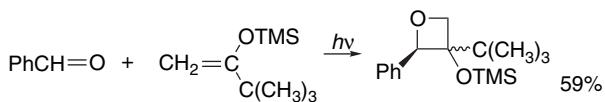


The reaction is stereospecific for at least some aliphatic ketones but not for aromatic carbonyls.¹⁹⁷ This result suggests that the reactive excited state is a singlet for aliphatics and a triplets for aromatics. With aromatic ketones, the regioselectivity of addition can usually be predicted on the basis of formation of the more stable of the two possible diradical intermediates obtained by bond formation between oxygen and the alkene.¹⁹⁸

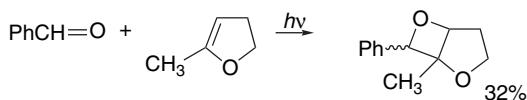
¹⁹⁷. N. C. Yang and W. Eisenhardt, *J. Am. Chem. Soc.*, **93**, 1277 (1971); D. R. Arnold, R. L. Hinman, and A. H. Glick, *Tetrahedron Lett.*, 1425 (1964); N. J. Turro and P. A. Wriede, *J. Am. Chem. Soc.*, **90**, 6863 (1968); J. A. Barltrop and H. A. J. Carless, *J. Am. Chem. Soc.*, **94**, 8761 (1972).

¹⁹⁸. A. Griesbach, S. Buhr, M. Fiegel, J. Lex, and H. Schmickler, *J. Org. Chem.*, **63**, 3847 (1998).

Stereochemistry can be interpreted in terms of conformation effects in the 1,4-biradical intermediates.¹⁹⁹ Vinyl enol ethers and enamides add to aromatic ketones to give 3-substituted oxetanes, usually with the *cis* isomer preferred.²⁰⁰

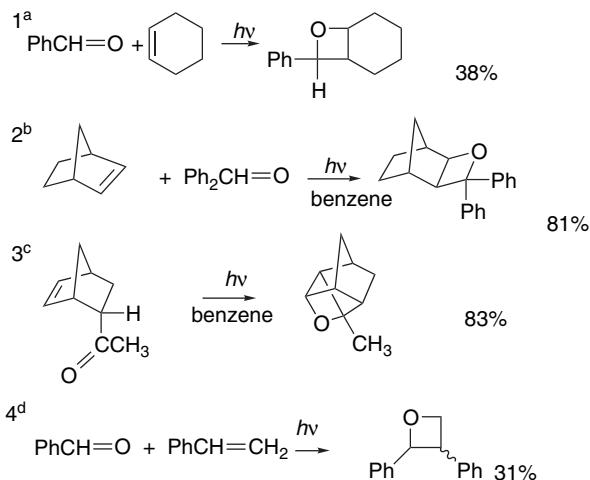


Ref. 200a



Ref. 199

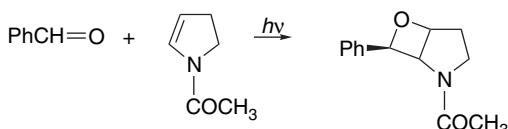
Scheme 6.11. Photocycloaddition Reactions of Carbonyl Compounds and Alkenes



- J. S. Bradshaw, *J. Org. Chem.*, **31**, 237 (1966).
- D. R. Arnold, A. H. Glick, and V. Y. Abraitys, *Org. Photochem. Synth.*, **1**, 51 (1971).
- R. R. Sauers, W. Schinksi, and B. Sickles, *Org. Photochem. Synth.*, **1**, 76 (1971).
- H. A. J. Carless, A. K. Maitra, and H. S. Trivedi *J. Chem. Soc., Chem. Commun.*, 984 (1979).

¹⁹⁹ A. G. Griesbach and S. Stadtmuller, *J. Am. Chem. Soc.*, **113**, 6923 (1991).

²⁰⁰ (a) T. Bach, *Tetrahedron Lett.*, **32**, 7037 (1991); (b) A. G. Griesbach and S. Stadtmuller, *J. Am. Chem. Soc.*, **113**, 6923 (1991); (c) T. Bach, *Liebigs Ann. Chem.*, 1627 (1997); T. Bach, *Synthesis*, 683 (1998).



Ref. 200c

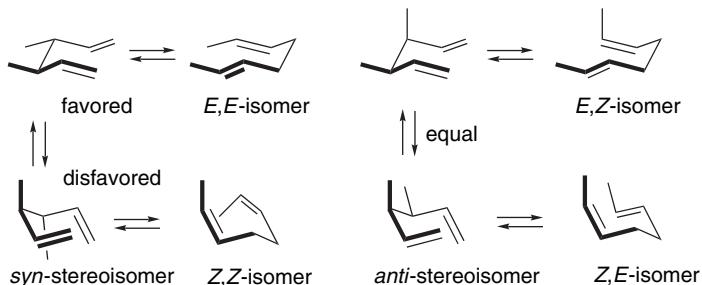
Some other examples of Paterno-Buchi reactions are given in Scheme 6.11.

6.4. [3,3]-Sigmatropic Rearrangements

The mechanistic basis of sigmatropic rearrangements was introduced in Chapter 10 of Part A. The sigmatropic process that is most widely applied in synthesis is the [3,3]-sigmatropic rearrangement. The principles of orbital symmetry establish that concerted [3,3]-sigmatropic rearrangements are allowed processes. Stereochemical predictions and analyses are based on the cyclic transition structure for a concerted reaction mechanism. Some of the various [3,3]-sigmatropic rearrangements that are used in synthesis are presented in outline form in Scheme 6.12.²⁰¹ We discuss these reactions in succeeding sections.

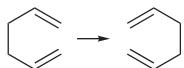
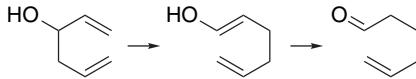
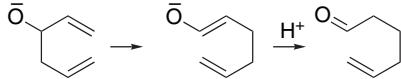
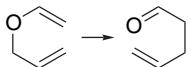
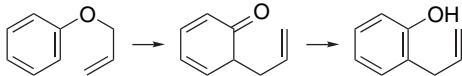
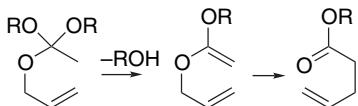
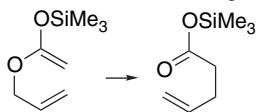
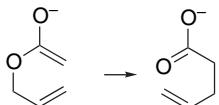
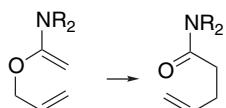
6.4.1. Cope Rearrangements

The Cope rearrangement is the conversion of a 1,5-hexadiene derivative to an isomeric 1,5-hexadiene by the [3,3]-sigmatropic mechanism. For unstrained compounds, the reaction occurs in the range of 150°–250°C. The reaction is both stereospecific and stereoselective. It is stereospecific in that a Z- or E-configurational relationship at either double bond is maintained in the TS and governs the relative configuration at the newly formed single bond in the product.²⁰² However, the relationship depends on the conformation of the TS. When a chair TS is favored the E,E- and Z,Z-dienes lead to *anti*-3,4-diastereomers, whereas the E,Z- and Z,E-isomers give the 3,4-*syn* product. TS conformation also determines the stereochemistry of the new double bond. If both E- and Z-stereoisomers are possible for the product, the product ratio reflects product (and TS) stability. The E-arrangement is normally favored for the newly formed double bonds. The stereochemical aspects of the Cope rearrangements for simple acyclic reactants are consistent with a chairlike TS in which the larger substituent at C(3) [or C(4)] adopts an equatorial-like conformation.



²⁰¹ For reviews of synthetic application of [3,3]sigmatropic rearrangements, see G. B. Bennett, *Synthesis*, 589 (1977); F. E. Ziegler, *Acc. Chem. Res.*, **10**, 227 (1977).

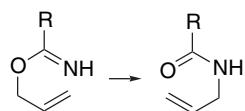
²⁰² W. v. E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

1^a Cope rearrangement2^b Oxy-Cope rearrangement3^c Anionic oxy-Cope rearrangement4^d Claisen rearrangement of allyl vinyl ethers5^d Claisen rearrangement of allyl phenyl ethers6^e Ortho ester Claisen rearrangement7^f Ireland-Claisen rearrangement of *O*-allyl-*O'*-trimethylsilyl ketene acetals8^g Ester enolate Claisen rearrangement9^h Claisen rearrangement of *O*-allyl-*N,N*-dialkyl ketene aminals

(Continued)

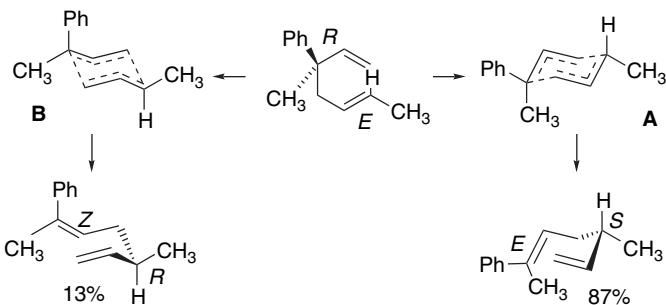
CHAPTER 6

*Concerted
Cycloadditions,
Unimolecular
Rearrangements, and
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10ⁱ Aza-Claisen rearrangement of *O*-allyl imidates

- a. S. J. Rhoads and N. R. Raulins, *Org. React.*, **22**, 1 (1975).
- b. J. A. Berson and M. Jones, Jr., *J. Am. Chem. Soc.*, **86**, 5019 (1964).
- c. D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975).
- d. D. S. Tarbell, *Org. React.*, **2**, 1 (1944).
- e. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.*, **92**, 741 (1970).
- f. R. E. Ireland and R. H. Mueller, *J. Am. Chem. Soc.*, **94**, 5898 (1972).
- g. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
- h. D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
- i. L. E. Overman, *Acc. Chem. Res.*, **13**, 218 (1980).

Owing to the concerted mechanism, chirality at C(3) [or C(4)] leads to enantiospecific formation of new stereogenic centers formed at C(1) [or C(6)].²⁰³ These relationships are illustrated in the example below. Both the configuration of the new stereocenter and the new double bond are those expected on the basis of a chairlike TS. Since there are two stereogenic centers, the double bond and the asymmetric carbon, there are four possible stereoisomers of the product. Only two are formed. The *E*-double bond isomer has the *S*-configuration at C(4) and the *Z*-isomer has the *R*-configuration. These are the products expected for a chair TS. The stereochemistry of the new double bond is determined by the relative stability of the two chair TSs. TS **B** is less favorable than **A** because of the axial placement of the larger phenyl substituent.

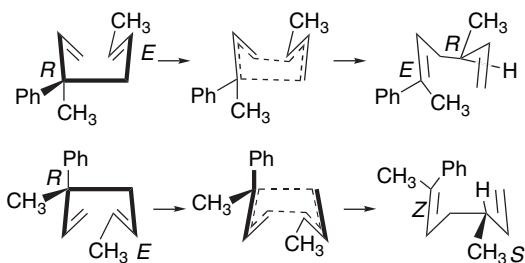


The products corresponding to boatlike TSs are usually not observed for acyclic dienes. However, this TS is allowed and if steric factors make a boat TS preferable to a chair, reaction can proceed through a boat. Thermochemical²⁰⁴ and computational²⁰⁵ studies indicate that the boat TS is intrinsically 6–10 kcal/mol higher in energy. Reactions that proceed through a boat TS have the reverse stereochemical relationships between the configuration at the stereogenic center and the double bond.

²⁰³ R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967); R. K. Hill, in *Asymmetric Synthesis*, Vol. 4, J. D. Morrison, ed., Academic Press, New York, 1984, pp. 503–572.

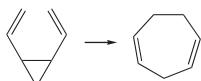
²⁰⁴ M. Goldstein and M. S. Benzon, *J. Am. Chem. Soc.*, **94**, 7147 (1972).

²⁰⁵ O. Wiest, K. A. Black, and K. N. Houk, *J. Am. Chem. Soc.*, **116**, 10336 (1995).

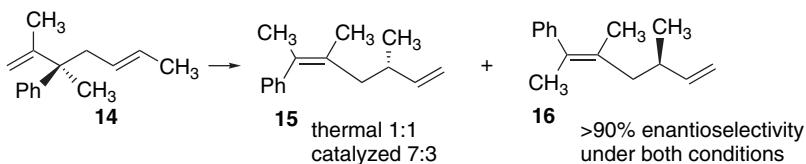


Cope rearrangements are reversible reactions and, as there is no change in the number or types of bonds as a result of the reaction, to a first approximation the total bond energy is unchanged. The position of the final equilibrium is governed by the relative stability of the starting material and product. In the example cited above, the equilibrium is favorable because the product is stabilized by conjugation of the alkene with the phenyl ring.

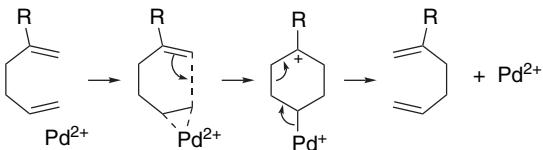
When ring strain is relieved, Cope rearrangements can occur at much lower temperatures and with complete conversion to ring-opened products. A striking example is the conversion of *cis*-divinylcyclopropane to 1,4-cycloheptadiene, a reaction that occurs readily below -40°C .²⁰⁶



Several transition metal ions and complexes, especially Pd(II) salts, have been found to catalyze Cope rearrangements.²⁰⁷ The catalyst that has been adopted for synthetic purposes is $\text{PdCl}_2(\text{CH}_3\text{CN})_2$, and with it the rearrangement of **14** to **15** and **16** occurs at room temperature, as contrasted to 240°C in its absence.²⁰⁸ The catalyzed reaction shows enhanced stereoselectivity and is consistent with a chairlike TS.



The mechanism for catalysis is formulated as a stepwise process in which the electrophilic character of Pd(II) facilitates the bond formation.²⁰⁹



When there is a hydroxy substituent at C(3) of the diene system, the Cope rearrangement product is an enol that is subsequently converted to the corresponding

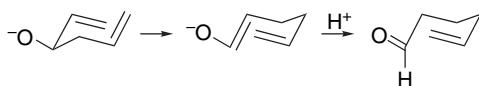
²⁰⁶ W. v. E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

²⁰⁷ R. P. Lutz, *Chem. Rev.*, **84**, 205 (1984).

²⁰⁸ L. E. Overman and F. M. Knoll, *J. Am. Chem. Soc.*, **102**, 865 (1980).

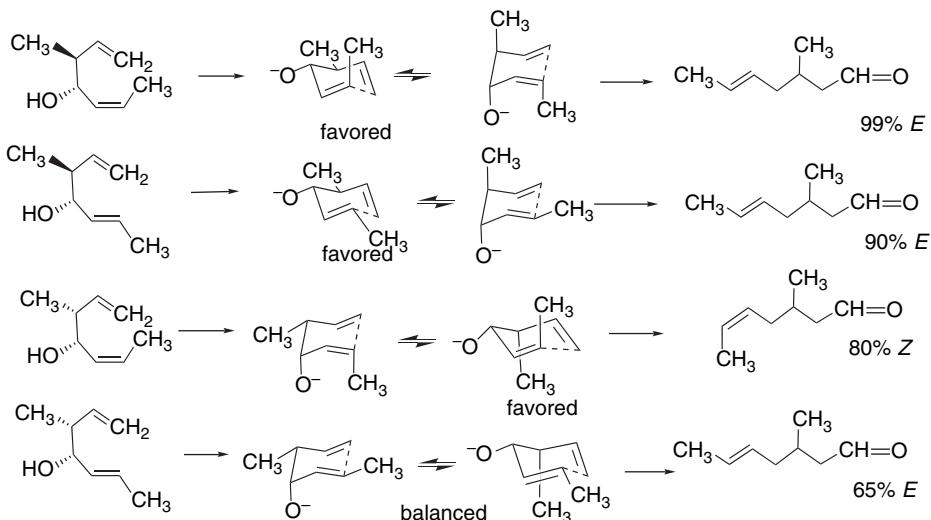
²⁰⁹ L. E. Overman and A. F. Renaldo, *J. Am. Chem. Soc.*, **112**, 3945 (1990).

carbonyl compound. This is called the *oxy-Cope rearrangement*.²¹⁰ The formation of the carbonyl compound provides a net driving force for the reaction.²¹¹



An important improvement in the oxy-Cope reaction was made when it was found that the reaction is strongly catalyzed by base.²¹² When the C(3) hydroxy group is converted to its alkoxide, the reaction is accelerated by a factor of 10^{10} – 10^{17} . These base-catalyzed reactions are called *anionic oxy-Cope rearrangements*, and their rates depend on the degree of cation coordination at the oxy anion. The reactivity trend is $K^+ > Na^+ > Li^+$. Catalytic amounts of tetra-*n*-butylammonium salts lead to accelerated rates in some cases. This presumably results from the dissociation of less reactive ion pair species promoted by the tetra-*n*-butylammonium ion.²¹³

The stereochemistry of acyclic anionic oxy-Cope rearrangements is consistent with a chair TS having a conformation that favors equatorial placement of both alkyl and oxy substituents and minimizes the number of 1,3-diaxial interactions.²¹⁴ For the reactions shown below, the double-bond configuration is correctly predicted on the basis of the most stable TS available in the first three reactions. In the fourth reaction, the TSs are of comparable energy and a 2:1 mixture of *E*- and *Z*-isomers is formed.



Silyl ethers of vinyl allyl alcohols can also be used in oxy-Cope rearrangements.²¹⁵ Known as the *siloxy-Cope rearrangement*, this methodology has been used in

²¹⁰ S. R. Wilson, *Org. React.*, **43**, 93 (1993); L. A. Paquette, *Angew. Chem. Int. Ed. Engl.*, **29**, 609 (1990); L. A. Paquette, *Tetrahedron*, **53**, 13971 (1997).

²¹¹ A. Viola, E. J. Iorio, K. K. Chen, G. M. Glover, U. Nayak, and P. J. Kocienski, *J. Am. Chem. Soc.*, **89**, 3462 (1967).

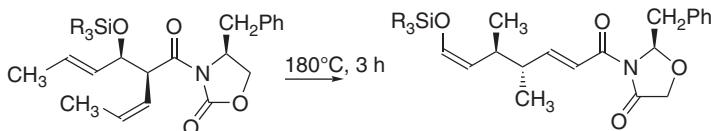
²¹² D. A. Evans and A. M. Golob, *J. Am. Chem. Soc.*, **97**, 4765 (1975); D. A. Evans, D. J. Balillargeon, and J. V. Nelson, *J. Am. Chem. Soc.*, **100**, 2242 (1978).

²¹³ M. George, T.-F. Tam, and B. Fraser-Reid, *J. Org. Chem.*, **50**, 5747 (1985).

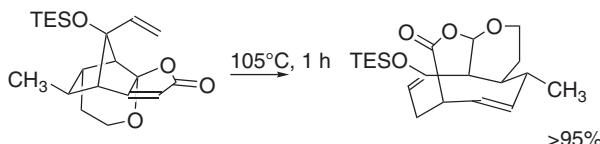
²¹⁴ K. Tomooka, S.-Y. Wei, and T. Nakai, *Chem. Lett.*, 43 (1991).

²¹⁵ R. W. Thies, M. T. Wills, A. W. Chin, L. E. Schick, and E. S. Walton, *J. Am. Chem. Soc.*, **95**, 5281 (1973).

connection with *syn*-selective aldol additions in stereoselective synthesis.²¹⁶ The use of the silyloxy group prevents reversal of the aldol addition, which would otherwise occur under anionic conditions. The reactions proceed at convenient rates at 140°–180° C.

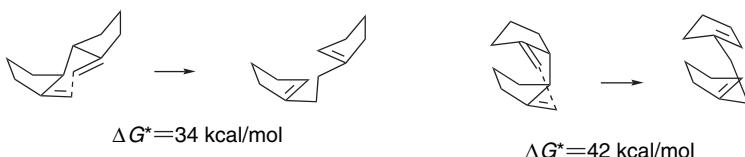


Ref. 217



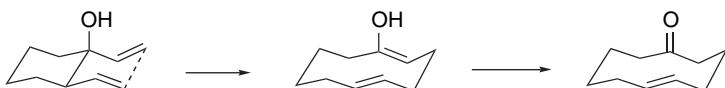
Ref. 218

Scheme 6.13 gives some examples of Cope and oxy-Cope rearrangements. Entry 1 shows a reaction that was done to compare the energy of chair and boat TSs. The chiral diastereomer shown can react through a chair TS and has a ΔG^* about 8 kcal/mol lower than the *meso* isomer, which must react through a boat TS. The equilibrium is biased toward product by the fact that the double bonds in the product are more highly substituted, and therefore more stable, than those in the reactant.



Entry 2 illustrates the reversibility of the Cope rearrangement. In this case, the equilibrium is closely balanced with the reactant benefiting from a more-substituted double bond, whereas the product is stabilized by conjugation. The reaction in Entry 3 involves a *cis*-divinylcyclopropane and proceeds at much lower temperature than the previous examples. The reaction was used in the preparation of an intermediate for the synthesis of pseudoguiane-type natural products.

Entries 4 and 5 illustrate the use of the oxy-Cope rearrangement in formation of medium-size rings. The *trans*-double bond in the product for Entry 4 arises from a chair TS.



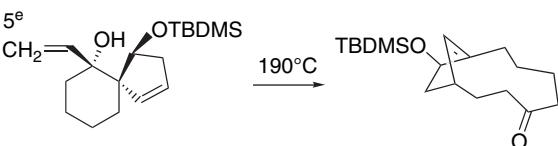
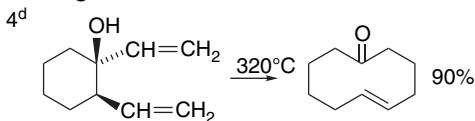
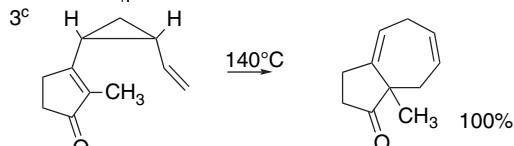
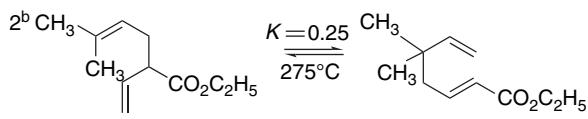
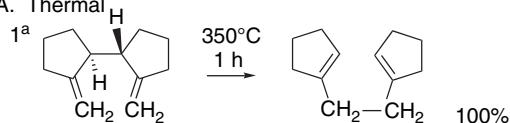
²¹⁶ C. Schneider and M. Rehfeuter, *Synlett*, 212 (1996); C. Schneider and M. Rehfeuter, *Tetrahedron*, **53**, 133 (1997); W. C. Black, A. Giroux, and G. Greidanus, *Tetrahedron Lett.*, **37**, 4471 (1996).

²¹⁷ C. Schneider, *Eur. J. Org. Chem.*, 1661 (1998).

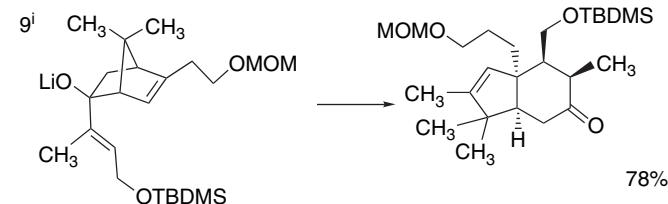
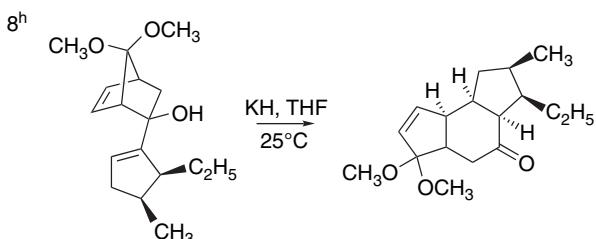
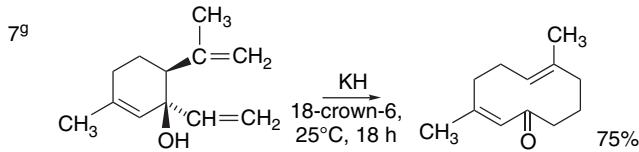
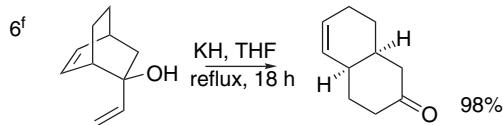
²¹⁸ M. M. Bio and J. L. Leighton, *J. Am. Chem. Soc.*, **121**, 890 (1999).

Scheme 6.13. Cope and Oxy-Cope Rearrangements of 1,5-Dienes

A. Thermal



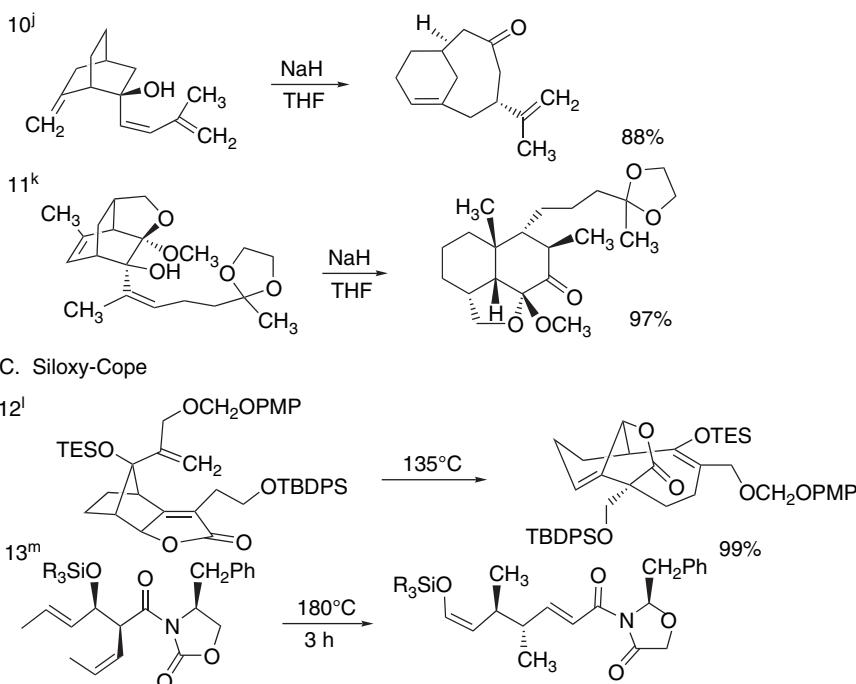
B. Anionic oxy-Cope



(Continued)

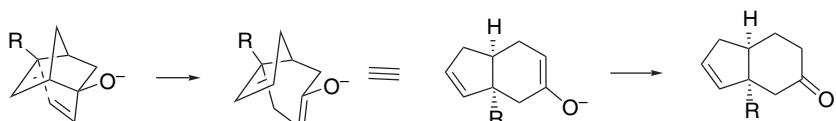
Scheme 6.13. (Continued)

SECTION 6.4

[3,3]-Sigmatropic Rearrangements

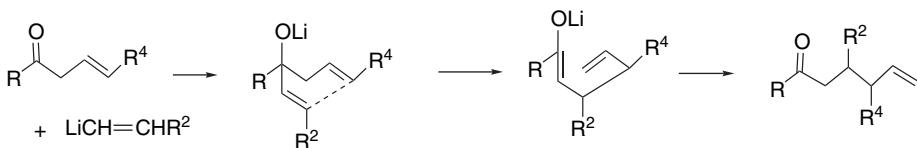
- a. K. J. Shea and R. B. Phillips, *J. Am. Chem. Soc.*, **102**, 3156 (1980).
- b. F. E. Ziegler and J. J. Piwinski, *J. Am. Chem. Soc.*, **101**, 1612 (1979).
- c. P. A. Wender, M. A. Eissenstat, and M. P. Filosa, *J. Am. Chem. Soc.*, **101**, 2196 (1979).
- d. E. N. Marvell and W. Whalley, *Tetrahedron Lett.*, 509 (1970).
- e. G. Ladouceur and L.A. Paquette, *Synthesis*, 185 (1992).
- f. D. A. Evans, A. M. Golob, N. S. Mandel, and G. S. Mandel, *J. Am. Chem. Soc.*, **100**, 8170 (1978).
- g. W. C. Still, *J. Am. Chem. Soc.*, **99**, 4186 (1977).
- h. L. A. Paquette, K. S. Learn, J. L. Romine, and H.-S. Lin, *J. Am. Chem. Soc.*, **110**, 879 (1988); L. A. Paquette, J. L. Romine, H.-S. Lin, and J. Wright, *J. Am. Chem. Soc.*, **112**, 9284 (1990).
- i. L. A. Paquette and F.-T. Hong, *J. Org. Chem.*, **68**, 6905 (2003).
- j. L. Gentric, I. Hanna, A. Huboux, and R. Zaghdoudi, *Org. Lett.*, **5**, 3631 (2003).
- k. D. S. Hsu and C.-C. Liao, *Org. Lett.*, **5**, 3631 (2003).
- l. D. L. J. Clive, S. Sun, V. Gagliardini, and M. K. Sano, *Tetrahedron Lett.*, **41**, 6259 (2000).
- m. C. Schneider, *Eur. J. Org. Chem.*, 1661 (1998).

The reaction in Entry 5 is a case in which the thermal conditions were preferable to the basic conditions because of the base sensitivity of the product. Entries 6 to 10 show anionic oxy-Cope reactions. Entries 6 and 7 are early examples of the application of the reaction in synthesis. Entries 8 and 9 involve rearrangements of bicyclo[2.2.1]hept-2-en-2-ol derivatives to give *cis*-fused bicyclo[4.3.0]non-7-en-3-ones.

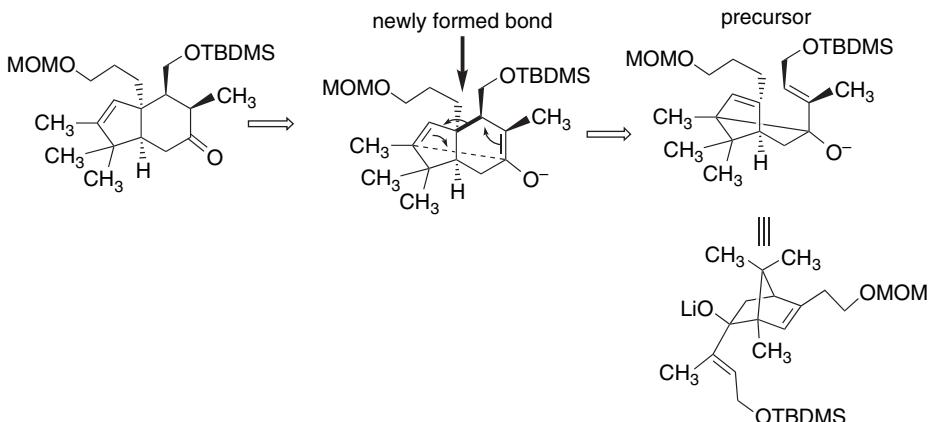


The rearrangement in Entry 9 occurs spontaneously on warming of the reaction mixture from addition of an organolithium reagent to form the vinyl carbinol unit. This is a very general means of constructing reactants for oxy-Cope rearrangements that leads

to carbon-carbon bond formation between C(2) of the vinyl lithium reagent and C(4) of the β,γ -enone.

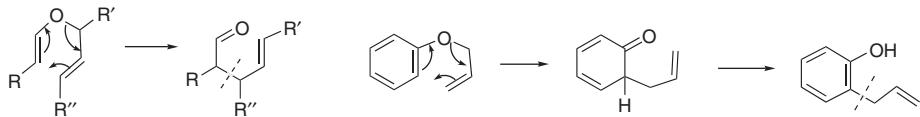


The reaction in Entry 10 demonstrated that a vinyl substituent in conjugation with the vinyl carbinol accelerates rearrangement. The reaction was considerably more facile than the corresponding reaction with a saturated isopropyl group. The reaction in Entry 11 was used in the synthesis of terpene derivatives. Entries 12 and 13 are examples of the siloxy-Cope version of the reaction. These entries illustrate the utility of the oxy-Cope reaction in the synthesis of ring systems. Some of these transformations may be difficult to recognize, at least at first glance. The retrosynthetic transformation can be recognized by identifying the δ,ϵ -enone and locating the bond that is formed in the rearrangement. For example, the retrosynthetic formulation of the reaction in Entry 9 identifies the precursor.

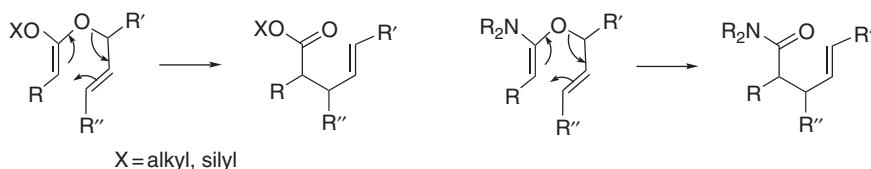


6.4.2. Claisen and Modified Claisen Rearrangements

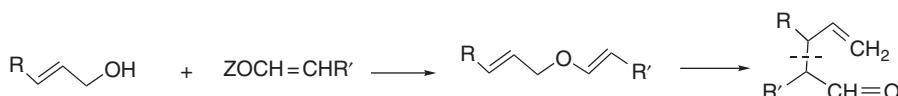
The basic pattern of the Claisen rearrangement is the conversion of a vinyl allyl ether to a γ,δ -enone. The reaction is also observed for allyl phenyl ethers, in which case the products are *o*-allylphenols.



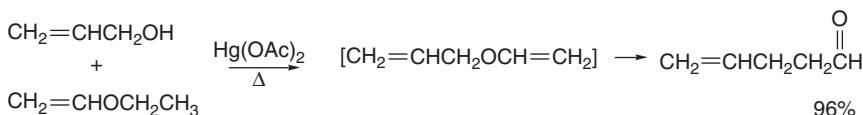
There are several synthetically important adaptations of the reaction. It can be applied to orthoesters (Section 6.4.2.2) or silyl ketene acetals (Section 6.4.2.3), in which case the products are γ,δ -unsaturated acids or esters. An analogous reaction using amide



6.4.2.1. Claisen Rearrangements of Allyl Vinyl Ethers. The [3,3]-sigmatropic rearrangement of allyl vinyl ethers leads to γ,δ -enones and is known as the *Claisen rearrangement*.²¹⁹ The reaction is mechanistically analogous to the Cope rearrangement and occurs at temperatures above 150°C. As the product is a carbonyl compound, the equilibrium is usually favorable. The reaction introduces an α -acyl alkyl group at the γ -carbon of the allylic alcohol, with 1,3-transposition of the allylic double bond.

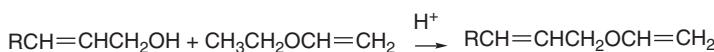


The reactants can be made from allylic alcohols by mercuric ion-catalyzed exchange with ethyl vinyl ether.²²⁰ The allyl vinyl ether need not be isolated and is often prepared under conditions that lead to its rearrangement. The simplest of all Claisen rearrangements, the conversion of allyl vinyl ether to 4-pentenal, typifies this process.



Ref. 221

Acid-catalyzed exchange can also be used to prepare the vinyl ethers.



Ref. 222

Vinyl ethers can also be generated by thermal elimination reactions. For example, base-catalyzed conjugate addition of allyl alcohols to phenyl vinyl sulfone generates 2-(phenylsulfinyl)ethyl ethers that can undergo elimination at 200°C.²²³ The sigmatropic

²¹⁹ F. E. Ziegler, *Chem. Rev.*, **88**, 1423 (1988); A. M. M. Castro, *Chem. Rev.*, **104**, 2939 (2004).

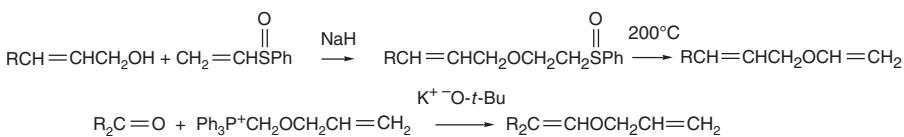
²²⁰ W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.*, **79**, 2828 (1957); D. B. Tulshian, R. Tsang, and B. Fraser-Reid, *J. Org. Chem.*, **49**, 2347 (1984).

²²¹ S. E. Wilson, *Tetrahedron Lett.*, 4651 (1975).

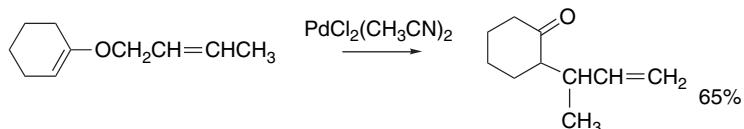
²²² G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 2091 (1967); R. Marbet and G. Saucy, *Helv. Chim. Acta*, **50**, 2095 (1967).

²²³ T. Mandai, S. Matsumoto, M. Kohama, M. Kawada, J. Tsuji, S. Saito, and T. Moriwake, *J. Org. Chem.*, **55**, 5671 (1990); T. Mandai, M. Ueda, S. Hagesawa, M. Kawada, J. Tsuji, and S. Saito, *Tetrahedron Lett.*, **31**, 4041 (1990).

rearrangement proceeds under these conditions. Allyl vinyl ethers can also be prepared by Wittig reactions using ylides generated from allyloxymethylphosphonium salts.²²⁴

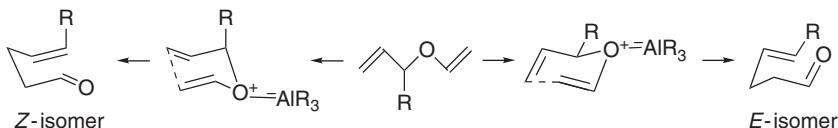


As with the Cope rearrangement, PdCl_2 can catalyze the Claisen rearrangement.

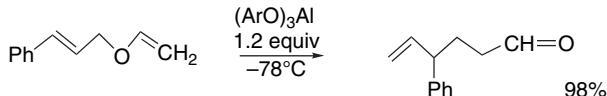


Ref. 225

However, it can also catalyze competing reactions and works best for relatively highly substituted systems.²²⁶ Catalysis of Claisen rearrangements has been achieved using highly hindered bis-(phenoxy)methylaluminum as Lewis acids.²²⁷ These reagents also have the ability to control the E:Z ratio of the products. Very bulky catalysts tend to favor the Z-isomer by forcing the α -substituent of the allyl group into an axial conformation.



tris-Aryloxyaluminum compounds are also effective catalysts for the Claisen rearrangement.²²⁸ When used in a 1.2 molar ratio, the rearrangement occurs at -78°C .



Some representative Claisen rearrangements are shown in Scheme 6.14. Entry 1 illustrates the application of the Claisen rearrangement in the introduction of a substituent at the junction of two six-membered rings. Introduction of a substituent at this type of position is frequently necessary in the synthesis of steroids and terpenes. In Entry 2, formation and rearrangement of a 2-propenyl ether leads to formation of a methyl ketone. Entry 3 illustrates the use of 3-methoxyisoprene to form the allylic ether. The rearrangement of this type of ether leads to introduction of isoprene structural units into the reaction product. Entry 4 involves an allylic ether prepared by O-alkylation of a β -keto enolate. Entry 5 was used in the course of synthesis of a diterpene lactone. Entry 6 is a case in which PdCl_2 catalyzes both the formation and rearrangement of the reactant.

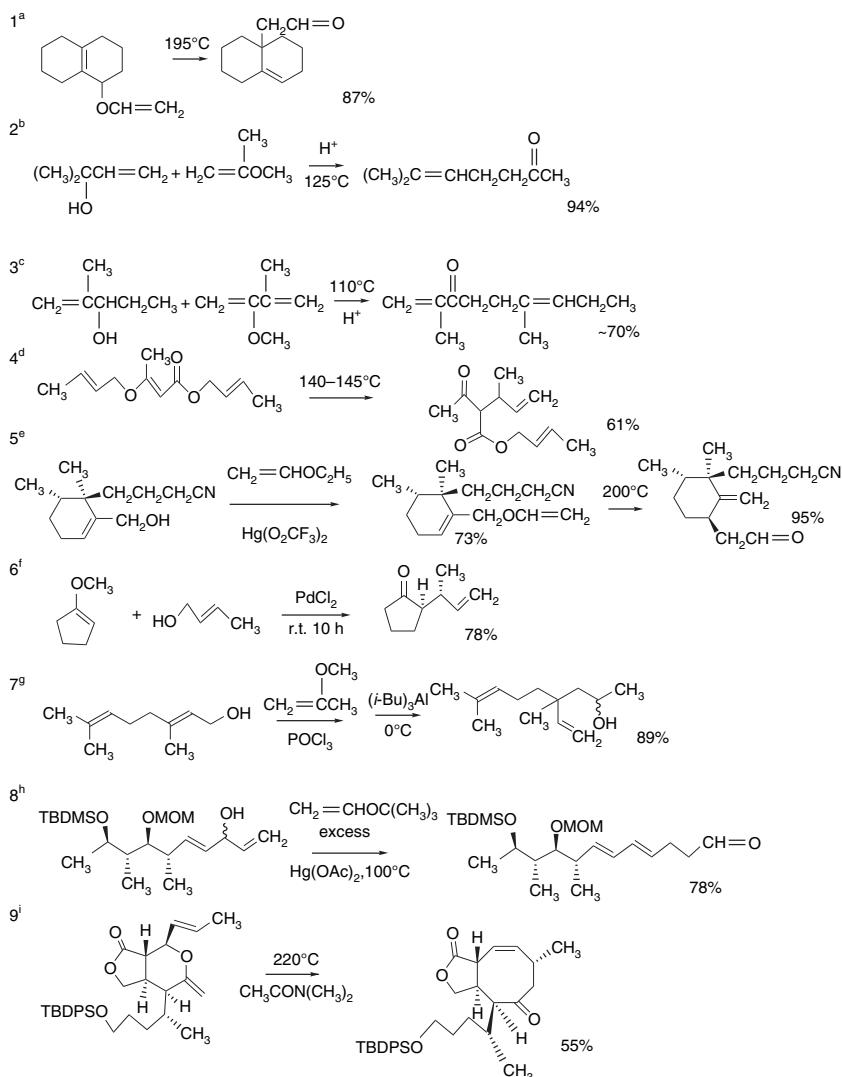
- ²²⁴. M. G. Kulkarni, D. S. Pendharkar, and R. M. Rasne, *Tetrahedron Lett.*, **38**, 1459 (1997).
- ²²⁵. J. L. van der Baan and F. Bickelhaupt, *Tetrahedron Lett.*, **27**, 6267 (1986).
- ²²⁶. M. Hiersemann and L. Abraham, *Eur. J. Org. Chem.*, 1461 (2002).
- ²²⁷. K. Nonoshita, H. Banno, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.*, **112**, 316 (1990).
- ²²⁸. S. Saito, K. Shimada, and H. Yamamoto, *Synlett*, 720 (1996).

Scheme 6.14. Claisen Rearrangements of Allyl Vinyl Ethers and Related Compounds

563

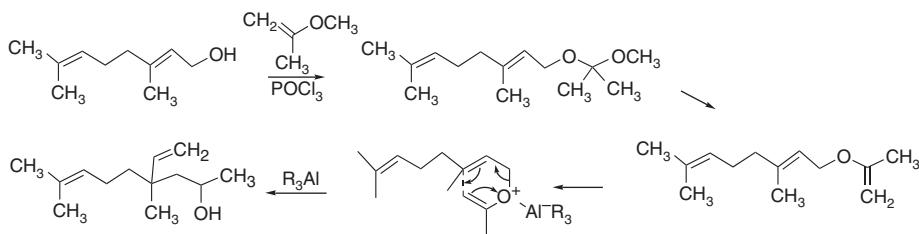
SECTION 6.4

[3,3]-*Sigmatropic*
Rearrangements



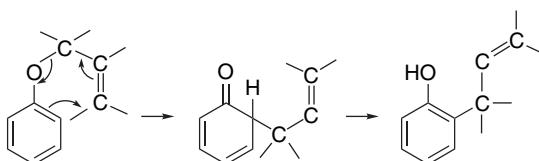
- a. A. W. Burgstahler and I. C. Nordin, *J. Am. Chem. Soc.*, **83**, 198 (1961).
 b. G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 2091 (1967).
 c. D. J. Faulkner and M. R. Petersen, *J. Am. Chem. Soc.*, **95**, 553 (1973).
 d. J. W. Ralls, R. E. Lundin, and G. F. Bailey, *J. Org. Chem.*, **28**, 3521 (1963).
 e. L. A. Paquette, T.-Z. Wang, S. Nang and C. M. G. Philippo, *Tetrahedron Lett.*, **34**, 3523 (1993).
 f. K. Mitami, K. Takahashi, and T. Nakai, *Tetrahedron Lett.*, **28**, 5879 (1987).
 g. S. D. Rychnovsky and J. L. Lee, *J. Org. Chem.*, **60**, 4318 (1995).
 h. T. Berkenbusch and R. Brueckner, *Chem. Eur. J.*, **10**, 1545 (2004).
 i. T.-Z. Wang, E. Pinard, and L. A. Paquette, *J. Am. Chem. Soc.*, **118**, 1309 (1996).

Entry 7 illustrates reaction conditions that were applicable to formation and rearrangement of an isopropenyl allylic ether. The tri-isopropylaluminum is thought to both catalyze the *sigmatropic* rearrangement and reduce the product ketone.

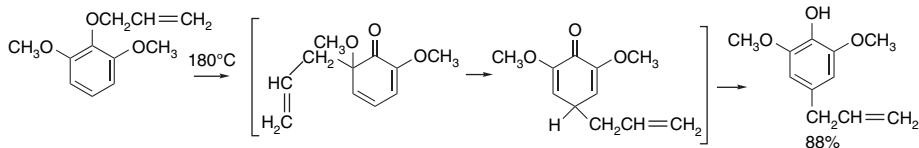


The reaction in Entry 8 was conducted in excess refluxing vinyl *t*-butyl ether, using 1.1 equivalent of $\text{Hg}(\text{OAc})_2$ to catalyze the exchange reaction. In Entry 9 a thermal reaction leads to formation of an eight-membered ring.

Aryl allyl ethers can also undergo [3,3]-sigmatropic rearrangement. In fact, Claisen rearrangements of allyl phenyl ethers to *ortho*-allyl phenols were the first [3,3]-sigmatropic rearrangements to be thoroughly studied.²²⁹ The reaction proceeds through a cyclohexadienone that enolizes to the stable phenol.

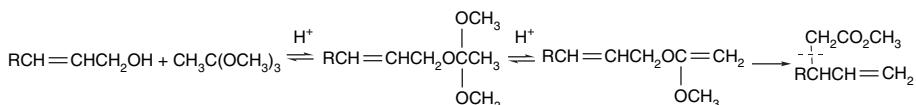


If both *ortho*-positions are substituted, the allyl group undergoes a second migration, giving the *para*-substituted phenol:



Ref. 230

6.4.2.2. Orthoester Claisen Rearrangements. There are several variations of the Claisen rearrangement that make it a powerful tool for the synthesis of γ,δ -unsaturated carboxylic acids. The *orthoester modification of the Claisen rearrangement* allows carboalkoxymethyl groups to be introduced at the γ -position of allylic alcohols.²³¹ A mixed orthoester is formed as an intermediate and undergoes sequential elimination and sigmatropic rearrangement.



²²⁹ S. J. Rhoads, in *Molecular Rearrangements*, Vol. 1, P. de Mayo, ed., Interscience, New York, 1963, pp. 655–684.

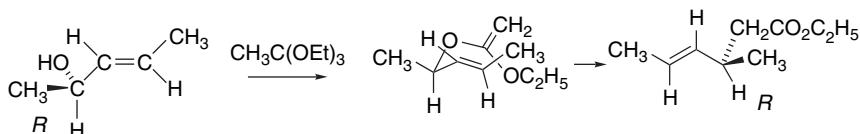
²³⁰ I. A. Pearl, *J. Am. Chem. Soc.*, **70**, 1746 (1948).

²³¹ W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Am. Chem. Soc.*, **92**, 741 (1970).

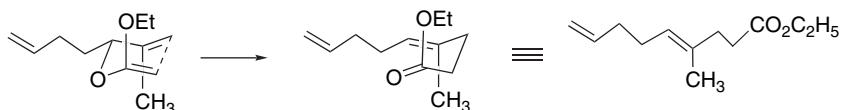
Both the exchange and elimination are catalyzed by the addition of a small amount of a weak acid, such as propanoic acid. These reactions are usually conducted at the reflux temperature of the orthoester, which is about 110°C for the trimethyl ester and 140°C for the triethyl ester. Microwave heating has been used and is reported to greatly accelerate orthoester-Claisen rearrangements.²³²

The mechanism and stereochemistry of the orthoester Claisen rearrangement is analogous to the Cope rearrangement. The reaction is stereospecific with respect to the double bond present in the initial allylic alcohol. In acyclic molecules, the stereochemistry of the product can usually be predicted on the basis of a chairlike TS.²³³ When steric effects or ring geometry preclude a chairlike structure, the reaction can proceed through a boatlike TS.²³⁴

High levels of enantiospecificity have been observed in the rearrangement of chiral reactants. This method can be used to establish the configuration of the newly formed carbon-carbon bond on the basis of the configuration of the C–O bond in the starting allylic alcohol. Treatment of (*2R, 3E*)-3-penten-2-ol with ethyl orthoacetate gives the ethyl ester of (*3R, 4E*)-3-methyl-4-hexenoic acid in 90% enantiomeric purity.²³⁵ The configuration of the new stereocenter is that predicted by a chairlike TS with the methyl group occupying a pseudoequatorial position.



Scheme 6.15 gives some representative examples of the orthoester Claisen rearrangement. Entry 1 is an example of the standard conditions for the orthoester Claisen rearrangement using triethyl orthoacetate as the reactant. The allylic alcohol is heated in an excess of the orthoester (5.75 equivalents) with 5 mol % of propanoic acid. Ethanol is distilled from the reaction mixture. The *E*-double bond arises from the chair TS.



The reaction in Entry 2, involving trimethyl orthoacetate, was effected in the course of synthesis of an insect juvenile hormone. The reaction is highly stereoselective (> 98%) for the *E*-isomer at the new double bond. The reactions in Entries 3 and 4 were used to introduce ester substituents on the nitrogen-containing rings. Note that in Entry 4 an orthobutanoate ester is used, demonstrating that longer-chain orthoesters

²³² A. Srikrishna, S. Nagaraju, and P. Kondaiah, *Tetrahedron*, **51**, 1809 (1995).

²³³ G. W. Daub, J. P. Edwards, C. R. Okada, J. W. Allen, C. T. Makey, M. S. Wells, A. S. Goldstien, M. J. Dibley, C. J. Wang, D. P. Ostercamp, S. Chung, P. S. Lunningham, and M. A. Berliner, *J. Org. Chem.*, **62**, 1976 (1997).

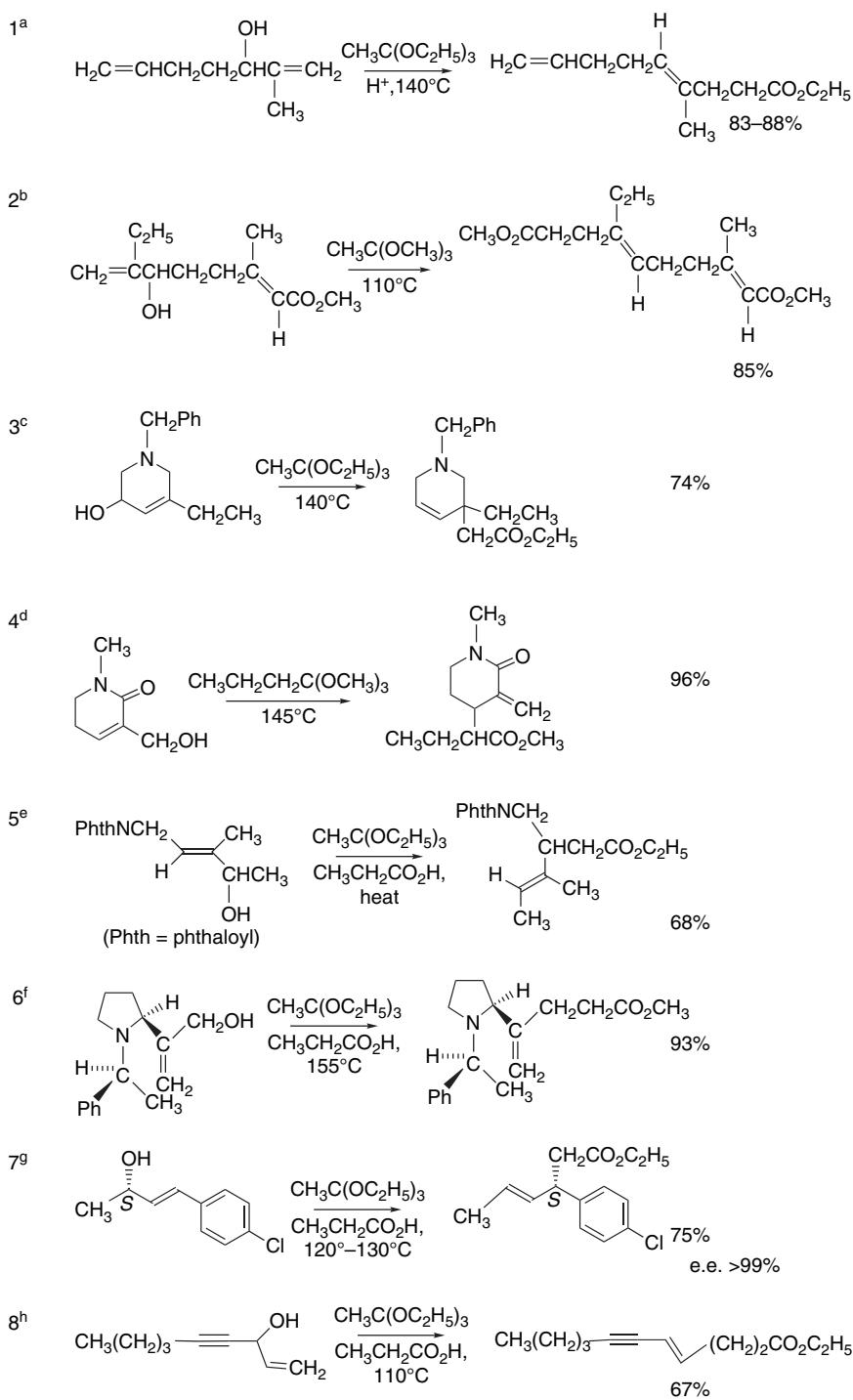
²³⁴ R. J. Cave, B. Lythgoe, D. A. Metcalf, and I. Waterhouse, *J. Chem. Soc., Perkin Trans. 1*, 1218 (1977); G. Buchi and J. E. Powell, Jr., *J. Am. Chem. Soc.*, **92**, 3126 (1970); J. J. Gajewski and J. L. Jiminez, *J. Am. Chem. Soc.*, **108**, 468 (1986).

²³⁵ R. K. Hill, R. Soman, and S. Sawada, *J. Org. Chem.*, **37**, 3737 (1972); **38**, 4218 (1973).

Scheme 6.15. Orthoester-Claisen Rearrangements

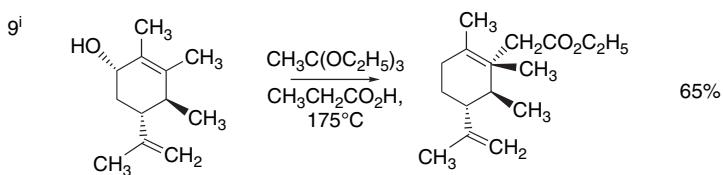
CHAPTER 6

*Concerted
Cycloadditions,
Unimolecular
Rearrangements, and
Thermal Eliminations*



(Continued)

Scheme 6.15. (Continued)



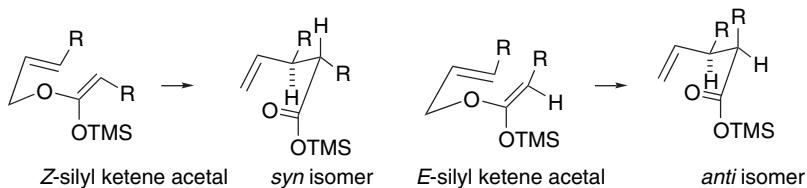
SECTION 6.4

[3,3]-Sigmatropic Rearrangements

- a. R. I. Trust and R. E. Ireland, *Org. Synth.*, **53**, 116 (1973).
 b. C. A. Hendrick, R. Schaub, and J. B. Siddall, *J. Am. Chem. Soc.*, **94**, 5374 (1972).
 c. F. E. Ziegler and G. B. Bennett, *J. Am. Chem. Soc.*, **95**, 7458 (1973).
 d. J. J. Plattner, R. D. Glass, and H. Rapoport, *J. Am. Chem. Soc.*, **94**, 8614 (1972).
 e. L. Serfass and P. J. Casara, *Bioorg. Med. Chem. Lett.*, **8**, 2599 (1998).
 f. D. N. A. Fox, D. Lathbury, M. F. Mahon, K. C. Molloy, and T. Gallagher, *J. Am. Chem. Soc.*, **113**, 2652 (1991).
 g. E. Brenna, N. Caraccia, C. Fuganti, and P. Graselli, *Tetrahedron: Asymmetry*, **8**, 3801 (1997).
 h. L. C. Passaro and F. X. Webster, *Synthesis*, 1187 (2003).
 i. A. Srikrishna and D. Vijaykumar, *J. Chem. Soc., Perkin Trans. I*, 2583 (2000).

are suitable for the reaction and permit the synthesis of α, α -disubstituted esters. The reaction in Entry 5 was used in the synthesis of protected analogs of γ -amino acids. The reaction gave the expected *E*-double bond. The reaction in Entry 6 was used in an enantiospecific synthesis of a pumiliotoxin alkaloid. Entry 7 presents a case of chirality transfer. The *S*-allylic alcohol generates the *S*-configuration at the new C–C bond with an e.e. of more than 99%. The reaction in Entry 8 was used in the synthesis of an insect pheromone, and the triple bond was eventually reduced to a *Z*-double bond. The reaction in Entry 9 was part of enantiospecific synthesis of more complex terpenoids from *R*-carvone. Note that in this case, the cyclic TS results in introduction of the ester substituent *syn* to the hydroxy group on the ring, which is a general result for cyclic reactants.

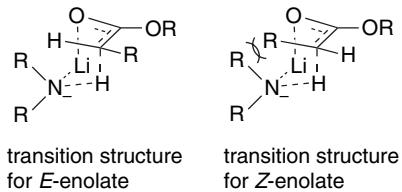
6.4.2.3. Rearrangements of Silyl Ketene Acetals and Ester Enolates. Esters of allylic alcohols can be rearranged to γ, δ -unsaturated carboxylic acids via the *O*-trimethylsilyl ethers of the ester enolate.²³⁶ These intermediates are called *silyl ketene acetals*. This version of the reaction, known as the *Ireland-Claisen rearrangement*,²³⁷ takes place under much milder conditions than the orthoester method. The reaction occurs at room temperature or slightly above. The stereochemistry of the silyl ketene acetal Claisen rearrangement is controlled not only by the configuration of the double bond in the allylic alcohol but also by the stereochemistry of the silyl ketene acetal. The chair TS predicts that the relative configuration at the newly formed C–C bond will be determined by the *E*- or *Z*-stereochemistry of the silyl ketene acetal.



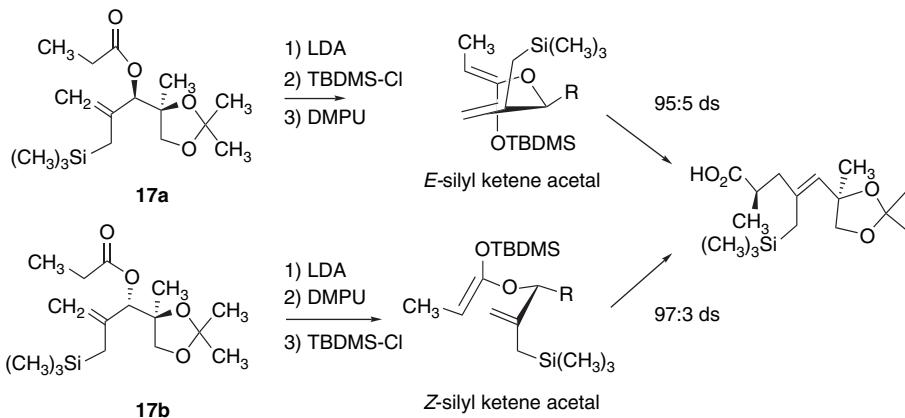
²³⁶ R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).

²³⁷ For reviews, see S. Pereira and M. Srebnik, *Aldrichimica Acta*, **26**, 17 (1993); Y. Chai, S. Hong, H. A. Lindsay, C. McFarland, and M. C. McIntosh, *Tetrahedron*, **58**, 2905 (2002).

The stereochemistry of the silyl ketene acetal can be controlled by the conditions of preparation. The base that is usually used for enolate formation is lithium diisopropylamide (LDA). If the enolate is prepared in pure THF, the *E*-enolate is generated and this stereochemistry is maintained in the silyl derivative. The preferential formation of the *E*-enolate can be explained in terms of a cyclic TS in which the proton is abstracted from the stereoelectronically preferred orientation perpendicular to the carbonyl plane. The carboxy substituent is oriented away from the alkyl groups on the amide base.

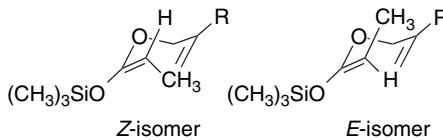


If HMPA is included in the solvent, the *Z*-enolate predominates.^{236,238} DMPU also favors the *Z*-enolate. The switch to the *Z*-enolate with HMPA or DMPU is attributed to a looser, perhaps acyclic TS being favored as the result of strong solvation of the lithium ion. The steric factors favoring the *E*-TS are therefore diminished.²³⁹ These general principles of solvent control of enolate stereochemistry are applicable to other systems.²⁴⁰ For example, by changing the conditions for silyl ketene acetal formation, the diastereomeric compounds **17a** and **17b** can be converted to the same product with high diastereoselectivity.²⁴¹

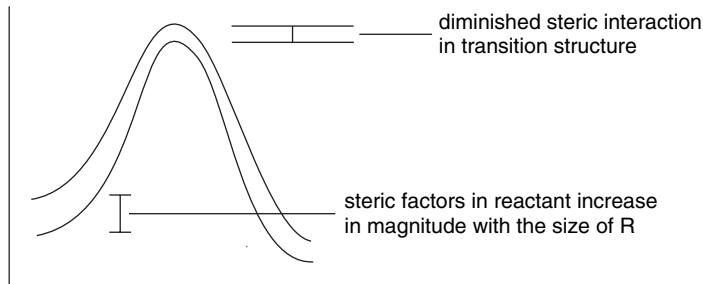


A number of steric effects on the rate of rearrangement have been observed and can be accommodated by the chairlike TS model.²⁴² The *E*-silyl ketene acetals rearrange

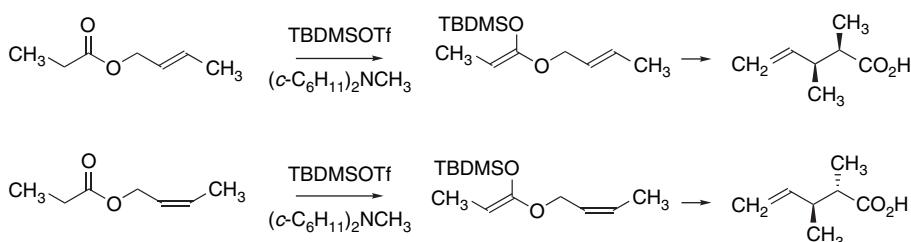
- ²³⁸. R. E. Ireland and A. K. Willard, *Tetrahedron Lett.*, 3975 (1975); R. E. Ireland, P. Wipf, and J. Armstrong, III, *J. Org. Chem.*, **56**, 650 (1991).
- ²³⁹. C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lamp, *J. Org. Chem.*, **45**, 1066 (1980).
- ²⁴⁰. J. Corset, F. Froment, M.-F. Lautie, N. Ratovelomanana, J. Seyden-Penne, T. Strzalko, and M. C. Roux-Schmitt, *J. Am. Chem. Soc.*, **115**, 1684 (1993).
- ²⁴¹. S. D. Hiscock, P. B. Hitchcock, and P. J. Parsons, *Tetrahedron*, **54**, 11567 (1998).
- ²⁴². C. S. Wilcox and R. E. Babston, *J. Am. Chem. Soc.*, **108**, 6636 (1986).



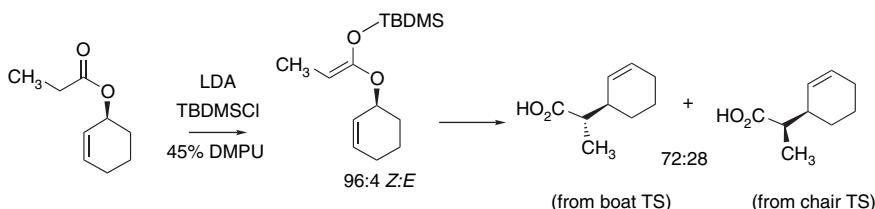
The size of the substituent R also influences the rate, with the rate increasing somewhat for both isomers as R becomes larger. It is believed that steric interactions with R are relieved as the C–O bond stretches. The rate acceleration reflects the higher ground state energy resulting from these steric interactions.



The silyl ketene acetal rearrangement can also be carried out by reaction of the ester with a silyl triflate and tertiary amine, without formation of the ester enolate. Optimum results are obtained with bulky silyl triflates and amines, e.g., *t*-butyldimethylsilyl triflate and *N*-methyl-*N,N*-dicyclohexylamine. Under these conditions the reaction is stereoselective for the Z-silyl ketene acetal and the stereochemistry of the allylic double bond determines the *syn* or *anti* configuration of the product.²⁴³



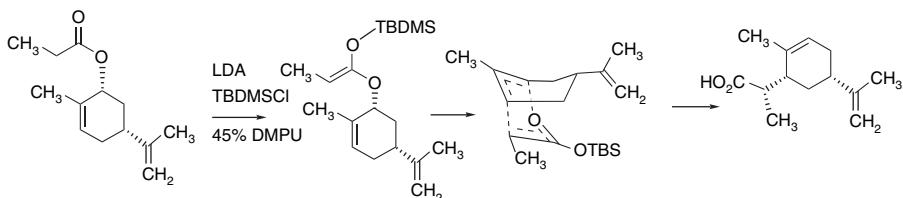
The stereochemistry of Ireland-Claisen rearrangements of cyclic compounds is sometimes indicative of reaction through a boat TS. For example, the major product from 2-cyclohexenyl propanoate is formed through a boat TS.²⁴⁴



²⁴³. M. Kobayashi, K. Matsumoto, E. Nakai, and T. Nakai, *Tetrahedron Lett.*, **37**, 3005 (1996).

²⁴⁴. (a) R. E. Ireland and P. Maienfisch, *J. Org. Chem.*, **53**, 640 (1988); (b) R. E. Ireland, P. Wipf, and J.D. Armstrong, *J. Org. Chem.*, **56**, 650 (1991); (c) R. E. Ireland, P. Wipf, and J.-N. Xiang, *J. Org. Chem.*, **56**, 3572 (1991).

The reason for the trend toward boat TSs in cyclic systems is the introduction of additional steric factors. For example, addition of methyl and isopropenyl substituents leads to a TS in which the cyclohexene ring adopts a boat conformation, whereas the TS is chairlike.



Heteroatoms, particularly oxygen, introduce electronic factors that favor boat TSs.

Computational modeling (B3LYP/6-31G*) of rearrangement of cyclohexenol identified the four potential TS geometries shown in Figure 6.14.²⁴⁵ Using the *O*-methyl enol ether as a model, a 2-cyclohexenyl ester prefers a *syn*-boat TS, in agreement with the experimental results. As in the experimental work, the placement of additional substituents alters the relative energies of these TSs.

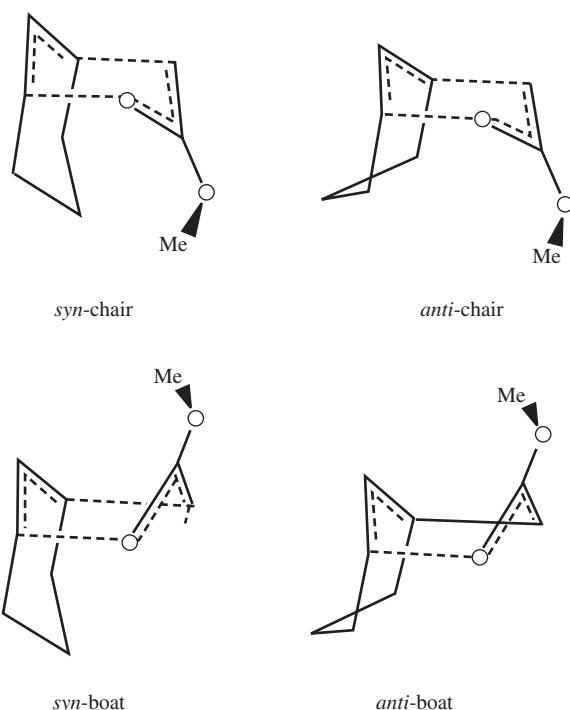
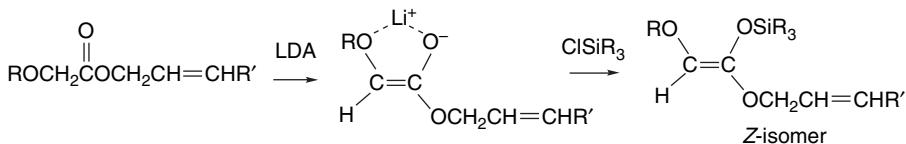
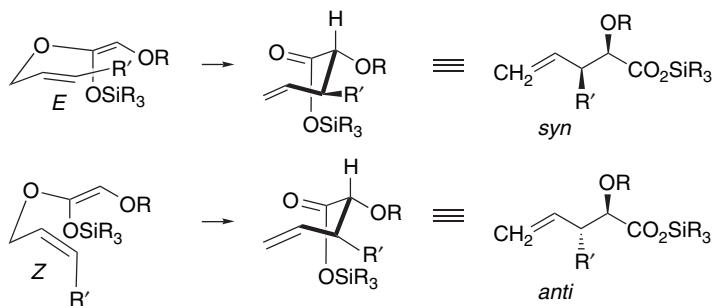


Fig. 6.14. Possible transition structures for [3,3]-sigmatropic rearrangement of 2-cyclohexenyl ester enol ethers. Adapted from *J. Org. Chem.*, **68**, 572 (2003), by permission of the American Chemical Society.

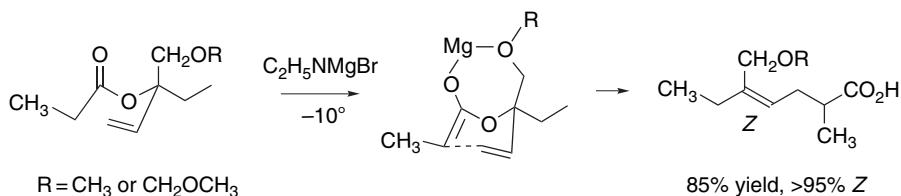
²⁴⁵ M. M. Khaledy, M. Y. S. Kalani, K. S. Khuong, K. N. Houk, V. Aviyente, R. Neier, N. Soldermann, and J. Velker, *J. Org. Chem.*, **68**, 572 (2003).



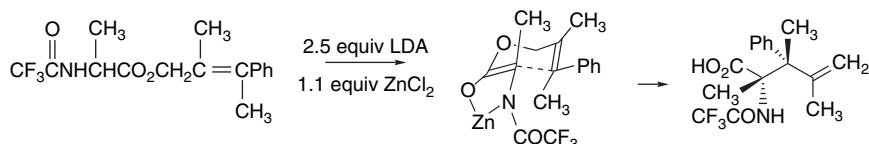
The configuration at the newly formed C–C bond is then controlled by the stereochemistry of the double bond in the allylic alcohol. The *E*-isomer gives a *syn* orientation, whereas the *Z*-isomer gives rise to *anti* stereochemistry.²⁴⁷



Similar chelation effects are present in α -alkoxymethyl derivatives. Magnesium enolates give predominantly the *Z*-enolate as a result of this chelation. The corresponding trimethylsilyl ketene acetals give *E,Z* mixtures.²⁴⁸



Enolates of allyl esters of α -amino acids are also subject to chelation-controlled Claisen rearrangement.²⁴⁹



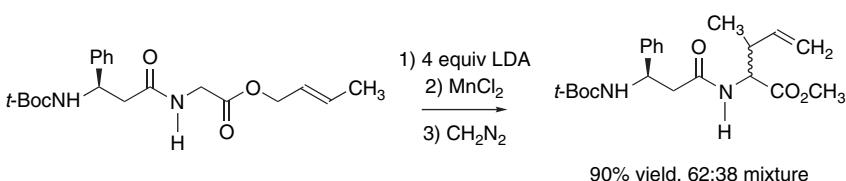
²⁴⁶ H. Frauenrath, in *Stereoselective Synthesis*, G. Helmchen, R. W. Hoffmann, J. Mulzer, and E. Schaumann, eds., Georg Thieme Verlag, Stuttgart, 1996.

²⁴⁷ T. J. Gould, M. Balestra, M. D. Wittman, J. A. Gary, L. T. Rossano, and J. Kallmerten, *J. Org. Chem.*, **52**, 3889 (1987); S. D. Burke, W. F. Fobare, and G. J. Pacofsky, *J. Org. Chem.*, **48**, 5221 (1983); P. A. Bartlett, D. J. Tanzella, and J. F. Barstow, *J. Org. Chem.*, **47**, 3941 (1982).

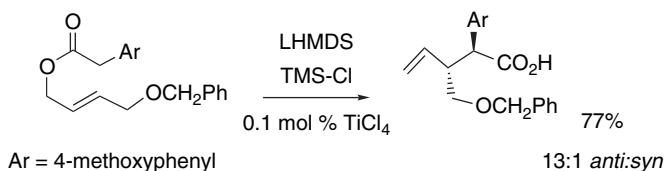
²⁴⁸ M. E. Krafft, O. A. Dasse, S. Jarrett, and A. Fierge, *J. Org. Chem.*, **60**, 5093 (1995).

²⁴⁹ U. Kazmaier, *Liebigs Ann. Chem.*, 285 (1997); U. Kazmaier, *J. Org. Chem.*, **61**, 3694 (1996); U. Kazmaier and S. Maier, *Tetrahedron*, **52**, 941 (1996).

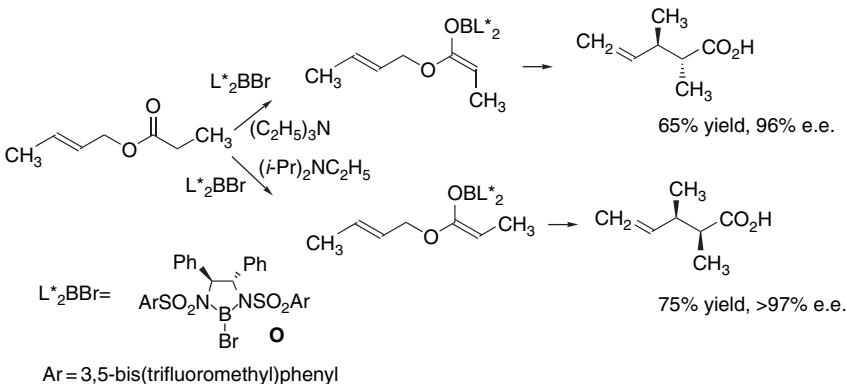
Various salts can achieve chelation but $ZnCl_2$ and $MgCl_2$ are suitable for most cases. The rearrangement is a useful reaction for preparing amino acid analogs and has also been applied to synthesis of modified dipeptides.²⁵⁰



Lewis acid catalysis of Ireland-Claisen rearrangements by $TiCl_4$ has been observed.²⁵¹ This methodology was employed in the synthesis of a novel type of anti-inflammatory drug candidate.²⁵²



The possibility of using chiral auxiliaries or chiral catalysts to achieve enantioselective Claisen rearrangements has been explored.²⁵³ One approach is to use chiral boron enolates. For example, enolates prepared with the chiral diazaborolidine bromide **O** lead to rearranged products of more than 95% enantiomeric excess.²⁵⁴



The enantioselectivity is consistent with a chairlike TS in which the stereocenters control the rotational preference for the sulfonyl groups that provide stereodifferentiation at the boron center.

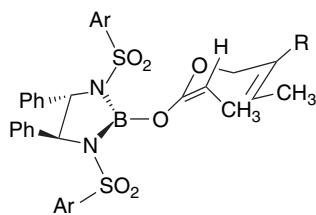
²⁵⁰ U. Kazmaier and S. Maier, *J. Chem. Soc., Chem. Commun.*, 2535 (1998).

²⁵¹ G. Koch, P. Janser, G. Kottirsch, and E. Romero-Giron, *Tetrahedron Lett.*, **43**, 4837 (2002).

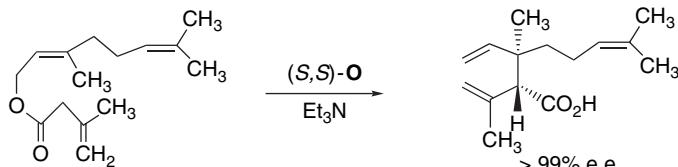
²⁵² G. Koch, G. Kottirsch, B. Wiefeld, and E. Kuesters, *Org. Proc. Res. Dev.*, **6**, 652 (2002).

²⁵³ D. Enders, M. Knopp, and R. Schiffers, *Tetrahedron: Asymmetry*, **7**, 1847 (1996).

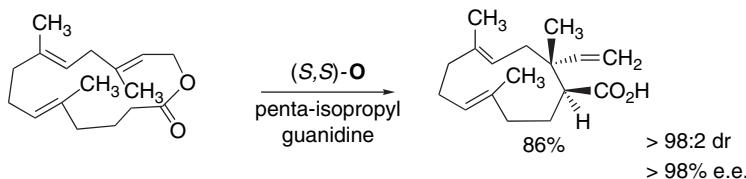
²⁵⁴ E. J. Corey and D.-H. Lee, *J. Am. Chem. Soc.*, **113**, 4026 (1991).



This methodology has been applied to both acyclic esters and macrocyclic lactones.



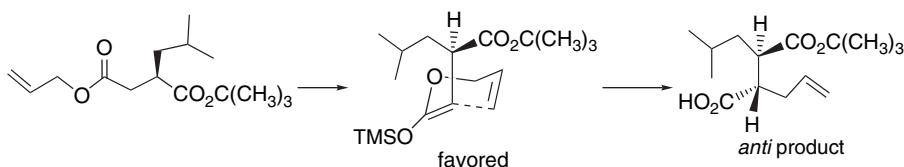
Ref. 255



Ref. 256

Scheme 6.16 gives some examples of Ireland-Claisen rearrangements of silyl ketene acetals and related intermediates. Entry 1 is an example from an early investigation of this version of the rearrangement. Entry 2 involves direct rearrangement of the enolate without silylation. The reaction in Entry 3 was used for stereoselective synthesis of the γ, δ -unsaturated acid, which was used in the synthesis of a butterfly pheromone. The TBDMS derivative gave a somewhat higher yield than the TMS derivative in this case. The reaction in Entry 4 was used in the conversion of carbohydrate-derived starting materials to structures found in ionophore antibiotics. The reaction conditions, which involved use of *premixed* LDA and TMS-Cl, were designed to avoid a competing β -elimination of the enolate by rapid silylation of the enolate.

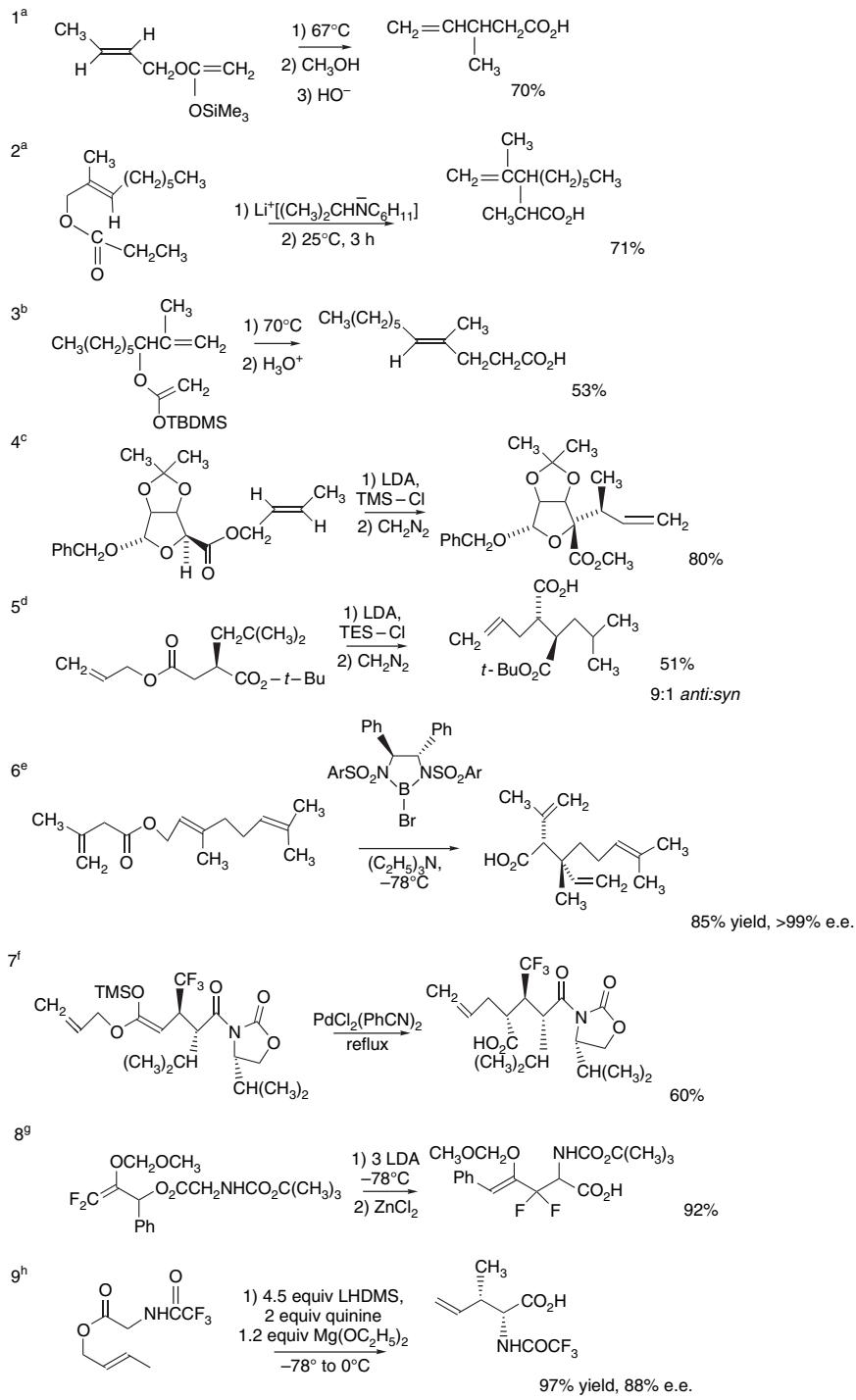
In Entry 5, the chirality at an alkylated succinate ester is maintained and a 9:1 dr favoring the *anti* product is achieved, based on a preferred orientation relative to the branched substituent.



²⁵⁵ E. J. Corey, B. E. Roberts, and B. R. Dixon, *J. Am. Chem. Soc.*, **117**, 193 (1995).

²⁵⁶ E. J. Corey and R. S. Kania, *J. Am. Chem. Soc.*, **118**, 1229 (1996).

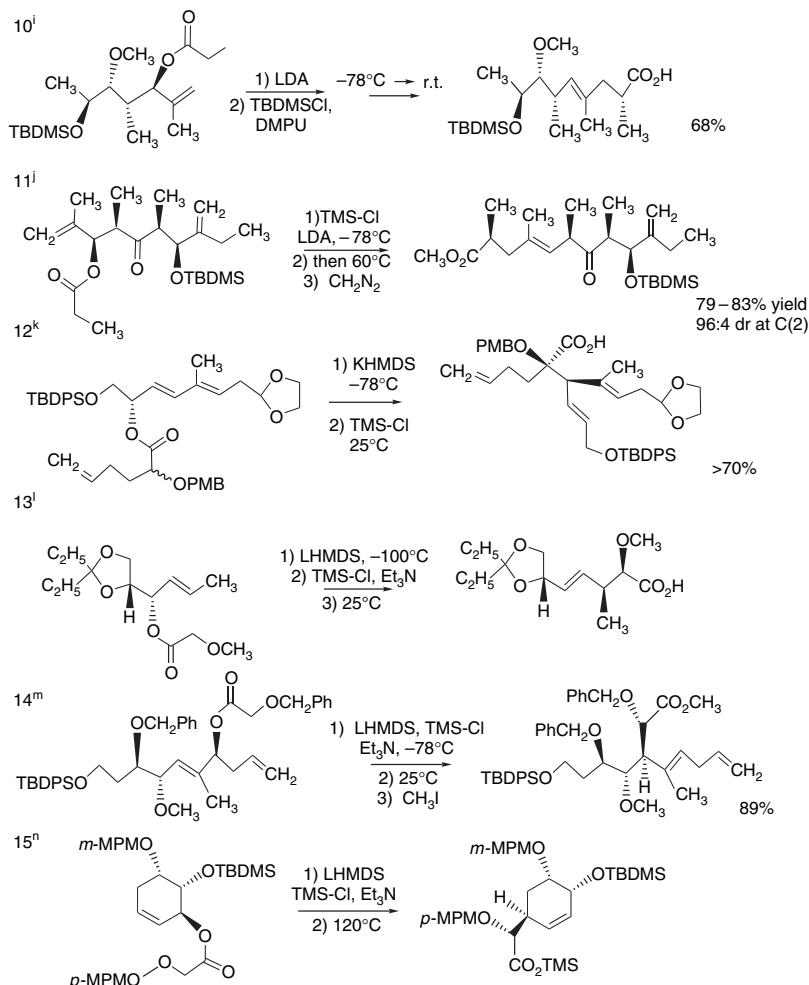
Scheme 6.16. Rearrangement of Silyl Ketene Acetals and Ester Enolates



(Continued)

Scheme 6.16. (Continued)

SECTION 6.4

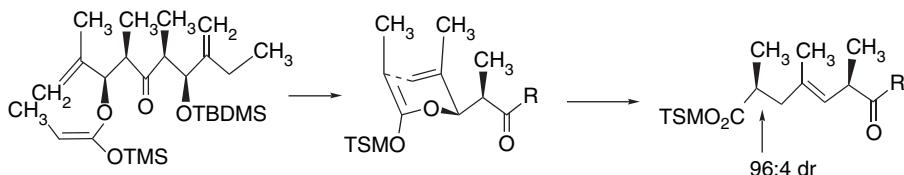
[3,3]-Sigmatropic Rearrangements

- a. R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, **98**, 2868 (1976).
- b. J. A. Katzenellenbogen and K. J. Cristy, *J. Org. Chem.*, **39**, 3315 (1974).
- c. R. E. Ireland and D. W. Norbeck, *J. Am. Chem. Soc.*, **107**, 3279 (1985).
- d. L. M. Pratt, S. A. Bowler, S. F. Courtney, C. Hidden, C. N. Lewis, F. M. Martin, and R. S. Todd, *Synlett*, 531 (1998).
- e. E. J. Corey, B. E. Roberts, and B. R. Dixon, *J. Am. Chem. Soc.*, **117**, 193 (1995).
- f. T. Yamazaki, N. Shinohara, T. Katzume, and S. Sato, *J. Org. Chem.*, **60**, 8140 (1995).
- g. J. M. Percy, M.E. Prime, and M J. Broadhurst, *J. Org. Chem.*, **63**, 8049 (1998).
- h. A. Kazmaier and A. Krebs, *Tetrahedron Lett.*, **40**, 479 (1999).
- i. P. R. Blakemore, P. J. Kocienski, A. Morley, and K. Muir, *J. Chem. Soc., Perkin Trans. 1*, 955 (1999).
- j. I. Paterson and A. N. Hulme, *J. Org. Chem.*, **60**, 3288 (1995).
- k. O. Bedell, A. Haudrecky, and Y. Langlois, *Eur. J. Org. Chem.*, 3813 (2004).
- l. S. D. Burke, J. Hong, J. R. Lennox, and A. P. Mongin, *J. Org. Chem.*, **63**, 6952 (1998).
- m. D. Kim, S. K. Ahn, H. Bae, W. J. Choi, and H. S. Kim, *Tetrahedron Lett.*, **38**, 4437 (1997).
- n. S. D. Burke, J. J. Letourneau, and M. Matulenko, *Tetrahedron Lett.*, **40**, 9 (1999).

Entry 6 is an example of application of the chiral diazaborolidine enolate method (see p. 572). Entry 7 involves generation of the silyl ketene acetal by silylation after conjugate addition of the enolate of 3-methylbutanoyloxazolidinone to allyl 3,3,3-trifluoroprop-2-enoate. A palladium catalyst improved the yield in the rearrangement

step. Entry 8 involves another fluorinated reactant. The reaction is an adaptation of the rearrangement of α -amido ester enolates, as discussed on p. 572, and involves a chelated enolate. Entry 9 is another example of this type of reaction. Use of quinine or quinidine with the chelating metal leads to enantioselectivity.

Entries 10 to 15 involve use of the Ireland-Claisen rearrangement in multistep syntheses. An interesting feature of Entry 11 is the presence of an unprotected ketone. The reaction was done by adding LDA to the ester, which was premixed with TMS-Cl and Et₃N. The reaction generates the *E*-silyl ketene acetal, which rearranges through a chair TS.

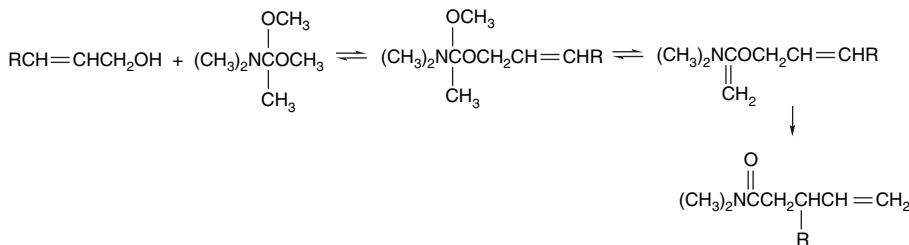


Entries 12 to 15 are examples of α -alkoxy (protected glycolate) esters. These reactions proceed through chelated TSs. (See the discussion on p. 571.) The TS for Entries 13 and 14 are shown below.



Entry 15 also demonstrates the suprafacial specificity with a cyclic allylic alcohol.

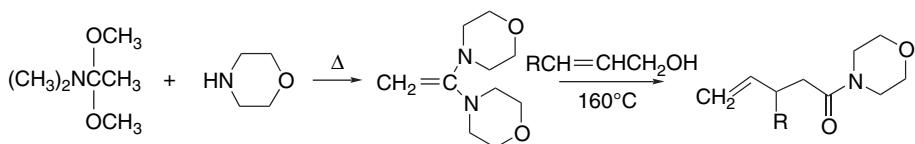
6.4.2.4. Claisen Rearrangements of Ketene Aminals and Imidates. A reaction that is related to the orthoester Claisen rearrangement utilizes an amide acetal, such as dimethylacetamide dimethyl acetal, in the exchange reaction with allylic alcohols.²⁵⁷ The products are γ , δ -unsaturated amides. The stereochemistry of the reaction is analogous to the other variants of the Claisen rearrangement.²⁵⁸



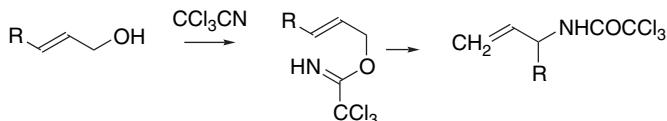
²⁵⁷ A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, **47**, 2425 (1964); D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, **52**, 1030 (1969).

²⁵⁸ W. Sucrow, M. Slopianka, and P. P. Calderia, *Chem. Ber.*, **108**, 1101 (1975).

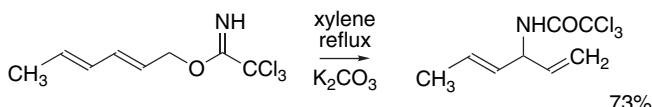
The rearrangement can be applied to other secondary amines by prior equilibration, which is driven forward by removal of the more volatile dimethylamine.²⁵⁹



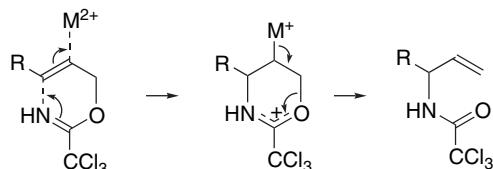
O-Allyl imide esters undergo [3,3]-sigmatropic rearrangements to *N*-allyl amides. Trichloromethyl imides can be made easily from allylic alcohols by reaction with trichloroacetonitrile. The rearrangement then provides trichloroacetamides of *N*-allylamines.²⁶⁰



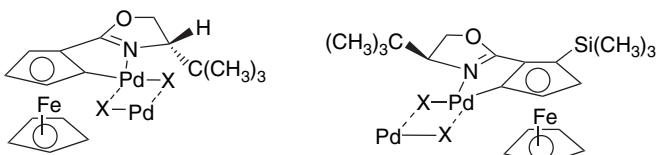
Yields in the reaction are sometimes improved by inclusion of K₂CO₃ in the reaction mixture.²⁶¹



Trifluoromethyl imides show similar reactivity.²⁶² Imide rearrangements are catalyzed by palladium salts.²⁶³ The mechanism is presumably similar to that for the Cope rearrangement (see p. 555).



Chiral Pd catalysts can achieve enantioselectivity. The best catalysts developed to date are dimeric ferrocenyl derivatives.²⁶⁴



^{259.} S. N. Gradl, J. J. Kennedy-Smith, J. Kim, and D. Trauner, *Synlett*, 411 (2002).

^{260.} L. E. Overman, *J. Am. Chem. Soc.*, **98**, 2901 (1976); L. E. Overman, *Acc. Chem. Res.*, **13**, 218 (1980).

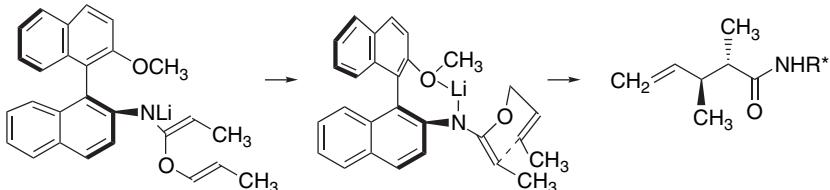
^{261.} T. Nishikawa, M. Asai, N. Ohayabu, and M. Isobe, *J. Org. Chem.*, **63**, 188 (1998).

^{262.} A. Chen, J. Savage, E. D. Thomas, and P. D. Wilson, *Tetrahedron Lett.*, **34**, 6769 (1993).

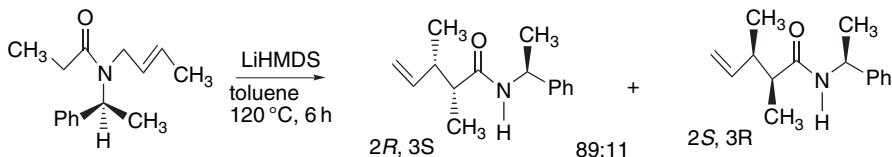
^{263.} L. E. Overman, *Angew. Chem. Int. Ed. Engl.*, **23**, 579 (1984); T. G. Schenck and B. Bosnich, *J. Am. Chem. Soc.*, **107**, 2058 (1985); P. Metz, C. Mues, and A. Schoop, *Tetrahedron*, **48**, 1071 (1992).

^{264.} Y. Donde and L. E. Overman, *J. Am. Chem. Soc.*, **121**, 2933 (1999).

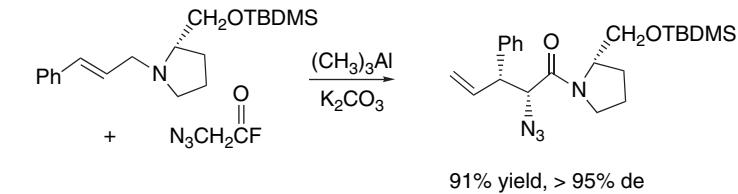
Imidate esters can also be generated by reaction of imidoyl chlorides and allylic alcohols. The lithium anions of these imidates, prepared using lithium diethylamide, rearrange at around 0°C. When a chiral amine is used, this reaction can give rise to enantioselective formation of γ, δ -unsaturated amides. Good results were obtained with a chiral binaphthylamine.²⁶⁵ The methoxy substituent is believed to play a role as a Li⁺ ligand in the reactive enolate.



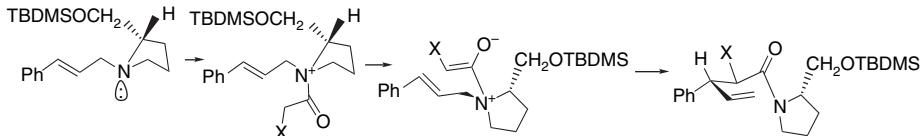
Enolates of *N*-allyl amides undergo [3,3]-sigmatropic rearrangement. This reaction is analogous to the ester enolate Claisen rearrangement, but the conditions required are more vigorous.²⁶⁶ An attractive feature of this reaction is that it permits introduction of a chiral group at nitrogen, which then has the potential to effect enantioselective formation of a new C–C bond. For example, α -arylethyl substituents induced enantioselectivity ranging from 3:1 to 11:1.



Analogous rearrangement occurs under much milder conditions when the reactant is a zwitterion generated by deprotonation of an acylammonium ion. Substituted pyrrolidines were used as the chiral auxiliary, with the highest enantioselectivity being achieved with a 2-TBDMS derivative.²⁶⁷



The preferred TS is a chair with the enolate oriented *syn* to the bulky pyrrolidine substituent. It was suggested that the *syn* acylation occurs through an envelope conformation of the pyrrolidine ring with the nitrogen electron pair oriented axially.

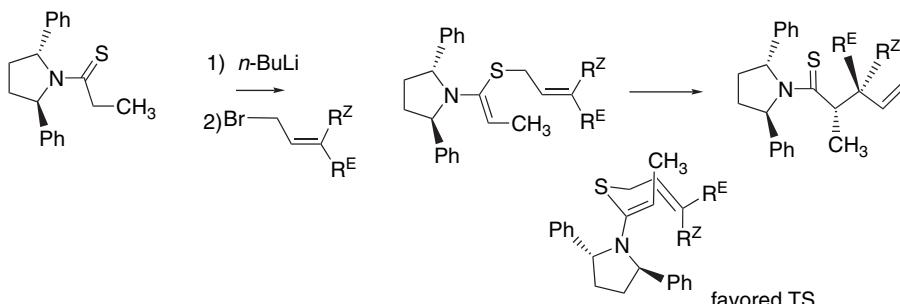


²⁶⁵ P. Metz and B. Hungerhoff, *J. Org. Chem.*, **62**, 4442 (1997).

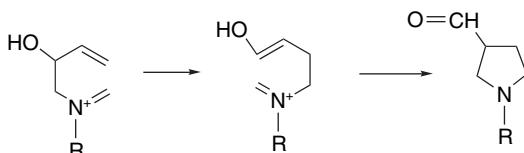
²⁶⁶ T. Tsunoda, M. Sakai, O. Sasaki, Y. Sato, Y. Hondo, and S. Ito, *Tetrahedron Lett.*, **33**, 1651 (1992).

²⁶⁷ S. Laabs, W. Munch, J.-W. Bats, and U. Nubbemeyer, *Tetrahedron*, **58**, 1317 (2002).

Another promising variant involves thioamides, which provide Z-thioenolates on deprotonation.²⁶⁸ Use of *trans*-2,4-diphenylpyrrolidine as the chiral auxiliary leads to good enantioselectivity.²⁶⁹ Allyl groups with *E*-configuration give mainly *anti* products with somewhat reduced diastereoselectivity. These results indicate that a steric interaction between the pyrrolidine substituent and the *Z*-allyl group is a controlling factor in diastereoselectivity.



The 2-azonia analog of the Cope rearrangement is estimated to be accelerated by 10^6 , relative to the unsubstituted system.²⁷⁰ The product of the rearrangement is an isomeric iminium ion, which is a mild electrophile. In synthetic applications, the reaction is often designed to generate this electrophilic site in a position that can lead to a cyclization by reaction with a nucleophilic site. For example, the presence of a 4-hydroxy substituent generates an enol that can react with the iminium ion intermediate to form a five-membered ring.²⁷¹



Scheme 6.17 gives some examples of the orthoamide and imidate versions of the Claisen rearrangement. Entry 1 applied the reaction in the synthesis of a portion of the alkaloid tabersonine. The reaction in Entry 2 was used in an enantiospecific synthesis of pravastatin, one of a family of drugs used to lower cholesterol levels. The product from the reaction in Entry 3 was used in a synthesis of a portion of the antibiotic rampamycin. Entries 4 and 5 were used in the synthesis of polycyclic natural products. Note that the reaction in Entry 4 also leads to isomerization of the double bond into conjugation with the ester group. Entries 1 to 5 all involve cyclic reactants, and the concerted TS ensures that the substituent is introduced *syn* to the original hydroxy substituent.

Entry 6 is analogous to a silyl ketene acetal rearrangement. The reactant in this case is an imide. Entry 7 is an example of $PdCl_2$ -catalyzed imidate rearrangement. Entry 8 is an example of an azonia-Cope rearrangement, with the monocyclic intermediate then undergoing an intramolecular Mannich condensation. (See Section 2.2.1 for a discussion of the Mannich reaction). Entry 9 shows a thioimidate rearrangement.

^{268.} Y. Tamaru, Y. Furukawa, M. Mizutani, O. Kitao, and Z. Yoshida, *J. Org. Chem.*, **48**, 3631 (1983).

^{269.} S. He, S. A. Kozmin, and V. H. Rawal, *J. Am. Chem. Soc.*, **122**, 190 (2000).

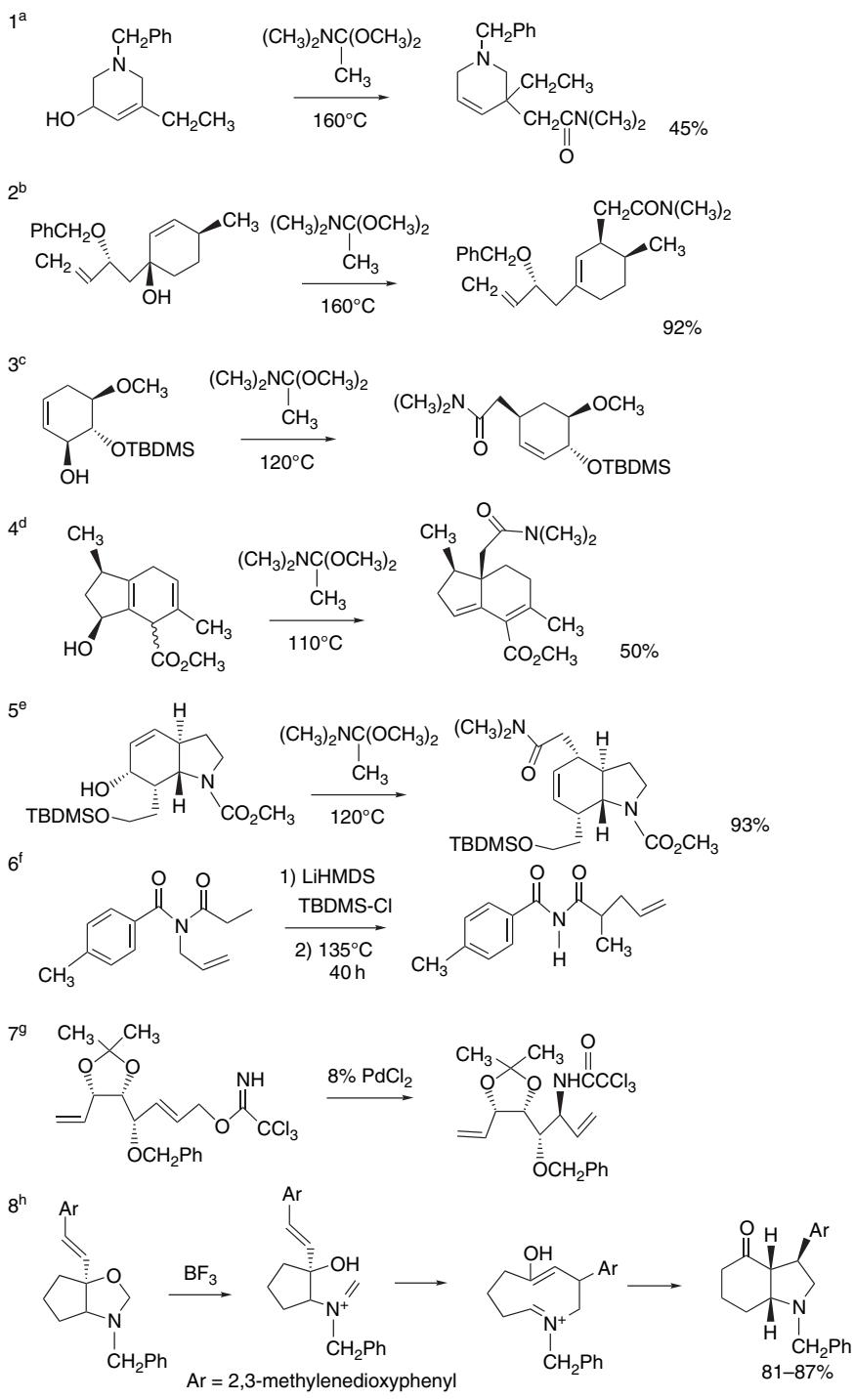
^{270.} L. A. Overman, *Acc. Chem. Res.*, **25**, 353 (1992).

^{271.} L. E. Overman and M. Kakimoto, *J. Am. Chem. Soc.*, **101**, 1310 (1979); L. E. Overman, M. Kakimoto, M. Okazaki, and G. P. Meier, *J. Am. Chem. Soc.*, **105**, 6622 (1983).

Scheme 6.17. Rearrangements of Orthoamides and Imides

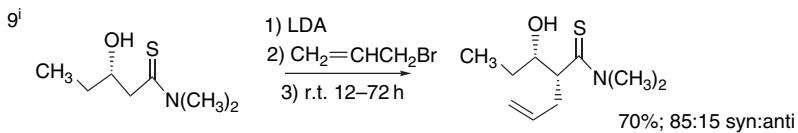
CHAPTER 6

*Concerted
Cycloadditions,
Unimolecular
Rearrangements, and
Thermal Eliminations*



(Continued)

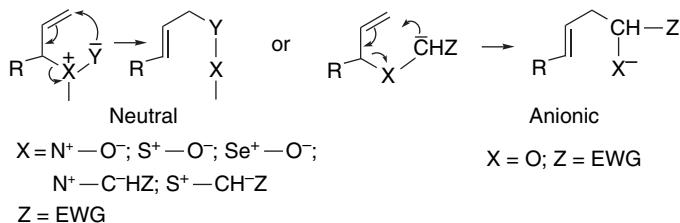
Scheme 6.17. (Continued)



- a. F. E. Ziegler and G. B. Bennett, *J. Am. Chem. Soc.*, **95**, 7458 (1973).
- b. A. R. Danielski, P. M. Wovkulich, and M. R. Uskokovic, *J. Org. Chem.*, **57**, 7133 (1992).
- c. K. C. Nicolaou, P. Bertinato, A. D. Piscopio, T. K. Chakraborty, and N. Minowa, *J. Chem. Soc., Chem. Commun.*, 619 (1993).
- d. T.-P. Loh and Q.-Y. Hu, *Org. Lett.*, **3**, 279 (2001).
- e. C.-Y. Chen and D. J. Hart, *J. Org. Chem.*, **58**, 3840 (1993).
- f. K. Neuschutz, J.-M. Simone, T. Thyrann, and R. Neier, *Helv. Chim. Acta*, **83**, 2712 (2000).
- g. H. Ovaa, J. D. C. Codee, B. Lastdrager, H. Overkleft, G. A. van der Marel, and J. H. van Boom, *Tetrahedron Lett.*, **40**, 5063 (1999).
- h. L. E. Overman and J. Shim, *J. Org. Chem.*, **58**, 4662 (1993).
- i. P. Beslin and B. Lelong, *Tetrahedron*, **53**, 17253 (1997).

6.5. [2,3]-Sigmatropic Rearrangements

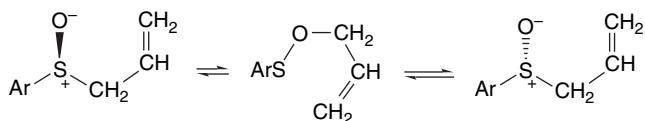
The [2,3]-sigmatropic class of rearrangements is represented by two generic charge types, neutral and anionic.



The rearrangements of allylic sulfoxides, selenoxides, and amine oxides are an example of the first type. Allylic sulfonium ylides and ammonium ylides also undergo [2,3]-sigmatropic rearrangements. Rearrangements of carbanions of allylic ethers are the major example of the anionic type. These reactions are considered in the following sections.

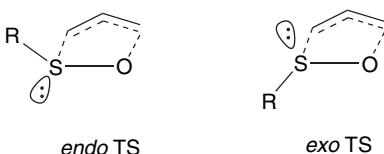
6.5.1. Rearrangement of Allylic Sulfoxides, Selenoxides, and Amine Oxides

The rearrangement of allylic sulfoxides to allylic sulfenates was first studied in connection with the mechanism of racemization of allyl aryl sulfoxides.²⁷² Although the allyl sulfoxide structure is strongly favored at equilibrium, rearrangement through the achiral allyl sulfenate provides a low-energy pathway for racemization.

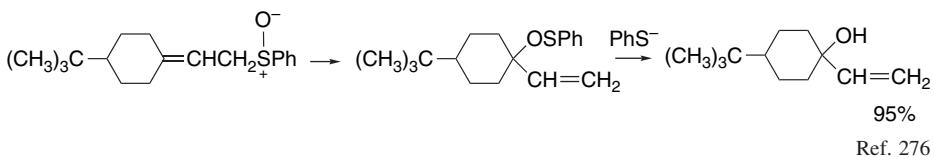


²⁷² R. Tang and K. Mislow, *J. Am. Chem. Soc.*, **92**, 2100 (1970).

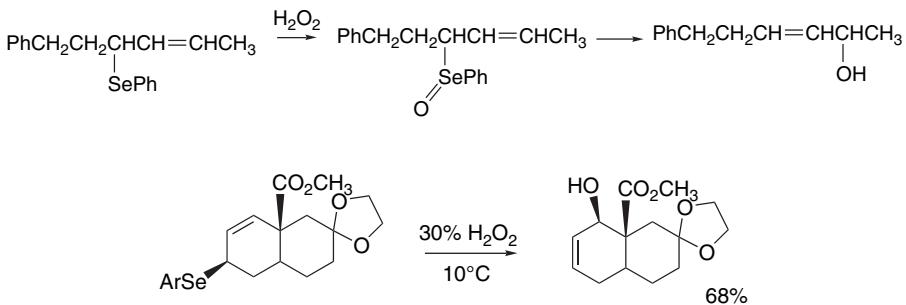
The reactions occur preferentially though an *endo* TS in which the sulfur substituent is oriented toward the allylic group.²⁷³ Computational studies (MP2/6-31G*) found the *endo* TS to be favored over the *exo* by 1.5–2.2 kcal/mol.²⁷⁴



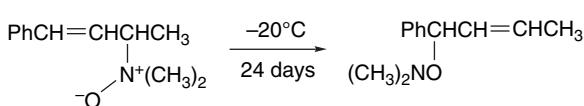
The allyl sulfoxide–allyl sulfenate rearrangement can be used to prepare allylic alcohols.²⁷⁵ The reaction is carried out in the presence of a reagent, such as phenylthiolate or trimethyl phosphite, that reacts with the sulfenate to cleave the S–O bond.



An analogous reaction occurs when allylic selenoxides are generated *in situ* by oxidation of allylic selenyl ethers.²⁷⁷



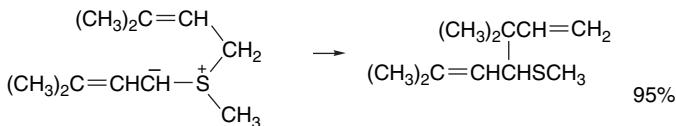
N-Allylamine oxides represent the general pattern for [2,3]-sigmatropic rearrangement where X = N and Y = O[−]. The rearrangement provides *O*-allyl hydroxylamine derivatives.



Ref. 279

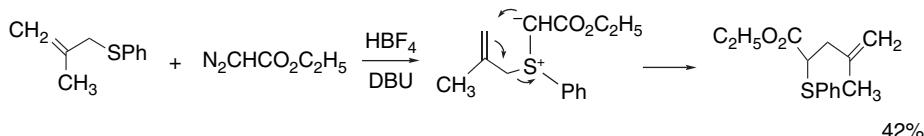
- ²⁷³ P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Am. Chem. Soc.*, **90**, 4869 (1968).
- ²⁷⁴ D. K. Jones-Hertzog and W. L. Jorgensen, *J. Am. Chem. Soc.*, **117**, 9077 (1995).
- ²⁷⁵ D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).
- ²⁷⁶ D. A. Evans, G. C. Andrews, and C. L. Sims, *J. Am. Chem. Soc.*, **93**, 4956 (1971).
- ²⁷⁷ H. J. Reich, *J. Org. Chem.*, **40**, 2570 (1975); D. L. J. Clive, G. Chittattu, N. J. Curtis, and S. M. Menchen, *Chem. Commun.*, 770 (1978).
- ²⁷⁸ P. A. Zoretic, R. J. Chambers, G. D. Marbury, and A. A. Riebiro, *J. Org. Chem.*, **50**, 2981 (1985).
- ²⁷⁹ Y. Yamamoto, J. Oda, and Y. Inouye, *J. Org. Chem.*, **41**, 303 (1976).

Allylic sulfonium ylides readily undergo [2,3]-sigmatropic rearrangement.²⁸⁰ The ylides are usually formed by deprotonation of the *S*-allyl sulfonium salts.

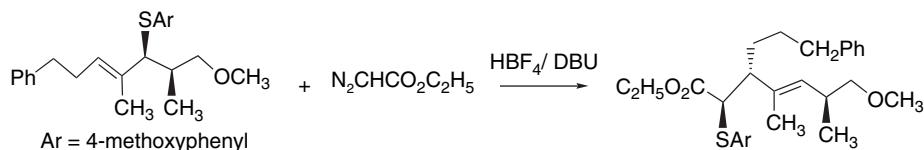


The reaction proceeds best when the ylide has a carbanion-stabilizing substituent. This reaction results in carbon–carbon bond formation and has found synthetic application in ring-expansion sequences for generation of medium-sized rings.

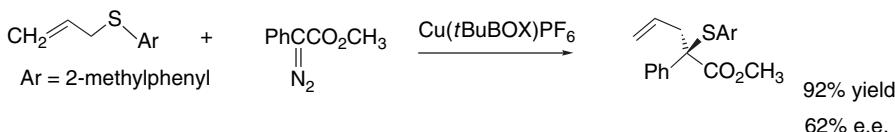
Sulfonium ylides can also be generated by *in situ* alkylation with diazo compounds. The alkylation can be carried out by reaction of a diazo compound with HBF₄ and DBU.²⁸¹ The reagents are added alternately in small portions and the reaction presumably proceeds by trapping of the carbocation generated by dediazonation and deprotonation.



Reactions of this type lead to preferential formation of the *anti* stereochemistry at the new C–C bond.



Sulfonium ylides can also be generated from diazo compounds under carbeneoid conditions by using metal catalysts. (See Section 10.2.3.2 for discussion of this means of carbene generation.) The reaction results in transposition of the ester fragment and the sulfide group to the γ -carbon of the allylic group. This reaction has been investigated using chiral catalysts such as Cu(*t*-BuBOX)PF₆. Modest enantioselectivity has been achieved using ethyl diazoacetate²⁸² and methyl phenyldiazoacetate²⁸³ as the carbene precursors.



²⁸⁰ J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *Chem. Commun.*, 537 (1968).

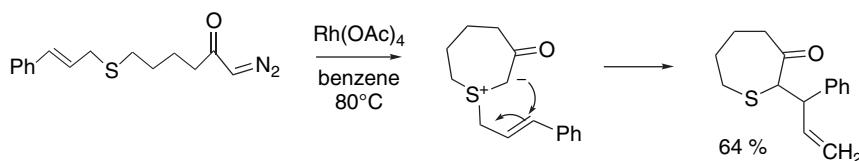
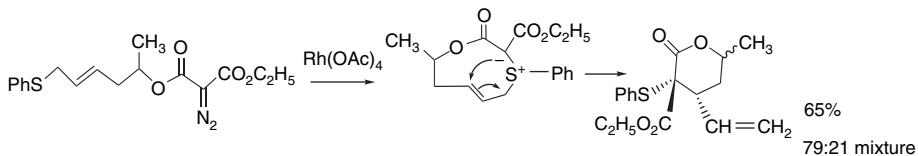
²⁸¹ M. J. Kurth, S. H. Tahir, and M. M. Olmstead, *J. Org. Chem.*, **55**, 2286 (1990); R. C. Hartley, S. Warren, and I. C. Richards, *J. Chem. Soc., Perkin Trans. 1*, 507 (1994).

²⁸² D. W. McMillen, N. Varga, B. A. Reed, and C. King, *J. Org. Chem.*, **65**, 2532 (2000).

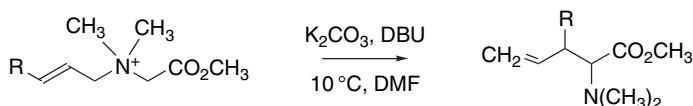
²⁸³ X. Zhang, Z. Qu, Z. Ma, W. Shi, X. Jin, and J. Wang, *J. Org. Chem.*, **67**, 5621 (2002).

CHAPTER 6

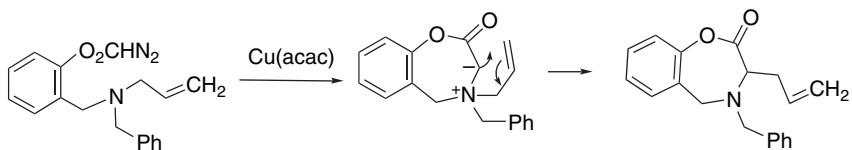
*Concerted
Cycloadditions,
Unimolecular
Rearrangements, and
Thermal Eliminations*



Ammonium ylides can also be generated when one of the nitrogen substituents has an anion stabilizing group on the α -carbon. For example, quaternary salts of *N*-allyl α -aminoesters readily rearrange to γ,δ -unsaturated α -aminoesters.²⁸⁶



Ammonium ylides can also be generated by the carbenoid route.



Ref. 287

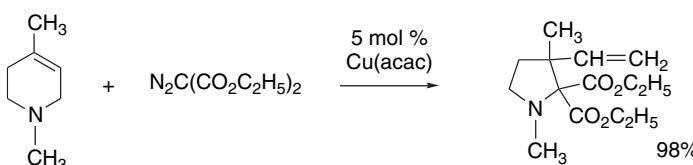
Copper-catalyzed reactions are particularly effective with α -diazo- β -dicarbonyl compounds such as diethyl diazomalonate.

²⁸⁴ F. Kido, S. C. Sinha, T. Abiko, M. Watanabe, and A. Yoshikoshi, *Tetrahedron*, **46**, 4887 (1990).

²⁸⁵ C. J. Moody and R. J. Taylor, *Tetrahedron*, **46**, 6501 (1990).

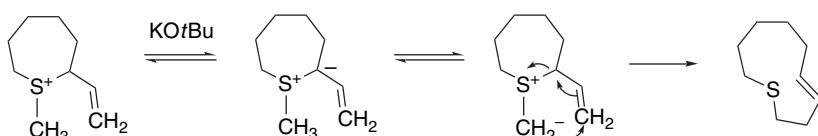
²⁸⁶ I. Coldham, M. L. Middleton, and P. L. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2951 (1997); I. Coldham, M. L. Middleton, and P. L. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 2817 (1998).

²⁸⁷ J. S. Clark and M. L. Middleton, *Org. Lett.*, **4**, 765 (2002).

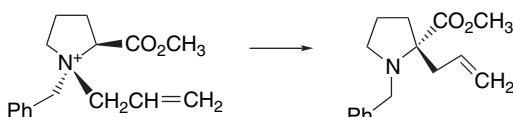


Ref. 288

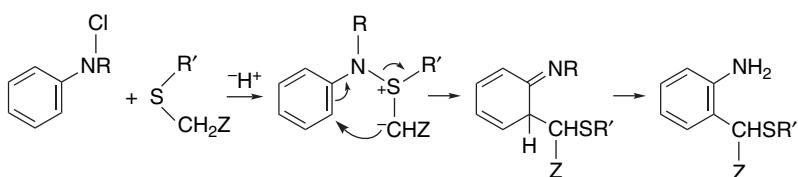
Scheme 6.18 illustrates typical reaction conditions for [2,3]-sigmatropic rearrangements of sulfonium and ammonium ylides. The reactant sulfonium salt used in Entry 1 is generated by alkylation of ethyl methylthioacetate and rearrangement occurs in the presence of potassium carbonate. Entries 2 and 3 show ring-expansion reactions. The reactant in Entry 2 has no activating group and the reaction presumably proceeds through a small equilibrium concentration of the methylide.



Entries 5 to 8 involve ammonium ylides. These reactions effect an N to C transfer of the substituent with 1,3-allylic transposition. In the case of Entry 7, the anionic stabilization is provided by a vinylogous ester group. The reaction in Entry 8 begins with N-allylation, which takes place *syn* to the ester group because of the *trans* orientation of the ester and benzyl groups, and the chirality is thereby induced at the nitrogen atom. The [2,3]-rearrangement then transfers chirality to C(2) of the pyrrolidine ring.



A useful method for *ortho*-alkylation of aromatic amines is based on [2,3]-sigmatropic rearrangement of *S*-anilinosulfonium ylides. These ylides are generated from anilinosulfonium ions, which can be prepared from *N*-chloroanilines and sulfides.²⁸⁹



This method is the basis for synthesis of nitrogen-containing heterocyclic compounds when Z is a carbonyl-containing substituent.²⁹⁰

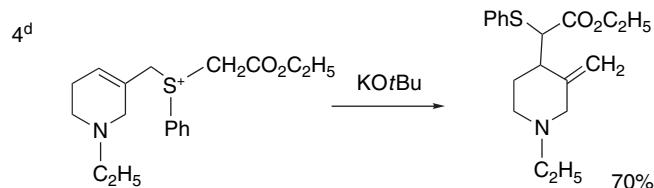
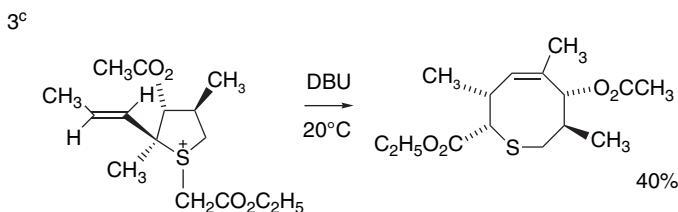
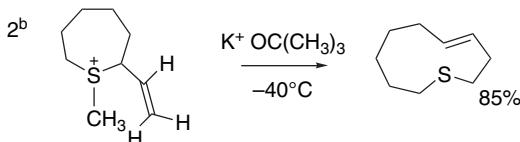
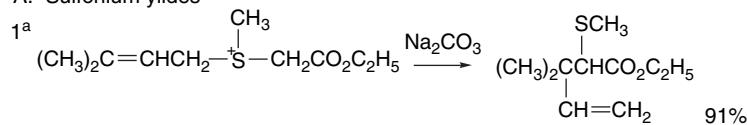
²⁸⁸ E. Roberts, J. P. Sancon, J. B. Sweeney, and J. A. Workman, *Org. Lett.*, **5**, 4775 (2003).

²⁸⁹ P. G. Gassman and G. D. Gruetzmacher, *J. Am. Chem. Soc.*, **96**, 5487 (1974); P. G. Gassman and H. R. Drewes, *J. Am. Chem. Soc.*, **100**, 7600 (1978).

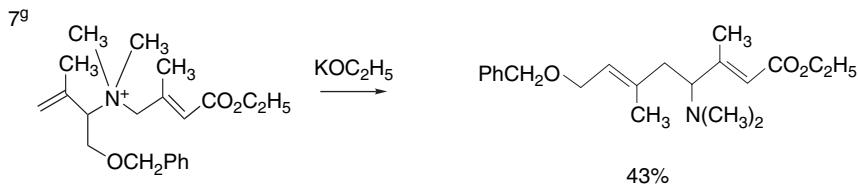
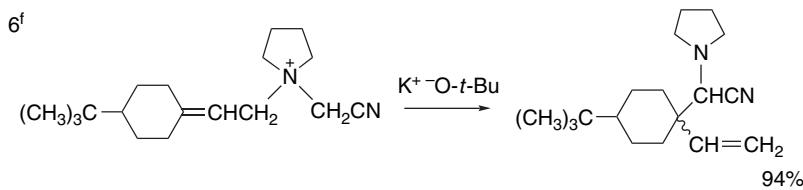
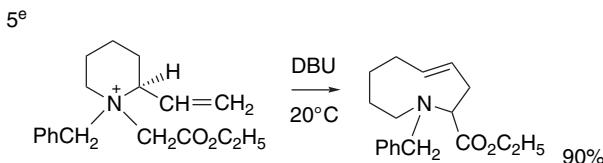
²⁹⁰ P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, Jr., *J. Am. Chem. Soc.*, **96**, 5495 (1974); P. G. Gassman and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5508 (1974); P. G. Gassman, G. Gruetzmacher, and T. J. van Bergen, *J. Am. Chem. Soc.*, **96**, 5512 (1974).

Scheme 6.18. Carbon-Carbon Bond Formation via [2,3]-Sigmatropic Rearrangements of Sulfonium and Ammonium Ylides

A. Sulfonium ylides



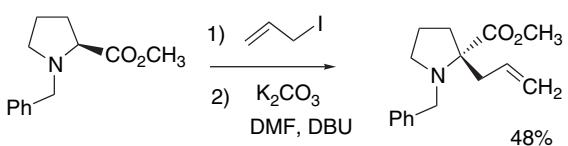
B. Ammonium ylides



(Continued)

Scheme 6.18. (Continued)

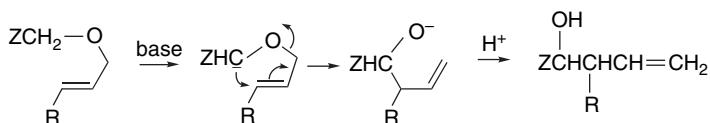
SECTION 6.5

*[2,3]-Sigmatropic Rearrangements*8^h

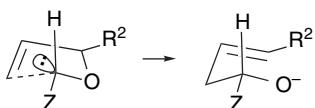
- a. K. Ogura, S. Furukawa, and G. Tsuchihashi, *J. Am. Chem. Soc.*, **102**, 2125 (1980).
- b. V. Cere, C. Paolucci, S. Pollicino, E. Sandri, and A. Fava, *J. Org. Chem.*, **43**, 4826 (1978).
- c. E. Vedejs and M. J. Mullins, *J. Org. Chem.*, **44**, 2947 (1979).
- d. R. C. Hartley, S. Warren, and I. C. Richards, *J. Chem. Soc., Perkin Trans. 2*, 507 (1994).
- e. E. Vedejs, M. J. Arco, D. W. Powell, J. M. Renga, and S. P. Singer, *J. Org. Chem.*, **43**, 4831 (1978).
- f. L. N. Mander and J. V. Turner, *Aust. J. Chem.*, **33**, 1559 (1980).
- g. K. Honda, I. Yoshii, and S. Inoue, *Chem. Lett.*, 671 (1996).
- h. A. P. A. Arbore, D. J. Cane-Honeysett, I. Coldham, and M. L. Middleton, *Synlett*, 236 (2000).

6.5.3. Anionic Wittig and Aza-Wittig Rearrangements

The [2,3]-sigmatropic rearrangement pattern is also observed with anionic species. The most important case for synthetic purposes is the *Wittig rearrangement*, in which a strong base converts allylic ethers to α -allylalkoxides.²⁹¹ Since the deprotonation at the α' -carbon must compete with deprotonation of the α -carbon in the allyl group, most examples involve a conjugated or EWG substituent Z.²⁹²



The stereochemistry of the Wittig rearrangement can be predicted in terms of a cyclic five-membered TS in which the α -substituent prefers an equatorial orientation.²⁹³



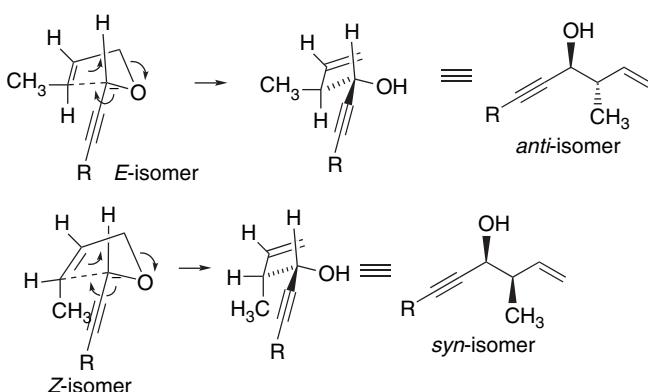
A consistent feature of the stereoselectivity is a preference for *E*-configuration at the newly formed double bond. The reaction can also show stereoselectivity at the newly formed single bond. This stereoselectivity has been carefully studied for the case in

²⁹¹ J. Kallmarten, in *Stereoselective Synthesis: Houben Weyl Methods in Organic Chemistry*, Vol E21d, R. W. Hoffmann, J. Mulzer, and E. Schaumann, eds., G. Thieme Verlag, Stuttgart, 1996, pp. 3810 ff.

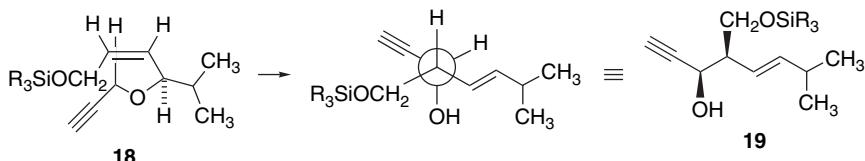
²⁹² For a review of [2,3]-sigmatropic rearrangement of allyl ethers, see T. Nakai and K. Mikami, *Chem. Rev.*, **86**, 885 (1986).

²⁹³ R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **18**, 563 (1979); K. Mikami, Y. Kimura, N. Kishi, and T. Nakai, *J. Org. Chem.*, **48**, 279 (1983); K. Mikami, K. Azuma, and T. Nakai, *Tetrahedron*, **40**, 2303 (1984); Y.-D. Wu, K. N. Houk, and J. A. Marshall, *J. Org. Chem.*, **55**, 1421 (1990).

which the substituent Z is an alkynyl group. The *E*-isomer leads to *anti* product and the *Z*-isomer to the *syn* product.

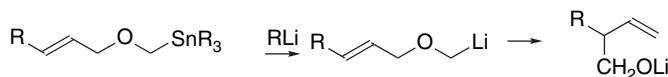


The preferred TS minimizes interaction between the Z and allylic substituents. This stereoselectivity is illustrated in the rearrangement of **18** to **19**.

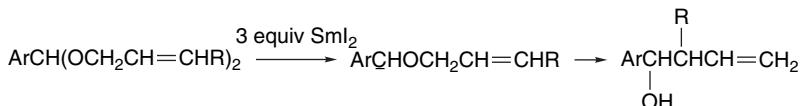


Ref. 294

There are other means of generating the anions of allyl ethers. One of the most useful for synthetic purposes involves a lithium-tin exchange on stannylmethyl ethers (see Section 7.1.2.4).²⁹⁵



Another means involves reduction of allylic acetals of aromatic aldehydes by SmI2.²⁹⁶



[2,3]-Sigmatropic rearrangements of anions of *N*-allyl amines have also been observed and are known as *aza-Wittig rearrangements*.²⁹⁷ The reaction requires anion stabilizing substituents and is favored by *N*-benzyl and by silyl or sulphenyl substituents.

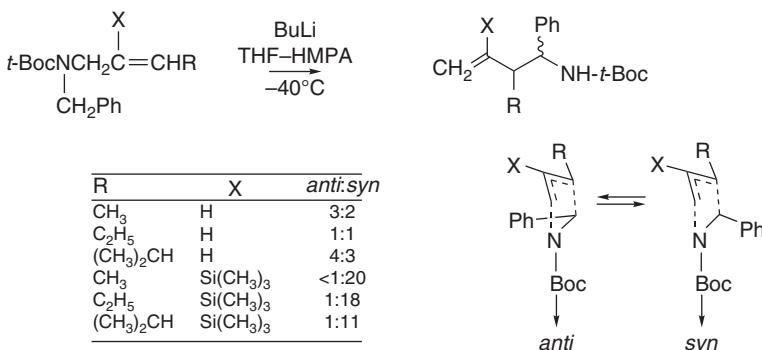
²⁹⁴ M. M. Midland and J. Gabriel, *J. Org. Chem.*, **50**, 1143 (1985).

²⁹⁵ W. C. Still and A. Mitra, *J. Am. Chem. Soc.*, **100**, 1927 (1978).

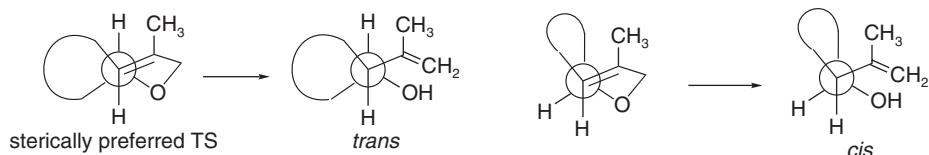
²⁹⁶ H. Hioki, K. Kono, S. Tani, and M. Kunishima, *Tetrahedron Lett.*, **39**, 5229 (1998).

²⁹⁷ C. Vogel, *Synlett*, 497 (1997).

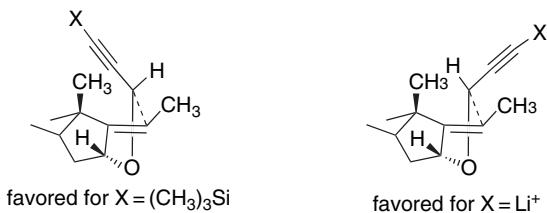
on the allyl group.²⁹⁸ The trimethylsilyl substituents can also influence the stereoselectivity of the reaction. The steric interactions between the benzyl group and allyl substituent govern the stereoselectivity and it is markedly improved in the trimethylsilyl derivatives.²⁹⁹



Some examples of synthetic application of the anionic Wittig rearrangement are given in Scheme 6.19. The reaction in Entry 1 provided a 93:7 ratio favoring the *syn* isomer, as expected for the preferred *endo* TS. Entry 2 is an example that employs the lithium-stannane exchange to generate the anion. The reaction in Entry 3 accomplishes a ring contraction. Under normal conditions, it is selective for the *trans* stereoisomer, as would be expected from steric factors in the TS. In the presence of HMPA, the *cis* isomer dominates, but the reason for the change is not known.



In Entry 4 the silyl group appears to introduce a controlling steric factor, leading to the observed stereoisomer. The unsubstituted terminal alkyne, which reacts through the dianion, gives the alternate isomer.



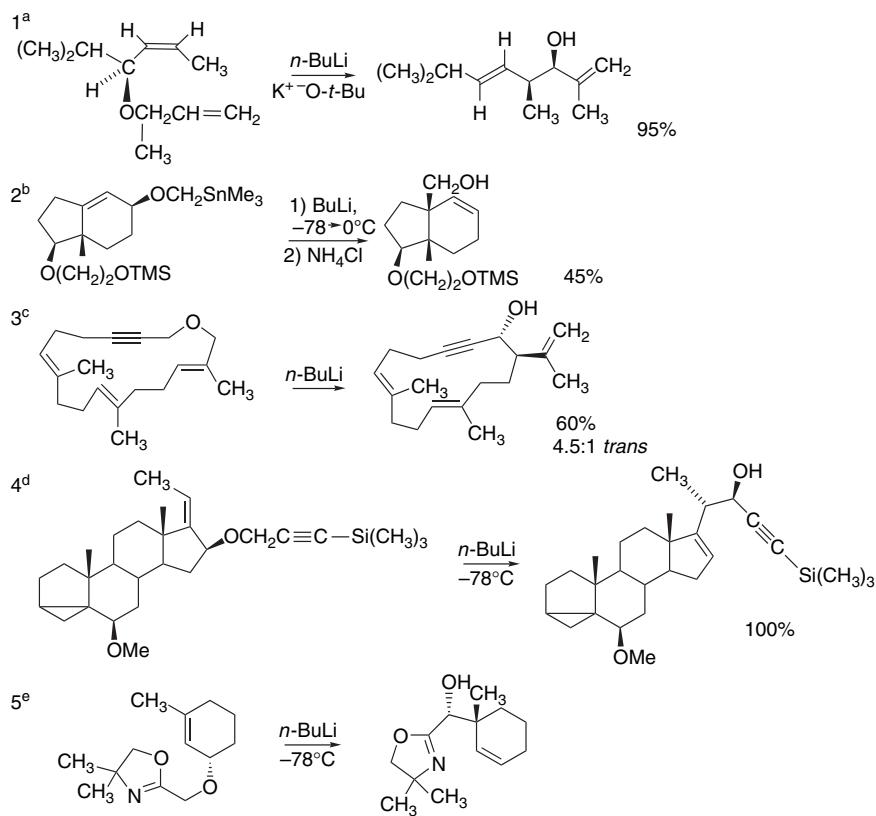
²⁹⁸ J. C. Anderson, S. C. Smith, and M. E. Swarbrick, *J. Chem. Soc., Perkin Trans. 1*, 1517 (1997).

²⁹⁹ J. C. Anderson, D. C. Siddons, S. C. Smith, and M. E. Swarbrick, *J. Org. Chem.*, **61**, 4820 (1996).

Scheme 6.19. [2,3]-Anionic Wittig Rearrangements

CHAPTER 6

*Concerted
Cycloadditions,
Unimolecular
Rearrangements, and
Thermal Eliminations*



a. D. J.-S. Tsai and M. M. Midland, *J. Am. Chem. Soc.*, **107**, 3915 (1985).

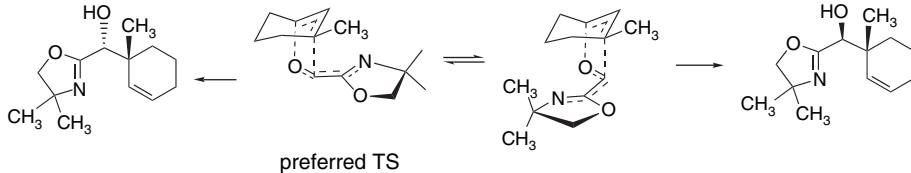
b. T. Sugimura and L. A. Paquette, *J. Am. Chem. Soc.*, **109**, 3017 (1987).

c. J. A. Marshall, T. M. Jenson, and D. S. De Hoff, *J. Org. Chem.*, **51**, 4316 (1986).

d. K. Mikami, K. Kawamoto, and T. Nakai, *Tetrahedron Lett.*, **26**, 5799 (1985).

e. M. H. Kress, B. F. Kaller, and Y. Kishi, *Tetrahedron Lett.*, **34**, 8047 (1993).

The stereoselectivity of the reaction in Entry 5 is also determined by steric factors. Note also that in this case the oxazoline ring serves to stabilize the anion.



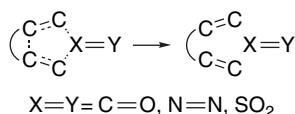
6.6. Unimolecular Thermal Elimination Reactions

This section describes reactions in which elimination to form a double bond or a new ring occurs as a result of thermal activation. There are several such thermal elimination reactions that are used in syntheses, some of which are concerted processes. The

activation energy requirements and stereochemistry of concerted elimination processes can be analyzed in terms of orbital symmetry considerations. Cheletropic eliminations are discussed in Section 6.6.1 and elimination of nitrogen from azo compounds in Section 6.6.2. We consider an important group of unimolecular β -elimination reactions in Section 6.6.3.

6.6.1. Cheletropic Elimination

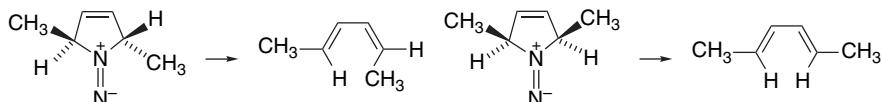
Cheletropic processes are defined as reactions in which two bonds are broken at a single atom. Concerted cheletropic reactions are subject to orbital symmetry analysis in the same way as cycloadditions and sigmatropic processes. In the elimination processes of interest here, the atom X is normally bound to other atoms in such a way that elimination gives rise to a stable molecule. In particular, elimination of SO_2 , N_2 , or CO from five-membered 3,4-unsaturated rings can be a facile process.



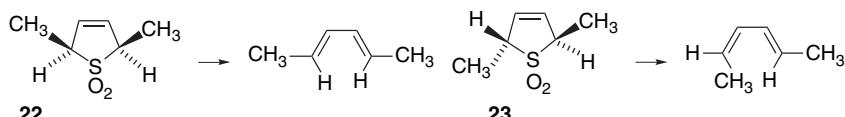
A good example of a concerted cheletropic elimination is the reaction of 3-pyrroline with *N*-nitrohydroxylamine, which gives rise to the diazene **21**, which then undergoes elimination of nitrogen.



Use of substituted systems has shown that the reaction is stereospecific.³⁰⁰ The groups on C(2) and C(5) of the pyrroline ring rotate in the disrotatory mode on going to product. This stereochemistry is consistent with conservation of orbital symmetry.



The most synthetically useful cheletropic elimination involves 2,5-dihydrothiophene-1,1-dioxides (sulfolene dioxides). At moderate temperatures they fragment to give dienes and sulfur dioxide.³⁰¹ The reaction is stereospecific. For example, the dimethyl derivatives **22** and **23** give the *E,E*- and *Z,E*-isomers of 2,4-hexadiene, respectively, at temperatures of 100°–150°C.³⁰² This stereospecificity corresponds to disrotatory elimination.

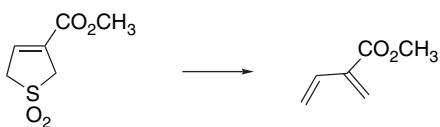


³⁰⁰ D. M. Lemal and S. D. McGregor, *J. Am. Chem. Soc.*, **88**, 1335 (1966).

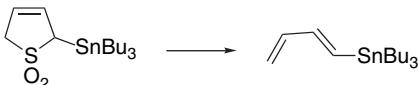
³⁰¹ W. L. Mock, in *Pericyclic Reactions*, Vol. II, A. P. Marchand and R. E. Lehr, eds., Academic Press, New York, 1977, Chap. 3.

³⁰² W. L. Mock, *J. Am. Chem. Soc.*, **88**, 2857 (1966); S. D. McGregor and D. M. Lemal, *J. Am. Chem. Soc.*, **88**, 2858 (1966).

Elimination of sulfur dioxide has proven to be a useful method for generating dienes that can undergo subsequent D-A addition.

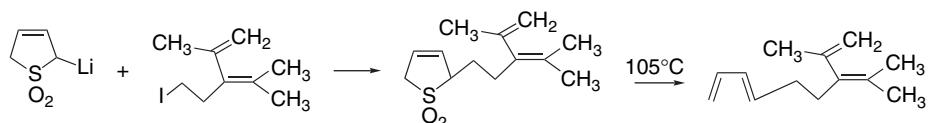


Ref. 303



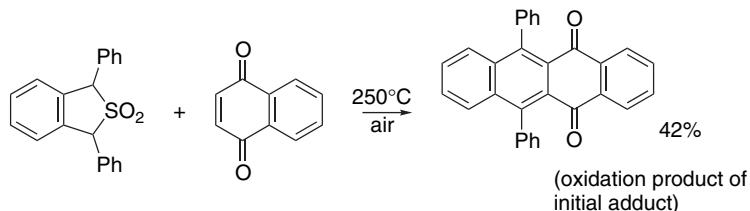
Ref. 304

Sulfolene dioxide is subject to α -lithiation and alkylation, and this reaction has been used to introduce the ring into more complex molecules.

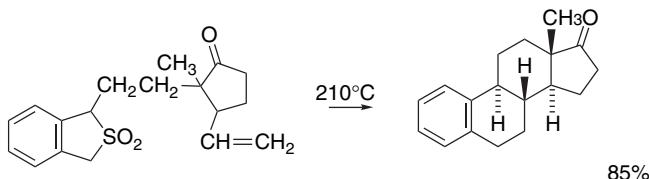


Ref. 305

Sulfolene dioxide thermolysis has also been applied to formation of *o*-quinodimethanes.



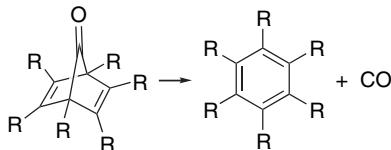
Ref. 306



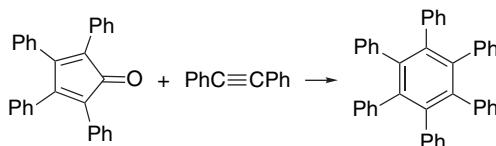
Ref. 307

- ³⁰³ J. M. McIntosh and R. A. Sieler, *J. Org. Chem.*, **43**, 4431 (1978).
- ³⁰⁴ A. M. Gomez, J. C. Lopez, and B. Fraser-Reid, *Synthesis*, 943 (1993).
- ³⁰⁵ J. D. Winkler, H. S. Kim, S. Kim, K. Ando, and K. N. Houk, *J. Org. Chem.*, **62**, 2957 (1997).
- ³⁰⁶ M. P. Cava, M. J. Mitchell, and A. A. Deana, *J. Org. Chem.*, **25**, 1481 (1960).
- ³⁰⁷ K. C. Nicolaou, W. E. Barnette, and P. Ma, *J. Org. Chem.*, **45**, 1463 (1980).

The elimination of carbon monoxide can occur by a concerted process in some cyclic ketones. The elimination of carbon monoxide from bicyclo[2.2.1]heptadien-7-ones is very facile. In fact, generation of bicyclo[2.2.1]heptadien-7-ones is usually accompanied by spontaneous decarbonylation.

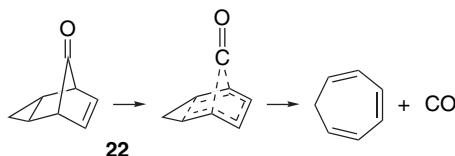


The ring system can be generated by D-A addition of a substituted cyclopentadienone and an alkyne. A reaction sequence involving addition followed by CO elimination can be used for the synthesis of highly substituted benzene rings.³⁰⁸



Ref. 309

The synthetic utility of cyclopentadienones is limited, however, because they are quite unstable. Exceptionally facile elimination of CO also takes place from **22**, in which homoaromaticity can facilitate elimination.



Ref. 310

6.6.2. Decomposition of Cyclic Azo Compounds

Another significant group of elimination reactions involves processes in which a small molecule is eliminated from a ring system and the two reactive sites that remain re-form a ring.



The most common example is decomposition of azo compounds, where $-X-Y-$ is $-N=N-$.³¹¹ The elimination of nitrogen from cyclic azo compounds can be carried

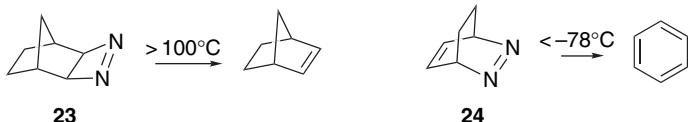
^{308.} M. A. Ogliaruso, M. G. Romanelli, and E. I. Becker, *Chem. Rev.*, **65**, 261 (1965).

^{309.} L. F. Fieser, *Org. Synth.*, **V**, 604 (1973).

^{310.} B. A. Halton, M. A. Battiste, R. Rehberg, C. L. Deyrup, and M. E. Brennan, *J. Am. Chem. Soc.*, **89**, 5964 (1967).

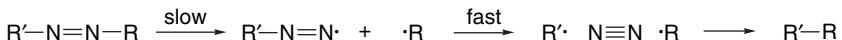
^{311.} P. S. Engel, *Chem. Rev.*, **80**, 99 (1980).

out either photochemically or thermally. Although the reaction usually does not proceed by a concerted mechanism, there are some special cases in which concerted elimination is possible. We consider these cases first and then move on to the more general case. An interesting illustration of the importance of orbital symmetry effects is the contrasting stability of azo compounds **23** and **24**. Compound **23** decomposes to norbornene and nitrogen only above 100°C . In contrast **24** eliminates nitrogen immediately on preparation, even at -78°C .³¹²

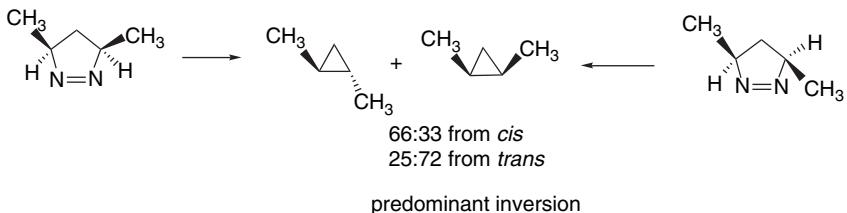


The reason for this difference is that if **23** were to undergo a concerted elimination it would have to follow the forbidden (high-energy) $[2\pi_s + 2\pi_s]$ pathway. For **24**, the elimination can take place by the allowed $[2\pi_s + 4\pi_s]$ pathway. Thus, these reactions are the reverse, respectively, of the $[2\pi_s + 2\pi_s]$ and $[2\pi_s + 4\pi_s]$ cycloadditions, and only the latter is an allowed concerted process. The temperature at which **23** decomposes is fairly typical for strained azo compounds and it presumably proceeds by a nonconcerted diradical mechanism. Since a C–N bond must be broken without concomitant compensation by carbon–carbon bond formation, the activation energy is higher than for a concerted process.

Although the concerted mechanism described in the preceding paragraph is available only to those azo compounds with appropriate orbital arrangements, the nonconcerted mechanism occurs at low enough temperatures to be synthetically useful. The elimination can also be carried out photochemically. These reactions presumably occur by stepwise elimination of nitrogen, and the ease of decomposition depends on the stability of the radical R^{\cdot} .



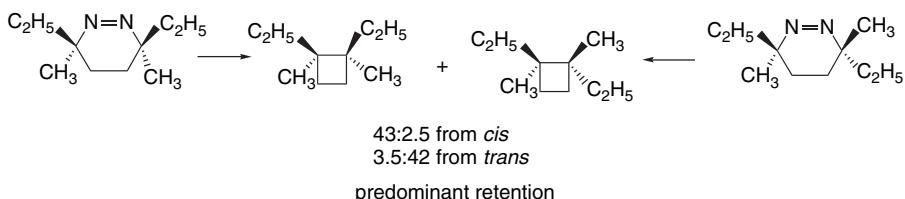
The stereochemistry of the nonconcerted reaction has been a topic of considerable study. Frequently, there is partial stereorandomization, indicating a short-lived diradical intermediate. The details vary from case to case, and both preferential inversion and retention of relative stereochemistry have been observed.



Ref. 313

³¹² N. Rieber, J. Alberts, J. A. Lipsky, and D. M. Lemal, *J. Am. Chem. Soc.*, **91**, 5668 (1969).

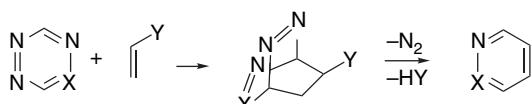
³¹³ R. J. Crawford and A. Mishra, *J. Am. Chem. Soc.*, **88**, 3963 (1966).



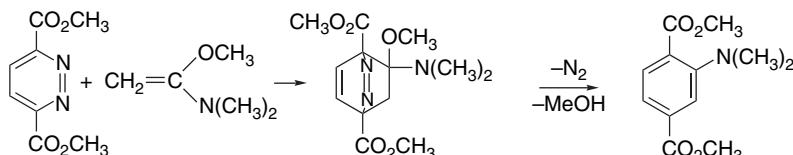
Ref. 314

These results can be interpreted in terms of competition between recombination of the diradical intermediate and conformational equilibration, which would destroy the stereochemical relationships present in the azo compound. The main synthetic application of azo compound decomposition is in the synthesis of cyclopropanes and other strained-ring systems. Some of the required azo compounds can be made by 1,3-dipolar cycloadditions of diazo compounds (see Section 6.2).

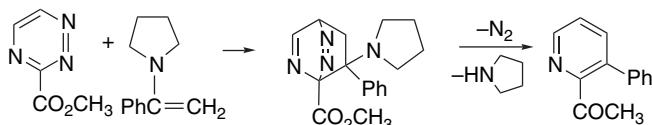
Elimination of nitrogen from D-A adducts of certain heteroaromatic rings has been useful in syntheses of substituted aromatic compounds.³¹⁵ Pyrazines, triazines, and tetrazines react with electron-rich dienophiles in inverse electron demand cycloadditions. The adducts then aromatize with loss of nitrogen and a dienophile substituent.³¹⁶



Pyridazine-3,6-dicarboxylate esters react with electron-rich alkenes to give adducts that undergo subsequent elimination to give terephthalate derivatives.³¹⁷



Similar reactions have been developed for 1,2,4-triazines and 1,2,4,5-tetrazines.



Ref. 318

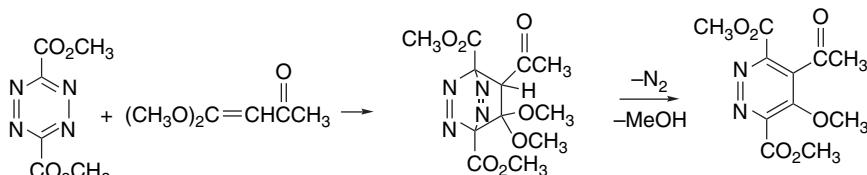
³¹⁴ P. D. Bartlett and N. A. Porter, *J. Am. Chem. Soc.*, **90**, 5317 (1968).

³¹⁵ D. L. Boger, *Chem. Rev.*, **86**, 781 (1986).

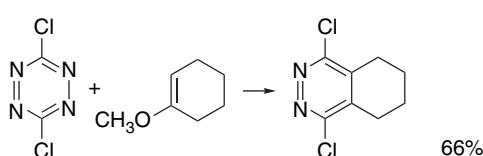
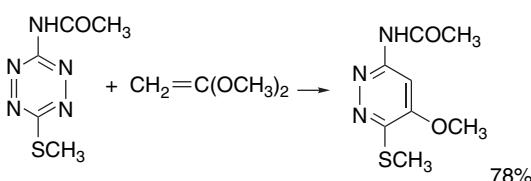
³¹⁶ D. L. Boger, *J. Heterocycl. Chem.*, **33**, 1519 (1996).

³¹⁷ H. Neunhoeffer and G. Werner, *Liebigs Ann. Chem.*, 437, 1955 (1973).

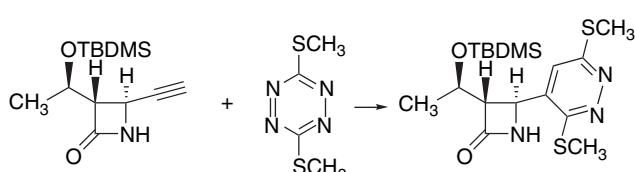
³¹⁸ D. L. Boger and J. S. Panek, *J. Am. Chem. Soc.*, **107**, 5745 (1985).



The heterocycles frequently carry substituents such as chloro, methylthio, or alkoxy-carbonyl.



Acetylenic dienophiles lead directly to aromatic adducts on loss of nitrogen.



6.6.3. β -Eliminations Involving Cyclic Transition Structures

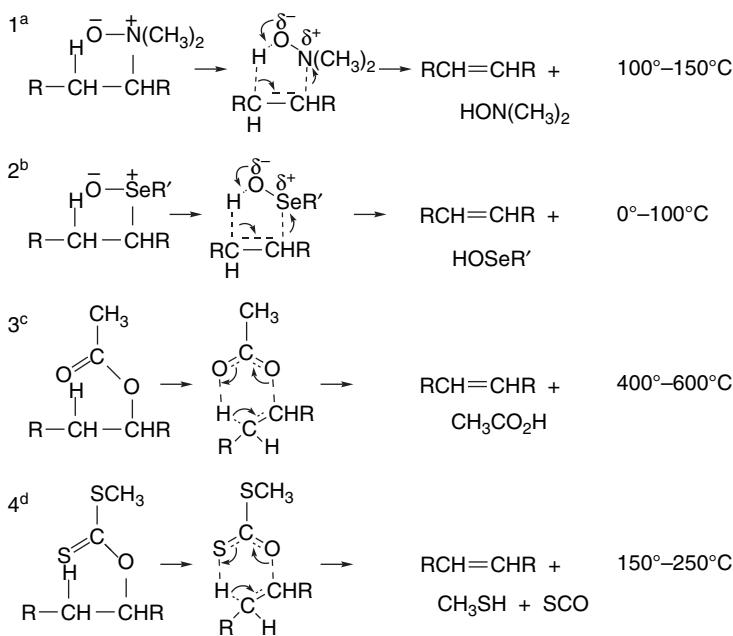
Another important family of elimination reactions has as its common mechanistic feature cyclic TSs in which an intramolecular hydrogen transfer accompanies elimination to form a new carbon-carbon double bond. Scheme 6.20 depicts examples of these reaction types. These are thermally activated unimolecular reactions that normally do not involve acidic or basic catalysts. There is, however, a wide variation in the temperature at which elimination proceeds at a convenient rate. The cyclic TS dictates that elimination occurs with *syn* stereochemistry. At least in a formal sense, all the reactions can proceed by a concerted mechanism. The reactions, as a group, are often referred to as *thermal syn eliminations*.

³¹⁹ D. L. Boger and R. S. Coleman, *J. Am. Chem. Soc.*, **109**, 2717 (1987).

³²⁰ D. L. Boger, R. P. Schaum, and R. M. Garbaccio, *J. Org. Chem.*, **63**, 6329 (1998).

³²¹ T. J. Sparey and T. Harrison, *Tetrahedron Lett.*, **39**, 5893 (1998).

³²² S. M. Sakya, T. W. Strohmeyer, S. A. Lang, and Y.-I. Lin, *Tetrahedron Lett.*, **38**, 5913 (1997).



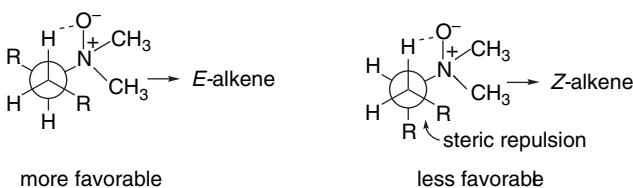
a. A. C. Cope and E. R. Trumbull, *Org. React.*, **11**, 317 (1960).

b. D. L. J. Clive, *Tetrahedron*, **34**, 1049 (1978).

c. C. H. De Puy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

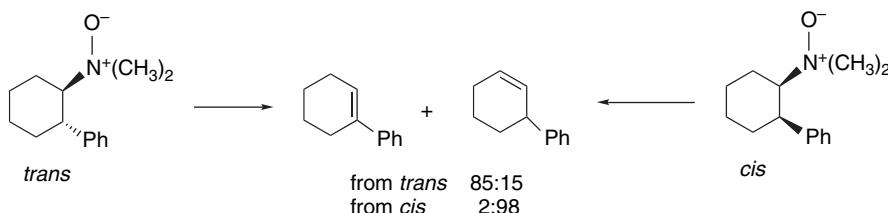
d. H. R. Nace, *Org. React.*, **12**, 57 (1962).

Amine oxide pyrolysis occurs at temperatures of 100°–150° C. The reaction can proceed at room temperature in DMSO.³²³ If more than one type of β-hydrogen can attain the eclipsed conformation of the cyclic TS, a mixture of alkenes is formed. The product ratio parallels the relative stability of the competing TSs. Usually more of the *E*-alkene is formed because of the larger steric interactions present in the TS leading to the *Z*-alkene, but the selectivity is generally not high.



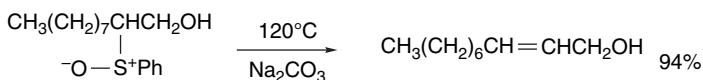
In cyclic systems, conformational effects and the requirement for a cyclic TS determine the product composition. This effect can be seen in the product ratios from pyrolysis of *N,N*-dimethyl-2-phenylcyclohexylamine-*N*-oxide.

³²³ D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Am. Chem. Soc.*, **84**, 1734 (1962).



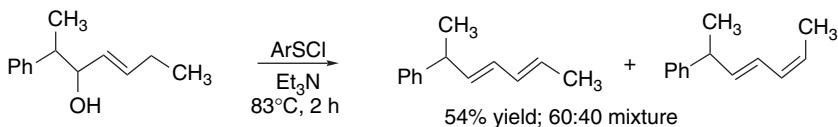
In the *trans* isomer, elimination to give a double bond conjugated with an aromatic ring is especially favorable. This presumably reflects both the increased acidity of the proton α to the phenyl ring and the stabilizing effect of the developing conjugation in the TS. In the *cis* isomer there is no *syn* hydrogen at the phenyl-substituted carbon and the nonconjugated regioisomer is formed. Amine oxides can be readily prepared from amines by oxidation with hydrogen peroxide or a peroxycarboxylic acid. Some typical examples of amine oxide elimination are given in Section A of Scheme 6.21.

Sulfoxides also undergo thermal elimination reactions. The elimination tends to give β , γ -unsaturation from β -hydroxysulfoxides and can be used to prepare allylic alcohols.



Ref. 324

Sulfoxide elimination in conjunction with [2,3]-sigmatropic rearrangement has been used to convert allylic alcohols to dienes.



Ref. 325

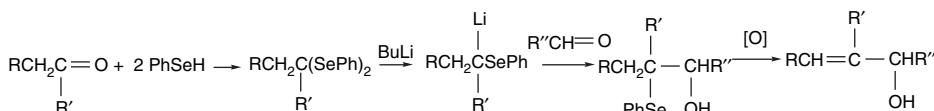
EWG substituents promote the removal of hydrogen, and sulfoxide eliminations are particularly favorable for β -keto and similar sulfoxides.

Selenoxides are even more reactive than sulfoxides toward β -elimination. In fact, many selenoxides react spontaneously when generated at room temperature. Synthetic procedures based on selenoxide eliminations usually involve synthesis of the corresponding selenide followed by oxidation and *in situ* elimination. We have already discussed examples of these procedures in Section 4.3.2, where the conversion of ketones and esters to their α , β -unsaturated derivatives is considered. Selenides can

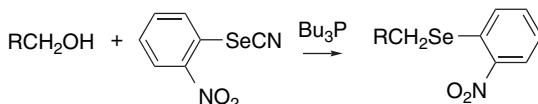
³²⁴ J. Nokami, K. Ueta, and R. Okawara, *Tetrahedron Lett.*, 4903 (1978).

³²⁵ H. J. Reich and S. Wollowitz, *J. Am. Chem. Soc.*, **104**, 7051 (1982).

also be prepared by electrophilic addition of selenenyl halides and related compounds to alkenes (see Section 4.1.6). Selenide anions are powerful nucleophiles and can displace halides or tosylates and open epoxides.³²⁶ Selenide substituents stabilize an adjacent carbanion, so α -selenenyl carbanions can be prepared. One procedure involves conversion of a ketone to a *bis*-selenoketal, which can then be cleaved by *n*-butyllithium.³²⁷ The carbanions in turn add to ketones to give β -hydroxyselenides.³²⁸ Elimination gives an allylic alcohol.



Alcohols can be converted to *o*-nitrophenylselenides by reaction with *o*-nitrophenyl selenocyanate and tri(*n*-butyl)phosphine.³²⁹



The selenides prepared by any of these methods can be converted to selenoxides by such oxidants as hydrogen peroxide, sodium metaperiodate, peroxycarboxylic acids, *t*-butyl hydroperoxide, or ozone.

Like amine oxide elimination, selenoxide eliminations normally favor formation of the *E*-isomer in acyclic structures. In cyclic systems the stereochemical requirements of the cyclic TS govern the product composition. Section B of Scheme 6.21 gives some examples of selenoxide eliminations.

Amine oxide and sulfoxide elimination TS structures have been compared by computations at the MP2/6-31G(*d*) level.³³⁰ The calculated E_a values are 26 and 33 kcal/mol, respectively. Kinetic isotope effects have also been calculated³³¹ and are in good agreement with experimental values. The experimental E_a values for sulfoxide eliminations are typically near 30 kcal/mol.³³² For aryl sulfoxides, the E_a is somewhat lower, around 25–28 kcal/mol. Several sulfoxide elimination reactions have been examined computationally.³³³ MP2/6-311+G(3df,2p) calculations gave generally good agreement with experimental values for ΔH , ΔH^\ddagger , and kinetic isotope effects.

³²⁶ D. L. J. Clive, *Tetrahedron*, **34**, 1049 (1978).

³²⁷ W. Dumont, P. Bayet, and A. Krief, *Angew. Chem. Int. Ed. Engl.*, **13**, 804 (1974).

³²⁸ D. Van Ende, W. Dumont, and A. Krief, *Angew. Chem. Int. Ed. Engl.*, **14**, 700 (1975); W. Dumont and A. Krief, *Angew. Chem. Int. Ed. Engl.*, **14**, 350 (1975).

³²⁹ P. A. Grieco, S. Gilman, and M. Nishizawa, *J. Org. Chem.*, **41**, 1485 (1976); A. Krief and A.-M. Laval, *Bull. Soc. Chim. Fr.*, **134**, 869 (1997).

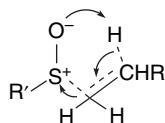
³³⁰ B. S. Jursic, *Theochem*, **389**, 257 (1997).

³³¹ R. D. Bach, C. Gonzalez, J. L. Andres, and H. B. Schlegel, *J. Org. Chem.*, **60**, 4653 (1995).

³³² D. W. Emerson, A. P. Craig, and I. W. Potts, Jr., *J. Org. Chem.*, **32**, 102, 3725 (1967); C. Walling and L. Ballyky, *J. Org. Chem.*, **29**, 2699 (1964).

³³³ J. W. Cubbage, Y. Guo, R. D. McCulla, and W. S. Jenks, *J. Org. Chem.*, **66**, 8722 (2001).

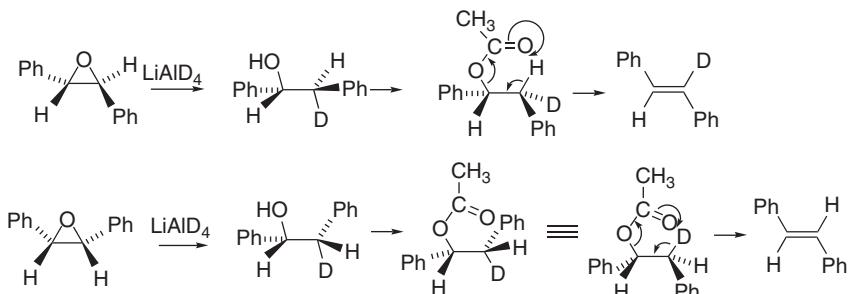
The minimum-energy TSs are planar and the O–H and C–H bond orders were usually less than 0.4 and less than 0.5, respectively, and the S–C bond order was less than 0.5. The C–C bond order was around 1.3. The reaction can be described as a concerted intramolecular proton transfer, with the sulfoxide oxygen acting as a base and the sulfur as a leaving group.



The TS for selenoxide elimination has also been examined computationally.³³⁴ The C–H bond cleavage runs ahead of the C–Se cleavage.

A third category of *syn* eliminations involves pyrolytic decomposition of esters with elimination of a carboxylic acid. The pyrolysis of acetate esters normally requires temperatures above 400°C and is usually a vapor phase reaction. In the laboratory this is done by using a glass tube in the heating zone of a small furnace. The vapors of the reactant are swept through the hot chamber by an inert gas and into a cold trap. Similar reactions occur with esters derived from long-chain acids. If the boiling point of the ester is above the decomposition temperature, the reaction can be carried out in the liquid phase, with distillation of the pyrolysis product.

Ester pyrolysis has been shown to be a *syn* elimination in the case of formation of stilbene by the use of deuterium labels.³³⁵



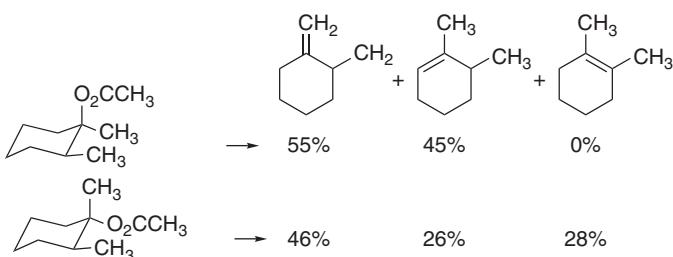
Although recognizing the existence of the concerted cyclic mechanism, it has been proposed that most preparative pyrolyses proceed as surface-catalyzed reactions.³³⁶

Mixtures of alkenes are formed when more than one type of β -hydrogen is present. In acyclic compounds the product composition often approaches that expected on a statistical basis from the number of each type of hydrogen. The *E*-alkene usually predominates over the *Z*-alkene for a given isomeric pair. In cyclic structures, elimination is in the direction that the cyclic mechanism can operate most favorably.

³³⁴ N. Kondo, H. Fueno, H. Fujimoto, M. Makino, H. Nakaoka, I. Aoki, and S. Uemura, *J. Org. Chem.*, **59**, 5254 (1994).

³³⁵ D. Y. Curtin and D. B. Kellom, *J. Am. Chem. Soc.*, **75**, 6011 (1953).

³³⁶ D. H. Wertz and N. L. Allinger, *J. Org. Chem.*, **42**, 698 (1977).

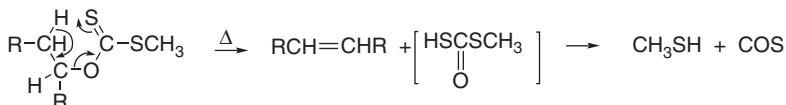


Ref. 336

Alcohols can be dehydrated via xanthate esters at temperatures that are much lower than those required for acetate pyrolysis. The preparation of xanthate esters involves reaction of the alkoxide with carbon disulfide. The resulting salt is alkylated with methyl iodide.



The elimination is often effected simply by distillation.



Product mixtures are observed when more than one type of β -hydrogen can participate in the reaction. As with the other *syn* thermal eliminations, there are no intermediates that are prone to skeletal rearrangement.

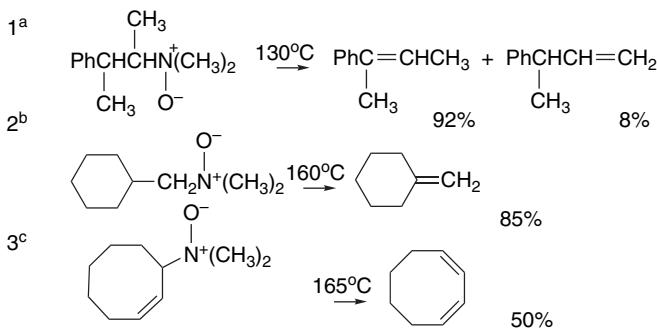
Scheme 6.21 gives some examples of thermal elimination reactions. Entries 1 to 3 show amine-oxide decompositions. The reaction in Entry 1 shows a preference for the conjugated product. This reaction was also conducted in dry DMSO, where it was found to proceed at 25°C.³³⁸ Entry 2 illustrates the use of the reaction to prepare methylenecyclohexane. The method is particularly useful in this case because there is no tendency for competing elimination or rearrangement to the more stable 1-methylcyclohexene. Entries 4 and 5 are sulfoxide eliminations. Entry 4 is favored by the conjugation of the phenyl group and occurs under very mild conditions. The conditions for elimination in Entry 5 are more typical. Entries 6 to 9 are selenoxide eliminations. In Entries 6 and 7, the selenide group is introduced by nucleophilic substitution. In Entry 8, electrophilic selenolactonization was used to synthesize the reactant. Although the yield of the product, oxete, in Entry 9 is quite low, this was one of the first preparations of this compound. Entries 10 to 12 are high-temperature acetate pyrolyses. Entries 13 to 17 are xanthate pyrolyses. In Entry 15, the use of DMSO as the solvent for the preparation of the dialcoholate was found to be advantageous.

³³⁶ D. H. Froemsdorf, C. H. Collins, G. S. Hammond, and C. H. DePuy, *J. Am. Chem. Soc.*, **81**, 643 (1959).

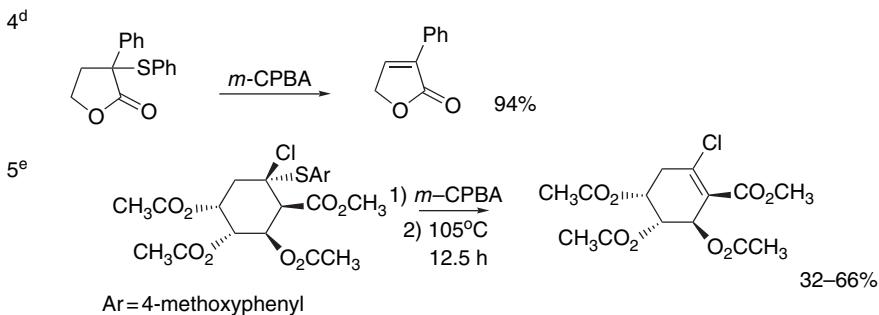
³³⁸ D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Am. Chem. Soc.*, **84**, 1734 (1962).

Scheme 6.21. Thermal Eliminations Via Cyclic Transition Structures

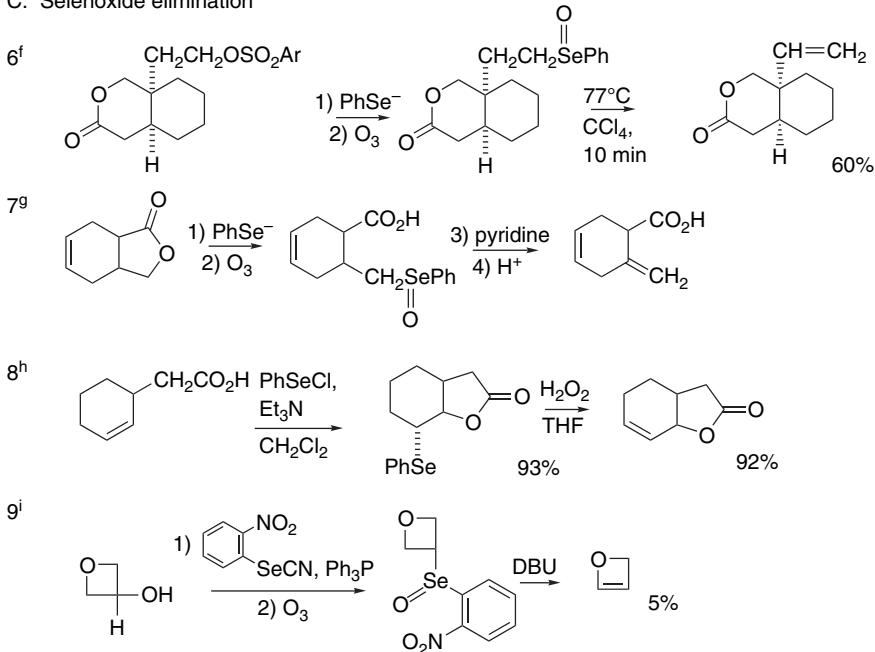
A. Amine oxide pyrolyses



B. Sulfoxide elimination



C. Selenoxide elimination



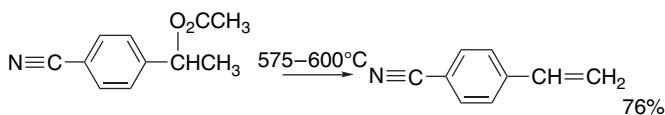
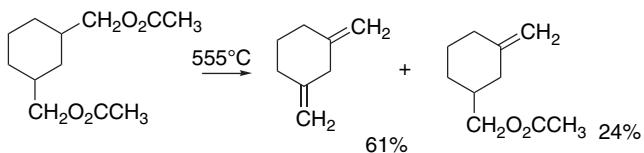
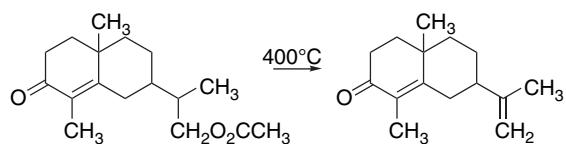
(Continued)

Scheme 6.21. (Continued)

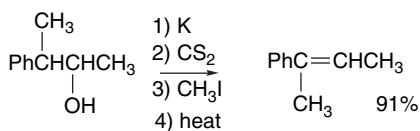
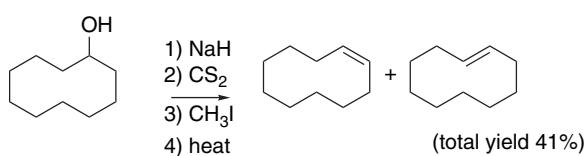
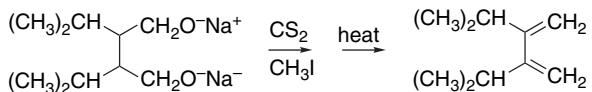
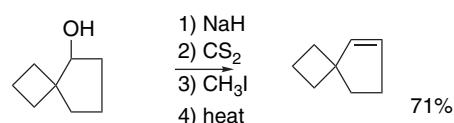
SECTION 6.6

Unimolecular Thermal Elimination Reactions

D. Acetate pyrolyses

10^j11^k12^l

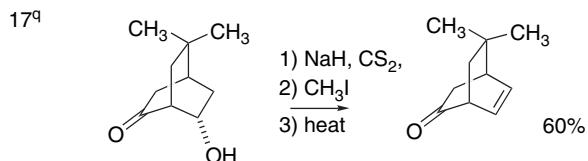
E. Xanthate ester pyrolyses

13^m14ⁿ15^o16^p

(Continued)

CHAPTER 6

*Concerted
Cycloadditions,
Unimolecular
Rearrangements, and
Thermal Eliminations*

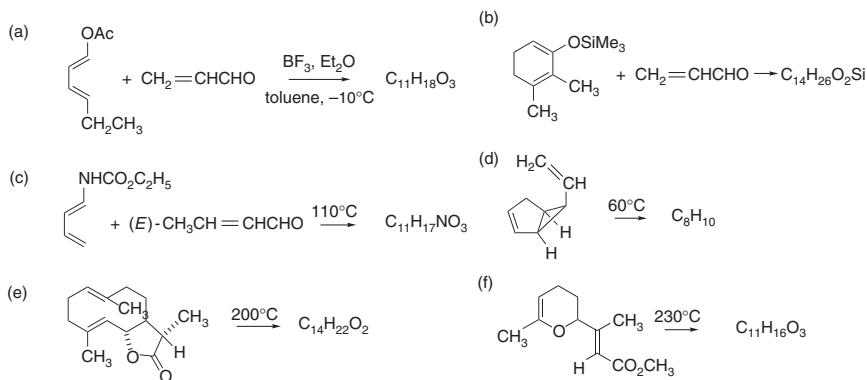


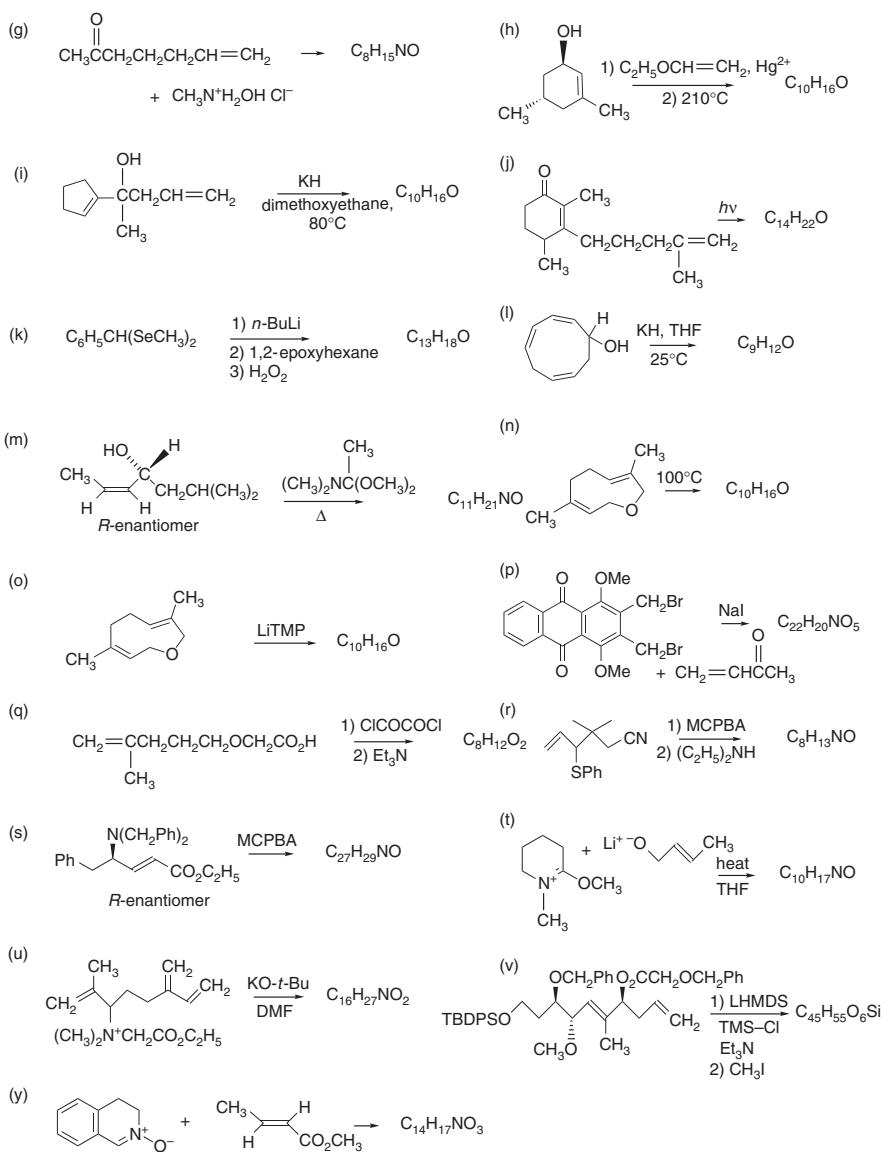
- a. D. J. Cram and J. E. McCarty, *J. Am. Chem. Soc.*, **76**, 5740 (1954).
- b. A. C. Cope, E. Ciganek, and N. A. LeBel, *J. Am. Chem. Soc.*, **81**, 2799 (1959); A. C. Cope and E. Ciganek, *Org. Synth.*, **IV**, 612 (1963).
- c. A. C. Cope and C. L. Bumgardner, *J. Am. Chem. Soc.*, **78**, 2812 (1956).
- d. J.-X. Gu and H. L. Holland, *Synth. Commun.*, **28**, 3305 (1998).
- e. R. H. Rich, B. M. Lawrence, and P. A. Bartlett, *J. Org. Chem.*, **59**, 693 (1994).
- f. R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, **41**, 1396 (1976).
- g. D. Liotta and H. Santiesteban, *Tetrahedron Lett.*, 4369 (1977); R. M. Scarborough, Jr., and A. B. Smith, III, *Tetrahedron Lett.*, 4361 (1977).
- h. K. C. Nicolaou and Z. Lysenko, *J. Am. Chem. Soc.*, **99**, 3185 (1977).
- i. L. E. Friedrich and P. Y. S. Lam, *J. Org. Chem.*, **46**, 306 (1981).
- j. C. G. Overberger and R. E. Allen, *J. Am. Chem. Soc.*, **68**, 722 (1946).
- k. W. J. Bailey and J. Economy, *J. Org. Chem.*, **23**, 1002 (1958).
- l. E. Piers and K. F. Cheng, *Can. J. Chem.*, **46**, 377 (1968).
- m. D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3883 (1949).
- n. A. T. Blomquist and A. Goldstein, *J. Am. Chem. Soc.*, **77**, 1001 (1955).
- o. A. de Groot, B. Evenhuis, and H. Wynberg, *J. Org. Chem.*, **33**, 2214 (1968).
- p. C. F. Wilcox, Jr., and C. G. Whitney, *J. Org. Chem.*, **32**, 2933 (1967).
- q. L. A. Paquette and H.-C. Tsai, *J. Org. Chem.*, **61**, 142 (1996).

Problems

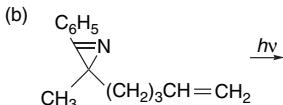
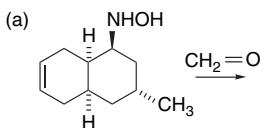
(References for these problems will be found on page 1280.)

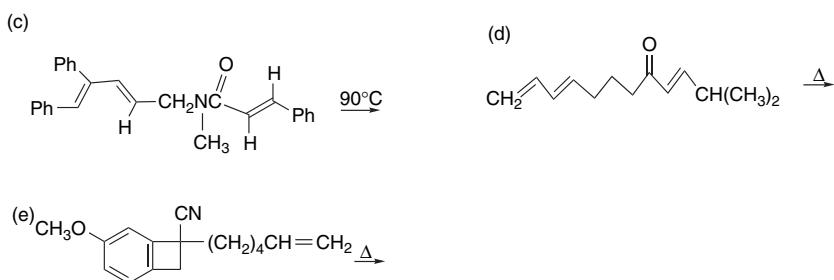
- 6.1. Predict the products of the following reactions on the basis of the reaction mechanism and anticipated transition structure. Be sure to consider all elements of stereochemistry. Unless otherwise specified, the reactants and reagents are racemic.



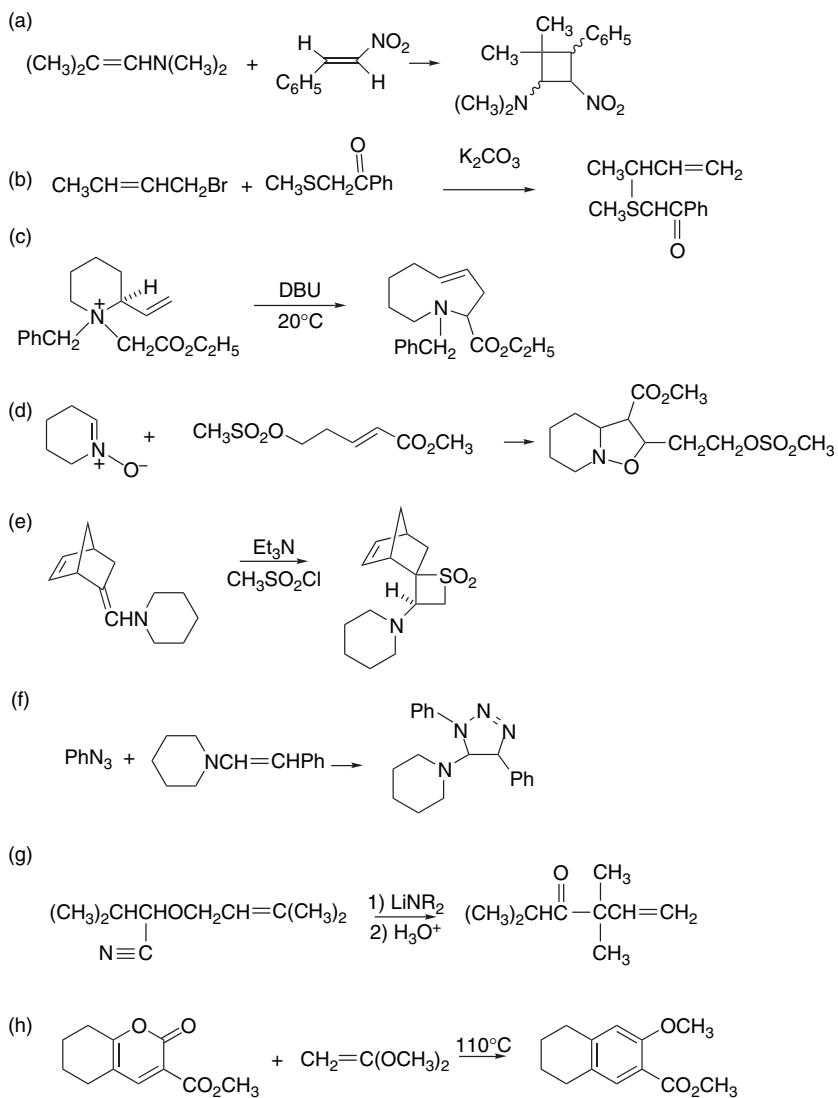


6.2. Intramolecular cycloaddition reactions occur under the conditions specified for each of the following reactions. Show the structures of the products of each reaction, including all aspects of stereochemistry and indicate the structure of the product-determining TS and any key intermediates.

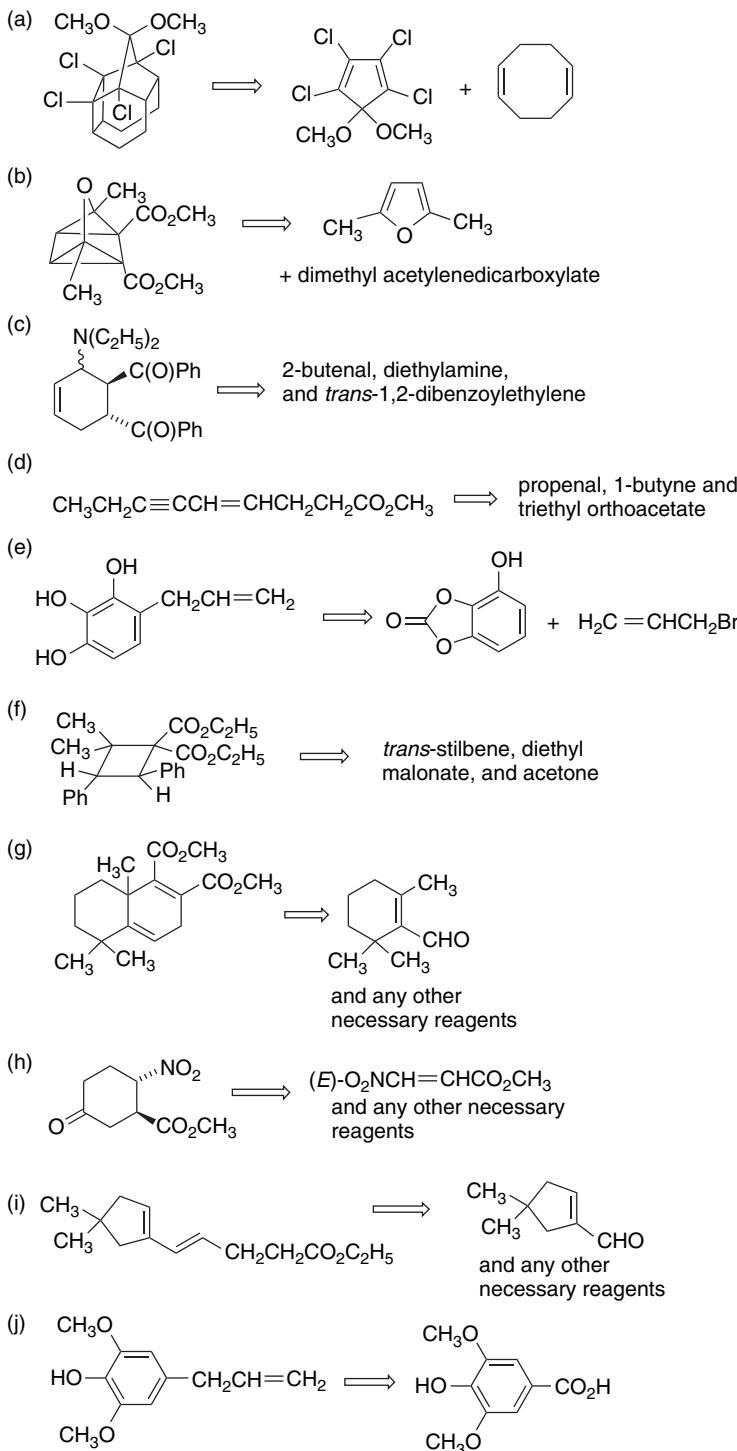


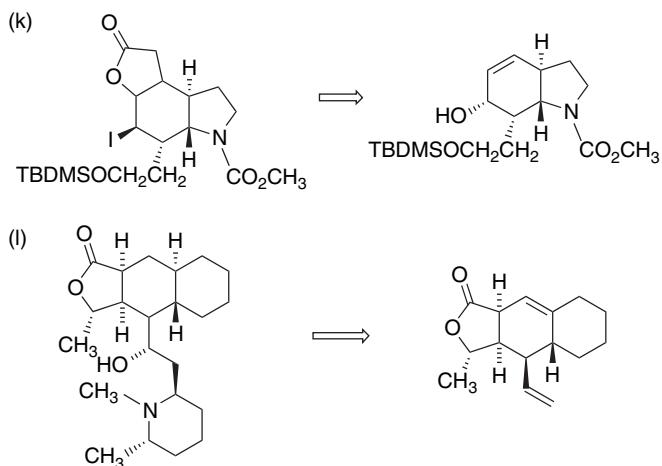


6.3. Indicate the mechanistic type to which each of these reactions belongs and write out a mechanism showing any intermediates.



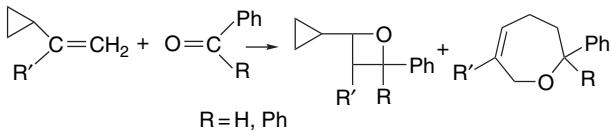
6.4. Apply retrosynthetic analysis to the following transformation and show how each of the target molecules could be prepared from the starting materials given. No more than three separate steps are needed in any of the syntheses.





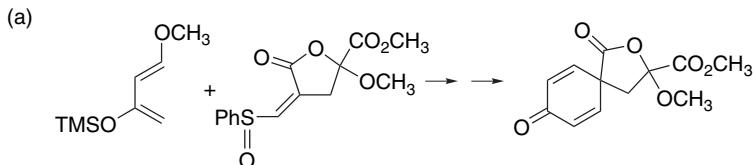
6.5. Suggest mechanisms by which the following transformations occur.

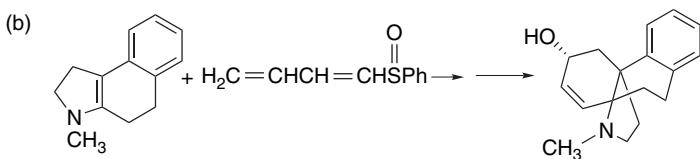
- The addition reaction of tetracyanoethylene and ethyl vinyl ether in acetone gives 94% of a [2 + 2] adduct and 6% of an adduct having the composition tetracyanoethylene + ethyl vinyl ether + acetone. If the [2 + 2] adduct is kept in contact with acetone for several days, it is completely converted to the minor product. What is a likely structure for the minor product? How is it formed in the original reaction and on standing in acetone?
- When vinylcyclopropane is irradiated with benzophenone or benzaldehyde both oxetane and oxepene products are obtained. How are the oxepenes formed?



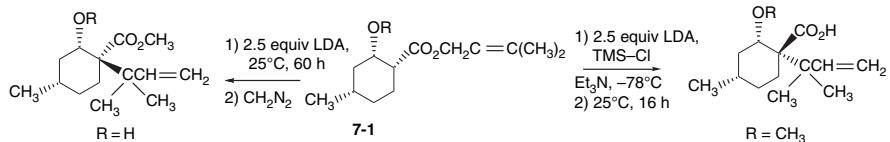
- A convenient preparation of 2-allylcyclohexanone involves simply heating the diallyl acetal of cyclohexanone in toluene containing a trace of *p*-toluenesulfonic acid and collecting a distillate of toluene and allyl alcohol.
- A solution of 2-butenal, 2-acetoxypropene, and dimethyl acetylenedicarboxylate refluxed in the presence of a small amount of an acid catalyst gives an 80% yield of dimethyl phthalate.

6.6. The following syntheses were carried by short tandem reaction sequences starting with the Diels-Alder reaction shown. Show the reagents and approximate reaction conditions required to complete the transformation.

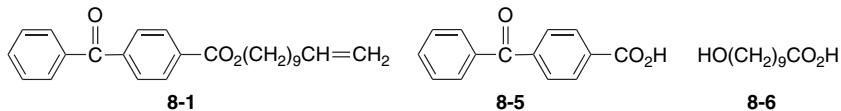




- 6.7. The ester **7-1** gives alternative stereoisomers when subjected to Claisen rearrangement as the lithium enolate or as the silyl ketene acetal. Analyze the respective transition structures and develop a rationale to explain these results.

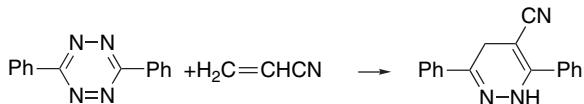


- 6.8. Photolysis of **8-1** gives an isomeric compound **8-2** in 83% yield. Alkaline hydrolysis of **8-2** affords a hydroxy carboxylic acid, **8-3**, $C_{25}H_{32}O_4$. Treatment of **8-2** with silica gel in hexane yields **8-4**, $C_{24}H_{28}O_2$. **8-4** is converted by $NaIO_4-KMnO_4$ to a mixture of **8-5** and **8-6**. What are the structures of **8-2**, **8-3**, and **8-4**?

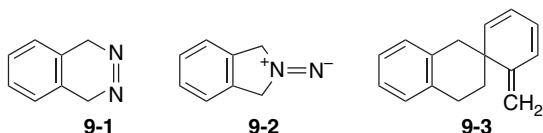


- 6.9. Suggest mechanisms for the following reactions that involve loss of N_2 .

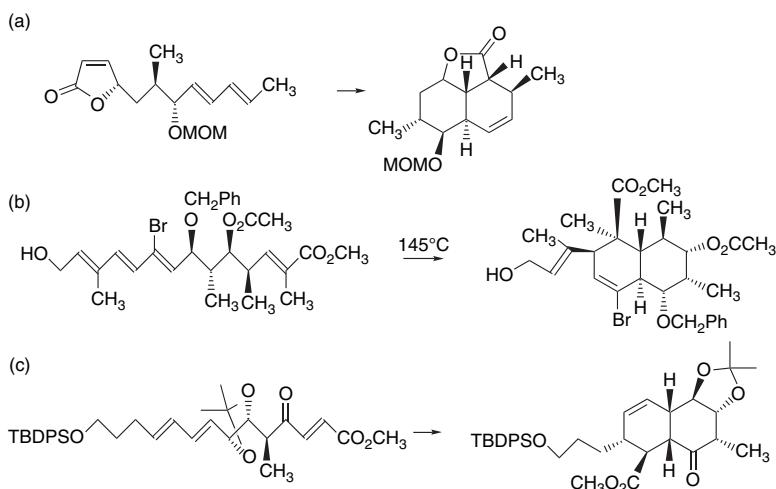
- a. 1,2,4,5-Tetrazines react with alkenes to give dihydropyridazines, as in the example below.



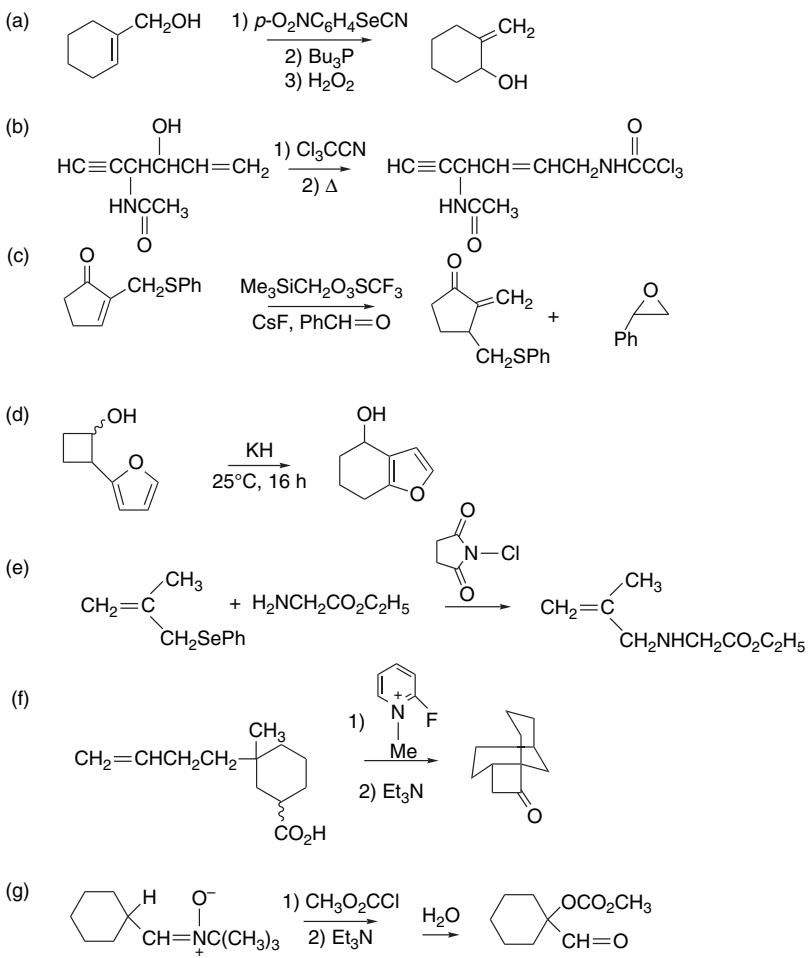
- b. Compounds **9-1** and **9-2** are both unstable toward loss of nitrogen at room temperature and both give **9-3** as the product.

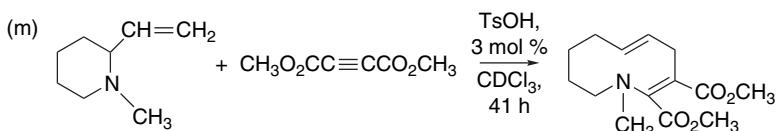
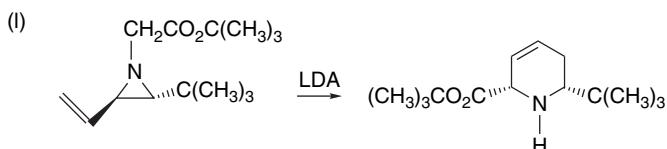
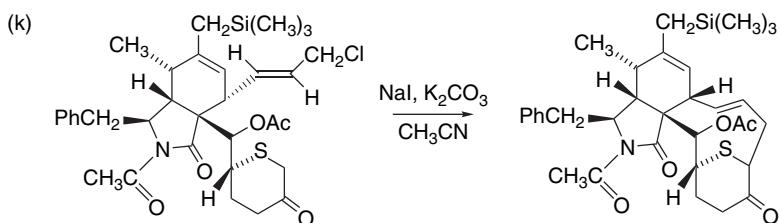
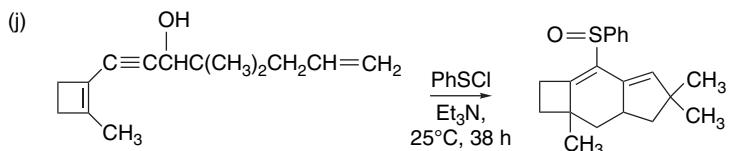
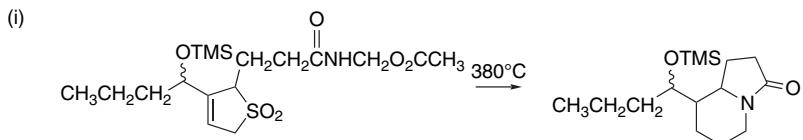
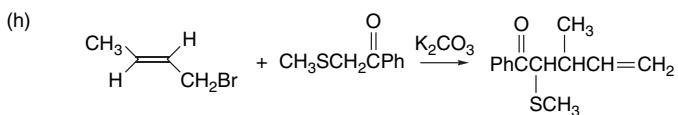


- 6.10. For each of the following reactions propose a transition structure that would account for the observed stereoselectivity. Identify important conformational and other features of the proposed transition structure.

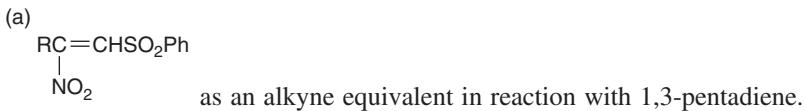


6.11. Provide an outline of the mechanisms of the following transformations.

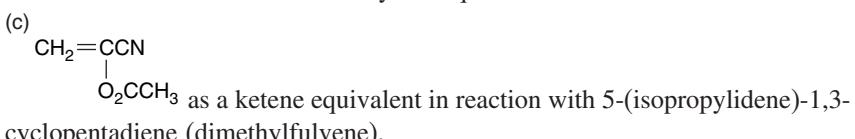




6.12. In each part, the molecule shown was employed as a synthetic equivalent in a cycloaddition reaction. Show a sequence of reactions by which the adduct can be converted to the desired product.



(b) $\text{PhSO}_2\text{CH}=\text{CHSi}(\text{CH}_3)_3$ as an acetylene equivalent in reaction with anthracene.



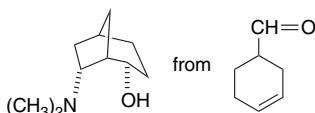
(d)

$\text{CH}_2=\text{CHNO}_2$ as a ketene equivalent in reaction with 5-methoxymethyl-1,3-cyclopentadiene.

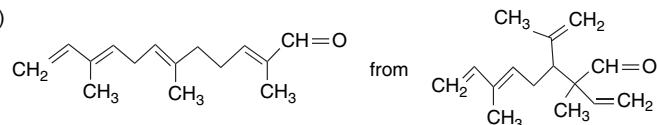
- 6.13. Suggest reaction sequences for accomplishing each of the following synthetic transformations.

(a) Squalene from succinaldehyde, 2-bromopropene, and 3-methoxy-2-methyl-1,3-butadiene.

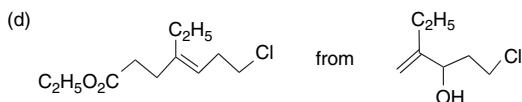
(b)



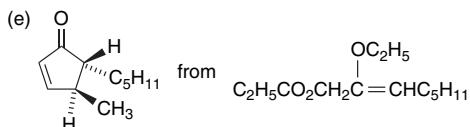
(c)



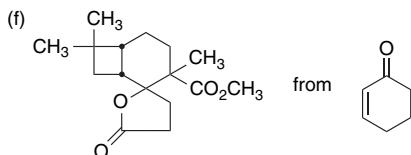
(d)



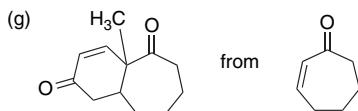
(e)



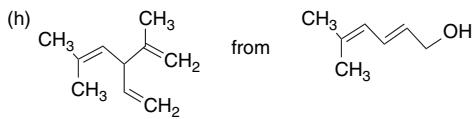
(f)



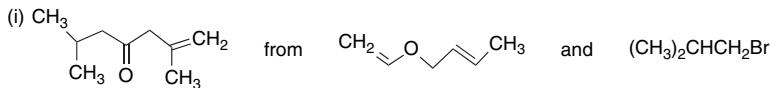
(g)



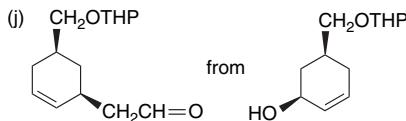
(h)

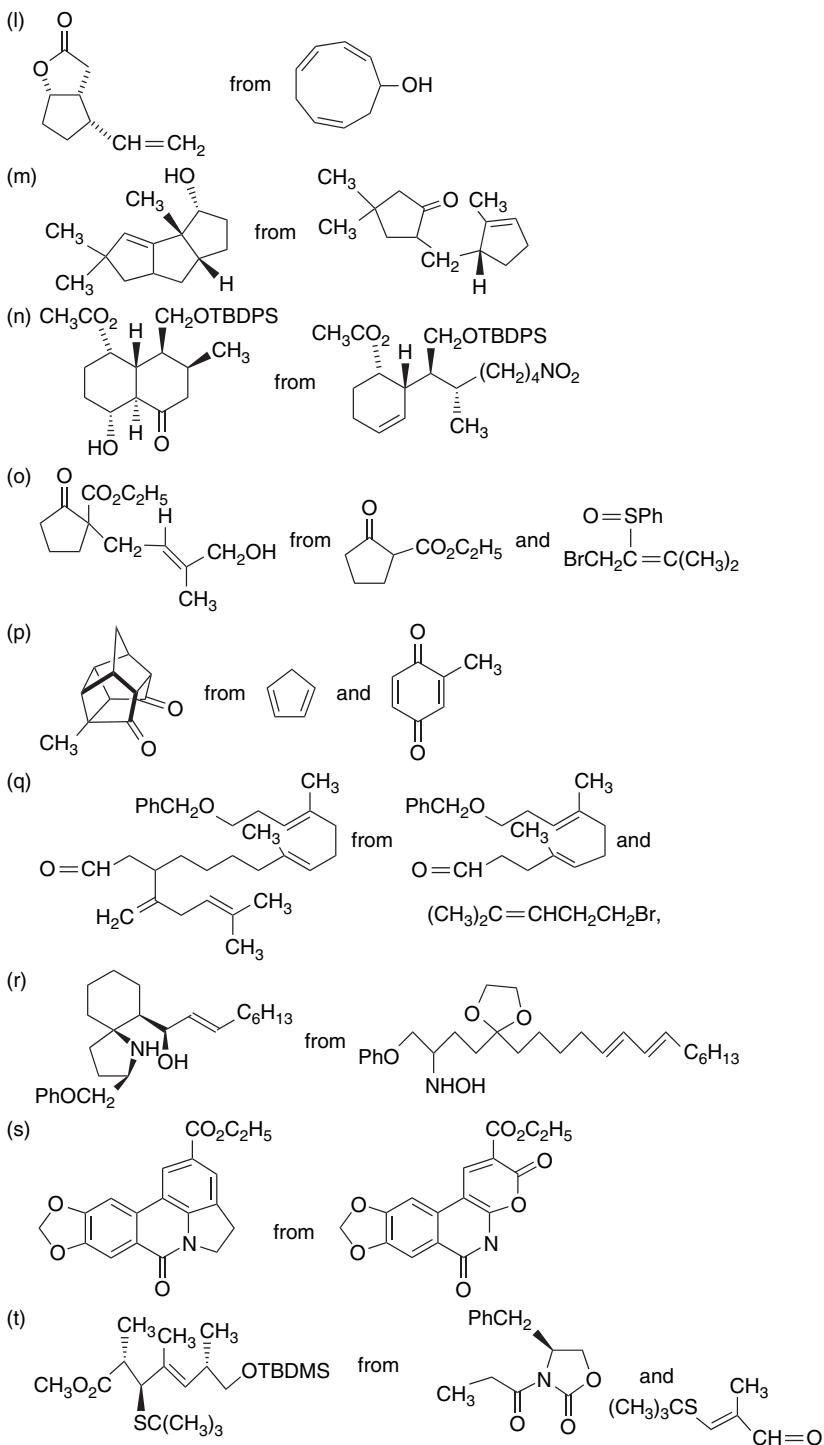


(i)

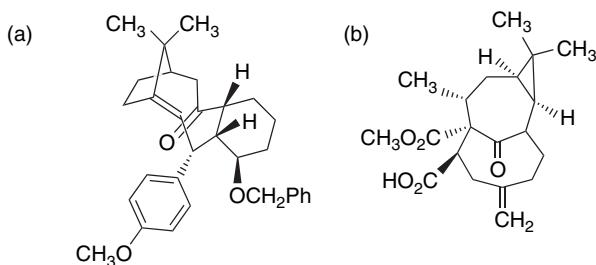


(j)

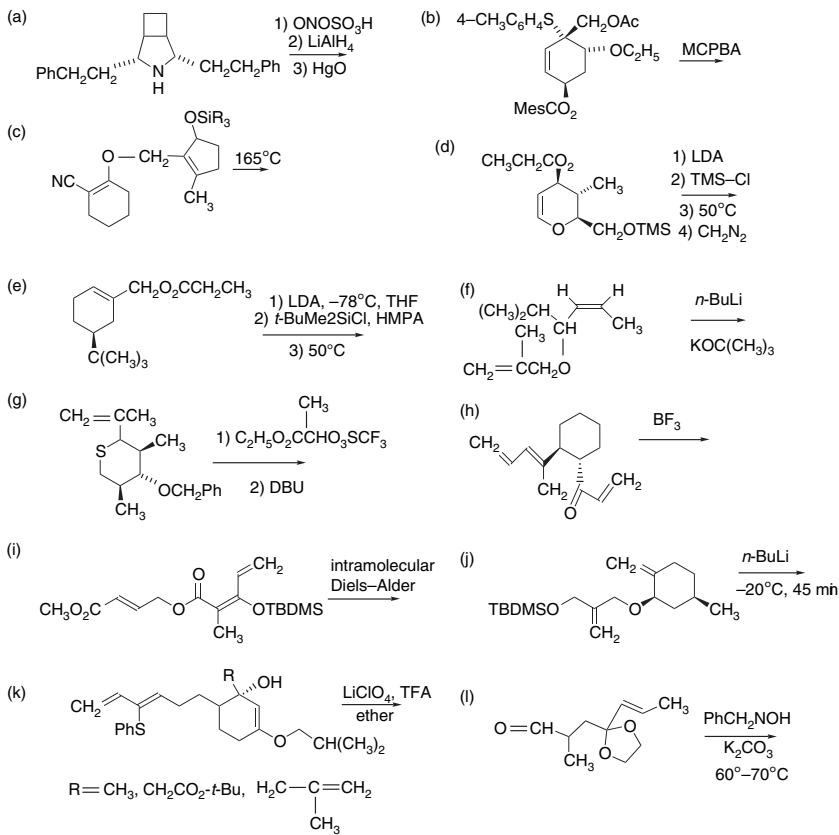




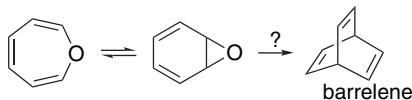
- 6.14. By retrosynthetic analysis, identify a precursor that could provide the desired product by a single pericyclic reaction. Indicate appropriate reaction conditions for the transformation you identify.



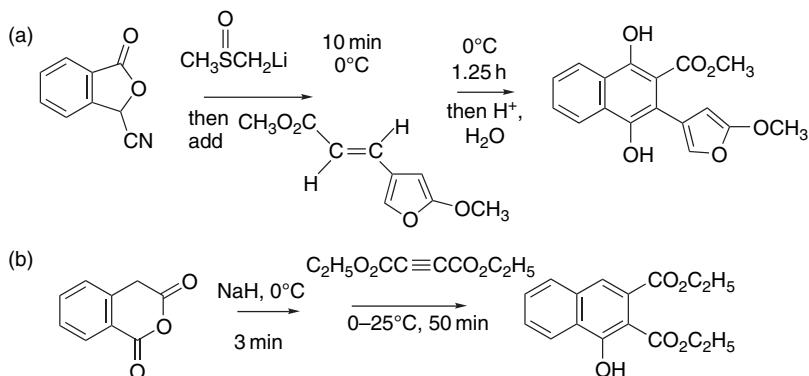
6.15. Predict the structure of the major product, including stereochemistry, of the following reactions. Draw the transition structures and identify the features that control the stereochemistry of the reaction.



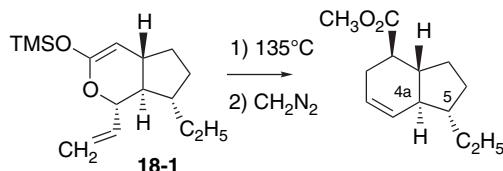
6.16. Oxepin is in equilibrium with benzene oxide by a [3,3]-sigmatropic shift. Advantage has been taken of this equilibrium to develop a short synthesis of barrelene. Outline a way that this could be done.



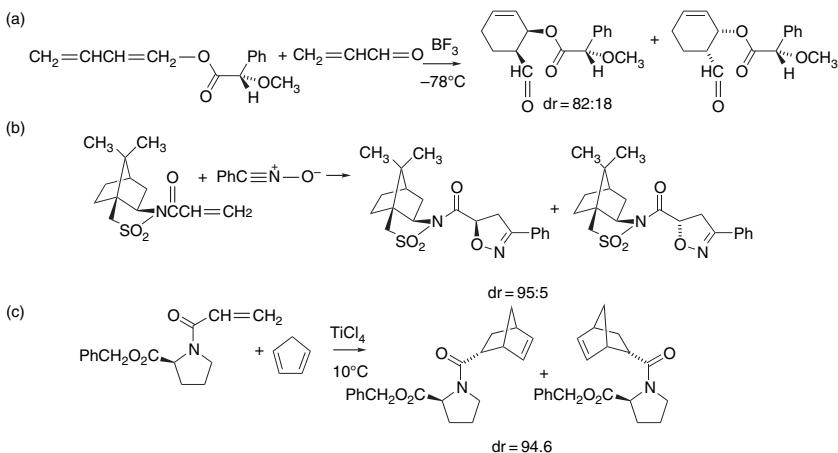
6.17. The following transformations involve generation of anionic intermediates that then undergo cycloaddition reactions. Identify the anion intermediate and outline the mechanism for each transformation.



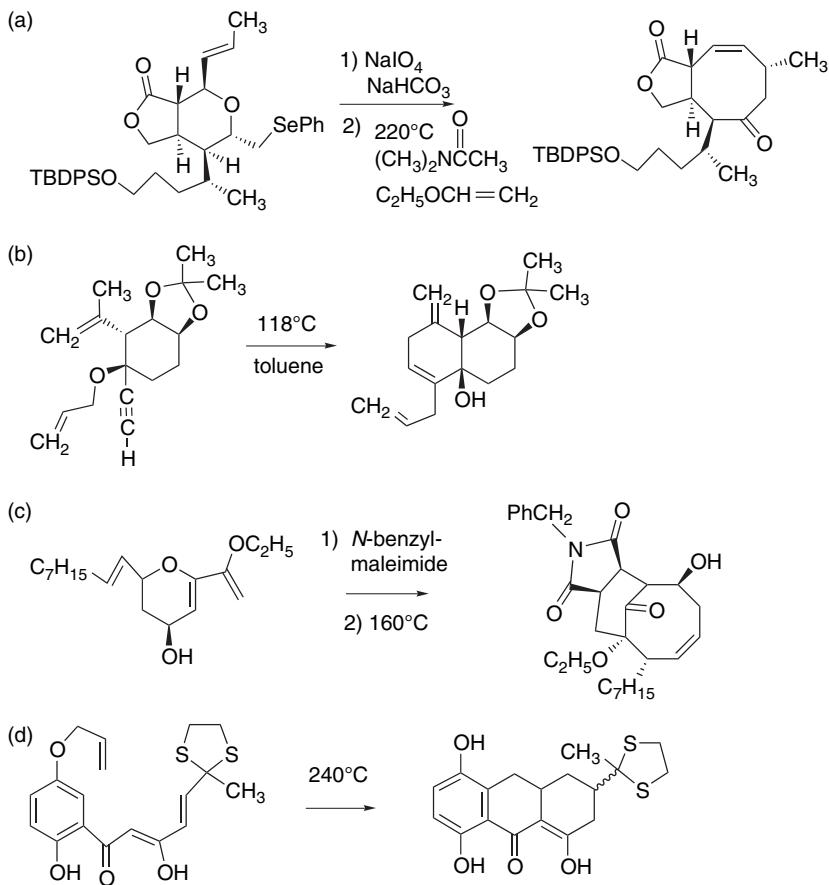
6.18. When the lactone silyl ketene acetal **18-1** is heated to 135°C a mixture of four stereoisomers is obtained. Although the major one is the expected [3,3]-sigmatropic rearrangement product, lesser amounts of other possible C(4a) and C(5) epimers are also formed. When the reaction mixture is heated to 100°C, partial conversion to the same mixture of stereoisomers is observed, but most of the product at this temperature is an acyclic triene ester. Suggest a structure for the triene ester and show how it can be formed. Discuss the significance of the observation of the triene ester for the lack of stereospecificity in the rearrangement.



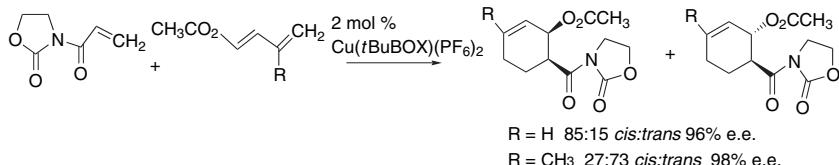
6.19. The following cycloaddition reactions involve chiral auxiliaries and proceed with a good degree of diastereoselectivity. Provide a rationalization of the formation of the preferred product on the basis of a TS.



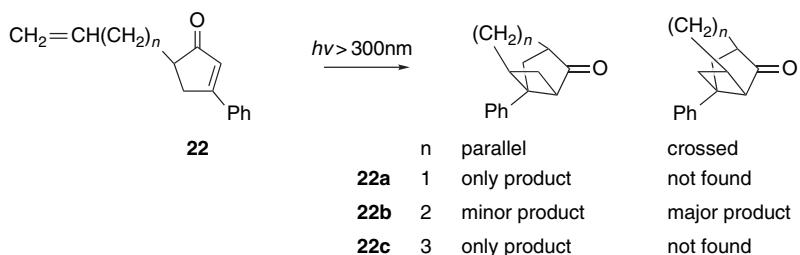
- 6.20. The following transformations involve two or more pericyclic reactions occurring in tandem during the process. Suggest a plausible sequence of reactions that can lead to the observed product.



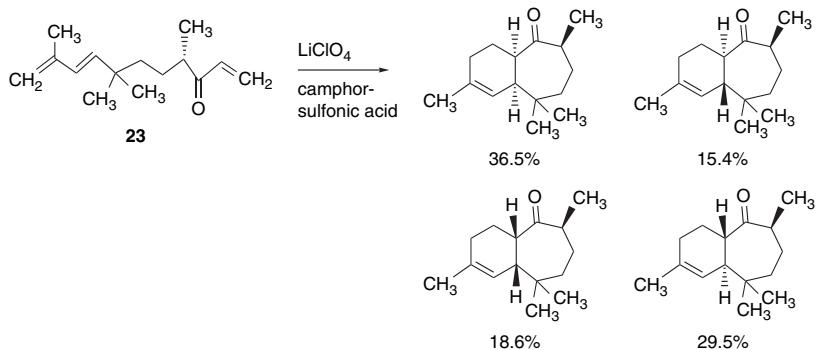
- 6.21. The Diels-Alder reaction of *N*-acryloyloxazolidinone catalyzed by Cu(*t*-Bu)BOX shows a reversal of stereoselectivity between 1-acetoxybutadiene and 1-acetoxy-3-methylbutadiene. The former gives a 85:15 *endo*:*exo* ratio, whereas the latter is 27:73 *endo*:*exo*. Explain this reversal in terms of the transition structure model given on p. 509.



- 6.22. The alkenyl cyclopentenone **22a-c** have been subjected to photolysis with the results shown below. Analyze these results in terms of the mechanistic interpretation given on p. 547.



6.23. The intramolecular Diels-Alder reaction of **23-1** carried out under LiClO₄ catalysis is rather nonselective. Use a molecular mechanics program to assess the energies of the competing TSs and products. Are the results in agreement with the experimental outcome?

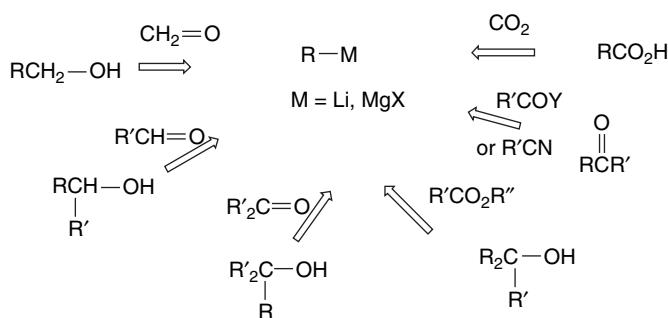


Organometallic Compounds of Group I and II Metals

Introduction

The use of organometallic reagents in organic synthesis had its beginning around 1900 when Victor Grignard discovered that alkyl and aryl halides react with magnesium metal to give homogeneous solutions containing organomagnesium compounds. The “Grignard reagents” proved to be highly reactive carbon nucleophiles and are still very useful synthetic reagents. Organolithium reagents came into synthetic use somewhat later, but are also very important for synthesis. The present chapter focuses on Grignard reagents and organolithium compounds. We also consider zinc, cadmium, mercury, indium, and lanthanide organometallics, which have more specialized places in synthetic methodology. Certain of the transition metals, such as copper, palladium, and nickel, which are also important in synthetic methodology, are discussed in Chapter 8.

The composition of the organolithium compounds is RLi or more accurately $(\text{RLi})_n$. The organomagnesium compounds are usually formulated as RMgX , with X being a halide. The organometallic derivatives of Group I and II metals provide reactive carbon nucleophiles. Reactivity increases in the order $\text{Li} < \text{Na} < \text{K}$ and $\text{MgX} < \text{CaX}$, but the lithium and magnesium reactions are by far the most commonly used. Organo-lithium and magnesium reagents react with polar multiple bonds, especially carbonyl groups, and provide synthetic routes to a variety of alcohols. Other electrophiles, such as acyl halides, nitriles, and CO_2 provide routes to ketones and carboxylic acids.



The Group IIB organometallics derived from zinc, cadmium, and mercury are considerably less reactive. The carbon-metal bonds in these compounds have more covalent character than for lithium or magnesium reagents. Zinc, cadmium, and mercury are distinct from other transition metals in having a d^{10} shell in the +2 oxidation state and their reactions usually do not involve changes in oxidation state. Although organozinc and cadmium reagents react with acyl chloride, reactions with other carbonyl compounds require either Lewis acids or chelates as catalysts. These catalyzed reactions make organozinc reagents particularly useful in additions to aldehydes. The lanthanides and indium organometallics are usually in the +3 oxidation state, which are also filled valence shells, and have a number of specialized applications that depend on their strong oxyphilic character.

7.1. Preparation and Properties of Organomagnesium and Organolithium Reagents

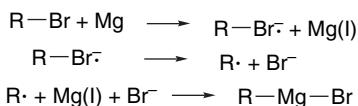
The compounds of lithium and magnesium are the most important of Group IA and IIA organometallics. The metals in these two groups are the most electropositive of the elements, and the polarity of the metal-carbon bond increases the electron density on carbon. This electronic distribution is responsible for the strong nucleophilicity and basicity of these compounds. There is a high ionic character in the carbon-metal bonds, but the compounds tend to exist as aggregates and have good solubility in some nonpolar solvents.

7.1.1. Preparation and Properties of Organomagnesium Reagents

The reaction of magnesium metal with an alkyl or aryl halide in diethyl ether is the standard method for synthesis of Grignard reagents. The order of reactivity of the halides is $\text{RI} > \text{RBr} > \text{RCl}$. The formation of Grignard reagents takes place at the metal surface. Reaction commences with an electron transfer to the halide and decomposition of the radical ion, followed by rapid combination of the organic group with a magnesium ion.¹ It

¹. H. R. Rogers, C. L. Hill, Y. Fujiwara, R. J. Rogers, H. L. Mitchell, and G. M. Whitesides, *J. Am. Chem. Soc.*, **102**, 217 (1980); J. F. Garst, J. E. Deutch, and G. M. Whitesides, *J. Am. Chem. Soc.*, **108**, 2490 (1986); E. C. Ashby and J. Oswald, *J. Org. Chem.*, **53**, 6068 (1988); H. M. Walborsky,

has been suggested that the reactions may involve reduction of the halide by clusters of magnesium atoms.²



Solutions of several Grignard reagents such as methylmagnesium bromide, ethylmagnesium bromide, and phenylmagnesium bromide are available commercially. Some Grignard reagents are formed more rapidly in tetrahydrofuran than in ether. This is true of vinylmagnesium bromide, for example.³ Other ether solvents such as dimethoxyethane can be used. For industrial purposes, where less volatile solvents are needed for reasons of safety, *bis*-2-butoxyethyl ether (butyl diglyme), bp 256°C, can be used. The solubility of Grignard reagents in ethers is the result of Lewis acid-base complex formation between the magnesium ion and the ether oxygens.

Under normal laboratory conditions magnesium metal is coated with an unreactive layer of Mg(OH)₂, and the reactions do not start until the organic halide diffuses through it. The reaction appears to begin at discrete sites,⁴ and accelerates as the surface coating breaks up, exposing more active surface. The ether solvents are probably involved and may assist dissociation of the metal ions from the surface. Various techniques for initiating the reactions, such as addition of small amounts of I₂ or BrCH₂CH₂Br, appear to involve the generation of Mg²⁺ salts, which serve to facilitate the reaction. Sonication or mechanical pretreatment can also be used to activate magnesium.⁵ Organic halides that are unreactive toward magnesium shavings can often be induced to react by using an extremely reactive form of magnesium that is obtained by reducing magnesium salts with sodium or potassium metal.⁶ Even alkyl fluorides, which are normally unreactive, form Grignard reagents under these conditions.

One of the fundamental questions about the mechanism is whether the radical is really “free” in the sense of diffusing from the metal surface.⁷ For alkyl halides, there is considerable evidence that the radicals behave similarly to alkyl free radicals.⁸ One test for the involvement of radical intermediates is to determine whether cyclization occurs in the 6-hexenyl system, where radical cyclization is rapid (see Part A, Section 12.2.2).

Acc. Chem. Res., **23**, 286 (1990); H. M. Walborsky and C. Zimmerman, *J. Am. Chem. Soc.*, **114**, 4996 (1992); C. Hamdouchi, M. Topolski, V. Goedken, and H. M. Walborsky, *J. Org. Chem.*, **58**, 3148 (1993); C. Hamdouchi and H. M. Walborsky, *Handbook of Grignard Reagents*, G. S. Silverman and P. E. Rakita, eds., Marcel Dekker, New York, 1996, pp. 145–218.

2. E. Paralez, J.-C. Negrel, A. Goursot, and M. Chanon, *Main Group Metal Chem.*, **21**, 69 (1998); E. Peralez, J.-C. Negrel, A. Gousset, and M. Chanon, *Main Group Metal Chem.*, **22**, 185 (1999).

3. D. Seyferth and F. G. A. Stone, *J. Am. Chem. Soc.*, **79**, 515 (1957); H. Normant, *Adv. Org. Chem.*, **2**, 1 (1960).

4. C. E. Teerlinck and W. J. Bowyer, *J. Org. Chem.*, **61**, 1059 (1996).

5. K. V. Baker, J. M. Brown, N. Hughes, A. J. Skarnulis, and A. Sexton, *J. Org. Chem.*, **56**, 698 (1991); J.-L. Luche and J.-C. Damain, *J. Am. Chem. Soc.*, **102**, 7926 (1980).

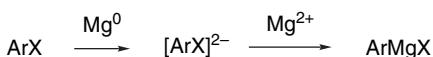
6. R. D. Rieke and S. E. Bales, *J. Am. Chem. Soc.*, **96**, 1775 (1974); R. D. Rieke, *Acc. Chem. Res.*, **10**, 301 (1977).

7. C. Walling, *Acc. Chem. Res.*, **24**, 255 (1991); J. F. Garst, F. Ungvary, R. Batlaw, and K. E. Lawrence, *J. Am. Chem. Soc.*, **113**, 5392 (1991).

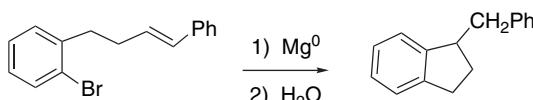
8. J. F. Garst and M. P. Soriaga, *Coord. Chem. Rev.*, **248**, 623 (2004); J. F. Garst and U. Ferenc, in *Grignard Reagents: New Developments*, H. G. Richey, Jr., ed., Wiley, Chichester, 2000, pp. 185–275.

Small amounts of cyclized products are obtained after the preparation of Grignard reagents from 5-hexenyl bromide.⁹ This indicates that cyclization of the intermediate radical competes to a small extent with combination of the radical with the metal. Quantitative kinetic models that compare competing processes are consistent with diffusion of the radicals from the surface.¹⁰ Alkyl radicals can be trapped with high efficiency by the nitroxide radical TMPO.¹¹ Nevertheless, there remains disagreement about the extent to which the radicals diffuse away from the metal surface.¹²

It seems likely that aryl, vinyl, and cyclopropyl halides react by an alternative mechanism, since the corresponding radicals are less stable than alkyl radicals. It has been suggested that these halides may react through a dianion.¹³



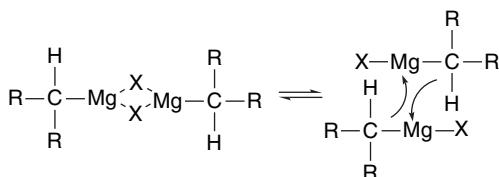
The radical cyclization test has been applied and although 2-(3-butenyl)phenyl halides give little if any cyclization, substituents that are expected to increase the rate of cyclization to around 10^9s^{-1} do give some cyclic product.¹⁴



The stereochemistry of Grignard reagents having stereogenic centers is another means of probing the structure and lifetime of intermediates. The preparation of Grignard reagents from alkyl halides normally occurs with stereochemical randomization at the reaction site. Stereoisomeric halides give rise to organomagnesium compounds of identical composition.¹⁵ The main exceptions to this generalization are cyclopropyl and alkenyl systems, which react with partial retention of configuration.¹⁶ Once formed, secondary alkylmagnesium compounds undergo stereochemical inversion only slowly. *Endo*- and *exo*-norbornylmagnesium bromide, for example, require 1 day at room temperature to reach equilibrium.¹⁷ NMR studies have demonstrated that inversion of configuration is quite slow, on the NMR time scale, even

- ^{9.} R. C. Lamb, P. W. Ayers, and M. K. Toney, *J. Am. Chem. Soc.*, **85**, 3483 (1963); R. C. Lamb and P. W. Ayers, *J. Org. Chem.*, **27**, 1441 (1962); C. Walling and A. Cioffari, *J. Am. Chem. Soc.*, **92**, 6609 (1970); H. W. H. J. Bodewitz, C. Blomberg, and F. Bickelhaupt, *Tetrahedron*, **31**, 1053 (1975); J. F. Garst and B. L. Swift, *J. Am. Chem. Soc.*, **111**, 241 (1989).
- ^{10.} J. F. Garst, B. L. Swift, and D. W. Smith, *J. Am. Chem. Soc.*, **111**, 234 (1989); J. F. Garst, *Acc. Chem. Res.*, **24**, 95 (1991).
- ^{11.} K. S. Root, C. L. Hill, L. M. Lawrence, and G. M. Whitesides, *J. Am. Chem. Soc.*, **111**, 5405 (1989); L. M. Lawrence and G. M. Whitesides, *J. Am. Chem. Soc.*, **102**, 2493 (1980).
- ^{12.} C. Hamdouchi and H. M. Walborsky, in *Handbook of Grignard Reagents*, G. S. Silverman and P. E. Rakita, eds., Marcel Dekker, New York, 1996, pp. 145–218; H. M. Walborsky, *Acc. Chem. Res.*, **23**, 286 (1990).
- ^{13.} J. F. Garst, J. R. Boone, L. Webb, K. E. Lawrence, J. T. Baxter, and F. Ungavary, *Inorg. Chim. Acta*, **296**, 52 (1999).
- ^{14.} N. Bodineau, J.-M. Mattalia, V. Thimokhin, K. Handoo, J.-C. Negrel, and M. Chanon, *Org. Lett.*, **2**, 2303 (2000).
- ^{15.} N. G. Krieghoff and D. O. Cowan, *J. Am. Chem. Soc.*, **88**, 1322 (1966).
- ^{16.} T. Yoshino and Y. Manabe, *J. Am. Chem. Soc.*, **85**, 2860 (1963); H. M. Walborsky and A. E. Young, *J. Am. Chem. Soc.*, **86**, 3288 (1964); H. M. Walborsky and B. R. Banks, *Bull. Soc. Chim. Belg.*, **89**, 849 (1980); H. M. Walborsky and J. Rachon, *J. Am. Chem. Soc.*, **111**, 1896 (1989); J. Rachon and H. M. Walborsky, *Tetrahedron Lett.*, **30**, 7345 (1988).
- ^{17.} F. R. Jensen and K. L. Nakamaye, *J. Am. Chem. Soc.*, **88**, 3437 (1966); N. G. Krieghoff and D. O. Cowan, *J. Am. Chem. Soc.*, **88**, 1322 (1966).

up to 170° C.¹⁸ In contrast, the inversion of configuration of primary alkylmagnesium halides is very fast.¹⁹ This difference in the primary and secondary systems may be the result of a mechanism for inversion that involves exchange of alkyl groups between magnesium atoms.

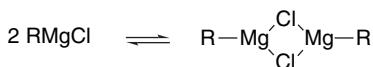


If bridged intermediates are involved, the larger steric bulk of secondary systems would retard the reaction. Steric restrictions may be further enhanced by the fact that organomagnesium reagents are often present as clusters (see below).

The usual designation of Grignard reagents as RMgX is a useful but incomplete representation of the composition of the compounds in ether solution. An equilibrium exists with magnesium bromide and the dialkylmagnesium.²⁰



The position of the equilibrium depends upon the solvent and the identity of the specific organic group, but in ether lies well to the left for simple aryl-, alkyl-, and alkenylmagnesium halides.²¹ Solutions of organomagnesium compounds in diethyl ether contain aggregated species.²² Dimers predominate in ether solutions of alkylmagnesium chlorides.



The corresponding bromides and iodides show concentration-dependent behavior and in very dilute solutions they exist as monomers. In tetrahydrofuran, there is less tendency to aggregate, and several alkyl and aryl Grignard reagents have been found to be monomeric in this solvent.

A number of Grignard reagents have been subjected to X-ray structure determination.²³ Ethylmagnesium bromide has been observed in both monomeric and dimeric forms in crystal structures.²⁴ Figures 7.1a and b show, respectively, the crystal structure

- ^{18.} E. Pechold, D. G. Adams, and G. Fraenkel, *J. Org. Chem.*, **36**, 1368 (1971).
- ^{19.} G. M. Whitesides, M. Witanowski, and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 2854 (1965); G. M. Whitesides and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 4878 (1965); G. Fraenkel and D. T. Dix, *J. Am. Chem. Soc.*, **88**, 979 (1966).
- ^{20.} K. C. Cannon and G. R. Krow, in *Handbook of Grignard Reagents*, G. S. Silverman and P. E. Rakita, eds., Marcel Dekker, New York, 1996, pp. 271–289.
- ^{21.} G. E. Parris and E. C. Ashby, *J. Am. Chem. Soc.*, **93**, 1206 (1971); P. E. M. Allen, S. Hagias, S. F. Lincoln, C. Mair, and E. H. Williams, *Ber. Bunsenges. Phys. Chem.*, **86**, 515 (1982).
- ^{22.} E. C. Ashby and M. B. Smith, *J. Am. Chem. Soc.*, **86**, 4363 (1964); F. W. Walker and E. C. Ashby, *J. Am. Chem. Soc.*, **91**, 3845 (1969).
- ^{23.} C. E. Holloway and M. Melnik, *Coord. Chem. Rev.*, **135**, 287 (1994); H. L. Uhm, in *Handbook of Grignard Reagents*, G. S. Silverman and P. E. Rakita, eds., Marcel Dekker, New York, 1996, pp. 117–144; F. Bickelhaupt, in *Grignard Reagents: New Developments*, H. G. Richey, Jr., ed., Wiley, New York, 2000, pp. 175–181.
- ^{24.} L. J. Guggenberger and R. E. Rundle, *J. Am. Chem. Soc.*, **90**, 5375 (1968); A. L. Spek, P. Voorbergen, G. Schat, C. Blomberg, and F. Bickelhaupt, *J. Organomet. Chem.*, **77**, 147 (1974).

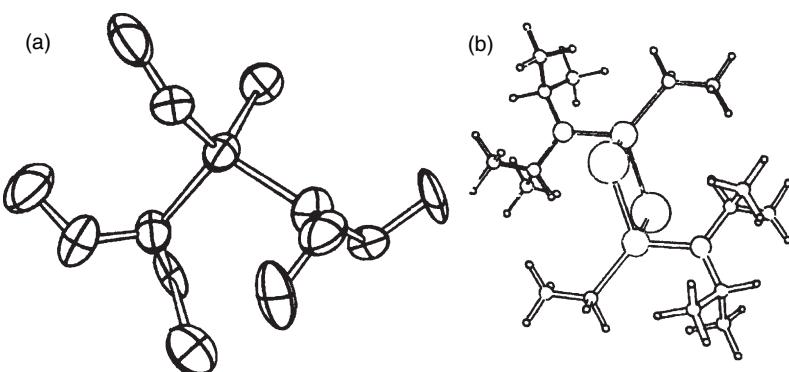


Fig. 7.1. Crystal structures of ethylmagnesium bromide: (a) Monomeric $C_2H_5MgBr[O(C_2H_5)_2]_2$. Reproduced from *J. Am. Chem. Soc.*, **90**, 5375 (1968), by permission of the American Chemical Society. (b) Dimeric $\{C_2H_5MgBr [O-(i-C_3H_7)_2]\}_2$. Reproduced from *J. Organomet. Chem.*, **77**, 147 (1974), by permission of Elsevier.

of the monomer with two diethyl ether molecules coordinated to magnesium and a dimeric structure with one diisopropyl ether molecule per magnesium.

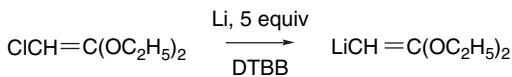
7.1.2. Preparation and Properties of Organolithium Compounds

7.1.2.1. Preparation Using Metallic Lithium. Most simple organolithium reagents can be prepared by reaction of an appropriate halide with lithium metal. The method is applicable to alkyl, aryl, and alkenyl lithium reagents.



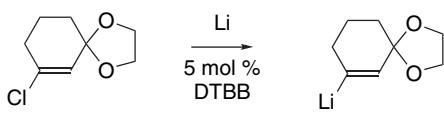
As with organomagnesium reagents, there is usually loss of stereochemical integrity at the site of reaction during the preparation of alkylolithium compounds.²⁵ Alkenyllithium reagents can usually be prepared with retention of configuration of the double bond.^{26,27}

For some halides, it is advantageous to use finely powdered lithium and a catalytic amount of an aromatic hydrocarbon, usually naphthalene or 4, 4'-di-*t*-butylbiphenyl (DTBB).²⁸ These reaction conditions involve either radical anions or dianions generated by reduction of the aromatic ring (see Section 5.6.1.2), which then convert the halide to a radical anion. Several useful functionalized lithium reagents have been prepared by this method. In the third example below, the reagent is trapped *in situ* by reaction with benzaldehyde.

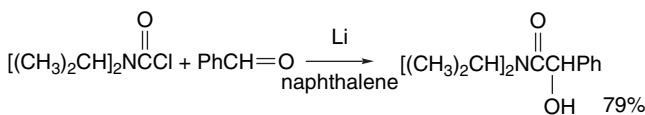


Ref. 29

- ²⁵ W. H. Glaze and C. M. Selman, *J. Org. Chem.*, **33**, 1987 (1968).
- ²⁶ M. Yus, R. P. Herrera, and A. Guijarro, *Chem. Eur. J.*, **8**, 2574 (2002).
- ²⁷ J. Millon, R. Lorne, and G. Linstrumelle, *Synthesis*, 434 (1975).
- ²⁸ M. Yus, *Chem. Soc. Rev.*, 155 (1996); D. J. Ramon and M. Yus, *Tetrahedron*, **52**, 13739 (1996).
- ²⁹ M. Si-Fofil, H. Ferrerira, J. Galak, and L. Duhamel, *Tetrahedron Lett.*, **39**, 8975 (1998).

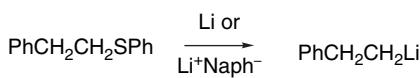


Ref. 30



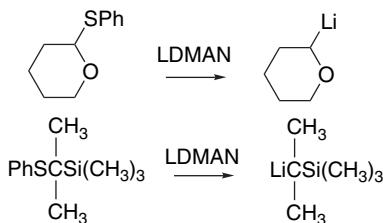
Ref. 31

Alkyllithium reagents can also be generated by reduction of sulfides.³² Alkenyl-lithium and substituted alkyllithium reagents can be prepared from sulfides,³³ and sulfides can be converted to lithium reagents by the catalytic electron transfer process described for halides.³⁴



Ref. 35

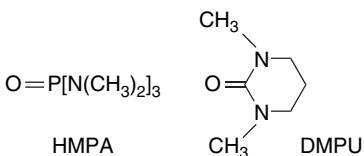
This technique is especially useful for the preparation of α -lithio ethers, sulfides, and silanes.³⁶ The lithium radical anions of naphthalene, 4,4'-di-*t*-butyldiphenyl (DTBB) or dimethylaminonaphthalene (LDMAN) are used as the reducing agent.



The simple alkyllithium reagents exist mainly as hexamers in hydrocarbon solvents.³⁷ In ethers, tetrameric structures are usually dominant.³⁸ The tetramers,

- ³⁰ A. Bachki, F. Foubelo, and M. Yus, *Tetrahedron*, **53**, 4921 (1997).
- ³¹ A. Guijarro, B. Mancheno, J. Ortiz, and M. Yus, *Tetrahedron*, **52**, 1643 (1993).
- ³² T. Cohen and M. Bhupathy, *Acc. Chem. Res.*, **22**, 152 (1989).
- ³³ T. Cohen and M. D. Doubleday, *J. Org. Chem.*, **55**, 4784 (1990); D. J. Rawson and A. I. Meyers, *Tetrahedron Lett.*, **32**, 2095 (1991); H. Liu and T. Cohen, *J. Org. Chem.*, **60**, 2022 (1995).
- ³⁴ F. Foubelo, A. Gutierrez, and M. Yus, *Synthesis*, 503 (1999).
- ³⁵ C. G. Screttas and M. Micha-Screttas, *J. Org. Chem.*, **43**, 1064 (1978); C. G. Screttas and M. Micha-Screttas, *J. Org. Chem.*, **44**, 113 (1979).
- ³⁶ T. Cohen and J. R. Matz, *J. Am. Chem. Soc.*, **102**, 6900 (1980); T. Cohen, J. P. Sherbine, J. R. Matz, R. R. Hutchins, B. M. McHenry, and P. R. Wiley, *J. Am. Chem. Soc.*, **106**, 3245 (1984); S. D. Rychnovsky, K. Plzak, and D. Pickering, *Tetrahedron Lett.*, **35**, 6799 (1994); S. D. Rychnovsky and D. J. Skalitzky, *J. Org. Chem.*, **57**, 4336 (1992).
- ³⁷ G. Fraenkel, W. E. Beckenbaugh, and P. P. Yang, *J. Am. Chem. Soc.*, **98**, 6878 (1976); G. Fraenkel, M. Henrichs, J. M. Hewitt, B. M. Su, and M. J. Geckle, *J. Am. Chem. Soc.*, **102**, 3345 (1980).
- ³⁸ H. L. Lewis and T. L. Brown, *J. Am. Chem. Soc.*, **92**, 4664 (1970); P. West and R. Waack, *J. Am. Chem. Soc.*, **89**, 4395 (1967); J. F. McGarry and C. A. Ogle, *J. Am. Chem. Soc.*, **107**, 1085 (1985); D. Seebach, R. Hassig, and J. Gabriel, *Helv. Chim. Acta*, **66**, 308 (1983); T. L. Brown, *Adv. Organomet. Chem.*, **3**, 365 (1965); W. N. Setzer and P. v. R. Schleyer, *Adv. Organomet. Chem.*, **24**, 354 (1985); W. Bauer, T. Clark, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **109**, 970 (1987).

in turn, are solvated with ether molecules.³⁹ Phenyllithium is tetrameric in cyclohexane and a mixture of monomer and dimer in THF.⁴⁰ Chelating ligands such as tetramethylethylenediamine (TMEDA) reduce the degree of aggregation.⁴¹ Strong donor molecules such as hexamethylphosphorotriamide (HMPA) and *N,N*-dimethylpropyleneurea (DMPU) also lead to more dissociated and more reactive organolithium reagents.⁴² NMR studies on phenyllithium show that TMEDA, other polyamine ligands, HMPA, and DMPU favor monomeric solvated species.⁴³



The crystal structures of many organolithium compounds have been determined.⁴⁴ Phenyllithium has been crystallized as an ether solvate. The structure is tetrameric with lithium and carbon atoms at alternating corners of a highly distorted cube. The lithium atoms form a tetrahedron and the carbons are associated with the faces of the tetrahedron. Each carbon is 2.33 Å from the three neighboring lithium atoms and an ether molecule is coordinated to each lithium atom. Figures 7.2a and b show, respectively, the Li–C cluster and the complete array of atoms, except for hydrogen.⁴⁵ Section 6.2 of Part A provides additional information on the structure of organolithium compounds.

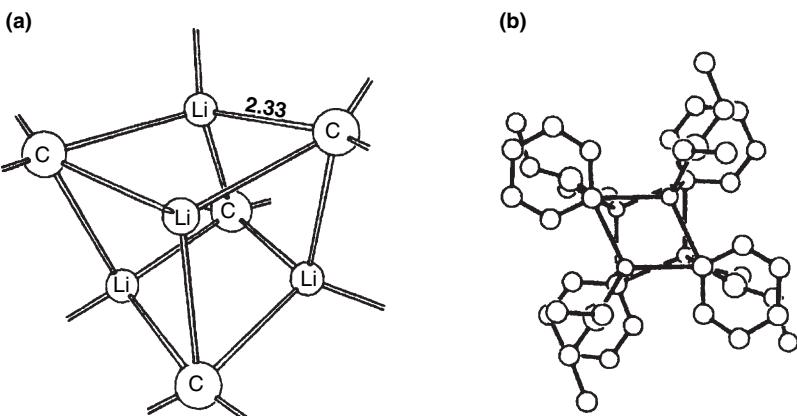


Fig. 7.2. Crystal structure of tetrameric phenyllithium diethyl etherate: (a) tetrameric C_4Li_4 cluster; (b) complete structure except for hydrogens. Reproduced from *J. Am. Chem. Soc.*, **105**, 5320 (1983), by permission of the American Chemical Society.

- ³⁹ P. D. Bartlett, C. V. Goebel, and W. P. Weber, *J. Am. Chem. Soc.*, **91**, 7425 (1969).
- ⁴⁰ L. M. Jackman and L. M. Scarmoutzos, *J. Am. Chem. Soc.*, **106**, 4627 (1984); O. Eppers and H. Gunther, *Helv. Chim. Acta*, **75**, 2553 (1992).
- ⁴¹ W. Bauer and C. Griesinger, *J. Am. Chem. Soc.*, **115**, 10871 (1993); D. Hoffmann and D. B. Collum, *J. Am. Chem. Soc.*, **120**, 5810 (1998).
- ⁴² H. J. Reich and D. P. Green, *J. Am. Chem. Soc.*, **111**, 8729 (1989).
- ⁴³ H. J. Reich, D. P. Green, M. A. Medina, W. S. Goldenberg, B. O. Gudmundsson, R. R. Dykstra, and N. H. Phillips, *J. Am. Chem. Soc.*, **120**, 7201 (1998).
- ⁴⁴ E. Weiss, *Angew. Chem. Int. Ed. Engl.*, **32**, 1501 (1993).
- ⁴⁵ H. Hope and P. P. Power, *J. Am. Chem. Soc.*, **105**, 5320 (1983).



7.1.2.2. Preparation by Lithiation. There are three other general methods that are very useful for preparing organolithium reagents. The first of these is *hydrogen-metal exchange* or *metallation*, which for the specific case of lithium is known as *lithiation*. This reaction is the usual method for preparing alkynylmagnesium and alkynyllithium reagents. The reactions proceed readily because of the relative acidity of the hydrogen bound to *sp* carbon.

The features that characterize the activating groups include an electron pair that can coordinate lithium and polarity that can stabilize the anionic character.⁵⁰ Geometric factors are also important. For amido groups, for example, it has been deduced by comparison of various cyclic systems that the preferred geometry is for the activating amide group to be coplanar with the position of lithiation.⁵¹ If competing nucleophilic attack is a possibility, as in tertiary amides, steric bulk is also an important factor. Consistent with the importance of polar and electrostatic effects in lithiation, a fluoro substituent is a good directing substituent. Amide bases such as LDA and LTMP give better results than alkynyllithium reagents. With these bases, fluorine was found to promote *ortho* lithiation selectively over such directing groups as methoxy and diethylaminocarbonyloxy.⁵²

⁴⁶ R. D. Clark and A. Jahangir, *Org. React.*, **47**, 1 (1995).

⁴⁷ D. W. Slocum and C. A. Jennings, *J. Org. Chem.*, **41**, 3653 (1976); J. M. Mallan and R. C. Rebb, *Chem. Rev.*, **69**, 693 (1969); H. W. Gschwend and H. R. Rodriguez, *Org. React.*, **26**, 1 (1979); V. Snieckus, *Chem. Rev.*, **90**, 879 (1990); C. Quesnelle, T. Iihama, T. Aubert, H. Perrier, and V. Snieckus, *Tetrahedron Lett.*, **33**, 2625 (1992); M. Iwao, T. Iihama, K. K. Mahalandabas, H. Perrier, and V. Snieckus, *J. Org. Chem.*, **54**, 24 (1989); L. A. Spangler, *Tetrahedron Lett.*, **37**, 3639 (1996).

⁴⁸ J. M. Muchowski and M. C. Venuti, *J. Org. Chem.*, **45**, 4798 (1980); P. Stanetty, H. Koller, and M. Mihovilovic, *J. Org. Chem.*, **57**, 6833 (1992); J. Mortier, J. Moyroud, B. Benneteau, and P.A. Cain, *J. Org. Chem.*, **59**, 4042 (1994).

⁴⁹ C. A. Townsend and L. M. Bloom, *Tetrahedron Lett.*, **22**, 3923 (1981); R. C. Ronald and M. R. Winkle, *Tetrahedron*, **39**, 2031 (1983); M. R. Winkle and R. C. Ronald, *J. Org. Chem.*, **47**, 2101 (1982).

⁵⁰ (a) N. J. R. van Eikema Hommes and P. v. R. Schleyer, *Angew. Chem. Int. Ed. Engl.*, **31**, 755 (1992); (b) N. J. R. van Eikema Hommes and P. v. R. Schleyer, *Tetrahedron*, **50**, 5903 (1994).

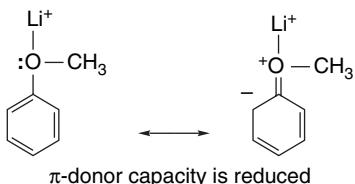
⁵¹ P. Beak, S. T. Kerrick, and D. J. Gallagher, *J. Am. Chem. Soc.*, **115**, 10628 (1993).

⁵² A. J. Bridges, A. Lee, E. C. Maduakor, and C. E. Schwartz, *Tetrahedron Lett.*, **33**, 7495 (1992); D. C. Furlano, S. N. Calderon, G. Chen, and K. L. Kirk, *J. Org. Chem.*, **53**, 3145 (1988).

Scheme 7.1 gives some examples of the preparation of organolithium compounds by lithiation. A variety of directing groups is represented, including methoxy (Entry 1), diethylaminocarbonyl (Entry 2), *N,N*-dimethylimidazolinyl (Entry 3), *t*-butoxycarbonylamido (Entry 4), carboxy (Entry 5), and neopentoxycarbonyl (Entry 6). In the latter case, LDA is used as the base to avoid nucleophilic addition to the carbonyl group. The tri-*i*-propyl borate serves to trap the lithiation product as it is formed and prevent further reactions with the ester carbonyl. Entry 7 is a typical lithiation of a heteroaromatic molecule, and Entry 8 shows the lithiation of methyl vinyl ether. The latter reaction is dependent on the coordination and polar effect of the methoxy group and the relative acidity of the sp^2 C–H bond. Entry 9 is an allylic lithiation, promoted by the trimethylsiloxy group. Entry 10 is an interesting lithiation of an epoxide. The silyl substituent also has a modest stabilizing effect (see Part A, Section 3.4.2).

Reaction conditions can be modified to accelerate the rate of lithiation when necessary. Addition of tertiary amines, especially TMEDA, facilitates lithiation⁵³ by coordination at the lithium and promoting dissociation of aggregated structures. Kinetic and spectroscopic evidence indicates that in the presence of TMEDA lithiation of methoxybenzene involves the solvated dimeric species $(BuLi)_2(TMEDA)_2$.⁵⁴ The reaction shows an isotope effect for the *o*-hydrogen, establishing that proton abstraction is rate determining.⁵⁵ It is likely that there is a precomplexation between the methoxybenzene and organometallic dimer.

The lithiation process has been modeled by MP2/6-31+G* calculations. The TSs for lithiation of fluorobenzene and methoxybenzene have lithium nearly in the aromatic plane and coordinated to the directing group as shown in Figure 7.3.⁵⁶ Although these structures represent lithiations as occurring through a monomeric species, similar effects are present in dimers or aggregates.^{50b} There is a considerable electrostatic component to the stabilization of the TS.^{50a} It has also been pointed out that the coordination of the Lewis acid Li⁺ at the methoxy or fluorine group decreases the π -donor capacity of the groups and accentuates their σ -EWG capacity. The combination of these interactions is responsible for the activating effects of these groups.

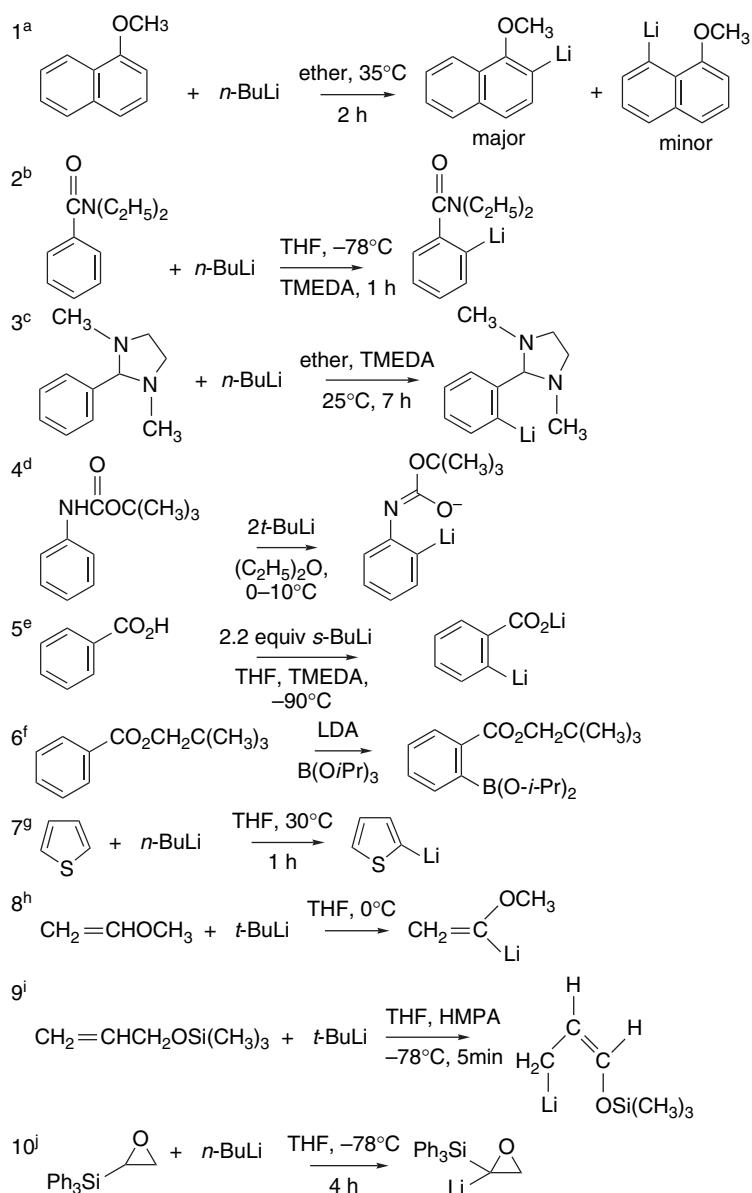


Lithiation of alkyl groups is also possible and again a combination of donor chelation and polar stabilization of anionic character is required. Amides and carbamates can be lithiated α to the nitrogen.

- ⁵³. G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964); R. West and P. C. Jones, *J. Am. Chem. Soc.*, **90**, 2656 (1968); S. Akiyama and J. Hooz, *Tetrahedron Lett.*, 4115 (1973); D. W. Slocum, R. Moon, J. Thompson, D. S. Coffey, J. D. Li, M. G. Slocum, A. Siegel, and R. Gayton-Garcia, *Tetrahedron Lett.*, **35**, 385 (1994); M. Khaldi, F. Chretien, and Y. Chapleur, *Tetrahedron Lett.*, **35**, 401 (1994); D. B. Collum, *Acc. Chem. Res.*, **25**, 448 (1992).
- ⁵⁴. R. A. Rennels, A. J. Maliakal, and D. B. Collum, *J. Am. Chem. Soc.*, **120**, 421 (1998).
- ⁵⁵. M. Stratakis, *J. Org. Chem.*, **62**, 3024 (1997).
- ⁵⁶. J. M. Saa, *Helv. Chim. Acta*, **85**, 814 (2002).

SECTION 7.1

Preparation and Properties of Organomagnesium and Organolithium Reagents

Scheme 7.1. Preparation of Organolithium Compounds by Metallation

- a. B. M. Graybill and D. A. Shirley, *J. Org. Chem.*, **31**, 1221 (1966).
 b. P. A. Beak and R. A. Brown, *J. Org. Chem.*, **42**, 1823 (1977); *J. Org. Chem.*, **44**, 4463 (1979).
 c. T. D. Harris and G. P. Roth, *J. Org. Chem.*, **44**, 2004 (1979).
 d. P. Stanetty, H. Koller, and M. Mihovilovic, *J. Org. Chem.*, **57**, 6833 (1992).
 e. B. Bennetau, J. Mortier, J. Moyroud, and J.-L. Guesnet, *J. Chem. Soc., Perkin Trans. I*, 1265 (1995).
 f. S. Caron and J. M. Hawkins, *J. Org. Chem.*, **63**, 2054 (1998).
 g. E. Jones and I. M. Moodie, *Org. Synth.*, **50**, 104 (1970).
 h. J. E. Baldwin, G. A. Hofle, and O. W. Lever, Jr., *J. Am. Chem. Soc.*, **96**, 7125 (1974).
 i. W. C. Still and T. L. Macdonald, *J. Org. Chem.*, **41**, 3620 (1976).
 j. J. J. Eisch and J. E. Galle, *J. Am. Chem. Soc.*, **98**, 4646 (1976).

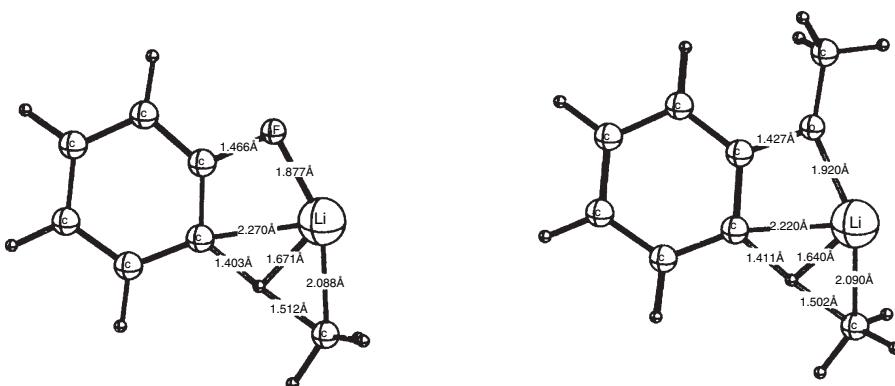
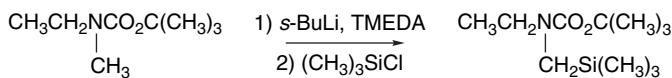
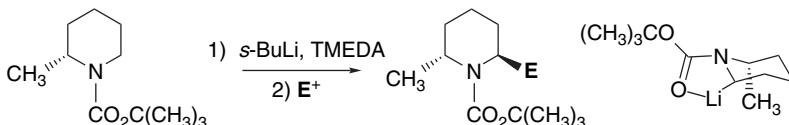


Fig. 7.3. Transition structures for lithiation of fluorobenzene (left) and methoxybenzene (right). Reproduced from *Tetrahedron*, **50**, 5903 (1994), by permission of Elsevier.

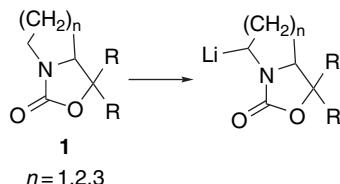


Ref. 57

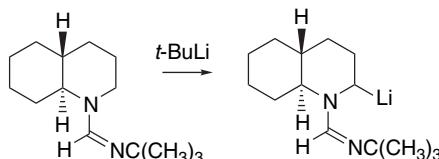


Ref. 58

Studies with bicyclic carbamates of general structure **1** indicated that proximity and alignment of the carbonyl oxygen to the lithiation site is a major factor in determining the rate of lithiation.⁵⁹



Bicyclic structures of this type are more reactive than monocyclic or acyclic carbamates, indicating that a relatively rigid orientation of the carbonyl group is favorable to lithiation. Substituted formamidines can also be lithiated.⁶⁰



⁵⁷. V. Snieckus, M. Rogers-Evans, P. Beak, W. K. Lee, E. K. Yum, and J. Freskos, *Tetrahedron Lett.*, **35**, 4067 (1994).

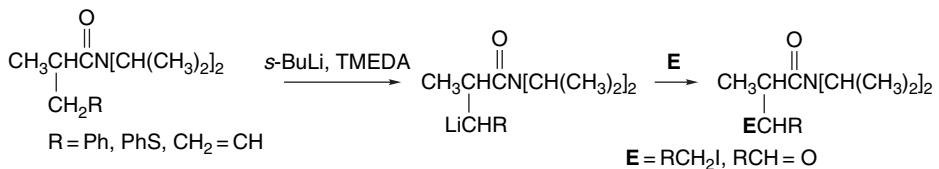
⁵⁸. P. Beak and W. K. Lee, *J. Org. Chem.*, **58**, 1109 (1993).

⁵⁹. K. M. B. Gross and P. Beak, *J. Am. Chem. Soc.*, **123**, 315 (2001).

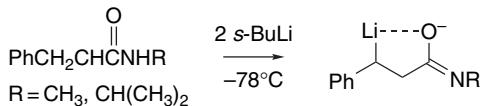
⁶⁰. A. I. Meyers and G. Milot, *J. Am. Chem. Soc.*, **115**, 6652 (1993).

SECTION 7.1

Preparation and Properties of Organomagnesium and Organolithium Reagents



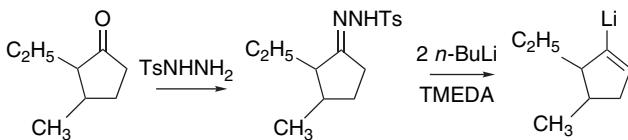
β -Lithiation has also been observed for deprotonated secondary amides of 3-phenylpropanoic acid.



Ref. 62

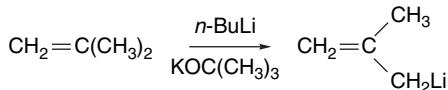
As with aromatic lithiation, the mechanism of directed lithiation in these systems appears to involve an association between the activating substituent and the lithiating agent.⁶³

Alkenyllithium compounds are intermediates in the *Shapiro reaction*, which is discussed in Section 5.7.2. The reaction can be run in such a way that the organolithium compound is generated in high yield and subsequently allowed to react with a variety of electrophiles.⁶⁴ This method provides a route to vinylolithium compounds starting from a ketone.



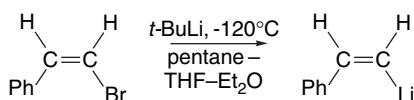
Ref. 65

Hydrocarbons lacking directing substituents are not very reactive toward metallation, but it has been found that a mixture of *n*-butyllithium and potassium *t*-butoxide⁶⁶ is sufficiently reactive to give allyl anions from alkenes such as isobutene.⁶⁷

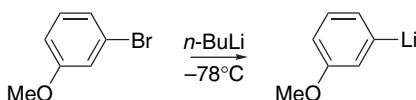


- ⁶¹. P. Beak, J. E. Hunter, Y. M. Jun, and A. P. Wallin, *J. Am. Chem. Soc.*, **109**, 5403 (1987); G. P. Lutz, A. P. Wallin, S. T. Kerrick, and P. Beak, *J. Org. Chem.*, **56**, 4938 (1991).
- ⁶². G. P. Lutz, H. Du, D. J. Gallagher, and P. Beak, *J. Org. Chem.*, **61**, 4542 (1996).
- ⁶³. W. Bauer and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **111**, 7191 (1989); P. Beak, S. T. Kerrick, and D. J. Gallagher, *J. Am. Chem. Soc.*, **115**, 10628 (1993).
- ⁶⁴. F. T. Bond and R. A. DiPietro, *J. Org. Chem.*, **46**, 1315 (1981); T. H. Chan, A. Baldassarre, and D. Massuda, *Synthesis*, 801 (1976); B. M. Trost and T. N. Nanninga, *J. Am. Chem. Soc.*, **107**, 1293 (1985).
- ⁶⁵. W. Barth and L. A. Paquette, *J. Org. Chem.*, **50**, 2438 (1985).
- ⁶⁶. L. Lochmann, J. Pospisil, and D. Lim, *Tetrahedron Lett.*, 257 (1966).
- ⁶⁷. M. Schlosser and J. Hartmann, *Angew. Chem. Int. Ed. Engl.*, **12**, 508 (1973); J. J. Bahl, R. B. Bates, and B. Gordon, III, *J. Org. Chem.*, **44**, 2290 (1979); M. Schlosser and G. Rauchshwalbe, *J. Am. Chem. Soc.*, **100**, 3258 (1978).

7.1.2.3. Preparation by Halogen-Metal Exchange. Halogen-metal exchange is another important method for preparation of organolithium reagents. The reaction proceeds in the direction of forming the more stable organolithium reagent, that is, the one derived from the more acidic organic compound. Thus, by use of the very basic organolithium compounds *n*-butyl- or *t*-butyllithium, halogen substituents at more acidic sp^2 carbons are readily exchanged to give the corresponding lithium compound. Halogen-metal exchange is particularly useful for converting aryl and alkenyl halides to the corresponding lithium compounds.



Ref. 68



Ref. 69

Halogen-metal exchange is a very fast reaction and is usually carried out at -60 to -120°C . This makes it possible to prepare aryllithium compounds containing functional groups, such as cyano and nitro, that react under the conditions required for preparation from lithium metal. Halogen-metal exchange is restricted for alkyl halides by competing reactions, but primary alkylolithium reagents can be prepared from iodides under carefully controlled conditions.⁷⁰

Retention of configuration is sometimes observed when organolithium compounds are prepared by halogen-metal exchange. The degree of retention is low for exchange of most alkyl systems,⁷¹ but it is normally high for cyclopropyl and vinyl halides.⁷² Once formed, both cyclopropyl and vinylolithium reagents retain their configuration at room temperature.

Scheme 7.2 gives some examples of preparation of organolithium compounds by halogen-metal exchange. Entries 1, 2, and 3 are representative low-temperature preparations of alkenyllithium reagents. Entry 4 involves a cyclopropyl bromide. Both the *cis* and *trans* isomers react with retention of configuration. In Entries 1, 3, and 4, two equivalents of *t*-butyllithium are required because the *t*-butyl halide formed by exchange consumes one equivalent. Entry 5 is an example of retention of configuration at a double bond. Entries 6 and 7 show aryl bromides with functional groups that

⁶⁸ N. Neumann and D. Seebach, *Tetrahedron Lett.*, 4839 (1976).

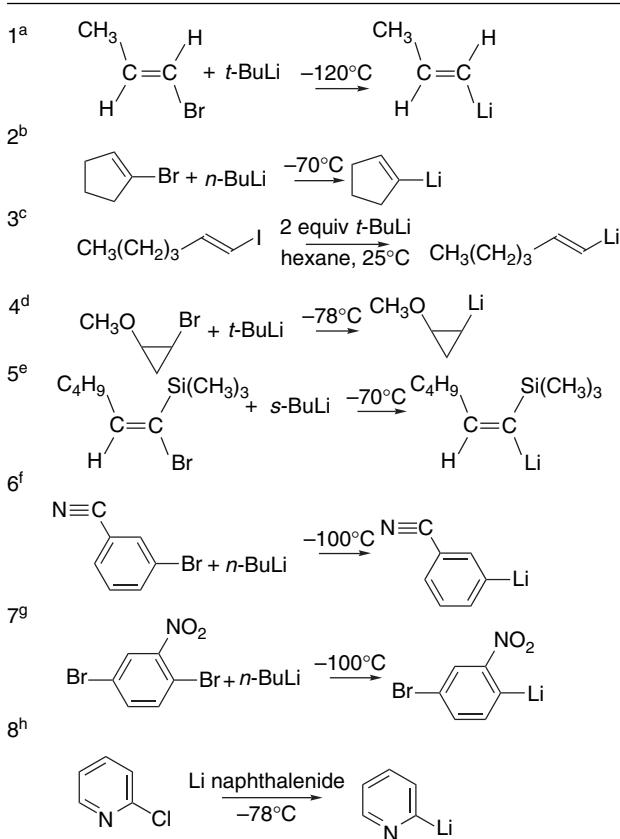
⁶⁹ T. R. Hoye, S. J. Martin, and D. R. Peck, *J. Org. Chem.*, **47**, 331 (1982).

⁷⁰ W. F. Bailey and E. R. Punzalan, *J. Org. Chem.*, **55**, 5404 (1990); E. Negishi, D. R. Swanson, and C. J. Rousset, *J. Org. Chem.*, **55**, 5406 (1990).

⁷¹ R. L. Letsinger, *J. Am. Chem. Soc.*, **72**, 4842 (1950); D. Y. Curtin and W. J. Koehl, Jr., *J. Am. Chem. Soc.*, **84**, 1967 (1962).

⁷² H. M. Walborsky, F. J. Impastato, and A. E. Young, *J. Am. Chem. Soc.*, **86**, 3283 (1964); D. Seyerth and L. G. Vaughan, *J. Am. Chem. Soc.*, **86**, 883 (1964); M. J. S. Dewar and J. M. Harris, *J. Am. Chem. Soc.*, **91**, 3652 (1969); E. J. Corey and P. Ulrich, *Tetrahedron Lett.*, 3685 (1975); N. Neumann and D. Seebach, *Tetrahedron Lett.*, 4839 (1976); R. B. Miller and G. McGarvey, *J. Org. Chem.*, **44**, 4623 (1979).

Scheme 7.2. Preparation of Organolithium Reagents by Halogen-Metal Exchange

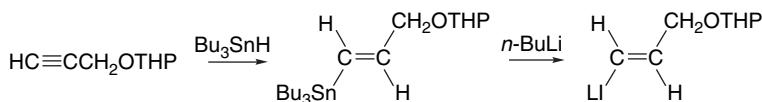


- a. H. Neuman and D. Seebach, *Tetrahedron Lett.*, 4839 (1976).
 b. J. Milton, R. Lorne, and G. Linsturmelle, *Synthesis*, 434 (1975).
 c. M. A. Peterson and R. Polt, *Synth. Commun.* **22**, 477 (1992).
 d. E. J. Corey and P. Ulrich, *Tetrahedron Lett.*, 3685 (1975).
 e. R. B. Miller and G. McGarvey, *J. Org. Chem.*, **44**, 4623 (1979).
 f. W. E. Parham and L. D. Jones, *J. Org. Chem.*, **41**, 1187 (1976).
 g. W. E. Parham and R. M. Piccirilli, *J. Org. Chem.*, **42**, 257 (1977).
 h. Y. Kondo, N. Murata, and T. Sakamoto, *Heterocycles*, **37**, 1467 (1994).

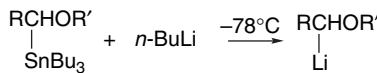
are reactive toward organometallic compounds at higher temperature, but which can undergo the halogen-metal reaction successfully at low temperature. Entry 8 is an example of the use of lithium naphthalenide for halogen-metal exchange.

7.1.2.4. Preparation by Metal-Metal Exchange. A third useful method of preparing organolithium reagents involves *metal-metal exchange* or *transmetallation*. The reaction between two organometallic compounds proceeds in the direction of placing the more electropositive metal at the more acidic carbon position. Exchanges between organotin reagents and alkylolithium reagents are particularly significant from a synthetic point of view. Terminal alkenyllithium compounds can be made from

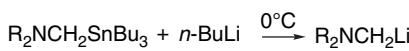
vinylstannanes, which are available by addition of stannanes to terminal alkynes (see Section 9.3.1).



Ref. 73

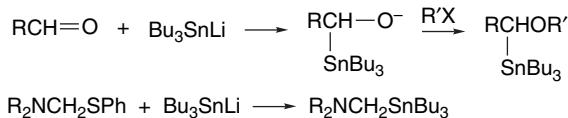


Ref. 74



Ref. 75

The α -tri-*n*-butylstannylyl derivatives needed for the latter two examples are readily available.



The exchange reactions of α -alkoxystannanes occur with retention of configuration at the carbon-metal bond.⁷⁶



7.2. Reactions of Organomagnesium and Organolithium Compounds

7.2.1. Reactions with Alkylating Agents

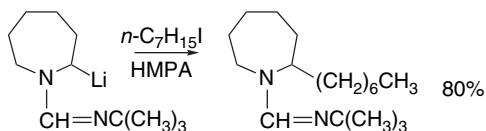
Organomagnesium and organolithium compounds are strongly basic and nucleophilic. Despite their potential to react as nucleophiles in S_N2 substitution reactions, this reaction is of limited utility in synthesis. One limitation on alkylation reactions is competition from electron transfer processes, which can lead to radical reactions. Methyl and other primary iodides usually give the best results in alkylation reactions.

⁷³ E. J. Corey and R. H. Wollenberg, *J. Org. Chem.*, **40**, 2265 (1975).

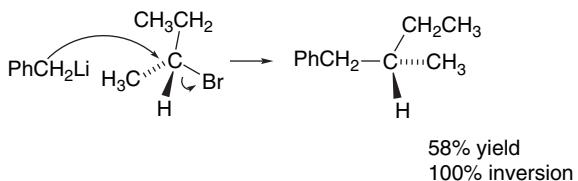
⁷⁴ W. C. Still, *J. Am. Chem. Soc.*, **100**, 1481 (1978).

⁷⁵ D. J. Peterson, *J. Am. Chem. Soc.*, **93**, 4027 (1971).

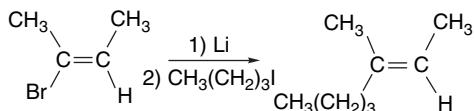
⁷⁶ W. C. Still and C. Sreekumar, *J. Am. Chem. Soc.*, **102**, 1201 (1980); J. S. Sawyer, A. Kucerovy, T. L. Macdonald, and G. J. McGarvey, *J. Am. Chem. Soc.*, **110**, 842 (1988).



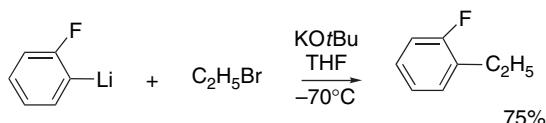
Organolithium reagents in which the carbanion is delocalized are more useful than alkylolithium reagents in alkylation reactions. Allyllithium and benzyllithium reagents can be alkylated and with secondary alkyl bromides and a high degree of inversion of configuration is observed.⁷⁸



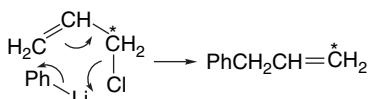
Alkenyllithium reagents can be alkylated in good yields by alkyl iodides and bromides.⁷⁹



The reactions of aryllithium reagents are accelerated by inclusion of potassium alkoxides.⁸⁰



Alkylation by allylic halides is usually a satisfactory reaction, and in this case the reaction may proceed through a cyclic mechanism.⁸¹ For example, when 1-¹⁴C-allyl chloride reacts with phenyllithium, about three-fourths of the product has the labeled carbon at the terminal methylene group.



77. A. I. Meyers, P. D. Edwards, W. F. Rieker, and T. R. Bailey, *J. Am. Chem. Soc.*, **106**, 3270 (1984); A. I. Meyers and G. Milot, *J. Am. Chem. Soc.*, **115**, 6652 (1993).

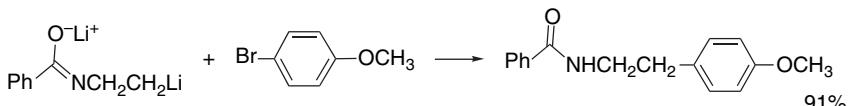
78. L. H. Sommer and W. D. Korte, *J. Org. Chem.*, **35**, 22 (1970).

79. J. Millon, R. Lorne, and G. Linstrumelle, *Synthesis*, 434 (1975).

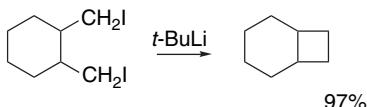
80. L. Brandsma, A. G. Mal'kina, L. Lochmann, and P. v. R. Schleyer, *Rec. Trav. Chim. Pays-Bas*, **113**, 529 (1994); L. Lochmann and J. Trekoval, *Coll. Czech. Chem. Commun.*, **51**, 1439 (1986).

81. R. M. Magid and J. G. Welch, *J. Am. Chem. Soc.*, **90**, 5211 (1968); R. M. Magid, E. C. Nieh, and R. D. Gandomj, *J. Org. Chem.*, **36**, 2099 (1971); R. M. Magid and E. C. Nieh, *J. Org. Chem.*, **36**, 2105 (1971).

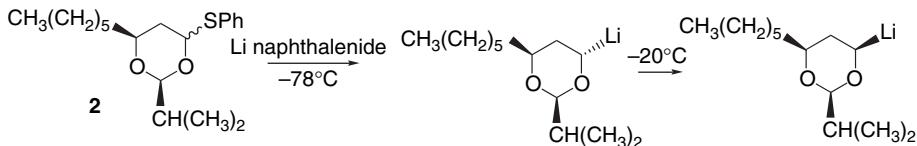
Coupling of certain lithiated reagents with aryl and vinyl halides is also possible.⁸² These reactions probably proceed by a fast halogen-lithium exchange, generating the alkyl halide, which then undergoes substitution. This reaction has been applied to β -lithiobenzamides.⁸³



Intramolecular reactions are useful for forming small rings. The reaction of 1,3-, 1,4-, and 1,5-diiodides with *t*-butyllithium is an effective means of ring closure, but 1,6-diiodides give very little cyclization.⁸⁴

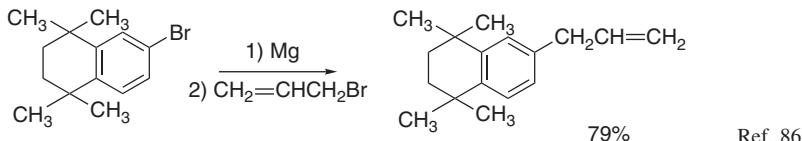


Functionalized organolithium reagents can be prepared and alkylated. The configuration of the dioxanyl reagent **2** proved to be subject to control.⁸⁵ The kinetically favored *trans* lithio derivative is converted to the more stable *cis* isomer at 20°C. Both isomers were methylated with *retention* of configuration at saturated carbon.

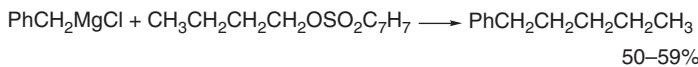


Both trialkylsilyl and trialkylstannyl halides usually give high yields of substitution products with organolithium reagents, and this is an important route to silanes and stannanes (see Section 9.2.1 and 9.3.1).

Grignard reagents are somewhat less reactive toward alkylation but can be of synthetic value, especially when methyl, allyl, or benzyl halides are involved.



Synthetically useful alkylation of Grignard reagents can also be carried out with alkyl sulfonates and sulfates.



Ref. 87

⁸². R. E. Merrill and E. Negishi, *J. Org. Chem.*, **39**, 3452 (1974).

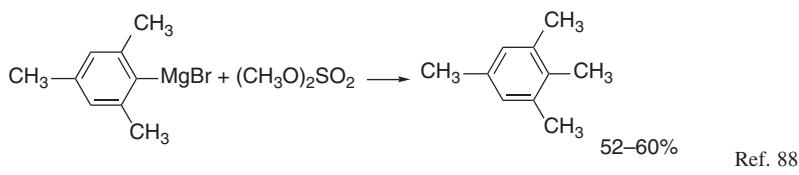
⁸³. J. Barluenga, J. M. Montserrat, and J. Florez, *J. Org. Chem.*, **58**, 5976 (1993).

⁸⁴. W. F. Bailey, R. P. Gagnier, and J. J. Patricia, *J. Org. Chem.*, **49**, 2098 (1984).

⁸⁵. S. D. Rychnovsky and D. J. Skalitzky, *J. Org. Chem.*, **57**, 4336 (1992).

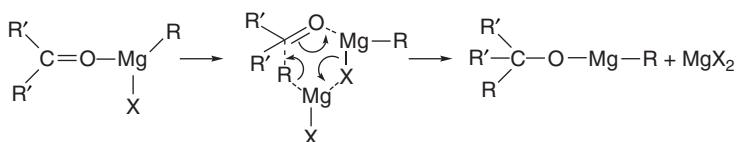
⁸⁶. J. Eustache, J.-M. Barnardon, and B. Shroot, *Tetrahedron Lett.*, **28**, 4681 (1987).

⁸⁷. H. Gilman and J. Robinson, *Org. Synth.*, **II**, 47 (1943).

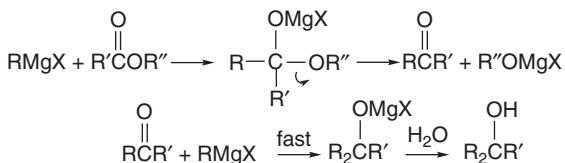


7.2.2. Reactions with Carbonyl Compounds

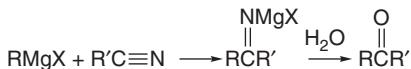
7.2.2.1. Reactions of Grignard Reagents. The most important reactions of Grignard reagents for synthesis involve addition to carbonyl groups. The TS for addition of Grignard reagents is often represented as a cyclic array containing the carbonyl group and two molecules of the Grignard reagent. There is considerable evidence favoring this mechanism involving a termolecular complex.⁸⁹



When the carbonyl carbon is substituted with a potential leaving group, the tetrahedral adduct can break down to regenerate a C=O bond and a second addition step can occur. Esters, for example are usually converted to tertiary alcohols, rather than ketones, in reactions with Grignard reagents.



Grignard reagents add to nitriles and, after hydrolysis of the reaction mixture, a ketone is obtained, with hydrocarbons being the preferred solvent for this reaction.⁹⁰



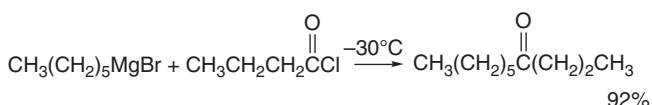
Ketones can also be prepared from acyl chlorides by reaction at low temperature using an excess of acyl chloride. Tetrahydrofuran is the preferred solvent.⁹¹ The reaction conditions must be carefully controlled to prevent formation of tertiary alcohol by addition of a Grignard reagent to the ketone as it is formed.

⁸⁸ L. I. Smith, *Org. Synth.*, **II**, 360 (1943).

⁸⁹ E. C. Ashby, R. B. Duke, and H. M. Neuman, *J. Am. Chem. Soc.*, **89**, 1964 (1967); E. C. Ashby, *Pure Appl. Chem.*, **52**, 545 (1980).

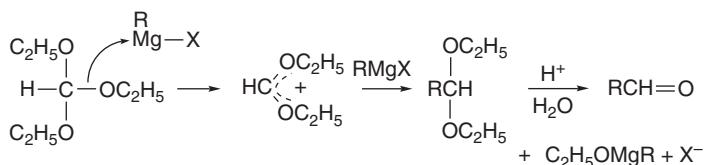
⁹⁰ P. Canonne, G. B. Foscolos, and G. Lemay, *Tetrahedron Lett.*, **21**, 155 (1980).

⁹¹ F. Sato, M. Inoue, K. Oguro, and M. Sato, *Tetrahedron Lett.*, 4303 (1979).

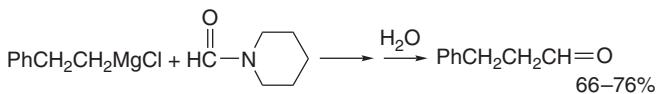


2-Pyridinethiolate esters, which are easily prepared from acyl chlorides, also react with Grignard reagents to give ketones (see Entry 6 in Scheme 7.3).⁹² *N*-Methoxy-*N*-methylamides are also converted to ketones by Grignard reagents (see Entries 17 and 18).

Aldehydes can be obtained by reaction of Grignard reagents with triethyl orthoformate. The addition step is preceded by elimination of one of the alkoxy groups to generate an electrophilic oxonium ion. The elimination is promoted by the magnesium ion acting as a Lewis acid.⁹³ The acetals formed by the addition are stable to the reaction conditions, but are hydrolyzed to aldehydes by aqueous acid.



Aldehydes can also be obtained from Grignard reagents by reaction with formamides, such as *N*-formylpiperidine. In this case, the initial adducts are stable and the aldehyde is not formed until hydrolysis during workup.



Ref. 94

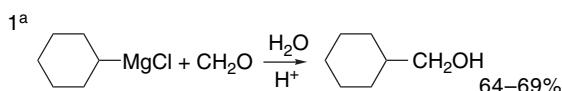
The addition of Grignard reagents to aldehydes, ketones, and esters is the basis for the synthesis of a wide variety of alcohols, and several examples are given in Scheme 7.3. Primary alcohols can be made from formaldehyde (Entry 1) or, with addition of two carbons, from ethylene oxide (Entry 2). Secondary alcohols are obtained from aldehydes (Entries 3 to 6) or formate esters (Entry 7). Tertiary alcohols can be made from esters (Entries 8 and 9) or ketones (Entry 10). Lactones give diols (Entry 11). Aldehydes can be prepared from trialkyl orthoformate esters (Entries 12 and 13). Ketones can be made from nitriles (Entries 14 and 15), pyridine-2-thiol esters (Entry 16), *N*-methoxy-*N*-methyl carboxamides (Entries 17 and 18), or anhydrides (Entry 19). Carboxylic acids are available by reaction with CO₂ (Entries 20 to 22). Amines can be prepared from imines (Entry 23). Two-step procedures that involve formation and dehydration of alcohols provide routes to certain alkenes (Entries 24 and 25).

⁹². T. Mukaiyama, M. Araki, and H. Takei, *J. Am. Chem. Soc.*, **95**, 4763 (1973); M. Araki, S. Sakata, H. Takai, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **47**, 1777 (1974).

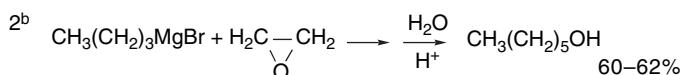
⁹³. E. L. Eliel and F. W. Nader, *J. Am. Chem. Soc.*, **92**, 584 (1970).

⁹⁴. G. A. Olah and M. Arvanaghi, *Org. Synth.*, **64**, 114 (1985); G. A. Olah, G. K. S. Prakash, and M. Arvanaghi, *Synthesis*, 228 (1984).

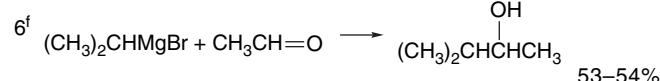
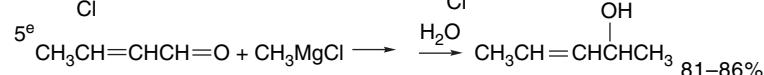
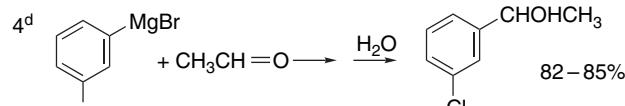
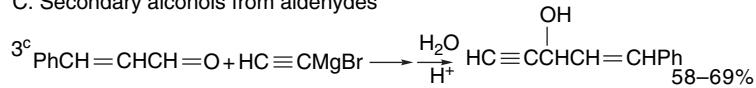
A. Primary alcohols from formaldehyde



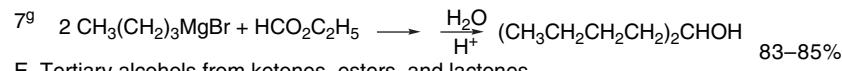
B. Primary alcohols from ethylene oxide



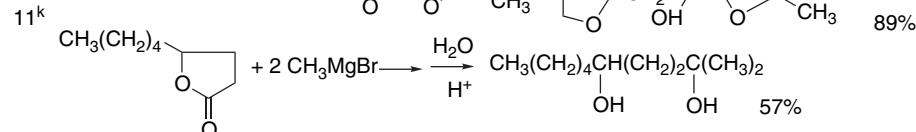
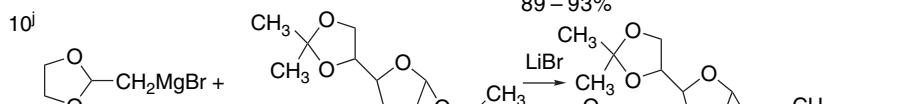
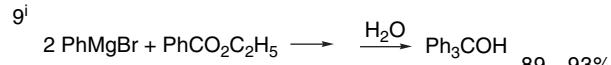
C. Secondary alcohols from aldehydes



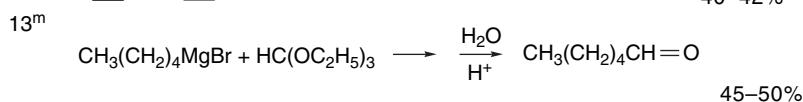
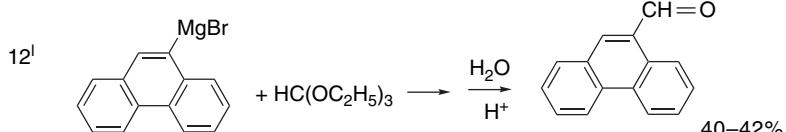
D. Secondary alcohols from formate esters



E. Tertiary alcohols from ketones, esters, and lactones



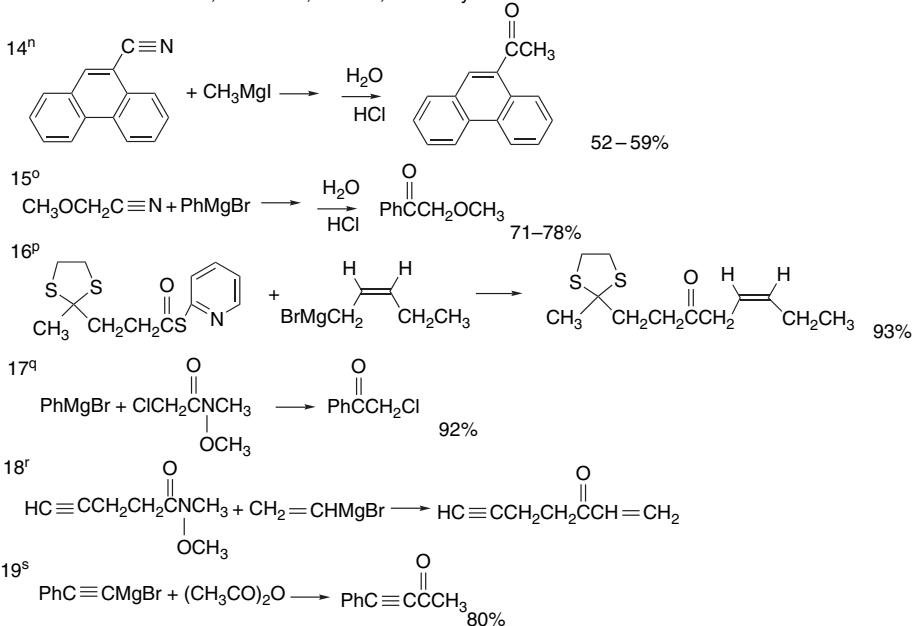
F. Aldehydes from triethyl orthoformate



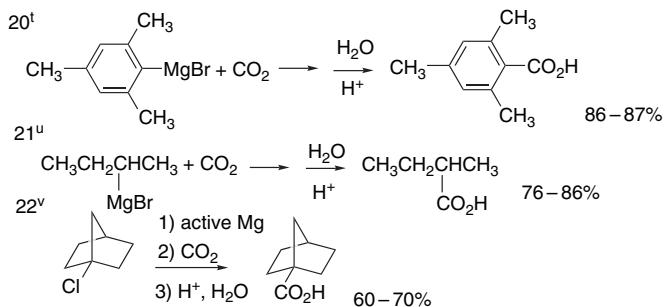
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Scheme 7.3. (Continued)

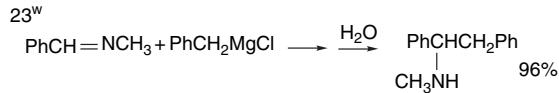
G. Ketones from nitriles, thioesters, amides, and anhydrides



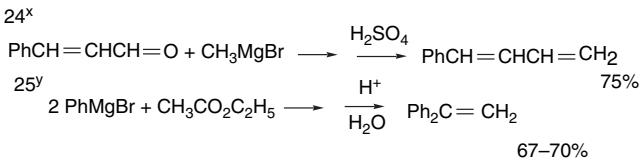
H. Carboxylic acids by carbonation



I. Amines from imines



J. Alkenes after dehydration of intermediate alcohols



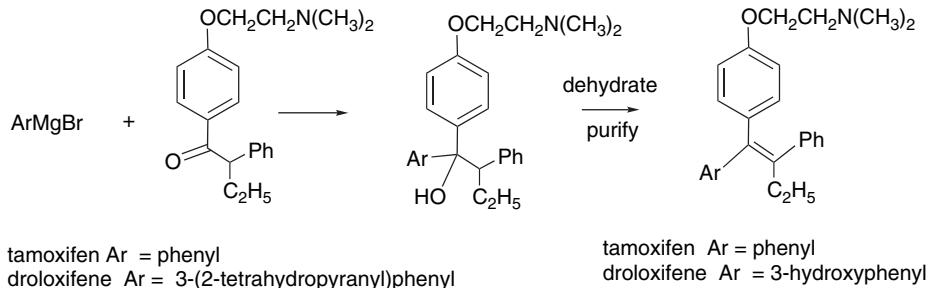
(Continued)

SECTION 7.2

Reactions of
Organomagnesium and
Organolithium
Compounds

- a. H. Gilman and W. E. Catlin, *Org. Synth.*, **I**, 182 (1932).
 b. E. E. Dreger, *Org. Synth.*, **I**, 299 (1932).
 c. L. Skatbol, E. R. H. Jones, and M. C. Whiting, *Org. Synth.*, **IV**, 792 (1963).
 d. C. G. Overberger, J. H. Saunders, R. E. Allen, and R. Gander, *Org. Synth.*, **III**, 200 (1955).
 e. E. R. Coburn, *Org. Synth.*, **III**, 696 (1955).
 f. N. L. Drake and G. B. Cooke, *Org. Synth.*, **II**, 406 (1943).
 g. G. H. Coleman and D. Craig, *Org. Synth.*, **II**, 179 (1943).
 h. W. W. Moyer and C. S. Marvel, *Org. Synth.*, **II**, 602 (1943).
 i. W. E. Bachman and H. P. Hetzner, *Org. Synth.*, **III**, 839 (1955).
 j. M. Schmeichel and H. Redlich, *Synthesis*, 1002 (1996).
 k. J. Colonge and R. Marey, *Org. Synth.*, **IV**, 601 (1963).
 l. C. A. Dornfeld and G. H. Coleman, *Org. Synth.*, **III**, 701 (1955).
 m. G. B. Bachman, *Org. Synth.*, **II**, 323 (1943).
 n. J. E. Callen, C. A. Dornfield, and G. H. Coleman, *Org. Synth.*, **III**, 26 (1955).
 o. R. B. Moffett and R. L. Shriner, *Org. Synth.*, **III**, 562 (1955).
 p. T. Mukaiyama, M. Araki, and H. Takei, *J. Am. Chem. Soc.*, **95**, 4763 (1973); M. Araki, S. Sakata, H. Takei, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **47**, 1777 (1974).
 q. R. Tillyer, L. F. Frey, D. M. Tschaen, and U.-H. Dolling, *Synlett*, 225 (1996).
 r. B. M. Trost and Y. Sih, *J. Am. Chem. Soc.*, **115**, 942 (1993).
 s. A. Zanka, *Org. Proc. Res. Dev.*, **2**, 60 (1998).
 t. D. M. Bowen, *Org. Synth.*, **III**, 553 (1955).
 u. H. Gilman and R. H. Kirby, *Org. Synth.*, **I**, 353 (1932).
 v. R. D. Rieke, S. E. Bales, P. M. Hudnall, and G. S. Poindexter, *Org. Synth.*, **59**, 85 (1977).
 w. R. B. Moffett, *Org. Synth.*, **IV**, 605 (1963).
 x. O. Grummitt and E. I. Beckner, *Org. Synth.*, **IV**, 771 (1963).
 y. C. F. H. Allen and S. Converse, *Org. Synth.*, **I**, 221 (1932).

Several Grignard reactions are used on an industrial scale in drug synthesis.⁹⁵ The syntheses of both tamoxifen and droloxitene, which are estrogen antagonists used in treatment of breast cancer and osteoporosis, respectively, involve Grignard addition reactions.⁹⁶

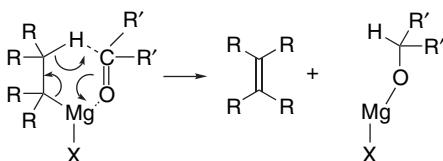


Grignard reagents are quite restricted in the types of functional groups that can be present in either the organometallic or the carbonyl compound. Alkene, ether, and acetal functionality usually causes no difficulty but unprotected OH, NH, SH, or carbonyl groups cannot be present and CN and NO₂ groups cause problems in many cases.

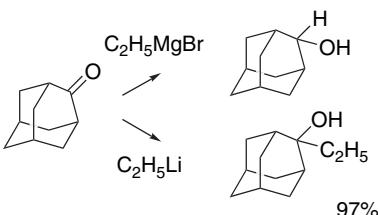
Grignard additions are sensitive to steric effects and with hindered ketones a competing process leading to reduction of the carbonyl group can occur. A cyclic TS is involved.

⁹⁵ F. R. Busch and D. M. DeAntonis, in *Grignard Reagents: New Developments*, H. G. Richey, Jr., ed., Wiley, New York, 2000, pp. 175–181.

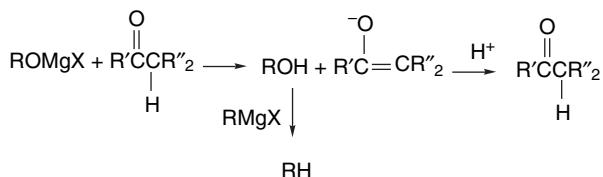
⁹⁶ R. McCaque, *J. Chem. Soc., Perkin Trans. 1*, 1011 (1987); M. Schickaneder, R. Loser, and M. Grill, US Patent, 5,047,431 (1991).



The extent of this reaction increases with the steric bulk of the ketone and Grignard reagent. For example, no addition occurs between diisopropyl ketone and isopropylmagnesium bromide, and the reduction product diisopropylcarbinol is formed in 70% yield.⁹⁷ Competing reduction can be minimized in troublesome cases by using benzene or toluene as the solvent.⁹⁸ Alkyllithium compounds are much less prone to reduction and are preferred for the synthesis of highly substituted alcohols. This is illustrated by the comparison of the reaction of ethyllithium and ethylmagnesium bromide with adamantine. A 97% yield of the tertiary alcohol is obtained with ethyllithium, whereas the Grignard reagent gives mainly the reduction product.⁹⁹



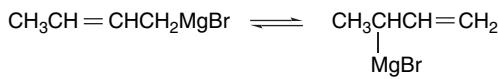
Enolization of the ketone is also sometimes a competing reaction. Since the enolate is unreactive toward nucleophilic addition, the ketone is recovered unchanged after hydrolysis. Enolization has been shown to be especially important when a considerable portion of the Grignard reagent is present as an alkoxide.¹⁰⁰ Alkoxides are formed as the addition reaction proceeds but can also be present as the result of oxidation of some of the Grignard reagent by oxygen during preparation or storage. As with reduction, enolization is most seriously competitive in cases where addition is retarded by steric factors.



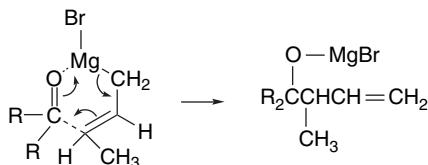
Structural rearrangements are not encountered with saturated Grignard reagents, but allylic and homoallylic systems can give products resulting from isomerization. NMR studies indicate that allylmagnesium bromide exists as a σ -bonded structure in which there is rapid equilibration of the two terminal carbons.¹⁰¹ Similarly,

- ⁹⁷. D. O. Cowan and H. S. Mosher, *J. Org. Chem.*, **27**, 1 (1962).
- ⁹⁸. P. Caronne, G. B. Foscolos, and G. Lemay, *Tetrahedron Lett.*, 4383 (1979).
- ⁹⁹. S. Landa, J. Vias, and J. Burkhard, *Coll. Czech. Chem. Commun.*, **72**, 570 (1967).
- ¹⁰⁰. H. O. House and D. D. Traficante, *J. Org. Chem.*, **28**, 355 (1963).
- ¹⁰¹. M. Schlosser and N. Stahle, *Angew. Chem. Int. Ed. Engl.*, **19**, 487 (1980); M. Stahle and M. Schlosser, *J. Organomet. Chem.*, **220**, 277 (1981).

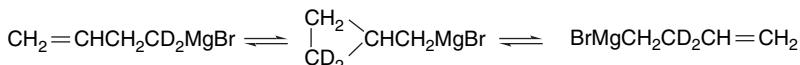
2-butenylmagnesium bromide and 1-methyl-2-propenylmagnesium bromide are in equilibrium in solution.



Addition products are often derived from the latter compound, although it is the minor component at equilibrium.¹⁰² Addition is believed to occur through a cyclic process that leads to an allylic shift.



3-Butenylmagnesium bromide is in equilibrium with a small amount of cyclopropylmethylmagnesium bromide. The existence of the mobile equilibrium has been established by deuterium-labeling techniques.¹⁰³ Cyclopropylmethylmagnesium bromide¹⁰⁴ (and cyclopropylmethyllithium¹⁰⁵) can be prepared by working at low temperature. At room temperature, the ring-opened 3-butenyl reagents are formed.



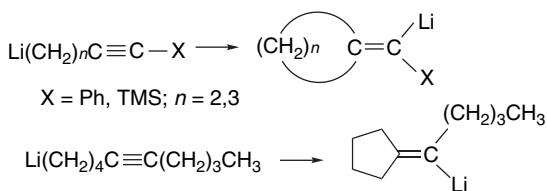
When the double bond is further removed, as in 5-hexenylmagnesium bromide, there is no evidence of a similar equilibrium.¹⁰⁶



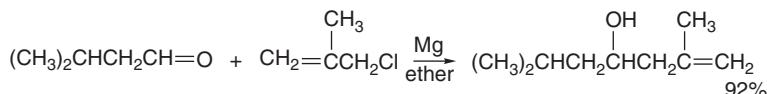
The corresponding lithium reagent remains uncyclized at -78°C , but cyclizes on warming.¹⁰⁷ γ -, δ -, and ϵ -Alkynyl lithium reagents undergo *exo* cyclization to α -cycloalkylidene isomers.¹⁰⁸ Anion-stabilizing substituents are required for the strained three- and four-membered rings, but not for the 5-*exo* cyclization. The driving

- ¹⁰². R. A. Benkeser, W. G. Young, W. E. Broxterman, D. A. Jones, Jr., and S. J. Piaseczynski, *J. Am. Chem. Soc.*, **91**, 132 (1969).
- ¹⁰³. M. E. H. Howden, A. Maercker, J. Burdon, and J. D. Roberts, *J. Am. Chem. Soc.*, **88**, 1732 (1966).
- ¹⁰⁴. D. J. Patel, C. L. Hamilton, and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 5144 (1965).
- ¹⁰⁵. P. T. Lansbury, V. A. Pattison, W. A. Clement, and J. D. Sidler, *J. Am. Chem. Soc.*, **86**, 2247 (1964).
- ¹⁰⁶. R. C. Lamb, P. W. Ayers, M. K. Toney, and J. F. Garst, *J. Am. Chem. Soc.*, **88**, 4261 (1966).
- ¹⁰⁷. W. F. Bailey, J. J. Patricia, V. C. Del Gobbo, R. M. Jarrett, and P. J. Okarma, *J. Org. Chem.*, **50**, 1999 (1985); W. F. Bailey, T. T. Nurmi, J. J. Patricia, and W. Wang, *J. Am. Chem. Soc.*, **109**, 2442 (1987); W. F. Bailey, A. D. Khanolkar, K. Gavaskar, T. V. Ovaska, K. Rossi, Y. Thiel, and K. B. Wiberg, *J. Am. Chem. Soc.*, **113**, 5720 (1991).
- ¹⁰⁸. W. F. Bailey and T. V. Ovaska, *J. Am. Chem. Soc.*, **115**, 3080 (1993).

force for cyclization is the formation of an additional C–C σ -bond and the formation of a more stable (sp^2 versus sp^3) carbanion.

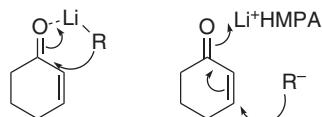


An alternative to preparation of organometallic reagents followed by reaction with a carbonyl compound is to generate the organometallic intermediate *in situ* in the presence of the carbonyl compound. The organometallic compound then reacts immediately with the carbonyl compound. This procedure is referred to as the *Barbier reaction*.¹⁰⁹ This technique has no advantage over the conventional one for most cases for magnesium or lithium reagents. However, when the organometallic reagent is very unstable, it can be a useful method. Allylic halides, which can be difficult to convert to Grignard reagents in good yield, frequently give better results in the Barbier procedure. Since solid metals are used, one of the factors affecting the rate of the reaction is the physical state of the metal. Ultrasonic irradiation has been found to have a favorable effect on the Barbier reaction, presumably by accelerating the generation of reactive sites on the metal surface.¹¹⁰



7.2.2.2. Reactions of Organolithium Compounds. The reactivity of organolithium reagents toward carbonyl compounds is generally similar to that of Grignard reagents. The lithium reagents are less likely to undergo the competing reduction reaction with ketones, however.

Organolithium compounds can add to α,β -unsaturated ketones by either 1,2- or 1,4-addition. The most synthetically important version of the 1,4-addition involves organocopper intermediates, and is discussed in Chap. 8. However, 1,4-addition is observed under some conditions even in the absence of copper catalysts. Highly reactive organolithium reagents usually react by 1,2-addition, but the addition of small amounts of HMPA has been found to favor 1,4-addition. This is attributed to solvation of the lithium ion, which attenuates its Lewis acid character toward the carbonyl oxygen.¹¹¹



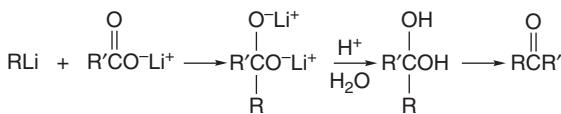
One reaction that is quite efficient for lithium reagents but poor for Grignard reagents is the synthesis of ketones from carboxylic acids.¹¹² The success of the

¹⁰⁹ C. Blomberg and F. A. Hartog, *Synthesis*, 18 (1977).

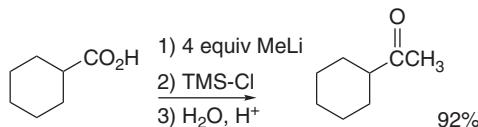
¹¹⁰ J.-L. Luche and J.-C. Damiano, *J. Am. Chem. Soc.*, **102**, 7926 (1980).

¹¹¹ H. J. Reich and W. H. Sikorski, *J. Org. Chem.*, **64**, 14 (1999).

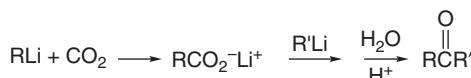
¹¹² M. J. Jorgenson, *Org. React.*, **18**, 1 (1971).



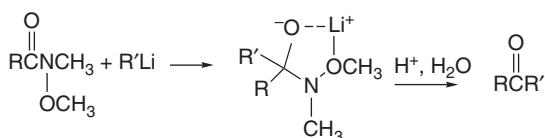
A study aimed at optimizing yields in this reaction found that carbinol formation was a major competing process if the reaction was not carried out in such a way that all of the lithium compound was consumed prior to hydrolysis.¹¹³ Any excess lithium reagent that is present reacts extremely rapidly with the ketone as it is formed by hydrolysis. Another way to avoid the problem of carbinol formation is to quench the reaction mixture with trimethylsilyl chloride.¹¹⁴ This procedure generates the disilyl acetal, which is stable until hydrolysis.



The synthesis of unsymmetrical ketones can be carried out in a tandem one-pot process by successive addition of two different alkylolithium reagents.¹¹⁵



N-Methyl-*N*-methoxyamides are also useful starting materials for preparation of ketones. Again, the reaction depends upon the stability of the tetrahedral intermediate against elimination and a second addition step. In this case chelation with the *N*-methoxy substituent is responsible.



Scheme 7.4 illustrates some of the important synthetic reactions in which organolithium reagents act as nucleophiles. The range of reactions includes S_N2 -type alkylation (Entries 1 to 3), epoxide ring opening (Entry 4), and formation of alcohols by additions to aldehydes and ketones (Entries 5 to 10). Note that in Entry 2, alkylation takes place mainly at the γ -carbon of the allylic system. The ratio favoring γ -alkylation

¹¹³. R. Levine, M. J. Karten, and W. M. Kadunce, *J. Org. Chem.*, **40**, 1770 (1975).

¹¹⁴ G. M. Rubottom and C. Kim, *J. Org. Chem.*, **48**, 1550 (1983).

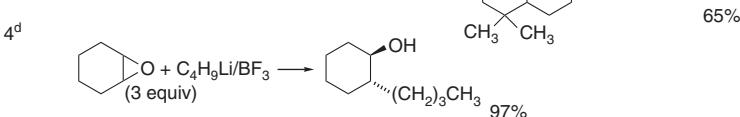
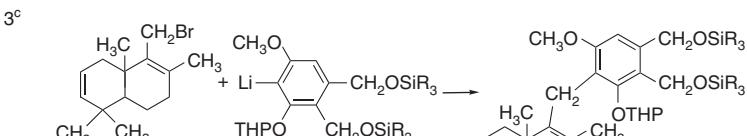
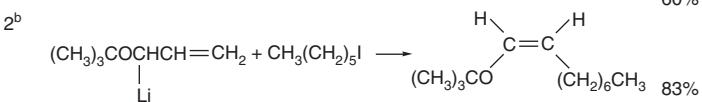
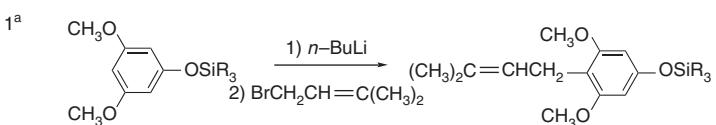
¹¹⁵. G. Zadel and E. Breitmaier, *Angew. Chem. Int. Ed. Engl.*, **31**, 1035 (1992).

Scheme 7.4. Synthetic Procedures Involving Organolithium Reagents

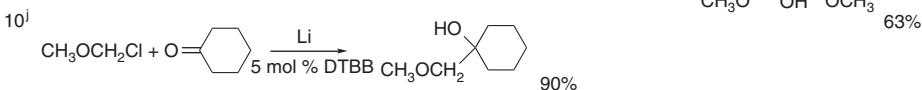
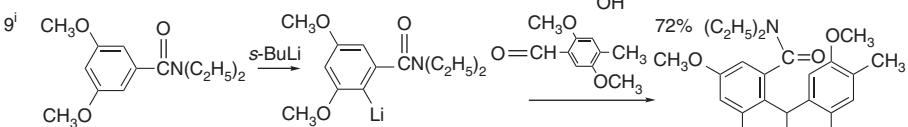
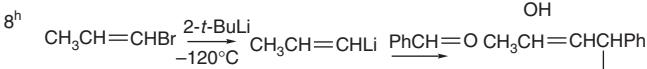
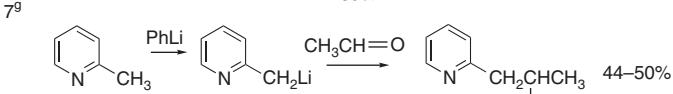
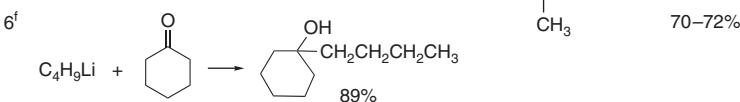
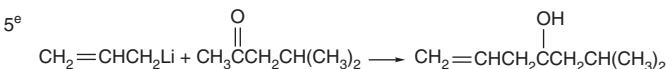
CHAPTER 7

Organometallic Compounds of Group I and II Metals

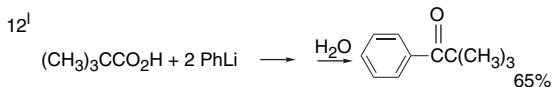
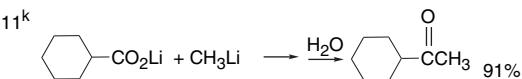
A. Alkylation



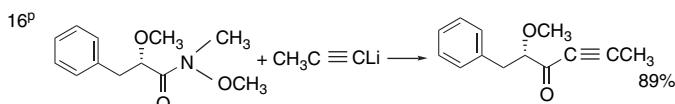
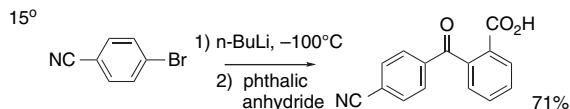
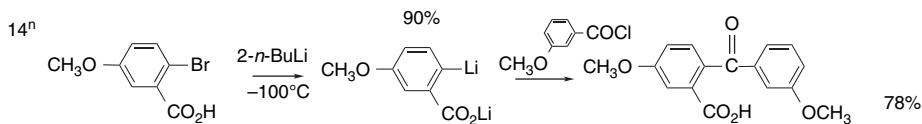
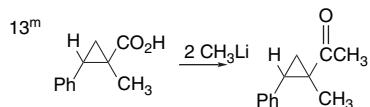
B. Reactions with aldehydes and ketones to give alcohols



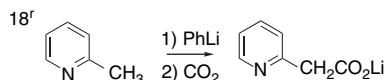
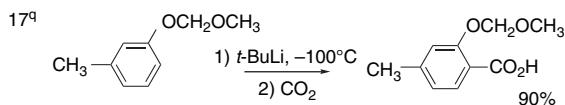
C. Reactions with carboxylic acids, acyl chlorides, acid anhydrides, and N-methoxyamides to give ketones



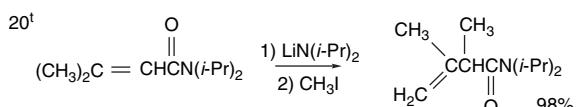
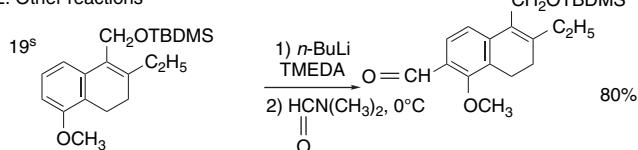
(Continued)



D. Reactions with carbon dioxide to give carboxylic acids

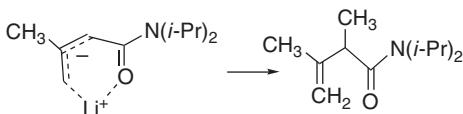


E. Other reactions



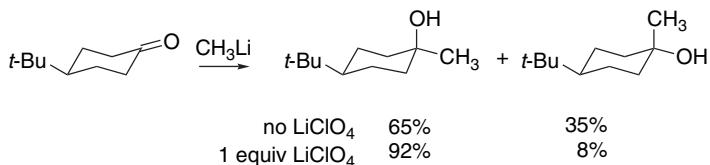
- a. T. L. Shih, M. J. Wyvratt, and H. Mrozik, *J. Org. Chem.*, **52**, 2029 (1987).
- b. D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Am. Chem. Soc.*, **96**, 5560 (1974).
- c. J. E. McMurry and M. D. Erion, *J. Am. Chem. Soc.*, **107**, 2712 (1985).
- d. M. J. Eis, J. E. Wrobel, and B. Ganem, *J. Am. Chem. Soc.*, **106**, 3693 (1984).
- e. Seydel and M. A. Weiner, *Org. Synth.*, **V**, 452 (1973).
- f. J. D. Buhler, *J. Org. Chem.*, **38**, 904 (1973).
- g. L. A. Walker, *Org. Synth.*, **III**, 757 (1955).
- h. H. Neumann and D. Seebach, *Tetrahedron Lett.*, 4839 (1976).
- i. S. O. diSilva, M. Watanabe, and V. Snieckus, *J. Org. Chem.*, **44**, 4802 (1979).
- j. A. Guijarro, B. Mandeno, J. Ortiz, and M. Yus, *Tetrahedron*, **52**, 1643 (1993).
- k. T. M. Bare and H. O. House, *Org. Synth.*, **49**, 81 (1969).
- l. R. Levine and M. J. Karten, *J. Org. Chem.*, **41**, 1176 (1976).
- m. C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *J. Am. Chem. Soc.*, **88**, 3347 (1966).
- n. W. E. Parham, C. K. Bradsher, and K. J. Edgar, *J. Org. Chem.*, **46**, 1057 (1981).
- o. W. E. Parham and R. M. Piccirilli, *J. Org. Chem.*, **41**, 1268 (1976).
- p. F. D'Aniello, A. Mann, and M. Taddei, *J. Org. Chem.*, **61**, 4870 (1996).
- q. R. C. Ronald, *Tetrahedron Lett.*, 3973 (1975).
- r. R. B. Woodward and E. C. Kornfeld, *Org. Synth.*, **III**, 413 (1955).
- s. A. S. Kende and J. R. Rizzi, *J. Am. Chem. Soc.*, **103**, 4247 (1981).
- t. M. Majewski, G. B. Mpango, M. T. Thomas, A. Wu, and V. Snieckus, *J. Org. Chem.*, **46**, 2029 (1981).

is higher for the *t*-butoxy ether than for ethers with smaller groups. There are several means of preparing ketones using organolithium reagents. Apart from addition to carboxylate salts (Entries 11 to 13), acylation with acyl chlorides (Entry 14), anhydrides (Entry 15), or *N*-methoxy-*N*-methylcarboxyamides (Entry 16) can be used. Carboxylic acids can be made by carbonation with CO₂ (Entries 17 and 18). Aldehydes can be prepared by reactions with DMF (Entry 19). Entry 20 is the alkylation of a stabilized allylic lithium reagent.



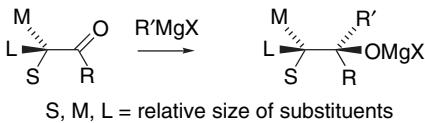
In addition to applications as nucleophiles, the lithium reagents have enormous importance in synthesis as bases and as lithiating reagents. The commercially available methyl, *n*-butyl, *s*-butyl, and *t*-butyl reagents are used frequently in this context.

7.2.2.3. Stereoselectivity of Addition to Ketones. The stereochemistry of the addition of both organomagnesium and organolithium compounds to cyclohexanones is similar.¹¹⁶ With unhindered ketones, the stereoselectivity is not high but there is generally a preference for attack from the equatorial direction to give the axial alcohol. This preference for the equatorial approach increases with the size of the alkyl group. With alkylolithium reagents, added salts improve the stereoselectivity. For example, one equivalent of LiClO₄, enhances the proportion of the axial alcohol in the addition of methylolithium to 4-*t*-butylcyclohexanone.¹¹⁷



Bicyclic ketones react with organometallic reagents to give the products of addition from the less hindered face of the carbonyl group.

The stereochemistry of addition of organometallic reagents to chiral carbonyl compounds parallels the behavior of the hydride reducing agents, as discussed in Section 5.3.2. Organometallic compounds were included in the early studies that established the preference for addition according to Cram's rule.¹¹⁸



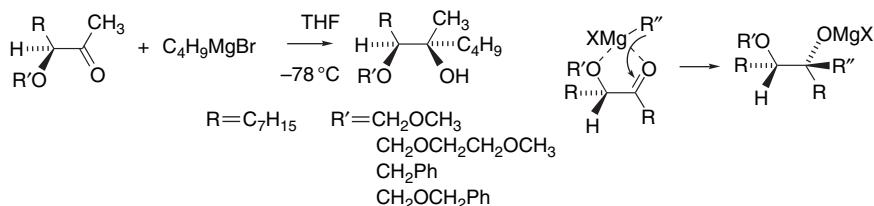
¹¹⁶ E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, **75**, 521 (1975).

¹¹⁷ E. C. Ashby and S. A. Noding, *J. Org. Chem.*, **44**, 4371 (1979).

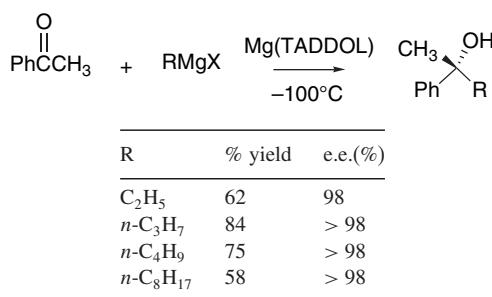
¹¹⁸ D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

The interpretation of the basis for this stereoselectivity can be made in terms of the steric, torsional, and stereochemical effects discussed in connection with reduction by hydrides. It has been found that crown ethers enhance stereoselectivity in the reaction of both Grignard reagents and alkylolithium compounds.¹¹⁹ This effect was attributed to decreased electrophilicity of the metal cations in the presence of the crown ether. The attenuated reactivity leads to greater selectivity.

For ketones and aldehydes in which adjacent substituents permit the possibility of chelation with a metal ion, the stereochemistry can often be interpreted in terms of the steric requirements of the chelated TS. In the case of α -alkoxyketones, for example, an assumption that both the alkoxy and carbonyl oxygens are coordinated with the metal ion and that addition occurs from the less hindered face of this chelate correctly predicts the stereochemistry of addition. The predicted product dominates by as much as 100:1 for several Grignard reagents.¹²⁰ Further supporting the importance of chelation is the correlation between rate and stereoselectivity. Groups that facilitate chelation cause an increase in both rate and stereoselectivity.¹²¹ This indicates that chelation not only favors a specific TS geometry, but also lowers the reaction barrier by favoring metal ion complexation.



The addition of a Grignard reagent to an unsymmetrical ketone generates a new stereogenic center and is potentially enantioselective in the presence of an element of chirality. Perhaps because the reactions are ordinarily very fast, there are relatively few cases in which such reactions are highly enantioselective. The magnesium salt of TADDOL promotes enantioselective additions to acetophenone.¹²² These particular reactions occur under heterogeneous conditions and are quite slow at -100°C . Although the details of the mechanism are unclear, the ligand must establish a chiral environment that controls the facial selectivity of the additions.



¹¹⁹ Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.*, **107**, 6411 (1985).

¹²⁰ W. C. Still and J. H. McDonald, III, *Tetrahedron Lett.*, 1031 (1980).

¹²¹ X. Chen, E. R. Hortelano, E. L. Eliel, and S. V. Frye, *J. Am. Chem. Soc.*, **112**, 6130 (1990).

¹²² B. Weber and D. Seebach, *Tetrahedron*, **50**, 6117 (1994).

7.3. Organometallic Compounds of Group IIB and IIIB Metals

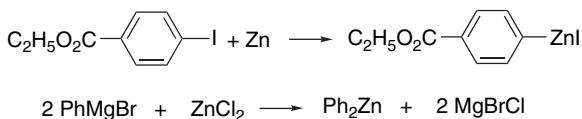
In this section we discuss organometallic derivatives of zinc, cadmium, mercury, and indium. These Group IIB and IIIB metals have the d^{10} electronic configuration in the +2 and +3 oxidation states, respectively. Because of the filled d level, the +2 or +3 oxidation states are quite stable and reactions of these organometallics do not usually involve changes in oxidation level. This property makes the reactivity patterns of Group IIB and IIIB organometallics more similar to derivatives of Group IA and IIA metals than to transition metals having vacancies in the d levels. The IIB metals, however, are less electropositive than the IA and IIA metals and the nucleophilicity of the organometallics is less than for organolithium or organomagnesium compounds. Many of the synthetic applications of these organometallics are based on this attenuated reactivity and involve the use of a specific catalyst to promote reaction.

7.3.1. Organozinc Compounds

Organozinc reagents have become the most useful of the Group IIB organometallics in terms of synthesis.¹²³ Although they are much less reactive than organolithium or organomagnesium reagents, their addition to aldehydes can be catalyzed by various Lewis acids or by coordinating ligands. They have proven particularly adaptable to enantioselective additions. There are also important reactions of organozinc reagents that involve catalysis by transition metals, and these reactions are discussed in Chapter 8.

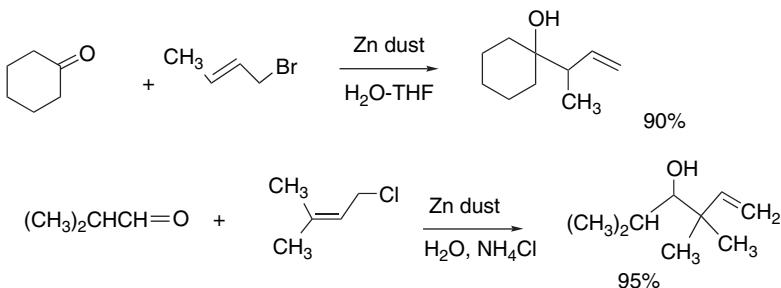
7.3.1.1. Preparation of Organozinc Compounds. Organozinc compounds can be prepared by reaction of Grignard or organolithium reagents with zinc salts. When Grignard reagents are treated with $ZnCl_2$ and dioxane, a dioxane complex of the magnesium halide precipitates, leaving a solution of the alkylzinc reagent. A one-pot process in which the organic halide, magnesium metal, and zinc chloride are sonicated is another method for their preparation.¹²⁴ Organozinc compounds can also be prepared from organic halides by reaction with highly reactive zinc metal.¹²⁵ Simple alkylzinc compounds, which are distillable liquids, can also be prepared from alkyl halides and a $Zn-Cu$ couple.¹²⁶ Dimethyl-, diethyl-, di-*n*-propyl-, and diphenylzinc are commercially available.

Arylzinc reagents can be made from aryl halides with activated zinc¹²⁷ or from Grignard reagents by metal-metal exchange with zinc salts.¹²⁸

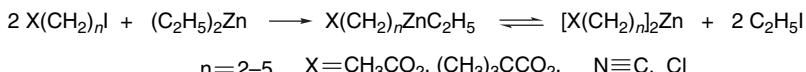


- ¹²³. E. Erdik, *Organozinc Reagents in Organic Synthesis*, CRC Publishing, Boca Raton, FL, 1996.
- ¹²⁴. J. Boersma, *Comprehensive Organometallic Chemistry*, G. Wilkinson, ed., Vol. 2, Pergamon Press, Oxford, 1982, Chap. 16; G. E. Coates and K. Wade, *Organometallic Compounds*, Vol. 1, 3rd Edition, Methuen, London, 1967, pp. 121–128.
- ¹²⁵. R. D. Rieke, P. T.-J. Li, T. P. Burns, and S. T. Uhm, *J. Org. Chem.*, **46**, 4323 (1981).
- ¹²⁶. C. R. Noller, *Org. Synth.*, **II**, 184 (1943).
- ¹²⁷. L. Zhu, R. M. Wehmeyer, and R. D. Rieke, *J. Org. Chem.*, **56**, 1445 (1991); T. Sakamoto, Y. Kondo, N. Murata, and H. Yamanaka, *Tetrahedron Lett.*, **33**, 5373 (1992).
- ¹²⁸. K. Park, K. Yuan, and W. J. Scott, *J. Org. Chem.*, **58**, 4866 (1993).

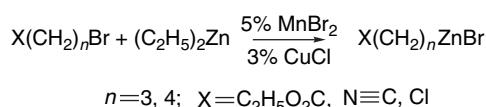
Allylic zinc reagents can be prepared *in situ* in aqueous solution in the presence of aldehydes.¹²⁹ These reactions show a strong preference for formation of the more branched product. This suggests that the reactions occur by coordination of the zinc reagent at the carbonyl oxygen and that addition proceeds by a cyclic mechanism, similar to that for allylic Grignard reagents. The kinetic isotope of the reaction measured under these conditions is consistent with a cyclic mechanism.¹³⁰



An attractive feature of organozinc reagents is that many functional groups that would interfere with organomagnesium or organolithium reagents can be present in organozinc reagents.^{131,132} Functionalized reagents can be prepared by halogen-metal exchange reactions with diethylzinc.¹³³ The reaction equilibrium is driven to completion by use of excess diethylzinc and removal of the ethyl iodide by distillation. The pure organozinc reagent can be obtained by removal of the excess diethylzinc under vacuum.



These reactions are subject to catalysis by certain transition metal ions and with small amounts of MnBr₂ or CuCl the reaction proceeds satisfactorily with alkyl bromides.¹³⁴



Another effective catalyst is Ni(acac)₂.¹³⁵

¹²⁹ C. Petrier and J.-L. Luche, *J. Org. Chem.*, **50**, 910 (1985).

¹³⁰ J. J. Gajewski, W. Bocain, N. L. Brichford, and J. L. Henderson, *J. Org. Chem.*, **67**, 4236 (2002).

¹³¹ P. Knochel, J. J. A. Perea, and P. Jones, *Tetrahedron*, **54**, 8275 (1998).

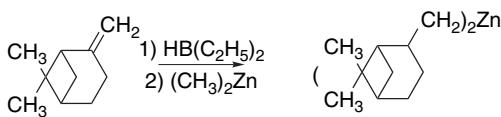
¹³² P. Knochel and R. D. Singer, *Chem. Rev.*, **93**, 2117 (1993); A. Boudier, L. O. Bromm, M. Lotz, and P. Knochel, *Angew. Chem. Int. Ed. Engl.*, **39**, 4415 (2000); P. Knochel, N. Millot, A. L. Rodriguez, and C. E. Tucker, *Org. React.*, **58**, 417 (2001).

¹³³ M. J. Rozema, A. R. Sidduri, and P. Knochel, *J. Org. Chem.*, **57**, 1956 (1992).

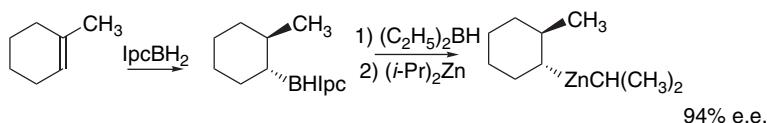
¹³⁴ I. Klemment, P. Knochel, K. Chau, and G. Cahiez, *Tetrahedron Lett.*, **35**, 1177 (1994).

¹³⁵ S. Vettel, A. Vaupel, and P. Knochel, *J. Org. Chem.*, **61**, 7473 (1996).

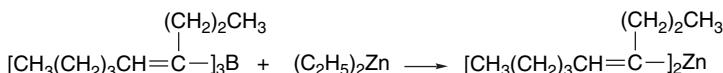
Organozinc reagents can also be prepared from trialkylboranes by exchange with dimethylzinc.¹³⁶



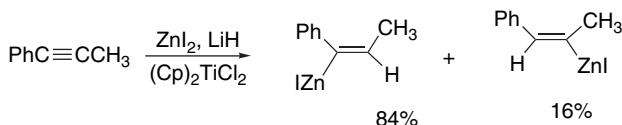
This route can be used to prepare enantiomerically enriched organozinc reagents by asymmetric hydroboration (see Section 4.5.3), followed by exchange with diisopropylzinc. Trisubstituted cycloalkenes such as 2-methyl or 2-phenylcyclohexene give an enantiomeric purity greater than 95%. The exchange reaction takes place with retention of configuration.¹³⁷



Exchange with boranes can also be used to prepare alkenylzinc reagents.¹³⁸



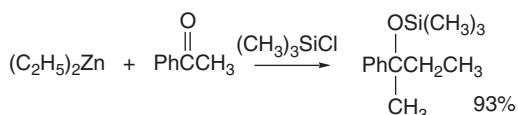
Alkenylzinc reagents can also be made from alkynes by $(\text{Cp})_2\text{TiCl}_2$ -catalyzed hydrozincation (see Section 4.6).¹³⁹ The reaction proceeds with high *syn* stereoselectivity, and the regioselectivity corresponds to relative carbanion stability.



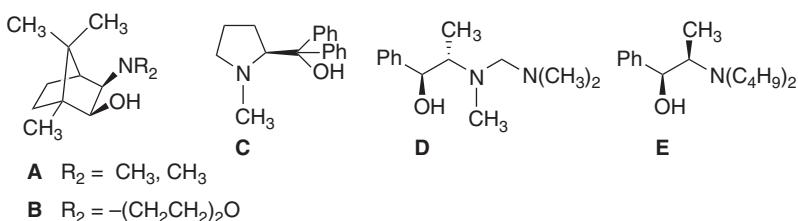
7.3.1.2. Reactions of Organozinc Compounds. Pure organozinc compounds are relatively unreactive toward addition to carbonyl groups, but the reactions are catalyzed by both Lewis acids and chelating ligands. When prepared *in situ* from ZnCl_2 and Grignard reagents, organozinc reagents add to carbonyl compounds to give carbinols.¹⁴⁰

- ¹³⁶. F. Langer, J. Waas, and P. Knochel, *Tetrahedron Lett.*, **34**, 5261 (1993); L. Schwink and P. Knochel, *Tetrahedron Lett.*, **35**, 9007 (1994); F. Langer, A. Devasagayari, P.-Y. Chavant, and P. Knochel, *Synlett*, 410 (1994); F. Langer, L. Schwink, A. Devasagayari, P.-Y. Chavant, and P. Knochel, *J. Org. Chem.*, **61**, 8229 (1996).
- ¹³⁷. A. Boudier, F. Flachsmann, and P. Knochel, *Synlett*, 1438 (1998).
- ¹³⁸. M. Srebnik, *Tetrahedron Lett.*, **32**, 2449 (1991); K. A. Agrios and M. Srebnik, *J. Org. Chem.*, **59**, 5468 (1994).
- ¹³⁹. Y. Gao, K. Harada, T. Hata, H. Urabe, and F. Sato, *J. Org. Chem.*, **60**, 290 (1995).
- ¹⁴⁰. P. R. Jones, W. J. Kauffman, and E. J. Goller, *J. Org. Chem.*, **36**, 186 (1971); P. R. Jones, E. J. Goller, and W. J. Kauffman, *J. Org. Chem.*, **36**, 3311 (1971).

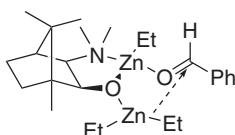
This must reflect activation of the carbonyl group by magnesium ion, since ketones are less reactive to pure dialkylzinc reagents and tend to react by reduction rather than addition.¹⁴¹ The addition of alkylzinc reagents is also promoted by trimethylsilyl chloride, which leads to isolation of silyl ethers of the alcohol products.¹⁴²



High degrees of enantioselectivity have been obtained when alkylzinc reagents react with aldehydes in the presence of chiral ligands.¹⁴³ Among several compounds that have been used as ligands are *exo*-(dimethylamino)norborneol (**A**),¹⁴⁴ its morpholine analog (**B**),¹⁴⁵ diphenyl(1-methylpyrrolin-2-yl)methanol (**C**),¹⁴⁶ as well as ephedrine derivatives **D**¹⁴⁷ and **E**.¹⁴⁸

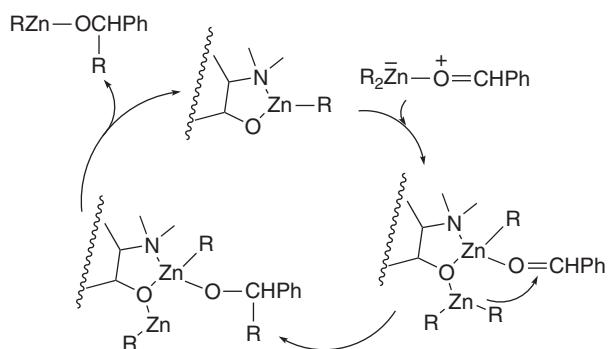


The enantioselectivity is the result of chelation of the chiral ligand to the zinc. The TS of the addition is believed to involve two zinc atoms. One zinc functions as a Lewis acid by coordination at the carbonyl oxygen and the other is the source of the nucleophilic carbon. The proposed TS for aminoalcohol **A**, for example, is shown below.¹⁴⁹



- ¹⁴¹ G. Giacomelli, L. Lardicci, and R. Santi, *J. Org. Chem.*, **39**, 2736 (1974).
- ¹⁴² S. Alvisi, S. Casolari, A. L. Costa, M. Ritiani, and E. Tagliavini, *J. Org. Chem.*, **63**, 1330 (1998).
- ¹⁴³ K. Soai, A. Ookawa, T. Kaba, and K. Ogawa, *J. Am. Chem. Soc.*, **109**, 7111 (1987); M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.*, **108**, 6071 (1986); W. Oppolzer and R. N. Rodinov, *Tetrahedron Lett.*, **29**, 5645 (1988); K. Soai and S. Niwa, *Chem. Rev.*, **92**, 833 (1992).
- ¹⁴⁴ M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.*, **108**, 6071 (1986); M. Kitamura, H. Oka, and R. Noyori, *Tetrahedron*, **55**, 3605 (1999).
- ¹⁴⁵ W. A. Nugent, *Chem. Commun.*, 1369 (1999).
- ¹⁴⁶ K. Soai, A. Ookawa, T. Kaba, and E. Ogawa, *J. Am. Chem. Soc.*, **109**, 7111 (1987).
- ¹⁴⁷ E. J. Corey and F. J. Hannon, *Tetrahedron Lett.*, **28**, 5233 (1987).
- ¹⁴⁸ K. Soai, S. Yokoyama, and T. Hayasaka, *J. Org. Chem.*, **56**, 4264 (1991).
- ¹⁴⁹ D. A. Evans, *Science*, **240**, 420 (1988); E. J. Corey, P.-W. Yuen, F. J. Hannon, and D. A. Wierda, *J. Org. Chem.*, **55**, 784 (1990); B. Goldfuss and K. N. Houk, *J. Org. Chem.*, **63**, 8998 (1998).

The catalytic cycle for these reactions is believed to involve dinuclear complexes formed among the zinc chelate, the aldehyde, and the zinc atom that releases the nucleophile.



The structures of the TSs have been explored computationally using combined B3LYP-MM methods.¹⁵⁰ There are four stereochemically distinct TSs, as shown in Figure 7.4. For the aminoalcohol ligands, the *anti-trans* arrangement is preferred. Steric factors destabilize the other TSs. The substituents on the ligand determine the facial selectivity of the aldehydes.

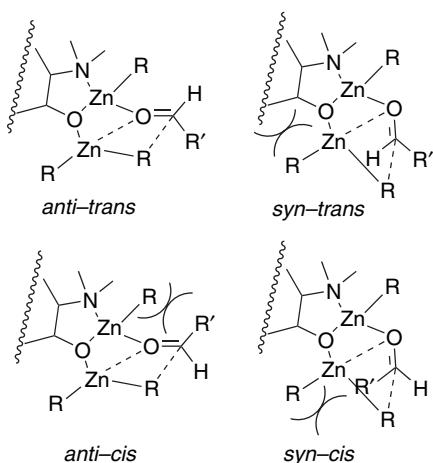
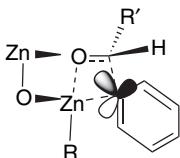


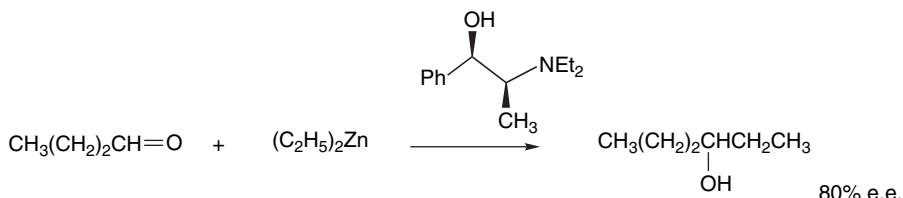
Fig. 7.4. Tricyclic transition structures for aminoalcohol catalysts: *syn* and *anti* refer to the relationship between the transferring group and the bidentate ligand; *cis* and *trans* refer to the relationship between the aldehyde substituent and the coordinating zinc. Reproduced from *J. Am. Chem. Soc.*, **125**, 5130 (2003), by permission of the American Chemical Society.

¹⁵⁰ T. Rasmussen and P.-O. Norrby, *J. Am. Chem. Soc.*, **125**, 5130 (2003).

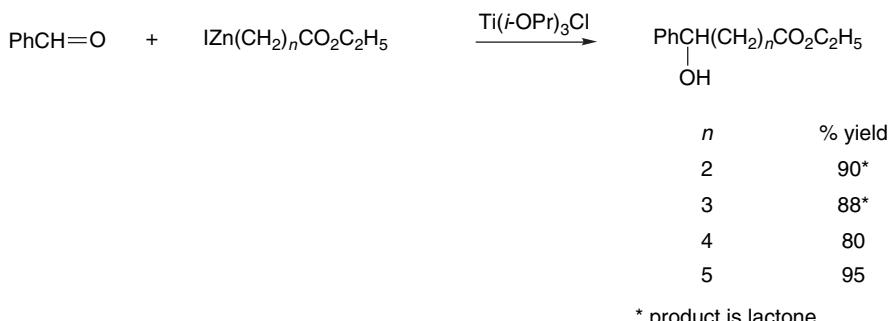
Aryl zinc reagents are considerably more reactive than alkylzinc reagents in these catalyzed additions to aldehydes.¹⁵¹ Within the same computational framework, phenyl transfer is found to have about a 10 kcal/mol advantage over ethyl transfer.¹⁵² This is attributed to participation of the π orbital of the phenyl ring and to the greater electronegativity of the phenyl ring, which enhances the Lewis acid character of the catalytic zinc.



Aspects of the scale-up of aminoalcohol-catalyzed organozinc reactions with aldehydes have been investigated using *N,N*-diethylnorephedrine as a catalyst.¹⁵³ In addition to examples with aromatic aldehydes, 3-hexanol was prepared in 80% e.e.



Additions to aldehydes are also catalyzed by Lewis acids, especially $\text{Ti}(i\text{-OPr})_4$ and trimethylsilyl chloride.¹⁵⁴ Reactions of β -, γ -, δ -, and ϵ -iodozinc esters with benzaldehyde are catalyzed by $\text{Ti}(i\text{-OPr})_3\text{Cl}$.¹⁵⁵



¹⁵¹ C. Bohm, N. Kesselgruber, N. Hermanns, J. P. Hildebrand, and G. Raabe, *Angew. Chem. Int. Ed. Engl.*, **40**, 1488 (2001); C. Bohm, J. P. Hildebrand, K. Muniz, and N. Hermanns, *Angew. Chem. Int. Ed. Engl.*, **40**, 3284 (2001).

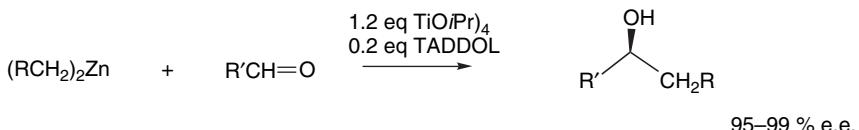
¹⁵² J. Rudolph, T. Rasmussen, C. Bohm, and P.-O. Norrby, *Angew. Chem. Int. Ed. Engl.*, **42**, 3002 (2003).

¹⁵³ J. Blacker, *Scale-Up of Chemical Processes*, Conference Proc., 1998; *Chem. Abstr.*, **133**, 296455 (2000).

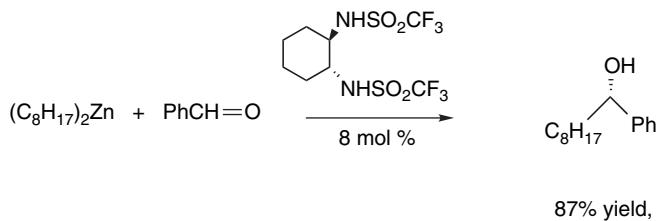
¹⁵⁴ D. J. Ramon and M. Yus, *Recent Res. Devel. Org. Chem.*, **2**, 489 (1998).

¹⁵⁵ H. Ochiai, T. Nishihara, Y. Tamaru, and Z. Yoshida, *J. Org. Chem.*, **53**, 1343 (1988).

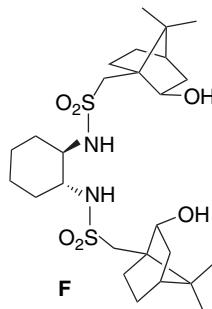
Lewis acid-catalyzed additions can be carried out in the presence of other chiral ligands that induce enantioselectivity.¹⁵⁶ Titanium TADDOL induces enantioselectivity in alkylzinc additions to aldehydes. A variety of aromatic, alkyl, and α , β -unsaturated aldehydes give good results with primary alkylzinc reagents.¹⁵⁷



The *bis*-trifluoromethanesulfonamide of *trans*-cyclohexane-1,2-diamine also leads to enantioselective additions in 80% or greater e.e.¹⁵⁸

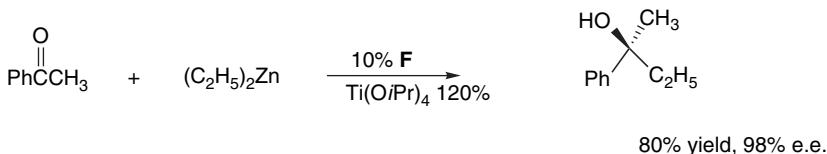


Ketones are less reactive than aldehydes toward organozinc reagents, and they are inherently less stereoselective because the differentiation is between two carbon substituents, rather than between a carbon substituent and hydrogen. Recently, a diol incorporating both *trans*-cyclohexanediamine and camphorsulfonic acid has proven effective in conjunction with titanium tetraisopropoxide.¹⁵⁹

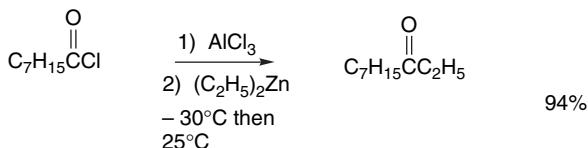


The active catalyst is probably a dinuclear species in which the chiral ligand replaces isopropoxide.

- ¹⁵⁶ D. Seebach, D. A. Plattner, A. K. Beck, Y. M. Wand, D. Hunziker, and W. Petter, *Helv. Chim. Acta*, **75**, 2171 (1992).
- ¹⁵⁷ D. Seebach, A. K. Beck, B. Schmidt, and Y. M. Wang, *Tetrahedron*, **50**, 4363 (1994); B. Weber and D. Seebach, *Tetrahedron*, **50**, 7473 (1994).
- ¹⁵⁸ F. Langer, L. Schwink, A. Devasagayaraj, P.-Y. Chavant, and P. Knochel, *J. Org. Chem.*, **61**, 8229 (1996); C. Lutz and P. Knochel, *J. Org. Chem.*, **62**, 7895 (1997).
- ¹⁵⁹ D. J. Ramon and M. Yus, *Angew. Chem. Int. Ed. Engl.*, **43**, 284 (2004); M. Yus, D. J. Ramon, and O. Prieto, *Tetrahedron: Asymmetry*, **13**, 2291 (2002); C. Garcia, L. K. La Rochelle, and P. J. Walsh, *J. Am. Chem. Soc.*, **124**, 10970 (2002); S.-J. Jeon and P. J. Walsh, *J. Am. Chem. Soc.*, **125**, 9544 (2003).



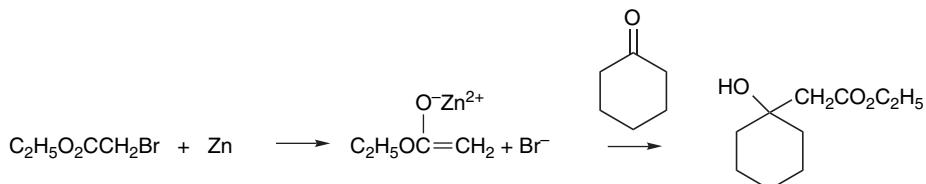
Lewis acids catalyze the reaction of alkylzinc reagents with acyl chlorides.¹⁶⁰ The reaction is also catalyzed by transition metals, as is discussed in Chapter 8.



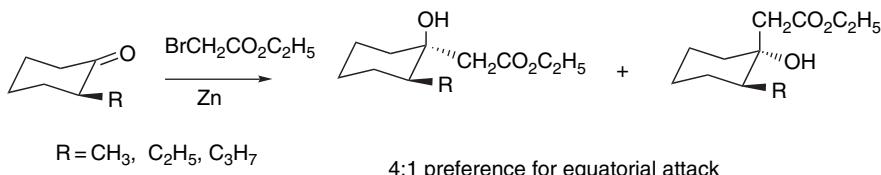
Immonium salts are sufficiently reactive to add organozinc halides in the absence of a catalyst.¹⁶¹ Diallylamines were used because of the ease of subsequent deallylation (see Section 3.5.2).



The *Reformatsky reaction* is a classical reaction in which metallic zinc, an α -haloester, and a carbonyl compound react to give a β -hydroxyester.¹⁶² The zinc and α -haloester react to form an organozinc reagent. Because the carboxylate group can stabilize the carbanionic center, the product is essentially the zinc enolate of the dehalogenated ester.¹⁶³ The enolate effects nucleophilic attack on the carbonyl group.



With 2-alkylcyclohexanones, the reaction shows a modest preference for equatorial attack.¹⁶⁴



¹⁶⁰ M. Arisawa, Y. Torisawa, M. Kawahara, M. Yamanaka, A. Nishida, and M. Nagakawa, *J. Org. Chem.*, **62**, 4327 (1997).

¹⁶¹ N. Millot, C. Piazza, S. Avolio, and P. Knochel, *Synthesis*, 941 (2000).

¹⁶² R. L. Shriner, *Org. React.*, **1**, 1 (1942); M. W. Rathke, *Org. React.*, **22**, 423 (1975); A. Furstner, *Synthesis*, 371 (1989); A. Furstner, in *Organozinc Reagents*, P. Knochel and P. Jones, eds., Oxford University Press, New York, 1999, pp. 287–305.

¹⁶³ W. R. Vaughan and H. P. Knoess, *J. Org. Chem.*, **35**, 2394 (1970).

¹⁶⁴ T. Matsumoto and K. Fukui, *Bull. Chem. Soc. Jpn.*, **44**, 1090 (1971).

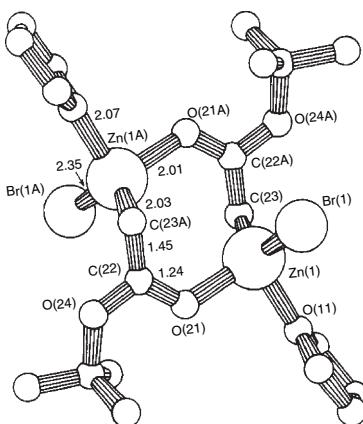
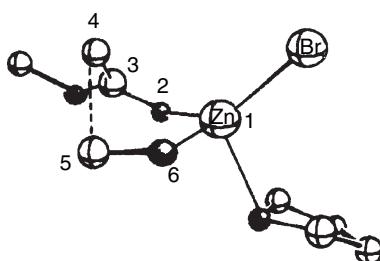


Fig. 7.5. Crystal structure of Reformatsky reagent of *t*-butyl bromoacetate crystallized from THF. Reproduced from *J. Chem. Soc., Chem. Commun.*, 553 (1983), by permission of the Royal Society of Chemistry.

The Reformatsky reaction is related to both organometallic and aldol addition reactions and probably involves a cyclic TS. The Reformatsky reagent from *t*-butyl bromoacetate crystallizes as a dimer having both O–Zn (enolate-like) and C–Zn (organometallic-like) bonds (see Figure 7.5).¹⁶⁵

It is believed that the reaction occurs through the monomer.¹⁶⁶ Semiempirical MO (PM3) calculations suggest a boat TS.¹⁶⁷ There do not seem to be any definitive experimental studies that define the mechanism precisely.



Several techniques have been used to “activate” the zinc metal and improve yields. For example, pretreatment of zinc dust with a solution of copper acetate gives a more reactive zinc-copper couple.¹⁶⁸ Exposure to trimethylsilyl chloride also activates the zinc.¹⁶⁹ Wilkinson’s catalyst, $\text{RhCl}(\text{PPh}_3)_3$, catalyzes formation of Reformatsky reagents from diethylzinc, and reaction occurs under very mild conditions.¹⁷⁰

¹⁶⁵. J. Dekker, J. Boersma, and G. J. M. van der Kerk, *J. Chem. Soc., Chem. Commun.*, 553 (1983).

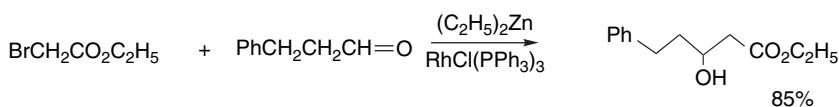
¹⁶⁶. M. J. S. Dewar and K. M. Merz, Jr., *J. Am. Chem. Soc.*, **109**, 6553 (1987).

¹⁶⁷. J. Maiz, A. Arrieta, X. Lopez, J. M. Ugalde, F. P. Cossio, and B. Lecea, *Tetrahedron Lett.*, **34**, 6111 (1993).

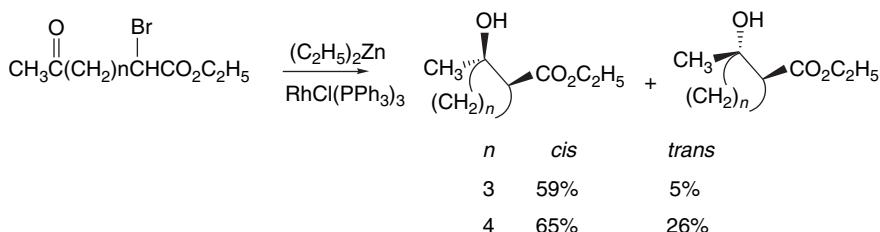
¹⁶⁸. E. Le Goff, *J. Org. Chem.*, **29**, 2048 (1964); L. R. Krebski, L. E. Lynch, S. M. Heilmann, and J. K. Rasmussen, *Tetrahedron Lett.*, **26**, 981 (1985).

¹⁶⁹. G. Picotin and P. Miginiac, *J. Org. Chem.*, **52**, 4796 (1987).

¹⁷⁰. K. Kanai, H. Wakabayashi, and T. Honda, *Org. Lett.*, **2**, 2549 (2000).

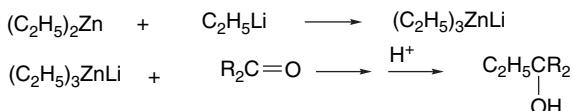


These conditions also provide good yields in intramolecular reactions. There is a preference for formation of the *cis* product for five- and six-membered rings.



Scheme 7.5 gives some examples of the Reformatsky reaction. Zinc enolates prepared from α -haloketones can be used as nucleophiles in mixed aldol condensations (see Section 2.1.3). Entry 7 is an example. This type of reaction can be conducted in the presence of the Lewis acid diethylaluminum chloride, in which case addition occurs at -20°C .¹⁷¹

7.3.1.3. Related Reactions Involving Organozinc Compounds. Organozinc reagents can be converted to anionic “zincate” species by reaction with organolithium compounds.¹⁷² These reagents react directly with aldehydes and ketones to give addition products.¹⁷³



The 1:1 zincate reagent is believed to be dimeric. At higher ratios of organolithium compounds, 2:1 and 3:1 species can be formed.¹⁷⁴

Zincate reagents can add to imines with or without Lewis acid catalysis. Alkylimines require BF_3 but imines of pyridine-2-carboxaldehyde react directly. If the imines are derived from chiral amines, diastereoselectivity is observed. Both α -phenylethyl amine and ethyl valinate have been tried. Higher enantioselectivity was observed with mixed magnesium reagents.¹⁷⁵

¹⁷¹ K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 7705 (1977).

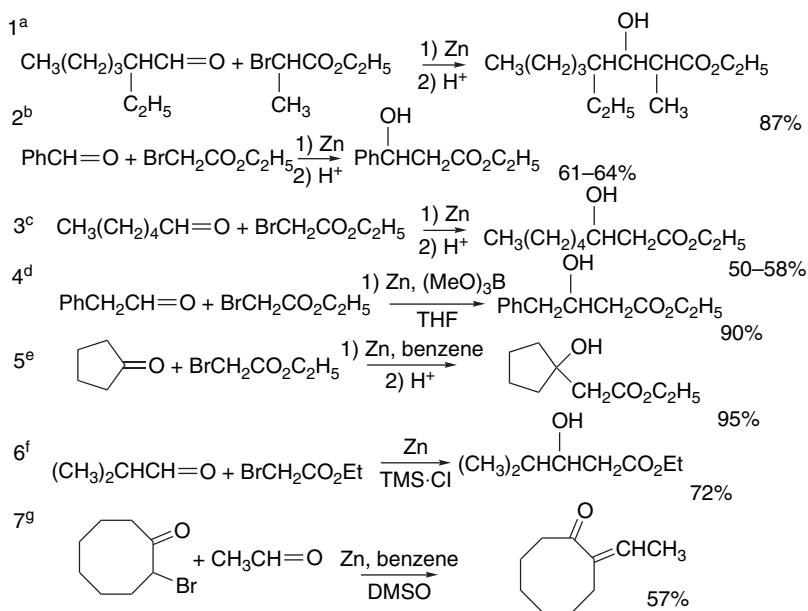
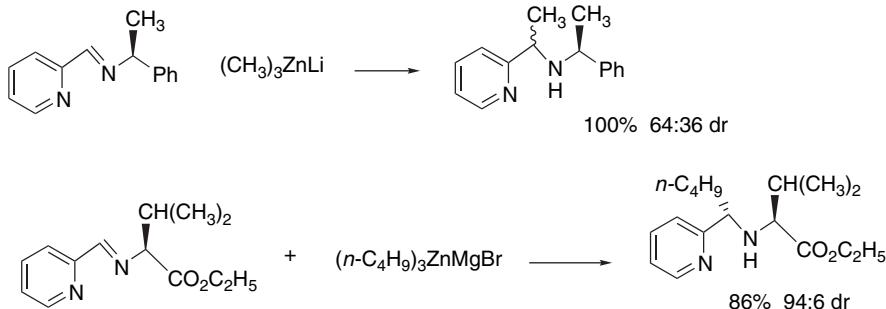
¹⁷² D. J. Linton, P. Shoeler, and A. E. H. Wheatley, *Coord. Chem. Rev.*, **223**, 53 (2001).

¹⁷³ C. A. Musser and H. G. Richey, Jr., *J. Org. Chem.*, **65**, 7750 (2000).

¹⁷⁴ M. Uchiyama, M. Kameda, O. Mishima, N. Yokoyama, M. Koike, Y. Kondo, and T. Sakamoto, *J. Am. Chem. Soc.*, **120**, 4934 (1998).

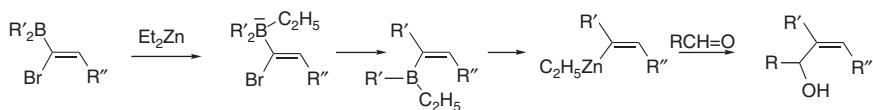
¹⁷⁵ G. Alvaro, P. Pacioni, and D. Savoia, *Chem. Eur. J.*, **3**, 726 (1997).

Scheme 7.5. Addition of Zinc Enolates to Carbonyl Compounds: the Reformatsky Reaction

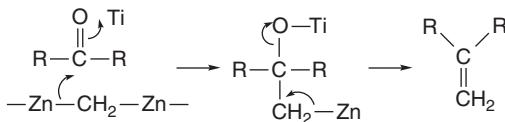
^a K. L. Rinehart, Jr., and E. G. Perkins, *Org. Synth.*, **IV**, 444 (1963).^b C. R. Hauser and D. S. Breslow, *Org. Synth.*, **III**, 408 (1955).^c J. W. Frankenfeld and J. J. Werner, *J. Org. Chem.*, **34**, 3689 (1969).^d M. W. Rathke and A. Lindert, *J. Org. Chem.*, **35**, 3966 (1971).^e J. F. Ruppert and J. D. White, *J. Org. Chem.*, **39**, 269 (1974).^f G. Picotin and P. Migniac, *J. Org. Chem.*, **52**, 4796 (1987).^g T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Am. Chem. Soc.*, **89**, 5727 (1967).

Organozinc reagents have been used in conjunction with α -bromovinylboranes in a tandem route to Z-trisubstituted allylic alcohols. After preparation of the vinylborane, reaction with diethylzinc effects migration of a boron substituent with inversion of configuration and exchange of zinc for boron.¹⁷⁶ Addition of an aldehyde then gives the allylic alcohol. The reaction is applicable to formaldehyde; alkyl and aryl aldehydes; and to methyl, primary, and secondary boranes.

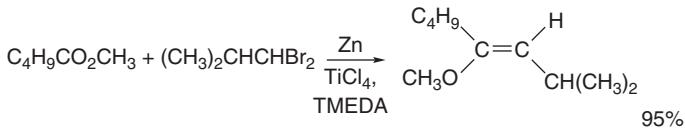
¹⁷⁶ Y. K. Chen and P. J. Walsh, *J. Am. Chem. Soc.*, **126**, 3702 (2004).



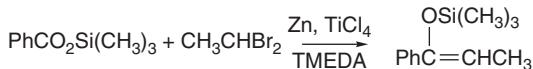
The reagent combination $\text{Zn}-\text{CH}_2\text{Br}_2-\text{TiCl}_4$ gives rise to an organometallic reagent known as *Lombardo's reagent*, which converts ketones to methylene groups.¹⁷⁷ The active reagent is presumed to be a dimetallated species that adds to the ketone under the influence of the Lewis acidity of titanium. β -Elimination then generates the methylene group.



Use of esters and 1,1-dibromoalkanes as reactants gives enol ethers.¹⁷⁸



A similar procedure starting with trimethylsilyl esters generates trimethylsilyl enol ethers.¹⁷⁹



Organozinc reagents are also used extensively in conjunction with palladium in a number of carbon-carbon bond-forming processes that are discussed in Section 8.2.

7.3.2. Organocadmium Compounds

Organocadmium compounds can be prepared from Grignard reagents or organolithium compounds by reaction with Cd(II) salts.¹⁸⁰ They can also be prepared directly from alkyl, benzyl, and aryl halides by reaction with highly reactive cadmium metal generated by reduction of Cd(II) salts.¹⁸¹



The reactivity of these reagents is similar to the corresponding organozinc compounds.

¹⁷⁷. K. Oshima, K. Takai, Y. Hotta, and H. Nozaki, *Tetrahedron Lett.*, 2417 (1978); L. Lombardo, *Tetrahedron Lett.*, **23**, 4293 (1982); L. Lombardo, *Org. Synth.*, **65**, 81 (1987).

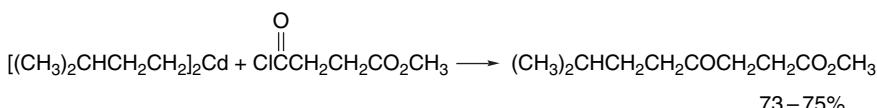
¹⁷⁸. T. Okazoe, K. Takai, K. Oshima, and K. Utimoto, *J. Org. Chem.*, **52**, 4410 (1987).

¹⁷⁹. K. Takai, Y. Kataoka, T. Okazoe, and K. Utimoto, *Tetrahedron Lett.*, **29**, 1065 (1988).

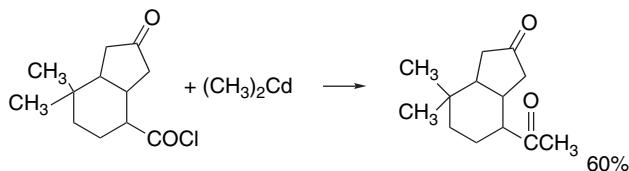
¹⁸⁰. P. R. Jones and P. J. Desio, *Chem. Rev.*, **78**, 491 (1978).

¹⁸¹. E. R. Burkhardt and R. D. Rieke, *J. Org. Chem.*, **50**, 416 (1985).

The most common application of organocadmium compounds has been in the preparation of ketones by reaction with acyl chlorides. A major disadvantage of the use of organocadmium reagents is the toxicity and environmental problems associated with use of cadmium, and this has limited the recent use of organocadmium reagents.



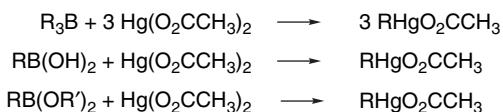
Ref. 182



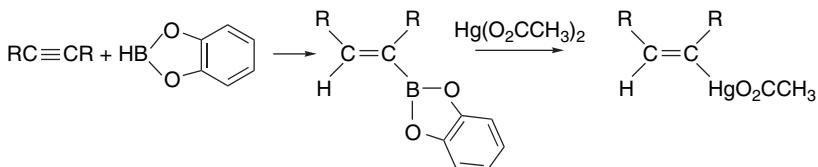
Ref. 183

7.3.3. Organomercury Compounds

There are several useful methods for preparation of organomercury compounds. The general metal-metal exchange reaction between mercury(II) salts and organolithium or magnesium compounds is applicable. The oxymercuration reaction discussed in Section 4.1.3 provides a means of acquiring certain functionalized organomercury reagents. Organomercury compounds can also be obtained by reaction of mercuric salts with trialkylboranes, although only primary alkyl groups react readily.¹⁸⁴ Other organoboron compounds, such as boronic acids and boronate esters also react with mercuric salts.



Alkenylmercury compounds can be prepared by hydroboration of an alkyne with catecholborane, followed by reaction with mercuric acetate.¹⁸⁵



¹⁸² J. Cason and F. S. Prout, *Org. Synth.*, **III**, 601 (1955).

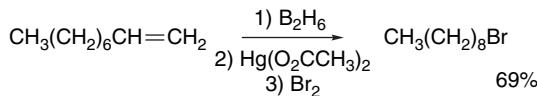
¹⁸³ M. Miyano and B. R. Dorn, *J. Org. Chem.*, **37**, 268 (1972).

¹⁸⁴ R. C. Larock and H. C. Brown, *J. Am. Chem. Soc.*, **92**, 2467 (1970); J. J. Tufariello and M. M. Hovey, *J. Am. Chem. Soc.*, **92**, 3221 (1970).

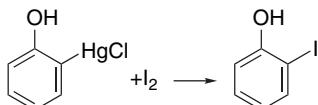
¹⁸⁵ R. C. Larock, S. K. Gupta, and H. C. Brown, *J. Am. Chem. Soc.*, **94**, 4371 (1972).

The organomercury compounds can be used in situ or isolated as organomercuric halides.

Organomercury compounds are weak nucleophiles and react only with very reactive electrophiles. They readily undergo electrophilic substitution by halogens.

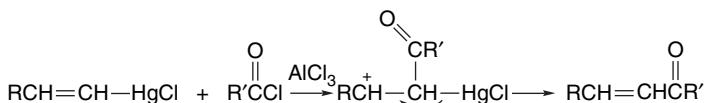


Ref. 184



Ref. 186

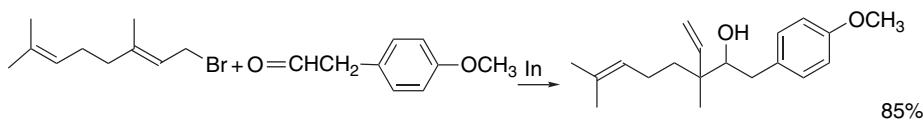
Organomercury reagents do not react with ketones or aldehydes but Lewis acids cause reaction with acyl chlorides.¹⁸⁷ With alkanyl mercury compounds, the reaction probably proceeds by electrophilic attack on the double bond with the regiochemistry being directed by the stabilization of the β -carbocation by the mercury.¹⁸⁸



Most of the synthetic applications of organomercury compounds are in transition metal-catalyzed processes in which the organic substituent is transferred from mercury to the transition metal in the course of the reaction. Examples of this type of reaction are considered in Chapter 8.

7.3.4. Organoindium Reagents

Indium is a Group IIIB metal and is a congener of aluminum. Considerable interest has developed recently in the synthetic application of organoindium reagents.¹⁸⁹ One of the properties that makes indium useful is that its first oxidation potential is less than that of zinc and even less than that of magnesium, making it quite reactive as an electron donor to halides. Indium metal reacts with allylic halides in the presence of aldehydes to give the corresponding carbinols.



Ref. 190

¹⁸⁶ F. C. Whitmore and E. R. Hanson, *Org. Synth.*, **I**, 326 (1941).

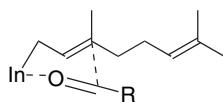
¹⁸⁷ A. L. Kurts, I. P. Beletskaya, I. A. Savchenko, and O. A. Reutov, *J. Organomet. Chem.*, **17**, 21 (1969).

¹⁸⁸ R. C. Larock and J. C. Bernhardt, *J. Org. Chem.*, **43**, 710 (1978).

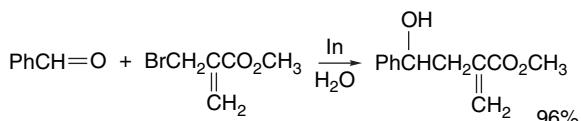
¹⁸⁹ P. Cintas, *Synlett*, 1087 (1995).

¹⁹⁰ S. Araki and Y. Butsugan, *J. Chem. Soc., Perkin Trans. 1*, 2395 (1991).

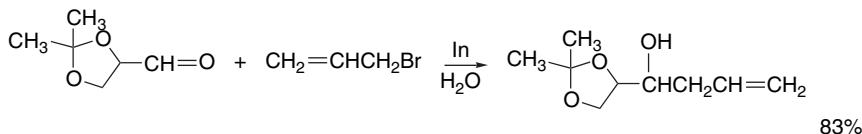
It is believed that the reaction proceeds through a cyclic TS and that the reagent is an In(I) species.¹⁹¹



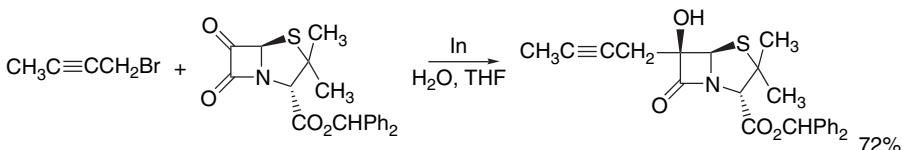
A striking feature of the reactions of indium and allylic halides is that they can be carried out in aqueous solution.¹⁹² The aldehyde traps the organometallic intermediate as it is formed.



The reaction has been found to be applicable to functionalized allylic halides and aldehydes.



Ref. 193



Ref. 194

7.4. Organolanthanide Reagents

The lanthanides are congeners of the Group IIIA metals scandium and yttrium, with the +3 oxidation state usually being the most stable. These ions are strong oxyphilic Lewis acids and catalyze carbonyl addition reactions by a number of nucleophiles. Recent years have seen the development of synthetic procedures involving lanthanide metals, especially cerium.¹⁹⁵ In the synthetic context, organocerium

¹⁹¹ T. H. Chan and Y. Yang, *J. Am. Chem. Soc.*, **121**, 3228 (1999).

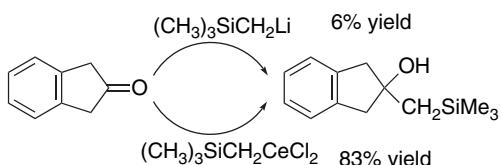
¹⁹² C.-J. Li and T. H. Chan, *Tetrahedron Lett.*, **32**, 7017 (1991); C.-J. Li, *Tetrahedron*, **52**, 5643 (1996).

¹⁹³ L. A. Paquette and T. M. Mitzel, *J. Am. Chem. Soc.*, **118**, 1931 (1996); L. A. Paquette and R. R. Rothhaar, *J. Org. Chem.*, **64**, 217 (1999).

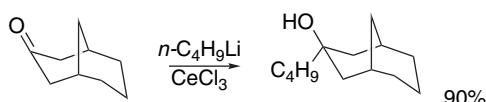
¹⁹⁴ Y. S. Cho, J. E. Lee, A. N. Pae, K. I. Choi, and H. Y. Yok, *Tetrahedron Lett.*, **40**, 1725 (1999).

¹⁹⁵ H. J. Liu, K.-S. Shia, X. Shange, and B.-Y. Zhu, *Tetrahedron*, **55**, 3803 (1999); R. Dalpozzo, A. De Nino, G. Bartoli, L. Sambrì, and E. Marcantonio, *Recent Res. Devel. Org. Chem.*, **5**, 181 (2001).

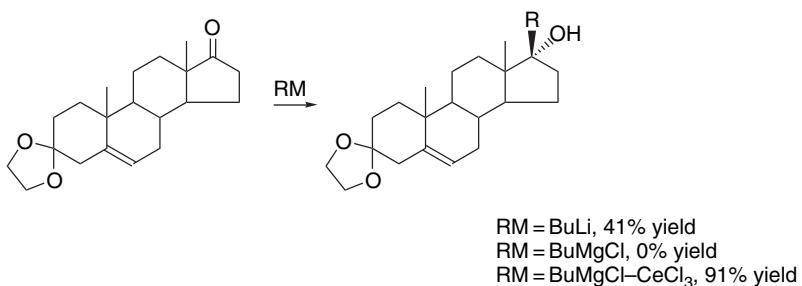
compounds are usually prepared by reaction of organolithium compounds with CeCl_3 .¹⁹⁶ The precise details of preparation of the CeCl_3 and its reaction with the organolithium compound can be important to the success of individual reactions.¹⁹⁷ The organocerium compounds are useful for addition to carbonyl compounds that are prone to enolization or are sterically hindered.¹⁹⁸ The organocerium reagents retain strong nucleophilicity but show a much reduced tendency to effect deprotonation. For example, in addition of trimethylsilylmethylolithium to relatively acidic ketones such as 2-indanone, the yield was greatly increased by use of the organocerium intermediate.¹⁹⁹



Organocerium reagents have been found to improve yields in additions to bicyclo[3.3.1]nonan-3-ones.²⁰⁰

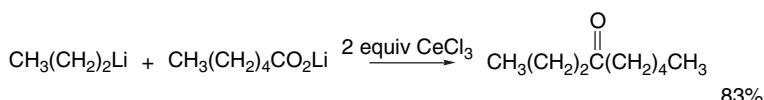


An organocerium reagent gave better yields than either the lithium or Grignard reagents in addition to carbonyl at the 17-position on steroids.²⁰¹ Additions of both Grignard and organolithium reagents can be catalyzed by 5–10 mol % of CeCl_3 .



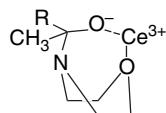
- ^{196.} T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, and M. Yokoyama, *J. Org. Chem.*, **49**, 3904 (1984).
- ^{197.} D. J. Clive, Y. Bu, Y. Tao, S. Daigneault, Y.-J. Wu, and G. Meignan, *J. Am. Chem. Soc.*, **120**, 10332 (1998); W. J. Evans, J. D. Feldman, and T. W. Ziller, *J. Am. Chem. Soc.*, **118**, 4581 (1996); V. Dimitrov, K. Kostova, and M. Genov, *Tetrahedron Lett.*, **37**, 6787 (1996).
- ^{198.} T. Inamoto, N. Takiyama, K. Nakamura, T. Hatajima, and Y. Kamiya, *J. Am. Chem. Soc.*, **111**, 4392 (1989).
- ^{199.} C. R. Johnson and B. D. Tait, *J. Org. Chem.*, **52**, 281 (1987).
- ^{200.} T. Momose, S. Takazawa, and M. Kirihara, *Synth. Commun.*, **27**, 3313 (1997).
- ^{201.} V. Dimitrov, S. Bratovanov, S. Simova, and K. Kostova, *Tetrahedron Lett.*, **36**, 6713 (1994); X. Li, S. M. Singh, and F. Labrie, *Tetrahedron Lett.*, **35**, 1157 (1994).

Cerium reagents have also been found to give improved yields in the reaction of organolithium reagents with carboxylate salts to give ketones.

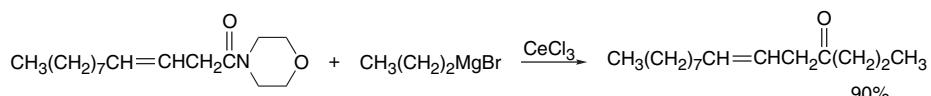


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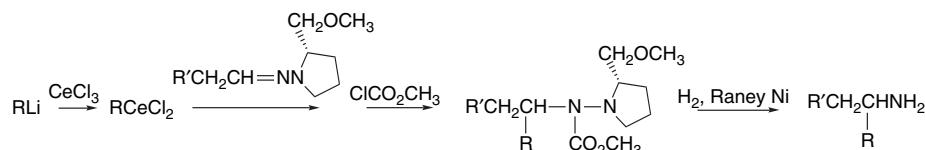
Amides, especially of piperidine and morpholine, give good yields of ketones on reaction with organocerium reagents.²⁰³ It has been suggested that the morpholine oxygen may interact with the oxyphilic cerium to stabilize the addition intermediate.



This procedure has been used with good results to prepare certain long-chain ketones that are precursors of pheromones.²⁰⁴



Organocerium reagents also show excellent reactivity toward nitriles and imines,²⁰⁵ and organocerium compounds were found to be the preferred organometallic reagent for addition to hydrazones in an enantioselective synthesis of amines.²⁰⁶



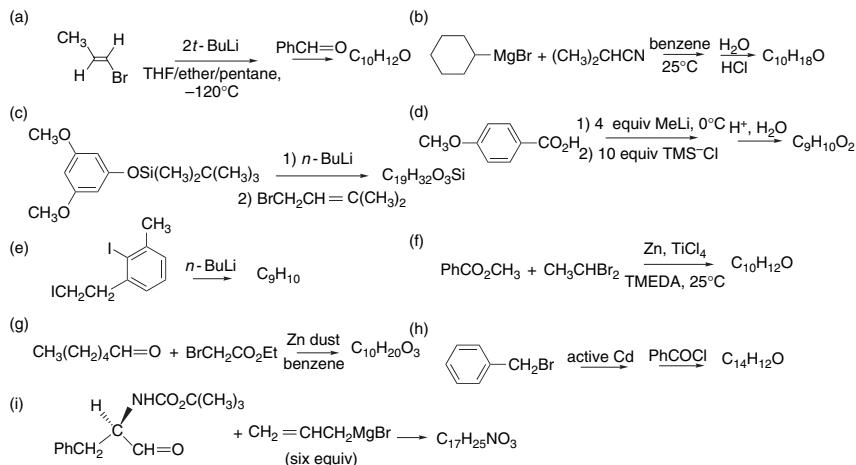
General References

- E. Erdik, *Organozinc Reagents in Organic Synthesis*, CRC Press, Boca Raton, FL, 1996.
- P. Knochel and P. Jones, Editors, *Organozinc Reagents*, Oxford University Press, Oxford, 1999.
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- G. S. Silverman and P. E. Rakita, eds., *Handbook of Grignard Reagents*, Marcel Dekker, New York, 1996.
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- B. J. Wakefield, *Organolithium Methods*, Academic Press, Orlando, FL, 1988.
- B. J. Wakefield, *Organomagnesium Methods in Organic Synthesis*, Academic Press, London, 1995.

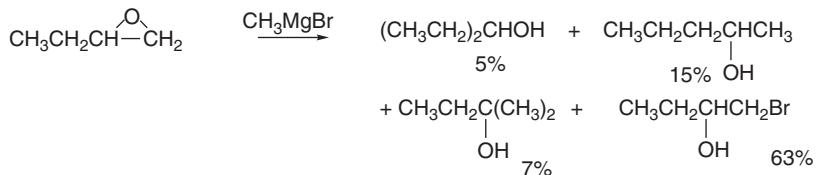
- ²⁰² Y. Ahn and T. Cohen, *Tetrahedron Lett.*, **35**, 203 (1994).
- ²⁰³ M. Kurosu and Y. Kishi, *Tetrahedron Lett.*, **39**, 4793 (1998).
- ²⁰⁴ M. Badioli, R. Ballini, M. Bartolacci, G. Bosica, E. Torregiani, and E. Marcantonio, *J. Org. Chem.*, **67**, 8938 (2002).
- ²⁰⁵ E. Ciganek, *J. Org. Chem.*, **57**, 4521 (1992).
- ²⁰⁶ S. E. Denmark, T. Weber, and D. W. Piotrowski, *J. Am. Chem. Soc.*, **109**, 2224 (1987).

(References for these problems will be found on page 1283.)

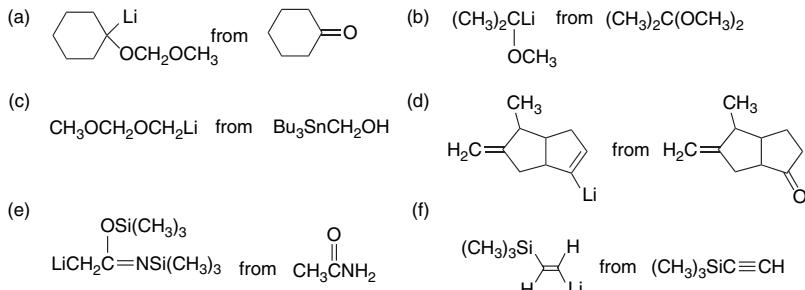
7.1. Predict the product of each of the following reactions. Be sure to consider and specify all aspects of stereochemistry involved in the reaction.



7.2. Reactions of the epoxide of 1-butene with CH_3Li gives a 90% yield of 3-pentanol. In contrast, reaction with CH_3MgBr under similar conditions gives an array of products, as indicated below. What is the basis for the difference in reactivity of these two organometallic compounds toward this epoxide?

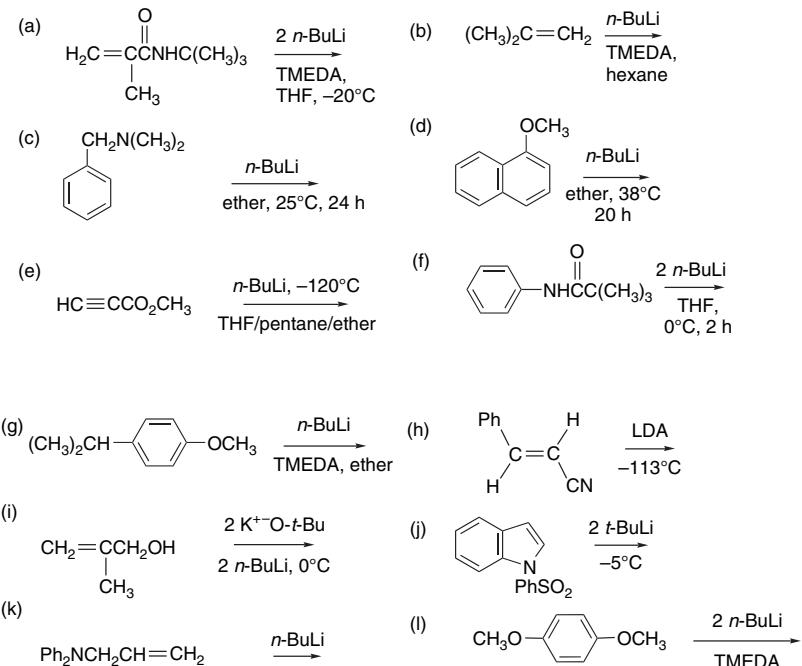


7.3. Devise an efficient synthesis for the following organometallic compound from the specified starting material.

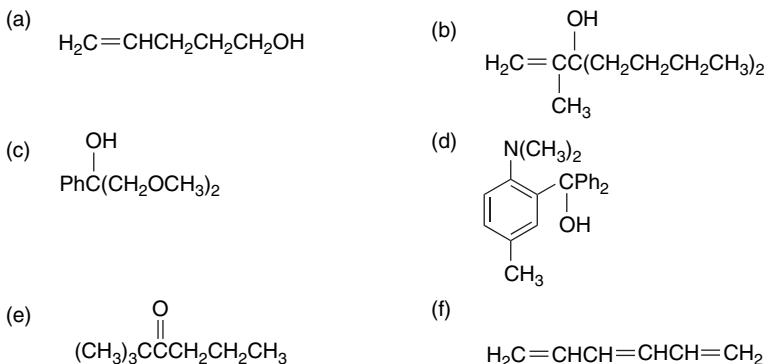


7.4. Each of the following compounds gives a product in which one or more lithium atoms has been introduced under the conditions specified. Predict the structure

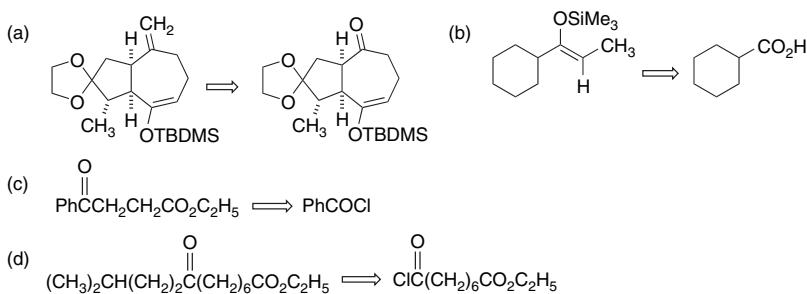
of the lithiated product on the basis of structural features known to promote lithiation and/or stabilization of lithiated species. The number of lithium atoms introduced is equal to the number of moles of lithium reagent used in each case.



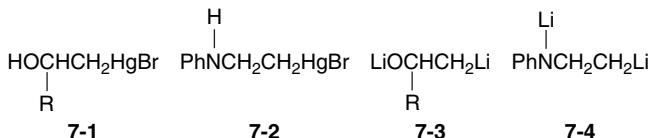
- 7.5. Each of the following compounds can be prepared by reactions of organometallic reagents and readily available starting materials. By retrosynthetic analysis, identify an appropriate organometallic reagent in each case and show how it can be prepared. Show how the desired product can be obtained from the organometallic reagent.



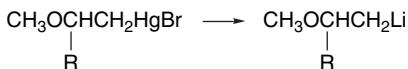
- 7.6. Identify an organometallic reagent that would permit formation of the product on the left of each equation from the specified starting material in a one-pot process.



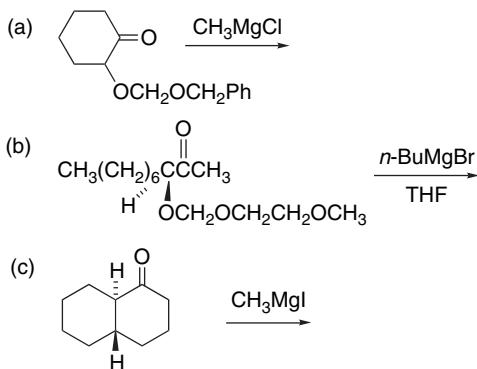
7.7. The solvomercuration reaction (Section 4.1.3) provides a convenient source of organomercury compounds such as **7-1** and **7-2**. How can these be converted to functionalized lithium compounds such as **7-3** and **7-4**?



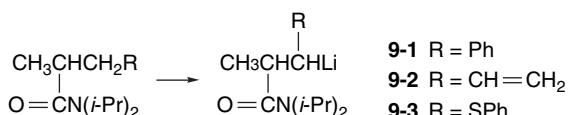
Would the procedure you have suggested also work for the following transformation? Explain your reasoning.



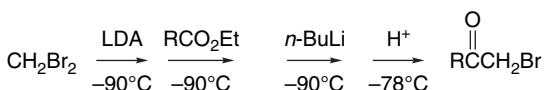
7.8. Predict the stereochemical outcome of the following reactions and indicate the basis for your prediction.



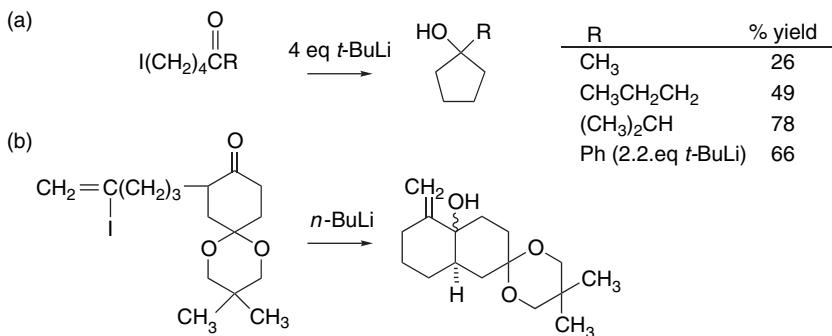
7.9. Tertiary amides **9-1**, **9-2**, and **9-3** are lithiated at the β -carbon, rather than the α -carbon by *s*-butyllithium-TMEDA. It is estimated that the intrinsic acidity of the α -position exceeds that of the β -position by about 9 p*K* units. What causes the β -deprotonation to be kinetically preferred?



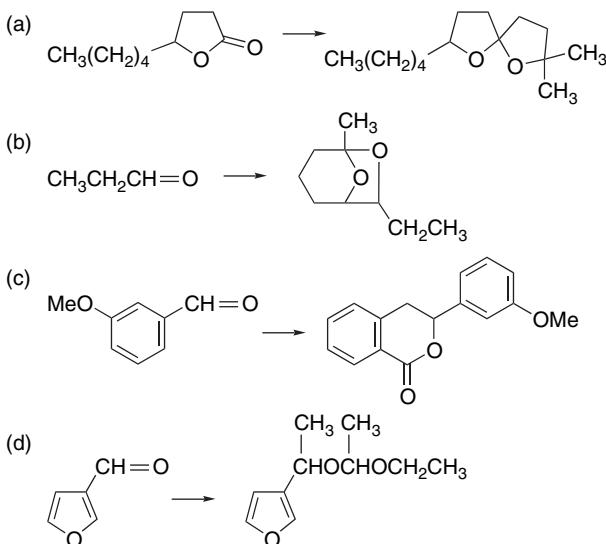
- 7.10. The following reaction sequence converts esters to bromomethyl ketones. Show the intermediates that are involved in each step of the sequence.

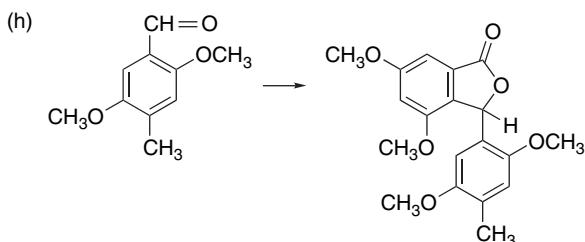
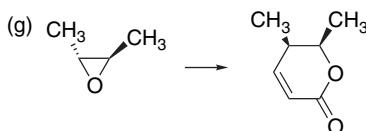
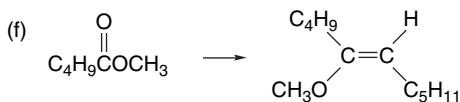
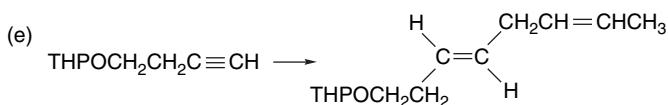


- 7.11. Normally, the reaction of an ester with one equivalent of a Grignard reagent leads to a mixture of tertiary alcohol, ketone, and unreacted ester. However, when allylic Grignard reagents are used in the presence of one equivalent of LDA, good yields of ketones are obtained. What is the role of the LDA in this process?
- 7.12. Several examples of intramolecular additions to carbonyl groups by organolithium reagents generated by halogen-metal exchange have been reported, such as the two examples shown below. What relative reactivity relationships must hold in order for such procedures to succeed?

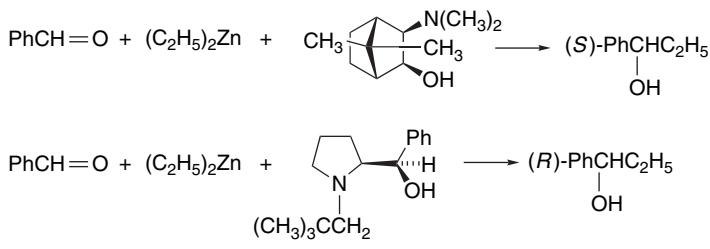


- 7.13. Short synthetic sequences (three steps or less) involving functionally substituted organometallic reagents can effect the following transformations. Suggest reaction sequences that would be effective for each case. Show how the required organometallic reagent can be prepared.

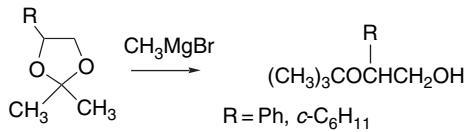




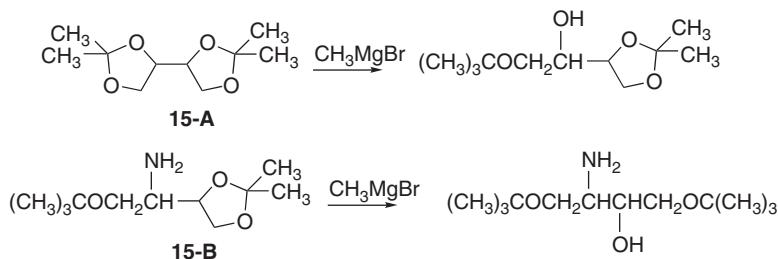
- 7.14. Catalytic amounts of chiral amino alcohols both catalyze the reactions of alkylzinc reagents with aldehydes and induce a high degree of enantioselectivity. Two examples are given below. Formulate a mechanism for this catalysis. Suggest transition structures consistent with the observed enantioselectivity.



- 7.15. When 4-substituted 2,2-dimethyl-1,3-dioxolanes react with Grignard reagents, the bond that is broken is the one at the oxygen attached to the less-substituted α -carbon. What factor(s) are likely the cause for this regioselectivity?



However, with **15-A** and **15-B**, the regioselectivity is reversed.



What factors might lead to the reversal in regioselectivity?

- 7.16. List several features of organocerium reagents that make them applicable to specific synthetic transformations. Give a specific example illustrating each feature.
- 7.17. Normally, organometallic reagents with potential leaving groups in the β -position decompose readily by elimination. Two examples of reagents with greater stability are described below. Indicate what structural feature(s) may be contributing to the relative stability of these reagents.
- Organozinc reagents with β -t-butoxycarbonylamino groups exhibit marginal stability. Replacement of the *t*-butoxycarbonyl by trifluoroacetamido groups improves the stability, as illustrated by the rate of decomposition shown in the Figure 7.P17.

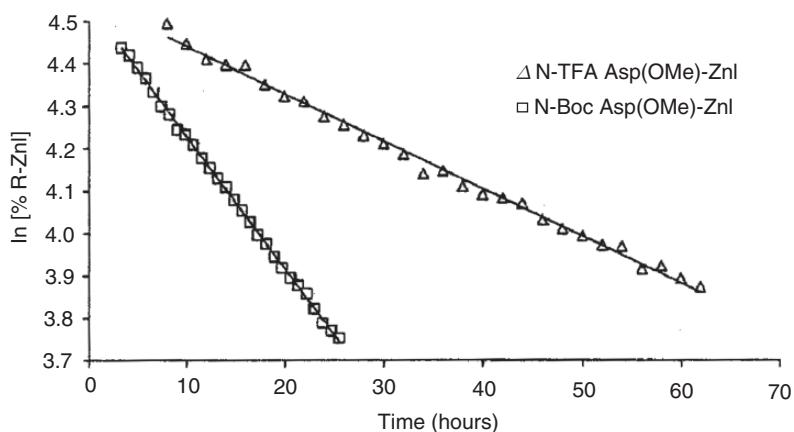
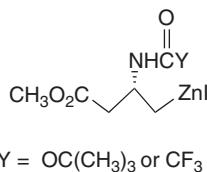
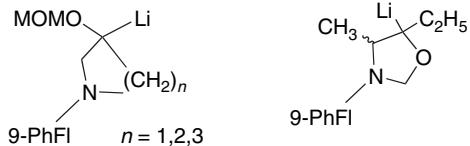


Fig. 7.P17. Comparative rates of decomposition of *t*-butoxycarbonylamino and trifluoroacetamido groups.

b. Certain β -lithio derivatives of cyclic amines are stable.

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PROBLEMS



9-PhFl = 9-Phenyl-9-fluorenyl