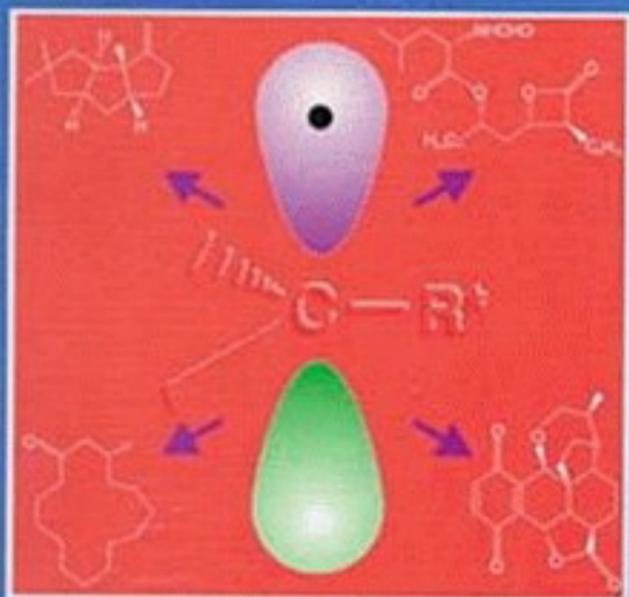


Dennis P. Curran • Ned A. Porter • Bernd Giese

Stereochemistry of Radical Reactions

Concepts, Guidelines, and
Synthetic Applications



Dennis P. Curran, Ned A. Porter,
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Stereochemistry of Radical Reactions



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Dennis P. Curran, Ned A. Porter, Bernd Giese

Stereochemistry of Radical Reactions

Concepts , Guidelines,
and Synthetic Applications

With a Foreword by
Ernest L. Eliel



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Foreword

Stereochemistry, which originated in the latter part of the 19th century, has had a remarkable renaissance in the last 40 years. This is probably due to the increased importance of organic synthesis, which, in turn, relates to the rise in importance of the pharmaceutical industry.

Because of the presence of often numerous chiral centers in natural products, diastereoselectivity is crucial in their synthesis. More recently, the realization that mirror image chemical compounds often differ substantially in their pharmacological properties has stimulated the development of methods of enantioselective synthesis.

When one surveys the literature of stereochemistry through the major pertinent textbooks of the postwar period, one realizes that the focus was initially almost exclusively on ionic processes: electrophilic and nucleophilic substitution and addition reactions and their reversal. Somewhat later pericyclic reactions came into purview. However, reactions involving radical intermediates are notoriously absent from these compendia. Until some 15 years ago the common wisdom among organic chemists was that radicals lack regio- and even chemoselectivity, not to mention stereoselectivity, and that their main and arguably exclusive usefulness was in a few chain reactions including radical initiated polymerizations.

All this has changed since about 1980. It was found that radical cyclization and addition reactions can often be carried out cleanly, notably in the presence of very efficient chain transfer reagents, such as tributyltin hydride, that prevent the formation of oligomers and polymers in radical additions to olefins. Subsequently it was found that, given the appropriate environment, such reactions can proceed with high stereoselectivity. The same tenets of conformational analysis that have proved useful in constructing schemes for stereoselective ionic reactions apply to radical processes as well. This, under appropriate circumstances, includes the use of chiral auxiliaries to effect enantioselective syntheses.

The three authors of the present book have played important roles in the development of stereoselective radical reactions. All three, individually, have previously written reviews on the subject. It is fortunate for organic chemists that they have now teamed up to write the first comprehensive book on the stereochemistry of radical reactions and its applications.

Ernest L. Eliel
June 1995

Preface

The study of stereoselective radical reactions has been a microcosm of the larger field of application of radical reactions in organic synthesis—a period of neglect has been followed by swift progress and exciting developments. The purpose of this book is to review the status of the field of stereoselective radical reactions. While diastereoselective radical cyclizations and reactions of cyclic radicals have been common for some time, it had been thought until recently that levels of stereoselectivity in these reactions would be low, allowing of course for a few exceptions. Acyclic diastereoccontrol has emerged only recently, but progress has been rapid. Enantioselective reactions of radicals are rare at present, but we believe that their development is now inevitable. We submit that stereoselective radical reactions are no different from other types of reactions—that they come in many flavors and at all levels of selectivity. The goals then become to learn which reactions will occur with high selectivity, and why.

In line with the title of the book, we will attempt to present the concepts that are needed to understand stereoselective radical reactions and the guidelines that are helpful to apply them. We will suggest repeatedly that stereoselective radical reactions can be understood, even predicted, by combining standard principles of conformational analysis of organic molecules with knowledge of structure and reactivity of radicals. We will illustrate these concepts and guidelines with synthetic applications that show how stereoselective radical reactions can be used to solve synthetic problems. We hope that the book will expand awareness of existing classes of stereoselective radical reactions and stimulate the development of new ones.

It is the thesis of this book that stereoselective radical reactions are both interesting and significant in their own right. The study of such reactions leads to a better understanding of the structure and reactions of organic radicals and opens new methods for the stereoselective synthesis of organic molecules. Furthermore, because there exist qualitative analogies between radical reactions and related ionic and pericyclic reactions, and because stereoselective radical reactions are often easier to understand and explain than their ionic and pericyclic counterparts, the stereoselectivity of radical reactions is of special interest across the field of asymmetric synthesis.

Therefore, the significance of stereoselective radical reactions spans the fields of stereochemistry and asymmetric synthesis.

We would like to gratefully acknowledge all the help that we received in preparing the text and figures for this book from Michele Russo, Suzanne Curran, Anne Ghosez-Giese, and Kitty Porter. We also thank our graduate students and postdoctoral coworkers, who helped in the proofreading of the book. Dennis Curran would like to thank the University of Basel for a "Reichstein Visiting Professorship" that greatly facilitated his contribution to the book. Ned Porter acknowledges receipt of an Alexander von Humboldt Senior Fellowship and the kind hospitality of Professor Dr. Christoph Rüchardt while this book was being written.

Dennis P. Curran, Ned Porter, Bernd Giese
July, 1995

Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Ad	adamantyl
Ar	aryl
Bn	benzyl
Bu	butyl
Bz	benzoyl
Cbz	carbobenzyloxy
DBU	diazabicycloundecane
DHP	dihydropyran
DME	dimethoxyethane
DTBP	di- <i>t</i> -butylperoxide
e ⁺	electron
Et	ethyl
Fmoc	fluorenylmethyloxy carbonate
HMPA	hexamethylphosphoramide
Im	imidazolyl
LDA	lithium diisopropylamide
mCPBA	<i>m</i> -chloroperbenzoic acid
Me	methyl
NBS	N-bromosuccinimide
OGLu(OAc) ₄	tetraacetylglucoside
PCC	pyridinium chlorochromate
Pr	propyl
PTOC	pyridine-2-thione carbonate
TBHP	<i>t</i> -butylhydroperoxide
Tf	trifluoromethanesulfonyl
Th	thiohydroxamate
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMS	trimethylsilyl
Tol	<i>p</i> -tolyl
TTMS	tris(trimethylsilyl)silicon hydride

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Stereochemistry of Radical Reactions

Concepts , Guidelines and Synthetic Applications

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Chapter 1

Radical Reactions in Organic Synthesis

1.1 Introduction

As recently as a decade ago, organic radicals were regarded as interesting reactive intermediates with limited synthetic potential. As a rule, radical reactions were thought to be “messy”, and the few “clean” radical reactions, like allylic and benzylic brominations with *N*-bromosuccinimide (NBS), were viewed as the exceptions that proved the rule. This view of radicals probably arose because of the notion that highly reactive intermediates could not be selective. The concept of selectivity pervades organic synthesis, and with good reason—selectivity is the key to high yields.

The logic that reactive intermediates such as radicals cannot participate in selective reactions with controlled, predictable outcomes is faulty. Research on the structures and reactions of organic radicals conducted largely by physical organic chemists in the 60s and 70s¹ laid the foundation for the synthetic explosion that followed in the 80s and is still ongoing.² Synthetic chemists gradually came to realize that it is only relative rates that are important for selectivity; the simple fact that radicals often react with high absolute rates is actually desirable, not undesirable. They began to realize the difference between radical/radical reactions, which often occur at the diffusion-controlled limit and are hence unselective, and radical/molecule reactions, which occur with a huge range of rate constants. They learned that the rates of radical/radical reactions are easily minimized by choosing reaction conditions in which radical concentrations are low, and that the rates of radical/molecule reactions—that is, the selectivities—can be adjusted by the experimenter over a wide range by choice of reaction partners, concentrations, temperature, and other variables.

Radical-molecule reactions are now recognized to frequently be both chemo- and regioselective. It is ironic that radical reactions, once thought to be capricious and unpredictable, have a higher level of predictability in

complex settings than most other types of reactions. This predictability is due to the large body of knowledge of radical rate constants³ and substituent effects in simple systems, and to the fact that these effects in simple systems can often be translated to complex systems in a straightforward fashion.

The idea that radical reactions cannot be highly stereoselective has been the last perceived selectivity barrier to fall. Indeed, this selectivity barrier is more than just perceived. Consider that a reaction providing a 95/5 ratio of diastereomers at room temperature requires an energy difference in the two diastereomeric transition states of 1.7 kcal/mol. If one views this energy difference as a percentage of the activation barrier, then transformations like Diels–Alder reactions, which typically have activation barriers of 25–35 kcal/mol, should be much easier to render stereoselective than radical reactions, which typically have activation barriers of 5–15 kcal/mol. On the other hand, consider that there are many very rapid organic reactions with low activation barriers (enolate alkylations, aldol reactions) that are routinely used in both diastereoselective and enantioselective synthesis. It has been our premise for some time that radicals are normal organic species subject to the same types of steric, electronic, and stereoelectronic interactions as all other organic molecules, and that these interactions can be both understood and used in a predictable fashion to control stereochemistry. This premise underlies the entire book.

The purpose of this book is to review the status of the field of stereoselective radical reactions. While diastereoselective radical cyclizations and reactions of cyclic radicals have been common for some time, it had been thought until recently that levels of stereoselectivity in these reactions would be low, allowing of course for a few exceptions. Acyclic diastereocontrol has emerged only recently, but progress has been rapid. Enantioselective reactions of radicals are rare at present, but we believe that their development is now inevitable. We submit that stereoselective radical reactions are no different from other types of reactions—that they come in many flavors and at all levels of selectivity. The goals then become to learn which reactions will occur with high selectivity, and why.

In line with the title of the book, we will attempt to present the concepts that are needed to understand stereoselective radical reactions and the guidelines that are helpful to apply them. We will suggest repeatedly that stereoselective radical reactions can be understood, even predicted, by combining standard principles of conformational analysis of organic

molecules⁴ with knowledge of structure and reactivity of radicals. We will illustrate these concepts and guidelines with synthetic applications that show how stereoselective radical reactions can be used to solve synthetic problems. We hope that the book will expand awareness of existing classes of stereoselective radical reactions and stimulate the development of new ones.

1.2 Principles of Radical Reactions

To understand stereoselectivity in radical reactions, it is first necessary to have a general understanding of the principles of radical reactions and how these principles impact on synthetic planning. There are a number of excellent books and reviews that treat this topic in depth.^{5–8} The goal of this section is to briefly recap some of the most important features of radical reactions in synthesis. Readers with significant experience in radical chemistry may wish to skip this section, while those with little experience may wish to augment it with additional information in the more comprehensive treatments.

1.2.1 General Considerations

Most of the radicals used in synthesis are transient, and they react with each other and with any other radicals present in the medium at the diffusion-controlled limit. For this reason, reaction conditions are usually chosen so that radical/radical reactions are avoided. Radical/molecule reactions are often conducted in chains, but methods based on oxidation and reduction are also important.

Radicals are now valued synthetic intermediates⁹ because they can be used for transformations that are often difficult to accomplish by other means and because these transformations typically occur under very mild conditions where both selectivity and tolerance of functional groups are high. The kinds of protection schemes that are often essential for synthetic sequences of ionic reactions are rarely required for radical reactions; carbonyl substituents and heteroatom-hydrogen bonds (OH, NH) do not usually pose problems in radical reactions. However, protecting groups may still be required for other steps in a synthetic sequence, and nearly all popular classes of protecting groups are tolerated in radical reactions. The kinds of

β -elimination reactions and 1,2-shifts that pervade anionic (organometallic) and cationic chemistry are rare in radical chemistry, and their occurrence is readily predicted.

1.2.2 Medium and Temperature Effects

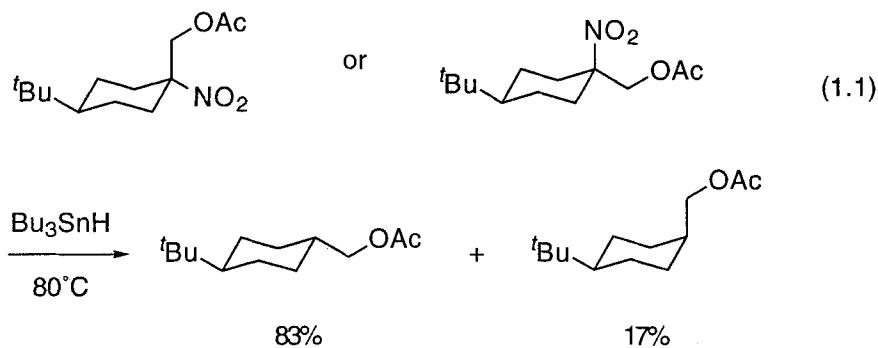
Since most radical reactions show small solvent effects, the choice of solvent is dictated not by the solvent effect on selectivity, but by other concerns. Though the rates of radical/molecule reactions are limited in principle by competing radical/radical reactions, the concentrations of radicals are so low that it is often the rates of radical/solvent reactions that limit the types of radical/molecule reactions that can be conducted. The choice of solvent is therefore dictated by the expected velocity of the desired reaction. With the exception of solvents like benzene (which reacts by radical addition), most solvents react with radicals by hydrogen atom transfer. For the slowest possible radical/molecule reactions, solvents like benzene, *tert*-butylbenzene, and *tert*-butyl alcohol are preferred. Because of its strong O–H bonds, water is also an excellent solvent for radical reactions if the reactants are soluble. This also means that dry solvents are not required. DMSO, acetonitrile, and methylene chloride are also useful. As the rates of the reactions to be conducted go up, the list of useful solvents expands to include almost all the popular organic solvents including alkanes, alcohols, ethers, and halocarbons. Supercritical CO₂ shows promise as an environmentally benign solvent for radical reactions.¹⁰

Temperature effects are of crucial concern for stereoselective reactions. Like many other transformations, radical reactions often provide increasing levels of stereoselectivity at lower temperatures, although the amount of improvement varies from reaction to reaction. Whether or not a given chain will propagate at low temperatures depends upon the rate of the slowest reaction in the chain. Cooling reduces the rates of all reactions, and chain propagation steps that were efficient at 80°C may no longer be fast enough at room temperature or –80°C. In short, the faster the steps that are involved in the chain, the lower the temperature at which the chain will still propagate. Chains will always get shorter at lower temperatures, so compensation by increased initiation is often required. There are now a number of chemical¹¹ and sonochemical¹² initiation methods that can be used to conduct chain reactions at low temperatures. Non-chain radical reactions can be conducted

at any temperature, provided of course that the rates of radical generation and reaction are rapid enough.

1.2.3 Stereochemical Features of Carbon-Centered Radicals

Stereochemical information associated with a bond to a radical precursor is usually lost upon formation of the radical. In other words, radical reactions are not stereospecific. Most alkyl radicals are thought to be either planar or very slightly pyramidal with a tiny barrier to inversion.¹³ With a few exceptions (like cyclopropanes), stereoisomeric radical precursors generate the same radical and ultimately provide the same products. A typical example of the identical reactions of a cyclohexyl radical generated from both axial and equatorial precursors is shown in Equation 1.1.¹⁴ Many other stereoisomeric cyclic and acyclic radical precursors behave likewise.



Electronegative substituents (oxygen, halogens, etc.) cause a radical to pyramidalize and raise its barrier to inversion. However, the inversion barrier generally remains low enough so that the same equilibrating mixture of pyramidal radicals is formed from either isomeric precursor. π -Conjugated alkyl radicals are generally held to be planar. Vinyl radicals are usually thought to be bent and rapidly inverting,¹⁵ though inversion can become slow with electronegative substituents.¹⁶ Certain π -conjugating substituents (like aryl groups) favor a linear structure for vinyl radicals.

The lack of stereospecificity in the reactions of stereoisomeric radical precursors can be viewed as a disadvantage (product configurations cannot be controlled by precursor configurations). But in another important sense it is a significant advantage: there is no need to develop a stereoselective

synthesis of the precursor. Reactions of either isomeric precursor or a mixture of both usually give the same results. (However, while the isomeric precursors generate the same radical, the rate of radical generation may not be the same.)

The two common scenarios for stereoselection in radical reactions are shown in Figure 1-1. The diagrams assume that there are two possible stereoisomeric products, P^1 and P^2 , and that each is derived from a single transition state. The interconverting radicals (case 2) and the isomeric reaction products (cases 1 and 2) are arbitrarily shown as being equal in energy. For a planar alkyl (or linear vinyl) radical (case 1), a single intermediate can access two diastereomeric transition states. For a pyramidal alkyl (or bent vinyl) radical (case 2), each interconverting intermediate accesses a single isomeric transition state. Case 2 is a typical example of Curtin–Hammett kinetics.¹⁷ The smaller the barrier to interconversions of the intermediates in case 2 and the closer these intermediates are in energy, the more similar the two scenarios become. However, transition states derived from pyramidalized radicals will probably have increased pyramidalization compared to those from planar radicals, and this can have stereochemical consequences for the relative energies of stereoisomeric transition states.

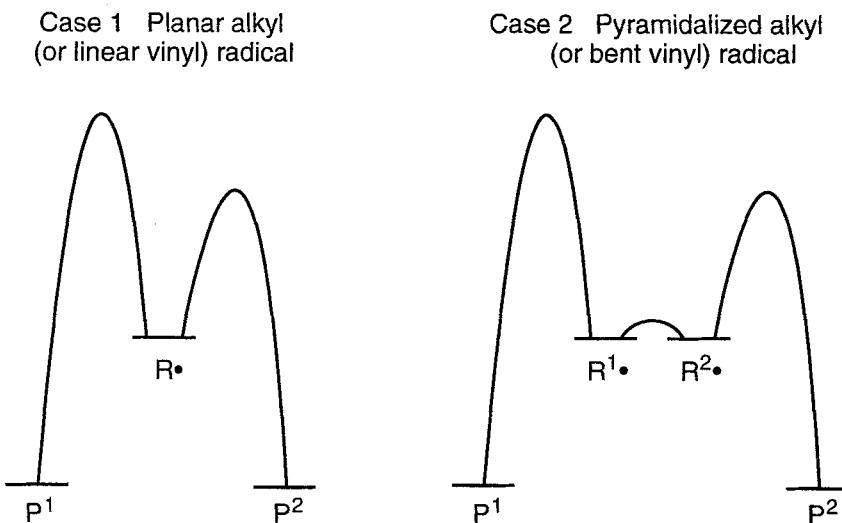


Figure 1-1. Energy Diagrams for Stereoselective Radical Reactions.

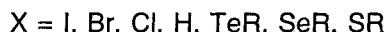
The case 2 scenario also applies to planar radicals that have different conformations as a result of a ring flip or bond rotation, but in reality this situation is often more complex. For example, in typical reactions of π -conjugated radicals with adjacent stereocenters (1,2-asymmetric induction), the radical has as many as three different conformations generated by rotation of the σ -bond adjacent to the radical. If each of these is allowed to be attacked from either face, then six different transition state conformations must be considered. However, it is usually possible to rule out higher energy conformations by using standard principles of conformational analysis, and thereby reduce the number of likely transition state candidates to two or three. The difficult part is evaluating the relative energies of these candidates.

The structure of a radical is then a key factor controlling the outcome of its reactions to provide stereoisomeric products. Information about radical structures typically comes from two sources: ab initio or semi-empirical calculations and ESR spectroscopy. Calculations on open shell structures, whether ground state or transition state, pose some additional problems compared to closed shell species, but they are being used more and more frequently and with evident success. ESR spectroscopy provides direct spectroscopic information about a radical under study or about a suitable model. Like NMR spectroscopy of closed shell molecules, ESR spectroscopy can provide useful information about both the structure and the conformation of a radical. Taken together, ESR spectroscopy and calculations make an especially powerful tool that will be used in subsequent chapters on a number of occasions to interpret results.

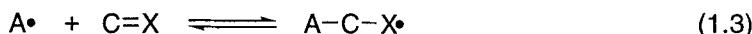
1.2.4 Reactions of Radicals

Aside from oxidations (to give cations) and reductions (to give anions or organometallic species), most radical/molecule reactions can be grouped into one of two large classes: 1) atom and group transfer reactions (sometimes called abstractions, homolytic substitutions or S_{H2} reactions), and 2) additions to π -bonds (or the reverse, which is usually called a β -fragmentation or a β -elimination). The diversity that is available from the reactions of radicals comes from the broad range of reactants that participate in these two fundamental classes of reactions.

In the first class of reactions, an atom or group is transferred from a closed shell molecule to a radical to provide a new closed shell molecule and a new radical (Eq. 1.2). Univalent atoms, especially iodine, bromine, hydrogen, and to a lesser extent chlorine, are frequently transferred in homolytic substitution reactions, as are chalcogenide groups like TeR, SeR, and, to a lesser extent SR. These reactions are frequently assumed to be concerted, as shown in Equation 1.2, although there is little direct experimental evidence to support this assumption. The rates of these types of reactions typically parallel their exothermicity. With a few significant exceptions (such as iodine transfer), endothermic reactions do not occur, so most homolytic substitutions are irreversible under typical preparative reaction conditions. Within a series of reactions of comparable exothermicities, reactions of the pairs with weaker forming and breaking bonds typically occur faster than those with stronger forming and breaking bonds. For example, iodides are usually transferred much faster than bromides and phenyl selenides are transferred faster than phenyl sulfides. Favorable polar effects can accelerate atom or group transfer reactions just as unfavorable polar effects can decelerate them.



Radical addition-elimination reactions come in many varieties (Eq. 1.3), and the rates of these processes are determined by an interplay between enthalpic, steric, and polar effects. Additions of carbon-centered radicals to alkenes and alkynes are usually exothermic and irreversible. These reactions are important in synthesis and they have been the subject of much study from the standpoint of substituent effects on rates.¹⁸ The importance of polar effects (pairing of nucleophilic radicals with electron poor alkenes, or the reverse) and steric effects are now well recognized. Enthalpic effects had been considered to be of lesser importance for some time, but they are making a comeback of late.¹⁹ Additions of carbon radicals to carbon heteroatom multiple bonds (CN, C=O, C=S) can be reversible. The addition of a radical to a π -bond followed by fragmentation of a different bond accomplishes a group transfer reaction, though by a different mechanism from the homolytic group transfer reactions described above.



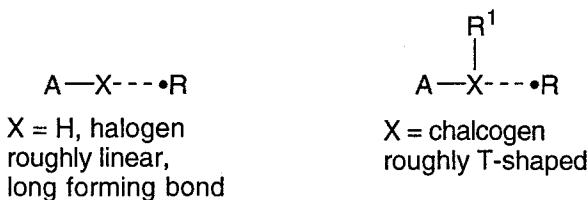
A = Carbon or heteroatom-centered radical
 X = Carbon or heteroatom

Additions of heteroatom-centered radicals such as $I\cdot$, $Br\cdot$, $PhS\cdot$, and $R_3Sn\cdot$ to carbon-carbon bonds are frequently reversible, in part because the addition reactions of these radicals form weaker bonds than additions of carbon-centered radicals.

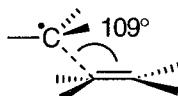
For intramolecular radical additions (radical cyclizations), the enthalpic and entropic effects of ring size and geometry are superimposed on the enthalpic, polar, and steric effects. Some of the key trends for radical cyclizations will be summarized in Chapter 2 for different ring sizes.

Figure 1-2 summarizes some very basic transition state models for radical reactions on which more sophisticated models for stereoselection often build. Radical atom transfer reactions probably proceed through a transition state where the forming and breaking bonds are roughly linear.²⁰ The reactions are usually thought of as concerted, but the possibility exists that the indicated transition state is actually an intermediate in a shallow energy well, especially for atoms like bromine and iodine. Group transfer

Atom Transfer Reactions Group Transfer Reactions



Radical Additions



Exothermic reaction, early transition state (TS)
 Forming C—C bond staggered and $> 2.0 \text{ \AA}$
 All carbons only slightly pyramidalized

Figure 1-2. Basic Transition State Models for Radical Reactions.

reactions of chalcogenides are thought to proceed through T-shaped structures, although there is still discussion about whether these structures are transition states or intermediates.²¹ Most synthetically useful reactions in this class are rapid and are expected to have early transition states with long forming bonds. The long forming bond and the linear transition state minimize the steric interactions between the incoming group and the radical leaving group, and even reagents like Bu₃SnH tend to behave as if they are small.

The transition structures for additions of carbon-centered radicals to alkenes have been determined at very high levels of theory. The picture that emerges is similar for the additions of nucleophilic and electrophilic radicals.²² The approach vector of the radical to the alkene is close to 109°. And even though the forming C–C bond is very long (> 2.0 Å), the substituents about this bond are staggered. Because these transition states are early, the sp² atoms of the alkene are only slightly pyramidalized. The amount of pyramidalization of the radical presumably depends on the structure of the radical and on its ease of pyramidalization. Calculations suggest that simple alkyl radicals are only slightly pyramidalized at the transition state.^{19,22}

1.3 Methods to Conduct Radical Reactions

While there are many different types of transformations that can be accomplished through the intermediacy of radicals, there are relatively few methods to conduct radical reactions. Suitable methods must: 1) generate radicals from non-radicals, 2) allow these radicals sufficient time to react, and 3) trap radicals to form stable closed shell products prior to the occurrence of radical/radical, radical/solvent, or undesirable radical/molecule reactions. The requirements sound stringent, but rate constants for many of the most popular types of reactions are now available, and it is usually not difficult to decide which method is appropriate and even to select suitable reaction conditions in advance.

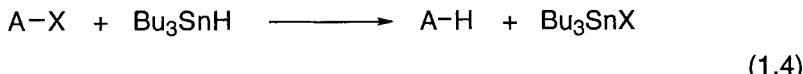
The following sections briefly review the methods that have been most commonly used to conduct stereoselective radical reactions. The presentation is designed more to refresh the memory of the reader, rather than to provide a detailed introduction. Such introductions are available elsewhere.^{3,5–9}

1.3.1 Chain Methods

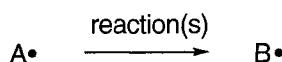
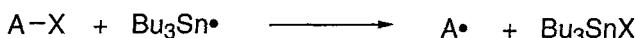
Radical reactions are most commonly conducted in chains because the chain transfer step conveniently links the generation of an initial radical from a radical precursor with the trapping of a final radical to make a stable product. Radical concentrations are limited by the rate of initiation, which is typically slow. Therefore, radical/radical reactions are uncommon.

1.3.1.1 Tributyltin and Tris(trimethylsilyl)silicon Hydride

These two compounds are the most popular among an increasing collection of reagents for conducting reactions by the “metal hydride” method. Equation 1.4 shows the chain for tributyltin hydride (Bu_3SnH),²³ and an analogous chain can be written for tris(trimethylsilyl)silicon hydride ((TMS)₃SiH or TTMS).²⁴ Abstraction of a suitable radical precursor X by the tributyltin radical ($Bu_3Sn\cdot$) generates the initial radical A \cdot , which then suffers a transformation (or series of transformations) to provide a new radical B \cdot . Hydrogen transfer then forms the final product B–H and regenerates the tributyltin radical to continue the chain.



Propagation



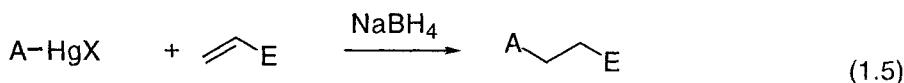
Competing reaction



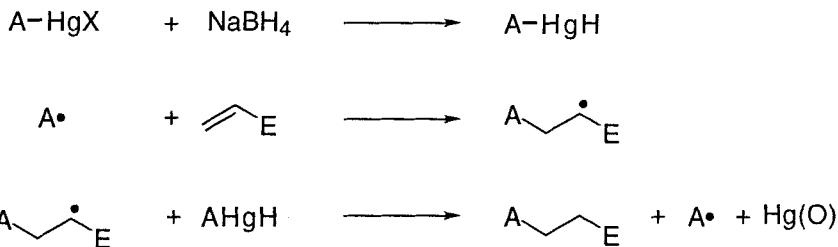
The standard problem in tin and silicon hydride reactions is the premature reduction of A \cdot (or another intermediate radical) by the reagent. If the rate of conversion A \cdot to B \cdot is slow, then it is common to use low

concentrations of the hydride reagent to reduce the rate of the competing reduction. In this regard, the use of tris(trimethylsilyl)silicon hydride can be advantageous because it is a poorer hydrogen donor than tributyltin hydride so lower rates of hydrogen transfer are achieved at higher overall reaction concentrations.²⁴ Tin reagents are toxic and it can be difficult to completely free reaction products from tin, so tris(trimethylsilyl)silicon hydride can have practical advantages as well. From the standpoint of reactivity, the two reagents are similar but not identical. For example, TTMS hydrosilylates alkenes, alkynes, aldehydes and ketones much more readily than tributyltin hydride hydrostannulates them.

Related reactions of in situ generated mercuric hydrides have also frequently been used to probe issues of stereoselectivity. These reactions are easy to conduct at 0–25 °C, and are rapid, clean, and easy to work up and purify. This transformation is typically used for the addition of a nucleophilic radical to an electron poor alkene, as summarized in Equation 1.5.²⁵



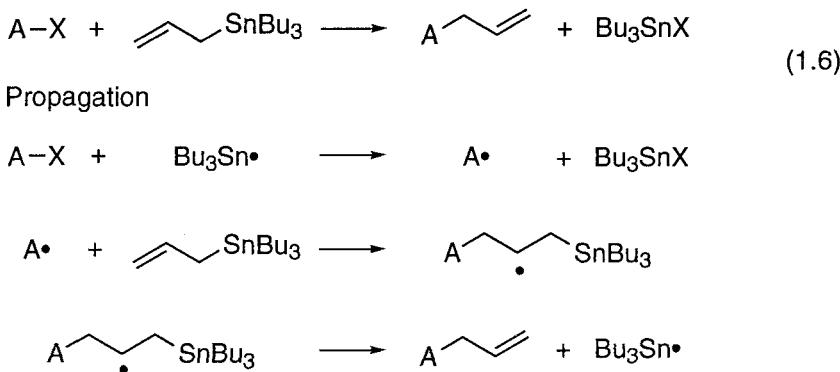
Mechanism



1.3.1.2 Allyltributylstannane

This reagent is the most popular among those in the class of reagents belonging to the “fragmentation method”. The accepted chain mechanism for allylation with allyltributylstannane is shown in Equation 1.6. Abstraction of X by the tributyltin radical is followed by addition of radical A• to allyltributylstannane. Rapid β-fragmentation then provides the allylated product and the tributyltin radical. This method has many of the

advantages of the metal hydride method without the associated liability of premature trapping by the metal hydride. Since the addition of most radicals to allyltributylstannane is not an especially fast reaction,²⁶ it is often possible to conduct one or more reactions in between radical generation and allylation. The power of the allylstannane method lies in the fact that the chain transfer reaction (β -fragmentation) is rapid and unimolecular. This differentiates the final radical from all other radicals. Many of the most sophisticated sequences of radical reactions capitalize on this selectivity asset. Reactions with allyl stannanes are very easy to conduct,²⁷ and a number of related reagents are also used.²⁸ Vinylations can also be accomplished by the fragmentation method.²⁹

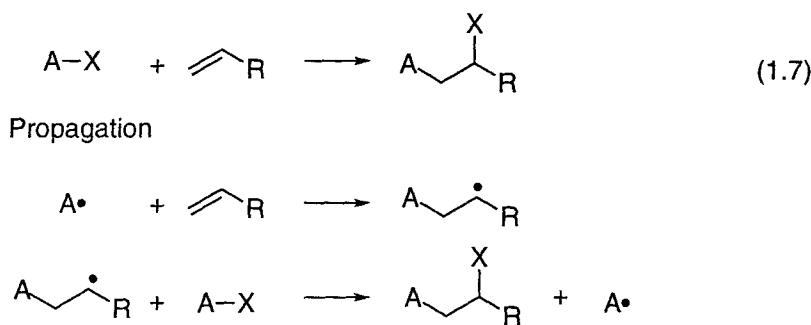


1.3.1.3 Atom and Group Transfer Reactions

Transformations in which the chain transfer step involves a homolytic substitution of a product radical with one of the precursors belong to the “atom (or group) transfer method”. Aside from an initiator, these reagents do not require any other added reagents. While hydrogen atom transfer reactions are well known, they have limited synthetic usefulness. Most stereoselective reactions in this class involve transfer of a halogen atom (usually Br or I) or a phenylselenium group.

A generalized mechanism for this class of reactions is shown in Equation 1.7. The atom or group in A–X is both the radical precursor and the radical trap, and the molecular formula of the product is typically the sum of the molecular formulas of the starting materials. This method has the

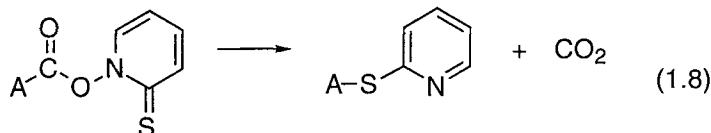
advantage that there is no competing reaction for radical A[•] (so slow reactions are readily conducted) but the disadvantage that the key atom transfer step must be fast enough to propagate the chain (the more exothermic, the better). The body of knowledge on rate constants and substituent effects of atom transfer reactions is useful for planning rapid chain transfer steps.³⁰



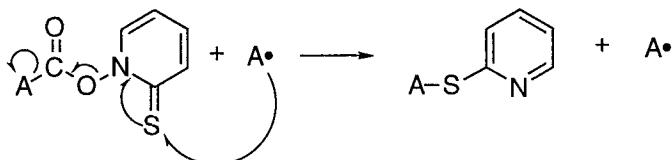
1.3.1.4 Thiohydroxamates

The “thiohydroxamate method” (sometimes called the “Barton method”) involves a thiopyridyl group transfer reaction, but it differs from the reactions above in that the group is transferred by an addition/elimination mechanism rather than a homolytic substitution (Eq. 1.8).³¹ Thiohydroxamate precursors are usually derived from carboxylic acids, and a decarboxylation occurs during the course of the reaction. In its simplest incarnation, the thiohydroxamate method is a decarboxylative thiopyridylation; the precursor thiohydroxamate ester serves as the trap for the product radical. Other reactions of radical A• (addition, cyclization) are possible provided that they are faster than reaction with the precursor. Furthermore, addition of better radical traps (X–Y) than the precursor provides an assortment of other products. In all of these more sophisticated reactions, the competing reaction of the initial radical A• with the thiohydroxamate can be minimized by keeping a low concentration of the thiohydroxamate.

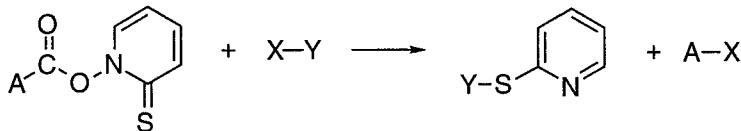
Basic reaction



Propagation



Added traps



1.3.2 Non-Chain Methods

Non-chain methods can involve radical/radical coupling, oxidation, or reduction. There are many variants of these types of reactions, and collectively they have been used only occasionally in stereoselective synthesis. Key features of individual reactions will be presented in relevant sections as needed. General discussions of the features of these reactions and how these features differ from chain reactions are available.⁶

Radical/radical coupling can only be selective if the rates of all possible couplings are not the same. This situation is usually established by using a persistent radical whose concentration builds to a level where it can selectively trap transient radicals. Reactions of organocobalt complexes are good examples of this method.³² Oxidative methods are often based on Mn(OAc)₃ and related reagents, and they generate radicals by oxidation of an enol or related intermediate and trap them by oxidation to a cation or by (oxidative) ligand transfer.³³ Reductive generation of radicals is usually followed by reductive trapping to form “anions” (organometallic reagents). Many one-electron reducing agents have been used; samarium(II) diiodide

and related reagents have a number of attractive features that have made them popular of late.³⁴

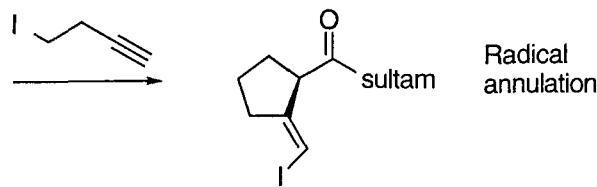
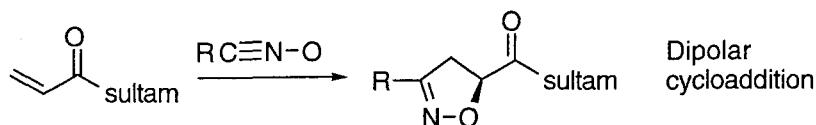
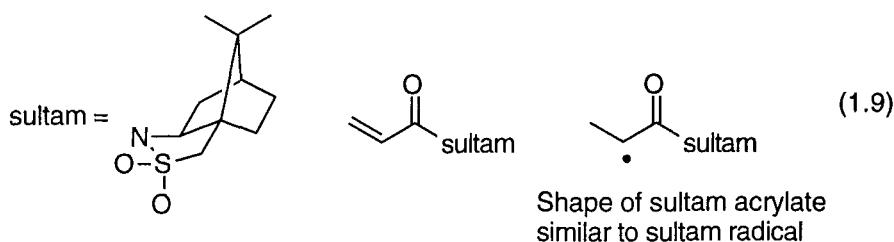
1.4 Comparisons of Stereoselective Radical Reactions with Ionic and Pericyclic Analogs

This book will promote the view that the comparison of stereoselective radical reactions with related ionic and pericyclic reactions is informative and instructive. A nice example is provided by the rapid development of stereoselective radical reactions in acyclic systems, where the thoughtful borrowing of design features from known ionic and pericyclic reactions resulted in very rapid progress (Chapters 4 and 5). As the knowledge of stereoselective radical processes increases, it now becomes possible to reverse the direction of information flow: to use knowledge from radical reactions to interpret existing or to design new ionic and pericyclic processes.

Illustrative examples of the productive interplay in both directions come from analogies between α -carbonyl radicals and related acrylates and enolates. These analogies are drawn in several chapters of the book. Spectroscopic studies and crystal structures of chiral acrylates have provided information on the shape of these molecules that has led to suggestions of how stereochemistry is controlled in pericyclic reactions. Combining this information with the expected geometric similarities of acrylates and α -carbonyl radicals in turn suggested which kinds of chiral radicals would give good levels of asymmetric induction and why. For example, the model for the stereoselective cycloaddition reactions of acrylate derivatives with Oppolzer's camphor sultam suggested that this would be a good chiral auxiliary in radical reactions—a suggestion that was borne out by experiment (Eq. 1.9). A number of other chiral auxiliaries have been similarly either transferred into radical chemistry or designed from scratch (see Chapter 5).

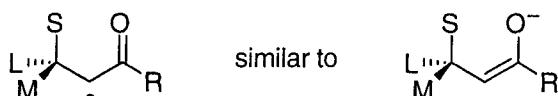
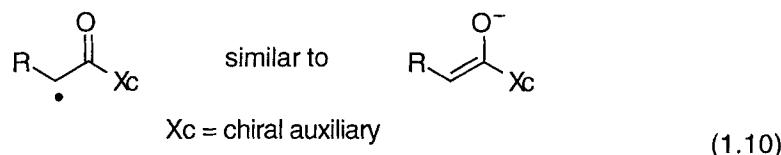
There are also a number of analogies in 1,2-asymmetric induction between the reactions of α -carbonyl radicals and related enolates (Eq. 1.10, see Chapter 4). In analyzing these analogies, we view the radical as a model for an imaginary enolate whose reactions are free from solvent, counterion, and aggregate effects. Freed from these effects, the reactions of the radical are easier to understand. The existence of a sustained stereochemical parallel between the reactions of a chiral radical and a related chiral enolate suggests

that the interpretation of the selectivity of the radical reactions also suffices to explain the enolate reactions. Influences of solvation, metal complexation or chelation, and aggregation are not conclusively ruled out by such parallels, but they are not required to explain the observations because the selectivity can come from the shape of the molecule itself and how this shape influences incoming reagents.

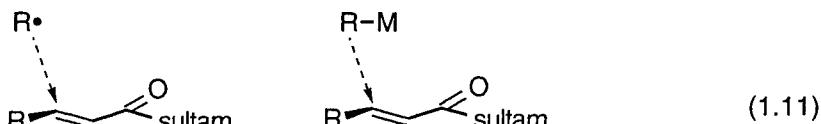


The use of radicals as models for enolates (rather than the reverse) may be counterintuitive. Because most enolates are stable, direct structural information about them is available by NMR spectroscopy, X-ray crystallography and other methods. With the important exception of ESR spectroscopy, there is little direct structural information on radicals. Nonetheless, because of aggregation, the kinetics of enolate reactions are often not well understood, and all the structural information is of limited value if one does not know the nature of the intermediate involved in the stereoselective reaction. In contrast, the structures of even the most complex

radicals can often be estimated from simple analogs. Because the intermediate in the stereoselective reaction is the free radical, the problem of stereoselectivity can be directly and realistically approached by intuitive modeling or calculations.



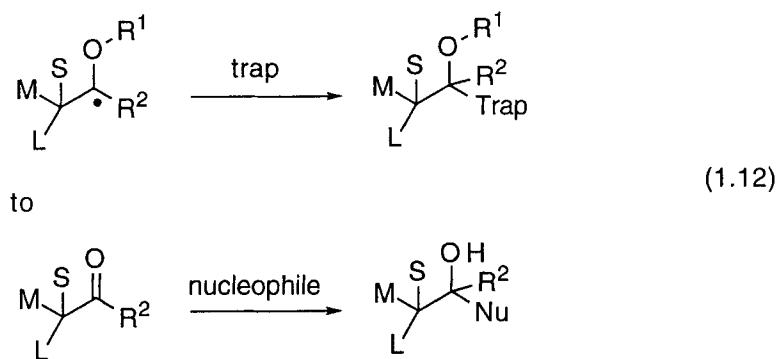
The lack of stereochemical parallel can be as informative as the existence of one. Consider for example the ionic and radical 1,4-addition reactions of Oppolzer's camphor sultam (Eq. 1.11). Radical additions to the β -carbon of sultam acrylates proceed with low selectivity (Chapter 5) because the approaching radical is too far away from the sultam to influence its face selectivity. In contrast, a number of types of nucleophilic addition reactions to the similar sultam acrylates occur with good to excellent levels of stereoselectivity.³⁵ This contrast suggests that simple models for the ionic reactions with the nucleophile approaching along the trajectory similar to that of the radical and being influenced by some group (or groups) on the sultam cannot be correct. The metal must play an active role in controlling face selectivity.



- Radical and nucleophile approach vectors are similar ~ 109°
- Radical additions give low stereoselection
- Nucleophile additions often give high stereoselection

Related analogies can be envisioned for many other pairs of substrates. For example, the analogy between α -oxy radicals and aldehydes or ketones

shown in Equation 1.12 is especially interesting. Reactions of α -oxy radicals with adjacent stereocenters provide insight into Felkin-Anh additions of nucleophiles to chiral aldehydes and ketones. This analogy is further discussed in Chapter 4. Analogies between radical cyclizations and related organometallic additions to double bonds (intramolecular carbometallations) also provide insights, as discussed in Chapter 2.



In short, it is the thesis of this book that stereoselective radical reactions are both interesting and significant in their own right. The study of such reactions leads to a better understanding of the structure and reactions of organic radicals and opens new methods for the stereoselective synthesis of organic molecules. Furthermore, because there exist qualitative analogies between radical reactions and related ionic and pericyclic reactions, and because stereoselective radical reactions are often easier to understand and explain than their ionic and pericyclic counterparts, the stereoselectivity of radical reactions is of special interest across the field of asymmetric synthesis.

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Chapter 2

Substrate Control: Radical Cyclizations

2.1 Introduction

The preparative importance of intramolecular radical additions to multiple bonds, hereafter called radical cyclizations, has grown at an astonishing rate over the last decade. Initially, radical cyclizations were studied from the standpoint of basic research on radicals.¹ Qualitative and quantitative understanding grew quickly, and cyclizations soon became popular as mechanistic probes for detecting the intermediacy of radicals.² These physical organic studies paved the way for the subsequent synthetic explosion. Thanks to the fruitful interplay between synthetic and physical organic chemistry, the chemo-, regio-, and stereoselectivities of many classes of radical cyclizations are today well understood, and such cyclizations have become reliable tools in synthesis.³ The goals of this chapter are to summarize the large body of literature on stereoselectivity in radical cyclizations, to provide rational guidelines for predicting the outcome of cyclizations, and to stimulate further studies in this continually evolving field.

A number of reviews treat the subject of radical cyclizations from several different standpoints.^{4–7} Although none focuses specifically on stereochemistry, all address issues of stereochemistry to some degree. These reviews also provide excellent overviews of the principles of chemo- and regioselectivity of radical cyclizations. Though stereoselectivity could have been comprehensively reviewed in just a few pages a decade ago,⁸ the number of radical cyclizations in which new stereocenters are created now far exceeds the capacity of this book. Therefore, examples will be selected with an eye towards illustrating general principles, and selected references will be provided. A treatise in the Houben-Weyl⁶ series provides an excellent compilation of cyclizations of carbon-centered radicals up to the late 1980s. A more recent monograph, which also includes heteroatom centered radicals, is now in press in *Organic Reactions*.⁹

Almost all of the stereoselective radical cyclizations presented in this chapter fall under the umbrella of substrate control, as defined in Chapter 1. Because the radical and the alkene are connected by definition, the location of the stereocenter (on the radical or the alkene) has no meaning. Further, the nature of the length and geometry of the connecting chain limit the possible orientations in the transition state. Finally, thanks to entropy, many types of radical cyclizations are much more general than their intermolecular analogs. For these reasons, radical cyclizations warrant a separate treatment from radical additions. Indeed, there are currently many more examples of stereoselective radical cyclizations than there are of additions.

This chapter will primarily cover two general classes of kinetically controlled radical cyclizations in which one or more new stereocenters are formed (Fig. 2-1): 1) cyclizations of achiral radicals bearing prostereogenic¹⁰ radical and alkene centers (these cyclizations can occur with simple diastereoselection, sometimes called mutual face selection,¹¹ and two racemic products can be formed), and 2) cyclizations of chiral radicals bearing prostereogenic radical or alkene atoms (if either the radical or the alkene is prostereogenic, then these cyclizations occur with relative asymmetric induction,¹¹ and if both the radical and the alkene are prostereogenic, then they occur with both relative asymmetric induction and simple diastereoselection). While these classes are illustrated in Figure 2-1 for alkenes, simple diastereoselection can occur with many types of doubly-bonded acceptors, and relative asymmetric induction can occur with both doubly- and triply-bonded acceptors. Both classes of reactions convert an sp² center (or centers) to a stereogenic sp³ center (or centers) through a face selective reaction. In the majority of examples of relative asymmetric induction, the existing stereocenter is located in the forming ring between the radical and the alkene (as shown in Fig. 2-1). There are just a few examples of substrate control where the existing stereocenter is outside the forming ring. Radical cyclizations involving chiral auxiliaries are conceptually similar to the related radical additions, and these are dealt with primarily in Chapter 5.

Several smaller classes of radical cyclizations will also be covered as will stereoselective radical reactions operating under thermodynamic control. Stereoselective cyclizations of chiral radicals that involve homolytic substitution (rather than addition to a multiple bond) will be treated briefly.

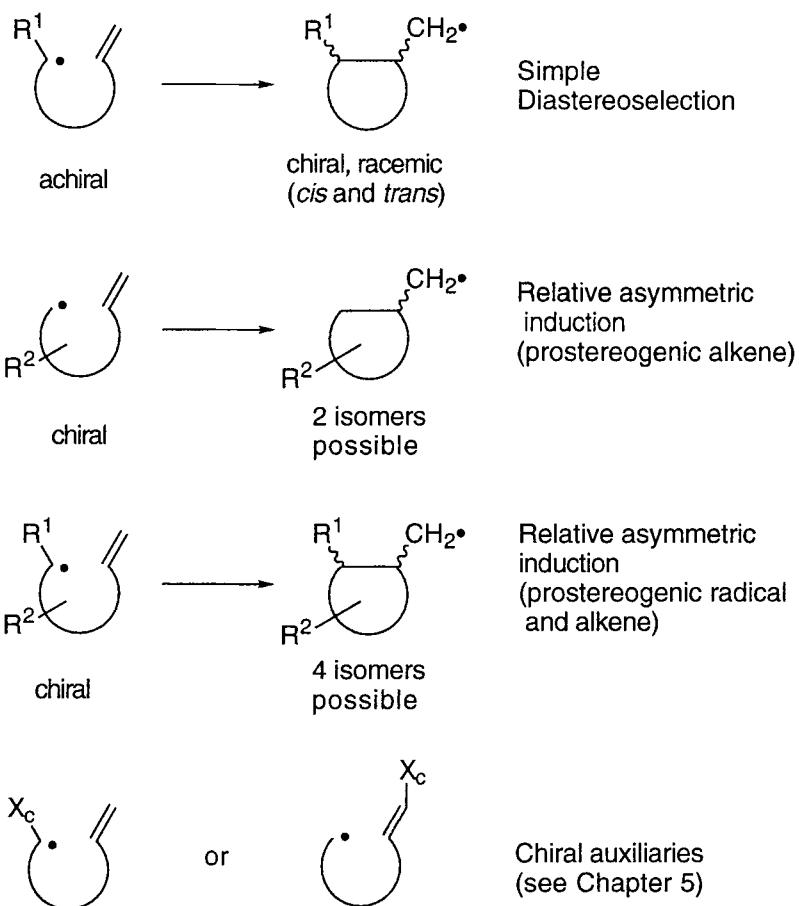


Figure 2-1. Major Classes of Stereoselective Radical Cyclizations.

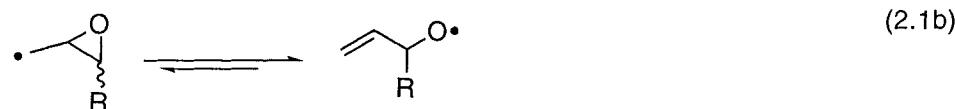
2.2 Face-Selective Radical Cyclizations to Multiple Bonds

This section is divided according to the length of the connecting chain between the radical and the acceptor, and then sub-divided by whether the cyclizations occur in an *exo* or *endo* fashion. Examples of recently introduced group-selective radical cyclizations will be provided separately. The majority of examples of stereoselective cyclizations are in the 5-*exo* and (to a lesser extent) 6-*exo* classes. These classes are emphasized, and their

sections are further appropriately sub-divided. Although some brief comments will be provided on the general features of radical cyclizations (rate, chemo- and regioselectivity), the reader is encouraged to consult other sources^{1,4–7} for better discussions of these features.

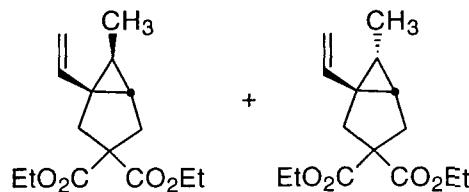
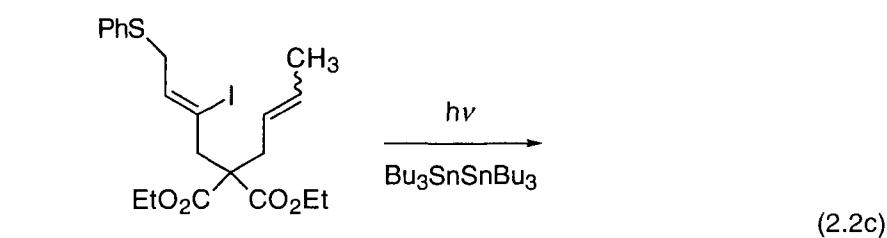
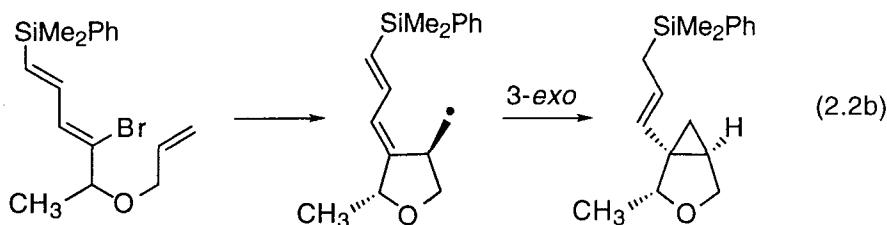
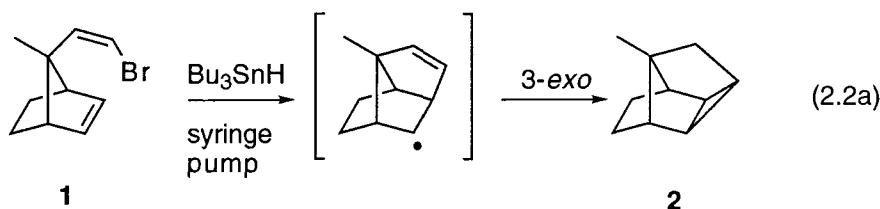
2.2.1 Butenyl and Related Radical Cyclizations

Butenyl radicals always cyclize in a 3-*exo* fashion, and these cyclizations are often quite rapid (Eq. 2.1). However, the rates of ring opening of the resulting cyclopropylcarbinyl radicals typically exceed ring closure, so butenyl radicals are favored at equilibrium.¹² The formation of one bond through a 3-*exo* cyclization and the ensuing cleavage of another bond is a powerful synthetic technique for ring expansion.¹³



Studies of stereoselectivity of 3-*exo* cyclizations of butenyl radicals (Eq. 2.1a) are complicated by the rapid reversal and unfavorable equilibrium, and establishing kinetic control in the closure of an acyclic butenyl radical is not easy. Related epoxyalkyl radicals (Eq. 2.1b) may also equilibrate very quickly.¹⁴ Products derived from a 3-*exo* cyclization can be trapped by building much of the ring strain of the cyclopropane into the precursor, by substituting the butenyl radical so as to stabilize the product cyclopropylcarbinyl radical, or by trapping the cyclopropylcarbinyl radical exceedingly rapidly.¹⁵ Most known examples capitalize on one of the first two approaches,¹⁶ and the 3-*exo* closures often occur in tandem reactions. The reduction of **1** shown in Equation 2.2a¹⁷ provides an example where “built in” ring strain may favor the formation of the 3-*exo* product **2**. Equation 2.2b shows an example where a less stable alkyl radical is converted to a more stable silylallyl radical in a 3-*exo* cyclization.¹⁸ These two cases are

representative of the kind of stereocontrol that has been observed in 3-*exo* cyclizations. The structure generally permits only one stereoisomer because the forming cyclopropane ring is fused to one or more small rings. Stereoisomers of the products shown in Equations 2.2a,b would have prohibitive strain energy. Equation 2.2c provides an example where the intermediate cyclopropylcarbinyl radical is trapped very rapidly by elimination of a thiophenyl radical. In addition to the two ring fusion stereocenters, a third stereocenter is formed in this example with a good level of selectivity in favor of the *exo* isomer (10/1).¹⁹



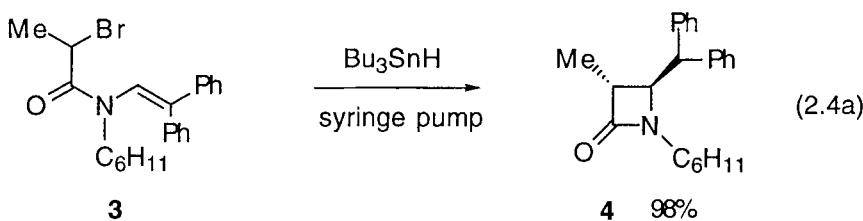
10/1, 48%

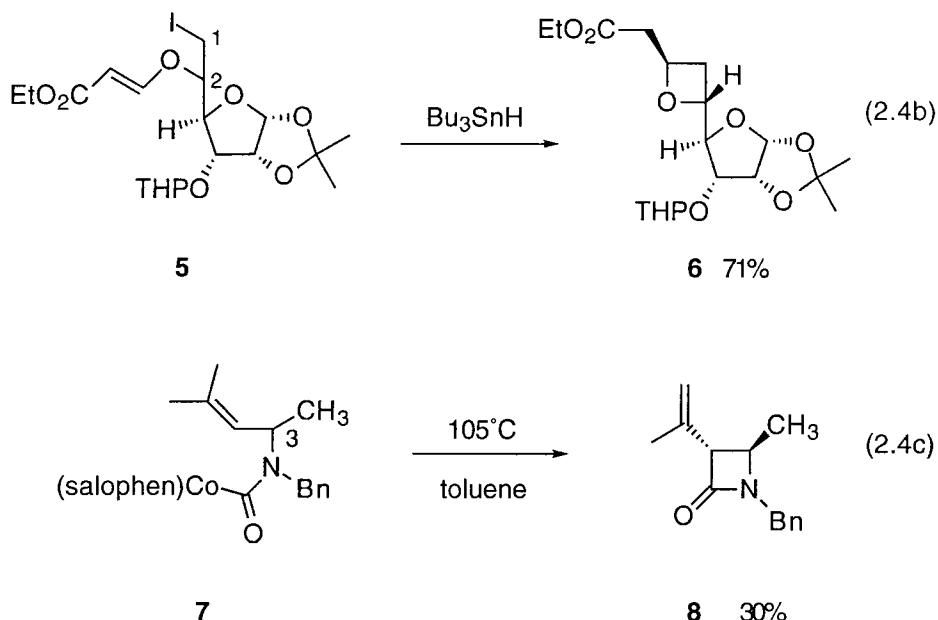
2.2.2 Pentenyl and Related Radical Cyclizations

Pentenyl radicals can cyclize in a *4-exo* or *5-end*o fashion. Though neither reaction is common, the stereoelectronically preferred *4-exo* pathway can be rapid enough to be useful if appropriate substituents are present.²⁰ These cyclizations may also be reversible, and indeed in the parent system (Eq. 2.3), the open pentenyl radical is favored at equilibrium over the closed cyclobutylcarbinyl radical.



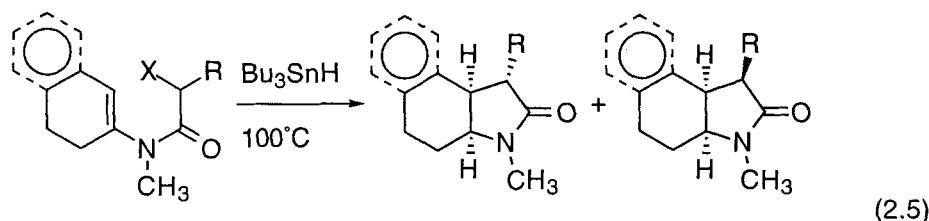
A number of highly stereoselective *4-exo* cyclizations of heteroatom-containing pentenyl radicals have been reported. In all cases, *trans*-disubstituted heterocycles are formed, even though the substitution patterns vary considerably. For example, in reactions involving simple diastereoselection, bromoacyl enamides like **3** close to *trans*-disubstituted β -lactams **4** upon addition of tributyltin hydride by syringe pump (Eq. 2.4a).²¹ In a reaction involving relative asymmetric induction, iodide **5** bearing a stereogenic center at C2 closes to give exclusively the *trans*-disubstituted oxetane **6** (Eq. 2.4b, both the precursor and product are mixtures of two diastereomers at the THP group).²² Likewise, acyl cobalt salophen **7** bearing a stereogenic center at C3 closes upon heating at 105°C to give exclusively the *trans* β -lactam **8**, albeit in a modest yield of 30% (Eq. 2.4c).²³ A closely related reaction was used as a key step in the synthesis of (\pm)-thienamycin.²³





In short, while *4-exo* cyclizations have a limited scope, those that do work seem disposed towards high selectivity. Since new substrates that undergo *4-exo* cyclizations have recently been discovered,²⁰ it should now be possible to conduct more systematic studies of stereoselectivity.

Bona fide examples of *5-endo* cyclizations²⁴ are even more rare than their *4-exo* counterparts. Enamides seem to be prone to unusual radical cyclizations (see the *4-exo* cyclizations in Eq. 2.4a), and a number of stereoselective *5-endo* cyclizations have been reported (Eq. 2.5).²⁵ Tin hydride promoted cyclizations of monocyclic enamides **9** provide bicyclic lactams **10/11** with variable selectivities, depending on the nature of R. In contrast, cyclizations of bicyclic enamides **12** to tricyclic lactams **13** occur with very high selectivity to place R on the *exo*-face of the newly formed ring fusion. In these reactions, two of the three new stereocenters are formed through simple diastereoselection in the *5-endo* cyclization, and the third is formed by hydrogen transfer from tin hydride (this is an example of a stereoselective reaction of a cyclic radical, a topic treated in Chapter 3).



Monocyclic

9a X = Cl, R = Me
9b X = Cl, R = Ph
9c X = SPh, R = SPh

10a	6/1	11a
10b	2/3	11b
10c	1/1	11c

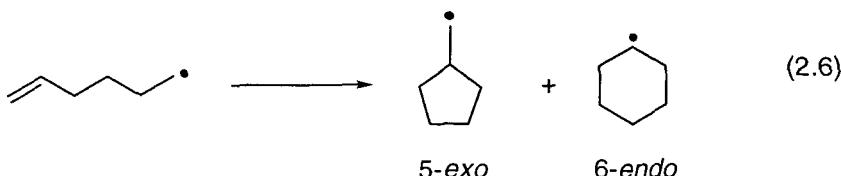
Bicyclic

12a X = Cl, R = Me
12b X = Cl, R = Ph

13a only	a (not formed)
13b only	b (not formed)

2.2.3 Hexenyl and Related Radical Cyclizations

Hexenyl radical cyclizations (Eq. 2.6) are frequently rapid, and they are the most popular class of cyclization both for mechanistic study and for synthetic application.^{1,4–9} Cyclizations of these radicals are typically irreversible at normal operating temperatures (-80°C to $+120^{\circ}\text{C}$), although the formation of strained cyclic products or the presence of radical stabilizing substituents can occasionally induce (partial) equilibration via reversible cyclization. Primarily for stereoelectronic reasons, *5-exo* cyclizations are generally favored over their *6-endo* counterparts. However, *6-endo* cyclizations are not as uncommon as was once thought. Substituent effects on *5-exo*/*6-endo* selectivity are quite well understood,^{1,4–9} and this makes it possible to predict the regioselectivities of new substrates with a good level of confidence.



2.2.3.1 5-*Exo* Cyclizations, the Beckwith–Houk Transition State Model

Stereoselective 5-*exo* cyclizations of substituted hexenyl radicals and their analogs comprise the largest body of stereoselective radical reactions. By presenting illustrative examples from the large number of published reactions, this sub-section will strive to provide an overview with an emphasis on established trends coupled with useful models for understanding these trends. The recent *Organic Reactions* chapter on “Radical Cyclizations” provides a significantly more comprehensive compilation of examples of stereoselective 5-*exo* cyclizations.⁹ Following a brief discussion on the Beckwith–Houk transition state model, examples will emerge in rough order of increasing complexity: reactions of acyclic systems with increasing numbers of stereocenters will be followed by reactions of cyclic systems.

The Beckwith–Houk transition state model currently serves as the basis for predictions and rationalizations of stereoselectivity in 5-*exo* hexenyl radical cyclizations. The power of the model lies in its simplicity and its adaptability. It is simple because it makes unambiguous predictions for most classes of radicals, and it is adaptable because, given a number of related examples, one can begin to understand which interactions are more or less important in the various competing transition states.

To work with the Beckwith–Houk transition state model requires first an understanding of the transition states of the hexenyl radical itself. Key details of the transition structures were first deduced by Beckwith,²⁶ and an in-depth understanding of these details was advanced by the calculations of Beckwith and Schiesser,²⁷ and Spellmeyer and Houk.²⁸ The oft-cited paper of Spellmeyer and Houk²⁸ provides a very nice discussion of the features of the transition states of hexenyl radical cyclizations and shows how these features are affected by the introduction of substituents.

Models of the transition structures for 5-*exo* hexenyl radical cyclizations result from uniting the features of the basic transition state for a simple bimolecular radical addition to an alkene (Chapter 1) with the principles of conformational analysis. The hexenyl radical can accommodate the preferred tetrahedral-like approach of the radical to the alkene by folding into either of two conformations (Fig. 2-2). The first conformation **14** was termed a “chair” by Beckwith, and this formed the basis of the first stereochemical model (often called the “Beckwith model”) for hexenyl radical cyclization.²⁶ The importance of the second conformation **15** was

recognized by Spellmeyer and Houk²⁸ as crucial to the understanding of many cyclizations, and this was in turn named a “boat”.

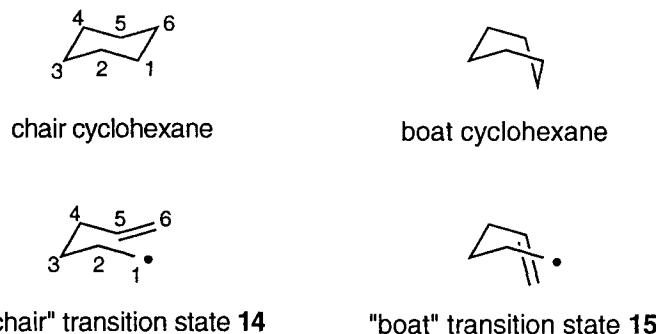


Figure 2-2. Transition Structures for Hexenyl Radical Cyclizations.

The “chair/boat” names for hexenyl radical transition states are now firmly rooted in the literature, although this is decidedly a mixed blessing. Compared to the cyclohexane “chair/boat” parents, the hexenyl radical transition states have both useful resemblances and significant differences. The “chair/boat” names nicely conjure up the shapes of the transition structures **14** and **15**, which also resemble “envelope” cyclopentanes with the terminal methylene group (C6) of the alkene *trans* (in chair **14**) or *cis* (in boat **15**) to the methylene group on the “open flap” (C3) of the envelope. The features resembling cyclohexane in the transition structures arise from the “stretching” of the C1–C5 bond of the product away from its equilibrium length of about 1.52 Å to a calculated length of 2.2 – 2.3 Å in both the boat and the chair. This distance is quite close to the C1–C3 atom distance across the ring in both chair and boat cyclohexane. The long forming bond releases both angle and torsional strain that will ultimately be present in the cyclopentane product. Atoms C2, C3, and C4 of transition structures **14** and **15** very much resemble their cyclohexane counterparts, and each has clear-cut “axial” and “equatorial” substituents.

Moving beyond these very useful features, the “chair/boat” analogy begins to break down. Unlike boat cyclohexane, which is 7 kcal/mol higher in energy than the chair conformer, boat transition structure **15** is calculated to be only about 1 kcal/mol higher than its chair conformer **14**.²⁸ A look at the Newman projections in Figure 2-3 shows that C6 in the hexenyl radical transition structures bears essentially no relationship to its analogs in

cyclohexane; in effect, there is little or no “flagpole interaction”. Further, both C1 and (especially) C5 are much closer to sp^2 than sp^3 hybridization, and this results in partial eclipsing about the C1–C2 and C4–C5 bonds. Unlike boat (significant eclipsing) and chair (no eclipsing) cyclohexane, the eclipsing in the boat and chair transition states is very similar because the two transition states simply interchange a vinyl methylene group with a vinyl hydrogen by a 180° rotation about the C4–C5 bond. Indeed, it is only C2–C4 of the hexenyl radical transition states that resemble C2–C4 (half) of cyclohexane. Since the C2–C4 half of a chair cyclohexane is identical to the C2–C4 half of a boat cyclohexane, the analogy begins to dissipate.

Given these similarities, it then becomes interesting to question why the chair transition state is 1 kcal/mol lower in energy than its boat counterpart? A simple answer to this question arises by considering the conformations of 1-butene—a shortened version of the hexenyl radical with the radical chopped off. 1-Butene adopts two low energy conformations, gauche and skew, about the allylic C–C bond, and the gauche rotamer is disfavored relative to the skew by about 0.5–1.0 kcal/mol.²⁹ This is similar to the energy difference between the boat transition state, which resembles gauche butene, and the chair transition state, which resembles skew-butene. Thus, energetic

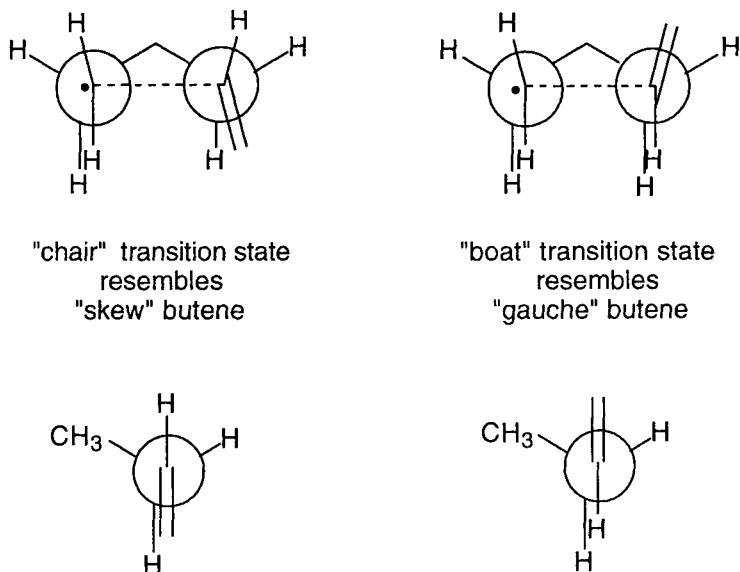


Figure 2-3. Newman Projections of Hexenyl Radical Transition States.

effects and explanations in chair and boat cyclohexane are quite misleading, and the small energy differences between the hexenyl radical transition states may result from allylic conformational preferences.

These general features of 5-*exo* transition states are probably not unique to radical cyclizations, but extend to many types of ionic and pericyclic reactions with early transition states. For example, cyclizations to make five-membered rings are often faster than related cyclizations making six-membered rings.³⁰ Though this trend is usually attributed to entropy, enthalpic effects may also contribute. The long forming bond in an early cyclization transition state may tend to make the geometry of the connecting chain resemble that of the next larger sized ring more than the actual forming ring. From the standpoint of torsional and angle strain, forming five-membered rings may more closely resemble six-membered rings, and forming six-membered rings may more closely resemble seven-membered rings. Energy differences in “chair” and “boat” transition structures to make cyclopentanes (for example in a hexenyl metal cyclization) may be unrelated to “chair/boat” cyclohexane, and instead may hinge on requirements of a given reaction. Some specific comparisons of radical and ionic reactions will be provided below.

We do not advocate the changing of the “boat/chair” transition state names, which are an integral simplifying feature in the Beckwith–Houk model for stereoselectivity. Figure 2-4 shows the application of this model for predicting the stereochemistry with C2, C3, or C4 substituted hexenyl radicals; substituents at C1 are conceptually different, as discussed below. The introduction of a stereocenter results in four transition structures: chair-equatorial, chair-axial, boat-equatorial, and boat-axial, as shown in Figure 2-4. For mono-substituted systems, the major product usually arises from the chair-equatorial transition structure. Thus, the “cyclohexane” analogy leads quickly to the prediction of the major product. The doubly disfavored “boat-axial” transition structure provides the same product, but it is thought to be too high in energy to be a significant contributor, and it is ignored in most analyses. Minor products can come from either or, more typically, both the chair-axial and boat-equatorial transition structures.

In analyses of stereoselectivity with multiple substituents, one attempts (intellectually or computationally) to evaluate the effects of substituents on the relative energies of the three principle transition structures. In several cases (see below), there is excellent evidence for the importance of boat

transition structures.³¹ Computational assessment of radical stereoselectivities is now quite advanced, and methods developed by both Beckwith²⁷ and Houk²⁸ reproduce diastereomer ratios of many stereoselective reactions quite well.

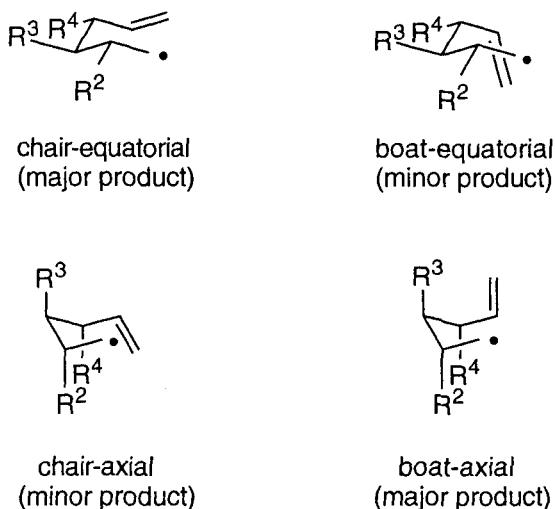


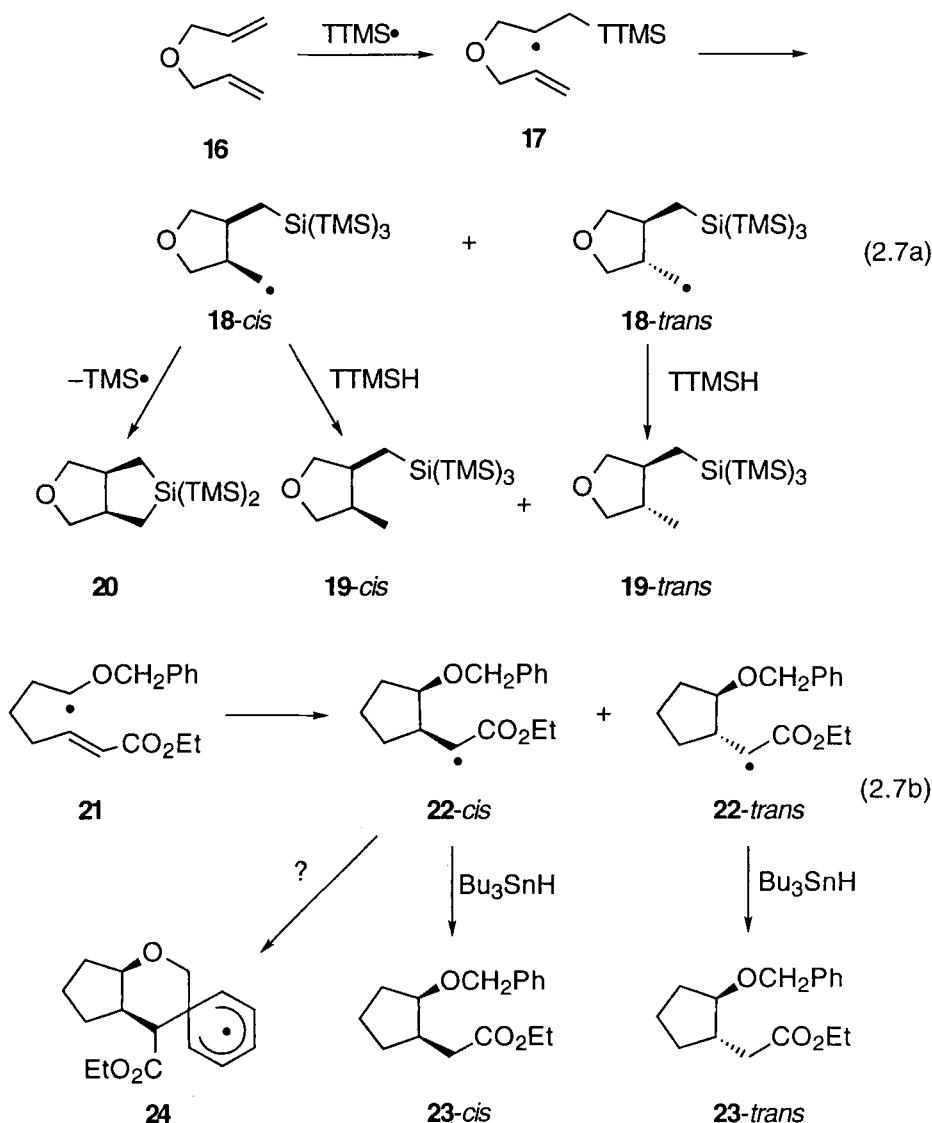
Figure 2-4. Substituents in Chair and Boat Transition Structures.

In practice, the Houk/Spellmeyer method is quite easy to use.²⁸ This is an application of force field modeling based on ab initio calculations. The “end user” needs to know only how to use standard force field calculations, and to input several special transition state atom types and parameters (which are now being included in some force fields). The “transition structure” calculation is essentially identical to calculating the ground state structure of a molecule in a force field. The initial parameters that Spellmeyer and Houk introduced have been periodically improved and augmented.³² The discussions of the individual substituents below will be presented in the context of the Beckwith/Houk model, and for each methyl derivative, the Spellmeyer/Houk calculations can be used to estimate the ratios of products derived from each of the four transition states.

2.2.3.2 Stereoselectivities of Acyclic Hexenyl Radicals

Prior to presenting individual substituent effects, an important caveat is in order. In presenting stereochemical ratios from the literature for com-

parison, one obviously assumes that these ratios are correct. In general, this assumption simply means that a careful, proper analysis has been conducted. However, in radical chemistry, it is quite possible that the accurately measured stereoselectivities of isomeric products do not equal the original selectivity of the reaction in question. This point is illustrated by a clear example in Equation 2.7a³³ and an ambiguous one in Equation 2.7b.³⁴

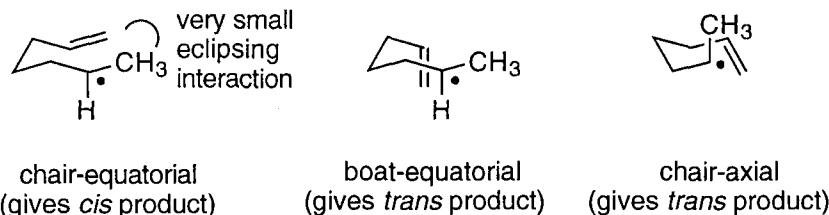
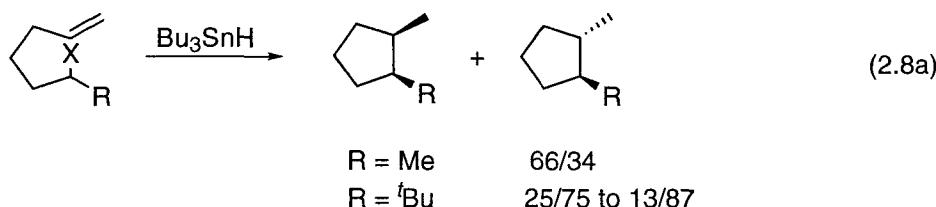


Hydrosilylation of **16** with TTMS at high concentrations provides a 3/1 mixture of **19-cis** and **19-trans** in good isolated yield. However, as the concentration of TTMS decreases, the yield of **19-cis** falls with an accompanying decrease in the *cis/trans* ratio. Two new products are formed, one of which is the intramolecular homolytic substitution product **20** (the other is simply the cyclic hydrosilylation product of **16** by the trimethylsilyl radical). Had these workers conducted this reaction at a single low concentration without carefully quantifying the products, they could easily have reported a fully correct experimental ratio of **19-cis/trans** that was at the same time an incorrect measure of partitioning of radical **17** towards **18-cis** and **18-trans**. Thus, one must ensure that the trapped products accurately reflect the desired ratio, taking care to consider that stereoisomeric radicals can react further (especially in intramolecular reactions) with large differences in rate.

The problems can sometimes be more subtle, especially at the low concentrations of bimolecular traps that are frequently used to permit slow intramolecular reactions to occur. For example, radical **21** (generated by the tin hydride method) cyclized to give trapped products **23-cis** and **23-trans** in a ratio of 1/2.8. At very low tin hydride concentrations, the ratio of **23 cis/trans** slowly decreased to about 1/4 without an experimentally significant change in the total isolated yield (50–60%). No new products were detected. In these experiments, the significance of the changing ratios is not clear. Equilibrium of radicals **22-cis** and **22-trans** by reversible cyclization is a possibility, but these types of radicals are not expected to equilibrate easily. A second possibility is that there may be a competing process that destroys **22-cis**. For example, **22-cis** might cyclize to **24**. In turn, **24** is a stable cyclohexadienyl radical that might not react with tin hydride at low concentrations and would instead react by other pathways. In principle, the two possibilities can be differentiated by careful quantitative kinetic experiments. In practice, the message is clear: a single cyclization experiment providing the “expected” products may still not provide an accurate ratio of the stereoselectivity unless it can be shown that the combined yield of these products is high.

This caveat notwithstanding, we expect that most of the literature ratios are correct. Yields of many radical cyclizations are high, and it is usually possible to anticipate when side reactions might consume stereoisomeric radicals at different rates.

1-Substituted Hexenyl Radicals: 1-Substituted hexenyl radicals are often achiral, and they close with simple diastereoselection to give racemic mixtures of *cis*- and *trans*-1,2-disubstituted cyclopentanes. Many types of 1-substituents have been studied, and the *cis/trans* ratios vary over a wide range. The behavior of the parent 1-methylhexenyl radical is typical of many of the members of this class (Eq. 2.8a). In accord with the Beckwith–Houk model, this provides *cis*-1,2-dimethylcyclopentane as the major stereoisomer, but the selectivity is modest (66/34 at 65°C). The major *cis* product arises mostly from the chair-equatorial transition state while the minor *trans* product probably comes from both the chair-axial and the boat-equatorial transition state.²⁸ In these transition states the “equatorial” position at C1 does not bear much resemblance to an equatorial cyclohexane substituent (see Fig. 2-2).

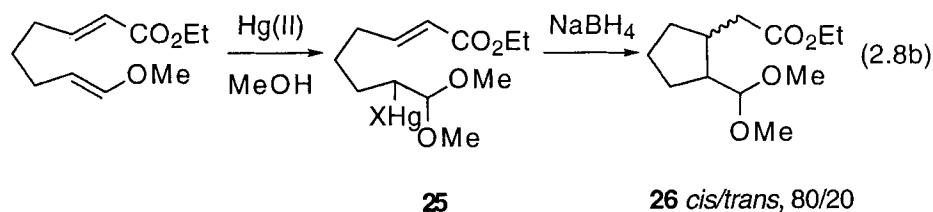


The underlying reasons for the commonly observed *cis* selectivity with 1-substituted hexenyl radicals have been the subject of some discussion. Because the methyl and methylene groups are nearly eclipsed in the chair-equatorial transition state, it appears that the *cis* product should be disfavored. However, the calculations of Spellmeyer and Houk²⁸ suggest that because the forming bond is very long, the energetic penalty for eclipsing these two groups is very small (< 1 kcal/mol). The same calculations suggest that the “axial” substituent on C1 is nearly eclipsed with an adjacent hydrogen on C2, while the “equatorial” substituent is better staggered. Furthermore, the

“equatorial” substituent is *anti* to the C2–C3 bond while the axial substituent is *gauche*. These two factors probably conspire to make the chair-equatorial transition state the lowest in energy.

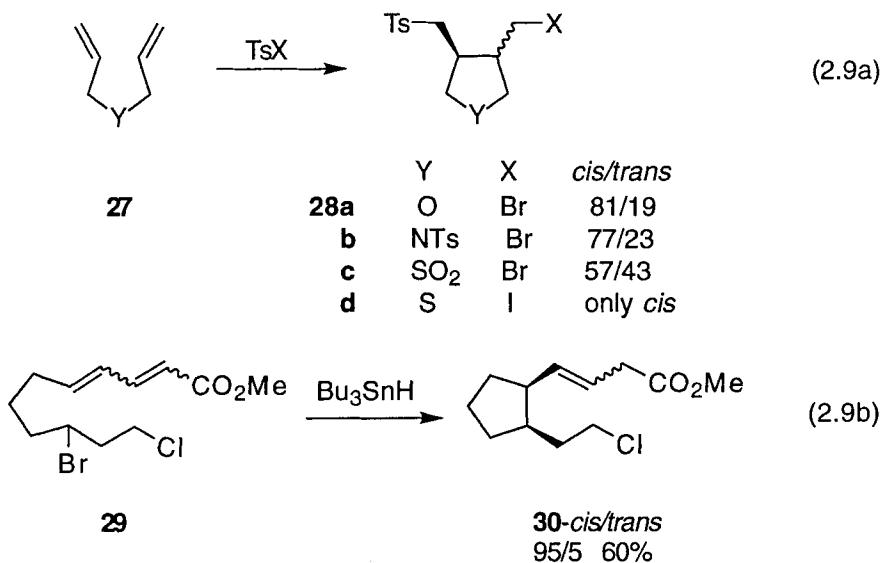
The cyclization of the 1-*tert*-butylhexenyl radical is an interesting case study comparing theory and experiment (Eq. 2.8a),³⁵ and it also provides a clear indication of the small magnitude of eclipsing interactions between the radical substituent and the alkene. Cyclization of this radical exhibits a *trans* selectivity that depends somewhat on the temperature and (surprisingly) the solvent. But the key point is that the *trans* selectivity ($81/19 \pm 6\%$) is really quite modest considering the large size of the *tert*-butyl group.

The following paragraphs provide a small sampling taken from the large number of cyclizations of 1-substituted hexenyl radicals. These examples were selected to illustrate a range of different substituents and *cis/trans* selectivities. Most substrates cyclize with *cis/trans* selectivities in the range of 60/40 to 85/15. The example shown in Equation 2.8b is typical. Cyclization of **25** by the mercury method provides **26-cis** and **26-trans** in high yield in a ratio of 80/20.³⁶

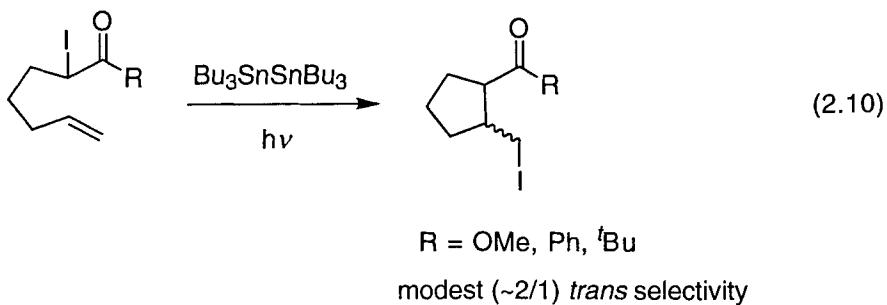
**25****26 cis/trans, 80/20**

A diverse collection of 1-alkyl and 1-heteroalkyl hexenyl radicals have been generated by tandem addition/cyclization reactions starting from 1,5-hexadiene and its oxygen and nitrogen analogs. With a few exceptions, modest *cis* selectivities are observed, with small variations as a function of substituents. Selected examples of cyclizations mediated by tosyl halides are shown in Equation 2.9a.³⁷ Other reagents can also be used.³⁸ In many of these reactions, the configurations of the products **28** have not been assigned by spectroscopic or chemical means. Instead, these configurations are often assigned by analogy or simply by using the Beckwith–Houk model. In a few cases, modest *trans* selectivity has been observed in these reactions,³⁹ and in one example^{38c} (see conversion of **27** to **28d**, Eq. 2.9a), a very high *cis* selectivity was reported. Several isolated experiments suggest that substrates

bearing linear chains of several atoms on both the radical carbon and the terminal alkene carbon give atypically high *cis* selectivities.²⁷ For example, cyclization of dienyl dihalide **29** (Eq. 2.9b) provides **30-cis** and **30-trans** in a ratio of 95/5.^{40,41}

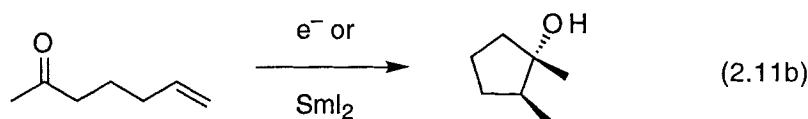
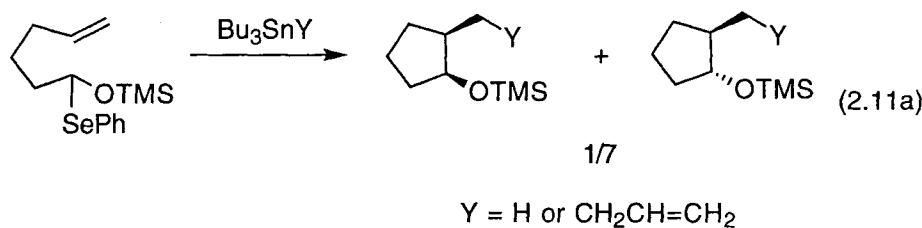


Reactions of carbonyl substituted radicals have been studied by a number of groups, and these are often conducted by the atom transfer method.⁴² Low selectivities are typically observed, and the *trans* isomer is frequently favored (Eq. 2.10). These selectivities do not depend very much on the presence of a terminal alkene substituent or on its geometry. Carbonyl groups like esters and amides can also be situated inside the



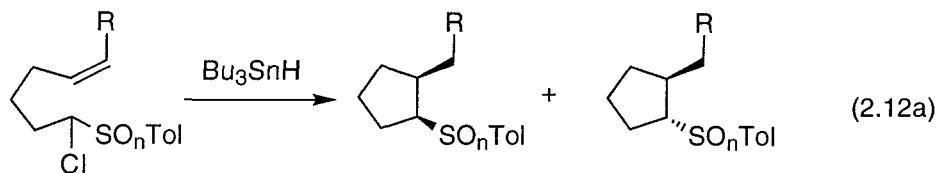
forming ring, and these reactions produce lactones or lactams, usually (but not always) with modest *cis* selectivities.⁴³

1-Heteroatom substituted hexenyl radicals also often cyclize with a low level of *cis* selectivity,⁴⁴ but there are some significant exceptions. Alkyl- and silyl-ether substituted radicals have a tendency to give increased amounts of the *trans* products, and selectivities can be reasonably good, as shown by the example in Equation 2.11a.⁴⁵ Ketyl radical anions cyclize with excellent *trans* selectivities (Eq. 2.11b),^{46,47} suggesting that electronic repulsion between the forming radical center and the negatively charged ketyl oxygen is significant in the transition state leading to the disfavored *cis* isomer. This same type of repulsion, though significantly reduced in magnitude, may account for the unexpected *trans* selectivities in cyclizations of some α -oxy radicals.



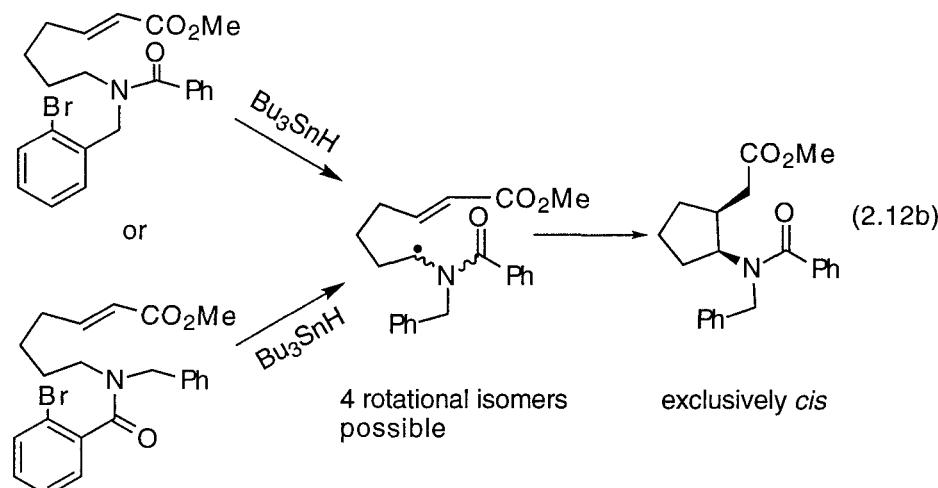
Sulfinyl- and sulfonyl-substituted radicals can also give good to excellent *trans* selectivities (Eq. 2.12a).⁴⁸ For these radicals, the selectivities are improved with either *cis*- or *trans*-alkene substituents. In the case of the sulfinyl radicals, significant 1,2-asymmetric induction by the stereogenic sulfinyl sulfur atom is not observed. Though most nitrogen-substituted radicals do not exhibit high selectivities,⁴⁴ *N*-benzyl benzamidoyl radicals cyclize to provide exclusively *cis*-products, albeit in modest yields (~50%).⁴⁹ To probe for the possibility that radical cyclization might be faster than rotation about amide and radical C–N bonds, two radical translocation precursors were used to generate benzamidoyl radicals in different initial conformations (Equation 2.12b). However, the results from the two precursors were the same. This suggests, though it does not rigorously prove,

that conformational interconversion of the radicals is faster than cyclization. Heteroatoms can also be located in the radical acceptor, but examples of high simple diastereoselection have not yet been discovered in these substrates.⁵⁰



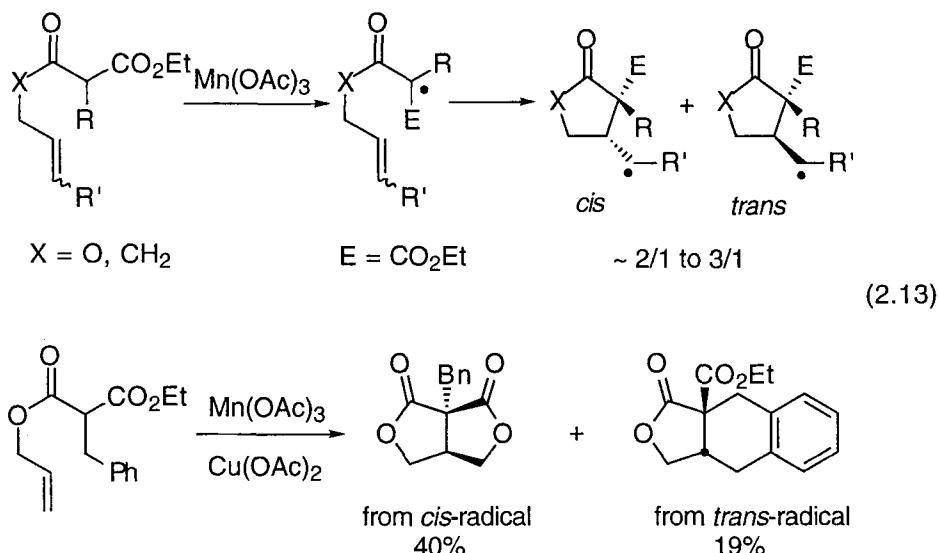
R	n	<i>cis/trans</i>
H	1	14/86
H	2	14/86
OMe	1	<i>trans</i> only
OMe	2	<i>trans</i> only

no 1,2-induction
if n = 1

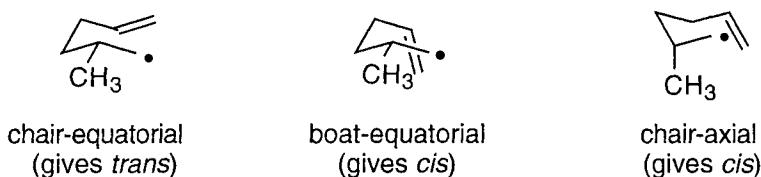
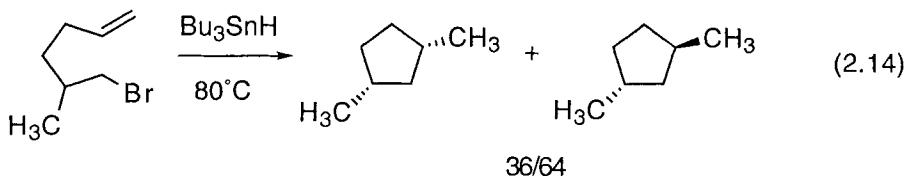


In general, 1,1-disubstituted hexenyl radicals are expected to cyclize with relatively low selectivities. About the best selectivities that have been observed in simple members of this class are the oxidative cyclizations of β -ketoesters and β -diesters promoted by manganese(III) acetate.^{51,52} Good evidence suggests that free tertiary radicals are involved in these reactions,⁵³ and stereoselectivities in the range of 2/1 to 3/1 are common. A typical example is shown in Equation 2.13. In the cyclizations of β -ketoester

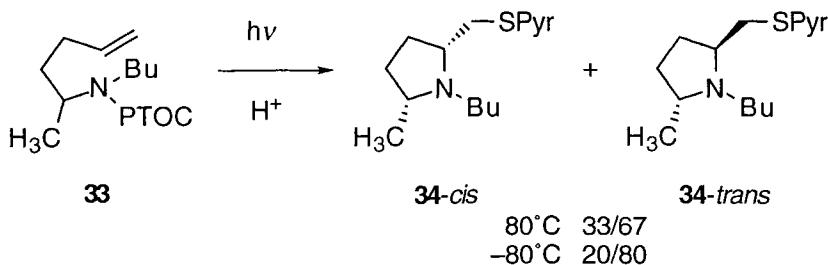
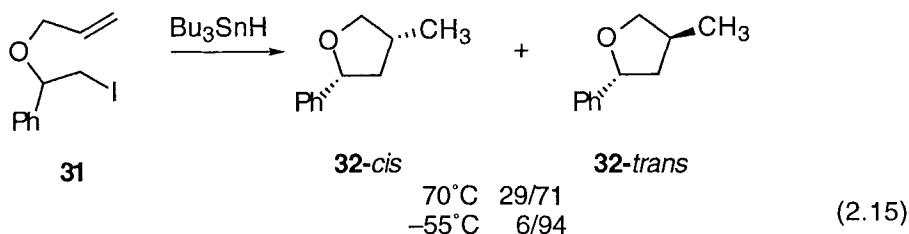
radicals, significant amounts of *6-endo* products form, and good stereo-selectivity has been observed (see below). Higher selectivities are observed in related cyclizations to form spirocyclic lactams.⁵⁴ *6-Exo* cyclizations of homologous radicals can occur with excellent selectivity (see section below for examples and stereochemical model). Cyclizations of related secondary radicals (Eq. 2.13, R = H) are highly *trans* selective,⁵¹ but this is because the acidic dicarbonyl products equilibrate under the reaction conditions.



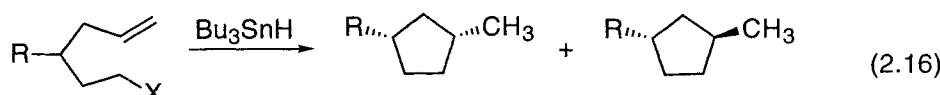
2-Substituted Hexenyl Radicals: The Beckwith–Houk model predicts that 2-substituted hexenyl radicals should cyclize to give predominantly *trans*-1,3-disubstituted cyclopentanes, and a survey of the literature suggests that this is a good generalization for carbon-centered radicals. The prototype 2-methylhexenyl radical provides a 36/64 ratio of *cis/trans*-1,3-dimethylcyclopentane, and the calculations of Spellmeyer and Houk²⁸ indicate that the major product comes from the chair-equatorial transition state while the minor product comes from both the chair-axial and the boat-equatorial transition states (Eq. 2.14).



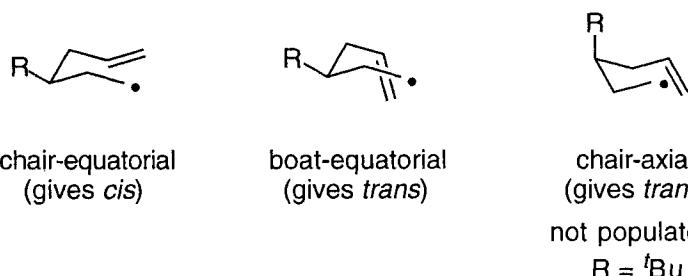
Other 2-substituted radicals tend to give variable *trans* selectivities, depending on the nature of the substituent and the chain. Smaller ether substituents exhibit almost no selectivity,⁵⁵ but large alkyl or aryl substituents give increased selectivities.⁵⁶ Reducing the temperature can also increase the selectivity, as shown by the conversion of **31** to **32** in Equation 2.15.⁵⁷ Isoelectronic ammonium radical cations also cyclize with modest *trans* selectivities (see cyclization of **33** to **34** in Eq. 2.15),⁵⁸ but the situation for 2-substituted aminyl radicals is less clear.⁵⁹



3-Substituted Hexenyl Radicals: The Beckwith–Houk model again fares well with simple 3-substituted hexenyl radicals. The predicted 1,3-*cis*-disubstituted cyclopentanes are typically observed to form with a modest *cis* selectivity; the parent 3-methylhexenyl radical closes to give 1,3-dimethylcyclopentane in a 71/29 ratio at 80°C (Eq. 2.16). Calculations again suggest that the chair-axial and boat-equatorial transition states conspire to produce the minor product. As expected from substituent effects, the 3-*tert*-butyl radical cyclizes especially rapidly, and the *cis/trans* selectivity is 85/15.⁶⁰ Since the large *tert*-butyl group presumably resists occupying an axial position, this 85/15 ratio is probably a good measure of the relative energy of the chair-equatorial to boat-equatorial transition states. The difference between the ratios for R = Me and R = *t*Bu is then a rough estimate of the contribution of the chair-axial transition state for R = Me. Since the nature of the 2- and 3-substituents is not expected to have a large effect on the relative energies of chair and boat transition states, this 85/15 ratio may be a maximum level of stereoselectivity (at 60°C – 80°C) that can be expected for simple radicals in these classes.^{61,62}

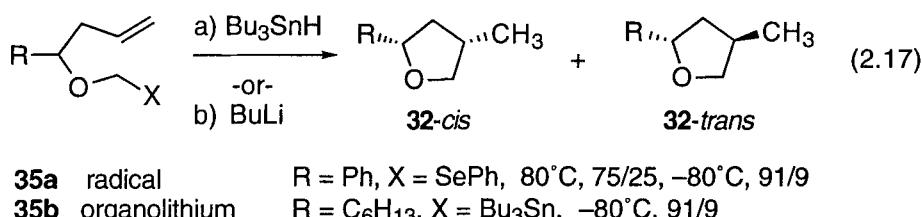


$$\begin{array}{ll} \text{R} = \text{Me} & 71/29 \\ \text{R} = {^t\text{Bu}} & 85/15 \end{array}$$

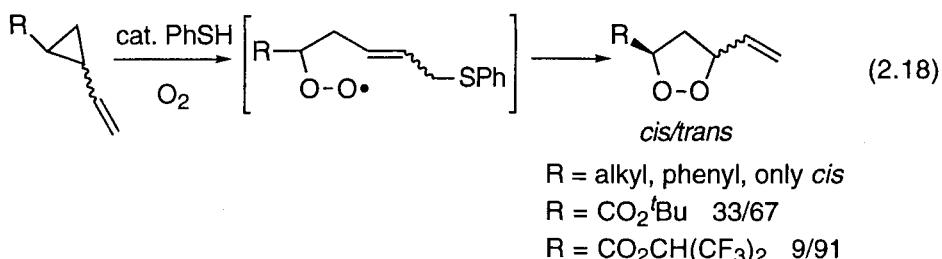


The ether analogs of 3-substituted hexenyl radicals have been studied, and both the 2- and 4-oxy⁶³ analogs cyclize with good to excellent selectivity. The 2-oxy (alkoxymethyl radical) system is interesting for a number of reasons, and Equation 2.17 shows an example of this type of

cyclization.⁶⁴ First, reduction of **35a** provides the same products (**32-cis/trans**) that are formed by reduction of **31** (Eq. 2.15); however, because of the juxtaposition of functional groups, these two precursors form isomeric radicals that cyclize with opposite selectivities. Once again, the cyclization of substrate **35a** is temperature-dependent, and the selectivity can be increased from a modest (75/25) to a good level (91/9). Finally, a closely related cyclization of an alkoxyethylolithium reagent derived from **35b** has been conducted,⁶⁵ and this provides a comparable product ratio (91/9) at -78 °C. This suggests that the more complex structure of the aggregated organolithium reagent does not play a major role in determining stereo-selectivity; the Beckwith–Houk model provides an adequate rationalization for this ionic reaction.

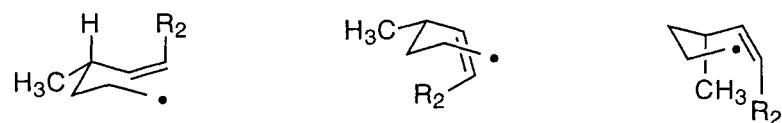
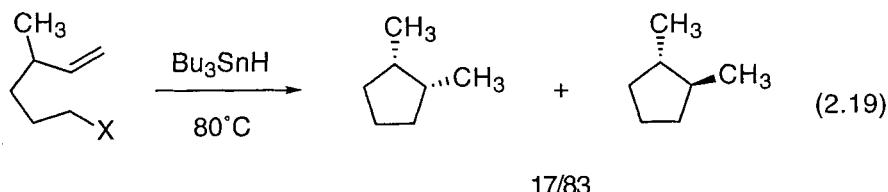


Cyclizations of peroxy radicals often provide very high levels of *cis* selectivity, as shown in Equation 2.18.⁶⁶ Reduction of the cyclic peroxide products provides a stereoselective route to 1,3-diols. For reasons that are not well understood, the presence of electronegative ester substituents erodes the *cis* selectivity, and certain fluorinated esters even provide good levels of *trans* selectivity.⁶⁷



4-Substituted Hexenyl Radicals: As a class, 4-substituted hexenyl radicals typically cyclize with the highest level of selectivity of any of the simple hexenyl radicals. Closure of the 4-methylhexenyl radical provides

predominantly the *trans* isomer, as expected from the Beckwith–Houk model, and the level of selectivity (*cis/trans* = 17/83 at 80°C) is the best of the methylhexenyl radical isomers (Eq. 2.19). Many other substrates exhibit better selectivities than this, and *cis/trans* ratios of 5/95 or better are common. The improved selectivity of the 4-substituted radicals is nicely interpreted within the Beckwith–Houk model by the theory of A-strain.⁶⁸ The chair-equatorial transition state is the lowest in energy, and the disposition of the allylic C4–C5 bond is near the minimum dictated by A-strain (C4–H bond nearly eclipsed to C=C bond). Both the chair-axial and the boat-equatorial transition states require less favored dispositions of this allylic bond, and they are therefore raised in energy relative to the chair-equatorial transition state. Because of the importance of A-strain, Z-disubstituted alkenes typically give very high levels of selectivity.

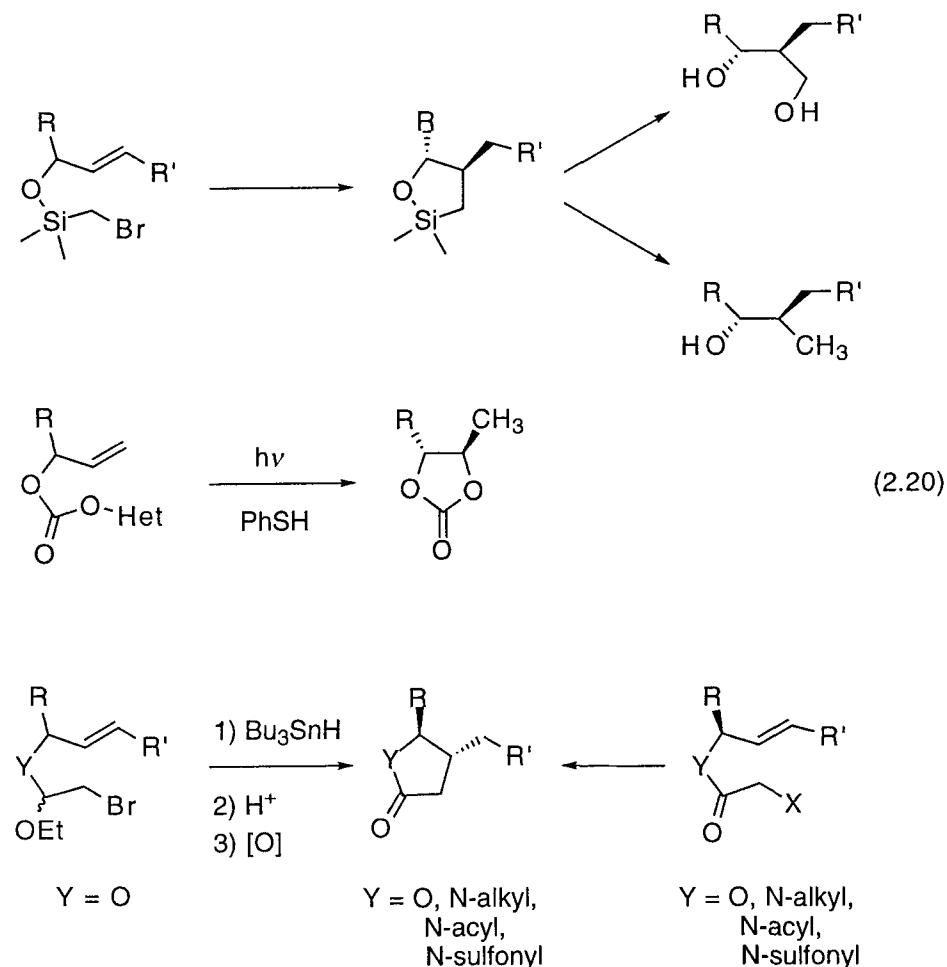


chair-equatorial
(minimizes A-strain) boat-equatorial
(C=C gauche to two C–C) chair-axial
(C=C eclipses Me)

Good selectivities if $R_2 = H$, excellent selectivities if $R_2 \neq H$

Equation 2.20 shows a few examples selected from the many stereoselective cyclizations in this class that have been reported.⁶⁹ Cyclizations of silylmethyl radicals can be used as a route to either alcohols or diols, depending on the processing of the products,⁷⁰ while carbonate radicals provide cyclic *trans*-carbonates that are precursors of *anti*-1,2-

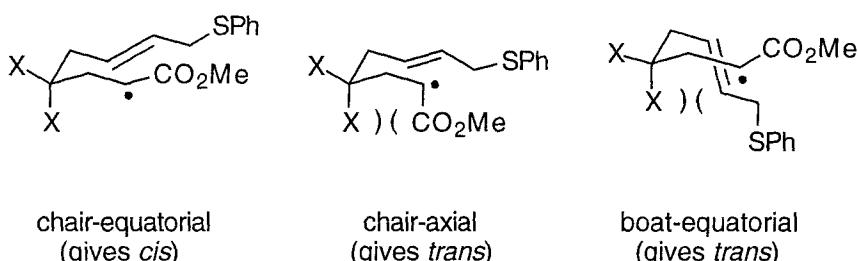
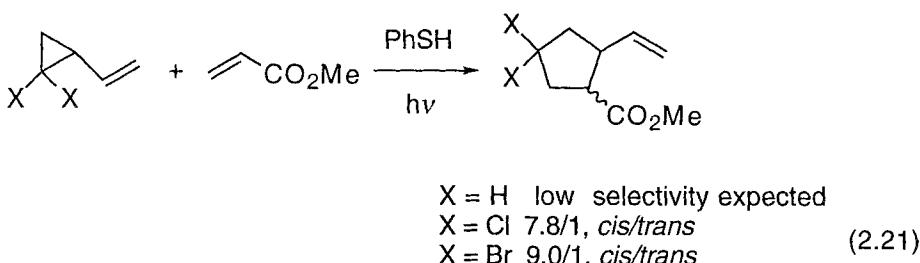
diols.⁷¹ Cyclizations of haloacetals,^{70b,72} haloesters⁷³ and haloamides⁷⁴ provide expeditious routes to lactones and lactams. During lactam formation, the use of sulfonyl or carbonyl nitrogen substituents tends to promote the formation of *cis* isomers as A-strain with the amide nitrogen comes into play. In this class of reactions, cyclizations of radicals again seem to occur with generally similar trends and comparable levels of selectivity to related ionic reactions.^{71b,75}



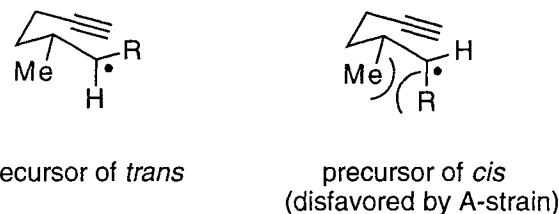
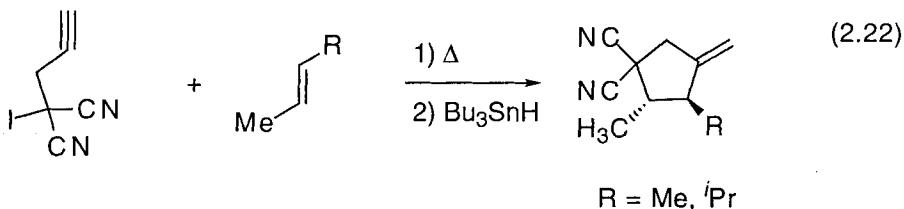
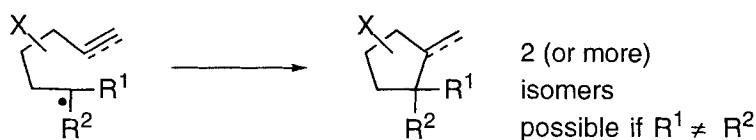
Combination Substituent Effects: Quite a few acyclic hexenyl radical substrates that bear multiple substituents have been reported. Depending on their locations and relative configurations, the substituents may work in concert or opposition. When the relative configurations of two substituents dictate that they are in opposition, a good rule of thumb is that the 4-substituent dominates due to A-strain (see above). Interpretation of the results of other systems within the framework of the Beckwith–Houk model usually requires the evaluation of the relative importance of the effects attributed to the various individual substituents. This can be difficult, especially when the effects are small. For this reason, this section will highlight only the few combination substituent effects that appear to have some generality.

One of the most important combination effects is the pairing of a terminal Z-alkene substituent with another ring substituent.⁷⁶ The basis level of selectivity is usually increased, and the effect is probably most powerful when the 4-position is substituted (see Eq. 2.19, above) because both the boat-equatorial and chair-axial transition states will be raised in energy. However, the boat-equatorial transition state should be raised in energy regardless of the position of the substituent, so a Z-terminal alkene substituent is expected to generally increase the stereoselectivity of many types of cyclizations.⁷⁷ This effect is a consequence of A-strain, and it is in no way unique to radicals.⁶⁸

The introduction of geminal substituents in the 3-position often increases the level of *cis* simple diastereoselection observed in the cyclizations of 1-substituted radicals; representative examples are shown in Equation 2.21.^{37e,78} Though the cyclization of the parent substrate (X = H) is not known, one expects (see Eq. 2.10) a very low selectivity. The 3,3-dichloro- and 3,3-dibromo analogs give good *cis* selectivities. This effect is nicely interpreted within the Beckwith–Houk model by positing that the “axial-like” 3-substituent increases the energy of either or both the chair-axial and boat-equatorial transition structures. Consistent with this, the presence of only one 3-substituent does not usually result in high simple diastereo-selection.^{45d,79} In general, this effect is not as large as the 1,3-diaxial effect in cyclohexanes would suggest, but since it is usually adding on to an inherent modest *cis* selectivity, it can be quite preparatively useful. Other types and locations of geminal substituents have also provided interesting results on occasion.⁸⁰



In a type of relative asymmetric induction that is very much analogous to the examples described above, the pairing of any radical bearing two different substituents with a stereocenter elsewhere on the radical results in the formation of (at least) two diastereomers (Eq. 2.22).^{45d,78,79} In this class of substrates, the pairing of 1- and 2-substituents has often been observed to give very high *trans* selectivities.⁸¹ Equation 2.22 shows a typical example, in which a single product is formed.⁸² In this example, the presence of the two cyano substituents is incidental to the observed selectivity. It is the interaction of the C2-methyl group with the radical substituent (R) that counts. Because an alkyne is the acceptor, there is no simple diastereoselection with this substrate. With alkene acceptors, the typical modest *cis* simple diastereoselection is not increased by the presence of the added 2-substituent. These results are also nicely explained by the Beckwith–Houk transition state model (see Eq. 2.22).

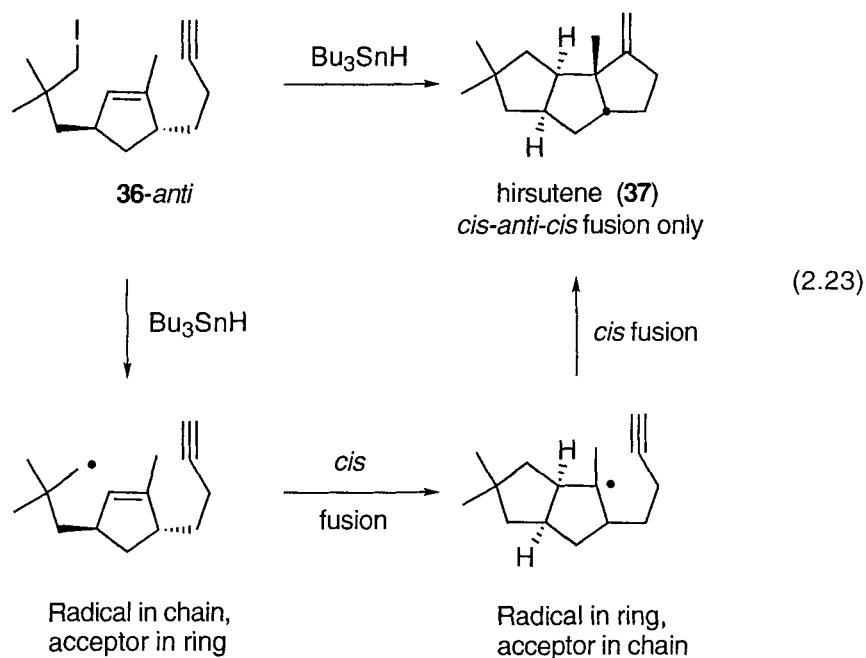


2.2.3.3 Stereoselectivities in Cyclic Systems

The presence of a pre-existing ring (or rings) in a hexenyl radical cyclization precursor results in the formation of a bicyclic (or polycyclic) product. Radical reactions have proven very popular for the construction of all sorts of polycyclic arrays, and the predictable, often high, levels of stereoselectivity associated with these types of reactions have contributed to this popularity. The existing ring(s) can contain the radical and/or the acceptor, or they can form all or part of the connection between the two. This classification can be further divided by the location of the existing stereocenter(s) and the type of asymmetric induction. Once again, this section will try to present reliable trends that have emerged from a number of related examples. These trends are often associated with the ring systems that are involved, and are not necessarily unique to *5-exo* cyclizations. Such general trends will be presented in the following section, and not repeated in subsequent sections on *6-endo* and *6-exo* cyclizations.

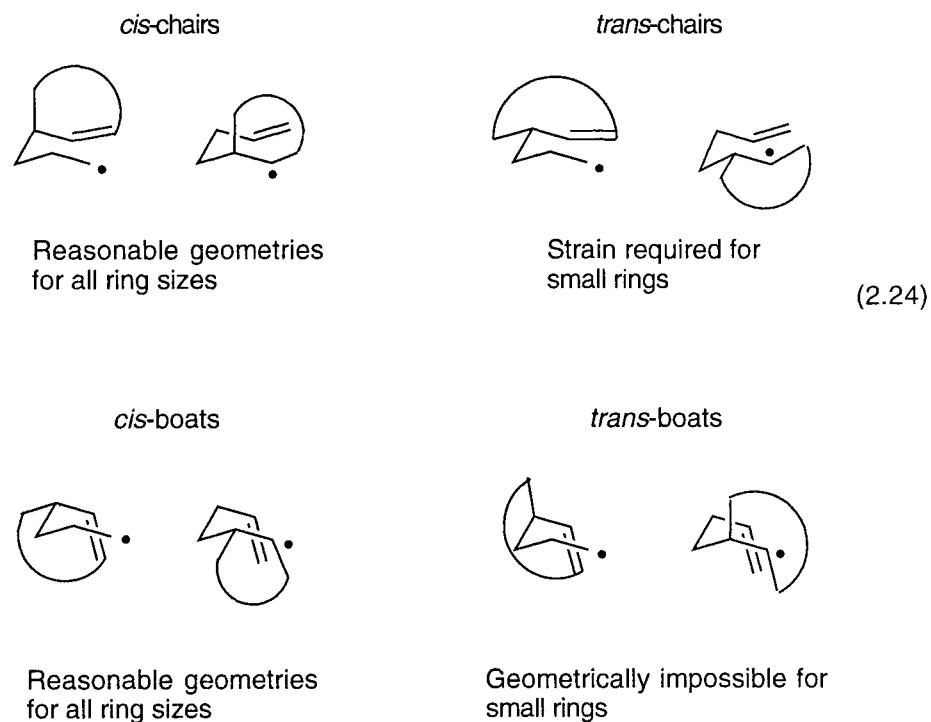
Fused Rings from Cyclic Radicals/Alkenes: Perhaps the most general guideline for cyclic systems involves the formation of fused rings: when a radical cyclization forms a ring fusion bond between two small rings, that

ring fusion is predominately or exclusively *cis*. “Small rings” are defined in this context as rings containing six or fewer atoms. This guideline holds independent of whether it is the radical or the alkene that is contained in the ring. A tandem cyclization that illustrates both possibilities is shown in Equation 2.23.⁸³ Reduction of **36-anti** provides hirsutene (**37**) through formation of two new 5,5-*cis* ring fusions. In the first cyclization, the acceptor is in the ring and the radical is on the chain, and in the second cyclization, these roles are reversed.



The stereoselectivity of these kinds of cyclizations typically contradicts the Beckwith–Houk model for acyclic substituents. The first cyclization is formally that of a 4-substituted hexenyl radical and the second is that of a 1,2-disubstituted hexenyl radical; in both cases, *trans* selectivities are expected (see Eqs. 2.20 and 2.22). This departure from the expected stereoselectivity based on acyclic models is readily understood in terms of the favored geometry for the transition state of radical addition. The presence of a short connecting chain between the cyclic alkene or radical and its partner readily permits the favored geometry in the transition states for the *cis* isomers, but ring strain must be introduced to reach acceptable geometries

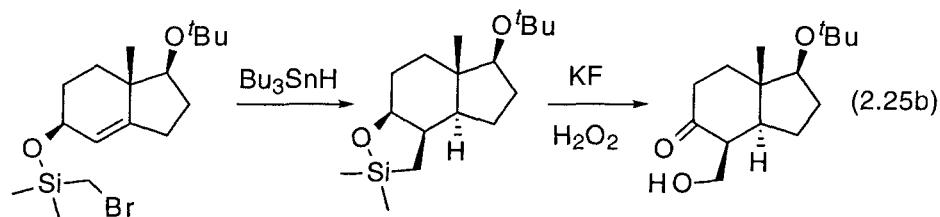
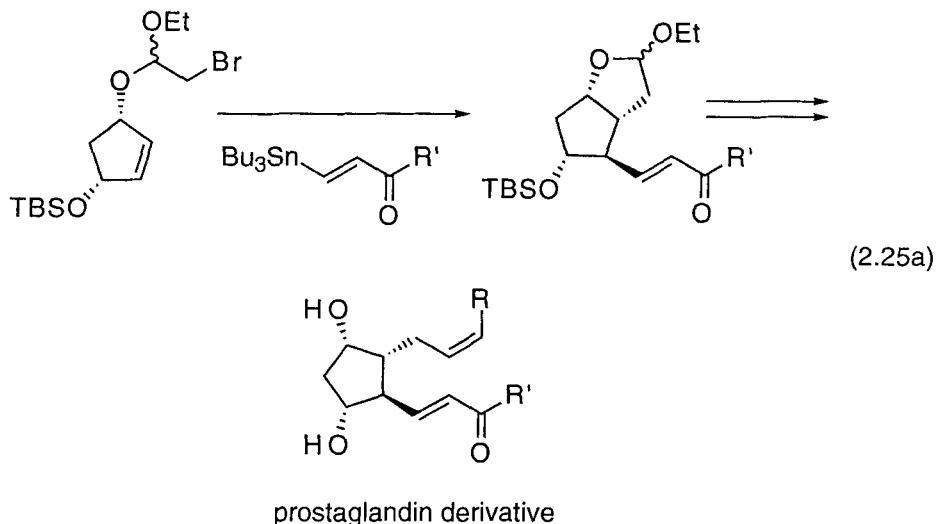
for transition states leading to the *trans* isomers (Eq. 2.24). In substrates with limited conformational mobility (see below), it is possible to make a precise analysis of the relative contributions of the various possible chair and boat transition states shown in Equation 2.24 to the product formation.



The literature is replete with examples of formations of *cis* ring fusions in these types of cyclizations.⁹ For formation of 5,5- and smaller¹⁴ fusions, *cis* selectivity is for all practical purposes complete: *trans* isomers are not observed. Formation of 6,5-⁸⁴ and even 6,6-ring fusions⁸⁵ also typically proceed with good to excellent *cis* selectivity. The same type of *cis* selectivity is frequently observed in nucleophilic additions to carbonyls or activated alkenes, which have similar approach trajectory requirements to those of radical additions.⁸⁶ As the size of one of the rings gets larger, local conformational effects⁸⁷ of the ring will begin to dominate, and either *cis* or *trans* ring fusion may predominate.⁸⁸ This has nicely been demonstrated in the formation of 5,8-fused rings;⁸⁹ changing substituents alters the local conformation of the eight-membered ring, and modulates the *cis/trans*

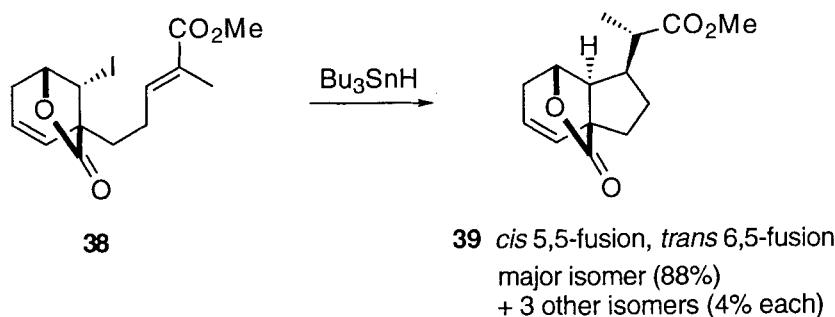
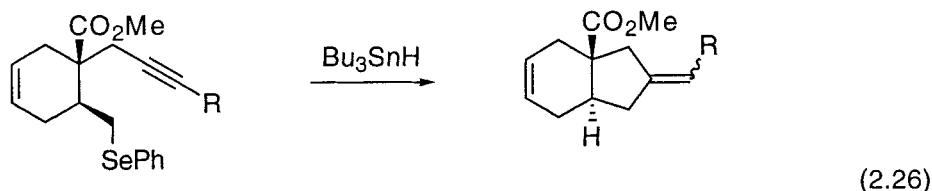
selectivity. With appropriate substituents and configurations, very high level of *trans* selectivity are possible.

This fusion effect has been frequently used in synthesis³ to control the relative configuration of ring substituents by combining it with a temporary connector such as a silyl ether or acetal.^{90,91} The two examples in Equations 2.25a,b^{92,93} suffice to illustrate the power of this approach, wherein a preexisting ring stereocenter is used to dictate the configuration of its newly formed neighbor. In both of these examples, an additional element of stereocontrol is imparted by a subsequent reaction of the cyclic radical (see Chapter 3).

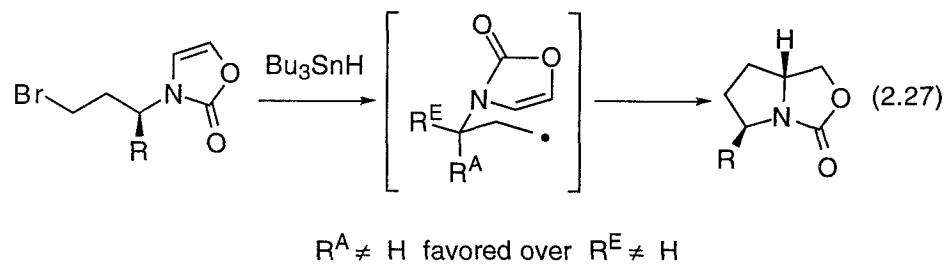


There are at least two ways to make *trans* fused small rings, as illustrated in Equation 2.26. The more obvious strategy is to use a precursor with the ultimate ring fusion bonds already *trans* configured, and to form a

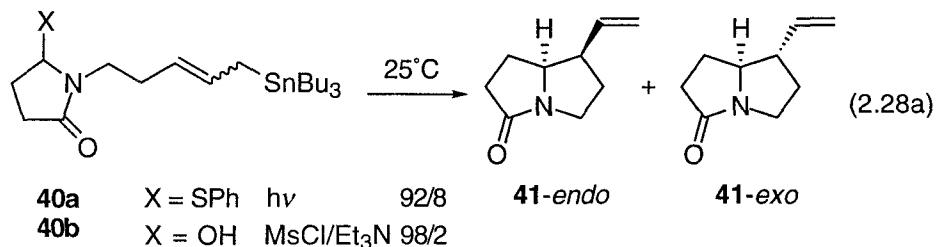
bond other than to the ring fusion. This strategy can be used to form 6,6-,⁹⁴ 6,5-,⁹⁵ and sometimes even 5,5-ring fusions.⁹⁶ In a more subtle approach, bridged radical precursors can also be used. In an early example that was influential for a number of reasons, Hart and coworkers observed that the cyclization of **38** provided mainly **39**.⁹⁷ Relevant to this ring fusion discussion, substrate **38** sets up a stereochemical competition; the bridged ring system requires either the 5,5- or the 6,5-fusion of the product **39** to be *trans*. Since the (smaller) 5,5-fusion has a higher *cis* preference, it is the 6,5-fusion that ends up *trans*. This type of stereocontrol has been used in the syntheses of pleurotin and axamide.⁹⁸ Also significant in this example are the *endo* stereoselectivity at the ring carbon bearing the propionate group (discussed below) and the stereoselectivity at the “off-ring” stereocenter (discussed in Chapter 4). These three stereochemical features, all of which are now quite general, result in a very powerful synthetic transformation.



When the existing bond to the ring is formed to an sp^2 nitrogen atom, another strategic possibility exists for controlling relative stereochemistry at a forming ring fusion. Equation 2.27 shows an example where a 3-substituent induced excellent selectivity in the closure to a cyclic urethane.⁹⁹ In the reaction, the major product comes from the chair-axial transition state because of A-strain, and high selectivities are observed in both 5-*exo* and 6-*exo* cyclizations.

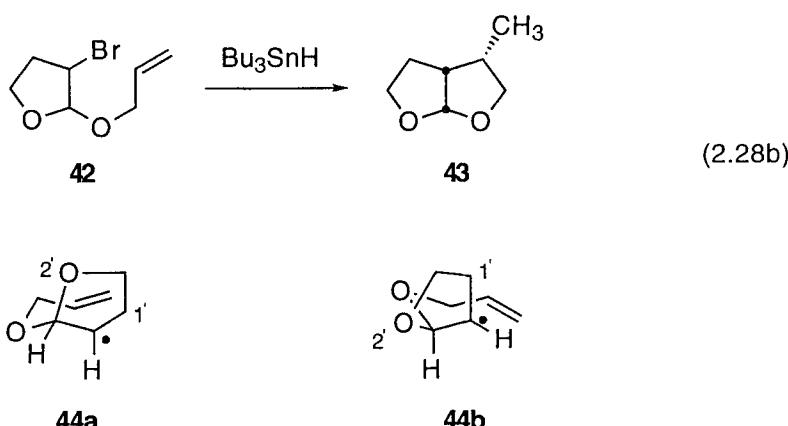


As illustrated by the conversion of **38** to **39**, the formation of a bicyclic ring by *5-exo* closure with formation of a ring fusion bond is often accompanied by an issue of simple diastereoselection. Because of the popularity of radical cyclizations in polycycle synthesis, this type of simple diastereoselection has frequently been studied, and a number of general trends have emerged. In *5-exo* closures to existing five-membered rings, the *endo* stereoisomer almost always predominates, and selectivity is good to excellent, as illustrated by the examples in Equations 2.28a-c. The cyclization of allylstannane **40a**¹⁰⁰ is representative of a class of related substrates;¹⁰¹ **41-endo** is favored over **41-exo** by a ratio of 92/8. Once again, this *endo* selectivity is not unique to radicals, and an ionic cyclization of **40b** through the intermediacy of an acyl iminium ion provides **40-endo/41-exo**, this time in an improved ratio of 98/2.

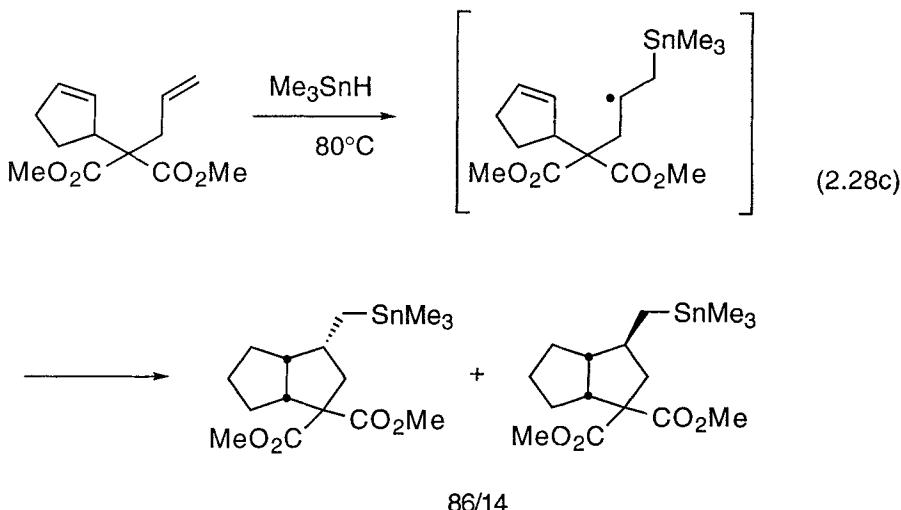


This simple diastereoselection is often coupled with relative asymmetric induction, as illustrated by the cyclization of **42** to provide exclusively **43** (Eq. 2.28b).¹⁰² Product **43** possesses a *cis*-ring fusion (see Eqs. 2.23-2.25) and simple diastereoselection again occurs to favor the *endo* isomer. The especially high selectivity observed in conversion of **42** to **43** may be attributed in part to the anomeric effect, which favors transition state **44a** over **44b**; however, the anomeric effect is not the only effect at play because good

endo selectivity is observed in other heterocyclic¹⁰³ and even fully carbocyclic radicals.^{83,104} Indeed, the levels of simple diastereoselection in these types of cyclizations are typically significantly higher than the levels in simple acyclic systems. Current computational models do not do a good job of predicting isomer ratios with these substrates,²⁸ and the reasons for this increased selectivity are not entirely clear. However, it has been suggested^{83b} that transition structures like **44a**, which have the existing ring fusion bond C2–O2' in an “axial” orientation and the radical substituent C1–O1' in an “equatorial” orientation allow for better SOMO/LUMO overlap than the flipped chair transition states like **44b**, which have the existing ring fusion bond “equatorial” and the radical substituent “axial”. Said another way, to direct the radical SOMO at the alkene LUMO within the constraints of the existing five-membered ring, the C1–C1' and C2–O2' bonds would rather be more nearly eclipsed (as in **44a**) than gauche (as in **44b**). This problem should diminish as the size of the existing ring increases.



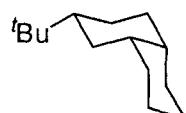
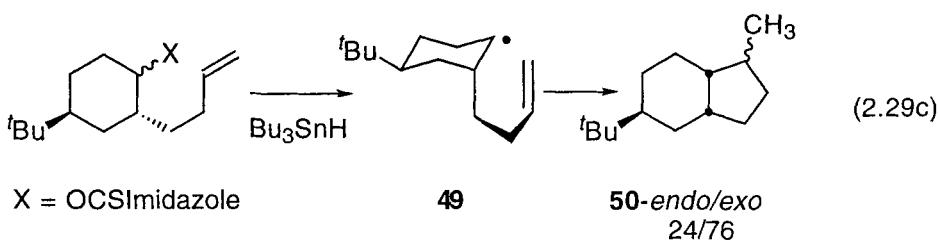
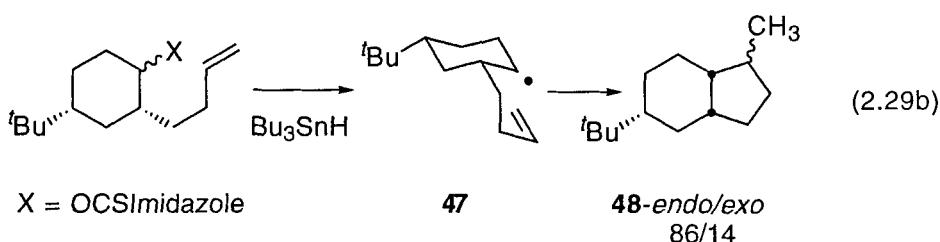
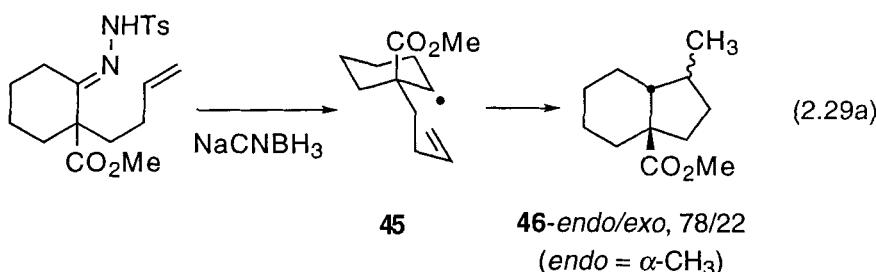
The example in Equation 2.28c illustrates that this trend is not unique to the reactions of cyclic radicals with alkenes in a chain substituent; related reactions of cyclic alkenes with radicals in a chain substituent often (but not always¹⁰⁵) proceed with good levels of *endo* (1,5-*cis*) selectivity.¹⁰⁶ The *endo* stereoisomer is often expected to be less stable than the *exo*, and if steric interactions in the *endo* position become too large, then *endo* selectivity can be eroded.^{105,107}



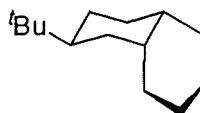
In *5-exo* closures of cyclohexyl radicals that form ring fusion bonds,¹⁰⁸ the situation is quite different (Eqs. 2.29a-c). With cyclohexane rings that can readily undergo chair/chair interconversions, moderate *endo* (*1,5-cis*) selectivities are typically observed. This is exemplified by the cyclization of **45** to give **46-*endo*** and **46-*exo*** in a ratio of 78/22 (Eq. 2.29a).¹⁰⁹ The level of *endo* selectivity is typically lower than for the related 5,5-rings (Eq. 2.28), and roughly comparable with that observed in acyclic systems. However, insightful studies by RajanBabu and Fukunaga showed that the direction of selectivity depends upon the orientation of the alkenyl side chain on the existing cyclohexyl ring.¹¹⁰ For example, cyclization of *cis*-3-butenyl-1-*tert*-butylcyclohexyl radical **47** provided **48-*endo/exo*** in a ratio of 86/14 (Eq. 2.29b), while cyclization of the *1,3-trans* isomer **49** provided **50-*endo/exo*** in a reversed ratio of 24/76. The similarity in ratios between flexible systems like **45** and rigid ones like **47** suggests that the flexible systems cyclize through a geometry with the acceptor side chain equatorial.

The reversed selectivity for formation of **50** compared to **46** and **48** is nicely interpreted by extending the Beckwith–Houk “cyclohexane” model for cyclization of simple hexenyl radicals to a “*cis*-decalin” model for cyclization of cyclohexyl radicals. This model is essentially that of RajanBabu;³¹ we have simply added the *cis*-decalin analogy. The parent *cis*-decalin is free to simultaneously flip both chairs, thereby interchanging all axial and equatorial substituents.¹¹¹ However, introduction of a *tert*-butyl

substituent fixes one of the chairs in the conformation with the *tert*-butyl group equatorial. This in turn fixes the other chair because chair/chair interconversions in *cis*-decalins are linked. Thus 2-*tert*-butyl-*cis*-decalin has two stereoisomers: **51**, which resembles transition structure **47**, and **52**, which resembles transition structure **49** (Eq. 2.29c).



51 *cis*-decalin isomer
resembling **47**



52 *cis*-decalin isomer
resembling **49**

The *tert*-butyl group has the effect of “locking” the hexenyl radical transition state into one of the two possible chairs. This is best illustrated by the triple Newman projections shown in Figure 2-5. The projection of transition state **47** shows that the butenyl side chain is situated equatorially on the existing cyclohexane ring and that the forming C–C bond is axial. This holds the hexenyl radical “chair” with the C1 substituent equatorial and the C2 substituent axial. The chair model predicts that the *endo* product should be favored, as observed. Inverting the carbon bearing the *tert*-butyl group flips both of the rings, and interchanges all of the axial and equatorial substituents. This is shown in the projection of **49**, which has the butenyl group axial and the forming C–C bond equatorial on the cyclohexane chair, and the C1-substituent axial and the C2-substituent equatorial on the hexenyl radical “chair”. The flipping of the hexenyl radical from one chair to the other, as enforced by the *cis*-decalin like nature of the transition states, nicely explains the observed reversal in selectivity. That freely flipping cyclohexyl radicals prefer transition states like **47** is nicely consistent with the observation in Equation 2.28b; small ring cyclic radicals prefer transition states with equatorial C1 groups and axial C2 groups on the hexenyl radical “chair.”

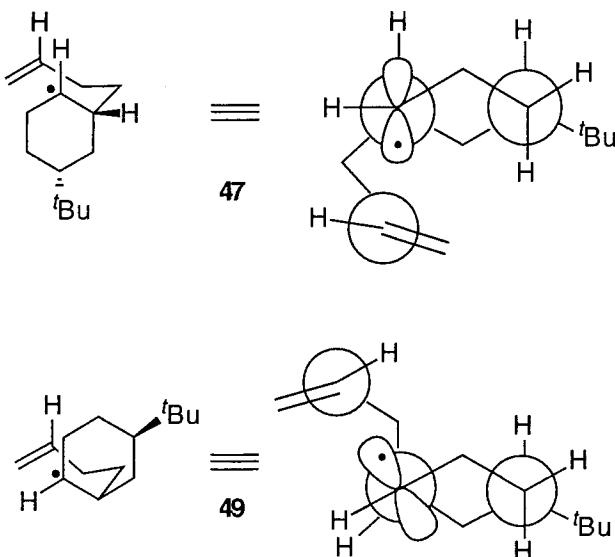
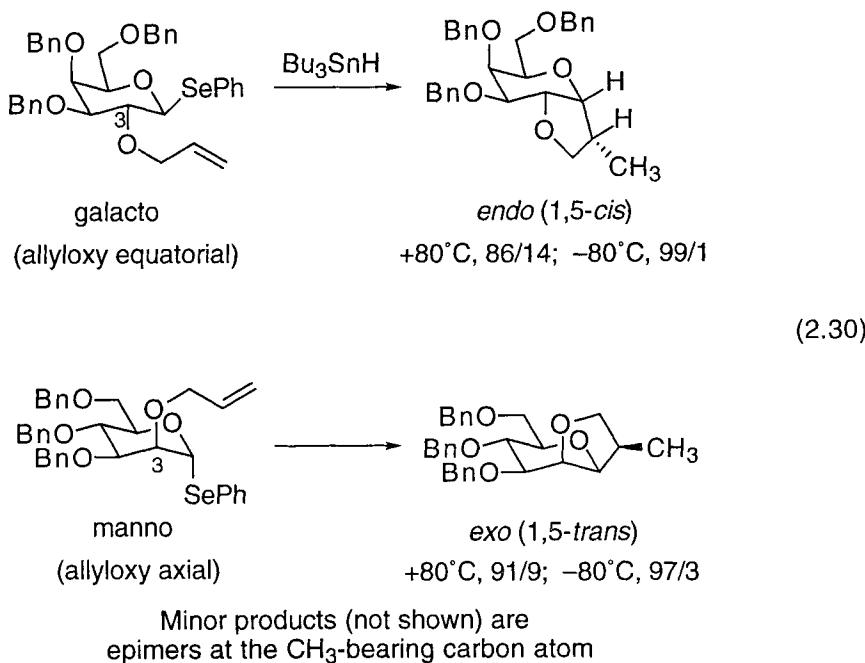


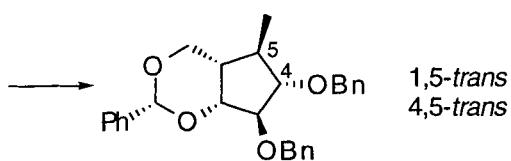
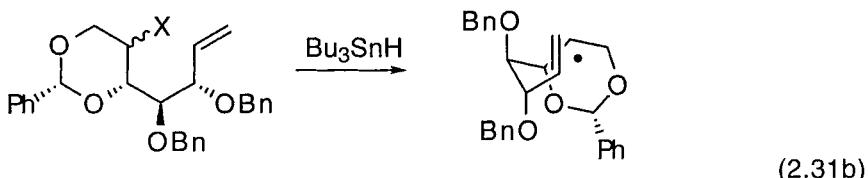
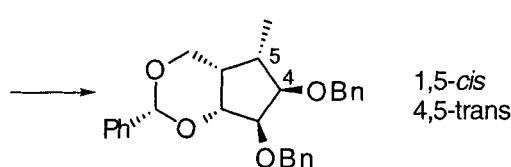
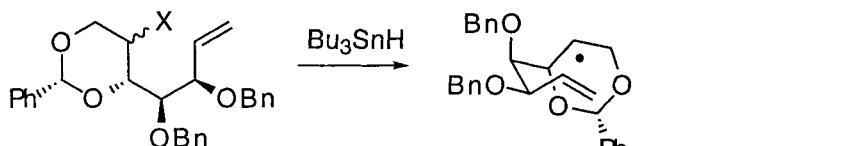
Figure 2-5. The “*cis*-Decalin” Model

Finally, the origin of the minor stereoisomers **48-exo** and **50-endo** is of interest. Since chair/chair interconversions are prohibited, the minor isomers in each case must come from boat-like hexenyl radical transition states. This analysis again confirms the relatively small energy differences between “chair” and “boat” hexenyl radical cyclizations, and reinforces the notion that levels of chair/boat selectivity of about 3/1 to 5/1 can be expected in systems without special biases.

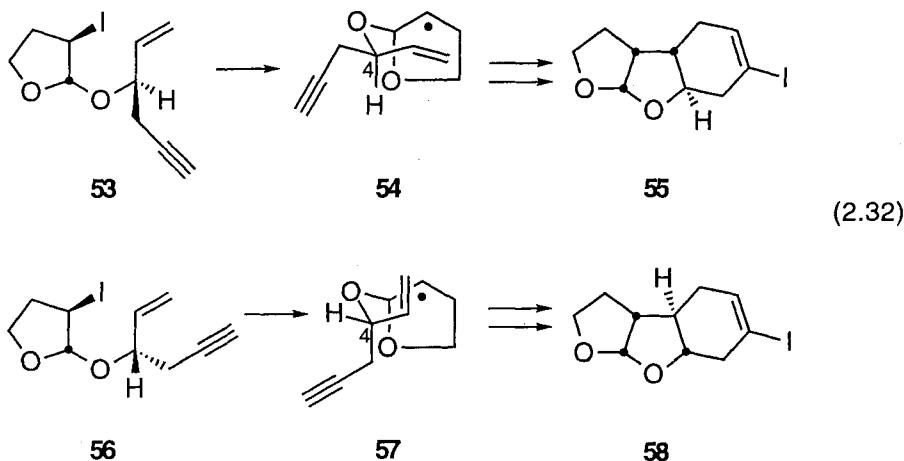
The “*cis*-decalin” model is especially useful in interpreting selectivities in cyclizations of various kinds of pyranose radicals,¹¹² as the two examples in Equation 2.30 illustrate.¹¹³ Galactose derivatives possess equatorial C3 acceptor side chains, and the derived anomeric radicals cyclize to provide *endo* products. Mannose derivatives possess axial C3 acceptor side chains, and the derived anomeric radicals cyclize to provide *exo* products. Selectivities can be very good, especially at low temperatures. Anomeric glucose radicals (not shown) appear to cyclize with anomalously low *endo* selectivities, but even this can be understood because boat pyranoses are important conformers for such radicals.¹¹⁴ (Just as with *cis*-decalin, the flipping of the pyranose ring from a chair to a boat flips the hexenyl radical “chair” and reverses the stereochemical prediction.)



While the major products usually result from one of the two possible chair hexenyl radical transition states, cyclizations of several substrates almost certainly provide major products through boat transition states.³¹ Consider the two cyclizations shown in Equation 2.31: in (2.31a) the 1,5-*cis* isomer predominates and in (2.31b) the 1,5-*trans* isomer is favored.¹¹⁵ Both substrates have a rigid six-membered ring radical that cyclizes to an equatorially situated alkene. Thus, one chair and one boat transition state are eliminated by the “*cis*-decalin” effect. In the example in Equation 2.31a, all the substituents on the hexenyl radical are in their favored orientations, and the expected 1,5-*cis* product is formed. In contrast, the chair transition state from the radical in Equation 2.31b places the 4-benzyloxy substituent in the “axial orientation”. The energetic effects of the 4-substituent are large due to A-strain, and this radical prefers to close via the alternative boat conformation.



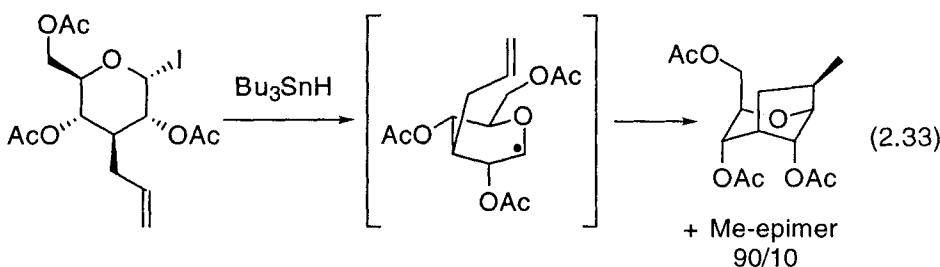
There is even one example of a highly selective reaction where the major product almost certainly comes from a boat-axial transition state! Consider the pair of cyclizations in Equation 2.32.¹¹⁶ Tandem cyclization of **53** by the atom transfer method provides tricycle **55** while diastereomer **56** provides isomeric tricycle **58**. The *trans* 5,6-ring fusion is established during the first cyclization, and the second cyclization then occurs in a *6-endo* fashion because the normally favored *5-exo* cyclization would provide a strained *trans*-fused bicyclooctane. The formation of product **54** is readily interpreted by the usual chair-equatorial transition state. (“Equatorial” refers to the orientation of the C4 substituent; in total **54** has one axial and two equatorial substituents.) The origin of product **58** is more intriguing. Chair-axial and boat-equatorial transition states are ruled out by the structure of **58**; the chair-axial transition state has the unfavorable orientation of the furan ring on C1/C2 (see Eq. 2.28b) and the boat transition state has the unfavorable axial C4 group. The chair-equatorial and boat-axial transition states both predict the correct product, and the inclination is to attribute the product to the chair-equatorial transition state. However, the chair-equatorial transition state has both of the unfavorable effects that individually sufficed to rule out the other two transition states, and the boat-axial isomer has neither! Thus it seems very likely that the indicated boat-axial transition state **57** provides the observed product **58**.



The examples in the preceding paragraphs provide very nice illustrations of how a detailed understanding of substituent effects is valuable.

Effects can either be combined to reinforce the normal preference for the chair-equatorial isomer or opposed to provide major products from any one of the three other transition states.

Bridged Rings from Cyclic Radicals/Alkenes: There are a large number of examples of reactions of cyclic radicals or cyclic alkenes (or both¹¹⁷) that form bridged ring products. In these cases, the geometric constraints imposed by the forming ring usually rule out two of the four possible transition states. Indeed, in most of the published examples, only a single isomer can be formed due to the substitution pattern and geometric constraints of the bridged product. However, there are a number of reactions where the formation of isomeric products is conceivable and where moderate to good stereoselectivities have been observed. For example, closure of the cyclic radical in Equation 2.33 occurs through a chair hexenyl radical transition state with a boat-shaped pyranose ring to provide mainly (90/10) the *exo* bicyclic.¹¹⁸ Related 5-*exo* and 6-*exo* cyclizations to form bridged rings have been observed in other carbohydrate settings.¹¹⁹



Polycycles from Acyclic Radicals and Alkenes with a Cyclic Connection: The previous discussion has focused on 5-hexenyl cyclizations of cyclic radicals or cyclic alkenes, but there are also many examples of cyclizations of hexenyl radicals with preexisting rings where neither the radical nor the alkene is cyclic. In these cases, the ring serves to connect the radical and the alkene in a number of different fashions. The rigidity imposed by the connecting ring often raises the energy of one or more of the transition states, so stereoselective cyclizations in this class are common. Several types of cyclizations are shown in Figure 2-6, and these include 2,3- and 3,4-connections (which lead to fused rings), 2,4-connections, (which lead to bridged rings), and 3,3- (and 2,2- and 4,4-) connections (which lead to spiro rings).

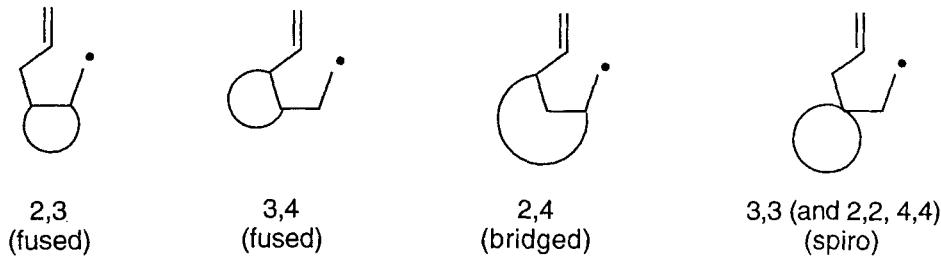
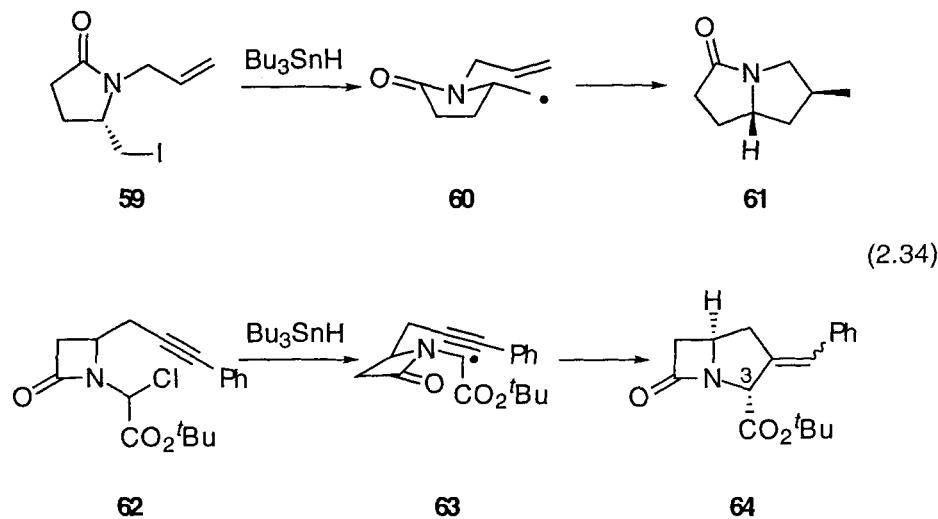


Figure 2-6. Ring Connections in Acyclic Radicals/Alkenes.

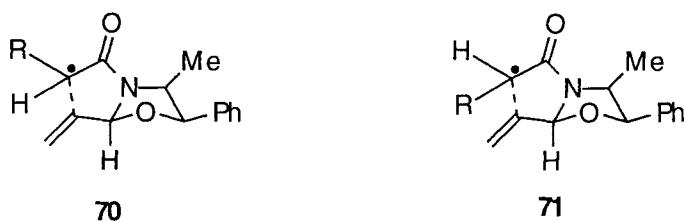
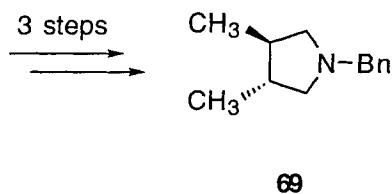
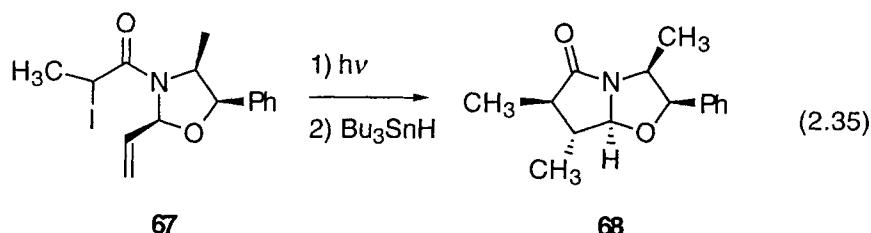
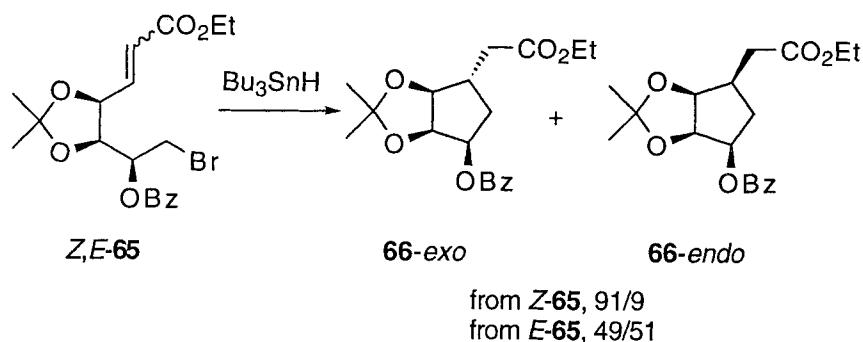
Most of the simple cases where the existing ring is fused in a 2,3-fashion to the forming ring involve lactams,¹²⁰ and two representative examples of these types of cyclizations are shown in Equation 2.34. Radical precursors like **59** are readily available in optically active form from pyroglutamic acid.¹²¹ Reductive cyclization of **59** generates a single stereoisomer **61**, whose formation can be rationalized as occurring through the chair-equatorial transition state **60**. Related cyclizations of carbamates and β -lactams bearing additional substituents occur with somewhat lower selectivity.^{122,123}



Interchanging the connection of the lactam ring in the hexenyl radical chain can also lead to good stereoselectivity, especially with β -lactams. For example, cyclization of **62** provides a mixture of *E/Z* isomers **64**, both of which have the α configuration at C3.¹²⁴ In this example, the phenyl group is required to accelerate the *5-exo* cyclization that forms the strained carbapenem ring; without this group, *6-endo* cyclization is favored. The stereoselectivity can be rationalized by chair transition state **63**. The axial orientation of the ester is presumably favored for the same reason that the α -ester of the carbapenem is favored over the corresponding β -isomer: serious interactions between the ester and the lactam carbonyls are avoided.

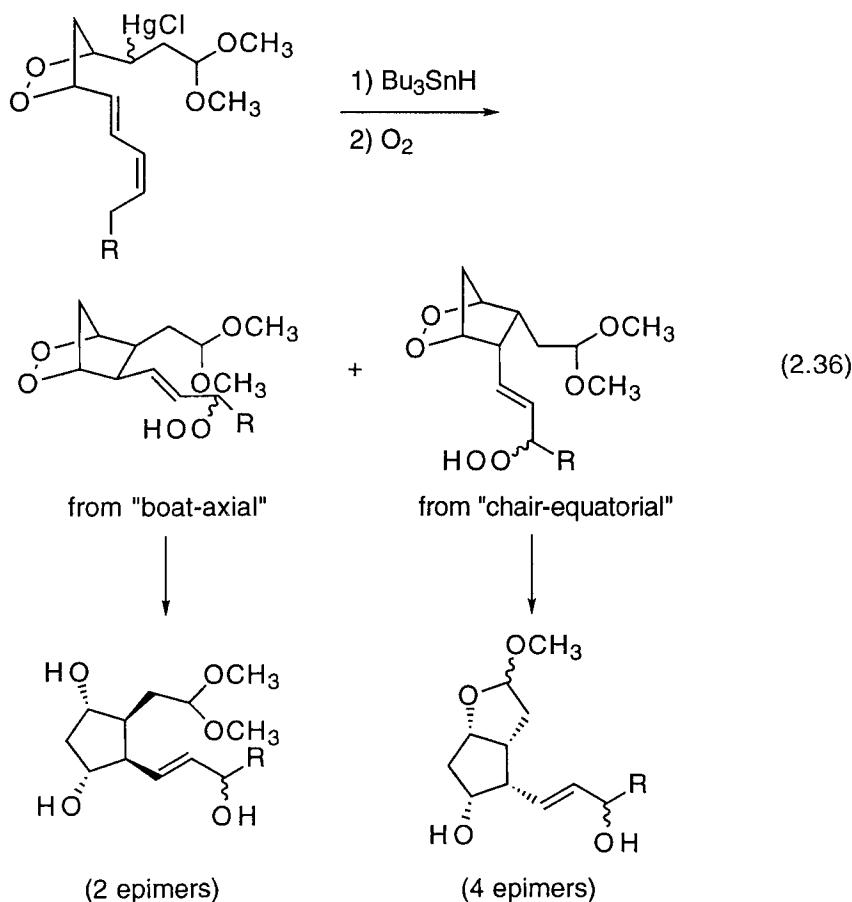
Substrates with a ring fused in a 3,4-fashion typically behave like simple 4-substituted hexenyl radicals—stereoselection is dictated by the 4-substituent, and is often good or excellent. Equation 2.35 shows representative examples of two popular types of cyclizations in this class.¹²⁵ Closure of Z-**65** provides **66-exo** and **66-endo** in a ratio of 91/9.^{76,126} As expected, the major *exo* product has a *trans* arrangement of the 4- and 5-substituents. Isomer *E*-**65** closes without appreciable selectivity.

A good number of cyclizations of 2-vinyl acylpyrrolidinones and β -lactams have been reported, and again the *exo* (*4,5-trans*) isomer is invariably obtained with very high selectivity.^{127,128} In an especially nice example,^{32b,c} atom transfer cyclization of nor-ephedrine derived acyl oxazolidine **67**, followed by tin hydride reductive deiodination, gives **68** as a single stereoisomer. Excision of the nor-ephedrine unit leaving behind the nitrogen atom provides optically pure pyrrolidine **69**. The stereoselectivity of this cyclization was reproduced by a modified version of the Spellmeyer–Houk force field model, which predicted that transition structure **70** was at least 2.5 kcal/mol lower in energy than its next competitor. Transition structure **70** is formally in the chair-axial class; however, this classification begins to lose meaning when there is only one sp^3 atom in the hexenyl radical unit. A more meaningful explanation is that the relative asymmetric induction (C4–C5) is controlled by the usual A-strain effect, and that the simple diastereoselection (C1–C5) is controlled by the conformational preferences of amide radicals (see Chapter 5). The transition state **71**, which leads to the normally favored 1,5-*cis* isomer, resembles a higher energy *E*-amide radical while transition state **70** resembles the favored *Z*-amide radical.



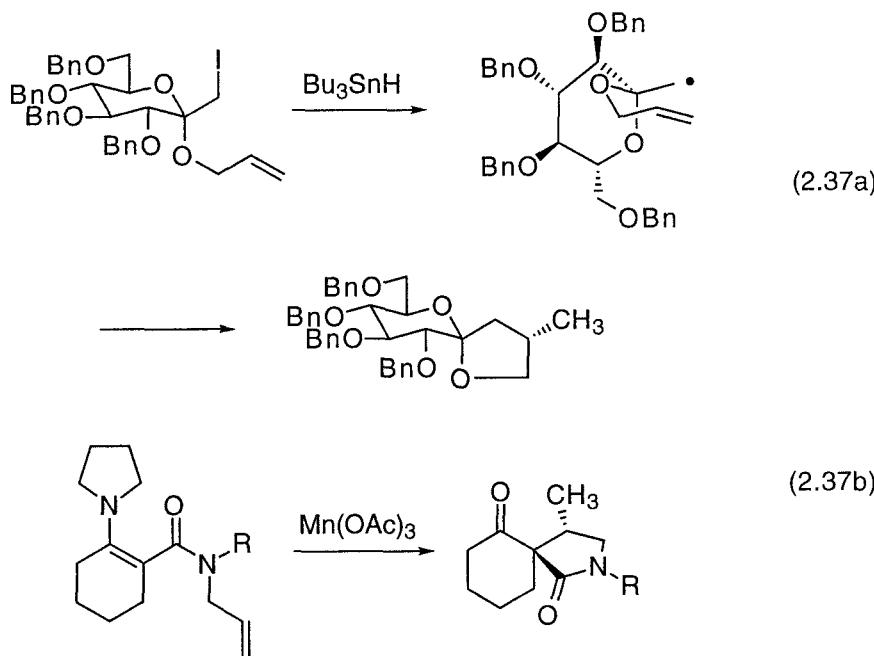
There are only a few examples of ring connection in the 2,4-fashion, and these lead to bridged rings. These examples suggest that there is a

significant bias towards 1,5-*cis* (bis-*exo* or bis-*endo*) products. Cyclization of the organomercurial shown in Equation 2.36 under oxidative conditions provides a mixture of intermediate bis-peroxides, all of which have the carbon side chains *cis* on the newly formed cyclopentane ring.¹²⁹ This type of synthetic reaction is directly related to prostaglandin biosynthesis; however, unlike the solution model reaction, the prostaglandin biosynthetic cyclization provides *trans* side chains. Very high selectivities are observed if one of the two *cis* isomers is disfavored for steric reasons.³⁶



Several stereoselective cyclizations to form spiro rings have also been described. In these, the existing ring is connected twice to a single carbon of the hexenyl radical unit. Equation 2.37a shows an example of relative

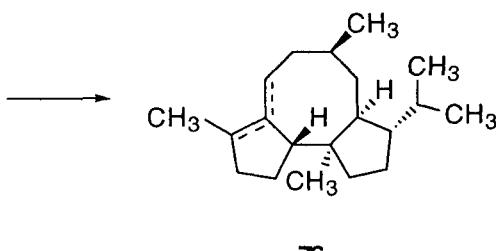
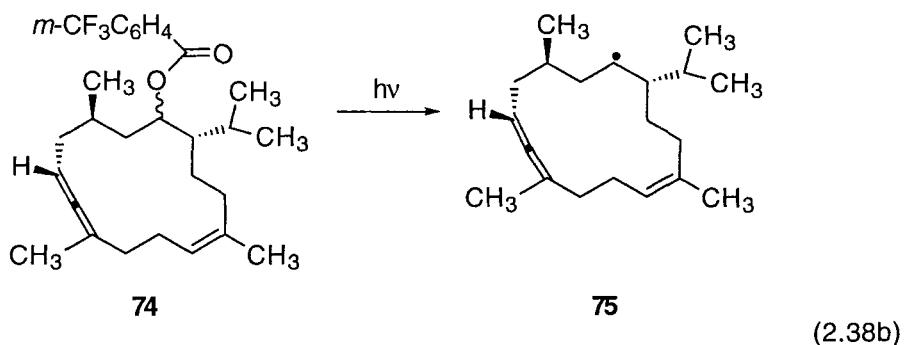
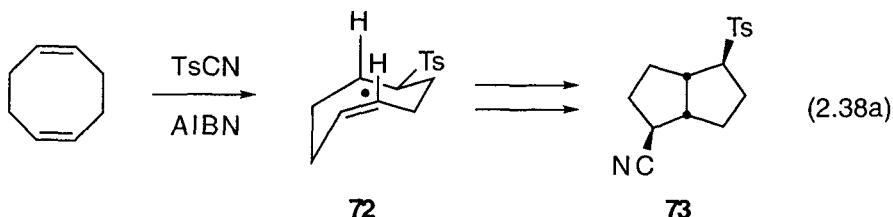
asymmetric induction in which a spiroketal is stereoselectively formed.¹³⁰ The selectivity here is probably influenced by the anomeric effect since the major isomer is formed through the hexenyl chair in which the C–O bond of the glucose ring is axial. Simple diastereoselection has also been observed,¹³¹ as illustrated by the example in Equation 2.37b.^{131a} This reaction probably proceeds through cyclization of a radical cation intermediate.



Transannular Cyclizations: Transannular cyclizations are a final important class of reactions that can occur with stereocontrol. In these reactions, either one or both atoms of the alkene are a part of the same ring as the carbon bearing the radical. If both atoms of the alkene are in the ring, the regiochemistry of each cyclization can be categorized as occurring through either an *exo* or an *endo* mode, depending upon which direction one chooses to count around the ring.

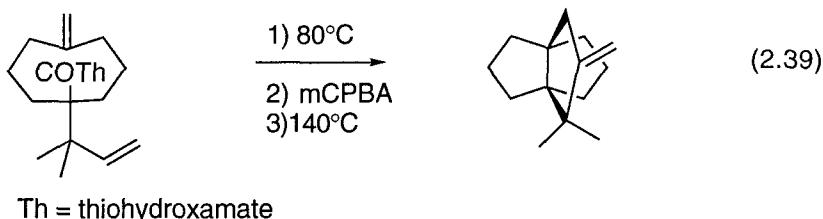
Equation 2.38 shows two examples of stereoselective transannular cyclizations. The most common type of cyclization is that of cyclooctenyl radicals like **72**.¹³² This radical formally closes in both *5-exo* and *5-endo* fashions, and the closure occurs with both relative asymmetric induction and

simple diastereoselection. The cyclization of **72** sets the relative configurations of three of the four stereocenters in the product **73**, and it probably occurs through the depicted chair-equatorial transition state. Subsequent cyano group transfer (an example of a selective reaction of a cyclic radical, see Chapter 3) from the less hindered face of the bicyclic radical (not shown) provides **73**. Conformational alternatives to transition state **72** are higher in energy either because the connecting chain between the radical and the alkene is too short to form a *trans*-fused arrangement of radical and alkene substituents or because the tosyl group resides in a crowded *endo* configuration. Related cyclizations to give 5,7-rings¹³³ also occur with high *cis* selectivities due to the constraints imposed by the chain connecting the radical and the alkene, but cyclizations to form 6,6 rings sometimes give mixtures.¹³⁴



Transannular cyclizations in larger rings occur with variable stereochemical outcomes. Cyclizations in large, highly flexible rings tend to occur with low stereoselectivity,¹³⁵ however, the introduction of substituents that limit the conformations available to a macrocycle can lead to high selectivities.¹³⁶ In perhaps the most dramatic example to date (Eq. 2.38b), cyclization of **74** provides **76** as a mixture of regioisomers, each of which is a single stereoisomer, in 50% yield.¹³⁷ This reaction involves two sequential stereoselective transannular cyclizations of radical **75**, and the outcomes of both cyclizations were predicted by the Spellmeyer–Houk MM2 model.

A few transannular cyclizations have also been reported in which the alkene acceptor is an *exo*-alkylidene macrocycle,¹³⁸ and a representative example is shown in Equation 2.39.¹³⁹ In these types of cyclizations, the formation of *trans*-fused rings becomes competitive when larger rings are involved.¹⁴⁰ There are also examples of stereoselective transannular cyclizations in which the radical-bearing carbon is *exocyclic* to the forming ring.¹⁴¹



2.2.3.4 6-*Endo* Cyclizations

A number of structural features can cause hexenyl radicals to stray from the normally favored 5-*exo* pathway for cyclization and adopt a 6-*endo* pathway instead. Although it is conceivable that substituents can be introduced to accelerate a 6-*endo* cyclization, most observations of 6-*endo* cyclizations have occurred in systems where 5-*exo* cyclizations are especially unfavorable; in other words, 6-*endo* cyclization occurs by default. Introduction of internal alkene substituents (C5) provides increased amounts of 6-*endo* products, as does the introduction of a ketone on C2. The nuclear substitution of second row elements, especially silicon, in the connecting chain also favors 6-*endo* cyclization by increasing the reach of the chain due to the longer bonds to these elements. A popular way to favor 6-*endo* cyclization has been to use ring strain in polycyclic systems. Since five-

membered rings are more strained than six, the introduction of an element of ring strain tends to retard a *5-exo* cyclization more than its *6-endo* competitor.

Intuition suggests that transition states for *6-endo* cyclizations should resemble “stretched” cyclohexanes. The stretching comes because the forming bond in the transition state is considerably longer than the final bond in the product. Calculations support this idea,^{27,28,32a} the *6-endo* cyclization of the hexenyl radical is calculated to occur through a chair-like transition structure **77-c** with one relatively long bond (Fig. 2-7). The staggering of the substituents about the forming C–C bond and the existing C–C bonds is quite good. By analogy to cyclohexane, a twist boat transition structure **77-tb** is also expected, and this is located computationally at an energy level about 2 kcal/mol higher than **77-c**.²⁸ As with the cyclohexane analogy for hexenyl radicals, the calculated difference in energy between the chair and twist boat transition structures (2 kcal/mol) is significantly smaller than the difference in energy (5.5 kcal/mol) between chair and twist boat cyclohexane.

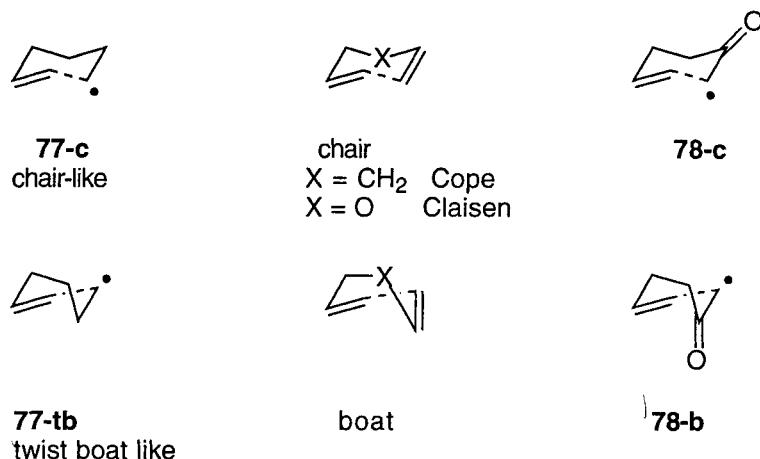
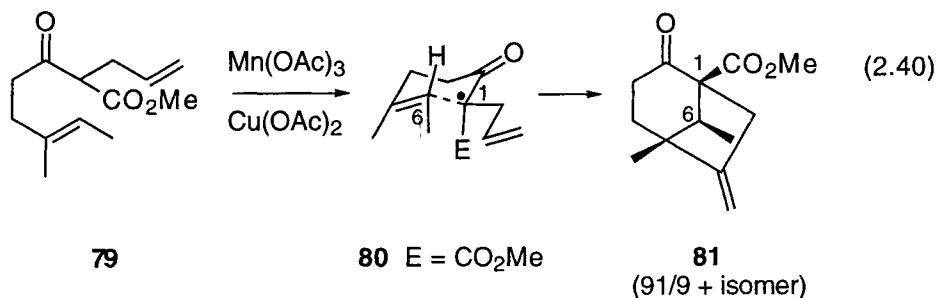


Figure 2-7. Transition Structures for *6-Endo* Cyclizations.

Drawing analogy between *6-endo* radical cyclizations and common 3,3-sigmatropic shifts such as the Claisen and Cope rearrangements¹⁴² is a good place to begin thinking about stereoselectivity in *6-endo* cyclizations. This analogy is especially good for keto-radicals like **78**,^{32a} but can also be

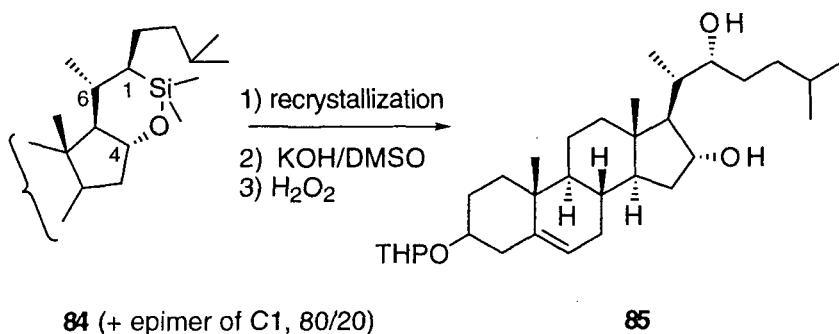
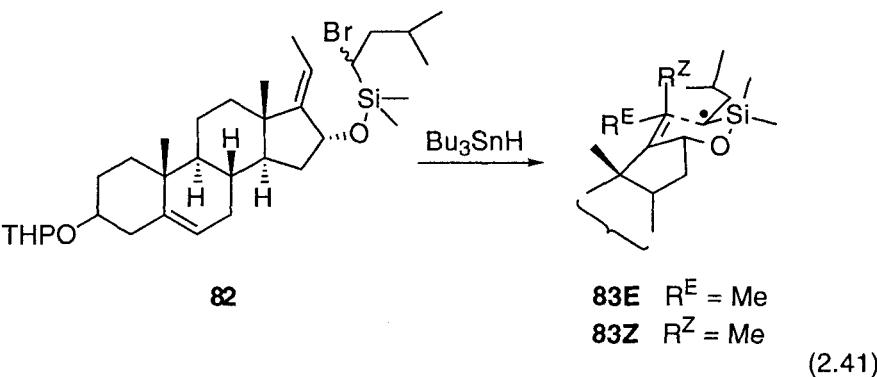
useful for the non-conjugated radicals **77**. Claisen and Cope rearrangements typically proceed through chair-like transition states with equatorial substituents; however, structural features can raise the energy of the chair-equatorial transition state, and major products occasionally come from chair-axial or boat transition states. There are important differences between the sigmatropic rearrangements and the radical cyclization transition states. Sigmatropic rearrangements have both forming and breaking σ -bonds, but in radical cyclizations there is only a forming σ -bond; no σ -bond breaks. Further, in the sigmatropic rearrangements, the “axial/equatorial” orientation of the substituents on both alkene termini are fixed by the alkene geometry (*E* or *Z*). This is true of only one terminus in the radical cyclization; the substituents on the radical terminus can adopt either position due to rotation. Finally, radical **77** bears an sp^3 carbon atom where the sigmatropic substrates have an sp^2 carbon atom (C2).

There are only a few examples of stereoselective *6-endo* cyclizations of acyclic substrates. Most prominent among these are cyclizations of β -keto-ester radicals, which can be generated either by oxidation with manganese acetate or by the atom transfer method.^{52,53,143} Tandem cyclization of **79** with manganese acetate provides **81** as a 91/9 mixture of stereoisomers (Eq. 2.40).^{143a} The relative configuration between C1 and C6 (simple diastereoselection) is determined in the initial *6-endo* cyclization, and the “sigmatropic-like” transition state model **80** nicely rationalizes the selectivity. The ester group adopts the axial position to minimize unfavorable dipole/dipole interactions with the ketone. This sets the orientation at C1, and the orientation at C6 is fixed by the *E*-alkene.

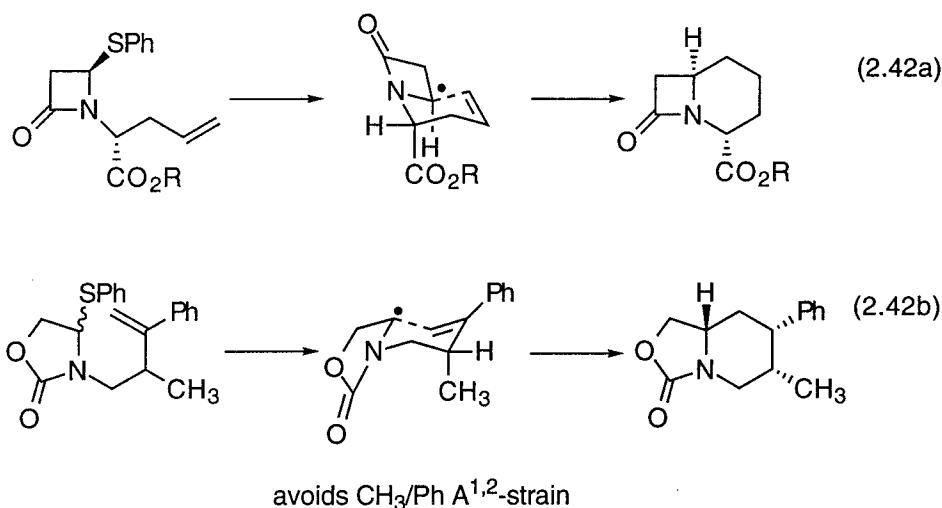


Most stereoselective *6-endo* cyclizations involve cyclic alkenes or cyclic radicals, and certain types of ring connectivity help to promote a *6-endo*

cyclization and to make it stereoselective.¹⁴⁴ The example in Equation 2.41 illustrates that the “silicon connection” is a very useful tool for functionalization of both *endo*-¹⁴⁵ and *exocyclic*¹⁴⁶ allylic alcohols. Cyclization of steroidal silyl ether **82** provides **84** as a mixture of two stereoisomers.¹⁴⁷ The relative asymmetric induction (C4 to C6) is complete, as is the stereoselectivity in the final hydrogen transfer step. The simple diastereoselection (C1/C6) occurs with 80/20 selectivity, and the chair-equatorial transition state **83E** correctly predicts the configuration of the major product. Recrystallization provides the pure major product **84**, which is then oxidized to give diol **85**. The model predicts that the cyclization of the stereoisomeric alkene should provide a diastereomeric product (see **83Z**), and this has been verified on one occasion; however, 6-*endo* cyclizations of these isomers are often slow, and direct reduction of the radical prior to cyclization often occurs. This rate-retarding effect of Z alkene substituents mimics a similar effect that is commonly observed in 3,3-sigmatropic rearrangements.

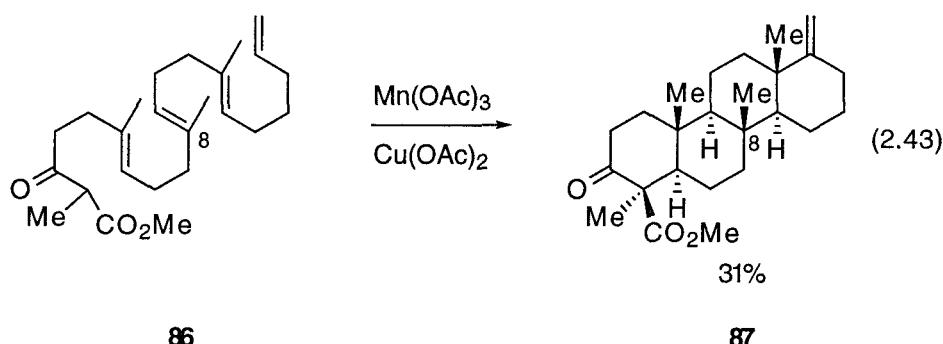


Substrates bearing β -lactams are prone to *6-endo* cyclizations due to ring strain, and such cyclizations are often stereoselective,¹⁴⁸ as shown by the example in Equation 2.42a.¹⁴⁹ The sole product arises from a chair-axial transition state to minimize A-strain between the amide carbonyl and the ester. The related cyclization shown in Equation 2.42b occurs through a chair-axial transition state because this minimizes A-strain between the aryl ring and the allylic methyl group.¹⁵⁰ In this second example, the ensuing hydrogen transfer is also stereoselective. There is even at least one example where a highly stereoselective *6-endo* cyclization occurs through a boat-like transition state.¹⁵¹



The most dramatic examples of stereoselective *6-endo* cyclizations of cyclic radicals are tandem cyclizations directed towards the steroid-like ring systems. The idea that polyenes might undergo radical cyclizations that resemble cationic cyclizations was posited some time ago.¹⁵² However, problems with slow *6-endo* cyclizations and competing *5-exo* cyclizations coupled with the stereoisomer problem probably discouraged further research. These problems notwithstanding, cyclization of **86** with manganese acetate and copper acetate in acetic acid provides **87** as a single isomer in 31% yield (Eq. 2.43)¹⁵³ Even this modest yield is remarkable when one considers the number of competing reactions at each stage. Three stereoselective *6-endo* cyclizations are followed by a selective *6-exo*

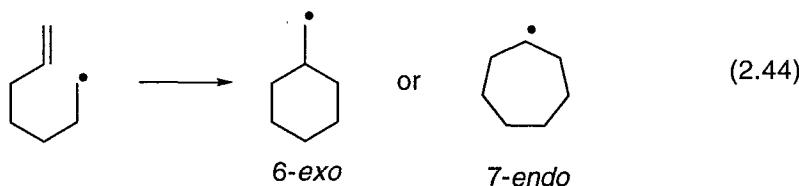
cyclization. Despite the presence of oxidants, it seems unlikely that any of the cyclizations occur through cation intermediates because: 1) the last cyclization requires a high energy primary cation intermediate, and 2) related cyclizations under non-oxidizing conditions occur with similar selectivities in yields sometimes exceeding 50%.¹⁵⁴



The high selectivities observed in these reactions have led to suggestions that the cyclizations may be concerted. However, there is no good evidence that sequences of radical rearrangements are concerted, and most of the observations can be rationalized with existing guidelines. The regio- and stereoselectivity of the first cyclization in Equation 2.43 are nicely consistent with the results in Equation 2.40. The exclusive *6-endo* mode for the second and third cyclizations is somewhat surprising, but this may be attributed to unusually slow *5-exo* cyclizations (a bond between two adjacent quaternary centers would be formed in the *5-exo* cyclizations). In this view, the C8 methyl group is crucial for promoting *6-endo* closure in the second cyclization. Since the methyl group does not exist in steroids, the direct application of this strategy to the actual steroid ring may not be possible. The stereoselectivity of these *6-endo* closures follows from the simple extension of the basic model in Figure 2-7 into a *trans*-decalin system. The last regio- and stereoselective *6-exo* cyclization is the most surprising. One might expect (see below) that *7-endo* cyclization and 1,5-hydrogen transfer reactions could compete, and that even in the *6-exo* product, considerable amount of *cis* CD-fusion should be observed (See Eq. 2.24). However, the modest yields (30-50%) suggest that competing pathways may be occurring, and further confirmation of the literature configuration assignments (some of which are still tentative) is desirable.

2.2.4 Heptenyl and Related Radical Cyclizations.

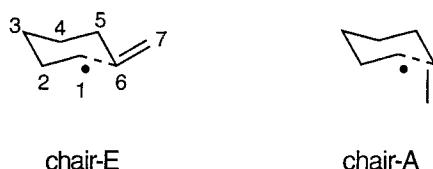
Heptenyl and related radicals can cyclize in a *6-exo* or *7-endo* fashion (Eq. 2.44). Although a fair number of *7-endo* cyclizations are known, *6-exo* cyclizations are more common, and most examples of stereoselective heptenyl radical cyclizations fall into this class. *6-Exo* cyclizations are usually slower than related *5-exo* cyclizations, and in some substrates 1,5-hydrogen transfer and *7-endo* cyclization can compete. There are a number of tactics for accelerating *6-exo* cyclizations, and the most common is probably activation of the alkene acceptor with an electron-withdrawing group.



The modeling of stereoselective *6-exo* cyclizations is not as advanced as that of *5-exo* systems; however, the simple structures shown in Figure 2-8 account for many observations. This model, which was first applied to peroxy radical cyclizations¹⁵⁵ and later extended to the depicted “all-carbon” radicals,⁴⁰ proposes that the two low energy transition states both resemble chairs with one stretched bond. The chair-E transition structure places the radical acceptor in an equatorial-like orientation while this group is axial-like in the chair-A transition state. Like the “chair” and “boat” hexenyl radical transition states, these two transition structures are interconverted by rotation around the allylic (C5–C6) bond. Introduction of a substituent on a carbon on the chain (C1–C5) then generates two pairs of transition states (chair-E, axial and equatorial, and chair-A, axial and equatorial). Other things being equal, the model predicts that the major product should derive from the transition state where both the acceptor and the substituent are equatorial (chair-E-equatorial).

Stereoselectivities in many simple carbocyclic systems are low,⁴⁰ but the model in Figure 2-8 predicts the major products more often than not. Examples with good selectivities are almost always accommodated by the model. Since these *6-exo* transition states are thought to have some

“cycloheptane” character, it is not at all clear that boat, twist boat, or other cycloheptane-like conformers should be rejected in the transition state analysis; however, to date they have not usually been considered.

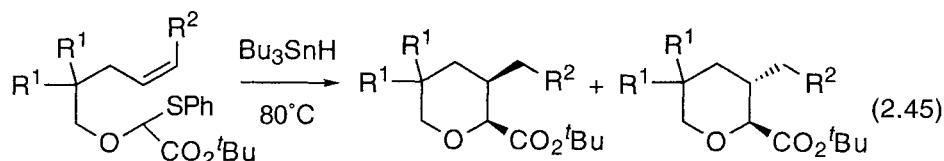


Chair-E model predicts *cis* products from 2- and 4-substituted radicals, and *trans* products from 1-, 3-, and 5-substituted radicals

Figure 2-8. Chair-Like Models for 6-*Exo* Cyclizations.

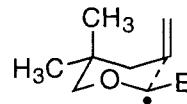
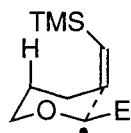
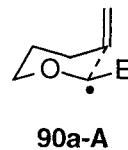
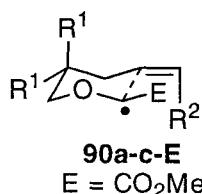
The model in Figure 2-8 predicts that simple diastereoselection with 1-substituted heptenyl radicals should occur to provide *trans*-1,6-disubstituted cyclohexanes. But similar to simple diastereoselection in hexenyl radicals, a range of selectivities has been observed and *cis/trans* mixtures are common.^{40a,156,157} However, addition of appropriate substituents can raise the levels of selectivity considerably, as shown by the examples in Equation 2.45.¹⁵⁸ Cyclization of **88a** provides **89a-cis/trans** in a ratio of only 38/62. A significant amount (about 18%) of the *7-endo* product is also formed (not shown). Cyclization of **88b** provides **89b-cis/trans** in an improved ratio of 17/83, and no *7-endo* product is formed. Cyclization of **88c** provides **89c-trans** as the only 6-*exo* stereoisomer, but the 6-*exo*/7-*endo* ratio is now about 50/50.

In these examples, the alkene substitution pattern controls the regioselectivity; the introduction of any terminal alkene substituent (whether *E* or *Z*) suppresses the *7-endo* product. The low stereoselectivity with **88a** suggests that transition states **90a-E** and **90a-A** are close in energy. The *Z*-alkene substituent raises the transition state of **90b-A** due to A-strain, and the *gem*-dimethyl group raises the energy of **90c-A** due to the 1,3-diaxial interaction. By reducing contributions from **90c-A**, the stereoselectivity is increased. These observations are representative of how the model can be used to design substrates that will cyclize stereoselectively in a 6-*exo* fashion.

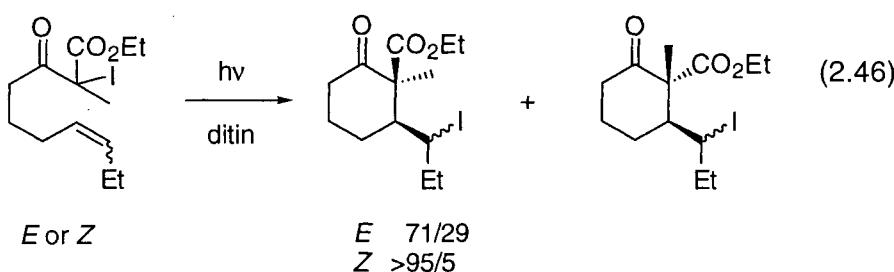


- 88a** $R^1 = R^2 = H$
- b** $R^1 = H, R^2 = \text{TMS}$
- c** $R^1 = \text{CH}_3, R^2 = H$

- | | | |
|----------------|-------|------------------|
| 89a-cis | 38/62 | 89a-trans |
| b | 17/83 | b |
| c | 0/100 | c |

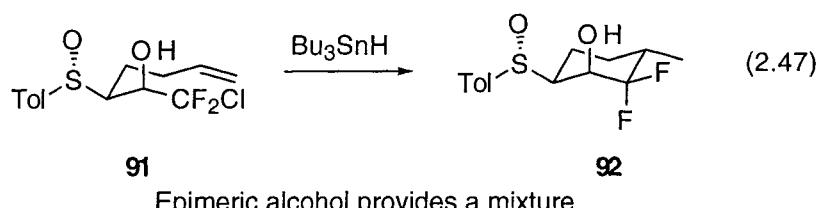


Substituted keto-ester radicals also cyclize with good simple diastereoselection, as shown by the example in Equation 2.46 conducted by the atom transfer method.^{51a,53} (There is no selectivity in the final atom transfer step.) Once again, the Z-alkene gives significantly improved selectivity. The orientation of the radical substituents is determined by dipole effects (see Eqs. 2.13 and 2.40).

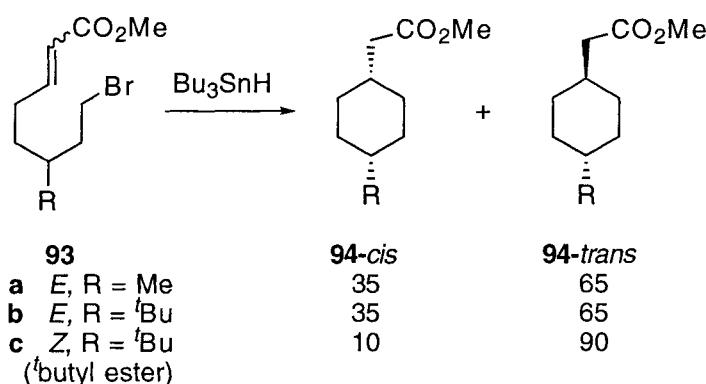


Equation 2.47 contains representative examples of relative asymmetric induction in *6-exo* cyclizations of radicals bearing 2-, 3-, 4-, and 5-substituents. A clear selectivity theme emerges: radicals with either a terminal Z-alkene substituent or an axial-like substituent oriented 1,3 to the alkene acceptor often provide high selectivities. This is consistent with the simple model in Figure 2-8, where minor products are suppressed by raising the energy of the chair-A transition state.

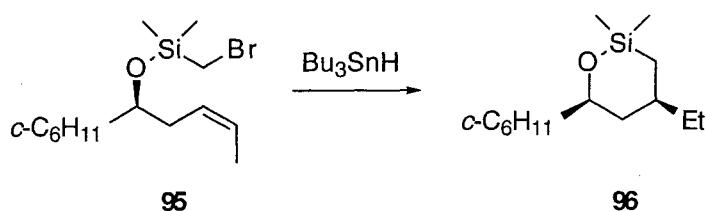
2-substituted

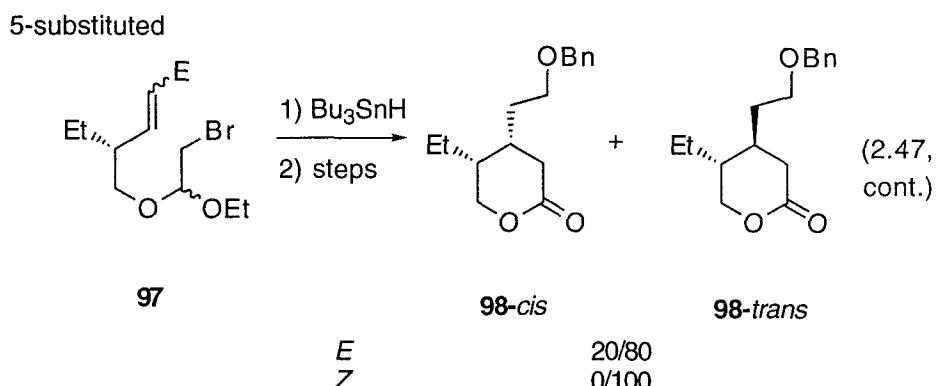


3-substituted



4-substituted





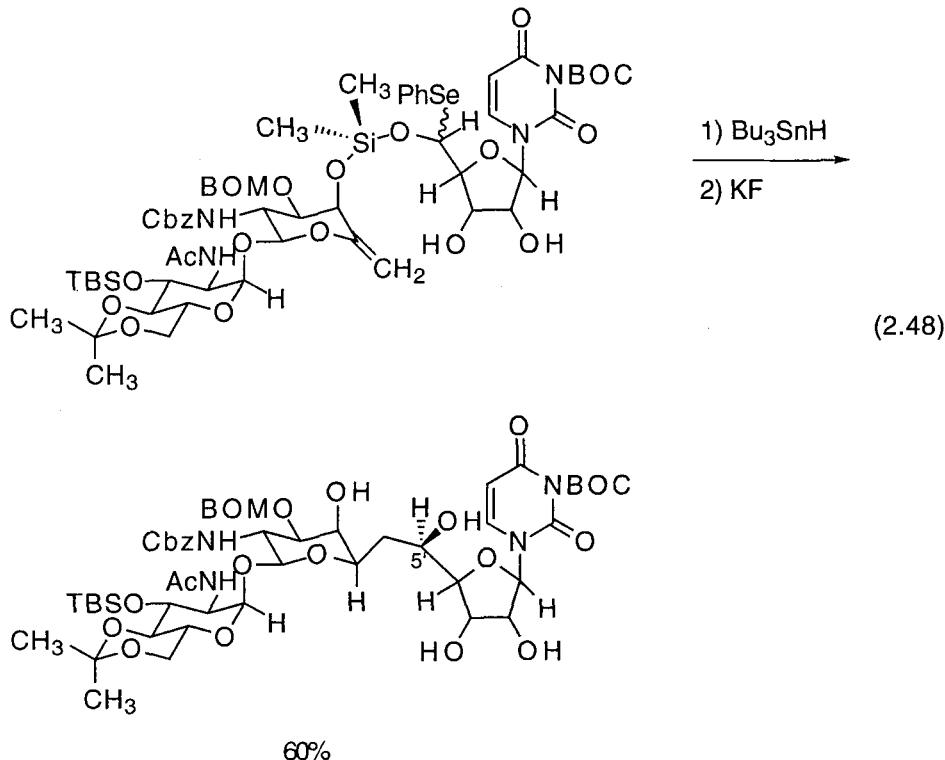
Cyclization of 2-hydroxy sulfoxide **91** provides a single product **92**.¹⁵⁹ In contrast, the epimeric alcohol (not shown), which bears an equatorial hydroxyl group in the transition state and the product, provides a mixture of stereoisomers. Cyclizations of 3-alkyl substrates **93a–c** provide further insight into transition state energetics.⁴⁰ The observation that the methyl- and *tert*-butyl-substituted (**93a,b**) precursors provide the same ratio of products **94-cis/trans** (35/65) strongly suggests that transition states with the alkyl group axial are not energetically significant. The minor product therefore derives predominately from the chair-A transition state (Fig. 2-8) with the alkyl group equatorial and the acceptor axial rather than from the transition state (not shown) with the alkyl group axial and the acceptor equatorial. The highest selectivity is exhibited with the *Z*-alkene **93c**.

Cyclizations of 4-substituted peroxy radicals occur with high *cis* selectivity. In another example of 4-substitution, cyclization of 4-cyclohexyl (bromomethyl)dimethylsilyl ether **95** provides **96** as a single isomer.¹⁶⁰ Again, the *Z*-alkene is probably crucial for good selectivity.

Many of the reported stereoselective *6-exo* cyclizations occur with substrates bearing an allylic stereocenter (5-substitution).¹⁶¹ As with the related *5-exo* cyclizations, these substituents tend to provide the best selectivities, and they are expected to dominate when multiple substituents are present. Cyclization of **97E** provides **98-cis/trans** in a ratio of 20/80.¹⁶² Due to A-strain, this level is already higher than that observed for *E*- or terminal alkenes bearing substituents in other positions. As expected, selectivities for *Z*-alkenes bearing a 5-substituent are very high; in the case at hand, only **98-trans** is formed.

There are a significant number of *6-exo* cyclizations involving cyclic radicals, cyclic acceptors, or cyclic connectors between the acceptor and radical. Examples of most of these systems will not be provided since they repeat features outlined either in the discussion on *5-exo* cyclizations or in the above discussion on *6-exo* cyclizations. Many examples of these types of *6-exo* cyclizations have already been cited in the analogous sections of *5-exo* cyclizations.

There are only a few examples of stereoselective *7-endo* cyclizations,¹⁶³ and general models have not yet emerged. However, the selective *7-endo* cyclization shown in Equation 2.48 was the featured step in a synthesis of tunicamycin V.¹⁶⁴ The level of selectivity in favor of the indicated C5' hydroxy epimer is about 88/12, but this selectivity can be reversed by protecting the furanoside hydroxy groups.



2.2.5 Higher Cyclizations

There are few intriguing *8-endo*,¹⁶⁵ *9-endo*,¹⁶⁶ and *10-endo*¹⁶⁷ cyclizations that occur with excellent stereoselectivity. Although the yields in these examples are often low or modest, they do provide encouragement for further stereochemical study in systems that participate in these less common modes of cyclization.

2.2.6 Radicals Bearing Stereocenters Outside the Cyclizing Unit

In contrast to the large body of data available on cyclizations of radicals bearing stereocenters along the connecting chain between the radical and the alkene, there are relatively few examples of stereoselective cyclizations of substrates bearing stereocenters not embedded in the connecting chain (sometimes called “extraannular”). Substrates in this class are shown in Figure 2-9, and they can have stereocenters attached to the radical or the alkene in substituents that are not part of the cyclizing unit, or the stereocenters can be attached to non-stereogenic atoms between the radical and the alkene.¹⁶⁸

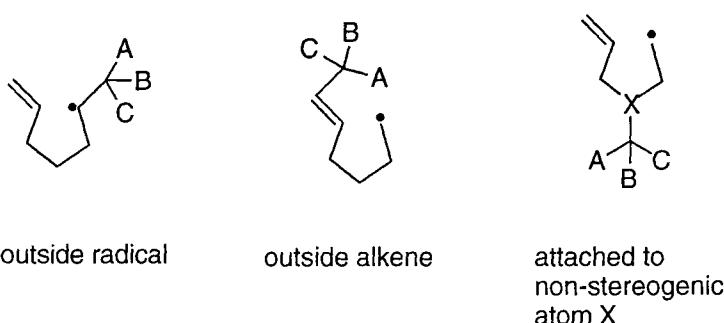
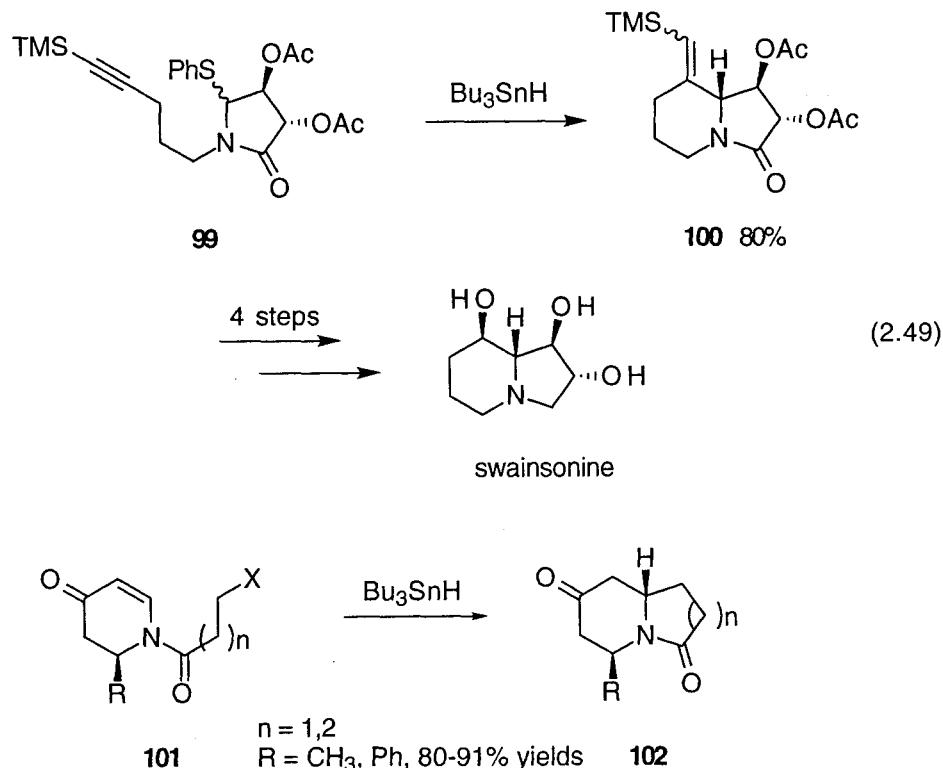


Figure 2-9. Radicals Bearing Stereocenters Outside the Ring.

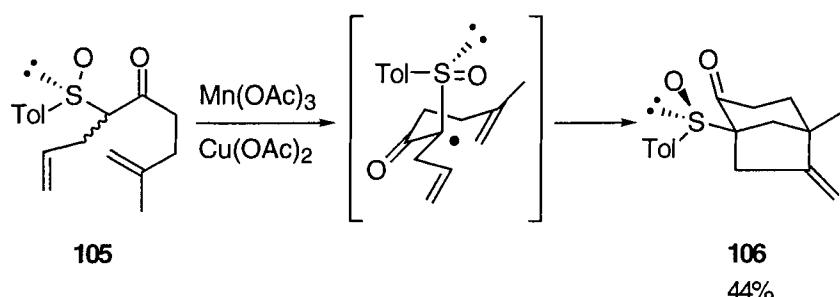
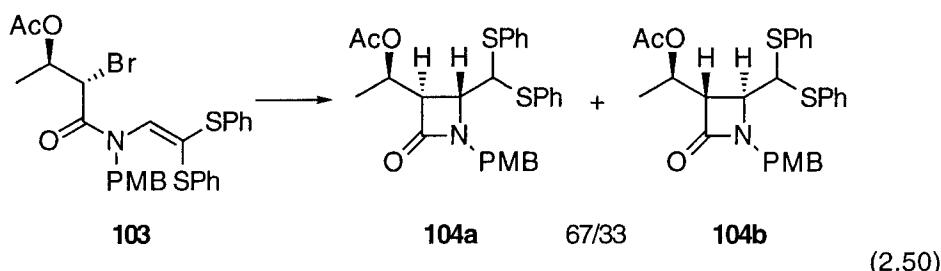
Examples of cyclizations of a cyclic radical and a cyclic alkene are presented in Equation 2.49. Lactam **99** is readily available from tartaric acid, and it is the precursor of a cyclic radical bearing an adjacent stereogenic center. Standard cyclization of **99** with tributyltin hydride provides **100** in

80% isolated yield, and a four step sequence converts **100** to the indolizidine natural product swainsonine.¹⁶⁹ In the radical cyclization, the alkyne reacts on the face opposite to the adjacent acetate group. Several related cyclizations of cyclic radicals are known,^{100,170} and there are also a number of cyclizations of cyclic alkenes or cyclic radicals bearing stereocenters to make spiro rings.¹⁷¹ Cyclizations of 4-pyridones **101** to provide indolizidinediones **102** are examples of reactions of cyclic alkenes bearing stereocenters outside the cyclizing unit.¹⁷² The selectivity in these cyclizations is controlled by A-strain (see Eq. 2.27). These selectivities are analogous to the bimolecular reactions of cyclic radicals and alkenes, which are discussed in detail in Chapter 3.



Equation 2.50 provides two examples of cyclizations of acyclic radicals bearing stereocenters. Both have close analogies in the bimolecular reactions of acyclic radicals. Cyclization of the α -amide radical derived from **103**

provides **104a** and **104b** with a low level of selectivity (67/33).¹⁷³ However, the large number of examples that have recently accumulated in related bimolecular reactions of acyclic radicals (see Chapter 4) suggest that higher selectivities might be observed by altering the substituents on the stereogenic center. Somewhat higher levels of selectivity have been observed when the stereocenter is attached to the alkene.¹⁷⁴



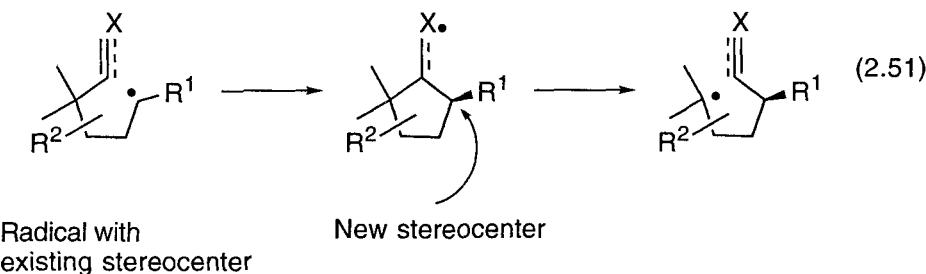
Like its related bimolecular counterparts, the cyclization of sulfoxide **105** occurs with excellent selectivity to provide bridged bicycle **106**.¹⁷⁵ The transition state model is related to the model for cyclization of a keto ester radical (Eq. 2.40). Unlike the related acyclic examples, the reductive removal of the sulfoxide (via a sulfone) with retention of configuration is possible with products like **106** because the bicyclic ring prohibits epimerization at the bridgehead position during the reduction.

The paucity of examples of these types of cyclizations is somewhat surprising. Given the good level of understanding of bimolecular reactions (radical additions, atom and group transfer reactions) of both cyclic and acyclic substrates, it should not be difficult to design and implement analogous cyclizations.

2.3 Stereocontrol in Cyclization/Fragmentation Sequences

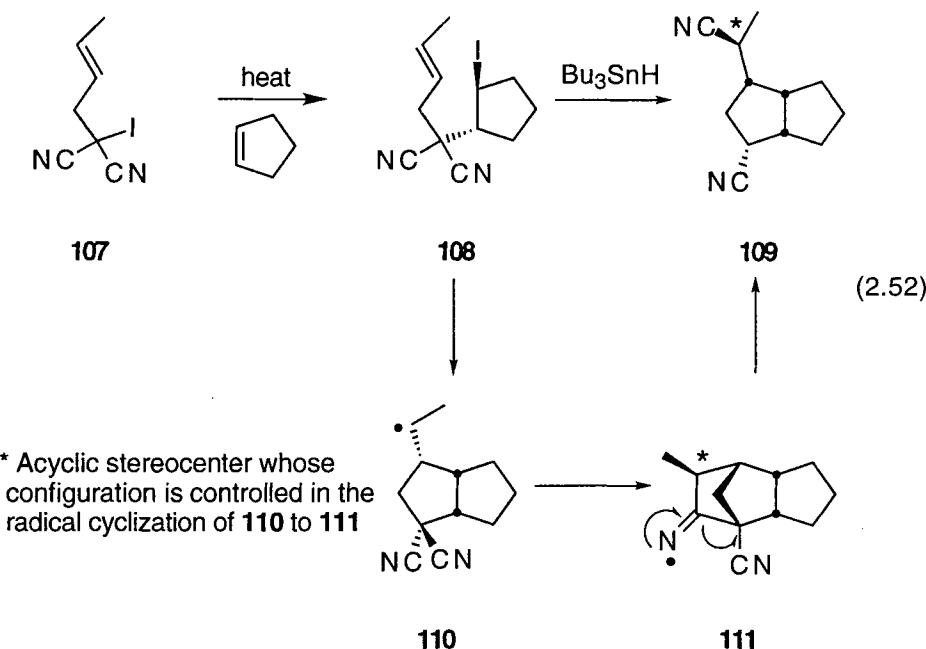
The use of a stereoselective cyclization process to indirectly control acyclic stereochemistry is a common strategy in synthesis. Following the generation of a cyclic stereogenic center, a subsequent ring cleavage reaction reveals a new acyclic stereogenic center. Radical cyclizations of halo-acetals and (haloalkyl)silyl ethers are popular incarnations of this strategy (Eqs. 2.20 and 2.25). In such reactions, the ring is formed in a radical cyclization, and it is later cleaved in a separate step by a traditional reaction such as hydrolysis or oxidation.

The reversibility of certain types of radical cyclizations offers rarely used but powerful possibilities for controlling the configurations of acyclic stereocenters in radical cyclizations on a much more rapid time scale. The strategy involves radical cyclization to a group such as cyano or formyl with formation of a new stereocenter. Subsequent radical fragmentation in the other direction then breaks the temporary ring, leaving the new stereocenter intact. This concept is pictured in Equation 2.51.



Consider the example shown in Equation 2.52.^{176a} Atom transfer addition of **107** to cyclopentene forms **108** in high yield. Slow addition of tributyltin hydride to a solution of **108** in benzene provides mainly bicyclooctane **109**. This sequence, which can be conducted in one flask, generates five stereogenic centers with a level of selectivity of about 20/1. Cyclization of the radical derived from **108** occurs in the expected *endo-cis* fashion (see Eqs. 2.28a,b) to provide **110**. In turn, **110** cyclizes stereoselectively to provide iminyl radical **111** with the methyl group at the new stereocenter on the *exo*-face of the bicyclo[2.2.1]heptane ring. Fragmentation of **111** in the other direction preserves this new stereocenter (which

is now acyclic), and generates a radical adjacent to the other nitrile. This last radical is reduced from the *exo* face by tin hydride. In addition to this example of cyano transfer, a related stereoselective phenyl transfer is known^{168a} and stereoselective formyl transfers are also be possible.^{176d}



2.4 Group-Selective Cyclizations

The majority of asymmetric radical cyclizations involve diastereotopic face selection in the reaction of a prosterogenic alkene or radical. However, face selectivity is not the only strategy available for the stereoselective transformation of a prosterogenic sp²-atom to an sp³-hybridized stereogenic center. The alternative strategy—diastereotopic group selectivity—has only recently been applied to the reactions of radicals, but with interesting consequences.

Several generic types of group-selective radical cyclizations are shown in Figure 2-10. In principle, group-selective reactions can involve either one radical precursor and two diastereotopic radical acceptors,¹⁷⁷ or two

diastereotopic radical precursors and one radical acceptor. These two classes of reactions are conceptually distinct, so they will be presented separately. Using the diastereotopic radical acceptor as an example, the reactions may be further classed either as under substrate control or under chiral auxiliary control. Depending on the structure of the radical and the acceptor, issues of face selectivity may be superimposed on the question of group selectivity. When this occurs, more than two products may be produced, depending on the relative levels of face and group selectivity.

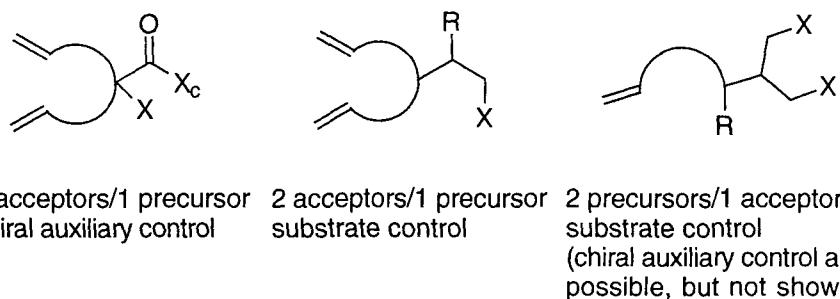


Figure 2-10. Classes of Diastereotopic Radical Cyclizations.

2.4.1 Two Acceptors/One Precursor

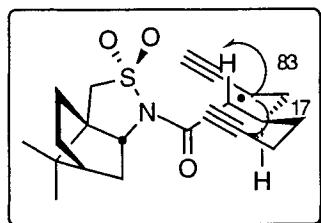
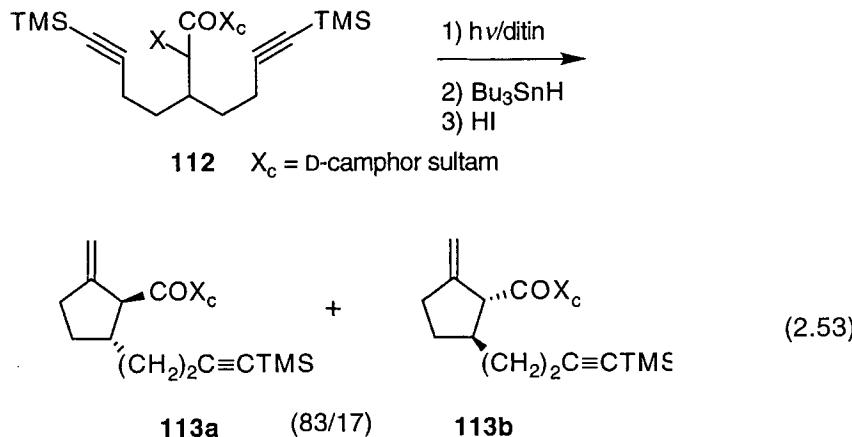
Although examples have only recently begun to emerge, diastereotopic group-selective radical reactions in this class are conceptually equivalent to their well studied forerunners in ionic and pericyclic chemistry.¹⁷⁸ In the radical reactions, group selection occurs at the level of a transient reactive intermediate (the radical), but this is of no special consequence in the analysis of competing pathways. The product ratio for competing cyclizations of two diastereotopic acceptors equals the rate constant ratio for the two cyclizations:

$$\frac{\% \text{ major diastereomer}}{\% \text{ minor diastereomer}} = \frac{k_f}{k_s}$$

k_f (k_{fast}) = the rate constant for cyclization to the major diastereomer

k_s (k_{slow}) = the rate constant for cyclization to the minor diastereomer

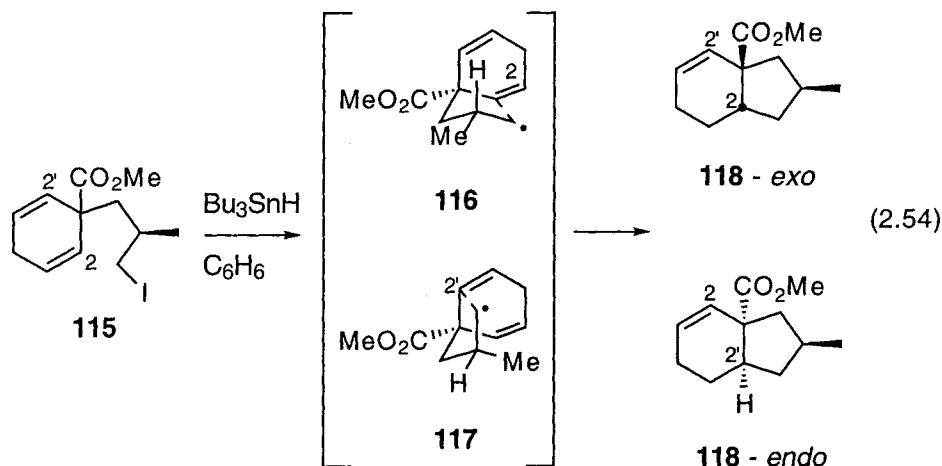
Equation 2.53 provides a simple example of a group selective radical cyclization of diyne **112** under chiral auxiliary control.¹⁷⁹ The structure of the substrate also raises an issue of relative asymmetric induction (a type of face selectivity), but by choosing a diyne (instead of a diene), there is no issue of simple diastereoselection (another type of face selectivity). Atom transfer cyclization of **112** at 7°C, followed by deiodination and desilylation, provides two of the four possible products, **113a** and **113b** in a ratio of 83/17. As expected (see Eq. 2.22), the relative asymmetric induction is complete; both products possess the 1,2-*trans* stereochemistry, as predicted by the Beckwith–Houk model. The 83/17 ratio of products is the level of group selectivity, and corresponds to the rate constant ratio for the reaction of radical **114** with the diastereotopic alkynes. The relative configuration of the major product **113a** is consistent with the prevailing model for face-selective reactions of Oppolzer's camphor sultam, although the group selectivity is somewhat lower than that usually observed for analogous face-selective reactions. Both the face-selective reactions and the sultam model are discussed in detail in Chapter 5.



114
Beckwith model:
predicts *trans* product
Sultam model:
predicts group selectivity

A number of other group-selective reactions of chiral radicals bearing Oppolzer's camphor sultam have been reported,¹⁷⁹ and the results suggest that general principles outlined in Chapter 5 on face-selective reactions of radicals bearing chiral auxiliaries should readily be extended to related group-selective reactions.

Equation 2.54 provides an example of a substrate-controlled group-selective radical cyclization.¹⁸⁰ Iodide **115**, which is readily prepared in optically pure form, cyclizes at 80°C under the influence of tin hydride to provide a 94/6 ratio of *exo* and *endo* products. At -80°C, the selectivity increases to 97/3. Although the Beckwith-Houk model was introduced for face-selective reactions, it can readily be extended to interpret this group-selective reaction. The two possible chair-like transition state models, one for cyclization to each diastereotopic alkene, are shown in Equation 2.54. Model **116** bears an equatorial-like methyl group while the methyl group in **117** is axial-like. Thus, the Beckwith-Houk model quickly and correctly predicts the major product of the reaction. (Indeed, in this case the substrate was actually designed from the model.)



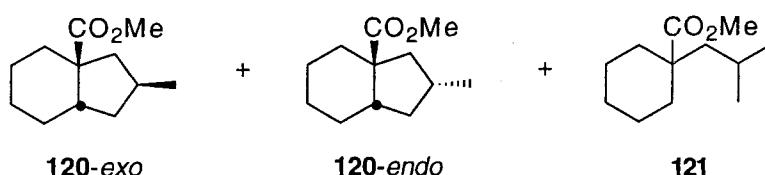
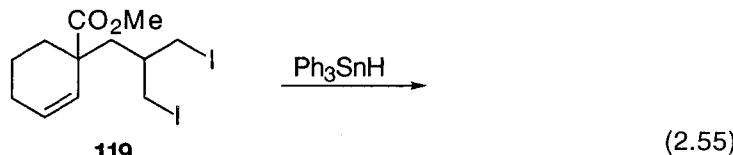
These two examples serve to illustrate that the understanding of group-selective radical reactions of substrates bearing one radical precursor and two radical acceptors should readily follow from the principles and guidelines outlined in this chapter for radical cyclizations and in Chapter 5 for chiral auxiliaries.

2.4.2 Two Precursors/One Acceptor

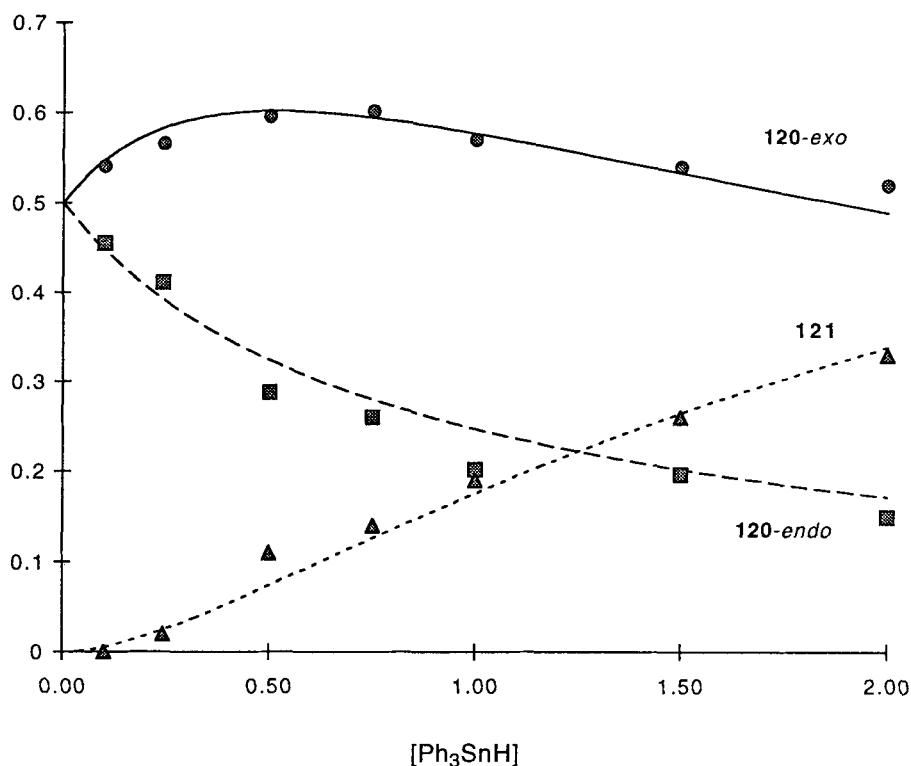
Radical reactions of substrates with two diastereotopic precursors and one acceptor are now being used to probe new methods and concepts in control of stereochemistry by group selection. Unlike the standard scenario, the substrate bearing the diastereotopic groups is not the actual reacting species. Instead, it is a precursor of diastereomeric radicals. The concepts that are emerging from these studies should apply to group-selective reactions of any type of diastereomeric intermediates.

The product ratios in the reactions of diastereotopic groups depend only on the relative rates of the competing reactions; the ratios are never influenced by the nature and concentration of the radical trap (although the total yields are, of course, influenced by the trap). In contrast, product ratios in the reactions of diastereomeric reactive intermediates (as opposed diastereotopic groups in the same molecule) depend on the relative rates of generation of the diastereomers and on their rates of cyclization and trapping. Product ratios can range from the ratio of generation of the reactive intermediates all the way to an arbitrary infinity, depending on the rate of the trapping reaction. However, obtaining very high product ratios can be associated with significant total yield reductions. This dependence of diastereomer ratios of intramolecular reactions on trapping rates of bimolecular reactions is counterintuitive, but it is readily shown both experimentally and by deriving kinetic equations.

Consider the reduction of **119** shown in Equation 2.55. This substrate is similar to compound **115** in Equation 2.54, except that one radical acceptor has been removed, and a diastereotopic radical precursor has been



added. The data for reduction of **119** at varying tin hydride concentrations under pseudo first order conditions are shown graphically in Figure 2-11. The line in Figure 2-11 is the solution to the rate equations for a cyclization rate constant ratio of 4 for the intermediate diastereomeric radicals.



The lines represent values calculated from the kinetic model using k_{fast} values of 5×10^7 with a $k_{\text{fast}}/k_{\text{slow}}$ ratio of 4.0 and a k_{H} of $2.0 \times 10^7 \text{ s}^{-1}$ plotted against experimentally determined yields.

Figure 2-11. Yields of **120-exo**, **120-endo**, and **121** at Varying Triphenyltin Hydride Concentrations.

At low tin hydride concentrations, the ratio of **120-exo** and **120-endo** is 50/50, and no doubly reduced product **121** is observed. As the tin hydride concentration increases, the yields of **120-exo** and **121** begin to increase, while the yield of **120-endo** decreases. The maximum yield of **120-exo** (60%) is reached at about 0.75 M. Although the yield of **120-exo** then declines, the ratio of **120-exo/endo** continues to increase because the yield of

120-*endo* declines faster. In the (hypothetical) limit, the yields of **120-exo** and **120-*endo*** both reach zero as the yield of the doubly reduced product **121** reaches 100%. This situation is quite different from the reactions of diastereotopic acceptors in Equation 2.54. Although the ratio of products must clearly depend on the relative rate of cyclizations (4) of the intermediate diastereomeric radicals, the product ratios do not equal this relative rate (except at a single concentration on the curve).

Figure 2-12 presents a mechanistic model for interpreting these observations. Radicals labeled “x” and “n” are precursors of *exo* and *endo* products, respectively. Although the iodides in **119** are diastereotopic, the

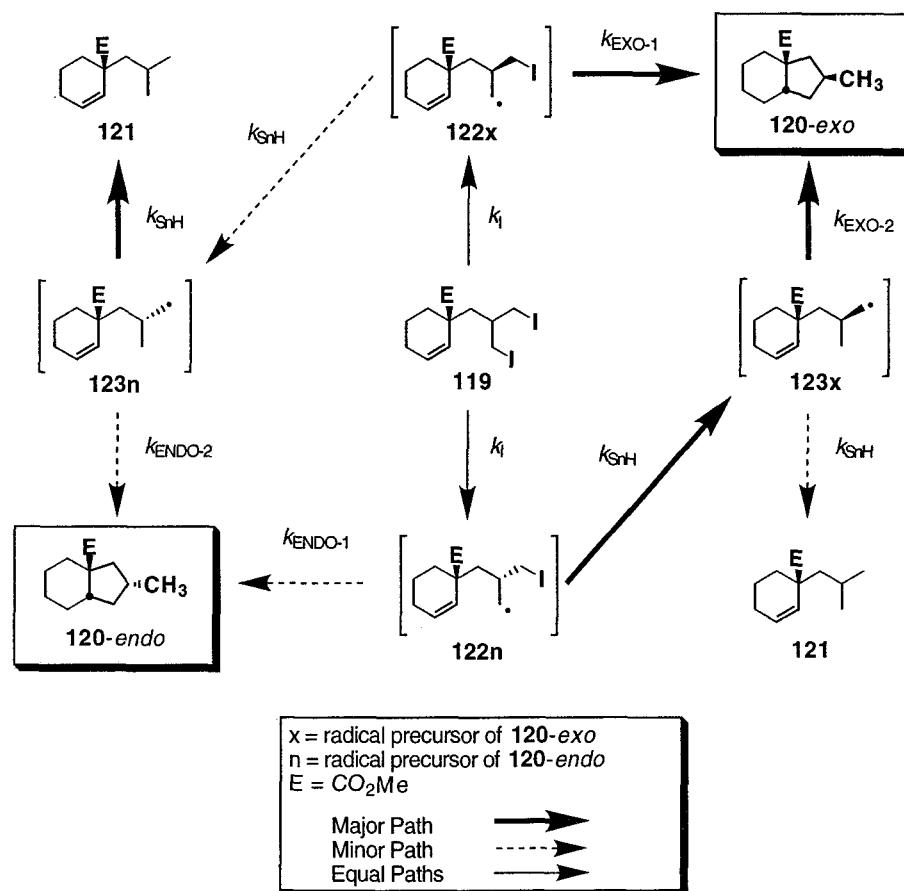


Figure 2-12. Kinetic Resolution of Diastereomeric Radicals.

initial generation of the diastereomeric radicals **122x** and **122n** by iodine abstraction with $\text{Ph}_3\text{Sn}\bullet$ is not expected to be stereoselective. Radicals **122x** and **122n** are generated with equal probability, and though they cyclize at different rates, both have adequate lifetime to cyclize completely when the tin hydride concentration is low. Subsequent hydrogen transfer and reductive deiodination provides **120-exo/endo** in a 50/50 ratio. Thus, at low tin hydride concentrations, the product ratio is determined by the relative ratios of iodine abstraction.

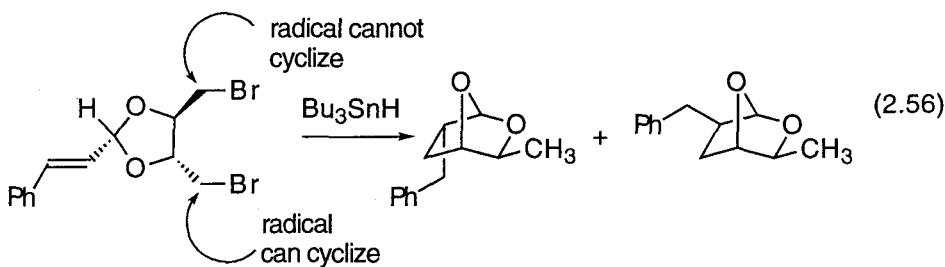
As the tin hydride concentration is increased, trapping of radicals begins to compete with cyclization. According to the Beckwith–Houk model, radical **122n** must cyclize with its iodomethyl group in an axial-like orientation and it therefore cyclizes 4 times more slowly than radical **122x**, whose iodomethyl group is equatorial-like. Said another way, trapping of **122n** by tin hydride is 4 times more likely than trapping of **122x**. Trapping of **122n** by Ph_3SnH followed by abstraction of the remaining iodide atom then generates a new radical **123x** in which the methyl group is now poised to cyclize in a pseudo-equatorial orientation to provide **120-exo**. By increasing the tin hydride concentration, the radical **122n** which seemed destined to provide **120-endo**, is now diverted to **120-exo**. The radical **122x** is more likely to cyclize than **122n**, but when it is reduced by tin hydride, then subsequent iodine abstraction provides a radical **123n** that could cyclize to **120-endo**. However, this requires the pseudo-axial disposition of the methyl group, so this radical is preferentially diverted towards the doubly reduced product **121**.

This simplified analysis captures the essence of the phenomenon. By setting the trapping rate ($k_H \bullet [\text{SnH}]$) between the rates of the faster (k_{exo}) and slower (k_{endo}) cyclizations, it is possible to effect a successive, convergent resolution of radicals **122x**, **122n**, **123x**, and **123n** towards product **120-exo** and away from **120-endo**. The arrows in Figure 2-12 show the major (bold) and minor (dotted) pathways for each intermediate radical. The analysis is not unique to radicals; instead it embodies a general strategy for group-selective intramolecular reactions of diastereotopic intermediates in competition with a bimolecular trapping reaction. A number of variations of this analysis can be envisioned.¹⁸¹

In the example in Equation 2.55, a very modest increase in yield (from 50% to 60%) is observed because the relative rates of k_{exo} and k_{endo} only differ by a factor of 4. According to the model rate laws, significantly better

product ratios will be obtained at higher rate ratios. For hypothetical competing cyclizations of diastereomeric radicals where the rate ratio is 200, the model suggests that the yield of the major product can now reach 91%, at which point the yield of the minor product is 5% and that of the doubly reduced product is 4%. By taking a modest sacrifice in the yield of the major product, the yield of the minor product can be reduced to below 1%. This type of scenario has recently been verified experimentally.¹⁸²

In the limit, one of the two competing reactions may be so slow that it cannot be observed under any conditions. This is the case for the reaction of dibromide **124**, shown in Equation 2.56.¹⁸³ One of the diastereomeric radicals cannot close because the product would be an “inside/outside” fused dioxabicyclo[2.2.1]heptane. This reaction effects a highly selective differentiation of the two bromides at the chain termini.¹⁸⁴



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Traditional diastereotopic reactions of functional groups have an inherent advantage over group selective reactions of diastereomeric intermediates because they can always provide a higher yield of the major product at a given rate constant ratio. For example, the reaction in Equation 2.55 and Figure 2-12 can only provide 60% maximum yield of the major product at a rate constant ratio of 4. In contrast, a traditional diastereotopic group-selective reaction requires no external trap and can (and usually does) provide an 80% yield of the major product (4/1). As the rate ratio increases, the difference between the two processes is reduced: at ratios of 200/1 the traditional process can provide 99.5% yield while the reactions of diastereomeric intermediates can provide 91% yield. At ratios above 500, the maximum yield of a diastereomeric process exceeds 97%, so the mathematical differences lose practical significance.

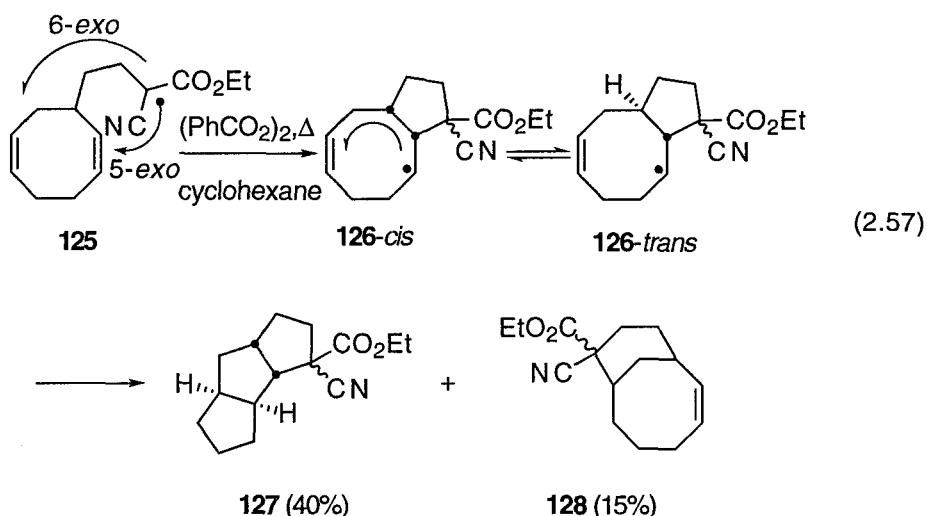
The group selective reactions of diastereomeric intermediates have at least two potential advantages over traditional diastereotopic reactions for functional groups. First, the traditional process requires that the two functional groups be present in the same molecule at the same time. This would require a diradical for radical reactions, and such species are difficult to generate and may well follow other reaction pathways. Thus, when reactive intermediates are involved, the new strategy offers new possibilities. Second, the maximum yield in a group-selective reaction of diastereomeric intermediates can significantly exceed the group selectivity in the initial step (in the hypothetical scenario above, the yield increases from 50%, which is the level of group-selectivity, to 92%). This can never happen in traditional diastereotopic group-selective reactions; the yield of the major product must always be equal to or lower than the initial level of selectivity. Thus, it should be possible to reinforce the selectivity and increase the yield of a traditional diastereotopic group-selective reaction if such a reaction generates stereoisomeric intermediates that are amenable to selective trapping.

2.5 Cyclizations under Thermodynamic Control

Since most popular types of radical cyclization are irreversible, the configurations of newly generated stereocenters are typically under kinetic control. However, a number of types of radical cyclizations are reversible under certain conditions, so the possibility for “thermodynamic control” exists. Radical reactions are almost never under true thermodynamic control at the product level because the final products are formed from radicals by irreversible steps. Thus, the ratio of products depends on the ratio of the equilibrating radicals and their relative rates of trapping. The situation is further complicated because it is relatively rare that all the possible forward and reverse reactions of the intermediate radicals are much faster than trapping. Thus, the intermediate radicals are usually not at true equilibrium either. Nonetheless, conducting reactions under “thermodynamic control” generally has the effect of producing product ratios that approach those expected based on equilibrium constants of the intermediate radicals.

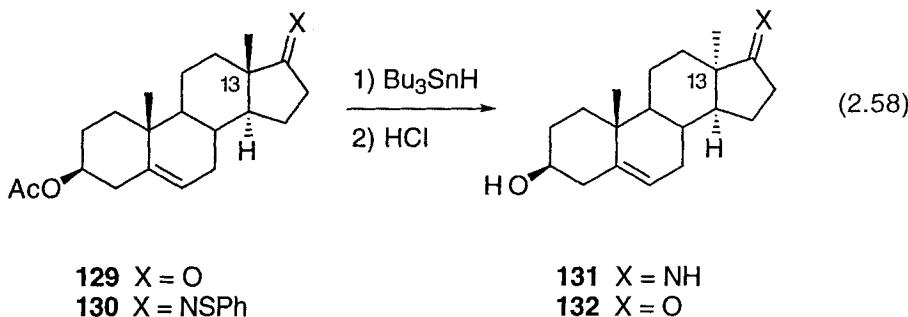
Cyclizations to alkenes can only rarely be conducted under (partially) equilibrating conditions. Factors aiding in establishing equilibration by reverse cyclization include the incorporation of strain, the loss of radical

stabilization¹⁸⁵ in the product radical relative to the starting radical, the use of high temperature, and the use of very poor radical traps. The example in Equation 2.57 illustrates the possibilities for “thermodynamic control”.¹⁸⁶ Cyclization of **125** by heating with excess benzoyl peroxide in cyclohexane at 150 °C provides **127** and **128** in 40 and 15% yields, respectively.

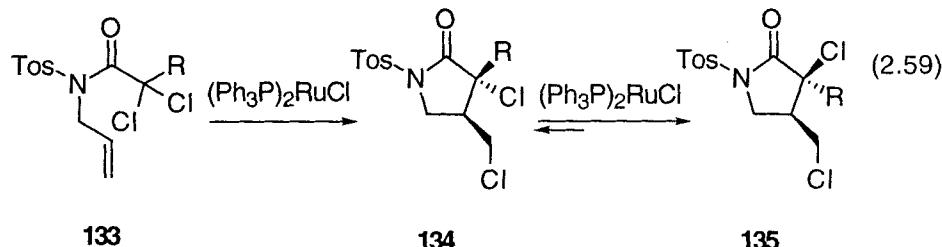


This reaction is believed to be under partial thermodynamic control. Cyclization of the radical derived by hydrogen abstraction from **125** is expected to give a mixture of **126-cis** and **126-trans**, but only **126-cis** can undergo cyclization at a reasonable rate to provide an unstrained tricycle. Thus, for substrates that undergo irreversible cyclization, the yield of tricycles like **127** is limited by the stereoselectivity of the first cyclization. However, with substrate **125** bearing two radical-stabilizing groups under conditions conducive to reverse radical cyclization (high temperature, poor radical trap [cyclohexane]), radicals **126-cis** and **126-trans** are thought to interconvert. This interconversion significantly boosts the yield of **127**. However, in this case there is a penalty to pay—the formation of the *6-exo* product **128**, which would not generally be expected in kinetically controlled cyclizations. It is highly unlikely that all the radicals in the system are in equilibrium (for example, both the *6-exo* cyclization and the transannular *5-exo* cyclization are probably irreversible under these conditions), but the partial equilibrium clearly shifts the product ratio in a predictable fashion.

Equation 2.58 shows a second approach to thermodynamic control in which an epimerization of a quaternary carbon center (C13) is accomplished.¹⁸⁷ Conversion of the CD-*trans* fused steroidal ketone **129** to the sulfenimine **130** (70%) followed by reduction with tin hydride provides the insoluble imine **131** possessing a CD-*cis* fusion. Hydrolysis with dilute HCl provides the epimerized steroidal ketone **132**. This unusual epimerization proceeds through fragmentation of the intermediate iminyl radical to a nitrile (see the related fragmentation in Equation 2.52) and recyclization to provide the more stable *cis*-CD fusion. Many radical cyclizations to aldehydes are also reversible, so similar possibilities exist for thermodynamic control when the rates of cyclization and trapping have appropriate relative velocities.¹⁸⁸

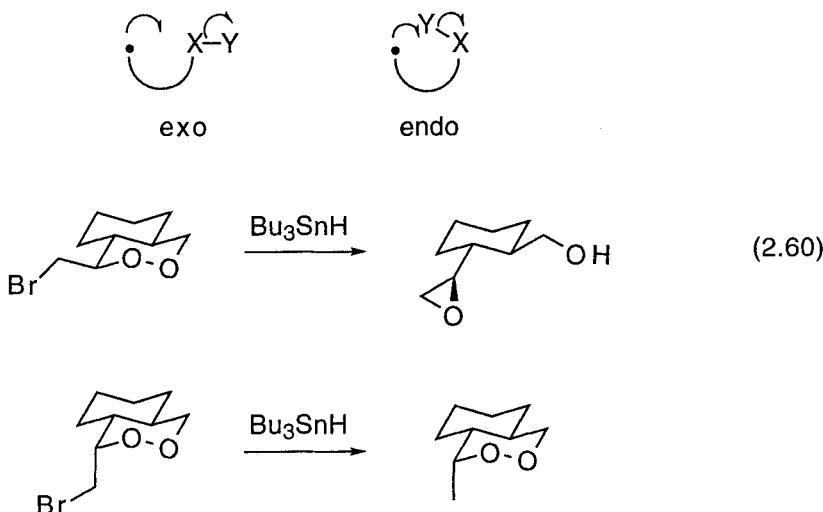


A third option for thermodynamic control of stereochemistry is shown in Equation 2.59.¹⁸⁹ This type of equilibration is the thermodynamic counterpart of the kinetic reactions of cyclic radicals described in Chapter 3. The cyclization of **133** leading ultimately to **134** and **135** is irreversible, but **134** and **135** are subsequently equilibrated by reversible chlorine atom transfer. This reaction is a true equilibration of products rather than radicals, although equilibrium is not necessarily easy to reach.



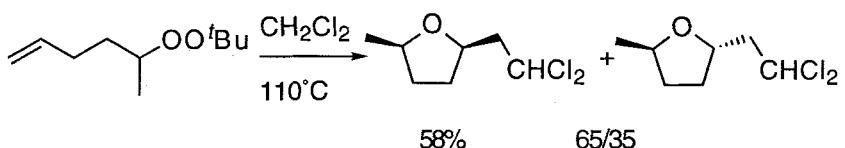
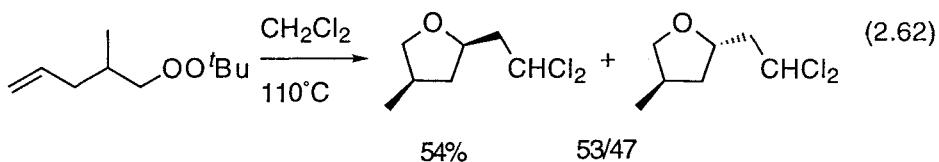
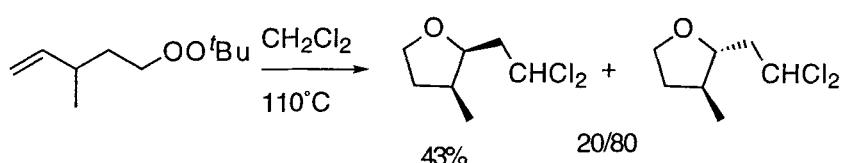
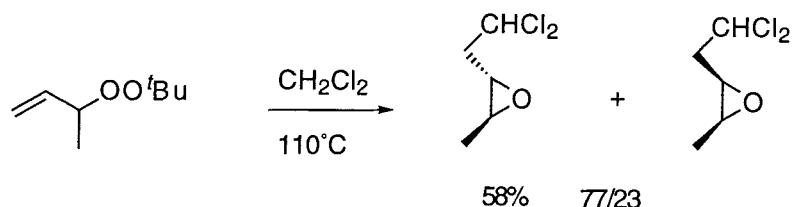
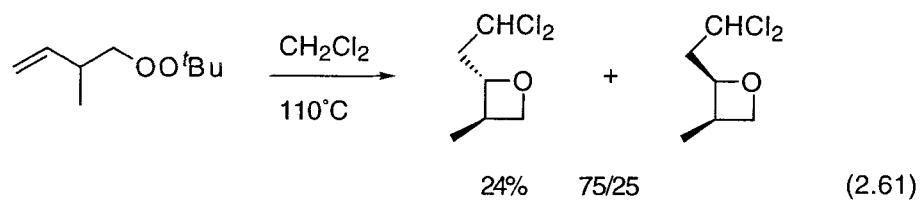
2.6 Cyclization by Intramolecular Homolytic Substitution

Radical cyclizations can also occur by an intramolecular substitution pathway, in which the radical cleaves a single rather than a multiple bond. These reactions can occur in an *exo* or *endo* fashion, as shown in Equation 2.60, and *exo* intramolecular homolytic substitutions are typically favored in formation of small rings. The homolytic cleavage almost always involves a weak inter-heteroatom bond, and the examples in Equation 2.60 show that the ability to obtain a suitable geometry for a back-side displacement is crucial.¹⁹⁰



There are a few examples of relative asymmetric induction in intramolecular homolytic substitution reactions of peroxides. Cyclizations occur in 3-*exo* and 4-*exo* modes to provide mainly *trans*-disubstituted oxetanes and oxiranes, as illustrated in Equation 2.61. The tandem addition/homolytic substitution reactions of unsaturated peroxides are conducted by the hydrogen transfer method.^{190b,191}

The effects of various substituents on the related 5-*exo* homolytic substitutions have also been studied, and representative examples are shown in Equation 2.62. As a rule, *trans* isomers are formed with modest selectivities for 1,2-disubstituted radicals, while 1,3- and 1,4-disubstituted radicals provide predominately *cis* isomers in low selectivities.



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Model

These guidelines differ for the related hexenyl radical cyclizations, where the *cis/trans* selectivity alternates around the ring for disubstituted substrates. Transition state model 136 accounts for these observations. The peroxide oxygen is placed on the “flap” of the envelope to allow the best possible alignment for backside attack. The favored isomer arises from the placement of R², R³, and R⁴ in the indicated positions. The good level of *trans* 1,2-selectivity observed for the vicinal system is reminiscent of the related radical cyclizations (Eq. 2.22).

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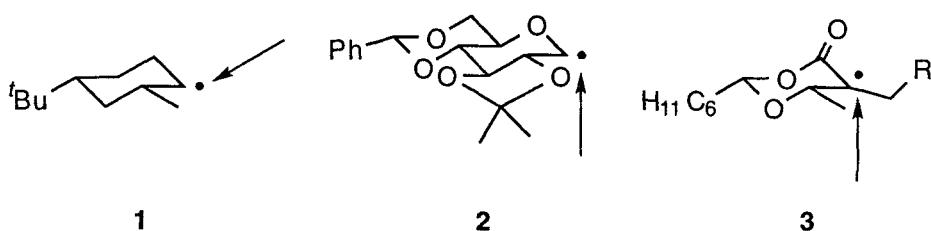
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Chapter 3

Substrate Control: Cyclic Systems

3.1 Cyclic Radicals

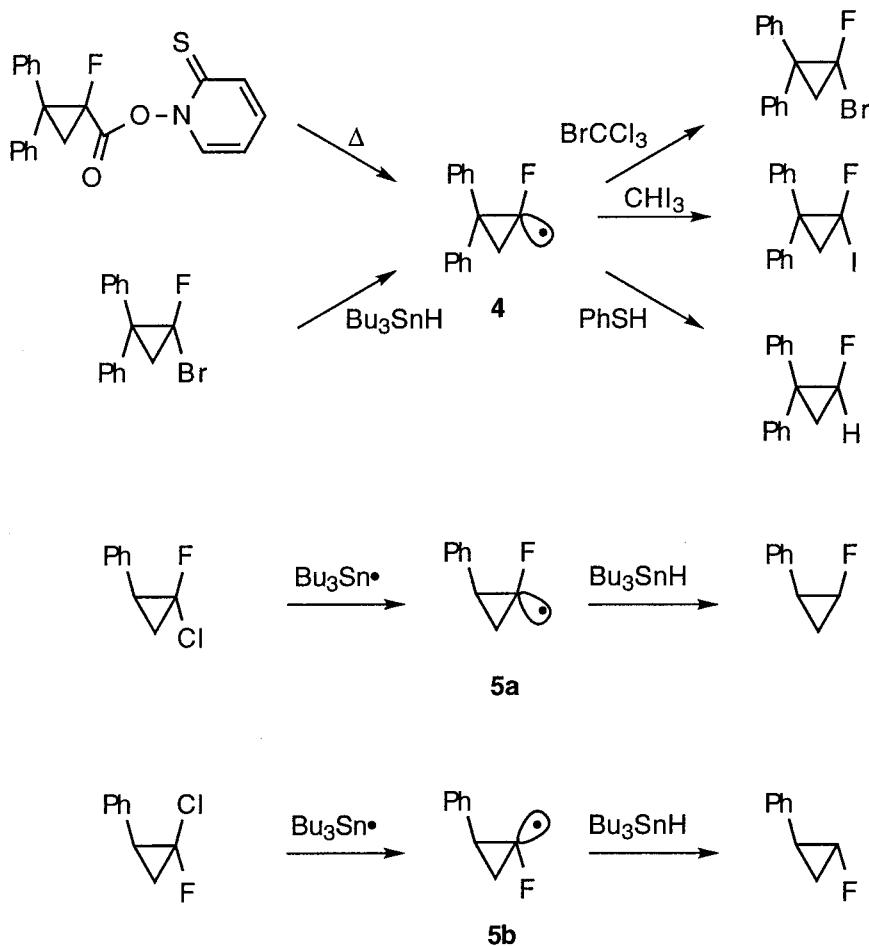
Substrate-controlled diastereoselection can usually be explained or predicted when the controlling stereocenter is incorporated into a cyclic four-, five- or six-membered radical.¹ With these ring systems the number of reactive conformers is reduced and the shielding substituent remains on one face of the ring system. Because of steric reasons the attack occurs preferentially *anti* to the shielding substituent as in radical **1**. In some examples, stereoelectronic effects (radical **2**) or specific shielding by exocyclic substituents at a prochiral center (radical **3**) can lead to *syn* addition.



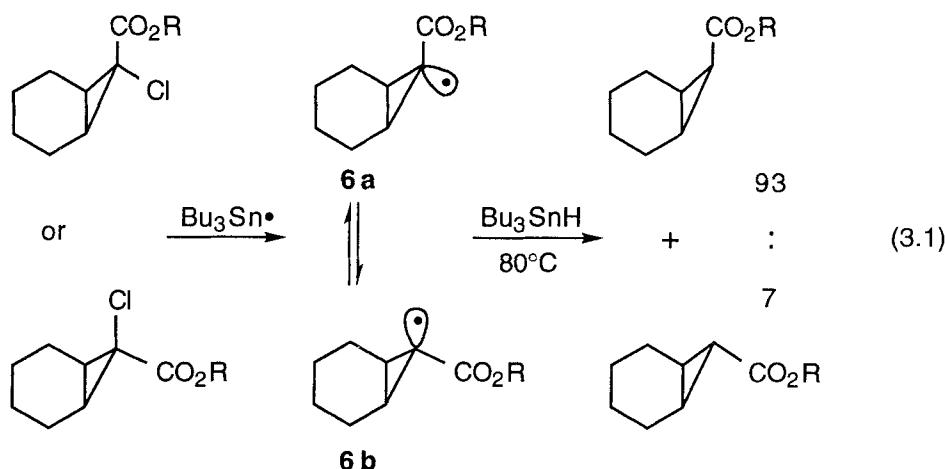
3.1.1 Three- and Four-Membered Cyclic Radicals

The diastereoselectivity of β -substituted cyclopropyl radicals depends upon the influence of the substituents on the rate of the inversion of the σ -radical, and, if inversion is fast, on the shielding of the two faces of the cyclopropyl ring. With α -fluoro-substituted cyclopropyl radicals like **4**, **5**,

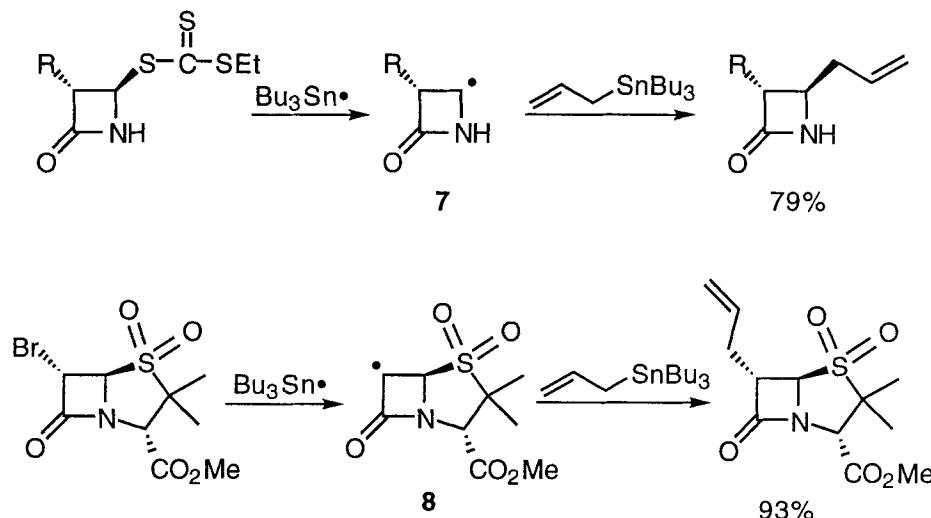
and **6**, the inversion rate is so slow that radical reactions can occur with retention of configuration.²



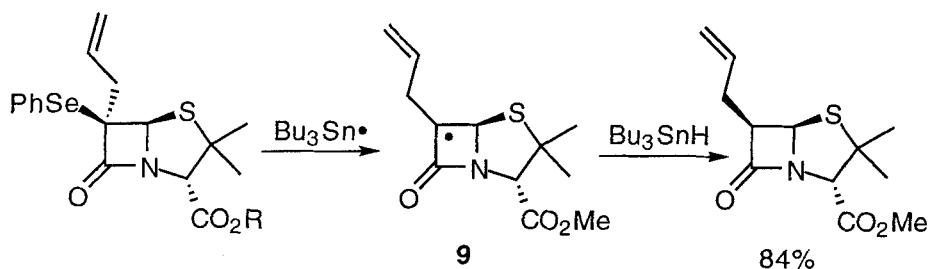
The use of higher reaction temperatures or the presence of α -substituents like chlorine, ester, nitrile or alkyl groups increases the inversion rate of the σ -radical, so that shielding effects can control the reaction.³ Equation 3.1 shows that bicyclic radical **6** is attacked predominantly from the convex side, independent of the configuration of the precursor. The stereochemistry can be influenced by the trapping reagent.^{3b}



Studies on stereoselective radical reactions with four-membered rings have focused mainly on β -lactam radicals. Attack *anti* to the shielding β -substituent predominates whether the radical center is positioned next to the nitrogen as in **7**⁴ or next to the carbonyl group as in **8**.⁵



The configuration of the product can be reversed by exchanging the substituent on the β -lactam with that on the trap. For example, hydrogen atom abstraction by the tertiary radical **9**⁶ gives the opposite substitution pattern of the product as compared to allylation of radical **8**.



3.1.2 Five-Membered Cyclic Radicals

3.1.2.1 Endocyclic Substituents

A β -substituent shields the *syn* face of cyclopentyl radical **10** so that *anti* attack predominates. The amount of *anti* attack depends upon the radical trap and upon the nature of the shielding substituent. Thus, by decreasing the reactivity of the alkene (Table 3-1 on left) or by increasing the bulk of the shielding substituents (Table 3-1 on right), the stereoselectivity increases.^{1,7}

Table 3-1. Dependence of the stereoselectivity of radical **10** on the trapping alkene and on the shielding substituent X

radical trap (X = OEt)	stereoselectivity (<i>anti</i> : <i>syn</i>)	β -substituent (acrylonitrile as trap)	stereoselectivity (<i>anti</i> : <i>syn</i>)
	72 : 28	OEt	77 : 23
	77 : 23	O <i>t</i> Bu	80 : 20
	88 : 12	NHAc	86 : 14
	90 : 10	Me	92 : 8

10

Figure 3-1 shows that the stereoselectivity of radicals **11–14** is similar to that of **10**.^{7–10}

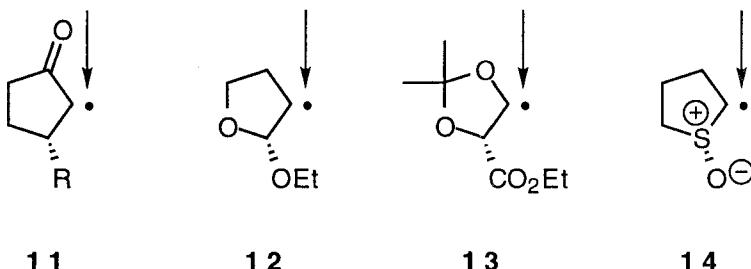
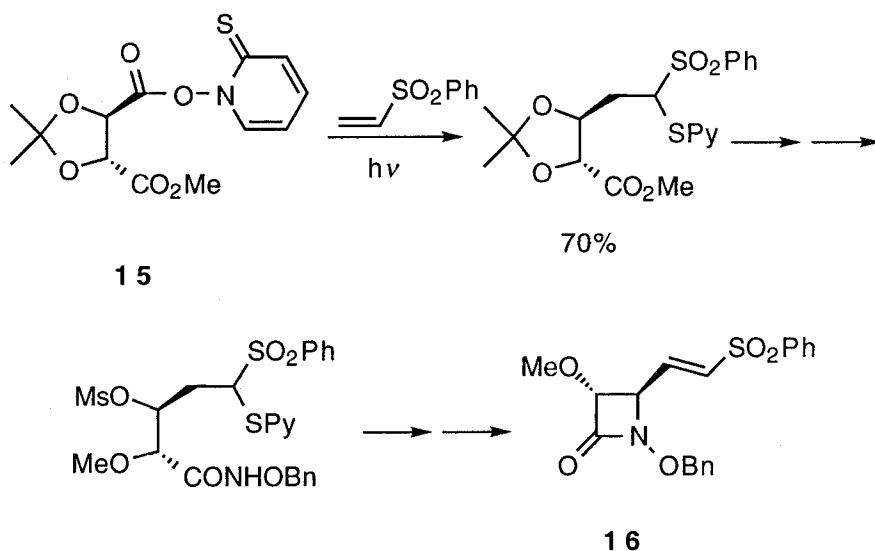


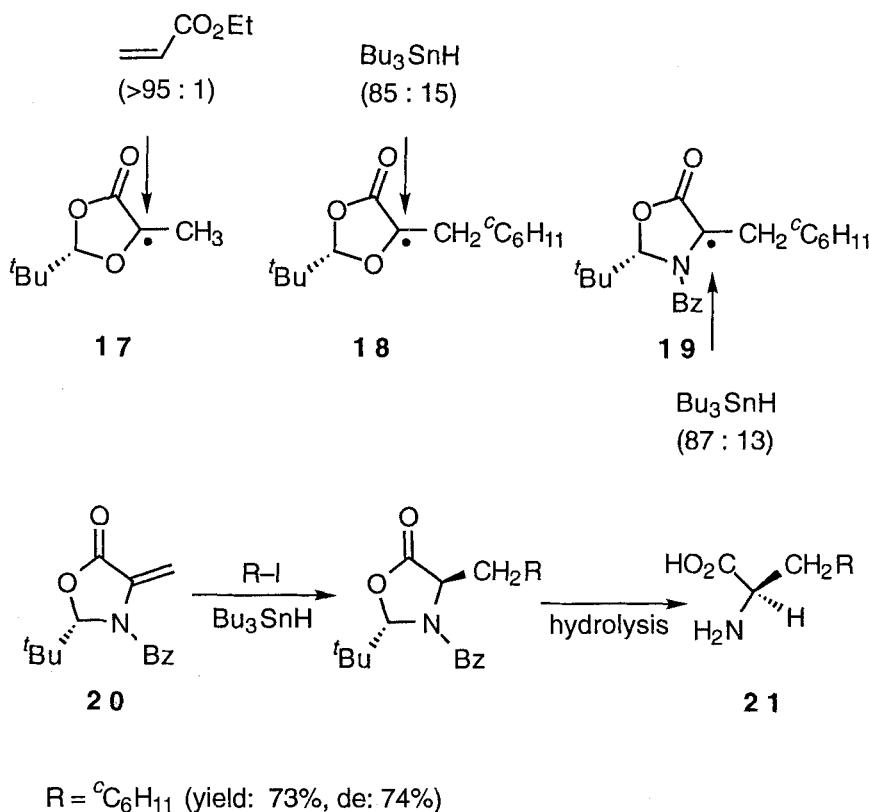
Figure 3-1. Anti Attack on Radicals 11–14.

This *anti* stereoselectivity in substituted five-membered rings was used in the synthesis of monobactam **16** starting from the Barton ester **15**.¹¹



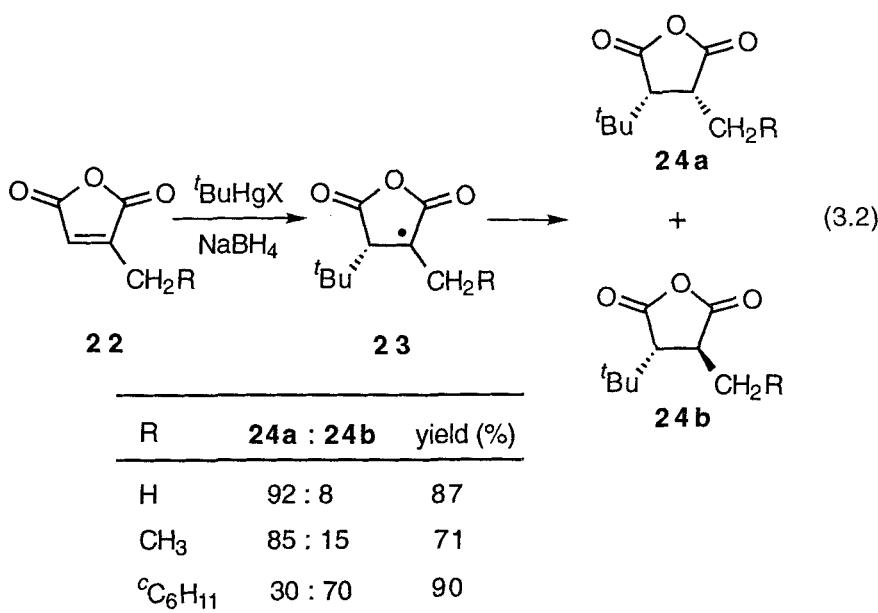
γ -Substituents as in radicals **17**¹² and **18**¹³ can also lead to *anti* addition products. Surprisingly, the substitution of the adjacent ring oxygen by an amide function (radical **19**) gives rise to *syn* attack.¹⁴ Perhaps the pyramidalization of the nitrogen and/or a preferred orientation of the substituent at the exocyclic prostereocenter (see Chapter 3.1.2.2) causes this

reversal of stereoselectivity. Radical addition reactions of alkene **20** can be used for the synthesis of α -amino acids **21**.¹⁴

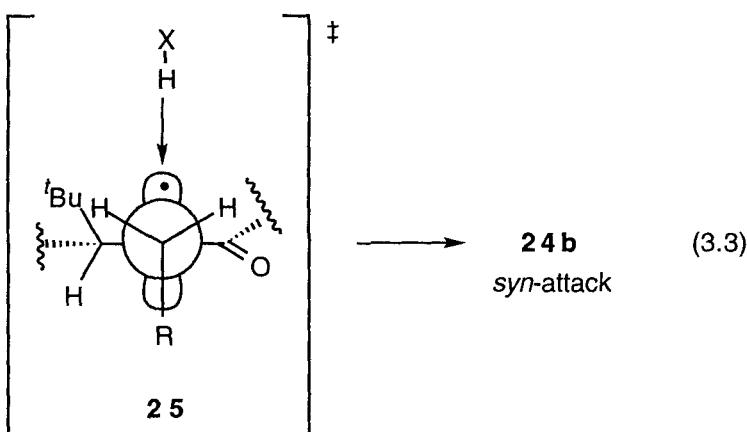


3.1.2.2 Exocyclic Substituents

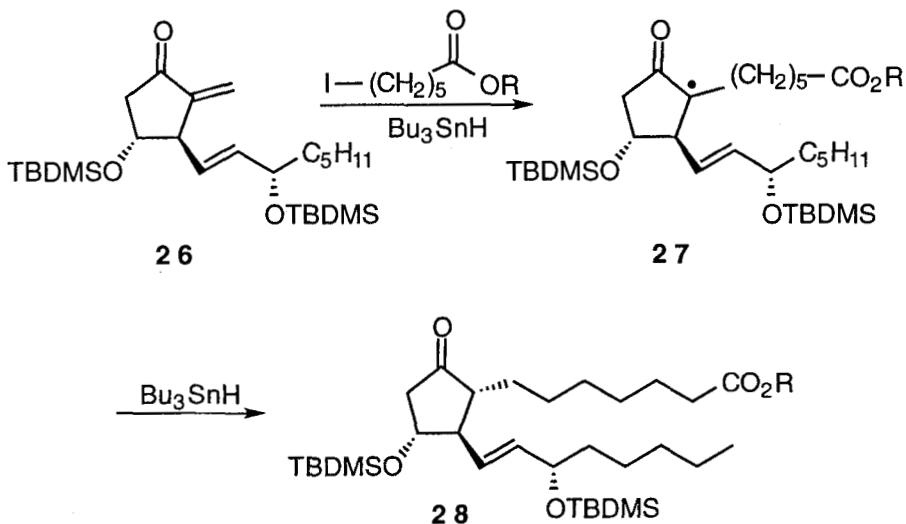
Radical reaction of methyl maleic anhydride (**22**, R = H) with $t\text{BuHgX}/\text{NaBH}_4$ yields mainly *cis* product **24a** (R = H) via *anti* attack at the intermediate radical **23** (R = H).¹⁵ The bulkier the attacking radical the more *cis* product is formed. Also the size and the reactivity of the hydrogen donor play a role.^{15c} But by increasing the size of substituent R, the amount of *syn* attack increases and the *trans* isomer **24b** even predominates when R = cyclohexyl (Eq. 3.2).¹⁶



According to AM1 calculations, transition state **25** is of lowest energy if R is bulky. In this transition state, the *tert*-butyl group and the substituent R are remote and one hydrogen atom at the prostereocenter points towards the bulky *tert*-butyl group and the other towards the carbonyl group (A-strain). The hydrogen atom abstraction occurs *anti* to a bulky substituent R at the prostereocenter and this corresponds to a *syn* attack with respect to the *tert*-butyl group at the stereogenic center (Eq. 3.3).¹⁶

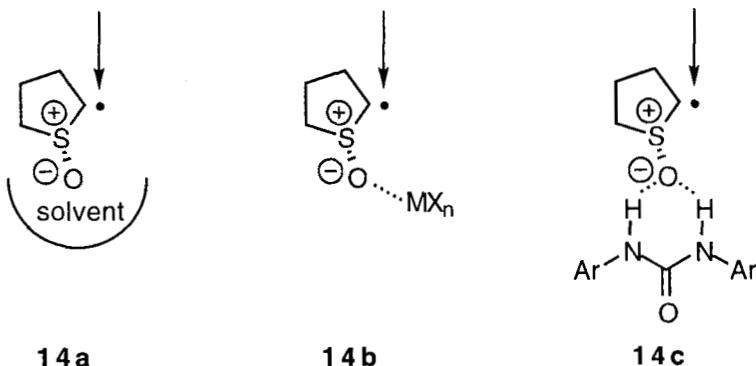


This effect was applied in the synthesis of prostaglandin **28** via radical addition to alkene **26**.¹⁷ The intermediate radical **27** is attacked by Bu_3SnH *syn* to the shielding alkenyl substituent. The configuration of the γ -substituent also favors this stereochemistry.



3.1.2.3 Additive and Medium Effects

The effective size of a polar substituent can be influenced by increasing the polarity of the solvent (**14a**), and by complexing with Lewis acids (**14b**) or hydrogen bond donors like diaryl ureas (**14c**).



Thus, the level of the *anti* attack of acrylonitrile or allylstannane to radicals **10**,¹ **14**,¹⁸ and **29**¹⁹ increases if the polarity of the solvent is raised, if hydrogen bond donors are added, or if Lewis acids like ZnBr₂, LiClO₄ or bulky organoaluminum compounds are present. Representative results are summarized in Table 3-2.

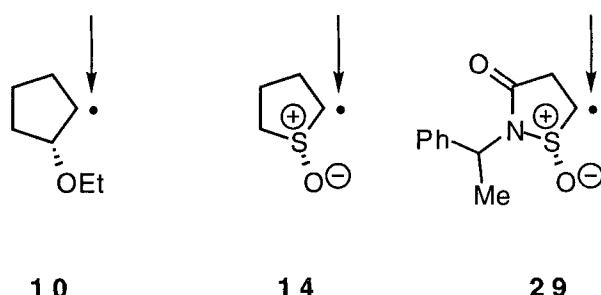


Table 3-2. Influence of the solvent and Lewis acid on the *anti:syn* ratio in the addition of acrylonitrile to **10** and allyltributylstannane to **14** and **29**

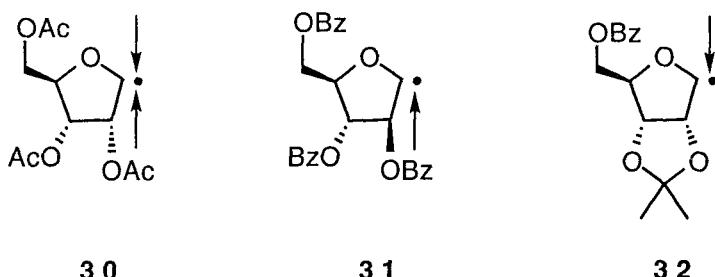
Radical	C ₆ H ₁₂	CH ₂ Cl ₂	THF	CH ₃ CN	C ₂ H ₅ OH	CF ₃ CH ₂ OH
10	68 : 32	77 : 23	76 : 24	81 : 19		
14	70 : 30 ^{a)}	82 : 18	69 : 31	77 : 23 ^{b)}	83 : 17	
	87 : 13 ^{c)}	98 : 2 ^{d)}	88 : 12 ^{e)}	90 : 10 ^{f)}		
29	90 : 10				94 : 6	98 : 2

^{a)} Benzene as solvent, ^{b)} C₂H₅CN as solvent, ^{c)} benzene as solvent in the presence of 1 equiv diaryl urea, ^{d)} in the presence of 1.1 equiv MAD (methyl-aluminum bis(4-methyl-2,6-di-*tert*-butylphenoxide), ^{e)} in the presence of ZnBr₂, ^{f)} In the presence of excess LiClO₄.

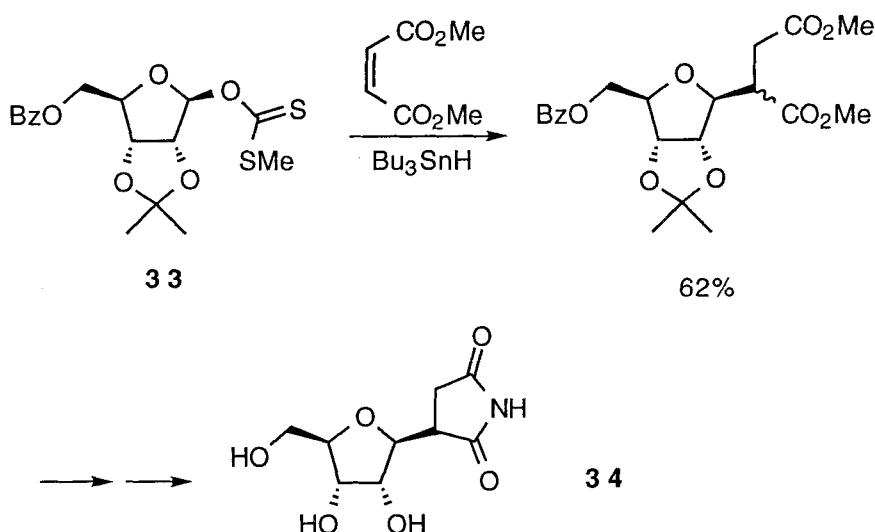
The solvents and Lewis acids influence the stereoselectivity by solvation or complexation of the shielding oxygen function, thereby increasing its effective size.

3.1.2.4 Multiple Substitution

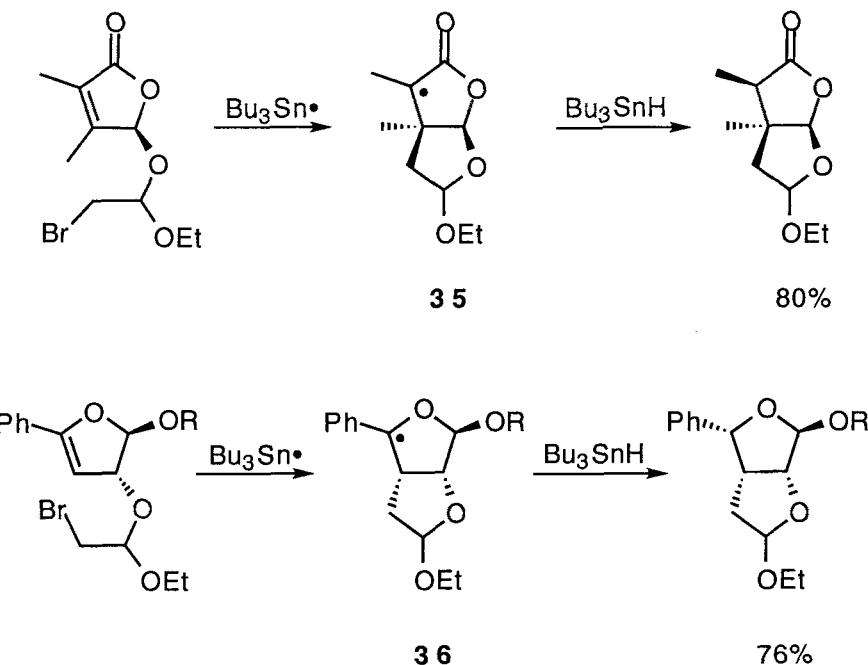
As expected, five-membered radicals with *trans* substituents often react with low stereoselectivity. Thus, radical **30** reacts completely unselectively.²⁰ However, inversion of the configuration at C-2 (radical **31**)²¹ or formation of a dioxolane ring (radical **32**)²² again yields products with high stereoselectivity.



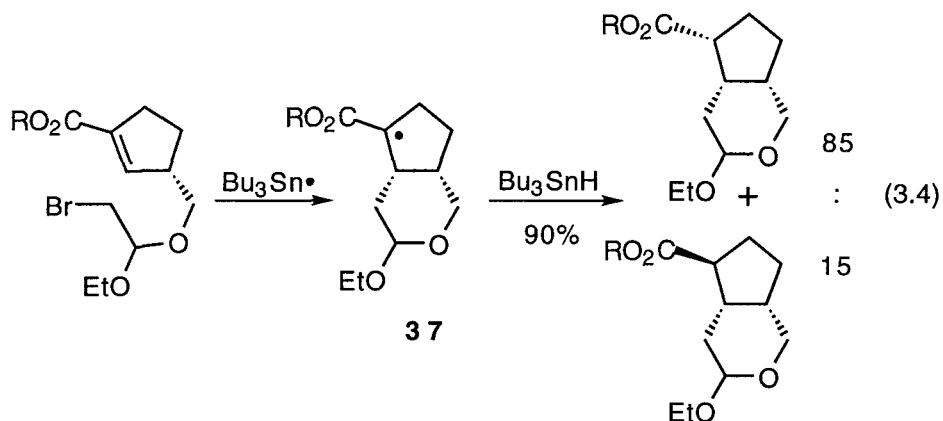
This shielding effect of an annulated ring has been used in the synthesis of showdomycin starting from xanthate **33**.²²



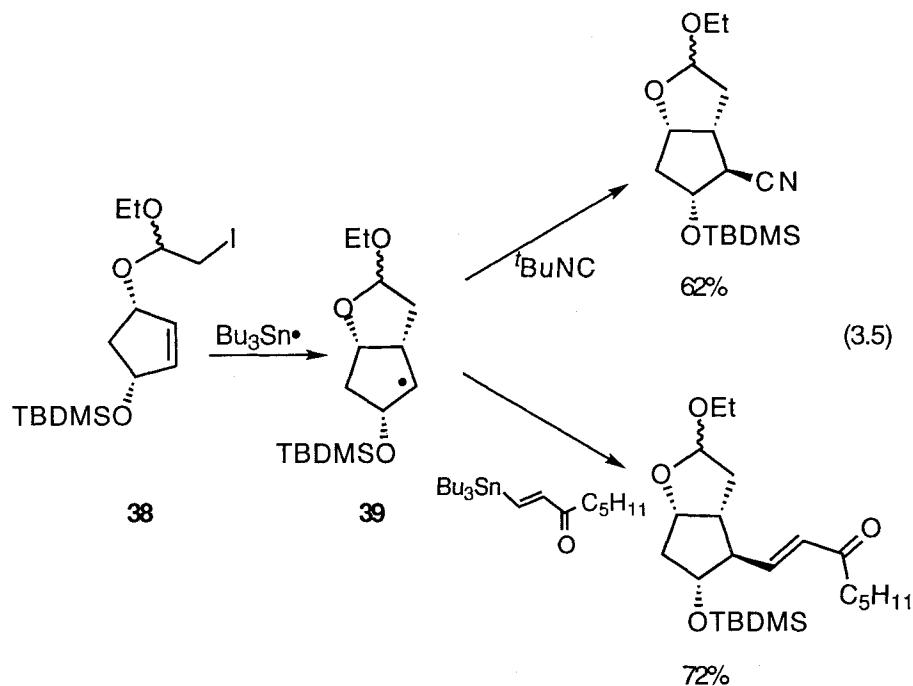
Shielding by a *cis*-annulated five-membered ring is very effective, as the stereoselective hydrogen atom abstractions of radicals **35**²³ and **36**²⁴ demonstrate.



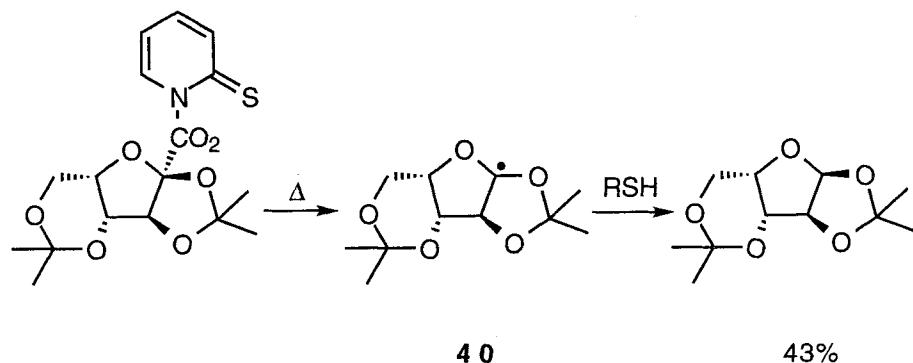
But annulation of a six-membered ring in radical **37** leads to lower stereoselectivity (Eq. 3.4).²⁵



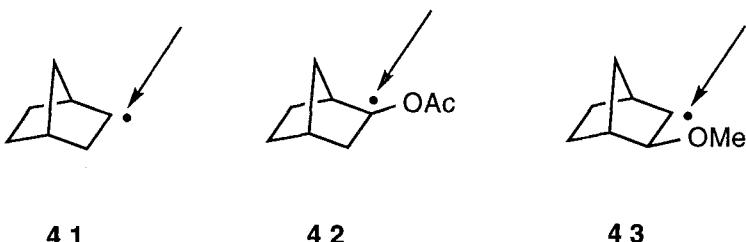
The three *cis* substituents of radical **39** generated via cyclization of **38** induce complete *anti* stereoselectivity in prostaglandin synthesis (Eq. 3.5).²⁶



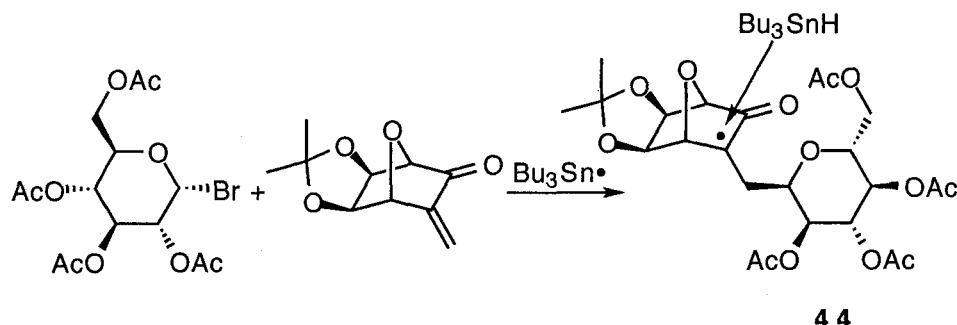
However, reaction from the concave side occurs in bridgehead radical **40**. The *cis*-annulation of the dioxolane ring is the driving force for the stereoselectivity.²⁷



A special class of bicyclic cyclopentyl radicals are norbornyl radicals like **41–43**. These are attacked predominantly from the *exo* side even if a methoxy group is shielding this face.^{7,28}

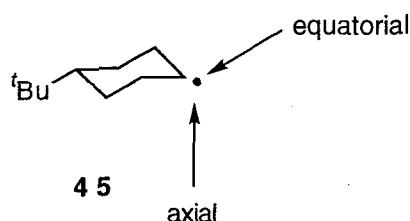


A selective hydrogen atom abstraction from the *exo* side of the oxanorbornyl radical **44** is a decisive step in the synthesis of C-disaccharides.²⁹



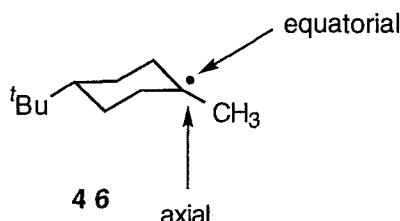
3.1.3 Six-Membered Cyclic Radicals

The reactions of unsubstituted and substituted cyclohexyl radicals show similar trends in stereoselectivity as the ionic reduction and alkylation reactions of the related cyclohexanones.³⁰ The stereoselectivity of *4-tert-butylcyclohexyl* radical **45** has been studied in detail.³¹ Ab initio and force field calculations show that axial attack is favored by torsional effects, whereas steric 1,3-repulsion favors equatorial attack. Thus, in abstraction reactions of small groups or atoms like OH, Cl, Br, or H, axial attack predominates. But addition to alkenes leads, in most cases, to preferential equatorial attack, especially if 1,2-disubstituted alkenes are used.



Reagent	axial : equatorial
$\text{RCO}_2 - \text{OH}$	80 : 20
$\text{Cl}_3\text{C} - \text{Cl}$	77 : 23
$\text{Bu}_3\text{Sn} - \text{D}$	70 : 30
$\text{Cl}_3\text{C} - \text{Br}$	69 : 31
$\text{H}_2\text{C} = \text{CHCN}$	45 : 55
$\text{H}_3\text{CCH} = \text{CHCN}$	26 : 74
$\text{iPrCH} = \text{CHCN}$	12 : 88

Because of 1,3-repulsion in the product, the related tertiary cyclohexyl radical **46** reacts to a higher degree from the axial position than the related secondary cyclohexyl radical **45**.



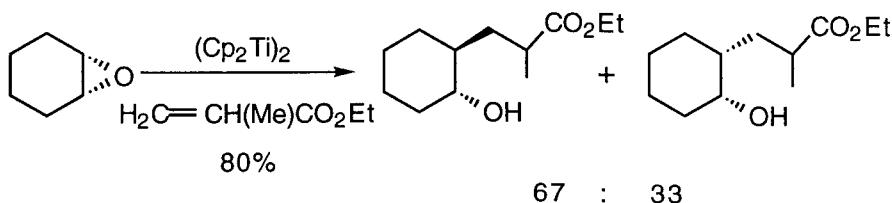
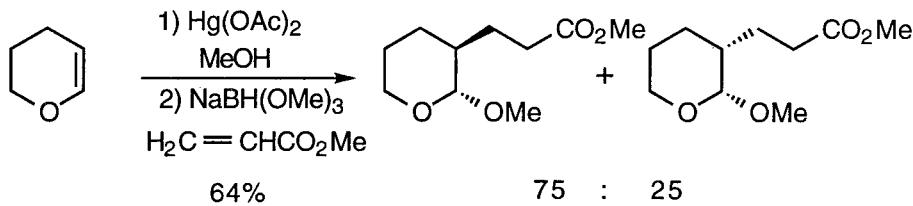
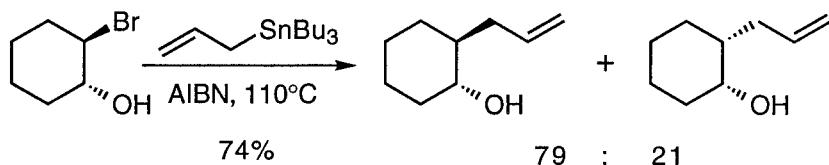
Reagent	axial : equatorial
$\text{Cl}_3\text{C} - \text{Cl}$	92 : 8
$\text{Bu}_3\text{Sn} - \text{H}$	89 : 11
$\text{H}_2\text{C} = \text{CHCN}$	64 : 36
$\text{H}_3\text{CCH} = \text{CHCN}$	40 : 60

3.1.3.1 Steric Effect of Substituents

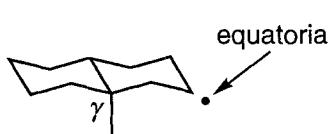
In general, *anti* attack is favored by β -substituents. An equatorial methyl group in **47** leads to an increase of the equatorial attack and an axial methyl group in **48** increases axial attack.³¹

	Reagent	Radical 47 axial : equatorial	Radical 48 axial : equatorial
47	$\text{RCO}_2 - \text{OH}$	—	90 : 10
48	$\text{Cl}_3\text{C} - \text{Cl}$	56 : 44	85 : 15
	$\text{Bu}_3\text{Sn} - \text{D}$	56 : 44	—
	$\text{Cl}_3\text{C} - \text{Br}$	51 : 49	85 : 15
	$\text{H}_2\text{C} = \text{CHCN}$	21 : 79	90 : 10
	$\text{H}_3\text{CCH} = \text{CHCN}$	<5 : 95	83 : 17

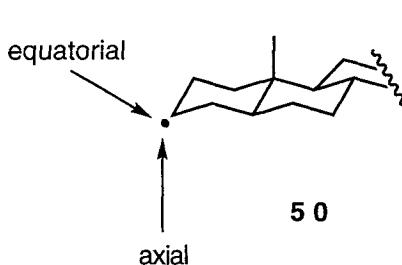
Oxygen functions in the β -position also act as shielding substituents.^{7,32}



Because of 1,3-interactions, the axial γ -substituent of radical **49** leads mainly to equatorial attack.³¹ An equatorial group in the γ -position seems to have only a negligible effect.

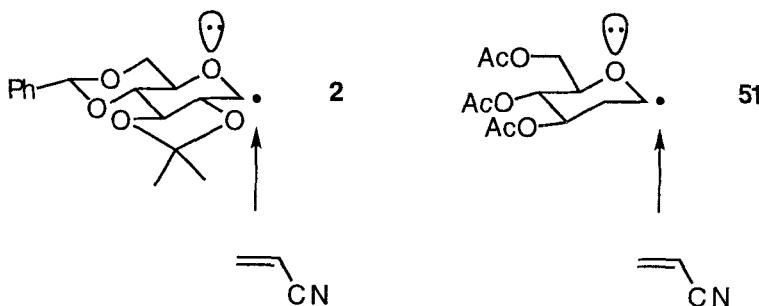
	Reagent	axial : equatorial
	$\text{Cl}_3\text{C}-\text{Cl}$	9 : 91
49	$\text{Cl}_3\text{C}-\text{Br}$	9 : 91
	$\text{H}_2\text{C}=\text{CHCN}$	3 : 97
	$\text{H}_3\text{CCH}=\text{CHCN}$	2 : >98

An axial δ -substituent influences the stereoselectivity only slightly. Thus, in the addition reaction of steroid radical **50**, the level of axial attack is slightly increased compared with radical **45**.

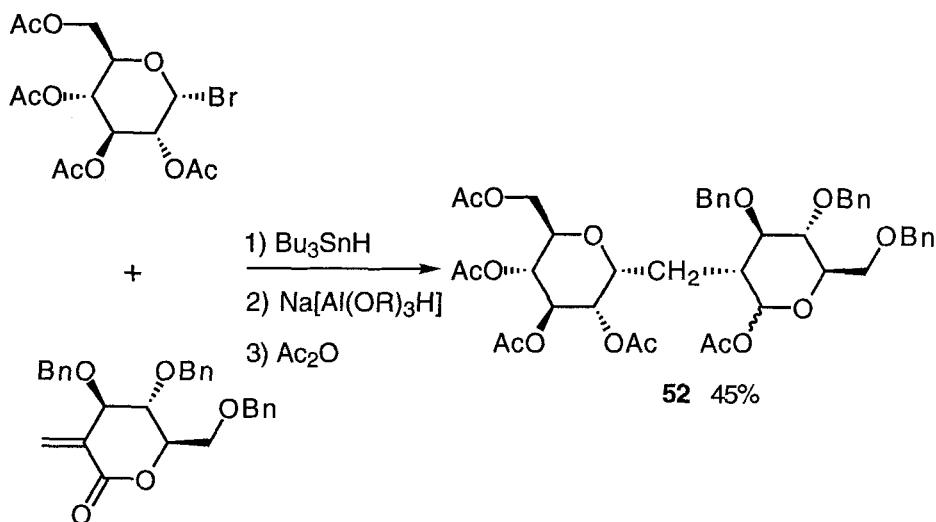
	Reagent	axial : equatorial
	$\text{H}_2\text{C}=\text{CHCN}$	70 : 30
50	$\text{H}_3\text{CCH}=\text{CHCN}$	35 : 65

3.1.3.2 Stereoelectronic Effects

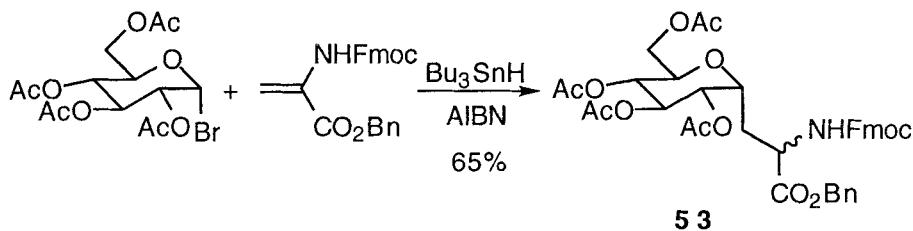
Stereoelectronic effects play an important role in reactions at the anomeric center of carbohydrate radicals. Thus, radicals **2** and **51** are attacked predominantly from the axial direction, although equatorial addition would be expected from 1,3-diaxial interactions and *syn* shielding by the β -substituent in **2**.^{20,33}



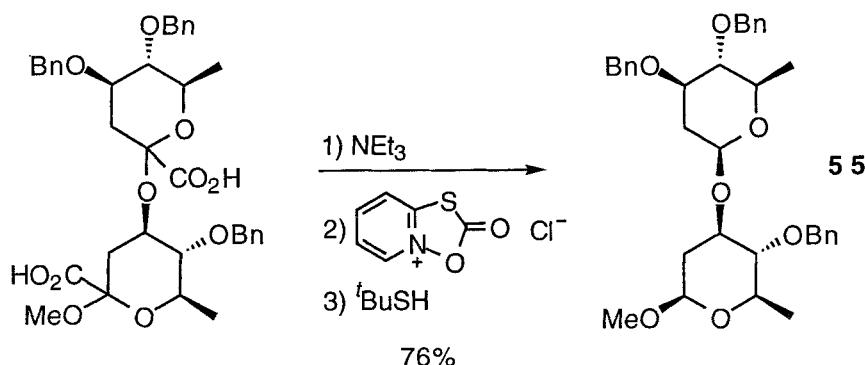
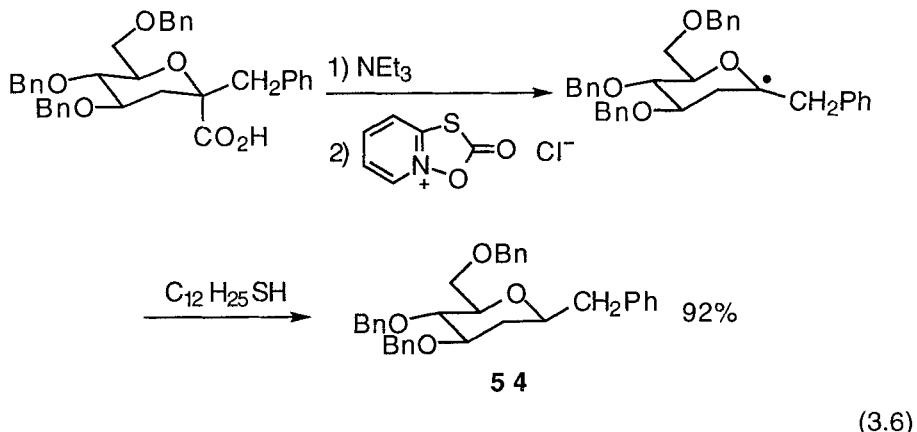
During the axial attack at radicals **2** and **51**, the single electron involved in forming the new bond and the electron pair at the oxygen remain in one plane so that a stabilizing interaction can occur. The highly selective C–C bond-forming reaction in the synthesis of C-kojibiose **52** uses this stereoelectronic effect.³⁴



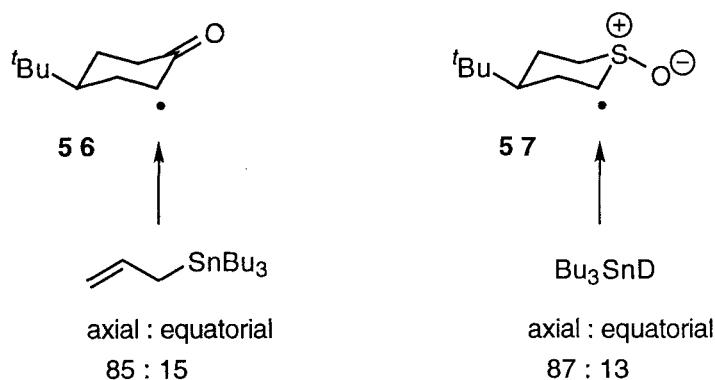
Amino acids can also be linked to carbohydrates by a C–C bond at the anomeric center. The stereoselectivity of the radical addition is very high but the stereoselectivity of the hydrogen atom abstraction at the acyclic radical forming product **53** is low.³⁵



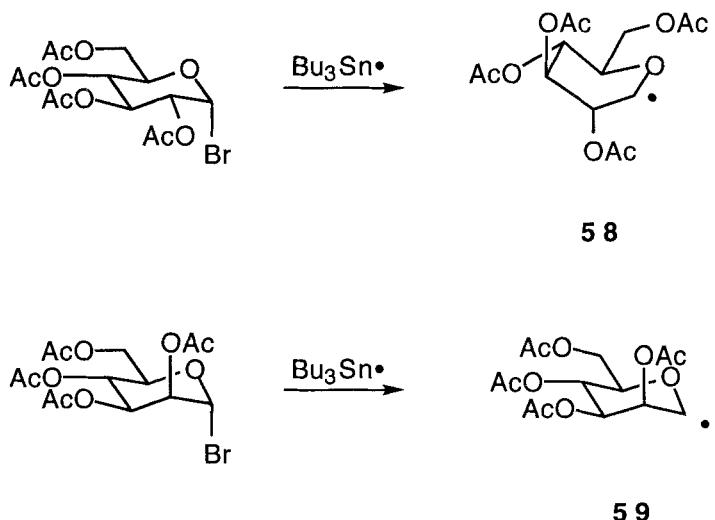
Equation 3.6 shows examples of axial hydrogen atom abstraction by the anomeric radical center. This yields β -linked C-glycoside **54**³⁶ and the analogous 2-deoxy- β -disaccharide **55**.³⁷



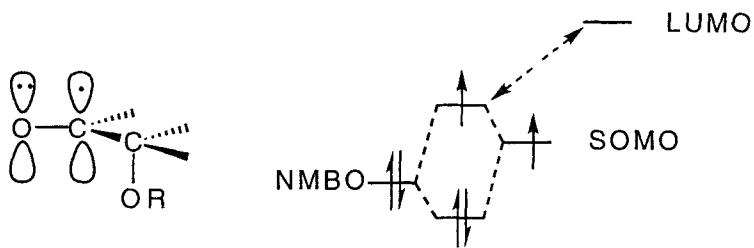
Stereoelectronic effects are not limited to carbohydrate radicals. Thus, the predominant axial attack on radicals **56** and **57** can also be explained by these interactions.^{38,39}



The conformations of radicals can also be influenced by stereoelectronic effects. For example, it has been demonstrated by ESR spectroscopy that glucosyl radical **58** adopts the boat conformation whereas mannosyl radical **59** remains in the chair conformation.⁴⁰



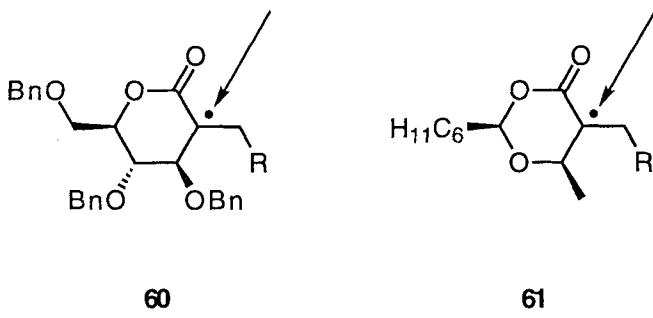
A conformation with the β -C–O bond in the plane of the singly occupied orbital (SOMO) at the anomeric radical center is favored because the energy of the SOMO is raised by interaction with the non-bonding electron pair (NMBO) of the ring oxygen. The energy gap between the SOMO and the lowest unoccupied orbital (LUMO) of the C–O bond is small enough so that the eclipsing interactions in the boat conformer **58** are compensated by this electronic interaction.⁴¹



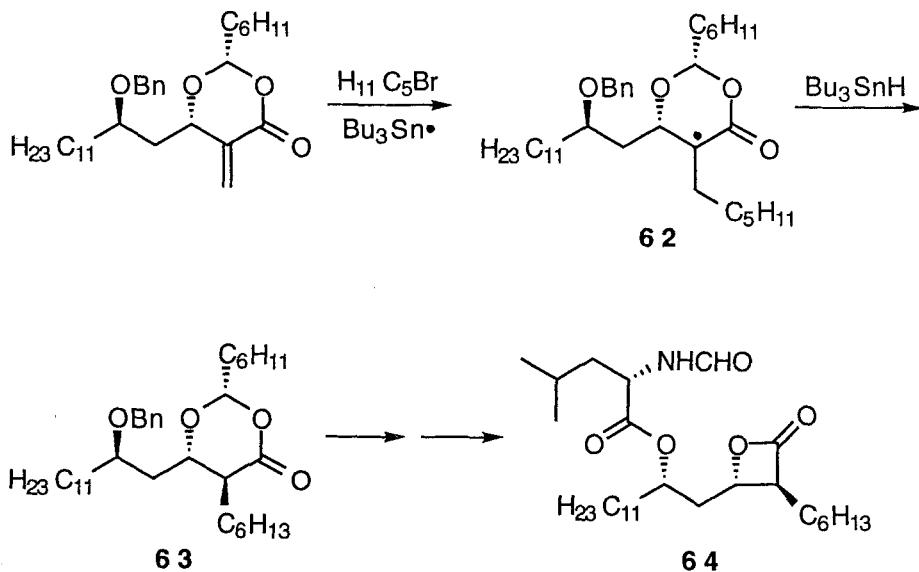
Carbohydrate radicals without the ring-oxygen in the α -position or without an electron withdrawing β -substituent do not change their conformation.^{41,42}

3.1.3.3 Exocyclic Substituents

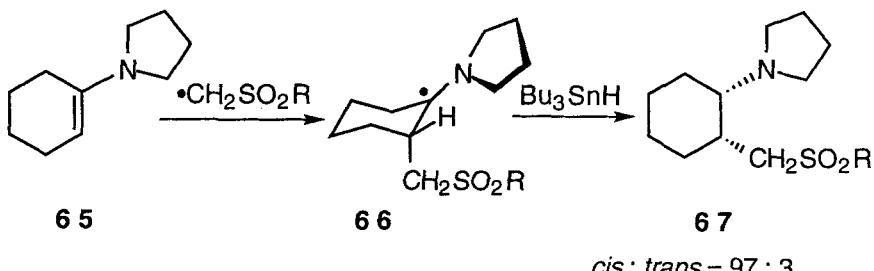
Substituents at exocyclic, prostereocenters can influence the stereo-selectivity. Thus, radicals **60** and **61** are attacked *syn* to the β -substituents at the stereogenic center.^{34,43} A transition state analogous to structure **25** wherein the substituent at the prostereocenter shields the *anti* face explains this *syn* selectivity. The selective *syn* attack at radical **60** leads to the C-kojibiose derivative **52**.



A new synthesis of tetrahydrolipstatin (**64**) uses this effect in a stereoselective hydrogen atom abstraction step (**62** \rightarrow **63**).⁴⁴



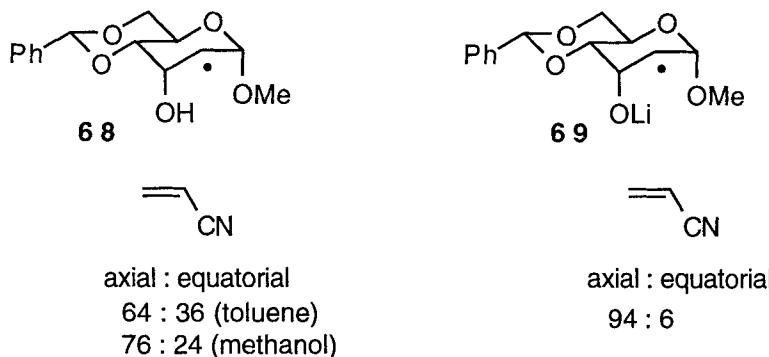
A substituent at the radical center can also influence the orientation of the β -substituent. The high stereoselectivity of the radical addition at enamine **65** can be explained by a preferred axial orientation of the β -substituent in the intermediate radical **66**. This orientation minimizes the allylic strain (see Chapter 4) between the aminoalkyl radical and the β -substituent and leads mainly to *cis* product **67** (*cis/trans* = 97/3).⁴⁵



3.1.3.4 Medium Effects

As with five-membered rings the stereoselectivity of six-membered cyclic radicals can also be influenced by the solvent or by salts if shielding β -oxygen functional groups are present. This can be demonstrated by the

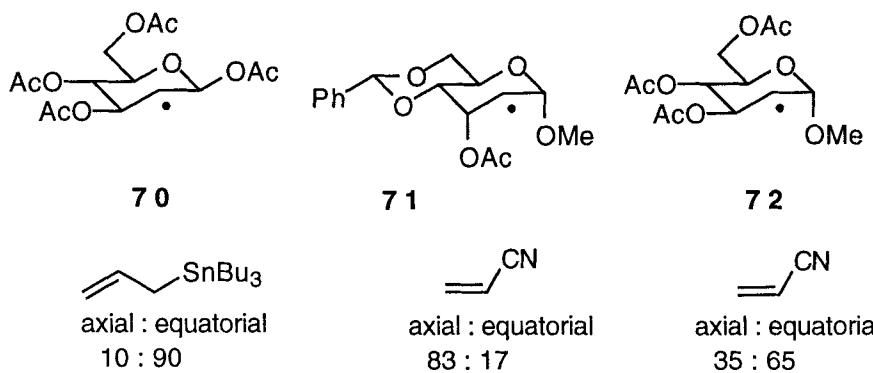
addition of acrylonitrile to glycosyl radical **68**. The axial/equatorial addition ratio increases slightly when the solvent is changed from toluene to methanol, and the lithium salt **69** reacts with high axial selectivity.^{1,46}



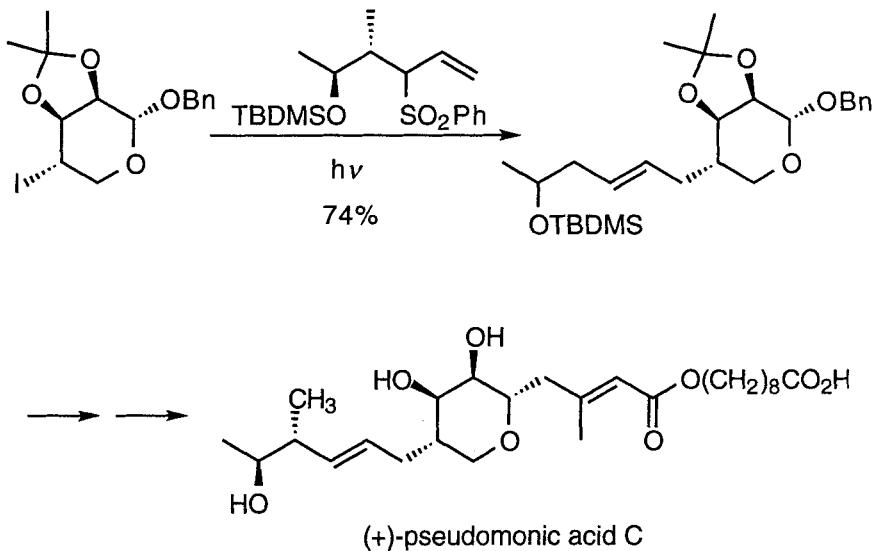
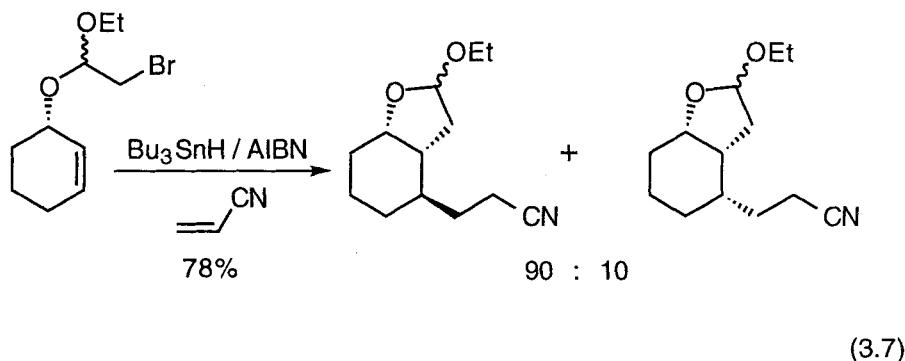
Clearly, solvation and/or coordination of the axial substituents increase the *axial* attack.

3.1.3.5 Multiple Substitution

In carbohydrate radicals, more than one substituent usually influences the stereoselectivity. As expected, *anti* attack increases if two β -substituents are *cis* to each other (radicals **70** and **71**) and low selectivity is observed with *trans* substituents (radical **72**).^{1,46}

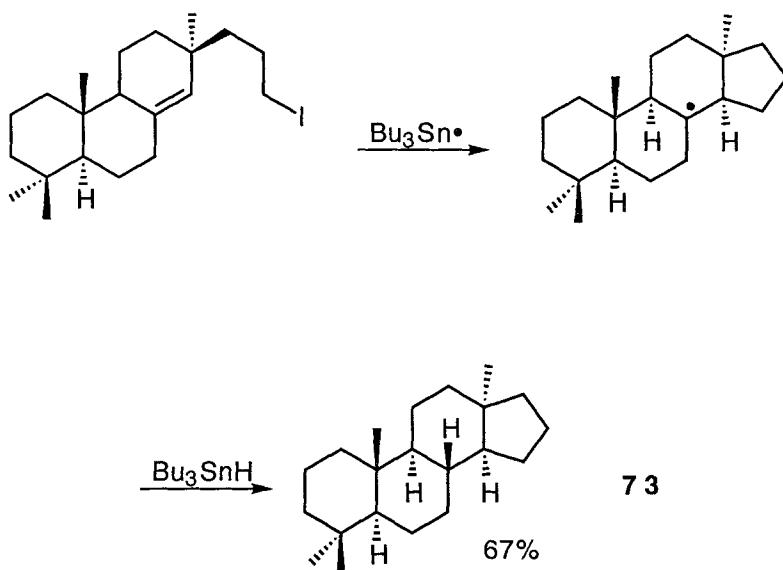


The examples of Equation 3.7 demonstrate that the *cis*-annulation of five-membered rings in β,γ -position also increases the level of *anti* attack.⁴⁷



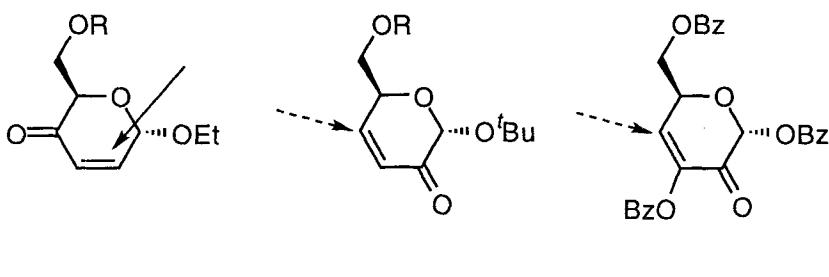
This selectivity decreases if the second ring is annulated in a *trans* fashion as it can occur if the second ring is a six-membered ring.

Bridgehead radicals between two six-membered rings preferentially yield *trans* annulated bicycles. In the synthesis of androsterane derivative 73, the *trans* ring fusion is obtained exclusively despite the strong steric hindrance due to a *cis* annulated cyclopentane ring and an axial methyl group in γ -position.⁴⁸

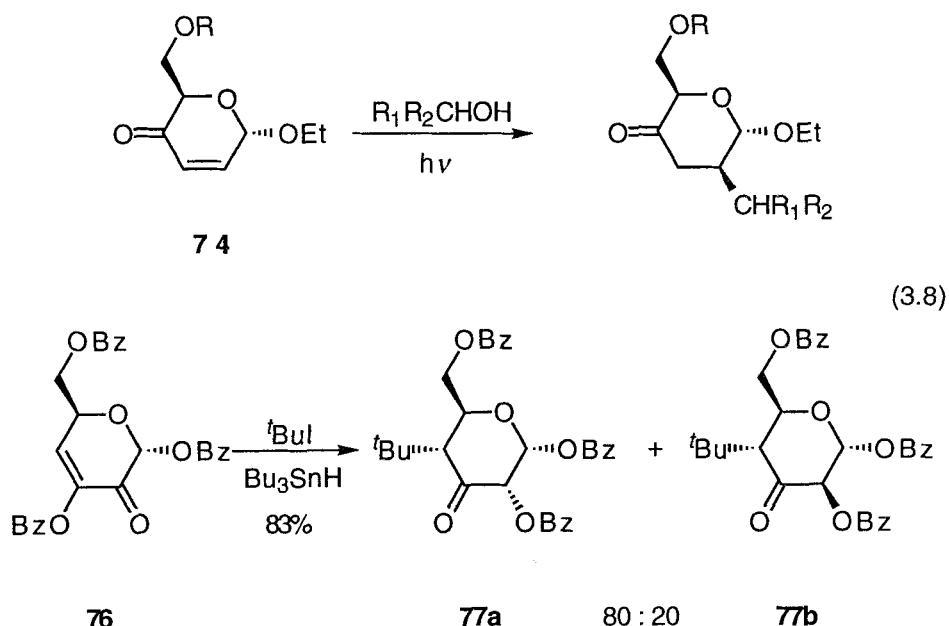


3.2 Cyclic Radical Traps

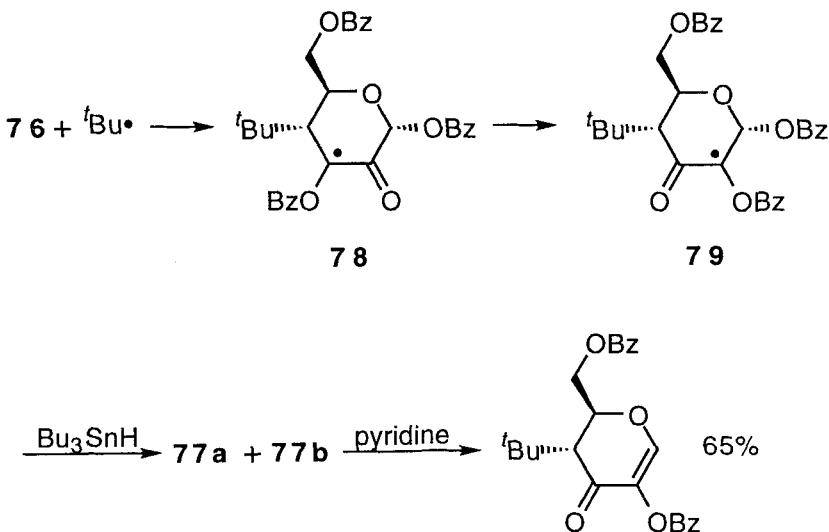
At present, stereoselective reactions with chiral, cyclic radical traps are limited to five- and six-membered alkenes. Radical addition to enolones **74**–**76** have been studied in detail. In all cases the addition occurs *anti* to the substituent that is β to the olefinic carbon undergoing attack.^{49,50}

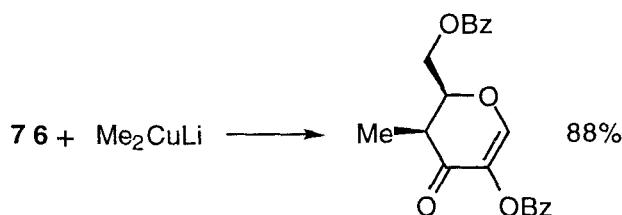


Examples of reactions of alkenes **74** and **76** are given in Equation 3.8.

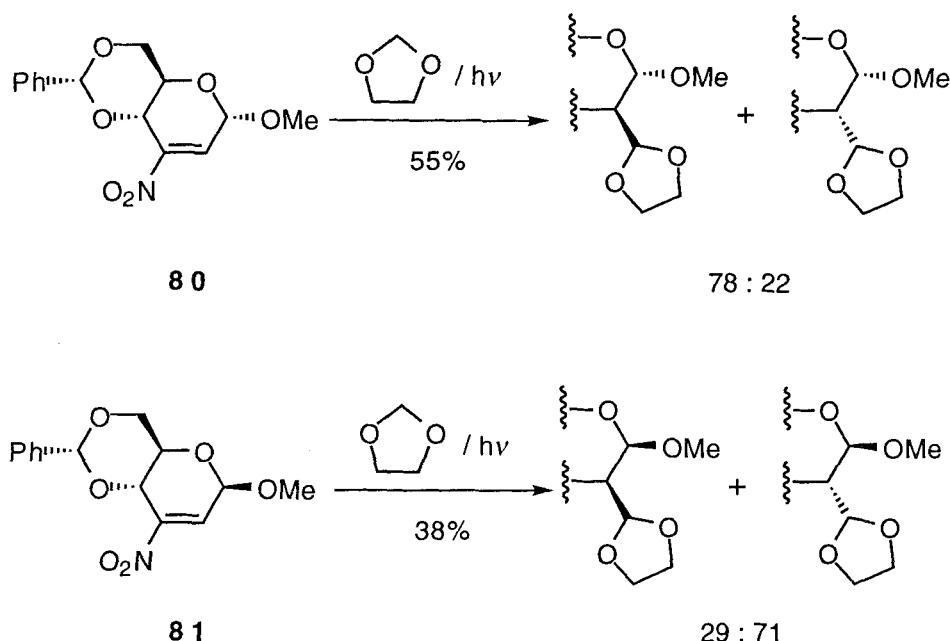


The reaction of enolone **76** gives radical **78**, which undergoes a migration of the benzoyl group (**78** → **79**) with subsequent hydrogen atom abstraction (**79** → **77a,b**).⁵⁰ Interestingly, the corresponding cuprate addition to **76** occurs with *cis* stereoselectivity.⁵¹

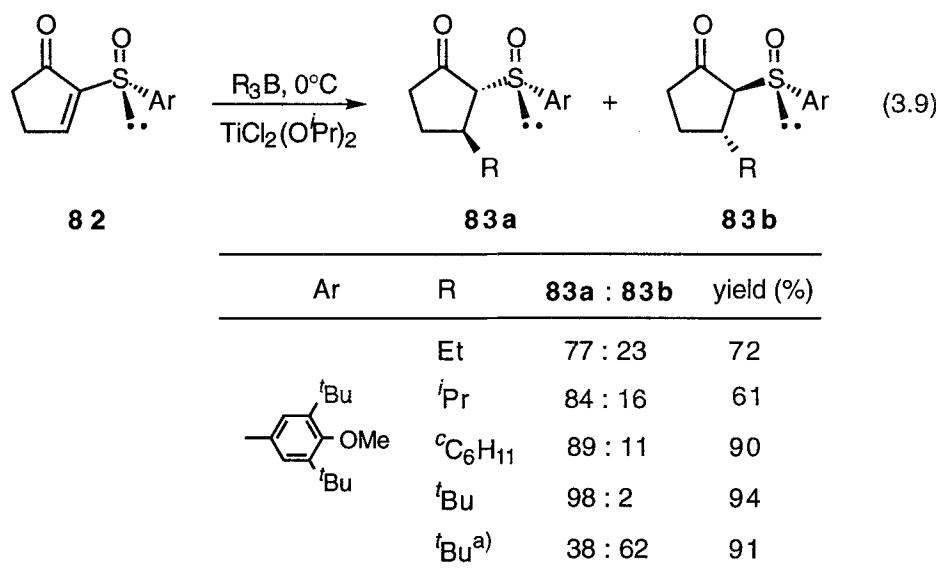




The stereoselectivity of the hydrogen atom abstraction is reversed when there is a β -methoxy group at the anomeric center of enolone **76**. In a similar way, α - and β -anomers **80** and **81** give C-*gluco-* and C-*manno-*configured products, respectively.⁵²

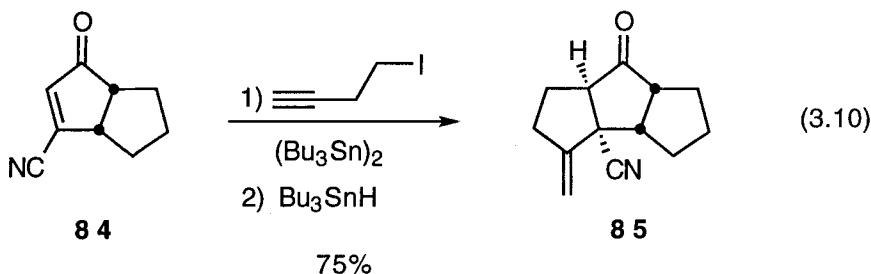


With α -sulfinylcyclopentenones, 1,3-induction by the stereogenic sulfinyl group can be observed if the aryl group carries bulky substituents. In most cases strong Lewis acids are needed for high stereoinduction. Thus, alkene **82** is attacked *anti* to the aryl group if the oxygen atoms of the ketone and the sulfoxide are chelated by a bidentate Lewis acid.⁵³ In the absence of this Lewis acid the stereoselectivity is low and reversed (Eq. 3.9).

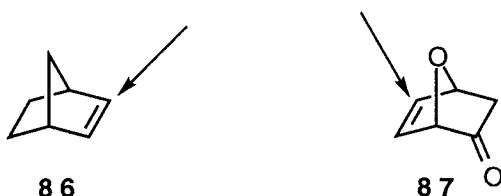


^{a)} without Lewis acid

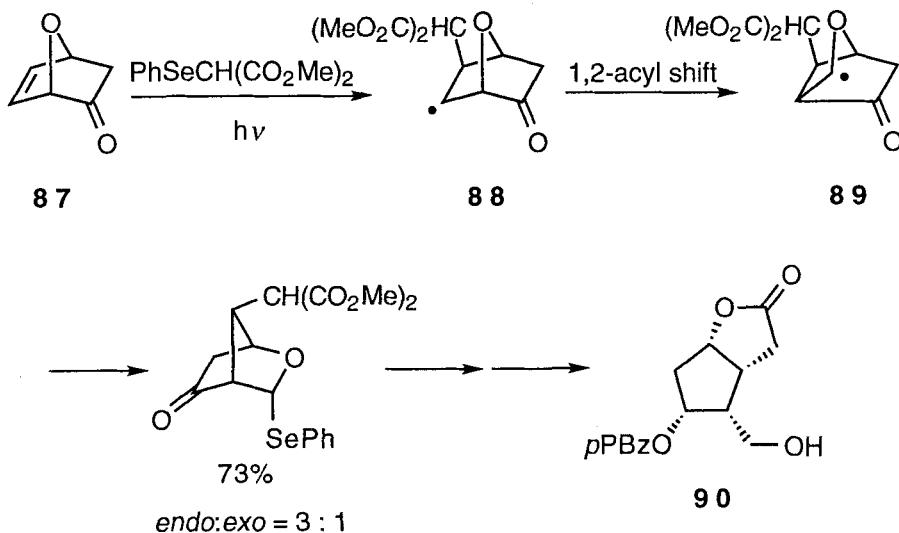
Equation 3.10 demonstrates that *cis*-annulation of a second ring yields the *anti* adduct with high stereoselectivity (**84** → **85**).⁵⁴



Norbornene **86**⁵⁵ and heterosubstituted norbornenes like **87**⁵⁶ are attacked also by radicals mainly from the *exo* face.



A synthesis of *cis*-Corey lactone **90** uses this type of stereoselectivity.⁵⁶ However, the intermediate radical **89** is attacked preferentially from the *endo* face because of the shielding effect of the *syn* substituent at the methylene bridge.



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Chapter 4

Substrate Control: Acyclic Systems

4.1 Acyclic Radicals

Whereas stereoselective reactions of cyclic radicals have been known since the extensive studies carried out in the 1980's,¹ reactions of acyclic radicals were long thought to be universally unselective. However, in the 1990's it became clear that acyclic systems can also react stereoselectively, and thorough work has led to an understanding and prediction of these reactions.²

A prerequisite for stereoselective reactions of acyclic radicals is the existence of a preferred conformation in which the substituents shield the two faces of the prochiral radical center to a different extent. Because activation energies for synthetically useful radical addition and abstraction reactions are low³ and their transition states are early, reactions of preferred ground state conformers lead to the major products in most cases. Figure 4-1 shows a radical that exists in the two minimum energy conformations **1A** and **1B**. According to ab initio calculations, the energies of these conformers differ by 1.5 kcal/mol.⁴ Attack of SiH₄ at conformer **1A** *anti* to the bulky *tert*-butyl group leads to a transition state **2A** that is 2.7 kcal/mol lower in energy than the analogous transition state **2B**.⁵ Thus, the most stable conformer of the radical leads to the most stable transition state. For a more quantitative analysis of this reaction, other modes of attack, especially the attack *syn* to the bulky group of conformer **1A**, must also be considered. In a quantum chemical treatment of a system whose two sp³ centers are connected to each other, six staggered transition states must be calculated.⁶

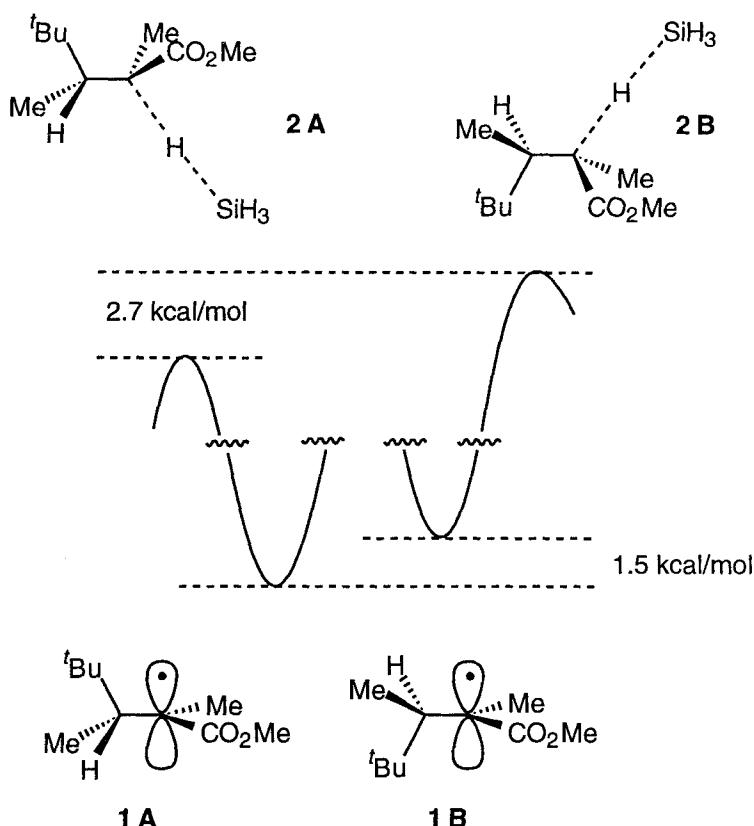
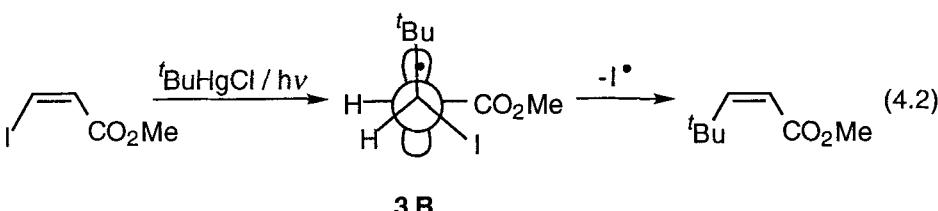
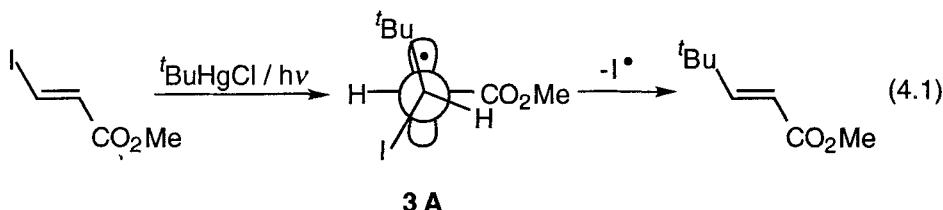


Figure 4-1. Energies of Ground State and Transition States of Ester-Substituted Radicals.

Intermolecular trapping reactions in which the major product results from the less stable conformer of the radical have not yet been identified. However such reactions are possible and it has been shown that a chiral olefin can yield the main product from its energetically unfavored conformer because the most stable conformer is too unreactive. These examples showing the importance of the Curtin–Hammett principle⁷ are described later on (Section 4.2).

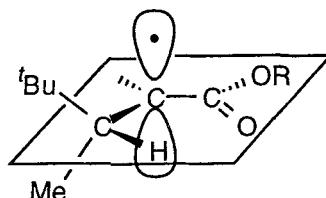
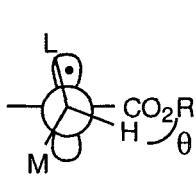
If the interconversion of two or more conformers is so slow that bimolecular trapping reactions can compete, the formation of the radical becomes important for the product ratio. In acyclic systems where the radical and the stereogenic centers are connected by single bonds, such cases seem to be very rare. But unimolecular reactions like the β -fragmentation of

an iodine atom in radicals **3A** and **3B** can compete with the equilibration of the radicals via rotation around the single bond. Therefore *E*-ido acrylate yields the *E*-product (Eq. 4.1) and *Z*-ido acrylate the *Z*-product (Eq. 4.2) predominantly.⁸



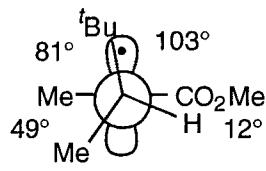
4.1.1 Allylic Strain Effects: Ester-Substituted Radicals

The question why conformer **1A** in Figure 4-1 is more stable than conformer **1B** is answered by allylic strain effects ($A^{1,3}$ -strain).⁹ ESR spectra and ab initio calculations have shown that ester-substituted radicals with a stereogenic center in β -position adopt the preferred conformation **4** where L is the large- and M the medium-sized substituent.^{4,5}



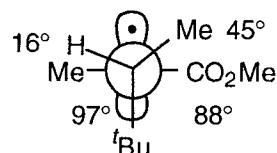
The ^{13}C coupling of 30 Gauss shows that radical **1** is a π radical and the ^1H β -coupling of 4.8 Gauss demonstrates that the dihedral angle between

the singly occupied orbital and the C–H bond at the stereogenic center is close to 90° .⁴ Thus, the dihedral angle θ between the C–H bond and the C–CO₂R bond is very small. According to ab initio calculations, conformer **1A** is 1.5 kcal/mol more stable than **1B**. In both conformers the bulky *tert*-butyl group is located in the middle between the two substituents at the radical center, but only in conformer **1A** does the small hydrogen atom point towards the oxygen atom of the vicinal ester group. Thus, allylic strain (A^{1,3}-strain) effects between the carbonyl group of the ester and the substituents at the stereogenic center favor conformer **1A**.

**1 A**

A-strain conformation

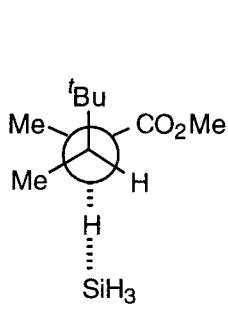
Energy ≡ 0.0
(kcal/mol)

**1 B**

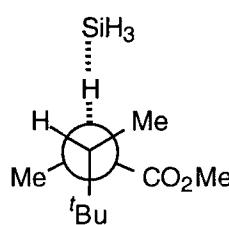
Felkin-Anh conformation

1.5

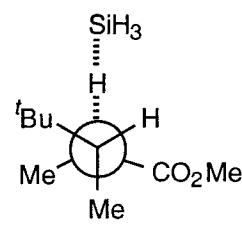
The two faces of radical **1** are shielded either by the *tert*-butyl or the methyl substituent. As expected, the attack *anti* to the *tert*-butyl group in the preferred conformer **1A** leads to the lowest energy transition state **2A**. According to ab initio calculations, the attack of SiH₄ *syn* to the *tert*-butyl group is 3.0 kcal/mol higher in energy (**1A** → **2C**). Interestingly, the attack

**2 A**

Energy ≡ 0.0
(kcal/mol)

**2 B**

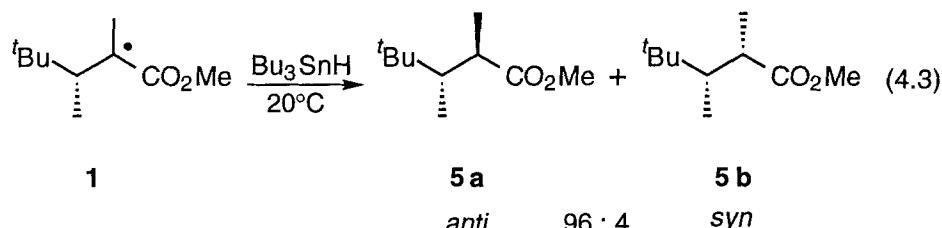
2.7

**2 C**

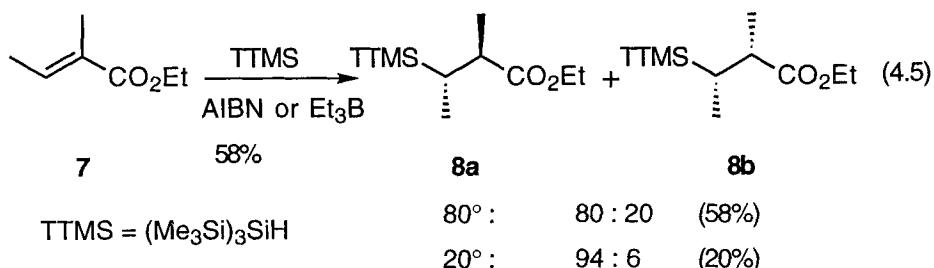
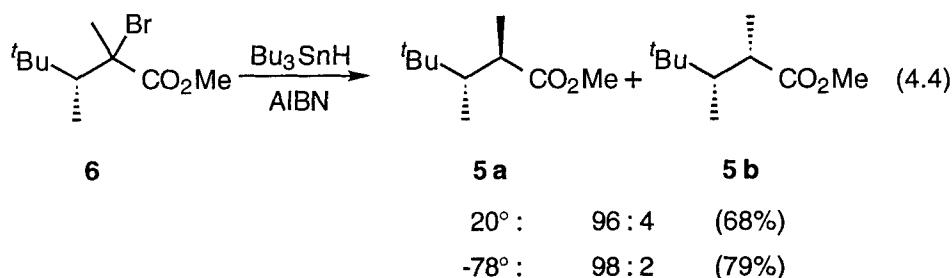
3.0

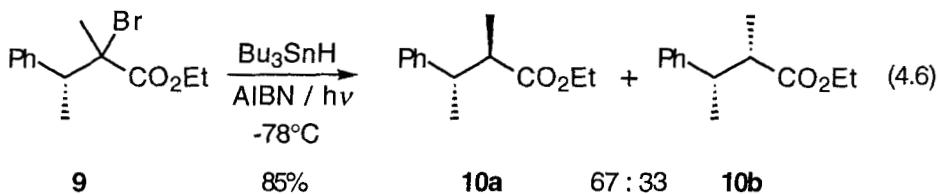
on the less stable conformer **1B** *anti* to the *tert*-butyl group leads to transition state **2B** that has energy similar to transition state **2C**.⁵

Thus, for the formation of the minor product, the attack on the less shielded face of the minor conformer as well as the attack on the more shielded face of the major conformer of the reacting radical should be considered. Transition state **2A** yields *anti* isomer **5a** whereas *syn* isomer **5b** is formed from **2B** and **2C**. The calculated product ratio for the reaction with SiH₄ is in good agreement with trapping experiments of radical **1** by Bu₃SnH (Eq. 4.3).⁴

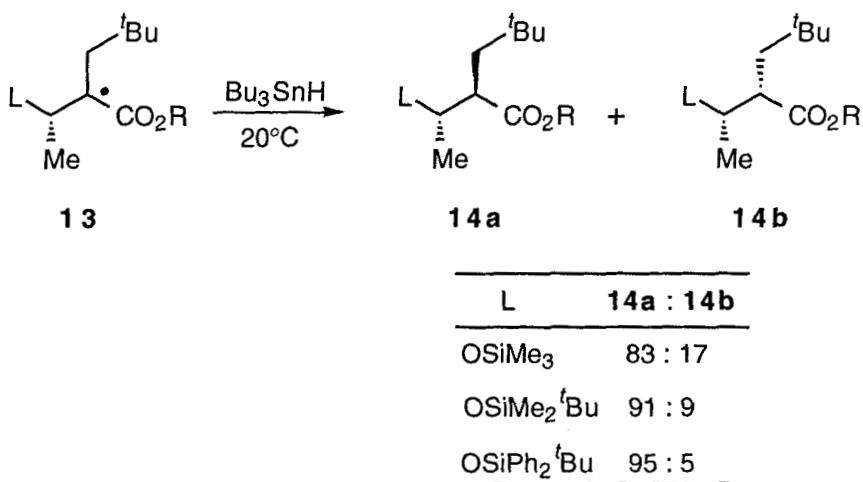
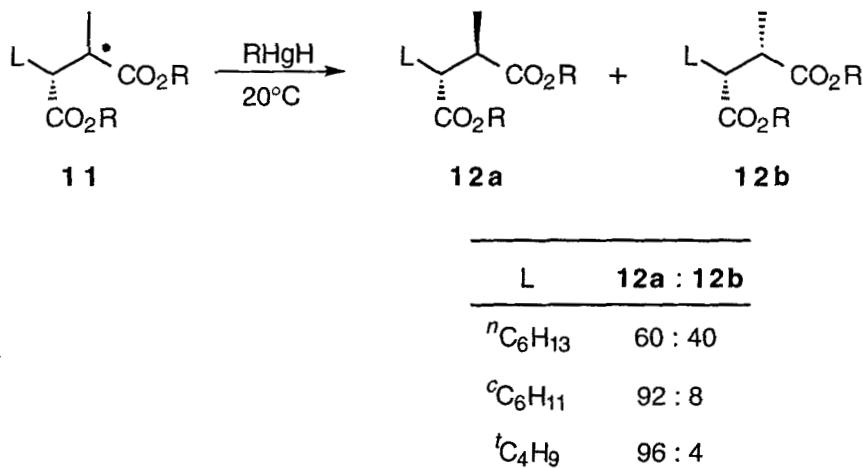


The stereoselectivities and yields of some reactions in which tertiary ester-substituted radicals are formed as intermediates are shown in Equations 4.4–4.6.^{4,10–12} Many of these reactions were carried out with racemates. In these cases, only one of the enantiomers is shown.



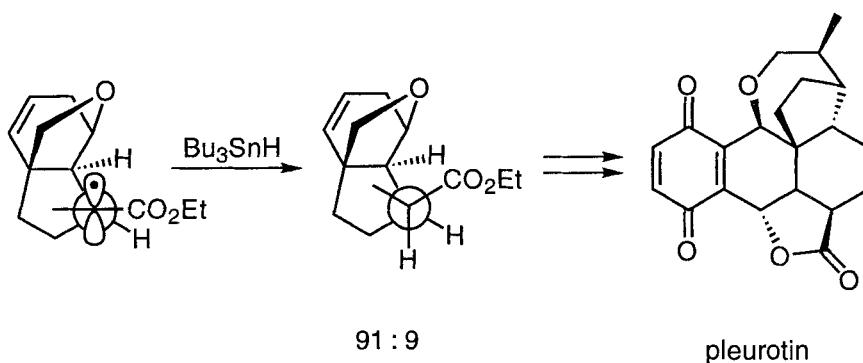


With tertiary ester-substituted radicals, the hydrogen abstraction always leads to preferred formation of the *anti* isomer **a**. A systematic variation of the L substituent on radicals **11** and **13** demonstrates that stereoselectivity also increases with increasing the size of L.¹³ The stereoselectivity of the

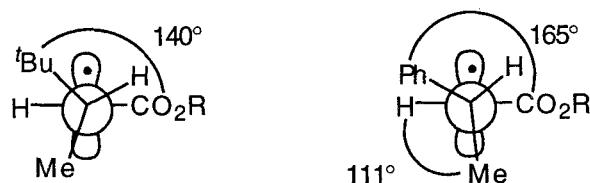


protonation of enolate anions, generated from ester substituted radicals **11** and **13** by reduction, shows the same trends as that of the hydrogen abstraction by the radicals. However, the magnitude of the stereoselectivity of the protonation depends very much upon the proton source.^{13b}

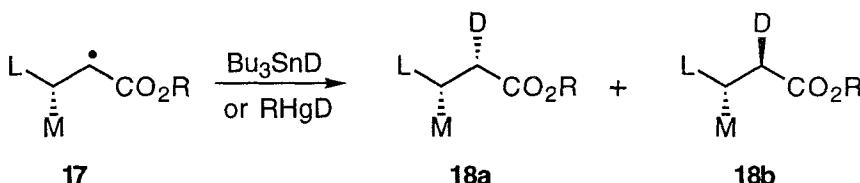
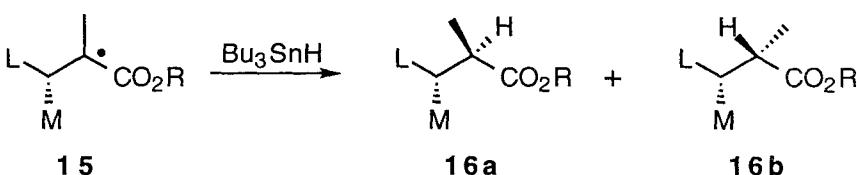
This type of stereoselection has been used in the synthesis of pleurotin.⁹



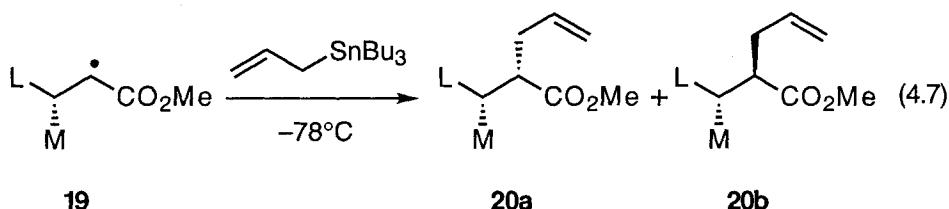
In a tertiary radical, the large group L is located in the middle between the two substituents at the radical center. But in secondary radicals the bulky group comes closer to the adjacent C-H bond because the A^{1,2}-strain is reduced.¹⁴ Thus, secondary radicals shown below adopt preferred conformations where the dihedral angle between the ester group and the *tert*-butyl and phenyl substituent is 140° and 165°, respectively. This makes the addition *syn* to these substituents less unfavorable than in the analogous tertiary radicals.



Therefore, secondary ester-substituted radicals **17** react with a lower stereoselectivity than tertiary radicals **15**.^{4,12,15}



Product ratio				
L	M	16a : 16b	18a : 18b	
tBu	Me	98 : 2	87 : 13	(-78°C)
tBu	CO ₂ R	98 : 2	88 : 12	(20°C)
Ph	Me	67 : 33	45 : 55	(-78°C)

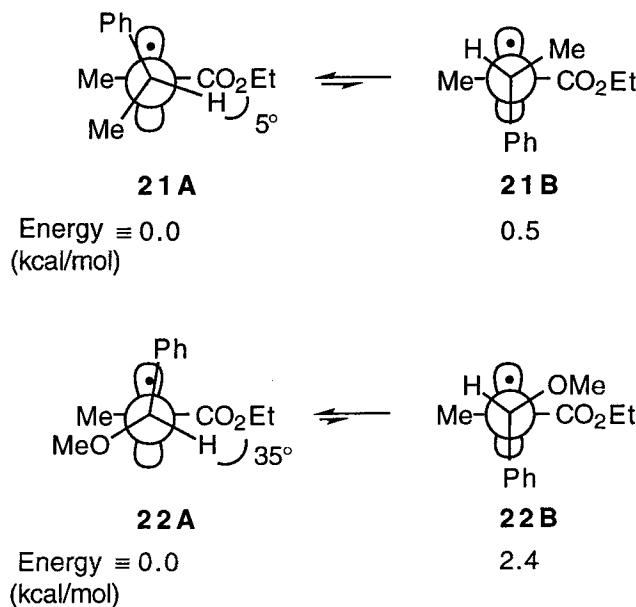


L	M	20a : 20b
tBu	Me	94 : 6
PhMe ₂ Si	Me	82 : 18
Ph	Me	42 : 58

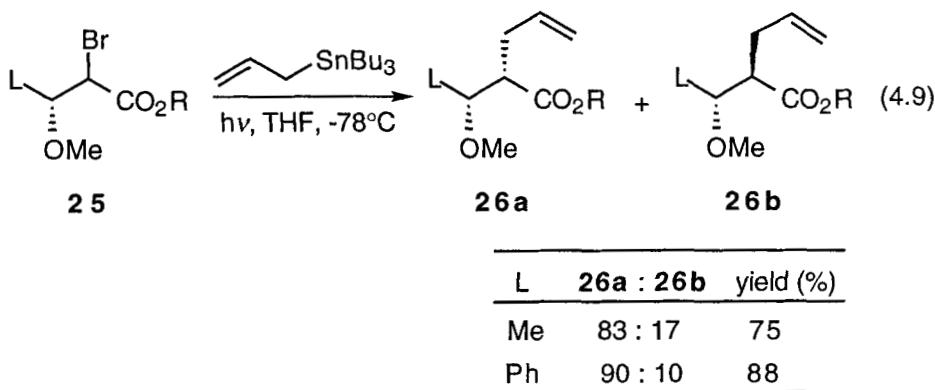
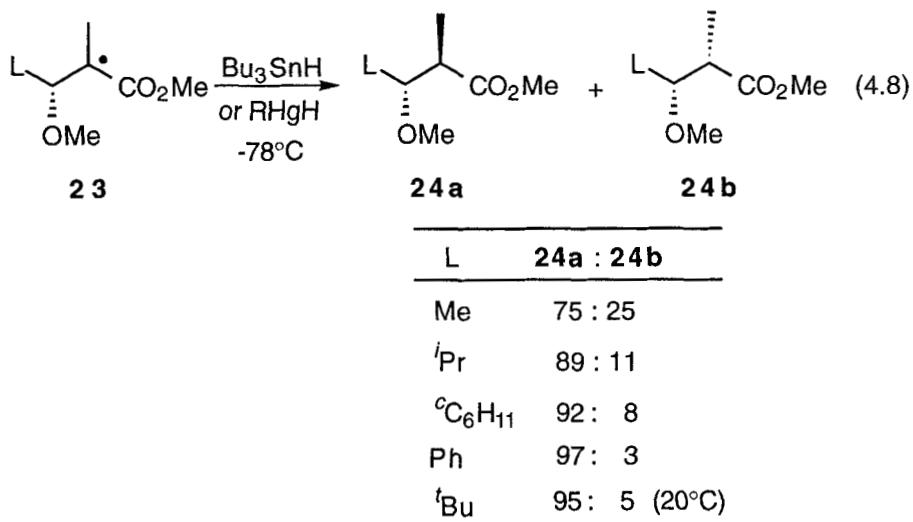
With phenyl as the large substituent, the stereoselectivity is already so low in tertiary radical **15** that the analogous secondary radical **17** reacts with a reversed stereoselectivity. Equation 4.7 shows that this influence of a phenyl substituent on the stereoselectivity has also been observed in allylation reactions of ester-substituted radicals.^{12,15a}

4.1.1.1 Effect of Polar Substituents

A polar substituent at the stereogenic center leads to a dipole-dipole repulsion with the ester group of the radical.¹⁶ This dipole-dipole interaction: (a) increases the dihedral angle between the ester group of the radical and the polar substituent, and (b) increases the energy difference between the two minimum energy conformations. Thus, ESR spectroscopy and quantum chemical calculations of radicals **21** and **22** demonstrate that the dihedral angle in the A-strain conformer increases from 5° to 35° if the methyl group (**21A**) is replaced by the methoxy group (**22A**).¹⁷ Therefore, the phenyl group shields the *syn* face in **22A** more effectively than in **21A**. In addition, the energy difference between the conformers increases from 0.5 kcal/mol (**21A** compared to **21B**) to 2.4 kcal/mol (**22A** compared to **22B**) so that **22B** is less important for the stereoselectivity than **21B**. As a consequence, the selectivity increases from 67/33 to 97/3.



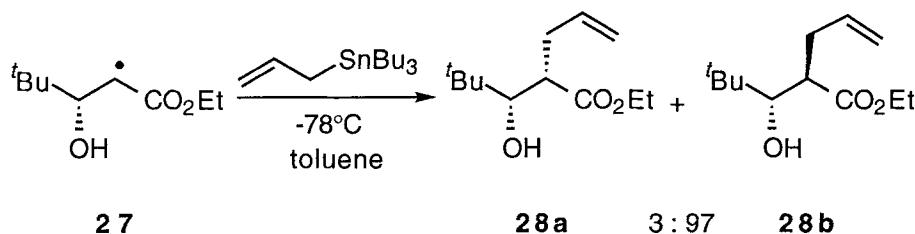
Several examples in the literature show high stereoselectivities for β -methoxy-substituted radicals in abstraction (Eq. 4.8)^{16,18,19} and addition (Eq. 4.9)^{15a} reactions.



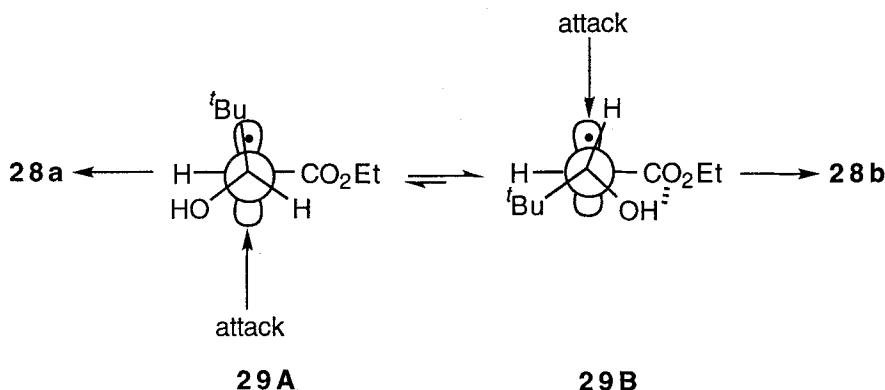
It is still a matter of discussion whether σ -donor substituents at the β -carbon atom of ester-substituted radicals stabilize a Cieplak²⁰ conformation to such an extent that they can increase the stereoselectivity.²¹

4.1.1.2 Hydrogen Bond and Complexation Effects

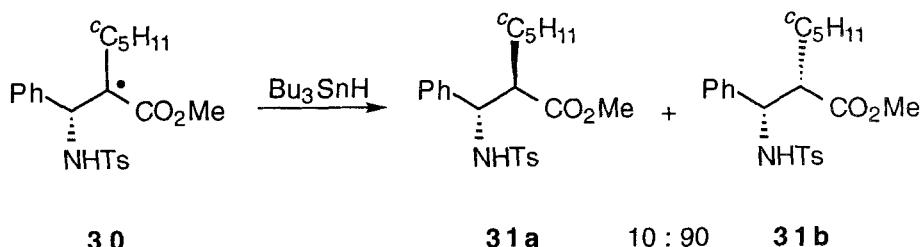
By analogy to the allylation reaction of bromide **25**, the ester-substituted radical **27** should yield **28a** as major allylation product. But, contrary to this expectation mainly **28b** is formed.^{15a,22}



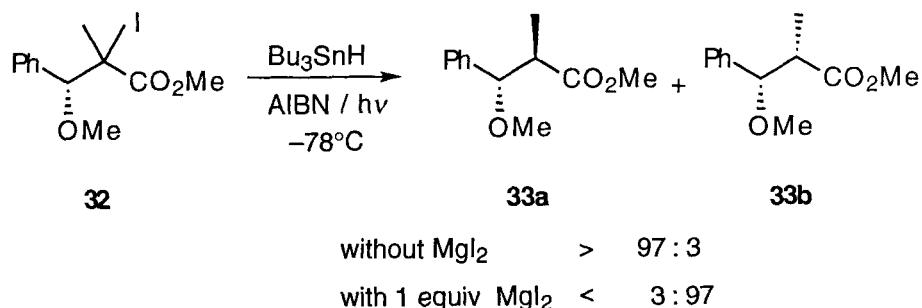
A possible explanation for this result is that hydrogen bonds stabilize conformer **29B** to such an extent that it becomes more stable than the A-strain conformer **29A**. However, studies on solvent effects are inconclusive. The model predicts that hydrogen bond acceptors like THF or DMSO should decrease or even reverse the selection. However, DMSO has very little effect on product ratios.^{22b}



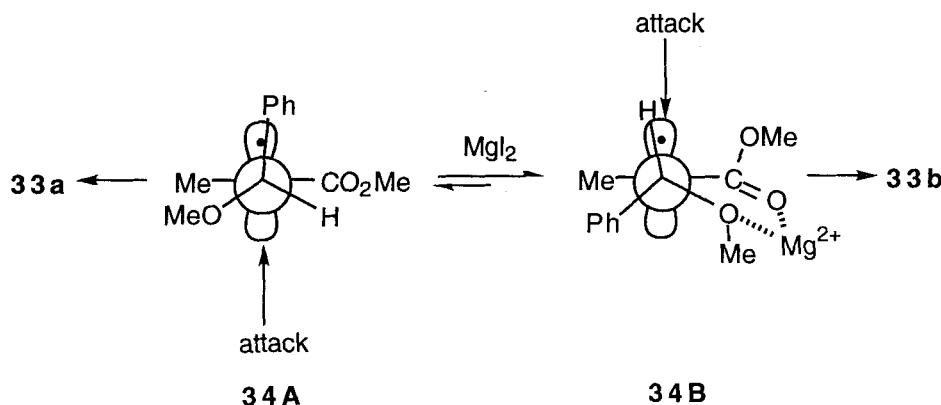
Hydrogen bonding between the N-H and C=O bond in radical **30** might also be the reason for the preferred formation of product **31b**.²³ In accord with this explanation, substitution of the amide hydrogen by a methyl group leads to the loss of 1,2-induction.



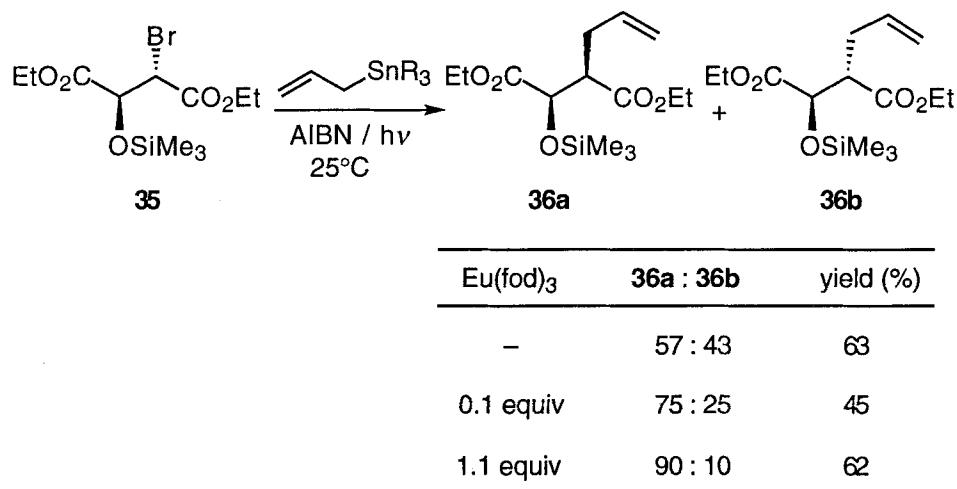
An effect of Lewis acids on the stereoselectivity of ester-substituted radicals has also been detected. Thus, inversion of the stereoselectivity was observed during the reduction^{24a} of **32** and the allylation,^{24b} of the corresponding secondary iodoester in the absence and in the presence of MgI_2 .



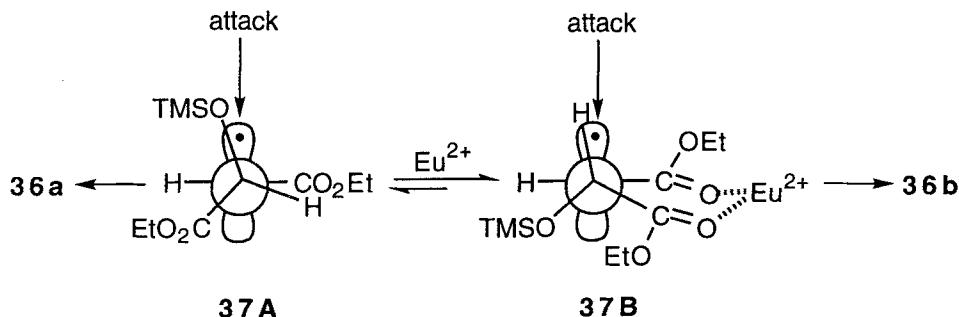
Complexation of the intermediate radical could be the reason for this effect. Whereas the uncomplexed allylic strain conformer **34A** is attacked from "below", complexation leads to conformer **34B** where the "lower"



face is shielded by the phenyl group. Thus, the stereoselectivities of the uncomplexed and the complexed radicals are opposite. The beneficial influence of complexing salts has been observed in the allylation reaction of bromide **35**, which reacts nearly unselectively in their absence. Addition of Eu(fod)₃ to the silylated radical precursor **35** leads to an increase of the stereoselectivity.²⁵

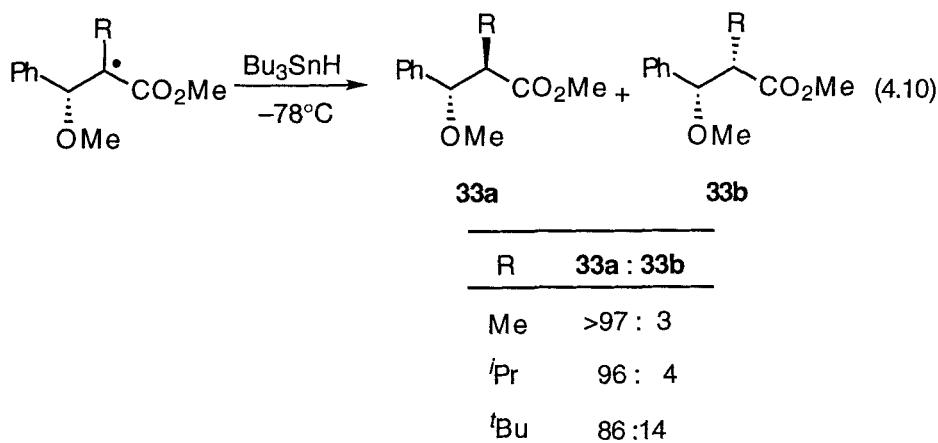


In this case, complexation presumably occurs between the two ester groups and favors conformer **37B**. Because the ester is larger than the TMSO substituent, the complexation now leads to an increase of the amount of the favored product rather than an inversion of the stereoselectivity as in radical **34**.

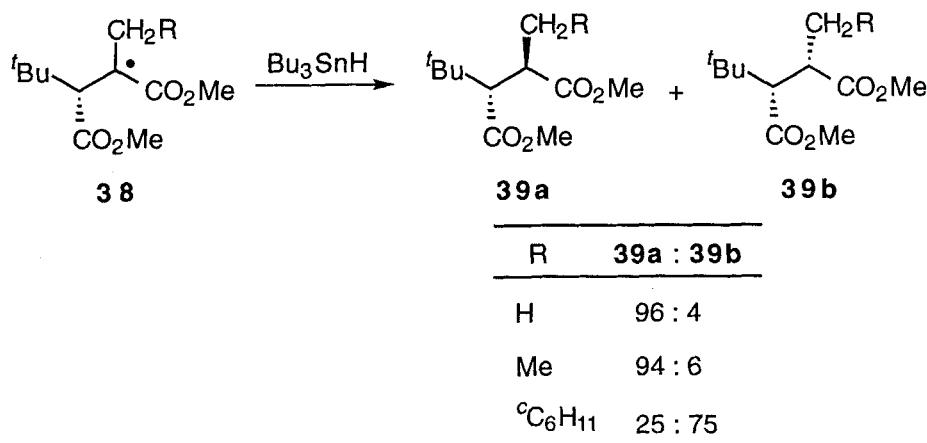


4.1.1.3 Effect of Substituents at the Prostereogenic Center

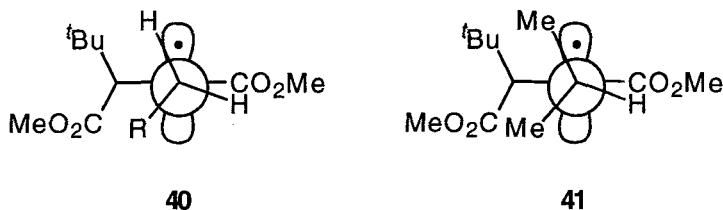
Because of the absence of the A^{1,2}-strain effect, secondary ester-substituted radicals generally react with a lower selectivity than tertiary radicals. But Equation 4.10 shows that increasing the bulk of the alkyl substituent at the radical center does not necessarily raise the stereoselectivity.^{12,16} With bulky substituents R, A^{1,2}-strain begins to compete with A^{1,3}-strain for the favored positioning of the C–H bond at the stereocenter.



By varying the substituent R at the prostereogenic center of radical 38, a reversal of stereoselectivity can occur. Thus, the ratio 39a/39b changes from 96/4 (R = H) via 94/6 (R = CH₃) to 25/75 (R = ^cC₆H₁₁).^{13,26}



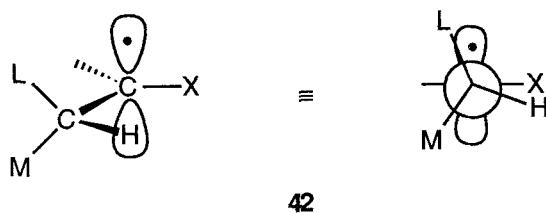
This effect can be explained by preferred conformer **40**. According to the A^{1,3}-strain, one of the hydrogen atoms of the prostereocenter points in the direction of the ester group. With a bulky substituent like a *tert*-butyl group at the stereogenic center, a conformation which places the substituent R at the prostereogenic center *anti* to the *tert*-butyl group should be favored. Thus, the R and *tert*-butyl substituents shield opposite faces and the selectivity is reduced or even inverted.

**40****41**

In agreement with this explanation, the isopropyl-substituted radical **41** reacts with high selectivity (95/5) because the two methyl groups are on opposite faces of the radical. Quantum chemical calculations support this model,¹⁷ which has an analogy in ionic reactions.²⁷

4.1.2 Allylic Strain-Inducing Substituents

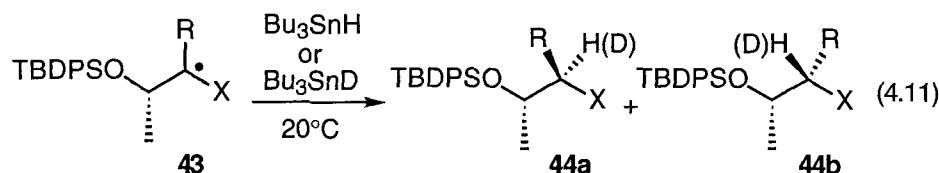
A prerequisite for the occurrence of A^{1,3}-strain effects is a planar substituent X that is in conjugation with the singly occupied orbital of radical **42**. This leads to a biased conformation in which the plane of substituent X is orthogonal to the p-orbital of the radical. Because of a strong steric interaction, conformation **42** is favored in which the small hydrogen atom of the stereogenic group points in the direction of radical substituent X. The substituent bisects the radical so that the large (L) and medium (M) groups

**42**

$X = \text{COR, CO}_2\text{R, CONR}_2, \text{aryl, NR}_2, \text{NO}_2$

are on opposite faces. Substituents X that follow this condition include: COR, CO₂R, CONR₂, aryl, NR₂, and NO₂.

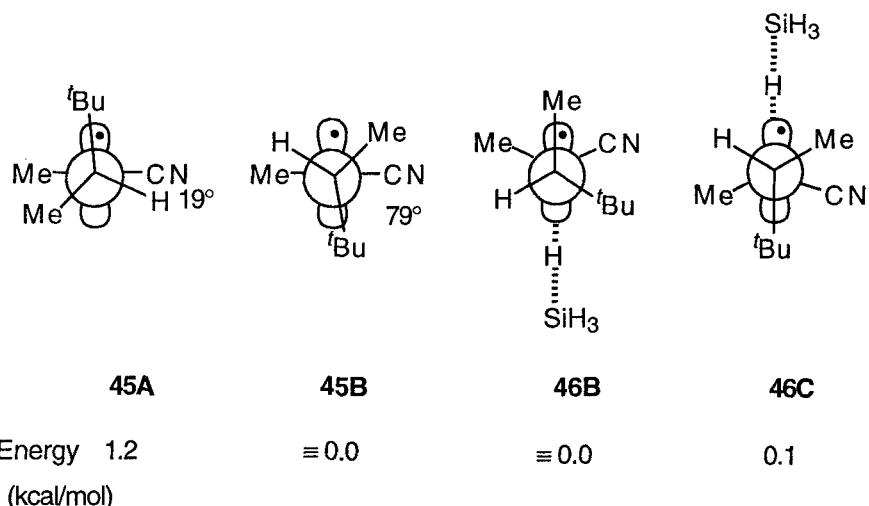
Equation 4.11 shows the stereoselectivity of a series of hydrogen or deuterium abstraction reactions of radical **43** in which the group at the stereogenic center remains constant but the substituent at the radical is changed.²⁸



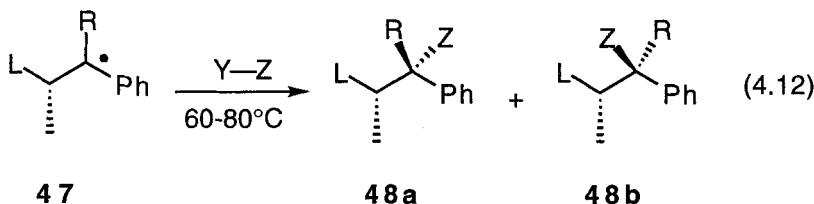
X	R	44a : 44b
COPh	CH ₂ ^t Bu	>97 : 3
CO ₂ Me	CH ₂ ^t Bu	95 : 5
CONMePh	CH ₃	80 : 20 (80°C)
C ₆ H ₅	CH ₃	91 : 9
	H	90 : 10 (80°C)
NO ₂	CH ₂ ^t Bu	86 : 14

Radicals **43** substituted by X = COR, CO₂R, CONR₂, C₆H₅, N(COR)₂, NO₂ react stereoselectively. But radicals with linear substituents (X = CN, Cl) or tetrahedral substituents (X = Me, SiMe₃, SnMe₃, SO₂Ph) are unselective (selectivity $\leq 2/1$).²⁸ A very bulky substituent like the *tert*-butyl group prefers a small dihedral angle with the C–H bond in the ground state and in the transition state. This can lead to high stereoselectivity.²⁹

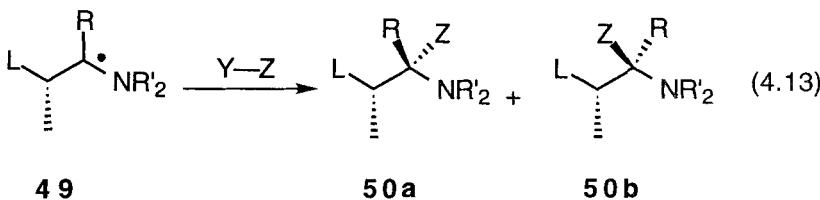
Ab initio calculations demonstrate the completely different situation of nitrile- as compared to ester-substituted radicals.¹⁴ With X = CN, the A^{1,3}-strain conformer **45A** is no longer favored. On the contrary, Felkin–Anh conformer **45B** seems to be more stable. But the two transition states **46B** (*anti* attack at **45B**) and **46C** (*syn* attack at **45B**) have equal energy so the reaction is unselective.



Although extensive stereochemical studies have been carried out only with ester-substituted radicals, the general importance of A-strain effects for aryl-^{13a,28,30} and amino-^{30a,31,32} substituted radicals has been proven by a sufficient number of experiments. Selected results are collected in Equations 4.12 and 4.13.



L	R	reagent	48a : 48b
CH(CN) ₂	Me	Bu ₃ Sn—H	80 : 20
OTBDPS	Me	Bu ₃ Sn—H	91 : 9
MeC(CN) ₂	H	Bu ₃ Sn—D	80 : 20
MeC(CN) ₂	H	(NC) ₂ MeC—I	84 : 16
MeC(CN) ₂	H	(NC) ₂ MeC—SePh	80 : 20

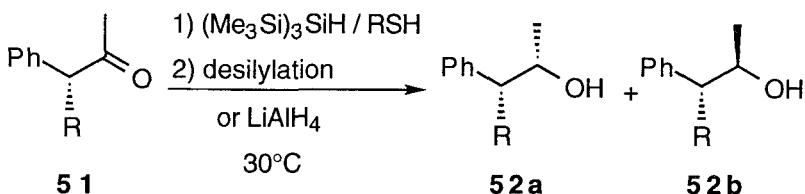


L	R	NR'₂	reagent	50a : 50b
CH ₂ SO ₂ Ph	Et		Bu ₃ Sn—H	93 : 7 (10°C)
<i>t</i> Bu	H		=CN	93 : 7 (16°C)
MeC(CN) ₂	H		(NC) ₂ MeC—SePh	90 : 10 (60°C)

The predictable stereoselectivity of radicals substituted by aryl or amino groups and their generation under neutral conditions suggests promising possibilities of these radical reactions for organic synthesis.

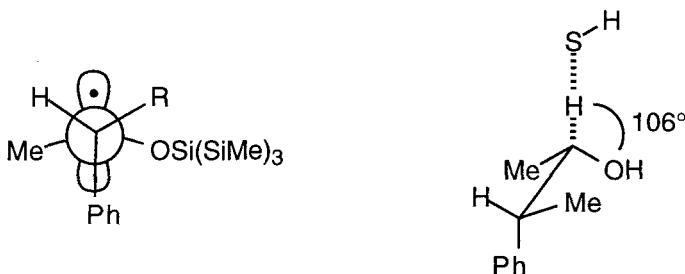
4.1.3 The Felkin-Anh Rule for Radicals

Reactions of radicals with oxygen substituents at the radical center often follow the Felkin–Anh rule. Thus, radical^{33a} and ionic³⁴ reductions of ketones **51** yield products **52a** and **52b** with comparable stereoselectivity.

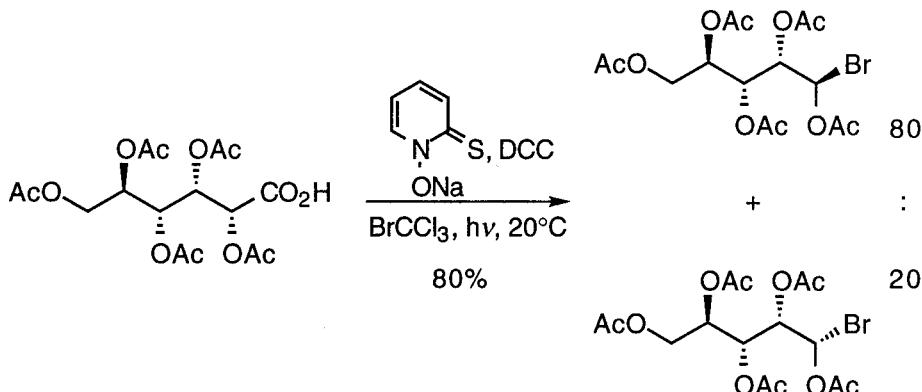
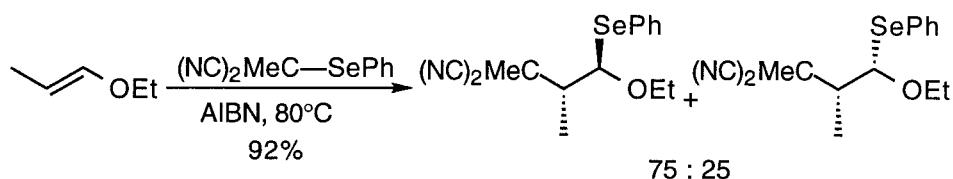
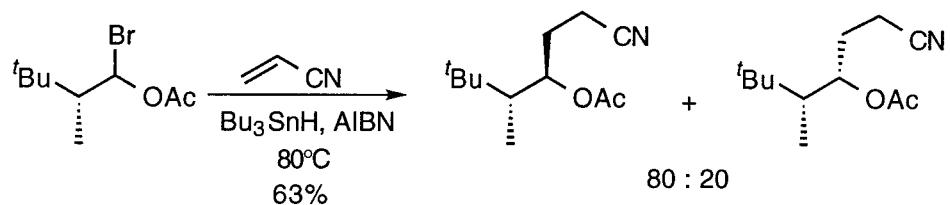


R	52a : 52b	
	(Me ₃ Si) ₃ SiH / RSH	LiAlH ₄
Me	74 : 26	74 : 26
iPr	93 : 7	93 : 7
tBu	84 : 16	89 : 11

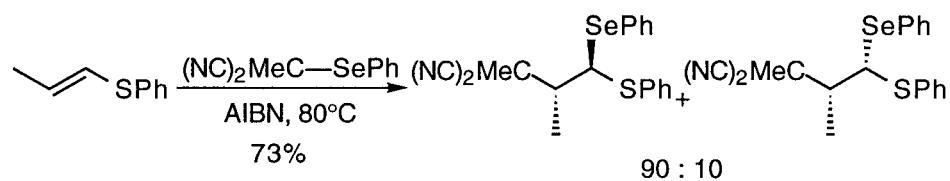
ESR experiments have demonstrated that the reaction of **51** with tris(trimethylsilyl)silane occurs via radical **53**. The ¹³C coupling constant of 61.4 Gauss proves that the tertiary α -oxy substituted alkyl radical is already bent in the ground state.³⁵ This bending increases on the way to the transition state. Ab initio calculations show that the transition state **54** for the hydrogen atom abstraction is similar to the Felkin–Anh transition state of the hydride addition to ketones.^{35,36}

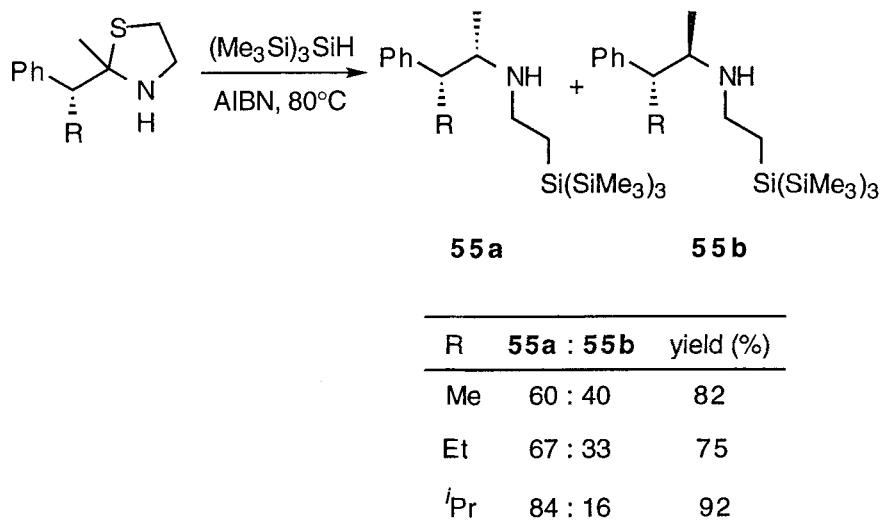
**53****54**

The Felkin–Anh rule can also be applied to C–C-, C–Se-, and C–Br bond formation reactions.^{30a,33,37}

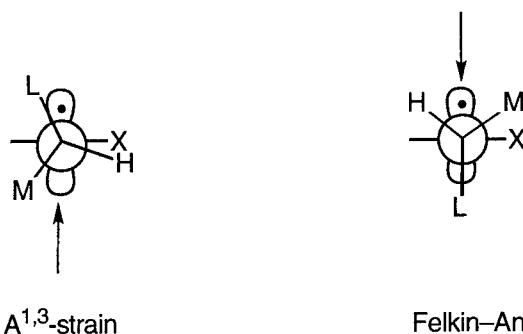


Not only oxygen but also thio^{30a} and primary amino³⁸ groups give rise to preferred formation of the Felkin–Anh products. Obviously the primary amino group is too small to induce A^{1,3}-strain.





Reactions following the Felkin–Anh rule typically give opposite stereoselectivity as compared to reactions governed by $A^{1,3}$ -strain. Thus, the direction of 1,2-induction depends upon the substituent X at the radical center, and the following broad generalizations can be drawn:



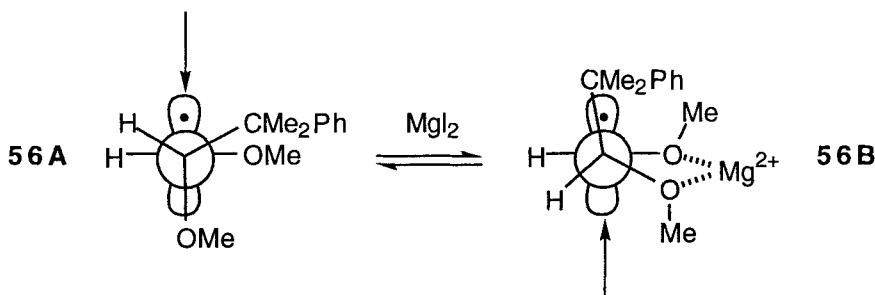
COR, CO₂R, CONR,
Ar, NR₂, NO₂

OR, SR, NHF

4.1.3.1 Complexation Effects

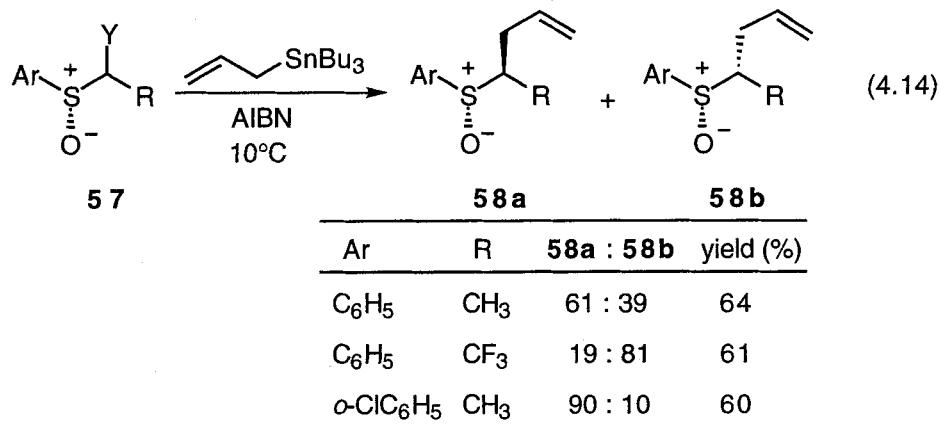
First experiments show that the reaction of alkoxyalkyl radicals with β -oxy substituents can occur via chelated transition states if Lewis acids like

$\text{SmI}_2^{39\text{a,b}}$ or $\text{MgI}_2^{39\text{c}}$ are present. Thus, in the absence of Lewis acids, radical **56** reacts predominantly via Felkin–Anh transition state **56A**. However, in the presence of 2.2 equiv of MgI_2 the stereoselectivity is reversed, and this reversal can be explained by attack at the chelated radical **56B**.^{39c}



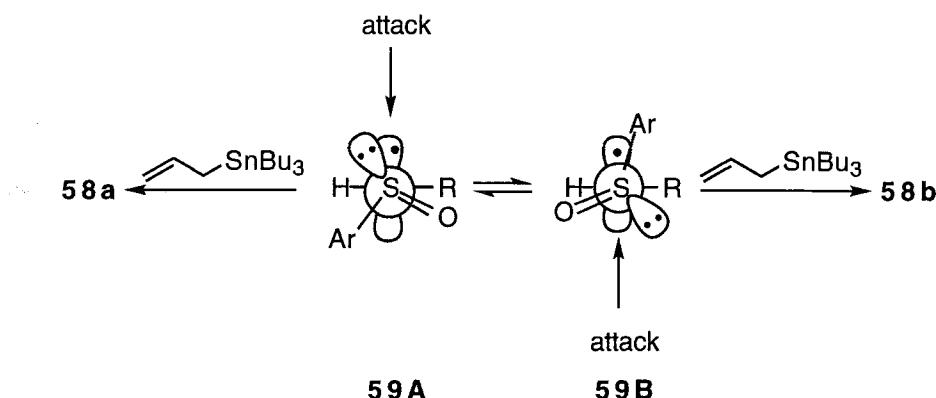
4.1.4 Sulfoxides and Phosphine Oxides

1,2-Induction also occurs in reactions of radicals that are substituted by a chiral sulfoxide or phosphine oxide group. Thus, sulfoxide **57** yields allylation products **58a** and **58b** with a ratio that depends upon the alkyl and aryl substituents (Eq. 4.14).⁴⁰

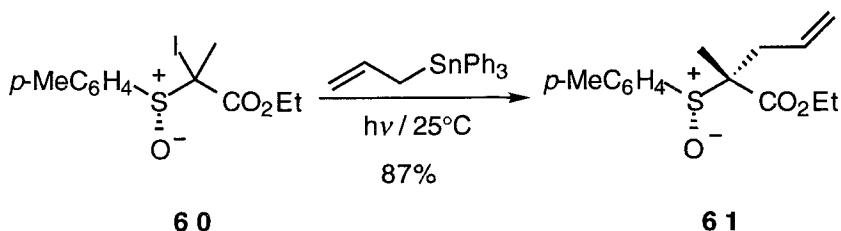


The substituent influence can be explained by conformations **59A** and **59B** of the radical intermediates. According to AM1 calculations,^{40a} conformer **59A** is slightly preferred in a radical with $\text{R} = \text{CH}_3$ and $\text{Ar} =$

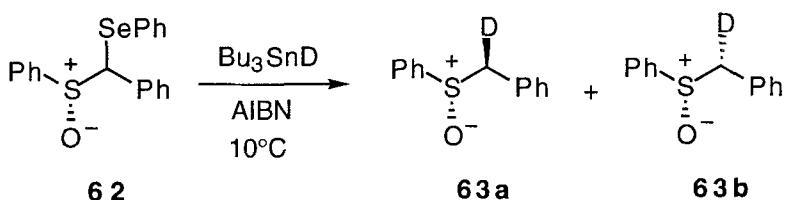
C_6H_5 , and **58a** is formed preferentially. Dipole-dipole repulsion between the group $R = CF_3$ and the S–O bond raises the energy of **59A** compared to **59B**, so that **58b** becomes the main product. But *ortho* aryl substituents favor conformer **59A** because of the increase in $A^{1,3}$ -strain and **58a** is formed predominantly.^{40b}



The influence of polar substituents at the radical center on the equilibrium between the radical conformers also explains the selective synthesis of **61** by radical allylation of **60**.⁴¹



Complexation of the S–O bond by a Lewis acid can give rise to high stereoselectivity. Thus, sulfoxide **62** is trapped by tributyltin deuteride stereoselectively in the presence of a bulky aluminium salt, although the reaction in the absence of this Lewis acid is nearly unselective.⁴²

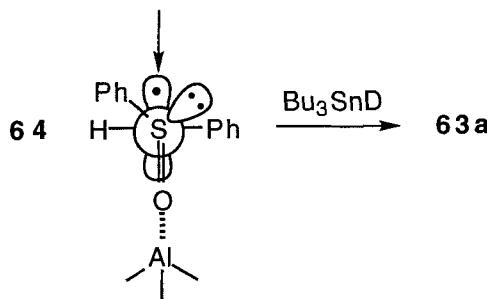


without Lewis acid 34 : 66 (87%)

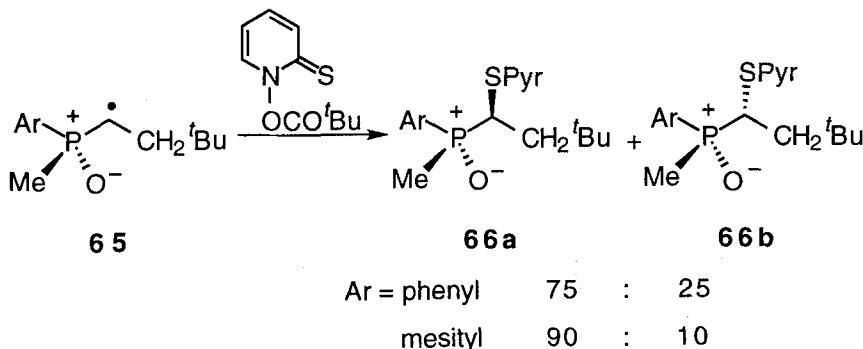
with Me-Al

>97 : 3 (84%)

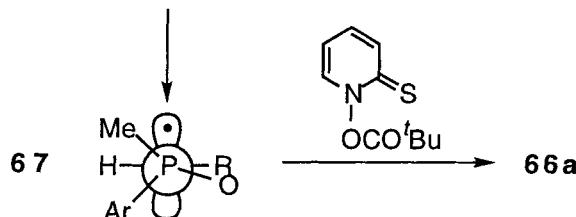
This high stereoselectivity is rationalized by conformer **64** in which the two phenyl groups and the bulky oxygen function are far away from each other. Attack *anti* to the complexed oxygen group leads to **63a**.



Phosphine oxide substituted radical **65** also reacts stereoselectively and yields **66a** as the main product. The selectivity increases by increasing the bulk of the aryl group.⁴³

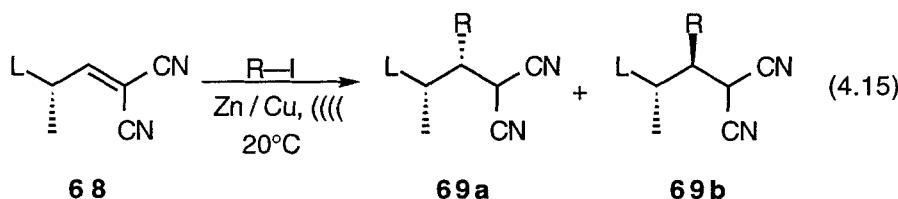


Preferred conformer **67**, which is analogous to the sulfoxide conformer **59A**, can explain this 1,2-stereoinduction.



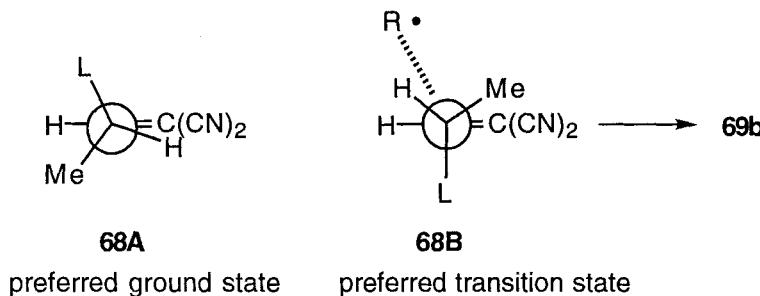
4.2 Acyclic Radical Traps

Acyclic alkenes with a stereogenic substituent at the carbon atom undergoing attack can react stereoselectively with radicals. Thus, the addition of $\text{R}\cdot$, generated by sonolysis of RI in the presence of Zn/Cu, to alkene **68** yields products **69a** and **69b**.⁴⁴ With increase of the bulk of L in the radical trap and of the radical $\text{R}\cdot$, the amount of product **69b** increases. If both substituents are *tert*-butyl groups, then the reaction is completely stereoselective (Eq. 4.15).



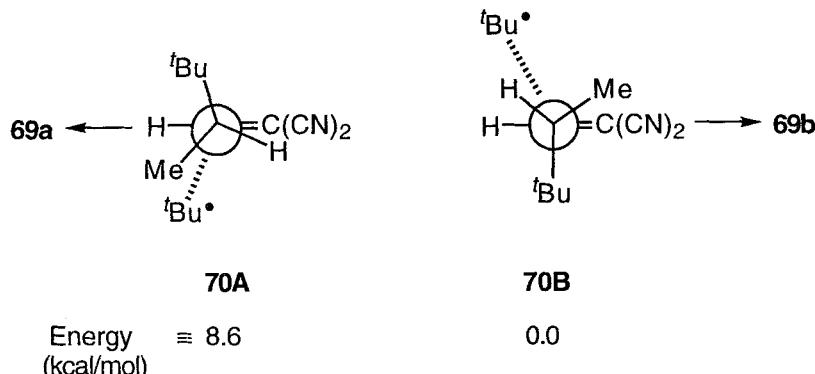
L	R	69a : 69b	yield (%)
<i>t</i> Bu	<i>t</i> Bu	<1 : 99	35
	<i>i</i> Pr	3 : 97	50
	Ph	14 : 86	75
	Et	50 : 50	20
	Me	62 : 38	50
<i>i</i> Pr	<i>t</i> Bu	14 : 86	45
Et	<i>t</i> Bu	30 : 70	61

This 1,2-stereoinduction (**68** → **69b**) is surprising because alkene **68** adopts the A^{1,3}-strain conformation **68A**. Therefore, according to the reactions of ester-substituted radicals (Chapter 4.1.1), addition *anti* to the shielding group L should give **69a** as the main product. But ab initio calculations have shown that Felkin–Anh transition state **68B** which leads to **69b** is of lowest energy.^{44a,b}

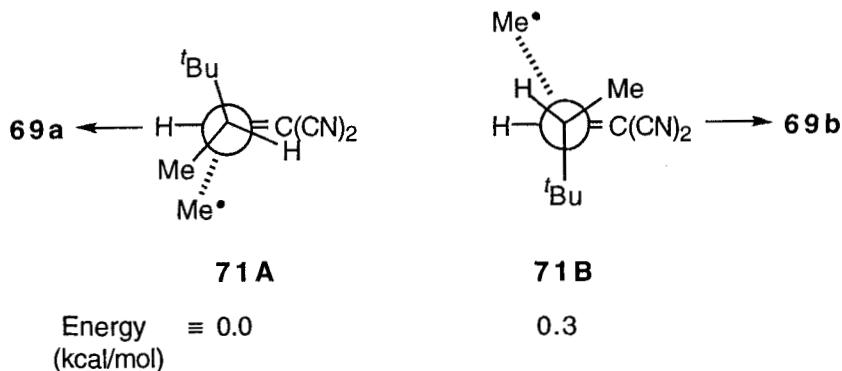


The reason for this unexpected stereochemistry is that the tetrahedral attack of the radical is shielded by the methyl- and the L substituents in the A-strain conformation to such a degree that attack after rotation to a conformation where hydrogen is the shielding substituent is energetically favored. Thus, the main product is formed from the less stable but more reactive conformer. This is a case, described by the Curtin-Hammett principle,⁷ where the transition states and not the ground states govern the stereoselectivity of the reaction.

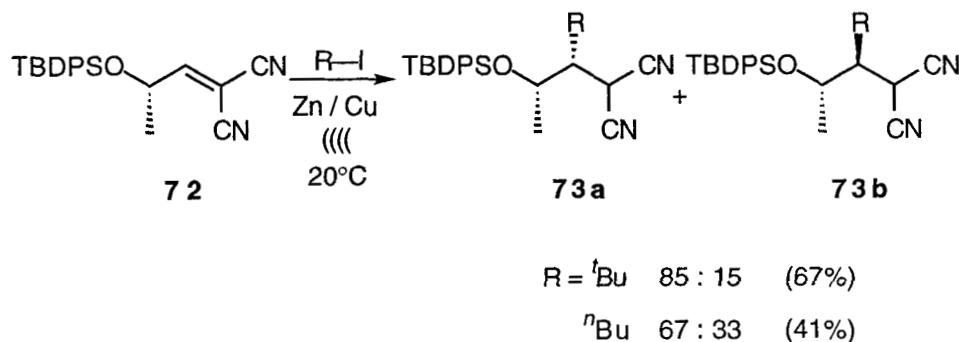
If both L and R are *tert*-butyl groups, ab initio calculations show that the Felkin–Anh transition state **70B** is much lower in energy than **70A**.^{44b}



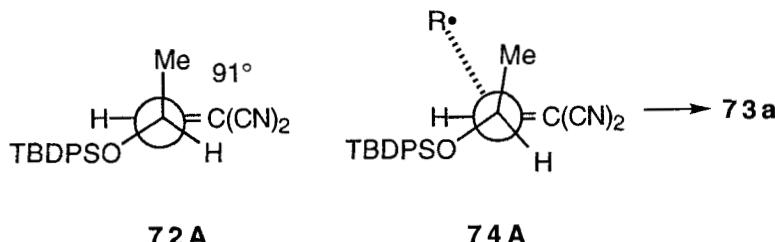
Only with the small methyl radical does the alkene **68** react via its A^{1,3}-strain conformer **71A**, which has a slightly lower energy than the Felkin-Anh conformer **71B**.^{44b}



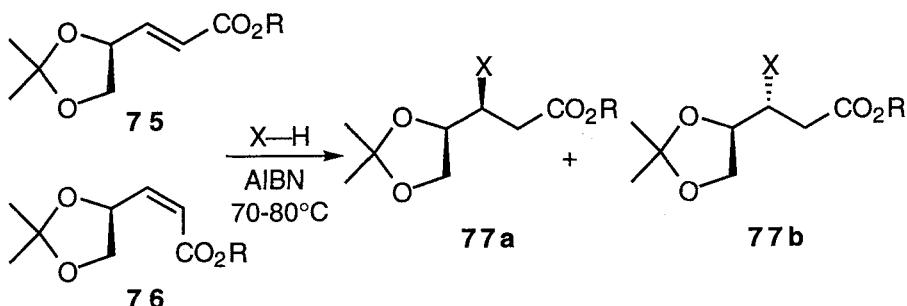
Interestingly, the silyloxy-substituted alkene **72** yields predominantly **73a**, but the 1,2-induction is relatively low.^{44b}



According to X-ray analysis alkene **72** adopts conformation **72A**. The face *anti* to the bulky siloxy group is open for a tetrahedral attack of radical R[•] and **74A** is the transition state of lowest energy.

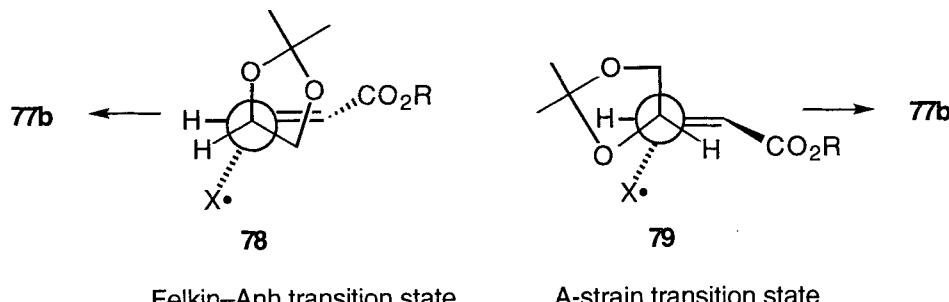


Both alkenes **75** and **76**, synthesized from *L*-glyceraldehyde, react to give predominantly product **77b**. Whereas the *E*-alkene **75** in most cases shows only moderate stereoselectivity, 1,2-stereoinduction for *Z*-alkene **76** is high.^{45,46}



X—H	alkene	77a : 77b	yield (%)
(Me ₃ Si) ₃ Si—H	75	2 : 98	95
Ph ₂ HSi—H	75	30 : 70	69
Bu ₃ Sn—H	75	30 : 70	93
^c C ₆ H ₁₁ I / Bu ₃ SnH	75	40 : 60	65
Ph ₂ HSi—H	76	9 : 91	75
^c C ₆ H ₁₁ I / Bu ₃ SnH	76	6 : 94	82

The reaction of *E*-alkene **75** could occur via Felkin–Anh transition state **78** whereas an A-strain transition state **79** might explain the 1,2-stereoinduction with *Z*-alkene **76**.⁴⁷



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Chapter 5

Chiral Auxiliary Control

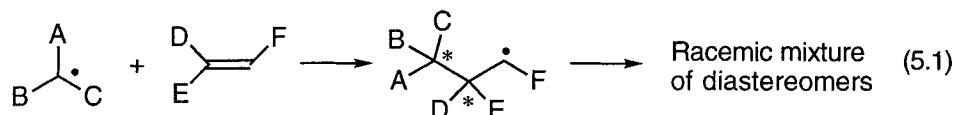
5.1 General Considerations

The configurations of new stereogenic centers formed from *acyclic* prostereogenic radical centers may be controlled by chiral groups attached to the radical. Free radical addition reactions to *acyclic* prostereogenic alkene centers may also be controlled by chiral groups attached to the alkene. If the resident chiral group attached to the radical or alkene may be subsequently removed after the stereochemically defining reaction, the group is designated as an auxiliary group or *chiral auxiliary*. For our purposes, the definition of an auxiliary group or chiral auxiliary is essentially the same one used in enolate alkylation and aldol chemistry,¹⁻³ and the requirements for control of configuration of new stereogenic centers are also based on concepts developed in carbanion and enamine chemistry.⁴ Simply stated, the orientation of the resident chiral group intended to control the configuration of the new stereogenic center formed must be fixed relative to the prostereogenic center and the chiral group must differentially shield that center's diastereotopic faces.⁵ This definition applies for chiral auxiliary groups attached to a radical or to a molecule with which a radical reacts.

Acyclic prostereogenic free radicals bearing chiral auxiliary groups have been examined in radical–molecule reactions that include radical addition and atom transfer chain propagation steps. Radical–radical chain termination reactions have also been examined with radicals bearing chiral auxiliary groups. Excellent acyclic stereoselectivity in radical–molecule propagation reactions has been achieved while only modest stereoselectivity has been observed for radical–radical termination reactions of species bearing chiral auxiliaries. Early reviews of auxiliary-controlled free radical reactions have appeared.^{5,6}

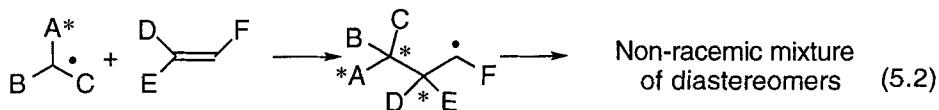
5.1.1 Radical Addition

For radical addition reactions^{7,8} of acyclic radicals or acyclic alkenes, two new stereogenic centers may be formed if the radical and the alkene are appropriately substituted. Thus, for a radical substituted with three different

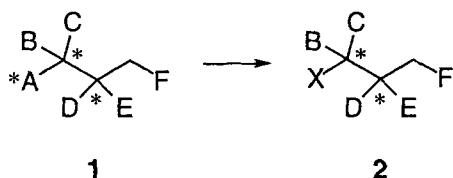


groups (Eq. 5.1, A, B, and C) that adds to a radical substituted with groups D, E, and F, the relative configuration of the two new centers indicated with (*) in Equation 5.1 is at issue, and *simple diastereoselection* may occur. If groups A-F are achiral, the product of radical addition will, of course, be formed as a racemic mixture of diastereomers and the diastereoselectivity of the addition process indicates the enrichment of one racemic diastereomer as compared to the other.

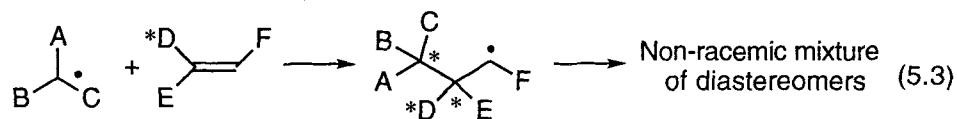
Chiral auxiliary control in radical addition is presented in Equation 5.2 where one of the groups A, B, or C on the radical has a stereogenic center (shown in Eq. 5.2 for group A*). The presence of chiral group A* in the radical may induce a bias in the configuration at either of the new stereogenic centers formed in the addition reaction.



If the chiral group A* is subsequently removed from a product of addition, for example **1** is transformed to product **2**, and if the configuration of the stereogenic centers is retained in this transformation, then group A* serves as a chiral auxiliary in the sequence. In practice, a radical such as the one shown in Equation 5.2 has frequently been reacted with achiral alkenes or with allyl stannanes such that only one new stereogenic center is formed in the addition reaction. Allylstannanes,^{9,10} allyl sulfides, and allyl halides^{11,12} react with carbon radicals by an addition–fragmentation process, see Chapter 1.



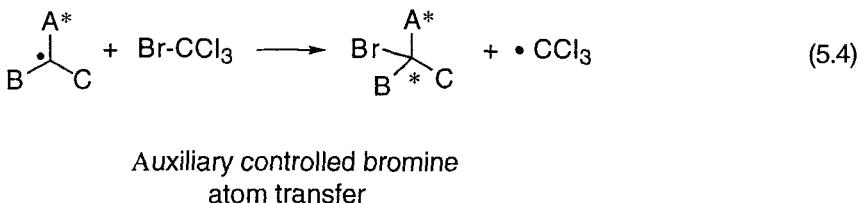
Equation 5.3 describes a radical addition reaction where a chiral group D^* resides on the alkene at the position undergoing free radical attack. The group may control the configuration of new stereogenic centers formed in the addition reaction and if the group is removed without a change of configuration at the new stereogenic centers formed in addition, then D^* serves as a chiral auxiliary group in the sequence. Substitution of a chiral group F^* on the alkene likewise leads to potential auxiliary control in a radical addition reaction.



5.1.2 Atom and Group Transfer Reactions

Atom and group transfer reactions are among the most common types of free radical chain propagation steps. Atom transfer reactions are key propagation steps in the halogenation of alkanes⁸ for example, and there are important examples of groups that are transferred in free radical propagation steps (see Chapter 1). Thus, thiopyridyl^{13,14} and the phenylselenyl groups^{15,16} are transferred in useful methodology.

If a prostereogenic radical undergoes an atom or group transfer propagation reaction, the configuration of the new stereogenic center formed in this propagation step may be potentially controlled by chiral groups in the radical or in the transfer reagent. If the resident chiral group on the radical is subsequently removed without compromising the configuration of the newly formed stereogenic center, then the resident group serves as a chiral auxiliary in the atom or group transfer process. In Equation 5.4 control of configuration is illustrated for a bromine atom transfer propagation step to a prostereogenic radical center with an attached chiral group.



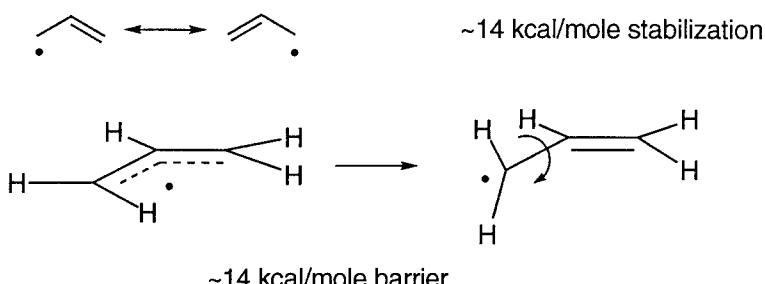
5.2 Auxiliary Group Attached to the Radical Center

We have suggested that the resident chiral group intended to control the configuration of the new acyclic stereogenic center must be fixed relative to the prostereogenic center and that the chiral group must differentially shield the center's diastereotopic faces. For discussions of this definition as it applies to chiral auxiliary groups attached to an acyclic radical, knowledge of radical structure and dynamics is imperative. We present here a brief review of structure and dynamics of radicals substituted with conjugating groups and of radicals α to esters and amides. Amide-substituted radicals are given particular emphasis in this discussion since it was with these radicals that some of the first examples of acyclic control of free radical stereochemistry were achieved.⁵

5.2.1 Radical Stabilization by Delocalization

Free alkyl radicals such as the ethyl radical are flexible species that might invert from one shallow pyramidal structure to another over energy barriers of less than ~1 kcal/mol.¹⁷ Substitution of groups capable of delocalizing the odd electron by conjugation lead to planar radical species. Thus, replacement of a hydrogen of the methyl radical by a benzene ring leads to a stabilized benzyl radical that is thought to have planar geometry. The planar benzyl radical is thermodynamically stabilized but it is kinetically labile,¹⁸ reacting with itself at the diffusion-controlled rate and with other molecules (for example, dioxygen) at rates approaching that of diffusion.

The allyl radical is stabilized by delocalization by about 14 kcal/mol¹⁹ and the barrier to rotation about one of the partial double bonds in allyl corresponds to this value (~14 kcal/mol) since loss of stabilization energy attends rotation, see Figure 5-1. Most radicals for which resonance structures

**Figure 5-1.** Stabilization by Delocalization for Allyl Radical.

like those shown in Figure 5-1 can be written are stabilized compared to the corresponding alkyl radical (allyl vs. propyl), and radicals that are stabilized by resonance are generally assumed to have planar structures.

Radicals substituted with electron-withdrawing conjugating groups such as CN, COOR, COR, and CONR₂ are also stabilized by delocalization and presumably all such radicals exist as planar species. Studies of substituted allyl radicals suggest that *trans* rather than *cis* geometries are preferred²⁰ consistent with simple strain arguments.

Evidence has been presented that radicals substituted adjacent (α) to a carbonyl such as **3** are stabilized by some 10–12 kcal/mol compared to an alkyl radical model,²¹ and spectroscopic investigations reveal²² that rotation about the C(α)-carbonyl bond of such radicals has a barrier of about the same magnitude. Thus, radicals **4** and **5** interconvert between two forms over an ~11–12 kcal/mol barrier (Fig. 5-2).²²

These two forms are presumably the *Z* and *E* geometric isomers of the radical, and the measured barrier apparently reflects the loss of radical stabilization (by delocalization) upon rotation about the radical–carbonyl bond. Rotation about the C(α)-carbonyl bond of an ester or amide is thus analogous to rotation about an allyl partial double bond as shown in Figure 5-1. Radical stabilization is lost because delocalization of the radical is forfeited at the transition state of the isomerization.

The nature of the group X attached to the carbonyl, in Figure 5-2, is expected to have an impact on the preferred geometry of radicals α to carbonyls. Esters apparently have *Z* and *E* isomers that differ very little in energy since the carbonyl oxygen and the OR group have very similar steric requirements for the geometry shown in Figure 5-2, structures *Z*-**4** and *E*-**4**. Consistent with this expectation, ESR evidence²² suggests that two con-

formations of radical **4** ($R = Me$) are present in roughly comparable amounts. The orientation of the ester (OR) group is therefore not “fixed” with respect to the radical center for radicals α to esters. Rather, there are two roughly comparable populations of structures that have the OR group fixed at different distances and with different orientations relative to the radical center.

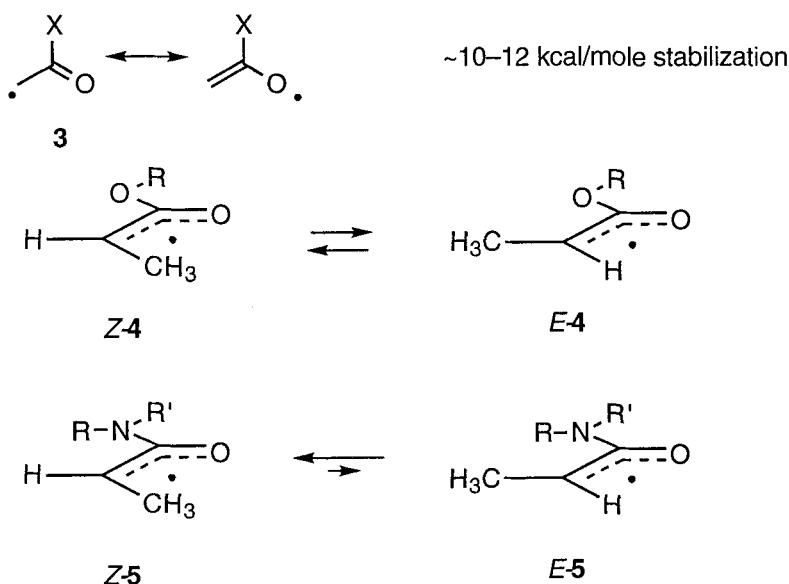


Figure 5-2. Stabilization and Conformations of Radicals Substituted α to Esters and Amides.

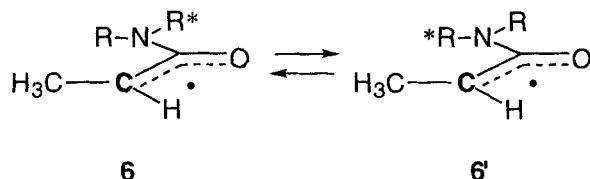
5.2.2 Structure and Dynamics of Radicals α to Amides

In contrast to radicals α to esters, radicals α to amides have a substantial preference for the *Z* geometry. This can be understood based upon simple steric arguments (see structure **5** in Figure 5-2). The carbonyl oxygen is smaller than the amide nitrogen and for radicals like **5**, substituents on the radical center occupy positions that are determined by the groups on the adjacent carbonyl carbon. For the radical **5**, the position of the methyl and hydrogen substituents on the radical center are fixed relative to the carbonyl oxygen and the amide nitrogen. The larger methyl group radical substituent,

compared to hydrogen, has a preferred orientation that is *Z* to the sterically smaller carbonyl oxygen (compared to nitrogen) carbonyl substituent. Steric effects control the geometry of radicals α to amides in exactly the same way that the geometry of a substituted allyl radical is controlled by 1,2 steric interactions.

The fact that the geometry of radicals α to amides can be fixed relative to the amide nitrogen group is critical to the use of amide derivatives as auxiliary groups in free radical reactions. Consider, for example, substitution of a chiral group at an ester oxygen or an amide nitrogen with the goal being the use of that chiral group to sterically shield one diastereotopic face of an α -ester or α -amide prostereogenic radical center (such as **4** and **5**). For an ester-derived radical, the orientation about the C(α)-C(O) bond is not secure and two conformations about this bond contribute to the overall shielding of the radical diastereotopic faces. For an amide-derived radical, this is not an issue since one conformation is preferred over the other by a substantial energy and the barrier for interconversion of the conformers is also substantial.

Another question of conformation arises for radicals α to esters and amides. There are two possible orientations about the O-C(O) and N-C(O) bonds and this fact exposes a potential fault in strategies based upon ester or amide auxiliary groups attached to radical centers. For example, consider a radical located α to an amide, **6**, substituted with a chiral group, R* on the amide nitrogen.

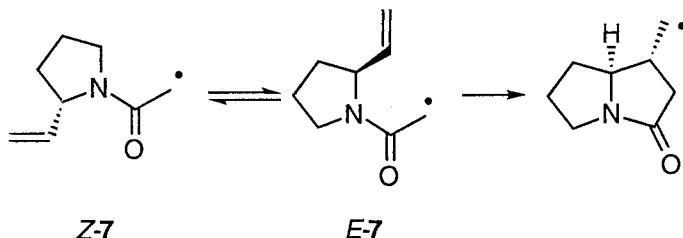


The position of the chiral group relative to the radical prostereogenic carbon center (shown as C for the structures) is critically dependent on the orientation about the amide bond. In conformation **6**, R* is *trans* to the radical carbon C while in conformation **6'**, the chiral group is *cis* with respect to this center.

The issue of conformational options must be settled for the chiral R* group to be useful as a chiral-controlling group. Furthermore, the conformation **6'** that has the chiral-controlling group closer (*cis*) to the

prostereogenic radical carbon would appear *a priori* to have a higher probability of ultimate success in stereocontrol than the conformation 6, where the controlling group is more remote (*trans*) from the carbon center.

There is evidence in the literature that relates to the dynamics of interconversions like $6 \rightleftharpoons 6'$. The radical 7 undergoes cyclization reluctantly at room temperature but at elevated temperatures, a good yield of bicyclic product is obtained under standard iodine atom transfer conditions.^{23,24} The problem with cyclization of 7 presumably relates to the fact that only conformer *E*-7 can cyclize and at low temperatures, this conformer cannot be accessed from *Z*-7. The barrier for this interconversion must be in excess of 12–15 kcal/mol. At higher temperatures, the conformational barrier can be traversed within the lifetime of the radical and interconversions of the unreactive and the reactive conformers occur, providing a cyclization option for the radical.



5.2.3 Amide Chiral Auxiliaries for Acyclic Free Radical Reactions

We suggest that the conformation about two bonds, $\text{C}(\alpha)\text{—C(O)}$ and $\text{C(O)}\text{—N}$, must be controlled for amide groups to be useful auxiliary groups. For prostereogenic radicals bearing an amide, an alkyl group, and a hydrogen atom, the orientation about the $\text{C}(\alpha)\text{—C(O)}$ bond is secure, the smaller H atom (compared to the alkyl) preferring the *cis* orientation to the larger nitrogen substituent (compared to the oxygen). For a radical center bearing two alkyl groups and an amide, the preferred orientation about $\text{C(O)}\text{—N}$ is not well-defined, and predictions about radical conformation and consequent reactions are difficult.

Control of the conformation about the $\text{C(O)}\text{—N}$ bond is also important, and several strategies present themselves as possible solutions to this question.

In Figure 5-3, amides derived from generalized cyclic amines are shown and the asterisk indicated for each structure represents the chirality of the amide that is of a nature to shield one diastereotopic face of the prostereogenic radical center. We have suggested⁵ solutions to the C(O)–N conformational problem that utilize C_2 symmetry, dipole-dipole effects, steric control, hydrogen bonding, and chelation.

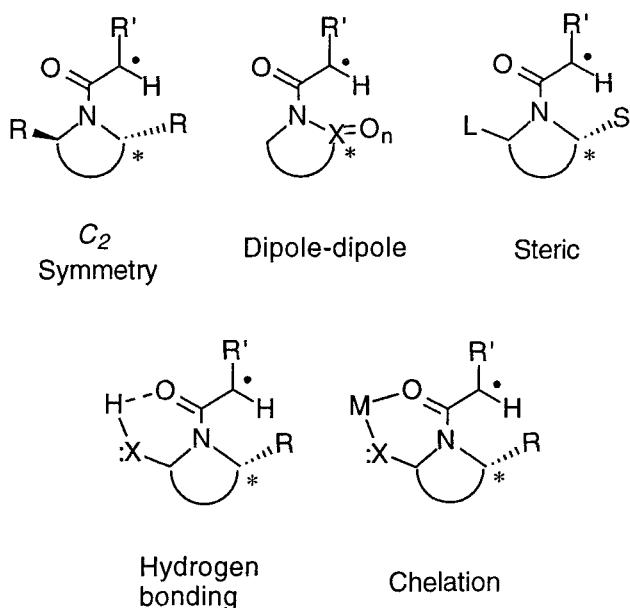


Figure 5-3. Strategies for Conformational Control of α -Amide Radicals.

Chelation has been used to control auxiliary group orientation extensively in enolate and cycloaddition chemistry.^{1–3} This approach introduces some unknowns when applied to free radical chemistry. The chemistry of free radical species has been developed with neutral, uncharged species and the chelation strategy introduces some interesting questions concerning the chemistries under conditions of a useful radical propagation sequence.

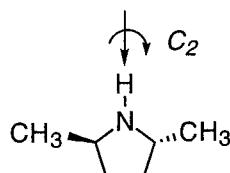
Construction of the amide from an amine having C_2 symmetry avoids the conformational issue with regard to C(O)–N since both orientations place a stereogenic center *cis* to the radical center. Dipole-dipole control of imide conformation would orient the dipole of a chiral $\text{X}=\text{O}_n$ group *trans* to the

carbonyl dipole and therefore *cis* to the prostereogenic radical center. Steric control of C(O)–N conformation, as shown in Figure 5-3, relies on large (–L) and small (–S) group substitution on the amide pairing with small (O=) and large (–CHR[•]) group substitution at the carbonyl carbon.

Of the strategies outlined in Figure 5-3, C_2 symmetry and dipole-dipole control of orientation were the first approaches used in acyclic auxiliary-controlled free radical addition reactions. Both of these strategies had been used successfully in chemistry involving neutral reactants (enamine alkylation and cycloaddition chemistry) and these precedents encouraged their early use in the chemistry of neutral free radical intermediates.

5.2.3.1 C_2 Symmetry

C_2 symmetry has been used extensively as a control element in stereochemical transformations.^{4,25} Whitesell⁴ has used 2,5-dimethylpyrrolidine effectively in enamine alkylation reactions and its efficacy in these transformations is understood based upon conformational control of the enamine as outlined in Figure 5-4. The carbon–nitrogen bond of the pyrrolidine has substantial double bond character and the C_2 symmetry of the pyrrolidine assures that the steric environment about the prostereogenic



Whitesell's pyrrolidine

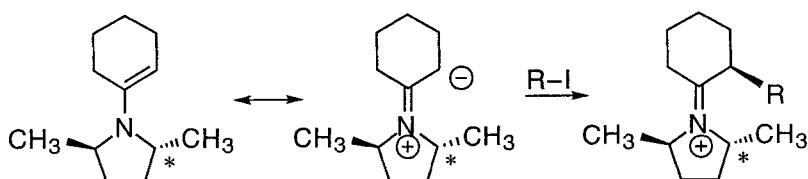
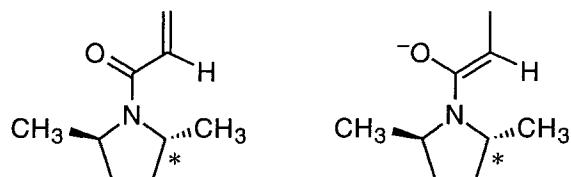
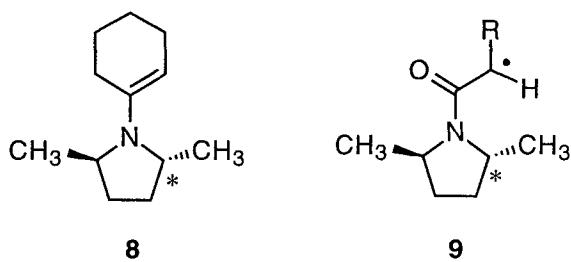


Figure 5-4. C_2 Symmetry and Alkylation of Enamines.

enamine center is identical for either conformer of the C=N bond. Alkylation of the enamine **8** introduces the alkyl group on the opposite face of the molecule to the resident methyl group (*). The methyl group identified with an asterisk is oriented *cis* to the prostereogenic reactant enamine center.

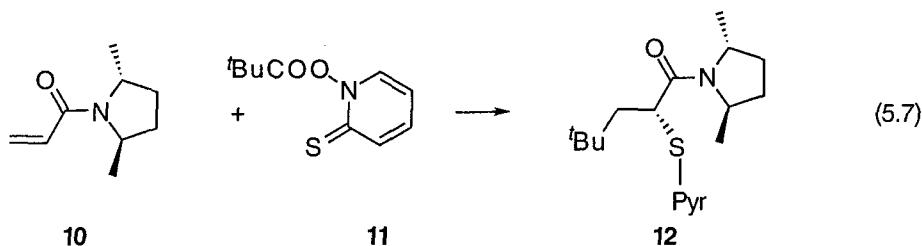
The structural analogy of the enamine **8** and amide-substituted free radicals is shown below. Both bonds between the prostereogenic reactive center on the enamine and the pyrrolidine nitrogen have substantial double bond character as do the bonds between the radical prostereogenic center and the amide nitrogen. The conformation about the C=C bond of the enamine is fixed since it is part of a ring while the conformation about the corresponding bond of the radical is fixed by 1,2 steric effects as described in Section 5.2.2. The acrylamide and the enolate shown below also have structures analogous to radical **9**.



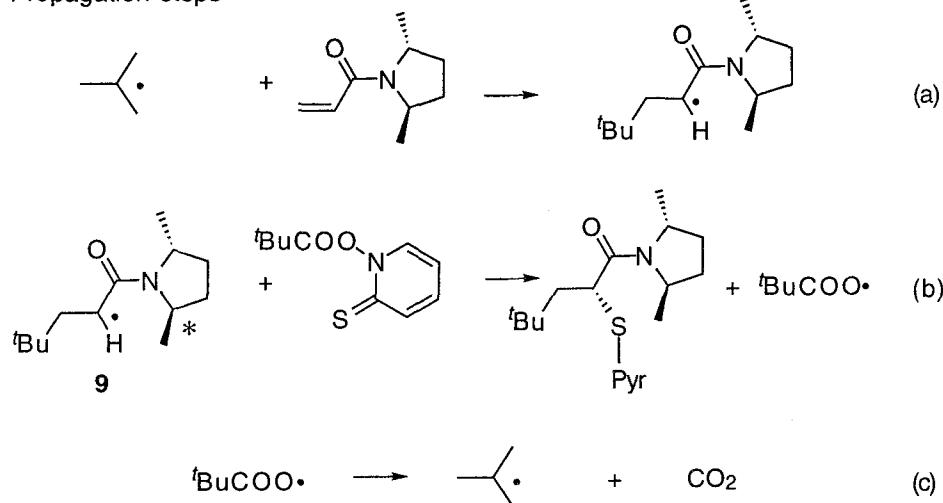
Radical **9** substituted with several different R groups can be generated in different propagation sequences and the stereochemical course of the reactions of this radical have been examined. Thus, radical **9** can be generated by abstraction of a halide from an appropriate precursor by a stannyl radical,^{26,27} by free radical addition to an alkene substituted with this amide group,²⁶ and by decarboxylation of an appropriate radical generated by Barton thiohydroxamate methodology.²⁷

Reaction of the acrylamide **10** with the thiohydroxamate ester of pivalic acid gives the addition compound **12** (Eq. 5.7) formed by the

sequence outlined in propagation steps (a), (b), and (c). The stereoselective free radical reaction in this sequence is a thiopyridyl group transfer to radical **9** (step b) and the major diastereomer formed in the transfer reaction (5.7/1) has the configuration at the new stereogenic center as shown. This is in accord with the predictions of radical conformation outlined in Section 5.2.3. The proximal stereogenic center of the pyrrolidine, shown in the scheme with an asterisk, shields the front diastereotopic face of the radical from reaction and the group transfer proceeds to the back face of the radical.

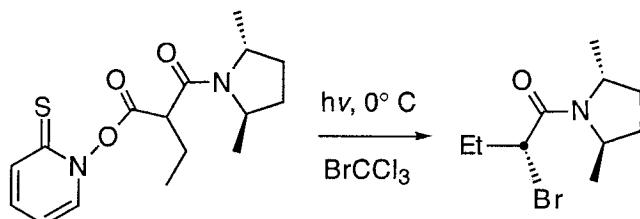


Propagation steps

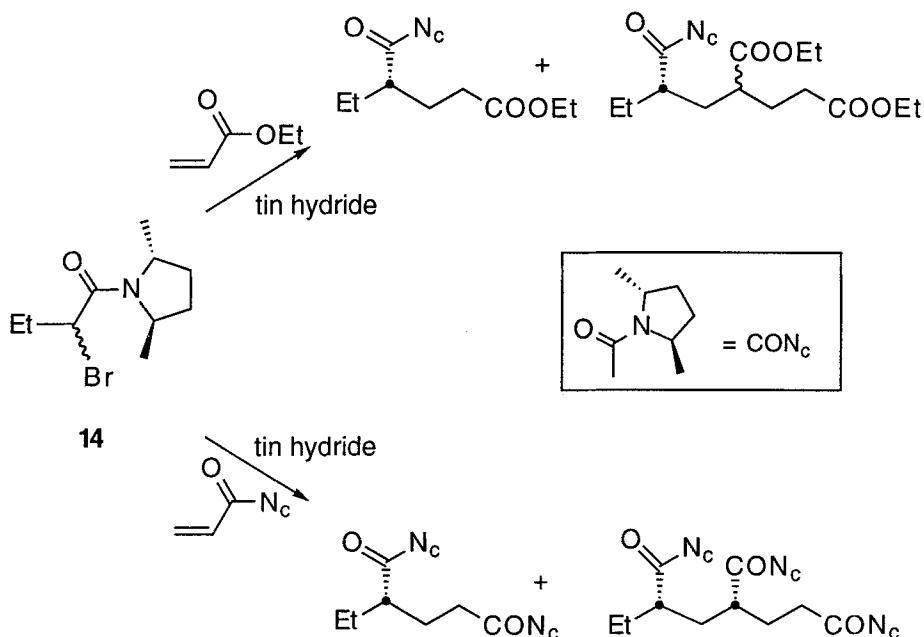


Halogen atom transfer to radical **9** also occurs with substantial selectivity. The Barton ester **13** reacts with bromotrichloromethane in a Hunsdiecker-type reaction to give a bromide with a selectivity of 17/1 at 0°C (iodide atom donors also lead selectively to the iodide). Here again, the configuration of the new stereogenic center formed in the sequence is

defined in the transfer reaction of radical **9** and the selectivity observed in the radical process compares favorably with the selectivity observed for iodination of the corresponding enolate.²⁷

**13**

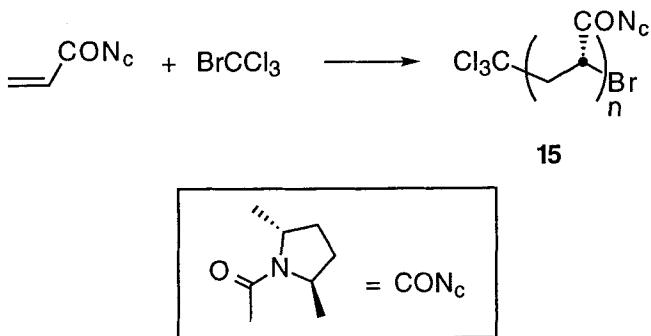
Radical addition of **9** (or its analogs) to alkenes also proceeds with significant control of configuration of the new stereogenic center formed in the process. Thus, reaction of the bromide **14**, ethyl acrylate and tributyltin hydride gives products of addition to **9** of one and two acrylates. The first radical addition occurs selectively while the second addition gives a nearly equal mixture of diastereomers. In the selective first addition step, the pyrrolidine amide serves as a stereocontrol element in the addition reaction



since it is attached directly to the prostereogenic radical undergoing addition. In the addition of the subsequent radical, there is no control element attached directly to the prostereogenic center, and the products with two possible configurations of the new stereogenic center are formed in nearly equal amounts.

Reaction of the bromide **14** with the acrylamide **10** and tributyltin hydride again gives rise to single and double addition products. In this case, not only is the first addition stereoselective but also the second addition is selective. In both steps, a dimethylpyrrolidine amide group is attached directly to the prostereogenic radical center undergoing addition and therefore the configuration of the new stereogenic center formed in each addition is “controlled” by the auxiliary group.

Chain transfer telomerization of the acrylamide **10** was carried out with BrCCl_3 as the chain transfer agent.²⁷ Products **15** with $n = 1-5$ were isolated by HPLC. For each telomer, one major diastereomer was observed and the configuration of each is presumably as shown in structure **15**. The configuration of the new stereogenic center formed in each addition reaction is controlled by the pyrrolidine auxiliary group that is “brought along” with the acrylamide at each addition step.

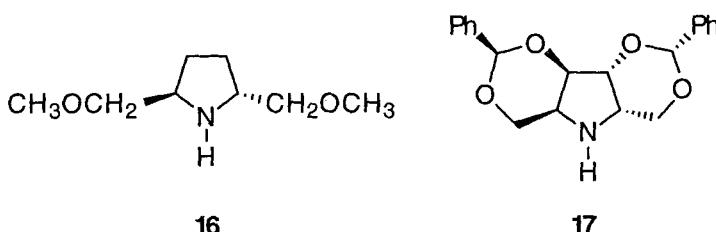


The study of dimethylpyrrolidine amides (and the related Oppolzer's sultam discussed in Section 5.2.3.2) was an important first step in stereoselective free radical chemistry because this research demonstrated the possibility that an auxiliary group could control the configuration of new stereogenic centers formed in radical atom and group transfers as well as in radical addition reactions. Nevertheless, there are problems with the dimethylpyrrolidine auxiliary group. First, although the auxiliary is effective, it is difficult to prepare. There are inconveniences associated with

most of the syntheses of optically pure 2,5-dimethylpyrrolidine that have been reported. The synthesis from alanine,²⁸ although reasonably efficient, sometimes requires a “training period” for one of the steps, a low temperature allylation of a primary iodide. An approach involving a yeast reduction of 2,5-hexanedione²⁹ has also been reported but this reduction is cumbersome on a large scale.

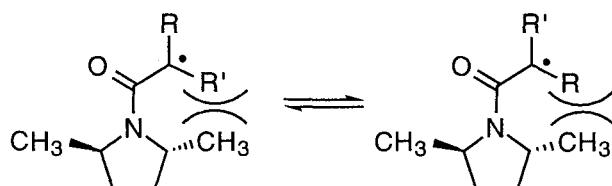
Another problem with 2,5-dimethylpyrrolidine as an auxiliary for free radical reactions is that this group is difficult to hydrolyze after reactions. Removal of the stereocontrol element is, of course, a requirement for use of an amine or amide as an auxiliary group. In spite of this requirement, hydrolyses of amides of 2,5-dimethylpyrrolidine are difficult and sometimes impossible, particularly for amides substituted at the α position.

Because of these limitations, other substructural units based upon C_2 symmetry have been used to control stereochemistry in free radical reactions. The amines **16** and **17** have a C_2 symmetry element, and they have recently been applied as auxiliary groups in free radical reactions.³⁰ The dimethoxy compound **16** should have essentially the same capacity to control the configuration of new stereogenic centers formed in free radical sequences as does 2,5-dimethylpyrrolidine. In the one reaction examined where a stereogenic center was formed from a prostereogenic radical, whereas the dimethylpyrrolidine gave an 85:15 diastereomer mixture (see Eq. 5.7), the opposite enantiomer of the dimethoxy compound gave a 14/86 product mixture. Syntheses of both **16**³¹ and **17**³² are reasonably straightforward and amides derived from these amines can be hydrolyzed under conditions that normally do not cause epimerization of centers α to amides, esters, and acids.³³ The use of the auxiliary groups **16** and **17** will be discussed in greater detail in Section 5.2.



The analysis of the stereoselectivity in radical reactions at prostereogenic radical centers α to amide auxiliary groups focuses on secondary stereogenic radical centers bearing the amide, an alkyl group, and hydrogen.

Stereoselective radical reactions at tertiary centers are more difficult to control. The reactions of tertiary radicals α to amides prepared from 2,5-dimethylpyrrolidine have been examined³⁴ and stereoselectivities observed are generally lower than those observed for secondary radicals. Analysis of the conformation about the $\bullet\text{C}-\text{C}(\text{O})$ bond is not straightforward for tertiary radicals since, unlike secondary radicals, there is no clearcut preference for one conformer based upon 1,2-steric interactions.



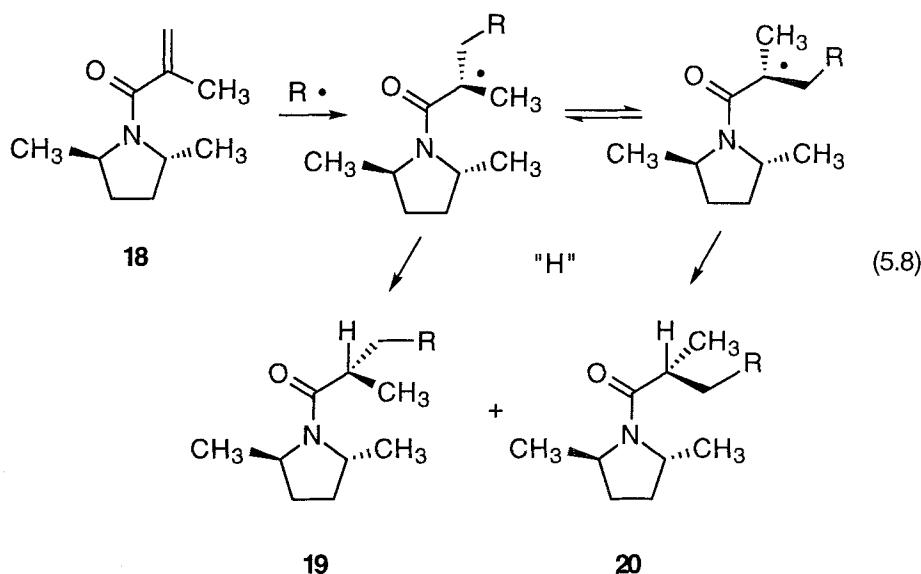
Radical additions to the methacrylamide **18** have been reported³⁴ and this alkene is substantially less reactive than the corresponding alkene **10** having no α methyl group. Tertiary butyl radicals add to **18** about forty times slower than they add to acrylamide **10**. The methacrylamide is apparently twisted because of steric compression and the activation of the alkene by the acrylamide carbonyl is reduced because of this distortion.

The stereoselectivity of the sequence described in Equation 5.8 depends on the group R that is added to the alkene. Thus, for R = *t*Bu, the product ratio **19/20** at 20° C is 90/10 while this ratio is 80/20 for addition of cyclohexyl and 67/33 for R = Me.

The configuration of the products formed in the addition to acrylamide **18** can be understood based upon a twisted radical intermediate. The hydrogen atom donor delivers hydrogen to this intermediate from the face of the radical *cis* to the small carbonyl oxygen. The addition of larger R radicals (*t*Bu) to **18** leads to a radical that has a substantial preference for one of the twisted conformers. The reactions of these radicals are therefore more selective than those where the radical added is smaller (for example, R = Me). The smaller reactant radical produces a product radical that has less of a bias for one twisted conformer compared to the other. The “twist sense” of the intermediate radical is controlled by the chiral auxiliary.

In support of the strain arguments presented above, alkenes like **18** have been analyzed by X-ray crystallography and the alkene-amide substructure is found to be substantially non-planar. The amide nitrogen- α methyl torsion angle is only 119° for one such alkene compared to 180° for

a completely planar system. Allylic strain causes distortion from planarity for the alkene and allylic strain would affect the intermediate radical in a similar way. The radical is more destabilized than is the alkene by this effect and the energetic price of nonplanarity increases as the addition reaction proceeds. Radical stabilization apparently requires a planar structure for maximum delocalization.



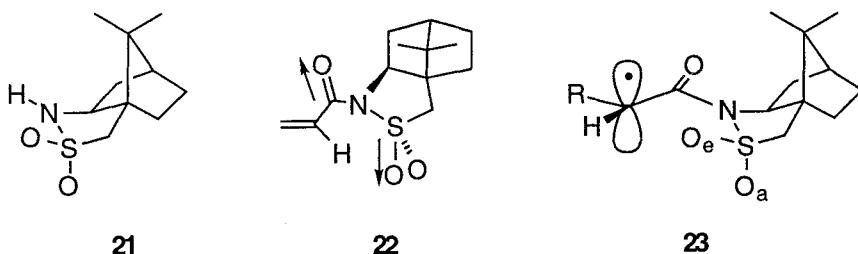
Amide auxiliary group control of configuration for tertiary pro-stereogenic radicals must be considered as one of the currently unsolved problems in free radical chemistry. The strategies for control that have emerged for secondary radicals cannot be applied in a straightforward way to the control of reactions of tertiary radicals.

5.2.3.2 Dipole–Dipole Conformational Control of Radicals

The *dipole–dipole* interaction is a potentially powerful conformational control element and such interactions have been used to account for the orientation of radicals³⁵ bearing an imide derived from camphor sulfonic acid—the so-called Oppolzer's sultam **21**.^{36,37}

The sultam has been used extensively in ionic reactions and chelation models have been proposed to rationalize the observed stereoselectivity. Thermal cycloaddition reactions of amides derived from the sultam are also stereoselective and dipole–dipole interactions are apparently important in

controlling the conformations of the amide. For the acrylamide **22** derived from the sultam, the dipoles of the carbonyl group and one of the sultam S=O bonds are oriented *trans* (*E*) about the C(O)–N bond to minimize energy and the SO₂ and vinyl carbon therefore have a Z orientation.



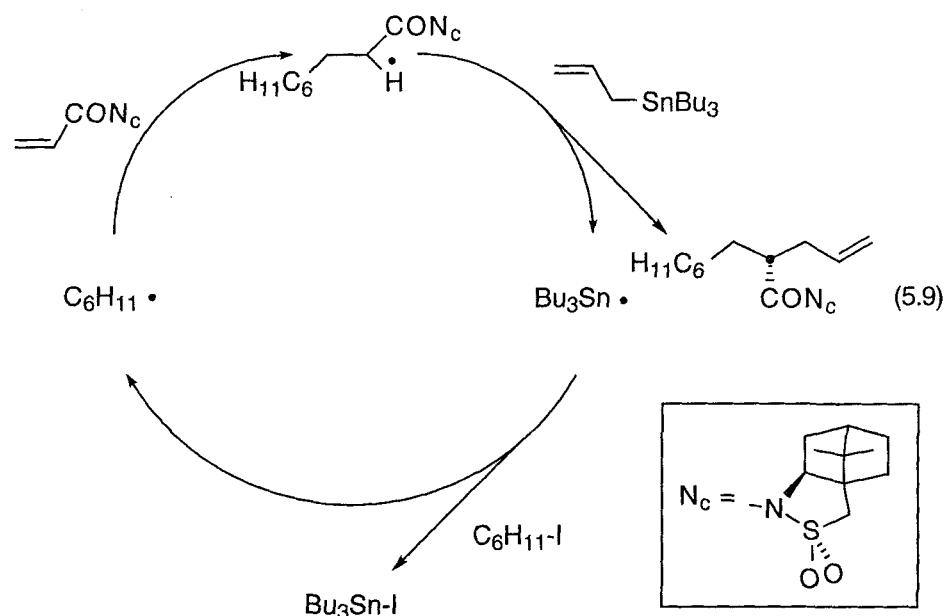
A secondary prostereogenic radical derived from the Oppolzer sultam-amide is shown in structure **23**. The *trans* dipole arrangement of the carbonyl and S=O_e dipole is shown in the structure. The orientation about the radical carbon–C(O) bond is such that the small group on the radical (H) is *cis* to the large amide nitrogen, the same arrangement that was suggested for this bond in radicals bearing the dimethylpyrrolidine amide.

Radicals with structure **23** react stereoselectively in several different propagation reactions.^{38,39} The reaction of the acrylamide **22** with alkyl iodides and allyltributylstannane⁴⁰ is particularly useful since three components, the alkene, an alkyl group and an allyl group are joined by the sequence. The chain sequence is shown in Equation 5.9 as is the 1/1/1 adduct formed. A nucleophilic cyclohexyl radical adds to the electron deficient alkene **22** to generate the radical **23** with R = CH₂-C₆H₁₁. Allyl transfer to this radical occurs (with a temperature dependent selectivity) giving an 11/1 product ratio at 80°C. This selectivity increases to over 20/1 at 0°C or below.

Telomers formed from the incorporation of two acrylamides (1/2/1 adducts) are also isolated, but these products are formed in a nearly 1/1 mixture of diastereomers, unlike the telomers formed from the dimethylpyrrolidine acrylamide.^{39,41}

There are some limitations to the allyl transfer sequence shown in Equation 5.9, the chief one being that the reaction does not propagate well at lower temperatures where the selectivity is highest. Yields go down as selectivity goes up. The culprit in the propagation sequence that is responsible for the poor reaction rate at lower temperatures is the allyl

transfer step. Indeed, the rate constant for allyl transfer from allyl stannanes⁴² is on the lower end of “acceptable” bimolecular rate constants that insure dominant propagation instead of termination. Improvements in the allyl chain transfer agent that permitted reactions to be carried out at low temperatures would be a welcome development.

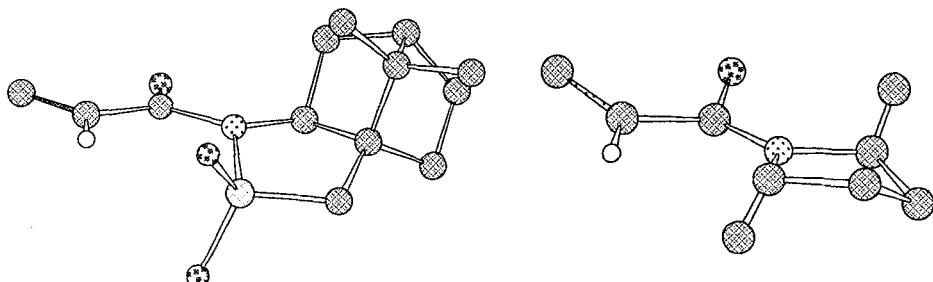


The alkene **22** is one of the most reactive mono-substituted alkenes studied in addition reactions with carbon radicals.⁴³ It reacts with cyclohexyl radical nearly 200 times faster than does styrene, presumably because **22** is very electrophilic. The imide carbonyl is apparently a stronger electron-withdrawing group than is $-\text{COOR}$, $-\text{CHO}$, $-\text{C(O)NR}_2$ or cyano. Cyclohexyl radical reacts with **22** even faster than it reacts with dimethylfumarate, an alkene substituted with two electron-withdrawing groups.

The rationale for stereoselectivity in reactions where the Oppolzer's sultam is used as an amide (in reality it is an imide) auxiliary has been debated.³⁵ Of the proposals put forward, the suggestion that one of the sultam oxygens serves to shield one face of the adjacent radical (for selectivity when it is attached directly to a radical) or the alkene (for cycloaddition reactions) would appear to have the most merit. Indeed, comparison of amides derived from the Oppolzer's sultam with those derived from 2,5-dimethylpyrrolidine is instructive. Single crystal X-ray analysis of

alkenes bearing the sultamimide and the pyrrolidine amide have shown that the axial sultam oxygen,^{37,44} labelled O_a in structure **23**, and the *cis* methyl group of the pyrrolidine occupy essentially the same positions in space relative to their corresponding α alkene carbons, see Figure 5-5a. It seems reasonable to suggest that, if anything, radicals bearing these auxiliary groups will be stiffer about the α,β bond (*i.e.* more prone to be planar) than the corresponding alkenes because of the requirement for delocalization.

a.) X-ray structures



b.) Models for radical facial selectivity

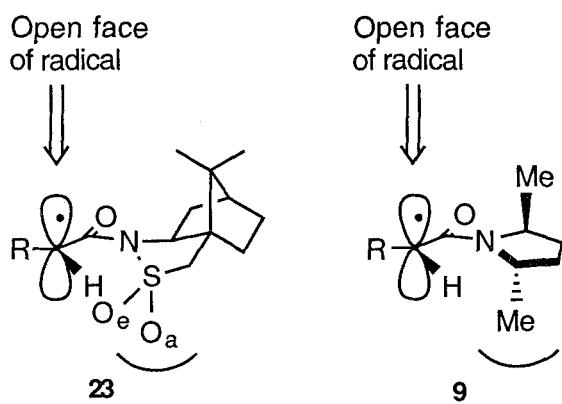
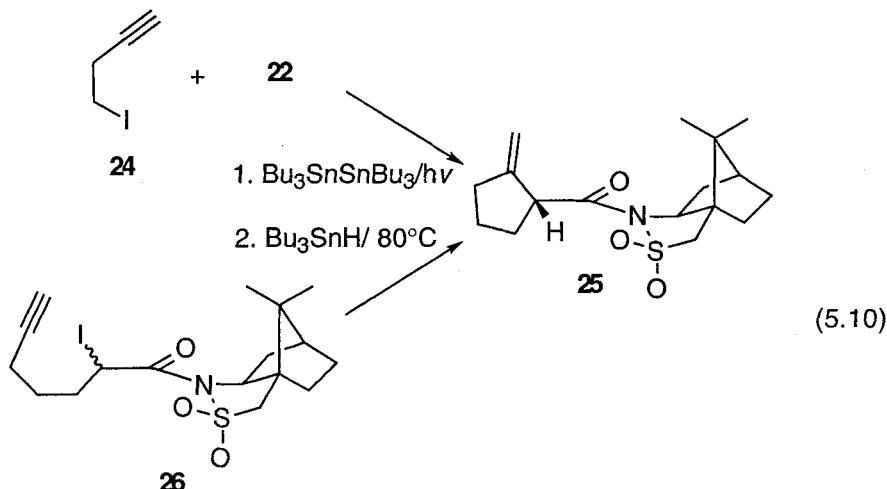


Figure 5-5. X-ray structure of Oppolzer Imide and 2,5-Dimethylpyrrolidine Amide and Models for Selectivity.

Translation of these alkene geometries from the X-ray analyses to the comparable radical geometries leads to the reasonable conclusion that Oa serves the same shielding role in reactions of radical **23** that the shielding methyl group serves for dimethylpyrrolidine amide radical **9**, see Figure 5-5b. The axial sultam oxygen and alkene α carbon are 1,4-separated by two partial double bonds and the axial methyl and alkene α carbon are also 1,4-separated by two partial double bonds. The Oppolzer's sultam is a "dimethylpyrrolidine in disguise".³⁵

Unlike the dimethylpyrrolidine, the Oppolzer sultam auxiliary is easy to remove from products of reaction by reduction or hydrolysis. It is commercially available as both enantiomers. It reasonably satisfies all of the requirements of a free radical chiral auxiliary group when attached to a prosterogenic secondary radical center (although improvements leading to higher selectivities at elevated temperatures would be welcome).

Other selective reactions utilizing the Oppolzer sultam have been reported. Atom transfer annulation of substrates bearing the sultam proceed in high yield with high selectivity. Thus, the reaction of acrylamide **22** with the iodide **24** gives the methylene cyclopentane **25**, a 6-*endo* cyclization product (not shown), and the diastereomer of **25** as a 27/3/1 product mixture. Essentially the same product distribution is obtained from atom transfer cyclization of **26** (Eq. 5.10).



The stereoselectivity of both of these reactions is determined in the cyclization step, and the configuration of the new stereogenic center formed is consistent with the model presented for radical **23**. Cyclization occurs to the face of the radical opposite from the axial sultam oxygen. Indeed, for all reactions where auxiliary groups have been used successfully in radical cyclization to control stereochemistry, the configuration of the new stereogenic center can be understood based upon the model developed for intermolecular radical reactions.

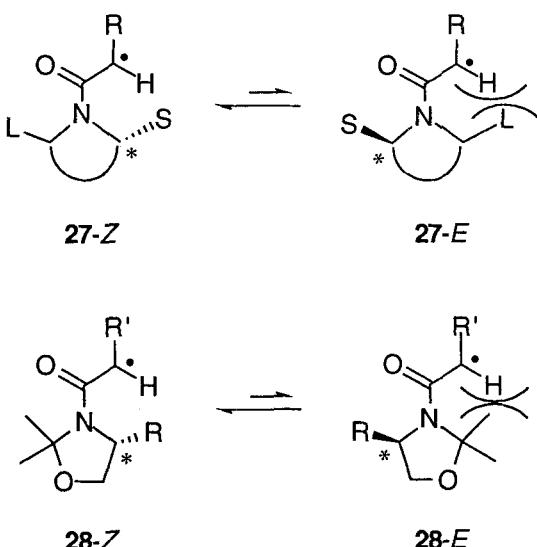
5.2.3.3 Steric Conformational Control of the Amide

A third strategy that has emerged for controlling the orientation about the carbonyl–nitrogen bond of an amide auxiliary group is based upon steric interactions of the groups attached to the amide nitrogen and the carbonyl group.^{44,45}



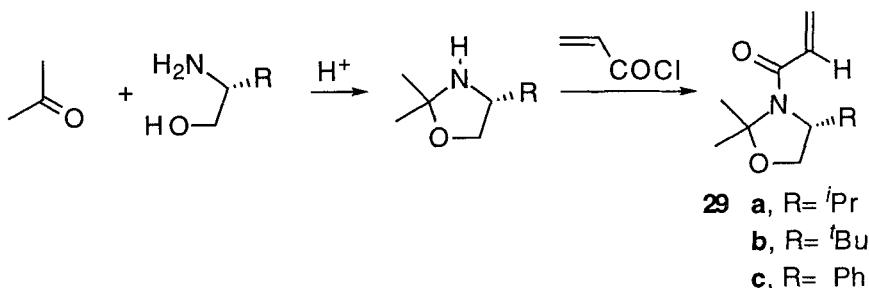
The large group attached to an amide nitrogen prefers to be *cis* to the small amide carbonyl and one anticipates this same preference for groups attached to nitrogen of radicals α to amides. Consider, for example, the radicals **27** and **28**. The carbonyl carbon of the amide is substituted by a small oxygen (S) and a larger substituted carbon atom bearing the radical (CHR^{\bullet}). With this steric difference to build upon, substitution on the amide nitrogen can assure that a chiral stereocontrolling center, indicated by the asterisk, resides *cis* to the radical center if that controlling center is smaller than the group on the other arm of the amide.

For both **27** and **28**, the “Z” conformation is presumably favored relative to conformation “E” because of steric effects. The stereogenic center of the amide of **27** is sterically less demanding than the arm of the amide having the large (L) group attached. For **28**, an amide derived from an oxazolidine, two methyl groups are attached at the quaternary α center of the heterocycle, making that arm of the amide larger than the one having the stereogenic center (indicated with an asterisk).



Oxazolidines are easy to prepare from amino alcohols (readily available from the corresponding amino acids). They have been used as auxiliary groups in thermal reactions of metal carbenes,⁴⁶ in cycloadditions,⁴⁷ in enolate alkylations,⁴⁸ and in radical cyclizations.⁴⁹ A general discussion of analogous amides that includes extensive X-ray analysis has been published.⁵⁰

Amino alcohols and acetone react to give oxazolidines that may be subsequently acylated *in situ* to give precursors to radical **28**. Thus, reaction of acetone with valinol, *tert*-leucinol, or phenylglycinol (TsOH catalysis) followed by acylation with acryloyl chloride gives the acylamides **29a-c** in yields in excess of 90%.⁴⁷ Single crystal X-ray structural analysis of several of the oxazolidine amides like **29** have been solved, and in every case examined, the quaternary group of the oxazolidine is *Z* with respect to the carbonyl oxygen and the carbonyl oxygen bisects the C-C-C bond angle of



the oxazolidine quaternary center. The single-crystal X-ray structure of acrylamide **29b** is shown in Figure 5-6.⁴⁵ For the alkyl substituted oxazolidines **29a** and **29b**, the local conformation about the amide linkage is relatively rigid since there is a close contact of the groups attached to the oxazolidine stereogenic center α to nitrogen and the alkene carbon bearing the amide. The H_a-H_b distance for **29b** is only 2.04 Å and the *tert*-butyl substituent is staggered about the C_{ring}-C_{t-Bu} bond with one of its *tert*-methyl groups situated over the alkene α center such that there is a “gear-like” arrangement of H_b and the *t*Bu group. Movement about the rotatable C(O)-C=C and C(O)-N bonds cannot occur without crowding the butyl group into the alkene α center or eclipsing the amide carbonyl oxygen with one of the methyls on the quaternary center of the oxazolidine.

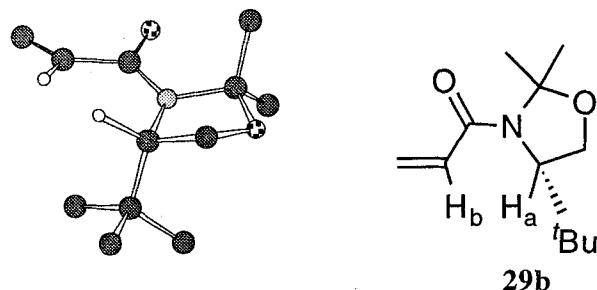


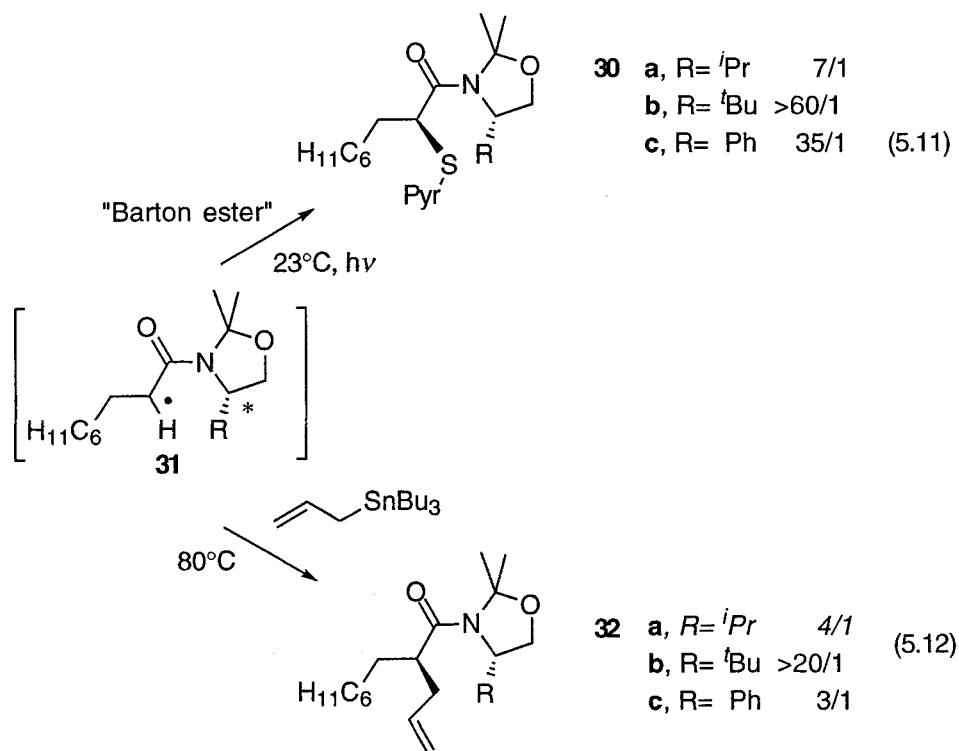
Figure 5-6. Portions of Single Crystal X-Ray Structure of Compound **29b**.

For the radical **28b** ($R = {}^t\text{Bu}$), one anticipates a structure very similar to the alkene **29b** with the possible exception that steric crowding may be even more severe. The rotatable C(O)-C=C bond of the alkene is replaced in the radical by a C(O)-C(\bullet)HR bond that is, presumably, resistant to torsion because of radical delocalization. The structural requirements for radical stabilization by delocalization of radical **28b** may not readily allow distortions about the C(O)-C(\bullet)HR bond.

The NMR spectra of acrylamides **29a-c** are of some interest with respect to the conformational issues raised above.⁴⁵ Two conformations for each of the alkenes can be identified in the room temperature ^1H NMR spectrum and NOE experiments allow assignment of the *Z* and *E* conformers. For the alkenes **29a** and **29c**, the *Z* conformer dominates the equilibrium by greater than ~8/1 while the *Z/E* ratio is only 2/1 for alkene **29b**. For a large

group at the stereogenic center on the oxazolidine, for example *t*Bu, the equilibrium in solution is shifted to a more equal distribution of conformers.

Radicals bearing the oxazolidine amide auxiliary group react with good selectivity in several atom and group transfers and in radical addition reactions. Addition of cyclohexyl radical to acrylamides **29a-c** followed by transfer of a thiopyridyl group from a Barton ester to the intermediate radical proceeds with good to excellent selectivity for each of the oxazolidines (Eq. 5.11). An X-ray analysis of **30b**, the product of the transfer for **29b**, is consistent with a geometry of allyl transfer to the radical



from above the plane of the radical intermediate shown in Equation 5.11⁴⁵. Allyl transfer from allyltributylstannane to the oxazolidine radical occurs with less selectivity than does thiopyridyl transfer (Eq. 5.12). The butyl substituted auxiliary gives excellent selectivities for this reaction, even at 70°C , and the products of the reaction can be hydrolyzed to the corresponding carboxylic acids without epimerization of the stereogenic center formed in the reaction. The major diastereomer of **32** formed for

each of the auxiliaries, R = *t*Bu, *i*Pr, and Ph is as shown in Equation 5.12. The configuration of the new stereogenic center is defined by transfer to the face of the radical opposite from the R group as shown for radical **31**.

The experiments with the oxazolidines described above, along with investigations of other transfer reactions and of radical additions, leads to the conclusion that selectivity obtained for the dimethylpyrrolidine auxiliary can be matched or surpassed by one of the oxazolidines in every reaction examined. The oxazolidine auxiliaries are prepared from commercially available amino alcohols as both enantiomers. The expense of some of the amino alcohols (and of the Oppolzer's sultam) makes their use prohibitive in some instances. Unfortunately, those amino alcohols that are cheap and readily available do not give the best selectivities in some reactions, where the auxiliary is attached to the radical center. The oxazolidine with R = *t*Bu, derived from *t*leucinol, gives the best selectivities and it is the most expensive of the amino alcohols.

Improvement in oxazolidine auxiliaries leading to higher selectivities at elevated temperatures is desirable although the oxazolidine with R = *t*Bu gives the best selectivities for allyl transfer and alkene addition at 80°C thus far reported. It seems likely that the auxiliaries recently reported³⁵ would also give high selectivities in allyl transfer. Some preliminary experiments with thiazolidines derived from cysteine indicate that these heterocycles may also serve as auxiliaries for free radical applications although no particular advantage over the oxazolidines has been demonstrated.

5.2.3.4 Telomerization and Polymerization

Addition reactions of radicals **31a-c** to alkenes have been investigated and these reactions generally proceed with good to excellent selectivities. The success of the auxiliaries in these addition reactions has led to a reinvestigation of the control of stereochemistry in polymerization,⁵¹ a problem that goes back nearly seven decades.⁵²

As early as 1929, even before the concept of long chain polymers was accepted, Staudinger correctly pointed out that in every addition reaction in a polymerization of vinyl monomers, a new stereogenic carbon is formed and that a polymer of n units will therefore have 2^n possible stereoisomers.⁵² The tertiary carbons formed in vinyl polymerization reactions can have two different configurations, *R* and *S*, and each addition reaction therefore doubles the number of stereoisomers in the growing polymer chain. Important polymer bulk properties such as tensile strength, melting point,

and solubility all depend on the stereochemistry of the polymer.^{53,54} Since free radical polymerization methods are convenient, the control of stereochemistry in free radical polymerization is of practical importance.

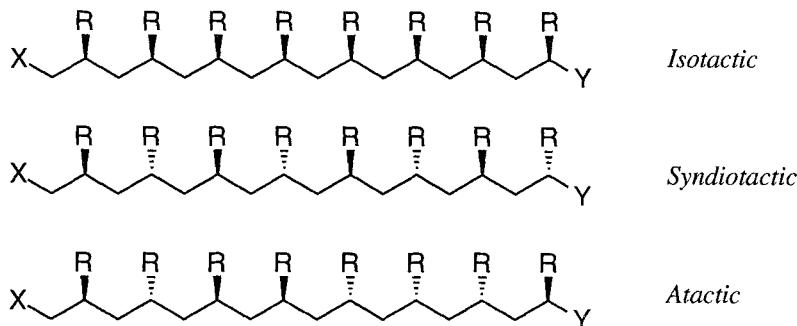


Figure 5-7. Polymer Tacticity.

The two simplest regular arrangements of stereochemistry along a polymer chain are the *isotactic* and the *syndiotactic* arrangements. In the *isotactic* arrangement, all the substituents are located on the same side of the plane representing the chain extended *all-trans* conformation. In the *syndiotactic* arrangement, the substituents alternate from one side of the plane to the other. The random relative arrangement of stereogenic centers is designated as *atactic* (Fig. 5-7).

Polymer tacticity can be controlled in anionic, cationic, and coordination polymerizations, but significant stereocontrol of free radical vinyl polymerization had not been achieved prior to 1992. An *atactic* polymer generally results from free radical polymerization.⁵⁵ Formation of stereoregular chains is primarily kinetically controlled since the energy difference between a *syndiotactic* sequence and an *isotactic* sequence is small, and either can be converted to an *atactic* arrangement under vigorous epimerization conditions.

In free radical polymerization, stereoregularity is determined by the rate difference for addition of a monomer in the growing chain yielding an *isotactic* (*meso*) sequence (k_m) or a *syndiotactic* (*racemic*) sequence (k_r). In the polymerization reaction shown in Figure 5-8, the important stereoregulating effect is a 1,3 steric interaction between the incoming monomer and the substituent (R) on the nearest stereogenic center. This

interaction is minimal due to the conformational mobility of the chain, which does not allow a fixed spatial relationship with respect to the radical. For example, the ratio of the two rate constants for methyl acrylate ($R = COOMe$) is only $k_r/k_m = 1.1$ at $0^\circ C$, and the resulting polymer is *atactic*.

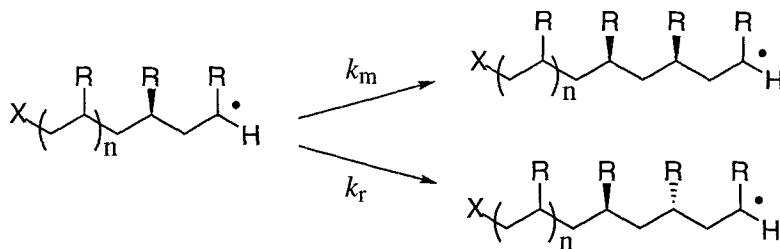


Figure 5-8. Generation of Stereogenic Centers in Radical Polymerization.

Moderate tacticity levels (up to 85/15 or 90/10, that is, k_m/k_r or $k_r/k_m \sim 5$ to 10) have been reported in polymerization of 1,1-disubstituted alkenes, especially bulky methacrylic esters,^{56,57} but high tacticity levels with monosubstituted alkenes have been elusive.

Consideration of control of tacticity in free radical polymerizations was accomplished by the use of ideas developed in free radical auxiliary-controlled acyclic stereoselection. Indeed, polymers formed from acrylamides such as **29** (bearing oxazolidine auxiliaries) are highly *isotactic*.⁵⁸

The control of stereochemistry imposed in each radical addition step assures that the configuration of each new stereogenic center formed in the addition will be the same as all other stereogenic centers present in the growing polymer chain.

Chiral auxiliary-controlled polymerization is illustrated in Figure 5-9, where the configuration-defining radical addition step is shown for polymerization of the oxazolidine acrylamides **29a-b**. The auxiliary group with the *S* configuration at the oxazolidine stereogenic center directs the addition of radical **33(n)** to acrylamide **29** from the back face of the prostereogenic radical center. The new stereogenic center in **33(n+1)** is therefore preferentially formed as a *meso* rather than a *racemic* diad. Subsequent diads will also be formed preferentially in the *meso* arrangement and the polymer will be net *isotactic* as a result.

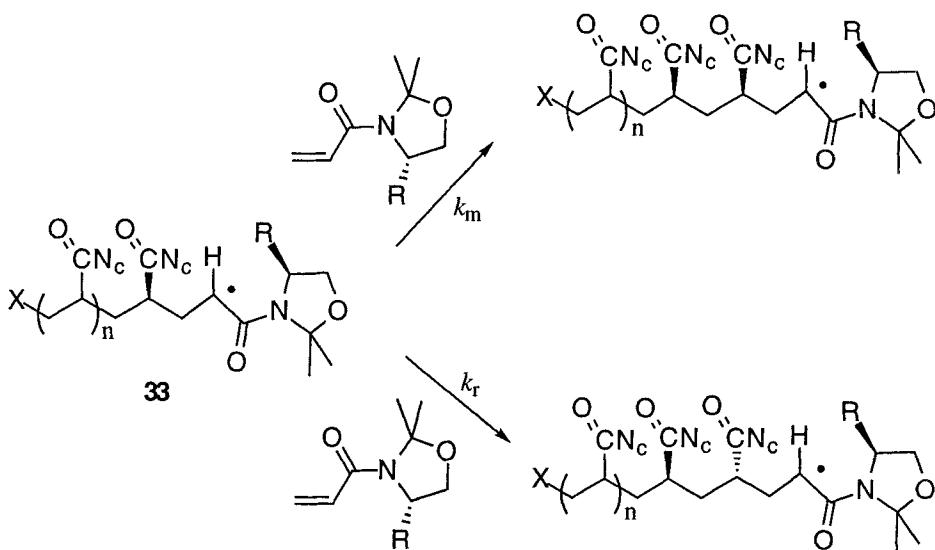


Figure 5-9. Chiral Auxiliary Control of Free Radical Polymerization.

The polymer formed from **29a-b** can be hydrolyzed, without detectable epimerization, to polyacrylic acid. This can be methylated with diazomethane to give polymethylacrylate. NMR analysis of these two derivative polymers gives information about the stereoselectivity of the polymerization, and such experiments lead to the conclusion that polymers formed from both **29a** and **29b** at 80°C have 88-92% *isotactic* diads.

A statistical model based upon chiral auxiliary control in each radical addition step shows that the selectivity for addition that gives 92% *isotactic* diad is on the order of 23/1. Addition of polymer radicals bearing both the *t*Bu and the *i*Pr oxazolidine auxiliary to their monomer is very selective and polymerizations at lower temperatures promise even better selectivities.

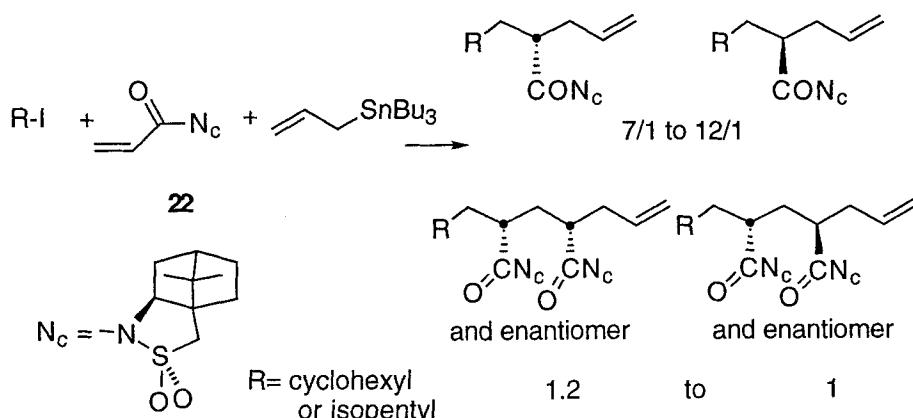
While the polymerization of **29b** (from *l*eucinol, R = *t*Bu) giving highly *isotactic* polymers is not surprising, similar selectivities were not necessarily expected from the valinol derived oxazolidine acrylamide, **29a** (R = *i*Pr). Allyl transfer from allyltributylstannane to radicals bearing the valinol-derived auxiliary proceed with selectivities of only 4/1 at 80°C, but polymers (and telomers) derived from similar radicals apparently react much more selectively.

The polymerization of the acrylimide **22** derived from Oppolzer's sultam has also been studied. Even though radicals bearing this auxiliary

give good selectivities in radical addition (12/1) and cyclization (20/1), the Oppolzer sultam is ineffective as an auxiliary in polymerization reactions. Polymers formed from the Oppolzer acrylamide have approximately 55% *isotactic* diads. They are, essentially, *atactic* polymers.^{39,41}

The reason for the failure of the sultam to control the configuration of new stereogenic centers formed in polymerization reactions is not entirely evident, but the effect is apparently expressed at a very early stage of polymerization. The $n = 2$ product formed from **22**, an alkyl iodide, and allyltributylstannane is formed as an approximately 55/45 *meso/racemic* diastereomeric mixture while the $n = 1$ product is formed selectively.

The results of polymerization and telomerization studies reported for acrylamides **22** and **29** suggest that 1,3 stereocontrol is exerted in competition with auxiliary control in the stereoselective step. For the Oppolzer sultam acrylamide, 1,3 and auxiliary control must be "mismatched" and the result is a polymer with a nearly 50/50 *isotactic/syndiotactic* diad ratio. This view is consistent with the fact that formation of the first stereogenic center occurs with substantial control of stereochemistry while subsequent centers are formed without control. In the first addition reaction, no 1,3 stereocontrol element is present while in subsequent additions, this effect comes into play.



As noted above, polymerization and allyl transfer reactions of the oxazolidine acrylamide **29** give products with a different stereochemical pattern than does the sultam acrylamide **22**. For the acrylamide **29a**, allyl transfer selectivity is only 4/1 at 80° but the polymer is still formed with an *m/r* diad ratio of 92/8. There is no diminution of the *isotactic* diad in the polymer

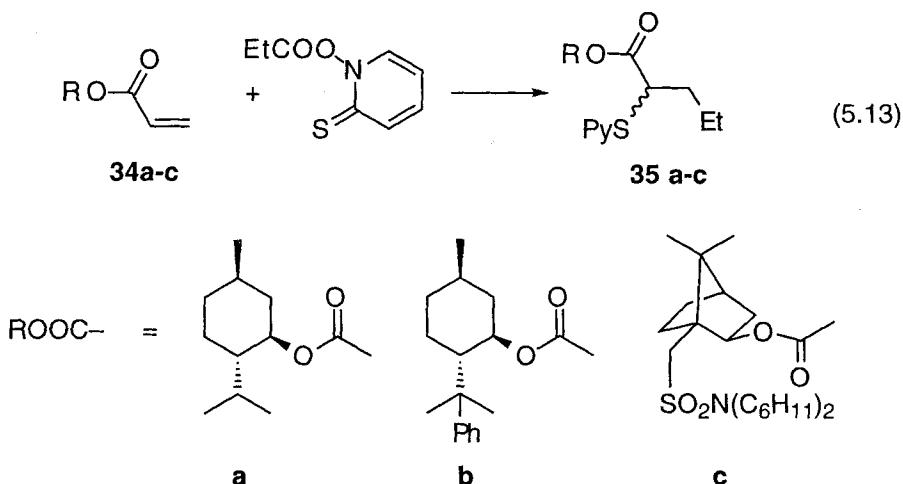
even though the auxiliary group with $R = i\text{Pr}$ is less selective in the single-step allyl transfer reaction than is the case for the auxiliary with $R = t\text{Bu}$.

This suggests that the growing polymer obtained from monomer **29** has a "matched" selectivity for auxiliary and 1,3 control.⁴¹ The "less effective" auxiliary **29**, $R = i\text{Pr}$ (in single allyl transfer reactions) can be used to exert a high level of control of configuration in the multiple addition sequence since 1,3-stereocontrol supplements normal auxiliary control for this auxiliary.

5.2.4 Ester Chiral Auxiliaries for Acyclic Free Radical Reactions

We have seen in previous sections that control of the conformation of radicals substituted α to amides is possible and that the control of conformation is a prerequisite for use of amides as chiral auxiliaries in acyclic free radical reactions. For radicals α to esters, the orientation about both the $\text{C}(\text{O})-\text{OR}$ bond and the $\text{HRC}\bullet-\text{C}(\text{O})\text{O}$ bond must be controlled for esters to be used as auxiliary groups. It has been more difficult to determine how to fix the conformations of esters than was the case for amides.

Early important studies by Crich and Davies demonstrate the problem encountered with ester auxiliary groups.⁵⁹ In these studies, outlined in Equation 5.13, thiopyridyl transfer was examined for the radicals generated by ethyl radical addition to three acrylates **34a-c** in a Barton ester mediated propagation.



For the menthol derivative at 15°C, 8% diastereomeric excess (d.e.) for product **35a** was determined. The phenyl derivative **34b** gives product with 56% d.e. at 10°C while the camphor sulfonamide **34c** gives product at -35°C with 66% d.e.

Hamon and coworkers⁶⁰ have observed substantially better selectivities for captodative substituted radicals bearing the 8-phenylmenthol auxiliary group than is observed for simple alkyl radicals having the same auxiliary. Thus, reaction of the ¹Boc protected 8-phenylmenthol ester of glycine **36** with NBS gives the bromide **37** with tentative configuration as shown in Figure 5-10 in 90% d.e. Treatment of this bromide with tributyltin deuteride at -78°C gives the deuterio derivative **38** with 90% d.e. The compound **38** can be hydrolyzed to deuterioglycine without epimerization, and this conversion establishes the configuration of **38**.

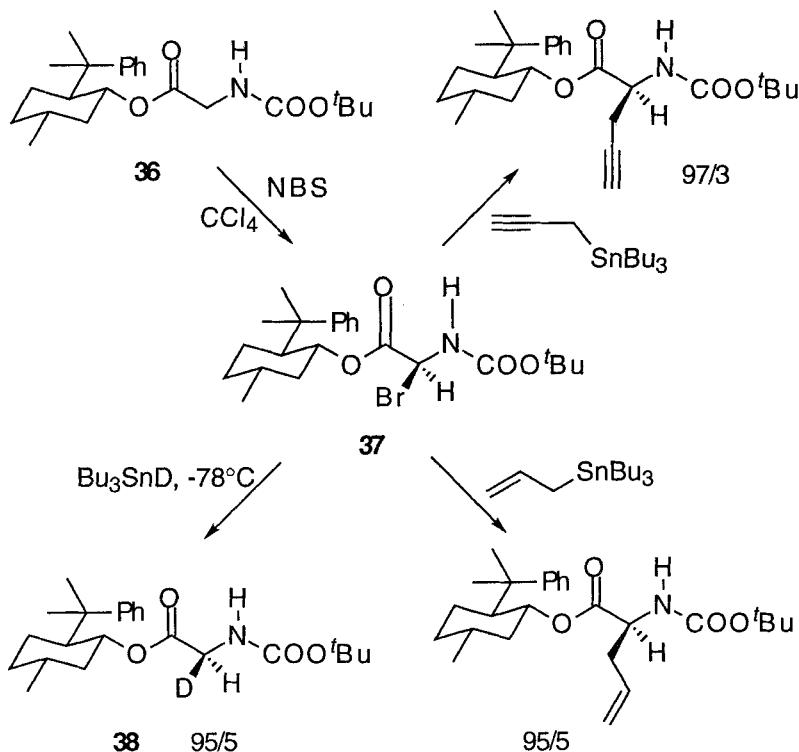
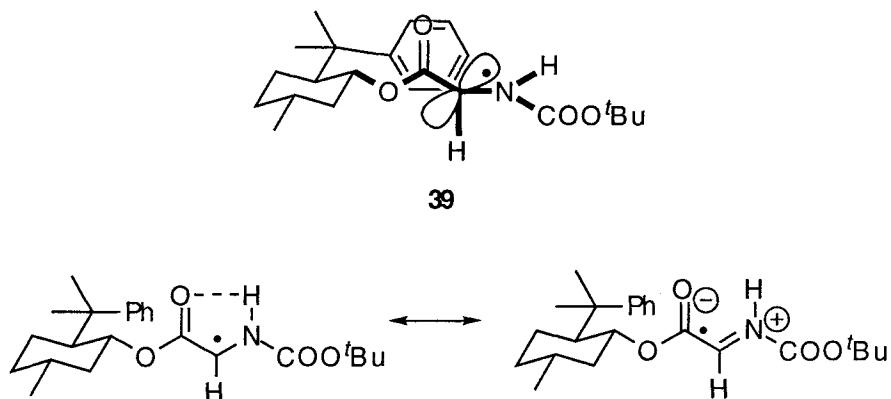


Figure 5-10. Stereochemistry of Transformations of an Amino Acid 8-Phenylmenthol Ester.

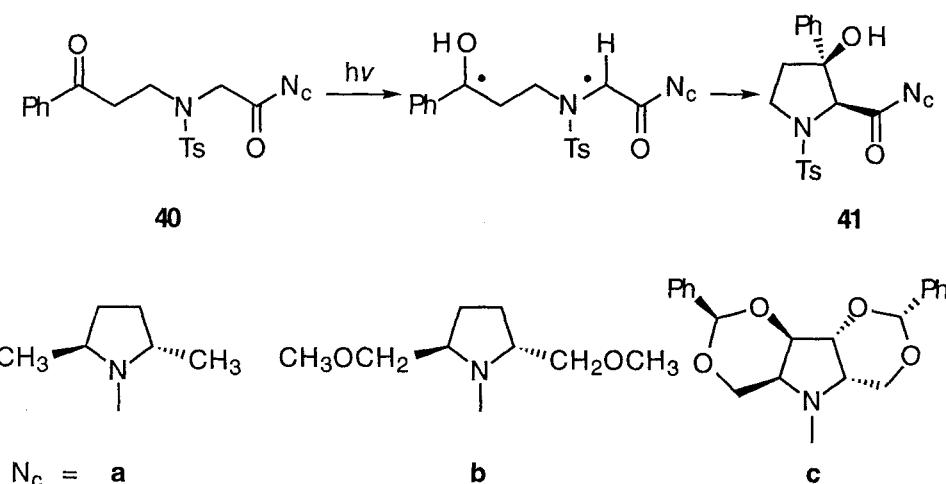
Allyl and propargyl transfer reactions of the radical **39** can also be achieved with excellent selectivity, see Figure 5-10, using allyltributylstannane or propargyltributylstannane. The latter result is somewhat surprising since a propargyl product is formed rather than an allene. All of these reactions apparently proceed through the same captodative radical **39** that reacts selectively in both atom and allyl transfer propagation steps. In the proposed conformation of **39** shown below, a phenyl group shields one face of the prostereogenic radical center. The conformation about the bonds attached directly to the radical-bearing carbon may be controlled by hydrogen bonding or a dipole-dipole interaction (written below as an aminium-ketyl resonance structure) leading to the fixed orientation required for a stereoselective reaction. The contrast in selectivities obtained for the captodative radicals and the simple α ester radicals is striking and must be due to the fact that the captodative radicals have a fixed conformation.



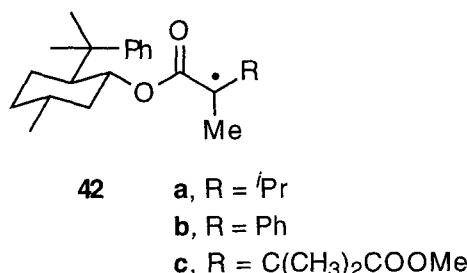
An additional aspect of this work deserves comment. Reaction of the deuterated compound **38** with NBS gives preferential deuterium removal k_D/k_H in a ratio of 73/27. The normal isotope effect (k_D/k_H) for such reactions of about 3 opposes the selectivity observed. This suggests a selectivity of about 9/1 in the step in which the radical is generated, the H(D) atom transfer. The diastereotopic α hydrogens have substantially different reactivity in the NBS transformation. We are not aware of previous examples of this phenomenon in acyclic free radical systems.

Another example of a stereoselective radical reaction from a captodative-substituted radical results from an apparent biradical coupling process. Thus, photolysis of the phenone **40a-c** gives the cyclopentanols **41a-c** with

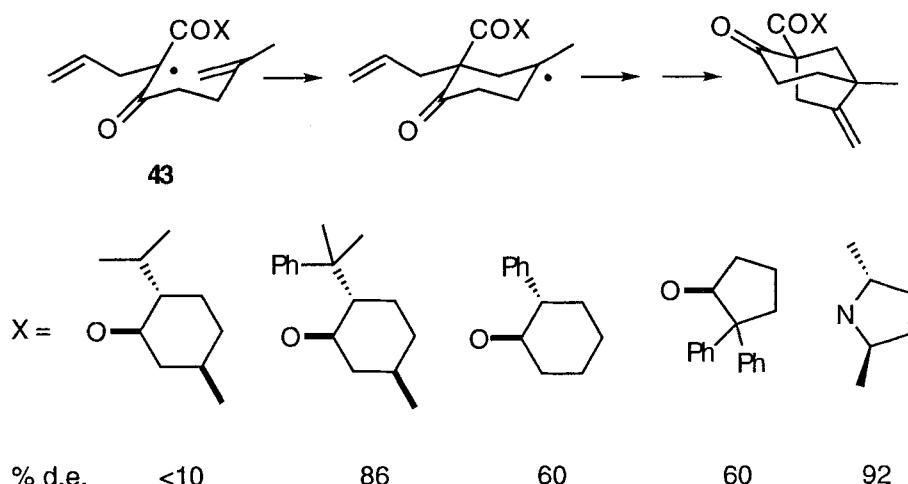
good selectivity for the pyrrolidine auxiliaries **b** (7/1) and **c** (>20/1).⁶¹ Early results with monodeuterated glycine derivatives indicate that the intramolecular hydrogen abstraction is not very stereoselective. It is therefore the radical–radical cyclization reaction that induces the stereochemistry.^{61b}



Tertiary radicals attached to an 8-phenylmenthol auxiliary group can react selectively with tin hydride if one of the alkyl groups attached to the radical center is secondary or tertiary.⁶² The steric requirements for radicals α to these menthyl esters must be quite subtle since **42a** reacts at -80°C with tin hydride to give a 95/5 product mixture while **42b** gives much poorer selectivity. Allyl transfer from allyl-tributylstannane does occur selectively (>99/1) at -80°C with **42b**, however. The radical **42c** reacts selectively with tin hydride even at elevated temperatures.

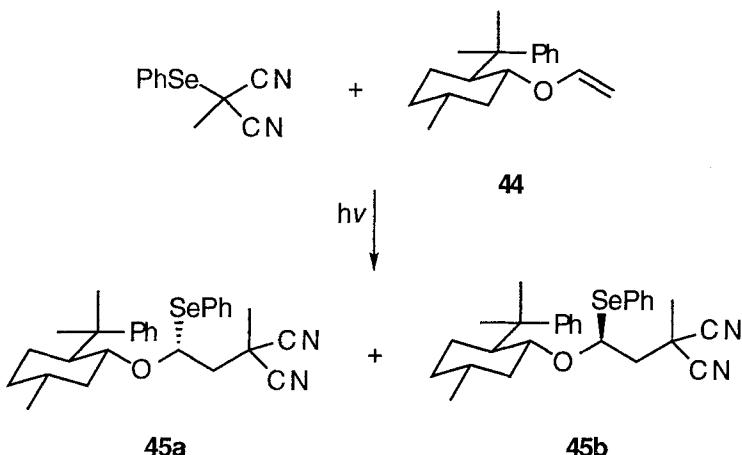


Snider and his collaborators have recently compared several ester auxiliary groups with 2,5-dimethylpyrrolidine amides in *6-endo* cyclization reactions of the radical **43**.⁶³ The selectivities obtained in cyclization generally mirror those observed in intermolecular addition reactions. These examples again illustrate that the models developed for intermolecular radical reactions can apparently be applied successfully to intramolecular additions (cyclizations). Given an auxiliary that is fixed relative to the radical center, selectivities that are obtained for inter- and intramolecular additions are comparable.



5.2.5 Chiral Auxiliaries for Electron-Rich Radicals

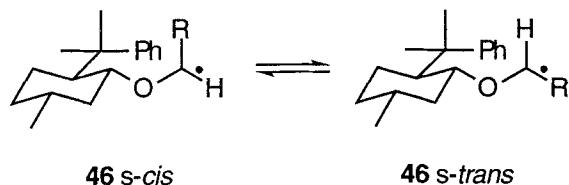
Stereoselective reactions with radicals bearing donor groups have not been investigated as thoroughly as have radicals with electron-withdrawing substituents. It appears, however, that significant control of stereochemical configuration may be obtained when radicals with chiral auxiliaries attached through an ether linkage are trapped.⁶⁴ Such radicals may be obtained by an efficient atom transfer addition of a selenomalononitrile to readily available enol ethers. Thus, reaction of the vinyl ether **44** with the selenomalonate gives the diastereomers **45a** and **45b** in a >40/1 ratio in 90% yield. A similar transformation with a vinyl ether derived from 2-phenylcyclohexanol gives products analogous to **45** with selectivity of 2.5/1.



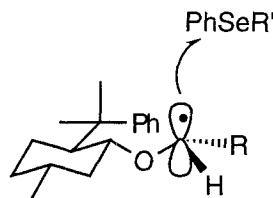
The interpretation of the selectivity of the selenyl transfer reactions is not straightforward. In reactions of radicals with auxiliary groups derived from amides and esters, conformational arguments about the radical are successfully made based upon the conformation of the corresponding alkene. There is apparent structural analogy between radical and alkene. In the case of radical intermediates in the reactions of **44**, application of this popular radical–alkene analogy does not correctly predict the product structure.

Spectroscopic and computational studies of **44** suggest⁶⁵ that the vinyl ether should exist as a mixture of the *s-cis* or *s-trans* forms with the *s-trans* form being slightly favored. The radical–alkene analogy would therefore suggest that the favored radical would be **46** in the *s-trans* form.

Transfer of the selenophenyl group would be expected to occur to the front face of **46** *s-trans* and the product **45b** is therefore predicted from this model. Since **45a** is the major diastereomer formed in the reaction, the alkene based model fails to predict the correct result.



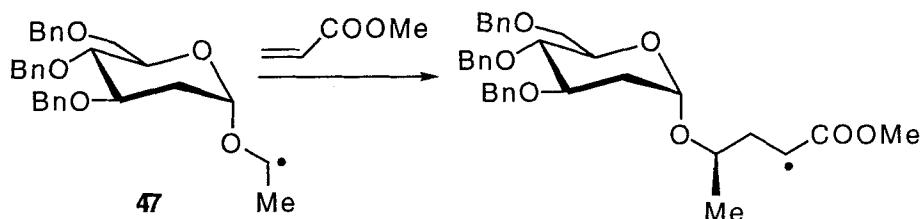
An alternative model consistent with the results based on a “product-like” transition state has been advanced. Calculations suggest^{65b,c} that transition states of α -oxy radicals are significantly pyramidalized, implying a “product-like” transition state. Inspection of single crystal X-ray structures of three of the products from a seleno-group transfer sequence shows that the largest group on the α stereogenic center formed in the transfer reaction adopts a W conformation through the ether oxygen. Based upon this



structure, the model for the transfer reaction is the radical in which selenyl transfer occurs to the top face of the radical. Studies of electron-rich radicals used to develop the product-like model are the first of their kind and more examples are obviously needed to verify models.

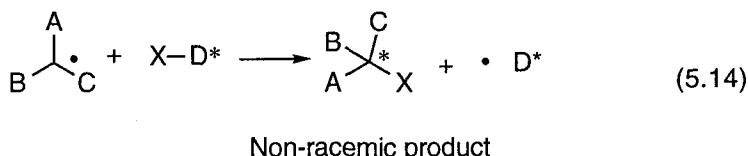
Garner *et al.*⁶⁶ have examined the addition reactions of radicals bearing acetal-based auxiliary groups derived from carbohydrates. The radical **47** adds to methyl acrylate in 60% yield with selectivity of 11/1 (-78°C) in this addition step. The D-sugar derived auxiliary leads to preferential addition to the *si*-face of the radical and the antipodal series will likely be accessible via the “pseudo-enantiomeric” auxiliary derived from L-rhamnose.

It has been suggested that entropic effects are, in part, responsible for the selectivity observed in the reactions of **47**, and this suggests caution when attempting to explain kinetic preferences in terms of enthalpic factors alone.

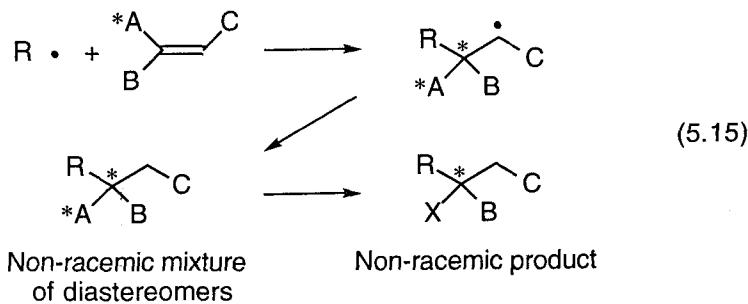


5.3 Auxiliary Group Attached to the Radical Trap

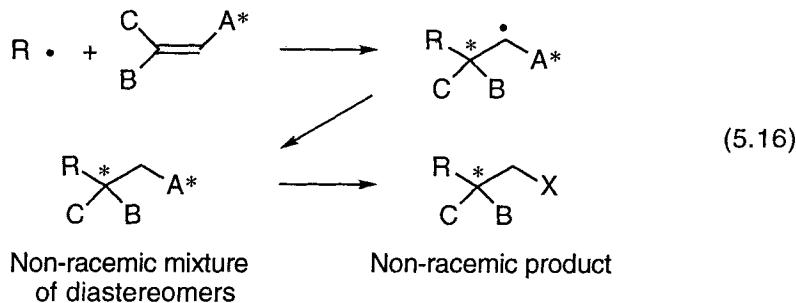
The reaction of a prostereogenic radical with a radical trap that has a resident chiral group can, in theory, give rise to asymmetric induction in the reaction product. Consider, for example, the transformation described in Equation 5.14. A chiral group D* plays an auxiliary (as opposed to substrate) role if the prostereogenic radical undergoes an atom or group transfer reaction with reagent X-D* that results in a product with a new stereogenic center (this particular example might be better designated as “reagent control” of stereochemistry). No examples of selective transformations such as the one outlined in Equation 5.14 have been reported. Reactions of this type are among the challenges that remain in the field.



Alkenes serve as radical traps and if a resident chiral group is attached to an alkene, the chiral group can play a chiral auxiliary role in radical addition reactions. Equation 5.15 illustrates a reaction in which the chiral auxiliary is attached to the center on the alkene undergoing addition, while Equation 5.16 shows an addition reaction in which the chiral group is attached to the center on the alkene remote from the addition. Subsequent removal of the chiral group A* gives a product having a new stereogenic center with a configuration that is defined by that of the auxiliary group.



Development of the strategies illustrated in Equations 5.15 and 5.16 requires knowledge of the favored ground state conformations of alkenes and early advances in this area relied heavily on arguments that had been applied to previous studies of enolate and enamine chemistry.



Auxiliary groups that have been successfully used to define the configuration of new centers derived from prostereogenic radicals are also successful in defining the configuration of centers formed from prostereogenic alkenes. Indeed, the first studies of acyclic auxiliary-controlled radical additions focused on auxiliary groups attached to the alkene (such as in Eq. 5.15) and subsequent studies with the same auxiliaries attached to the radical showed that the alkene–radical structural analogy was valid.

5.3.1 Auxiliaries Attached to the Alkene Carbon Undergoing Addition

Free radical addition to α,β -unsaturated amides of 2,5-dimethylpyrrolidine provided the first examples of auxiliary-controlled free radical addition to alkenes.^{67,68} The lowest energy conformation of such an α,β -unsaturated amide is shown in Figure 5-11. The orientation about the alkene–carbonyl bond is fixed in the Z conformation and C_2 symmetry makes the conformation about the carbonyl–amide nitrogen bond unimportant. In this lowest energy conformation, one diastereotopic face of the alkene is protected from addition by the proximal methyl group that is situated 1,4 with respect to the prostereogenic alkene center.

Free radical macrocyclization of the olefin **48** bearing the dimethylpyrrolidine amide gives rise to four diastereomeric products in 65–70%

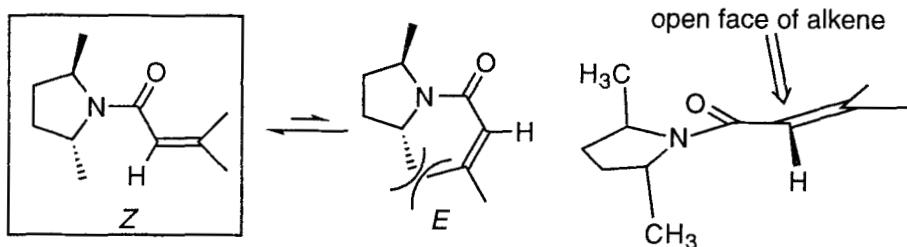
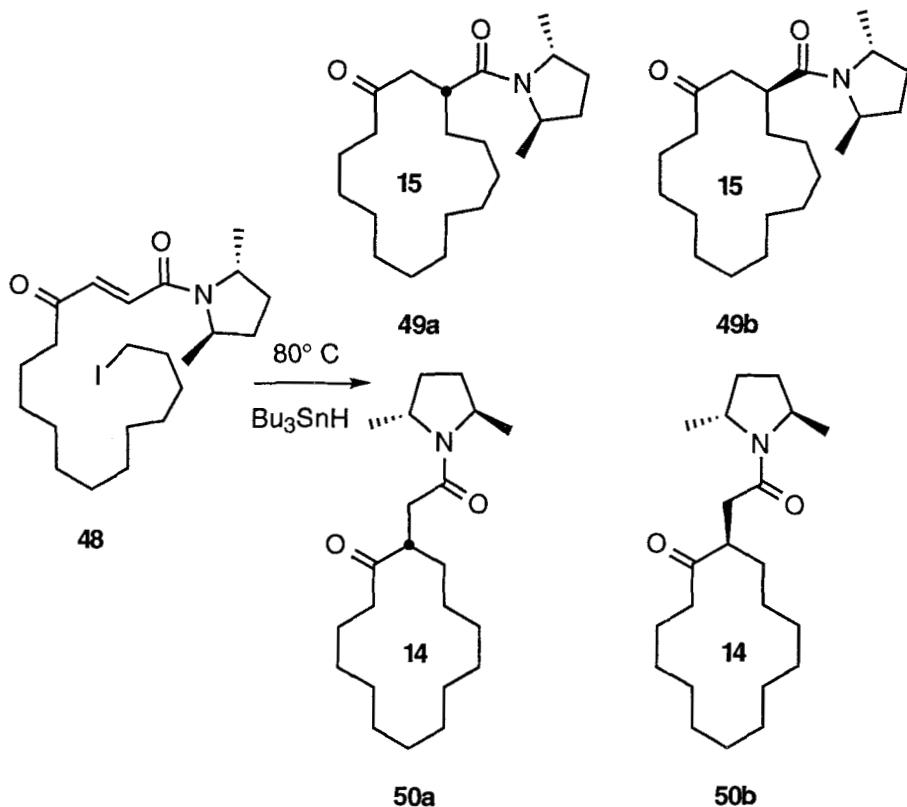
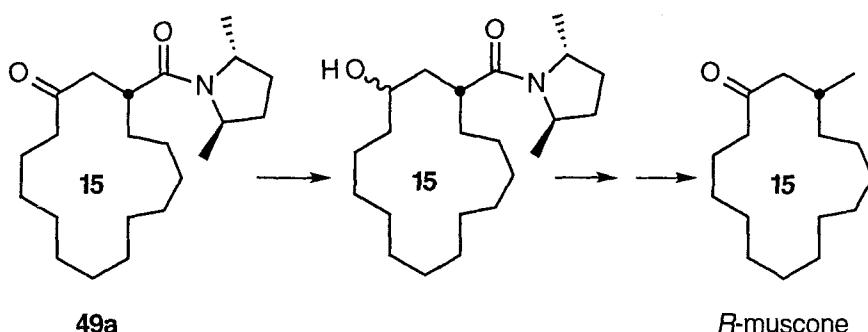


Figure 5-11. Conformation of 2,5-Dimethylpyrrolidine Amide.

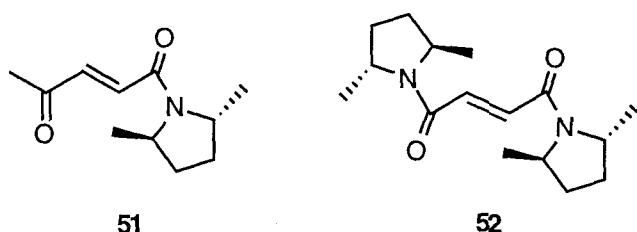
yield.⁶⁷ Two diastereomeric products, **49a** and **49b**, result from an *endo* cyclization, addition of the primary radical to the end of the alkene nearest to the amide. At 80°C, these two fifteen-membered ring products are formed with a selectivity of approximately 14/1, **49a** being the major product formed. Two diastereomeric *exo* cyclization products, **50a** and **50b**, are



formed as a 1/1 mixture. The ratio of regioisomers, **49/50**, is also 1/1 in this macrocyclization. The diastereomer **49a** has been converted to the natural product *R*-muscone to confirm the configuration of the new stereogenic center formed in the macrocyclization.⁶⁷ The hydrolysis of the product amide requires reduction of the ketone to the alcohol before acid hydrolysis. The alcohol presumably assists in the hydrolysis by serving as an internal nucleophile in the reaction.



Intermolecular addition of primary, secondary, or tertiary radicals to the unsymmetric alkene **51** or to the symmetric fumaric diamide **52** results in stereoselective product formation.⁶⁸ For **52**, regioselectivity is not an issue while for **51**, regioisomers may form from addition of radicals at the ketone or amide “end” of the alkene. There is essentially no regioselectivity observed in the addition of primary hexyl, secondary cyclohexyl, or tertiary butyl radicals to **51** and products that result from addition to the ketone “end” of the alkene are formed without diastereoselectivity. Products from radical addition to the amide end of **51** or to the fumaric diamide are formed with appreciable diastereoselectivity, this selectivity being dependent on whether the radical is primary, secondary, or tertiary and also on temperature.



Addition of cyclohexyl or *tert*-butyl radicals to **52** gives essentially one diastereomer at room temperature (50/1 for cyclohexyl and 80/1 for *tert*-butyl). Primary hexyl radical adds to the “amide end” of **51** with a selectivity of only 9/1 at 80°C while lowering the temperature to 0°C increases the selectivity to over 16/1.

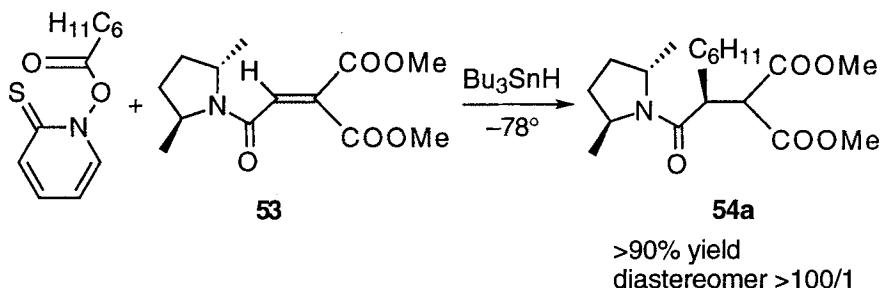
A molecular mechanics analysis of the alkene **51** gives a low-energy arrangement that is in accord with the conformational analysis presented in Figure 5-11. The planar conformation, shown in Figure 5-12, has the *s-cis* unsaturated amide arrangement. Approach of the radical to the alkene carbon at the amide end on a nucleophilic trajectory suggests a facial bias in the addition as can be seen in the Figure. The proximate methyl substituent on the pyrrolidine protects the bottom face from addition while the other methyl substituent is remote from the trajectory of approach of the radical to the top face of the alkene. While the prediction of selectivity presented here is based on alkene ground state arguments, the early transition state implied in radical additions makes this assumption seem reasonable.



Figure 5-12. View of Low Energy MM2 Conformation for Alkene **51**.
(Some hydrogens are omitted for clarity.)

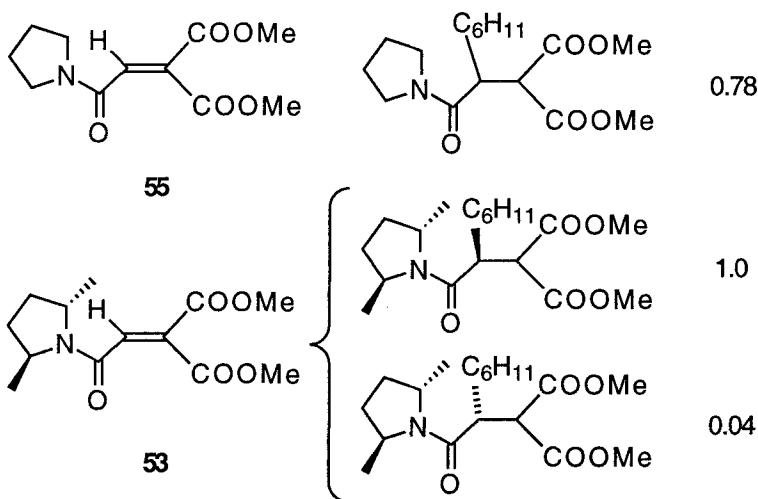
$$\ln \frac{k_1}{k_2} = \frac{\Delta H_2^\ddagger - \Delta H_1^\ddagger}{R T} - \frac{\Delta S_2^\ddagger - \Delta S_1^\ddagger}{R} \quad (5.17)$$

The selectivity data can be treated by an Arrhenius approach to provide information about the competing transition states. In a competition experiment, a plot of $\ln k$ of the competing processes versus $1/T$ gives a line with slope related to $\Delta\Delta H^\ddagger$ and intercept related to $\Delta\Delta S^\ddagger$, according to Equation 5.17. When the data are treated in this way, $\Delta\Delta H^\ddagger$'s are obtained in the range of 1.5 to 3 kcal/mole along with $\Delta\Delta S^\ddagger$'s that are near 0 eu.⁶⁸ This analysis suggests that the selectivity observed is enthalpy-derived and this is consistent with the qualitative analysis of the selectivity that is based on steric shielding of one face of the alkene by the pyrrolidine methyl group. The transition state enthalpy effects are greatest for tertiary (*tert*-butyl) radicals (~3 kcal/mole), smaller for secondary (cyclohexyl) radicals (1.7–2.7 kcal/mole), and smallest for primary (hexyl) radicals (~1.4 kcal/mole) in accord with the steric origins of the selectivity.



The trisubstituted alkene **53** reacts selectively with radicals at low temperature, giving high yields of addition products.⁶⁹ For example, the Barton ester of cyclohexyl carboxylic acid, alkene **53** and tributyltin hydride react at -78°C to give over 90% of one diastereomer, **54a**. Tin hydride apparently intercepts the addition radical and the chain is then propagated by stannyli radical addition to the Barton ester.

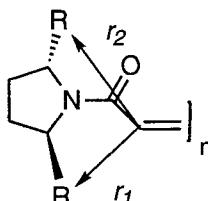
Competition experiments have been carried out at room temperature in which the alkenes **53** and **55** compete for cyclohexyl radical.⁷⁰ The results of these competitions are shown in Table 5-1. These data show that the selectivity in the addition reaction results from a reduction in rate of addition to the hindered face of **53** relative to the model compound **55** and the open diastereotopic face of **53**.

Table 5-1. Competition rate constants for addition of cyclohexyl to alkenes **53** and **55**

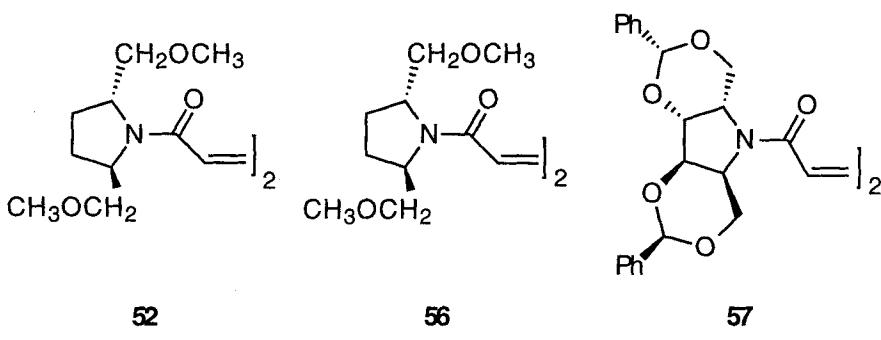
The *C*₂ symmetric amines **16** and **17** have been examined as auxiliaries in radical addition to fumaric diamides **56** and **57**. Addition of hexyl, cyclohexyl, and *tert*-butyl radicals to the fumaramides was carried out at 0°C and the selectivities were compared for the three alkenes **52**, **56**, and **57**.³⁰

Table 5-2. Diastereoselectivities for addition of hexyl, cyclohexyl and *tert*-butyl to alkenes **52**, **56** and **57** at 0°C and distance between alkene carbon and pyrrolidine-shielding substituent

alkene	<i>r</i> ₁	<i>r</i> ₂ (Å)	<u>selectivity</u>		
			hexyl	cyclohexyl	<i>tert</i> -butyl
52	3.3	4.3	16/1	50/1	80/1
56	3.3	4.4	35/1	67/1	112/1
57	3.1	4.3	>200/1	>200/1	>200/1



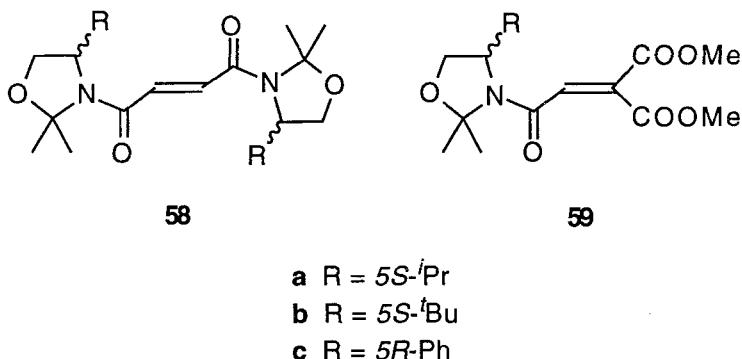
Single crystal X-ray analysis of the diamides provides a basis for understanding the selectivity of addition. This selectivity has been attributed to the differential shielding of the diastereotopic alkene faces by the proximate substituent on the pyrrolidine auxiliary and X-ray analysis shows that the closer the substituent to the alkene center undergoing addition, the more selective is the addition reaction. Table 5-2 presents the selectivity for addition of hexyl, cyclohexyl, and *tert*-butyl radicals to the fumaric diamides along with the distance between the alkene carbon and the pyrrolidine shielding substituent. The C_2 symmetric auxiliary group **17** gives extremely high selectivities in every case examined and this auxiliary group can be readily hydrolyzed, making it potentially useful in most synthetic applications.

**52****56****57**

One problem that plagues all of the strategies for the use of auxiliaries attached to prosterogenic radicals or alkenes is the fact that auxiliary groups that generally lead to high diastereoselectivities also tend to give lower product yields. The strategic approach is to utilize groups that have substantial steric hindrance and while this is necessary for maximum selectivity, it may also lower the rate of addition to the alkene, particularly in the case of bulky radicals. The yield for addition of *tert*-butyl radical to **57** is only 24%, for example, while the yields of products from cyclohexyl and hexyl radicals are excellent for this alkene. This is unusual because *tert*-butyl is more nucleophilic than hexyl and cyclohexyl and usually gives better yields in additions to electron-poor alkenes.

Oxazolidines have given mixed results when utilized as auxiliaries attached to the carbon of an alkene undergoing addition.⁴⁵ For **58c** and **59c**, the diastereomeric products of cyclohexyl radical addition are formed without selectivity in a ratio of 1.1/1 at 0°C. Even at -78°C utilizing Barton

ester precursors and photochemical initiation, selectivity for the reaction of **58c** was only 1.3/1. Addition to the alkene derived from an isopropyl substituted oxazolidine **59a** gives a diastereomer product mixture of 7/1 at 0°C while the *tert*-butyl substituted analog **6b** gives essentially one product of addition, with a product diastereomer ratio in excess of 80/1 at 0°C. Based upon the solid-state conformations of the alkenes **58** and **59**, one can speculate on the reasons for the observed selectivity of the addition reactions described above. For the alkyl substituted oxazolidines, **a** and **b**, the local conformation around the amide linkage is relatively rigid since there is a close contact of the groups attached to the oxazolidine stereogenic center α to nitrogen and the alkene carbon bearing the amide. This carbon–carbon distance for **59b** is only 2.04 Å and in the solid state the *tert*-butyl substituent has one of its methyl groups situated over the alkene, shielding one face from addition (Fig. 5-6).



For oxazolidines substituted at the stereogenic center *via* an sp^2 hybridized atom, the solid-state conformation places the planar substituent (phenyl or carbomethoxy) orthogonal to the alkene α carbon. This is illustrated in Figure 5-13 for one of the amide linkages of the fumaramide **58c**. Partial rotation about the C(O)–C=C and C(O)–N single bonds is possible and the amide substructure of the molecule is presumably mobile because of the fact that the phenyl group acts like a toothless gear and does not fix the auxiliary with respect to the alkene α center.

The arguments made for the solid-state conformation of the alkenes discussed above also presumably apply to the transition state for addition of the cyclohexyl radical. Thus, in the transition state for addition, the phenyl group of the substrates **58c** and **59c** can slip away from a radical attacking

either face of the alkene by rotation about the C(O)–C=C and C(O)–N single bonds and this auxiliary therefore does not provide facial selectivity. The geometry of the *tert*-butyl oxazolidine, on the other hand, is fixed in the transition state in an arrangement analogous to the solid-state conformation, resulting in high facial selectivity.

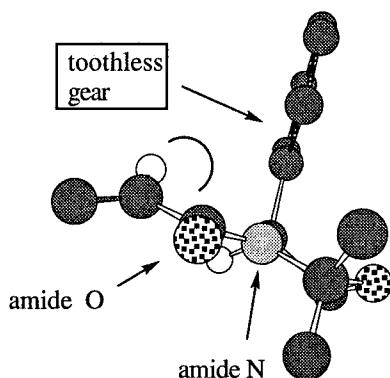
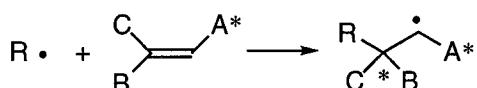
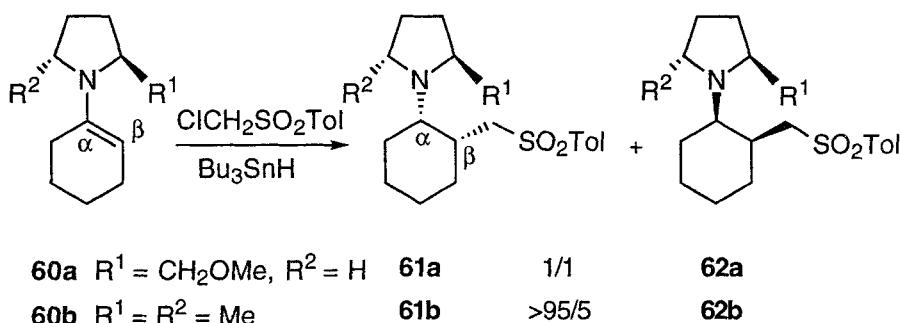


Figure 5-13. Portion of Single Crystal X-ray of **58c**.

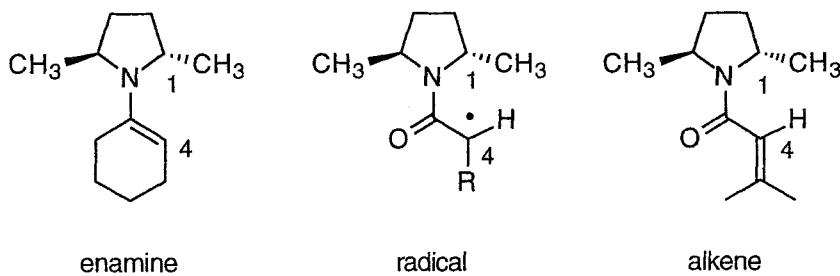
5.3.2 Auxiliaries Attached to the Remote Alkene Carbon



Renaud has developed the chemistry of addition of electrophilic radicals to enamines in tin hydride mediated reactions⁷¹ and has explored the use of 2,5-dimethylpyrrolidine as an auxiliary group to control absolute configuration in reactions of this type.⁷² These examples do not involve acyclic stereocontrol since a bond is formed to an existing ring. The auxiliary is attached by a freely rotating single bond, however, and the principles that emerge should be applicable to acyclic systems. Radical additions to enamines **60a** and **60b** were conducted by the tin hydride method. With prolinol-derived enamine **60a**, no stereoselectivity was observed at the alkene position β to the nitrogen, although high *cis* selectivity was observed. The C_2 symmetric dimethylpyrrolidine enamine **60b** provided essentially a single product **61b**.



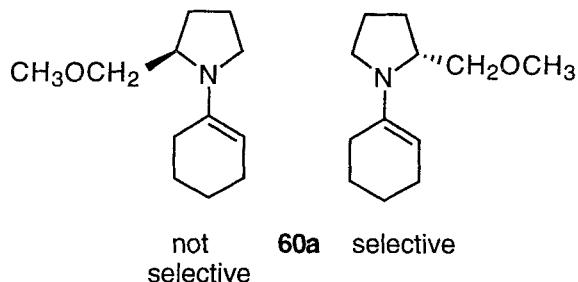
The understanding of the selectivity observed in these reactions follows directly from the principles outlined for additions of radicals bearing pyrrolidine amides and in the additions of radicals to unsaturated pyrrolidine amides. The resident chiral group in the enamine, the radical, and the alkene is placed in an analogous position 1,4 to the prostereogenic center that undergoes reaction for all three species. Bonding between the chiral group and the prostereogenic center is such that the four atoms are coplanar. The shielding group occupies essentially the same region in space for each and one expects, on this basis, that selectivity should be similar.



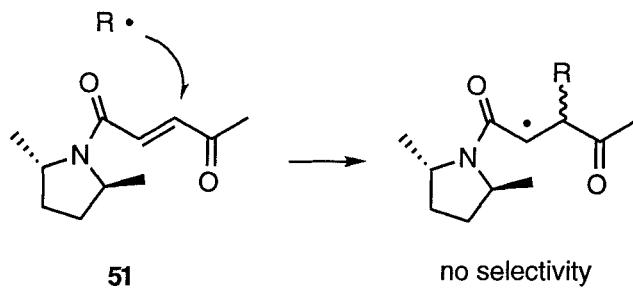
One can understand why the enamine **60a** is not a useful auxiliary in reactions with electrophilic radicals on the basis of this model. In one conformation of the enamine selectivity would be expected while in the other conformation one expects little or no selectivity.

Control of configuration in radical addition to alkenes bearing an auxiliary group at the carbon remote from the center of addition presents a more difficult problem than the one encountered when the auxiliary is attached directly to the carbon undergoing attack. The auxiliary group is removed by an additional atom from the prostereogenic center in this case and control of configuration would therefore appear to be more difficult. In

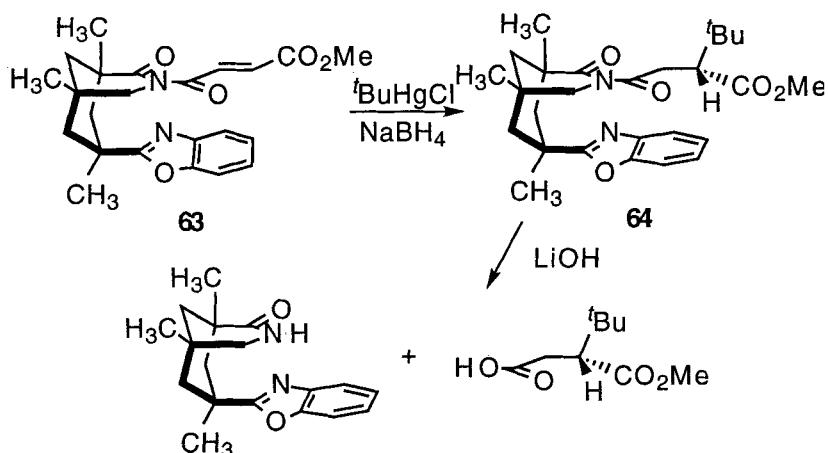
spite of this, successes have been reported for what has been termed β -selectivity.



Control of the configuration of the remote alkene center in radical addition to α,β -unsaturated amides or esters presents a challenge.^{73,74} Recall that addition of radicals β to the dimethylpyrrolidine amide of **51** gives products with no selectivity.⁶⁸ Auxiliary groups like the dimethylpyrrolidine amide direct addition of radicals to the remote carbon of the alkene but this carbon is “beyond the reach” of the auxiliary. To provide a solution to this regio- and stereoselectivity problem, the “Rebek” imide was constructed to serve as an auxiliary group for the unsymmetrical fumaric acid derivative **63**.^{73,74} Imides are more electron withdrawing than simple esters and “polar” effects direct radical addition to the position remote from the auxiliary group of the unsymmetrical alkene. At 0°C, addition of *tert*-butyl to **63** gives an 88/9 mixture of products derived from addition at the position β to the amide while addition to the α position accounts for 3% of the addition products. The addition can be carried out at -40°C and under these conditions, a 70% yield of a 97/3 mixture of **64** and its diastereomer is obtained.



The model presented in Figure 5-14 can be used to rationalize the observed high levels of stereoselection in radical addition to **63**. Good conformational control is provided by the dipole repulsion of the imide carbonyls and the *s-cis* preference of the fumaroyl OC–C α,β bond. The benzoxazole extends far enough from the Kemp triacid template to shield the face of the alkene at the β -position.



The “Rebek” imide can also be used as an auxiliary group to control the configuration of a stereogenic center formed from a radical. Thus, when this auxiliary is attached as an amide to α -iodopropionic acid, compound **65**, and an allyl group transfer reaction is carried out at 80°C , a 96/4 product mixture is obtained. Cyclization reactions of radicals bearing this auxiliary group also proceed with high diastereoselectivity (99/1).

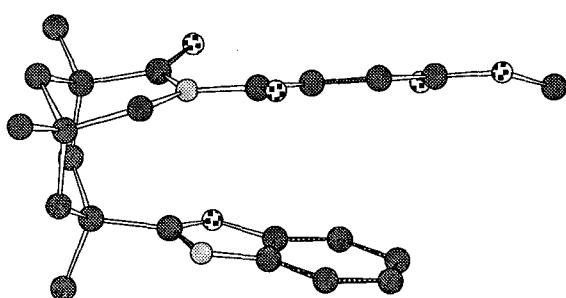
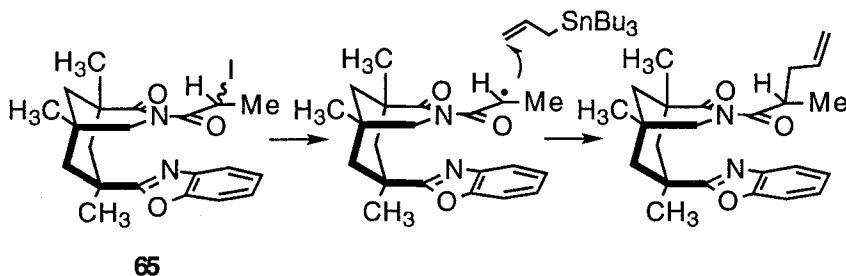
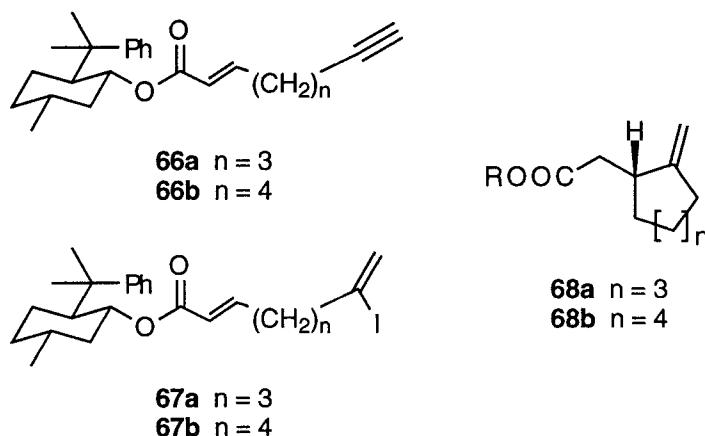


Figure 5-14. MM2 Minimized Structure for **63**.
(Hydrogens omitted for clarity)

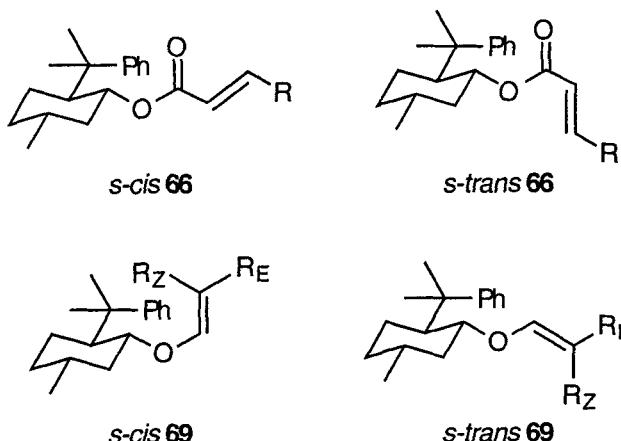
While the Kemp triacid-derived groups described here give unprecedented stereoselectivities and fulfill most of the requirements of a useful auxiliary group, a principal disadvantage that attends their use is the rather lengthy synthesis involved in their construction. An auxiliary group that provided the same alkene facial shielding as these imides but that was more readily available would be a valuable addition.



Ester auxiliaries of 8-phenylmenthol have been used in radical cyclizations to control the configuration of the stereogenic center formed at the position β to the ester group. The tin hydride mediated cyclization^{75,76} of the enynes **66a** and **66b** gives rise to cyclization products **68** with only modest stereoselectivity (58/42 for both **66a** and **66b**). If the reaction is carried out in the presence of Lewis acids such as *iso*-Bu₃Al, selectivity improves to over 80/20.

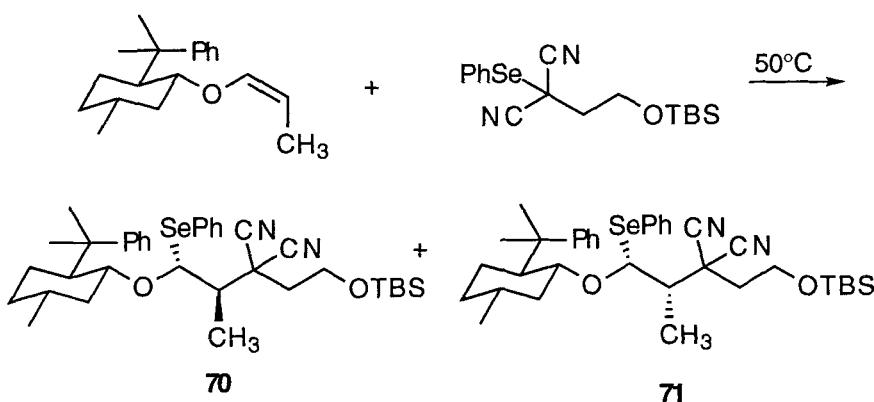


The tin hydride addition to alkynes does not occur efficiently at low temperatures and in order to explore the reaction over a larger temperature range the iodides **67a** and **67b** were examined. The reaction of **67(a or b)** at -78°C with tin hydride in the presence of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxy) gives product with diastereoselectivity in excess of 92%.



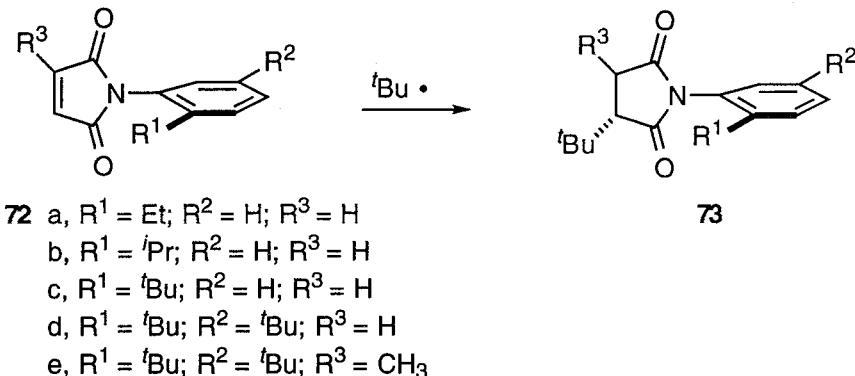
Lewis acids fix the conformations of acrylates in the *s-trans* arrangement⁷⁷ and the reactions of **66** and **67** carried out in the presence of bulky acids gives products that result from cyclizations onto α,β -unsaturated systems having this apparent conformation.

Control of the conformation of ethers derived from 8-phenylmenthol also allows stereoselective additions to these electron rich alkenes.⁶⁴ The *E*



stereoisomer of **69** (R_E = methyl, R_Z = H) should exist as a mixture of the *s-cis* and *s-trans* conformers, and addition of electrophilic malononitrile radicals to this isomer gives rise to a 1/1.9 mixture of products **70** and **71**. Addition of the same radical to the Z diastereomer (R_E = H, R_Z = methyl) gives rise to a 10/1 product mixture. The Z isomer exists exclusively in the *s-trans* conformer and addition of the radical occurs from the alkene face opposite from the phenyl substituent.

Restricted rotation about axially disymmetric bonds has been used to induce selectivity in radical addition reactions to alkenes.⁷⁸ The systems examined include the imides **72a-e** and the amide **74**. Addition of *tert*-butyl radical to **72a** gives a 55/45 ratio of chiral racemic atropisomeric product **73a** at room temperature while addition to the isopropyl-substituted compound **72b** gives an initial product ratio of 90/10. The product distribution changes with time for product **73b**, after standing for one hour at room temperature the product mixture is 52/48. Addition of *tert*-butyl radical to **73c** gives a 94/6 product mixture and equilibration (to give a 65/35 distribution) of this product requires heating to 120°C. Addition of *tert*-butyl radical to **72d** gives a product mixture of 93/7 while cyclohexyl addition gives only a 77/23 mixture.



The crystal structure of **72d** is presented in Figure 5-15. One face of the alkene is protected from addition by the *ortho* alkyl substituent and this differential facial shielding is responsible for the selectivity observed in the addition. Larger *ortho* aromatic groups give rise to higher selectivities and the interconversion of atropisomers is also dependent on the size of the *ortho* aromatic substituents. The atropisomer equilibration occurs readily for

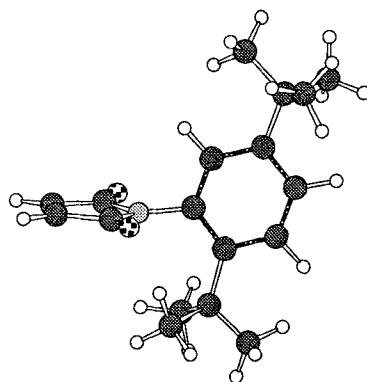
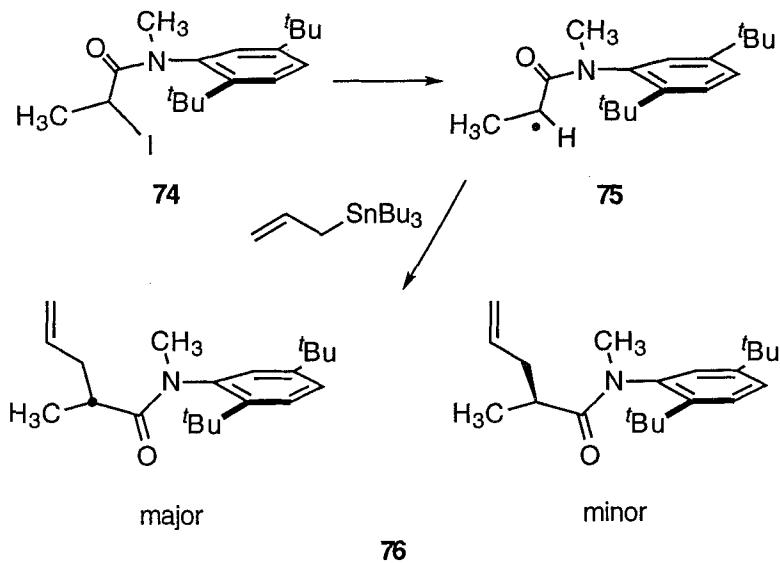


Figure 5-15. Single Crystal X-ray Structure of **73d**.

73a and **b** while elevated temperatures are required for this interconversion when the *ortho* aromatic substituent is *tert*-butyl, **73c, d** and **e**. Addition of radicals to the racemic chiral analog **72e** gives yields and atroposelectivities comparable to those obtained from the achiral imides **a-d**.



Atroposelectivity is not limited to cyclic substrates. Reactions of the radical **75**, generated from the corresponding iodide **74**, with allyltributylstannane give product **76** in a ratio of 93/7. The radical is shielded by the *ortho* aromatic substituent and allylation presumably occurs from the face opposite this substituent.

5.4 Comparison of Chiral Auxiliaries in Radicals and Carbanions

Reactions involving the use of chiral auxiliaries and neutral free radical reactive intermediates with radical traps provide interesting comparisons with the reactions of carbanions (or more precisely organometallics) bearing the same auxiliary groups. Carbanion chemistry provided a framework for the development of stereoselective free radical reactions⁵ but interpretation of stereoselectivity in radical chemistry may well be more straightforward than comparable interpretations in the reactions of carbanions.

Radical chemistry provides one significant advantage not enjoyed by carbanion chemistry, the structure of the reactive intermediate is known or can be reasonably assumed in free radical chemistry. This assumption is not necessarily valid for reactions of carbanions, where a corresponding counterion and aggregation of the reactive intermediate and their counterions usually complicates interpretation of reactions of these species.^{1–3,79} Indeed, the reactive species that undergoes allylation (with allyl bromide) in the reactions of lithium enolates is open to debate while the same issue is not in doubt for the allylation of radicals with allyltributylstannane. One can therefore develop models for stereoselectivity with some confidence in radical chemistry while the same confidence is probably not warranted in the construction of models for stereoselective carbanion reactions.

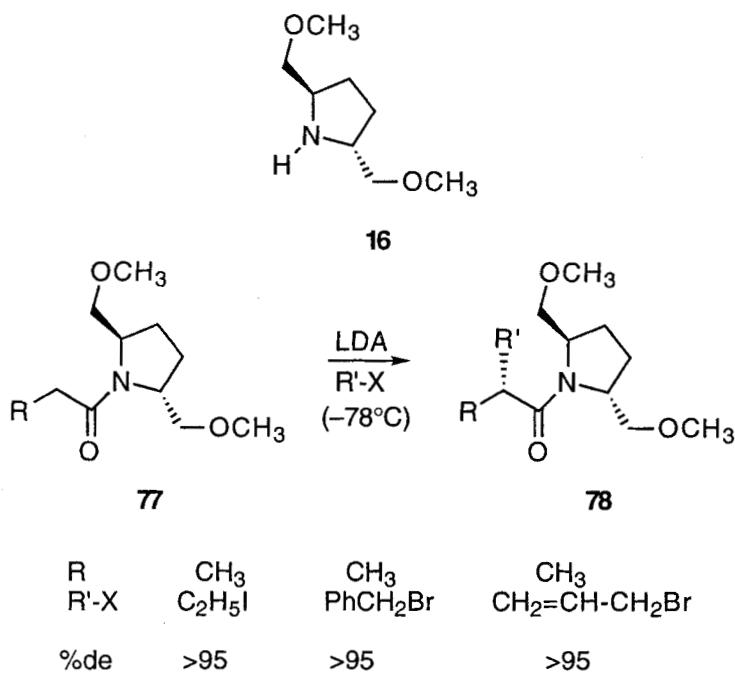
One could argue that the reaction of a neutral radical with a neutral radical trap in solution should provide the aggregate-free standard of comparison for the reactions of enolates. Both radical and enolate anion are stabilized by delocalization and their geometries are expected to be similar. Given the same geometry, one expects that steric effects of attached auxiliaries would be comparable for enolates and radicals and that stereoselectivities for analogous reactions would therefore be comparable.

5.4.1 Chiral Auxiliary on the Radical

Consider the reactions of radicals and carbanions that are located α to amides bearing chiral auxiliaries. C_2 symmetric auxiliaries have been examined in allylation reactions for radicals (as described in Section 5.2.3.1) and in alkylation reactions for the amide enolates.⁴ For example, Katsuki has examined the alkylation of carboxyamide enolates with the use of 2,5-disubstituted pyrrolidine **16** as a chiral auxiliary.⁸⁰ Generation of the enol-

ate of **77** with LDA followed by alkylation with several alkyl halides at low temperature gives the product **78** with diastereoselectivities in excess of 95%.

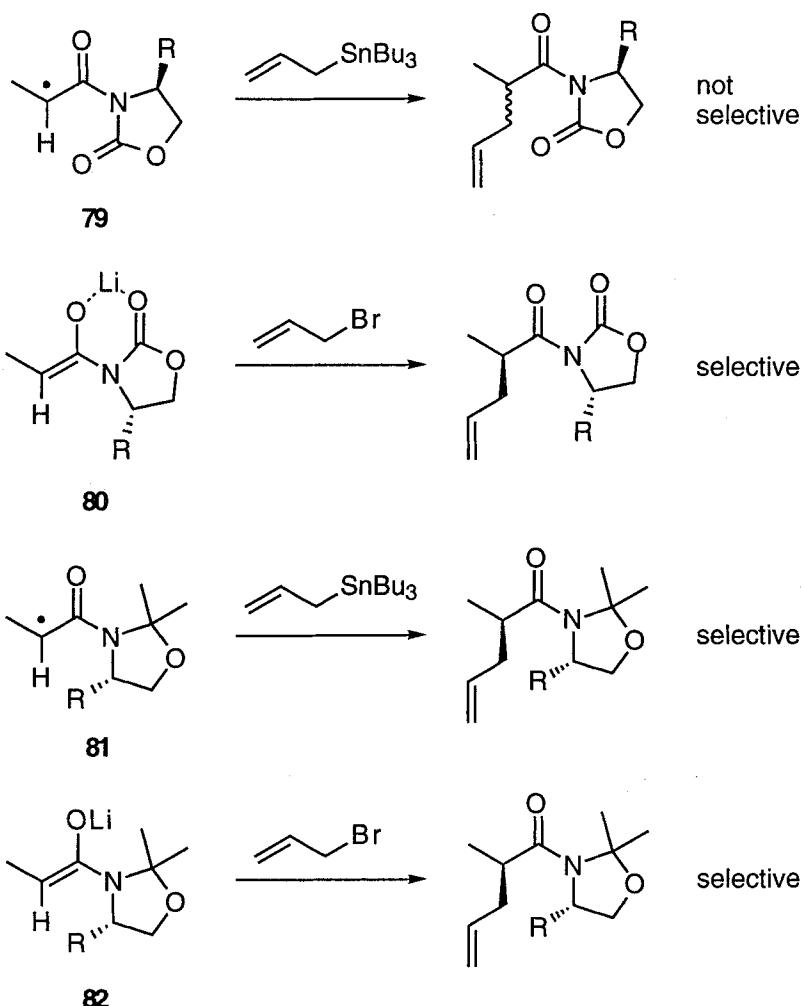
Diastereoselectivities obtained in reactions of radicals substituted with **16** and analogous auxiliaries are comparable to those that are observed in enolate alkylation, see Section 5.2.3.1. Even though the amide enolates aggregate, and the precise structure of the reactive species is difficult to determine, the reactive species behaves, in comparison with “free” radicals, as if it were a “free” species.



Stereoselectivities observed in free radical reactions utilizing other auxiliary groups compare directly to stereoselectivities determined in the reactions of enolates. Oppolzer's sultam is a useful auxiliary for reactions of radicals and of the corresponding enolates and the selectivity obtained for both reactive intermediates are comparable.³⁸ Indeed, if aggregation of enolates does not interfere, one expects all auxiliary groups that give useful selectivities in reactions where they are attached to amide or ester free radicals to give similar selectivities in reactions of the corresponding enolates.

In contrast, not all auxiliaries that are useful in enolate chemistry provide useful levels of diastereoselectivity in the reactions of radicals. The

well-known Evans oxazolidinone enolate auxiliaries fail to provide useful selectivity in the reactions of analogous radicals. This is most reasonably understood on the basis of the models **79** and **80**. The carbonyl dipoles of **79** are opposed and this conformation places the stereogenic center of the oxazolidinone remote from the α radical center. Chelation of the lithium counterion of the enolate **80** brings the chiral center of the oxazolidinone Z with respect to the α enolate center and selectivity is observed in the reactions of this species.

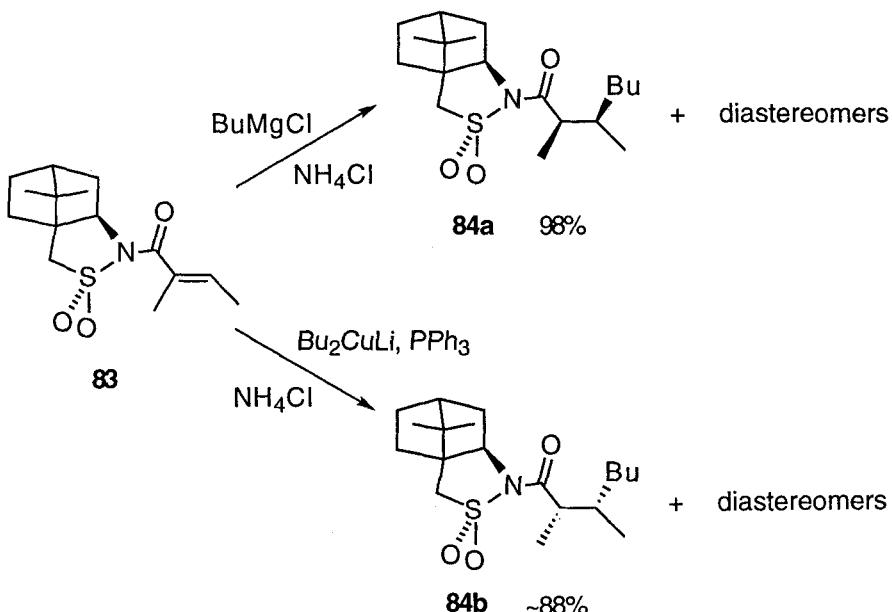


Oxazolidine auxiliaries give selective reactions in both free radical and enolate chemistry. Thus, **81** and **82** both give highly selective reactions with

allyltributylstannane or allyl bromide.⁸¹ Lithium chelation is not important for the enolate in this case and the radical and carbanion reactions give similar results. The *gem*-dimethyl substituents of the oxazolidine apparently control the conformation of the radical and the enolate, see Section 5.2.3.3.

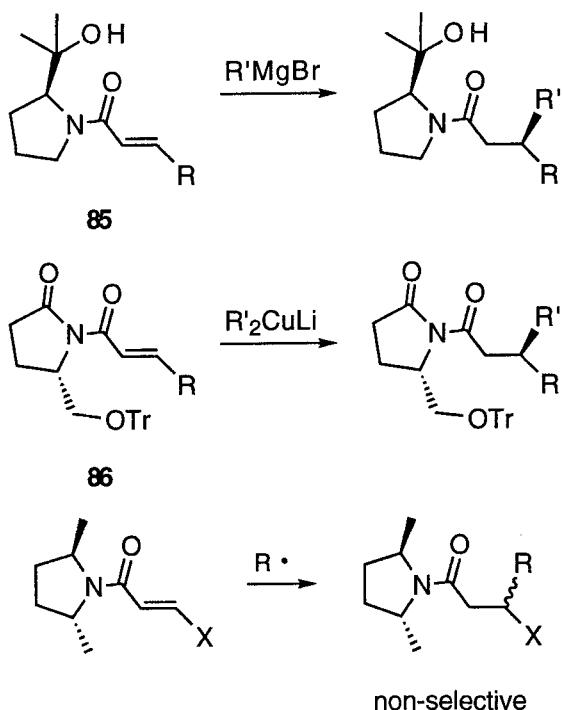
5.4.2 Chiral Auxiliary on the Radical Trap

Asymmetric induction in nucleophilic addition to electron deficient alkenes has been studied extensively.⁸² Significant diastereoselectivity may be achieved in 1,4-addition reactions of Grignard or cuprate reagents to alkenes substituted with chiral auxiliary groups.⁸³ Alkenes substituted with Oppolzer's sultam undergo selective addition of nucleophiles even though the auxiliary group is attached to the alkene carbon remote from the center of addition. Thus, addition of BuMgCl to alkene **83** gives **84a** as 98% of the diastereomer product mixture while addition of the cuprate gives diastereomer **84b**. Grignard addition to **85** gives the 1,4-addition product with a diastereomeric excess of 50–88%⁸⁴ and cuprate addition to **86** proceeds with diastereoselectivity of 77–97%.⁸⁵

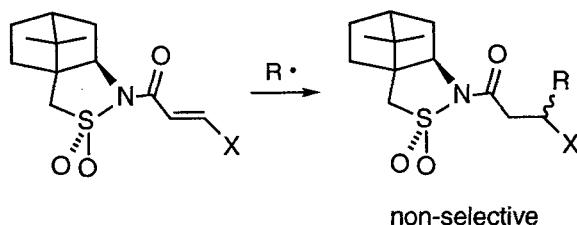


The contrast of stereoselectivity observed in radical (non-selective) and carbanion (selective) addition reactions supports the proposal that the

reactive species in carbanion addition is a complex of the nucleophile and the alkene. Such suggestions have been made for the reactions of alkene **83**; a complex of two Grignard species and the alkene has been proposed as the reactive species in additions.^{84a} Radical chemistry serves as the standard of comparison for a “free” species and requires the suggestion that complexes are involved in the comparable nucleophilic additions.



In contrast to carbanion 1,4-additions of **83**, **85** and **86**, free radical additions to alkenes bearing analogous auxiliary groups on the remote carbon occur with no selectivity. Thus, free radical addition to the β -carbon of an alkene substituted with any of the C_2 symmetric auxiliary groups or with Oppolzer's sultam occurs without selectivity.



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Stereochemistry of Radical Reactions

Concepts , Guidelines and Synthetic Applications

by Dennis P. Curran, Ned A. Porter & Bernd Giese

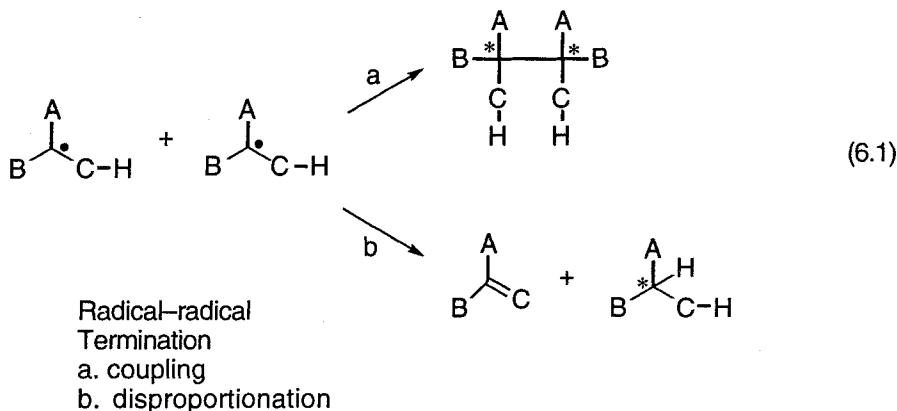
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Chapter 6

Pair Reactions, Rearrangements and Formation of Alkenes from Radicals

6.1 Radical Pairs

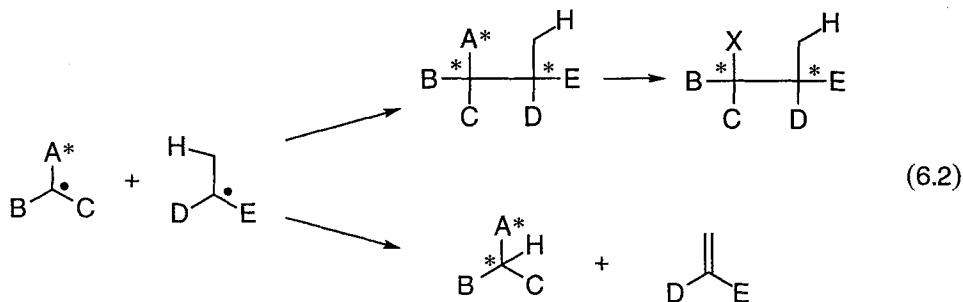
Free radicals are generated in pairs and radical chain reactions terminate when two free radicals encounter and react. A radical pair can exist as a triplet or a singlet and only the singlet can terminate to give ground state products. The two common reactions of carbon radicals that lead to chain termination are radical–radical coupling, Equation 6.1a, and radical-radical disproportionation, Equation 6.1b.¹ These termination reactions are diffusion-controlled for most radical species—every diffusive encounter of two free radicals leads to a termination event.²



For radical coupling reactions, two new stereogenic centers may be formed if the two radicals are appropriately substituted. Thus, for a radical substituted with three different groups (Eq. 6.1, A, B, and C) that undergoes homocoupling, two new stereogenic centers are formed and the possibility of *simple diastereoselection* exists. Disproportionation of radicals can also raise

stereochemical issues. Thus, disproportionation can lead to a new stereogenic center if the radical receiving the hydrogen in the disproportionation is prostereogenic.

If groups A–C are achiral, the product of radical coupling will, of course, be formed as a racemic mixture of diastereomers and the diastereoselectivity of the coupling process indicates the enrichment of one racemic diastereomer as compared to the other. Chiral auxiliary control in radical coupling is presented in Equation 6.2 where one of the groups A, B, or C on the radical has a stereogenic center. The presence of chiral group A* in the radical may induce a bias in the configuration of any stereogenic center formed in the coupling process.

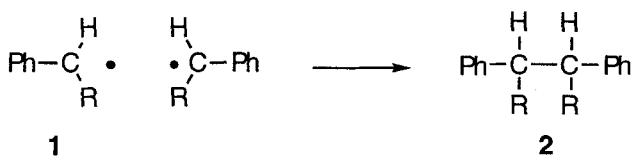


If the chiral group A* is subsequently removed from a product of addition, and the configuration of every stereogenic center is retained in this transformation, then group A* serves as a chiral auxiliary in the sequence.

6.1.1 Radical Pair Coupling

The stereoselectivity of radical–radical coupling has been studied extensively.³ Pairs of benzylic radicals (generated by hydrogen atom abstraction from the hydrocarbon precursor) couple with a slight bias for the *meso* product. Thus, the radicals **1** couple to give a *meso* product that makes up 51–58% of the product mixture, the selectivity of coupling depending on the R substituent.⁴

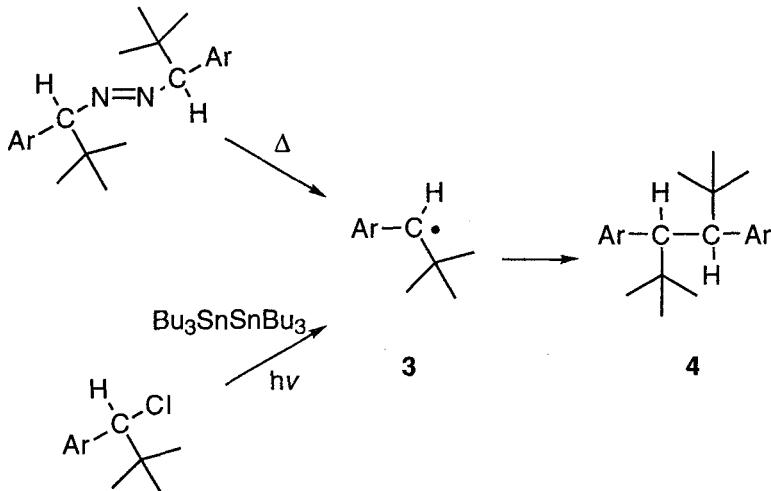
Rüchardt^{5,6} has examined the selectivity of coupling of several α -aryl neopentyl radicals **3**. The radicals are generated as pairs from azo precursors or as single radicals from a reaction of a chloride with $Bu_3Sn\bullet$ radicals. The



R	$\textbf{2} (\pm) : meso$
Me	0.96
<i>i</i> Pr	0.81
<i>t</i> Bu	0.72

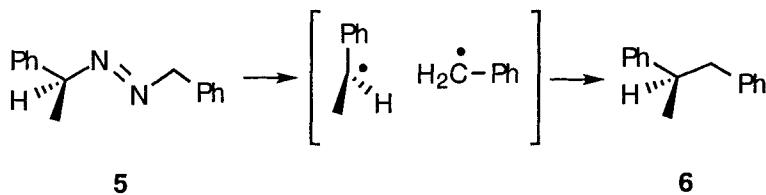
selectivity of coupling depends dramatically on the nature of the aryl group. The slight preference for the *meso* product observed for the phenyl-substituted radical **3a** is altered by *para* substitution. The chloro-substituted radical **3c**, for example, gives predominantly the (\pm) coupling product, **4c**. The tetraryl-substituted radical **3d** gives dimer **4d** with exceptionally high (\pm) selectivity.

A thorough investigation of the coupling of radical **3d** was carried out⁶ and selectivity was found to be temperature dependent. The enthalpy of



3	Ar	4 (\pm) : meso
a		0.8
b		0.5
c		1.3
d		22

activation has been derived for the *meso* and (\pm) dimerization processes and ΔH^\ddagger for the (\pm) reaction is lower than that of the *meso* coupling by 2.8 kcal/mol. The high stereoselectivity for coupling of **3d** is therefore enthalpy-controlled, caused mainly by the steric repulsions between the approaching radicals. The coupling of the hindered and stabilized benzylic radicals **3a-d** gives products with stereoselectivity independent of the method of generation of the radicals. Generation of radicals in single events, (from the chloride precursor) or in pairs (from the azo compound) give comparable results.

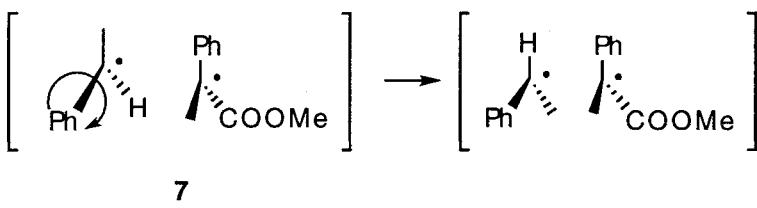


For radicals that are less hindered than **3**, cage phenomena can affect the stereoselectivity of the coupling products. Chiral azo compounds that generate prosterogenic radicals upon decomposition couple to give products that reflect, to some extent, the configuration of the azo precursor.

The azo compound **5** decomposes in chlorobenzene at 107°C to give product **6** with some retention of configuration.⁷ In the presence of ~1 M

butyl thiol, **6** is formed with 13% retention of configuration while in the absence of this radical scavenger, the product is formed with only 8% enantiomeric excess. These data are interpreted based upon a "memory effect" in the geminate radical pair formed in decomposition of the diazene. The stereoselective coupling apparently occurs in the solvent cage, the initial radical pair formed having a configuration derived from the azo precursor. In-cage coupling gives the product with 13% retention while escape of the geminate pair gives products that are formed with random stereochemical configuration.⁸

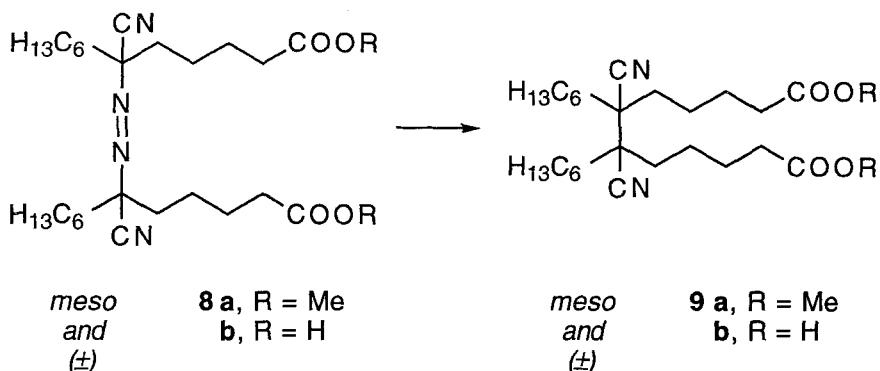
The dynamics of reorientation of radical pairs depend on the size of the radicals and on the local environment (*i.e.* crystalline media, micellar, viscous solvent, etc.). The racemization of the radical pair **7** occurs preferentially by reorientation of the smaller phenylethyl radical.⁹ Rotation of this radical in the pair apparently occurs with a free energy of activation about 0.7 kcal/mol lower than rotation of the larger radical.



Crystals provide rigid matrices for reactions of radical pairs, and pairs generated in crystalline environments couple with high retention of configuration of the pair precursor.¹⁰ Micellar media also affect the stereoselectivity of radical pair coupling processes. The twin-chain surfactant **8** decomposes¹¹ to give *meso* and (\pm) coupling products and the stereoselectivity of the transformation depends on the configuration of the azo starting material and the medium of decomposition.¹² When the dimethyl ester of the *meso* or (\pm) precursor undergoes thermal or photochemical decomposition in benzene, the product succinodinitriles are formed with substantial loss of configuration. Under these conditions, the *meso* diazene gives the product **9** with a *meso*/ (\pm) ratio of 1.05.

Photochemical decomposition of the dicarboxylates **8b** in pH 10 buffer at concentrations below the CMC (critical micelle concentration) for the

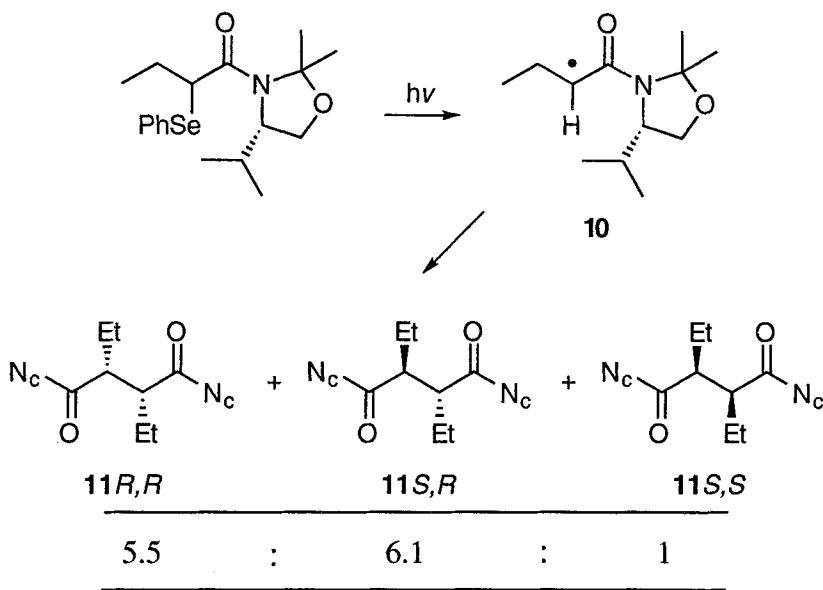
compounds (< 3 mM) gives product **9b** with substantial retention of configuration of the starting diazene. Under these conditions, the (\pm) diazene gives product with a (\pm)/*meso* ratio of 3.5/1 and *meso* **8b** gives product with a (\pm)/*meso* ratio of 1/3.5. In water, reorientation of the radical pair before coupling is significantly more difficult than in organic solvent.



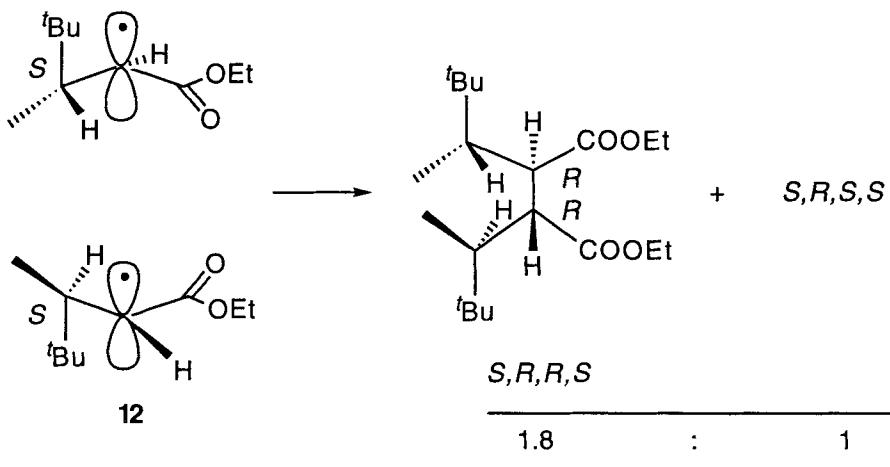
Photodecompositions carried out above the CMC give different results for the *meso* and (\pm) diazenes. In micelles the (\pm) diazene gives product with a (\pm)/*meso* product ratio of 7/1 while *meso* **8b** gives product with a (\pm)/*meso* ratio of only 1/2.5. The decomposition of (\pm) **8b** is more stereoselective in micellar aggregates than for non-micellar decomposition while the *meso* compound decomposes with less selectivity at concentrations above the CMC as compared to decomposition at sub-CMC concentrations. A rationale for the differential selectivity for the *meso* and (\pm) decompositions above and below the CMC based upon the preferred conformation of the diazene precursor has been presented.^{12,13}

Control of stereochemistry in coupling reactions by auxiliary groups, by substrate control of acyclic radicals, or by substrate control in cyclic radicals has been only modest. Auxiliary groups that exert stereocontrol in radical addition or atom-transfer processes offer minimal control in radical–radical coupling reactions. Thus, the radical **10** generated from the selenide precursor by photolysis, couples to give the three diastereomeric succinic diamides **11**.¹⁴

The expected statistical product distribution of the coupling product is 1/2/1 so the auxiliary does influence the coupling process to a measurable extent. The *R,R* coupling product does indeed result from coupling to the

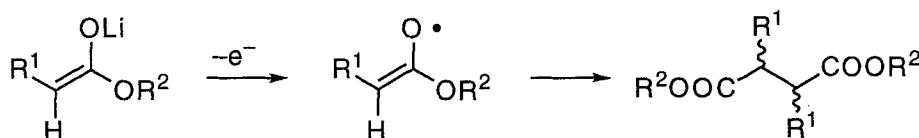


face of each radical that is open, unprotected by the auxiliary, and it is this product of the three that is favored most significantly over the expected statistical amount.



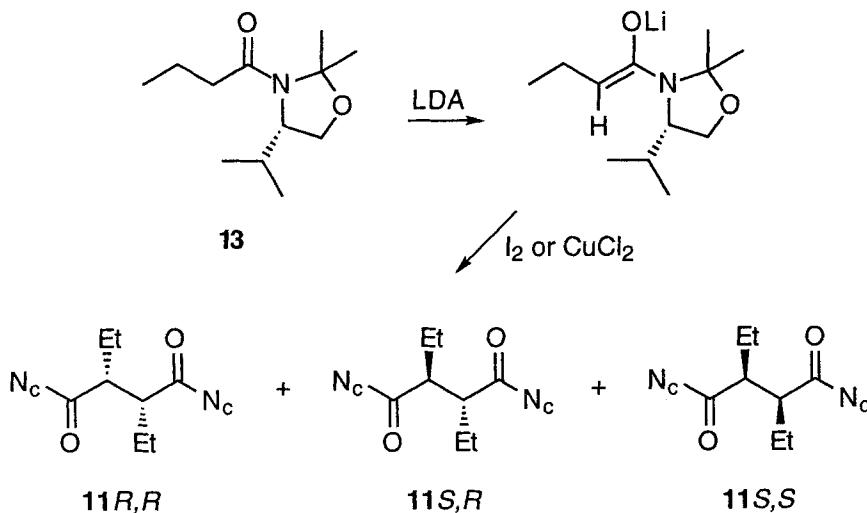
Substrate control of cyclic or acyclic radical coupling has also been achieved with modest stereoselectivity. Only two of the three possible dimerization products are formed from the radical **12** at 80°C, the **S,R,R,S** product, resulting from coupling of the “open” face of both radicals, being

the major one isolated.¹⁵ The *S,S,S,S* product, resulting from coupling from the hindered face of both radicals, is not observed. Modest selectivity has also been observed in the dimerization of chiral cyclic radicals.¹⁶



Oxidative coupling of enolates has been studied extensively and radical–radical coupling mechanisms have been suggested for the process.¹⁷ This procedure has been used for the preparation of several natural products.¹⁸ A variety of oxidants have been used to initiate the process, $CuCl_2$ and I_2 giving good to moderate yields of the coupling for ester enolates and for carboxylate dianions.

The stereoselectivity of enolate coupling depends on the substituents R^1 and R^2 . For the ester enolate where R^1 = phenyl and R^2 = ethyl, the coupling product is formed with a $(\pm)/meso$ product ratio of 1/5. Coupling of the analogous carboxylate dianion, R^1 = phenyl and R^2 = Li, gives diphenylsuccinate product in a $(\pm)/meso$ product ratio of 11/1.



Coupling of amide enolates bearing chiral auxiliaries gives succinic diamide products with very high stereoselectivity. Thus, coupling of the lithium anion of **13** by I_2 or $CuCl_2$ oxidation gives the *R,R* diastereomer of **11**

essentially free of the other diastereomers. Since authentic radical coupling that leads to these products gives a product mixture that contains the succinic diamide products in a ratio $R,R/S,R/S,S$ of 5.5/6.1/1,¹⁹ the enolate oxidation pathway cannot proceed by coupling of free radical intermediates.¹⁴

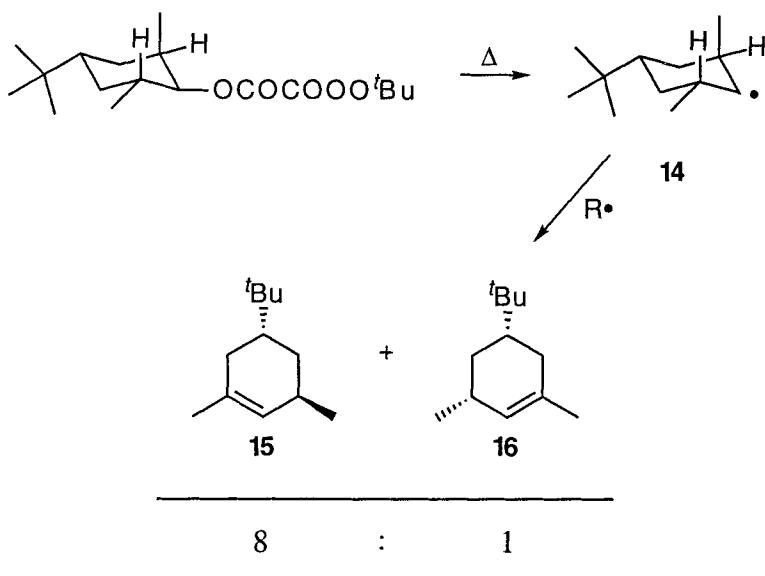
6.1.2 Radical Pair Disproportionation

Radical disproportionation/coupling (k_D/k_C) ratios depend on temperature and solvent viscosity.²⁰ Even if the sum of the rate constants for coupling and disproportionation equals the diffusion-controlled rate, anisotropic effects of the radicals in the encounter pair are apparently important in determining the (k_D/k_C) ratio. Some orientations of the radical pair lead to radical–radical coupling while other orientations give only disproportionation. The dynamics of radical pair reorientation phenomena depend on solvent and temperature and calculated (k_D/k_C) product distributions match experimental results.

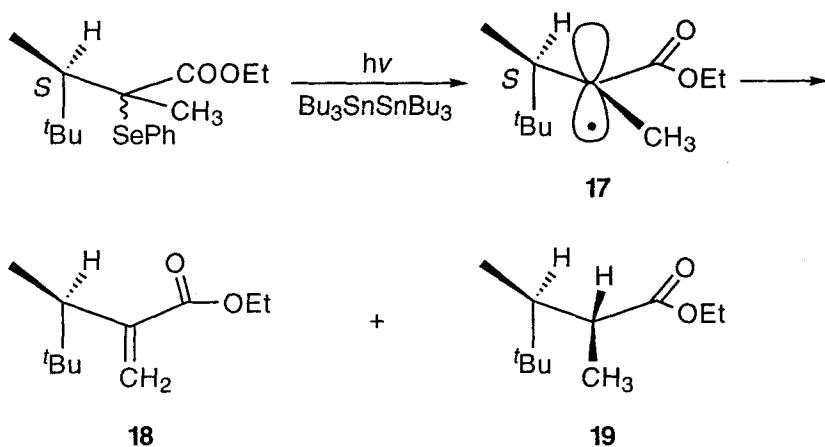
The stereoselectivity of radical–radical disproportionation has not been studied extensively. Stereochemistry may be important in disproportionation if the β -hydrogen atom is transferred from a stereogenic center or if this hydrogen atom is transferred to a prosterogenic radical. Anisotropic effects should be important in disproportionation reactions where stereochemistry is a consideration. One orientation of a radical pair leading to a particular stereochemical outcome may be more reactive than another orientation of that pair leading to the opposite stereochemical result. One may therefore expect stereoselective disproportionation processes from radical pairs even though such reactions are diffusion-controlled.

The stereoselectivity of disproportionation of a radical in which the β -hydrogen is attached to a stereogenic center has been examined for the radical **14**. Generation of **14** from a *tert*-butyl oxalate perester in cyclohexane at 100°C gives the alkenes **15** and **16** by disproportionation.²¹ The ratio of **15/16** is about 8/1, indicating that the pseudoaxial hydrogen atom is preferentially transferred in the disproportionation event.

The selectivity in the disproportionation of **14** can be understood based on the stereoelectronics of the hydrogen atom transfer. The pseudoaxial hydrogen atom can align itself parallel to the radical orbital such that the developing π bond is formed in its ground state geometry while transfer of the pseudoequatorial hydrogen cannot achieve a transition state with this same low energy geometry.

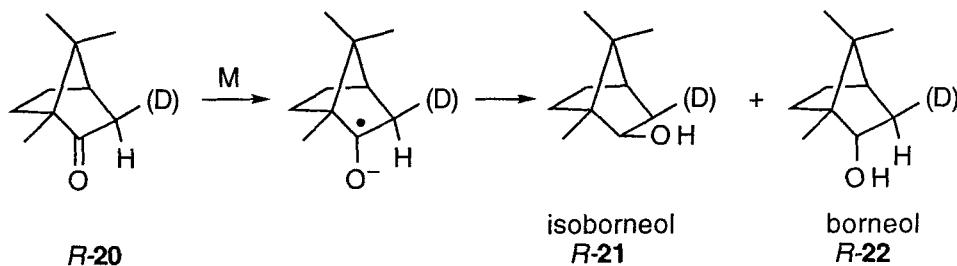


Disproportionation of radicals by hydrogen atom transfer to a prosteriotropic radical center may occur with high stereoselectivity. The radical **17**, generated by photolysis of the phenylselenide, gives the two disproportionation products **18** and **19** in a 1/1 ratio. The product **19** is formed in a diastereomer ratio that is temperature dependent, 53/1 at -78°C , and 25/1 at room temperature.¹⁵ The product diastereomer formed in the disproportionation is the one predicted based upon ground-state conformational arguments presented for these radicals.²²



The substrate-controlled selectivity for the disproportionation of **17** is comparable to the selectivity obtained for radical molecule hydrogen atom transfers of the same radical. Tributyltin hydride, for example, gives a selectivity of 25/1 in its reactions with radical **17** at room temperature.²³

Stereoselective disproportionations of ketyl radical anions have been proposed in dissolving metal reductions of camphor.^{24,25} Experiments with specifically labelled camphor, *R*-**20-d**, indicate that only *exo* deuterium atoms are transferred; that the extent of transfer into isoborneol (**21**) is the same for the pure *R*-**20** and *RS*-**20**; and that the extent of deuterium transfer into borneol (**22**) is greater from *RS*-**20** than for *R*-**20**. One concludes from the labelling studies that in the unlabelled reduction, only the *exo* hydrogen is transferred, that the isoborneols are formed via a homochiral transfer of a hydrogen from the *exo* to the *endo* position, and that the borneols are formed via homochiral and heterochiral transfers from the *exo* to the *exo* position,



While the mechanism of camphor reduction is complex (a fourth order statistical fit of the rate determining step vs. substrate has been made), isoborneols are generated with enantiomeric enrichments that are strongly amplified with respect to the enrichment of the starting camphor. The homochiral process that leads to isoborneol is essentially a double Horeau duplication.²⁴

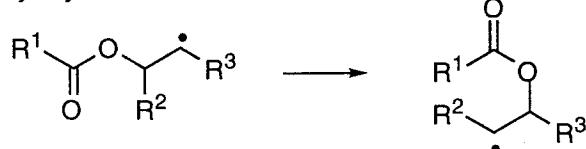
6.2 Radical Rearrangements

Many structural rearrangements that occur by free radical mechanisms amount to intramolecular examples of intermolecular free radical reactions. Free radical cyclization-fragmentation sequences are the basis of many structural rearrangements and these processes correspond to intramolecular variants of well known intermolecular addition and β -fragmentation processes.

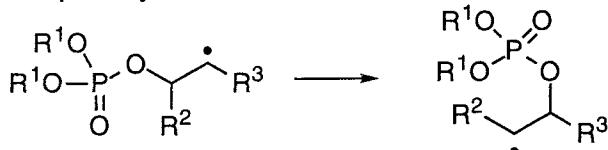
We will not consider here rearrangements that proceed by established mechanisms analogous to intermolecular reactions. Such rearrangements have been discussed extensively elsewhere²⁶ and the stereochemistry of such processes has also been the focus of extensive discussion. We have discussed the stereochemical aspects of radical cyclization in Chapter 2.

There are some rearrangements where mechanisms have been suggested, however, that do not have precedent in intermolecular transformations. Prominent examples of rearrangements with no known intermolecular counterpart are the [3,2] rearrangements of β -acyloxy, β -phosphatoxy, and allylperoxy radicals. The mechanism of each of these transformations has been the subject of extensive debate and there are novel stereochemical aspects observed for each of the rearrangements.

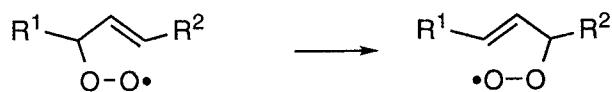
β -Acyloxy



β -Phosphatoxy

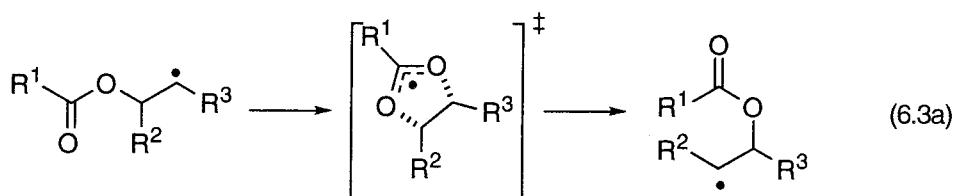


Allylperoxy

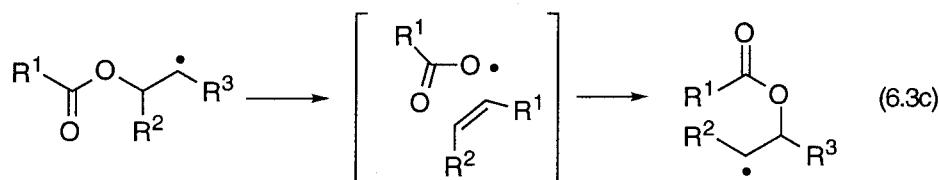
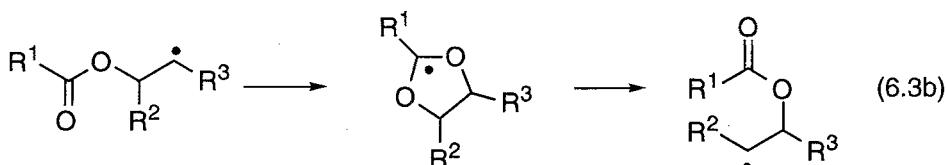


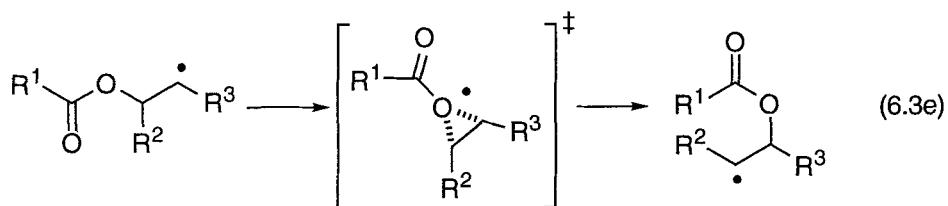
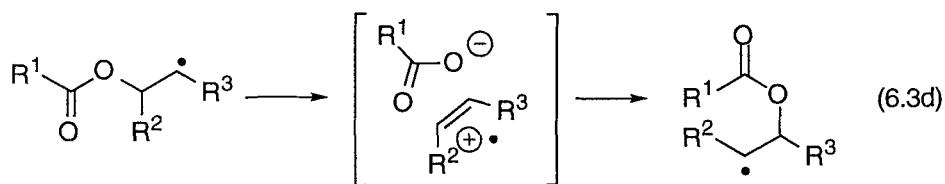
6.2.1 The β -(Acyloxy)alkyl Rearrangement

The rearrangement of acyloxy groups was originally observed in a study of radical addition to allyl acetates. In early studies, an open-shell pericyclic mechanism proceeding via a five-membered ring transition state had been suggested (Eq. 6.3a).²⁷⁻²⁹ Other mechanisms (Eqs. 6.3b-e) have been proposed and conflicting evidence has been presented that leaves the mechanistic question still unsettled.

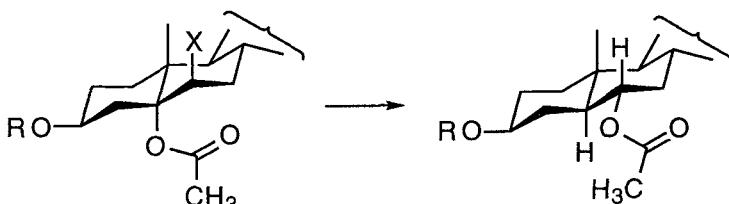
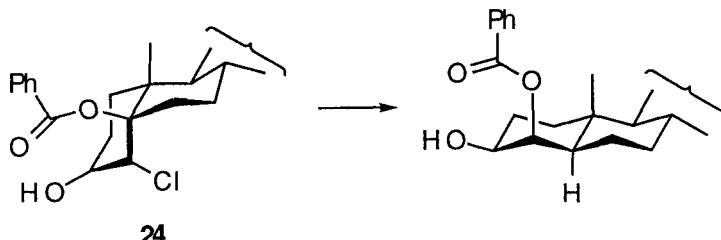


Studies with ^{18}O labeled ester radicals indicate that, for acyclic radicals, the labeling pattern is inverted during the rearrangement. Radicals with the label in the ester carbonyl oxygen rearrange to radicals with the label in the ester ether-type oxygen. This would appear to rule out the mechanisms outlined in Equations 6.3c-e from consideration. Mechanism 6.3b is not supported by experiments in which the intermediate dioxolanyl radical is independently generated and is trapped by hydrogen atom donors. Such trapping products are not isolated during the course of rearrangements. Thus, the first series of experiments addressing the mechanistic issue pointed to a mechanism involving a cyclic transition state but not a cyclic radical for the rearrangement (Eq. 6.3a). Subsequent studies showed that the rate of rearrangement is dependent on solvent polarity and on the anion stabilizing capability of the rearranging ester group.³⁰ This observation has been taken as evidence for the anion-radical cation pair (Eq. 6.3d). This mechanism requires unprecedented behavior for a pair species to account for the labeling studies, however. The carboxylate oxygens are not randomized during rearrangement and if a pair is an intermediate, it must be a tightly bound pair to account for the labeling results.



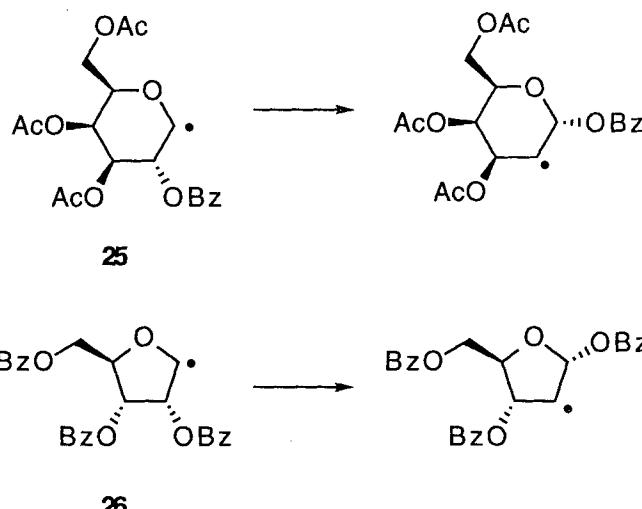


Examination of systems involving cyclic rearrangement frameworks give interesting stereochemical results. The rearrangements of β -acyloxy groups in steroids and carbohydrates proceeds with very high stereoselectivity. Thus, the two steroid β -acyloxy radicals **23** and **24** rearrange with migration of the ester group along only one face of the steroid.³¹ The acetoxy group migrates across the α face for **23** while rearrangement of the benzyloxy of **24** occurs on the β face of the steroid.

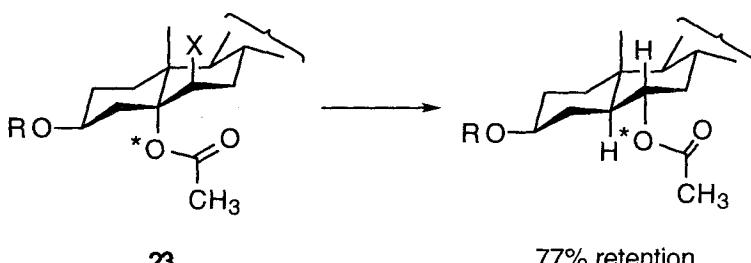
**23****24**

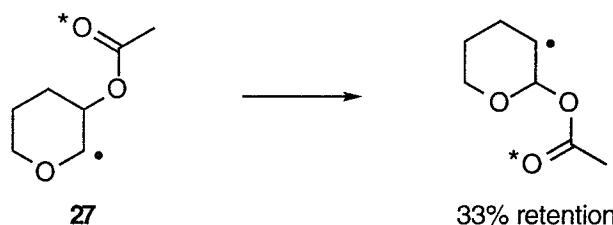
The rearrangement has been used in the synthesis of 2-deoxy sugars.^{32,33} Generation of the radical at the anomeric center from the

corresponding halide or selenide yields a product that results from a highly stereoselective migration of a β -acetoxy or benzoyloxy group. Examples of such rearrangements include the radicals **25** and **26**. Rearrangement in **25** occurs across the α face while rearrangement of the furanose radical **26** is also highly stereoselective, in this case also across the α face of the ring.



Oxygen labeling studies in systems having a cyclic framework provide some interesting contrasts to the studies described for acyclic radicals. Examination of the radical **25** labeled in the carbonyl oxygen of the migrating benzoyloxy group indicates that the labeling pattern is inverted during the rearrangement, analogous to the studies reported for acyclic radicals. In contrast, rearrangement of **23** labeled in the ester ether-type oxygen gives product with substantial (77%) retention of the label in the product ether-type oxygen^{34,35} while **27** rearranges with 33% retention of the label in the carbonyl position.³⁶

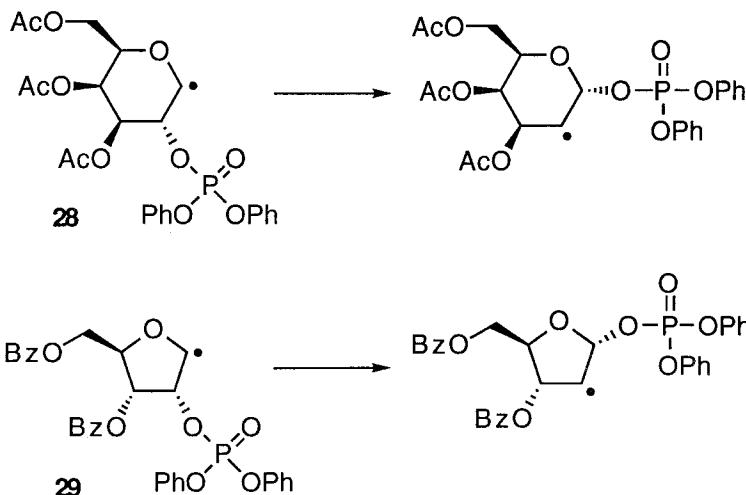


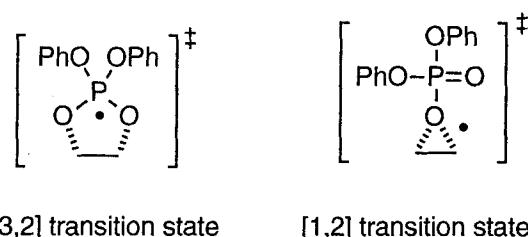


One conclusion from these studies is that there are competing mechanisms for the reaction, the pericyclic process (Eq. 6.3a) and the radical cation-anion pair mechanism (Eq. 6.3d) and that the extent of scrambling of the label depends on the partition of the two mechanistic pathways. An alternate explanation is an intermediate pair species that does not fully relax the carbonyl and ether-type oxygens of the migrating group and that collapses with stereochemical retention of configuration. A pair species that is so short-lived that the oxygens of a carboxylate do not relax would surely couple with stereochemical retention of configuration.

6.2.2 The β -(Phosphatoxy)alkyl Rearrangement

The rearrangement of β -phosphatoxy radicals analogous to the β -carboxy rearrangement is of interest because of its potential importance in free radical reactions of nucleic acids. The reaction has been examined for a number of substrates and the rate of the phosphatoxy rearrangement is apparently somewhat more rapid than that of the carboxy process.

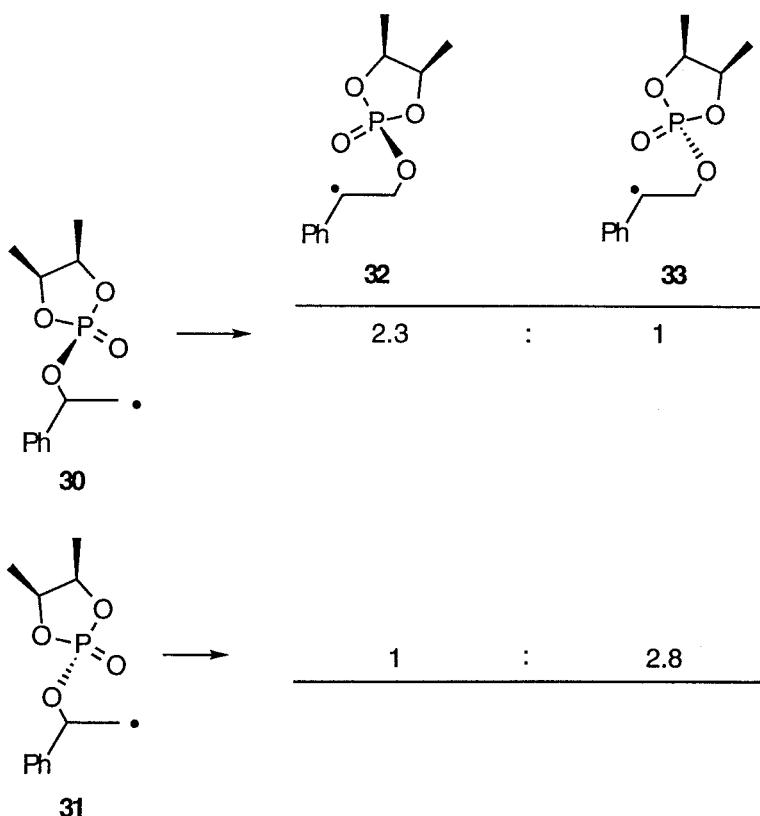




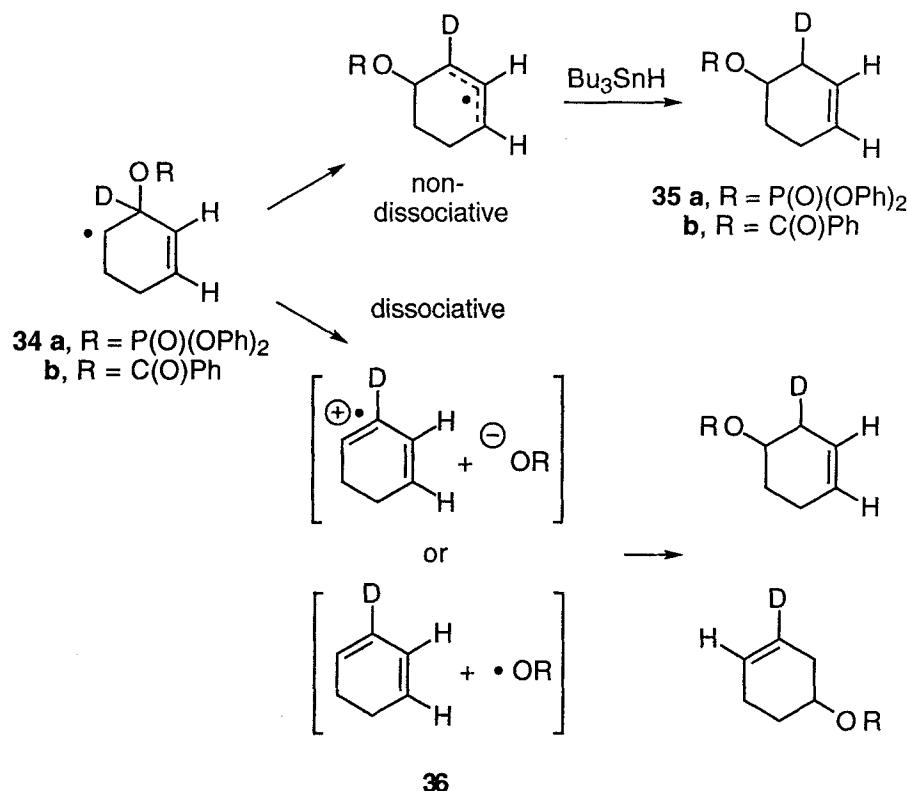
Examination of systems involving cyclic rearrangement frameworks give interesting stereochemical results. The rearrangements of β -phosphatoxy groups in carbohydrates proceeds with very high stereoselectivity.^{37,38} The rearrangement has been used in the synthesis of 2-deoxy disaccharides and 2-deoxyribonucleosides. Generation of the radical at the anomeric center from the corresponding halide or selenide yields a product that results from a highly stereoselective migration of a β -diphenylphosphatoxy group. Examples of such transformations include the radicals **28** and **29**, in which rearrangement occurs across the α face of the ring in both cases. The 2-deoxy sugars formed by rearrangement with a phosphate group at the anomeric center are reactive towards substitution with alcohol and amine nucleophiles.

Studies in systems having a cyclic phosphate framework indicate that the rearrangement proceeds with retention of configuration in the migrating phosphatoxy group.³⁹ The cyclic phosphate radical **30** gives the products **32** and **33** in a ratio of 2.3/1 while rearrangement of the diastereomeric radical **31** gives the products in a 1/2.8 ratio. Other substrates give retention/inversion product ratios between 1.3/1 and 3/1.

There is net retention of configuration of the migrating phosphoryl in every system examined but the substantial (and variable) loss of selectivity in the series of rearrangements would appear to cast doubt on a pericyclic transition state for the process. It would indeed be fortuitous if pericyclic [3,2] and [1,2] transition states were so close in energy to allow competing mechanisms. The same comment could be made about the β -acyloxy rearrangements where both inversion and retention of the carboxyl oxygen have been observed.



The homoallylic radicals **34a** and **34b** provide clever probes for both the acyloxy and phosphatoxy rearrangements.⁴⁰ A non-dissociative mechanism for the rearrangement would give the homoallylic product **35a** (or **35b**) with deuterium label only at the allylic position. Rearrangement by a fragmentation-recombination mechanism would give the same product, but with label scrambled between the allylic and vinylic positions. The fragmentation-recombination mechanism is shown proceeding through the pair species **36** (as either a neutral or ion-pair species, See Equations 6.3c and 6.3d for the carboxyl rearrangement).

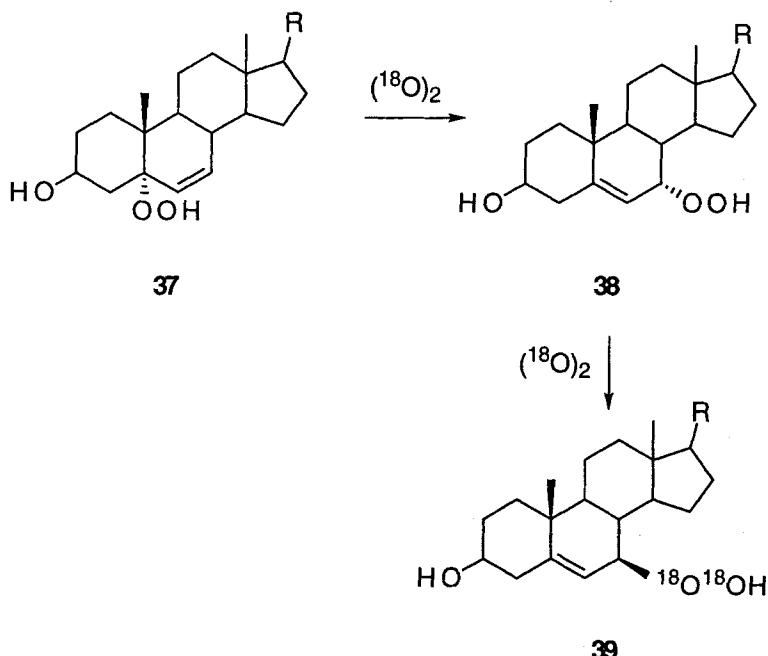


The results of the rearrangements of the radicals **34a** and **34b** provide no evidence for the fragmentation pathway. Product **35** is formed with label only in the allylic position. If a fragmentation-collapse sequence occurs, it must occur via an intermediate pair that is not fully relaxed and if the pair species does not live long enough for reorientation, its proposal as a reaction intermediate is inappropriate. The results of these studies, taken together with the oxygen labeling studies of **23** and **27** and the stereochemical information obtained from the rearrangement of the cyclic phosphate radicals **30** and **31** do not, however, provide a consistent mechanistic picture for either the acyloxy or phosphatoxy rearrangements.

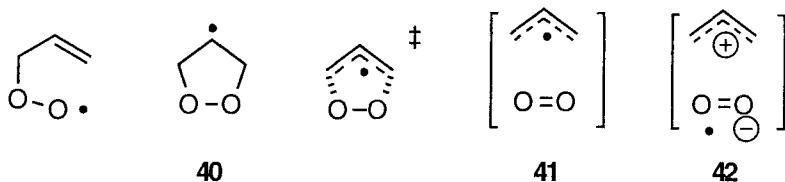
6.2.3 The Allylperoxy Rearrangement

Allylperoxy rearrangements have been known since the late 1950s but the mechanism is still open to debate. Rearrangements of cholesterol hydroperoxides were among the first studied. The tertiary hydroperoxide 5α -

hydroperoxy- 3β -hydroxy-cholest-6-ene (**37**) slowly rearranges to its secondary allylic isomer **38** with complete retention of the α configuration.⁴¹

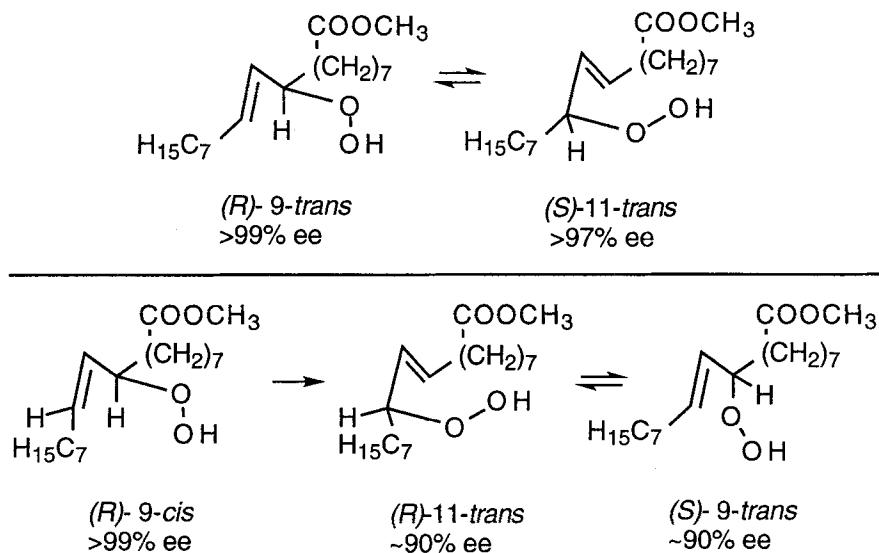


Hydroperoxide **38** undergoes a slower epimerization to the 7 β -hydroperoxide (**39**).⁴² No atmospheric ^{18}O incorporation is observed in the 7 α -hydroperoxy-3 β -hydroxycholest-5-ene (**38**) whereas the epimerization of this product to 7 β -hydroperoxy-3 β -hydroxycholest-5-ene (**39**) occurs with ~80% ^{18}O incorporation.^{43,44} It was suggested that the rearrangement of **37** to **38** involves a concerted [2,3] allylperoxy rearrangement, whereas the second rearrangement of **38** to **39** proceeds through a dissociative mechanism. Theoretical investigations failed to find the concerted pericyclic transition state, proposed for the rearrangement.⁴⁵ These calculations did, however, reveal a dioxolanyl radical **40** close in energy to the allylperoxy radical. Radical **40** has a barrier to formation from the peroxy in excess of 40 kcal/mol, while β -fragmentation of the peroxy to the allyl radical-dioxygen pair requires only 22 kcal/mol. Theory therefore suggests that the [2,3] allylperoxy rearrangement proceeds by this lower energy β -fragmentation process, via the radical-dioxygen pair **41** or the allyl cation-superoxide pair, **42**.

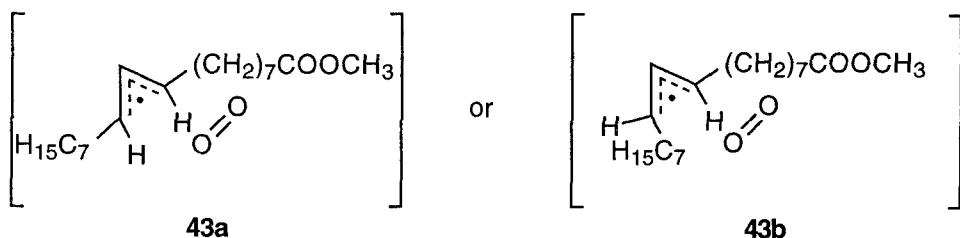


Work on acyclic systems was first reported by Brill in 1965, and his studies appear to rule out the dioxolanyl radical **40** as an intermediate.^{46,47} The stereochemical course of the allylperoxy rearrangement was also studied with hydroperoxides derived from oleic acid.⁴⁸

The rearrangement is highly stereoselective. Rearrangement products derived from *trans* starting hydroperoxides have the opposite configuration from the starting compound while products derived from *cis* starting hydroperoxides have the same configuration as the starting compound. As an example, the (*R*)-9-*trans* hydroperoxide with enantiomeric excess > 99% rearranges at 22°C to yield a mixture of (*R*)-9-*trans* and (*S*)-11-*trans* compounds with enantiomeric excess in the latter compound of 97%. Under identical conditions, (*R*)-9-*cis* hydroperoxide with enantiomeric excess > 99% rearranges at 22°C to yield a mixture of (*R*)-11-*trans* and (*S*)-9-*trans* compounds with enantiomeric excess in both products of ~90%.



The stereoselectivity of the rearrangement is consistent with a concerted mechanism via an envelope-like transition state that results in transfer of chirality across the allyl system or with a mechanism involving a very tight allyl-oxygen pair **43** (**a** from the *trans* precursor and **b** from the *cis*) which collapses with predominant retention of configuration.



The rearrangement proceeds with little incorporation of atmospheric oxygen at room temperature in viscous solvents. At higher temperatures, studies of the rearrangement under labeled molecular oxygen in solvents of different viscosity provide mechanistic insights. In short, it has been reported that incorporation of labeled oxygen from the atmosphere occurs but that this incorporation is dependent on solvent viscosity and temperature, as is the stereoselectivity of the rearrangement.^{49,50} In more viscous solvents and at lower temperatures, less atmospheric oxygen is incorporated in the product of rearrangement and the rearrangement is more stereoselective. In octadecane at 60°C, for example, the rearrangement of an *E* alkene derived from methyl oleate gives product with over 96% enantiomeric excess and with incorporation of ~2% atmospheric oxygen. In hexane, substantially more atmospheric oxygen is incorporated and a corresponding decrease in stereoselectivity is observed.

The simplest mechanism for the rearrangement consistent with the experimental results and theoretical investigations involves the allyl-radical dioxygen caged pair that collapses at a diffusion-controlled rate with stereochemical memory. The caged pair shown might have substantial charge-transfer character. Allyl radicals that diffuse into solution incorporate ¹⁸O₂ with racemization of configuration. This gives evidence of a planar allyl radical intermediate that escapes from the initial solvent cage. The pair collapse ¹⁶O-product apparently forms with a high degree of stereoselectivity compared to other known radical pair reactions. The stereochemical-oxygen labeling studies indicate that solvent viscosity affects the partitioning between escape and collapse of the allyl radical-dioxygen caged pair. An increase in

solvent viscosity results in a decrease in escape product and a corresponding increase in pair collapse product.

6.2.4 [3,2] Radical Rearrangement Mechanisms

While the mechanisms of the acyloxy, phosphatoxy, and allylperoxy rearrangements are open to debate, the data obtained for the three systems are remarkably similar. The rearrangements proceed with high stereoselectivity for some molecular frameworks while in others a substantial loss of configuration is observed during rearrangement. Atom labeling studies indicate complete retention of configuration for some molecular frameworks while for others substantial scrambling of labels occurs. For one of the systems, allylperoxy, scrambling of peroxy label with atmospheric oxygen can be substantial although the extent of this scrambling depends on the molecular framework, the temperature, and the solvent viscosity.

One mechanistic picture that emerges is that there are several competing mechanistic pathways. This argument seems unconvincing, particularly since competing concerted processes are required in some cases ([1,2] and [2,3] rearrangements) and competing concerted and pair escape mechanisms must be advanced in other examples. While this picture is of course possible, the suggestion that transition states for such a diverse set of processes are of nearly the same energy requires a fortunate set of circumstances indeed.

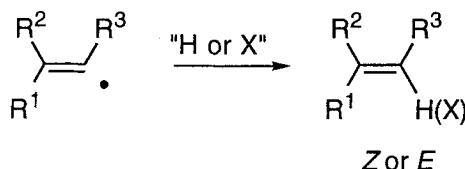
Pair rearrangement mechanisms have been written for each of the rearrangements and the evidence against such pairs generally cited is the high stereoselectivity or label retention observed during the rearrangement. The suggestion that intermediate pair species couple with high stereoselectivity and with little geometric relaxation has generally been used to rule out such pair mechanisms. We note that the chemistry of radical pairs is such that stereoselective processes can occur within a caged pair (Section 6.1).

Geminate pairs proposed in the rearrangements discussed here may be quite different from simple radical pairs, however. Significant charge transfer has been proposed for each of the rearrangements and the chemistry of such charged radical ion pair species is unknown. Radical ion pairs, in particular, may be tightly bound species and the coupling of these pairs may be stereoselective. The intermediacy of geminate radical pairs, radical ion pairs, or radical dioxygen pairs is not ruled out by the observation of a stereoselective coupling event.

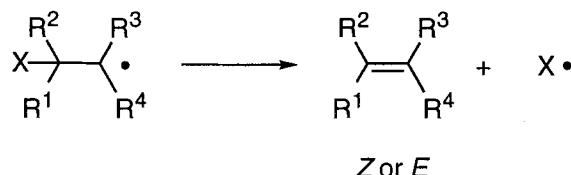
6.3 Alkene-Forming Reactions

Free radicals serve as olefin precursors and useful procedures for the stereoselective construction of alkenes have been reported. Methods for the

Vinyl radical hydrogen abstraction



Radical β Fragmentation



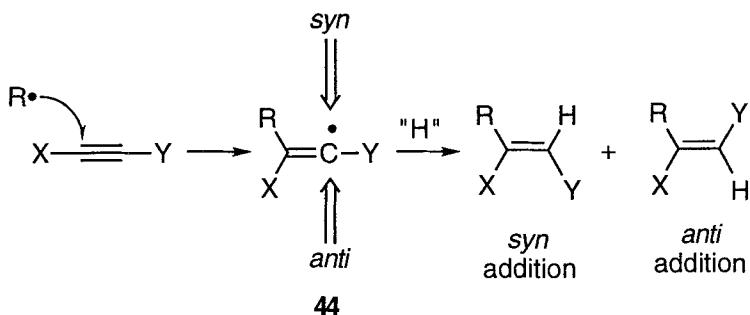
construction of carbon–carbon double bonds from vinyl radicals as well as from radicals bearing β leaving groups have been developed and stereochemistry is an issue if the radical precursors are appropriately substituted.

6.3.1 Vinyl Radical Hydrogen Abstraction

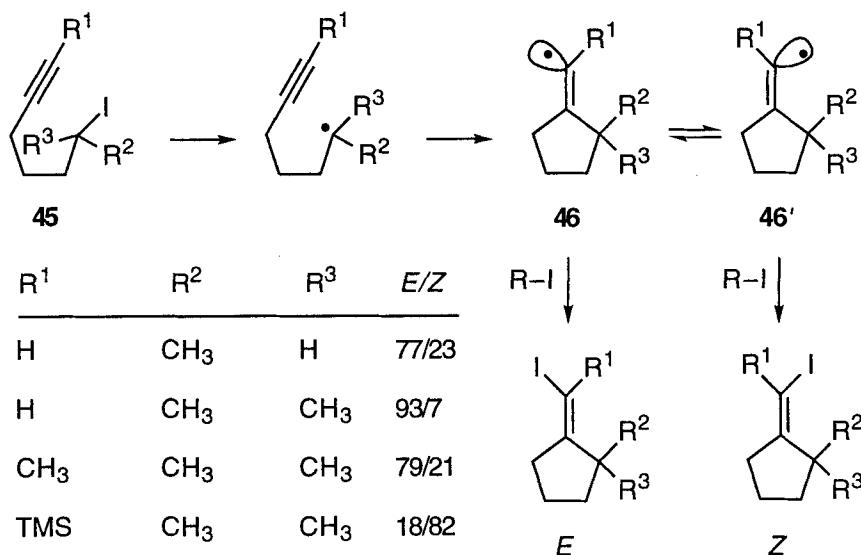
Unconjugated vinyl radicals are known to be sp^2 hybridized and to invert with a very low barrier.⁵¹ Tin hydride reduction of *E* or *Z*-2-bromo-2-butene gives an *E/Z*-2-butene product mixture of 65/35, suggesting that vinyl radical inversion is more rapid than reaction with tin hydride.^{52,53} While tin hydride reactions with vinyl radicals give product mixtures that are independent of the stereochemistry of the the vinyl radical precursor, it has been suggested that in the reactions of BrCCl_3 with vinyl radicals the inversion of the radical competes with bromine atom transfer.⁵⁴

The stereochemistry of products formed in the intermolecular addition of radicals to alkynes has been investigated.⁵⁵ The stereoselectivity of the H atom transfer to the conjugated vinyl radical **44** depends on the steric bulk of the R group. Thus, for X = H and Y = Ph, when R = *tert*-butyl, the *anti/syn*

ratio is 93/7 while for R = cyclohexyl, the partitioning of these two pathways gives an *anti/syn* ratio of 70/30. For radicals substituted with Y = COOR, selectivity is substantially lower for both R = *tert*-butyl and cyclohexyl. The stereoselectivity of transformations of radical **44** depends on the reactivity of the hydrogen atom donor.^{55c}



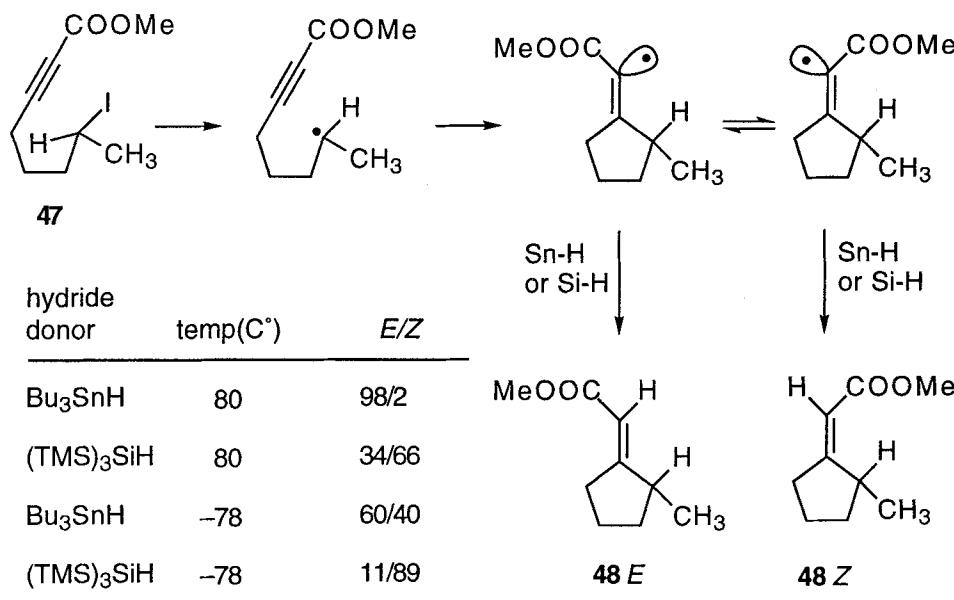
Vinyl radicals can be efficiently generated by radical cyclization and the stereochemistry of products formed from cyclizations to alkynes have been investigated. Atom transfer cyclization of **45**, for example, gives the vinyl radical **46** and iodine atom transfer to **46** gives the *Z* and *E* product iodides.⁵⁶



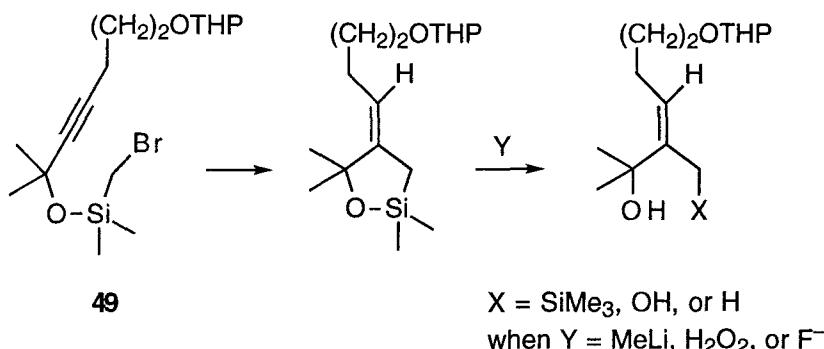
Even though iodine atom transfer is fast, the interconversion of radicals **46** and **46'** is apparently faster and the ratio of products formed depends on

the equilibrium constant for the interconverting radicals and the rate constant of atom transfer to each radical. For $R^1 = H$ and R^2 and $R^3 = CH_3$, one sees a predominance of the *E* product since the atom donor delivers iodide to the radical remote from the *gem*-dimethyl substituents. Increasing the size of R^1 while maintaining the size of R^2 and R^3 shifts the radical equilibrium to favor **46'** and this gives more *Z* product in the mixture formed.

The cyclization of secondary alkyl radicals to α,β -alkynyl esters proceeds stereoselectively to give either *E* or *Z* exocyclic alkenes, depending upon the reaction conditions.⁵⁷ Reaction of iodide **47** with tin hydride at 80°C gives the product **48** with an *E/Z* ratio that depends on the temperature and hydride donor. The high stereoselectivity of the cyclization at 80°C with tin hydride results from the fact that tin radicals isomerize double bonds at elevated temperatures.⁵⁸ The *E* alkene formed under these conditions is a thermodynamic product. The *Z* alkene is favored with the silane hydrogen donor since product equilibration apparently does not occur with silyl radicals⁵⁹ and the observed 34/66 alkene mixture represents a kinetic product distribution. The preference for formation of the *Z* alkene under these conditions results from hindrance of approach of the bulky silane to the radical that is the *E* alkene precursor. At -78°C this effect becomes even more substantial and the *Z* alkene dominates the product mixture by 89/11.

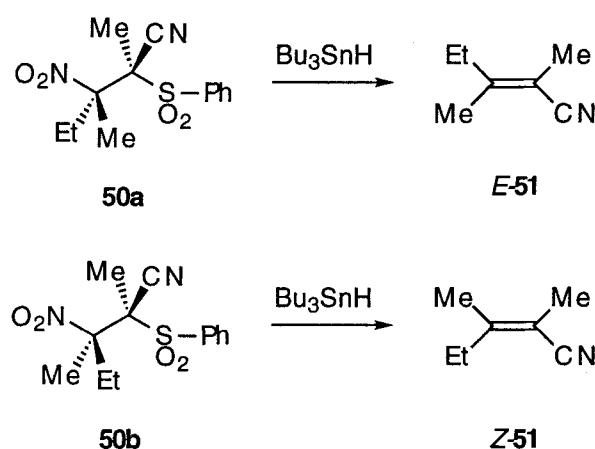


Stereoselectivities in excess of 99% can be achieved in cyclization reactions of the dimethylsilyl propargyl ether **49**.⁶⁰



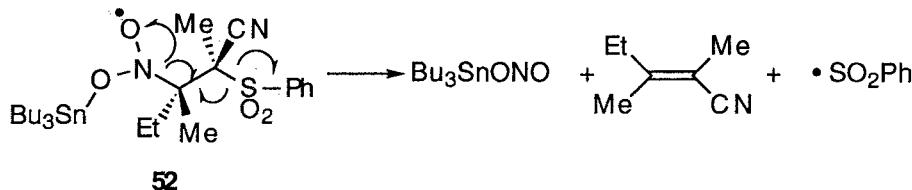
6.3.2 Radical β -Fragmentation

Alkenes have been prepared by radical eliminations induced by tin hydride from a host of substrates including *vic*-dibromides, β -bromosulfides and β -nitrosulfones.⁶¹ Most of these eliminations proceed without significant stereoselectivity with the notable exception of β -nitrosulfides and β -nitrosulfones, which give elimination products with very high stereoselectivity in some cases.⁶² As an example, the separated diastereomers of the β -nitrosulfone **50** undergo clean conversion to the tetrasubstituted olefins **51** on reaction with tin hydride at 80°C. The diastereomer **50a** gives only the *E* product while **50b** gives the *Z* product exclusively.

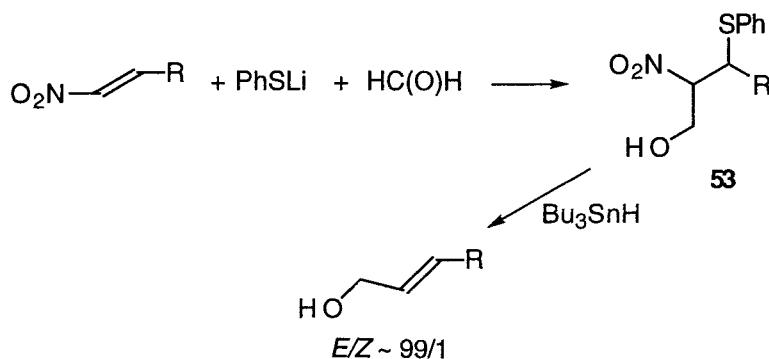


Elimination reactions leading to trisubstituted alkenes are less stereo-selective than reactions giving tetrasubstituted alkenes and the selectivity depends on the leaving group, β -sulfides being less selective than β -sulfoxides which are, in turn, less selective than elimination reactions from β -sulfones.

A mechanism has been proposed for the elimination that involves a synchronous (or near synchronous) cleavage of the tin radical adduct **52**. It has been suggested that even if the C–N bond cleavage of **52** is more advanced than that of the C–S bond, the bulky sulfonyl and nitroxide groups inhibit rotation about the central C–C bond during the elimination reaction.⁶³



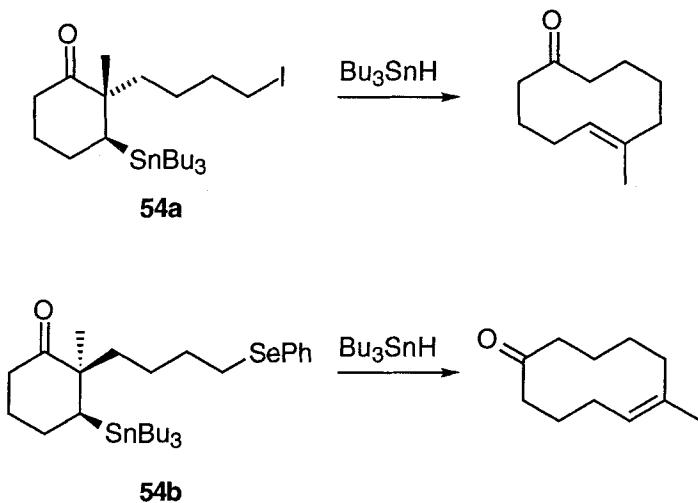
Allylic alcohols can be prepared by a two step procedure involving addition of thiolate and formaldehyde to nitro alkanes followed by tin hydride mediated radical elimination of the β -nitrosulfide, **53**.⁶⁴ The *E* alkene is formed with greater than 99% d.e. in most cases even though the precursor β -nitrosulfide is a mixture of diastereomers. It seems likely that the product mixture is under thermodynamic control since tin hydride will equilibrate alkenes under conditions similar to those used in the elimination reaction.⁵⁷



Alkoxy radicals with γ -stannylyl groups undergo fragmentation reactions that generate alkenes.⁶⁵ This reaction, which amounts to two consecutive β -fragmentations, gives rise to olefins with stereochemical control.

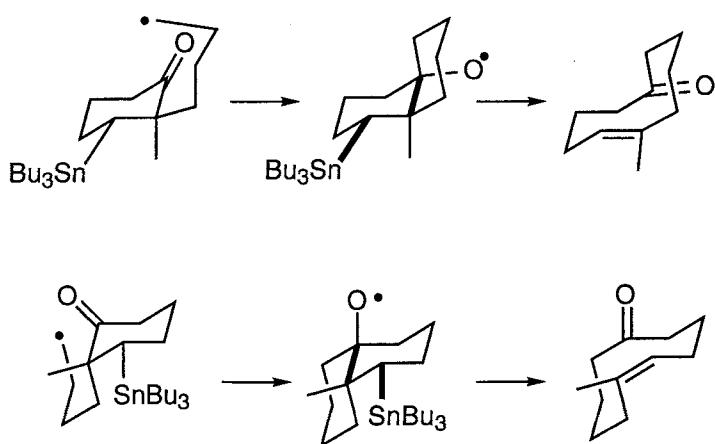


This fragmentation reaction has been coupled with intramolecular addition of carbon radicals to ketones, providing a stereoselective sequence to medium ring alkenes.⁶⁶ Reaction of the iodide **54a** with tin hydride/AIBN at 80°C gives the cycloalkene product having only the *E* double bond in the ring while the diastereomer **54b** gives only the *Z* cycloalkene under similar conditions.



It is evident that the olefin geometry is controlled by the stereochemistry of the precursor, the *trans*-precursor gives *E* product and the *cis*-precursor gives *Z* product. This result is expected based upon an *anti* relationship of the alkoxy and the stannylyl leaving group. Thus, generation of the radical from the iodo or phenylselenide precursor is followed by addition of the radical to the cyclohexanone carbonyl, giving an alkoxy radical that then fragments stereoselectively. This approach gives significant amounts of reduction product when the α -carbon is substituted with a hydrogen rather than a

methyl group. Labeling experiments indicate that in this case, intramolecular hydrogen atom transfer competes with addition to the carbonyl. There is a substantial product isotope effect observed when the α -deutero compound is reacted. The deuterium 1,5-transfer is suppressed relative to the corresponding hydrogen atom transfer and more carbonyl addition-fragmentation is observed.



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