

Reactions Involving Transition Metals

Introduction

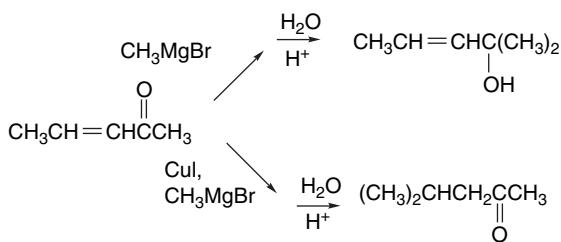
In this chapter we discuss important synthetic reactions that involve transition metal compounds and intermediates. Reactions involving copper and palladium, the transition metals that have the widest applications in synthesis, are discussed in the first two sections. In the third section, we consider several other transition metals, including nickel, rhodium, and cobalt. In contrast to lithium, magnesium, and zinc, where the organometallic reagents are used in stoichiometric quantities, many of the transition metal reactions are catalytic processes. The mechanisms are described in terms of *catalytic cycles* that show the role of the catalytic species in the reaction and its regeneration. Another distinguishing feature of transition metal reactions is that they frequently involve changes in oxidation state at the metal atom. In the final two sections we deal with transition metal–catalyzed alkene exchange (*metathesis*) reactions and organometallic compounds that feature π bonding of the organic component.

8.1. Organocopper Intermediates

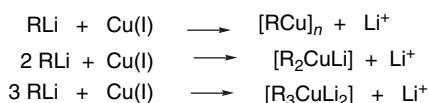
8.1.1. Preparation and Structure of Organocopper Reagents

The synthetic application of organocopper compounds received a major impetus from the study of the catalytic effect of copper salts on reactions of Grignard reagents with α, β -unsaturated ketones.¹ Although Grignard reagents normally add to such compounds to give the 1,2-addition product, the presence of catalytic amounts of Cu(I) results in conjugate addition. Mechanistic study pointed to a very fast reaction by an organocopper intermediate.

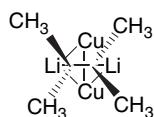
¹. H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).



Subsequently, much of the development of organocupper chemistry focused on stoichiometric reagents prepared from organolithium compounds. Several types of organometallic compounds can result from reactions of organolithium reagents with copper(I) salts.² Metal-metal exchange reactions using a 1:1 ratio of lithium reagent and a copper(I) salt give alkylcopper compounds that tend to be polymeric and are less useful in synthesis than the 2:1 or 3:1 “ate” compounds.



The 2:1 species are known as *cuprates* and are the most common synthetic reagents. Disubstituted Cu(I) species have the $3d^{10}$ electronic configuration and would be expected to have linear geometry. The Cu is a center of high electron density and nucleophilicity, and in solution, lithium dimethylcuprate exists as a dimer $[\text{LiCu}(\text{CH}_3)_2]_2$.³ The compound is often represented as four methyl groups attached to a tetrahedral cluster of lithium and copper atoms. However, in the presence of LiI, the compound seems to be a monomer of composition $(\text{CH}_3)_2\text{CuLi}$.⁴



Discrete diarylcuprate anions have been observed in crystals in which the lithium cation is complexed by crown ethers.⁵ Both tetrahedral Ph_4Cu_4^- and linear $[\text{Ph}_2\text{Cu}]^-$ units have been observed in complex cuprates containing $(\text{CH}_3)_2\text{S}$ as a ligand. $[(\text{Ph})_3\text{Cu}]^{2-}$ units have also been observed as parts of larger aggregates.⁶ Larger clusters of composition $[(\text{Ph}_6\text{Cu}_4)\text{Li}]^-$ and $[\text{Ph}_6\text{Cu}_4\text{Mg-OEt}_2]$ have been characterized by crystallography,⁷ as shown in Figure 8.1.

Cuprates with two different copper ligands have been developed. These compounds have important advantages in cases in which one of the substituents

2. E. C. Ashby and J. J. Lin, *J. Org. Chem.*, **42**, 2805 (1977); E. C. Ashby and J. J. Watkins, *J. Am. Chem. Soc.*, **99**, 5312 (1977).
3. R. G. Pearson and C. D. Gregory, *J. Am. Chem. Soc.*, **98**, 4098 (1976); B. H. Lipshutz, J. A. Kozlowski, and C. M. Breneman, *J. Am. Chem. Soc.*, **107**, 3197 (1985).
4. A. Gerold, J. T. B. H. Jastrezebski, C. M. P. Kronenburg, N. Krause, and G. Van Koten, *Angew. Chem. Int. Ed. Engl.*, **36**, 755 (1997).
5. H. Hope, M. M. Olmstead, P. P. Power, J. Sandell, and X. Xu, *J. Am. Chem. Soc.*, **107**, 4337 (1985).
6. M. M. Olmstead and P. P. Power, *J. Am. Chem. Soc.*, **112**, 8008 (1990).
7. S. I. Khan, P. G. Edwards, H. S. H. Yuan, and R. Bau, *J. Am. Chem. Soc.*, **107**, 1682 (1985).

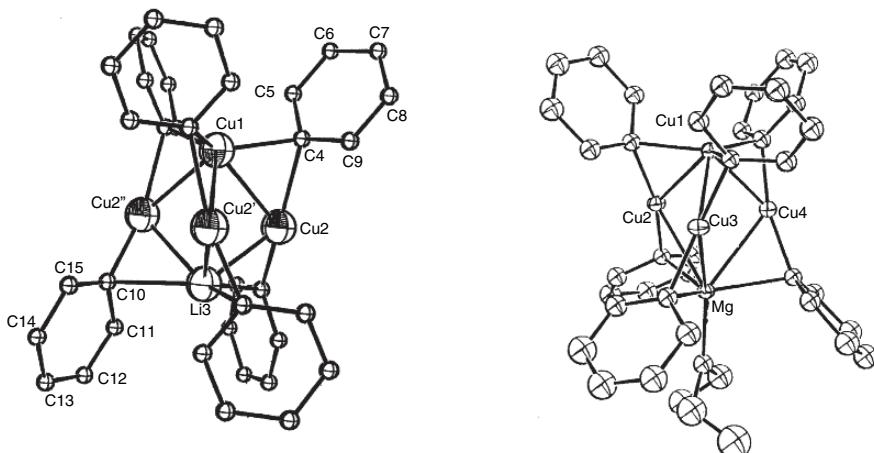


Fig. 8.1. Crystal structures of $[(\text{Ph}_6\text{Cu}_4)\text{Li}]^-$ (left) and $[\text{Ph}_6\text{Cu}_4\text{Mg}(\text{OEt}_2)]$ (right). Reproduced from *J. Am. Chem. Soc.*, **107**, 1682 (1985), by permission of the American Chemical Society.

is derived from a valuable synthetic intermediate. The group R, representing alkyl, alkenyl, or aryl, is normally transferred in preference to the other copper ligand. Table 8.1 presents some of these mixed cuprate reagents and summarizes their reactivity. The group listed first is the nonreactive copper ligand and R is the organic group that is delivered as a nucleophile.

There has been a great deal of study concerning the effect of solvents and other reaction conditions on the stability and reactivity of organocuprate species.⁸ These studies have found, for example, that $(\text{CH}_3)_2\text{S}-\text{CuBr}$, a readily prepared and purified complex of CuBr, is an especially reliable source of Cu(I) for cuprate preparation.⁹ Copper(I) cyanide and iodide are also generally effective and, in some cases, preferable.¹⁰

An important type of mixed cuprate is prepared from a 2:1 ratio of an alkylolithium and CuCN.¹¹ Called *higher-order cyanocuprates*, their composition is $\text{R}_2\text{CuCNLi}_2$ in THF solution, but it is thought that most of the molecules are probably present as dimers. The cyanide does not seem to be bound directly to the copper, but rather to the lithium cations.¹² The dimers most likely adopt an eight-membered ring motif.¹³

⁸ R. H. Schwartz and J. San Filippo, Jr., *J. Org. Chem.*, **44**, 2705 (1979).

⁹ H. O. House, C.-Y. Chu, J. M. Wilkins, and M. J. Umen, *J. Org. Chem.*, **40**, 1460 (1975).

¹⁰ B. H. Lipshutz, R. S. Wilhelm, and D. M. Floyd, *J. Am. Chem. Soc.*, **103**, 7672 (1981); S. H. Bertz, C. P. Gibson, and G. Dabbagh, *Tetrahedron Lett.*, **28**, 4251 (1987); B. H. Lipshutz, S. Whitney, J. A. Kozlowski, and C. M. Breneman, *Tetrahedron Lett.*, **27**, 4273 (1986).

¹¹ B. H. Lipshutz, R. S. Wilhelm, and J. Kozlowski, *Tetrahedron*, **40**, 5005 (1984); B. H. Lipshutz, *Synthesis*, 325 (1987).

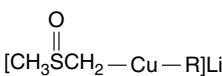
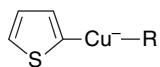
¹² T. M. Barnhart, H. Huang, and J. E. Penner-Hahn, *J. Org. Chem.*, **60**, 4310 (1995); J. P. Snyder and S. H. Bertz, *J. Org. Chem.*, **60**, 4312 (1995); T. L. Semmler, T. M. Barnhart, J. E. Penner-Hahn, C. E. Tucker, P. Knochel, M. Bohme, and G. Frenking, *J. Am. Chem. Soc.*, **117**, 12489 (1995); S. H. Bertz, G. B. Miao, and M. Eriksson, *J. Chem. Soc., Chem. Commun.*, 815 (1996).

¹³ E. Nakamura and S. Mori, *Angew. Chem. Int. Ed. Engl.*, **39**, 3750 (2000).

Table 8.1. Mixed-Ligand Organocopper Reagents

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Transition Metals

Mixed ligand reagent	Reactivity and properties	Reference
[R'C≡C—Cu—R]Li	Conjugate addition to α,β -unsaturated ketones and certain esters	a
[ArS—Cu—R]Li	Nucleophilic substitution and conjugate addition to unsaturated ketones; ketones from acyl chlorides	b,c
[(CH ₃) ₃ CO—Cu—R]Li	Nucleophilic substitution and conjugate addition to α,β -unsaturated ketones	b
[(c-C ₆ H ₁₁) ₂ N—Cu—R]Li	Normal range of nucleophilic reactivity; improved thermal stability	d
[Ph ₂ P—Cu—R]Li	Normal range of nucleophilic reactivity; improved thermal stability	d
	Normal range of nucleophilic reactivity; improved thermal stability	e
[N≡C—Cu—R]Li	Efficient opening of epoxides	f
[N≡C—CuR ₂]Li ₂	Nucleophilic substitution, conjugate addition	g
	Nucleophilic substitution, conjugate addition and epoxide ring-opening	h
[(CH ₃) ₃ CCH ₂ —Cu—R]Li	Conjugate addition	i
[(CH ₃) ₃ SiCH ₂ —Cu—R]Li	High reactivity, thermal stability	j
{[(CH ₃) ₃ Si] ₂ N—Cu—R}Li	High reactivity, thermal stability	j
BF ₃ —Cu—R	Conjugate addition, including acrylate esters and acrylonitrile; S _N 2' substitution of allylic halides	k

a. H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 3893 (1973); E. J. Corey, D. Floyd, and B. H. Lipshutz, *J. Org. Chem.*, **43**, 3418 (1978).

b. G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Am. Chem. Soc.*, **95**, 7788 (1973).

c. G. H. Posner and C. E. Whitten, *Org. Synth.*, **58**, 122 (1975).

d. S. H. Bertz, G. Dabbagh, and G. M. Villacorta, *J. Am. Chem. Soc.*, **104**, 5824 (1982).

e. C. R. Johnson and D. S. Dhanoa, *J. Org. Chem.*, **52**, 1885 (1987).

f. R. D. Acker, *Tetrahedron Lett.*, 3407 (1977); J. P. Marino and N. Hatanaka, *J. Org. Chem.*, **44**, 4667 (1979).

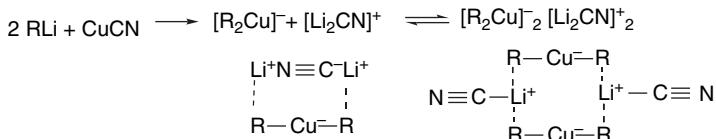
g. B. H. Lipshutz and S. Sengupta, *Org. React.*, **41**, 135 (1992).

h. H. Malmberg, M. Nilsson, and C. Ullénius, *Tetrahedron Lett.*, **23**, 3823 (1982); B. H. Lipshutz, M. Koernen, and D. A. Parker, *Tetrahedron Lett.*, **28**, 945 (1987).

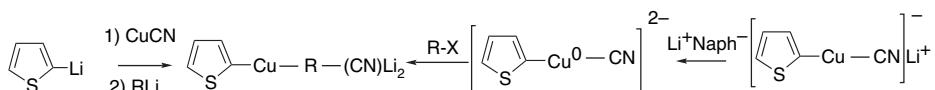
i. C. Lutz, P. Jones, and P. Knochel, *Synthesis*, 312 (1999).

j. S. H. Bertz, M. Eriksson, G. Miao, and J. P. Snyder, *J. Am. Chem. Soc.*, **118**, 10906 (1996).

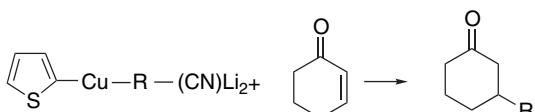
k. K. Maruyama and Y. Yamamoto, *J. Am. Chem. Soc.*, **99**, 8068 (1977); Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.*, **100**, 3240 (1978).



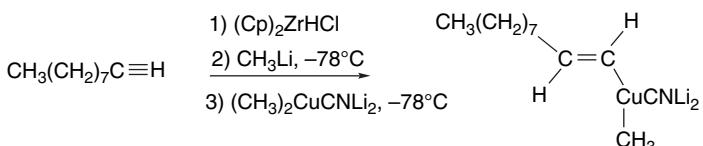
These reagents are qualitatively similar in reactivity to other cuprates but they are more stable than the dialkylcuprates. As cyanocuprate reagents usually transfer only one of the two organic groups, it is useful to incorporate a group that does not transfer, and the 2-thienyl group has been used for this purpose.¹⁴ Usually, these reagents are prepared from an organolithium reagent, 2-thienyllithium, and CuCN. These reagents can also be prepared by reaction of an alkyl halide with 2-thienylcopper. The latter method is compatible with functionalized alkyl groups.¹⁵



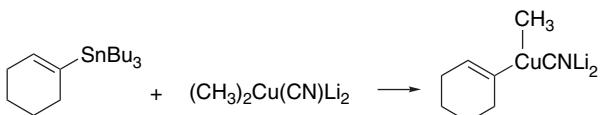
In a mixed alkyl-thienyl cyanocuprate, only the alkyl substituent is normally transferred as a nucleophile.



Another type of mixed cyanocuprate has both methyl and alkenyl groups attached to copper. Interestingly, these reagents selectively transfer the alkenyl group in conjugate addition reactions.¹⁶ These reagents can be prepared from alkynes via hydrozirconation, followed by metal-metal exchange.¹⁷



Alkenylcyanocuprates can also be made by metal-metal exchange from alkenylstananes.¹⁸



¹⁴ B. H. Lipshutz, J. A. Kozlowski, D. A. Parker, S. L. Nguyen, and K. E. McCarthy, *J. Organomet. Chem.*, **285**, 437 (1985); B. H. Lipshutz, M. Koerner, and D. A. Parker, *Tetrahedron Lett.*, **28**, 945 (1987).

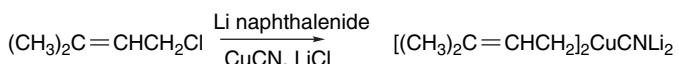
¹⁵ R. D. Rieke, W. R. Klein, and T.-S. Wu, *J. Org. Chem.*, **58**, 2492 (1993).

¹⁶ B. H. Lipshutz, R. S. Wilhelm, and J. A. Kozlowski, *J. Org. Chem.*, **49**, 3938 (1984).

¹⁷ B. H. Lipshutz and E. L. Ellsworth, *J. Am. Chem. Soc.*, **112**, 7440 (1990).

¹⁸ J. R. Behling, K. A. Babiak, J. S. Ng, A. L. Campbell, R. Moretti, M. Koerner, and B. H. Lipshutz, *J. Am. Chem. Soc.*, **110**, 2641 (1988).

The 1:1 organocopper reagents can be prepared directly from the halide and highly reactive copper metal prepared by reducing Cu(I) salts with lithium naphthalenide.¹⁹ This method of preparation is advantageous for organocuprates containing substituents that are incompatible with organolithium compounds. For example, nitrophenyl and cyanophenyl copper reagents can be prepared in this way, as can alkylcopper reagents having ester and cyano substituents.²⁰ Allylic chlorides and acetates can also be converted to cyanocuprates by reaction with lithium naphthalenide in the presence of CuCN and LiCl.²¹

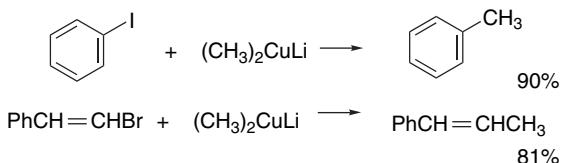


Organocupper reagents can also be prepared from Grignard reagents, which are generated and used *in situ* by adding a Cu(I) salt, typically the bromide, iodide, or cyanide.

8.1.2. Reactions Involving Organocupper Reagents and Intermediates

The most characteristic feature of the organocuprate reagents is that they are excellent *soft nucleophiles*, showing greater reactivity in S_N2 , S_N2' , and conjugate addition reactions than toward direct addition at carbonyl groups. The most important reactions of organocuprate reagents are nucleophilic displacements on halides and sulfonates, epoxide ring opening, conjugate additions to α,β -unsaturated carbonyl compounds, and additions to alkynes.²² These reactions are discussed in more detail in the following sections.

8.1.2.1. S_N2 and S_N2' Reactions with Halides and Sulfonates. Corey and Posner discovered that lithium dimethylcuprate can replace iodine or bromine by methyl in a wide variety of compounds, including aryl, alkenyl, and alkyl derivatives. This halogen displacement reaction is more general and gives higher yields than displacements with Grignard or lithium reagents.²³



¹⁹ G. W. Ebert and R. D. Rieke, *J. Org. Chem.*, **49**, 5280 (1984); *J. Org. Chem.*, **53**, 4482 (1988); G. W. Ebert, J. W. Cheasty, S. S. Tehrani, and E. Aouad, *Organometallics*, **11**, 1560 (1992); G. W. Ebert, D. R. Pfennig, S. D. Suchan, and T. J. Donovan, Jr., *Tetrahedron Lett.*, **34**, 2279 (1993).

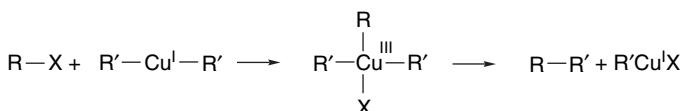
²⁰ R. M. Wehmeyer and R. D. Rieke, *J. Org. Chem.*, **52**, 5056 (1987); T.-C. Wu, R. M. Wehmeyer, and R. D. Rieke, *J. Org. Chem.*, **52**, 5059 (1987); R. M. Wehmeyer and R. D. Rieke, *Tetrahedron Lett.*, **29**, 4513 (1988).

²¹ D. E. Stack, B. T. Dawson, and R. D. Rieke, *J. Am. Chem. Soc.*, **114**, 5110 (1992).

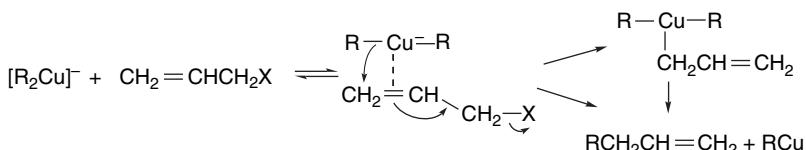
²² For reviews of the reactions of organocupper reagents, see G. H. Posner, *Org. React.*, **19**, 1 (1972); G. H. Posner, *Org. React.*, **22**, 253 (1975); G. H. Posner, *An Introduction to Synthesis Using Organocupper Reagents*, Wiley, New York, 1980; N. Krause and A. Gerold, *Angew. Chem. Int. Ed. Engl.*, **36**, 187 (1997).

²³ E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 3911 (1967).

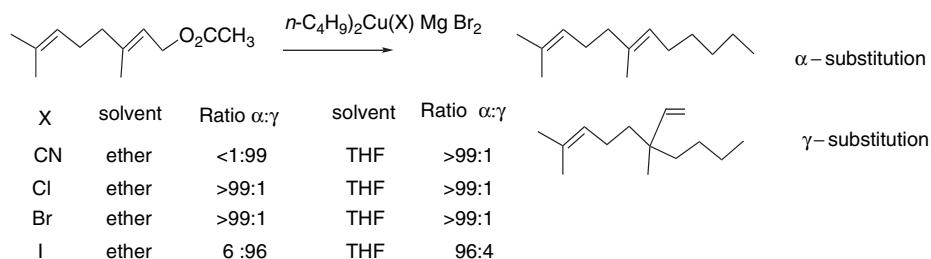
Secondary bromides and tosylates react with inversion of stereochemistry, as in the classical S_N2 substitution reaction.²⁴ Alkyl iodides, however, lead to racemized product. Aryl and alkenyl halides are reactive, even though the direct displacement mechanism is not feasible. For these halides, the overall mechanism probably consists of two steps: an *oxidative addition* to the metal, after which the oxidation state of the copper is +3, followed by combination of two of the groups from the copper. This process, which is very common for transition metal intermediates, is called *reductive elimination*. The $[R'_2Cu]^-$ species is linear and the oxidative addition takes place perpendicular to this moiety, generating a T-shaped structure. The reductive elimination occurs between adjacent R and R' groups, accounting for the absence of R'-R' coupling product.



Allylic halides usually give both S_N2 and S_N2' products, although the mixed organocopper reagent $RCu-BF_3$ is reported to give mainly the S_N2' product.²⁵ Other leaving groups can also be used, including acetate and phosphate esters. Allylic acetates undergo displacement with an allylic shift (S_N2' mechanism).²⁶ The allylic substitution process may involve initial coordination with the double bond.²⁷



For substituted allylic systems, both α - and γ -substitution can occur. Reaction conditions can influence the α - versus γ -selectivity. For example, the reaction of geranyl acetate with several butylcopper reagents was explored. Essentially complete α - or γ -selectivity could be achieved by modification of conditions.²⁸ In ether both $CuCN$ and CuI led to preferential γ -substitution, whereas α -substitution was favored for all anions in THF.



²⁴ C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.*, **95**, 7783 (1973); B. H. Lipshutz and R. S. Wilhelm, *J. Am. Chem. Soc.*, **104**, 4696 (1982); E. Hebert, *Tetrahedron Lett.*, **23**, 415 (1982).

²⁵ K. Maruyama and Y. Yamamoto, *J. Am. Chem. Soc.*, **99**, 8068 (1977).

²⁶ R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Am. Chem. Soc.*, **92**, 735 (1970); E. E. van Tamelen and J. P. McCormick, *J. Am. Chem. Soc.*, **92**, 737 (1970).

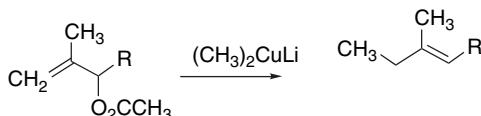
²⁷ H. L. Goering and S. S. Kantner, *J. Org. Chem.*, **49**, 422 (1984).

²⁸ E. S. M. Persson and J. E. Backvall, *Acta Chem. Scand.*, **49**, 899 (1995).

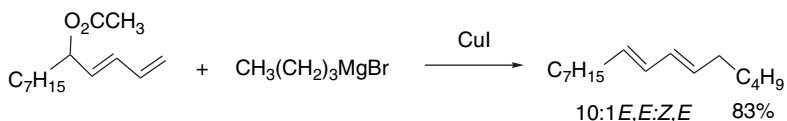
3-Acetoxy-2-methyl-1-alkenes react primarily at C(1), owing to steric factors.²⁹

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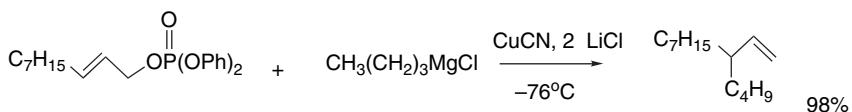
Reactions Involving
Transition Metals



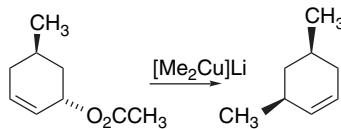
5-Acetoxy-1,3-alkadienes give mainly ϵ -alkylation with dialkylcopper-magnesium reagents.³⁰



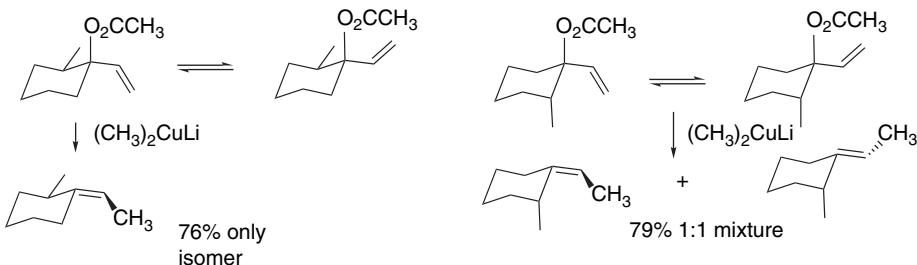
High γ -selectivity has been observed for allylic diphenyl phosphate esters.²⁹



The reaction of cyclic allylic acetates shows a preference for *anti* stereochemistry.³¹



The preferred stereoelectronic arrangement is perpendicular alignment of the acetate with respect to the double bond. For example, the *cis* and *trans* isomers of 1-vinyl-2-methylcyclohexyl acetate show divergent stereochemical results. Only the exocyclic *E*-isomer is formed from the *cis* compound, whereas the *trans* compound gives a 1:1 mixture of the *E*- and *Z*-isomers. This is the result of a strongly preferred conformation for the *cis* isomer, as opposed to a mixture of conformations for the *trans* isomer.³²

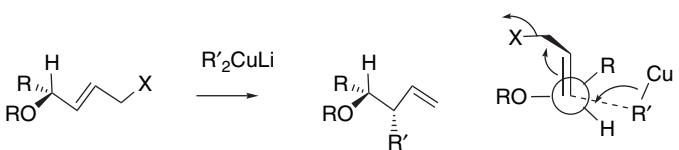


²⁹. R. J. Anderson, C. A. Hendrick, and J. B. Siddall, *J. Am. Chem. Soc.*, **92**, 735 (1970).

³⁰. N. Nakanishi, S. Matsubara, K. Utimoto, S. Kozima, and R. Yamaguchi, *J. Org. Chem.*, **56**, 3278 (1991).

³¹. H. L. Goering and V. D. Singleton, Jr., *J. Am. Chem. Soc.*, **98**, 7854 (1976); H. L. Goering and C. C. Tseng, *J. Org. Chem.*, **48**, 3986 (1983).

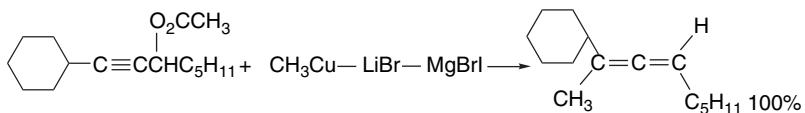
³². P. Crabbe, J. M. Dollat, J. Gallina, J. L. Luche, E. Velarde, M. L. Maddox, and L. Tokes, *J. Chem. Soc., Perkin Trans. I*, 730 (1978).



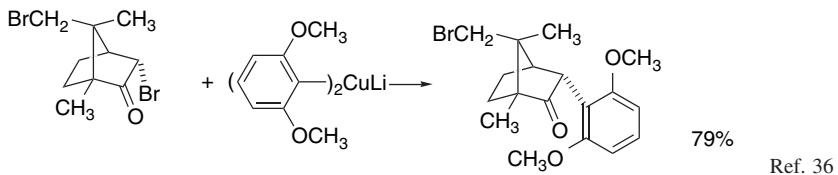
Similar results were obtained using *n*-BuMgBr-CuCN and tertiary allylic acetates, although under these conditions there is competition from S_N2' substitution with primary acetates.³³ The stereoselectivity is reversed with a hydroxy group, indicating a switch to a chelated TS.

<chem>C4H9-CH2-CH=CC(C(=O)C)C(C)(C)OR</chem>	$\xrightarrow[10 \text{ mol \% CuCN}]{2 \text{ eq } C_4H_9MgBr}$	<chem>C4H9-CH2-CH(C(C)(C)C(=O)C)C(C)(C)OR</chem>	yield	dr(anti:syn)
<chem>C4H9-CH2-CH=CC(C(=O)C)C(C)(C)OR</chem>		<chem>C4H9-CH2-CH(C(C)(C)C(=O)C)C(C)(C)OR</chem>		
PhCH ₂	72			86:4
CH ₃ OCH ₂	80			>98:2
TBDMS	89			90:10
H	84			7:93

Propargylic acetates, halides, and sulfonates usually react with a double-bond shift to give Allenes.³⁴ Some direct substitution product can be formed as well. A high ratio of allenic product is usually found with CH₃Cu-LiBr-MgBrI, which is prepared by addition of methylmagnesium bromide to a 1:1 LiBr-CuI mixture.³⁵



Halogens α to carbonyl groups can be successfully coupled using organocupper reagents. For example, 3,9-dibromocamphor is selectively arylated α to the carbonyl.



Scheme 8.1 gives several examples of the use of coupling reactions of organocuprate reagents with halides and acetates. Entries 1 to 3 are examples of the

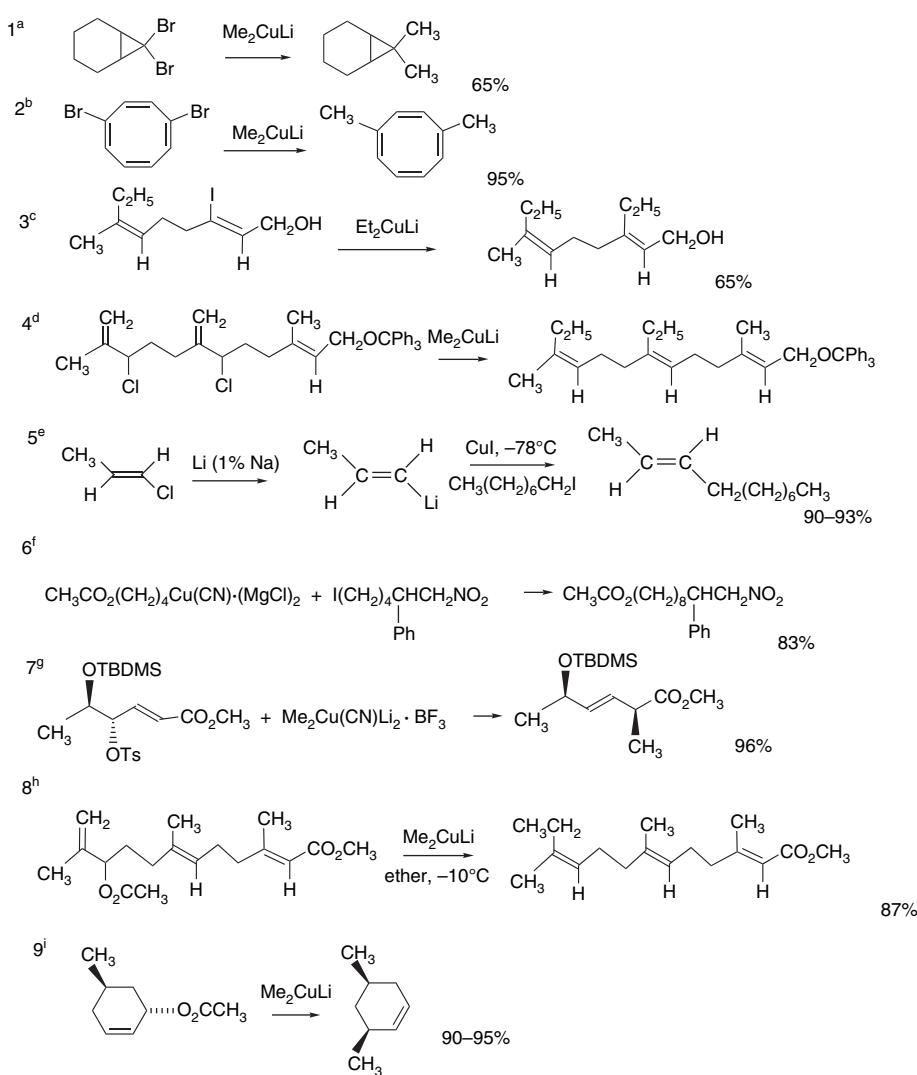
³³ J. L. Belelie and J. M. Chong, *J. Org. Chem.*, **67**, 3000 (2002).

³⁴ P. Rona and P. Crabbe, *J. Am. Chem. Soc.*, **90**, 4733 (1968); R. A. Amos and J. A. Katzenellenbogen, *J. Org. Chem.*, **43**, 555 (1978); D. J. Pasto, S.-K. Chou, E. Fritzen, R. H. Shults, A. Waterhouse, and G. F. Hennion, *J. Org. Chem.*, **43**, 1389 (1978).

³⁵ T. L. Macdonald, D. R. Reagan, and R. S. Brinkmeyer, *J. Org. Chem.*, **45**, 4740 (1980).

³⁶ V. Vaillancourt and F. F. Albizatti, *J. Org. Chem.*, **51**, 3627 (1992).

Scheme 8.1. Nucleophilic Substitution Reactions of Organocupper Reagents



a. E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 3911 (1967).

b. W. E. Konz, W. Hecht, and R. Huisgen, *J. Am. Chem. Soc.*, **92**, 4104 (1970).

c. E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Am. Chem. Soc.*, **90**, 5618 (1968).

d. E. E. van Tamelen and J. P. McCormick, *J. Am. Chem. Soc.*, **92**, 737 (1970).

e. G. Linstrumelle, J. K. Krieger, and G. M. Whitesides, *Org. Synth.*, **55**, 103 (1976).

f. C. E. Tucker and P. Knochel, *J. Org. Chem.*, **58**, 4781 (1993).

g. T. Ibuka, T. Nakao, S. Nishii, and Y. Yamamoto, *J. Am. Chem. Soc.*, **108**, 7420 (1986).

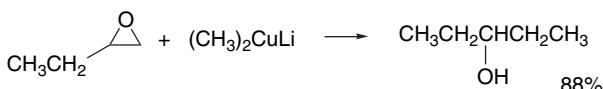
h. R. L. Anderson, C. A. Henrick, J. B. Siddall, and R. Zurfluh, *J. Am. Chem. Soc.*, **94**, 5379 (1972).

i. H. L. Goering and V. D. Singleton, Jr., *J. Am. Chem. Soc.*, **98**, 7854 (1976).

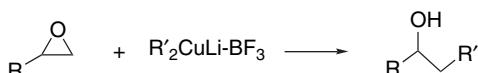
use of dialkylcuprates. In each case the halide is not susceptible to S_N2 substitution, but the oxidative addition mechanism is feasible. Entry 4 is an example of S_N2' substitution. This reaction, carried out simultaneously at two allylic chloride moieties, was used in the synthesis of the “juvenile hormone” of the moth *Cecropia*. Entry

5 illustrates the alkylation of a vinyl halide with retention of configuration at each stage of the reaction. Entry 6 is an example of a functionalized mixed magnesium-cyanocuprate reagent, which was prepared from an organozinc reagent by treatment with $(\text{CH}_3)_2\text{CuCNMg}_2\text{Cl}_2$. Entry 7 is an S_N2' displacement on a tosylate that occurs stereospecifically. Entries 8 and 9 are S_N2' displacements of allylic acetates.

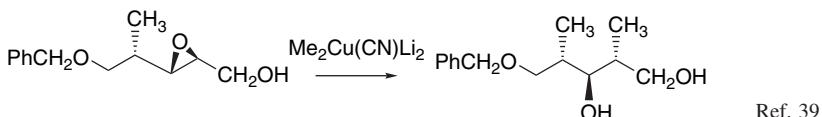
8.1.2.2. Opening of Epoxides. Organocopper reagents are excellent nucleophiles for opening epoxide rings. Saturated epoxides are opened in good yield by lithium dimethylcuprate.³⁷ The methyl group is introduced at the less hindered carbon of the epoxide ring.



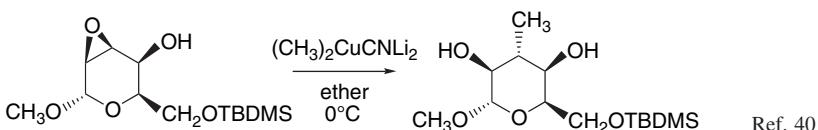
Even mixed reagents with Lewis acids attack at the less-substituted position, indicating dominance of the nucleophilic bond making over the electrophilic component of ring opening.³⁸



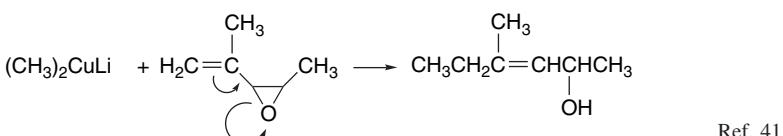
The predictable regio- and stereochemistry make these reactions valuable in establishing stereochemistry in both acyclic and cyclic systems.



With cyclohexene epoxides, the ring opening is *trans*-diaxial.



Epoxides with alkenyl substituents undergo alkylation at the double bond with a double-bond shift accompanying ring opening, leading to formation of allylic alcohols.



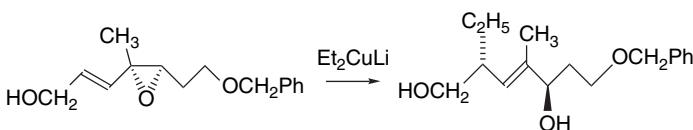
³⁷ C. R. Johnson, R. W. Herr, and D. M. Wieland, *J. Org. Chem.*, **38**, 4263 (1973).

³⁸ A. Alexis, D. Jachiet, and J. F. Normant, *Tetrahedron*, **42**, 5607 (1986).

³⁹ A. B. Smith, III, B. A. Salvatore, K. G. Hull, and J. J.-W. Duan, *Tetrahedron Lett.*, **32**, 4859 (1991).

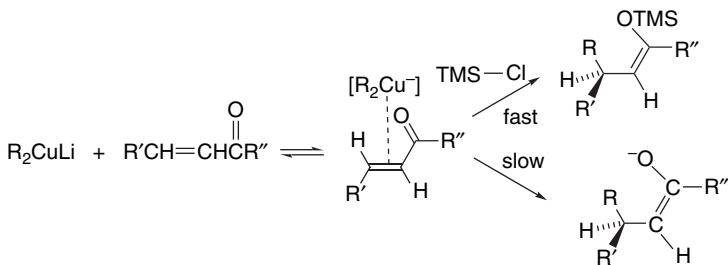
⁴⁰ R. G. Linde, M. Egbertson, R. S. Coleman, A. B. Jones, and S. J. Danishefsky, *J. Org. Chem.*, **55**, 2771 (1990).

⁴¹ R. J. Anderson, *J. Am. Chem. Soc.*, **92**, 4978 (1970); R. W. Herr and C. R. Johnson, *J. Am. Chem. Soc.*, **92**, 4979 (1970); J. A. Marshall, *Chem. Rev.*, **89**, 1503 (1989).

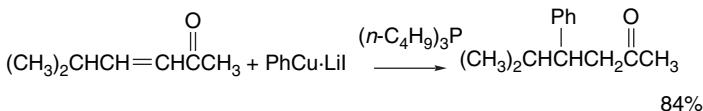


Ref. 42

8.1.2.3. Conjugate Addition Reactions. All of the types of mixed cuprate reagents described in Scheme 8.1 react by conjugate addition with enones. A number of improvements in methodology for carrying out the conjugate addition reactions have been introduced. The addition is accelerated by trimethylsilyl chloride alone or in combination with HMPA.⁴³ Under these conditions the initial product is a silyl enol ether. The mechanism of the catalysis remains uncertain, but it appears that the silylating reagent intercepts an intermediate and promotes carbon-carbon bond formation, as well as trapping the product by O-silylation.⁴⁴

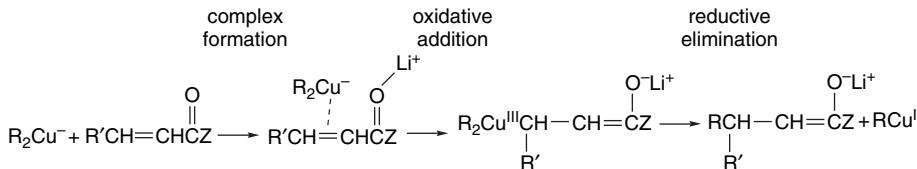


This technique also greatly improves yields of conjugate addition of cuprates to α, β -unsaturated esters and amides.⁴⁵ Trimethylsilyl cyanide also accelerates conjugate addition.⁴⁶ Another useful reagent is prepared from a 1:1:1 ratio of organolithium reagent, CuCN, and $\text{BF}_3\text{-O}(\text{C}_2\text{H}_5)_2$.⁴⁷ The BF_3 appears to interact with the cyanocuprate reagent, giving a more reactive species.⁴⁸ The efficiency of the conjugate addition reaction is also improved by the inclusion of trialkylphosphines.⁴⁹ Even organocupper reagents prepared from a 1:1 ratio of organolithium compounds are reactive in the presence of phosphines.⁵⁰



- ⁴². J. A. Marshall, T. D. Crute, III, and J. D. Hsi, *J. Org. Chem.*, **57**, 115 (1992).
- ⁴³. E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **26**, 6019 (1985); E. Nakamura, S. Matsuzawa, Y. Horiguchi, and I. Kuwajima, *Tetrahedron Lett.*, **27**, 4029 (1986); S. Matsuzawa, Y. Horiguchi, E. Nakamura, and I. Kuwajima, *Tetrahedron*, **45**, 449 (1989); C. R. Johnson and T. J. Marren, *Tetrahedron Lett.*, **28**, 27 (1987); S. H. Bertz and G. Dabbagh, *Tetrahedron*, **45**, 425 (1989); S. H. Bertz and R. A. Smith, *Tetrahedron*, **46**, 4091 (1990); K. Yamamoto, H. Ogura, J. Jukuta, H. Inoue, K. Hamada, Y. Sugiyama, and S. Yamada, *J. Org. Chem.*, **63**, 4449 (1998); M. Kanai, Y. Nakagawa, and K. Tomioka, *Tetrahedron*, **55**, 3831 (1999).
- ⁴⁴. M. Eriksson, A. Johansson, M. Nilsson, and T. Olsson, *J. Am. Chem. Soc.*, **118**, 10904 (1996).
- ⁴⁵. A. Alexakis, J. Berlan, and Y. Besace, *Tetrahedron Lett.*, **27**, 1047 (1986).
- ⁴⁶. B. H. Lipshutz and B. James, *Tetrahedron Lett.*, **34**, 6689 (1993).
- ⁴⁷. T. Ibuka, N. Akimoto, M. Tanaka, S. Nishii, and Y. Yamamoto, *J. Org. Chem.*, **54**, 4055 (1989).
- ⁴⁸. B. H. Lipshutz, E. L. Ellsworth, and T. J. Siahaan, *J. Am. Chem. Soc.*, **111**, 1351 (1989); B. H. Lipshutz, E. L. Ellsworth, and S. H. Dimock, *J. Am. Chem. Soc.*, **112**, 5869 (1990).
- ⁴⁹. M. Suzuki, T. Suzuki, T. Kawagishi, and R. Noyori, *Tetrahedron Lett.*, 1247 (1980).
- ⁵⁰. T. Kawabata, P. A. Grieco, H.-L. Sham, H. Kim, J. Y. Jaw, and S. Tu, *J. Org. Chem.*, **52**, 3346 (1987).

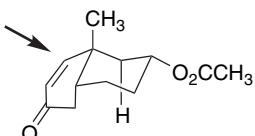
The mechanism of conjugate addition reactions probably involves an initial complex between the cuprate and enone.⁵¹ The key intermediate for formation of the new carbon-carbon bond is an adduct formed between the enone and the organocupper reagent. The adduct is formulated as a Cu(III) species, which then undergoes reductive elimination. The lithium ion also plays a key role, presumably by Lewis acid coordination at the carbonyl oxygen.⁵² Solvent molecules also affect the reactivity of the complex.⁵³ The mechanism can be outlined as occurring in three steps.



Isotope effects indicate that the collapse of the adduct by reductive elimination is the rate-determining step.⁵⁴ Theoretical treatments of the mechanism suggest similar intermediates. (See Section 8.1.2.7 for further discussion of the computational results.)⁵⁵

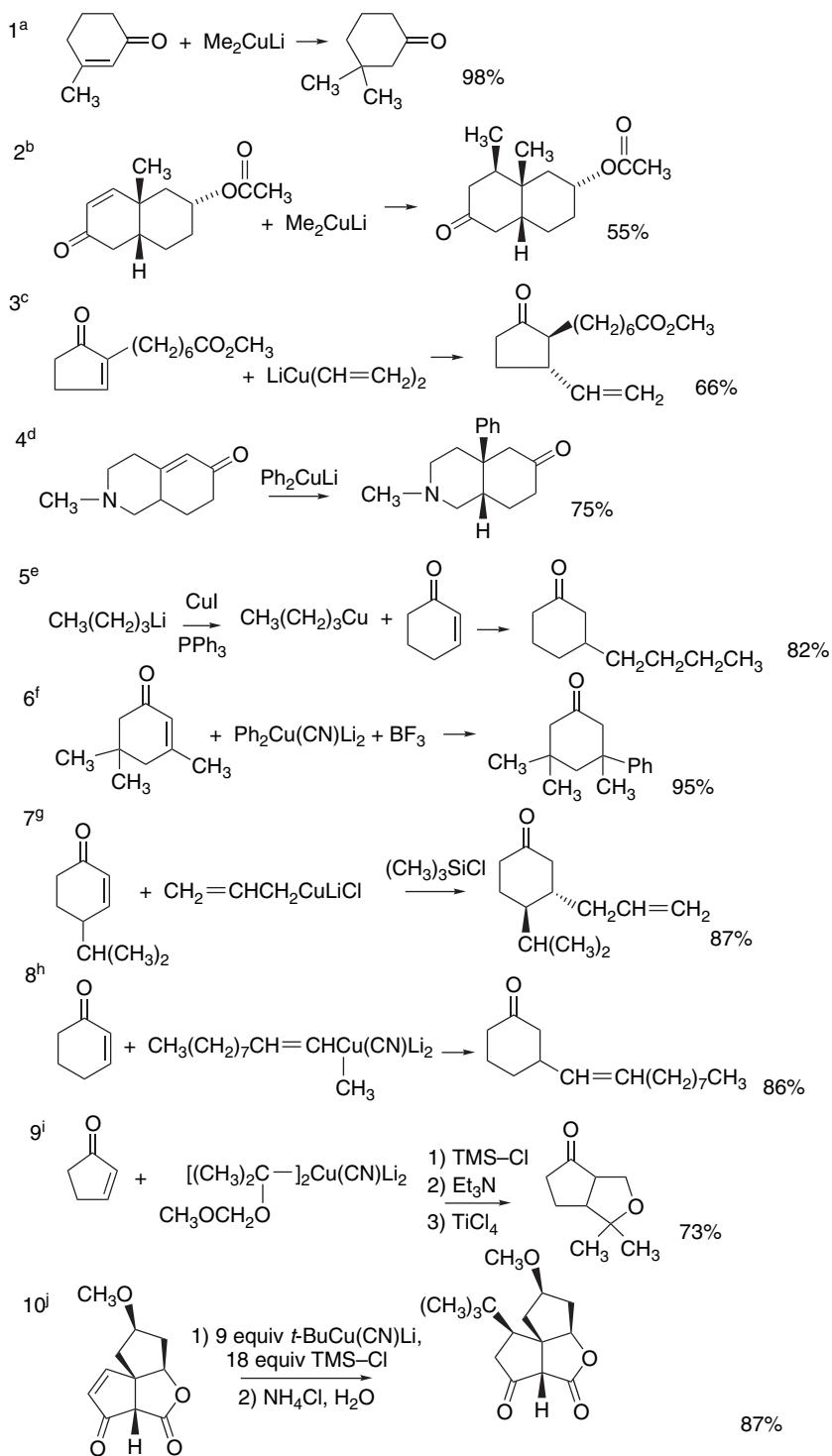
There is a correlation between the reduction potential of the carbonyl compounds and the ease of reaction with cuprate reagents.⁵⁶ The more easily it is reduced, the more reactive the compound toward cuprate reagents. Compounds such as α , β -unsaturated esters and nitriles, which are not as easily reduced as the corresponding ketones, do not react as readily with dialkylcuprates, even though they are good acceptors in classical Michael reactions with carbanions. α , β -Unsaturated esters are marginal in terms of reactivity toward standard dialkylcuprate reagents, and β -substitution retards reactivity. The $RCu\text{-}BF_3$ reagent combination is more reactive toward conjugated esters and nitriles,⁵⁷ and additions to hindered α , β -unsaturated ketones are accelerated by BF_3 .⁵⁸

There have been many applications of conjugate additions in synthesis. Some representative reactions are shown in Scheme 8.2. Entries 1 and 2 are examples of addition of lithium dimethylcuprate to cyclic enones. The stereoselectivity exhibited in Entry 2 is the result of both steric and stereoelectronic effects that favor the approach *syn* to the methyl substituent. In particular, the axial hydrogen at C(6) hinders the α approach.



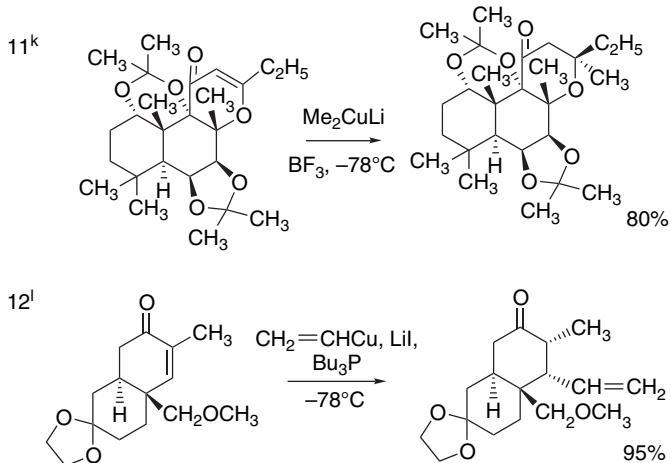
- ⁵¹ S. R. Krauss and S. G. Smith, *J. Am. Chem. Soc.*, **103**, 141 (1981); E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **26**, 6015 (1985); E. J. Corey and F. J. Hannon, *Tetrahedron Lett.*, **31**, 1393 (1990).
- ⁵² H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976); H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97**, 2770, 2778 (1975); H. O. House and K. A. J. Snoble, *J. Org. Chem.*, **41**, 3076 (1976); S. H. Bertz, G. Dabbagh, J. M. Cook, and V. Honkan, *J. Org. Chem.*, **49**, 1739 (1984).
- ⁵³ C. J. Kingsbury and R. A. J. Smith, *J. Org. Chem.*, **62**, 4629, 7637 (1997).
- ⁵⁴ D. E. Frantz, D. A. Singleton, and J. P. Snyder, *J. Am. Chem. Soc.*, **119**, 3383 (1997).
- ⁵⁵ E. Nakamura, S. Mori, and K. Morukuma, *J. Am. Chem. Soc.*, **119**, 4900 (1997); S. Mori and E. Nakamura, *Chem. Eur. J.*, **5**, 1534 (1999).
- ⁵⁶ H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 3893 (1973); B. H. Lipshutz, R. S. Wilhelm, S. T. Nugent, R. D. Little, and M. M. Baizer, *J. Org. Chem.*, **48**, 3306 (1983).
- ⁵⁷ Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.*, **100**, 3240 (1978); Y. Yamamoto, *Angew. Chem. Int. Ed. Engl.*, **25**, 947 (1986).
- ⁵⁸ A. B. Smith, III, and P. J. Jerris, *J. Am. Chem. Soc.*, **103**, 194 (1981).

Scheme 8.2. Conjugate Addition Reactions of Organocopper Reagents



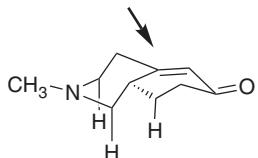
(Continued)

Scheme 8.2. (Continued)



- a. H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966).
- b. J. A. Marshall and G. M. Cohen, *J. Org. Chem.*, **36**, 877 (1971).
- c. F. S. Alvarez, D. Wren, and A. Prince, *J. Am. Chem. Soc.*, **94**, 7823 (1972).
- d. N. Finch, L. Blanchard, R. T. Puckett, and L. H. Werner, *J. Org. Chem.*, **39**, 1118 (1974).
- e. M. Suzuki, T. Suzuki, T. Kawagishi, and R. Noyori, *Tetrahedron Lett.*, **21**, 1247 (1980).
- f. B. H. Lipshutz, D. A. Parker, J. A. Kozlowski, and S. L. Nguyen, *Tetrahedron Lett.*, **25**, 5959 (1984).
- g. B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock, and R. A. J. Smith, *J. Am. Chem. Soc.*, **112**, 4404 (1990).
- h. B. H. Lipshutz and E. L. Ellsworth, *J. Am. Chem. Soc.*, **112**, 7440 (1990).
- i. R. J. Linderman and A. Godfrey, *J. Am. Chem. Soc.*, **110**, 6249 (1988).
- j. E. J. Corey and K. Kamiyama, *Tetrahedron Lett.*, **31**, 3995 (1990).
- k. B. Delpach and R. Lett, *Tetrahedron Lett.*, **28**, 4061 (1987).
- l. T. Kawabata, P. Grieco, H. L. Sham, H. Kim, J. Y. Jaw, and S. Tu, *J. Org. Chem.*, **52**, 3346 (1987).

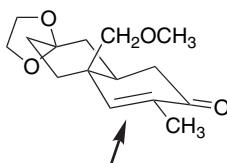
In Entry 3, the *trans* stereochemistry arises at the stage of the protonation of the enolate. Entry 4 gives rise to a *cis* ring juncture, as does the corresponding carbocyclic compound.⁵⁹ Models suggest that this is the result of a steric differentiation arising from the axial hydrogens on the α -face of the molecule.



Entries 5 to 9 illustrate some of the modified reagents and catalytic procedures. Entry 5 uses a phosphine-stabilized reagent, whereas Entry 6 includes BF_3 . Entry 7 involves use of TMS-Cl. Entries 8 and 9 involve cyanocuprates. In Entry 9, the furan ring is closed by a Mukaiyama-aldo reaction subsequent to the conjugate addition (Section 2.1.4).

⁵⁹. S. M. McElvain and D. C. Remy, *J. Am. Chem. Soc.*, **82**, 3960 (1960).

Entries 10 to 12 illustrate the use of organocupper conjugate addition in the synthesis of relatively complex molecules. The installation of a *t*-butyl group adjacent to a quaternary carbon in Entry 10 requires somewhat forcing conditions, but proceeds in good yield. In Entry 11, the addition is to a vinylogous ester, illustrating the ability of the BF_3 -modified reagents to react with less electrophilic systems. Steric shielding by the axial methoxymethyl substituent accounts for the stereoselectivity observed in Entry 12.



Prior to protonolysis, the products of conjugate addition are enolates and, therefore, potential nucleophiles. A useful extension of the conjugate addition method is to combine it with an alkylation step that adds a substituent at the α -position.⁶⁰ Several examples of this *tandem conjugate addition-alkylation* method are given in Scheme 8.3. In Entry 1 the characteristic β -attack on the *cis* decalone ring is observed (see Scheme 8.2, Entry 2). The alkylation gives a $\beta : \alpha$ ratio of 60:40. In Entry 2, the methylation occurs *anti* to the 4-substituent, presumably because of steric factors. These reactions are part of the synthesis of the cholesterol-lowering drug compactin. Entry 3 illustrates a pattern that has been extensively developed for the synthesis of prostaglandins. In this case, the dioxolane ring controls the stereoselectivity of the conjugate addition step and steric factors lead to *anti* alkylation and formation the *trans* product. Entry 4 is a part of a steroid synthesis. This reaction shows a 4:1 preference for methylation from the β -face (*syn* to the substituent). In Entry 5, the conjugate addition is followed by a Robinson annulation. The product provides a C,D-ring segment of the steroid skeleton.

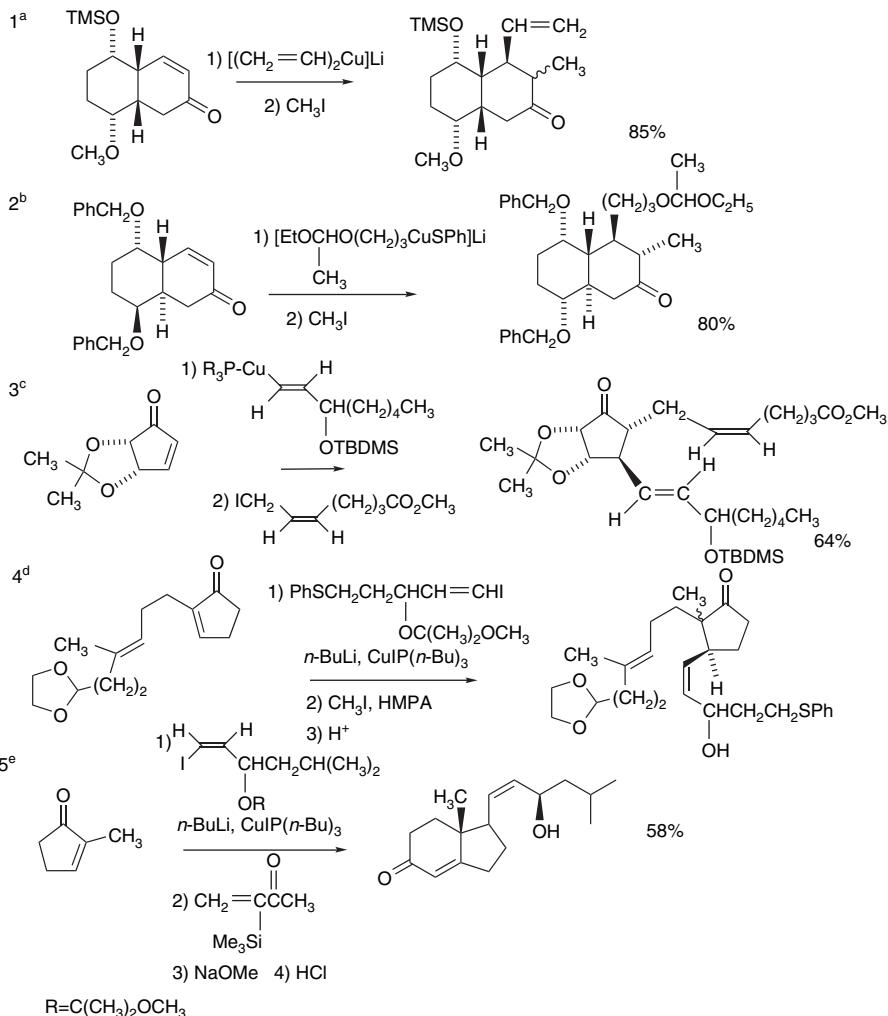
8.1.2.4. Copper-Catalyzed Reactions. The cuprate reagents that were discussed in the preceding sections are normally prepared by reaction of an organolithium reagent with a copper(I) salt, using a 2:1 ratio of lithium reagent to copper(I). There are also valuable synthetic procedures that involve organocupper intermediates that are generated in the reaction system by use of only a catalytic amount of a copper salt.⁶¹ Coupling of Grignard reagents and primary halides and tosylates can be catalyzed by Li_2CuCl_4 .⁶² This method was used, for example, to synthesize long-chain carboxylic acids in more than 90% yield.⁶³

⁶⁰. For a review of such reactions, see R. J. K. Taylor, *Synthesis*, 364 (1985).

⁶¹. For a review, see E. Erdik, *Tetrahedron*, **40**, 641 (1984).

⁶². M. Tamura and J. Kochi, *Synthesis*, 303 (1971); T. A. Baer and R. L. Carney, *Tetrahedron Lett.*, 4697 (1976).

⁶³. S. B. Mirviss, *J. Org. Chem.*, **54**, 1948 (1989); see also M. R. Kling, C. J. Eaton, and A. Poulos, *J. Chem. Soc., Perkin Trans. 1*, 1183 (1993).



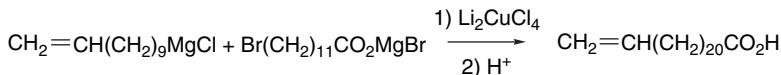
a. N. N. Girotra, R. A. Reamer, and N. L. Wendler, *Tetrahedron Lett.*, **25**, 5371 (1984).

b. N.-Y. Wang, C.-T. Hsu, and C. J. Sih, *J. Am. Chem. Soc.*, **103**, 6538 (1981).

c. C. R. Johnson and T. D. Penning, *J. Am. Chem. Soc.*, **110**, 4726 (1988).

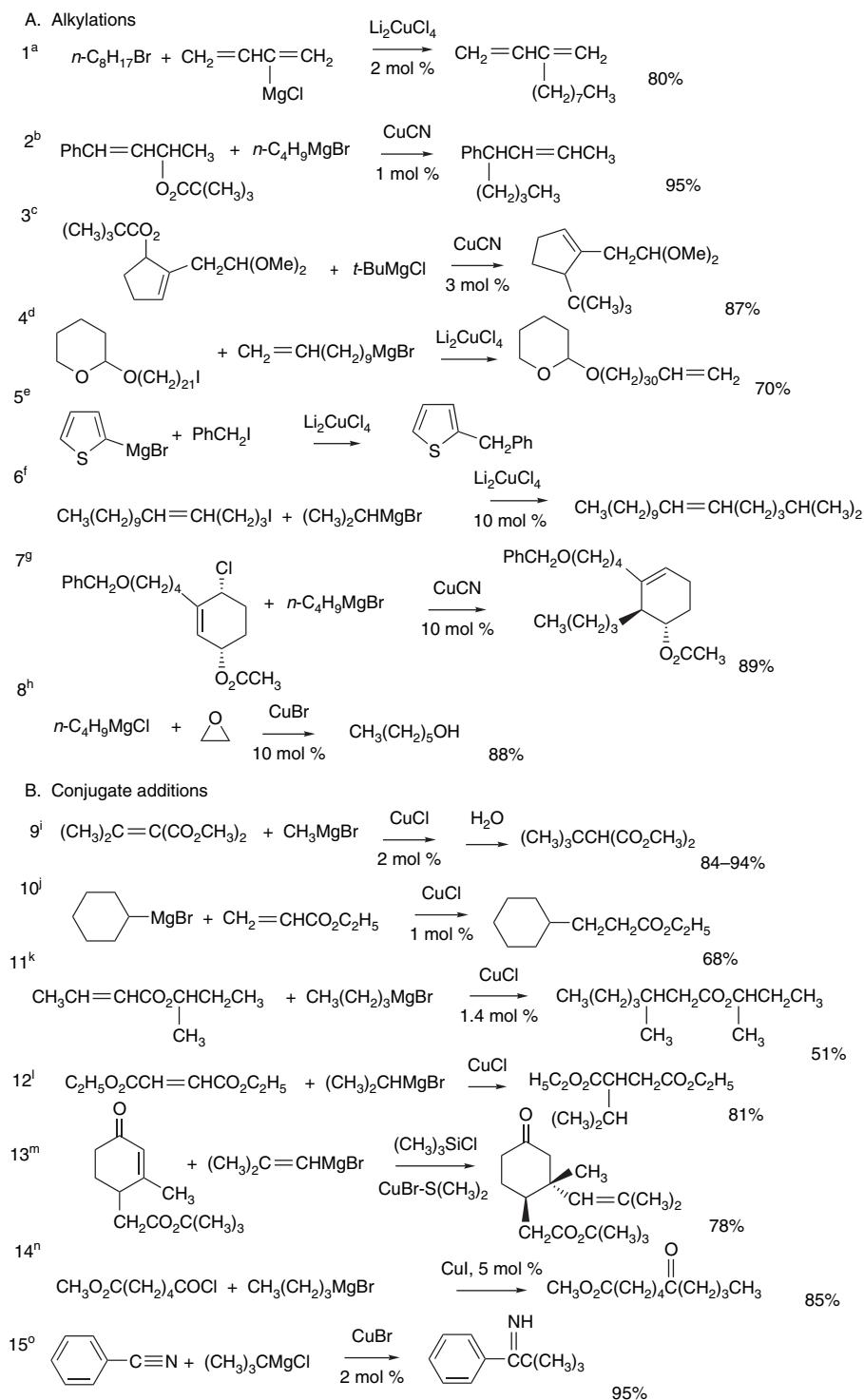
d. T. Takahashi, K. Shimizu, T. Doi, and J. Tsuji, *J. Am. Chem. Soc.*, **110**, 2674 (1988).

e. T. Takahashi, H. Okumoto, J. Tsuji, and N. Harada, *J. Org. Chem.*, **49**, 948 (1984).



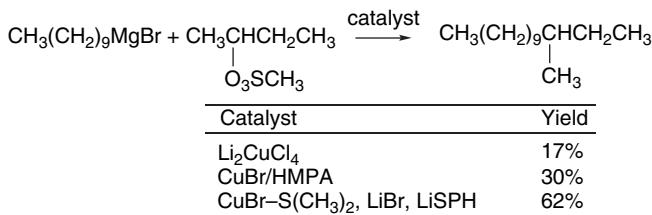
Another excellent catalyst for coupling is a mixture of CuBr-S(CH₃)₂, LiBr, and LiSPh. This catalyst can effect coupling of a wide variety of Grignard reagents with tosylates and mesylates and is superior to Li₂CuCl₄ in coupling with secondary sulfonates.⁶⁴

⁶⁴. D. H. Burns, J. D. Miller, H.-K. Chan, and M. O. Delaney, *J. Am. Chem. Soc.*, **119**, 2125 (1997).

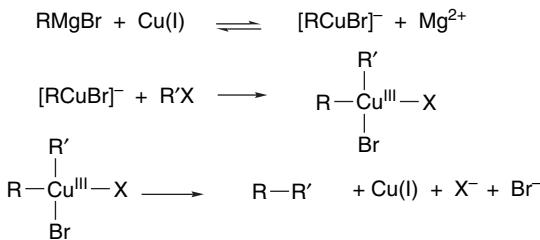


(Continued)

- a. S. Nunomoto, Y. Kawakami, and Y. Yamashita, *J. Org. Chem.*, **48**, 1912 (1983).
 b. C. C. Tseng, S. D. Paisley, and H. L. Goering, *J. Org. Chem.*, **51**, 2884 (1986).
 c. E. J. Corey and A. V. Gavai, *Tetrahedron Lett.*, **29**, 3201 (1988).
 d. U. F. Heiser and B. Dobner, *J. Chem. Soc., Perkin Trans. 1*, 809 (1997).
 e. Y.-T. Ku, R. R. Patel, and D. P. Sawick, *Tetrahedron Lett.*, **37**, 1949 (1996).
 f. E. Keinan, S. C. Sinha, A. Sinha-Bagchi, Z.-M. Wang, X.-L. Zhang, and K. B. Sharpless, *Tetrahedron Lett.*, **33**, 6411 (1992).
 g. D. Tanner, M. Sellen, and J. Backvall, *J. Org. Chem.*, **54**, 3374 (1989).
 h. G. Huynh, F. Derguini-Boumechal, and G. Linstrumelle, *Tetrahedron Lett.*, 1503 (1979).
 i. E. L. Eliel, R. O. Hutchins, and M. Knoeber, *Org. Synth.*, **50**, 38 (1971).
 j. S.-H. Liu, *J. Org. Chem.*, **42**, 3209 (1977).
 k. T. Kindt-Larsen, V. Bitsch, I. G. K. Andersen, A. Jart, and J. Munch-Petersen, *Acta Chem. Scand.*, **17**, 1426 (1963).
 l. V. K. Andersen and J. Munch-Petersen, *Acta Chem. Scand.*, **16**, 947 (1962).
 m. Y. Horiguchi, E. Nakamura, and I. Kuwajima, *J. Am. Chem. Soc.*, **111**, 6257 (1989).
 n. T. Fujisawa and T. Sato, *Org. Synth.*, **66**, 116 (1988).
 o. F. J. Weiberth and S. S. Hall, *J. Org. Chem.*, **52**, 3901 (1987).



These reactions presumably involve fast metal-metal exchange (see Section 7.1.2.4) generating a more nucleophilic organocopper intermediate. The reductive elimination regenerates an active Cu(I) species.



Other examples of catalytic substitutions can be found in Section A of Scheme 8.4.

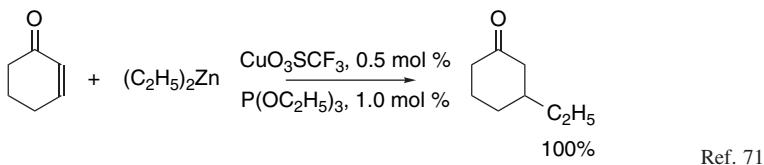
Conjugate addition to α, β -unsaturated esters can often be effected by copper-catalyzed reaction with a Grignard reagent. Other reactions, such as epoxide ring opening, can also be carried out under catalytic conditions. Some examples of catalyzed additions and alkylations are given in Scheme 8.4. These reactions are similar to those carried out with the stoichiometric reagents and presumably involve catalytic cycles that regenerate the active organocopper species. A remarkable aspect of these reactions is that the organocopper cycle must be fast compared to normal organomagnesium reactions, since in many cases there is a potential for competing reactions. The alkylations include several substitutions on allylic systems (Entries 2, 3, and 7). Entry 8 shows that the catalytic process is also applicable to epoxide ring opening. The latter example is a case in which an allylic chloride is displaced in preference to an acetate. The conditions have been observed in related systems to be highly regio- (S_N2') and stereo- (*anti*) specific.⁶⁵ The conjugate additions in Entries 9 to 12 show

⁶⁵. J.-E. Backvall, *Bull. Soc. Chim. Fr.*, 665 (1987).

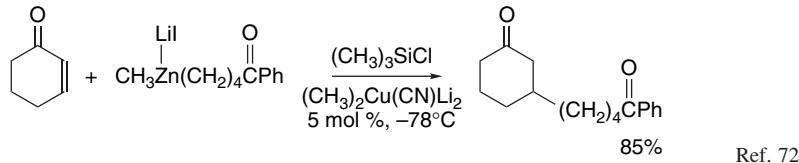
that esters and enones (Entry 13) are reactive to the catalytic processes involving Grignard reagents. Entries 14 and 15 illustrate ketone syntheses from acyl chlorides and nitriles, respectively.

8.1.2.5. Mixed Organocopper-Zinc Reagents. The preparation of organozinc reagents is discussed in Section 7.3.1. Many of these reagents can be converted to mixed copper-zinc organometallics that have useful synthetic applications.⁶⁶ A virtue of these reagents is that they can contain a number of functional groups that are not compatible with the organolithium route to cuprate reagents. The mixed copper-zinc reagents are not very basic and can be prepared and allowed to react in the presence of weakly acidic functional groups that would protonate more basic organometallic reagents; for example, reagents containing secondary amide or indole groups can be prepared.⁶⁷ They are good nucleophiles and are especially useful in conjugate addition. Mixed zinc reagents can also be prepared by addition of CuCN to organozinc iodides.⁶⁸ They are analogous to the cyanocuprates prepared from alkylolithium and CuCN, but with Zn²⁺ in place of Li⁺, and react with enones, nitroalkenes, and allylic halides.⁶⁹

In addition to the use of stoichiometric amounts of cuprate or cyanocuprate reagents for conjugate addition, there are also procedures that require only a catalytic amount of copper and use organozinc reagents as the stoichiometric reagent.⁷⁰ Simple organozinc reagents, such as diethylzinc, undergo conjugate addition with 0.5 mol % CuO₃SCF₃ in the presence of a phoshine or phosphite.

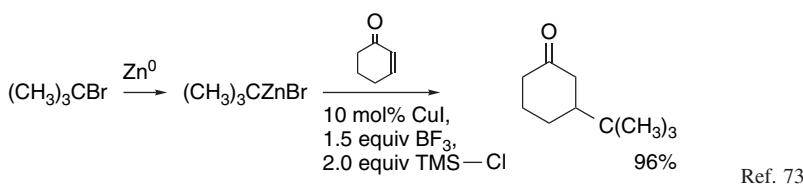


In the presence of LiI, TMS-Cl, and a catalytic amount of (CH₃)₂CuCNLi₂, conjugate addition of functionalized organozinc reagents occurs in good yield.



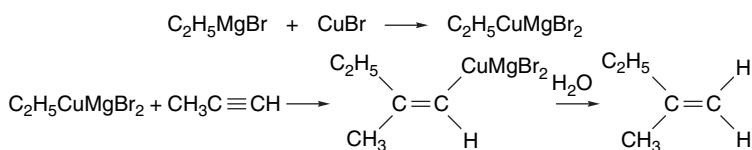
Either CuI or CuCN (10 mol %) in conjunction with BF₃ and TMS-Cl catalyze addition of alkylzinc bromides to enones.

- ⁶⁶. P. Knochel and R. D. Singer, *Chem. Rev.*, **93**, 2117 (1993); P. Knochel, *Synlett*, 393 (1995).
- ⁶⁷. H. P. Knoess, M. T. Furlong, M. J. Rozema, and P. Knochel, *J. Org. Chem.*, **56**, 5974 (1991).
- ⁶⁸. P. Knochel, J. J. Almena Perea, and P. Jones, *Tetrahedron*, **54**, 8275 (1998).
- ⁶⁹. P. Knochel, M. C. P. Yeh, S. C. Berk, and J. Talbert, *J. Org. Chem.*, **53**, 2390 (1988); M. C. P. Yeh and P. Knochel, *Tetrahedron Lett.*, **29**, 2395 (1988); S. C. Berk, P. Knochel, and M. C. P. Yeh, *J. Org. Chem.*, **53**, 5789 (1988); H. G. Chou and P. Knochel, *J. Org. Chem.*, **55**, 4791 (1990).
- ⁷⁰. B. H. Lipshutz, *Acc. Chem. Res.*, **30**, 277 (1997).
- ⁷¹. A. Alexakis, J. Vastra, and P. Mageney, *Tetrahedron Lett.*, **38**, 7745 (1997).
- ⁷². B. H. Lipshutz, M. R. Wood, and R. J. Tirado, *J. Am. Chem. Soc.*, **117**, 6126 (1995).



Several examples of mixed organocopper-zinc reagents in synthesis are given in Scheme 8.5. Entries 1 and 2 show the use of functionalized reagents prepared from the corresponding iodides by reaction with zinc, followed by CuCN-LiCl. Entry 3 uses a similar reagent to prepare a prostaglandin precursor. Note the slightly different pattern from Entry 3 in Scheme 8.4; in the present case the addition is to an exocyclic methylene group rather than to an endocyclic cyclopentenone. Entry 4 involves generation of a mixed reagent directly from an iodide, followed by conjugate addition to methyl acrylate. Entries 5 and 6 are substitutions on allylic systems. The arylzinc reagent used in Entry 5 was prepared from 2-nitrophenyllithium, which was prepared by halogen-metal exchange, as discussed on p. 632. Entry 7 is a stereospecific S_N2' displacement on an allylic methanesulfonate. Entry 8 is a substitution on a β -sulfonyloxy enone. The zinc reagent is mixed dialkyl zinc. This reaction may proceed by conjugate addition to give the enolate, followed by elimination of the triflate group. Entry 9 shows the use of a tertiary mixed zinc reagent in the preparation of a ketone.

8.1.2.6. Carbometallation with Mixed Organocopper Compounds. Mixed copper-magnesium reagents analogous to the lithium cuprates can be prepared.⁷⁴ The precise structural nature of these compounds, often called *Normant reagents*, has not been determined. Individual species with differing Mg:Cu ratios may be in equilibrium.⁷⁵ These reagents undergo addition to terminal acetylenes to generate alkenylcopper reagents. The addition is stereospecifically *syn*.



The alkenylcopper adducts can be worked up by protonolysis, or they can be subjected to further elaboration by alkylation or electrophilic substitution.

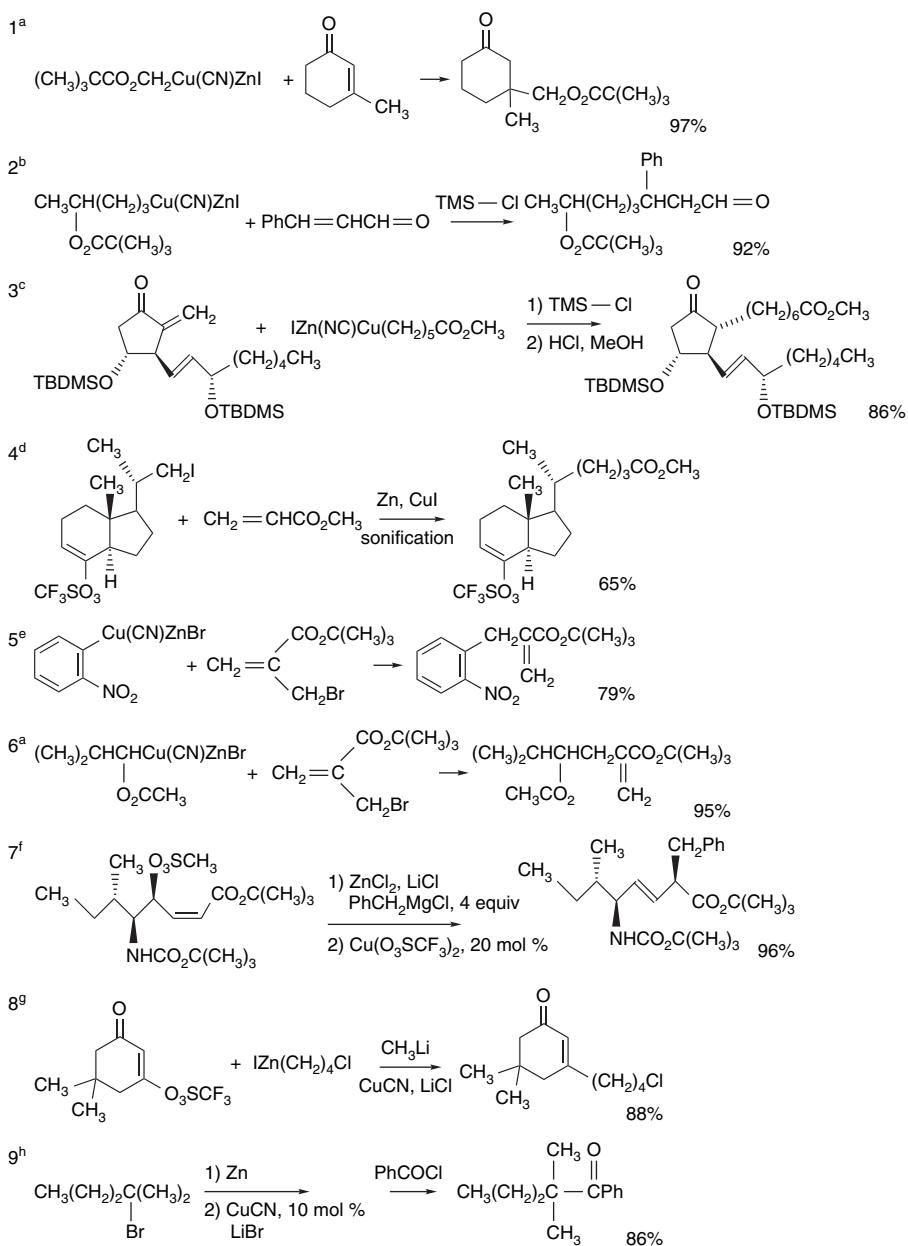
Mixed copper-zinc reagents also react with alkynes to give alkenylcopper species that can undergo subsequent electrophilic substitution.

⁷³. R. D. Rieke, M. V. Hanson, J. D. Brown, and Q. J. Niu, *J. Org. Chem.*, **61**, 2726 (1996).

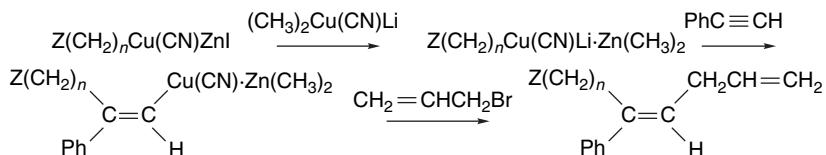
⁷⁴. J. F. Normant and M. Bourgain, *Tetrahedron Lett.*, 2583 (1971); J. F. Normant, G. Cahiez, M. Bourgain, C. Chuit, and J. Villieras, *Bull. Soc. Chim. Fr.*, 1656 (1974); H. Westmijze, J. Meier, H. J. T. Bos, and P. Vermeer, *Recl. Trav. Chim. Pays Bas*, **95**, 299, 304 (1976).

⁷⁵. E. C. Ashby, R. S. Smith, and A. B. Goel, *J. Org. Chem.*, **46**, 5133 (1981); E. C. Ashby and A. B. Goel, *J. Org. Chem.*, **48**, 2125 (1983).

Scheme 8.5. Conjugate Addition and Substitution Reactions of Mixed Organocopper-Zinc Reagents

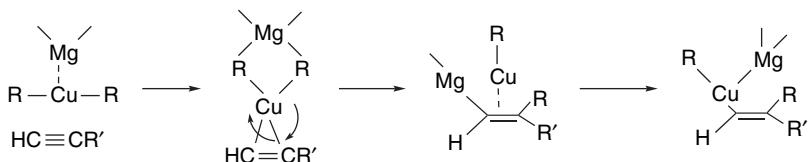


- a. P. Knochel, T. S. Chou, C. Jubert, and D. Rajagopal, *J. Org. Chem.*, **58**, 588 (1993).
 b. M. C. P. Yeh, P. Knochel, and L. E. Santa, *Tetrahedron*, **29**, 3887 (1988).
 c. H. Tsujiyama, N. Ono, T. Yoshino, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, **31**, 4481 (1990).
 d. J. P. Sestalo, J. L. Mascarenas, L. Castedo, and A. Mourina, *J. Org. Chem.*, **58**, 118 (1993).
 e. C. Tucker, T. N. Majid, and P. Knochel, *J. Am. Chem. Soc.*, **114**, 3983 (1992).
 f. N. Fujii, K. Nakai, H. Habashita, H. Yoshizawa, T. Ibuka, F. Garrido, A. Mann, Y. Chounann, and Y. Yamamoto, *Tetrahedron Lett.*, **34**, 4227 (1993).
 g. B. H. Lipshutz and R. W. Vivian, *Tetrahedron Lett.*, **40**, 2871 (1999).
 h. R. D. Rieke, M. V. Hanson, and Q. J. Niu, *J. Org. Chem.*, **61**, 2726 (1996).



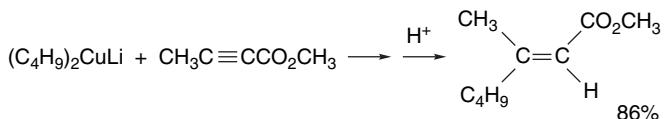
Ref. 76

The mechanism of carbometallation has been explored computationally.⁷⁷ The reaction consists of an oxidative addition to the triple bond forming a cyclic Cu(III) intermediate. The rate-determining step is reductive elimination to form a vinyl magnesium (or zinc) reagent, which then undergoes transmetallation to the alkenyl-copper product.



Some additional examples are given in Scheme 8.6. The electrophiles that have been used successfully include iodine (Entries 2 and 3) and cyanogen chloride (Entry 4). The adducts can undergo conjugate addition (Entry 5), alkylation (Entry 6), or epoxide ring opening (Entries 7 and 8). The latter reaction is an early step of a synthesis of epothilone B.

The lithium cuprate reagents are not as reactive toward terminal alkynes as mixed magnesium or zinc reagents. The stronger Lewis acid character of Mg^{2+} , as compared to Li^+ , is believed to be the reason for the enhanced reactivity of the magnesium reagents. However, lithium dialkylcuprates do react with conjugated acetylenic esters, with *syn* addition being kinetically preferred.⁷⁸



The intermediate adduct can be substituted at the α -position by a variety of electrophiles, including acyl chlorides, epoxides, aldehydes, and ketones.⁷⁹

8.1.2.7. Mechanistic Interpretation of the Reactivity of Organocupper Compounds. The coupling with halides and tosylates, epoxide ring openings, and conjugate additions discussed in the preceding sections illustrate the nucleophilicity of the organocupper reagents. The nucleophilicity is associated with relatively high-energy filled *d* orbitals that are present in Cu(I), which has a $3d^{10}$ electronic configuration. The role of

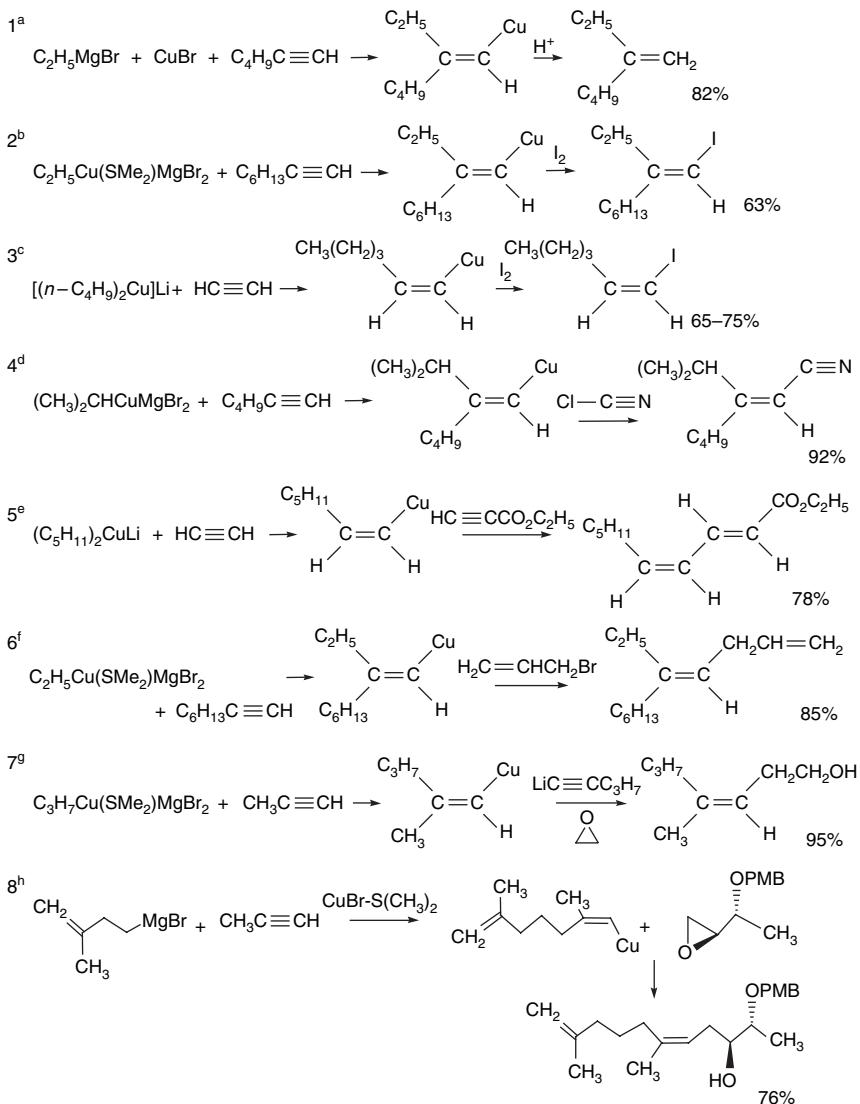
⁷⁶ S. A. Rao and P. Knochel, *J. Am. Chem. Soc.*, **113**, 5735 (1991).

⁷⁷ S. Mori, A. Hirai, M. Nakamura, and E. Nakamura, *Tetrahedron*, **56**, 2805 (2000).

⁷⁸ R. J. Anderson, V. L. Corbin, G. Cotterrell, G. R. Cox, C. A. Henrick, F. Schaub, and J. B. Siddall, *J. Am. Chem. Soc.*, **97**, 1197 (1975).

⁷⁹ J. P. Marino and R. G. Linderman, *J. Org. Chem.*, **48**, 4621 (1983).

Scheme 8.6. Generation and Reactions of Alkenylcopper Reagents from Alkynes



a. J. F. Normant, G. Cahiez, M. Bourgain, C. Chuit, and J. Villerias, *Bull. Chim. Soc. Fr.*, 1656 (1974).

b. N. J. LaLima, Jr., and A. B. Levy, *J. Org. Chem.*, **43**, 1279 (1978).

c. A. Alexakis, G. Cahiez, and J. F. Normant, *Org. Synth.*, **62**, 1 (1984).

d. H. Westmijze and P. Vermeer, *Synthesis*, 784 (1977).

e. A. Alexakis, J. Normant, and J. Villeras, *Tetrahedron Lett.*, 3461 (1976).

f. R. S. Iyer and P. Helquist, *Org. Synth.*, **64**, 1 (1985).

g. P. R. McGuirk, A. Marfat, and P. Helquist, *Tetrahedron Lett.*, 2465 (1978).

h. M. Valluri, R. M. Hindupur, P. Bijou, G. Labadie, J.-C. Jung, and M. A. Avery, *Org. Lett.*, **3**, 3607 (2001).

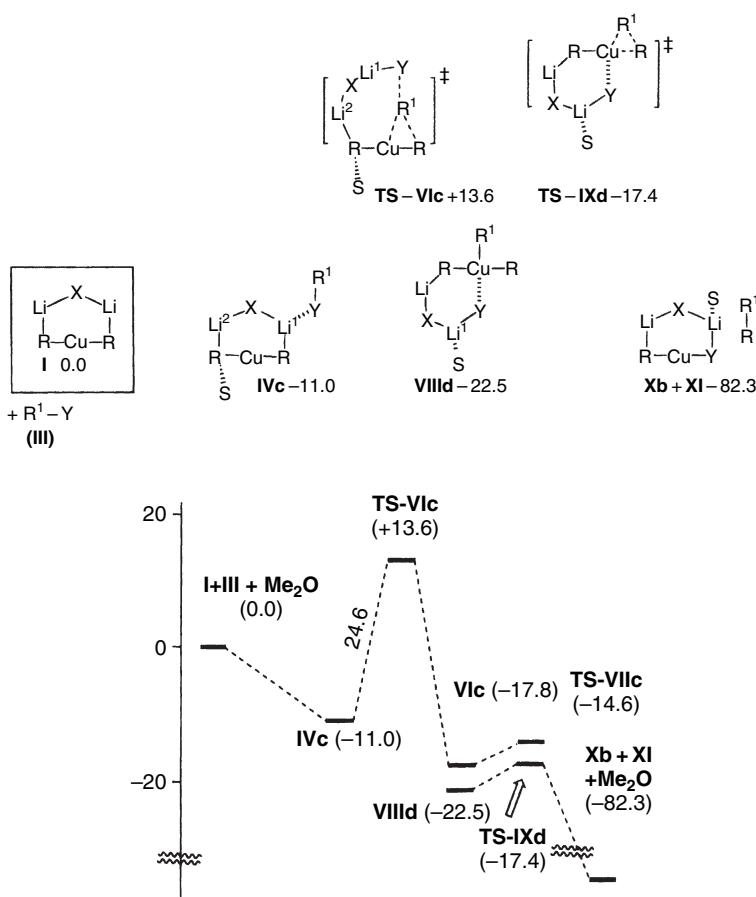


Fig. 8.2. Computational energy profile (B3LYP/631A) for reaction of $(\text{CH}_3)_2\text{CuLi-LiCl}$ with CH_3Br including one solvent (CH_3OCH_3) molecule. Adapted from *J. Am. Chem. Soc.*, **122**, 7294 (2000), by permission of the American Chemical Society.

the copper-lithium clusters has been explored computationally (B3LYP/631A) for reactions with methyl bromide,⁸⁰ ethylene oxide,⁸⁰ acrolein,⁸¹ and cyclohexenone.⁸² In the case of methyl bromide, the reaction was studied both with and without a solvation model. The results in the case of inclusion of one molecule of solvent (CH_3OCH_3) are shown in Figure 8.2. The rate-determining step is the conversion of a complex of the reactant cluster, $[(\text{CH}_3)_2\text{CuLi-LiCl}-\text{CH}_3\text{Br}]$, to a tetracoordinate Cu(III) species. The calculated barrier is 13.6 kcal/mol. The reductive elimination step has a very low barrier (~ 5 kcal/mol).

The ring opening of ethylene oxide was studied with CH_3SCH_3 as the solvent molecule and is summarized in Figure 8.3. The crucial TS again involves formation of the C–Cu bond and occurs with assistance from Li^+ . As with methyl bromide, the reductive elimination has a low barrier. Incorporation of BF_3 leads to a structure **TS-XXXi** (insert in Figure 8.3) in which BF_3 assists the epoxide ring opening. The

⁸⁰ S. Mori, E. Nakamura, and K. Morokuma, *J. Am. Chem. Soc.*, **122**, 7294 (2000).

⁸¹ E. Nakamura, S. Mori, and K. Morokuma, *J. Am. Chem. Soc.*, **119**, 4900 (1997).

⁸² S. Mori and E. Nakamura, *Chem. Eur. J.*, **5**, 1534 (1999).

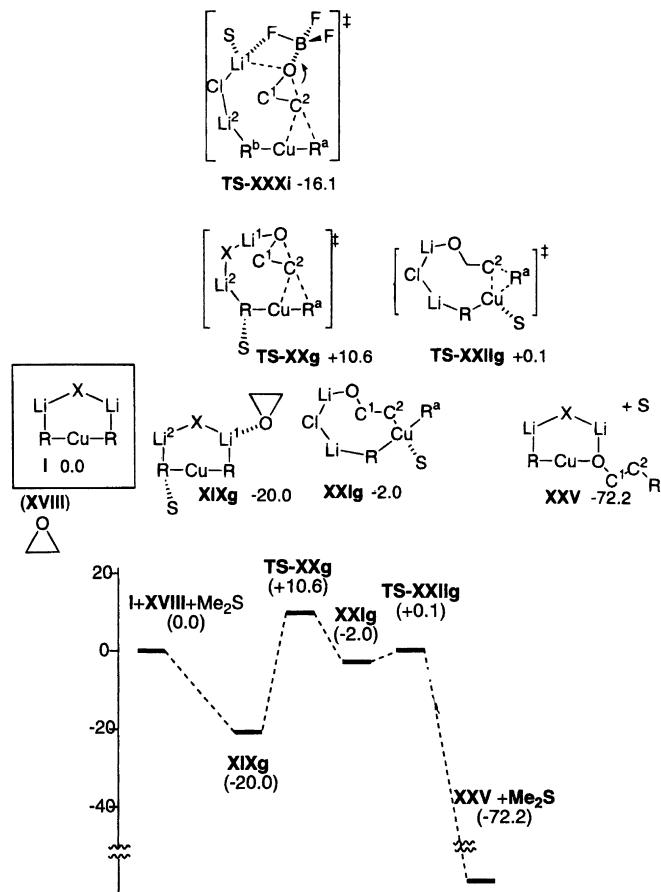


Fig. 8.3. Computational energy profile (B3LYP/631A) for reaction of $(\text{CH}_3)_2\text{Cu}-\text{LiCl}-(\text{CH}_3)_2\text{S}$ with ethylene oxide. The insert (TS-XXXi) is a TS that incorporates BF_3 , but not $(\text{CH}_3)_2\text{S}$. Adapted from *J. Am. Chem. Soc.*, **122**, 7294 (2000), by permission of the American Chemical Society.

stabilization of the TS leads to a reduction of almost 37 kcal/mol in the computed E_a relative to TS XXg .

The nucleophilicity of the organocuprate cluster derives mainly from the filled copper $3d_z^2$ orbital, in combination with the carbon orbital associated with bonding to copper. These orbitals for the TS for reaction with methyl bromide and ethylene oxide are shown in Figure 8.4.

The conjugate addition reaction has also been studied computationally. B3LYP/631A calculations of the reaction of $[(\text{CH}_3)_2\text{CuLi}]_2$ with acrolein gives the TS and intermediates depicted in Figure 8.5.⁸¹ Three intermediates and three TSs are represented. The first structure is a complex of the reactants (**CP1i**), which involves coordination of the acrolein oxygen to a lithium cation in the reactant. The second intermediate (**CP1l**) is a π complex in which the cluster is opened. A key feature of the mechanism is the third intermediate **CPop**, which involves interaction of *both* lithium ions with the carbonyl oxygen. Moreover, in contrast to the reactions with halides and epoxides, it is the *reductive elimination step that is rate determining*. The calculated barrier for this step is 10.4 kcal/mol.

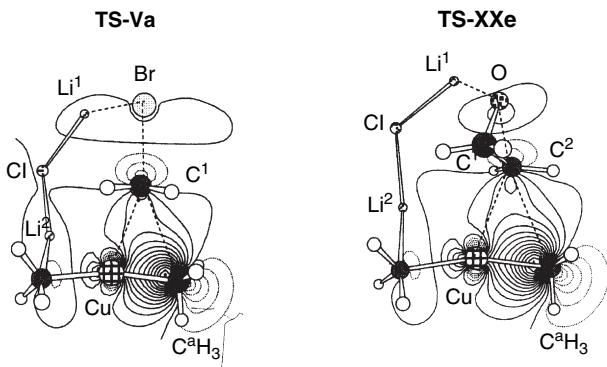


Fig. 8.4. Representation of the orbital involved in C–Cu bond formation in the reaction of $(\text{CH}_3)_2\text{CuLi-LiCl}$ with methyl bromide (left) and ethylene oxide (right). Reproduced from *J. Am. Chem. Soc.*, **122**, 7294 (2000), by permission of the American Chemical Society.

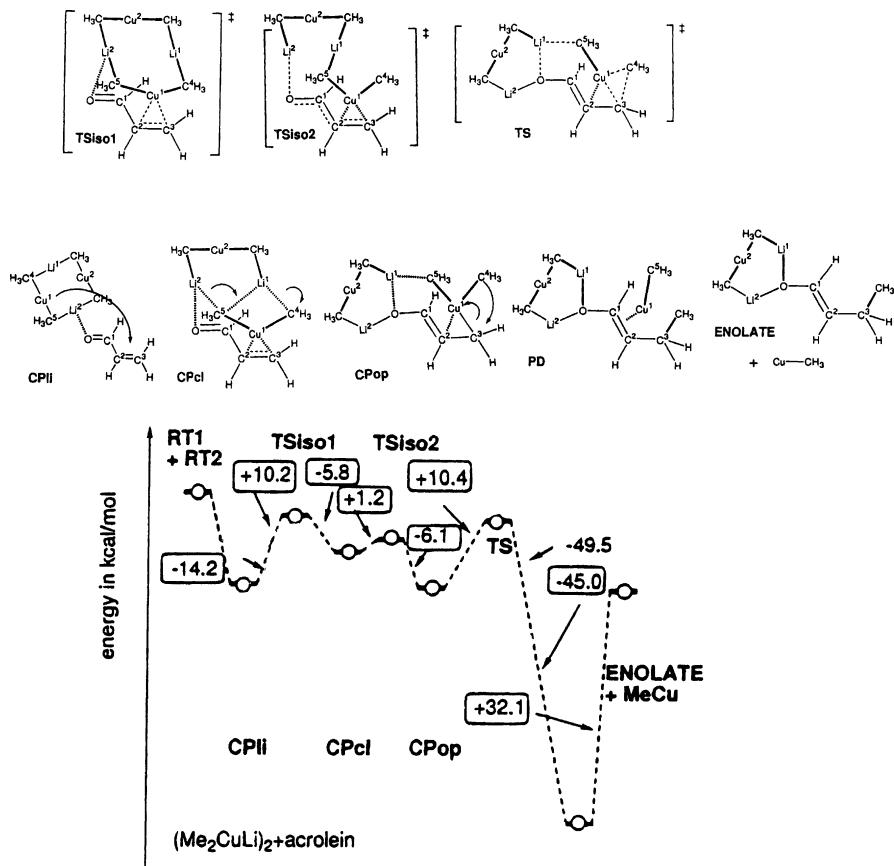
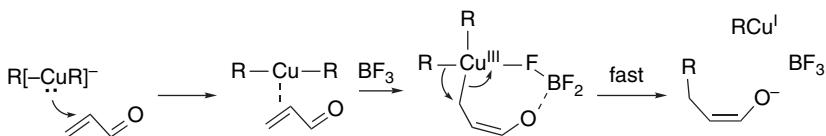


Fig. 8.5. Computational reaction profile (B3LYP/631A) for reaction of $[(\text{CH}_3)_2\text{CuLi}]_2$ with acrolein. Adapted from *J. Am. Chem. Soc.*, **119**, 4900 (1997), by permission of the American Chemical Society.

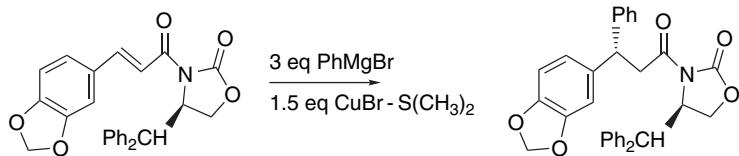
The role of BF_3 catalysis in the conjugate addition was also explored.⁸³ Inclusion of BF_3 results in a considerable stabilization of the reaction complex, but there is also a lowered barrier for the rate-determining reductive elimination. This suggests that BF_3 functions primarily at the Cu(III) stage by facilitating the decomposition of the Cu(III) intermediate.



A similar sequence of intermediates and TSs was found for the reaction of cyclohexenone.⁸² In this case, both axial and equatorial approaches were examined. At the crucial rate- and product-determining TS for C–C bond formation, the axial pathway is favored by 1.7 kcal/mol, in agreement with experimental results from conformationally biased cyclohexenones. Nearly all of the difference is due to factors in the cyclohexenone ring and transferring methyl group. This result suggests that analysis of stereoselectivity of cuprate conjugate additions should focus on the relative energies of the competing TS for the C–C bond-forming step. These computational studies comport well with a variety of product, kinetic, and spectroscopic studies that have been applied to determining the mechanism of organocuprates and related reagents.⁸⁴

Visual models and additional information on Organocuprate Intermediates can be found in the Digital Resource available at: Springer.com/carey-sundberg.

8.1.2.8. Enantioselective Reactions of Organocopper Reagents. Several methods have been developed for achieving enantioselectivity with organocopper reagents. Chiral auxiliaries can be used; for example, oxazolidinone auxiliaries have been utilized in conjugate additions. The outcome of these reactions can be predicted on the basis of steric control of reactant approach, as for other applications of the oxazolidinone auxiliaries.

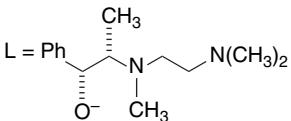


Ref. 85

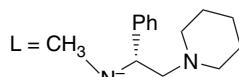
Conjugate addition reactions involving organocopper intermediates can be made enantioselective by using chiral ligands.⁸⁶ Several mixed cuprate reagents containing

- ⁸³. E. Nakamura, M. Yamanaka, and S. Mori, *J. Am. Chem. Soc.*, **122**, 1826 (2000).
- ⁸⁴. E. Nakamura and S. Mori, *Angew. Chem. Int. Ed. Engl.*, **39**, 3750 (2000).
- ⁸⁵. M. P. Sibi, M. D. Johnson, and T. Punniyamurthy, *Can. J. Chem.*, **79**, 1546 (2001).
- ⁸⁶. N. Krause and A. Gerold, *Angew. Chem. Int. Ed. Engl.*, **36**, 186 (1997); N. Krause, *Angew. Chem. Int. Ed. Engl.*, **37**, 283 (1998).

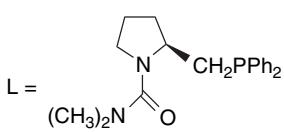
chiral ligands have been investigated to determine the degree of enantioselectivity that can be achieved. The combination of diethylzinc and cyclohexenone has been studied extensively, and several amide and phosphine ligands have been explored. Enantioselectivity can also be observed using Grignard reagents with catalytic amounts of copper. Scheme 8.7 shows some examples of these reactions using various chiral ligands.



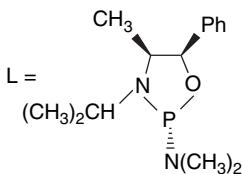
Ref. 87



Ref. 88

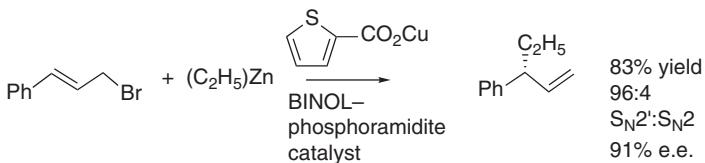


Ref. 89



Ref. 90

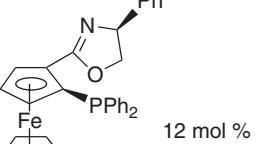
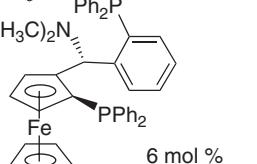
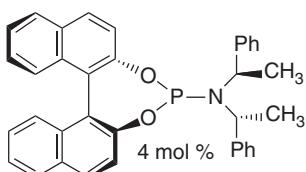
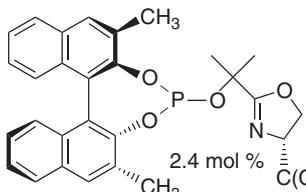
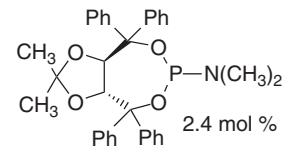
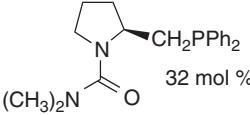
Enantioselective catalysis of S_N2' alkylation has been achieved.⁹¹ A BINOL-phosphoramidite catalyst (*o*-methoxyphenyl analog) similar to that in Entry 3 in Scheme 8.7 gave good results.



8.1.2.9. Aryl-Aryl Coupling Using Organocopper Reagents. Organocopper intermediates are also involved in several procedures for coupling of two aromatic reactants to form a new carbon-carbon bond. A classic example of this type of reaction is the *Ullman coupling* of aryl halides, which is done by heating an aryl halide with a copper-bronze alloy.⁹² Good yields by this method are limited to halides with EWG substituents.⁹³ Mechanistic studies have established the involvement of arylcopper

- ^{87.} E. J. Corey, R. Naef, and F. J. Hannon, *J. Am. Chem. Soc.*, **108**, 7144 (1986).
- ^{88.} N. M. Swingle, K. V. Reddy, and B. L. Rossiter, *Tetrahedron*, **50**, 4455 (1994); G. Miao and B. E. Rossiter, *J. Org. Chem.*, **60**, 8424 (1995).
- ^{89.} M. Kanai and K. Tomioka, *Tetrahedron Lett.*, **35**, 895 (1994); **36**, 4273, 4275 (1995).
- ^{90.} A. Alexakis, J. Frutos, and P. Mageney, *Tetrahedron: Asymmetry*, **4**, 2427 (1993).
- ^{91.} K. Tissot-Croset, D. Polet, and A. Alexakis, *Angew. Chem. Int. Ed. Engl.*, **43**, 2426 (2004).
- ^{92.} P. E. Fanta, *Chem. Rev.*, **64**, 613 (1964); P. E. Fanta, *Synthesis*, **9** (1974).
- ^{93.} R. C. Fuson and E. A. Cleveland, *Org. Synth.*, **III**, 339 (1955).

Scheme 8.7. Catalytic Enantioselective Conjugate Addition to Cyclohexenone

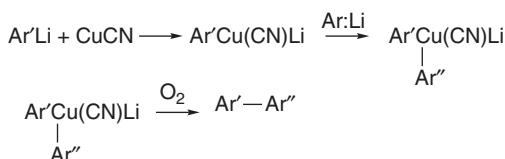
Entry	Reactant	Catalyst	Ligand	Yield	e.e.
1 ^a	$n\text{-C}_4\text{H}_9\text{MgCl}$	CuI 10 mol %		97	83
2 ^b	$\text{C}_2\text{H}_5\text{MgBr}$	CuCl 3 mol %		69	96
3 ^c	$(\text{C}_2\text{H}_5)_2\text{Zn}$	$\text{Cu}(\text{O}_3\text{SCF}_3)_2$ 2 mol %		94	>98
4 ^d	$(\text{C}_2\text{H}_5)_2\text{Zn}$	$\text{Cu}(\text{O}_3\text{SCF}_3)_2$ 2 mol %		96	90
5 ^e	$(\text{C}_2\text{H}_5)_2\text{Zn}$	$\text{Cu}(\text{O}_3\text{SCF}_3)_2$ 1.2 mol %		90	71
6 ^f	$n\text{-C}_4\text{H}_9\text{MgCl}$	CuI 8 mol %		92	90

- a. E. L. Stangeland and T. Sammakia, *Tetrahedron*, **53**, 16503 (1997).
 b. B. L. Feringa, R. Badorrey, D. Pena, S. R. Harutyunyan, and A. J. Minnaard, *Proc. Natl. Acad. Sci. USA*, **101**, 5834 (2004).
 c. B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, and A. H. M. de Vries, *Angew. Chem. Int. Ed. Engl.*, **36**, 2620 (1997).
 d. A. K. H. Knobel, I. H. Escher, and A. Pfaltz, *Synlett*, 1429 (1997); I. H. Escher and A. Pfaltz, *Tetrahedron*, **56**, 2879 (2000).
 e. E. Keller, J. Maurer, R. Naasz, T. Schader, A. Meetsma, and B. L. Feringa, *Tetrahedron: Asymmetry*, **9**, 2409 (1998).
 f. M. Kanai, Y. Nakagawa, and K. Tomioka, *Tetrahedron*, **55**, 3843 (1999).

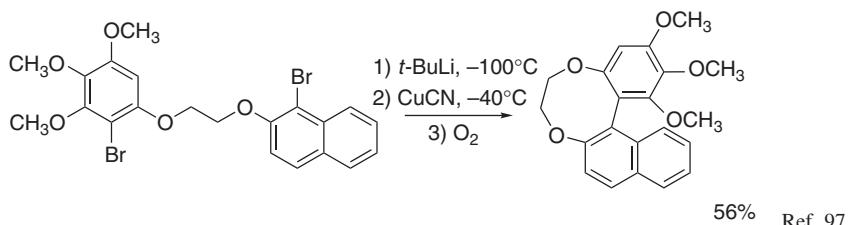
intermediates. Soluble Cu(I) salts, particularly the triflate, effect coupling of aryl halides at much lower temperatures and under homogeneous conditions.⁹⁴



Arylcopper intermediates can be generated from organolithium compounds, as in the preparation of cuprates.⁹⁵ These compounds react with a second aryl halide to provide unsymmetrical biaryls in a reaction that is essentially a variant of the cuprate alkylation process discussed on p. 680. An alternative procedure involves generation of a mixed diarylcyanocuprate by sequential addition of two different aryllithium reagents to CuCN, which then undergo decomposition to biaryls on exposure to oxygen.⁹⁶ The second addition must be carried out at very low temperature to prevent equilibration with the symmetrical diarylcyanocuprates.



Intramolecular variations of this reaction have been achieved.



8.1.2.10. Summary of Synthetic Reactions of Organocopper Reagents and Intermediates. The synthetic procedures involving organocopper reagents and intermediates offer a wide range of carbon-carbon bond-forming reactions. Coupling of alkyl, alkenyl, and aryl groups and the various mixed combinations can be achieved. The coupling of allylic reagents encompasses acetates, sulfonates, and phosphates, as well as halides. These reactions often occur with allylic transposition. Both direct and vinylogous

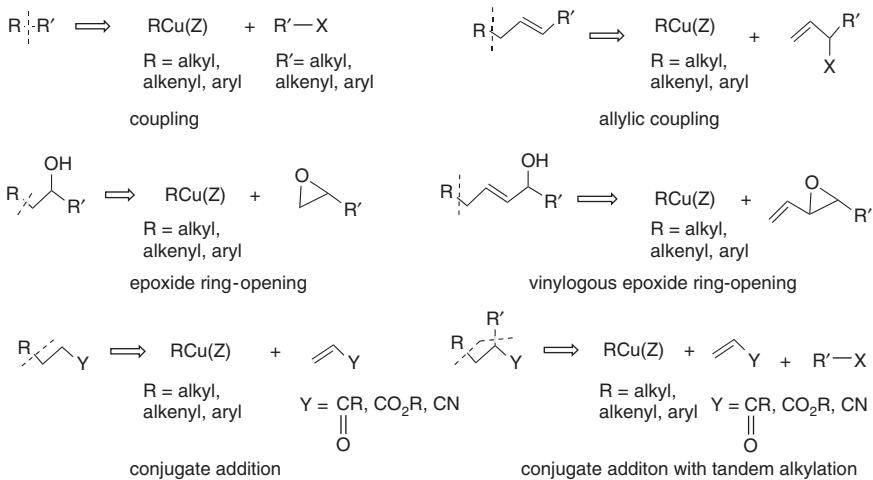
⁹⁴ T. Cohen and I. Cristea, *J. Am. Chem. Soc.*, **98**, 748 (1976).

⁹⁵ F. E. Ziegler, I. Chliwner, K. W. Fowler, S. J. Kanfer, S. J. Kuo, and N. D. Sinha, *J. Am. Chem. Soc.*, **102**, 790 (1980).

⁹⁶ B. H. Lipshutz, K. Siegmann, and E. Garcia, *Tetrahedron*, **48**, 2579 (1992); B. H. Lipshutz, K. Siegmann, E. Garcia, and F. Kayser, *J. Am. Chem. Soc.*, **115**, 9276 (1993).

⁹⁷ B. H. Lipshutz, F. Kayser, and N. Maullin, *Tetrahedron Lett.*, **35**, 815 (1994).

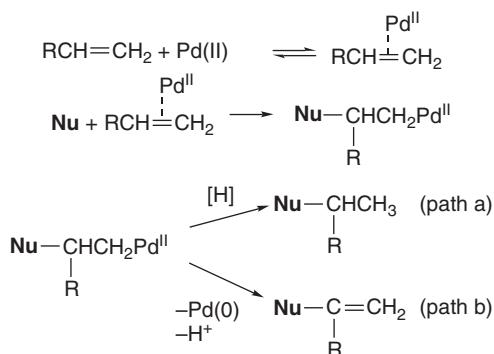
epoxide ring-opening reactions are available for the synthesis of alcohols. The reactants for conjugate addition include α, β -unsaturated ketones, esters, amides, and nitriles, and these reactions can be combined with tandem alkylation. These synthetic transformations are summarized below.



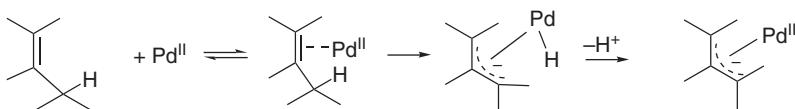
8.2. Reactions Involving Organopalladium Intermediates

Organopalladium intermediates are very important in synthetic organic chemistry. Usually, organic reactions involving palladium do not involve the preparation of stoichiometric organopalladium reagents. Rather, organopalladium species are generated *in situ* during the course of the reaction. In the most useful processes only a *catalytic amount* of palladium is used. The overall reaction mechanisms typically involve several steps in which organopalladium species are formed, react with other reagents, give product, and are regenerated in a catalytically active form. Catalytic processes have both economic and environmental advantages. Since, in principle, the catalyst is not consumed, it can be used to make product without generating by-products. Some processes use *solid phase catalysts*, which further improve the economic and environmental advantages of catalyst recovery. Reactions that involve chiral catalysts can generate enantiomerically enriched or pure materials from achiral starting materials. In this section we focus on carbon–carbon bond formation, but in Chapter 11 we will see that palladium can also catalyze aromatic substitution reactions.

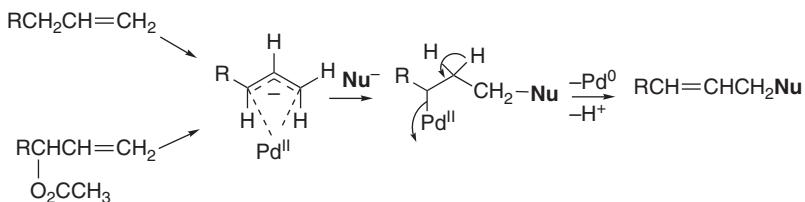
Several types of organopalladium intermediates are of primary importance in the reactions that have found synthetic applications. Alkenes react with Pd(II) to give π complexes that are subject to *nucleophilic attack*. These reactions are closely related to the solvomercuration reactions discussed in Section 4.1.3. The products that are formed from the resulting intermediates depend upon specific reaction conditions. The palladium can be replaced by hydrogen under reductive conditions (path a). In the absence of a reducing agent, elimination of Pd(0) and a proton occurs, leading to net substitution of a vinyl hydrogen by the nucleophile (path b). We return to specific examples of these reactions shortly.



A second major group of organopalladium intermediates are π -allyl complexes, which can be obtained from Pd(II) salts, allylic acetates, and other compounds having potential leaving groups in an allylic position.⁹⁸ The same type of π -allyl complex can be prepared directly from alkenes by reaction with PdCl_2 or $\text{Pd}(\text{O}_2\text{CCF}_3)_2$.⁹⁹ The reaction with alkenes occurs by electrophilic attack on the π electrons followed by loss of a proton. The proton loss probably proceeds via an unstable species in which the hydrogen is bound to palladium.¹⁰⁰



These π -allyl complexes are moderately *electrophilic*¹⁰¹ in character and react with a variety of nucleophiles, usually at the less-substituted allylic terminus. After nucleophilic addition occurs, the resulting organopalladium intermediate usually breaks down by elimination of $\text{Pd}(0)$ and H^+ . The overall transformation is an allylic substitution.



Another general process involves the reaction of Pd(0) species with halides or sulfonates by *oxidative addition*, generating reactive intermediates having the organic group attached to Pd(II) by a σ bond. The oxidative addition reaction is very useful for aryl and alkenyl halides, but the products from saturated alkyl halides often decompose by β -elimination. The σ -bonded species formed by oxidative addition can react with alkenes and other unsaturated compounds to form new carbon-carbon bonds. The

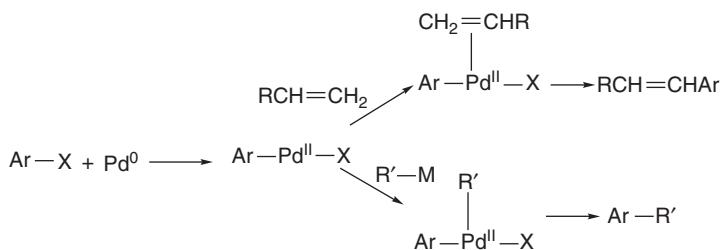
⁹⁸. R. Huttel, *Synthesis*, 225 (1970); B. M. Trost, *Tetrahedron*, **33**, 2615 (1977).

⁹⁹. B. M. Trost and P. J. Metzner, *J. Am. Chem. Soc.*, **102**, 3572 (1980); B. M. Trost, P. E. Strege, L. Weber, T. J. Fullerton, and T. J. Dietsche, *J. Am. Chem. Soc.*, **100**, 3407 (1978).

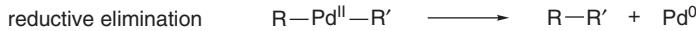
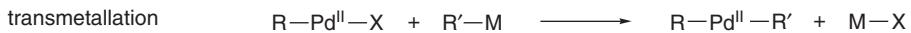
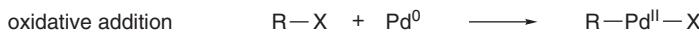
¹⁰⁰. D. R. Chrisope, P. Beak, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **110**, 230 (1988).

¹⁰¹. O. Kuhn and H. Mayr, *Angew. Chem. Int. Ed. Engl.*, **38**, 343 (1998).

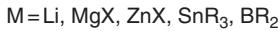
σ -bound species also react with a variety of organometallic reagents to give coupling products.



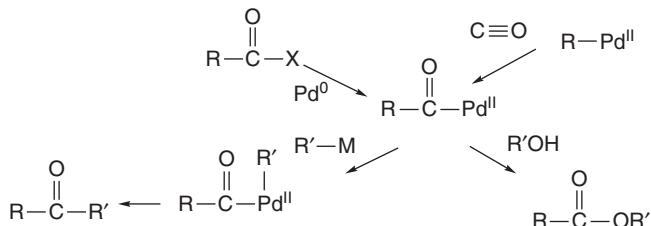
These are called *cross-coupling reactions* and usually involve three basic steps: oxidative addition, transmetallation, and reductive elimination. In the transmetallation step an organic group is transferred from the organometallic reagent to palladium.



The organometallic reagents that give such reactions include organomagnesium, organolithium, and organozinc compounds, stannanes, and even organoboron compounds. The reactions are very general for sp^2-sp^2 and sp^2-sp coupling and in some systems can also be applied to sp^2-sp^3 coupling. Most of these procedures involve phosphine or related ligands.

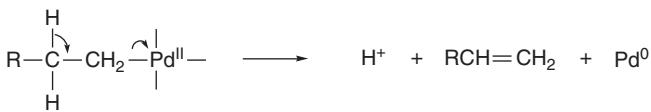


Organopalladium intermediates are also involved in the synthesis of ketones and other carbonyl compounds. These reactions involve acylpalladium intermediates, which can be made from acyl halides or by reaction of an organopalladium species with carbon monoxide. A second organic group, usually arising from an organometallic reagent, can then form a ketone. Alternatively, the acylpalladium intermediate may react with nucleophilic solvents such as alcohols to form esters.

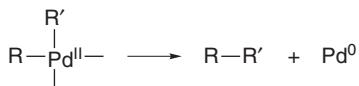


In considering the mechanisms involved in organopalladium chemistry, several general points should be kept in mind. Frequently, reactions involving organopalladium

intermediates are done in the presence of phosphine ligands, which play a key role by influencing the reactivity at palladium. Another general point concerns the relative weakness of the C–Pd bond and, especially, the instability of alkylpalladium species in which there is a β -hydrogen.

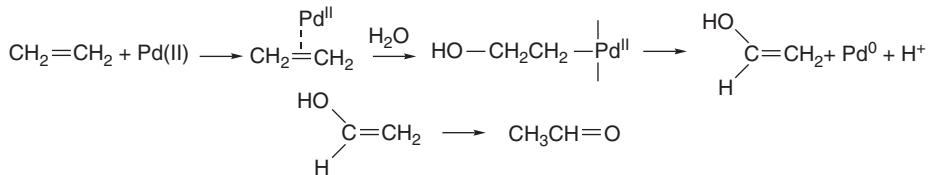


The final stage in many palladium-mediated reactions is the elimination of Pd(0) and H⁺ to generate a carbon–carbon double bond. This tendency toward elimination distinguishes organopalladium species from most of the organometallic species we have discussed up to this point. Finally, organopalladium(II) species with two organic substituents show the same tendency to react with recombination of the organic groups by reductive elimination that is exhibited by copper(III) intermediates. This reductive elimination generates the new carbon–carbon bond.

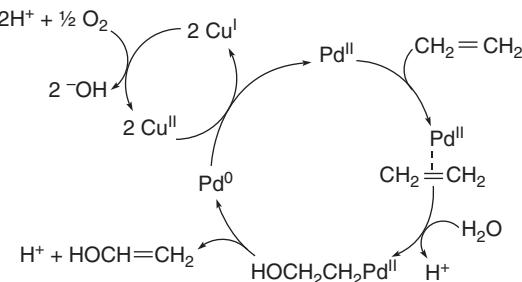


8.2.1. Palladium-Catalyzed Nucleophilic Addition and Substitution

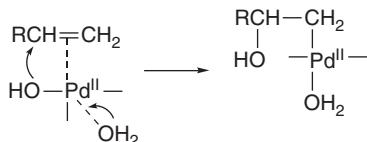
8.2.1.1. The Wacker Reaction and Related Oxidations. An important industrial process based on Pd-alkene complexes is the *Wacker reaction*, a catalytic method for conversion of ethene to acetaldehyde. The first step is addition of water to the Pd(II)-activated alkene. The addition intermediate undergoes the characteristic elimination of Pd(0) and H⁺ to generate the enol of acetaldehyde.



The reaction is run with only a catalytic amount of Pd. The co-reagents CuCl₂ and O₂ serve to reoxidize the Pd(0) to Pd(II). The net reaction consumes only alkene and oxygen.

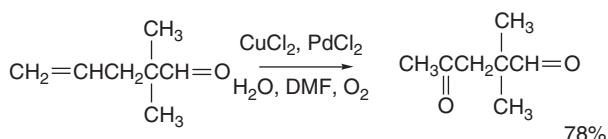


The relative reactivity profile of the simple alkenes toward Wacker oxidation is quite shallow and in the order ethene > propene > 1-butene > *E*-2-butene > *Z*-2-butene.¹⁰² This order indicates that steric factors outweigh electronic effects and is consistent with substantial nucleophilic character in the rate-determining step. (Compare with oxymercuration; see Part A, Section 5.8.) The addition step is believed to occur by an internal ligand transfer through a four-center mechanism, leading to *syn* addition.

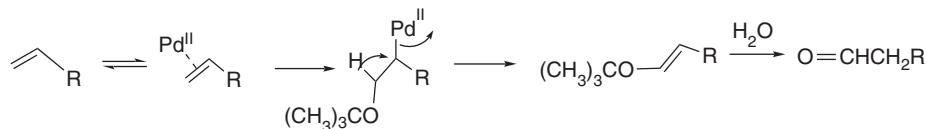


The stereochemistry, however, is sensitive to the concentration of chloride ion, shifting to *anti* when chloride is present.¹⁰³

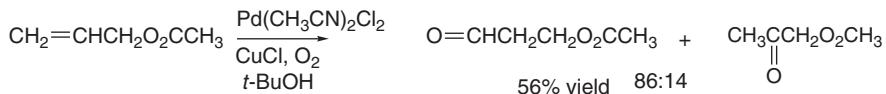
The Wacker reaction can also be applied to laboratory-scale syntheses.¹⁰⁴ When the Wacker conditions are applied to terminal alkenes, methyl ketones are formed.¹⁰⁵



This regiochemistry is consistent with the electrophilic character of Pd(II) in the addition step. Solvent and catalyst composition can affect the regiochemistry of the Wacker reaction. Use of *t*-butanol as the solvent was found to increase the amount of aldehyde formed from terminal alkenes, and is attributed to the greater steric requirement of *t*-butanol. Hydrolysis of the enol ether then leads to the aldehyde.



These conditions are particularly effective for allyl acetate.¹⁰⁶



¹⁰² K. Zaw and P. M. Henry, *J. Org. Chem.*, **55**, 1842 (1990); A. Lambert, E. G. Derouane, and I. V. Kozhevnikov, *J. Catal.*, **211**, 445 (2002).

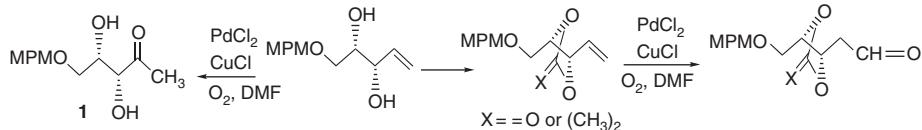
¹⁰³ O. Hamed, P. M. Henry, and C. Thompson, *J. Org. Chem.*, **64**, 7745 (1999).

¹⁰⁴ J. M. Takacs and X.-T. Jiang, *Current Org. Chem.*, **7**, 369 (2003).

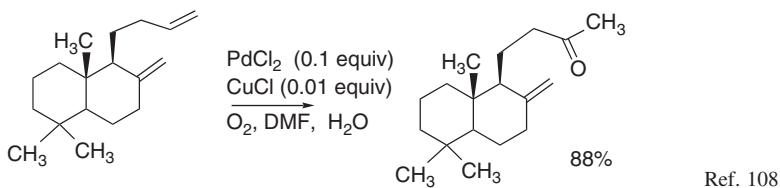
¹⁰⁵ (a) J. Tsuji, I. Shimizu, and K. Yamamoto, *Tetrahedron Lett.*, 2975 (1976); J. Tsuji, H. Nagashima, and H. Nemoto, *Org. Synth.*, **62**, 9 (1984); (c) D. Pauley, F. Anderson, and T. Hudlicky, *Org. Synth.*, **67**, 121 (1988); (d) K. Janusziewicz and H. Alper, *Tetrahedron Lett.*, **25**, 5159 (1983); (e) K. Janusziewicz and D. J. H. Smith, *Tetrahedron Lett.*, **26**, 2263 (1985).

¹⁰⁶ B. L. Feringa, *J. Chem. Soc., Chem. Commun.*, 909 (1986); T. T. Wenzel, *J. Chem. Soc., Chem. Commun.*, 862 (1993).

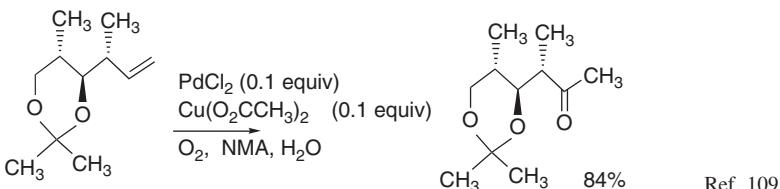
Both the regiochemistry and stereochemistry of Wacker oxidation can be influenced by substituents that engage in chelation with Pd. Whereas a single γ -alkoxy function leads to a mixture of aldehyde and ketone, more highly oxygenated systems such as the acetonide or carbonate of the diol **1** lead to dominant aldehyde formation.¹⁰⁷ The diol itself gives only ketone, which perhaps indicates that steric factors are also important.



The two reactions shown below are examples of the use of the Wacker reaction in multistep synthesis. In the first case, selectivity is achieved between two terminal alkene units on the basis of a difference in steric accessibility. Both reactions use a reduced amount of Cu(I) salt. In the second reaction this helps to minimize hydrolysis of the acid-sensitive dioxane ring.

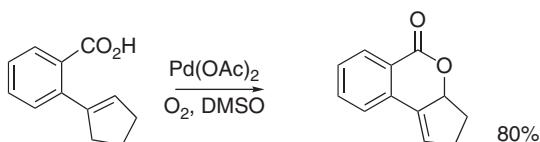


Ref. 108



Ref. 109

Palladium(II) like Hg(II) can induce intramolecular nucleophilic addition, but this is followed by elimination of Pd(0) and H⁺. For example, γ , δ - and δ , ϵ -unsaturated carboxylic acids can be cyclized to unsaturated lactones by Pd(OAc)₂ in DMSO in the presence of O₂. Although Cu(OAc)₂ can be included as a catalyst for reoxidation of the Pd(0), it is not necessary.¹¹⁰



Similarly, phenols with unsaturated side chains can form five- and six-membered rings. In these systems the quaternary carbon imposes the β , γ -elimination. As with the above

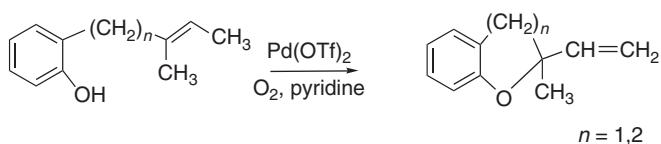
¹⁰⁷ S.-K. Kang, K.-Y. Jung, J.-U. Chung, E.-Y. Namkoong, and T.-H. Kim, *J. Org. Chem.*, **60**, 4678 (1995).

¹⁰⁸ H. Toshima, H. Oikawa, T. Toyomasu, and T. Sassa, *Tetrahedron*, **56**, 8443 (2000).

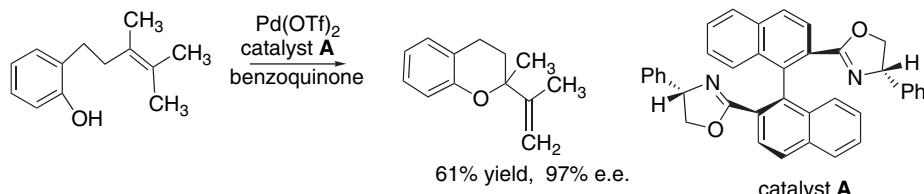
¹⁰⁹ A. B. Smith, III, Y. S. Cho, and G. K. Friestad, *Tetrahedron Lett.*, **39**, 8765 (1998).

¹¹⁰ R. C. Larock and T. R. Hightower, *J. Org. Chem.*, **58**, 5298 (1993).

cyclization, a copper co-oxidant is not needed. The pyridine is evidently involved in accelerating the oxidation of Pd(0) by O₂.¹¹¹

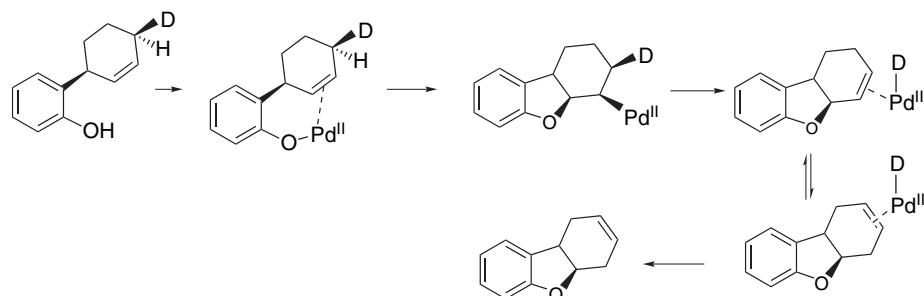


Cyclizations of this type can be carried out with high enantioselectivity using a chiral *bis*-oxazoline catalyst.



Ref. 112

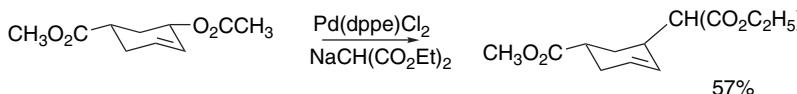
A deuterium-labeling study of a reaction of this type demonstrated *syn* stereoselectivity in both the oxypalladation and β -elimination, which indicates that the cyclization occurs by internal migration, rather than by an *anti* nucleophilic capture.¹¹³ This particular system also gives products from double-bond migration that occurs by reversible Pd(II)-D addition-elimination.



8.2.1.2. Nucleophilic Substitution of π -Allyl Palladium Complexes. π -Allyl palladium species are subject to a number of useful reactions that result in allylation of nucleophiles.¹¹⁴ The reaction can be applied to carbon-carbon bond formation using relatively stable carbanions, such as those derived from malonate esters and β -sulfonyl esters.¹¹⁵ The π -allyl complexes are usually generated *in situ* by reaction of an allylic acetate with a catalytic amount of *tetrakis*-(triphenylphosphine)palladium

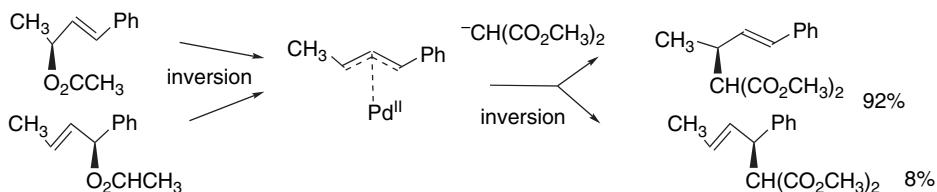
- ¹¹¹. R. M. Trend, Y. K. Ramtohul, E. M. Ferreira, and B. M. Stoltz, *Angew. Chem. Int. Ed. Engl.*, **42**, 2892 (2003).
- ¹¹². Y. Uozumi, K. Kato, and T. Hayashi, *J. Am. Chem. Soc.*, **119**, 5063 (1997).
- ¹¹³. T. Hayashi, K. Yamasaki, M. Mimura, and Y. Uozumi, *J. Am. Chem. Soc.*, **126**, 3036 (2004).
- ¹¹⁴. G. Consiglio and R. M. Waymouth, *Chem. Rev.*, **89**, 257 (1989).
- ¹¹⁵. B. M. Trost, W. P. Conway, P. E. Strege, and T. J. Dietsche, *J. Am. Chem. Soc.*, **96**, 7165 (1974); B. M. Trost, L. Weber, P. E. Strege, T. J. Fullerton, and T. J. Dietsche, *J. Am. Chem. Soc.*, **100**, 3416 (1978); B. M. Trost, *Acc. Chem. Res.*, **13**, 385 (1980).

or a chelated diphosphine complex.¹¹⁶ The reactive Pd(0) species is regenerated in an elimination step.



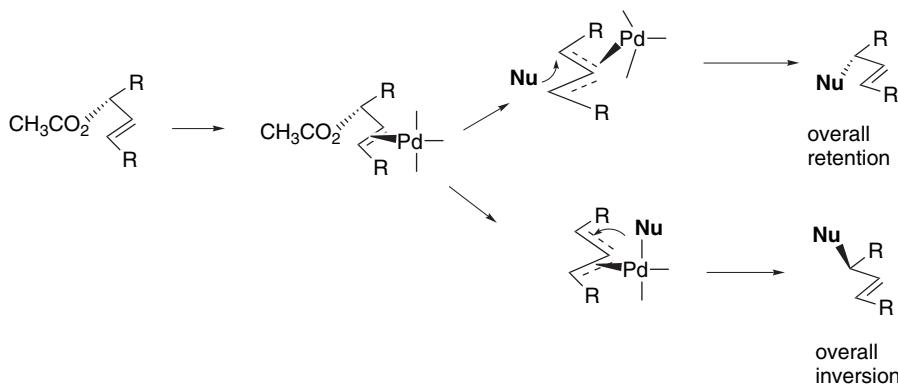
Ref. 117

For unsymmetrical allylic systems both the regiochemistry and stereochemistry of the substitution are critical issues. The palladium normally bonds *anti* to the acetate leaving group. The same products are obtained from 2-acetoxy-4-phenyl-3-butene and 1-acetoxy-1-phenyl-2-butene, indicating a common intermediate. The same product mixture is also obtained from the *Z*-reactants, indicating rapid *E,Z*-equilibration in the allylpalladium intermediate.¹¹⁸



In the presence of chiral phosphine ligands, there is also rapid epimerization to the most stable diastereomeric π -allyl complex. The stereoselectivity arises in the reaction with the nucleophile.¹¹⁹

Mechanistically, the nucleophilic addition can occur either by internal ligand transfer or by external attack. Generally, softer more stable nucleophiles (e.g., malonate enolates) are believed to react by the external mechanism and give *anti* addition, whereas harder nucleophiles (e.g., hydroxide) are delivered by internal ligand transfer with *syn* stereochemistry.¹²⁰



Both the regiochemistry and stereochemistry are influenced by reaction conditions. A striking example is a complete switch to 3-alkylation of dimethyl malonate

¹¹⁶ B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **102**, 4730 (1980).

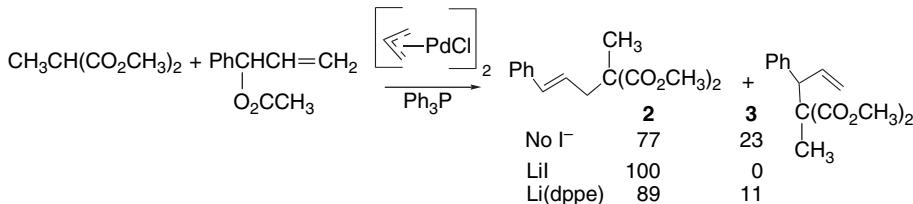
¹¹⁷ B. M. Trost and P. E. Strege, *J. Am. Chem. Soc.*, **99**, 1649 (1977).

¹¹⁸ T. Hayashi, A. Yamamoto, and T. Hagiwara, *J. Org. Chem.*, **51**, 723 (1986).

¹¹⁹ P. B. Mackenzie, J. Whelan, and B. Bosnich, *J. Am. Chem. Soc.*, **107**, 2046 (1985).

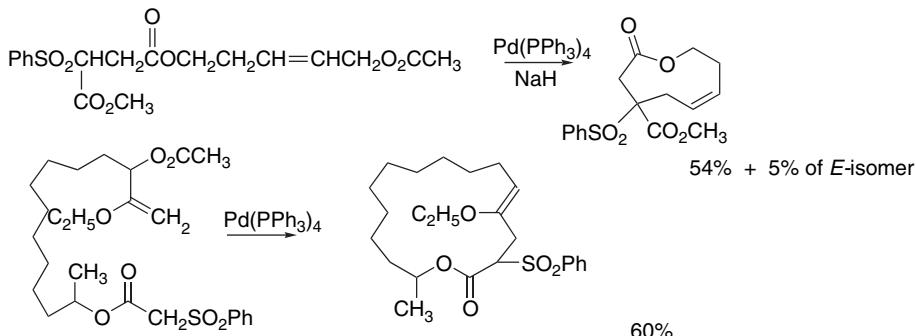
¹²⁰ A. Heumann and M. Reglier, *Tetrahedron*, **51**, 975 (1995).

anion by 1-phenylprop-2-enyl acetate in the presence of iodide ion. In the absence of iodide, using 2 mol % catalyst, the ratio of **2** to **3** is about 4:1. When 2 mol % iodide is added, only **2** is formed. This change is attributed to the involvement of a catalytic species in which I^- is present as a Pd ligand. The effect is diminished when a chelating diphosphine ligand is used, presumably because addition of I^- to the Pd ligand sphere is prevented by the chelate.

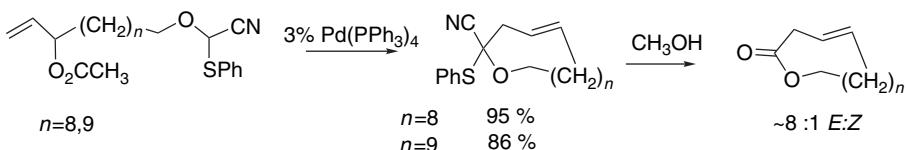


Ref. 121

The allylation reaction has also been used to form rings. β -Sulfonyl esters have proven particularly useful in this application for formation of both medium and large rings.¹²² In some cases medium-sized rings are formed in preference to six- and seven-membered rings.¹²³

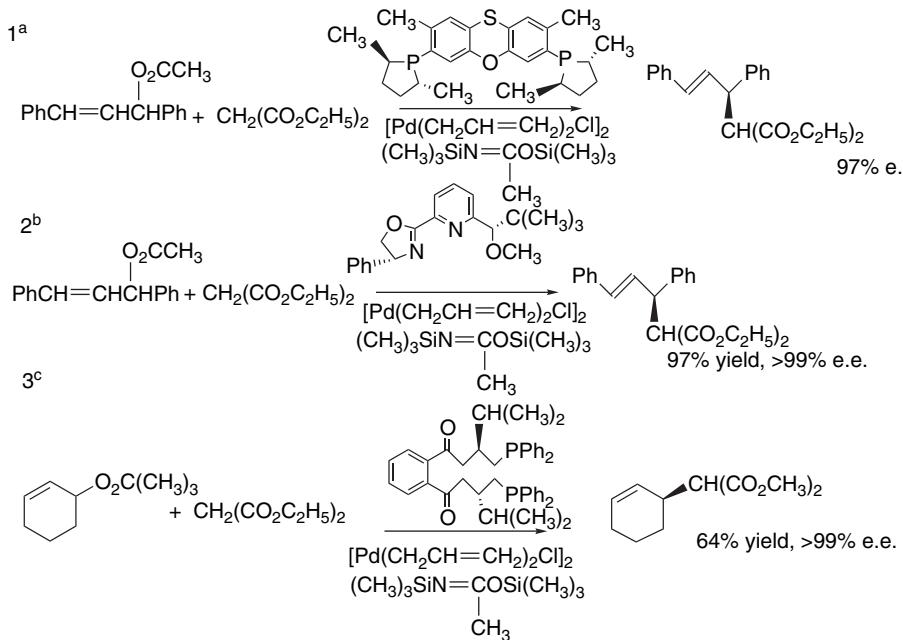


The sulfonyl substituent can be removed by reduction after the ring closure (see Section 5.6.2). Other appropriate reactants are α -phenylthio nitriles, which can be hydrolyzed to lactones.¹²⁴



Allylation reactions can be made highly enantioselective by the use of various chiral phosphine ligands.¹²⁵ Examples are included in Scheme 8.8.

- ¹²¹. M. Kawatsura, Y. Uozumi, and T. Hayashi, *J. Chem. Soc., Chem. Commun.*, 217 (1998).
- ¹²². B. M. Trost, *Angew. Chem. Int. Ed. Engl.*, **28**, 1173 (1989).
- ¹²³. B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **102**, 4743 (1980); B. M. Trost and S. J. Brickner, *J. Am. Chem. Soc.*, **105**, 568 (1983); B. M. Trost, B. A. Vos, C. M. Brzezowski, and D. P. Martina, *Tetrahedron Lett.*, **33**, 717 (1992).
- ¹²⁴. B. M. Trost and J. R. Granja, *J. Am. Chem. Soc.*, **113**, 1044 (1991).
- ¹²⁵. S. J. Sesay and J. M. J. Williams, in *Advances in Asymmetric Synthesis*, Vol. 3, A. Hassner, ed., JAI Press, Stamford, CT, 1998, pp. 235–271; G. Helmchen, *J. Organomet. Chem.*, **576**, 203 (1999).



a. P. Dierks, S. Ramdeehul, L. Barley, A. DeCian, J. Fischer, P. C. J. Kramer, P. W. N. M. van Leeuwen, and J. A. Osborne, *Angew. Chem. Int. Ed. Engl.*, **37**, 3116 (1998).

b. K. Nordstrom, E. Macedo, and C. Moberg, *J. Org. Chem.*, **62**, 1604 (1997); U. Bremberg, F. Rahm, and C. Moberg, *Tetrahedron: Asymmetry*, **9**, 3437 (1998).

c. A. Saitoh, M. Misawa, and T. Morimoto, *Tetrahedron: Asymmetry*, **10**, 1025 (1999).

8.2.2. The Heck Reaction

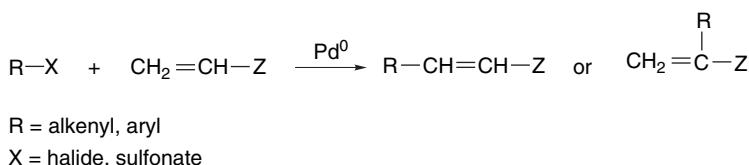
Another important type of reactivity of palladium, namely oxidative addition to Pd(0), is the foundation for several methods of forming carbon-carbon bonds. Aryl¹²⁶ and alkenyl¹²⁷ halides react with alkenes in the presence of catalytic amounts of palladium to give net substitution of the halide by the alkenyl group. The reaction, known as the *Heck reaction*,¹²⁸ is quite general and has been observed for simple alkenes, aryl-substituted alkenes, and substituted alkenes such as acrylate esters, vinyl ethers, and *N*-vinylamides.¹²⁹

¹²⁶ H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.*, **96**, 1133 (1974); R. F. Heck, *Acc. Chem. Res.*, **12**, 146 (1979); R. F. Heck, *Org. React.*, **27**, 345 (1982).

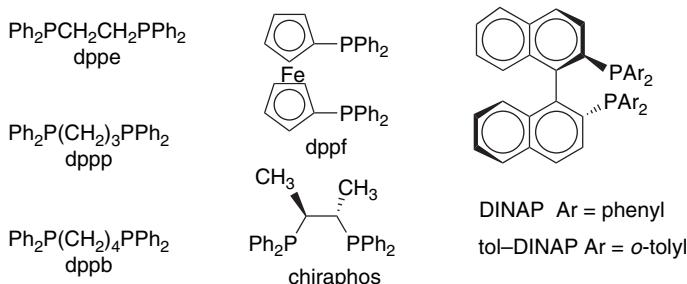
¹²⁷ B. A. Patel and R. F. Heck, *J. Org. Chem.*, **43**, 3898 (1978); B. A. Patel, J. I. Kim, D. D. Bender, L. C. Kao, and R. F. Heck, *J. Org. Chem.*, **46**, 1061 (1981); J. I. Kim, B. A. Patel, and R. F. Heck, *J. Org. Chem.*, **46**, 1067 (1981).

¹²⁸ I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, **100**, 3009 (2000); B. C. G. Soderberg, *Coord. Chem. Rev.*, **224**, 171 (2002); G. T. Crisp, *Chem. Soc. Rev.*, **27**, 427 (1998).

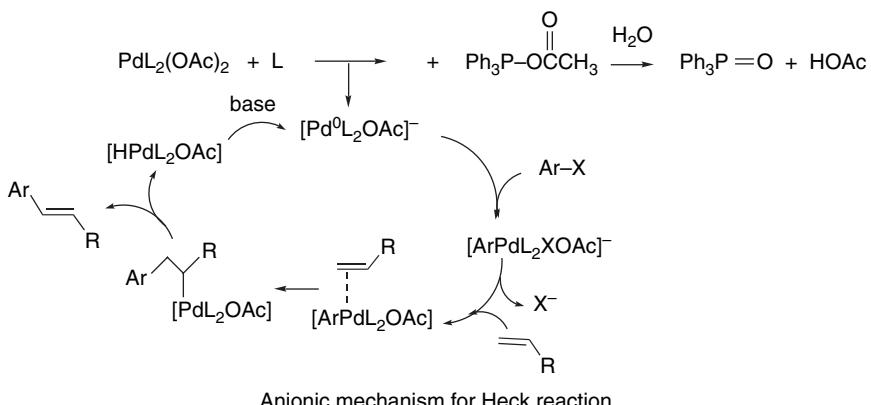
¹²⁹ C. B. Ziegler, Jr., and R. F. Heck, *J. Org. Chem.*, **43**, 2941 (1978); W. C. Frank, Y. C. Kim, and R. F. Heck, *J. Org. Chem.*, **43**, 2947 (1978); C. B. Ziegler, Jr., and R. F. Heck, *J. Org. Chem.*, **43**, 2949 (1978); H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.*, **96**, 1133 (1974); C. A. Busacca, R. E. Johnson, and J. Swestock, *J. Org. Chem.*, **58**, 3299 (1993).



Many procedures use $\text{Pd}(\text{OAc})_2$ or other Pd(II) salts as catalysts with the catalytically active Pd(0) being generated in situ. The reactions are usually carried out in the presence of a phosphine ligand, with *tris*-*o*-tolylphosphine being preferred in many cases. *Tris*-(2-furyl)phosphine (tfp) is also used frequently. Several chelating diphosphines, shown below with their common abbreviations, are also effective. Phosphites are also good ligands.¹³⁰



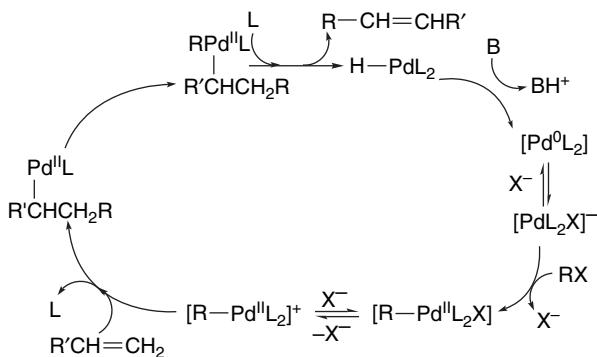
The reaction is initiated by oxidative addition of the halide or sulfonate to a Pd(0) species generated in situ from the Pd(II) catalyst. The arylpalladium(II) intermediate then forms a π complex with the alkene, which rearranges to a σ complex by carbon–carbon bond formation. The σ complex decomposes by β -elimination with regeneration of Pd(0). Both of these reactions occur with *syn* stereoselectivity. The Heck reaction often uses of $\text{Pd}(\text{OAc})_2$ as the palladium source along with a triarylphosphine and a tertiary amine. Under these conditions it has been proposed that the initiation of the reaction involves formation of an anionic complex $[\text{Pd}(\text{L})_2\text{OAc}]^-$.¹³¹ This is a 16-electron species and is considered to be the active form of Pd for the oxidative addition. The base is crucial in maintaining the equilibrium in favor of the active anionic form after the reductive elimination. This is called the *anionic mechanism*. Note that the phosphine ligand is also the reducing agent for formation of the active Pd(0) species.



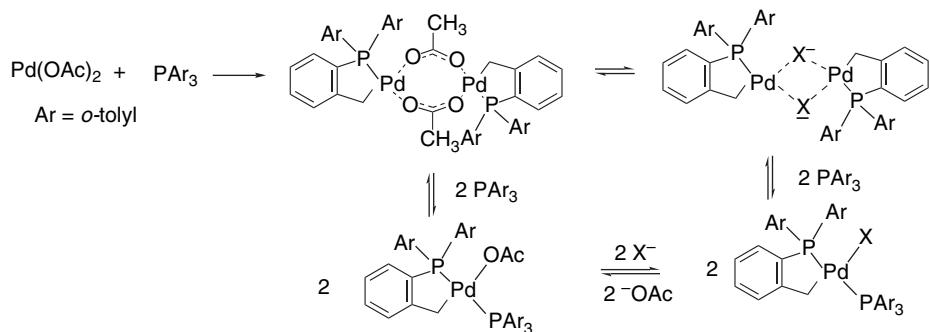
¹³⁰ M. Beller and A. Zapt, *Synlett*, 792 (1998).

¹³¹ A. Amatore and A. Jutand, *Acc. Chem. Res.*, **33**, 314 (2000).

Several different Pd(0) species can be involved in both the oxidative addition and π -coordination steps, depending on the anions and ligands present. Because of the equilibria involving dissociation of phosphine ligands and anions, there is dependence on their identity and concentration.¹³² High halide concentration promotes formation of the anionic species $[\text{PdL}_2\text{X}]^-$ by addition of a halide ligand. Use of trifluoromethanesulfonate anions promotes dissociation of the anion from the Pd(II) adduct and accelerates complexation with electron-rich alkenes. The presence of metal ions that bind the halide, e.g., Ag^+ , also promotes dissociation. Reactions that proceed through a dissociated species are called *cationic* and are expected to have a more electrophilic interaction with the alkene. A base is included to neutralize the proton released in the β -elimination step. The catalytic cycle under these conditions is shown below.



It appears that a modified mechanism operates when *tris-(o-tolyl)phosphine* is used as the ligand,¹³³ and this phosphine has been found to form a *palladacycle*. Much more stable than noncyclic Pd(0) complexes, this compound is also more reactive toward oxidative addition. As with the other mechanisms, various halide adducts or halide-bridged compounds may enter into the overall mechanism.

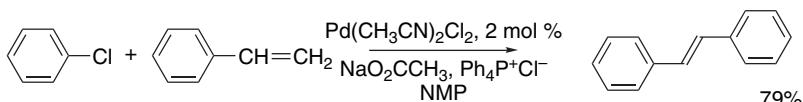


¹³² W. Cabri, I. Candiani, S. De Bernardinis, F. Francalanci, S. Penco, and R. Santi, *J. Org. Chem.*, **56**, 5796 (1991); F. Ozawa, A. Kubo, and T. Hayashi, *J. Am. Chem. Soc.*, **113**, 1417 (1991).

¹³³ W. A. Hermann, C. Brossmer, K. Ofele, C.-P. Reisinger, T. Priermeier, M. Beller, and H. Fischer, *Angew. Chem. Int. Ed. Engl.*, **34**, 1844 (1995).

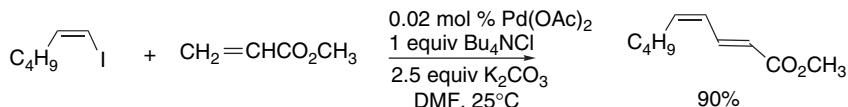
Several modified reaction conditions have been developed. One involves addition of silver salts, which activate the halide toward displacement.¹³⁴ Use of sodium bicarbonate or sodium carbonate in the presence of a phase transfer catalyst permits especially mild conditions to be used for many systems.¹³⁵ Tetraalkylammonium salts also often accelerate reaction.¹³⁶ Solid phase catalysts in which the palladium is complexed by polymer-bound phosphine groups have also been developed.¹³⁷

Aryl chlorides are not very reactive under normal Heck reaction conditions but reaction can be achieved by inclusion of tetraphenylphosphonium salts with Pd(OAc)₂ or PdCl₂ as the catalysts.¹³⁸



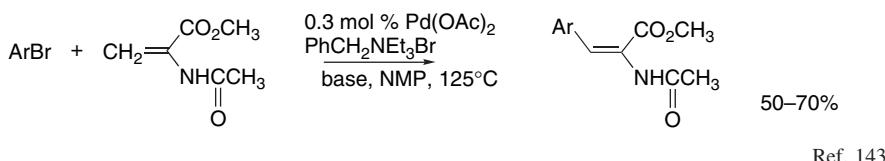
Pretreatment with nickel bromide causes normally unreactive aryl chlorides to undergo Pd-catalyzed substitution,¹³⁹ and aryl and vinyl triflates have been found to be excellent substrates for Pd-catalyzed alkylations.¹⁴⁰

Heck reactions can be carried out in the absence of phosphine ligands.¹⁴¹ These conditions usually involve Pd(OAc)₂ as a catalyst, along with a base and a phase transfer salt such as tetra-*n*-butylammonium bromide. These conditions were originally applied to stereospecific coupling of vinyl iodides with ethyl acrylate and methyl vinyl ketone.



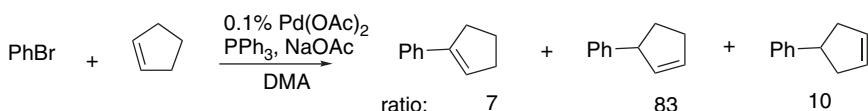
Several optimization studies have been carried out under these phosphine-free conditions. The reaction of bromobenzene and styrene was studied using Pd(OAc)₂ as the catalyst, and potassium phosphate and *N,N*-dimethylacetamide (DMA) were found to be the best base and solvent. Under these conditions, the Pd content can be reduced to as low as 0.025 mol %.¹⁴² The reaction of substituted bromobenzenes with methyl α -acetamidoacrylate has also been studied carefully, since the products are potential precursors of modified amino acids. Good results were obtained using either *N,N*-diisopropylethylamine or NaOAc as the base.

- ¹³⁴. M. M. Abelman, T. Oh, and L. E. Overman, *J. Org. Chem.*, **52**, 4130 (1987); M. M. Abelman and L. E. Overman, *J. Am. Chem. Soc.*, **110**, 2328 (1988).
- ¹³⁵. T. Jeffery, *J. Chem. Soc., Chem. Commun.*, 1287 (1984); T. Jeffery, *Tetrahedron Lett.*, **26**, 2667 (1985); T. Jeffery, *Synthesis*, 70 (1987); R. C. Larock and S. Babu, *Tetrahedron Lett.*, **28**, 5291 (1987).
- ¹³⁶. A. de Meijere and F. E. Meyer, *Angew. Chem. Int. Ed. Engl.*, **33**, 2379 (1994); R. Grigg, *J. Heterocycl. Chem.*, **31**, 631 (1994); T. Jeffery, *Tetrahedron*, **52**, 10113 (1996).
- ¹³⁷. C.-M. Andersson, K. Karabelas, A. Hallberg, and C. Andersson, *J. Org. Chem.*, **50**, 3891 (1985).
- ¹³⁸. M. T. Reetz, G. Lehmer, and R. Schwickard, *Angew. Chem. Int. Ed.*, **37**, 481 (1998).
- ¹³⁹. J. J. Bozell and C. E. Vogt, *J. Am. Chem. Soc.*, **110**, 2655 (1988).
- ¹⁴⁰. A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, **109**, 5478 (1987); K. Karabelas and A. Hallberg, *J. Org. Chem.*, **53**, 4909 (1988).
- ¹⁴¹. T. Jeffery, *Tetrahedron Lett.*, **26**, 2667 (1985); T. Jeffery, *Synthesis*, 70 (1980).
- ¹⁴². Q. Yao, E. P. Kinney, and Z. Yang, *J. Org. Chem.*, **68**, 7528 (2003).

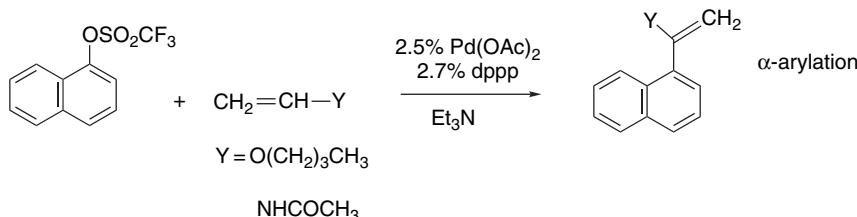


Low Pd concentrations are beneficial in preventing precipitation of inactive Pd metal.¹⁴⁴ Small Pd clusters can be observed in phosphine-free systems,¹⁴⁵ and these particles may serve as catalysts or, alternatively, as reservoirs of Pd for formation of soluble reactive species.

The regiochemistry of the Heck reaction is determined by the competitive removal of the β -proton in the elimination step. Mixtures are usually obtained if more than one type of β -hydrogen is present. Often there is also double-bond migration that occurs by reversible Pd-H elimination-addition sequences. For example, the reaction of cyclopentene with bromobenzene leads to all three possible double-bond isomers.¹⁴⁶



Substituents with stronger electronic effects can influence the competition between α - and β -arylation. Alkenes having EWG substituents normally result in β -arylation. However, alkenes with donor substituents give a mixture of α - and β -regioisomers. The regiochemistry can be controlled to some extent by specific reaction conditions. Bidentate phosphines such as dppp and dppf promote α -arylation of alkenes with donor substituents such as alkoxy, acetoxy, and amido. These reactions are believed to occur through the more electrophilic form of Pd(II) generated by dissociation of the triflate anion (cationic mechanism).¹⁴⁷ Electronic factors favor migration of the aryl group to the α -carbon. The combination of the bidentate ligand and triflate leaving group increases the importance of electronic effects on the regiochemistry.

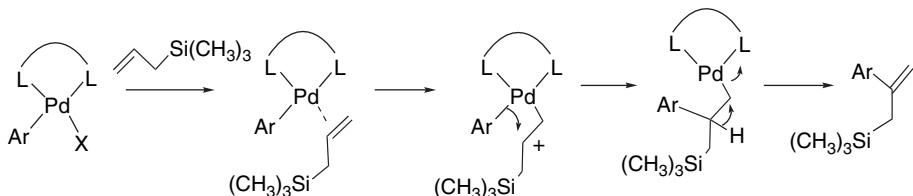


Substituents without strong donor or acceptor character (e.g., phenyl, succinimido) give mixtures. The reason for the increased electronic sensitivity is thought to be the

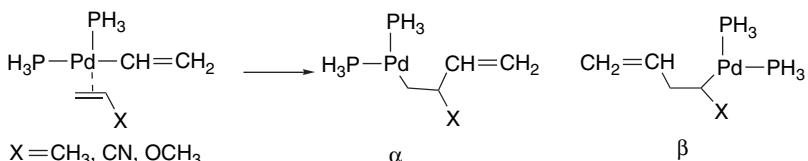
- ^{143.} C. E. Williams, J. M. C. A. Mulders, J. G. de Vries, and A. H. M. de Vries, *J. Organomet. Chem.*, **687**, 494 (2003).
- ^{144.} A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Hendrickx, and J. G. de Vries, *Org. Lett.*, **5**, 3285 (2003).
- ^{145.} M. T. Reetz and E. Westermann, *Angew. Chem. Int. Ed. Engl.*, **39**, 165 (2000).
- ^{146.} C. G. Hartung, K. Kohler, and M. Beller, *Org. Lett.*, **1**, 709 (1999).
- ^{147.} W. Cabri, I. Cardiani, A. Bedeschi, and R. Santi, *J. Org. Chem.*, **55**, 3654 (1990); W. Cabri, I. Cardiani, A. Bedeschi, and R. Santi, *J. Org. Chem.*, **57**, 3558 (1992). W. Cabri, I. Cardiani, A. Bedeschi, S. Penco, and R. Santi, *J. Org. Chem.*, **57**, 1481 (1992).

involvement of a cationic, as opposed to a neutral, complex. The triflate anion is more likely to be dissociated than a halide.

Allylic silanes show a pronounced tendency to react at the α -carbon in the presence of bidentate ligands.¹⁴⁸ This regiochemistry is attributed to the preferential stabilization of cationic character by the silyl substituent. The bidentate ligands enhance the electrophilic character of the TS, and the cation stabilization of the silyl group becomes the controlling factor.



There have been several computational studies of electronic effects on the regioselectivity of the Heck reaction. Vinyl migration was studied for $X = \text{CH}_3, \text{CN}$, and OCH_3 using PH_3 as the ligand model.¹⁴⁹ Differences were calculated for the best α - and β -migration TS for each substituent. The differences were as follows: CH_3 : α -migration favored by 0.1 kcal/mol; CN : β -migration favored by 4 kcal/mol; OCH_3 : α -migration favored by 2 kcal/mol.



Examination of the HOMO and LUMO orbitals in these TSs indicates that the electronic effect operates mainly through the LUMO. The EWG cyano tends to localize the LUMO on the β -carbon, whereas ERG substituents have the opposite effect. Similar trends were found for Pd coordinated by diimine ligands.¹⁵⁰ These results indicate that the Markovnikov rule applies with the more electrophilic Pd complexes. When steric effects become dominant, the Pd adds to the less hindered position.

The Heck reaction has been applied to synthesis of intermediates and in multi-stage syntheses. Some examples are given in Scheme 8.9. Entries 1 and 2 illustrate both the β -regioselectivity and selectivity for aryl iodides over bromides. Entries 3 and 4 show conditions that proved favorable for cyclohexene. These examples also indicate preferential *syn* Pd-H elimination, since this accounts for formation of the 3-substituted cyclohexene as the major product.

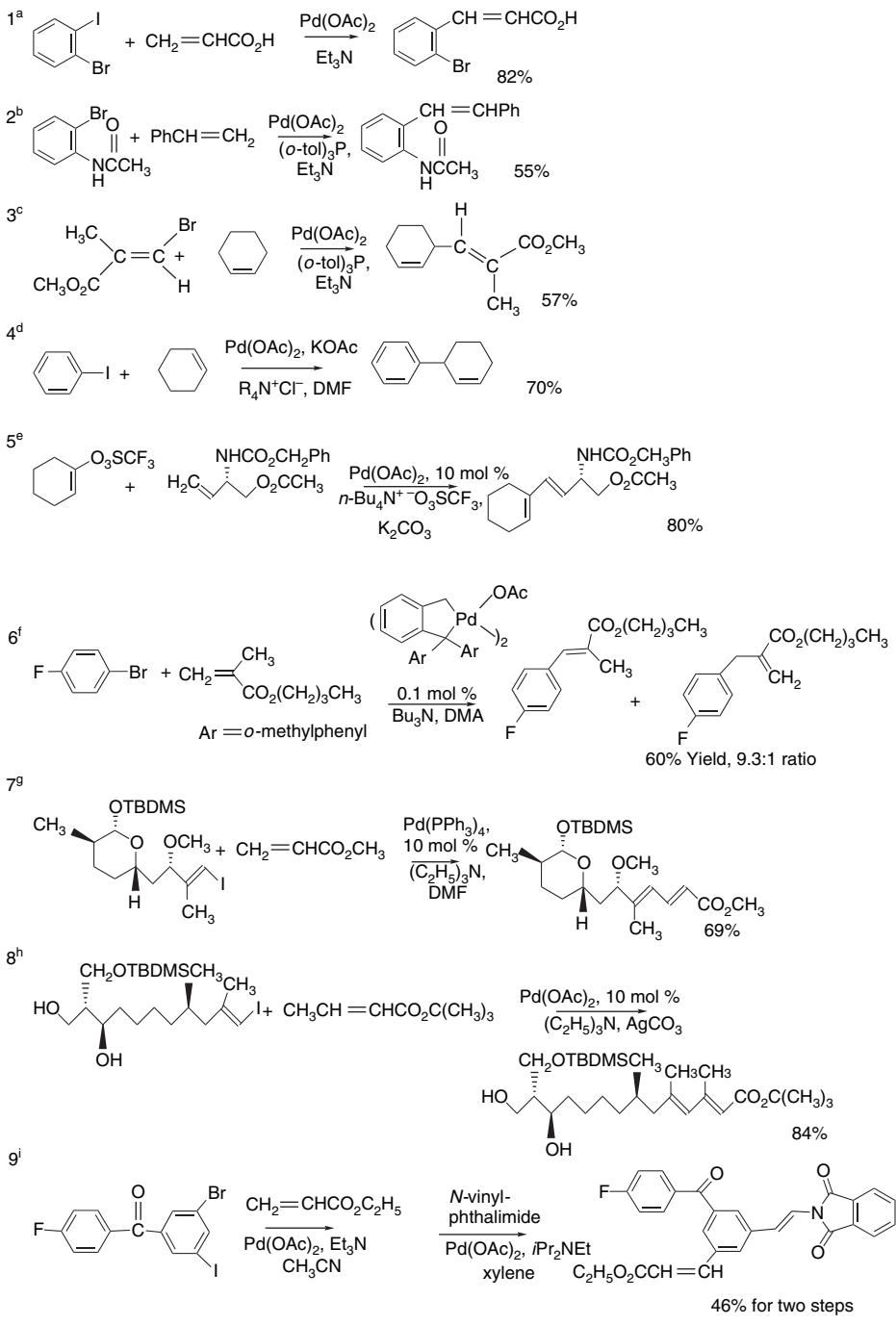
¹⁴⁸ K. Olofsson, M. Larhed, and A. Hallberg, *J. Org. Chem.*, **63**, 5076 (1998).

¹⁴⁹ R. J. Deeth, A. Smith, and J. M. Brown, *J. Am. Chem. Soc.*, **126**, 7144 (2004).

¹⁵⁰ H. V. Schenck, B. Åkermark, and M. Svensson, *J. Am. Chem. Soc.*, **125**, 3503 (2003).

SECTION 8.2

Reactions Involving
Organopalladium
Intermediates



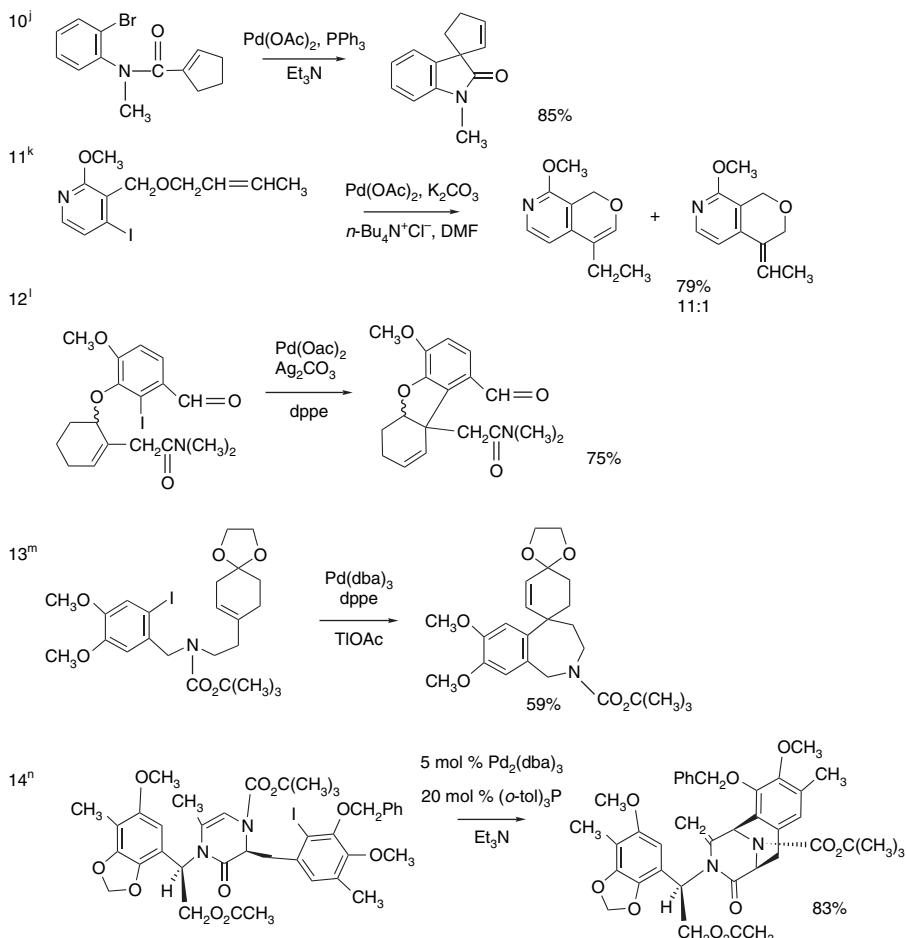
(Continued)

Scheme 8.9. (Continued)

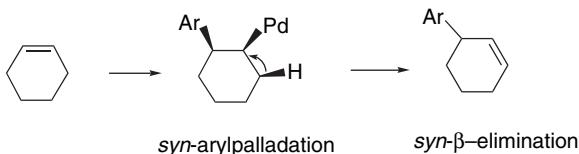
CHAPTER 8

Reactions Involving
Transition Metals

Intramolecular reactions



- a. J. E. Plevyak, J. E. Dickerson, and R. F. Heck, *J. Org. Chem.*, **44**, 4078 (1979).
- b. P. de Mayo, L. K. Sydnes, and G. Wenska, *J. Org. Chem.*, **45**, 1549 (1980).
- c. J.-I. Kim, B. A. Patel, and R. F. Heck, *J. Org. Chem.*, **46**, 1067 (1981).
- d. R. C. Larock and B. E. Baker, *Tetrahedron Lett.*, **29**, 905 (1988).
- e. G. T. Crisp and M. G. Gebauer, *Tetrahedron*, **52**, 12465 (1996).
- f. M. Beller and T. H. Riermeier, *Tetrahedron Lett.*, **37**, 6535 (1996).
- g. L. Harris, K. Jarowicki, P. Kocienski, and R. Bell, *Synlett*, 903 (1996).
- h. P. M. Wovkulich, K. Shankaran, J. Kiegel, and M. R. Uskokovic, *J. Org. Chem.*, **58**, 832 (1993); T. Jeffery and J.-C. Galland, *Tetrahedron Lett.*, **35**, 4103 (1994).
- i. D. C. Waite and C. P. Mason, *Org. Proc. Res. Devel.*, **2**, 116 (1998).
- j. M. M. Abelman, T. Oh, and L. E. Overman, *J. Org. Chem.*, **59**, 4130 (1987).
- k. F. G. Fang, S. Xie, and M. W. Lowery, *J. Org. Chem.*, **59**, 6142 (1994).
- l. P. J. Parsons, M. D. Charles, D. M. Harvey, L. R. Sumoreeah, A. Skell, G. Spoors, A. L. Gill, and S. Smith, *Tetrahedron Lett.*, **42**, 2209 (2001).
- m. C. Bru, C. Thal, and C. Guillou, *Org. Lett.*, **5**, 1845 (2003).
- n. A. Endo, A. Yanagisawa, M. Abe, S. Tohma, T. Kan, and T. Fukuyama, *J. Am. Chem. Soc.*, **124**, 6552 (2002).



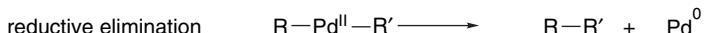
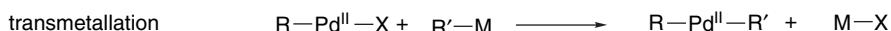
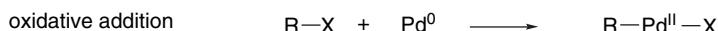
Entry 5 illustrates use of a vinyl triflate under the “phosphine-free” conditions. Entry 6 achieved exceptionally high catalyst efficiency by using a palladacycle-type catalyst. Entries 7 and 8 show the introduction of acrylate ester groups using functionalized alkenyl iodides. Entry 9 demonstrates two successive Heck reactions employed in a large-scale synthesis of a potential thromboxane receptor antagonist. These reactions were carried out in the absence of any phosphine ligand. The greater reactivity of the iodide over the bromide permits the sequential introduction of the two substituents.

There are numerous examples of intramolecular Heck reactions,¹⁵¹ such as in Entries 10 to 14. Entry 11 is part of a synthesis of the antitumor agent camptothecin. The Heck reaction gives an 11:1 endocyclic-exocyclic mixture. Entries 12–14 are also steps in syntheses of biologically active substances. Entry 12 is part of a synthesis of maritidine, an alkaloid with cytotoxic properties; the reaction in Entry 13 is on a route to galanthamine, a potential candidate for treatment of Alzheimer’s disease; and Entry 14 is a key step in the synthesis of a potent antitumor agent isolated from a marine organism.

8.2.3. Palladium-Catalyzed Cross Coupling

Palladium can catalyze carbon-carbon bond formation between aryl or vinyl halides and sulfonates and a wide range of organometallic reagents in *cross-coupling reactions*.¹⁵² The organometallic reagents used include organolithium, organomagnesium, and organozinc reagents, as well as cuprates, stannanes, and organoboron compounds. The reaction is quite general for formation of sp^2-sp^2 and sp^2-sp bonds in biaryls, dienes, polyenes, and enynes. There are also some reactions that can couple alkyl organometallic reagents, but these are less general because of the tendency of alkylpalladium intermediates to decompose by β -elimination. Arylation of enolates also can be effected by palladium catalysts.

The basic steps in the cross-coupling reaction include oxidative addition of the aryl or vinyl halide (or sulfonate) to Pd(0), followed by transfer of an organic group from the organometallic to the resulting Pd(II) intermediate (*transmetallation*). The disubstituted Pd(II) intermediate then undergoes reductive elimination, which gives the product by carbon bond formation and regenerates the catalytically active Pd(0) oxidation level.

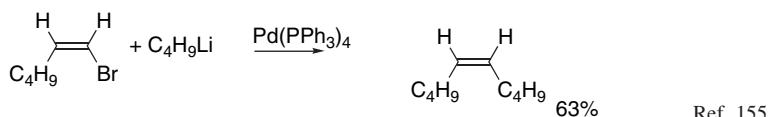
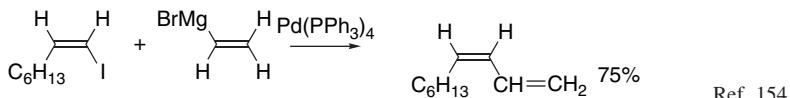


¹⁵¹ J. Link, *Org. React.*, **60**, 157 (2002).

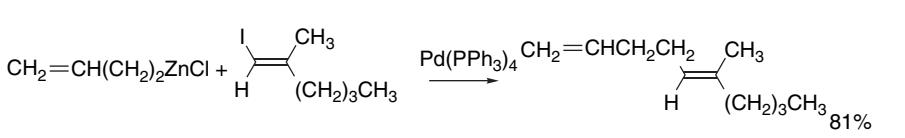
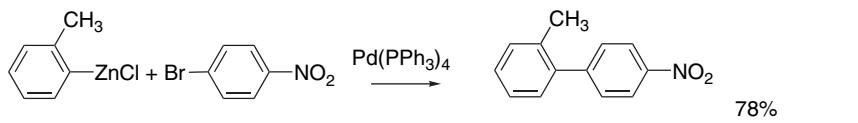
¹⁵² F. Diederich and P. J. Stang, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, New York, 1998; S. P. Stanforth, *Tetrahedron*, **54**, 263 (1998).

Ligands and anions play a crucial role in determining the rates and equilibria of the various steps by controlling the detailed coordination environment at palladium.¹⁵³ In the next section we discuss coupling reactions involving organolithium, organo-magnesium, organozinc, and organocupper reagents. We then proceed to arylation of enolates mediated by palladium catalysts. Subsequent sections consider cross coupling with stannanes (*Stille reaction*) and boron compounds (*Suzuki reaction*).

8.2.3.1. Coupling with Organometallic Reagents. Tetrakis-(triphenylphosphine) palladium catalyzes coupling of alkenyl halides with Grignard reagents and organo-lithium reagents. The reactions proceed with retention of configuration at the double bond.



Organozinc compounds are also useful in palladium-catalyzed coupling with aryl and alkenyl halides. Procedures for arylzinc,¹⁵⁶ alkenylzinc,¹⁵⁷ and alkylzinc¹⁵⁸ reagents have been developed. The ferrocenyldiphosphine dppf has been found to be an especially good Pd ligand for these reactions.¹⁵⁹



¹⁵³ P. J. Stang, M. H. Kowalski, M. D. Schiavelli, and D. Longford, *J. Am. Chem. Soc.*, **111**, 3347 (1989); P. J. Stang and M. H. Kowalski, *J. Am. Chem. Soc.*, **111**, 3356 (1989); M. Portnoy and D. Milstein, *Organometallics*, **12**, 1665 (1993).

¹⁵⁴ M. P. Dang and G. Linstrumelle, *Tetrahedron Lett.*, 191 (1978).

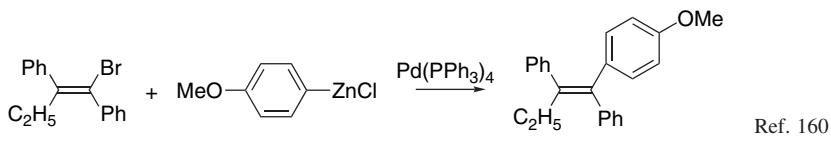
¹⁵⁵ M. Yamamura, I. Moritani, and S. Murahashi, *J. Organometal. Chem.*, **91**, C39 (1975).

¹⁵⁶ E. Negishi, A. O. King, and N. Okukado, *J. Org. Chem.*, **42**, 1821 (1977); E. Negishi, T. Takahashi, and A. O. King, *Org. Synth.*, **66**, 67 (1987).

¹⁵⁷ U. H. Lauk, P. Skrabal, and H. Zollinger, *Helv. Chim. Acta*, **68**, 1406 (1985); E. Negishi, T. Takahashi, S. Baba, D. E. Van Horn, and N. Okukado, *J. Am. Chem. Soc.*, **109**, 2393 (1987); J.-M. Duffault, J. Einhorn, and A. Alexakis, *Tetrahedron Lett.*, **32**, 3701 (1991).

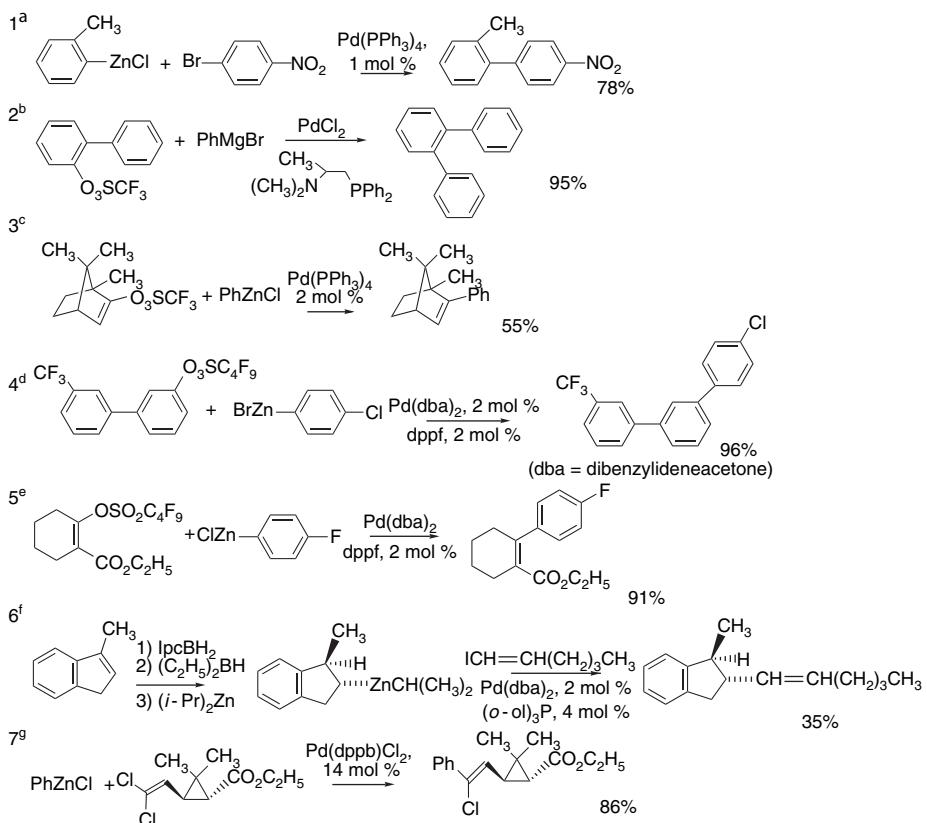
¹⁵⁸ E. Negishi, L. F. Valente, and M. Kobayashi, *J. Am. Chem. Soc.*, **102**, 3298 (1980).

¹⁵⁹ T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, and K. Hirotsu, *J. Am. Chem. Soc.*, **106**, 158 (1984).



Scheme 8.10 shows some representative coupling reactions with organomagnesium and organozinc reagents. Entry 1 shows a biaryl coupling accomplished using an arylzinc reagent. Entry 2 involves the use of a chelating ligand with an aryl triflate. The *bis*-phosphines dppe, dppp, and dppb were also effective for this coupling. Entry 3 is an example of use of a vinyl triflate. Entries 4 and 5 illustrate the use of perfluorobutanesulfonate (nonaflate) as an alternative leaving group to triflate. The organozinc

Scheme 8.10. Palladium-Catalyzed Cross Coupling of Organometallic Reagents with Halides and Sulfonates



a. E. Negishi, T. Takahashi, and A. O. King, *Org. Synth.*, **VIII**, 430 (1993).

b. T. Kamikawa and T. Hayashi, *Synlett*, 163 (1997).

c. G. Stork and R. C. A. Isaacs, *J. Am. Chem. Soc.*, **112**, 7399 (1990).

d. M. Rottlander and P. Knochel, *J. Org. Chem.*, **63**, 203 (1998).

e. F. Bellina, D. Ciucci, R. Rossi, and P. Vergamini, *Tetrahedron*, **55**, 2103 (1999).

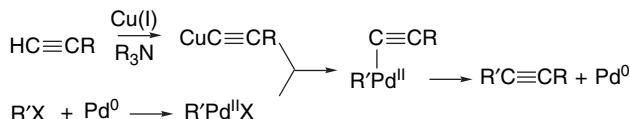
f. A. Boudier and P. Knochel, *Tetrahedron Lett.*, **40**, 687 (1999).

g. A. Minato, *J. Org. Chem.*, **56**, 4052 (1991).

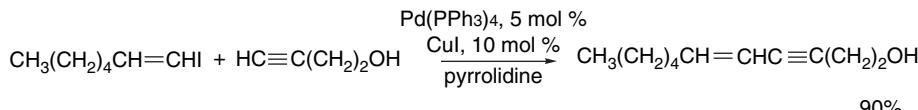
¹⁶⁰. R. B. Miller and M. I. Al-Hassan, *J. Org. Chem.*, **50**, 2121 (1985).

reagent in Entry 4 was prepared by the hydroboration route (see Section 7.3.1.1). The reaction in Entry 7 was used to prepare analogs of the pyrethrin insecticides. There was a substantial difference in the reactivity of the two chlorides, permitting the stereoselective synthesis.

There are a number of procedures for coupling of terminal alkynes with halides and sulfonates, a reaction that is known as the *Sonogashira reaction*.¹⁶¹ A combination of Pd(PPh₃)₄ and Cu(I) effects coupling of terminal alkynes with vinyl or aryl halides.¹⁶² The reaction can be carried out directly with the alkyne, using amines for deprotonation. The alkyne is presumably converted to the copper acetylide, and the halide reacts with Pd(0) by oxidative addition. Transfer of the acetylidy group to Pd results in reductive elimination and formation of the observed product.

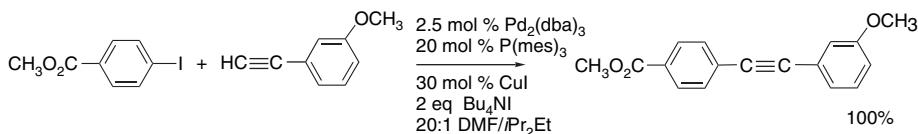


The original conditions used amines as solvents or cosolvents. Several other bases can replace the amine. Tetrabutylammonium hydroxide or fluoride can be used in THF (see Entry 1 in Scheme 8.11).¹⁶³ Tetrabutylammonium acetate is also effective with aryl iodides and EWG-substituted aryl bromides (Entry 2).¹⁶⁴ Use of alkenyl halides in this reaction has proven to be an effective method for the synthesis of enynes¹⁶⁵ (see also Entries 5 and 6 in Scheme 8.11).



Ref. 166

Several hindered phosphine ligands give enhanced reactivity. Aryl iodides can be coupled at low temperature using $\text{Pd}_2(\text{dba})_3$ and *tris*-(mesityl)phosphine.



Ref. 167

$\text{Pd}_2(\text{dba})_3$ with *tris-t*-butylphosphine is an effective catalyst and functions in the absence of copper.¹⁶⁸

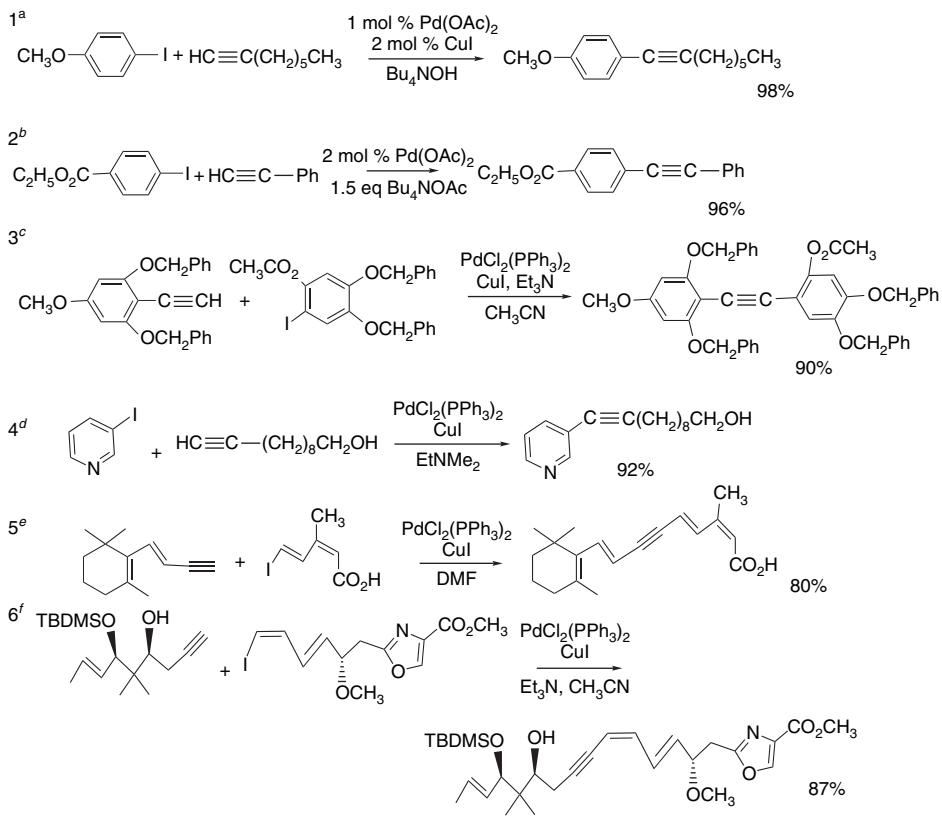
161. R. R. Tykwinski, *Angew. Chem. Int. Ed. Engl.*, **42**, 1566 (2003).
 162. K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.*, 4467 (1975).
 163. A. Mori, T. Shimada, T. Kondo, and A. Sekiguchi, *Synlett*, 649 (2001).
 164. S. Urgaonkar and J. G. Verkade, *J. Org. Chem.*, **69**, 5752 (2004).
 165. V. Ratovelomana and G. Linstrumelle, *Synth. Commun.*, **11**, 917 (1981); L. Crombie and M. A. Horsham, *Tetrahedron Lett.*, **28**, 4879 (1987); G. Just and B. O'Connor, *Tetrahedron Lett.*, **29**, 753 (1988); D. Guillerm and G. Linstrumelle, *Tetrahedron Lett.*, **27**, 5857 (1986).
 166. M. Alami, F. Ferri, and G. Linstrumelle, *Tetrahedron Lett.*, **34**, 6403 (1993).
 167. K. Nakamura, H. Okubo, and M. Yamaguchi, *Synlett*, 549 (1999).
 168. V. P. W. Bohm and W. A. Herrmann, *Eur. J. Org. Chem.*, 3679 (2000).

Scheme 8.11. Palladium-Catalyzed Coupling of Alkynes

727

SECTION 8.2

Reactions Involving
Organopalladium
Intermediates



a. S. Uragonkar and J. G. Verkade, *J. Org. Chem.*, **69**, 5752 (2004).

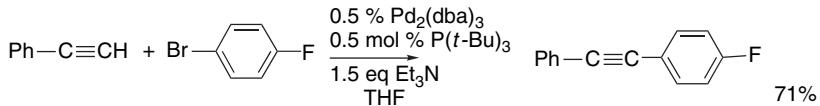
b. A. Mori, T. Shimada, T. Kondo, and A. Sekiguchi, *Synlett*, 649 (2001).

c. C. C. Li, Z. X. Xie, Y. D. Zhang, J. H. Chen, and Z. Yang, *Org. Lett.*, **5**, 3919 (2003).

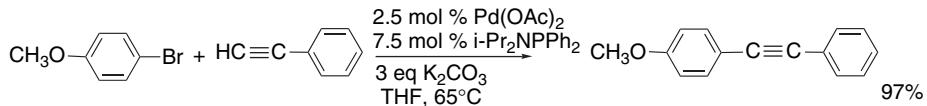
d. J. Krauss and F. Bracher, *Arch. Pharm.*, **337**, 371 (2004).

e. M. Abarbri, J. Thibonnet, J.-L. Parrain, and A. Duchene, *Tetrahedron Lett.*, **43**, 4703 (2002).

f. M. C. Hillier, A. T. Price, and A. I. Meyers, *J. Org. Chem.*, **66**, 6037 (2001).

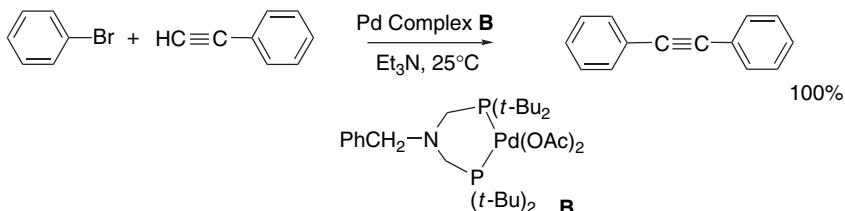


Various aminophosphines have also been found to catalyze coupling in the absence of copper.



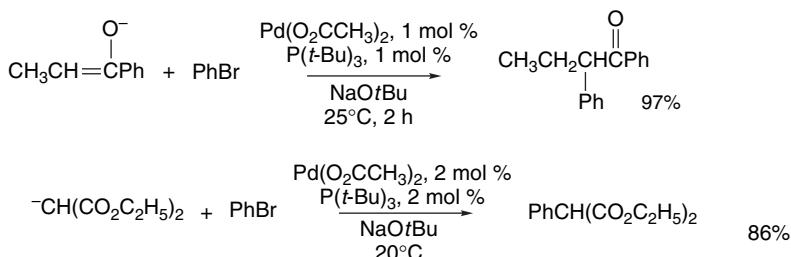
Ref. 169

¹⁶⁹ J. Cheng, Y. Sun, F. Wang, M. Guo, J.-H. Xu, Y. Pan, and Z. Zhang, *J. Org. Chem.*, **69**, 5428 (2004).

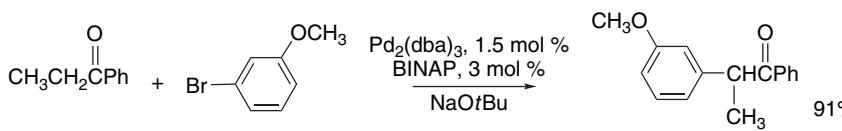


Ref. 170

8.2.3.2. Palladium-Catalyzed Arylation of Enolates. Very substantial progress has been made in the use of Pd-catalyzed cross coupling for arylation of enolates and enolate equivalents. This reaction provides an important method for arylation of enolates, which is normally a difficult transformation to accomplish.¹⁷¹ A number of phosphine ligands have been found to promote these reactions. Bulky trialkyl phosphines such as *tris*-(*t*-butyl)phosphine with a catalytic amount of Pd(OAc)₂ results in phenylation of the enolates of aromatic ketones and diethyl malonate.¹⁷²

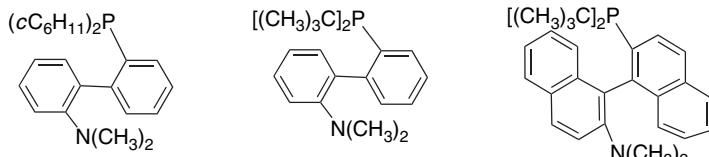


Phenylation has also been achieved with the diphosphine ligands BINAP and tol-BINAP.



Ref. 173

Several biphenylphosphines with 2'-amino substituents are also effective in arylation of ester enolates.¹⁷⁴ Among the esters that were successfully arylated were *t*-butyl acetate, *t*-butyl propanoate, and ethyl phenylacetate. The ester enolates were generated with LiHMDS.



¹⁷⁰ D. Mery, K. Heuze, and D. Astruc, *Chem. Commun.*, 1934 (2003).

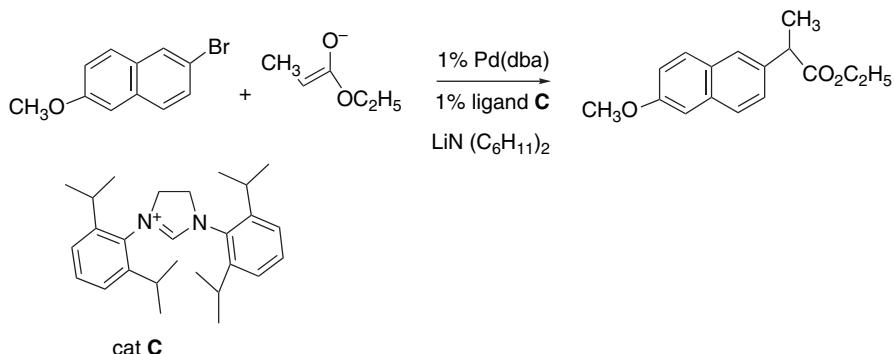
¹⁷¹ D. A. Culkin and J. F. Hartwig, *Acc. Chem. Res.*, **36**, 234 (2003).

¹⁷² M. Kawatsura and J. E. Hartwig, *J. Am. Chem. Soc.*, **121**, 1473 (1999).

¹⁷³ M. Palucki and S. L. Buchwald, *J. Am. Chem. Soc.*, **119**, 11108 (1997).

¹⁷⁴ W. A. Moradi and S. L. Buchwald, *J. Am. Chem. Soc.*, **123**, 7996 (2001).

Carbenoid imidazolidene ligands such as **C** can also be used in conjunction with Pd(dba)₂, and this method has been applied to α -arylpropanoic acids (NSAIDS) such as naproxen.¹⁷⁵

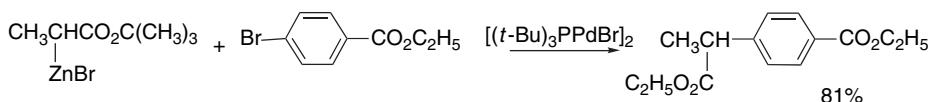


Highly arylated ketones have been prepared successfully. For example, arylation of the enolate of the deoxybenzoin **4** gives 1,1,2-triarylethanones that are related to substances such as tamoxifen.¹⁷⁶



Similar reactions have been carried out using polymer-supported catalysts.¹⁷⁷

Arylations have also been extended to zinc enolates of esters (Reformatsky reagents).¹⁷⁸



These conditions can also be applied to enolates prepared from α -halo amides.

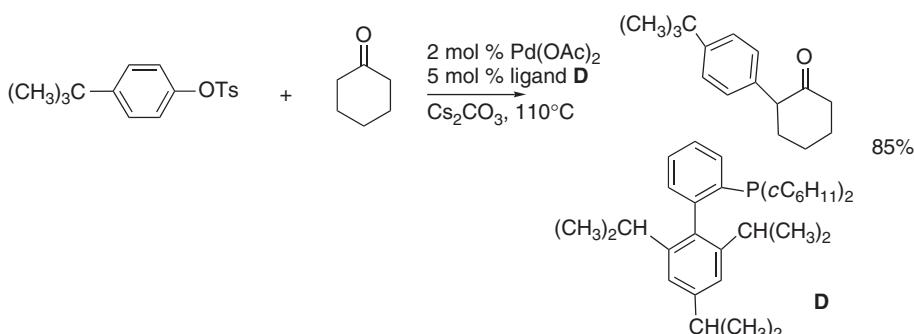
¹⁷⁵. M. Jorgensen, S. Lee, X. Liu, J. P. Wolkowski, and J. F. Hartwig, *J. Am. Chem. Soc.*, **124**, 12557 (2002).

¹⁷⁶. F. Churruca, R. SanMartin, I. Tellitu, and E. Dominguez, *Org. Lett.*, **4**, 1591 (2002).

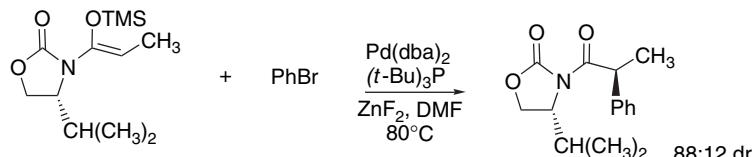
¹⁷⁷. F. Churruca, R. SanMartin, M. Carrill, I. Tellitu, and E. Dominguez, *Tetrahedron*, **60**, 2393 (2004).

¹⁷⁸. T. Hama, X. Liu, D. A. Culkin, and J. F. Hartwig, *J. Am. Chem. Soc.*, **125**, 11176 (2003).

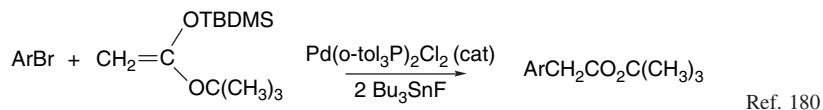
Enolate arylation has also been extended to aryl tosylates. The preferred catalyst includes a very bulky biphenyl phosphine **D**.¹⁷⁹



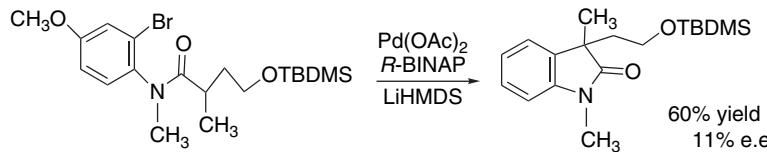
Conditions for arylation of enolate equivalents have also been developed. In the presence of ZnF_2 , silyl enol ethers, silyl ketene acetals, and similar compounds react. For example, the TMS derivatives of *N*-acyl oxazolidinones can be arylated.



Arylacetate esters have been generated by coupling aryl bromides with stannylenolates generated from silyl ketene acetals.



Intramolecular arylations are possible and several studies have examined the synthesis of biologically active compounds such as oxindoles.¹⁸¹ For example, a synthesis of physovenine has been reported using this methodology.



Ref. 182

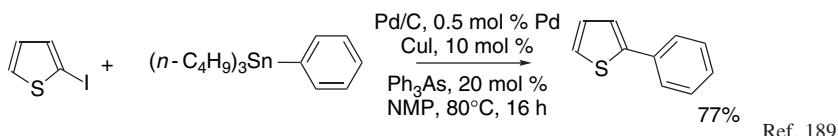
¹⁷⁹ H. N. Nguyen, X. Huang, and S. L. Buchwald, *J. Am. Chem. Soc.*, **125**, 11818 (2003).

¹⁸⁰ F. Agnelli and G. A. Sulikowski, *Tetrahedron Lett.*, **39**, 8807 (1998).

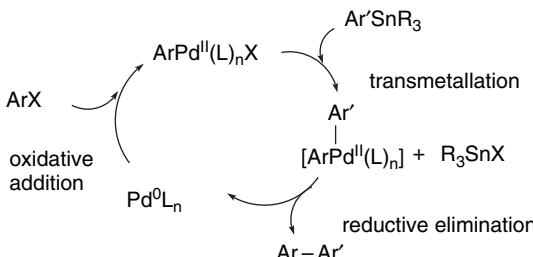
¹⁸¹ S. Lee and J. F. Hartwig, *J. Org. Chem.*, **66**, 3402 (2001).

¹⁸² T. Y. Zhang and H. Zhong, *Tetrahedron Lett.*, **43**, 1363 (2002).

8.2.3.3. Coupling with Stannanes. Another important group of cross-coupling reactions, known as *Stille reactions*, uses aryl and alkenyl stannanes as the organometallic component.¹⁸³ The reactions are carried out with Pd(0) catalysts in the presence of phosphine ligands and have proven to be very general with respect to the halides that can be used. Benzylic, aryl, alkenyl, and allylic halides can all be utilized,¹⁸⁴ and the groups that can be transferred from tin include alkyl, alkenyl, aryl, and alkynyl. The approximate order of the effectiveness of transfer of groups from tin is alkynyl > alkenyl > aryl > methyl > alkyl, so unsaturated groups are normally transferred selectively.¹⁸⁵ Subsequent studies have found better ligands, including *tris*(2-furyl)phosphine¹⁸⁶ and triphenylarsine.¹⁸⁷ Aryl-aryl coupling rates are increased by the presence of a Cu(I) cocatalyst,¹⁸⁸ which has led to a simplified protocol in which Pd-C catalyst, along with CuI and Ph₃As, gives excellent yields of biaryls.



The general catalytic cycle of the Stille reaction involves oxidative addition, transmetallation, and reductive elimination.



The role of the ligands is both to stabilize the Pd(0) state and to “tune” the reactivity of the palladium. The outline mechanism above does not specify many detailed aspects of the reaction that are important to understanding the effect of ligands, added salts, and solvents. Moreover, it does not address the stereochemistry, either in terms of the Pd center (tetracoordinate? pentacoordinate?, *cis*?, *trans*?) or of the reacting carbon groups (inversion?, retention?). Some of these issues are addressed by a more detailed mechanism.¹⁹⁰

¹⁸³ J. K. Stille, *Angew. Chem. Int. Ed. Engl.*, **25**, 508 (1986); T. N. Mitchell, *Synthesis*, 803 (1992); V. Farina, V. Krishnamurthy, and W. J. Scott, *Org. React.*, **50**, 1 (1998).

¹⁸⁴ F. K. Sheffy, J. P. Godschalk, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 4833 (1984); I. P. Beltskaya, *J. Organomet. Chem.*, **250**, 551 (1983); J. K. Stille and B. L. Groth, *J. Am. Chem. Soc.*, **109**, 813 (1987).

¹⁸⁵ J. W. Labadie and J. K. Stille, *J. Am. Chem. Soc.*, **105**, 6129 (1983).

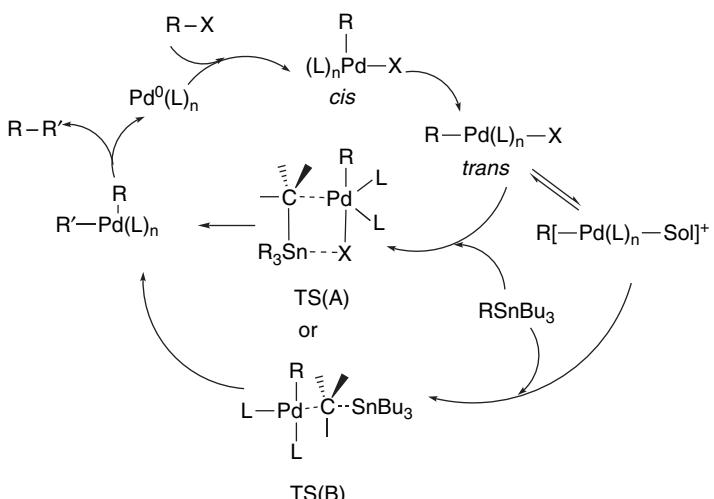
¹⁸⁶ V. Farina and B. Krishnan, *J. Am. Chem. Soc.*, **113**, 9585 (1991).

¹⁸⁷ V. Farina, B. Krishnan, D. R. Marshall, and G. P. Roth, *J. Org. Chem.*, **58**, 5434 (1993).

¹⁸⁸ V. Farina, S. Kapadia, B. Krishnan, C. Wang, and L. S. Liebeskind, *J. Org. Chem.*, **59**, 5905 (1994).

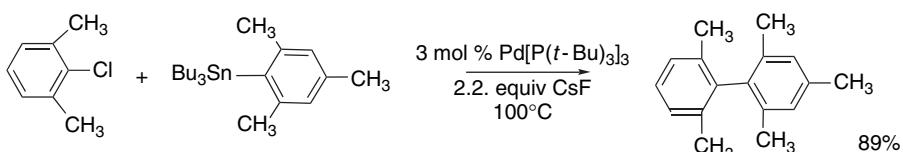
¹⁸⁹ G. P. Roth, V. Farina, L. S. Liebeskind, and E. Pena-Cabrera, *Tetrahedron Lett.*, **36**, 2191 (1995).

¹⁹⁰ P. Espinet and A. Echavarren, *Angew. Chem. Int. Ed. Engl.*, **43**, 4704 (2004).



The oxidative addition is considered to give a *cis* Pd complex that can rearrange to the more stable *trans* complex. The mechanism also takes account of the possibility of exchange of the ligands by solvent (or anions that may be present). This mechanism suggests that the transmetallation can occur either with retention (TS-A) or inversion (TS-B), which is consistent with experimental observations of both outcomes. The reductive elimination is believed to occur from a *cis* complex, and the ligands can play a role in promoting this configuration. The ligands can also affect the rate and position of the off-on equilibria. Thus there are several factors that affect the detailed kinetics of the reaction and these can be manipulated in optimization of the reaction conditions. Especially when triflates are used as the electrophilic reactant, added LiCl can have a beneficial effect. The chloride is believed to facilitate the oxidative addition step by reversible formation of an anionic complex that is more nucleophilic than the neutral species. (Compare with the anionic mechanisms for the Heck reaction on p. 716.)¹⁹¹ The harder triflate does not have this effect. Acetate ions can also accelerate the reaction.¹⁹² Copper salts are believed to shift the extent of ligation at the palladium by competing for the phosphine ligand.¹⁹³ The kinetics of Stille reactions catalyzed by triphenylarsine have been studied in some detail.¹⁹⁴ In this system, displacement of an arsine ligand by solvent DMF precedes the transmetallation step.

Various phosphine ligands have been employed. *Tris-(t-butyl)phosphine* is an excellent ligand and is applicable to both vinyl and arylstannanes, including sterically hindered ones. Aryl chlorides are reactive under these conditions.¹⁹⁵



¹⁹¹ C. Amatore, A. Jutand, and A. Suarez, *J. Am. Chem. Soc.*, **115**, 9531 (1993); C. Amatore and A. Jutand, *Acc. Chem. Res.*, **33**, 314 (2000).

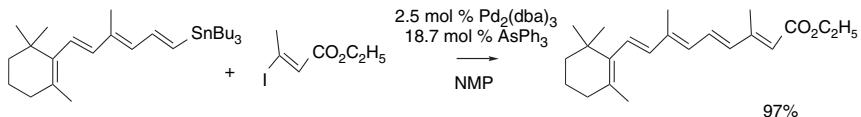
¹⁹² C. Amatore, E. Carre, A. Jutand, M. M'Barki, and G. Meyer, *Organometallics*, **14**, 5605 (1995).

¹⁹³ A. L. Casado and P. Espinet, *Organometallics*, **22**, 1305 (2003).

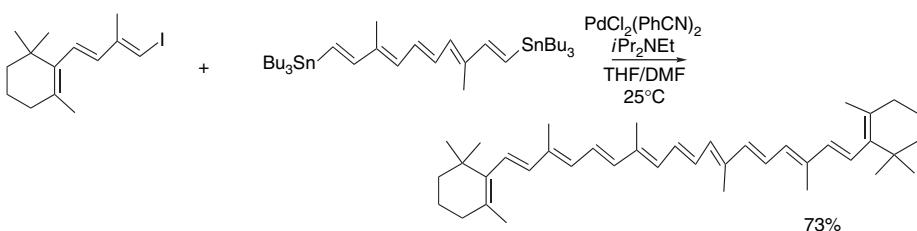
¹⁹⁴ C. Amatore, A. A. Bahsoun, A. Jutand, G. Meyer, N. A. Ndidi, and L. Ricard, *J. Am. Chem. Soc.*, **125**, 4212 (2003).

¹⁹⁵ A. F. Littke, L. Schwarz, and G. C. Fu, *J. Am. Chem. Soc.*, **124**, 6343 (2002).

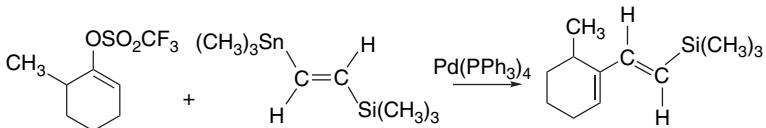
The Stille reaction can be used with alkenyl stannanes, alkenyl halides, and triflates,¹⁹⁶ and the reactions occur with retention of configuration at both the halide and stannane. These methods are applicable to stereospecific syntheses of materials such as the retinoids.¹⁹⁷



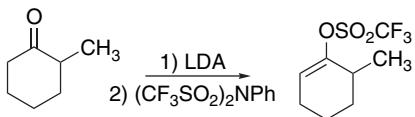
Carotene has been synthesized from a symmetrical 1,10-bis-(tri-*n*-butyl stannyly) decapentaene.¹⁹⁸



The versatility of Pd-catalyzed coupling of stannanes has been extended by the demonstration that alkenyl triflates are also reactive.¹⁹⁹



The alkenyl triflates can be prepared from ketones,²⁰⁰ and methods are available for regioselective preparation of alkenyl triflates from unsymmetrical ketones.²⁰¹



The coupling reaction can tolerate a number of functional groups, as illustrated by a step in the synthesis of the antibiotic nisamycin.

¹⁹⁶ W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, **108**, 3033 (1986).

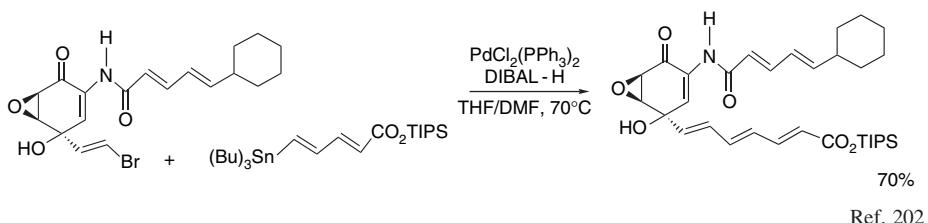
¹⁹⁷ B. Dominguez, B. Iglesias, and A. R. de Lera, *Tetrahedron*, **55**, 15071 (1999).

¹⁹⁸ B. Vaz, R. Alvarez, and A. R. de Lera, *J. Org. Chem.*, **67**, 5040 (2002).

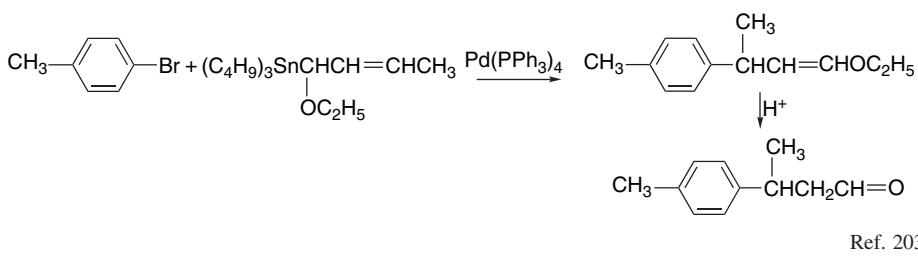
¹⁹⁹ W. J. Scott, G. T. Crisp, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 4630 (1984); W. J. Scott and J. E. McMurry, *Acc. Chem. Res.*, **21**, 47 (1988).

²⁰⁰ P. J. Stang, M. Hanack, and L. R. Subramanian, *Synthesis*, 85 (1982).

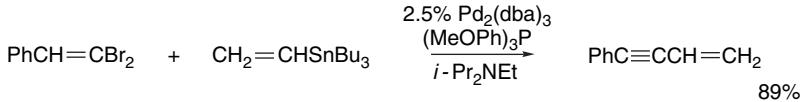
²⁰¹ J. E. McMurry and W. J. Scott, *Tetrahedron Lett.*, **24**, 979 (1983).



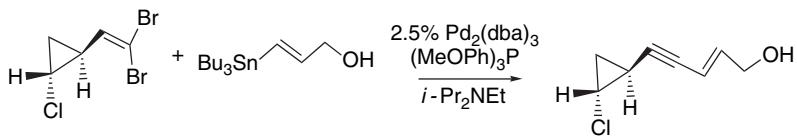
The Stille coupling reaction is very versatile with respect to the functionality that can be carried in both the halide and the tin reagent. Groups such as ester, nitrile, nitro, cyano, and formyl can be present, which permits applications involving “masked functionality.” For example, when the coupling reaction is applied to 1-alkoxy-2-butenylstannanes, the double-bond shift leads to a vinyl ether that can be hydrolyzed to an aldehyde.



Alkenylstannanes react with 1,1-dibromoalkenes to give enynes.²⁰⁴ These reactions are thought to involve elimination of the elements of HBr prior to reductive elimination.



This reaction has been used in the synthesis of a portion of callipeltoside, a substance with anticancer activity.



The most problematic cases for the Stille reaction involve coupling saturated systems. The tendency for β -elimination of alkylpalladium compounds requires special conditions. *Bis*-(dialkylamino)cyclohexylphosphines have shown considerable success

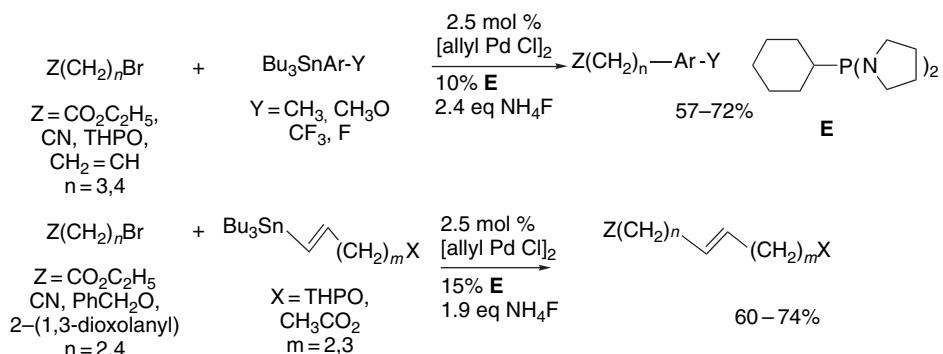
²⁰². P. Wipf and P. D. G. Coish, *J. Org. Chem.*, **64**, 5053 (1999).

²⁰³. A. Duchene and J.-P. Quintard, *Synth. Commun.*, **15**, 873 (1987).

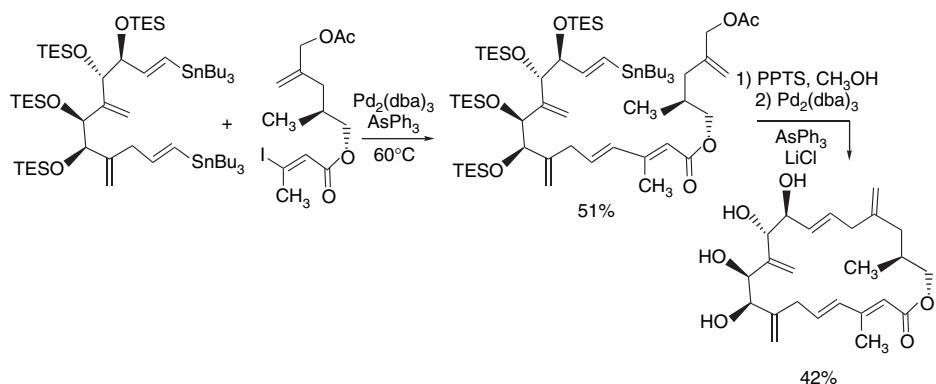
²⁰⁴. W. Shen and L. Wang, *J. Org. Chem.*, **64**, 8873 (1999).

²⁰⁵. H. F. Olivo, F. Velazquez, and H. C. Trevisan, *Org. Lett.*, **2**, 4055 (2000).

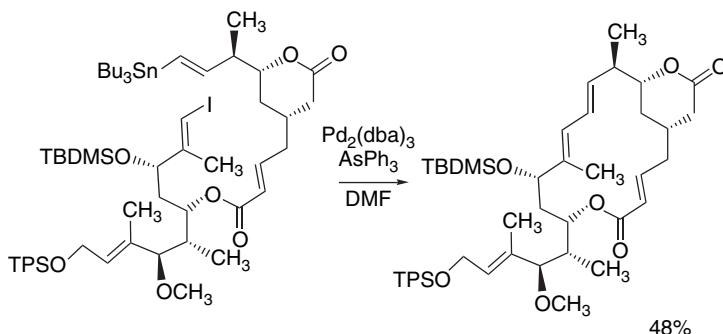
in promoting coupling of saturated primary bromides and iodides with alkenyl and aryl stannanes.²⁰⁶



The Stille reaction has been successfully applied to a number of macrocyclic ring closures.²⁰⁷ In a synthesis of amphotidinolide A, the two major fragments were coupled via a selective Stille reaction, presumably governed by steric factors. After deprotection the ring was closed by coupling the second vinyl stannane group with an allylic acetate.²⁰⁸



A similar cross-coupling reaction was used for macrocyclization in the synthesis of rhizoxin A.²⁰⁹



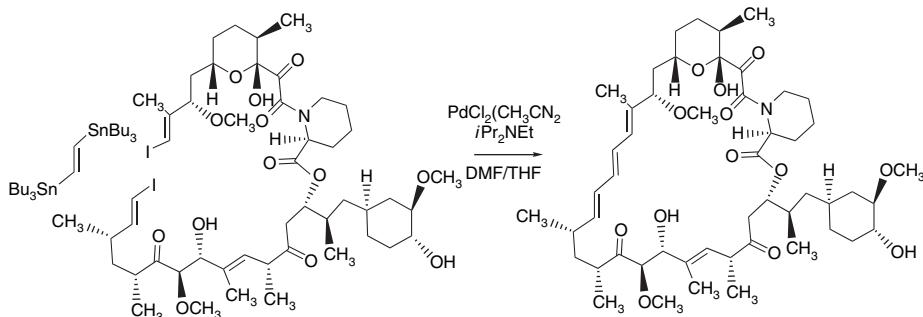
²⁰⁶ H. Tang, K. Menzel, and G. C. Fu, *Angew. Chem. Int. Ed. Engl.*, **42**, 5079 (2003).

²⁰⁷ M. A. J. Dunton and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1235 (1999).

²⁰⁸ H. W. Lam and G. Pattenden, *Angew. Chem. Int. Ed. Engl.*, **41**, 508 (2002).

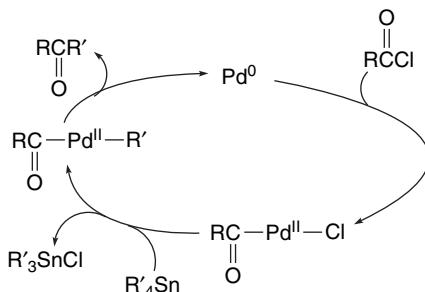
²⁰⁹ I. S. Mitchell, G. Pattenden, and J. P. Stonehouse, *Tetrahedron Lett.*, **43**, 493 (2002).

A striking example of a macrocyclic closure is found in the double “stitching” done in the final step of the synthesis of the immunosuppressant rapamycin. *Bis-1,2-(tri-*n*-butylstannyl)ethene* reacted with the diiodide to close a 31-membered ring in 28% yield at 70% conversion. The intermediate iodostannane (from a single coupling) was also isolated in about 30% yield and could be cyclized in a second step.²¹⁰



Some other examples of Pd-catalyzed coupling of organostannanes with halides and triflates are given in Scheme 8.12. Entries 1 and 2 are early examples that show that the reaction can be done with either ERG or EWG substituents on the aromatic ring. Entry 3 is an example of the use of an aryl triflate. Entry 5 was developed in the exploration of the synthetic potential of cyclobutendiones. Entries 6 to 11 are various alkenyl-alkenyl and alkenyl-aryl couplings using iodides and triflates. Entries 12 to 14 involve heterocyclic structures in the synthesis of several antibiotics. Entry 15 involves coupling of a protected glycoside with a vinyl triflate and an α -oxystannane. Entry 16 involves an alkynylstannane and generates a deca-1,6-diyne ring. Entries 17 and 18 show the use of allylic and benzylic bromides.

Procedures for the synthesis of ketones based on coupling of organostannanes with acyl halides have also been developed.²¹¹ The catalytic cycle is similar to that involved in coupling with aryl halides. The scope of compounds to which the reaction is applicable includes tetra-*n*-butylstannane. This example indicates that the reductive elimination step competes successfully with β -elimination.

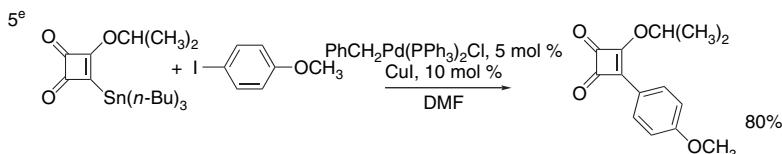
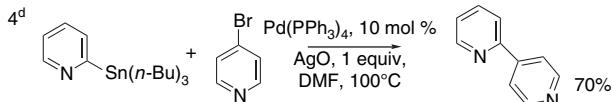
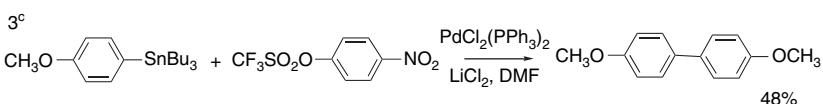
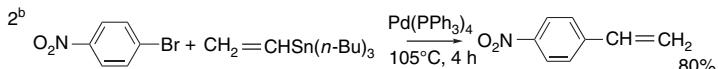
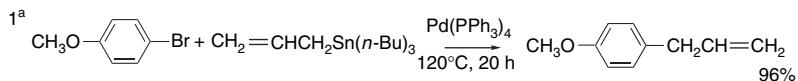


Scheme 8.13 gives some examples of these reactions.

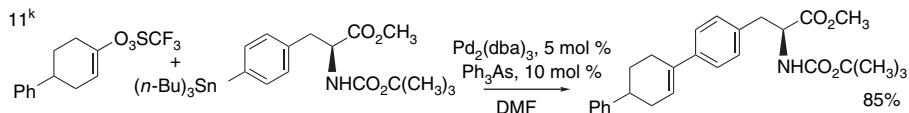
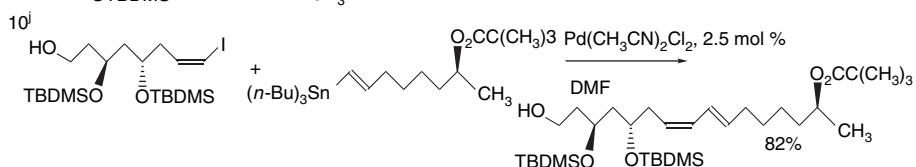
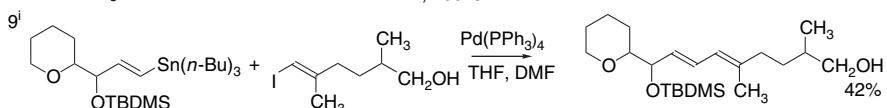
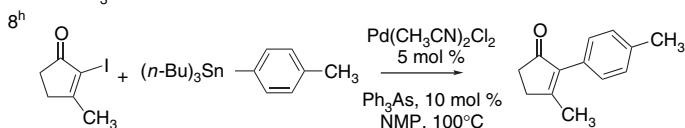
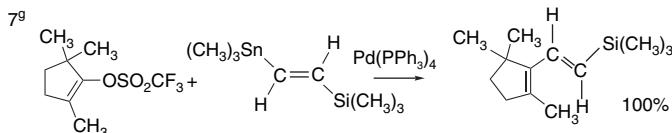
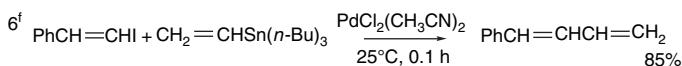
- ²¹⁰. K. C. Nicolaou, T. K. Chakraborty, A. D. Piscopio, N. Minowa, and P. Bertinato, *J. Am. Chem. Soc.*, **115**, 4419 (1993).
- ²¹¹. D. Milstein and J. K. Stille, *J. Org. Chem.*, **44**, 1613 (1979); J. W. Labadie and J. K. Stille, *J. Am. Chem. Soc.*, **105**, 6129 (1983).

Scheme 8.12. Palladium-Catalyzed Coupling of Stannanes with Halides and Sulfonates

A. Aryl halides

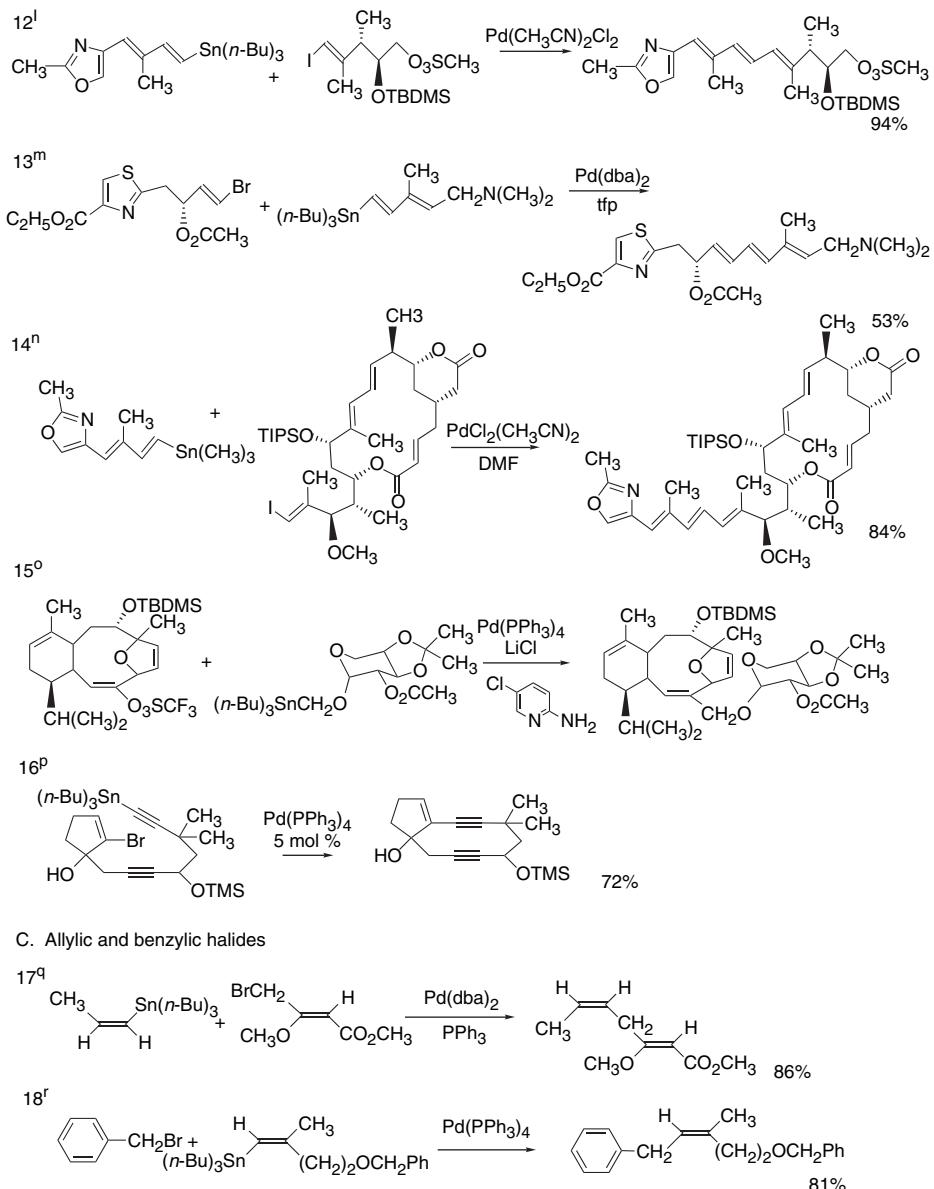


B. Alkenyl halides and sulfonates



(Continued)

Scheme 8.12. (Continued)



- a. M. Kosugi, K. Sasazawa, Y. Shimizu, and T. Migata, *Chem. Lett.*, 301 (1977).
- b. D. R. McKean, G. Parrinello, A. F. Renaldo, and J. K. Stille, *J. Org. Chem.*, **52**, 422 (1987).
- c. J. K. Stille, A. M. Echavarren, R. M. Williams, and J. A. Hendrix, *Org. Synth.*, **IX**, 553 (1998).
- d. J. Malm, P. Bjork, S. Gronowitz, and A.-B. Hornfeldt, *Tetrahedron Lett.*, **33**, 2199 (1992).
- e. L. S. Liebeskind and R. W. Fengl, *J. Org. Chem.*, **55**, 5359 (1990).
- f. J. K. Stille and B. L. Groh, *J. Am. Chem. Soc.*, **109**, 813 (1987).
- g. W. J. Scott, G. T. Crisp, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 4630 (1984).
- h. C. R. Johnson, J. P. Adams, M. P. Braun, and C. B. W. Senanayake, *Tetrahedron Lett.*, **33**, 919 (1992).
- i. E. Claus and M. Kalesse, *Tetrahedron Lett.*, **40**, 4157 (1999).
- j. A. B. Smith, III, and G. R. Ott, *J. Am. Chem. Soc.*, **120**, 3935 (1998).
- k. E. Morera and G. Ortar, *Synlett*, 1403 (1997).
- l. J. D. White, M. A. Holoboski, and N. J. Green, *Tetrahedron Lett.*, **38**, 7333 (1997).
- m. D. Romo, R. M. Rzasa, H. E. Shea, K. Park, J. M. Langenhan, L. Sun, A. Akhiezer, and J. O. Liu, *J. Am. Chem. Soc.*, **120**, 12237 (1998).

(Continued)

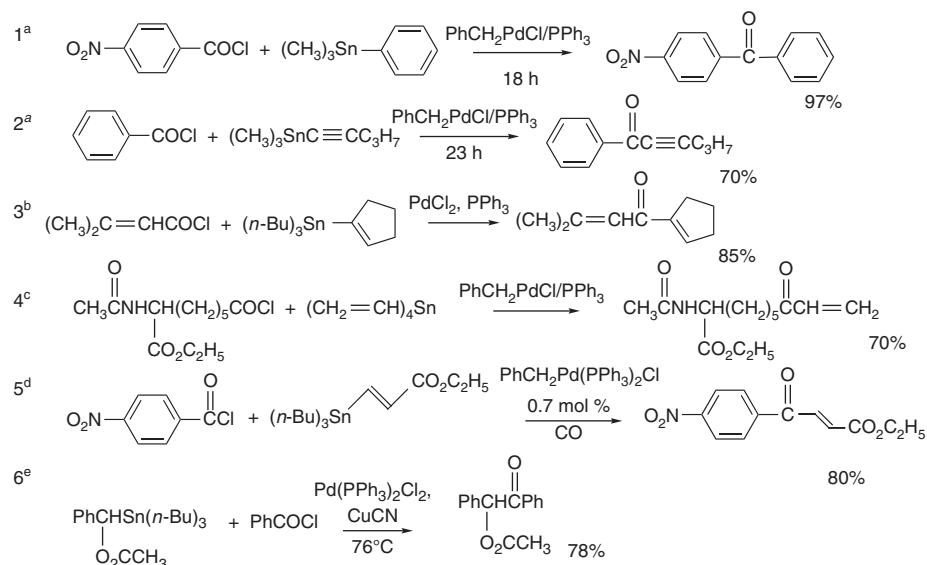
- n. J. D. White, P. R. Blakemore, N. J. Green, E. B. Hauser, M. A. Holoboski, L. E. Keown, C. S. N. Kolz, and B. W. Phillips, *J. Org. Chem.*, **67**, 7750 (2002).
- o. X.-T. Chen, B. Zhou, S. K. Bhattacharya, C. E. Gutteridge, T. R. R. Pettus, and S. Danishefsky, *Angew. Chem. Int. Ed. Engl.*, **37**, 789 (1999).
- p. M. Hirama, K. Fujiwara, K. Shigematsu, and Y. Fukazawa, *J. Am. Chem. Soc.*, **111**, 4120 (1989).
- q. F. K. Sheffy, J. P. Godschalk, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 4833 (1984).
- r. J. Hibino, S. Matsubara, Y. Morizawa, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, **25**, 2151 (1984).

SECTION 8.2

Reactions Involving
Organopalladium
Intermediates

8.2.3.4. Coupling with Organoboron Reagents. The *Suzuki reaction* is a palladium-catalyzed cross-coupling reaction in which the organometallic component is a boron compound.²¹² The organoboron compounds that undergo coupling include boronic acids,²¹³ boronate esters,²¹⁴ and boranes.²¹⁵ The overall mechanism is closely related to that of the other cross-coupling methods. The aryl halide or triflate reacts with the Pd(0) catalyst by oxidative addition. The organoboron compound serves as the source of the

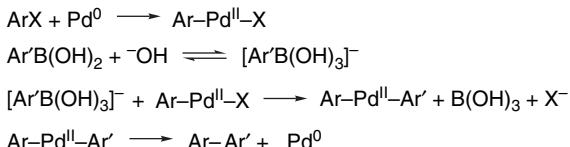
Scheme 8.13. Synthesis of Ketones from Acyl Chlorides and Stannanes



- a. J. W. Labadie, D. Tueting, and J. K. Stille, *J. Org. Chem.*, **48**, 4634 (1983).
 b. W. F. Goure, M. E. Wright, P. D. Davis, S. S. Labadie, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 6417 (1984).
 c. D. H. Rich, J. Singh, and J. H. Gardner, *J. Org. Chem.*, **48**, 432 (1983).
 d. A. F. Renaldo, J. W. Labadie, and J. K. Stille, *Org. Synth.*, **67**, 86 (1988).
 e. J. Ye, R. K. Bhatt, and J. R. Falck, *J. Am. Chem. Soc.*, **116**, 1 (1994).

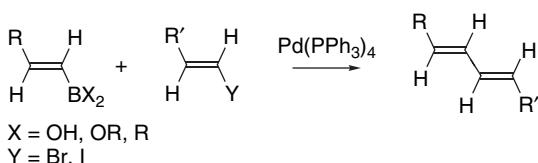
- ²¹² N. Miyaura, T. Yanagi, and A. Suzuki, *Synth. Commun.*, **11**, 513 (1981); A. Miyaura and A. Suzuki, *Chem. Rev.*, **95**, 2457 (1995); A. Suzuki, *J. Organomet. Chem.*, **576**, 147 (1999).
²¹³ W. R. Roush, K. J. Moriarty, and B. B. Brown, *Tetrahedron Lett.*, **31**, 6509 (1990); W. R. Roush, J. S. Warmus, and A. B. Works, *Tetrahedron Lett.*, **34**, 4427 (1993); A. R. de Lera, A. Torrado, B. Iglesias, and S. Lopez, *Tetrahedron Lett.*, **33**, 6205 (1992).
²¹⁴ T. Oh-e, N. Miyaura, and A. Suzuki, *Synlett*, 221 (1990); J. Fu, B. Zhao, M. J. Sharp, and V. Sniekus, *J. Org. Chem.*, **56**, 1683 (1991).
²¹⁵ T. Oh-e, N. Miyaura, and A. Suzuki, *J. Org. Chem.*, **58**, 2201 (1993); Y. Kobayashi, T. Shimazaki, H. Taguchi, and F. Sato, *J. Org. Chem.*, **55**, 5324 (1990).

second organic group by transmetalation, and the disubstituted Pd(II) intermediate then undergoes reductive elimination. It appears that either the oxidative addition or the transmetalation can be rate determining, depending on reaction conditions.²¹⁶ With boronic acids as reactants, base catalysis is normally required and is believed to involve the formation of the more reactive boronate anion in the transmetalation step.²¹⁷



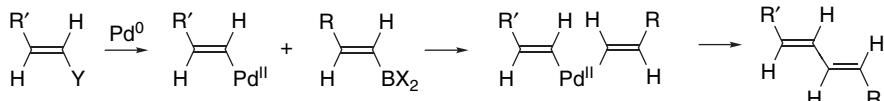
In some synthetic applications, specific bases such as Cs_2CO_3 ²¹⁸ or TlOH ²¹⁹ have been found preferable to NaOH . Cesium fluoride can play a similar function by forming fluoroborate anions.²²⁰ In addition to aryl halides and triflates, aryldiazonium ions can be the source of the electrophilic component in coupling with arylboronic acids.²²¹ Conditions for effecting Suzuki coupling in the absence of phosphine ligands have been developed.²²² One of the potential advantages of the Suzuki reaction, especially when boronic acids are used, is that the boric acid is a more innocuous by-product than the tin-derived by-products generated in Stille-type couplings.

Alkenylboronic acids, alkenyl boronate esters, and alkenylboranes can be coupled with alkenyl halides by palladium catalysts to give dienes.²²³

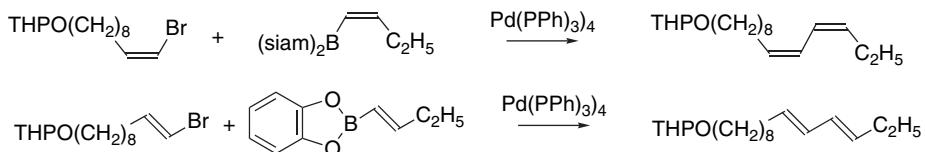


These reactions proceed with retention of double-bond configuration in both the boron derivative and the alkenyl halide. The oxidative addition by the alkenyl halide, transfer

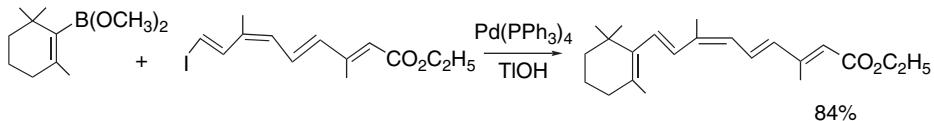
- ²¹⁶ G. B. Smith, G. C. Dezeny, D. L. Hughes, A. D. King, and T. R. Verhoeven, *J. Org. Chem.*, **59**, 8151 (1994).
- ²¹⁷ K. Matos and J. B. Soderquist, *J. Org. Chem.*, **63**, 461 (1998).
- ²¹⁸ A. F. Little and G. C. Fu, *Angew. Chem. Int. Ed. Engl.*, **37**, 3387 (1998).
- ²¹⁹ J. Uenishi, J.-M. Beau, R. W. Armstrong, and Y. Kishi, *J. Am. Chem. Soc.*, **109**, 4756 (1987); J. C. Anderson, H. Namli, and C. A. Roberts, *Tetrahedron*, **53**, 15123 (1997).
- ²²⁰ S. W. Wright, D. L. Hageman, and L. D. McClure, *J. Org. Chem.*, **59**, 6095 (1994).
- ²²¹ S. Darses, T. Jeffery, J.-P. Genet, J.-L. Brayer, and J.-P. Demoute, *Tetrahedron Lett.*, **37**, 3857 (1996); S. Darses, T. Jeffery, J.-L. Brayer, J.-P. Demoute, and J.-P. Genet, *Bull. Soc. Chim. Fr.*, **133**, 1095 (1996); S. Sengupta and S. Bhattacharyya, *J. Org. Chem.*, **62**, 3405 (1997).
- ²²² T. L. Wallow and B. M. Novak, *J. Org. Chem.*, **59**, 5034 (1994); D. Badone, M. B. R. Cardamone, A. Ielmini, and U. Guzzi, *J. Org. Chem.*, **62**, 7170 (1997).
- ²²³ (a) N. Miyaura, K. Yamada, H. Sugino, and A. Suzuki, *J. Am. Chem. Soc.*, **107**, 972 (1985); (b) N. Miyaura, M. Satoh, and A. Suzuki, *Tetrahedron Lett.*, **27**, 3745 (1986); (c) F. Bjorkling, T. Norin, C. R. Unelius, and R. B. Miller, *J. Org. Chem.*, **52**, 292 (1987).



Both alkanyl disiamylboranes and *B*-alkenylcatecholboranes also couple stereospecifically with alkenyl bromides.²²⁴

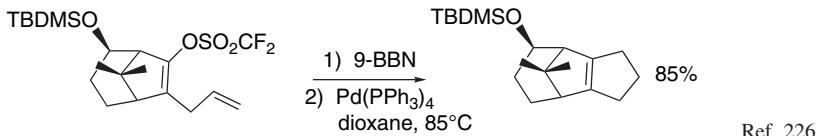


Boronate esters have been used for the preparation of polyunsaturated systems such as retinoic acid esters.



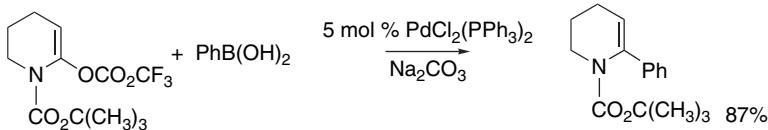
Ref. 225

Intramolecular Suzuki reactions have been done by hydroboration followed by coupling.



Ref. 226

Triflates prepared from *N*-alkoxycarbonyllactams can be coupled with aryl and alkanylboronic acids.²²⁷



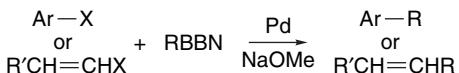
²²⁴ (a) N. Miyaura, K. Yamada, H. Sugimoto, and A. Suzuki, *J. Am. Chem. Soc.*, **107**, 972 (1985); (b) N. Miyaura, T. Ishiyama, M. Ishikawa, and A. Suzuki, *Tetrahedron Lett.*, **27**, 6369 (1986); (c) N. Miyaura, M. Satoh, and A. Suzuki, *Tetrahedron Lett.*, **27**, 3745 (1986); (d) Y. Satoh, H. Serizawa, N. Miyaura, S. Hara, and A. Suzuki, *Tetrahedron Lett.*, **29**, 1811 (1988).

²²⁵ Y. Pazos, B. Iglesias, and A. R. de Lera, *J. Org. Chem.*, **66**, 8483 (2001).

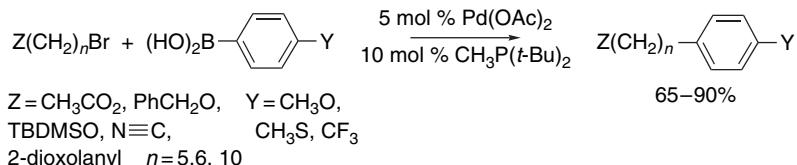
²²⁶ K. Shimada, M. Nakamura, T. Suzuka, J. Matsui, R. Tatsumi, K. Tsutsumi, T. Morimoto, H. Kurosawa, and K. Kakiuchi, *Tetrahedron Lett.*, **44**, 1401 (2003).

²²⁷ E. G. Occhiato, A. Trabocchi, and A. Guarna, *J. Org. Chem.*, **66**, 2459 (2001).

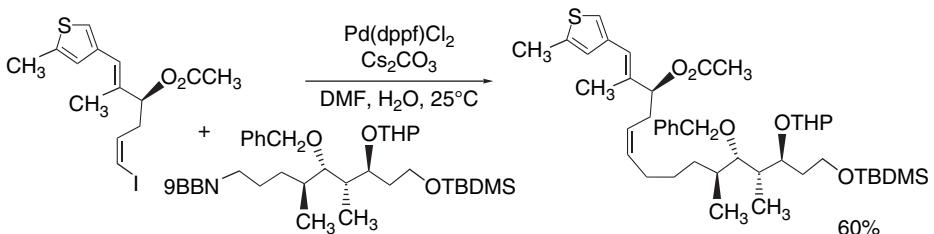
Alkyl substituents on boron in 9-BBN derivatives can be coupled with either vinyl or aryl halides through Pd catalysts.^{224b} This is an especially interesting reaction because of its ability to effect coupling of saturated alkyl groups. Palladium-catalyzed couplings of alkyl groups by most other methods often fail because of the tendency for β -elimination.



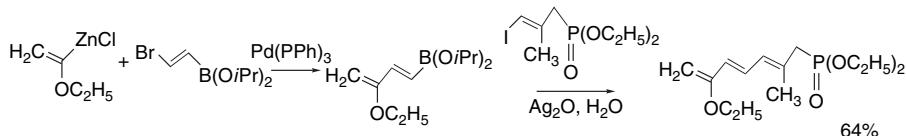
One catalyst that has been found amenable to alkyl systems is $\text{CH}_3\text{P}(t\text{-Bu})_2$ or the corresponding phosphonium salt.²²⁸ A range of substituted alkyl bromides were coupled with arylboronic acids.



Suzuki couplings have been used in the synthesis of complex molecules. For example, coupling of two large fragments of the epothilone A structure was accomplished in this way.²²⁹



A portion of the side chain of calyculin was prepared by a tandem reaction sequence that combined an alkenylzinc reagent with 2-bromoethenylboronate, followed by Suzuki coupling with a vinyl iodide in the same pot.²³⁰

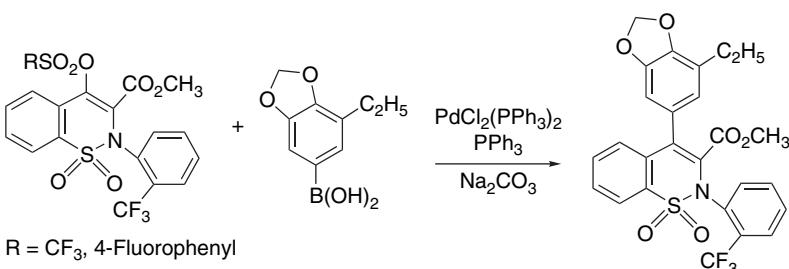


There are also several examples of the use of Suzuki reactions in scale-up synthesis of drug candidates. In the synthesis of CI-1034, an endothelin antagonist, a triflate,

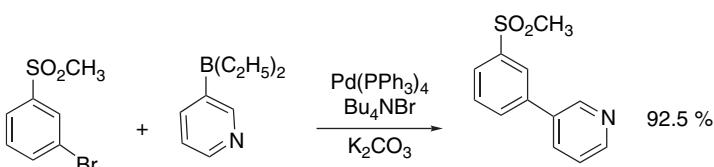
²²⁸ J. H. Kirchoff, M. R. Netherton, I. D. Hills, and G. C. Fu, *J. Am. Chem. Soc.*, **124**, 13662 (2002).

²²⁹ B. Zhu and J. S. Panek, *Org. Lett.*, **2**, 2575 (2000); see also A. Balog, D. Meng, T. Kamenecka, P. Bertinato, D.-S. Su, E. J. Sorensen, and S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.*, **35**, 2801 (1996).

²³⁰ A. B. Smith, III, G. K. Friestad, J. Barbosa, E. Bertounesque, J. J.-W. Duan, K. G. Hull, M. Iwashima, Y. Qui, P. G. Spoors, and B. A. Salvatore, *J. Am. Chem. Soc.*, **121**, 10478 (1999).

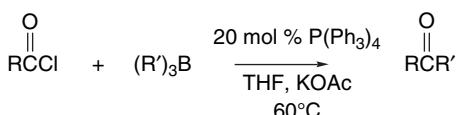


A coupling of a 3-pyridylborane was used in the synthesis of a potential CNS agent.²³² The product (278 kg) was isolated in 92.5% yield as the methanesulfonate salt.



Scheme 8.14 gives some examples of cross coupling using organoboron reagents. Entries 1 to 3 illustrate biaryl coupling. The conditions in Entry 1 are appropriate for the relatively unreactive chlorides. The conditions in Entries 2 and 3 involve no phosphine ligands. The reactions in Entries 4 and 5 illustrate the use of diazonium ions as reactants. Entry 6 illustrates the use of highly substituted reactants. Entry 7 involves use of a cyclic boronate ester. Entries 8 and 9 pertain to heteroaromatic rings. Entry 10 shows the use of a solid-supported reactant. Part B of Scheme 8.14 illustrates several couplings of alkenylboron reagents including catecholboranes (Entries 11 and 12), boronate esters (Entry 13), and boronic acids (Entries 14 and 15). The latter reaction was applied to the synthesis of a retinoate ester. Entry 16 employs a lactone-derived triflate. Entries 17 to 20 are examples of the use of Suzuki couplings in multistage synthesis. Entries 21 to 24 illustrate the applicability of the reaction to alkylboranes. Entry 25 applies phosphine-free conditions to an allylic bromide.

Ketones can also be prepared by palladium-catalyzed reactions of boranes or boronic acids with acyl chlorides. Both saturated and aromatic acyl chlorides react with trialkylboranes in the presence of $\text{Pd}(\text{PPh}_3)_4$.²³³



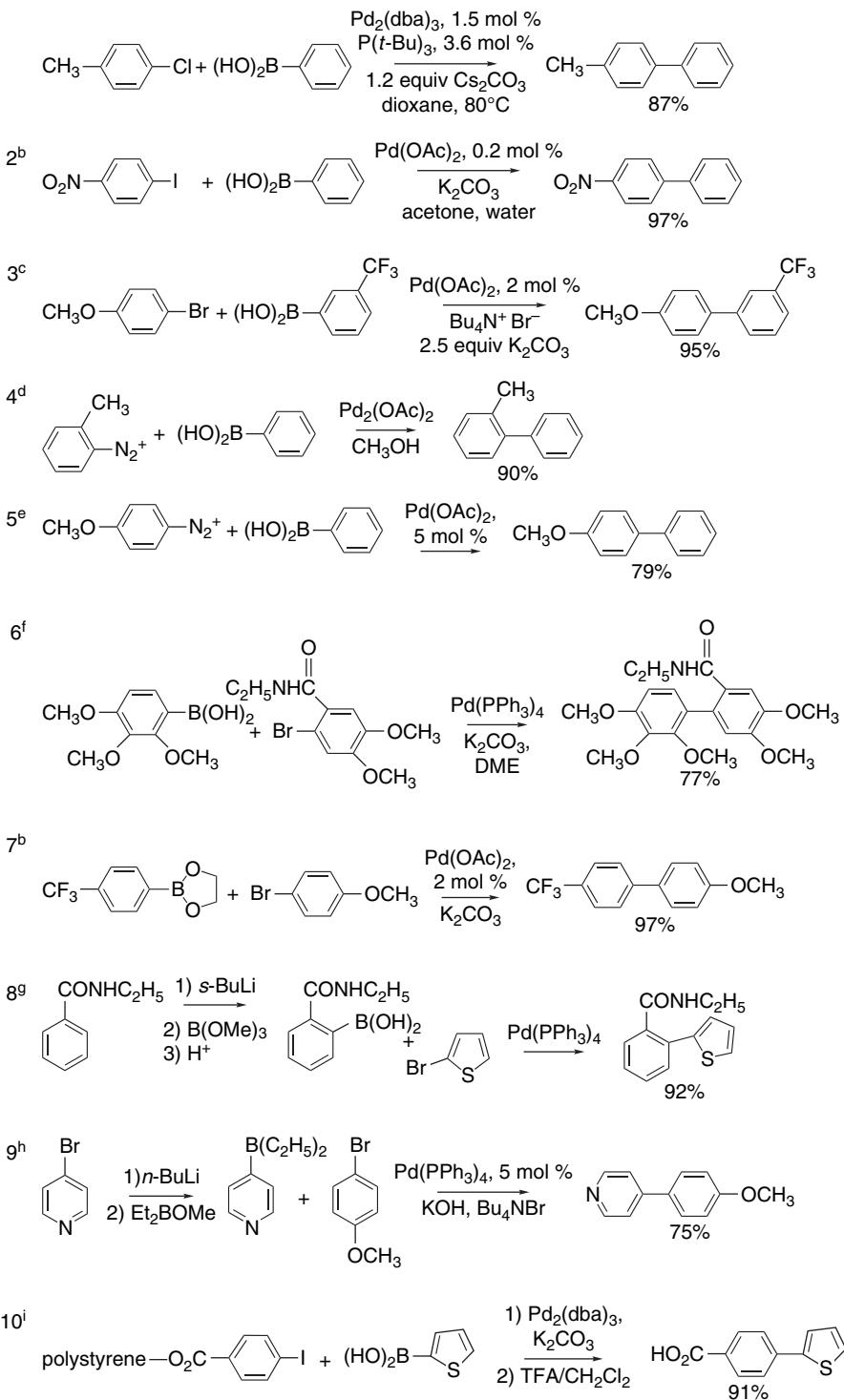
²³¹ T. E. Jacks, D. T. Belmont, C. A. Briggs, N. M. Horne, G. D. Kanter, G. L. Karrick, J. J. Krikke, R. J. McCabe, J. G. Mustakis, T. N. Nanniga, G. S. Risedorph, R. E. Seamans, R. Skeean, D. D. Winkle, and T. M. Zennie, *Org. Proc. Res. Dev.*, **8**, 201 (2004).

²³² M. F. Lipton, M. A. Mauragis, M. T. Maloney, M. F. Veley, D. W. Vander Bor, J. J. Newby, R. B. Appell, and E. D. Daugs, *Org. Proc. Res. Dev.*, **7**, 385 (2003).

²³³ G. W. Kabalka, R. R. Malladi, D. Tejedor, and S. Kelly, *Tetrahedron Lett.*, **41**, 999 (2000).

Scheme 8.14. Palladium-Catalyzed Cross Coupling of Organoboron Reagents

A. Biaryl formation

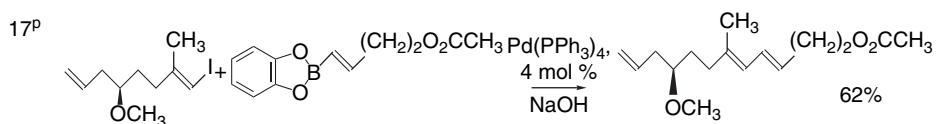
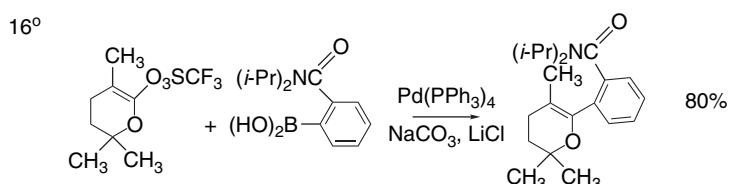
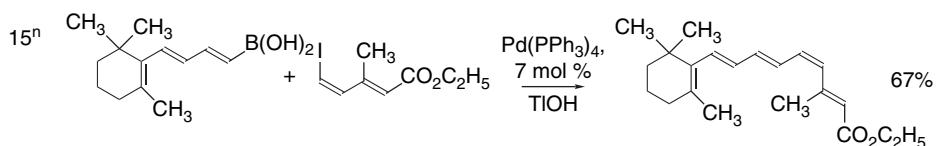
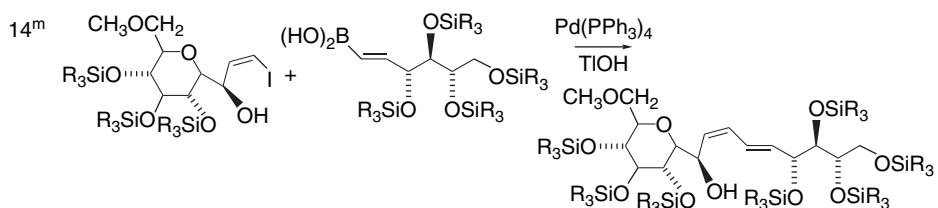
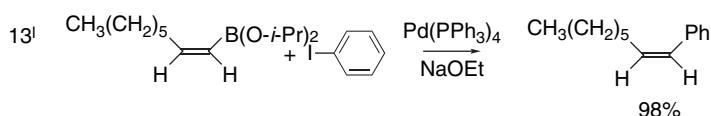
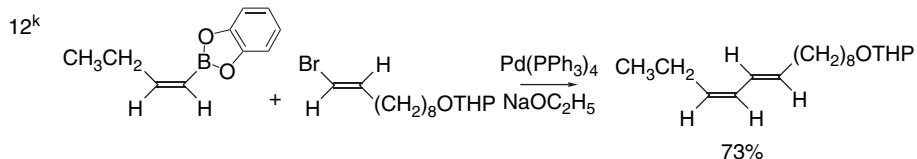
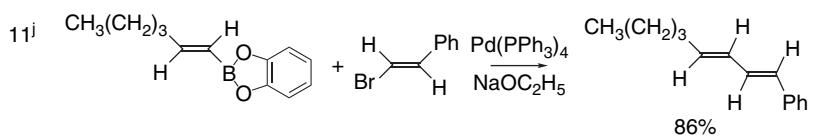


(Continued)

B. Alkenylboranes and alkylboronic acids

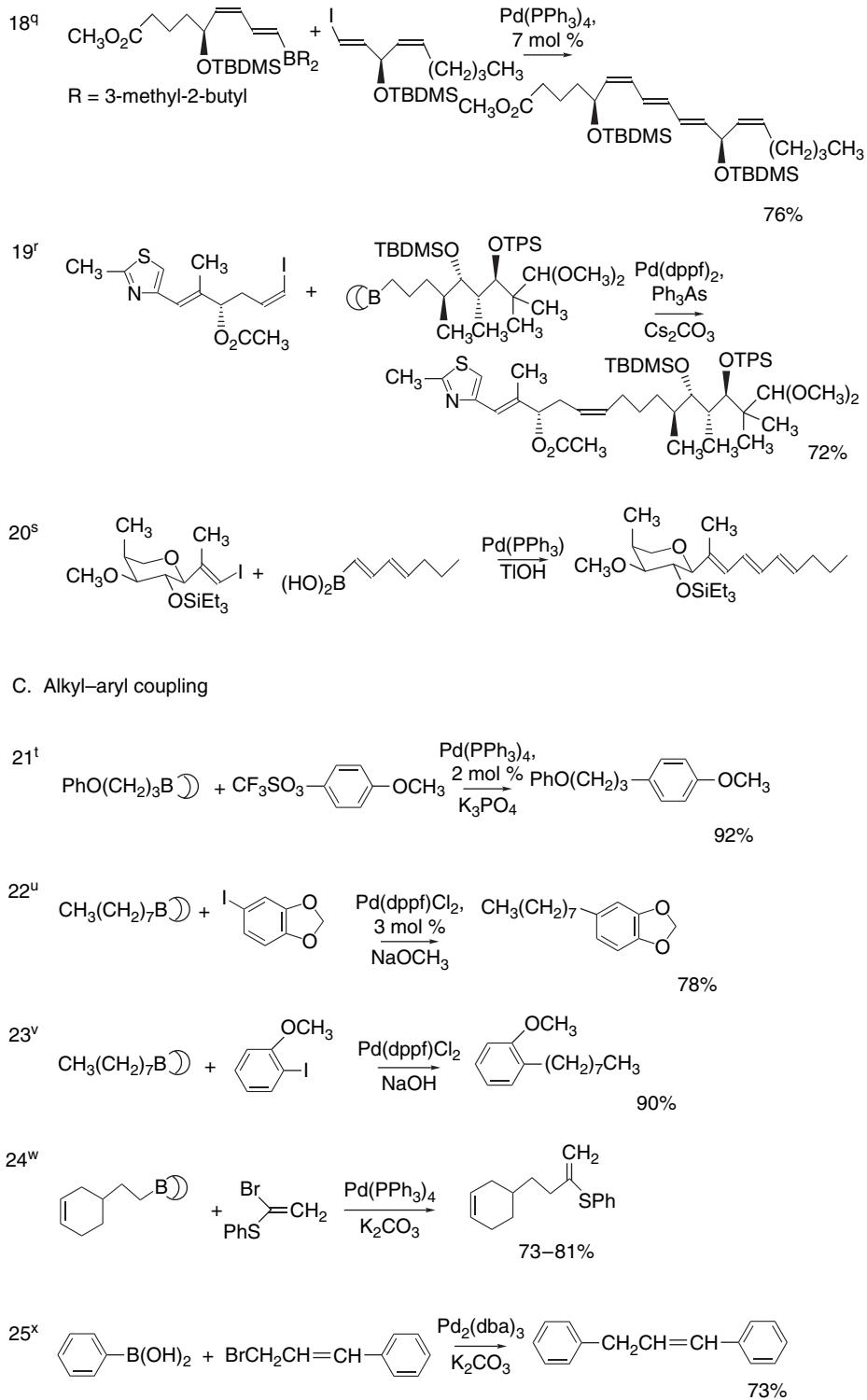
SECTION 8.2

Reactions Involving
Organopalladium
Intermediates



(Continued)

Scheme 8.14. (Continued)



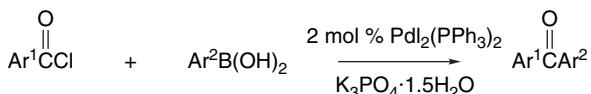
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SECTION 8.2

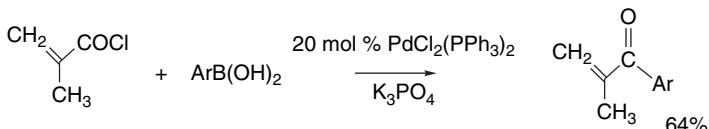
Reactions Involving
Organopalladium
Intermediates

- a. F. Little and G. C. Fu, *Angew. Chem. Int. Ed. Engl.*, **37**, 3387 (1998).
 b. T. L. Wallow and B. M. Novak, *J. Org. Chem.*, **59**, 5034 (1994).
 c. D. Badone, M. Baroni, R. Cardamone, A. Ielmini, and U. Guzzi, *J. Org. Chem.*, **62**, 7170 (1997).
 d. S. Darses, T. Jeffery, J.-L. Brayer, J.-P. Demoute, and J.-P. Genet, *Bull. Soc. Chim. Fr.* **133**, 1095 (1996); S. Sengupta and S. Bhattacharyya, *J. Org. Chem.*, **62**, 3405 (1997).
 e. S. Darses, T. Jeffery, J.-P. Genet, J.-L. Brayer, and J.-P. Demoute, *Tetrahedron Lett.*, **37**, 3857 (1996).
 f. B. I. Alo, A. Kandil, P. A. Patil, M. J. Sharp, M. A. Siddiqui, and V. Snieckus, *J. Org. Chem.*, **56**, 3763 (1991).
 g. J. Sharp and V. Snieckus, *Tetrahedron Lett.*, **26**, 5997 (1985).
 h. M. Ishikura, T. Ohta, and M. Terashima, *Chem. Pharm. Bull.*, **33**, 4755 (1985).
 i. J. W. Guiles, S. G. Johnson, and W. V. Murray, *J. Org. Chem.*, **61**, 5169 (1996).
 j. N. Miyaura, K. Yamada, H. Sugimoto, and A. Suzuki, *J. Am. Chem. Soc.*, **107**, 972 (1985).
 k. F. Bjorkling, T. Norin, C. R. Unelius, and R. B. Miller, *J. Org. Chem.*, **52**, 292 (1987).
 l. N. Miyaura, M. Satoh, and A. Suzuki, *Tetrahedron Lett.*, **27**, 3745 (1986).
 m. J. Uenishi, J.-M. Beau, R. W. Armstrong, and Y. Kishi, *J. Am. Chem. Soc.*, **109**, 4756 (1987).
 n. A. R. de Lera, A. Torrado, B. Iglesias, and S. Lopez, *Tetrahedron Lett.*, **33**, 6205 (1992).
 o. M. A. F. Brandao, A. B. de Oliveira, and V. Snieckus, *Tetrahedron Lett.*, **34**, 2437 (1993).
 p. J. D. White, T. S. Kim, and M. Nambu, *J. Am. Chem. Soc.*, **119**, 103 (1997).
 q. Y. Kobayashi, T. Shimazaki, H. Taguchi, and F. Sato, *J. Org. Chem.*, **55**, 5324 (1990).
 r. D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **119**, 10073 (1997).
 s. A. G. M. Barrett, A. J. Bennett, S. Menzer, M. L. Smith, A. J. P. White, and D. J. Williams, *J. Org. Chem.*, **64**, 162 (1999).
 t. T. Oh-e, N. Miyaura, and A. Suzuki, *J. Org. Chem.*, **58**, 2201 (1993).
 u. N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh, and A. Suzuki, *J. Am. Chem. Soc.*, **111**, 314 (1989).
 v. N. Miyaura, T. Ishiyama, M. Ishikawa, and A. Suzuki, *Tetrahedron Lett.*, **27**, 6369 (1986).
 w. T. Ishiyama, N. Miyaura, and A. Suzuki, *Org. Synth.*, **71**, 89 (1993).
 x. M. Moreno-Manas, F. Pajuelo, and R. Pleixarts, *J. Org. Chem.*, **60**, 2396 (1995).

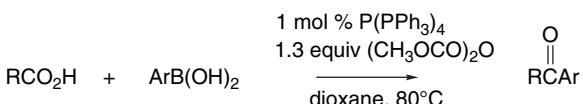
Aromatic acyl chlorides also react with arylboronic acids to give ketones.²³⁴



α,β -Unsaturated acyl chlorides can also be converted to ketones by reaction with arylboronic acids.²³⁵



Ketones can also be prepared directly from carboxylic acids by activation as mixed anhydrides by dimethyl dicarbonate.²³⁶ These conditions were used successfully with alkanoic and alkanedioic acids, as well as aromatic acids.



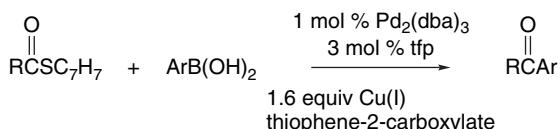
In all these reactions, the acylating reagent reacts with the active Pd(0) catalyst to give an acyl Pd(II) intermediate. Transmetalation by the organoboron derivative and reductive elimination generate the ketone.

²³⁴ Y. Urawa and K. Ogura, *Tetrahedron Lett.*, **44**, 271 (2003).

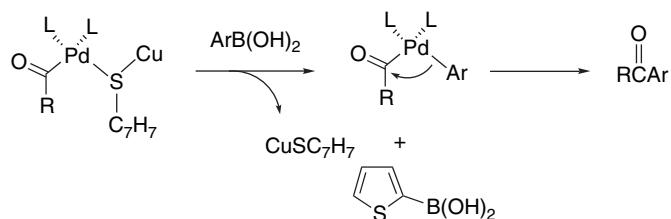
²³⁵ Y. Urawa, K. Nishiura, S. Souda, and K. Ogura, *Synthesis*, 2882 (2003).

²³⁶ R. Kakino, H. Narahashi, I. Shimizu, and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, **75**, 1333 (2002).

Ketones can also be prepared from 4-methylphenylthiol esters. These reactions require a stoichiometric amount of a Cu(I) salt and the thiophene-2-carboxylate was used.²³⁷



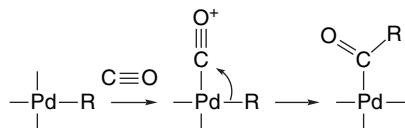
The copper salt is believed to function by promoting the transmetalation stage.



These reaction conditions were applicable to the thiol esters of alkanoic, heteroaromatic, and halogenated acetic acids.

8.2.4. Carbonylation Reactions

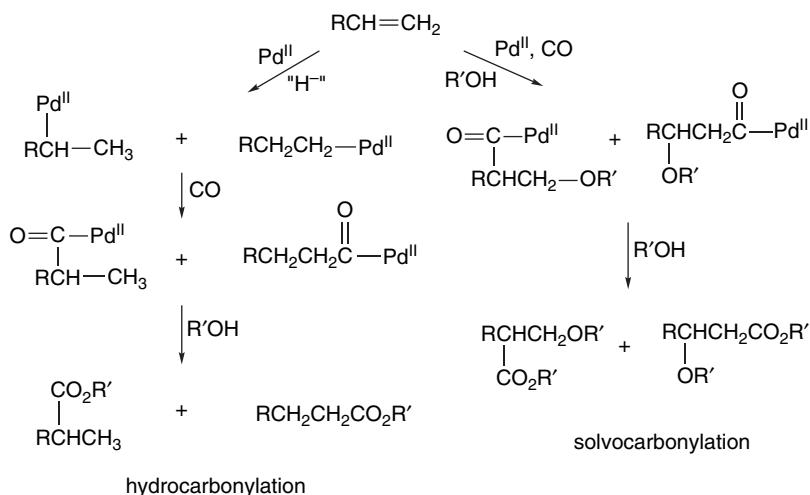
Carbonylation reactions involve coordination of carbon monoxide to palladium and a transfer of an organic group from palladium to the coordinated carbon monoxide.



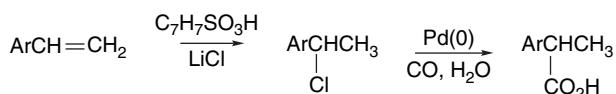
Carbonylation reactions have been observed using both Pd(II)-alkene complexes and σ -bonded Pd(II) species formed by oxidative addition. Under reductive conditions, the double bond can be *hydrocarbylated*, resulting in the formation of a carboxylic acid or ester.²³⁸ In nucleophilic solvents, the intermediate formed by *solvopalladation* is intercepted by carbonylation and addition of nucleophilic solvent. In both types of reactions, regioisomeric products are possible.

²³⁷ L. S. Liebeskind and J. Srogl, *J. Am. Chem. Soc.*, **122**, 11260 (2000).

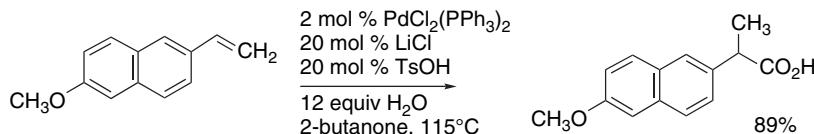
²³⁸ B. El Ali and H. Alper, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 2, E. Negishi and A. de Meijere, eds., Wiley-Interscience, New York, 2000, pp. 2333–2349.



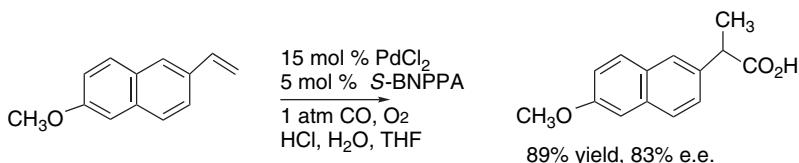
8.2.4.1. Hydrocarbonylation. The hydrocarbonylation reaction can be applied to the synthesis of α -arylpropanoic acids of the NSAIDS type.²³⁹ For this synthesis to be effective, selective carbonylation of the more-substituted sp^2 carbon is required. Although many carbonylation conditions are unselective, $PdCl_2(PPh_3)_2$ with *p*-toluenesulfonic acid and LiCl achieves excellent selectivity, which is thought to involve the formation of a benzylic chloride intermediate.



Naproxen can be synthesized in 89% yield with 97.5% regioselectivity under these conditions.



This reaction has been done with good enantioselectivity using 1, 1'-binaphthyl-2, 2'-diyl hydrogen phosphate (BNPPA) as a chiral ligand.²⁴⁰

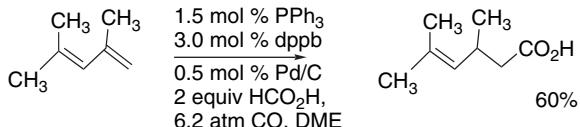


When conducting hydrocarbonylations with dienes, it was found that a mixture of nonchelating and bidentate phosphine ligands was beneficial.²⁴¹

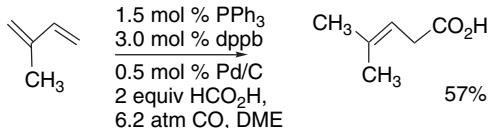
²³⁹ A Seayad, S. Jayasree, and R. V. Chaudhari, *Org. Lett.*, **1**, 459 (1999).

²⁴⁰ H. Alper and N. Hamel, *J. Am. Chem. Soc.*, **112**, 2803 (1990).

²⁴¹ G. Vasapollo, A. Somasunderam, B. El Ali, and H. Alper, *Tetrahedron Lett.*, **35**, 6203 (1994).

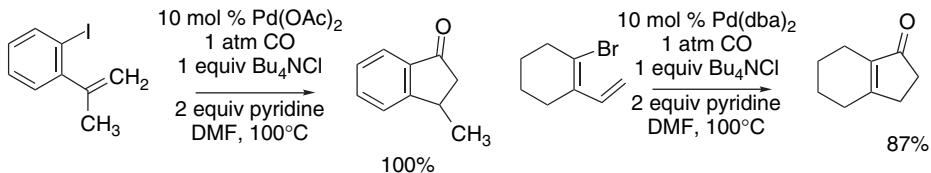


In some cases double-bond migration was noted, as for isoprene.

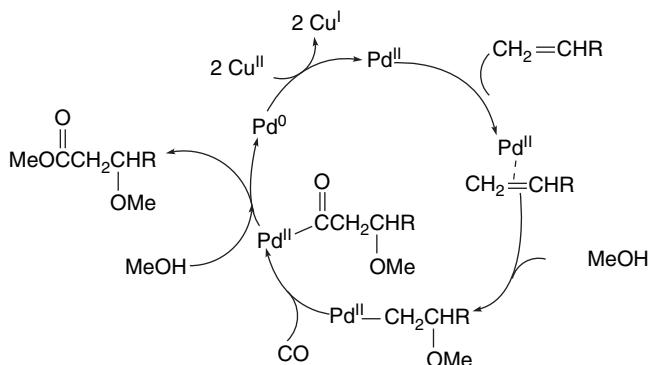


Esters can be formed when the hydrocarbonylation reaction is carried out in an alcohol.²⁴² Although hydrocarbonylation is the basis for conversion of alkenes to carboxylic acids on an industrial scale, it has seen only limited application in laboratory synthesis.

Olefin hydrocarbonylation can be used in conjunction with oxidative addition to prepare indanones and cyclopentenones, but the reaction is limited to terminal alkenes.²⁴³



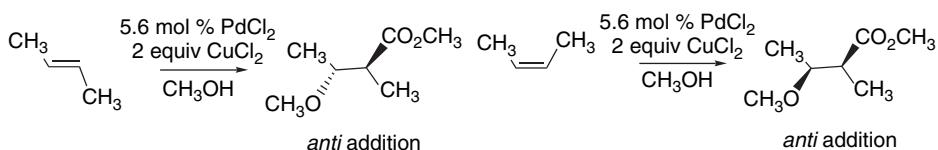
8.2.4.2. Solvocarbonylation. In solvocarbonylation, a substituent is introduced by a nucleophilic addition to a π complex of the alkene. The acylpalladium intermediate is then captured by a nucleophilic solvent such as an alcohol. A catalytic process that involves Cu(II) reoxidizes Pd(0) to the Pd(II) state.²⁴⁴



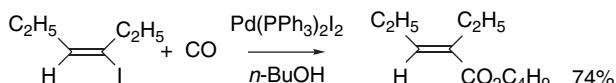
²⁴² S. Oi, M. Nomura, T. Aiko, and Y. Inoue, *J. Mol. Catal. A.*, **115**, 289 (1997).

²⁴³ S. V. Gagnier and R. C. Larock, *J. Am. Chem. Soc.*, **125**, 4804 (2003).

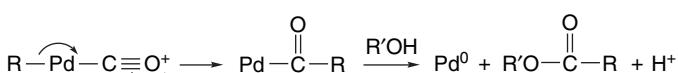
²⁴⁴ D. E. James and J. K. Stille, *J. Am. Chem. Soc.*, **98**, 1810 (1976).



Organopalladium(II) intermediates generated from halides or triflates by oxidative addition react with carbon monoxide in the presence of alcohols to give carboxylic acids²⁴⁶ or esters.²⁴⁷



The carbonyl insertion step takes place by migration of the organic group from the metal to the coordinated carbon monoxide, generating an acylpalladium species. This intermediate can react with nucleophilic solvent, releasing catalytically active Pd(0).

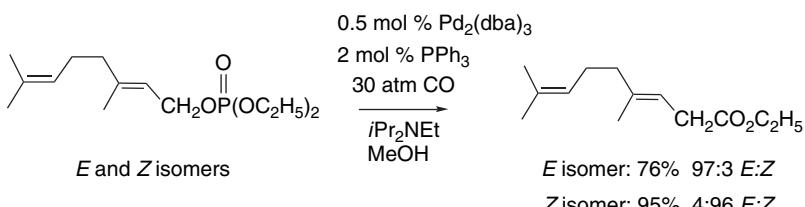


The detailed mechanisms of such reactions have been shown to involve addition and elimination of phosphine ligands. The efficiency of individual reactions can often be improved by careful choice of added ligands.

Allylic acetates and phosphates can be readily carbonylated.²⁴⁸ Carbonylation usually occurs at the less-substituted end of the allylic system and with inversion of configuration in cyclic systems.



The reactions are accelerated by bromide salts, which are thought to exchange for acetate in the π -allylic complex. The reactions of acyclic compounds occur with minimal *E*:*Z* isomerization. This result implies that the π -allyl intermediate is captured by carbonylation faster than *E*:*Z* isomerization occurs.



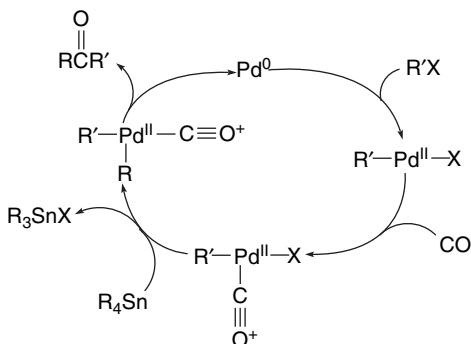
²⁴⁵ D. E. James, L. F. Hines, and J. K. Stille, *J. Am. Chem. Soc.*, **98**, 1806 (1976).

²⁴⁶ S. Cacchi and A. Lupi, *Tetrahedron Lett.*, **37**, 3939 (1992).

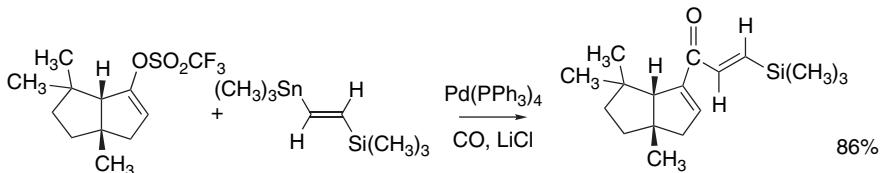
²⁴⁷ A. Schoenberg, I. Bartoletti, and R. F. Heck, *J. Org. Chem.*, **39**, 3318 (1974); S. Cacchi, E. Morena, and G. Ortar, *Tetrahedron Lett.*, **26**, 1109 (1985).

²⁴⁸ S. Murahashi, Y. Imada, Y. Taniguchi, and S. Higashiura, *J. Org. Chem.*, **58**, 1538 (1993).

Coupling of organostannanes with halides in a carbon monoxide atmosphere leads to ketones by incorporation of a carbonylation step.²⁴⁹ The catalytic cycle is similar to that involved in the coupling of alkyl or aryl halides. These reactions involve a migration of one of the organic substituents to the carbonyl carbon, followed by reductive elimination.



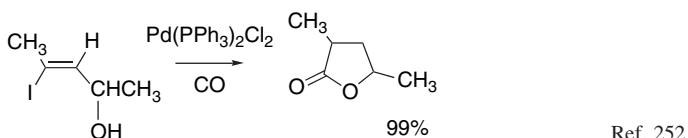
This method can also be applied to alkenyl triflates.



Ref. 250

Carbonylation reactions can be carried out with a boronic acid as the nucleophilic component.²⁵¹

Application of the carbonylation reaction to halides with appropriately placed hydroxy groups leads to lactone formation. In this case the acylpalladium intermediate is trapped intramolecularly.



Ref. 252

Carbonylation can also be carried out as a tandem reaction in intramolecular Heck reactions.

²⁴⁹ M. Tanaka, *Tetrahedron Lett.*, 2601 (1979); D. Milstein and J. K. Stille, *J. Org. Chem.*, **44**, 1613 (1979); J. W. Labadie and J. K. Stille, *J. Am. Chem. Soc.*, **105**, 6129 (1983); A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, **110**, 1557 (1988).

²⁵⁰ G. T. Crisp, W. J. Scott, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 7500 (1984).

²⁵¹ T. Ishiyama, H. Kizaki, N. Miyaura, and A. Suzuki, *Tetrahedron Lett.*, **34**, 7595 (1993); T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki, and N. Miyaura, *J. Org. Chem.*, **63**, 4726 (1998).

²⁵² A. Cowell and J. K. Stille, *J. Am. Chem. Soc.*, **102**, 4193 (1980).

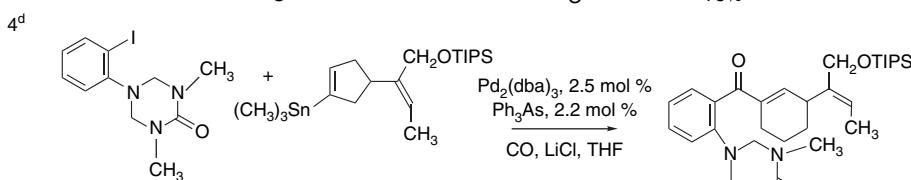
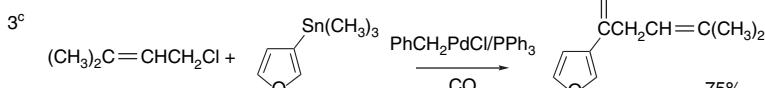
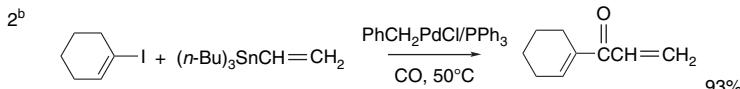
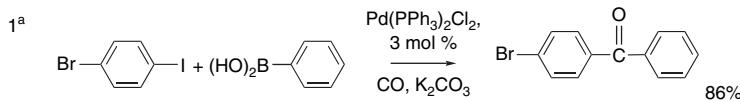
Scheme 8.15. Synthesis of Ketones, Esters, Carboxylic Acids, and Amides by Palladium-Catalyzed Carbonylation and Acylation

753

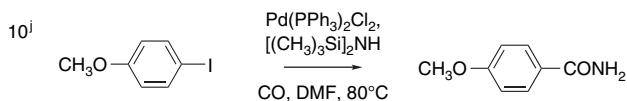
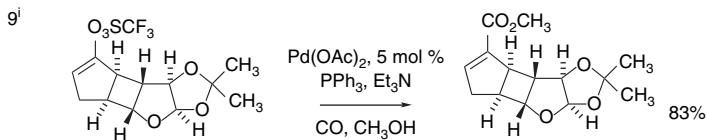
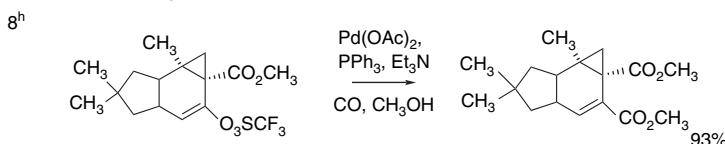
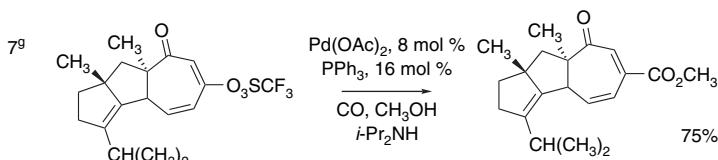
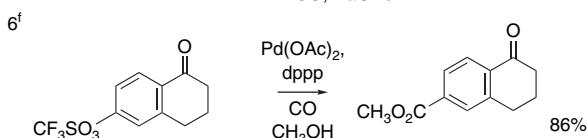
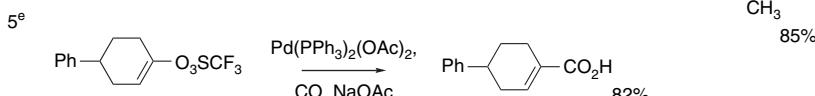
SECTION 8.2

Reactions Involving
Organopalladium
Intermediates

A. Ketones by carbonylation



B. Esters, acids and amides

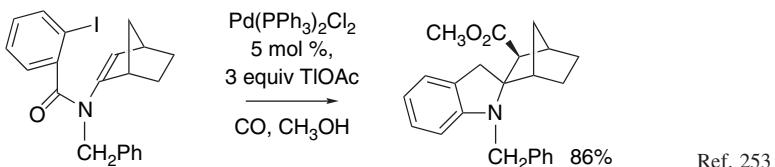


(Continued)

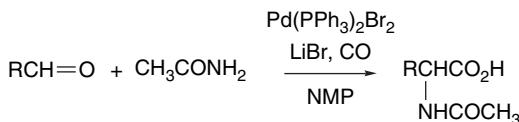
CHAPTER 8

Reactions Involving
Transition Metals

- a. T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki, and N. Miyaura, *J. Org. Chem.*, **63**, 4726 (1998).
 b. W. F. Goure, M. E. Wright, P. D. Davis, S. S. Labadie, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 6417 (1984).
 c. F. K. Sheffy, J. P. Godschalk, and J. K. Stille, *J. Am. Chem. Soc.*, **106**, 4833 (1984).
 d. S. R. Angle, J. M. Fervig, S. D. Knight, R. W. Marquis, Jr., and L. E. Overman, *J. Am. Chem. Soc.*, **115**, 3966 (1993).
 e. S. Cacchi and A. Lupi, *Tetrahedron Lett.*, **33**, 3939 (1992).
 f. U. Gerlach and T. Wollmann, *Tetrahedron Lett.*, **33**, 5499 (1992).
 g. B. B. Snider, N. H. Vo, and S. V. O'Neill, *J. Org. Chem.*, **63**, 4732 (1998).
 h. S. K. Thompson and C. H. Heathcock, *J. Org. Chem.*, **55**, 3004 (1990).
 i. A. B. Smith III, G. A. Sulikowski, M. M. Sulikowski, and K. Fujimoto, *J. Am. Chem. Soc.*, **114**, 2567 (1992).
 j. E. Morea and G. Ortar, *Tetrahedron Lett.*, **39**, 2835 (1998).



It can also be done by in situ generation of other types of electrophiles. For example, good yields of *N*-acyl α -amino acids are formed in a process in which an amide and aldehyde combine to generate a carbinolamide and, presumably, an acyliminium ion. The organopalladium intermediate is then carbonylated prior to reaction with water.²⁵⁴



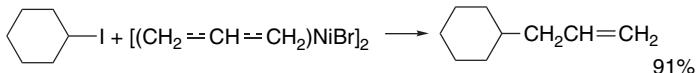
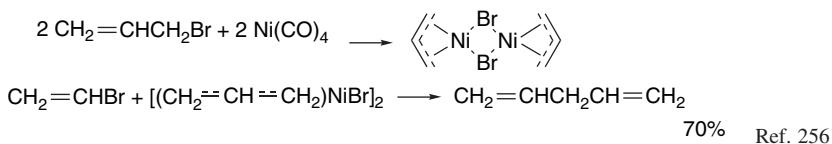
Scheme 8.15 gives some examples of carbonylations and acylations involving stannane reagents. Entry 1 illustrates synthesis of diaryl ketones from aryl halides and arylboronic acids. Entries 2 and 3 use stannanes as the nucleophilic reactant. Entry 4 was carried out as part of the synthesis of the *Strychnos* alkaloid akuammicine. The triazinone ring serves to protect the aromatic amino group. Entries 5 and 6 introduce carboxy groups using vinyl and aryl triflates, respectively. Entries 8 and 9 are similar reactions carried out during the course of multistage syntheses. Entry 10 illustrates direct formation of an amide by carbonylation.

8.3. Reactions Involving Other Transition Metals

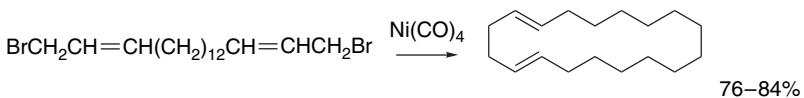
8.3.1. Organonickel Compounds

The early synthetic processes using organonickel compounds involved the coupling of allylic halides, which react with nickel carbonyl, $\text{Ni}(\text{CO})_4$, to give π -allyl complexes. These complexes react with a variety of halides to give coupling products.²⁵⁵

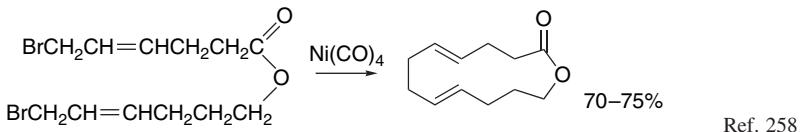
- ²⁵³. R. Grigg, P. Kennewall, and A. J. Teasdale, *Tetrahedron Lett.*, **33**, 7789 (1992).
²⁵⁴. M. Beller, M. Eckert, F. M. Vollmuller, S. Bogdanovic, and H. Geissler, *Angew. Chem. Int. Ed. Engl.*, **36**, 1494 (1997); M. Beller, W. A. Maradi, M. Eckert, and H. Neumann, *Tetrahedron Lett.*, **40**, 4523 (1999).
²⁵⁵. M. F. Semmelhack, *Org. React.*, **19**, 115 (1972).



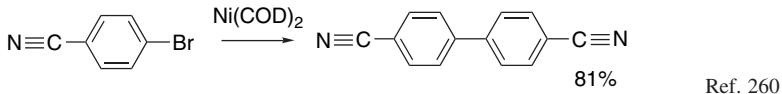
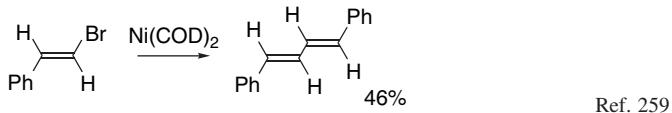
Nickel carbonyl effects coupling of allylic halides when the reaction is carried out in very polar solvents such as DMF or DMSO. This coupling reaction has been used intramolecularly to bring about cyclization of *bis*-allylic halides and was found useful in the preparation of large rings.



Ref. 257



Nickel carbonyl is an extremely toxic substance, but a number of other nickel reagents with generally similar reactivity can be used in its place. The Ni(0) complex of 1,5-cyclooctadiene, Ni(COD)₂, can effect coupling of allylic, alkenyl, and aryl halides.



Tetrakis-(triphenylphosphine)nickel(0) is an effective reagent for coupling aryl halides,²⁶¹ and medium rings can be formed in intramolecular reactions.

²⁵⁶ E. J. Corey and M. F. Semmelhack, *J. Am. Chem. Soc.*, **89**, 2755 (1967).

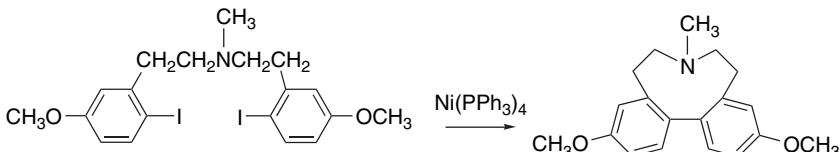
²⁵⁷ E. J. Corey and E. K. W. Wat, *J. Am. Chem. Soc.*, **89**, 2757 (1967).

²⁵⁸ E. J. Corey and H. A. Kirst, *J. Am. Chem. Soc.*, **94**, 667 (1972).

²⁵⁹ M. F. Semmelhack, P. M. Helquist, and J. D. Gorzynski, *J. Am. Chem. Soc.*, **94**, 9234 (1972).

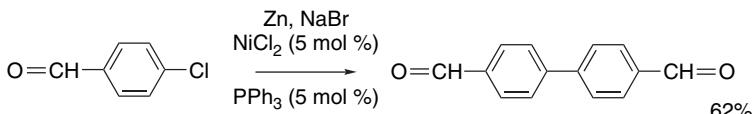
²⁶⁰ M. F. Semmelhack, P. M. Helquist, and L. D. Jones, *J. Am. Chem. Soc.*, **93**, 5908 (1971).

²⁶¹ A. S. Kende, L. S. Liebeskind, and D. M. Braitsch, *Tetrahedron Lett.*, 3375 (1975).

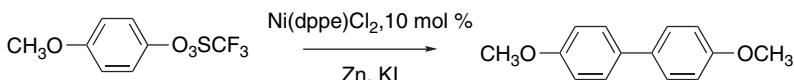


Ref. 262

The homocoupling of aryl halides and triflates can be made catalytic in nickel by using zinc as a reductant for *in situ* regeneration of the active Ni(0) species.

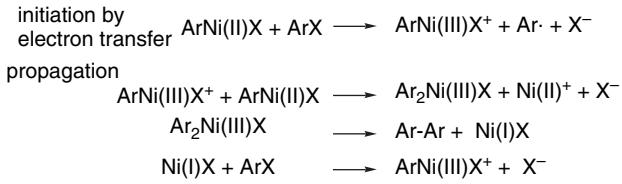


Ref. 263



Ref. 265

Mechanistic study of the aryl couplings has revealed the importance of the changes in redox state that are involved in the reaction.²⁶⁵ Ni(I), Ni(II), and Ni(III) states are believed to be involved. Changes in the degree of coordination by phosphine ligands are also thought to be involved, but these have been omitted in the mechanism shown here. The detailed kinetics of the reaction are inconsistent with a mechanism involving only formation and decomposition of a biarylnickel(II) intermediate. The key aspects of the mechanism are: (1) the oxidative addition involving a Ni(I) species, and (2) the reductive elimination that occurs via a diaryl Ni(III) intermediate and regenerates Ni(I).



Nickel(II) salts are able to catalyze the coupling of Grignard reagents with alkenyl and aryl halides. A soluble *bis*-phosphine complex, $\text{Ni(dppe)}_2\text{Cl}_2$, is a particularly effective catalyst.²⁶⁶ The main distinction between this reaction and Pd-catalyzed cross

²⁶². S. Brandt, A. Marfat, and P. Helquist, *Tetrahedron Lett.*, 2193 (1979).

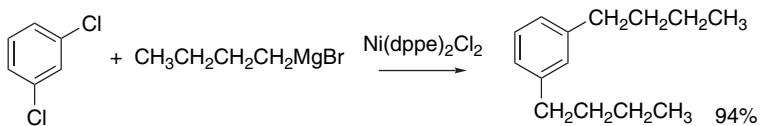
²⁶³. M. Zembayashi, K. Tamao, J. Yoshida, and M. Kumada, *Tetrahedron Lett.*, 4089 (1977); I. Colon and D. R. Kelly, *J. Org. Chem.*, **51**, 2627 (1986).

²⁶⁵. A. Jutand and A. Mosleh, *J. Org. Chem.*, **62**, 261 (1997).

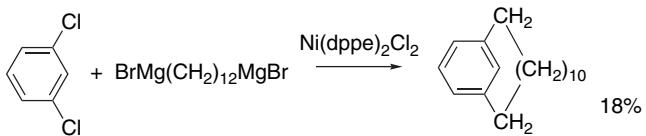
²⁶⁵. T. T. Tsou and J. K. Kochi, *J. Am. Chem. Soc.*, **101**, 7547 (1979); L. S. Hegedus and D. H. P. Thompson, *J. Am. Chem. Soc.*, **107**, 5663 (1985); C. Amatore and A. Jutand, *Organometallics*, **7**, 2203 (1988).

²⁶⁶. K. Tamao, K. Sumitani, and M. Kumada, *J. Am. Chem. Soc.*, **94**, 4374 (1972).

coupling is that the nickel reaction can be more readily extended to saturated alkyl groups because of a reduced tendency toward β -elimination.

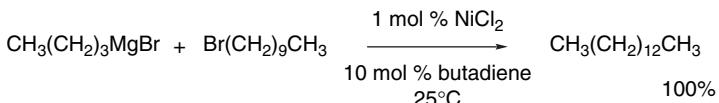


The reaction has been applied to the synthesis of cyclophane-type structures by use of dihaloarenes and Grignard reagents from α, ω -dihalides.

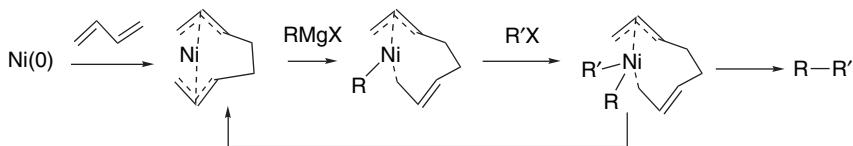


Ref. 267

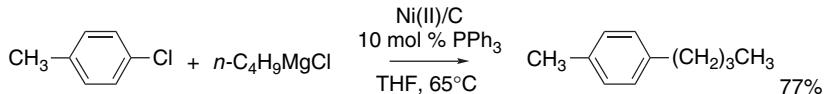
Recent discoveries have expanded the utility of nickel-catalyzed coupling reactions. Inclusion of butadiene greatly improves the efficiency of the reactions.²⁶⁸



These reaction conditions are applicable to primary chlorides, bromides, and tosylates. The active catalytic species appears to be a *bis*- π -allyl complex formed by dimerization of butadiene.



A preparation of Ni(II) on charcoal can also be used as the catalyst. It serves as a reservoir of active Ni(0) formed by reduction by the Grignard reagent.²⁶⁹



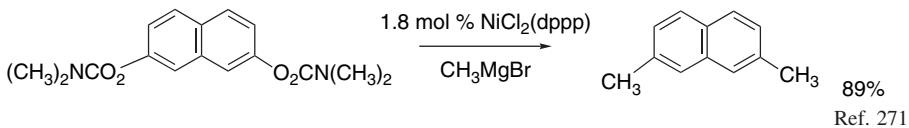
Aryl carbamates are also reactive toward nickel-catalyzed coupling.²⁷⁰ Since the carbamates can be readily prepared from phenols, they are convenient starting materials.

²⁶⁷ K. Tamno, S. Kodama, T. Nakatsuka, Y. Kiso, and A. Kumada, *J. Am. Chem. Soc.*, **97**, 4405 (1975).

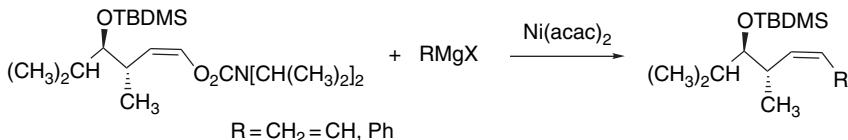
²⁶⁸ J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, and N. Kambe, *J. Am. Chem. Soc.*, **124**, 4222 (2002).

²⁶⁹ S. Tasler and R. H. Lipshutz, *J. Org. Chem.*, **68**, 1190 (2003).

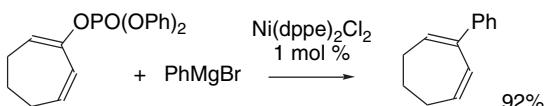
²⁷⁰ S. Sengupta, M. Leite, D. S. Raslan, C. Quesnelle, and V. Snieckus, *J. Org. Chem.*, **57**, 4066 (1992).



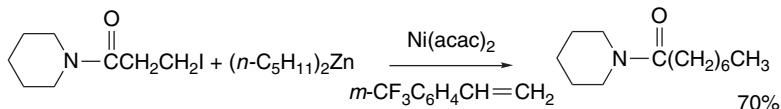
Vinyl carbamates are also reactive.



Similarly, nickel catalysis permits the extension of cross coupling to vinyl phosphates, which are in some cases more readily obtained and handled than vinyl triflates.²⁷³

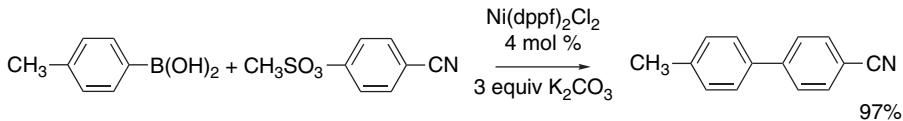


Nickel acetylacetonate, $\text{Ni}(\text{acac})_2$, in the presence of a styrene derivative promotes coupling of primary alkyl iodides with organozinc reagents. The added styrene serves to stabilize the active catalytic species, and of the derivatives examined, *m*-trifluoromethylstyrene was the best.²⁷⁴



This method can extend Ni-catalyzed cross coupling to functionalized organometallic reagents.

Nickel can also be used in place of Pd in Suzuki-type couplings of boronic acids. The main advantage of nickel in this application is that it reacts more readily with aryl chlorides²⁷⁵ and methanesulfonates²⁷⁶ than do the Pd systems. These reactants may be more economical than iodides or triflates in large-scale syntheses.



²⁷¹ C. Dallaire, I. Kolber, and M. Gringas, *Org. Synth.*, **78**, 42 (2002).

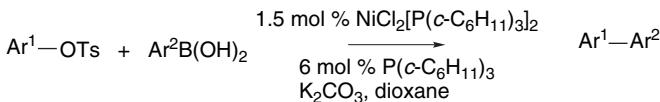
²⁷² F.-H. Poree, A. Clavel, J.-F. Betzer, A. Pancrazi, and J. Ardisson, *Chem. Eur. J.*, 7553 (2003).

²⁷³ A. Sofia, E. Karlstrom, K. Itami, and J.-E. Backvall, *J. Org. Chem.*, **64**, 1745 (1999); Y. Nan and Z. Yang, *Tetrahedron Lett.*, **40**, 3321 (1999).

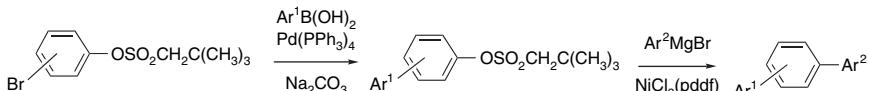
²⁷⁴ R. Giovannini, T. Studemann, G. Dussin, and P. Knochel, *Angew. Chem. Int. Ed. Engl.*, **37**, 2387 (1998); R. Giovannini, T. Studemann, A. Devasagayaraj, G. Dussin, and P. Knochel, *J. Org. Chem.*, **64**, 3544 (1999).

²⁷⁵ S. Saito, M. Sakai, and N. Miyaura, *Tetrahedron Lett.*, **37**, 2993 (1996); S. Saito, S. Oh-tani, and N. Miyaura, *J. Org. Chem.*, **62**, 8024 (1997).

²⁷⁶ V. Percec, J.-Y. Bae, and D. H. Hill, *J. Org. Chem.*, **60**, 1060 (1995); M. Ueda, A. Saitoh, S. Oh-tani, and N. Miyaura, *Tetrahedron*, **54**, 13079 (1998).

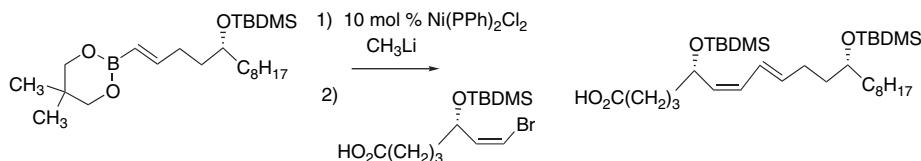


Nickel catalysis has been used in a sequential synthesis of terphenyls, starting with 2-, 3-, or 4-bromophenyl neopentanesulfonates. Conventional Pd-catalyzed Suzuki conditions were used for the first step involving coupling of the bromide and then nickel catalysis was utilized for coupling the sulfonate.



Ref. 278

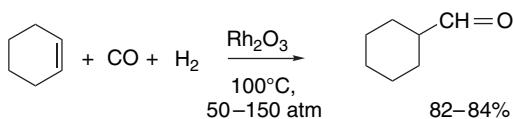
These coupling reactions can also be done with boronate esters activated by conversion to “ate” reagents by reaction with alkylolithium compounds.²⁷⁹ For example, analogs of leukotrienes have been synthesized in this way.



Ref. 280

8.3.2. Reactions Involving Rhodium and Cobalt

Rhodium and cobalt participate in several reactions that are of value in organic syntheses. Rhodium and cobalt are active catalysts for the reaction of alkenes with hydrogen and carbon monoxide to give aldehydes, known as *hydroformylation*.²⁸¹



Ref. 282

²⁷⁷ D. Zim, V. R. Lando, J. Dupont, and A. L. Monteiro, *Org. Lett.*, **3**, 3049 (2001).

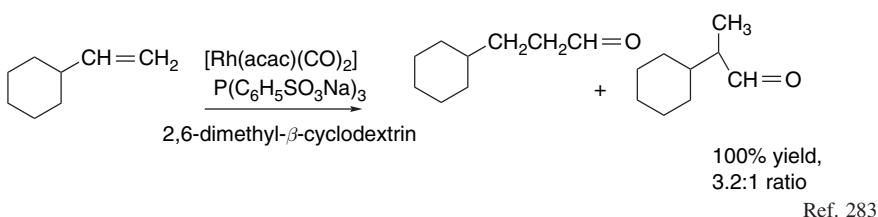
²⁷⁸ C.-H. Cho, I.-S. Kim, and K. Park, *Tetrahedron*, **60**, 4589 (2004).

²⁷⁹ Y. Kobayashi, Y. Nakayama, and R. Mizojiri, *Tetrahedron*, **54**, 1053 (1998).

²⁸⁰ Y. Nakayama, G. B. Kumar, and Y. Kobayashi, *J. Org. Chem.*, **65**, 707 (2000).

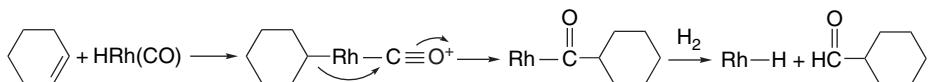
²⁸¹ R. L. Pruett, *Adv. Organometal. Chem.*, **17**, 1 (1979); H. Siegel and W. Himmeli, *Angew. Chem. Int. Ed. Engl.*, **19**, 178 (1980); J. Falbe, *New Syntheses with Carbon Monoxide*, Springer Verlag, Berlin, 1980.

²⁸² P. Pino and C. Botteghi, *Org. Synth.*, **57**, 11 (1977).

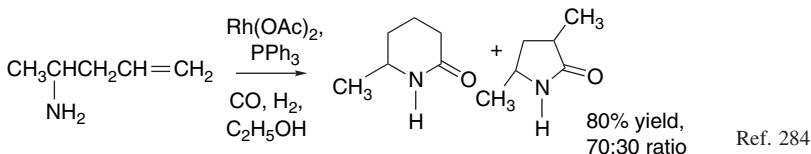


Ref. 283

The key steps in the reaction are addition of hydridorhodium to the double bond of the alkene and migration of the alkyl group to the complexed carbon monoxide. Hydrogenolysis then leads to the aldehyde.

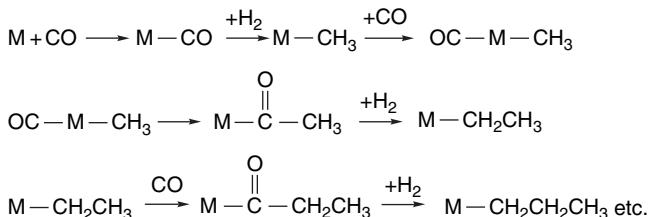


Carbonylation can also be carried out under conditions in which the acyrlrhodium intermediate is trapped by internal nucleophiles.



Ref. 284

The steps in the hydroformylation reaction are closely related to those that occur in the *Fischer-Tropsch process*, which is the reductive conversion of carbon monoxide to alkanes and occurs by a repetitive series of carbonylation, migration, and reduction steps that can build up a hydrocarbon chain.



The Fischer-Tropsch process is of considerable economic interest because it is the basis of conversion of carbon monoxide to synthetic hydrocarbon fuels, and extensive work has been done on optimization of catalyst systems.

The carbonylation step that is involved in both hydroformylation and the Fischer-Tropsch reaction can be reversible. Under appropriate conditions, rhodium catalyst can be used for the decarbonylation of aldehydes²⁸⁵ and acyl chlorides.²⁸⁶

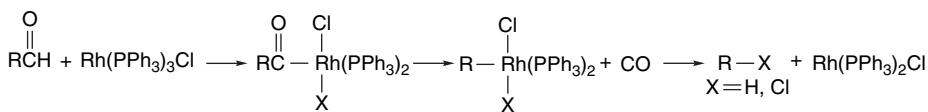


²⁸³. E. Monflier, S. Tilloy, G. Fremy, Y. Castanet, and A. Mortreux, *Tetrahedron Lett.*, **36**, 9481 (1995).

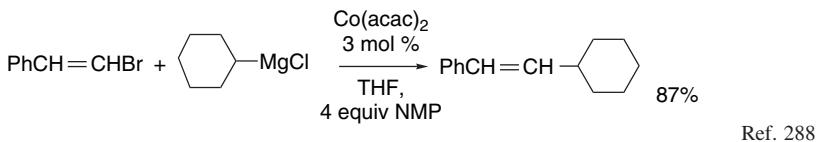
²⁸⁴. D. Anastasiou and W. R. Jackson, *Tetrahedron Lett.*, **31**, 4795 (1990).

²⁸⁵. J. A. Kampmeier, S. H. Harris, and D. K. Wedgaertner, *J. Org. Chem.*, **45**, 315 (1980); J. M. O'Connor and J. Ma, *J. Org. Chem.*, **57**, 5074 (1992).

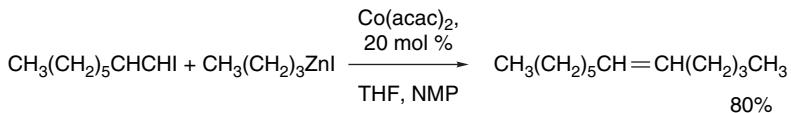
²⁸⁶. J. K. Stille and M. T. Regan, *J. Am. Chem. Soc.*, **96**, 1508 (1974); J. K. Stille and R. W. Fries, *J. Am. Chem. Soc.*, **96**, 1514 (1974).



Although the very early studies of transition metal–catalyzed coupling of organometallic reagents included cobalt salts, the use of cobalt for synthetic purposes is quite limited. Vinyl bromide and iodides couple with Grignard reagents in good yield, but a good donor ligand such as NMP or DMPU is required as a cocatalyst.

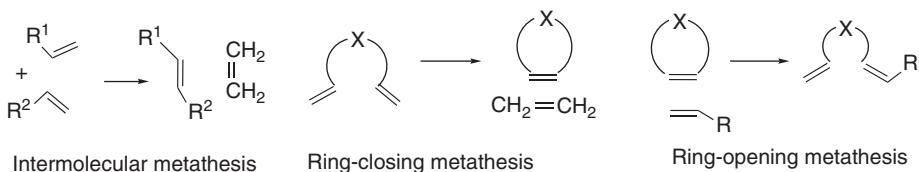


$\text{Co}(\text{acac})_2$ also catalyzes cross coupling of organozinc reagents under these conditions.²⁸⁹



8.4. The Olefin Metathesis Reaction

Several transition metal complexes can catalyze the exchange of partners of two double bonds. Known as the *olefin metathesis reaction*, this process can be used to close or open rings, as well to interchange double-bond components.

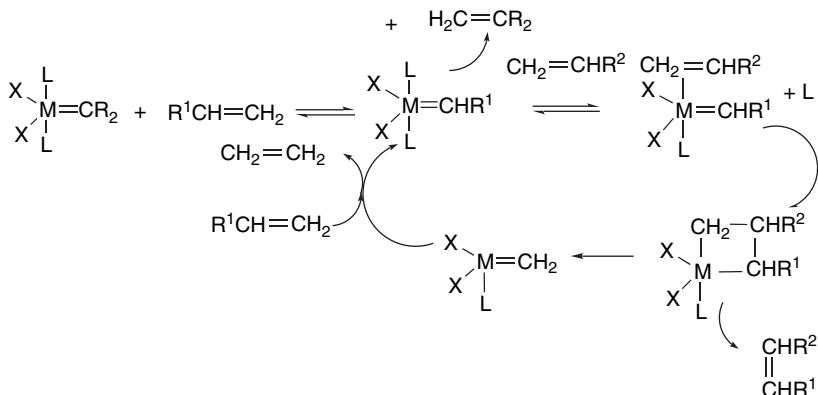


²⁸⁷ J. E. Baldwin, T. C. Barden, R. L. Pugh, and W. C. Widdison, *J. Org. Chem.*, **52**, 3303 (1987).

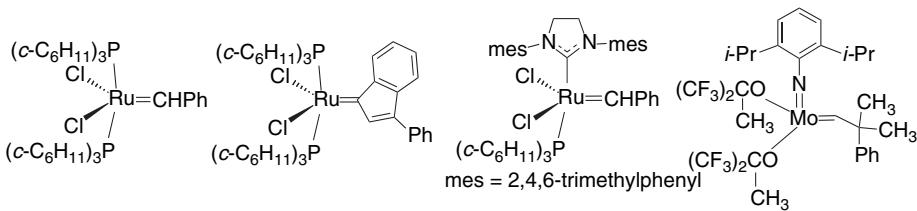
²⁸⁸ G. Cahiez and H. Avedissian, *Tetrahedron Lett.*, **39**, 6159 (1998).

²⁸⁹ H. Avedissian, L. Berillon, G. Cahiez, and P. Knochel, *Tetrahedron Lett.*, **39**, 6163 (1998).

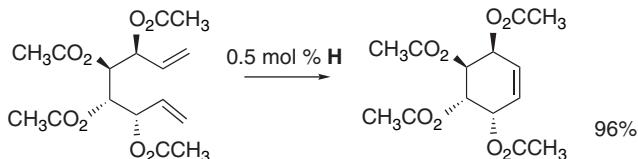
The catalysts are metal–carbene complexes that react with the alkene to form a metalocyclobutane intermediate.²⁹⁰ If the metalloocyclobutane breaks down in the alternative path from its formation, an exchange of the double-bond components occurs.



The most commonly used catalyst is the benzylidene complex of $\text{RuCl}_2[\text{P}(c-\text{C}_6\text{H}_{11})_3]_2$, **F**, which is called the *Grubbs catalyst*, but several other catalysts are also reactive. Catalyst **H**, which is known as the *second-generation Grubbs catalyst*, is used extensively.

**F**²⁹¹**G**²⁹²**H**²⁹³**I**²⁹⁴

In laboratory synthesis, these catalysts have been utilized primarily to form both common and large rings by coupling two terminal alkenes.²⁹⁵ For example, catalyst **H** has been used to synthesize the highly oxygenated cyclohexenes known as conduritols.



²⁹⁰ J.-L. Herisson and Y. Chauvin, *Makromol. Chem.*, **141**, 161 (1971).

²⁹¹ P. Schwab, R. H. Grubbs, and J. W. Ziller, *J. Am. Chem. Soc.*, **118**, 100 (1996).

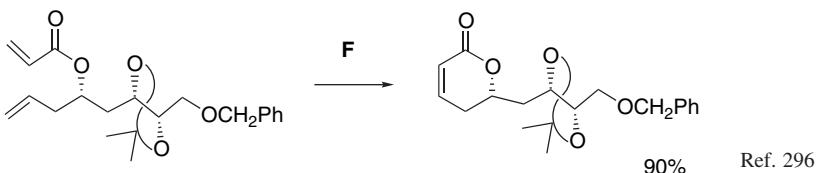
²⁹² A. Furstner, M. Liebl, A. F. Hill, and J. D. E. T. Winton-Ely, *Chem. Commun.*, 601 (1999); A. Furstner, O. Guth, A. Duffels, G. Seidel, M. Liebl, B. Gabor, and R. Mynott, *Chem. Eur. J.*, **7**, 4811 (2001).

²⁹³ M. Scholl, T. M. Trnka, J. P. Morgan, and R. H. Grubbs, *Tetrahedron Lett.*, **40**, 2247 (1999); J. A. Love, M. S. Sanford, M. W. Day, and R. H. Grubbs, *J. Am. Chem. Soc.*, **125**, 10103 (2003).

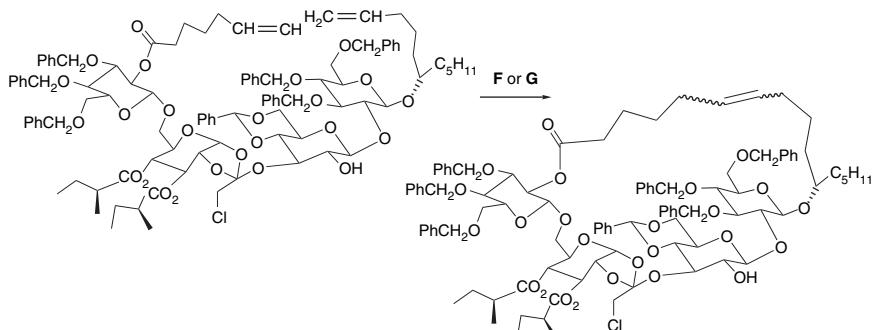
²⁹⁴ R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. Di Mare, and M. O'Regan, *J. Am. Chem. Soc.*, **112**, 3875 (1999).

²⁹⁵ D. L. Wright, *Curr. Org. Chem.*, **3**, 211 (1999); A. Deiters and S. F. Martin, *Chem. Rev.*, **104**, 2199 (2004).

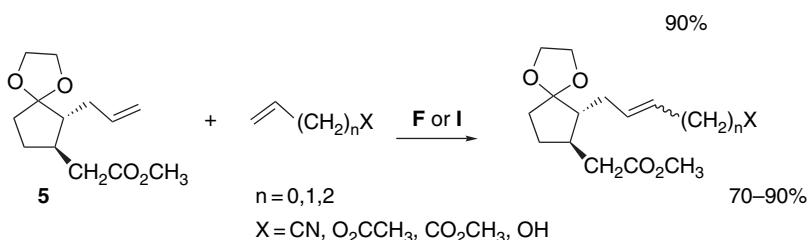
Various heterocyclic rings can be closed, as in the formation of an α, β -unsaturated lactone ring in the synthesis of peloruside A (see also Entries 3 and 5 of Scheme 8.16).



Some of the most impressive successes have come in the synthesis of large rings. Several research groups employed the ring-closing metathesis reaction in the synthesis of epothilone and analogs (see Entry 8 of Scheme 8.14).²⁹⁷ A large ring incorporating a tetrasaccharide unit was synthesized in essentially quantitative yield using either catalyst **F** or **G**. The newly formed double bond is 9:1 *E*:*Z*.



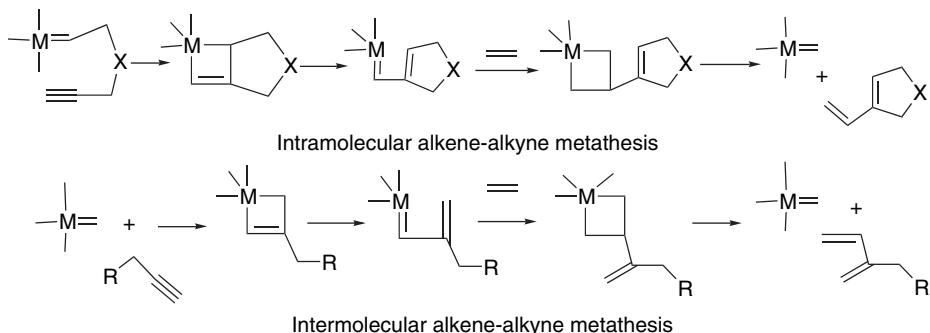
Olefin metathesis can also be used in intermolecular reactions.²⁹⁹ For example, a variety of functionally substituted side chains were introduced by exchange with the terminal double bond in **5**.³⁰⁰ These reactions gave *E*:*Z* mixtures.



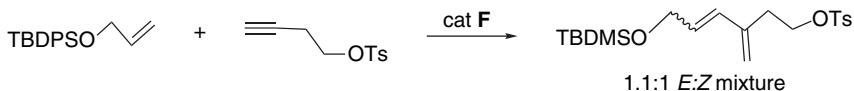
The effectiveness of these intermolecular reactions depends on the relative reactivity of the two components, since self-metathesis leading to dimeric products will occur if one compound is more reactive than the other.

- ²⁹⁶ A. K. Ghosh and J.-H. Kim, *Tetrahedron Lett.*, **44**, 3967 (2003).
- ²⁹⁷ K. C. Nicolaou, H. Vallberg, N. P. King, F. Roschangar, Y. He, D. Vourloumis, and C. G. Nicolaou, *Chem. Eur. J.*, **3**, 1957 (1997); D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **119**, 10073 (1997); K. Biswas, H. Lin, J. T. Nijardarson, M. D. Chappell, T.-C. Chou, Y. Guan, W. P. Tong, L. He, S. B. Horwitz, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **124**, 9825 (2002).
- ²⁹⁸ A. Furstner, F. Jeanjean, P. Razon, C. Wirtz, and P. Mynott, *Chem. Eur. J.*, **320** (2003).
- ²⁹⁹ S. J. Connon and S. Blechert, *Angew. Chem. Int. Ed. Engl.*, **42**, 1900 (2003).
- ³⁰⁰ O. Brummer, A. Ruckert, and S. Blechert, *Chem. Eur. J.*, **3**, 441 (1997).

Triple bonds can also participate in the metathesis reaction. Intramolecular reactions give vinylcycloalkenes, whereas intermolecular reactions provide conjugated dienes.³⁰¹ The mechanism is similar to that for α, ω -diene metathesis, but in contrast to diene cyclization, no carbon atoms are lost.³⁰²

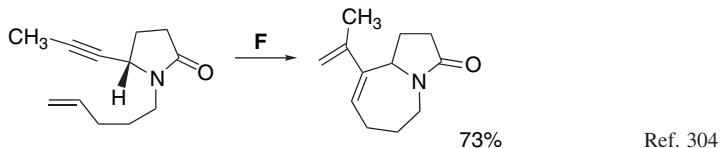


The reaction has been applied in several synthetic contexts. The intermolecular reaction has been used to construct the conjugated diene side chain of mycothiazole, an antibiotic isolated from a sponge.

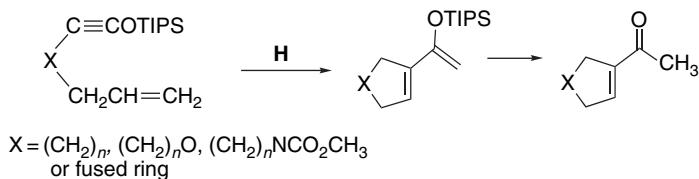


Ref. 303

The intermolecular version has been used in alkaloid synthesis.



When the intramolecular version is applied to silyloxyalkynes, the ultimate products are acetyl cycloalkenes.³⁰⁵



This reaction was used to prepare an intermediate suitable for synthesis of the sesquiterpenes α - and β -eremophilane and related structures.³⁰⁶

³⁰¹ S. T. Diver and A. J. Giessert, *Synthesis*, 466 (2004).

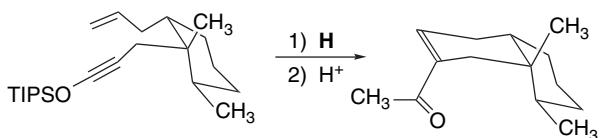
³⁰² R. Stragies, M. Schuster, and S. Blechert, *Angew. Chem. Int. Ed. Engl.*, **36**, 2518 (1997).

³⁰³ S. Rodriguez-Conesa, P. Candal, C. Jimenez, and J. Rodriguez, *Tetrahedron Lett.*, **42**, 6699 (2001).

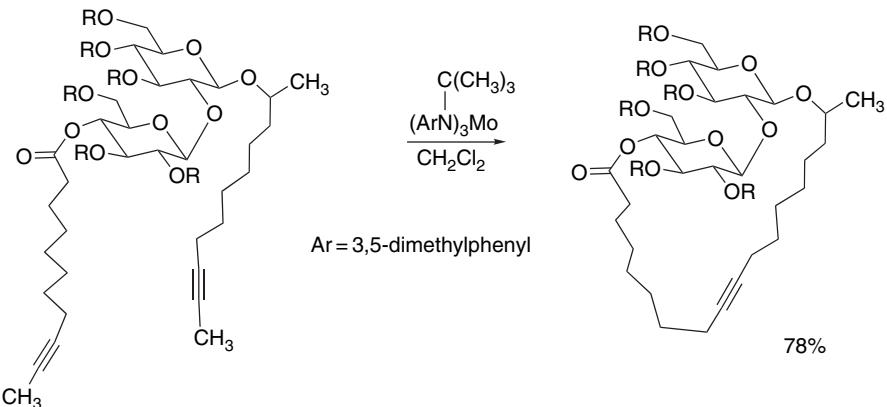
³⁰⁴ A. Kinoshita and M. Mori, *J. Org. Chem.*, **61**, 8356 (1996).

³⁰⁵ M. P. Schramm, D. S. Reddy, and S. A. Kozmin, *Angew. Chem. Int. Ed. Engl.*, **40**, 4274 (2001).

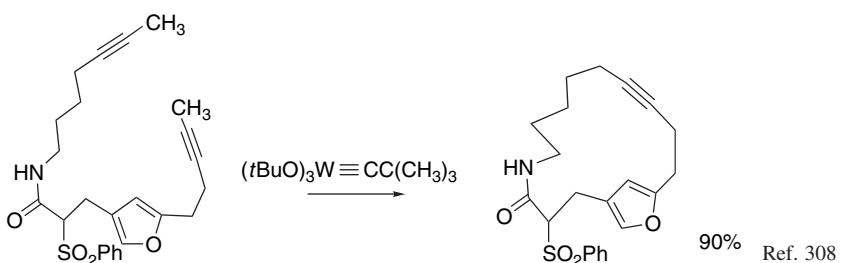
³⁰⁶ D. S. Reddy and S. A. Kozmin, *J. Org. Chem.*, **69**, 4860 (2004).



Diyynes can be employed in intramolecular ring-closing metathesis. Several catalysts involving Mo and W have been investigated. These cyclizations can be combined with semihydrogenation to give macrocycles with Z-double bonds.



Ref. 307



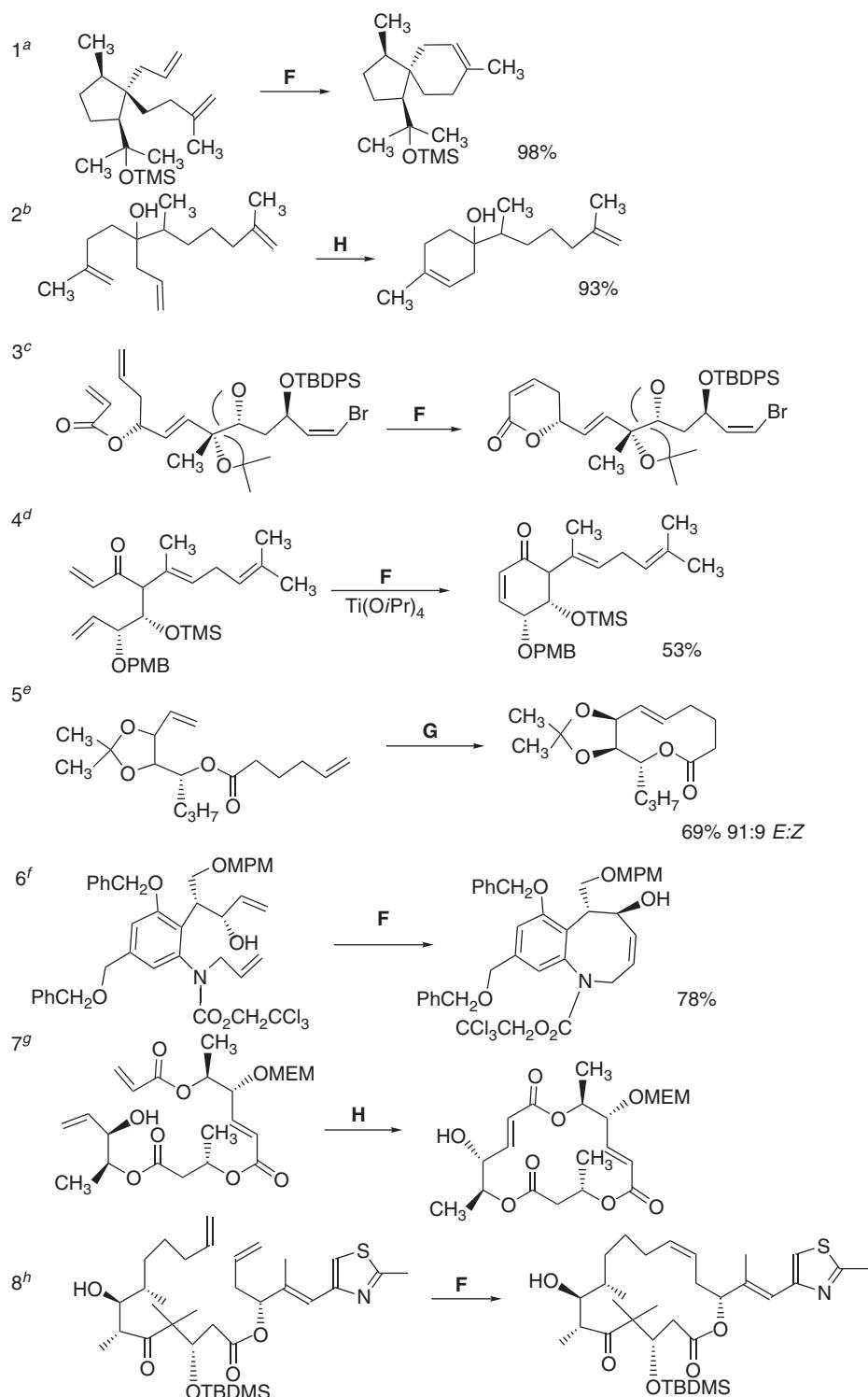
Scheme 8.16 gives some examples of the synthetic application of the olefin metathesis reaction. Entry 1 is the synthesis of a structure related to a flour beetle aggregation pheromone. Entry 2 was used in the synthesis of a component of sandalwood oil. These two examples illustrate use of the ring-closing metathesis in the synthesis of common rings. Entry 3 forms an α,β -unsaturated lactone and was used in the synthesis of fostriecin, which has anticancer activity. Entry 4 forms a cyclohexenone. Generally, alkenes with EWG substituents have somewhat reduced reactivity and in this case a mild Lewis acid cocatalyst was required. Entry 5 illustrates the synthesis of a medium-sized ring. In this case, catalyst **G** showed a preference for the *E*-double bond but a catalyst similar to **H** formed the *Z*-isomer. This difference was attributed to more rapid reversibility and thermodynamic control in the latter case. Entry 6 also shows the formation of a medium-size ring. Entries 7 and 8 illustrate the application of the ring-closing metathesis to large rings, with Entry 8 being an example of the synthesis of epothilone by this method.

³⁰⁷ A. Furstner, O. Guth, A. Rumbo, and S. Seidel, *J. Am. Chem. Soc.*, **121**, 11108 (1999).

³⁰⁸ A. Furstner, K. Radkowski, J. Grabowski, C. Wirtz, and R. Mynott, *J. Org. Chem.*, **65**, 8758 (2000).

Scheme 8.16. Examples of the Ring-Closing Olefin Metathesis Reaction

CHAPTER 8

Reactions Involving
Transition Metals

(Continued)

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 b. J. M. Mörgenthaler and D. Spitzner, *Tetrahedron Lett.*, **45**, 1171 (2004).
 c. Y. K. Reddy and J. R. Falck, *Org. Lett.*, **4**, 969 (2002).
 d. J.-G. Boiteau, P. Van de Weghe, and J. Eustache, *Org. Lett.*, **3**, 2737 (2001).
 e. A. Furstner, K. Radkowski, C. Wirtz, R. Goddard, C. W. Lehmann, and R. Mynott, *J. Am. Chem. Soc.*, **124**, 7061 (2002).
 f. I. M. Fellows, D. E. Kaelin, Jr., and S. F. Martin, *J. Am. Chem. Soc.*, **122**, 10781 (2000).
 g. Y. Matsuya, T. Kawaguchi, and H. Nemoto, *Org. Lett.*, **5**, 2939 (2003).
 h. Z. Yang, Y. He, D. Vourloumis, H. Vallberg, and K. C. Nicolaou, *Angew. Chem. Int. Ed. Engl.*, **36**, 166 (1997).

8.5. Organometallic Compounds with π -Bonding

The organometallic reactions discussed in the previous sections in most cases involved intermediates carbon-metal with σ bonds, although examples of π bonding with alkenes and allyl groups were also encountered. The reactions emphasized in this section involve compounds in which organic groups are bound to the metal through delocalized π systems. Among the classes of organic compounds that can serve as π ligands are alkenes, allyl groups, dienes, the cyclopentadienide anion, and aromatic compounds. There are many such compounds, and we illustrate only a few examples. The bonding of polyenes in π complexes is the result of two major contributions. The filled π orbital acts as an electron donor to empty d orbitals of the metal ion. There is also a contribution to bonding, called “back bonding,” from a filled metal orbital interacting with ligand π^* orbitals. These two types of bonding are illustrated in Figure 8.6. These same general bonding concepts apply to all the other π organometallics. The details of structure and reactivity of the individual compound depend on such factors as: (a) the number of electrons that can be accommodated by the metal; (b) the oxidation level of the metal; and (c) the electronic character of other ligands on the metal.

Alkene-metal complexes are usually prepared by a process by which some other ligand is dissociated from the metal. Both thermal and photochemical reactions are used.

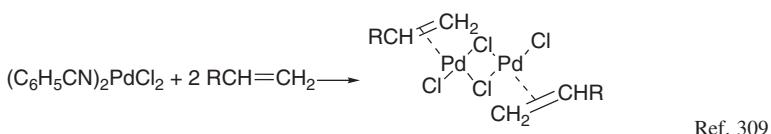
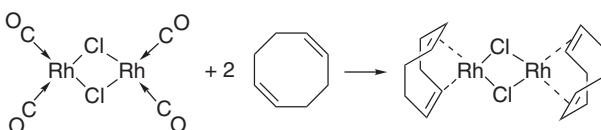


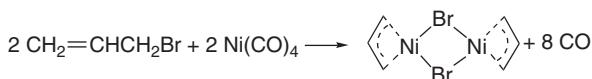
Fig. 8.6. Representation of π bonding in an alkene-metal cation complex.

³⁰⁹ M. S. Kharasch, R. C. Seyler, and F. R. Mayo, *J. Am. Chem. Soc.*, **60**, 882 (1938).

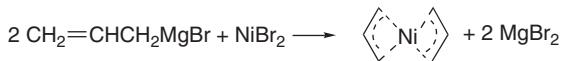


Ref. 310

π -Allyl complexes of palladium were described in Section 8.2.1. Similar π -allyl complexes of nickel can be prepared either by oxidative addition on Ni(0) or by transmetalation of a Ni(II) salt. Some reactions of these allyl nickel species are discussed in Section 8.3.1.



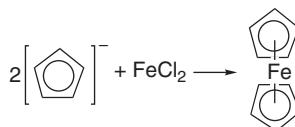
Ref. 311



Ref. 312

Organic ligands having a cyclic array of four carbon atoms have been of particular interest in connection with the chemistry of cyclobutadiene. Organometallic compounds containing cyclobutadiene as a ligand were first prepared in 1965.³¹³ The carbocyclic ring in the cyclobutadiene–iron tricarbonyl complex reacts as an aromatic ring and can undergo electrophilic substitutions.³¹⁴ Subsequent studies showed that oxidative decomposition of the complex can liberate cyclobutadiene, which is trapped by appropriate reactants.³¹⁵ Some examples of these reactions are given in Scheme 8.17.

One of the most familiar of the π -organometallic compounds is ferrocene, a neutral compound that is readily prepared from cyclopentadienide anion and iron(II).³¹⁶



Numerous chemical reactions have been carried out on ferrocene and its derivatives.³¹⁷ The molecule behaves as an electron-rich aromatic system, and electrophilic substitution reactions occur readily. Reagents that are relatively strong oxidizing agents, such as the halogens, effect oxidation at iron and destroy the compound.

³¹⁰ J. Chatt and L. M. Venanzi, *J. Chem. Soc.*, 4735 (1957).

³¹¹ E. J. Corey and M. F. Semmelhack, *J. Am. Chem. Soc.*, **89**, 2755 (1967).

³¹² D. Walter and G. Wilke, *Angew. Chem. Int. Ed. Engl.*, **5**, 151 (1966).

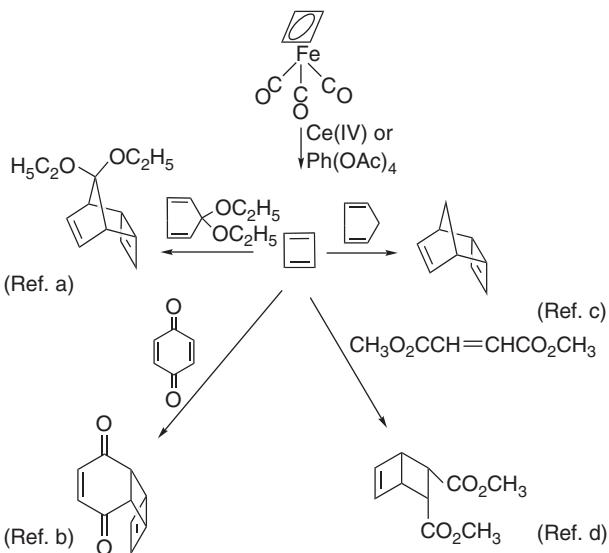
³¹³ G. F. Emerson, L. Watts, and R. Pettit, *J. Am. Chem. Soc.*, **87**, 131 (1965); R. Pettit and J. Henery, *Org. Synth.*, **50**, 21 (1970).

³¹⁴ J. D. Fitzpatrick, L. Watts, G. F. Emerson, and R. Pettit, *J. Am. Chem. Soc.*, **87**, 3254 (1965).

³¹⁵ R. H. Grubbs and R. A. Grey, *J. Am. Chem. Soc.*, **95**, 5765 (1973).

³¹⁶ G. Wilkinson, *Org. Synth.*, **IV**, 473, 476 (1963).

³¹⁷ A. Federman Neto, A. C. Pelegrino, and V. A. Darin, *Trends in Organometallic Chem.*, **4**, 147 (2002).



a. J. C. Barborak and R. Pettit, *J. Am. Chem. Soc.*, **89**, 3080 (1967).

b. J. C. Barborak, L. Watts, and R. Pettit, *J. Am. Chem. Soc.*, **88**, 1328 (1966).

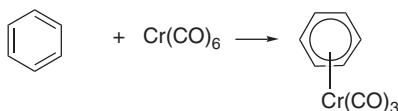
c. L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Am. Chem. Soc.*, **88**, 623 (1966).

d. P. Reeves, J. Henery, and R. Pettit, *J. Am. Chem. Soc.*, **91**, 3889 (1969).

Many other π -organometallic compounds have been prepared. In the most stable of these, the total number of electrons contributed by the ligands (e.g., four for allyl anions and six for cyclopentadiene anion) plus the valence electrons on the metal atom or ion is usually 18, to satisfy the *effective atomic number rule*.³¹⁸

Metal	6	9
Ligands	12	9
Total	18	18

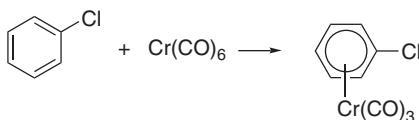
One of the most useful types of π complexes of aromatic compounds from the synthetic point of view are chromium tricarbonyl complexes obtained by heating benzene or other aromatics with $\text{Cr}(\text{CO})_6$.



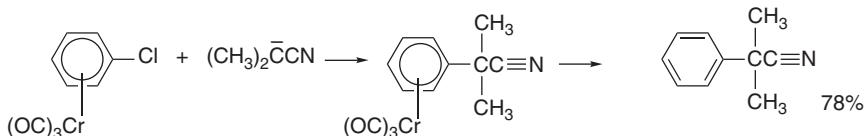
Ref. 319

³¹⁸ M. Tsutsui, M. N. Levy, A. Nakamura, M. Ichikawa, and K. Mori, *Introduction to Metal π -Complex Chemistry*, Plenum Press, New York, 1970, pp. 44–45; J. P. Collman, L. S. Hegedus, J. R. Norton, and R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, 1987, pp. 166–173.

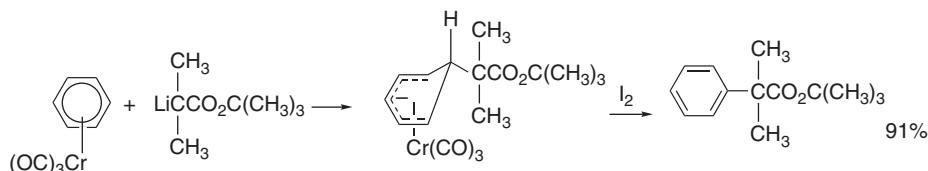
³¹⁹ W. Strohmeier, *Chem. Ber.*, **94**, 2490 (1961).



The $\text{Cr}(\text{CO})_3$ unit in these compounds is strongly electron withdrawing and activates the ring to nucleophilic attack. Reactions with certain carbanions results in arylation.³²¹

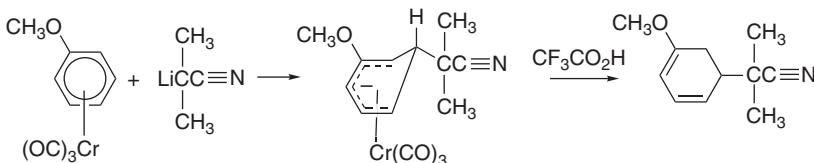


In compounds in which the aromatic ring does not have a leaving group, addition occurs. The intermediate can be oxidized by I_2 .



Ref. 322

Existing substituent groups such as CH_3 , OCH_3 , and $^+\text{N}(\text{CH}_3)_3$ exert a directive effect, often resulting in a major amount of the *meta* substitution product.³²³ The intermediate adducts can be converted to cyclohexadiene derivatives if the adduct is protonolyzed.³²⁴



Not all carbon nucleophiles will add to arene chromium tricarbonyl complexes. For example, alkylolithium reagents and simple ketone enolates do not give adducts.³²⁵

Organometallic chemistry is a very large and active field of research and new compounds, reactions, and useful catalysts are being discovered at a rapid rate. These developments have had a major impact on organic synthesis and future developments can be expected.

³²⁰ J. F. Bunnett and H. Hermann, *J. Org. Chem.*, **36**, 4081 (1971).

³²¹ M. F. Semmelhack and H. T. Hall, *J. Am. Chem. Soc.*, **96**, 7091 (1974).

³²² M. F. Semmelhack, H. T. Hall, M. Yoshifiji, and G. Clark, *J. Am. Chem. Soc.*, **97**, 1247 (1975); M. F. Semmelhack, H. T. Hall, Jr., R. Farina, M. Yoshifiji, G. Clark, T. Bargar, K. Hirotsu, and J. Clardy, *J. Am. Chem. Soc.*, **101**, 3535 (1979).

³²³ M. F. Semmelhack, G. R. Clark, R. Farina, and M. Saeman, *J. Am. Chem. Soc.*, **101**, 217 (1979).

³²⁴ M. F. Semmelhack, J. J. Harrison, and Y. Thebtaranonth, *J. Org. Chem.*, **44**, 3275 (1979).

³²⁵ R. J. Card and W. S. Trahanovsky, *J. Org. Chem.*, **45**, 2555, 2560 (1980).

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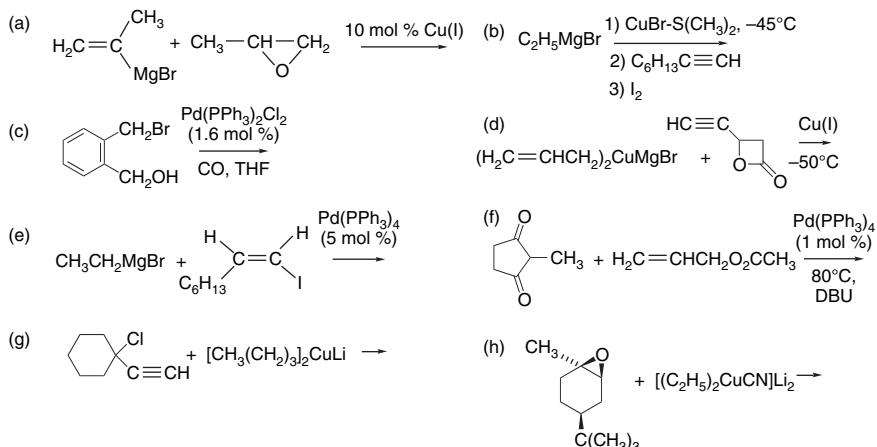
Organopalladium Reactions

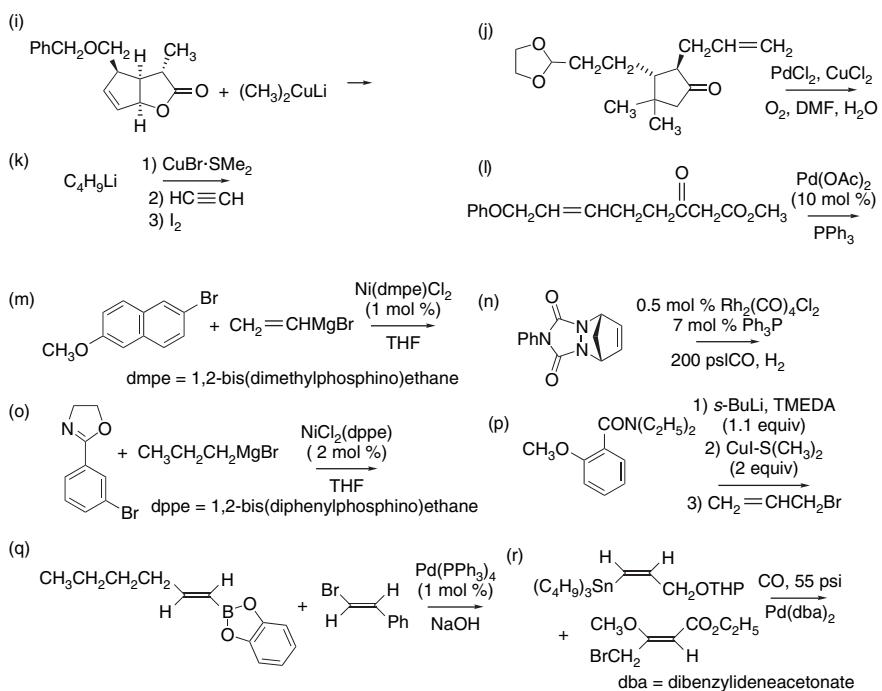
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- J. Tsuji, *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, New York, 1996.

Problems

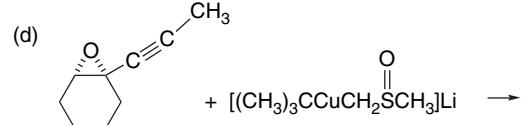
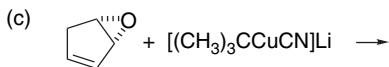
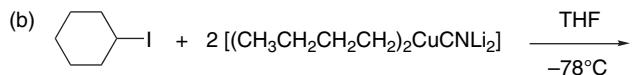
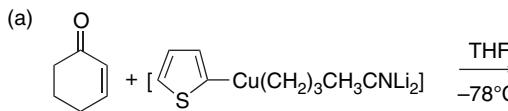
(References for these problems will be found on page 1284.)

- 8.1. Predict the product of the following reactions. Be sure to specify all elements of regiochemistry and stereochemistry.

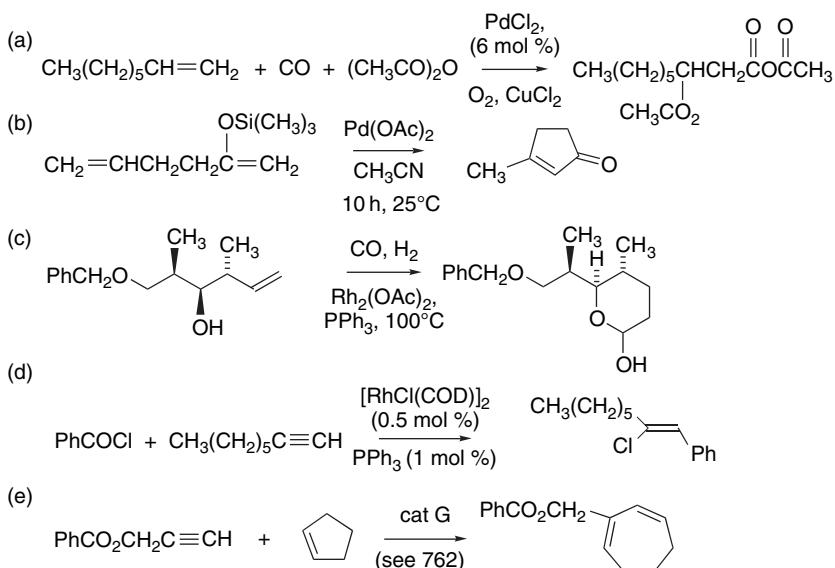




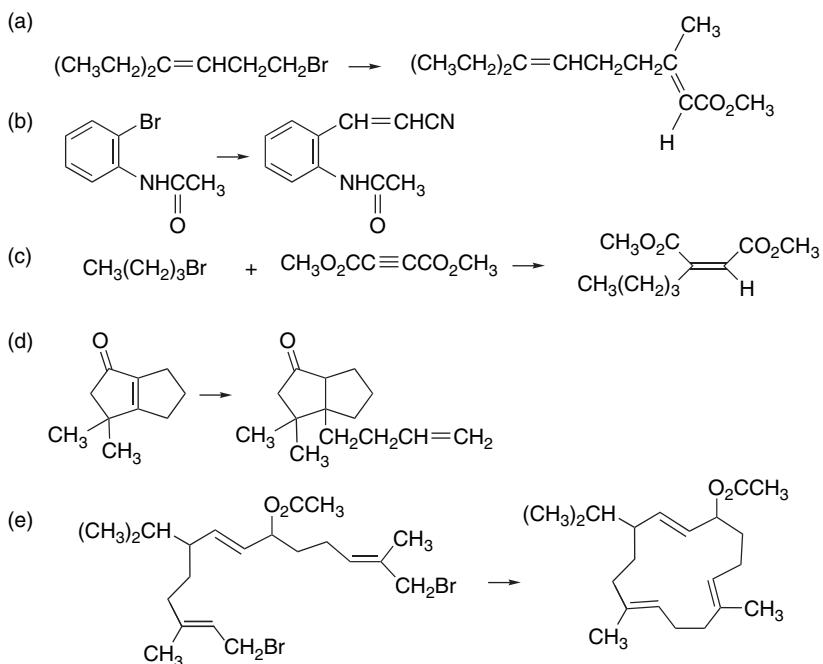
8.2. Give the products expected from each of the following reactions involving mixed cuprate reagents.

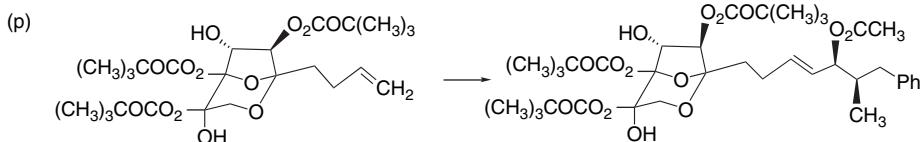
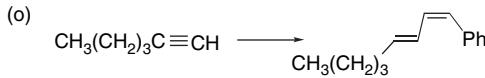
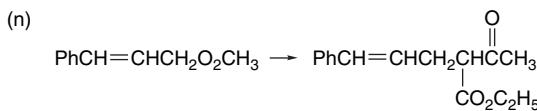
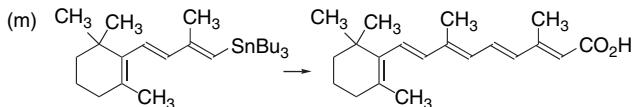
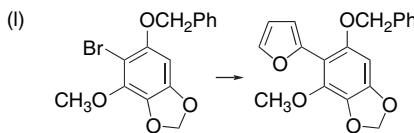
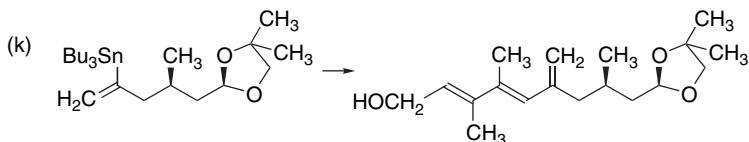
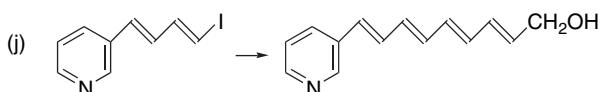
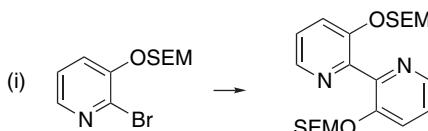
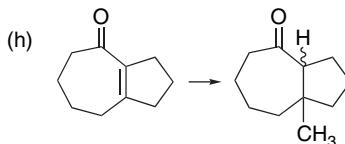
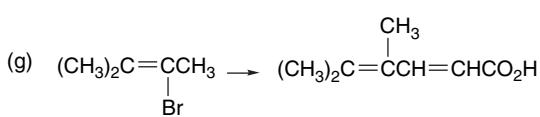
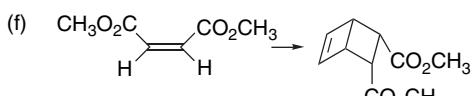


8.3. Write a mechanism for each of the following reactions that accounts for the observed product and is in accord with other information that is available concerning the reaction.

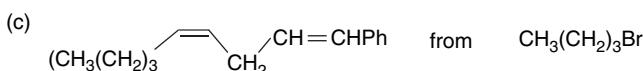
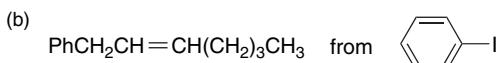
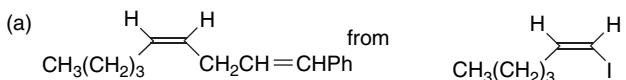


8.4. Indicate appropriate conditions and reagents for effecting the following transformations. Identify necessary co-reactants, reagents, and catalysts. One-pot processes are possible in all cases.

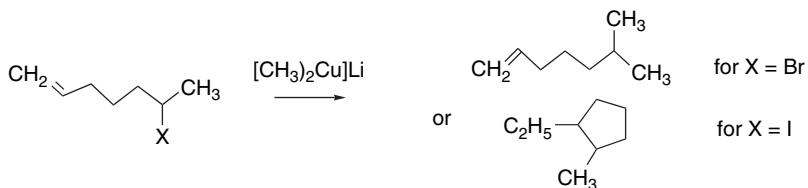




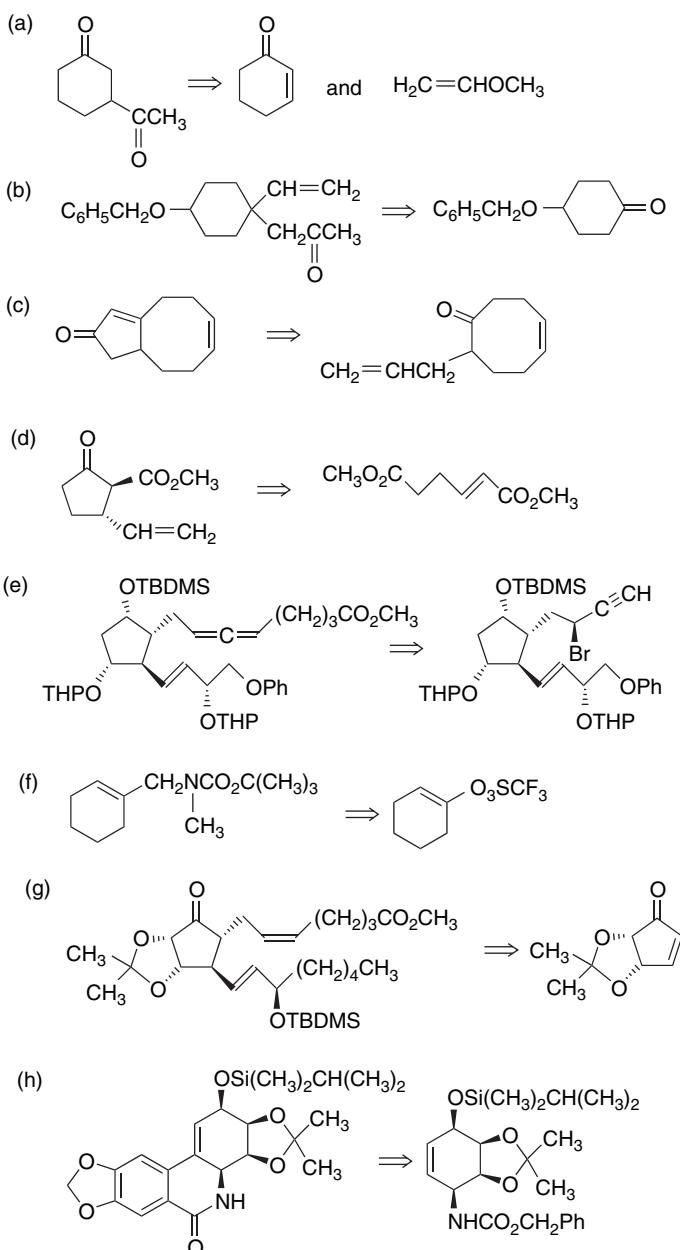
8.5. Vinyltriphenylphosphonium ion has been found to react with cuprate reagents by nucleophilic addition, generating an ylide that can react with aldehydes to give alkenes. In another version of the reaction, an intermediate formed by the reaction of the cuprate with acetylene adds to vinyltriphenylphosphonium ion to generate an ylide intermediate. Show how these reactions can be used to prepare the following products from the specified starting materials.



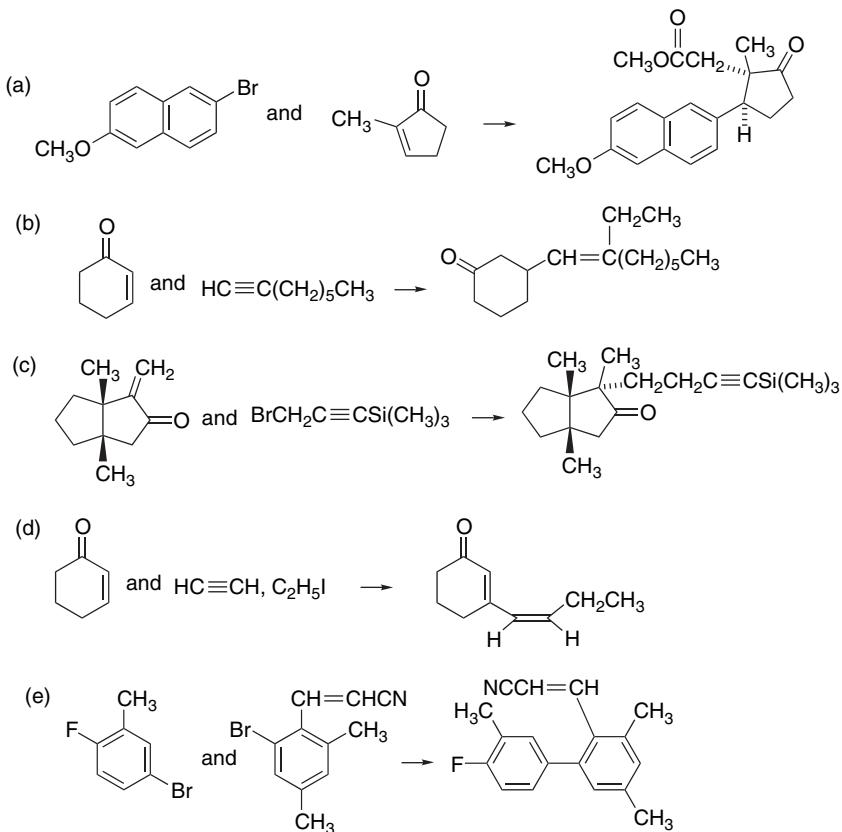
8.6. It has been observed that the reaction of $[(C_2H_5)_2Cu]Li$ or $[(C_2H_5)_2CuCNLi_2]$ with 2-iodooctane proceeds with racemization in both cases. On the other hand, the corresponding bromide reacts with nearly complete inversion of configuration with both reagents. When 6-halo-2-heptenes are used in similar reactions with $[(CH_3)_2Cu]Li$, the iodide gives a cyclic product 1-ethyl-2-methylcyclopentane, whereas the bromide gives mainly 6-methyl-1-heptene. Propose a mechanism that accounts for the different behavior of the iodides as compared to the bromides.



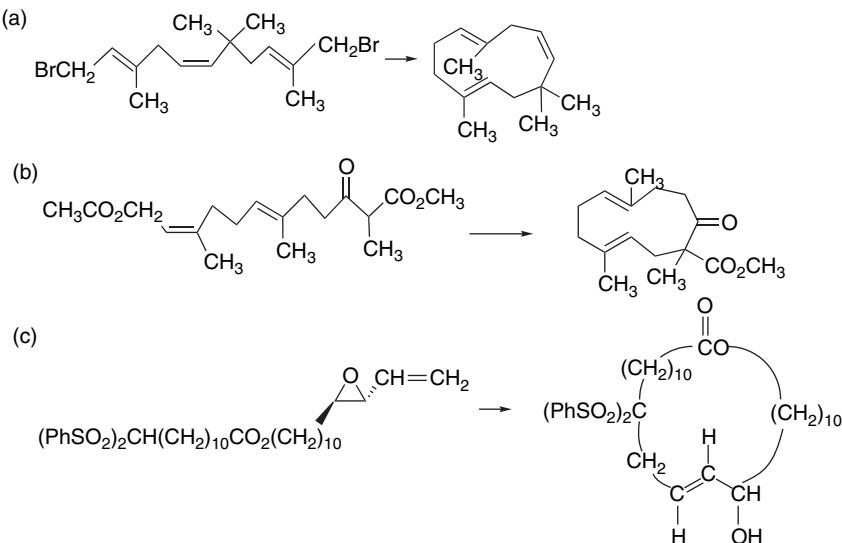
8.7. Short synthetic sequences involving no more than three steps can be used to prepare the compound shown on the left from the potential starting materials on the right. Suggest an appropriate series of reactions involving one or more organometallic reagent for each transformation.



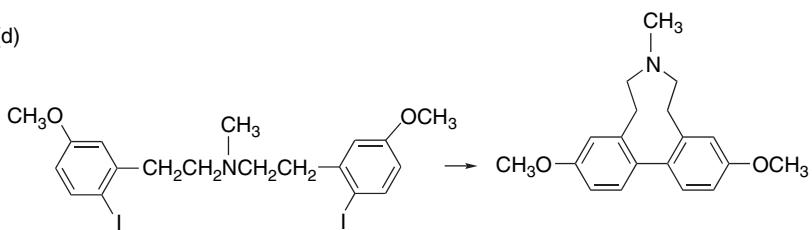
- 8.8. The conversions shown below can be carried out in multistep, but one-pot, reactions in which none of the intermediates needs to be isolated. Show how you would perform the transformations by suggesting a sequence of reagents and the approximate reaction conditions.



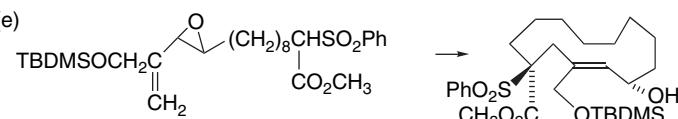
8.9. A number of syntheses of medium- and large-ring compounds that involve transition metal reagents or catalysts have been described. Suggest an organometallic reagent or catalyst that could bring about each of the following transformations.



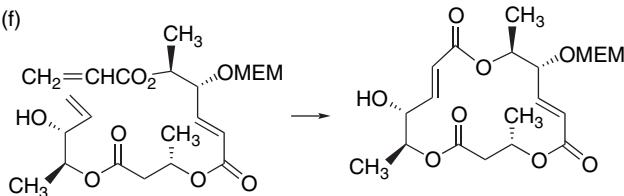
(d)



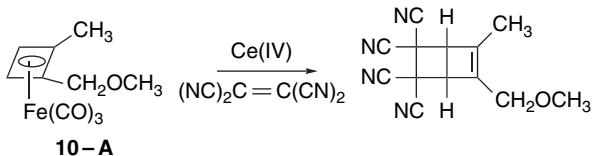
(e)



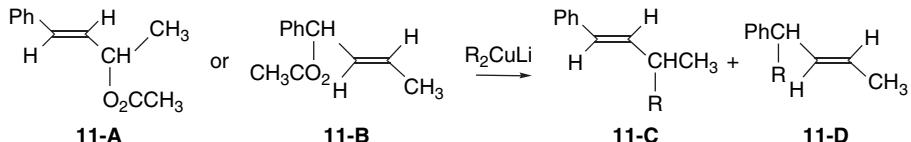
(f)



- 8.10. The cyclobutadiene complex **10-A** can be prepared in enantiomerically pure form. When the complex is decomposed by an oxidizing reagent in the presence of a potential trapping agent, the products are racemic. When the reaction is carried out only to partial completion, the unreacted complex remains enantiomerically pure. Discuss the relevance of these results to the following question: “In oxidative decomposition of cyclobutadiene–iron tricarbonyl complexes, is the cyclobutadiene released from the complex before or after it has reacted with the trapping reagent?”

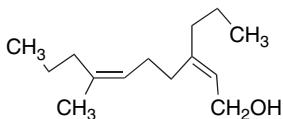


- 8.11. When the isomeric allylic acetates **11-A** and **11-B** react with dialkylcuprates, they give very similar product mixtures that contain mainly **11-C** with a small amount of **11-D**. Discuss the mechanistic implications of the formation of essentially the same product mixture from both reactants.

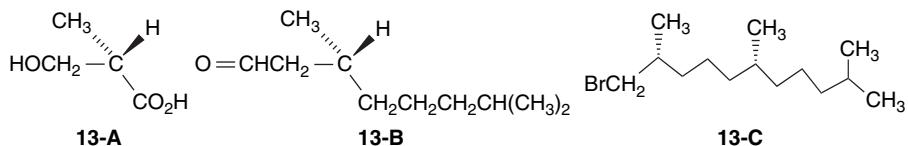


- 8.12. The compound shown below is a constituent of the pheromone of the codling moth. It has been synthesized using *n*-propyl bromide, propyne, 1-pentyne,

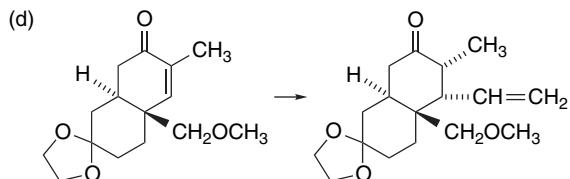
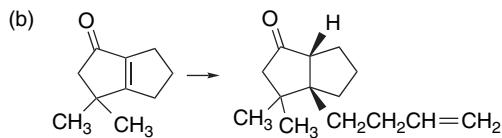
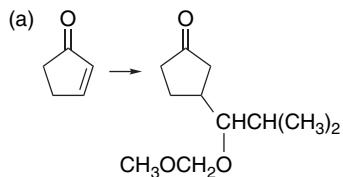
ethylene oxide, and CO_2 as the source of the carbon atoms. Devise a route for such a synthesis. Hint: Extensive use of organocopper reagents is the basis for the synthesis.



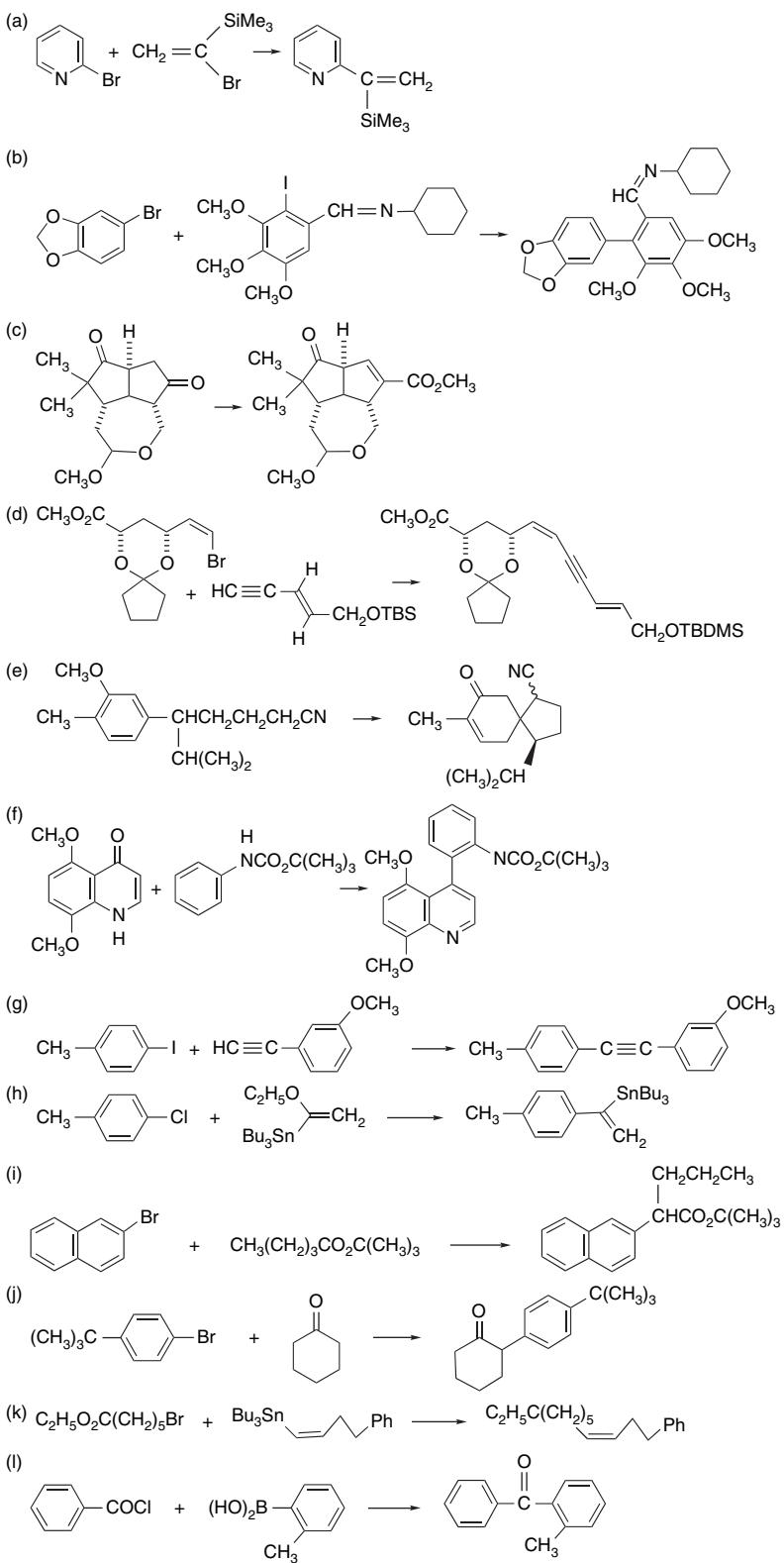
- 8.13. (*S*)-3-Hydroxy-2-methylpropanoic acid, **13-A**, can be obtained in enantiomerically pure form from isobutyric acid by a microbiological oxidation. The aldehyde **13-B** is available from a natural product, pulegone, also in enantiomerically pure form. Devise a synthesis of enantiomerically pure **13-C**, a compound of interest as a starting material for the synthesis of α -tocopherol (vitamin E).



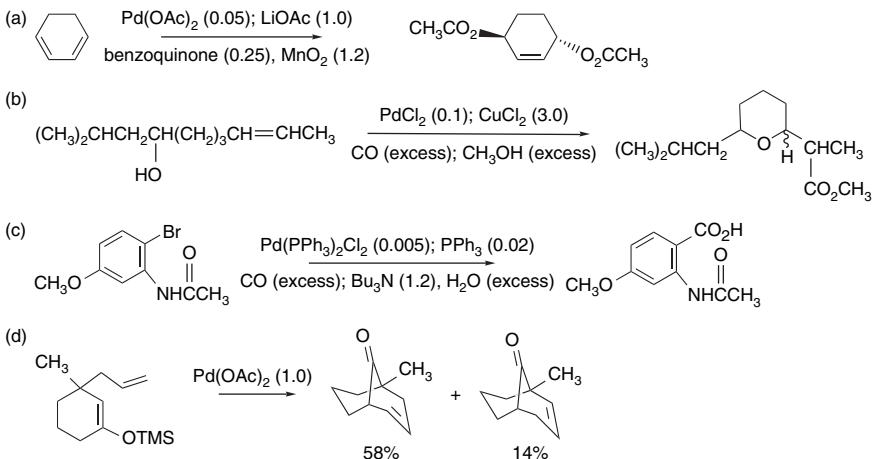
- 8.14. Each of the following conjugate additions can be carried out in good yield under optimized conditions. Consider the special factors in each case and suggest a reagent and reaction conditions that would be expected to give good yields.



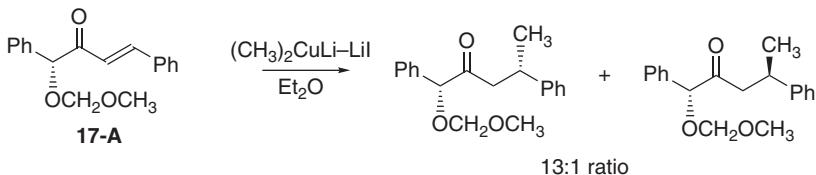
- 8.15. Each of the following synthetic transformations can be accomplished by use of organometallic reagents and/or catalysts. Indicate a sequence of reactions that will permit each of the syntheses to be completed.



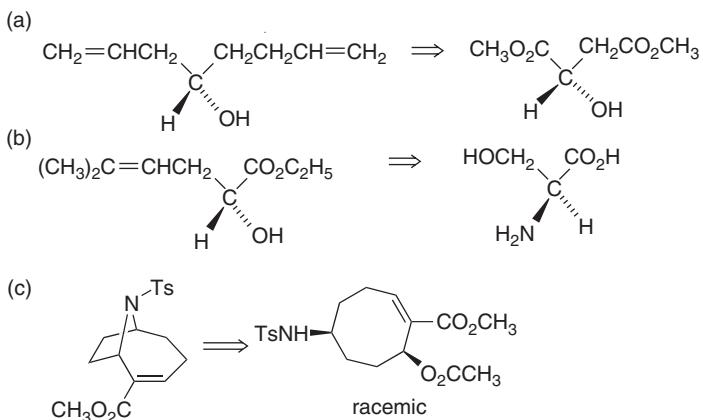
8.16. Each of the following reactions can be accomplished with a palladium reagent or catalyst. Write a detailed mechanism for each reaction. The number of equivalents of each reagent is given in parentheses. Specify the oxidation state of Pd in the intermediates. Be sure your mechanism accounts for the regeneration of catalytically active species in those reactions that are catalytic in palladium.



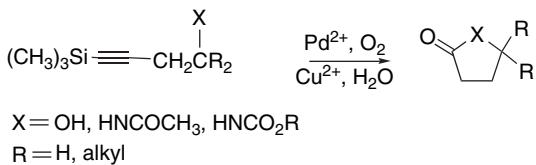
8.17. The reaction of lithium dimethylcuprate with **17-A** shows considerable 1,4-diastereoselectivity. Offer an explanation, including a transition structure.



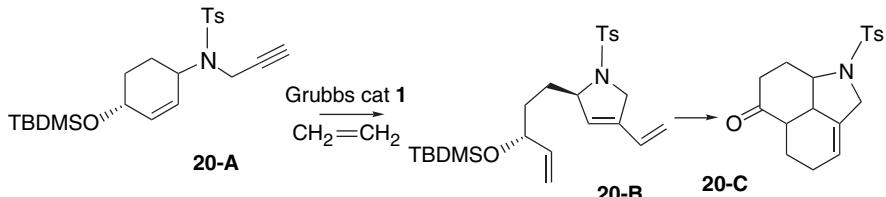
8.18. The following transformations have been carried out to yield a specific enantiomer using organometallic reagents. Devise a strategy by which organometallic reagents or catalysts can be used to prepare the desired compound from the specified starting material.



- 8.19. Under the conditions of the Wacker oxidation, 4-trimethylsilyl-3-alkyn-1-ols give γ -lactones. Similarly, *N*-carbamoyl or *N*-acetyl 4-trimethylsilyl-3-alkynamines cyclize to γ -lactams. Formulate a mechanism for these reactions. (Hint: In D_2O , the reaction gives 3,3-dideuterated products.)



- 8.20. The tricyclic compound **20-C**, a potential intermediate for alkaloid synthesis, has been prepared by an intramolecular Diels-Alder reaction of the ketone obtained by deprotection and oxidation of **20-B**. Compound **20-B** was prepared from **20-A** using alkyne-ethene metathesis chemistry. Show the mechanistic steps involved in conversion of **20-A** to **20-B**.



Carbon-Carbon Bond-Forming Reactions of Compounds of Boron, Silicon, and Tin

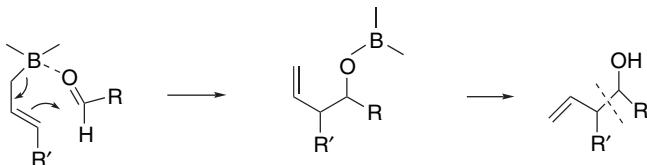
Introduction

In this chapter we discuss the use of boron, silicon, and tin compounds to form carbon-carbon bonds. These elements are at the metal-nonmetal boundary, with boron being the most and tin the least electronegative of the three. The neutral alkyl derivatives of boron have the formula R_3B , whereas silicon and tin are tetravalent compounds, R_4Si and R_4Sn . These compounds are relatively volatile nonpolar substances that exist as discrete molecules and in which the carbon-metal bonds are largely covalent. By virtue of the electron deficiency at boron, the boranes are Lewis acids. Silanes do not have strong Lewis acid character but can form pentavalent adducts with hard bases such as alkoxides and especially fluoride. Silanes with halogen or sulfonate substituents are electrophilic and readily undergo nucleophilic displacement. Stannanes have the potential to act as Lewis acids when substituted by electronegative groups such as halogens. Either displacement of a halide or expansion to pentacoordinate or hexacoordinate structures is possible.

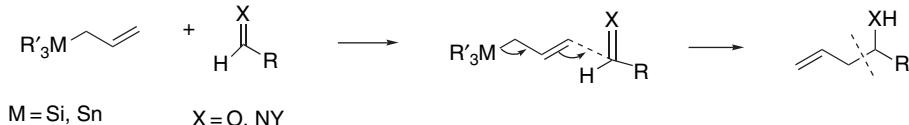
In contrast to the transition metals, where there is often a change in oxidation level at the metal during the reaction, there is usually no change in oxidation level for boron, silicon, and tin compounds. The synthetically important reactions of these three groups of compounds involve transfer of a carbon substituent with one (radical equivalent) or two (carbanion equivalent) electrons to a reactive carbon center. Here we focus on the nonradical reactions and deal with radical reactions in Chapter 10. We have already introduced one important aspect of boron and tin chemistry in the transmetallation reactions involved in Pd-catalyzed cross-coupling reactions, discussed

in Section 8.2.3. This chapter emphasizes the use of boranes, silanes, and stannanes as sources of nucleophilic carbon groups toward a variety of electrophiles, especially carbonyl compounds.

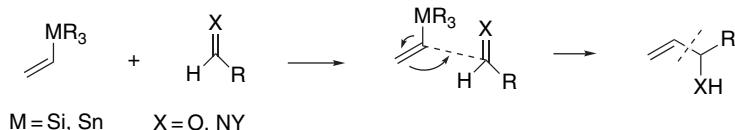
Allylic derivatives are particularly important in the case of boranes, silanes, and stannanes. Allylic boranes effect nucleophilic addition to carbonyl groups via a cyclic TS that involves the Lewis acid character of the borane. 1,3-Allylic transposition occurs through the cyclic TS.



Allylic silanes and stannanes react with various electrophiles with demetallation. These reactions can occur via several related mechanisms. Both types of reagents can deliver allylic groups to electrophilic centers such as carbonyl and iminium.



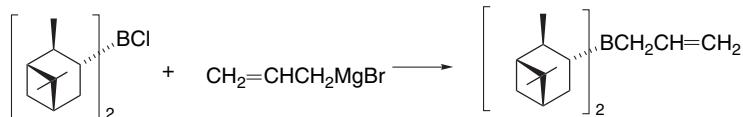
Alkenyl silanes and stannanes have the potential for nucleophilic delivery of vinyl groups to a variety of electrophiles. Demetallation also occurs in these reactions, so the net effect is substitution for the silyl or the stannyll group.



9.1. Organoboron Compounds

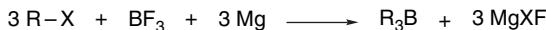
9.1.1. Synthesis of Organoboranes

The most widely used route to organoboranes is hydroboration, introduced in Section 4.5.1, which provides access to both alkyl- and alkenylboranes. Aryl-, methyl-, allylic, and benzylboranes cannot be prepared by hydroboration, and the most general route to these organoboranes is by reaction of an organometallic compound with a halo- or alkoxyboron derivative.¹



¹. H. C. Brown and P. K. Jadhav, *J. Am. Chem. Soc.*, **105**, 2092 (1983).

Alkyl, aryl, and allyl derivatives of boron can be prepared directly from the corresponding halides, BF_3 , and magnesium metal. This process presumably involves in situ generation of a Grignard reagent, which then displaces fluoride from boron.²



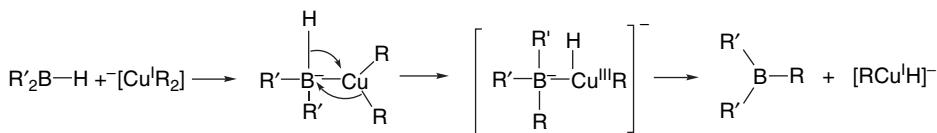
Alkoxy groups can be displaced from boron by alkyl- or aryllithium reagents. The reaction of diisopropoxy boranes with an organolithium reagent, for example, provides good yields of unsymmetrically disubstituted isopropoxyboranes.³



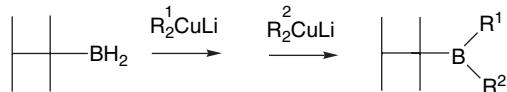
Organoboranes can also be made using organocupper reagents. One route to methyl and aryl derivatives is by reaction of a dialkylborane, such as 9-BBN, with a cuprate reagent.⁴



These reactions occur by oxidative addition at copper, followed by decomposition of the Cu(III) intermediate.



Two successive reactions with different organocuprates can convert the xylborane to an unsymmetrical trialkylborane.⁵



In addition to trialkylboranes, various alkoxyboron compounds have prominent roles in synthesis. Some of these, such as catecholboranes (see, p. 340) can be made by hydroboration. Others are made by organometallic or related substitution reactions. Alkoxyboron compounds are usually named as esters. Compounds with one alkoxy group are esters of borinic acids and are called *borinates*. Compounds with two alkoxy groups are called *boronates*. Trialkoxyboron compounds are *borates*.

R_2BOH	$\text{R}_2\text{BOR}'$	RB(OH)_2	RB(OR)_2	B(OH)_3	B(OR')_3
borinic acid	borinate	boronic acid	boronate	boric acid	borate

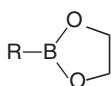
² H. C. Brown and U. S. Racherla, *J. Org. Chem.*, **51**, 427 (1986).

³ H. C. Brown, T. E. Cole, and M. Srebnik, *Organometallics*, **4**, 1788 (1985).

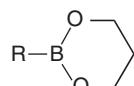
⁴ C. G. Whiteley and I. Zwane, *J. Org. Chem.*, **50**, 1969 (1985).

⁵ C. G. Whiteley, *Tetrahedron Lett.*, **25**, 5563 (1984).

The cyclic five- and six-membered boronate esters are used frequently. Their systematic names are 1,3,2-dioxaborolane and 1,3,2-dioxaborinanes, respectively.



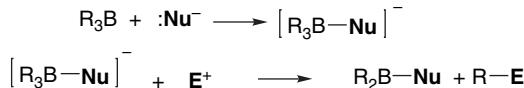
1,3,2-dioxaborolane



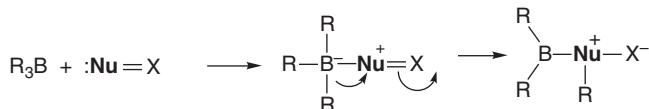
1,3,2-dioxaborinane

9.1.2. Carbonylation and Other One-Carbon Homologation Reactions

The reactions of organoboranes that we discussed in Chapter 4 are valuable methods for introducing functional groups such as hydroxy, amino, and halogen into alkenes. In this section we consider carbon-carbon bond-forming reactions of boron compounds.⁶ Trivalent organoboranes are not very nucleophilic but they are moderately reactive Lewis acids. Most reactions in which carbon-carbon bonds are formed involve a tetracoordinate intermediate that has a negative charge on boron. Adduct formation weakens the boron-carbon bonds and permits a transfer of a carbon substituent with its electrons. The general mechanistic pattern is shown below.



The electrophilic center is sometimes generated from the Lewis base by formation of the adduct, and the reaction proceeds by migration of a boron substituent.



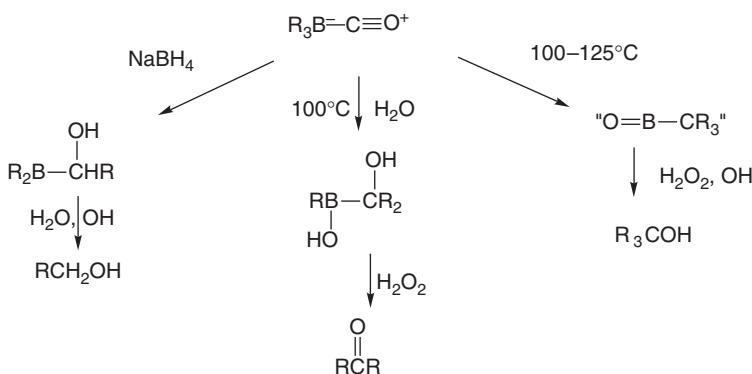
A significant group of reactions of this type involves the reactions of organoboranes with carbon monoxide, which forms Lewis acid-base complexes with the organoboranes. In these adducts the boron bears a formal negative charge and carbon is electrophilic because the triply bound oxygen bears a formal positive charge. The adducts undergo boron to carbon migration of the alkyl groups. The reaction can be controlled so that it results in the migration of one, two, or all three of the boron substituents.⁷ If the organoborane is heated with carbon monoxide to 100°–125 °C, all of the groups migrate and a tertiary alcohol is obtained after workup by oxidation. The presence of water causes the reaction to cease after migration of two groups from boron to carbon. Oxidation of the reaction mixture at this stage gives a ketone.⁸ Primary alcohols are obtained when the carbonylation is carried out in the presence of

⁶. For a review of this topic, see E. Negishi and M. Idacavage, *Org. React.*, **33**, 1 (1985).

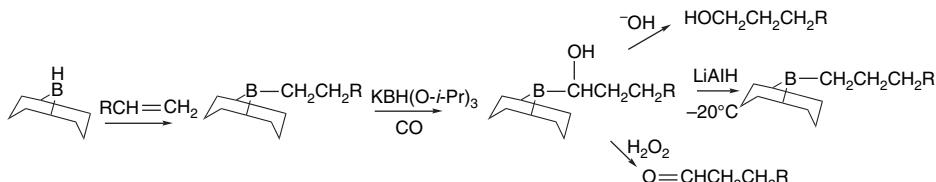
⁷. H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.*, **89**, 2737 (1967).

⁸. H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.*, **89**, 2738 (1967).

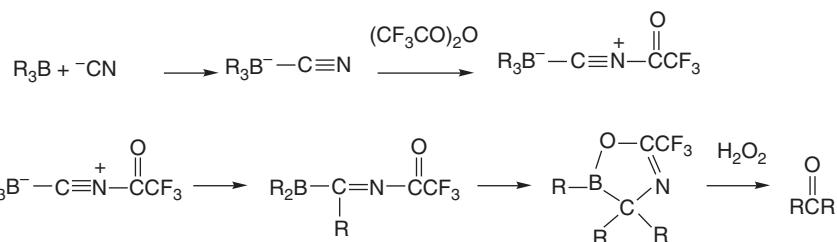
sodium borohydride or lithium borohydride.⁹ The product of the first migration step is reduced and subsequent hydrolysis gives a primary alcohol.



In this synthesis of primary alcohols, only one of the three groups in the organoborane is converted to product. This disadvantage can be overcome by using a dialkylborane, particularly 9-BBN, in the initial hydroboration. (See p. 338 to review the abbreviations of some of the common boranes.) After carbonylation and B → C migration, the reaction mixture can be processed to give an aldehyde, an alcohol, or the homologated 9-alkyl-BBN.¹⁰ The utility of 9-BBN in these procedures is the result of the minimal tendency of the bicyclic ring to undergo migration.



Several alternative procedures have been developed in which other reagents replace carbon monoxide as the migration terminus.¹¹ The most generally applicable of these methods involves the use of cyanide ion and trifluoroacetic anhydride (TFAA). In this reaction the borane initially forms an adduct with cyanide ion. The migration is induced by N-acylation of the cyano group by TFAA. Oxidation and hydrolysis then give a ketone.

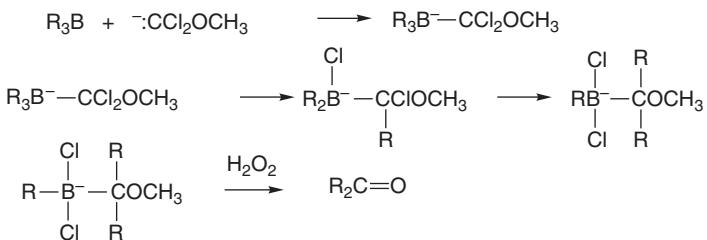


⁹. M. W. Rathke and H. C. Brown, *J. Am. Chem. Soc.*, **89**, 2740 (1967).

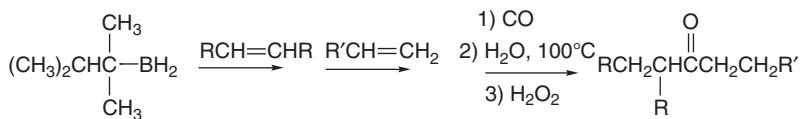
¹⁰. H. C. Brown, E. F. Knights, and R. A. Coleman, *J. Am. Chem. Soc.*, **91**, 2144 (1969); H. C. Brown, T. M. Ford, and J. L. Hubbard, *J. Org. Chem.*, **45**, 4067 (1980).

¹¹. H. C. Brown and S. M. Singh, *Organometallics*, **5**, 998 (1986).

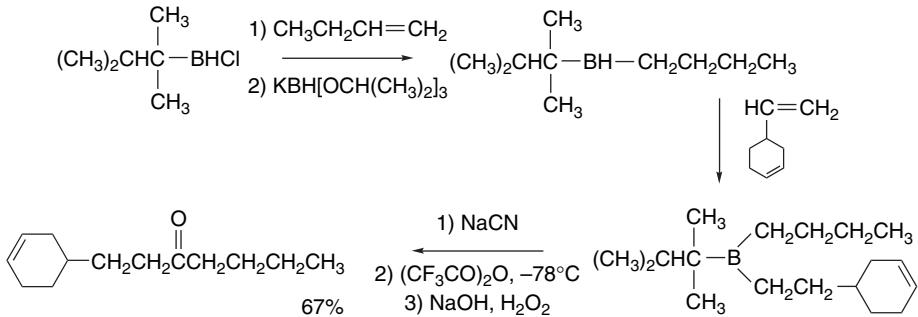
Another useful reagent for introduction of the carbonyl carbon is dichloromethyl methyl ether. In the presence of a hindered alkoxide base, it is deprotonated and acts as a nucleophile toward boron. Rearrangement then ensues with migration of two boron substituents. Oxidation gives a ketone.



Unsymmetrical ketones can be made by using either thexyloborane or thexylichloroborane.¹² Thexyloborane works well when one of the desired carbonyl substituents is derived from a moderately hindered alkene. Under these circumstances, a clean monoalkylation of thexyloborane can be accomplished, which is then followed by reaction with a second alkene and carbonylation.



Thexylichloroborane can be alkylated and then converted to a dialkylborane by a reducing agent such as $\text{KBH}[\text{OCH}(\text{CH}_3)_2]_3$, an approach that is preferred for terminal alkenes.

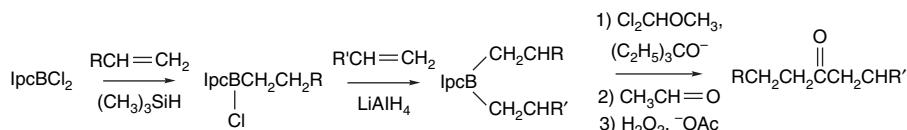


The success of both of these methods depends upon the thexy group being noncompetitive with the other groups in the migration steps.

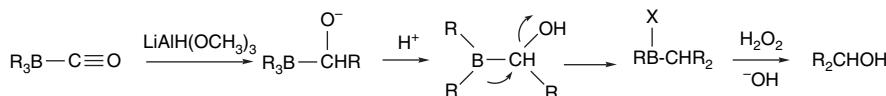
The formation of unsymmetrical ketones can also be done starting with IpcBCl_2 . Sequential reduction and hydroboration are carried out with two different alkenes. The first reduction can be done with $(\text{CH}_3)_3\text{SiH}$, but the second stage requires LiAlH_4 .

¹² H. C. Brown and E. Negishi, *J. Am. Chem. Soc.*, **89**, 5285 (1967); S. U. Kulkarni, H. D. Lee, and H. C. Brown, *J. Org. Chem.*, **45**, 4542 (1980).

In this procedure, dichloromethyl methyl ether is used as the source of the carbonyl carbon.¹³



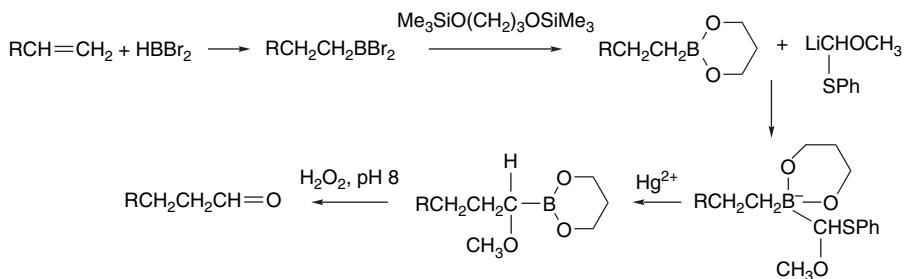
Scheme 9.1 shows several examples of one-carbon homologations involving boron to carbon migration. Entry 1 illustrates the synthesis of a symmetrical tertiary alcohol. Entry 2 involves interception of the intermediate after the first migration by reduction. Acid then induces a second migration. This sequence affords secondary alcohols.



Entries 3 to 5 show the use of alternative sources of the one carbon unit. In Entry 3, a tertiary alcohol is formed with one of the alkyl groups being derived from the dithioacetal reagent. Related procedures have been developed for ketones and tertiary alcohols using 2-lithio-2-alkyl-1,3-benzodithiole as the source of the linking carbon.¹⁴ Problem 9.3 deals with the mechanisms of these reactions.

Section B of the Scheme 9.1 shows several procedures for the synthesis of ketones. Entry 6 is the synthesis of a symmetrical ketone by carbonylation. Entry 7 illustrates the synthesis of an unsymmetrical ketone by the hexylborane method and also demonstrates the use of a functionalized olefin. Entries 8 to 10 illustrate synthesis of ketones by the cyanide-TFAA method. Entry 11 shows the synthesis of a bicyclic ketone involving intramolecular hydroboration of 1,5-cyclooctadiene. Entry 12 is another ring closure, generating a potential steroid precursor.

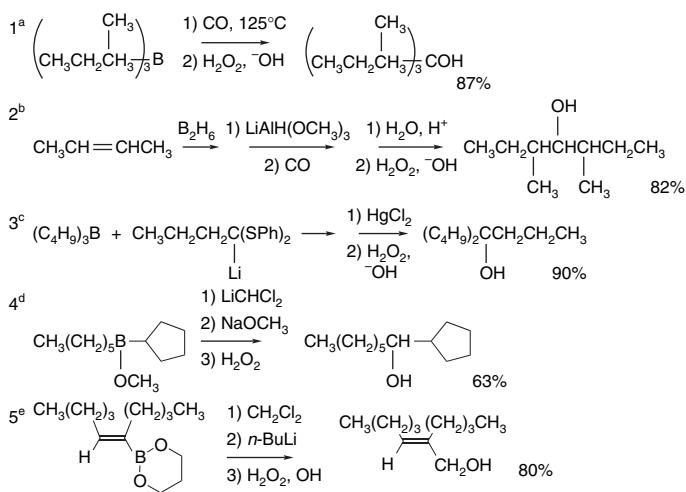
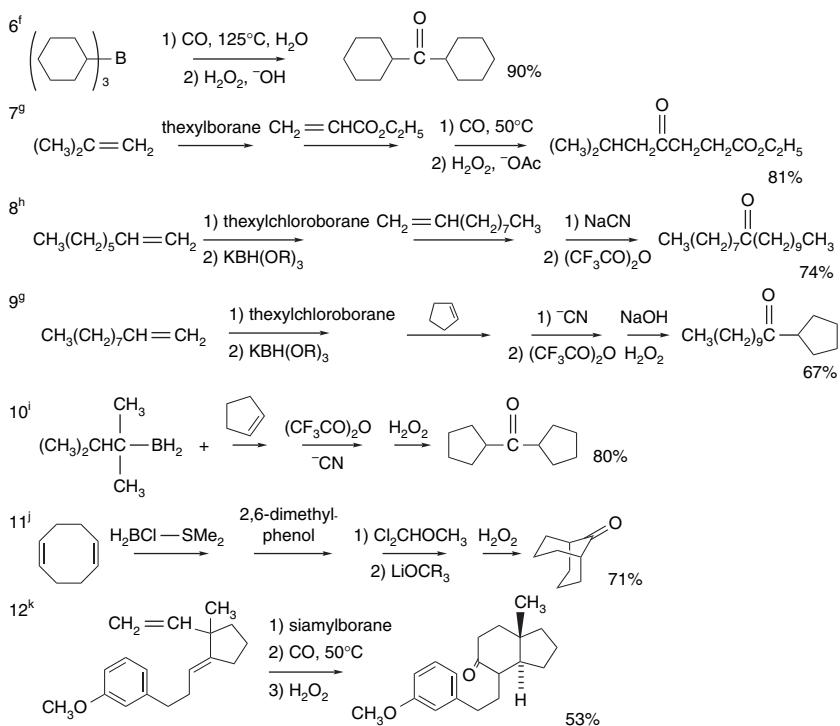
Section C illustrates the synthesis of aldehydes by boron homologation. Entry 13 is an example of synthesis of an aldehyde from an alkene using 9-BBN for hydroboration. Entry 14 illustrates an efficient process for one-carbon homologation to aldehydes that is based on cyclic boronate esters. These can be prepared by hydroboration of an alkene with dibromoborane, followed by conversion of the dibromoborane to the cyclic boronate. The homologation step is carried out by addition of methoxy(phenylthio)methylolithium to the boronate. The migration step is induced by mercuric ion. Use of chiral boranes and boronates leads to products containing groups of retained configuration.¹⁵



^{13.} H. C. Brown, S. V. Kulkarni, U. S. Racherla, and U. P. Dhokte, *J. Org. Chem.*, **63**, 7030 (1998).

^{14.} S. Ncube, A. Pelter, and K. Smith, *Tetrahedron Lett.*, 1893, 1895 (1979).

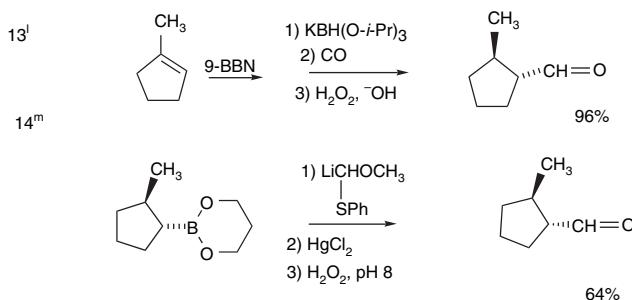
^{15.} M. V. Rangaishenvi, B. Singaram, and H. C. Brown, *J. Org. Chem.*, **56**, 3286 (1991).

Scheme 9.1. Homologation and Coupling of Organoboranes by Carbon Monoxide and Other One-Carbon Donors**A. Formation of alcohols****B. Formation of ketones**

(Continued)

Scheme 9.1. (Continued)

C. Formation of aldehydes

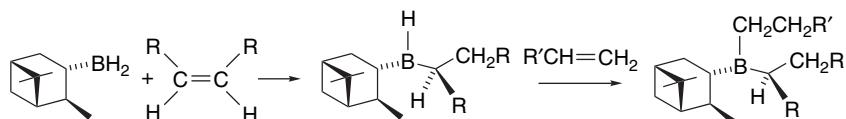


SECTION 9.1

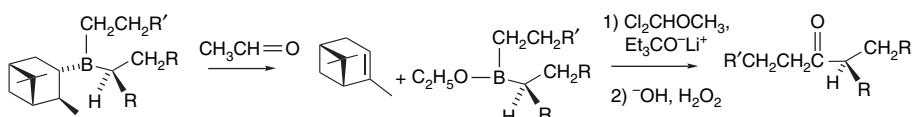
Organoboron Compounds

- a. H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.*, **89**, 2737 (1967).
- b. J. L. Hubbard and H. C. Brown, *Synthesis*, 676 (1978).
- c. R. J. Hughes, S. Ncube, A. Pelter, K. Smith, E. Negishi, and T. Yoshida, *J. Chem. Soc., Perkin Trans. I*, 1172 (1977); S. Ncube, A. Pelter, and K. Smith, *Tetrahedron Lett.*, 1893, 1895 (1979).
- d. H. C. Brown, T. Imai, P. T. Perumal, and B. Singaram, *J. Org. Chem.*, **50**, 4032 (1985).
- e. H. C. Brown, A. S. Phadke, and N. G. Bhat, *Tetrahedron Lett.*, **34**, 7845 (1993).
- f. H. C. Brown and M. W. Rathke, *J. Am. Chem. Soc.*, **89**, 2738 (1967).
- g. H. C. Brown and E. Negishi, *J. Am. Chem. Soc.*, **89**, 5285 (1967).
- h. S. U. Kulkarni, H. D. Lee, and H. C. Brown, *J. Org. Chem.*, **45**, 4542 (1980).
- i. A. Pelter, K. Smith, M. G. Hutchings, and K. Rowe, *J. Chem. Soc., Perkin Trans. I*, 129 (1975).
- j. H. C. Brown and S. U. Kulkarni, *J. Org. Chem.*, **44**, 2422 (1979).
- k. T. A. Bryson and W. E. Pye, *J. Org. Chem.*, **42**, 3214 (1977).
- l. H. C. Brown, J. L. Hubbard, and K. Smith, *Synthesis*, 701 (1979).
- m. H. C. Brown and T. Imai, *J. Am. Chem. Soc.*, **105**, 6285 (1983).

As can be judged from the preceding discussion, organoboranes are versatile intermediates for formation of carbon-carbon bonds. An important aspect of all of these synthetic procedures involving boron to carbon migration is that they occur with *retention of the configuration of the migrating group*. Since effective procedures for enantioselective hydroboration have been developed (see Section 4.5.3), these reactions offer the opportunity for enantioselective synthesis. A sequence for enantioselective formation of ketones starts with hydroboration by mono(isopinocampheyl)borane, (*Ipc* BH_2), which can be obtained in high enantiomeric purity.¹⁶ The hydroboration of a prochiral alkene establishes a new stereocenter. A third alkyl group can be introduced by a second hydroboration step.



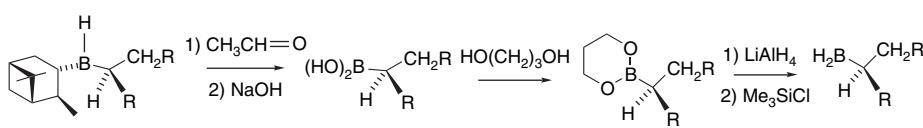
The trialkylborane can be transformed to a dialkyl(ethoxy)borane by heating with acetaldehyde, which releases the original chiral α -pinene. Finally application of one of the carbonylation procedures outlined in Scheme 9.1 gives a chiral ketone.¹⁷ The enantiomeric excess observed for ketones prepared in this way ranges from 60–90%.



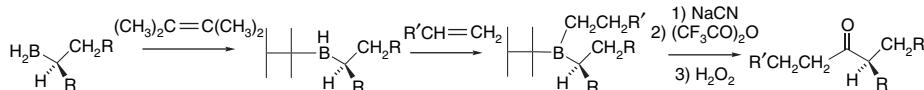
¹⁶ H. C. Brown, P. K. Jadhav, and A. K. Mandal, *J. Org. Chem.*, **47**, 5074 (1982).

¹⁷ H. C. Brown, R. K. Jadhav, and M. C. Desai, *Tetrahedron*, **40**, 1325 (1984).

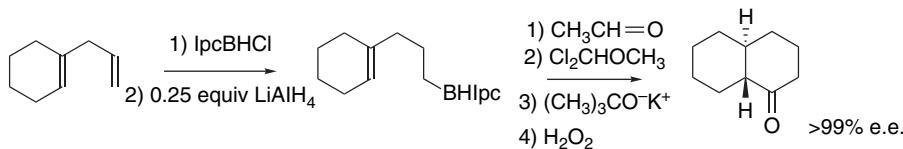
Higher enantiomeric purity can be obtained by a modified procedure in which the monoalkylborane intermediate is prepared by reduction of a cyclic boronate.¹⁸



Subsequent steps involve introduction of a thexyl group and then the second ketone substituent. Finally, the ketone is formed by the cyanide-TFAA method.

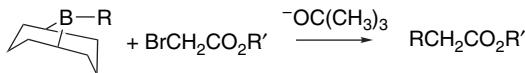


By starting with enantiomerically enriched IpcBHCl, it is possible to construct chiral cyclic ketones. For example, stepwise hydroboration of 1-allylcyclohexene and ring construction provides *trans*-1-decalone in greater than 99% e.e.¹⁹



9.1.3. Homologation via α -Haloenolates

Organoboranes can also be used to construct carbon-carbon bonds by several other types of reactions that involve migration of a boron substituent to carbon. One such reaction involves α -halo carbonyl compounds.²⁰ For example, ethyl bromoacetate reacts with trialkylboranes in the presence of base to give alkylated acetic acid derivatives in excellent yield. The reaction is most efficiently carried out with a 9-BBN derivative. These reactions can also be effected with β -alkenyl derivatives of 9-BBN to give β,γ -unsaturated esters.²¹

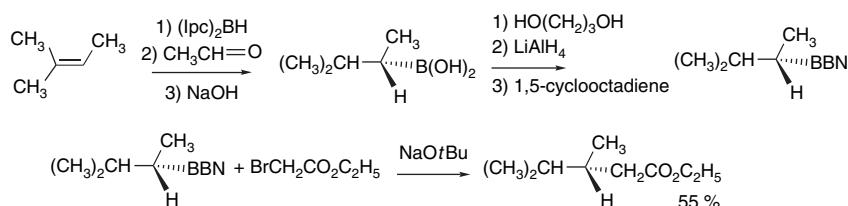


¹⁸ H. C. Brown, R. K. Bakshi, and B. Singaram, *J. Am. Chem. Soc.*, **110**, 1529 (1988); H. C. Brown, M. Srebnik, R. K. Bakshi, and T. E. Cole, *J. Am. Chem. Soc.*, **109**, 5420 (1987).

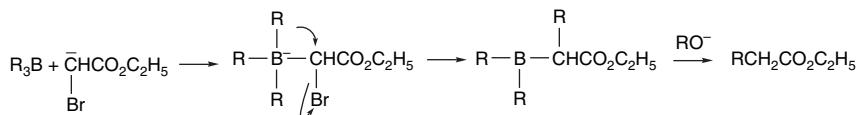
¹⁹ H. C. Brown, V. K. Mahindroo, and U. P. Dhokte, *J. Org. Chem.*, **61**, 1906 (1996); U. P. Dhokte, P. M. Pathare, V. K. Mahindroo, and H. C. Brown, *J. Org. Chem.*, **63**, 8276 (1998).

²⁰ H. C. Brown, M. M. Rogic, M. W. Rathke, and G. W. Kabalka, *J. Am. Chem. Soc.*, **90**, 818 (1968); H. C. Brown and M. M. Rogic, *J. Am. Chem. Soc.*, **91**, 2146 (1969).

²¹ H. C. Brown, N. G. Bhat, and J. B. Cambell, Jr., *J. Org. Chem.*, **51**, 3398 (1986).

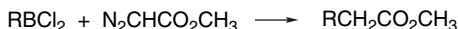


The mechanism of these alkylations involves a tetracoordinate boron intermediate formed by addition of the enolate of the α -bromo ester to the organoborane. The migration then occurs with displacement of bromide ion. In agreement with this mechanism, retention of configuration of the migrating group is observed.²³



α -Halo ketones and α -halo nitriles undergo similar reactions.²⁴

A closely related reaction employs α -diazo esters or α -diazo ketones.²⁵ With these compounds, molecular nitrogen acts as the leaving group in the migration step. The best results are achieved using dialkylchloroboranes or monoalkyldichloroboranes.



A number of these alkylation reactions are illustrated in Scheme 9.2. Entries 1 and 2 are typical examples of α -halo ester reactions. Entry 3 is a modification in which the highly hindered base potassium 2,6-di-*t*-butylphenoxide is used. Similar reaction conditions can be used with α -halo ketones (Entries 4 and 5) and nitriles (Entry 6). Entries 7 to 9 illustrate the use of diazo esters and diazo ketones. Entry 10 shows an application of the reaction to the synthesis of an amide.

9.1.4. Stereoselective Alkene Synthesis

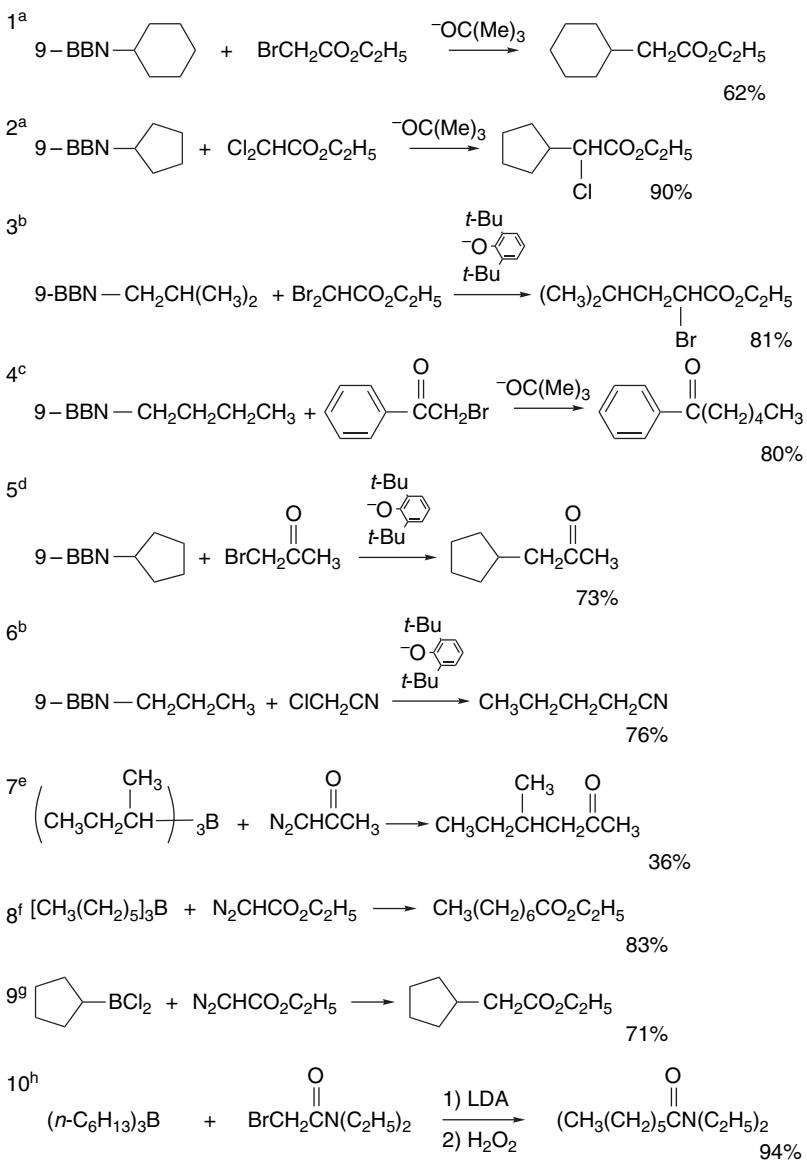
Several methods for stereoselective alkene synthesis are based on boron intermediates. One approach involves alkenylboranes, which can be prepared from terminal alkynes. Procedures have been developed for the synthesis of both *Z*- and *E*-alkenes.

²² H. C. Brown, N. N. Joshi, C. Pyun, and B. Singaram, *J. Am. Chem. Soc.*, **111**, 1754 (1989).

²³ H. C. Brown, M. M. Rogic, M. W. Rathke, and G. W. Kabalka, *J. Am. Chem. Soc.*, **91**, 2151 (1969).

²⁴ H. C. Brown, M. M. Rogic, H. Nambu, and M. W. Rathke, *J. Am. Chem. Soc.*, **91**, 2147 (1969); H. C. Brown, H. Nambu, and M. M. Rogic, *J. Am. Chem. Soc.*, **91**, 6853, 6855 (1969).

²⁵ H. C. Brown, M. M. Midland, and A. B. Levy, *J. Am. Chem. Soc.*, **94**, 3662 (1972); J. Hooz, J. N. Bridson, J. G. Calzada, H. C. Brown, M. M. Midland, and A. B. Levy, *J. Org. Chem.*, **38**, 2574 (1973).

Scheme 9.2. Homologation of Boranes by α -Halocarbonyl and Related Compounds

a. H. C. Brown and M. M. Rogic, *J. Am. Chem. Soc.*, **91**, 2146 (1969).

b. H. C. Brown, H. Nambu, and M. M. Rogic, *J. Am. Chem. Soc.*, **91**, 6855 (1969).

c. H. C. Brown, M. M. Rogic, H. Nambu, and M. W. Rathke, *J. Am. Chem. Soc.*, **91**, 2147 (1969).

d. H. C. Brown, H. Nambu, and M. M. Rogic, *J. Am. Chem. Soc.*, **91**, 6853 (1969).

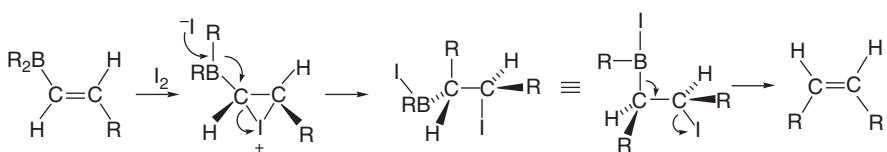
e. J. Hooz and S. Linke, *J. Am. Chem. Soc.*, **90**, 5936 (1968).

f. J. Hooz and S. Linke, *J. Am. Chem. Soc.*, **90**, 6891 (1968).

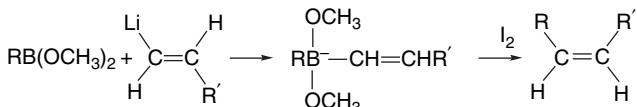
g. J. Hooz, J. N. Bridson, J. G. Caldaza, H. C. Brown, M. M. Midland, and A. B. Levy, *J. Org. Chem.*, **38**, 2574 (1973).

h. N.-S. Li, M.-Z. Deng, and Y.-Z. Huang, *J. Org. Chem.*, **58**, 6118 (1993).

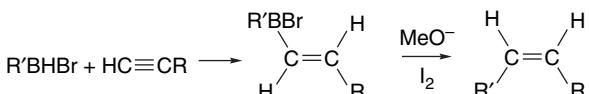
Treatment of alkenyldialkylboranes with iodine results in the formation of the *Z*-alkene with migration of one boron substituent.²⁶



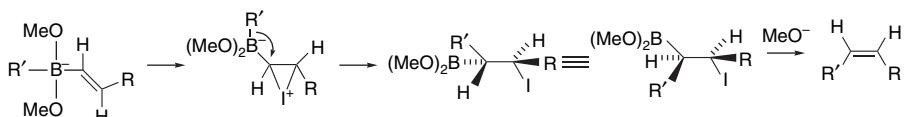
Similarly, alkenyllithium reagents add to dimethyl boronate to give adducts that decompose to *Z*-alkenes on treatment with iodine.²⁷



The synthesis of *Z*-alkenes can also be carried out starting with an alkylbromoborane, in which case migration presumably follows replacement of the bromide by methoxide.²⁸



The stereoselectivity of these reactions arises from a base-induced *anti* elimination after the migration. The elimination is induced by addition of methoxide to the boron, generating an anionic center.



E-Alkenes can be prepared by several related reactions.²⁹ Hydroboration of a bromoalkyne generates an α -bromoalkenylborane. On treatment with methoxide ion these intermediates undergo $B \rightarrow C$ migration to give an alkyl alkenylborinate. Protonolysis generates an *E*-alkene.



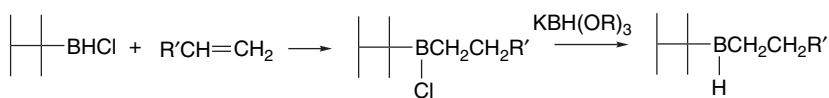
²⁶ G. Zweifel, H. Arzoumanian, and C. C. Whitney, *J. Am. Chem. Soc.*, **89**, 3652 (1967); G. Zweifel, R. P. Fisher, J. T. Snow, and C. C. Whitney, *J. Am. Chem. Soc.*, **93**, 6309 (1971).

²⁷ D. A. Evans, T. C. Crawford, R. C. Thomas, and J. A. Walker, *J. Org. Chem.*, **41**, 3947 (1976).

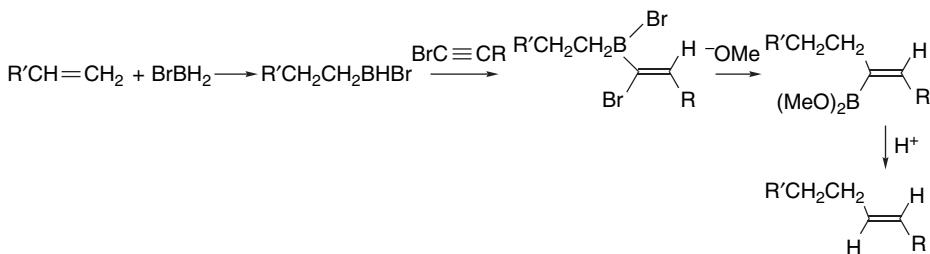
²⁸ H. C. Brown, D. Basavaiah, S. U. Kulkarni, N. G. Bhat, and J. V. N. Vara Prasad, *J. Org. Chem.*, **53**, 239 (1988).

²⁹ H. C. Brown, D. Basavaiah, S. U. Kulkarni, H. P. Lee, E. Negishi, and J.-J. Katz, *J. Org. Chem.*, **51**, 5270 (1986).

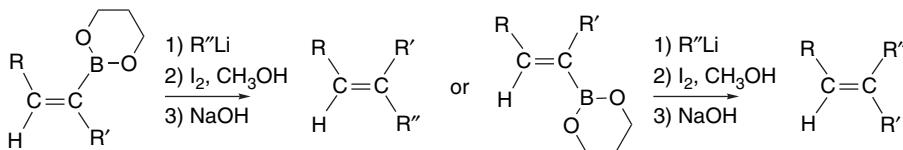
The dialkylboranes can be prepared from the hexylchloroborane. The hexyl group does not normally migrate.



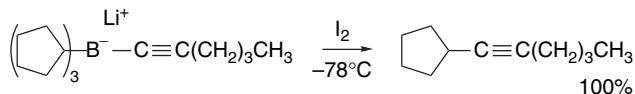
A similar strategy involves initial hydroboration by BrBH_2 .³⁰



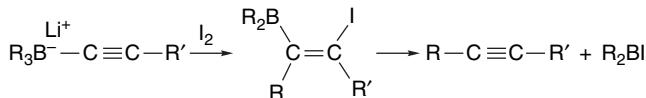
Stereoselective syntheses of trisubstituted alkenes are based on *E*- and *Z*-alkenyldioxaborinanes. Reaction with an alkylolithium reagent forms an “ate” adduct that rearranges on treatment with iodine in methanol.³¹



Both alkynes and alkenes can be obtained from adducts of terminal alkynes and boranes. Reaction with iodine induces migration and results in the formation of the alkylated alkyne.³²



The mechanism involves electrophilic attack by iodine at the triple bond, which induces migration of an alkyl group from boron. This is followed by elimination of dialkyliodoboron.

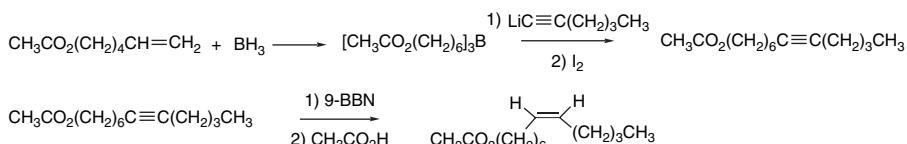


³⁰ H. C. Brown, T. Imai, and N. G. Bhat, *J. Org. Chem.*, **51**, 5277 (1986); H. C. Brown, D. Basavaiah, and S. U. Kulkarni, *J. Org. Chem.*, **47**, 3808 (1982).

³¹ H. C. Brown and N. G. Bhat, *J. Org. Chem.*, **53**, 6009 (1988).

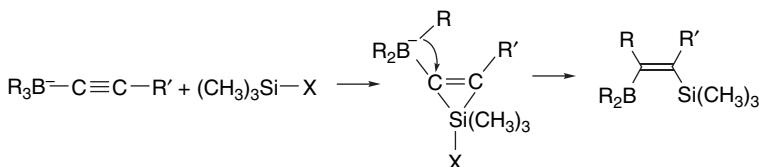
³² A. Suzuki, N. Miyaura, S. Abiko, M. Itoh, H. C. Brown, J. A. Sinclair, and M. M. Midland, *J. Am. Chem. Soc.*, **95**, 3080 (1973); A. Suzuki, N. Miyaura, S. Abiko, M. Itoh, M. M. Midland, J. A. Sinclair, and H. C. Brown, *J. Org. Chem.*, **51**, 4507 (1986).

If the alkyne is hydroborated and then protonolyzed a *Z*-alkene is formed. This method was used to prepare an insect pheromone containing a *Z*-double bond.

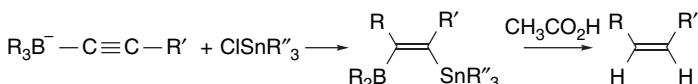


Ref. 33

The B \rightarrow C migration can also be induced by other types of electrophiles. Trimethylsilyl chloride or trimethylsilyl triflate induces a stereospecific migration to form β -trimethylsilyl alkanylboranes having *cis* silicon and boron substituents.³⁴ It has been suggested that this stereospecificity arises from a silicon-bridged intermediate.

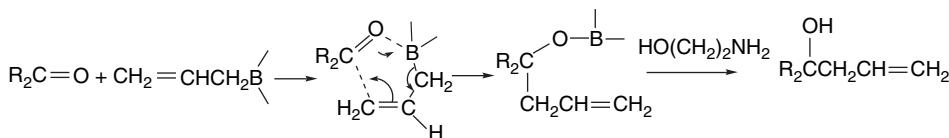


Tributyltin chloride also induces migration and gives the product in which the C–Sn bond is *cis* to the C–B bond. Protonolysis of both the C–Sn and C–B bonds by acetic acid gives the corresponding *Z*-alkene.³⁵



9.1.5. Nucleophilic Addition of Allylic Groups from Boron Compounds

Allylic boranes such as 9-allyl-9-BBN react with aldehydes and ketones to give allylic carbinols. The reaction begins by Lewis acid-base coordination at the carbonyl oxygen, which both increases the electrophilicity of the carbonyl group and weakens the C–B bond to the allyl group. The dipolar adduct then reacts through a cyclic TS. Bond formation takes place at the γ -carbon of the allyl group and the double bond shifts.³⁶ After the reaction is complete, the carbinol product is liberated from the borinate ester by displacement with ethanolamine. Yields for a series of aldehydes and ketones were usually above 90% for 9-allyl-9-BBN.



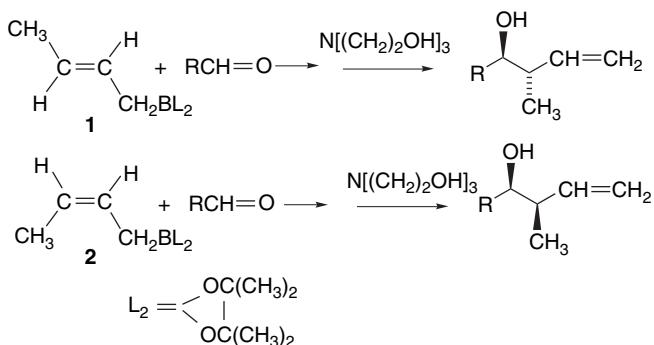
³³ H. C. Brown and K. K. Wang, *J. Org. Chem.*, **51**, 4514 (1986).

³⁴ P. Binger and R. Koester, *Synthesis*, 309 (1973); E. J. Corey and W. L. Seibel, *Tetrahedron Lett.*, **27**, 905 (1986).

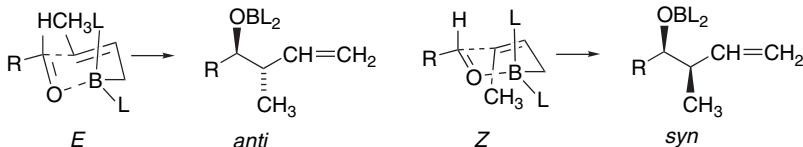
³⁵ K. K. Wang and K.-H. Chu, *J. Org. Chem.*, **49**, 5175 (1984).

³⁶ G. W. Kramer and H. C. Brown, *J. Org. Chem.*, **42**, 2292 (1977).

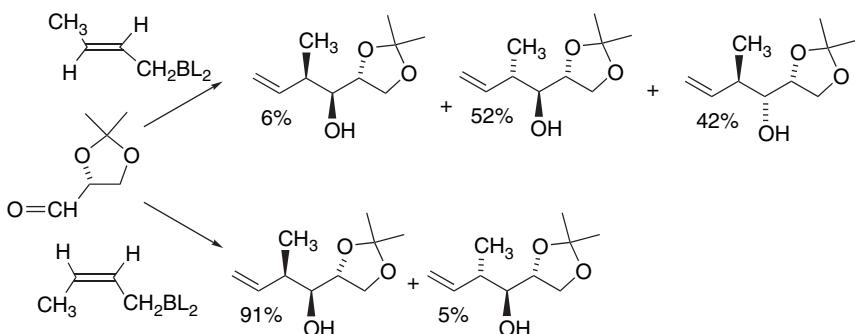
The cyclic mechanism predicts that the addition reaction will be stereospecific with respect to the geometry of the double bond in the allylic group, and this has been demonstrated to be the case. The *E*- and *Z*-2-but enyl cyclic boronates **1** and **2** were synthesized and allowed to react with aldehydes. The *E*-boronate gave the carbinol with *anti* stereochemistry, whereas the *Z*-boronate resulted in the *syn* product.³⁷



This stereochemistry is that predicted by a cyclic TS in which the aldehyde substituent occupies an equatorial position.

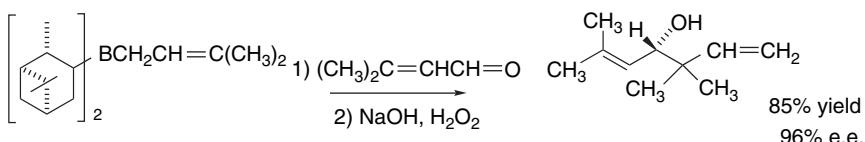


The diastereoselectivity observed in simple systems led to investigation of enantiomerically pure aldehydes. It was found that the *E*- and *Z*-2-but enylboronates both exhibit high *syn-anti* diastereoselectivity with chiral α -substituted aldehydes. However, only the *Z*-isomer also exhibited high selectivity toward the diastereotopic faces of the aldehyde.³⁸

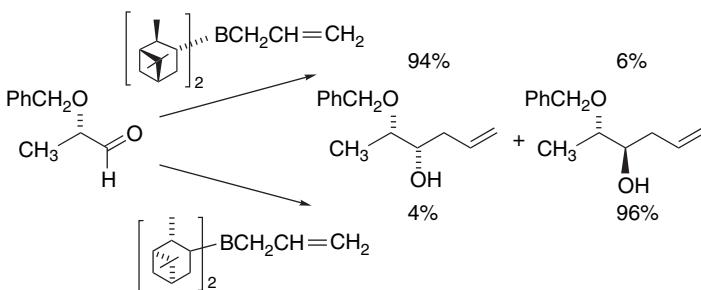


The allylation reaction has been extended to enantiomerically pure allylic boranes and borinates. For example, the 3-methyl-2-but enyl derivative of $(\text{Ipc})_2\text{BH}$ reacts with aldehydes to give carbinols of greater than 90% e.e. in most cases.³⁹

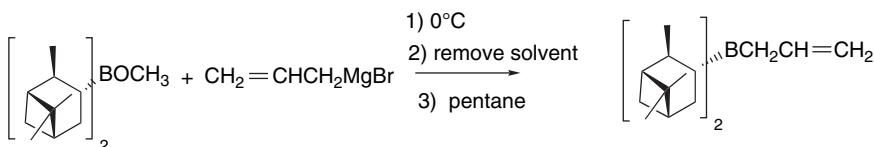
- ³⁷. R. W. Hoffmann and H.-J. Zeiss, *J. Org. Chem.*, **46**, 1309 (1981); K. Fujita and M. Schlosser, *Helv. Chim. Acta*, **65**, 1258 (1982).
- ³⁸. W. R. Roush, M. A. Adam, A. E. Walts, and D. J. Harris, *J. Am. Chem. Soc.*, **108**, 3422 (1986).
- ³⁹. H. C. Brown and P. K. Jadhav, *Tetrahedron Lett.*, **25**, 1215 (1984); H. C. Brown, P. K. Jadhav, and K. S. Bhat, *J. Am. Chem. Soc.*, **110**, 1535 (1988).



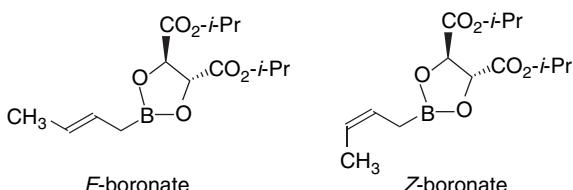
β -Allyl-bis-(isopinocampheyl)borane exhibits high stereoselectivity in reactions with chiral α -substituted aldehydes.⁴⁰ The stereoselectivity is *reagent controlled*, in that there is no change in stereoselectivity between the two enantiomeric boranes in reaction with a chiral aldehyde. Rather, the configuration of the product is determined by the borane. Both enantiomers of $(\text{Ipc})_2\text{BH}$ are available, so either enantiomer can be prepared from a given aldehyde.



It has been found that conditions in which purified allylic boranes are used give even higher enantioselectivity and faster reactions than the reagents prepared and used *in situ*. The boranes are prepared from Grignard reagents and evidently the residual Mg^{2+} salts inhibit the addition reaction. Magnesium-free borane solutions can be obtained by precipitation and extracting the borane into pentane. These purified reagents react essentially instantaneously with typical aldehydes at -100°C .⁴¹



Another extensively developed group of allylic boron reagents for enantioselective synthesis is derived from tartrates.⁴²

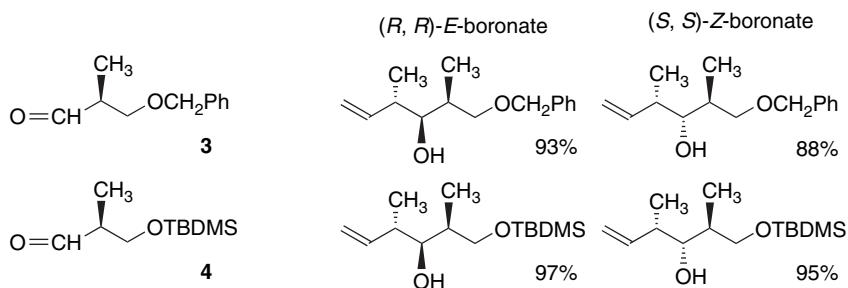


⁴⁰ H. C. Brown, K. S. Bhat, and R. S. Randad, *J. Org. Chem.*, **52**, 319 (1987); H. C. Brown, K. S. Bhat, and R. S. Randad, *J. Org. Chem.*, **54**, 1570 (1989).

⁴¹ U. S. Racherla and H. C. Brown, *J. Org. Chem.*, **56**, 401 (1991).

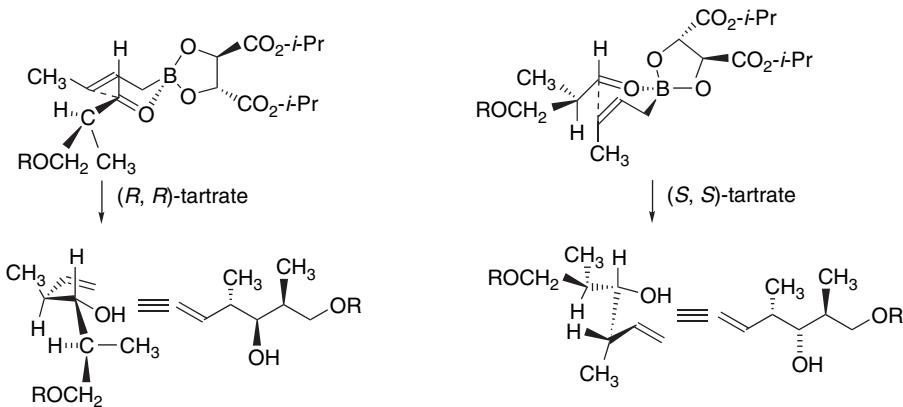
⁴² W. R. Roush, K. Ando, D. B. Powers, R. L. Halterman, and A. Palkowitz, *Tetrahedron Lett.*, **29**, 5579 (1988); W. R. Roush, L. Banfi, J. C. Park, and L. K. Hong, *Tetrahedron Lett.*, **30**, 6457 (1989).

With unhindered aldehydes such as cyclohexanecarboxaldehyde, the diastereoselectivity is higher than 95%, with the *E*-boronate giving the *anti* adduct and the *Z*-boronate giving the *syn* adduct. Enantioselectivity is about 90% for the *E*-boronate and 80% for the *Z*-boronate. With more hindered aldehydes, such as pivalaldehyde, the diastereoselectivity is maintained but the enantioselectivity drops somewhat. These reagents also give excellent double stereodifferentiation when used with chiral aldehydes. For example, the aldehydes **3** and **4** give at least 90% enantioselection with both the *E*- and *Z*-boronates.⁴³



These reagents exhibit reagent control of stereoselectivity and have proven to be very useful in stereoselective synthesis of polyketide natural products, which frequently contain arrays of alternating methyl and oxygen substituents.⁴⁴

The enantioselectivity is consistent with cyclic TSs. The key element determining the orientation of the aldehyde within the TS is the interaction of the aldehyde group with the tartrate ligand.



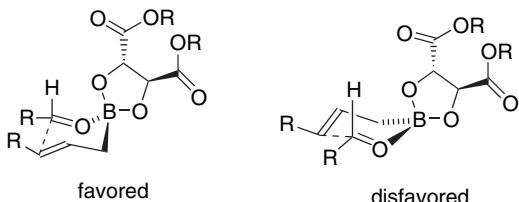
The preferred orientation results from the greater repulsive interaction between the carbonyl groups of the aldehyde and ester in the disfavored orientation.⁴⁵ There is also an attractive electrostatic interaction between the ester carbonyl and the aldehyde

⁴³. W. R. Roush, A. D. Palkowitz, and M. A. J. Palmer, *J. Org. Chem.*, **52**, 316 (1987); W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz, and R. L. Halterman, *J. Am. Chem. Soc.*, **112**, 6339 (1990); W. R. Roush, A. D. Palkowitz, and K. Ando, *J. Am. Chem. Soc.*, **112**, 6348 (1990).

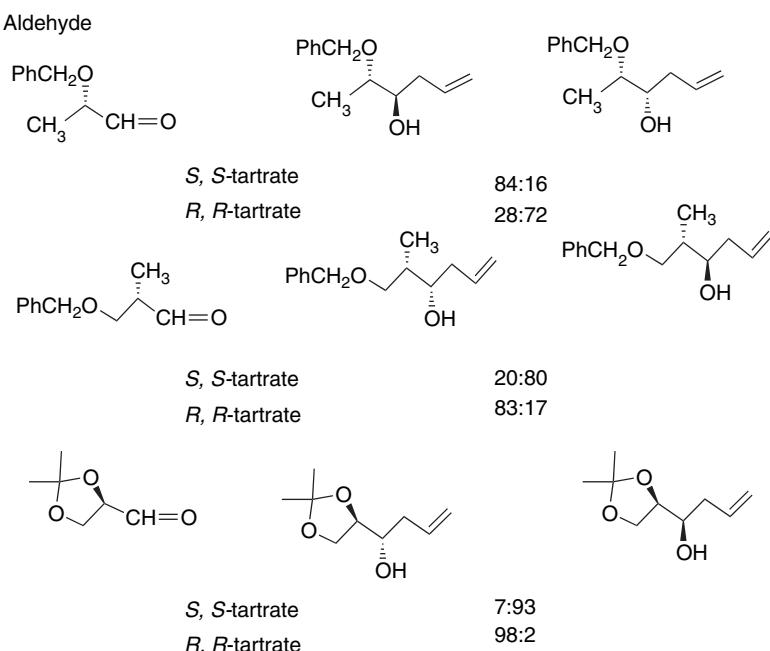
⁴⁴. W. R. Roush and A. D. Palkowitz, *J. Am. Chem. Soc.*, **109**, 953 (1987).

⁴⁵. W. R. Roush, A. E. Walts, and L. K. Hoong, *J. Am. Chem. Soc.*, **107**, 8186 (1985); W. R. Roush, L. K. Hoong, M. A. J. Palmer, and J. C. Park, *J. Org. Chem.*, **55**, 4109 (1990).

carbon.⁴⁶ This orientation and the *E*- or *Z*-configuration of the allylic group as part of a chair TS determine the stereochemistry of the product.



Detailed studies have been carried out on the stereoselectivity of α - and β -substituted aldehydes toward the tartrate boronates.⁴⁷ α -Benzylxy and β -benzyloxy- α -methylpropionaldehyde gave approximately 4:1 diastereoselectivity with both the *R, R*- and *S, S*-enantiomers. The stereoselectivity is reagent (tartrate) controlled. The acetonide of glyceraldehydes showed higher stereoselectivity.



The tartrate-based allylboration reaction has been studied computationally using B3LYP/6-31G* calculations.⁴⁶ The ester groups were modeled by formyl. It was concluded that the major factor in determining enantioselectivity is a favorable electrostatic interaction between a formyl oxygen lone pair and the positively polarized carbon of the reacting aldehyde. This gives rise to a calculated energy difference of 1.6 kcal/mol between the best *si* and the best *re* TS (see Figure 9.1). In the preferred conformation of the TS, the formyl carbonyl is nearly in the plane of the dioxaborolane ring. This orientation has been calculated to be optimal for α -oxy esters⁴⁸ and is observed in the crystal structure of the tartrate ligands.⁴⁹

⁴⁶ B. W. Gung, X. Xue, and W. R. Roush, *J. Am. Chem. Soc.*, **124**, 10692 (2002).

⁴⁷ W. R. Roush, L. K. Hoong, M. A. J. Palmer, J. A. Straub, and A. D. Palkowitz, *J. Org. Chem.*, **55**, 4117 (1990).

⁴⁸ K. B. Wiberg and K. E. Laiding, *J. Am. Chem. Soc.*, **109**, 5935 (1987).

⁴⁹ W. R. Roush, A. M. Ratz, and J. A. Jablonowski, *J. Org. Chem.*, **57**, 2047 (1992).

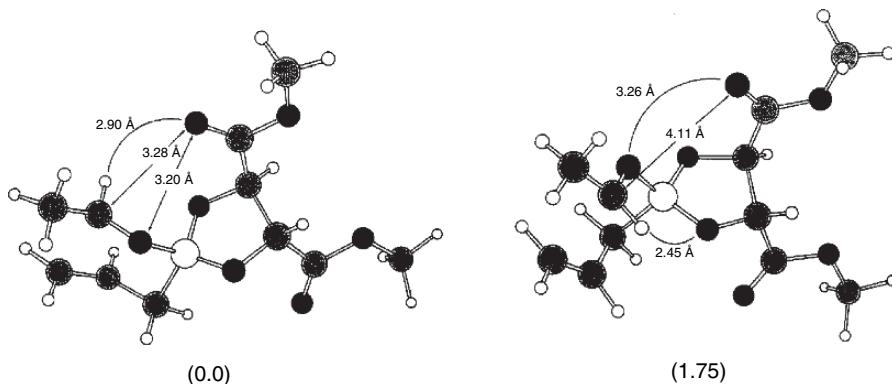
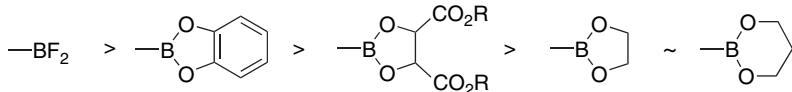


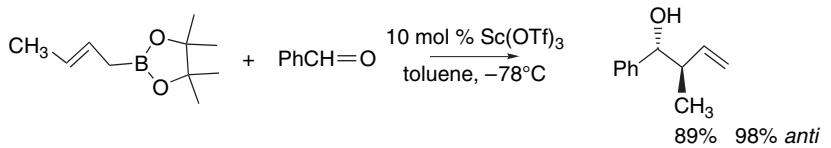
Fig. 9.1. Most favorable *si* and *re* transition structures for allylboration of acetaldehyde. The *si* TS is favored by 1.75 kcal/mol, which is attributed to an electrostatic attraction between a formyl carbonyl oxygen lone pair and the acetaldehyde carbonyl carbon. In the *re* TS, there is a repulsive interaction between lone pairs on the formyl and acetaldehyde carbonyl oxygens. Reproduced from *J. Am. Chem. Soc.*, **124**, 10692 (2002), by permission of the American Chemical Society.

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

Another computational study examined the effect that the boron ligands might have on the reactivity of allyl derivatives.⁵⁰ The order found is shown below and is related to the level of the boron LUMO. The dominant factor seems to be the π -donor capacity of the ligands. The calculated order is consistent with experimental data.⁵¹



Recently the scope of the allylboration has been expanded by the discovery that it is catalyzed by certain Lewis acids, especially $\text{Sc}(\text{OTf})_3$.⁵² The catalyzed reaction exhibits the same high diastereoselectivity as the uncatalyzed reaction, which indicates that it proceeds through a cyclic TS.



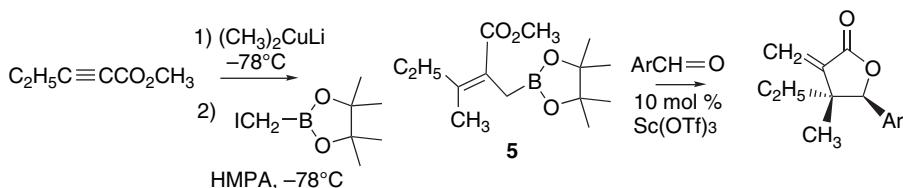
Ref. 52b

⁵⁰ K. Omoto and H. Fujimoto, *J. Org. Chem.*, **63**, 8331 (1998).

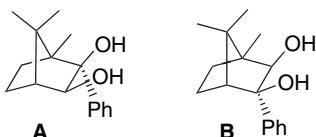
⁵¹ H. C. Brown, U. S. Racherla, and P. J. Pellechia, *J. Org. Chem.*, **55**, 1868 (1990).

⁵² (a) J. W. J. Kennedy and D. G. Hall, *J. Am. Chem. Soc.*, **124**, 11586 (2002); (b) T. Ishiyama, T.-A. Ahiko, and N. Miyaura, *J. Am. Chem. Soc.*, **124**, 12414 (2002).

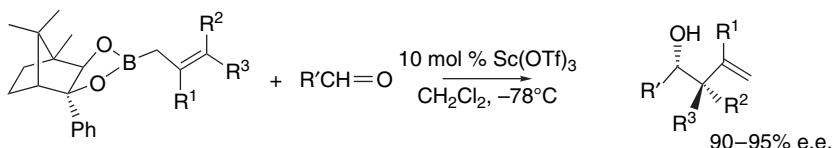
The catalysis has made reactions of certain functionalized boronates possible. For example, a carbocupration and alkylation allowed the synthesis of boronate **5**. Reaction with aldehydes gave α -methylene lactones with high stereoselectivity.⁵³



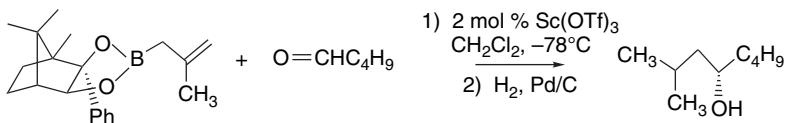
The catalysis has been extended for use with chiral boronates and those from the phenyl-substituted bornane diol derivatives **A** and **B**⁵⁴ have been found to be particularly effective.⁵⁵



These reagents have been utilized for allyl-, 2-methylallyl-, and *E*- and *Z*-2-but enyl derivatives. Enantioselectivity of 90–95% is achieved with alkyl- and aryl-, as well as α - and β -siloxy aldehydes.



This method has been applied to the synthesis of (*S*)-2-methyl-4-octanol, an aggregation pheromone of *Metamasius hemipterus*.⁵⁶



Mechanistic studies have suggested that the TS involves bonding of Sc^{3+} to one of the boronate oxygens,⁵⁷ which is consistent with the observation that the catalysts do not have much effect on the rate of allylic boranes. The phenyl substituent on the

⁵³ J. W. J. Kennedy and D. G. Hall, *J. Org. Chem.*, **69**, 4412 (2004).

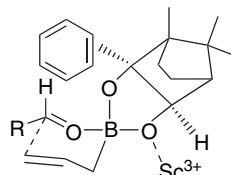
⁵⁴ T. Herold, U. Schrott, and R. W. Hoffmann, *Chem. Ber.*, **114**, 359 (1981).

⁵⁵ H. Lachance, X. Lu, M. Gravel, and D. G. Hall, *J. Am. Chem. Soc.*, **125**, 10160 (2003).

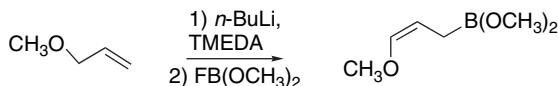
⁵⁶ M. Gravel, H. Lachance, X. Lu, and D. G. Hall, *Synthesis*, 1290 (2004).

⁵⁷ V. Rauniyar and D. G. Hall, *J. Am. Chem. Soc.*, **126**, 4518 (2004).

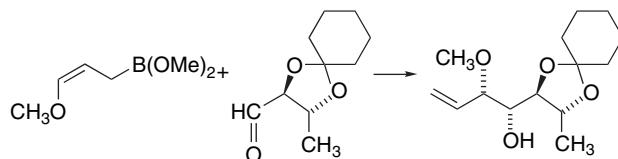
boronate is thought to assist in the aldehyde binding through a $\pi-\pi^*$ interaction with the aromatic ring.



Various functionalized allylic boronates have been prepared.⁵⁸ *Z*-3-Methoxy derivatives can be prepared by lithiation of allyl methyl ether and substitution.⁵⁹

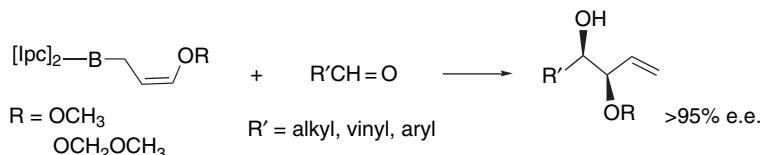


They react with aldehydes to give α -methoxy alcohols.

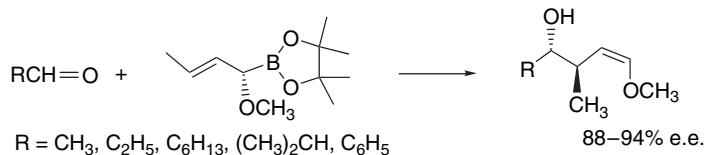


Ref. 60

Oxygenated allylic derivatives of $(\text{Ipc})_2\text{BH}$ also show excellent diastereoselectivity.



1-Methoxy-2-but enyl pinacol boronates show good stereoselectivity toward achiral aldehydes.⁶¹



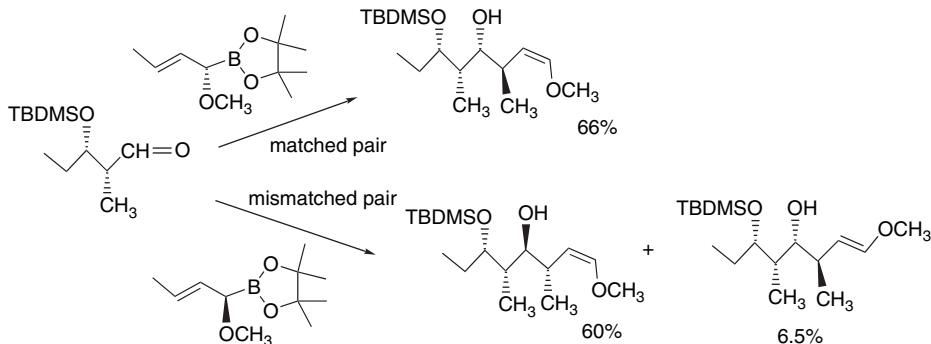
These reagents were also examined with chiral α -substituted aldehydes. The allylboration reagent dominates the enantioselectivity in both matched and mismatched pairs.

⁵⁸. P. G. M. Wuts, P. A. Thompson, and G. R. Callen, *J. Org. Chem.*, **48**, 5398 (1983); E. Moret and M. Schlosser, *Tetrahedron Lett.*, **25**, 4491 (1984).

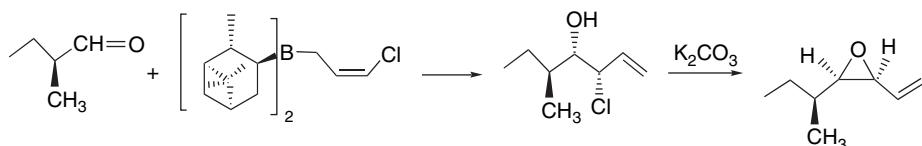
⁵⁹. P. G. M. Wuts and S. S. Bigelow, *J. Org. Chem.*, **47**, 2498 (1982); K. Fujita and M. Schlosser, *Helv. Chim. Acta*, **65**, 1258 (1982).

⁶⁰. W. R. Roush, M. R. Michaelides, D. F. Tai, and W. K. M. Chong, *J. Am. Chem. Soc.*, **109**, 7575 (1987).

⁶¹. R. W. Hoffmann and S. Dresely, *Chem. Ber.*, **122**, 903 (1989).



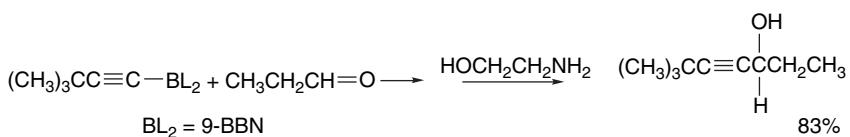
Chloro-substituted $[Ipc]_2BH$ derivatives have proven useful for enantioselective synthesis of vinyl epoxides.⁶²



Allyl tetrafluoroborates are also useful allylboration reagents. They can be made from allylic boronic acids and are stable solids.⁶³ The reaction with aldehydes is mediated by BF_3 , which is believed to provide the difluoroborane by removing a fluoride. The addition reactions occur with high stereoselectivity, indicating a cyclic TS.



β -Alkynyl derivatives of 9-BBN act as mild sources of nucleophilic acetylenic groups. Reaction occurs with both aldehydes and ketones, but the rate is at least 100 times faster for aldehydes.⁶⁴



The facility with which the transfer of acetylenic groups occurs is associated with the relative stability of the *sp*-hybridized carbon. This reaction is an alternative to the more common addition of magnesium or lithium salts of acetylides to aldehydes.

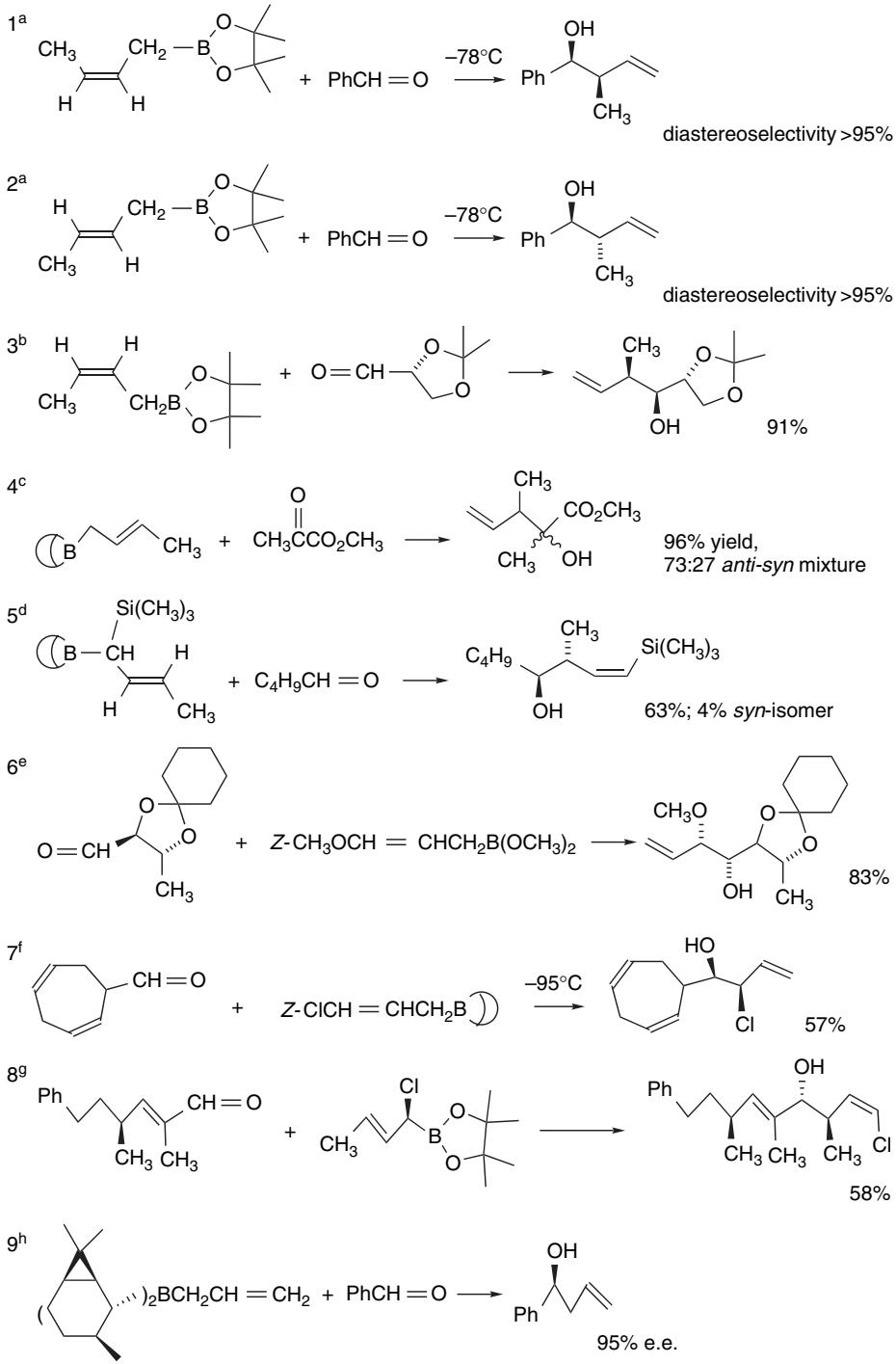
Scheme 9.3 illustrates some examples of syntheses of allylic carbinols via allylic boranes and boronate esters. Entries 1 and 2 are among the early examples that

⁶². S. Hu, S. Jayaraman, and A. C. Oehschlager, *J. Org. Chem.*, **63**, 8843 (1998).

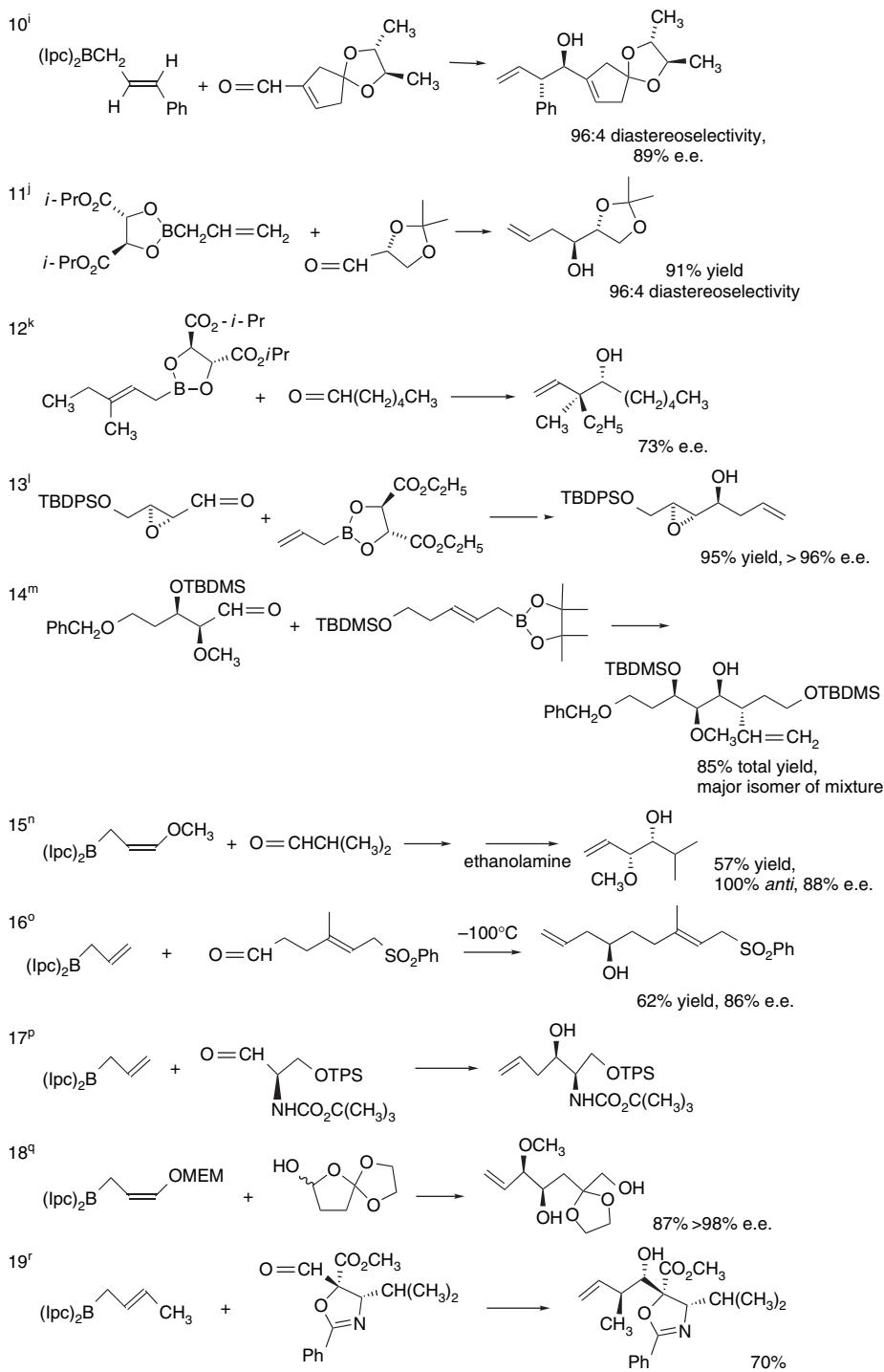
⁶³. R. A. Batey, A. N. Thandani, D. V. Smil, and A. J. Lough, *Synthesis*, 990 (2000).

⁶⁴. H. C. Brown, G. A. Molander, S. M. Singh, and U. S. Racherla, *J. Org. Chem.*, **50**, 1577 (1985).

Scheme 9.3. Addition Reactions of Allylic Boranes and Carbonyl Compounds



(Continued)



(Continued)

Scheme 9.3. (Continued)

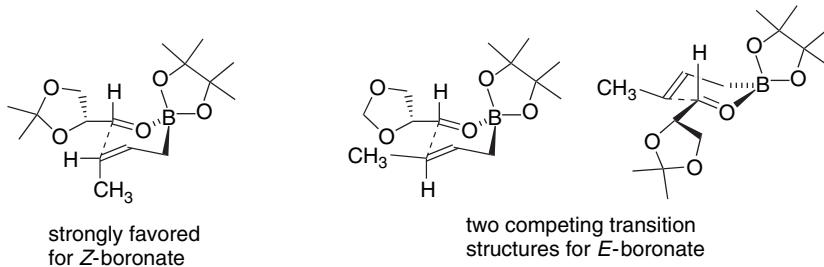
CHAPTER 9

Carbon-Carbon

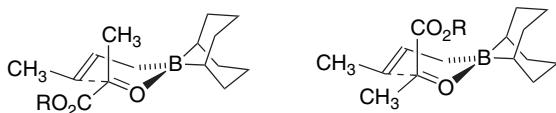
Bond-Forming Reactions
of Compounds of Boron,
Silicon, and Tin

- a. R. W. Hoffmann and H.-J. Zeiss, *J. Org. Chem.*, **46**, 1309 (1981).
- b. W. R. Roush and A. E. Walts, *Tetrahedron Lett.*, **26**, 3427 (1985); W. R. Roush, M. A. Adam, and D. J. Harris, *J. Org. Chem.*, **50**, 2000 (1985).
- c. Y. Yamamoto, K. Maruyama, T. Komatsu, and W. Ito, *J. Org. Chem.*, **51**, 886 (1986).
- d. Y. Yamamoto, H. Yatagai, and K. Maruyama, *J. Am. Chem. Soc.*, **103**, 3229 (1981).
- e. W. R. Roush, M. R. Michaelides, D. F. Tai, and W. K. M. Chong, *J. Am. Chem. Soc.*, **109**, 7575 (1987).
- f. C. Hertweck and W. Boland, *Tetrahedron Lett.*, **53**, 14651 (1997).
- g. H. C. Brown, R. S. Randad, K. S. Bhat, M. Zaidlewicz, and U. S. Racherla, *J. Am. Chem. Soc.*, **112**, 2389 (1990).
- h. R. W. Hoffmann, E. Haeberlin, and T. Rolide, *Synthesis*, 207 (2002).
- i. L. K. Truesdale, D. Swanson, and R. C. Sun, *Tetrahedron Lett.*, **26**, 5009 (1985).
- j. W. R. Roush, A. E. Walts, and L. K. Hoong, *J. Am. Chem. Soc.*, **107**, 8186 (1985).
- k. Y. Yamamoto, S. Hara, and A. Suzuki, *Synlett*, 883 (1996).
- l. W. R. Roush, J. A. Straub, and M. S. Van Nieuwenhze, *J. Org. Chem.*, **56**, 1636 (1985).
- m. P. G. M. Wuts and S. S. Bigelow, *J. Org. Chem.*, **53**, 5023 (1988).
- n. H. C. Brown, P. K. Jadhav, and K. S. Bhat, *J. Am. Chem. Soc.*, **110**, 1535 (1988).
- o. M. Z. Hoemann, K. A. Agrios, and J. Aube, *Tetrahedron*, **53**, 11087 (1997).
- p. K. C. Nicolaou, M. E. Bunnage, and K. Koide, *Chem. Eur. J.*, **1**, 454 (1995).
- q. A. L. Smith, E. N. Pitsinos, C.-K. Hwang, Y. Mizuno, H. Saimoto, G. R. Scarlato, T. Suzuki, and K. C. Nicolaou, *J. Am. Chem. Soc.*, **115**, 7612 (1993).
- r. T. Sunazuka, T. Nagamitsu, K. Matsuzaki, H. Tanaka, S. Omura, and A. B. Smith, III, *J. Am. Chem. Soc.*, **115**, 5302 (1993).

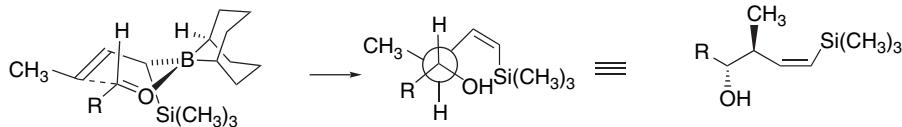
demonstrate the high diastereoselectivity of the allylboration reaction. Entry 3 examines the facial selectivity of glyceraldehyde acetonide toward the achiral reagents derived from butenyl pinacol borane. It was found that the reaction with the *Z*-2-butenyl derivative is highly enantioselective, the *E*-isomer was much less so. It was suggested that steric interaction of the *E*-methyl group with the dioxolane in the expected TS ring led to involvement of a second transition structure.



Entry 4 shows the reaction of 9-(*E*-2-butenyl)-9BBN with methyl pyruvate. This reaction is not very stereoselective, which is presumably due to a modest preference for the orientation of the methyl and methoxycarbonyl groups in the TS. Only use of an extremely sterically demanding pyruvic ester achieved high diastereoselectivity.



R	product ratio	
CH ₃	73	27
Ph	80	20
2,6-diMePh	75	25
2,4,6-tri- <i>t</i> -BuPh	100	0



Entries 6 and 7 involve functionalized allyl groups, with a Z- γ -methoxy group in Entry 6 and a Z- γ -chloro group in Entry 7. Both give *syn* products; in the case of Entry 7 the chlorohydrin was cyclized to the *cis* epoxide, which is a pheromone (lamoxirene) of a species of algae. Entry 8 is another example of the use of a chloro-substituted allylic borane. Entry 9 involves one of the alternatives to $(Ipc)_2BH$ for enantioselective allylation. In Entry 10, both the aldehyde and allyl group contain chiral centers, but the borane is presumably the controlling factor in the stereoselectivity. Entries 11 to 13 demonstrate several enantioselective reactions using the tartrate-derived chiral auxiliaries. Entry 14 is an example of *reactant-controlled* stereochemistry involving the achiral β -allyl pinacol borane. This reaction proceeded with low stereochemical control to give four isomers in a ratio of 18:3.4:1.4:1. Entry 15 shows high diastereoselectivity and enantioselectivity in a reaction with a Z- γ -methoxyallyl-(*Ipc*)₂-borane. Entries 16 to 19 are examples of the use of allylboration in multistage syntheses. Entry 16 involves magnesium-free conditions (see p. 799). Entry 17 was used to construct balanol, a PKC inhibitor, and demonstrates *reagent control* of stereochemistry by allyl-B(*Ipc*)₂ without interference from the protected α -amino and β -hydroxy substituents. Entries 18 and 19 also involve functionalized aldehydes.

9.2. Organosilicon Compounds

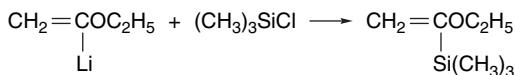
9.2.1. Synthesis of Organosilanes

Silicon is similar in electronegativity to carbon. The carbon-silicon bond is quite strong (~ 75 kcal) and trialkylsilyl groups are stable to many of the reaction conditions that are used in organic synthesis. Much of the repertoire of synthetic organic chemistry can be used for elaboration of organosilanes.⁶⁵ For example, the Grignard reagent derived from chloromethyltrimethylsilane is a source of nucleophilic $CH_2Si(CH_3)_3$ units. Two of the most general means of synthesis of organosilanes are nucleophilic displacement of halogen from a halosilane by an organometallic reagent and addition of silanes at multiple bonds (*hydrosilation*). Organomagnesium and organolithium compounds react with trimethylsilyl chloride to give the corresponding tetrasubstituted silanes.



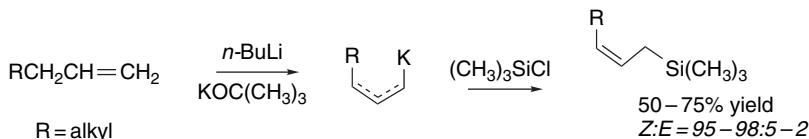
⁶⁵. L. Birkofe and O. Stuhl, in *The Chemistry of Organic Silicon Compounds*, S. Patai and Z. Rappoport, eds., Wiley-Interscience, 1989, New York, Chap. 10.

⁶⁶. R. K. Boeckman, Jr., D. M. Blum, B. Ganem, and N. Halvey, *Org. Synth.*, **58**, 152 (1978).

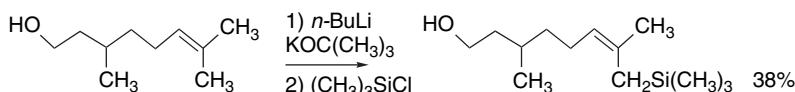


Ref. 67

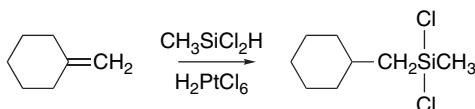
Metallation of alkenes with $n\text{-BuLi-KOC}(\text{CH}_3)_3$ provides a route that is stereoselective for *Z*-allylic silanes.⁶⁸ (See p. 632 for discussion of this metallation method.)



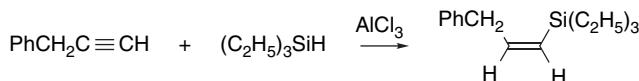
These conditions are also applicable to functionalized systems that are compatible with metallation by this “superbase.”⁶⁹



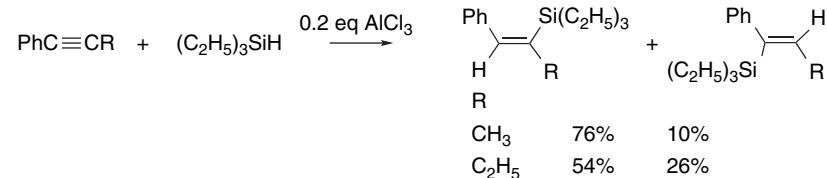
Silicon substituents can be introduced into alkenes and alkynes by hydrosilation.⁷⁰ This reaction, in contrast to hydroboration, does not occur spontaneously, but it can be carried out in the presence of catalysts such as H_2PtCl_6 , hexachloroplatinic acid. Other catalysts are also available.⁷¹ Halosilanes are more reactive than trialkylsilanes.⁷²



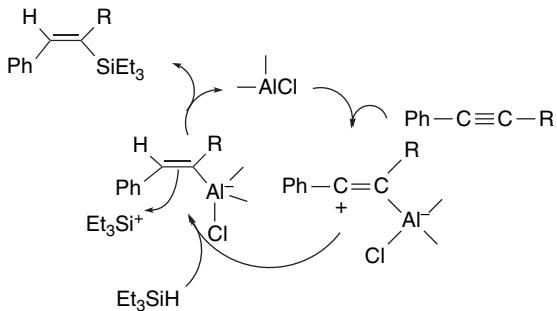
Alkenylsilanes can be made by Lewis acid–catalyzed hydrosilation of alkynes. Both AlCl_3 and $\text{C}_2\text{H}_5\text{AlCl}_2$ are effective catalysts.⁷³ The reaction proceeds by net *anti* addition, giving the *Z*-alkenylsilane. The reaction is regioselective for silylation of the terminal carbon.



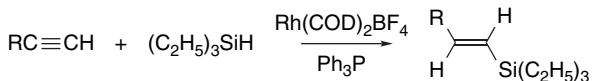
- ⁶⁷. R. F. Cunico and C.-P. Kuan, *J. Org. Chem.*, **50**, 5410 (1985).
- ⁶⁸. O. Desponds, L. Franzini, and M. Schlosser, *Synthesis*, 150 (1997).
- ⁶⁹. E. Moret, L. Franzini, and M. Schlosser, *Chem. Ber.*, **130**, 335 (1997).
- ⁷⁰. J. L. Speier, *Adv. Organomet. Chem.*, **17**, 407 (1979); E. Lukenvics, *Russ. Chem. Rev. (Engl. Transl.)*, **46**, 264 (1977); N. D. Smith, J. Mancuso, and M. Lautens, *Chem. Rev.*, **100**, 3257 (2000); M. Brunner, *Angew. Chem. Int. Ed. Engl.*, **43**, 2749 (2004); B. M. Trost and Z. T. Ball, *Synthesis*, 853 (2005).
- ⁷¹. A. Onopchenko and E. T. Sabourin, *J. Org. Chem.*, **52**, 4118 (1987). H. M. Dickens, R. N. Hazeldine, A. P. Mather, and R. V. Parish, *J. Organomet. Chem.*, **161**, 9 (1978); A. J. Cornish and M. F. Lappert, *J. Organomet. Chem.*, **271**, 153 (1984).
- ⁷². T. G. Selin and R. West, *J. Am. Chem. Soc.*, **84**, 1863 (1962).
- ⁷³. N. Asao, T. Sudo, and Y. Yamamoto, *J. Org. Chem.*, **61**, 7654 (1996); T. Sudo, N. Asao, V. Gevorgyan, and Y. Yamamoto, *J. Org. Chem.*, **64**, 2494 (1999).



The reaction is formulated as an electrophilic attack by the aluminum halide, followed by hydride abstraction and transmetalation. A vinyl cation intermediate can account for both the regiochemistry and the stereochemistry.

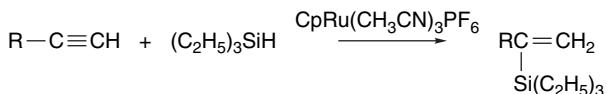


A variety of transition metal complexes catalyze hydrosilylation of alkynes. Catalysis of hydrosilylation by rhodium gives *E*-alkenylsilanes from 1-alkynes.⁷⁴

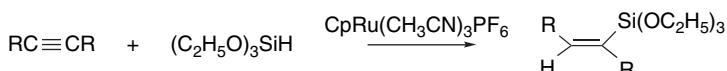


Ref. 75

$\text{CpRu}(\text{CH}_3\text{CN})_3\text{PF}_6$ catalyzes hydrosilylation of both terminal and internal alkynes. With this catalyst, addition exhibits the opposite regiochemistry.



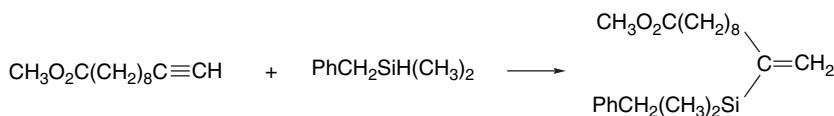
With internal alkynes, the stereochemistry of addition is *anti*.



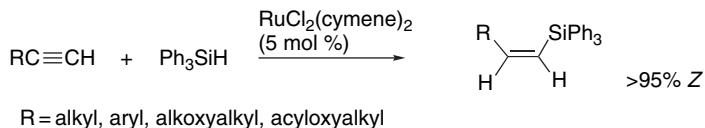
⁷⁴. R. Takeuchi, S. Nitta, and D. Watanabe, *J. Org. Chem.*, **60**, 3045 (1995).

⁷⁵. B. M. Trost and Z. T. Ball, *J. Am. Chem. Soc.*, **123**, 12726 (2001).

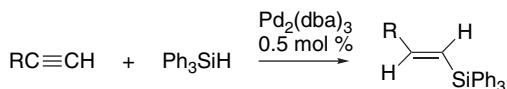
This method has been used to prepare alkenyl benzylidemethylsilanes.⁷⁶ These derivatives are amenable to synthetic transformation involving F⁻-mediated debenzylation.



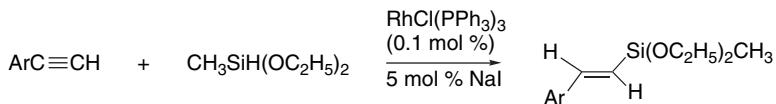
Other ruthenium-based catalysts are also active. Ruthenium dichloride–cymene complex is stereoselective for formation of the *Z*-vinyl silanes from terminal alkynes.



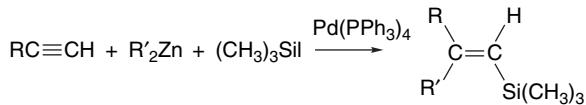
Palladium-phosphine catalysts have also been used in the addition of triphenylsilane.⁷⁷ In this case, the *E*-silane is formed.



High stereoselectivity was noted with Wilkinson's catalyst in the reaction of arylalkynes with diethoxymethylsilane. Interestingly, the stereoselectivity was dependent on the order of mixing of the reagents and the catalyst. When the alkyne was added to a mixture of catalyst and silane, the *Z*-isomer was formed. Reversing the order and adding the silane to an alkyne-catalyst mixture led to formation of the *E*-product.⁷⁸



Tandem *syn* addition of alkyl and trimethylsilyl groups can be accomplished with dialkylzinc and trimethylsilyl iodide in the presence of a Pd(0) catalyst.⁷⁹

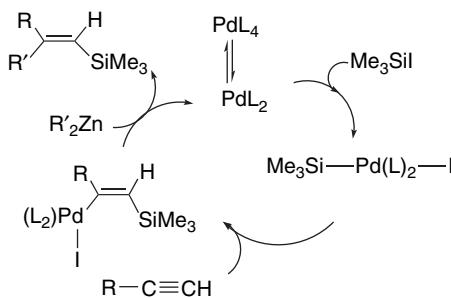


⁷⁶ B. M. Trost, M. R. Machacek, and Z. T. Ball, *Org. Lett.*, **5**, 1895 (2003).

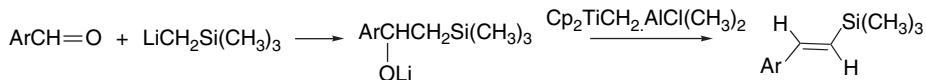
⁷⁷ D. Motoda, H. Shinokubo, and K. Oshima, *Synlett*, 1529 (2002).

⁷⁸ A. Mori, E. Takahisa, H. Kajiro, K. Hirabayashi, Y. Nishihara, and T. Hiyama, *Chem. Lett.*, 443 (1998).

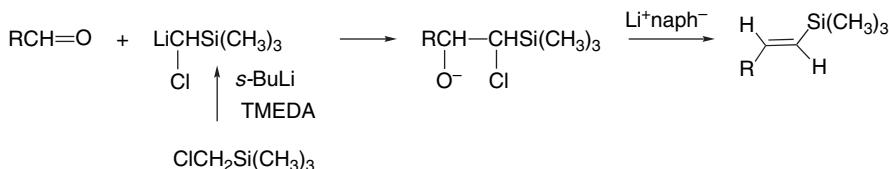
⁷⁹ N. Chatani, N. Amishiro, T. Morii, T. Yamashita, and S. Murai, *J. Org. Chem.*, **60**, 1834 (1995).



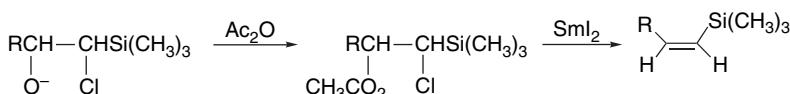
Several variations of the Peterson reaction have been developed for synthesis of alkenylsilanes.⁸⁰ *E*-β-Arylvinylsilanes can be obtained by dehydration of β-silyloxy alkoxides formed by addition of lithiomethyl trimethylsilane to aromatic aldehydes. Specific Lewis acids have been found to be advantageous for the elimination step.⁸¹



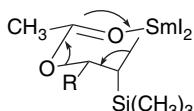
Alkenylsilanes can be prepared from aldehydes and ketones using lithio(chloromethyl)trimethylsilane. The adducts are subjected to a reductive elimination by lithium naphthalenide. This procedure is stereoselective for the *E*-isomer with both alkyl and aryl aldehydes.⁸²



The adducts can be directed toward *Z*-alkenylsilanes by acetylation and reductive elimination using SmI₂.⁸³



The stereoselectivity in this case is attributed to elimination through a cyclic TS, but is considerably reduced with aryl aldehydes.



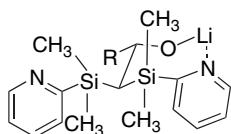
⁸⁰ C. Trindle, J.-T. Hwang, and F. A. Carey, *J. Org. Chem.*, **38**, 2664 (1973); P. F. Hudrik, E. L. Agwaramgbo, and A. M. Hudrik, *J. Org. Chem.*, **54**, 5613 (1989).

⁸¹ M. L. Kwan, C. W. Yeung, K. L. Breno, and K. M. Doxsee, *Tetrahedron Lett.*, **42**, 1411 (2001).

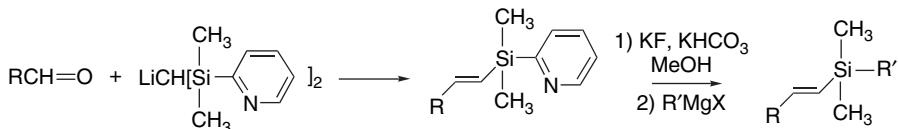
⁸² J. Barluenga, J. L. Fernandez-Simon, J. M. Concellon, and M. Yus, *Synthesis*, 234 (1988).

⁸³ J. M. Concellon, P. L. Bernad, and E. Bardales, *Org. Lett.*, **3**, 937 (2001).

Specialized silyl substituents have been developed. High yields of *E*-alkenylsilanes were obtained using *bis*-(dimethyl-2-pyridyl)silylmethyllithium.⁸⁴ The stereoselectivity is attributed to a cyclic TS for the addition step.

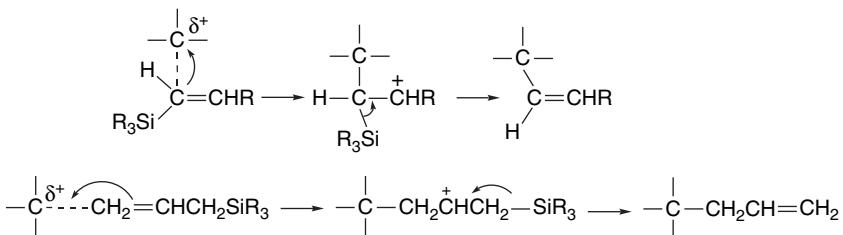


If necessary for further applications, the 2-pyridyl group can be exchanged by alkyl in a two-step sequence that takes advantage of the enhanced leaving-group ability of the 2-pyridyl group.

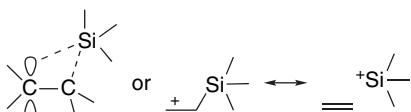


9.2.2. General Features of Carbon-Carbon Bond-Forming Reactions of Organosilicon Compounds

Alkylsilanes are not very nucleophilic because there are no high-energy electrons in the sp^3 - sp^3 carbon-silicon bond. Most of the valuable synthetic procedures based on organosilanes involve either alkenyl or allylic silicon substituents. The dominant reactivity pattern involves attack by an electrophilic carbon intermediate at the double bond that is followed by desilylation. Attack on alkenylsilanes takes place at the α -carbon and results in overall replacement of the silicon substituent by the electrophile. Attack on allylic groups is at the γ -carbon and results in loss of the silicon substituent and an allylic shift of the double bond.



The crucial influence on the reactivity pattern in both cases is the *very high stabilization that silicon provides for carbocationic character at the β -carbon atom*. This stabilization is attributed primarily to hyperconjugation with the C-Si bond (see Part A, Section 3.4.1).⁸⁵

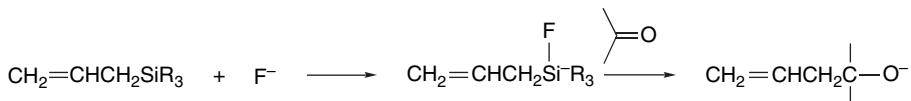


⁸⁴ K. Itami, T. Nokami, and J. Yoshida, *Org. Lett.*, **2**, 1299 (2000).

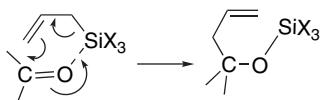
⁸⁵ S. G. Wierschke, J. Chandrasekhar, and W. L. Jorgensen, *J. Am. Chem. Soc.*, **107**, 1496 (1985); J. B. Lambert, G. Wang, R. B. Finzel, and D. H. Teramura, *J. Am. Chem. Soc.*, **109**, 7838 (1987).

Most reactions of alkenyl and allylic silanes require strong carbon electrophiles and Lewis acid catalysts are often involved. The most useful electrophiles from a synthetic standpoint are carbonyl compounds, iminium ions, and electrophilic alkenes.

There are also some reactions of allylic silanes that proceed through anionic silicate species. These reactions usually involve activation by fluoride and result in transfer of an allylic anion.

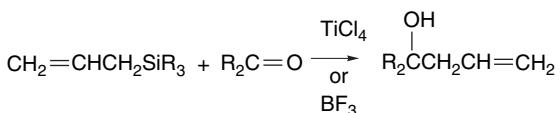


Trichloro- and trifluorosilanes introduce another dimension into the reactivity of allylic silanes. The silicon in these compounds is electrophilic and can expand to pentacoordinate and hexacoordinate structures. These reactions can occur through a cyclic or chelated TS.

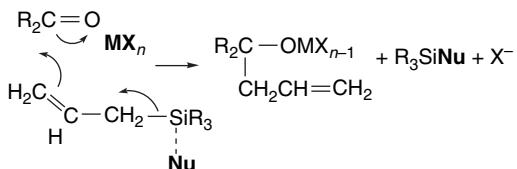


9.2.3. Addition Reactions with Aldehydes and Ketones

A variety of electrophilic catalysts promote the addition of allylic silanes to carbonyl compounds.⁸⁶ The original catalysts included typical Lewis acids such as TiCl_4 or BF_3 .⁸⁷ This reaction is often referred to as the *Sakurai reaction*.



These reactions involve activation of the carbonyl group by the Lewis acid. A nucleophile, either a ligand from the Lewis acid or the solvent, assists in the desilylation step.

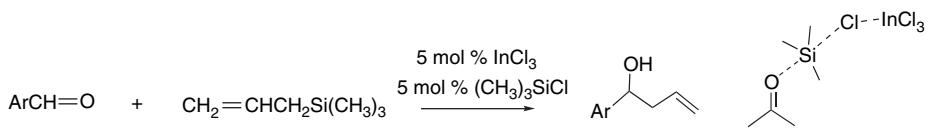


Various other Lewis acids have been explored as catalysts, and the combination $\text{InCl}_3\text{-}(\text{CH}_3)_3\text{SiCl}$ has been found to be effective.⁸⁸ The catalysis requires both components and is attributed to assistance from O-silylation of the carbonyl compound.

⁸⁶ A. Hosomi, *Acc. Chem. Res.*, **21**, 200 (1988); I. Fleming, J. Dunoques, and R. Smithers, *Org. React.*, **37**, 57 (1989).

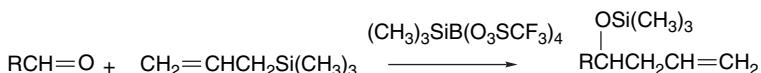
⁸⁷ A. Hosomi and H. Sakurai, *Tetrahedron Lett.*, 1295 (1976).

⁸⁸ Y. Onishi, T. Ito, M. Yasuda, and A. Baba, *Eur. J. Org. Chem.*, 1578 (2002); Y. Onishi, T. Ito, M. Yasuda, and A. Baba, *Tetrahedron*, **58**, 8227 (2002).

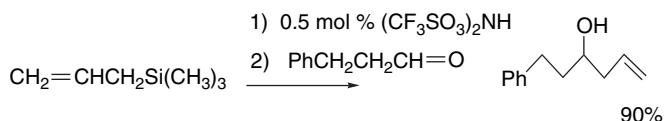


Lanthanide salts, such as $\text{Sc}(\text{O}_3\text{SCF}_3)_3$, are also effective catalysts.⁸⁹

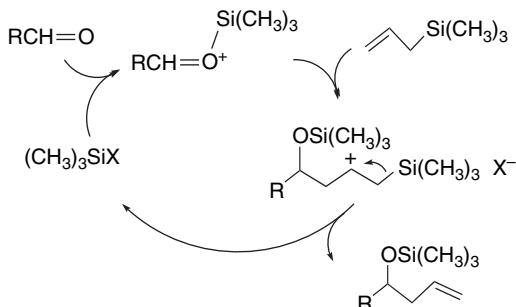
Silylating reagents such as TMSI and TMS triflate have only a modest catalytic effect, but the still more powerful silylating reagent $(\text{CH}_3)_3\text{SiB}(\text{O}_3\text{SCF}_3)_4$ does induce addition to aldehydes.⁹⁰



In another procedure, $(\text{CH}_3)_3\text{SiN}(\text{O}_3\text{SCF}_3)$ is generated in situ from triflimide.⁹¹



These reagents initiate a catalytic cycle that regenerates the active silylation species.⁹² (See p. 83 for a similar cycle in the Mukaiyama reaction.)



Although the allylation reaction is formally analogous to the addition of allylic boranes to carbonyl derivatives, it does not normally occur through a cyclic TS. This is because, in contrast to the boranes, the silicon in allylic silanes has little Lewis acid character and does not coordinate at the carbonyl oxygen. The stereochemistry of addition of allylic silanes to carbonyl compounds is consistent with an acyclic TS. The *E*-stereoisomer of 2-but enyl(trimethyl)silane gives nearly exclusively the product in

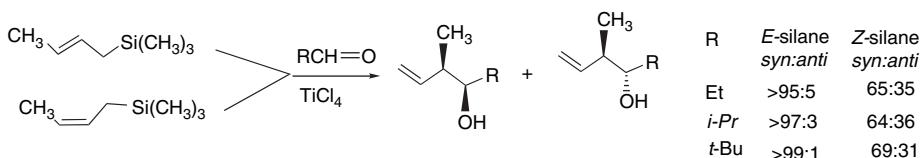
89. V. K. Aggarwal and G. P. Vennall, *Tetrahedron Lett.*, **37**, 3745 (1996).

90. A. P. Davis and M. Jaspars, *Angew. Chem. Int. Ed. Engl.*, **31**, 470 (1992).

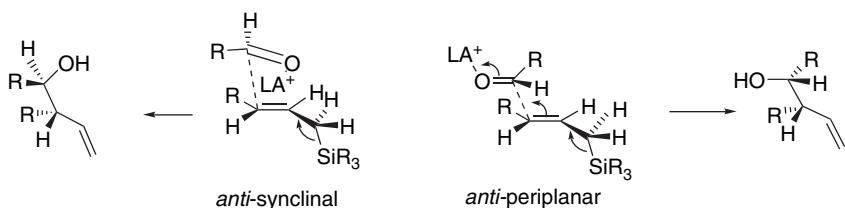
91. K. Ishihara, Y. Hiraiwa, and H. Yamamoto, *Synlett*, 1851 (2001).

92. T. K. Hollis and B. Bosnich, *J. Am. Chem. Soc.*, **117**, 4570 (1995).

which the newly formed hydroxyl group is *syn* to the methyl substituent; the *Z*-isomer is also modestly selective for the *syn* isomer.⁹³

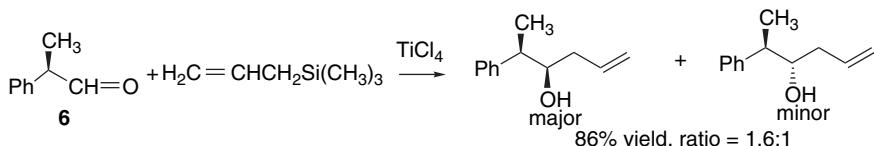


Both *anti*-synclinal and *anti*-periplanar TSs are considered to be feasible. These differ in the relative orientation of the C=C and C=O bonds. The *anti*-synclinal arrangement is usually preferred.⁹⁴



The addition reaction of allylsilane to acetaldehyde with BF_3 as the Lewis acid has been modeled computationally.⁹⁵ The lowest-energy TSs found, which are shown in Figure 9.2, were of the synclinal type, with dihedral angles near 60° . Although the structures are acyclic, there is an apparent electrostatic attraction between the fluorine and the silicon that imparts some cyclic character to the TS. Both *anti* and *syn* structures were of comparable energy for the model. However, steric effects that arise by replacement of hydrogen on silicon with methyl are likely to favor the *anti* TS.

When chiral aldehydes such as **6** are used, there is a modest degree of diastereoselectivity in the direction predicted by an open Felkin TS.⁹⁶



⁹³ T. Hayashi, K. Kabeto, I. Hamachi, and M. Kumada, *Tetrahedron Lett.*, **24**, 2865 (1983).

⁹⁴ S. E. Denmark and N. G. Almstead, *J. Org. Chem.*, **59**, 5130 (1994).

⁹⁵ A. Bottino, A. L. Costa, D. Di Tommaso, I. Rossi, and E. Tagliavini, *J. Am. Chem. Soc.*, **119**, 12131 (1997).

⁹⁶ M. Nakada, Y. Urano, S. Kobayashi, and M. Ohno, *J. Am. Chem. Soc.*, **110**, 4826 (1988).

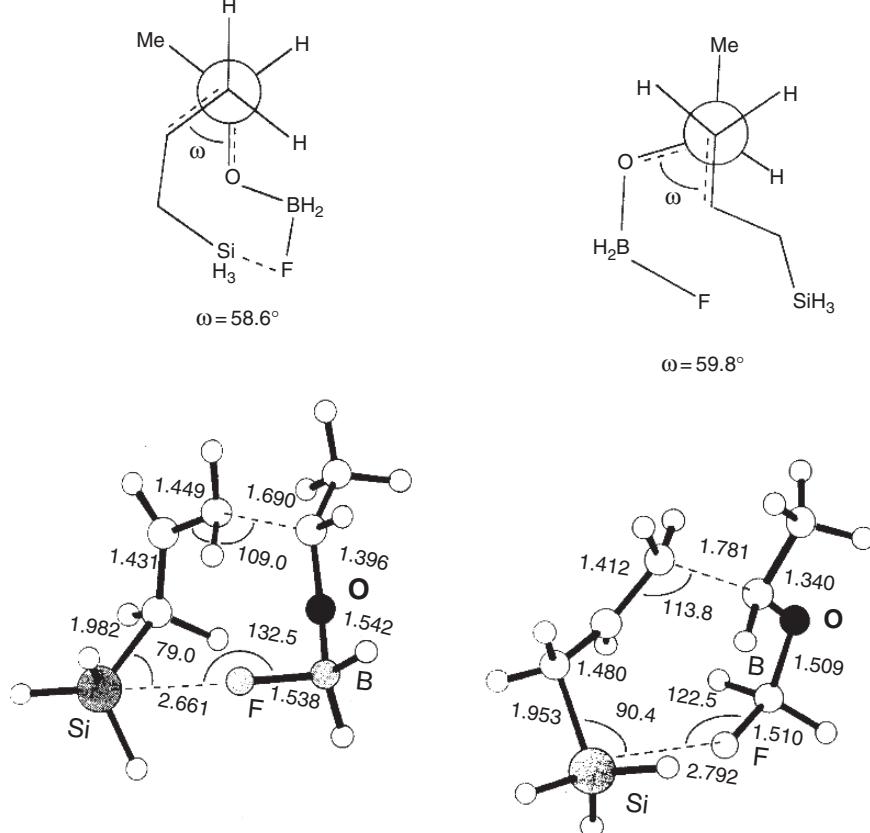
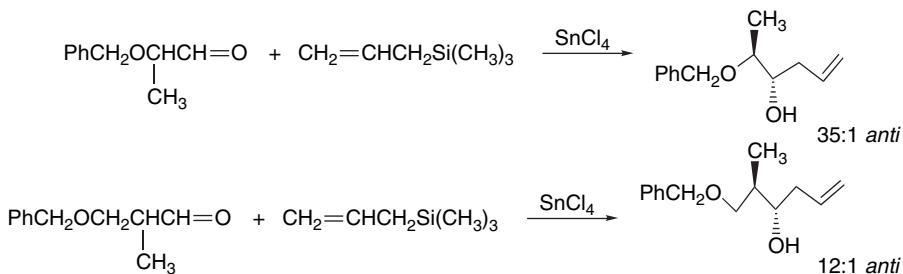


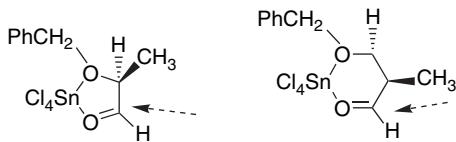
Fig. 9.2. Most favorable transition structures for reaction of allylsilane with acetaldehyde-fluoroborane: (left) *anti* synclinal; (right) *syn* synclinal. Reproduced from *J. Am. Chem. Soc.*, **119**, 12131 (1997), by permission of the American Chemical Society.

Aldehydes with α - or β -benzyloxy substituents react with allyltrimethylsilane in the presence of SnCl_4 to give high yields of product resulting from chelation control.⁹⁷



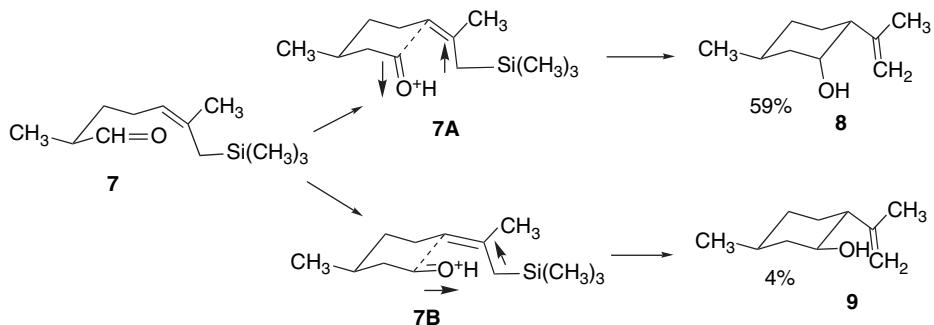
⁹⁷ C. H. Heathcock, S. Kiyooka, and T. Blumenkopf, *J. Org. Chem.*, **49**, 4214 (1984).

The stereochemistry is consistent with approach of the silane *anti* to the methyl substituent.

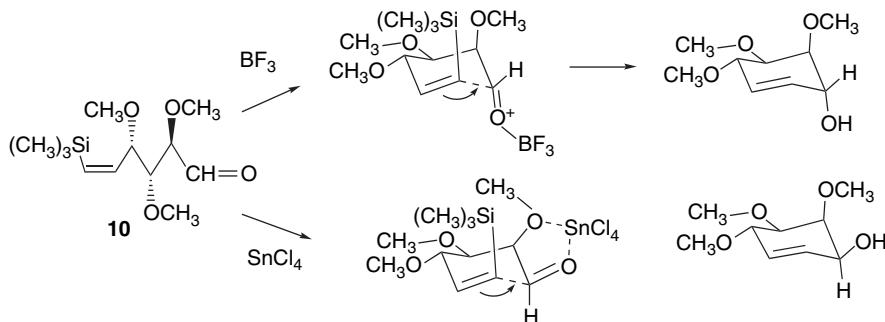


In contrast, BF_3 showed very low stereoselectivity, consistent with its inability to form a chelate.

Intramolecular reactions can also occur between carbonyl groups and allylic silanes. These reactions frequently show good stereoselectivity. For example, **7** cyclizes primarily to **8** with 4% of **9** as a by-product. The two other possible stereoisomers are not observed.⁹⁸ The stereoselectivity is attributed to a preference for TS **7A** over TS **7B**. These are both synclinal structures but differ stereoelectronically. In **7A**, the electron flow is approximately *anti* parallel, whereas in **7B** it is skewed. It was suggested that this difference may be the origin of the stereoselectivity.



The differential in chelation capacity between BF_3 and SnCl_4 was used to control the stereochemistry of the cyclization of the vinyl silane **10**.⁹⁹ With BF_3 , the reaction proceeds through a nonchelated TS and the stereochemistry at the new bond is *trans*. With SnCl_4 , a chelated TS leads to the *cis* diastereomer.



Both ketals¹⁰⁰ and enol ethers¹⁰¹ can be used as electrophiles in place of aldehydes with appropriate catalysts. Trimethylsilyl iodide can be used in catalytic quantities

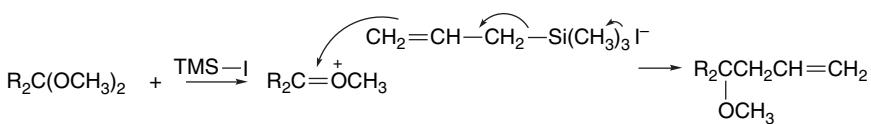
⁹⁸ M. Schlosser, L. Franzini, C. Bauer, and F. Leroux, *Chem. Eur. J.*, **7**, 1909 (2001).

⁹⁹ M. C. McIntosh and S. M. Weinreb, *J. Org. Chem.*, **56**, 5010 (1991).

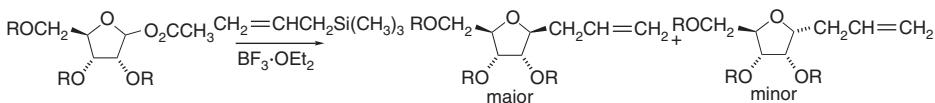
¹⁰⁰ T. K. Hollis, N. P. Robinson, J. Whelan, and B. Bosnich, *Tetrahedron Lett.*, **34**, 4309 (1993).

¹⁰¹ T. Yokozawa, K. Furuhashi, and H. Natsume, *Tetrahedron Lett.*, **36**, 5243 (1995).

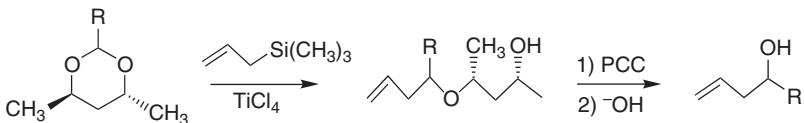
because it is regenerated by recombination of iodide ion with silicon in the desilylation step.¹⁰²



This type of reaction has been used for the extension of the carbon chain of protected carbohydrate acetals.¹⁰³



Reaction of allylic silanes with enantiomerically pure 1,3-dioxanes has been found to proceed with moderate enantioselectivity.¹⁰⁴ The homoallylic alcohol can be liberated by oxidation followed by base-catalyzed β -elimination. The alcohols obtained in this way are formed in $70 \pm 5\%$ e.e.



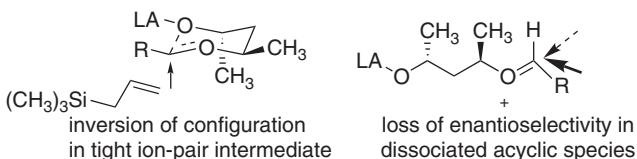
The enantioselectivity is dependent on several reaction variables, including the Lewis acid and the solvent. The observed stereoselectivity appears to reflect differences in the precise structure of the electrophilic species generated. Mild Lewis acids tend to react with inversion of configuration at the reaction site, whereas very strong Lewis acids cause loss of enantioselectivity. The strength of the Lewis acid, together with related effects of solvent and other experimental variables, determines the nature of the electrophile. With mild Lewis acids, a tight ion pair favors inversion, whereas stronger Lewis acids cause complete dissociation to an acyclic species. These two species represent extremes of behavior and intermediate levels of enantioselectivity are also observed.¹⁰⁵

¹⁰². H. Sakurai, K. Sasaki, and A. Hosomi, *Tetrahedron Lett.*, **22**, 745 (1981).

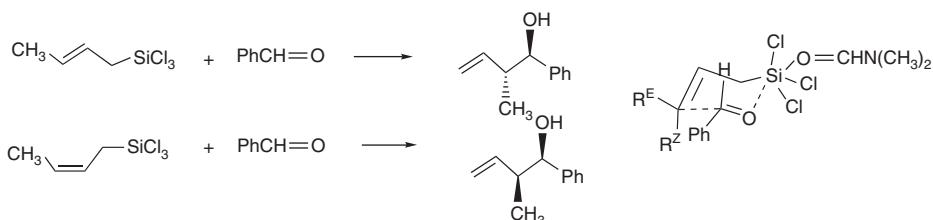
¹⁰³. A. P. Kozikowski, K. L. Sorgi, B. C. Wang, and Z. Xu, *Tetrahedron Lett.*, **24**, 1563 (1983).

¹⁰⁴. P. A. Bartlett, W. S. Johnson, and J. D. Elliott, *J. Am. Chem. Soc.*, **105**, 2088 (1983).

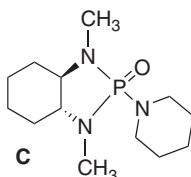
¹⁰⁵. S. E. Denmark and N. G. Almstead, *J. Am. Chem. Soc.*, **113**, 8089 (1991).



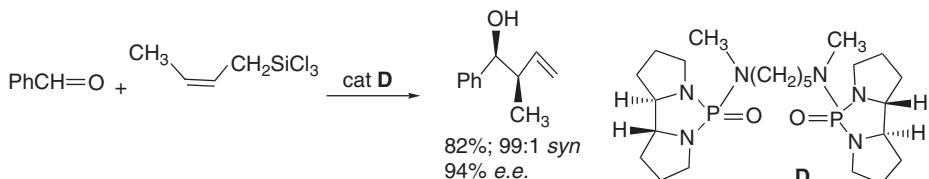
Although most studies of alkenyl and allylic silanes have been done with trialkylsilyl analogs, the reactivity of the system can be adjusted by varying the silicon substituents. Allylic trichlorosilanes react with aldehydes in DMF to give homoallylic alcohols.¹⁰⁶ The reactions are highly stereoselective with respect to the silane geometry and give the product expected for a cyclic TS. The reaction is thought to proceed through a hexacoordinate silicon intermediate.



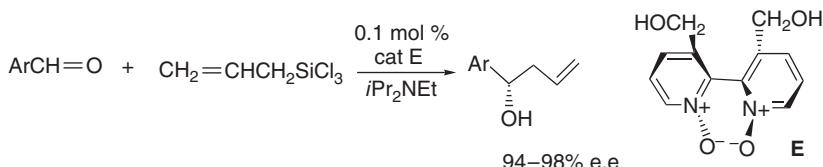
Allylic trichlorosilanes have shown promise in the development of methods for enantioselective reactions by use of chiral phosphoramides such as **C**.



Mechanistic studies suggested that two phosphoramido molecules were involved.¹⁰⁷ This led to the development of linked phosphoramides such as **D**.¹⁰⁸



The axially chiral 2,2'-bipyridine **E** is also an effective enantioselective catalyst for addition of allyltrichlorosilane to aldehydes.¹⁰⁹



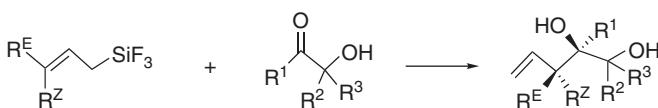
¹⁰⁶ S. Kobayashi and K. Nishio, *J. Org. Chem.*, **59**, 6620 (1994).

¹⁰⁷ S. E. Denmark and J. Fu, *J. Am. Chem. Soc.*, **123**, 9488 (2001).

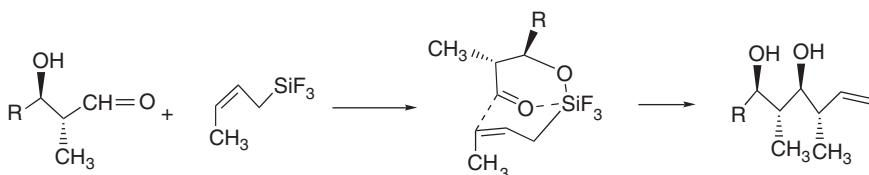
¹⁰⁸ S. E. Denmark and J. Fu, *J. Am. Chem. Soc.*, **125**, 2208 (2003).

¹⁰⁹ T. Shimada, A. Kina, S. Ikeda, and T. Hayashi, *Org. Lett.*, **4**, 2799 (2002).

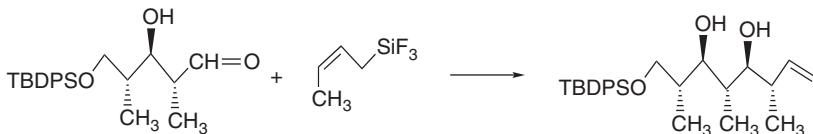
The use of trifluorosilanes permits reactions through hexacoordinate silicon, which presents an opportunity for chelation control. For example, α -hydroxy ketones give *syn* diols.¹¹⁰



Advantage of this chelation has been taken in the construction of compounds with several contiguous chiral centers. *Z*-2-Butenyl trifluorosilanes give *syn*-1,3-diols on reaction with *anti*- β -hydroxy- α -methyl aldehydes.¹¹¹ The stereoselectivity is consistent with a chelated bicyclic TS.

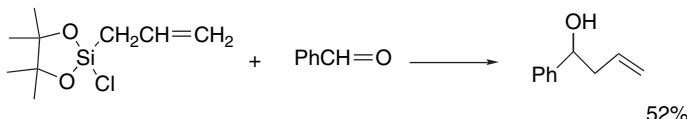


This methodology was applied to construct the all *anti* stereochemistry for a segment of the antibiotic zincophorin.



The corresponding *syn*- β -hydroxy- α -methyl aldehydes do not react through a chelated TS,¹¹² which appears to be due to steric factors that raise the bicyclic TS by several kcal relative to the *anti* isomers. The monocyclic six-membered TS does not incorporate these factors and the *syn* isomer reacts through a monocyclic TS. Figure 9.3 depicts the competing TSs and their relative energies as determined by MNDO calculations.

The electrophilicity of silicon is enhanced in five-membered ring structures. Chloro dioxasilolanes, oxazasilolidines, and diazasilolidines react with aldehydes in the absence of an external Lewis acid catalyst.¹¹³



¹¹⁰ K. Sato, M. Kira, and H. Sakurai, *J. Am. Chem. Soc.*, **111**, 6429 (1989).

¹¹¹ S. R. Chemler and W. R. Roush, *J. Org. Chem.*, **63**, 3800 (1998).

¹¹² S. R. Chemler and W. R. Roush, *J. Org. Chem.*, **68**, 1319 (2003).

¹¹³ J. W. A. Kinnaird, P. Y. Ng, K. Kubota, X. Wang, and J. L. Leighton, *J. Am. Chem. Soc.*, **124**, 7920 (2002).

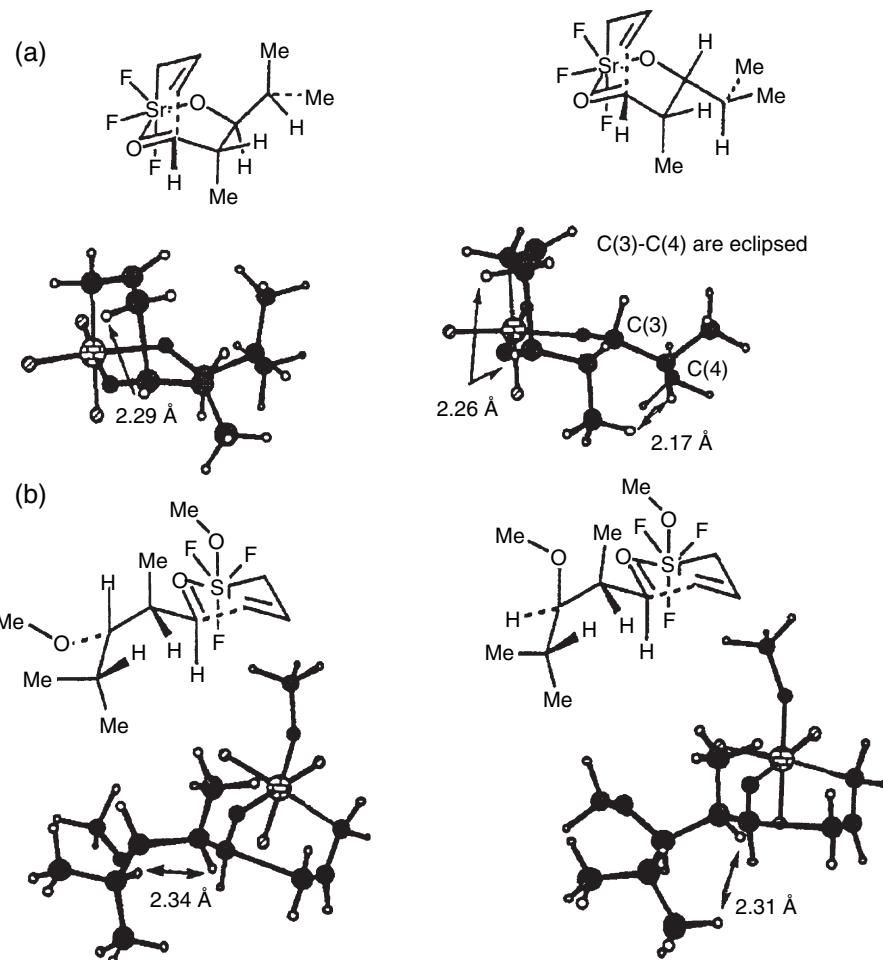
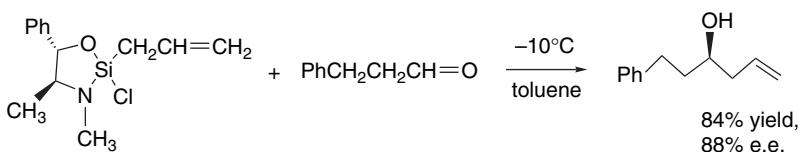


Fig. 9.3. Comparison of chelated bicyclic and nonchelated monocyclic transition structures for addition of allyl trifluorosilane to *syn*- and *anti*-3-methoxy-2,4-dimethylpentanal based on MNDO computations: (a) chelated bicyclic transition structures differ by 6 kcal/mol owing to nonbonded interactions in the *syn* case; (b) nonchelated monocyclic transition structures are of comparable energy for both isomers. Reproduced from *J. Org. Chem.*, **68**, 1319 (2003), by permission of the American Chemical Society.

The oxazasilolidine derived from pseudoephedrine incorporates chirality around the silicon and leads to enantioselective addition.

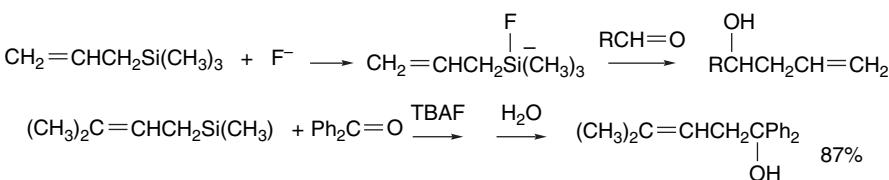


While trifluoro and other halosilanes function by increased *electrophilicity* at silicon, *nucleophilic* reactivity of allylic silanes can be enhanced by formation of anionic adducts (silicates). Reaction of allylic silanes with aldehydes and ketones can

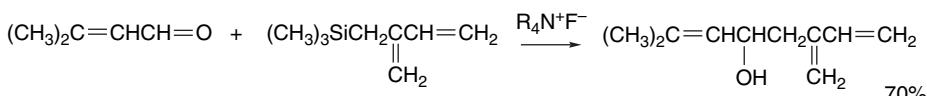
be induced by fluoride ion. Fluoride adds at silicon to form a hypervalent anion having enhanced nucleophilicity.¹¹⁴



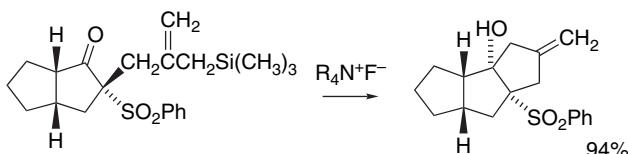
The THF-soluble salt tetrabutylammonium fluoride (TBF) is a common source of fluoride. An alternative reagent is tetrabutylammonium triphenyldifluorosilicate (TBAF).¹¹⁵ Unsymmetrical allylic anions generated in this way react with ketones at their less-substituted terminus.



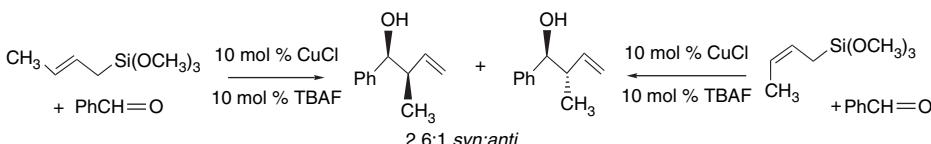
An allylic silane of this type serves as a reagent for the introduction of isoprenoid structures.¹¹⁶



Fluoride-induced desilylation has also been used to effect ring closures.¹¹⁷



Allylic trimethoxysilanes are activated by a catalytic combination of CuCl and TBAF.¹¹⁸ The mechanism of this reaction is not entirely clear, but it seems to involve fluoride activation of the silane. These reactions are stereoconvergent for the isomeric 2-butenyl silanes, indicating that reaction occurs through an acyclic TS.



^{114.} A. Hosomi, A. Shirahata, and H. Sakurai, *Tetrahedron Lett.*, 3043 (1978); G. G. Furin, O. A. Vyazankina, B. A. Gostevsky, and N. S. Vyazankin, *Tetrahedron*, **44**, 2675 (1988).

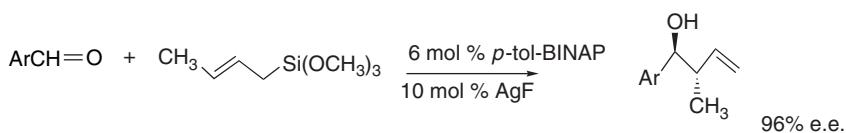
¹¹⁵ A. S. Pilcher and P. De Shong, *J. Org. Chem.*, **61**, 6901 (1996).

¹¹⁶. A. S. Fischer and F. De Shong, *J. Org. Chem.*, **61**, 6901 (1996).

¹¹⁷ B. M. Trost and J. E. Vincent, *J. Am. Chem. Soc.*, **102**, 5680 (1980); B. M. Trost and D. P. Curran, *J. Am. Chem. Soc.*, **103**, 7380 (1981).

^{118.} S. Yamasaki, K. Fujii, R. Wada, M. Kanai, and M. Shibasaki, *J. Am. Chem. Soc.*, **124**, 6536 (2002).

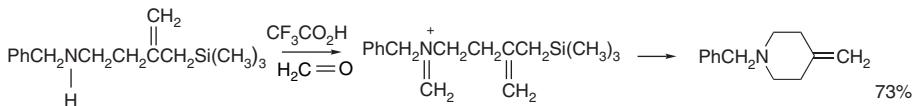
p-Tol-BINAP-AgF effects enantioselective additions with trimethoxysilanes.¹¹⁹ These reactions give *anti* products, regardless of the configuration of the allylic silane.



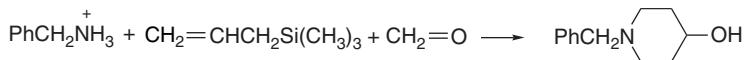
The combination BINAP-Ag₂O-KF with 18-crown-6 also leads to high enantioselectivity.¹²⁰

9.2.4. Reactions with Iminium Ions

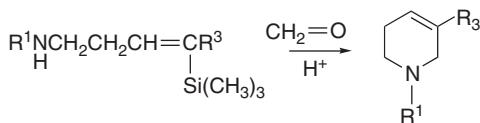
Iminium ions are reactive electrophiles toward both alkenyl and allylic silanes. Useful techniques for closing nitrogen-containing rings are based on *in situ* generation of iminium ions from amines and formaldehyde.¹²¹



When primary amines are employed, the initially formed 3-butenylamine undergoes a further reaction forming 4-piperidinols.¹²²



Reactions of this type can also be observed with 4-(trimethylsilyl)-3-alkenylamines.¹²³



Mechanistic investigation in this case has shown that there is an equilibrium between an alkenyl silane and an allylic silane by a rapid 3,3-sigmatropic process. The cyclization occurs through the more reactive allylic silane.

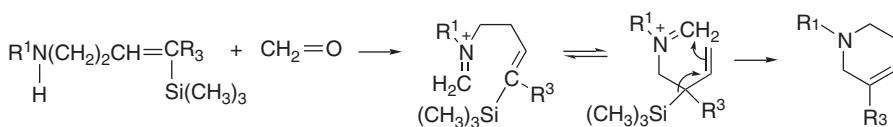
¹¹⁹. A. Yanagisawa, H. Kageyama, Y. Nakatsuka, K. Asakawa, Y. Matsumoto, and H. Yamamoto, *Angew. Chem. Int. Ed. Engl.*, **38**, 3701 (1999).

¹²⁰. M. Wadamoto, N. Ozasa, A. Yanagisawa, and H. Yamamoto, *J. Org. Chem.*, **68**, 5593 (2003).

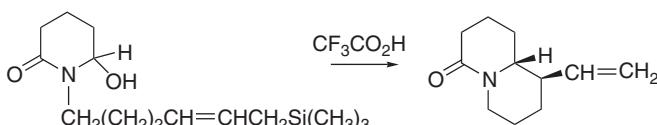
¹²¹. P. A. Grieco and W. F. Fobare, *Tetrahedron Lett.*, **27**, 5067 (1986).

¹²². S. D. Larsen, P. A. Grieco, and W. F. Fobare, *J. Am. Chem. Soc.*, **108**, 3512 (1986).

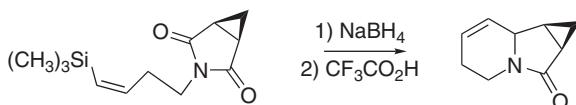
¹²³. C. Flann, T. C. Malone, and L. E. Overman, *J. Am. Chem. Soc.*, **109**, 6097 (1987).



N-Acyliminium ions, which are even more reactive toward allylic and alkenylsilanes, are usually obtained from imides by partial reduction (see Section 2.2.2). The partially reduced *N*-acylcarbinolamines can then generate acyliminium ions. Such reactions have been employed in intramolecular situations with both allylic and vinyl silanes.



Ref. 124



Ref. 125

9.2.5. Acylation Reactions

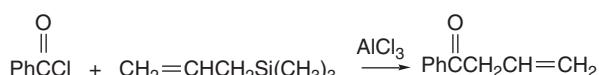
Reaction of alkenyl silanes with acid chlorides is catalyzed by aluminum chloride or stannic chloride.¹²⁶



Titanium tetrachloride induces reaction with dichloromethyl methyl ether to give α , β -unsaturated aldehydes.¹²⁷

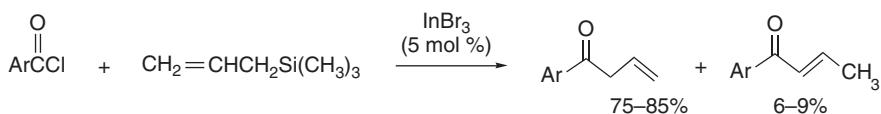


Similar conditions are used to effect reactions of allylsilanes with acyl halides, resulting in β , γ -unsaturated ketones.¹²⁸



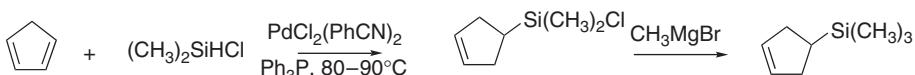
- ¹²⁴. H. Hiemstra, M. H. A. M. Sno, R. J. Vijn, and W. N. Speckamp, *J. Org. Chem.*, **50**, 4014 (1985).
- ¹²⁵. G. Kim, M. Y. Chu-Moyer, S. J. Danishefsky, and G. K. Schulte, *J. Am. Chem. Soc.*, **115**, 30 (1993).
- ¹²⁶. I. Fleming and A. Pearce, *J. Chem. Soc., Chem. Commun.*, 633 (1975); W. E. Fristad, D. S. Dime, T. R. Bailey, and L. A. Paquette, *Tetrahedron Lett.*, 1999 (1979).
- ¹²⁷. K. Yamamoto, O. Nunokawa, and J. Tsuji, *Synthesis*, 721 (1977).
- ¹²⁸. J.-P. Pillot, G. Deleris, J. Dunogues, and R. Calas, *J. Org. Chem.*, **44**, 3397 (1979); R. Calas, J. Dunogues, J.-P. Pillot, C. Biran, F. Pisciotti, and B. Arreguy, *J. Organomet. Chem.*, **85**, 149 (1975).

Indium tribromide also gives good yields, with minor isomerization to the α , β -isomers.¹²⁹

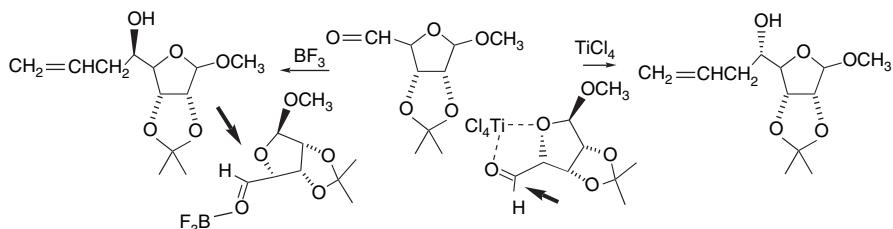


These reactions probably involve acylium ions as the electrophiles.

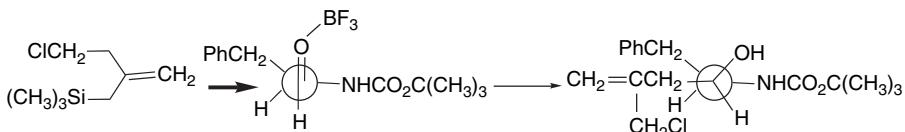
Scheme 9.4 shows some representative reactions of allylic and alkenyl silanes. Entry 1 involves 3-trimethylsilylcyclopentene, which can be made by hydrosilylation of cyclopentadiene by chlorodimethylsilane, followed by reaction with methylmagnesium bromide.



Entry 2 was reported as part of a study of the stereochemistry of addition of allyltrimethylsilane to protected carbohydrates. Use of BF_3 as the Lewis acid, as shown, gave the product from an open TS, whereas TiCl_4 led to the formation of the alternate stereoisomer through chelation control. Similar results were reported for a protected galactose.



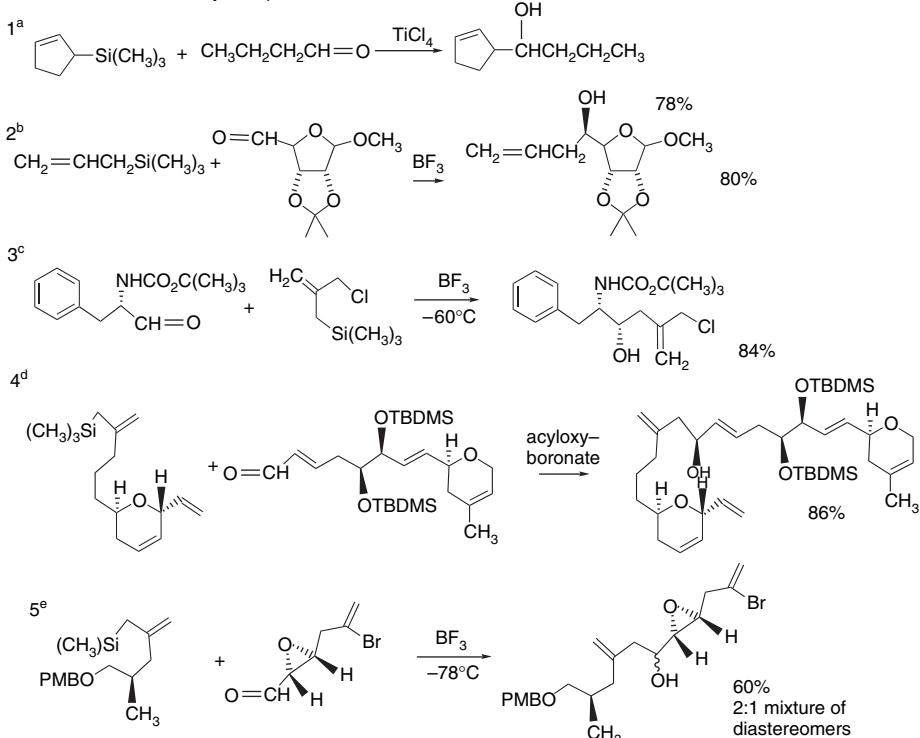
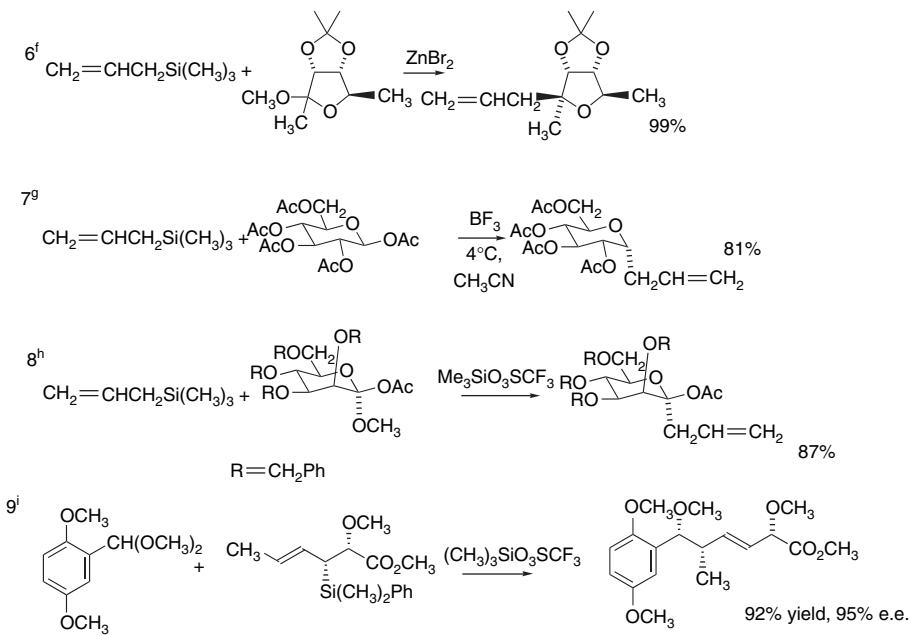
In Entry 3, BF_3 -mediated addition exhibits a preference for the Felkin stereochemistry.



Entries 4 and 5 are examples of use of the Sakurai reaction to couple major fragments in multistage synthesis. In Entry 4 an unusual catalyst, a chiral acyloxyboronate (see p. 126) was used to effect an enantioselective coupling. (See p. 847 for another application of this catalyst.) Entry 5 was used in the construction of amphinolinolide P, a compound with anticancer activity.

Entries 6 to 8 demonstrate addition of allyl trimethylsilane to protected carbohydrate acetals. This reaction can be a valuable method for incorporating the chirality of carbohydrates into longer carbon chains. In cases involving cyclic acetals, reactions occur through oxonium ions and the stereochemistry is governed by steric and stereo-electronic effects of the ring. Note that Entry 8 involves the use of trimethylsilyl

¹²⁹ J. S. Yadav, B. V. S. Reddy, M. S. Reddy, and G. Parimala, *Synthesis*, 2390 (2003).

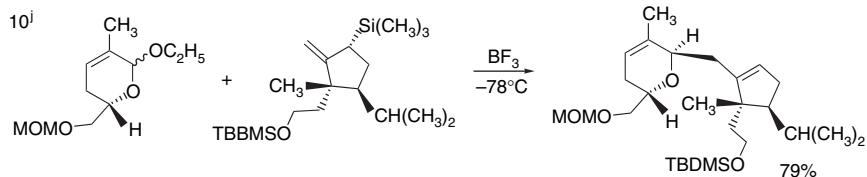
Scheme 9.4. Reactions of Alkenyl and Allylic Silanes with Aldehydes, Ketones, Acetals,
Iminium Ions, and Acyl Halides**A. Reactions with carbonyl compounds****B. Reactions with acetals and related compounds**

(Continued)

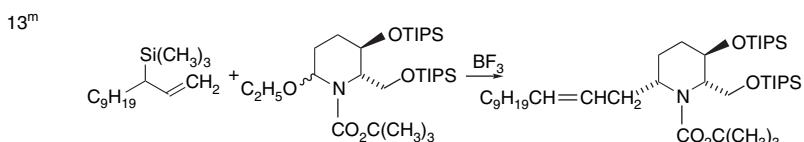
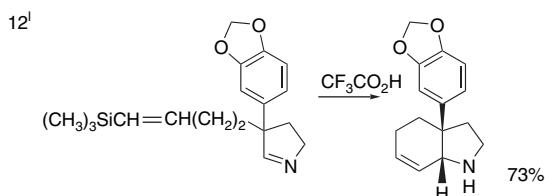
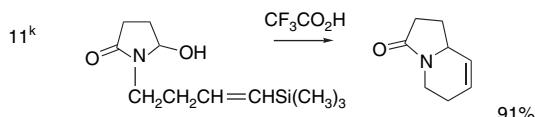
Scheme 9.4. (Continued)

SECTION 9.2

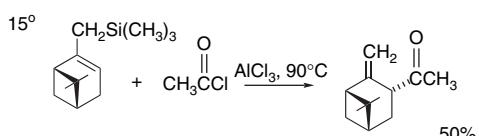
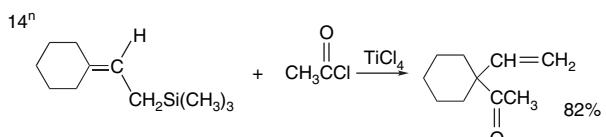
Organosilicon Compounds



C. Reactions with Iminium ions

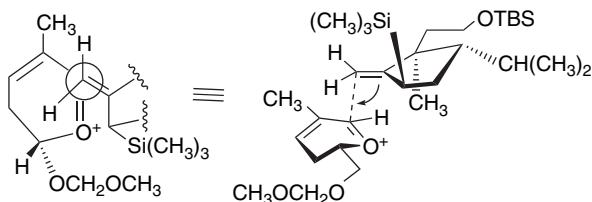


D. Acylation reactions



- a. I. Ojima, J. Kumagai, and Y. Miyazawa, *Tetrahedron Lett.*, 1385 (1977).
- b. S. Danishefsky and M. De Ninno, *Tetrahedron Lett.*, **26**, 823 (1985).
- c. F. D'Aniello and M. Taddei, *J. Org. Chem.*, **57**, 5247 (1992).
- d. P. A. Wender, S. G. Hegde, R. D. Hubbard, and L. Zhang, *J. Am. Chem. Soc.*, **124**, 4956 (2002).
- e. D. R. Williams, B. J. Myers, and L. Mi, *Org. Lett.*, **2**, 945 (2000).
- f. H. Suh and C. S. Wilcox, *J. Am. Chem. Soc.*, **110**, 470 (1988).
- g. A. Giannis and K. Sanshoff, *Tetrahedron Lett.*, **26**, 1479 (1985).
- h. A. Hosomi, Y. Sakata, and H. Sakurai, *Tetrahedron Lett.*, **25**, 2383 (1984).
- i. J. S. Panek and M. Yang, *J. Am. Chem. Soc.*, **113**, 6594 (1991).
- j. D. R. Williams and R. W. Heidebrecht, Jr., *J. Am. Chem. Soc.*, **125**, 1843 (2003).
- k. C. Flann, T. C. Malone, and L. E. Overman, *J. Am. Chem. Soc.*, **109**, 6097 (1987).
- l. L. E. Overman and R. M. Burk, *Tetrahedron Lett.*, **25**, 5739 (1984).
- m. I. Ojima and E. S. Vidal, *J. Org. Chem.*, **63**, 7999 (1998).
- n. I. Fleming and I. Paterson, *Synthesis*, 446 (1979).
- o. J. P. Pillot, G. Deleris, J. Dunogues, and R. Calas, *J. Org. Chem.*, **44**, 3397 (1979).

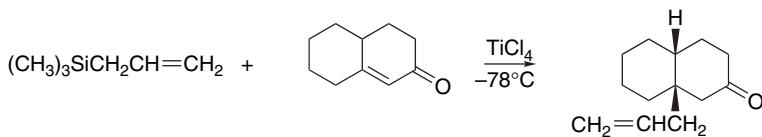
triflate as the catalyst. Entry 9 is a case of substrate control of enantioselectivity. Both high diastereoselectivity and enantioselectivity at the new chiral center were observed. The reaction is believed to proceed through an *O*-methyloxonium and to involve an open TS. Entry 10 involves generation of a cyclic oxonium ion. The observed stereochemistry is consistent with a synclinal orientation in the TS.



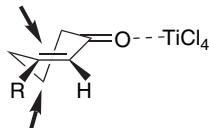
Entries 11 to 13 are examples of iminium ion and acyliminium ion reactions. Note that in Entries 11 and 12, vinyl, rather than allylic, silane moieties are involved. Entries 14 and 15 illustrate the synthesis of β , γ -unsaturated ketones by acylation of allylic silanes.

9.2.6. Conjugate Addition Reactions

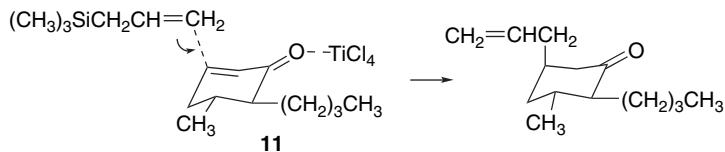
Allylic silanes act as nucleophilic species toward α , β -unsaturated ketones in the presence of Lewis acids such as $TiCl_4$.¹³⁰



The stereochemistry of this reaction in cyclic systems is in accord with expectations for stereoelectronic control. The allylic group approaches from a trajectory that is appropriate for interaction with the LUMO of the conjugated system.¹³¹



The stereoselectivity then depends on the conformation of the enone and the location of substituents that establish a steric bias for one of the two potential directions of approach. In the ketone **11**, the preferred approach is from the β -face, since this permits maintaining a chair conformation as the reaction proceeds.¹³²

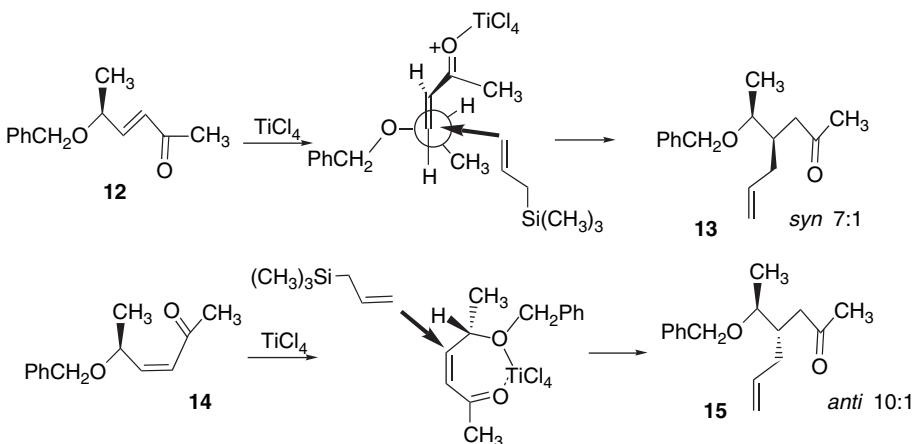


¹³⁰ A. Hosomi and H. Sakurai, *J. Am. Chem. Soc.*, **99**, 1673 (1977).

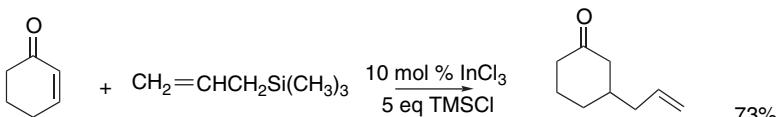
¹³¹ T. A. Blumenkopf and C. H. Heathcock, *J. Am. Chem. Soc.*, **105**, 2354 (1983).

¹³² W. R. Roush and A. E. Walts, *J. Am. Chem. Soc.*, **106**, 721 (1984).

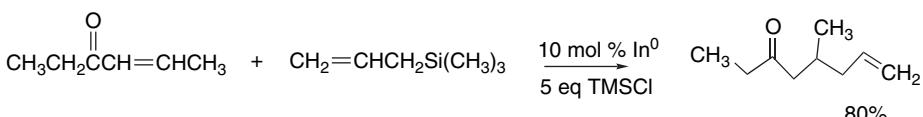
Conjugate addition to acyclic enones is subject to chelation control when TiCl_4 is used as the Lewis acid. Thus, whereas the *E*-enone **12** gives *syn* product **13** via an acyclic TS, the *Z*-isomer **14** reacts through a chelated TS to give **15**.¹³³



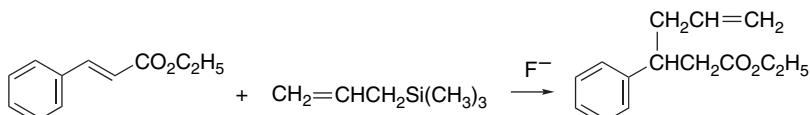
Conjugate additions of allylic silanes to enones are also catalyzed by $\text{InCl}_3\text{-TMSCl}$.¹³⁴



The reaction can also be carried out using indium metal. Under these conditions InCl_3 is presumably generated *in situ*.¹³⁵



Conjugate addition can also be carried out by fluoride-mediated disilylation. A variety of α,β -unsaturated esters and amides have been found to undergo this reaction.¹³⁶

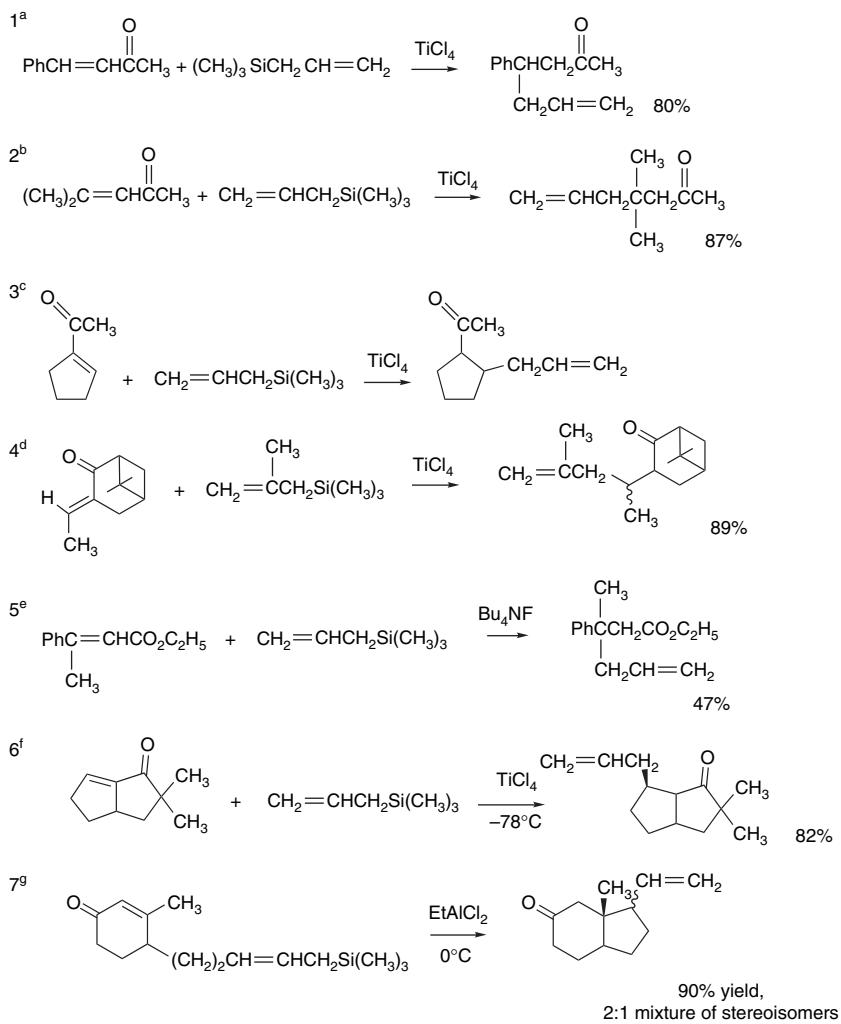


¹³³ C. H. Heathcock, S. Kiyooka, and T. A. Blujenkopf, *J. Org. Chem.*, **49**, 4214 (1984).

¹³⁴ P. H. Lee, K. Lee, S.-Y. Sung, and S. Chang, *J. Org. Chem.*, **66**, 8646 (2001); Y. Onishi, T. Ito, M. Yasuda, and A. Baba, *Eur. J. Org. Chem.*, 1578 (2002).

¹³⁵ P. H. Lee, D. Seoomon, S. Kim, K. Nagaiah, S. V. Damle, and K. Lee, *Synthesis*, 2189 (2003).

¹³⁶ G. Majetich, A. Casares, D. Chapman, and M. Behnke, *J. Org. Chem.*, **51**, 1745 (1986).

Scheme 9.5. Conjugate Addition of Allylic Silanes to α, β -Unsaturated Enones

a. H. Sakurai, A. Hosmoni, and J. Hayashi, *Org. Synth.*, **62**, 86 (1984).

b. D. H. Hua, *J. Am. Chem. Soc.*, **108**, 3835 (1986).

c. H. O. House, P. C. Gaa, and D. Van Derveer, *J. Org. Chem.*, **48**, 1661 (1983).

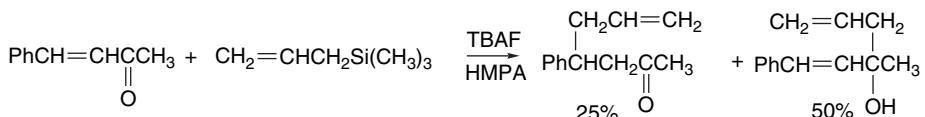
d. T. Yanami, M. Miyashita, and A. Yoshikoshi, *J. Org. Chem.*, **45**, 607 (1980).

e. G. Majetich, A. Casares, D. Chapman, and M. Behnke, *J. Org. Chem.*, **51**, 1745 (1986).

f. C. E. Davis, B. C. Duffy, and R. M. Coates, *Org. Lett.*, **2**, 2717 (2000).

g. D. Schinzer, S. Solyom, and M. Becker, *Tetrahedron Lett.*, **26**, 1831 (1985).

With unsaturated aldehydes, 1,2-addition occurs and with ketones both the 1,2- and 1,4-products are formed.

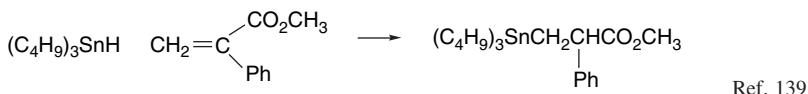
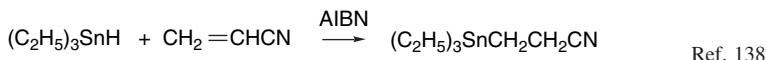


Some examples of conjugate addition reactions of allylic silanes are given in Scheme 9.5. Entries 1 to 3 illustrate the synthesis of several β -allyl ketones. Note that Entry 2 involves the creation of a quaternary carbon. Entry 4 was used in the synthesis of a terpenoid ketone, (+)-nootkatone. Entry 5 illustrates fluoride-mediated addition using tetrabutylammonium fluoride. These conditions were found to be especially effective for unsaturated esters. In Entry 6, the addition is from the convex face of the ring system. Entry 7 illustrates a ring closure by intramolecular conjugate addition.

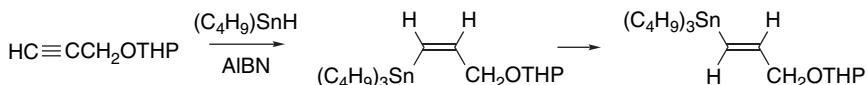
9.3. Organotin Compounds

9.3.1. Synthesis of Organostannanes

The readily available organotin compounds include tin hydrides (stannanes) and the corresponding chlorides, with the tri-*n*-butyl compounds being the most common. Trialkylstannanes can be added to carbon–carbon double and triple bonds. The reaction is usually carried out by a radical chain process,¹³⁷ and the addition is facilitated by the presence of radical-stabilizing substituents.

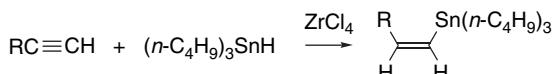


With terminal alkynes, the stannyll group is added at the unsubstituted carbon and the *Z*-stereoisomer is initially formed but is readily isomerized to the *E*-isomer.¹⁴⁰



The reaction with internal acetylenes leads to a mixture of both regioisomers and stereoisomers.¹⁴¹

Lewis acid-catalyzed hydrostannylation has been observed using ZrCl_4 . With terminal alkynes the *Z*-alkenylstannane is formed.¹⁴² These reactions are probably similar in mechanism to Lewis acid-catalyzed additions of silanes (see p. 811).



^{137.} H. G. Kuivila, *Adv. Organomet. Chem.*, **1**, 47 (1964).

^{138.} A. J. Leusink and J. G. Noltes, *Tetrahedron Lett.*, 335 (1966).

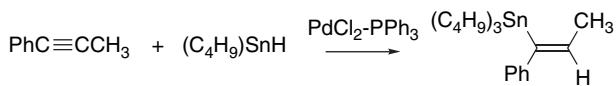
^{139.} I. Fleming and C. J. Urch, *Tetrahedron Lett.*, **24**, 4591 (1983).

^{140.} E. J. Corey and R. H. Wollenberg, *J. Org. Chem.*, **40**, 2265 (1975).

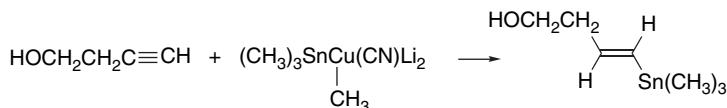
^{141.} H. E. Ensley, R. R. Buescher, and K. Lee, *J. Org. Chem.*, **47**, 404 (1982).

^{142.} N. Asao, J.-X. Liu, T. Sudoh, and Y. Yamamoto, *J. Org. Chem.*, **61**, 4568 (1996).

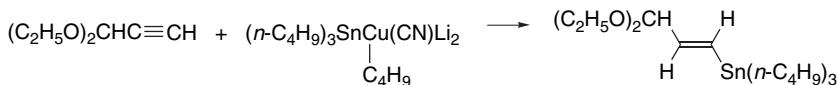
Palladium-catalyzed procedures have also been developed for addition of stannanes to alkynes,¹⁴³ and these reactions usually occur by *syn* addition.



Hydrostannylation of terminal alkynes can also be achieved by reaction with stannyl-cyanocuprates.

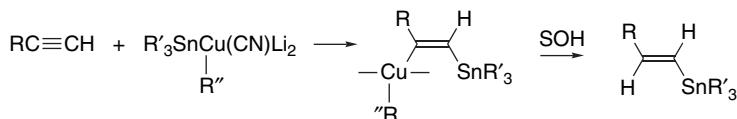


Ref. 144



Ref. 145

These reactions proceed via a *syn* addition followed by protonolysis.



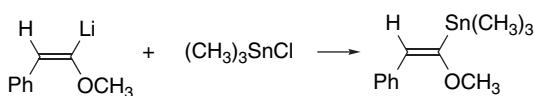
Allylic stannanes can be prepared from allylic halides and sulfonates by displacement with or LiSnMe_3 or LiSnBu_3 .¹⁴⁶ They can also be prepared by Pd-catalyzed substitution of allylic acetates and phosphates using $(\text{C}_2\text{H}_5)_2\text{AlSn}(\text{n-C}_4\text{H}_9)_3$.¹⁴⁷

Another major route for synthesis of stannanes is reaction of an organometallic reagent with a trisubstituted halostannane, which is the normal route for the preparation of aryl stannanes.



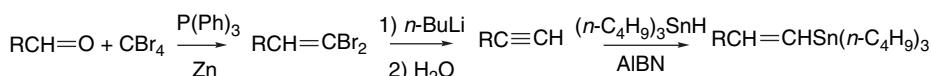
Ref. 148

- ¹⁴³ H. X. Zhang, F. Guibe, and G. Balavoine, *Tetrahedron Lett.*, **29**, 619 (1988); M. Benechie, T. Skrydstrup, and F. Khuong-Huu, *Tetrahedron Lett.*, **32**, 7535 (1991); N. D. Smith, J. Mancuso, and M. Lautens, *Chem. Rev.*, **100**, 3257 (2000).
- ¹⁴⁴ I. Beaudet, J.-L. Parrain, and J.-P. Quintard, *Tetrahedron Lett.*, **32**, 6333 (1991).
- ¹⁴⁵ A. C. Oehlschlager, M. W. Hutzinger, R. Aksela, S. Sharma, and S. M. Singh, *Tetrahedron Lett.*, **31**, 165 (1990).
- ¹⁴⁶ E. Winter and R. Bruckner, *Synlett*, 1049 (1994); G. Naruta and K. Maruyama, *Chem. Lett.*, 881 (1979); G. E. Keck and S. D. Tonnes, *Tetrahedron Lett.*, **34**, 4607 (1993); S. Weigand and R. Bruckner, *Synthesis*, 475 (1996).
- ¹⁴⁷ B. M. Trost and J. W. Herndon, *J. Am. Chem. Soc.*, **106**, 6835 (1984); S. Matsubara, K. Wakamatsu, J. Morizawa, N. Tsuboniwa, K. Oshima, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **58**, 1196 (1985).
- ¹⁴⁸ C. Eaborn, A. R. Thompson, and D. R. M. Walton, *J. Chem. Soc. C*, 1364 (1967); C. Eaborn, H. L. Hornfeld, and D. R. M. Walton, *J. Chem. Soc. B*, 1036 (1967).

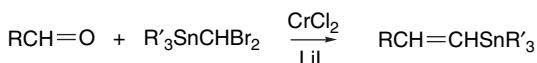


Ref. 149

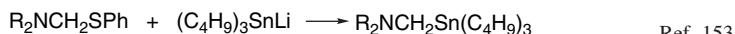
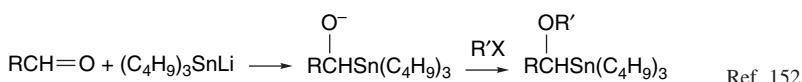
There are several procedures for synthesis of terminal alkenyl stannanes that involve addition to aldehydes. A well-established three-step sequence culminates in a radical addition to a terminal alkyne.¹⁵⁰



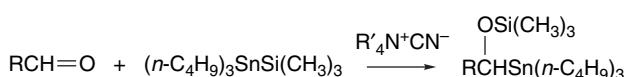
Another sequence involves a dibromomethyl(trialkyl)stannane as the starting material. On reaction with CrCl_2 , addition to the aldehyde is followed by reductive elimination.¹⁵¹



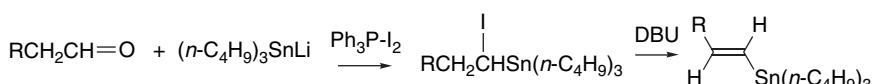
Deprotonated trialkylstannanes are potent nucleophiles. Addition to carbonyl groups or iminium intermediates provides routes to α -alkoxy- and α -aminoalkylstannanes.



α -Silyoxystannanes can be prepared directly from aldehydes and tri-*n*-butyl(trimethylsilyl)stannane.¹⁵⁴



Addition of tri-*n*-butylstannyllithium to aldehydes followed by iodination and dehydrohalogenation gives primarily *E*-alkenylstannanes.¹⁵⁵



¹⁴⁹ J. A. Soderquist and G. J.-H. Hsu, *Organometallics*, **1**, 830 (1982).

¹⁵⁰ E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 3769 (1972).

¹⁵¹ M. D. Cliff and S. G. Payne, *Tetrahedron Lett.*, **36**, 763 (1995); D. M. Hodgson, *Tetrahedron Lett.*, **33**, 5603 (1992); D. M. Hodgson, L. T. Boulton, and G. N. Maw, *Tetrahedron Lett.*, **35**, 2231 (1994).

¹⁵² W. C. Still, *J. Am. Chem. Soc.*, **100**, 1481 (1978).

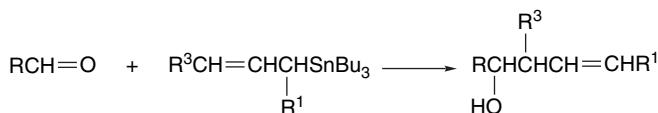
¹⁵³ D. J. Peterson, *J. Am. Chem. Soc.*, **93**, 4027 (1971).

¹⁵⁴ R. M. Bhatt, J. Ye, and J. R. Falck, *Tetrahedron Lett.*, **35**, 4081 (1994).

¹⁵⁵ J. M. Chong and S. B. Park, *J. Org. Chem.*, **58**, 523 (1993).

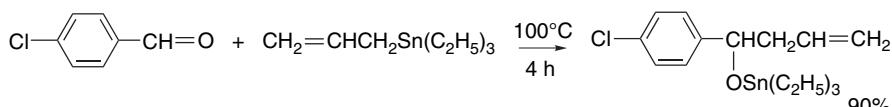
9.3.2. Carbon-Carbon Bond-Forming Reactions

As with the silanes, the most useful synthetic procedures involve electrophilic attack on alkenyl and allylic stannanes. The stannanes are considerably more reactive than the corresponding silanes because there is more anionic character on carbon in the C–Sn bond and it is a weaker bond.¹⁵⁶ The most useful reactions in terms of syntheses involve the Lewis acid–catalyzed addition of allylic stannanes to aldehydes.¹⁵⁷ The reaction occurs with allylic transposition.



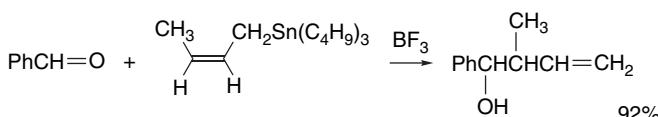
There are also useful synthetic procedures in which organotin compounds act as carbanion donors in transition metal–catalyzed reactions, as discussed in Section 8.2.3.3. Organotin compounds are also very important in free radical reactions, as is discussed in Chapter 10.

9.3.2.1. Reactions of Allylic Trialkylstannanes. Allylic organotin compounds are not sufficiently reactive to add directly to aldehydes or ketones, although reactions with aldehydes do occur with heating.



Ref. 158

Use of Lewis acid catalysts allows allylic stannanes to react under mild conditions. As is the case with allylic silanes, a double-bond transposition occurs in conjunction with destannylation.¹⁵⁹



The stereoselectivity of addition to aldehydes has been of considerable interest.¹⁶⁰ With benzaldehyde the addition of 2-but enylstannanes catalyzed by BF_3 gives the *syn* isomer, irrespective of the stereochemistry of the butenyl group.¹⁶¹

¹⁵⁶ J. Burfeindt, M. Patz, M. Mueller, and H. Mayr, *J. Am. Chem. Soc.*, **120**, 3629 (1998).

¹⁵⁷ B. W. Gung, *Org. React.*, **64**, 1 (2004).

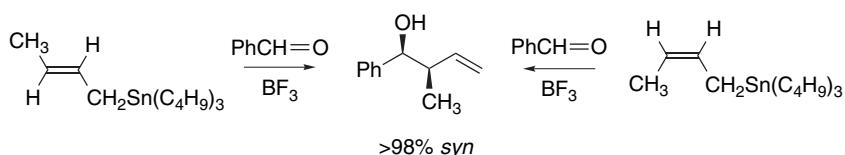
¹⁵⁸ K. König and W. P. Neumann, *Tetrahedron Lett.*, 495 (1967).

¹⁵⁹ H. Yatagai, Y. Yamamoto, and K. Maruyama, *J. Am. Chem. Soc.*, **102**, 4548 (1980); Y. Yamamoto, H. Yatagai, Y. Naruta, and K. Maruyama, *J. Am. Chem. Soc.*, **102**, 7107 (1989).

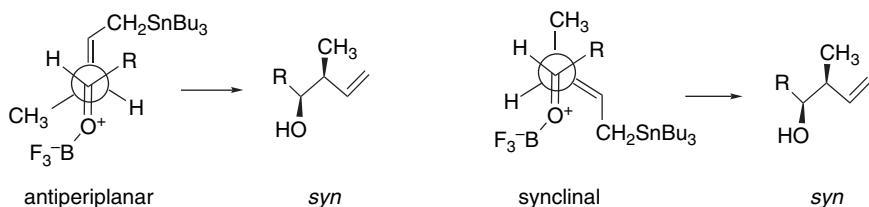
¹⁶⁰ Y. Yamamoto, *Acc. Chem. Res.*, **20**, 243 (1987); Y. Yamamoto and N. Asao, *Chem. Rev.*, **93**, 2207 (1993).

¹⁶¹ (a) Y. Yamamoto, H. Yatagai, H. Ishihara, and K. Maruyama, *Tetrahedron*, **40**, 2239 (1984);

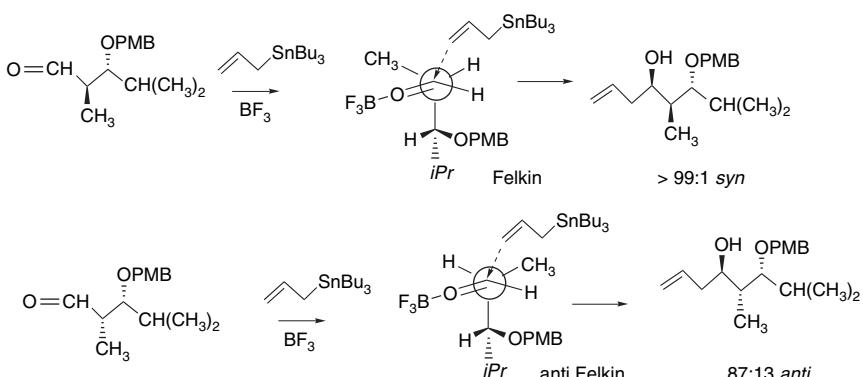
(b) G. E. Keck, K. A. Savin, E. N. K. Cressman, and D. E. Abbott, *J. Org. Chem.*, **59**, 7889 (1994).



Synclinal and antiperiplanar conformations of the TS are possible. The two TSs are believed to be close in energy and either may be involved in individual systems. An electronic π interaction between the stannane HOMO and the carbonyl LUMO, as well as polar effects appear to favor the synclinal TS and can overcome the unfavorable steric effects.^{161b,162} Generally the synclinal TS seems to be preferred for intramolecular reactions. The steric effects that favor the antiperiplanar TS are not present in intramolecular reactions, since the aldehyde and the stannane substituents are then part of the intramolecular linkage.



With chiral aldehydes, reagent approach is generally consistent with a Felkin model.¹⁶³ This preference can be reinforced or opposed by the effect of other stereocenters. For example, the addition of allyl stannane to 1,4-dimethyl-3-(4-methoxybenzyloxy)pentanal is strongly in accord with the Felkin model for the *anti* stereoisomer but is anti-Felkin for the *syn* isomer.

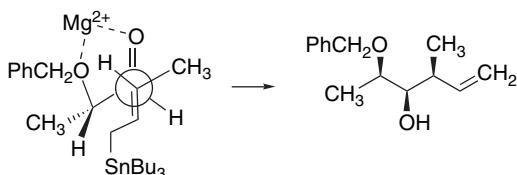


When an aldehyde subject to chelation control is used, the *syn* stereoisomer dominates, with MgBr₂ as the Lewis acid.¹⁶⁴

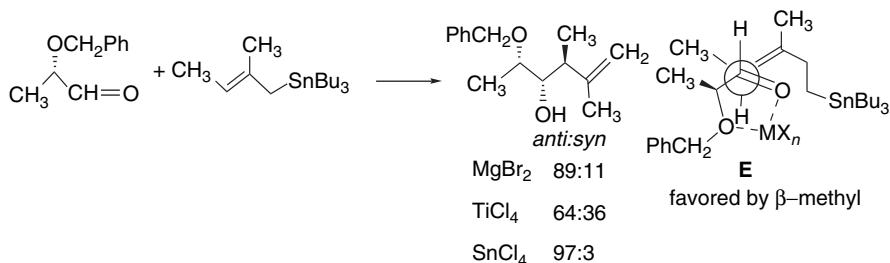
¹⁶². S. E. Denmark, E. J. Weber, T. Wilson, and T. M. Willson, *Tetrahedron*, **45**, 1053 (1989).

¹⁶³. D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, and A. B. Livingston, *J. Am. Chem. Soc.*, **117**, 6619 (1995); D. A. Evans, M. J. Dart, J. L. Duffy, and M. G. Yang, *J. Am. Chem. Soc.*, **118**, 4322 (1996).

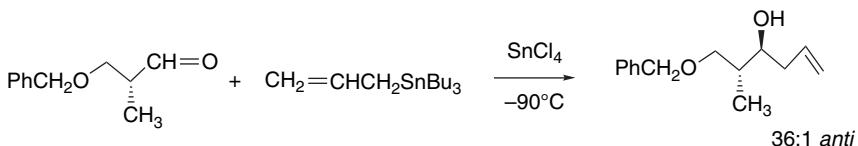
¹⁶⁴. G. E. Keck and E. P. Boden, *Tetrahedron Lett.*, **25**, 265 (1984); G. E. Keck, D. E. Abbott, and M. R. Wiley, *Tetrahedron Lett.*, **28**, 139 (1987).



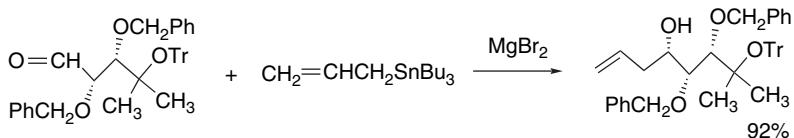
The introduction of a β -methyl group shifts the stereoselectivity to *anti*, indicating a preference for TS E. There is some dependence on the Lewis acid. For example, the reaction below gives a high ratio of chelation control with $MgBr_2$ and $SnCl_4$, but not with $TiCl_4$.¹⁶⁵



β -Oxy substituents can also lead to chelation control. Excellent stereoselectivity is observed using $SnCl_4$ at low temperature.¹⁶⁶



The chelation control approach has been used during the synthesis of the C(13)–C(19) fragment of a marine natural product called calculin A-D.¹⁶⁷

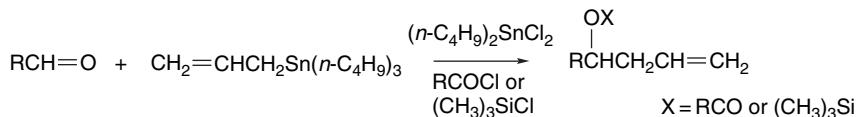
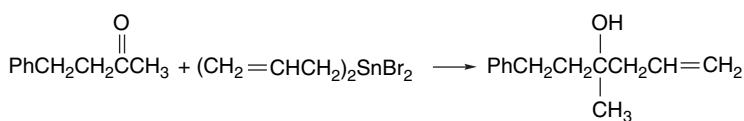


9.3.2.2. Reactions of Allylic Halostannanes. Various allyl halostannanes can transfer allyl groups to carbonyl compounds. In this case the reagent acts both as a Lewis acid and as the source of the nucleophilic allyl group. Reactions involving halostannanes are believed to proceed through cyclic TSs.

¹⁶⁵ K. Mikami, K. Kawamoto, T.-P. Loh, and T. Nakai, *J. Chem. Soc., Chem. Commun.*, 1161 (1990).

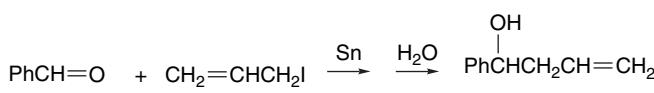
¹⁶⁶ G. E. Keck and D. E. Abbott, *Tetrahedron Lett.*, **25**, 1883 (1984); R. J. Linderman, K. P. Cusack, and M. R. Jaber, *Tetrahedron Lett.*, **37**, 6649 (1996).

¹⁶⁷ O. Hara, Y. Hamada, and T. Shiori, *Synlett*, 283–285 (1991).

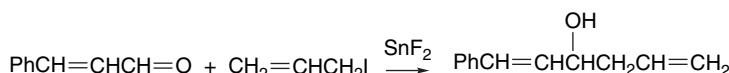


Ref. 168

The halostannanes can also be generated *in situ* by reactions of allylic halides with tin metal or stannous halides.

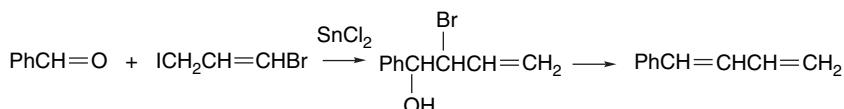


Ref. 169



Ref. 169

The allylation reaction can be adapted to the synthesis of terminal dienes by using 1-bromo-3-iodopropene and stannous chloride. The elimination step is a reductive elimination of the type discussed in Section 5.8. Excess stannous chloride acts as the reducing agent.



Ref. 170

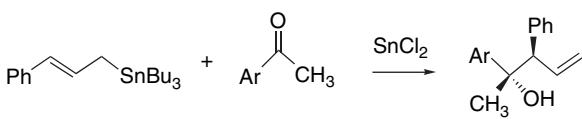
Allylic Sn(II) species are believed to be involved in reactions of allylic trialkyl stannanes in the presence of SnCl_2 . These reactions are particularly effective in acetonitrile, which appears to promote the exchange reaction. Ketones as well as aldehydes are reactive under these conditions.¹⁷¹

¹⁶⁸. T. Mukaiyama and T. Harada, *Chem. Lett.*, 1527 (1981).

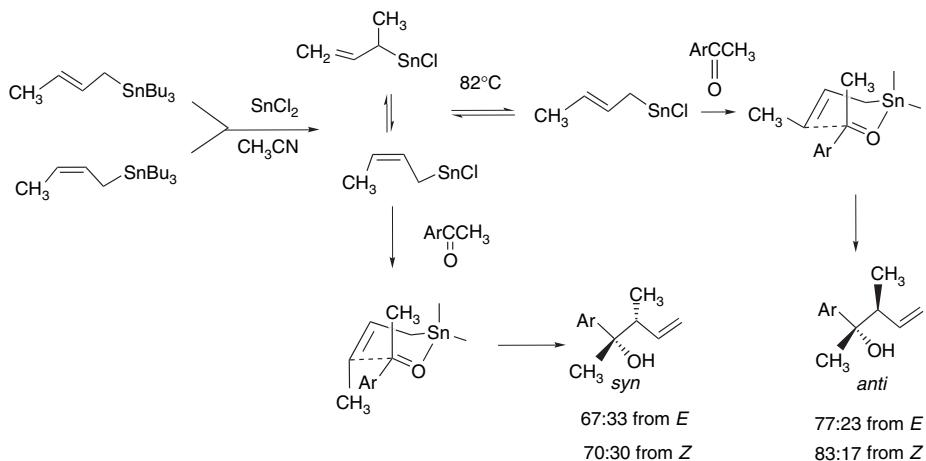
¹⁶⁹. T. Mukaiyama, T. Harada, and S. Shoda, *Chem. Lett.*, 1507 (1980).

¹⁷⁰. J. Auge, *Tetrahedron Lett.*, **26**, 753 (1985).

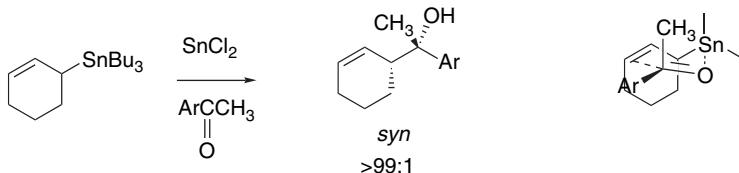
¹⁷¹. (a) M. Yasuda, Y. Sugawa, A. Yamamoto, I. Shibata, and A. Baba, *Tetrahedron Lett.*, **37**, 5951 (1996); (b) M. Yasuda, K. Hirata, M. Nishino, A. Yamamoto, and A. Baba, *J. Am. Chem. Soc.*, **124**, 13442 (2002).



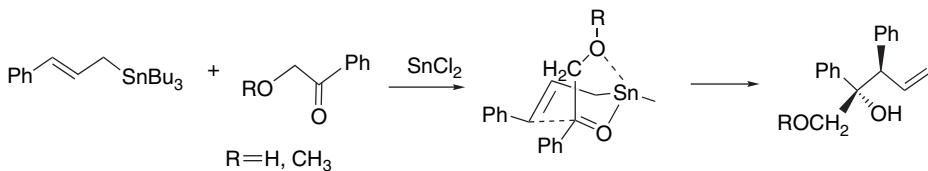
The *anti* stereochemistry is consistent with a cyclic TS, but the reaction is stereoconvergent for the *E*- and *Z*-2-butenylstannanes, indicating that isomerization must occur at the transmetalation stage. The adducts are equilibrated at 82 °C and under these conditions the *anti* product is isolated on workup.



Cyclic allylstannanes give *syn* products with high selectivity.



The reaction with α -hydroxy and α -methoxy ketones under these conditions are chelation controlled.

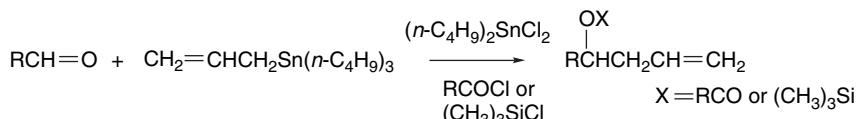


Use of di-(*n*-butyl)stannyldichloride along with an acyl or silyl halide leads to addition of allylstannanes to the aldehydes.^{172a,172} Reaction is also promoted by butylstannyl trichloride.¹⁷³ Both SnCl₄ and SnCl₂ also catalyze this kind of addition.

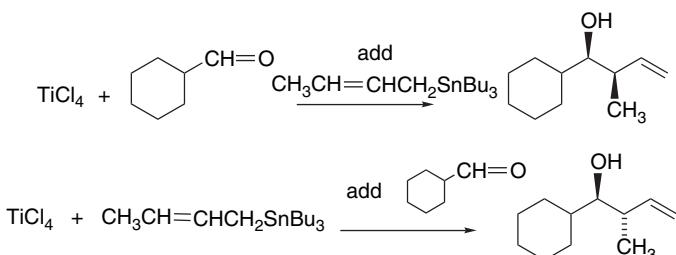
¹⁷². J. K. Whitesell and R. Apodaca, *Tetrahedron Lett.*, **37**, 3955 (1996).

¹⁷³. H. Miyake and K. Yamamura, *Chem. Lett.*, 1369 (1992); H. Miyake and K. Yamamura, *Chem. Lett.*, 1473 (1993).

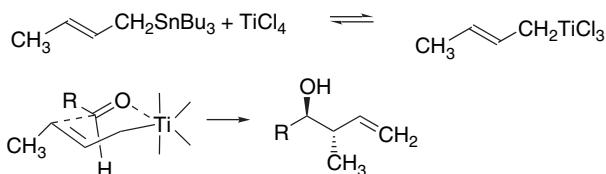
Reactions of tetraallylstannanes with aldehydes catalyzed by SnCl_4 also appear to involve a halostannane intermediate. It can be demonstrated by NMR that there is a rapid redistribution of the allyl group.¹⁷⁴ Reactions with these halostannanes are believed to proceed through a cyclic TS.



9.3.2.3. Reactions Involving Transmetallation. With certain Lewis acids, the reaction may involve a prior transmetallation. This introduces several additional factors into the analysis of the stereoselectivity, as the stereochemistry of the transmetallation has to be considered. Reactions involving halo titanium and halo tin intermediates formed by transmetallation can proceed through a cyclic TS. When TiCl_4 is used as the catalyst, the stereoselectivity depends on the order of addition of the reagents. When *E*-2-but enylstannane is added to a TiCl_4 -aldehyde mixture, *syn* stereoselectivity is observed. When the aldehyde is added to a premixed solution of the 2-but enylstannane and TiCl_4 , the *anti* isomer predominates.¹⁷⁵



The formation of the *anti* stereoisomer is attributed to involvement of a butenyltitanium intermediate formed by rapid exchange with the butenylstannane. This intermediate then reacts through a cyclic TS.

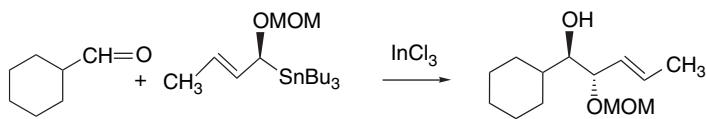


Indium chloride in polar solvents such as acetone or acetonitrile leads to good diastereoselectivity with cyclohexanecarboxaldehyde and other representative aldehydes.¹⁷⁶

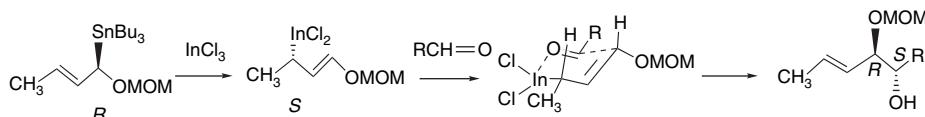
¹⁷⁴ S. E. Denmark, T. Wilson, and T. M. Willson, *J. Am. Chem. Soc.*, **110**, 984 (1988); G. E. Keck, M. B. Andrus, and S. Castellino, *J. Am. Chem. Soc.*, **111**, 8136 (1989).

¹⁷⁵ G. E. Keck, D. E. Abbott, E. P. Boden, and E. J. Enholm, *Tetrahedron Lett.*, **25**, 3927 (1984).

¹⁷⁶ J. A. Marshall and K. W. Hinkle, *J. Org. Chem.*, **60**, 1920 (1995).

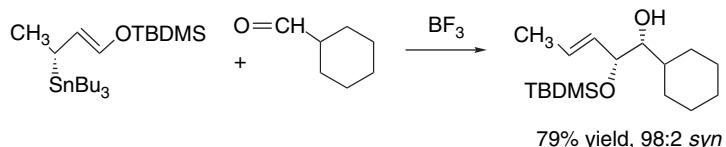


These reactions are believed to proceed via transmetallation. Configurational inversion occurs at both the transmetallation and addition steps, leading to overall retention of the allylic stereochemistry.

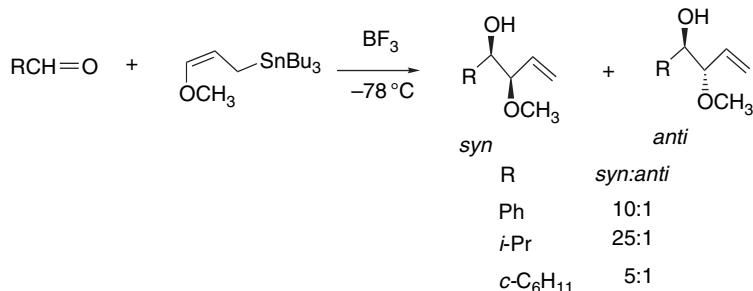


These reagents are useful in enantioselective synthesis and are discussed further in the following section.

9.3.2.4. γ -Oxygen-Substituted Stannanes. Oxygenated allylic stannanes have been synthesized and used advantageously in several types of syntheses. Both α - and γ -alkoxy and silyloxy stannane can be prepared by several complementary methods.¹⁷⁷ *E*- γ -Alkoxy and silyloxy allylic stannanes react with aldehydes to give primarily *syn* adducts.¹⁷⁸



Allylic silanes with γ -alkoxy substituents also give a preference for the *syn* stereochemistry.¹⁷⁹



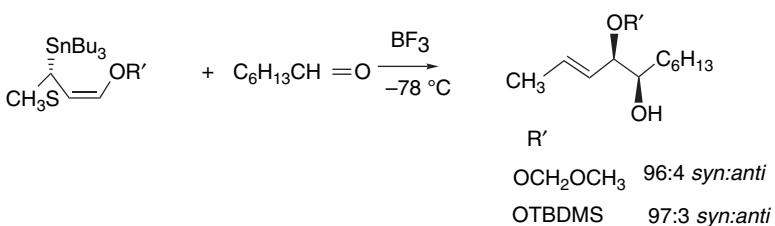
Improved stereoselectivity is observed with methoxymethoxy (MOM) and TBDMOSO substituents.¹⁸⁰

¹⁷⁷ J. A. Marshall, *Chem. Rev.*, **96**, 31 (1996).

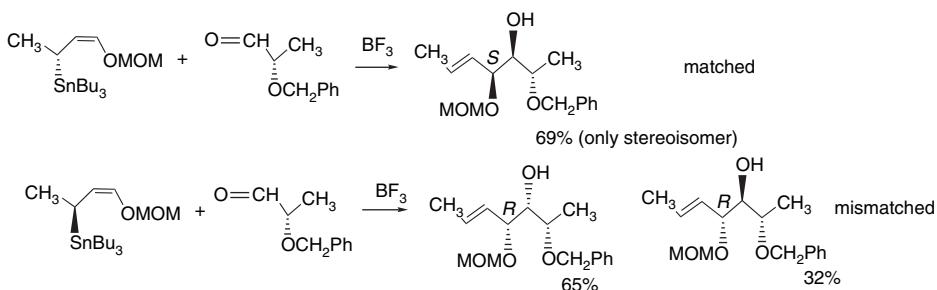
¹⁷⁸ J. A. Marshall, J. A. Jablonowski, and L. M. Elliott, *J. Org. Chem.*, **60**, 2662 (1995).

¹⁷⁹ M. Koreeda and Y. Tanaka, *Tetrahedron Lett.*, **28**, 143 (1987).

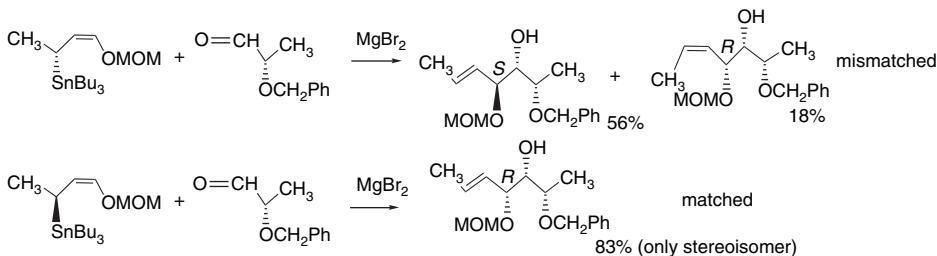
¹⁸⁰ J. A. Marshall and J. A. Welmaker, *J. Org. Chem.*, **57**, 7158 (1992).



Use of oxygenated stannanes with α -substituted aldehydes leads to matched and mismatched combinations.¹⁸¹ For example, with the γ -MOM derivative and α -benzyloxypropanal, the matched pair gives a single stereoisomer of the major product, whereas the mismatched pair gives a 67:33 *syn:anti* mixture. The configuration at the alkoxy-substituted center is completely controlled by the chirality of the stannane.



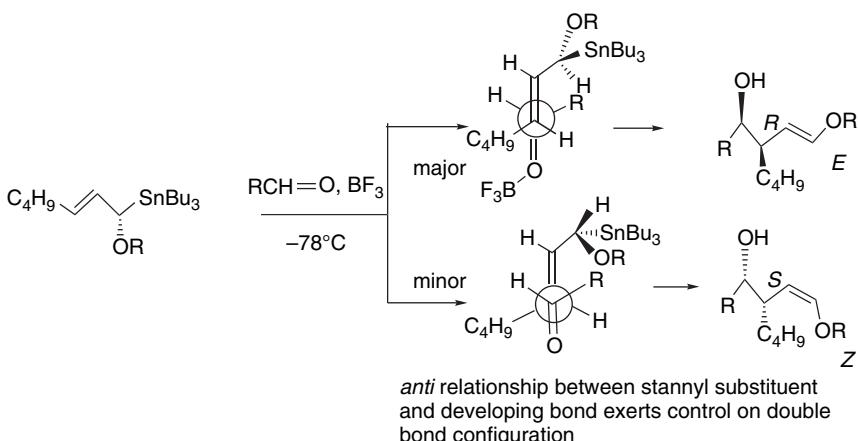
Use of $MgBr_2$, which results in chelation control, reverses the matched and mismatched combinations.



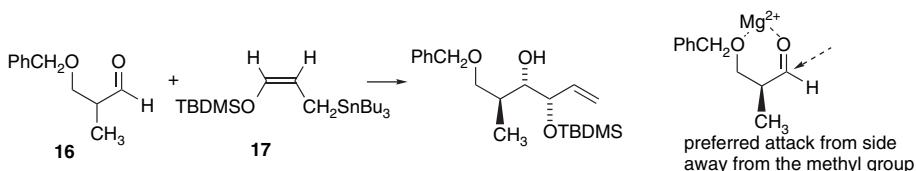
9.3.2.5. Enantioselective Addition Reactions of Allylic Stannanes. There have been several studies of the enantiomers of α -oxygenated alkenyl stannanes. The chirality of the α -carbon exerts powerful control on enantioselectivity with the preference for the stanny group to be *anti* to the forming bond. This is presumably related to the stereoelectronic effect that facilitates the transfer of electron density from the tin to the forming double bond.¹⁸²

¹⁸¹. J. A. Marshall, J. A. Jablonowski, and G. P. Luke, *J. Org. Chem.*, **59**, 7825 (1994).

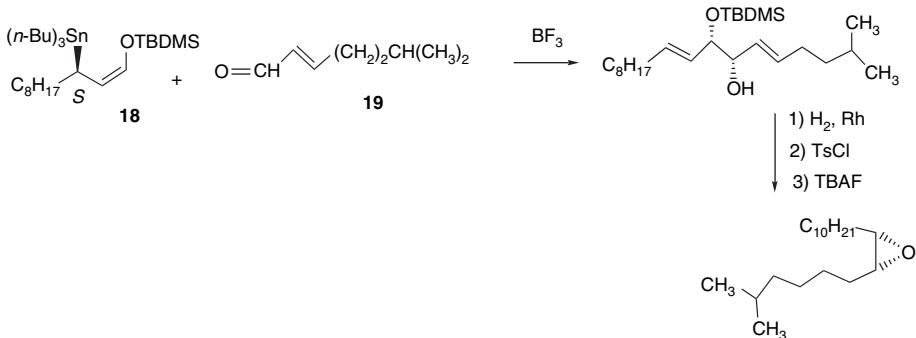
182. J. A. Marshall and W. Y. Gung, *Tetrahedron*, **45**, 1043 (1989).



Allylic stannanes with γ -oxygen substituents have been used to build up polyoxygenated carbon chains. For example, **16** reacts with the stannane **17** to give a high preference for the stereoisomer in which the two oxygen substituents are *anti*. This stereoselectivity is consistent with chelation control.¹⁸³



The substrate-controlled addition of **18** to **19** proceeded with good enantioselectivity and was used to prepare the epoxide (+)-dispalure, a gypsy moth pheromone.¹⁸⁴

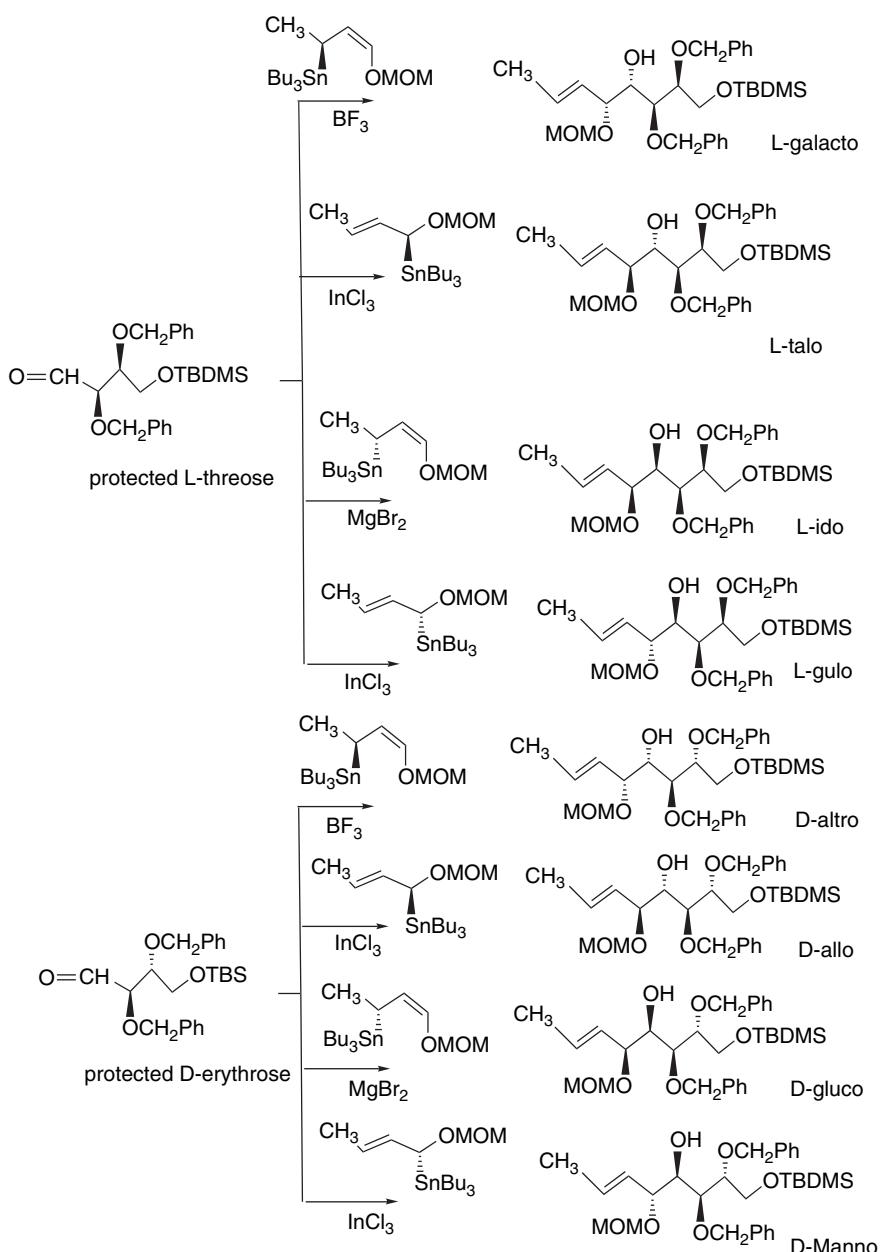


Reagent-controlled stereoselectivity can provide stereochemical relationships over several centers when a combination of acyclic and chelation control and cyclic TS resulting from transmetallation is utilized. In reactions mediated by BF_3 or MgBr_2 the new centers are *syn*. Indium reagents can be used to create an *anti* relationship between two new chiral centers. The indium reagents are formed by transmetallation and react

^{183.} G. E. Keck, K. A. Savin, E. N. K. Cressman, and D. E. Abbott, *J. Org. Chem.*, **59**, 7889 (1994).

^{184.} J. A. Marshall, J. A. Jablonowski, and H. Jiang, *J. Org. Chem.*, **64**, 2152 (1999).

through cyclic TSs leading to *anti* stereochemistry at the new bond. The complementary relationship has been used to construct all eight possible hexose configurations.¹⁸⁵

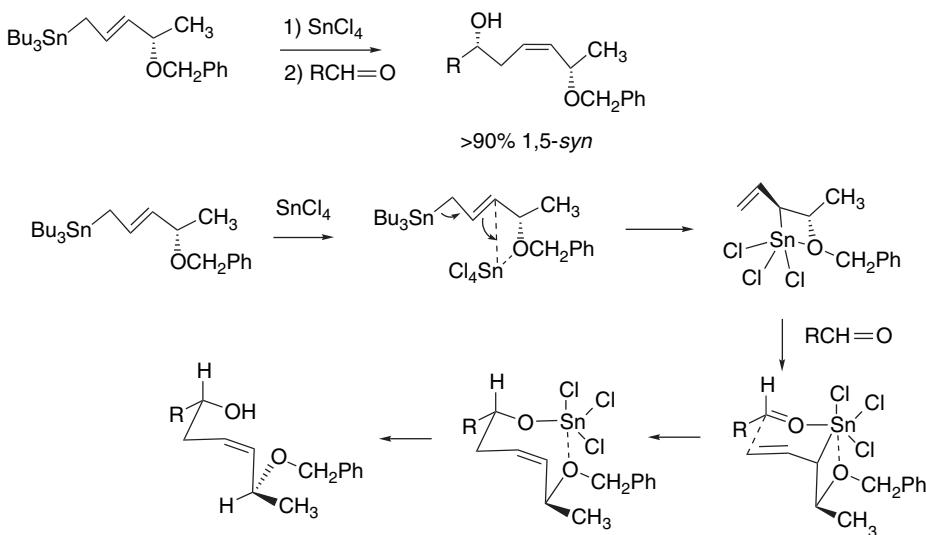


More remote oxygen substituents can also influence stereochemistry. 4-Benzylxyloxy-2-pentenyl tri-*n*-butylstannane exhibits excellent enantioselectivity in reactions with aldehydes.¹⁸⁶ This reaction is believed to involve chelation of the

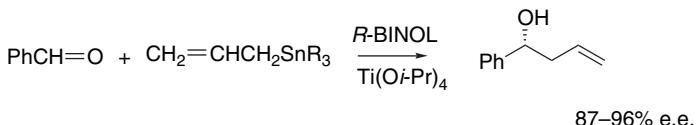
¹⁸⁵ J. A. Marshall and K. W. Hinkle, *J. Org. Chem.*, **61**, 105 (1996).

¹⁸⁶ E. J. Thomas, *J. Chem. Soc. Chem. Commun.*, 411 (1997); A. H. McNeill and E. J. Thomas, *Synthesis*, 322 (1998).

benzyloxy group in both the transmetalation and addition steps. The transmetalation is thought to involve coordination with SnCl_4 through the benzyloxy group that is maintained in the addition step.



Allylstannane additions to aldehydes can be made enantioselective by use of chiral catalysts. A catalyst prepared from the chiral binaphthols *R*- or *S*-BINOL and $\text{Ti}(\text{O}-i\text{-Pr})_4$ achieves 85–95% enantioselectivity.¹⁸⁷



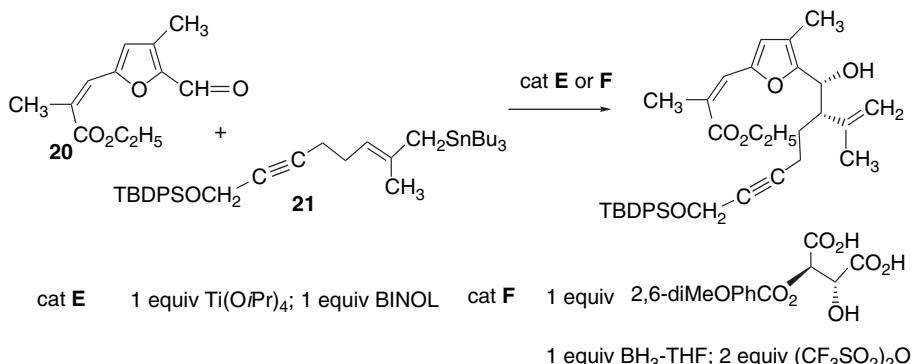
BINAP-AgF gives good enantioselectivity, especially for the major *anti* product in the addition of 2-butenylstannanes to benzaldehyde.¹⁸⁸ This system appears to be stereoconvergent, suggesting that isomerization of the 2-butene system occurs, perhaps by transmetalation.



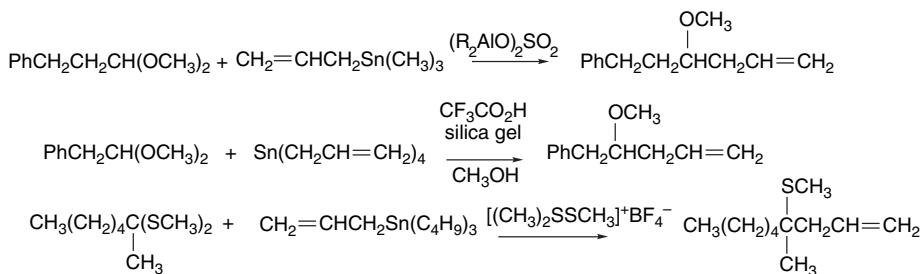
¹⁸⁷ G. E. Keck, K. H. Tarbet, and L. S. Geraci, *J. Am. Chem. Soc.*, **115**, 8467 (1993); A. L. Costa, M. G. Piazza, E. Tagliavini, C. Trombini, and A. Umani-Ronchi, *J. Am. Chem. Soc.*, **115**, 7001 (1993); G. E. Keck and L. S. Geraci, *Tetrahedron Lett.*, **34**, 7827 (1993); G. E. Keck, D. Krishnamurthy, and M. C. Grier, *J. Org. Chem.*, **58**, 6543 (1993).

¹⁸⁸ A. Yanagisawa, H. Nakashima, Y. Nakatsuka, A. Ishiba, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **74**, 1129 (2001).

The coupling of the achiral stannane **20** and aldehyde **21** was achieved with fair to good enantioselectivity and fair yield using chiral catalysts. Ti-BINOL gave 52% e.e. and 31% yield, whereas an acyloxyborane catalyst (see p. 127) gave 90% e.e. and 24% yield.¹⁸⁹



Lewis acid-mediated ionization of acetals also generates electrophilic carbon intermediates that react readily with allylic stannanes.¹⁹⁰ Dithioacetals can be activated by the sulfonium salt $[(\text{CH}_3)_2\text{SSCH}_3]^+\text{BF}_4^-$.¹⁹¹



Scheme 9.6 gives some other examples of Lewis acid-catalyzed reactions of allylic stannanes with carbonyl compounds. Entry 1 demonstrates the *syn* stereoselectivity observed with *E*-allylic systems. Entries 2 and 3 illustrate the use of mono- and dihalostannanes in reactions with acetone. Entry 4 involves addition to acrolein, using Bu_2SnCl_2 as the catalyst. This reaction was run at room temperature for 24 h and gave exclusively the *Z*-configuration of the new double bond. It seems likely that this is the result of thermodynamic control. Entry 5 involves an α -ethoxyallylstannane and shows *syn* stereoselectivity. Entry 6 involving an α -benzyloxy aldehyde occurred with high chelation control. The addition in Entry 7 involves *in situ* generation of an allylic stannane and favored the *anti* stereoisomer by about 4:1. Entry 8 was used to establish relative stereochemistry in a short synthesis of racemic Prelog-Djerassi lactone. Although the methoxycarbonyl group is a potential chelating ligand, the use of

¹⁸⁹ J. A. Marshall and J. Liao, *J. Org. Chem.*, **63**, 5962 (1998).

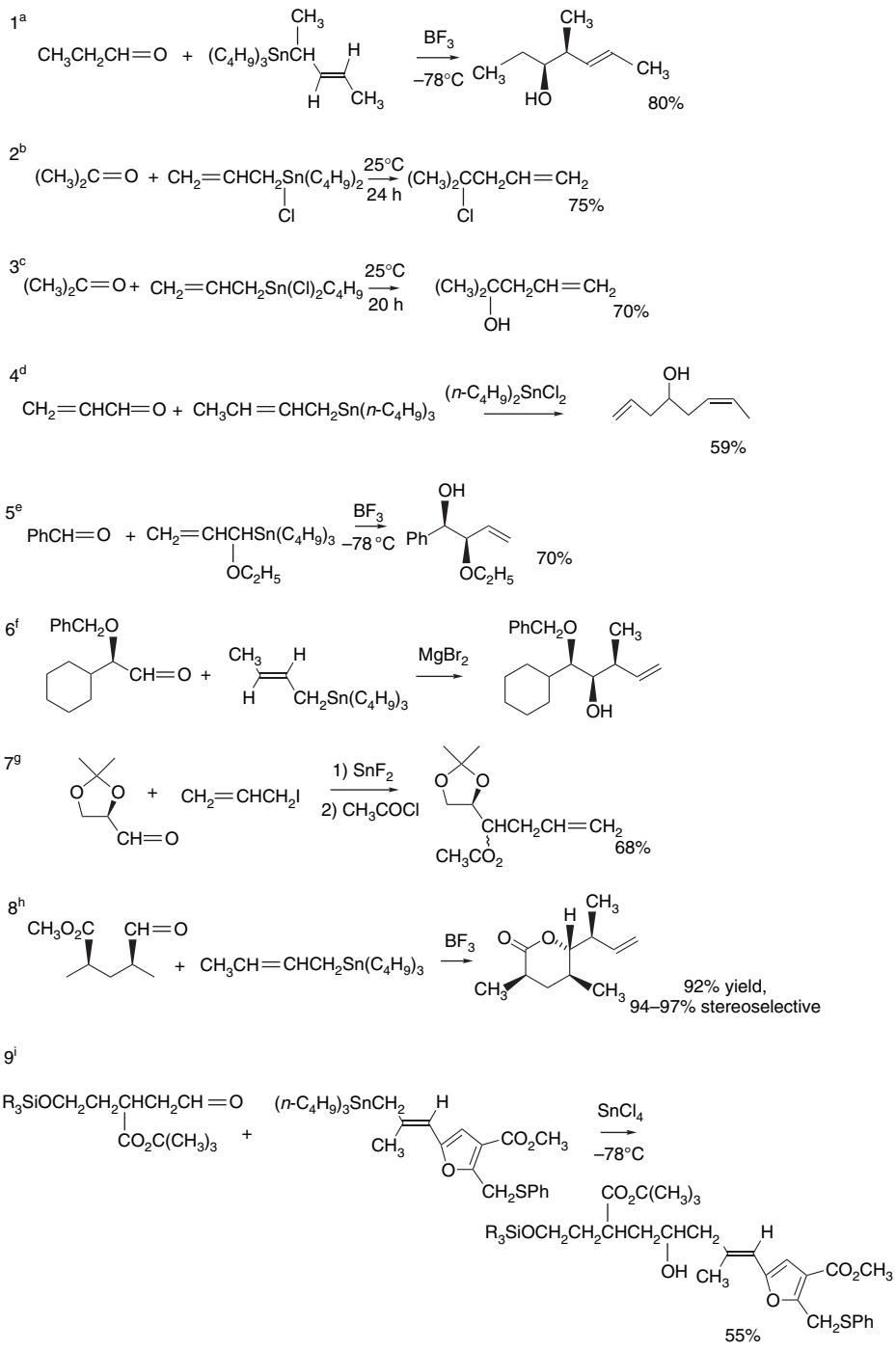
¹⁹⁰ A. Hosomi, H. Iguchi, M. Endo, and H. Sakurai, *Chem. Lett.*, 977 (1979).

¹⁹¹ B. M. Trost and T. Sato, *J. Am. Chem. Soc.*, **107**, 719 (1985).

Scheme 9.6. Reactions of Allylic Stannanes with Carbonyl Compounds

CHAPTER 9

*Carbon-Carbon
Bond-Forming Reactions
of Compounds of Boron,
Silicon, and Tin*

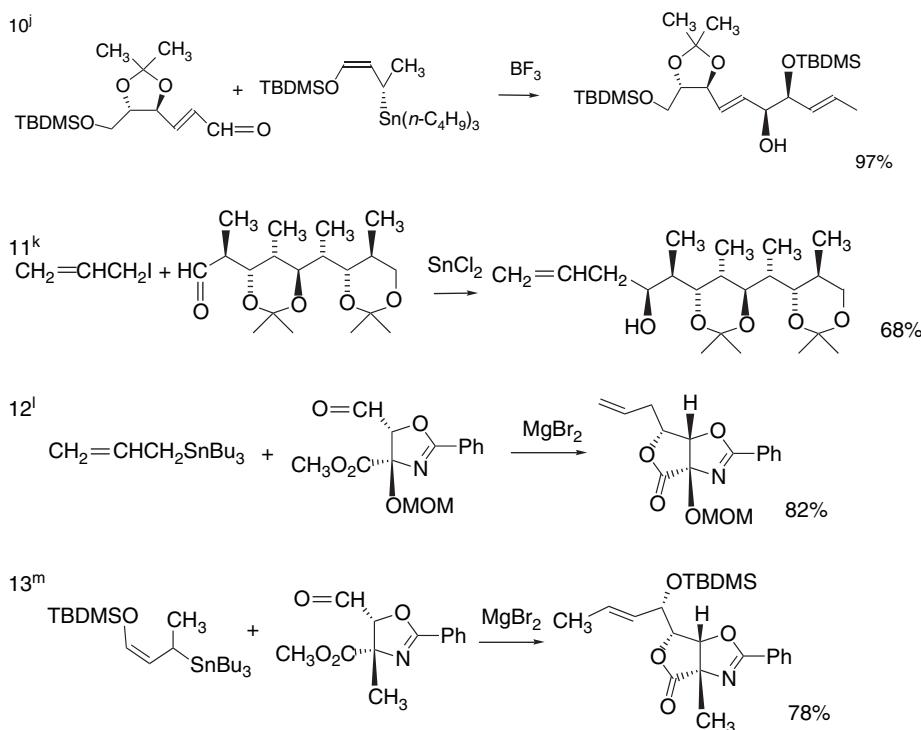


(Continued)

Scheme 9.6. (Continued)

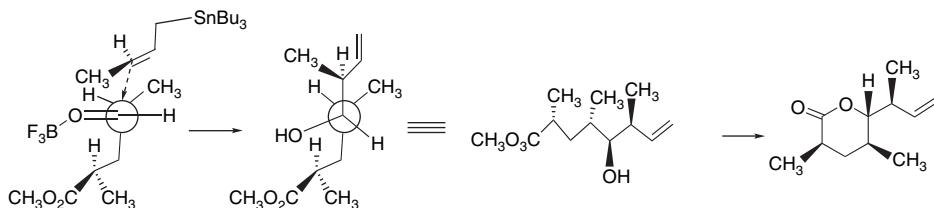
SECTION 9.3

Organotin Compounds



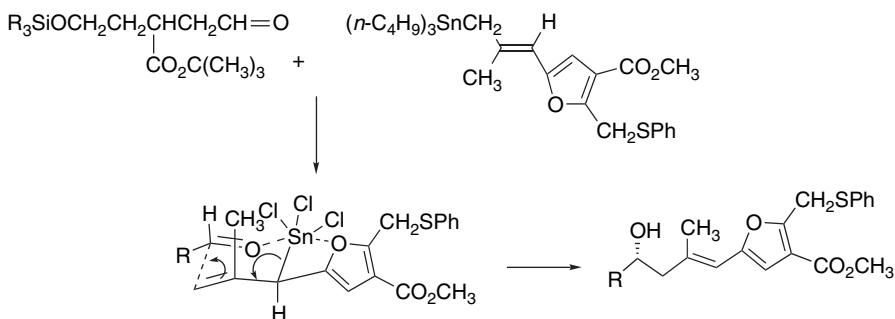
- a. M. Koreeda and Y. Tanaka, *Chem. Lett.*, 1297 (1982).
 b. V. Peruzzo and G. Tagliavini, *J. Organomet. Chem.*, **162**, 37 (1978).
 c. A. Gambaro, V. Peruzzo, G. Plazzogna, and G. Tagliavini, *J. Organomet. Chem.*, **197**, 45 (1980).
 d. L. A. Paquette and G. D. Maynard, *J. Am. Chem. Soc.*, **114**, 5018 (1992).
 e. D.-P. Quintard, B. Elissondo, and M. Pereyre, *J. Org. Chem.*, **48**, 1559 (1983).
 f. G. E. Keck and E. P. Boden, *Tetrahedron Lett.*, **25**, 1879 (1984).
 g. T. Harada and T. Mukaiyama, *Chem. Lett.*, 1109 (1981).
 h. K. Maruyama, Y. Ishiara, and Y. Yamamoto, *Tetrahedron Lett.*, **22**, 4235 (1981).
 i. L. A. Paquette and P. C. Astles, *J. Org. Chem.*, **58**, 165 (1993).
 j. J. A. Marshall, S. Beaudoin, and K. Lewinski, *J. Org. Chem.*, **58**, 5876 (1993).
 k. H. Nagaoka, and Y. Kishi, *Tetrahedron*, **37**, 3873 (1981).
 l. K.-Y. Lee, C.-Y. Oh, Y.-H. Kim, J. E. Joo, and W.-H. Ham, *Tetrahedron Lett.*, **43**, 9361 (2002).
 m. K.-Y. Lee, C.-Y. Oh, and W.-H. Ham, *Org. Lett.*, **4**, 4403 (2002).

BF₃ should involve an open TS. The observed stereochemistry is *syn* but the approach is anti-Felkin.

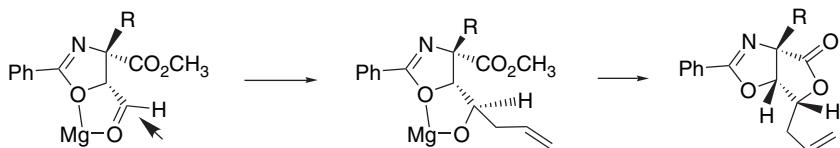


Entry 9 was used in the synthesis of a furanocembranolide. This reaction presumably proceeds through a trichlorostannane intermediate and involves allylic

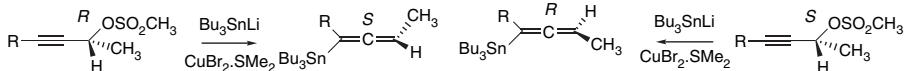
shift at both the transmetalation and addition steps, resulting in restoration of the original allylic structure.



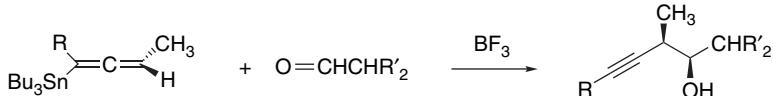
Entry 10 was used in conjunction with dihydroxylation in the enantiospecific synthesis of polyols. Entry 11 illustrates the use of SnCl_2 with a protected polypropionate. Entries 12 and 13 result in the formation of lactones, after MgBr_2 -catalyzed additions to heterocyclic aldehyde having ester substituents. The stereochemistry of both of these reactions is consistent with approach to a chelate involving the aldehyde oxygen and oxazoline oxygen.



9.3.2.6. Allenyl Stannanes. Allenyl stannanes are a useful variation of the allylic stannanes.¹⁹² They can be made in enantiomerically pure form by S_N2' displacements on propargyl tosylates.¹⁹³



The allenic stannanes react with aldehydes under the influence of Lewis acids such as BF_3 and MgBr_2 . Unbranched aldehydes are not very stereoselective, but branched aldehydes show a strong preference for the *syn* adduct.

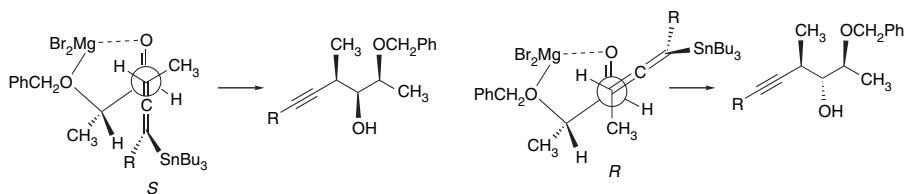


With α -benzyloxypropanal, using MgBr_2 as the Lewis acid, chelation control is observed. The stereospecificity is determined by an *anti* orientation of the C–Sn bond

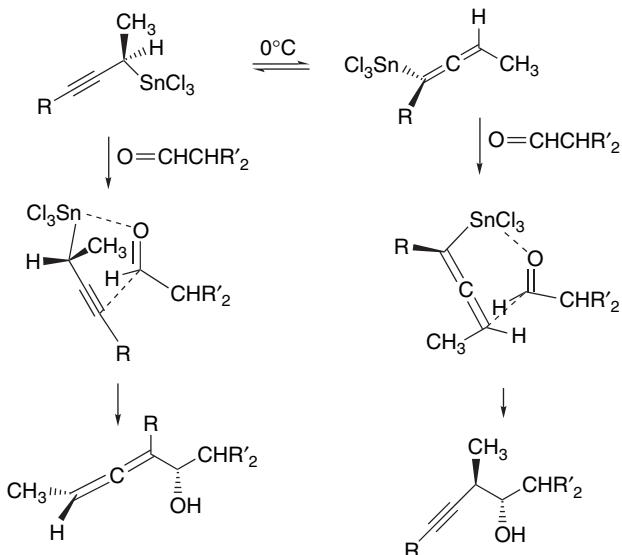
¹⁹² J. A. Marshall, *Chem. Rev.*, **96**, 31 (1996).

¹⁹³ J. A. Marshall and X. Wang, *J. Org. Chem.*, **56**, 3211 (1991).

and the forming C–C bond. As a result, the (*S*) reactant gives a *syn* adduct, whereas the (*R*) reactant gives the *anti* isomer.



The allenic stannanes can be transmetallated by treatment with SnCl_4 , a reaction that results in the formation of a propargyl stannane. If the transmetallation reaction is allowed to equilibrate at 0°C , an allenic structure is formed. These reagents add stereospecifically to the aldehyde through cyclic TSs.¹⁹⁴



The combination of reagents and methods can provide for stereochemical control of addition to α -substituted aldehydes.¹⁹⁵ An application of the methodology can be found in the synthesis of (+)-discodermolide that was carried out by J. A. Marshall and co-workers and is described in Scheme 13.69.

9.4. Summary of Stereoselectivity Patterns

In this chapter, we have seen a number of instances of stereoselectivity. Although they are affected by specific substitution patterns, every case can be recognized as conforming to one of several general patterns.

1. Reactions proceeding through a monocyclic TS with substrate control: These reactions exhibit predictable stereoselectivity determined by the monocyclic

¹⁹⁴ J. A. Marshall and J. Perkins, *J. Org. Chem.*, **60**, 3509 (1995).

¹⁹⁵ J. A. Marshall, J. F. Perkins, and M. A. Wolf, *J. Org. Chem.*, **60**, 5556 (1995).

Scheme 9.7. Summary of Stereoselectivity of Allylic Reagents in Carbonyl Addition Reactions

Monocyclic TS	Open TS	Chelation TS	Stereoconvergent
Allylboration with β -allylic boranes and boronates	Lewis acid-catalyzed addition of allylic silanes	Lewis acid-catalyzed addition of allylic silanes and stannanes α - and β -oxy aldehydes	SnCl_2 -mediated addition of allylic to stannanes aryl methyl ketones
Addition of allylic trihalo stannanes to aldehydes	Lewis Acid-catalyzed addition of allylic stannanes		

TS, which is usually based on the chair (Zimmerman-Traxler) model. This pattern is particularly prevalent for the allylic borane reagents, where the Lewis acidity of boron promotes a tight cyclic TS, but at the same time limits the possibility of additional chelation. The dominant factors in these cases are the *E*- or *Z*-configuration of the allylic reagent and the conformational preferences of the reacting aldehyde (e.g., a Felkin-type preference.)

- Reactions proceeding through open TS: In this group, exemplified by BF_3 -catalyzed additions of allylic silanes and stannanes, the degree of stereochemical control is variable and often moderate. The stereoselectivity depends on steric factors in the open TS and can differ significantly for the *E*- and *Z*-isomers of the allylic reactant.
- Reactions through chelated TS: Reactions of α - or β -oxy-substituted aldehydes often show chelation-controlled stereoselectivity with Lewis acids that can accommodate five or six ligands. Chelation with substituents in the allylic reactant can also occur. The overall stereoselectivity depends on steric and stereoelectronic effects in the chelated TS.
- Stereoconvergence owing to reactant or product equilibration: We also saw several cases where the product composition was the same for stereoisomeric reactants, e.g., for *E*- and *Z*-allylic reactants. This can occur if there is an intermediate step in the mechanism that permits *E*- and *Z*-equilibration or if the final stereoisomeric product can attain equilibrium.

Scheme 9.7 gives examples of each of these types of stereoselectivities. The analysis of any particular system involves determination of the nature of the reactant, e.g., has transmetallation occurred, the coordination capacity of the Lewis acid, and the specific steric and stereoelectronic features of the two reactants.

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 B. M. Trost, ed., *Stereodirected Synthesis with Organoboranes*, Springer, Berlin, 1995.

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W. Weber, *Silicon Reagents for Organic Synthesis*, Springer, Berlin, 1983.

Organotin Compounds

A. G. Davies, *Organotin Chemistry*, VCH, Weinheim, 1997.

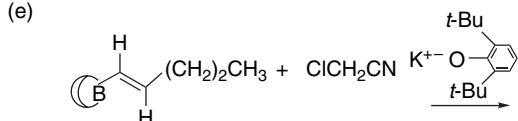
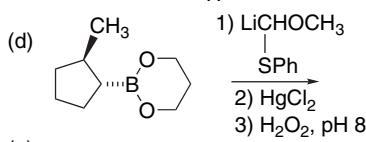
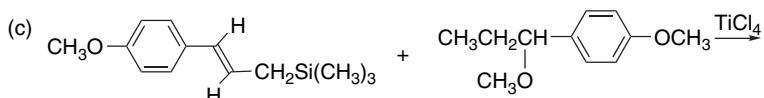
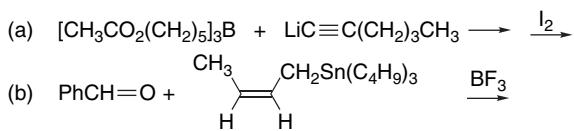
S. Patai, ed., *The Chemistry of Organic Germanium, Tin and Lead Compounds*, Wiley-Interscience, New York, 1995.

M. Pereyre, J.-P. Quintard, and A. Rahm, *Tin in Organic Synthesis*, Butterworths, London, 1983.

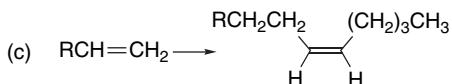
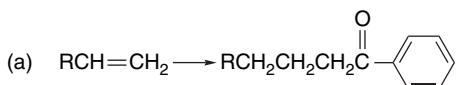
Problems

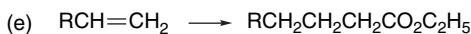
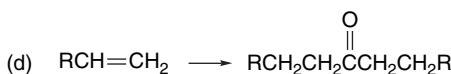
(References for these problems will be found on page 1286.)

9.1. Give the expected product(s) for the following reactions:

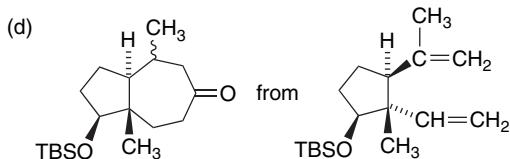
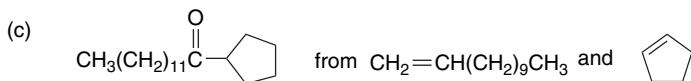
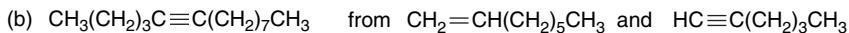
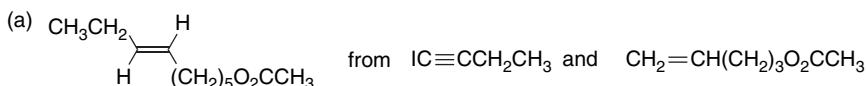


9.2. Starting with an alkene $\text{RCH} = \text{CH}_2$, indicate how an organoborane intermediate could be used for each of the following synthetic transformations:

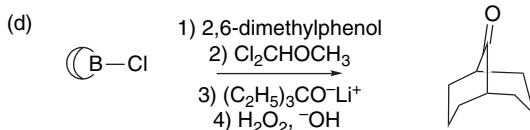
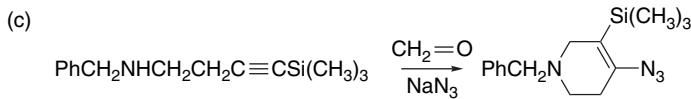
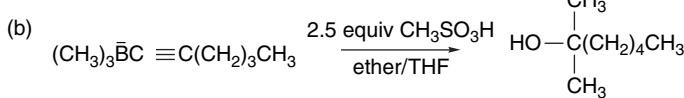
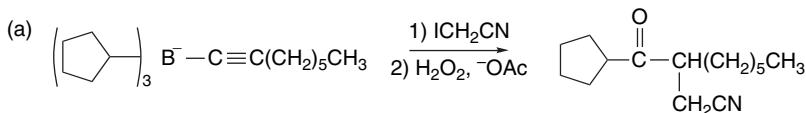




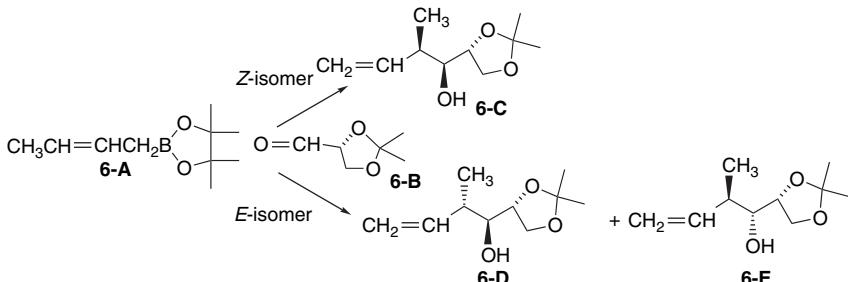
- 9.3. Scheme 9.1 describes reactions with several lithiated compounds, including dichloromethane, dichloromethyl methyl ether, phenylthiomethyl methyl ether, and phenylthioacetals. Compare the structure of these reagents and the final products for these reactions. Develop a mechanistic outline that encompasses these reactions. Discuss the features that these reagents have in common with one another and with carbon monoxide.
- 9.4. Each of the following transformations was performed advantageously with a thexyloborane derivative. Give appropriate reactants, reagents, and reaction conditions for effecting the following syntheses in a one-pot" process.



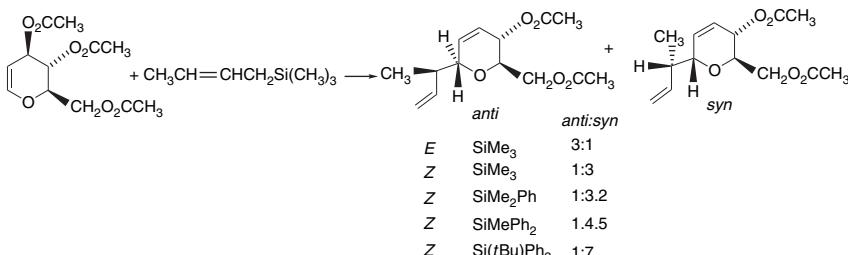
- 9.5. Provide mechanisms for the formation of the new carbon-carbon bonds in each of the following reactions:



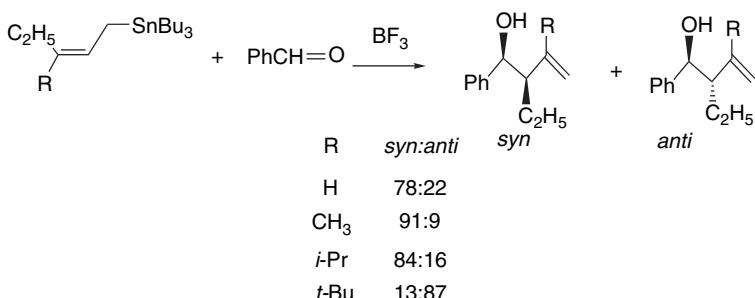
- a. When the *E*- and *Z*-isomers of 2-butenyl-1,3,2-dioxaborolane **6-A** react with aldehyde **6-B**, the *Z*-isomer gives *syn* product **6-C** with greater than 90% stereoselectivity. The *E*-isomer, however, gives a nearly 1:1 mixture of two *anti* products **6-D** and **6-E**.



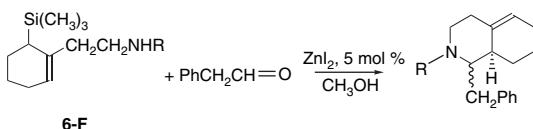
- b. The reaction of several $\Delta^{2,3}$ -pyran acetates with allyl trimethylsilane under the influence of Lewis acids gives 2-allyl- $\Delta^{3,4}$ -pyrans. The stereochemistry depends on whether the *E*- or *Z*-allylsilane is used. There is a preference for *anti* stereochemistry at the new bond with the *E*-silane but *syn* stereochemistry with the *Z*-silane. The preference for the *syn* stereochemistry is increased by use of a more bulky silyl substituent. Analyze the competing transition structures for the *E*- and *Z*-silanes and suggest an explanation for the observed stereoselectivity.



- c. In the reaction of 2-pentenyl tri-*n*-butylstannanes with benzaldehyde and BF_3 , the diastereoselectivity is dependent on the identity of the 3-substituent group. Offer an explanation in terms of possible transition structures.



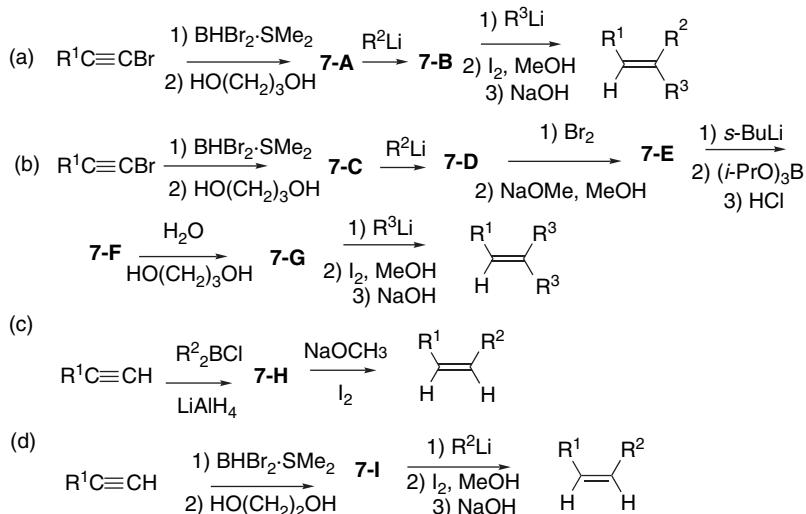
- d. It is observed that the stereoselectivity of cyclizative condensation of aminoalkyl silane **6-F** depends on the steric bulk of the amino substituent. Offer an explanation for this observation in terms of the transition structure for the addition reaction.



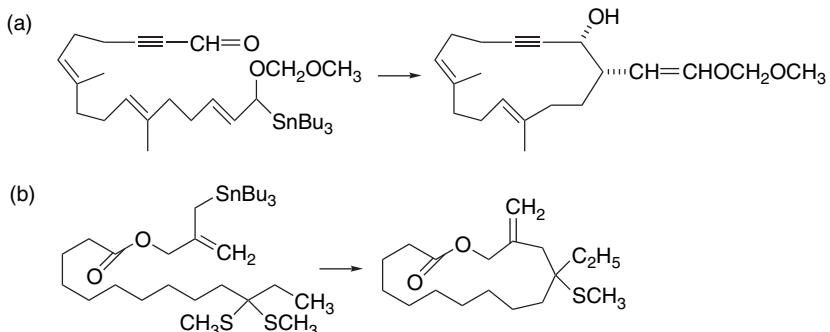
R	Yield (%)	<i>trans:cis</i> ratio
CH ₃ ^a	68	20:80
PhCH ₂	88	58:42
Ph ₂ CH	73	>99:1
Dibenzocycloheptyl	67	>99:1

^a Ph(CH₃)₂Si instead of (CH₃)₃Si.

- 9.7. A number of procedures for stereoselective synthesis of alkenes involving alkenylboranes have been developed. For each of the reactions given below, show the structure of the intermediates and outline the mechanism in sufficient detail to account for the observed stereoselectivity.



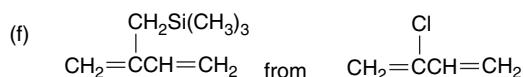
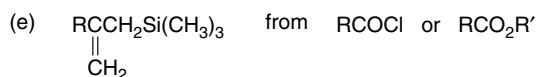
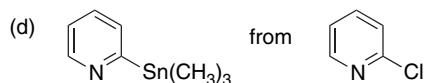
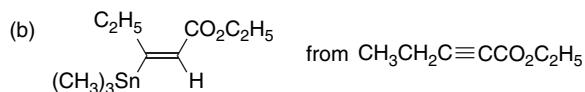
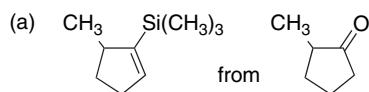
- 9.8. Suggest reagents and reaction conditions that would be effective for the following cyclization reactions:



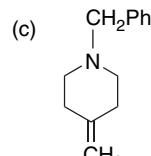
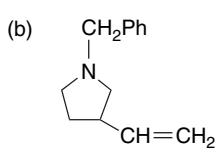
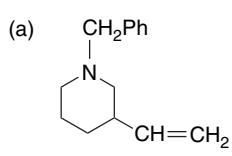
- 9.9. Show how the following silanes and stannanes can be synthesized from the suggested starting material.

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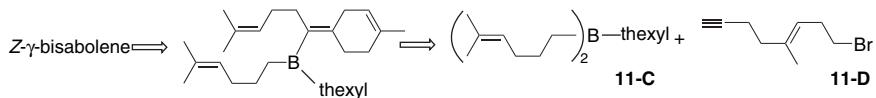
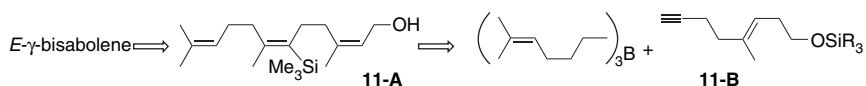
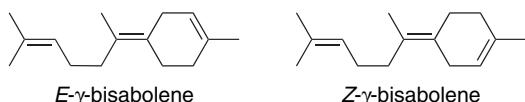
PROBLEMS



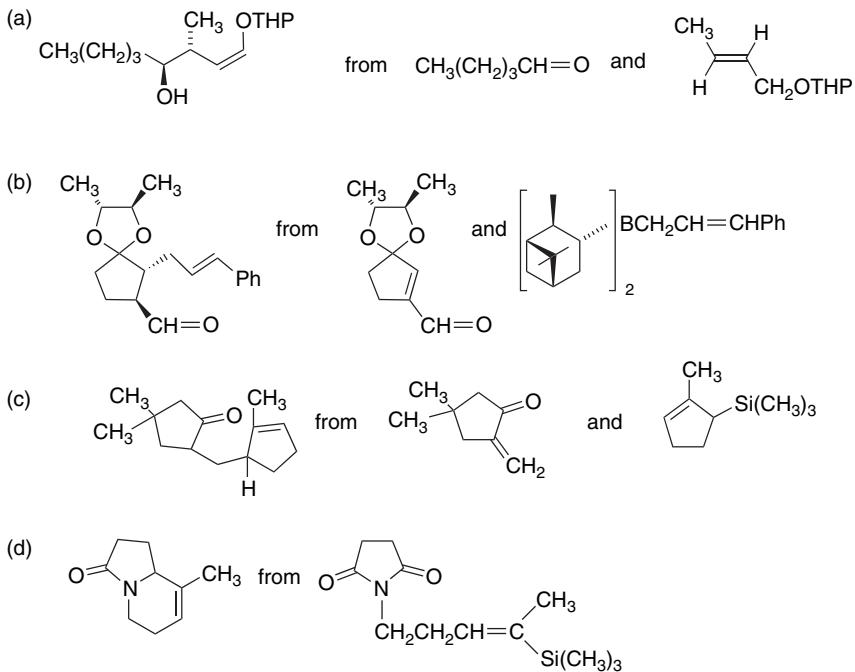
- 9.10. Each of the unsaturated cyclic amines shown below has been synthesized by reaction of an amino-substituted allylic silane under iminium ion cyclization conditions ($\text{CH}_2=\text{O}$, TFA). By retrosynthetic analysis, identify the appropriate precursor for each cyclization. Suggest a method of synthesis of each of the required amines.



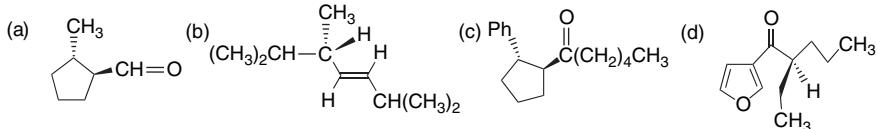
- 9.11. Both *E*- and *Z*-isomers of the terpene γ -bisabolene have been isolated from natural sources. The synthesis of these compounds can be achieved by stereoselective alkene syntheses using borane intermediates. An outline of each synthesis is given below. Indicate the reaction conditions that would permit the stereoselective synthesis of each isomer.



9.12. By retrosynthetic analysis, devise a sequence of reactions that would provide the desired compound from the indicated starting materials.

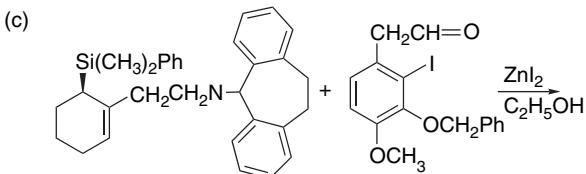
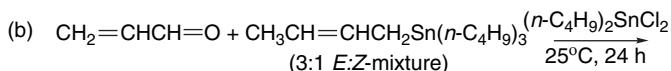
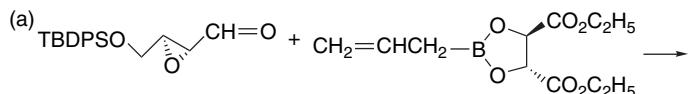


9.13. Show how the following compounds could be prepared in high enantiomeric purity using enantiopure boranes as reactants.



9.14. Show how organoborane intermediates can be used to synthesize the gypsy moth pheromone *E, Z*- $\text{CH}_3\text{CO}_2(\text{CH}_2)_4\text{CH}=\text{CH}(\text{CH}_2)_2\text{CH}=\text{CH}(\text{CH}_2)_3\text{CH}_3$ from hept-6-ynyl acetate, allyl bromide, and 1-hexyne.

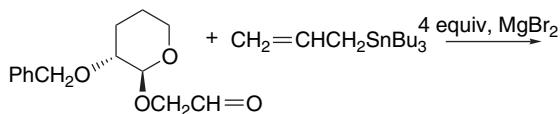
9.15. Predict the major stereoisomer that will be formed in the following reactions. Show the transition structure that is the basis for your response.



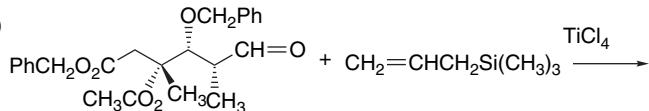
(d)



(e)

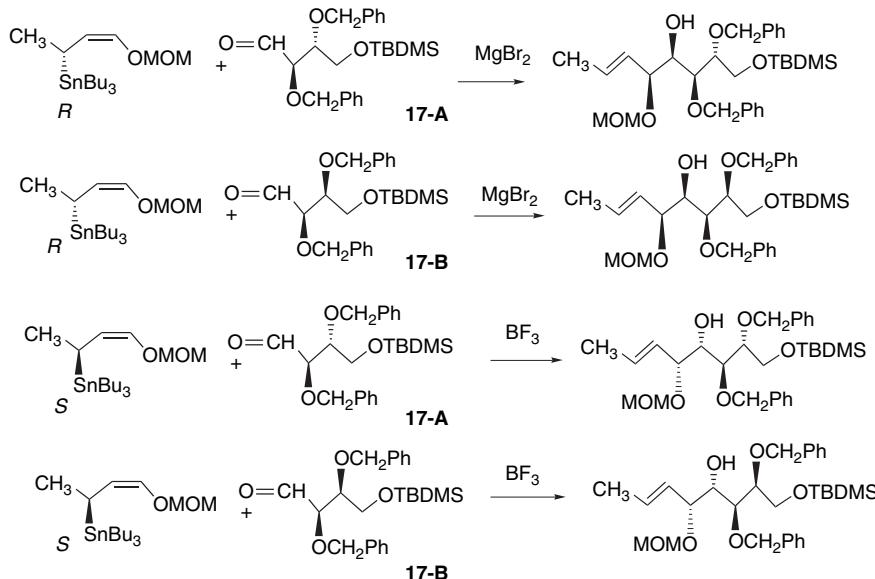


(f)

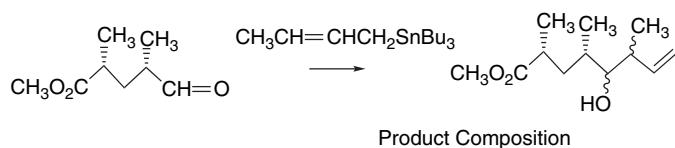


9.16. The stereoselectivity of the β -carboethoxyallylic boronate derived from the *endo*-phenyl auxiliary **A** (p. 803) toward *R*- and *S*-glyceraldehyde acetonide has been investigated. One enantiomer gives the *anti* product in 98:2 ratio, whereas the other favors the *syn* product by a 65:35 ratio. Based on the proposed transition structure for this boronate, determine which combination leads to the higher stereoselectivity and which to the lower. Propose the favored transition structure in each case.

9.17. The *R*- and *S*-enantiomers of *Z*-3-methoxymethyl-1-methylpropenylstannane have been allowed to react with the protected erythrose- and threose-derived aldehydes **17-A** and **17-B**. The products are shown below. Indicate the preferred transition structure for each combination.

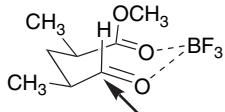


- 9.18. In the original report of the reaction in Entry 8 of Scheme 9.6, it was found that use of three equivalents of BF_3 led to loss of stereoselectivity, but not yield.

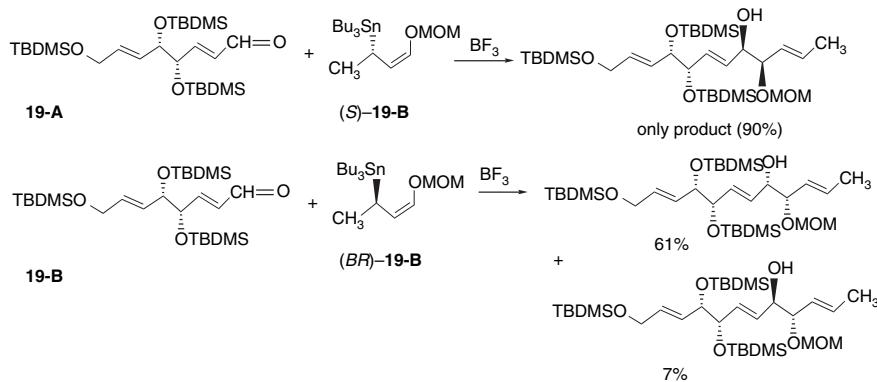


Equiv BF_3	Total Yield	<i>anti</i> <i>anti</i> -Felkin	<i>anti</i> Felkin	<i>syn</i> <i>Felkin</i>	<i>syn</i> <i>anti</i> -Felkin
1	92	94–97	3–4	1	1
2	90	83–91	5–9	1–3	2–5
3	90	41	10	17	32

These results were attributed to a preference for an eight-membered chelated transition structure that was lost in the presence of excess BF_3 because of coordination of a second BF_3 at the ester group. What objections would you raise to this explanation? What alternative would you propose?



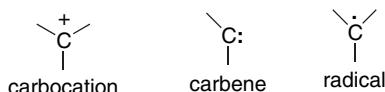
- 9.19. The aldehyde **19-A** shows differential stereoselectivity toward the enantiomeric stannanes **(S)-19-B** and **(R)-19-B**. The former aldehyde gives a single product in high yield, whereas the latter gives a somewhat lower yield and a mixture of two stereoisomers under the same conditions and is a mixture of two stereoisomers. Propose TSs to account for each product and indicate the reasons for the enhanced stereoselectivity of **(S)-19-B**.



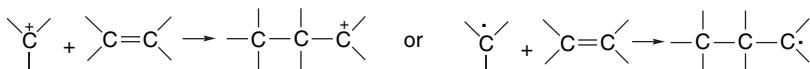
Reactions Involving Carbocations, Carbenes, and Radicals as Reactive Intermediates

Introduction

Trivalent carbocations, carbanions, and radicals are the most fundamental classes of reactive intermediates. The basic aspects of the structural and reactivity features of these intermediates were introduced in Chapter 3 of Part A. Discussion of carbanion intermediates in synthesis began in Chapter 1 of the present volume and continued through several further chapters. The focus in this chapter is on *electron-deficient reactive intermediates*, including carbocations, carbenes, and carbon-centered radicals. Both carbocations and carbenes have a carbon atom with *six valence electrons* and are therefore *electron-deficient* and *electrophilic* in character, and they have the potential for skeletal rearrangements. We also discuss the use of carbon radicals to form carbon–carbon bonds. Radicals react through homolytic bond-breaking and bond-forming reactions involving intermediates with *seven valence electrons*.



A common feature of these intermediates is that they are of high energy, compared to structures with completely filled valence shells. Their lifetimes are usually very short. Bond formation involving carbocations, carbenes, and radicals often occurs with low activation energies. This is particularly true for addition reactions with alkenes and other systems having π bonds. These reactions replace a π bond with a σ bond and are usually exothermic.



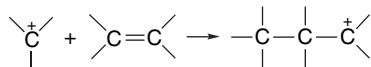
Owing to the low barriers to bond formation, *reactant conformation* often plays a decisive role in the outcome of these reactions. Carbocations, carbene, and radicals frequently undergo very efficient *intramolecular reactions* that depend on the proximity of the reaction centers. Conversely, because of the short lifetimes of the intermediates, reactions through unfavorable conformations are unusual. Mechanistic analyses and synthetic designs that involve carbocations, carbenes, and radicals must pay particularly close attention to conformational factors.

10.1. Reactions and Rearrangement Involving Carbocation Intermediates

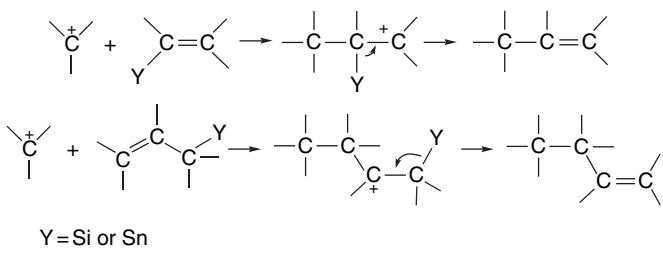
In this section, the emphasis is on carbocation reactions that modify the carbon skeleton, including carbon-carbon bond formation, rearrangements, and fragmentation reactions. The fundamental structural and reactivity characteristics of carbocations toward nucleophilic substitution were explored in Chapter 4 of Part A.

10.1.1. Carbon-Carbon Bond Formation Involving Carbocations

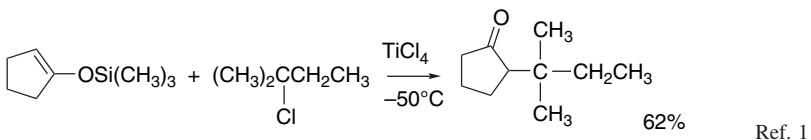
10.1.1.1. Intermolecular Alkylation by Carbocations. The formation of carbon-carbon bonds by electrophilic attack on the π system is a very important reaction in aromatic chemistry, with both Friedel-Crafts alkylation and acylation following this pattern. These reactions are discussed in Chapter 11. There also are useful reactions in which carbon-carbon bond formation results from electrophilic attack by a carbocation on an alkene. The reaction of a carbocation with an alkene to form a new carbon-carbon bond is both kinetically accessible and thermodynamically favorable.



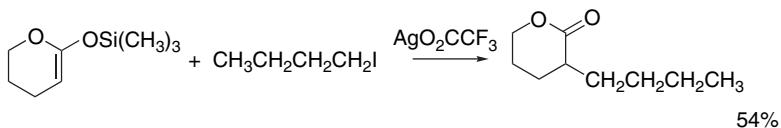
There are, however, serious problems that must be overcome in the application of this reaction to synthesis. The product is a new carbocation that can react further. Repetitive addition to alkene molecules leads to polymerization. Indeed, this is the mechanism of acid-catalyzed polymerization of alkenes. There is also the possibility of rearrangement. A key requirement for adapting the reaction of carbocations with alkenes to the synthesis of small molecules is control of the reactivity of the newly formed carbocation intermediate. Synthetically useful carbocation-alkene reactions require a suitable termination step. We have already encountered one successful strategy in the reaction of alkenyl and allylic silanes and stannanes with electrophilic carbon (see Chapter 9). In those reactions, the silyl or stannylyl substituent is eliminated and a stable alkene is formed. The increased reactivity of the silyl- and stannylyl-substituted alkenes is also favorable to the synthetic utility of carbocation-alkene reactions because the reactants are more nucleophilic than the product alkenes.



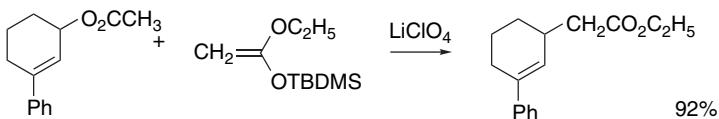
Silyl enol ethers and silyl ketene acetals also offer both enhanced reactivity and a favorable termination step. Electrophilic attack is followed by desilylation to give an α -substituted carbonyl compound. The carbocations can be generated from tertiary chlorides and a Lewis acid, such as TiCl_4 . This reaction provides a method for introducing tertiary alkyl groups α to a carbonyl, a transformation that cannot be achieved by base-catalyzed alkylation because of the strong tendency for tertiary halides to undergo elimination.



Secondary benzylic bromides, allylic bromides, and α -chloro ethers can undergo analogous reactions using ZnBr_2 as the catalyst.² Primary iodides react with silyl ketene acetals in the presence of AgO_2CCF_3 .³



Alkylations via an allylic cation have been observed using LiClO_4 to promote ionization.⁴



These reactions provide examples of intermolecular carbocation alkylations. Despite the feasibility of this type of reaction, the requirements for good yields are stringent and the number of its synthetic applications is limited.

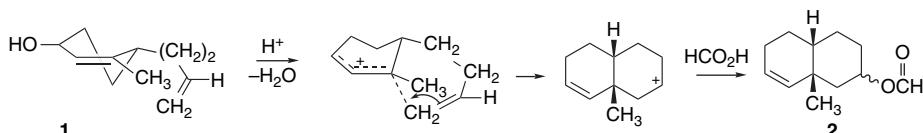
¹. M. T. Reetz, I. Chatziiosifidis, U. Loewe, and W. F. Maier, *Tetrahedron Lett.*, 1427 (1979); M. T. Reetz, I. Chatziiosifidis, F. Huebner, and H. Heimbach, *Org. Synth.*, **62**, 95 (1984).

². I. Paterson, *Tetrahedron Lett.*, 1519 (1979).

³. C. W. Jefford, A. W. Sledeski, P. Lelandais, and J. Boukouvalas, *Tetrahedron Lett.*, **33**, 1855 (1992).

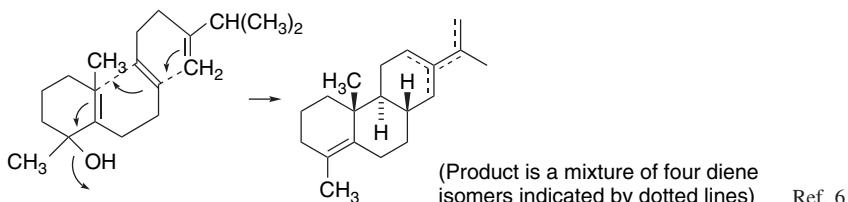
⁴. W. H. Pearson and J. M. Schkeryantz, *J. Org. Chem.*, **57**, 2986 (1992).

10.1.1.2. Polyene Cyclization. Perhaps the most synthetically useful of the carbocation alkylation reactions is the cyclization of polyenes having two or more double bonds positioned in such a way that successive bond-forming steps can occur. This process, called *Polyene cyclization*, has proven to be an effective way of making polycyclic compounds containing six-membered and, in some cases, five-membered rings. The reaction proceeds through an electrophilic attack and requires that the double bonds that participate in the cyclization be properly positioned. For example, compound **1** is converted quantitatively to **2** on treatment with formic acid. The reaction is initiated by protonation and ionization of the allylic alcohol and is terminated by nucleophilic capture of the cyclized secondary carbocation.



Ref. 5

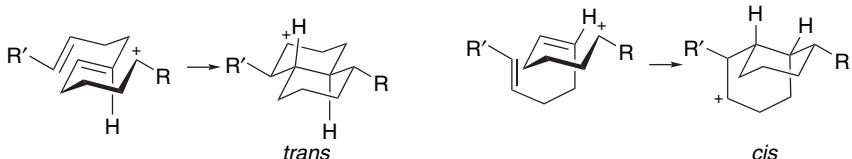
More extended polyenes can cyclize to tricyclic systems.



(Product is a mixture of four diene isomers indicated by dotted lines)

Ref. 6

These cyclizations are usually highly stereoselective, with the stereochemical outcome being determined by the reactant conformation.⁷ The stereochemistry of the products in the decalin system can be predicted by assuming that cyclization occurs through conformations that resemble chair cyclohexane rings. The stereochemistry at ring junctures is that resulting from *anti* attack at the participating double bonds.



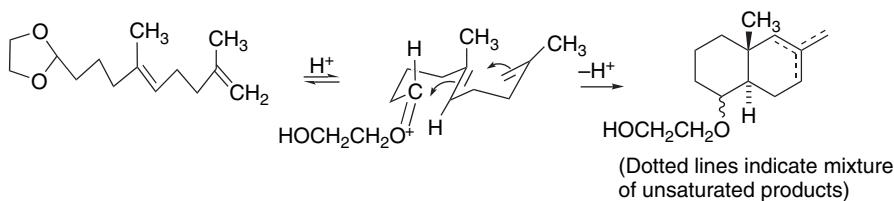
To be of maximum synthetic value, the generation of the cationic site that initiates cyclization must involve mild reaction conditions. Formic acid and stannic chloride are effective reagents for cyclization of polyunsaturated allylic alcohols. Acetals generate oxonium ions in acidic solution and can also be used to initiate the cyclization of polyenes.⁸

5. W. S. Johnson, P. J. Neustaedter, and K. K. Schmiegel, *J. Am. Chem. Soc.*, **87**, 5148 (1965).

6. W. J. Johnson, N. P. Jensen, J. Hooz, and E. J. Leopold, *J. Am. Chem. Soc.*, **90**, 5872 (1968).

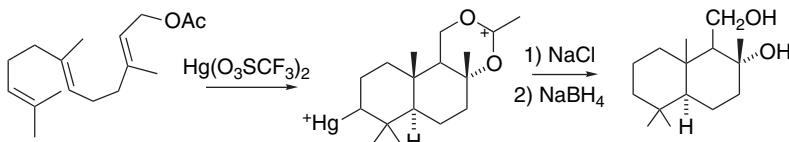
7. W. S. Johnson, *Acc. Chem. Res.*, **1**, 1 (1968); P. A. Bartlett, in *Asymmetric Synthesis*, Vol. 3, J. D. Morrison, ed., Academic Press, New York, 1984, Chap. 5.

8. A. van der Gen, K. Wiedhaup, J. J. Swoboda, H. C. Dunathan, and W. S. Johnson, *J. Am. Chem. Soc.*, **95**, 2656 (1973).



Another significant method for generating the electrophilic site is acid-catalyzed epoxide ring opening.⁹ Lewis acids such as BF_3 , SnCl_4 , CH_3AlCl_2 , or $\text{TiCl}_3(\text{O}-i\text{-Pr})$ can be used,¹⁰ as illustrated by Entries 4 to 7 in Scheme 10.1.

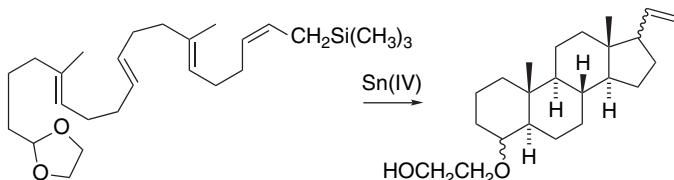
Mercuric ion is capable of inducing cyclization of polyenes.



Ref. 11

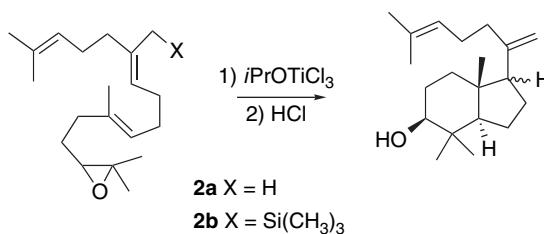
The particular example shown also has a special mechanism for stabilization of the cyclized carbocation. The adjacent acetoxy group is captured to form a stabilized dioxanylium cation. After reductive demercuration (see Section 4.1.3) and hydrolysis, a diol is isolated.

As the intermediate formed in a polyene cyclization is a carbocation, the isolated product is often found to be a mixture of closely related compounds resulting from competing modes of reaction. The products result from capture of the carbocation by solvent or other nucleophile or by deprotonation to form an alkene. Polyene cyclizations can be carried out on reactants that have structural features that facilitate transformation of the carbocation to a stable product. Allylic silanes, for example, are stabilized by desilylation.¹²

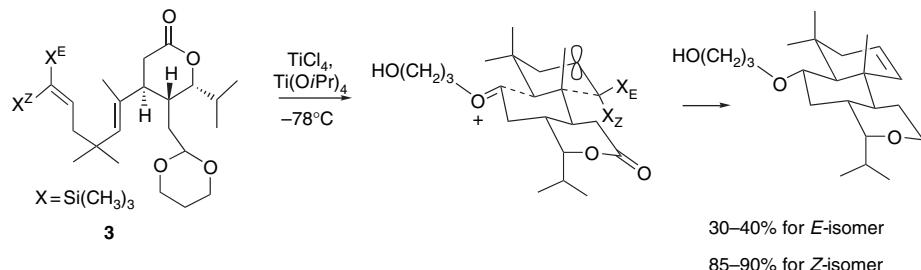


The incorporation of silyl substituents not only provides for specific reaction products but can also improve the effectiveness of polyene cyclization. For example, although cyclization of **2a** gave a mixture containing at least 17 products, the allylic silane **2b** gave a 79% yield of a 1:1 mixture of stereoisomers.¹³ This is presumably due to the enhanced reactivity and selectivity of the allylic silane.

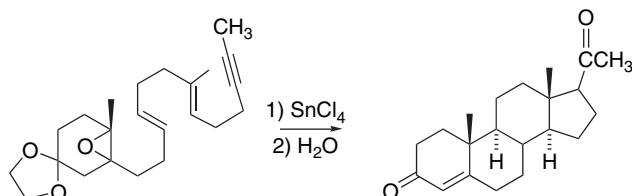
- ^{9.} E. E. van Tamelen and R. G. Nadeau, *J. Am. Chem. Soc.*, **89**, 176 (1967).
- ^{10.} E. J. Corey and M. Sodeoka, *Tetrahedron Lett.*, **33**, 7005 (1991); P. V. Fish, A. R. Sudhakar, and W. S. Johnson, *Tetrahedron Lett.*, **34**, 7849 (1993).
- ^{11.} M. Nishizawa, H. Takenaka, and Y. Hayashi, *J. Org. Chem.*, **51**, 806 (1986); E. J. Corey, J. G. Reid, A. G. Myers, and R. W. Hahl, *J. Am. Chem. Soc.*, **109**, 918 (1987).
- ^{12.} W. S. Johnson, Y.-Q. Chen, and M. S. Kellogg, *J. Am. Chem. Soc.*, **105**, 6653 (1983).
- ^{13.} P. V. Fish, *Tetrahedron Lett.*, **35**, 7181 (1994).



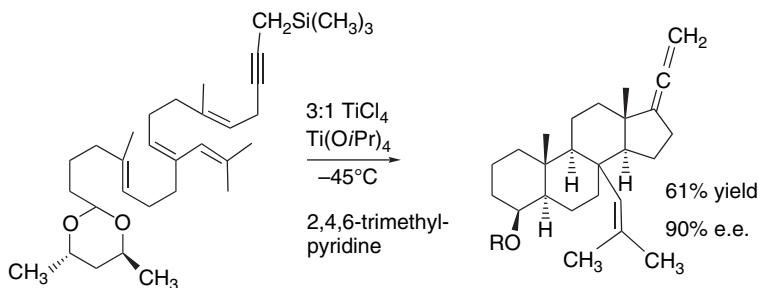
The efficiency of cyclization can also be affected by stereoelectronic factors. For example, there is a significant difference in the efficiency of the cyclization of the *Z*- and *E*-isomers of **3**. Only the *Z*-isomer presents an optimal alignment for electronic stabilization.¹⁴ These effects of the terminating substituent point to considerable concerted character for the cyclizations.



When a cyclization sequence is terminated by an alkyne, vinyl cations are formed. Capture of water leads to formation of a ketone.¹⁵



Use of chiral acetal groups can result in enantioselective cyclization.¹⁶

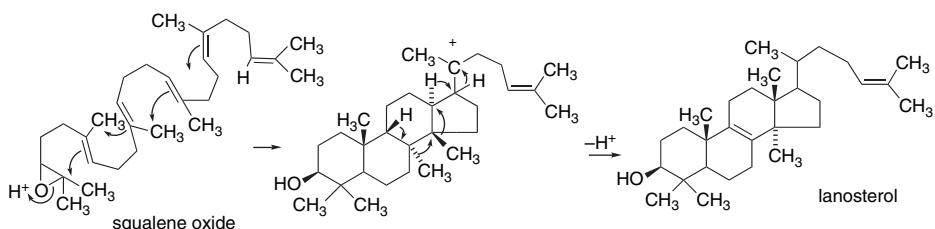


¹⁴. S. D. Burke, M. E. Kort, S. M. S. Strickland, H. M. Organ, and L. A. Silks, III, *Tetrahedron Lett.*, **35**, 1503 (1994).

¹⁵. E. E. van Tamelen and J. R. Hwu, *J. Am. Chem. Soc.*, **105**, 2490 (1983).

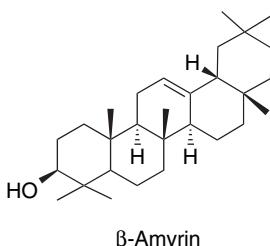
¹⁶. D. Guay, W. S. Johnson, and U. Schubert, *J. Org. Chem.*, **54**, 4731 (1989).

Polyene cyclizations are of substantial value in the synthesis of polycyclic terpene natural products. These syntheses resemble the processes by which the polycyclic compounds are assembled in nature. The most dramatic example of biosynthesis of a polycyclic skeleton from a polyene intermediate is the conversion of squalene oxide to the steroid lanosterol. In the biological reaction, an enzyme not only induces the cationic cyclization but also holds the substrate in a conformation corresponding to stereochemistry of the polycyclic product.¹⁷ In this case, the cyclization is terminated by a series of rearrangements.



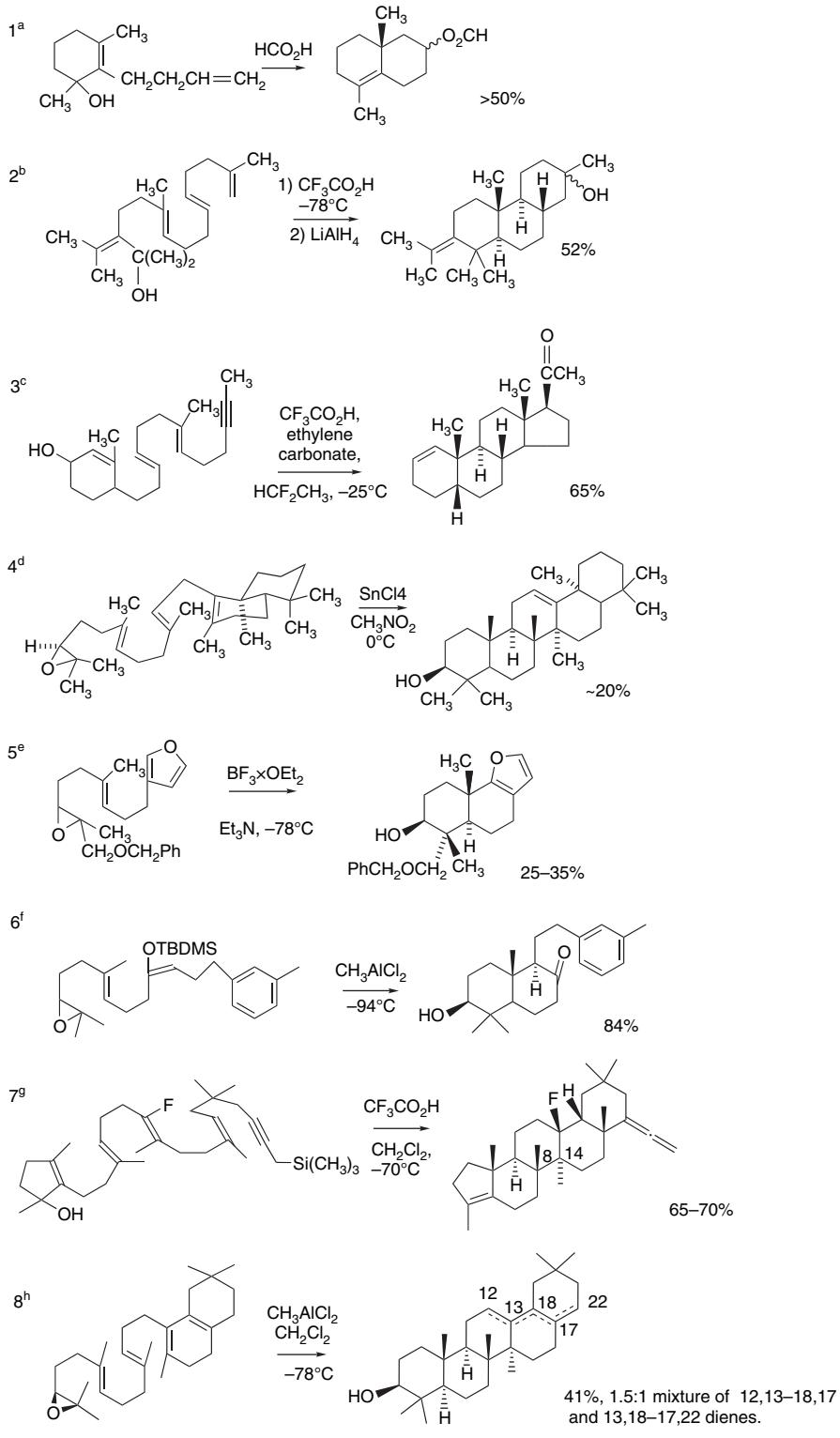
Scheme 10.1 gives some representative examples of laboratory syntheses involving polyene cyclization. The cyclization in Entry 1 is done in anhydrous formic acid and involves the formation of a symmetric tertiary allylic carbocation. The cyclization forms a six-membered ring by attack at the terminal carbon of the vinyl group. The bicyclic cation is captured as the formate ester. Entry 2 also involves initiation by a symmetric allylic cation. In this case, the triene unit cyclizes to a tricyclic ring system. Entry 3 results in the formation of the steroidal skeleton with termination by capture of the alkynyl group and formation of a ketone. The cyclization in Entry 4 is initiated by epoxide opening.

Entries 5 and 6 also involve epoxide ring opening. In Entry 5 the cyclization is terminated by electrophilic substitution on the highly reactive furan ring. In Entry 6 a silyl enol ether terminates the cyclization sequence, leading to the formation of a ketone. Entry 7 incorporates two special features. The terminal propargylic silane generates an allene. The fluoro substituent was found to promote the formation of the six-membered D ring by directing the regiochemistry of formation of the C(8)–C(14) bond. After the cyclization, the five-membered A ring was expanded to a six-membered ring by oxidative cleavage and aldol condensation. The final product of this synthesis was β -amyrin. Entry 8 also led to the formation of β -amyrin and was done using the enantiomerically pure epoxide.



¹⁷. D. Cane, *Chem. Rev.*, **90**, 1089 (1990); I. Abe, M. Rohmer, and G. D. Prestwich, *Chem. Rev.*, **93**, 2189 (1993); K. U. Wendt and G. E. Schulz, *Structure*, **6**, 127 (1998).

Scheme 10.1. Polyene Cyclizations



(Continued)

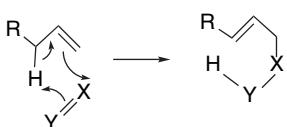
Scheme 10.1. (Continued)

- a. J. A. Marshall, N. Cohen, and A. R. Hochstetler, *J. Am. Chem. Soc.*, **88**, 3408 (1966).
 b. W. S. Johnson and T. K. Schaaf, *J. Chem. Soc., Chem. Commun.*, 611 (1969).
 c. B. E. McCarry, R. L. Markezich, and W. S. Johnson, *J. Am. Chem. Soc.*, **95**, 4416 (1973).
 d. E. E. van Tamelen, R. A. Holton, R. E. Hopla, and W. E. Konz, *J. Am. Chem. Soc.*, **94**, 8228 (1972).
 e. S. P. Tanis, Y.-H. Chuang, and D. B. Head, *J. Org. Chem.*, **53**, 4929 (1988).
 f. E. J. Corey, G. Luo, and L. S. Lin, *Angew. Chem. Int. Ed. Engl.*, **37**, 1126 (1998).
 g. W. S. Johnson, M. S. Plummer, S. P. Reddy, and W. R. Bartlett, *J. Am. Chem. Soc.*, **115**, 515 (1993).
 h. E. J. Corey and J. Lee, *J. Am. Chem. Soc.*, **115**, 8873 (1993).

SECTION 10.1

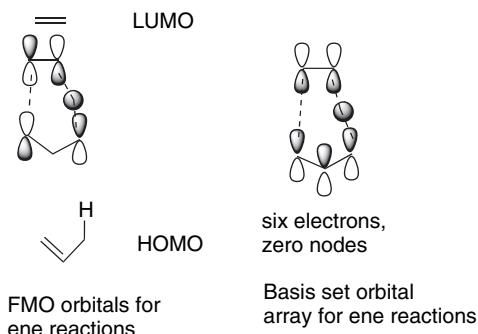
Reactions and
Rearrangement
Involving Carbocation
Intermediates

10.1.1.3. Ene and Carbonyl-Ene Reactions. Certain double bonds undergo electrophilic addition reactions with alkenes in which an allylic hydrogen is transferred to the reactant. This process is called the *ene reaction* and the electrophile is known as an *enophile*.¹⁸ When a carbonyl group serves as the enophile, the reaction is called a *carbonyl-ene reaction* and leads to β,γ -unsaturated alcohols. The reaction is also called the *Prins reaction*.



A variety of double bonds give reactions corresponding to the pattern of the ene reaction. Those that have been studied from a mechanistic and synthetic perspective include alkenes, aldehydes and ketones, imines and iminium ions, triazoline-2,5-diones, nitroso compounds, and singlet oxygen, $^1\text{O}=\text{O}$. After a mechanistic overview of the reaction, we concentrate on the carbon–carbon bond-forming reactions. The important and well-studied reaction with $^1\text{O}=\text{O}$ is discussed in Section 12.3.2.

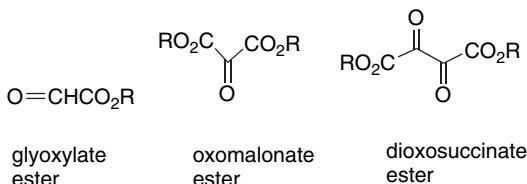
The concerted mechanism shown above is allowed by the Woodward-Hoffmann rules. The TS involves the π electrons of the alkene and enophile and the σ electrons of the allylic C–H bond. The reaction is classified as a $[\pi_2 + \pi_2 + \sigma_2]$ and either an FMO or basis set orbital array indicates an allowed concerted process.



Because the enophiles are normally the electrophilic reagent, their reactivity increases with addition of EWG substituents. Ene reactions between unsubstituted alkenes have high-energy barriers, but compounds such as acrylate or propynoate esters

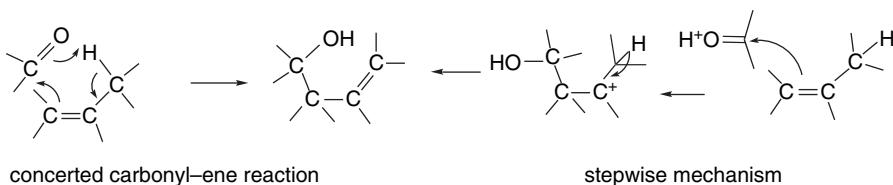
¹⁸. For reviews of the ene reaction, see H. M. R. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **8**, 556 (1969); W. Oppolzer, *Pure Appl. Chem.*, **53**, 1181 (1981); K. Mikami and M. Shimizu, *Chem. Rev.*, **92**, 1020 (1992).

or, especially, maleic anhydride are more reactive. Similarly, for carbonyl compounds, glyoxylate, oxomalonate, and dioxosuccinate esters are among the typical reactants under thermal conditions.

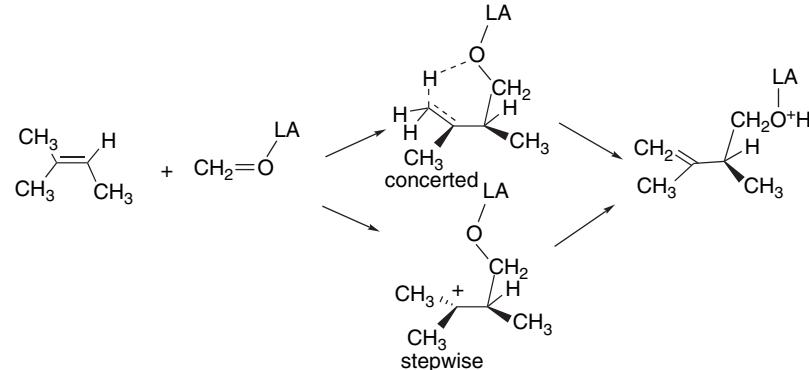


Mechanistic studies have been designed to determine if the concerted cyclic TS provides a good representation of the reaction. A systematic study of all the *E*- and *Z*-decene isomers with maleic anhydride showed that the stereochemistry of the reaction could be accounted for by a concerted cyclic mechanism.¹⁹ The reaction is only moderately sensitive to electronic effects or solvent polarity. The ρ value for reaction of diethyl oxomalonate with a series of 1-arylcyclopentenes is -1.2 , which would indicate that there is little charge development in the TS.²⁰ The reaction shows a primary kinetic isotope effect indicative of C–H bond breaking in the rate-determining step.²¹ There is good agreement between measured isotope effects and those calculated on the basis of TS structure.²² These observations are consistent with a concerted process.

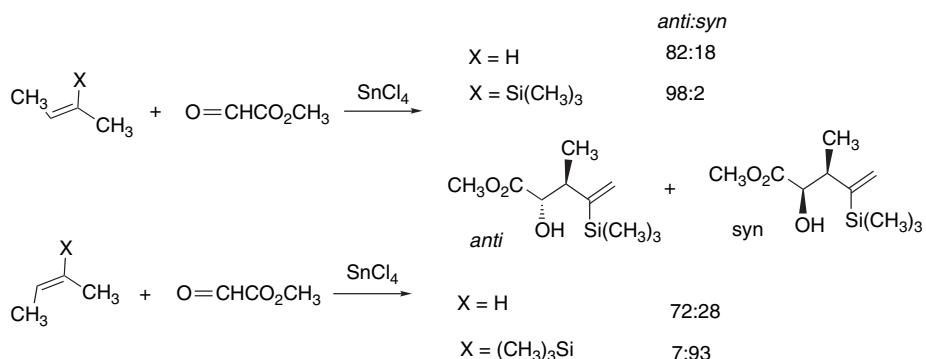
The carbonyl–ene reaction is strongly catalyzed by Lewis acids,²³ such as BF_3 , $SnCl_4$, and $(CH_3)_2AlCl$.^{24,25} Coordination of a Lewis acid at the carbonyl group increases its electrophilicity and allows reaction to occur at or below room temperature. The reaction becomes much more polar under Lewis acid catalysis and is more sensitive to solvent polarity²⁶ and substituent effects. For example, the ρ for 1-arylcyclopentenes with diethyl oxomalonate goes from -1.2 for the thermal reaction to -3.9 for a $SnCl_4$ -catalyzed reaction. Mechanistic analysis of Lewis acid–catalyzed reactions indicates they are electrophilic substitution processes. At one mechanistic extreme, this might be a concerted reaction. At the other extreme, the reaction could involve formation of a carbocation. In synthetic practice, the reaction is often carried out using Lewis acid catalysts and probably is a stepwise process.



- ¹⁹. S. H. Nahm and H. N. Cheng, *J. Org. Chem.*, **57**, 5093 (1996).
- ²⁰. H. Kwart and M. Brechbiel, *J. Org. Chem.*, **47**, 3353 (1982).
- ²¹. F. R. Benn and J. Dwyer, *J. Chem. Soc., Perkin Trans. 2*, 533 (1977); O. Achmatowicz and J. Szymoniak, *J. Org. Chem.*, **45**, 4774 (1980); H. Kwart and M. Brechbiel, *J. Org. Chem.*, **47**, 3353 (1982).
- ²². D. A. Singleton and C. Hang, *Tetrahedron Lett.*, **40**, 8939 (1999).
- ²³. B. B. Snider, *Acc. Chem. Res.*, **13**, 426 (1980).
- ²⁴. K. Mikami and M. Shimizu, *Chem. Rev.*, **92**, 1020 (1992).
- ²⁵. M. F. Salomon, S. N. Pardo, and R. G. Salomon, *J. Org. Chem.*, **49**, 2446 (1984); *J. Am. Chem. Soc.*, **106**, 3797 (1984).
- ²⁶. P. Laszlo and M. Teston-Henry, *J. Phys. Org. Chem.*, **4**, 605 (1991).



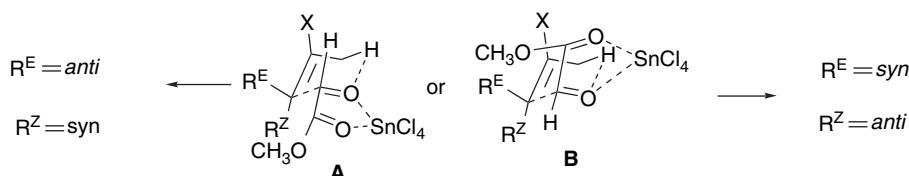
The best carbonyl components for these reactions are highly electrophilic compounds such as glyoxylate, pyruvate, and oxomalonate esters, as well as chlorinated and fluorinated aldehydes. Most synthetic applications of the carbonyl-ene reaction utilize Lewis acids. Although such reactions may be stepwise in character, the stereochemical outcome is often consistent with a cyclic TS. It was found, for example, that steric effects of trimethylsilyl groups provide a strong stereochemical influence.²⁸



These results are consistent with two competing TSs differing in the facial orientation of the glyoxylate ester group. When X=H, the interaction with the ester group is small and the R^Z-ester interaction controls the stereochemistry. When the silyl group is present, there is a strong preference for TS A, which avoids interaction of the silyl group with the ester substituents.

²⁷ D. A. Singleton and C. Hang, *J. Org. Chem.*, **65**, 895 (2000).

²⁸ K. Mikami, T. P. Loh, and T. Nakai, *J. Am. Chem. Soc.*, **112**, 6737 (1990).



The mechanisms of simple ene reactions, such as those involving propene with ethene and formaldehyde, have been explored computationally. Concerted mechanisms and E_a values in general agreement with experiment are found using B3LYP/6-31G*,²⁹ MP2/6-31G*,³⁰ and MP4/6-31G*³¹ computations. Yamanaka and Mikami used HF/6-31G* computations to compare the TS for ene reactions of propene with ethene and formaldehyde, and also for SnCl_4 - and AlCl_3 -catalyzed reactions with methyl glyoxylate.³² The TS geometries and NPA charges are given in Figure 10.1. The ethene and formaldehyde TSs are rather similar, with the transferring hydrogen being positive in character, more so with formaldehyde than ethene. The catalyzed reactions are much more asynchronous, with C–C bond formation quite advanced. The two catalyzed reaction TSs correlate nicely with the observed stereoselectivity of the reaction. The stereochemistry of the 2-butene-methyl glyoxylate reaction shows a strong dependence on the Lewis acid that is used. The SnCl_4 -catalyzed reaction gives the *anti* product via an *exo* TS, whereas AlCl_3 , gives the *syn* product via an *endo* TS. The glyoxylate is chelated with SnCl_4 , but not with AlCl_3 , which leads to a difference in the orientation

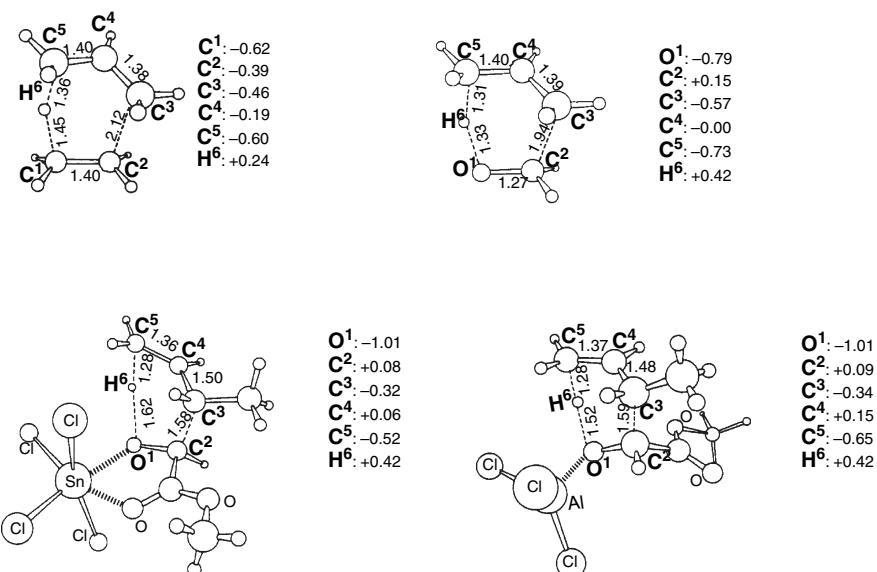


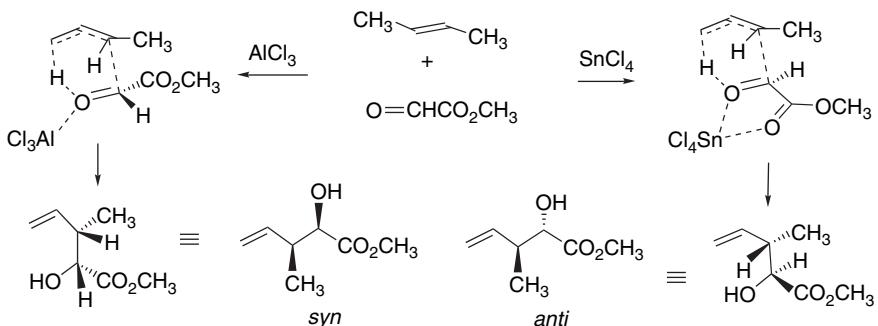
Fig. 10.1. Minimum-energy transition structures for ene reactions: (a) propene and ethene; (b) propene and formaldehyde; (c) butene and methyl glyoxylate– SnCl_4 ; (d) butene and methyl glyoxylate– AlCl_3 . Reproduced from *Helv. Chim. Acta*, **85**, 4264 (2002), by permission of Wiley-VCH.

²⁹ Q. Deng, B. E. Thomas, IV, K. N. Houk, and P. Dowd, *J. Am. Chem. Soc.*, **119**, 6902 (1997).

³⁰ J. Pranata, *Int. J. Quantum Chem.*, **62**, 509 (1997).

³¹ S. M. Bachrach and S. Jiang, *J. Org. Chem.*, **62**, 8319 (1997).

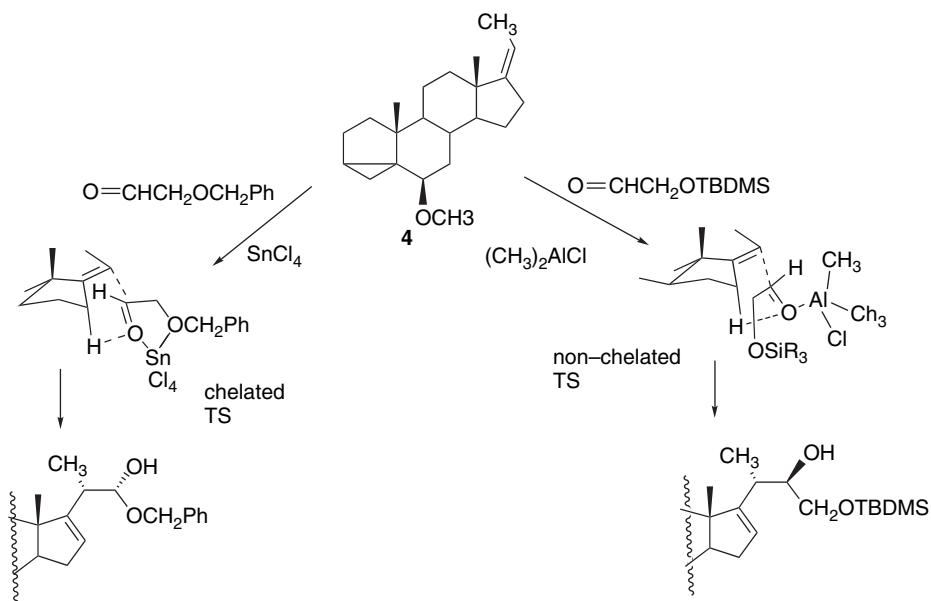
³² M. Yamanaka and K. Mikami, *Helv. Chim. Acta*, **85**, 4264 (2002).



Despite the cyclic character of these TSs, both the bond distances and charge distribution are characteristic of a high degree of charge separation, with the butenyl fragment assuming the character of an allylic carbocation.

Visual models, additional information and exercises on the Carbonyl-Ene Reaction can be found in the Digital Resource available at: Springer.com/carey-sundberg.

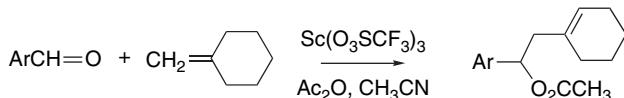
Examples of catalyst control of stereoselectivity have been encountered in the course of the use of the ene reaction to elaborate a side chain on the steroid nucleus. The steroid **4** gave stereoisomeric products, depending on the catalysts and specific aldehyde that were used.³³ This is attributed to the presence of a chelated structure in the case of the $SnCl_4$ catalyst.



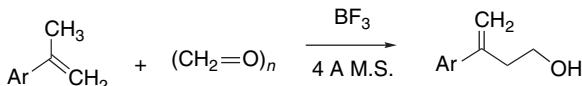
³³ K. Mikami, H. Kishino, and T.-P. Loh, *J. Chem. Soc., Chem. Commun.*, 495 (1994).

The stereoselectivity of the $(\text{CH}_3)_2\text{AlCl}$ -catalyzed reaction has also been found to be sensitive to the steric bulk of the aldehyde.³⁴

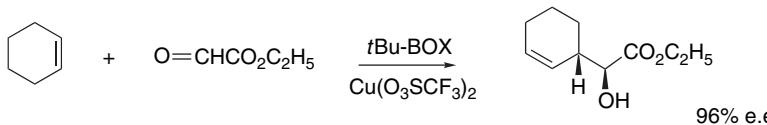
The use of Lewis acid catalysts greatly expands the synthetic utility of the carbonyl-ene reaction. Aromatic aldehydes and acrolein undergo the ene reaction with activated alkenes such as enol ethers in the presence of $\text{Yb}(\text{fod})_3$.³⁵ $\text{Sc}(\text{O}_3\text{SCF}_3)_3$ has also been used to catalyze carbonyl-ene reactions.³⁶



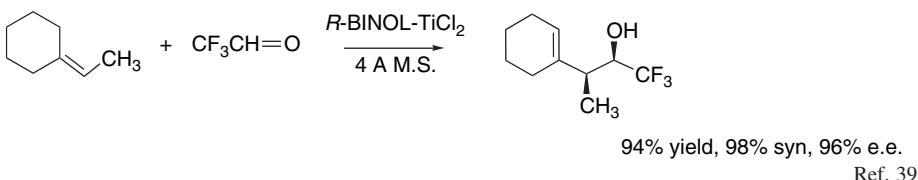
Among the more effective conditions for reaction of formaldehyde with α -methylstyrenes is BF_3 in combination with 4A molecular sieves.³⁷



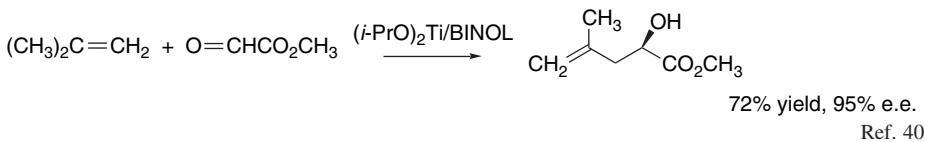
The function of the molecular sieves in this case is believed to be as a base that sequesters the protons, which otherwise would promote a variety of side reactions. With chiral catalysts, the carbonyl ene reaction becomes enantioselective. Among the successful catalysts are diisopropoxyTi(IV)BINOL and copper-BOX complexes.



Ref. 38

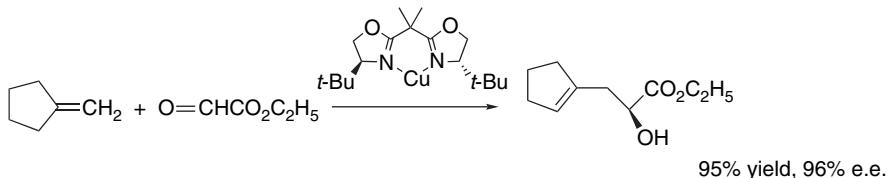


Ref. 39



Ref. 40

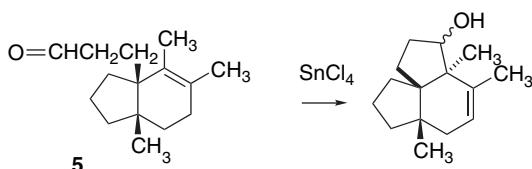
- ³⁴ T. A. Houston, Y. Tanaka, and M. Koreeda, *J. Org. Chem.*, **58**, 4287 (1993).
- ³⁵ M. A. Ciufolini, M. V. Deaton, S. R. Zhu, and M. Y. Chen, *Tetrahedron*, **53**, 16299 (1997); M. A. Ciufolini and S. Zhu, *J. Org. Chem.*, **63**, 1668 (1998).
- ³⁶ V. K. Aggarawal, G. P. Vennall, P. N. Davey, and C. Newman, *Tetrahedron Lett.*, **39**, 1997 (1998).
- ³⁷ T. Okachi, K. Fujimoto, and M. Onaka, *Org. Lett.*, **4**, 1667 (2002).
- ³⁸ D. A. Evans, C. S. Burgey, N. A. Paras, T. Vojkovsky, and S. W. Tregay, *J. Am. Chem. Soc.*, **120**, 5824 (1998).
- ³⁹ K. Mikami, T. Yajima, T. Takasaki, S. Matsukawa, M. Terada, T. Uchimaru, and M. Maruta, *Tetrahedron*, **52**, 85 (1996).
- ⁴⁰ K. Mikami, M. Terada, and T. Nakai, *J. Am. Chem. Soc.*, **112**, 3949 (1990).



Ref. 41

The enantioselectivity of the BINOL-Ti(IV)-catalyzed reactions can be interpreted in terms of several fundamental structural principles.⁴² The aldehyde is coordinated to Ti through an apical position and there is also a O—HC=O hydrogen bond involving the formyl group. The most sterically favored approach of the alkene toward the complexed aldehyde then leads to the observed product. Figure 10.2 shows a representation of the complexed aldehyde and the TS structure for the reaction.

Most carbonyl-ene reactions used in synthesis are intramolecular and can be carried out under either thermal or catalyzed conditions,⁴³ but generally Lewis acids are used. Stannic chloride catalyzes cyclization of the unsaturated aldehyde **5**.



Ref. 44

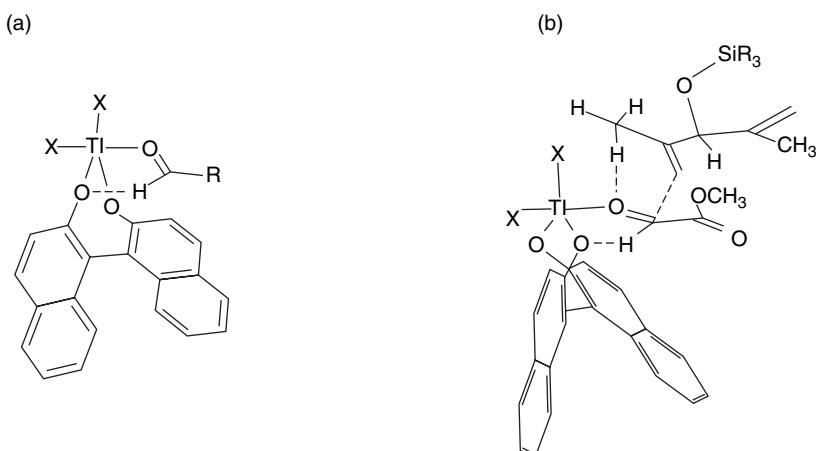
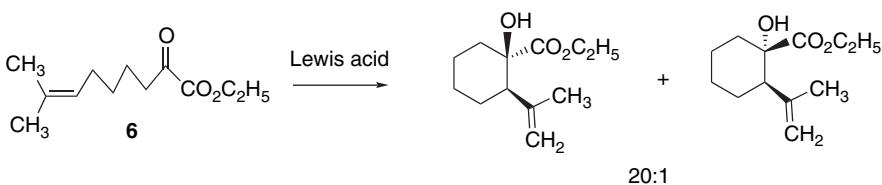


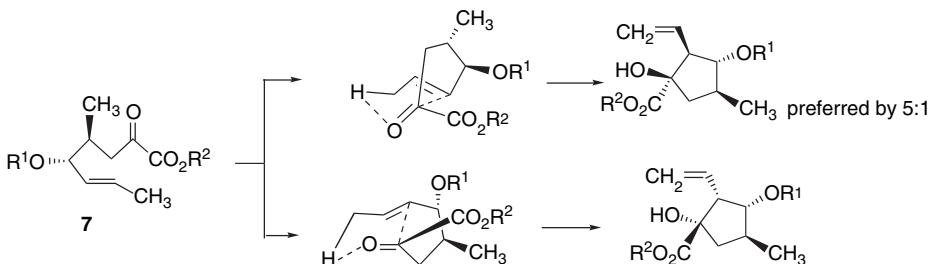
Fig. 10.2. Structures of complexed aldehyde reagent (a) and transition structure (b) for enantioselective catalysis of the carbonyl-ene reaction by BINOL-Ti(IV). Reproduced from *Tetrahedron Lett.*, **38**, 6513 (1997), by permission of Elsevier.

- ⁴¹. D. A. Evans, S. W. Tregay, C. S. Burgey, N. A. Paras, and T. Vojkovsky, *J. Am. Chem. Soc.*, **122**, 7936 (2000).
- ⁴². E. J. Corey, D. L. Barnes-Seeman, T. W. Lee and S. N. Goodman, *Tetrahedron Lett.*, **38**, 6513 (1997).
- ⁴³. W. Oppolzer and V. Snieckus, *Angew. Chem. Int. Ed. Engl.*, **17**, 476 (1978).
- ⁴⁴. L. A. Paquette and Y.-K. Han, *J. Am. Chem. Soc.*, **103**, 1835 (1981).

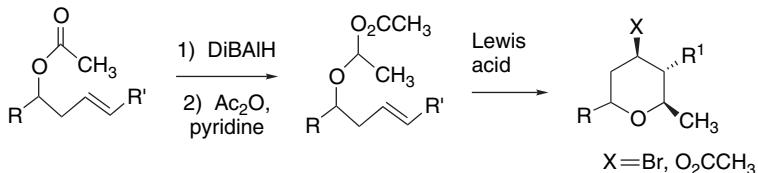
The cyclization of the α -ketoester **6** can be effected by $Mg(ClO_4)_2$, $Yb(OTf)_3$, $Cu(OTf)_2$, or $Sc(OTf)_3$.⁴⁵ The reaction exhibits a 20:1 preference for formation of the *trans*-2-(1-methylpropenyl) isomer. The reaction can be conducted with greater than 90% e.e. using $Cu(OTf)_2$ or $Sc(OTf)_3$ with the *t*-Bu-BOX ligand.



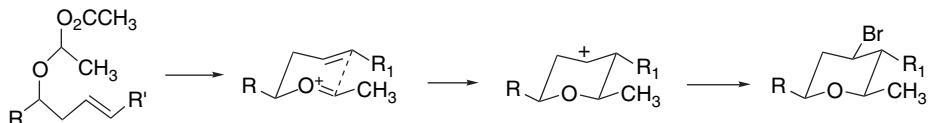
As an example of a thermal reaction, **7** cyclizes at 180°C. The reaction is stereoselective and the two stereoisomers can be formed from competing cyclic TSs.⁴⁶



Carbonyl-ene reactions can be carried out in combination with other kinds of reactions. Mixed acetate acetals of γ,δ -enols, which can be prepared from the corresponding acetate esters, undergo cyclization with nucleophilic capture. When $SnBr_4$ is used for cyclization, the 4-substituent is bromine, whereas BF_3 in acetic acid gives acetates.⁴⁷



The reaction stereochemistry is consistent with a cyclic TS.



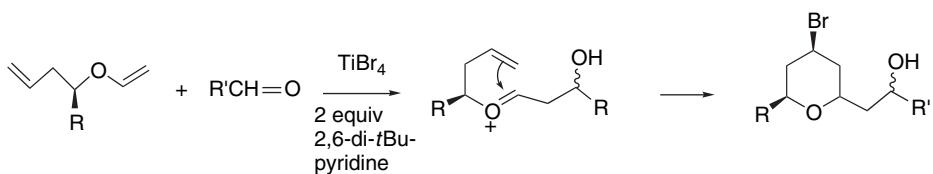
A tandem combination initiated by a Mukaiyama reaction generates an oxonium ion that cyclizes to give a tetrahydropyran rings.⁴⁸

⁴⁵ D. Yang, M. Yang, and N.-Y. Zhu, *Org. Lett.*, **5**, 3749 (2003).

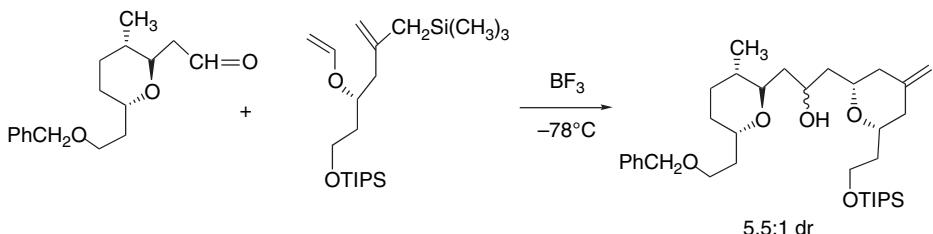
⁴⁶ H. Helmboldt, J. Rehbein, and M. Hiersemann, *Tetrahedron Lett.*, **45**, 289 (2004).

⁴⁷ J. J. Jaber, K. Mitsui, and S. D. Rychnovsky, *J. Org. Chem.*, **66**, 4679 (2001).

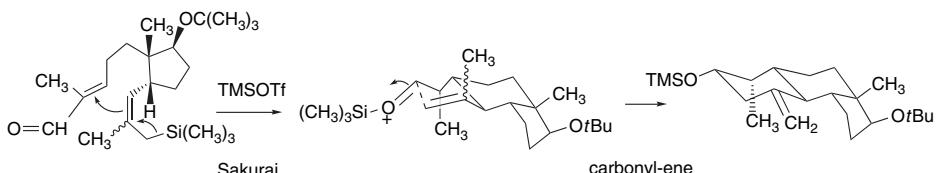
⁴⁸ B. Patterson and S. D. Rychnovsky, *Synlett*, 543 (2004).



This reaction has been used in coupling two fragments in a synthesis of leucascandrolide, a cytotoxic substance isolated from a sponge.⁴⁹

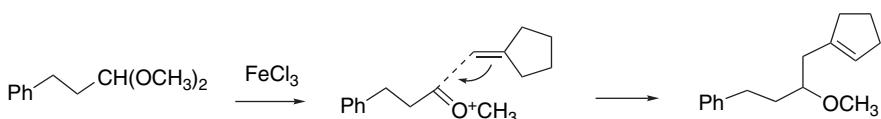


A tandem Sakurai-carbonyl-ene sequence was used to create a tricyclic skeleton in the synthesis of a steroid-like structure.⁵⁰



Section 10.1.2.2 describes another tandem reaction sequence involving a carbonyl-ene reaction.

Scheme 10.2 gives some examples of ene and carbonyl-ene reactions. Entries 1 and 2 are thermal ene reactions. Entries 3 to 7 are intermolecular ene and carbonyl-ene reactions involving Lewis acid catalysts. Entry 3 is interesting in that it exhibits a significant preference for the terminal double bond. Entry 4 demonstrates the reactivity of methyl propionate as an enophile. Nonterminal alkenes tend to give cyclobutenes with this reagent combination. The reaction in Entry 5 uses an acetal as the reactant, with an oxonium ion being the electrophilic intermediate.



Entry 6 uses diisopropoxytitanium with racemic BINOL as the catalyst. Entry 7 shows the use of $(\text{CH}_3)_2\text{AlCl}$ with a highly substituted aromatic aldehyde. The product

⁴⁹. D. J. Kopecky and S. D. Rychnosky, *J. Am. Chem. Soc.*, **123**, 8420 (2001).

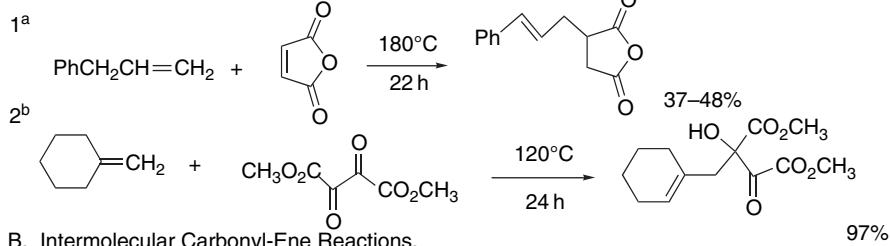
50. L. F. Tietze and M. Rischer, *Angew. Chem. Int. Ed. Engl.*, **31**, 1221 (1992).

Scheme 10.2. Ene and Carbonyl-Ene Reactions

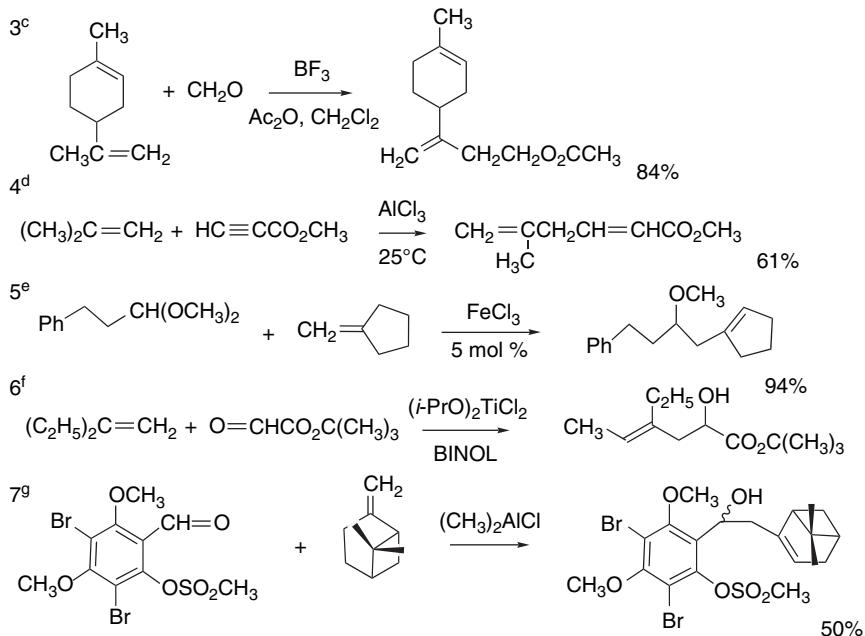
CHAPTER 10

Reactions Involving
Carbocations, Carbenes,
and Radicals as Reactive
Intermediates

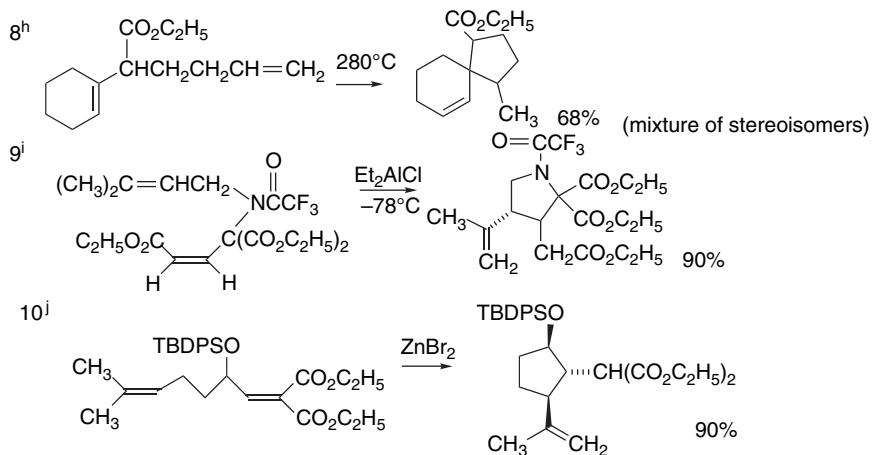
A. Thermal Ene Reactions.



B. Intermolecular Carbonyl-Ene Reactions.



C. Intramolecular Ene Reactions.

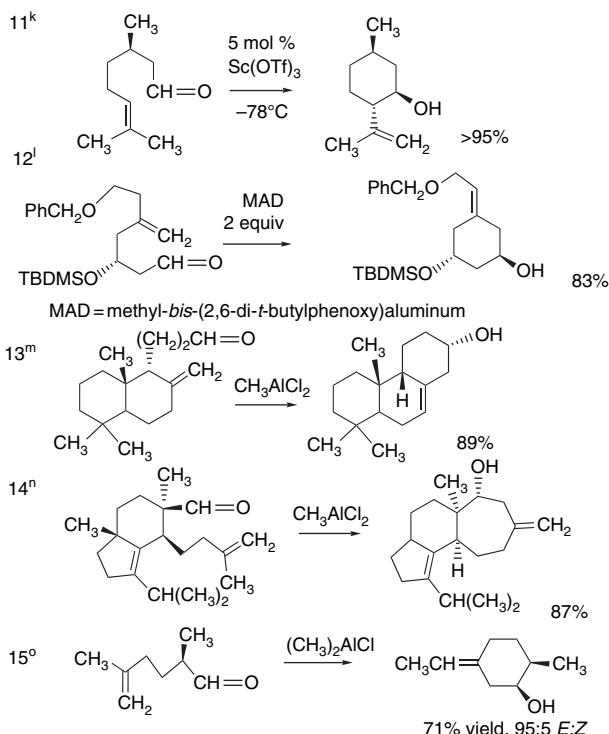


(Continued)

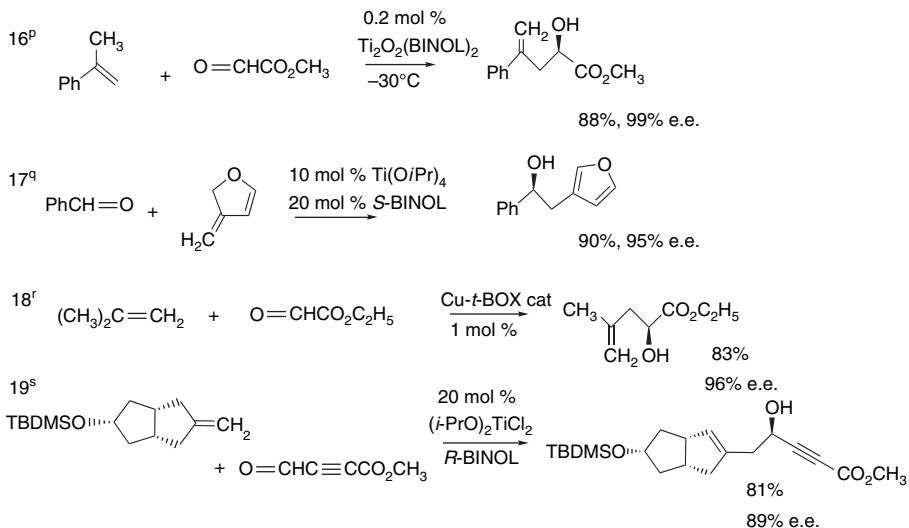
Scheme 10.2. (Continued)

SECTION 10.1

Reactions and
Rearrangement
Involving Carbocation
Intermediates



D. Enantioselective Carbonyl Ene Reactions.



(Continued)

Scheme 10.2. (Continued)

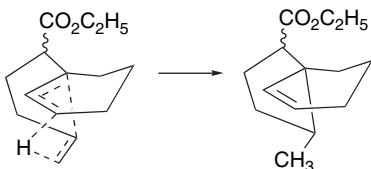
CHAPTER 10

Reactions Involving Carbocations, Carbenes, and Radicals as Reactive Intermediates

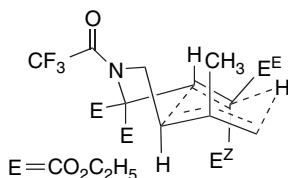
- a. C. S. Rondestvedt, Jr., *Org. Synth.*, **IV**, 766 (1963).
- b. P. Beak, Z. Song, and J. E. Resek, *J. Org. Chem.*, **57**, 944 (1992).
- c. A. T. Blomquist and R. J. Himics, *J. Org. Chem.*, **33**, 1156 (1968).
- d. B. B. Snider, D. J. Rodini, R. S. E. Conn, and S. Sealfon, *J. Am. Chem. Soc.*, **101**, 5283 (1979).
- e. A. Ladepeche, E. Tam, J.-E. Arcel, and L. Ghosez, *Synthesis*, 1375 (2004).
- f. M. A. Brimble and M. K. Edmonds, *Synth. Commun.*, **26**, 243 (1996).
- g. M. Majewski and G. W. Bantle, *Synth. Commun.*, **20**, 2549 (1990); M. Majewski, N. M. Irvine, and G. W. Bantle, *J. Org. Chem.*, **59**, 6697 (1994).
- h. W. Oppolzer, K. K. Mahalanabis, and K. Battig, *Helv. Chim. Acta*, **60**, 2388 (1977).
- i. W. Oppolzer and C. Robbiani, *Helv. Chim. Acta*, **63**, 2010 (1980).
- j. T. K. Sarkar, B. K. Ghorai, S. K. Nandy, B. Mukherjee, and A. Banerji, *J. Org. Chem.*, **62**, 6006 (1997).
- k. V. K. Aggarwal, G. P. Vennall, P. N. Davey, and C. Newman, *Tetrahedron Lett.*, **39**, 1997 (1998).
- l. L. F. Courtney, M. Lange, M. R. Uskokovics, and P. M. Wovkulich, *Tetrahedron Lett.*, **39**, 3363 (1998).
- m. J.-M. Weibel and D. Heissler, *Synlett*, 391 (1993).
- n. B. B. Snider, N. H. Vo, and S. V. O'Neill, *J. Org. Chem.*, **63**, 4732 (1998).
- o. J. A. Marshall and M. W. Andersen, *J. Org. Chem.*, **57**, 5851 (1992).
- p. M. Terada and K. Mikami, *J. Chem. Soc., Chem. Commun.*, 833 (1994).
- q. W. H. Miles, E. J. Fialcowitz, and E. S. Halstead, *Tetrahedron*, **57**, 9925 (2001).
- r. D. A. Evans, S. W. Tregay, C. S. Burgey, N. A. Paras, and T. Vojkovsky, *J. Am. Chem. Soc.*, **122**, 7936 (2000).
- s. K. Mikami, A. Yoshida, and Y. Matsumoto, *Tetrahedron Lett.*, **37**, 8515 (1996).

was used in syntheses of derivatives of robustadial, which are natural products from *Eucalyptus* that have antimalarial activity.

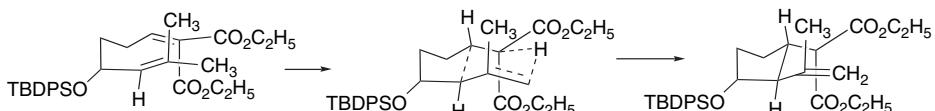
Entries 8 to 15 are examples of intramolecular reactions. Entry 8 involves two unactivated double bonds and was carried out at a temperature of 280°C. The product was a mixture of epimers at the ester site but the methyl group and cyclohexenyl double bond are *cis*, which indicates that the reaction occurred entirely through an *endo* TS.



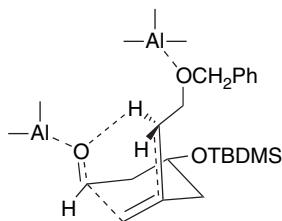
The reaction in Entry 9 was completely stereospecific. The corresponding *E*-isomer gave mainly the *cis* isomer. These results are consistent with a cyclic TS for the hydrogen transfer.



The stereoselectivity of the reaction in Entry 10 is also consistent with a TS in which the hydrogen is transferred through a chairlike TS.



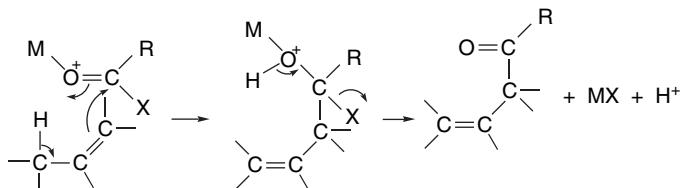
Entry 11 illustrates the facility of a $\text{Sc}(\text{OTf})_3$ -mediated reaction. The catalyst in Entry 12 is a hindered *bis*-phenoxyaluminum compound. The proton removal



Entries 13 to 15 are examples of high-yield cyclizations of aldehydes effected by CH_3AlCl_2 .

Section D of Scheme 10.2 shows some enantioselective reactions. Entry 16 illustrates the enantioselective reaction of methyl glyoxylate with a simple alkene. The catalyst is a dioxido-bridged dimer of Ti(BINOL) prepared azeotropically from BINOL and $\text{TiCl}_2(\text{O}-i\text{-Pr})_2$. Entry 17 also uses a Ti(BINOL) catalyst. The methylenedihydrofuran substrate is highly reactive owing to the donor effect of the vinyl ether and the stabilization provided by formation of the aromatic furan ring. Entry 18 shows the use of a Cu-BOX catalysts to achieve a highly enantioselective reaction between isobutene and ethyl glyoxylate. The reaction in Entry 19 was done with a $(i\text{-PrO})_2\text{TiCl}_2-(R)\text{-BINOL}$ and the product had an e.e. of 89%.

10.1.1.4. Reactions with Acylium Ions. Alkenes react with acyl halides or acid anhydrides in the presence of a Lewis acid catalyst to give β,γ -unsaturated ketones. The reactions generally work better with cyclic than acyclic alkenes.

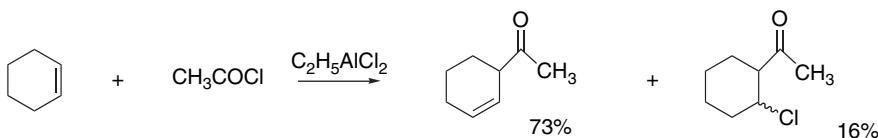


It has been suggested that the kinetic preference for formation of β,γ -unsaturated ketones results from an intramolecular deprotonation, as shown in the mechanism above.⁵¹ The carbonyl-ene and alkene acylation reactions have several similarities. Both reactions occur most effectively in intramolecular circumstances and provide a useful method for ring closure. Although both reactions appear to occur through highly polarized TSs, there is a strong tendency toward specificity in the proton abstraction step. This specificity and other similarities in the reaction are consistent with a cyclic formulation of the mechanism.

A variety of reaction conditions have been examined for acylation of alkenes by acyl chlorides. With the use of Lewis acid catalysts, reaction typically occurs

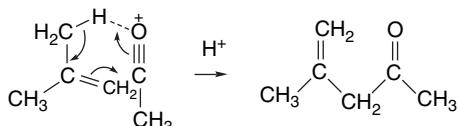
⁵¹ P. Beak and K. R. Berger, *J. Am. Chem. Soc.*, **102**, 3848 (1980).

to give both β,γ -enones and β -haloketones.⁵² One of the more effective catalysts is ethylaluminum dichloride.⁵³

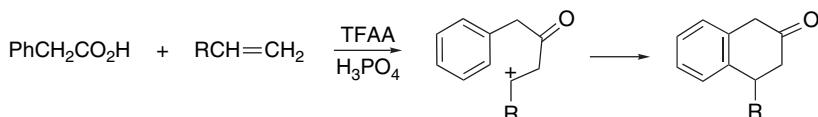


Zinc chloride also gives good results, especially with cyclic alkenes.⁵¹

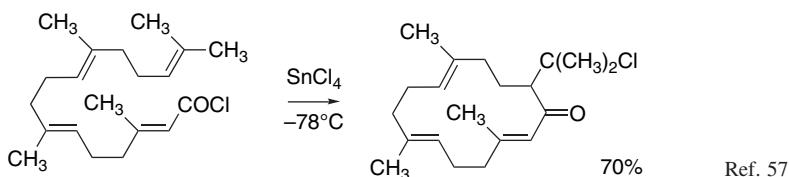
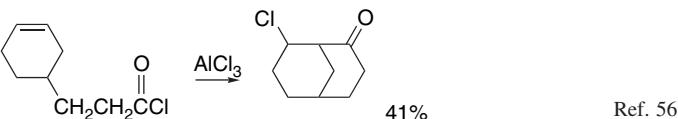
A similar reaction occurs between alkenes and acylium ions, as in the reaction between 2-methylpropene, and the acylium ion leads regiospecifically to β,γ -enones.⁵⁴ A concerted mechanism has been suggested to account for this regiochemical preference.



Highly reactive mixed anhydrides can also promote acylation. Phenylacetic acid reacts with alkenes to give 2-tetralones in TFAA-H₃PO₄.⁵⁵ This reaction involves an intramolecular Friedel-Crafts alkylation subsequent to the acylation.



The acylation reaction has been most synthetically useful in intramolecular reactions. The following examples are illustrative.



⁵² See, e.g., T. S. Cantrell, J. M. Harless, and B. L. Strasser, *J. Org. Chem.*, **36**, 1191 (1971); L. Rand and R. J. Dolinski, *J. Org. Chem.*, **31**, 3063 (1966).

⁵³ B. B. Snider and A. C. Jackson, *J. Org. Chem.*, **47**, 5393 (1982).

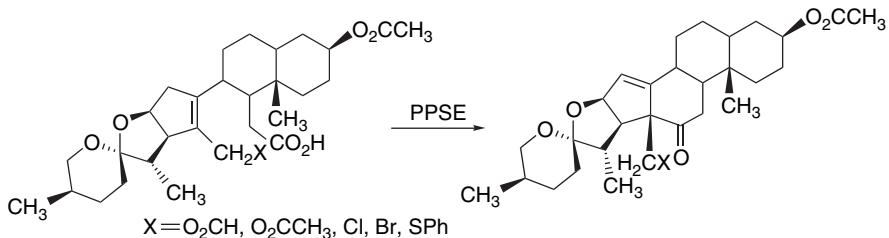
⁵⁴ H. M. R. Hoffmann and T. Tsushima, *J. Am. Chem. Soc.*, **99**, 6008 (1977).

⁵⁵ A. D. Gray and T. P. Smyth, *J. Org. Chem.*, **66**, 7113 (2001).

⁵⁶ E. N. Marvell, R. S. Knutson, T. McEwen, D. Sturmer, W. Federici, and K. Salisbury, *J. Org. Chem.*, **35**, 391 (1970).

⁵⁷ T. Kato, M. Suzuki, T. Kobayashi, and B. P. Moore, *J. Org. Chem.*, **45**, 1126 (1980).

Several successful cyclizations of quite complex structures were achieved using polyphosphoric acid trimethylsilyl ester, a viscous material that contains reactive anhydrides of phosphoric acid.⁵⁸ Presumably the reactive acylating agent is a mixed phosphoric anhydride of the carboxylic acid.

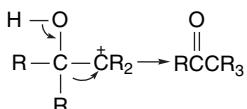


Ref. 59

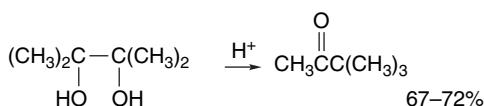
10.1.2. Rearrangement of Carbocations

Carbocations, as we learned in Chapter 4 of Part A, can readily rearrange to more stable isomers. To be useful in synthesis, such reactions must be controlled and predictable. This goal can be achieved on the basis of substituent effects and stereoelectronic factors. Among the most important rearrangements in synthesis are those directed by oxygen substituents, which can provide predictable outcomes on the basis of electronic and stereoelectronic factors.

10.1.2.1. Pinacol Rearrangement. Carbocations can be stabilized by the migration of hydrogen, alkyl, alkenyl, or aryl groups, and, occasionally, even functional groups can migrate. A mechanistic discussion of these reactions is given in Section 4.4.4 of Part A. Reactions involving carbocation rearrangements can be complicated by the existence of competing rearrangement pathways. Rearrangements can be highly selective and, therefore, reliable synthetic reactions when the structural situation is such as to strongly favor a particular reaction path. One example is the reaction of carbocations having a hydroxy group on an adjacent carbon, which leads to the formation of a carbonyl group.



A reaction that follows this pattern is the acid-catalyzed conversion of diols to ketones, which is known as the *pinacol rearrangement*.⁶⁰ The classic example of this reaction is the conversion of 2,3-dimethylbutane-2,3-diol(pinacol) to methyl *t*-butyl ketone (pinacolone).⁶¹



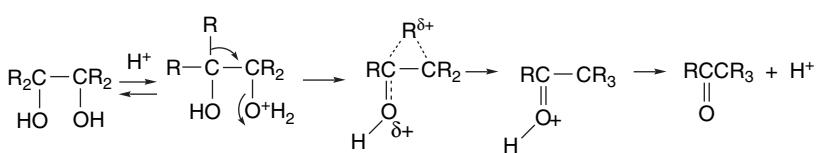
⁵⁸ K. Yamamoto and H. Watanabe, *Chem. Lett.*, 1225 (1982).

⁵⁹ W. Li and P. L. Fuchs, *Org. Lett.*, **5**, 4061 (2003).

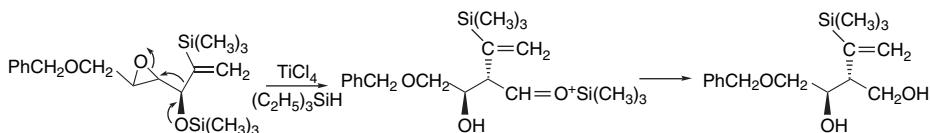
⁶⁰ C. J. Collins, *Q. Rev.*, **14**, 357 (1960).

⁶¹ G. A. Hill and E. W. Flosdorf, *Org. Synth.*, **I**, 451 (1932).

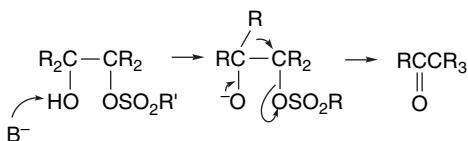
The acid-catalyzed mechanism involves carbocation formation and substituent migration assisted by the hydroxy group.



Under acidic conditions, the more easily ionized C–O bond generates the carbocation, and migration of one of the groups from the adjacent carbon ensues. Both stereochemistry and “migratory aptitude” are factors in determining the extent of migration of the different groups. The issue of the electronic component in migratory aptitude has been examined by calculating (MP2/6-31G*) the relative energy for several common groups in a prototypical TS for migration. The order is vinyl > cyclopropyl > alkynyl > methyl ~ hydrogen.⁶² The tendency for migration of alkenyl groups is further enhanced by ERG substituents and selective migration of trimethylsilyl-substituted groups has been exploited in pinacol rearrangements.⁶³ In the example shown, the triethylsilane serves to reduce the intermediate silyloxonium ion and generate a primary alcohol.



Another method for achieving selective pinacol rearrangement involves synthesis of a glycol monosulfonate ester. These compounds rearrange under the influence of base.

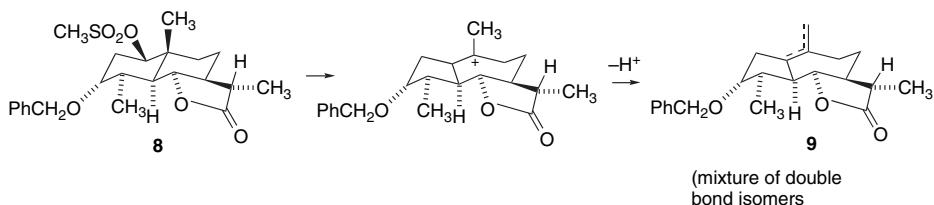


Rearrangements of monosulfonates permit greater control over the course of the rearrangement because ionization occurs only at the sulfonylated alcohol. These reactions have been of value in the synthesis of ring systems, especially terpenes, as illustrated by Entries 3 and 4 in Scheme 10.3.

In cyclic systems that enforce structural rigidity or conformational bias, the course of the rearrangement is controlled by stereoelectronic factors. The carbon substituent that is *anti* to the leaving group is the one that undergoes migration. In cyclic systems such as **8**, for example, selective migration of the ring fusion bond occurs because

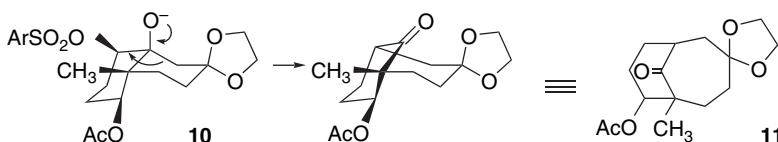
⁶² K. Nakamura and Y. Osamura, *J. Am. Chem. Soc.*, **115**, 9112 (1993).

⁶³ K. Suzuki, T. Ohkuma, and G. Tsuchihashi, *Tetrahedron Lett.*, **26**, 861 (1985); K. Suzuki, M. Shimazaki, and G. Tsuchihashi, *Tetrahedron Lett.*, **27**, 6233 (1986); M. Shimazaki, M. Morimoto, and K. Suzuki, *Tetrahedron Lett.*, **31**, 3335 (1990).



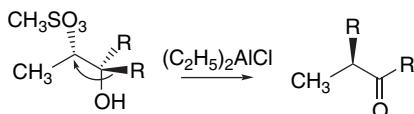
Ref. 64

Similarly, **10** gives **11** by antiperiplanar migration.

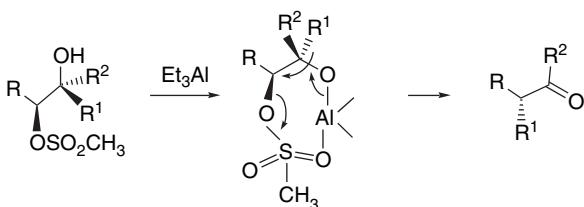


Ref. 65

Rearrangement of diol monosulfonates can also be done using Lewis acids. These conditions lead to *inversion of configuration* at the migration terminus, as would be implied by a concerted mechanism.⁶⁶



Triethylaluminum is also effective in catalyzing rearrangement of monosulfonate with high stereospecificity. The reactions are believed to proceed through a cyclic TS.⁶⁷



The reactants can be prepared by chelation-controlled addition of organometallic reagents to α -(1-ethoxyethoxy)methyl ketones. Selective sulfonylation occurs at the

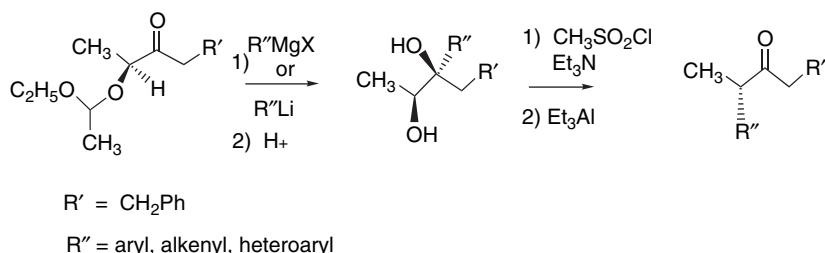
⁶⁴ M. Ando, A. Akahane, H. Yamaoka, and K. Takase, *J. Org. Chem.*, **47**, 3909 (1982).

⁶⁵ C. H. Heathcock, E. G. Del Mar, and S. L. Graham, *J. Am. Chem. Soc.*, **104**, 1907 (1982).

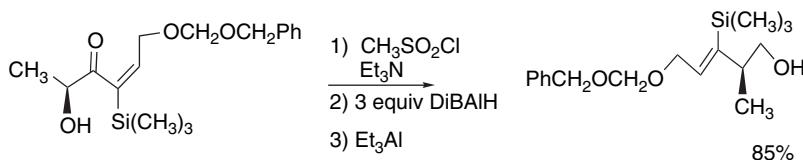
⁶⁶ G. Tsuchihashi, K. Tomooka, and K. Suzuki, *Tetrahedron Lett.*, **25**, 4253 (1984).

⁶⁷ K. Suzuki, E. Katayama, and G. Tsuchihashi, *Tetrahedron Lett.*, **24**, 4997 (1983); K. Suzuki, E. Katayama, and G. Tsuchihashi, *Tetrahedron Lett.*, **25**, 1817 (1984); T. Shinohara and K. Suzuki, *Synthesis*, 141 (2003).

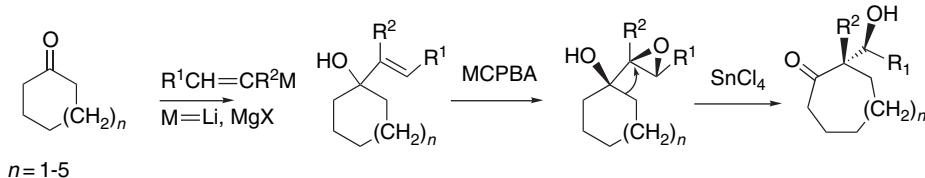
less hindered secondary hydroxy group. The rearranged ketones were obtained in greater than 99% e.e.



A related method was applied in the course of synthesis of a precursor of a macrolide antibiotic, protomycinolide IV. The migrating group was an α -trimethylsilylalkenyl group.⁶⁸ In this procedure, the DiBAIH first reduces the ketone and then, after rearrangement, reduces the aldehyde to a primary alcohol.



Stereospecific ring expansion can be done by taking advantage of the hydroxy-directed epoxidation and SnCl_4 -mediated rearrangement of 1-hydroxycycloalkyl epoxides.⁶⁹



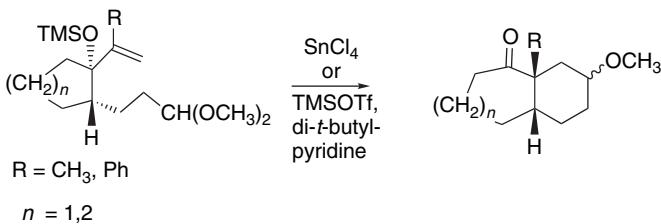
The overall transformation of this sequence corresponds to the aldol addition of an aldehyde with a cyclic ketone. The actual aldol addition frequently proceeds with low stereocontrol, so this sequence constitutes a method for stereoselective synthesis of the aldol adducts. The reaction has been done with several Lewis acids, including SnCl_4 , BF_3 , and $\text{Ti}(\text{O}-i\text{-Pr})_3\text{Cl}$.

10.1.2.2. Pinacol Rearrangement in Tandem with the Carbonyl-Ene Reaction.

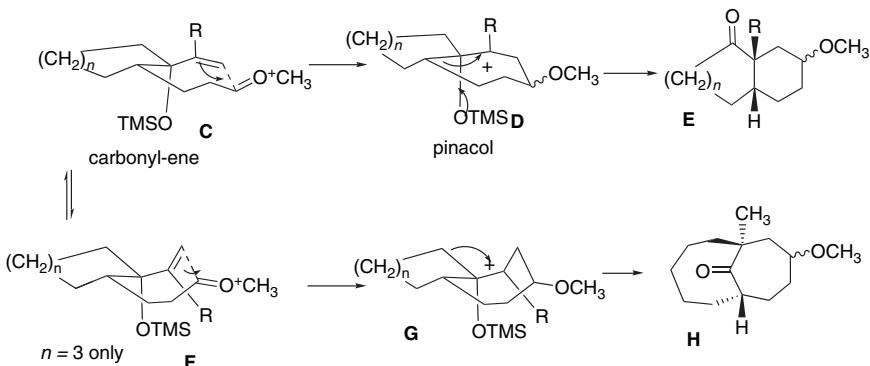
Overman and co-workers have developed protocols in which pinacol rearrangement

⁶⁸. K. Suzuki, K. Tomooka, E. Katayama, T. Matsumoto, and G. Tsuchihashi, *J. Am. Chem. Soc.*, **108**, 5221 (1986).

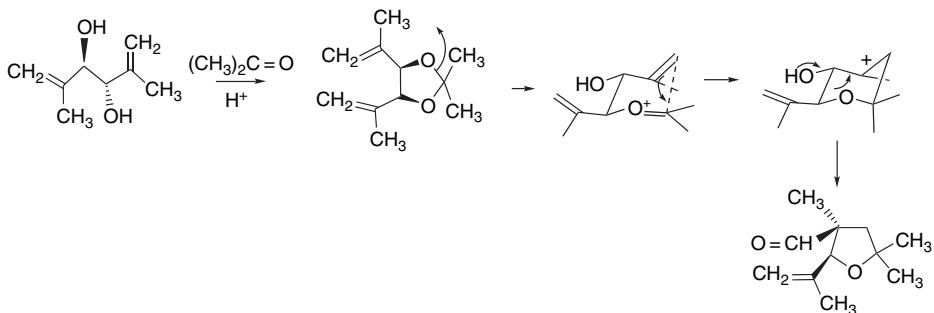
⁶⁹. S. W. Baldwin, P. Chen, N. Nikolic, and D. C. Weinheimer, *Org. Lett.*, **2**, 1193 (2000); C. M. Marson, A. Khan, R. A. Porter, and A. J. A. Cobb, *Tetrahedron Lett.*, **43**, 6637 (2002).



These reactions appear to proceed through the sequence **C** \rightarrow **D** \rightarrow **E**. When the seven-membered analog ($n = 3$) reacts, two products are formed. The more flexible seven-membered ring accommodates the competing sequence. **F** \rightarrow **G** \rightarrow **H**.



The carbonyl-ene–pinacol sequence has also been observed in reactions leading to the formation of tetrahydrofurans.⁷¹

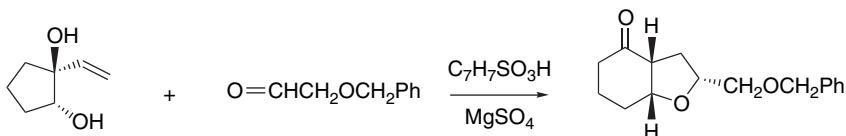
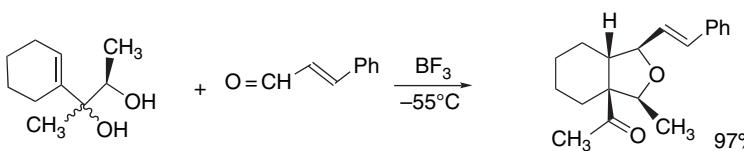


The reaction has been developed for the synthesis of both oxygen heterocycles and carbocyclic compounds.⁷²

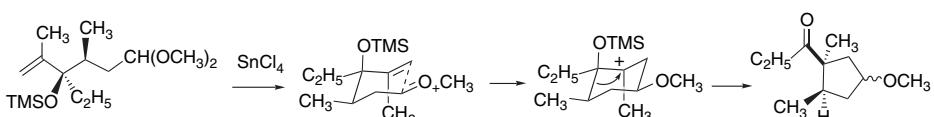
⁷⁰. S. Ando, K. P. Minor, and L. E. Overman, *J. Org. Chem.*, **62**, 6379 (1997).

⁷¹. P. Martinet and G. Moussel, *Bull. Soc. Chim. Fr.*, 4093 (1971); C. M. Gasparski, P. M. Herrinton, L. E. Overman, and J. P. Wolfe, *Tetrahedron Lett.*, **41**, 9431 (2000).

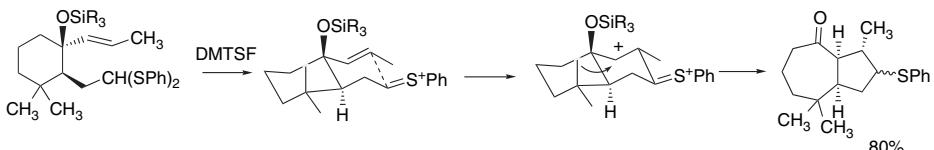
⁷². L. E. Overman, *Acc. Chem. Res.*, **25**, 352 (1992); L. E. Overman and L. D. Pennington, *J. Org. Chem.*, **68**, 7143 (2003).



These reactions can also be adapted to carbocyclic ring formation and expansion.

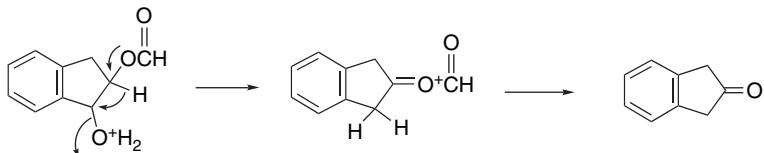


Ref. 75



Ref. 76

Scheme 10.3 gives some examples of pinacol and related rearrangements. Entry 1 is a rearrangement done under strongly acidic conditions. The selectivity leading to ring expansion results from the preferential ionization of the diphenylcarbinol group. Entry 2, a preparation of 2-indanone, involves selective ionization at the benzylic alcohol, followed by a hydride shift.



Entries 3 and 4 are examples of stereospecific *anti* migrations governed by the stereochemistry of the sulfonate leaving group. These transformations are parts of synthetic schemes that use available terpene starting materials for synthesis of more complex natural products. The ring expansion in Entry 5 was used to form an eight-membered ring found in certain diterpenes. This highly efficient and selective rearrangement

⁷³. D. W. C. MacMillan, L. E. Overman, and L. D. Pennington, *J. Am. Chem. Soc.*, **123**, 9033 (2001).

⁷⁴. M. J. Brown, T. Harrison, P. M. Herrinton, M. H. Hopkins, K. D. Hutchinson, P. Mishra, and L. E. Overman, *J. Am. Chem. Soc.*, **113**, 5365 (1991).

⁷⁵. T. C. Gahman and L. E. Overman, *Tetrahedron*, **58**, 6473 (2002).

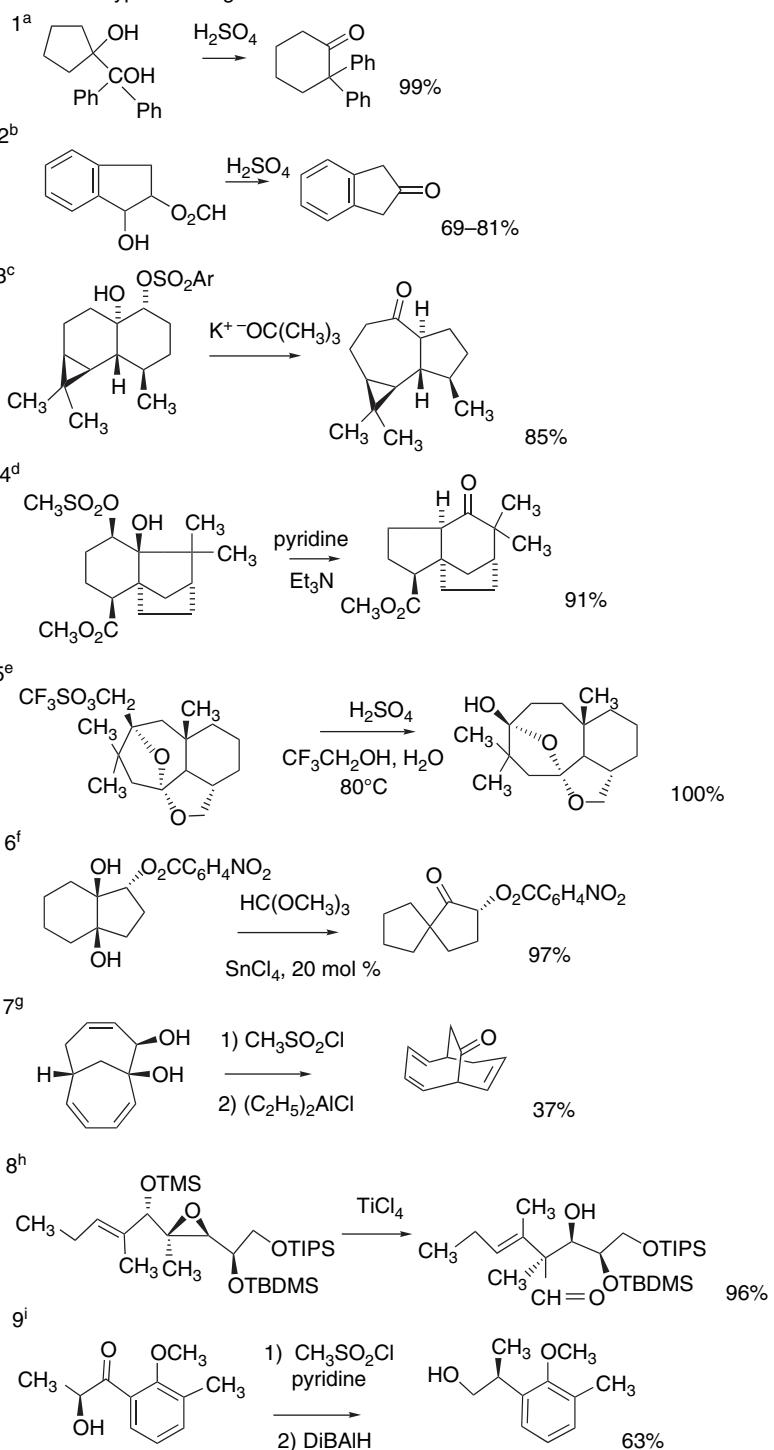
⁷⁶. A. D. Lebsack, L. E. Overman, and R. J. Valenteckovich, *J. Am. Chem. Soc.*, **123**, 4851 (2001).

Scheme 10.3. Rearrangements Promoted by Adjacent Heteroatoms

SECTION 10.1

Reactions and
Rearrangement
Involving Carbocation
Intermediates

A. Pinacol-type rearrangements



(Continued)

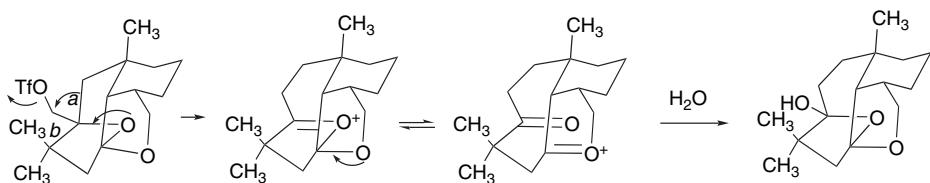
Scheme 10.3. (Continued)

CHAPTER 10

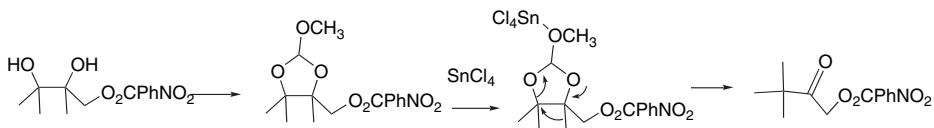
Reactions Involving
Carbocations, Carbenes,
and Radicals as Reactive
Intermediates

- a. H. E. Zaugg, M. Freifelder, and B. W. Horrom, *J. Org. Chem.*, **15**, 1191 (1950).
 b. J. E. Horan and R. W. Schliessler, *Org. Synth.*, **41**, 53 (1961).
 c. G. Buchi, W. Hofheinz, and J. V. Paukstelis, *J. Am. Chem. Soc.*, **91**, 6473 (1969).
 d. D. F. MacSweeney and R. Ramage, *Tetrahedron*, **27**, 1481 (1971).
 e. P. Magnus, C. Diorazio, T. J. Donohoe, M. Giles, P. Pye, J. Tarrant, and S. Thom, *Tetrahedron*, **52**, 14147 (1996).
 f. Y. Kita, Y. Yoshida, S. Mihara, D.-F. Fang, K. Higuchi, A. Furukawa, and H. Fujioka, *Tetrahedron Lett.*, **38**, 8315 (1997).
 g. J. H. Rigby and K. R. Fales, *Tetrahedron Lett.*, **39**, 1525 (1998).
 h. K. D. Eom, J. V. Raman, H. Kim, and J. K. Cha, *J. Am. Chem. Soc.*, **125**, 5415 (2003).
 i. H. Arimoto, K. Nishimura, M. Kuramoto, and D. Uemura, *Tetrahedron Lett.*, **39**, 9513 (1998).

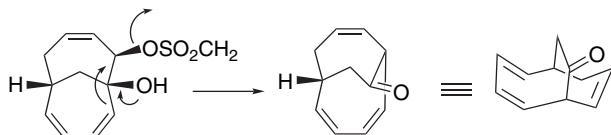
presumably proceeds with participation of the adjacent oxygen, which accounts for the specific migration of bond *a* over bond *b*.



Entry 6 illustrates a significant regioselectivity in that two tertiary alcohol groups are present in the reactant. This reaction is thought to involve a cyclic orthoester. The preferred rupture of the C–O bond distal to the *p*-nitrobenzoyloxy group is likely due to the dipolar effect of the C–O bond on ionization. No migration of the oxy-substituted ring is observed, indicating that the *p*-nitrobenzoyloxy group minimizes any potential electron donation by the oxygen.

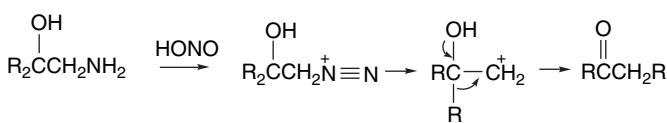


Entry 7 involves formation and ionization of a secondary allylic sulfonate and migration of a dienyl group.

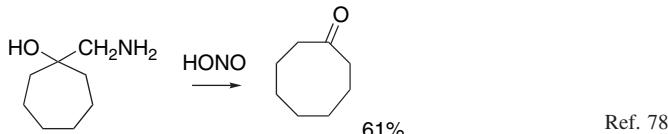


Entry 8 involves a migration initiated by epoxide ring opening. This reaction involves migration of a vinyl substituent. Entry 9 is a stereospecific migration of the aryl group. The DiBALH both promotes the rearrangement and reduces the product aldehyde.

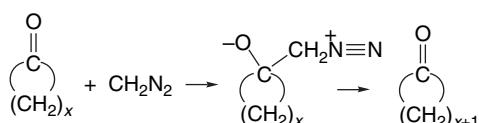
10.1.2.3. Rearrangements Involving Diazonium Ions. Aminomethyl carbinols yield ketones when treated with nitrous acid. The reaction proceeds by formation and rearrangement of diazonium ions. The diazotization reaction generates the same type of β -hydroxycarbocation that is involved in the pinacol rearrangement.



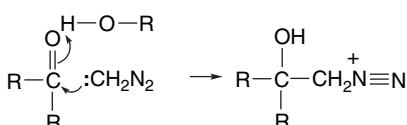
This reaction has been used to form ring-expanded cyclic ketones, a procedure known as the *Tiffeneau-Demjanov reaction*.⁷⁷



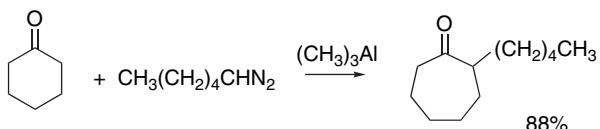
The reaction of ketones with diazomethane sometimes leads to a ring-expanded ketone in synthetically useful yields.⁷⁹ The reaction occurs by addition of the diazomethane, followed by elimination of nitrogen and migration.



The rearrangement proceeds via essentially the same intermediate that is involved in the Tiffeneau-Demjanov reaction. Since the product is also a ketone, subsequent addition of diazomethane can lead to higher homologs. The best yields are obtained when the starting ketone is substantially more reactive than the product. For this reason, strained ketones work especially well. Higher diazoalkanes can also be used in place of diazomethane. The reaction is found to be accelerated by alcoholic solvents. This effect probably involves the hydroxy group being hydrogen bonded to the carbonyl oxygen and serving as a proton donor in the addition step.⁸⁰



Trimethylaluminum also promotes ring expansion by diazoalkanes.⁸¹



Ketones react with esters of diazoacetic acid in the presence of Lewis acids such as BF_3 and SbCl_5 .⁸²

⁷⁷ P. A. S. Smith and D. R. Baer, *Org. React.*, **11**, 157 (1960).

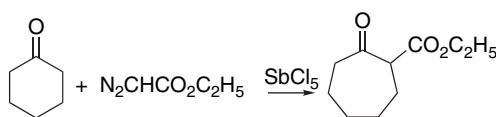
⁷⁸ F. F. Blicke, J. Azuara, N. J. Dorrenbos, and E. B. Hotelling, *J. Am. Chem. Soc.*, **75**, 5418 (1953).

⁷⁹ C. D. Gutsche, *Org. React.*, **8**, 364 (1954).

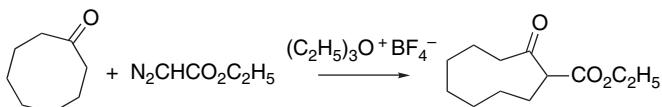
⁸⁰ J. N. Bradley, G. W. Cowell, and A. Ledwith, *J. Chem. Soc.*, 4334 (1964).

⁸¹ K. Maruoka, A. B. Concepcion, and H. Yamamoto, *J. Org. Chem.*, **59**, 4725 (1994).

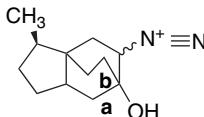
⁸² H. J. Liu and T. Ogino, *Tetrahedron Lett.*, 4937 (1973); W. T. Tai and E. W. Warnhoff, *Can. J. Chem.*, **42**, 1333 (1964); W. L. Mock and M. E. Hartman, *J. Org. Chem.*, **42**, 459 (1977); V. Dave and E. W. Warnhoff, *J. Org. Chem.*, **48**, 2590 (1983).



These reactions involve addition of the diazo ester to an adduct of the carbonyl compound and the Lewis acid. Elimination of nitrogen then triggers migration. Triethyloxonium tetrafluoroborate also effects ring expansion of cyclic ketones by ethyl diazoacetate.⁸³



Scheme 10.4 gives some examples of synthetic applications of rearrangements of diazonium ions. The diazotization rearrangement in Entry 1 was used to assemble the four contiguous stereogenic centers of the oxygenated cyclopentane ring found in prostaglandins. The synthesis started with *cis,cis*-1,3,5-cyclohexanetriol. Entry 2 uses trimethylsilyl cyanide addition, followed by LiAlH₄ reduction to generate the amino alcohol. The minor product in this reaction is formed by competing migration of the bridgehead carbon. The reaction was part of a synthesis of the terpene cedrene. Entry 3 is an example of the use of diazomethane to effect ring expansion of a strained ketone. The reaction was carried out by generating the diazomethane in situ. Entry 4 is an example of BF₃-mediated addition and rearrangement using ethyl diazoacetate. In Entry 5, the diazo group was generated in situ, and the intramolecular addition-rearrangement occurs at 25°C and under alkaline conditions. In this case there is little selectivity between the two competing migration possibilities.



10.1.3. Related Rearrangements

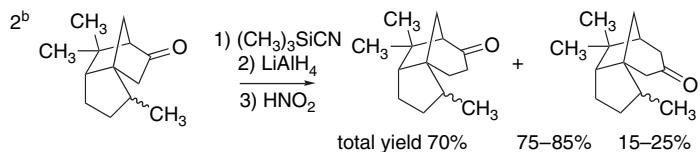
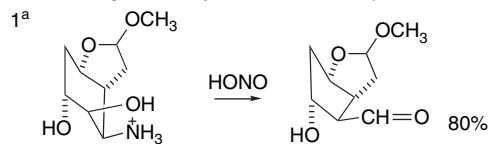
The subjects of this section are two reactions that do not actually involve carbocation intermediates. They do, however, result in carbon to carbon rearrangements that are structurally similar to the pinacol rearrangement. In both reactions cyclic intermediates are formed, at least under some circumstances. In the *Favorskii rearrangement*, an α -halo ketone rearranges to a carboxylic acid or ester. In the *Ramberg-Bäcklund reaction*, an α -halo sulfone gives an alkene.

10.1.3.1. The Favorskii Rearrangement. When treated with base, α -halo ketones undergo a skeletal change that is similar to the pinacol rearrangement. The most commonly used bases are alkoxide ions, which lead to esters as the reaction products. This reaction is known as the *Favorskii rearrangement*.⁸⁴

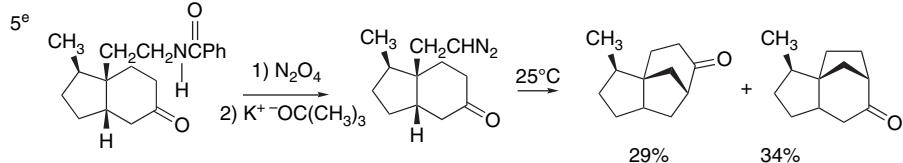
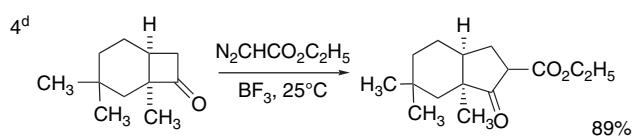
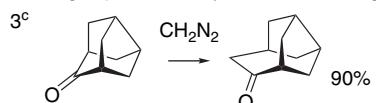
⁸³ L. J. MacPherson, E. K. Bayburt, M. P. Capparelli, R. S. Bohacek, F. H. Clarke, R. D. Ghai, Y. Sakane, C. J. Berry, J. V. Peppard, and A. J. Trapani, *J. Med. Chem.*, **36**, 3821 (1993).

⁸⁴ A. S. Kende, *Org. React.*, **11**, 261 (1960); A. A. Akhrem, T. K. Ustyuyuk, and Y. A. Titov, *Russ. Chem. Rev.* (English Transl.), **39**, 732 (1970).

SECTION 10.1

Reactions and
Rearrangement
Involving Carbocation
IntermediatesA. Rearrangement of β -amino alcohols by diazotization

B. Ring expansion of cyclic ketones using diazo compounds



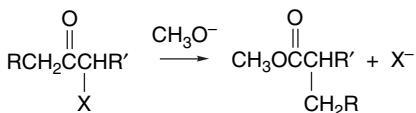
a. R. B. Woodward, J. Gosteli, I. Ernest, R. J. Friary, G. Nestler, H. Raman, R. Sitrin, C. Suter, and J. K. Whitesell, *J. Am. Chem. Soc.*, **95**, 6853 (1973).

b. E. G. Breitholle and A. G. Fallis, *J. Org. Chem.*, **43**, 1964 (1978).

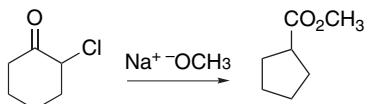
c. Z. Majerski, S. Djigas, and V. Vinkovic, *J. Org. Chem.*, **44**, 4064 (1979).

d. H. J. Liu and T. Ogina, *Tetrahedron Lett.*, 4937 (1973).

e. P. R. Vettel and R. M. Coates, *J. Org. Chem.*, **45**, 5430 (1980).



If the ketone is cyclic, a ring contraction occurs.

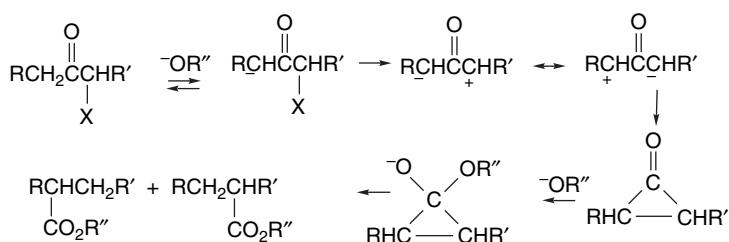


Ref. 85

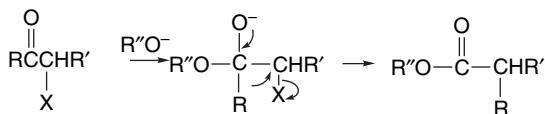
There is evidence that the rearrangement involves cyclopropanones or their open 1,3-dipolar equivalents as reaction intermediates.⁸⁶

⁸⁵. D. W. Goheen and W. R. Vaughan, *Org. Synth.*, **IV**, 594 (1963).

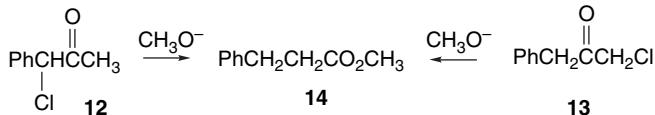
⁸⁶. F. G. Bordwell, T. G. Scamehorn, and W. R. Springer, *J. Am. Chem. Soc.*, **91**, 2087 (1969); F. G. Bordwell and J. G. Strong, *J. Org. Chem.*, **38**, 579 (1973).



There is also a mechanism that can operate in the absence of an acidic α -hydrogen. This process, called the *semibenzilic rearrangement*, is closely related to the pinacol rearrangement. A tetrahedral intermediate is formed by nucleophilic addition to the carbonyl group and the halide serves as the leaving group.

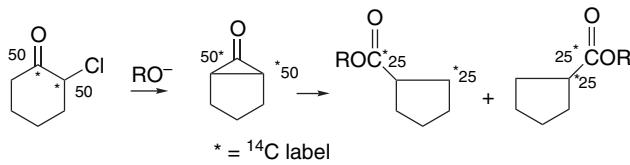


The net structural change is the same for both mechanisms. The energy requirements of the cyclopropanone and semibenzilic mechanism may be fairly closely balanced.⁸⁷ Cases of operation of the semibenzilic mechanism have been reported even for compounds having a hydrogen available for enolization.⁸⁸ Among the evidence that the cyclopropanone mechanism operates is the demonstration that a symmetrical intermediate is involved. The isomeric chloro ketones **12** and **13**, for example, lead to the same ester.



Ref. 37

The occurrence of a symmetrical intermediate has also been demonstrated by ^{14}C labeling in the case of α -chlorocyclohexanone.⁸⁹



Numbers refer to percentage of label at each carbon.

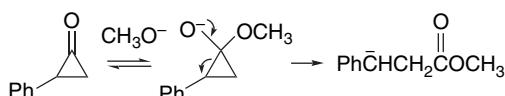
When the two carbonyl substituents are identical, either the cyclopropanone or the dipolar equivalent is symmetric. As the α - and α' -carbons are electronically similar (identical in symmetrical cases) in these intermediates, the structure of the ester product

⁸⁷. V. Moliner, R. Castillo, V. S. Safont, M. Oliva, S. Bohn, I. Tunon, and J. Andres, *J. Am. Chem. Soc.*, **119**, 1941 (1997).

⁸⁸. E. W. Warnhoff, C. M. Wong, and W. T. Tai, *J. Am. Chem. Soc.*, **90**, 514 (1968).

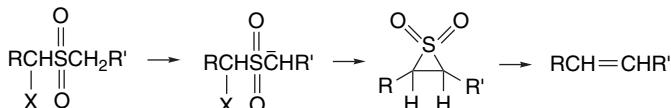
⁸⁹. R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

cannot be predicted directly from the structure of the reacting haloketone. Instead, the identity of the product is governed by the direction of ring opening of the cyclopropanone intermediate. The dominant mode of ring opening is expected to be the one that forms the more stable of the two possible ester enolates. For this reason, a phenyl substituent favors breaking the bond to the substituted carbon, but an alkyl group directs the cleavage to the less-substituted carbon.⁹⁰ That both **12** and **13** above give the same ester, **14**, is illustrative of the directing effect that the phenyl group has on the ring-opening step.



Scheme 10.5 gives some examples of Favorskii rearrangements. Entries 1 and 2 are examples of classical reaction conditions, the latter involving a ring contraction. Entry 3 is an interesting ring contraction-elimination. The reaction was shown to be highly stereospecific, with the *cis*-dibromide giving exclusively the *E*-double bond, whereas the *trans*-dibromide gave mainly the *Z*-double bond. Entry 4 is a ring contraction leading to the formation of an interesting strained-cage hydrocarbon skeleton. Entry 5 is a step in the synthesis of the natural analgesic epibatidine.

10.1.3.2. The Ramberg-Bäcklund Reaction. α -Halosulfones undergo a related rearrangement known as the *Ramberg-Bäcklund reaction*.⁹¹ The carbanion formed by deprotonation gives an unstable thirane dioxide that decomposes with elimination of sulfur dioxide. This elimination step is considered to be a concerted cycloelimination.

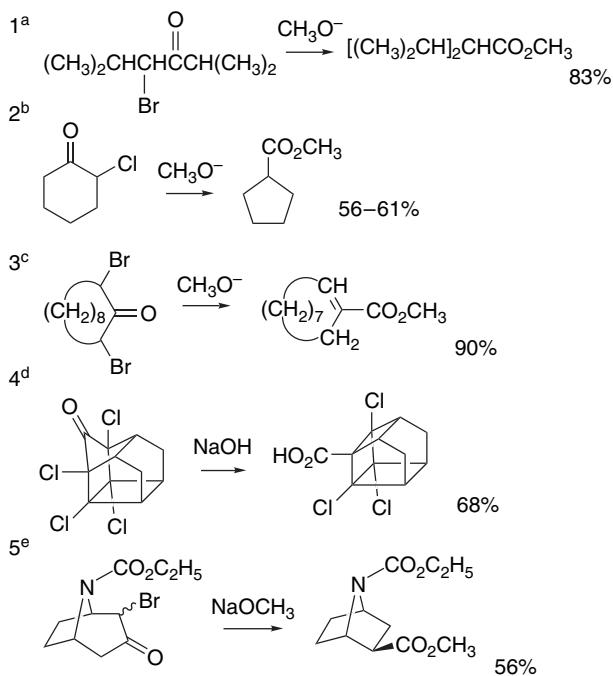


The overall transformation is the conversion of the carbon-sulfur bonds to a carbon-carbon double bond. The original procedure involved halogenation of a sulfide, followed by oxidation to the sulfone. Recently, the preferred method has reversed the order of the steps. After the oxidation, which is normally done with a peroxy acid, halogenation is done under basic conditions by use CBr_2F_2 or related polyhalomethanes for the halogen transfer step.⁹² This method was used, for example, to synthesize 1,8-diphenyl-1,3,5,7-octatetraene.

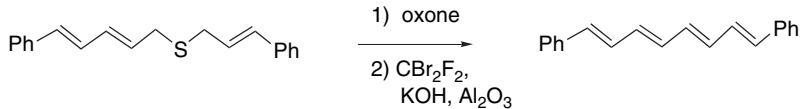
⁹⁰ C. Rappe, L. Knutsson, N. J. Turro, and R. B. Gagosian, *J. Am. Chem. Soc.*, **92**, 2032 (1970).

⁹¹ L. A. Paquette, *Acc. Chem. Res.*, **1**, 209 (1968); L. A. Paquette, in *Mechanism of Molecular Migrations*, Vol. 1, B. S. Thyagarajan, ed., Wiley-Interscience, New York, 1968, Chap. 3; L. A. Paquette, *Org. React.*, **25**, 1 (1977); R. J. K. Taylor, *J. Chem. Soc., Chem. Commun.*, 217 (1999); R. J. K. Taylor and G. Casy, *Org. React.*, **62**, 357 (2003).

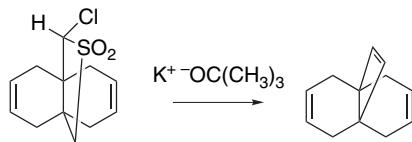
⁹² T.-L. Chan, S. Fong, Y. Li, T.-O. Mau, and C.-D. Poon, *J. Chem. Soc., Chem. Commun.*, 1771 (1994); X.-P. Cao, *Tetrahedron*, **58**, 1301 (2002).

Scheme 10.5. Base-Mediated Rearrangements of α -Haloketones

- a. S. Sarel and M. S. Newman, *J. Am. Chem. Soc.*, **78**, 5416 (1956).
 b. D. W. Goheen and W. R. Vaughan, *Org. Synth.*, **IV**, 594 (1963).
 c. E. W. Garbisch, Jr., and J. Wohllebe, *J. Org. Chem.*, **33**, 2157 (1968).
 d. R. J. Stedman, L. S. Miller, L. D. Davis, and J. R. E. Hoover, *J. Org. Chem.*, **35**, 4169 (1970).
 e. D. Bai, R. Xu, G. Chu, and X. Zhu, *J. Org. Chem.*, **61**, 4600 (1996).

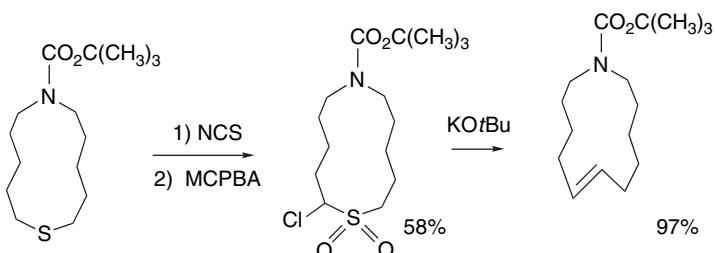


The Ramberg-Bäcklund reaction has found several applications. Owing to the concerted nature of the elimination, it can be applied to both small and large rings containing a double bond.



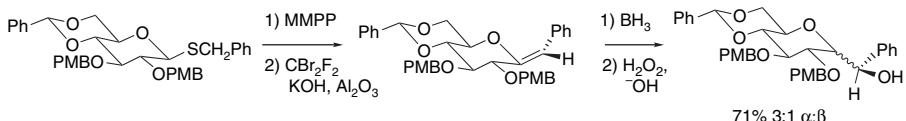
Ref. 93

⁹³. L. A. Paquette, J. C. Philips, and R. E. Wingard, Jr., *J. Am. Chem. Soc.*, **93**, 4516 (1971).



Ref. 94

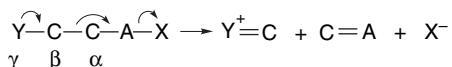
A recently developed application of the Ramberg-Bäcklund reaction is the synthesis of C-glycosides. The required thioethers can be prepared easily by exchange with a thiol. The application of the Ramberg-Bäcklund conditions then leads to an exocyclic vinyl ether that can be reduced to the C-nucleoside.⁹⁵ Entries 3 and 4 in Scheme 10.6 are examples. The vinyl ether group can also be transformed in other ways. In the synthesis of partial structures of the antibiotic altromycin, the vinyl ether product was subjected to diastereoselective hydroboration.



Scheme 10.6 gives some examples of the Ramberg-Bäcklund reaction. Entry 1 was used to prepare analogs of the antimalarial compound artemisinin for biological evaluation. The reaction in Entry 2 was used to install the side chain in a synthesis of the chrysomycin type of antibiotic. Entries 3 and 4 are examples of formation of C-glycosides.

10.1.4. Fragmentation Reactions

The classification *fragmentation* applies to reactions in which a carbon-carbon bond is broken. One structural feature that permits fragmentation to occur readily is the presence of a carbon that can accommodate carbocationic character β to a developing electron deficiency. This type of reaction, known as the *Grob fragmentation*, occurs particularly readily when the γ -atom is a heteroatom, such as nitrogen or oxygen, that has an unshared electron pair that can stabilize the new cationic center.⁹⁶



The fragmentation can be concerted or stepwise. The concerted mechanism is restricted to molecular geometry that is appropriate for continuous overlap of the participating

⁹⁴. I. MaGee and E. J. Beck, *Can. J. Chem.*, **78**, 1060 (2000).

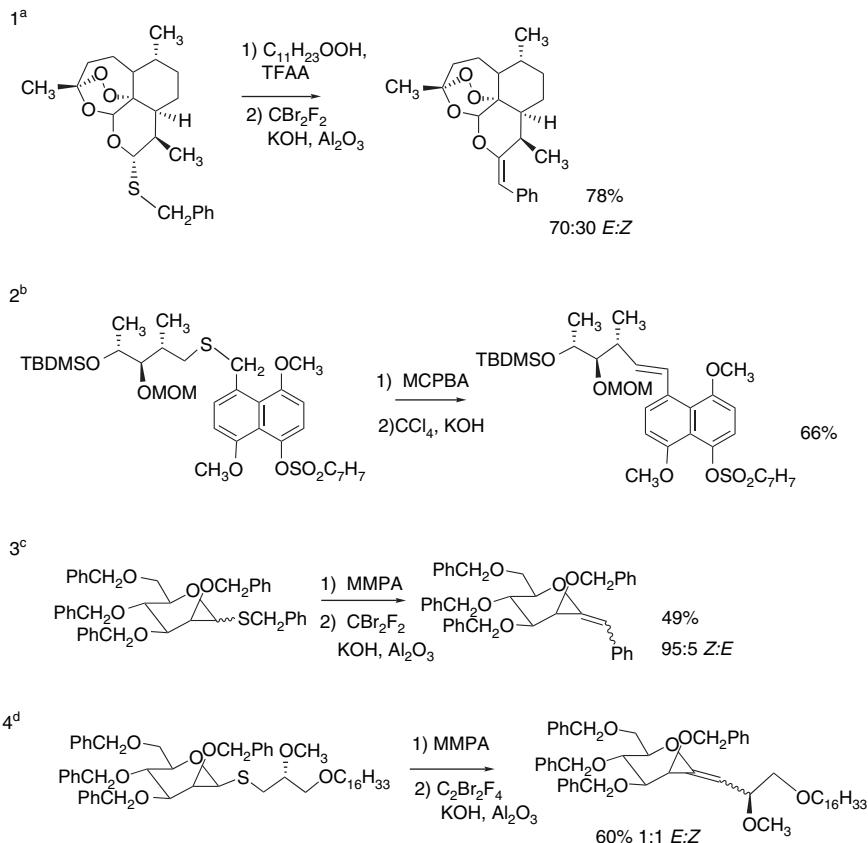
⁹⁵. F. K. Griffin, D. E. Paterson, P. V. Murphy, and R. J. K. Taylor, *Eur. J. Org. Chem.*, 1305 (2002).

⁹⁶. C. A. Grob, *Angew. Chem. Int. Ed. Engl.*, **8**, 535 (1969).

Scheme 10.6. Ramberg-Bäcklund Reaction

CHAPTER 10

Reactions Involving
Carbocations, Carbenes,
and Radicals as Reactive
Intermediates



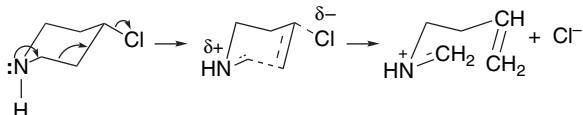
a. S. Oh, I. H. Jeong, W.-S. Shin, and S. Lee, *Biorg. Med. Chem. Lett.*, **14**, 3683 (2004).

b. D. J. Hart, G. H. Merriman, and D. G. J. Young, *Tetrahedron*, **52**, 14437 (1996).

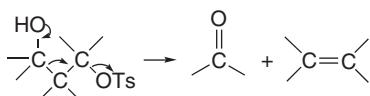
c. P. S. Belica and R. W. Franck, *Tetrahedron Lett.*, **39**, 8225 (1998).

d. G. Yang, R. W. Franck, H. S. Byun, R. Bittman, P. Samadder, and G. Arthur, *Org. Lett.*, **1**, 2149 (1999).

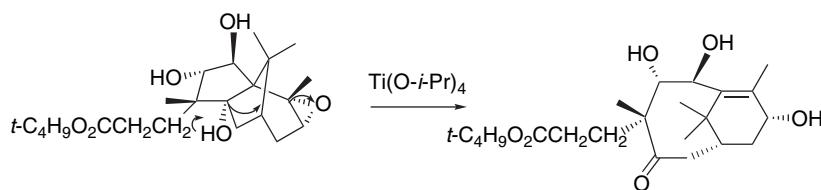
orbitals. An example is the solvolysis of 4-chloropiperidine, which is faster than the solvolysis of chlorocyclohexane and occurs by fragmentation of the C(2)–C(3) bond.⁹⁷



1,3-Diols or β-hydroxy ethers are particularly useful substrates for fragmentation. If the diol or hydroxy ether is converted to a monotosylate, the remaining oxy group can promote fragmentation.

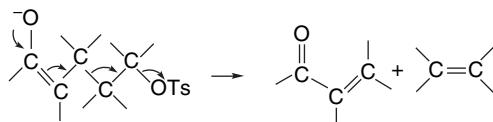


⁹⁷. R. D'Arcy, C. A. Grob, T. Kaffenberger, and V. Krasnobajew, *Helv. Chim. Acta*, **49**, 185 (1966).

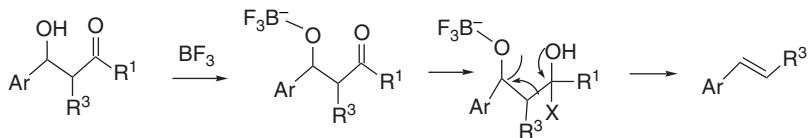


Ref. 98

Similarly, a carbonyl group at the fifth carbon from a leaving group, reacting as the enolate, promotes fragmentation with formation of an enone.⁹⁹ This is a *vinylogous* analog of the Grob fragmentation.

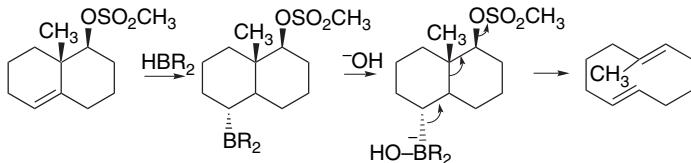


β -Hydroxyketones are also subject to fragmentation. Lewis acids promote fragmentation of mixed aldol products derived from aromatic aldehydes.¹⁰⁰



The same fragmentation is effected by $\text{Yb}(\text{OTf})_3$ on heating with the aldol adduct in the absence of solvent.¹⁰¹

Organoboranes undergo fragmentation if a good leaving group is present on the δ -carbon.¹⁰² The reactive intermediate is the tetrahedral borate formed by addition of hydroxide ion at boron.



Ref. 103

^{98.} R. A. Holton, R. R. Juo, H. B. Kim, A. Q. Williams, S. Harusawa, P. E. Lowenthal, and S. Yogai, *J. Am. Chem. Soc.*, **110**, 6558 (1988).

^{99.} J. M. Brown, T. M. Cresp, and L. N. Mander, *J. Org. Chem.*, **42**, 3984 (1977); D. A. Clark and P. L. Fuchs, *J. Am. Chem. Soc.*, **101**, 3567 (1979).

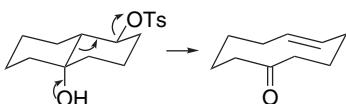
^{100.} G. W. Kabalka, N.-S. Li, D. Tejedor, R. R. Malladi, and S. Trotman, *J. Org. Chem.*, **64**, 3157 (1999).

^{101.} M. Curini, F. Epifano, F. Maltese, and M. C. Marcottullio, *Chem. Eur. J.*, 1631 (2003).

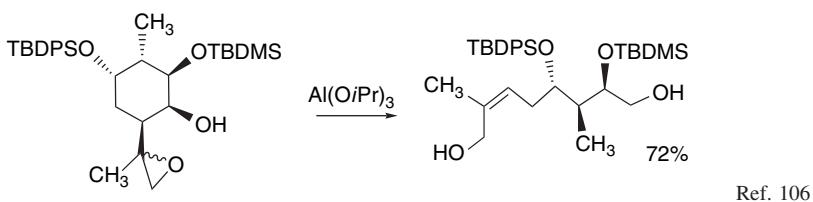
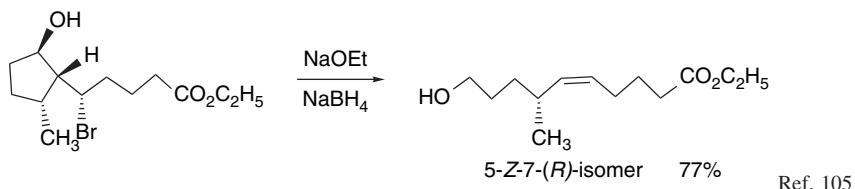
^{102.} J. A. Marshall, *Synthesis*, 229 (1971); J. A. Marshall and G. L. Bundy, *J. Chem. Soc., Chem. Commun.*, 854 (1967); P. S. Wharton, C. E. Sundin, D. W. Johnson, and H. C. Kluender, *J. Org. Chem.*, **37**, 34 (1972).

^{103.} J. A. Marshall and G. L. Bundy, *J. Am. Chem. Soc.*, **88**, 4291 (1966).

The usual synthetic objective of a fragmentation reaction is the construction of a medium-sized ring from a fused ring system. As the fragmentation reactions are usually concerted stereoselective processes, the stereochemistry is predictable. In 3-hydroxy tosylates, the fragmentation is most favorable for a geometry in which the carbon–carbon bond being broken is in an *anti*-periplanar relationship to the leaving group.¹⁰⁴ Other stereochemical relationships in the molecule are retained during the concerted fragmentation. In the case below, for example, the newly formed double bond has the *E*-configuration.



Fragmentation reactions can also be used to establish stereochemistry of acyclic systems based on stereochemical relationships built into cyclic reactants. In both the examples shown below, the aldehyde group generated by fragmentation was reduced *in situ*.



Scheme 10.7 provides some additional examples of fragmentation reactions that have been employed in a synthetic context. Entry 1 was used in the late stages of the synthesis of (\pm)-hinesol, an example of a terpene possessing a spiro[4,5]decane skeleton. The fragmentation provides the spiro ring system with a vinyl side chain. Entry 2 illustrates the formation of a medium ring by fragmentation of a bicyclic system. In this case LiAlH₄ serves as a base and also reduces the carbonyl group in the product, but closely related reactions were carried out with the more usual alkoxide bases. The reaction in Entry 3 was developed during exploration of the

¹⁰⁴. P. S. Wharton and G. A. Hiegel, *J. Org. Chem.*, **30**, 3254 (1965); C. H. Heathcock and R. A. Badger, *J. Org. Chem.*, **37**, 234 (1972).

¹⁰⁵. Y. M. A. W. Lamers, G. Rusu, J. B. P. A. Wijnberg, and A. de Groot, *Tetrahedron*, **59**, 9361 (2003).

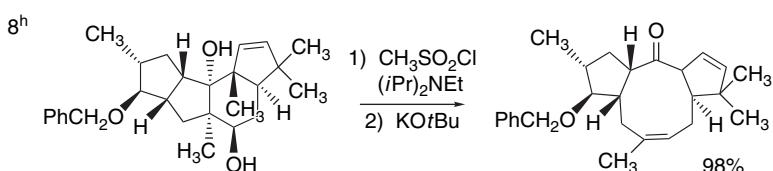
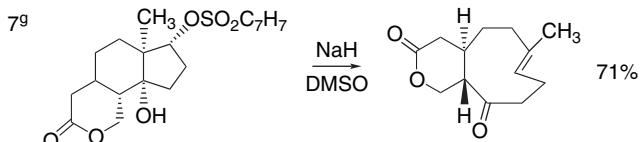
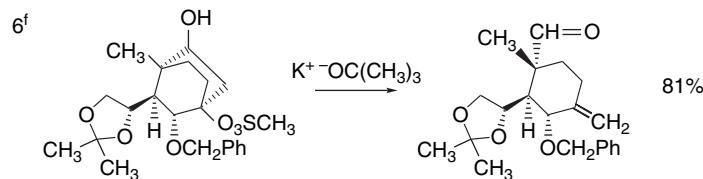
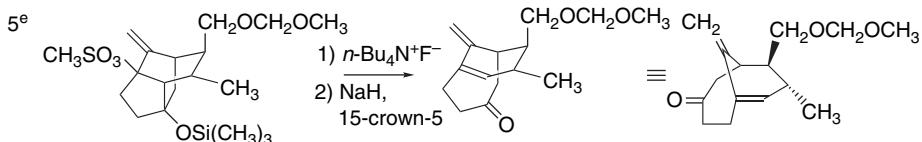
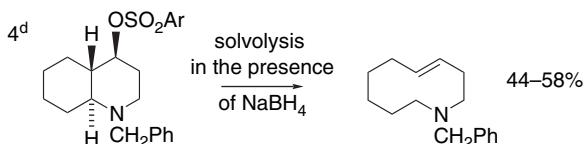
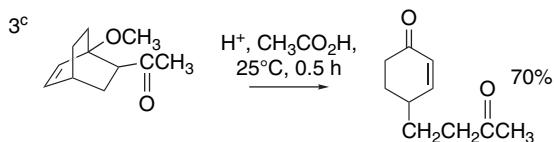
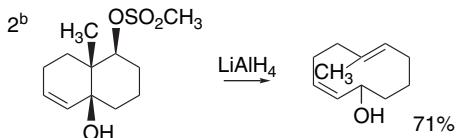
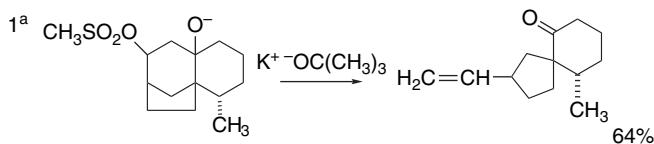
¹⁰⁶. X. Z. Zhao, Y. Q. Tu, L. Peng, X. Q. Li, and Y. X. Jia, *Tetrahedron Lett.*, **45**, 3213 (2004).

Scheme 10.7. Synthetic Applications of Fragmentation Reactions

SECTION 10.1

Reactions and
Rearrangement
Involving Carbocation
Intermediates

A. Heteroatom-promoted fragmentation

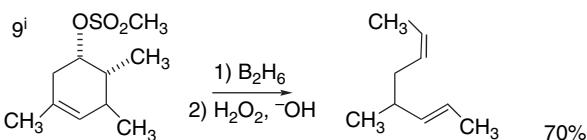
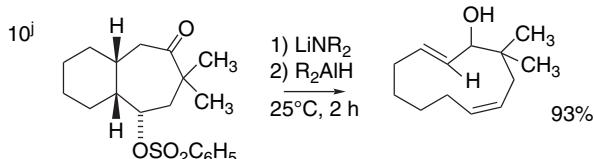


(Continued)

CHAPTER 10

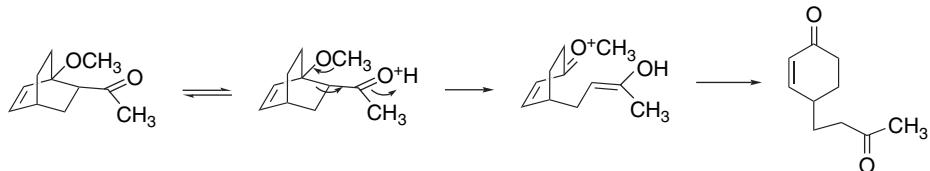
Reactions Involving
Carbocations, Carbenes,
and Radicals as Reactive
Intermediates

B. Boronate fragmentation

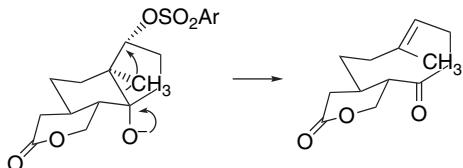
C. δ -Tosyloxy fragmentation

- a. J. A. Marshall and S. F. Brady, *J. Org. Chem.*, **35**, 4068 (1970).
- b. J. A. Marshall, W. F. Huffman, and J. A. Ruth, *J. Am. Chem. Soc.*, **94**, 4691 (1972).
- c. A. J. Birch and J. S. Hill, *J. Chem. Soc., C*, 419 (1966).
- d. J. A. Marshall and J. H. Babler, *J. Org. Chem.*, **34**, 4186 (1969).
- e. T. Yoshimitsu, M. Yanagiya, and H. Nagoka, *Tetrahedron Lett.*, **40**, 5215 (1999).
- f. Y. Hirai, T. Suga, and H. Nagaoka, *Tetrahedron Lett.*, **38**, 4997 (1997).
- g. D. Rennenberg, H. Pfander, and C. J. Leumann, *J. Org. Chem.*, **65**, 9069 (2000).
- h. L. A. Paquette, J. Yang, and Y. O. Long, *J. Am. Chem. Soc.*, **124**, 6542 (2002).
- i. J. A. Marshall and J. H. Babler, *Tetrahedron Lett.*, 3861 (1970).
- j. D. A. Clark and P. L. Fuchs, *J. Am. Chem. Soc.*, **101**, 3567 (1979).

chemistry of the reactant, which is readily available by a Diels-Alder reaction of 1-methoxycyclohexadiene. This acid-catalyzed fragmentation is induced by protonation of the acetyl group.

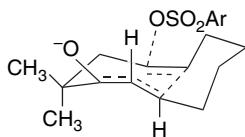


Entry 4 involves nitrogen participation and formation of an iminium ion that is reduced by NaBH_4 . The reaction in Entry 5 creates an 11-methylenebicyclo[4.3.1]undecen-3-one structure found in a biologically active natural product. Note that this fragmentation creates a bridgehead double bond. Entry 6 involves construction of a portion of the taxol structure. The reaction in Entry 7 is stereospecific, leading to the *E*-double bond.



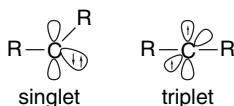
Entry 8 was used to create the central nine-membered ring system found in the diterpene jatrophatrione. Entry 9 is an example of a boronate fragmentation (see p. 899). Entry 10 illustrates enolate fragmentation. The reaction presumably proceeds

through an extended conformation that aligns the enolate and sulfonate leaving group advantageously and results in an *E*-double bond.



10.2. Reactions Involving Carbenes and Related Intermediates

Carbenes can be included with carbanions, carbocations, and carbon-centered radicals as being among the fundamental intermediates in the reactions of carbon compounds. Carbenes are neutral divalent derivatives of carbon. As would be expected from their electron-deficient nature, most carbenes are highly reactive. Depending upon the mode of generation, a carbene can be formed in either the singlet or the triplet state, no matter which is lower in energy. The two electronic configurations have different geometry and reactivity. A conceptual picture of the bonding in the singlet assumes sp^2 hybridization at carbon, with the two unshared electrons in an sp^2 orbital. The p orbital is unoccupied. The R—C—R angle would be expected to be contracted slightly from 120° because of the electronic repulsions between the unshared electron pair and the electrons in the two bonding σ orbitals. The bonds in a triplet carbene are considered to be formed from sp orbitals with the unpaired electrons being in two equivalent p orbitals. This bonding arrangement corresponds to a linear structure.

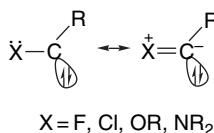


Both theoretical and experimental studies have provided more detailed information about carbene structure. Molecular orbital calculations lead to the prediction of H—C—H angles for methylene of roughly 135° for the triplet and about 105° for the singlet. The triplet is calculated to be about 8 kcal/mol lower in energy than the singlet.¹⁰⁷ Experimental determinations of the geometry of CH_2 accord with the theoretical results. The H—C—H angle of the triplet state, as determined from the ESR spectrum is 125° – 140° . The H—C—H angle of the singlet state is found to be 102° by electronic spectroscopy. The available evidence is consistent with the triplet being the ground state species.

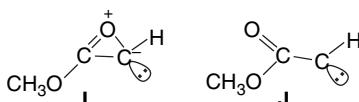
Substituents perturb the relative energies of the singlet and triplet states. In general, alkyl groups resemble hydrogen as a substituent and dialkylcarbenes are ground state

¹⁰⁷ J. F. Harrison, *Acc. Chem. Res.*, **7**, 378 (1974); P. Saxe, H. F. Shaefer, and N. C. Hardy, *J. Phys. Chem.*, **85**, 745 (1981); C. C. Hayden, M. Newmark, K. Shobatake, R. K. Sparks, and Y. T. Lee, *J. Chem. Phys.*, **76**, 3607 (1982); R. K. Lengel and R. N. Zare, *J. Am. Chem. Soc.*, **100**, 739 (1978); C. W. Bauschlicher, Jr., and I. Shavitt, *J. Am. Chem. Soc.*, **100**, 739 (1978); A. R. W. M. Kellar, P. R. Bunker, T. J. Sears, K. M. Evenson, R. Saykally, and S. R. Langhoff, *J. Chem. Phys.*, **79**, 5251 (1983).

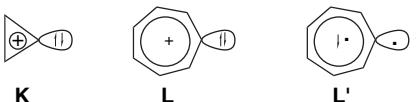
triplets. Substituents that act as electron-pair donors stabilize the singlet state more than the triplet state by delocalization of an electron pair into the empty p orbital.¹⁰⁸



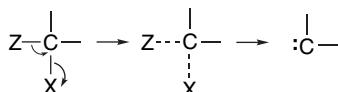
The presence of more complex substituent groups complicates the description of carbene structure. Furthermore, since carbenes are high-energy species, structural entities that would be unrealistic for more stable species must be considered. As an example, one set of MO calculations¹⁰⁹ arrives at structure **I** as a better description of carbomethoxycarbene than the conventional structure **J**.



π -Delocalization involving divalent carbon in conjugated cyclic systems has been studied in the interesting species cyclopropenylidene (**K**)¹¹⁰ and cycloheptatrienylidene (**L**).¹¹¹ In these molecules the empty p orbital on the carbene carbon can be part of the aromatic π system and be delocalized over the entire ring. Currently available data indicate that the ground state structures for both **K** and **L** are singlets, but for **L**, the most advanced theoretical calculations indicate that the most stable singlet structure has an electronic configuration in which one of the nonbonded electrons is in the π orbital.¹¹²

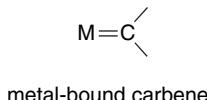


There are a number of ways of generating carbenes that will be discussed shortly. In some cases, the reactions involve complexes or precursors of carbenes rather than the carbene per se. For example, carbenes can be generated by α -elimination reactions. Under some circumstances the question arises as to whether the carbene has a finite lifetime, and in some cases a completely free carbene structure is never attained.

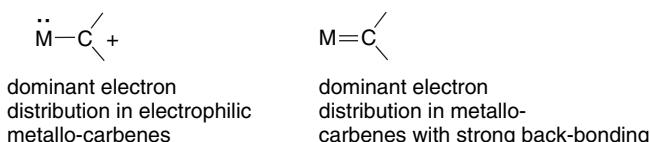


- ¹⁰⁸. N. C. Baird and K. F. Taylor, *J. Am. Chem. Soc.*, **100**, 1333 (1978); J. F. Harrison, R. C. Liedtke, and J. F. Liebman, *J. Am. Chem. Soc.*, **101**, 7162 (1979); P. H. Mueller, N. G. Rondan, K. N. Houk, J. F. Harrison, D. Hooper, B. H. Willen, and J. F. Liebman, *J. Am. Chem. Soc.*, **103**, 5049 (1981).
- ¹⁰⁹. R. Noyori and M. Yamanaka, *Tetrahedron Lett.*, 2851 (1980).
- ¹¹⁰. H. P. Reisenauer, G. Maier, A. Reimann, and R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **23**, 641 (1984); T. J. Lee, A. Bunge, and H. F. Schaefer, III, *J. Am. Chem. Soc.*, **107**, 137 (1985); J. M. Bofill, J. Farras, S. Olivella, A. Sole, and J. Vilarrasa, *J. Am. Chem. Soc.*, **110**, 1694 (1988).
- ¹¹¹. R. J. McMahon and O. L. Chapman, *J. Am. Chem. Soc.*, **108**, 1713 (1986); M. Kusaz, H. Luerssen, and C. Wentrup, *Angew. Chem. Int. Ed. Engl.*, **25**, 480 (1986); C. L. Janssen and H. F. Schaefer, III, *J. Am. Chem. Soc.*, **109**, 5030 (1987); M. W. Wong and C. Wentrup, *J. Org. Chem.*, **61**, 7022 (1996).
- ¹¹². S. Matzinger, T. Bally, E. V. Patterson, and R. J. McMahon, *J. Am. Chem. Soc.*, **118**, 1535 (1996); P. R. Schreiner, W. L. Karney, P. v. R. Schleyer, W. T. Borden, T. P. Hamilton, and H. F. Schaefer, III, *J. Org. Chem.*, **61**, 7030 (1996).

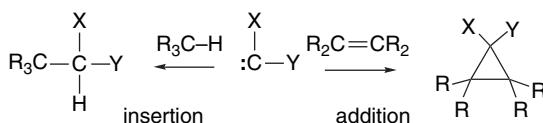
When a reaction appears to involve a species that reacts as expected for a carbene but must still be at least partially bound to other atoms, the term *carbenoid* is used. Some carbenelike processes involve transition metal ions. In many of these reactions, the divalent carbene is bound to the metal. Some compounds of this type are stable, whereas others exist only as transient intermediates. In most cases, the reaction involves the metal-bound carbene, rather than a free carbene.



The stability and reactivity of metallocarbenes depends on the degree of back donation from the metal to the carbene. If this is small, the metallocarbenes are highly reactive and electrophilic in character. If back bonding is substantial, the carbon will be less electrophilic, and the reactions are more likely to involve the metal.



Carbenes and carbenoids can add to double bonds to form cyclopropanes or insert into C–H bonds.



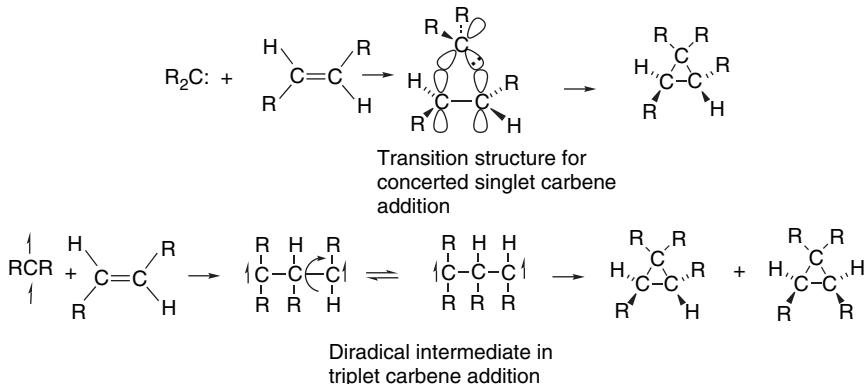
These reactions have *very low activation energies* when the intermediate is a “free” carbene. Intermolecular insertion reactions are inherently nonselective. The course of intramolecular reactions is frequently controlled by the proximity of the reacting groups.¹¹³ Carbene intermediates can also be involved in rearrangement reactions. In the sections that follow we also consider a number of rearrangement reactions that probably do not involve carbene intermediates, but lead to transformations that correspond to those of carbenes.

10.2.1. Reactivity of Carbenes

From the point of view of both synthetic and mechanistic interest, much attention has been focused on the addition reaction between carbenes and alkenes to give cyclopropanes. Characterization of the reactivity of substituted carbenes in addition reactions has emphasized stereochemistry and selectivity. The reactivities of singlet and triplet states are expected to be different. The triplet state is a diradical, and would be expected to exhibit a selectivity similar to free radicals and other species with unpaired electrons. The singlet state, with its unfilled *p* orbital, should be electrophilic and exhibit reactivity patterns similar to other electrophiles. Moreover, a triplet addition

¹¹³ S. D. Burke and P. A. Grieco, *Org. React.*, **26**, 361 (1979).

process must go through a 1,3-diradical intermediate that has two unpaired electrons of the same spin. In contrast, a singlet carbene can go to a cyclopropane in a single concerted step.¹¹⁴ As a result, it was predicted that additions of singlet carbenes would be stereospecific, whereas those of triplet carbenes would not be.¹¹⁵ This expectation has been confirmed and the stereoselectivity of addition reactions with alkenes is used as a test for the involvement of the singlet versus triplet carbene in specific reactions.¹¹⁶



The radical versus electrophilic character of triplet and singlet carbenes also shows up in relative reactivity patterns given in Table 10.1. The relative reactivity of singlet dibromomocarbene toward alkenes is more similar to electrophiles (bromination, epoxidation) than to radicals ($\cdot CCl_3$).

Carbene reactivity is strongly affected by substituents.¹¹⁷ Various singlet carbenes have been characterized as nucleophilic, ambiphilic, and electrophilic as shown in Table 10.2. This classification is based on relative reactivity toward a series of both nucleophilic alkenes, such as tetramethylethylene, and electrophilic ones, such as acrylonitrile. The principal structural feature that determines the reactivity of the carbene is the ability of the substituent to act as an electron donor. For example, dimethoxycarbene is devoid of electrophilicity toward alkenes because of electron donation by the methoxy groups.¹¹⁸

Table 10.1. Relative Rates of Addition to Alkenes^a

Alkene	$\cdot CCl_3$	$\cdot CBr_2$	Br_2	Epoxidation
2-Methylpropene	1.0	1.0	1.0	1.0
Styrene	>19	0.4	0.6	0.1
2-Methyl-2-butene	0.17	3.2	1.9	13.5

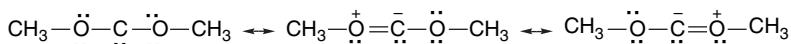
a. P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 5430 (1956).

- ¹¹⁴ A. E. Keating, S. R. Merrigan, D. A. Singleton, and K. N. Houk, *J. Am. Chem. Soc.*, **121**, 3933 (1999).
- ¹¹⁵ P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 5430 (1956).
- ¹¹⁶ R. C. Woodworth and P. S. Skell, *J. Am. Chem. Soc.*, **81**, 3383 (1959); P. S. Skell, *Tetrahedron*, **41**, 1427 (1985).
- ¹¹⁷ A comprehensive review of this topic is given by R. A. Moss, in *Carbenes*, M. Jones, Jr., and R. A. Moss, eds., John Wiley & Sons, New York, 1973, pp. 153–304; R. A. Moss, *Acc. Chem. Res.*, **22**, 15 (1989). More recent work is reviewed in the series *Reactive Intermediates*, R. A. Moss, M. S. Platz, and M. Jones, Jr., eds., Wiley, New York, 2004, Chap. 7.
- ¹¹⁸ D. M. Lemal, E. P. Gosselink, and S. D. McGregor, *J. Am. Chem. Soc.*, **88**, 582 (1966).

Table 10.2. Classification of Carbenes on the Basis of Reactivity toward Alkenes^a

Nucleophilic	Ambiphilic	Electrophilic
$(CH_3O)_2C$	CH_3OCCl	Cl_2C
$CH_3OCN(CH_3)_2$	CH_3OCF	$PhCCl$
		CH_3CCl
		$BrCCO_2C_2H_5$

a. R. A. Moss and R. C. Munjai, *Tetrahedron Lett.*, 4721 (1979); R. A. Moss, *Acc. Chem. Res.*, **13**, 58 (1980); R. A. Moss, *Acc. Chem. Res.*, **22**, 15 (1989).



Absolute rates have been measured for some carbene reactions. The rate of addition of phenylchlorocarbene shows a small dependence on alkene substituents, but as expected for a very reactive species, the range of reactivity is quite narrow.¹¹⁹ The rates are comparable to moderately fast bimolecular addition reactions of radicals (see Part A, Table 11.3).

9.97×10^6	3.32×10^6	2.24×10^6	1.10×10^6	1.54×10^5

Absolute rate of addition of phenylchlorocarbene, $k M^{-1}s^{-1}$

The rates of phenylchlorocarbene have also been compared with the fluoro and bromo analogs.¹²⁰ The data show slightly decreased rates in the order Br > Cl > F. The alkene reactivity difference is consistent with an electrophilic attack. These reactions have low activation barriers and the reactivity differences are dominated by entropy effects.

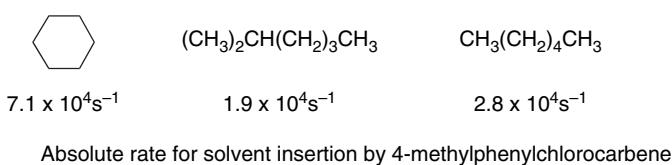
PhCBr	4.0×10^6
PhCCl	2.2×10^6
PhCF	9.3×10^5

Absolute rate of addition, $k M^{-1}s^{-1}$

¹¹⁹. N. Soundararajan, M. S. Platz, J. E. Jackson, M. P. Doyle, S.-M. Oon, M. J. H. Liu, and S. M. Anand, *J. Am. Chem. Soc.*, **110**, 7143 (1988).

¹²⁰. R. A. Moss, W. Lawrynowicz, N. J. Turro, I. R. Gould, and Y. Cha, *J. Am. Chem. Soc.*, **108**, 7028 (1986).

There is a small dependence on the rate of solvent insertion reactions for saturated hydrocarbons.¹²¹ Benzene is much less reactive.



An HSAB analysis of singlet carbene reactivity based on B3LYP/6-31G* computations has calculated the extent of charge transfer for substituted alkenes,¹²² and the results are summarized in Figure 10.3. The trends are as anticipated for changes in structure of both the carbene and alkene. The charge transfer interactions are consistent with HOMO-LUMO interactions between the carbene and alkene. Similarly, a correlation was found for the global electrophilicity parameter, ω , and the ΔN_{\max} parameters (see Topic 1.5, Part A for definition of these DFT-based parameters).¹²³

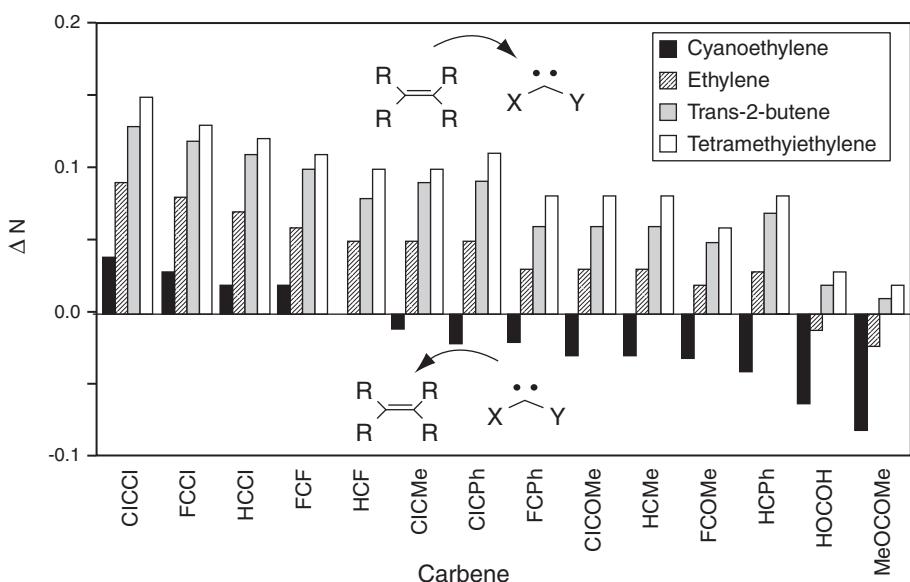
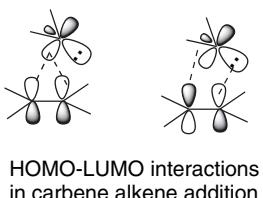


Fig. 10.3. Net charge transfer (ΔN) calculated for substituted carbenes with several alkenes. Reproduced from *J. Org. Chem.*, **64**, 7061 (1999), by permission of the American Chemical Society.

¹²¹ R. Bonneau and M. T. H. Liu, *J. Photochem. Photobiol. A*, **68**, 97 (1992).

¹²² F. Mendez and M. A. Garcia-Garibay, *J. Org. Chem.*, **64**, 7061 (1999).

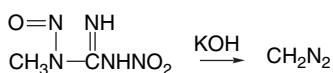
¹²³ P. Perez, *J. Phys. Chem. A*, **107**, 522 (2003).

There are several ways of generating carbene intermediates. Some of the most general routes are summarized in Scheme 10.8 and are discussed in the succeeding paragraphs.

SECTION 10.2

*Reactions Involving
Carbenes and Related
Intermediates*

10.2.2.1. Carbenes from Diazo Compounds. Decomposition of diazo compounds to form carbenes is a quite general reaction that is applicable to diazomethane and other diazoalkanes, diazoalkenes, and diazo compounds with aryl and acyl substituents. The main restrictions on this method are the limitations on synthesis and limited stability of the diazo compounds. The smaller diazoalkanes are toxic and potentially explosive, and they are usually prepared immediately before use. The most general synthetic routes involve base-catalyzed decomposition of *N*-nitroso derivatives of amides, ureas, or sulfonamides, as illustrated by several reactions used for the preparation of diazomethane.



Ref. 124

Scheme 10.8. General Methods for Generation of Carbenes

Precursor	Conditions	Products	Ref.
Diazoalkanes $\text{R}_2\text{C}=\text{N}^+=\text{N}^-$	Photolysis, thermolysis or metal catalysis	$\text{R}_2\text{C}: + \text{N}_2$	a
Salts of sulfonylhydrazones $[\text{R}_2\text{C}=\text{NNSO}_2\text{Ar}]^-$	Photolysis or thermolysis; diazoalkanes are intermediates	$\text{R}_2\text{C}: + \text{N}_2 + \text{ArSO}_2^-$	b
Diazirines 	Photolysis	$\text{R}_2\text{C}: + \text{N}_2$	c
Alkyl halides $\text{R}_2\text{CH}-\text{X}$	Strong base, including metalation	$\text{R}_2\text{C}: + \text{X}^- + \text{B}-\text{H}$	d
α -Haloalkylmercury compounds 	Thermolysis	$\text{R}_2\text{C}: + \text{HgXZ}$	e

a. W. J. Baron, M. R. DeCamp, M. E. Hendrick, M. Jones, Jr., R. H. Levin, and M. B. Sohn, in *Carbenes*, M. Jones, Jr., and R. A. Moss, eds. John Wiley & Sons, New York, 1973, pp. 1–151.

b. W. B. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

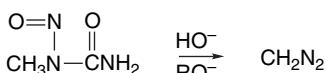
c. H. M. Frey, *Adv. Photochem.*, **4**, 225 (1966); R. A. G. Smith and J. R. Knowles, *J. Chem. Soc., Perkin Trans. 2*, 686 (1975); T. C. Celius and J. P. Toscano, *CRC Handbook of Organo Photochemistry and Photobiology*, 2nd Edition, 2004, pp 92/1–92/10.

d. W. Kirmse, *Carbene Chemistry*, Academic Press, New York, 1971, pp. 96–109, 129–149.

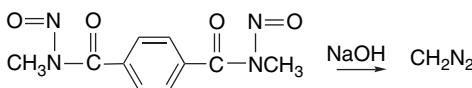
e. D. Seyerth, *Acc. Chem. Res.* **5**, 65 (1972).

¹²⁴ M. Neeman and W. S. Johnson, *Org. Synth.*, **V**, 245 (1973).

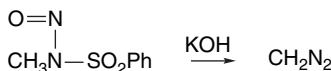
Reactions Involving Carbocations, Carbenes, and Radicals as Reactive Intermediates



Ref. 125

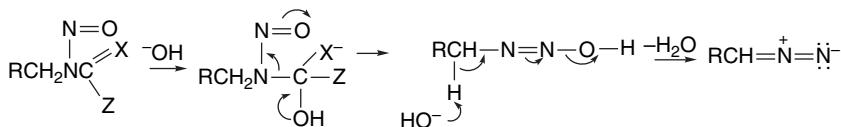


Ref. 126

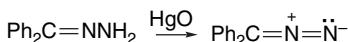


Ref. 127

The details of the base-catalyzed decompositions vary somewhat but the mechanisms involve two essential steps.¹²⁸ The initial reactants undergo a base-catalyzed addition-elimination to form an alkyl diazoate. This is followed by a deprotonation of the α -carbon and elimination of hydroxide.



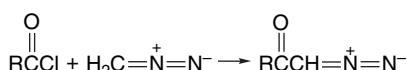
Diazo compounds can also be obtained by oxidation of the corresponding hydrazone,¹²⁹ the route that is most common when one of the substituents is an aromatic ring.



Ref. 130

The higher diazoalkanes can be made by $\text{Pb}(\text{O}_2\text{CCH}_3)_4$ oxidation of hydrazones.¹²⁹

α -Diazoketones are especially useful in synthesis.¹³¹ There are several methods of preparation. Reaction of diazomethane with an acyl chloride results in formation of a diazomethyl ketone.



The HCl generated in this reaction destroys one equivalent of diazomethane, but this can be avoided by including a base, such as triethylamine, to neutralize the acid.¹³²

¹²⁵ F. Arndt, *Org. Synth.*, **II**, 165 (1943).

¹²⁶ T. J. de Boer and H. J. Backer, *Org. Synth.*, **IV**, 250 (1963).

¹²⁷ J. A. Moore and D. E. Reed, *Org. Synth.*, **V**, 351 (1973).

¹²⁸ W. M. Jones, D. L. Muck, and T. K. Tandy, Jr., *J. Am. Chem. Soc.*, **88**, 3798 (1966); R. A. Moss, *J. Org. Chem.*, **31**, 1082 (1966); D. E. Applequist and D. E. McGreer, *J. Am. Chem. Soc.*, **82**, 1965 (1960); S. M. Hecht and J. W. Kozarich, *J. Org. Chem.*, **38**, 1821 (1973); E. H. White, J. T. DePinto, A. J. Polito, I. Bauer, and D. F. Roswell, *J. Am. Chem. Soc.*, **110**, 3708 (1988).

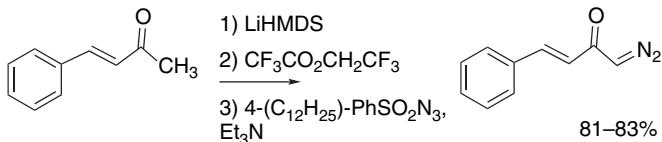
¹²⁹ T. L. Holton and H. Shechter, *J. Org. Chem.*, **60**, 4725 (1995).

¹³⁰ L. I. Smith and K. L. Howard, *Org. Synth.*, **III**, 351 (1955).

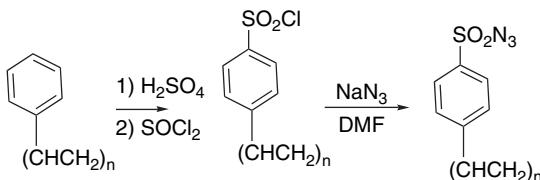
¹³¹ T. Ye and M. A. McKervey, *Chem. Rev.*, **94**, 1091 (1994).

¹³² M. S. Newman and P. Beall, III, *J. Am. Chem. Soc.*, **71**, 1506 (1949); M. Berebom and W. S. Fones, *J. Am. Chem. Soc.*, **71**, 1629 (1949); L. T. Scott and M. A. Minton, *J. Org. Chem.*, **42**, 3757 (1977).

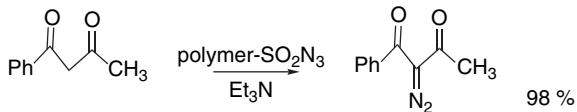
Cyclic α -diazoketones, which are not available from acyl chlorides, can be prepared by reaction of an enolate equivalent with a sulfonyl azide, in a reaction known as *diazo transfer*.¹³³ Various arenesulfonyl azides¹³⁴ and methanesulfonyl azide¹³⁵ are used most frequently. Because of the potential explosion hazard of sulfonyl azides, safety is a factor in choosing the reagent. 4-Dodecylbenzenesulfonyl azide has been recommended on the basis of relative thermal stability.¹³⁶ This reagent has been used in an *Organic Synthesis* preparation of 1-diazo-4-phenylbut-3-en-2-one.¹³⁷



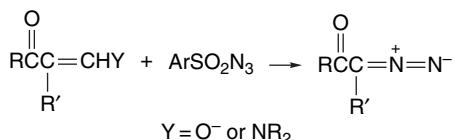
A polymer bound arenesulfonyl azide can be prepared from polystyrene.¹³⁸



This reagent effects diazo transfer in good yield.



Several types of compounds can act as the carbon nucleophile in diazo transfer, including the oxymethylene¹³⁹ or dialkylaminomethylene¹⁴⁰ derivatives of the ketone. These activating substituents are lost during these reactions.



¹³³ F. W. Bollinger and L. D. Tuma, *Synlett*, 407 (1996).

¹³⁴ J. B. Hendrickson and W. A. Wolf, *J. Org. Chem.*, **33**, 3610 (1968); J. S. Baum, D. A. Shook, H. M. L. Davies, and H. D. Smith, *Synth. Commun.*, **17**, 1709 (1987); L. Lombardo and L. N. Mander, *Synthesis*, 368 (1980).

¹³⁵ D. F. Taber, R. E. Ruckle, and M. J. Hennessy, *J. Org. Chem.*, **51**, 4077 (1986); R. L. Danheiser, D. S. Casebier, and F. Firooznia, *J. Org. Chem.*, **60**, 8341 (1995).

¹³⁶ L. D. Tuma, *Thermochimica Acta*, **243**, 161 (1994).

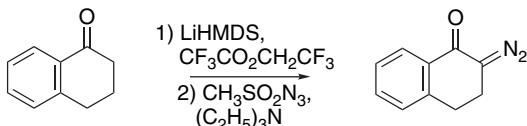
¹³⁷ R. L. Danheiser, R. F. Miller, and R. G. Brisbois, *Org. Synth.*, **73**, 134 (1996).

¹³⁸ G. M. Green, N. P. Peet, and W. A. Metz, *J. Org. Chem.*, **66**, 2509 (2001).

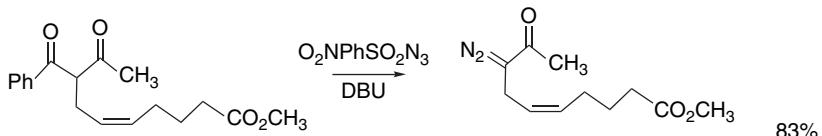
¹³⁹ M. Regitz and G. Heck, *Chem. Ber.*, **97**, 1482 (1964); M. Regitz, *Angew. Chem. Int. Ed. Engl.*, **6**, 733 (1967).

¹⁴⁰ M. Rosenberger, P. Yates, J. B. Hendrickson, and W. Wolf, *Tetrahedron Lett.*, 2285 (1964); K. B. Wiberg, B. L. Furtek, and L. K. Olli, *J. Am. Chem. Soc.*, **101**, 7675 (1979).

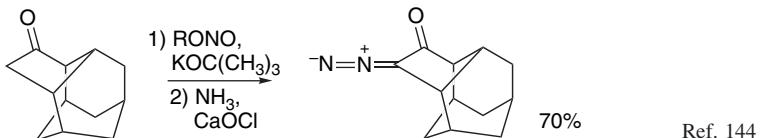
α -Trifluoroacetyl derivatives of ketones are also useful substrates for diazo transfer reactions.¹⁴¹ They are made by enolate acylation using 2,2,2-trifluoroethyl trifluoroacetate. The trifluoroacetyl group is cleaved during diazo transfer.



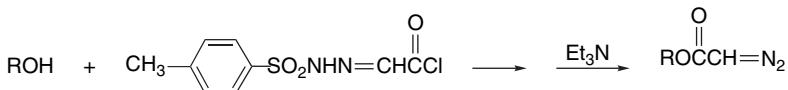
Benzoyl groups are also selectively cleaved during diazo transfer. This method has been used to prepare diazo ketones and diazo esters.¹⁴²



α -Diazo ketones can also be made by first converting the ketone to an α -oximino derivative by nitrosation and then oxidizing the oximino ketone with chloramine.¹⁴³



α -Diazo esters can be prepared by esterification of alcohols with the tosylhydrazone of glyoxyloyl chloride, followed by reaction with triethylamine.¹⁴⁵



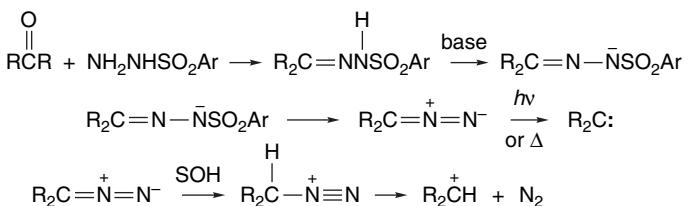
The driving force for decomposition of diazo compounds to carbenes is the formation of the very stable nitrogen molecule. Activation energies for decomposition of diazoalkanes in the gas phase are about 30 kcal/mol. The requisite energy can also be supplied by photochemical excitation. It is often possible to control the photochemical process to give predominantly singlet or triplet carbene. Direct photolysis leads to the singlet intermediate when the dissociation of the excited diazoalkene is faster than intersystem crossing to the triplet state. The triplet carbene is the principal intermediate in photosensitized decomposition of diazoalkanes. (See Part A, Chapter 12 to review photosensitization.)

Reaction of diazo compounds with a variety of transition metal compounds leads to evolution of nitrogen and formation of products of the same general type as those formed by thermal and photochemical decomposition of diazoalkanes. These transition

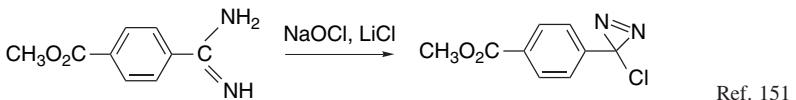
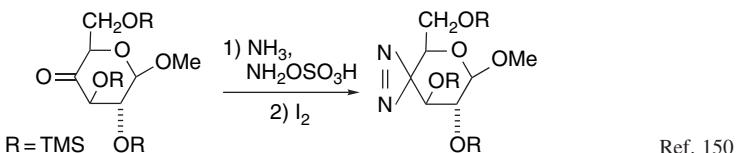
- ¹⁴¹. R. L. Danheiser, R. F. Miller, R. G. Brisbois, and S. Z. Park, *J. Org. Chem.*, **55**, 1959 (1990).
- ¹⁴². D. F. Taber, D. M. Gleave, R. J. Herr, K. Moody, and M. J. Hennessy, *J. Org. Chem.*, **60**, 1093 (1995).
- ¹⁴³. T. N. Wheeler and J. Meinwald, *Org. Synth.*, **52**, 53 (1972).
- ¹⁴⁴. T. Sasaki, S. Eguchi, and Y. Hirako, *J. Org. Chem.*, **42**, 2981 (1977).
- ¹⁴⁵. E. J. Corey and A. G. Myers, *Tetrahedron Lett.*, **25**, 3559 (1984).

metal-catalyzed reactions involve carbeneoid intermediates in which the carbene is bound to the metal.¹⁴⁶ The metals that have been used most frequently in synthetic reactions are copper and rhodium, and these reactions are discussed in Section 10.2.3.2

10.2.2.2. Carbenes from Sulfonylhydrazones. The second method listed in Scheme 10.8, thermal or photochemical decomposition of salts of arenesulfonylhydrazones, is actually a variation of the diazoalkane method, since diazo compounds are intermediates. The conditions of the decomposition are usually such that the diazo compound reacts immediately on formation.¹⁴⁷ The nature of the solvent plays an important role in the outcome of sulfonylhydrazone decompositions. In protic solvents, the diazoalkane can be diverted to a carbocation by protonation.¹⁴⁸ Aprotic solvents favor decomposition via the carbene pathway.



10.2.2.3. Carbenes from Diazirines. The diazirine precursors of carbenes (Scheme 10.8, Entry 3) are cyclic isomers of diazo compounds. The strain of the small ring and the potential for formation of nitrogen make them highly reactive toward loss of nitrogen on photoexcitation. Diazirines have been used mainly in mechanistic investigations of carbenes. They are, in general, somewhat less easily available than diazo compounds or arenesulfonylhydrazones. However, there are several useful synthetic routes.¹⁴⁹



¹⁴⁶ W. R. Moser, *J. Am. Chem. Soc.*, **91**, 1135, 1141 (1969); M. P. Doyle, *Chem. Rev.*, **86**, 919 (1986); M. Brookhart, and H. B. Studabaker *Chem. Rev.*, **87**, 411 (1987).

¹⁴⁷ G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, and H. Shechter, *J. Am. Chem. Soc.*, **87**, 935 (1965).

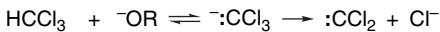
¹⁴⁸ J. H. Bayless, L. Friedman, F. B. Cook, and H. Shechter, *J. Am. Chem. Soc.*, **90**, 531 (1968).

¹⁴⁹ For reviews of synthesis of diazirines, see E. Schmitz, *Dreiringe mit Zwei Heteroatomen*, Springer Verlag, Berlin, 1967, pp. 114–121; E. Schmitz, *Adv. Heterocycl. Chem.*, **24**, 63 (1979); H. W. Heine, in *Chem. Heterocycl. Compounds*, Vol. 42, Part 2, A. Hassner, ed., Wiley-Interscience, New York, 1983, pp. 547–628.

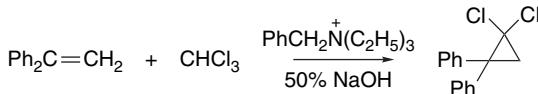
¹⁵⁰ G. Kurz, J. Lehmann, and R. Thieme, *Carbohydrate Res.*, **136**, 125 (1983).

¹⁵¹ D. F. Johnson and R. K. Brown, *Photochem. Photobiol.*, **43**, 601 (1986).

10.2.2.4. Carbenes from Halides by α -Elimination. The α -elimination of hydrogen halide induced by strong base (Scheme 10.8, Entry 4) is restricted to reactants that do not have β -hydrogens, because dehydrohalogenation by β -elimination dominates when it can occur. The classic example of this method of carbene generation is the generation of dichlorocarbene by base-catalyzed decomposition of chloroform.¹⁵²



Both phase transfer and crown ether catalysis have been used to promote α -elimination reactions of chloroform and other haloalkanes.¹⁵³ The carbene can be trapped by alkenes to form dichlorocyclopropanes.



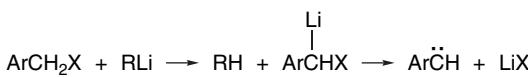
Ref. 154

Dichlorocarbene can also be generated by sonication of a solution of chloroform with powdered KOH.¹⁵⁵

α -Elimination also occurs in the reaction of dichloromethane and benzyl chlorides with alkylolithium reagents. The carbanion stabilization provided by the chloro and phenyl groups makes the lithiation feasible.



Ref. 156



Ref. 157

The reactive intermediates under some conditions may be the carbenoid α -haloalkyllithium compounds or carbene-lithium halide complexes.¹⁵⁸ In the case of the trichloromethylolithium to dichlorocarbene conversion, the equilibrium lies heavily to the side of trichloromethylolithium at -100°C .¹⁵⁹ The addition reaction with alkenes seems to involve dichlorocarbene, however, since the pattern of reactivity toward different alkenes is identical to that observed for the free carbene in the gas phase.¹⁶⁰

¹⁵² J. Hine, *J. Am. Chem. Soc.*, **72**, 2438 (1950); J. Hine and A. M. Dowell, Jr., *J. Am. Chem. Soc.*, **76**, 2688 (1954).

¹⁵³ W. P. Weber and G. W. Gokel, *Phase Transfer Catalysis in Organic Synthesis*, Springer Verlag, New York, 1977, Chaps. 2–4.

¹⁵⁴ E. V. Dehmlow and J. Schoenfeld, *Liebigs Ann. Chem.*, **744**, 42 (1971).

¹⁵⁵ S. L. Regen and A. Singh, *J. Org. Chem.*, **47**, 1587 (1982).

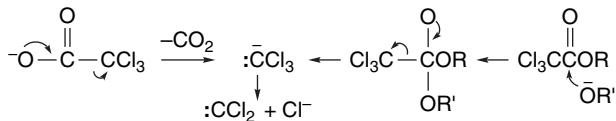
¹⁵⁶ G. Köbrich, H. Trapp, K. Flory, and W. Drischel, *Chem. Ber.*, **99**, 689 (1966); G. Köbrich and H. R. Merkle, *Chem. Ber.*, **99**, 1782 (1966).

¹⁵⁷ G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **82**, 5723 (1960).

¹⁵⁸ G. Köbrich, *Angew. Chem. Int. Ed. Engl.*, **6**, 41 (1967).

¹⁵⁹ W. T. Miller, Jr., and D. M. Whalen, *J. Am. Chem. Soc.*, **86**, 2089 (1964); D. F. Hoeg, D. I. Lusk, and A. L. Crumbliss, *J. Am. Chem. Soc.*, **87**, 4147 (1965).

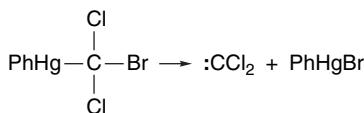
¹⁶⁰ P. S. Skell and M. S. Cholod, *J. Am. Chem. Soc.*, **91**, 6035, 7131 (1969); P. S. Skell and M. S. Cholod, *J. Am. Chem. Soc.*, **92**, 3522 (1970).



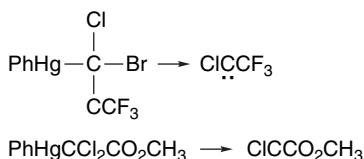
The applicability of these methods is restricted to polyhalogenated compounds, since the inductive effect of the halogen atoms is necessary for facilitating formation of the carbanion.

Hindered lithium dialkylamides can generate aryl-substituted carbenes from benzyl halides.¹⁶² Reaction of α,α -dichlorotoluene or α,α -dibromotoluene with potassium *t*-butoxide in the presence of 18-crown-6 generates the corresponding α -halophenylcarbene.¹⁶³ The relative reactivity data for carbenes generated under these latter conditions suggest that they are “free.” The potassium cation would be expected to be strongly solvated by the crown ether and it is evidently not involved in the carbene-generating step.

10.2.2.5. Carbenes from Organomercury Compounds. The α -elimination mechanism is also the basis for the use of organomercury compounds for carbene generation (Scheme 10.8 , Entry 5). The carbon–mercury bond is much more covalent than the C–Li bond, however, so the mercury reagents are generally stable at room temperature and can be isolated. They decompose to the carbene on heating.¹⁶⁴ Addition reactions occur in the presence of alkenes. The decomposition rate is not greatly influenced by the alkene. This observation implies that the rate-determining step is generation of the carbene from the organomercury precursor.¹⁶⁵



A variety of organomercury compounds that can serve as precursors of substituted carbenes have been synthesized. For example, carbenes with carbomethoxy or trifluoromethyl substituents can be generated in this way.¹⁶⁶



¹⁶¹. W. E. Parham and E. E. Schweizer, *Org. React.*, **13**, 55 (1963).

¹⁶². R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.*, **95**, 581 (1973).

¹⁶³. R. A. Moss and F. G. Pilkiewicz, *J. Am. Chem. Soc.*, **96**, 5632 (1974).

¹⁶⁴. D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J. H. Treiber, and S. R. Dowd, *J. Am. Chem. Soc.*, **87**, 4259 (1965).

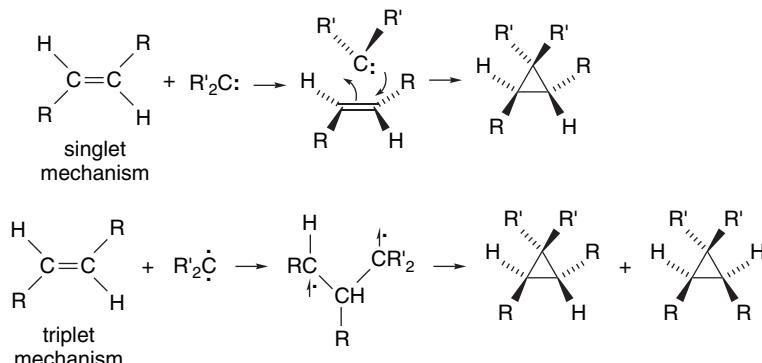
¹⁶⁵. D. Seyferth, J. Y.-P. Mui, and J. M. Burlitch, *J. Am. Chem. Soc.*, **89**, 4953 (1967).

¹⁶⁶. D. Seyferth, D. C. Mueller, and R. L. Lambert, Jr., *J. Am. Chem. Soc.*, **91**, 1562 (1969).

The addition reaction of alkenes and phenylmercuric bromide typically occurs at about 80°C. Phenylmercuric iodides are somewhat more reactive and may be advantageous in reactions with relatively unstable alkenes.¹⁶⁷

10.2.3. Addition Reactions

Addition reactions with alkenes to form cyclopropanes are the most studied reactions of carbenes, both from the point of view of understanding mechanisms and for synthetic applications. A concerted mechanism is possible for singlet carbenes. As a result, the stereochemistry present in the alkene is retained in the cyclopropane. With triplet carbenes, an intermediate 1,3-diradical is involved. Closure to cyclopropane requires spin inversion. The rate of spin inversion is slow relative to rotation about single bonds, so mixtures of the two possible stereoisomers are obtained from either alkene stereoisomer.



Reactions involving free carbenes are very exothermic since two new σ bonds are formed and only the alkene π bond is broken. The reactions are very fast and, in fact, theoretical treatment of the addition of singlet methylene to ethylene suggests that there is no activation barrier.¹⁶⁸ The addition of carbenes to alkenes is an important method for synthesis of many types of cyclopropanes and several of the methods for carbene generation listed in Scheme 10.8 have been adapted for use in synthesis. Scheme 10.9, at the end of this section, gives a number of specific examples.

10.2.3.1. Cyclopropanation with Halomethylzinc Reagents. A very effective means for conversion of alkenes to cyclopropanes by transfer of a CH_2 unit involves reaction with methylene iodide and a zinc-copper couple, referred to as the *Simmons-Smith reagent*.¹⁶⁹ The reactive species is iodomethylzinc iodide.¹⁷⁰ The transfer of methylene occurs stereospecifically. Free $:\text{CH}_2$ is not an intermediate. Entries 1 to 3 in Scheme 10.9 are typical examples.

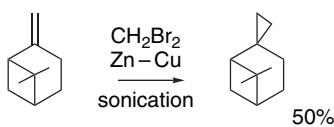
¹⁶⁷ D. Seyferth and C. K. Haas, *J. Org. Chem.*, **40**, 1620 (1975).

¹⁶⁸ B. Zurawski and W. Kutzelnigg, *J. Am. Chem. Soc.*, **100**, 2654 (1978).

¹⁶⁹ H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **80**, 5323 (1958); H. E. Simmons and R. D. Smith, **81**, 4256 (1959); H. E. Simmons, T. L. Cairns, S. A. Vladuchick, and C. M. Hoiness, *Org. React.*, **20**, 1 (1973); W. B. Motherwell and C. J. Nutley, *Contemporary Org. Synth.*, **1**, 219 (1994); A. B. Charette and A. Beauchemin, *Org. React.*, **58**, 1 (2001).

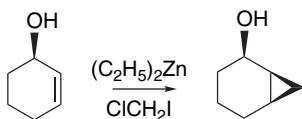
¹⁷⁰ A. B. Charette and J.-F. Marcoux, *J. Am. Chem. Soc.*, **118**, 4539 (1996).

A modified version of the Simmons-Smith reaction uses dibromomethane and in situ generation of the Cu-Zn couple.¹⁷¹ Sonication is used in this procedure to promote reaction at the metal surface.



Ref. 172

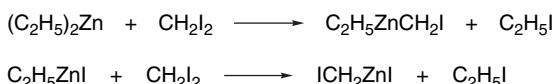
Another useful reagent combination involves diethylzinc and diiodomethane or chloroiodomethane.



Ref. 173

Several modifications of the Simmons-Smith procedure have been developed in which an electrophile or Lewis acid is included. Inclusion of acetyl chloride accelerates the reaction and permits the use of dibromomethane.¹⁷⁴ Titanium tetrachloride has similar effects in the reactions of unfunctionalized alkenes.¹⁷⁵ Reactivity can be enhanced by inclusion of a small amount of trimethylsilyl chloride.¹⁷⁶ The Simmons-Smith reaction has also been found to be sensitive to the purity of the zinc used. Electrolytically prepared zinc is much more reactive than zinc prepared by metallurgic smelting, and this has been traced to small amounts of lead in the latter material.

The nature of reagents prepared under different conditions has been explored both structurally and spectroscopically.¹⁷⁷ $\text{C}_2\text{H}_5\text{ZnCH}_2\text{I}$, $\text{Zn}(\text{CH}_2\text{I})_2$, and ICH_2ZnI are all active methylene transfer reagents.



A crystal structure has been obtained for $\text{Zn}(\text{CH}_2\text{I})_2$ complexed with *exo,exo*-2,3-dimethoxybornane and is shown in Figure 10.4.

Computational studies were done on several ClZnCH_2Cl models, and the results are summarized in Figure 10.5.¹⁷⁸ A minimal TS consisting of ClZnCH_2Cl and ethene shows charge transfer mainly to the departing Cl; that is, the ethene displaces chloride in the zinc coordination sphere. The model can be elaborated by inclusion of ZnCl_2 ,

¹⁷¹ E. C. Friedrich, J. M. Demek, and R. Y. Pong, *J. Org. Chem.*, **50**, 4640 (1985).

¹⁷² S. Sawada and Y. Inouye, *Bull. Chem. Soc. Jpn.*, **42**, 2669 (1969); N. Kawabata, T. Nakagawa, T. Nakao, and S. Yamashita, *J. Org. Chem.*, **42**, 3031 (1977); J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968).

¹⁷³ J. Furukawa, N. Kawabata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968); S. Miyano and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **46**, 892 (1973); S. E. Denmark and J. P. Edwards, *J. Org. Chem.*, **56**, 6974 (1991).

¹⁷⁴ E. C. Friedrich and E. J. Lewis, *J. Org. Chem.*, **55**, 2491 (1990).

¹⁷⁵ E. C. Friedrich, S. E. Lunetta, and E. J. Lewis, *J. Org. Chem.*, **54**, 2388 (1989).

¹⁷⁶ K. Takai, T. Kakikuchi, and K. Utimoto, *J. Org. Chem.*, **59**, 2671 (1994).

¹⁷⁷ S. E. Denmark, J. P. Edwards, and S. R. Wilson, *J. Am. Chem. Soc.*, **114**, 2592 (1992); A. B. Charette and J.-F. Marcoux, *J. Am. Chem. Soc.*, **118**, 4539 (1996).

¹⁷⁸ M. Nakamura, A. Hirai, and E. Nakamura, *J. Am. Chem. Soc.*, **125**, 2341 (2003).

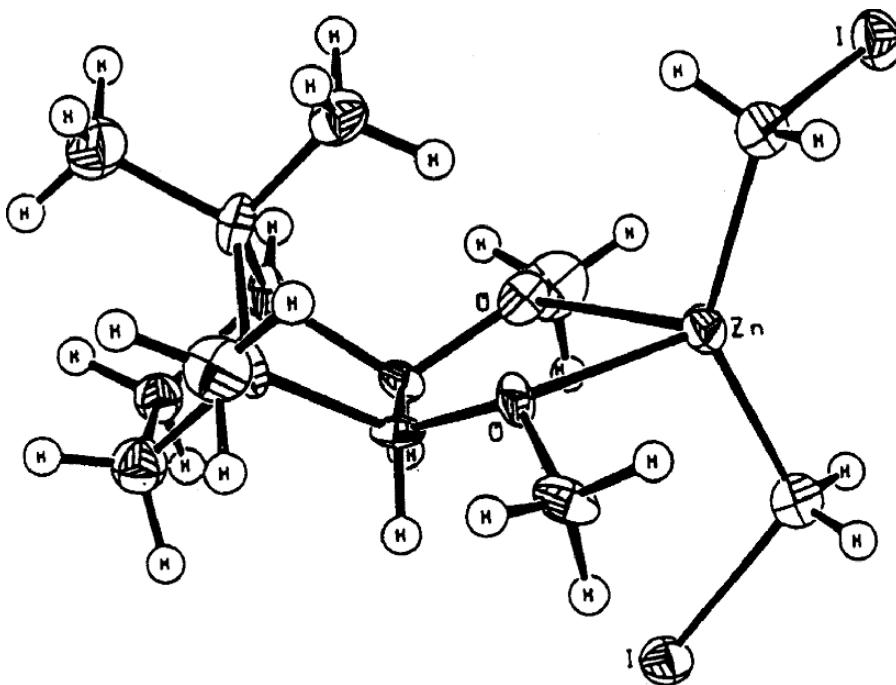


Fig. 10.4. Crystal structure of one molecule of $\text{Zn}(\text{CH}_2)_2$ complexed with *exo,exo*-2,3-dimethoxybornane. Reproduced from *J. Am. Chem. Soc.*, **114**, 2592 (1992), by permission of the American Chemical Society.

which is present under most experimental conditions and can have an accelerating effect. Models were also calculated for the directing and activating effect of allylic hydroxy groups. Definitive results were not obtained for this case, but an aggregated structure with the oxygen coordinated to zinc is plausible.

Other reagents have been developed in which one of the zinc ligands is an oxy anion. Compounds with trifluoroacetate anions are prepared by protonolysis of C_2H_5 or CH_2I groups on zinc.¹⁷⁹

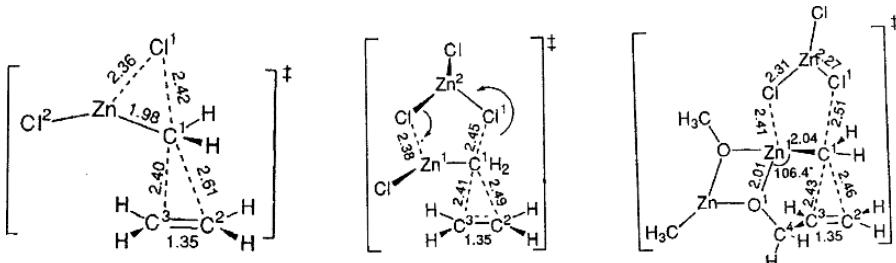


Fig. 10.5. Transition structures for CH_2 transfer from $\text{ClCH}_2\text{ZnCl}_2$ and $\text{ClZnCH}_2\text{Cl-ZnCl}_2$ to ethene and to coordinated allyl alcohol. Reproduced from *J. Am. Chem. Soc.*, **125**, 2341 (2003), by permission of the American Chemical Society.

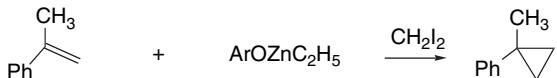
¹⁷⁹ J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie, and Y. Shi, *J. Org. Chem.*, **69**, 327 (2004).



Iodomethylzinc phenoxides can be prepared in a similar fashion. The best phenols are the 2,4,6-trihalophenols and the readily available 2,4,6-trichlorophenol was examined most thoroughly.¹⁸⁰

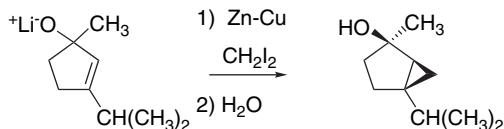


This reagent can achieve better than 90% yields for a variety of unactivated alkenes.

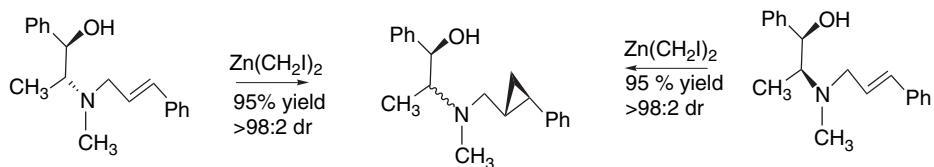


The reactivity of the oxy anions is in the order $\text{CF}_3\text{CO}_2^- > \text{ArO}^- >> \text{RO}^-$.

In molecules containing hydroxy groups, the CH_2 unit is selectively introduced on the side of the double bond *syn* to the hydroxy group in the Simmons-Smith reaction and related cyclopropanations. This indicates that the reagent is complexed to the hydroxy group and that the complexation facilitates the addition. Entries 3 and 4 in Scheme 10.9 illustrate the stereodirective effect of the hydroxy group. It is evidently the Lewis base character of the group that is important, in contrast to the hydrogen bonding that is involved in epoxidation. The lithium salts of allylic alcohols are also strongly activated, even more so than the alcohols. This reactivity has been used to advantage in the preparation of relatively unstable products.¹⁸¹



While amino groups alone are not effective directing groups, both ephedrine and pseudoephedrine derivatives give high diastereoselectivity. This is evidently due to chelation by the hydroxy group, as both auxiliaries give the same facial selectivity despite differing in configuration at the nitrogen position.¹⁸²



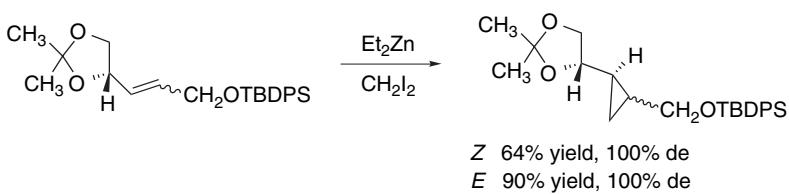
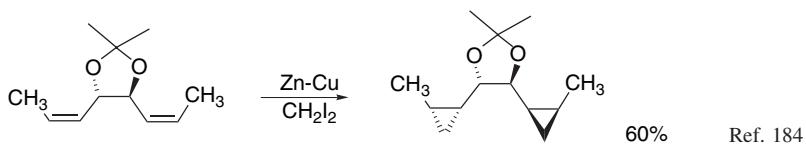
Dioxolanyl oxygens are also effective directing groups.¹⁸³

^{180.} A. B. Charette, S. Francouer, J. Martel, and N. Wilb, *Angew. Chem. Int. Ed. Engl.*, **39**, 4539 (2000).

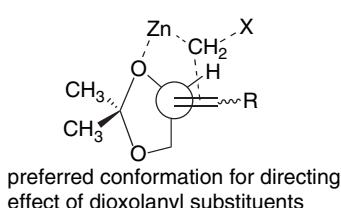
^{181.} D. Chang, T. Kreethadumrongdat, and T. Cohen, *Org. Lett.*, **3**, 2121 (2001).

^{182.} V. K. Aggarwal, G. Y. Fang, and G. Meek, *Org. Lett.*, **5**, 4417 (2003).

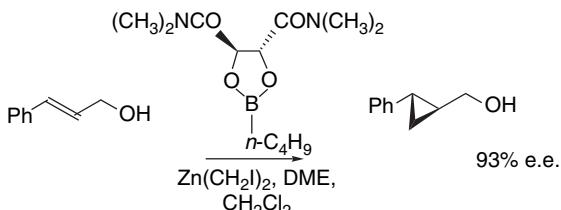
^{183.} A. G. M. Barrett, K. Kasdorf, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1781 (1994).



The stereoselectivity is accounted for by a TS in which the allylic oxygen is coordinated to the zinc.



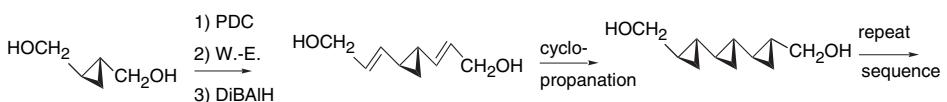
The directive effect of allylic hydroxy groups can be used in conjunction with chiral catalysts to achieve enantioselective cyclopropanation. The chiral ligand used is a boronate ester derived from the *N,N,N',N'*-tetramethyl amide of tartaric acid.¹⁸⁶ Similar results are obtained using the potassium alkoxide, again indicating the Lewis base character of the directive effect.



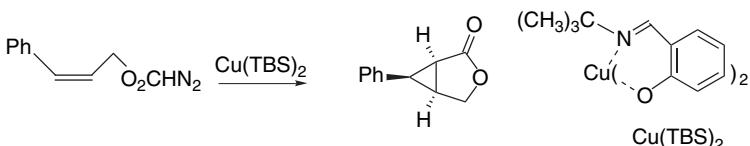
These conditions were used to make natural products containing several successive cyclopropane rings.¹⁸⁷



- ¹⁸⁴. T. Onoda, R. Shirai, Y. Koiso, and S. Iwasaki, *Tetrahedron Lett.*, **37**, 4397 (1996).
- ¹⁸⁵. T. Morikawa, H. Sasaki, R. Hanai, A. Shibuya, and T. Taguchi, *J. Org. Chem.*, **59**, 97 (1994).
- ¹⁸⁶. A. B. Charette and H. Juteau, *J. Am. Chem. Soc.*, **116**, 2651 (1994); A. B. Charette, S. Prescott, and C. Brochu, *J. Org. Chem.*, **60**, 1081 (1995).
- ¹⁸⁷. A. B. Charette and H. Lebel, *J. Am. Chem. Soc.*, **118**, 10327 (1996).

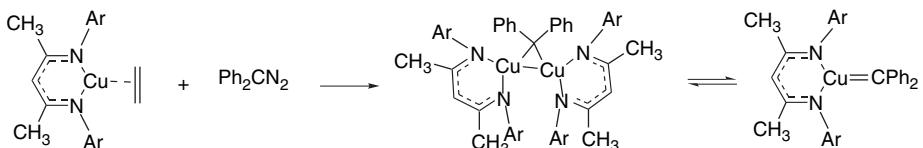


10.2.3.2. Metal-Catalyzed Cyclopropanation. Carbene addition reactions can be catalyzed by several transition metal complexes. Most of the synthetic work has been done using copper or rhodium complexes and we focus on these. The copper-catalyzed decomposition of diazo compounds is a useful reaction for formation of substituted cyclopropanes.¹⁸⁸ The reaction has been carried out with several copper salts,¹⁸⁹ and both Cu(I) and Cu(II) triflate are useful.¹⁹⁰ Several Cu(II)salen complexes, such as the *N-t*-butyl derivative, which is called Cu(TBS)₂, have become popular catalysts.¹⁹¹



Ref. 192

An NMR and structural study characterized the intermediates generated from diimine catalysts on reaction with diazodiphenylmethane.¹⁹³ The dominant species in solution is dinuclear, but a monomeric metallocarbene species can be detected.



The monomeric species can be isolated as a solid in the case of the *N,N'*-dimesityl derivative. The crystal structures of both dimeric and monomeric structures are shown in Figure 10.6.

¹⁸⁸ W. Kirmse, *Angew. Chem. Int. Ed. Engl.*, **42**, 1088 (2003).

¹⁸⁹ W. von E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963); J. P. Chesick, *J. Am. Chem. Soc.*, **84**, 3250 (1962); H. Nozaki, H. Takaya, S. Moriuti, and R. Noyori, *Tetrahedron*, **24**, 3655 (1968); R. G. Salomon and J. K. Kochi, *J. Am. Chem. Soc.*, **95**, 3300 (1973); M. E. Alonso, P. Jano, and M. I. Hernandez, *J. Org. Chem.*, **45**, 5299 (1980); T. Hudlicky, F. J. Koszyk, T. M. Kutchan, and J. P. Sheth, *J. Org. Chem.*, **45**, 5020 (1980); M. P. Doyle and M. L. Truell, *J. Org. Chem.*, **49**, 1196 (1984); E. Y. Chen, *J. Org. Chem.*, **49**, 3245 (1984).

¹⁹⁰ R. T. Lewis and W. B. Motherwell, *Tetrahedron Lett.*, **29**, 5033 (1988).

¹⁹¹ E. J. Corey and A. G. Myers, *Tetrahedron Lett.*, **25**, 3559 (1984); J. D. Winkler and E. Gretler, *Tetrahedron Lett.*, **32**, 5733 (1991).

¹⁹² S. F. Martin, R. E. Austin, and C. J. Oalmann, *Tetrahedron Lett.*, **31**, 4731 (1990).

¹⁹³ X. Dai and T. H. Warren, *J. Am. Chem. Soc.*, **126**, 10085 (2004).

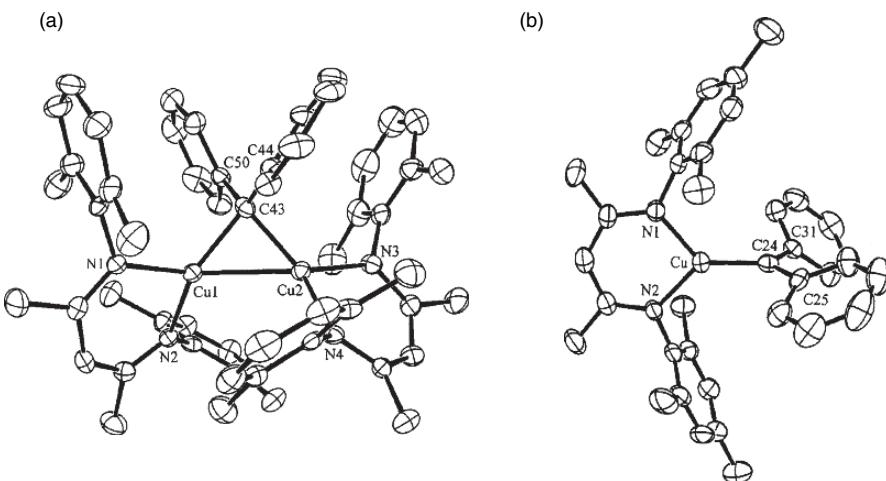
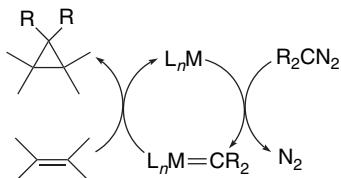


Fig. 10.6. Dimeric ($\text{Ar} = 2,6\text{-dimethylphenyl}$) (a) and monomeric ($\text{Ar} = 2,4,6\text{-trimethylphenyl}$) (b) copper complexes with diphenylcarbene. Reproduced from *J. Am. Chem. Soc.*, **126**, 10085 (2004), by permission of the American Chemical Society.

There has also been computational investigation of copper-catalyzed carbenoid addition reactions, as shown in Figure 10.7.¹⁹⁴ These computational studies agree with experimental investigations in identifying nitrogen extrusion as the rate-determining step. The addition step is a direct carbene transfer, as opposed to involving a metallo-cyclobutane intermediate.

Various other transition metal complexes are also useful, including rhodium,¹⁹⁵ palladium,¹⁹⁶ and molybdenum¹⁹⁷ compounds. The catalytic cycle can generally be represented as shown below.¹⁹⁸



- ¹⁹⁴. J. M. Fraile, J. I. Garcia, V. Martinez-Merino, J. A. Mayoral, and L. Salvatella, *J. Am. Chem. Soc.*, **123**, 7616 (2001); T. Rasmussen, J. F. Jensen, N. Ostergaard, D. Tanner, T. Ziegler, and P.-O. Norrby, *Chem. Eur. J.*, **8**, 177 (2002).
- ¹⁹⁵. S. Bien and Y. Segal, *J. Org. Chem.*, **42**, 1685 (1977); A. J. Anciaux, A. J. Hubert, A. F. Noels, N. Petiniot, and P. Teyssie, *J. Org. Chem.*, **45**, 695 (1980); M. P. Doyle, W. H. Tamblyn, and V. Baghari, *J. Org. Chem.*, **46**, 5094 (1981); D. F. Taber and R. E. Ruckle, Jr., *J. Am. Chem. Soc.*, **108**, 7686 (1986).
- ¹⁹⁶. R. Paulissen, A. J. Hubert, and P. Teyssie, *Tetrahedron Lett.*, 1465 (1972); U. Mende, B. Raduchel, W. Skuballa, and H. Vorbruggen, *Tetrahedron Lett.*, 629 (1975); M. Suda, *Synthesis*, 714 (1981); M. P. Doyle, L. C. Wang, and K.-L. Loh, *Tetrahedron Lett.*, **25**, 4087 (1984); L. Strekowski, M. Visnick, and M. A. Battiste, *J. Org. Chem.*, **51**, 4836 (1986).
- ¹⁹⁷. M. P. Doyle and J. G. Davidson, *J. Org. Chem.*, **45**, 1538 (1980); M. P. Doyle, R. L. Dorow, W. E. Buhro, J. H. Tamblyn, and M. L. Trudell, *Organometallics*, **3**, 44 (1984).
- ¹⁹⁸. M. P. Doyle, *Chem. Rev.*, **86**, 919 (1986).

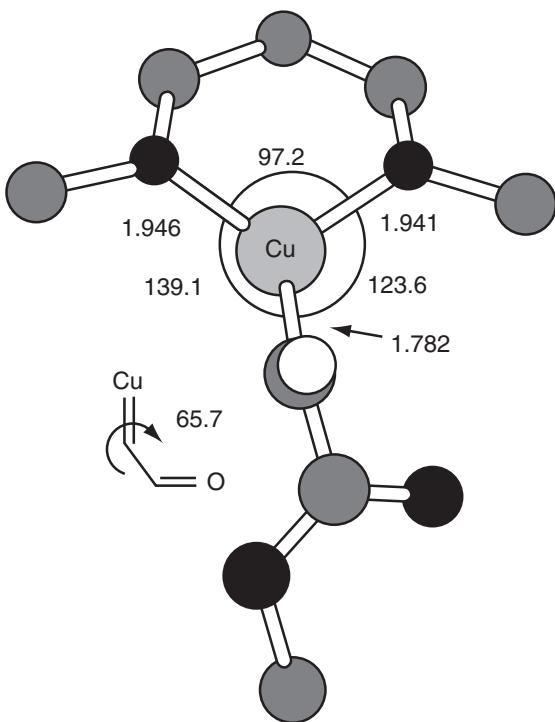
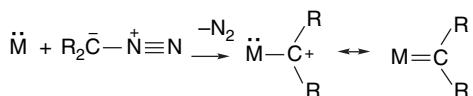
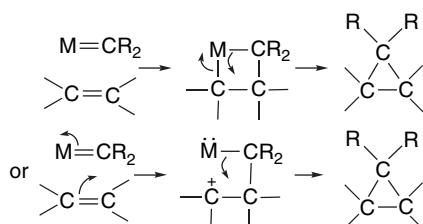


Fig. 10.7. Computational (B3LYP/6-31G(d)) minimum-energy structure of carbomethoxycarbene derivative of copper *N,N'*-dimethylpropane-1,3-diimine. Reproduced from *J. Am. Chem. Soc.*, **123**, 7616 (2001), by permission of the American Chemical Society.

The metal–carbene complexes are electrophilic in character. They can, in fact, be represented as metal-stabilized carbocations.

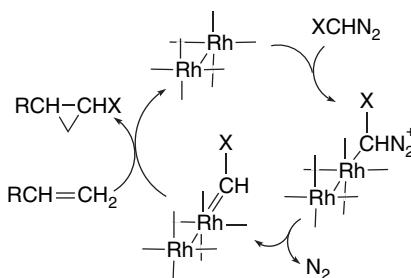


In most transition metal–catalyzed reactions, one of the carbene substituents is a carbonyl group, which further enhances the electrophilicity of the intermediate. There are two general mechanisms that can be considered for cyclopropane formation. One involves formation of a four-membered ring intermediate that incorporates the metal. The alternative represents an electrophilic attack giving a polar species that undergoes 1,3-bond formation.

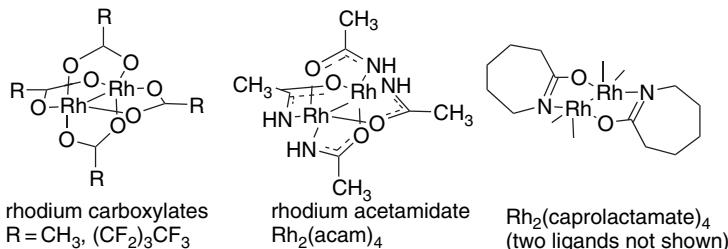


Since the additions are normally stereospecific with respect to the alkene, if an open-chain intermediate is involved it must collapse to product more rapidly than single-bond rotations that would destroy the stereoselectivity.

In recent years, much attention has been focused on rhodium-mediated carbenoid reactions. One goal has been to understand how the rhodium ligands control reactivity and selectivity, especially in cases in which both addition and insertion reactions are possible. These catalysts contain Rh–Rh bonds but function by mechanisms similar to other transition metal catalysts.

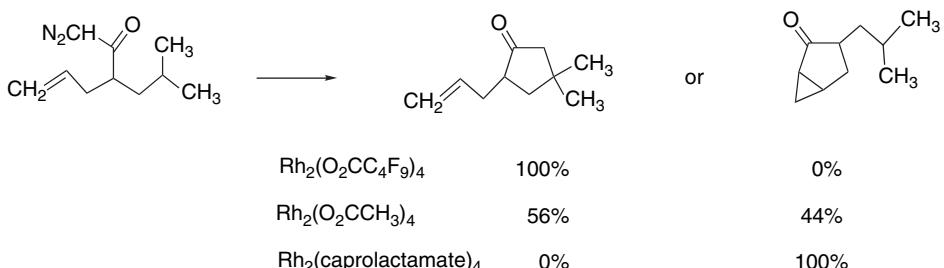


The original catalyst was $\text{Rh}_2(\text{O}_2\text{CCH}_3)_4$, but other carboxylates such as nonafluorobutanoate and amide anions, such as those from acetamide and caprolactam, also have good catalytic activity.¹⁹⁹



The ligands adjust the electrophilicity of the catalyst with the nonafluorobutanoate being more electrophilic and the amido ligands less electrophilic than the acetate. These catalysts show differing reactivity. For example, $\text{Rh}_2(\text{O}_2\text{C}_4\text{F}_9)_4$ was found to favor aromatic substitution over cyclopropanation, whereas $\text{Rh}_2(\text{caprolactamate})_4$ was selective for cyclopropanation.²⁰⁰ In competition between tertiary alkyl insertion versus cyclopropanation, the order in favor of cyclopropanation is also $\text{Rh}_2(\text{caprolactamate})_4 > \text{Rh}_2(\text{O}_2\text{CCH}_3)_4 > \text{Rh}_2(\text{O}_2\text{CC}_4\text{F}_9)_4$. These predictable selectivity patterns have made the rhodium catalysts useful in a number of synthetic applications.²⁰¹ For example, $\text{Rh}_2(\text{O}_2\text{C}_4\text{F}_9)_4$ gave exclusively insertion, whereas $\text{Rh}_2(\text{caprolactamate})_4$ gave exclusively cyclopropanation. $\text{Rh}_2(\text{O}_2\text{CCH}_3)_4$ gave a mixture of the two products.²⁰²

- ¹⁹⁹. M. P. Doyle, V. Bagheri, T. J. Wandless, N. K. Harn, D. B. Brinker, C. T. Eagle, and K.-L. Loh, *J. Am. Chem. Soc.*, **112**, 1906 (1990).
- ²⁰⁰. A. Padwa, D. J. Austin, A. T. Price, M. A. Semones, M. P. Doyle, M. N. Protopova, W. R. Winchester, and A. Tran, *J. Am. Chem. Soc.*, **115**, 8669 (1993).
- ²⁰¹. M. P. Doyle and D. Forbes, *Chem. Rev.*, **98**, 911 (1998); C. A. Merlic and A. L. Zechman, *Synthesis*, 1137 (2003).
- ²⁰². A. Padwa, D. J. Austin, S. F. Hornbuckle, and M. A. Semones, *J. Am. Chem. Soc.*, **114**, 1874 (1992).



Mechanistic and computational studies have elucidated some of the key details of the reactions. A kinetic study of $\text{Rh}_2[\text{O}_2\text{CC}(\text{CH}_3)_3]_4$ involving several different reaction types established that the rate-determining step in the rhodium-catalyzed reactions is loss of nitrogen.²⁰³ The basic mechanism and reaction energy profile are given in Figure 10.8. In addition, certain reactants and solvents were shown to have an inhibitory effect by competing with the diazo compound for coordination at the rhodium center. For example, anisole has such an effect.

Another study combined measurement of kinetic isotope effects with computational modeling of the TS.²⁰⁴ The computed energy profile suggests that there is no barrier for the reaction of styrene with the carbene complex from methyl diazoacetate. In contrast, a barrier of about 12 kcal/mol is found for methyl 2-diazobut-3-enoate. This is consistent with experimental work showing that alkenyl and aryl-substituted diazo esters have greater selectivity. Figure 10.9 shows the computed TS for the reaction of the phenyl-substituted ester with styrene. The addition is highly asynchronous and has an early TS. The kinetic isotope effects calculated for this model are in excellent agreement with the experimental values.

This study also gives a good account of the stereoselectivity of the 2-diazobut-3-enoate addition reaction with styrene. There is a preference for the ester group

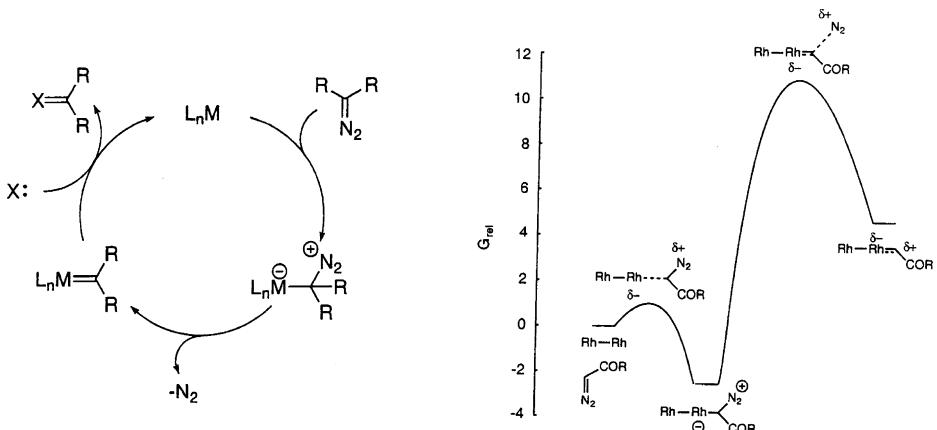


Fig. 10.8. Basic catalytic cycle and energy profile for rhodium-catalyzed carbenoid reactions. Reproduced from *J. Am. Chem. Soc.*, **124**, 1014 (2002), by permission of the American Chemical Society.

²⁰³. M. C. Pirrung, H. Liu, and A. T. Morehead, Jr., *J. Am. Chem. Soc.*, **124**, 1014 (2002).

²⁰⁴. D. T. Nowlan, III, T. M. Gregg, H. M. L. Davies, and D. A. Singleton, *J. Am. Chem. Soc.*, **125**, 15902 (2003).

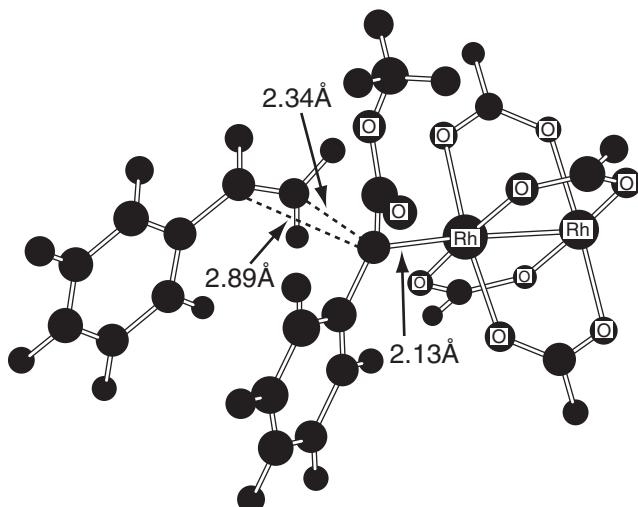
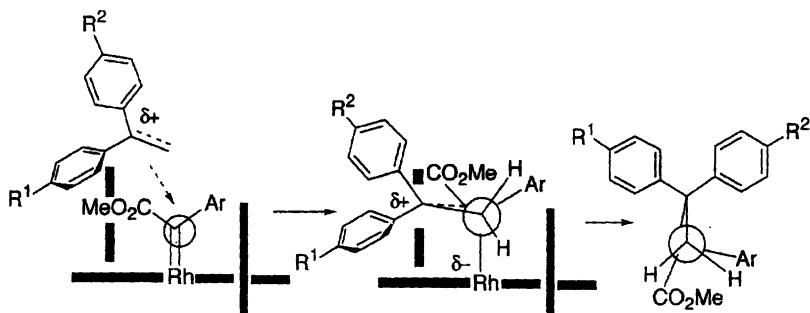


Fig. 10.9. Computed transition structure for addition of methyl phenyl-diazoacetate to styrene from B3LYP/6-31G*/LANL2DZ computations. Reproduced from *J. Am. Chem. Soc.*, **125**, 15902 (2003), by permission of the American Chemical Society.

to be *trans* to the phenyl group. The calculated difference between the two TSs is 1.7 kcal/mol. The main difference is the closer approach of the phenyl group to the ester oxygen in the disfavored TS. Steric interactions with the ester group also explain why *trans*-disubstituted alkenes are unreactive with this catalyst, whereas *cis*-alkenes are reactive (see Figure 10.10). We will see shortly that the same TS feature can account for the enantioselectivity of chiral rhodium catalysts.

As would be expected for a highly electrophilic species, rhodium-catalyzed carbenoid additions are accelerated by aryl substituents, as well as by other cation-stabilizing groups on the alkene reactant.²⁰⁵ When applied to 1,1-diarylethenes, ERG substituents favor the position *trans* to the ester group.²⁰⁶ This can be understood in terms of maximizing the interaction between this ring and the reacting double bond.



²⁰⁵ H. M. L. Davies and S. A. Panaro, *Tetrahedron*, **56**, 4871 (2000).

²⁰⁶ H. M. L. Davies, T. Nagashima, and J. L. Klino, III, *Org. Lett.*, **2**, 823 (2000).

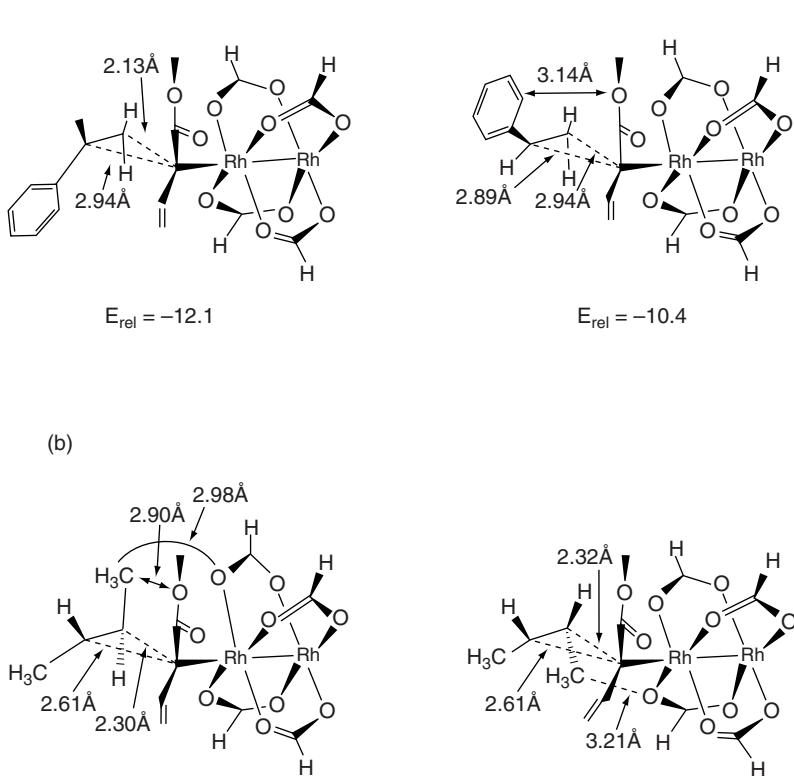


Fig. 10.10. Steric interactions in rhodium-catalyzed addition of methyl 2-diazobut-3-enoate to styrene (a) and *cis* and *trans* butene (b). Reproduced from *J. Am. Chem. Soc.*, **125**, 15902 (2003), by permission of the American Chemical Society.

10.2.3.3. Other Cyclopropanation Methods. Haloalkylmercury compounds are also useful in synthesis. The addition reactions are usually carried out by heating the organomercury compound with the alkene. Two typical examples are given in Section C of Scheme 10.9.

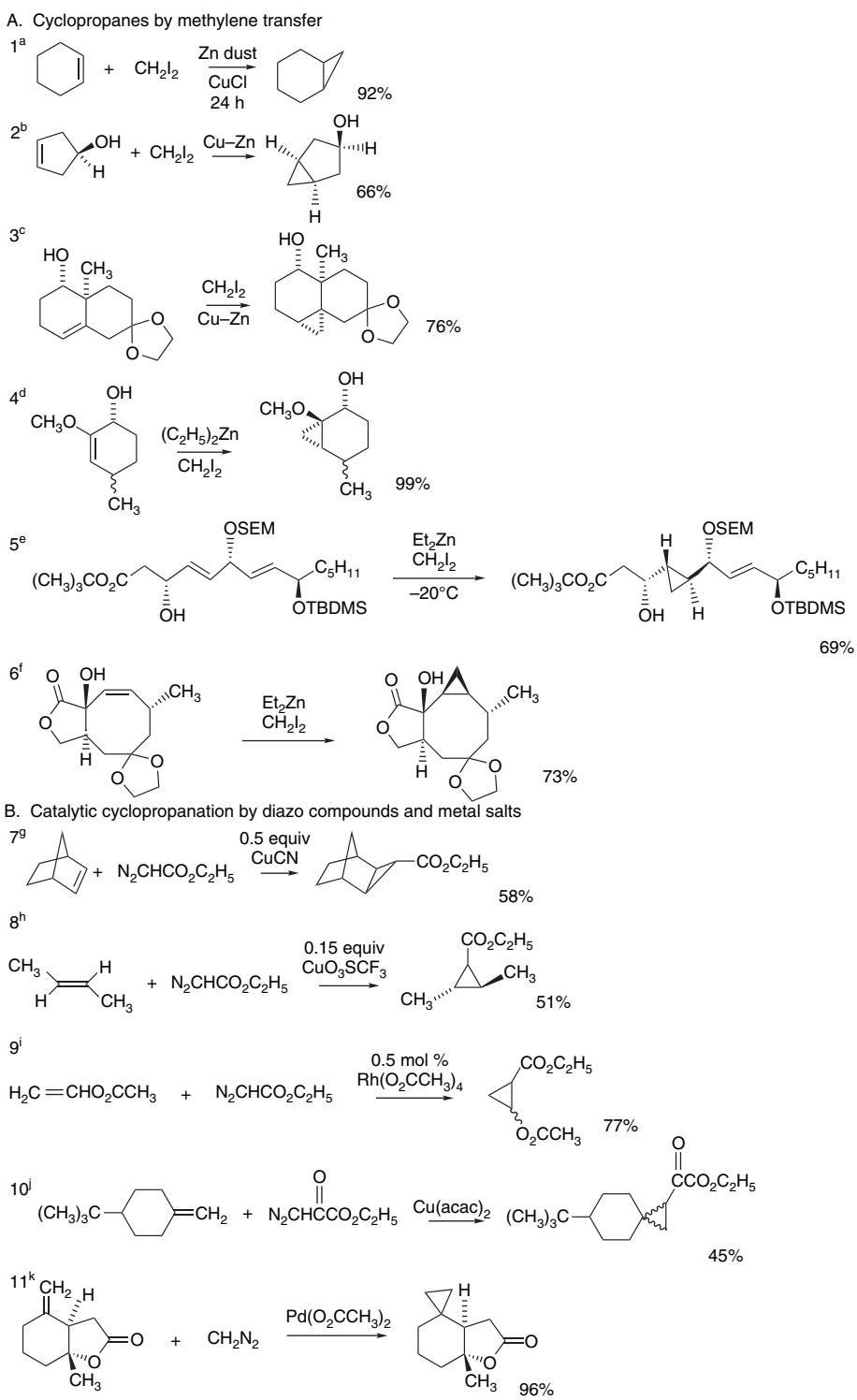
The addition of dichlorocarbene, generated from chloroform, to alkenes gives dichlorocyclopropanes. The procedures based on lithiated halogen compounds have been less generally used in synthesis. Section D of Scheme 10.9 gives a few examples of addition reactions of carbenes generated by α -elimination.

10.2.3.4. Examples of Cyclopropanations. Scheme 10.9 illustrates some of these cyclopropanation methods. Section A pertains to the Simmons-Smith type of cyclopropanation. Entry 1 is an example using readily available sources of the cyclopropanation reagent. Only a modest excess of the reagents was needed, and good yields were obtained from several unfunctionalized cycloalkenes under these conditions. Entry 2 is a case of an allylic alcohol and illustrates the hydroxy-directing effect. Entries 3 to 6 are also examples of the directive effect of hydroxy groups in ring systems. Entry 4 was done using the diethylzinc-diiodomethane conditions. The vinyl ether group is expected to be quite reactive because of the electrophilic character of the methylene transfer reaction. Entry 5 illustrates the application of the hydroxy-directing

Scheme 10.9. Cyclopropane Formation by Carbenoid Addition

CHAPTER 10

Reactions Involving
Carbocations, Carbenes,
and Radicals as Reactive
Intermediates



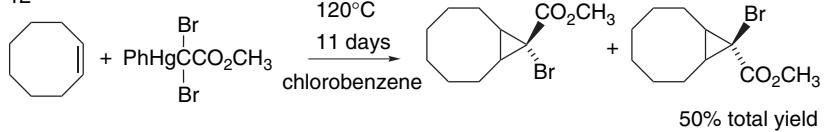
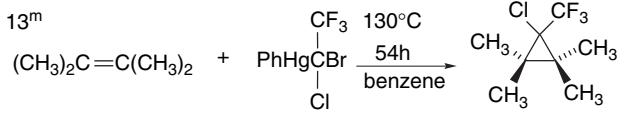
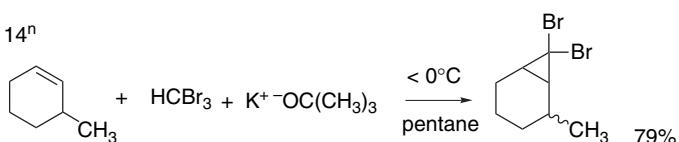
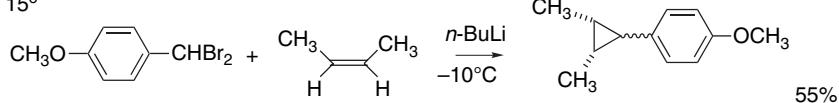
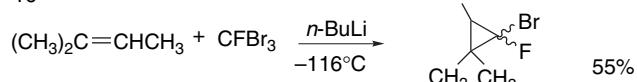
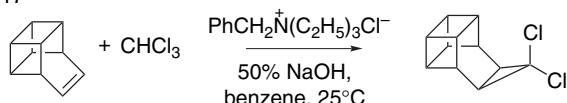
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Scheme 10.9. (Continued)

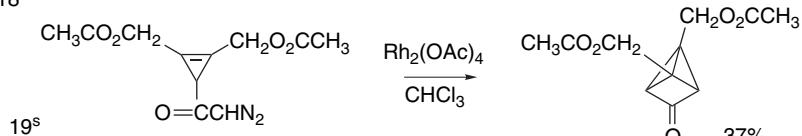
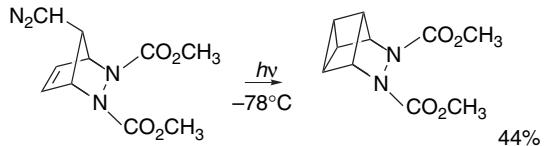
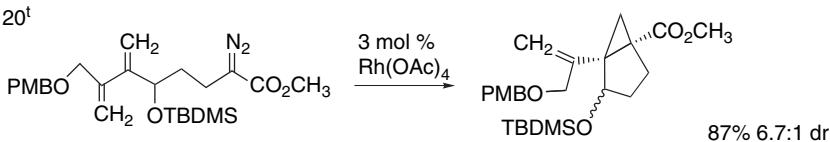
SECTION 10.2

Reactions Involving
Carbenes and Related
Intermediates

C. Cyclopropane formation using haloalkylmercurials

12^l13^mD. Reactions of carbenes generated by α -elimination14ⁿ15^o16^p17^q

E. Intramolecular cyclopropanation reactions

18^r19^s20^t

(Continued)

Scheme 10.9. (Continued)

CHAPTER 10

Reactions Involving
Carbocations, Carbenes,
and Radicals as Reactive
Intermediates

- a. R. J. Rawson and I. T. Harrison, *J. Org. Chem.*, **35**, 2057 (1970).
- b. S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **83**, 3235 (1961).
- c. P. A. Grieco, T. Oguir, C.-L. J. Wang, and E. Williams, *J. Org. Chem.*, **42**, 4113 (1977).
- d. R. C. Gadwood, R. M. Lett, and J. E. Wissinger, *J. Am. Chem. Soc.*, **108**, 6343 (1986).
- e. Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, T. Ibuka, H. Ohishi, and Y. Takemoto, *J. Org. Chem.*, **66**, 81 (2001).
- f. L. A. Paquette, J. Ezquerra, and W. He, *J. Org. Chem.*, **60**, 1435 (1995).
- g. R. R. Sauers and P. E. Sonnent, *Tetrahedron*, **20**, 1029 (1964).
- h. R. G. Salomon and J. K. Kochi, *J. Am. Chem. Soc.*, **95**, 3300 (1973).
- i. A. J. Anciaux, A. J. Hubert, A. F. Noels, N. Petinot, and P. Teyssie, *J. Org. Chem.*, **45**, 695 (1980).
- j. M. E. Alonso, P. Jano, and M. I. Hernandez, *J. Org. Chem.*, **45**, 5299 (1980).
- k. L. Stekowski, M. Visnick, and M. A. Battiste, *J. Org. Chem.*, **51**, 4836 (1986).
- l. D. Seyerth, D. C. Mueller, and R. L. Lambert, Jr., *J. Am. Chem. Soc.*, **91**, 1562 (1969).
- m. D. Seyerth and D. C. Mueller, *J. Am. Chem. Soc.*, **93**, 3714 (1971).
- n. L. A. Paquette, S. E. Wilson, R. P. Henzel, and G. R. Allen, Jr., *J. Am. Chem. Soc.*, **94**, 7761 (1972).
- o. G. L. Closs and R. A. Moss, *J. Am. Chem. Soc.*, **86**, 4042 (1964).
- p. D. J. Burton and J. L. Hahnfeld, *J. Org. Chem.*, **42**, 828 (1977).
- q. T. T. Sasaki, K. Kanematsu, and N. Okamura, *J. Org. Chem.*, **40**, 3322 (1975).
- r. P. Dowd, P. Garner, R. Schappert, H. Ingartiner, and A. Goldman, *J. Org. Chem.*, **47**, 4240 (1982).
- s. B. M. Trost, R. M. Cory, P. H. Scudder, and H. B. Neubold, *J. Am. Chem. Soc.*, **95**, 7813 (1973).
- t. K. C. Nicolaou, M. H. D. Postema, N. D. Miller, and G. Yang, *Angew. Chem. Int. Ed. Engl.*, **36**, 2821 (1997).

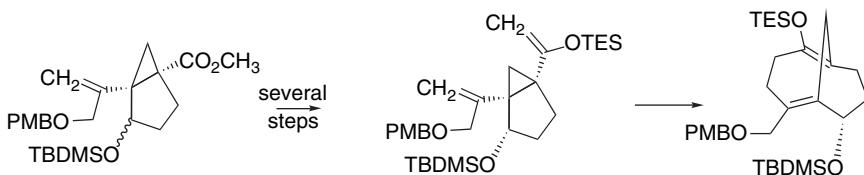
effect in an acyclic system. Not only is the hydroxy group stereodirective, but it also provides selectivity with respect to the two double bonds. The reaction in Entry 6 was carried out in the course of synthesis of crenulide derivatives, which are obtained from seaweed.

Section B gives some examples of metal-catalyzed cyclopropanations. In Entries 7 and 8, Cu(I) salts are used as catalysts for intermolecular cyclopropanation by ethyl diazoacetate. The *exo* approach to norbornene is anticipated on steric grounds. In both cases, the Cu(I) salts were used at a rather high ratio to the reactants. Entry 9 illustrates use of Rh₂(O₂CCH₃)₄ as the catalyst at a much lower ratio. Entry 10 involves ethyl diazopyruvate, with copper acetylacetone as the catalyst. The stereoselectivity of this reaction was not determined. Entry 11 shows that Pd(O₂CCH₃) is also an active catalyst for cyclopropanation by diazomethane.

Section C shows cases involving organomercury reagents, which are useful for introducing functionalized cyclopropane rings when the necessary reagents can be obtained as mercury compounds. The very vigorous conditions needed for these reactions indicate the relatively low reactivity of the organomercury compounds toward α -elimination.

Section D illustrates formation of carbenes from halides by α -elimination. The carbene precursors are formed either by deprotonation (Entries 14 and 17) or halogen-metal exchange (Entries 15 and 16). The carbene additions can take place at low temperature. Entry 17 is an example of generation of dichlorocarbene from chloroform under phase transfer conditions.

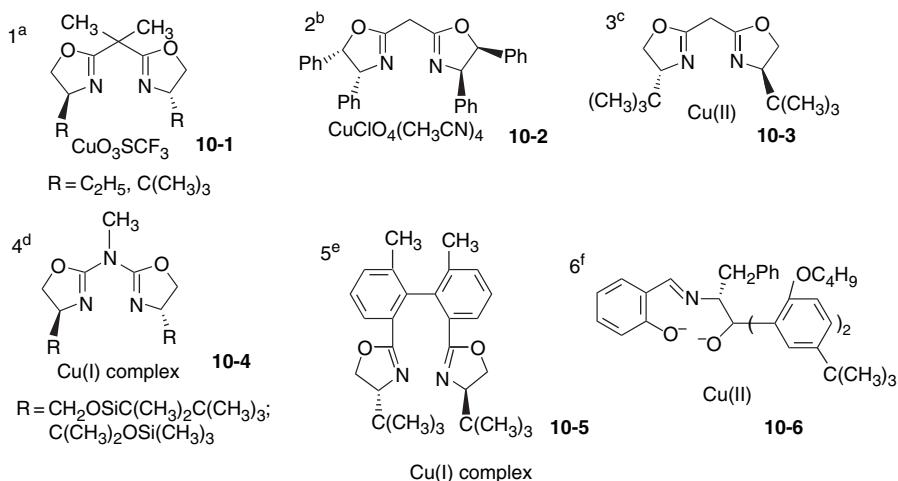
Intramolecular carbene addition reactions have a special importance in the synthesis of strained-ring compounds. Because of the high reactivity of carbene or carbenoid species, the formation of highly strained bonds is possible. The strategy for synthesis is to construct a potential carbene precursor, such as a diazo compound or di- or trihalo compound that can undergo intramolecular addition to give the desired structure. Section E of Scheme 10.9 gives some representative examples. Entries 18 and 19 are cases of formation of strained compounds. The reaction in Entry 20 shows a preference between the two double bonds, based on proximity, and establishes a ring system that subsequently undergoes a divinylcyclopropane rearrangement to generate a nine-membered ring.



10.2.3.5. Enantioselective Cyclopropanation. Enantioselective versions of both copper and rhodium cyclopropanation catalysts are available. The copper-imine class of catalysts is enantioselective when chiral imines are used. Some of the chiral ligands that have been utilized in conjunction with copper salts are shown in Scheme 10.10.

Several chiral ligands have been developed for use with the rhodium catalysts, among them are pyrrolidinones and imidazolidinones.²⁰⁷ For example, the lactamate of pyroglutamic acid gives enantioselective cyclopropanation reactions.

Scheme 10.10. Chiral Copper Catalysts Used in Enantioselective Cyclopropanation



a. D. A. Evans, K. A. Woerpel, M. M. Hinman, and M. M. Faul, *J. Am. Chem. Soc.*, **113**, 726 (1991); D. A. Evans, K. A. Woerpel, and M. I. Scott, *Angew. Chem. Int. Ed. Engl.*, **31**, 430 (1992).

b. R. E. Lowenthal and S. Masamune, *Tetrahedron Lett.*, **32**, 7373 (1991).

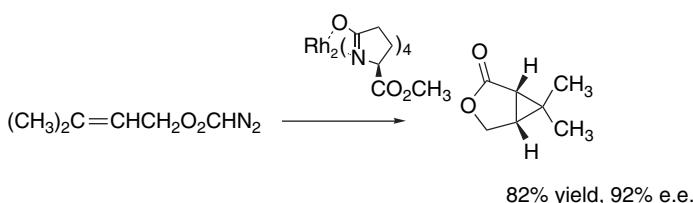
c. R. E. Lowenthal, A. Abiko, and S. Masamune, *Tetrahedron Lett.*, **31**, 6005 (1990).

d. A. Pfaltz, *Acc. Chem. Res.*, **26**, 339 (1993).

e. T. G. Gant, M. C. Noe, and E. J. Corey, *Tetrahedron Lett.*, **36**, 8745 (1995).

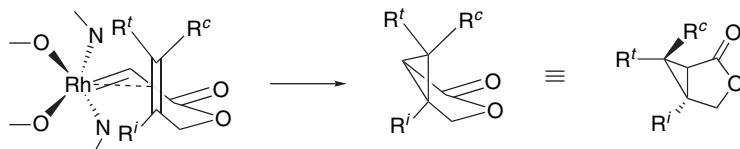
f. T. Aratani, Y. Yoneyoshi, and T. Nagase, *Tetrahedron Lett.*, **23**, 685 (1982).

²⁰⁷ M. P. Doyle, R. E. Austin, A. S. Bailey, M. P. Dwyer, A. B. Dyatkin, A. V. Kalinin, M. M.-Y. Kwan, S. Liras, C. J. Oalmann, R. J. Pieters, M. N. Protopopova, C. E. Raab, G. H. P. Roos, Q. L. Zhou, and S. F. Martin, *J. Am. Chem. Soc.*, **117**, 5763 (1995); M. P. Doyle, A. B. Dyatkin, M. N. Protopopova, C. I. Yang, G. S. Miertschin, W. R. Winchester, S. H. Simonsen, V. Lynch, and R. Ghosh, *Rec. Trav. Chim. Pays-Bas*, **114**, 163 (1995); M. P. Doyle, *Pure Appl. Chem.*, **70**, 1123 (1998); M. P. Doyle and M. N. Protopopova, *Tetrahedron*, **54**, 7919 (1998); M. P. Doyle and D. C. Forbes, *Chem. Rev.*, **98**, 911 (1998).



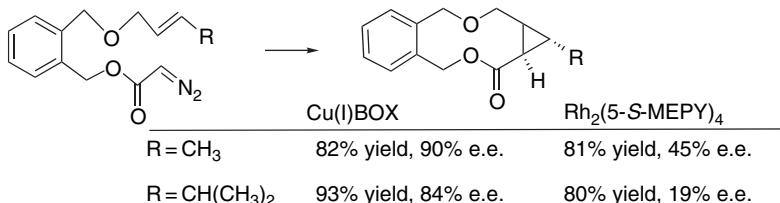
The 1-acetyl and 1-benzoyl derivatives of 4-carbomethoxyimidazolinone are also effective catalysts. Another group of catalysts is made up of *N*-arenenesulfonylprolinates. The structures and abbreviations are given in Scheme 10.11. The PY series of catalysts is derived from pyroglutamic acid, whereas the IM and OX designations apply to imidazolines and oxazolines, respectively. The designations ME and NE refer to methyl and neopentyl esters, and MA and PA indicate amides of acetic acid and phenylacetic acid, respectively. Only two of the four ligands that are present are shown.

A comparison of several of the PY and IM types of catalysts in intramolecular reactions of allylic diazoacetates led to a consistent model for the enantioselectivity. The highest e.e. values are observed for *cis*-substituted allylic esters. Both R^t and Rⁱ are directed toward the catalyst and introduce steric interactions that detract from enantioselectivity.²⁰⁸



The 1-arenenesulfonylprolinate catalysts have been studied computationally.²⁰⁹ A computed TS and conceptual model that is consistent with experimentally observed enantioselectivity is shown in Figure 10.11. The arenenesulfonyl groups block one of the directions of approach to the carbene catalyst and also orient the alkene substituent away from the metal center.

Several of the copper and rhodium catalysts were compared in an intramolecular cyclopropanation.²¹⁰ For the reaction leading to formation of a 10-membered ring, shown below, the copper catalysts gave higher enantioselectivity, but there were many subtleties, depending on ring size and other structural features in related systems.



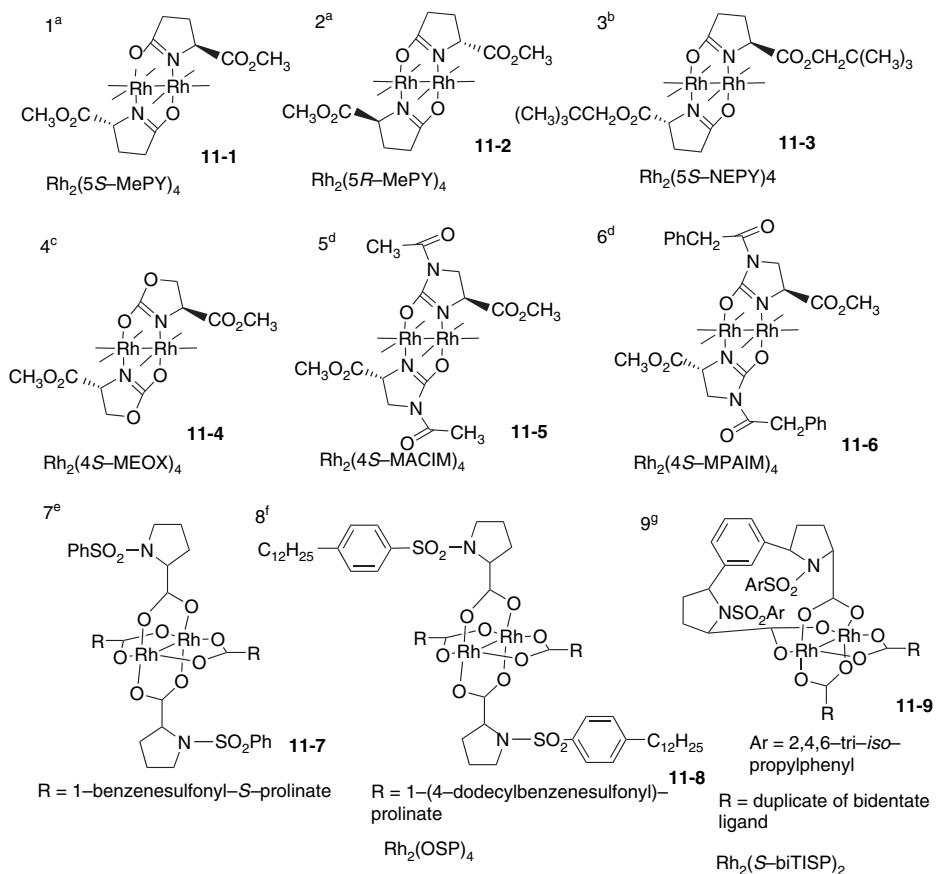
²⁰⁸ M. P. Doyle, R. E. Austin, A. S. Bailey, M. P. Dwyer, A. B. Dyatkin, A. V. Kalinin, M. M. Y. Kwan, S. Liras, C. J. Oalmann, R. J. Pieters, M. N. Protopopova, C. E. Raab, G. H. P. Roos, Q.-L. Zhou, and S. F. Martin, *J. Am. Chem. Soc.*, **117**, 5763 (1995).

²⁰⁹ D. T. Nowlan, III, T. M. Gregg, H. M. L. Davies, and D. A. Singleton, *J. Am. Chem. Soc.*, **125**, 15902 (2003).

²¹⁰ M. P. Doyle, W. Hu, B. Chapman, A. B. Marnett, C. S. Peterson, J. P. Vitale, and S. A. Stanley, *J. Am. Chem. Soc.*, **122**, 5718 (2000).

SECTION 10.2

Reactions Involving
Carbenes and Related
Intermediates



- a. M. P. Doyle, R. J. Pieters, S. F. Martin, R. E. Austin, P. J. Oallmann, and P. Mueller, *J. Am. Chem. Soc.*, **113**, 1423 (1991); M. P. Doyle, W. R. Winchester, J. A. A. Hoorn, V. Lynch, S. H. Simonsen, and R. Ghosh, *J. Am. Chem. Soc.*, **115**, 9968 (1993).
- b. M. P. Doyle, A. van Oeveren, L. J. Westrum, M. N. Protopopova, and W. T. Clayton, Jr., *J. Am. Chem. Soc.*, **113**, 8982 (1991).
- c. M. P. Doyle, A. B. Dyatkin, M. N. Protopopova, C. I. Yang, C. S. Miertschin, W. R. Winchester, S. H. Simonsen, V. Lynch, and R. Ghosh, *Recl. Trav. Chim. Pays-Bas*, **114**, 163 (1995).
- d. M. P. Doyle, A. B. Dyatkin, G. H. P. Roos, F. Canas, D. A. Pierson, A. van Basten, P. Mueller, and P. Polleux, *J. Am. Chem. Soc.*, **116**, 4507 (1994).
- e. M. A. McKervey and T. Ye, *J. Chem. Soc., Chem. Commun.*, 823 (1992).
- f. H. M. L. Davies and D. K. Hutcheson, *Tetrahedron Lett.*, **34**, 7243 (1993); H. M. L. Davies, P. R. Bruzinski, D. H. Lake, N. Kong, and M. J. Fall, *J. Am. Chem. Soc.*, **118**, 6897 (1996).
- g. H. M. L. Davies and S. A. Panaro, *Tetrahedron Lett.*, **40**, 5287 (1999).

Scheme 10.12 gives some examples of enantioselective cyclopropanations. Entry 1 uses the *bis-t*-butyloxazoline (BOX) catalyst. The catalytic cyclopropanation in Entry 2 achieves both stereo- and enantioselectivity. The electronic effect of the catalysts (see p. 926) directs the alkoxy-substituted ring *trans* to the ester substituent (87:13 ratio), and very high enantioselectivity was observed. Entry 3 also used the *t*-butyl-BOX catalyst. The product was used in an enantioselective synthesis of the alkaloid quebrachamine. Entry 4 is an example of enantioselective methylene transfer using the tartrate-derived dioxaborolane catalyst (see p. 920). Entry 5 used the Rh₂[5(S)-MePY]₄

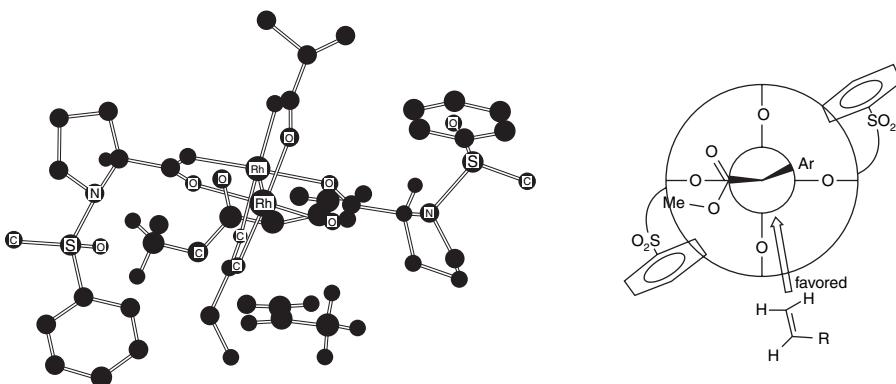
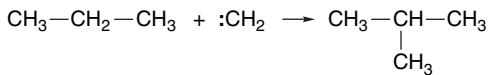


Fig. 10.11. General schematic model for favored approach of alkenes to 1-arenesulfonylproline catalysts (right); and B3LYP/6-31G*/LANL2DZ computational model of preferred approach of propene to 1-carbomethoxyprop-2-enylidene complex with Rh₂(1-benzenesulfonylproline)₂(isobutyrate)₂ (left). Reproduced from *J. Am. Chem. Soc.*, **125**, 15902 (2003), by permission of the American Chemical Society.

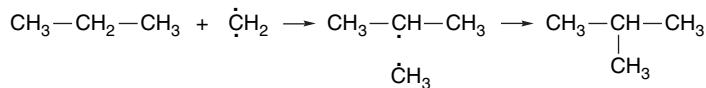
catalyst. Entry 6 is an intramolecular cyclopropanation done using a *bis*-(oxazolinyl) biphenyl catalyst (see Scheme 10.10, Entry 5).

10.2.4. Insertion Reactions

Insertion reactions are processes in which a reactive intermediate, in this case a carbene, interposes itself into an existing bond. In terms of synthesis, this usually involves C–H bonds. Many singlet carbenes are sufficiently reactive that insertion can occur as a one-step process.



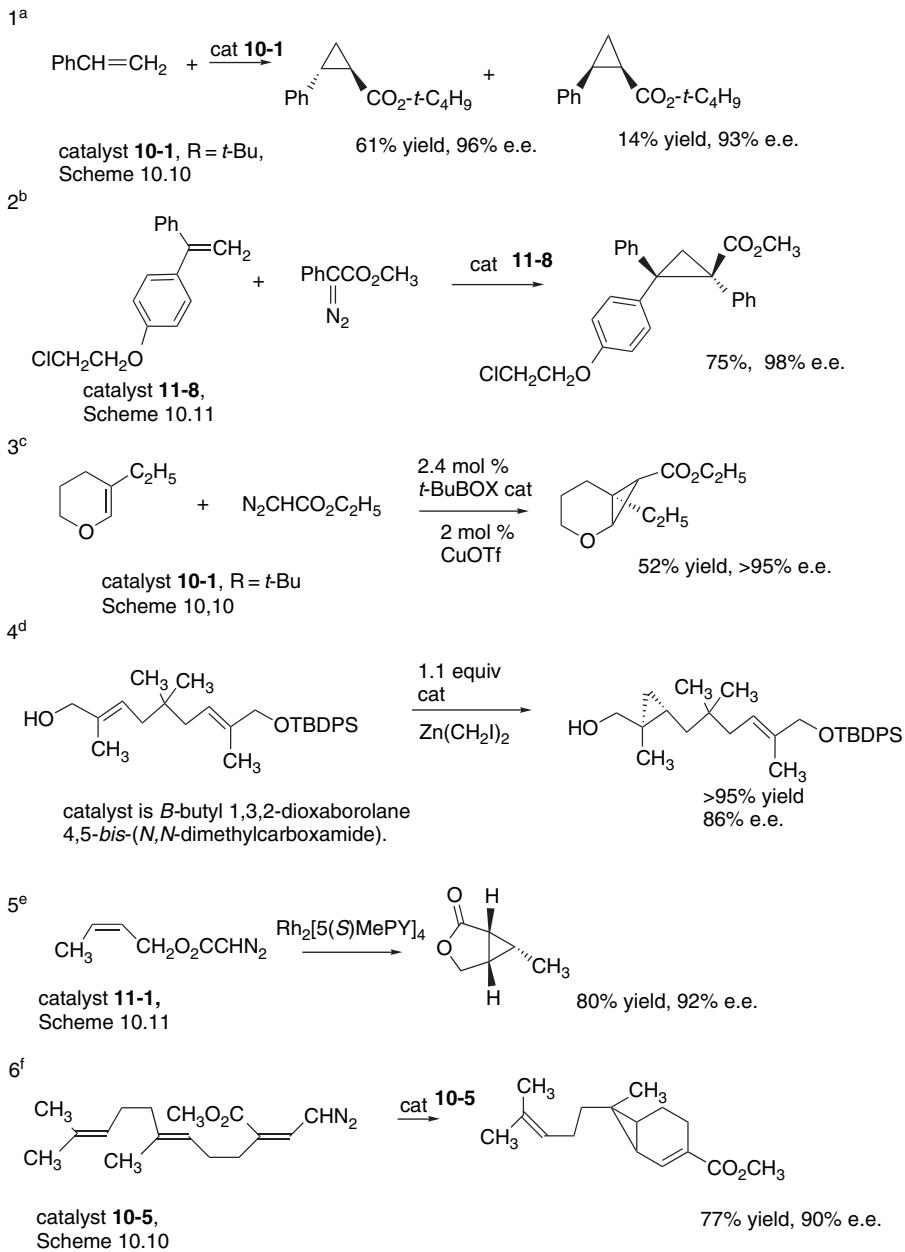
The same products can be formed by a two-step hydrogen abstraction and recombination involving a triplet carbene.



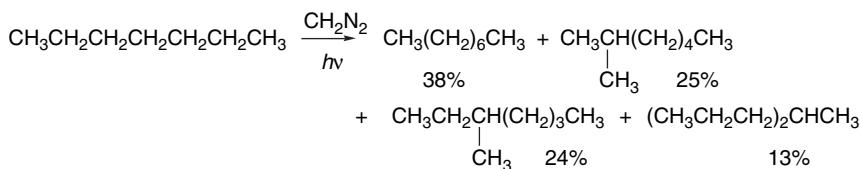
It is sometimes difficult to distinguish clearly between these mechanisms, but determination of reaction stereochemistry provides one approach. The true one-step insertion must occur with complete *retention of configuration*. The results for the two-step process will depend on the rate of recombination in competition with stereorandomization of the radical pair intermediate.

Owing to the high reactivity of the intermediates involved, intermolecular carbene insertion reactions are not very selective. The distribution of products from the photolysis of diazomethane in heptane, for example, is almost exactly that expected on a statistical basis.²¹¹

²¹¹ D. B. Richardson, M. C. Simmons, and I. Dvoretzky, *J. Am. Chem. Soc.*, **83**, 1934 (1961).

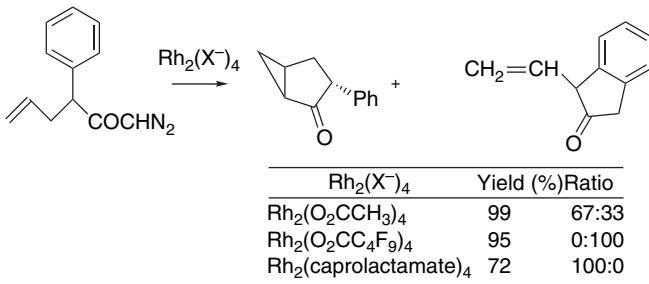


- a. D. A. Evans, K. A. Woerpel, M. M. Hinman, and M. M. Faul, *J. Am. Chem. Soc.*, **113**, 726 (1991).
 - b. H. M. L. Davies, T. Nagashima, and J. L. Klino, III, *Org. Lett.*, **2**, 823 (2000).
 - c. O. Temme, S.-A. Taj, and P. G. Andersson, *J. Org. Chem.*, **63**, 6007 (1998).
 - d. A. B. Charette and H. Juteau, *Tetrahedron*, **53**, 16277 (1997).
 - e. S. M. Berberich, R. J. Cherney, J. Colucci, C. Courillon, L. S. Geraci, T. A. Kirkland, M. A. Marx, M. Schneider, and S. F. Martin, *Tetrahedron*, **59**, 6819 (2003).
 - f. T. G. Grant, M. C. Noe, and E. J. Corey, *Tetrahedron Lett.*, **36**, 8745 (1995).



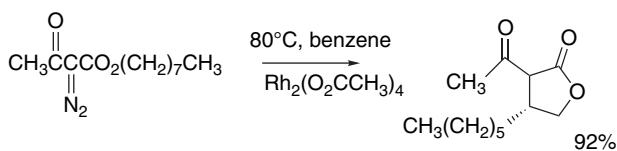
There is some increase in selectivity with functionally substituted carbenes, but it is still not high enough to prevent formation of mixtures. Phenylchlorocarbene gives a relative reactivity ratio of 2.1:1:0.09 in insertion reactions with *i*-propylbenzene, ethylbenzene, and toluene.²¹² For cycloalkanes, tertiary positions are about 15 times more reactive than secondary positions toward phenylchlorocarbene.²¹³ Carbethoxycarbene inserts at tertiary C–H bonds about three times as fast as at primary C–H bonds in simple alkanes.²¹⁴ Owing to low selectivity, intermolecular insertion reactions are seldom useful in syntheses. Intramolecular insertion reactions are of considerably more value. Intramolecular insertion reactions usually occur at the C–H bond that is closest to the carbene and good yields can frequently be achieved. Intramolecular insertion reactions can provide routes to highly strained structures that would be difficult to obtain in other ways.

Rhodium carboxylates have been found to be effective catalysts for intramolecular C–H insertion reactions of α -diazo ketones and esters.²¹⁵ In flexible systems, five-membered rings are formed in preference to six-membered ones. Insertion into methine hydrogen is preferred to a methylene hydrogen. Intramolecular insertion can be competitive with intramolecular addition. Product ratios can to some extent be controlled by the specific rhodium catalyst that is used.²¹⁶ In the example shown, insertion is the exclusive reaction with $\text{Rh}_2(\text{O}_2\text{CC}_4\text{F}_9)_4$, whereas only addition occurs with $\text{Rh}_2(\text{caprolactamate})_4$, which indicates that the more electrophilic carbenoids favor insertion.

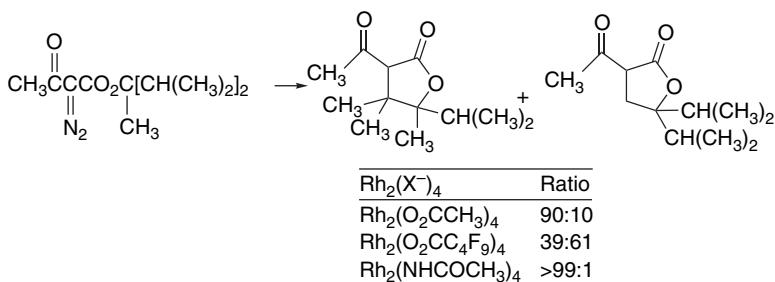


The insertion reaction can be used to form lactones from α -diazo- β -keto esters.

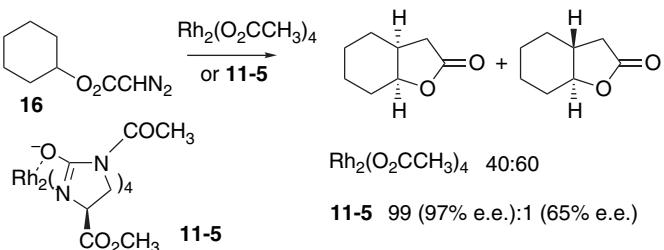
- ²¹². M. P. Doyle, J. Taunton, S.-M. Oon, M. T. H. Liu, N. Soundararajan, M. S. Platz, and J. E. Jackson, *Tetrahedron Lett.*, **29**, 5863 (1988).
- ²¹³. R. M. Moss and S. Yan, *Tetrahedron Lett.*, **39**, 9381 (1998).
- ²¹⁴. W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **83**, 1989 (1961).
- ²¹⁵. D. F. Taber and E. H. Petty, *J. Org. Chem.*, **47**, 4808 (1982); D. F. Taber and R. E. Ruckle, Jr., *J. Am. Chem. Soc.*, **108**, 7686 (1986).
- ²¹⁶. (a) M. P. Doyle, L. J. Westrum, W. N. E. Wolthuis, M. M. See, W. P. Boone, V. Bagheri, and M. M. Pearson, *J. Am. Chem. Soc.*, **115**, 958 (1993); (b) A. Padwa and D. J. Austin, *Angew. Chem. Int. Ed. Engl.*, **33**, 1797 (1994).



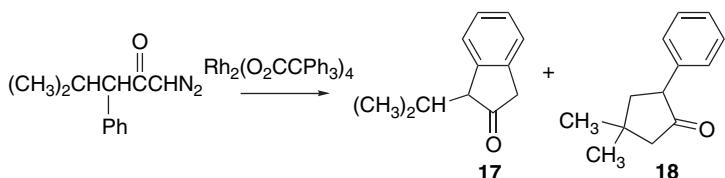
When the reactant provides more than one kind of hydrogen for insertion, the catalyst can influence selectivity. For example, $\text{Rh}_2(\text{acam})_4$ gives exclusively insertion at a tertiary position, whereas $\text{Rh}_2(\text{O}_2\text{CC}_4\text{F}_9)_4$ leads to nearly a statistical mixture.^{217a} The attenuated reactivity of the amidate catalyst enhances selectivity.



Stereoselectivity is also influenced by the catalysts. For example, **16** can lead to either *cis* or *trans* products. Although $\text{Rh}_2(\text{O}_2\text{CCH}_3)_4$ is unselective, the $\text{Rh}_2(\text{MACIM})_4$ catalyst **11-5** (Scheme 10.11) is selective for the *cis* isomer and also gives excellent enantioselectivity in the major product.²¹⁷



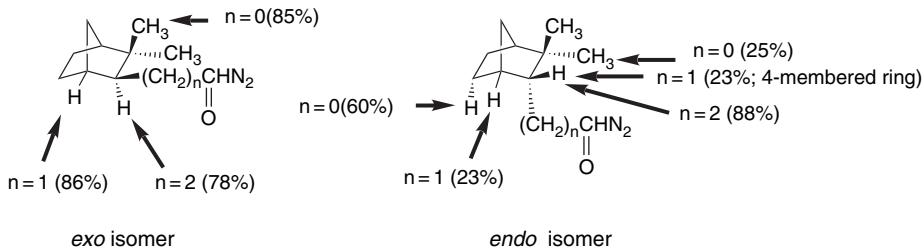
Certain sterically hindered rhodium catalysts also lead to improved selectivity. For example, rhodium triphenylacetate improves the selectivity for **17** over **18** from 5:1 to 99:1.²¹⁸



²¹⁷ M. P. Doyle, A. B. Dyatkin, G. H. P. Roos, F. Canas, D. A. Pierson, and A. van Basten, *J. Am. Chem. Soc.*, **116**, 4507 (1994).

²¹⁸ S. Hashimoto, N. Watanabe, and S. Ikegami, *J. Chem. Soc., Chem. Commun.*, 1508 (1992); S. Hashimoto, N. Watanabe, and S. Ikegami, *Tetrahedron Lett.*, **33**, 2709 (1992).

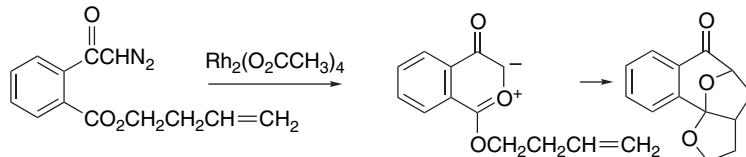
Intramolecular insertion reactions show a strong preference for formation of five-membered rings.²¹⁹ This was seen in a series of α -diazomethyl ketones of increasing chain length. With only one exception, all of the products were five-membered lactones.²²⁰ In the case of $n = 3$, the cyclization occurs in the side chain, again forming a five-membered ring.



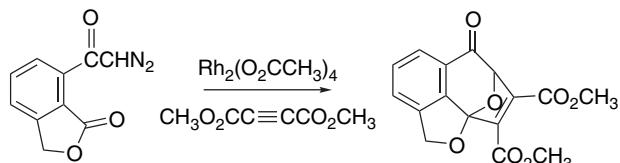
Scheme 10.13 gives some additional examples of intramolecular insertion reactions. Entries 1 and 2 were done under the high-temperature conditions of the Bamford-Stevens reaction (see p. 913). Entries 3 to 5 are metal-catalyzed intramolecular reactions in which 5-membered rings are formed. Entries 6 and 7 result in generation of strained rings by insertion into proximate C–H bonds. The insertion in Entry 6 via a diazirine was done in better yield (92%) by thermolysis (200°C) of the corresponding tosylhydrazone salt. Entry 8 is a case of enantioselective insertion, using one of the *N*-acyl methoxycarbonylimidazolonato rhodium catalysts.

10.2.5. Generation and Reactions of Ylides by Carbenoid Decomposition

Compounds in which a carbonyl or other nucleophilic functional group is close to a carbenoid carbon can react to give ylide intermediate.²²¹ One example is the formation of carbonyl ylides that go on to react by 1,3-dipolar addition. Both intramolecular and intermolecular cycloadditions have been observed.



Ref. 222



Ref. 221

²¹⁹ D. F. Taber and R. E. Ruckle, Jr., *J. Am. Chem. Soc.*, **108**, 7686 (1986).

²²⁰ H. R. Sonawane, N. S. Bellur, J. R. Ahuja, and D. G. Kulkarni, *J. Org. Chem.*, **56**, 1434 (1991).

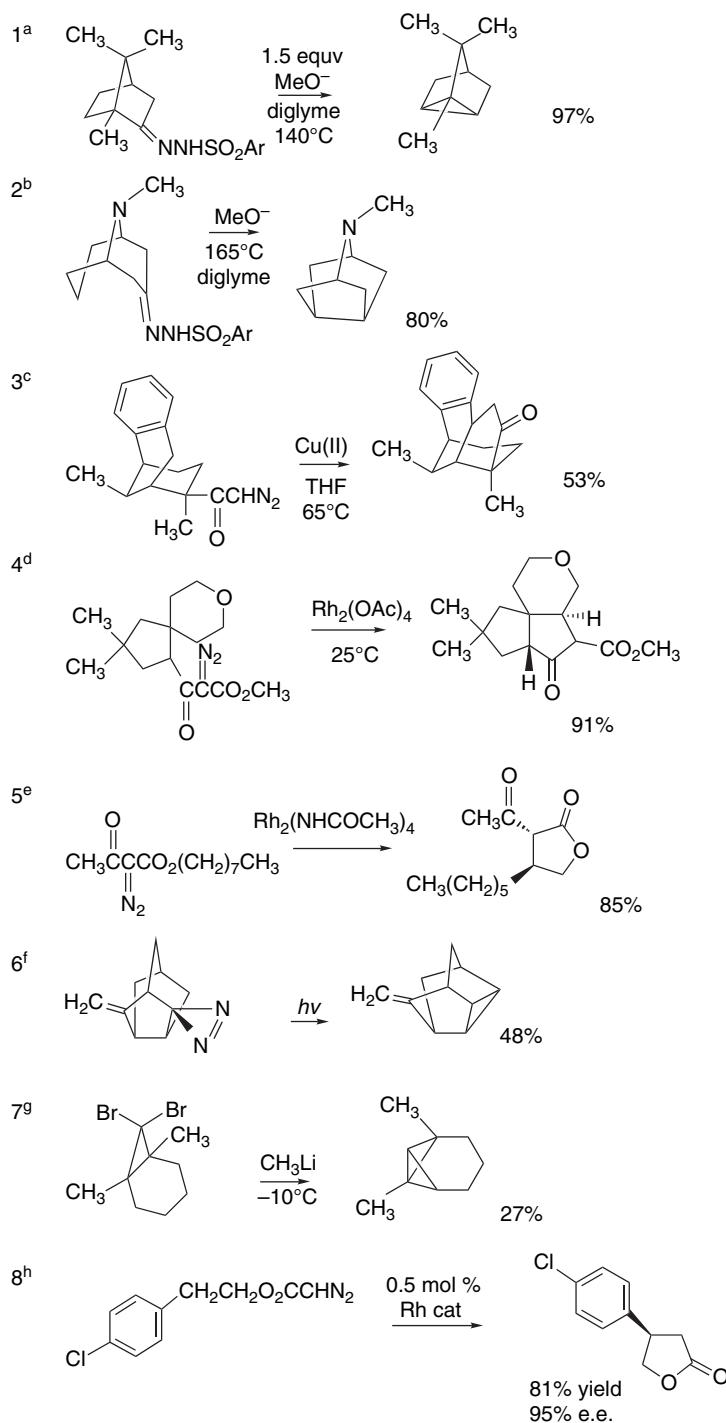
²²¹ A. Padwa and S. F. Hornbuckle, *Chem. Rev.*, **91**, 263 (1991).

²²² A. Padwa, S. P. Carter, H. Nimmesgern, and P. D. Stull, *J. Am. Chem. Soc.*, **110**, 2894 (1988).

Scheme 10.13. Intramolecular Carbene-Insertion Reactions

SECTION 10.2

Reactions Involving
Carbenes and Related
Intermediates



catalyst is *tetrakis-[N-phenylpropanoyl-4-methoxycarbonylimidazolonato] dirhodium*

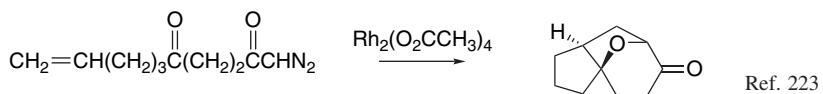
(Continued)

Scheme 10.13. (Continued)

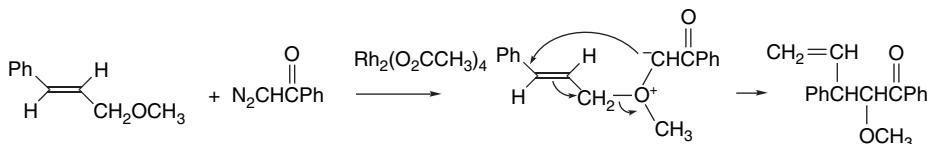
CHAPTER 10

Reactions Involving
Carbocations, Carbenes,
and Radicals as Reactive
Intermediates

- a. R. H. Shapiro, J. H. Duncan, and J. C. Clopton, *J. Am. Chem. Soc.*, **89**, 1442 (1967).
 b. T. Sasaki, S. Eguchi, and T. Kiriyama, *J. Am. Chem. Soc.*, **91**, 212 (1969).
 c. U. R. Ghatak and S. Chakrabarty, *J. Am. Chem. Soc.*, **94**, 4756 (1972).
 d. D. F. Taber and J. L. Schuchardt, *J. Am. Chem. Soc.*, **107**, 5289 (1985).
 e. M. P. Doyle, V. Bagheri, M. M. Pearson, and J. D. Edwards, *Tetrahedron Lett.*, **30**, 7001 (1989).
 f. Z. Majerski, Z. Hamersak, and R. Sarac-Arneri, *J. Org. Chem.*, **53**, 5053 (1988).
 g. L. A. Paquette, S. E. Williams, R. P. Henzel, and G. R. Allen, Jr., *J. Am. Chem. Soc.*, **94**, 7761 (1972).
 h. M. P. Doyle and W. Hu, *Chirality*, **14**, 169 (2002).

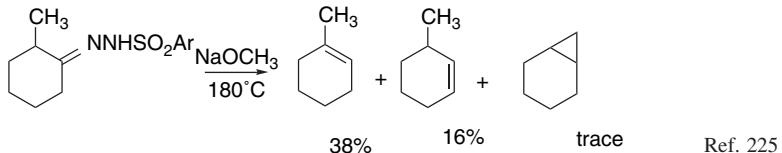


Allylic ethers and acetals can react with carbenoid reagents to generate oxonium ylides that undergo [2,3]-sigmatropic shifts.²²⁴

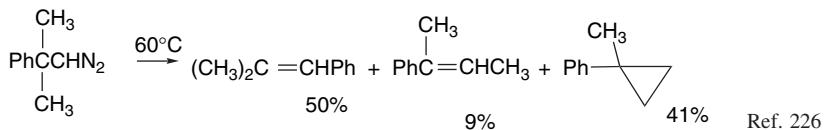


10.2.6. Rearrangement Reactions

The most common rearrangement reaction of alkyl carbenes is the shift of hydrogen, generating an alkene. This mode of stabilization predominates to the exclusion of most intermolecular reactions of aliphatic carbenes and often competes with intramolecular insertion reactions. For example, the carbene generated by decomposition of the tosylhydrazone of 2-methylcyclohexanone gives mainly 1- and 3-methylcyclohexene rather than the intramolecular insertion product.



Carbenes can also be stabilized by migration of alkyl or aryl groups. 2-Methyl-2-phenyl-1-diazopropane provides a case in which products of both phenyl and methyl migration, as well as intramolecular insertion, are observed.



²²³ A. Padwa, S. F. Hornbuckle, G. E. Fryxell, and P. D. Stull, *J. Org. Chem.*, **54**, 819 (1989).

²²⁴ M. P. Doyle, V. Bagheri, and N. K. Harn, *Tetrahedron Lett.*, **29**, 5119 (1988).

²²⁵ J. W. Wilt and W. J. Wagner, *J. Org. Chem.*, **29**, 2788 (1964).

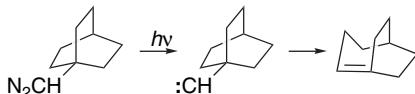
²²⁶ H. Philip and J. Keating, *Tetrahedron Lett.*, 523 (1961).

Bicyclo[3.2.2]non-1-ene, a strained bridgehead alkene, is generated by rearrangement when bicyclo[2.2.2]octyl diazomethane is photolyzed.²²⁷

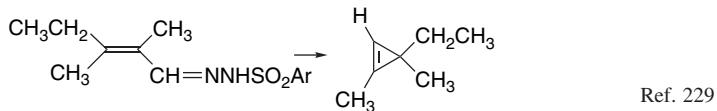
941

SECTION 10.2

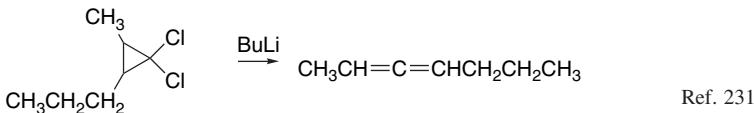
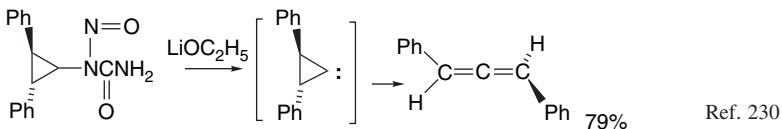
Reactions Involving Carbenes and Related Intermediates



Carbene centers adjacent to double bonds (vinyl carbenes) usually cyclize to cyclopropenes.²²⁸

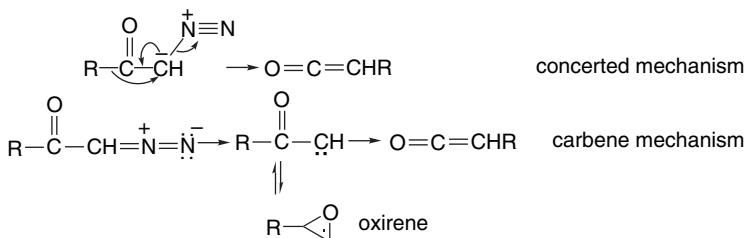


Cyclopropylidenes undergo ring opening to give allenes. Reactions that would be expected to generate a cyclopropylidene therefore lead to allene, often in preparatively useful yields.



10.2.7. Related Reactions

There are several reactions that are conceptually related to carbene reactions but do not involve carbene, or even carbonoid, intermediates. Usually, these are reactions in which the generation of a carbene is circumvented by a concerted rearrangement process. Important examples of this type are the thermal and photochemical reactions of α -diazo ketones. When α -diazo ketones are decomposed thermally or photochemically, they usually rearrange to ketenes, in a reaction known as the *Wolff rearrangement*.²³²



²²⁷ M. S. Gudipati, J. G. Radziszewski, P. Kaszynski, and J. Michl, *J. Org. Chem.*, **58**, 3668 (1993).

²²⁸ G. L. Closs, L. E. Closs, and W. A. Böll, *J. Am. Chem. Soc.*, **85**, 3796 (1963).

²²⁹ E. J. York, W. Dittmar, J. R. Stevenson, and R. G. Bergman, *J. Am. Chem. Soc.*, **95**, 5680 (1973).

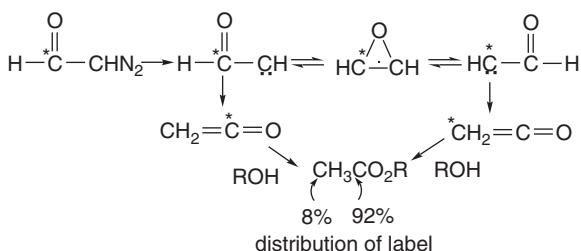
²³⁰ W. M. Jones, J. W. Wilson, Jr., and F. B. Tutwiler, *J. Am. Chem. Soc.*, **85**, 3309 (1963).

²³¹ W. R. Moore and H. R. Ward, *J. Org. Chem.*, **25**, 2073 (1960).

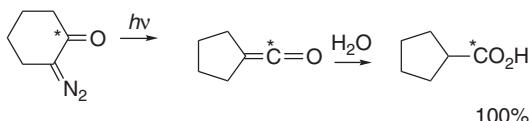
²³² W. Kirmse, *Eur. J. Org. Chem.*, 2193 (2002); T. Ye and M. A. McKervey, *Chem. Rev.*, **94**, 1091 (1994).

If this reaction proceeds in a concerted fashion, a carbene intermediate is avoided. Mechanistic studies have been aimed at determining whether migration is concerted with the loss of nitrogen. The conclusion that has emerged is that a carbene is generated in photochemical reactions but that the reaction can be concerted under thermal conditions.

A related issue is whether the carbene, when it is involved, is in equilibrium with a ring-closed isomer, an oxirene.²³³ This aspect of the reaction has been probed using isotopic labeling. If a symmetrical oxirene is formed, the label should be distributed to both the carbonyl and α -carbon. A concerted reaction or a carbene intermediate that did not equilibrate with the oxirene should have label only in the carbonyl carbon. The extent to which the oxirene is formed depends on the structure of the diazo compound. For diazoacetaldehyde, photolysis leads to only 8% migration of label, which would correspond to formation of 16% of the product through the oxirene.²³⁴



The diphenyl analog shows about 20–30% rearrangement.²³⁵ α -Diazocyclohexanone gives no evidence of an oxirene intermediate, since all the label remains at the carbonyl carbon.²³⁶



The reactivity of diazo carbonyl compounds appears to be related to the conformational equilibria between *s-cis* and *s-trans* conformations. A concerted rearrangement is favored by the *s-cis* conformation.²³⁷ The *t*-butyl compound **19**, which exists in the *s-trans* conformation, gives very little di-*t*-butylketene on photolysis.²³⁸ A similarly

²³³ M. Torres, E. M. Lown, H. E. Gunning, and O. P. Strausz, *Pure Appl. Chem.*, **52**, 1623 (1980); E. G. Lewars, *Chem. Rev.*, **83**, 519 (1983); M. A. Blaustein and J. A. Berson, *Tetrahedron Lett.*, **22**, 1081 (1981); A. P. Scott, R. H. Nobes, H. F. Schaeffer, III, and L. Radom, *J. Am. Chem. Soc.*, **116**, 10159 (1994).

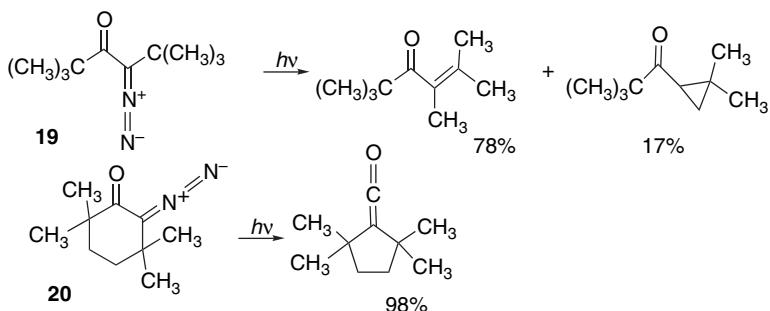
²³⁴ K.-P. Zeller, *Tetrahedron Lett.*, 707 (1977); see also Y. Chiang, A. J. Kresge, and V. V. Popik, *J. Chem. Soc., Perkin Trans. 2*, 1107 (1999).

²³⁵ K.-P. Zeller, H. Meier, H. Kolshorn, and E. Mueller, *Chem. Ber.*, **105**, 1875 (1972).

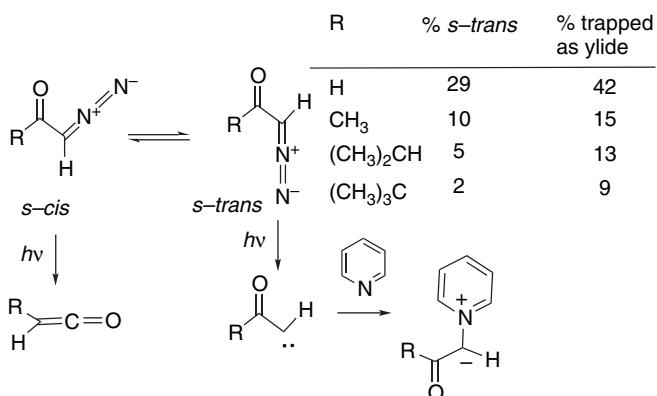
²³⁶ U. Timm, K.-P. Zeller, and H. Meier, *Tetrahedron*, **33**, 453 (1977).

²³⁷ F. Kaplan and G. K. Meloy, *J. Am. Chem. Soc.*, **88**, 950 (1966).

²³⁸ M. S. Newman and A. Arkell, *J. Org. Chem.*, **24**, 385 (1959).



In a flash photolysis study of a series of diazo carbonyl compounds, a correlation was found between the amount of carbene that could be trapped by pyridine and the amount of *s-trans* ketone.²⁴⁰



Flash photolysis of benzoyl and naphthoyl diazomethane, which should exist in the *s-cis* conformation, led to ketene intermediates within the duration of the pulse (~ 20 ns).²⁴¹

The main synthetic application of the Wolff rearrangement is for the one-carbon homologation of carboxylic acids.²⁴² In this procedure, a diazomethyl ketone is synthesized from an acyl chloride. The rearrangement is then carried out in a nucleophilic solvent that traps the ketene to form a carboxylic acid (in water) or an ester (in alcohols). Silver oxide is often used as a catalyst, since it seems to promote the rearrangement over carbene formation.²⁴³

The photolysis of cyclic α -diazoketones results in ring contraction to a ketene, which can be isolated as the corresponding ester.

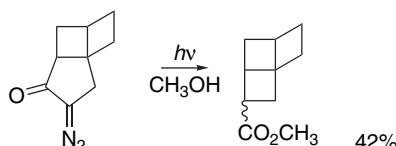
²³⁹. F. Kaplan and M. L. Mitchell, *Tetrahedron Lett.*, 759 (1979).

²⁴⁰ J. P. Toscano and M. S. Platz, *J. Am. Chem. Soc.*, **117**, 4712 (1995).

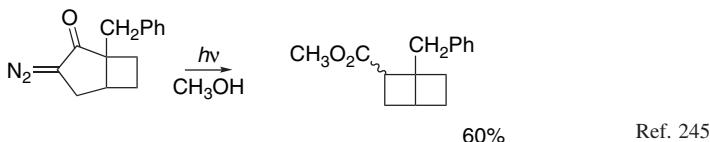
²⁴¹ Y. Chiang, A. J. Kresge, and V. V. Popik, *J. Am. Chem. Soc.*, **121**, 5930 (1999).

242. T. Chang, A. J. Kropski, and V. V. Popik, *J. Am. Chem. Soc.*, **121**, 5930 (1999).
 W. E. Bachmann and W. S. Stuve, *Org. React.*, **1**, 38 (1942); L. L. Rodina and I. K. Korobitsyna, *Russ. Chem. Rev. (English Transl.)*, **36**, 260 (1967); W. Ando, in *Chemistry of Diazonium and Diazo Groups*, S. Patai, ed., John Wiley, New York (1978), pp. 458–475; H. Meier and K.-P. Zeller, *Angew. Chem. Int. Ed. Engl.*, **14**, 32 (1975).

²⁴³ T. Hudlicky and J. P. Sheth, *Tetrahedron Lett.*, 2667 (1979).



Ref. 244

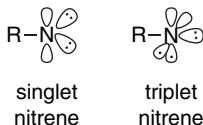


Ref. 245

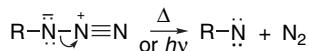
Scheme 10.14 gives some other examples of Wolff rearrangement reactions. Entries 1 and 2 are reactions carried out under the classical silver ion catalysis conditions. Entry 3 is an example of a thermolysis. Entries 4 to 7 are ring contractions done under photolytic conditions. Entry 8, done using a silver catalyst, was a step in the synthesis of macbecin, an antitumor antibiotic. Entry 9, a step in the synthesis of a drug candidate, illustrates direct formation of an amide by trapping the ketene intermediate with an amine.

10.2.8. Nitrenes and Related Intermediates

The nitrogen analogs of carbenes are called nitrenes. As with carbenes, both singlet and triplet electronic states are possible.



The triplet state is usually the ground state for non-conjugated structures, but either species can be involved in reactions. The most common method for generating nitrene intermediates, analogous to formation of carbenes from diazo compounds, is by thermolysis or photolysis of azides.²⁴⁶



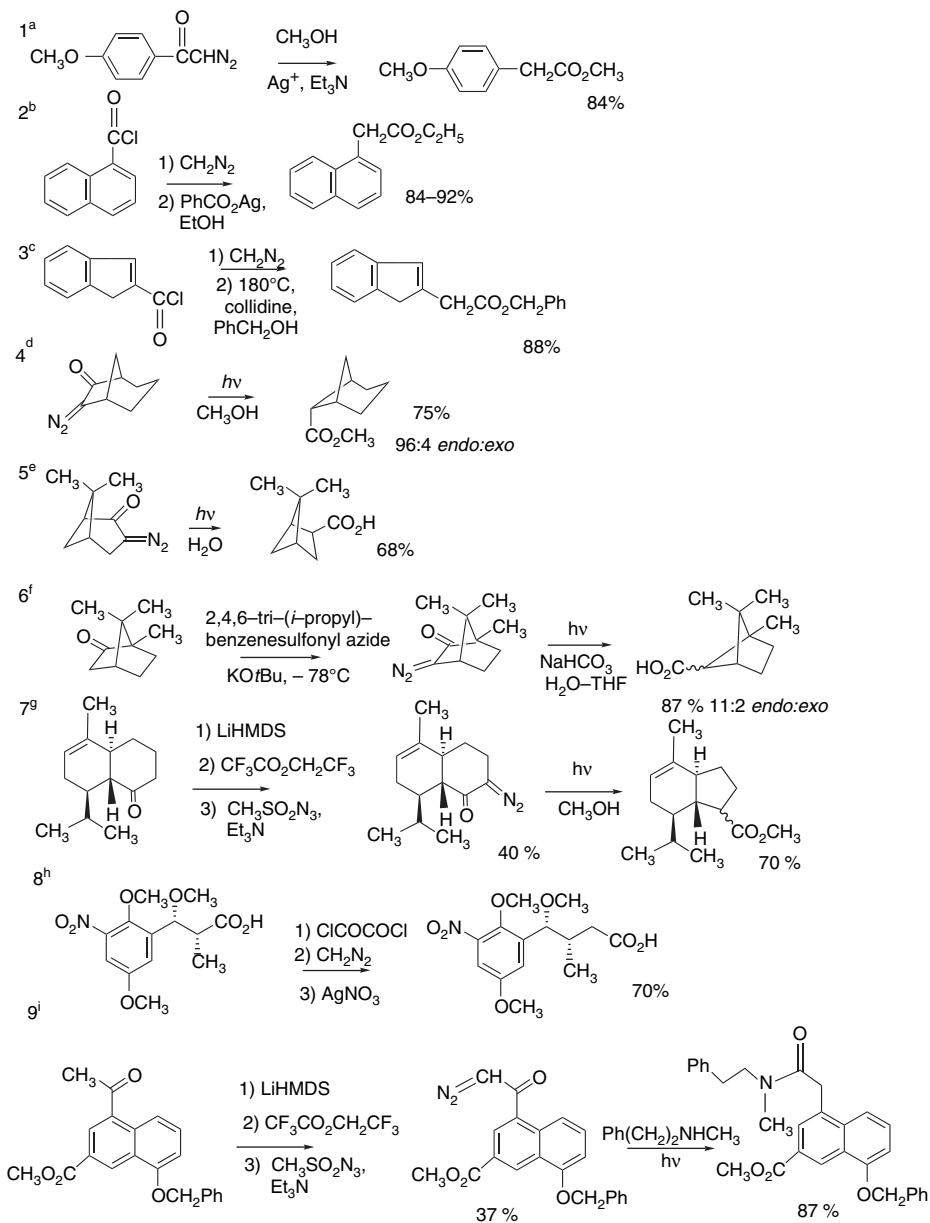
The types of azides that have been used for generation of nitrenes include alkyl,²⁴⁷ aryl,²⁴⁸ acyl,²⁴⁹ and sulfonyl²⁵⁰ derivatives.

- ²⁴⁴ K. B. Wiberg, L. K. Olli, N. Golembeski, and R. D. Adams, *J. Am. Chem. Soc.*, **102**, 7467 (1980).
- ²⁴⁵ K. B. Wiberg, B. L. Furtek, and L. K. Olli, *J. Am. Chem. Soc.*, **101**, 7675 (1979).
- ²⁴⁶ E. F. V. Scriven, ed., *Azides and Nitrenes: Reactivity and Utility*, Academic Press, Orlando, FL, 1984.
- ²⁴⁷ F. D. Lewis and W. H. Saunders, Jr., in *Nitrenes*, W. Lwowski, ed., Interscience, New York, 1970, pp. 47–98; E. P. Kyba, in *Azides and Nitrenes*, E. F. V. Scriven, ed., Academic Press, Orlando, FL, 1984, pp. 2–34.
- ²⁴⁸ P. A. Smith, in *Nitrenes*, W. Lwowski, ed., Interscience, New York, 1970, pp. 99–162; P. A. S. Smith, in *Azides and Nitrenes*, E. F. V. Scriven, ed., Academic Press, Orlando, FL, 1984, pp. 95–204.
- ²⁴⁹ W. Lwowski, in *Nitrenes*, W. Lwowski, ed., Interscience, New York, 1970, pp. 185–224; W. Lwowski, in *Azides and Nitrenes*, E. F. V. Scriven, ed., Academic Press, Orlando, FL, 1984, pp. 205–246.
- ²⁵⁰ D. S. Breslow, in *Nitrenes*, W. Lwowski, ed., Interscience, New York, 1970, pp. 245–303; R. A. Abramovitch and R. G. Sutherland, *Fortschr. Chem. Forsch.*, **16**, 1 (1970).

Scheme 10.14. Wolff Rearrangements of α -Diazoketones

SECTION 10.2

Reactions Involving
Carbenes and Related
Intermediates



a. M. S. Newman and P. F. Beal, III, *J. Am. Chem. Soc.*, **72**, 5163 (1950).

b. V. Lee and M. S. Newman, *Org. Synth.*, **50**, 77 (1970).

c. E. D. Bergmann and E. Hoffmann, *J. Org. Chem.*, **26**, 3555 (1961).

d. K. B. Wiberg and B. A. Hess, Jr., *J. Org. Chem.*, **31**, 2250 (1966).

e. J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 2857 (1960).

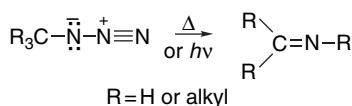
f. T. Uyehara, N. Takehara, M. Ueno, and T. Sato, *Bull. Chem. Soc. Jpn.*, **68**, 2687 (1995).

g. D. F. Taber, S. Kong, and S. C. Malcolm, *J. Org. Chem.*, **63**, 7953 (1998).

h. D. A. Evans, S. J. Miller, M. D. Ennis, and P. L. Ornstein, *J. Org. Chem.*, **57**, 1067 (1992); D. A. Evans, S. J. Miller, and M. D. Ennis, *J. Org. Chem.*, **58**, 471 (1993).

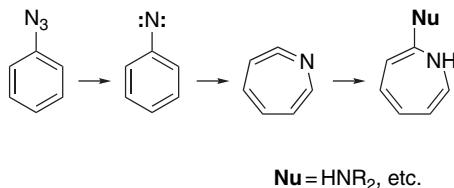
i. I. Pendrak and P. A. Chambers, *J. Org. Chem.*, **60**, 3249 (1995).

The characteristic reaction of an alkyl nitrene is migration of one of the substituents to nitrogen, giving an imine.

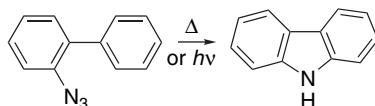


Intramolecular insertion and addition reactions are very rare for alkyl nitrenes. In fact, it is not clear that the nitrenes are formed as discrete species. The migration may be concerted with elimination, as is often the case in the Wolff rearrangement.²⁵¹

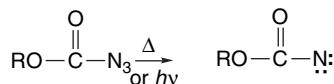
Aryl nitrenes also generally rearrange rather than undergo addition or insertion reactions.²⁵²



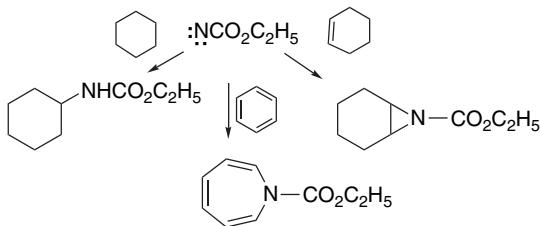
A few intramolecular insertion reactions, especially in aromatic systems, go in good yield.²⁵³



The nitrenes that most consistently give addition and insertion reactions are carboalkoxynitrenes generated from alkyl azidoformates.



These intermediates undergo addition reactions with alkenes and aromatic compounds and insertion reactions with saturated hydrocarbons.²⁵⁴



²⁵¹ R. M. Moriarty and R. C. Reardon, *Tetrahedron*, **26**, 1379 (1970); R. A. Abramovitch and E. P. Kyba, *J. Am. Chem. Soc.*, **93**, 1537 (1971); R. M. Moriarty and P. Serridge, *J. Am. Chem. Soc.*, **93**, 1534 (1971).

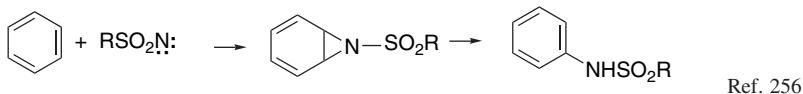
²⁵² O. L. Chapman and J.-P. LeRoux, *J. Am. Chem. Soc.*, **100**, 282 (1978); O. L. Chapman, R. S. Sheridan, and J.-P. LeRoux, *Rec. Trav. Chim. Pays-Bas*, **98**, 334 (1979); R. J. Sundberg, S. R. Suter, and M. Brenner, *J. Am. Chem. Soc.*, **94**, 573 (1972).

²⁵³ P. A. S. Smith and B. B. Brown, *J. Am. Chem. Soc.*, **73**, 2435, 2438 (1951); J. S. Swenton, T. J. Ikeler, and B. H. Williams, *J. Am. Chem. Soc.*, **92**, 3103 (1970).

²⁵⁴ W. Lwowski, *Angew. Chem. Int. Ed. Engl.*, **6**, 897 (1967).

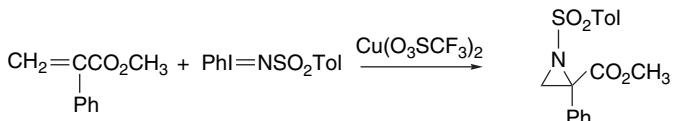
Carboalkoxynitrenes are somewhat more selective than the corresponding carbenes, showing selectivities of roughly 1:10:40 for the primary, secondary, and tertiary positions in 2-methylbutane in insertion reactions.

Sulfonylnitrenes are formed by thermal decomposition of sulfonyl azides.²⁵⁵ Insertion reactions occur with saturated hydrocarbons.²⁵⁵ With aromatic compounds the main products are formally insertion products, but they are believed to be formed through addition intermediates.



Ref. 256

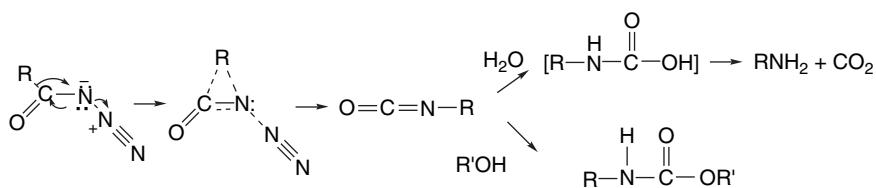
Aziridination of alkenes can be carried out using *N*-(*p*-toluenesulfonylimino)phenyliodinane and copper triflate or other copper salts.²⁵⁷ These reactions are mechanistically analogous to metal-catalyzed cyclopropanation. Rhodium acetate also acts as a catalyst.²⁵⁸ Other arenesulfonyliminoiodinanes can be used,²⁵⁹ as can chloroamine T²⁶⁰ and bromoamine T.²⁶¹ The range of substituted alkenes that react includes acrylate esters.²⁶²



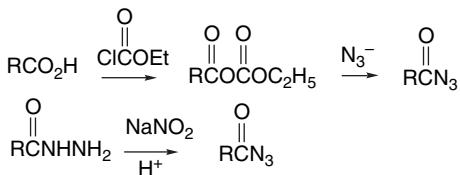
10.2.9. Rearrangements to Electron-Deficient Nitrogen

In contrast to the rather limited synthetic utility of nitrenes, there is an important group of reactions in which migration occurs to electron-deficient nitrogen. One of the most useful of these reactions is the *Curtius rearrangement*,²⁶³ which has the same relationship to acyl nitrene intermediates that the Wolff rearrangement has to acyl carbenes. This reaction is usually considered to be a concerted process in which migration accompanies loss of nitrogen.²⁶⁴ The temperature required for reaction is in the vicinity of 100°C. The initial product is an isocyanate that can be isolated or trapped by a nucleophilic solvent. The migrating group retains its stereochemical configuration.

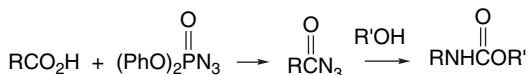
- ^{255.} D. S. Breslow, M. F. Sloan, N. R. Newburg, and W. B. Renfrow, *J. Am. Chem. Soc.*, **91**, 2273 (1969).
- ^{257.} R. A. Abramovitch, G. N. Knaus, and V. Uma, *J. Org. Chem.*, **39**, 1101 (1974).
- ^{257.} D. A. Evans, M. M. Faulk, and M. T. Bilodeau, *J. Am. Chem. Soc.*, **116**, 2742 (1994).
- ^{258.} P. Mueller, C. Baud, and Y. Jacquier, *Tetrahedron*, **52**, 1543 (1996).
- ^{259.} M. J. Sodergren, D. A. Alonso, and P. G. Andersson, *Tetrahedron: Asymmetry*, **8**, 3563 (1991); M. J. Sodergren, D. A. Alonso, A. V. Bedekar, and P. G. Andersson, *Tetrahedron Lett.*, **38**, 6897 (1997).
- ^{260.} D. P. Albone, P. S. Aujla, P. C. Taylor, S. Challenger, and A. M. Derrick, *J. Org. Chem.*, **63**, 9569 (1998).
- ^{261.} R. Vyas, B. M. Chandra, and A. V. Bedekar, *Tetrahedron Lett.*, **39**, 4715 (1998).
- ^{262.} P. Dauban and R. H. Dodd, *Tetrahedron Lett.*, **39**, 5739 (1998).
- ^{263.} P. A. S. Smith, *Org. React.*, **3**, 337 (1946).
- ^{264.} S. Linke, G. T. Tisue, and W. Lwowski, *J. Am. Chem. Soc.*, **89**, 6308 (1967).



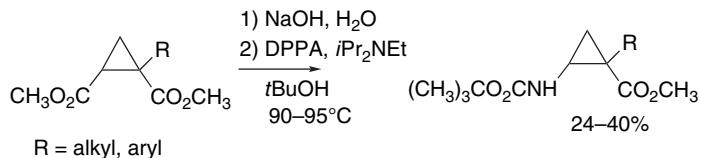
The acyl azide intermediates are prepared either by reaction of sodium azide with a reactive acylating agent or by diazotization of an acyl hydrazide. An especially convenient version of the former process is treatment of the carboxylic acid with ethyl chloroformate to form a mixed anhydride, which then reacts with azide ion.²⁶⁵



The transformation can also be carried out on the acid using diphenylphosphoryl azide (DPPA).²⁶⁶

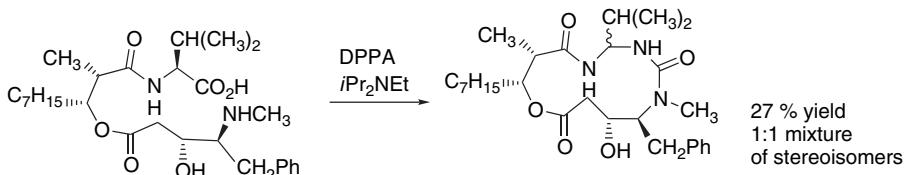


This version of the Curtius rearrangement has been applied to the synthesis of amino acid analogs and structures containing amino acids. Several *cis*-2-aminocyclopropane carboxylate esters were prepared by selective hydrolysis of cyclopropane-1,2-dicarboxylates, followed by reaction with DPPA.²⁶⁷



$\text{R} = \text{alkyl, aryl}$

The Curtius reaction has occasionally been used in formation of medium²⁶⁸ and large²⁶⁹ rings, usually in modest yield.



²⁶⁵ J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).

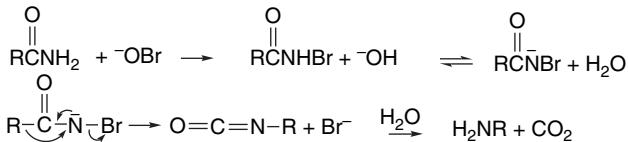
²⁶⁶ D. Kim and S. M. Weinreb, *J. Org. Chem.*, **43**, 125 (1978).

²⁶⁷ S. Mangelinckx and N. De Kimpe, *Tetrahedron Lett.*, **44**, 1771 (2003).

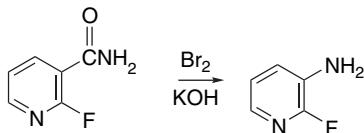
²⁶⁸ C. Hermann, G. C. G. Pais, A. Geyer, S. M. Kuhnert, and M. E. Maier, *Tetrahedron*, **56**, 8461 (2000).

²⁶⁹ Y. Hamada, M. Shibata, and T. Shioiri, *Tetrahedron Lett.*, **26**, 5155, 5159 (1985).

Another reaction that can be used for conversion of carboxylic acids to the corresponding amines with loss of carbon dioxide is the *Hofmann rearrangement*. The classic reagent is hypobromite ion, which reacts to form an *N*-bromoamide intermediate. Like the Curtius reaction, this rearrangement is believed to be a concerted process and proceeds through an isocyanate intermediate.

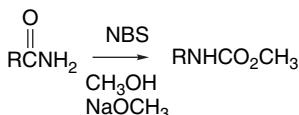


The reaction is useful in the conversion of aromatic carboxylic acids to aromatic amines.

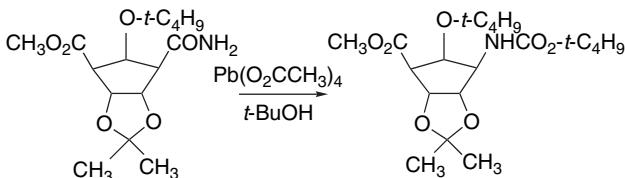


Ref. 270

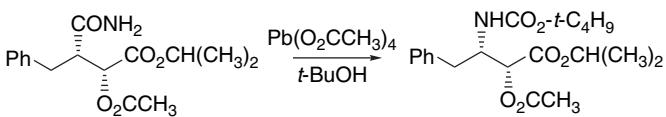
Use of *N*-bromosuccinimide in the presence of sodium methoxide or DBU in methanol traps the isocyanate intermediate as a carbamate.²⁷¹



Direct oxidation of amides can also lead to Hofmann-type rearrangement with formation of amines or carbamates. One reagent that is used is $\text{Pb}(\text{O}_2\text{CCH}_3)_4$.



Ref. 272



Ref. 273

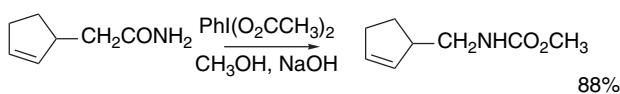
²⁷⁰ G. C. Finger, L. D. Starr, A. Roe, and W. J. Link, *J. Org. Chem.*, **27**, 3965 (1962).

²⁷¹ X. Huang and J. W. Keillor, *Tetrahedron Lett.*, **38**, 313 (1997); X. Huang, M. Said, and J. W. Keillor, *J. Org. Chem.*, **62**, 7495 (1997); J. W. Keillor and X. Huang, *Org. Synth.*, **78**, 234 (2002).

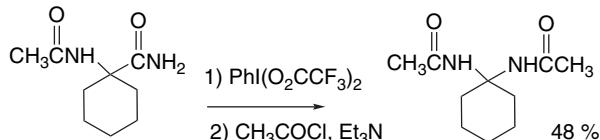
²⁷² A. Ben Cheikh, L. E. Craine, S. G. Recher, and J. Zemlicka, *J. Org. Chem.*, **53**, 929 (1988).

²⁷³ R. W. Dugger, J. L. Ralbovsky, D. Bryant, J. Commander, S. S. Massett, N. A. Sage, and J. R. Selvidio, *Tetrahedron Lett.*, **33**, 6763 (1992).

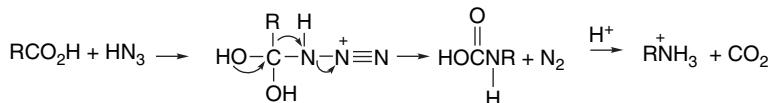
Phenyliodonium diacetate,^{274,275} and phenyliodonium *bis*-trifluoroacetate,²⁷⁶ are also useful oxidants for converting amides to carbamates.



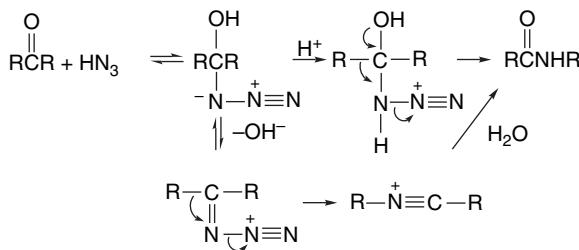
Among the recent applications of the Hofmann reaction has been the preparation of relatively unstable geminal diamides and carbinolamides. For example, 1,1-diacetamidocyclohexane can be prepared in this way.²⁷⁷



Carboxylic acids and esters can also be converted to amines with loss of the carbonyl group by reaction with hydrazoic acid, HN_3 , which is known as the *Schmidt reaction*.²⁷⁸ The mechanism is related to that of the Curtius reaction. An azido intermediate is generated by addition of hydrazoic acid to the carbonyl group. The migrating group retains its stereochemical configuration.

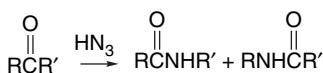


Reaction with hydrazoic acid converts ketones to amides.

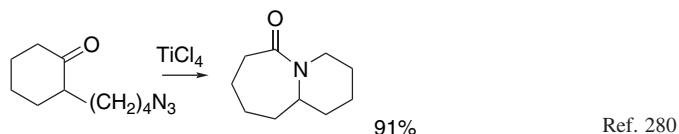
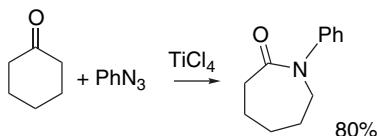


Unsymmetrical ketones can give mixtures of products because it is possible for either group to migrate.

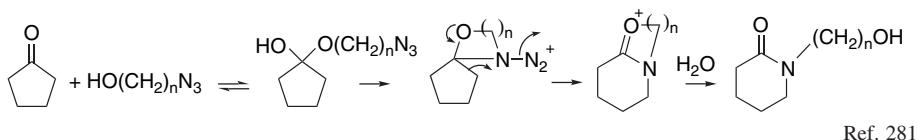
- ^{274.} R. M. Moriarty, C. J. Chany, II, R. K. Vaid, O. Prakash, and S. M. Tuladar, *J. Org. Chem.*, **58**, 2478 (1993).
- ^{275.} L.-H. Zhang, G. S. Kaufman, J. A. Pesti, and J. Yin, *J. Org. Chem.*, **62**, 6918 (1997).
- ^{276.} G. M. Loudon, A. S. Radhakrishna, M. R. Almond, J. K. Blodgett, and R. H. Boutin, *J. Org. Chem.*, **49**, 4272 (1984).
- ^{277.} M. C. Davis, D. Stasko, and R. D. Chapman, *Synth. Commun.*, **33**, 2677 (2003).
- ^{278.} H. Wolff, *Org. React.*, **3**, 307 (1946); P. A. S. Smith, in *Molecular Rearrangements*, P. de Mayo ed., Vol. 1, Interscience, New York, 1963, pp. 507–522.



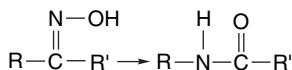
Both inter- and intramolecular variants of the Schmidt reaction in which an alkyl azide effects overall insertion have been observed.



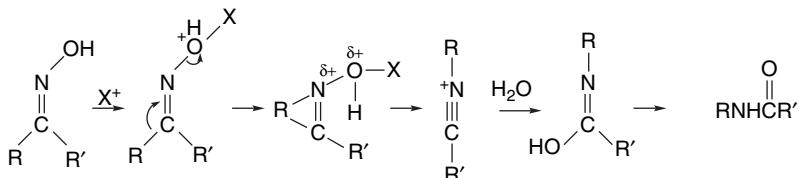
These reactions are especially favorable for β - and γ -hydroxy azides, where reaction can proceed through a hemiketal intermediate.



Another important reaction involving migration to electron-deficient nitrogen is the *Beckmann rearrangement*, in which oximes are converted to amides.²⁸²



A variety of protic acids, Lewis acids, acid anhydrides, or acyl and sulfonyl halides can cause the reaction to occur. The mechanism involves conversion of the oxime hydroxy group to a leaving group. Ionization and migration then occur as a concerted process, with the group that is *anti* to the oxime leaving group migrating. The migration results in formation of a nitrilium ion, which captures a nucleophile. Eventually hydrolysis leads to the amide.



²⁷⁹ J. Aube and G. L. Milligan, *J. Org. Chem.*, **57**, 1635 (1992).

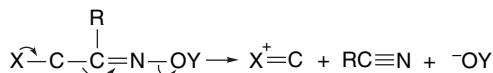
²⁸⁰ J. Aube and G. L. Milligan, *J. Am. Chem. Soc.*, **113**, 8965 (1991).

²⁸¹ V. Gracias, K. E. Frank, G. L. Milligan, and J. Aube, *Tetrahedron*, **53**, 16241 (1997).

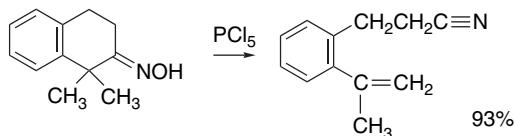
²⁸² L. G. Donaruma and W. Z. Heldt, *Org. React.*, **11**, 1 (1960); P. A. S. Smith, *Open Chain Nitrogen Compounds*, Vol. II, W. A. Benjamin, New York, 1966, pp. 47–54; P. A. S. Smith, in *Molecular Rearrangements*, Vol. 1, P. de Mayo, ed., Interscience, New York, 1973, pp. 483–507; G. R. Krow, *Tetrahedron*, **37**, 1283 (1981); R. E. Gawley, *Org. React.*, **35**, 1 (1988).

The migrating group retains its configuration. Some reaction conditions can lead to *syn-anti* isomerization at a rate exceeding rearrangement, and when this occurs, a mixture of products is formed. The reagents that have been found least likely to cause competing isomerization are phosphorus pentachloride and *p*-toluenesulfonyl chloride.²⁸³

A fragmentation reaction occurs if one of the oxime substituents can give rise to a relatively stable carbocation. Fragmentation is very likely to occur if a nitrogen, oxygen, or sulfur atom is present α to the oximino group.



Fragmentation can also occur when the α -carbon can support cationic character.

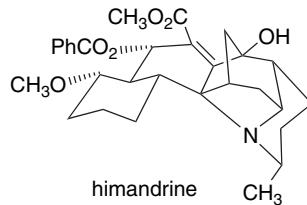


Ref. 284

Section D of Scheme 10.15 provides some examples of the Beckmann rearrangement.

Section A of Scheme 10.15 contains a number of examples of Curtius rearrangements. Entry 1 is an example carried out in a nonnucleophilic solvent, permitting isolation of the isocyanate. Entries 2 and 3 involve isolation of the amine after hydrolysis of the isocyanate. In Entry 2, the dihydrazide intermediate is isolated as a solid and diazotized in aqueous solution, from which the amine is isolated as the dihydrochloride. Entry 3 is an example of the mixed anhydride procedure (see p. 948). The first stage of the reaction is carried out in acetone and the thermolysis of the acyl azide is done in refluxing toluene. The crude isocyanate is then hydrolyzed in acidic water. Entry 4 is a reaction that demonstrates the retention of configuration during rearrangement.

Entries 5 to 8 are synthetic applications in more complex molecules. Entries 5 and 6 illustrate the diphenylphosphoroyl azide method. Entry 7 was used in the late stages of the synthesis of an antitumor macrolide, zampanolide, to introduce the amino group. The ultimate target molecule in Entry 8 is himandrine, one of several polycyclic alkaloids isolated from an ancient plant species.



²⁸³. R. F. Brown, N. M. van Gulick, and G. H. Schmid, *J. Am. Chem. Soc.*, **77**, 1094 (1955); J. C. Craig and A. R. Naik, *J. Am. Chem. Soc.*, **84**, 3410 (1962).

²⁸⁴. R. T. Conley and R. J. Lange, *J. Org. Chem.*, **28**, 210 (1963).

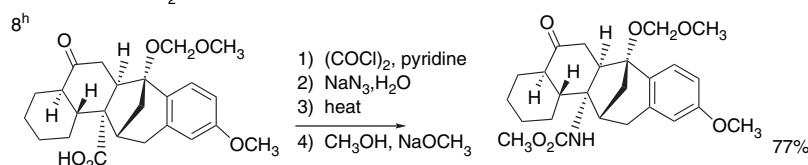
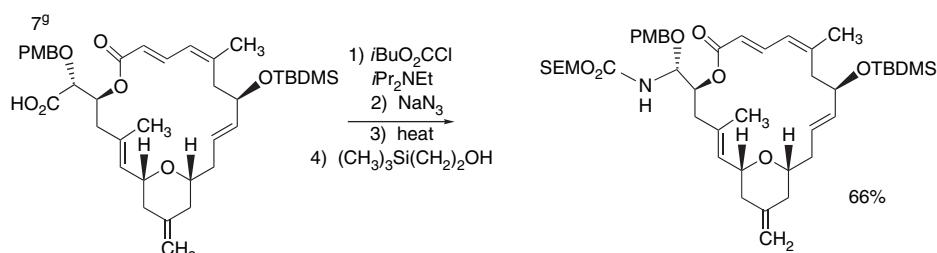
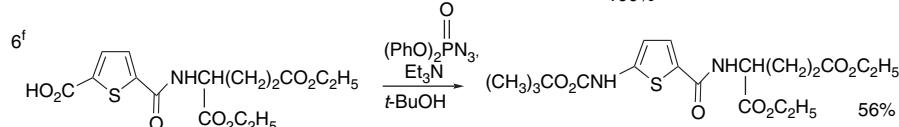
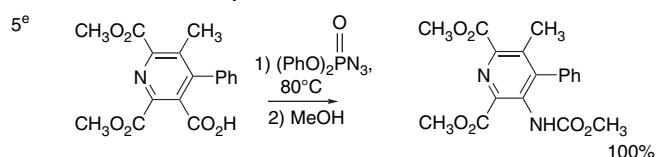
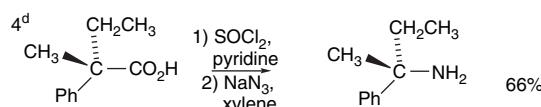
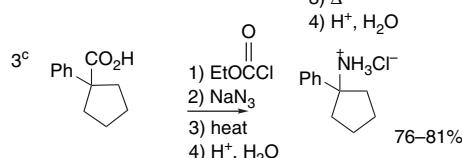
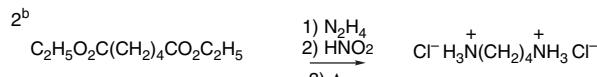
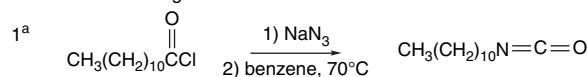
Scheme 10.15. Rearrangement to Electron-Deficient Nitrogen

953

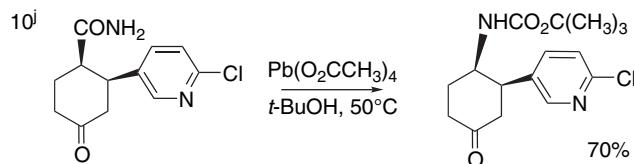
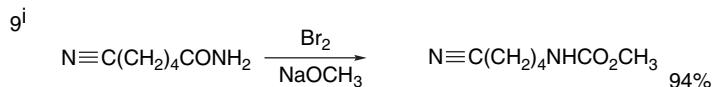
SECTION 10.2

Reactions Involving
Carbenes and Related
Intermediates

A. Curtius Rearrangements



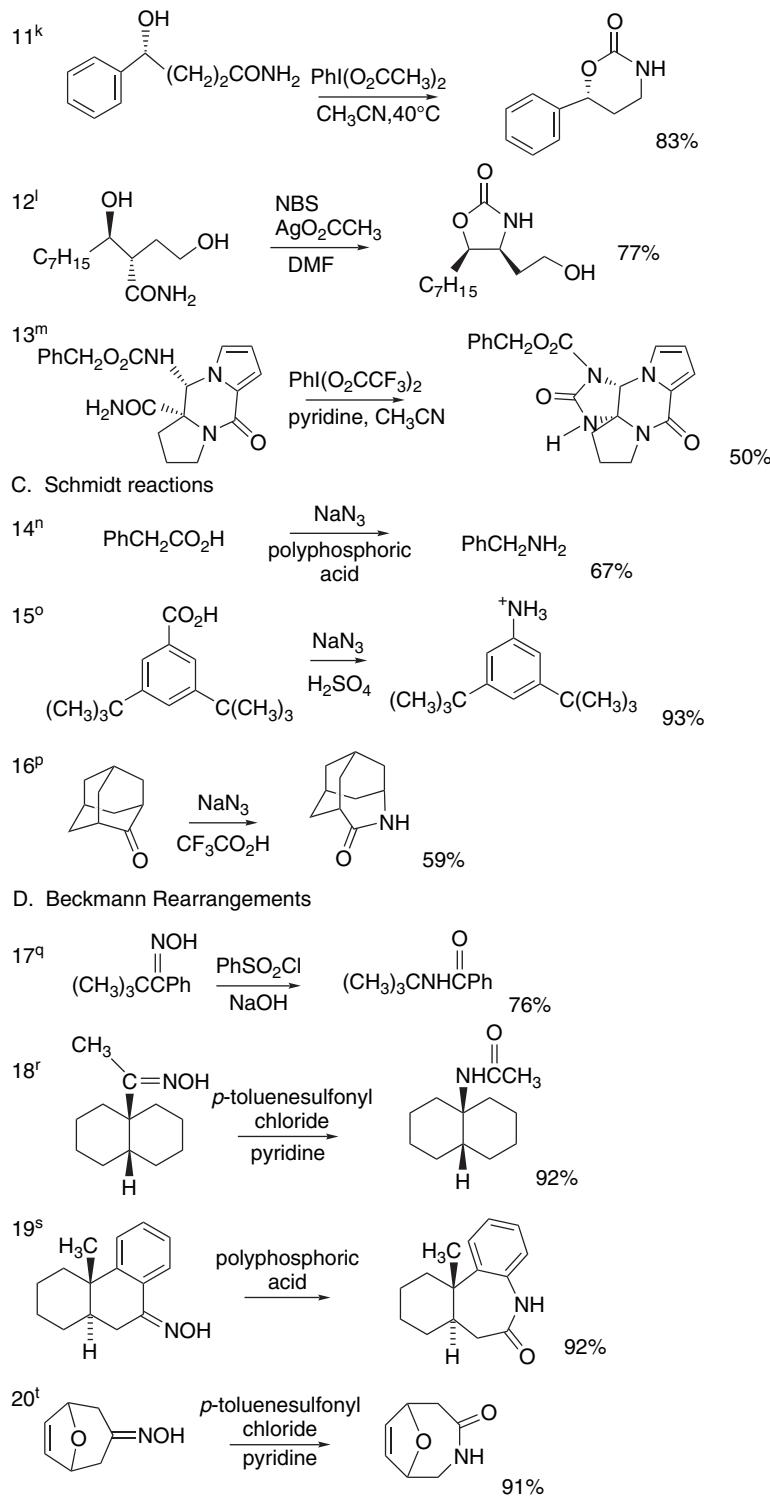
B. Hofmann Rearrangements.



(Continued)

CHAPTER 10

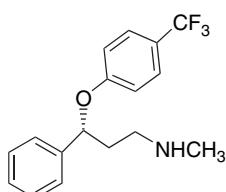
Reactions Involving
Carbocations, Carbenes,
and Radicals as Reactive
Intermediates



(continued)

- a. C. F. H. Allen and A. Bell, *Org. Synth.*, **III**, 846 (1955).
 b. P. A. S. Smith, *Org. Synth.*, **IV**, 819 (1963).
 c. C. Kaiser and J. Weinstock, *Org. Synth.*, **51**, 48 (1971).
 d. D. J. Cram and J. S. Bradshaw, *J. Am. Chem. Soc.*, **85**, 1108 (1963).
 e. D. Kim and S. M. Weinreb, *J. Org. Chem.*, **43**, 125 (1975).
 f. S. L. Cao, R. Wan, and Y.-P. Feng, *Synth. Commun.*, **33**, 3519 (2003).
 g. A. B. Smith, III, I. G. Safonov, and R. M. Corbett, *J. Am. Chem. Soc.*, **124**, 11102 (2002).
 h. P. D. O'Connor, L. N. Mander, and M. M. W. McLachlan, *Org. Lett.*, **6**, 703 (2004).
 i. R. Shapiro, R. DiCosimo, S. M. Hennessey, B. Stieglitz, O. Campopiano, and G. C. Chiang, *Org. Process Res. Dev.*, **5**, 593 (2001).
 j. D. A. Evans, K. A. Scheidt, and C. W. Downey, *Org. Lett.*, **3**, 3009 (2001).
 k. J. W. Hilborn, Z.-H. Lu, A. R. Jurgens, Q. K. Fang, P. Byers, S. A. Wald, and C. H. Senanayake, *Tetrahedron Lett.*, **42**, 8919 (2001).
 l. T. Hakogi, Y. Monden, M. Taichi, S. Iwama, S. Fujii, K. Ikeda, and S. Katsumura, *J. Org. Chem.*, **67**, 4839 (2002).
 m. K. G. Poullennec and D. Romo, *J. Am. Chem. Soc.*, **125**, 6344 (2003).
 n. R. M. Palmere and R. T. Conley, *J. Org. Chem.*, **35**, 2703 (1970).
 o. J. W. Elder and R. P. Mariella, *Can. J. Chem.*, **41**, 1653 (1963).
 p. T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, **35**, 4109 (1970).
 q. R. F. Brown, N. M. van Gulick, and G. H. Schmid, *J. Am. Chem. Soc.*, **77**, 1094 (1955).
 r. R. K. Hill and O. T. Chortyk, *J. Am. Chem. Soc.*, **84**, 1064 (1962).
 s. R. A. Barnes and M. T. Beachem, *J. Am. Chem. Soc.*, **77**, 5388 (1955).
 t. S. R. Wilson, R. A. Sawicki, and J. C. Huffman, *J. Org. Chem.*, **46**, 3887 (1981).

Section B shows some Hofmann rearrangements. Entry 9, using basic conditions with bromine, provided an inexpensive route to an intermediate for a commercial synthesis of an herbicide. Entry 10, which uses the $\text{Pb}(\text{OAc})_4$ conditions (see p. 949), was utilized in an enantiospecific synthesis of the naturally occurring analgesic ($-$)-epibatidine. Entry 11 uses phenyliodonium diacetate as the reagent. The product is the result of cyclization of the intermediate isocyanate and was used in an enantioselective synthesis of the antianxiety drug (*R*)-fluoxetine.

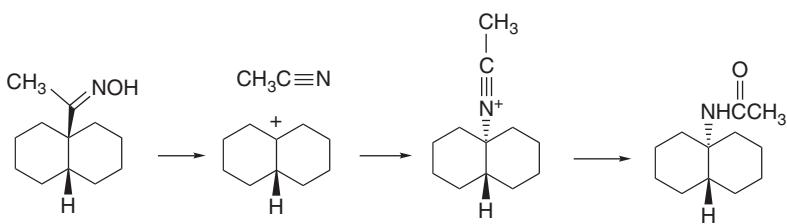


(R)-Fluoxetine

Entries 12 and 13 also involve cyclization of the isocyanate intermediates.

Section C of Scheme 10.15 shows some Schmidt reactions. Entry 14 is a procedure using polyphosphoric acid, whereas Entry 15 was done in H_2SO_4 . Entry 16 is a case of conversion of a cyclic ketone, adamantanone, to the corresponding lactam.

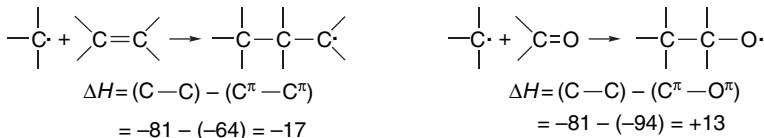
Section D shows some representative Beckmann rearrangements. Entry 17 shows a selective migration of a *t*-butyl group and illustrates the use of oxime sulfonates to control regioselectivity. The opposite regioisomer, resulting from migration of the phenyl group, was observed using HCl in acetic acid. Entry 18 illustrates another aspect of the stereochemistry of the Beckmann rearrangement. As shown, use of the benzenesulfonate led to retention of the *cis* ring juncture. When the reaction was done in H_2SO_4 or polyphosphoric acid, the *trans* isomer was formed, presumably as the result of fragmentation to a tertiary carbocation.



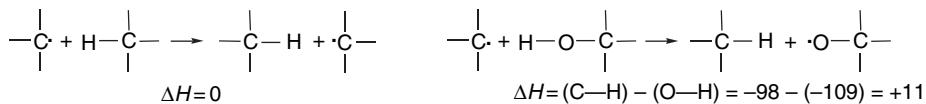
Entries 19 and 20 are examples of lactam formation by ring expansion of cyclic oximes.

10.3. Reactions Involving Free Radical Intermediates

The fundamental mechanisms of free radical reactions were considered in Chapter 11 of Part A. Several mechanistic issues are crucial in development of free radical reactions for synthetic applications.²⁸⁵ Free radical reactions are usually chain processes, and the lifetimes of the intermediate radicals are very short. To meet the synthetic requirements of high selectivity and efficiency, all steps in a desired sequence must be fast in comparison with competing reactions. Owing to the requirement that all the steps be fast, only steps that are exothermic or very slightly endothermic can participate in chain processes. Comparison between addition of a radical to a carbon-carbon double bond and addition to a carbonyl group can illustrate this point.



This comparison suggests that of these two similar reactions, only alkene additions are likely to be a part of an efficient radical chain sequence. Radical additions to carbon-carbon double bonds can be further enhanced by radical stabilizing groups. Addition to a carbonyl group, in contrast, is endothermic. In fact, the reverse fragmentation reaction is commonly observed (see Section 10.3.6) A comparison can also be made between abstraction of hydrogen from carbon as opposed to oxygen.



The reaction endothermicity establishes a *minimum* for the activation energy; whereas abstraction of a hydrogen atom from carbon is a feasible step in a chain process, abstraction of a hydrogen atom from a hydroxy group is unlikely. Homolytic cleavage of an O—H bond is likely only if the resulting oxygen radical is stabilized, such as in phenoxy radicals formed from phenols.

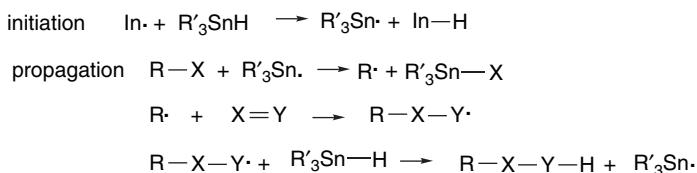


²⁸⁵ C. Walling, *Tetrahedron*, **41**, 3887 (1985).

There is a good deal of information available about the absolute rates of free radical reactions. A selection from these data is given in Table 11.3 of Part A. If the steps in a projected reaction sequence correspond to reactions for which absolute rates are known, this information can allow evaluation of the kinetic feasibility of the reaction sequence.

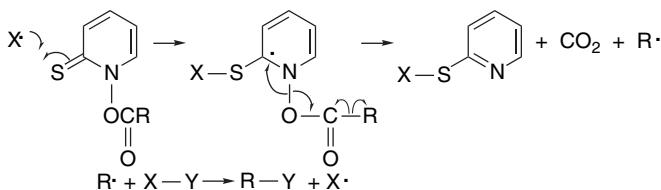
10.3.1. Sources of Radical Intermediates

There is a discussion of some of the sources of radicals for mechanistic studies in Section 11.1.4 of Part A. Some of the reactions discussed there, particularly the use of azo compounds and peroxides as initiators, are also important in synthetic chemistry. One of the most useful sources of free radicals in preparative chemistry is the reaction of halides with stannyl radicals. Stannanes undergo hydrogen abstraction reactions and the stannyl radical can then abstract halogen from the alkyl group. For example, net addition of an alkyl group to a reactive double bond can follow halogen abstraction by a stannyl radical.



This generalized reaction sequence consumes the halide, the stannane, and the reactant $\text{X}=\text{Y}$, and effects addition to the organic radical and a hydrogen atom to the $\text{X}=\text{Y}$ bond. The order of reactivity of organic halides toward stannyl radicals is iodides > bromides > chlorides.

Esters of *N*-hydroxypyridine-2-thione are another versatile source of radicals,²⁸⁶ where the radical is formed by decarboxylation of an adduct formed by attack at sulfur by the chain-carrying radical.²⁸⁷ The generalized chain sequence is as follows.

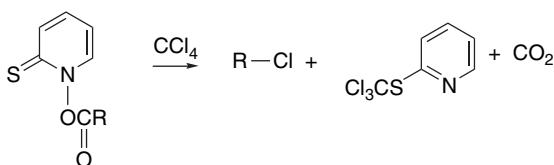


When $\text{X}-\text{Y}$ is $\text{R}_3\text{Sn}-\text{H}$ the net reaction is decarboxylation and reduction of the original acyloxy group. Halogen atom donors can also participate in such reactions.

²⁸⁶ D. Crich, *Aldrichimica Acta*, **20**, 35 (1987); D. H. R. Barton, *Aldrichimica Acta*, **23**, 3 (1990).

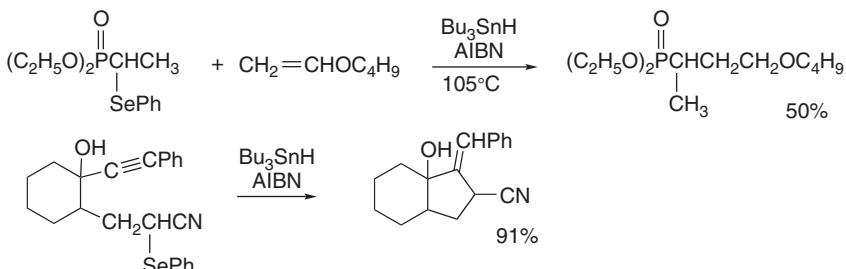
²⁸⁷ D. H. R. Barton, D. Crich, and W. B. Motherwell, *Tetrahedron*, **41**, 3901 (1985); D. H. R. Barton, D. Crich, and G. Kretzschmar, *J. Chem. Soc., Perkin Trans. 1*, 39 (1986); D. H. R. Barton, D. Bridson, I. Fernandez-Picot, and S. Z. Zard, *Tetrahedron*, **43**, 2733 (1987).

When X–Y is $\text{Cl}_3\text{C}–\text{Cl}$, the final product is a chloride.²⁸⁸ Use of $\text{Cl}_3\text{C}–\text{Br}$ gives the corresponding bromide.²⁸⁹

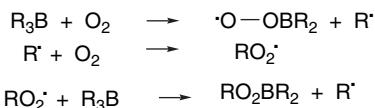


The precise reaction conditions for optimal yields depend upon the specific reagents and both thermal²⁹⁰ and photochemical²⁹¹ conditions have been developed. Phenyl thionocarbonates are easily prepared and are useful in radical generating reactions.²⁹² A variety of other thiono esters, including xanthates and imidazolyl thionocarbonates also can be used.²⁹³

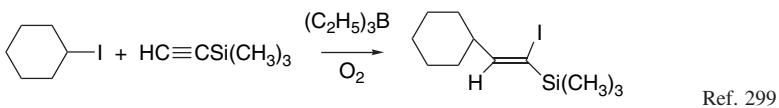
Selenyl groups can be abstracted by stannyl radicals from alkyl and acyl selenides to generate the corresponding radicals.²⁹⁴ Among the types of compounds that react by selenyl transfer are α -selenylphosphonates²⁹⁵ and α -selenylcyanides.²⁹⁶ The radicals generated can undergo addition and/or cyclization. The chain reaction is propagated by abstraction of hydrogen from the stannane.



Trialkylboranes, especially triethylborane, are used in conjunction with O_2 to generate radicals.²⁹⁷ The alkyl radicals are generated by breakdown of a borane-oxygen adduct. An advantage this method has over many other radical initiation systems is that it proceeds at low temperature, e.g., -78°C .

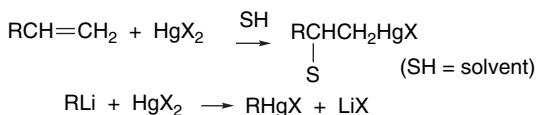


- ²⁸⁸ D. H. R. Barton, D. Crich, and W. B. Motherwell, *Tetrahedron Lett.*, **24**, 4979 (1983).
- ²⁸⁹ D. H. R. Barton, R. Lacher, and S. Z. Zard, *Tetrahedron Lett.*, **26**, 5939 (1983).
- ²⁹⁰ D. H. R. Barton, J. L. Jaszberenyi, and D. Tang, *Tetrahedron Lett.*, **54**, 3381 (1993).
- ²⁹¹ J. Bouvin, E. Crepon, and S. Z. Zard, *Tetrahedron Lett.*, **32**, 199 (1991).
- ²⁹² M. J. Robins, J. S. Wilson, and F. Hansske, *J. Am. Chem. Soc.*, **105**, 4059 (1983).
- ²⁹³ D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. I*, 1574 (1975).
- ²⁹⁴ J. Pfenninger, C. Heuberger, and W. Graf, *Helv. Chim. Acta*, **63**, 2328 (1980); D. L. Boger and R. J. Mathivink, *J. Org. Chem.*, **53**, 3377 (1988); D. L. Boger and R. J. Mathivink, *J. Org. Chem.*, **57**, 1429 (1992).
- ²⁹⁵ P. Balczewski, W. M. Pietrzykowski, and M. Mikolajczyk, *Tetrahedron*, **51**, 7727 (1995).
- ²⁹⁶ D. L. J. Clive, T. L. B. Boivin, and A. G. Angoh, *J. Org. Chem.*, **52**, 4943 (1987).
- ²⁹⁷ C. Ollivier and P. Renaud, *Chem. Rev.*, **101**, 3415 (2001).

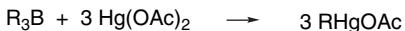


These reactions result in *iodine atom transfer* and introduce a potential functional group into the product. The trialkylborane method of radical generation can also be used in conjunction with either tri-*n*-butyl stannane or *tris*-(trimethylsilyl)silane, in which case the product is formed by hydrogen atom transfer.

The reductive decomposition of alkylmercury compounds is also a useful source of radicals.³⁰⁰ The organomercury compounds are available by oxymercuration (see Section 4.1.3) or from organometallic compounds as a result of metal-metal exchange (see Section 7.3.3).

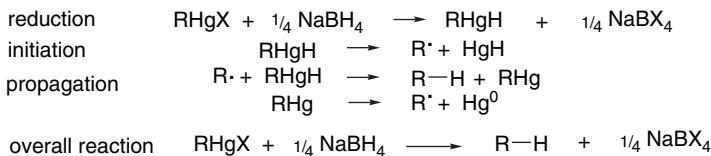


Alkylmercury reagents can also be prepared from alkyl boranes.



Ref. 301

The mercuric hydride formed by reduction undergoes chain decomposition to generate alkyl radicals.



10.3.2. Addition Reactions of Radicals with Substituted Alkenes

The most general method for formation of new carbon-carbon bonds via radical intermediates involves addition of the radical to an alkene. The reaction generates a new radical that can propagate a chain sequence. The preferred alkenes for trapping alkyl

²⁹⁸. H. C. Brown and M. M. Midland, *Angew. Chem. Int. Ed. Engl.*, **11**, 692 (1972); K. Nozaki, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, **29**, 1041 (1988).

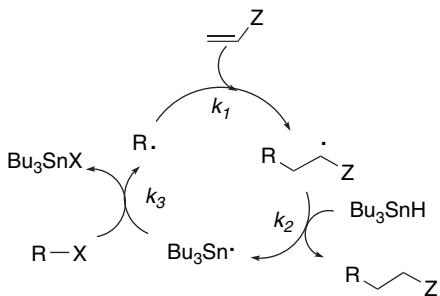
²⁹⁹. Y. Ichinose, S. Matsunaga, K. Fugami, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, **30**, 3155 (1989).

³⁰⁰. G. A. Russell, *Acc. Chem. Res.*, **22**, 1 (1989).

³⁰¹. R. C. Larock and H. C. Brown, *J. Am. Chem. Soc.*, **92**, 2467 (1976).

radicals are ethene derivatives with electron-attracting groups, such as cyano, ester, or other carbonyl substituents.³⁰² There are three factors that make such compounds particularly useful: (1) alkyl radicals are relatively *nucleophilic* and react at enhanced rates with alkenes having EWG substituents; (2) alkenes with such substituents exhibit a good degree of regioselectivity, resulting from a combination of steric and radical-stabilizing effects of the substituent; (3) the EWG substituent makes the adduct radical *more electrophilic* and increases the rate of the subsequent hydrogen abstraction step. The “nucleophilic” versus “electrophilic” character of radicals can be understood in terms of the FMO description of substituent effects on radicals. The three most important cases are outlined in Figure 10.12. An ERG in the radical raises the energy of the SOMO, which increases the stabilizing interaction with the LUMO of alkenes having EWG substituents. In the opposite combination, an EWG substituent on the radicals lowers the SOMO and the strongest interaction is with the alkene HOMO.

This interaction is stabilizing because of lowering of the alkene HOMO. Radicals for addition reactions can be generated by halogen atom abstraction by stannyl radicals. The chain mechanism for alkylation of alkyl halides by reaction with a substituted alkene is outlined below. There are three reactions in the propagation cycle of this chain mechanism: addition, hydrogen atom abstraction, and halogen atom transfer.



The rates of each of these steps must exceed competing chain termination reactions in order for good yields to be obtained. The most important competitions are between: (a) the addition step k_1 and reaction of the intermediate $\text{R}\cdot$ with Bu_3SnH , and (b) between the H abstraction step k_2 and addition to another molecule of the alkene. If

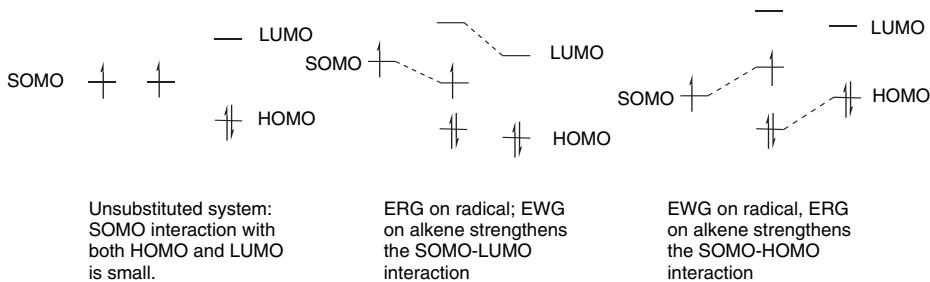
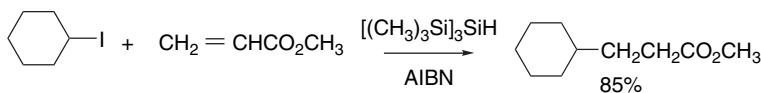
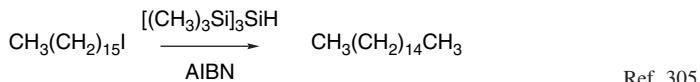


Fig. 10.12. Frontier orbital interpretation of radical substituent effects.

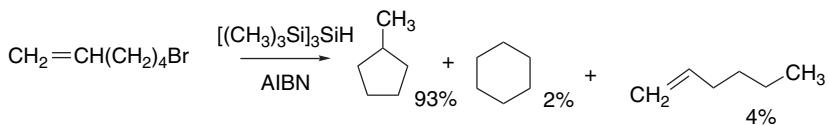
³⁰² B. Giese, *Angew. Chem. Int. Ed. Engl.*, **22**, 753 (1983); B. Giese, *Angew. Chem. Int. Ed. Engl.*, **24**, 553 (1985).

the addition step k_1 is not fast enough, the radical R· will abstract H from the stannane and the overall reaction will simply be dehalogenation. If step k_2 is not fast relative to a successive addition step, formation of oligomers containing several alkene units will occur. For good yields R· must be more reactive to the substituted alkene than is $\text{RCH}_2\text{C}\cdot\text{HZ}$ and $\text{RCH}_2\text{C}\cdot\text{HZ}$ must be more reactive toward Bu_3SnH than is R·. These requirements are met when Z is an electron-attracting group. Yields are also improved if the concentration of Bu_3SnH is kept low to minimize the reductive dehalogenation, which can be done by adding the stannane slowly as the reaction proceeds. Another method is to use only a small amount of the trialkyltin hydride along with a reducing agent, such as NaBH_4 or NaBH_3CN , that can regenerate the reactive stannane.³⁰³ Radicals formed by fragmentation of thionocarbonates and related thiono esters can also be trapped by reactive alkenes. The mechanism of radical generation from thiono esters was discussed in connection with the Barton deoxygenation method in Section 5.5.

Although most radical reactions involving chain propagation by hydrogen atom transfer can be done using trialkylstannanes, several silanes have been investigated as alternatives.³⁰⁴ *Tris*-(trimethylsilyl)silane reacts with alkyl radicals at about one-tenth the rate of *tri-n*-butylstannane. The *tris*-(trimethylsilyl)silyl radical is reactive toward iodides, sulfides, selenides, and thiono esters, permitting chain transfer. Thus it is possible to substitute *tris*-(trimethylsilyl)silane for *tri-n*-butylstannane in reactions such as dehalogenations, radical additions, and cyclizations. A virtue of the silane donors is that they avoid the tin-containing by-products of stannane reactions that can cause purification problems.



Ref. 306



Ref. 306

Alkyl radicals generated by reduction of organomercury compounds can also add to alkenes having EWG groups. Radicals are generated by reduction of the organomercurial by NaBH_4 or a similar reductant. These techniques have been

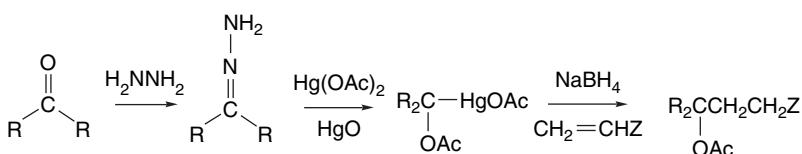
³⁰³ B. Giese, J. A. Gonzalez-Gomez, and T. Witzel, *Angew. Chem. Int. Ed. Engl.*, **23**, 69 (1984).

³⁰⁴ C. Chatgilialoglu, *Acc. Chem. Res.*, **25**, 188 (1991).

³⁰⁵ C. Chatgilialoglu, A. Guerrini, and G. Sesoni, *Synlett*, 219 (1990).

³⁰⁶ B. Giese, B. Kopping, and C. Chatgilialoglu, *Tetrahedron Lett.*, **30**, 681 (1989).

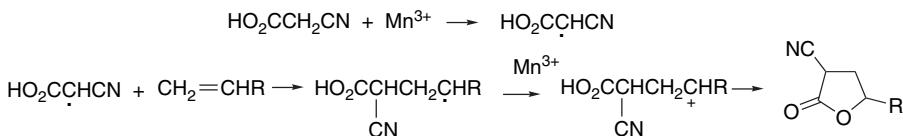
applied to β -hydroxy-,³⁰⁷ β -alkoxy-,³⁰⁸ and β -amido-³⁰⁹ alkylmercury derivatives. α -Acetoxyalkylmercury compounds can be prepared from hydrazones by mercuric oxide and mercuric acetate.



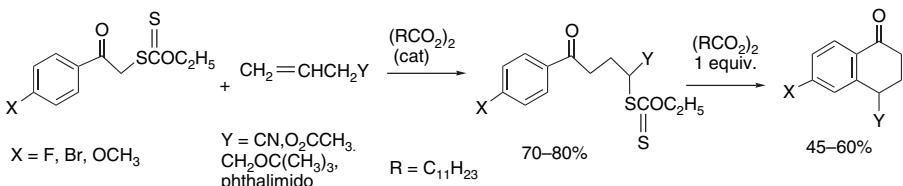
Ref. 310

Several other examples of addition reactions involving organomercury compounds are given in Section B of Scheme 10.16 at the end of this section.

There are also reactions in which electrophilic radicals react with relatively nucleophilic alkenes. These reactions are exemplified by a group of procedures in which a radical intermediate is formed by oxidation of readily enolizable compounds. This reaction was initially developed for β -ketoacids,³¹¹ and the method has been extended to β -diketones, malonic acids, and cyanoacetic acid.³¹² The radicals formed by the addition step are rapidly oxidized to cations, which give rise to the final product by intramolecular capture of a carboxylate group.



Phenacyl radicals can be generated from the corresponding xanthates and add in good yield to various substituted propenes. The products of the reaction can then be cyclized to tetralones using an equivalent of a peroxide.³¹³



^{307.} A. P. Kozikowski, T. R. Nieduzak, and J. Scripko, *Organometallics*, **1**, 675 (1982).

^{308.} B. Giese and K. Heuck, *Chem. Ber.*, **112**, 3759 (1979); B. Giese and U. Luening, *Synthesis*, 735 (1982).

^{309.} A. P. Kozikowski and J. Scripko, *Tetrahedron Lett.*, **24**, 2051 (1983).

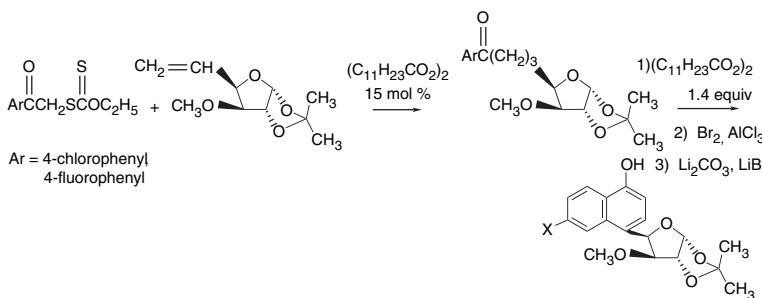
^{310.} B. Giese and U. Erfort, *Chem. Ber.*, **116**, 1240 (1983).

^{311.} E. Heiba and R. M. Dessau, *J. Org. Chem.*, **39**, 3456 (1974).

^{312.} E. J. Corey and M. C. Kang, *J. Am. Chem. Soc.*, **106**, 5384 (1984); E. J. Corey and A. W. Gross, *Tetrahedron Lett.*, **26**, 4291 (1985); W. E. Fristad and S. S. Hershberger, *J. Org. Chem.*, **50**, 1026 (1985).

^{313.} A. Liard, B. Quiclet-Sire, R. N. Saicic, and S. Z. Zard, *Tetrahedron Lett.*, **38**, 1759 (1997).

This methodology has been applied to carbohydrate derivatives and provides a route to certain C-aryl glycosides.

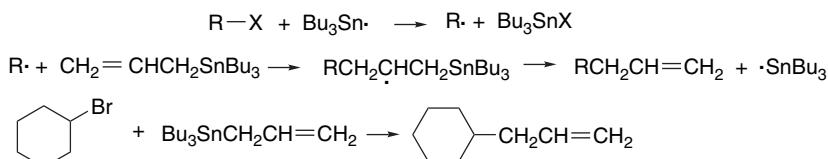


Ref. 314

Scheme 10.16 gives some examples of radical addition reactions. Entry 1 is a typical alkylation reaction using Bu_3SnH as the chain carrier and hydrogen atom donor. The reaction was done at 100°C in toluene by slow (syringe pump) addition of one equivalent of Bu_3SnH . Five equivalents of methyl acrylate was used. Entry 2 utilized in situ generation of Bu_3SnH . This carbohydrate-derived bromide could not be added successfully to acrylonitrile or methyl acrylate under standard conditions. A tenfold excess of phenyl vinyl sulfone was used. In Entry 3, a carbohydrate-derived acrylate is the reactant. The stannane was added by syringe pump and a 20-fold excess of the iodoacetamide was used. In Entry 4, the unprotected carbohydrate hydroxy group was converted to a xanthate ester and then added to acrylonitrile. The stereoselectivity is determined by conformational factors that establish a preference for the direction of reagent approach. Radicals with a large bias can give highly stereoselective reactions.

Entry 5 is an example of the use of *tris*-(trimethylsilyl)silane as the chain carrier. Entries 6 to 11 show additions of radicals from organomercury reagents to substituted alkenes. In general, the stereochemistry of these reactions is determined by reactant conformation and steric approach control. In Entry 9, for example, addition is from the *exo* face of the norbornyl ring. Entry 12 is an example of addition of an acyl radical from a selenide. These reactions are subject to competition from decarbonylation, but the relatively slow decarbonylation of aroyl radicals (see Part A, Table 11.3) favors addition in this case.

Allylic stannanes are an important class of compounds that undergo substitution reactions with alkyl radicals. The chain is propagated by elimination of the trialkylstanny radical.³¹⁵ The radical source must have some functional group that can be abstracted by trialkylstanny radicals. In addition to halides, both thiono esters³¹⁶ and selenides³¹⁷ are reactive.



³¹⁴ A. Cordero-Vargas, B. Quiclet-Sire, and S. Z. Zard, *Tetrahedron Lett.*, **45**, 7335 (2004).

³¹⁵ G. E. Keck and J. B. Yates, *J. Am. Chem. Soc.*, **104**, 5829 (1982).

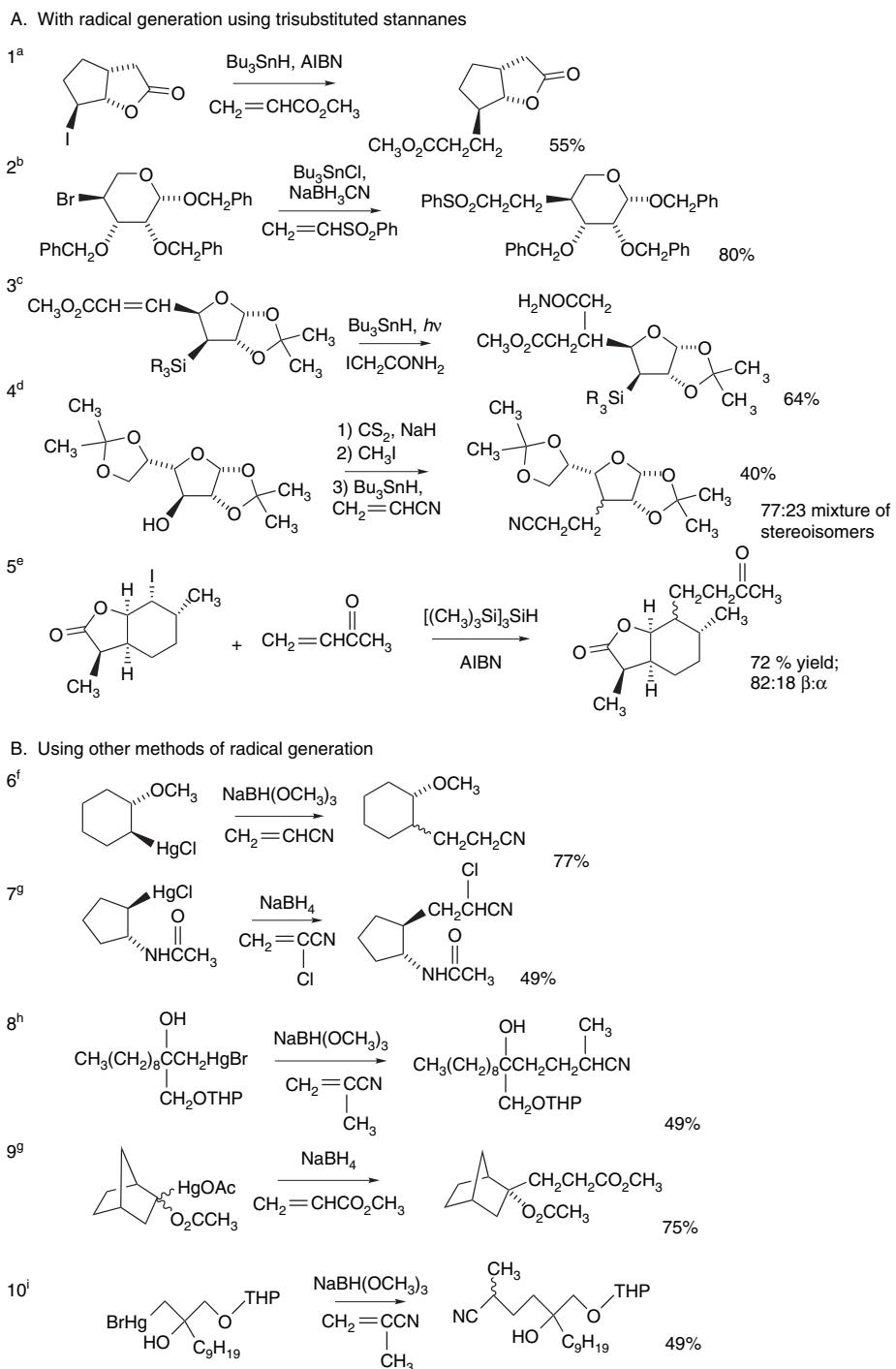
³¹⁶ G. E. Keck, D. F. Kachensky, and E. J. Enholm, *J. Org. Chem.*, **49**, 1462 (1984).

³¹⁷ R. R. Webb and S. Danishefsky, *Tetrahedron Lett.*, **24**, 1357 (1983); T. Toru, T. Okumura, and Y. Ueno, *J. Org. Chem.*, **55**, 1277 (1990).

Scheme 10.16. Addition of Alkyl Radicals to Alkenes

CHAPTER 10

Reactions Involving Carbocations, Carbenes, and Radicals as Reactive Intermediates

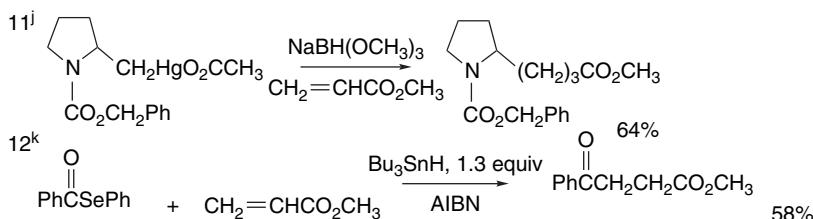


(Continued)

Scheme 10.16. (Continued)

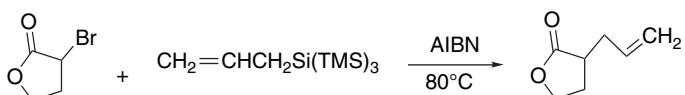
SECTION 10.3

Reactions Involving Free Radical Intermediates

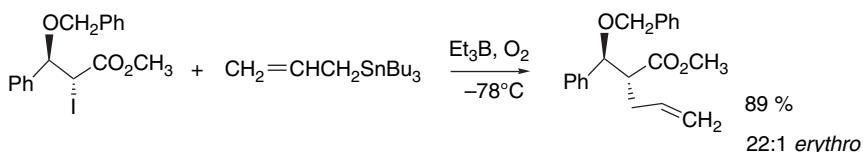


- a. S. D. Burke, W. B. Fobare, and D. M. Arminsteadt, *J. Org. Chem.*, **47**, 3348 (1982).
- b. M. V. Rao and M. Nagarajan, *J. Org. Chem.*, **53**, 1432 (1988).
- c. G. Sacripante, C. Tan, and G. Just, *Tetrahedron Lett.*, **26**, 5643 (1985).
- d. B. Giese, J. A. Gonzalez-Gomez, and T. Witzel, *Angew. Chem. Int. Ed. Engl.*, **23**, 69 (1984).
- e. J. S. Yadav, R. S. Babu, and G. Sabitha, *Tetrahedron Lett.*, **44**, 387 (2003).
- f. B. Giese and K. Heuck, *Chem. Ber.*, **112**, 3759 (1979).
- g. R. Henning and H. Urbach, *Tetrahedron Lett.*, **24**, 5343 (1983).
- h. A. P. Kozikowski, T. R. Nieduzak, and J. Scripko, *Organometallics*, **1**, 675 (1982).
- i. B. Giese and U. Erfort, *Chem. Ber.*, **116**, 1240 (1983).
- j. S. Danishefsky, E. Taniyama, and R. P. Webb, II, *Tetrahedron Lett.*, **24**, 11 (1983).
- k. D. L. Boger and R. J. Mathvink, *J. Org. Chem.*, **57**, 1429 (1992).

Allyl tris-(trimethylsilyl)silane can react similarly.³¹⁸



Allylation reactions can be initiated by triethylboron. This procedure has been found to give improved stereoselectivity in acyclic allylations.³¹⁹



Scheme 10.17 illustrates allylation by reaction of radical intermediates with allyl stannanes. The first entry uses a carbohydrate-derived xanthate as the radical source. The addition in this case is highly stereoselective because the shape of the bicyclic ring system provides a steric bias. In Entry 2, a primary phenylthiocarbonate ester is used as the radical source. In Entry 3, the allyl group is introduced at a rather congested carbon. The reaction is completely stereoselective, presumably because of steric features of the tricyclic system. In Entry 4, a primary selenide serves as the radical source. Entry 5 involves a tandem alkylation-allylation with triethylboron generating the ethyl radical that initiates the reaction. This reaction was done in the presence of a Lewis acid, but lanthanide salts also give good results.

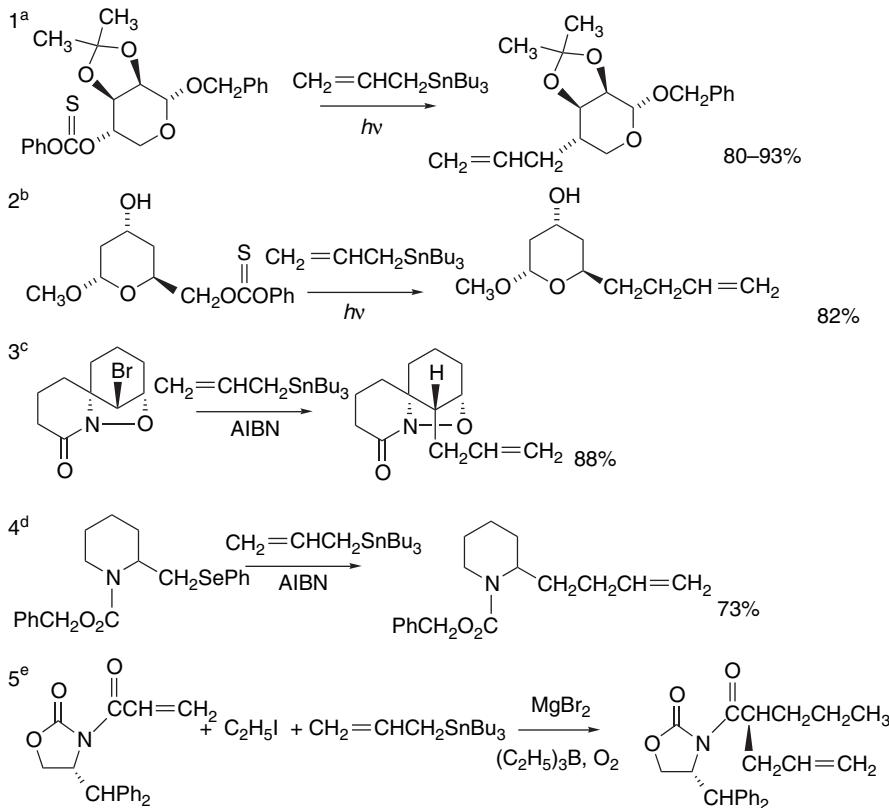
³¹⁸ C. Chatgilialoglu, C. Ferreri, M. Ballestri, and D. P. Curran, *Tetrahedron Lett.*, **37**, 6387 (1996).

³¹⁹ Y. Guindon, J. F. Lavallee, L. Boisvert, C. Chabot, D. Delorme, C. Yoakim, D. Hall, R. Lemieux, and B. Simoneau, *Tetrahedron Lett.*, **32**, 27 (1991).

Scheme 10.17. Allylation of Radical Centers

CHAPTER 10

Reactions Involving
Carbocations, Carbenes,
and Radicals as Reactive
Intermediates



a. G. E. Keck, D. F. Kachensky, and E. J. Enholm, *J. Org. Chem.*, **50**, 4317 (1985).

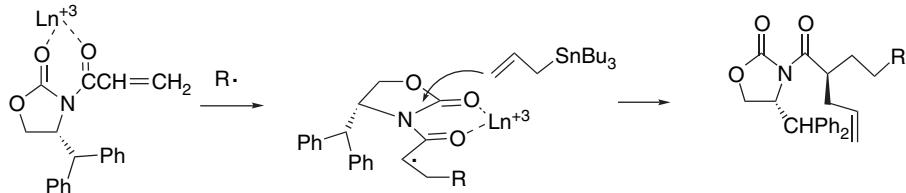
b. G. E. Keck and D. F. Kachensky, *J. Org. Chem.*, **51**, 2487 (1986).

c. G. E. Keck and J. B. Yates, *J. Org. Chem.*, **47**, 3590 (1982).

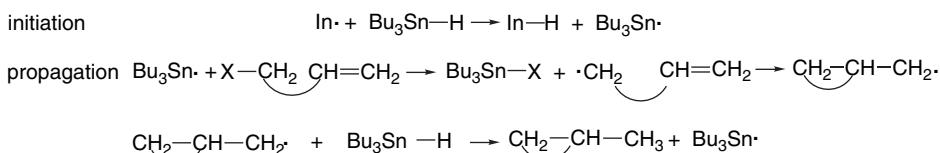
d. R. R. Webb, II, and S. Danishefsky, *Tetrahedron Lett.*, **24**, 1357 (1983).

e. M. P. Sibi and J. Ji, *J. Org. Chem.*, **61**, 6090 (1996).

These reactions exhibit excellent diastereoselectivity derived from the chiral oxazolidinone auxiliary. The Lewis acid forms a chelate with the oxazoline and presumably also serves to enhance reactivity. In addition to ethyl, other primary, secondary, and tertiary alkyl radicals, as well as acetyl and benzoyl radicals were used successfully in analogous reactions.



Cyclization of radical intermediates is an important method for ring synthesis.³²⁰ The key step involves addition of a radical center to an unsaturated functional group. Many of these reactions involve halides as the source of the radical intermediate. The radicals are normally generated by halogen atom abstraction using a trialkylstannane as the reagent and AIBN as the initiator. The cyclization step must be fast relative to hydrogen abstraction from the stannane. The chain is propagated when the cyclized radical abstracts hydrogen from the stannane.



From a synthetic point of view, the regioselectivity and stereoselectivity of the cyclization are of paramount importance. As discussed in Section 11.2.3.3 of Part A, the order of preference for cyclization of alkyl radicals is 5-*exo* > 6-*endo*; 6-*exo* > 7-*endo*; 8-*endo* > 7-*exo* because of stereoelectronic preferences. For relatively rigid cyclic structures, proximity and alignment factors determined by the specific geometry of the ring system are of major importance. Theoretical analysis of radical addition indicates that the major interaction of the attacking radical is with the alkene LUMO.³²¹ The preferred direction of attack is not perpendicular to the π system, but rather at an angle of about 110°.

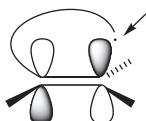


Figure 10.13 shows the preferred geometries and calculated energy differences based on MM2 modeling.

Another major influence on the direction of cyclization is the presence of substituents. Attack at a less hindered position is favored by both steric effects and the stabilizing effect that most substituents have on a radical center. These have been examined by DFT (UB3LYP/6-31+G**) calculations, and the results for 5-hexenyl radicals are shown in Figure 10.14. For the unsubstituted system, the 5-*exo* chair TS is favored over the 6-*endo* chair by 2.7 kcal/mol. A 5-methyl substituent disfavors the 5-*exo* relative to the 6-*endo* mode by 0.7 kcal/mol, whereas a 6-methyl substituent increases the preference for the 5-*exo* TS to 3.3 kcal/mol.³²²

³²⁰ D. P. Curran, *Synthesis*, 417 (1988); *Synthesis*, 489 (1988); C. P. Jasperse, D. P. Curran, and T. L. Fervig, *Chem. Rev.*, **91**, 1237 (1991); K. C. Majumdar, P. K. Basu, and P. P. Mukhopadhyay, *Tetrahedron*, **60**, 6239 (2004).

³²¹ A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, **41**, 3925 (1985); D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.*, **52**, 959 (1987).

³²² A. G. Leach, R. Wang, G. E. Wohlhieter, S. I. Khan, M. E. Jung, and K. N. Houk, *J. Am. Chem. Soc.*, **125**, 4271 (2003).

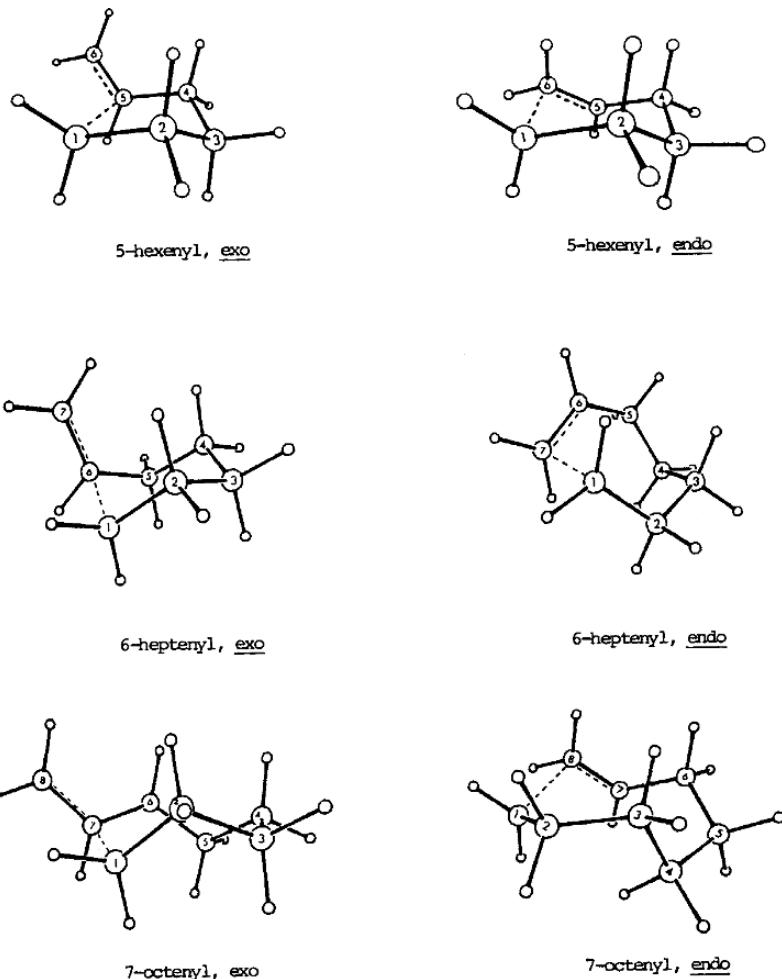
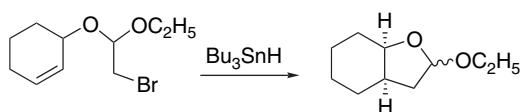


Fig. 10.13. MM2 models of *exo* and *endo* cyclization transition structures for 5-hexenyl, 6-heptenyl, and 7-octenyl radicals. Reproduced from *Tetrahedron*, **41**, 3925 (1985), by permission of Elsevier.

Radical cyclization reactions have been extensively applied in synthesis. Among the first systems to be studied were unsaturated mixed acetals of bromoacetaldehyde.³²³



³²³ G. Stork, R. Mook, Jr., S. A. Biller, and S. D. Rychnovsky, *J. Am. Chem. Soc.*, **105**, 3741 (1983).

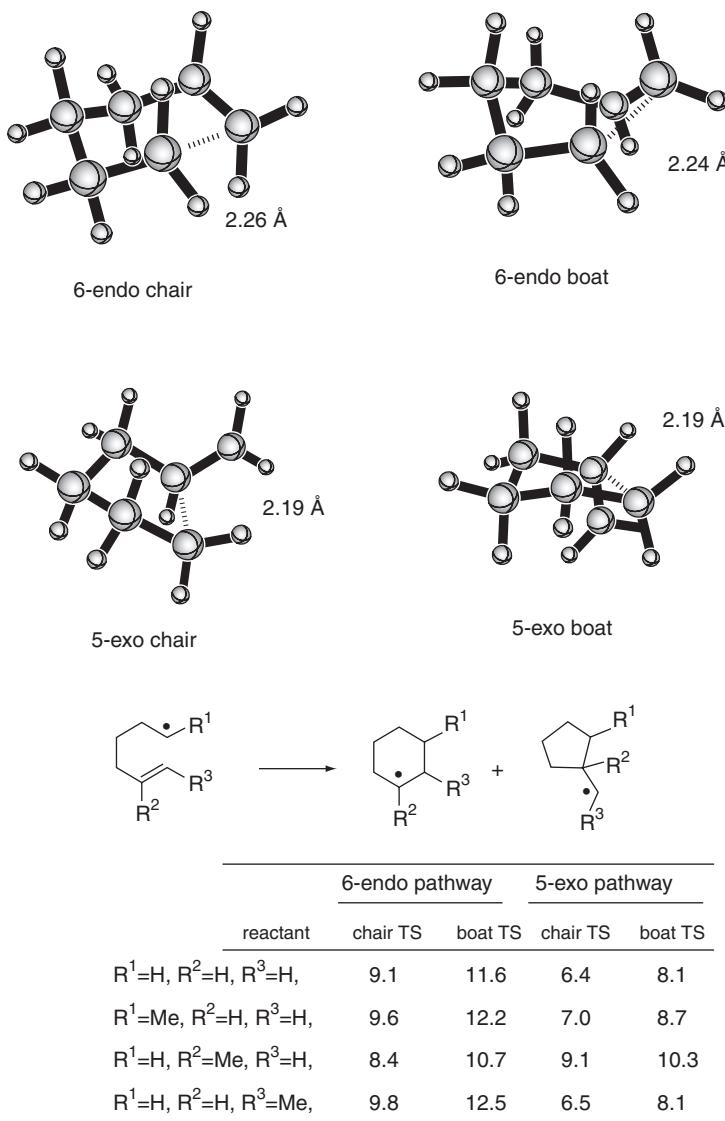
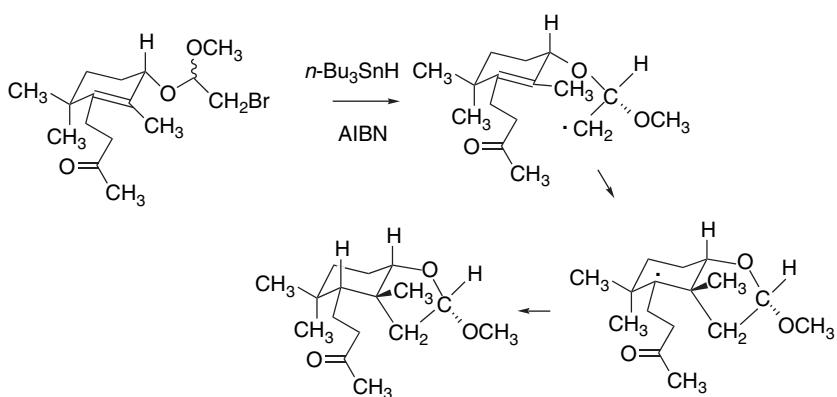


Fig. 10.14. Relative energies of 5-*exo* and 6-*endo* transition structures. Insert shows the effect of methyl substituents. Reproduced from *J. Am. Chem. Soc.*, **125**, 4271 (2003), by permission of the American Chemical Society.

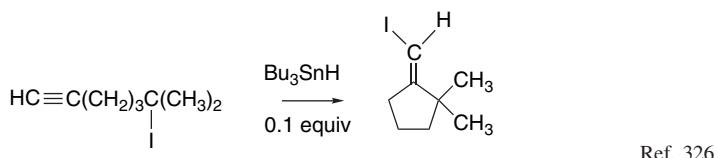
This reaction has subsequently been used in a number of other cases.³²⁴ The five-membered rings are usually fused in a *cis* manner, minimizing strain. When cyclization is followed by hydrogen abstraction, the hydrogen atom is normally delivered from the less hindered side of the molecule. The following example illustrates these generalizations. The initial tetrahydrofuran ring closure gives the *cis*-fused ring. The subsequent hydrogen abstraction is from the less hindered axial direction.³²⁵

³²⁴. X. J. Salom-Roig, F. Denes, and P. Renaud, *Synthesis*, 1903 (2004).

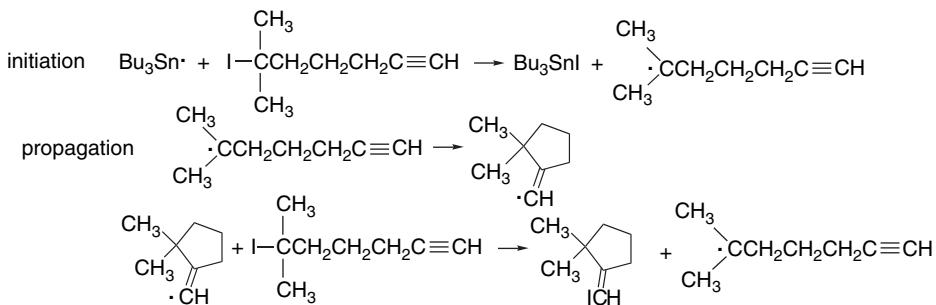
³²⁵. M. J. Begley, H. Bhandal, J. H. Hutchinson, and G. Pattenden, *Tetrahedron Lett.*, **28**, 1317 (1987).



Reaction conditions have been developed in which the cyclized radical can react in some manner other than hydrogen atom abstraction. One such reaction is an iodine atom transfer. The cyclization of 2-iodo-2-methyl-6-heptyne is a structurally simple example.



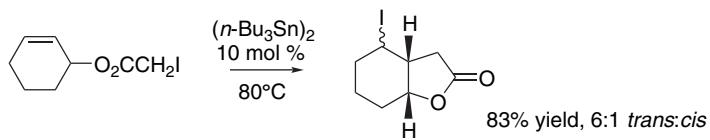
In this reaction, the trialkylstannane serves to initiate the chain sequence but it is present in low concentration to minimize the rate of hydrogen atom abstraction from the stannane. Under these conditions, the chain is propagated by iodine atom abstraction.



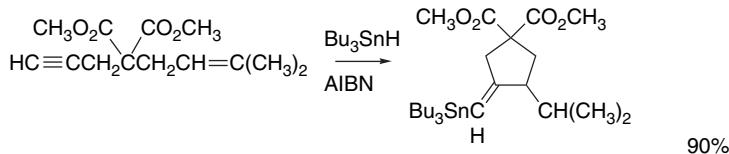
The fact that the cyclization is directed toward an acetylenic group and leads to formation of an alkenyl radical is significant. Formation of a saturated iodide could lead to a more complex product mixture because the cyclized product could undergo iodine atom transfer and proceed to add to a second unsaturated center. Vinyl iodides are much less reactive and the reaction product is unreactive. Owing to the potential

³²⁶ D. P. Curran, M.-H. Chen, and D. Kim, *J. Am. Chem. Soc.*, **108**, 2489 (1986); D. P. Curran, M.-H. Chen, and D. Kim, *J. Am. Chem. Soc.*, **111**, 6265 (1989).

for competition from reduction by the stannane, other reaction conditions have been developed to promote cyclization. Hexabutylditin can be used.³²⁷

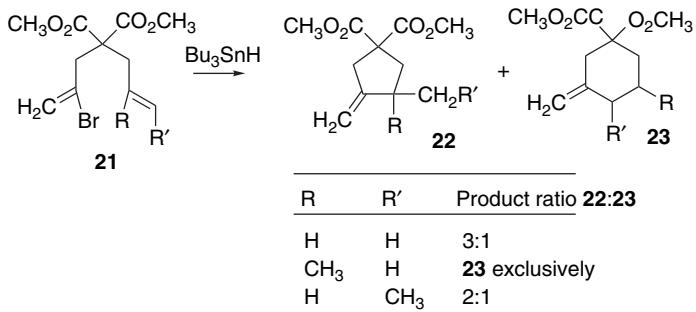


Alkenyl radicals generated by addition of trialkylstanny radicals to terminal alkynes can undergo cyclization with a nearby double bond.

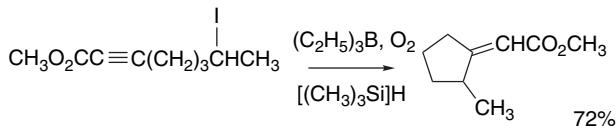


Ref. 328

The addition of a vinyl radical to a double bond is usually favorable thermodynamically because a more stable alkyl radical is formed. The vinyl radical can be generated by dehalogenation of vinyl bromides or iodides. An early study provided examples of both five-and six-membered rings being formed.³²⁹ The six-membered ring is favored when a branching substituent is introduced.



An alternative system for initiating radical cyclization uses triethylborane and oxygen. Under these conditions, *tris*-(trimethylsilyl)silane is an effective hydrogen donor.³³⁰



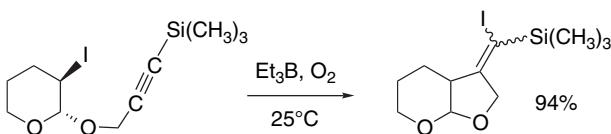
³²⁷ D. P. Curran and J. Tamine, *J. Org. Chem.*, **56**, 2746 (1991).

³²⁸ G. Stork and R. Mook, Jr., *J. Am. Chem. Soc.*, **109**, 2829 (1987).

³²⁹ G. Stork and N. H. Baine, *J. Am. Chem. Soc.*, **104**, 2321 (1982).

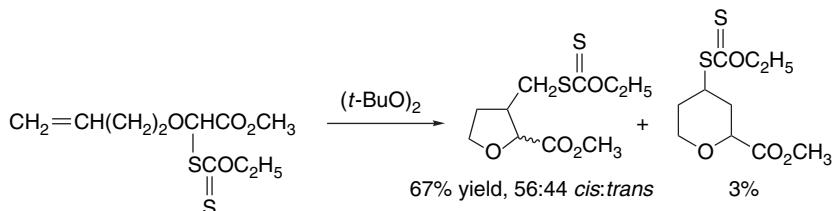
³³⁰ (a) T. B. Lowinger and L. Weiler, *J. Org. Chem.*, **57**, 6099 (1992); (b) P. A. Evans and J. D. Roseman, *J. Org. Chem.*, **61**, 2252 (1996).

These cyclizations can also be carried out without a hydrogen donor, in which case the chain is propagated by iodine atom transfer.³³¹ If necessary, ethyl iodide can be added to facilitate iodine atom transfer.



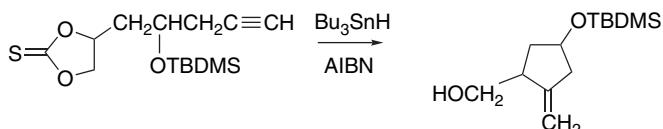
Ref. 332

Intramolecular additions have also been accomplished using xanthate and thiono-carbonates.



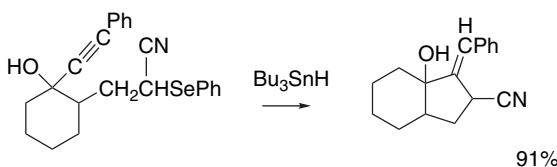
Ref. 333

When a hydrogen donor is present, the product results from reduction.

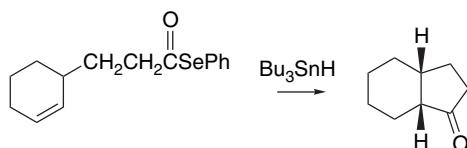


Ref. 334

Cyclization of both alkyl and acyl radicals generated by selenide abstraction have also been observed.



Ref. 335



Ref. 336

³³¹ T. J. Woltering and H. M. R. Hoffman, *Tetrahedron*, **51**, 7389 (1995).

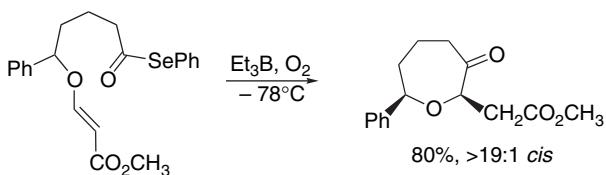
³³² Y. Ichinose, S. J. Matsunaga, K. Fugami, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, **30**, 3155 (1989).

³³³ J. H. Udding, J. P. M. Giesselsink, H. Hiemstra, and W. N. Speckamp, *J. Org. Chem.*, **59**, 6671 (1994).

³³⁴ F. E. Ziegler and C. A. Metcalf, III, *Tetrahedron Lett.*, **33**, 3117 (1992).

³³⁵ D. L. J. Clive, T. L. B. Boivin, and A. G. Angoh, *J. Org. Chem.*, **52**, 4943 (1987).

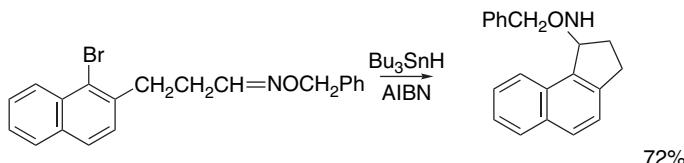
³³⁶ D. L. Boger and R. J. Mathvink, *J. Org. Chem.*, **53**, 3377 (1988).



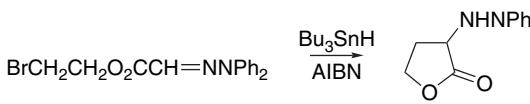
Ref. 330b

10.3.4. Additions to C=N Double Bonds

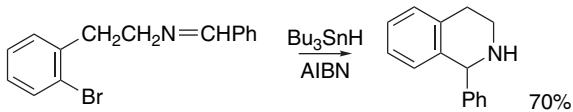
Several functional groups containing carbon-nitrogen double bonds can participate in radical cyclizations. Among these are oxime ethers, imines, and hydrazones.³³⁷ Hydrazones and oximes are somewhat more reactive than imines, evidently because the adjacent substituents can stabilize the radical center at nitrogen.³³⁸ Cyclization at these functional groups leads to amino- substituted products.



Ref. 339



Ref. 340



Ref. 341

A radical cyclization of this type was used to synthesize the 4-amino-5-hydroxyhexahydroazepine group found in the PKC inhibitor balanol. The cyclization involves an α -stannyloxy radical formed by addition of the stannyl radical to the aldehyde oxygen.

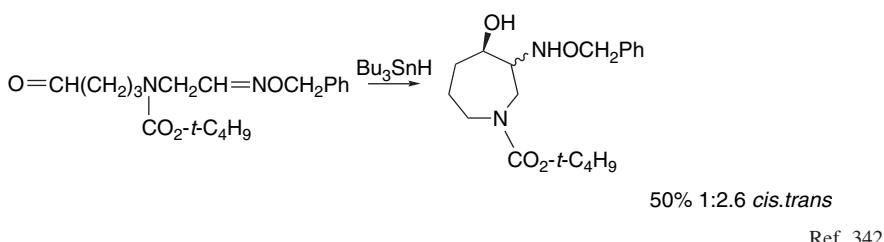
³³⁷ G. K. Friestad, *Tetrahedron*, **57**, 5461 (2001).

³³⁸ A. G. Fallis and I. M. Brinza, *Tetrahedron*, **53**, 17543 (1997).

³³⁹ J. W. Grissom, D. Klingberg, S. Meyenburg, and B. L. Stallman, *J. Org. Chem.*, **59**, 7876 (1994).

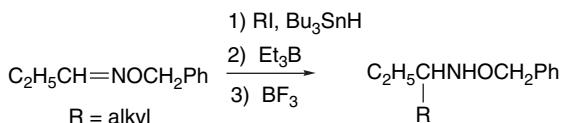
³⁴⁰ D. L. J. Clive and J. Zhang, *J. Chem. Soc., Chem. Commun.*, 549 (1997).

³⁴¹ M. J. Tomaszewski and J. Warkentin, *Tetrahedron Lett.*, **33**, 2123 (1992).

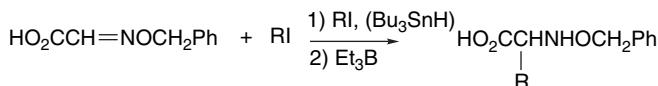


Ref. 342

The reactivity of oxime ethers as radical acceptors is enhanced by Lewis acids, BF_3 , being the most effective.³⁴³



Addition to oxime ethers of glyoxylic acid generates *N*-benzyloxymino acids. These reactions have been done in both organic solvents³⁴⁴ and aqueous mixtures.³⁴⁵ The reactions can be done with or without Bu_3SnH as a chain carrier.



Scheme 10.18 gives some additional examples of cyclization reactions involving radical intermediates. Section A pertains to reactions of alkyl halides. Entry 1 is an early example of the application of a radical cyclization and was used in the synthesis of the terpenes sativene and copacamphene. Entry 2 is an example of the use of the β -bromo- α -ethoxyethyl group in radical cyclization. Ring strain effects dictate the formation of the *cis*-fused five-membered ring, and the stereochemistry of the decalin ring junction is then controlled by the shape of the tricyclic radical intermediate, resulting in good stereochemical control. Entry 3 involves addition of an alkenyl radical. Entry 4 involves generation of a vinyl radical that undergoes stereoequilibration faster than cyclization. The 6-*endo* mode of cyclization is favored by both steric and radical stabilization effects. Entry 5 is an 5-*exo* cyclization. Several similar reactions showed a preference of about 8:1 for generation of the *anti* stereochemical relationship at the two new stereocenters. Another noteworthy feature of this reaction is the successful reaction between a relatively electrophilic radical and the acrylate moiety. Entry 6 has several interesting aspects. The reaction proceeds by iodine atom transfer and the cyclization mode is 9-*endo*. The initiation is by triethylborane and the reaction gives much higher yields in water than in benzene. The efficiency of the cyclization and the solvent sensitivity are probably related to reactant conformation. Entry 7 is another iodine atom transfer cyclization initiated by triethylboron. Entry 8 involves 5-*exo* addition to a alkynylsilane.

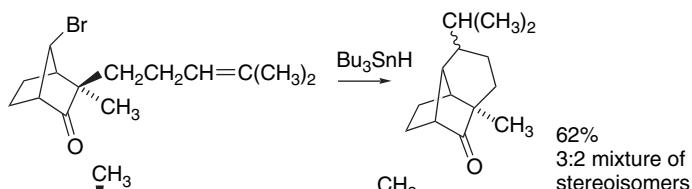
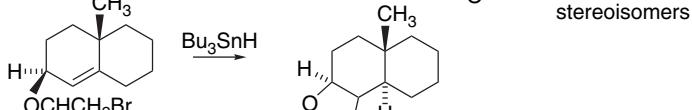
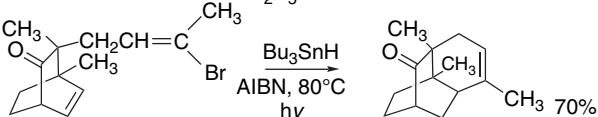
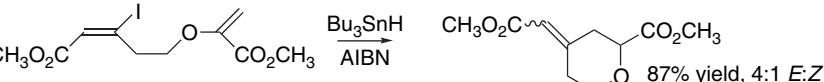
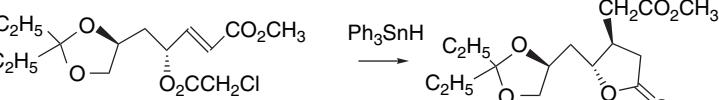
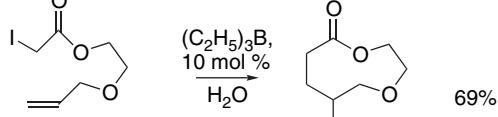
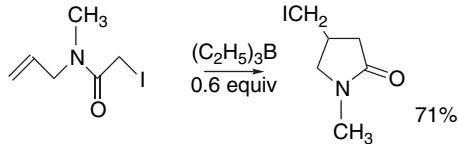
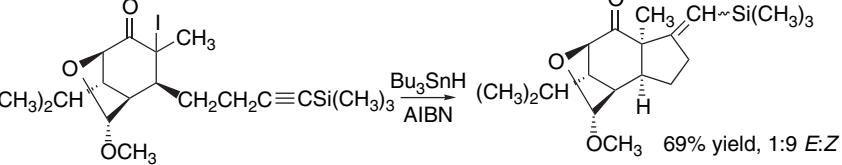
³⁴² H. Miyabe, M. Torieda, K. Inoue, K. Tajiri, T. Kiguchi, and T. Naito, *J. Org. Chem.*, **63**, 4397 (1998).

³⁴³ H. Miyabe, M. Ueda, and T. Naito, *Synlett*, 1140 (2004).

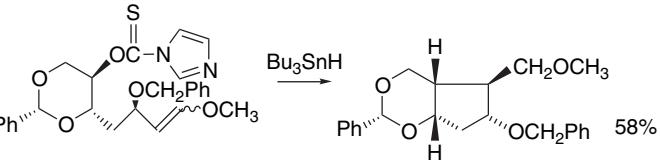
³⁴⁴ H. Miyabe, M. Ueda, N. Yoshioka, and T. Naito, *Synlett*, 465 (1999); H. Miyabe, M. Ueda, N. Yoshioka, K. Yamakawa, and T. Naito, *Tetrahedron*, **56**, 2413 (2000).

³⁴⁵ H. Miyabe, M. Ueda, and T. Naito, *J. Org. Chem.*, **65**, 5043 (2000).

A. Cyclizations of halides terminated by hydrogen atom abstraction or halogen atom transfer

^{1a}^{2b}^{3c}^{4d}^{5e}^{6f}^{7g}^{8h}

B. Cyclization of thiono esters, sulfides, and selenides

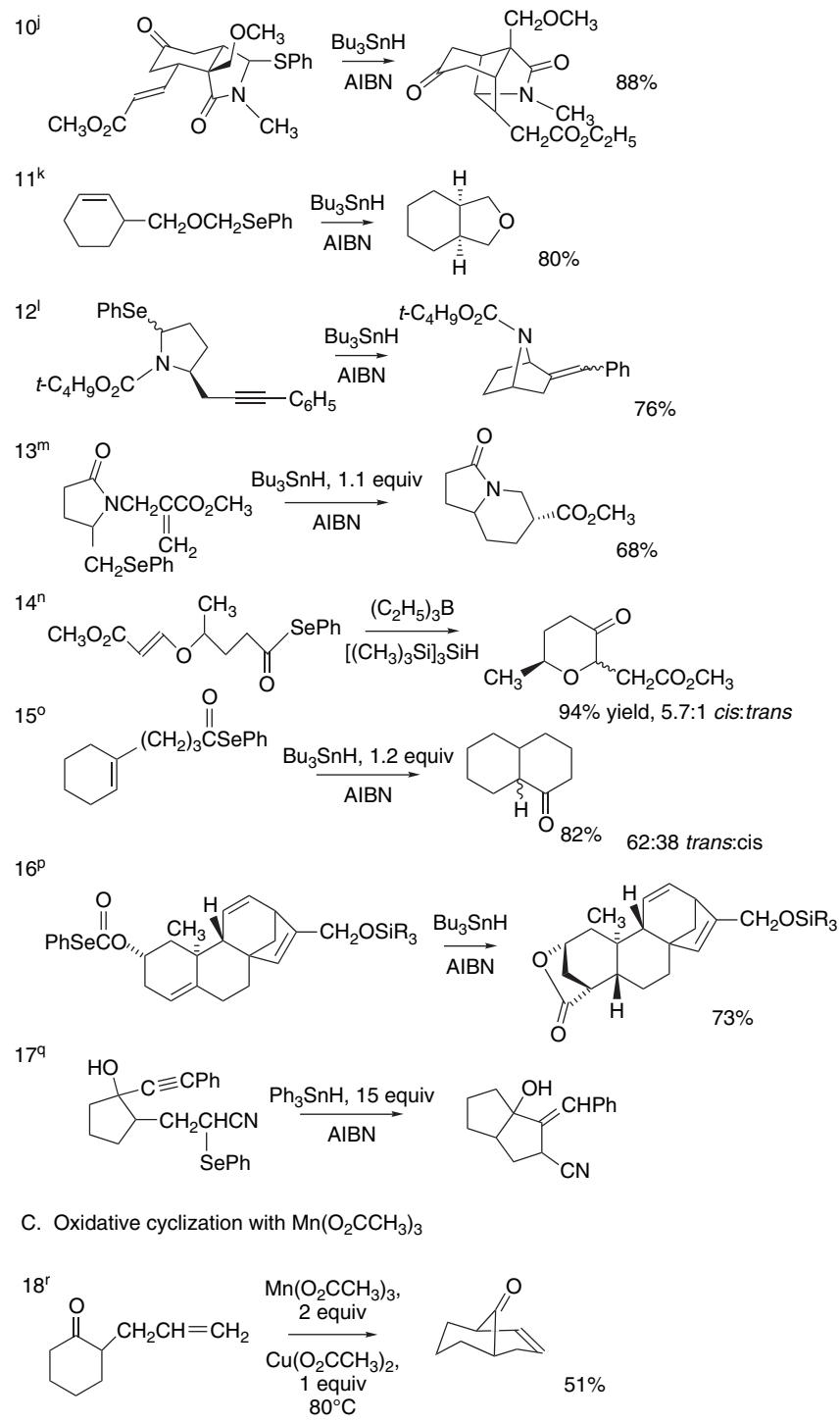
⁹ⁱ

(Continued)

Scheme 10.18. (Continued)

CHAPTER 10

Reactions Involving
Carbocations, Carbenes,
and Radicals as Reactive
Intermediates

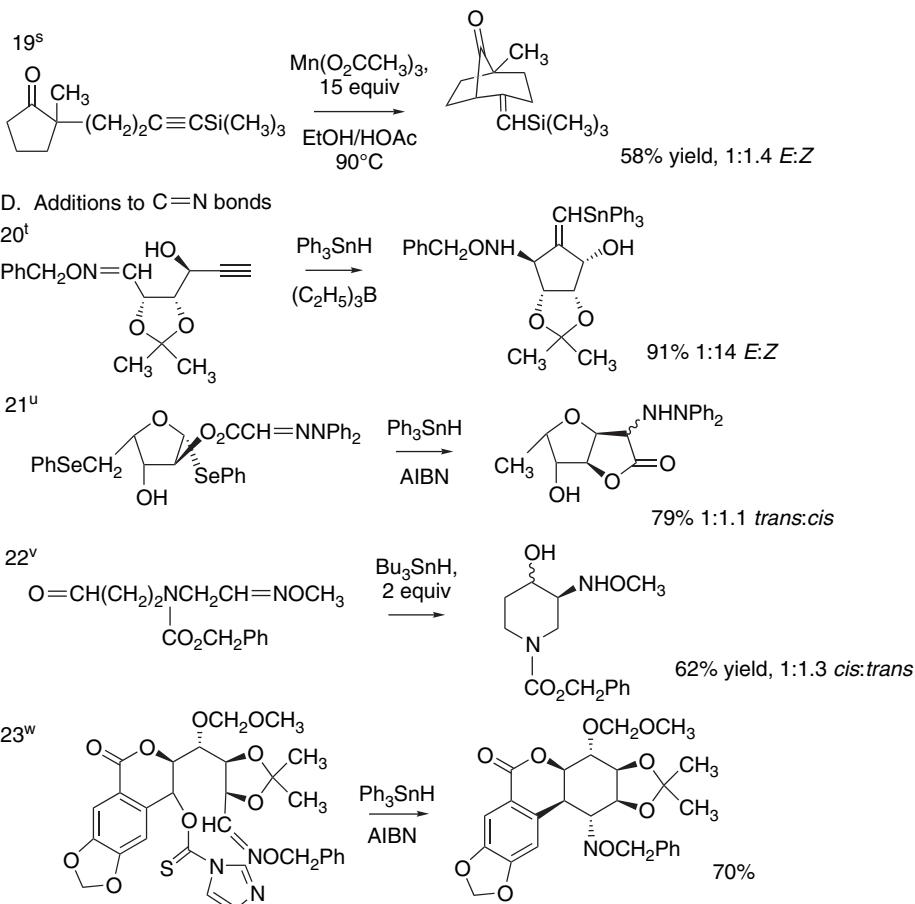


(continued)

Scheme 10.18. (Continued)

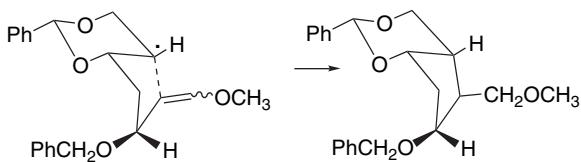
SECTION 10.3

Reactions Involving Free Radical Intermediates

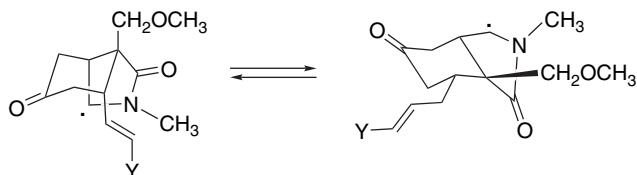


- a. P. Bakuzis, O. O. S. Campos, and M. L. F. Bakuzis, *J. Org. Chem.*, **41**, 3261 (1976).
- b. G. Stork and M. Kahn, *J. Am. Chem. Soc.*, **107**, 500 (1985).
- c. G. Stork and N. H. Baine, *Tetrahedron Lett.*, **26**, 5927 (1985).
- d. R. J. Maguire, S. P. Munt, and E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 2853 (1998).
- e. S. Hanessian, R. DiFabio, J.-F. Marcoux, and M. Prud'homme, *J. Org. Chem.*, **55**, 3436 (1990).
- f. H. Yorimitsu, T. Nakamura, H. Shinokubo, and K. Oshima, *J. Org. Chem.*, **63**, 8604 (1998).
- g. M. Ikeda, H. Teranishi, K. Nozaki, and H. Ishibashi, *J. Chem. Soc., Perkin Trans. 1*, 1691 (1998).
- h. C.-K. Sha, R.-T. Chiu, C.-F. Yang, N.-T. Yao, W.-H. Tseng, F.-L. Liao, and S.-L. Wang, *J. Am. Chem. Soc.*, **119**, 4130 (1997).
- i. T. V. RajanBabu, *J. Org. Chem.*, **53**, 4522 (1988).
- j. J.-K. Choi, D.-C. Ha, D. J. Hart, C.-S. Lee, S. Ramesh, and S. Wu, *J. Org. Chem.*, **54**, 279 (1989).
- k. V. H. Rawal, S. P. Singh, C. Dufour, and C. Michoud, *J. Org. Chem.*, **56**, 5245 (1991).
- l. D. L. J. Clive and V. S. C. Yeh, *Tetrahedron Lett.*, **39**, 4789 (1998).
- m. S. Knapp and F. S. Gibson, *J. Org. Chem.*, **57**, 4802 (1992).
- n. P. A. Evans and J. D. Roseman, *J. Org. Chem.*, **61**, 2252 (1996).
- o. D. L. Boger and R. J. Mathvink, *J. Org. Chem.*, **57**, 1429 (1992).
- p. A. K. Singh, R. K. Bakshi, and E. J. Corey, *J. Am. Chem. Soc.*, **109**, 6187 (1987).
- q. D. L. J. Clive, T. L. B. Boivin, and A. G. Angoh, *J. Org. Chem.*, **52**, 4943 (1987).
- r. B. McC. Cole, L. Han, and B. B. Snider, *J. Org. Chem.*, **61**, 7832 (1996).
- s. S. V. O'Neill, C. A. Quickley, and B. B. Snider, *J. Org. Chem.*, **62**, 1970 (1997).
- t. J. Marco-Contelles, C. Destabel, P. Gallego, J. L. Chiara, and M. Bernabe, *J. Org. Chem.*, **61**, 1354 (1996).
- u. J. Zhang and D. L. J. Clive, *J. Org. Chem.*, **64**, 1754 (1999).
- v. T. Naito, K. Nakagawa, T. Nakamura, A. Kasei, I. Ninomiya, and T. Kiguchi, *J. Org. Chem.*, **64**, 2003 (1999).
- w. G. E. Keck, S. F. McHardy, and J. A. Murry, *J. Org. Chem.*, **64**, 4465 (1999).

Section B of Scheme 10.18 shows examples of the use of sulfides, thiono esters, and selenides as radical sources. The imidazolyl thionocarbamate group used in Entry 9 is one of the thioester groups developed as a source of radicals. In this particular reaction, the phenylthionocarbonate group is even more effective. The ring closure generates an *anti* relationship between the benzyloxy and methoxymethyl substituents. This stereochemistry is consistent with a boatlike TS that may be preferred in order to maintain the preferred conformation of the dioxane ring while avoiding allylic strain in the side chain.



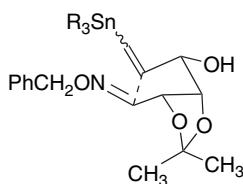
Entry 10 shows the occurrence of *5-exo* cyclization. The radical in this case is generated from an amino sulfide. This reaction requires a specific, somewhat disfavored conformation of the reactant in order for cyclization to occur. When the unsubstituted vinyl substituent was used, no cyclization occurred. However, increasing the reactivity of the double bond by adding the ester substituent led to successful cyclization.



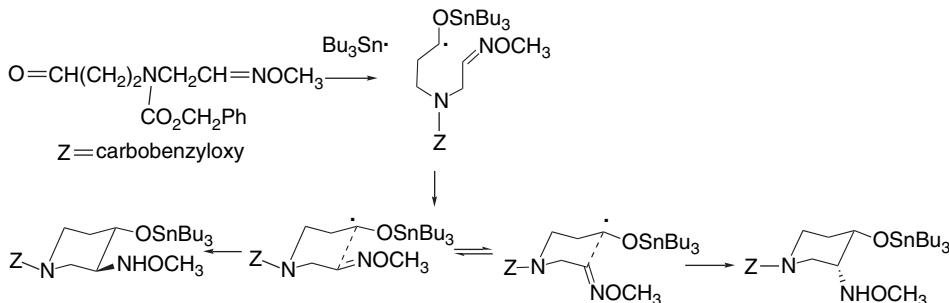
Entry 11 involves generation and cyclization of an alkoxyethyl radical from a selenide. The cyclization mode is the anticipated *5-exo* with a *cis* ring juncture. This is a case in which the electronic characteristics of the radical are not particularly favorable (ERG oxygen in the radical), but cyclization nevertheless proceeds readily. The reaction in Entry 12 was used to prepare a precursor of epibatidine. Entry 13 shows a *6-endo* cyclization that is favored by steric factors. The *6-endo* cyclization is also favored with a tetrahydropyranloxy substituent in place of the ester, indicating that the electronic effect is not important. Entries 14 to 16 involve acyl radicals generated from selenides. The preferred *6-endo* cyclization in Entry 15 is thought to be due to the preference for the less-substituted end of the double bond. Entry 17 is an example of a *5-exo-dig* cyclization.

Entries 18 to 19 pertain to cyclizations of electrophilic radicals generated by oxidations. Entry 18 is the prototype for cyclization of a number of more highly substituted systems. The reaction outcome is consistent with oxidation of the less-substituted enolic position followed by a *6-endo* cyclization. The cyclized radical is then oxidized and deprotonated. In Entry 19, the vinyl radical formed by cyclization is reduced by hydrogen abstraction from the solvent ethanol.

Entries 20 to 23 involve additions to C=N double bonds in oxime ethers and hydrazones. These reactions result in installation of a nitrogen substituent on the newly formed rings. Entry 20 involves the addition of the triphenylstannyl radical to the terminal alkyne followed by cyclization of the resulting vinyl radical. The product can be proto-destannylated in good yield. The ring closure generates an *anti* relationship for the amino substituent, which is consistent with the TS shown below.



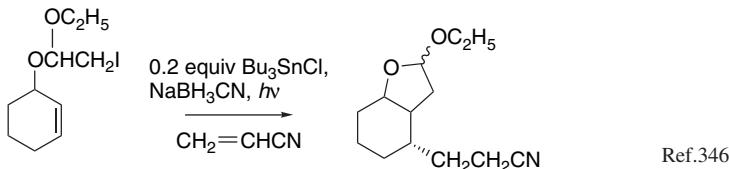
Entry 21 involves addition to a glyoxylic hydrazone and the *cis* ring junction is dictated by strain effects. The primary phenylselenenyl group is reductively removed under the reaction conditions. Entry 22 involves generation of a stannyloxy radical by addition of the stannyl radical at the carbonyl oxygen. Cyclization then ensues, with the *cis-trans* ratio being determined by the conformation of the cyclization TS.



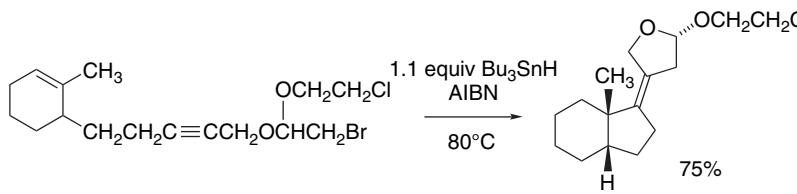
Entry 23 was part of a synthesis of the pancratistatin structure. The lactone ring was used to control the stereochemistry at the cyclization center. Noncyclic analogs gave a mixture of stereoisomers at this center. In this reaction, triphenylstannane gave much better yields than tri-*n*-butylstannane.

10.3.5. Tandem Radical Cyclizations and Alkylation

The synthetic scope of radical cyclizations can be further extended by tandem trapping by an electrophilic alkene.



Alkenyl radicals generated by intramolecular addition to a triple bond can add to a nearby double bond, resulting in a tandem cyclization process.

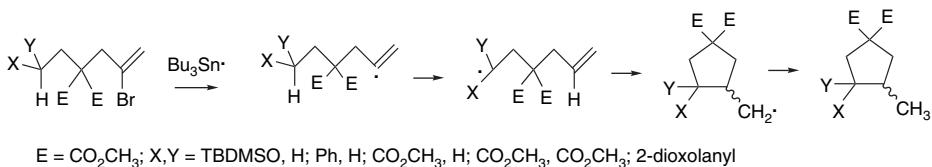


Ref. 347

³⁴⁶ G. Stork and P. M. Sher, *J. Am. Chem. Soc.*, **108**, 303 (1986).

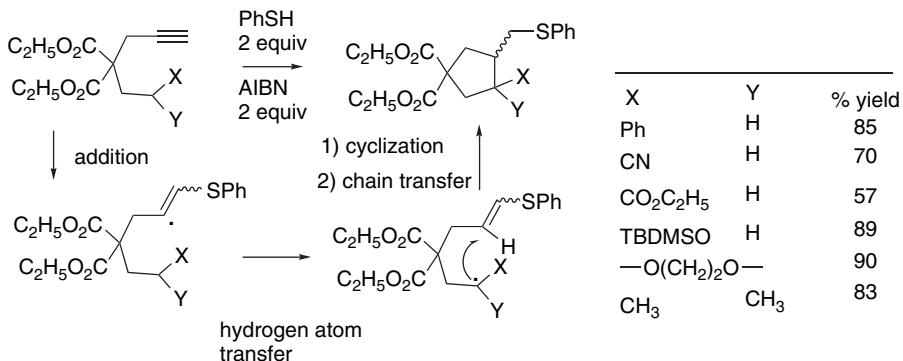
³⁴⁷ G. Stork and R. Mook, Jr., *J. Am. Chem. Soc.*, **105**, 3720 (1983).

As with carbocation-initiated polyene cyclizations, radical cyclizations can proceed through several successive steps if the steric and electronic properties of the reactant provide potential reaction sites. Cyclization may be followed by a second intramolecular step or by an intermolecular addition or alkylation. Intermediate radicals can be constructed so that hydrogen atom transfer can occur as part of the overall process. For example, 2-bromohexenes having radical stabilizing substituents at C(6) can undergo cyclization after a hydrogen atom transfer step.³⁴⁸



The success of such reactions depends on the intramolecular hydrogen transfer being faster than hydrogen atom abstraction from the stannane reagent. In the example shown, hydrogen transfer is favored by the thermodynamic driving force of radical stabilization, by the intramolecular nature of the hydrogen transfer, and by the steric effects of the central quaternary carbon. This substitution pattern often favors intramolecular reactions as a result of conformational effects.

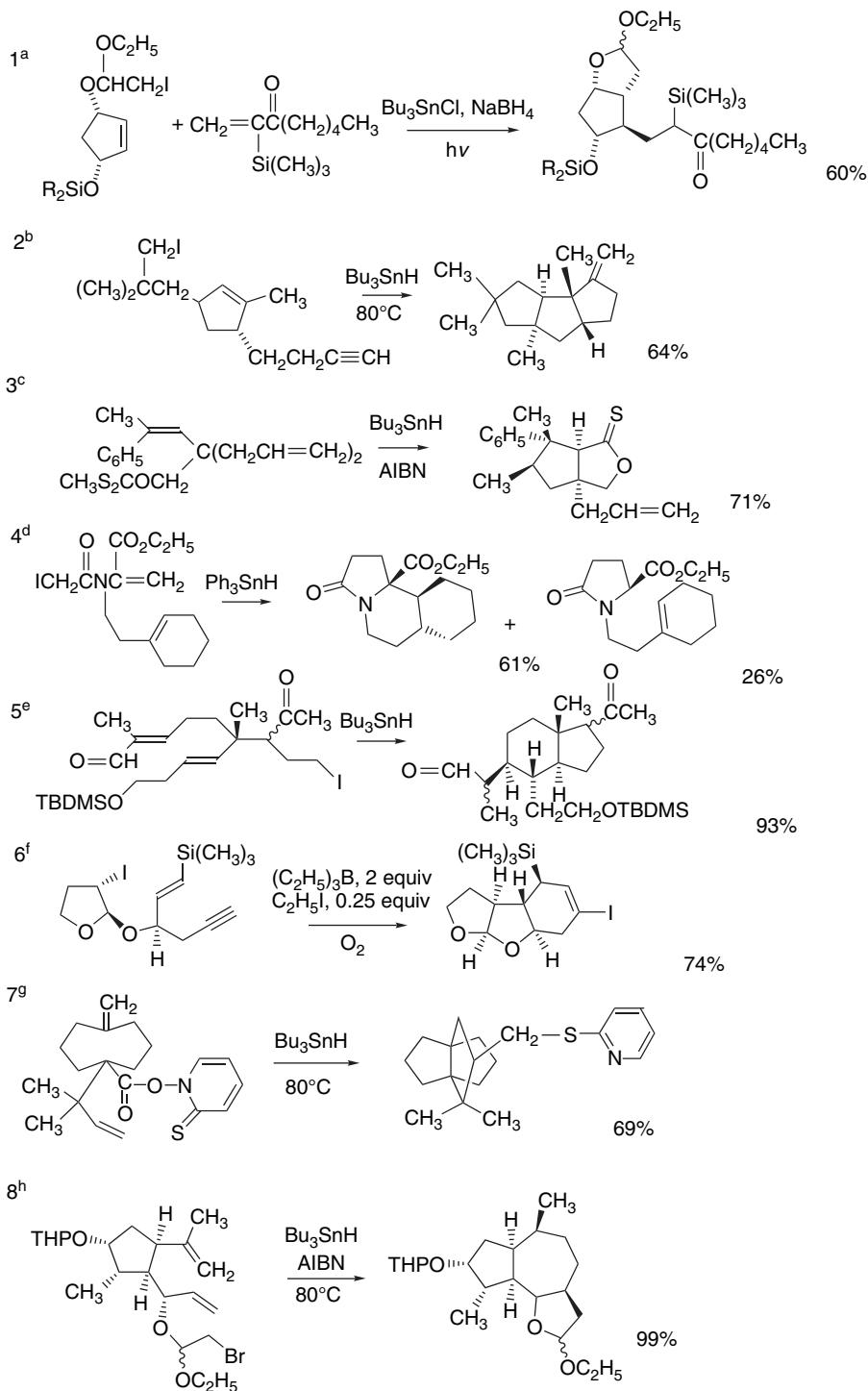
This type of cyclization has also been carried out using thiophenol to generate the reactive radicals. Good yields were obtained for both EWG and ERG substituents.³⁴⁹



Scheme 10.19 gives some other examples of tandem radical reactions. Entry 1 was used to construct the disubstituted cyclopentane system found in the prostaglandins. The first 5-*exo* cyclization to generate the tetrahydrofuran ring is followed by intermolecular trapping of the radical by the α -(trimethylsilyl)enone. In Entry 2, a primary radical was generated and adds to the cyclopentene, generating a tertiary radical that adds to the terminal alkyne. Both ring junctions are *cis*. In Entry 3, a reactive radical is generated from the xanthate groups, and it adds to the styrene double bond faster than

³⁴⁸ D. P. Curran, D. Kim, H. T. Liu, and W. Shen, *J. Am. Chem. Soc.*, **110**, 5900 (1988).

³⁴⁹ F. Beaufils, F. Denes, and P. Renaud, *Org. Lett.*, **6**, 2563 (2004).

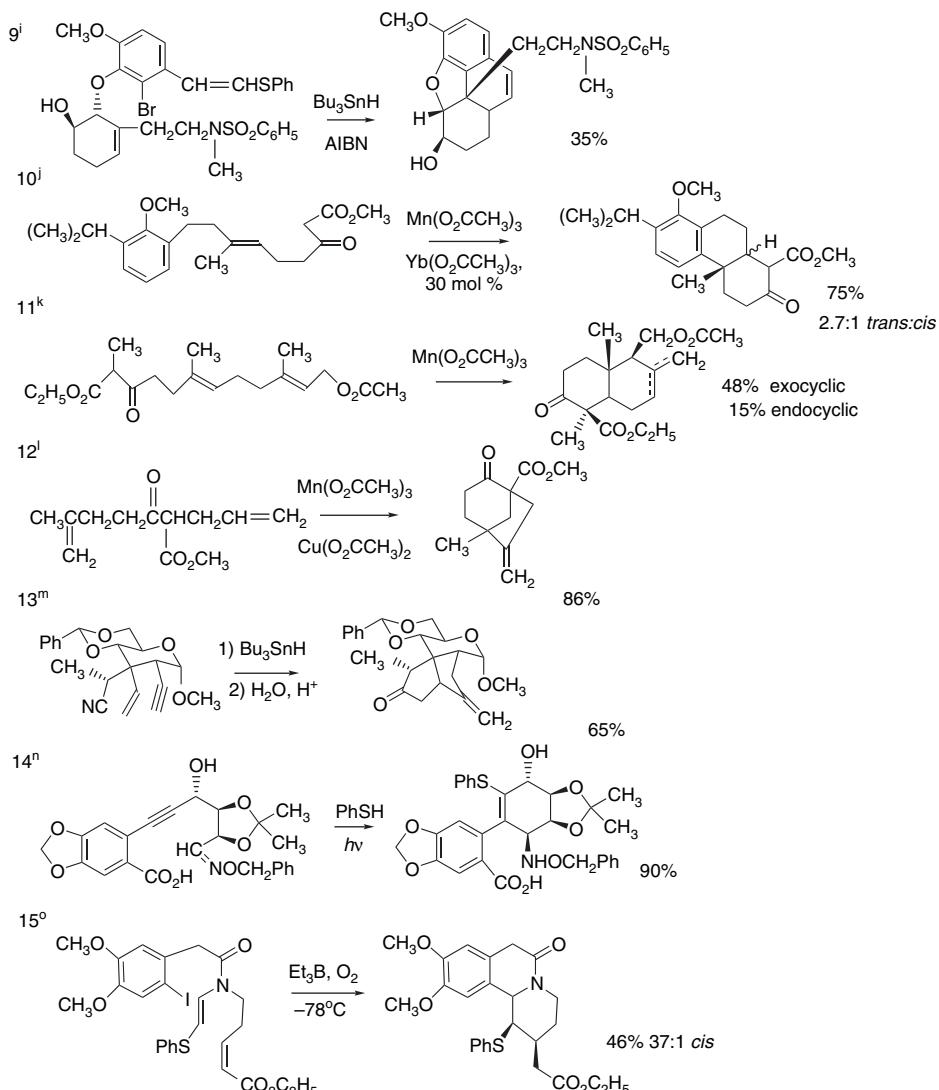


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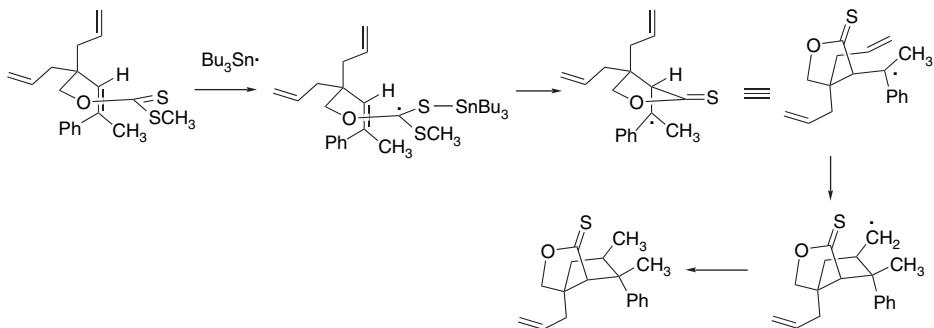
Scheme 10.19. (Continued)

CHAPTER 10

Reactions Involving
Carbocations, Carbenes,
and Radicals as Reactive
Intermediates

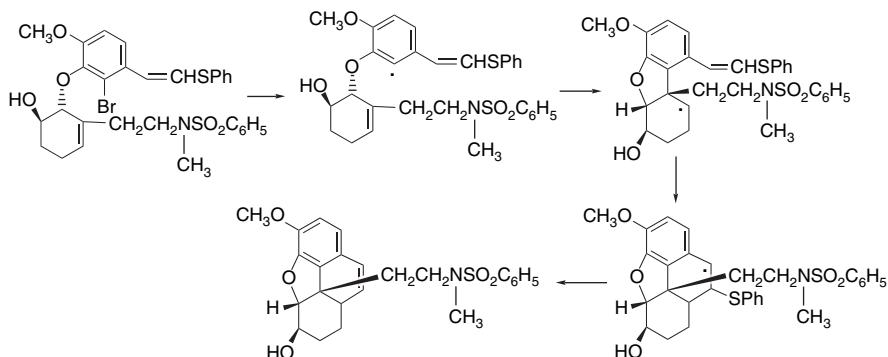


- a. G. Stork, P. M. Sher, and H.-L. Chen, *J. Am. Chem. Soc.*, **108**, 6384 (1986).
- b. D. P. Curran and D. W. Rakiewicz, *Tetrahedron*, **41**, 3943 (1985).
- c. S. Isawa, M. Yamamoto, S. Kohmoto, and K. Yamada, *J. Org. Chem.*, **56**, 2849 (1991).
- d. S. R. Baker, A. F. Parsons, J.-F. Pons, and M. Wilson, *Tetrahedron Lett.*, **39**, 7197 (1998); S. R. Baker, K. I. Burton, A. F. Parsons, J.-F. Pons, and M. Wilson, *J. Chem. Soc., Perkin Trans. 1*, 427 (1999).
- e. T. Takahshi, S. Tomida, Y. Sakamoto, and H. Yamada, *J. Org. Chem.*, **62**, 1912 (1997).
- f. M. Breithor, U. Herden, and H. M. R. Hoffmann, *Tetrahedron*, **53**, 8401 (1997).
- g. D. P. Curran and W. Shen, *Tetrahedron*, **49**, 755 (1993).
- h. E. Lee, J. W. Lim, C. H. Yoon, Y.-S. Sung, Y. K. Kim, M. Yun, and S. Kim, *J. Am. Chem. Soc.*, **119**, 8391 (1995).
- i. K. A. Parker and D. Fokas, *J. Am. Chem. Soc.*, **114**, 9688 (1992).
- j. D. Yang, X.-Y. Ye, S. Gu, and M. Xu, *J. Am. Chem. Soc.*, **121**, 5579 (1999).
- k. M. A. Dombroski, S. A. Kates, and B. B. Snider, *J. Am. Chem. Soc.*, **112**, 2759 (1990).
- l. B. B. Snider, R. Mohan, and S. A. Kates, *Tetrahedron Lett.*, **28**, 841 (1987).
- m. H. Pak, I. I. Canalda, and B. Fraser-Reid, *J. Org. Chem.*, **55**, 3009 (1990).
- n. G. E. Keck, T. T. Wager, and J. F. D. Rodriguez, *J. Am. Chem. Soc.*, **121**, 5176 (1999).
- o. H. Ishibashi, M. Inomata, M. Ohba, and M. Ikeda, *Tetrahedron Lett.*, **40**, 1149 (1999).



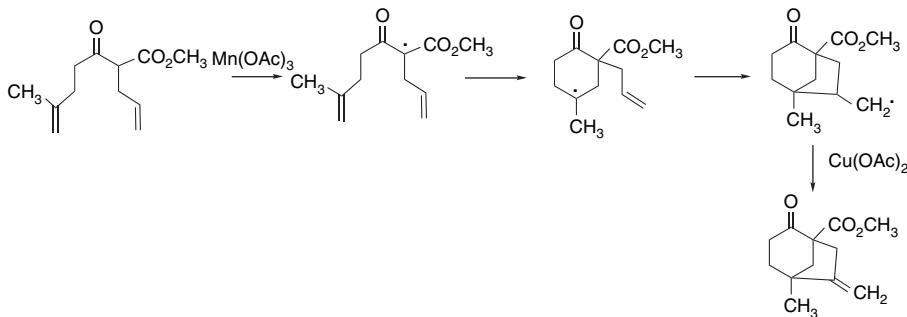
In Entry 4, the initial cyclization is evidently a *5-endo* process, which in this case is strongly favored by the substitution pattern (capto-dative substituents; see Part A, Section 11.1.6). Most of the cyclized radical then undergoes addition to the cyclohexene ring, generating the major product. In this step, the *6-endo* process is favored both thermodynamically (*5,6-* versus *5,5*-ring fusion) and by the less-substituted nature of the double bond in this mode. Entry 5 illustrates creation of a CD fragment of the steroid ring system, with side chains in place to create the B ring. The stereochemistry at the ring junction and substitution sites was highly selective. Entry 6 involves a *5-exo* cyclization followed by a *6-endo-dig* cyclization. It was found that the selectivity of the tandem sequence was improved by the trimethylsilyl substituent. Entry 7 was used in the synthesis of the carbon skeleton of the terpene modhephene. The sequence consists of two *5-exo* cyclizations, the first of which is transannular. In Entry 8, the first step is a *5-exo* cyclization of a bromoacetaldehyde acetal. This is followed by a *7-endo* cyclization that is favored by the steric and substituent effects of the isopropenyl group. The hydrogen abstraction at the terminal tertiary radical site is highly stereoselective because of ring geometry.

In Entry 9, the initial reaction involves *5-exo* addition of the aryl radical to the more-substituted end of the cyclohexene double bond, followed by a *6-endo* addition to the phenylthiovinyl group. The reaction is completed by elimination of the phenylthio radical. The product is an intermediate in the synthesis of morphine.



Entries 10 to 12 are examples of oxidative generation of radicals, followed by tandem cyclization. The reaction in Entry 10 includes a lanthanide catalyst. Entry 11

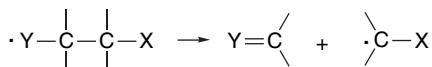
results in the formation of the *trans* decalin product. The by-products of this reaction suggest that the first cyclization is a radical reaction but that oxidation to the tertiary carbocation occurs prior to the second cyclization. Entry 12 involves a tandem process in which the intermediate radical is captured by the second double bond. The presence of Cu(II) results in oxidation of the cyclized radical to an alkene.



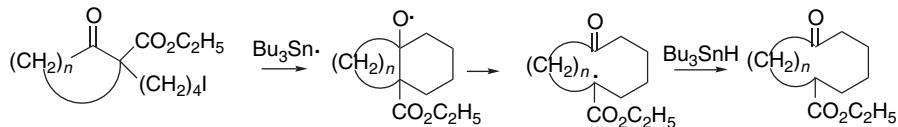
Entries 13 to 15 involve adding to carbon-nitrogen multiple bonds. The reaction in Entry 13 is initiated by addition of the stanny radical to the terminal alkyne. Cyclization generates a primary radical that adds to the cyano group. Cyano groups are not particularly good radical traps, but in this case the group is in close proximity to the radical center. The imine formed by the addition is hydrolyzed and the vinylstannane undergoes proto-destannylation on exposure to silica. In Entry 14, a vinyl radical is generated by thiyl radical addition, followed by cyclization with the oximino ether. Entry 15 involves generation of an aryl radical using the triethylborane system. The low temperature available under these conditions results in much higher stereoselectivity at the acetate side chain than the reaction initiated by a stanny radical.

10.3.6. Fragmentation and Rearrangement Reactions

Fragmentation is the reverse of radical addition. Fragmentation of radicals is often observed to be fast when the overall transformation is exothermic.

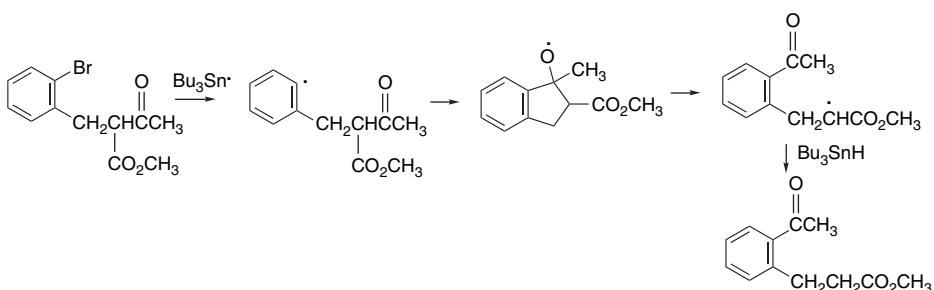


The fragmentation of alkoxy radicals is especially favorable because the formation of a carbonyl bond makes such reactions exothermic. Rearrangements of radicals frequently occur by a series of addition-fragmentation steps. The following two reactions involve radical rearrangements that proceed through addition-elimination sequences.



Ref. 350

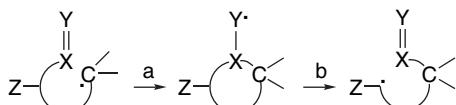
³⁵⁰ P. Dowd and S.-C. Choi, *J. Am. Chem. Soc.*, **109**, 6548 (1987).



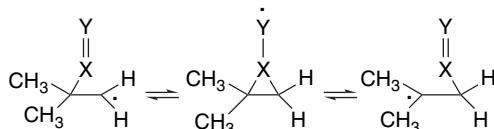
Ref. 351a

Both of these transformations feature addition of a carbon-centered radical to a carbonyl group, followed by fragmentation to a more stable radical. The rearranged radical then abstracts hydrogen from the co-reactant $n\text{-Bu}_3\text{SnH}$. The addition step must be fast relative to hydrogen abstraction because if this is not the case, simple reductive dehalogenation will occur. The fragmentation step is usually irreversible for two reasons: (1) the reverse addition is endothermic; (2) the product radical is substituted by the electron-withdrawing alkoxy carbonyl group and is unreactive to addition to carbonyl bonds.

The two reactions above are examples of a more general reactivity pattern.³⁵¹



The unsaturated group $\text{X}=\text{Y}$ that is formally “transferred” by the rearrangement process can be $\text{C}=\text{C}$, $\text{C}=\text{O}$, $\text{C}=\text{N}$, or any other group that fulfills the following general criteria: (1) the addition step **a** must be fast relative to other potentially competing reactions; and (2) the group Z must stabilize the product radical so that the overall process is energetically favorable. A direct comparison of the ease with which unsaturated groups migrate by cyclization-fragmentation has been made for the case of 1,2-migration.



In this system, the overall driving force is the conversion of a primary radical to a tertiary one ($\Delta H \sim -5$ kcal) and the activation barrier incorporates strain associated with formation of the three-membered ring. Rates and activation energies for several migrating groups were determined.³⁵² A noteworthy feature is the low reactivity of

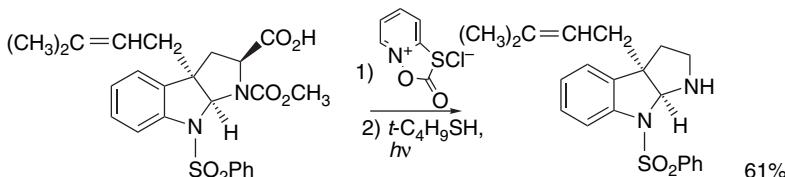
³⁵¹ (a) A. L. J. Beckwith, D. M. O’Shea, and S. W. Westwood, *J. Am. Chem. Soc.*, **110**, 2565 (1988); (b) R. Tsang, J. K. Pickson, Jr., H. Pak, R. Walton, and B. Fraser-Reid, *J. Am. Chem. Soc.*, **109**, 3484 (1987).

³⁵² D. A. Lindsay, J. Lusztyk, and K. U. Ingold, *J. Am. Chem. Soc.*, **106**, 7087 (1984).

alkyne and cyano groups, which is due to the additional strain introduced in the three-membered ring by the sp^2 carbon. Aryl groups are also relatively unreactive because of the loss of aromaticity in the cyclic intermediate.

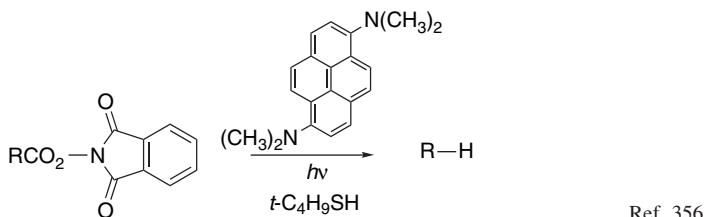
	$X=Y$					
	$\begin{array}{c} (\text{CH}_3)_3\text{C} \\ \\ \text{HC}=\text{CH}_2 \end{array}$	$\begin{array}{c} \text{C}=\text{O} \\ \\ \text{C}=\text{O} \end{array}$	$\begin{array}{c} \text{C}_6\text{H}_5 \\ \\ \text{C}_6\text{H}_4 \end{array}$	$\begin{array}{c} -\text{C}\equiv\text{C}(\text{CH}_3)_3 \\ \\ \text{C}\equiv\text{N} \end{array}$	93	0.9
$k_r (\text{s}^{-1})$	10^7	1.7×10^5	7.6×10^3	11.8	12.8	16.4
$E_a (\text{kcal/mol})$	5.7	7.8	11.8			

Among the most useful radical fragmentation reactions from a synthetic point of view are decarboxylations and fragmentations of alkoxy radicals. The use of *N*-hydroxy-2-thiopyridine esters for decarboxylation is quite general. Several procedures and reagents are available for preparation of the esters,³⁵³ and the reaction conditions are compatible with many functional groups.³⁵⁴ *t*-Butyl mercaptan and thiophenol can serve as hydrogen atom donors.



Ref. 355

Esters of *N*-hydroxyphthalimide can also be used for decarboxylation. Photolysis in the presence of an electron donor and a hydrogen atom donor leads to decarboxylation. Carboxyl radicals are formed by one-electron reduction of the phthalimide ring.



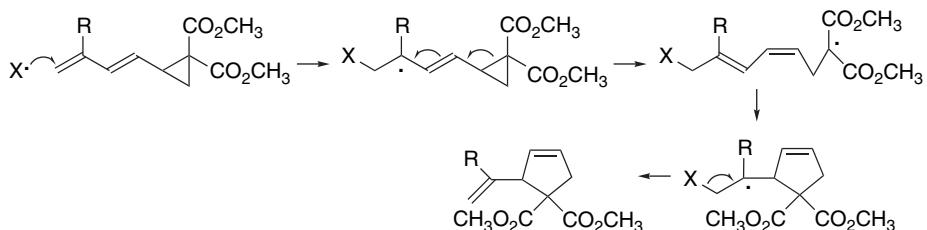
Ref. 356

Fragmentation of cyclopropylcarbinyl radicals has been incorporated into several synthetic schemes.³⁵⁷ For example, 2-dienyl-1,1-(dimethoxycarbonyl)-cyclopropanes undergo ring expansion to cyclopentenes.

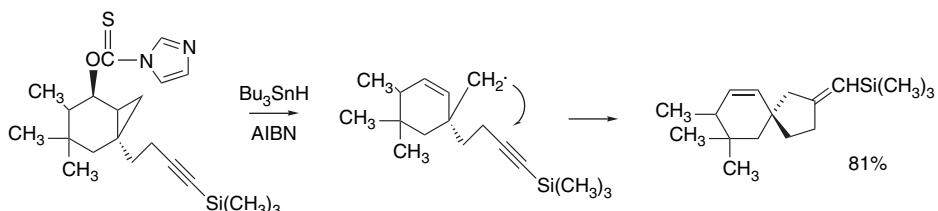
- ³⁵³. F. J. Sardina, M. H. Howard, M. Morningstar, and H. Rapoport, *J. Org. Chem.*, **55**, 5025 (1990); D. Bai, R. Xu, G. Chu, and X. Zhu, *J. Org. Chem.*, **61**, 4600 (1996).
- ³⁵⁴. D. H. R. Barton, D. Crich, and W. B. M. Motherwell, *Tetrahedron*, **41**, 3901 (1985).
- ³⁵⁵. M. Bruncko, D. Crich, and R. Samy, *J. Org. Chem.*, **59**, 5543 (1994).
- ³⁵⁶. K. Okada, K. Okamoto, and M. Oda, *J. Am. Chem. Soc.*, **110**, 8736 (1988).
- ³⁵⁷. P. Dowd and W. Zhang, *Chem. Rev.*, **93**, 2091 (1993).

Ref. 358

These reactions presumably involve terminal addition of the chain-carrying radical, followed by fragmentation and recyclization.

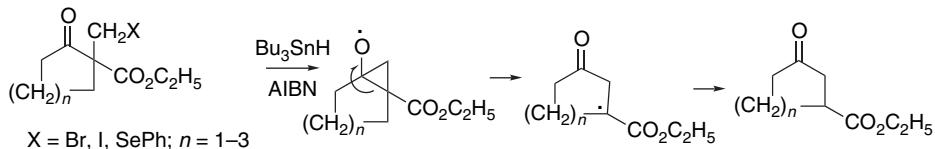


Other intramolecular cyclizations can follow generation and fragmentation of cyclopropylcarbinyl radicals. In the example below, the fragmented radical adds to the alkyne.



Ref. 359

Cyclic α -halomethyl or α -phenylselenenylnethyl β -ketoesters undergo one-carbon ring expansion via transient cyclopropylalkoxy radicals.³⁶⁰

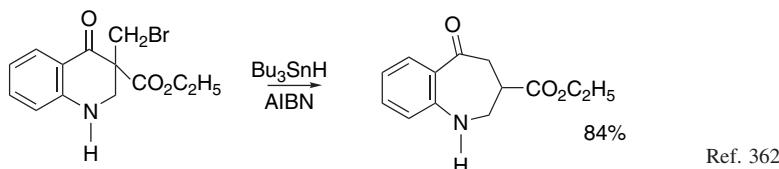
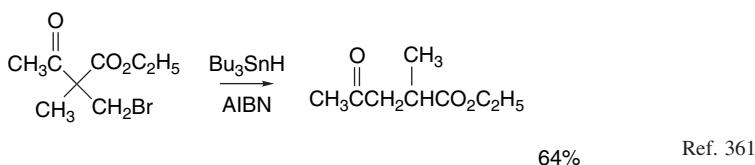


Comparable cyclization-fragmentation sequences have been developed for acyclic and heterocyclic systems.

³⁵⁸ K. Miura, K. Fagami, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, **29**, 1543 (1988).

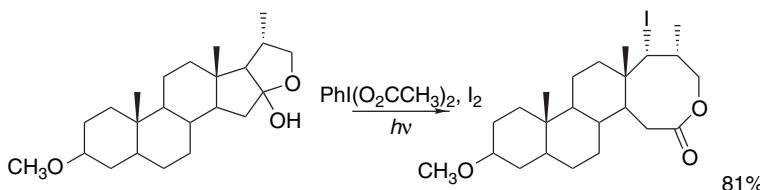
³⁵⁹ R. A. Batey, J. D. Harling, and W. R. Motherwell, *Tetrahedron*, **46**, 8031 (1992).

³⁶⁰ P. Dowd and S.-C. Choi, *Tetrahedron*, **45**, 77 (1989); A. L. J. Beckwith, D. M. O'Shea, and S. W. Westwood, *J. Am. Chem. Soc.*, **110**, 2565 (1988), P. Dowd and S.-C. Choi, *Tetrahedron*, **48**, 4773 (1992).

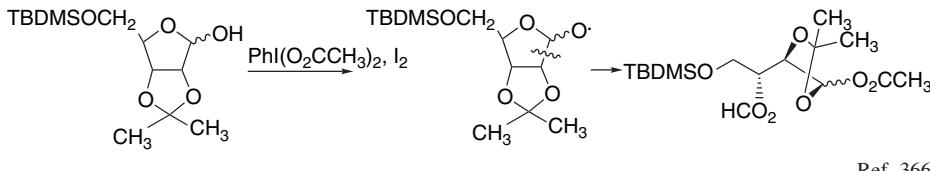


Similar reactions can be conducted using *tris*-(trimethylsilyl)silane as the hydrogen atom donor.³⁶³

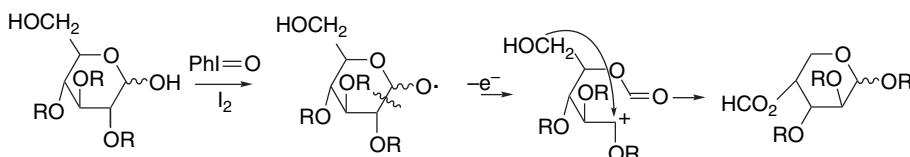
Fragmentation of alkoxy radicals finds use in construction of medium-size rings.³⁶⁴ One useful reagent combination is phenyliodonium diacetate and iodine.³⁶⁵ The radical formed by fragmentation is normally oxidized to the corresponding carbocation and trapped by iodide or another nucleophile.



This reagent also can cleave the C(1)–C(2) bond in furanose carbohydrates.



When the 5-hydroxy group is unprotected, it can capture the fragmented intermediate.³⁶⁷



³⁶¹ P. Dowd and S.-C. Choi, *Tetrahedron*, **45**, 77 (1989).

³⁶² Z. B. Zheng and P. Dowd, *Tetrahedron Lett.*, **34**, 7709 (1993); P. Dowd and S.-C. Choi, *Tetrahedron*, **47**, 4847 (1991).

³⁶³ M. Sugi and H. Togo, *Tetrahedron*, **58**, 3171 (2002).

³⁶⁴ L. Yet, *Tetrahedron*, **55**, 9349 (1999).

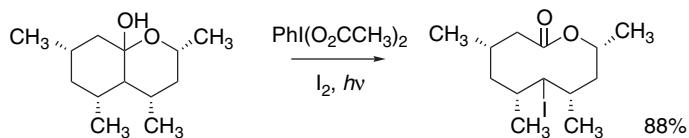
³⁶⁵ R. Freire, J. J. Marrero, M. S. Rodriguez, and E. Suarez, *Tetrahedron Lett.*, **27**, 383 (1986); M. T. Arencibia, R. Freire, A. Perales, M. S. Rodriguez, and E. Suarez, *J. Chem. Soc., Perkin Trans. 1*, 3349 (1991).

³⁶⁶ P. de Armas, C. G. Francisco, and E. Suarez, *Angew. Chem. Int'l. Ed. Engl.*, **31**, 772 (1992).

³⁶⁷ P. de Armas, C. G. Francisco, and E. Suarez, *J. Am. Chem. Soc.*, **115**, 8865 (1993).

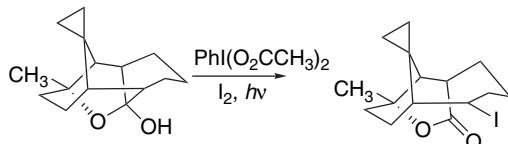
SECTION 10.3

Reactions Involving Free Radical Intermediates



Ref. 368

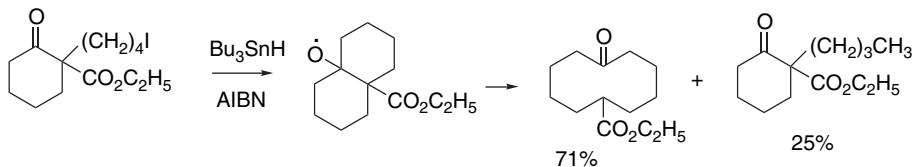
Similarly, bicyclic hemiacetals fragment to medium-size lactones.



Ref. 369

These reactions are believed to proceed through hypoiodite intermediates.

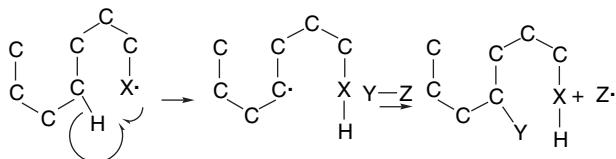
Alkoxy radical fragmentation is also involved in ring expansion of 3- and 4-haloalkyl cyclohexanones. The radical formed by halogen atom abstraction adds to the carbonyl group, after which fragmentation to the carboethoxy-stabilized radical occurs.³⁷⁰



The by-product results from competing reduction of the radical by hydrogen atom abstraction.

10.3.7. Intramolecular Functionalization by Radical Reactions

In this section we focus on intramolecular functionalization. Such reactions normally achieve selectivity on the basis of proximity of the reacting centers. In acyclic molecules, intramolecular functionalization normally involves hydrogen atom abstraction via a six-membered cyclic TS. The net result is introduction of functionality at the δ -atom in relation to the radical site.

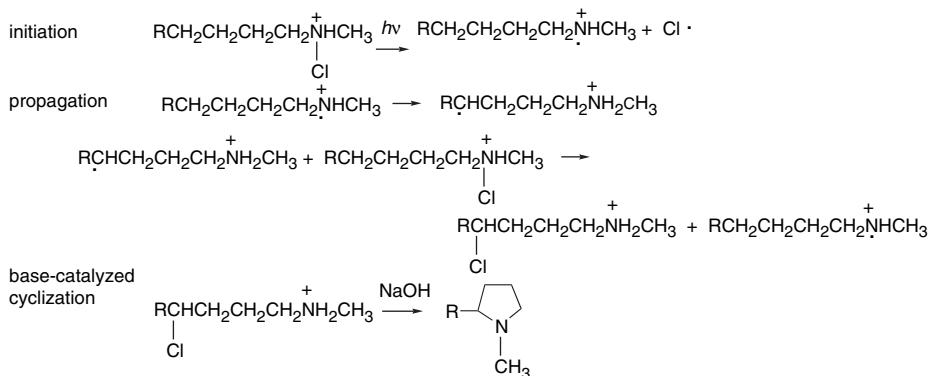


^{368.} M. Kaino, Y. Naruse, K. Ishihara, and H. Yamamoto, *J. Org. Chem.*, **55**, 5814 (1990).

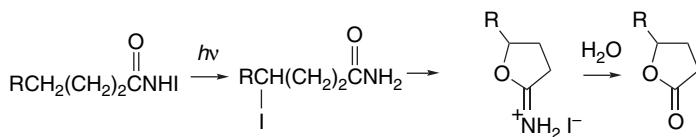
^{369.} J. Lee, J. Oh, S. Jin, J.-R. Choi, J. L. Atwood, and J. K. Cha, *J. Org. Chem.*, **59**, 6955 (1994).

^{370.} P. Dowd and S.-C. Choi, *Tetrahedron*, **45**, 77 (1989); P. Dowd and S.-C. Choi, *J. Am. Chem. Soc.*, **109**, 6548 (1987).

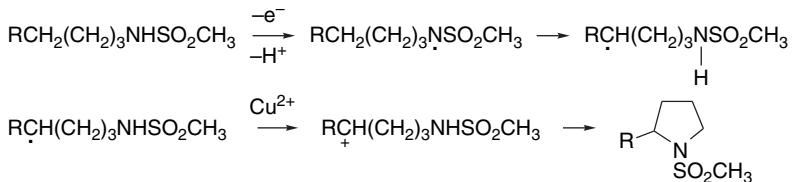
One example of this type of reaction is the photolytically initiated decomposition of *N*-chloroamines in acidic solution, which is known as the *Hofmann-Loeffler-Freytag reaction*.³⁷¹ The initial products are δ -chloroamines, but these are usually converted to pyrrolidines by intramolecular nucleophilic substitution.



A closely related procedure results in formation of γ -lactones. Amides are converted to *N*-idoamides by reaction with iodine and *t*-butyl hypochlorite. Photolysis of the *N*-idoamides gives lactones via iminolactone intermediates.³⁷²



Steps similar to the Hofmann-Loeffler reaction are also involved in cyclization of *N*-alkylmethanesulfonamides by oxidation with $\text{Na}_2\text{S}_2\text{O}_4$ in the presence of cupric ion.³⁷³



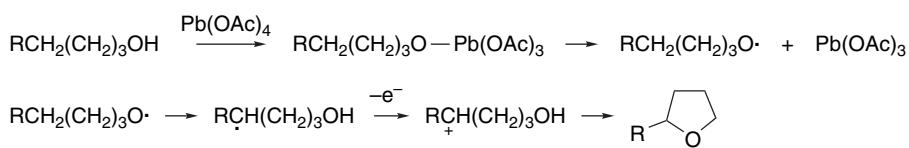
There are also useful intramolecular functionalization methods that involve hydrogen atom abstraction by oxygen radicals. The conditions that were originally developed involved thermal or photochemical dissociation of alkoxy derivative of Pb(IV) generated by exchange with Pb(OAc)_4 .³⁷⁴ These decompose, giving alkoxy

³⁷¹ M. E. Wolff, *Chem. Rev.*, **63**, 55 (1963).

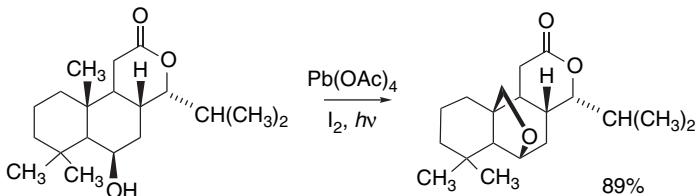
³⁷² D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 181 (1965).

³⁷³ G. I. Nikishin, E. I. Troyansky, and M. Lazareva, *Tetrahedron Lett.*, **26**, 1877 (1985).

³⁷⁴ K. Heusler, *Tetrahedron Lett.*, 3975 (1964).

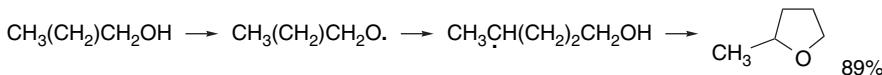


Current procedures include iodine and are believed to involve a hypoiodite intermediate.³⁷⁵

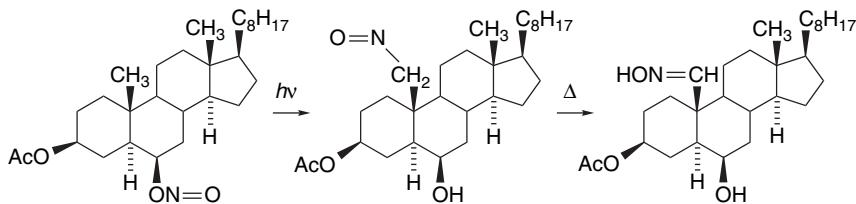


Ref. 376

The reactions can also be effected by phenyliodonium diacetate.³⁷⁷ A mechanistic prototype can be found in the conversion of pentanol to 2-methyltetrahydrofuran. The secondary radical is most likely captured by iodine or oxidized to the carbocation prior to cyclization.³⁷⁸



Alkoxy radicals are also the active hydrogen-ab abstracting species in a procedure that involves photolysis of nitrite esters. This reaction was originally developed as a method for functionalization of methyl groups in steroids.³⁷⁹



It has found other synthetic applications.

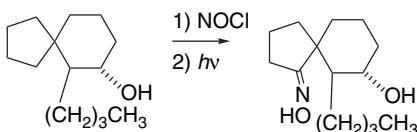
³⁷⁵ K. Heusler, P. Wieland, and C. Meystre, *Org. Synth.*, **V**, 692 (1973); K. Heusler and J. Kalvoda, *Angew. Chem. Int. Ed. Engl.*, **3**, 525 (1964).

³⁷⁶ S. D. Burke, L. A. Silks, III, and S. M. S. Strickland, *Tetrahedron Lett.*, **29**, 2761 (1988).

³⁷⁷ J. I. Concepcion, C. G. Francisco, R. Hernandez, J. A. Salazar, and E. Suarez, *Tetrahedron Lett.*, **25**, 1953 (1984).

³⁷⁸ J. L. Courtneidge, J. Lusztyk, and D. Page, *Tetrahedron Lett.*, **35**, 1003 (1994).

³⁷⁹ D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **83**, 4076 (1961).



Ref. 380

These reactions depend on the proximity of the alkoxy radical to a particular hydrogen for selectivity.

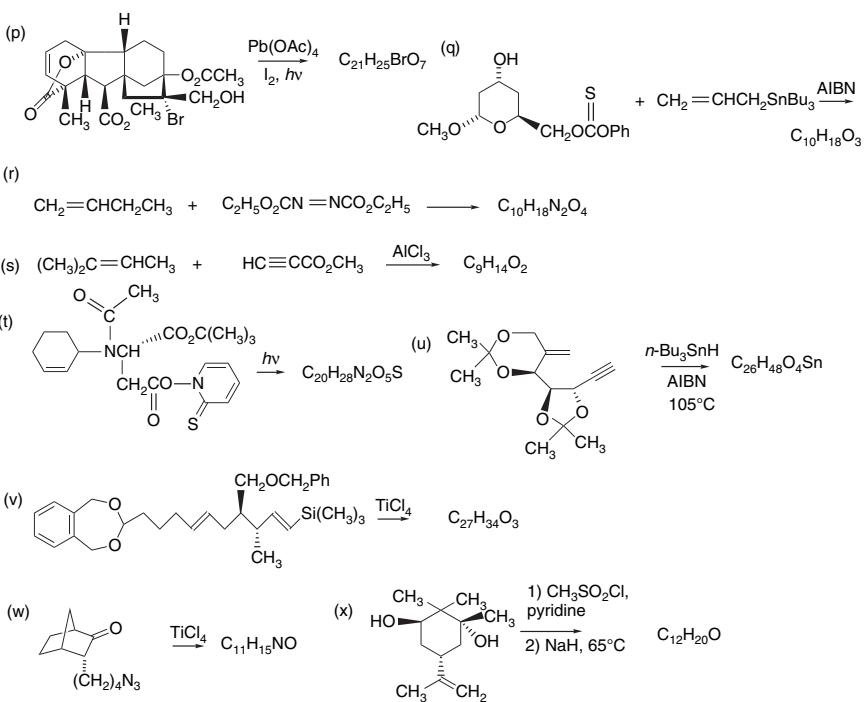
Problems

(References for these problems will be found on page 1287.)

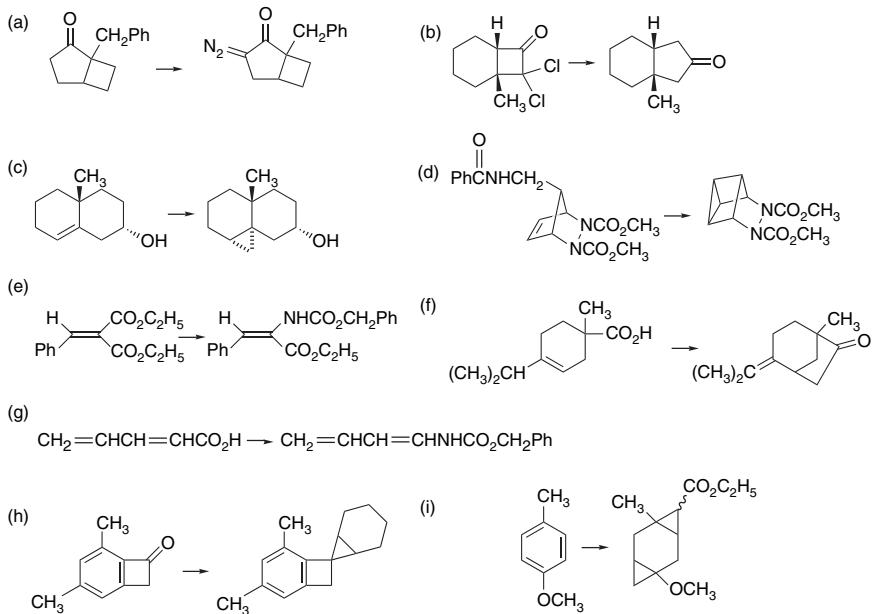
10.1. Indicate the major product to be expected in the following reactions:

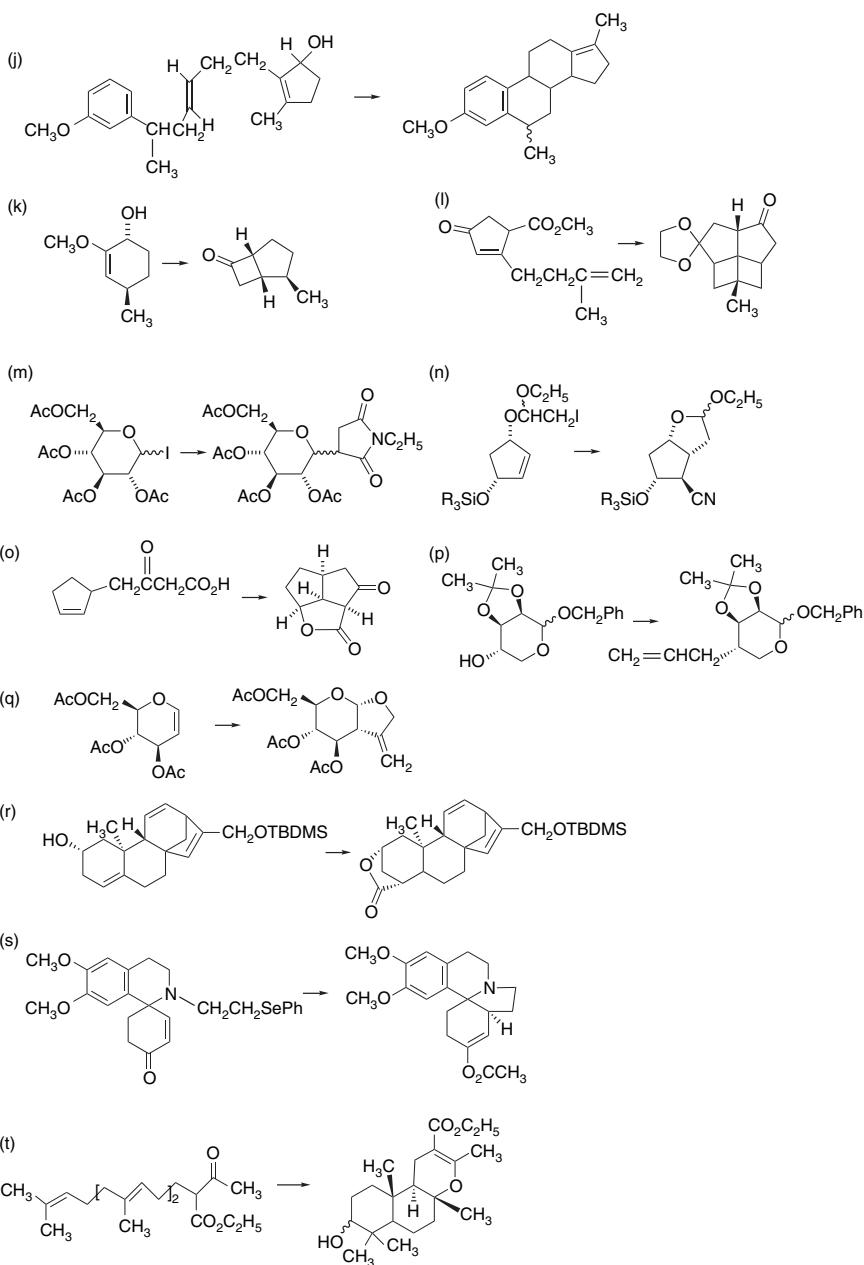
- (a) + $\text{CHCl}_3 \xrightarrow[\text{NaOH, H}_2\text{O}]{\text{PhCH}_2\text{N}(\text{C}_2\text{H}_5)_3\text{Cl}}$ $\text{C}_7\text{H}_{10}\text{Cl}_2$
- (b) + $\text{CH}_3\text{OCN}_3 \xrightarrow{\Delta}$ $\text{C}_{12}\text{H}_{19}\text{NO}_2$
- (c) + $\text{CFCI}_3 \xrightarrow[n\text{-BuLi}]{-120^\circ\text{C}}$ $\text{C}_7\text{H}_{12}\text{F}_2$
- (d) + $\text{PhHgCF}_3 \xrightarrow[12\text{ h}]{80^\circ\text{C}}$ $\text{C}_9\text{H}_{14}\text{F}_2$
- (e) $\xrightarrow{\text{NaOCH}_3}$ C_6H_{10}
- (f) + $\text{N}_2\text{CHCCOC(CH}_3)_3\text{O} \xrightarrow{\text{Rh}_2(\text{OAc})_4}$ $\text{C}_{13}\text{H}_{18}\text{O}_3$
- (g) + $\text{CH}_3\text{O}^- \rightarrow \text{C}_{11}\text{H}_{14}\text{O}_2$
- (h) + $\text{CH}_2\text{N}_2 \rightarrow \text{C}_6\text{H}_4\text{N}_2\text{O}_2$
- (i) $\xrightarrow[\text{nitrobenzene}]{\Delta}$ C_5H_{10} (two products)
- (j) $\xrightarrow{\text{NaH}}$ $\text{C}_{14}\text{H}_{24}\text{O}_2$
- (k) $\xrightarrow[3) \text{NaBH}_4]{1) \text{Hg(O}_3\text{SCF}_3)_2/\text{PhN}(\text{CH}_3)_2, 2) \text{NaCl}}$ $\text{C}_{20}\text{H}_{34}\text{O}_2$
- (l) $\xrightarrow{(CH_3)_3SiO_3SCF_3, 10 \text{ mol } \%}$ $\text{C}_{11}\text{H}_{19}\text{N}$
- (m) $\xrightarrow{\text{K}^-\text{OC(CH}_3)_3}$ $\text{C}_{11}\text{H}_{16}\text{O}$
- (n) $\xrightarrow{\text{Rh}_2(\text{O}_2\text{CCH}_3)_4}$ $\text{C}_9\text{H}_{14}\text{O}_3$
- (o) $\xrightarrow{\text{PCl}_5}$ $\text{C}_{14}\text{H}_{16}\text{N}_2$

³⁸⁰ E. J. Corey, J. F. Arnett, and G. N. Widiger, *J. Am. Chem. Soc.*, **97**, 430 (1975).

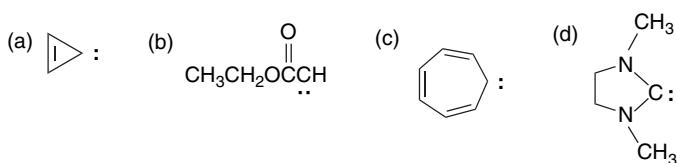


10.2. Indicate appropriate reagents and reaction conditions or a short reaction sequence that could be expected to effect the following transformations:

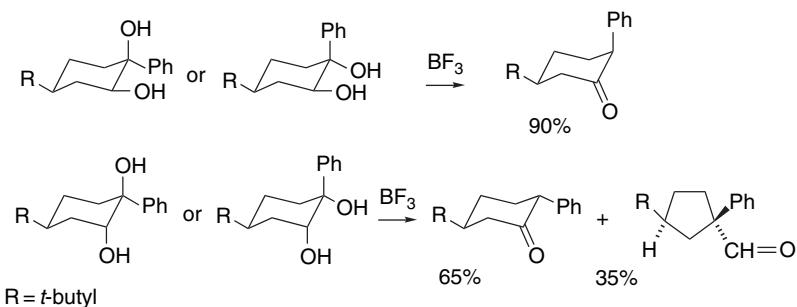




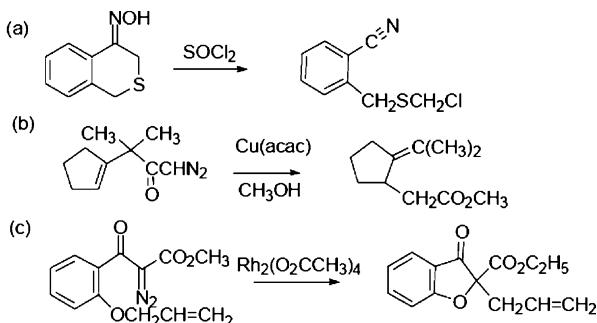
- 10.3. Each of the following carbenes has been predicted to have a singlet ground state, either as the result of qualitative structural considerations or theoretical calculations. Indicate what structural features might stabilize the singlet state in each case.



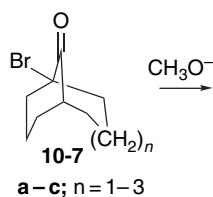
- 10.4. The hydroxy group in *E*-cycloocten-3-ol determines the stereochemistry of the reaction with the Simmons-Smith reagent. By examining a model, predict the stereochemistry of the product.
- 10.5. Discuss the significance of the relationship between reactant stereochemistry and product composition exhibited in the reactions shown below.



- 10.6. Suggest a mechanistic rationalization for the following reactions. Point out the structural features that contribute to the unusual or abnormal course of the reaction. What product would have been expected if the reaction followed a “normal” course.



- 10.7. It has been found that the bromo ketones **10-7a-c** can rearrange by either the cyclopropanone or the semibenzilic mechanism, depending on the size of the ring and the reaction conditions. Suggest two experiments that would permit you to distinguish between the two mechanisms under a given set of circumstances.

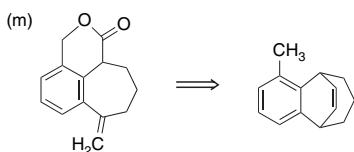
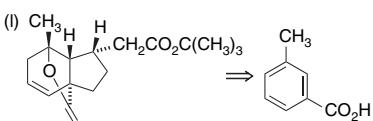
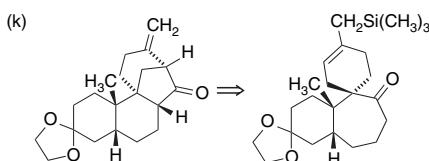
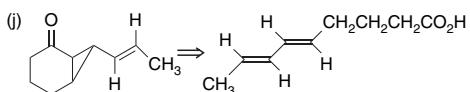
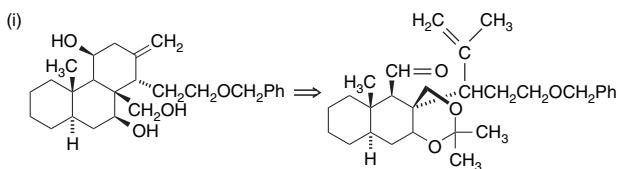


10.8. Predict the major product of the following reactions:

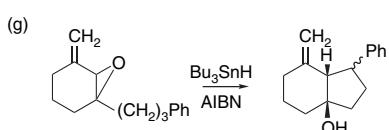
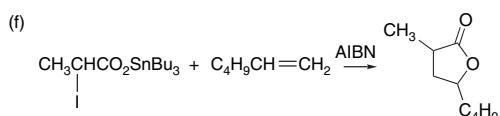
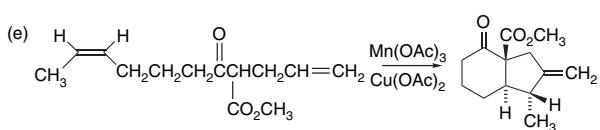
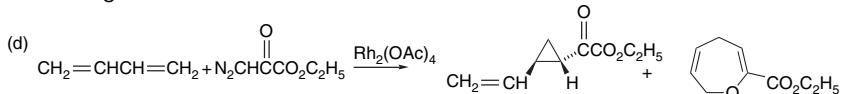
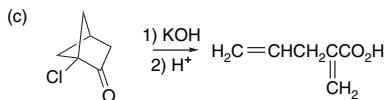
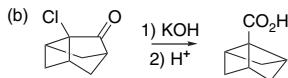
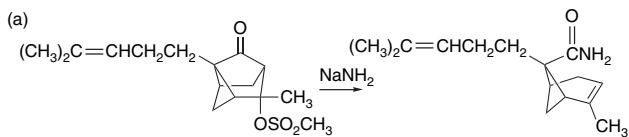
- (a)
- (b)
- (c)
- (d)
- (e)
- (f)
- (g)

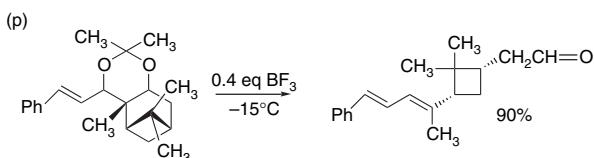
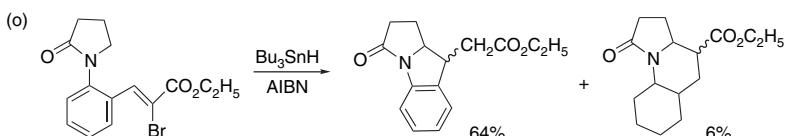
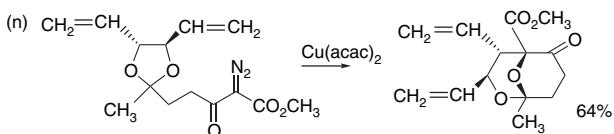
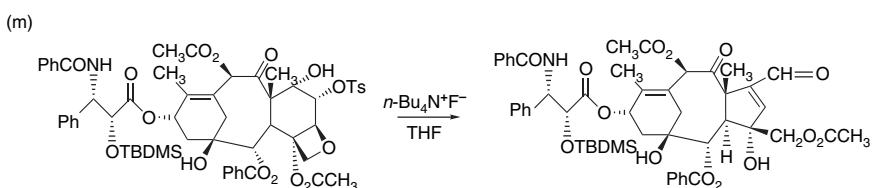
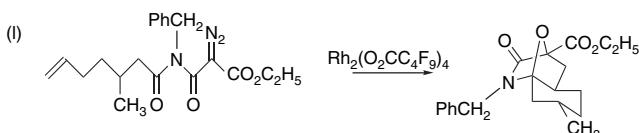
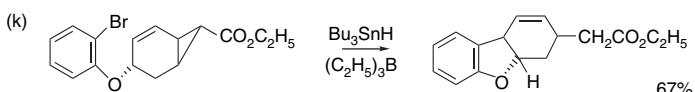
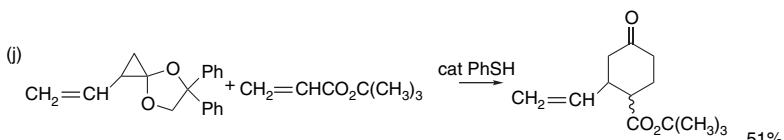
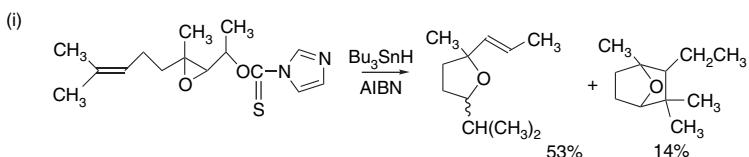
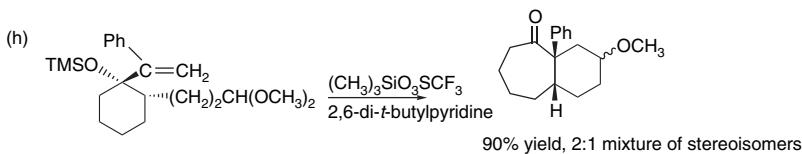
10.9. Short reaction series can effect formation of the desired material on the left from the starting material on the right. Devise an appropriate reaction sequence.

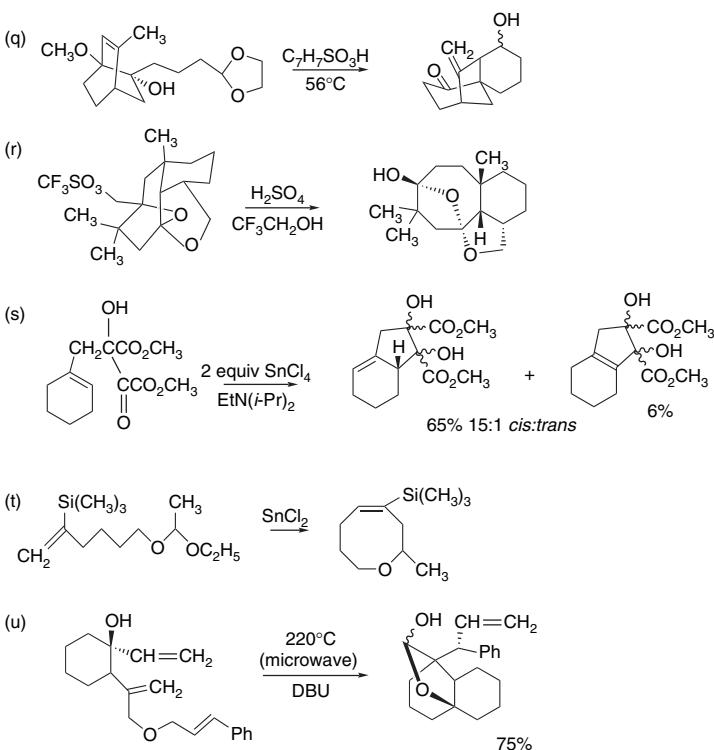
- (a)
- (b)
- (c)
- (d)
- (e)
- (f)
- (g)
- (h)



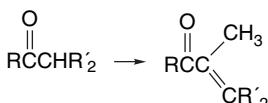
10.10. Formulate mechanisms for the following reactions:



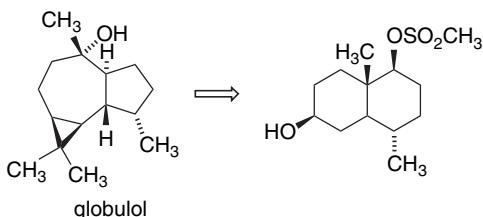




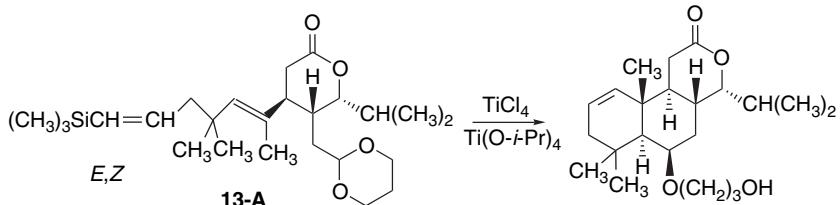
- 10.11. A sequence of reactions for conversion of acyclic and cyclic ketones into α,β -unsaturated ketones with insertion of a $=\text{CHCH}_3$ unit has been developed. The method uses 1-lithio-1,1-dichloroethane as a key carbeneoid reagent. The overall sequence involves three steps, one of them before and one after the carbeneoid reaction. By analysis of the bonding changes and application of your knowledge of carbene reactions, devise a reaction sequence that would accomplish the transformation.



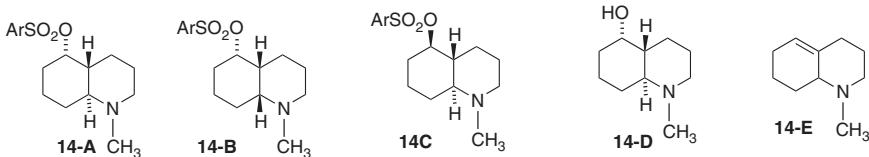
- 10.12. The synthesis of globulol from the octalin derivative shown proceeds in four stages. These include, not necessarily in sequence, addition of a carbene, a fragmentation reaction, and acid-catalyzed cyclization of a cyclodeca-2,7-dienol. The final step of the synthesis converts a dibromocyclopropane to the dimethylcyclopropane structure using dimethylcuprate. Using retrosynthetic analysis, devise an appropriate sequence of reactions and suggest reagents for each step.



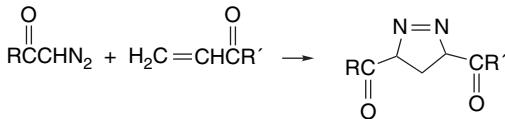
- 10.13. Both the *E*- and *Z*-isomers of vinylsilane **13-A** have been subjected to polyene cyclization using $\text{TiCl}_4\text{-Ti(O-}i\text{-Pr)}_4$. Although the *Z*-isomer gives an 85–90% yield, the *E*-isomer affords only a 30–40% yield. Offer an explanation.



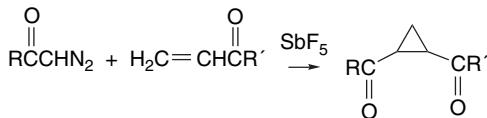
- 10.14. Each of the three dehydroquinoline sulfonates shown below gives a different product composition on solvolysis. One gives 9-methylamino-*E*-non-5-enal, one gives 9-methylamino-*Z*-non-5-enal, and one gives a mixture of the two quinoline derivatives **14-D** and **14-E**. Deduce which compound gives rise to which product. Explain your reasoning.



- 10.15. Normally, the dominant reaction between acyl diazo compounds and simple α,β -unsaturated carbonyl compounds is a cycloaddition.

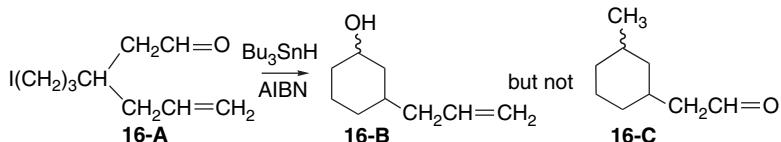


If, however, the reaction is run in the presence of a Lewis acid, particularly SbF_5 , the reaction takes a different course, giving a diacyl cyclopropane.



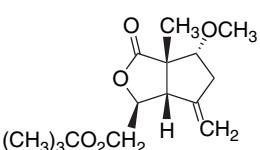
Formulate a mechanism to account for the altered course of the reaction in the presence of SbF_5 .

- 10.16. Compound **16-A** on reaction with Bu_3SnH in the presence of AIBN gives **16-B** rather than **16-C**. How is **16-B** formed? Why is **16-C** not formed? What relationship do these results have to the rate data given on p. 986?

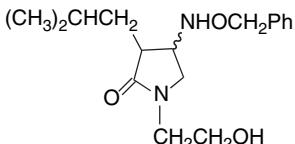


- 10.17. The following molecules have been synthesized by radical cyclization and tandem radical cyclizations. Identify the bond or bonds that could be formed by radical cyclizations and suggest an appropriate reactant and reaction conditions that would lead to the specified products.

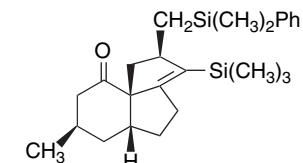
(a)



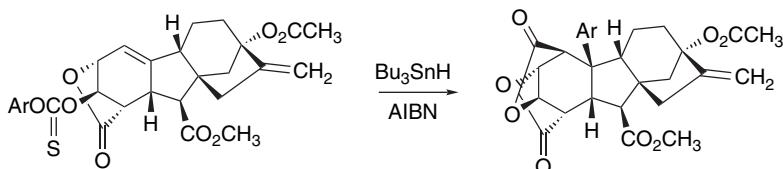
(b)



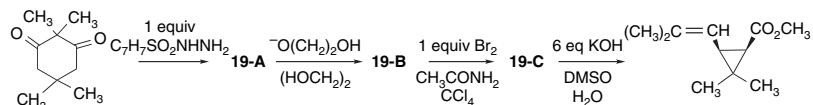
(c)



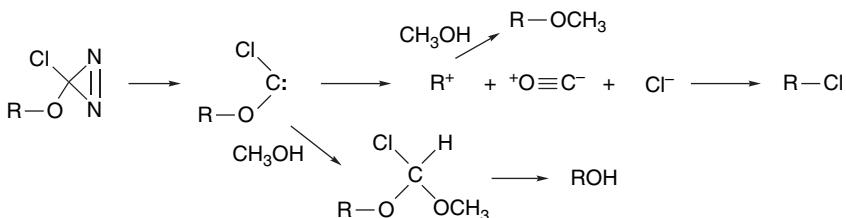
- 10.18. Attempted deoxygenation of several β -aryl thiono carbonates gave the unexpected product shown. In contrast, the corresponding α -isomers gave the desired deoxygenation product. Account for the formation of the observed products, and indicate why these products are not formed from the α -stereoisomers.



- 10.19. *cis*-Chrysanthemic acid has been synthesized through three intermediates using the reaction conditions shown. Assign structures to the intermediates and indicate the nature of each of the reactions.



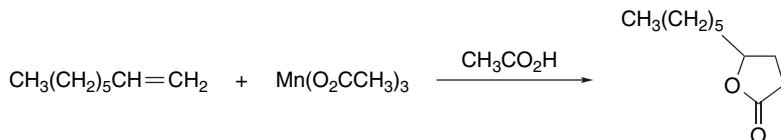
- 10.20. The photolysis of alkoxy chlorodiazirines generates carbenes. The reaction has been examined in pentane and CH_2Cl_2 with increasing amounts of methanol. Three products, the bridgehead chloride, bridgehead ether, and bridgehead alcohol are formed. The former two products arise from fragmentation of the carbene. The last results from trapping of the carbene prior to fragmentation.



The activation energies for the fragmentation of the carbene in CH_2Cl_2 were calculated by the B3LYP/6-31G* method to be 14.6, 2.2, and -0.95 for the bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, and adamantyl systems, respectively. Are the product trends consistent with these computational results, which presumably reflect the relative stability of the carbocation formed by the fragmentation?

[MeOH]	pentane			CH_2Cl_2		
	R-Cl	R-OCH ₃	R-OH	R-Cl	R-OCH ₃	R-OH
R = bicyclo[2.2.1]heptyl						
0				100		
0.25	15	3	82	64	trace	35
0.50	23	trace	77	59	1	40
1.00	45	trace	55	57	2	41
R = bicyclo[2.2.2]octyl						
0				100		
0.25	38	19	43	60	8	32
0.50	34	19	47	52	13	35
1.00	40	20	40	45	21	34
R = adamantyl						
0				100		
0.25	81	trace	19	93	trace	7
0.50	83	trace	17	91	trace	9
1.00	83	trace	17	79	10	11

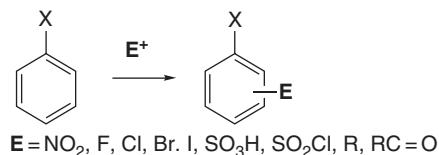
- 10.21 a. The oxidation of norbornadiene by *t*-butyl perbenzoate and Cu(I) leads to 7-*t*-butoxynorbornadiene. Similarly, oxidation with dibenzoyl peroxide and CuBr leads to 7-benzoyloxynorbornadiene. In both reactions, when a 2-deuterated sample of norbornadiene is used, the deuterium is found distributed among all positions in the product in approximately equal amounts. Provide a mechanism that can account for this result.
- b. A very direct synthesis of certain lactones involves heating an alkene with a carboxylic acid and the Mn(III) salt of the acid. Suggest a mechanism by which this reaction might occur.



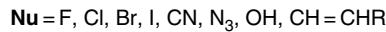
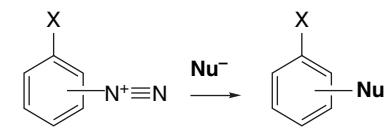
Aromatic Substitution Reactions

Introduction

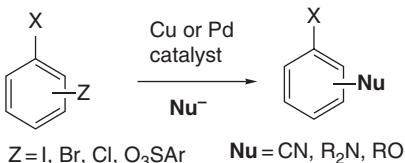
This chapter is concerned with reactions that introduce or replace substituent groups on aromatic rings. The synthetic methods for aromatic substitution were among the first to be developed. The basic mechanistic concepts for electrophilic aromatic substitution and some of the fundamental reactions are discussed in Chapter 9 of Part A. These reactions provide methods for introduction of nitro groups, the halogens, sulfonic acids, and alkyl and acyl groups. The regioselectivity of these reactions depends upon the nature of the existing substituent and can be *ortho*, *meta*, or *para* selective.



A second group of aromatic substitution reactions involves aryl diazonium ions. As for electrophilic aromatic substitution, many of the reactions of aromatic diazonium ions date to the nineteenth century. There have continued to be methodological developments for substitution reactions of diazonium intermediates. These reactions provide routes to aryl halides, cyanides, and azides, phenols, and in some cases to alkenyl derivatives.



Direct nucleophilic displacement of halide and sulfonate groups from aromatic rings is difficult, although the reaction can be useful in specific cases. These reactions can occur by either addition-elimination (Section 11.2.2) or elimination-addition (Section 11.2.3). Recently, there has been rapid development of metal ion catalysis, and old methods involving copper salts have been greatly improved. Palladium catalysts for nucleophilic substitutions have been developed and have led to better procedures. These reactions are discussed in Section 11.3.



Several radical reaction have some synthetic application, including radical substitution (Section 11.4.1) and the S_{RN}1 reaction (Section 11.4.2).

11.1. Electrophilic Aromatic Substitution

The basic mechanistic concepts and typical electrophilic aromatic substitution reactions are discussed in Sections 9.1 and 9.4 of Part A. In the present section, we expand on that material, with particular emphasis on synthetic methodology.

11.1.1. Nitration

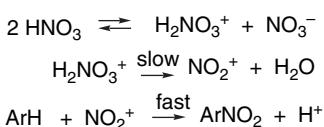
Nitration is the most important method for introduction of nitrogen functionality on aromatic rings. Nitro compounds can be reduced easily to the corresponding amino derivatives, which can provide access to diazonium ions. There are several reagent systems that are useful for nitration. A major factor in the choice of reagent is the reactivity of the ring to be nitrated. Nitration is a very general reaction and satisfactory conditions can normally be developed for both activated and deactivated aromatic compounds. Since each successive nitro group reduces the reactivity of the ring, it is easy to control conditions to obtain a mononitration product. If polynitration is desired, more vigorous conditions are used.

Concentrated nitric acid can effect nitration but it is not as reactive as a mixture of nitric acid with sulfuric acid. The active nitrating species in both media is the nitronium ion, NO₂⁺, which is formed by protonation and dissociation of nitric acid. The concentration of NO₂⁺ is higher in the more strongly acidic sulfuric acid than in nitric acid.

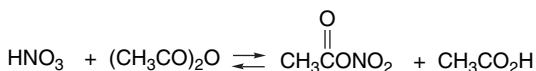


Nitration can also be carried out in organic solvents, with acetic acid and nitromethane being common examples. In these solvents the formation of the NO₂⁺ is often the rate-controlling step.¹

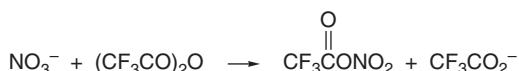
¹. E. D. Hughes, C. K. Ingold, and R. I. Reed, *J. Chem. Soc.*, 2400 (1950); J. G. Hoggett, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 1 (1969); K. Schofield, *Aromatic Nitration*, Cambridge University Press, Cambridge, 1980, Chap. 2.



Another useful medium for nitration is a solution prepared by dissolving nitric acid in acetic anhydride, which generates acetyl nitrate. This reagent tends to give high *ortho:para* ratios for some nitrations.²

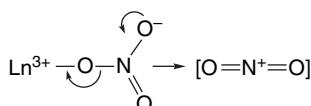


A convenient procedure involves reaction of the aromatic in chloroform or dichloromethane with a nitrate salt and trifluoroacetic anhydride.³ Presumably trifluoroacetyl nitrate is generated under these conditions.



Acetic anhydride and trifluoroacetic anhydride have both been used in conjunction with nitric acid and zeolite β . This system gives excellent *para* selectivity in many cases.⁴ The improved selectivity is thought to occur as a result of nitration within the zeolite pores, which may restrict access to the *ortho* position; see, e.g., Entry 7 in Scheme 11.1.

Nitration can be catalyzed by lanthanide salts. For example, the nitration of benzene, toluene, and naphthalene by aqueous nitric acid proceeds in good yield in the presence of $\text{Yb}(\text{O}_3\text{SCF}_3)_3$.⁵ The catalysis presumably results from an oxyphilic interaction of nitrate ion with the cation, which generates or transfers the NO_2^+ ion.⁶ This catalytic procedure uses a stoichiometric amount of nitric acid and avoids the excess strong acidity associated with conventional nitration conditions.



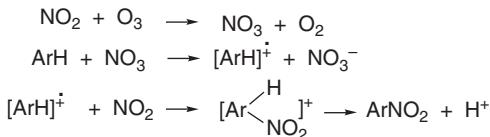
A variety of aromatic compounds can be nitrated using $\text{Sc}(\text{O}_3\text{SCF}_3)_3$, with LiNO_3 or $\text{Al}(\text{NO}_3)_3$ and acetic anhydride (see Scheme 11.1, Entry 9).⁷

Salts containing the nitronium ion can be prepared and are reactive nitrating agents. The tetrafluoroborate salt has been used most frequently,⁸ but the

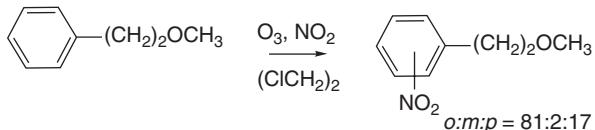
- ^{2.} A. K. Sparks, *J. Org. Chem.*, **31**, 2299 (1966).
- ^{3.} J. V. Crivello, *J. Org. Chem.*, **46**, 3056 (1981).
- ^{4.} K. Smith, T. Gibbins, R. W. Millar, and R. P. Claridge, *J. Chem. Soc., Perkin Trans. 1*, 2753 (2000); K. Smith, A. Musson, and G. A. DeBoos, *J. Org. Chem.*, **63**, 8448 (1998).
- ^{5.} F. J. Walker, A. G. M. Barrett, D. C. Braddock, and D. Ramprasad, *J. Chem. Soc., Chem. Commun.*, 613 (1997).
- ^{6.} F. J. Walker, A. G. M. Barrett, D. C. Braddock, R. M. McKinnell, and D. Ramprasad, *J. Chem. Soc., Perkin Trans. 1*, 867 (1999).
- ^{7.} A. Kawada, S. Takeda, K. Yamashita, H. Abe, and T. Harayama, *Chem. Pharm. Bull.*, **50**, 1060 (2002).
- ^{8.} S. J. Kuhn and G. A. Olah, *J. Am. Chem. Soc.*, **83**, 4564 (1961); G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **84**, 3684 (1962); G. A. Olah, S. C. Narang, J. A. Olah, and K. Lammertsma, *Proc. Natl. Acad. Sci., USA*, **79**, 4487 (1982); C. L. Dwyer and C. W. Holzapfel, *Tetrahedron*, **54**, 7843 (1998).

trifluoromethansulfonate can also be prepared readily.⁹ Nitrogen heterocycles such as pyridine and quinoline form *N*-nitro salts on reaction with NO_2BF_4^- .¹⁰ These *N*-nitro heterocycles in turn can act as nitrating reagents, in a reaction called *transfer nitration* (see Scheme 11.1, Entry 10).

Another nitration procedure uses ozone and nitrogen dioxide.¹¹ With aromatic hydrocarbons and activated derivatives, this nitration is believed to involve the radical cation of the aromatic reactant.



Compounds such as phenylacetate esters and phenylethyl ethers, which have oxygen substituents that can serve as directing groups, show high *ortho*:*para* ratios under these conditions.¹² These reactions are believed to involve coordination of the NO_2^+ at the substituent oxygen, followed by intramolecular transfer.



Scheme 11.1 gives some examples of nitration reactions. Entries 1 to 3 are cases involving mixed nitric and sulfuric acids. Entry 2 illustrates the *meta*-directing effect of the protonated amino substituent. Entry 3 is an example of dinitration. Entry 4 involves an activated ring, and nitric acid suffices for nitration. At first glance, the position of substitution might seem surprising, but it may be that the direct resonance interaction of the 4-methoxy group with the formyl group attenuates its donor effect, leading to dominance of the 3-methoxy group.



Entry 5 is an example of nitration in acetic anhydride. An interesting aspect of this reaction is its high selectivity for the *ortho* position. Entry 6 is an example of the use of trifluoroacetic anhydride. Entry 7 illustrates the use of a zeolite catalyst with improved *para* selectivity. With mixed sulfuric and nitric acids, this reaction gives a 1.8:1 *para*:*ortho* ratio. Entry 8 involves nitration using a lanthanide catalyst, whereas Entry 9 illustrates catalysis by $\text{Sc}(\text{O}_3\text{SCF}_3)_3$. Entry 10 shows nitration done directly with $\text{NO}_2^+\text{BF}_4^-$, and Entry 11 is also a transfer nitration. Entry 12 is an example of the use of the NO_2-O_3 nitration method.

⁹ C. L. Coon, W. G. Blucher, and M. E. Hill, *J. Org. Chem.*, **38**, 4243 (1973).

¹⁰ G. A. Olah, S. C. Narang, J. A. Olah, R. L. Pearson, and C. A. Cupas, *J. Am. Chem. Soc.*, **102**, 3507 (1980).

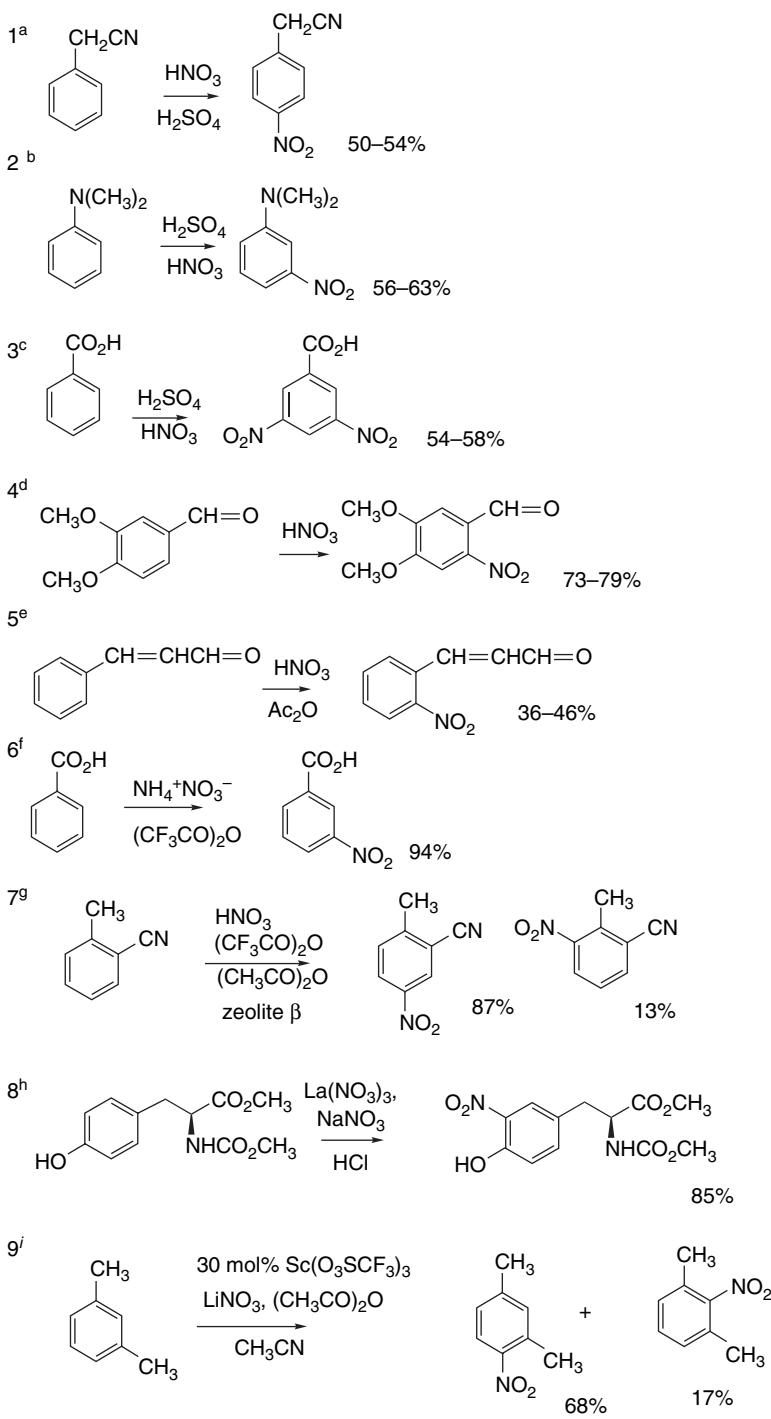
¹¹ H. Suzuki and T. Mori, *J. Chem. Soc., Perkin Trans. 2*, 677 (1996); N. Noryama, T. Mori, and H. Suzuki, *Russ. J. Org. Chem.*, **34**, 1521 (1998).

¹² H. Suzuki, T. Takeuchi, and T. Mori, *J. Org. Chem.*, **61**, 5944 (1996).

Scheme 11.1. Aromatic Nitration

SECTION 11.1

Electrophilic Aromatic Substitution

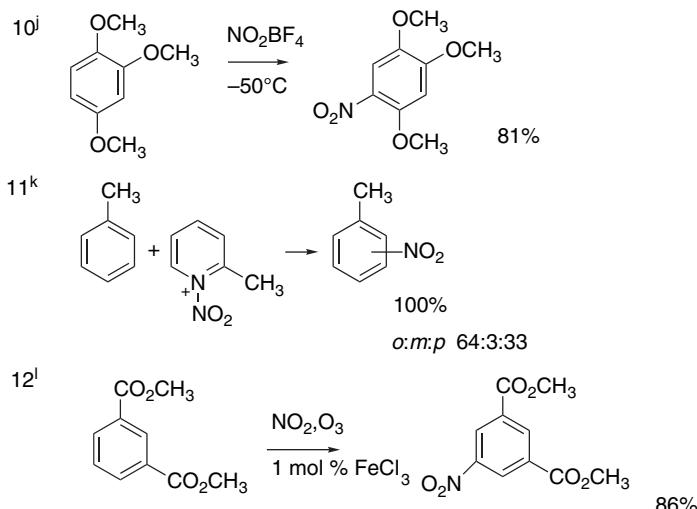


(Continued)

Scheme 11.1. (Continued)

CHAPTER 11

Aromatic Substitution Reactions

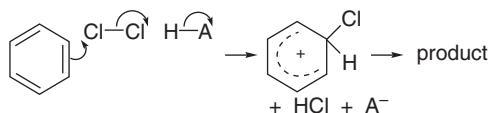


- a. G. R. Robertson, *Org. Synth.*, **I**, 389 (1932).
- b. H. M. Fitch, *Org. Synth.*, **III**, 658 (1955).
- c. R. Q. Brewster, B. Williams, and R. Phillips, *Org. Synth.*, **III**, 337 (1955).
- d. C. A. Fettscher, *Org. Synth.*, **IV**, 735 (1963).
- e. R. E. Buckles and M. P. Bellis, *Org. Synth.*, **IV**, 722 (1963).
- f. J. V. Criewello, *J. Org. Chem.*, **46**, 3056 (1981).
- g. K. Smith, T. Gibbins, R. W. Millar, and R. P. Claridge, *J. Chem. Soc., Perkin Trans. 1*, 2753 (2000).
- h. D. Ma and W. Tang, *Tetrahedron Lett.*, **39**, 7369 (1998).
- i. A. Kawada, S. Takeda, K. Yamashita, H. Abe, and T. Harayama, *Chem. Pharm. Bull.*, **50**, 1060 (2002).
- j. C. L. Dwyer and C. W. Holzapfel, *Tetrahedron*, **54**, 7843 (1998).
- k. C. A. Cupas and R. L. Pearson, *J. Am. Chem. Soc.*, **90**, 4742 (1968).
- l. M. Nose, H. Suzuki, and H. Suzuki, *J. Org. Chem.*, **66**, 4356 (2001).

11.1.2. Halogenation

The introduction of the halogens onto aromatic rings by electrophilic substitution is an important synthetic procedure. Chlorine and bromine are reactive toward aromatic hydrocarbons, but Lewis acid catalysts are normally needed to achieve desirable rates. Elemental fluorine reacts very exothermically and careful control of conditions is required. Molecular iodine can effect substitution only on very reactive aromatics, but a number of more reactive iodination reagents have been developed.

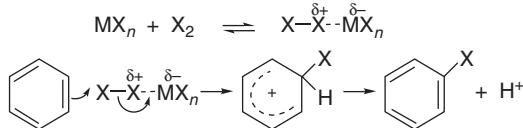
Rate studies show that chlorination is subject to acid catalysis, although the kinetics are frequently complex.¹³ The proton is believed to assist Cl–Cl bond breaking in a reactant-Cl₂ complex. Chlorination is much more rapid in polar than in nonpolar solvents.¹⁴ Bromination exhibits similar mechanistic features.



¹³. L. M. Stock and F. W. Baker, *J. Am. Chem. Soc.*, **84**, 1661 (1962); L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **81**, 1063 (1959); R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc.*, **82**, 4547 (1960); L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **79**, 5169 (1957).

¹⁴. L. M. Stock and A. Himoe, *J. Am. Chem. Soc.*, **83**, 4605 (1961).

For preparative reactions, Lewis acid catalysts are used. Zinc chloride or ferric chloride can be used in chlorination, and metallic iron, which generates ferric bromide, is often used in bromination. The Lewis acid facilitates cleavage of the halogen-halogen bond.



N-Bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) are alternative halogenating agents. Activated aromatics, such as 1,2,4-trimethoxybenzene, are brominated by NBS at room temperature.¹⁵ Both NCS and NBS can halogenate moderately active aromatics in nonpolar solvents by using HCl¹⁶ or HClO₄¹⁷ as a catalyst. Many other “positive halogen” compounds can act as halogenating agents. (See Table 4.2 for examples of such reagents.)

A wide variety of aromatic compounds can be brominated. Highly reactive ones, such as anilines and phenols, may undergo bromination at all activated positions. More selective reagents such as pyridinium bromide perbromide or tetraalkylammonium tribromides can be used in such cases.¹⁸ Moderately reactive compounds such as anilides, haloaromatics, and hydrocarbons can be readily brominated and the usual directing effects control the regiochemistry. Use of Lewis acid catalysts permits bromination of rings with deactivating substituents, such as nitro and cyano.

Halogenations are strongly catalyzed by mercuric acetate or trifluoroacetate. These conditions generate acyl hypohalites, which are the active halogenating agents. The trifluoroacetyl hypohalites are very reactive reagents. Even nitrobenzene, for example, is readily brominated by trifluoroacetyl hypobromite.¹⁹

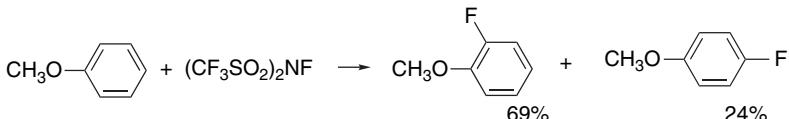


A solution of bromine in CCl₄ containing sulfuric acid and mercuric oxide is also a reactive brominating agent.²⁰

Fluorination can be carried out using fluorine diluted with an inert gas. However, great care is necessary to avoid uncontrolled reaction.²¹ Several other reagents have been devised that are capable of aromatic fluorination.²² Acetyl hypofluorite can be prepared in situ from fluorine and sodium acetate.²³ This reagent effects fluorination

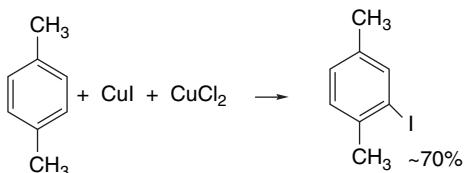
- ^{15.} M. C. Carreno, J. L. Garcia Ruano, G. Sanz, M. A. Toledo, and A. Urbano, *J. Org. Chem.*, **60**, 5328 (1995).
- ^{16.} B. Andersh, D. L. Murphy, and R. J. Olson, *Synth. Commun.*, **30**, 2091 (2000).
- ^{17.} Y. Goldberg and H. Alper, *J. Org. Chem.*, **58**, 3072 (1993).
- ^{18.} W. P. Reeves and R. M. King, II, *Synth. Commun.*, **23**, 855 (1993); J. Berthelot, C. Guette, P. L. Desbene, and J. J. Basselier, *Can. J. Chem.*, **67**, 2061 (1989); S. Kajigaishi, T. Kakinami, T. Inoue, M. Kondo, H. Nakamura, M. Fujikawa, and T. Okamoto, *Bull. Chem. Soc. Jpn.*, **61**, 597 (1988); S. Kajigaishi, T. Kakinami, T. Yamasaki, S. Fujisaki, M. Fujikawa, and T. Okamoto, *Bull. Chem. Soc. Jpn.*, **61**, 2681 (1988); S. Gervat, E. Leonel, J.-Y. Barraud, and V. Ratovelomanana, *Tetrahedron Lett.*, **34**, 2115 (1993). M. K. Chaudhuri, A. J. Khan, B. K. Patel, D. Dey, W. Kharmawphlang, T. R. Lakshimprabha, and G. C. Mandal, *Tetrahedron Lett.*, **39**, 8163 (1998).
- ^{19.} J. R. Barnett, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **94**, 6129 (1972).
- ^{20.} S. A. Khan, M. A. Munawar, and M. Siddiq, *J. Org. Chem.*, **53**, 1799 (1988).
- ^{21.} F. Cacace, P. Giacomello, and A. P. Wolf, *J. Am. Chem. Soc.*, **102**, 3511 (1980).
- ^{22.} S. T. Purrington, B. S. Kagan, and T. B. Patrick, *Chem. Rev.*, **86**, 997 (1986).
- ^{23.} O. Lerman, Y. Tor, and S. Rozen, *J. Org. Chem.*, **46**, 4629 (1981); O. Lerman, Y. Tor, D. Hebel, and S. Rozen, *J. Org. Chem.*, **49**, 806 (1984); G. W. M. Visser, C. N. M. Bakker, B. W. v. Halteren, J. D. M. Herscheid, G. A. Brinkman, and A. Hoekstra, *J. Org. Chem.*, **51**, 1886 (1986).

of activated aromatics. Although this procedure does not avoid the special precautions necessary for manipulation of elemental fluorine, it does provide a system with much greater selectivity. Acetyl hypofluorite shows a strong preference for *o*-fluorination of alkoxy and acetamido-substituted rings. *N*-Fluoro-*bis*-(trifluoromethansulfonyl)amine (*N*-fluorotriflimide) displays similar reactivity and can fluorinate benzene and activated aromatics.²⁴



Several *N*-fluoro derivatives of 1,4-diazabicyclo[2.2.2]octane are useful for aromatic fluorination.²⁵

Iodinations can be carried out by mixtures of iodine and various oxidants such as periodic acid,²⁶ I_2O_5 ,²⁷ NO_2 ,²⁸ and $\text{Ce}(\text{NH}_3)_2(\text{NO}_3)_6$.²⁹ A mixture of cuprous iodide and a cupric salt can also effect iodination.³⁰



Iodination of moderately reactive aromatics can be effected by mixtures of iodine and silver or mercuric salts.³¹ Hypoiodites are presumably the active iodinating species. *Bis*-(pyridine)iodonium salts can iodinate benzene and activated derivatives in the presence of strong acids such as HBF_4 or $\text{CF}_3\text{SO}_3\text{H}$.³²

Scheme 11.2 shows some representative halogenation reactions. Entries 1 and 2 involve Lewis acid-catalyzed chlorination. Entry 3 is an acid-catalyzed chlorination using NCS as the reagent. Entry 4 shows a high-yield chlorination of acetanilide by *t*-butyl hypochlorite. This seems to be an especially facile reaction, since anisole is not chlorinated under these conditions, and may involve the *N*-chloroamide as an intermediate. Entry 5 describes a large-scale chlorination done with NCS. The product was used for the synthesis of sulamserod, a drug candidate.

- ²⁴. S. Singh, D. D. DesMarteau, S. S. Zuberi, M. Whitz, and H.-N. Huang, *J. Am. Chem. Soc.*, **109**, 7194 (1987).
- ²⁵. T. Shamma, H. Buchholz, G. K. S. Prakash, and G. A. Olahn, *Israel J. Chem.*, **39**, 207 (1999); A. J. Poss and G. A. Shia, *Tetrahedron Lett.*, **40**, 2673 (1999); T. Umemoto and M. Nagayoshi, *Bull. Chem. Soc. Jpn.*, **69**, 2287 (1996).
- ²⁶. H. Suzuki, *Org. Synth.*, **VI**, 700, (1988).
- ²⁷. L. C. Brazdil and C. J. Cutler, *J. Org. Chem.*, **61**, 9621 (1996).
- ²⁸. Y. Noda and M. Kashima, *Tetrahedron Lett.*, **38**, 6225 (1997).
- ²⁹. T. Sugiyama, *Bull. Chem. Soc. Jpn.*, **54**, 2847 (1981).
- ³⁰. W. C. Baird, Jr., and J. H. Surridge, *J. Org. Chem.*, **35**, 3436 (1970).
- ³¹. Y. Kobayashi, I. Kumadaki, and T. Yoshida, *J. Chem. Res. (Synopses)*, 215 (1977); R. N. Hazeldine and A. G. Sharpe, *J. Chem. Soc.*, 993 (1952); W. Minnis, *Org. Synth.*, **II**, 357 (1943); D. E. Janssen and C. V. Wilson, *Org. Synth.*, **IV**, 547 (1963); N.-W. Sy and B. A. Lodge, *Tetrahedron Lett.*, **30**, 3769 (1989).
- ³². J. Barluenga, J. M. Gonzalez, M. A. Garcia-Martin, P. J. Campos, and G. Asensio, *J. Org. Chem.*, **58**, 2058 (1993).

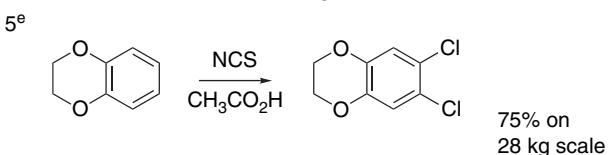
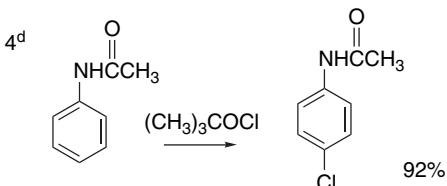
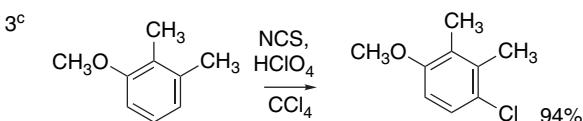
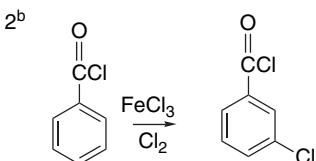
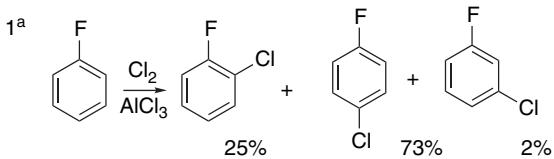
Scheme 11.2. Aromatic Halogenation

1011

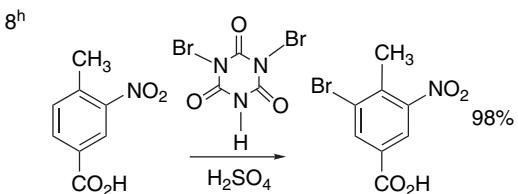
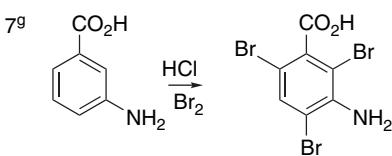
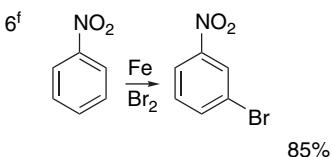
SECTION 11.1

Electrophilic Aromatic Substitution

A. Chlorination

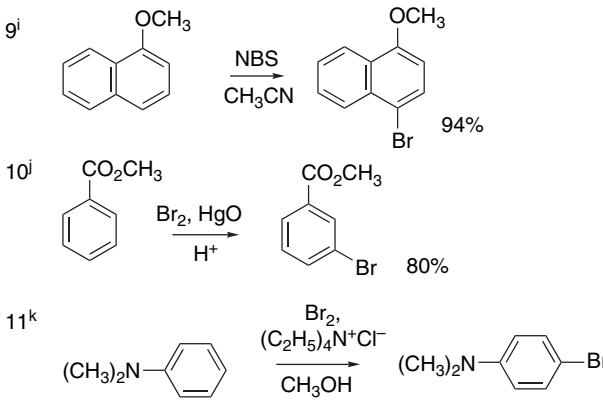


B. Bromination

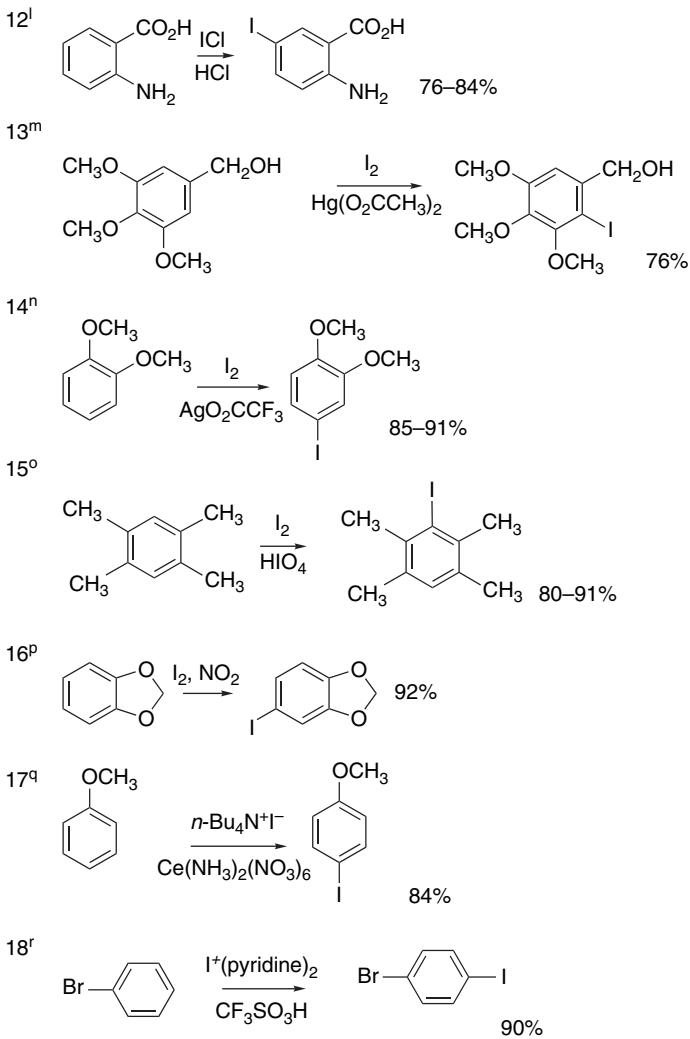


(Continued)

Scheme 11.2. (Continued)



C. Iodination

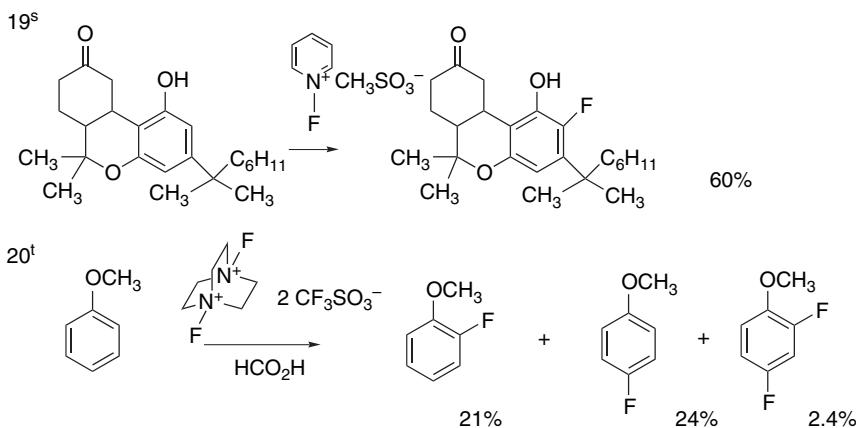


(Continued)

D. Fluorination

SECTION 11.1

Electrophilic Aromatic Substitution



- a. G. A. Olah, S. J. Kuhn, and B. A. Hardi, *J. Am. Chem. Soc.*, **86**, 1055 (1964).
 b. E. Hope and G. F. Riley, *J. Chem. Soc.*, **121**, 2510 (1922).
 c. V. Goldberg and H. Alper, *J. Org. Chem.*, **58**, 3072 (1993).
 d. I. Lengyel, V. Cesare, and R. Stephan, *Synth. Commun.*, **28**, 1891 (1998).
 e. B. A. Kowalczyk, J. Robinson, III, and J. O. Gardner, *Org. Proc. Res. Dev.*, **5**, 116 (2001).
 f. J. R. Johnson and C. G. Gauerke, *Org. Synth.*, **I**, 123 (1941).
 g. M. M. Robison and B. L. Robison, *Org. Synth.*, **IV**, 947 (1963).
 h. A. R. Leeds, S. D. Boettger, and B. Ganem, *J. Org. Chem.*, **45**, 1098 (1980).
 i. M. C. Carreno, J. L. Garcia Russo, G. Sanz, M. A. Toledo, and A. Urbano, *J. Org. Chem.*, **60**, 5328 (1995).
 j. S. A. Khan, M. A. Munawar, and M. Siddiq, *J. Org. Chem.*, **53**, 1799 (1988).
 k. S. Gervat, E. Leonel, J.-Y. Barraud, and V. Ratovelomanana, *Tetrahedron Lett.*, **34**, 2115 (1993).
 l. V. H. Wallingford and P. A. Krueger, *Org. Synth.*, **II**, 349 (1943).
 m. F. E. Ziegler and J. A. Schwartz, *J. Org. Chem.*, **43**, 985 (1978).
 n. D. E. Janssen and C. V. Wilson, *Org. Synth.*, **IV**, 547 (1963).
 o. H. Suzuki, *Org. Synth.*, **51**, 94 (1971).
 p. Y. Noda and M. Kashima, *Tetrahedron Lett.*, **38**, 6225 (1997).
 q. T. Sugiyama, *Bull. Chem. Soc. Jpn.*, **54**, 2847 (1981).
 r. J. Barluenga, J. M. Gonzalez, M. A. Garcia-Martin, P. J. Campos, and G. Asensio, *J. Org. Chem.*, **58**, 2058 (1993).
 s. M. A. Tius, J. K. Kawakami, W. A. G. Hill, and A. Makriyannis, *J. Chem. Soc., Chem. Commun.*, 2085 (1996).
 t. T. Umemoto and M. Nagayoshi, *Bull. Chem. Soc. Jpn.*, **69**, 2287 (1996).

Entry 6 is a case of *meta* bromination of a deactivated aromatic. Entry 7 is a case in which all activated positions are brominated. It is interesting that the reaction occurs in acidic solution. It may be that each successive bromine addition accelerates the reaction by decreasing the basicity of the aniline and increasing the amount that is present in the neutral form. Entry 8 employs dibromoisocyanuric acid in concentrated H_2SO_4 as a brominating reagent. These conditions have been found useful for unreactive aromatics. Entry 9 is an example of bromination using NBS. Entry 10 uses bromine and mercuric oxide under conditions that were found effective for deactivated aromatics. Entry 11 describes conditions that are applicable for bromination of anilines. It is suggested that the reaction may involve formation of methyl hypobromite as the active bromination reagent.

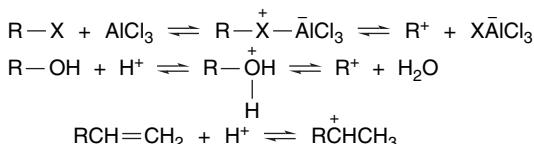
Entries 12 to 18 show iodinations under various conditions. The reaction in Entry 12, using iodine monochloride, is done in concentrated HCl, but presumably occurs through the neutral form of the reactant ($pK_1 = 2.17$). Entries 13 and 14 involve reactions activated by mercuric and silver salts, respectively, and probably involve the

hypoiodites as the active reagents. Entry 15 uses iodine and periodic acid, a reagent combination that was found effective for moderately activated aromatics. The $I_2\text{-NO}_2$ combination illustrated in Entry 16 is also applicable to activated species. Entry 17 illustrates an oxidative procedure that can be used with moderately activated aromatics such as the methyl and methoxy derivatives of benzene. The *bis*-pyridine-iodonium reagent shown in Entry 18 was used with two equivalents of a strong acid, either HBF_4 or $\text{CF}_3\text{SO}_3\text{H}$, in dichloromethane. These conditions were applicable even to deactivated aromatics, such as methyl benzoate and nitrobenzene.

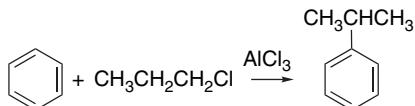
Entries 19 and 20 are fluorinations. In Entry 19, the fluorination is on an activated ring in the antinausea drug nabilone. Entry 20 illustrates the use *N,N'*-difluoro-1,4-diazabicyclo[2.2.2]octane ditriflate.

11.1.3. Friedel-Crafts Alkylation

Friedel-Crafts alkylation reactions are an important method for introducing carbon substituents on aromatic rings. The reactive electrophiles can be either discrete carbocations or polarized complexes that contain a reactive leaving group. Various combinations of reagents can be used to generate alkylating species. Alkylations usually involve alkyl halides and Lewis acids or reactions of alcohols or alkenes with strong acids.



Owing to the involvement of carbocations, Friedel-Crafts alkylations can be accompanied by rearrangement of the alkylating group. For example, isopropyl groups are often introduced when *n*-propyl reactants are used.³³



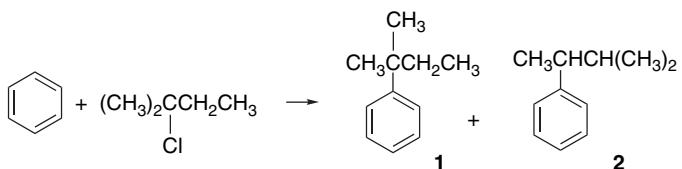
Similarly, under a variety of reaction conditions, alkylation of benzene with either 2-chloro or 3-chloropentane gives rise to a mixture of both 2-pentyl- and 3-pentylbenzene.³⁴

Rearrangement can also occur after the initial alkylation. The reaction of 2-chloro-2-methylbutane with benzene is an example of this behavior.³⁵ With relatively mild Friedel-Crafts catalysts such as BF_3 or FeCl_3 , the main product is **1**. With AlCl_3 , equilibration of **1** and **2** occurs and the equilibrium favors **2**. The rearrangement is the result of product equilibration via reversibly formed carbocations.

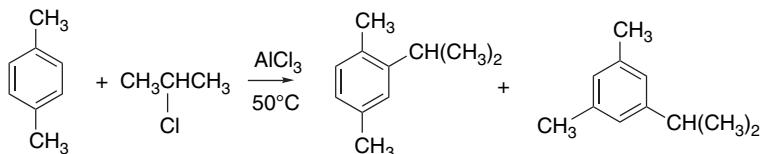
³³ S. H. Sharman, *J. Am. Chem. Soc.*, **84**, 2945 (1962).

³⁴ R. M. Roberts, S. E. McGuire, and J. R. Baker, *J. Org. Chem.*, **41**, 659 (1976).

³⁵ A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **35**, 3717 (1970); R. M. Roberts and S. E. McGuire, *J. Org. Chem.*, **35**, 102 (1970).



Alkyl groups can also migrate from one position to another on the ring.³⁶ Such migrations are also thermodynamically controlled and proceed in the direction of minimizing steric interactions between substituents.



The relative reactivity of Friedel-Crafts catalysts has not been described in a quantitative way, but comparative studies using a series of benzyl halides has resulted in the qualitative groupings shown in Table 11.1. Proper choice of catalyst can minimize subsequent product equilibrations.

The Friedel-Crafts alkylation reaction does not proceed successfully with aromatic reactants having EWG substituents. Another limitation is that each alkyl group that is introduced *increases the reactivity of the ring toward further substitution*, so polyalkylation can be a problem. Polyalkylation can be minimized by using the aromatic reactant in excess.

Apart from the alkyl halide–Lewis acid combination, two other sources of carbocations are often used in Friedel-Crafts reactions. Alcohols can serve as carbocation precursors in strong acids such as sulfuric or phosphoric acid. Alkylation can also be effected by alcohols in combination with BF_3 or AlCl_3 .³⁷ Alkenes can serve as alkylating agents when a protic acid, especially H_2SO_4 , H_3PO_4 , and HF, or a Lewis acid, such as BF_3 and AlCl_3 , is used as a catalyst.³⁸

Stabilized carbocations can be generated from allylic and benzylic alcohols by reaction with $\text{Sc}(\text{O}_3\text{SCF}_3)_3$ and results in formation of alkylation products from benzene and activated derivatives.³⁹

Table 11.1. Relative Activity of Friedel-Crafts Catalysts^a

Very active	Moderately active	Mild
AlCl_3 , AlBr_3 ,	InCl_3 , InBr_3 , SbCl_4 ,	BCl_3 , SnCl_4 ,
GaCl_3 , GaCl_2 ,	FeCl_3 , $\text{AlCl}_3-\text{CH}_3\text{NO}_2$,	TiCl_4 , TiBr_4 ,
SbF_5 , MoCl_5 ,	$\text{SbF}_5-\text{CH}_3\text{NO}_2$	FeCl_2

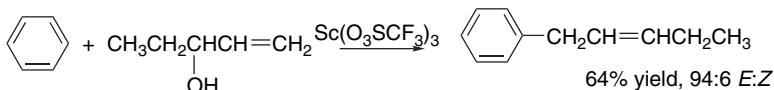
a. G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.*, **94**, 7448 (1972).

³⁶ R. M. Roberts and D. Shieghthong, *J. Am. Chem. Soc.*, **86**, 2851 (1964).

³⁷ A. Schriesheim, in *Friedel-Crafts and Related Reactions*, Vol. II, G. Olah, ed., Interscience, New York, 1964, Chap. XVIII.

³⁸ S. H. Patinkin and B. S. Friedman, in *Friedel-Crafts and Related Reactions*, Vol. II, G. Olah, ed., Interscience, New York, 1964, Chap. XIV.

³⁹ T. Tsuchimoto, K. Tobita, T. Hiyama, and S. Fukuzawa, *Synlett*, 557 (1996); T. Tsuchimoto, K. Tobita, T. Hiyama, and S. Fukuzawa, *J. Org. Chem.*, **62**, 6997 (1997).

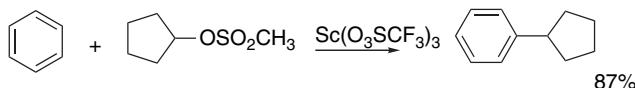


This kind of reaction has been used to synthesize α -tocopherol, in a reaction that involves alkylation, followed by cyclization involving the phenyl hydroxy group.

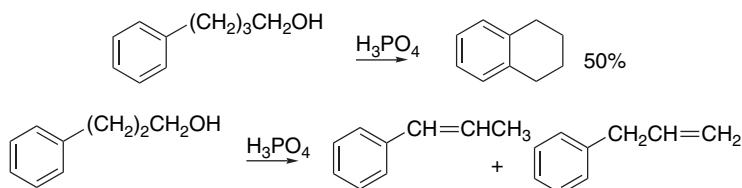


Ref. 40

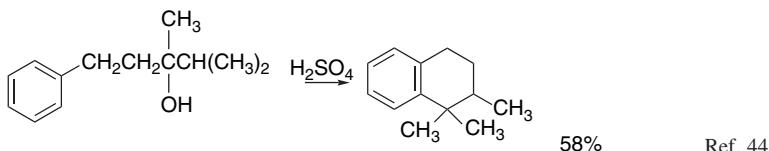
Methanesulfonate esters of secondary alcohols also give Friedel-Crafts products in the presence of $\text{Sc}(\text{O}_3\text{SCF}_3)_3$ ⁴¹ or $\text{Cu}(\text{O}_3\text{SCF}_3)_2$.⁴²



Friedel-Crafts alkylation can occur intramolecularly to form a fused ring. Intramolecular Friedel-Crafts reactions provide an important method for constructing polycyclic hydrocarbon frameworks. It is somewhat easier to form six-membered than five-membered rings in such reactions. Thus, whereas 4-phenyl-1-butanol gives a 50% yield of a cyclized product in phosphoric acid, 3-phenyl-1-propanol is mainly dehydrated to alkenes.⁴³



If a potential carbocation intermediate can undergo a hydride or alkyl shift, this shift occurs in preference to closure of the five-membered ring.



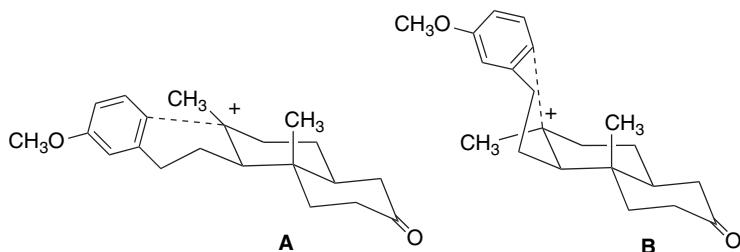
- ⁴⁰. M. Matsui, N. Karibe, K. Hayashi, and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, **68**, 3569 (1995).
⁴¹. H. Kotsuki, T. Ohishi, and M. Inoue, *Synlett*, 255 (1998); H. Kotsuki, T. Ohishi, M. Inoue, and T. Kojima, *Synthesis*, 603 (1999).
⁴². R. P. Singh, R. M. Kamble, K. L. Chandra, P. Saravaran, and V. K. Singh, *Tetrahedron*, **57**, 241 (2001).
⁴³. A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **34**, 3571 (1969).
⁴⁴. A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **37**, 4227 (1972).

These results reflect a rather general tendency for $6 > 5, 7$ in ring closure by intramolecular Friedel-Crafts reactions.^{44,45} The difficulty in forming five-membered rings may derive from steric and electronic factors. Some strain must develop because of the sp^2 carbons included in the ring. Perhaps more important is the need for approach perpendicular to the ring. With three of the five carbons coplanar, it is difficult to align the empty p orbital of the carbocation with the π system.



Scheme 11.3 gives some examples of both inter- and intramolecular Friedel-Crafts alkylations. Entry 1 is carried out using $AlCl_3$ in an excess of refluxing benzene. Entry 2 was also done using benzene as the solvent, but this reaction is done at $0^\circ C$. A tertiary carbocation is generated by protonation of the double bond. Entry 3 involves alkylation by both bromo substituents in the reactant. The reaction is carried out in excess benzene, using $AlBr_3$. Entry 4 demonstrates the ability of a typical aromatic sulfonic acid to generate a reactive carbocation by alkene protonation. The reaction was carried out in excess toluene at $105^\circ C$. Note the relatively weak position selectivity (see also Part A, Section 9.4.4). Secondary alkyl tosylates are also sources of reactive carbocations under these conditions.

Entries 5 to 7 show intramolecular reactions. Entry 5 is an example of formation of a polycyclic ring system. The product is a 3:1 mixture of $\beta:\alpha$ methyl isomers at the new ring junction, and reflects a preference for TS A over TS B.



Entry 6 involves formation of a stabilized benzylic carbocation and results in a very efficient closure of a six-membered ring. Entry 7 involves an activated ring. The reaction was done using enantiomerically pure alcohol, but, as expected for a carbocation intermediate, the product was nearly racemic (6% e.e.). This cyclization was done enantiospecifically by first forming the $Cr(CO)_3$ complex (see Section 8.5).

11.1.4. Friedel-Crafts Acylation

Friedel-Crafts acylation generally involves reaction of an acyl halide and Lewis acid such as $AlCl_3$, SbF_5 , or BF_3 . Bismuth(III) triflate is also a very active acylation catalyst.⁴⁶ Acid anhydrides can also be used in some cases. For example, a combination

⁴⁵. R. J. Sundberg and J. P. Laurino, *J. Org. Chem.*, **49**, 249 (1984); S. R. Angle and M. S. Louie, *J. Org. Chem.*, **56**, 2853 (1991).

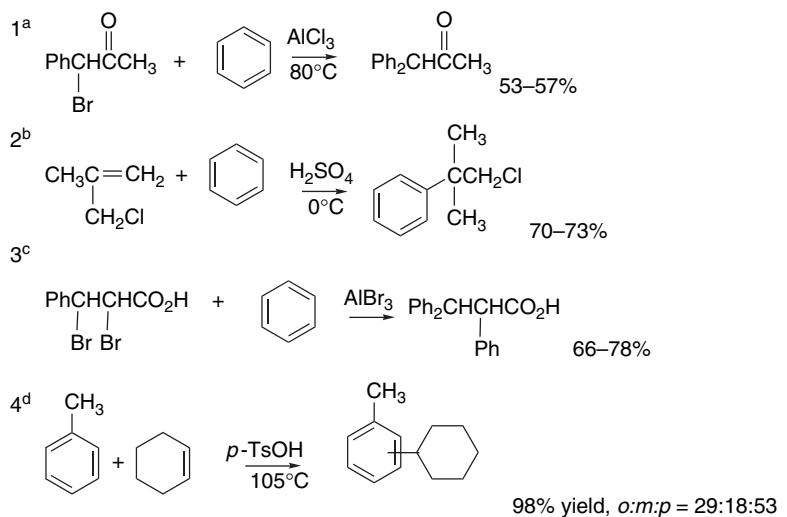
⁴⁶. C. Le Roux and J. Dubac, *Synlett*, 181 (2002); J. R. Desmurs, M. Labrouillere, C. Le Roux, H. Gaspard, A. Laporterie, and J. Dubac, *Tetrahedron Lett.*, **38**, 8871 (1997); S. Repichet, C. LeRoux, J. Dubac, and J.-R. Desmurs, *Eur. J. Org. Chem.*, 2743 (1998).

Scheme 11.3. Friedel-Crafts Alkylation Reactions

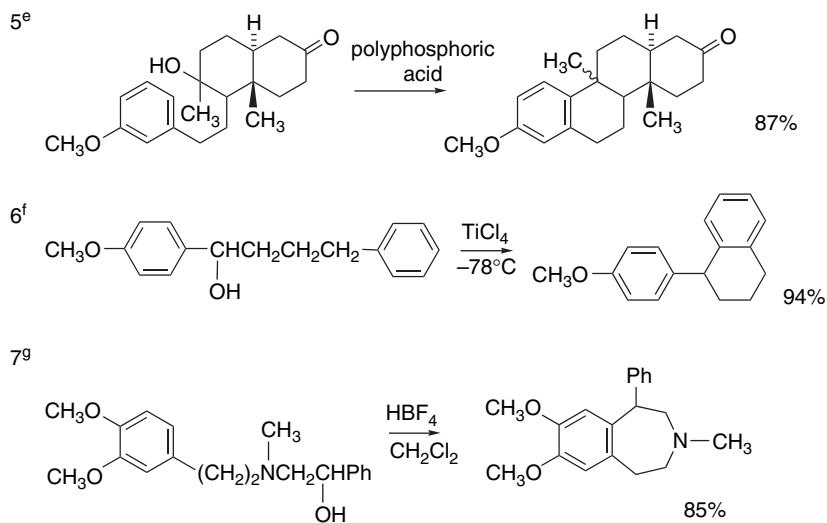
CHAPTER 11

Aromatic Substitution
Reactions

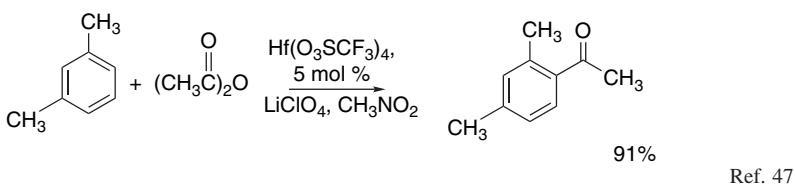
A. Intermolecular reactions



B. Intramolecular Friedel-Crafts cyclizations



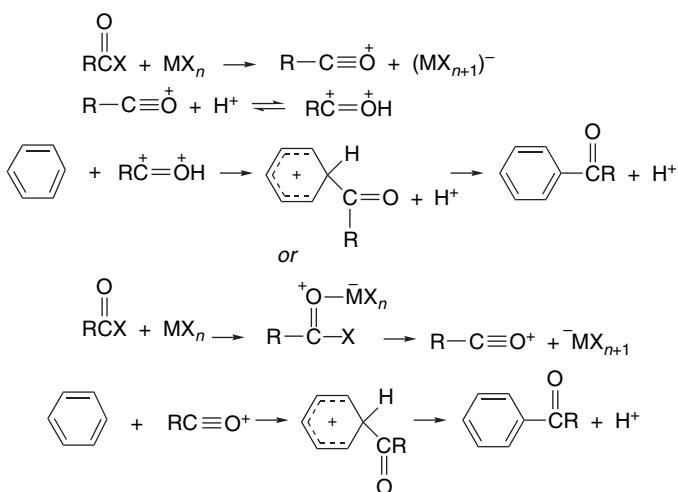
- a. E. M. Shultz and S. Mickey, *Org. Synth.*, **III**, 343 (1955).
 b. W. T. Smith, Jr., and J. T. Sellas, *Org. Synth.*, **IV**, 702 (1963).
 c. C. P. Krimmol, L. E. Thielen, E. A. Brown, and W. J. Heidtke, *Org. Synth.*, **IV**, 960 (1963).
 d. M. P. D. Mahindaratne and K. Wimalasena, *J. Org. Chem.*, **63**, 2858 (1998).
 e. R. E. Ireland, S. W. Baldwin, and S. C. Welch, *J. Am. Chem. Soc.*, **94**, 2056 (1972).
 f. S. R. Angle and M. S. Louie, *J. Org. Chem.*, **56**, 2853 (1991).
 g. S. J. Coote, S. G. Davies, D. Middlemiss, and A. Naylor, *Tetrahedron Lett.*, **30**, 3581 (1989).



Ref. 47

Mixed anhydrides with trifluoroacetic acid are particularly reactive acylating agents.⁴⁸ For example, Entry 5 in Scheme 11.4 shows the use of a mixed anhydride in the course of synthesis of the anticancer agent tamoxifen.

As in the alkylation reaction, the reactive intermediate in Friedel-Crafts acylation can be a dissociated acylium ion or a complex of the acyl chloride and Lewis acid.⁴⁹ Recent mechanistic studies have indicated that with benzene and slightly deactivated derivatives, it is the *protonated acylium ion* that is the kinetically dominant electrophile.⁵⁰



Regioselectivity in Friedel-Crafts acylations can be quite sensitive to the reaction solvent and other procedural variables.⁵¹ In general, *para* attack predominates for

⁴⁷ I. Hachiya, M. Moriwaki, and S. Kobayashi, *Tetrahedron Lett.*, **36**, 409 (1995); A. Kawada, S. Mitamura, and S. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 183 (1996); I. Hachiya, M. Moriwaki, and S. Kobayashi, *Bull. Chem. Soc. Jpn.*, **68**, 2053 (1995).

⁴⁸ E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Teddar, *J. Chem. Soc.*, 719 (1951); C. Galli, *Synthesis*, 303 (1979); B. C. Ranu, K. Ghosh, and U. Jana, *J. Org. Chem.*, **61**, 9546 (1996).

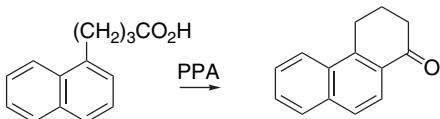
⁴⁹ F. R. Jensen and G. Goldman, in *Friedel-Crafts and Related Reactions*, Vol. III, G. Olah, ed., Interscience, New York, 1964, Chap. XXXVI.

⁵⁰ Y. Sato, M. Yato, T. Ohwada, S. Saito, and K. Shudo, *J. Am. Chem. Soc.*, **117**, 3037 (1995).

⁵¹ For example, see L. Friedman and R. J. Honour, *J. Am. Chem. Soc.*, **91**, 6344 (1969).

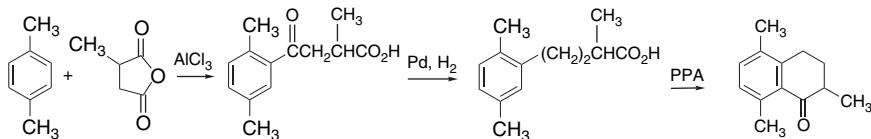
alkylbenzenes.⁵² The percentage of *ortho* attack increases with the electrophilicity of the acylium ion and as much as 50% *ortho* product is observed with the formylium and 2,4-dinitrobenzoylium ions.⁵³ Rearrangement of the acyl group is not a problem in Friedel-Crafts acylation. Neither is polyacylation, because the first acyl group serves to deactivate the ring to further attack. For these reasons, it is often preferable to introduce primary alkyl groups by a sequence of acylation followed by reduction of the acyl group (see Section 5.7.1).

Intramolecular acylations are very common, and the normal conditions involving an acyl halide and Lewis acid can be utilized. One useful alternative is to dissolve the carboxylic acid in polyphosphoric acid (PPA) and heat to effect cyclization. This procedure probably involves formation of a mixed phosphoric-carboxylic anhydride.⁵⁴



Cyclizations can also be carried out with an esterified oligomer of phosphoric acid called “polyphosphate ester,” which is chloroform soluble.⁵⁵ Another reagent of this type is trimethylsilyl polyphosphate (Scheme 11.4, Entry 13).⁵⁶ Neat methanesulfonic acid is also an effective reagent for intramolecular Friedel-Crafts acylation (Scheme 11.4, Entry 14).⁵⁷

A classical procedure for fusing a six-membered ring to an aromatic ring uses succinic anhydride or a derivative. An intermolecular acylation is followed by reduction and an intramolecular acylation. The reduction step is necessary to provide a more reactive ring for the second acylation.



Ref. 58

Scheme 11.4 shows some other representative Friedel-Crafts acylation reactions. Entries 1 and 2 show typical Friedel-Crafts acylation reactions using AlCl_3 . Entries 3 and 4 are similar, but include some functionality in the acylating reagents. Entry 5 involves formation of a mixed trifluoroacetic anhydride, followed by acylation in 85% H_3PO_4 . The reaction was conducted on a kilogram scale and provides a starting material for the synthesis of tamoxifen. Entry 6 illustrates the use of bismuth triflate as

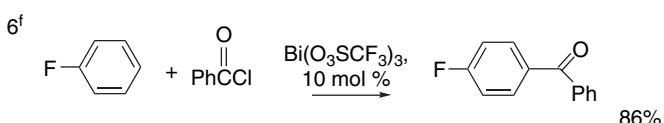
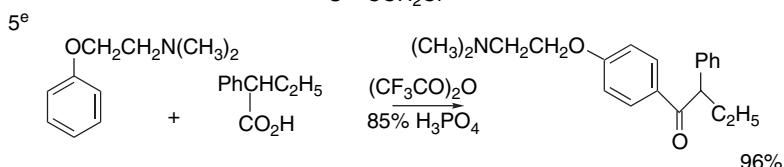
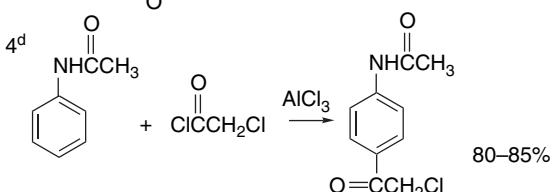
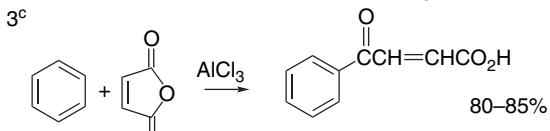
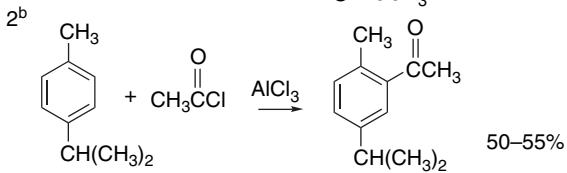
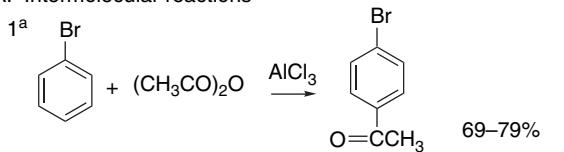
- ⁵². H. C. Brown, G. Marino, and L. M. Stock, *J. Am. Chem. Soc.*, **81**, 3310 (1959); H. C. Brown and G. Marino, *J. Am. Chem. Soc.*, **81**, 5611 (1959); G. A. Olah, M. E. Moffatt, S. J. Kuhn, and B. A. Hardie, *J. Am. Chem. Soc.*, **86**, 2198 (1964).
- ⁵³. G. A. Olah and S. Kobayashi, *J. Am. Chem. Soc.*, **93**, 6964 (1971).
- ⁵⁴. W. E. Bachmann and W. J. Horton, *J. Am. Chem. Soc.*, **69**, 58 (1947).
- ⁵⁵. Y. Kanaoka, O. Yonemitsu, K. Tanizawa, and Y. Ban, *Chem. Pharm. Bull.*, **12**, 773 (1964); T. Kametani, S. Takano, S. Hibino, and T. Terui, *J. Heterocycl. Chem.*, **6**, 49 (1969).
- ⁵⁶. E. M. Berman and H. D. H. Showalter, *J. Org. Chem.*, **54**, 5642 (1989).
- ⁵⁷. V. Premasagar, V. A. Palaniswamy, and E. J. Eisenbraun, *J. Org. Chem.*, **46**, 2974 (1981).
- ⁵⁸. E. J. Eisenbraun, C. W. Hinman, J. M. Springer, J. W. Burnham, T. S. Chou, P. W. Flanagan, and M. C. Hamming, *J. Org. Chem.*, **36**, 2480 (1971).

Scheme 11.4. Friedel-Crafts Acylation Reactions

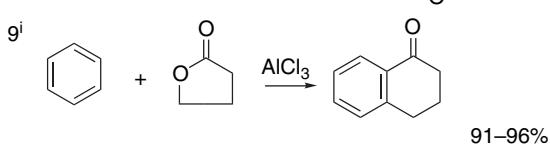
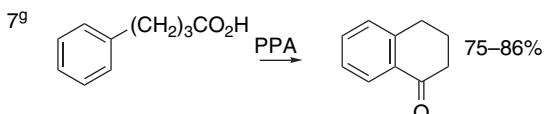
SECTION 11.1

Electrophilic Aromatic Substitution

A. Intermolecular reactions



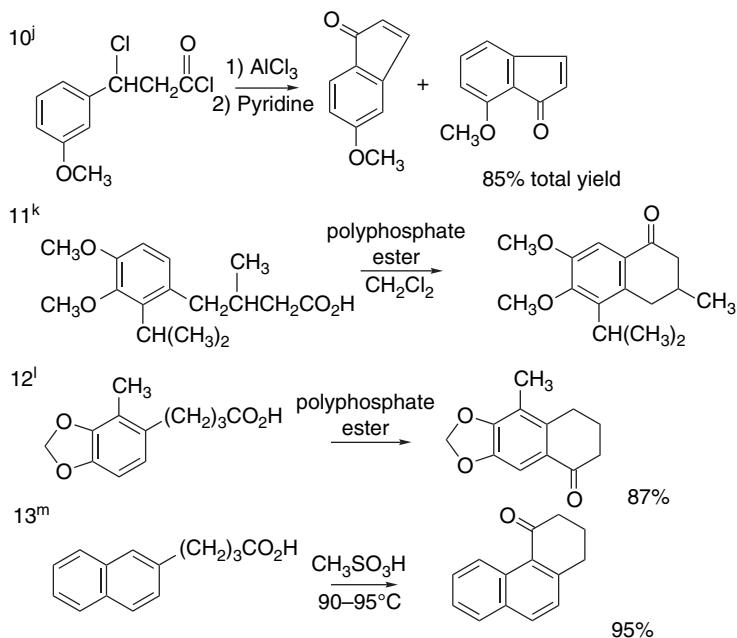
B. Intramolecular friedel–crafts acylations



(Continued)

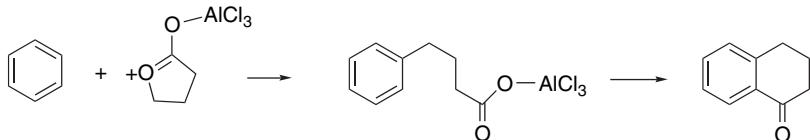
Scheme 11.4. (Continued)

CHAPTER 11

Aromatic Substitution
Reactions

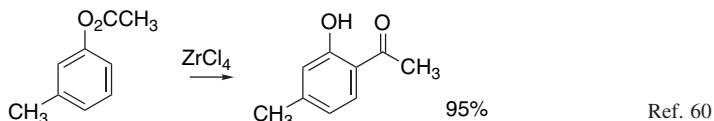
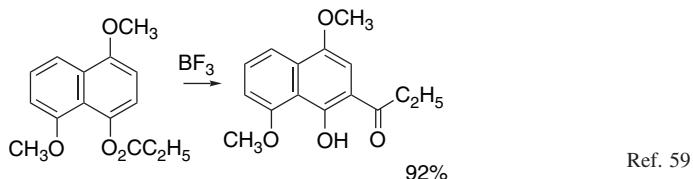
- a. R. Adams and C. R. Noller, *Org. Synth.*, **I**, 109 (1941).
- b. C. F. H. Allen, *Org. Synth.*, **II**, 3 (1943).
- c. O. Grummitt, E. I. Becker, and C. Miesse, *Org. Synth.*, **III**, 109 (1955).
- d. J. L. Leiserson and A. Weissberger, *Org. Synth.*, **III**, 183 (1955).
- e. T. P. Smythe and B. W. Corby, *Org. Process Res. Dev.*, **1**, 264 (1997).
- f. J. R. Desmurs, M. Labrouillere, C. Le Roux, H. Gaspard, A. Laporterie, and J. Dubac, *Tetrahedron Lett.*, **38**, 8871 (1997).
- g. L. Arsnijevic, V. Arsenijevic, A. Horeua, and J. Jaques, *Org. Synth.*, **53**, 5 (1973).
- h. E. L. Martin and L. F. Fieser, *Org. Synth.*, **II**, 569 (1943).
- i. C. E. Olson and A. F. Bader, *Org. Synth.*, **IV**, 898 (1963).
- j. M. B. Floyd and G. R. Allen, Jr., *J. Org. Chem.*, **35**, 2647 (1970).
- k. M. C. Venuti, *J. Org. Chem.*, **46**, 3124 (1981).
- l. G. Esteban, M. A. Lopez-Sanchez, E. Martinez, and J. Plumet, *Tetrahedron*, **54**, 197 (1998).
- m. V. Premasagar, V. A. Palaniswamy, and E. J. Eisenbraun, *J. Org. Chem.*, **46**, 2974 (1981).

a Lewis acid. Entries 7 and 8 exemplify typical conditions for intramolecular Friedel-Crafts reactions. In Entry 9, both alkylation and acylation occur, presumably in that order.



In Entry 10, intramolecular acylation is followed by dehydrohalogenation. Entries 11 and 12 illustrate the use of polyphosphate ester. The cyclization in Entry 13 is done in neat methanesulfonic acid.

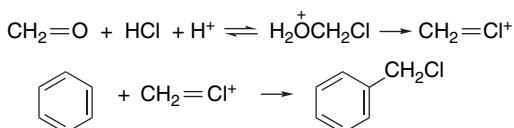
A special case of aromatic acylation is the *Fries rearrangement*, which is the conversion of an ester of a phenol to an *o*-acyl phenol by a Lewis acid.



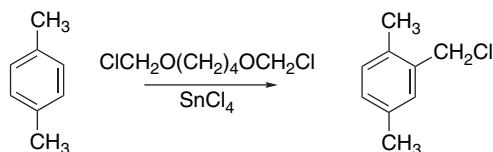
Lanthanide triflates are also good catalysts for Fries rearrangements.⁶¹

11.1.5. Related Alkylation and Acylation Reactions

There are a number of variations of the Friedel-Crafts reactions that are useful in synthesis. The introduction of chloromethyl substituents is brought about by reaction with formaldehyde in concentrated hydrochloric acid and halide salts, especially zinc chloride.⁶² The reaction proceeds with benzene and activated derivatives. The reactive electrophile is probably the chloromethylium ion.



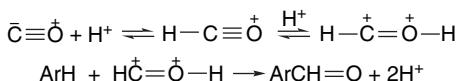
Chloromethylation can also be carried out using various chloromethyl ethers and SnCl_4 .⁶³



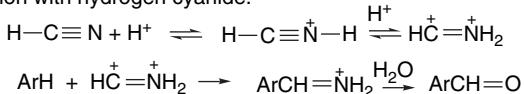
Carbon monoxide, hydrogen cyanide, and nitriles also react with aromatic compounds in the presence of strong acids or Friedel-Crafts catalysts to introduce formyl or acyl substituents. The active electrophiles are believed to be *dication*s resulting from diprotonation of CO, HCN, or the nitrile.⁶⁴ The general outlines of the mechanisms of these reactions are given below.

- ⁵⁹. Y. Naruta, Y. Nishgaichi, and K. Maruyama, *J. Org. Chem.*, **53**, 1192 (1988).
- ⁶⁰. D. C. Harrowven and R. F. Dainty, *Tetrahedron Lett.*, **37**, 7659 (1996).
- ⁶¹. S. Kobayahis, M. Moriwaki, and J. Hachiya, *Bull. Chem. Soc. Jpn.*, **70**, 267 (1997).
- ⁶². R. C. Fuson and C. H. McKeever, *Org. React.*, **1**, 63 (1942); G. A. Olah and S. H. Yu, *J. Am. Chem. Soc.*, **97**, 2293 (1975).
- ⁶³. G. A. Olah, D. A. Beal, and J. A. Olah, *J. Org. Chem.*, **41**, 1627 (1976); G. A. Olah, D. A. Bell, S. H. Yu, and J. A. Olah, *Synthesis*, 560 (1974).
- ⁶⁴. M. Yato, T. Ohwada, and K. Shudo, *J. Am. Chem. Soc.*, **113**, 691 (1991); Y. Sato, M. Yato, T. Ohwada, S. Saito, and K. Shudo, *J. Am. Chem. Soc.*, **117**, 3037 (1995).

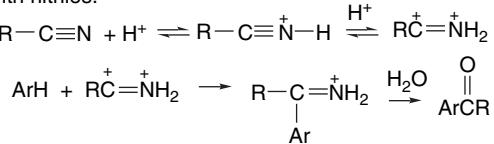
a. Formylation with carbon monoxide:



b. Formylation with hydrogen cyanide:



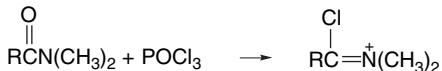
c. Acylation with nitriles:



Many specific examples of these reactions can be found in reviews in the *Organic Reactions* series.⁶⁵ Dichloromethyl ethers are also precursors of the formyl group via alkylation catalyzed by $SnCl_4$ or $TiCl_4$.⁶⁶ The dichloromethyl group is hydrolyzed to a formyl group.



Another useful method for introducing formyl and acyl groups is the *Vilsmeier-Haack reaction*.⁶⁷ *N,N*-dialkylamides react with phosphorus oxychloride or oxalyl chloride⁶⁸ to give a chloroiminium ion, which is the reactive electrophile.



This species acts as an electrophile in the absence of any added Lewis acid, but only rings with ERG substituents are reactive.

Scheme 11.5 gives some examples of these acylation reactions. Entry 1 is an example of a chloromethylation reaction. Entry 2 is a formylation using carbon monoxide. Entry 3 is an example of formylation via *bis*-chloromethyl ether. A cautionary note on this procedure is the potent carcinogenicity of this reagent. Entries 4 and 5 are examples of formylation and acetylation, using HCN and acetonitrile, respectively. Entries 6 to 8 are examples of Vilsmeier-Haack reactions, all of which are conducted on strongly activated aromatics.

- ⁶⁵. N. N. Crounse, *Org. React.*, **5**, 290 (1949); W. E. Truce, *Org. React.*, **9**, 37 (1957); P. E. Spoerri and A. S. DuBois, *Org. React.*, **5**, 387 (1949); see also G. A. Olah, L. Ohannesian, and M. Arvanaghi, *Chem. Rev.*, **87**, 671 (1987).
- ⁶⁶. P. E. Sonnet, *J. Med. Chem.*, **15**, 97 (1972); C. H. Hassall and B. A. Morgan, *J. Chem. Soc., Perkin Trans. 1*, 2853 (1973); R. Halterman and S.-T. Jan, *J. Org. Chem.*, **56**, 5253 (1991).
- ⁶⁷. G. Martin and M. Martin, *Bull. Soc. Chim. Fr.*, 1637 (1963); S. Seshadri, *J. Sci. Ind. Res.*, **32**, 128 (1973); C. Just, in *Iminium Salts in Organic Chemistry*, H. Bohme and H. G. Viehe, eds., Vol. 9 in *Advances in Organic Chemistry: Methods and Results*, Wiley-Interscience, 1976, pp. 225–342.
- ⁶⁸. J. N. Frekos, G. W. Morrow, and J. S. Swenton, *J. Org. Chem.*, **50**, 805 (1985).

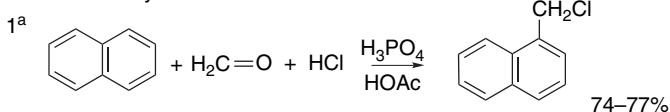
Scheme 11.5. Other Electrophilic Aromatic Substitutions Related to Friedel-Crafts Reactions

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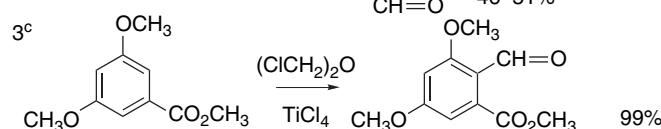
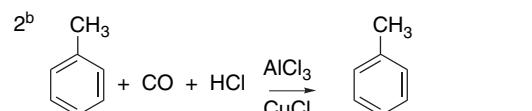
SECTION 11.1

Electrophilic Aromatic Substitution

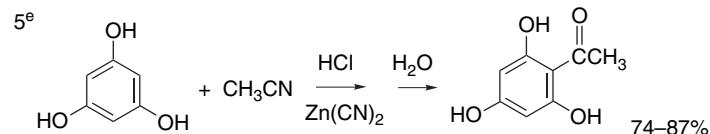
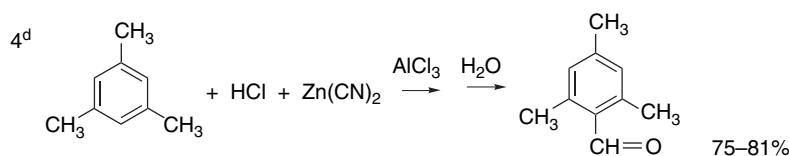
A. Chloromethylation



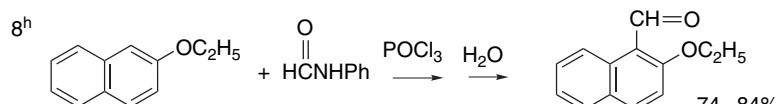
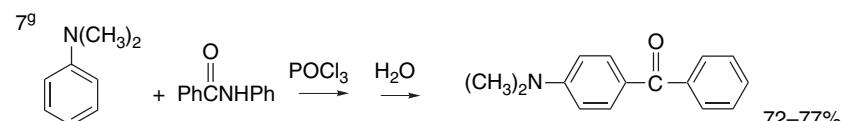
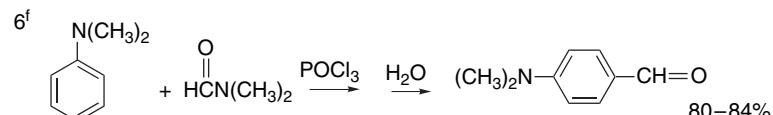
B. Formylation



C. Acylation with cyanide and nitriles



D. Vilsmeier–Haack acylation



a. C. Grummitt and A. Buck, *Org. Synth.*, **III**, 195 (1955).

b. G. H. Coleman and D. Craig, *Org. Synth.*, **II**, 583 (1943).

c. C. H. Hassall and B. A. Morgan, *J. Chem. Soc., Perkin Trans. 1*, 2853 (1973).

d. R. C. Fuson, E. C. Horning, S. P. Rowland, and M. L. Ward, *Org. Synth.*, **III**, 549 (1955).

e. K. C. Gulati, S. R. Seth, and K. Venksataraman, *Org. Synth.*, **II**, 522 (1943).

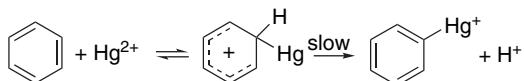
f. E. Campaigne and W. L. Archer, *Org. Synth.*, **IV**, 331 (1963).

g. C. D. Hurd and C. N. Webb, *Org. Synth.*, **I**, 217 (1941).

h. J. H. Wood and R. W. Bost, *Org. Synth.*, **III**, 98 (1955).

11.1.6. Electrophilic Metallation

Aromatic compounds react with mercuric salts to give arylmercury compounds.⁶⁹ Mercuric acetate or mercuric trifluoroacetate are the usual reagents.⁷⁰ The reaction shows substituent effects that are characteristic of electrophilic aromatic substitution.⁷¹ Mercuration is one of the few electrophilic aromatic substitutions in which proton loss from the σ complex is rate determining. Mercuration of benzene shows an isotope effect $k_H/k_D = 6$,⁷² which indicates that the σ complex must be formed reversibly.



The synthetic utility of the mercuration reaction derives from subsequent transformations of the arylmercury compounds. As indicated in Section 7.3.3, these compounds are only weakly nucleophilic, but the carbon-mercury bond is reactive to various electrophiles. They are particularly useful for synthesis of nitroso compounds. The nitroso group can be introduced by reaction with nitrosyl chloride⁷³ or nitrosonium tetrafluoroborate⁷⁴ as the electrophile. Arylmercury compounds are also useful in certain palladium-catalyzed reactions, as discussed in Section 8.2.

Thallium(III), particularly as the trifluoroacetate salt, is also a reactive electrophilic metallating species, and a variety of synthetic schemes based on arylthallium intermediates have been devised.⁷⁵ Arylthallium compounds are converted to chlorides or bromides by reaction with the appropriate cupric halide.⁷⁶ Reaction with potassium iodide gives aryl iodides.⁷⁷ Fluorides are prepared by successive treatment with potassium fluoride and boron trifluoride.⁷⁸ Procedures for converting arylthallium compounds to nitriles and phenols have also been described.⁷⁹

The thallium intermediates can be useful in directing substitution to specific positions when the site of thallation can be controlled in an advantageous way. The two principal means of control are chelation and the ability to effect thermal equilibration of arylthallium intermediates. Oxygen-containing groups normally direct thallation to the *ortho* position by a chelation effect. The thermodynamically favored position is

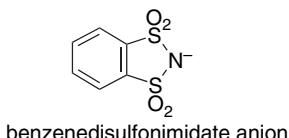
- ⁶⁹. W. Kitching, *Organomet. Chem. Rev.*, **3**, 35 (1968).
- ⁷⁰. A. J. Kresge, M. Dubeck, and H. C. Brown, *J. Org. Chem.*, **32**, 745 (1967); H. C. Brown and R. A. Wirkkala, *J. Am. Chem. Soc.*, **88**, 1447, 1453, 1456 (1966).
- ⁷¹. H. C. Brown and C. W. McGary, Jr., *J. Am. Chem. Soc.*, **77**, 2300, 2310 (1955); A. J. Kresge and H. C. Brown, *J. Org. Chem.*, **32**, 756 (1967); G. A. Olah, I. Hashimoto, and H. C. Lin, *Proc. Natl. Acad. Sci., USA*, **74**, 4121 (1977).
- ⁷². C. Perrin and F. H. Westheimer, *J. Am. Chem. Soc.*, **85**, 2773 (1963); A. J. Kresge and J. F. Brennan, *J. Org. Chem.*, **32**, 752 (1967); C. W. Fung, M. Khorramdel-Vahad, R. J. Ranson, and R. M. G. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 267 (1980).
- ⁷³. L. I. Smith and F. L. Taylor, *J. Am. Chem. Soc.*, **57**, 2460 (1935); S. Terabe, S. Kuruma, and R. Konaka, *J. Chem. Soc., Perkin Trans. 2*, 1252 (1973).
- ⁷⁴. L. M. Stock and T. L. Wright, *J. Org. Chem.*, **44**, 3467 (1979).
- ⁷⁵. E. C. Taylor and A. McKillop, *Acc. Chem. Res.*, **3**, 338 (1970).
- ⁷⁶. S. Uemura, Y. Ikeda, and K. Ichikawa, *Tetrahedron*, **28**, 5499 (1972).
- ⁷⁷. A. McKillop, J. D. Hunt, M. J. Zelesko, J. S. Fowler, E. C. Taylor, G. McGillivray, and F. Kienzle, *J. Am. Chem. Soc.*, **93**, 4841 (1971); M. L. dos Santos, G. C. de Magalhaes, and R. Braz Filho, *J. Organomet. Chem.*, **526**, 15 (1996).
- ⁷⁸. E. C. Taylor, E. C. Bigham, and D. K. Johnson, *J. Org. Chem.*, **42**, 362 (1977).
- ⁷⁹. S. Uemura, Y. Ikeda, and K. Ichikawa, *Tetrahedron*, **28**, 3025 (1972); E. C. Taylor, H. W. Altland, R. H. Danforth, G. McGillivray, and A. McKillop, *J. Am. Chem. Soc.*, **92**, 3520 (1970).

11.2. Nucleophilic Aromatic Substitution

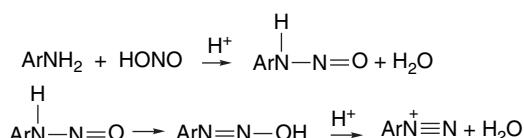
Synthetically important substitutions of aromatic compounds can also be done by nucleophilic reagents. There are several general mechanism for substitution by nucleophiles. Unlike nucleophilic substitution at saturated carbon, aromatic nucleophilic substitution does not occur by a single-step mechanism. The broad mechanistic classes that can be recognized include addition-elimination, elimination-addition, and metal-catalyzed processes. (See Section 9.5 of Part A to review these mechanisms.) We first discuss diazonium ions, which can react by several mechanisms. Depending on the substitution pattern, aryl halides can react by either addition-elimination or elimination-addition. Aryl halides and sulfonates also react with nucleophiles by metal-catalyzed mechanisms and these are discussed in Section 11.3.

11.2.1. Aryl Diazonium Ions as Synthetic Intermediates

The first widely used intermediates for nucleophilic aromatic substitution were the aryl diazonium salts. Aryl diazonium ions are usually prepared by reaction of an aniline with nitrous acid, which is generated in situ from a nitrite salt.⁸¹ Unlike aliphatic diazonium ions, which decompose very rapidly to molecular nitrogen and a carbocation (see Part A, Section 4.1.5), aryl diazonium ions are stable enough to exist in solution at room temperature and below. They can also be isolated as salts with nonnucleophilic anions, such as tetrafluoroborate or trifluoroacetate.⁸² Salts prepared with *o*-benzenedisulfonimidate also appear to have potential for synthetic application.⁸³

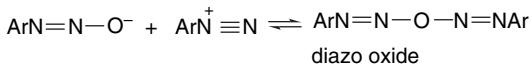
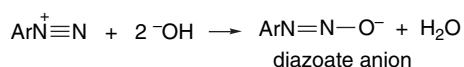


The steps in forming a diazonium ion are addition of the nitrosonium ion, ^+NO , to the amino group, followed by elimination of water.

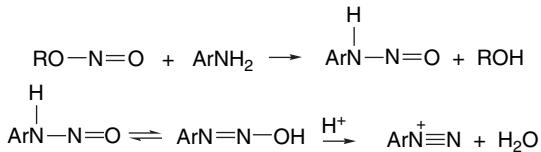


- ^{80.} A. McKillop, J. D. Hunt, M. J. Zelesko, J. S. Fowler, E. C. Taylor, G. McGillivray, and F. Kienzle, *J. Am. Chem. Soc.*, **93**, 4841 (1971); M. L. dos Santas, G. C. de Mangalhaes, and R. Braz Filho, *J. Organomet. Chem.*, **526**, 15 (1996).
- ^{81.} H. Zollinger, *Azo and Diazo Chemistry*, Interscience, New York, 1961; S. Patai, ed., *The Chemistry of Diazonium and Diazo Groups*, Wiley, New York, 1978, Chaps. 8, 11, and 14; H. Saunders and R. L. M. Allen, *Aromatic Diazo Compounds*, 3rd Edition, Edward Arnold, London, 1985.
- ^{82.} C. Colas and M. Goeldner, *Eur. J. Org. Chem.*, 1357 (1999).
- ^{83.} M. Barbero, M. Crisma, I. Degani, R. Fochi, and P. Perracino, *Synthesis*, 1171 (1998); M. Barbero, I. Degani, S. Dughera, and R. Fochi, *J. Org. Chem.*, **64**, 3448 (1999).

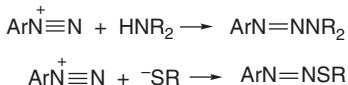
In alkaline solution, diazonium ions are converted to diazoate anions, which are in equilibrium with diazo oxides.⁸⁴



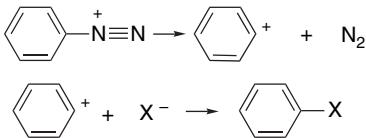
In addition to the aqueous method for diazotization, diazonium ions can be generated in organic solvents by reaction with alkyl nitrites.



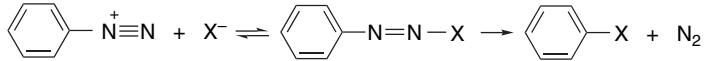
Diazonium ions form stable adducts with certain nucleophiles such as secondary amines and sulfide anions.⁸⁵ These compounds can be used as precursors of diazonium ion intermediates.



The wide utility of aryl diazonium ions as synthetic intermediates results from the excellence of N₂ as a leaving group. There are several general mechanisms by which substitution can occur. One involves unimolecular thermal decomposition of the diazonium ion, followed by capture of the resulting aryl cation by a nucleophile. The phenyl cation is very unstable (see Part A, Section 3.4.1.1) and therefore highly unselective.⁸⁶ Either the solvent or an anion can act as the nucleophile.



Another general mechanism for substitution is adduct formation followed by collapse of the adduct with loss of nitrogen.

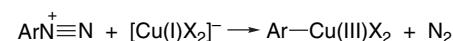


⁸⁴ E. S. Lewis and M. P. Hanson, *J. Am. Chem. Soc.*, **89**, 6268 (1967).

⁸⁵ M. L. Gross, D. H. Blank, and W. M. Welch, *J. Org. Chem.*, **58**, 2104 (1993); S. A. Haroutounian, J. P. DiZio, and J. A. Katzenellenbogen, *J. Org. Chem.*, **56**, 4993 (1991).

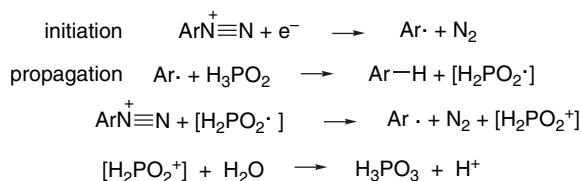
⁸⁶ C. G. Swain, J. E. Sheats, and K. G. Harbison, *J. Am. Chem. Soc.*, **97**, 783 (1975).

A third mechanism involves redox processes,⁸⁷ and is particularly likely to operate in reactions in which copper salts are used as catalysts.⁸⁸



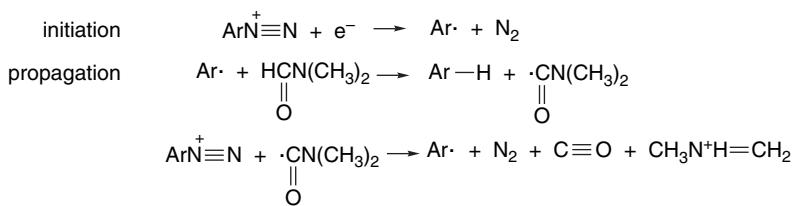
Examples of the three mechanistic types are, respectively: (a) hydrolysis of diazonium salts to phenols⁸⁹; (b) reaction with azide ion to form aryl azides⁹⁰; and (c) reaction with cuprous halides to form aryl chlorides or bromides.⁹¹ In the paragraphs that follow, these and other synthetically useful reactions of diazonium intermediates are considered. The reactions are organized on the basis of the group that is introduced, rather than on the mechanism involved. It will be seen that the reactions that are discussed fall into one of the three general mechanistic types.

11.2.1.1. Reductive Dediazonization. Replacement of a nitro or amino group by hydrogen is sometimes required as a sequel to a synthetic operation in which the substituent was used to control the position selectivity of a prior transformation. The best reagents for reductive dediazonation are hypophosphorous acid, H₃PO₂,⁹² and NaBH₄.⁹³ The reduction by H₃PO₂ is substantially improved by catalysis with cuprous oxide.⁹⁴ The reduction by H₃PO₂ proceeds by one-electron reduction followed by loss of nitrogen and formation of the phenyl radical.⁹⁵ The hypophosphorous acid then serves as a hydrogen atom donor.



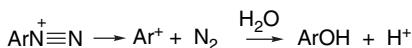
An alternative method for reductive dediazonation involves in situ diazotization by an alkyl nitrite in dimethylformamide.⁹⁶ This reduction is a chain reaction with the solvent acting as the hydrogen atom donor.

87. C. Galli, *Chem. Rev.*, **88**, 765 (1988).
88. T. Cohen, R. J. Lewarchik, and J. Z. Tarino, *J. Am. Chem. Soc.*, **97**, 783 (1975).
89. E. S. Lewis, L. D. Hartung, and B. M. McKay, *J. Am. Chem. Soc.*, **91**, 419 (1969).
90. C. D. Ritchie and D. J. Wright, *J. Am. Chem. Soc.*, **93**, 2429 (1971); C. D. Ritchie and P. O. I. Virtanen, *J. Am. Chem. Soc.*, **94**, 4966 (1972).
91. J. K. Kochi, *J. Am. Chem. Soc.*, **79**, 2942 (1957); S. C. Dickerman, K. Weiss, and A. K. Ingberman, *J. Am. Chem. Soc.*, **80**, 1904 (1958).
92. N. Kornblum, *Org. React.*, **2**, 262 (1944).
93. J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 1251 (1961).
94. S. Korzeniowski, L. Blum, and G. W. Gokel, *J. Org. Chem.*, **42**, 1469 (1977).
95. N. Kornblum, G. D. Cooper, and J. E. Taylor, *J. Am. Chem. Soc.*, **72**, 3013 (1950).
96. M. P. Doyle, J. F. Dellaria, Jr., B. Siegfried, and S. W. Bishop, *J. Org. Chem.*, **42**, 3494 (1977); J. H. Markgraf, R. Chang, J. R. Cort, J. L. Durant, Jr., M. Finkelstein, A. W. Gross, M. H. Lavyne, W. M. Moore, R. C. Peterson, and S. D. Ross, *Tetrahedron*, **53**, 10009 (1997).

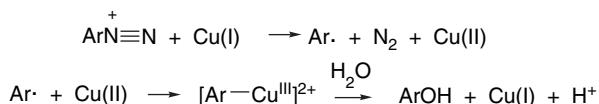


This reaction can be catalyzed by FeSO_4 .⁹⁷

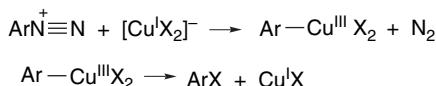
11.2.1.2. Phenols from Diazonium Ion Intermediates. Aryl diazonium ions can be converted to phenols by heating in water. Under these conditions, there is probably formation of a phenyl cation.



By-products from capture of nucleophilic anions may be observed.⁵³ Phenols can be formed under milder conditions by an alternative redox mechanism.⁹⁸ The reaction is initiated by cuprous oxide, which effects reduction and decomposition to an aryl radical, and is run in the presence of Cu(II) salts. The radical is captured by Cu(II) and converted to the phenol by reductive elimination. This procedure is very rapid and gives good yields of phenols over a range of structural types.



11.2.1.3. Aryl Halides from Diazonium Ion Intermediates. Replacement of diazonium groups by halides is a valuable alternative to direct halogenation for the preparation of aryl halides. Aryl bromides and chlorides are usually prepared by a reaction using the appropriate Cu(I) salt, which is known as the *Sandmeyer reaction*. Under the classic conditions, the diazonium salt is added to a hot acidic solution of the cuprous halide.⁹⁹ The Sandmeyer reaction occurs by an oxidative addition reaction of the diazonium ion with Cu(I) and halide transfer from a Cu(III) intermediate.



Good yields of chlorides have also been obtained for reaction of isolated diazonium tetrafluoroborates with $\text{FeCl}_2\text{-FeCl}_3$ mixtures.¹⁰⁰ It is also possible to convert anilines to aryl halides by generating the diazonium ion in situ. Reaction of anilines with alkyl nitrites and Cu(II) halides in acetonitrile gives good yields of aryl chlorides and bromides.¹⁰¹

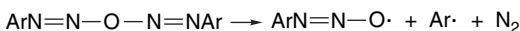
^{97.} F. W. Wassmundt and W. F. Kiesman, *J. Org. Chem.*, **60**, 1713 (1995).

^{98.} T. Cohen, A. G. Dietz, Jr., and J. R. Miser, *J. Org. Chem.*, **42**, 2053 (1977).

^{99.} W. A. Cowdrey and D. S. Davies, *Q. Rev. Chem. Soc.*, **6**, 358 (1952); H. H. Hodgson, *Chem. Rev.*, **40**, 251 (1947).

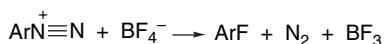
^{100.} K. Daasbjerg and H. Lund, *Acta Chem. Scand.*, **46**, 157 (1992).

^{101.} M. P. Doyle, B. Sigfried, and J. F. Dellaria, Jr., *J. Org. Chem.*, **42**, 2426 (1977).

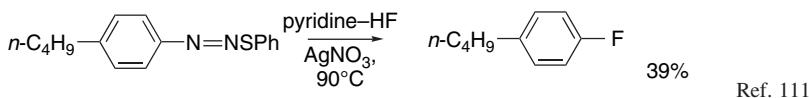


The reaction can be carried out efficiently using aryl diazonium tetrafluoroborates with crown ethers, polyethers, or phase transfer catalysts.¹⁰³ In solvents that can act as halogen atom donors, the radicals react to give aryl halides. Bromotrichloromethane gives aryl bromides, whereas methyl iodide and diiodomethane give iodides.¹⁰⁴ The diazonium ions can also be generated by *in situ* methods. Under these conditions bromoform and bromotrichloromethane have been used as bromine donors and carbon tetrachloride is the best chlorine donor.¹⁰⁵ This method was used successfully for a challenging chlorodeamination in the vancomycin system (Entry 6, Scheme 11.6).

Fluorine substituents can also be introduced via diazonium ions. One procedure is to isolate aryl diazonium tetrafluoroborates. These decompose thermally to give aryl fluorides.¹⁰⁶ Called the *Schiemann reaction*, it probably involves formation of an aryl cation that abstracts fluoride ion from the tetrafluoroborate anion.¹⁰⁷



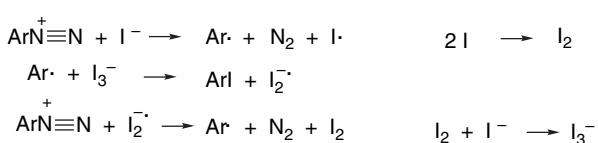
Hexfluorophosphate salts behave similarly.¹⁰⁸ The diazonium tetrafluoroborates can be prepared either by precipitation from an aqueous solution by fluoroboric acid¹⁰⁹ or by anhydrous diazotization in ether, THF, or acetonitrile using *t*-butyl nitrite and boron trifluoride.¹¹⁰ Somewhat milder reaction conditions can be achieved by reaction of aryl diazo sulfide adducts with pyridine-HF in the presence of AgF or AgNO₃.



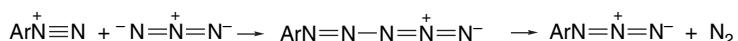
Aryl diazonium ions are converted to iodides in high yield by reaction with iodide salts. This reaction is initiated by reduction of the diazonium ion by iodide. The aryl radical then abstracts iodine from either I₂ or I₃⁻. A chain mechanism then proceeds

- ^{102.} C. Rüchardt and B. Freudenberg, *Tetrahedron Lett.*, 3623 (1964); C. Rüchardt and E. Merz, *Tetrahedron Lett.*, 2431 (1964).
- ^{103.} S. H. Korzeniowski and G. W. Gokel, *Tetrahedron Lett.*, 1637 (1977).
- ^{104.} S. H. Korzeniowski and G. W. Gokel, *Tetrahedron Lett.*, 3519 (1977); R. A. Bartsch and I. W. Wang, *Tetrahedron Lett.*, 2503 (1979); W. C. Smith and O. C. Ho, *J. Org. Chem.*, **55**, 2543 (1990).
- ^{105.} J. I. G. Cadogan, D. A. Roy, and D. M. Smith, *J. Chem. Soc. C*, 1249 (1966).
- ^{106.} A. Roe, *Org. React.*, **5**, 193 (1949).
- ^{107.} C. G. Swain and R. J. Rogers, *J. Am. Chem. Soc.*, **97**, 799 (1975).
- ^{108.} M. S. Newman and R. H. B. Galt, *J. Org. Chem.*, **25**, 214 (1960).
- ^{109.} E. B. Starkey, *Org. Synth.*, **II**, 225 (1943); G. Schiemann and W. Winkelmuller, *Org. Synth.*, **II**, 299 (1943).
- ^{110.} M. P. Doyle and W. J. Bryker, *J. Org. Chem.*, **44**, 1572 (1979).
- ^{111.} S. A. Haroutounian, J. P. DiZio, and J. A. Katzenellenbogen, *J. Org. Chem.*, **56**, 4993 (1991).

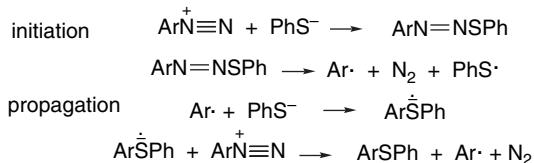
and consumes I^- and ArN_2^+ .¹¹² Evidence for the involvement of radicals includes the isolation of cyclized products from *o*-allyl derivatives.



11.2.1.4. Introduction of Other Nucleophiles Using Diazonium Ion Intermediates. Cyano and azido groups are also readily introduced via diazonium intermediates. The former involves a copper-catalyzed reaction analogous to the Sandmeyer reaction. Reaction of diazonium salts with azide ion gives adducts that smoothly decompose to nitrogen and the aryl azide.⁵⁶



Aryl thiolates react with aryl diazonium ions to give diaryl sulfides. This reaction is believed to be a radical chain process, similar to the mechanism for reaction of diazonium ions with iodide ion.¹¹³



Scheme 11.6 gives some examples of the various substitution reactions of aryl diazonium ions. Entries 1 to 6 are examples of reductive dediazonization. Entry 1 is an older procedure that uses hydrogen abstraction from ethanol for reduction. Entry 2 involves reduction by hypophosphorous acid. Entry 3 illustrates use of copper catalysis in conjunction with hypophosphorous acid. Entries 4 and 5 are DMF-mediated reductions, with ferrous catalysis in the latter case. Entry 6 involves reduction by NaBH_4 .

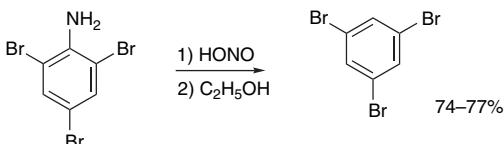
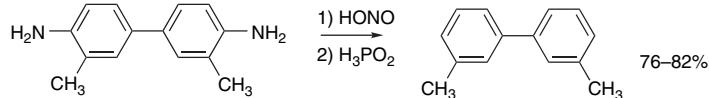
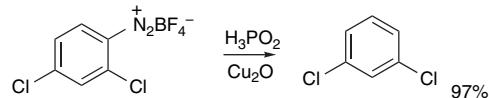
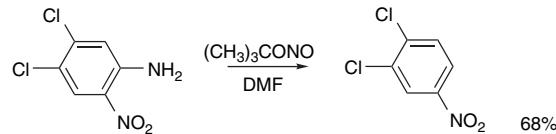
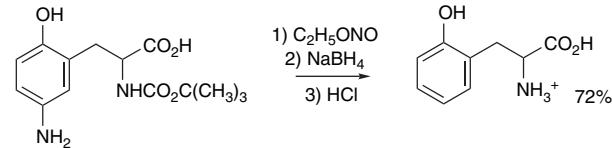
Entries 7 and 8 illustrate conversion of diazonium salts to phenols. Entries 9 and 10 use the traditional conditions for the Sandmeyer reaction. Entry 11 is a Sandmeyer reaction under *in situ* diazotization conditions, whereas Entry 12 involves halogen atom transfer from solvent. Entry 13 is an example of formation of an aryl iodide. Entries 14 and 15 are Schiemann reactions. The reaction in Entry 16 was used to introduce a chlorine substituent on vancomycin. Of several procedures investigated, the CuCl-CuCl_2 catalysis of chlorine atom transfer form CCl_4 proved to be the best. The diazonium salt was isolated as the tetrafluoroborate after *in situ* diazotization. Entries 17 and 18 show procedures for introducing cyano and azido groups, respectively.

¹¹². P. R. Singh and R. Kumar, *Aust. J. Chem.*, **25**, 2133 (1972); A. Abeywickrema and A. L. J. Beckwith, *J. Org. Chem.*, **52**, 2568 (1987).

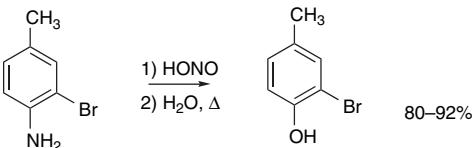
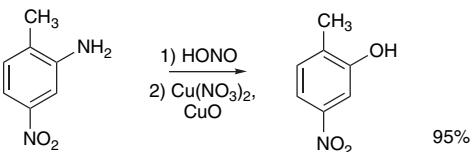
¹¹³. A. N. Abeywickrema and A. L. J. Beckwith, *J. Am. Chem. Soc.*, **108**, 8227 (1986).

Scheme 11.6. Aromatic Substitution via Diazonium Ions

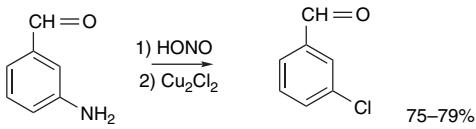
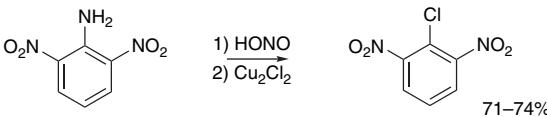
A. Replacement by hydrogen

1^a2^b3^c4^d5^e6^f

B. Replacement by hydroxyl

7^g8^h

C. Replacement by halogen

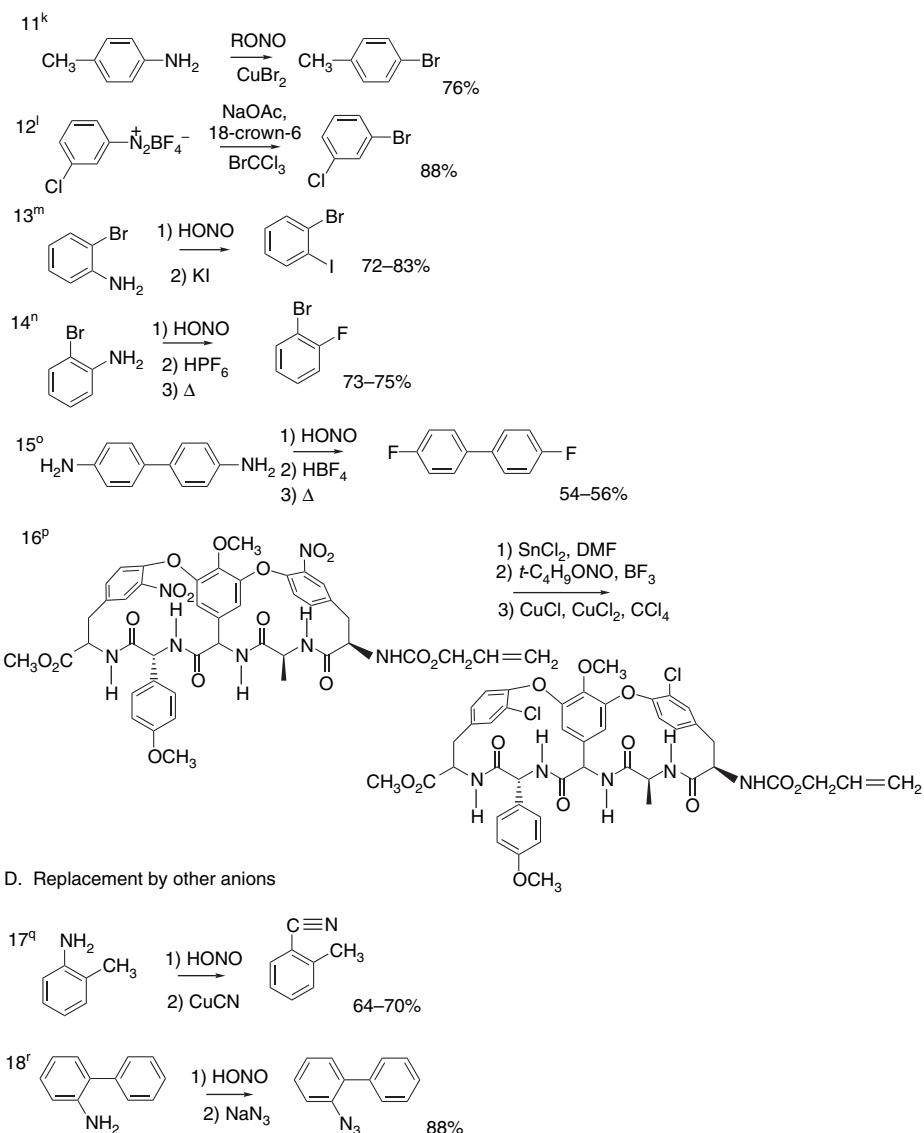
9ⁱ10^j

(Continued)

Scheme 11.6. (Continued)

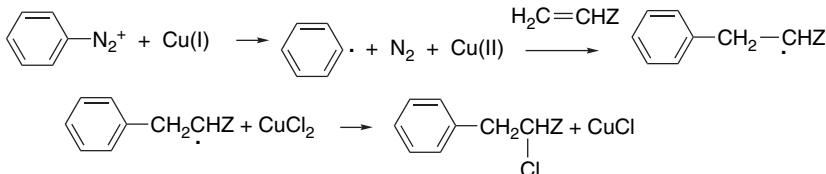
CHAPTER 11

Aromatic Substitution Reactions



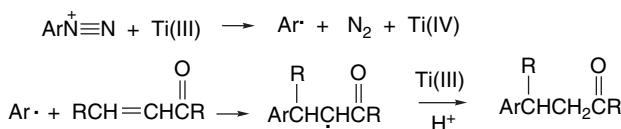
- a. G. H. Coleman and W. F. Talbot, *Org. Synth.*, **II**, 592 (1943).
 b. N. Kornblum, *Org. Synth.*, **III**, 295 (1955).
 c. S. H. Korzeniowski, L. Blum, and G. W. Gokel, *J. Org. Chem.*, **42**, 1469 (1977).
 d. M. P. Doyle, J. F. Dellaria, Jr., B. Siegfried, and S. W. Bishop, *J. Org. Chem.*, **42**, 3494 (1977).
 e. F. W. Wassmundt and W. F. Kiesman, *J. Org. Chem.*, **60**, 1713 (1995).
 f. C. Dugave, *J. Org. Chem.*, **60**, 601 (1995).
 g. H. E. Ungnade and E. F. Orwoll, *Org. Synth.*, **III**, 130 (1943).
 h. T. Cohen, A. G. Dietz, Jr., and J. R. Miser, *J. Org. Chem.*, **42**, 2053 (1977).
 i. J. S. Buck and W. S. Ide, *Org. Synth.*, **II**, 130 (1943).
 j. F. D. Gunstone and S. H. Tucker, *Org. Synth.*, **IV**, 160 (1963).
 k. M. P. Doyle, B. Siegfried, and J. F. Dellaria, Jr., *J. Org. Chem.*, **42**, 2426 (1977).
 l. S. H. Korzeniowski and G. W. Gokel, *Tetrahedron Lett.*, 3519 (1977).
 m. H. Heaney and I. T. Millar, *Org. Synth.*, **40**, 105 (1960).
 n. K. G. Rutherford and W. Redmond, *Org. Synth.*, **43**, 12 (1963).
 o. G. Schiemann and W. Winkelmuller, *Org. Synth.*, **II**, 188 (1943).
 p. C. Vergne, M. Bois-Choussy, and J. Zhu, *Synlett*, 1159 (1998).
 q. H. T. Clarke and R. R. Read, *Org. Synth.*, **I**, 514 (1941).
 r. P. A. S. Smith and B. B. Brown, *J. Am. Chem. Soc.*, **73**, 2438 (1951).

11.2.1.5. Meerwein Arylation Reactions. Aryl diazonium ions can also be used to form certain types of carbon-carbon bonds. The copper-catalyzed reaction of diazonium ions with conjugated alkenes results in arylation of the alkene, known as the *Meerwein arylation reaction*.¹¹⁴ The reaction sequence is initiated by reduction of the diazonium ion by Cu(I). The aryl radical adds to the alkene to give a new β -aryl radical. The final step is a ligand transfer that takes place in the copper coordination sphere. An alternative course is oxidation-deprotonation, which gives a styrene derivative.



The reaction gives better yield with dienes, styrenes, or alkenes substituted with EWGs than with simple alkenes. These groups increase the rate of capture of the aryl radical. The standard conditions for the Meerwein arylation employ aqueous solutions of diazonium ions. Conditions for *in situ* diazotization by *t*-butyl nitrite in the presence of CuCl₂ and acrylonitrile or styrene are also effective.¹¹⁵

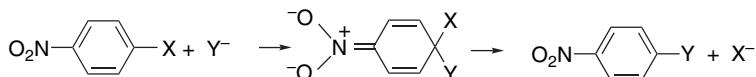
Reduction of aryl diazonium ions by Ti(III) in the presence of α,β -unsaturated ketones and aldehydes leads to β -arylation and formation of the saturated ketone or aldehyde. The early steps in this reaction parallel the copper-catalyzed reaction. However, rather than being oxidized, the radical formed by the addition step is reduced by Ti(III).¹¹⁶



Scheme 11.7 illustrates some arylation of alkenes by diazonium ions. Entries 1 to 4 are typical conditions. Entry 5 illustrates generation of the diazonium ion under *in situ* conditions. Entry 6 is an example of the reductive conditions using Ti(III).

11.2.2. Substitution by the Addition-Elimination Mechanism

The addition of a nucleophile to an aromatic ring, followed by elimination of a substituent, results in nucleophilic substitution. The major energetic requirement for this mechanism is formation of the addition intermediate. The addition step is greatly facilitated by strongly electron-attracting substituents, and nitroaromatics are the best reactants for nucleophilic aromatic substitution. Other EWGs such as cyano, acetyl, and trifluoromethyl also enhance reactivity.



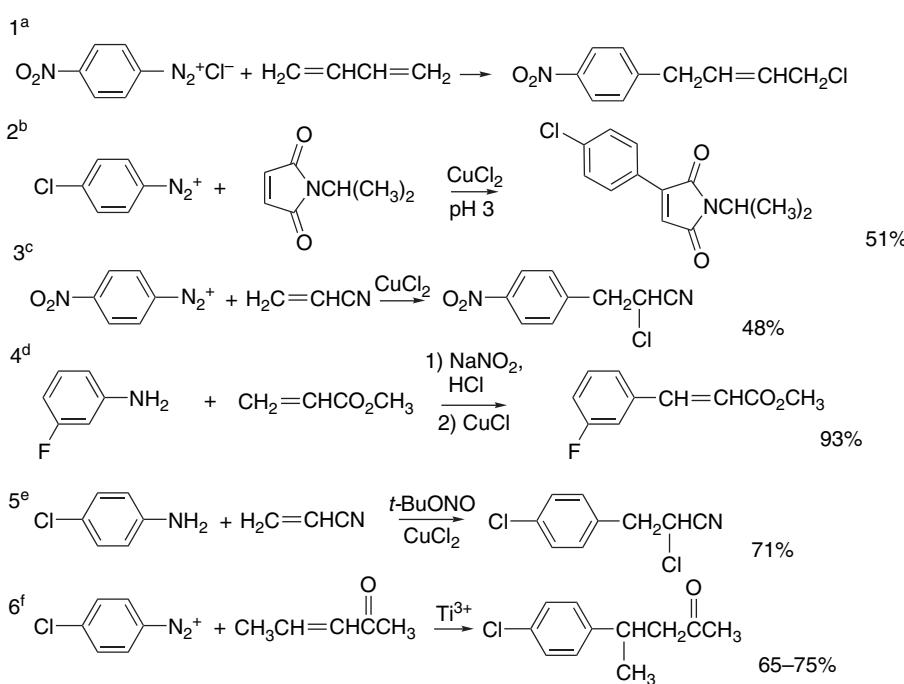
¹¹⁴ C. S. Rondestvedt, Jr., *Org. React.*, **11**, 189 (1960); C. S. Rondestvedt, *Org. React.*, **24**, 225 (1976); A. V. Dombrovskii, *Russ. Chem. Rev. (Engl. Transl.)*, **53**, 943 (1984).

¹¹⁵ M. P. Doyle, B. Siegfried, R. C. Elliot, and J. F. Dellaria, Jr., *J. Org. Chem.*, **42**, 2431 (1977).

¹¹⁶ A. Citterio and E. Vismara, *Synthesis*, 191 (1980); A. Citterio, A. Cominelli, and F. Bonavoglia, *Synthesis*, 308 (1986).

Scheme 11.7. Meerwein Arylation Reactions

CHAPTER 11

Aromatic Substitution
Reactions

a. G. A. Ropp and E. C. Coyner, *Org. Synth.*, **IV**, 727 (1963).

b. C. S. Rondestvedt, Jr., and O. Vogel, *J. Am. Chem. Soc.*, **77**, 2313 (1955).

c. C. F. Koelsch, *J. Am. Chem. Soc.*, **65**, 57 (1943).

d. G. Theodoridis and P. Malamus, *J. Heterocycl. Chem.*, **28**, 849 (1991).

e. M. P. Doyle, B. Siegfried, R. C. Elliott, and J. F. Dellaria, Jr., *J. Org. Chem.*, **42**, 2431 (1977).

f. A. Citterio and E. Vismara, *Synthesis*, 191 (1980); A. Citterio, *Org. Synth.*, **62**, 67 (1984).

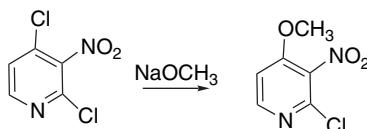
Nucleophilic substitution occurs when there is a potential leaving group present at the carbon at which addition occurs. Although halides are the most common leaving groups, alkoxy, cyano, nitro, and sulfonyl groups can also be displaced. The leaving group ability does not necessarily parallel that found for nucleophilic substitution at saturated carbon. As a particularly striking example, fluoride is often a better leaving group than the other halogens in nucleophilic aromatic substitution. The relative reactivity of the *p*-halonitrobenzenes toward sodium methoxide at 50°C is F(312) >> Cl(1) > Br (0.74) > I (0.36).¹¹⁷ A principal reason for the order I > Br > Cl > F in S_N2 reactions is the carbon-halogen bond strength, which increases from I to F. The carbon-halogen bond strength is not so important a factor in nucleophilic aromatic substitution because bond breaking is not ordinarily part of the rate-determining step. Furthermore, the highly electronegative fluorine favors the addition step more than the other halogens.

The addition-elimination mechanism has been used primarily for arylation of oxygen and nitrogen nucleophiles. There are not many successful examples of arylation of carbanions by this mechanism. A major limitation is the fact that aromatic nitro

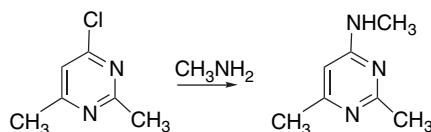
¹¹⁷. G. P. Briner, J. Mille, M. Liveris, and P. G. Lutz, *J. Chem. Soc.*, 1265 (1954).

compounds often react with carbanions by electron transfer processes.¹¹⁸ However, substitution by carbanions can be carried out under the conditions of the $S_{RN}1$ reaction (see Section 11.4).

The pyridine family of heteroaromatic nitrogen compounds is reactive toward nucleophilic substitution at the C(2) and C(4) positions. The nitrogen atom serves to activate the ring toward nucleophilic attack by stabilizing the addition intermediate. This kind of substitution reaction is especially important in the chemistry of pyrimidines.

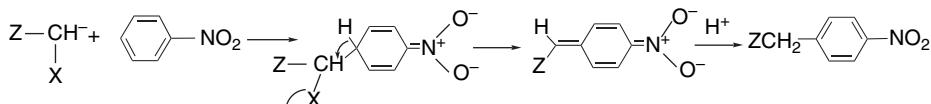


Ref. 119



Ref. 120

A variation of the aromatic nucleophilic substitution process in which the leaving group is part of the entering nucleophile has been developed and is known as *vicarious nucleophilic aromatic substitution*. These reactions require a strong EWG substituent such as a nitro group but require no halide or other leaving group. The reactions proceed through addition intermediates.¹²¹



The combinations Z = CN, RSO₂, CO₂R, and SR and X = F, Cl, Br, I, ArO, ArS, and (CH₃)₂NCS₂ are among those that have been demonstrated.¹²²

Scheme 11.8 gives some examples of addition-elimination reactions. Entries 1 and 2 illustrate typical *o*- and *p*-nitrophenylation of amines. Note the rather vigorous conditions that are required. Entry 3 shows a rather unusual case in which an acetyl group is the activating substituent. Good yields were obtained for a number of amines in polar aprotic solvents. The corresponding chloro and bromo derivative were much less reactive. Entry 4 represents a case of a very electrophilic aromatic ring, but

¹¹⁸ R. D. Guthrie, in *Comprehensive Carbanion Chemistry*, Part A, E. Bunzel and T. Durst, eds., Elsevier, Amsterdam, 1980, Chap. 5.

¹¹⁹ J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **9**, 354 (1966).

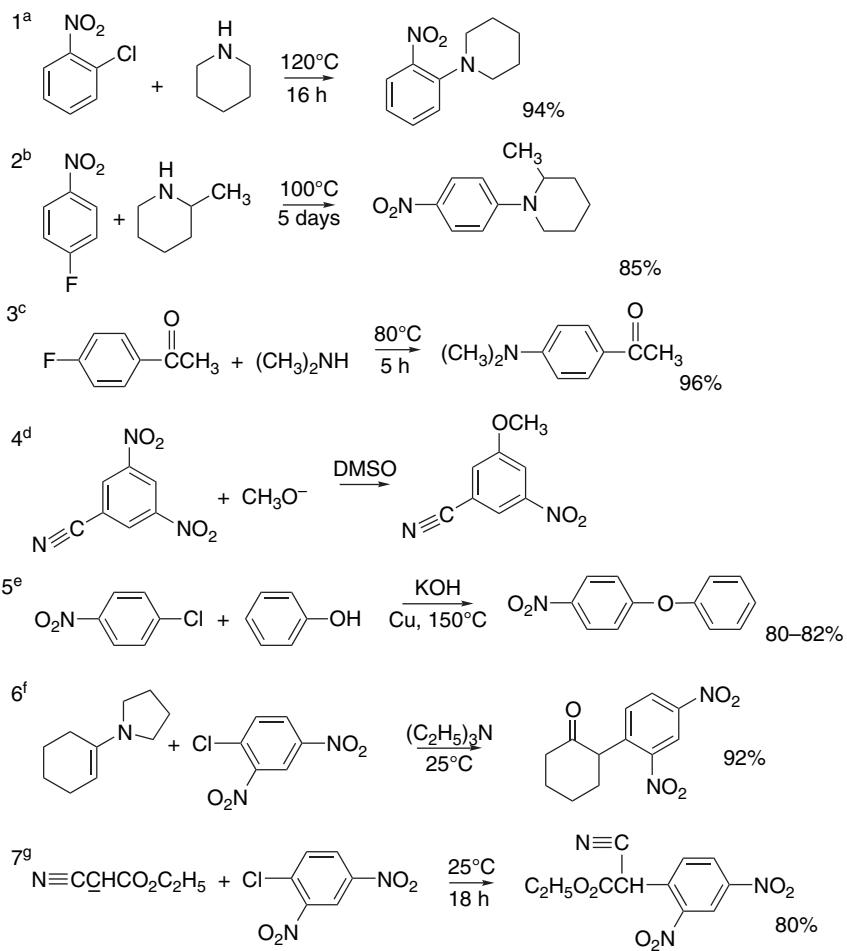
¹²⁰ D. J. Brown, B. T. England, and J. M. Lyall, *J. Chem. Soc. C*, 226 (1966).

¹²¹ M. Makosza, T. Lemek, A. Kwast, and F. Terrier, *J. Org. Chem.*, **67**, 394 (2002); M. Makosza and A. Kwast, *J. Phys. Org. Chem.*, **11**, 341 (1998).

¹²² M. Makosza and J. Winiarski, *J. Org. Chem.*, **45**, 1534 (1980); M. Makosza, J. Golinski, and J. Baran, *J. Org. Chem.*, **49**, 1488 (1984); M. Makosza and J. Winiarski, *J. Org. Chem.*, **49**, 1494 (1984); M. Makosza and J. Winiarski, *J. Org. Chem.*, **49**, 5272 (1984); M. Makosza and J. Winiarski, *Acc. Chem. Res.*, **20**, 282 (1987); M. Makosza and K. Wojciechowski, *Liebigs Ann. Chem./Recueil*, 1805 (1997).

Scheme 11.8. Nucleophilic Aromatic Substitution

CHAPTER 11

Aromatic Substitution
Reactions

a. S. D. Ross and M. Finkelstein, *J. Am. Chem. Soc.*, **85**, 2603 (1963).

b. F. Pietra and F. Del Cima, *J. Org. Chem.*, **33**, 1411 (1968).

c. H. Bader, A. R. Hansen, and F. J. McCarty, *J. Org. Chem.*, **31**, 2319 (1966).

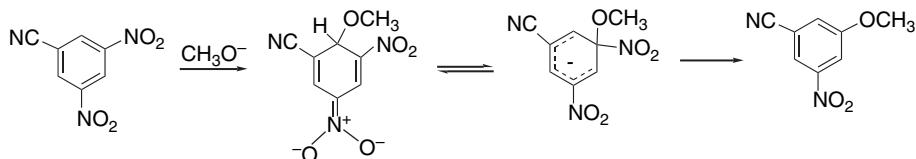
d. E. J. Fendler, J. H. Fendler, N. I. Arthur, and C. E. Griffin, *J. Org. Chem.*, **37**, 812 (1972).

e. R. O. Brewster and T. Groening, *Org. Synth.*, **II**, 445 (1943).

f. M. E. Kuehne, *J. Am. Chem. Soc.*, **84**, 837 (1962).

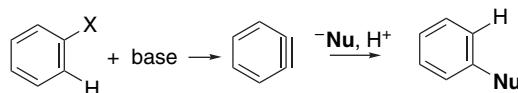
g. H. R. Snyder, E. P. Merica, C. G. Force, and E. G. White, *J. Am. Chem. Soc.*, **80**, 4622 (1958).

the favored addition intermediate does not have a potential leaving group. Reaction evidently occurs through a minor adduct.

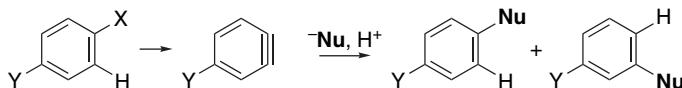


11.2.3. Substitution by the Elimination-Addition Mechanism

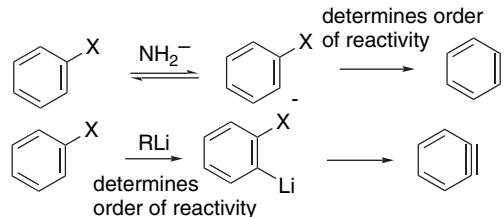
The elimination-addition mechanism involves a highly unstable intermediate called *dehydrobenzene* or *benzyne*.¹²³ (See Section 10.6 of Part A for a discussion of the structure of benzyne.)



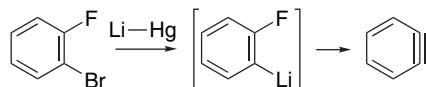
A unique feature of this mechanism is that the entering nucleophile does not necessarily become bound to the carbon to which the leaving group was attached.



The elimination-addition mechanism is facilitated by electronic effects that favor removal of a hydrogen from the ring as a proton. Relative reactivity also depends on the halide. The order Br > I > Cl >> F has been established in the reaction of aryl halides with KNH₂ in liquid ammonia¹²⁴ and has been interpreted as representing a balance of two effects. The polar order favoring proton removal would be F > Cl > Br > I, but this is largely overwhelmed by the ease of bond breaking, which is I > Br > Cl > F. With organolithium reagents in ether solvents, the order of reactivity is F > Cl > Br > I, which indicates that the acidity of the ring hydrogen is the dominant factor governing reactivity.¹²⁵



Benzyne can also be generated from *o*-dihaloaromatics. Reaction with lithium amalgam or magnesium results in the formation of transient organometallic compounds that decompose with elimination of lithium halide. *o*-Fluorobromobenzene is the usual starting material in this procedure.¹²⁶



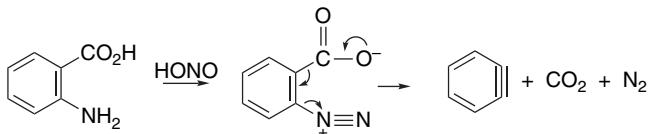
¹²³ R. W. Hoffmann, *Dehydrobenzene and Cycloalkynes*, Academic Press, New York, 1967.

¹²⁴ F. W. Bergstrom, R. E. Wright, C. Chandler, and W. A. Gilkey, *J. Org. Chem.*, **1**, 170 (1936).

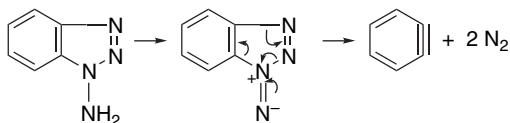
¹²⁵ R. Huisgen and J. Sauer, *Angew. Chem.*, **72**, 91 (1960).

¹²⁶ G. Wittig and L. Pohmer, *Chem. Ber.*, **89**, 1334 (1956); G. Wittig, *Org. Synth.*, **IV**, 964 (1963).

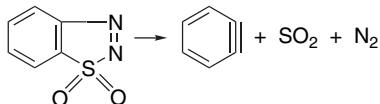
There are several methods for generation of benzyne in addition to base-catalyzed elimination of hydrogen halide from a halobenzene and some of these are more generally applicable for preparative work. Probably the most useful method is diazotization of *o*-aminobenzoic acids.¹²⁷ Loss of nitrogen and carbon dioxide follows diazotization and generates benzyne. This method permits generation of benzyne in the presence of a number of molecules with which it can react.



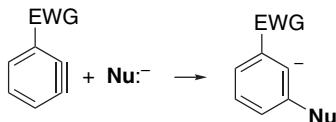
Oxidation of 1-aminobenzotriazole also serves as a source of benzyne under mild conditions. An oxidized intermediate decomposes with loss of two molecules of nitrogen.¹²⁸



Another heterocyclic molecule that can serve as a benzyne precursor is benzothiadiazole-1,1-dioxide, which decomposes with elimination of nitrogen and sulfur dioxide.¹²⁹



Addition of nucleophiles such as ammonia or alcohols, or their conjugate bases, to benzenes takes place very rapidly. The addition is believed to involve capture of the nucleophile by benzyne, followed by protonation to give the substitution product.¹³⁰ Electronegative groups tend to favor addition of the nucleophile at the more distant end of the “triple bond,” since this permits stabilization of the developing negative charge. Selectivity is usually not high, however, and formation of both possible products from monosubstituted benzenes is common.¹³¹



¹²⁷ M. Stiles, R. G. Miller, and U. Burckhardt, *J. Am. Chem. Soc.*, **85**, 1792 (1963); L. Friedman and F. M. Longullo, *J. Org. Chem.*, **34**, 3089 (1969).

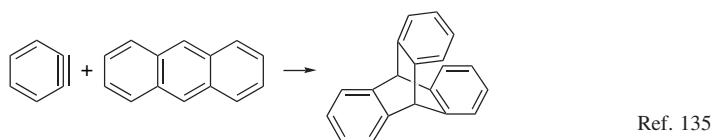
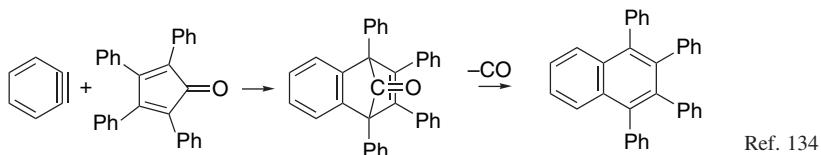
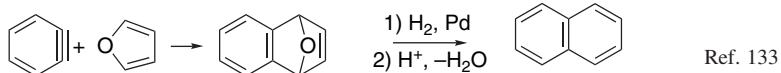
¹²⁸ C. D. Campbell and C. W. Rees, *J. Chem. Soc. C*, 742, 752 (1969); S. E. Whitney and B. Rickborn, *J. Org. Chem.*, **53**, 5595 (1988); H. Hart and D. Ok, *J. Org. Chem.*, **52**, 3835 (1987).

¹²⁹ G. Wittig and R. W. Hoffmann, *Org. Synth.*, **47**, 4 (1967); G. Wittig and R. W. Hoffmann, *Chem. Ber.*, **95**, 2718, 2729 (1962).

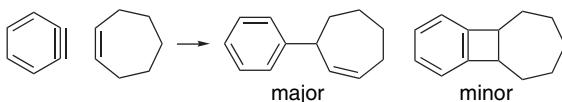
¹³⁰ J. F. Bunnett, D. A. R. Happer, M. Patsch, C. Pyun, and H. Takayama, *J. Am. Chem. Soc.*, **88**, 5250 (1966); J. F. Bunnett and J. K. Kim, *J. Am. Chem. Soc.*, **95**, 2254 (1973).

¹³¹ E. R. Biehl, E. Nieh, and K. C. Hsu, *J. Org. Chem.*, **34**, 3595 (1969).

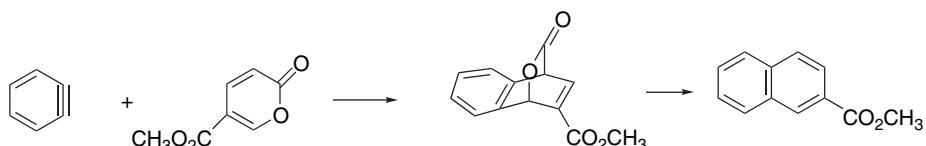
When benzyne is generated in the absence of another reactive molecule it dimerizes to biphenylene.¹³² In the presence of dienes, benzyne is a very reactive dienophile and [4 + 2] cycloaddition products are formed. The adducts with furans can be converted to polycyclic aromatic compounds by elimination of water. Similarly, cyclopentadienones can give a new aromatic ring by loss of carbon monoxide. Pyrones give adducts that can aromatize by loss of CO₂, as illustrated by Entry 7 in Scheme 11.9.



Benzyne gives both [2 + 2] cycloaddition and ene reaction products with simple alkenes.¹³⁶



Scheme 11.9 illustrates some of the types of compounds that can be prepared via benzyne intermediates. Entry 1 is an example of the generation of benzyne in a strongly basic DMSO solution. Entry 2 is a Diels-Alder reaction involving in situ generation of benzyne. The adduct was used to synthesize several polycyclic strained-ring systems having fused benzene rings. Entry 3 illustrates the formation of benzyne from *o*-bromofluorobenzene by reaction with magnesium. The benzyne undergoes a Diels-Alder reaction with anthracene. Entry 4 also uses this method of benzyne generation and results in a [2 + 2] cycloaddition with an enamine. Entry 5 is photolytic generation of benzyne employing phthaloyl peroxide. This method seems to have been used only rarely. Entry 6 shows a case of intramolecular trapping of benzyne by a nitrile-stabilized carbanion. Entry 7 is a Diels-Alder reaction with a pyrone, in which the adduct undergoes decarboxylation under the reaction conditions.



¹³². F. M. Logullo, A. H. Seitz, and L. Friedman, *Org. Synth.*, **V**, 54 (1973).

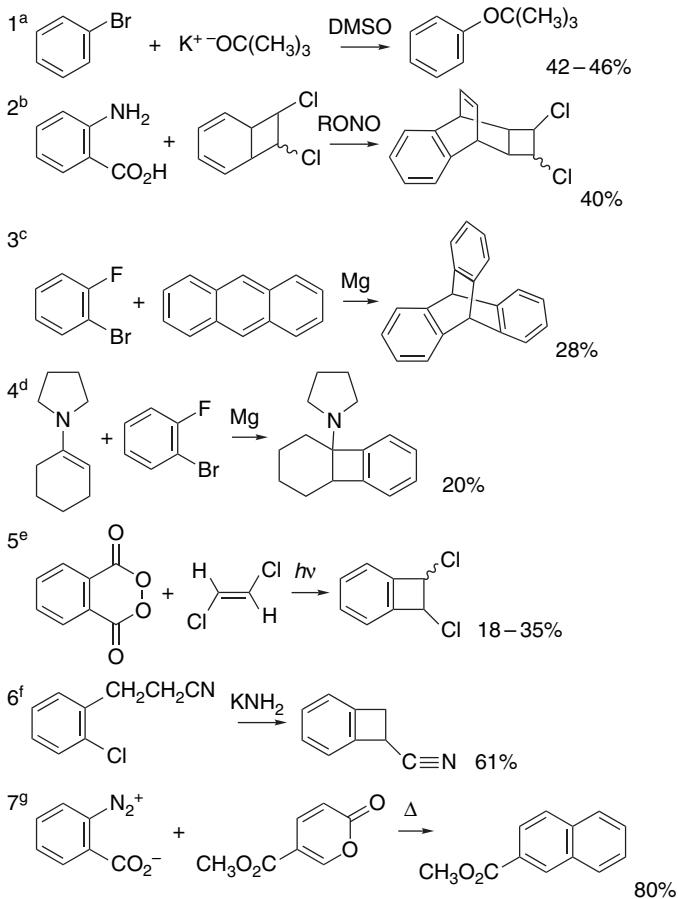
¹³³. G. Wittig and L. Pohmer, *Angew. Chem.*, **67**, 348 (1955).

¹³⁴. L. F. Fieser and M. J. Haddadin, *Org. Synth.*, **V**, 1037 (1973).

¹³⁵. L. Friedman and F. M. Logullo, *J. Org. Chem.*, **34**, 3089 (1969).

¹³⁶. P. Crews and J. Beard, *J. Org. Chem.*, **38**, 522 (1973).

Scheme 11.9. Syntheses via Benzyne Intermediates



a. M. R. V. Sahyun and D. J. Cram, *Org. Synth.*, **45**, 89 (1965).

b. L. A. Paquette, M. J. Kukla, and J. C. Stowell, *J. Am. Chem. Soc.*, **94**, 4920 (1972).

c. G. Wittig, *Org. Synth.*, **IV**, 964 (1963).

d. M. E. Kuehne, *J. Am. Chem. Soc.*, **84**, 837 (1962).

e. M. Jones, Jr., and M. R. DeCamp, *J. Org. Chem.*, **36**, 1536 (1971).

f. J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).

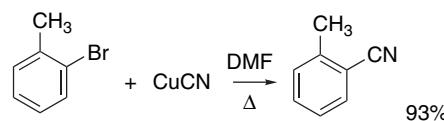
g. S. Escudero, D. Perez, E. Guitan, and L. Castedo, *Tetrahedron Lett.*, **38**, 5375 (1997).

11.3. Transition Metal–Catalyzed Aromatic Substitution Reactions

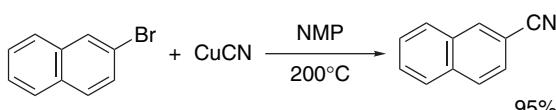
11.3.1. Copper-Catalyzed Reactions

As noted in Section 11.2.2, nucleophilic substitution of aromatic halides lacking activating substituents is generally difficult. It has been known for a long time that the nucleophilic substitution of aromatic halides can be catalyzed by the presence of copper metal or copper salts.¹³⁷ Synthetic procedures based on this observation are used to prepare aryl nitriles by reaction of aryl bromides with Cu(I)CN. The reactions are usually carried out at elevated temperature in DMF or a similar solvent.

¹³⁷ J. Lindley, *Tetrahedron*, **40**, 1433 (1984).

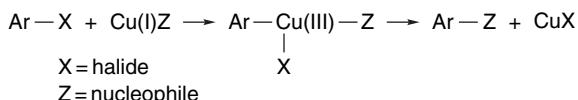


Ref. 138

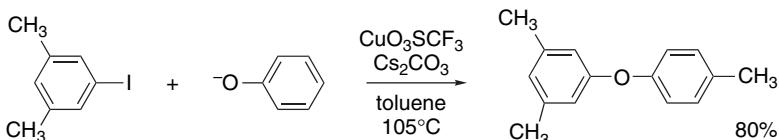


Ref. 139

A general mechanistic description of the copper-promoted nucleophilic substitution involves an oxidative addition of the aryl halide to Cu(I) followed by collapse of the arylcopper intermediate with a ligand transfer (reductive elimination).¹⁴⁰



Several other kinds of nucleophiles can be arylated by copper-catalyzed substitution. Among the reactive nucleophiles are carboxylate ions,¹⁴¹ alkoxide ions,¹⁴² amines,¹⁴³ phthalimide anions,¹⁴⁴ thiolate anions,¹⁴⁵ and acetylides.¹⁴⁶ In some of these reactions there is competitive reduction of the aryl halide to the dehalogenated arene, which is attributed to protonolysis of the arylcopper intermediate. Most of these reactions are carried out at high temperature under heterogeneous conditions using copper powder or copper bronze as the catalyst. The general mechanism suggests that these catalysts act as sources of Cu(I) ions. Homogeneous reactions can be carried out using soluble Cu(I) salts, particularly Cu(I)O₃SCF₃.¹⁴⁷ These reactions occur under milder conditions than those using other sources of copper. The range and effectiveness of coupling aryl halides and phenolates to give diaryl ethers is improved by use of CsCO₃.¹⁴⁸ Reaction occurs in refluxing toluene.



Some reactions of this type are accelerated further by use of naphthoic acid as an additive. This effect is believed to result from formation of a mixed anionic cuprate

¹³⁸ L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961).

¹³⁹ M. S. Newman and H. Bode, *J. Org. Chem.*, **26**, 2525 (1961).

¹⁴⁰ T. Cohen, J. Wood, and A. G. Dietz, *Tetrahedron Lett.*, 3555 (1974).

¹⁴¹ T. Cohen and A. H. Lewin, *J. Am. Chem. Soc.*, **88**, 4521 (1966).

¹⁴² R. G. R. Bacon and S. C. Rennison, *J. Chem. Soc. C*, 312 (1969).

¹⁴³ A. J. Paine, *J. Am. Chem. Soc.*, **109**, 1496 (1987).

¹⁴⁴ R. G. R. Bacon and A. Karim, *J. Chem. Soc., Perkin Trans. I*, 272 (1973).

¹⁴⁵ H. Suzuki, H. Abe, and A. Osuka, *Chem. Lett.*, 1303 (1980); R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1108 (1964).

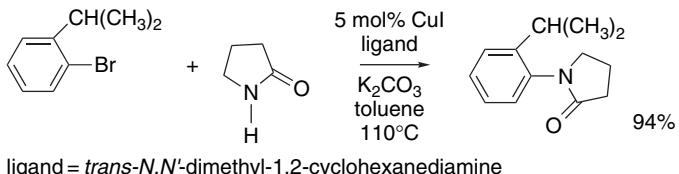
¹⁴⁶ C. E. Castro, R. Havlin, V. K. Honwad, A. Malte, and S. Moje, *J. Am. Chem. Soc.*, **91**, 6464 (1969).

¹⁴⁷ T. Cohen and J. G. Tirpak, *Tetrahedron Lett.*, 143 (1975).

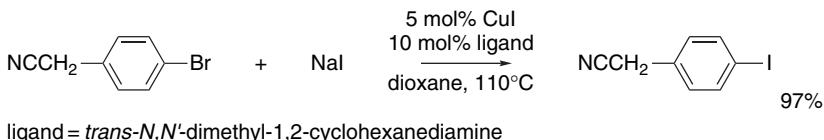
¹⁴⁸ J. F. Marcoux, S. Doye, and S. L. Buchwald, *J. Am. Chem. Soc.*, **119**, 10539 (1997).

having naphthoate as one of the ligands. The Cs^+ salts are beneficial in maximizing the solubility of the phenolate and naphthoates.

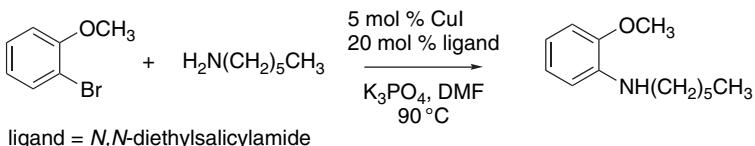
It has been found that a number of bidentate ligands greatly expand the scope of copper catalysis. Copper(I) iodide used in conjunction with a chelating diamine is a good catalyst for amidation of aryl bromides. Of several diamines that were examined, *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine was among the best. These conditions are applicable to aryl bromides and iodides with either ERG or EWG substituents, as well as to relatively hindered halides. The nucleophiles that are reactive under these conditions include acyclic and cyclic amides.¹⁴⁹



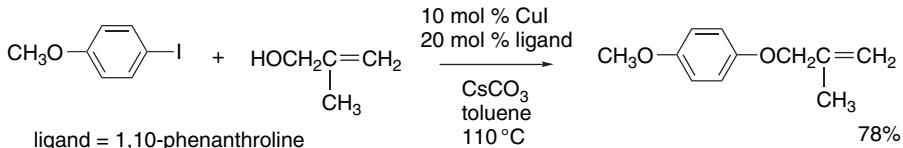
This catalytic system also promotes exchange of iodide for bromide on aromatic rings.¹⁵⁰ The reaction is an equilibrium process that is driven forward by the low solubility of NaBr in the solvent, dioxane.



The *N,N*-diethylamide of salicylic acid is a useful ligand in conjunction with CuI and permits amination of aryl bromides by primary alkylamines.¹⁵¹



Copper(I) iodide with 1,10-phenanthroline catalyzes substitution of aryl iodides by alcohols. The reaction can be done either in excess alcohol or in toluene.¹⁵²



These copper-catalyzed reactions are generally applicable to aryl halides with either EWG or ERG substituents. The order of reactivity is I > Br > Cl > OSO_2R , which is consistent with an oxidative addition mechanism.

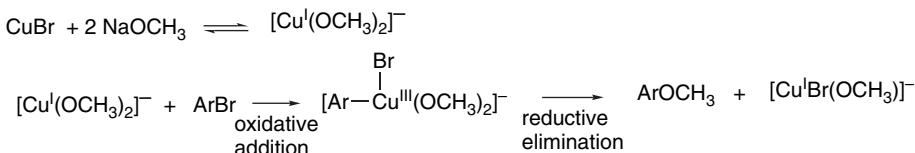
¹⁴⁹. A. Klapars, X. Huang, and S. L. Buchwald, *J. Am. Chem. Soc.*, **124**, 7421 (2002).

¹⁵⁰. A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, **124**, 14844 (2002).

¹⁵¹. F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, **5**, 793 (2003).

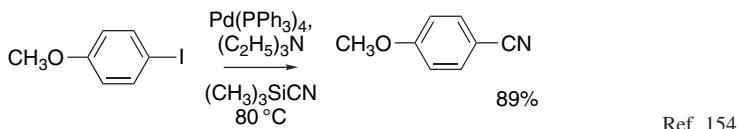
¹⁵². M. Wolter, G. Nordmann, G. E. Job, and S. L. Buchwald, *Org. Lett.*, **4**, 973 (2002).

One aspect of the copper catalytic system that has received attention is the identity of the active catalytic species. In the case of displacement of aryl bromides by methoxide ion in the presence of CuBr, it has been suggested that the active species is Cu(I)(OCH₃)₂, an anionic cuprate.¹⁵³



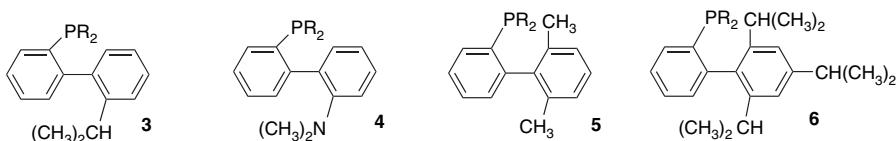
11.3.2. Palladium-Catalyzed Reactions

In Section 8.2.3.2, we discussed arylation of enolates and enolate equivalents using palladium catalysts. Related palladium-phosphine combinations are very effective catalysts for aromatic nucleophilic substitution reactions. For example, conversion of aryl iodides to nitriles can be done under mild conditions with Pd(PPh₃)₄ as a catalyst.



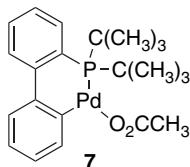
A great deal of effort has been devoted to finding efficient catalysts for substitution by oxygen and nitrogen nucleophiles.¹⁵⁵ These studies have led to optimization of the catalysis with ligands such as triarylphosphines,¹⁵⁶ bis-phosphines such as BINAP,¹⁵⁷ dppf,¹⁵⁸ and phosphines with additional chelating substituents.¹⁵⁹ Among the most effective catalysts are highly hindered trialkyl phosphines such as tri-*t*-butyl and tricyclohexylphosphine.¹⁶⁰ A series of 2-biphenylphosphines **3–6** has also been found to have excellent activity.¹⁶¹

- ¹⁵³. H. L. Aalten, C. van Koten, D. M. Grove, T. Kuilman, O. G. Piekstra, L. A. Hulshof, and R. A. Sheldon, *Tetrahedron*, **45**, 5565 (1989).
- ¹⁵⁴. N. Chatani and T. Hanafusa, *J. Org. Chem.*, **51**, 4714 (1986).
- ¹⁵⁵. S. L. Buchwald, A. S. Guram, and R. A. Rennels, *Angew. Chem. Int. Ed. Engl.*, **34**, 1348 (1995); J. F. Hartwig, *Synlett*, 329 (1997); J. F. Hartwig, *Angew. Chem. Int. Ed. Engl.*, **37**, 2047 (1998); J. P. Wolfe, S. Wagaw, J. F. Marcoux, and S. L. Buchwald, *Acc. Chem. Res.*, **31**, 805 (1998); J. F. Hartwig, *Acc. Chem. Res.*, **31**, 852 (1998); B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, **576**, 125 (1999).
- ¹⁵⁶. J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, **61**, 1133 (1996); J. Louie and J. F. Hartwig, *Tetrahedron Lett.*, **36**, 3609 (1995).
- ¹⁵⁷. J. P. Wolfe, S. Wagaw, and S. L. Buchwald, *J. Am. Chem. Soc.*, **118**, 7215 (1996).
- ¹⁵⁸. M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, **118**, 7217 (1996).
- ¹⁵⁹. D. W. Old, J. P. Wolfe, and S. L. Buchwald, *J. Am. Chem. Soc.*, **120**, 9722 (1998); B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc.*, **120**, 7369 (1998); S. Vyskocil, M. Smrcina, and P. Kocovsky, *Tetrahedron Lett.*, **39**, 9289 (1998).
- ¹⁶⁰. M. Nishiyama, T. Yamamoto, and Y. Koie, *Tetrahedron Lett.*, **39**, 617 (1998); N. P. Reddy and M. Tanaka, *Tetrahedron Lett.*, **38**, 4807 (1997).
- ¹⁶¹. M. C. Harris, X. Huang, and S. L. Buchwald, *Org. Lett.*, **4**, 2885 (2002); D. W. Old, J. P. Wolfe, and S. L. Buchwald, *J. Am. Chem. Soc.*, **120**, 9722 (1998); H. Tomori, J. M. Fox, and S. L. Buchwald, *J. Org. Chem.*, **65**, 5334 (2000).

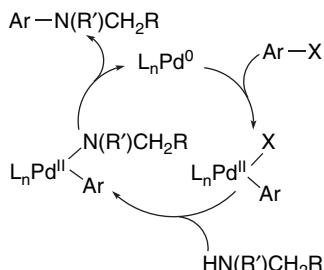


$R = t\text{-Bu, } c\text{-C}_6\text{H}_{11}$

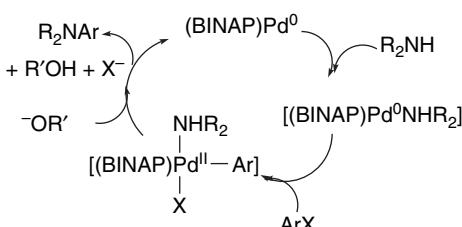
A stable palladacycle **7** derived from biphenyl is also an active catalyst.¹⁶²



In addition to bromides and iodides, the reaction has been successfully extended to chlorides,¹⁶³ triflates,¹⁶⁴ and nonafluorobutanesulfonates (nonaflates).¹⁶⁵ These reaction conditions permit substitution in both electron-poor and electron-rich aryl systems by a variety of nitrogen nucleophiles, including alkyl or aryl amines and heterocycles. These reactions proceed via a catalytic cycle involving Pd(0) and Pd(II) intermediates.



Some of the details of the mechanism may differ for various catalytic systems. There have been kinetic studies on two of the amination systems discussed here. The results of a study of the kinetics of amination of bromobenzene using $\text{Pd}_2(\text{dba})_3$, BINAP, and sodium *t*-amyloxide in toluene were consistent with the oxidative addition occurring *after* addition of the amine at Pd. The reductive elimination is associated with *deprotonation of the aminated palladium complex*.¹⁶⁶



¹⁶² D. Zim and S. L. Buchwald, *Org. Lett.*, **5**, 2413 (2003).

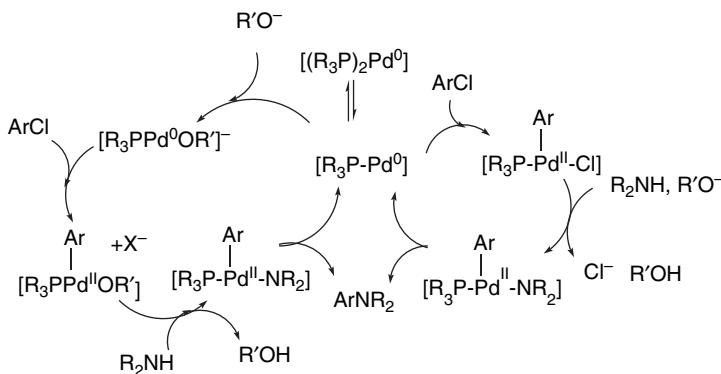
¹⁶³ X. Bei, A. S. Guram, H. W. Turner, and W. H. Weinberg, *Tetrahedron Lett.*, **40**, 1237 (1999).

¹⁶⁴ J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, **62**, 1264 (1997); J. Louie, M. S. Driver, B. C. Hamann, and J. T. Hartwig, *J. Org. Chem.*, **62**, 1268 (1997).

¹⁶⁵ K. W. Anderson, M. Mendez-Perez, J. Priego, and S. L. Buchwald, *J. Org. Chem.*, **68**, 9563 (2003).

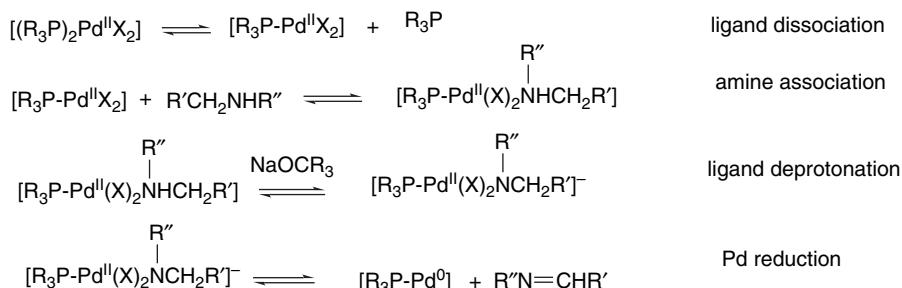
¹⁶⁶ U. K. Singh, E. R. Strieter, D. G. Blackmond, and S. L. Buchwald, *J. Am. Chem. Soc.*, **124**, 14104 (2002).

A study of the reaction of chlorobenzene with *N*-methylaniline in the presence of $\text{Pd}[\text{P}(t\text{-Bu})_3]_2$ and several different bases indicated that two mechanisms may occur concurrently, with their relative importance depending on the base, as indicated in the catalytic cycle below. The cycle on the right depicts oxidative addition followed by ligation by the deprotonated amine. The cycle on the left suggests that oxidative addition occurs on an anionic adduct of the catalyst and the base, followed by exchange with the amine ligand.¹⁶⁷



A comparison of several of the biphenylphosphine ligands has provided some insight into the mechanism of catalyst activation.¹⁶⁸ The results of this study suggest that dissociation of the diphosphino to a monophosphino complex is an essential step in catalyst activation, which would explain why some of the most hindered phosphines are among the best catalyst ligands. This study also indicated that deprotonation of the amine ligand is an essential step. Finally, in catalyst systems that are based on Pd(II) salts, there must be a mechanism for reduction to the active Pd(0) species. In the case of amines, this may occur by reduction by the amine ligand.

Steps in Catalyst Activation



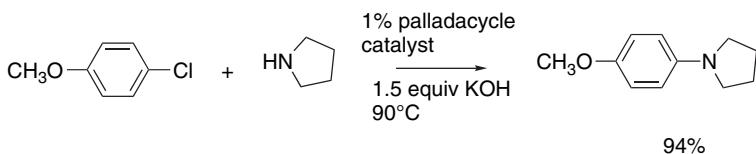
The various palladium species can be subject to decomposition and deposition of palladium metal, which generally leads to catalyst inactivation. Apart from their effect on the catalyst activity, the ligands and bases also affect catalyst longevity.

Most of the synthetic applications to date have been based on empirical screening and comparison of ligand systems for effectiveness. A number of useful procedures have been developed. Aryl chlorides are generally less reactive than iodides and

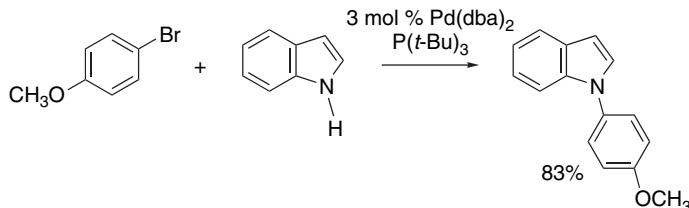
¹⁶⁷ L. M. Alcazar-Roman and J. F. Hartwig, *J. Am. Chem. Soc.*, **123**, 12905 (2001).

¹⁶⁸ E. R. Strieter, D. G. Blackmond, and S. L. Buchwald, *J. Am. Chem. Soc.*, **125**, 13978 (2003).

bromides. The palladacycle **7** (see p. 1046), was used successfully in the amination of aryl chlorides.¹⁶⁹

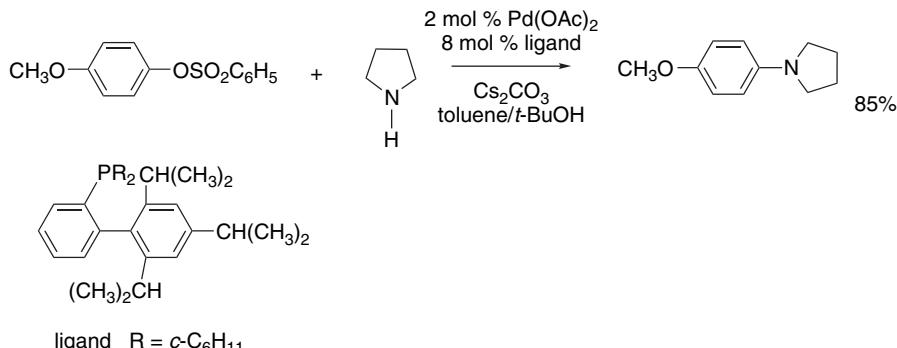


Palladium-catalyzed substitution can also be applied to nonbasic nitrogen heterocycles, such as indoles, in the absence of strong bases.



Ref. 170

Except for the perfluoro cases, aryl sulfonates are generally less reactive than the halides. However certain catalyst systems can achieve reactions with benzenesulfonates and tosylates. The hindered biphenylphosphines are the most effective ligands.



Ref. 171

These conditions were also successfully applied to arylation of amides and carbamates.



¹⁶⁹ D. Zim and S. L. Buchwald, *Org. Lett.*, **5**, 2413 (2003).

¹⁷⁰ J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, and L. M. Alcazar-Roman, *J. Org. Chem.*, **64**, 5575 (1999).

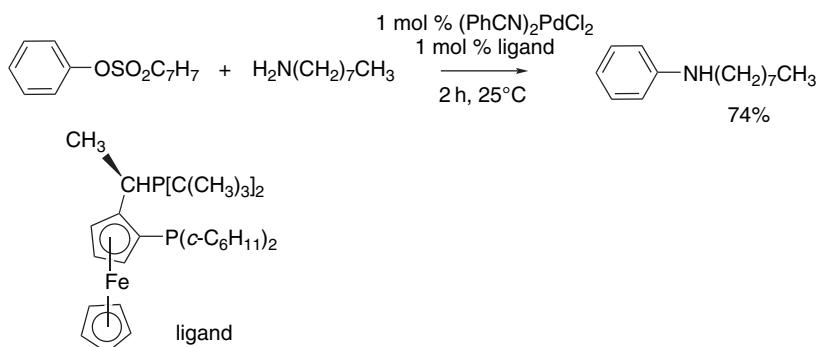
¹⁷¹ X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, and S. L. Buchwald, *J. Am. Chem. Soc.*, **125**, 6653 (2003).

Amination of tosylates has been achieved using a hindered ferrocenyldiphosphine ligand.¹⁷²

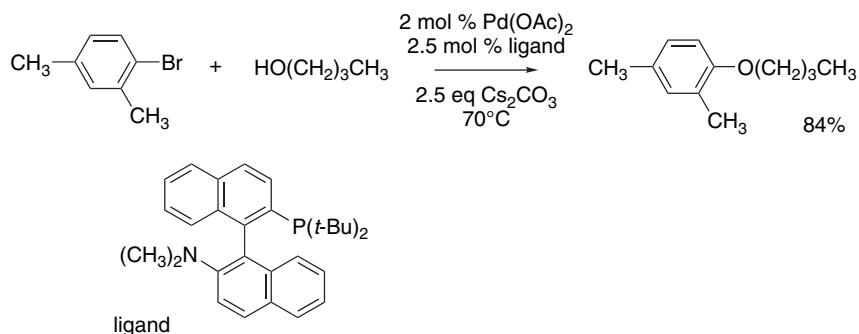
1049

SECTION 11.3

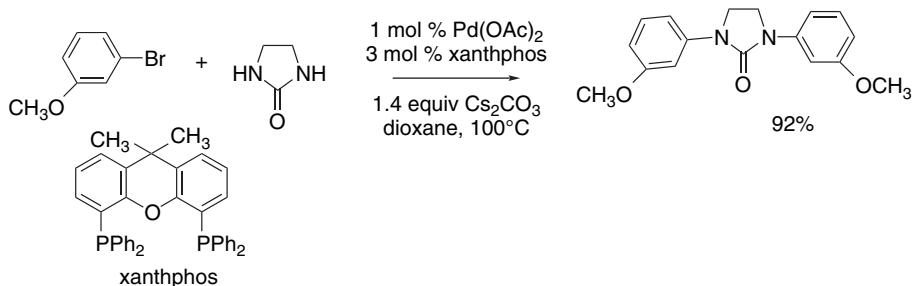
Transition
Metal-Catalyzed
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Similar reactions have been used for substitution by alkoxide and phenoxide nucleophiles. Hindered binaphthyl ligands have proven useful in substitutions by alcohols.¹⁷³



Palladium acetate in conjunction with a diphosphine ligand, xanthphos, is active for arylation of amides, ureas, oxazolidinones and sulfonamides.¹⁷⁴



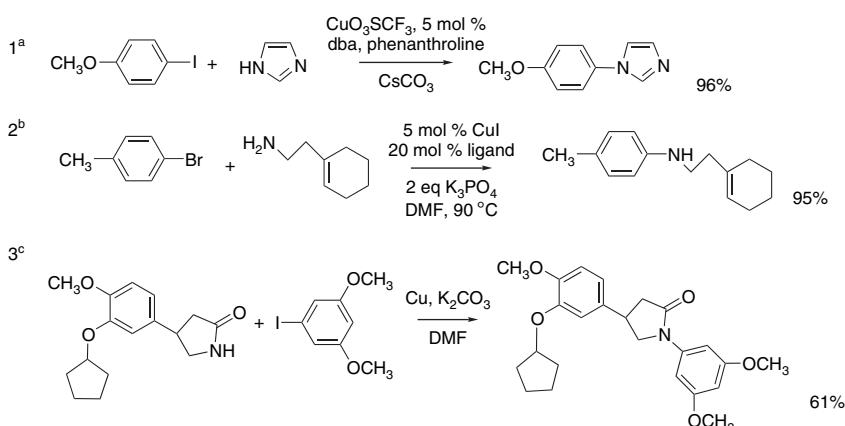
¹⁷². A. H. Roy and J. F. Hartwig, *J. Am. Chem. Soc.*, **125**, 8704 (2003).

¹⁷³. K. E. Torracca, X. Huang, C. A. Parrish, and S. L. Buchwald, *J. Am. Chem. Soc.*, **123**, 10770 (2001).

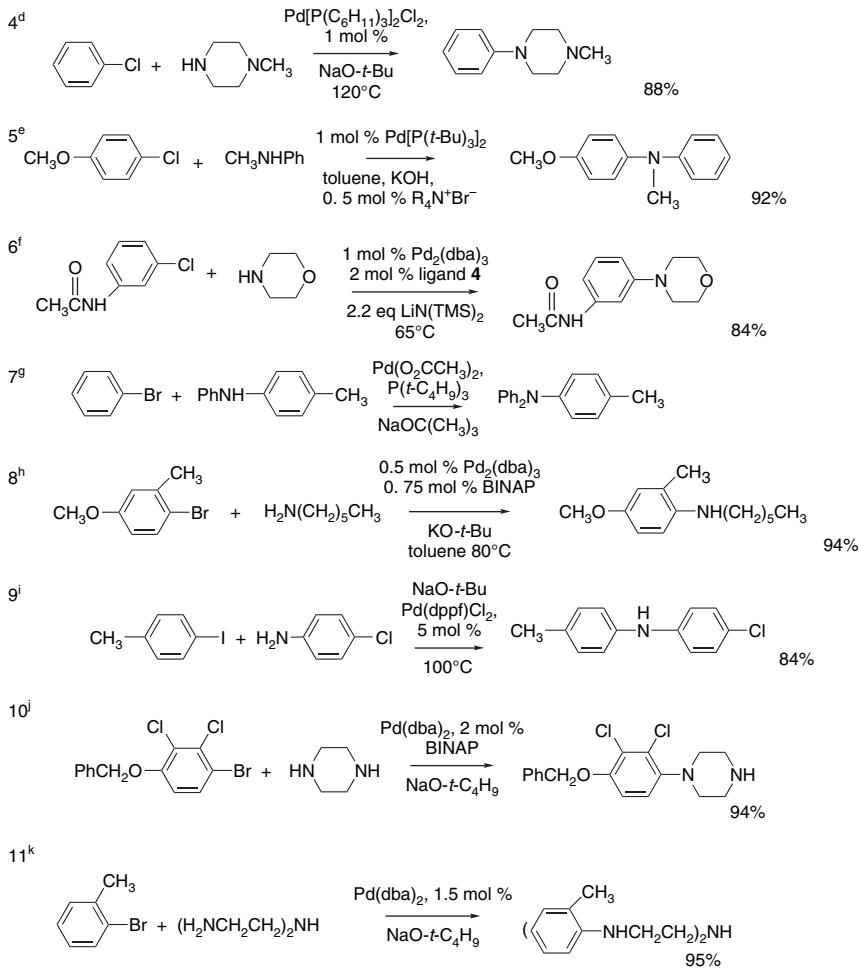
¹⁷⁴. J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.*, **124**, 6043 (2002).

Scheme 11.10. Copper- and Palladium-Catalyzed Aromatic Substitution

A. Copper-catalyzed substitution



B. Palladium-catalyzed substitution with nitrogen nucleophiles

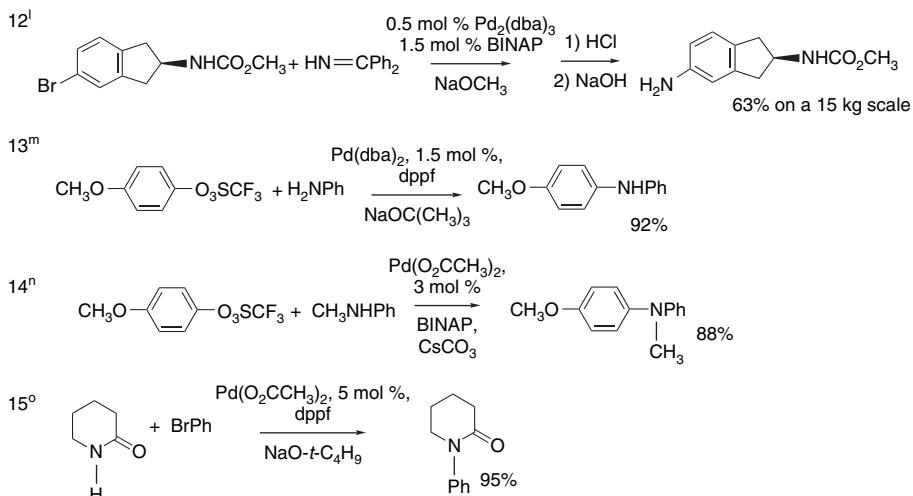


(Continued)

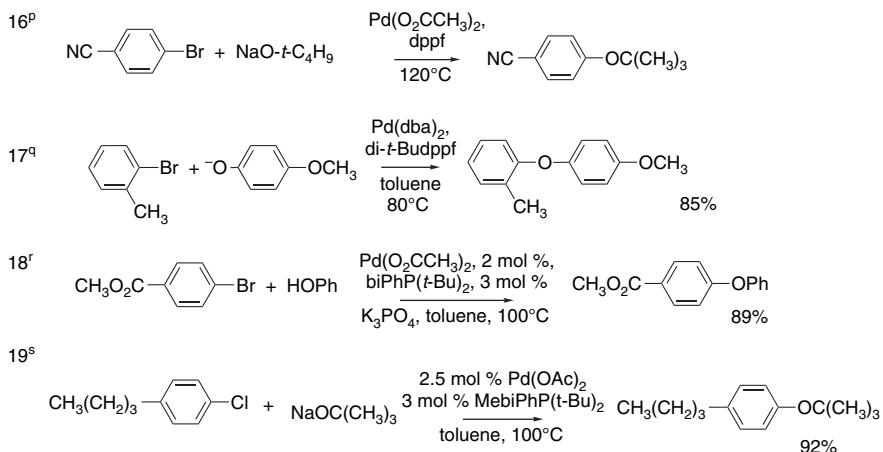
Scheme 11.10. (Continued)

1051

SECTION 11.3

Transition
Metal-Catalyzed
Aromatic Substitution
Reactions

C. Palladium-catalyzed reactions with oxygen nucleophiles.



- a. A. Kiyomori, J.-F. Marcoux, and S. L. Buchwald, *Tetrahedron Lett.*, **40**, 2657 (1999).
- b. F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, **5**, 793 (2003).
- c. E. Aeblischer, E. Bacher, F. W. J. Demitz, T. H. Keller, M. Kurzmeyer, M. L. Ortiz, E. Pombo-Villar, and H.-P. Weber, *Heterocycles*, **48**, 2225 (1998).
- d. N. P. Reddy and M. Tanaka, *Tetrahedron Lett.*, **38**, 4807 (1997).
- e. R. Kuwano, M. Utsunomiya, and J. F. Hartwig, *J. Org. Chem.*, **67**, 6479 (2002).
- f. M. C. Harris, X. Huang, and S. L. Buchwald, *Org. Lett.*, **4**, 2885 (2002).
- g. T. Yamamoto, M. Nishiyama, and Y. Koie, *Tetrahedron Lett.*, **39**, 2367 (1998).
- h. K. E. Torraca, X. Huang, C. A. Parrish, and S. L. Buchwald, *J. Am. Chem. Soc.*, **123**, 10770 (2001).
- i. M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, **118**, 7217 (1996).
- j. S. Morita, K. Kitano, J. Matsubara, T. Ohtani, Y. Kawano, K. Otsubo, and M. Uchida, *Tetrahedron*, **54**, 4811 (1998).
- k. Y. Hong, C. H. Senanayake, T. Xiang, C. P. Vandenbossche, G. J. Tanoury, R. P. Bakale, and S. A. Wald, *Tetrahedron Lett.*, **39**, 3121 (1998).
- l. M. Prashad, B. Hu, D. Har, O. Repic, T. J. Blacklock, and M. Avemoglu, *Adv. Synth. Catal.*, **343**, 461 (2001).
- m. J. Louie, M. S. Driver, B. C. Hamann, and J. F. Hartwig, *J. Org. Chem.*, **62**, 1268 (1997).
- n. J. Ahman and S. L. Buchwald, *Tetrahedron Lett.*, **38**, 6363 (1997).
- o. W. C. Shakespeare, *Tetrahedron Lett.*, **40**, 2035 (1999).
- p. G. Mann and J. F. Hartwig, *J. Org. Chem.*, **62**, 5413 (1997).
- q. G. Mann, C. Incarvito, A. L. Rheingold, and J. F. Hartwig, *J. Am. Chem. Soc.*, **121**, 3224 (1999).
- r. A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, and S. L. Buchwald, *J. Am. Chem. Soc.*, **121**, 4369 (1999).
- s. C. A. Parrish and S. L. Buchwald, *J. Org. Chem.*, **66**, 2498 (2001).

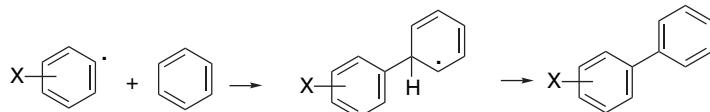
Some other examples of metal-catalyzed substitutions are given in Scheme 11.10. Entries 1 to 3 are copper-catalyzed reactions. Entry 1 is an example of arylation of imidazole. Both dibenzylideneacetone and 1,10-phenanthroline were included as ligands and Cs_2CO_3 was used as the base. Entry 2 is an example of amination by a primary amine. The ligand used in this case was *N,N*-diethylsalicylalimide. These conditions proved effective for a variety of primary amines and aryl bromides with both ERG and EWG substituents. Entry 3 is an example of more classical conditions. The target structure is a phosphodiesterase inhibitor of a type used in treatment of asthma. Copper powder was used as the catalyst.

The remainder of the entries in Scheme 11.10 depict palladium-catalyzed reactions. Entries 4 to 6 are examples of aminations of aryl chlorides. In Entry 4, a Pd(II) salt with a hindered phosphine ligand was used as the catalyst. Entry 5 uses the Pd(0)-tri-(*t*-butyl)phosphine complex as the catalyst in conjunction with a phase transfer salt. The reaction was done in a water-toluene mixture and these conditions were applicable to chlorides with both ERG and EWG substituents. Entry 6 used the biphenyl ligand **4** (see p. 1046). LiHMDS was a particularly good base in this case. Entries 7 to 11 use bromides (or iodides) as reactants and *t*-alkoxides as bases. In cases where the catalyst source is a Pd(II) salt, catalyst activation by reduction is necessary. Entry 12 is a large-scale amination carried out using the imine of benzophenone as the nucleophile, with subsequent hydrolysis to provide the amine. Entries 13 and 14 use aryl triflates as reactants. Again, the palladium sources must be reduced as part of catalyst activation. Entry 15 is an example of arylation of an amide. The conditions are similar to those for amination, and subsequent studies have shown that many other nonbasic nitrogen compounds can be arylated (e.g. see p. 1049). Entries 16 to 19 involve alkoxide and phenoxide nucleophiles. The best ligands for these reactions seem to be highly hindered phosphines.

11.4. Aromatic Substitution Reactions Involving Radical Intermediates

11.4.1. Aromatic Radical Substitution

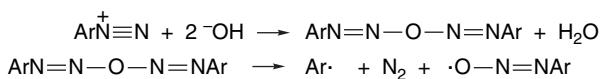
Aromatic rings are moderately reactive toward addition of free radicals (see Part A, Section 12.2) and certain synthetically useful substitution reactions involve free radical substitution. One example is the synthesis of biaryls.¹⁷⁵



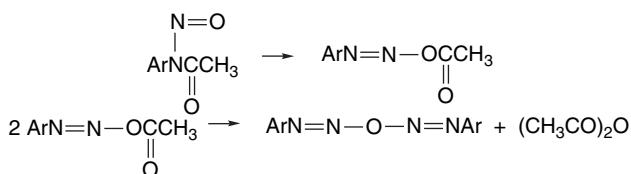
There are some inherent limits to the usefulness of such reactions. Radical substitutions are only moderately sensitive to substituent directing effects, so substituted reactants usually give a mixture of products. This means that the practical utility is limited to symmetrical reactants, such as benzene, where the position of attack

¹⁷⁵. W. E. Bachmann and R. A. Hoffman, *Org. React.*, **2**, 224 (1944); D. H. Hey, *Adv. Free Radical Chem.*, **2**, 47 (1966).

is immaterial. The best sources of aryl radicals are aryl diazonium ions and *N*-nitrosoacetanilides. In the presence of base, diazonium ions form diazooxides, which decompose to aryl radicals.¹⁷⁶



In the classical procedure, base is added to a two-phase mixture of the aqueous diazonium salt and an excess of the aromatic that is to be substituted. Improved yields can be obtained by using polyethers or phase transfer catalysts with solid aryl diazonium tetrafluoroborate salts in an excess of the aromatic reactant.¹⁷⁷ Another source of aryl radicals is *N*-nitrosoacetanilides, which rearrange to diazonium acetates and give rise to aryl radicals via diazo oxides.¹⁷⁸



A procedure for arylation involving *in situ* diazotization has also been developed.¹⁷⁹

Scheme 11.11 gives some representative preparative reactions based on these methods. Entry 1 is an example of the classical procedure. Entry 2 uses crown-ether catalysis. These reactions were conducted in the aromatic reactant as the solvent. In the study cited for Entry 2, it was found that substituted aromatic reactants such as toluene, anisole, and benzonitrile tended to give more *ortho* substitution product than expected on a statistical basis.¹⁸⁰ The nature of this directive effect does not seem to have been studied extensively. Entries 3 and 4 involve *in situ* decomposition of *N*-nitrosoamides. Entry 5 is a case of *in situ* nitrosation.

11.4.2. Substitution by the S_{RN}1 Mechanism

The mechanistic aspects of the S_{RN}1 reaction were discussed in Section 11.6 of Part A. The distinctive feature of the S_{RN}1 mechanism is an electron transfer between the nucleophile and the aryl halide.¹⁸¹ The overall reaction is normally a chain process.

¹⁷⁶. C. Rüchardt and B. Freudenberg, *Tetrahedron Lett.*, 3623 (1964); C. Rüchardt and E. Merz, *Tetrahedron Lett.*, 2431 (1964); C. Galli, *Chem. Rev.*, **88**, 765 (1988).

¹⁷⁷. J. R. Beadle, S. H. Korzeniowski, D. E. Rosenberg, G. J. Garcia-Slanga, and G. W. Gokel, *J. Org. Chem.*, **49**, 1594 (1984).

¹⁷⁸. J. I. G. Cadogan, *Acc. Chem. Res.*, **4**, 186 (1971); *Adv. Free Radical Chem.*, **6**, 185 (1980).

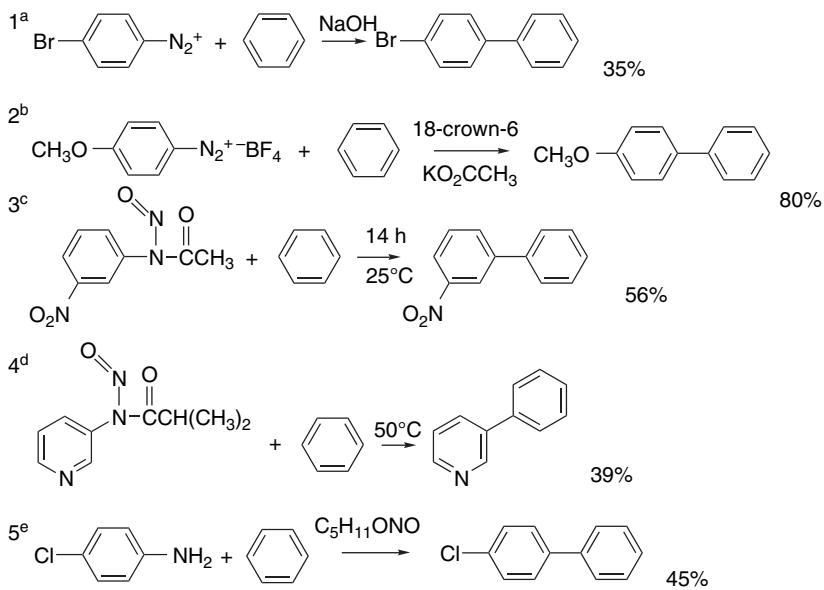
¹⁷⁹. J. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962).

¹⁸⁰. See also T. Inukai, K. Kobayashi, and O. Shinmura, *Bull. Chem. Soc. Jpn.*, **35**, 1576 (1962).

¹⁸¹. J. F. Bunnett, *Acc. Chem. Res.*, **11**, 413 (1978); R. A. Rossi and R. H. de Rossi, *Aromatic Substitution by the S_{RN}1 Mechanism*, ACS Monograph Series, No. 178, American Chemical Society, Washington, DC, 1983.

Scheme 11.11. Synthesis of Biaryls by Radical Substitution

CHAPTER 11

Aromatic Substitution
Reactions

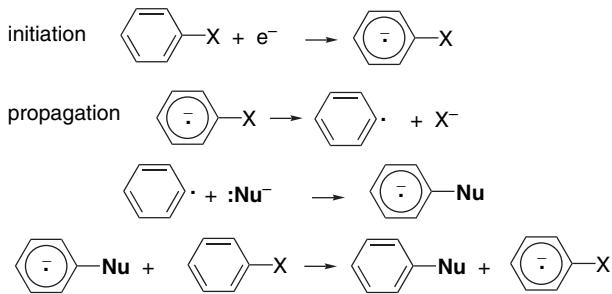
a. M. Gomberg and W. E. Bachman, *Org. Synth.*, **I**, 113 (1941).

b. S. H. Korzeniowski, L. Blum, and G. W. Gokel, *Tetrahedron Lett.*, 1871 (1977); J. R. Beadle, S. H. Korzeniowski, D. E. Rosenberg, B. J. Garcia-Slanga, and G. W. Gokel, *J. Org. Chem.*, **49**, 1594 (1984).

c. W. E. Bachmann and R. A. Hoffman, *Org. React.*, **2**, 249 (1944).

d. H. Rapoport, M. Lick, and G. J. Kelly, *J. Am. Chem. Soc.*, **74**, 6293 (1952).

e. J. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962).



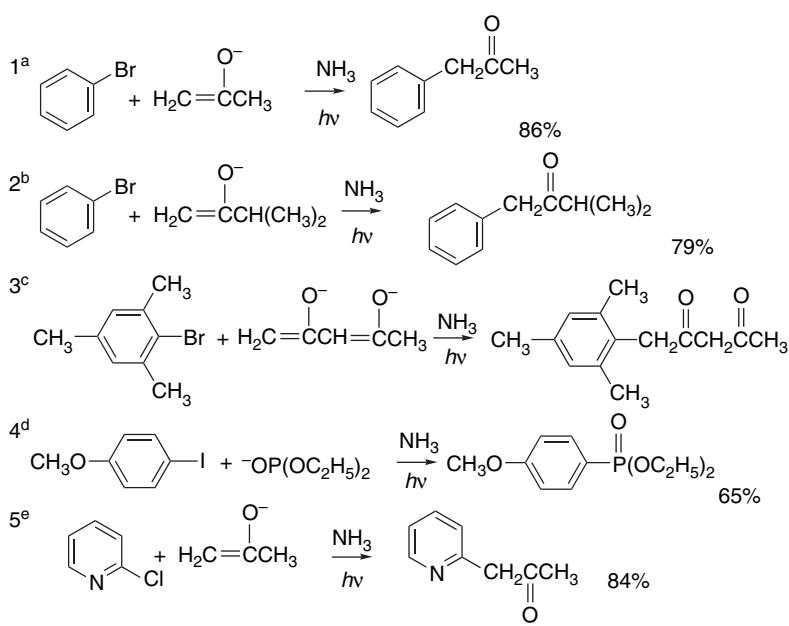
A potential advantage of the $S_{RN}1$ mechanism is that it is not particularly sensitive to the nature of other aromatic ring substituents, although EWG substituents favor the nucleophilic addition step. For example, chloropyridines and chloroquinolines are excellent reactants.¹⁸² A variety of nucleophiles undergo the reaction, although not always in high yield. The nucleophiles that have been found to participate in

¹⁸² J. V. Hay, T. Hudlicky, and J. F. Wolfe, *J. Am. Chem. Soc.*, **97**, 374 (1975); J. V. Hay and J. F. Wolfe, *J. Am. Chem. Soc.*, **97**, 3702 (1975); A. P. Komin and J. F. Wolfe, *J. Org. Chem.*, **42**, 2481 (1977); R. Beugelmans, M. Bois-Choussy, and B. Boudet, *Tetrahedron*, **24**, 4153 (1983).

$S_{RN}1$ substitution include ketone enolates,¹⁸³ ester enolates,¹⁸⁴ amide enolates,¹⁸⁵ 2,4-pentanedione dianion,¹⁸⁶ pentadienyl and indenyl carbanions,¹⁸⁷ phenolates,¹⁸⁸ diethyl phosphite anion,¹⁸⁹ phosphides,¹⁹⁰ and thiolates.¹⁹¹ The reactions are frequently initiated by light, which promotes the initiating electron transfer. As for other radical chain processes, the reaction is sensitive to substances that can intercept the propagation intermediates.

Scheme 11.12 provides some examples of the preparative use of the $S_{RN}1$ reaction. Entries 1 and 2 involve arylations of ketone enolates, whereas Entry 3 involves a dianion. Entry 4 is an example of a convenient preparation of arylphosphonates. Entry 5 is an example of application of the $S_{RN}1$ reaction to a chloropyridine.

Scheme 11.12. Aromatic Substitution by the $S_{RN}1$ Mechanism



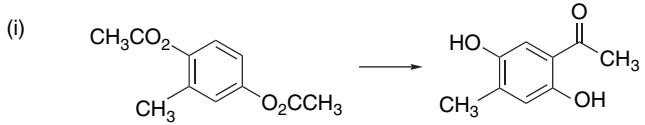
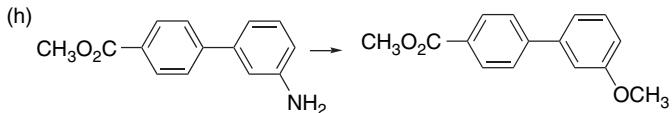
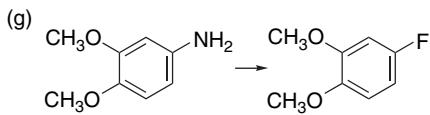
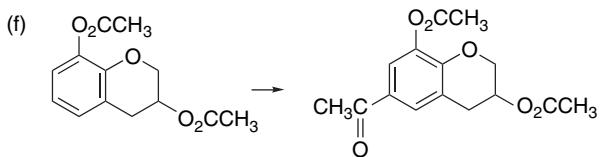
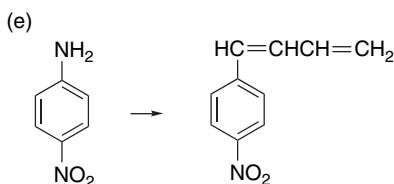
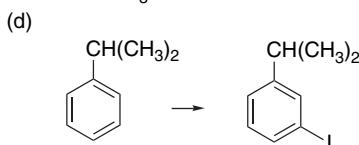
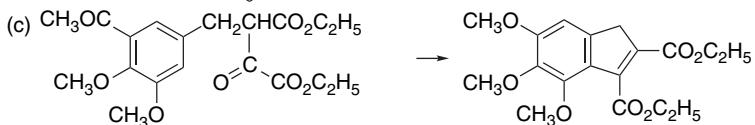
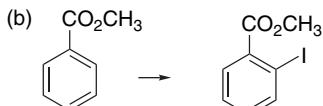
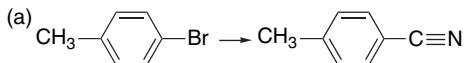
- a. R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 1407 (1973).
- b. M. F. Semmelhack and T. Bargar, *J. Am. Chem. Soc.*, **102**, 7765 (1980).
- c. J. F. Bunnett and J. E. Sundberg, *J. Org. Chem.*, **41**, 1702 (1976).
- d. J. F. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3612 (1974).
- e. A. P. Komin and J. F. Wolfe, *J. Org. Chem.*, **42**, 2481 (1977).

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- ¹⁸⁴ J.-W. Wong, K. J. Natalie, Jr., G. C. Nwokogu, J. S. Pisipati, S. Jyothi, P. T. Flaherty, T. D. Greenwood, and J. F. Wolfe, *J. Org. Chem.*, **62**, 6152 (1997).
- ¹⁸⁵ R. A. Rossi and R. A. Alonso, *J. Org. Chem.*, **45**, 1239 (1980).
- ¹⁸⁶ J. F. Bunnett and J. E. Sundberg, *J. Org. Chem.*, **41**, 1702 (1976).
- ¹⁸⁷ R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 3020 (1973).
- ¹⁸⁸ A. B. Pierini, M. T. Baumgartner, and R. A. Rossi, *Tetrahedron Lett.*, **29**, 3429 (1988).
- ¹⁸⁹ J. F. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3612 (1974); A. Boumekouez, E. About-Jaudet, N. Collignon, and P. Savignac, *J. Organomet. Chem.*, **440**, 297 (1992).
- ¹⁹⁰ E. Austin, R. A. Alonso, and R. A. Rosi, *J. Org. Chem.*, **56**, 4486 (1991).
- ¹⁹¹ J. F. Bunnett and X. Creary, *J. Org. Chem.*, **39**, 3173, 3611 (1974); J. F. Bunnett and X. Creary, *J. Org. Chem.*, **40**, 3740 (1975).

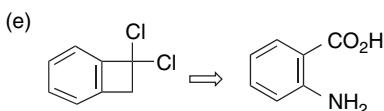
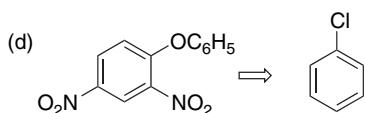
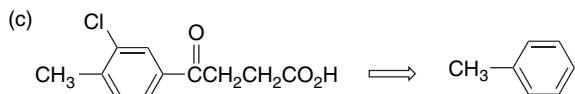
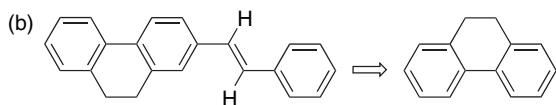
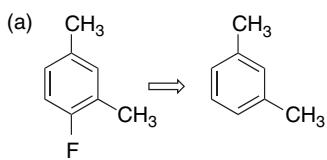
Problems

(References for these problems will be found on page 1289.)

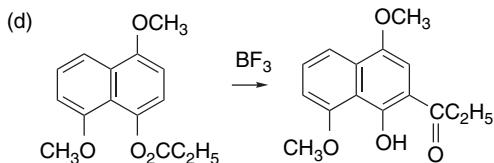
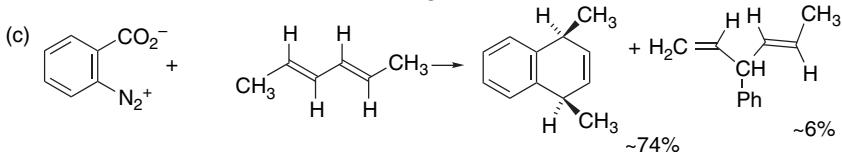
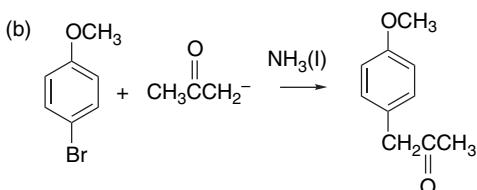
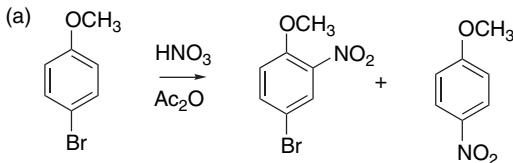
11.1. Give reagents and reaction conditions that would accomplish each of the following transformations. Multistep schemes are not necessary. Be sure to choose conditions that would lead to the desired isomer as the major product.

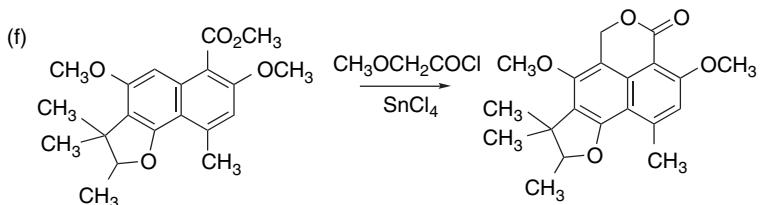
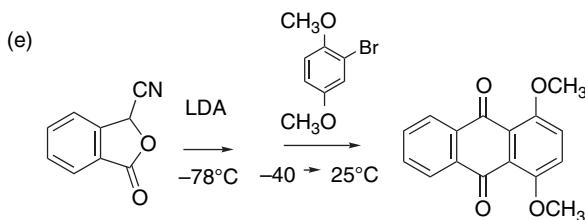


11.2. Suggest a short series of reactions that would be expected to transform the material on the right into the desired product shown on the left.

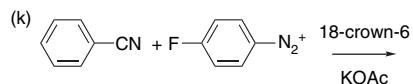
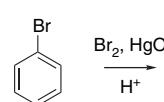
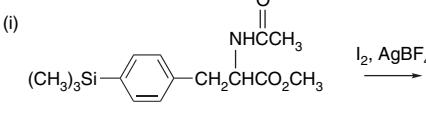
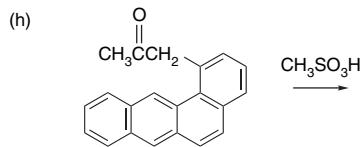
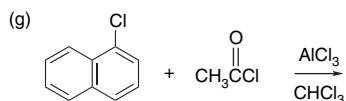
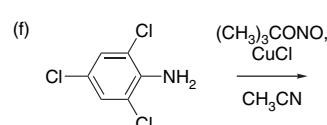
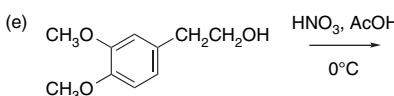
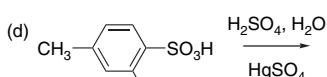
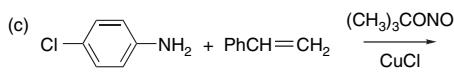
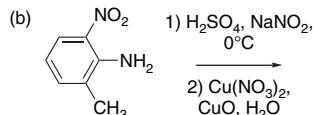
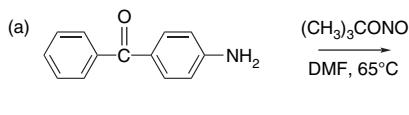


11.3. Write mechanisms that would account for the following reactions:





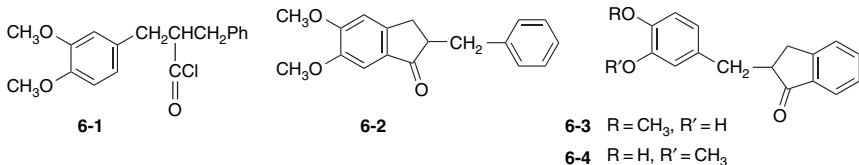
11.4. Predict the product(s) of the following reactions. If more than one product is expected, indicate which will be major and which will be minor.



11.5. Suggest efficient syntheses of *o*-, *m*-, and *p*-fluoropropiophenone from benzene and other necessary reagents.

11.6. Treatment of compound **6-1** in dibromomethane with one equivalent of aluminum bromide yields **6-2** as the only product in 78% yield. When three equivalents of

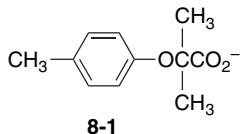
aluminum bromide are used, compounds **6-3** and **6-4** are obtained in a combined yield of 97%. Suggest an explanation for these observations.



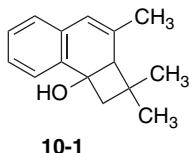
- 11.7. Some data on the alkylation of naphthalene by 2-bromopropane using AlCl_3 under different conditions are given below. What factors are responsible for the differing product ratios for the two solvents, and why does the product ratio change with time?

Time (min)	$\alpha:\beta$ Product ratio	
	Solvent	
	CS_2	CH_3NO_2
5	4:96	83:17
15	2.5:97.5	74:26
45	2:98	70:30

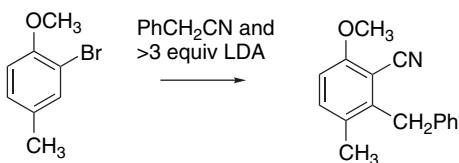
- 11.8. Addition of a solution of bromine and potassium bromide to a solution of the carboxylate salt **8-1** results in the precipitation of a neutral compound having the formula $\text{C}_{11}\text{H}_{13}\text{BrO}_3$. Spectroscopic data show that the compound is nonaromatic. Suggest a structure and discuss the mechanistic significance of its formation.



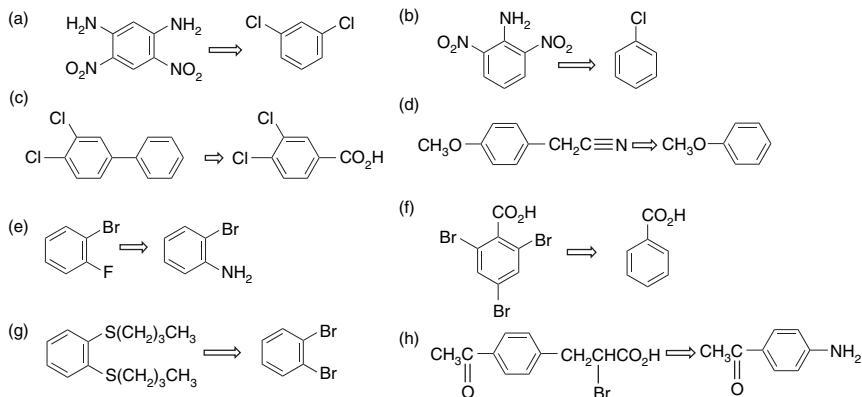
- 11.9. Benzaldehyde, benzyl methyl ether, benzoic acid, methyl benzoate, and phenylacetic acid all undergo thallation initially in the *ortho* position. Explain this observation.
- 11.10. Reaction of 3,5,5-trimethyl-2-cyclohexenone with three equivalents of NaNH_2 in THF generates the corresponding enolate. When bromobenzene is added and the solution stirred for 4 h, the product **10-1** is isolated in 30% yield. Formulate a mechanism for this transformation.



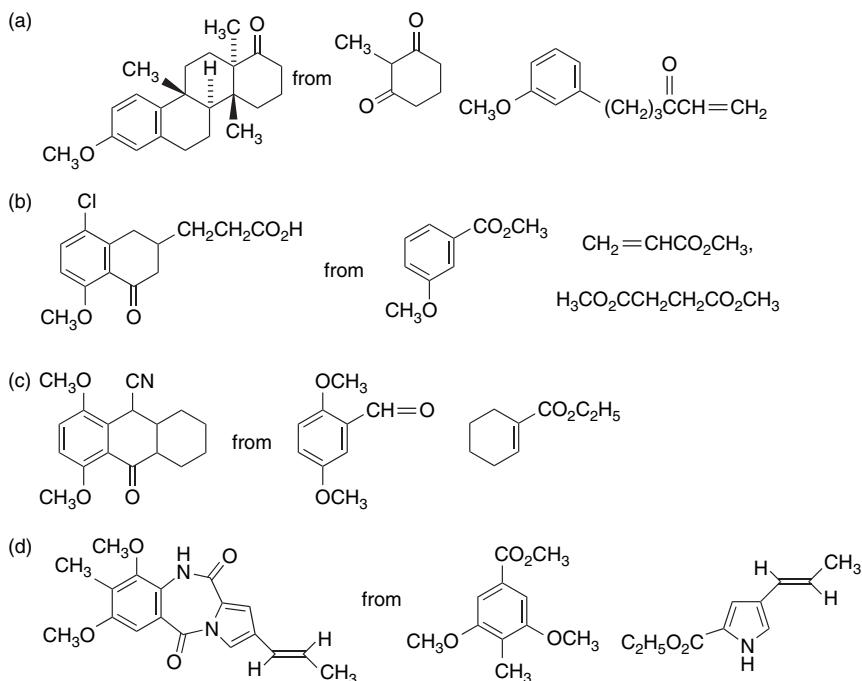
- 11.11. When phenylacetonitrile is converted to its anion in the presence of excess LDA and then allowed to react with 2-bromo-4-methyl-1-methoxybenzene, the product contains both a benzyl and cyano substituent. Propose a mechanism for this reaction.

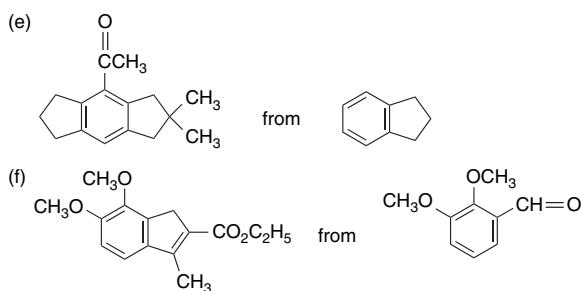


11.12. Suggest a reaction sequence that would permit synthesis of the following aromatic compounds from the starting material indicated on the right.

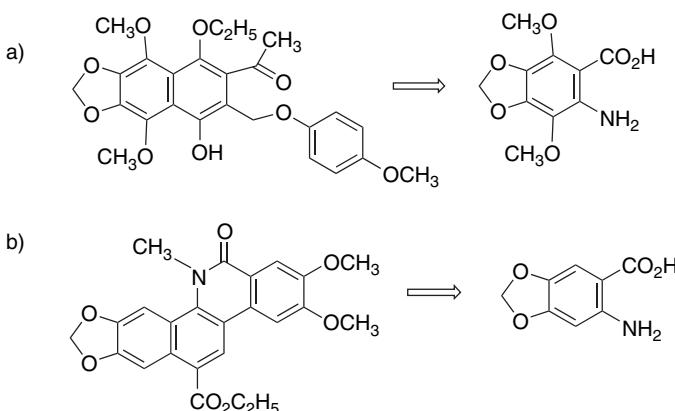


11.13. Aromatic substitution reactions are key steps in the multistep synthetic sequences that effect the following transformations. Suggest a sequence of reactions that could effect the desire syntheses.

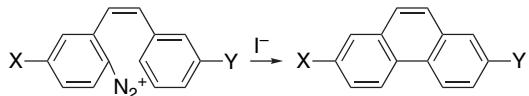




- 11.14. The following intermediates in the synthesis of naturally occurring materials have been synthesized by reactions based on a benzyne intermediate. The benzyne precursor is shown. By retrosynthetic analysis identify an appropriate co-reactant that would form the desired compound.

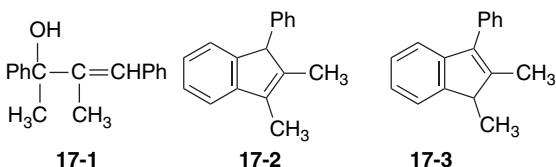


- 11.15. Aryltrimethylsilanes has been found to be a useful complement to direct thallation in the preparation of arylthallium(III) intermediates. The thallium(III) replaces the silyl substituent and the scope of the reaction is expanded to include some EWGs, such as trifluoromethyl. How does the silyl group function in these systems?
- 11.16. The Pschorr reaction is a method of synthesis of phenanthrenes from diazotized Z-2-aminostilbenes. A traditional procedure involves heating with a copper catalyst. Improved yields are often observed, however, if the diazonium ion is treated with iodide ion. Suggest a mechanism for the iodide-catalyzed reaction.

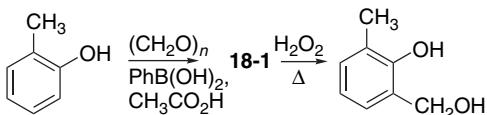


- 11.17. When compound **17-1** is dissolved in FSO_3H at -78°C , NMR spectroscopy shows that a carbocation is formed. If the solution is then allowed to warm to -10°C , a different ion forms. The first ion gives compound **17-2** when

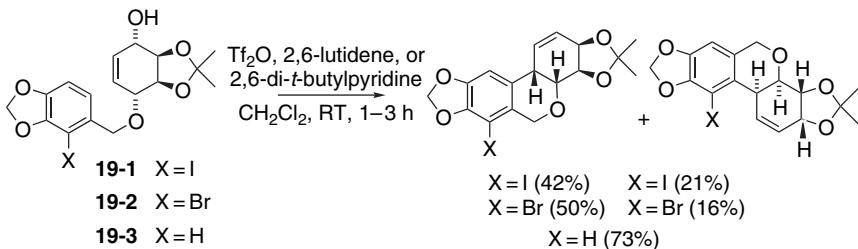
quenched with base, whereas the second ion gives **17-3**. What are the structures of the two carbocations, and why do they give different products on quenching?



- 11.18. Various phenols can be selectively hydroxymethylated at the *ortho* position by heating with paraformaldehyde and phenylboronic acid. An intermediate **18-1** having the formula $C_{14}H_{13}O_2B$ for the case shown can be isolated prior to the oxidation. Suggest a structure for the intermediate and comment on its role in the reaction.



- 11.19. The electrophilic cyclization of **19-1** and **19-2** gives two isomers, but with the unsubstituted reactant **19-3**, only a single stereoisomer is formed. Explain the origin of the isomers and the absence of isomer formation in the case of **19-3**.



- 11.20. Entry 5 in Scheme 11.4 is a step in the synthesis of the anticancer drug tamoxifen. Explain why the 2-phenylbutanoyl group is introduced in preference to a trifluoroacetyl group.

Oxidations

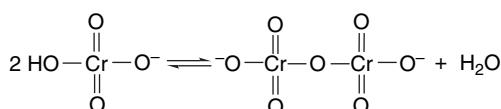
Introduction

This chapter is concerned with reactions that transform a functional group to a more highly oxidized derivative by removal of hydrogen and/or addition of oxygen. There are a great many oxidation methods, and we have chosen the reactions for discussion on the basis of their utility in synthesis. As the reactions are considered, it will become evident that the material in this chapter spans a broader range of mechanisms than most of the previous chapters. Owing to this range, the chapter is organized according to the functional group transformation that is accomplished. This organization facilitates comparison of the methods available for effecting a given synthetic transformation. The major sections consider the following reactions: (1) oxidation of alcohols; (2) addition of oxygen at double bonds; (3) allylic oxidation; (4) oxidative cleavage of double bonds; (5) oxidative cleavage of other functional groups; (6) oxidations of aldehydes and ketones; and (7) oxidation at unfunctionalized positions. The oxidants are grouped into three classes: transition metal derivatives; oxygen, ozone, and peroxides; and other reagents.

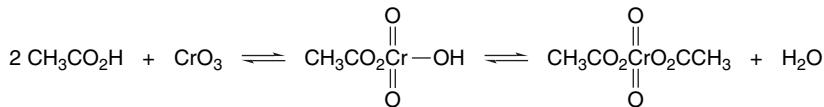
12.1. Oxidation of Alcohols to Aldehydes, Ketones, or Carboxylic Acids

12.1.1. Transition Metal Oxidants

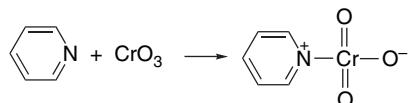
The most widely employed transition metal oxidants for alcohols are based on Cr(VI). The specific reagents are generally prepared from chromic trioxide, CrO_3 , or a dichromate salt, $[\text{Cr}_2\text{O}_7]^{2-}$. The form of Cr(VI) in aqueous solution depends upon concentration and pH; the pK_1 and pK_2 of H_2CrO_4 are 0.74 and 6.49, respectively. In dilute solution, the monomeric acid chromate ion $[\text{HCrO}_3]^-$ is the main species present; as concentration increases, the dichromate ion dominates.



In acetic acid, Cr(VI) is present as mixed anhydrides of acetic acid and chromic acid.¹

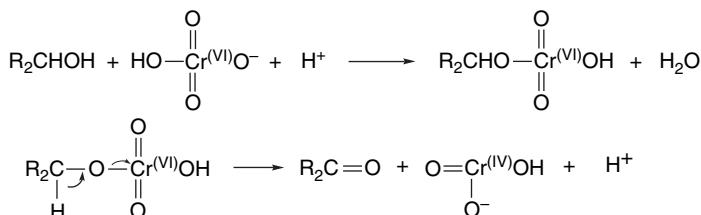


In pyridine, an adduct involving Cr–N bonding is formed.

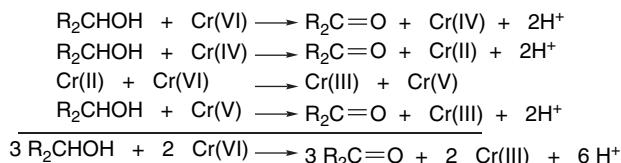


The oxidation state of Cr in each of these species is (VI) and they are all powerful oxidants. The precise reactivity depends on the solvent and the chromium ligands, so substantial selectivity can be achieved by the choice of the particular reagent and conditions.

The general mechanism of alcohol oxidation involves coordination of the alcohol at chromium and a rate-determining deprotonation.



An important piece of evidence for this mechanism is the fact that a primary isotope effect is observed when the α -hydrogen is replaced by deuterium.² The Cr(IV) that is produced in the initial step is not stable and is capable of a further oxidation. It is believed that Cr(IV) is reduced to Cr(II), which is then oxidized by Cr(VI) generating Cr(V). This mechanism accounts for the overall stoichiometry of the reaction.³



¹. K. B. Wiberg, *Oxidation in Organic Chemistry*, Part A, Academic Press, New York, 1965, pp. 69–72.

². F. H. Westheimer and N. Nicolaides, *J. Am. Chem. Soc.*, **71**, 25 (1949).

³. S. L. Scott, A. Bakac, and J. H. Esperson, *J. Am. Chem. Soc.*, **114**, 4205 (1992); J. F. Perez-Benito and C. Arias, *Can. J. Chem.*, **71**, 649 (1993).

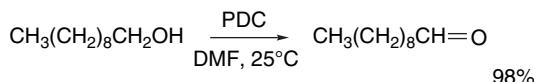
SECTION 12.1

Oxidation of Alcohols to Aldehydes, Ketones, or Carboxylic Acids

Various experimental conditions have been used for oxidations of alcohols by Cr(VI) on a laboratory scale, and several examples are shown in Scheme 12.1. Entry 1 is an example of oxidation of a primary alcohol to an aldehyde. The propanal is distilled from the reaction mixture as oxidation proceeds, which minimizes overoxidation. For secondary alcohols, oxidation can be done by addition of an acidic aqueous solution containing chromic acid (known as *Jones' reagent*) to an acetone solution of the alcohol. Oxidation normally occurs rapidly, and overoxidation is minimal. In acetone solution, the reduced chromium salts precipitate and the reaction solution can be decanted. Entries 2 to 4 in Scheme 12.1 are examples of this method.

The chromium trioxide-pyridine complex is useful in situations when other functional groups might be susceptible to oxidation or the molecule is sensitive to acid.⁴ A procedure for utilizing the CrO₃-pyridine complex, which was developed by Collins,⁵ has been widely adopted. The CrO₃-pyridine complex is isolated and dissolved in dichloromethane. With an excess of the reagent, oxidation of simple alcohols is complete in a few minutes, giving the aldehyde or ketone in good yield. A procedure that avoids isolation of the complex can further simplify the experimental operations.⁶ Chromium trioxide is added to pyridine in dichloromethane. Subsequent addition of the alcohol to this solution results in oxidation in high yield. Other modifications for use of the CrO₃-pyridine complex have been developed.⁷ Entries 5 to 9 in Scheme 12.1 demonstrate the excellent results that have been reported using the CrO₃-pyridine complex in dichloromethane. Entries 5 and 6 involve conversion of primary alcohols to aldehydes, Entry 7 describes preparation of the reagent *in situ*, and Entry 8 is an example of application of these conditions to a primary alcohol. The conditions described in Entry 9 were developed to optimize the oxidation of sensitive carbohydrates. It was found that inclusion of 4A molecular sieves and a small amount of acetic acid accelerated the reaction.

Another very useful Cr(VI) reagent is pyridinium chlorochromate (PCC), which is prepared by dissolving CrO₃ in hydrochloric acid and adding pyridine to obtain a solid reagent having the composition CrO₃Cl·pyrH.⁸ This reagent can be used in amounts close to the stoichiometric ratio. Entries 10 and 11 are examples of the use of PCC. Reaction of pyridine with CrO₃ in a small amount of water gives pyridinium dichromate (PDC), which is also a useful oxidant.⁹ As a solution in DMF or a suspension in dichloromethane, this reagent oxidizes secondary alcohols to ketones. Allylic primary alcohols give the corresponding aldehydes. Depending upon the conditions, saturated primary alcohols give either an aldehyde or the corresponding carboxylic acid.



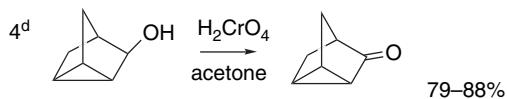
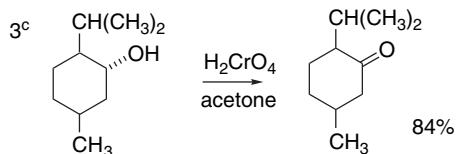
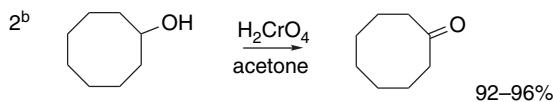
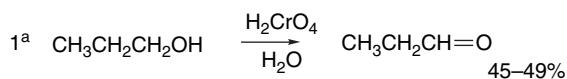
- ⁴ G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953); W. S. Johnson, W. A. Vredenburgh, and J. E. Pike, *J. Am. Chem. Soc.*, **82**, 3409 (1960); W. S. Allen, S. Bernstein, and R. Little, *J. Am. Chem. Soc.*, **76**, 6116 (1954).
- ⁵ J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).
- ⁶ R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
- ⁷ J. Herscovici, M.-J. Egron, and K. Antonakis, *J. Chem. Soc., Perkin Trans. 1*, 1967 (1982); E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 399 (1979); S. Czernecki, C. Georgoulis, C. L. Stevens, and K. Vijayakumaran, *Tetrahedron Lett.*, **26**, 1699 (1985).
- ⁸ E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975); G. Piancatelli, A. Scettri, and M. D'Auria, *Synthesis*, 245 (1982).
- ⁹ E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 399 (1979).

Scheme 12.1. Oxidation with Chromium(VI) Reagents

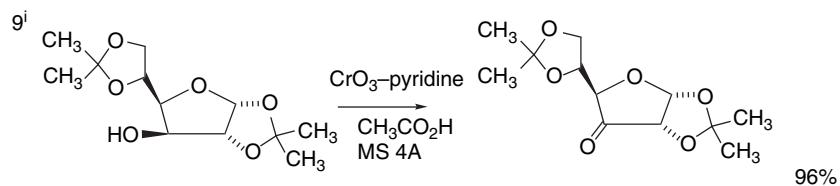
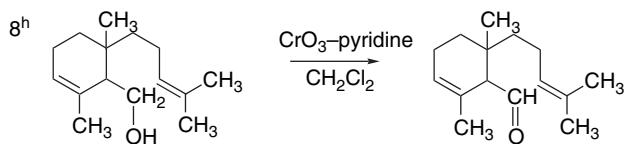
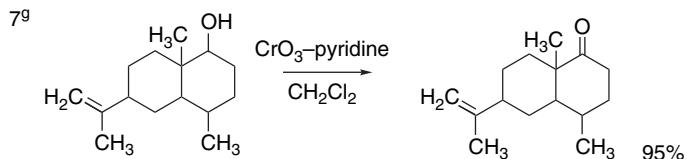
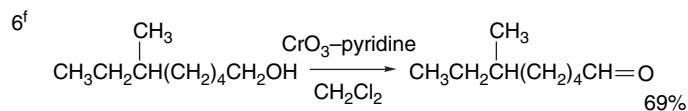
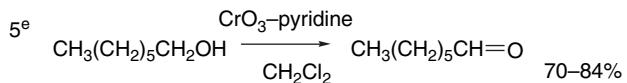
CHAPTER 12

Oxidations

A. Chromic acid solutions



B. Chromium trioxide–pyridine

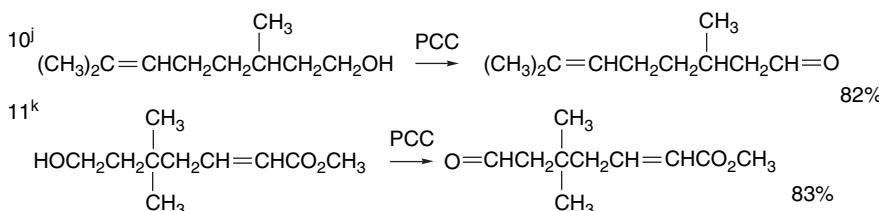


(Continued)

SECTION 12.1

Oxidation of Alcohols to
Aldehydes, Ketones,
or Carboxylic Acids

C. Pyridinium chlorochromate



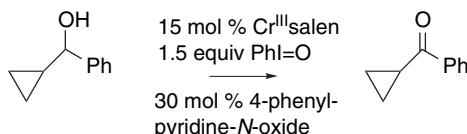
- a. C. D. Hurd and R. N. Meinert, *Org. Synth.*, **II**, 541 (1943).
- b. E. J. Eisenbraun, *Org. Synth.*, **V**, 310 (1973).
- c. H. C. Brown, C. P. Garg, and K.-T. Liu, *J. Org. Chem.*, **36**, 387 (1971).
- d. J. Meinwald, J. Crandall, and W. E. Hymans, *Org. Synth.*, **V**, 866 (1973).
- e. J. C. Collins and W. W. Hess, *Org. Synth.*, **52**, 5 (1972).
- f. J. I. DeGraw and J. O. Rodin, *J. Org. Chem.*, **36**, 2902 (1971).
- g. R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
- h. M. A. Schwartz, J. D. Crowell, and J. H. Musser, *J. Am. Chem. Soc.*, **94**, 4361 (1972).
- i. C. Czernecki, C. Gerogoulis, C. L. Stevens, and K. Vijayakumaran, *Tetrahedron Lett.*, **26**, 1699 (1985).
- j. E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
- k. R. D. Little and G. W. Muller, *J. Am. Chem. Soc.*, **103**, 2744 (1981).

Although Cr(VI) oxidants are very versatile and efficient, they have one drawback, which becomes especially serious in larger-scale work: the toxicity and environmental hazards associated with chromium compounds. The reagents are used in stoichiometric or excess amount and the Cr(III) by-products must be disposed of safely.

Potassium permanganate, KMnO_4 , is another powerful transition metal oxidant, but it has found relatively little application in the oxidation of alcohols to ketones and aldehydes. The reagent is less selective than Cr(VI), and overoxidation is a problem. On the other hand, manganese(IV) dioxide is quite useful.¹⁰ This reagent, which is selective for allylic and benzylic alcohols, is prepared by reaction of $\text{Mn}(\text{II})\text{SO}_4$ with KMnO_4 and sodium hydroxide. The precise reactivity of MnO_2 depends on its mode of preparation and the extent of drying.¹¹

Scheme 12.2 shows various types of alcohols that are most susceptible to MnO_2 oxidation. Entries 1 and 2 illustrate the application of MnO_2 to simple benzylic and allylic alcohols. In Entry 2, the MnO_2 was activated by azeotropic drying. Entry 3 demonstrates the application of the reagent to cyclopropylcarbinols. Entry 4 is an application to an acyloin. Entry 5 involves oxidation of a sensitive conjugated system.

A reagent system that is selective for allylic, benzylic, and cyclopropyl alcohols uses iodosobenzene in conjunction with a Cr(III)(salen) complex.¹²

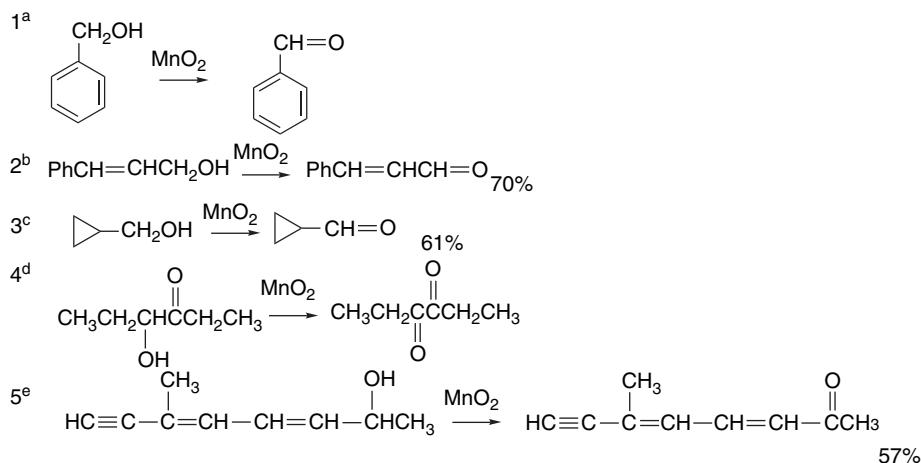


¹⁰. D. G. Lee, in *Oxidation*, Vol. 1, R. L. Augustine, ed., Marcel Dekker, New York, 1969, pp. 66–70; A. J. Fatiadi, *Synthesis*, 65 (1976); A. J. Fatiadi, *Synthesis*, 133 (1976).

¹¹. J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952); I. M. Goldman, *J. Org. Chem.*, **34**, 1979 (1969).

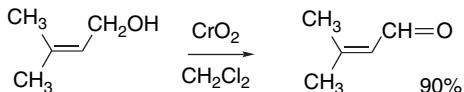
¹². W. Adam, F. G. Gelacha, C. R. Saha-Moeller, and V. R. Stegmann, *J. Org. Chem.*, **65**, 1915 (2000); see also S. S. Kim and D. W. Kim, *Synlett*, 1391 (2003).

Scheme 12.2. Oxidation of Alcohols with Manganese Dioxide

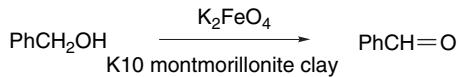


- a. E. F. Pratt and J. F. Van De Castle, *J. Org. Chem.*, **26**, 2973 (1961).
 b. I. M. Goldman, *J. Org. Chem.*, **34**, 1979 (1969).
 c. L. Crombie and J. Crossley, *J. Chem. Soc.*, 4983 (1963).
 d. E. P. Papadopoulos, A. Jarrar, and C. H. Issidorides, *J. Org. Chem.*, **31**, 615 (1966).
 e. J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Janssen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

Another recently developed oxidant is CrO_2 , a solid known as Magtrieve™ that is prepared commercially (for other purposes), which oxidizes allylic and benzylic alcohols in good yield.¹³ It is also reactive toward saturated alcohols. Because the solid remains ferromagnetic, it can be recovered by use of a magnet and can be reactivated by exposure to air at high temperature, making it environmentally benign.



Another possible alternative oxidant that has recently been investigated is an Fe(VI) species, potassium ferrate, K_2FeO_4 , supported on montmorillonite clay.¹⁴ This reagent gives clean, high-yielding oxidation of benzylic and allylic alcohols, but saturated alcohols are less reactive.

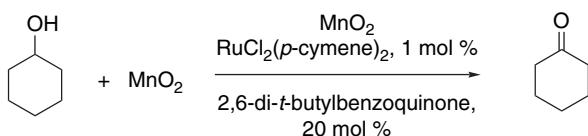


A catalytic system that extends the reactivity of MnO_2 to saturated secondary alcohols has been developed.¹⁵ This system consists of a Ru(II) salt, $\text{RuCl}_2(p\text{-cymene})_2$, and 2,6-di-*t*-butylbenzoquinone.

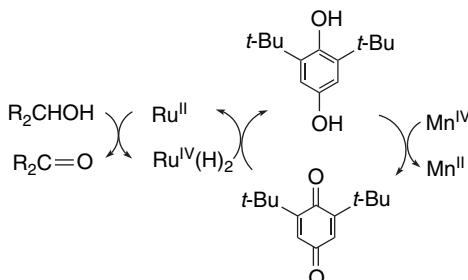
¹³. R. A. Lee and D. S. Donald, *Tetrahedron Lett.*, **38**, 3857 (1997).

¹⁴. L. Delaude and P. Laszlo, *J. Org. Chem.*, **61**, 6360 (1996).

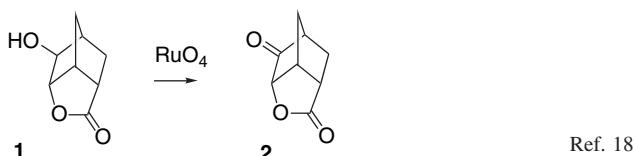
¹⁵. U. Karlsson, G. Z. Wang, and J.-E. Backvall, *J. Org. Chem.*, **59**, 1196 (1994).



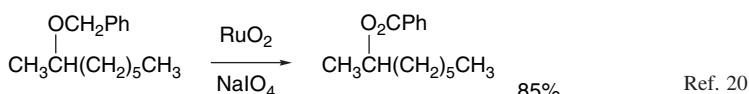
Ruthenium is the active oxidant and benzoquinone functions as an intermediary hydride transfer agent.



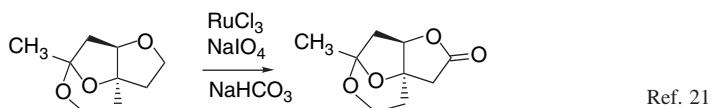
Another reagent that finds application of oxidations of alcohols to ketones is ruthenium tetroxide. The oxidations are typically carried out using a catalytic amount of the ruthenium source, e.g., RuCl_3 , with NaIO_4 or NaOCl as the stoichiometric oxidant.¹⁶ Acetonitrile is a favorable solvent because of its ability to stabilize the ruthenium species that are present.¹⁷ For example, the oxidation of **1** to **2** was successfully achieved with this reagent after a number of other methods failed.



Ruthenium tetroxide is a potent oxidant, however, and it readily attacks carbon-carbon double bonds.¹⁹ Primary alcohols are oxidized to carboxylic acids, methyl ethers give methyl esters, and benzyl ethers are oxidized to benzoate esters.



This reagent has been used in multistep syntheses to convert a tetrahydrofuran ring into a γ -lactone.



¹⁶ P. E. Morris, Jr., and D. E. Kiely, *J. Org. Chem.*, **52**, 1149 (1987).

¹⁷ P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, **46**, 3936 (1981).

¹⁸ R. M. Moriarty, H. Gopal, and T. Adams, *Tetrahedron Lett.*, 4003 (1970).

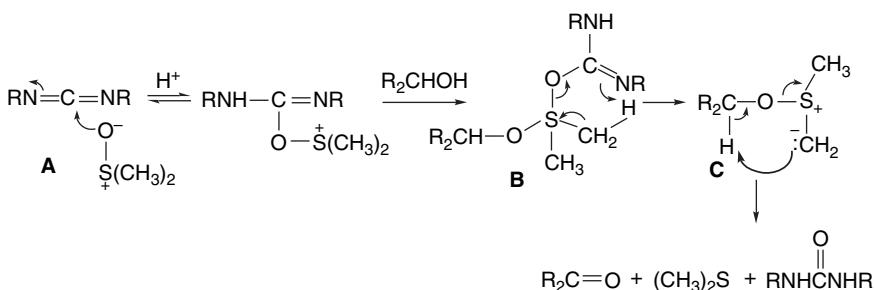
¹⁹ J. L. Courtney and K. F. Swansborough, *Rev. Pure Appl. Chem.*, **22**, 47 (1972); D. G. Lee and M. van den Engh, in *Oxidation*, Part B, W. S. Trahanovsky, ed., Academic Press, New York, 1973, Chap. IV.

²⁰ P. F. Schuda, M. B. Cichowitz, and M. P. Heinmann, *Tetrahedron Lett.*, **24**, 3829 (1983).

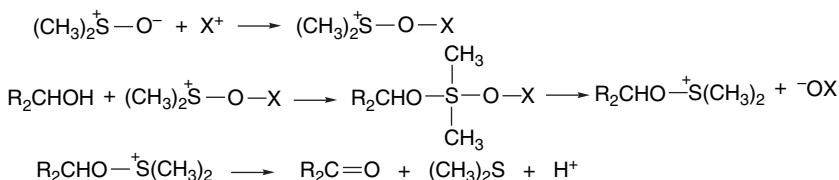
²¹ J.-S. Han and T. L. Lowary, *J. Org. Chem.*, **68**, 4116 (2003).

12.1.2. Other Oxidants

12.1.2.1. Oxidations Based on Dimethyl Sulfoxide. A very useful group of procedures for oxidation of alcohols to ketones employs dimethyl sulfoxide (DMSO) and any one of several electrophilic reagents, such as dicyclohexylcarbodiimide (DCCI), acetic anhydride, trifluoroacetic anhydride (TFAA), oxalyl chloride, or sulfur trioxide.²² The original procedure involved DMSO and DCCI.²³ The mechanism of the oxidation involves formation of intermediate **A** by nucleophilic attack by DMSO on the carbodiimide, followed by reaction of the intermediate with the alcohol.²⁴ A proton transfer leads to an alkoxysulfonium ylide that is converted to product by an intramolecular proton transfer and elimination.



The activation of DMSO toward the addition step can be accomplished by other electrophiles. All of these reagents are believed to form a sulfoxonium species by electrophilic attack at the sulfoxide oxygen. The addition of the alcohol and the departure of the sulfoxide oxygen as part of a leaving group generates an intermediate comparable to **C** in the carbodiimide mechanism.



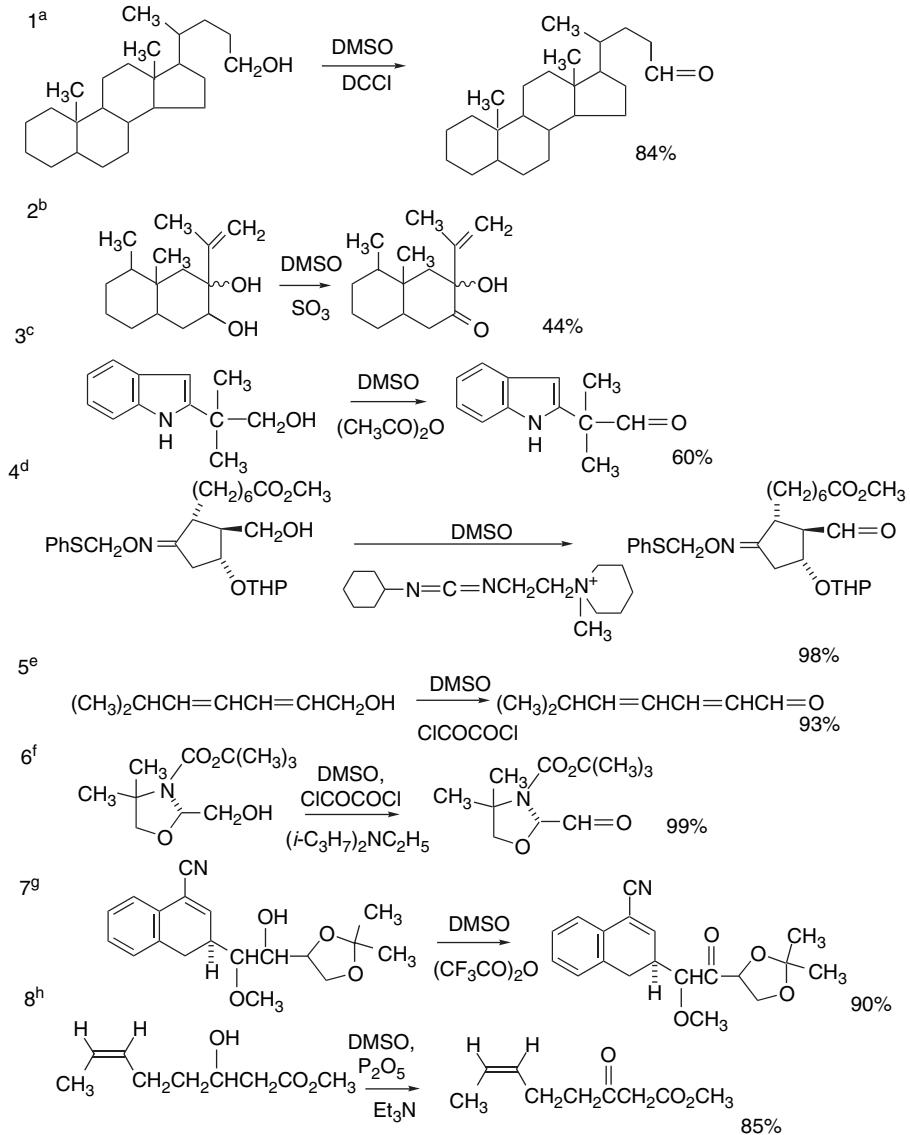
Preparatively useful procedures based on acetic anhydride,²⁵ trifluoroacetic anhydride,²⁶ and oxalyl chloride²⁷ have been developed. The last method, known as the *Swern oxidation*, is currently the most popular.

Scheme 12.3 gives some representative examples of these methods. Entry 1 is an example of the original procedure using DCCI. Entries 2 and 3 use SO_3 and $(\text{CH}_3\text{CO})_2\text{O}$, respectively, as the electrophilic reagents. Entry 3 is noteworthy in successfully oxidizing an alcohol without effecting the sensitive indole ring. Entry 4 is

- ²² A. J. Mancuso and D. Swern, *Synthesis*, 165 (1981); T. T. Tidwell, *Synthesis*, 857 (1990).
- ²³ K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661, 5670 (1965).
- ²⁴ J. G. Moffatt, *J. Org. Chem.*, **36**, 1909 (1971).
- ²⁵ J. D. Albright and L. Goldman, *J. Am. Chem. Soc.*, **89**, 2416 (1967).
- ²⁶ J. Yoshimura, K. Sato, and H. Hashimoto, *Chem. Lett.*, 1327 (1977); K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, **41**, 957 (1976); S. L. Huang, K. Omura, and D. Swern, *J. Org. Chem.*, **41**, 3329 (1976).
- ²⁷ A. J. Mancuso, S.-L. Huang, and D. Swern, *J. Org. Chem.*, **43**, 2480 (1978).

SECTION 12.1

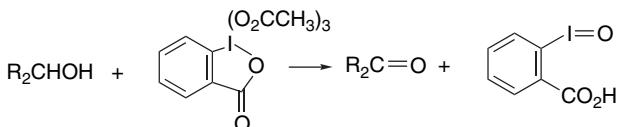
Oxidation of Alcohols to Aldehydes, Ketones, or Carboxylic Acids



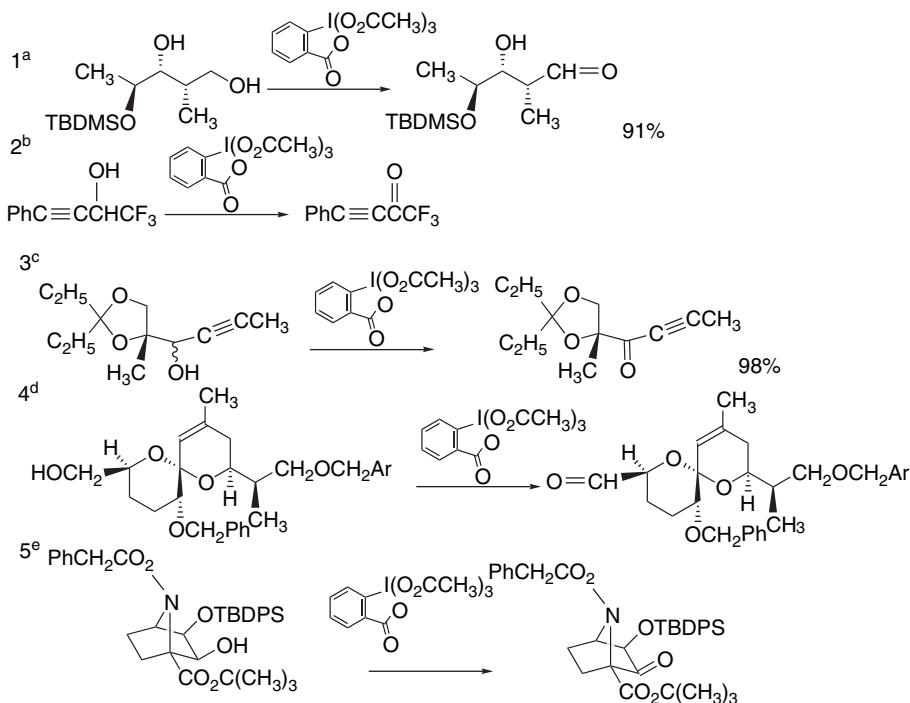
- a. J. G. Moffat, *Org. Synth.*, **47**, 25 (1967).
 - b. J. A. Marshall and G. M. Cohen, *J. Org. Chem.*, **36**, 877 (1971).
 - c. E. Houghton and J. E. Saxton, *J. Chem. Soc. C*, 595 (1969).
 - d. N. Finch, L. D. Vecchia, J. J. Fitt, R. Stephani, and I. Vlatta, *J. Org. Chem.*, **38**, 4412 (1973).
 - e. W. R. Roush, *J. Am. Chem. Soc.*, **102**, 1390 (1980).
 - f. A. Dondoni and D. Perrone, *Synthesis*, 527 (1997).
 - g. R. W. Franck and T. V. John, *J. Org. Chem.*, **45**, 1170 (1987).
 - h. D. F. Taber, J. C. Amadio Jr. and K.-Y. Jung, *J. Org. Chem.*, **52**, 5621 (1987).

an example of the use of a water-soluble carbodiimide as the activating reagent. The modified carbodiimide facilitates product purification by providing for easy removal of the urea by-product. Entries 5 and 6 are examples of the Swern procedure. Entry 7 uses TFAA as the electrophile. Entry 8, which uses the inexpensive reagent P_2O_5 as the electrophile, was conducted on a 60-g scale.

12.1.2.2. Oxidation by the Dess-Martin Reagent. Another reagent that has become important for laboratory synthesis is known as the *Dess-Martin reagent*,²⁸ which is a hypervalent iodine(V) compound.²⁹ The reagent is used in inert solvents such as chloroform or acetonitrile and gives rapid oxidation of primary and secondary alcohols. The by-product, *o*-iodosobenzoic acid, can be extracted with base and recycled.



Scheme 12.4. Oxidation by the Dess-Martin Reagent



a. P. R. Blakemore, P. J. Kocienski, A. Morley, and K. Muir, *J. Chem. Soc., Perkin Trans. I*, 955 (1999).

b. R. J. Linderman and D. M. Graves, *Tetrahedron Lett.*, **28**, 4259 (1987).

c. S. D. Burke, J. Hong, J. R. Lennox, and A. P. Mongin, *J. Org. Chem.*, **63**, 6952 (1998).

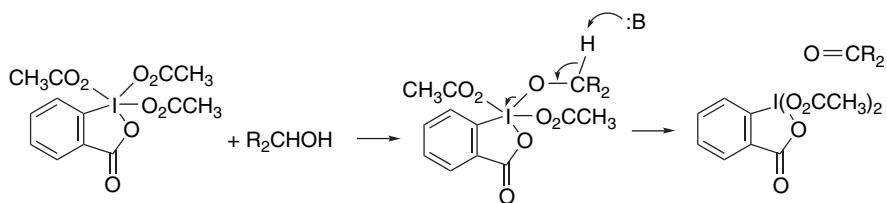
d. S. F. Sabes, R. A. Urbanek, and C. J. Forsyth, *J. Am. Chem. Soc.*, **120**, 2534 (1998).

e. B. P. Hart and H. Rapoport, *J. Org. Chem.*, **64**, 2050 (1999).

²⁸. D. B. Dess and J. C. Martin, *J. Org. Chem.*, **48**, 4155 (1983); R. E. Ireland and L. Liu, *J. Org. Chem.*, **58**, 2899 (1993); S. D. Meyer and S. L. Schreiber, *J. Org. Chem.*, **59**, 7549 (1994).

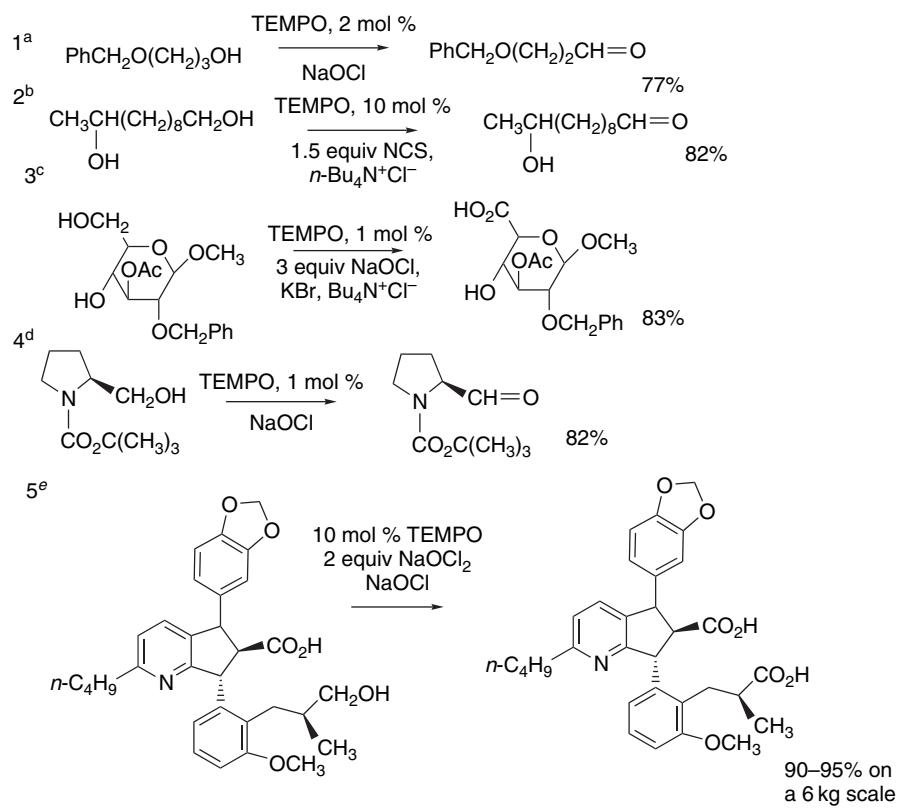
²⁹. T. Wirth and U. H. Hirt, *Synthesis*, 471 (1999).

The mechanism of the Dess-Martin oxidation involves exchange of the alcohol for acetate, followed by proton removal.³⁰



Scheme 12.4 shows several examples of the use of the Dess-Martin reagent.

Scheme 12.5. Oxidations Using TEMPO



a. B. G. Szczepankiewicz and C. H. Heathcock, *Tetrahedron*, **53**, 8853 (1997).

b. J. Einhorn, C. Einhorn, F. Ratajczak, and J.-L. Pierre, *J. Org. Chem.*, **61**, 7452 (1996).

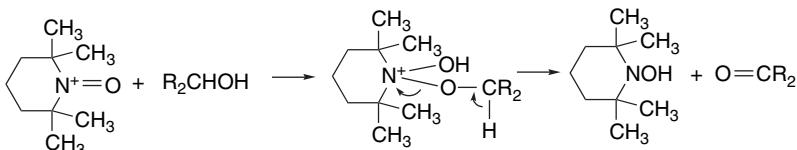
c. N. J. Davis and S. L. Flitsch, *Tetrahedron Lett.*, **34**, 1181 (1993).

d. M. R. Leanna, T. J. Sowin, and H. E. Morton, *Tetrahedron Lett.*, **33**, 5029 (1992).

e. Z. J. Song, M. Zhao, R. Desmond, P. Devine, D. M. Tscaen, R. Tillyer, L. Frey, R. Heid, F. Xu, B. Foster, J. Li, R. Reamer, R. Volante, E. J. Grabowski, U. H. Dolling, P. J. Reider, S. Okada, Y. Kato, and E. Mano, *J. Org. Chem.*, **64**, 9658 (1999).

³⁰. S. De Munari, M. Frigerio, and M. Santagostino, *J. Org. Chem.*, **61**, 9272 (1996).

12.1.2.3. Oxidations Using Oxoammonium Ions. Another oxidation procedure uses an oxoammonium ion, usually derived from the stable nitroxide tetramethylpiperidine nitroxide, TEMPO, as the active reagent.³¹ It is regenerated in a catalytic cycle using hypochlorite ion³² or NCS³³ as the stoichiometric oxidant. These reactions involve an intermediate adduct of the alcohol and the oxoammonium ion.

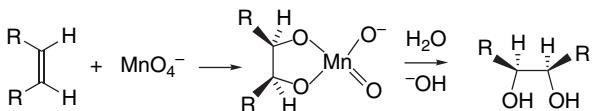


One feature of this oxidation system is that it can selectively oxidize primary alcohols in preference to secondary alcohols, as illustrated by Entry 2 in Scheme 12.5. The reagent can also be used to oxidize primary alcohols to carboxylic acids by a subsequent oxidation with sodium chlorite.³⁴ Entry 3 shows the selective oxidation of a primary alcohol in a carbohydrate to a carboxylic acid without affecting the secondary alcohol group. Entry 5 is a large-scale preparation that uses NaClO₂ in conjunction with bleach as the stoichiometric oxidant.

12.2. Addition of Oxygen at Carbon-Carbon Double Bonds

12.2.1. Transition Metal Oxidants

12.2.1.1. Dihydroxylation of Alkenes. The higher oxidation states of certain transition metals, particularly the permanganate ion and osmium tetroxide, are effective reagents for addition of two oxygen atoms at a carbon-carbon double bond. Under carefully controlled reaction conditions, potassium permanganate can effect conversion of alkenes to glycols. However, this oxidant is capable of further oxidizing the glycol with cleavage of the carbon-carbon bond. A cyclic manganese ester is an intermediate in these oxidations. Owing to the cyclic nature of this intermediate, the glycols are formed by *syn* addition.



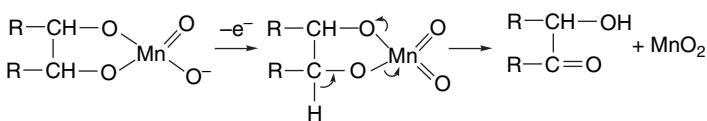
³¹ N. Merbouh, J. M. Bobbitt, and C. Brueckner, *Org. Prep. Proced. Int.*, **36**, 3 (2004).

³² R. Siedlecka, J. Skarzewski, and J. Mlochowski, *Tetrahedron Lett.*, **31**, 2177 (1990); T. Inokuchi, S. Matsumoto, T. Nishiyama, and S. Torii, *J. Org. Chem.*, **55**, 462 (1990); P. L. Anelli, S. Banfi, F. Montanari, and S. Quici, *J. Org. Chem.*, **54**, 2970 (1989); M. R. Leanna, T. J. Sowin, and H. E. Morton, *Tetrahedron Lett.*, **33**, 5029 (1992).

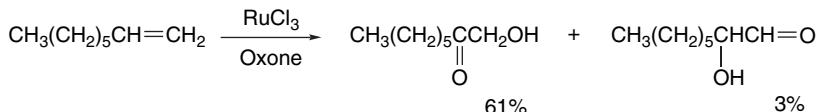
³³ J. Einhorn, C. Einhorn, F. Ratajczak, and J.-L. Pierre, *J. Org. Chem.*, **61**, 7452 (1996).

³⁴ P. M. Wovkulich, K. Shankaran, J. Kiegel, and M. R. Uskokovic, *J. Org. Chem.*, **58**, 832 (1993).

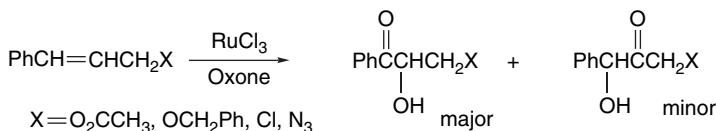
Ketols are also observed as products of permanganate oxidation of alkenes. The ketols are believed to be formed as a result of oxidation of the cyclic intermediate.³⁵



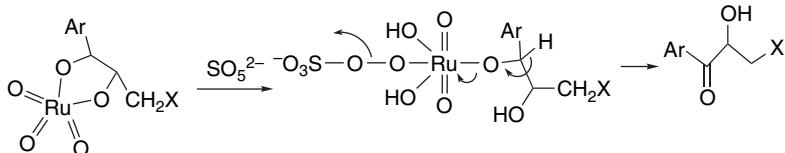
Ruthenium tetroxide can also be used in the oxidation of alkenes. Conditions that are selective for formation of ketols have been developed.³⁶ Use of 1 mol % of RuCl₃ and five equivalents of KHSO₅ (Oxone®) in an ethyl acetate-acetonitrile-water mixture gives mainly hydroxymethyl ketones from terminal alkenes.



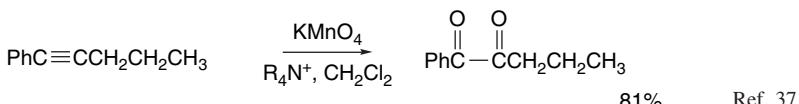
With aryl-substituted alkenes, the aryl ketone is the major product.



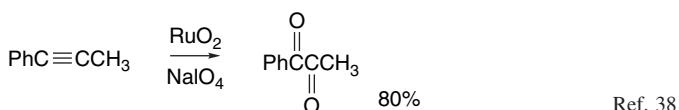
The mechanistic basis of this method depends on the use of excess peroxyulfate so that the major pathway leads to ketol rather than diol.



Permanganate ion can be used to oxidize acetylenes to diones.



A mixture of NaIO₄ and RuO₂ in a heterogeneous solvent system is also effective for this transformation.



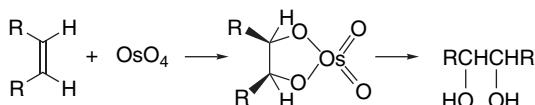
³⁵. S. Wolfe, C. F. Ingold, and R. U. Lemieux, *J. Am. Chem. Soc.*, **103**, 938 (1981); D. G. Lee and T. Chen, *J. Am. Chem. Soc.*, **111**, 7534 (1989).

³⁶. B. Plietker, *J. Org. Chem.*, **69**, 8287 (2004).

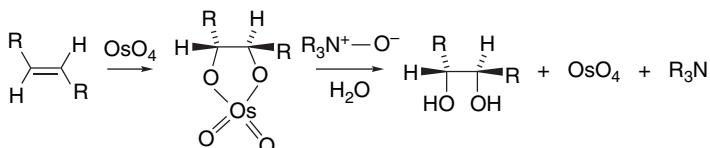
³⁷. D. G. Lee and V. S. Chang, *J. Org. Chem.*, **44**, 2726 (1979).

³⁸. R. Zibuck and D. Seebach, *Helv. Chim. Acta*, **71**, 237 (1988).

The most widely used reagent for oxidation of alkenes to glycols is osmium tetroxide. Osmium tetroxide is a highly selective oxidant that gives glycols by a stereospecific *syn* addition.³⁹ The reaction occurs through a cyclic osmate ester that is formed by a [3 + 2] cycloaddition.⁴⁰



The reagent is toxic and expensive but these disadvantages are minimized by methods that use only a catalytic amount of osmium tetroxide. A very useful procedure involves an amine oxide such as morpholine-*N*-oxide as the stoichiometric oxidant.⁴¹



t-Butyl hydroperoxide,⁴² barium chloride,⁴³ or potassium ferricyanide⁴⁴ can also be used as oxidants in catalytic procedures.

Scheme 12.6 provides some examples of oxidations of alkenes to glycols by both permanganate and osmium tetroxide. The oxidation by KMnO₄ in Entry 1 is done in cold aqueous solution. The reaction is very sensitive to the temperature control during the reaction. The reaction in Entry 2 was also done by the catalytic OsO₄ method using *N*-methylmorpholine-*N*-oxide in better (80%) yield. Note that the hydroxy groups are introduced from the less hindered face of the double bond. Entries 3 to 5 illustrate several of the catalytic procedures for OsO₄ oxidation. In each case the reaction is a stereospecific *syn* addition. Note also that in Entries 4 and 5 the double bond is conjugated with an EWG substituent, so the range of the reaction includes deactivated alkenes.

Osmium tetroxide oxidations can be highly enantioselective in the presence of chiral ligands. The most highly developed ligands are derived from the cinchona alkaloids dihydroquinidine (DHQD) and dihydroquinine (DHQ).⁴⁵ The most effective

- ^{39.} M. Schroeder, *Chem. Rev.*, **80**, 187 (1980).
- ^{40.} A. J. DelMonte, J. Haller, K. N. Houk, K. B. Sharpless, D. A. Singleton, T. Strassner, and A. A. Thomas, *J. Am. Chem. Soc.*, **119**, 9907 (1997); U. Pidun, C. Boehme, and G. Frenking, *Angew. Chem. Int'l. Ed. Engl.*, **35**, 2817 (1997).
- ^{41.} V. Van Rheezen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett.*, 1973 (1976).
- ^{42.} K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc.*, **98**, 1986 (1976); K. Akashi, R. E. Palermo, and K. B. Sharpless, *J. Org. Chem.*, **43**, 2063 (1978).
- ^{43.} L. Plaha, J. Weichert, J. Zvacek, S. Smolik, and B. Kakac, *Collect. Czech. Chem. Commun.*, **25**, 237 (1960); A. S. Kende, T. V. Bentley, R. A. Mader, and D. Ridge, *J. Am. Chem. Soc.*, **96**, 4332 (1974).
- ^{44.} M. Minato, K. Yamamoto, and J. Tsuji, *J. Org. Chem.*, **55**, 766 (1990); K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, and X.-L. Zhang, *J. Org. Chem.*, **57**, 2768 (1992); J. Eames, H. J. Mitchell, A. Nelson, P. O'Brien, S. Warren, and P. Wyatt, *Tetrahedron Lett.*, **36**, 1719 (1995).
- ^{45.} H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev.*, **94**, 2483 (1994).

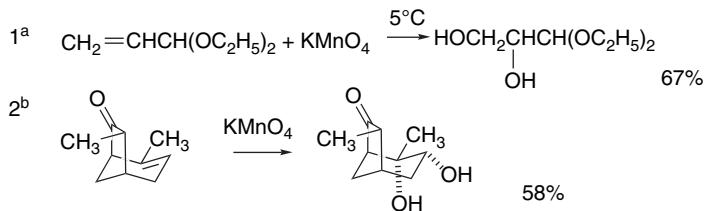
Scheme 12.6. Examples of *syn* Dihydroxylation of Alkenes

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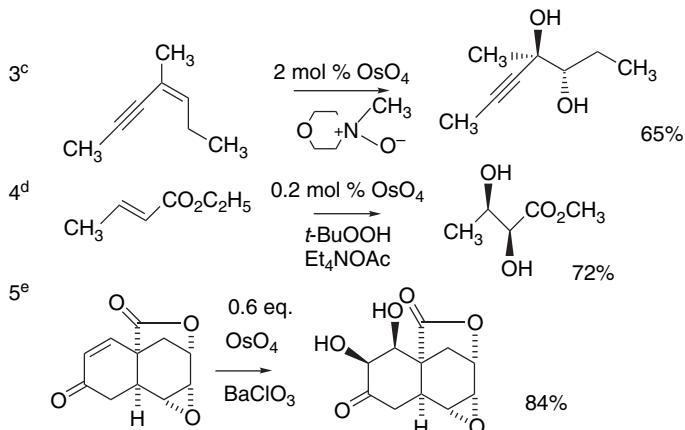
SECTION 12.2

Addition of Oxygen at
Carbon-Carbon Double
Bonds

A. Potassium permanganate



B. Osmium tetroxide

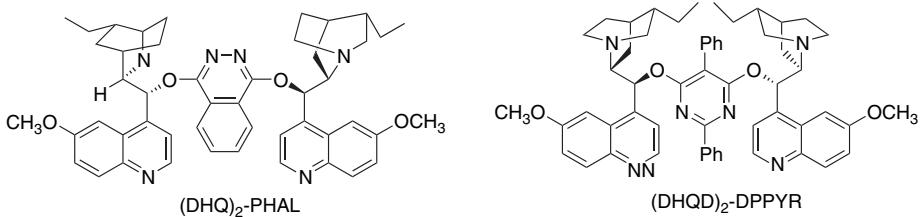
a. E. J. Witzeman, W. L. Evans, H. Haas, and E. F. Schroeder, *Org. Synth.*, **II**, 307 (1943).b. S. D. Larsen and S. A. Monti, *J. Am. Chem. Soc.*, **99**, 8015 (1977).c. E. J. Corey, P. B. Hopkins, S. Kim, S. Yoo, K. P. Nambiar, and J. R. Falck, *J. Am. Chem. Soc.*, **101**, 7131 (1979).d. K. Akashi, R. E. Palermo, and K. B. Sharpless, *J. Org. Chem.*, **43**, 2063 (1978).e. S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, *J. Am. Chem. Soc.*, **99**, 6066 (1977).

ligands are dimeric derivatives of these alkaloids.⁴⁶ These ligands both induce high enantioselectivity and accelerate the reaction.⁴⁷ Potassium ferricyanide is usually used as the stoichiometric oxidant. Optimization of the reaction conditions permits rapid and predictable dihydroxylation of many types of alkenes.⁴⁸ The premixed catalysts are available commercially and are referred to by the trade name AD-mix™. Several heterocyclic compounds including phthalazine (PHAL), pyrimidine (PYR), pyridazine (PYDZ), and diphenylpyrimidine (DPPYR) have been used as linking groups for the alkaloids.

⁴⁶. (a) G. A. Crispino, K. S. Jeong, H. C. Kolb, Z.-M. Wang, D. Xu, and K. B. Sharpless, *J. Org. Chem.*, **58**, 3785 (1993); (b) G. A. Crispino, A. Makita, Z.-M. Wang, and K. B. Sharpless, *Tetrahedron Lett.*, **35**, 543 (1994); (c) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, and X.-L. Zhang, *J. Org. Chem.*, **57**, 2768 (1992); (d) W. Amberg, Y. L. Bennani, R. K. Chadha, G. A. Crispino, W. D. Davis, J. Hartung, K. S. Jeong, Y. Ogino, T. Shibata, and K. B. Sharpless, *J. Org. Chem.*, **58**, 844 (1993); (e) H. Becker, S. B. King, M. Taniguchi, K. P. M. Vanhessche, and K. B. Sharpless, *J. Org. Chem.*, **60**, 3940 (1995).

⁴⁷. P. G. Anderson and K. B. Sharpless, *J. Am. Chem. Soc.*, **115**, 7047 (1993).

⁴⁸. T. Gobel and K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.*, **32**, 1329 (1993).



Empirical analysis led to the predictive model for enantioselectivity shown in Figure 12.1.^{46c,49} The two alkaloids are of opposite chirality and give enantiomeric products. The commercial reagents are designated AD-mix- α and AD-mix- β . The configuration of the products can be predicted by a model based on the relative size of the substituent groups. *E*-Alkenes give the best fit to the binding pocket and give the highest reactivity and enantioselectivity.

There have been two computational studies of the basis for the catalysis and enantioselectivity. A study of the reaction of styrene with the (DHQD)₂PYDZ ligand was done using a hybrid DFT/MM protocol.⁵⁰ Two orientations of the styrene molecule were found that were about 3.0 kcal/mol more favorable than any of the others. These TSs are shown in Figure 12.2. Both these structures predict the observed *R*-configuration for the product. Most of the difference among the various structures is found in the MM terms and they are exothermic, that is, there are *net attractive forces involved in the binding of the reactant*. The second study used stilbene as the reactant and (DHQD)₂PHAL as the catalyst ligand.⁵¹ This study arrives at the TS shown in Figure 12.3. The two phenyl groups of stilbene occupy *both* of the sites found for the two low-energy TSs for styrene.

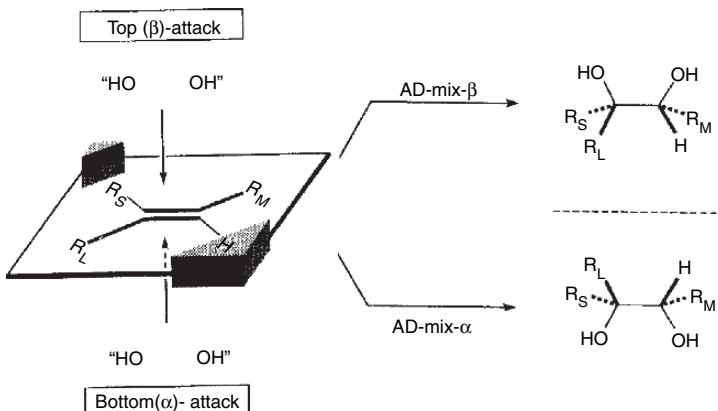


Fig. 12.1. Predictive model for enantioselective dihydroxylation by dimeric alkaloid catalysts. (DHQD)₂ catalysts give β -approach; (DHQ)₂ catalysts give α -approach. Reproduced from *J. Org. Chem.*, **57**, 2768 (1992), by permission of the American Chemical Society.

⁴⁹ H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev.*, **94**, 2483 (1994).

⁵⁰ G. Ujaque, F. Maseras, and A. Lledos, *J. Am. Chem. Soc.*, **121**, 1317 (1999).

⁵¹ P.-O. Norrby, T. Rasmussen, J. Haller, T. Strassner, and K. N. Houk, *J. Am. Chem. Soc.*, **121**, 10186 (1999).

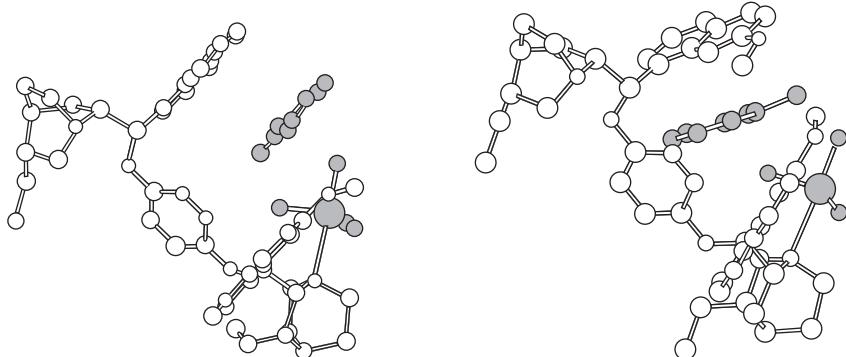


Fig. 12.2. Two lowest-energy transition structures for oxidation of styrene by $(DHQD)_2PYDZ-OsO_4$ catalysts. The structure on the left is about 0.4 kcal more stable than the one on the right. Both structures predict the formation of *R*-styrene oxide. Reproduced from *J. Am. Chem. Soc.*, **121**, 1317 (1999), by permission of the American Chemical Society.

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

Scheme 12.7 gives some examples of enantioselective hydroxylations using these reagents. Entry 1 is an allylic ether with a terminal double bond. *para*-Substituted derivatives also gave high e.e. values, but some *ortho* substituents led to lower e.e. values. Entry 2 is one of several tertiary allylic alcohols that gave excellent results. Entry 3 is a *trans*-substituted alkene with rather large (but unbranched) substituents. The inclusion of methanesulfonamide, as in this example, has been found to be beneficial for di- and trisubstituted alkenes. It functions by speeding the hydrolysis of the osmate ester intermediate. The product in this case goes on to cyclize to the

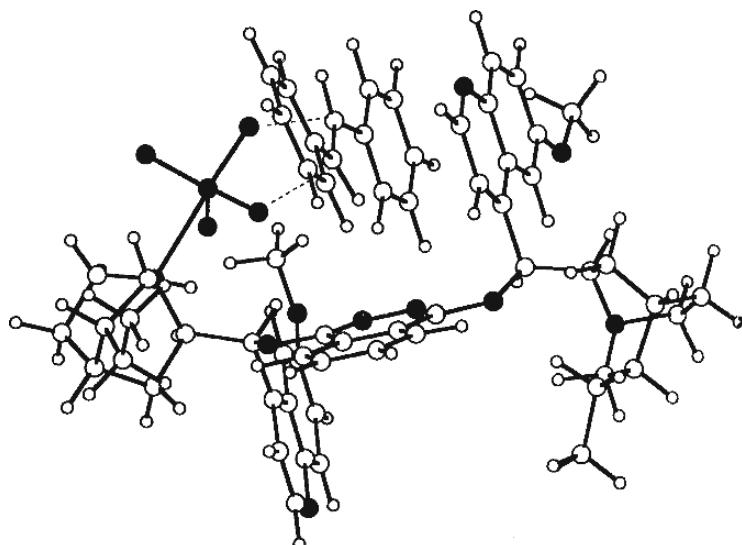
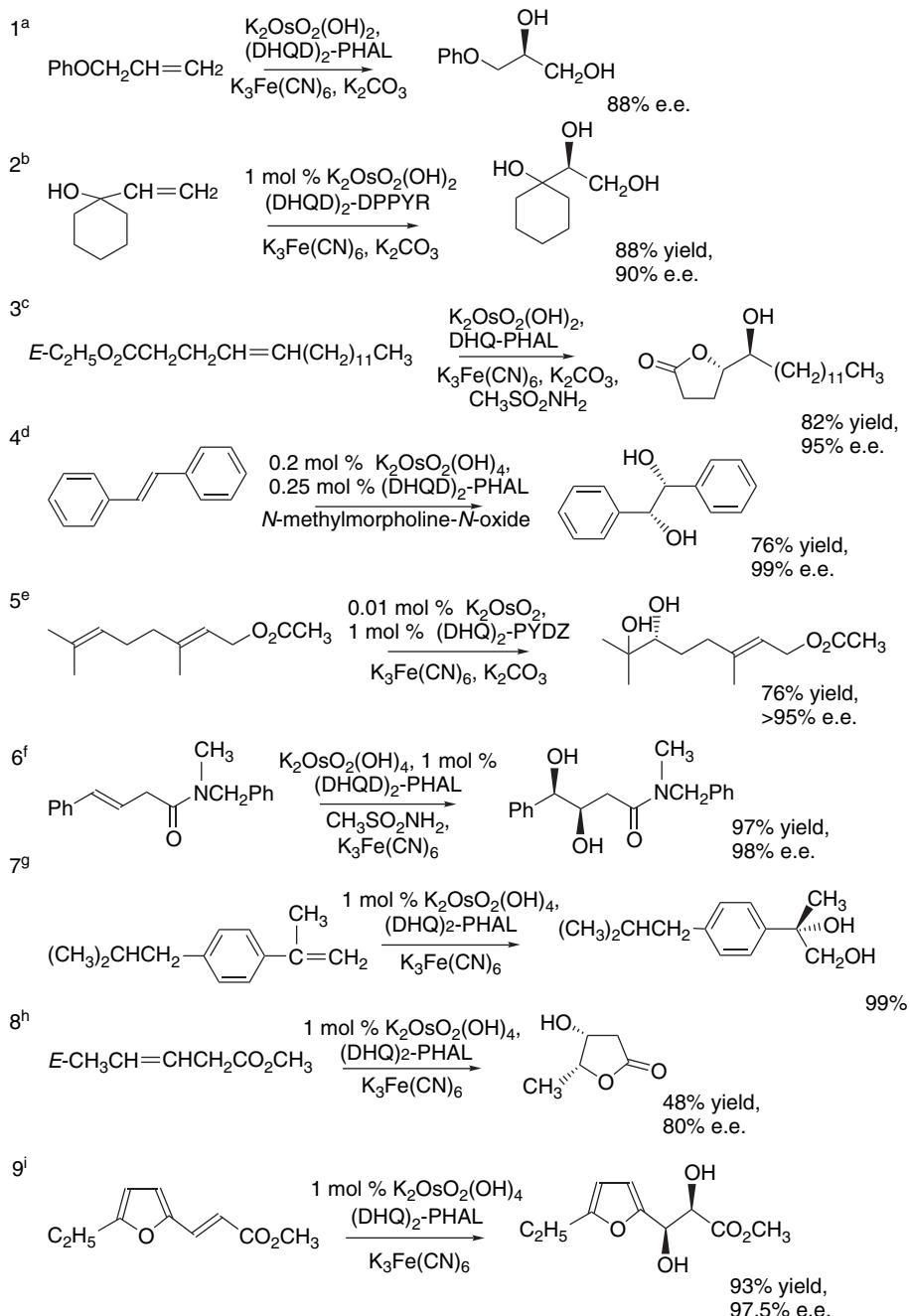


Fig. 12.3. Transition structure for oxidation of stilbene by $(DHQD)_2PHAL-OsO_4$ catalyst. Reproduced from *J. Am. Chem. Soc.*, **121**, 10186 (1999), by permission of the American Chemical Society.

Scheme 12.7. Enantioselective Osmium-Catalyzed Dihydroxylation of Alkenes



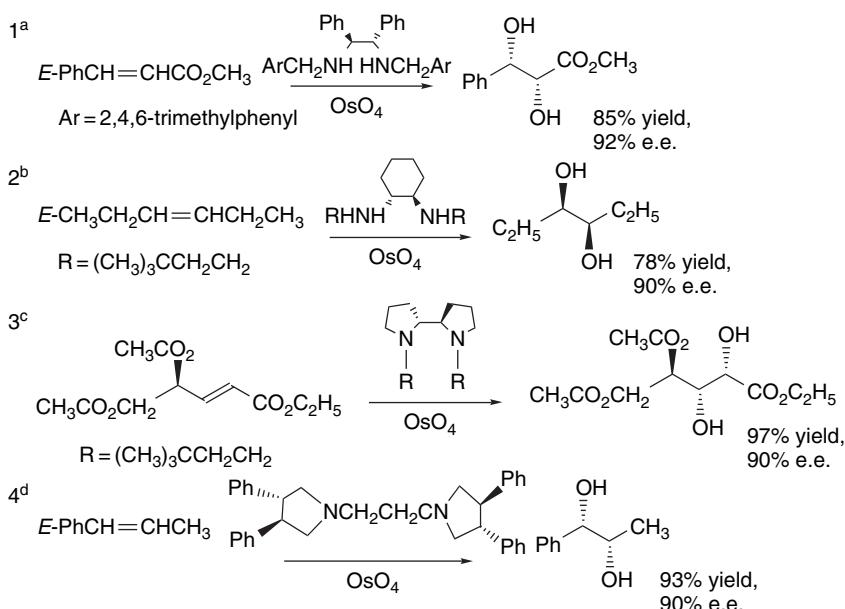
- a. Z.-M. Wang, X.-L. Zhang, and K. B. Sharpless, *Tetrahedron Lett.*, **34**, 2267 (1993).
 b. Z.-M. Wang and K. B. Sharpless, *Tetrahedron Lett.*, **34**, 8225 (1993).
 c. Z.-M. Wang, X.-L. Zhang, K. B. Sharpless, S. C. Sinha, A. Sinha-Bagchi, and E. Keinan, *Tetrahedron Lett.*, **33**, 6407 (1992).
 d. H. T. Chang and K. B. Sharpless, *J. Org. Chem.*, **61**, 6456 (1996).
 e. E. J. Corey, M. C. Noe, and W.-C. Shieh, *Tetrahedron Lett.*, **34**, 5995 (1993).
 f. Y. L. Bennani and K. B. Sharpless, *Tetrahedron Lett.*, **34**, 2079 (1993).
 g. H. Ishibashi, M. Maeki, J. Yagi, M. Ohba, and T. Kanai, *Tetrahedron*, **55**, 6075 (1999).
 h. T. Berkenbusch and R. Bruckner, *Tetrahedron*, **54**, 11461 (1998).
 i. T. Taniguchi, M. Takeuchi, and K. Ogasawara, *Tetrahedron: Asymmetry*, **9**, 1451 (1998).

observed lactone. This particular oxidation was also carried out with $(DHQD)_2\text{-PHAL}$, which gave the enantiomeric lactone. Entry 4 is an optimized oxidation of stilbene that was done on a 1-kg scale. Entry 5 is the dihydroxylation of geranyl acetate that shows selectivity for the 6,7-double bond. Entry 6 involves an unsaturated amide and required somewhat higher catalyst loading than normal. Entry 7 provided a starting material for the enantioselective synthesis of *S*-ibuprofen. The reaction in Entry 8 was used to prepare the lactone shown (and its enantiomer) as starting materials for enantioselective synthesis of several natural products. The furan synthesized in Entry 9 was used to prepare a natural material by a route involving eventual oxidation of the furan ring.

Various other chiral diamines have also been explored for use with OsO_4 , some of which are illustrated in Scheme 12.8. They presumably function by forming hexacoordinate chelates with OsO_4 . The reactant in Entry 3 also raises the issue of diastereoselectivity with respect to the allylic substituent. Normally, the dihydroxylation is *anti* toward such substituents.⁵² There are thus matched and mismatched combinations with the chiral osmium ligand. The *R, R*-diamine shown gives the matched combination and leads to high diastereoselectivity, as well as high enantioselectivity.

12.2.1.2. Transition Metal–Catalyzed Epoxidation of Alkenes. Other transition metal oxidants can convert alkenes to epoxides. The most useful procedures involve *t*-butyl hydroperoxide as the stoichiometric oxidant in combination with vanadium or

Scheme 12.8. Enantioselective Hydroxylation Using Chiral Diamines



a. E. J. Corey, P. D. Jardine, S. Virgil, P.-W. Yuen, and R. D. Connell, *J. Am. Chem. Soc.*, **111**, 9243 (1989).

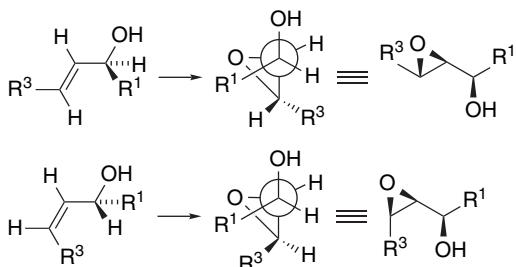
b. S. Hannessian, P. Meffre, M. Girard, S. Beaudoïn, J.-Y. Sanceau, and Y. Bennani, *J. Org. Chem.*, **58**, 1991 (1993).

c. T. Oishi, K. Iida, and M. Hirama, *Tetrahedron Lett.*, **34**, 3573 (1993).

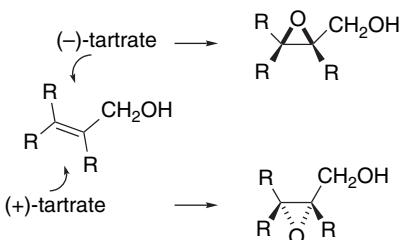
d. K. Tomioka, M. Nakajima, and K. Koga, *Tetrahedron Lett.*, **31**, 1741 (1990).

⁵² J. K. Cha, W. J. Christ, and Y. Kishi, *Tetrahedron*, **40**, 2247 (1984).

titanium compounds. The most reliable substrates for oxidation are allylic alcohols. The hydroxy group of the alcohol plays both an activating and stereodirecting role in these reactions. *t*-Butyl hydroperoxide and a catalytic amount of VO(acac)₃ convert allylic alcohols to the corresponding epoxides in good yields.⁵³ The reaction proceeds through a complex in which the allylic alcohol is coordinated to vanadium by the hydroxy group. In cyclic alcohols, this results in epoxidation *cis* to the hydroxy group. In acyclic alcohols the observed stereochemistry is consistent with a TS in which the double bond is oriented at an angle of about 50° to the coordinated hydroxy group. This TS leads to diastereoselective formation of the *syn*-alcohol. This stereoselectivity is observed for both *cis*- and *trans*-disubstituted allylic alcohols.⁵⁴



The epoxidation of allylic alcohols can also be effected by *t*-butyl hydroperoxide and titanium tetraisopropoxide. When enantiomerically pure tartrate ligands are included, the reaction is highly enantioselective. This reaction is called the *Sharpless asymmetric epoxidation*.⁵⁵ Either the (+) or (−) tartrate ester can be used, so either enantiomer of the desired product can be obtained.

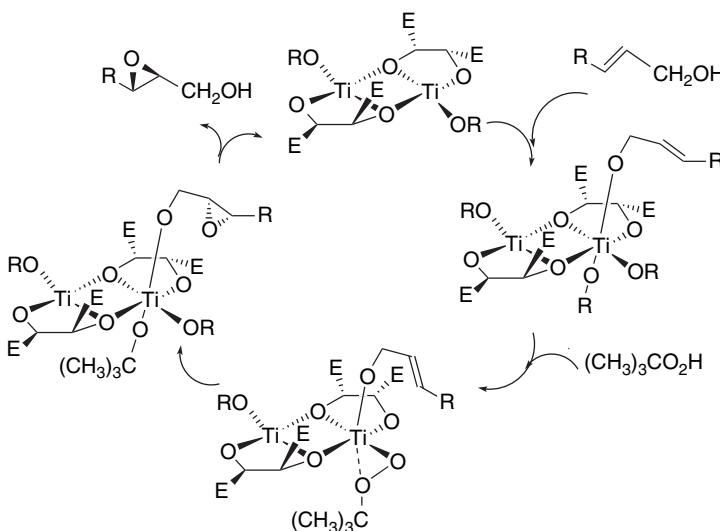


The mechanism by which the enantioselective oxidation occurs is generally similar to that for the vanadium-catalyzed oxidations. The allylic alcohol serves to coordinate the substrate to titanium. The tartrate esters are also coordinated at titanium, creating a chiral environment. The active catalyst is believed to be a dimeric species, and the mechanism involves rapid exchange of the allylic alcohol and *t*-butylhydroperoxide at the titanium ion.

⁵³ K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).

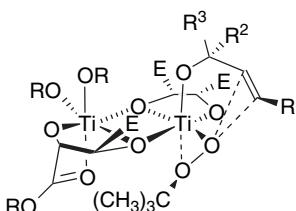
⁵⁴ E. D. Mihelich, *Tetrahedron Lett.*, 4729 (1979); B. E. Rossiter, T. R. Verhoeven, and K. B. Sharpless, *Tetrahedron Lett.*, 4733 (1979).

⁵⁵ For reviews, see A. Pfenniger, *Synthesis*, 89 (1986); R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, I. Ojima, ed., VCH Publishers, New York, 1993, pp. 103–158.



This method has proven to be an extremely useful means of synthesizing enantiomerically enriched compounds. Various improvements in the methods for carrying out the Sharpless oxidation have been developed.⁵⁶ The reaction can be done with catalytic amounts of titanium isopropoxide and the tartrate ligand.⁵⁷ This procedure uses molecular sieves to sequester water, which has a deleterious effect on both the rate and enantioselectivity of the reaction.

The orientation of the reactants is governed by the chirality of the tartrate ligand. In the TS an oxygen atom from the peroxide is transferred to the double bond. The enantioselectivity is consistent with a TS such as that shown below.⁵⁸



There has been a DFT (BLYP/6-31G*) study of the TS and its relationship to the enantioselectivity of the reaction.⁵⁹ The strategy used was to build up the model by successively adding components. First the titanium coordination sphere, including an alkene and peroxide group, was modeled (Figure 12.4a). In Figure 12.4b, the diol

- ⁵⁶. J. G. Hill, B. E. Rossiter, and K. B. Sharpless, *J. Org. Chem.*, **48**, 3607 (1983); L. A. Reed, III, S. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **104**, 6468 (1982).
- ⁵⁷. R. M. Hanson and K. B. Sharpless, *J. Org. Chem.*, **51**, 1922 (1986); Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765 (1987).
- ⁵⁸. V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 6237 (1981); K. B. Sharpless, S. S. Woodard, and M. G. Finn, *Pure Appl. Chem.*, **55**, 1823 (1983); M. G. Finn and K. B. Sharpless, in *Asymmetric Synthesis*, Vol. 5, J. D. Morrison, ed., Academic Press, New York, 1985, Chap 8; M. G. Finn and K. B. Sharpless, *J. Am. Chem. Soc.*, **113**, 113 (1991); B. H. McKee, T. H. Kalantar, and K. B. Sharpless, *J. Org. Chem.*, **56**, 6966 (1991); For an alternative description of the origin of enantioselectivity, see E. J. Corey, *J. Org. Chem.*, **55**, 1693 (1990).
- ⁵⁹. Y.-D. Wu and D. F. W. Lai, *J. Am. Chem. Soc.*, **117**, 11327 (1995).

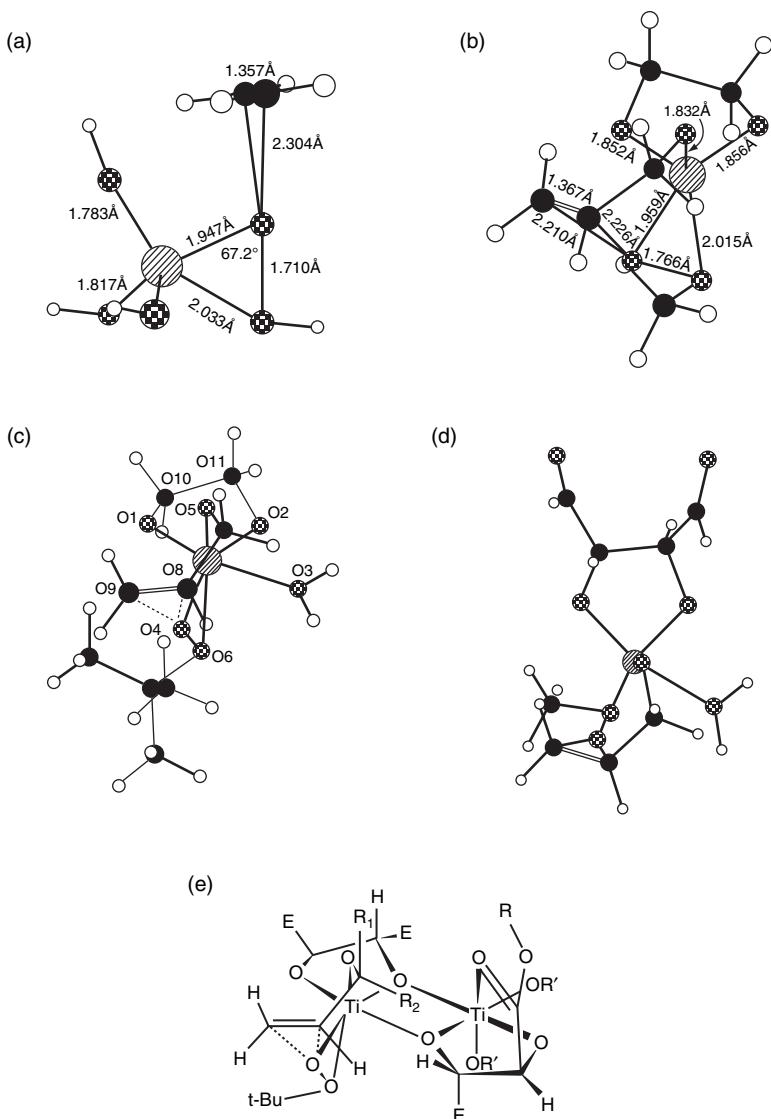


Fig. 12.4. Successive models of the transition state for Sharpless epoxidation. (a) the hexacoordinate Ti core with uncoordinated alkene; (b) Ti with methylhydroperoxide, allyl alcohol, and ethanediol as ligands; (c) monomeric catalytic center incorporating *t*-butylhydroperoxide as oxidant; (d) monomeric catalytic center with formyl groups added; (e) dimeric transition state with chiral tartrate model ($\text{E} = \text{CH} = \text{O}$). Reproduced from *J. Am. Chem. Soc.*, **117**, 11327 (1995), by permission of the American Chemical Society.

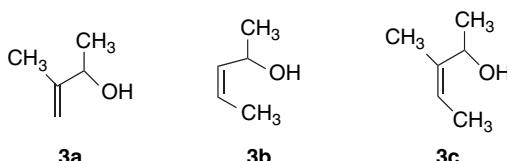
ligand and allylic alcohol were added to the coordination sphere. Then the steric bulk associated with the hydroperoxide was added (Figure 12.4c), and finally the tartrate ligands were added (using formyl groups as surrogates; Figure 12.4d). This led successively to TSs of increasingly detailed structure. The energies were minimized to identify the most stable structure at each step. The key features of the final TS model are the following: (1) The peroxide-titanium interaction has a spiro, rather than

planar, arrangement in the TS for oxygen transfer. (2) The orientation of the alkyl group of the peroxide plays a key role in the enantioselectivity, which is consistent with the experimental observation that less bulky hydroperoxides give much lower enantioselectivity. (3) The C–O bond of the allylic alcohol bisects the Ti–O bond formed by the water and peroxy ligands. (4) The tartrate groups at the active catalytic center are in equatorial positions and do not coordinate to titanium. This implies a conformation flip of the diolate ring as part of the activation process, since the ester groups are in axial positions in the dimeric catalyst.

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

Owing to the importance of the allylic hydroxy group in coordinating the reactant to the titanium, the structural relationship between the double bond and the hydroxy group is crucial. Homoallylic alcohols can be oxidized but the degree of enantioselectivity is reduced. Interestingly, the facial selectivity is reversed from that observed with allylic alcohols.⁶⁰ Compounds lacking a coordinating hydroxy group are not reactive under the standard reaction conditions.

Substituted allylic alcohols also exhibit diastereoselectivity. A DFT study has examined the influence of alkyl substituents in the allylic alcohol on the stereoselectivity.⁶¹ Alcohols **3a**, **3b**, and **3c** were studied. The catalytic entity was modeled by $\text{Ti}(\text{OH})_4\text{-CH}_3\text{OOH}$. This approach neglects the steric influence of the *t*-butyl and tartrate ester groups and focuses on the structural features of the allylic alcohols, which are placed on the catalytic core in their minimum energy conformation. Figure 12.5 shows these conformations. The TS structural parameters were derived from the Wu-Lai TS model (see Figure 12.4). The relative energies of the TSs leading to the *erythro* and *threo* products for each alcohol were compared (Figure 12.6). A solvent dielectric chosen to simulate CH_2Cl_2 was used. The general conclusion drawn from this study is that the reactant conformation is the critical feature determining the diastereoselectivity of the epoxidation.



In allylic alcohols with $\text{A}^{1,3}$ strain, the main product is *syn*. A methyl substituent at R^4 leads to the methyl group being positioned *anti* to the complexed oxidant. If R^4 is hydrogen, a TS with the methyl group in an “inside” position is favored, as shown in Figure 12.6.

The two TSs for **3a** are shown in Figure 12.7. **TS A** also has a more favorable orientation of the spiro ring structure. The ideal angle is 90° , at which point the two rings are perpendicular. This angle is 78.2° in **TS A** and 36.2° in **TS B**. **TS A** has a $\text{O}(1)\text{-C}(2)\text{-C}(3)\text{-C}(4)$ angle of 35.6° , **TS B** has a corresponding angle of 96.1° . Based on the reactant conformational profile, this will introduce about 0.7 kcal more

⁶⁰. B. E. Rossiter and K. B. Sharpless, *J. Org. Chem.*, **49**, 3707 (1984).

⁶¹. M. Cui, W. Adam, J. H. Shen, X. M. Luo, X. J. Tan, K. X. Chen, R. Y. Ji, and H. L. Jiang, *J. Org. Chem.*, **67**, 1427 (2002).

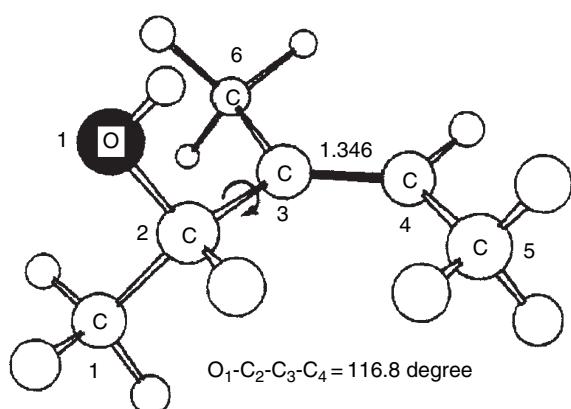
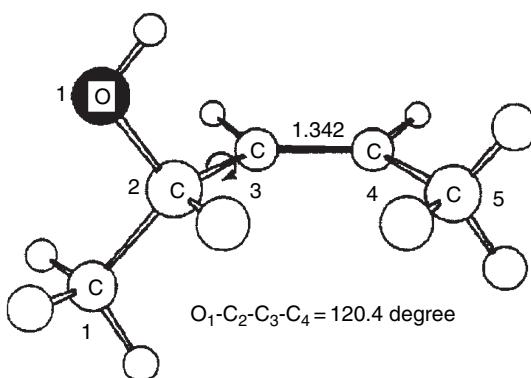
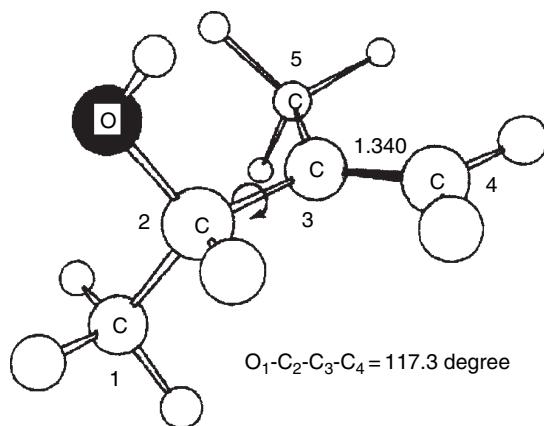


Fig. 12.5. Minimum energy conformations for allylic alcohol. **3a**, **3b**, and **3c**. Reproduced from *J. Org. Chem.*, **67**, 1427 (2002), by permission of the American Chemical Society.

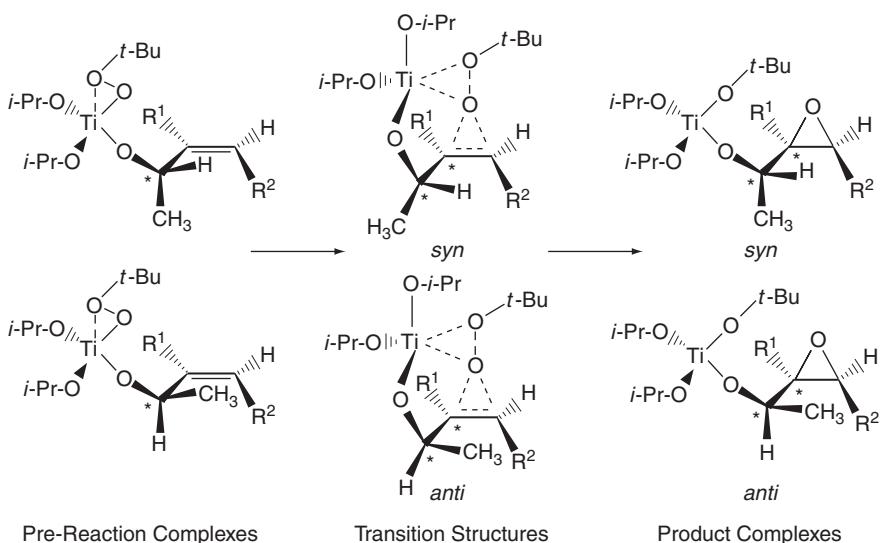


Fig. 12.6. Conformational factors affecting *syn* and *anti* diastereoselectivity in Sharpless epoxidation. If substituent $R^4 > H$, $A^{1,3}$ strain favors the *syn* product. If $R^4 = H$, the preferred transition structure leads to *anti* product. Reproduced from *J. Org. Chem.*, **67**, 1427 (2002), by permission of the American Chemical Society.

strain in **TS B** than in **TS A**. Similar analyses were done on the two TSs for **3b** and **3c**. The TS energies were used to compare computational ΔE_a with experimental diastereoselectivity. Whereas **TS A** is favored for **3a**, **TS B** is favored for **3b** and **3c**, in agreement with the experimental stereoselectivity.

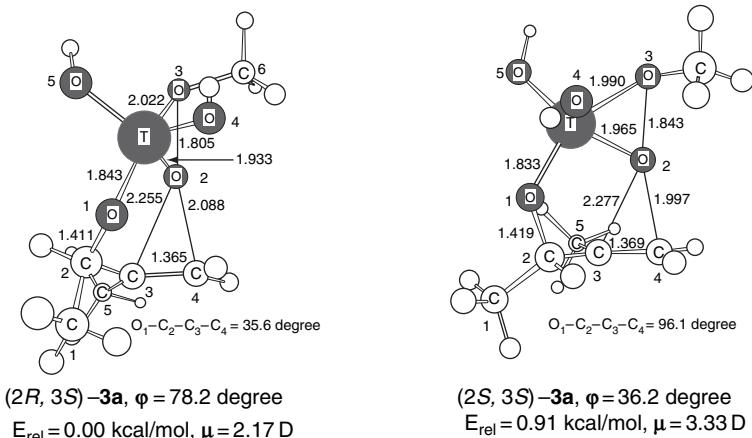
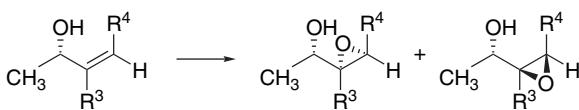


Fig. 12.7. Alternate orientations of 3-methylbut-3-en-1-ol (**3a**) in the transition state for Ti-mediated epoxidation. Angle ϕ is the inter-ring angle of the spiro rings. Reproduced from *J. Org. Chem.*, **67**, 1427 (2002), by permission of the American Chemical Society.

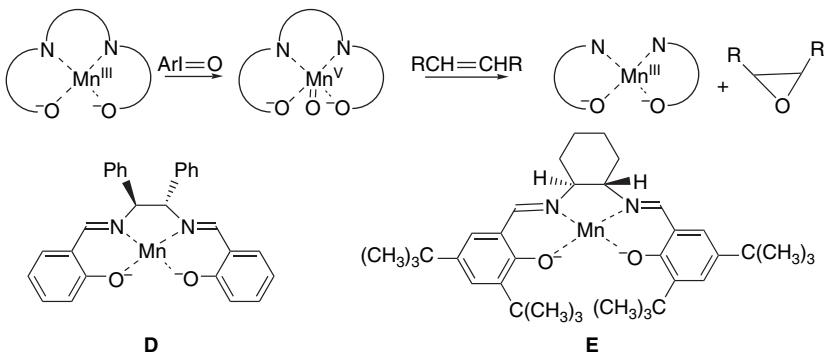


	R ³	R ⁴	predicted	observed
3a	CH ₃	H	12:88	22:78
3b	H	CH ₃	92:8	91:9
3c	CH ₃	CH ₃	77:23	83:17

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

Scheme 12.9 gives some examples of enantioselective oxidation of allylic alcohols. Entry 1 is a representative procedure, as documented in an *Organic Syntheses* preparation. The reaction in Entry 2 was used to prepare a starting material for synthesis of leukotriene C-1. Entry 3 is an example incorporating the use of molecular sieves. The reaction in Entry 4 was the departure point in a synthesis of part of the polyether antibiotic X-206. Entry 5 is another example of the procedure using molecular sieves. The catalyst loading in this reaction is 5%. The reaction in Entry 6 is diastereoselective for the *anti* isomer. Entry 7 also shows a case of diastereoselectivity, in this instance with respect to the 4-methyl group. Note that both of these reactions involve oxidation of the alkene from the same face, although they differ in configuration at C(4). Thus, the enantioselectivity is under reagent control.

Several catalysts that can effect enantioselective epoxidation of unfunctionalized alkenes have been developed, most notably manganese complexes of diimines derived from salicylaldehyde and chiral diamines (salens).⁶²



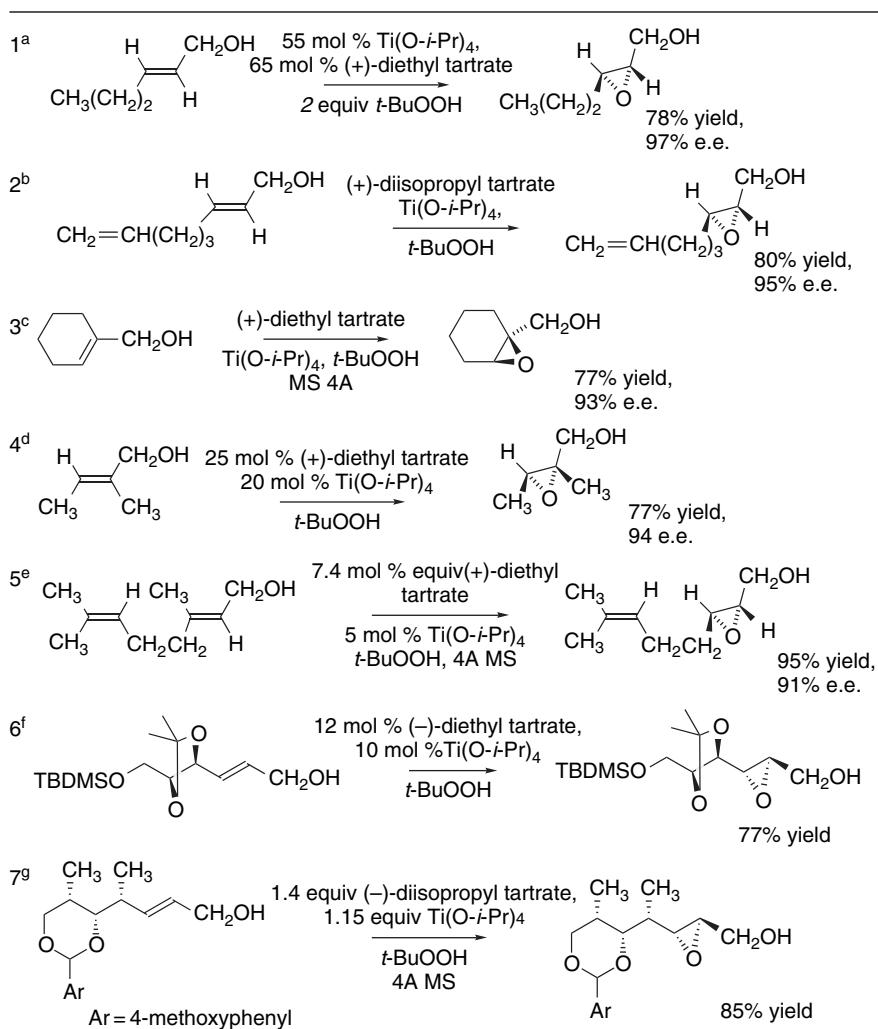
These catalysts are used in conjunction with a stoichiometric amount of an oxidant and the active oxidant is believed to be an oxo Mn(V) species. The stoichiometric oxidants that have been used include NaOCl,⁶³ periodate,⁶⁴ and amine oxides.⁶⁵ Various other

⁶². W. Zhang, J. L. Loebach, S. R. Wilson, and E. N. Jacobsen, *J. Am. Chem. Soc.*, **112**, 2801 (1990); E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, and L. Deng, *J. Am. Chem. Soc.*, **113**, 7063 (1991).

⁶³. W. Zhang and E. N. Jacobsen, *J. Org. Chem.*, **56**, 2296 (1991); B. D. Brandes and E. N. Jacobsen, *J. Org. Chem.*, **59**, 4378 (1994).

⁶⁴. P. Pietikainen, *Tetrahedron Lett.*, **36**, 319 (1995).

⁶⁵. M. Palucki, P. J. Pospisil, W. Zhang, and E. N. Jacobsen, *J. Am. Chem. Soc.*, **116**, 9333 (1994).



a. J. G. Hill and K. B. Sharpless, *Org. Synth.*, **63**, 66 (1985).

b. B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 464 (1981).

c. Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765 (1987).

d. D. A. Evans, S. L. Bender, and J. Morris, *J. Am. Chem. Soc.*, **110**, 2506 (1988).

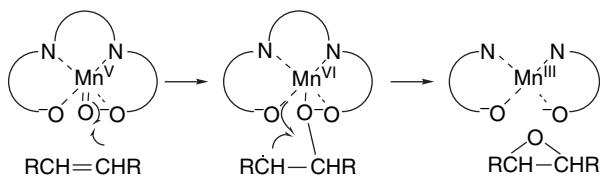
e. R. M. Hanson and K. B. Sharpless, *J. Org. Chem.*, **51**, 1922 (1986).

f. A. K. Ghosh and Y. Wang, *J. Org. Chem.*, **64**, 2789 (1999).

g. J. A. Marshall, Z.-H. Lu, and B. A. Johns, *J. Org. Chem.*, **63**, 817 (1998).

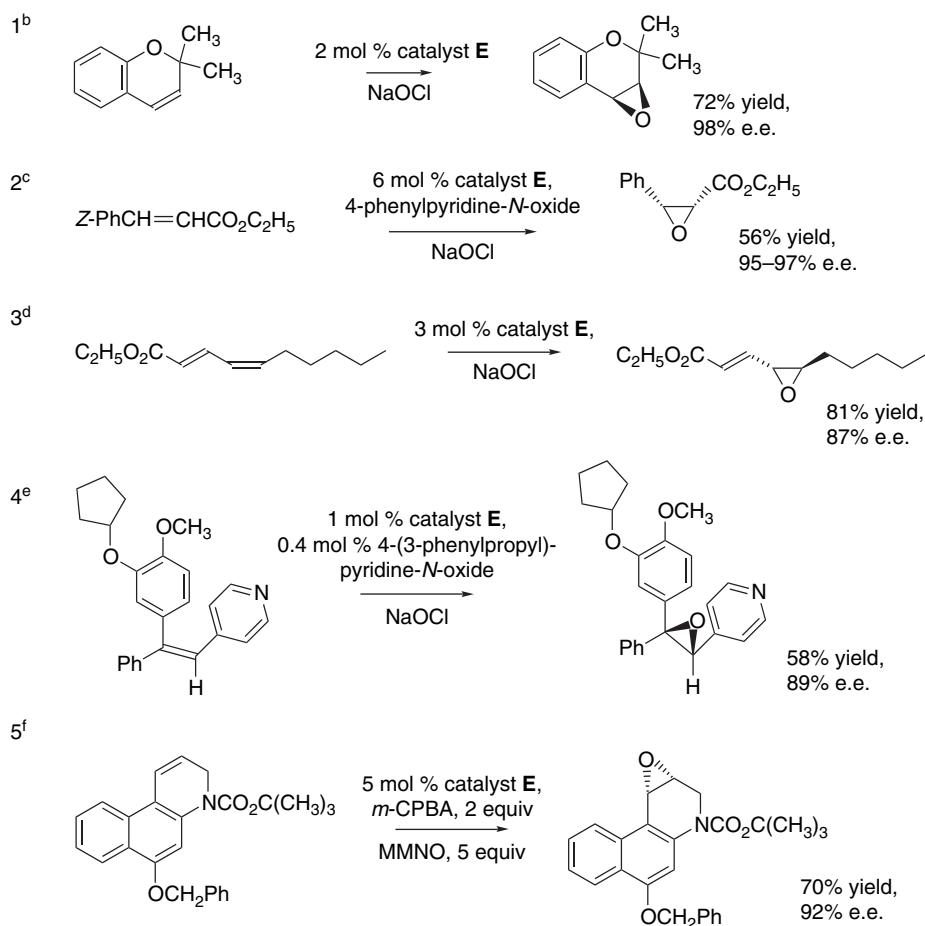
chiral salen-type ligands have also been explored.⁶⁶ These epoxidations are not always stereospecific with respect to the alkene geometry, which is attributed to an electron transfer mechanism that involves a radical intermediate.

⁶⁶. N. Hosoya, R. Irie, and T. Katsuki, *Synlett*, 261 (1993); S. Chang, R. M. Heid, and E. N. Jacobsen, *Tetrahedron Lett.*, **35**, 669 (1994).



Scheme 12.10 gives some examples of these oxidations. Entry 1 is one of several aryl-conjugated alkenes that were successfully epoxidized. Entry 2 is a reaction that was applied to enantioselective synthesis of the taxol side chain. Entry 3 demonstrates

Scheme 12.10. Enantioselective Epoxidation with Chiral Manganese Catalysts^a



a. The structure of catalyst E is shown on p. 1088.

b. E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, and L. Deng, *J. Am. Chem. Soc.*, **113**, 7063 (1991).

c. L. Deng and E. N. Jacobsen, *J. Org. Chem.*, **57**, 4320 (1992).

d. S. Chang, N. H. Lee, and E. N. Jacobsen, *J. Org. Chem.*, **58**, 6939 (1993).

e. J. E. Lynch, W.-B. Choi, H. R. O. Churchill, R. P. Volante, R. A. Reamer, and R. G. Ball, *J. Org. Chem.*, **62**, 9223 (1997).

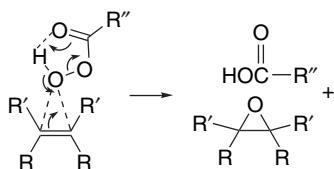
f. D. L. Boger, J. A. McKie, and C. W. Boyce, *Synlett*, 515 (1997).

chemoselectivity for the 4,5-double bond in a dienoate ester. This case also illustrates the occurrence of isomerization during the epoxidation. Entry 4 is a step in the enantioselective synthesis of CDP840, a phosphodiesterase inhibitor. The reaction in Entry 5 provided a starting material for the synthesis of the DNA-alkylating antitumor agent CC-1065.

12.2.2. Epoxides from Alkenes and Peroxidic Reagents

12.2.2.1. Epoxidation by Peroxy Acids and Related Reagents. The most general reagents for conversion of simple alkenes to epoxides are peroxycarboxylic acids.⁶⁷ *m*-Chloroperoxybenzoic acid⁶⁸ (MCPBA) is a particularly convenient reagent. The magnesium salt of monoperoxyphthalic acid is an alternative.⁶⁹ Potassium hydrogen peroxytsulfate, which is sold commercially as Oxone®, is a convenient reagent for epoxidations that can be done in aqueous methanol.⁷⁰ Peroxyacetic acid, peroxybenzoic acid, and peroxytrifluoroacetic acid have also been used frequently for epoxidation. All of the peroxycarboxylic acids are potentially hazardous materials and require appropriate precautions.

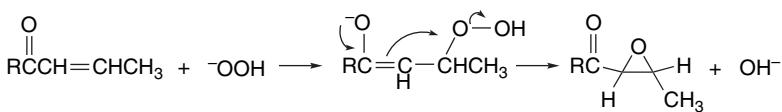
It has been demonstrated that ionic intermediates are not involved in the epoxidation reaction. The reaction rate is not very sensitive to solvent polarity.⁷¹ Stereospecific *syn* addition is consistently observed. The oxidation is therefore believed to be a concerted process. A representation of the transition structure is shown below.



The rate of epoxidation of alkenes is increased by alkyl groups and other ERG substituents and the reactivity of the peroxy acids is increased by EWG substituents.⁷² These structure-reactivity relationships demonstrate that the peroxyacid acts as an electrophile in the reaction. Decreased reactivity is exhibited by double bonds that are conjugated with strongly electron-attracting substituents, and more reactive peroxyacids, such as trifluoroperoxyacetic acid, are required for oxidation of such compounds.⁷³ Electron-poor alkenes can also be epoxidized by alkaline solutions of

- ⁶⁷. D. Swern, *Organic Peroxides*, Vol. II, Wiley-Interscience, New York, 1971, pp. 355–533; B. Plesnicar, in *Oxidation in Organic Chemistry*, Part C, W. Trahanovsky, ed., Academic Press, New York, 1978, pp. 211–253.
- ⁶⁸. R. N. McDonald, R. N. Steppel, and J. E. Dorsey, *Org. Synth.*, **50**, 15 (1970).
- ⁶⁹. P. Brougham, M. S. Cooper, D. A. Cummerison, H. Heaney, and N. Thompson, *Synthesis*, 1015 (1987).
- ⁷⁰. R. Bloch, J. Abecassis, and D. Hassan, *J. Org. Chem.*, **50**, 1544 (1985).
- ⁷¹. N. N. Schwartz and J. N. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964).
- ⁷². B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955).
- ⁷³. W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).

hydrogen peroxide or *t*-butyl hydroperoxide. A quite different mechanism, involving conjugate nucleophilic addition, operates in this case.⁷⁴



There have been a number of computational studies of the epoxidation reaction. These studies have generally found that the hydrogen-bonded peroxy acid is approximately perpendicular to the axis of the double bond, giving a spiro structure.⁷⁵ Figure 12.8 shows TS structures and E_a values based on B3LYP/6-31G* computations. The E_a trend is as expected for an electrophilic process: $\text{OCH}_3 < \text{CH}_3 \sim \text{CH} = \text{CH}_2 < \text{H} < \text{CN}$. Similar trends were found in MP4/6-31G* and QCISD/6-31G* computations.

The stereoselectivity of epoxidation with peroxycarboxylic acids has been well studied. Addition of oxygen occurs preferentially from the less hindered side of the molecule. Norbornene, for example, gives a 96:4 *exo:endo* ratio.⁷⁶ In molecules where two potential modes of approach are not very different, a mixture of products is formed.

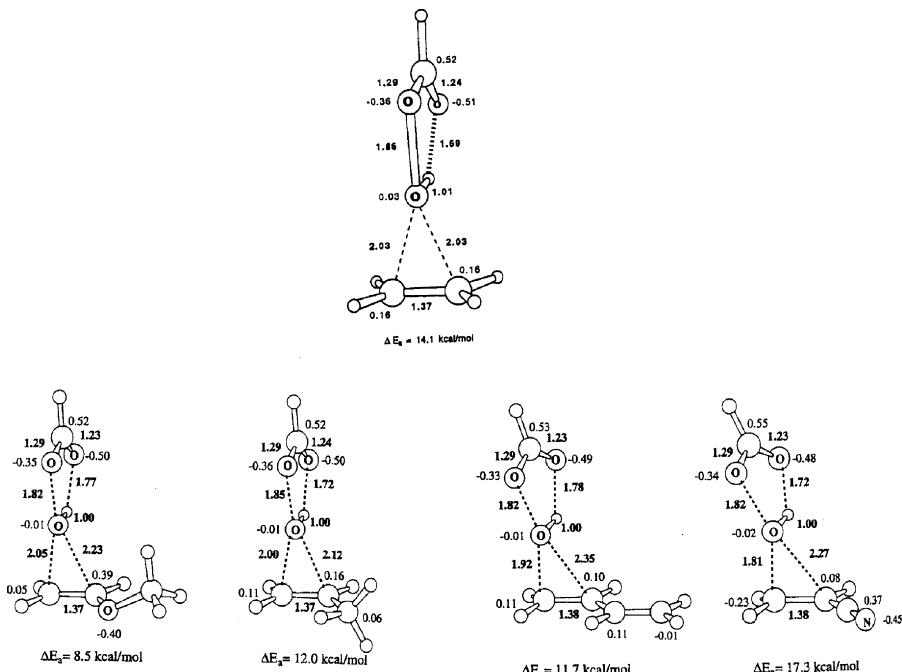
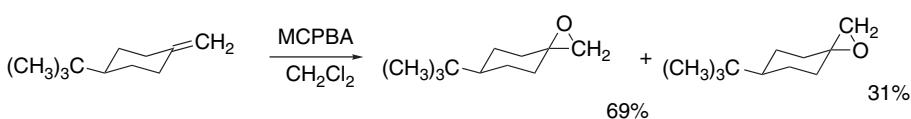


Fig. 12.8. Comparison of epoxidation transition structures and activation energies for ethene and substituted ethenes. Reproduced from *J. Am. Chem. Soc.*, **119**, 10147 (1997), by permission of the American Chemical Society.

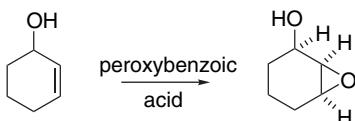
⁷⁴ C. A. Bunton and G. J. Minkoff, *J. Chem. Soc.*, 665 (1949).

⁷⁵ R. D. Bach, M. N. Glukhovtsev, and C. Gonzalez, *J. Am. Chem. Soc.*, **120**, 9902 (1998); K. N. Houk, J. Liu, N. C. DeMello, and K. R. Condroski, *J. Am. Chem. Soc.*, **119**, 10147 (1997).

⁷⁶ H. Kwart and T. Takeshita, *J. Org. Chem.*, **28**, 670 (1963).



Hydroxy groups exert a directive effect on epoxidation and favor approach from the side of the double bond closest to the hydroxy group.⁷⁸ Hydrogen bonding between the hydroxy group and the reagent evidently stabilizes the TS.



This is a strong directing effect that can exert stereochemical control even when steric effects are opposed. Entries 4 and 5 in Scheme 12.11 illustrate the hydroxy-directing effect. Other substituents capable of hydrogen bonding, in particular amides, also can exert a *syn*-directing effect.⁷⁹

The hydroxy-directing effect has been studied computationally, as the hydrogen bond can have several possible orientations.⁸⁰ Studies on 2-propen-1-ol show the same preference for the spiro TS as for unfunctionalized alkenes. There is a small preference for hydrogen bonding to a peroxy oxygen, as opposed to the carbonyl oxygen. The TSs for conformations of 2-propen-1-ol that are not hydrogen-bonded are 2–3 kcal/mol higher in energy than the best of the hydrogen-bonded structures. For substituted allylic alcohols, A^{1,2} and A^{1,3} strain comes into play. Figure 12.9 shows the structures and relative energies of the four possible TSs for prop-2-en-1-ol. The *syn,exo* structure with hydrogen-bonding to the transferring oxygen is preferred to the *endo* structure, in which the hydrogen-bonding is to the carbonyl oxygen.

Torsional effects are important in cyclic systems. A PM3 study of the high stereoselectivity of compounds **4a-d** found torsional effects to be the major difference between the diastereomeric TSs.⁸¹ The computed TSs for **4a** are shown in Figure 12.10. The structures all show similar stereoselectivity, regardless of the presence and nature of a 3-substituent.

- ⁷⁷. R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **32**, 1363 (1967).
- ⁷⁸. H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).
- ⁷⁹. F. Mohamadi and M. M. Spees, *Tetrahedron Lett.*, **30**, 1309 (1989); P. G. M. Wuts, A. R. Ritter, and L. E. Pruitt, *J. Org. Chem.*, **57**, 6696 (1992); A. Jemmal, W. Bets, K. Luthman, I. Csoregh, and U. Hacksell, *J. Org. Chem.*, **60**, 1026 (1995); P. Kovacs and I. Stary, *J. Org. Chem.*, **55**, 3236 (1990); A. Armstrong, P. A. Barsanti, P. A. Clarke, and A. Wood, *J. Chem. Soc., Perkin Trans. 1*, 1373 (1996).
- ⁸⁰. M. Freccero, R. Gandolfi, M. Sarzi-Amade, and A. Rastelli, *J. Org. Chem.*, **64**, 3853 (1999); M. Freccero, R. Gandolfi, M. Sarzi-Amade, and A. Rastelli, *J. Org. Chem.*, **65**, 2030 (2000).
- ⁸¹. M. J. Lucero and K. N. Houk, *J. Org. Chem.*, **63**, 6973 (1998).

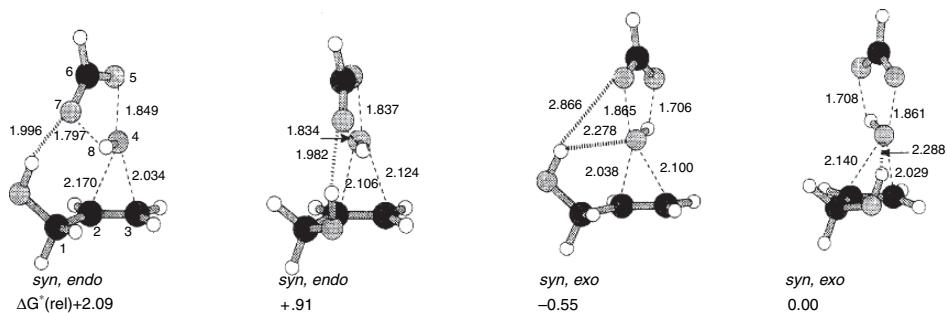
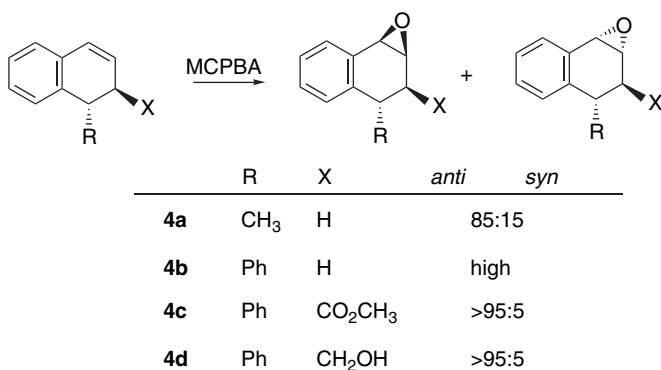


Fig. 12.9. Structure and relative energies of four modes of hydrogen bonding in transition structures for epoxidation of 2-propen-1-ol by peroxyformic acid. Relative energies are from B3LYP/6-311G*-level computations with a solvation model for CH_2Cl_2 , $\epsilon = 8.9$. Reproduced from *J. Org. Chem.*, **64**, 3853 (1999), by permission of the American Chemical Society.



Even in the absence of a 3-substituent (**4a**, **4b**) and with only a small 4-methyl group (**4a**), the stereoselectivity is high. The preference arises from the staggered relationship between the forming C–O bond and the axial allylic hydrogen.

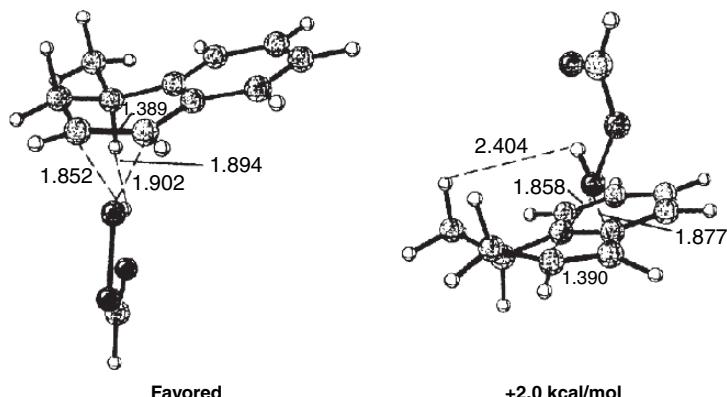
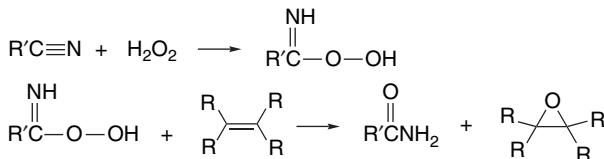
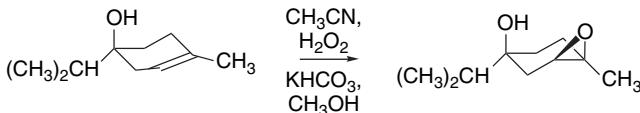


Fig. 12.10. Comparison of *trans*- and *cis*-oriented transition structures for epoxidation of 1-methyl-1,2-dihydronaphthalene. Reproduced from *J. Org. Chem.*, **63**, 6973 (1998), by permission of the American Chemical Society.

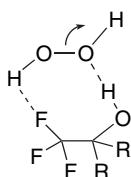


At least in some cases, the hydroxy-directing effect also operates for this version of the reaction.



Scheme 12.11 gives some examples of epoxidation using peroxyacids and related reagents. Entry 1 shows standard epoxidation conditions applied to styrene. The reaction in Entry 2 uses typical epoxidation conditions and also illustrates the approach from the less hindered face of the molecule. In Entry 3, the selectivity for the more-substituted double bond was used to achieve regioselectivity. Entries 4 and 5 illustrate stereochemical control by hydroxy participation. The reaction in Entry 6 is an example of diastereoselectivity, most likely due to hydrogen bonding by the amide group. Entries 7 and 8 are cases of application of nucleophilic peroxidation conditions to alkenes conjugated with EWG substituents. In Entry 9, the more reactive trifluoroperoxyacetic acid was used to oxidize a deactivated double bond. Entry 10 is an example of use of the peroxyimidic acid conditions.

There is interest in being able to use H_2O_2 directly as an epoxidizing reagent because it is the ultimate source of most peroxides. The reactivity of H_2O_2 is substantially enhanced in hexafluoro-2-propanol (HFIP) and other polyfluorinated alcohols such as nonafluoro-*t*-butanol.⁸⁴ Either 30 or 60% H_2O_2 can oxidize alkenes to epoxides in these solvents. The system shows the normal trend of higher reactivity for more-substituted alkenes. The activation is attributed to polarization of the H_2O_2 by hydrogen bonding with the β -fluoroalcohols. The fluoro substituents also increase the acidity of the hydroxy group.



⁸². G. B. Payne, *Tetrahedron*, **18**, 763 (1962); R. D. Bach and J. W. Knight, *Org. Synth.*, **60**, 63 (1981); L. A. Arias, S. Adkins, C. J. Nagel, and R. D. Bach, *J. Org. Chem.*, **48**, 888 (1983).

⁸³. W. C. Frank, *Tetrahedron: Asymmetry*, **9**, 3745 (1998).

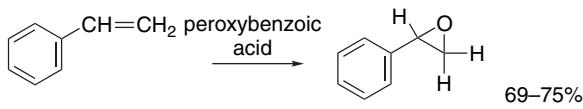
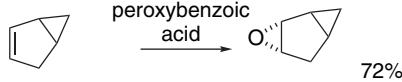
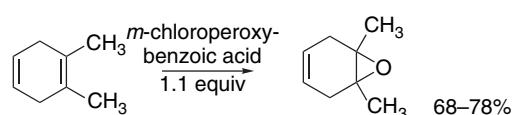
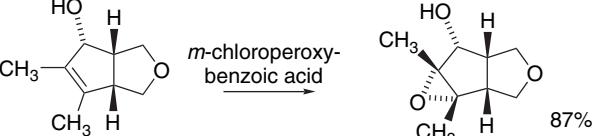
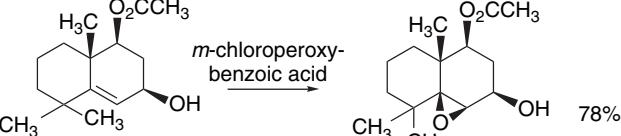
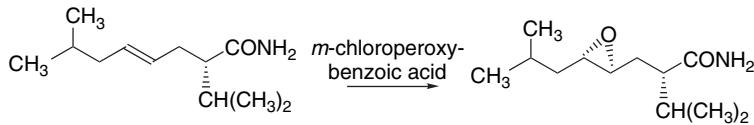
⁸⁴. K. Neumann and R. Neumann, *Org. Lett.*, **2**, 2861 (2000).

Scheme 12.11. Synthesis of Epoxides from Alkenes Using Peroxy Acids

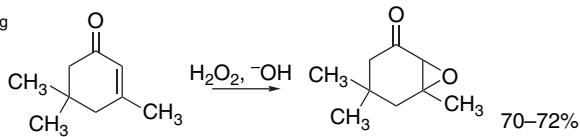
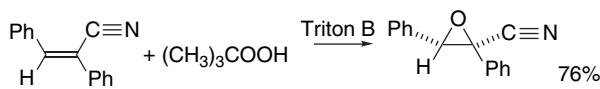
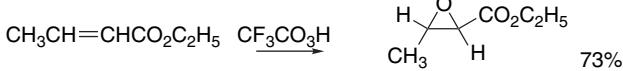
CHAPTER 12

Oxidations

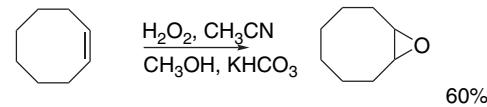
A. Oxidation of alkenes with peroxy acids

^{1a}^{2b}^{3c}^{4d}^{5e}^{6f}

B. Epoxidation of electrophilic alkenes

^{7g}^{8h}⁹ⁱ

C. Epoxidation with peroxyimidic Acids

^{10j}

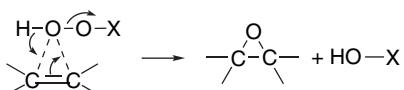
(Continued)

- a. H. Hibbert and P. Burt, *Org. Synth.*, **I**, 481 (1932).
 b. E. J. Corey and R. L. Dawson, *J. Am. Chem. Soc.*, **85**, 1782 (1963).
 c. L. A. Paquette and J. H. Barrett, *Org. Synth.*, **49**, 62 (1969).
 d. R. M. Scarborough, Jr., B. H. Toder, and A. B. Smith, III, *J. Am. Chem. Soc.*, **102**, 3904 (1980).
 e. M. Miyashita and A. Yoshikoshi, *J. Am. Chem. Soc.*, **96**, 1917 (1974).
 f. P. G. M. Wuts, A. R. Ritter, and L. E. Pruitt, *J. Org. Chem.*, **57**, 6696 (1992).
 g. R. L. Wasson and H. O. House, *Org. Synth.*, **IV**, 552 (1963).
 h. G. B. Payne and P. H. Williams, *J. Org. Chem.*, **26**, 651 (1961).
 i. W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).
 j. R. D. Bach and J. W. Knight, *Org. Synth.*, **60**, 63 (1981).

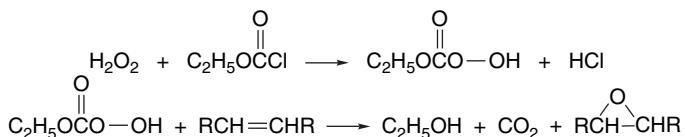
SECTION 12.2

Addition of Oxygen at
Carbon-Carbon Double
Bonds

A variety of electrophilic reagents have been examined with the objective of activating H_2O_2 to generate a good epoxidizing agent. In principle, any species that can convert one of the hydroxy groups to a good leaving group can generate a reactive epoxidizing reagent.

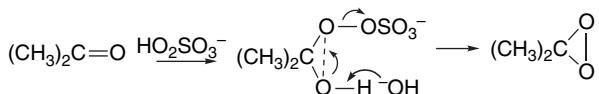


In practice, promising results have been obtained for several systems. For example, fair to good yields of epoxides are obtained when a two-phase system consisting of alkene and ethyl chloroformate is stirred with a buffered basic solution of hydrogen peroxide. The active oxidant is presumed to be *O*-ethyl peroxyacetic acid.⁸⁵



Although these reagent combinations are not as generally useful as the peroxycarboxylic acids, they serve to illustrate that epoxidizing activity is not unique to the peroxyacids.

12.2.2.2. Epoxidation by Dioxirane Derivatives. Another useful epoxidizing agent is dimethyldioxirane (DMDO),⁸⁶ which is generated by *in situ* reaction of acetone and peroxymonosulfate in buffered aqueous solution. Distillation gives about a 0.1 *M* solution of DMDO in acetone.⁸⁷

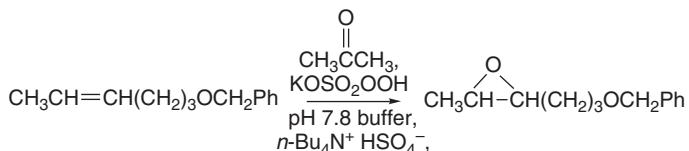


⁸⁵. R. D. Bach, M. W. Klein, R. A. Ryntz, and J. W. Holubka, *J. Org. Chem.*, **44**, 2569 (1979).

⁸⁶. R. W. Murray, *Chem. Rev.*, **89**, 1187 (1989); W. Adam and L. P. Hadjiarapoglou, *Topics Current Chem.*, **164**, 45 (1993); W. Adam, A. K. Smerz, and C. G. Zhao, *J. Prakt. Chem., Chem. Zeit.*, **339**, 295 (1997).

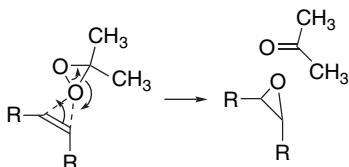
⁸⁷. R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, **50**, 2847 (1985); W. Adam, J. Bialas, and L. Hadjiarapoglou, *Chem. Ber.*, **124**, 2377 (1991).

Higher concentrations of DMDO can be obtained by extraction of a 1:1 aqueous dilution of the distillate by CH_2Cl_2 , CHCl_3 , or CCl_4 .⁸⁸ Another method involves in situ generation of DMDO under phase transfer conditions.⁸⁹



The yields and rates of oxidation by DMDO under these in situ conditions depend on pH and other reaction parameters.⁹⁰

Various computational models agree that the reaction occurs by a concerted mechanism.⁹¹ Comparison between epoxidation by peroxy acids and dioxiranes suggests that they have similar transition structures.



Kinetics and isotope effects are consistent with this mechanism.⁹² The reagent is electrophilic in character and reaction is facilitated by ERG substituents in the alkene. A B3LYP/6-31G* computation found the transition structures and E_a values shown in Figure 12.11.

Similarly to peroxycarboxylic acids, DMDO is subject to *cis* or *syn* stereoselectivity by hydroxy and other hydrogen-bonding functional groups.⁹³ However a study of several substituted cyclohexenes in $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ suggested a dominance by steric effects. In particular, the hydroxy groups in cyclohex-2-enol and

- ^{88.} M. Gilbert, M. Farrert, F. Sanchez-Baeza, and A. Messeguer, *Tetrahedron*, **53**, 8643 (1997).
- ^{89.} S. E. Denmark, D. C. Forbes, D. S. Hays, J. S. DePue, and R. G. Wilde, *J. Org. Chem.*, **60**, 1391 (1995).
- ^{90.} M. Frohn, Z.-X. Wang, and Y. Shi, *J. Org. Chem.*, **63**, 6425 (1998); A. O'Connell, T. Smyth, and B. K. Hodnett, *J. Chem. Technol. Biotech.*, **72**, 60 (1998).
- ^{91.} R. D. Bach, M. N. Glukhovtsev, C. Gonzalez, M. Marquez, C. M. Estevez, A. G. Baboul, and H. Schlegel, *J. Phys. Chem.*, **101**, 6092 (1997); K. N. Houk, J. Liu, N. C. DeMello, and K. R. Condroski, *J. Am. Chem. Soc.*, **119**, 10147 (1997); C. Jenson, J. Liu, K. N. Houk, and W. L. Jorgensen, *J. Am. Chem. Soc.*, **119**, 12982 (1987); R. D. Bach, M. N. Glukhovtsev, and C. Canepa, *J. Am. Chem. Soc.*, **120**, 775 (1998); M. Freccero, R. Gandolfi, M. Sarzi-Amadei, and A. Rastelli, *Tetrahedron*, **54**, 6123 (1998); J. Liu, K. N. Houk, A. Dinoi, C. Fusco, and R. Curci, *J. Org. Chem.*, **63**, 8565 (1998); R. D. Bach, O. Dmitrenko, W. Adam, and S. Schambony, *J. Am. Chem. Soc.*, **125**, 924 (2003).
- ^{92.} W. Adam, R. Paredes, A. K. Smerz, and L. A. Veloza, *Liebigs Ann. Chem.*, 547 (1997); A. L. Baumstark, E. Michaleabaeza, A. M. Navarro, and H. D. Banks, *Heterocycl. Commun.*, **3**, 393 (1997); Y. Angelis, X. Zhang, and M. Orfanopoulos, *Tetrahedron Lett.*, **37**, 5991 (1996).
- ^{93.} R. W. Murray, M. Singh, B. L. Williams, and H. M. Moncrief, *J. Org. Chem.*, **61**, 1830 (1996); G. Asensio, C. Boix-Bernardini, C. Andreu, M. E. Gonzalez-Nunez, R. Mello, J. O. Edwards, and G. B. Carpenter, *J. Org. Chem.*, **64**, 4705 (1999).

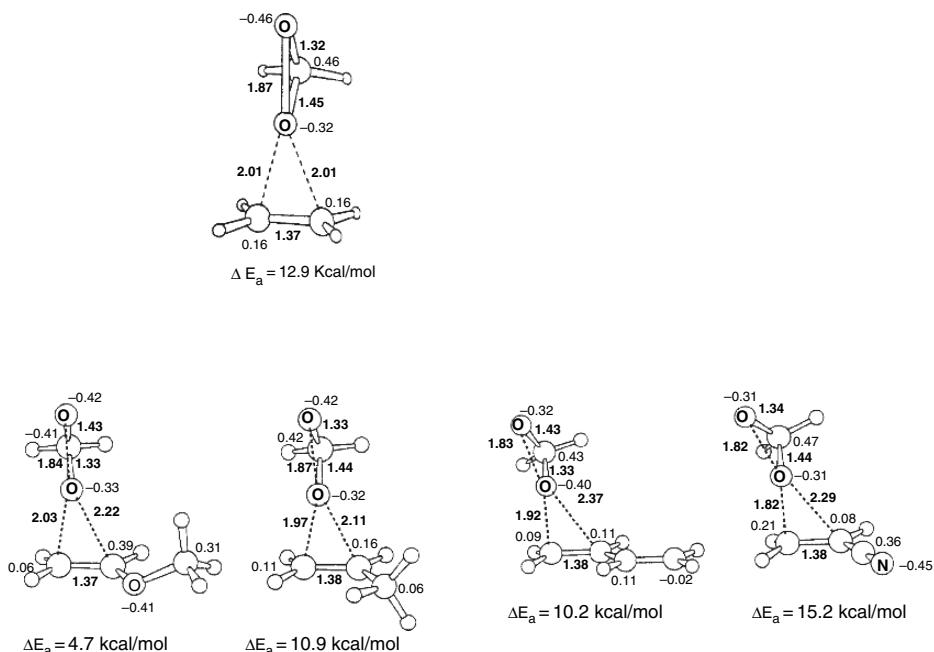
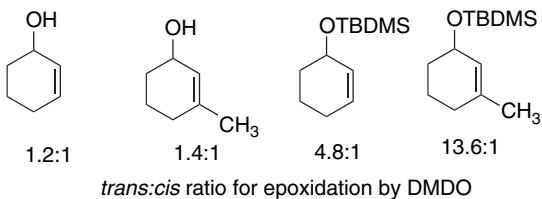
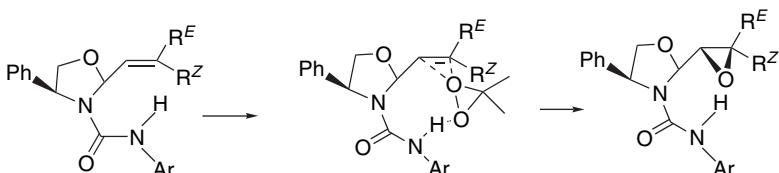


Fig. 12.11. Transition structures and E_a values for epoxidation of ethene and substituted derivatives by dimethyloxirane. Reproduced from *J. Am. Chem. Soc.*, **119**, 10147 (1997), by permission of the American Chemical Society.

3-methylcyclohex-2-enol were not very strongly *syn* directing.⁹⁴ The hydroxylic solvent may minimize any directive effect by competing hydrogen bonding.⁹⁵



Directing effects have also been attributed to more remote substituents, as, e.g., a urea NH.



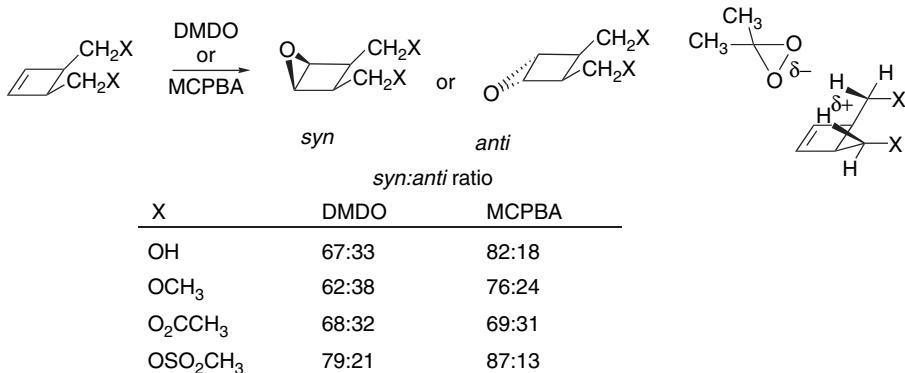
Ref. 96

⁹⁴. D. Yang, G.-S. Jiao, Y.-C. Yip, and M.-K. Wong, *J. Org. Chem.*, **64**, 1635 (1999).

⁹⁵. W. Adam, R. Paredes, A. K. Smerz, and L. A. Veloza, *Eur. J. Org. Chem.*, 349 (1998).

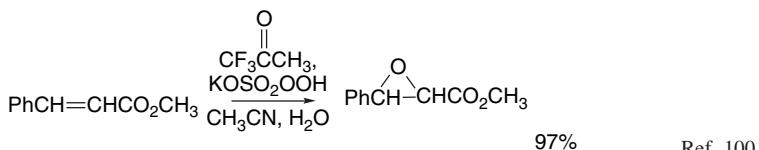
⁹⁶. W. Adam, K. Peters, E.-M. Peters, and S. B. Schambony, *J. Am. Chem. Soc.*, **123**, 7228 (2001).

Several disubstituted 3,4-dimethylcyclobutenes show *syn* selectivity. The mesylate groups were strongly *syn* directive, with the hydroxy, methoxy, and acetoxy groups being somewhat less so.⁹⁷ The same groups were even more strongly *syn* directing with MCPBA. The effects are attributed to an attractive electrostatic interaction of the relatively positive methylene hydrogens and the oxygens of the dioxirane and peroxy acid.



For other substituents, both steric and dipolar factors seem to have an influence and several complex reactants have shown good stereoselectivity, although the precise origin of the stereoselectivity is not always evident.⁹⁸

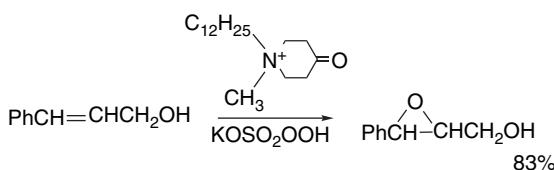
Other ketones besides acetone can be used for *in situ* generation of dioxiranes by reaction with peroxyulfate or another suitable peroxide. More electrophilic ketones give more reactive dioxiranes. 3-Methyl-3-trifluoromethylidioxirane is a more reactive analog of DMDO.⁹⁹ This reagent, which is generated *in situ* from 1,1,1-trifluoroacetone, can oxidize less reactive compounds such as methyl cinnamate.



Hexafluoroacetone and hydrogen peroxide in buffered aqueous solution can epoxidize alkenes and allylic alcohols.¹⁰¹ *N,N*-Dialkylpiperidin-4-one salts are also good catalysts for epoxidation.¹⁰² The polar effect of the quaternary nitrogen enhances the

- ⁹⁷. M. Freccero, R. Gandolfi, and M. Sarzi-Amade, *Tetrahedron*, **55**, 11309 (1999).
- ⁹⁸. R. C. Cambie, A. C. Grimsdale, P. S. Rutledge, M. F. Walker, and A. D. Woodgate, *Austr. J. Chem.*, **44**, 1553 (1991); P. Boricelli and P. Lupattelli, *J. Org. Chem.*, **59**, 4304 (1994); R. Curci, A. Detomaso, T. Prencipe, and G. B. Carpenter, *J. Am. Chem. Soc.*, **116**, 8112 (1994); T. C. Henninger, M. Sabat, and R. J. Sundberg, *Tetrahedron*, **52**, 14403 (1996).
- ⁹⁹. R. Mello, M. Fiorentino, O. Sciacevolli, and R. Curci, *J. Org. Chem.*, **53**, 3890 (1988).
- ¹⁰⁰. D. Yang, M.-K. Wong, and Y.-C. Yie, *J. Org. Chem.*, **60**, 3887 (1995).
- ¹⁰¹. R. P. Heggs and B. Ganem, *J. Am. Chem. Soc.*, **101**, 2484 (1979); A. J. Biloski, R. P. Hegge, and B. Ganem, *Synthesis*, 810 (1980); W. Adam, H.-G. Degen, and C. R. Saha-Moller, *J. Org. Chem.*, **64**, 1274 (1999).
- ¹⁰². S. E. Denmark, D. C. Forbes, D. S. Hays, J. S. DePue, and R. G. Wilde, *J. Org. Chem.*, **60**, 1391 (1995).

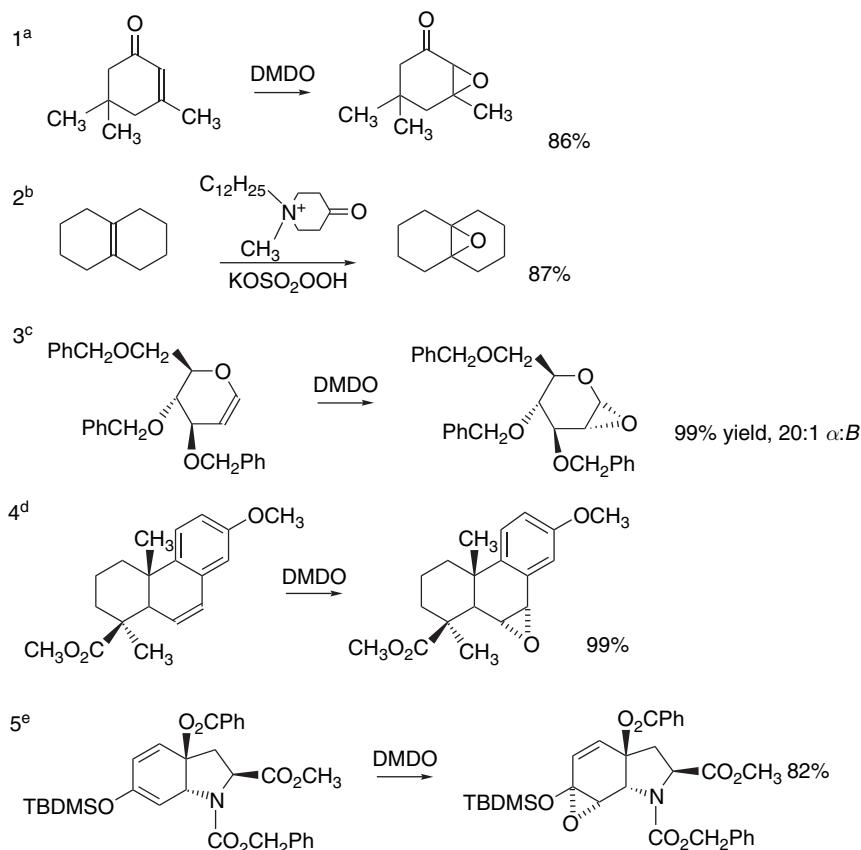
reactivity of the ketone toward nucleophilic addition and also makes the dioxirane intermediate more reactive.



The cyclic sulfone 4-thiopyrone-*S*, *S*-dioxide also exhibits enhanced reactivity as a result of the effect of the sulfone dipole.¹⁰³

Scheme 12.12 gives some examples of epoxidations involving dioxiranes. Entry 1 indicates the ability of the reagent to epoxidize deactivated double bonds. Entry 2

Scheme 12.12. Epoxidation by Dioxiranes



a. W. Adam, L. Hadjarpaglou, and B. Nestler, *Tetrahedron Lett.*, **31**, 331 (1990).

b. S. E. Denmark, D. C. Forbes, D. S. Hays, J. S. DePue, and R. G. Wilde, *J. Org. Chem.*, **60**, 1391 (1995).

c. R. L. Halcomb and S. J. Danishefsky, *J. Am. Chem. Soc.*, **111**, 6661 (1989).

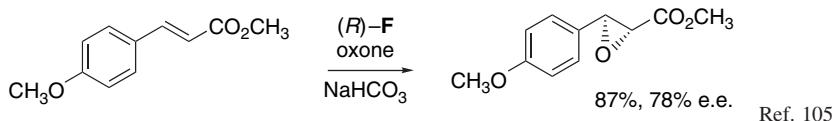
d. R. C. Cambie, A. C. Grimsdale, P. S. Rutledge, M. F. Walker, and P. D. Woodgate, *Aust. J. Chem.*, **44**, 1553 (1991).

e. T. C. Henninger, M. Sabat, and R. J. Sundberg, *Tetrahedron*, **52**, 14403 (1996).

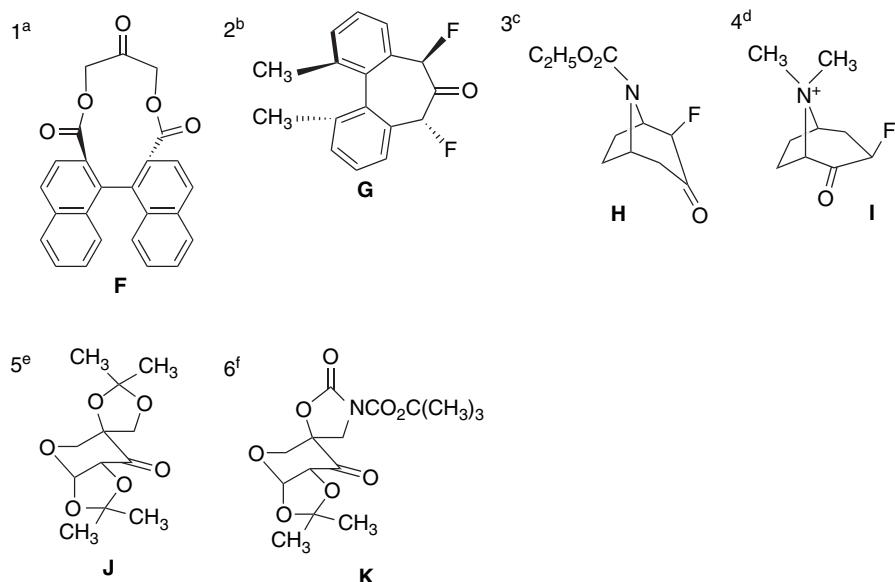
¹⁰³ D. Yang, Y.-C. Yip, G.-S. Jiao, and M.-K. Wong, *J. Org. Chem.*, **63**, 8952 (1998).

illustrates the use of a piperidone salt for in situ generation of a dioxirane. The long alkyl chain imparts phase transfer capability to the ketone. The dioxirane is generated in the aqueous phase but can carry out the epoxidation in the organic phase. Entries 3 to 5 are examples of stereoselective epoxidations. In each case, high stereoselectivity is observed in the presence of nearby functional groups. The exact origins of the stereoselectivity are not clear.

A number of chiral ketones have been developed that are capable of enantioselective epoxidation via dioxirane intermediates.¹⁰⁴ Scheme 12.13 shows the structures of some chiral ketones that have been used as catalysts for enantioselective epoxidation. The BINAP-derived ketone shown in Entry 1, as well as its halogenated derivatives, have shown good enantioselectivity toward di- and trisubstituted alkenes.



Scheme 12.13. Chiral Ketones Used for Enantioselective Epoxidation



a. D. Yang, M.-K. Wong, Y.-C. Yip, X.-C. Wang, M.-W. Tang, J.-H. Zheng, and K. K. Cheung, *J. Am. Chem. Soc.*, **120**, 5943 (1998).

b. S. E. Denmark and Z. C. Wu, *Synlett*, 847 (1999); M. Frohn and Y. Shi, *Synthesis*, 1979 (2000).

c. A. Armstrong, G. Ahmed, B. Dominguez-Fernandez, B. R. Hayter, and J. S. Wailes, *J. Org. Chem.*, **67**, 8610 (2002).

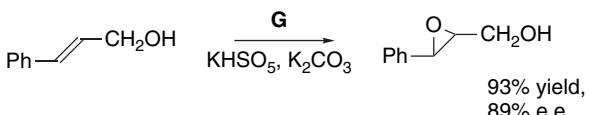
d. S. E. Denmark and H. Matsuhashi, *J. Org. Chem.*, **67**, 3479 (2002).

e. Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, and Y. Shi, *J. Am. Chem. Soc.*, **119**, 11224 (1997).

f. H. Tian, X. She, H. Yu, L. Shu, and Y. Shi, *J. Org. Chem.*, **67**, 2435 (2002).

¹⁰⁴. D. Yang, *Acc. Chem. Res.*, **37**, 497 (2004); Y. Shi, *Acc. Chem. Res.*, **37**, 488 (2004).

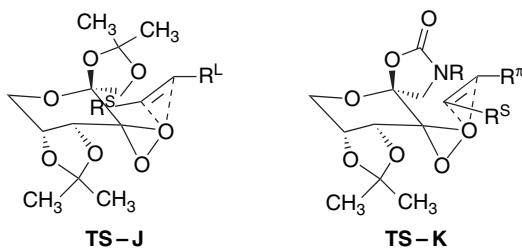
¹⁰⁵. T. Furutani, R. Imashiro, M. Hatsuda, and M. Seki, *J. Org. Chem.*, **67**, 4599 (2002).



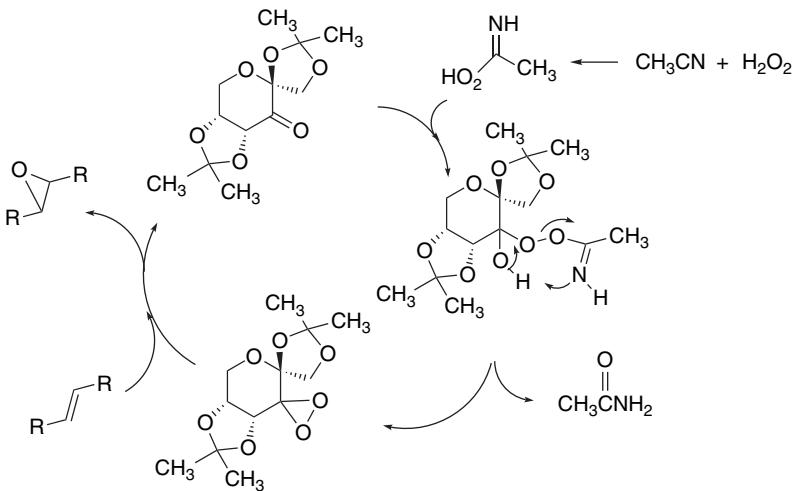
SECTION 12.2

Addition of Oxygen at
Carbon-Carbon Double
Bonds

The fluorinated tropones **H** and **I** also show good reactivity and are enantioselective in favorable cases, but show considerable dependence on reactant structure. The carbohydrate structures **J** and **K** also benefit from a polar effect of the adjacent oxygens and give good enantioselectivity with a variety of *trans* di- and trisubstituted alkenes. The oxazolidinone derivative **K** also shows good enantioselectivity toward *cis*-substituted and terminal alkenes. Transition structures **TS J** and **TS K** have been suggested for epoxidation by these ketones. It has been noted that alkenes with conjugated π systems have a preferred orientation toward the oxazolidinone ring.



These ketones can also be used in kinetic resolutions.¹⁰⁷ The carbohydrate-derived ketones have been used in conjunction with acetonitrile and H₂O₂. The reactions are believed to proceed through dioxiranes generated by a catalytic cycle involving a peroxyimidic acid.¹⁰⁸



¹⁰⁶ S. E. Denmark and Z. C. Wu, *Synlett*, 847 (1999); M. Frohn and Y. Shi, *Synthesis*, 1979 (2000).

¹⁰⁷ D. Yang, G.-S. Jiao, Y.-C. Yip, T.-H. Lai, and M.-K. Wong, *J. Org. Chem.*, **66**, 4619 (2001); M. Frohn, X. Zhou, J.-R. Zhang, Y. Tang, and Y. Shi, *J. Am. Chem. Soc.*, **121**, 7718 (1999).

¹⁰⁸ L. Shu and Y. Shi, *Tetrahedron*, **57**, 5213 (2001).

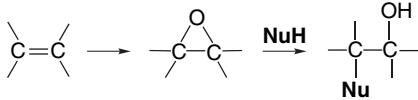
12.2.3. Subsequent Transformations of Epoxides

Epoxides are useful synthetic intermediates and the conversion of an alkene to an epoxide is often part of a more extensive molecular transformation.¹⁰⁹ In many instances advantage is taken of the reactivity of the epoxide ring toward nucleophiles to introduce additional functionality. Since epoxide ring opening is usually stereospecific, such reactions can be used to establish stereochemical relationships between adjacent substituents. Such two- or three-step operations can accomplish specific oxidative transformations of an alkene that may not be easily accomplished in a single step. Scheme 12.14 provides a preview of the type of reactivity to be discussed.

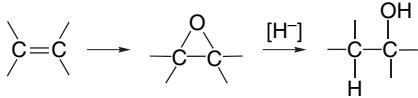
12.2.3.1. Nucleophilic and Solvolytic Ring Opening. Epoxidation may be preliminary to solvolytic or nucleophilic ring opening in synthetic sequences. Epoxides can undergo ring opening under either basic or acidic conditions. Base-catalyzed reactions, in which the nucleophile provides the driving force for ring opening, usually involve breaking the epoxide bond at the less-substituted carbon, since this is the position most accessible to nucleophilic attack.¹¹⁰ These reactions result in an *anti* relationship between the epoxide oxygen and the nucleophile. The situation in acid-catalyzed reactions is more complex. The bonding of a proton to the oxygen weakens the C–O bonds and facilitates rupture by weak nucleophiles. If the C–O bond is largely intact at the TS, the nucleophile becomes attached to the less-substituted position for the same steric reasons that were cited for nucleophilic ring opening. If, on the other hand, C–O rupture is more complete at the TS, the opposite orientation is observed. This change in regiochemistry results from the ability of the more-substituted carbon to better stabilize the developing positive charge.

Scheme 12.14. Synthetic Transformations of Epoxides

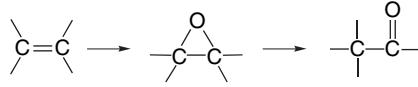
A. Epoxidation followed by nucleophilic ring opening



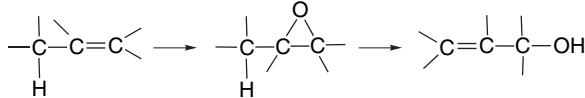
B. Epoxidation followed by reductive ring opening



C. Epoxidation followed by rearrangement to a carbonyl compound

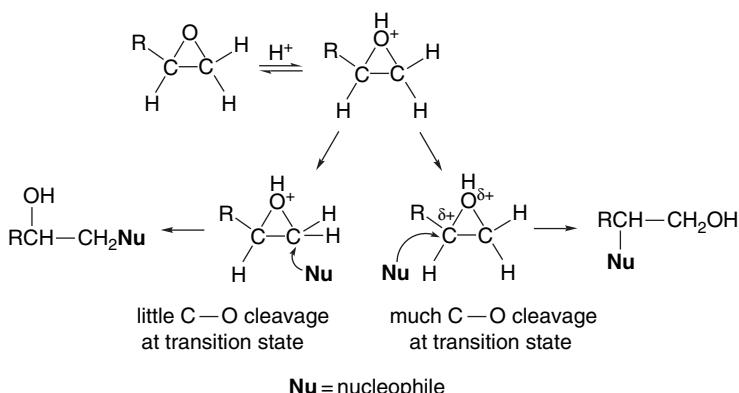


D. Epoxidation followed by ring opening to an allylic alcohol

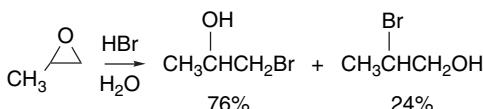


¹⁰⁹. J. G. Smith, *Synthesis*, 629 (1984).

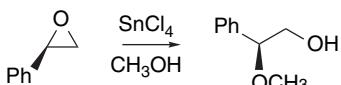
¹¹⁰. R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).



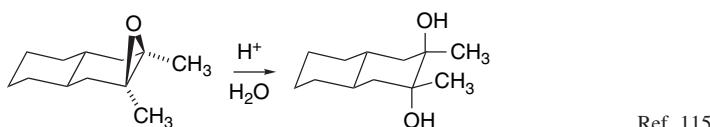
When simple aliphatic epoxides such as propylene oxide react with hydrogen halides, the dominant product has the halide at the less-substituted primary carbon.¹¹¹



Substituents that further stabilize a carbocation intermediate lead to reversal of the mode of addition.¹¹² The case of styrene oxide hydrolysis has been carefully examined. Under acidic conditions, the bond breaking is exclusively at the benzylic position. Under basic conditions, ring opening occurs at both epoxide carbons.¹¹³ Styrene also undergoes highly regioselective ring opening in the presence of Lewis acids. For example, methanolysis is catalyzed by SnCl_4 and occurs with greater than 95% attack at the benzyl carbon and with high inversion.¹¹⁴ The stereospecificity indicates a concerted nucleophilic opening of the complexed epoxide.



In cyclic systems, ring opening gives the diaxial diol.



Under some circumstances, acid-catalyzed ring opening of 2,2-disubstituted epoxides by sulfuric acid in dioxane goes with high *inversion* at the tertiary center.¹¹⁶

¹¹¹. C. A. Stewart and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76**, 1259 (1954).

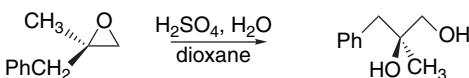
¹¹². S. Winstein and L. L. Ingraham, *J. Am. Chem. Soc.*, **74**, 1160 (1952).

¹¹³. R. Lin and D. L. Whalen, *J. Org. Chem.*, **59**, 1638 (1994); J. J. Blumenstein, V. C. Ukachukwa, R. S. Mohan, and D. Whalen, *J. Org. Chem.*, **59**, 1638 (1994).

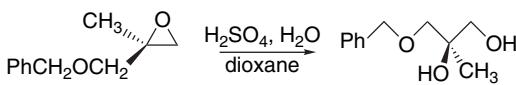
¹¹⁴. C. Moberg, L. Rakos, and L. Tottie, *Tetrahedron Lett.*, **33**, 2191 (1992).

¹¹⁵. B. Rickborn and D. K. Murphy, *J. Org. Chem.*, **34**, 3209 (1969).

¹¹⁶. R. V. A. Orru, S. F. Mayer, W. Kroutil, and K. Faber, *Tetrahedron*, **54**, 859 (1998).



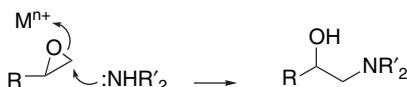
Ref. 117



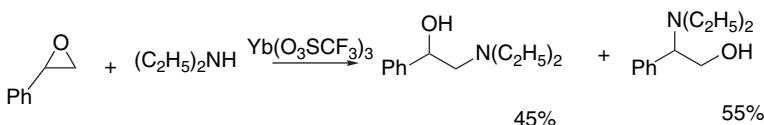
Ref. 118

Under somewhat modified conditions (H_2SO_4 on silica), this reaction has been successfully applied to a complex alkaloid structure.¹¹⁹

Recently a number of procedures for epoxide ring opening that feature the oxyphilic Lewis acids, including lanthanides, have been developed. LiClO_4 , LiO_3SCF_3 , $\text{Mg}(\text{ClO}_4)_2$, $\text{Zn}(\text{O}_3\text{SCF}_3)_2$, and $\text{Yb}(\text{O}_3\text{SCF}_3)_3$ have been shown to catalyze epoxide ring opening.¹²⁰ The cations catalyze *anti* addition of amines at the less-substituted carbon, which is consistent with a Lewis acid–assisted nucleophilic ring opening.

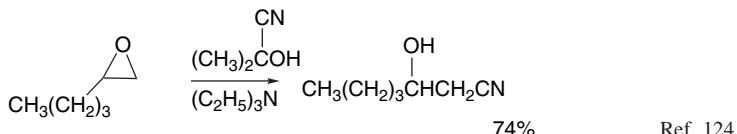


Styrene oxide gives mixtures of C- α and C- β attack, as a result of competition between the activated benzylic site and the primary site.



The same salts can be used to catalyze ring opening by other nucleophiles such as azide ion¹²¹ and cyanide ion.¹²²

A variety of reaction conditions have been developed for nucleophilic ring opening by cyanide.¹²³ Heating an epoxide with acetone cyanohydrin (which serves as the cyanide source) and triethylamine leads to ring opening at the less-substituted position.



¹¹⁷ R. V. A. Orru, I. Osprian, W. Kroutil, and K. Faber, *Synthesis*, 1259 (1998).

¹¹⁸ A. Steinreiber, H. Hellstrom, S. F. Mayer, R. V. A. Orru, and K. Faber, *Synlett*, 111 (2001).

¹¹⁹ M. E. Kuehne, Y. Qin, A. E. Huot, and S. L. Bane, *J. Org. Chem.*, **66**, 5317 (2001).

¹²⁰ M. Chini, P. Crotti, and F. Macchia, *Tetrahedron Lett.*, **31**, 4661 (1990); M. Chini, P. Crotti, L. Favero, F. Macchia, and M. Pineschi, *Tetrahedron Lett.*, **35**, 433 (1994); J. Auge and F. Leroy, *Tetrahedron Lett.*, **37**, 7715 (1996).

¹²¹ M. Chini, P. Crotti, and F. Macchia, *Tetrahedron Lett.*, **31**, 5641 (1990); P. Van de Weghe and J. Collin, *Tetrahedron Lett.*, **36**, 1649 (1995).

¹²² M. Chini, P. Crotti, L. Favero, and F. Macchia, *Tetrahedron Lett.*, **32**, 4775 (1991).

¹²³ R. A. Smiley and C. J. Arnold, *J. Org. Chem.*, **25**, 257 (1960); J. A. Ciaccio, C. Stanescu, and J. Bontemps, *Tetrahedron Lett.*, **33**, 1431 (1992).

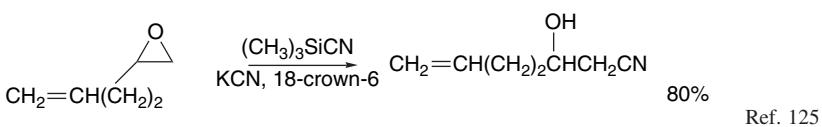
¹²⁴ D. Mitchell and T. M. Koenig, *Tetrahedron Lett.*, **33**, 3281 (1992).

Trimethylsilyl cyanide in conjunction with KCN and a crown ether also results in nucleophilic ring opening.

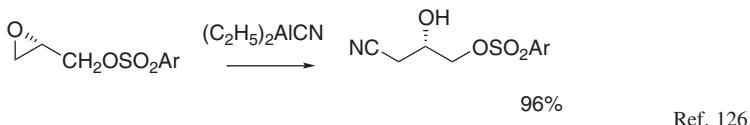
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SECTION 12.2

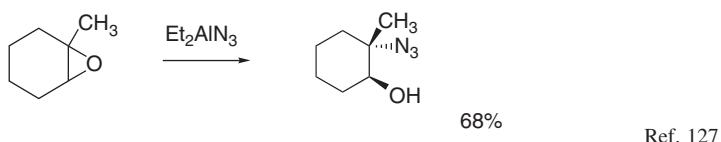
Addition of Oxygen at
Carbon-Carbon Double
Bonds



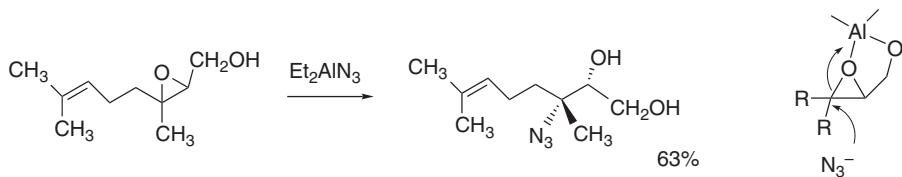
Diethylaluminum cyanide can also be used for preparation of β -hydroxynitriles.



Similarly, diethylaluminum azide gives β -azido alcohols. The epoxide of 1-methylcyclohexene gives the tertiary azide, indicating that the regiochemistry is controlled by bond cleavage, but with diaxial stereoselectivity.



Epoxides of allylic alcohols exhibit chelation-controlled regioselectivity.¹²⁸



Scheme 12.15 gives some examples of both acid-catalyzed and nucleophilic ring openings of epoxides. Entries 1 and 2 are cases in which epoxidation and solvolysis are carried out without isolation of the epoxide. Both cases also illustrate the preference for *anti* stereochemistry. The regioselectivity in Entry 3 is indicative of dominant bond cleavage in the TS. The reaction in Entry 4 was studied in a number of solvents. The product results from net *syn* addition as a result of phenonium ion participation. The *cis*-epoxide also gives mainly the *syn* product, presumably via isomerization to the

¹²⁵. M. B. Sassaman, G. K. Surya Prakash, and G. A. Olah, *J. Org. Chem.*, **55**, 2016 (1990).

¹²⁶. J. M. Klunder, T. Onami, and K. B. Sharpless, *J. Org. Chem.*, **54**, 1295 (1989).

¹²⁷. H. B. Mereyala and B. Frei, *Helv. Chim. Acta*, **69**, 415 (1986).

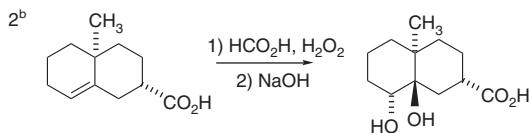
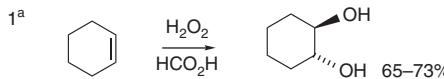
¹²⁸. F. Benedetti, F. Berti, and S. Norbedo, *Tetrahedron Lett.*, **39**, 7971 (1998); C. E. Davis, J. L. Bailey, J. W. Lockner, and R. M. Coates, *J. Org. Chem.*, **68**, 75 (2003).

Scheme 12.15. Nucleophilic and Solvolytic Ring Opening of Epoxides

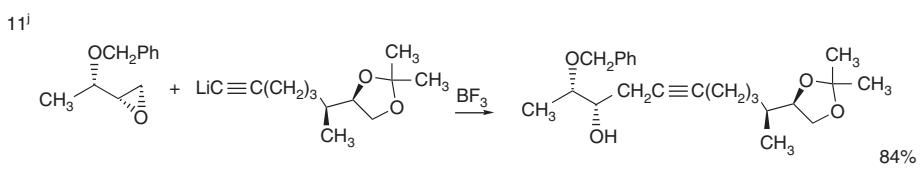
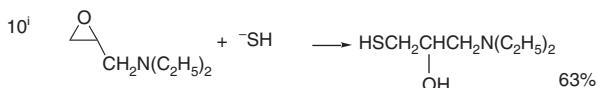
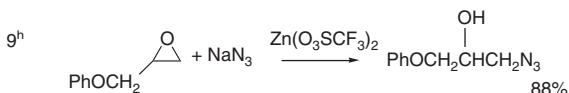
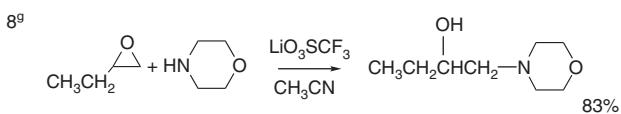
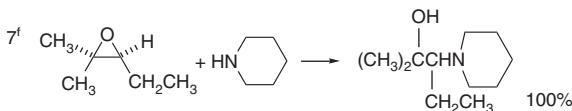
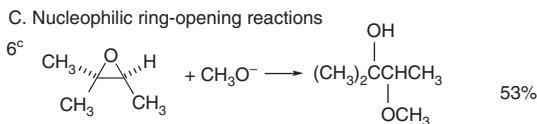
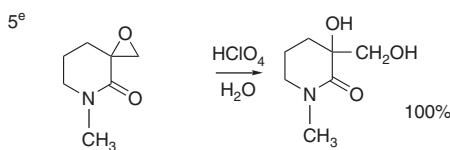
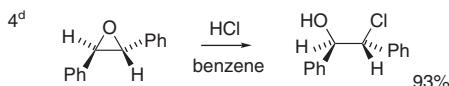
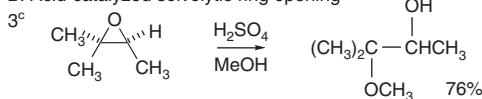
CHAPTER 12

Oxidations

A. Epoxidation with solvolysis of the intermediate epoxide



B. Acid-catalyzed solvolytic ring opening



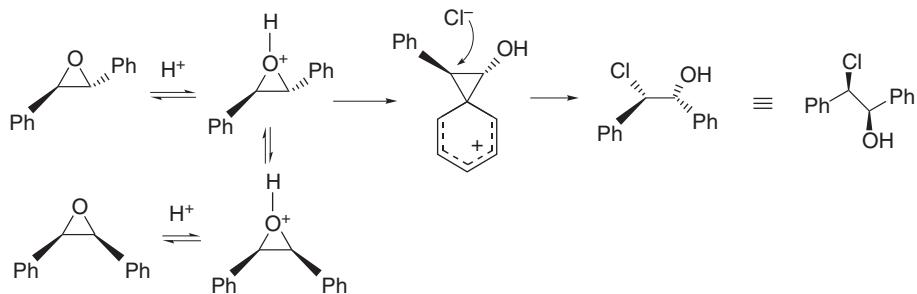
(Continued)

- a. A. Roebuck and H. Adkins, *Org. Synth.*, **III**, 217 (1955).
 b. T. R. Kelly, *J. Org. Chem.*, **37**, 3393 (1972).
 c. S. Winstein and L. L. Ingraham, *J. Am. Chem. Soc.*, **74**, 1160 (1952).
 d. G. Berti, F. Bottari, P. L. Ferrarinii, and B. Macchia, *J. Org. Chem.*, **30**, 4091 (1965).
 e. M. L. Rueppel and H. Rapoport, *J. Am. Chem. Soc.*, **94**, 3877 (1972).
 f. T. Colclough, J. I. Cunneen, and C. G. Moore, *Tetrahedron*, **15**, 187 (1961).
 g. J. Auge and F. Leroy, *Tetrahedron Lett.*, **37**, 7715 (1996).
 h. M. Chini, P. Crotti, and F. Macchia, *Tetrahedron Lett.*, **31**, 5641 (1990).
 i. D. M. Burness and H. O. Bayer, *J. Org. Chem.*, **28**, 2283 (1963).
 j. Z. Liu, C. Yu, R.-F. Wang, and G. Li, *Tetrahedron Lett.*, **39**, 5261 (1998).

SECTION 12.2

Addition of Oxygen at
Carbon-Carbon Double
Bonds

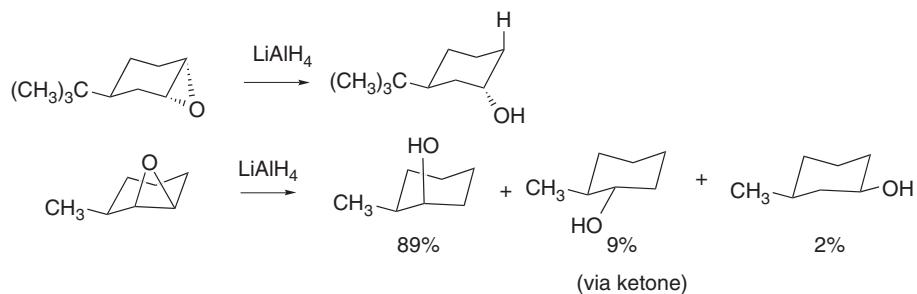
more stable *trans* isomer by reversible ring opening and formation of the more stable *trans*-phenonium ion.



Entry 5 is an example of synthetic application of acid-catalyzed ring opening.

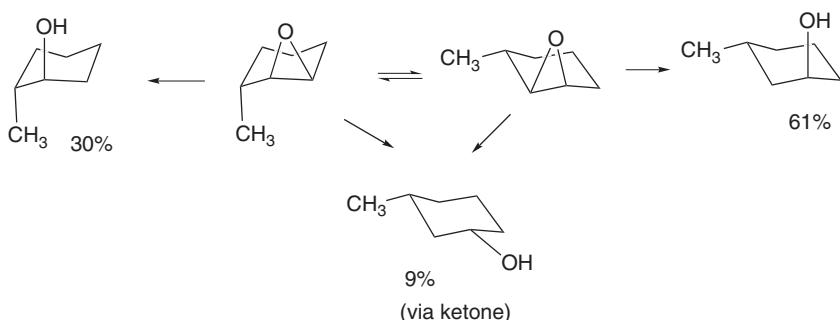
Entries 6 to 11 are examples of nucleophilic ring opening. Each of these entries displays the expected preference for reaction at the less hindered carbon. Entries 8 and 9 involve metal ion catalysis. Entry 11, which involves carbon-carbon bond formation, was part of a synthesis of epothilone A.

12.2.3.2. Reductive Ring Opening. Epoxides can be reduced to saturated alcohols. Lithium aluminum hydride acts as a nucleophilic reducing agent and the hydride is added at the less-substituted carbon atom of the epoxide ring. Substituted cyclohexene oxides prefer diaxial ring opening. A competing process, which accounts for about 10% of the product in the examples shown, involves rearrangement to the cyclohexanone (see below) by hydride shift, followed by reduction.¹²⁹

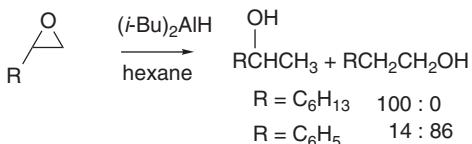


¹²⁹ B. Rickborn and J. Quartucci, *J. Org. Chem.*, **29**, 3185 (1964); B. Rickborn and W. Z. Lamke, II, *J. Org. Chem.*, **32**, 537 (1967).

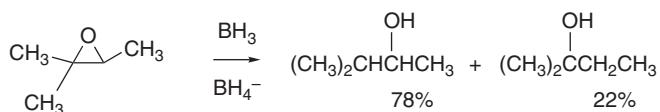
The *trans*-3-methyl isomer appears to react through two conformers, with the axial methyl conformer giving *trans*-2-methylcyclohexanol.



Lithium triethylborohydride is more reactive than LiAlH_4 and is superior for epoxides that are resistant to reduction.¹³⁰ Reduction by dissolving metals, such as lithium in ethylenediamine,¹³¹ also gives good yields. Di-*i*-butylaluminum hydride also reduces epoxides. 1,2-Epoxyoctane gives 2-octanol in excellent yield, and styrene oxide gives a 1:6 mixture of the secondary and primary alcohols.¹³² This relationship indicates that nucleophilic ring opening controls the regiochemistry for 1,2-epoxyoctane but that ring cleavage at the benzylic position is the major factor for styrene oxide.



Diborane in THF reduces epoxides, but the yields are low, and other products are formed by pathways that result from the electrophilic nature of diborane.¹³³ Better yields are obtained when BH_4^- is included in the reaction system, but the electrophilic nature of diborane is still evident because the dominant product results from addition of the hydride at the more-substituted carbon.¹³⁴



The overall transformation of alkenes to alcohols that is accomplished by epoxidation and reduction corresponds to alkene hydration. Assuming a nucleophilic ring opening by hydride addition at the less-substituted carbon, the reaction corresponds to the Markovnikov orientation. This reaction sequence is therefore an alternative to the hydration methods discussed in Chapter 4 for converting alkenes to alcohols.

¹³⁰ S. Krishnamurthy, R. M. Schubert, and H. C. Brown, *J. Am. Chem. Soc.*, **95**, 8486 (1973).

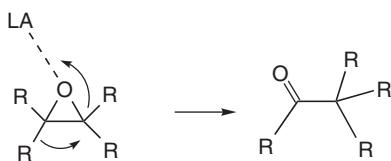
¹³¹ H. C. Brown, S. Ikegami, and J. H. Kawakami, *J. Org. Chem.*, **35**, 3243 (1970).

¹³² J. J. Eisch, Z.-R. Liu, and M. Singh, *J. Org. Chem.*, **57**, 1618 (1992).

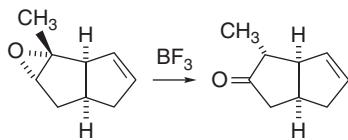
¹³³ D. J. Pasto, C. C. Cumbo, and J. Hickman, *J. Am. Chem. Soc.*, **88**, 2201 (1966).

¹³⁴ H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc.*, **90**, 2686 (1968).

12.2.3.3. Rearrangement of Epoxides to Carbonyl Compounds. Epoxides can be isomerized to carbonyl compounds by Lewis acids.¹³⁵ This reaction is closely related to the pinacol rearrangement (see p. 883). The epoxide oxygen functions as the leaving group and becomes the oxygen in the new carbonyl group.

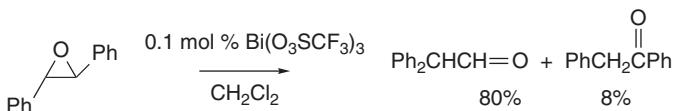


Carbocation intermediates are involved and the structure and stereochemistry of the product are determined by the factors that govern substituent migration in the carbocation. Clean, high-yield reactions can be expected only where structural or conformational factors promote a selective rearrangement. Boron trifluoride is frequently used as the reagent.

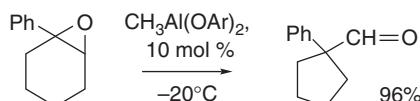


Ref. 136

Catalytic amounts of $\text{Bi}(\text{O}_3\text{SCF}_3)_3$ also promote this rearrangement.¹³⁷



Bulky diaryloxymethylaluminum reagents are also effective for this transformation.



Ar = 2,6-di-*t*-butyl-4-bromophenyl

Ref. 138

This reagent is selective for rearrangement to aldehydes in cases where BF_3 , SnCl_4 , and SbF_5 give mixtures.¹³⁹

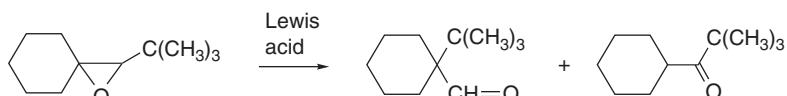
¹³⁵ J. N. Coxon, M. P. Hartshorn, and W. J. Rae, *Tetrahedron*, **26**, 1091 (1970).

¹³⁶ J. K. Whitesell, R. S. Matthews, M. A. Minton, and A. M. Helbling, *J. Am. Chem. Soc.*, **103**, 3468 (1981).

¹³⁷ K. A. Bhatia, K. J. Eash, N. M. Leonard, M. C. Oswald, and R. S. Mohan, *Tetrahedron Lett.*, **42**, 8129 (2001).

¹³⁸ K. Maruoka, S. Nagahara, T. Ooi, and H. Yamamoto, *Tetrahedron Lett.*, **30**, 5607 (1989).

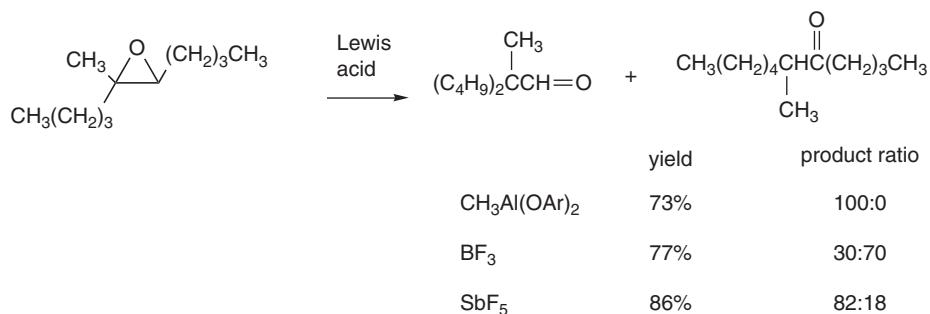
¹³⁹ K. Maruoka, T. Ooi, and H. Yamamoto, *Tetrahedron*, **48**, 3303 (1992); K. Maruoka, N. Murase, R. Bureau, T. Ooi, and H. Yamamoto, *Tetrahedron*, **50**, 3663 (1994).



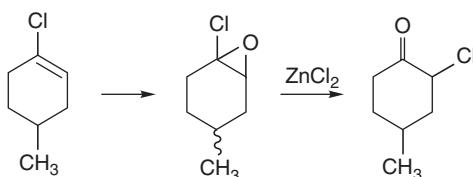
yield product ratio

$\text{CH}_3\text{Al}(\text{OAr})_2$	72%	100:0
BF_3	55%	33:67
SnCl_4	72%	50:50
SbF_5	79%	15:85

This selectivity is attributed to the steric bulk of the aluminum reagent favoring the migration of the larger alkyl group. The same selectivity pattern is observed with unbranched substituents.

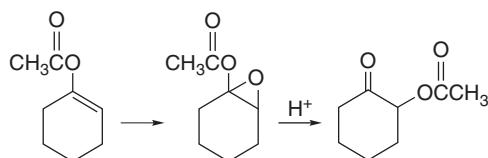


Double bonds having oxygen and halogen substituents are susceptible to epoxidation, and the reactive epoxides that are generated serve as intermediates in some useful synthetic transformations in which the substituent migrates to the other carbon of the original double bond. Vinyl chlorides furnish haloepoxides that can rearrange to α -haloketones.



Ref. 140

When this reaction sequence is applied to enol esters or enol ethers, the result is α -oxygenation of the starting carbonyl compound. Enol acetates form epoxides that rearrange to α -acetoxyketones.

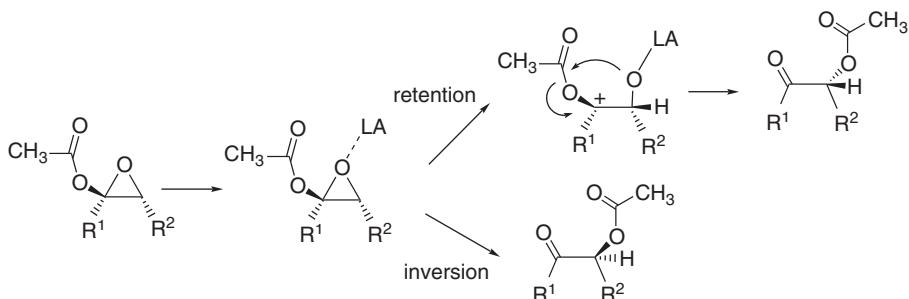


Ref. 141

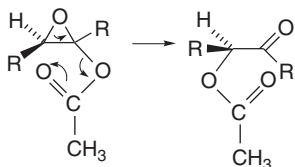
¹⁴⁰. R. N. McDonald and T. E. Tabor, *J. Am. Chem. Soc.*, **89**, 6573 (1967).

¹⁴¹. K. L. Williamson, J. I. Coburn, and M. F. Herr, *J. Org. Chem.*, **32**, 3934 (1967).

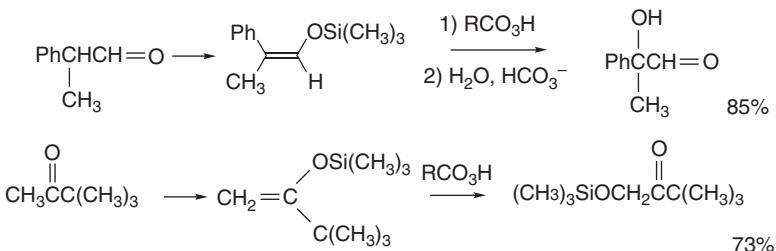
The stereochemistry of the reaction depends on the Lewis acid. Protic acids favor retention of configuration, as does TMSOTf. Most metal halides give mixtures of inversion and retention, but $\text{Al}(\text{CH}_3)_3$ gives dominant inversion.¹⁴² Inversion is suggestive of direct carbonyl group participation.



The reaction can also be done thermally. The stereochemistry of the thermal rearrangement of the acetoxy epoxides involves inversion at the carbon to which the acetoxy group migrates,¹⁴³ and reaction probably proceeds through a cyclic TS.



A more synthetically reliable version of this reaction involves epoxidation of silyl enol ethers. Epoxidation of the silyl enol ethers followed by aqueous workup gives α -hydroxyketones and α -hydroxyaldehydes.¹⁴⁴

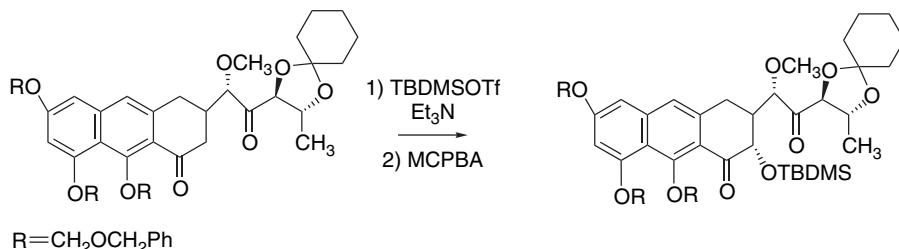


The epoxidation can be done either with peroxy acids or DMDO. In the former case, the rearrangement is catalyzed by the carboxylic acid that is formed, whereas with DMDO, the intermediate epoxides can sometimes be isolated.

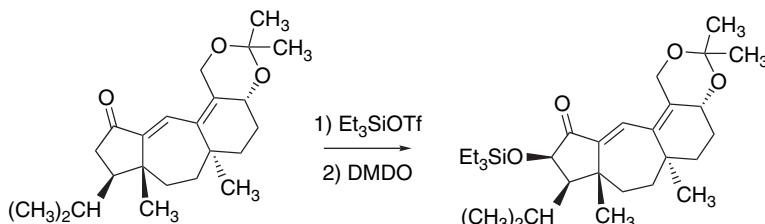
¹⁴². Y. Zhu, L. Shu., Y. Tu, and Y. Shi, *J. Org. Chem.*, **66**, 1818 (2001).

¹⁴³. K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

¹⁴⁴. A. Hassner, R. H. Reuss, and H. W. Pinnick, *J. Org. Chem.*, **40**, 3427 (1975).



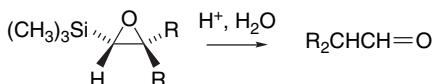
Ref. 145



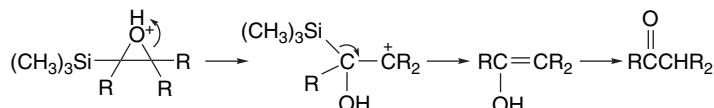
Ref. 146

The oxidation of silyl enol ethers with the osmium tetroxide–amine oxide combination also leads to α -hydroxyketones in generally good yields.¹⁴⁷

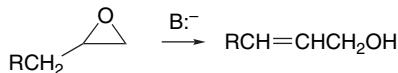
Epoxides derived from vinylsilanes are converted by mildly acidic conditions into ketones or aldehydes.¹⁴⁸



The regioselective ring opening of the silyl epoxides is facilitated by the stabilizing effect that silicon has on a positive charge in the β -position. This facile transformation permits vinylsilanes to serve as the equivalent of carbonyl groups in multistep synthesis.¹⁴⁹



12.2.3.4. Base-Catalyzed Ring Opening of Epoxides. Base-catalyzed ring opening of epoxides provides a route to allylic alcohols.¹⁵⁰



¹⁴⁵ W. R. Roush, M. R. Michaelides, D. F. Tai, and W. K. M. Chong, *J. Am. Chem. Soc.*, **109**, 7575 (1987).

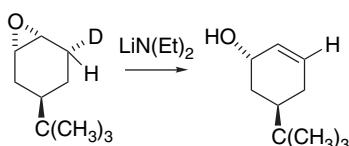
¹⁴⁶ M. Mandal and S. J. Danishefsky, *Tetrahedron Lett.*, **45**, 3831 (2004).

¹⁴⁷ J. P. McCormick, W. Tomasik, and M. W. Johnson, *Tetrahedron Lett.*, 607 (1981).

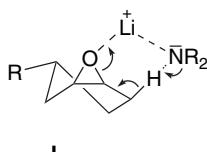
¹⁴⁸ G. Stork and E. Colvin, *J. Am. Chem. Soc.*, **93**, 2080 (1971).

¹⁴⁹ G. Stork and M. E. Jung, *J. Am. Chem. Soc.*, **96**, 3682 (1974).

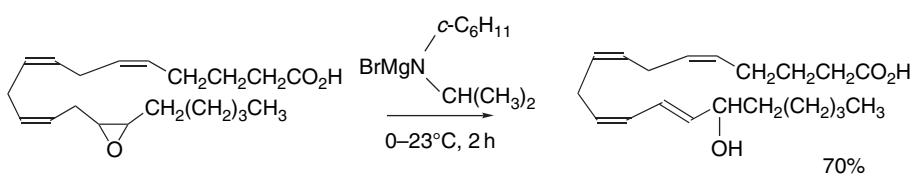
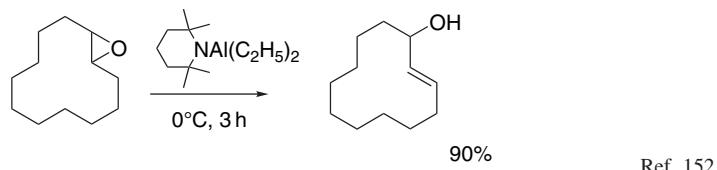
¹⁵⁰ J. K. Crandall and M. Apparu, *Org. React.*, **29**, 345 (1983).



A TS represented by structure **L** accounts for this stereochemistry. Such an arrangement is favored by ion pairing that would bring the amide anion and lithium cation into close proximity. Simultaneous coordination of the lithium ion at the epoxide results in a *syn* elimination.



Among other reagents that effect epoxide ring opening are diethylaluminum 2,2,6,6-tetramethylpiperidide and magnesium *N*-cyclohexyl-*N*-(*i*-propyl)amide.



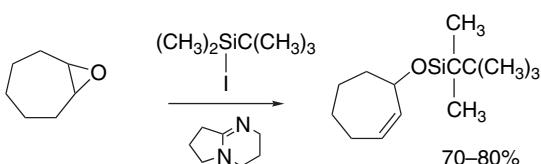
These reagents are appropriate even for very sensitive molecules. Their efficacy is presumably due to the Lewis acid effect of the aluminum and magnesium ions. The hindered nature of the amide bases also minimizes competition from nucleophilic ring opening.

¹⁵¹. R. P. Thummel and B. Rickborn, *J. Am. Chem. Soc.*, **92**, 2064 (1970).

¹⁵². A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **96**, 6513 (1974).

¹⁵³. E. J. Corey, A. Marfat, J. R. Falck, and J. O. Albright, *J. Am. Chem. Soc.*, **102**, 1433 (1980).

Epoxides can also be converted to allylic alcohols using electrophilic reagents. The treatment of epoxides with trialkyl silyl iodides and an organic base gives the silyl ether of the corresponding allylic alcohols.¹⁵⁴



Similar ring openings have been achieved using trimethylsilyl triflate and 2,6-di-*t*-butylpyridine.¹⁵⁵

Each of these procedures for epoxidation and ring opening is the equivalent of an allylic oxidation of a double bond with migration of the double bond.

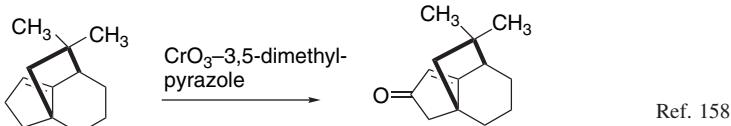


In Section 12.3, other means of effecting this transformation are described.

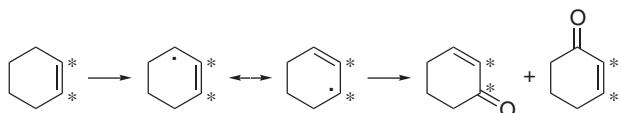
12.3. Allylic Oxidation

12.3.1. Transition Metal Oxidants

Carbon-carbon double bonds, apart from being susceptible to addition of oxygen or cleavage, can also react at allylic positions. Synthetic utility requires that there be good selectivity between the possible reactions. Among the transition metal oxidants, the CrO₃-pyridine reagent in methylene chloride¹⁵⁶ and a related complex in which 3,5-dimethylpyrazole replaces pyridine¹⁵⁷ are the most satisfactory for allylic oxidation.



Several pieces of mechanistic evidence implicate allylic radicals or cations as intermediates in these oxidations. Thus ¹⁴C in cyclohexene is distributed in the product cyclohexenone indicating that a symmetrical allylic intermediate is involved at some stage.¹⁵⁹



¹⁵⁴. M. R. Detty, *J. Org. Chem.*, **45**, 924 (1980); M. R. Detty and M. D. Seiler, *J. Org. Chem.*, **46**, 1283 (1981).

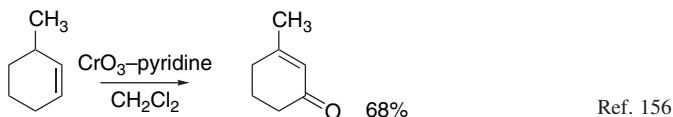
¹⁵⁵. S. F. Martin and W. Li, *J. Org. Chem.*, **56**, 642 (1991).

¹⁵⁶. W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969).

¹⁵⁷. W. G. Salmond, M. A. Barta, and J. L. Havens, *J. Org. Chem.*, **43**, 2057 (1978); R. H. Schlessinger, J. L. Wood, A. J. Poos, R. A. Nugent, and W. H. Parson, *J. Org. Chem.*, **48**, 1146 (1983).

¹⁵⁸. A. B. Smith, III, and J. P. Konopelski, *J. Org. Chem.*, **49**, 4094 (1984).

¹⁵⁹. K. B. Wiberg and S. D. Nielsen, *J. Org. Chem.*, **29**, 3353 (1964).



Detailed mechanistic understanding of the allylic oxidation has not been developed. One possibility is that an intermediate oxidation state of Cr, specifically Cr(IV), acts as the key reagent by abstracting hydrogen.¹⁶⁰

Several catalytic systems based on copper can also achieve allylic oxidation. These reactions involve induced decomposition of peroxy esters (see Part A, Section 11.1.4). When chiral copper ligands are used, enantioselectivity can be achieved. Table 12.1 shows some results for the oxidation of cyclohexene under these conditions.

12.3.2. Reaction of Alkenes with Singlet Oxygen

Among the oxidants that add oxygen at carbon-carbon double bonds is singlet oxygen.¹⁶¹ For most alkenes this reaction proceeds with the removal of an allylic

Table 12.1. Enantioselective Copper-Catalyzed Allylic Oxidation of Cyclohexene

	Catalyst	Yield%	e.e.%
1 ^a		43	80
2 ^b		73	75
3 ^c		19	42
4 ^d		67	50

a. M. B. Andrus and X. Chen, *Tetrahedron*, **53**, 16229 (1997).

b. G. Sekar, A. Datta Gupta, and V. K. Singh, *J. Org. Chem.*, **62**, 2961 (1998).

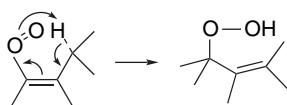
c. K. Kawasaki and T. Katsuki, *Tetrahedron*, **53**, 6337 (1997).

d. M. J. Sodergren and P. G. Andersson, *Tetrahedron Lett.*, **37**, 7577 (1996).

¹⁶⁰ P. Mueller and J. Rocek, *J. Am. Chem. Soc.*, **96**, 2836 (1974).

¹⁶¹ H. H. Wasserman and R. W. Murray, eds., *Singlet Oxygen*, Academic Press, New York, 1979; A. A. Frimer, *Chem. Rev.*, **79**, 359 (1979); A. Frimer, ed., *Singlet Oxygen*, CRC Press, Boca Raton, FL, 1985; C. S. Foote and E. L. Clennan, in *Active Oxygen in Chemistry*, C. S. Foote, J. S. Valentine, A. Greenberg, and J. F. Lieberman, eds., Blackie Academic & Professional, London, 1995, pp. 105–140; M. Prein and W. Adam, *Angew. Chem. Int. Ed. Engl.*, **35**, 477 (1996); M. Orfanopoulos, *Molec. Supramolec. Photochem.*, **8**, 243 (2001).

hydrogen and shift of the double bond to provide an allylic hydroperoxide as the initial product.



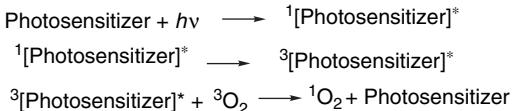
The allylic hydroperoxides generated by singlet oxygen oxidation are normally reduced to the corresponding allylic alcohol. The net synthetic transformation is then formation of an allylic alcohol with transposition of the double bond.

A number of methods of generating singlet oxygen are summarized in Scheme 12.16. Singlet oxygen is usually generated from oxygen by dye-sensitized photoexcitation. Porphyrins are also often used as sensitizers. An alternative chemical means of generating $^1\text{O}_2$ involves the reaction of hydrogen peroxide with sodium hypochlorite (Entry 2). The method in Entry 3 involves formation of unstable trioxaphosphetane intermediates from O_3 and phosphine or phosphate esters. The adducts are formed at low temperature (-70°C) and decomposition with generation of singlet oxygen occurs at about -35°C . The peroxide intermediate in Entry 4 is formed by photolytic addition of oxygen to diphenylanthracene and reacts at around 80°C to generate $^1\text{O}_2$. The method in Entry 5 involves formation of an unstable precursor of $^1\text{O}_2$, a trialkylsilyl hydrotrioxide. The half-life of the adduct is roughly 2.5 min at -60°C .

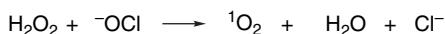


Scheme 12.16. Generation of Singlet Oxygen

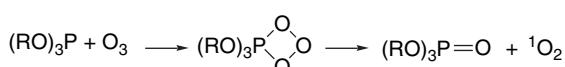
1^a



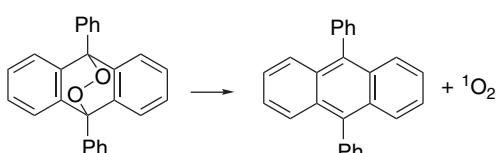
2^b



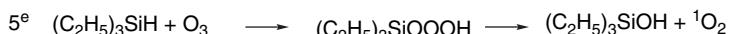
3^c



4^d



5^e



a. C. S. Foote and S. Wexler, *J. Am. Chem. Soc.*, **86**, 3880 (1964).

b. C. S. Foote and S. Wexler, *J. Am. Chem. Soc.*, **86**, 3879 (1964).

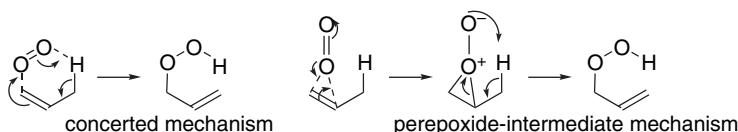
c. R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.*, **90**, 537 (1968).

d. H. H. Wasserman, J. R. Sheffler, and J. L. Cooper, *J. Am. Chem. Soc.*, **94**, 4991 (1972).

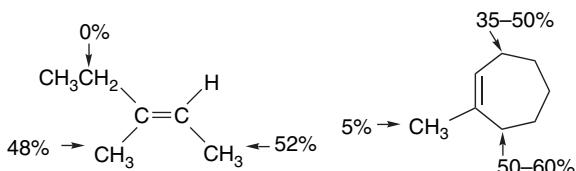
e. E. J. Corey, M. M. Mehrotra, and A. U. Khan, *J. Am. Chem. Soc.*, **108**, 2472 (1986).

Singlet oxygen decays to the ground state triplet at a rate that is strongly dependent on the solvent.¹⁶² Measured half-lives range from about 700 μs in carbon tetrachloride to 2 μs in water. The choice of solvent can therefore have a pronounced effect on the efficiency of oxidation; the longer the singlet state lifetime, the more likely it is that reaction with the alkene can occur.

The reactivity order of alkenes is that expected for attack by an electrophilic reagent. Reactivity increases with the number of alkyl substituents.¹⁶³ Terminal alkenes are relatively inert. The reaction has a low ΔH^\ddagger and relative reactivity is dominated by entropic factors.¹⁶⁴ Steric effects govern the direction of approach of the oxygen, so the hydroperoxy group is usually introduced on the less hindered face of the double bond. A key mechanistic issue in singlet oxygen oxidations is whether it is a concerted process or involves an intermediate formulated as a “perepoxide.” Most of the available evidence points to the perepoxide mechanism.¹⁶⁵



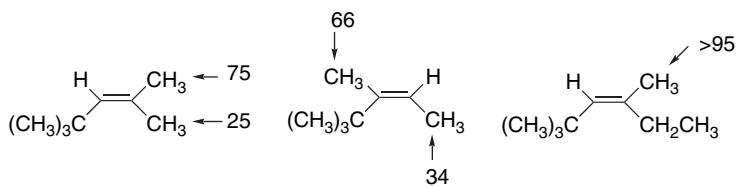
Many alkenes present several different allylic hydrogens, and in this type of situation it is important to be able to predict the degree of selectivity.¹⁶⁶ A useful generalization is that *there is a preference for removal of a hydrogen from the more congested side of the double bond.*¹⁶⁷



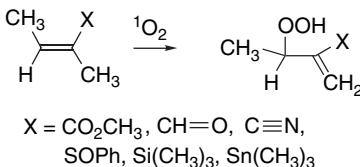
This “*cis* effect” is ascribed to a more favorable TS when the singlet O₂ can interact with two allylic hydrogens. The stabilizing interaction has been described both in FMO¹⁶⁸ and hydrogen-bonding¹⁶⁹ terminology and can be considered an electrostatic effect. The *cis* effect does not apply to alkene having *t*-butyl substituents.¹⁷⁰ There are

- ¹⁶². P. B. Merkel and D. R. Kearns, *J. Am. Chem. Soc.*, **94**, 1029, 7244 (1972); P. R. Ogilby and C. S. Foote, *J. Am. Chem. Soc.*, **105**, 3423 (1983); J. R. Hurst, J. D. McDonald, and G. B. Schuster, *J. Am. Chem. Soc.*, **104**, 2065 (1982).
- ¹⁶³. K. R. Kopecky and H. J. Reich, *Can. J. Chem.*, **43**, 2265 (1965); C. S. Foote and R. W. Denny, *J. Am. Chem. Soc.*, **93**, 5162 (1971); A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961).
- ¹⁶⁴. J. R. Hurst and G. B. Schuster, *J. Am. Chem. Soc.*, **104**, 6854 (1982).
- ¹⁶⁵. M. Orfanopoulos, I. Smonou, and C. S. Foote, *J. Am. Chem. Soc.*, **112**, 3607 (1990); M. Statakis, M. Orfanopoulos, J. S. Chen, and C. S. Foote, *Tetrahedron Lett.*, **37**, 4105 (1996).
- ¹⁶⁶. M. Stratakis and M. Orfanopoulos, *Tetrahedron*, **56**, 1595 (2000).
- ¹⁶⁷. M. Orfanopoulos, M. B. Grdina, and L. M. Stephenson, *J. Am. Chem. Soc.*, **101**, 275 (1979); K. H. Schulte-Elte, B. L. Muller, and V. Rautenstrauch, *Helv. Chim. Acta*, **61**, 2777 (1978); K. H. Schulte-Elte and V. Rautenstrauch, *J. Am. Chem. Soc.*, **102**, 1738 (1980).
- ¹⁶⁸. L. M. Stephenson, *Tetrahedron Lett.*, 1005 (1980).
- ¹⁶⁹. J. R. Hurst, S. L. Wilson, and G. B. Schuster, *Tetrahedron*, **41**, 2191 (1985).
- ¹⁷⁰. M. Stratakis and M. Orfanopoulos, *Tetrahedron Lett.*, **36**, 4291 (1995).

probably two reasons for this: the *t*-butyl group does not provide any allylic hydrogens and its steric bulk may interfere with approach by ${}^1\text{O}_2$.

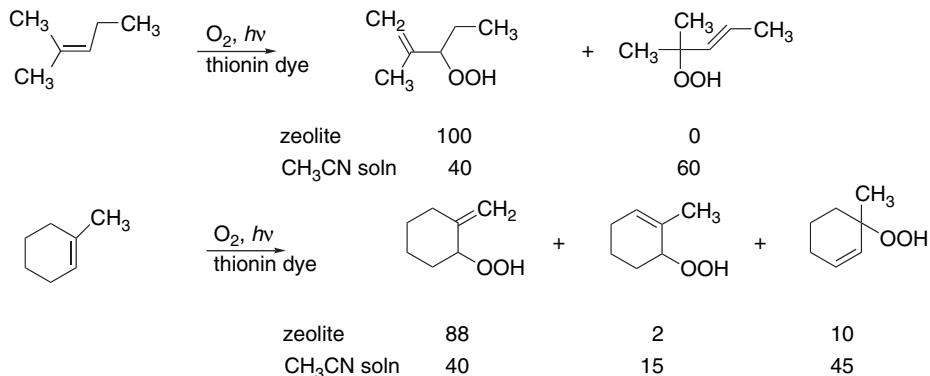


Polar functional groups such as carbonyl, cyano, and sulfoxide, as well as silyl and stannyl groups, exert a strong directing effect, favoring proton removal from the geminal methyl group.¹⁷¹



Hydroxy¹⁷² and amino¹⁷³ groups favor *syn* stereoselectivity. This is similar to the substituent effects observed for peroxy acids and suggests that the substituents may stabilize the TS by hydrogen bonding.

Recently techniques have been developed for ${}^1\text{O}_2$ oxidations in zeolite cavities.¹⁷⁴ The photosensitizer is absorbed in the zeolite and generation of ${}^1\text{O}_2$ and reaction with the alkene occurs within the cavity. The reactions under these conditions show changes in both regiochemistry¹⁷⁵ and stereoselectivity. The *cis* effect is reduced and there is a preference for hydrogen abstraction from methyl groups.



¹⁷¹ E. L. Clennan, X. Chen, and J. J. Koola, *J. Am. Chem. Soc.*, **112**, 5193 (1990); M. Orfanopoulos, M. Stratakis, and Y. Elemes, *J. Am. Chem. Soc.*, **112**, 6417 (1990); W. Adam and M. J. Richter, *Tetrahedron Lett.*, **34**, 8423 (1993).

¹⁷² W. Adam and B. Nestler, *J. Am. Chem. Soc.*, **114**, 6549 (1992); W. Adam and B. Nestler, *J. Am. Chem. Soc.*, **115**, 5041 (1993); M. Stratakis, M. Orfanopoulos, and C. S. Foote, *Tetrahedron Lett.*, **37**, 7159 (1996).

¹⁷³ H.-G. Brunker and W. Adam, *J. Am. Chem. Soc.*, **117**, 3976 (1995).

¹⁷⁴ X. Li and V. Ramamurthy, *J. Am. Chem. Soc.*, **118**, 10666 (1996).

¹⁷⁵ J. Shailaja, J. Sivaguru, R. J. Robbins, V. Ramamurthy, R. B. Sunoj, and J. Chandrasekhar, *Tetrahedron*, **56**, 6927 (2000); E. L. Clennan and J. P. Sram, *Tetrahedron*, **56**, 6945 (2000); M. Stratakis, C. Rabalakos, G. Mpourmpakis, and L. G. Froudakis, *J. Org. Chem.*, **68**, 2839 (2003).

These changes in regio- and stereochemistry are likely due to conformation changes and electrostatic factors within the cavity. The intrazeolite oxidations can be improved by use of fluorocarbon solvents, owing to an enhanced lifetime of $^1\text{O}_2$ and to improved occupancy of the cavity by hydrocarbons in this solvent.¹⁷⁶

The singlet oxidation mechanism has been subject of a comparative study by kinetic isotope effects and computation of the reaction energy surface.¹⁷⁷ The reaction is described as proceeding through the perepoxide structure, but rather than being a distinct intermediate, this structure occurs at a saddle point on the energy surface; that is, there is no barrier to the second stage of the reaction, the hydrogen abstraction. Figure 12.12 is a representation of such a surface and Figure 12.13 shows the computed geometric characteristics for the perepoxides from Z-2-butene and 2,3-dimethyl-2-butene. This study also gives a consistent account for the *cis* effect. The perepoxide structure for engagement of the *cis* hydrogens is of lower energy than the corresponding structure involving the *trans* hydrogens. The *cis* transition structure is attained earlier and retains the synchronous character of the TSs from the symmetrical alkenes, as shown in Figure 12.14.

Scheme 12.17 gives some examples of oxidations by singlet oxygen. The reaction in Entry 1 was used to demonstrate that $^1\text{O}_2$ can be generated from H_2O_2 and ClO^- . Similarly, the reaction in Entry 2 was used to verify that the phosphite-ozone adducts

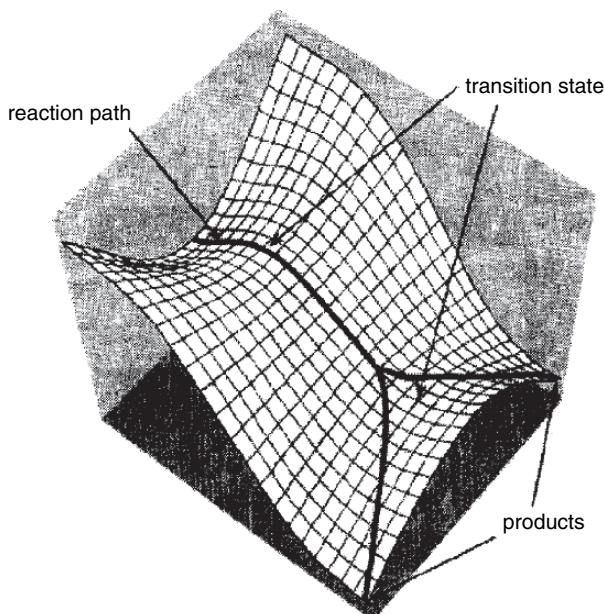


Fig. 12.12. Three-dimensional energy surface showing adjacent transition structures without an intervening intermediate. Reproduced from *J. Am. Chem. Soc.*, **125**, 1319 (2003), by permission of the American Chemical Society.

¹⁷⁶ A. Pace and E. L. Clennan, *J. Am. Chem. Soc.*, **124**, 11236 (2002).

¹⁷⁷ D. A. Singleton, C. Hang, M. J. Szymanksi, M. P. Meyer, A. G. Leach, K. T. Kuwata, J. S. Chen, A. Greer, C. S. Foote, and K. N. Houk, *J. Am. Chem. Soc.*, **125**, 1319 (2003).

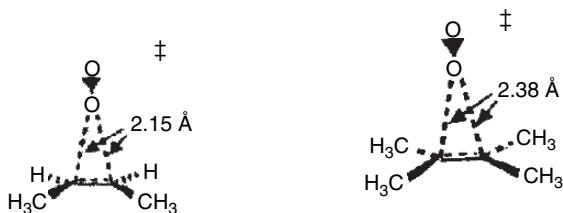
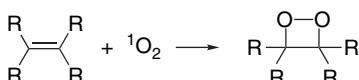


Fig. 12.13. Peroxide transition structures from Z-2-butene and 2,3-dimethyl-2-butene. Reproduced from *J. Am. Chem. Soc.*, **125**, 1319 (2003), by permission of the American Chemical Society.

can serve as a ${}^1\text{O}_2$ source. The reactions in Entries 3 and 4 are representative photo-sensitized procedures with subsequent reduction of the hydroperoxide. Entry 5 used tetra-(perfluorophenyl)porphyrin as the photosensitizer. This compound, as well as the tetra-(2,6-dichlorophenyl) analog, is reported to have improved stability to degradation under the reaction conditions. In this case the intermediate hydroperoxide was dehydrated to an enone using acetic anhydride. This reaction was carried out on a 25-g scale.

Certain compounds react with singlet oxygen in a different manner, giving dioxetanes as products.¹⁷⁸



This reaction is not usually a major factor with alkenes bearing only alkyl groups, but is important for vinyl ethers and other alkenes with donor substituents. These



Fig. 12.14. Competing *cis* abstraction and *trans* abstraction transition structures for hydroperoxide formation 2-methyl-2-butene. Adapted *J. Am. Chem. Soc.*, **125**, 1319 (2003), by permission of the American Chemical Society.

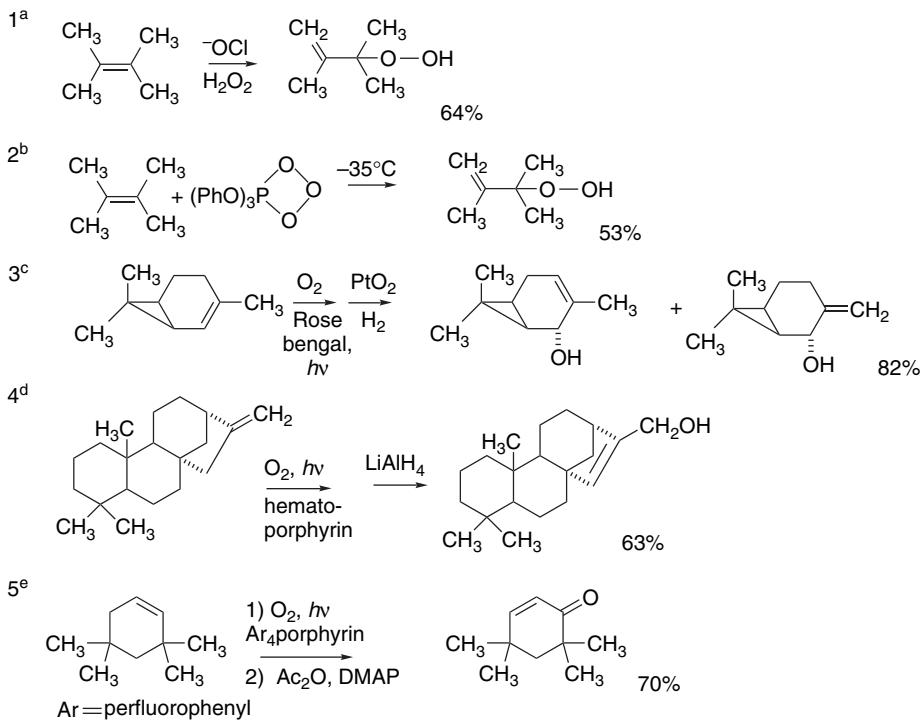
¹⁷⁸ W. Fenical, D. R. Kearns, and P. Radlick, *J. Am. Chem. Soc.*, **91**, 3396 (1969); S. Mazur and C. S. Foote, *J. Am. Chem. Soc.*, **92**, 3225 (1970); P. D. Bartlett and A. P. Schaap, *J. Am. Chem. Soc.*, **92**, 3223 (1970).

Scheme 12.17. Oxidation of Alkenes with Singlet Oxygen

1123

SECTION 12.3

Allylic Oxidation



a. C. S. Foote, S. Wexler, W. Ando, and R. Higgins, *J. Am. Chem. Soc.*, **90**, 975 (1968).

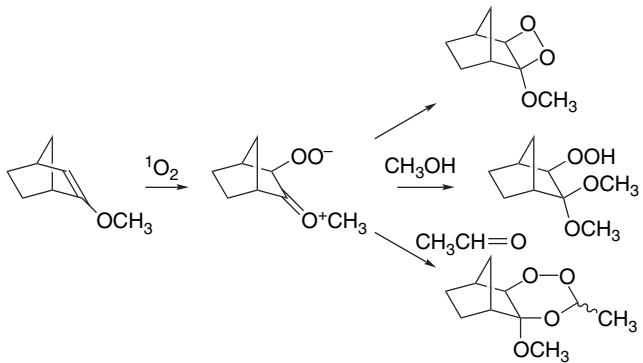
b. R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.*, **91**, 5358 (1969).

c. K. Gollnick and G. Schade, *Tetrahedron Lett.*, 2335 (1966).

d. R. A. Bell, R. E. Ireland, and L. N. Mander, *J. Org. Chem.*, **31**, 2536 (1966).

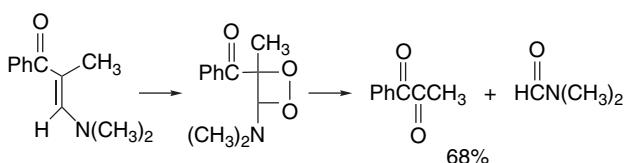
e. H. Quast, T. Dietz, and A. Witzel, *Liebigs Ann. Chem.*, 1495 (1995).

reactions are believed to proceed via zwitterionic intermediates that can be diverted by appropriate trapping reagents.¹⁷⁹

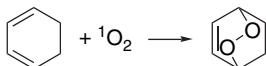


¹⁷⁹. C. W. Jefford, S. Kohmoto, J. Boukouvalas, and U. Burger, *J. Am. Chem. Soc.*, **105**, 6498 (1983).

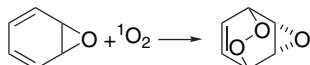
Enaminoketones undergo a clean oxidative cleavage to α -diketones, presumably through a dioxetane intermediate.¹⁸⁰



Singlet oxygen undergoes [4 + 2] cycloaddition with dienes.



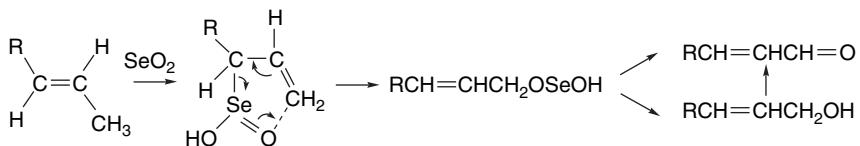
Ref. 181



Ref. 182

12.3.3. Other Oxidants

Selenium dioxide is a useful reagent for allylic oxidation of alkenes. The products can include enones, allylic alcohols, or allylic esters, depending on the reaction conditions. The mechanism consists of three essential steps: (a) an electrophilic “ene” reaction with SeO_2 , (b) a [2,3]-sigmatropic rearrangement that restores the original location of the double bond, and (c) solvolysis of the resulting selenium ester.¹⁸³



The allylic alcohols that are the initial oxidation products can be further oxidized to carbonyl groups by SeO_2 and the conjugated carbonyl compound is usually isolated. If the alcohol is the desired product, the oxidation can be run in acetic acid, in which case acetate esters are formed.

The mechanism of the reaction has been studied by determining isotope effects for 2-methyl-2-butene and comparing them with predicted values.¹⁸⁴ The isotope effect at the vinyl hydrogen is 0.92 ± 0.01 , which is consistent with rehybridization. B3LYP/6-31G* computations located several related TSs with E_a values in the range of 6.0–8.9 kcal/mol. These TSs give calculated isotope effects in good agreement with the experimental values. Although these results are not absolutely definitive, they are consistent with the other evidence for a concerted ene-type mechanism as the first step in SeO_2 oxidation.

¹⁸⁰. H. H. Wasserman and J. L. Ives, *J. Am. Chem. Soc.*, **98**, 7868 (1976).

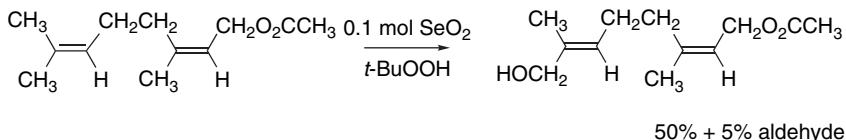
¹⁸¹. C. S. Foote, S. Wexler, W. Ando, and R. Higgins, *J. Am. Chem. Soc.*, **90**, 975 (1968).

¹⁸². C. H. Foster and G. A. Berchtold, *J. Am. Chem. Soc.*, **94**, 7939 (1972).

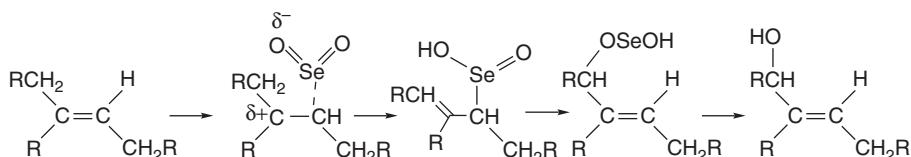
¹⁸³. K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **94**, 7154 (1972).

¹⁸⁴. D. A. Singleton and C. Hang, *J. Org. Chem.*, **65**, 7554 (2000).

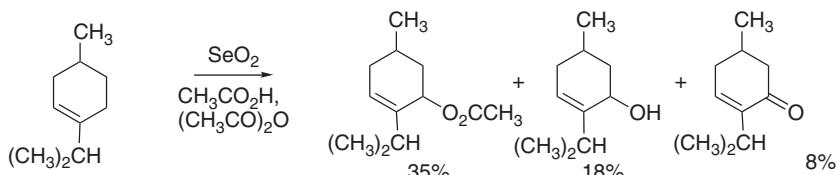
Although the traditional conditions for effecting SeO_2 oxidations involve use of a stoichiometric or excess amount of SeO_2 , it is also possible to carry out the reaction with 1.5–2 mol % SeO_2 , using *t*-butyl hydroperoxide as a stoichiometric oxidant. Under these conditions, the allylic alcohol is the major product and is obtained in good yields, even from alkenes that are poorly reactive under the traditional conditions.¹⁸⁵



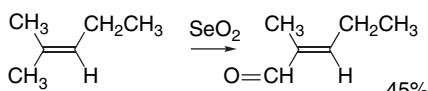
Trisubstituted alkenes are oxidized selectively at the more-substituted end of the carbon-carbon double bond, indicating that the ene reaction step is electrophilic in character.



Ref. 186



Selenium dioxide reveals a useful stereoselectivity when applied to trisubstituted *gem*-dimethyl alkenes. The products are predominantly the *E*-allylic alcohol or unsaturated aldehyde.¹⁸⁷

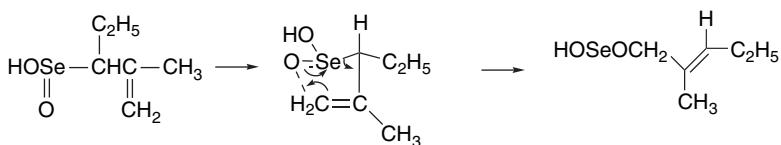


This stereoselectivity can be explained by a five-membered TS for the sigma-tropic rearrangement step. The observed *E*-stereochemistry results if the larger alkyl substituent adopts a pseudoequatorial conformation.

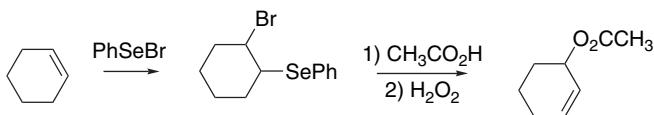
¹⁸⁵ M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc.*, **99**, 5526 (1977).

¹⁸⁶ T. Suga, M. Sugimoto, and T. Matsuura, *Bull. Chem. Soc. Jpn.*, **36**, 1363 (1963).

¹⁸⁷ U. T. Bhalerao and H. Rapoport, *J. Am. Chem. Soc.*, **93**, 4835 (1971); G. Buchi and H. Wuest, *Helv. Chim. Acta*, **50**, 2440 (1967).

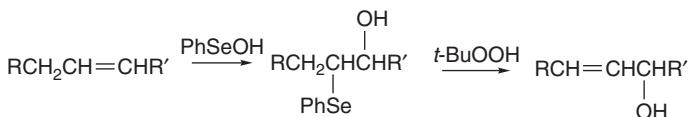


The equivalent to allylic oxidation of alkenes, but with allylic transposition of the carbon-carbon double bond, can be carried out by an indirect oxidative process involving addition of an electrophilic arylselenenyl reagent, followed by oxidative elimination of selenium. In one procedure, addition of an arylselenenyl halide is followed by solvolysis and oxidative elimination.



Ref. 188

This reaction depends upon the facile solvolysis of β -haloselenides and the facile oxidative elimination of a selenoxide, which was discussed in Section 6.6.3. An alternative method, which is experimentally simpler, involves reaction of alkenes with a mixture of diphenyl diselenide and phenylseleninic acid.¹⁸⁹ The two selenium reagents generate an electrophilic selenium species, phenylselenenic acid, PhSeOH.



The elimination is promoted by oxidation of the addition product to the selenoxide by *t*-butyl hydroperoxide. The regioselectivity in this reaction is such that the hydroxy group becomes bound at the more-substituted end of the carbon-carbon double bond. The regioselectivity of the addition step follows Markovnikov's rule with PhSe⁺ acting as the electrophile. The elimination step specifically proceeds away from the oxygen functionality.

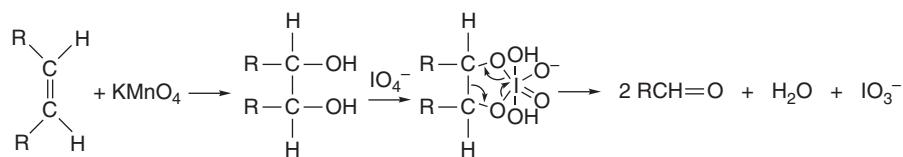
12.4. Oxidative Cleavage of Carbon-Carbon Double Bonds

12.4.1. Transition Metal Oxidants

The most selective methods for cleaving organic molecules at carbon-carbon double bonds involve glycols as intermediates. Oxidations of alkenes to glycols was discussed in Section 12.2.1. Cleavage of alkenes can be carried out in one operation under mild conditions by using a solution containing periodate ion and a catalytic

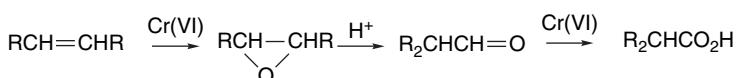
¹⁸⁸ K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **39**, 429 (1974); D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 100 (1974).

¹⁸⁹ T. Hori and K. B. Sharpless, *J. Org. Chem.*, **43**, 1689 (1978).



Osmium tetroxide used in combination with sodium periodate can also effect alkene cleavage.¹⁹¹ Successful oxidative cleavage of double bonds using ruthenium tetroxide and sodium periodate has also been reported.¹⁹² In these procedures the osmium or ruthenium can be used in substoichiometric amounts because the periodate reoxidizes the metal to the tetroxide state. Entries 1 to 4 in Scheme 12.18 are examples of these procedures. Entries 5 and 6 show reactions carried out in the course of multistep syntheses. The reaction in Entry 5 followed a 5-*exo* radical cyclization and served to excise an extraneous carbon. The reaction in Entry 6 followed introduction of the allyl group by enolate alkylation. The aldehyde group in the product was used to introduce an amino group by reductive alkylation (see Section 5.3.1.2).

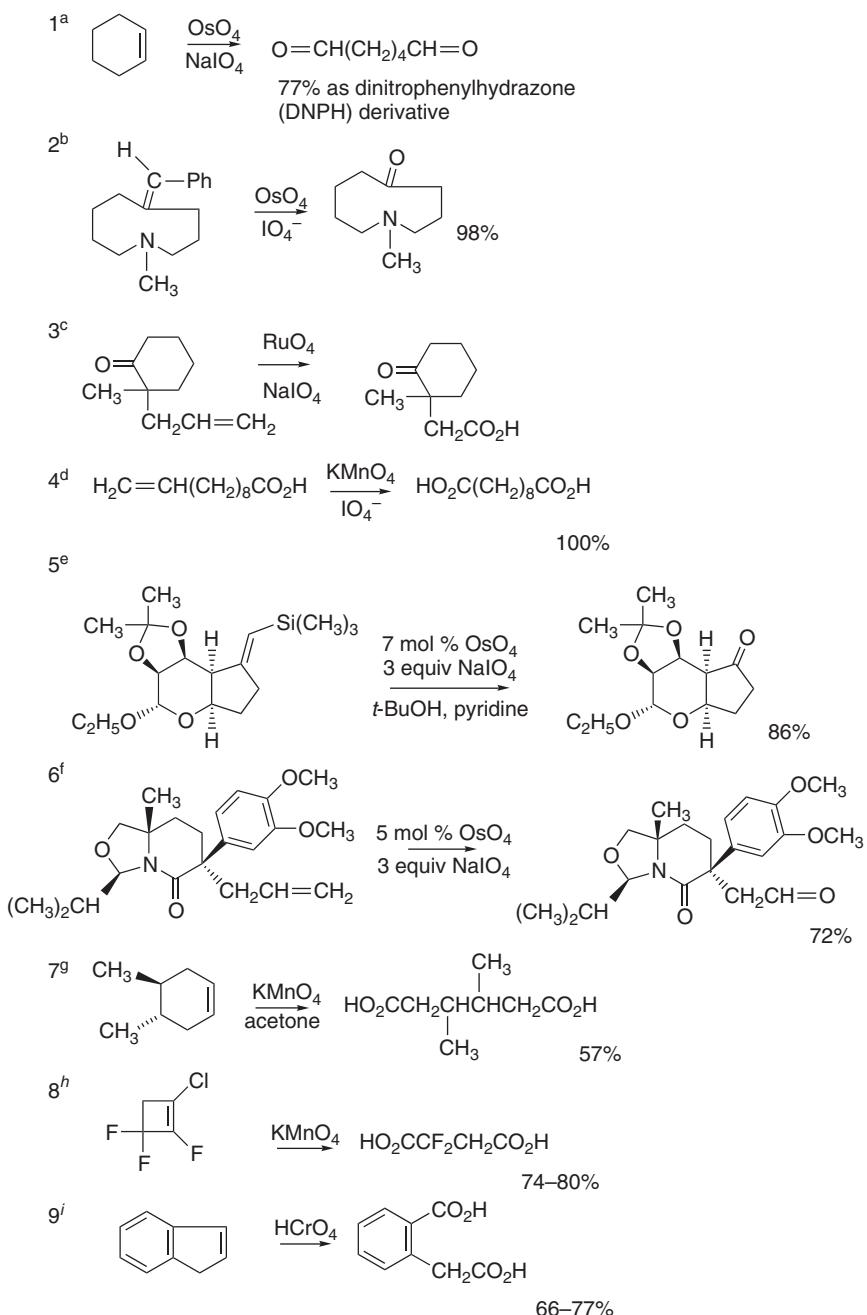
The strong oxidants Cr(VI) and MnO₄⁻ can also be used for oxidative cleavage of double bonds, provided there are no other sensitive groups in the molecule. The permanganate oxidation proceeds first to the diols and ketols, as described earlier (see p. 1075), and these are then oxidized to carboxylic acids or ketones. Good yields can be obtained provided care is taken to prevent subsequent oxidative degradation of the products. The oxidation of cyclic alkenes by Cr(VI) reagents can be a useful method for formation of dicarboxylic acids. The initial oxidation step appears to yield an epoxide that undergoes solvolytic ring opening to a glycol or glycol monoester, which is then oxidatively cleaved.¹⁹³ Two possible complications that can be encountered are competing allylic attack and skeletal rearrangement. Allylic attack can lead to eventual formation of a dicarboxylic acid that has lost one carbon atom. Pinacol-type rearrangements of the epoxide or glycol intermediates can give rise to rearranged products.



Entries 7 to 9 in Scheme 12.18 are illustrative of these oxidative ring cleavages.

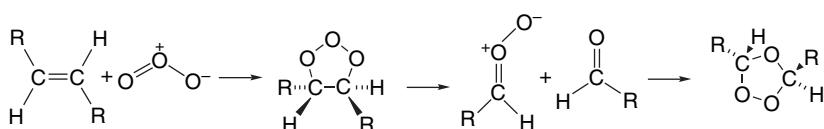
- ¹⁹⁰. R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710 (1955); E. von Rudloff, *Can. J. Chem.*, **33**, 1714 (1955).
- ¹⁹¹. R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956); H. Vorbrueggen and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 2990 (1962).
- ¹⁹². W. G. Dauben and L. E. Friedrich, *J. Org. Chem.*, **37**, 241 (1972); B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 464 (1981); J. W. Patterson, Jr., and D. V. Krishna Murthy, *J. Org. Chem.*, **48**, 4413 (1983).
- ¹⁹³. J. Rocek and J. C. Drozd, *J. Am. Chem. Soc.*, **92**, 6668 (1970); A. K. Awasthy and J. Rocek, *J. Am. Chem. Soc.*, **91**, 991 (1969).

Scheme 12.18. Oxidative Cleavage of Carbon-Carbon Double Bonds Using Transition Metal Oxidants



- a. R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).
 b. M. G. Reinecke, L. R. Kray, and R. F. Francis, *J. Org. Chem.*, **37**, 3489 (1972).
 c. A. A. Asselin, L. G. Humber, T. A. Dobson, J. Komlossy, and R. R. Martel, *J. Med. Chem.*, **19**, 787 (1976).
 d. R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).
 e. T. Honda, M. Hoshi, K. Kanai, and M. Tsubuki, *J. Chem. Soc., Perkin Trans. I*, 2091 (1994).
 f. A. I. Meyers, R. Hanreich, and K. T. Wanner, *J. Am. Chem. Soc.*, **107**, 7776 (1985).
 g. W. C. M. C. Kokke and F. A. Varkvasser, *J. Org. Chem.*, **39**, 1535 (1974).
 h. N. S. Raasch and J. E. Castle, *Org. Synth.*, **42**, 44 (1962).
 i. O. Grummitt, R. Egan, and A. Buck, *Org. Synth.*, **III**, 449 (1955).

The reaction of alkenes with ozone is a general and selective method of cleaving carbon-carbon double bonds.¹⁹⁴ Application of low-temperature spectroscopic techniques has provided information about the rather unstable intermediates in the ozonolysis process. These studies, along with isotopic-labeling results, have provided an understanding of the reaction mechanism.¹⁹⁵ The two key intermediates in ozonolysis are the 1,2,3-trioxolane, or initial ozonide, and the 1,2,4-trioxolane, or ozonide. The first step of the reaction is a 1,3-dipolar cycloaddition to give the 1,2,3-trioxolane. This is followed by a fragmentation and recombination to give the isomeric 1,2,4-trioxolane. Ozone is a very electrophilic 1,3-dipole because of the accumulation of electronegative oxygen atoms in the ozone molecule. The cycloaddition, fragmentation, and recombination are all predicted to be exothermic on the basis of thermochemical considerations.¹⁹⁶



The products isolated after ozonolysis depend upon the conditions of workup. Simple hydrolysis leads to the carbonyl compounds and hydrogen peroxide, and these can react to give secondary oxidation products. It is usually preferable to include a mild reducing agent that is capable of reducing peroxidic bonds. The current practice is to use dimethyl sulfide, though numerous other reducing agents have been used, including zinc,¹⁹⁷ trivalent phosphorus compounds,¹⁹⁸ and sodium sulfite.¹⁹⁹ If the alcohols resulting from the reduction of the carbonyl cleavage products are desired, the reaction mixture can be reduced with NaBH₄.²⁰⁰ Carboxylic acids are formed in good yields from aldehydes when the ozonolysis reaction mixture is worked up in the presence of excess hydrogen peroxide.²⁰¹

Several procedures that intercept the intermediates have been developed. When ozonolysis is done in alcoholic solvents, the carbonyl oxide fragmentation product can be trapped as an α -hydroperoxy ether.²⁰² Recombination to the ozonide is then prevented, and the carbonyl compound formed in the fragmentation step can also be

¹⁹⁴ P. S. Bailey, *Ozonization in Organic Chemistry*, Vol. 1, Academic Press, New York, 1978.

¹⁹⁵ R. P. Lattimer, R. L. Kuczkowski, and C. W. Gillies, *J. Am. Chem. Soc.*, **96**, 348 (1974); C. W. Gillies, R. P. Lattimer, and R. L. Kuczkowski, *J. Am. Chem. Soc.*, **96**, 1536 (1974); G. Klopman and C. M. Joiner, *J. Am. Chem. Soc.*, **97**, 5287 (1975); P. S. Bailey and T. M. Ferrell, *J. Am. Chem. Soc.*, **100**, 899 (1978); I. C. Histasune, K. Shinoda, and J. Heicklen, *J. Am. Chem. Soc.*, **101**, 2524 (1979); J.-I. Choe, M. Srinivasan, and R. L. Kuczkowski, *J. Am. Chem. Soc.*, **105**, 4703 (1983). R. L. Kuczkowski, in *1,3-Dipolar Cycloaddition Chemistry*, A. Padwa, ed., Wiley-Interscience, New York, Vol. 2, Chap. 11, 1984; R. L. Kuczkowski, *Chem. Soc. Rev.*, **21**, 79 (1992); C. Geletneky and S. Barger, *Eur. J. Chem.*, 1625 (1998); K. Schank, *Helv. Chim. Acta*, **87**, 2074 (2004).

¹⁹⁶ P. S. Nangia and S. W. Benson, *J. Am. Chem. Soc.*, **102**, 3105 (1980).

¹⁹⁷ S. M. Church, F. C. Whitmore, and R. V. McGrew, *J. Am. Chem. Soc.*, **56**, 176 (1934).

¹⁹⁸ W. S. Knowles and Q. E. Thompson, *J. Org. Chem.*, **25**, 1031 (1960).

¹⁹⁹ R. H. Callighan and M. H. Wilt, *J. Org. Chem.*, **26**, 4912 (1961).

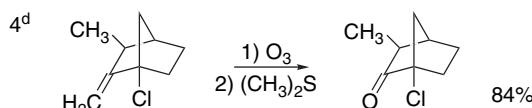
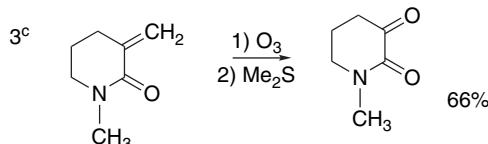
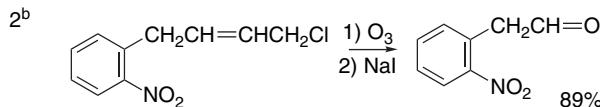
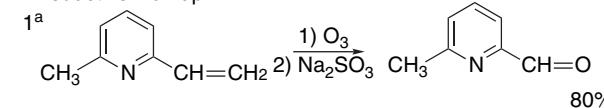
²⁰⁰ F. L. Greenwood, *J. Org. Chem.*, **20**, 803 (1955).

²⁰¹ A. L. Henne and P. Hill, *J. Am. Chem. Soc.*, **65**, 752 (1943).

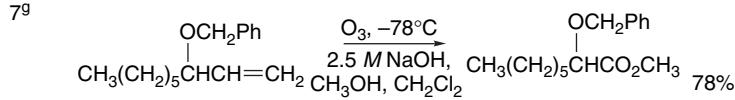
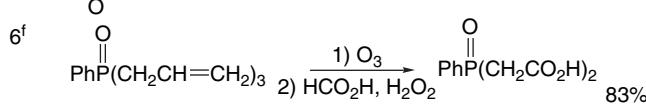
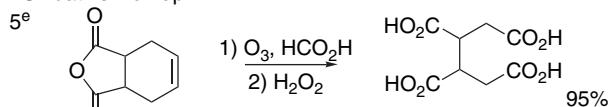
²⁰² W. P. Keaveney, M. G. Berger, and J. J. Pappas, *J. Org. Chem.*, **32**, 1537 (1967).

Scheme 12.19. Ozonolysis Reactions

A. Reductive workup

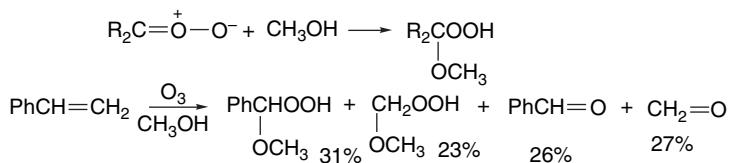


B. Oxidative workup



- a. R. H. Callighan and M. H. Wilt, *J. Org. Chem.*, **26**, 4912 (1961).
 - b. W. E. Noland and J. H. Sellstedt, *J. Org. Chem.*, **31**, 345 (1966).
 - c. M. L. Rueppell and H. Rapoport, *J. Am. Chem. Soc.*, **94**, 3877 (1972).
 - d. J. V. Paukstelis and B. W. Macharia, *J. Org. Chem.*, **38**, 646 (1973).
 - e. J. E. Franz, W. S. Knowles, and C. Ousch, *J. Org. Chem.*, **30**, 4328 (1965).
 - f. J. L. Eichelberger and J. K. Stille, *J. Org. Chem.*, **36**, 1840 (1971).
 - g. J. A. Marshall and A. W. Garofalo, *J. Org. Chem.*, **58**, 3675 (1993).

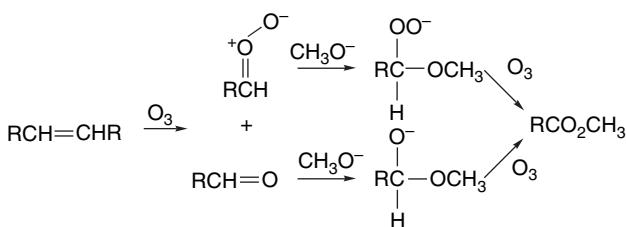
isolated. If the reaction mixture is then treated with dimethyl sulfide, the hydroperoxide is reduced and the second carbonyl compound is also formed in good yield.²⁰³



Ozonolysis in the presence of NaOH or NaOCH₃ in methanol with CH₂Cl₂ as a cosolvent leads to formation of esters. This transformation proceeds by trapping both

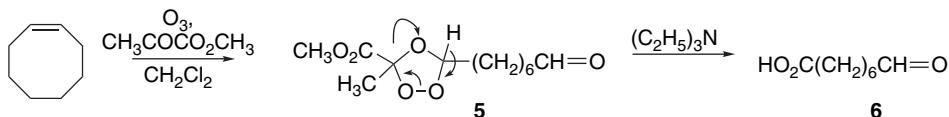
²⁰³. J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

the carbonyl oxide and aldehyde products of the fragmentation step.²⁰⁴ The anionic adducts are then oxidized by O₃.



Cyclooctene gives dimethyl octanedioate under these conditions.

Especially reactive carbonyl compounds such as methyl pyruvate can trap the carbonyl oxide component. For example, ozonolysis of cyclooctene in the presence of methyl pyruvate leads to **5**; when treated with triethylamine **5** is converted to **6**, in which the two carbons of the original double bond have been converted to different functionalities.²⁰⁵



Scheme 12.19 illustrates some cases in which ozonolysis reactions have been used in the course of syntheses. Entries 1 to 4 are examples of use of ozonolysis to introduce carbonyl groups under reductive workup. Entries 5 and 6 involve oxidative workup and give dicarboxylic acid products. The reaction in Entry 7 is an example of direct generation of a methyl ester by methoxide trapping.

12.5. Oxidation of Ketones and Aldehydes

12.5.1. Transition Metal Oxidants

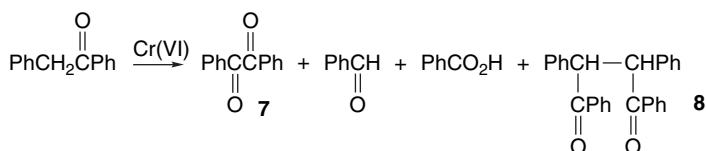
Ketones are oxidatively cleaved by Cr(VI) or Mn(VII) reagents. The reaction is sometimes of utility in the synthesis of difunctional molecules by ring cleavage. The mechanism for both reagents is believed to involve an enol intermediate.²⁰⁶ A study involving both kinetic data and quantitative product studies has permitted a fairly complete description of the Cr(VI) oxidation of benzyl phenyl ketone.²⁰⁷ The products include both oxidative-cleavage products and benzil, **7**, which results from oxidation α to the carbonyl. In addition, the dimeric product **8**, which is suggestive of radical intermediates, is formed under some conditions.

²⁰⁴ J. A. Marshall and A. W. Gordon, *J. Org. Chem.*, **58**, 3675 (1993).

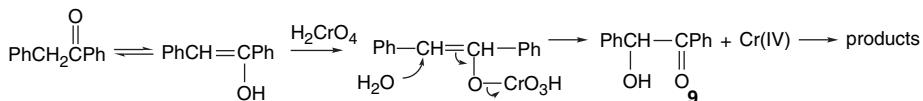
²⁰⁵ Y.-S. Hon and J.-L. Yan, *Tetrahedron*, **53**, 5217 (1997).

²⁰⁶ K. B. Wiberg and R. D. Geer, *J. Am. Chem. Soc.*, **87**, 5202 (1965); J. Rocek and A. Riehl, *J. Am. Chem. Soc.*, **89**, 6691 (1967).

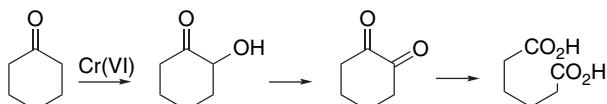
²⁰⁷ K. B. Wiberg, O. Aniline, and A. Gatzke, *J. Org. Chem.*, **37**, 3229 (1972).



Both the diketone and the cleavage products were shown to arise from an α -hydroxyketone intermediate (benzoin) **9**.

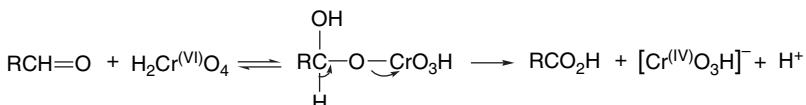


The coupling product is considered to involve a radical intermediate formed by one-electron oxidation, probably effected by Cr(IV). Similarly, the oxidation of cyclohexanone involves 2-hydroxycyclohexanone and 1,2-cyclohexanedione as intermediates.²⁰⁸



Owing to the efficient oxidation of alcohols to ketones, alcohols can be used as the starting materials in oxidative cleavages. The conditions required are more vigorous than for the alcohol to ketone transformation (see Section 12.1.1).

Aldehydes can be oxidized to carboxylic acids by both Mn(VII) and Cr(VI). Fairly detailed mechanistic studies have been carried out for Cr(VI). A chromate ester of the aldehyde hydrate is believed to be formed, and this species decomposes in the rate-determining step by a mechanism similar to the one that operates in alcohol oxidations.²⁰⁹



Effective conditions for oxidation of aldehydes to carboxylic acids with KMnO₄ involve use of *t*-butanol and an aqueous NaH₂PO₄ buffer as the reaction medium.²¹⁰ Buffered sodium chlorite is also a convenient oxidant.²¹¹ Both KMnO₄ and NaClO₂ can be used in the form of solid-supported materials, using silica and ion exchange resins, respectively,²¹² which permits facile workup of the product. Silver oxide is one of the older reagents used for carrying out the aldehyde to carboxylic acid oxidation.

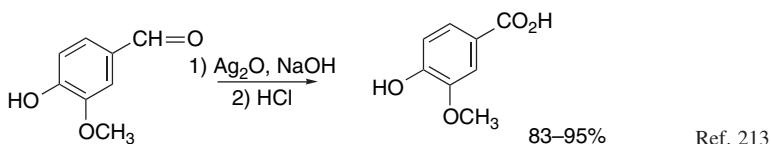
^{208.} J. Rocek and A. Riehl, *J. Org. Chem.*, **32**, 3569 (1967).

^{209.} K. B. Wiberg, *Oxidation in Organic Chemistry*, Part A, Academic Press, New York, 1965, pp. 172–178.

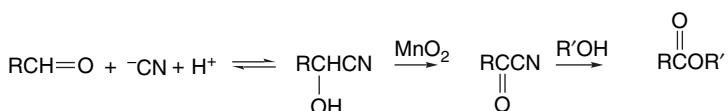
^{210.} A. Abiko, J. C. Roberts, T. Takemasa, and S. Masamune, *Tetrahedron Lett.*, **27**, 4537 (1986).

^{211.} E. Dalcanale and F. Montanari, *J. Org. Chem.*, **51**, 567 (1986); J. P. Bayle, F. Perez, and J. Cortieu, *Bull. Soc. Chim. Fr.*, 565 (1996); E. J. Corey and G. A. Reichard, *Tetrahedron Lett.*, **34**, 6973 (1993); P. M. Wovkulich, K. Shankaran, J. Kiegel, and M. R. Uskokovic, *J. Org. Chem.*, **58**, 832 (1993); B. R. Babu and K. K. Balasubramaniam, *Org. Prep. Proc. Int.*, **26**, 123 (1994).

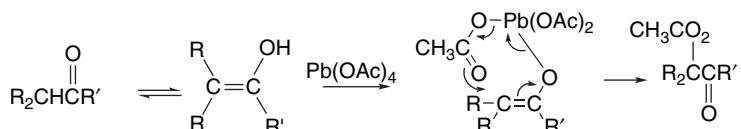
^{212.} T. Takemoto, K. Yasuda, and S. V. Ley, *Synlett*, 1555 (2001).



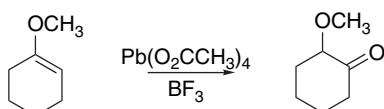
The reaction of aldehydes with MnO_2 in the presence of cyanide ion in an alcoholic solvent is a convenient method of converting aldehydes directly to esters.²¹⁴ This reaction involves the cyanohydrin as an intermediate. The initial oxidation product is an acyl cyanide, which is solvolyzed under these reaction conditions.



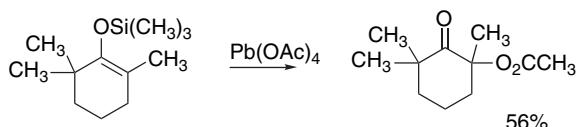
Lead tetraacetate can effect oxidation of carbonyl groups, leading to formation of α -acetoxy ketones,²¹⁵ but the yields are seldom high. Boron trifluoride can be used to catalyze these oxidations. It is presumed to function by catalyzing the formation of the enol, which is thought to be the reactive species.²¹⁶ With unsymmetrical ketones, products from oxidation at both α -methylene groups are found.²¹⁷



With enol ethers, $\text{Pb}(\text{OCCH}_3)_4$ gives α -methoxyketones.²¹⁸



Introduction of oxygen α to a ketone function can also be carried out via the silyl enol ether. Lead tetraacetate gives the α -acetoxy ketone.²¹⁹



²¹³ I. A. Pearl, *Org. Synth.*, **IV**, 972 (1963).

²¹⁴ E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Am. Chem. Soc.*, **90**, 5616 (1968).

²¹⁵ R. Criegee, in *Oxidation in Organic Chemistry*, Part A, K. B. Wiberg, ed., Academic Press, New York, 1965, pp. 305–312.

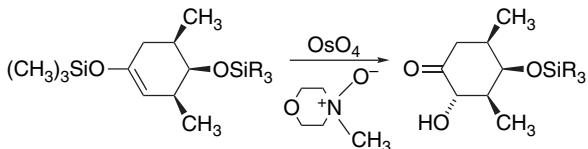
²¹⁶ J. D. Cocker, H. B. Henbest, G. H. Philipps, G. P. Slater, and D. A. Thomas, *J. Chem. Soc.*, 6 (1965).

²¹⁷ S. Moon and H. Bohm, *J. Org. Chem.*, **37**, 4338 (1972).

²¹⁸ V. S. Singh, C. Singh, and D. K. Dikshit, *Synth. Commun.*, **28**, 45 (1998).

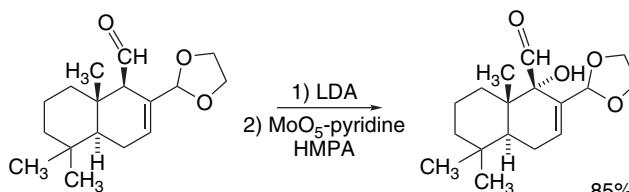
²¹⁹ G. M. Rubottom, J. M. Gruber, and K. Kincaid, *Synth. Commun.*, **6**, 59 (1976); G. M. Rubottom and J. M. Gruber, *J. Org. Chem.*, **42**, 1051 (1977); G. M. Rubottom and H. D. Juve, Jr., *J. Org. Chem.*, **48**, 422 (1983).

α -Hydroxyketones can be obtained from silyl enol ethers by oxidation using a catalytic amount of OsO_4 with an amine oxide serving as the stoichiometric oxidant.²²⁰



Ref. 221

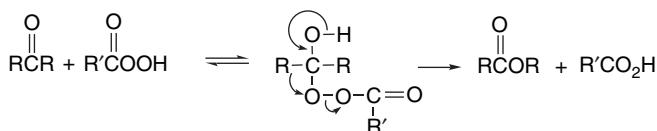
Other procedures for α -oxidation of ketones are based on prior generation of the enolate. Among the reagents used is a molybdenum compound, MoO_5 -pyridine-HMPA, which is prepared by dissolving MoO_3 in hydrogen peroxide, followed by addition of HMPA. This reagent oxidizes the enolates of aldehydes, ketones, esters, and lactones to the corresponding α -hydroxy compound.²²²



Ref. 223

12.5.2. Oxidation of Ketones and Aldehydes by Oxygen and Peroxidic Compounds

12.5.2.1. Baeyer-Villiger Oxidation of Ketones. In the presence of acid catalysts, peroxy compounds are capable of oxidizing ketones by insertion of an oxygen atom into one of the carbon-carbon bonds at the carbonyl group. Known as the *Baeyer-Villiger oxidation*,²²⁴ the mechanism involves a sequence of steps that begins with addition to the carbonyl group, followed by peroxide bond cleavage with migration to oxygen.



²²⁰ J. P. McCormick, W. Tomaszik, and M. W. Johnson, *Tetrahedron Lett.*, **22**, 607 (1981).

²²¹ R. K. Boeckman, Jr., J. E. Starrett, Jr., D. G. Nickell, and P.-E. Sun, *J. Am. Chem. Soc.*, **108**, 5549 (1986).

²²² E. Vedejs, *J. Am. Chem. Soc.*, **96**, 5945 (1974); E. Vedejs, D. A. Engler, and J. E. Telschow, *J. Org. Chem.*, **43**, 188 (1978); E. Vedejs and S. Larsen, *Org. Synth.*, **64**, 127 (1985).

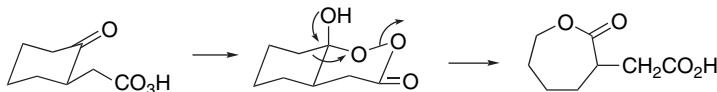
²²³ S. P. Tanis and K. Nakanishi, *J. Am. Chem. Soc.*, **101**, 4398 (1979).

²²⁴ C. H. Hassall, *Org. React.*, **9**, 73 (1957); G. R. Krow, *Org. React.*, **43**, 252 (1993); M. Renz and B. Beunier, *Eur. J. Org. Chem.*, 737 (1999); G.-J. ten Brink, I. W. C. E. Arends, and R. A. Sheldon, *Chem. Rev.*, **104**, 4105 (2004).

The concerted O–O heterolysis-migration is usually the rate-determining step.²²⁵ The reaction is catalyzed by protic and Lewis acids,²²⁶ including $\text{Sc}(\text{O}_3\text{SCF}_3)_3$ ²²⁷ and $\text{Bi}(\text{O}_3\text{SCF}_3)_3$.²²⁸

When the reaction involves an unsymmetrical ketone, the structure of the product depends on which group migrates. A number of studies have been directed at ascertaining the basis of migratory preference in the Baeyer-Villiger oxidation, and a general order of likelihood of migration has been established: *tert*-alkyl, *sec*-alkyl>benzyl, phenyl>*pri*-alkyl>cyclopropyl>methyl.²²⁹ Thus, methyl ketones uniformly give acetate esters resulting from migration of the larger group.²³⁰ A major factor in determining which group migrates is the ability to accommodate partial positive charge. In *para*-substituted phenyl groups, ERG substituents favor migration.²³¹ Similarly, silyl substituents enhance migratory aptitude of alkyl groups.²³² As is generally true of migration to an electron-deficient center, the configuration of the migrating group is retained in Baeyer-Villiger oxidations.

Steric and conformational factors are also important, especially in cyclic systems.²³³ There is a preference for the migration of the group that is antiperiplanar with respect to the peroxide bond. In relatively rigid systems, this effect can outweigh the normal preference for the migration of the more branched group.²³⁴



This stereoelectronic effect also explains the contrasting regioselectivity of *cis*- and *trans*-2-fluoro-4-*t*-butylcyclohexanone.²³⁵ As a result of a balance between its polar effect and hyperconjugation, the net effect of a fluoro substituent in acyclic systems is small. However, in 2-fluorocyclohexanones an unfavorable dipole-dipole interaction comes into play for the *cis* isomer and preferential migration of the fluoro-substituted carbon is observed.

²²⁵ Y. Ogata and Y. Sawaki, *J. Org. Chem.*, **37**, 2953 (1972).

²²⁶ G. Stukul, *Angew. Chem. Int'l. Ed. Engl.*, **37**, 1199 (1998).

²²⁷ H. Kotsuki, K. Arimura, T. Araki, and T. Shinohara, *Synlett*, 462 (1999).

²²⁸ M. M. Alam, R. Varala, and S. R. Adapa, *Synth. Commun.*, **33**, 3035 (2003).

²²⁹ H. O. House, *Modern Synthetic Reactions*, 2nd Edition, W. A. Benjamin, Menlo Park, CA, 1972, p. 325.

²³⁰ P. A. S. Smith, in *Molecular Rearrangements*, P. de Mayo, ed., Interscience, New York, 1963, pp. 457–591.

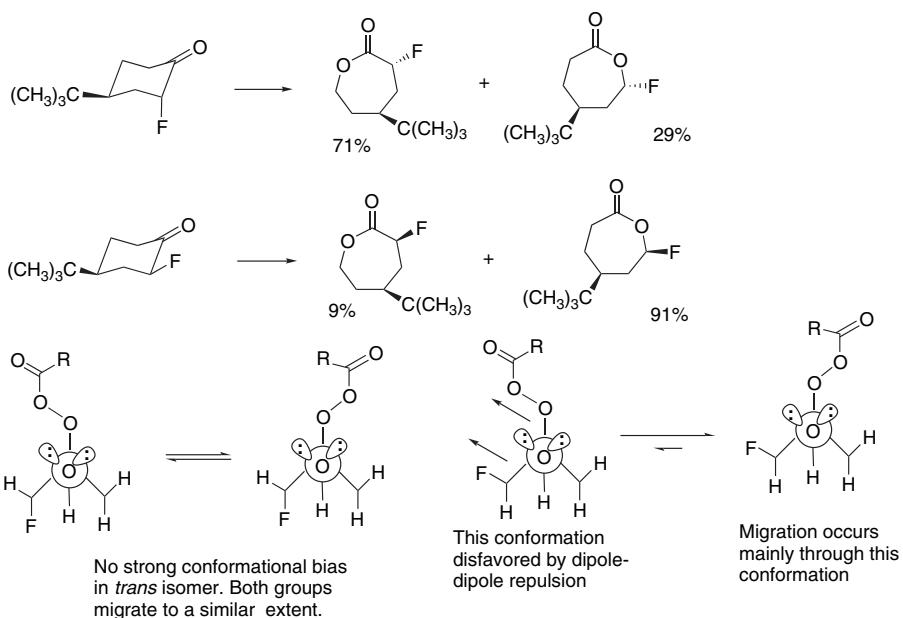
²³¹ W. E. Doering and L. Speers, *J. Am. Chem. Soc.*, **72**, 5515 (1950).

²³² P. F. Hudrik, A. M. Hudrik, G. Nagendrappa, T. Yimenu, E. T. Zellers, and E. Chin, *J. Am. Chem. Soc.*, **102**, 6894 (1980).

²³³ M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *J. Am. Chem. Soc.*, **80**, 6393 (1958); J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.*, **82**, 5235 (1960); P. M. Goodman and Y. Kishi, *J. Am. Chem. Soc.*, **120**, 9392 (1998).

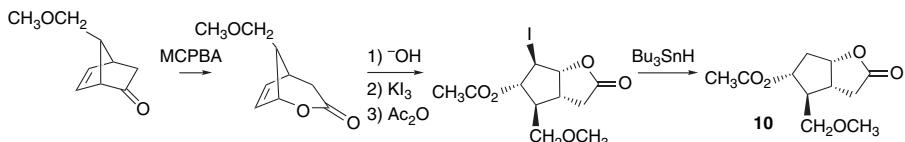
²³⁴ S. Chandrasekhar and C. D. Roy, *J. Chem. Soc., Perkin Trans. 2*, 2141 (1994).

²³⁵ C. M. Crudden, A. C. Chen, and L. A. Calhoun, *Angew. Chem. Int. Ed. Engl.*, **39**, 2852 (2000).



In 2-(trifluoromethyl)cyclohexanone, the methylene group migrates in preference to the trifluoromethylmethine group,²³⁶ owing primarily to the EWG effect of the trifluoromethyl group. The computational energy profile, shown in Figure 12.15, indicates that the reaction proceeds through a minor conformation of the adduct in which the trifluoromethyl group is axial. The same regioselectivity is computed for the adduct having the peroxy substituent in an equatorial position, but this adduct is about 1 kcal/mol higher in energy.

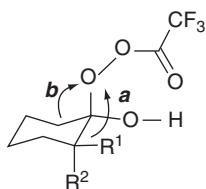
The Baeyer-Villiger reaction has found considerable application in the synthesis of prostaglandins. One common pattern involves the use of bicyclo[2.2.1]heptan-2-one derivatives, which are generally obtained by Diels-Alder reactions. For example, compound **10** is known as the *Corey lactone* and has played a prominent role in the synthesis of prostaglandins.²³⁷ This compound was originally prepared by a Baeyer-Villiger oxidation of 7-(methoxymethyl)bicyclo[2.2.1]hept-5-en-2-one.²³⁸



²³⁶ Y. Itoh, M. Yamanaka, and K. Mikami, *Org. Lett.*, **5**, 4803 (2003).

²³⁷ R. Bansal, G. F. Cooper, and E. J. Corey, *J. Org. Chem.*, **56**, 1329 (1991).

²³⁸ E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc.*, **91**, 5675 (1969).



CP1, TS1: $R^1 = CF_3$, $R^2 = H$, **a**

CP2, TS2: $R^1 = CF_3$, $R^2 = H$, **b**

CP3, TS3: $R^1 = H$, $R^2 = CF_3$, **a**

CP4, TS4: $R^1 = H$, $R^2 = CF_3$, **b**

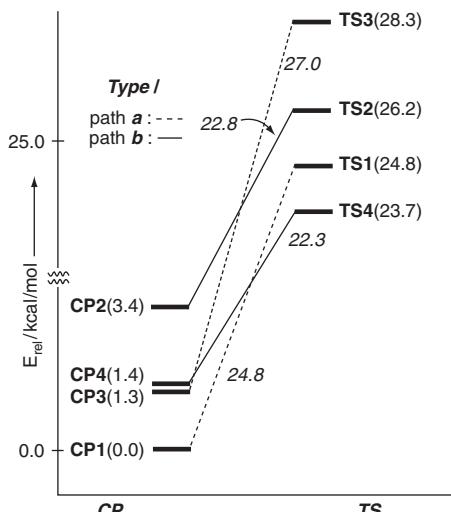


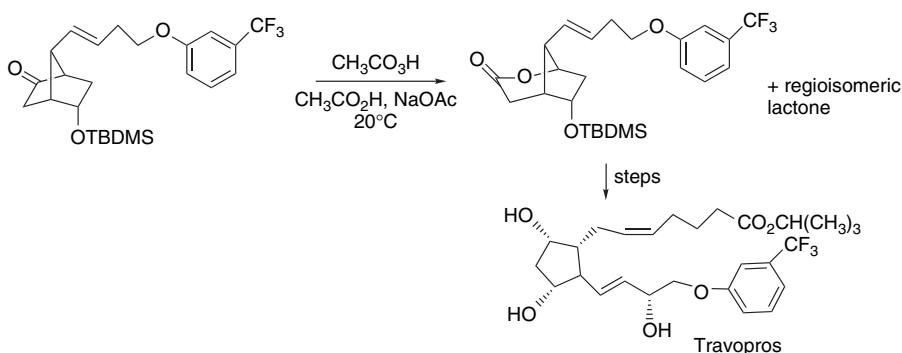
Fig. 12.15. Computational comparison of reactants (adducts) and transition structures for Baeyer-Villiger oxidation of 2-(trifluoromethyl)cyclohexanone by peroxytrifluoroacetic acid. Reproduced from *Org. Lett.*, **5**, 4803 (2003), by permission of the American Chemical Society.

This intermediate has the oxygenation and pattern and *trans*-disubstitution pattern found in the prostaglandins. Several syntheses of similar intermediates have been developed.²³⁹

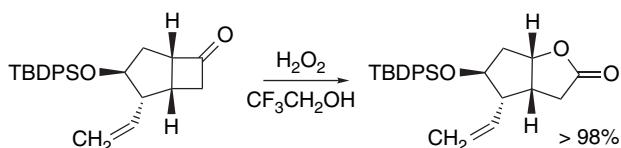
In the synthesis of Travoprost, an antiglaucoma agent, a bicyclo[2.2.1]heptan-2-one is converted to a lactone.²⁴⁰ The commercial process uses peroxyacetic acid as the oxidant and gives a 40% yield. The regioselectivity in this case is only 3:1 but the unwanted isomer can be removed by selective hydrolysis.

²³⁹ I. Vesely, V. Kozmík, V. Dedek, J. Paleček, J. Mostecký, and I. Stibor, *Coll. Czech. Chem. Commun.*, **54**, 1683 (1989); J. S. Bindra, A. Grodski, T. K. Schaaf, and E. J. Corey, *J. Am. Chem. Soc.*, **95**, 7522 (1973).

²⁴⁰ L. T. Boulton, D. Brick, M. E. Fox, M. Jackson, I. C. Lennon, R. McCague, N. Parkin, D. Rhodes, and G. Ruecroft, *Org. Proc. Res. Dev.*, **6**, 128 (2002).



A series of 2-vinyl-3-silyloxybicyclo[3.2.0]heptan-6-ones has also been converted to prostanoid lactones in excellent yield but variable regioselectivity. Some of the best regioselectivity was obtained using H_2O_2 in trifluoroethanol (see p. 1097).²⁴¹ The strained cyclobutanone ring and the relatively unreactive terminal vinyl group favor the desired reaction in preference to alkene epoxidation.



Some typical examples of Baeyer-Villiger oxidations are shown in Scheme 12.20. Entry 1 uses peroxyacetic acid, the original reagent discovered by Baeyer and Villiger. Entries 2 and 3 generate lactones in good yield from cyclic ketones using peroxyacetic acid. Entry 3 also illustrates the preference for the migration of the more branched group. Entry 4 is a case of formation of an acetate ester from a methyl ketone. Entry 5 illustrates the use of magnesium monoperoxyphthalate and also shows the normal preference for migration of the more branched group. The reaction in Entry 6 exhibits very high regioselectivity. Although this example is consistent with the generalization that the more branched group will migrate, there may be other factors associated with ring geometry that lead to the complete regioselectivity. Entries 7 and 8 use peroxytrifluoroacetic acid and again illustrate the conversion of methyl ketones to acetate esters.

12.5.2.2. Oxidation of Enolates and Enolate Equivalents. Although ketones are essentially inert to molecular oxygen, enolate anions are susceptible to oxidation. The combination of oxygen and a strong base has found some utility in the introduction of an oxygen function at carbanionic sites.²⁴² Hydroperoxides are the initial products of such oxidations, but when DMSO or some other substance capable of reducing the hydroperoxide is present, the corresponding alcohol is isolated. A procedure that has met with

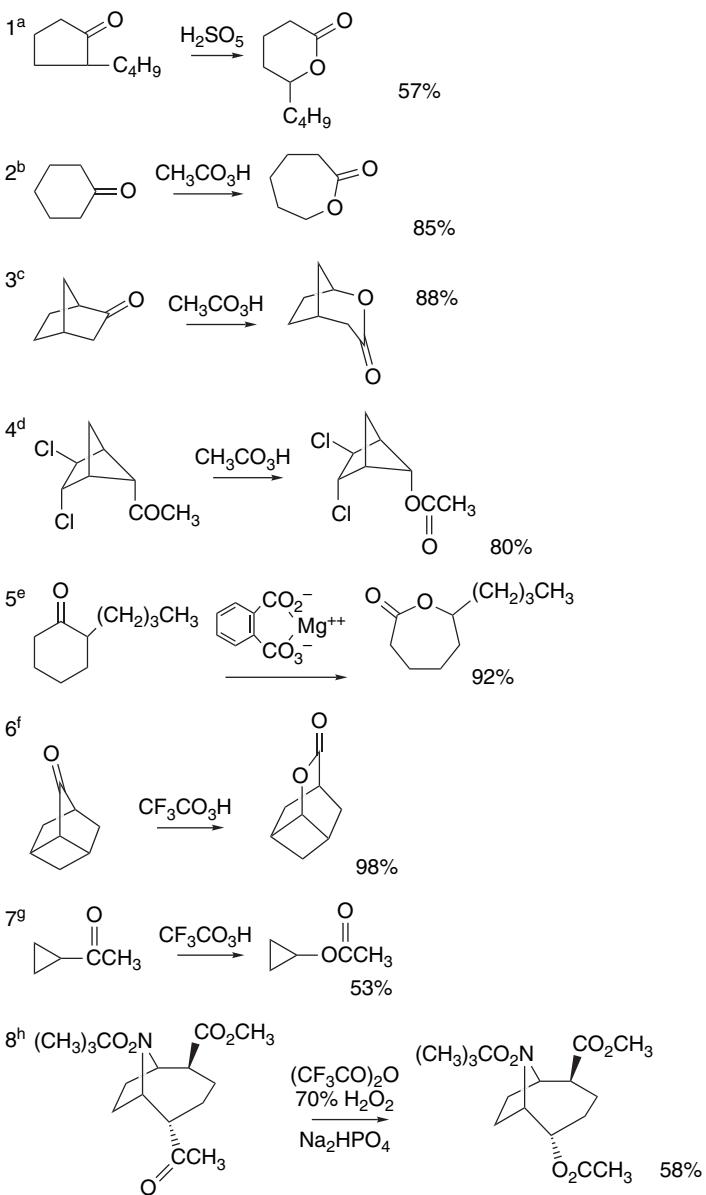
²⁴¹. D. Depre, L.-Y. Chen, and L. Ghosez, *Tetrahedron*, **59**, 6797 (2003).

²⁴². J. N. Gardner, T. L. Popper, F. E. Carlon, O. Gnoj, and H. L. Herzog, *J. Org. Chem.*, **33**, 3695 (1968).

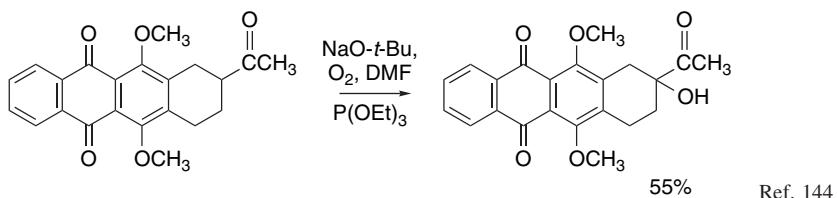
Scheme 12.20. Baeyer-Villiger Oxidation

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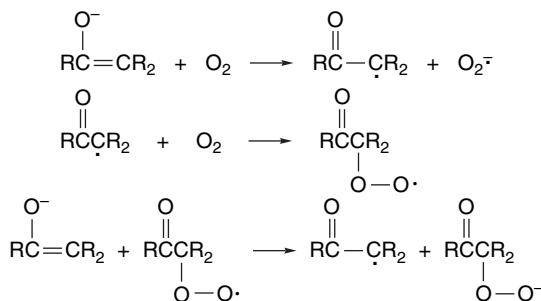
SECTION 12.5

Oxidation of Ketones
and Aldehydesa. T. H. Parliament, M. W. Parliament, and J. S. Fagerson, *Chem. Ind.*, 1845 (1966).b. P. S. Strarcher and B. Phillips, *J. Am. Chem. Soc.*, **80**, 4079 (1958).c. J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc.*, **82**, 5235 (1960).d. K. B. Wiberg and R. W. Ubersax, *J. Org. Chem.*, **37**, 3827 (1972).e. M. Hirano, S. Yakabe, A. Satoh, J. H. Clark, and T. Morimoto, *Synth. Commun.*, **26**, 4591 (1996); T. Mino, S. Masuda, M. Nishio, and M. Yamashita, *J. Org. Chem.*, **62**, 2633 (1997).f. S. A. Monti and S.-S. Yuan, *J. Org. Chem.*, **36**, 3350 (1971).g. W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).h. F. J. Sardina, M. H. Howard, M. Morningstar, and H. Rapoport, *J. Org. Chem.*, **55**, 5025 (1990).

considerable success involves oxidation in the presence of a trialkyl phosphite.²⁴³ The intermediate hydroperoxide is efficiently reduced by the phosphite ester.

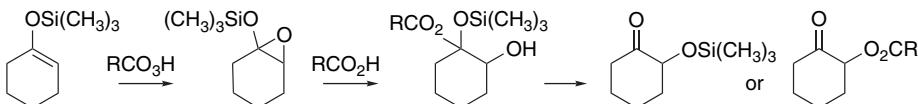


This oxidative process has been successful with ketones,²⁴⁴ esters,²⁴⁵ and lactones.²⁴⁶ Hydrogen peroxide can also be used as the oxidant, in which case the alcohol is formed directly.²⁴⁷ The mechanisms for the oxidation of enolates by oxygen is a radical chain autoxidation in which the propagation step involves electron transfer from the carbanion to a hydroperoxy radical.²⁴⁸



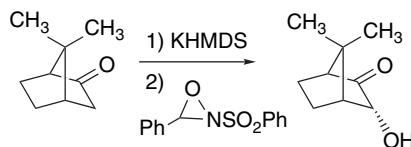
Arguments for a nonchain reaction between the enolate and oxygen to give the hydroperoxide anion directly have been advanced as well.²⁴⁹

The silyl enol ethers of ketones are also oxidized to α -hydroxy ketones by *m*-chloroperoxybenzoic acid. If the reaction workup includes acylation, α -acyloxy ketones are obtained.²⁵⁰ These reactions proceed by initial epoxidation of the silyl enol ether, which then undergoes ring opening. Subsequent transfer of either the *O*-acyl or *O*-TMS substituent occurs, depending on the reaction conditions.

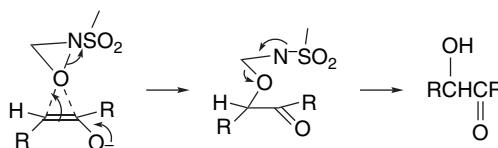


- ²⁴³ J. N. Gardner, F. E. Carlon, and O. Gnoj, *J. Org. Chem.*, **33**, 3294 (1968).
- ²⁴⁴ F. A. J. Kerdesky, R. J. Ardecky, M. V. Lashmikanthan, and M. P. Cava, *J. Am. Chem. Soc.*, **103**, 1992 (1981).
- ²⁴⁵ E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc.*, **97**, 6908 (1975).
- ²⁴⁶ J. J. Plattner, R. D. Gless, and H. Rapoport, *J. Am. Chem. Soc.*, **94**, 8613 (1972); R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *J. Am. Chem. Soc.*, **93**, 5576 (1971).
- ²⁴⁷ G. Buchi, K. E. Matsumoto, and H. Nishimura, *J. Am. Chem. Soc.*, **93**, 3299 (1971).
- ²⁴⁸ G. A. Russell and A. G. Bemix, *J. Am. Chem. Soc.*, **88**, 5491 (1966).
- ²⁴⁹ H. R. Gersmann and A. F. Bickel, *J. Chem. Soc. B*, 2230 (1971).
- ²⁵⁰ G. M. Rubottom, J. M. Gruber, R. K. Boeckman, Jr., M. Ramaiah, and J. B. Medwick, *Tetrahedron Lett.*, 4603 (1978); G. M. Rubottom and J. M. Gruber, *J. Org. Chem.*, **43**, 1599 (1978); G. M. Rubottom, M. A. Vazquez, and D. R. Pelegrina, *Tetrahedron Lett.*, 4319 (1974).

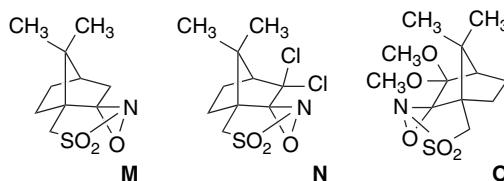
N-Sulfonyloxaziridines are useful reagents for oxidation of enolates to α -hydroxyketones.²⁵¹ The best results are frequently achieved by using KHMDS to form the enolate. The hydroxylation occurs preferentially from the less hindered enolate face.



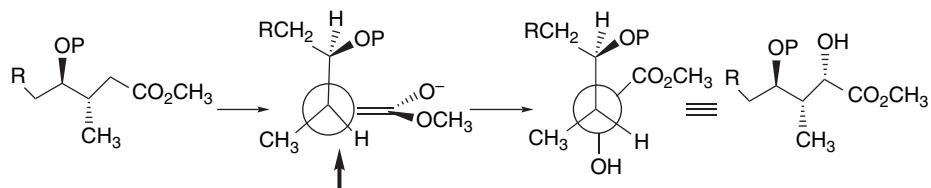
The mechanism of oxygen transfer is believed to involve nucleophilic opening of the oxaziridine, followed by collapse of the resulting *N*-sulfonylcarbinolamine.²⁵²



These reagents exhibit good stereoselectivity toward chiral reactants, such as acyloxazolidinones.²⁵³ Chiral oxaziridine reagents have been developed that can achieve enantioselective oxidation of enolates to α -hydroxyketones.²⁵⁴



Scheme 12.21 gives some examples of enolate oxidation using *N*-sulfonyloxaziridines. Entries 1 to 3 are examples of enantioselective oxidations using chiral oxaziridines with racemic reactants. In Entry 4, the stereoselectivity is presumably controlled by the reactant shape. The analog with all *cis* stereochemistry at the cyclobutane ring also gave oxidation from the less hindered face of the molecule. Entry 5 is an example of diastereoselective oxidation. The observed *syn* selectivity is consistent with reactant conformation being the controlling factor in reagent approach.



²⁵¹ F. A. Davis, L. C. Vishwakarma, J. M. Billmers, and J. Finn, *J. Org. Chem.*, **49**, 3241 (1984); L. C. Vishwakarma, O. D. Stringer, and F. A. Davis, *Org. Synth.*, **66**, 203 (1988).

²⁵² F. A. Davis, A. C. Sheppard, B.-C. Chen, and M. S. Haque, *J. Am. Chem. Soc.*, **112**, 6679 (1990).

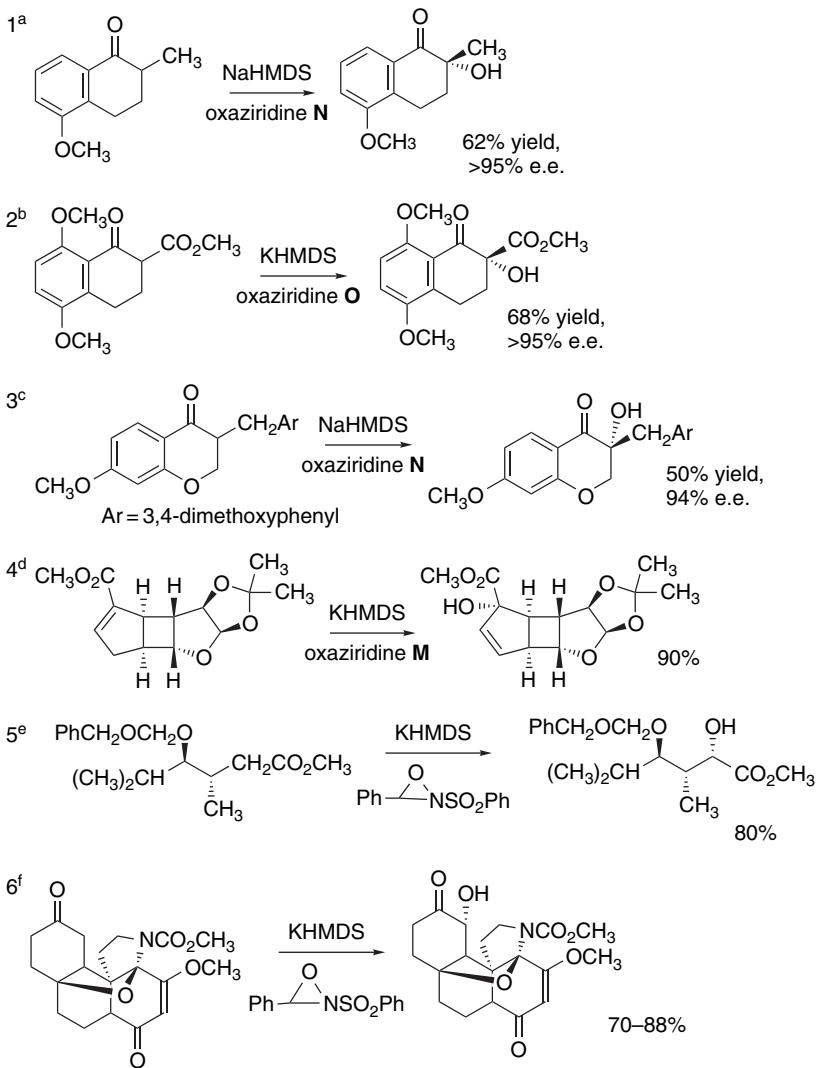
²⁵³ D. A. Evans, M. M. Morrissey, and R. L. Dorow, *J. Am. Chem. Soc.*, **107**, 4346 (1985).

²⁵⁴ F. A. Davis and B.-C. Chen, *Chem. Rev.*, **92**, 919 (1992).

Scheme 12.21. Oxidation of Enolates by Oxaziridines

CHAPTER 12

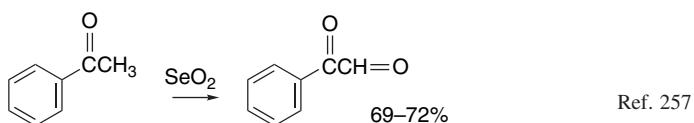
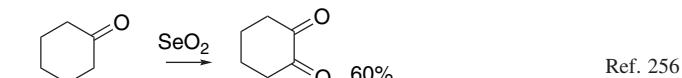
Oxidations



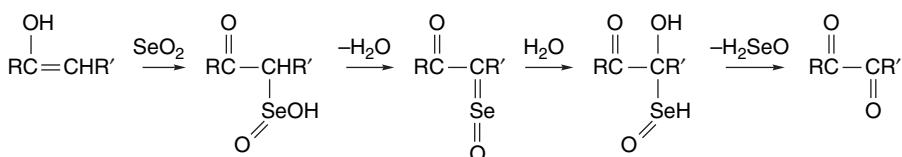
- a. F. A. Davis and M. C. Weismiller, *J. Org. Chem.*, **55**, 3715 (1990).
 b. F. A. Davis, A. Kumar, and B.-C. Chen, *Tetrahedron Lett.*, **32**, 867 (1991).
 c. F. A. Davis and B.-C. Chen, *J. Org. Chem.*, **58**, 1751 (1993).
 d. A. B. Smith, III, G. A. Sulikowski, M. M. Sulikowska, and K. Fujimoto, *J. Am. Chem. Soc.*, **114**, 2567 (1992).
 e. S. Hanessian, Y. Gai, and W. Wang, *Tetrahedron Lett.*, **37**, 7473 (1996).
 f. M. A. Tius and M. A. Kerr, *J. Am. Chem. Soc.*, **114**, 5959 (1992).

Both the regio- and stereochemistry of Entry 6 are of interest. The regioselectivity is imposed by the rigid ring geometry, which favors enolization at the observed position. Inspection of a molecular model also shows that α -face of the enolate is more accessible.

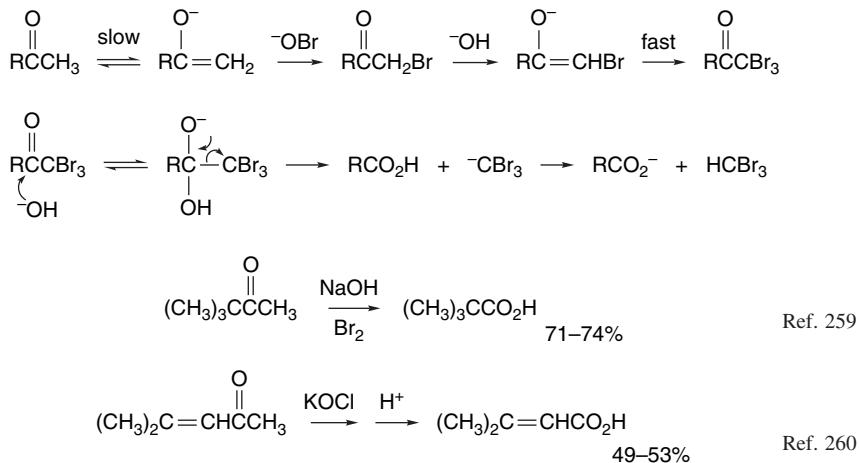
Selenium dioxide can be used to oxidize ketones and aldehydes to α -dicarbonyl compounds. The reaction often gives high yields of products when there is a single type of CH_2 group adjacent to the carbonyl group. In unsymmetrical ketones, oxidation usually occurs at the CH_2 that is most readily enolized.²⁵⁵



The oxidation is regarded as taking place by an electrophilic attack of selenium dioxide (or selenous acid, H_2SeO_3 , the hydrate) on the enol of the ketone or aldehyde. This is followed by hydrolytic elimination of the selenium.²⁵⁸



Methyl ketones are degraded to the next lower carboxylic acid by reaction with hypochlorite or hypobromite ions. The initial step in these reactions involves base-catalyzed halogenation. The α -haloketones are more reactive than their precursors, and rapid halogenation to the trihalo compound results. Trihalomethyl ketones are susceptible to alkaline cleavage because of the inductive stabilization provided by the halogen atoms.



²⁵⁵. E. N. Trachtenberg, in *Oxidation*, Vol. 1, R. L. Augustine, ed., Marcel Dekker, New York, 1969, Chap. 3.

²⁵⁶. C. C. Hach, C. V. Banks, and H. Diehl, *Org. Synth.*, **IV**, 229 (1963).

²⁵⁷. H. A. Riley and A. R. Gray, *Org. Synth.*, **II**, 509 (1943).

²⁵⁸. K. B. Sharpless and K. M. Gordon, *J. Am. Chem. Soc.*, **98**, 300 (1976).

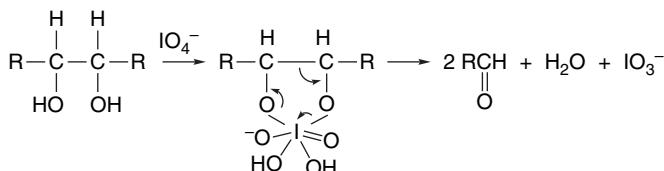
²⁵⁹. L. T. Sandborn and E. W. Bousquet, *Org. Synth.*, **1**, 512 (1932).

²⁶⁰. L. I. Smith, W. W. Prichard, and L. J. Spillane, *Org. Synth.*, **III**, 302 (1955).

12.6. Selective Oxidative Cleavages at Functional Groups

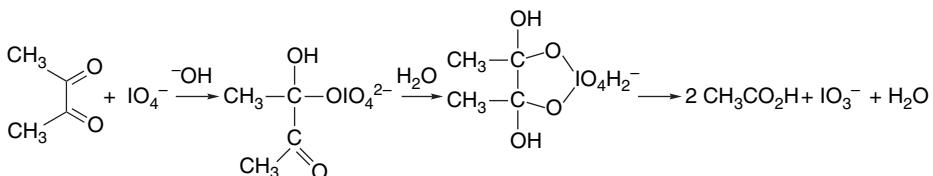
12.6.1. Cleavage of Glycols

As discussed in connection with cleavage of double bonds by permanganate-periodate or osmium tetroxide-periodate (see p. 1127), the glycol unit is susceptible to mild oxidative cleavage. The most commonly used reagent for this oxidative cleavage is the periodate ion.²⁶¹ The fragmentation is believed to occur via a cyclic adduct of the glycol and the oxidant.



Structural features that retard formation of the cyclic intermediate decrease the reaction rate. For example, *cis*-1,2-dihydroxycyclohexane is substantially more reactive than the *trans* isomer.²⁶² Glycols in which the geometry of the molecule precludes the possibility of a cyclic intermediate are essentially inert to periodate.

Certain other combinations of adjacent functional groups are also cleaved by periodate. Diketones are cleaved to carboxylic acids, and it is proposed that a reactive cyclic intermediate is formed by nucleophilic attack on the diketone.²⁶³



α -Hydroxy ketones and α -amino alcohols are also subject to oxidative cleavage, presumably by a similar mechanism.

Lead tetraacetate is an alternative reagent to periodate for glycol cleavage. It is particularly useful for glycals that have low solubility in the aqueous media used for periodate reactions. A cyclic intermediate is suggested by the same kind of stereochemistry-reactivity relationship discussed for periodate.²⁶⁴ Unlike periodate, however, glycals that cannot form cyclic intermediates are eventually oxidized. For example, *trans*-9,10-dihydroxydecalin is oxidized, but the rate is 100 times less than for the *cis* isomer.²⁶⁵ Thus, whereas a cyclic mechanism appears to provide the lowest-energy pathway for this oxidative cleavage, it is not the only possible mechanism. Both

²⁶¹ C. A. Bunton, in *Oxidation in Organic Chemistry*, Part A, K. B. Wiberg, ed., Academic Press, New York, 1965, pp. 367–388; A. S. Perlin, in *Oxidation*, Vol. 1, R. L. Augustine, ed., Marcel Dekker, New York, 1969, pp. 189–204.

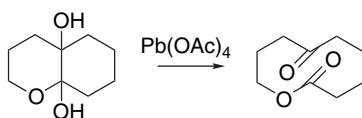
²⁶² C. C. Price and M. Knell, *J. Am. Chem. Soc.*, **64**, 552 (1942).

²⁶³ C. A. Bunton and V. J. Shiner, *J. Chem. Soc.*, 1593 (1960).

²⁶⁴ C. A. Bunton, in *Oxidation in Organic Chemistry*, K. Wiberg, ed., Academic Press, New York, 1965, pp. 398–405; W. S. Trahanovsky, J. R. Gilmore, and P. C. Heaton, *J. Org. Chem.*, **38**, 760 (1973).

²⁶⁵ R. Criegee, E. Hoeger, G. Huber, P. Kruck, F. Markscheffel, and H. Schellenberger, *Liebigs Ann. Chem.*, **599**, 81 (1956).

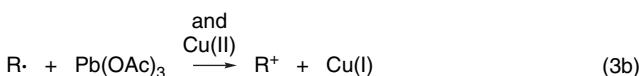
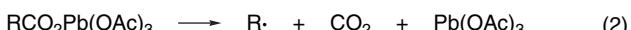
the periodate cleavage and lead tetraacetate oxidation can be applied synthetically to the generation of medium-sized rings when the glycol is at the junction of two rings.



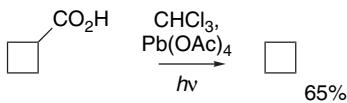
Ref. 266

12.6.2. Oxidative Decarboxylation

Carboxylic acids are oxidized by lead tetraacetate. Decarboxylation occurs and the product may be an alkene, alkane or acetate ester, or under modified conditions a halide. A free radical mechanism operates and the product composition depends on the fate of the radical intermediate.²⁶⁷ The reaction is catalyzed by cupric salts, which function by oxidizing the intermediate radical to a carbocation (Step 3b in the mechanism). Cu(II) is more reactive than $\text{Pb}(\text{OAc})_4$ in this step.



Alkanes are formed when the radical intermediate abstracts hydrogen from solvent faster than it is oxidized to the carbocation. This reductive step is promoted by good hydrogen donor solvents. It is also more prevalent for primary alkyl radicals because of the higher activation energy associated with formation of primary carbocations. The most favorable conditions for alkane formation involve photochemical decomposition of the carboxylic acid in chloroform, which is a relatively good hydrogen donor.



Ref. 268

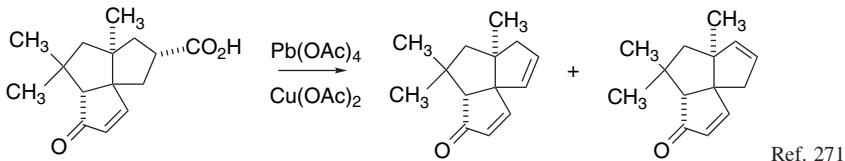
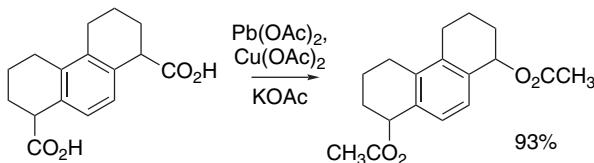
Normally, the dominant products are the alkene and acetate ester, which arise from the carbocation intermediate by, respectively, elimination of a proton and capture of an acetate ion.²⁶⁹

²⁶⁶. T. Wakamatsu, K. Akasaka, and Y. Ban, *Tetrahedron Lett.*, 2751, 2755 (1977).

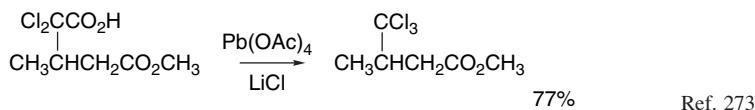
²⁶⁷. R. A. Sheldon and J. K. Kochi, *Org. React.*, **19**, 279 (1972).

²⁶⁸. J. K. Kochi and J. D. Bacha, *J. Org. Chem.*, **33**, 2746 (1968).

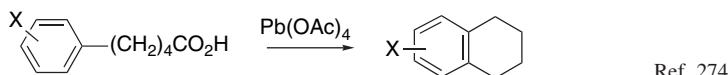
²⁶⁹. J. D. Bacha and J. K. Kochi, *Tetrahedron*, **24**, 2215 (1968).



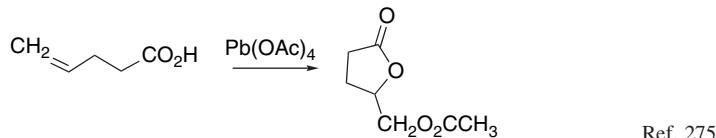
In the presence of lithium chloride, the product is the corresponding chloride.²⁷²



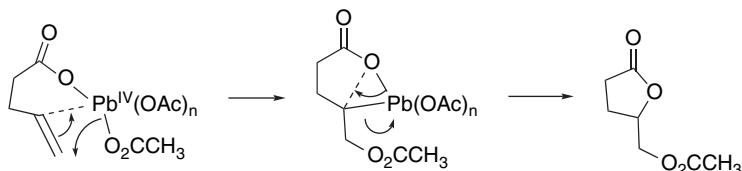
5-Arylpentanoic acids give tetrahydronaphthalenes, a reaction that is consistent with a radical cyclization.



On the other hand, γ , δ -unsaturated acids give lactones that involve cyclization without decarboxylation.



These products can be formed by a ligand transfer from an intermediate in which the double bond is associated with the Pb.



²⁷⁰ P. Caluwe and T. Pepper, *J. Org. Chem.*, **53**, 1786 (1988).

²⁷¹ D. D. Sternbach, J. W. Hughes, D. E. Bardi, and B. A. Banks, *J. Am. Chem. Soc.*, **107**, 2149 (1985).

²⁷² J. K. Kochi, *J. Org. Chem.*, **30**, 3265 (1965).

²⁷³ S. E. de Laszlo and P. G. Williard, *J. Am. Chem. Soc.*, **107**, 199 (1985).

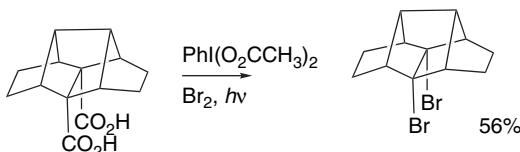
²⁷⁴ D. I. Davies and C. Waring, *J. Chem. Soc. C*, 1865 (1968).

²⁷⁵ M. G. Moloney, E. Nettleton, and K. Smithies, *Tetrahedron Lett.*, **43**, 907 (2002).

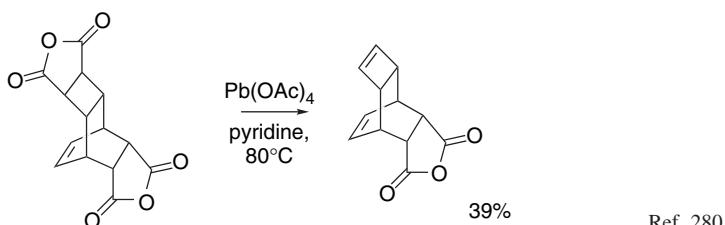
A related method for conversion of carboxylic acids to bromides with decarboxylation is the *Hunsdiecker reaction*.²⁷⁶ The usual method for carrying out this transformation involves heating the carboxylic acid with mercuric oxide and bromine.



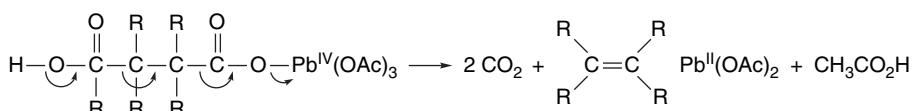
The overall transformation can also be accomplished by reaction of thallium(I) carboxylate with bromine.²⁷⁸ Phenylliodonium diacetate and bromine also lead to brominative decarboxylation.²⁷⁹



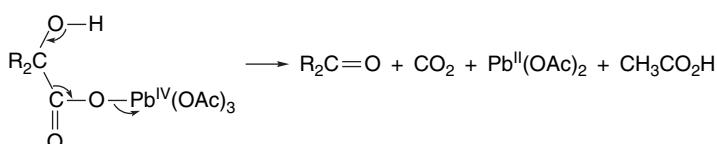
1,2-Dicarboxylic acids undergo *bis*-decarboxylation on reaction with lead tetraacetate to give alkenes. This reaction has been of occasional use for the synthesis of strained alkenes.



The reaction can occur by a concerted fragmentation process initiated by a two-electron oxidation.



A concerted mechanism is also possible for α -hydroxycarboxylic acids, and these compounds readily undergo oxidative decarboxylation to ketones.²⁸¹



²⁷⁶ C. V. Wilson, *Org. React.*, **9**, 332 (1957); R. A. Sheldon and J. Kochi, *Org. React.*, **19**, 326 (1972).

²⁷⁷ J. S. Meek and D. T. Osuga, *Org. Synth.*, **V**, 126 (1973).

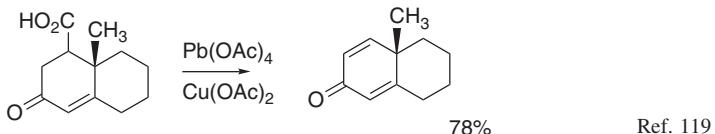
²⁷⁸ A. McKillop, D. Bromley, and E. C. Taylor, *J. Org. Chem.*, **34**, 1172 (1969).

²⁷⁹ P. Camps, A. E. Lukach, X. Pujol, and S. Vazquez, *Tetrahedron*, **56**, 2703 (2000).

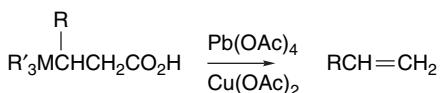
²⁸⁰ E. Grovenstein, Jr., D. V. Rao, and J. W. Taylor, *J. Am. Chem. Soc.*, **83**, 1705 (1961).

²⁸¹ R. Criegee and E. Büchner, *Chem. Ber.*, **73**, 563 (1940).

γ -Ketocarboxylic acids are oxidatively decarboxylated to enones.²⁸² This reaction is presumed to proceed through the usual oxidative decarboxylation, with the carbocation intermediate being efficiently deprotonated because of the developing conjugation.



Oxidation of β -silyl and β -stannyl acids leads to loss of the substituent and alkene formation.²⁸³



12.7. Oxidations at Unfunctionalized Carbon

Attempts to achieve selective oxidations of hydrocarbons or other compounds when the desired site of attack is remote from an activating functional group are faced with several difficulties. With powerful transition-metal oxidants, the initial oxidation products are almost always more susceptible to oxidation than the starting material. When a hydrocarbon is oxidized, it is likely to be oxidized to a carboxylic acid, with chain cleavage by successive oxidation of alcohol and carbonyl intermediates. There are a few circumstances under which oxidations of hydrocarbons can be synthetically useful processes. One group involves catalytic industrial processes. Much effort has been expended on the development of selective catalytic oxidation processes and several have economic importance. We focus on several reactions that are used on a laboratory scale.

The most general hydrocarbon oxidation is the oxidation of side chains on aromatic rings. Two factors contribute to making this a high-yield procedure, despite the use of strong oxidants. First, the benzylic position is susceptible to hydrogen abstraction by the oxidants.²⁸⁴ Second, the aromatic ring is resistant to attack by Mn(VII) and Cr(VI) reagents that oxidize the side chain.

Scheme 12.22 provides some examples of the oxidation of aromatic alkyl substituents to carboxylic acid groups. Entries 1 to 3 are typical oxidations of aromatic methyl groups to carboxylic acids. Entries 4 and 5 bring the carbon adjacent to the aromatic ring to the carbonyl oxidation level.

Selective oxidations are possible for certain bicyclic hydrocarbons.²⁸⁵ Here, the bridgehead position is the preferred site of initial attack because of the order of reactivity of C–H bonds, which is $3^\circ > 2^\circ > 1^\circ$. The tertiary alcohols that are the initial oxidation products are not easily further oxidized. The geometry of the bicyclic rings (*Bredt's rule*) prevents both dehydration of the tertiary bridgehead alcohols and further oxidation to ketones. Therefore, oxidation that begins at a bridgehead position

²⁸² J. E. McMurry and L. C. Blaszcak, *J. Org. Chem.*, **39**, 2217 (1974).

²⁸³ H. Nishiyama, M. Matsumoto, H. Arai, H. Sakaguchi, and K. Itoh, *Tetrahedron Lett.*, **27**, 1599 (1986).

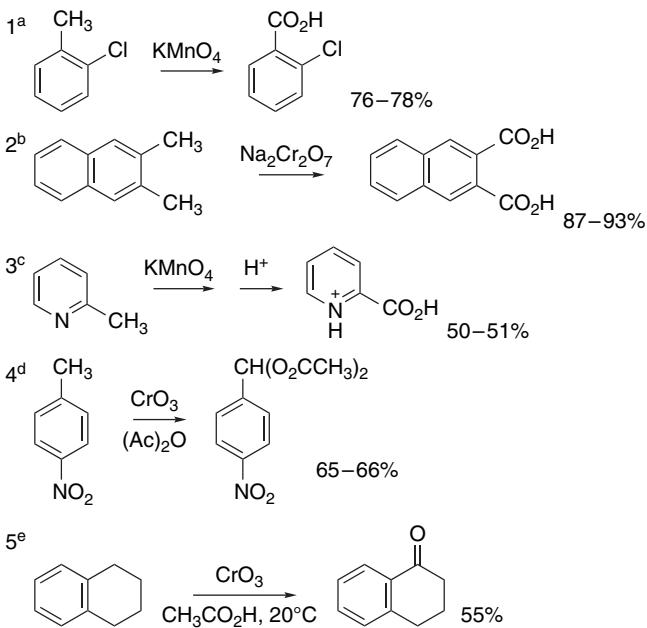
²⁸⁴ K. A. Gardner, L. L. Kuehnert, and J. M. Mayer, *Inorg. Chem.*, **36**, 2069 (1997).

²⁸⁵ R. C. Bingham and P. v. R. Schleyer, *J. Org. Chem.*, **36**, 1198 (1971).

Scheme 12.22. Side Chain Oxidation of Aromatic Compounds

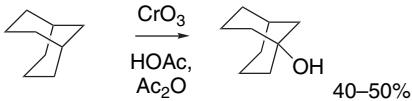
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SECTION 12.7

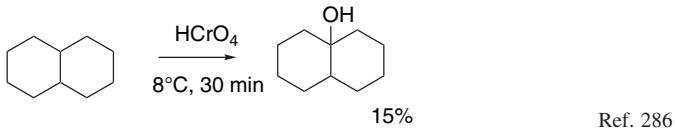
Oxidations at
Unfunctionalized Carbon

- a. H. T. Clarke and E. R. Taylor, *Org. Synth.*, **II**, 135 (1943).
 b. L. Friedman, *Org. Synth.*, **43**, 80 (1963); L. Friedman, D. L. Fishel, and H. Shechter, *J. Org. Chem.*, **30**, 1453 (1965).
 c. A. W. Singer and S. M. McElvain, *Org. Synth.*, **III**, 740 (1955).
 d. T. Nishimura, *Org. Synth.*, **IV**, 713 (1963).
 e. J. W. Burnham, W. P. Duncan, E. J. Eisenbraun, G. W. Keen, and M. C. Hamming, *J. Org. Chem.*, **39**, 1416 (1974).

stops at the alcohol stage. Chromic acid oxidation has been the most useful reagent for functionalizing unstrained bicyclic hydrocarbons. The reaction fails for strained bicyclic compounds such as norbornane because the reactivity of the bridgehead position is lowered by the unfavorable energy of radical or carbocation intermediates.



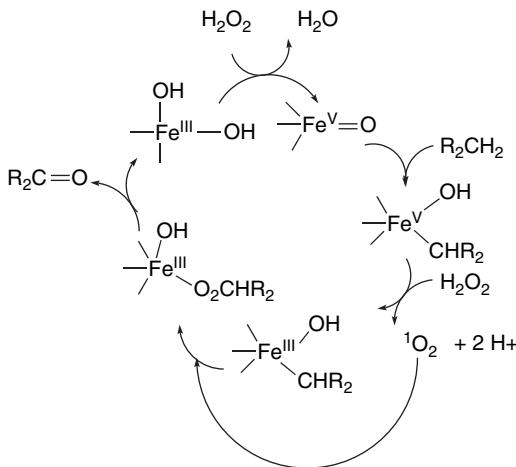
Other successful selective oxidations of hydrocarbons by Cr(VI) have been reported—for example, the oxidation of *cis*-decalin to the corresponding alcohol—but careful attention to reaction conditions is required.



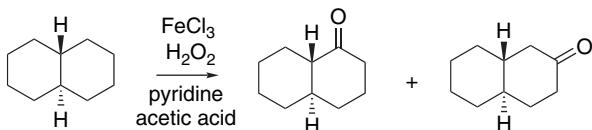
Ref. 286

²⁸⁶ K. B. Wiberg and G. Foster, *J. Am. Chem. Soc.*, **83**, 423 (1961).

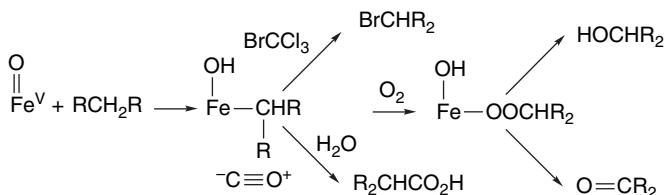
Interesting hydrocarbon oxidations have been observed using Fe(II) catalysts with oxygen or hydrogen peroxide as the oxidant. These catalytic systems have become known as “Gif chemistry” after the location of their discovery in France.²⁸⁷ An improved system involving Fe(III), picolinic acid, and H₂O₂ has been developed. The reactive species generated in these systems is believed to be at the Fe(V)=O oxidation level.²⁸⁸ The key step is hydrogen abstraction from the hydrocarbon by this Fe(V)=O intermediate.



Oxidation of *trans*-decalin leads to a mixture of 1- and 2-*trans*-decalone.²⁸⁹



The initial intermediates containing C–Fe bonds can be diverted by reagents such as CBrCl₃ or CO, among others.²⁹⁰



²⁸⁷ D. H. R. Barton and D. Doller, *Acc. Chem. Res.*, **25**, 504 (1992); D. H. R. Barton, *Chem. Soc. Rev.*, **25**, 237 (1996); D. H. R. Barton, *Tetrahedron*, **54**, 5805 (1998).

²⁸⁸ D. H. R. Barton, S. D. Beviere, W. Chavasiri, E. Csuhai, D. Doller, and W. G. Liu, *J. Am. Chem. Soc.*, **114**, 2147 (1992).

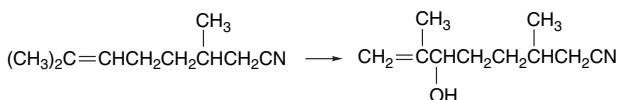
²⁸⁹ U. Schuchardt, M. J. D. M. Jannini, D. T. Richens, M. C. Guerreiro, and E. V. Spinace, *Tetrahedron*, **57**, 2685 (2001).

²⁹⁰ D. H. R. Barton, E. Csuhai, and D. Doller, *Tetrahedron Lett.*, **33**, 3413 (1992); D. H. R. Barton, E. Csuhai, and D. Doller, *Tetrahedron Lett.*, **33**, 4389 (1992).

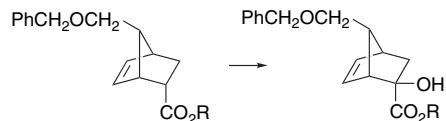
(References for these problems will be found on page 1290.)

12.1. Indicate an appropriate oxidant for carrying out the following transformations.

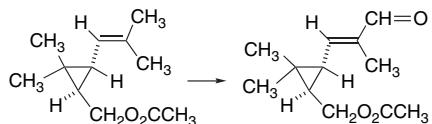
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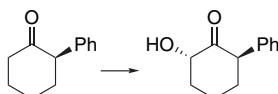
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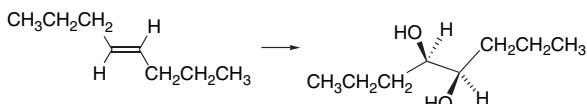
(c)



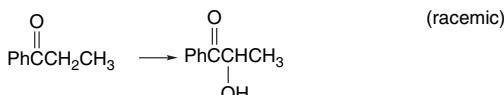
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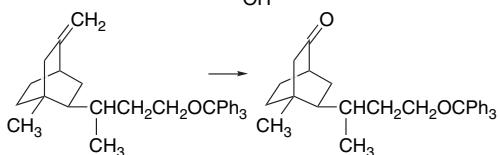
(e)



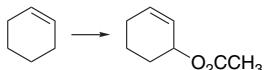
(f)



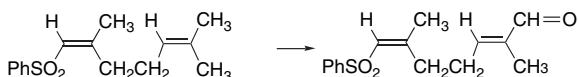
(g)



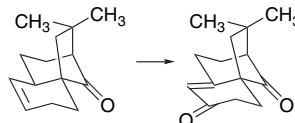
(h)

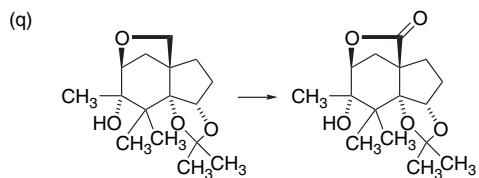
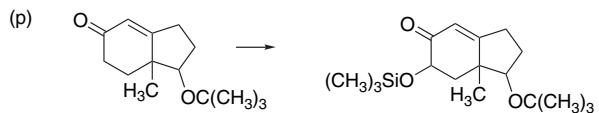
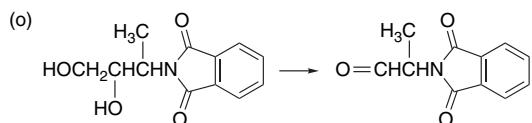
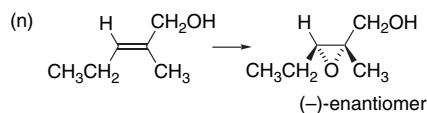
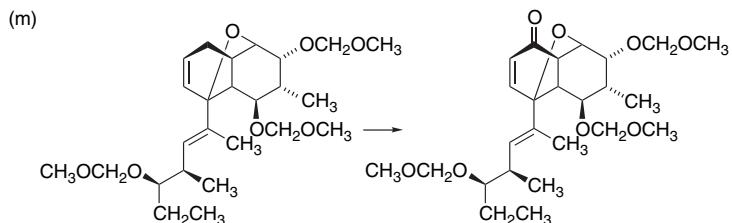
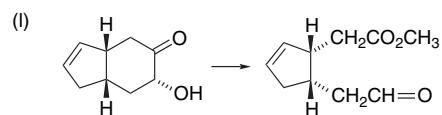
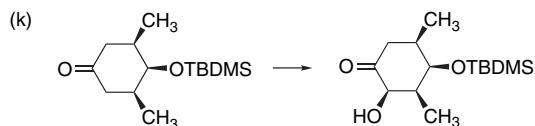


(i)

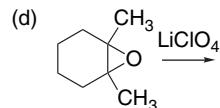
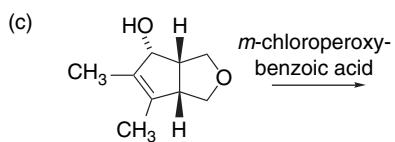
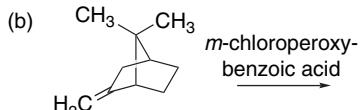
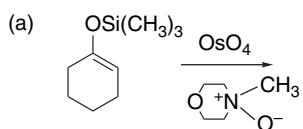


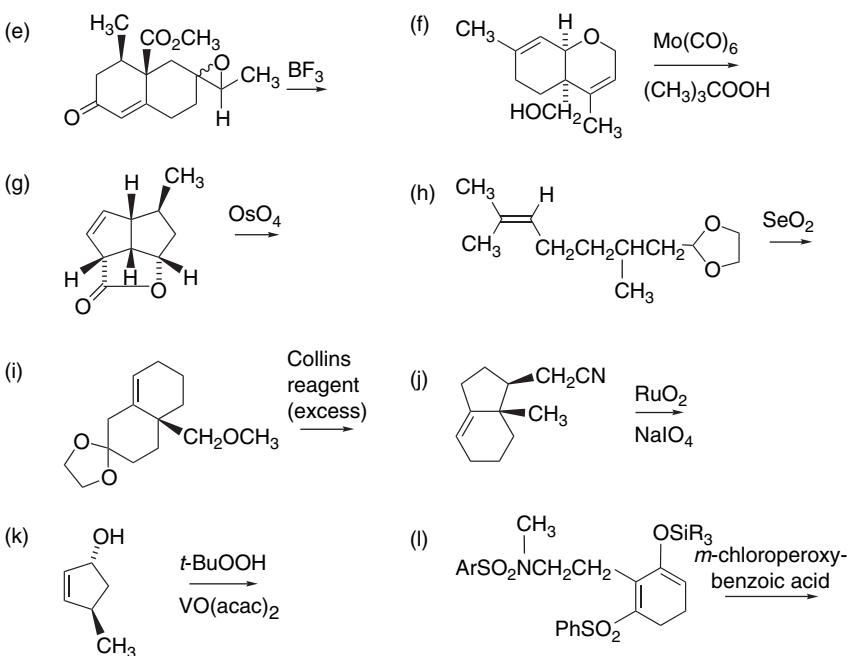
(j)





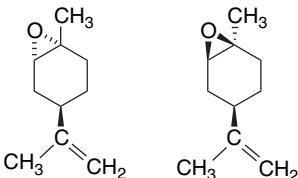
12.2. Predict the products of the following reactions. Be careful to consider all stereochemical aspects.



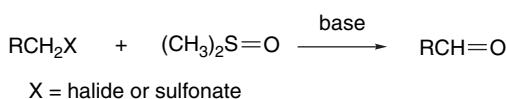


12.3. In chromic acid oxidation of stereoisomeric cyclohexanols, it is usually found that axial hydroxy groups react more rapidly than equatorial groups. For example, *trans*-4-*t*-butylcyclohexanol is less reactive (by a factor of 3.2) than the *cis* isomer. An even larger difference is noted with *cis*- and *trans*-3,3,5-trimethylcyclohexanol. The axial hydroxy in the *trans* isomer is 35 times more reactive than then equatorial hydroxy in the *cis* isomer, even though it is in a more hindered environment. A general relationship is found for pairs of epimeric cyclohexanols in that the ratio of the rates of the isomers is approximately equal to the equilibrium constant for equilibration of the isomers: $k_{\text{ax}}/k_{\text{eq}} \sim K_{\text{ax}/\text{eq}}$. Are these data compatible with the mechanism given on p. 1064? What additional details do these data provide about the reaction mechanism? Explain.

12.4. Predict the products from opening of the two stereoisomeric epoxides derived from limonene shown below by reaction with (a) acetic acid and (b) dimethylamine.

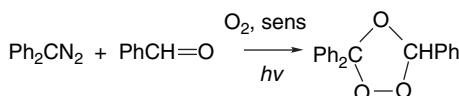


12.5. The direct oxidative conversion of primary halides and sulfonates to aldehydes can be carried out by reaction with DMSO under alkaline conditions. Formulate a mechanism for this reaction.

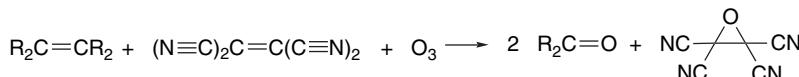


12.6. The following questions pertain to the details of mechanism of ozonolysis under modified conditions.

- a. A method for synthesis of ozonides that involves no ozone has been reported. It consists of photosensitized oxidation of diazo compounds in the presence of an aldehyde. Suggest a mechanism for this reaction.

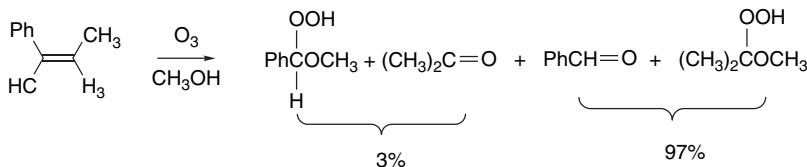


- b. Overoxidation of carbonyl products during ozonolysis can be prevented by addition of tetracyanoethylene to the reaction mixture. The stoichiometry of the reaction is then:



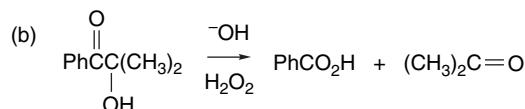
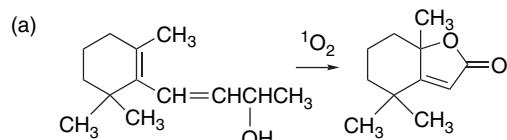
Propose a mechanism that would account for the effect of tetracyanoethylene. Does your mechanism suggest that tetracyanoethylene would be a particularly effective alkene for this purpose? Explain.

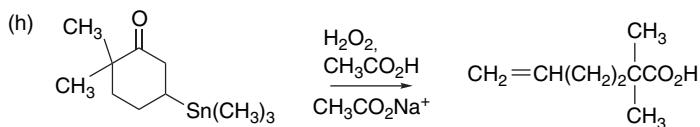
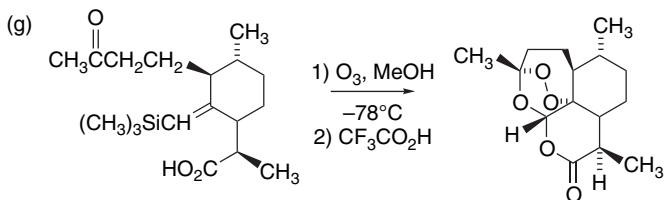
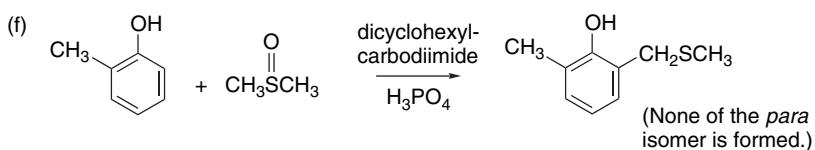
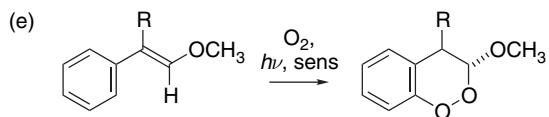
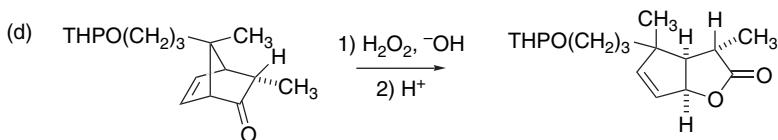
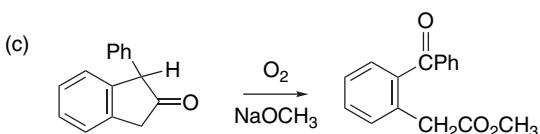
- c. It has been found that when unsymmetrical alkenes are ozonized in methanol, there is often a large preference for one cleavage mode of the initial ozonide over the other. For example:



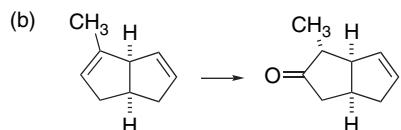
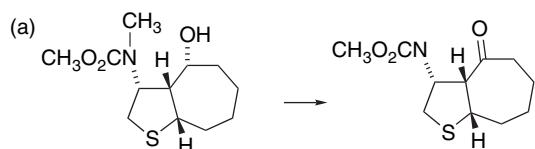
Account for this selectivity.

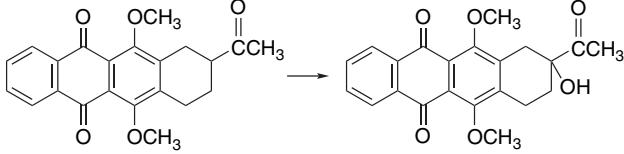
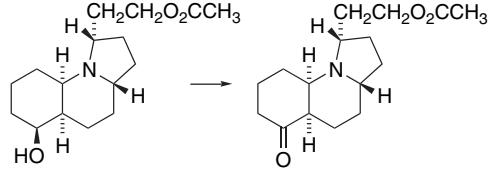
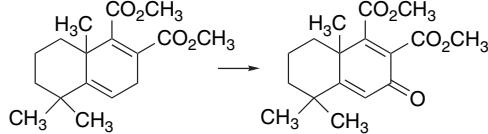
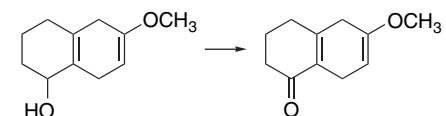
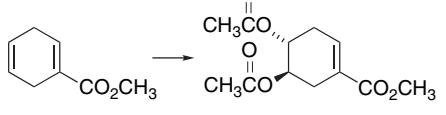
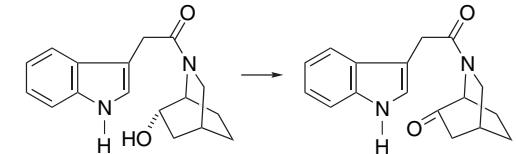
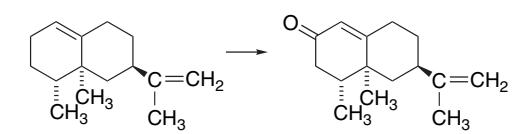
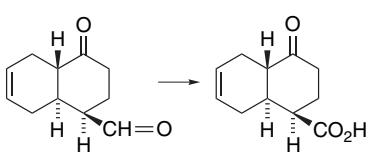
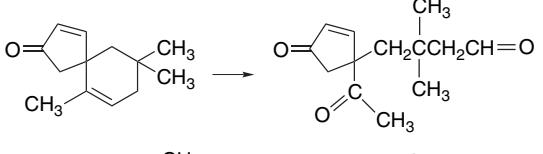
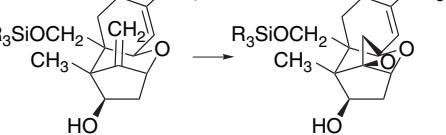
- 12.7. Suggest mechanisms by which the “abnormal” oxidations shown below could occur.



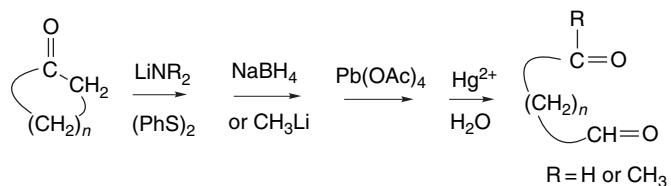


12.8. Indicate one or more satisfactory oxidants for effecting the following transformations. Each molecule poses issues of selectivity or the need to preserve a sensitive functional group. Select oxidants that can avoid the installation of protecting groups. In most cases, a one-pot reaction is possible, and in no case is a sequence of more than three steps required. Explain the reason for your choice of reagent(s).

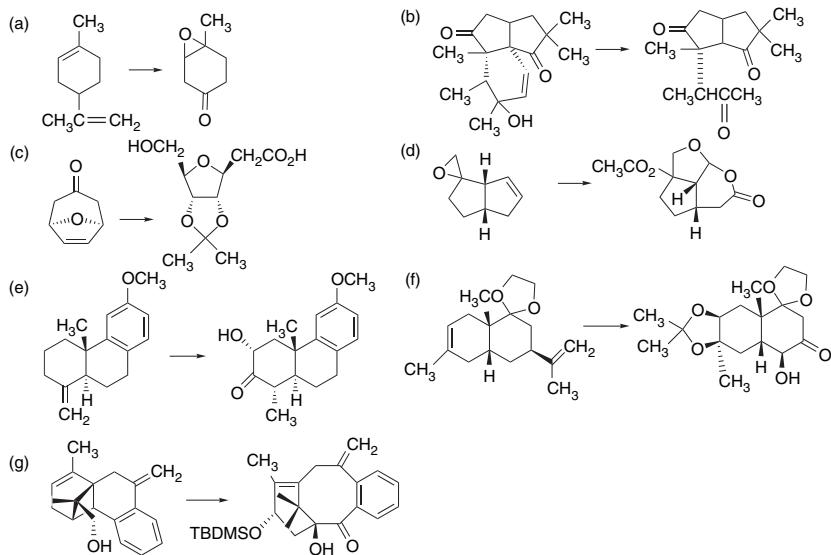


- (c) 
- (d) 
- (e) 
- (f) 
- (g) 
- (h) 
- (i) 
- (j) 
- (k) 
- (l) 

12.9. A method for oxidative cleavage of cyclic ketones involves a four-stage process. First, the ketone is converted to an α -phenylthio derivative (see Section 4.3.2). The ketone is then converted to an alcohol, either by reduction with NaBH_4 or by addition of an organolithium reagent. The alcohol is then treated with $\text{Pb}(\text{OAc})_4$ to give an oxidation product in which the hydroxy group has been acetylated and an additional oxygen added to the β -thioalcohol. Aqueous hydrolysis of this intermediate in the presence of Hg^{2+} gives a dicarbonyl compound. Formulate likely structures for the products of each step in this sequence.

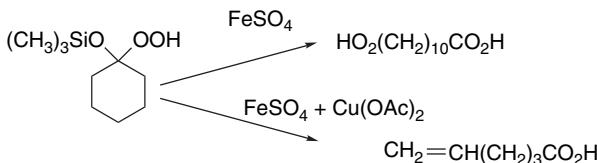


12.10. The transformations shown below have been carried out using reaction sequences involving several oxidation steps. Devise a series of steps that could accomplish these transformations and suggest reagents that would be suitable for each step. Some sequences may also require nonoxidative steps, such as introduction or removal of protecting groups.

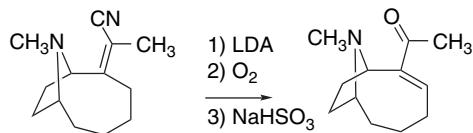


12.11. Provide mechanistic interpretations of the following reactions.

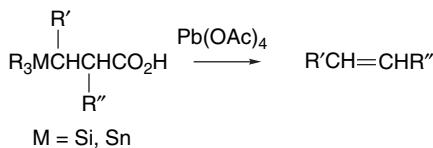
- a. Account for the products formed under the following conditions. In particular, why does the inclusion of cupric acetate change the course of the reaction?



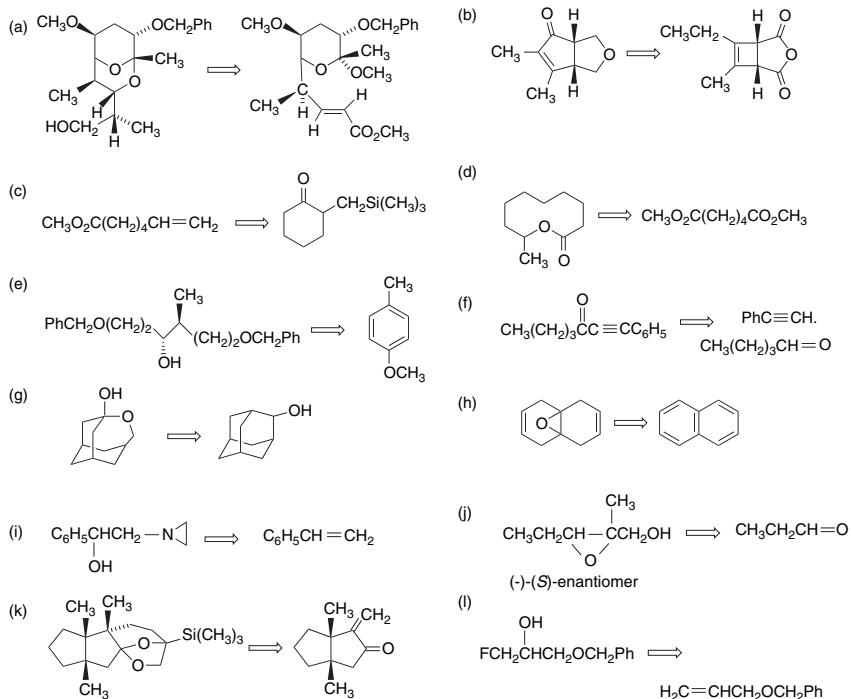
b. Account for this oxidative decyanation.

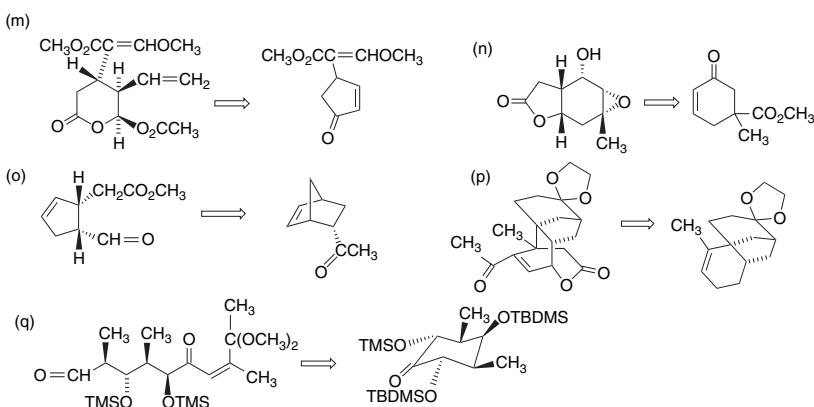


c. It is found that the oxidative decarboxylation of β -silyl and β -stannyl carboxylic acids is substantially accelerated by cupric acetate.

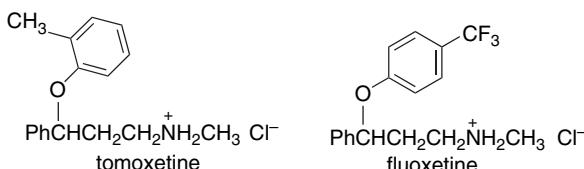


12.12. Use retrosynthetic analysis to devise a sequence of reactions that could accomplish the formation of the structure on the left from the potential precursor on the right.

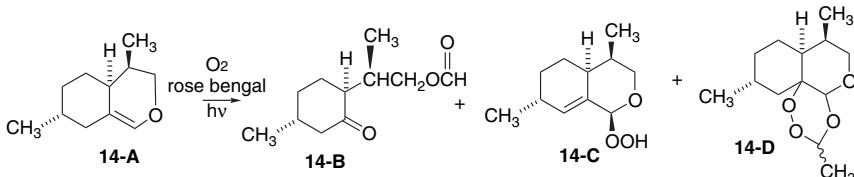




- 12.13. Tomoxetine and fluoxetine are antidepressants. Both enantiomers of each compound can be prepared enantiospecifically starting from cinnamyl alcohol. Give a reaction sequence that will accomplish this objective.



- 12.14. The irradiation of **14-A** in the presence of rose bengal and oxygen in methanol gives **14-B** as the only observable product (72% yield). When the irradiation is carried out in acetaldehyde as solvent, the yield of **14-B** is reduced to 54% and two additional products, **14-C** (19%) and **14-D** (17%), are formed. Account for the formation of each product.



- 12.15. Analyze the following data on the product ratios obtained in the epoxidation of 3-substituted cyclohexenes by dimethyldioxirane. What are the principal factors that determine the stereoselectivity?

Substituent	<i>trans:cis</i> ^a
OH	66:34 ^b
OH	15:85
OCH ₃	85:15
O ₂ CCH ₃	62:38
CO ₂ CH ₃	68:32
CO ₂ H	84:16

(Continued)

Substituent	<i>trans:cis</i> ^a
NHCOPh	3:97
Cl	90:10 ^c
CF ₃	90:10 ^c
CH ₃	47:53
(CH ₃) ₂ CHCH ₂	54:46
(CH ₃) ₃ C	95:5 ^c
Ph	85:15

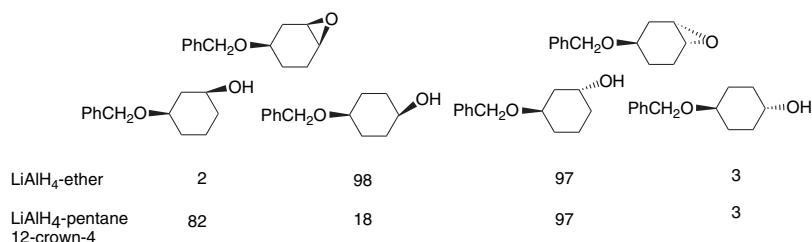
a. Solvent is 9:1 CCl₄-acetone except as noted otherwise.

b. Solvent is 9:1 methanol-acetone.

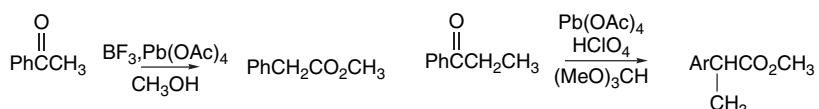
c. Solvent is acetone.

12.16. Offer a mechanistic explanation for the following observations.

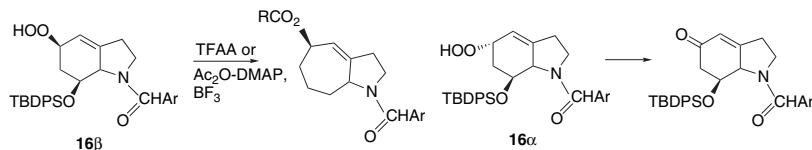
- a. A change from ether as solvent to pentane with 12-crown-4 reverses the stereoselectivity of LiAlH₄ reduction of *cis*-3-benzyloxycyclohexene oxide, but not the *trans* isomer.



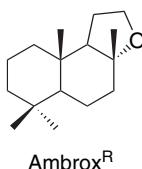
- b. In the presence of a strong protic acid or a Lewis acid, acetophenones and propiophenones rearrange to arylalkanoic acid on reaction with Pb(OAc)₄.



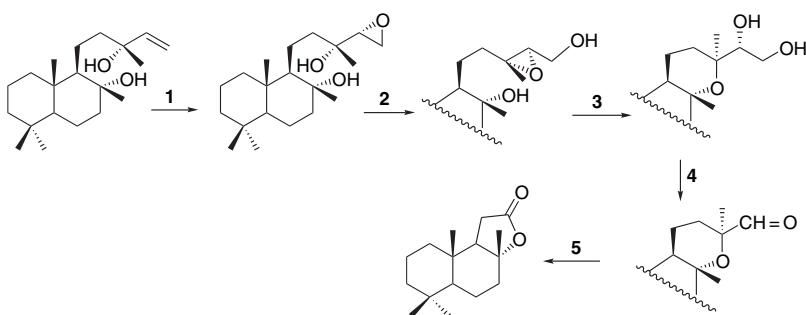
- c. Acylation leads to reaction of the hydroperoxides **16β** and **16α**, but the products are different. In **16β**, the vinyl substituent migrates giving ring expansion, whereas with **16α** an enone is formed.



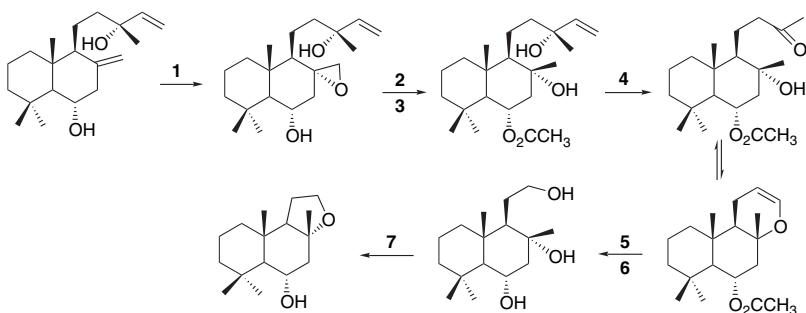
- 12.17. Various terpene-derived materials are important in the formulation of fragrances and flavors. One example is the tricyclic furan shown below, which is commercially used under the trademark Ambrox.[®] The synthetic sequences below have been developed to prepare related structures. Suggest reagents for each step in these sequences.



- a. This sequence was developed to avoid the use of transition metal reagents and minimize by-products.



- b. The following sequence led to the 6- α -hydroxy derivative.



- 12.18. The closely related enones **18-A** and **18-B** give different products when treated with Pb(OAc)₄ in CH₃CN. Formulate mechanisms to account for both products and identify the factor(s) that lead to the divergent structures.

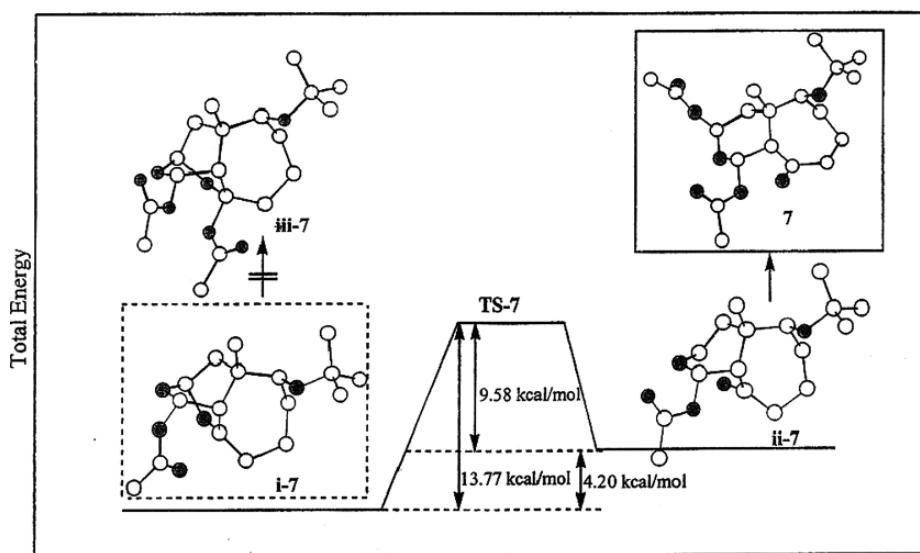
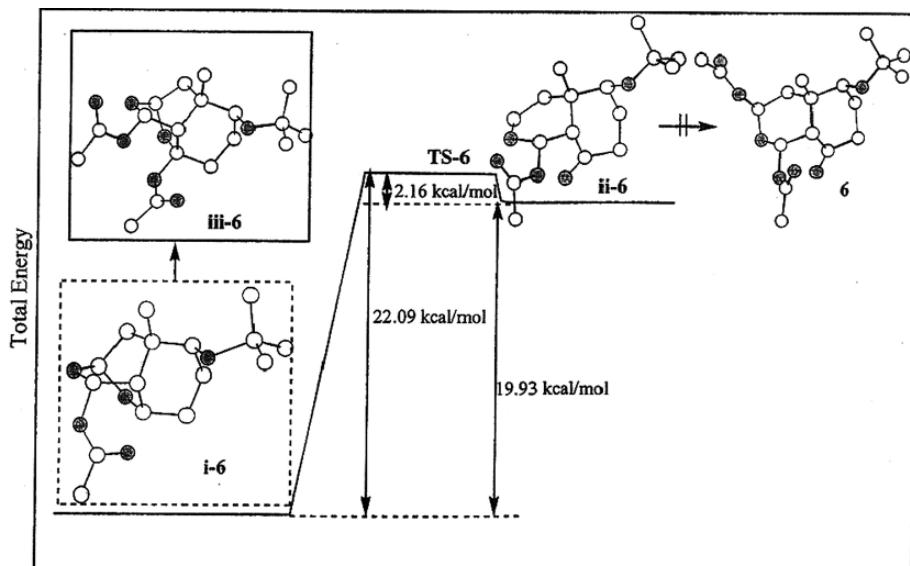
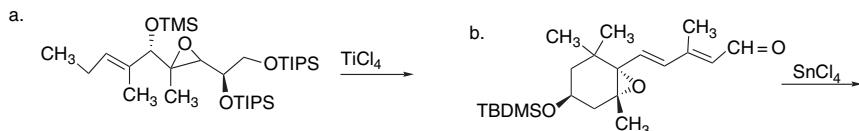


Fig. 12.P18. Comparison of the computed energy profiles for **18-A** and **18-B**. Reproduced from *J. Org. Chem.*, **67**, 2447 (2002), by permission of the American Chemical Society.

12.19. Predict the structure and stereochemistry of the Lewis acid-catalyzed rearrangement of the following epoxides.



Multistep Syntheses

Introduction

The reactions discussed in the preceding chapters provide tools for synthesizing new and complex molecules, but a strategy for using these reactions is essential for successful multistep syntheses. The sequence of individual reactions must be planned so that the reactions are mutually compatible with the final synthetic goal. Certain functional groups can interfere with prospective reactions and such problems must be avoided either by a modification of the sequence or by temporarily masking (protecting) the interfering group. *Protective groups* are used to temporarily modify functionality, which is then restored when the protecting group is removed. Another approach is to use a *synthetic equivalent group* in which a particular functionality is introduced as an alternative structure that can subsequently be converted to the desired group.

Protective groups and synthetic equivalent groups are tactical tools of multistep syntheses. They are the means, along with the individual synthetic methods, to reach the goal of a completed synthesis, and these tactical steps must be incorporated into an overall synthetic plan. A synthetic plan is normally created on the basis of a *retrosynthetic analysis*, which involves identification of the particular bonds that can be formed to obtain the desired molecule. Depending on the complexity of the synthetic target, the retrosynthetic analysis may be obvious or intricate. A synthetic plan identifies potential starting materials and reactions that can lead to the desired molecule, and most such plans involve a combination of *linear sequences* and *convergent steps*. Linear sequences construct the target molecule step-by-step by incremental additions and functional group transformations. Convergent steps bring together larger segments of the molecule that have been created by linear sequences. As the overall synthetic yield is the multiplication product of the yield of each of the individual steps in the synthesis, incorporation of a convergent step improves overall yield by reducing the length of the linear sequences. After discussing some general aspects of synthetic analysis and planning, we summarize several syntheses that illustrate application of multistep synthetic methods to representative molecules. In the final sections of the chapter, we consider solid phase synthesis and its application to polypeptide, poly-nucleotide, and combinatorial syntheses.

13.1. Synthetic Analysis and Planning

13.1.1. Retrosynthetic Analysis

The tools available to the synthetic chemist consist of an extensive catalog of reactions and the associated information on such issues as stereoselectivity and mutual reactivity. This knowledge permits a judgment on the applicability of a particular reaction in a synthetic sequence. Broad mechanistic insight is also crucial to synthetic analysis. The relative position of functional groups in a potential reactant may lead to specific interactions or reactions. The ability to recognize such complications enables appropriate adjustments to the synthetic plan. Mechanistic concepts can guide optimization of reaction conditions. They are as well the basis for developing new reactions that may be necessary in a particular situation.

The planning of a synthesis involves a critical comparative evaluation of alternative reaction sequences that could reasonably be expected to lead to the desired structure from appropriate starting materials. In general, the complexity of a synthetic plan increases with the size of the molecule and with increasing numbers of functional groups and stereogenic centers. The goal of synthetic analysis is to recognize possible pathways to the target compound and to develop a suitable sequence of synthetic steps. In general, a large number of syntheses of any given compound are possible. The objective of synthetic analysis and planning is to develop a reaction sequence that will complete the desired synthesis efficiently within the constraints that apply.

The restrictions that apply depend on the purposes for which the synthesis is being done. A synthesis of a material to be prepared in substantial quantity may impose a limitation on the cost of the starting materials. Syntheses for commercial production must meet such criteria as economic feasibility, acceptability of by-products, and safety. Syntheses of structures having several stereogenic centers must deal with the problem of stereoselectivity. If an enantiomerically pure material is to be synthesized, the means of controlling absolute configuration must be considered. The development of a satisfactory plan is the chemist's intellectual challenge and it puts a premium on creativity and ingenuity. There is no single correct solution. Although there is no established routine by which a synthetic plan can be formulated, general principles that can guide synthetic analysis and planning have been described.¹

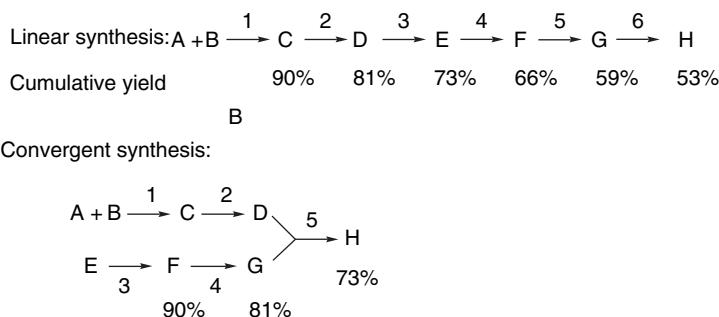
The initial step in creating a synthetic plan involves a *retrosynthetic analysis*. The structure of the molecule is dissected step by step along reasonable pathways to successively simpler compounds until molecules that are acceptable as starting materials are identified. Several factors enter into this process, and all are closely interrelated. The recognition of *bond disconnections* allows the molecule to be broken down into *key intermediates*. Such disconnections must be made in such a way that it is feasible to form the bonds by some synthetic process. The relative placement of potential functionality strongly influences which bond disconnections are preferred. To emphasize that these disconnections must correspond to transformations that can be conducted in the synthetic sense, they are sometimes called *antisynthetic transforms*, i.e., the reverse of synthetic steps. An open arrow symbol, \Rightarrow , is used to indicate an antisynthetic transform.

Retrosynthetic analysis can identify component segments of a target molecule that can serve as key intermediates, and the subunits that are assembled to construct

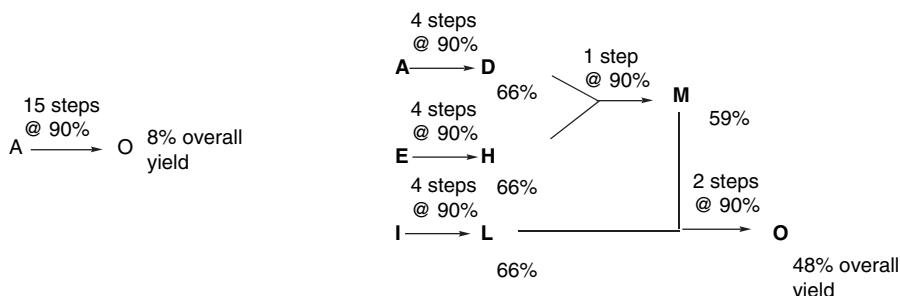
¹. E. J. Corey and X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, 1989.

them are sometimes called *synthons*. Synthons must not only correspond structurally to the desired subunit, but they must also have appropriate reactivity to allow bond formation with adjacent subunits. For example, in the case of aldol reactions, one reagent must serve as the electrophile and the other as the nucleophile. In a ring construction by a Diels-Alder reaction, the diene and dienophile must have compatible reactivity. Similarly, in bond constructions done using organometallic intermediates, the synthons must possess appropriate mutual reactivity.

The overall synthetic plan consists of a sequence of reactions designed to construct the total molecular framework from the key intermediates. The plan should take into account the advantages of a *convergent synthesis*. The purpose of making a synthesis more convergent is to shorten its overall length. In general, it is desirable to construct the molecule from a few key segments that can be combined late in the synthesis rather than build the molecule step-by-step from a single starting material. The overall yield is the multiplication product of the yields for all the individual steps. Overall yields decrease with the increasing number of steps to which the original starting material is subjected.² One of the characteristics of a multistep sequence is the *longest linear sequence*, which is the maximum number of steps from an original starting material to the final product. For example, in the case below, a single convergency that reduces the longest linear sequence from six to three improves the overall yield from 53% to 73% if the yield was 90% in each transformation.



Splitting a 15-step synthesis into three branches of four steps each will improve the yield from 8% to 48% if each step occurs in 90% yield.



After a plan for assembly of the key intermediates into the molecular framework has been developed, the details of incorporation and transformation of functional

². A formal analysis of the concept of convergency has been presented by J. B. Hendrickson, *J. Am. Chem. Soc.*, **99**, 5439 (1977).

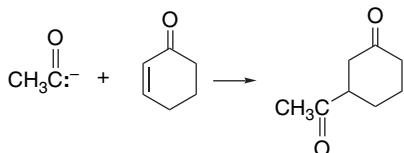
groups are considered. It is frequently necessary to interconvert functional groups, which may be done to develop a particular kind of reactivity at a center or to avoid interference with a reaction step. Protective groups and synthetic equivalent groups are important for planning of functional group transformations. Owing to the large number of procedures for interconverting the common functional groups, achieving the final array of functionality is often less difficult than establishing the overall molecular skeleton and stereochemistry.

The synthetic plan must also provide for control of stereochemistry. In the case of cyclic compounds, advantage often can be taken of the facial preferences of the rings and the stereoselectivity of reagents to establish the stereochemistry of substituents. For example, the *syn*-directive effect of hydroxy groups in epoxidation (see p. 1093) or the strong preference for *anti* addition in iodolactonization (see p. 311) can be used to determine the configuration of new stereogenic centers. Similarly, the cyclic TS of sigmatropic rearrangements often allows predictable stereoselectivity. Chiral auxiliaries and catalysts provide means of establishing configuration in enantioselective syntheses. A plan for a stereo- or enantioselective synthesis must include the basis for controlling the configuration at each stereocenter.

The care with which a synthesis is analyzed and planned will have a great impact on the likelihood of its success. The investment of material and effort that is made when the synthesis is begun may be lost if the plan is faulty. Even with the best of planning, however, unexpected problems are often encountered. This circumstance again tests the ingenuity of the chemist to devise a modified plan that can overcome the unanticipated obstacle.

13.1.2. Synthetic Equivalent Groups

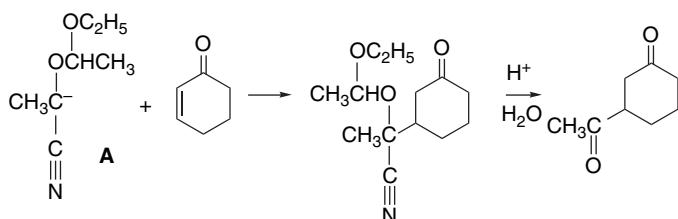
Retrosynthetic analysis may identify a need to use *synthetic equivalent groups*. These groups are synthons that correspond structurally to a subunit of the target structure, but in which the reactivity of the functionality is masked or modified. As an example, suppose the transformation shown below was to be accomplished.



The electrophilic α,β -unsaturated ketone is reactive toward nucleophiles, but the nucleophile that is required, an acyl anion, is not normally an accessible entity. There are several potential reagents that could introduce the desired acyl anion in a masked form. The masked functionality used in place of an inaccessible species is called a synthetically equivalent group. Often the concept of “*umpolung*” is involved in devising synthetic equivalent groups. The term *umpolung* refers to the formal reversal of the normal polarity of a functional group.³ Acyl groups are normally *electrophilic*, but a synthetic operation may require the transfer of an acyl group as a *nucleophile*. The *acyl anion* is an *umpolung* equivalent of the electrophilic acylium cation.

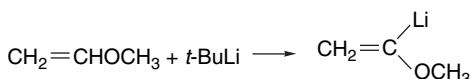
³ For a general discussion and many examples of the use of the *umpolung* concept, see D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **18**, 239 (1979).

Owing to the great importance of carbonyl groups in synthesis, a substantial effort has been devoted to developing nucleophilic equivalents for introduction of acyl groups.⁴ One successful method involves a three-step sequence in which an aldehyde is converted to an O-protected cyanohydrin. The α -alkoxynitrile is then deprotonated, generating a nucleophilic carbanion A.⁵ After carbon-carbon bond formation, the carbonyl group can be regenerated by hydrolysis of the cyanohydrin. This sequence has been used to solve the problem of introducing an acetyl group at the β -position of cyclohexenone.⁶

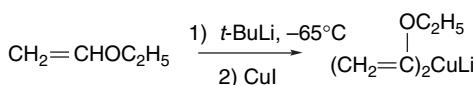


Ref. 5

α -Lithiovinyl ethers and the corresponding cuprates are other examples of acyl anion equivalents.

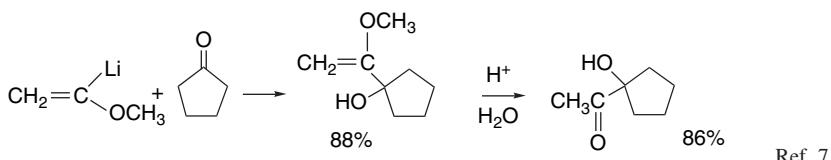


Ref. 7



Ref. 8

These reagents are capable of adding the α -alkoxyvinyl group to electrophilic centers. Subsequent hydrolysis can generate the carbonyl group and complete the desired transformation.



Ref. 7

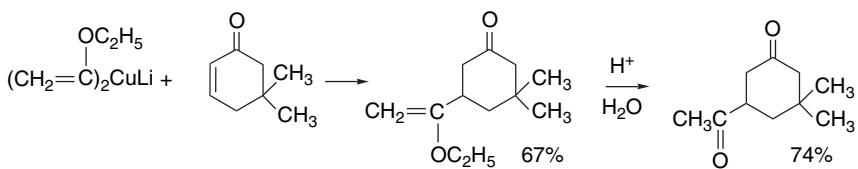
⁴ For a review of acyl anion synthons, see T. A. Hase and J. K. Koskimies, *Aldrichica Acta*, **15**, 35 (1982).

⁵ G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **93**, 5286 (1971); *J. Am. Chem. Soc.*, **96**, 5272 (1974).

⁶ For further discussion of synthetic applications of the carbanions of O-protected cyanohydrins, see J. D. Albright, *Tetrahedron*, **39**, 3207 (1983).

⁷ J. E. Baldwin, G. A. Hoefle, and O. W. Lever, Jr., *J. Am. Chem. Soc.*, **96**, 7125 (1974).

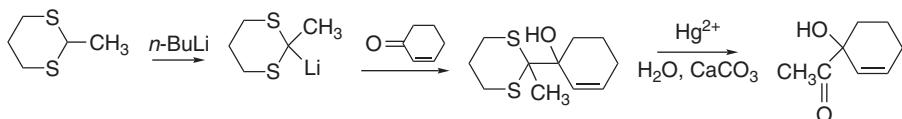
⁸ R. K. Boeckman, Jr., and K. J. Bruza, *J. Org. Chem.*, **44**, 4781 (1979).



Ref. 8

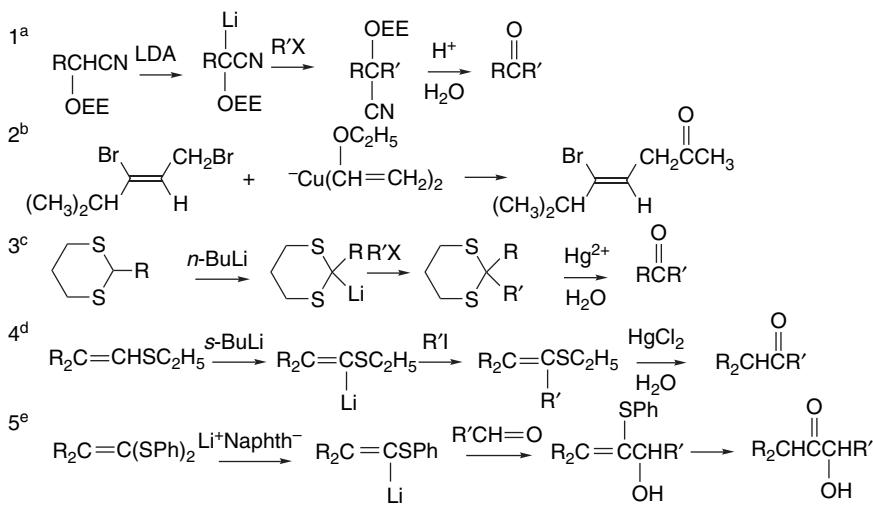
Lithiation of vinyl thioethers⁹ and vinyl carbamates¹⁰ also provides acyl anion equivalents.

Sulfur compounds are useful as nucleophilic acyl equivalents. The most common reagents of this type are 1,3-dithianes, which on lithiation provide a nucleophilic acyl equivalent. In dithianes an umpolung is achieved on the basis of the carbanion-stabilizing ability of the sulfur substituents. The lithio derivative is a reactive nucleophile toward alkyl halides and carbonyl compounds.¹¹



1,3-Dithianes have found considerable application in multistep syntheses.¹² Scheme 13.1 summarizes some examples of synthetic sequences that employ acyl anion equivalents.

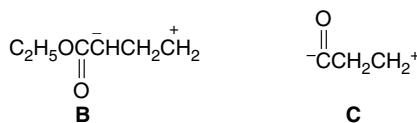
Scheme 13.1. Synthetic Sequences Using Acyl Anion Equivalents

a. G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **93**, 5236 (1971).b. P. Canonne, R. Boulanger, and P. Angers, *Tetrahedron Lett.*, **32**, 5861 (1991).c. D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975).d. K. Oshima, K. Shimoji, H. Takahashi, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **95**, 2694 (1973).e. T. Cohen and R. B. Weisenfeld, *J. Org. Chem.*, **44**, 3601 (1979).9. K. Oshima, K. Shimoji, H. Takahashi, and H. Nozaki, *J. Am. Chem. Soc.*, **95**, 2694 (1973).10. S. Sengupta and V. Sniekus, *J. Org. Chem.*, **55**, 5680 (1990).11. D. Seebach and E. J. Corey, *J. Org. Chem.*, **40**, 231 (1975); B. H. Lipshutz and E. Garcia, *Tetrahedron Lett.*, **31**, 7261 (1990).12. M. Yus, C. Najera, and F. Foubelo, *Tetrahedron*, **59**, 6147 (2003); A. B. Smith, III, and C. M. Adams, *Acc. Chem. Res.*, **37**, 365 (2004).

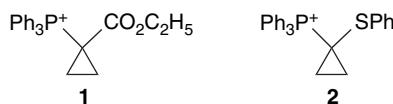
Another synthetic equivalent that has been extensively developed corresponds to the propanal “homoenolate,” $-\text{CH}_2\text{CH}_2\text{CH}=\text{O}$.¹³ This structure is the umpolung equivalent of an important electrophilic reagent, the α,β -unsaturated aldehyde acrolein. Scheme 13.2 illustrates some of the propanal homoenolate equivalents that have been developed. In general, the reagents used for these transformations are reactive toward electrophiles such as alkyl halides and carbonyl compounds. Several general points can be made about the reagents in Scheme 13.2. First, it should be noted that they all deliver the aldehyde functionality in a masked form, such as an acetal or enol ether. The aldehyde is liberated in a final step from the protected precursor. Several of the reagents involve delocalized allylic anions, which gives rise to the possibility of electrophilic attack at either the α - or γ -position of the allylic group. In most cases, the γ -attack that is necessary for the anion to function as a propanal homoenolate is dominant. In Entry 1, the 2-methoxycyclopropyllithium is used to form a cyclopropyl carbinol. The methoxy group serves both to promote fragmentation of the cyclopropyl ring and to establish the aldehyde oxidation level. In Entry 2, the lithiation product of allyl methyl ether serves as a nucleophile and the aldehyde group is liberated by hydrolysis. Entry 3 is similar, but uses a trimethylsilyl ether. In Entry 4, allylic lithiation of an *N*-allylamine provides a nucleophile and can subsequently be hydrolyzed to the aldehyde.

In Entry 5, the carbanion-stabilizing ability of the sulfonyl group enables lithiation and is then reductively removed after alkylation. The reagent in Entry 6 is prepared by dilithiation of allyl hydrosulfide using *n*-butyllithium. After nucleophilic addition and S-alkylation, a masked aldehyde is present in the form of a vinyl thioether. Entry 7 uses the epoxidation of a vinyl silane to form a γ -hydroxy aldehyde masked as a cyclic acetal. Entries 8 and 9 use nucleophilic cuprate reagents to introduce alkyl groups containing aldehydes masked as acetals.

The concept of developing reagents that are the synthetic equivalent of inaccessible species can be taken another step by considering dipolar species. For example, structures **B** and **C** incorporate both electrophilic and nucleophilic centers. Such reagents might be incorporated into ring-forming schemes, since they have the ability, at least formally, of undergoing cycloaddition reactions.

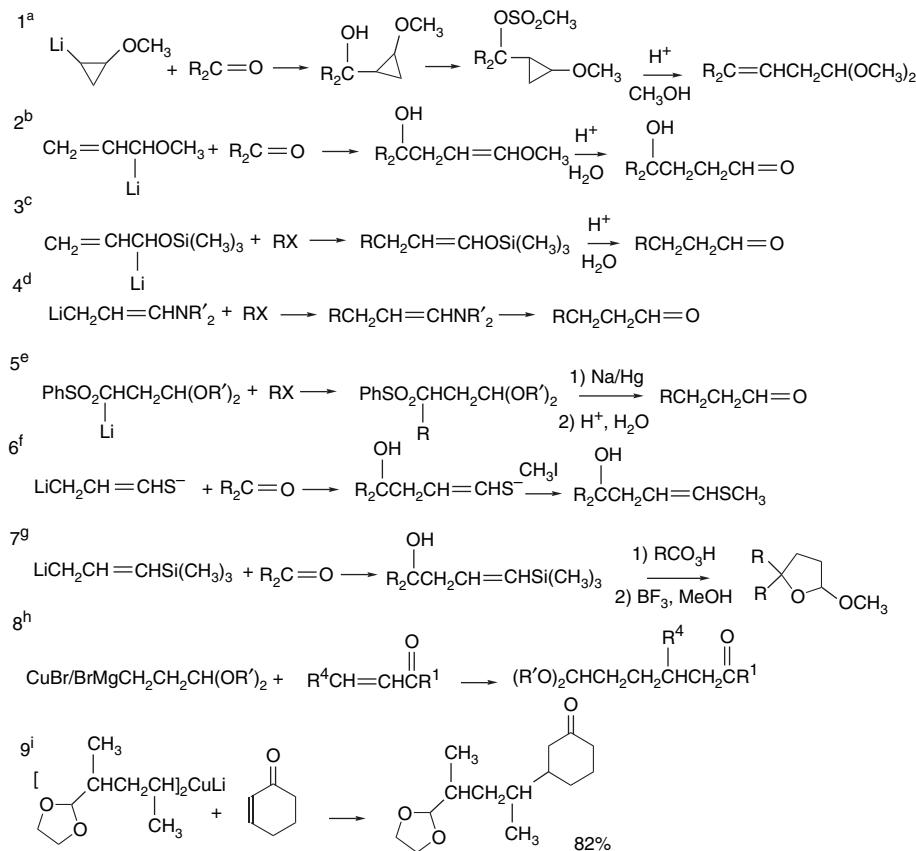


Among the real chemical species that have been developed along these lines are the cyclopropyl phosphonium ions **1** and **2**.



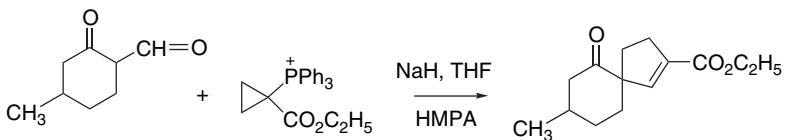
¹³. For reviews of homoenolate anions, see J. C. Stowell, *Chem. Rev.*, **84**, 409 (1984); N. H. Werstiuk, *Tetrahedron*, **39**, 205 (1983).

Scheme 13.2. Synthetic Sequences Using Homoenolate Synthetic Equivalents



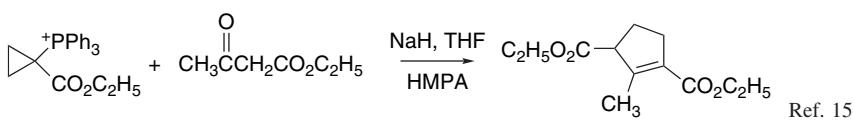
- a. E. J. Corey and P. Ulrich, *Tetrahedron Lett.*, 3685 (1975).
- b. D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Am. Chem. Soc.*, **96**, 5560 (1974).
- c. W. C. Still and T. L. Macdonald, *J. Am. Chem. Soc.*, **96**, 5561 (1974).
- d. H. Ahlbrecht and J. Eichler, *Synthesis*, 672 (1974); S. F. Martin and M. T. DuPriest, *Tetrahedron Lett.*, 3925 (1977); H. Ahlbrecht, G. Bonnet, D. Enders, and G. Zimmerman, *Tetrahedron Lett.*, **21**, 3175 (1980). e. M. Julia and B. Badet, *Bull. Soc. Chim. Fr.*, 1363 (1975); K. Kondo and D. Tunemoto, *Tetrahedron Lett.*, 1007 (1975).
- f. K.-H. Geiss, B. Seuring, R. Pieter, and D. Seebach, *Angew. Chem. Int. Ed. Engl.*, **13**, 479 (1974); K.-H. Geiss, D. Seebach, and B. Seuring, *Chem. Ber.*, **110**, 1833 (1977).
- g. E. Ehlinger and P. Magnus, *J. Am. Chem. Soc.*, **102**, 5004 (1990).
- h. A. Marfat and P. Helquist, *Tetrahedron Lett.*, 4217 (1978); A. Leone-Bay and L. A. Paquette, *J. Org. Chem.*, **47**, 4172 (1982).
- i. J. P. Cherkaukas and T. Cohen, *J. Org. Chem.*, **57**, 6 (1992).

The phosphonium salt **1** reacts with β -ketoesters and β -ketoaldehydes to give excellent yields of cyclopentenecarboxylate esters.

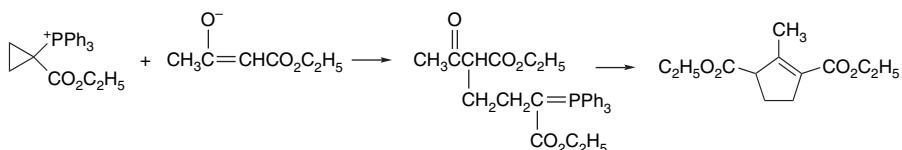


Ref. 14

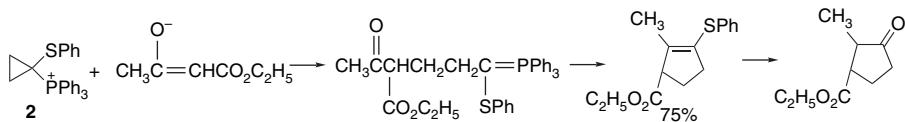
¹⁴. W. G. Dauben and D. J. Hart, *J. Am. Chem. Soc.*, **99**, 7307 (1977).



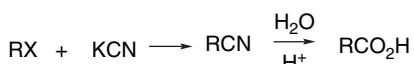
Several steps are involved in these reactions. First, the enolate of the β -ketoester opens the cyclopropane ring. The polarity of this process corresponds to that in the formal synthon **B** because the cyclopropyl carbons are electrophilic. The product of the ring-opening step is a stabilized Wittig ylide, which can react with the ketone carbonyl to form the carbocyclic ring.



The phosphonium ion **2** reacts similarly with enolates to give vinyl sulfides. The vinyl sulfide group can then be hydrolyzed to a ketone. The overall transformation corresponds to the reactivity of the dipolar synthon **C**.



Many other examples of synthetic equivalent groups have been developed. For example, in Chapter 6 we discussed the use of diene and dienophiles with masked functionality in the Diels-Alder reaction. It should be recognized that there is no absolute difference between what is termed a “reagent” and a “synthetic equivalent group.” For example, we think of potassium cyanide as a reagent, but the cyanide ion is a nucleophilic equivalent of a carboxy group. This reactivity is evident in the classical preparation of carboxylic acids from alkyl halides via nitrile intermediates.



The important point is that synthetic analysis and planning should not be restricted to the specific functionalities that appear in the target molecules. These groups can be incorporated as masked equivalents by methods that would not be possible for the functional group itself.

13.1.3. Control of Stereochemistry

The degree of control of stereochemistry that is necessary during synthesis depends on the nature of the molecule and the objective of the synthesis. The issue

¹⁵. P. L. Fuchs, *J. Am. Chem. Soc.*, **96**, 1607 (1974).

¹⁶. J. P. Marino and R. C. Landick, *Tetrahedron Lett.*, 4531 (1975).

becomes critically important when the target molecule has several stereogenic centers, such as double bonds, ring junctions, and asymmetric carbons. The number of possible stereoisomers is 2^n , where n is the number of stereogenic centers. Failure to control stereochemistry of intermediates in the synthesis of a compound with several centers of stereochemistry leads to a mixture of stereoisomers that will, at best, result in a reduced yield of the desired product and may generate inseparable mixtures. For properties such as biological activity, obtaining the correct stereoisomer is crucial.

We have considered stereoselectivity for many of the reactions that are discussed in the earlier chapters. In ring compounds, for example, stereoselectivity can frequently be predicted on the basis of conformational analysis of the reactant and consideration of the steric and stereoelectronic factors that influence reagent approach. In the *diastereoselective synthesis* of a chiral compound in racemic form, it is necessary to control the *relative configuration* of all stereogenic centers. Thus in planning a synthesis, the stereochemical outcome of all reactions that form new double bonds, ring junctions, or asymmetric carbons must be incorporated into the synthetic plan. In a completely stereoselective synthesis, each successive stereochemical feature is introduced in the proper relationship to existing stereocenters, but this ideal is often difficult to achieve. When a reaction is not completely stereoselective, the product will contain one or more diastereomers of the desired product. This requires either a purification or some manipulation to correct the stereochemistry. Fortunately, diastereomers are usually separable, but the overall efficiency of the synthesis is decreased with each such separation. Thus, high stereoselectivity is an important goal of synthetic planning.

If the compound is to be obtained in enantiomerically pure form, an *enantioselective synthesis* must be developed. As discussed in Section A.2.5, the stereochemical control may be based on chirality in the reactants, auxiliaries, reagents, and/or catalysts. There are several general approaches that are used to obtain enantiomerically pure material by synthesis. One is based on incorporating a *resolution* into the synthetic plan. This approach involves use of racemic or achiral starting materials and resolving some intermediate in the synthesis. In a synthesis based on a resolution, the steps subsequent to the resolution step must meet two criteria: (1) they must not disturb the configuration at existing stereocenters, and (2) new centers of stereochemistry must be introduced with the correct configuration relative to those that already exist. A second general approach is to use an *enantiomerically pure starting material*. Highly enantioselective reactions, such as the Sharpless epoxidation, can be used to prepare enantiomerically pure starting materials. There are a number of naturally occurring materials, or substances derived from them, that are available in enantiomerically pure form.¹⁷

Enantioselective synthesis can also be based on *chiral reagents*. Examples are hydroboration or reduction using one of the commercial available borane reagents. Again, a completely enantioselective synthesis must be capable of controlling the stereochemistry of all newly introduced stereogenic centers so that they have the proper relationship to the chiral centers that exist in the starting material. When this is not achieved, the desired stereoisomer must be separated and purified. A fourth method for enantioselective synthesis involves the use of a stoichiometric amount of a *chiral auxiliary*. This is an enantiomerically pure material that can control the stereochemistry of one or more reaction steps in such a way as to give product having the desired configuration. When the chiral auxiliary has achieved its purpose, it can be

¹⁷. For a discussion of this approach to enantioselective synthesis, see S. Hanessian, *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon Press, New York, 1983.

eliminated from the molecule. As in syntheses involving resolution or enantiomerically pure starting materials, subsequent steps must give the correct configuration of newly created stereocenters. Another approach to enantioselective synthesis is to use a *chiral catalyst* in a reaction that creates one or more stereocenters. If the catalyst operates with complete efficiency, an enantiomerically pure material will be obtained. Subsequent steps must control the configuration of newly introduced stereocenters.

In practice, any of these approaches might be the most effective for a given synthesis. If they are judged on the basis of absolute efficiency in the use of a chiral material, the ranking is resolution < chiral reactant < chiral reagent < chiral auxiliary < enantioselective catalyst. A resolution process inherently employs only half of the original racemic material. A chiral starting material can, in principle, be used with 100% efficiency, but it is consumed and cannot be reused. A chiral reagent is also consumed, but in principle it can be regenerated, as is done for certain organoboranes (see p. 350). A chiral auxiliary must be used in a stoichiometric amount but it can be recovered. A chiral catalyst, in principle, can produce an unlimited amount of an enantiomerically pure material.

The key issue for synthesis of pure stereoisomers, in either racemic or enantiomerically pure form, is that the configuration at newly created stereocenters be controlled in some way. This can be accomplished by several different methods. Existing functional groups may exert a steric or stereoelectronic influence on the reaction center. For instance, an existing functional group may control the approach of a reagent by coordination, which occurs, for example, in hydroxy-directed cyclopropanation (see p. 919). An existing chiral center may control reactant conformation and, thereby, the direction of approach of a reagent.

Generally, the closer the reaction occurs to an existing stereogenic center, the more likely the reaction is to exhibit high stereoselectivity. For example, the creation of adjacent stereogenic centers in aldol and organometallic addition reactions is generally strongly influenced by adjacent substituents leading to a preference for a *syn* or *anti* disposition of the new substituent. We also encountered some examples of *1,3-asymmetric induction*, as, for example, the role of chelates in reduction of β -hydroxy ketones (p. 412), in chelation control of Mukaiyama addition reactions (p. 94), and in hydroboration (Section p. 342). More remote chiral centers are less likely to influence stereoselectivity and examples of, e.g., 1,4- and 1,5-asymmetric induction, are less common. Whatever the detailed mechanism, the synthetic plan must include the means by which the required stereochemical control is to be achieved. If this cannot be done, the price to be paid is a separation of stereoisomers and the resulting reduction in overall yield.

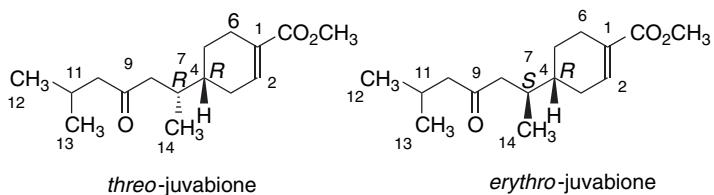
13.2. Illustrative Syntheses

In this section, we consider several syntheses of six illustrative compounds. We examine the retrosynthetic plans and discuss crucial bond-forming steps and the means of stereochemical control. In this discussion, we have the benefit of hindsight in being able to look at successfully completed syntheses. This retrospective analysis can serve to illustrate the issues that arise in planning a synthesis and provide examples of solutions that have been developed. The individual syntheses also provide many examples of the synthetic transformations presented in the previous chapters and of the use of protective groups in the synthesis of complex molecules. The syntheses shown

span a period of several decades and in some cases new reagents and protocols may have been developed since a particular synthesis was completed. Owing to limitations of space, only key steps are discussed although all the steps are shown in the schemes. Usually, only the reagent is shown, although other reaction components such as acids, bases, or solvents may also be of critical importance to the success of the reaction.

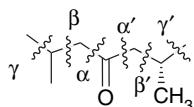
13.2.1. Juvabione

Juvabione is a terpene-derived ketoester that has been isolated from various plant sources. There are two stereoisomers, both of which occur naturally with *R*-configuration at C(4) of the cyclohexene ring and are referred to as *erythro*- and *threo*-juvabione. The 7(*S*)-enantiomer is sometimes called epijuвabione. Juvabione exhibits “juvenile hormone” activity in insects; that is, it can modify the process of metamorphosis.¹⁸



In considering the retrosynthetic analysis of juvabione, two factors draw special attention to the bond between C(4) and C(7). First, this bond establishes the stereochemistry of the molecule. The C(4) and C(7) carbons are stereogenic centers and their relative configuration determines the diastereomeric structure. In a stereocontrolled synthesis, it is necessary to establish the desired stereochemistry at C(4) and C(7). The C(4)–C(7) bond also connects the side chain to the cyclohexene ring. As a cyclohexane derivative is a logical candidate for one key intermediate, the C(4)–C(7) bond is a potential bond disconnection.

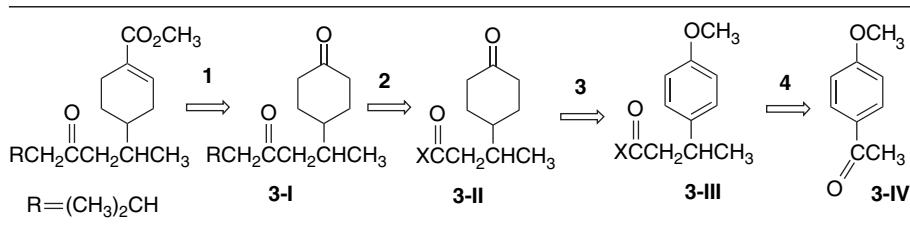
Other bonds that merit attention are those connecting C(7) through C(11). These could be formed by one of the many methods for the synthesis of ketones. Bond disconnections at carbonyl centers can involve the O=C-C(α) (acylation, organometallic addition), the C(α)–C(β) bond (enolate alkylation, aldol addition), or C(β)–C(γ) bond (conjugate addition to enone).



The only other functional group is the conjugated unsaturated ester. This functionality is remote from the stereocenters and the ketone functionality, and does not play a key role in most of the reported syntheses. Most of the syntheses use cyclic starting materials. Those in Schemes 13.4 and 13.5 lead back to a *para*-substituted aromatic ether. The syntheses in Schemes 13.7 and 13.8 begin with an accessible terpene intermediate. The syntheses in Schemes 13.10 and 13.11 start with cyclohexenone. Scheme 13.3 presents a retrosynthetic analysis leading to the key intermediates used for the syntheses in

¹⁸. For a review, see Z. Wimmer and M. Romanuk, *Coll. Czech. Chem. Commun.*, **54**, 2302 (1989).

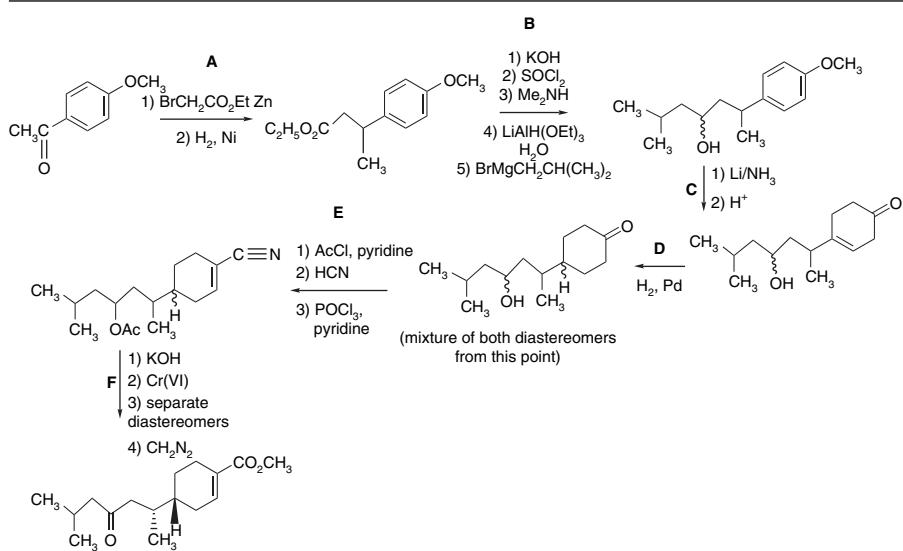
Scheme 13.3. Retrosynthetic Analysis of Juvabione with Disconnection to 4-Methoxyacetophenone



SECTION 13.2

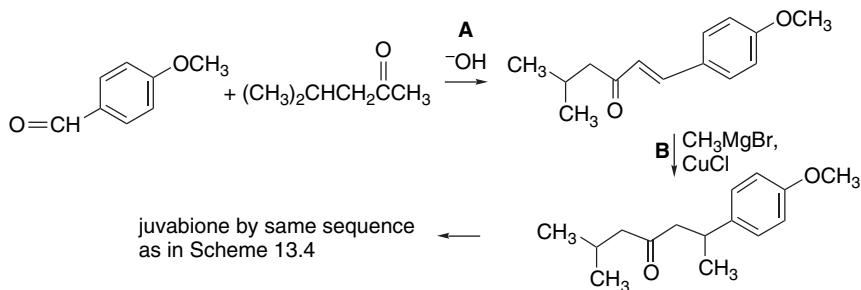
Illustrative Syntheses

Scheme 13.4. Juvabione Synthesis: K. Mori and M. Matsui^a



a. K. Mori and M. Matsui, *Tetrahedron*, **24**, 3127 (1968).

Scheme 13.5. Juvabione Synthesis: K. S. Ayyar and G. S. K. Rao^a



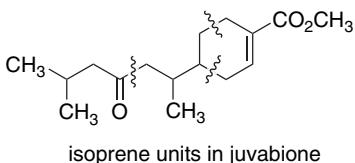
a. K. S. Ayyar and G. S. K. Rao, *Can. J. Chem.*, **46**, 1467 (1968).

Schemes 13.4 and 13.5. These syntheses use achiral reactants and provide mixtures of both stereoisomers. The final products are racemic. The first disconnection is that of the ester functionality, which corresponds to a strategic decision that the ester group can be added late in the synthesis. Disconnection **2** identifies the C(9)–C(10) bond as one that can be formed by addition of some nucleophilic group corresponding to C(10)–C(13) to the carbonyl center at C(9). This corresponds to disconnection α shown above. The third retrosynthetic transform recognizes that the cyclohexanone ring could be obtained by a Birch reduction of an appropriately substituted aromatic ether. The methoxy substituent would provide for correct placement of the cyclic carbonyl group. The final disconnection identifies a simple starting material, 4-methoxyacetophenone.

A synthesis corresponding to this pattern that is shown in Scheme 13.4 relies on well-known reaction types. The C(4)–C(7) bond was formed by a Reformatsky reaction. The adduct was dehydrated during work-up and the product was hydrogenated after purification. The ester group was converted to the corresponding aldehyde by Steps **B**-1 through **B**-4. Step **B**-5 introduced the C(10)–C(13) isobutyl group by Grignard addition to an aldehyde. In this synthesis, the relative configuration at C(4) and C(7) was established by the hydrogenation in Step **D**. In principle, this reaction could be diastereoselective if the adjacent chiral center at C(7) strongly influenced the direction of addition of hydrogen. In practice, the reduction was not very selective and a mixture of isomers was obtained. Steps **E** and **F** introduced the C(1) ester group.

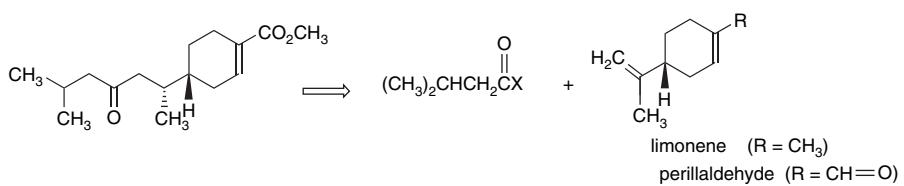
The synthesis in Scheme 13.5 also makes use of an aromatic starting material and follows a retrosynthetic plan similar to that in Scheme 13.3. The starting material was 4-methoxybenzaldehyde. This synthesis was somewhat more convergent in that the entire side chain except for C(14) was introduced as a single unit by a mixed aldol condensation in step **A**. The C(14) methyl was introduced by a copper-catalyzed conjugate addition in Step **B**.

Scheme 13.6 is a retrosynthetic outline of the syntheses in Schemes 13.7 to 13.9. The common feature of these syntheses is the use of terpene-derived starting materials. The use of such a starting material is suggested by the terpenoid structure of juvabione, which can be divided into “isoprene units.”

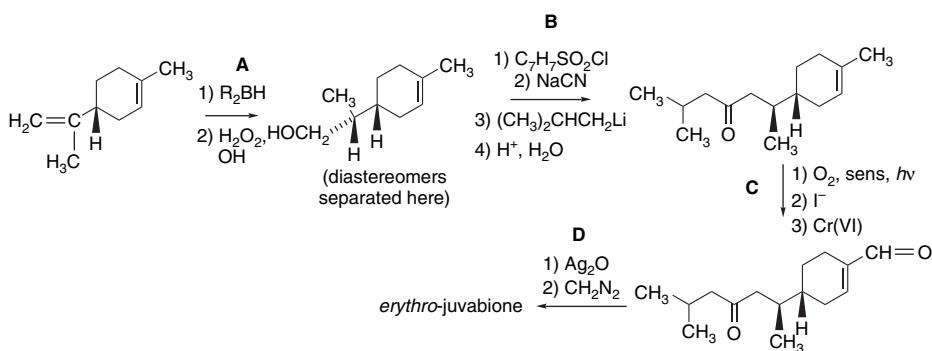


The synthesis shown in Scheme 13.7 used limonene as the starting material ($R = CH_3$ in Scheme 13.6), whereas Schemes 13.8 and 13.9 use the corresponding aldehyde ($R = CH=O$). The use of these starting materials focuses attention on the means of attaching the C(9)–C(13) side chain. Furthermore, since the starting material is an enantiomerically pure terpene, enantioselectivity controlled by the chiral center at C(4) of the starting material might be feasible. In the synthesis in Scheme 13.7, the C(4)–C(7) stereochemistry was established in the hydroboration that is the first step of the synthesis. This reaction showed only very modest stereoselectivity and a 3:2 mixture of diastereomers was obtained and separated. The subsequent steps do not affect these stereogenic centers. The side chain was elaborated by adding *i*-butyllithium to a nitrile. The synthesis in Scheme 13.7 used a three-step oxidation sequence to oxidize the C(15) methyl group to a carboxy group. The first reaction was oxidation

Scheme 13.6. Retrosynthetic Analysis of Juvabione with Disconnection to the Terpene Limonene

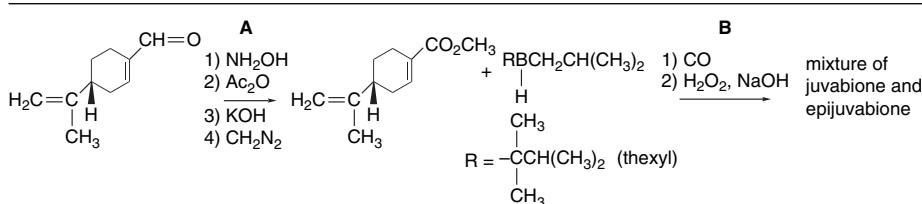


Scheme 13.7. Juvabione Synthesis: B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy^a



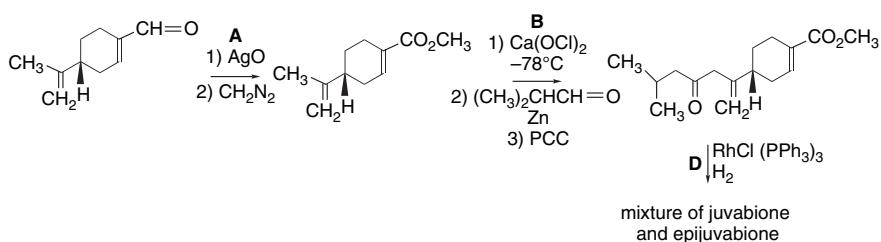
a. B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy, *J. Am. Chem. Soc.*, **92**, 336 (1970).

Scheme 13.8. Juvabione Synthesis: E. Negishi, M. Sabanski, J. J. Katz, and H. C. Brown^a



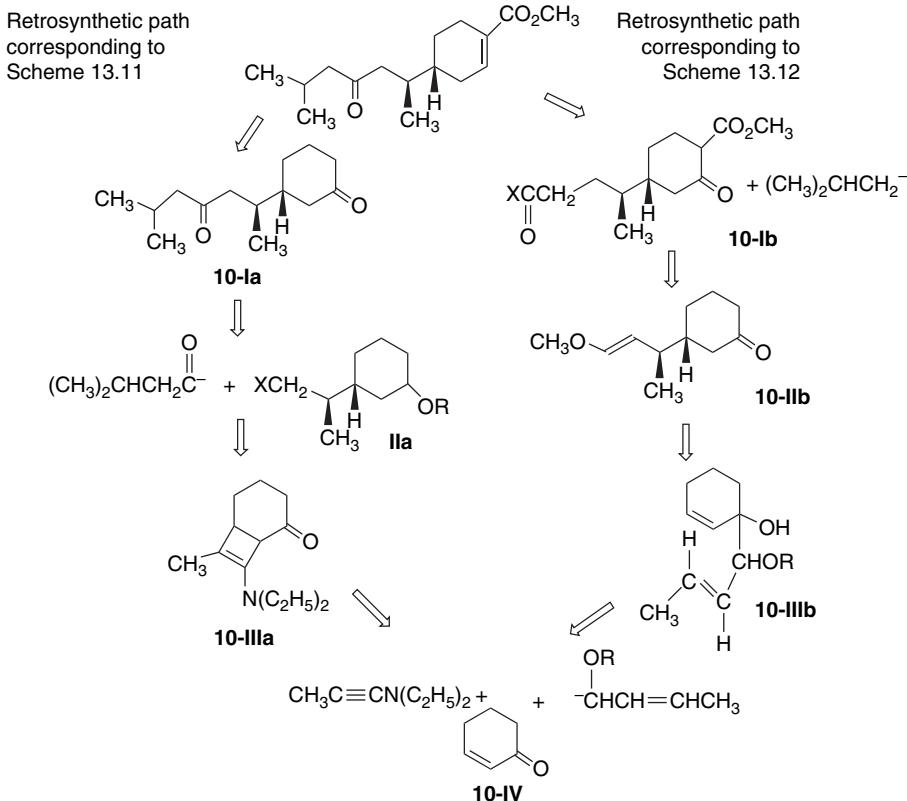
a. E. Negishi, M. Sabanski, J. J. Katz, and H. C. Brown, *Tetrahedron*, **32**, 925 (1976).

Scheme 13.9. Juvabione Synthesis: A. A. Carveiro and I. G. P. Viera^a

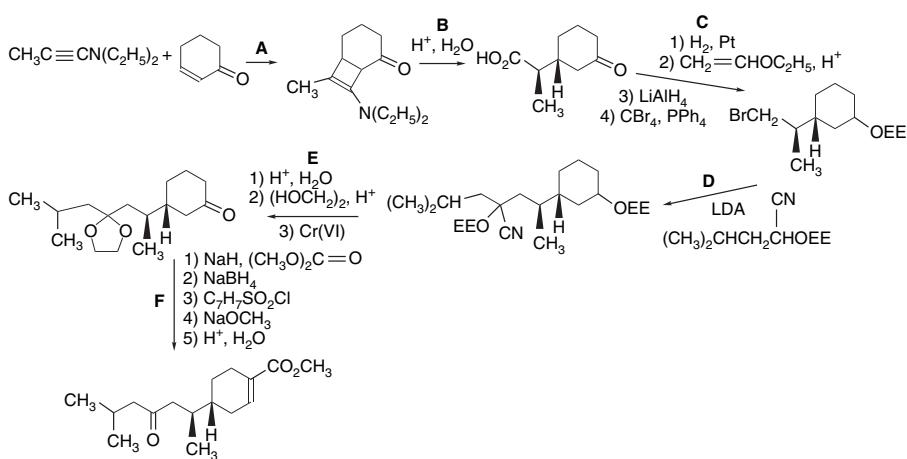


a. A. A. Carveiro and L. G. P. Viera, *J. Braz. Chem. Soc.*, **3**, 124 (1992).

Scheme 13.10. Retrosynthetic Analysis of Juvabione with Alternative Disconnections to Cyclohex-2-enone



Scheme 13.11. Juvabione Synthesis: J. Ficini, J. D'Angelo, and J. Noire^a



a. J. Ficini, J. D'Angelo, and J. Noire, *J. Am. Chem. Soc.*, **96**, 1213 (1974).

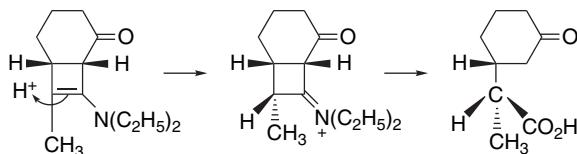
by singlet oxygen to give a mixture of hydroperoxides, with oxygen bound mainly at C(2). The mixture was reduced to the corresponding alcohols, which was then oxidized to the acid via an aldehyde intermediate.

In Scheme 13.8, the side chain was added in one step by a borane carbonylation reaction. This synthesis is very short and the first four steps were used to transform the aldehyde group in the starting material to a methyl ester. The stereochemistry at C(4)–C(7) is established in the hydroboration in Step **B**, in which the C(7)–H bond is formed. A 1:1 mixture of diastereomers resulted, indicating that the configuration at C(4) has little influence on the direction of approach of the borane reagent.

Another synthesis, shown in Scheme 13.9, that starts with the same aldehyde (perillaldehyde) was completed more recently. The C(8)–C(9) bond was established by an allylic chlorination and addition of the corresponding zinc reagent to isobutyraldehyde. In this synthesis, the C(7) stereochemistry was established by a homogeneous hydrogenation of a methylene group, but this reaction also produces both stereoisomers.

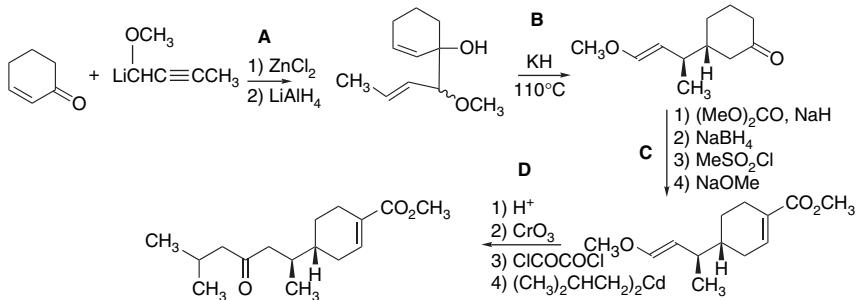
The first diastereoselective syntheses of juvabione are described in Schemes 13.11 and 13.12. Scheme 13.10 is a retrosynthetic analysis corresponding to these syntheses, which have certain similarities. Both syntheses started with cyclohexenone, and there is a general similarity in the fragments that were utilized, although the order of construction differs, and both led to (\pm)-juvabione.

A key step in the synthesis in Scheme 13.11 was a cycloaddition between an electron-rich ynamine and the electron-poor enone. The cyclobutane ring was then opened in a process that corresponds to retrosynthetic step **10-IIa** \Rightarrow **10-IIIa** in Scheme 13.10. The crucial step for stereochemical control occurs in Step **B**. The stereoselectivity of this step results from preferential protonation of the enamine from the less hindered side of the bicyclic intermediate.

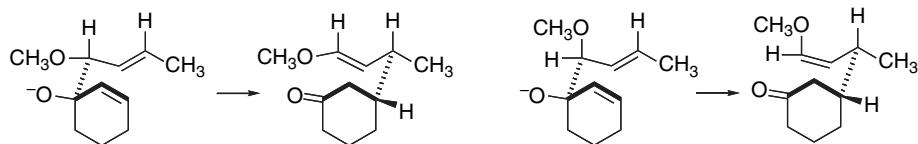


The cyclobutane ring was then cleaved by hydrolysis of the enamine and ring opening of the resulting β -diketone. The relative configuration of the chiral centers is unaffected by subsequent transformations, so the overall sequence is stereoselective. Another key step in this synthesis is Step **D**, which corresponds to the transformation **10-IIa** \Rightarrow **10-Ia** in the retrosynthesis. A protected cyanohydrin was used as a nucleophilic acyl anion equivalent in this step. The final steps of the synthesis in Scheme 13.11 employed the C(2) carbonyl group to introduce the carboxy group and the C(1)–C(2) double bond.

The stereoselectivity achieved in the synthesis in Scheme 13.12 is the result of a preferred conformation for the base-catalyzed oxy-Cope rearrangement in Step **B**. Although the intermediate used in Step **B** was a mixture of stereoisomers, both gave predominantly the desired relative stereochemistry at C(4) and C(7). The stereoselectivity is based on the preferred chair conformation for the TS of the oxy-Cope rearrangement.

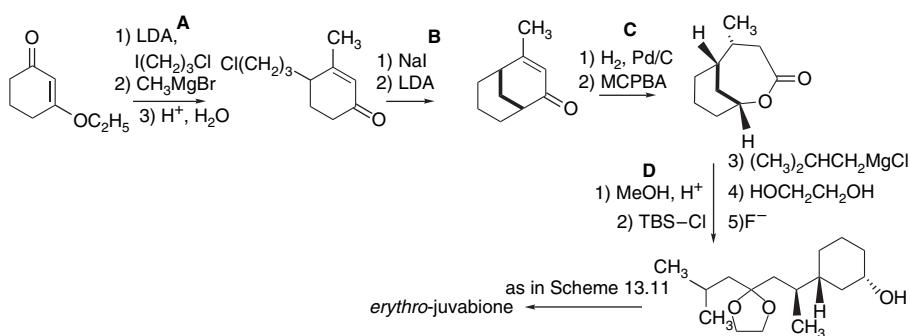
Scheme 13.12. Juvabione Synthesis: D. A. Evans and J. V. Nelson^a

a. D. A. Evans and J. V. Nelson, *J. Am. Chem. Soc.*, **102**, 774 (1980).



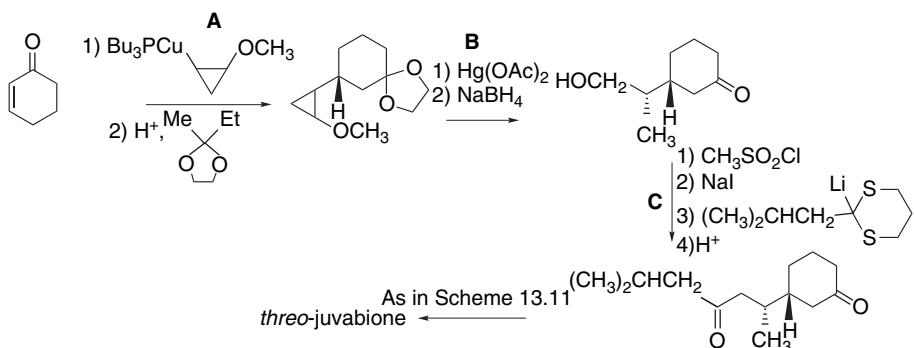
The synthesis in Scheme 13.13 leads diastereospecifically to the *erythro* stereoisomer. An intramolecular enolate alkylation in Step B gave a bicyclic intermediate. The relative configuration of C(4) and C(7) was established by the hydrogenation in Step C. The hydrogen is added from the less hindered *exo* face of the bicyclic enone. This reaction is an example of the use of geometric constraints of a ring system to control relative stereochemistry.

The *threo* stereoisomer was the major product obtained by the synthesis in Scheme 13.14. This stereochemistry was established by the conjugate addition in Step A, where a significant (4–6:1) diastereoselectivity was observed. The C(4)–C(7) stereochemical relationship was retained through the remainder of the synthesis. The other special features of this synthesis are in Steps B and C. The mercuric acetate–mediated cyclopropane ring opening was facilitated by the alkoxy substituent.¹⁹ The reduction by NaBH₄ accomplished both demercuration and reduction of the aldehyde group.

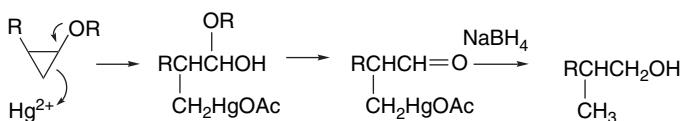
Scheme 13.13. Juvabione Synthesis: A. G. Schultz and J. P. Dittami^a

a. A. G. Schultz and J. P. Dittami, *J. Org. Chem.*, **49**, 2615 (1984).

¹⁹. A. DeBoer and C. H. DePuy, *J. Am. Chem. Soc.*, **92**, 4008 (1970).

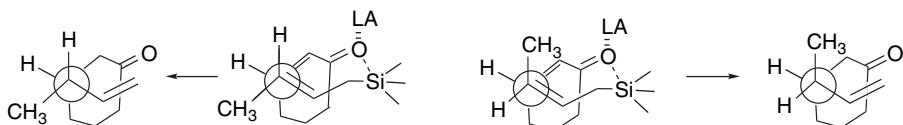


a. D. J. Morgans, Jr., and G. B. Feigelson, *J. Am. Chem. Soc.*, **105**, 5477 (1983).



In Step C a dithiane anion was used as a nucleophilic acyl anion equivalent to introduce the C(10)–C(13) isobutyl group.

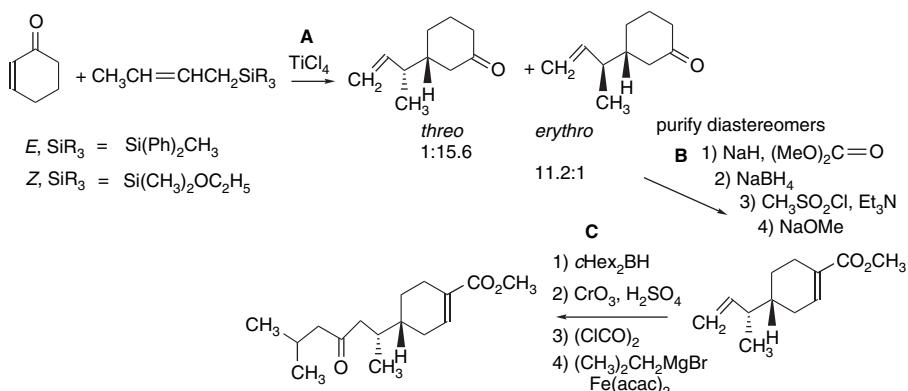
In the synthesis shown in Scheme 13.15, racemates of both *erythro*- and *threo*-juvabione were synthesized by parallel routes. The isomeric intermediates were obtained in greater than 10:1 selectivity by choice of the *E*- or *Z*-silanes used for conjugate addition to cyclohexenone (Michael-Mukaiyama reaction). Further optimization of the stereoselectivity was achieved by the choice of the silyl substituents. The observed stereoselectivity is consistent with synclinal TSs for the addition of the crotyl silane reagents.



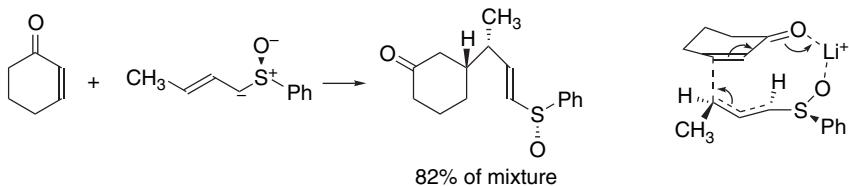
The purified diastereomeric intermediates were then converted to the juvabione stereoisomers.

Except for the syntheses using terpene-derived starting materials (Schemes 13.7, 13.8, and 13.9), the previous juvabione syntheses all gave racemic products. Some of the more recent juvabione syntheses are *enantiospecific*. The synthesis in Scheme 13.16 relied on a chiral sulfoxide that undergoes stereoselective addition to cyclohexenone to establish the correct relative and absolute configuration at C(4) and C(7). The origin of the stereoselectivity is a chelated TS that leads to the observed product.²⁰

²⁰. M. R. Binns, R. K. Haynes, A. G. Katsifis, P. A. Schober, and S. C. Vonwiller, *J. Am. Chem. Soc.*, **110**, 5411 (1988).

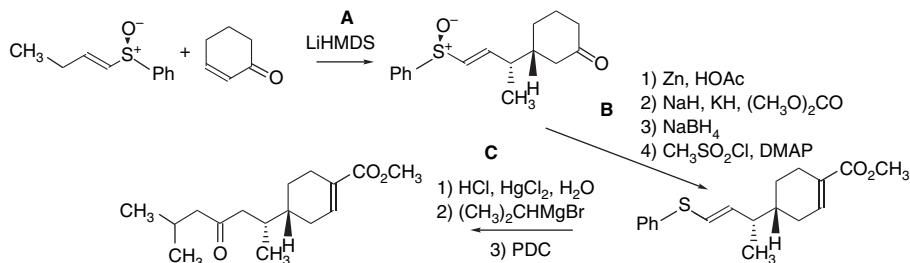
Scheme 13.15. Juvabione Synthesis: T. Tokoroyama and L.-R. Pan^a

a. T. Tokoroyama and L.-R. Pan, *Tetrahedron Lett.*, **30**, 197 (1989).



The sulfoxide substituent was also used to introduce the C(10)–C(13) fragment and was reduced to a vinyl sulfide in Step B-1. In Step C-1, the vinyl sulfide was hydrolyzed to an aldehyde, which was elaborated by addition of isobutylmagnesium bromide.

Scheme 13.17 depicts a synthesis based on enantioselective reduction of bicyclo[2.2.2]octane-2,6-dione by Baker's yeast.²¹ This is an example of desymmetrization (see Part A, Topic 2.2). The unreduced carbonyl group was converted to an alkene by the Shapiro reaction. The alcohol was then reoxidized to a ketone. The enantiomerically pure intermediate was converted to the lactone by Baeyer-Villiger oxidation and an allylic rearrangement. The methyl group was introduced stereoselectively from the *exo* face of the bicyclic lactone by an enolate alkylation in Step C-1.

Scheme 13.16. Juvabione Synthesis: H. Watanabe, H. Shimizu, and K. Mori^a

a. H. Watanabe, H. Shimizu, and K. Mori, *Synthesis*, 1249 (1994).

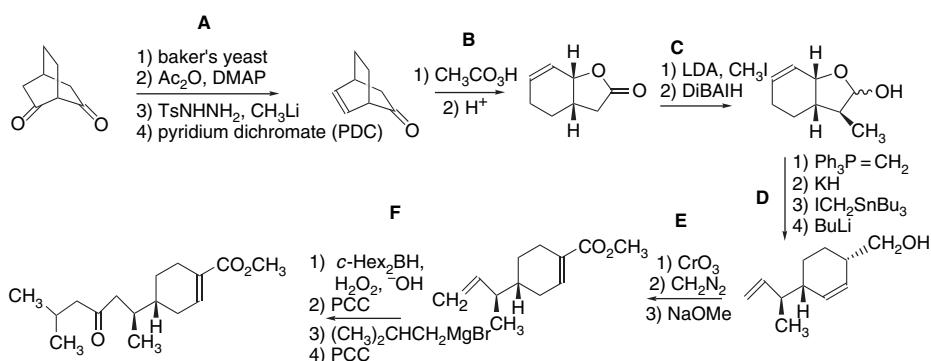
²¹. K. Mori and F. Nagano, *Biocatalysis*, **3**, 25 (1990).

Scheme 13.17. Juvabione Synthesis: E. Nagano and K. Mori^a

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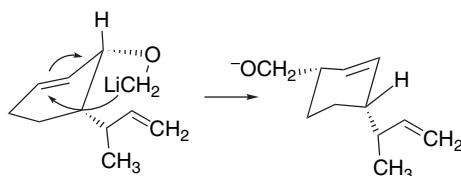
SECTION 13.2

Illustrative Syntheses

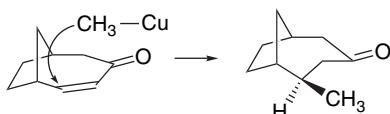


a. E. Nagano and K. Mori, *Biosci. Biotechnol. Biochem.*, **56**, 1589 (1992).

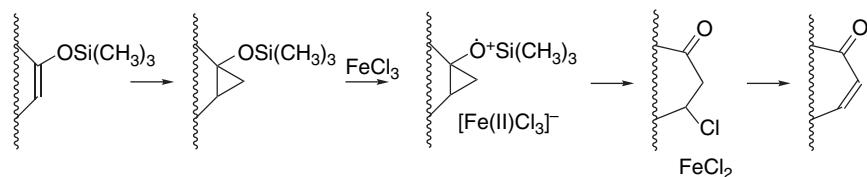
A final crucial step in this synthesis was an anionic [2,3]-sigmatropic rearrangement of an allylic ether in Step **D**-4 to introduce the C(1) carbon.



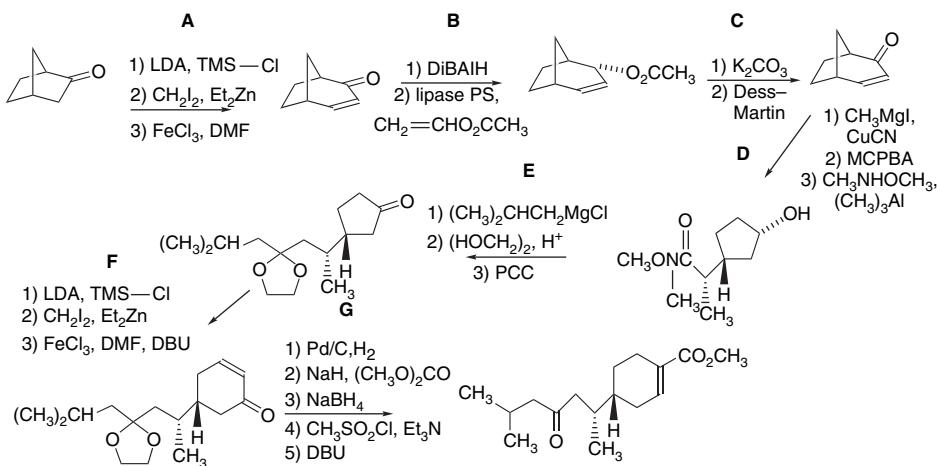
Another enantioselective synthesis, shown in Scheme 13.18, involves an early kinetic resolution of the alcohol intermediate in Step **B**-2 by lipase PS. The stereochemistry at the C(7) methyl group is controlled by the *exo* selectivity in the conjugate addition (Step **D**-1).



The bicyclic ring is then cleaved by a Baeyer-Villiger reaction in Step **D**-2. Another interesting feature of this synthesis is the ring expansions used in sequences **A** and **F**. Trimethylsilyl enol ethers were treated with Simmons-Smith reagent to form cyclopropyl silyl ethers. These undergo oxidative cleavage and ring expansion when treated with FeCl_3 and the α -chloro ketones are then dehydrohalogenated by DBU.²²

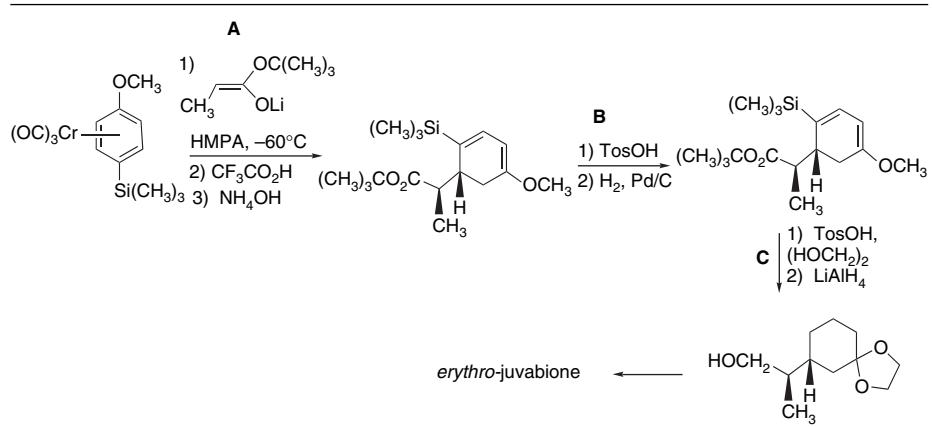


²² V. Ito, S. Fujii, and T. Saegusa, *J. Org. Chem.*, **41**, 2073 (1976).

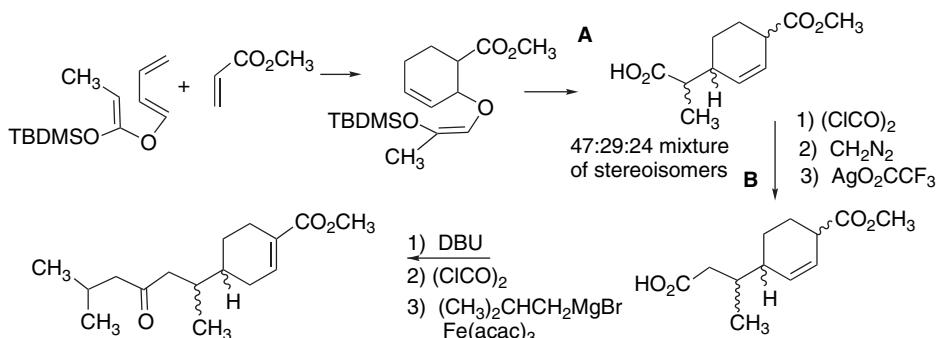
Scheme 13.18. Juvabione Synthesis: K. Ogasawara and Co-workers^a

a. H. Nagata, T. Taniguchi, M. Kawamura, and K. Ogasawara, *Tetrahedron Lett.*, **40**, 4207 (1999).

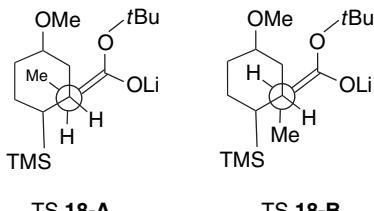
The juvabione synthesis in Scheme 13.19 exploited both the regiochemical and stereochemical features of the starting material, the Cr(CO)₃ complex of 4-methoxyphenyltrimethylsilane. The lithium enolate of *t*-butyl propanoate was added, resulting in a 96:4 ratio of *meta*:*ortho* adducts. The addition was also highly stereoselective, giving a greater than 99:1 preference for the *erythro* stereochemistry. This is consistent with reaction through TS 18-A in preference to TS 18-B to avoid a *gauche* interaction between the enolate methyl and the trimethylsilyl substituent.

Scheme 13.19. Juvabione Synthesis: A. J. Pearson, H. Paramahamsan, and J. D. Dudones^a

a. A. J. Pearson, H. Paramahamsan, and J. D. Dudones, *Org. Lett.*, **6**, 2121 (2004).



a. N. Soldermann, J. Velker, O. Vallat, H. Stoeckli-Evans, and R. Neier, *Helv. Chim. Acta*, **83**, 2266 (2000).



TS 18-A

TS 18-B

The reaction product was converted to an intermediate that had previously been converted to *erythro*-juvabione.

The synthesis in Scheme 13.20 features a tandem Diels-Alder reaction and Ireland-Claisen [3,3]-sigmatropic shift as the key steps. Although this strategy was very efficient in constructing the carbon structure, it was not very stereoselective. The major isomer results from an *endo* TS for the Diels-Alder reaction and a [3,3]-sigmatropic rearrangement through a boat TS. Three stereoisomers were obtained in the ratio 47:29:24. These were not separated but were converted to a 4:1 mixture of (\pm)-juvabione and (\pm)-epijuвabione by Arndt-Eistert homologation, DBU-based conjugation, and addition of the isobutyl group by a Fe(acac)₃-catalyzed Grignard addition.

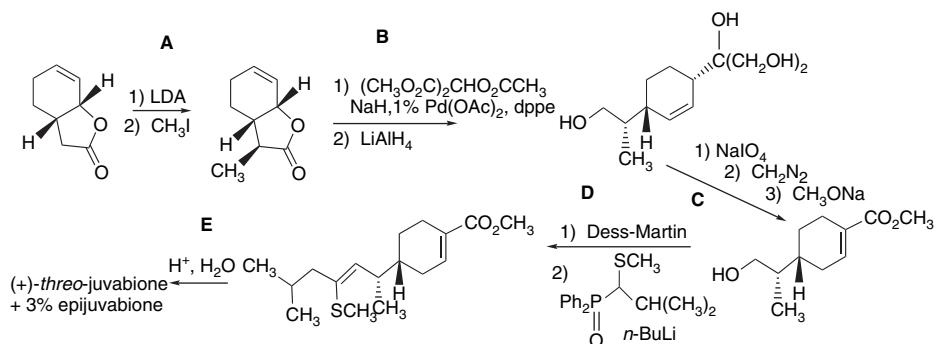
The synthesis in Scheme 13.21 starts with a lactone that is available in enantiomerically pure form. It was first subjected to an enolate alkylation that was stereocontrolled by the convex shape of the *cis* ring junction (Step A). A stereospecific Pd-mediated allylic substitution followed by LiAlH₄ reduction generated the first key intermediate (Step B). This compound was oxidized with NaIO₄, converted to the methyl ester, and subjected to a base-catalyzed conjugation. After oxidation of the primary alcohol to an aldehyde, a Wittig-Horner olefination completed the side chain.

The enantioselective synthesis in Scheme 13.22 is based on stereoselective reduction of an α , β -unsaturated aldehyde generated from (–)-(S)-limonene (Step A). The reduction was done by Baker's yeast and was completely enantioselective. The diastereoselectivity was not complete, generating an 80:20 mixture, but the diastereomeric alcohols were purified at this stage. After oxidation to the aldehyde, the remainder of the side chain was introduced by a Grignard addition. The ester function

Scheme 13.21. Juvabione Synthesis: E. J. Bergner and G. Helmchen^a

CHAPTER 13

Multistep Syntheses

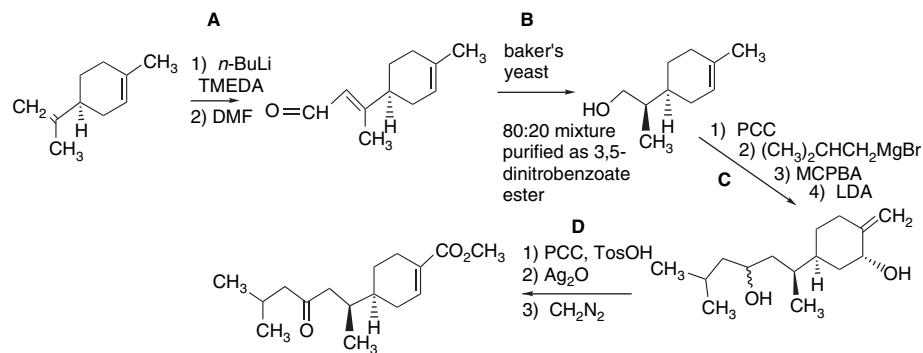
^a E. J. Bergner and G. Helmchen, *J. Org. Chem.*, **65**, 5072 (2000).

was introduced by a base-catalyzed opening of the epoxide to an allylic alcohol (Step C-4), which then underwent oxidation with allylic transposition (Step D-1).

Several other syntheses of juvabione have also been completed.²³

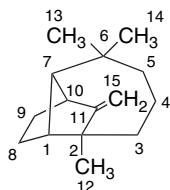
13.2.2. Longifolene

Longifolene is a tricyclic sesquiterpene. It is a typical terpene hydrocarbon in terms of the structural complexity. The synthetic challenge lies in construction of the bicyclic ring system. Schemes 13.24 through 13.33 describe nine separate syntheses of longifolene. We wish to particularly emphasize the methods for carbon-carbon bond formation used in these syntheses. There are four stereogenic centers in longifolene,

Scheme 13.22. Juvabione Synthesis. C. Fuganti and S. Serra^a^a C. Fuganti and S. Serra, *J. Chem. Soc., Perkin Trans. 1*, 97 (2000).

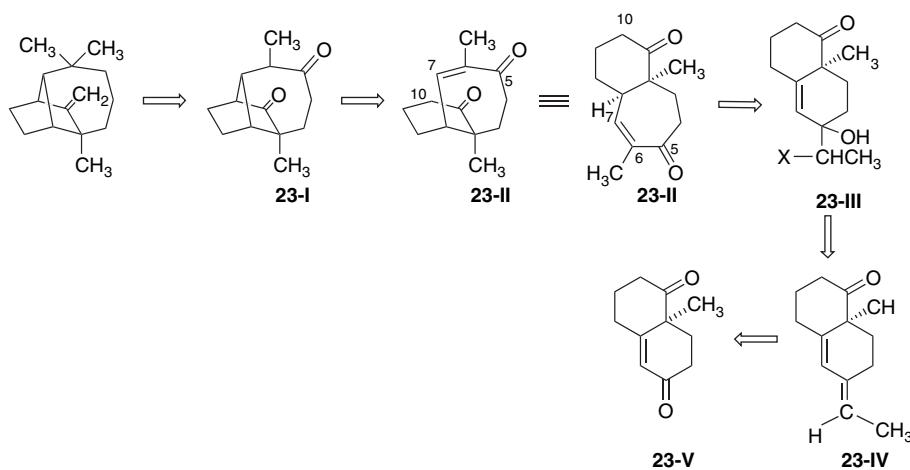
²³ A. A. Drabkina and Y. S. Tsizin, *J. Gen. Chem. USSR (English Transl.)*, **43**, 422, 691 (1973); R. J. Crawford, U. S. Patent, 3,676,506; *Chem. Abstr.*, **77**, 113889e (1972); A. J. Birch, P. L. Macdonald, and V. H. Powell, *J. Chem. Soc. C*, 1469 (1970); B. M. Trost and Y. Tamaru, *Tetrahedron Lett.*, 3797 (1975); M. Fujii, T. Aida, M. Yoshihara, and A. Ohno, *Bull. Chem. Soc. Jpn.*, **63**, 1255 (1990).

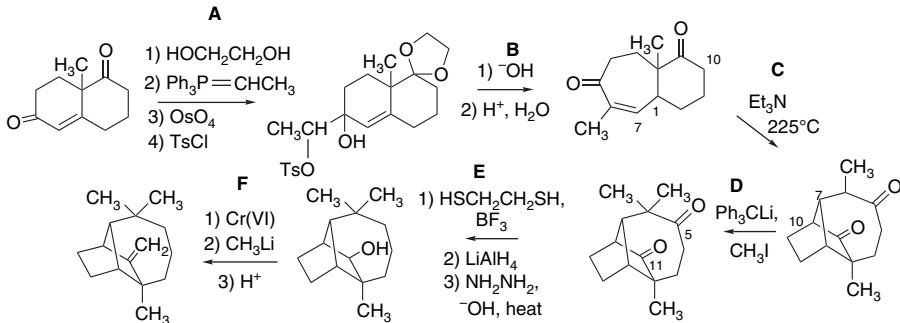
but they are not independent of one another because the geometry of the ring system requires that they have a specific relative relationship. That does not mean stereochemistry can be ignored, however, since the formation of the various rings will fail if the reactants do not have the proper stereochemistry.



The first successful synthesis of longifolene was described in detail by E. J. Corey and co-workers in 1964. Scheme 13.23 presents a retrosynthetic analysis corresponding to this route. A key disconnection is made on going from **23-I** \Rightarrow **23-II**. This transformation simplifies the tricyclic to a bicyclic skeleton. For this disconnection to correspond to a reasonable synthetic step, the functionality in the intermediate to be cyclized must engender mutual reactivity between C(7) and C(10). This is achieved in diketone **23-II**, because an enolate generated by deprotonation at C(10) can undergo an intramolecular Michael addition to C(7). The stereochemistry requires that the ring junction be *cis*. Retrosynthetic Step **23-II** \Rightarrow **23-III** is attractive because it suggests a decalin derivative as a key intermediate. Methods for preparing this type of structure are well developed, since they are useful intermediates in the synthesis of other terpenes as well as steroids. Can a chemical reaction be recognized that would permit **23-III** \Rightarrow **23-II** to proceed in the synthetic sense? The hydroxy to carbonyl transformation with migration corresponds to the pinacol rearrangement (Section 10.1.2.1). The retrosynthetic transformation **23-II** \Rightarrow **23-III** corresponds to a workable synthetic step if the group X in **23-III** is a leaving group that could promote the rearrangement. The other transformations in the retrosynthetic plan, **23-III** \Rightarrow **23-IV** \Rightarrow **23-V**, are straightforward in concept and lead to identification of **23-V** as a potential starting material.

Scheme 13.23. Retrosynthesis of Longifolene Corresponding to the Synthesis in Scheme 13.24

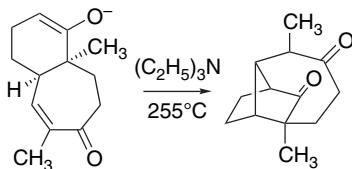


Scheme 13.24. Longifolene Synthesis: E. J. Corey and Co-Workers^a

a. E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Am. Chem. Soc.*, **86**, 478 (1964).

Compound **23-V** is known as the Wieland-Miescher ketone and can be obtained by Robinson annulation of 2-methylcyclohexane-1,3-dione.

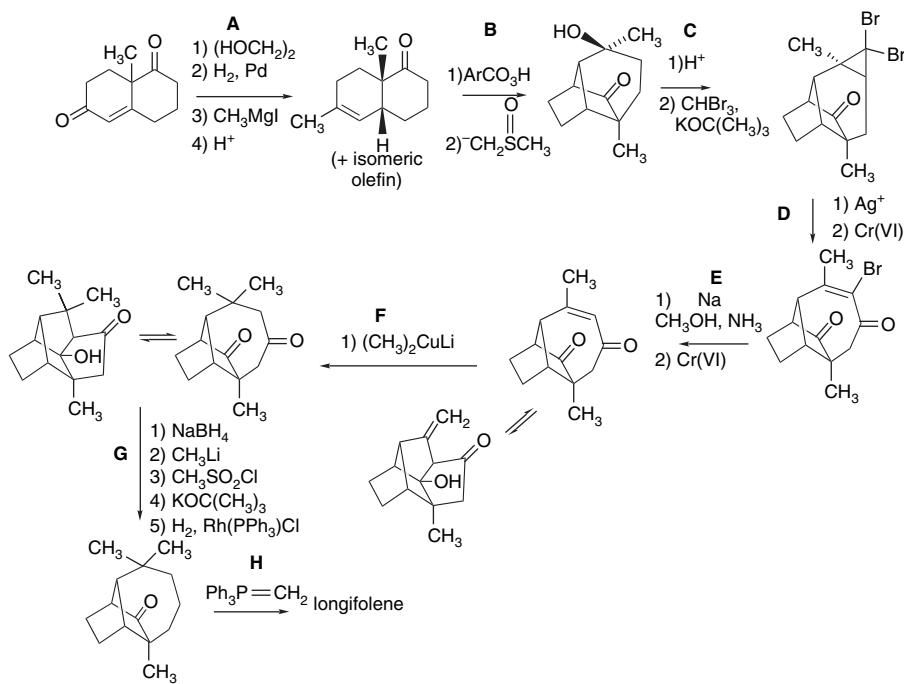
The synthesis was carried out as shown in Scheme 13.24. A diol was formed and selectively tosylated at the secondary hydroxy group (Step A-4). Base then promoted the skeletal rearrangement in Step B-1 by a pinacol rearrangement corresponding to **23-II** \Rightarrow **23-III** in the retrosynthesis. The key intramolecular Michael addition was accomplished using triethylamine under high-temperature conditions.



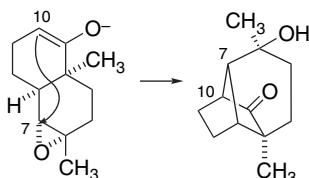
The cyclization requires that the intermediate have a *cis* ring fusion. The stereochemistry of the ring junction was established when the double bond was moved into conjugation in Step B-2. The product was not stereochemically characterized, and need not be, because the stereochemically important site at C(1) can be epimerized under the basic cyclization conditions. Thus, the equilibration of the ring junction through a dienol allows the cyclization to proceed to completion from either stereoisomer.

After the crucial cyclization in Step C, the subsequent transformations effect the addition of the remaining methyl and methylene groups by well-known methods. Step E accomplishes a selective reduction of one of the two carbonyl groups to a methylene by taking advantage of the difference in the steric environment of the two carbonyls. Selective protection of the less hindered C(5) carbonyl was done using a thionocarbonate. The C(11) carbonyl was then reduced to give the alcohol, after which C(5) was reduced to a methylene group under Wolff-Kishner conditions. The hydroxy group at C(11) provided the reactive center necessary to introduce the C(15) methylene group via methylolithium addition and dehydration in Step F.

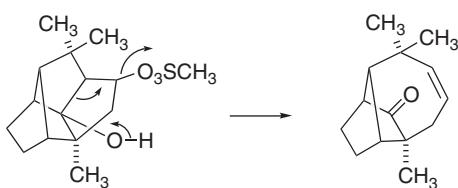
The Wieland-Miescher ketone was also the starting material for the synthesis in Scheme 13.25. The key bond closure was performed on a bicyclo[4.4.0]decane ring system. An enolate was used to open an epoxide ring in Step B-2. The ring juncture must be *cis* to permit the intramolecular epoxide ring opening. The required *cis* ring fusion was established during the catalytic hydrogenation in Step A.

Scheme 13.25. Longifolene Synthesis: J. E. McMurry and S. J. Isser^a

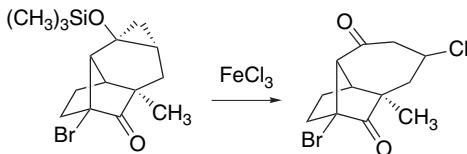
a. J. E. McMurry and S. J. Isser, *J. Am. Chem. Soc.*, **94**, 7132 (1972).



The key cyclization in Step **B-2** was followed by a sequence of steps that effected a ring expansion via a carbene addition and cyclopropyl halide solvolysis. The products of Steps **E** and **F** are interesting in that the tricyclic structures are largely converted to tetracyclic derivatives by intramolecular aldol reactions. The extraneous bond was broken in Step **G**. First a diol was formed by $NaBH_4$ reduction and this was converted via the lithium alkoxide to a monomesylate. The resulting β -hydroxy mesylate is capable of a concerted fragmentation, which occurred on treatment with potassium *t*-butoxide.

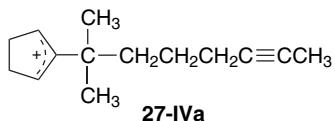


Longifolene has also been synthesized from (\pm) Wieland-Miescher ketone by a series of reactions that feature an intramolecular enolate alkylation and ring expansion, as shown in Scheme 13.26. The starting material was converted to a dibromo ketone via the bis-silyl enol ether in the first sequence of reactions. This intermediate underwent an intramolecular enolate alkylation to form the C(7)–C(10) bond. The ring expansion was then done by conversion of the ketone to a silyl enol ether, cyclopropanation, and treatment of the siloxycyclopropane with FeCl_3 .



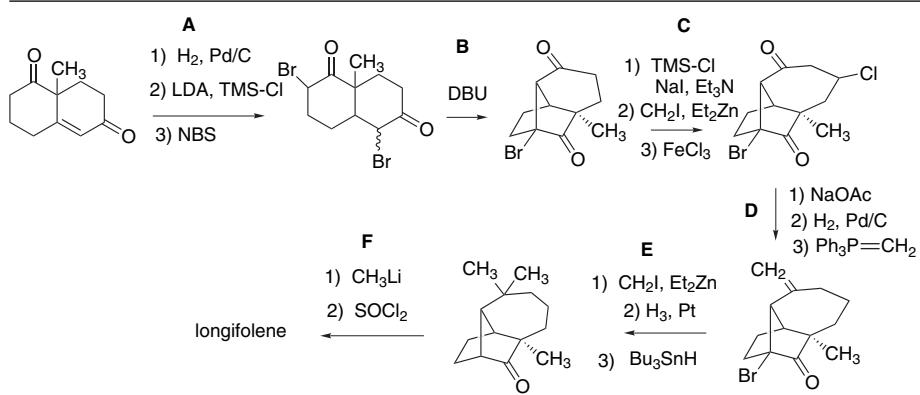
The final stages of the synthesis involved introduction of the final methyl group by Simmons-Smith cyclopropanation and reductive opening of the cyclopropane ring.

A retrosynthetic analysis corresponding to the synthesis in Scheme 13.28 is given in Scheme 13.27. The striking feature of this synthesis is the structural simplicity of the key intermediate **27-IV**. A synthesis according to this scheme generates the tricyclic skeleton in a single step from a monocyclic intermediate. The disconnection **27-III-27-IV** corresponds to a cationic cyclization of the highly symmetric allylic cation **27-IVa**.

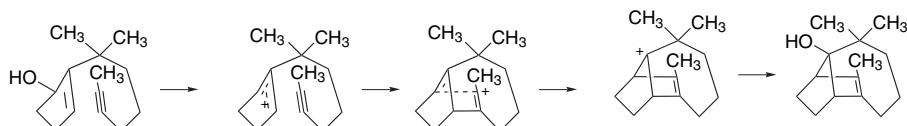
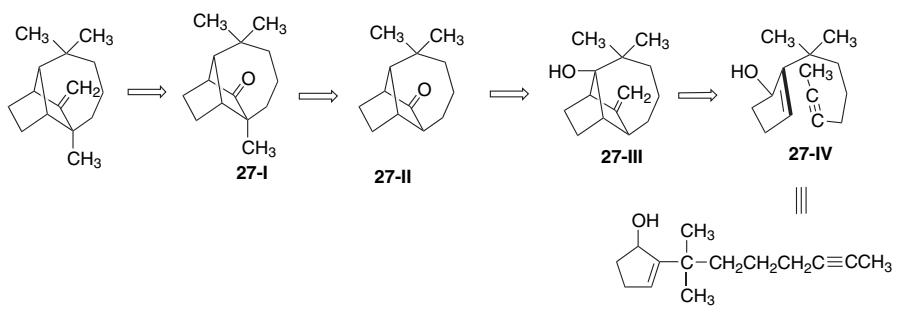


No issues of stereochemistry arise until the carbon skeleton is formed, at which point all of the stereocenters are in the proper relative relationship. The structures of the successive intermediates, assuming a stepwise mechanism for the cationic cyclization, are shown below.

Scheme 13.26. Longifolene Synthesis: S. Karimi and P. Tavares^a

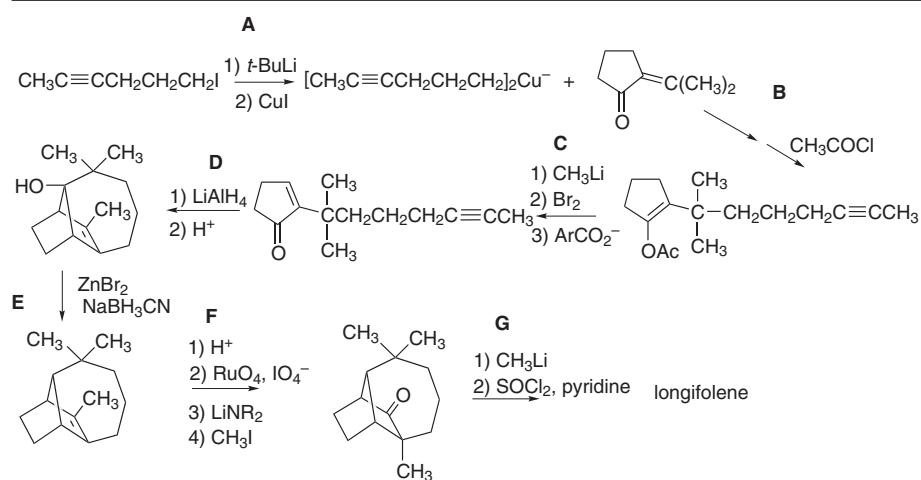


a. S. Karimi, *J. Nat. Prod.*, **64**, 406 (2001); S. Karimi and P. Tavares, *J. Nat. Prod.*, **66**, 520 (2003).

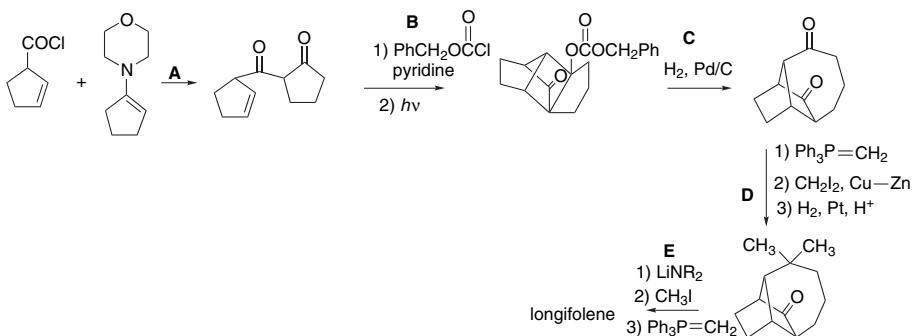


Evidently, these or closely related intermediates are accessible and reactive, since the synthesis was successfully achieved as outlined in Scheme 13.28. In addition to the key cationic cyclization in Step **D**, interesting transformations were carried out in Step **E**, where a bridgehead tertiary alcohol was reductively removed, and in Step **F**, where a methylene group, which was eventually reintroduced, had to be removed. The endocyclic double bond, which is strained because of its bridgehead location, was isomerized to the exocyclic position and then cleaved with $\text{RuO}_4/\text{IO}_4^-$. The enolate of the ketone was then used to introduce the C(12) methyl group in Steps **F-3** and **F-4**.

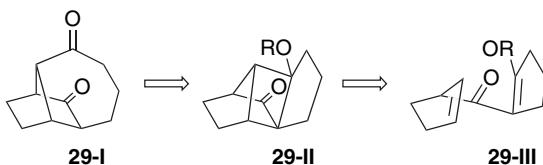
The synthesis in Scheme 13.29 also uses a remarkably simple starting material to achieve the construction of the tricyclic skeleton. A partial retrosynthetic analysis is outlined below.

Scheme 13.28. Longifolene Synthesis: W. S. Johnson and Co-Workers^a

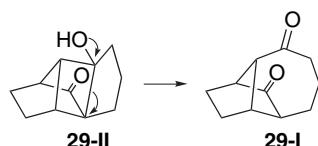
a. R. A. Volkmann, G. C. Anderson, and W. S. Johnson, *J. Am. Chem. Soc.*, **97**, 4777 (1975).

Scheme 13.29. Longifolene Synthesis: W. Oppolzer and T. Godel^a

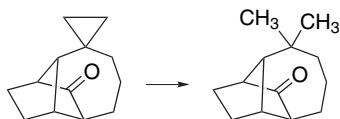
a. W. Oppolzer and T. Godel, *J. Am. Chem. Soc.*, **100**, 2583 (1978); W. Oppolzer and T. Godel, *Helv. Chim. Acta*, **67**, 1154 (1984).



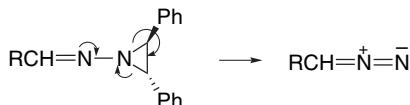
Intermediate **29-I** contains the tricyclic skeleton of longifolene, shorn of its substituents, but containing carbonyl groups suitably placed so that the methyl groups at C(2) and C(6) and the C(11) methylene can be introduced. The retrosynthetic Step **29-I** \Rightarrow **29-II** corresponds to an intramolecular aldol addition. However, **29-II** is clearly strained relative to **29-I**, and so (with OR = OH) should open to **29-I**.



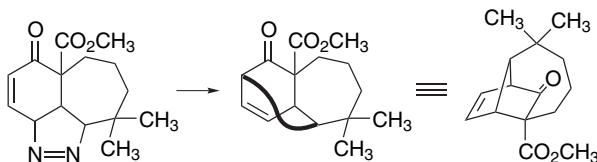
How might **29-II** be obtained? The four-membered ring suggests that a photochemical [2 + 2] cycloaddition might be useful, and this, in fact, was successful (Scheme 13.29, Step **B**). The cyclopentanone intermediate was converted to an enol carbonate. After photolysis, the carbobenzyloxy group was removed by hydrogenolysis, which led to opening of the strained aldol to the diketo intermediate. After liberation of the hydroxy group, the extra carbon-carbon bond between C(2) and C(6) was broken by a spontaneous retro-aldol reaction. Step **D** in this synthesis is an interesting way of introducing the geminal dimethyl groups. It proceeds through a cyclopropane intermediate that is cleaved by hydrogenolysis. In Step **E**, the C(12) methyl group was introduced by enolate alkylation and the C(15) methylene group was installed by a Wittig reaction.



The synthesis of longifolene in Scheme 13.30 commenced with a Birch reduction and tandem alkylation of methyl 2-methoxybenzoate (see Section 5.6.1.2). Step **C** is an intramolecular cycloaddition of a diazoalkane that is generated from an aziridinoimine intermediate.

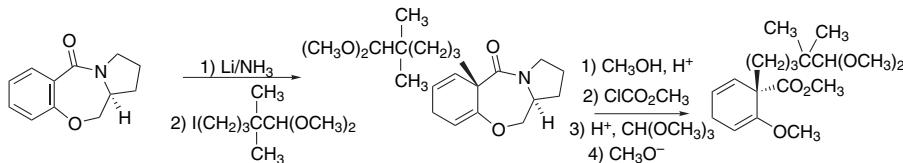


The thermolysis of the adduct generates a diradical (or the corresponding dipolar intermediate), which then closes to the desired carbon skeleton.



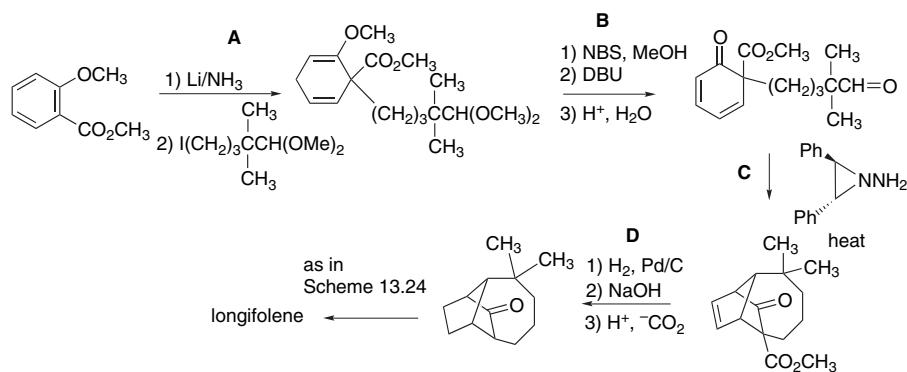
The cyclization product was converted to an intermediate that was used in the longifolene synthesis described in Scheme 12.24.

The synthesis in Scheme 13.30 was also done in such a way as to give enantiomerically pure longifolene. A starting material, whose chirality is derived from the amino acid L-proline, was enantioselectively converted to the product of Step **A** in Scheme 13.30.



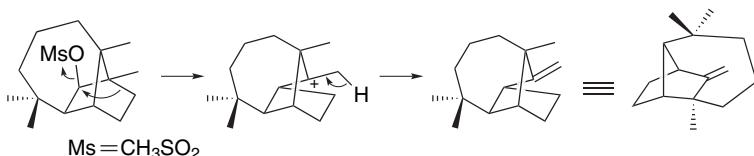
This chiral intermediate, when carried through the reaction sequence in Scheme 13.30, generated the enantiomer of natural longifolene. Thus D-proline would have to be used to generate the natural enantiomer.

Scheme 13.30. Longifolene Synthesis: A. G. Schultz and S. Puig^a

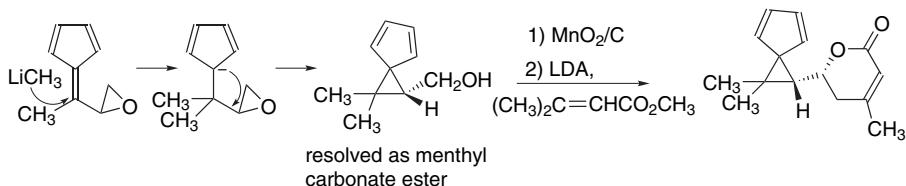


a. A. G. Schultz and S. Puig, *J. Org. Chem.*, **50**, 915 (1985).

An enantiospecific synthesis of longifolene was done starting with camphor, a natural product available in enantiomerically pure form (Scheme 13.31). The tricyclic ring was formed in Step **C** by an intramolecular Mukaiyama reaction. The dimethyl substituents were formed in Step **E-1** by hydrogenolysis of the cyclopropane ring. The final step of the synthesis involved a rearrangement of the tricyclic ring that was induced by solvolysis of the mesylate intermediate.

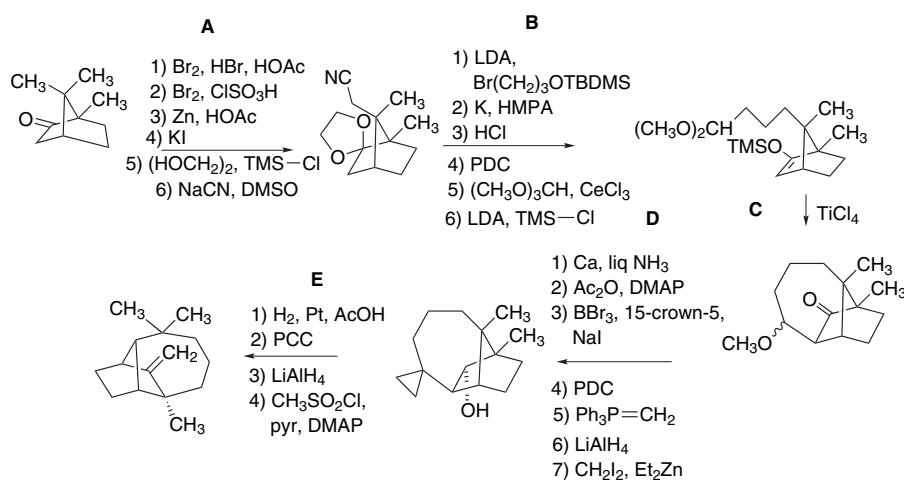


Another enantiospecific synthesis of longifolene shown in Scheme 13.32 used an intramolecular Diels-Alder reaction as a key step. An alcohol intermediate was resolved in sequence **B** by formation and separation of a menthyl carbonate. After oxidation, the dihydropyrone ring was introduced by γ -addition of the ester enolate of methyl 3-methylbutenoate, followed by cyclization.

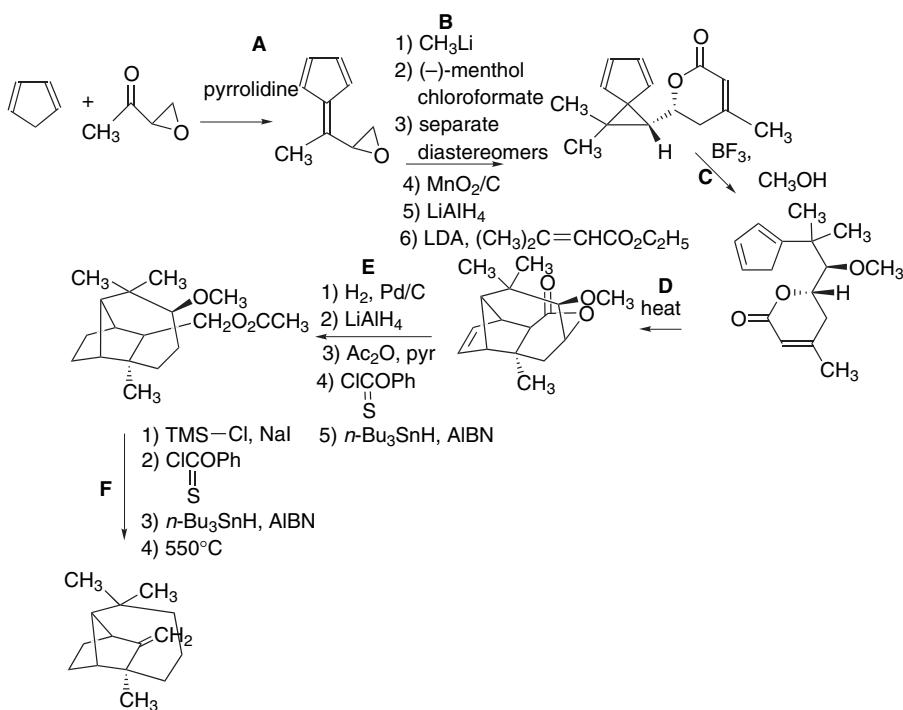


The dihydropyrone ring then served as the dienophile in the intramolecular Diels-Alder (IMDA) cycloaddition that was conducted in a microwave oven. The cyclopentadiene

Scheme 13.31. Longifolene Synthesis: D. L. Kuo and T. Money^a

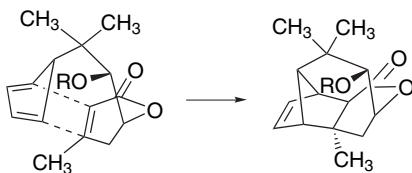


a. D. L. Kuo and T. Money, *Can. J. Chem.*, **66**, 1794 (1988).



a. B. Lei and A. G. Fallis, *J. Am. Chem. Soc.*, **112**, 4609 (1990); B. Lei and A. G. Fallis, *J. Org. Chem.*, **58**, 2186 (1993).

ring permits rapid equilibration of the diene isomers by 1,5-hydrogen shifts and the most stable IMDA TS leads to the desired product.

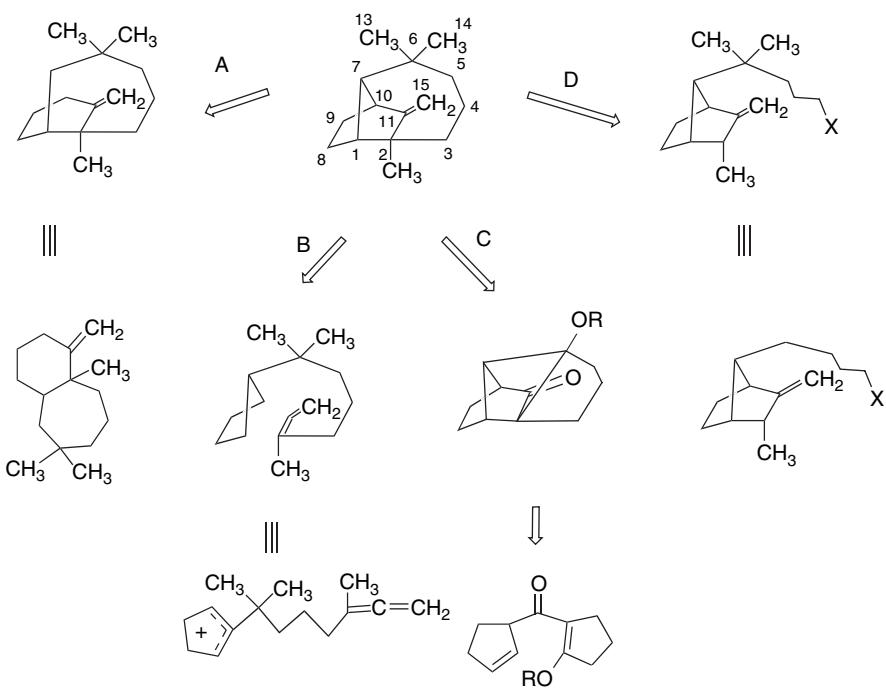


The final step of this synthesis used a high-temperature acetate pyrolysis to introduce the exocyclic double bond of longifolene.

Scheme 13.33 shows broad retrosynthetic formulations of the longifolene syntheses that are discussed in this subsection. Four different patterns of bond formation are represented. In **A**, the C(7)–C(10) bond is formed from a bicyclic intermediate. This pattern corresponds to the syntheses in Schemes 13.24, 13.25, 12.26, and 13.29. In retrosynthesis **B**, there is concurrent formation of the C(1)–C(2) and C(10)–C(11) bonds, as in the synthesis in Scheme 13.28. This is also the pattern found in the synthesis in Scheme 13.32. The synthesis in Scheme 13.29 corresponds to retrosynthesis **C**, in which the C(1)–C(2) and C(6)–C(7) bonds are formed and an extraneous bond between C(2) and C(5) is broken. Finally, retrosynthesis **D**, corresponding to formation of the C(2)–C(3) bond, is represented by the synthesis in Scheme 13.31.

These syntheses of longifolene provide good examples of the approaches that are available for construction of polycyclic ring compounds. In each case, a set of

Scheme 13.33. Summary of Some Retrosynthetic Patterns in Longifolene Syntheses



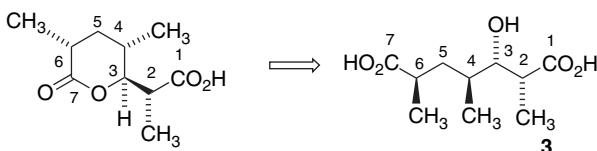
functionalities that have the potential for *intramolecular* reaction was assembled. After assembly of the carbon framework, the final functionality changes were effected. It is the necessity for the formation of the carbon skeleton that determines the functionalities that are present at the ring-closure stage. After the ring structure is established, necessary adjustments of the functionalities are made.

13.2.3. Prelog-Djerassi Lactone

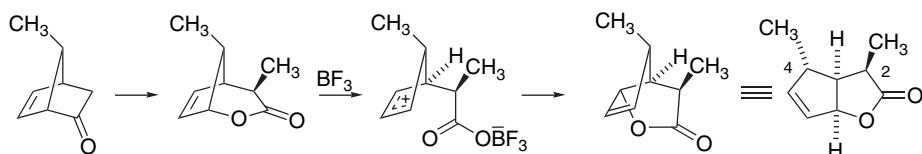
The Prelog-Djerassi lactone (abbreviated here as P-D lactone) was originally isolated as a degradation product during structural investigations of antibiotics. Its open-chain equivalent **3** is typical of the methyl-branched carbon chains that occur frequently in macrolide and polyether antibiotics. The compound serves as a test case for the development of methods of control of stereochemistry in such polymethylated structures. There have been more than 20 different syntheses of P-D lactone.²⁴ We focus here on some of those that provide enantiomerically pure product, as they illustrate several of the methods for enantioselective synthesis.²⁵

²⁴ For references to many of these syntheses, see S. F. Martin and D. G. Guinn, *J. Org. Chem.*, **52**, 5588 (1987); H. F. Chow and I. Fleming, *Tetrahedron Lett.*, **26**, 397 (1985); S. F. Martin and D. E. Guinn, *Synthesis*, 245 (1991).

²⁵ For other syntheses of enantiomerically pure Prelog-Djerassi lactone, see F. E. Ziegler, A. Kneisley, J. K. Thottathil, and R. T. Wester, *J. Am. Chem. Soc.*, **110**, 5434 (1988); A. Nakano, S. Takimoto, J. Inanaga, T. Katsuki, S. Ouchida, K. Inoue, M. Aiga, N. Okukado, and M. Yamaguchi, *Chem. Lett.*, 1019 (1979); K. Suzuki, K. Tomooko, T. Matsumoto, E. Katayama, and G. Tsuchihashi, *Tetrahedron*

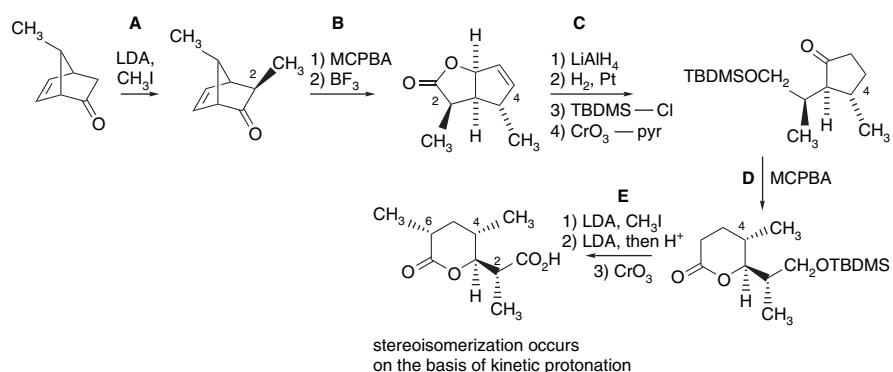


The synthesis in Scheme 13.34 is based on a bicyclic starting material that can be prepared in enantiomerically pure form. In the synthesis, C(7) of the norbornenone starting material becomes C(4) of P-D lactone and the methyl group in the starting material becomes the C(4) methyl substituent. The sequence uses the cyclic starting material to control facial selectivity. The configuration of the C(3) hydroxy and C(2) and C(6) methyl groups must be established relative to the C(4) stereocenter. The *exo*-selective alkylation in Step A established the configuration at C(2). The Baeyer–Villiger oxidation in Step B was followed by a Lewis acid–mediated allylic rearrangement, which is suprafacial. This stereoselectivity is dictated by the preference for maintaining a *cis* ring juncture at the five-membered rings.



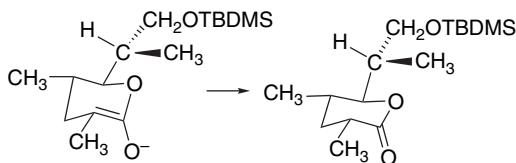
The stereochemistry of the C(3) hydroxy was established in Step D. The Baeyer–Villiger oxidation proceeds with retention of configuration of the migrating group (see Section 12.5.2), so the correct stereochemistry is established for the C–O bond. The final stereocenter for which configuration must be established is the methyl group at C(6) that was introduced by an enolate alkylation in Step E, but this reaction was not very stereoselective. However, since this center is adjacent to the lactone carbonyl, it can be epimerized through the enolate. The enolate was formed and quenched with acid. The kinetically preferred protonation from the axial direction provides the correct stereochemistry at C(6).

Scheme 13.34. Prelog–Djerassi Lactone Synthesis: P. A. Grieco and Co-Workers^a

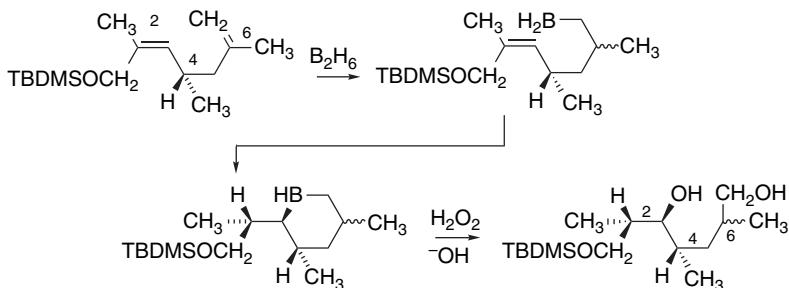


a. P. A. Grieco, Y. Ohfune, Y. Yokoyama, and W. Owens, *J. Am. Chem. Soc.*, **101**, 4749 (1979).

Lett., **26**, 3711 (1985); M. Isobe, Y. Ichikawa, and T. Goto, *Tetrahedron Lett.*, **22**, 4287 (1981); M. Mori, T. Chuman, and K. Kato, *Carbohydrate Res.*, **129**, 73 (1984).



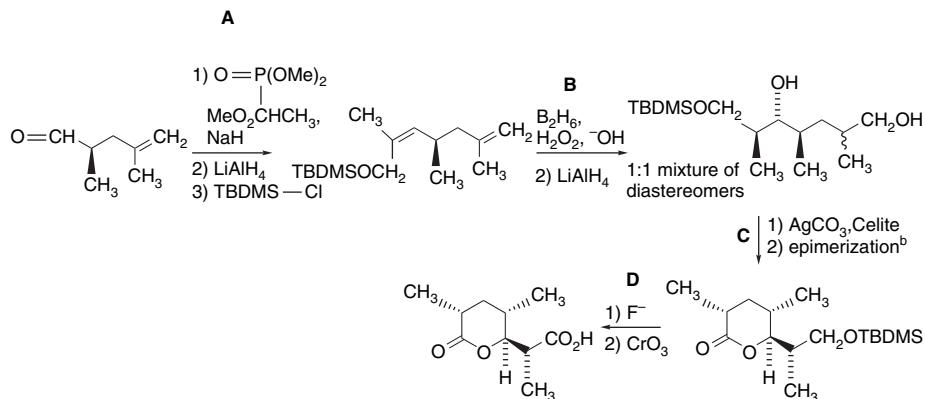
Another synthesis of P-D lactone that is based on an enantiomerically pure starting material is shown in Scheme 13.35. The stereocenter in the starting material is destined to become C(4) in the final product. Steps **A** and **B** served to extend the chain to provide a seven-carbon 1,5-diene. The configuration of two of the three remaining stereocenters is controlled by the hydroboration step, which is a stereospecific *syn* addition (Section 4.5.1). In 1,5-dienes of this type, an intramolecular hydroboration occurs and establishes the configuration of the two newly formed C–B and C–H bonds.



There was, however, no significant selectivity in the initial hydroboration of the terminal double bond. As a result, both configurations are formed at C(6). This problem was overcome using the epimerization process from Scheme 13.34.

The syntheses in Schemes 13.36 to 13.40 are conceptually related. They begin with symmetric achiral derivatives of *meso*-2,4-dimethylglutaric acid and utilize various approaches to the *desymmetrization* of the *meso* starting material. In Scheme 13.36

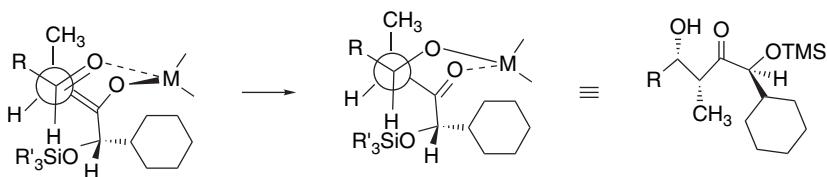
Scheme 13.35. Prelog-Djerassi Lactone Synthesis: W. C. Still and K. R. Shaw^a



a. W. C. Still and K. R. Shaw, *Tetrahedron Lett.*, **22**, 3725 (1981).

b. Epimerization as in Scheme 13.34.

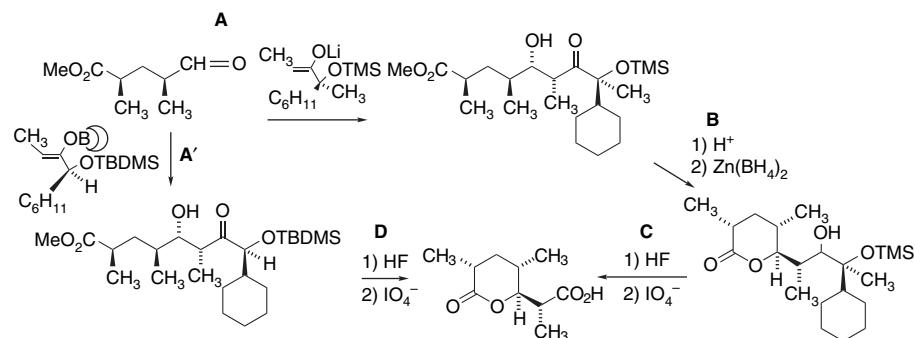
the starting material was prepared by reduction of the half-ester of *meso*-2,4-dimethylglutaric acid. The use of the *meso*-diacid ensures the correct *relative configuration* of the C(4) and C(6) methyl substituents. The half-acid was resolved and the correct enantiomer was reduced to the aldehyde. The stereochemistry at C(2) and C(3) was established by stereoselective aldol condensation methodology. Both the lithium enolate and the boron enolate methods were employed. The use of bulky enolates enhances the stereoselectivity. The enol derivatives were used in enantiomerically pure form so the condensations are examples of *double stereodifferentiation* (Section 2.1.5.3). The stereoselectivity observed in the reactions is that predicted by a cyclic TS for the aldol condensations.



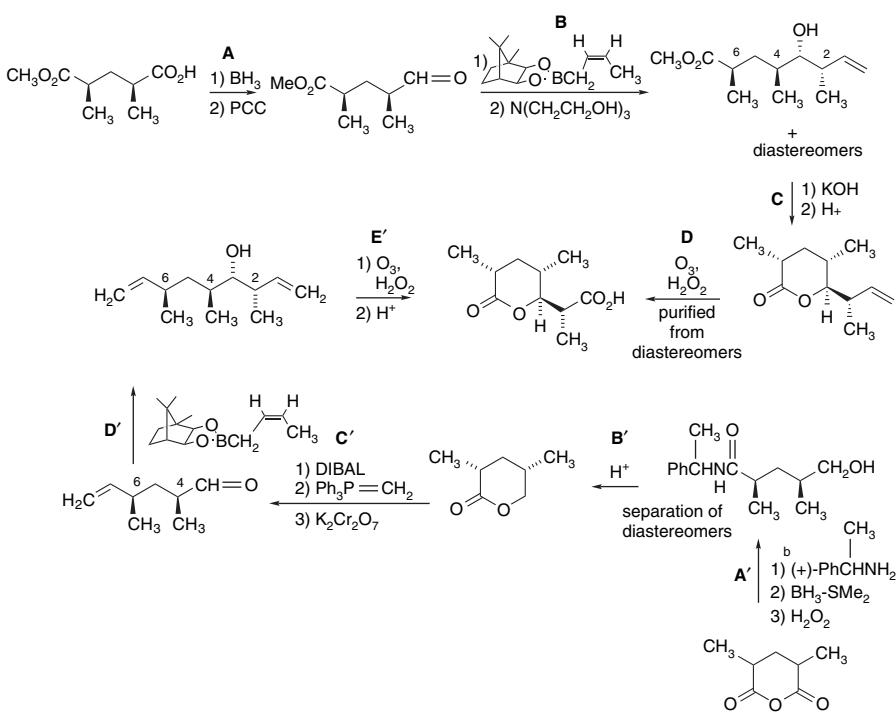
The synthesis in Scheme 13.37 also used a *meso*-3,4-dimethylglutaric acid as the starting material. Both the resolved aldehyde employed in Scheme 13.36 and a resolved half-amide were successfully used as intermediates. The configuration at C(2) and C(3) was controlled by addition of a butenylborane to an aldehyde (see Section 9.1.5). The boronate was used in enantiomerically pure form so that stereoselectivity was enhanced by *double stereodifferentiation*. The allylic additions carried out by the butenylboronates do not appear to have been quite as highly stereoselective as the aldol condensations used in Scheme 13.36, since a minor diastereoisomer was formed in the boronate addition reactions.

The synthesis in Scheme 13.38 is based on an interesting kinetic differentiation in the reactivity of two centers that are structurally identical, but diastereomeric. A *bis*-amide of *meso*-2,4-dimethylglutaric acid and a chiral thiazoline was formed in Step A. The thiazoline is derived from the amino acid cysteine. The two amide carbonyls in this *bis*-amide are nonequivalent by virtue of the diastereomeric relationship established

Scheme 13.36. Prelog-Djerassi Lactone Synthesis: S. Masamune and Co-Workers^a



a. S. Masamune, S. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem. Int. Ed. Engl.*, **19**, 557 (1980); S. Masamune, M. Hirama, S. Mori, S. A. Ali, and D. S. Garvey, *J. Am. Chem. Soc.*, **103**, 1568 (1981).

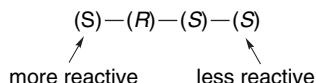
Scheme 13.37. Prelog-Djerassi Lactone Synthesis: R. W. Hoffmann and Co-Workers^a

a. R. W. Hoffmann, H.-J. Zeiss, W. Ladner, and S. Tabche, *Chem. Ber.*, **115**, 2357 (1982).

b. Resolved via α -phenylethylamine salt; S. Masamune, S. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem. Int. Ed. Engl.*, **19**, 557 (1980).

by the stereogenic centers at C(2) and C(4) in the glutaric acid portion of the structure. One of the centers reacted with a 97:3 preference with the achiral amine piperidine.

Two amide bonds are in
nonequivalent stereochemical
environments



In Step **D** another thiazoline chiral auxiliary, also derived from cysteine, was used to achieve double stereodifferentiation in an aldol addition. A tin enolate was used. The stereoselectivity of this reaction parallels that of aldol reactions carried out with lithium or boron enolates. After the configuration of all the centers was established, the synthesis proceeded to P-D lactone by functional group modifications.

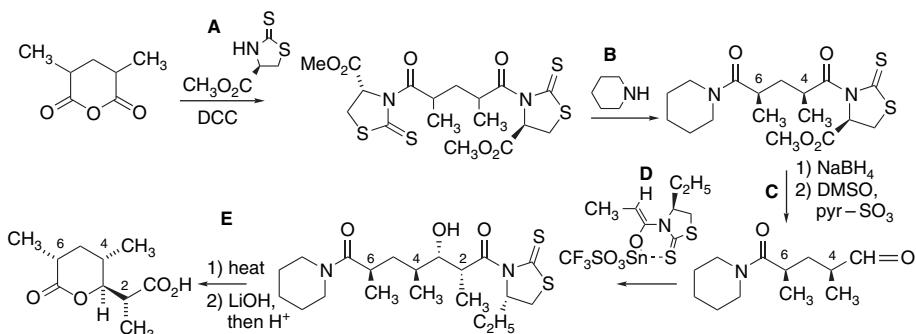
A very short and efficient synthesis based on the desymmetrization principle is shown in Scheme 13.39. *meso*-2,4-Dimethylglutaraldehyde reacted selectively with the diethylboron enolate derived from a bornanesultam chiral auxiliary. This reaction established the stereochemistry at the C(2) and C(3) centers. The dominant aldol product results from an anti-Felkin stereoselectivity with respect to the C(4) center.

Scheme 13.38. Prelog-Djerassi Lactone Synthesis: Y. Nagao and Co-Workers^a

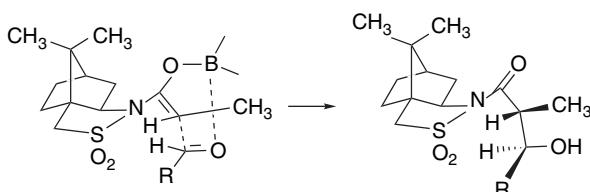
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SECTION 13.2

Illustrative Syntheses

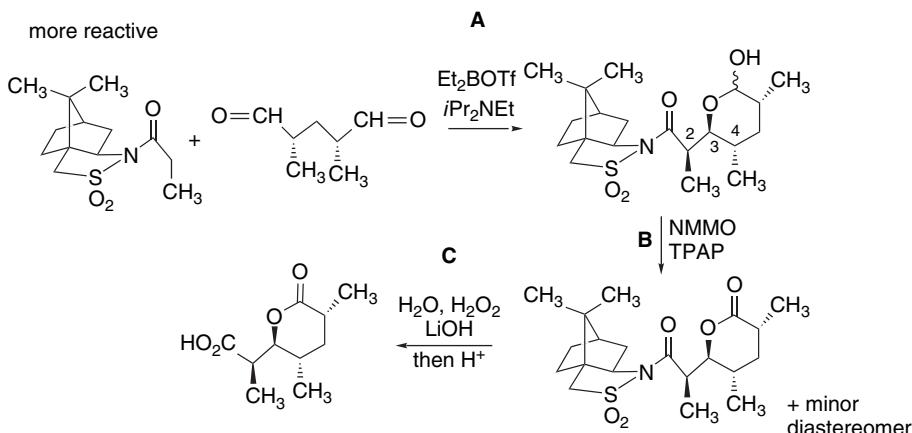


a. Y. Nagao, T. Inoue, K. Hashimoto, Y. Hagiwara, M. Ochiai, and E. Fujita, *J. Chem. Soc., Chem. Commun.*, 1419 (1985).

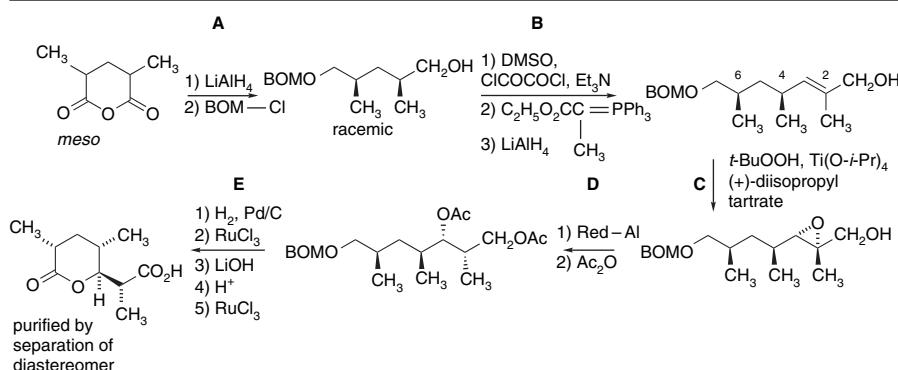


The adduct cyclized to a lactol mixture that was oxidized by TPAP-NMMO to give the corresponding lactones in an 8:1 ratio (86% yield). Hydrolysis in the presence of H_2O_2 gave the P-D lactone and recovered chiral auxiliary.

The synthesis in Scheme 13.40 features a catalytic asymmetric epoxidation (see Section 12.2.1.2). By use of *meso*-2,4-dimethylglutaric anhydride as the starting material, the proper relative configuration at C(4) and C(6) is ensured. The epoxidation directed by the (+)-tartrate catalyst controls the configuration established at C(2) and C(3) by the epoxidation. Although the epoxidation is highly selective in

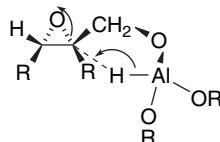
Scheme 13.39. Prelog-Djerassi Lactone Synthesis: W. Oppolzer and Co-Workers^a

a. W. Oppolzer, E. Walther, C. Perez Balado, and J. De Brabander, *Tetrahedron Lett.*, **38**, 809 (1997).

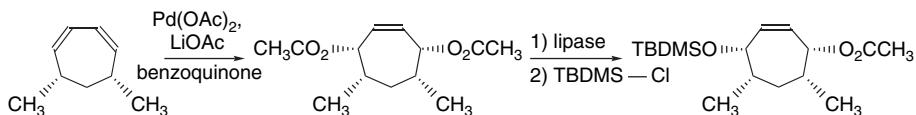
Scheme 13.40. Prelog-Djerassi Lactone Synthesis: M. Yamaguchi and Co-Workers^a

a. M. Honda, T. Katsuki, and M. Yamaguchi, *Tetrahedron Lett.*, **25**, 3857 (1984).

establishing the configuration at C(2) and C(3), the configuration at C(4) and C(6) does not strongly influence the reaction; a mixture of diastereomeric products was formed and then separated at a later stage in the synthesis. The reductive ring opening in Step **D** occurs with dominant inversion to establish the necessary (*R*)-configuration at C(2). The preference for 1,3-diol formation is characteristic of reductive ring opening by Red-Al of epoxides derived from allylic alcohols.²⁶ Presumably, initial coordination at the hydroxy group and intramolecular delivery of hydride is responsible for this stereoselectivity.



The synthesis in Scheme 13.41 is also built on the desymmetrization concept but uses a very different intermediate. *cis*-5,7-Dimethylcycloheptadiene was acetoxylated with $\text{Pd}(\text{OAc})_2$ and the resulting all-*cis*-diacetate intermediate was enantioselectively hydrolyzed with a lipase to give a monoacetate that was protected as the TBDSM ether. An *anti S_N2'* displacement by dimethyl cuprate established the correct configuration of the C(2) methyl substituent. Oxidative ring cleavage and lactonization gave the final product.



There have been several syntheses of P-D lactone that were based on carbohydrate-derived starting materials. The starting material used in Scheme 13.42 was prepared from a carbohydrate produced in earlier work.²⁷ The relative stereochemistry at C(4)

²⁶. P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, and S. M. Viti, *J. Org. Chem.*, **47**, 1378 (1982); S. M. Viti, *Tetrahedron Lett.*, **23**, 4541 (1982); J. M. Finan and Y. Kishi, *Tetrahedron Lett.*, **23**, 2719 (1982).

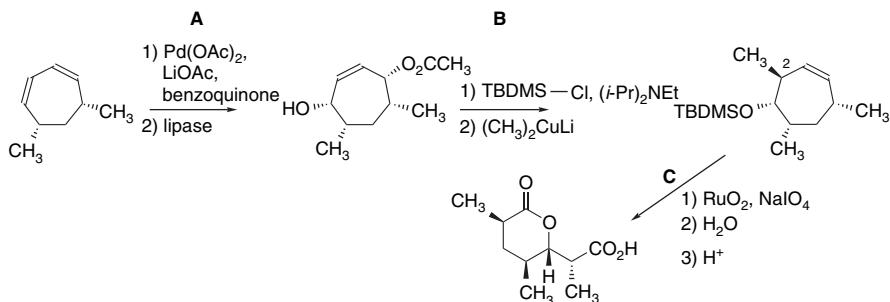
²⁷. M. B. Yunker, D. E. Plaumann, and B. Fraser-Reid, *Can. J. Chem.*, **55**, 4002 (1977).

Scheme 13.41. Prelog-Djerassi Lactone Synthesis: A. J. Pearson and Y.-S. Lai^a

1203

SECTION 13.2

Illustrative Syntheses

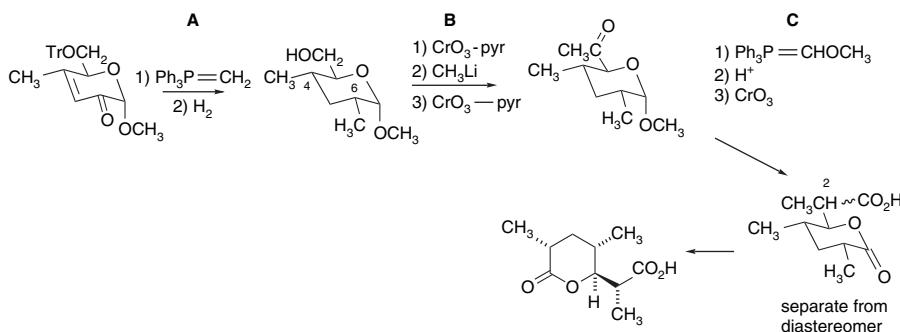


a. A. J. Pearson and Y.-S. Lai, *J. Chem. Soc., Chem. Commun.*, 442 (1988).

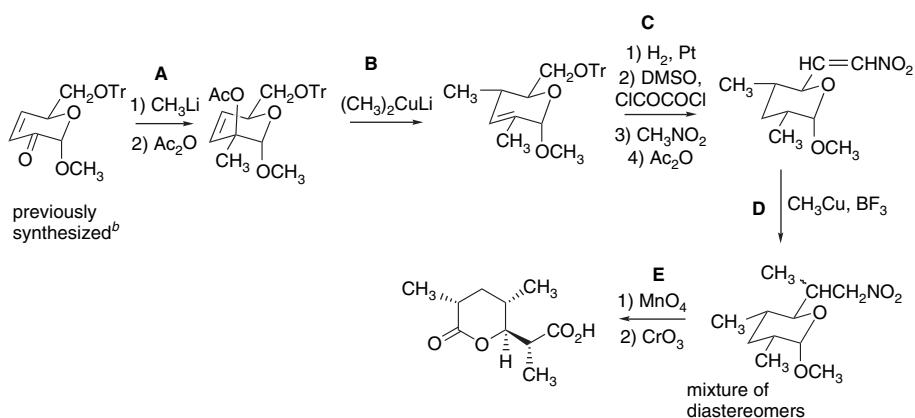
and C(6) was established by the hydrogenation in Step A-2. This *syn* hydrogenation is not completely stereoselective, but provided a 4:1 mixture favoring the desired stereoisomer. The stereoselectivity is presumably the result of preferential absorption from the less hindered β -face of the molecule. The configuration of C(2) was established by protonation during the hydrolysis of the enol ether in Step C-2. This step was not stereoselective, so a separation of diastereomers after the oxidation in Step C-3 was required.

The synthesis in Scheme 13.43 also began with carbohydrate-derived starting material and uses catalytic hydrogenation in Step C-1 to establish the stereochemical relationship between the C(4) and C(6) methyl groups. As was the case in Scheme 13.42, the configuration at C(2) was not controlled in this synthesis and separation of the diastereomeric products was necessary. This synthesis used an organocupper reagent to introduce both the C(4) and C(2) methyl groups. The former was introduced by S_N2' allylic substitution in Step B and the latter by conjugate addition to a nitroalkene in Step D.

The synthesis in Scheme 13.44 is also based on a carbohydrate-derived starting material. It controlled the stereochemistry at C(2) by means of the stereoselectivity of the Ireland-Claisen rearrangement in Step A (see Section 6.4.2.3). The ester enolate was formed under conditions in which the *E*-enolate is expected to predominate. Heating the resulting silyl enol ether gave a 9:1 preference for the expected stereoisomer. The

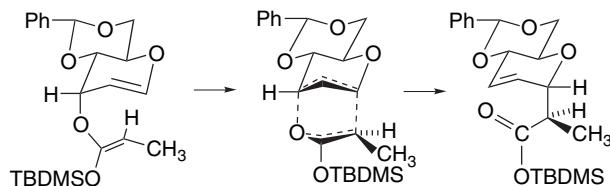
Scheme 13.42. Prelog-Djerassi Lactone Synthesis: S. Jarosz and B. Fraser-Reid^a

a. S. Jarosz and B. Fraser-Reid, *Tetrahedron Lett.*, 22, 2533 (1981).

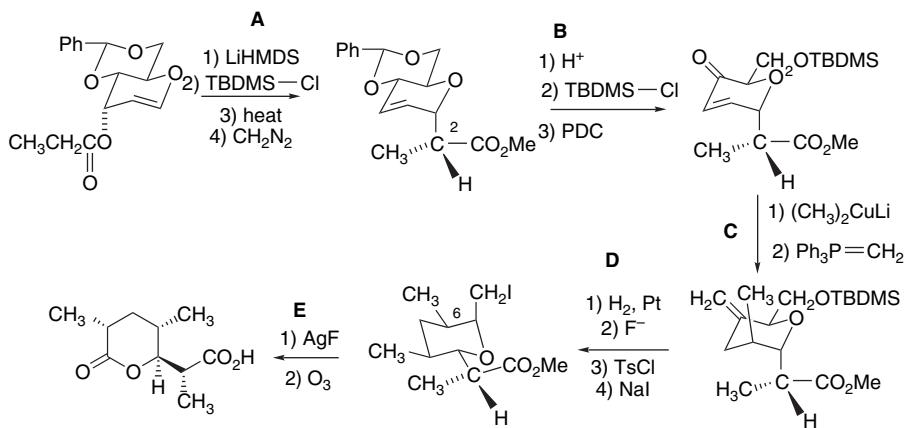
Scheme 13.43. Prelog-Djerassi Lactone Synthesis: N. Kawauchi and H. Hashimoto^a

a. N. Kawauchi and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **60**, 1441 (1987).
 b. N. L. Holder and B. Fraser-Reid, *Can. J. Chem.*, **51**, 3357 (1973).

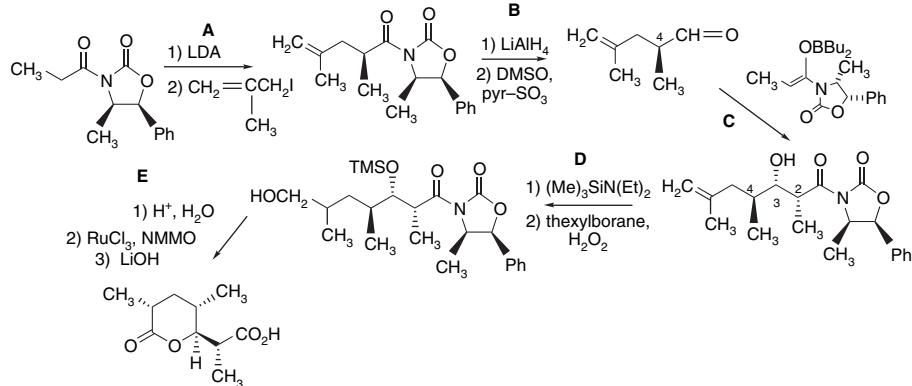
preferred TS, which is boatlike, minimizes the steric interaction between the bulky silyl substituent and the ring structure.



The stereochemistry at C(4) and C(6) was then established. The cuprate addition in Step C occurred *anti* to the substituent at C(2) of the pyran ring. After a Wittig

Scheme 13.44. Prelog-Djerassi Lactone Synthesis: R. E. Ireland and J. P. Daub^a

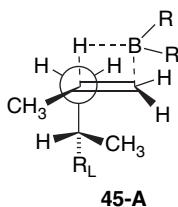
a. R. E. Ireland and J. P. Daub, *J. Org. Chem.*, **46**, 479 (1981).



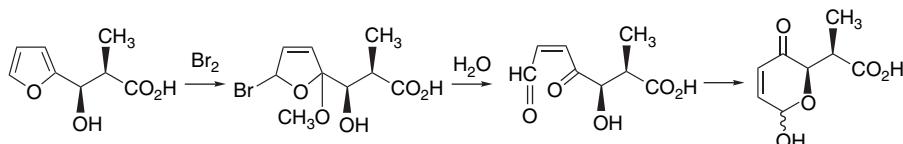
a. D. A. Evans and J. Bartroli, *Tetrahedron Lett.*, **23**, 807 (1982).

methylenation, the catalytic hydrogenation in Step **D** established the stereochemistry at C(6). The lactone carbonyl was introduced by β -elimination and ozonolysis.

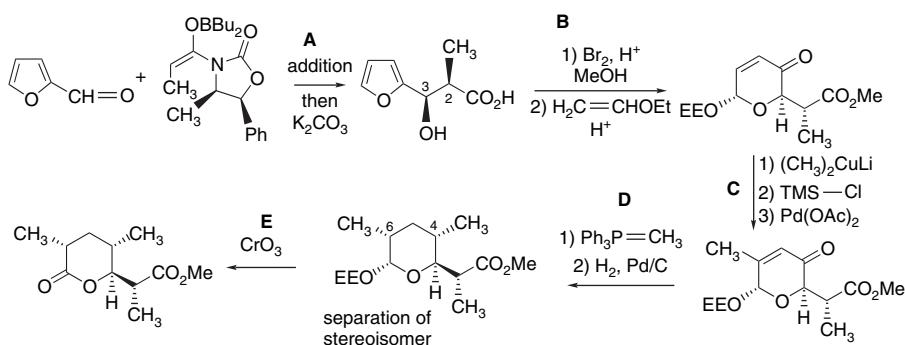
The syntheses in Schemes 13.45 and 13.46 illustrate the use of oxazolidinone chiral auxiliaries in enantioselective synthesis. Step **A** in Scheme 13.45 established the configuration at the carbon that becomes C(4) in the product. This is an enolate alkylation in which the steric effect of the oxazolidinone chiral auxiliary directs the approach of the alkylating group. Step **C** also used the oxazolidinone structure. In this case, the enol borinate is formed and condensed with an aldehyde intermediate. This stereoselective aldol addition established the configuration at C(2) and C(3). The configuration at the final stereocenter at C(6) was established by the hydroboration in Step **D**. The selectivity for the desired stereoisomer was 85:15. Stereoselectivity in the same sense has been observed for a number of other 2-methylalkenes in which the remainder of the alkene constitutes a relatively bulky group.²⁸ A TS such as **45-A** can rationalize this result.



In the synthesis in Scheme 13.46, a stereoselective aldol addition was used to establish the configuration at C(2) and C(3) in Step **A**. The furan ring was then subjected to an electrophilic addition and solvolytic rearrangement in Step **B**.



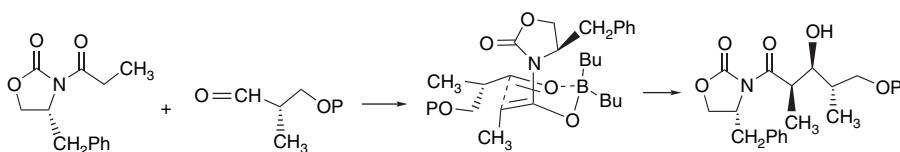
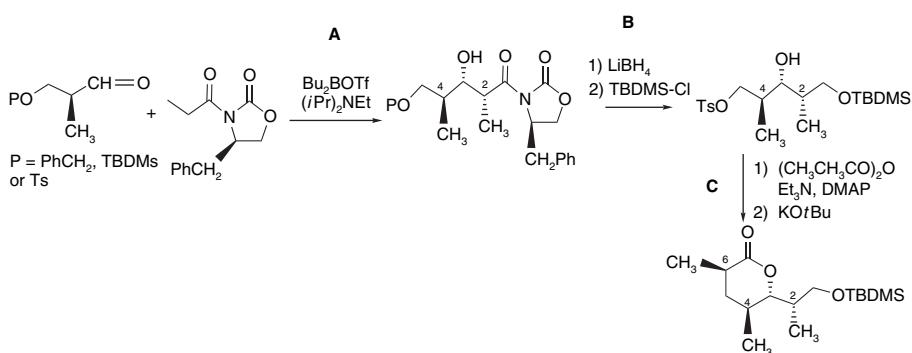
²⁸. D. A. Evans, J. Bartroli, and T. Godel, *Tetrahedron Lett.*, **23**, 4577 (1982).

Scheme 13.46. Prelog-Djerassi Lactone Synthesis: S. F. Martin and D. E. Guinn^a

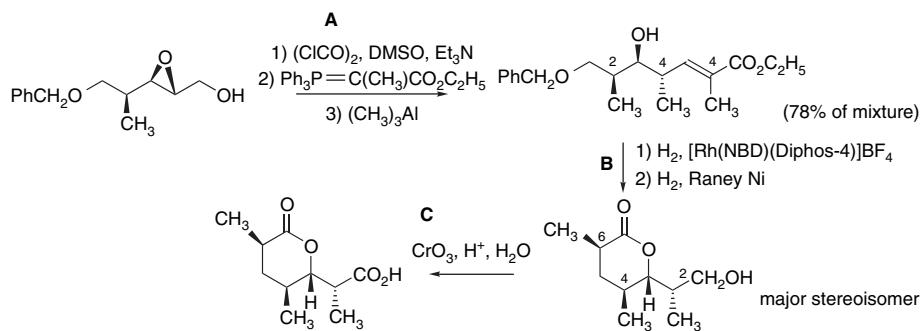
a. S. F. Martin and D. E. Guinn, *J. Org. Chem.*, **52**, 5588 (1987).

The protection of the hemiacetal hydroxyl in Step **B-2** was followed by a purification of the dominant stereoisomer. In Step **C-1**, the addition of the C(6) methyl group gave predominantly the undesired α -stereoisomer. The enolate was trapped as the trimethylsilyl ether and oxidized to the enone by $\text{Pd}(\text{OAc})_2$. The enone from sequence **C** was then subjected to a Wittig reaction. As in several of the other syntheses, the hydrogenation in Step **D-2** was used to establish the configuration at C(4) and C(6).

The synthesis in Scheme 13.47 was also based on use of a chiral auxiliary and provided the TBDMS-protected derivative of P-D lactone in the course of synthesis of the macrolide portion of the antibiotic 10-deoxymethymycin. The relative stereochemistry at C(2)-C(3) was obtained by addition of the dibutylboron enolate of an N-propanoyl oxazolidinone. The addition occurs with *syn* anti-Felkin stereochemistry.

Scheme 13.47. Prelog-Djerassi Lactone Synthesis: R. A. Pilli and Co-Workers^a

a. R. A. Pilli, C. K. Z. de Andrade, C. R. O. Souto, and A. de Meijere, *J. Org. Chem.*, **63**, 7811 (1998).



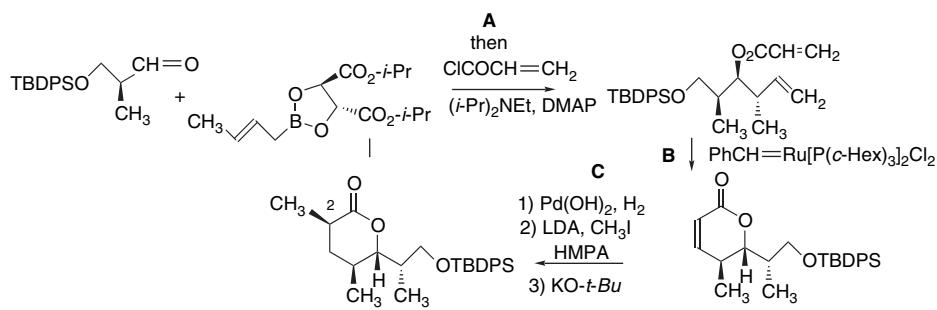
a. M. Miyashita, M. Hoshino, A. Yoshikoshi, K. Kawamine, K. Yoshihara, and H. Irie, *Chem. Lett.*, 1101 (1992).

Removal of the chiral auxiliary and reduction gave an intermediate that had differentiated terminal hydroxy groups. Although the sequence was initially carried out on the benzyl or TBDMS-protected aldehyde, with subsequent removal of the protecting group, it was found that the aldol addition could be carried out directly on the tosylate, providing a shorter route. A propanoyl group was added at Step C-1 and provided the remainder of the carbon chain. The lactone ring was closed by an intramolecular enolate alkylation. This step is not highly stereoselective, but equilibration (see Scheme 13.34) gave the desired stereoisomer in a 10:1 ratio.

The synthesis in Scheme 13.48 used stereospecific ring opening of an epoxide by trimethylaluminum to establish the stereochemistry of the C(4) methyl group. The starting material was made by enantiospecific epoxidation of the corresponding allylic alcohol.²⁹ The hydrogenation in Step B-1 achieved about 3:1 stereoselectivity at C(2). Removal of the benzyl protecting group by hydrogenolysis then gave the lactone.

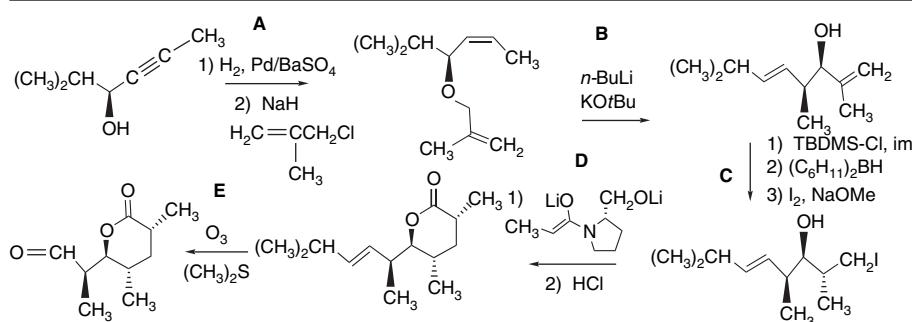
The synthesis in Scheme 13.49 features use of an enantioselective allylic boronate reagent derived from diisopropyl tartrate to establish the C(4) and C(5) stereochemistry. The ring is closed by an olefin metathesis reaction. The C(2) methyl group was introduced by alkylation of the lactone enolate. The alkylation is not stereoselective, but base-catalyzed epimerization favors the desired stereoisomer by 4:1.

Scheme 13.49. Prelog-Djerassi Lactone Synthesis: J. Cossy, D. Bauer, and V. Bellosta^a



a. J. Cossy, D. Bauer, and V. Bellosta, *Tetrahedron Lett.*, **40**, 4187 (1999).

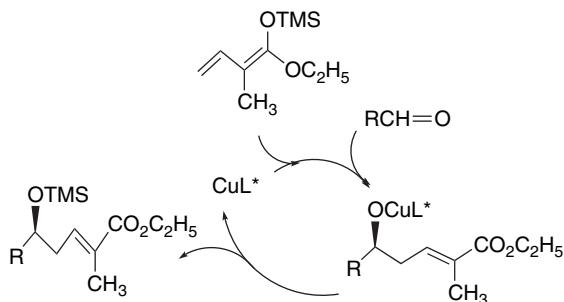
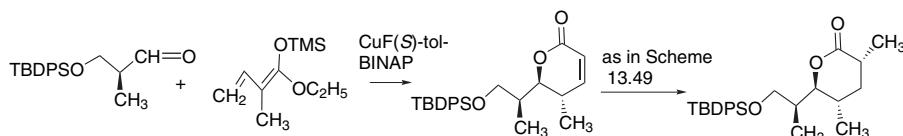
²⁹. H. Nagaoka and Y. Kishi, *Tetrahedron*, **37**, 3873 (1981).

Scheme 13.50. Prelog-Djerassi Lactone Synthesis: D. J.-S. Tsai and M. M. Midland^a

a. D. J.-S. Tsai and M. M. Midland, *J. Am. Chem. Soc.*, **107**, 3915 (1985).

The synthesis in Scheme 13.50 used the stereoselectivity of a [2,3]-sigmatropic rearrangement as the basis of stereochemical control. The starting material was prepared by enantioselective reduction of the corresponding ketone using S-Alpine-Borane. The sigmatropic rearrangement of the lithium anion in Step **B** gave 97:3 stereoselectivity for the *syn* isomer (see p. 588). After protection, this intermediate was selectively hydroborated with $(C_6H_{11})_2BH$ and converted to the iodide. The hydroboration in Step **C**-2 establishes the stereochemistry at C(4) with 15:1 stereoselectivity. The iodide was then used in conjunction with a chiral auxiliary to create the C(2)–C(3) bond by alkylation of the amide enolate.

A recent synthesis of P-D lactone (Scheme 13.51) used an enantioselective catalytic approach. A conjugate addition of a silyl ketene acetal derived from an unsaturated ester gave an unsaturated lactone intermediate. The catalyst is $CuF-(S)\text{-tol}\text{-BINAP}$.³⁰ The catalytic cycle for the reaction is shown below.

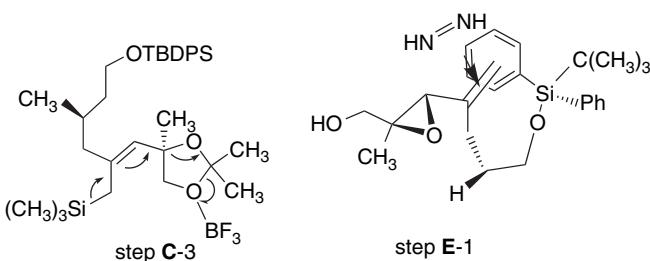
Scheme 13.51. Prelog-Djerassi Lactone Synthesis: J.-M. Campagne and Co-Workers^a

a. G. Bluet, B. Bazan-Tejeda, and J.-M. Campagne, *Org. Lett.*, **3**, 3807 (2001).

³⁰ J. Krueger and E. M. Carreira, *J. Am. Chem. Soc.*, **120**, 837 (1998).

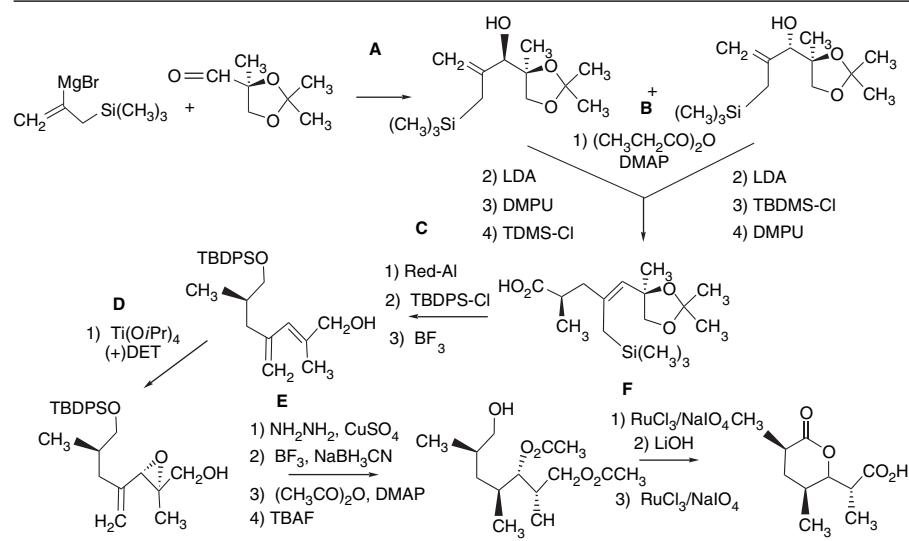
The reaction was very stereoselective for the correct P-D lactone configuration. The synthesis, which is outlined in Scheme 13.51, was completed by the sequence shown in Scheme 13.49.

The synthesis shown in Scheme 13.52 started with an enantiomerically pure protected aldehyde. Reaction with a Grignard reagent installed an allylic silane. This reaction gave a mixture of alcohols, but both were converted to the same intermediate by taking advantage of selective formation of *E*- or *Z*-silyl ketene acetal prior to an Ireland-Claisen rearrangement. These stereoconvergent transformations are described on p. 568. Two subsequent steps are noteworthy. In Step C-3, a BF_3 -mediated opening of the dioxolane ring triggers a desilylation. In Step E-1, the diimide reduction occurs with excellent stereoselectivity. This is attributed to a π -stacking interaction with the TBDPS protecting group, since no similar effect was noted with the TBDS group.



The final lactonization and oxidation were done as in Scheme 13.40.

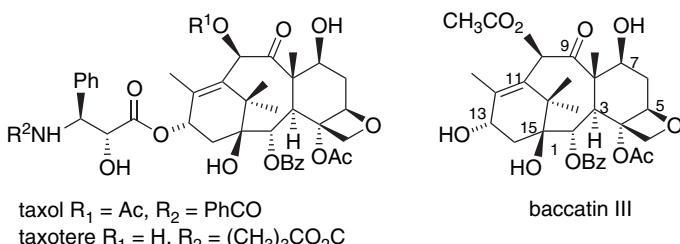
Scheme 13.52. Prelog-Djerassi Lactone Synthesis: P. J. Parsons and Co-Workers^a



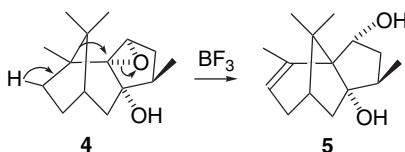
a. S. D. Hiscock, P. B. Hitchcock, and P. J. Parsons, *Tetrahedron*, **54**, 11567 (1998).

13.2.4. Baccatin III and Taxol

Taxol³¹ was first discovered to have anticancer activity during a screening of natural substances,³² and it is currently an important drug in cancer chemotherapy. Several Taxol analogs differing in the side-chain substitution, such as taxotere, also have good activity.³³ Production of Taxol directly from plant sources presented serious problems because the plants are slow growing and the Taxol content is low. However, the tetracyclic ring system is found in a more available material, Baccatin III, which can be converted to Taxol by introduction of the side chain.³⁴ The combination of important biological activity, the limited natural sources, and the interesting structure made Taxol a target of synthetic interest during the 1990s. Among the challenging aspects of the structure from a synthetic point of view are the eight-membered ring, the bridgehead double bond, and the large number of oxygen functional groups. Several syntheses of Baccatin III and closely related tetracyclic Taxol precursors have been reported.



The first synthesis of Taxol was completed by Robert Holton and co-workers and is outlined in Scheme 13.53. One of the key steps occurs early in the synthesis in sequence A and effects fragmentation of **4** to **5**. The intermediate epoxide **4** was prepared from a sesquiterpene called “patchino.”³⁵ The epoxide was then converted to **5** by a BF_3 -mediated rearrangement.



Another epoxidation, followed by fragmentation gave the bicyclic intermediate that contains the eight-membered ring and bridgehead double bond properly positioned for conversion to Taxol (Steps B-2 and B-3).

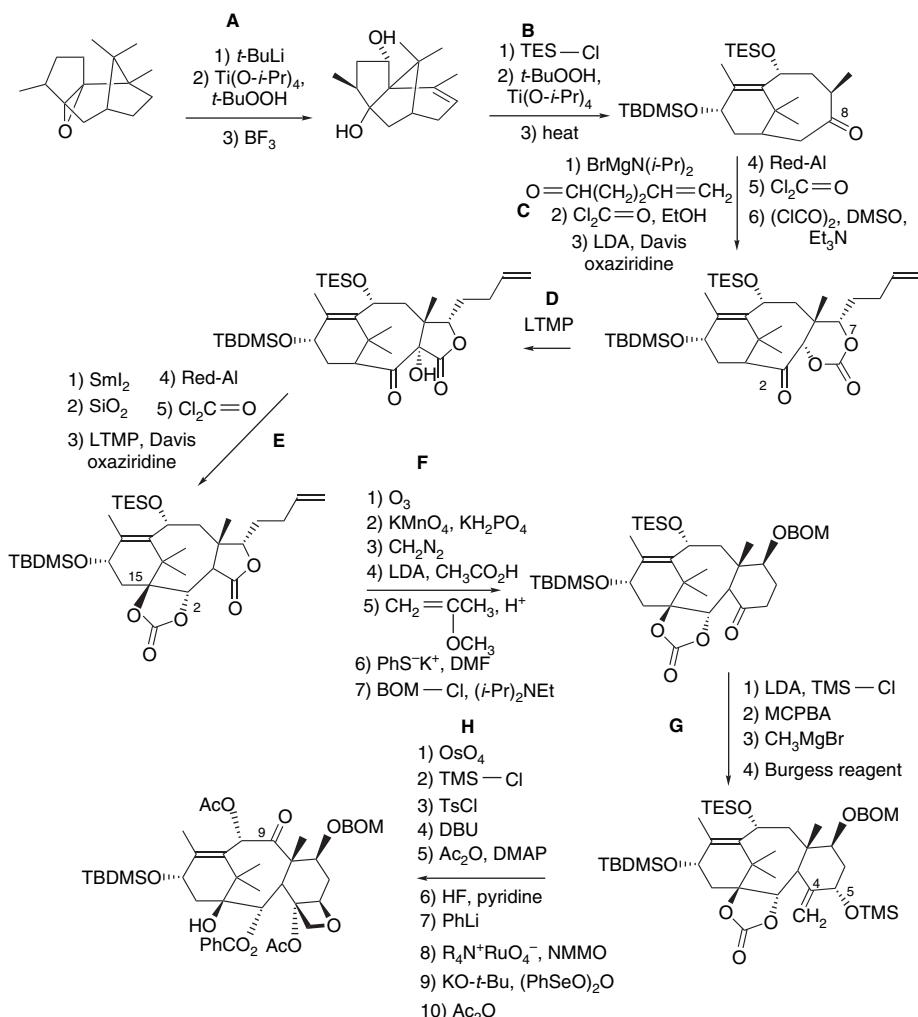
- ³¹ Taxol is a registered trade name of Bristol-Myers Squibb. The generic name is paclitaxel.
- ³² M. C. Wani, H. L. Taylor, M. E. Wall, D. Coggon, and A. McPhail, *J. Am. Chem. Soc.*, **93**, 2325 (1971); M. E. Wall and M. C. Wani, *Alkaloids*, **50**, 509 (1998).
- ³³ M. Suffness, ed., *Taxol: Science and Applications*, CRC Press, Boca Raton, FL, 1995.
- ³⁴ J.-N. Denis, A. E. Greene, D. Guenard, F. Gueritte-Vogelein, L. Mangatal, and P. Potier, *J. Am. Chem. Soc.*, **110**, 5917 (1988); R. A. Holton, Z. Zhang, P. A. Clarke, H. Nadizadeh, and D. J. Procter, *Tetrahedron Lett.*, **39**, 2883 (1998).
- ³⁵ R. A. Holton, R. R. Juo, H. B. Kim, A. D. Williams, S. Harusawa, R. E. Lowenthal, and S. Yogai, *J. Am. Chem. Soc.*, **110**, 6558 (1988).

Scheme 13.53. Baccatin III Synthesis: R. A. Holton and Co-Workers^a

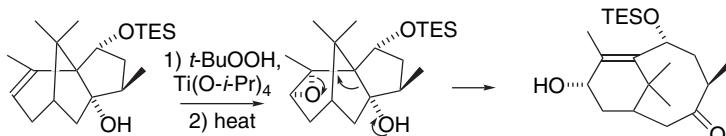
1211

SECTION 13.2

Illustrative Syntheses

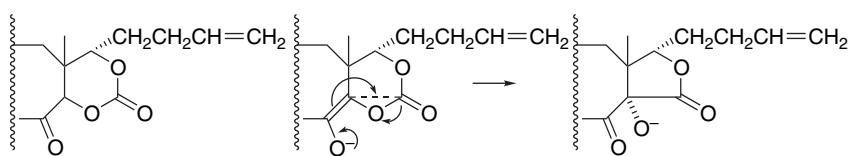


a. R. A. Holton, C. Somoza, H.-B. Kim, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, and J. H. Lin, *J. Am. Chem. Soc.*, **116**, 1597 (1994); R. A. Holton, H.-B. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, and J. H. Liu, *J. Am. Chem. Soc.*, **116**, 1599 (1994).



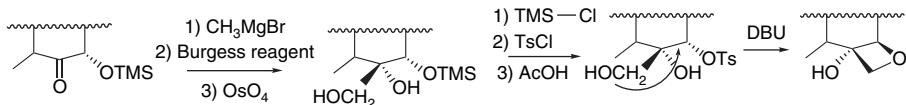
The next phase of the synthesis was construction of the C-ring. An aldol addition was used to introduce a 3-but enyl group at C(8) and the product was trapped as a carbonate ester. The Davis oxaziridine was then used to introduce an oxygen at C(2). After reduction of the C(3) oxygen, a cyclic carbonate was formed, and C(2) was converted

to a carbonyl group by Swern oxidation. In Step **D** this carbonate was rearranged to a lactone.

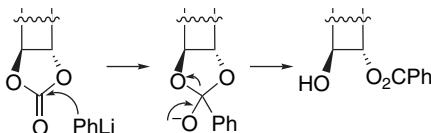


Reaction sequence **E** removed an extraneous oxygen by SmI_2 reduction and installed an oxygen at C(15) by enolate oxidation. The C(1) and C(15) hydroxy groups were protected as a carbonate in Step **E-5**. After oxidation of the terminal vinyl group, the C-ring was constructed by a Dieckmann cyclization in Step **F-4**. After temporary protection of the C(7) hydroxy as the MOP derivative, the β -ketoester was subjected to nucleophilic decarboxylation by phenylthiolate and reprotected as the BOM ether (Steps **F-5**, **F-6**, and **F-7**).

An oxygen substituent was introduced at C(5) by MCPBA oxidation of a silyl enol ether (Steps **G-1** and **G-2**). An exocyclic methylene group was introduced at C(4) by a methyl Grignard addition followed by dehydration with Burgess reagent (**G-3**). The oxetane ring was constructed in Steps **H-1** to **H-4**. The double bond was hydroxylated with OsO_4 and a sequence of selective transformations of the triol provided the hydroxy tosylate, which undergoes intramolecular nucleophilic substitution to form the oxetane ring.

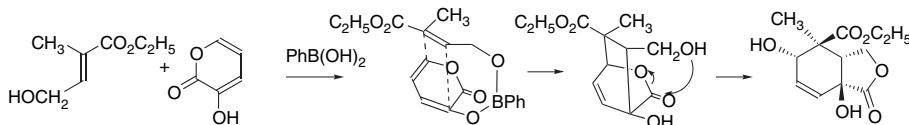


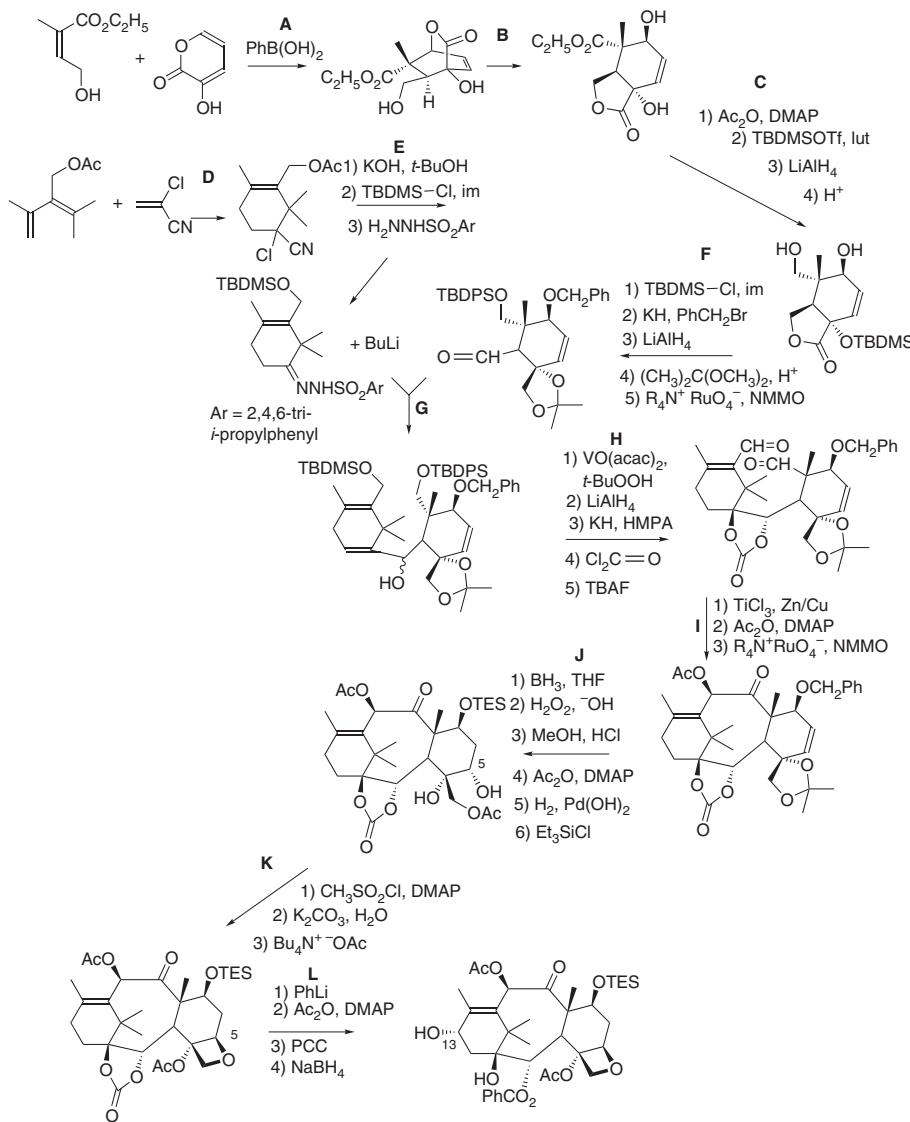
In Step **H-7** the addition of phenyllithium to the cyclic carbonate group neatly generates the C(2) benzoate group. A similar reaction was used in several other Taxol syntheses.



The final phase of the synthesis is introduction of the C(9) oxygen by phenylselenenic anhydride (Step **H-9**) and acetylation.

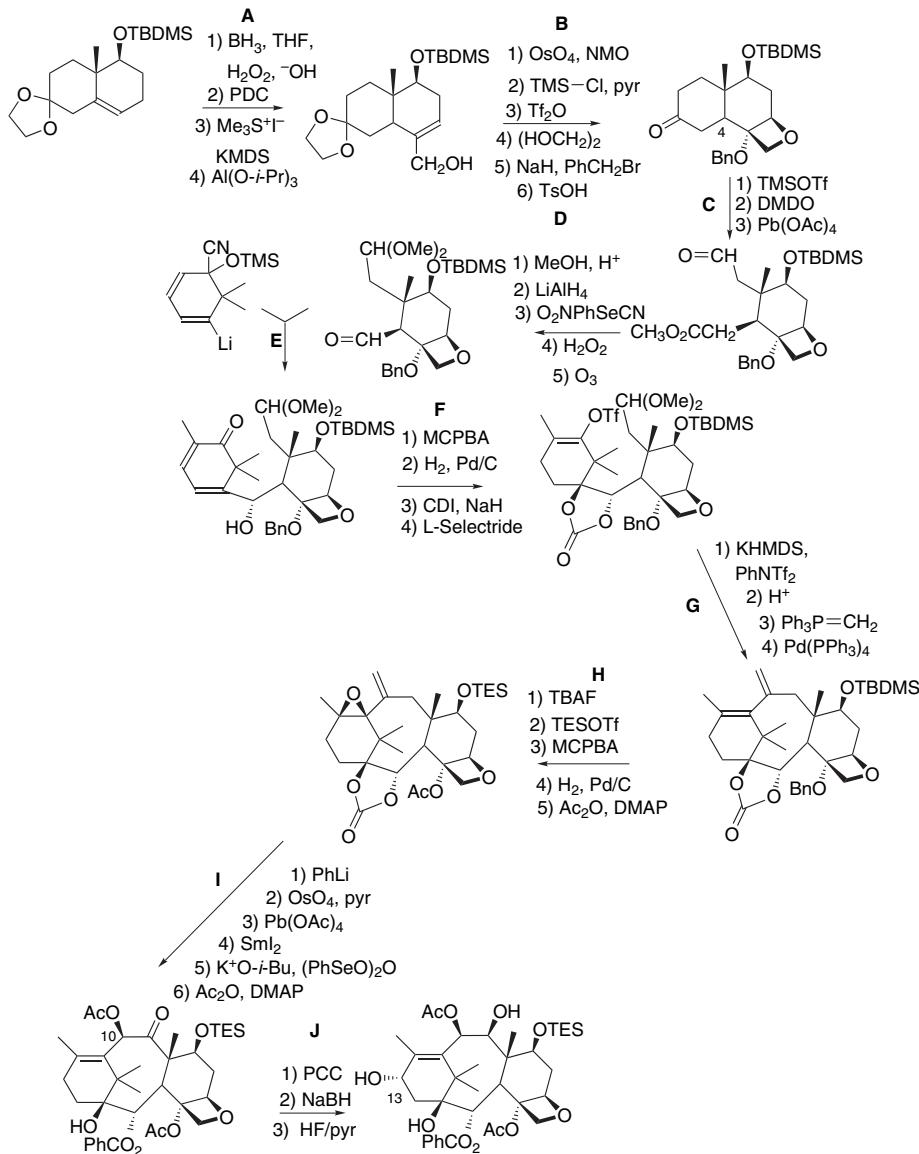
The Baccatin III synthesis by K. C. Nicolaou and co-workers is summarized in Scheme 13.54. Diels-Alder reactions are prominent in forming the early intermediates. In Step **A** the pyrone ring served as the diene. This reaction was facilitated by phenylboronic acid, which brings the diene and dienophile together as a boronate, permitting an intramolecular reaction.



Scheme 13.54. Baccatin III Synthesis: K. C. Nicolaou and Co-Workers^a

- a. K. C. Nicolaou, P. G. Nantermet, H. Ueno, R. K. Guy, E. A. Couladouros, and E. J. Sorenson, *J. Am. Chem. Soc.*, **117**, 624 (1995); K. C. Nicolaou, J.-J. Liu, Z. Yang, H. Ueno, E. J. Sorenson, C. F. Clairborne, R. K. Guy, C.-K. Hwang, M. Nakada, and P. G. Nantermet, *J. Am. Chem. Soc.*, **117**, 634 (1995); K. C. Nicolaou, Z. Zhang, J.-J. Liu, P. G. Nantermet, C. F. Clairborne, J. Renaud, R. K. Guy, and K. S. Shibayama, *J. Am. Chem. Soc.*, **117**, 645 (1995); K. C. Nicolaou, H. Ueno, J.-J. Liu, P. G. Nantermet, Z. Yang, J. Renaud, K. Paulvannan, and R. Chadha, *J. Am. Chem. Soc.*, **117**, 653 (1995).

The formation of the A-ring in Step **D** used α -chloroacrylonitrile as a ketene synthon. The A-ring and C-ring were brought together in Step **G** by an organolithium addition to the aldehyde. The lithium reagent was generated by a Shapiro reaction. An oxygen was introduced at C(1) by hydroxy-directed epoxidation in Step **H-1** and reductive ring opening of the epoxide in Step **H-2**. The eight-membered B-ring was then closed by a titanium-mediated reductive coupling of a dialdehyde in Step **I-1**. The oxetane

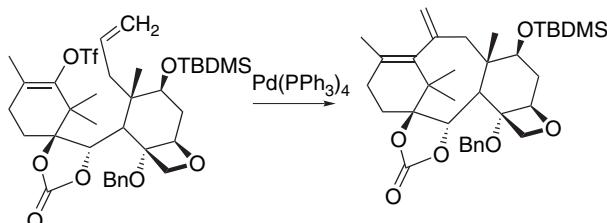
Scheme 13.55. Baccatin III Synthesis: S. J. Danishefsky and Co-Workers^a

a. S. J. Danishefsky, J. J. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn, and M. J. Di Grandi, *J. Am. Chem. Soc.*, **118**, 2843 (1996).

ring was closed in sequence **K** by an intramolecular O-alkylation with inversion at C(5). The C(13) oxygen was introduced late in the synthesis by an allylic oxidation using PCC (Step **L-3**).

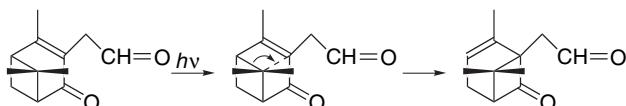
The synthesis of S. J. Danishefsky's group is outlined in Scheme 13.55. The starting material is a protected derivative of the Wieland-Miescher ketone. The oxetane ring is formed early in this synthesis. An epoxide is formed using dimethylsulfonium methylide (Step A-3) and opened to an allylic alcohol in Step A-4. The double bond

was dihydroxylated using OsO_4 . The cyclization occurs via the C(5) triflate and was done in ethylene glycol. After cyclization, the tertiary hydroxy at C(4) was protected by benzylation and the ketal protecting group was removed. The cyclohexanone ring was then cleaved by oxidation of the silyl enol ether. The A-ring was introduced in Step **E** by use of a functionalized lithium reagent. The closure of the B-ring was done by an intramolecular Heck reaction involving a vinyl triflate at Step **G-4**.

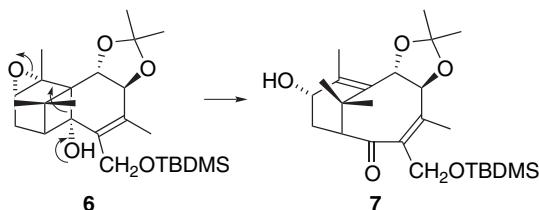


The late functionalization included the introduction of the C(10) and C(13) oxygens, which was done by phenylselenenic anhydride oxidation of the enolate in Step **I-5** and by allylic oxidation at C(13) in Step **J-1**. These oxidative steps are similar to transformations in the Holton and Nicolaou syntheses.

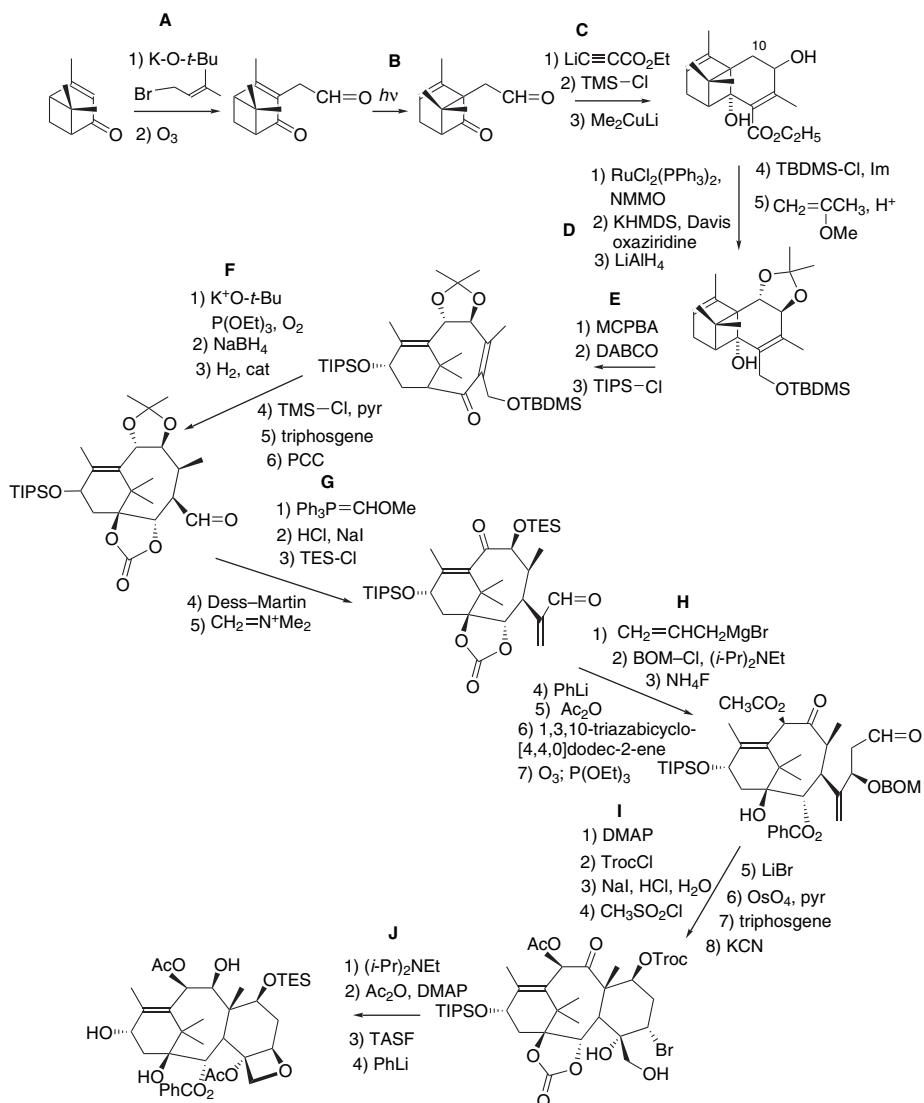
The synthesis of the Taxol in Scheme 13.56 by P. A. Wender and co-workers at Stanford University began with an oxidation product of the readily available terpene pinene. One of the key early steps was the photochemical rearrangement in Step **B**.



A six-membered ring was then constructed in reaction sequence **C** by addition of lithiated ethyl propynoate and a tandem conjugate addition-cyclization. The C(10) oxygen was introduced by enolate oxidation in Step **D-2**. Another key step is the fragmentation induced by treatment first with MCPBA and then with DABCO (Steps **E-1** and **E-2**). The four-membered ring is fragmented in the process, forming the eight-membered ring with its bridgehead double bond and providing the C(13) oxygen substituent.



The C(1) oxygen was introduced at Step **F-1** by enolate oxidation. The C-ring was constructed by building up a substituent at C(16) (Steps **G** and **H**). After forming the benzoate at C(2) in Step **H-4**, the C(9) acetoxy ketone undergoes transposition. This is an equilibrium process that goes to about 55% completion. An aldehyde was generated by ozonolysis of the terminal allylic double bond. This group was used to close the C-ring by an aldol cyclization in Step **I-1**. This step completed the construction of the

Scheme 13.56. Baccatin III Synthesis: P. A. Wender and Co-Workers^a

a. P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, C. Granicher, J. B. Houze, J. Janichen, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, T. P. Mucciaro, M. Muhlebach, M. G. Natchus, H. Paulsen, D. B. Rawlins, J. Satkofsky, A. J. Shuker, J. C. Sutton, R. E. Taylor, and K. Tomooka, *J. Am. Chem. Soc.*, **119**, 2755 (1997); P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, J. B. Houze, N. E. Krauss, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, M. G. Natchus, A. J. Shuker, J. C. Sutton, and R. E. Taylor, *J. Am. Chem. Soc.*, **119**, 2757 (1997).

carbon framework. The synthesis was completed by formation of the oxetane ring by the sequence I-3 to I-8, followed by the cyclization in Step J-1.

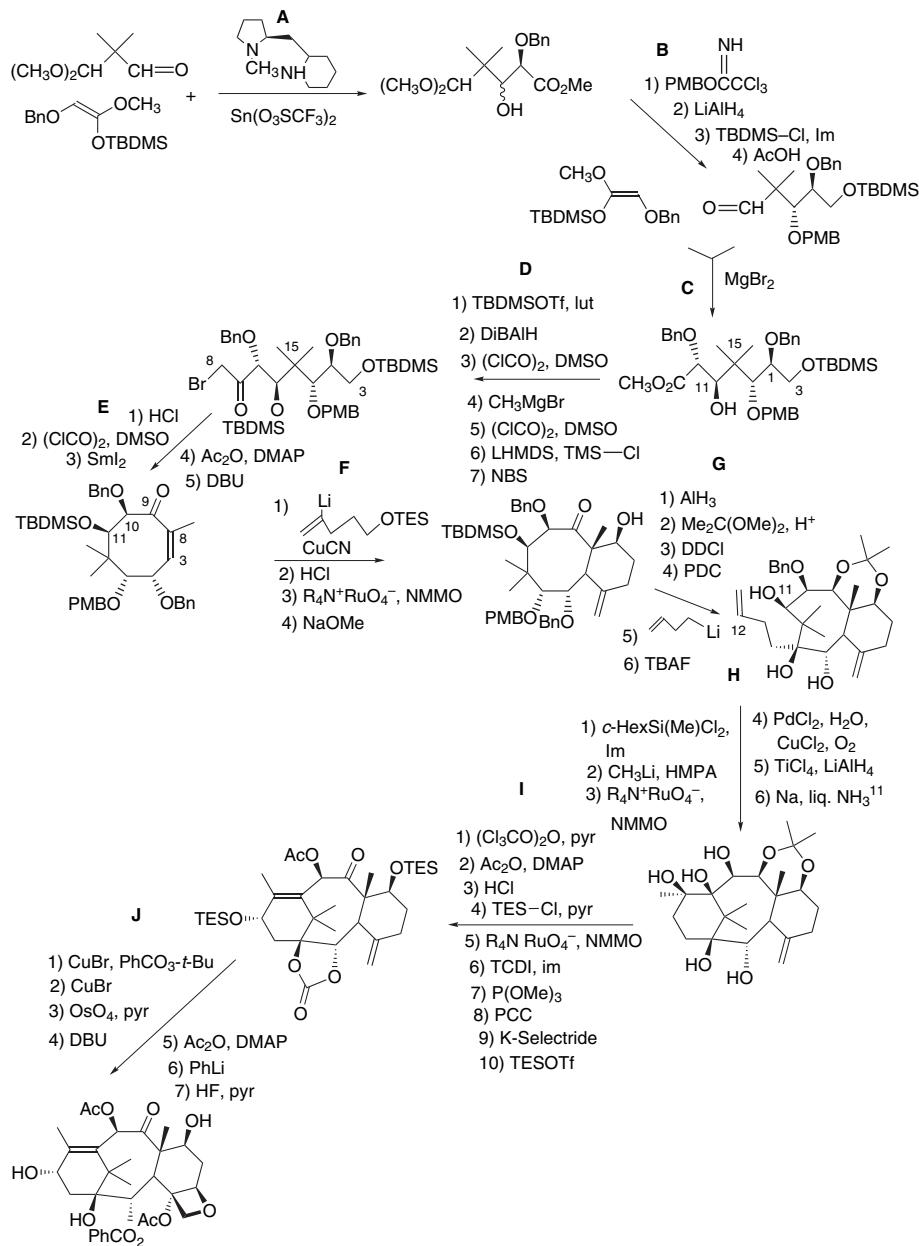
The synthesis of Baccatin III shown in Scheme 13.57, which was completed by a group led by the Japanese chemist Teruaki Mukaiyama, takes a different approach for the previous syntheses. Much of the stereochemistry was built into the B-ring by a series of acyclic aldol additions in Steps A through D. A silyl ketene acetal derivative

Scheme 13.57. Baccatin III Synthesis: T. Mukaiyama and Co-Workers^a

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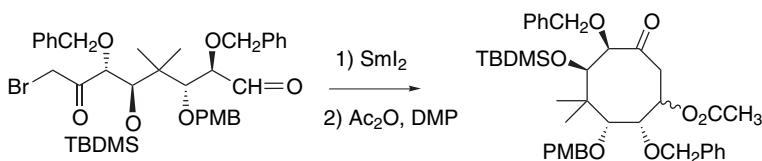
SECTION 13.2

Illustrative Syntheses

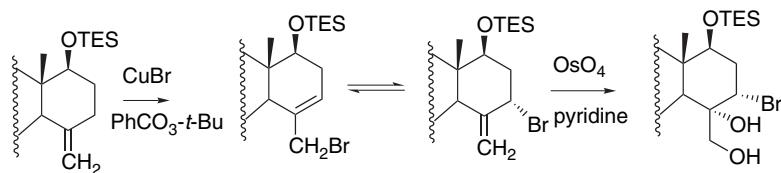


a. T. Mukaiyama, I. Shiina, H. Iwadare, M. Saitoh, T. Nishimura, N. Ohkawa, H. Sakoh, K. Nishimura, Y. Tani, M. Hasegawa, K. Yamada, and K. Saitoh, *Chem. Eur. J.*, **5**, 121 (1999).

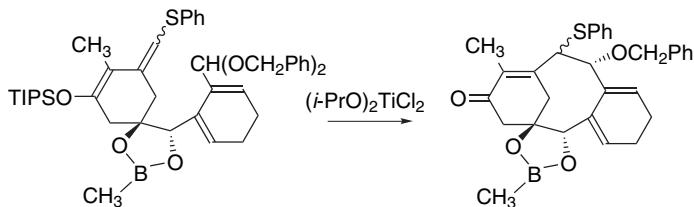
of methyl α -benzyloxyacetate served as the nucleophile in Steps A and C. The C(10)–C(11) bond is formed in Step C using MgBr_2 to promote the Mukaiyama addition, which forms the correct stereoisomer with 4:1 diastereoselectivity. The B-ring was closed in Step E-3 by a samarium-mediated cyclization, forming the C(3)–C(8) bond.



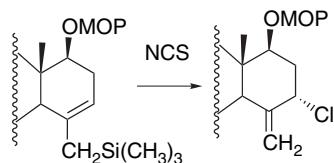
The C(4)–C(7) segment was added by a cuprate conjugate addition in Step F-1. The C-ring was then closed using an intramolecular aldol addition in Step F-4. The A-ring was closed by a Ti-mediated reductive coupling between carbonyl groups at C(11) and C(12) in Step H-5. The C(11)–C(12) double bond was introduced from the diol by deoxygenation of the thiocarbonate (Steps I-6 and I-7). The final sequence for conversion to Baccatin III, which began with a copper-mediated allylic oxidation at C(5), also involves an allylic rearrangement of the halide that is catalyzed by CuBr. The exocyclic double bond was then used to introduce the final oxygens needed to perform the oxetane ring closure.

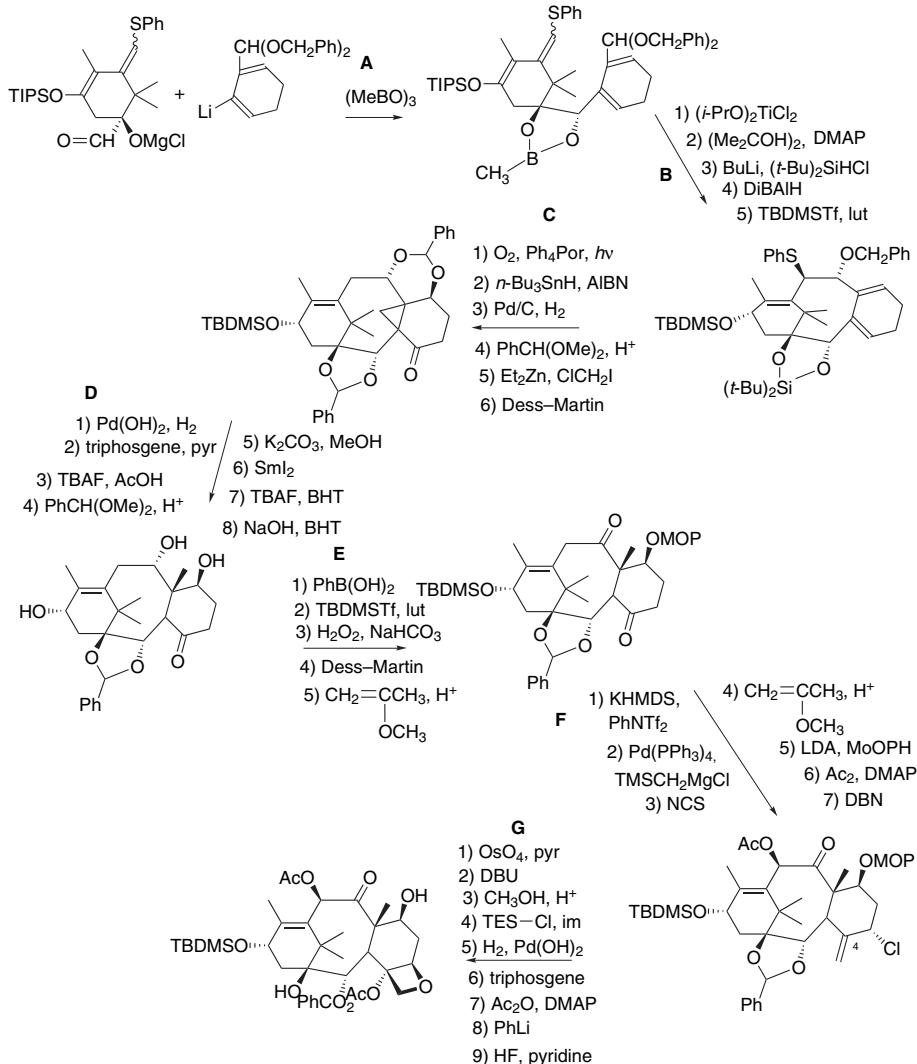


Another Japanese group developed the Baccatin III synthesis shown in Scheme 13.58. The eight-membered B-ring was closed early in the synthesis using a Lewis acid–induced Mukaiyama reaction (Step B-1), in which a trimethylsilyl dienol ether served as the nucleophile.



Oxygen was introduced at C(4) and C(7) by a singlet O₂ cycloaddition in Step C-1. The peroxide bond was cleaved and the phenylthio group removed by Bu₃SnH in Step C-2. The C(19) methyl group was introduced via a cyclopropanation in Step C-5, followed by a reduction in Step D-1. A Pd-catalyzed cross-coupling reaction was used to introduce a trimethylsilylmethyl group at C(4) via an enol triflate in Step F-2. The vinyl silane was then subjected to chlorination in Step F-3. The chlorine eventually serves as the leaving group for oxetane ring formation in Step G-2.





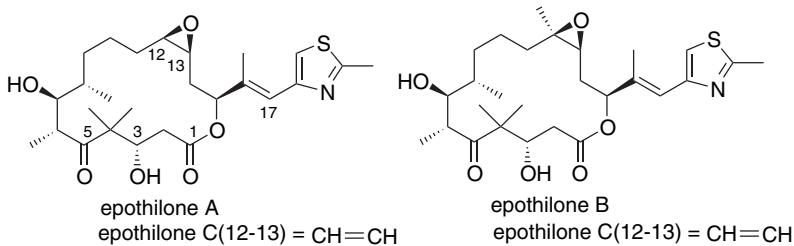
a. K. Morihara, R. Hara, S. Kawahara, T. Nishimori, N. Nakamura, H. Kusama, and I. Kuwajima, *J. Am. Chem. Soc.*, **120**, 12980 (1998); H. Kusama, R. Hara, S. Kawahara, T. Nishimori, H. Kashima, N. Nakamura, K. Morihara, and I. Kuwajima, *J. Am. Chem. Soc.*, **122**, 3811 (2000).

These syntheses of Baccatin III illustrate the versatility of current methodology for ring closure and functional group interconversions. The Holton, Nicolaou, Danishefsky, and Wender syntheses of Baccatin III employ various cyclic intermediates and take advantage of stereochemical features built into these rings to control subsequent reaction stereochemistry. As a reflection of the numerous oxygens in Baccatin III, each of the syntheses makes use of enolate oxidation, alkene hydroxylation, and related oxidation reactions. These syntheses also provide numerous examples of the selective use of protective groups to achieve distinction between the several hydroxy groups that are present in the intermediates. The Mukaiyama synthesis in Scheme 13.57 is somewhat different in approach in that it uses acyclic intermediates to introduce

several of the stereocenters. Perhaps because of the structure, none of these syntheses is particularly convergent. The Nicolaou, Danishefsky, and Kusama syntheses achieve some convergence by coupling the A-ring and the C-ring and then forming the B-ring. The Holton and Wender syntheses take advantage of available natural substances as starting materials.

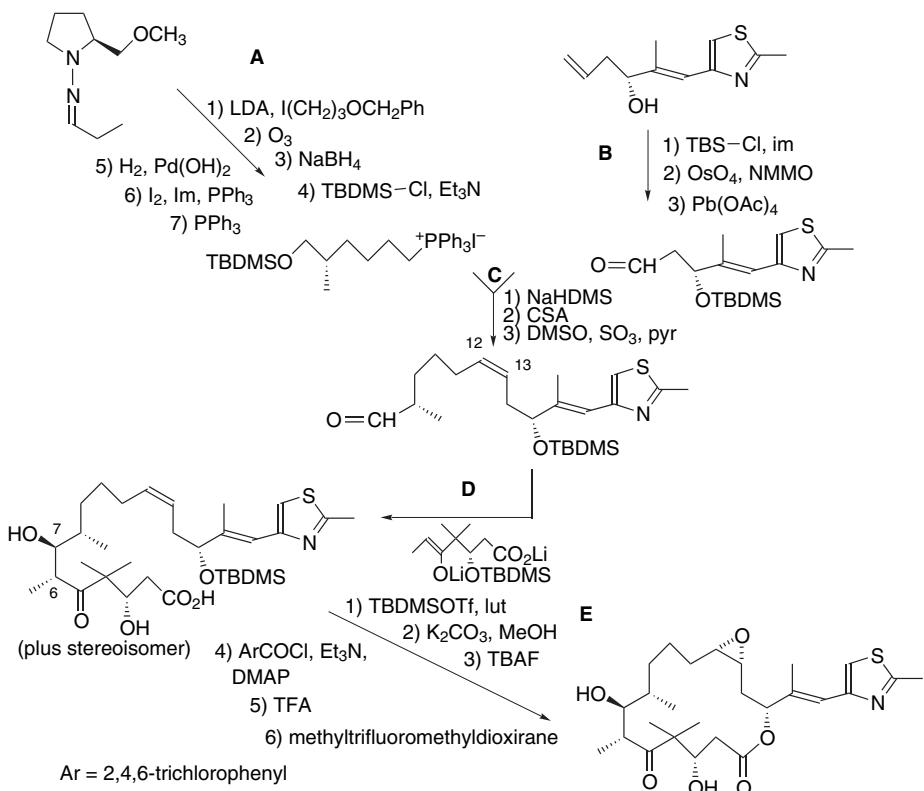
13.2.5. Epothilone A

The epothilones are natural products containing a 16-membered lactone ring that are isolated from mycobacteria. Epothilones A–D differ in the presence of the C(12)–C(13) epoxide and in the C(12) methyl group. Although structurally very different from Taxol, they have a similar mechanism of anticancer action and epothilone A and its analogs are of substantial current interest as chemotherapeutic agents.³⁶ Schemes 13.59 to 13.66 summarize eight syntheses of epothilone A. Several syntheses of epothilone B have also been completed.³⁷



Two critical objectives for planning the synthesis of epothilone A are the control of the configuration of the stereocenters and the closure of the 16-membered ring. There are eight stereocenters, including the C(16)–C(17) double bond. As the 16-membered lactone ring is quite flexible, it does not impose strong facial stereoselectivity. Instead, the stereoselective synthesis of epothilone A requires building the correct stereochemistry into acyclic precursors that are cyclized later in the synthesis. The stereocenters at C(3), C(6), C(7), and C(8) are adjacent to a potential aldol connection

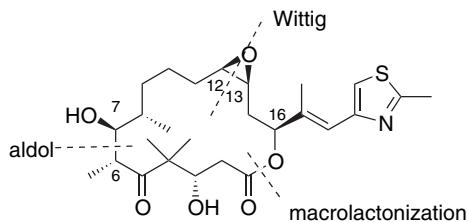
- ³⁶. T. C. Chou, X. G. Zhang, C. R. Harris, S. D. Kuduk, A. Balog, K. A. Savin, J. R. Bertino, and S. J. Danishefsky, *Proc. Natl. Acad. Sci. USA*, **95**, 15978 (1998).
- ³⁷. J. Mulzer, A. Mantoulidis, and E. Ohler, *Tetrahedron Lett.*, **39**, 8633 (1998); D. S. Sa, D. F. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, Y. H. Zheng, T.-C. Chou, L. He, and S. B. Horowitz, *Angew. Chem. Int. Ed. Engl.*, **36**, 757 (1997); A. Balog, C. Harris, K. Savin, S. G. Zhang, T. C. Chou, and S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.*, **37**, 2675 (1998); D. Shinzer, A. Bauer, and J. Schieber, *Synlett*, 861 (1998); S. A. May and P. A. Grieco, *J. Chem. Soc., Chem. Commun.*, 1597 (1998); K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, and Z. Yang, *J. Am. Chem. Soc.*, **119**, 7974 (1997); K. C. Nicolaou, D. Hepworth, M. R. V. Finlay, B. Wershkun, and A. Bigot, *J. Chem. Soc., Chem. Commun.*, 519 (1999); D. Schinzer, A. Bauer, and J. Schieber, *Chem. Eur. J.*, **5**, 2492 (1999); J. D. White, R. G. Carter, and K. F. Sundermann, *J. Org. Chem.*, **64**, 684 (1999); J. Mulzer, A. Moantoulidis, and E. Oehler, *J. Org. Chem.*, **65**, 7456 (2000); J. Mulzer, G. Karig, and P. Pojarliev, *Tetrahedron Lett.*, **41**, 7635 (2000); D. Sawada, M. Kanai, and M. Shibasaki, *J. Am. Chem. Soc.*, **122**, 10521 (2000); S. C. Sinha, J. Sun, G. P. Miller, M. Wartmann, and R. A. Lerner, *Chem. Eur. J.*, **7**, 1691 (2001); J. D. White, R. G. Carter, K. F. Sundermann, and M. Wartmann, *J. Am. Chem. Soc.*, **123**, 5407 (2001); H. J. Martin, P. Pojarliev, H. Kahlig, and J. Mulzer, *Chem. Eur. J.*, **7**, 2261 (2001); R. E. Taylor and Y. Chen, *Org. Lett.*, **3**, 2221 (2001); M. Valluri, R. M. Hindupur, P. Bijoy, G. Labadie, J.-C. Jung, and M. A. Avery, *Org. Lett.*, **3**, 3607 (2001); N. Martin and E. J. Thomas, *Tetrahedron Lett.*, **42**, 8373 (2001); M. S. Ermolenko and P. Potier, *Tetrahedron Lett.*, **43**, 2895 (2002); J. Sun and S. C. Sinha, *Angew. Chem. Int. Ed. Engl.*, **41**, 1381 (2002); J.-C. Jung, R. Kache, K. K. Vines, Y.-S. Zheng, P. Bijoy, M. Valluri, and M. A. Avery, *J. Org. Chem.*, **69**, 9269 (2004).



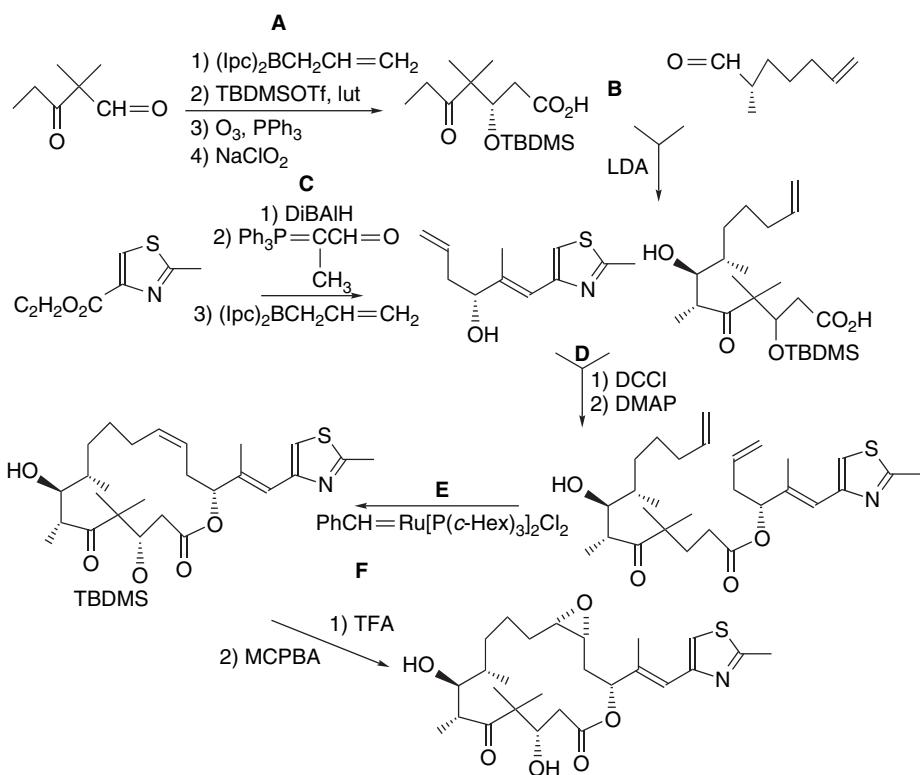
a. K. C. Nicolaou, F. Sarabia, S. Ninkovic, and Z. Yang, *Angew. Chem. Int. Ed. Engl.*, **36**, 525 (1997); K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, and Z. Yang, *J. Am. Chem. Soc.*, **119**, 7974 (1997).

between C(6) and C(7) and are amenable to control by aldol methodology. Introduction of the epoxide by epoxidation requires a Z-double bond. Several methods for ring closure have been used, but the two most frequently employed are macrolactonization (see Section 3.4) and alkene metathesis (see Section 8.4).

K. C. Nicolaou's group at Scripps Research Institute developed two synthetic routes to epothilone A. One of the syntheses involves closure of the lactone ring as a late step. Three major fragments were synthesized. The bond connection at C(6)–C(7) was made by an aldol reaction. The C(12)–C(13) bond was formed by a Wittig reaction and later epoxidized. The ring was closed by macrolactonization.



Scheme 13.60. Epothilone A Synthesis by Olefin Metathesis: K. C. Nicolaou and Co-Workers^a

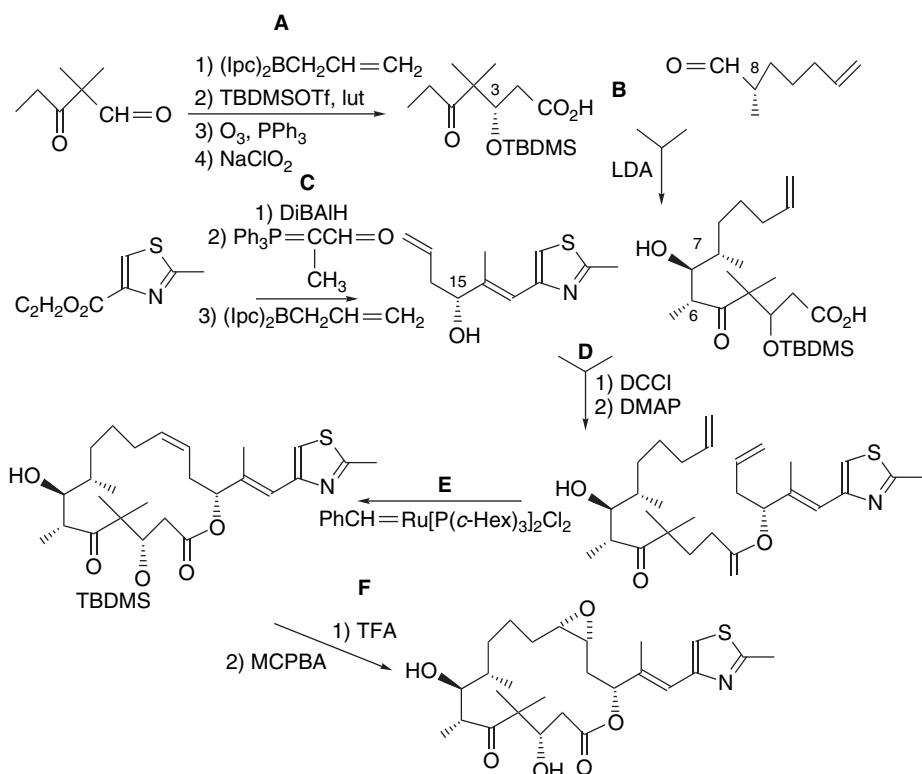


a. Z. Yang, Y. He, D. Vourloumis, H. Vallberg, and K. C. Nicolaou, *Angew. Chem. Int. Ed. Engl.*, **36**, 166 (1997).

This synthesis is shown in Scheme 13.59. Two enantiomerically pure starting materials were brought together by a Wittig reaction in Step C. The aldol addition in Step D was diastereoselective for the *anti* configuration, but gave a 1:1 mixture with the 6*S*, 7*R*-diastereomer. The stereoisomers were separated after Step E-2. The macrolactonization (Step E-4) was accomplished by a mixed anhydride (see Section 3.4.1). The final epoxidation was done using 3-methyl-3-trifluoromethyl dioxirane.

The second synthesis from the Nicolaou group is shown in Scheme 13.60. The disconnections were made at the same bonds as in the synthesis in Scheme 13.59. The C(1)–C(6) segment contains a single stereogenic center, which was established in Step A-1 by enantioselective allylboration. The C(6)–C(7) configuration was established by the aldol addition in Step B. The aldolization was done with the dianion and gave a 2:1 mixture with the 6*S*, 7*R* diastereomer. The two fragments were brought together by esterification in Step D. The synthesis used an olefin metathesis reaction to construct the 16-membered ring (Step E). This reaction gave a 1.4:1 ratio of *Z:E* product, which was separated by chromatography.

The olefin metathesis reaction was also a key feature of the synthesis of epothilone A completed by a group at the Technical University in Braunschweig, Germany (Scheme 13.61). This synthesis employs a series of stereoselective additions to create the correct substituent stereochemistry. Two enantiomerically pure starting materials



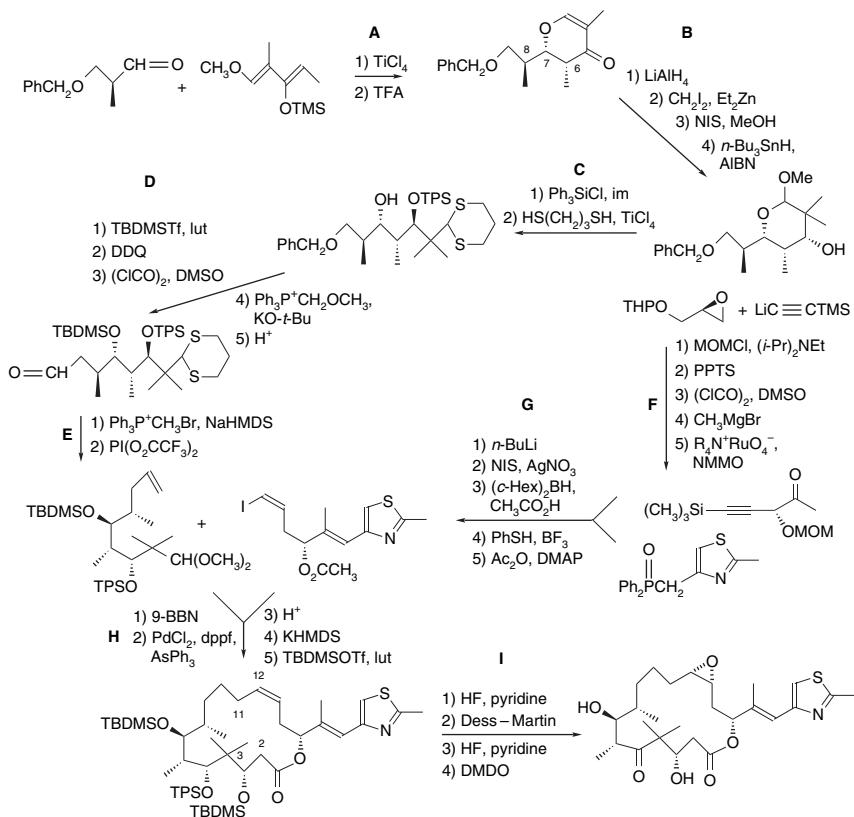
a. D. Schinzer, A. Limberg, A. Bauer, O. M. Bohm, and M. Cordes, *Angew. Chem. Int. Ed. Engl.*, **36**, 523 (1997); D. Schinzer, A. Bauer, O. M. Bohm, A. Limberg, and M. Cordes, *Chem. Eur. J.*, **5**, 2483 (1999).

were used, containing the C(3) and C(8) stereocenters. Step **B** used a stereoselective aldol addition to bring these two fragments together and to create the stereocenters at C(6) and C(7). The thiazole ring and the C(13)–C(15) fragment were constructed in sequence **C**. The configuration at C(15) was established by enantioselective allylboration in Step **C-3**. The two segments were coupled by esterification at Step **D**, and the ring was closed by olefin metathesis (Step **E**). The metathesis reaction gave a 1.7:1 ratio favoring the Z-isomer. The synthesis was completed by deprotection and epoxidation, after which the stereoisomers were separated by chromatography. This group has also completed a synthesis based on a macrolactonization approach.³⁸

Samuel Danishefsky's group at the Sloan Kettering Institute for Cancer Research in New York has also been active in the synthesis of the natural epothilones and biologically active analogs. One of their syntheses also used the olefin metathesis reaction (not shown). The synthesis in Scheme 13.62 used an alternative approach to create the macrocycle, as indicated in the retrosynthetic scheme. The stereochemistry at C(6), C(7), and C(8) was established by a TiCl_4 -mediated cyclocondensation (Step **A**). The thiazole-containing side chain was created by reaction sequences **F** and **G**. The

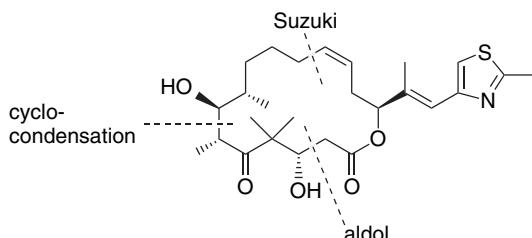
³⁸ D. Schinzer, A. Bauer, and J. Schieber, *Chem. Eur. J.*, **5**, 2483 (1999).

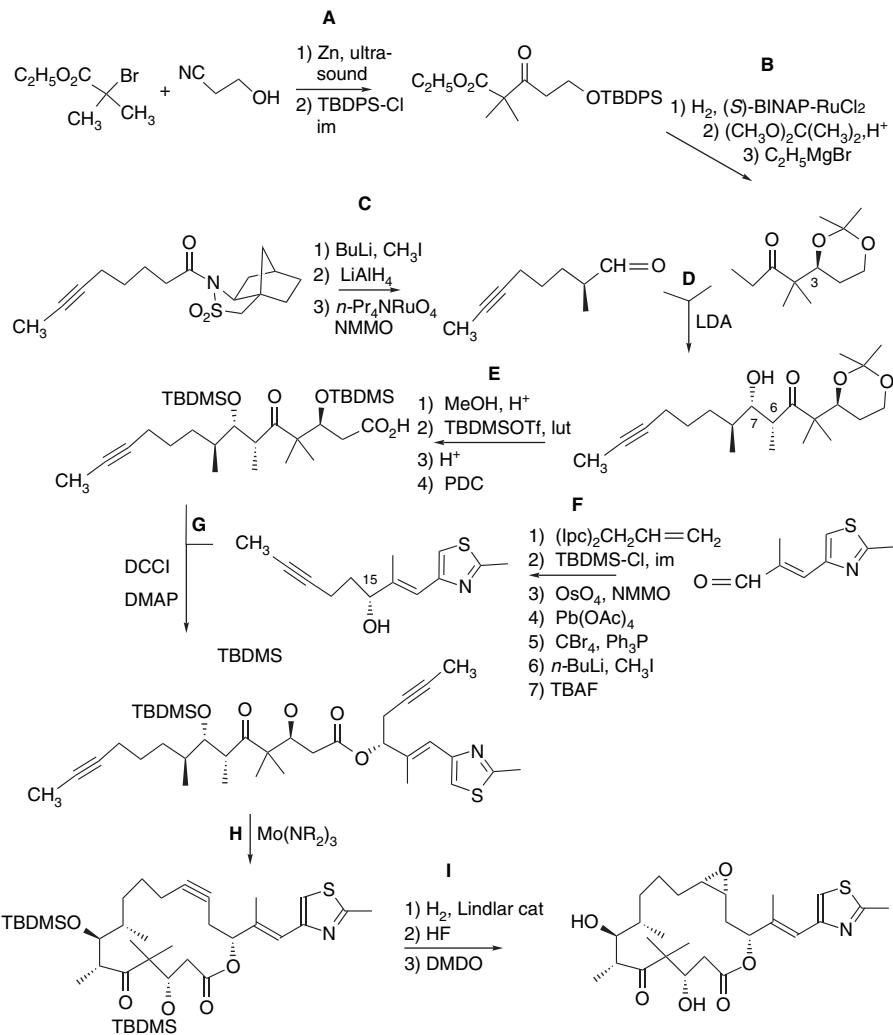
Scheme 13.62. Epothilone A Synthesis by Macroaldol Cyclization: S. J. Danishefsky and Co-Workers^a



a. A. Balog, D. Meng, T. K. Kamenecka, P. Bertinato, D.-S. Su, E. J. Sorensen, and S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl.*, **35**, 2801 (1996); D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen, and S. J. Danishefsky, *J. Am. Chem. Soc.*, **119**, 10073 (1997).

Z-vinyl iodide was obtained by hydroboration and protonolysis of an iodoalkyne. The two major fragments were coupled by a Suzuki reaction at Steps **H**-1 and **H**-2 between a vinylborane and vinyl iodide to form the C(11)–C(12) bond. The macrocyclization was done by an aldol addition reaction at Step **H**-4. The enolate of the C(2) acetate adds to the C(3) aldehyde, creating the C(2)–C(3) bond and also establishing the configuration at C(3). The final steps involve selective deprotection and oxidation at C(5), deprotection at C(3) and C(7), and epoxidation.

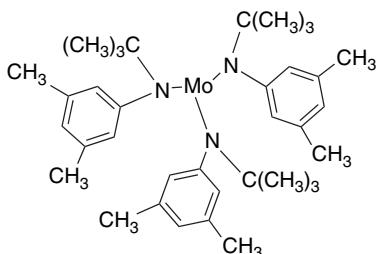




a. A. Furstner, C. Mathes, and C. W. Lehmann, *Chem. Eur. J.*, **7**, 5299 (2001).

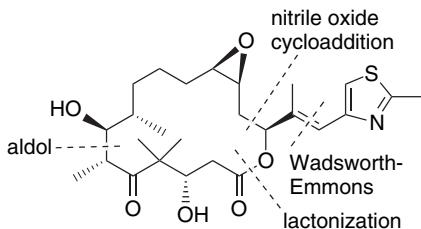
The epothilone A synthesis shown in Scheme 13.63 involves an *alkyne metathesis reaction*. The first subunit was constructed using a Reformatsky-type addition to 3-hydroxypropanonitrile. The configuration at C(3) was established by an enantioselective hydrogenation using (S)-(BINAP)RuCl² under acidic conditions. A bornane-sultam chiral auxiliary was used to establish the stereochemistry at C(8) by alkylation (Step C-1). The stereochemistry at the C(6)-C(7) bond was established by an aldol addition at Step D. The thiazole segment was constructed from a conjugated enal, which was subjected to enantioselective allylboration using (+)-Ipc₂BCH₂CH=CH₂ in Step F-1. This reaction established the configuration at C(5). A terminal alkyne was then installed by the Corey-Fuchs procedure (see p. 835). The lithium acetylide was methylated in situ using CH₃I. A DMAP-DCCI esterification was then used to couple the two major fragments and set the stage for the alkyne metathesis at Step H. The

catalyst is a molybdenum amide, which is one of a family of catalysts that show good activity in alkyne metathesis. The use of alkyne metathesis avoids the complication of formation of both *Z*- and *E*-isomers, which sometimes occurs in olefin metathesis.

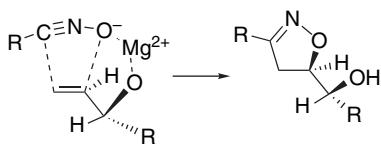


The yield in the metathesis reaction was 80% and was followed by a Lindlar reduction. The synthesis was completed by epoxidation with DMDO.

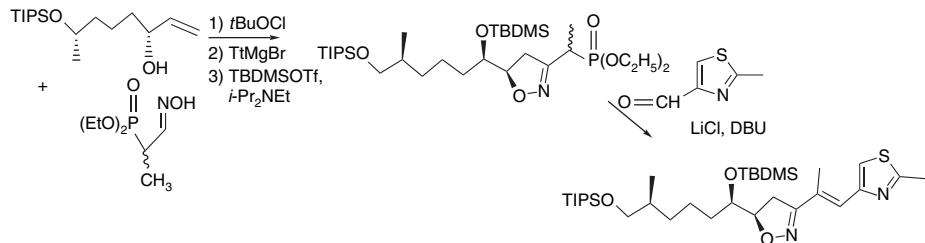
The synthesis in Scheme 13.64 was carried out by E. Carreira and co-workers at ETH in Zurich, Switzerland. A key step in the synthesis in Scheme 13.64 is a stereoselective cycloaddition using a phosphonyl-substituted nitrile oxide, which was used to form the C(16)–C(17) bond and install the C(15) oxygen.



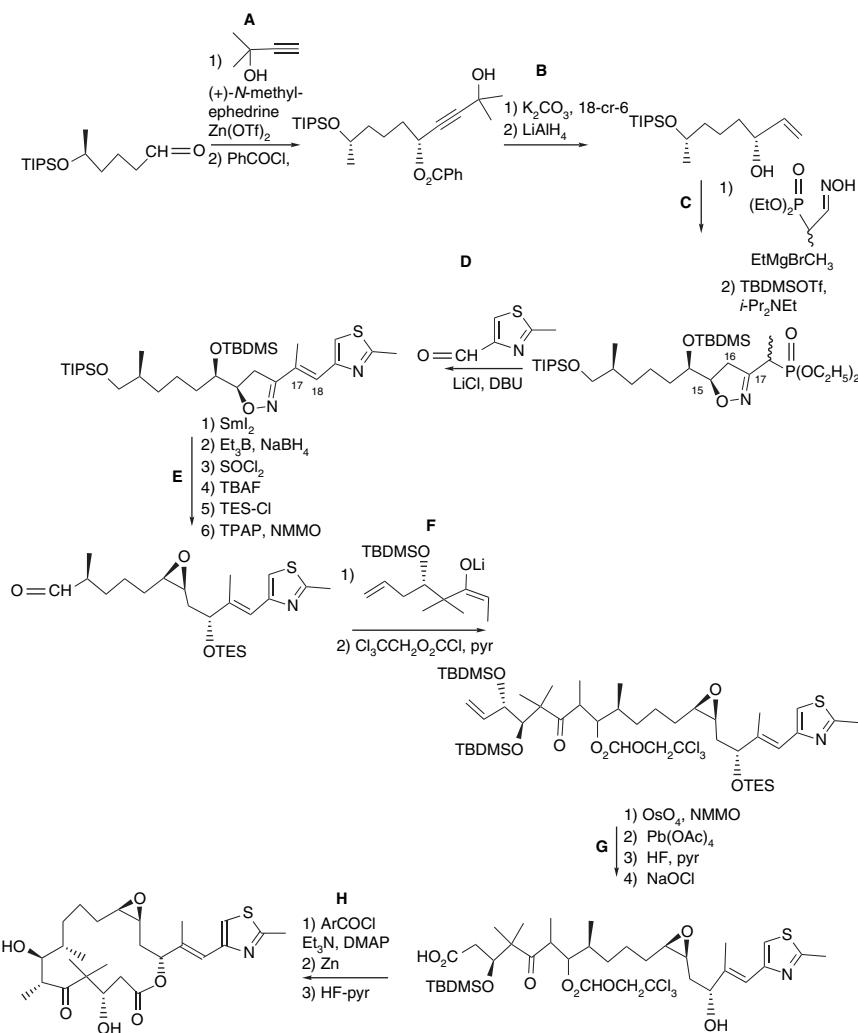
The C(6)–C(15) segment was synthesized by Steps **C-1** and **C-2**. The stereoselectivity of the cycloaddition reaction between the nitrile oxide and allylic alcohol is the result of a chelated TS involving the Mg alkoxide.³⁹



After the cycloaddition, the thiazole ring was introduced via a Wadsworth-Emmons reaction at Step **D**, forming the C(17)–C(18) bond.

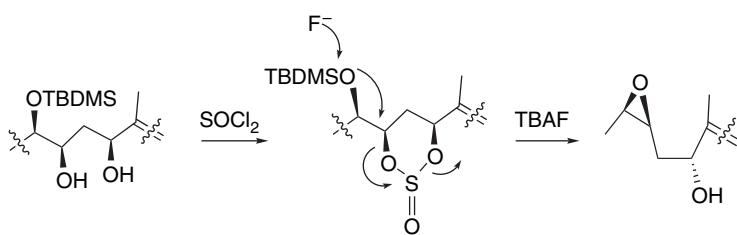


³⁹. S. Kanemasa, M. Nishiuchi, A. Kanimura, and K. Hori, *J. Am. Chem. Soc.*, **116**, 2324 (1994); S. Fukuda, A. Kanimura, S. Kanemasa, and K. Hori, *Tetrahedron*, **56**, 1637 (2000).

Scheme 13.64. Epothilone A Synthesis: J. W. Bode and E. M. Carreira^a

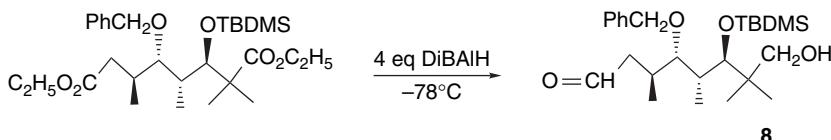
a. J. W. Bode and E. M. Carreira, *J. Am. Chem. Soc.*, **123**, 3611 (2001); *J. Org. Chem.*, **66**, 6410 (2001).

The reduction of the isoxazoline ring after the cycloaddition was not successful with the usual reagents (see p. 532), but SmI₂ accomplished the reaction. In contrast to the epoxidation used as the final step in most of the other epothilone A syntheses, the epoxide was introduced through a sulfite intermediate. Deprotection of C(15) leads to intramolecular displacement at the sulfite with formation of the epoxide (Steps E-3 and E-4).



The C(1)–C(6) and C(7)–C(17) fragments were joined by an aldol addition via a lithium enolate (Step F-1), and the ring was closed by a macrolactonization.

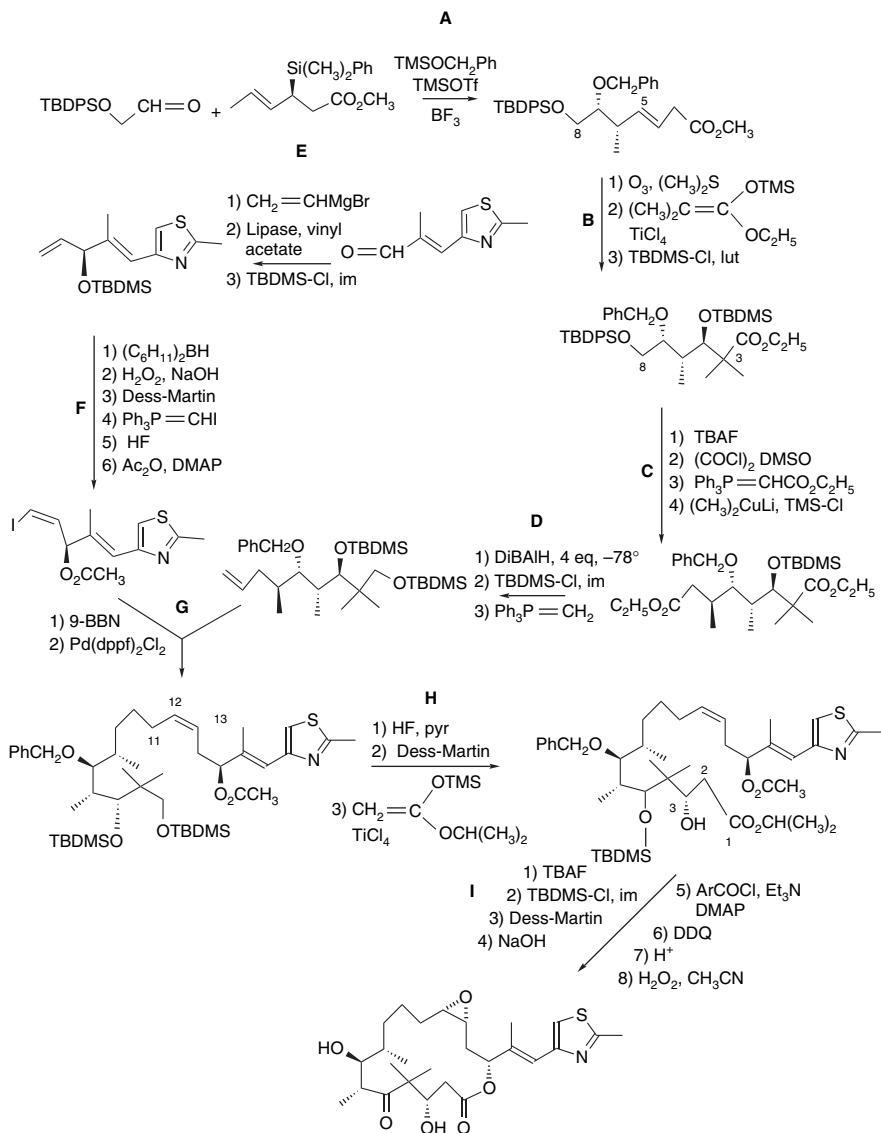
The synthesis of epothilone A in Scheme 13.65 features the use of chiral allylic silanes that were obtained by kinetic resolution using *Pseudomonas* AK lipase. The C(5)–C(8) fragment was synthesized by condensing the enantiomerically pure silane with a TBDPS-protected aldehyde in the presence of BF_3 . The adduct was then subjected to a chelation-controlled aldol addition using TiCl_4 , adding C(3) and C(4). After protecting group manipulation and oxidation, the chain was extended by two carbons using a Wittig reaction in Step C-3. The methyl group at C(8) was added by a stereoselective cuprate conjugate addition in Step C-4. The intermediate was then converted to **8** using a DiBALH reduction under conditions that discriminated between the two ester groups (Step D-1). The more hindered group was reduced to the primary alcohol, leaving the less hindered one at the aldehyde level. This selectivity probably arises as a result of the lesser stability of the more hindered partially reduced intermediate. (See p. 401 to review the mechanism of DiBALH reduction.)



The aldehyde was then converted to the terminal alkene via a Wittig reaction (Step D-3).

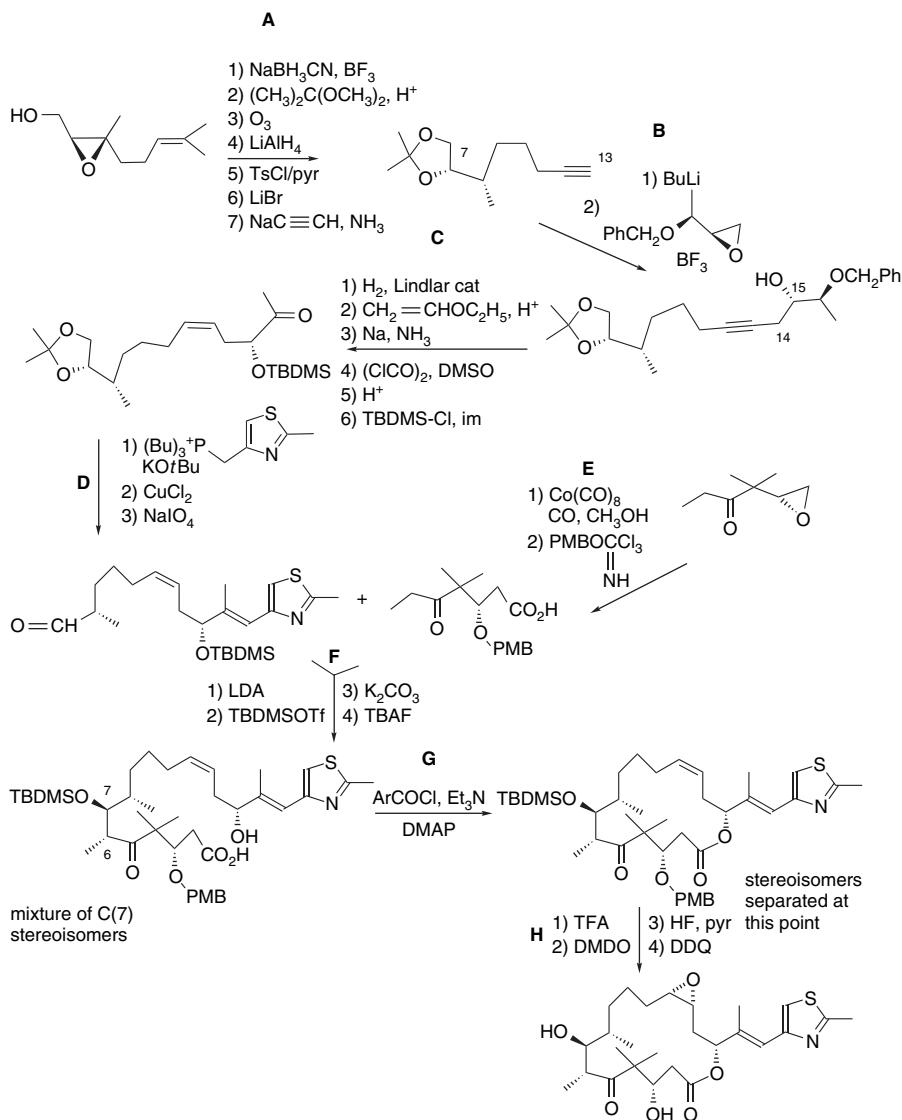
A kinetic resolution was also used to establish the configuration of the thiazole portion. An allylic aldehyde was subjected to kinetic resolution by ester exchange with vinyl acetate in Step E-2 (see Topic 2.2, Part A). The resolved alcohol was protected and subjected to hydroboration, oxidation, and a Wittig reaction to introduce the Z-vinyl iodide. The two fragments were coupled using the Suzuki reaction and the final two carbons were installed by another TiCl_4 -mediated silyl ketene acetal addition in sequence H. The stereochemistry at C(3) presented some problems, but use of the silyl ketene acetal of the isopropyl ester provided an 8:1 mixture favoring the desired diastereomer. The isopropyl ester was used to slow competing lactonization of the intermediate. The macrolactonization was done under the Yamaguchi conditions. The synthesis was completed by epoxidation using the peroxyimidic acid generated in situ from acetonitrile and hydrogen peroxide.

The synthesis shown in Scheme 13.66 starts with the Sharpless asymmetric epoxidation product of geraniol. The epoxide was opened with inversion of configuration by $\text{NaBH}_3\text{CN}\text{-BF}_3$. The double bond was cleaved by ozonolysis and converted to the corresponding primary bromide. The terminal alkyne was introduced by alkylation of



a. B. Zhu and J. S. Panek, *Eur. J. Org. Chem.*, 1701 (2001).

sodium acetylide, completing the synthesis of the C(7)–C(13) segment (Steps A-4 to A7). The BF_3 -mediated epoxide ring opening in Step B-2 occurred with inversion of configuration, establishing the configuration at C(15). The Z-stereochemistry at the C(12)–C(13) double bond was established by reduction over a Lindlar catalyst. An EE protecting group was used during the Swern oxidation (Step C-4) but then replaced by a TBDMS group for the Wittig reaction and beyond. The chirality of the C(1)–C(6) segment was established by a kinetic resolution of an epoxide by selective ring opening

Scheme 13.66. Epothilone A Synthesis: Z.-Y. Liu and Co-Workers^a

a. Z.-Y. Liu, Z.-C. Chen, C.-Z. Yu, R.-F. Wang, R.-Z. Zhang, C.-S. Huang, Z. Yan, D.-R. Cao, J.-B. Sun, and G. Li, *Chem. Eur. J.*, **8**, 3747 (2002).

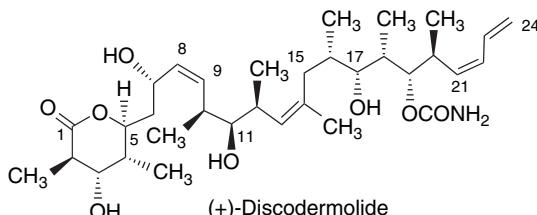
catalyzed by a chiral salen-Co(III) complex.⁴⁰ The resolved epoxide was converted to an ester by a $\text{Co}_2(\text{CO})_8$ -catalyzed carbonylation in Step E-1. The C(6)–C(7) bond was formed by an aldol reaction of a *dianion* of the intermediate. The product was a 1:1 mixture of diastereomers. After protecting group manipulations, this adduct was cyclized by macrolactonization. The two diastereomers were separated prior to completion of the synthesis by deprotection and epoxidation.

⁴⁰ M. Tokunaga, J. F. Larwo, F. Kakiuchi, and E. N. Jacobsen, *Science*, **277**, 936 (1997).

Although each of the epothilone syntheses has its unique features, there are several recurring themes. Each synthesis uses one or more enantiopure compound as a starting material. All except the Danishefsky synthesis in Scheme 13.62 utilize the ester bond as a major disconnection. Most also use the C(12)–C(13) double bond as a second major disconnection, and several make the synthetic connection by the alkene (or alkyne) metathesis reaction. Others make the C(11)–C(12) disconnection and use a Suzuki coupling reaction in the synthetic sense to form the C(10)–C(11) bond. Wittig reactions figure prominently in the assembly of the thiazole-containing side chain. The configuration of the isolated stereocenter at C(15) is established by use of an enantiopure starting material (Schemes 13–59, 13–62, 13–64, and 13–66), an enantioselective reagent (Schemes 13–60, 13–61, and 13–63), or a kinetic resolution (Scheme 13–65). The stereochemical issues present are in the C(3)–C(8) segment and are addressed mainly by aldol reaction stereoselectivity.

13.2.6. Discodermolide

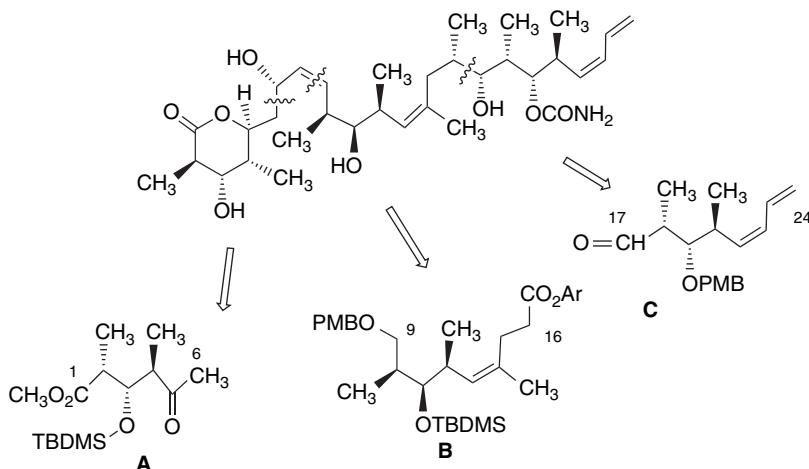
(+)-Discodermolide is a natural product isolated from a deep-water sponge found in the Caribbean Sea. The compound is probably produced by a symbiotic microorganism and isolation is not currently a practical source of the material. Like Taxol and epothilone A, (+)-discodermolide is a microtubule stabilizing agent with a promising profile of antitumor activity. A significant feature of the discodermolide structure is the three CH₃-OH-CH₃ triads that establish the configuration of nine stereogenic centers. The C(2)–C(4) and C(18)–C(20) triads are *syn*, *anti*, whereas the C(10)–C(12) triad is *anti*, *syn*. Seven syntheses are described here. Recently, major elements of two of these syntheses have been combined to provide sufficient material for Phase I clinical trials of (+)-discodermolide.



The first (+)-discodermolide synthesis was completed by Stuart Schreiber's group at Harvard University and is outlined in Scheme 13.68. This synthesis was carried through for both enantiomers and established the absolute configuration of the natural material. The retrosynthetic plan outlined in Scheme 13.67 emphasizes the stereochemical triads found at C(2)–C(4), C(10)–C(12) and C(18)–C(20) and was designed to use a common chiral starting material. Each of the segments contains one of the stereochemical triads.

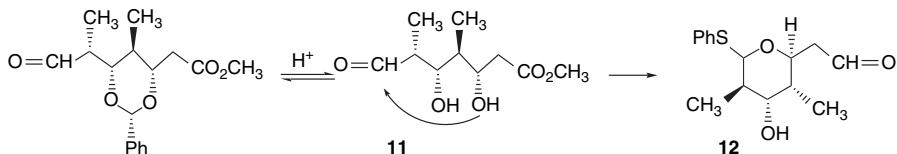
The starting material for the synthesis, methyl (*S*)-3-hydroxy-2-methylpropanoate, was converted to the corresponding aldehyde by reduction. The aldehyde was then converted to the diastereomeric homoallylic alcohols **9** and **10** using a chiral crotonylboronate (Scheme 13.68). The stereochemistry at C(5) was established by formation of the phenyldioxane ring by conjugate addition of a hemiacetal intermediate in Step A-3. After oxidation of C(1) to the aldehyde level the compound was rearranged to **11**, which eventually furnished the lactone terminus. The aldehyde group was introduced

Scheme 13.67. Retrosynthetic Analysis of (+)-Discodermolide to Fragments containing Stereotriads^a



a. D. T. Hung, J. B. Nerenberg, and S. L. Schreiber, *J. Am. Chem. Soc.*, **118**, 11054 (1996).

prior to coupling by reductions of the *N*-methyl-*N*-methyl amide by LiAlH₄ (Steps **B**-5 to **B**-7). This fragment was carried through most of the synthesis as the corresponding phenylthio acetal.



The stereoisomeric alcohol **10** was converted to the C(9)–C(15) fragment by a Z-selective Wadsworth-Emmons reaction, followed by reduction of the ester group in Steps **C**-1 to **C**-4. The alcohol was protected as the pivalate ester and then converted to a terminal alkyne using dimethyl diazomethylphosphonate. The C(1)–C(7) and C(8)–C(15) fragments were coupled by a Ni-catalyzed Cr(II) reaction in Step **E**. After reduction to the Z-alkene, the allylic alcohol was converted to the bromide via a mesylate. This set the stage for coupling with the C(16)–C(24) segment by enolate alkylation. The C(16) methyl group was installed at this point by a second alkylation (Step **H**-2). When the alkylation was carried out with this methyl group already in place, the C(16) epimer of (+)-discodermolide was obtained. The final conversion to (+)-discodermolide was achieved after carbamoylation of the C(19) hydroxy group. This group promoted stereoselective reduction at C(17) using a bulky hydride reducing agent. Deprotection then gave (+)-discodermolide.

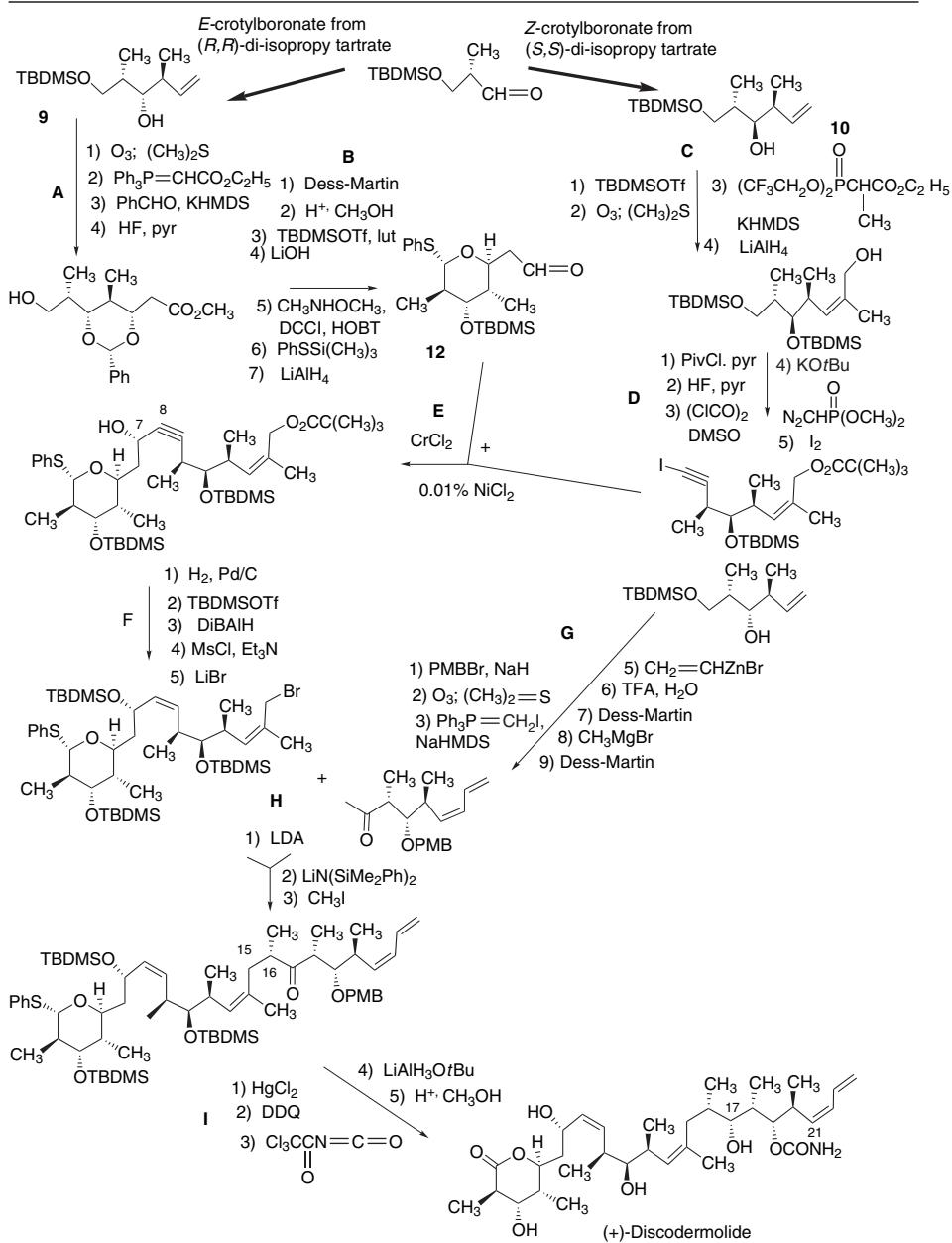
The synthesis of (+)-discodermolide in Scheme 13.69 was completed in James Marshall's laboratory at the University of Virginia and applies allenylmetal methodology at key stages. The starting material was O-protected (*S*)-3-hydroxy-2-methylpropanal. An enantiopure butynyl mesylate was the other starting material. The CH₃–OH–CH₃ stereochemical triad was established by addition to the aldehyde using Pd-catalyzed reaction with an allenyl zinc reagent generated from a butenyl

Scheme 13.68. Synthesis of Discodermolide: S. L. Schreiber and Co-Workers^a

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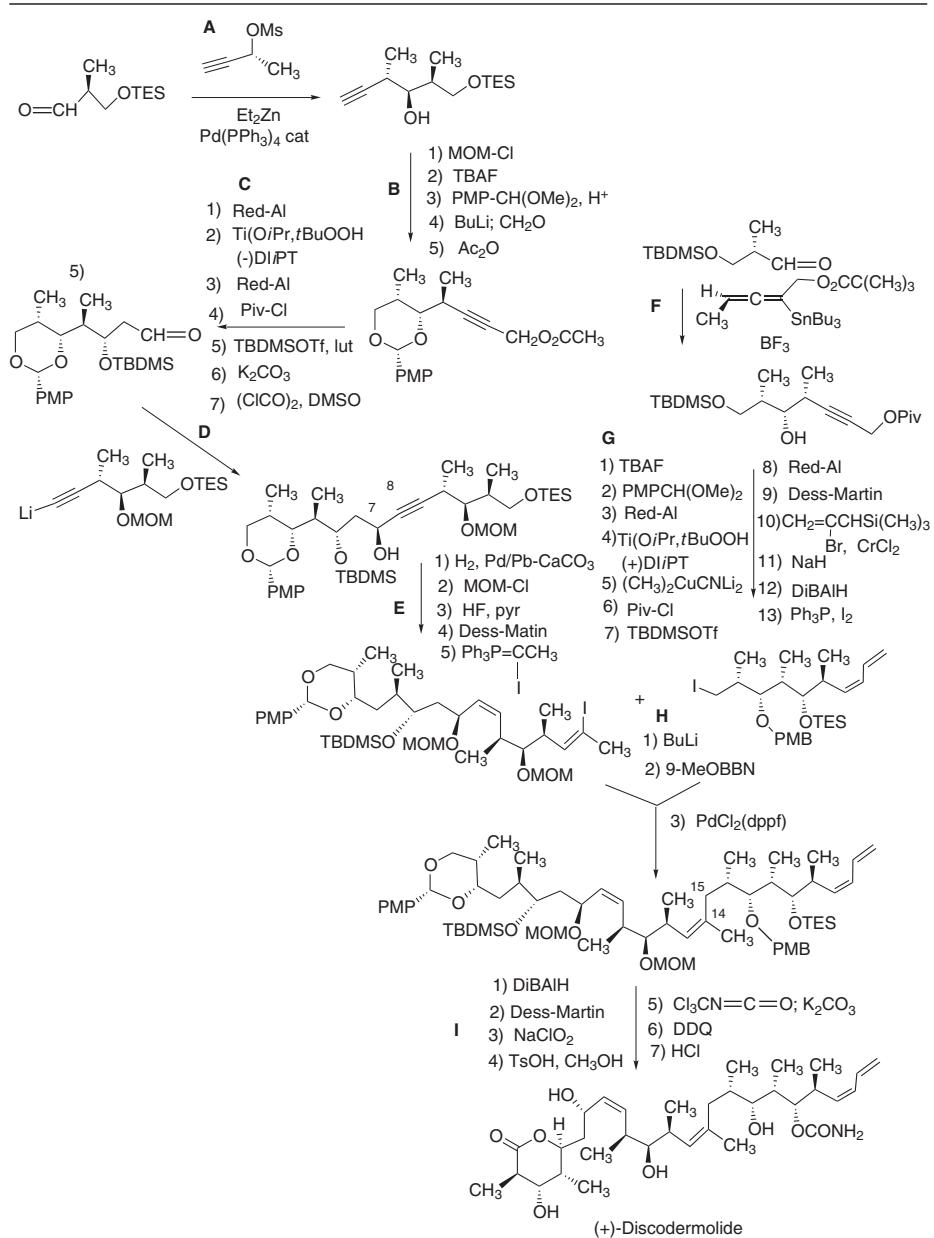
SECTION 13.2

Illustrative Syntheses



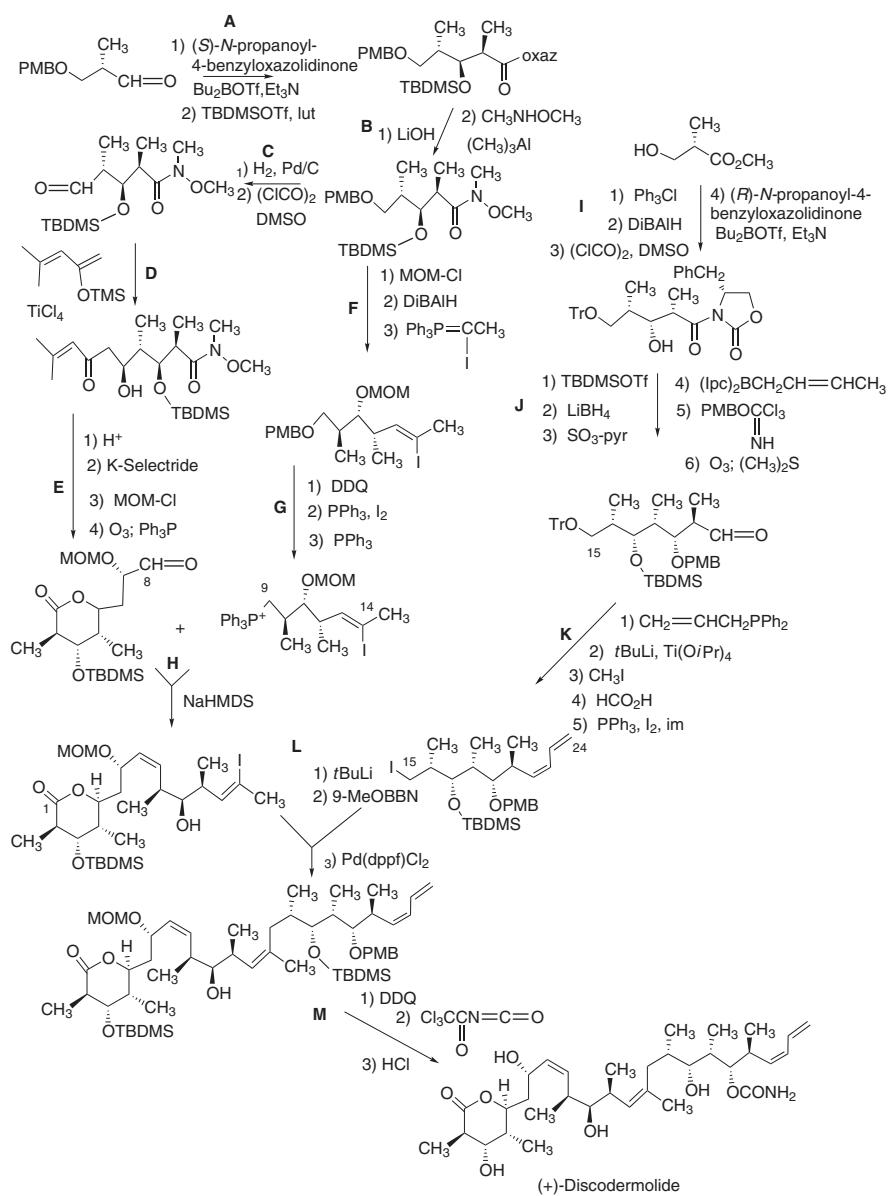
a. D. T. Hung, J. B. Nerenberg, and S. L. Schreiber, *J. Am. Chem. Soc.*, **118**, 11054 (1996).

mesylate (Step A). The adduct was cyclized as a 1,3-dioxane and further elaborated to an aldehyde intermediate. Reduction to an allylic alcohol by Red-Al was followed by Sharpless epoxidation. The epoxide was opened by a second Red-Al reduction. After protecting group manipulation, the aldehyde functional group was obtained by Swern oxidation. (Steps C-1 to C-7). This aldehyde was coupled

Scheme 13.69. Discodermolide Synthesis: J. A. Marshall and Co-Workers^a

a. J. A. Marshall, Z.-H. Lu, and B. A. Johns, *J. Org. Chem.*, **63**, 817 (1998); J. A. Marshall and B. A. Johns, *J. Org. Chem.*, **63**, 7885 (1998).

with a protected alkyne, forming the C(7)–C(8) bond (Step D). Reduction with a Lindlar catalyst gave the Z-double bond, which provided C(1)–C(13) of the discodermolide skeleton with the correct stereochemistry. A terminal vinyl iodide including C(14) and its methyl substituent was introduced by a Wittig reaction using 1-iodoethylidenetriphenylphosphorane.



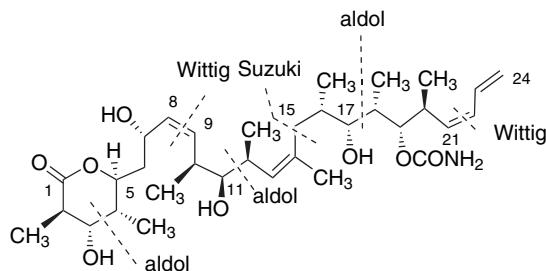
a. A. B. Smith, III, B. S. Freeze, M. Xian, and T. Hirose, *Org. Lett.*, **7**, 1825 (2005).

The C(15)–C(24) segment was constructed by addition of a chiral allenylstannane reagent to the starting aldehyde in Step F. The propargyl acetate terminus was reduced by DiBAIH, giving an allylic alcohol that was subjected to Sharpless asymmetric epoxidation. The methyl substituent at C(20) was added by nucleophilic opening of the epoxide with dimethylcyanocuprate. This segment was extended to include the terminal diene unit in G-9 and G-10. The terminal diene unit was

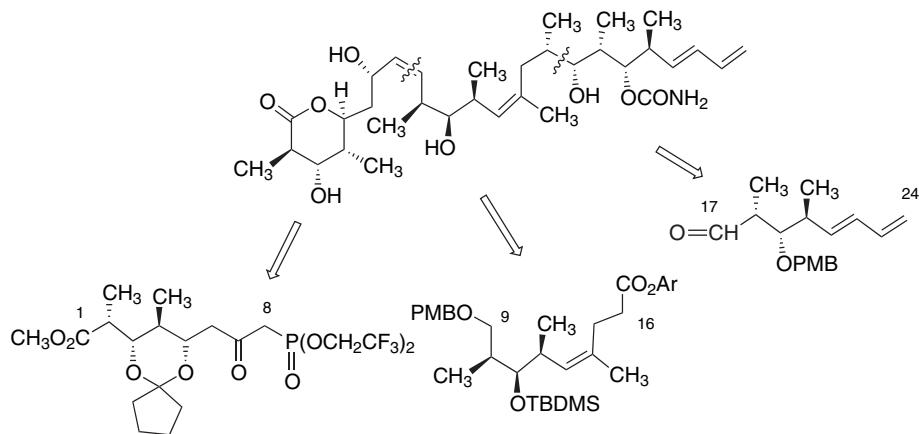
introduced by CrCl_2 -mediated addition in Step **G-10**, followed by base-induced elimination from the β -hydroxysilane.

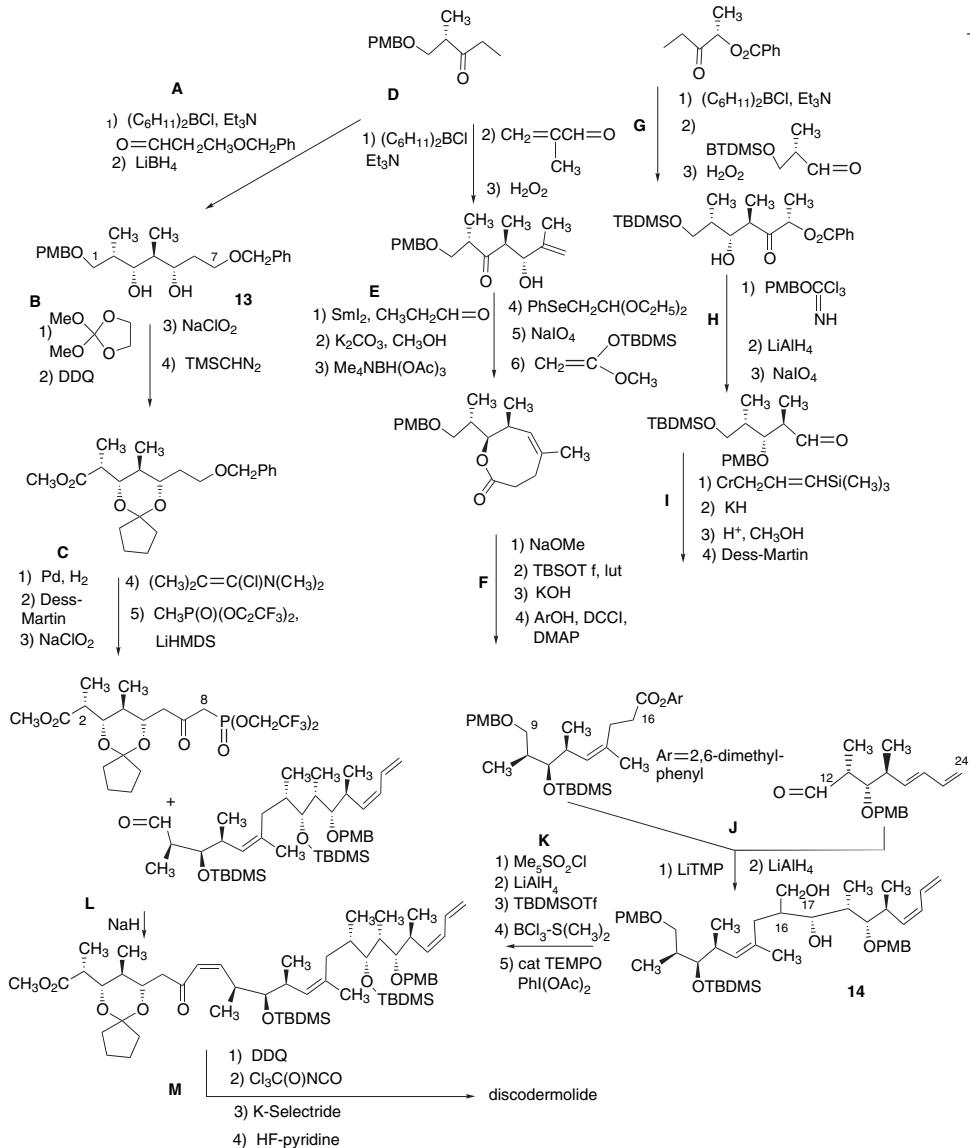
The two major subunits were coupled by a Suzuki reaction in Step **H-3**. The synthesis was then completed by reductive opening of the 1,3-dioxane ring, oxidation of the terminal alcohol to the carboxylic acid, carbamoylation, deprotection, and lactonization.

The synthesis of discodermolide in Scheme 13.70 was developed by A. B. Smith, III, and co-workers at the University of Pennsylvania. The synthesis shown in the scheme, which is the result of refinement of several previous syntheses from this laboratory, used a common precursor prepared in Steps **A** and **B**. The stereochemistry of the fragments was established by use of oxazolidinone chiral auxiliaries. The boron enolate of *N*-propanoyl-4-benzylloxazolidinone was added to PMP-protected (*S*)-3-hydroxy-2-methylpropanal in Step **A**. The chiral auxiliary was then replaced by an *N*-methoxy-*N*-methylamide in Step **B**. This intermediate was used for the construction of the C(1)–C(8) and C(9)–C(14) segments. The connection between these two fragments was made by a Wittig reaction at Step **H**. The C(15)–C(21) segment was also derived from an oxazolidinone chiral auxiliary, in this case the (*R*)-enantiomer. The configuration at C(20) was established by allylboration (Step **J-4**). The terminal diene was introduced by a Wittig reaction in Step **K-1**. The two major segments were then coupled at the C(14)–C(15) bond by using the Suzuki reaction in Step **L**. The final steps involve deprotection and installation of the carbamoyl group. The overall yield for this version is 9% with a longest linear sequence of 17 steps.



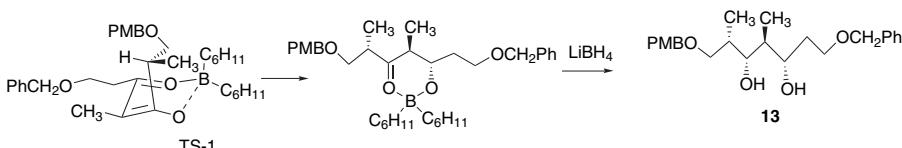
Scheme 13.71 shows the most recent version of a synthesis of (+)-discodermolide developed by Ian Paterson's group at Cambridge University. The synthesis was based on three major subunits and used boron enolate aldol addition reactions to establish the stereochemistry.





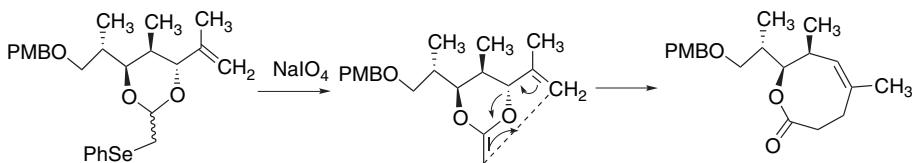
a. I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, and N. Sereinig, *J. Am. Chem. Soc.*, **123**, 9535 (2001); I. Paterson, O. Delgado, G. J. Florence, I. Lyother, J. P. Scott, and N. Sereinig, *Org. Lett.*, **5**, 35 (2003); I. Paterson and I. Lyother, *J. Org. Chem.*, **70**, 5494 (2005).

The synthesis of the C(1)–C(6) subunit was based on addition of an enol boronate to 3-benzyloxypropanal through TS-1. Immediate reduction of the chelate is also stereoselective and provides the intermediate **13**. These steps establish the configuration at C(2)–C(5).



The diol was protected and the C-terminal group converted to a methyl ester in sequence **B**. A phosphonate group was installed at C(7) via an acylation reaction in Step **C-5**. Successive oxidations of the primary and deprotected secondary alcohol gave the C(1)–C(8) intermediate.

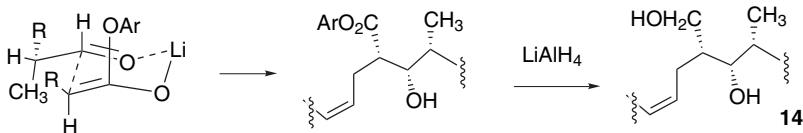
The C(9)–C(16) subunit was synthesized from the same starting material. The chain was extended by a boron enolate addition to 2-methylpropenal (Step **D-2**). After introduction of a double bond by selenoxide elimination in Step **E-4**, a Claisen rearrangement was used to generate an eight-membered lactone ring (Step **E-6**).



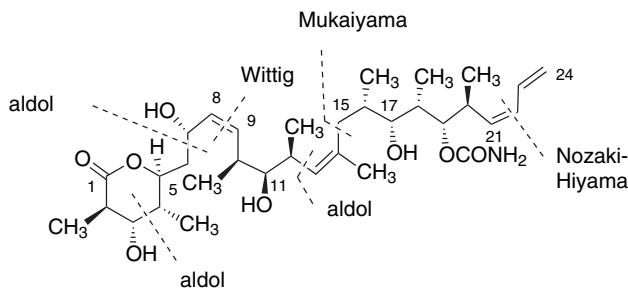
The lactone ring was then opened and the carboxy group converted to a hindered phenolic ester (Step **F-4**), providing the C(9)–C(16) intermediate.

The synthesis of the C(17)–C(24) segment also began with a diastereoselective boron enolate aldol addition. The adduct was protected and converted to an aldehyde in sequence **H**. The terminal diene unit was installed using a γ -silylallyl chromium reagent, which generates a β -hydroxysilane. Peterson elimination using KH then gave the *Z*-diene.

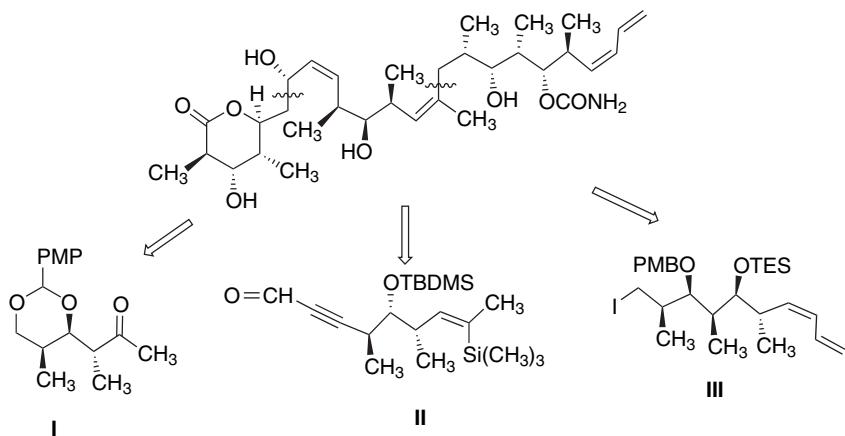
The three fragments were then coupled. The C(16)–C(17) bond was established by addition of the lithium enolate of the aryl ester in the C(9)–C(16) fragment with the aldehyde group of the C(17)–C(24) fragment. The stereochemistry is consistent with the cyclic aldol addition TS. The adduct was immediately reduced to the diol **14** by LiAlH₄.



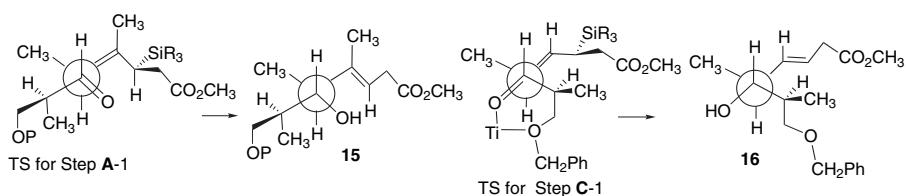
The primary hydroxymethyl group at C(16) was deoxygenated via the mesitylenesulfonate. After removal of the PMP protecting group, a sterically demanding oxidant, TEMPO-PhI(OAc)₂, was used to selectively oxidize the primary alcohol group to an aldehyde. The Still-Gennari version of the Wadsworth-Emmons reaction was used to couple with the C(1)–C(8) fragment in Step **L**. This reaction proceeded with 5:1 *Z* : *E* selectivity and led to isolation of the *Z*-product in 73% yield. The PMB protecting group was then removed and the carbamate group introduced at C(19). The remaining protecting groups were then removed and the lactonization completed the synthesis.

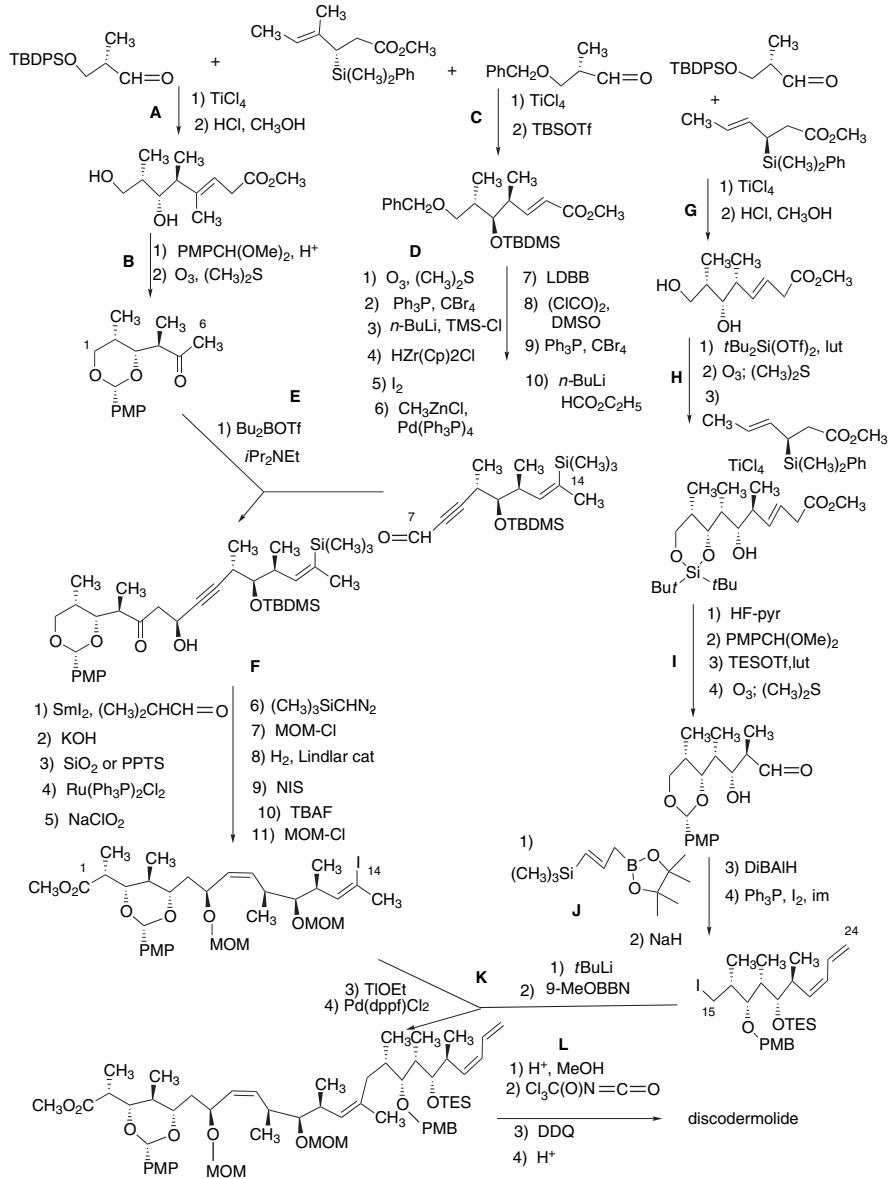


The synthesis outlined in Scheme 13.72 was carried out by James Panek's group at Boston University and is based on three key intermediates that were synthesized from two closely related methyl 3-(dimethylphenylsilyl)hex-4-enoates.



The stereochemistry was controlled by Lewis acid–induced addition of the allylic silanes to aldehydes. The reaction of the silane with O-protected (*S*)-3-hydroxy-2-methylpropanal provides **15**. The silane reacted with the benzyl-protected analog to provide **16**.



Scheme 13.72. Discodermolide Synthesis: J. S. Panek and A. Arefolov^a

a. A. Arefolov and J. S. Panek, *J. Am. Chem. Soc.*, **127**, 5596 (2005).

These intermediates were then converted to the fragments **I** and **II**, respectively. Intermediate **15** was protected as a cyclic acetal and then ozonized to give segment **I**. In the synthesis of the **II** fragment the adduct was extended by two Corey-Fuchs sequences with in situ functionalization to provide the alkyne intermediate **II** (Steps **D-2** and **D-9**). Trimethylsilyl and methyl groups were introduced at C(14) and a formyl group was added at C(8). The fragments **I** and **II** were coupled by boron enolate methodology and a single stereoisomer was obtained in 88% yield (Step **E**).

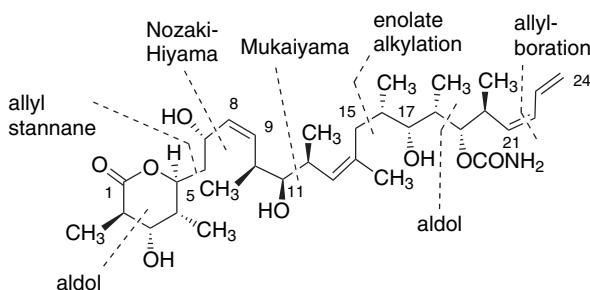
The coupled fragments were then converted to a vinyl iodide. The key steps were a Z-selective Lindlar reduction and iodinolysis of the vinyl silane, which was done using NIS in acetonitrile (sequence **F-1** to **F-11**).

The C(15)–C(24) segment **C** was created by two successive additions of the allylic silane synthons (Steps **G-1** and **H-3**). The unsaturated esters resulting from the additions were subjected to ozonolysis. The terminal diene unit was added using a silyl-substituted allylic boronate and then subjected to base-mediated elimination. The coupling of the **I-II** and **III** segments was done by Suzuki methodology. It was also carried out in somewhat lower yield using a zinc reagent prepared from the vinyl iodide. The synthesis was completed by deprotection and lactonization. There are a total of 42 steps, with the longest linear sequence being 27 steps, in overall 21% yield.

The synthesis of discodermolide in Scheme 13.73 was completed at the University of California, Berkeley by D. C. Myles and co-workers. The synthesis began with a TiCl_4 -mediated cycloaddition that gave a dihydropyrone intermediate that contains the stereochemistry at C(10)–C(12) and the Z-configuration at the C(13)–C(14) double bond. Reduction and H^+ -promoted Ferrier rearrangement gave a lactol containing C(9)–C(15) (Steps **B-1** and **B-2**). This lactol was converted to an allylic iodide, providing one of the key intermediates, **II**.

The stereochemistry at C(18)–C(20) was established using an oxazolidinone chiral auxiliary (Step **D-1**). Carbon-16 and its methyl substituent were added by a Grignard addition in Step **D-4**. The C(9)–C(15) and C(16)–C(21) segments were joined by enolate alkylation (Step **E**). Under optimum conditions, a 6:1 preference for the desired stereoisomer at C(16) was achieved. The stereochemistry at C(17) was established by LiAlH_4 reduction in the presence of LiI, with 8:1 stereoselectivity. An iodovinyl group containing C(8) was installed using iodomethylenetriphenylphosphorane, giving a *Z* : *E* isomer ratio of 20:1 (Step **G-2**). The terminal diene unit was installed using a γ -silylallylboronate, followed by base-mediated *syn* elimination (Steps **G-5** and **G-6**). The carbamate group was then installed, completing the synthesis of intermediate **III**.

The synthesis of the C(1)–C(7) fragment began with allylstannylation (Step **H**). The C(1)–C(2) terminus was introduced using the dibutylboron enolate of an oxazolidinone chiral auxiliary. The C(8)–C(24) fragment was added via a $\text{NiCl}_2\text{-CrCl}_2$ coupling. This reaction was improved by inclusion of a chiral *bis*-pyridine ligand. Sequential deprotection and lactonization afforded discodermolide. The overall yield was 1.5% based on a 22-step longest linear sequence.

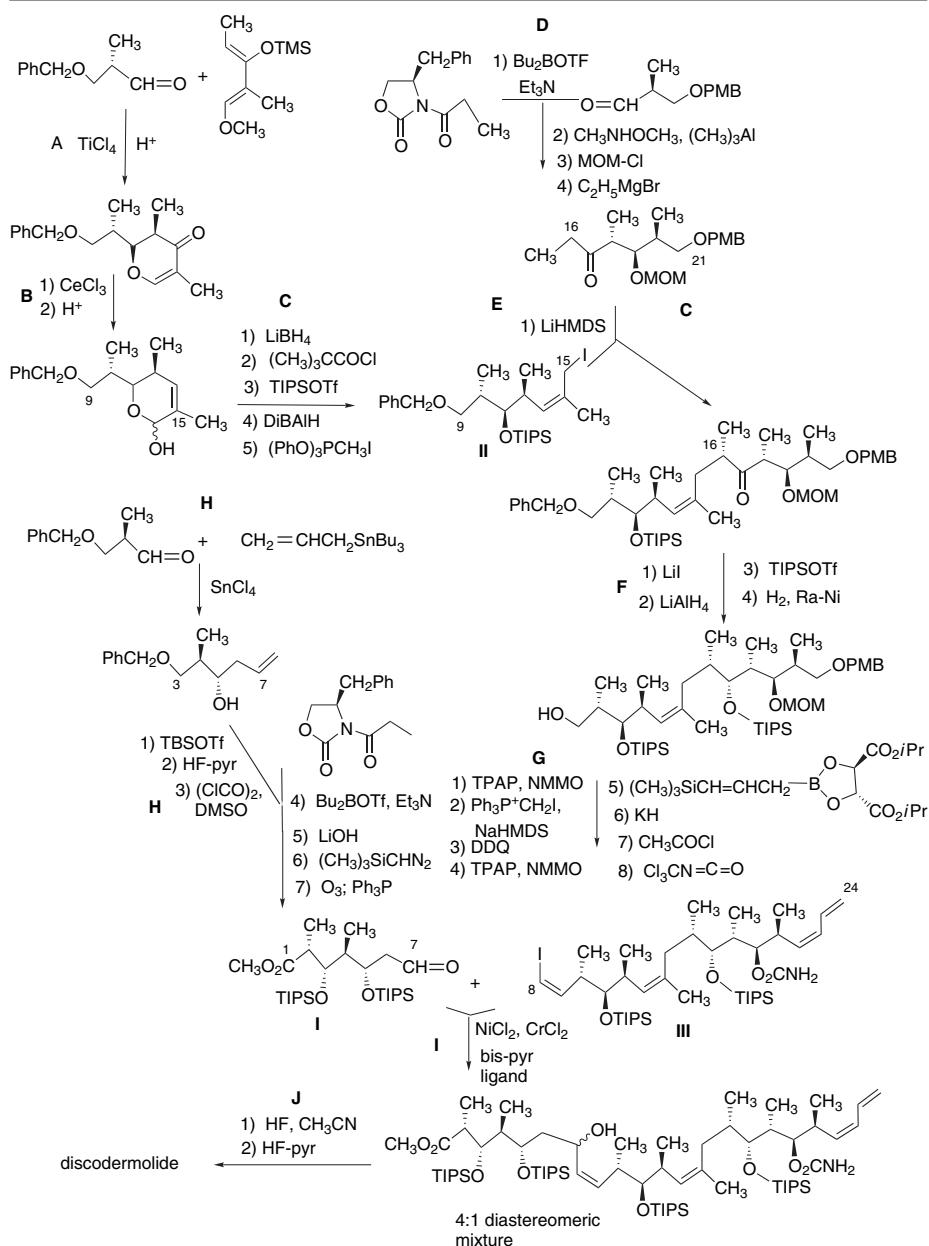


The synthesis of (+)-discodermolide shown in Scheme 13.74 was developed in the laboratories of the Novartis Pharmaceutical Company and was designed to provide sufficient material for initial clinical trials. The synthesis is largely based on the one

Scheme 13.73. Discodermolide Synthesis: D. C. Myles Co-workers^a

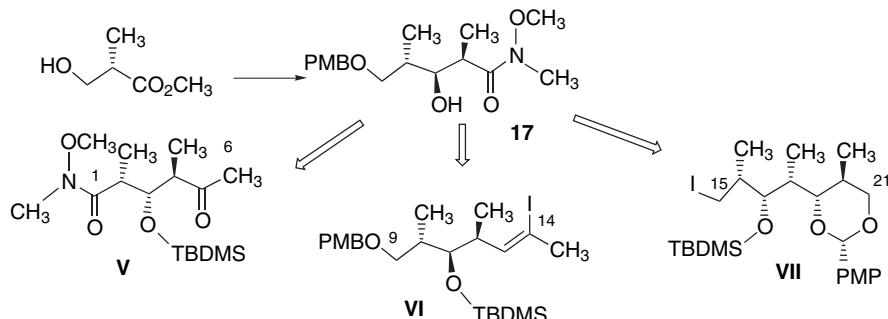
CHAPTER 13

Multistep Syntheses



a. S. S. Harried, C. P. Lee, G. Yang, T. I. H. Lee, and D. C. Myles, *J. Org. Chem.*, **68**, 6646 (2003).

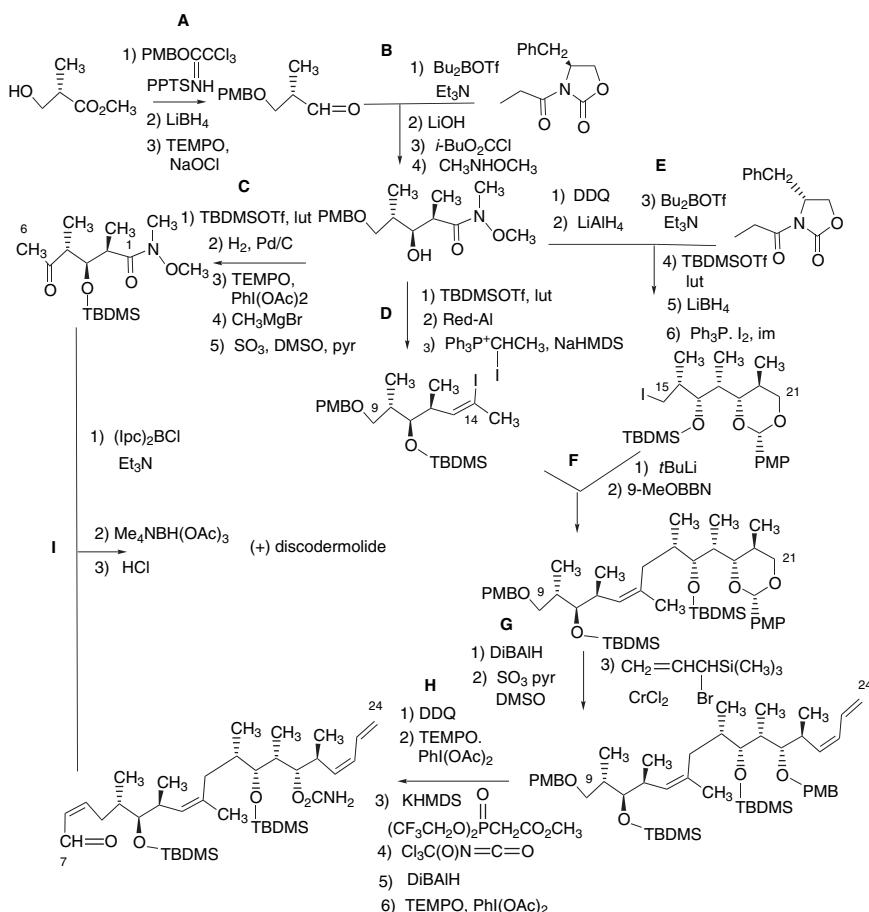
by A. B. Smith, III, and co-workers (Scheme 13.70), with the final stages being based on the synthesis in Scheme 13.71. The synthesis begins with a single starting material having one stereogenic center and proceeds through Smith's common intermediate **17** to three segments containing the stereochemical triads.



A number of modifications were made to meet scale-up requirements. In the preparation of the common intermediate, LiBH₄ was used in place of LiAlH₄ in Step A-2 and a TEMPO-NaOCl oxidation was used in place of Swern oxidation in Step A-3. Some reactions presented difficulty in the scale-up. For example, the boron enolate aldolization in Step B-1 gave about 50% yield on the 20- to 25-kg scale as opposed to greater than 75% on a 50-g scale. The amide formation in Step B-3 was modified to eliminate the use of trimethylaluminum, and the common intermediate **17** could be prepared on a 30-kg scale using this modified sequence. The synthesis of the C(1)-C(6) segment **V** was done by Steps C-1 to C-5 in 66% yield on the scale of several kg.

The C(9)-C(14) segment **VI** was prepared by Steps D-1 to D-3. The formation of the vinyl iodide in Step D-3 was difficult and proceeded in only 25–30% yield. The C(15)-C(21) segment **VII** was synthesized from the common intermediate **17** by Steps E-1 to E-6. A DDQ oxidation led to formation of a 1,3-dioxane ring in Step E-1. The *N*-methoxy amide was converted to an aldehyde by LiAlH₄ reduction and the chain was extended to include C(14) and C(15) using a boron enolate of an oxazolidinone chiral auxiliary. After reductive removal of the chiral auxiliary, the primary alcohol group was converted to a primary iodide. The overall yield for these steps was about 25%.

The C(9)-C(14) and C(15)-C(21) segments were then coupled using Suzuki methodology (Step F). The terminal diene unit was then introduced in Steps G-1 to G-3. The cyclic acetal was reduced with DiBAIH, restoring the PMB protecting group and deprotecting the C(21) hydroxy. This primary alcohol was oxidized to the aldehyde and coupled with an allylic silane using CrCl₂, as in Scheme 13.69. The chain was then extended by adding C(7) and C(8) using the Z-selective Still-Gennari modification of the Wadsworth-Emmons reaction (Step H-3) and the ester was converted to an aldehyde. This permitted the final coupling with the C(1)-C(6) fragment using a boron enolate prepared from (Ipc)₂BCl. The optimized procedure gave the product in 50–55% yield with stereoselectivity of about 4:1. A process for converting the minor diastereomer to the desired product was developed. The final reduction was done with [(CH₃)₄N]⁺[BH(OAc)₃]⁻. Removal of the final silyl protecting group and lactonization gave (+)-discodermolide. The overall synthesis involved 39 steps.

Scheme 13.74. Discodermolide Synthesis: Novartis Group^a

- a. S. J. Mickel, G. H. Sedelmeier, D. Niederer, R. Daeffler, A. Osmani, K. Shreiner, M. Seeger-Weibel, B. Berod, K. Schaefer, R. Gamboni, S. Chen, W. Chen, C. T. Jagoe, F. R. Kinder, Jr., M. Loo, K. Prasad, O. Repic, W.-C. Shieh, R.-M. Wang, L. Waykole, D. D. Xu, and S. Xue, *Org. Proc. Res. Dev.*, **8**, 92 (2004); S. J. Mickel, G. H. Sedelmeier, D. Niederer, F. Schuerch, D. Grimalt, G. Koch, R. Daeffler, A. Osmani, A. Hirni, K. Schaefer, R. Gamboni, A. Bach, A. Chaudhary, S. Chen, W. Chen, B. Hu, C. T. Jagoe, H.-Y. Kim, F. R. Kinder, Jr., Y. Liu, Y. Lu, J. McKenna, M. Prasad, T. M. Ramsey, O. Repic, L. Rogers, W.-C. Shieh, R.-M. Wang, and L. Waykole, *Org. Proc. Res. Dev.*, **8**, 101 (2004); S. J. Mickel, G. H. Sedelmeier, D. Niederer, F. Schuerch, G. Koch, E. Kuesters, R. Daeffler, A. Osmani, M. Seeger-Weibel, E. Schmid, A. Hirni, K. Schaefer, R. Gamboni, A. Bach, S. Chen, W. Chen, P. Geng, C. T. Jagoe, F. R. Kinder, Jr., G. T. Lee, J. McKenna, T. M. Ramsey, O. Repic, L. Rogers, W.-C. Shieh, R.-M. Wang, and L. Waykole, *Org. Proc. Res. Dev.*, **8**, 107 (2004); S. J. Mickel, G. H. Sedelmeier, D. Niederer, F. Schuerch, M. Seger, K. Schreiner, R. Daeffler, A. Osmani, D. Bixel, O. Loiseleur, J. Cercus, H. Stettler, K. Schaefer, R. Gamboni, A. Bach, G.-P. Chen, W. Chen, P. Geng, G. T. Lee, E. Loesser, J. McKenna, F. R. Kinder, Jr., K. Konigberger, K. Prasad, T. M. Ramsey, N. Reel, O. Repic, L. Rogers, W.-C. Shieh, R.-M. Wang, L. Waykole, S. Xue, G. Florence, and I. Paterson, *Org. Proc. Res. Dev.*, **8**, 113 (2004); S. J. Mickel, D. Niederer, R. Daeffler, A. Osmani, E. Kuesters, E. Schmid, K. Schaefer, R. Gamboni, W. Chen, E. Loeser, F. R. Kinder, Jr., K. Konigberger, K. Prasad, T. M. Ramsey, O. Repic, R.-M. Wang, G. Florence, I. Lyothier, and I. Paterson, *Org. Proc. Res. Dev.*, **8**, 122 (2004).

These syntheses of (+)-discodermolide provide examples of the application of several current methods for control of acyclic stereochemistry. They illustrate the use of allylic boronates, allenyl stannanes, oxazolidinone auxiliaries, boron enolates, and allylic silanes to achieve enantioselective formation of key intermediates. Wittig and Suzuki reactions figure prominently in the coupling of key intermediates. Several of the syntheses use β -hydroxy silane elimination to introduce the terminal diene. The discodermolide structure lends itself to a high degree of convergency, and the relationship among the three stereochemical triads permits utilization of common starting materials, which contributes to overall synthetic efficiency. The composite synthesis completed by the Novartis group provides an insight into the logistics of scale-up of a synthesis of this complexity. The synthesis described in Scheme 13.74 produced 60 g of pure (+)-discodermolide. The effort involved about 40 chemists and was carried out over a period of 20 months.

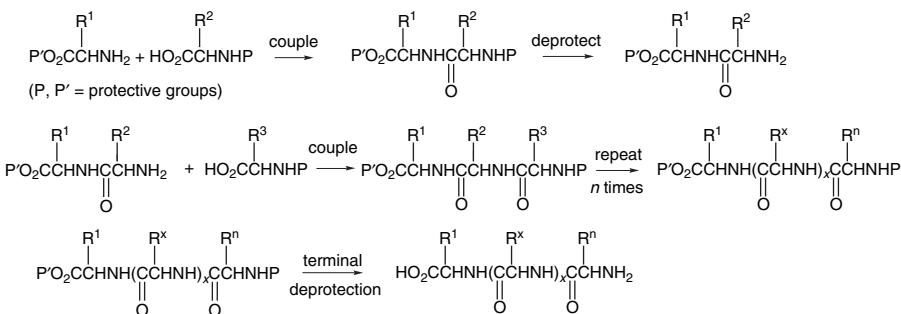
13.3. Solid Phase Synthesis

The syntheses discussed in the previous sections were all carried out in *solution phase* and intermediates were isolated and purified. There is another general approach to multistep synthesis in which the starting material is attached to a solid support. The sequence of synthetic steps is then carried out with the various intermediates remaining attached to the solid support. Called *solid phase synthesis*, this approach has a potential advantage in that excess reagents and by-products can simply be washed away after each step. When the synthesis is complete, the product can be detached from the support. Another potential advantage of solid phase synthesis is that the operations can be automated. A particular sequence for addition of reactants, reagents, and solvents for removal of soluble material can be established. Instruments can then be programmed to carry out these operations.

The most highly developed applications of solid phase methods are in the syntheses of polypeptides and oligonucleotides. These molecules consist of linear sequences of individual amino acids or nucleotides. The connecting bonds are the same for each subunit: amides for polypeptides and phosphate esters for the polynucleotides. The synthesis can be carried out by sequentially adding the amino acids or nucleotides and coupling reagents. The ability to synthesize polypeptides and oligonucleotides of known sequence is of great importance in a number of biological applications. Although these molecules can be synthesized by synthetic manipulations in solution, they are now usually synthesized by solid phase methods, using automated repetitive cycles of deprotection and coupling. Another important application of solid phase synthesis is in combinatorial synthesis, where the goal is to make a large number of related molecules by systematic variation of the individual components.

13.3.1. Solid Phase Polypeptide Synthesis

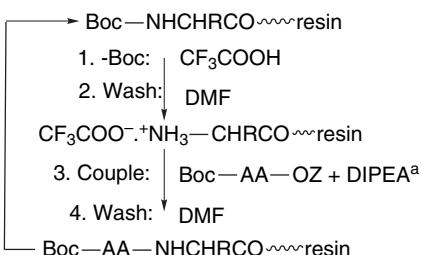
The techniques for automated solid phase synthesis were first highly developed for polypeptides and the method is abbreviated as *SPPS*. Polypeptide synthesis requires the sequential coupling of the individual amino acids. After each unit is added, it must be deprotected for use in the next coupling step.



Excellent solution methods involving alternative cycles of deprotection and coupling are available for peptide synthesis,⁴¹ and the techniques have been adapted to solid phase synthesis.⁴² The N-protected carboxy terminal amino acid is linked to the solid support, which is usually polystyrene with divinylbenzene cross-linking. The amino group is then deprotected and the second N-protected amino acid is introduced and coupled. The sequence of deprotection and coupling is then continued until the synthesis is complete. Each deprotection and coupling step must go in very high yield. Because of the iterative nature of solid phase synthesis, errors accumulate throughout the process. For the polypeptide to be of high purity, the conversion must be very efficient at each step.

The first version of SPPS to be developed used the *t*-Boc group as the amino-protecting group. *t*-Boc can be cleaved with relatively mild acidic treatment and TFA is usually used. The original coupling reagents utilized for SPPS were carbodiimides. In addition to dicyclohexylcarbodiimide (DCCI), *N,N'*-diisopropylcarbodiimide (DIPCDI) is often used. The mechanism of peptide coupling by carbodiimides was

Scheme 13.75. *t*-Boc Protocol for Solid Phase Peptide Synthesis

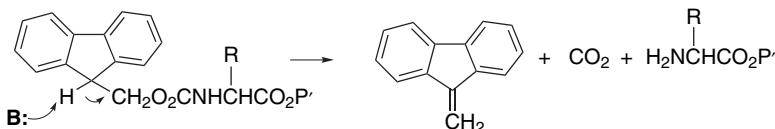


a. OZ = active ester; DIPEA = diisopropylethylamine

- ⁴¹ M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*, 2nd Edition, Springer Verlag, Berlin, 1994; V. J. Hruby, and J.-P. Mayer, in *Bioorganic Chemistry: Peptides and Proteins*, S. Hecht, ed. Oxford University Press, Oxford, 1998, pp. 27–64.
- ⁴² R. B. Merrifield, *Meth. Enzymol.*, **289**, 3 (1997); R. B. Merrifield, in *Peptides: Synthesis, Structure, and Applications*, B. Gutte, ed., Academic Press, San Diego, CA, p. 93; E. Atherton and R. C. Sheppard, *Solid Phase Peptide Synthesis*, IRL Press, Oxford, 1989; P. Lloyd-Williams, F. Albericio, and E. Giralt, *Chemical Synthesis of Peptides and Proteins*, CRC Press, Boca Raton, FL, 1997.

discussed in Section 3.4. Currently, the optimized versions of the *t*-Boc protocol can provide polypeptides of 60–80 residues in high purity.⁴³ The protocol for using *t*-Boc protection is outlined in Scheme 13.75

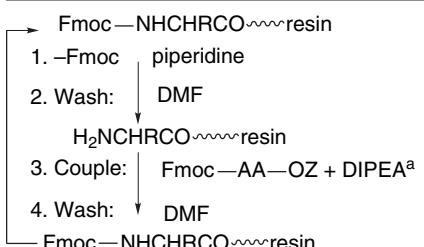
A second method that uses the fluorenylmethoxycarboxy (Fmoc) protecting group has been developed.⁴⁴ The Fmoc group is stable to mild acid and to hydrogenation, but it is cleaved by basic reagents via fragmentation triggered by deprotonation at the acidic 9-position of the fluorene ring. The protocol for SPPS using the Fmoc group is shown in Scheme 13.76.



In both the *t*-Boc and Fmoc versions of SPPS, the amino acids with functional groups in the side chain also require protecting groups. These protecting groups are designed to stay in place throughout the synthesis and then are removed when the synthesis is complete. The serine and threonine hydroxyl groups can be protected as benzyl ethers. The ϵ -amino group of lysine can be protected as the trifluoroacetyl derivative or as a sulfonamide derivative. The imidazole nitrogen of histidine can also be protected as a sulfonamide. The indole nitrogen of tryptophan is frequently protected as a formyl derivative. The exact choice of protecting group depends upon the deprotection-coupling sequence being used.

The original version of SPPS attached the carboxy terminal residue directly to the resin as a benzylic ester using chloromethyl groups attached to the polymer. At the present time the attachment is done using “linking groups.” Two of the more common linking groups are shown. These groups have the advantage of permitting

Scheme 13.76. Fmoc Protocol for Solid Phase Peptide Synthesis

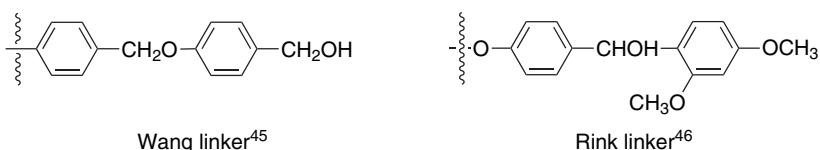


a. OZ = active ester; DIPEA = diisopropylethylamine

⁴³. M. Schnolzer, P. Alewood, A. Jones, D. Alewood, and S. B. H. Kent, *Int. J. Peptide Protein Res.*, **40**, 180 (1992); M. Schnolzer and S. B. H. Kent, *Science*, **256**, 221 (1992).

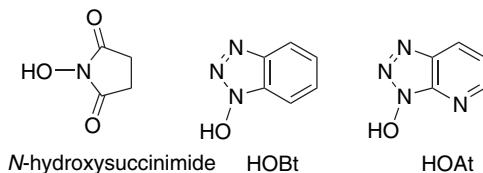
⁴⁴. L. A. Carpino and G. Y. Han, *J. Org. Chem.*, **37**, 3404 (1972); G. B. Fields and R. L. Noble, *Int. J. Peptide Protein Res.*, **35**, 161 (1990); D. A. Wellings and E. Atherton, *Meth. Enzymol.*, **289**, 44 (1997); W. C. Chan and P. D. White, ed., *Fmoc Solid Phase Peptide Synthesis: A Practical Approach*, Oxford University Press, Oxford, 2000.

milder conditions for the final removal of the polypeptide from the solid support. The C-terminal amino acid is attached to the hydroxy group of the linker.



In the *t*-Boc protocol, the most common reagent for final removal of the peptide from the solid support is anhydrous hydrogen fluoride. Although this is a hazardous reagent, commercial systems designed for safe handling are available. In the Fmoc protocol milder acidic reagents can be used for cleavage from the resin. The alkoxybenzyl group at the linker can be cleaved by TFA. Often, a scavenger, such as thioanisole, is used to capture the cations formed by cleavage of *t*-Boc protecting groups from side-chain substituents.

At the present time, the coupling is usually done via an activated ester (see Section 3.4). The coupling reagent and one of several *N*-hydroxy heterocycles are first allowed to react to form the activated ester, followed by coupling with the deprotected amino group. The most frequently used compounds are *N*-hydroxysuccinimide, 1-hydroxybenzotriazole (HOBr), and 1-hydroxy-7-azabenzotriazole (HOAt).⁴⁷



Another family of coupling reagents frequently used with the Fmoc method is related to *N*-hydroxybenzotriazole and *N*-hydroxy 7-azabenzotriazole but also incorporates phosphonium or amidinium groups. The latter can exist in either the O-(uronium) or *N*-(guanidinium) forms.⁴⁸ Both can effect coupling. The former are more reactive but isomerize to the latter. Which form is present depends on the protocol of preparation, including the amine used and the time before addition of the carboxylic acid.⁴⁹ The

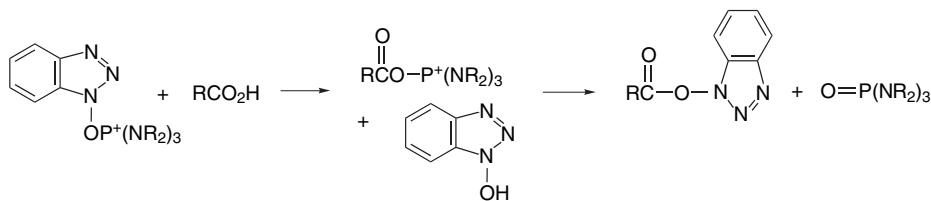
⁴⁵ S. Wang, *J. Am. Chem. Soc.*, **95**, 1328 (1993).

⁴⁶ H. Rink, *Tetrahedron Lett.*, **28**, 3787 (1987); M. S. Bernatowicz, S. B. Daniels, and H. Koster, *Tetrahedron Lett.*, **30**, 4645 (1989); R. S. Garigipati, *Tetrahedron Lett.*, **38**, 6807 (1997).

⁴⁷ F. Albericio and L. A. Carpio, *Meth. Enzymol.*, **289**, 104 (1997).

⁴⁸ L. A. Carpio, H. Imazumi, A. El-Faham, F. J. Ferrer, C. Zhang, Y. Lee, B. M. Foxman, P. Henklein, C. Hanay, C. Muegge, H. Wenschuh, J. Klose, M. Beyermann, and M. Beinert, *Angew. Chem. Int. Ed. Engl.*, **41**, 441 (2002); T. K. Srivastava, W. Haq, S. Bhanumati, D. Velmurugan, U. Sharma, N. R. Jagannathan, and S. B. Katti, *Protein and Peptide Lett.*, **8**, 39 (2001).

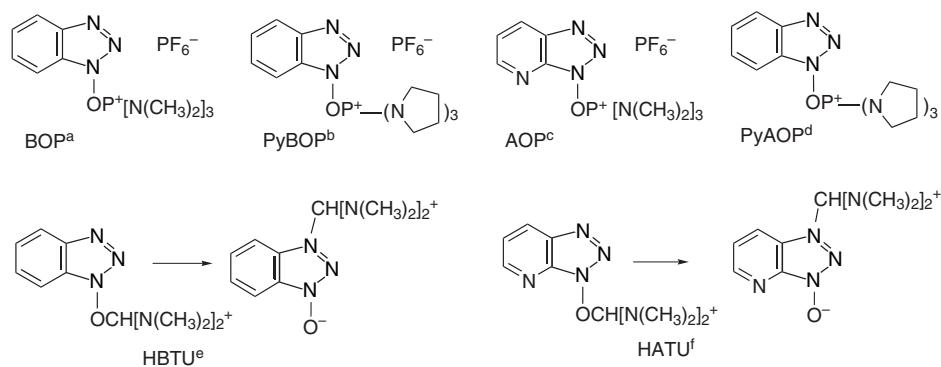
⁴⁹ L. A. Carpio and A. El-Faham, *Tetrahedron*, **55**, 6813 (1999); L. A. Carpio and F. J. Ferrer, *Org. Lett.*, **3**, 2793 (2001); F. Albericio, J. M. Bofill, A. El-Faham, and S. A. Kates, *J. Org. Chem.*, **63**, 9678 (1998).



The structures and abbreviations of these reagents are given in Scheme 13.77.

The development of highly efficient protection-deprotection and coupling schemes has made the synthesis of polypeptides derived from the standard amino acids a highly efficient process. Additional challenges can come into play when other amino acids are involved. The HATU reagent, for example, has been applied to *N*-methyl amino acids, as in the case of cyclosporin A, an undecapeptide that is important in preventing transplant rejection. Seven of eleven amino acids are *N*-methylated. The synthesis of cyclosporin analogs has been completed by both solution and solid phase methods. Scheme 13.78 summarizes this synthesis. Fmoc protecting groups were used. Unlike the case of normal amino acids, quantitative coupling was not achieved, even when the coupling cycle was repeated twice for each step. Therefore, after each coupling cycle, a *capping step* using acetic anhydride was done to prevent carrying unextended material to the next phase. The final macrocyclization was done using propylphosphonic anhydride and DMAP, a reaction that presumably proceeds through a mixed phosphonic anhydride.⁵¹

Scheme 13.77. Phosphonium, Uronium, and Guanidinium Coupling Reagents



a. B. Castro, J. R. Dormoy, G. Evin, and C. Selve, *Tetrahedron Lett.*, 1219 (1975).

b. J. Coste, D. Le-Nguyen, and B. Castro, *Tetrahedron Lett.*, **31**, 205 (1990).

c. L. A. Carpino, A. El-Faban, C. A. Minor, and F. Albericio, *J. Chem. Soc., Chem. Commun.*, 201 (1994).

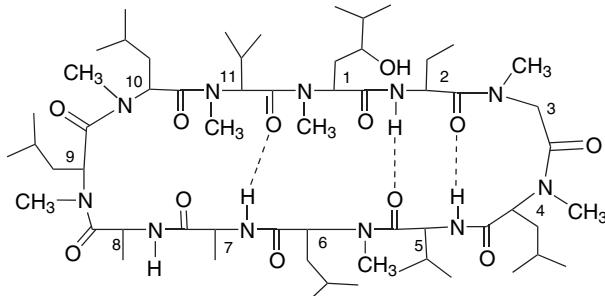
d. F. Albericio, M. Cases, J. Alsina, S. A. Triolo, L. A. Carpino, and S. A. Kates, *Tetrahedron Lett.*, **38**, 4853 (1997).

e. R. Knorr, A. Trezciak, W. Barnwarth, and D. Gillessen, *Tetrahedron Lett.*, **30**, 1927 (1989).

f. L. A. Carpino, *J. Am. Chem. Soc.*, **115**, 4397 (1993).

⁵⁰. J. Coste, E. Frerot, and P. Jouin, *J. Org. Chem.*, **59**, 2437 (1994).

⁵¹. R. M. Wegner, *Helv. Chim. Acta*, **67**, 502 (1984); W. J. Colucci, R. D. Tung, J. A. Petri, and D. H. Rich, *J. Org. Chem.*, **55**, 2895 (1990).

Scheme 13.78. Synthesis of a Cyclosporin Analog by Solid Phase Peptide Synthesis^a

Cyclosporin A

D-Ala-MeLeu-MeLeu-MeVal-MeLeu-Abu-Sar-MeLeu-Val-MeLeu-DAla —link—○

coupling reagent and yield	8	9	10	11	1	2	3	4	5	6	7
HOAt	70	84	73	78							
HATU	95	75	50	62	98						

a. Y. M. Angell, C. Garcia-Echeverria, and D. H. Rich, *Tetrahedron Lett.*, **35**, 5981 (1994); Y. M. Angell, T. L. Thomas, G. R. Flentke, and D. H. Rich, *J. Am. Chem. Soc.*, **117**, 7279 (1995). The analog contains *N*-methylleucine at position 1.

13.3.2. Solid Phase Synthesis of Oligonucleotides

Synthetic oligonucleotides are very important tools in the study and manipulation of DNA, including such techniques as site-directed mutagenesis and DNA amplification by the polymerase chain reaction. The techniques for chemical synthesis of oligonucleotides are highly developed. Very efficient automated methodologies based on solid phase synthesis are used extensively in fields that depend on the availability of defined DNA sequences.⁵²

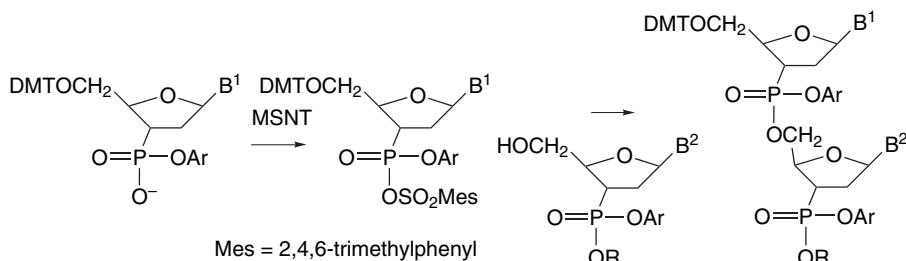
The construction of oligonucleotides proceeds from the four nucleotides by formation of a new phosphorus oxygen bond. The potentially interfering nucleophilic sites on the nucleotide bases are protected. The benzoyl group is usually used for the 6-amino group of adenosine and the 4-amino group of cytidine, whereas the *i*-butyroyl group is used for the 2-amino group of guanosine. These amides are cleaved by ammonia after the synthesis is completed. The nucleotides are protected at the 5'-hydroxy group as ethers, usually with the 4,4'-dimethoxytrityl (DMT) group.

In the early solution phase syntheses of oligonucleotides, coupling of phosphate diesters was used. A mixed 3'-ester with one aryl substituent, usually *o*-chlorophenyl, was coupled with a deprotected 5'-OH nucleotide. The coupling reagents were sulfonyl halides, particularly 2,4,6-tri-*i*-propylbenzenesulfonyl chloride,⁵³ and the reactions proceeded by formation of reactive sulfonate esters. Coupling conditions

⁵². S. L. Beaucage and M. H. Caruthers, in *Bioorganic Chemistry: Nucleic Acids*, S. M. Hecht, ed., Oxford University Press, Oxford, 1996, pp. 36–74.

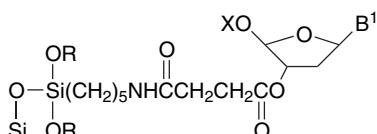
⁵³. C. B. Reese, *Tetrahedron*, **34**, 3143 (1978).

have subsequently been improved and a particularly effective coupling reagent is 1-mesitylenesulfonyl-3-nitrotriazole (MSNT).⁵⁴



Current solid phase synthesis of oligonucleotides relies on coupling at the phosphite oxidation level. The individual nucleotides are introduced as phosphoramidites and the technique is called the *phosphoramidite method*.⁵⁵ The *N,N*-diisopropyl phosphoramidites are usually used. The third phosphorus substituent is methoxy or 2-cyanoethoxy. The cyanoethyl group is easily removed by mild base (β -elimination) after completion of the synthesis. The coupling is accomplished by tetrazole, which displaces the amine substituent to form a reactive phosphite that undergoes coupling. After coupling, the phosphorus is oxidized to the phosphoryl level by iodine or another oxidant. The most commonly used protecting group for the 5'-OH is the 4,4'-dimethoxytrityl group (DMT), which is removed by mild acid. The typical cycle of deprotection, coupling, and oxidation is outlined in Scheme 13.79. One feature of oligonucleotide synthesis is the use of a *capping step*, an acetylation that follows coupling, the purpose of which is to permanently block any 5'-OH groups that were not successfully coupled. This prevents the addition of a nucleotide at the site in the succeeding cycle, terminates the further growth of this particular oligonucleotide, and avoids the synthesis of oligonucleotides with single-base deletions. The capped oligomers are removed in the final purification.

Silica or porous glass is usually used as the solid phase in oligonucleotide synthesis. The support is functionalized through an amino group attached to the silica surface. There is a secondary linkage through a succinate ester to the terminal 3'-OH group.

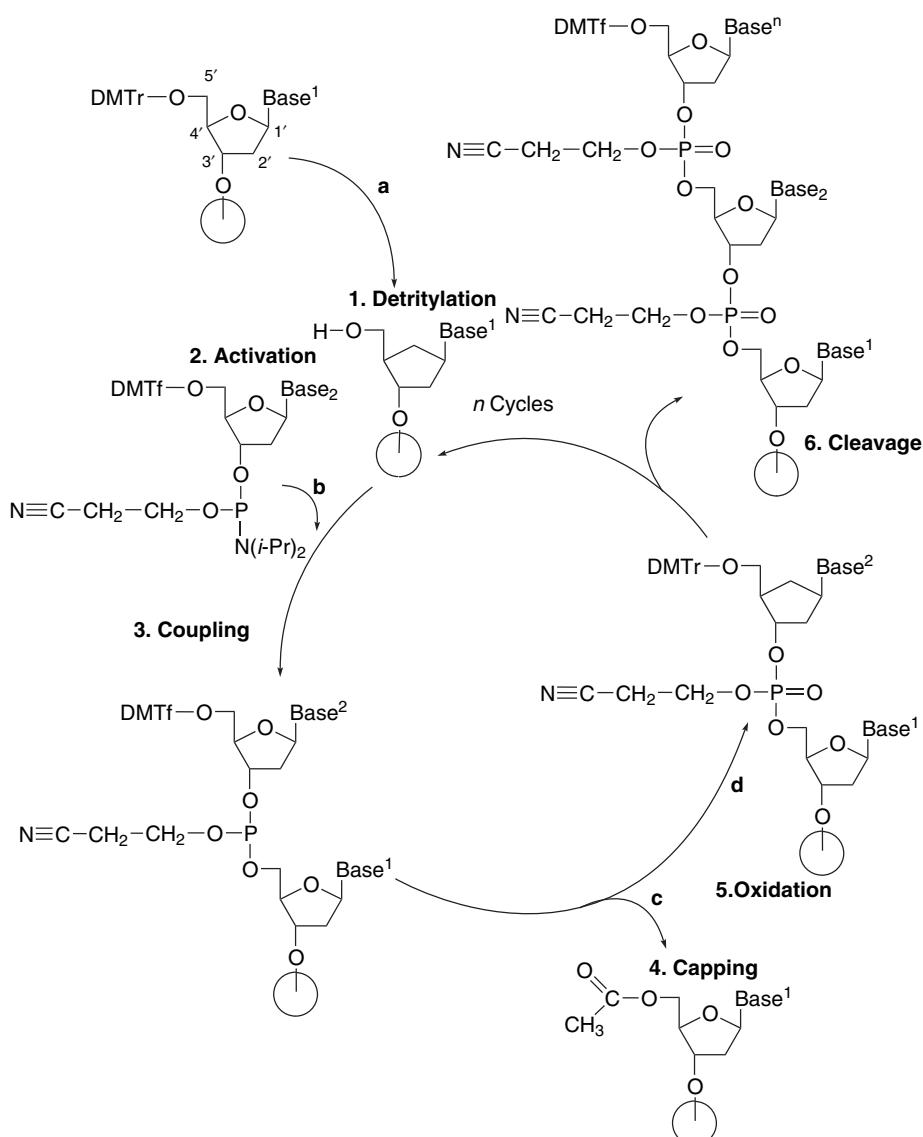


Although use of automated oligonucleotide synthesis is widespread, work continues on the optimization of protecting groups, coupling conditions, and deprotection methods, as well as on the automated devices.⁵⁶

⁵⁴ J. B. Chattapadyaya and C. B. Reese, *Tetrahedron Lett.*, **20**, 5059 (1979).

⁵⁵ R. L. Letsinger and W. B. Lunsford, *J. Am. Chem. Soc.*, **98**, 3655 (1976); S. L. Beaucage and M. H. Caruthers, *Tetrahedron Lett.*, **22**, 1859 (1981); M. H. Caruthers, *J. Chem. Ed.*, **66**, 577 (1989); S. L. Beaucage and R. P. Iyer, *Tetrahedron*, **48**, 2223 (1992).

⁵⁶ G. A. Urbina, G. Grubler, A. Weiber, H. Echner, S. Stoeva, J. Schernthaner, W. Gross, and W. Voelter, *Z. Naturforsch.*, **B53**, 1051 (1998); S. Rayner, S. Brignac, R. Bumeister, Y. Belosludtsev, T. Ward, O. Grant, K. O'Brien, G. A. Evans, and H. R. Garner, *Genome Res.*, **8**, 741 (1998).

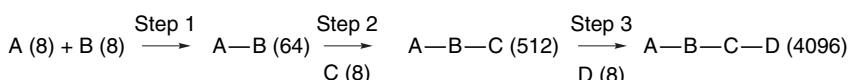
Scheme 13.79. Protocol for Automated Solid-Phase Synthesis of Oligonucleotides^a

Reagents: **a:** 3% $\text{Cl}_3\text{CCO}_2\text{H}$ in CH_2Cl_2 ; **b:** 3% tetrazole in CH_3CN ; **c₁:** 10% Ac_2O and 10% 2,6-lutidine in THF; **c₂:** 7% 1-methylimidazole in THF; **d:** 3% I_2 , 2% H_2O , 2% pyridine in THF.

a. G. A. Urbina, G. Gruebler, A. Weiler, H. Echner, S. Stoeva, J. Schernthaler, W. Grass, and W. Voelter, *Z. Naturforsch.* **B53**, 1051 (1998).

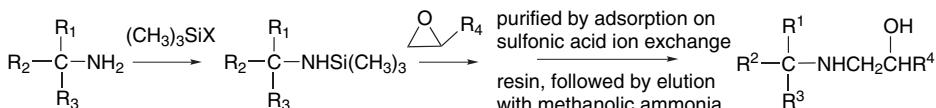
13.4. Combinatorial Synthesis

Over the past decade the techniques of *combinatorial synthesis* have received much attention. Solid phase synthesis of polypeptides and oligonucleotides are especially adaptable to combinatorial synthesis, but the method is not limited to these fields. The goal of combinatorial synthesis is to prepare a large number of related



The objective of traditional multistep synthesis is the preparation of a single pure compound, but combinatorial synthesis is designed to make many related molecules.⁵⁷ The purpose is often to have a large collection (library) of compounds for evaluation of biological activity. A goal of combinatorial synthesis is *structural diversity*, that is, systematic variation in subunits and substituents so as to explore the effect of a range of structural entities. In this section, we consider examples of the application of combinatorial methods to several kinds of compounds.

One approach to combinatorial synthesis is to carry out a series of conventional reactions in parallel with one another. For example, a matrix of six starting materials, each treated with eight different reactants will generate 48 reaction products. Splitting each reaction mixture and using a different reactant for each portion can further expand the number of final compounds. However, relatively little savings in effort is achieved by running the reactions in parallel, since each product must be separately isolated and purified. The reaction sequence below was used to create a 48-component library by reacting six amines with each of eight epoxides. Several specific approaches were used to improve the purity of the product and maximize the efficiency of the process. First, the amines were monosilylated to minimize the potential for interference from dialkylation of the amine. The purification process was also chosen to improve efficiency. Since the desired products are basic, they are retained by acidic ion exchange resins. The products were absorbed on the resin and nonbasic impurities were washed out, followed by elution of the products by methanolic ammonia.⁵⁸



A considerable improvement in efficiency can be achieved by solid phase synthesis.⁵⁹ The first reactant is attached to a solid support through a linker group, as was described for polypeptide and oligonucleotide synthesis. The individual reaction steps are then conducted on the polymer-bound material. Use of solid phase methodology has several advantages. Excess reagents can be used to drive individual steps to completion and obtain high yields. The purification after each step is also simplified, since excess reagents and by-products are simply rinsed from the solid support. The process can be automated, greatly reducing the manual effort required.

When solid phase synthesis is combined with sample splitting, there is a particularly useful outcome.⁶⁰ The solid support can be used in the form of small beads, and

⁵⁷. A. Furka, *Drug Dev. Res.*, **36**, 1 (1995).

⁵⁸. A. J. Shuker, M. G. Siegel, D. P. Matthews, and L. O. Weigel, *Tetrahedron Lett.*, **38**, 6149 (1997).

⁵⁹. A. R. Brown, P. H. H. Hermkens, H. C. J. Ottenheijm, and D. C. Rees, *Synlett*, 817 (1998).

⁶⁰. A. Furka, F. Sebestyen, M. Asgedon, and G. Dibo, *Int. J. Peptide Protein Res.*, **37**, 487 (1991); K. S. Lam, M. Lebl, and V. Krchnak, *Chem. Rev.*, **97**, 411 (1997).

the starting point is a collection of beads, each with one initial starting material. After each reaction step the beads are recombined and divided again. As the collection of beads is split and recombined during the combinatorial synthesis, each bead acquires a particular compound, depending on its history of exposure to the reagents, *but every bead in a particular split has the same compound, since their reaction histories are identical*. Figure 13.1 illustrates this approach for three steps, each using three different reactants. However, in the end all of the beads are together and there must be some means of establishing the identity of the compound attached to any particular bead. In some cases it is possible to detect compounds with the desired property while they are still attached to the bead. This is true for some assays of biological or catalytic activity that can be performed under heterogeneous conditions.

Another approach is to tag the beads with identifying markers that encode the sequence of reactants and thus the structure of the product attached to a particular bead.⁶¹ One method of coding involves attachment of a chemically identifiable tag,

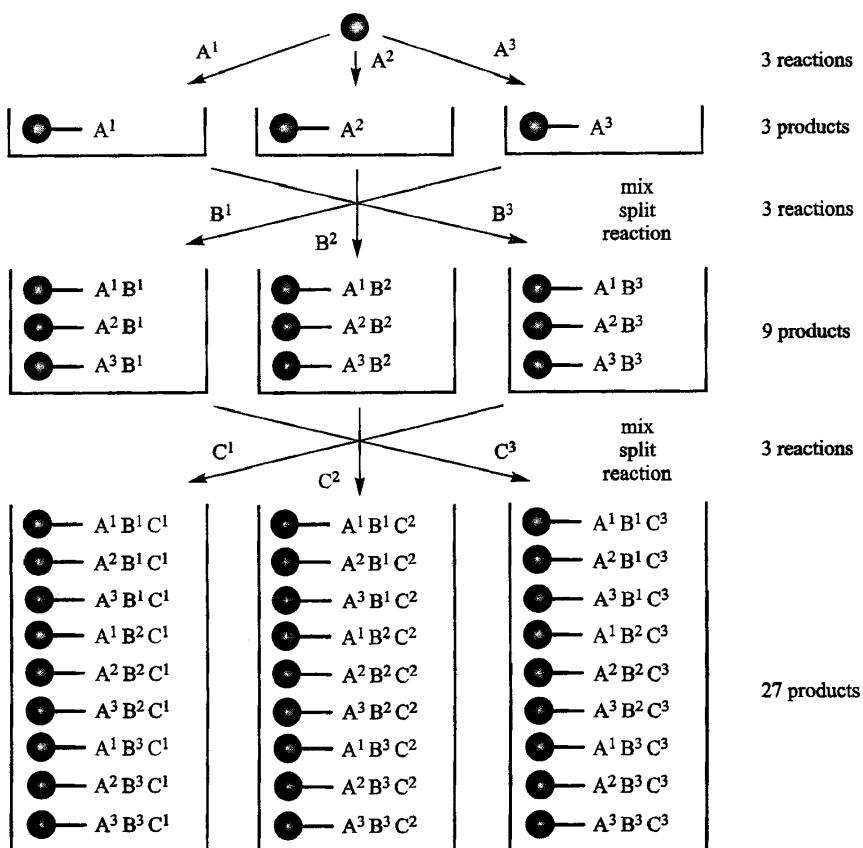


Fig. 13.1. Splitting method for combinatorial synthesis on solid support. Reproduced from F. Balkenhol, C. von dem Bussche-Huenefeld, A. Lansky, and C. Zechel, *Angew. Chem. Int. Ed. Engl.*, **35**, 2288 (1996), by permission of Wiley-VCH.

⁶¹ S. Brenner and R. A. Lerner, *Proc. Natl. Acad. Sci. USA*, **89**, 5381 (1993).

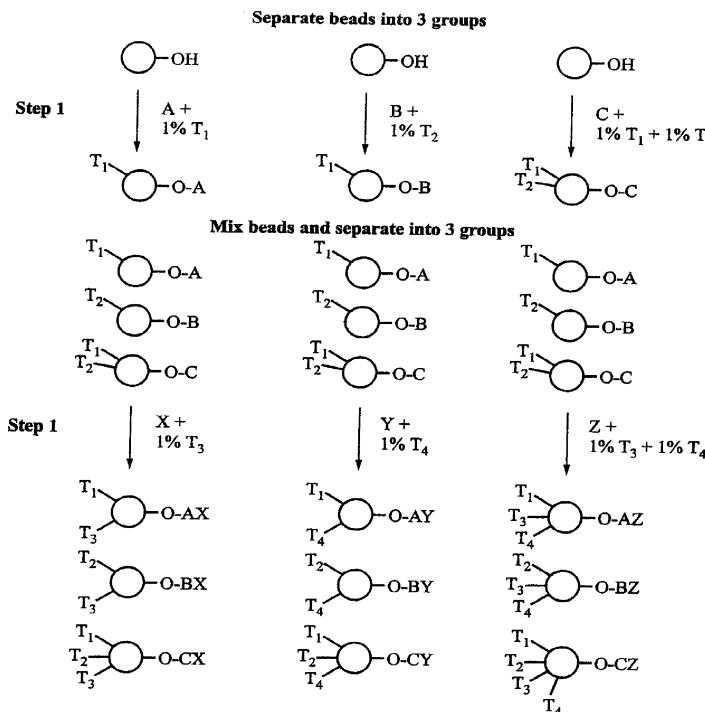
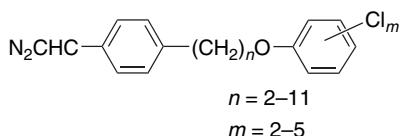


Fig. 13.2. Use of chemical tags to encode the sequence in a combinatorial synthesis on a solid support. Reproduced from W. C. Still, *Acc. Chem. Res.*, **29**, 155 (1996), by permission of the American Chemical Society.

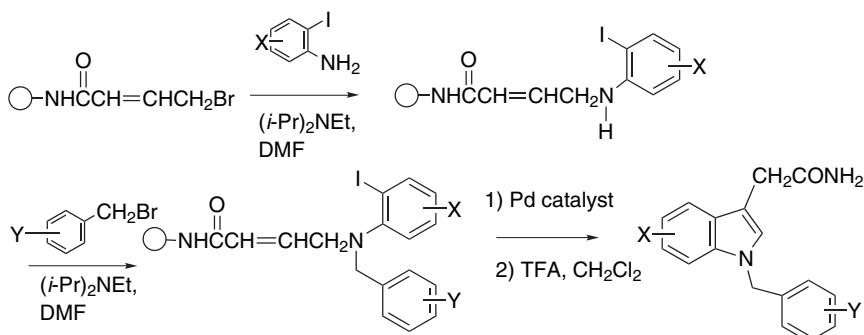
as illustrated in Figure 13.2.⁶² After each combinatorial step, a different chemical tag is applied to each of the splits before they are recombined. The tags used for this approach are a series of chlorinated aromatic ethers that can be detected and identified by mass spectrometry. The tags are attached to the polymer support by a Rh-catalyzed carbenoid insertion reaction. Detachment is done by oxidizing the methoxyphenyl linker with CAN. Any bead that shows interesting biological activity can then be identified by analyzing the code provided by the chemical tags for that particular bead.



Combinatorial approaches can be applied to the synthesis of any type of molecule that can be built up from a sequence of individual components, for example, in reactions forming heterocyclic rings.⁶³ The equations below represent an approach to preparing differentially substituted indoles.

⁶². H. P. Nestler, P. A. Bartlett, and W. C. Still, *J. Org. Chem.*, **59**, 4723 (1994); C. Barnes, R. H. Scott, and S. Babasubramanian, *Recent Res. Develop. Org. Chem.*, **2**, 367 (1998).

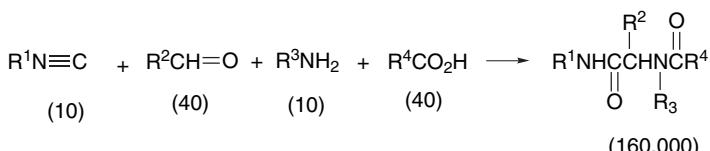
⁶³. A. Netzi, J. M. Ostresh, and R. A. Houghten, *Chem. Rev.*, **97**, 449 (1997).



Ref. 64

There is nothing to prevent incorporation of additional diversity by continuing to build on a side chain at one of the substituent sites.

Another kind of combinatorial synthesis can be applied to reactions that assemble the product from several components in a single step, a *multicomponent reaction*. A particularly interesting four-component reaction is the *Ugi reaction*, which generates dipeptides from an isocyanide, an aldehyde, an amine, and a carboxylic acid.



For example, use of 10 different isocyanides and amines, along with 40 different aldehydes and carboxylic acids has the potential to generate 160,000 different dipeptide analogs.⁶⁵ This system was explored by synthesizing arbitrarily chosen sets of 20 compounds that were synthesized in parallel. The biological assay data from these 20 combinations were then used to select the next 20 combinations for synthesis. The synthesis-assay-selection process was repeated 20 times. At the end of this process the average inhibitory concentration of the set of 20 products had been decreased from 1 mM to less than 1 μM.

A library of over 3000 spirooxindoles was created based on a sequence of four reactions.⁶⁶ The synthetic sequence is based on the total synthesis of a natural product called (-)-spirotryprostatin B.⁶⁷ A morpholinone chiral auxiliary, aldehyde, and an oxindole condense to give the ring system. Substituents were then added by replacement of the iodine by one of several terminal alkynes. Simultaneous deprotection occurred at the allyl ester. These carboxylic acids were converted to amides using a variety of amines and coupling with PyBOP. The final reaction in the sequence was acylation of the oxindole nitrogen. At each stage in the library creation, certain alkynes or amines reacted poorly and were excluded from the library, which was eventually derived from eight alkynes, twelve amines, and four acylation reagents. As outlined in Scheme 13.80, this synthesis has the potential to prepare 3104 different

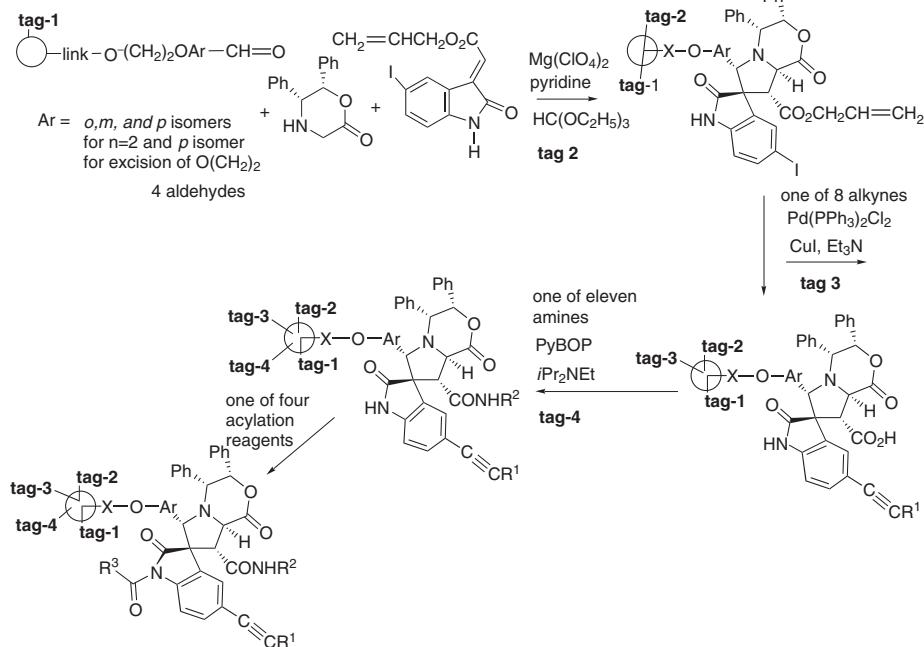
64. H.-C. Zhang and B. E. Maryanoff, *J. Org. Chem.*, **62**, 1804 (1997).
 65. L. Weber, S. Walbaum, C. Broger, and K. Gubernator, *Angew. Chem. Int. Ed. Engl.*, **34**, 2280 (1995).
 66. M. M.-C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein, and S. L. Schreiber, *J. Am. Chem. Soc.*, **126**, 16077 (2004).
 67. P. R. Sebahar, H. Osada, T. Usui, and R. M. Williams, *Tetrahedron*, **58**, 6311 (2002).

Scheme 13.80. Creation of a Combinatorial Library of Spirooxindoles^a

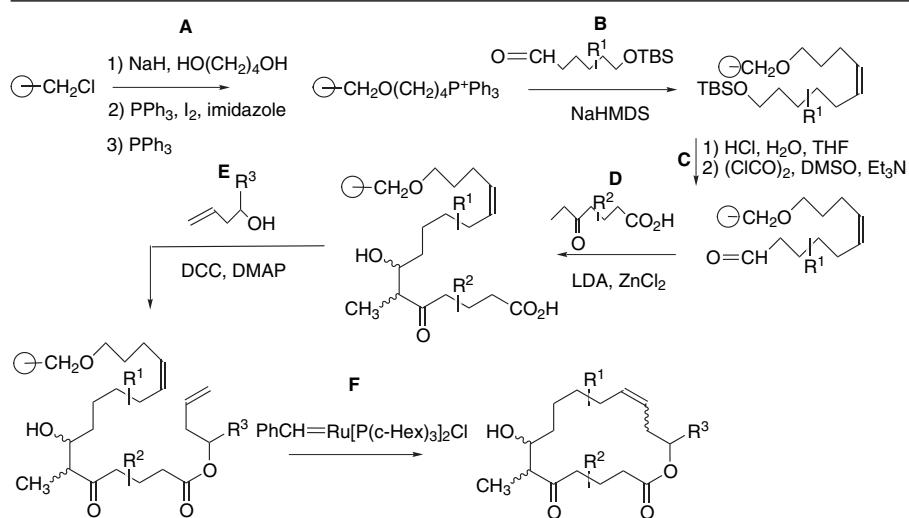
1257

SECTION 13.4

Combinatorial Synthesis



a. M. M.-C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein, and S. L. Schreiber, *J. Am. Chem. Soc.*, **126**, 16077 (2004).

Scheme 13.81. Combinatorial Synthesis of Epothilone Analogs Using Microreactors^a

a. K. C. Nicolaou, D. Vorloumis, T. Li, J. Pastor, N. Winssinger, Y. He, S. Ninkovic, F. Sarabia, H. Vallberg, F. Roschager, N. P. King, M. R. V. Finlay, P. Giannakakou, D. Verdier-Pinard, and E. Hamel, *Angew. Chem. Int. Ed. Engl.*, **36**, 2097 (1997).

compounds, including those lacking a particular substituent (skip) (4 aldehydes \times 2 morpholines \times 1 oxindole) = 8 core structures \times $(1 + 8 \times 12) \times 4 = 3104$ different compounds. A version of the chemical tagging method was used for coding the beads.⁶⁸ Analysis of a sample of the beads indicated that at least 82% of them contained the desired compound in greater than 80% purity.

The epothilone synthesis in Scheme 13.59 (p. 1221) has been used as the basis for a combinatorial approach to epothilone analogs.⁶⁹ The acyclic precursors were

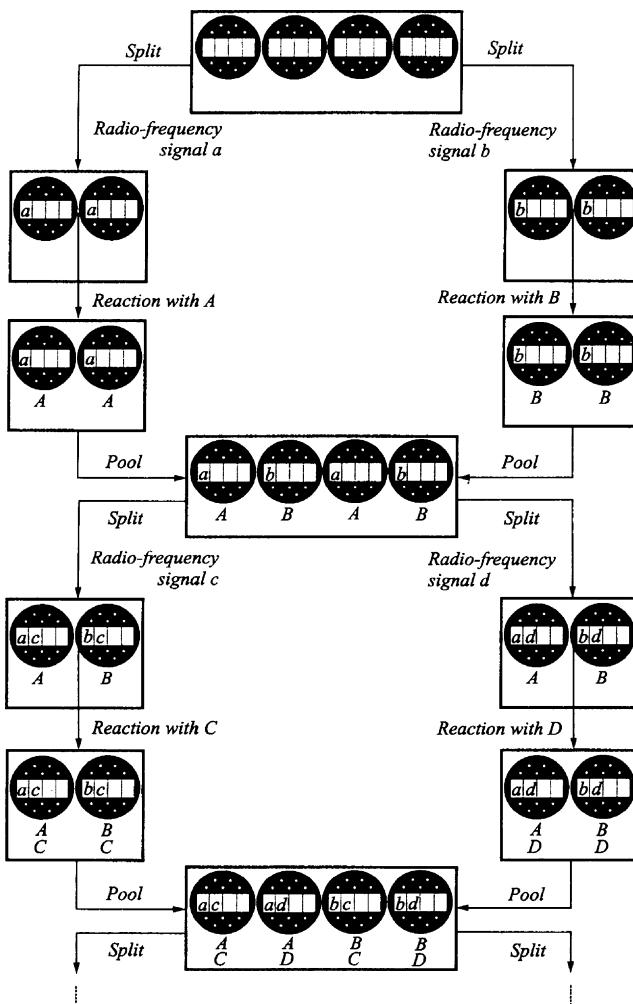


Fig. 13.3. Radio-frequency tagging of microreactors for combinatorial synthesis on a solid support. Reproduced from K. C. Nicolaou, X.-Y. Xiao, Z. Parandoosh, A. Senyei, and M. P. Nova, *Angew. Chem. Int. Ed. Engl.*, **34**, 2289 (1995), by permission of Wiley-VCH.

- ⁶⁸. H. B. Blackwell, L. Perez, R. A. Stavenger, J. A. Tallarico, E. Cope-Etough, M. A. Foley, and S. L. Schreiber, *Chem. Biol.*, **8**, 1167 (2001).
- ⁶⁹. K. C. Nicolaou, N. Wissinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, S. Yang, T. Li, P. Giannakakou, and E. Hamel, *Nature*, **387**, 268 (1997); K. C. Nicolaou, D. Vourloumis, T.

synthesized and attached to a solid support resin by Steps **A** and **B** in Scheme 13.81. The cyclization and disconnection from the resin was then done by the olefin metathesis reaction in Step **F**. The aldol condensation in Step **D** was not highly stereoselective. Similarly, olefin metathesis gave a mixture of *E*- and *Z*-stereoisomers, so the product of each combinatorial sequence was a mixture of four isomers. These were separated by thin-layer chromatography prior to bioassay. In this project, reactants **A** (three variations), **B** (three variations), and **C** (five variations) were used, generating 45 possible combinations. The stereoisomeric products increase this to 180 (45×4).

In this study a nonchemical means of encoding the identity of each compound was used. The original polymer-bound reagent was placed in a porous microreactor that is equipped with a radiofrequency device that can be used for identification.⁷⁰ The porous microreactors permit reagents to diffuse into the polymer-bound reactants, but the polymer cannot diffuse out. At each split, the individual microreactors are coded to identify the reagent that is used. When the synthesis is complete, the sequence of signals recorded in the radiofrequency device identifies the product that has been assembled in that particular reactor. Figure 13.3 illustrates the principle of this coding method.

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⁷⁰ K. C. Nicolaou, Y.-Y. Xiao, Z. Parandoosh, A. Senyei, and M. P. Nova, *Angew. Chem. Int. Ed. Engl.*, **34**, 2289 (1995); E. J. Moran, S. Sarshar, J. F. Cargill, M. M. Shahbaz, A. Lio, A. M. M. Mjalli, and R. W. Armstrong, *J. Am. Chem. Soc.*, **117**, 10787 (1995).

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Solid Phase Synthesis

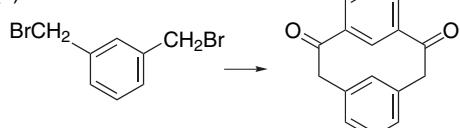
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Problems

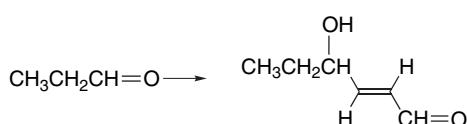
(References for these problems will be found on page 1292.)

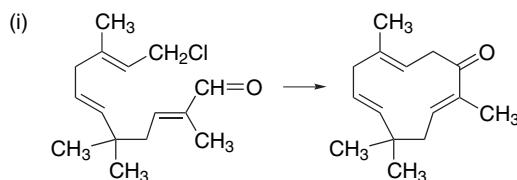
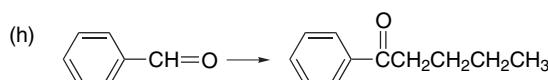
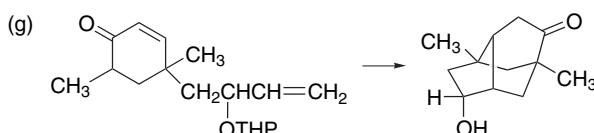
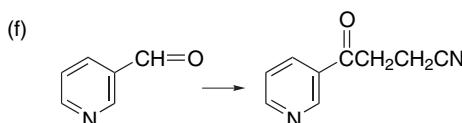
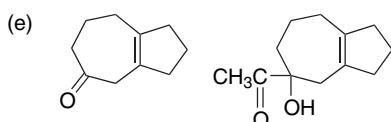
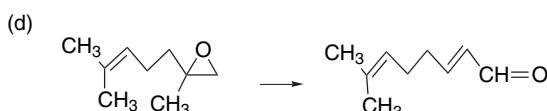
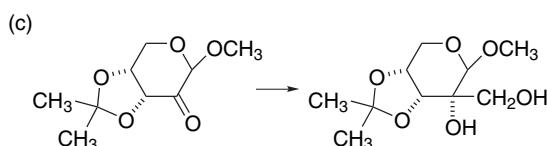
- 13.1. Show how synthetic equivalent groups could be used to carry out each of the following transformations:

(a)

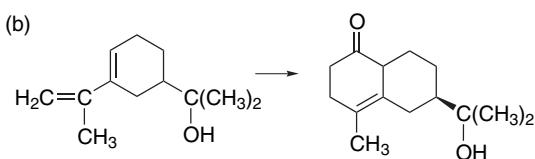
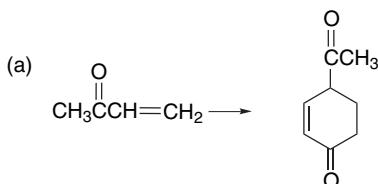


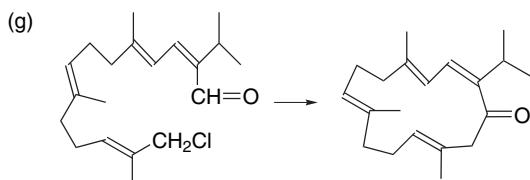
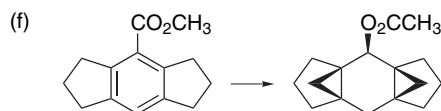
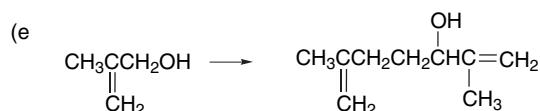
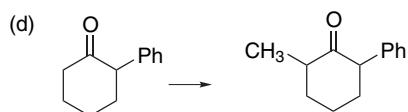
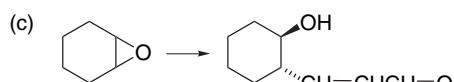
(b)



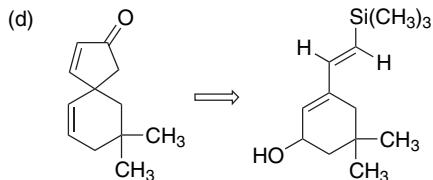
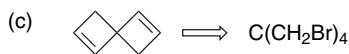
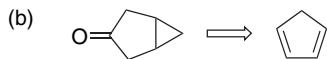
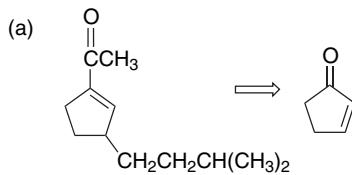


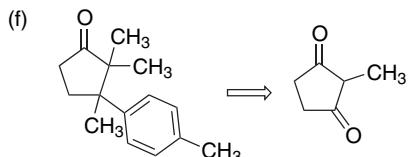
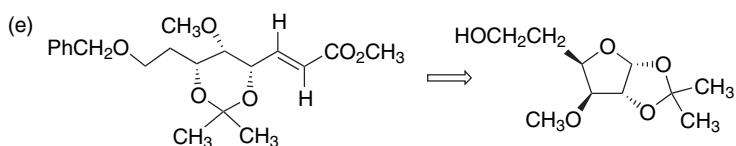
13.2. Indicate a reagent or short synthetic sequence that would accomplish each of the following transformations:



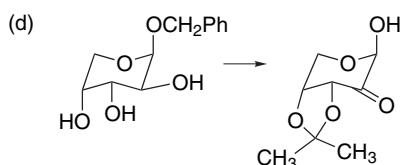
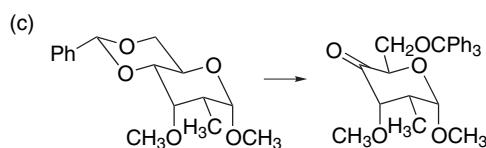
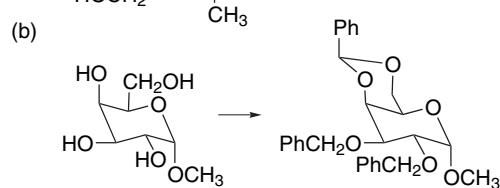
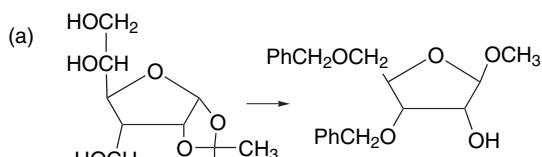


13.3. Indicate reagents or short reaction sequences that could accomplish the synthesis of the target on the left from the starting material on the right.

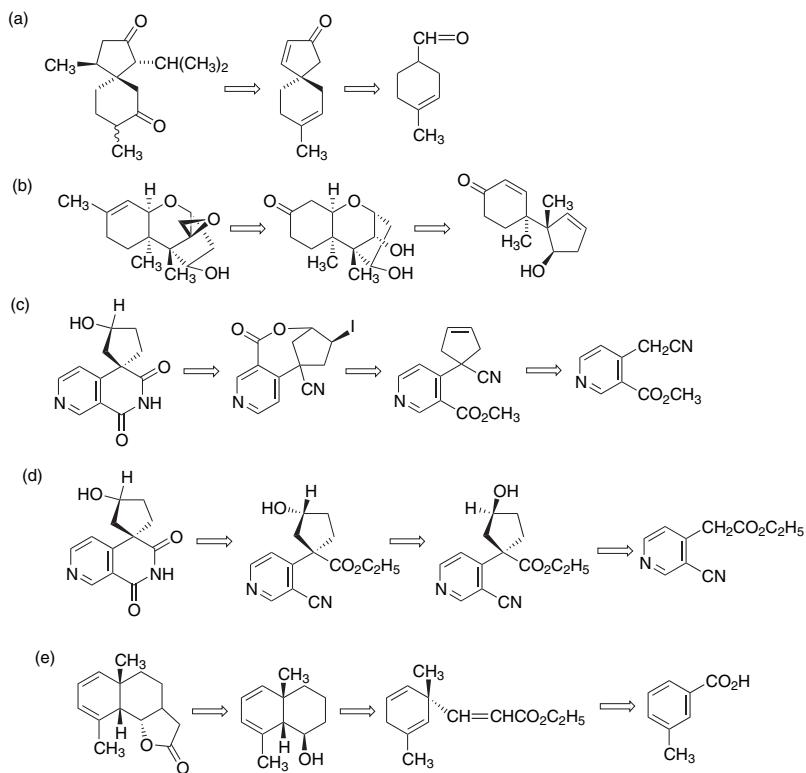




13.4. As they are available from natural sources in enantiomerically pure form, carbohydrates are useful starting materials for syntheses of enantiomerically pure compounds. However, the multiple hydroxy groups require versatile methods for selective protection, reaction, and deprotection. Show how appropriate manipulation of protecting groups and/or selective reagents could be used to effect the following transformations.

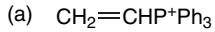


13.5. Several synthetic transformations that are parts of total syntheses of natural products are summarized by retrosynthetic outlines. For each retrosynthetic transform suggest a reagent or short reaction sequence that could accomplish the forward synthetic conversion. The proposed route should be diastereoselective but need not be enantioselective.

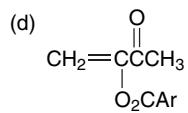
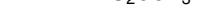
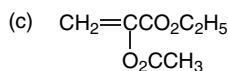
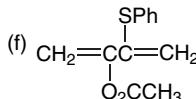
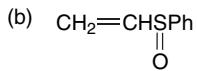
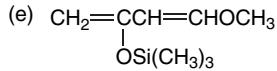


13.6. Diels-Alder reactions are attractive for synthetic application because of the predictable regio- and stereochemistry. There are, however, limitations on the types of compounds that can serve as dienophiles or dienes. As a result, the idea of synthetic equivalence has been exploited by development of dienophiles and dienes that meet the reactivity requirements of the Diels-Alder reaction and can then be converted to the desired structure. For each of the dienophiles and dienes given below, suggest a Diels-Alder reaction and subsequent transformation(s) that would give a product not directly attainable by a Diels-Alder reaction. Give the structure of the diene or dienophile “synthetic equivalent” and indicate why the direct Diels-Alder reaction is not possible.

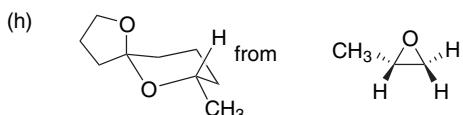
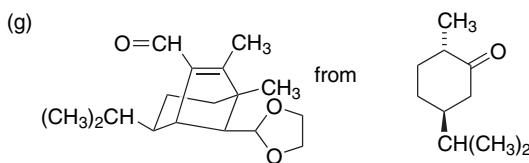
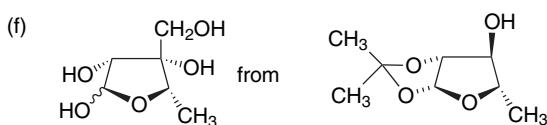
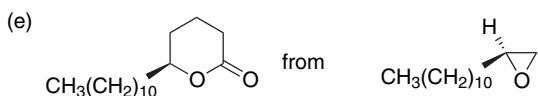
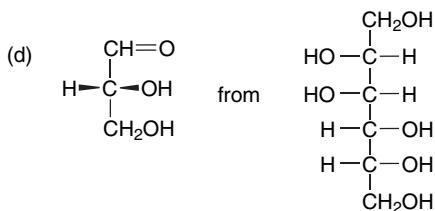
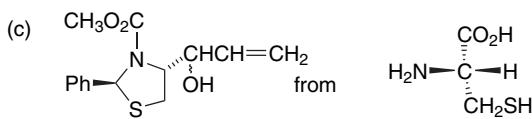
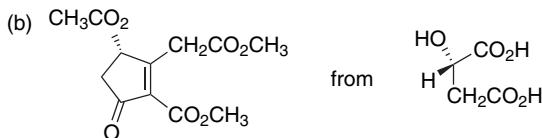
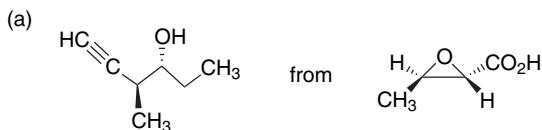
Dienophiles



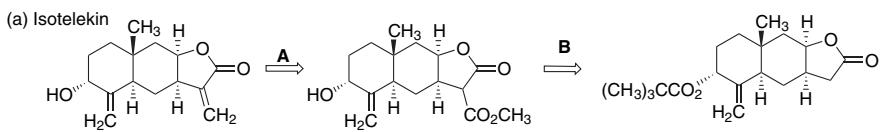
Dienes



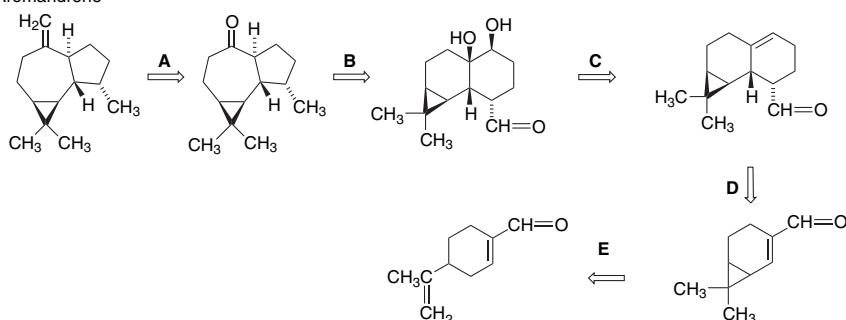
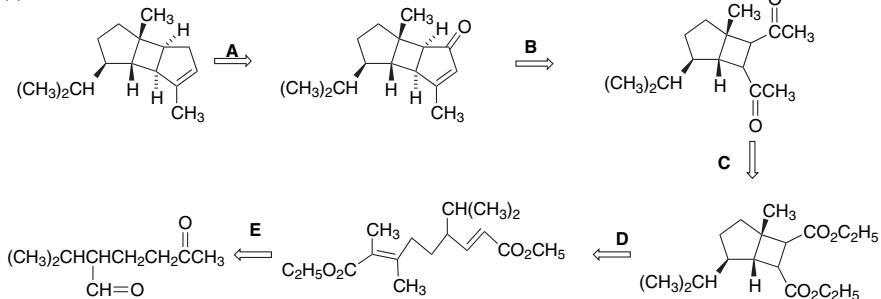
13.7. One approach to the synthesis of enantiomerically pure compounds is to start with an available enantiomerically pure substance and effect the synthesis by a series of enantiospecific reactions. Devise a sequence of reactions that would be appropriate for the following syntheses based on enantiomerically pure starting materials.



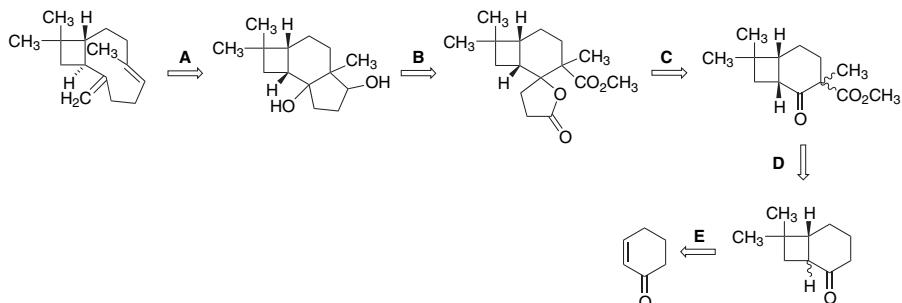
13.8. Several syntheses of terpenoids are outlined in retrosynthetic form. Suggest a reagent or short reaction sequence that could accomplish each lettered transformation in the synthetic direction. The structures refer to racemic material.



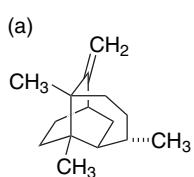
(b) Aromandrene

(c) α -Bourbonene

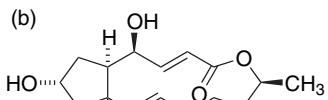
(d) Caryophyllene



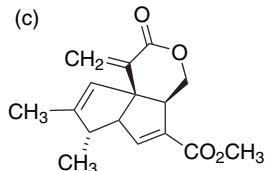
13.9 Use retrosynthetic analysis to suggest syntheses of the following compounds. Develop at least three outline schemes. Discuss the relative merits of the schemes and develop a fully elaborated synthetic plan for the most promising retrosynthetic scheme.



seychellene

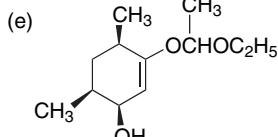
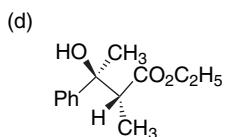
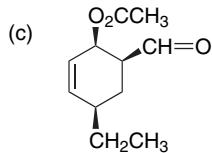
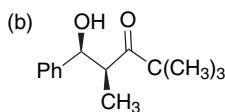
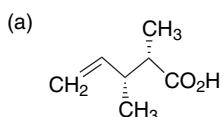


brefeldin A

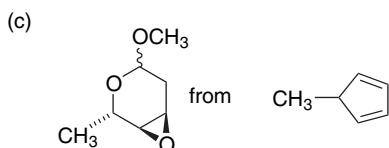
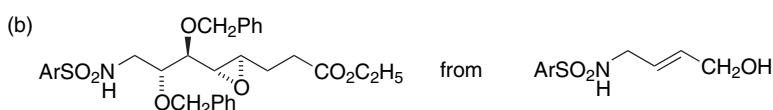
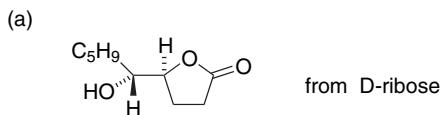


pentalenolactone E

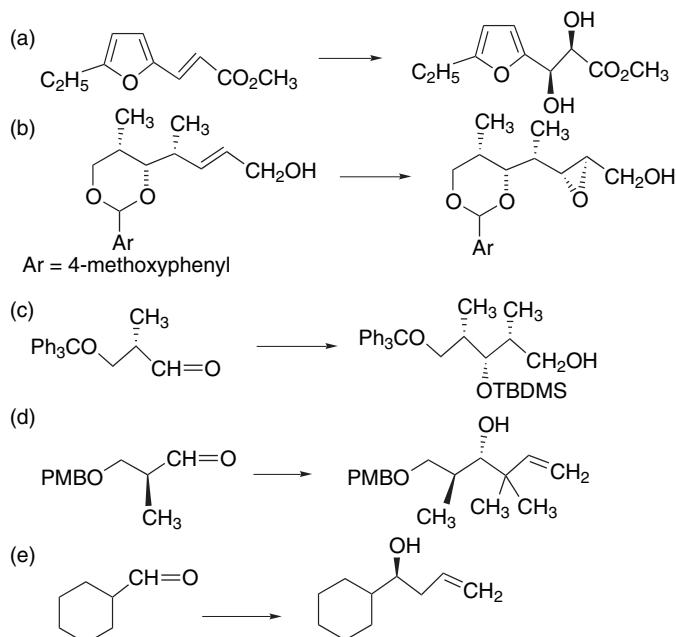
13.10. Suggest a method for diastereoselective synthesis of the following compounds:



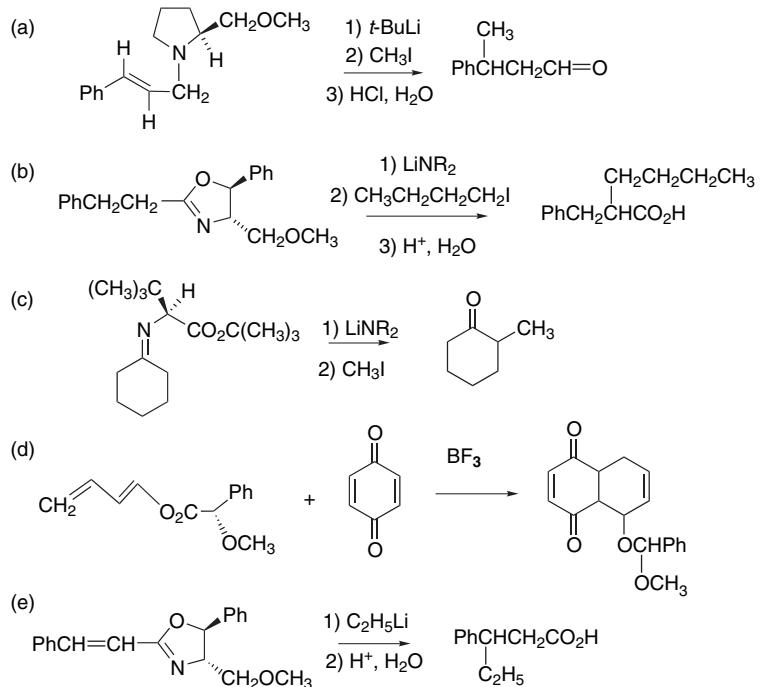
13.11. Devise a route that could be used for synthesis of the desired compound in high enantiomeric purity from the suggested starting material.

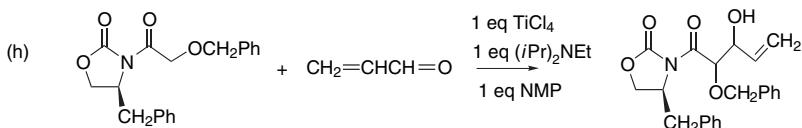
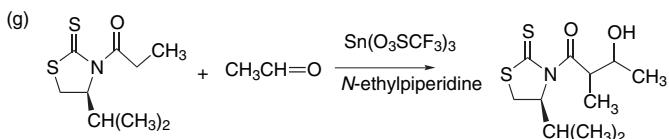
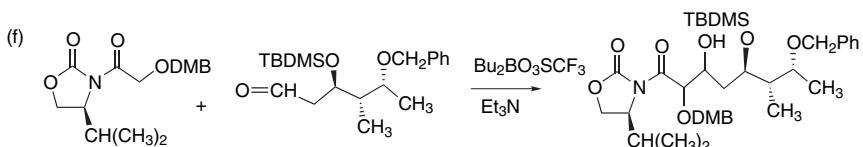


13.12. Select a reagent that will achieve the following syntheses with high enantioselectivity.

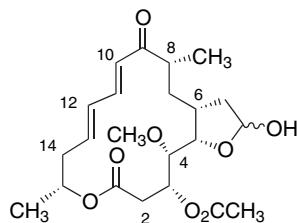


13.13. The following reactions use chiral auxiliaries to achieve enantioselectivity. By consideration of possible TSSs, predict the absolute configuration of the major product of each reaction.



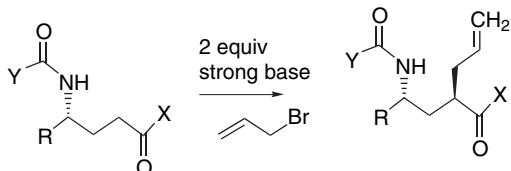


- 13.14. The macrolide carbonolide B contains six stereogenic centers at sp^3 carbons. Devise a strategy for synthesis of carbonolide B and in particular for establishing the stereochemistry of the C(1)–C(8) segment of the molecule.



carbonolide B

- 13.15. 4-(Acylamino)-substituted carboxylate esters and amides can be alkylated with good *anti*-2,4 stereoselectivity using two equivalents of a strong base. The stereoselectivity is independent of the steric bulk of the remainder of the carboxylate structure. Propose a TS that is consistent with these observations.



R	Y	X
CH ₃	CF ₃	OCH ₃
(CH ₃) ₂ CHCH ₂	CF ₃	OCH ₃
PhCH ₂	CF ₃	OCH ₃
PhCH ₂	CF ₃	N(CH ₃) ₂
PhCH ₂	CF ₃	N(CH ₃)OCH ₃
CH ₃	(CH ₃) ₃ CO	OCH ₃
(CH ₃) ₂ CH	(CH ₃) ₃ CO	OCH ₃

- 13.16. Using as a designation of a “step” each numbered reagent or reagent combination in Schemes 13.54 to 13.59 for the synthesis of the Taxol precursors shown there, outline the syntheses in terms of convergence and determine the longest linear sequence (as on p. 1166). In general, these Taxol syntheses are quite linear in character. Is there a structural reason for this tendency toward linearity?

References for Problems

Chapter 1

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