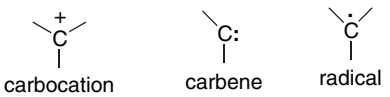
10

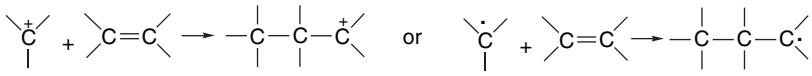
Reactions Involving Carbocations, Carbenes, and Radicals as Reactive Intermediates

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.



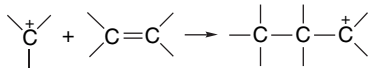
Owing to the low barriers to bond formation, *reactant conformation* often plays a decisive role in the outcome of these reactions. Carbocations, carbene, and radicals frequently undergo very efficient *intramolecular reactions* that depend on the proximity of the reaction centers. Conversely, because 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

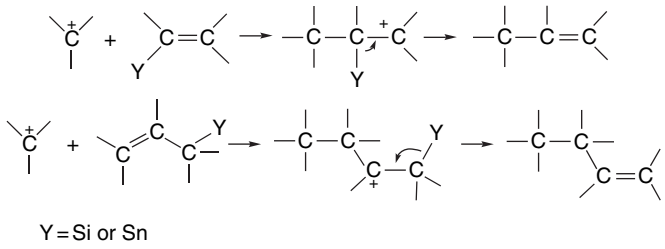
In this section, the emphasis is on carbocation reactions that modify the carbon skeleton, including carbon-carbon bond formation, rearrangements, and fragmentation reactions. The fundamental structural and reactivity characteristics of carbocations toward nucleophilic substitution were explored in Chapter 4 of Part A.

10.1.1. Carbon-Carbon Bond Formation Involving Carbocations

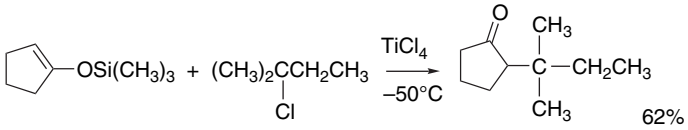
10.1.1.1. Intermolecular Alkylation by Carbocations. The formation of carbon-carbon bonds by electrophilic attack on the π system is a very important reaction in aromatic chemistry, with both Friedel-Crafts alkylation and acylation following this pattern. These reactions are discussed in Chapter 11. 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 stannyl substituent is eliminated and a stable alkene is formed. The increased reactivity of the silyl- and stannyl-substituted alkenes is also favorable to the synthetic utility of carbocation-alkene reactions because the reactants are more nucleophilic than the product alkenes.

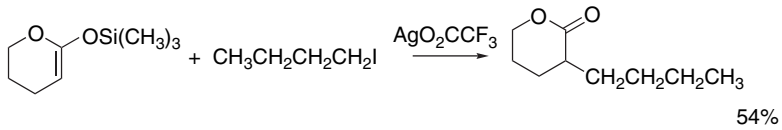


Silyl enol ethers and silyl ketene acetals also offer both enhanced reactivity and a favorable termination step. Electrophilic attack is followed by desilylation to give an α-substituted carbonyl compound. The carbocations can be generated from tertiary chlorides and a Lewis acid, such as $TiCl_4$. This 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.

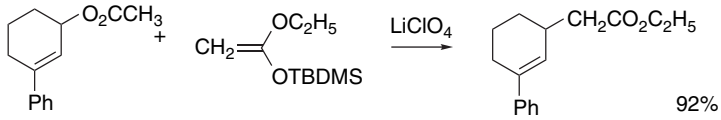


Ref. 1

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]



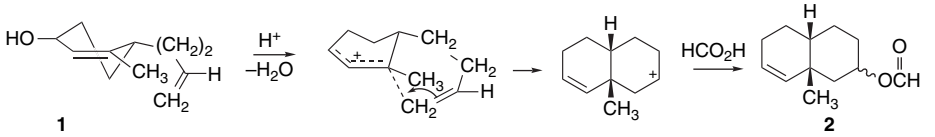
Alkylations via an allylic cation have been observed using $LiClO_4$ to promote ionization.[4]



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.

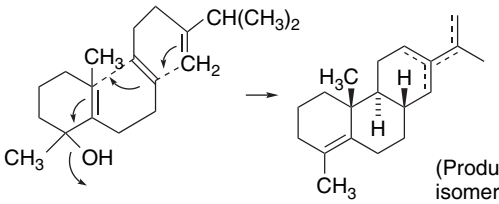
1. M. T. Reetz, I. Chatziiosifidis, U. Loewe, and W. F. Maier, *Tetrahedron Lett.*, 1427 (1979); M. T. Reetz, I. Chatziiosifidis, F. Huebner, and H. Heimbach, *Org. Synth.*, **62**, 95 (1984).
2. I. Paterson, *Tetrahedron Lett.*, 1519 (1979).
3. C. W. Jefford, A. W. Sledeski, P. Lelandais, and J. Boukouvalas, *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.



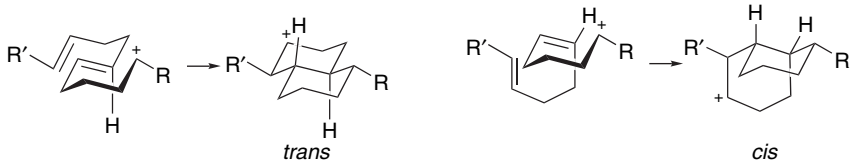
Ref. 5

More extended polyenes can cyclize to tricyclic systems.



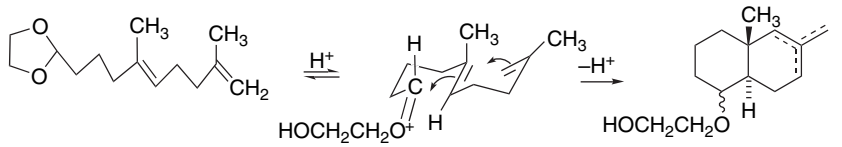
Ref. 6

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]

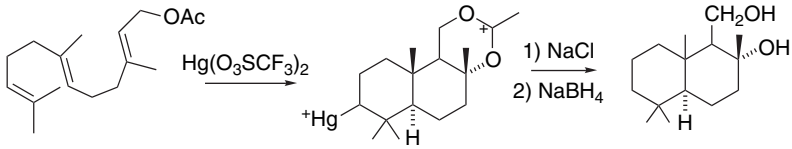
5. W. S. Johnson, P. J. Neustaedter, and K. K. Schmiegel, *J. Am. Chem. Soc.*, **87**, 5148 (1965).
6. W. J. Johnson, N. P. Jensen, J. Hooz, and E. J. Leopold, *J. Am. Chem. Soc.*, **90**, 5872 (1968).
7. W. S. Johnson, *Acc. Chem. Res.*, **1**, 1 (1968); P. A. Bartlett, in *Asymmetric Synthesis*, Vol. 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).



(Dotted lines indicate mixture of unsaturated products)

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 $TiCl_3$(O-*i*-Pr) can be used,[10] as illustrated by Entries 4 to 7 in Scheme 10.1.

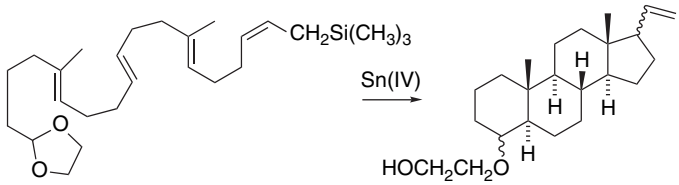
Mercuric ion is capable of inducing cyclization of polyenes.



Ref. 11

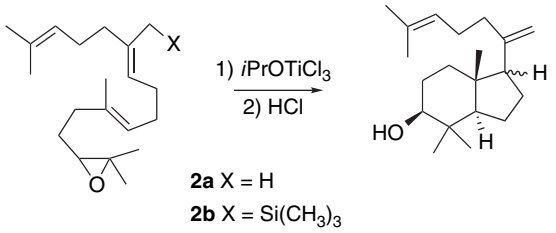
The particular example shown also has a special mechanism for stabilization of the cyclized carbocation. The adjacent acetoxy group is captured to form a stabilized dioxanylium cation. After reductive demercuration (see Section 4.1.3) and hydrolysis, a diol is isolated.

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:l mixture of stereoisomers.[13] This is presumably due to the enhanced reactivity and selectivity of the allylic silane.

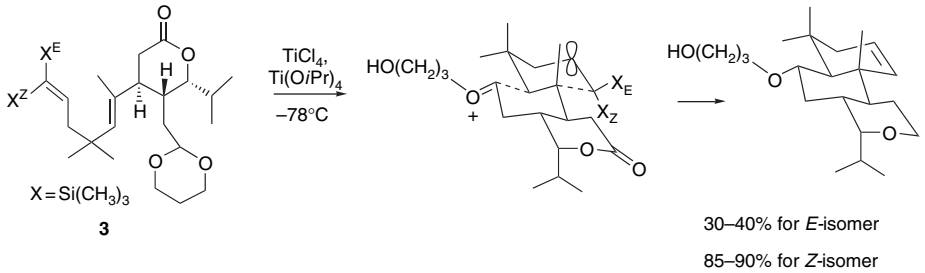
9. E. E. van Tamelen and R. G. Nadeau, *J. Am. Chem. Soc.*, **89**, 176 (1967).
10. E. J. Corey and M. Sodeoka, *Tetrahedron Lett.*, **33**, 7005 (1991); P. V. Fish, A. R. Sudhakar, and W. S. Johnson, *Tetrahedron Lett.*, **34**, 7849 (1993).
11. M. Nishizawa, H. Takenaka, and Y. Hayashi, *J. Org. Chem.*, **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).



2a X = H

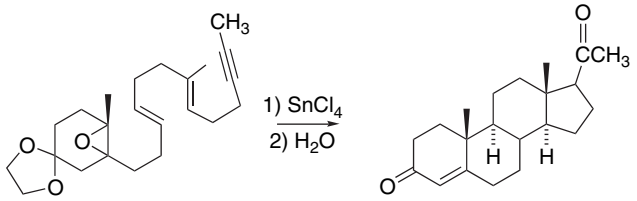
2b X = $Si(CH_3)_3$

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.

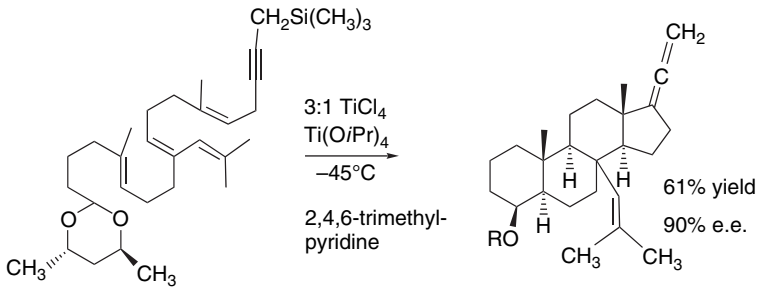


3

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]

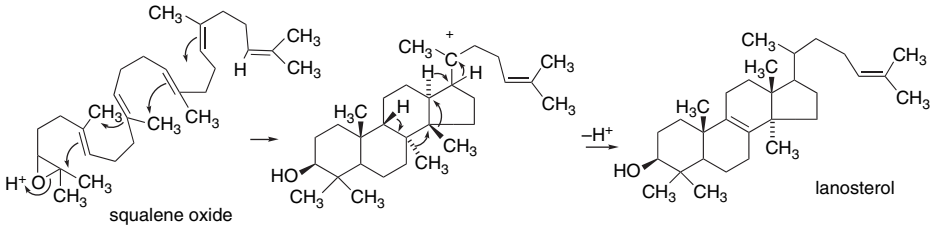


[14] S. D. Burke, M. E. Kort, S. M. S. Strickland, H. M. Organ, and L. A. Silks, III, *Tetrahedron Lett.*, **35**, 1503 (1994).

[15] E. E. van Tamelen and J. R. Hwu, *J. Am. Chem. Soc.*, **105**, 2490 (1983).

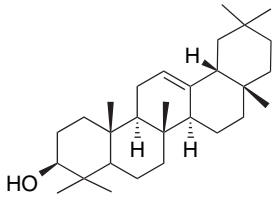
[16] D. Guay, W. S. Johnson, and U. Schubert, *J. Org. Chem.*, **54**, 4731 (1989).

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 to 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.

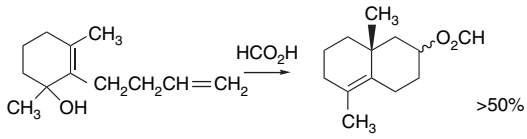


β-Amyrin

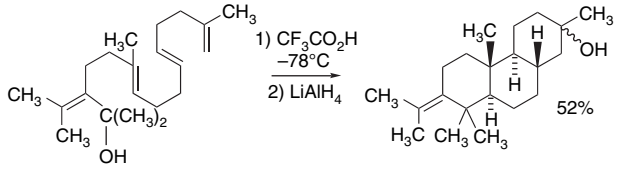
[17] D. Cane, *Chem. Rev.*, **90**, 1089 (1990); I. Abe, M. Rohmer, and G. D. Prestwich, *Chem. Rev.*, **93**, 2189 (1993); K. U. Wendt and G. E. Schulz, *Structure*, **6**, 127 (1998).

Scheme 10.1. Polyene Cyclizations

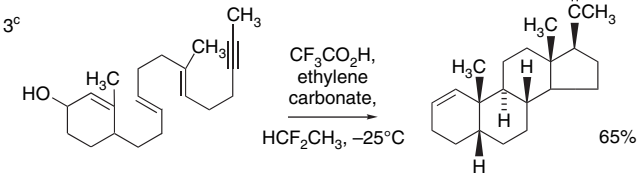
1[a]



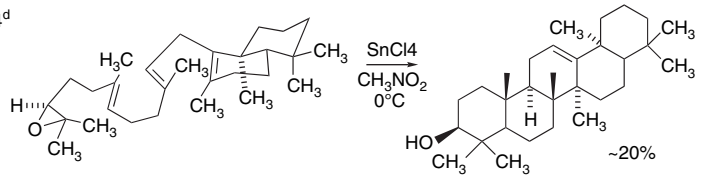
2[b]



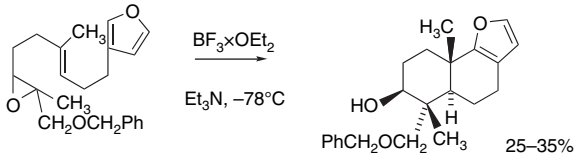
3[c]



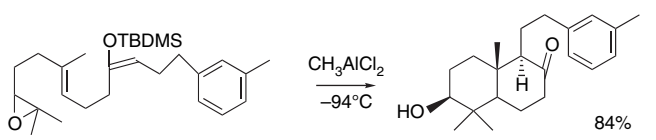
4[d]



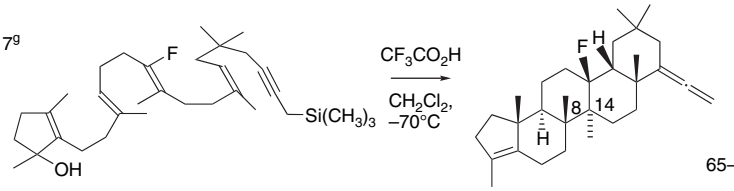
5[e]



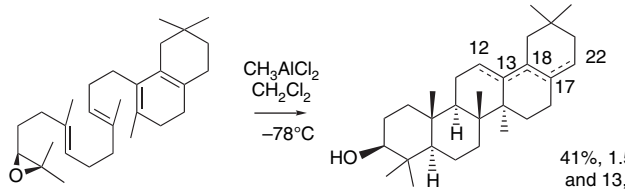
6[f]



7[g]



8[h]

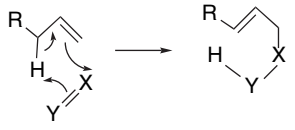


(*Continued*)

Scheme 10.1. (*Continued*)

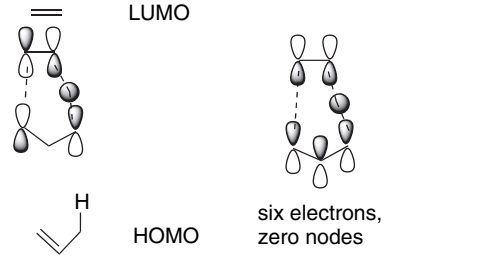
a. J. A. Marshall, N. Cohen, and A. R. Hochstetler, *J. Am. Chem. Soc.*, **88**, 3408 (1966).
b. W. S. Johnson and T. K. Schaaf, *J. Chem. Soc., Chem. Commun.*, 611 (1969).
c. B. E. McCarry, R. L. Markezich, and W. S. Johnson, *J. Am. Chem. Soc.*, **95**, 4416 (1973).
d. E. E. van Tamelen, R. A. Holton, 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).

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, $^1O{=}O$. After a mechanistic overview of the reaction, we concentrate on the carbon-carbon bond-forming reactions. The important and well-studied reaction with $^1O{=}O$ is discussed in Section 12.3.2.

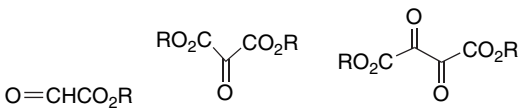
The concerted mechanism shown above is allowed by the Woodward-Hoffmann rules. The TS involves the π electrons of the alkene and enophile and the σ electrons of the allylic C−H bond. The reaction is classified as a $[\pi 2 + \pi 2 + \sigma 2]$ and either an FMO or basis set orbital array indicates an 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).

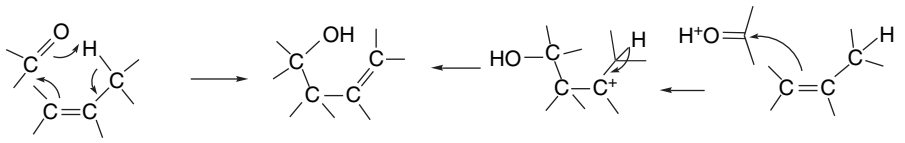
or, especially, maleic anhydride are more reactive. Similarly, for carbonyl compounds, glyoxylate, oxomalonate, and dioxosuccinate esters are among the typical reactants under thermal conditions.



glyoxylate ester | oxomalonate ester | dioxosuccinate ester

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.

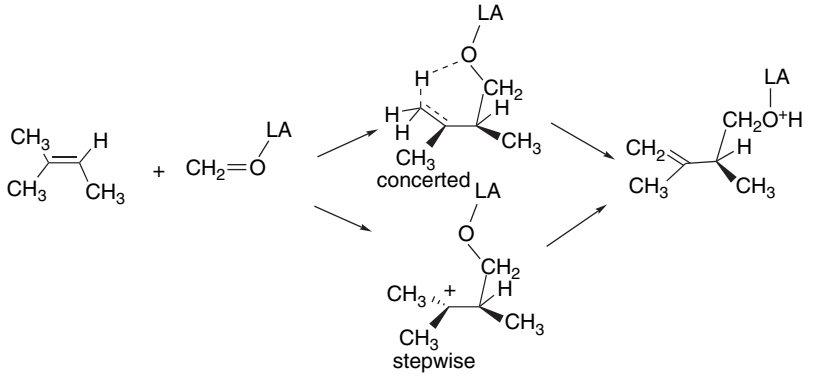
The carbonyl-ene reaction is strongly catalyzed by Lewis acids,[23] such as BF_3, $SnCl_4$, and $(CH_3)_2AlCl$.[24,25] Coordination of a Lewis acid at the carbonyl group increases its electrophilicity and allows reaction to occur at or below room temperature. The reaction becomes much more polar under Lewis acid catalysis and is more sensitive to solvent polarity[26] 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.



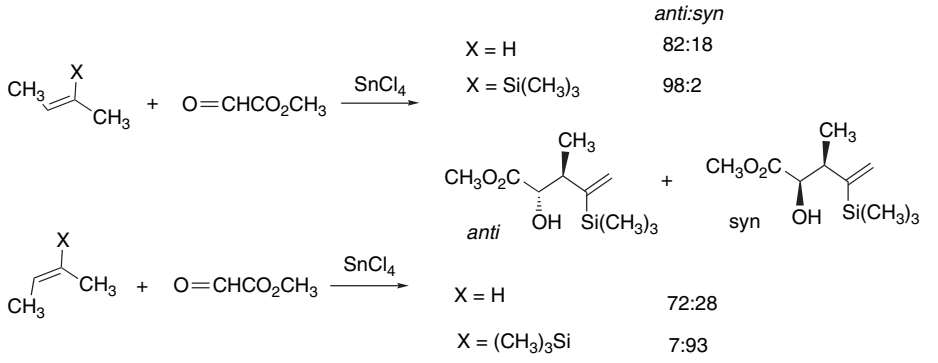
concerted carbonyl–ene reaction | stepwise mechanism

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 experimental isotope effects have been measured for the reaction of 2-methylbutene with formaldehyde with diethylaluminum chloride as the catalyst,[27] and are consistent with a stepwise mechanism or a concerted mechanism with a large degree of bond formation at the TS. B3LYP/6-31G* computations using H^+ as the Lewis acid favored a stepwise mechanism.

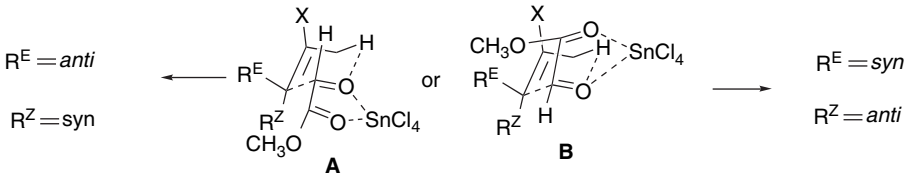


The best carbonyl components for these reactions are highly electrophilic compounds such as glyoxylate, pyruvate, and oxomalonate esters, as well as chlorinated and fluorinated aldehydes. Most synthetic applications of the carbonyl-ene reaction utilize Lewis acids. Although such reactions may be stepwise 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

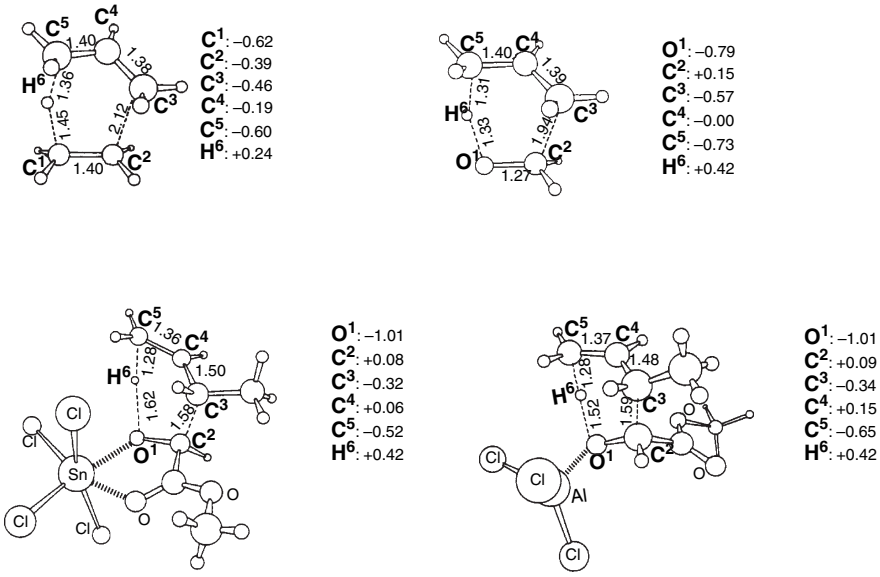
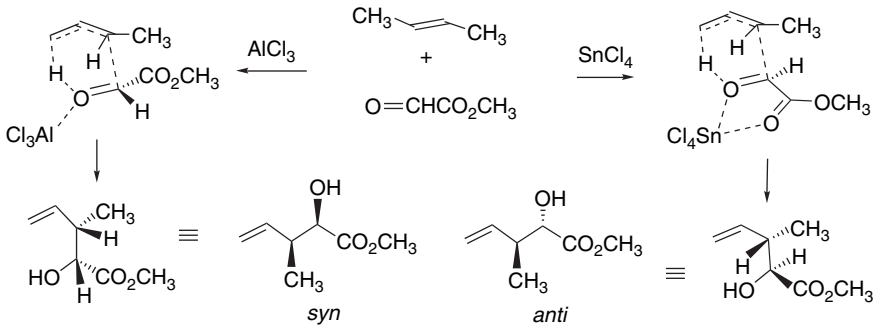


Fig. 10.1. Minimum-energy transition structures for ene reactions: (a) propene and ethene; (b) propene and formaldehyde; (c) butene and methyl glyoxylate–$SnCl_4$; (d) butene and methyl glyoxylate–$AlCl_3$. Reproduced from *Helv. Chim. Acta*, **85**, 4264 (2002), by permission of Wiley-VCH.

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).

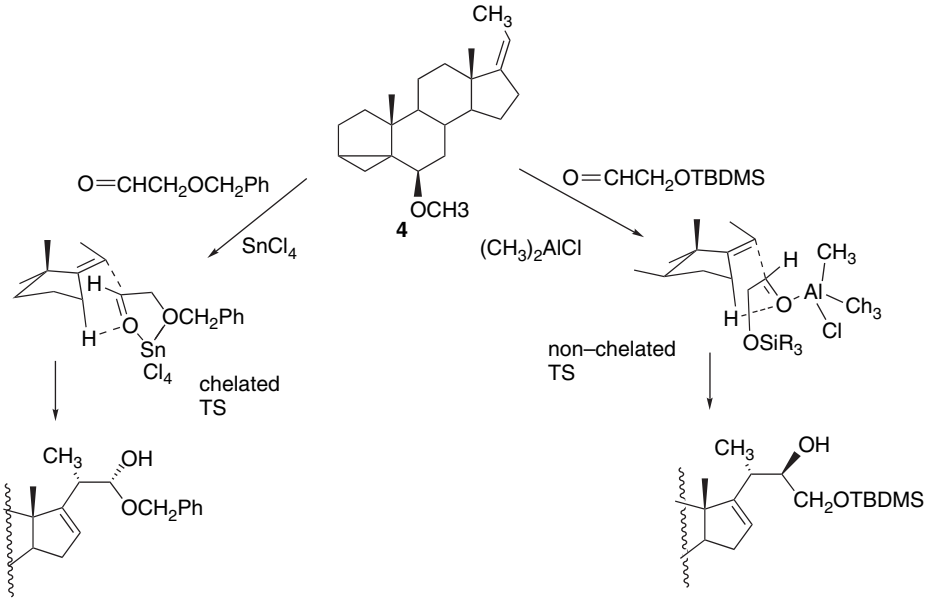
of the unshared electrons on the ester oxygen. The *exo* TS is believed to be favored by an electrostatic interaction between the oxygen and C(4).



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.

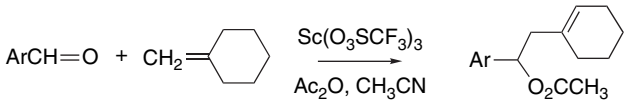
Examples of catalyst control of stereoselectivity have been encountered in the course of the use of the ene reaction to elaborate a side chain on the steroid nucleus. The steroid **4** gave stereoisomeric products, depending on the catalysts and specific aldehyde that were used.[33] This is attributed to the presence of a chelated structure in the case of the $SnCl_4$ catalyst.



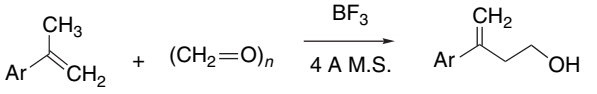
[33] K. Mikami, H. Kishino, and T.-P. Loh, *J. Chem. Soc., Chem. Commun.*, 495 (1994).

The stereoselectivity of the $(CH_3)_2AlCl$-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 $Yb(fod)_3$.[35] $Sc(O_3SCF_3)_3$ has also been used to catalyze carbonyl-ene reactions.[36]

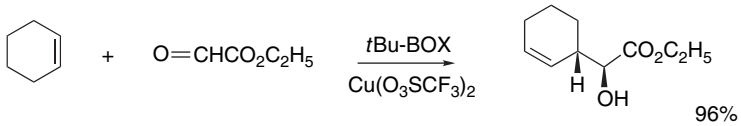


Among the more effective conditions for reaction of formaldehyde with α-methylstyrenes is BF_3 in combination with 4A molecular sieves.[37]



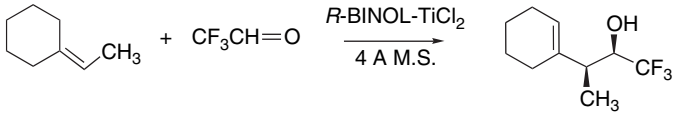
The function of the molecular sieves in this case is believed to be as a base that sequesters the protons, which otherwise would promote a variety of side reactions.

With chiral catalysts, the carbonyl ene reaction becomes enantioselective. Among the successful catalysts are diisopropoxyTi(IV)BINOL and copper-BOX complexes.



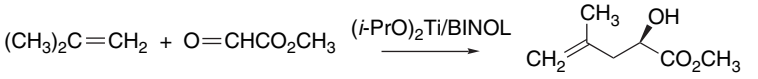
96% e.e.

Ref. 38



94% yield, 98% syn, 96% e.e.

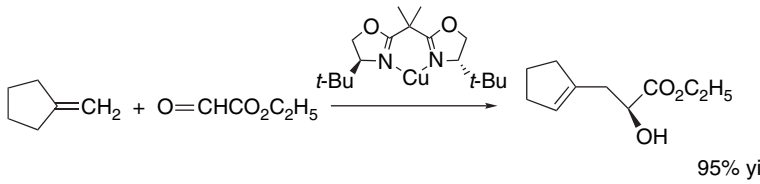
Ref. 39



72% yield, 95% e.e.

Ref. 40

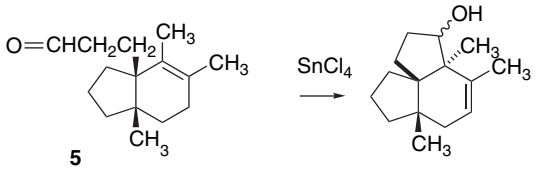
34. T. A. Houston, Y. Tanaka, and M. Koreeda, *J. Org. Chem.*, **58**, 4287 (1993).
35. M. A. Ciufolini, M. V. Deaton, S. R. Zhu, and M. Y. Chen, *Tetrahedron*, **53**, 16299 (1997); M. A. Ciufolini and S. Zhu, *J. Org. Chem.*, **63**, 1668 (1998).
36. V. K. Aggarawal, G. P. Vennall, P. N. Davey, and 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**.



5

Ref. 44

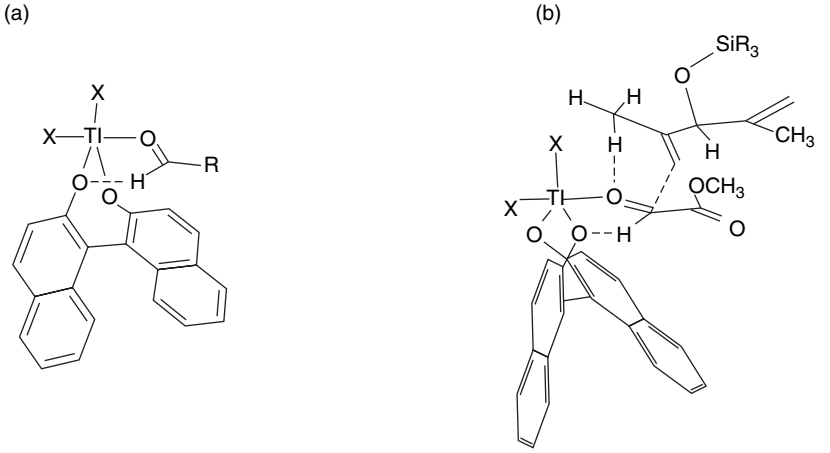
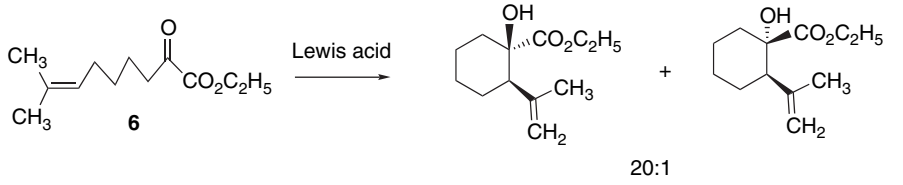


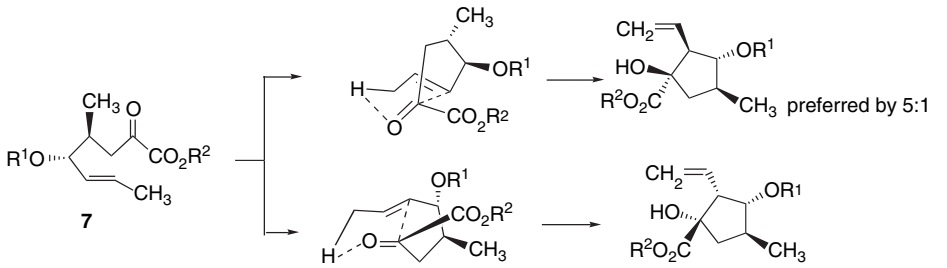
Fig. 10.2. Structures of complexed aldehyde reagent (a) and transition structure (b) for enantioselective catalysis of the carbonyl-ene reaction by BINOL-Ti(IV). Reproduced from *Tetrahedron Lett.*, **38**, 6513 (1997), by permission of Elsevier.

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).

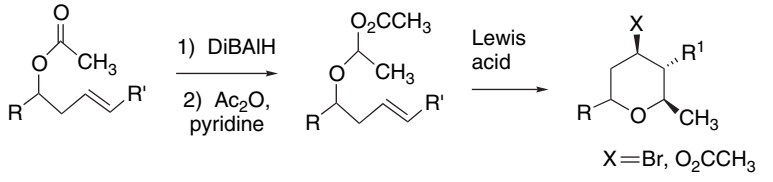
The cyclization of the α-ketoester **6** can be effected by $Mg(ClO_4)_2$, $Yb(OTf)_3$, $Cu(OTf)_2$, or $Sc(OTf)_3$.[45] The reaction exhibits a 20:1 preference for formation of the *trans*-2-(1-methylpropenyl) isomer. The reaction can be conducted with greater than 90% e.e. using $Cu(OTf)_2$ or $Sc(OTf)_3$ with the *t*-Bu-BOX ligand.



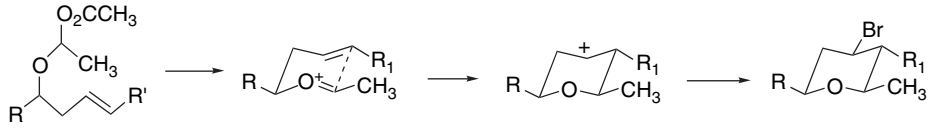
As an example of a thermal reaction, **7** cyclizes at 180°C. The reaction is stereoselective and the two stereoisomers can be formed from competing cyclic TSs.[46]



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]

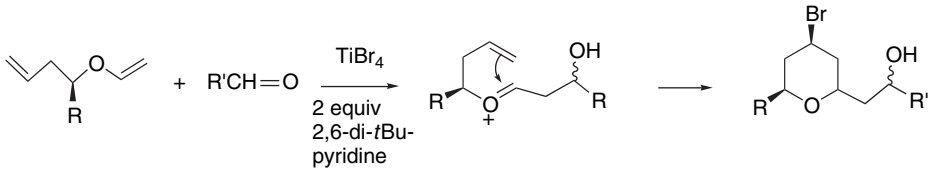


The reaction stereochemistry is consistent with a cyclic TS.

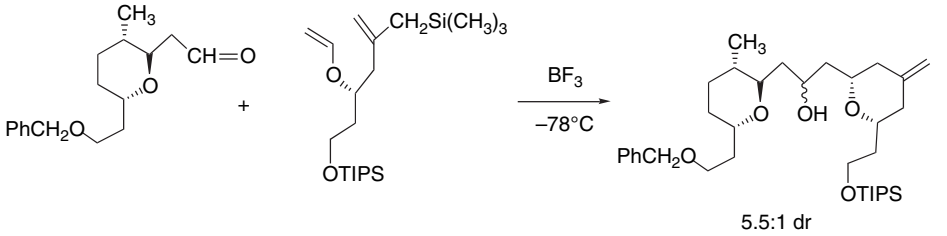


A tandem combination initiated by a Mukaiyama reaction generates an oxonium ion that cyclizes to give a tetrahydropyran rings.[48]

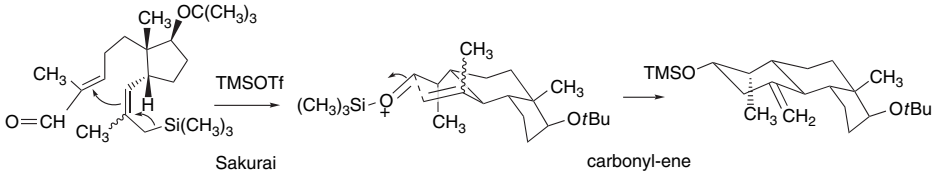
45. D. Yang, M. Yang, and N.-Y. Zhu, *Org. Lett.*, **5**, 3749 (2003).
46. H. Helmboldt, J. Rehbein, and M. Hiersemann, *Tetrahedron Lett.*, **45**, 289 (2004).
47. J. J. Jaber, K. Mitsui, and S. D. Rychnovsky, *J. Org. Chem.*, **66**, 4679 (2001).
48. B. Patterson and S. D. Rychnovsky, *Synlett*, 543 (2004).



This reaction has been used in coupling two fragments in a synthesis of leucascandrolide, a cytotoxic substance isolated from a sponge.[49]

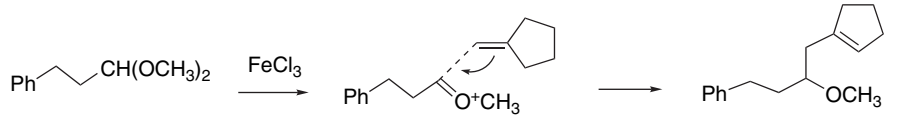


A tandem Sakurai-carbonyl-ene sequence was used to create a tricyclic skeleton in the synthesis of a steroidal structure.[50]



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 propynoate 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.



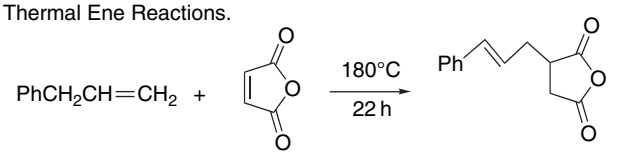
Entry 6 uses diisopropoxytitanium with racemic BINOL as the catalyst. Entry 7 shows the use of $(CH_3)_2AlCl$ with a highly substituted aromatic aldehyde. The product

[49] D. J. Kopecky and S. D. Rychnovsky, *J. Am. Chem. Soc.*, **123**, 8420 (2001).
[50] L. F. Tietze and M. Rischer, *Angew. Chem. Int. Ed. Engl.*, **31**, 1221 (1992).

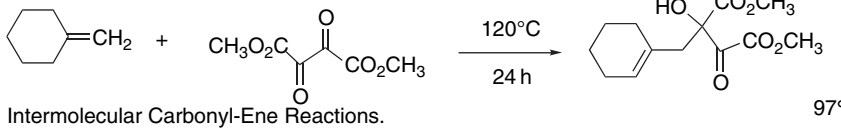
Scheme 10.2. Ene and Carbonyl-Ene Reactions

A. Thermal Ene Reactions.

1[a]

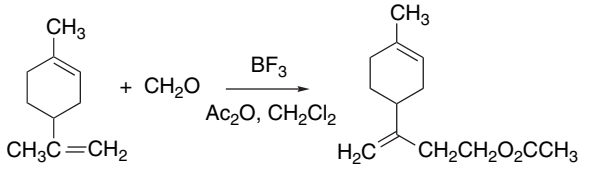


2[b]

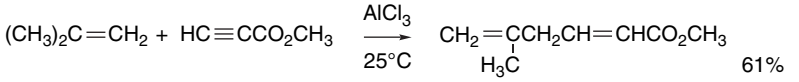


B. Intermolecular Carbonyl-Ene Reactions.

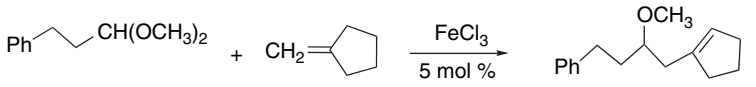
3[c]



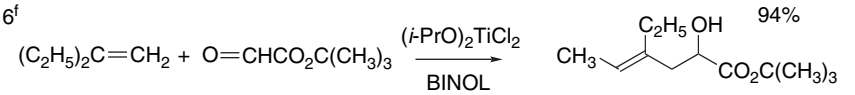
4[d]



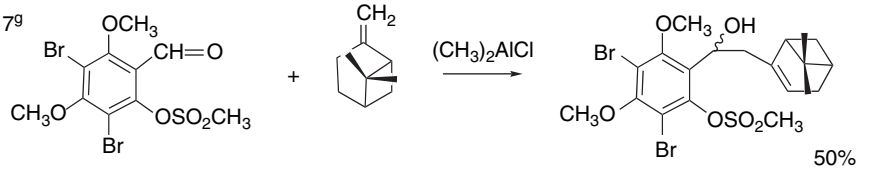
5[e]



6[f]

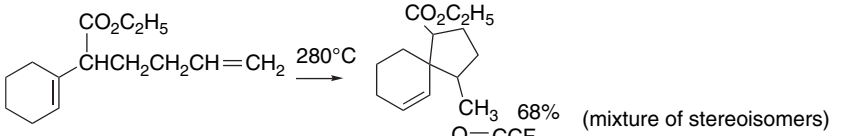


7[g]

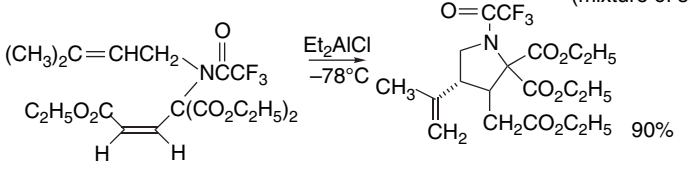


C. Intramolecular Ene Reactions.

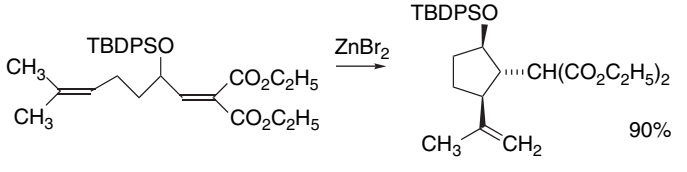
8[h]



9[i]



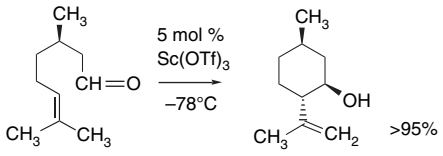
10[j]



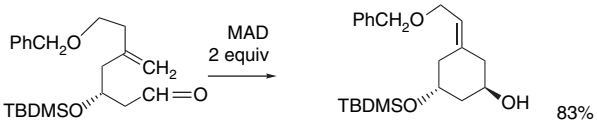
(*Continued*)

Scheme 10.2. (*Continued*)

11[k]

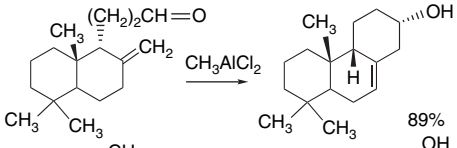


12[l]

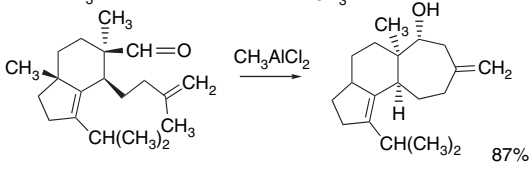


MAD = methyl-*bis*-(2,6-di-*t*-butylphenoxy)aluminum

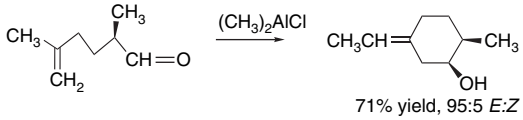
13[m]



14[n]



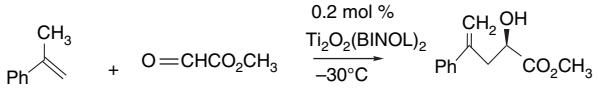
15[o]



71% yield, 95:5 *E:Z*

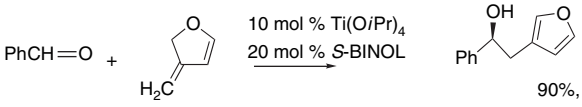
D. Enantioselective Carbonyl Ene Reactions.

16[p]



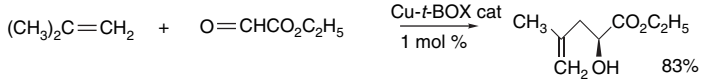
88%, 99% e.e.

17[q]

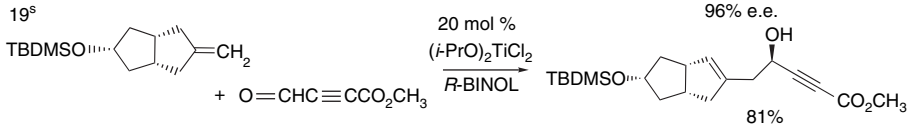


90%, 95% e.e.

18[r]



19[s]



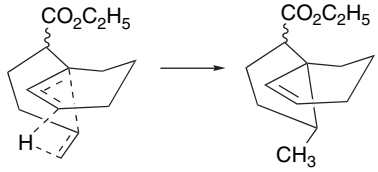
(*Continued*)

Scheme 10.2. (*Continued*)

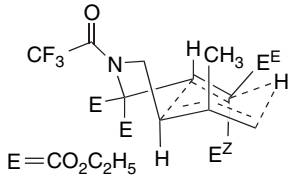
a. C. S. Rondestvedt, Jr., *Org. Synth.*, **IV**, 766 (1963).
b. P. Beak, Z. Song, and J. E. Resek, *J. Org. Chem.*, **57**, 944 (1992).
c. A. T. Blomquist and R. J. Himics, *J. Org. Chem.*, **33**, 1156 (1968).
d. B. B. Snider, D. J. Rodini, R. S. E. Conn, and S. Sealfon, *J. Am. Chem. Soc.*, **101**, 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.

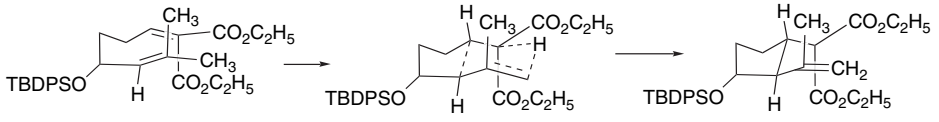
Entries 8 to 15 are examples of intramolecular reactions. Entry 8 involves two unactivated double bonds and was carried out at a temperature of 280°C. The product was a mixture of epimers at the ester site but the methyl group and cyclohexenyl double bond are *cis*, which indicates that the reaction 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.

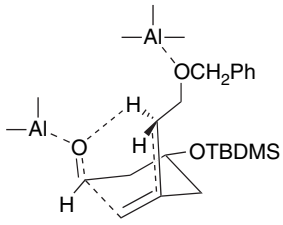


The stereoselectivity of the reaction in Entry 10 is also consistent with a TS in which the hydrogen is transferred through a chairlike TS.



Entry 11 illustrates the facility of a $Sc(OTf)_3$-mediated reaction. The catalyst in Entry 12 is a hindered *bis*-phenoxyaluminum compound. The proton removal

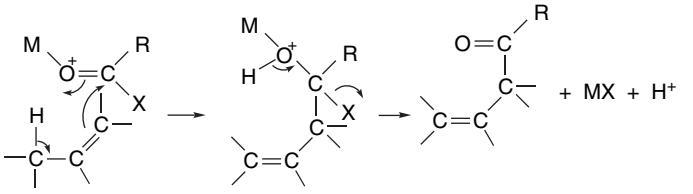
in Entry 12 is highly stereoselective, giving rise to a single exocyclic double-bond isomer. This stereochemistry is consistent with a TS that incorporates the six-membered hydrogen transfer TS into a bicyclic framework.



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 $TiCl_2$(O-*i*-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-PrO)$_2$TiCl$_2$-(*R*)-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.

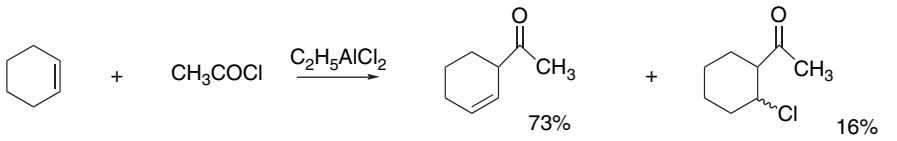


It has been suggested that the kinetic preference for formation of β,γ-unsaturated ketones results from an intramolecular deprotonation, as shown in the mechanism above.[51] The carbonyl-ene and alkene acylation reactions have several similarities. Both reactions occur most effectively in intramolecular 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

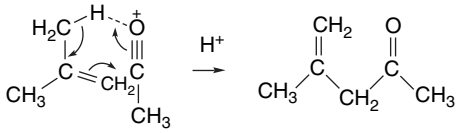
[51] P. Beak and K. R. Berger, *J. Am. Chem. Soc.*, **102**, 3848 (1980).

to give both β,γ-enones and β-haloketones.[52] One of the more effective catalysts is ethylaluminum dichloride.[53]

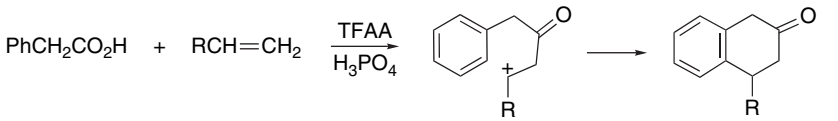


Zinc chloride also gives good results, especially with cyclic alkenes.[51]

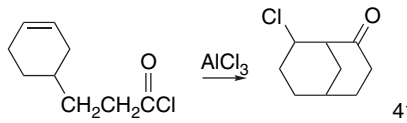
A similar reaction occurs between alkenes and acylium ions, as in the reaction between 2-methylpropene, and the acetylium ion leads regiospecifically to β,γ-enones.[54] A concerted mechanism has been suggested to account for this regiochemical preference.



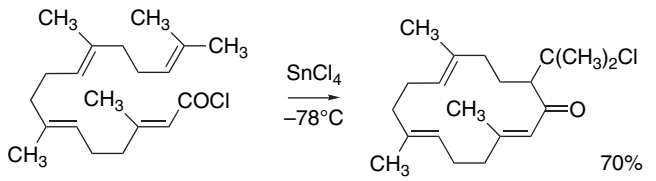
Highly reactive mixed anhydrides can also promote acylation. Phenylacetic acid reacts with alkenes to give 2-tetralones in TFAA-H_3PO_4.[55] This reaction involves an intramolecular Friedel-Crafts alkylation subsequent to the acylation.



The acylation reaction has been most synthetically useful in intramolecular reactions. The following examples are illustrative.



Ref. 56



Ref. 57

[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).

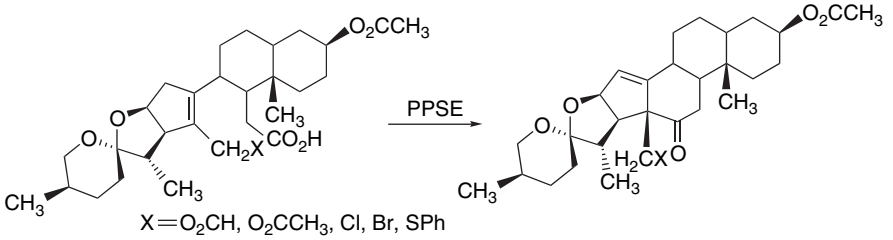
[54] H. M. R. Hoffmann and T. Tsushima, *J. Am. Chem. Soc.*, **99**, 6008 (1977).

[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.

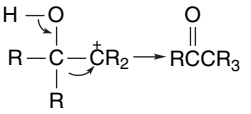


Ref. 59

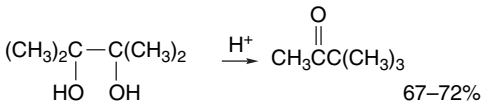
10.1.2. Rearrangement of Carbocations

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.

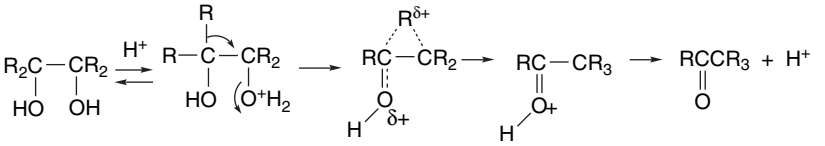


A reaction that follows this pattern is the acid-catalyzed conversion of diols to ketones, which is known as the *pinacol rearrangement*.[60] The classic example of this reaction is the conversion of 2,3-dimethylbutane-2,3-diol(pinacol) to methyl *t*-butyl ketone (pinacolone).[61]

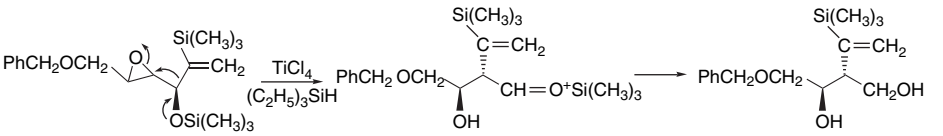


58. K. Yamamoto and H. Watanabe, *Chem. Lett.*, 1225 (1982).
59. W. Li and P. L. Fuchs, *Org. Lett.*, **5**, 4061 (2003).
60. C. J. Collins, *Q. Rev.*, **14**, 357 (1960).
61. G. A. Hill and E. W. Flosdorf, *Org. Synth.*, **I**, 451 (1932).

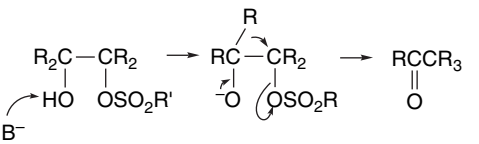
The acid-catalyzed mechanism involves carbocation formation and substituent migration assisted by the hydroxy group.



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.



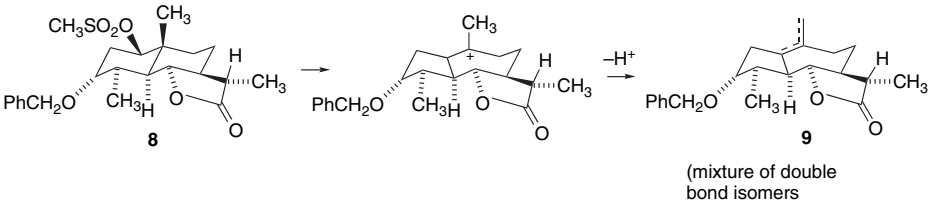
Rearrangements of monosulfonates permit greater control over the course of the rearrangement because ionization occurs only at the sulfonylated alcohol. These reactions have been of value in the synthesis of ring systems, especially terpenes, as illustrated by Entries 3 and 4 in Scheme 10.3.

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).

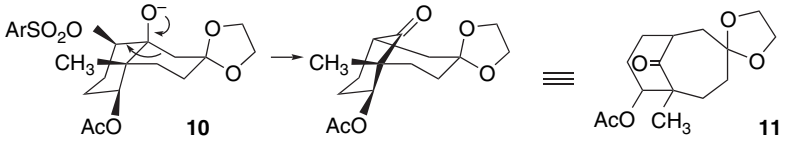
63. K. Suzuki, T. Ohkuma, and G. Tsuchihashi, *Tetrahedron Lett.*, **26**, 861 (1985); K. Suzuki, M. Shimazaki, and G. Tsuchihashi, *Tetrahedron Lett.*, **27**, 6233 (1986); M. Shimazaki, M. Morimoto, and K. Suzuki, *Tetrahedron Lett.*, **31**, 3335 (1990).

of this stereoelectronic effect. In both cyclic and acyclic systems, the rearrangement takes place with *retention of configuration* at the migrating group.



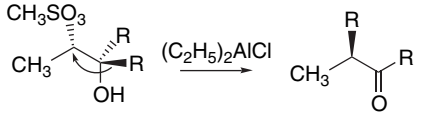
Ref. 64

Similarly, **10** gives **11** by antiperiplanar migration.

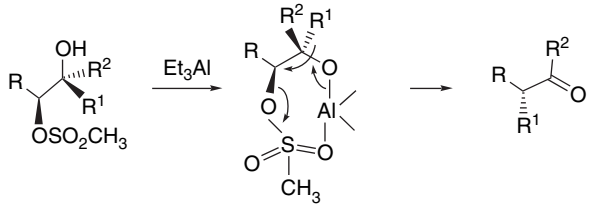


Ref. 65

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]



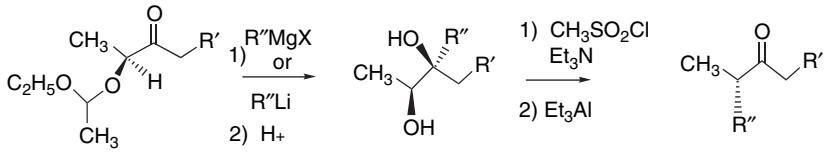
Triethylaluminum is also effective in catalyzing rearrangement of monosulfonate with high stereospecificity. The reactions are believed to proceed through a cyclic TS.[67]



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).

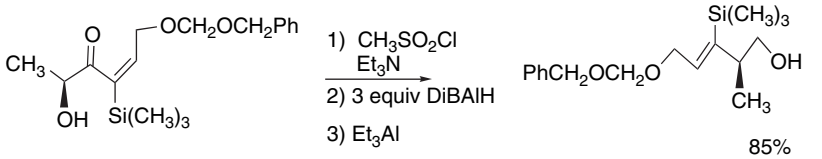
less hindered secondary hydroxy group. The rearranged ketones were obtained in greater than 99% e.e.



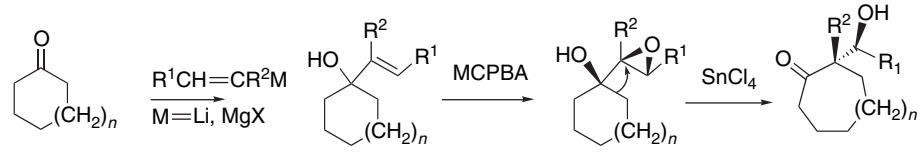
R′ = CH_2Ph

R″ = aryl, alkenyl, heteroaryl

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 DiBAlH first reduces the ketone and then, after rearrangement, reduces the aldehyde to a primary alcohol.



Stereospecfic ring expansion can be done by taking advantage of the hydroxy-directed epoxidation and $SnCl_4$-mediated rearrangement of 1-hydroxycycloalkyl epoxides.[69]



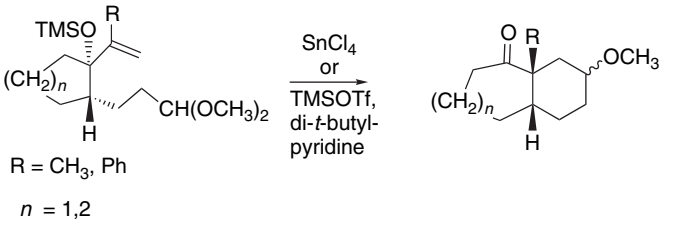
n = 1-5

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 $Ti(O\text{-}i\text{-}Pr)_3Cl$.

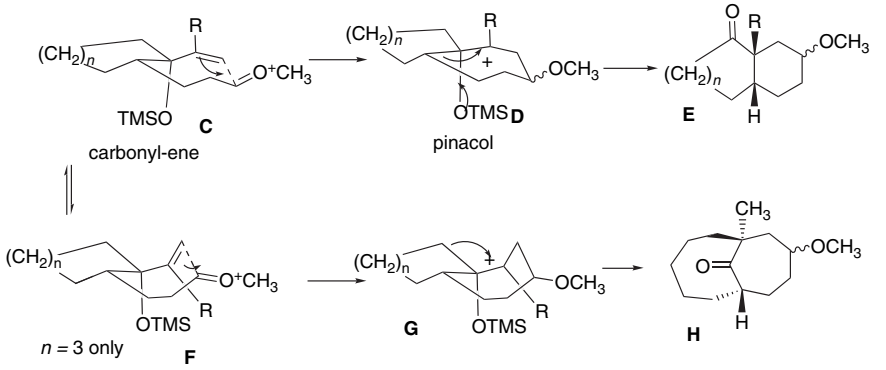
10.1.2.2. Pinacol Rearrangement in Tandem with the Carbonyl-Ene Reaction. Overman and co-workers have developed protocols in which pinacol rearrangement

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. Weinseimer, *Org. Lett.*, **2**, 1193 (2000); C. M. Marson, A. Khan, R. A. Porter, and A. J. A. Cobb, *Tetrahedron Lett.*, **43**, 6637 (2002).

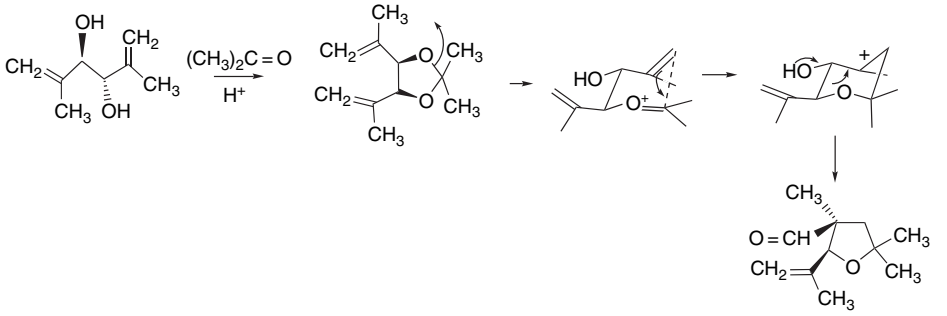
occurs in tandem with a carbonyl-ene reaction and results in both a ring closure and ring expansion.[70]



These reactions appear to proceed through the sequence $\mathbf{C} \rightarrow \mathbf{D} \rightarrow \mathbf{E}$. When the seven-membered analog (n = 3) reacts, two products are formed. The more flexible seven-membered ring accommodates the competing sequence. $\mathbf{F} \rightarrow \mathbf{G} \rightarrow \mathbf{H}$.

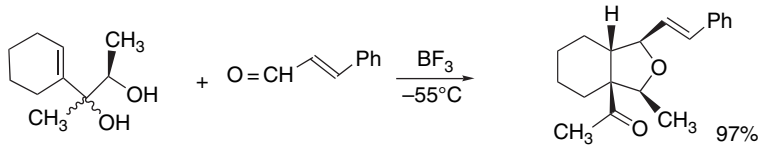


The carbonyl-ene–pinacol sequence has also been observed in reactions leading to the formation of tetrahydrofurans.[71]

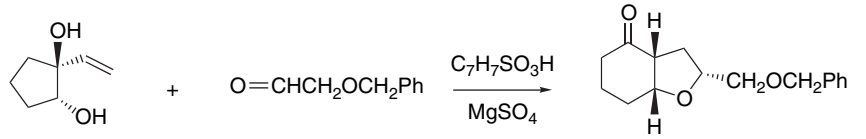


The reaction has been developed for the synthesis of both oxygen heterocycles and carbocyclic compounds.[72]

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).

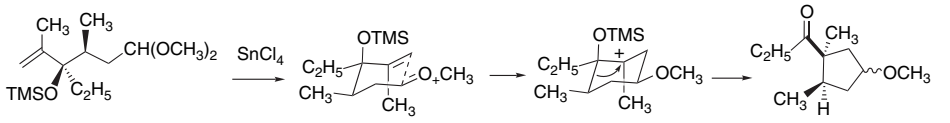


Ref. 73

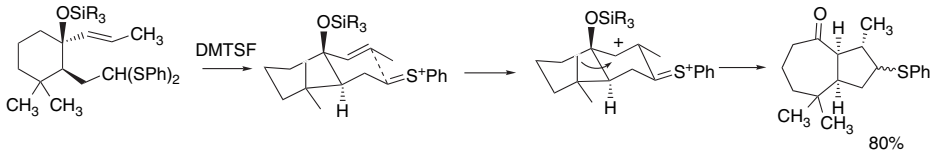


Ref. 74

These reactions can also be adapted to carbocyclic ring formation and expansion.

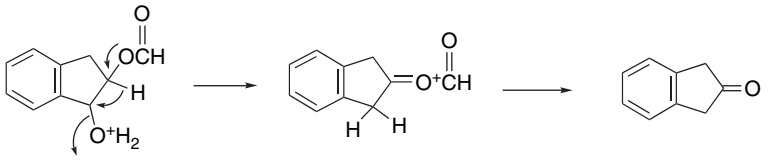


Ref. 75



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.



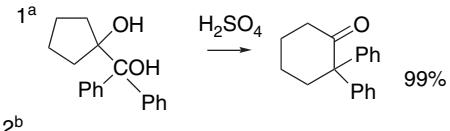
Entries 3 and 4 are examples of stereospecific *anti* migrations governed by the stereochemistry of the sulfonate leaving group. These transformations are parts of synthetic schemes that use available terpene starting materials for synthesis of more complex natural products. The ring expansion in Entry 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. Valentekovich, *J. Am. Chem. Soc.*, **123**, 4851 (2001).

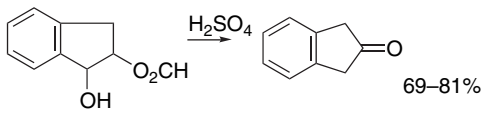
Scheme 10.3. Rearrangements Promoted by Adjacent Heteroatoms

A. Pinacol-type rearrangements

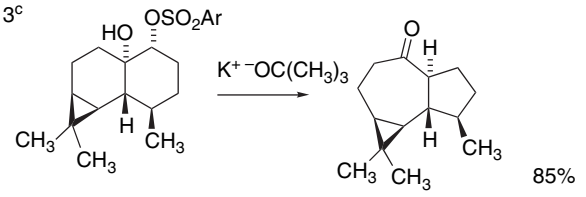
1[a]



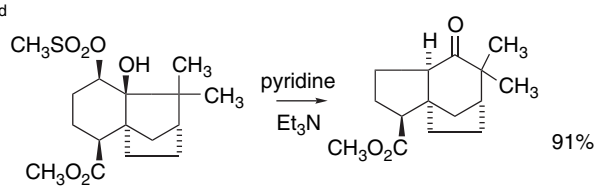
2[b]



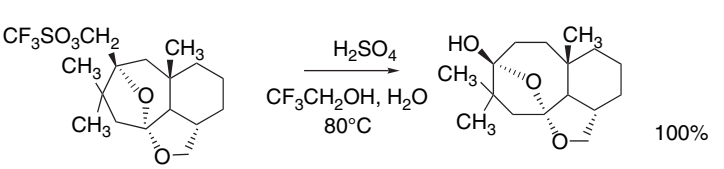
3[c]



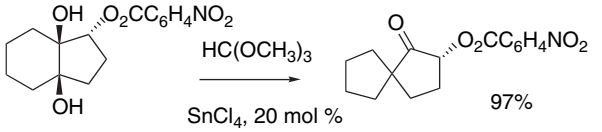
4[d]



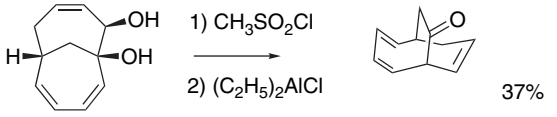
5[e]



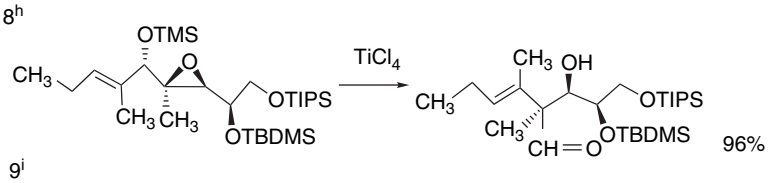
6[f]



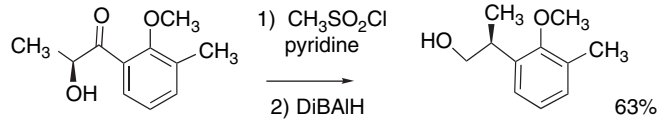
7[g]



8[h]



9[i]

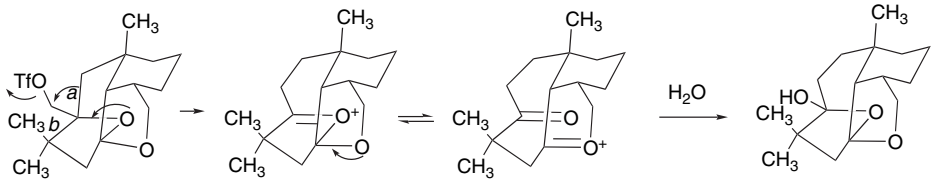


(*Continued*)

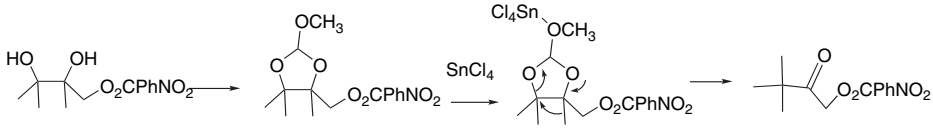
Scheme 10.3. (*Continued*)

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).

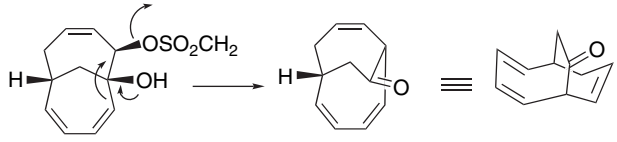
presumably proceeds with participation of the adjacent oxygen, which accounts for the specific migration of bond *a* over bond *b*.



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.

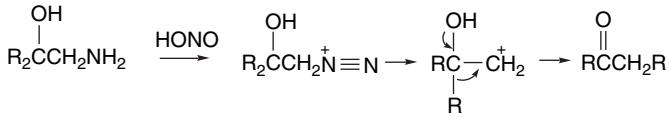


Entry 7 involves formation and ionization of a secondary allylic sulfonate and migration of a dienyl group.

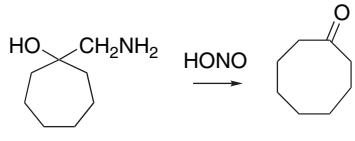


Entry 8 involves a migration initiated by epoxide ring opening. This reaction involves migration of a vinyl substituent. Entry 9 is a stereospecific migration of the aryl group. The DiBAlH both promotes the rearrangement and reduces the product aldehyde.

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.

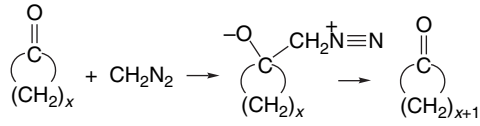


This reaction has been used to form ring-expanded cyclic ketones, a procedure known as the *Tiffeneau-Demjanov reaction*.[77]

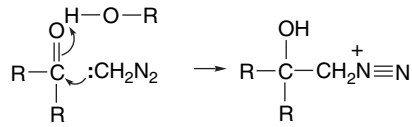


61% Ref. 78

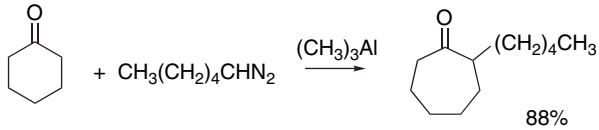
The reaction of ketones with diazomethane sometimes leads to a ring-expanded ketone in synthetically useful yields.[79] The reaction occurs by addition of the diazomethane, followed by elimination of nitrogen and migration.



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]



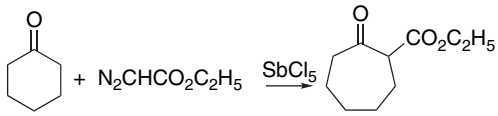
Trimethylaluminum also promotes ring expansion by diazoalkanes.[81]



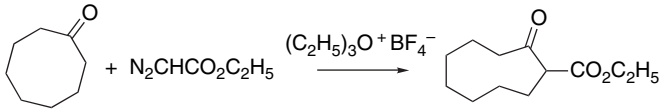
88%

Ketones react with esters of diazoacetic acid in the presence of Lewis acids such as BF_3 and $SbCl_5$.[82]

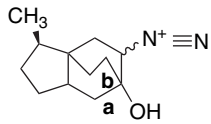
77. P. A. S. Smith and D. R. Baer, *Org. React.*, **11**, 157 (1960).
78. F. F. Blicke, J. Azuara, N. J. Dorrenbos, and E. B. Hotelling, *J. Am. Chem. Soc.*, **75**, 5418 (1953).
79. C. D. Gutsche, *Org. React.*, **8**, 364 (1954).
80. J. N. Bradley, G. W. Cowell, and A. Ledwith, *J. Chem. Soc.*, 4334 (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 $LiAlH_4$ 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 BF_3-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-Backlund 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]

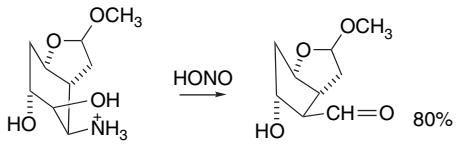
[83] L. J. MacPherson, E. K. Bayburt, M. P. Capparelli, R. S. Bohacek, F. H. Clarke, R. D. Ghai, Y. Sakane, C. J. Berry, J. V. Peppard, and A. J. Trapani, *J. Med. Chem.*, **36**, 3821 (1993).

[84] A. S. Kende, *Org. React.*, **11**, 261 (1960); A. A. Akhrem, T. K. Ustynyuk, and Y. A. Titov, *Russ. Chem. Rev.* (English Transl.), **39**, 732 (1970).

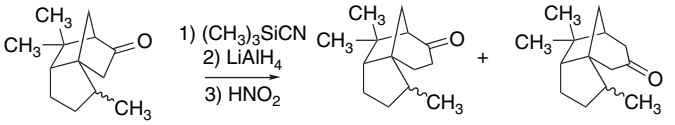
Scheme 10.4. Rearrangement Involving Diazonium Ions

A. Rearrangement of β-amino alcohols by diazotization

1[a]



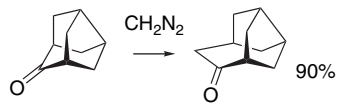
2[b]



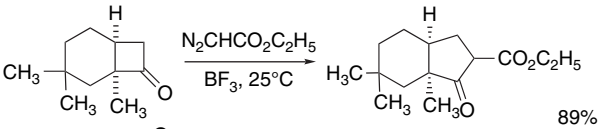
total yield 70% 75–85% 15–25%

B. Ring expansion of cyclic ketones using diazo compounds

3[c]

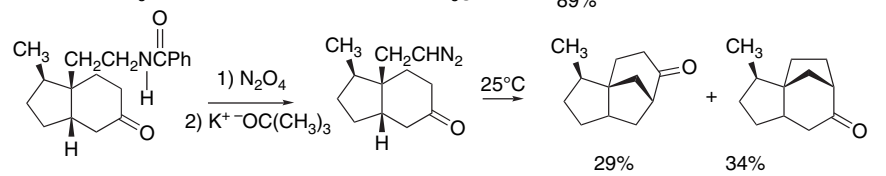


4[d]



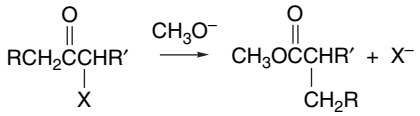
89%

5[e]

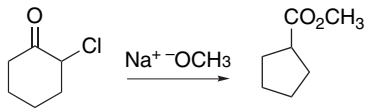


29% 34%

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).



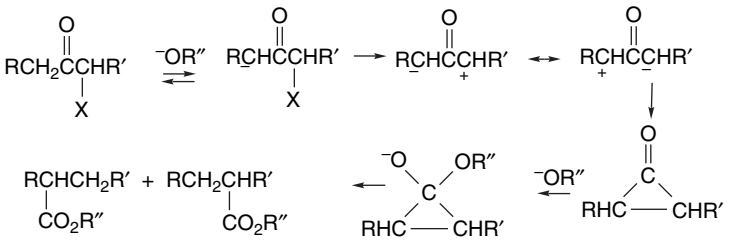
If the ketone is cyclic, a ring contraction occurs.



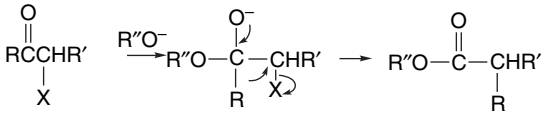
Ref. 85

There is evidence that the rearrangement involves cyclopropanones or their open 1,3-dipolar equivalents as reaction intermediates.[86]

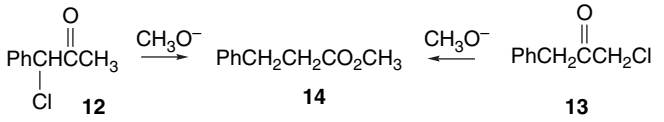
85. D. W. Goheen and W. R. Vaughan, *Org. Synth.*, **IV**, 594 (1963).
86. F. G. Bordwell, T. G. Scamehorn, and W. R. Springer, *J. Am. Chem. Soc.*, **91**, 2087 (1969); F. G. Bordwell and J. G. Strong, *J. Org. Chem.*, **38**, 579 (1973).



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.

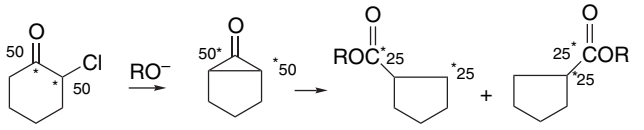


The net structural change is the same for both mechanisms. The energy requirements of the cyclopropanone and semibenzilic mechanism may be fairly closely balanced.[87] Cases of operation of the semibenzilic mechanism have been reported even for compounds having a hydrogen available for enolization.[88] 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]



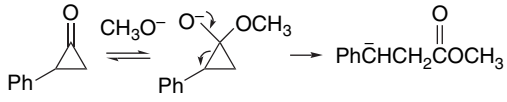
* = ^{14}C label

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

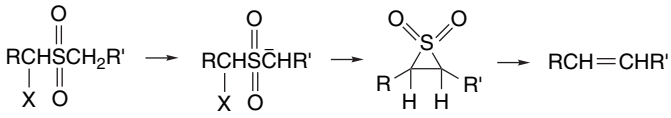
87. V. Moliner, R. Castillo, V. S. Safont, M. Oliva, S. Bohn, I. Tunon, and J. Andres, *J. Am. Chem. Soc.*, **119**, 1941 (1997).
88. E. W. Warnhoff, C. M. Wong, and W. T. Tai, *J. Am. Chem. Soc.*, **90**, 514 (1968).
89. R. B. Loftfield, *J. Am. Chem. Soc.*, **73**, 4707 (1951).

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.

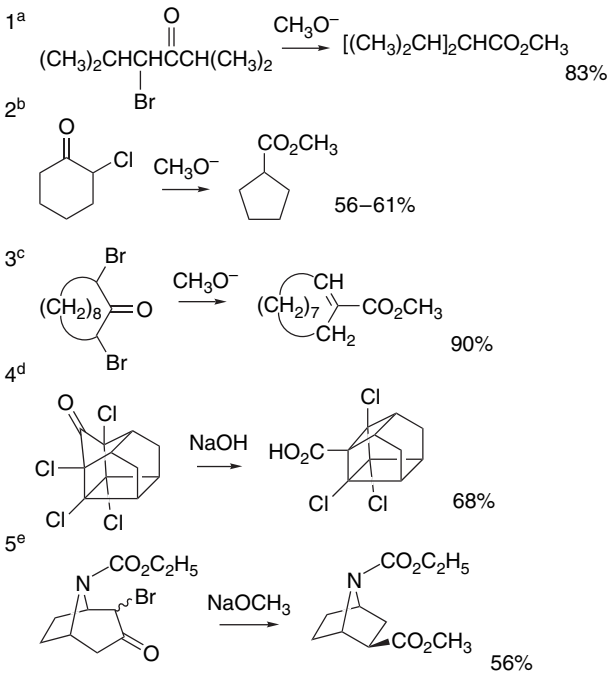
10.1.3.2. The Ramberg-Backlund Reaction. α-Halosulfones undergo a related rearrangement known as the *Ramberg-Backlund reaction*.[91] The carbanion formed by deprotonation gives an unstable thiirane dioxide that decomposes with elimination of sulfur dioxide. This elimination step is considered to be a concerted cycloelimination.



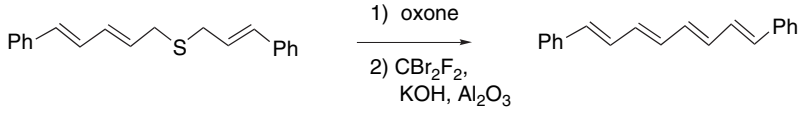
The overall transformation is the conversion of the carbon-sulfur bonds to a carbon-carbon double bond. The original procedure involved halogenation of a sulfide, followed by oxidation to the sulfone. Recently, the preferred method has reversed the order of the steps. After the oxidation, which is normally 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).

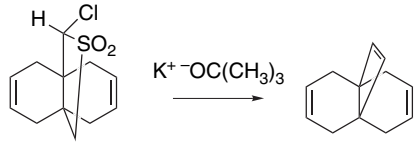
Scheme 10.5. Base-Mediated Rearrangements of α-Haloketones



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).

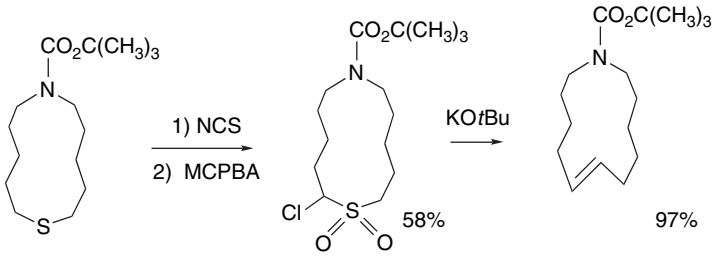


The Ramberg-Backlund reaction has found several applications. Owing to the concerted nature of the elimination, it can applied to both small and large rings containing a double bond.



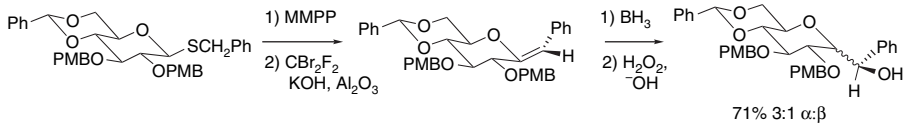
Ref. 93

93. L. A. Paquette, J. C. Philips, and R. E. Wingard, Jr., *J. Am. Chem. Soc.*, **93**, 4516 (1971).



Ref. 94

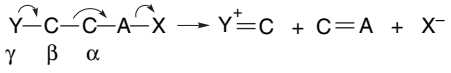
A recently developed application of the Ramberg-Backlund reaction is the synthesis of C-glycosides. The required thioethers can be prepared easily by exchange with a thiol. The application of the Ramberg-Backlund conditions then leads to an exocyclic vinyl ether that can be reduced to the C-nucleoside.[95] 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-Backlund 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

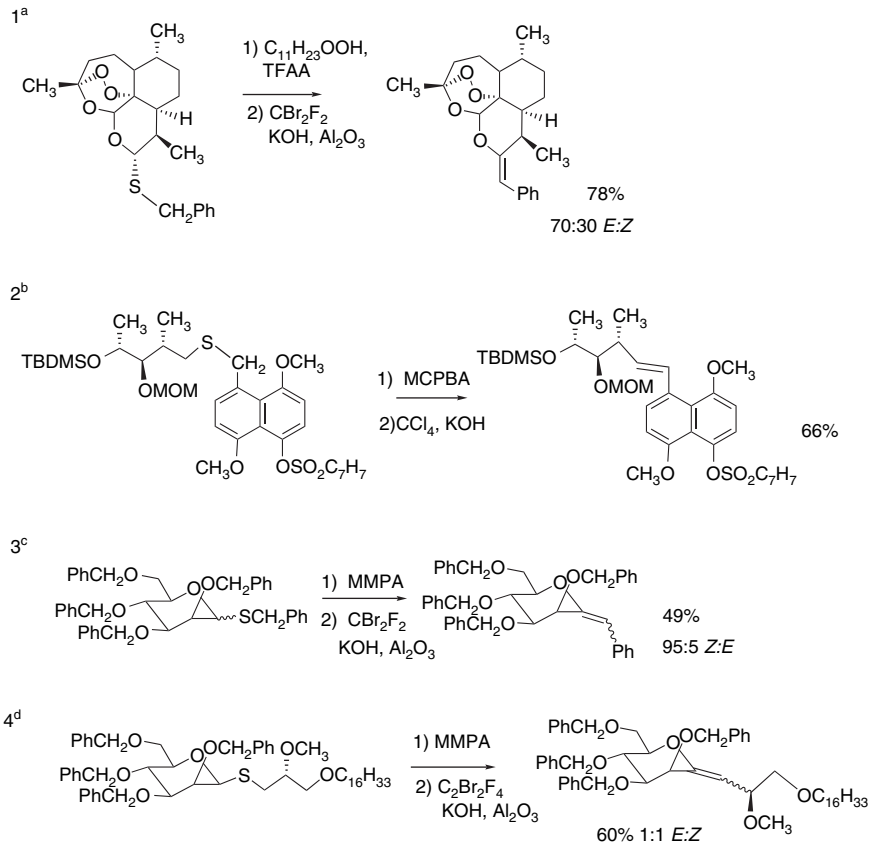
The classification *fragmentation* applies to reactions in which a carbon-carbon bond is broken. One structural feature that permits fragmentation to occur readily is the presence of a carbon that can accommodate carbocationic character β to a developing electron deficiency. This type of reaction, known 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

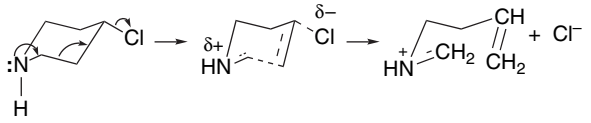
94. I. MaGee and E. J. Beck, *Can. J. Chem.*, **78**, 1060 (2000).
95. F. K. Griffin, D. E. Paterson, P. V. Murphy, and R. J. K. Taylor, *Eur. J. Org. Chem.*, 1305 (2002).
96. C. A. Grob, *Angew. Chem. Int. Ed. Engl.*, **8**, 535 (1969).

Scheme 10.6. Ramberg-Backlund Reaction

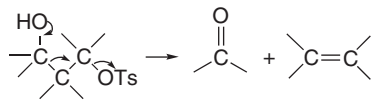


a. S. Oh, I. H. Jeong, W.-S. Shin, and S. Lee, *Biorg. Med. Chem. Lett.*, **14**, 3683 (2004).
b. D. J. Hart, G. H. Merriman, and D. G. J. Young, *Tetrahedron*, **52**, 14437 (1996).
c. P. S. Belica and R. W. Franck, *Tetrahedron Lett.*, **39**, 8225 (1998).
d. G. Yang, R. W. Franck, H. S. Byun, R. Bittman, 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]

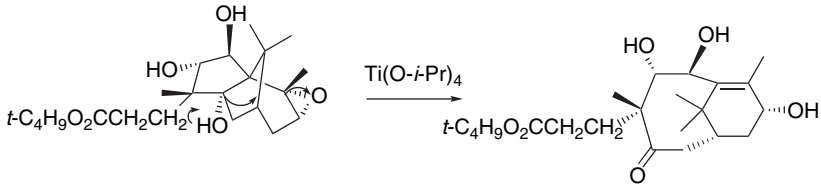


1,3-Diols or β-hydroxy ethers are particularly useful substrates for fragmentation. If the diol or hydroxy ether is converted to a monotosylate, the remaining oxy group can promote fragmentation.



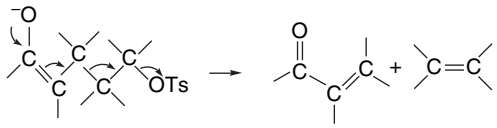
97. R. D'Arcy, C. A. Grob, T. Kaffenberger, and V. Krasnobajew, *Helv. Chim. Acta*, **49**, 185 (1966).

This reaction can be used in synthesis of medium-sized rings by cleavage of specific bonds. An example of this reaction pattern can be seen in a fragmentation used to construct the ring structure found in the taxane group of diterpenes.

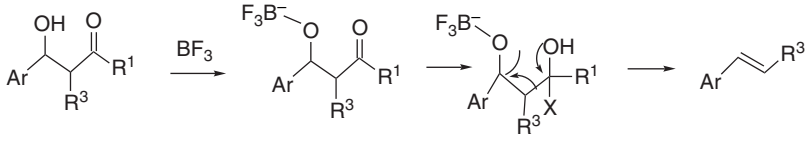


Ref. 98

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.

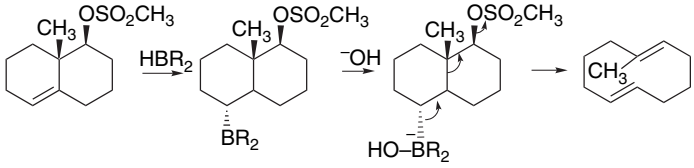


β-Hydroxyketones are also subject to fragmentation. Lewis acids promote fragmentation of mixed aldol products derived from aromatic aldehydes.[100]



The same fragmentation is effected by $Yb(OTf)_3$ on heating with the aldol adduct in the absence of solvent.[101]

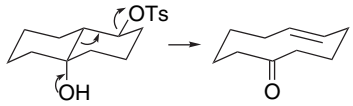
Organoboranes undergo fragmentation if a good leaving group is present on the δ-carbon.[102] The reactive intermediate is the tetrahedral borate formed by addition of hydroxide ion at boron.



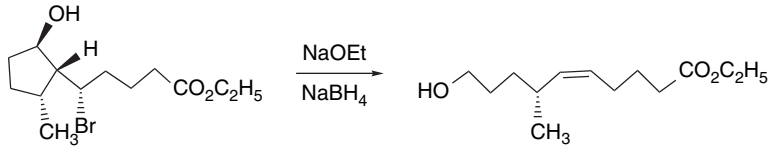
Ref. 103

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. Marcotullio, *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).

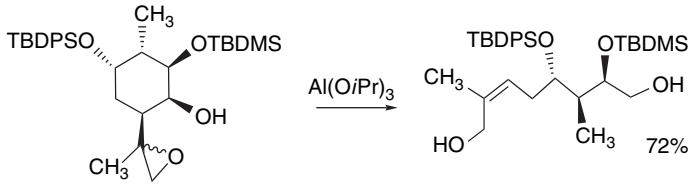
The usual synthetic objective of a fragmentation reaction is the construction of a medium-sized ring from a fused ring system. As the fragmentation reactions are usually concerted stereoselective processes, the stereochemistry is predictable. In 3-hydroxy tosylates, the fragmentation is most favorable 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.



Ref. 105



Ref. 106

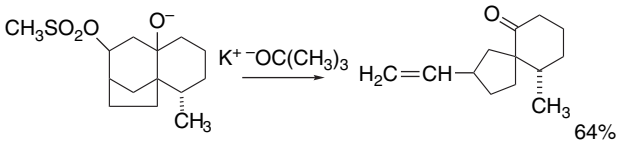
Scheme 10.7 provides some additional examples of fragmentation reactions that have been employed in a synthetic context. Entry 1 was used in the late stages of the synthesis of (±)-hinesol, an example of a terpene possessing a spiro[4,5]decane skeleton. The fragmentation provides the spiro ring system with a vinyl side chain. Entry 2 illustrates the formation of a medium ring by fragmentation of a bicyclic system. In this case $LiAlH_4$ 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

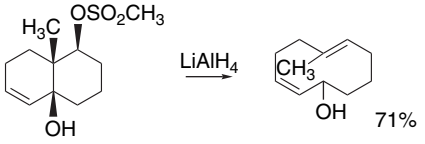
A. Heteroatom-promoted fragmentation

1[a]



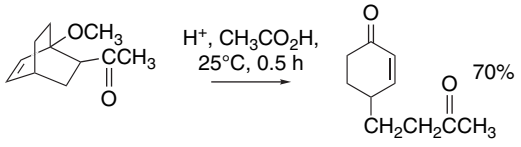
64%

2[b]



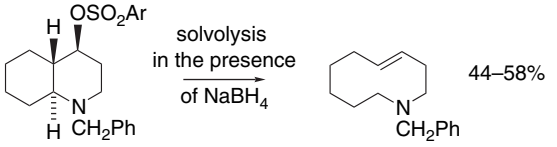
71%

3[c]



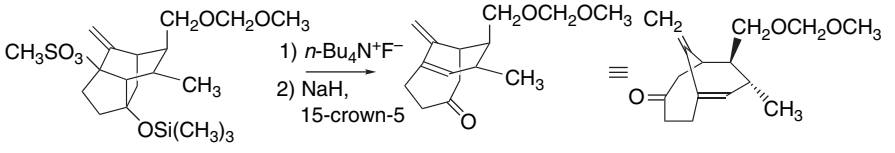
70%

4[d]

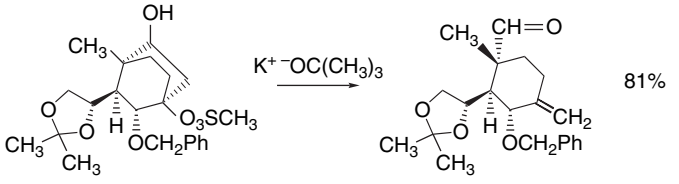


44–58%

5[e]

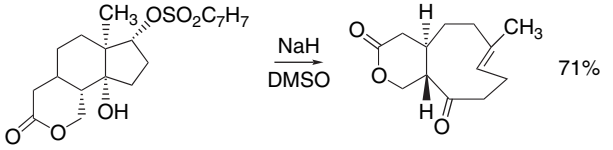


6[f]



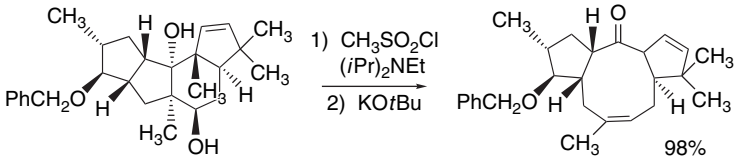
81%

7[g]



71%

8[h]

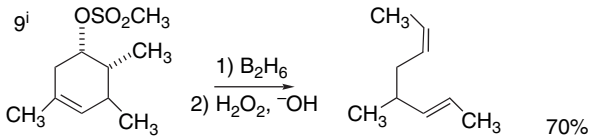


98%

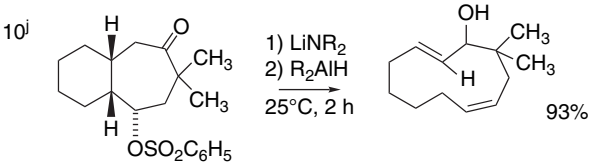
(*Continued*)

Scheme 10.7. (*Continued*)

B. Boronate fragmentation

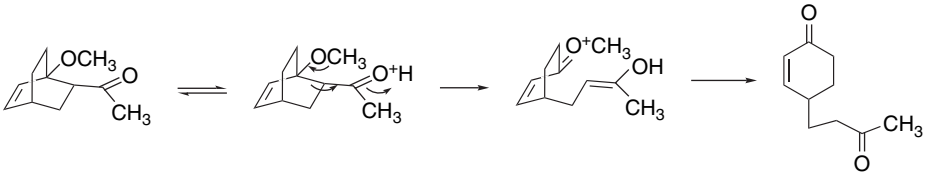


C. δ-Tosyloxy fragmentation

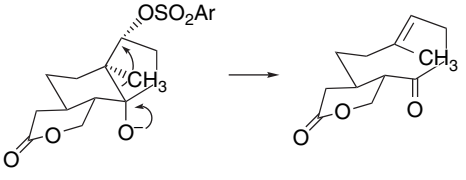


a. J. A. Marshall and S. F. Brady, *J. Org. Chem.*, **35**, 4068 (1970).
b. J. A. Marshall, W. F. Huffman, and J. A. Ruth, *J. Am. Chem. Soc.*, **94**, 4691 (1972).
c. A. J. Birch and J. S. Hill, *J. Chem. Soc., C*, 419 (1966).
d. J. A. Marshall and J. H. Babler, *J. Org. Chem.*, **34**, 4186 (1969).
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.

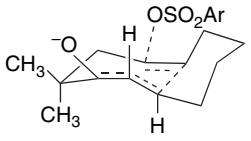


Entry 4 involves nitrogen participation and formation of an iminium ion that is reduced by $NaBH_4$. The reaction in Entry 5 creates an 11-methylenebicyclo[4.3.1]undecen-3-one structure found in a biologically active natural product. Note that this fragmentation creates a bridgehead double bond. Entry 6 involves construction of a portion of the taxol structure. The reaction in Entry 7 is stereospecific, leading to the *E*-double bond.



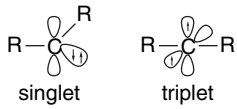
Entry 8 was used to create the central nine-membered ring system found in the diterpene jatrophatrione. Entry 9 is an example of a boronate fragmentation (see p. 899). Entry 10 illustrates enolate fragmentation. The reaction presumably proceeds

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.

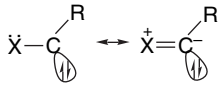


Both theoretical and experimental studies have provided more detailed information about carbene structure. Molecular orbital calculations lead to the prediction of H−C−H angles for methylene of roughly 135° for the triplet and about 105° for the singlet. The triplet is calculated to be about 8 kcal/mol 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

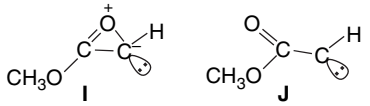
[107] J. F. Harrison, *Acc. Chem. Res.*, **7**, 378 (1974); P. Saxe, H. F. Shaefer, and N. C. Hardy, *J. Phys. Chem.*, **85**, 745 (1981); C. C. Hayden, M. Newmark, K. Shobatake, R. K. Sparks, and Y. T. Lee, *J. Chem. Phys.*, **76**, 3607 (1982); R. K. Lengel and R. N. Zare, *J. Am. Chem. Soc.*, **100**, 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]



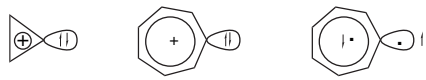
X = F, Cl, OR, NR_2

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 calculations[109] arrives at structure **I** as a better description of carbomethoxycarbene than the conventional structure **J**.



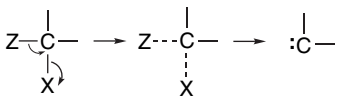
I **J**

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]



K **L** **L'**

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.

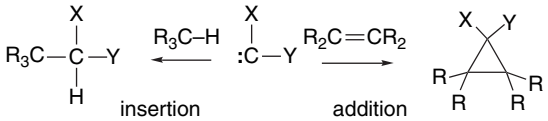
metal-bound carbene

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.

dominant electron distribution in electrophilic metallo-carbenes

dominant electron distribution in metallo-carbenes with strong back-bonding

Carbenes and carbenoids can add to double bonds to form cyclopropanes or insert into C−H bonds.



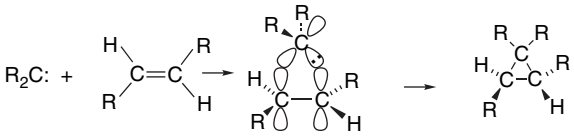
These reactions have *very low activation energies* when the intermediate is a "free" carbene. Intermolecular insertion reactions are inherently nonselective. The course of intramolecular reactions is frequently controlled by the proximity of the reacting groups.[113] Carbene intermediates can also be 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

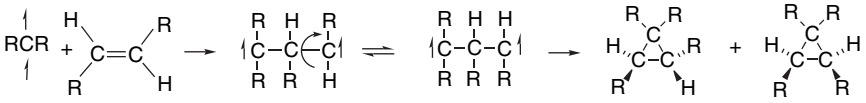
From the point of view of both synthetic and mechanistic interest, much attention has been focused on the addition reaction between carbenes and alkenes to give cyclopropanes. Characterization of the reactivity of substituted carbenes in addition reactions has emphasized stereochemistry and selectivity. 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]



Transition structure for concerted singlet carbene addition



Diradical intermediate in triplet carbene addition

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 dibromocarbene 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	$\cdot CCl_3$	$:CBr_2$	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

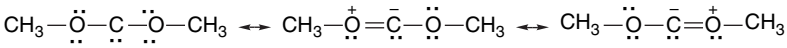
a. P. S. Skell and A. Y. Garner, *J. Am. Chem. Soc.*, **78**, 5430 (1956).

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).

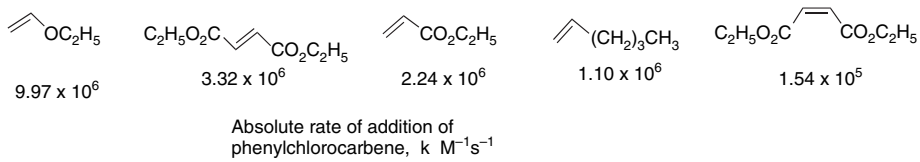
Table 10.2. Classification of Carbenes on the Basis of Reactivity toward Alkenes[a]

Nucleophilic	Ambiphilic	Electrophilic
$(CH_3O)_2C$	CH_3OCCl	Cl_2C
$CH_3OCN(CH_3)_2$	CH_3OCF	PhCCl
		CH_3CCl
		$BrCCO_2C_2H_5$

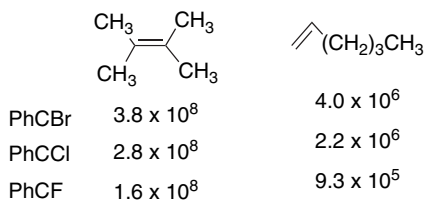
a. R. A. Moss and R. C. Munjai, *Tetrahedron Lett.*, 4721 (1979); R. A. Moss, *Acc. Chem. Res.*, **13**, 58 (1980); R. A. Moss, *Acc. Chem. Res.*, **22**, 15 (1989).



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).



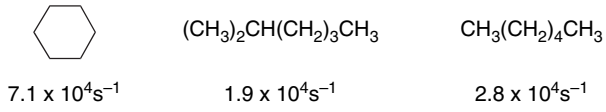
The rates of phenylchlorocarbene have also been compared with the fluoro and bromo analogs.[120] The data show slightly decreased rates in the order Br > Cl > F. The alkene reactivity difference is consistent with an electrophilic attack. These reactions have low activation barriers and the reactivity differences are dominated by entropy effects.



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).

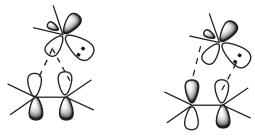
120. R. A. Moss, W. Lawrynowicz, N. J. Turro, I. R. Gould, and Y. Cha, *J. Am. Chem. Soc.*, **108**, 7028 (1986).

There is a small dependence on the rate of solvent insertion reactions for saturated hydrocarbons.[121] Benzene is much less reactive.



Absolute rate for solvent insertion by 4-methylphenylchlorocarbene

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]



HOMO-LUMO interactions
in carbene alkene addition

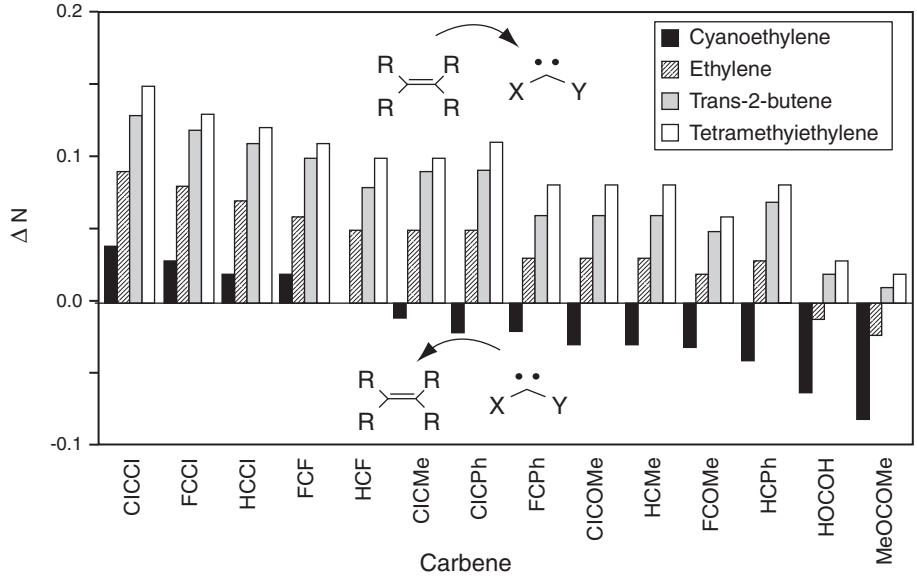


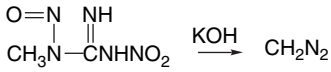
Fig. 10.3. Net charge transfer (ΔN) calculated for substituted carbenes with several alkenes. Reproduced from *J. Org. Chem.*, **64**, 7061 (1999), by permission of the American Chemical Society.

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).

10.2.2. Generation of Carbenes

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.

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.



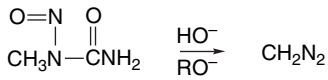
Ref. 124

Scheme 10.8. General Methods for Generation of Carbenes

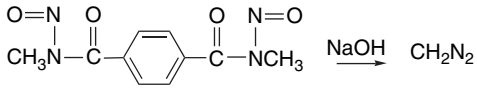
Precursor	Conditions	Products	Ref.
Diazoalkanes $R_2C{=}N^+{=}N^-$	Photolysis, thermolysis or metal catalysis	$R_2C{:} + N_2$	a
Salts of sulfonylhydrazones $[R_2C{=}NNSO_2Ar]^-$	Photolysis or thermolysis; diazoalkanes are intermediates	$R_2C{:} + N_2 + ArSO_2^-$	b
Diazirines 	Photolysis	$R_2C{:} + N_2$	c
Alkyl halides $R_2CH{-}X$	Strong base, including metalation	$R_2C{:} + X^- + B{-}H$	d
α-Haloalkylmercury compounds 	Thermolysis	$R_2C{:} + HgXZ$	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. Seyferth, *Acc. Chem. Res.* **5**, 65 (1972).

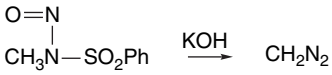
[124.] M. Neeman and W. S. Johnson, *Org. Synth.*, **V**, 245 (1973).



Ref. 125

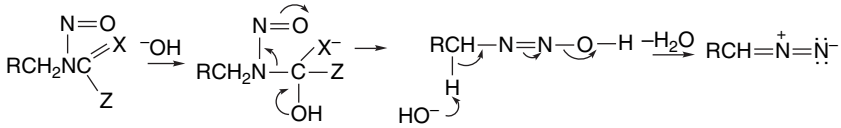


Ref. 126

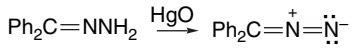


Ref. 127

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.



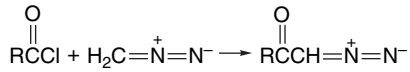
Diazo compounds can also be obtained by oxidation of the corresponding hydrazone,[129] the route that is most common when one of the substituents is an aromatic ring.



Ref. 130

The higher diazoalkanes can be made by $Pb(O_2CCH_3)_4$ oxidation of hydrazones.[129]

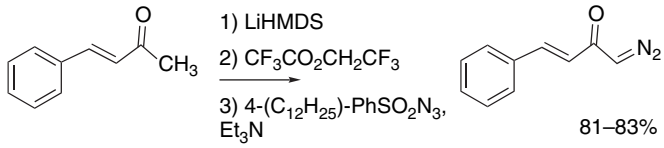
α-Diazoketones are especially useful in synthesis.[131] There are several methods of preparation. Reaction of diazomethane with an acyl chloride results in formation of a diazomethyl ketone.



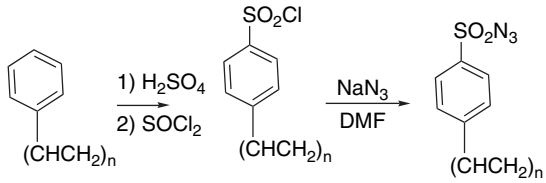
The HCl generated in this reaction destroys one equivalent of diazomethane, but this can be avoided by including a base, such as triethylamine, to neutralize the acid.[132]

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).

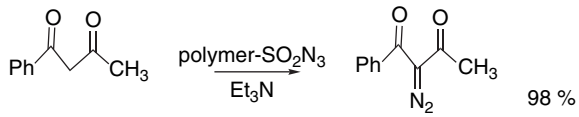
Cyclic α-diazoketones, which are not available from acyl chlorides, can be prepared by reaction of an enolate equivalent with a sulfonyl azide, in a reaction known as *diazo transfer*.[133] Various arenesulfonyl azides[134] and methanesulfonyl azide[135] are used most frequently. Because of the potential 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]



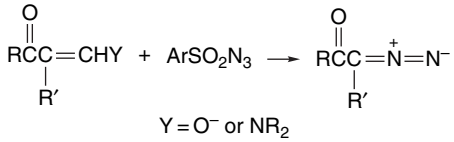
A polymer bound arenesulfonyl azide can be prepared from polystyrene.[138]



This reagent effects diazo transfer in good yield.

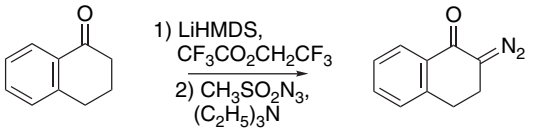


Several types of compounds can act as the carbon nucleophile in diazo transfer, including the oxymethylene[139] or dialkylaminomethylene[140] derivatives of the ketone. These activating substituents are lost during these reactions.

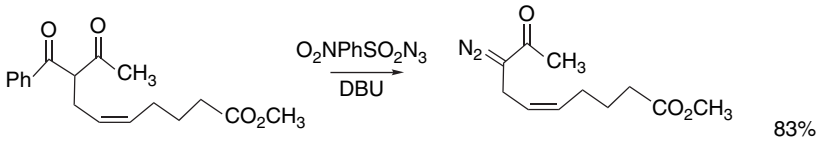


133. F. W. Bollinger and L. D. Tuma, *Synlett*, 407 (1996).
134. J. B. Hendrickson and W. A. Wolf, *J. Org. Chem.*, **33**, 3610 (1968); J. S. Baum, D. A. Shook, H. M. L. Davies, and H. D. Smith, *Synth. Commun.*, **17**, 1709 (1987); L. Lombardo and L. N. Mander, *Synthesis*, 368 (1980).
135. D. F. Taber, R. E. Ruckle, and M. J. Hennessy, *J. Org. Chem.*, **57**, 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).

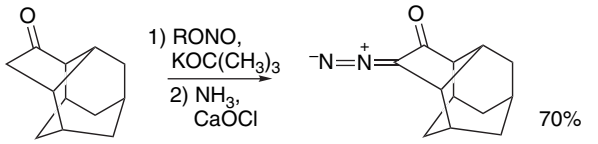
α-Trifluoroacetyl derivatives of ketones are also useful substrates for diazo transfer reactions.[141] They are made by enolate acylation using 2,2,2-trifluoroethyl trifluoroacetate. The trifluoroacetyl group is cleaved during diazo transfer.



Benzoyl groups are also selectively cleaved during diazo transfer. This method has been used to prepare diazo ketones and diazo esters.[142]

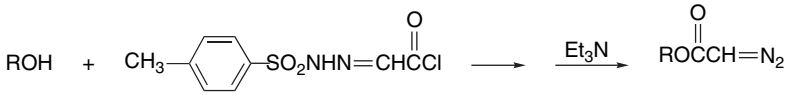


α-Diazo ketones can also be made by first converting the ketone to an α-oximino derivative by nitrosation and then oxidizing the oximino ketone with chloramine.[143]



Ref. 144

α-Diazo esters can be prepared by esterification of alcohols with the tosylhydrazone of glyoxyloyl chloride, followed by reaction with triethylamine.[145]



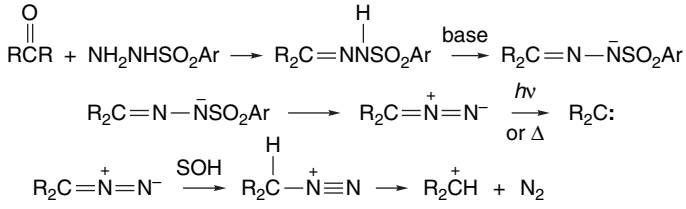
The driving force for decomposition of diazo compounds to carbenes is the formation of the very stable nitrogen molecule. Activation energies for decomposition of diazoalkanes in the gas phase are about 30 kcal/mol. The requisite energy can also be supplied by photochemical excitation. It is often possible 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

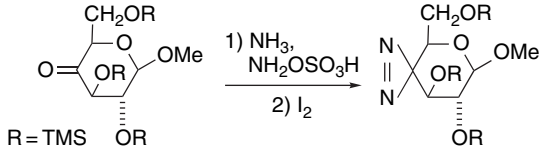
141. R. L. Danheiser, R. F. Miller, R. G. Brisbois, and S. Z. Park, *J. Org. Chem.*, **55**, 1959 (1990).
142. D. F. Taber, D. M. Gleave, R. J. Herr, K. Moody, and M. J. Hennessy, *J. Org. Chem.*, **60**, 1093 (1995).
143. T. N. Wheeler and J. Meinwald, *Org. Synth.*, **52**, 53 (1972).
144. T. Sasaki, 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 carbenoid 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

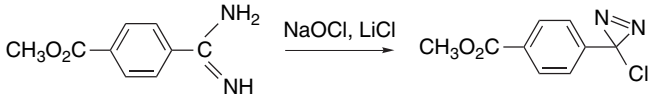
10.2.2.2. Carbenes from Sulfonylhydrazones. The second method listed in Scheme 10.8, thermal or photochemical decomposition of salts of arenesulfonylhydrazones, is actually a variation of the diazoalkane method, since diazo compounds are intermediates. The conditions of the decomposition are usually 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]



Ref. 150



Ref. 151

[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).

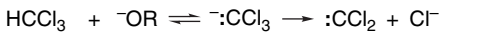
[148] J. H. Bayless, L. Friedman, F. B. Cook, and H. Shechter, *J. Am. Chem. Soc.*, **90**, 531 (1968).

[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.

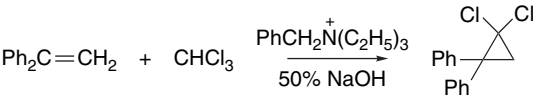
[150] G. Kurz, J. Lehmann, and R. Thieme, *Carbohydrate Res.*, **136**, 125 (1983).

[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]



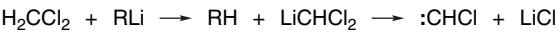
Both phase transfer and crown ether catalysis have been used to promote α-elimination reactions of chloroform and other haloalkanes.[153] The carbene can be trapped by alkenes to form dichlorocyclopropanes.



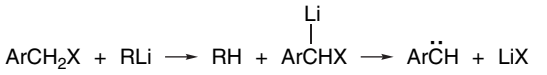
Ref. 154

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 alkyllithium reagents. The carbanion stabilization provided by the chloro and phenyl groups makes the lithiation feasible.



Ref. 156

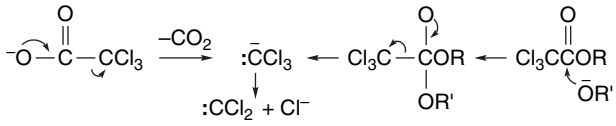


Ref. 157

The reactive intermediates under some conditions may be the carbenoid α-haloalkyllithium compounds or carbene-lithium halide complexes.[158] In the case of the trichloromethyllithium to dichlorocarbene conversion, the equilibrium lies heavily to the side of trichloromethyllithium 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. Schoenefeld, *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. Kobrich 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. Kobrich, *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).

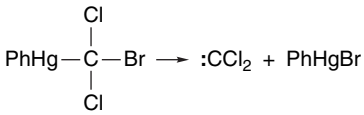
A method that provides an alternative route to dichlorocarbene is the decarboxylation of trichloroacetic acid.[161] The decarboxylation generates the trichloromethyl anion, which decomposes to the carbene. Treatment of alkyl trichloroacetates with an alkoxide also generates dichlorocarbene.



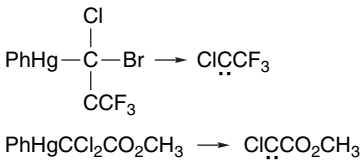
The applicability of these methods is restricted to polyhalogenated compounds, since the inductive effect of the halogen atoms is necessary for facilitating formation of the carbanion.

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]

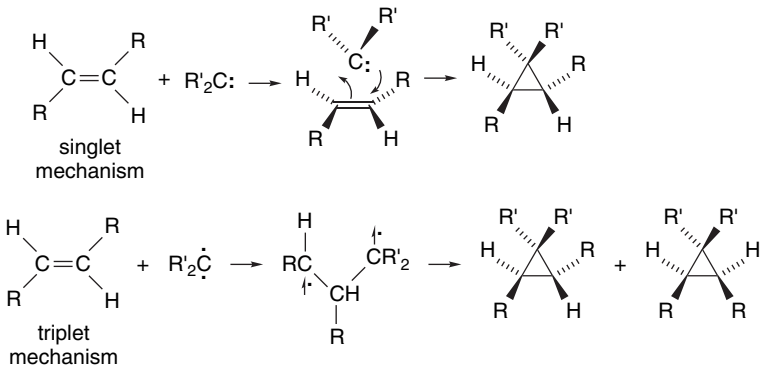


[161] W. E. Parham and E. E. Schweizer, *Org. React.*, **13**, 55 (1963).
[162] R. A. Olofson and C. M. Dougherty, *J. Am. Chem. Soc.*, **95**, 581 (1973).
[163] R. A. Moss and F. G. Pilkiewicz, *J. Am. Chem. Soc.*, **96**, 5632 (1974).
[164] D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. 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.

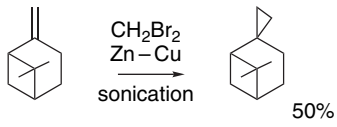


Reactions involving free carbenes are very exothermic since two new σ bonds are formed and only the alkene π bond is broken. The reactions are very fast and, in fact, theoretical treatment of the addition of singlet methylene to ethylene suggests that there is no activation barrier.[168] The addition 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 **:**CH_2 is not an intermediate. Entries 1 to 3 in Scheme 10.9 are typical examples.

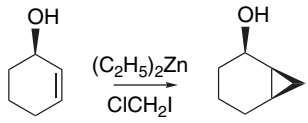
[167] D. Seyferth and C. K. Haas, *J. Org. Chem.*, **40**, 1620 (1975).
[168] B. Zurawski and W. Kutzelnigg, *J. Am. Chem. Soc.*, **100**, 2654 (1978).
[169] H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **80**, 5323 (1958); H. E. Simmons and R. D. Smith, **81**, 4256 (1959); H. E. Simmons, T. 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] $C_2H_5ZnCH_2I$, $Zn(CH_2I)_2$, and ICH_2ZnI are all active methylene transfer reagents.

$$(C_2H_5)_2Zn + CH_2I_2 \longrightarrow C_2H_5ZnCH_2I + C_2H_5I$$

$$C_2H_5ZnI + CH_2I_2 \longrightarrow ICH_2ZnI + C_2H_5I$$

A crystal structure has been obtained for $Zn(CH_2I)_2$ 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).

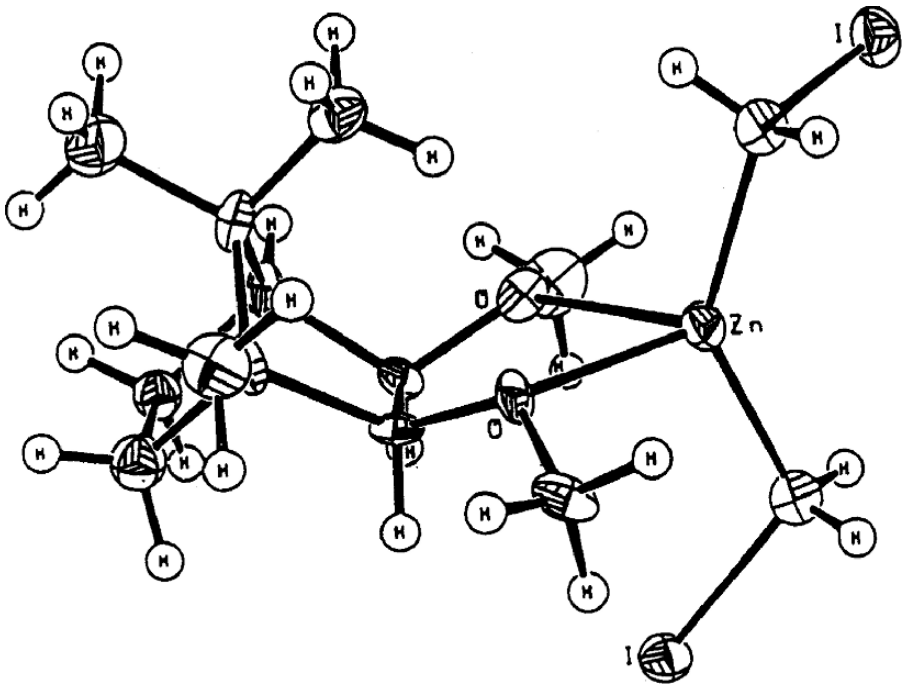


Fig. 10.4. Crystal structure of one molecule of $Zn(CH_2I)_2$ complexed with *exo*,*exo*-2,3-dimethoxybornane. Reproduced from *J. Am. Chem. Soc.*, **114**, 2592 (1992), by permission of the American Chemical Society.

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]

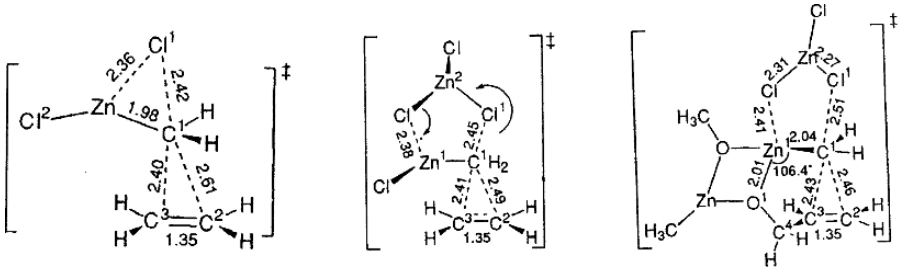
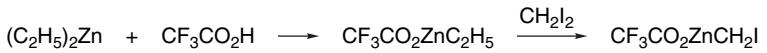


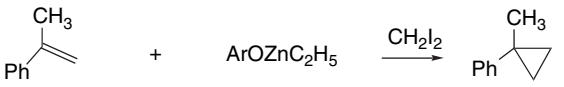
Fig. 10.5. Transition structures for CH_2 transfer from $ClCH_2ZnCl_2$ and $ClZnCH_2Cl$-$ZnCl_2$ to ethene and to coordinated allyl alcohol. Reproduced from *J. Am. Chem. Soc.*, **125**, 2341 (2003), by permission of the American Chemical Society.

[179.] J. C. Lorenz, J. Long, Z. Yang, S. Xue, Y. Xie, and Y. Shi, *J. Org. Chem.*, **69**, 327 (2004).



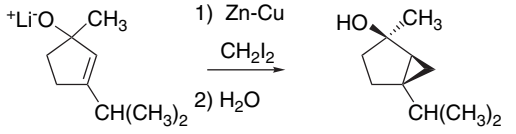
Iodomethylzinc phenoxides can be prepared in a similar fashion. The best phenols are the 2,4,6-trihalophenols and the readily available 2,4,6-trichlorophenol was examined most thoroughly.[180]

This reagent can achieve better than 90% yields for a variety of unactivated alkenes.

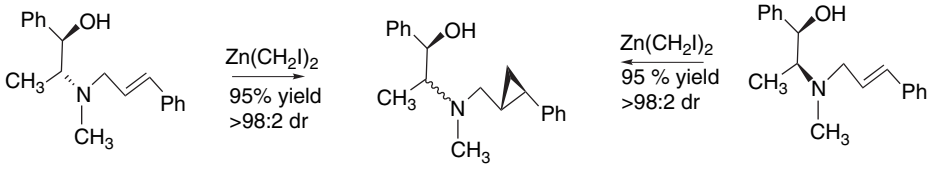


The reactivity of the oxy anions is in the order $CF_3CO_2^- > ArO^- >> RO^-$.

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]

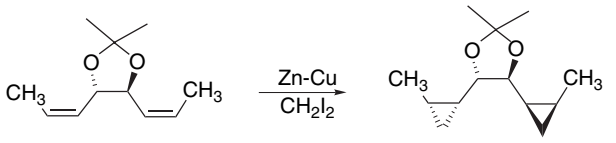


While amino groups alone are not effective directing groups, both ephedrine and pseudoephedrine derivatives give high diastereoselectivity. This is evidently due to chelation by the hydroxy group, as both auxiliaries give the same facial selectivity despite differing in configuration at the nitrogen position.[182]

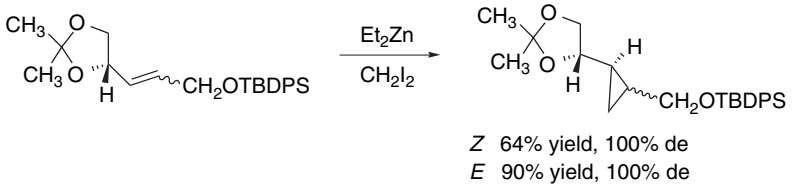


Dioxolanyl oxygens are also effective directing groups.[183]

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).

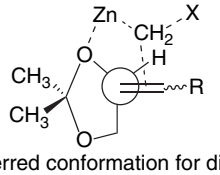


Ref. 184



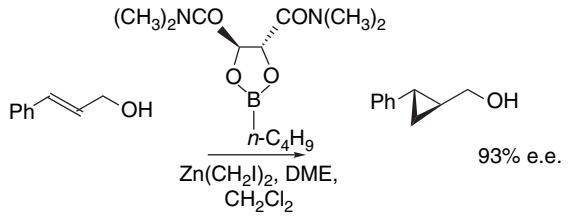
Ref. 185

The stereoselectivity is accounted for by a TS in which the allylic oxygen is coordinated to the zinc.



preferred conformation for directing effect of dioxolanyl substituents

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]

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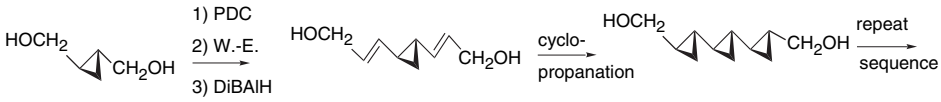
[184.] T. Onoda, R. Shirai, Y. Koiso, and S. Iwasaki, *Tetrahedron Lett.*, **37**, 4397 (1996).

[185.] T. Morikawa, H. Sasaki, R. Hanai, A. Shibuya, and T. Taguchi, *J. Org. Chem.*, **59**, 97 (1994).

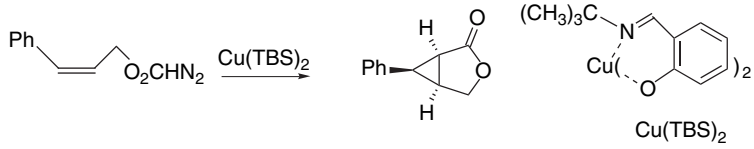
[186.] A. B. Charette and H. Juteau, *J. Am. Chem. Soc.*, **116**, 2651 (1994); A. B. Charette, S. Prescott, and C. Brochu, *J. Org. Chem.*, **60**, 1081 (1995).

[187.] A. B. Charette and H. Lebel, *J. Am. Chem. Soc.*, **118**, 10327 (1996).

The starting material was *trans*-cyclopropane-1,2-dimethanol. The contiguous cyclopropane units were added by two iterative sequences of oxidation–Wadsworth-Emmons–reduction–cyclopropanation.

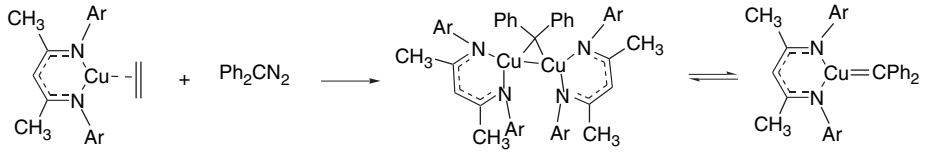


10.2.3.2. Metal-Catalyzed Cyclopropanation. Carbene addition reactions can be catalyzed by several transition metal complexes. Most of the synthetic work has been done using copper or rhodium complexes and we focus on these. The copper-catalyzed decomposition of diazo compounds is a useful reaction for 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).

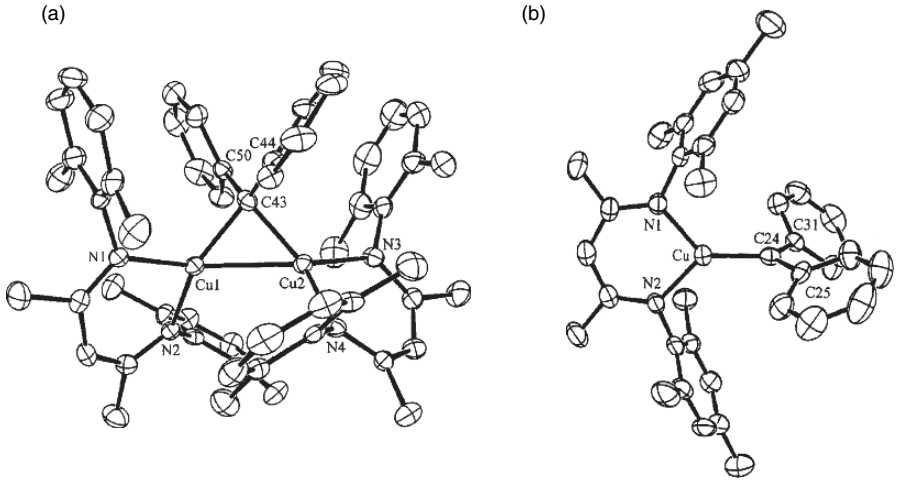
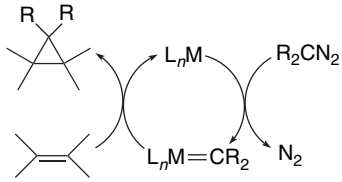


Fig. 10.6. Dimeric (Ar = 2,6-dimethylphenyl) (a) and monomeric (Ar = 2,4,6-trimethylphenyl) (b) copper complexes with diphenylcarbene. Reproduced from *J. Am. Chem. Soc.*, **126**, 10085 (2004), by permission of the American Chemical Society.

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 metallocyclobutane intermediate.

Various other transition metal complexes are also useful, including rhodium,[195] palladium,[196] and molybdenum[197] 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).

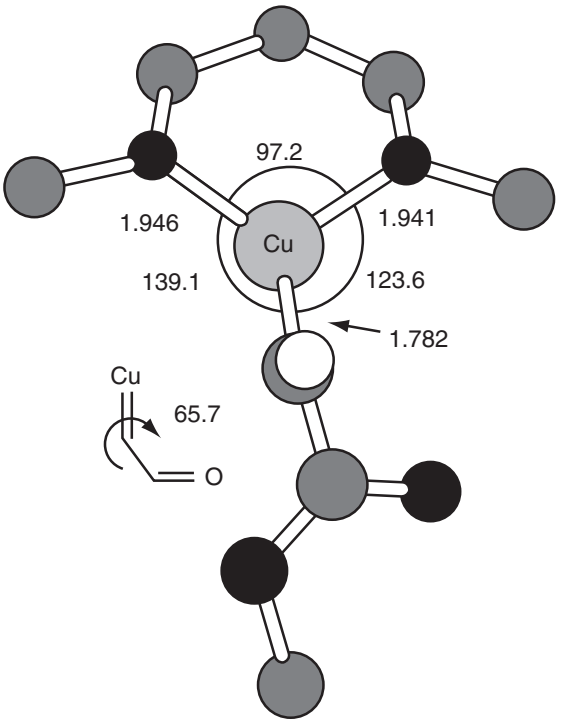
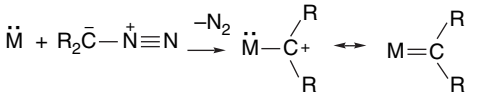
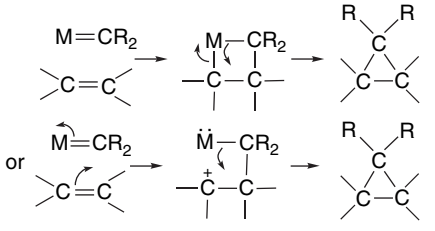


Fig. 10.7. Computational (B3LYP/6-31G(*d*)) minimum-energy structure of carbomethoxycarbene derivative of copper *N*,*N*′-dimethylpropane-1,3-diimine. Reproduced from *J. Am. Chem. Soc.*, **123**, 7616 (2001), by permission of the American Chemical Society.

The metal-carbene complexes are electrophilic in character. They can, in fact, be represented as metal-stabilized carbocations.

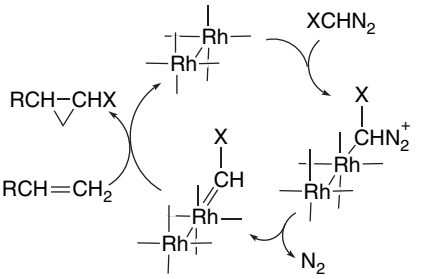


In most transition metal–catalyzed reactions, one of the carbene substituents is a carbonyl group, which further enhances the electrophilicity of the intermediate. There are two general mechanisms that can be considered for cyclopropane formation. One involves formation of a four-membered ring intermediate that incorporates the metal. The alternative represents an electrophilic attack giving a polar species that undergoes 1,3-bond formation.

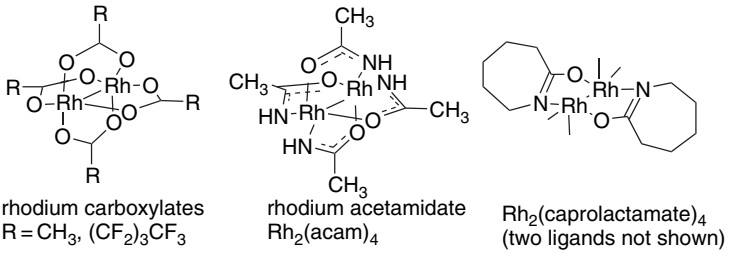


Since the additions are normally stereospecific with respect to the alkene, if an open-chain intermediate is involved it must collapse to product more rapidly than single-bond rotations that would destroy the stereoselectivity.

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 $Rh_2(O_2CCH_3)_4$, but other carboxylates such as nonafluorobutanoate and amide anions, such as those from acetamide and caprolactam, also have good catalytic activity.[199]



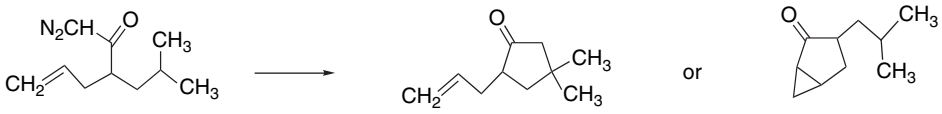
The ligands adjust the electrophilicity of the catalyst with the nonafluorobutanoate being more electrophilic and the amido ligands less electrophilic than the acetate. These catalysts show differing reactivity. For example, $Rh_2(O_2C_4F_9)_4$ was found to favor aromatic substitution over cyclopropanation, whereas Rh_2(caprolactamate)$_4$ was selective for cyclopropanation.[200] In competition between tertiary alkyl insertion versus cyclopropanation, the order in favor of cyclopropanation is also Rh_2(caprolactamate)$_4$ > $Rh_2(O_2CCH_3)_4$ > $Rh_2(O_2CC_4F_9)_4$. These predictable selectivity patterns have made the rhodium catalysts useful in a number of synthetic applications.[201] For example, $Rh_2(O_2C_4F_9)_4$ gave exclusively insertion, whereas Rh_2(caprolactamate)$_4$ gave exclusively cyclopropanation. $Rh_2(O_2CCH_3)_4$ 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).



$Rh_2(O_2CC_4F_9)_4$	100%	0%
$Rh_2(O_2CCH_3)_4$	56%	44%
Rh_2(caprolactamate)$_4$	0%	100%

Mechanistic and computational studies have elucidated some of the key details of the reactions. A kinetic study of $Rh_2[O_2CC(CH_3)_3]_4$ 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

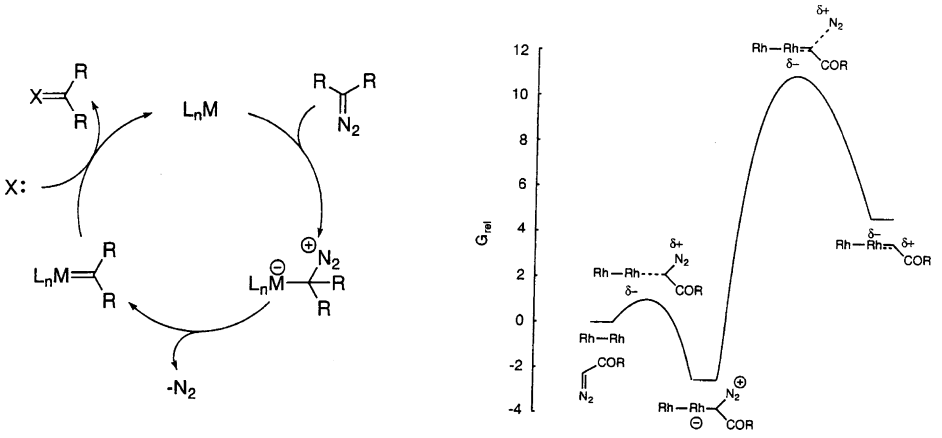


Fig. 10.8. Basic catalytic cycle and energy profile for rhodium-catalyzed carbenoid reactions. Reproduced from *J. Am. Chem. Soc.*, **124**, 1014 (2002), by permission of the American Chemical Society.

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).

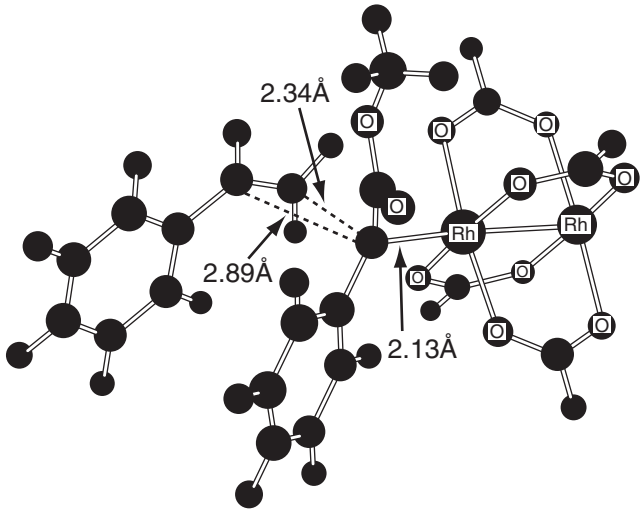
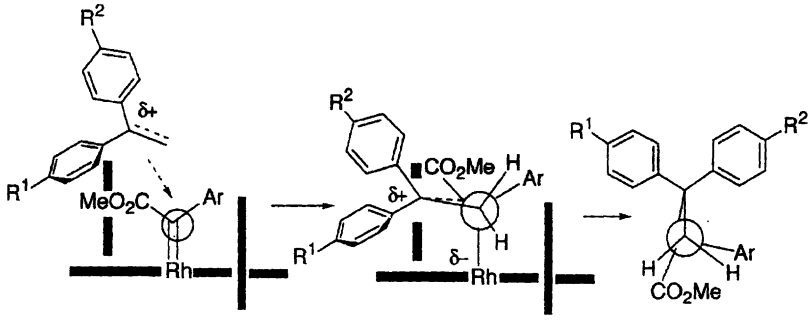


Fig. 10.9. Computed transition structure for addition of methyl phenyldiazoacetate to styrene from B3LYP/6-31G*/LANL2DZ computations. Reproduced from *J. Am. Chem. Soc.*, **125**, 15902 (2003), by permission of the American Chemical Society.

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).

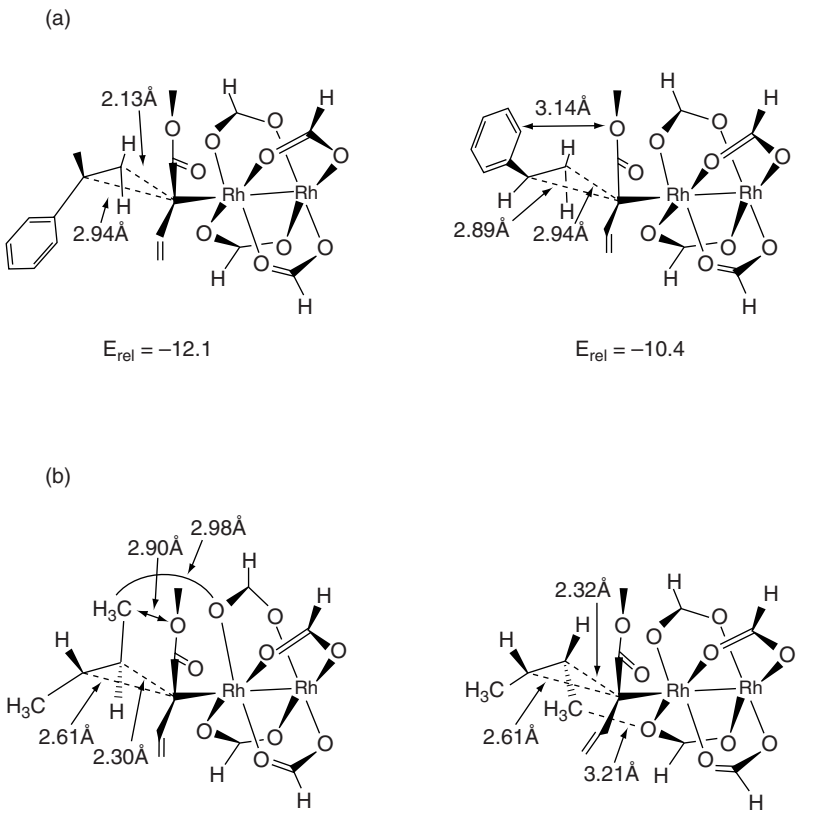


Fig. 10.10. Steric interactions in rhodium-catalyzed addition of methyl 2-diazobut-3-enoate to styrene (a) and *cis* and *trans* butene (b). Reproduced from *J. Am. Chem. Soc.*, **125**, 15902 (2003), by permission of the American Chemical Society.

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.

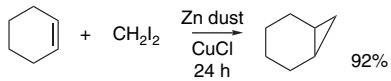
The addition of dichlorocarbene, generated from chloroform, to alkenes gives dichlorocyclopropanes. The procedures based on lithiated halogen compounds have been less generally used in synthesis. Section D of Scheme 10.9 gives a few examples of addition reactions of carbenes generated by α-elimination.

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 of 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

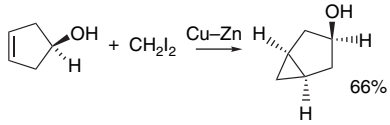
Scheme 10.9. Cyclopropane Formation by Carbenoid Addition

A. Cyclopropanes by methylene transfer

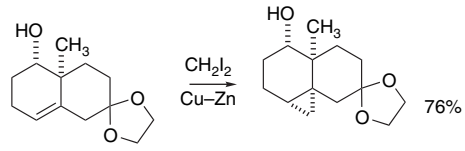
1[a]



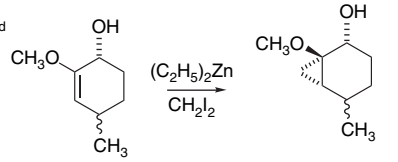
2[b]



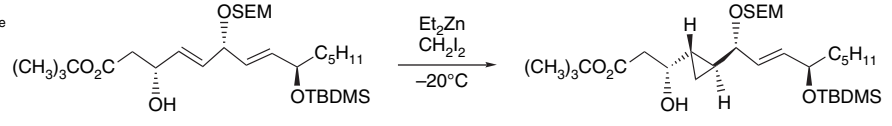
3[c]



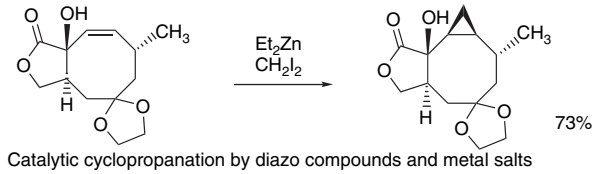
4[d]



5[e]

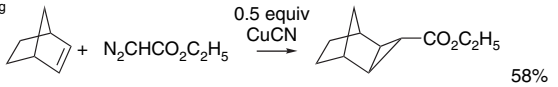


6[f]

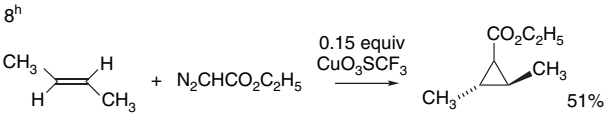


B. Catalytic cyclopropanation by diazo compounds and metal salts

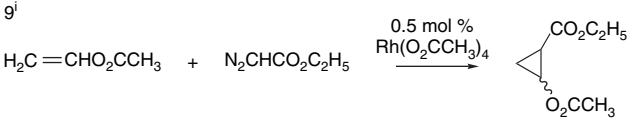
7[g]



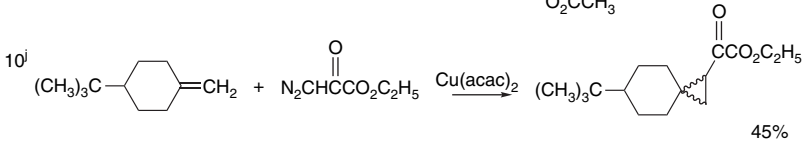
8[h]



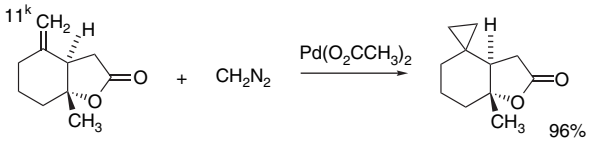
9[i]



10[j]



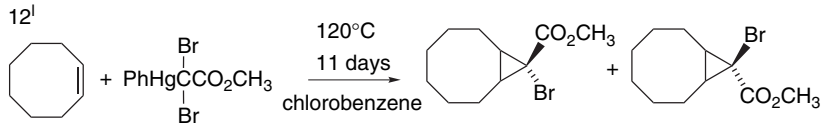
11[k]



(*Continued*)

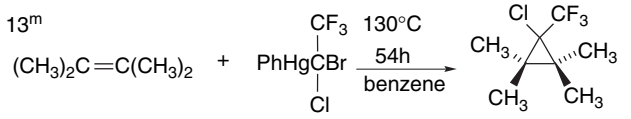
C. Cyclopropane formation using haloalkylmercurials

12[l]



50% total yield

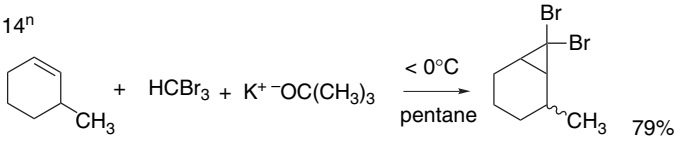
13[m]



58%

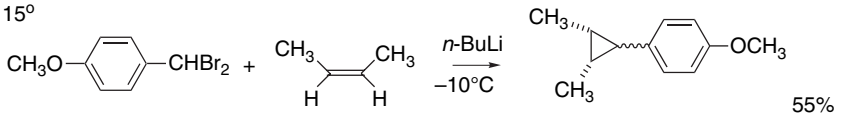
D. Reactions of carbenes generated by α-elimination

14[n]



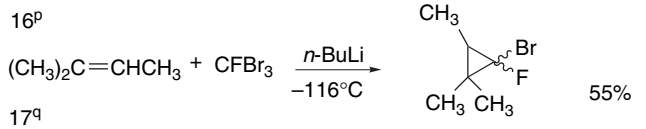
79%

15[o]



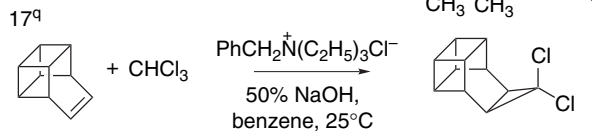
55%

16[p]



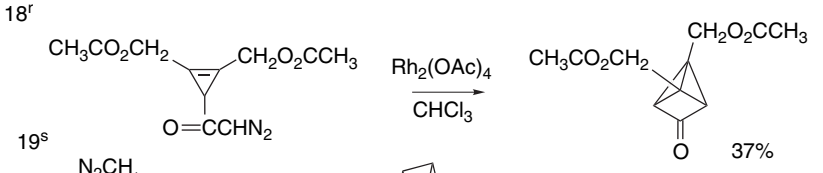
55%

17[q]



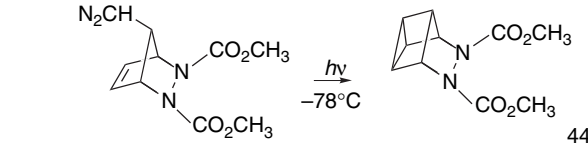
E. Intramolecular cyclopropanation reactions

18[r]



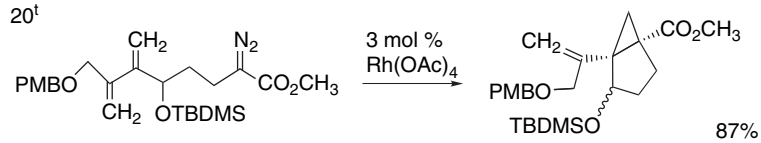
37%

19[s]



44%

20[t]



87% 6.7:1 dr

(*Continued*)

Scheme 10.9. (*Continued*)

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. Sonnett, *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. Petiniot, 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. Seyferth, D. C. Mueller, and R. L. Lambert, Jr., *J. Am. Chem. Soc.*, **91**, 1562 (1969).
m. D. Seyferth 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. Irngartiner, 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).

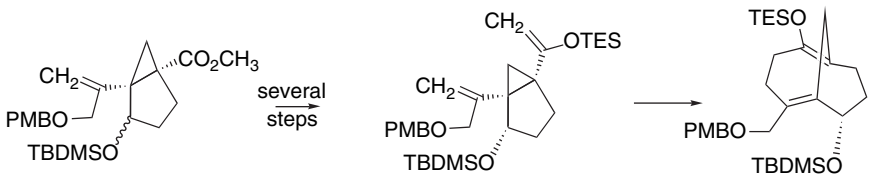
effect in an acyclic system. Not only is the hydroxy group stereodirective, but it also provides selectivity with respect to the two double bonds. The reaction in Entry 6 was carried out in the course of synthesis of crenulide derivatives, which are obtained from seaweed.

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 $Rh_2(O_2CCH_3)_4$ as the catalyst at a much lower ratio. Entry 10 involves ethyl diazopyruvate, with copper acetylacetonate as the catalyst. The stereoselectivity of this reaction was not determined. Entry 11 shows that $Pd(O_2CCH_3)$ 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.

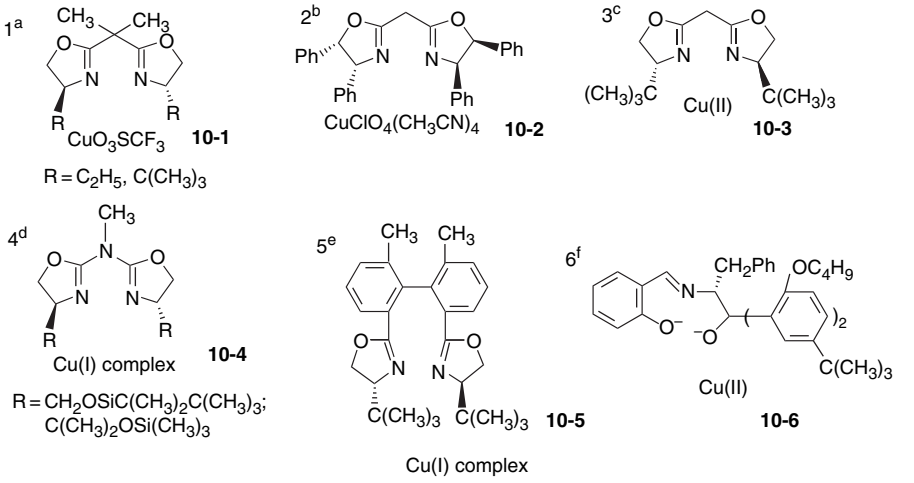
Intramolecular carbene addition reactions have a special importance in the synthesis of strained-ring compounds. Because of the high reactivity of carbene or carbenoid species, the formation of highly strained bonds is possible. The strategy for synthesis is to construct a potential carbene precursor, 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.

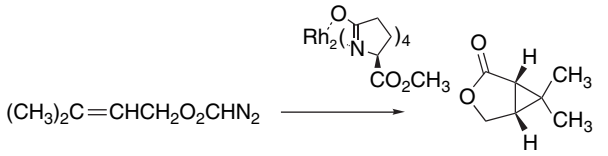
Several chiral ligands have been developed for use with the rhodium catalysts, among them are pyrrolidinones and imidazolidinones.[207] For example, the lactamate of pyroglutamic acid gives enantioselective cyclopropanation reactions.

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).

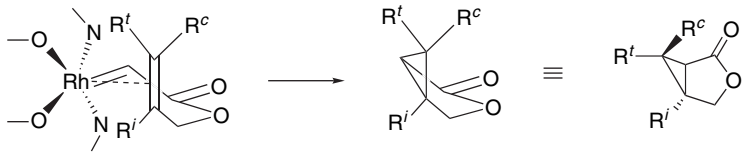
207. M. P. Doyle, R. E. Austin, A. S. Bailey, M. P. Dwyer, A. B. Dyatkin, A. V. Kalinin, M. M.-Y. Kwan, S. Liras, C. J. Oalmann, R. J. Pieters, M. N. Protopopova, C. E. Raab, G. H. P. Roos, Q. L. Zhou, and S. F. Martin, *J. Am. Chem. Soc.*, **117**, 5763 (1995); M. P. Doyle, A. B. Dyatkin, M. N. Protopopova, 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).



82% yield, 92% e.e.

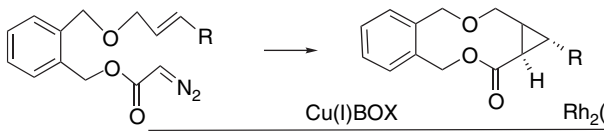
The 1-acetyl and 1-benzoyl derivatives of 4-carbomethoxyimidazolinone are also effective catalysts. Another group of catalysts is made up of *N*-arenesulfonylprolinates. The structures and abbreviations are given in Scheme 10.11. The PY series of catalysts is derived from pyroglutamic acid, whereas the 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 *amide*s 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 R^i are directed toward the catalyst and introduce steric interactions that detract from enantioselectivity.[208]



The 1-arenesulfonylprolinate 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 arenesulfonyl 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.



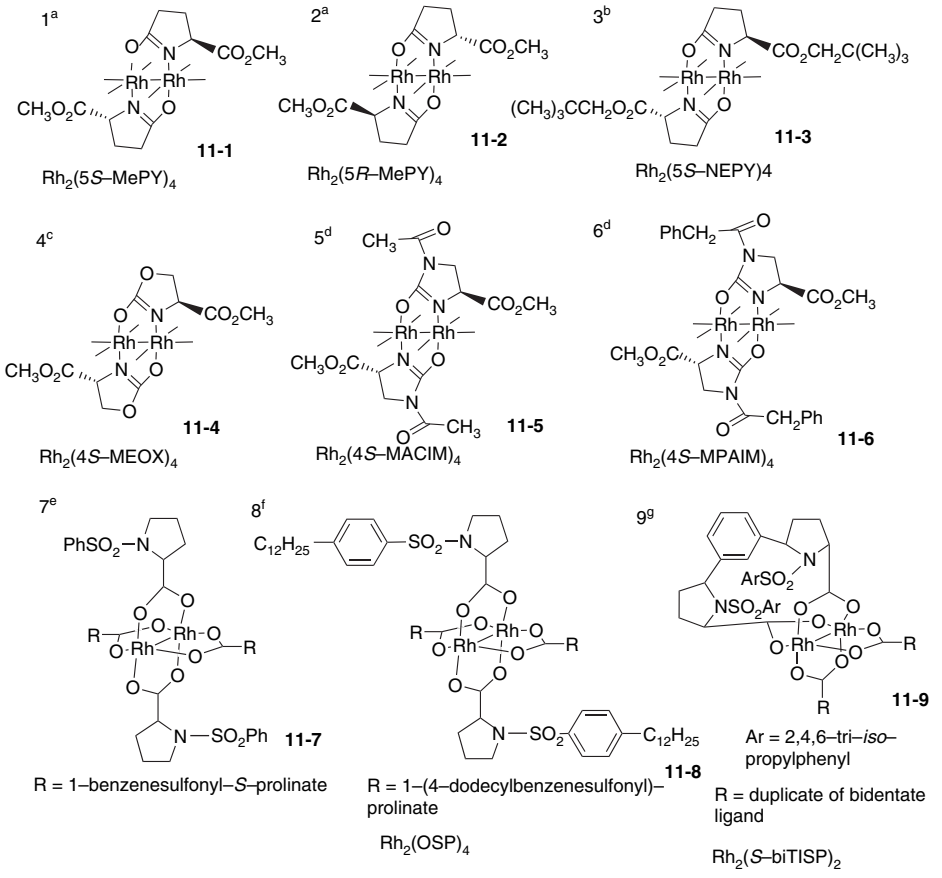
	Cu(I)BOX	Rh_2(5-*S*-MEPY)$_4$
R = CH_3	82% yield, 90% e.e.	81% yield, 45% e.e.
R = $CH(CH_3)_2$	93% yield, 84% e.e.	80% yield, 19% e.e.

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).

Scheme 10.11. Chiral Dirhodium Catalysts



a. M. P. Doyle, R. J. Pieters, S. F. Martin, R. E. Austin, P.. J. Oalmann, 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 $Rh_2[5(S)\text{-MePY}]_4$

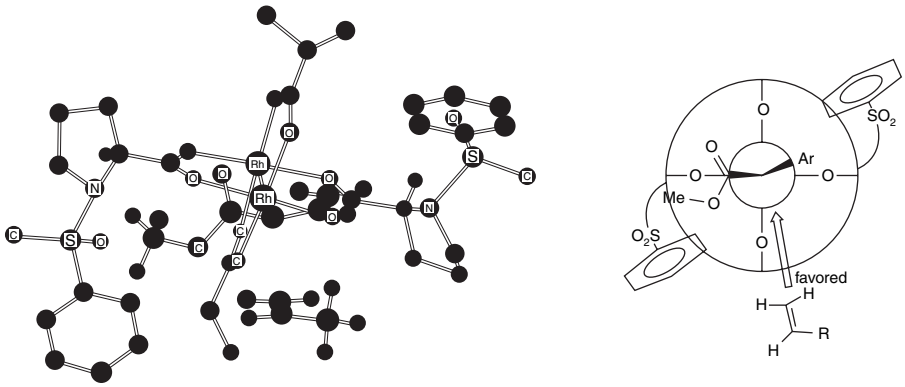


Fig. 10.11. General schematic model for favored approach of alkenes to 1-arenesulfonylprolinate catalysts (right); and B3LYP/6-31G*/LANL2DZ computational model of preferred approach of propene to 1-carbomethoxyprop-2-enylidene complex with Rh_2(1-benzenesulfonylprolinate)$_2$(isobutyrate)$_2$ (left). 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.

$$CH_3{-}CH_2{-}CH_3 \;+\; {:}CH_2 \longrightarrow CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_3$$

The same products can be formed by a two-step hydrogen abstraction and recombination involving a triplet carbene.

$$CH_3{-}CH_2{-}CH_3 \;+\; \dot{C}H_2 \longrightarrow CH_3{-}\underset{\displaystyle \dot{C}H_3}{\underset{|}{\dot{C}H}}{-}CH_3 \longrightarrow CH_3{-}\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}CH_3$$

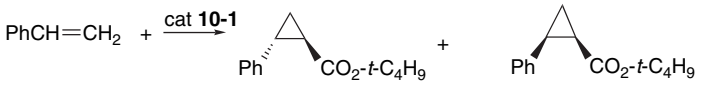
It is sometimes difficult to distinguish clearly between these mechanisms, but determination of reaction stereochemistry provides one approach. The true one-step insertion must occur with complete *retention of configuration*. The results for the two-step process will depend on the rate of recombination 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).

Scheme 10.12. Enantioselective Cyclopropanation

1[a]

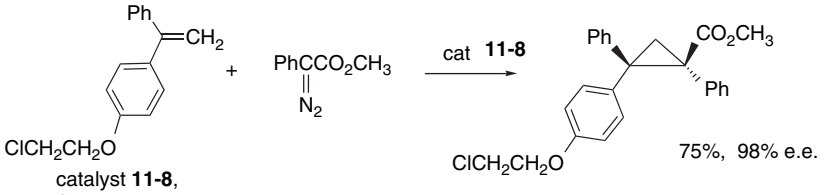


catalyst **10-1**, R = *t*-Bu, Scheme 10.10

61% yield, 96% e.e.

14% yield, 93% e.e.

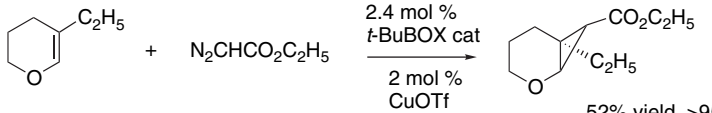
2[b]



catalyst **11-8**, Scheme 10.11

75%, 98% e.e.

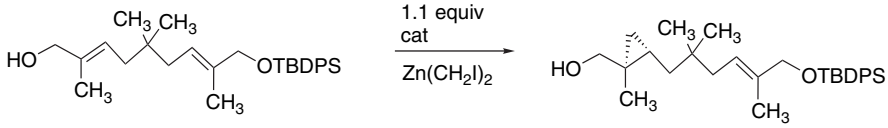
3[c]



catalyst **10-1**, R = *t*-Bu Scheme 10,10

52% yield, >95% e.e.

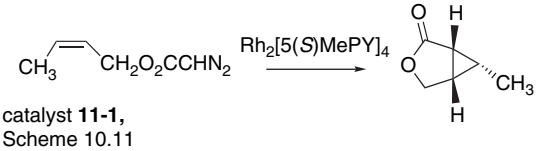
4[d]



catalyst is *B*-butyl 1,3,2-dioxaborolane 4,5-*bis*-(*N,N*-dimethylcarboxamide).

>95% yield
86% e.e.

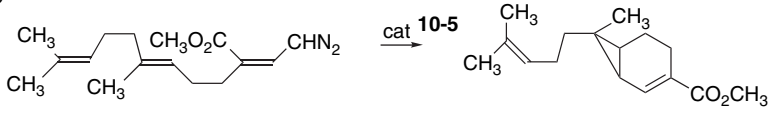
5[e]



catalyst **11-1,** Scheme 10.11

80% yield, 92% e.e.

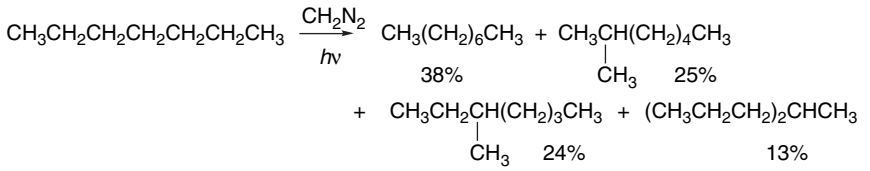
6[f]



catalyst **10-5**, Scheme 10.10

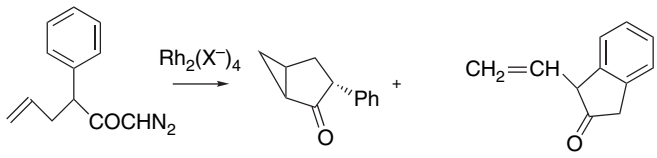
77% yield, 90% e.e.

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.

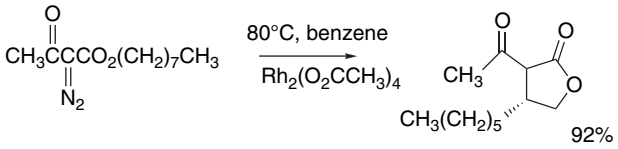
Rhodium carboxylates have been found to be effective catalysts for intramolecular C−H insertion reactions of α-diazo ketones and esters.[215] In flexible systems, five-membered rings are formed in preference to six-membered ones. Insertion into methine hydrogen is preferred to a methylene hydrogen. Intramolecular 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 $Rh_2(O_2CC_4F_9)_4$, whereas only addition occurs with Rh_2(caprolactamate)$_4$, which indicates that the more electrophilic carbenoids favor insertion.



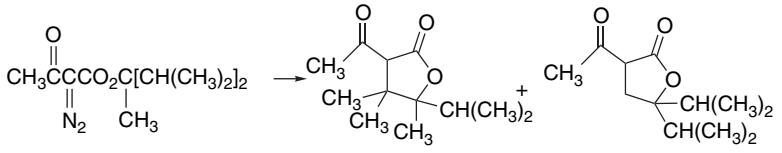
$Rh_2(X^-)_4$	Yield (%)	Ratio
$Rh_2(O_2CCH_3)_4$	99	67:33
$Rh_2(O_2CC_4F_9)_4$	95	0:100
Rh_2(caprolactamate)$_4$	72	100:0

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).

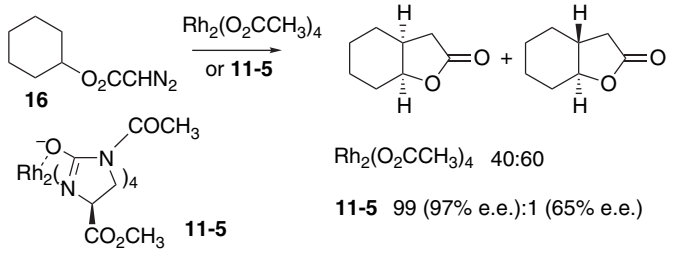


When the reactant provides more than one kind of hydrogen for insertion, the catalyst can influence selectivity. For example, $Rh_2(acam)_4$ gives exclusively insertion at a tertiary position, whereas $Rh_2(O_2CC_4F_9)_4$ leads to nearly a statistical mixture.[217a] The attenuated reactivity of the amidate catalyst enhances selectivity.

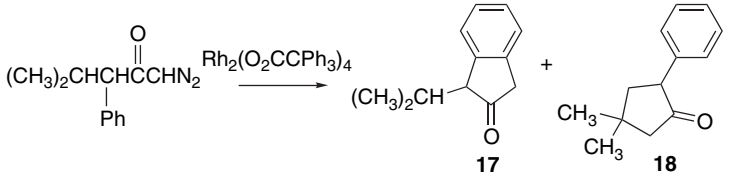


$Rh_2(X^-)_4$	Ratio
$Rh_2(O_2CCH_3)_4$	90:10
$Rh_2(O_2CC_4F_9)_4$	39:61
$Rh_2(NHCOCH_3)_4$	>99:1

Stereoselectivity is also influenced by the catalysts. For example, **16** can lead to either *cis* or *trans* products. Although $Rh_2(O_2CCH_3)_4$ is unselective, the $Rh_2(MACIM)_4$ catalyst **11-5** (Scheme 10.11) is selective for the *cis* isomer and also gives excellent enantioselectivity in the major product.[217]

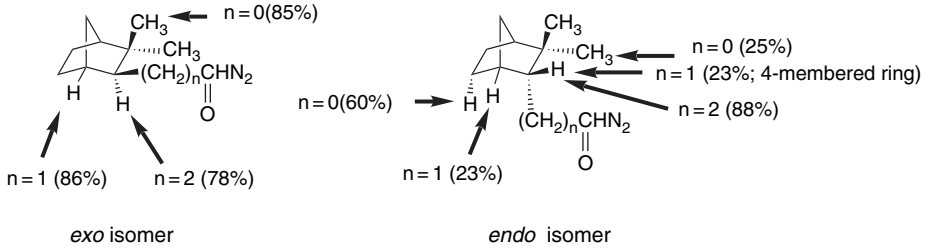


Certain sterically hindered rhodium catalysts also lead to improved selectivity. For example, rhodium triphenylacetate improves the selectivity for **17** over **18** from 5:1 to 99:1.[218]



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).

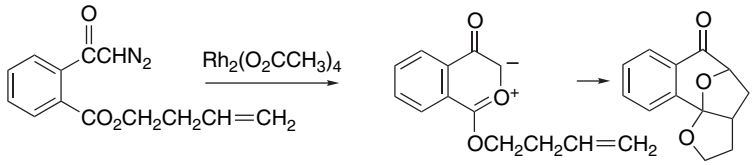
Intramolecular insertion reactions show a strong preference for formation of five-membered rings.[219] This was seen in a series of α-diazomethyl ketones of increasing chain length. With only one exception, all of the products were five-membered lactones.[220] In the case of $n = 3$, the cyclization occurs in the side chain, again forming a five-membered ring.



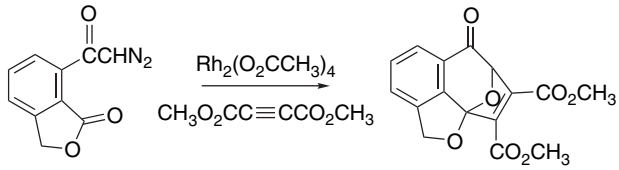
Scheme 10.13 gives some additional examples of intramolecular insertion reactions. Entries 1 and 2 were done under the high-temperature conditions of the Bamford-Stevens reaction (see p. 913). Entries 3 to 5 are metal-catalyzed intramolecular reactions in which 5-membered rings are formed. Entries 6 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

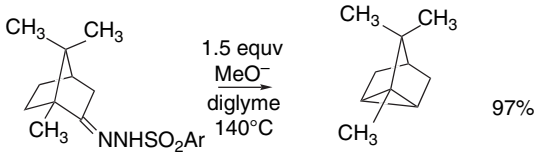


Ref. 221

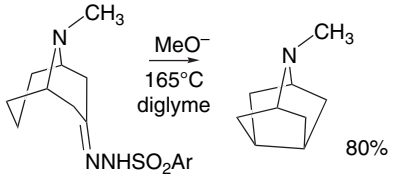
219. D. F. Taber and R. E. Ruckle, Jr., *J. Am. Chem. Soc.*, **108**, 7686 (1986).
220. H. R. Sonawane, N. S. Bellur, J. R. Ahuja, and D. G. Kulkarni, *J. Org. Chem.*, **56**, 1434 (1991).
221. A. Padwa and S. F. Hornbuckle, *Chem. Rev.*, **91**, 263 (1991).
222. A. Padwa, S. P. Carter, H. Nimmesgern, and P. D. Stull, *J. Am. Chem. Soc.*, **110**, 2894 (1988).

Scheme 10.13. Intramolecular Carbene-Insertion Reactions

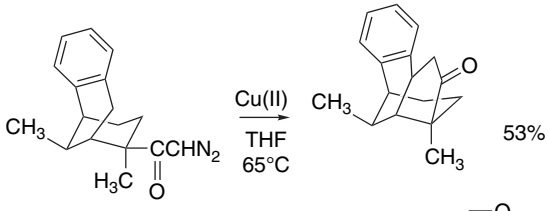
1[a]



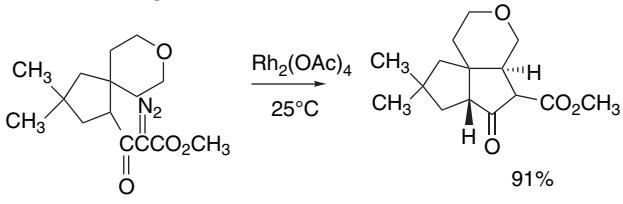
2[b]



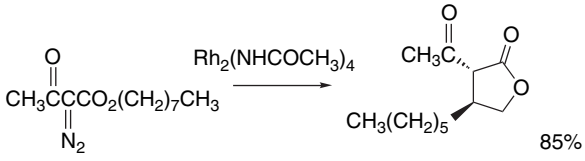
3[c]



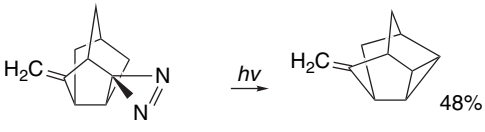
4[d]



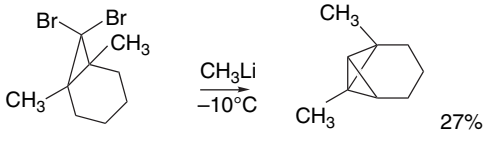
5[e]



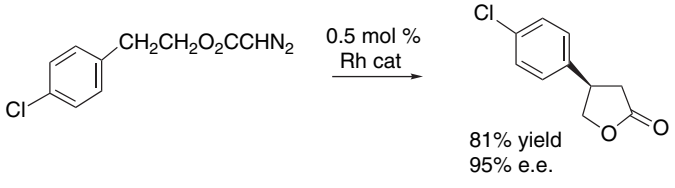
6[f]



7[g]



8[h]

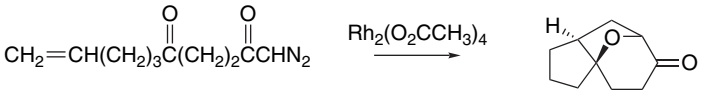


catalyst is *tetrakis*-[*N*-phenylpropanoyl-4-methoxycarbonylimidazolonato] dirhodium

(*Continued*)

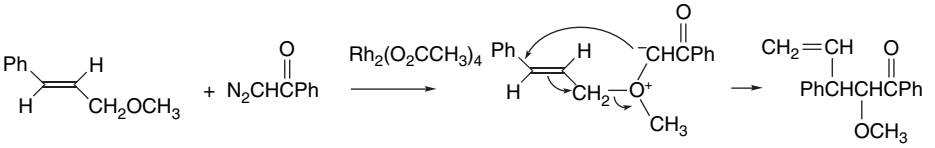
Scheme 10.13. (*Continued*)

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).



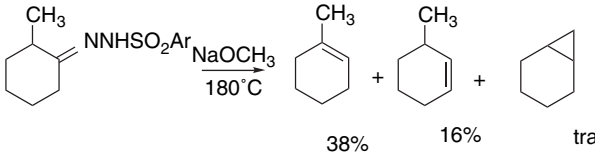
Ref. 223

Allylic ethers and acetals can react with carbenoid reagents to generate oxonium ylides that undergo [2,3]-sigmatropic shifts.[224]



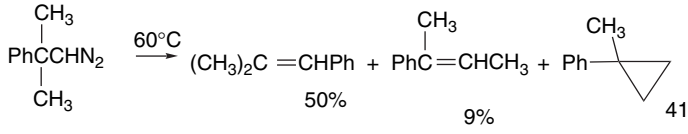
10.2.6. Rearrangement Reactions

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.



Ref. 225

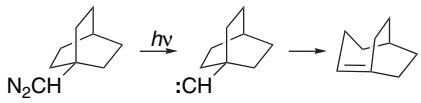
Carbenes can also be stabilized by migration of alkyl or aryl groups. 2-Methyl-2-phenyl-1-diazopropane provides a case in which products of both phenyl and methyl migration, as well as intramolecular insertion, are observed.



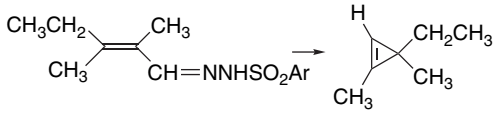
Ref. 226

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]octyldiazomethane is photolyzed.[227]

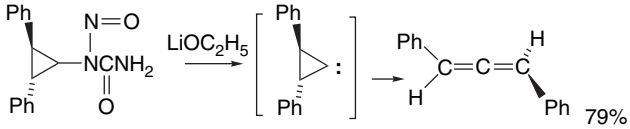


Carbene centers adjacent to double bonds (vinyl carbenes) usually cyclize to cyclopropenes.[228]

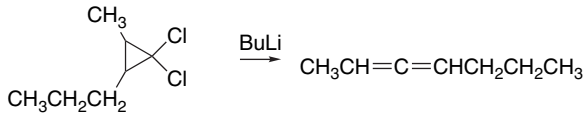


Ref. 229

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.



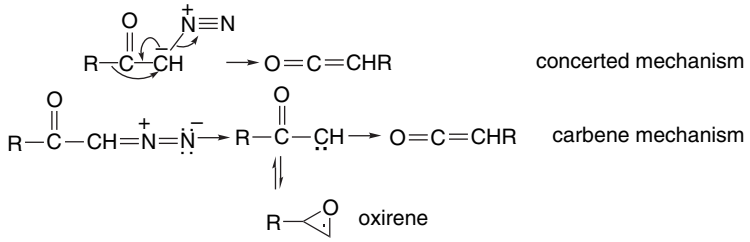
Ref. 230



Ref. 231

10.2.7. Related Reactions

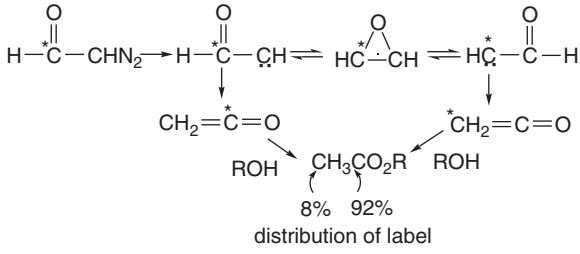
There are several reactions that are conceptually related to carbene reactions but do not involve carbene, or even carbenoid, intermediates. Usually, these are reactions in which the generation of a carbene is circumvented by a concerted rearrangement process. Important examples of this type are the 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]



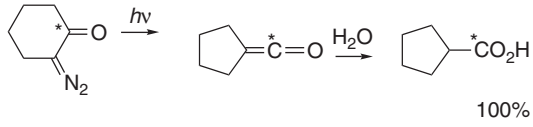
227. M. S. Gudipati, J. G. Radziszewski, P. Kaszynski, and J. Michl, *J. Org. Chem.*, **58**, 3668 (1993).
228. G. L. Closs, L. E. Closs, and W. A. Böll, *J. Am. Chem. Soc.*, **85**, 3796 (1963).
229. E. J. York, W. Dittmar, J. R. Stevenson, and R. G. Bergman, *J. Am. Chem. Soc.*, **95**, 5680 (1973).
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]



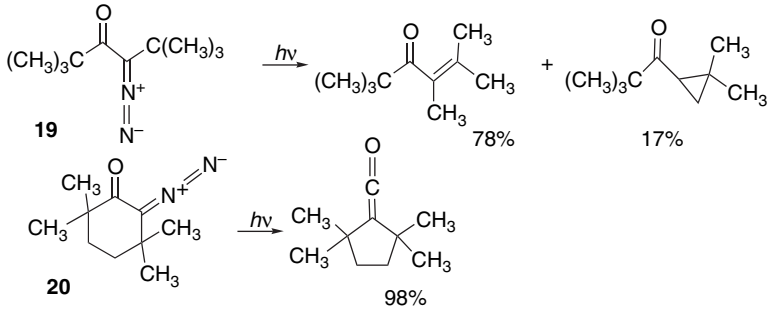
The diphenyl analog shows about 20–30% rearrangement.[235] α-Diazocyclohexanone gives no evidence of an oxirene intermediate, since all the label remains at the carbonyl carbon.[236]



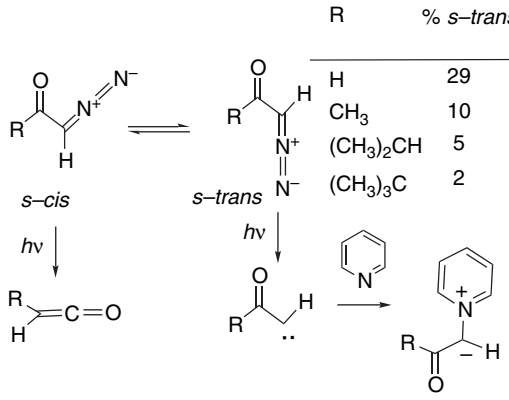
The reactivity of diazo carbonyl compounds appears to be related to the conformational equilibria between *s-cis* and *s-trans* conformations. A concerted rearrangement is favored by the *s-cis* conformation.[237] The *t*-butyl compound **19**, which exists in the *s-trans* conformation, gives very little 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).

substituted cyclic diazoketone **20**, which is in the *s-cis* conformation, gives a high yield of the ring-contracted ketene.[239]



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]



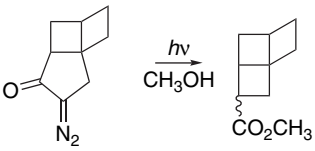
R	% *s–trans*	% trapped as ylide
H	29	42
CH_3	10	15
$(CH_3)_2CH$	5	13
$(CH_3)_3C$	2	9

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 ($\sim$ 20 ns).[241]

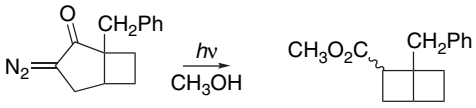
The main synthetic application of the Wolff rearrangement is for the one-carbon homologation of carboxylic acids.[242] In this procedure, a diazomethyl ketone is synthesized from an acyl chloride. The rearrangement is then carried out in a nucleophilic solvent that traps the ketene to form a carboxylic 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. 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).



42% Ref. 244

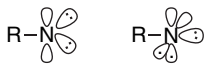


60% Ref. 245

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.

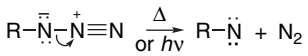
10.2.8. Nitrenes and Related Intermediates

The nitrogen analogs of carbenes are called nitrenes. As with carbenes, both singlet and triplet electronic states are possible.



singlet nitrene triplet nitrene

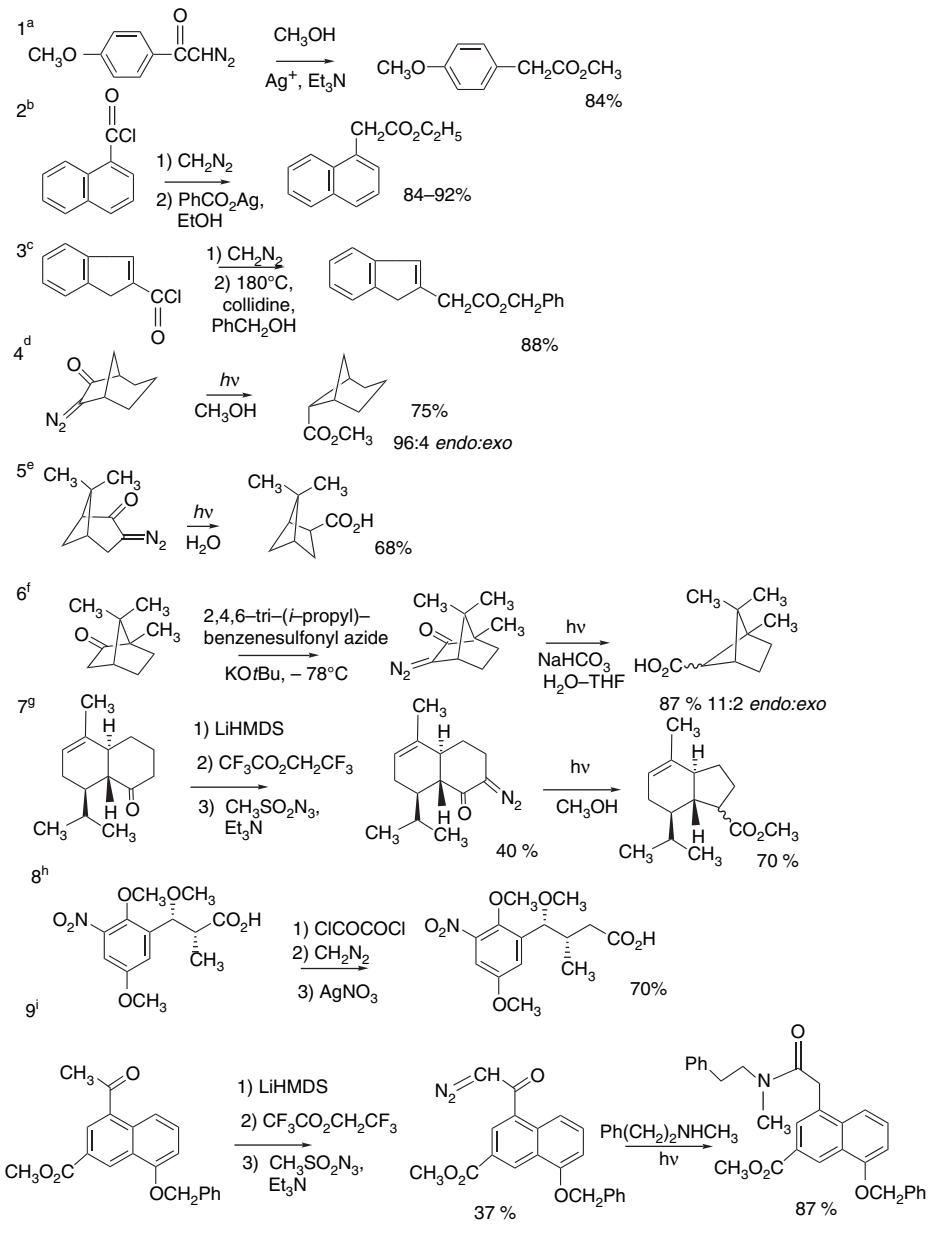
The triplet state is usually the ground state for non-conjugated structures, but either species can be involved in reactions. The most common method for generating nitrene intermediates, analogous to formation of carbenes from diazo compounds, is by thermolysis or photolysis of azides.[246]



The types of azides that have been used for generation of nitrenes include alkyl,[247] aryl,[248] acyl,[249] and sulfonyl[250] derivatives.

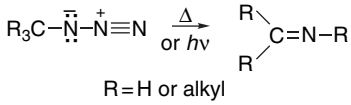
244. K. B. Wiberg, L. K. Olli, N. Golembeski, and R. D. Adams, *J. Am. Chem. Soc.*, **102**, 7467 (1980).
245. K. B. Wiberg, B. L. Furtek, and L. K. Olli, *J. Am. Chem. Soc.*, **101**, 7675 (1979).
246. E. F. V. Scriven, ed., *Azides and Nitrenes: Reactivity and Utility*, Academic Press, Orlando, FL, 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, *Fortshr. Chem. Forsch.*, **16**, 1 (1970).

Scheme 10.14. Wolff Rearrangements of α-Diazoketones



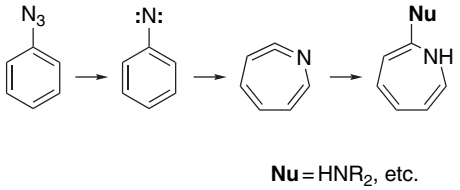
a. M. S. Newman and P. F. Beal, III, *J. Am. Chem. Soc.*, **72**, 5163 (1950).
b. V. Lee and M. S. Newman, *Org. Synth.*, **50**, 77 (1970).
c. E. D. Bergmann and E. Hoffmann, *J. Org. Chem.*, **26**, 3555 (1961).
d. K. B. Wiberg and B. A. Hess, Jr., *J. Org. Chem.*, **31**, 2250 (1966).
e. J. Meinwald 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.

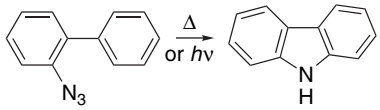


Intramolecular insertion and addition reactions are very rare for alkyl nitrenes. In fact, it is not clear that the nitrenes are formed as discrete species. The migration may be concerted with elimination, as is often the case in the Wolff rearrangement.[251]

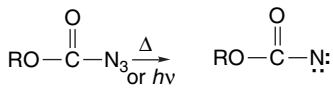
Aryl nitrenes also generally rearrange rather than undergo addition or insertion reactions.[252]



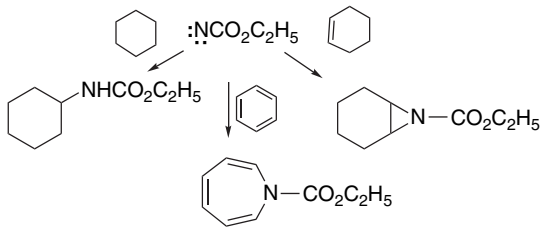
A few intramolecular insertion reactions, especially in aromatic systems, go in good yield.[253]



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).

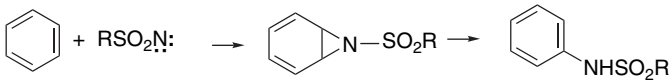
[252] O. L. Chapman and J.-P. LeRoux, *J. Am. Chem. Soc.*, **100**, 282 (1978); O. L. Chapman, R. S. Sheridan, and J.-P. LeRoux, *Rec. Trav. Chim. Pays-Bas*, **98**, 334 (1979); R. J. Sundberg, S. R. Suter, and M. Brenner, *J. Am. Chem. Soc.*, **94**, 573 (1972).

[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).

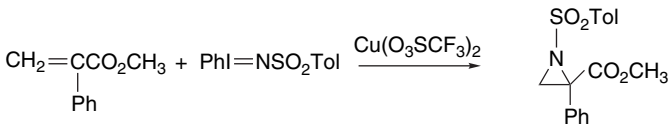
Carboalkoxynitrenes are somewhat more selective than the corresponding carbenes, showing selectivities of roughly 1:10:40 for the primary, secondary, and tertiary positions in 2-methylbutane in insertion reactions.

Sulfonylnitrenes are formed by thermal decomposition of sulfonyl azides. 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

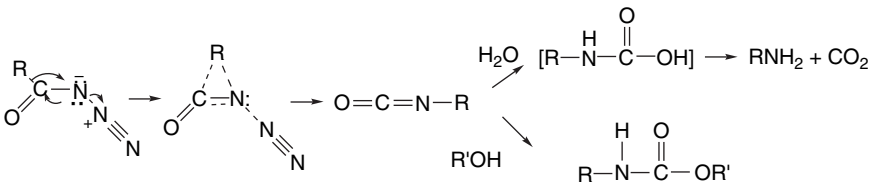
Aziridination of alkenes can be carried out using *N*-(*p*-toluenesulfonylimino) phenyliodinane and copper triflate or other copper salts.[257] These reactions are mechanistically analogous to metal-catalyzed cyclopropanation. Rhodium acetate also acts as a catalyst.[258] Other arenesulfonyliminoiodinanes can be used,[259] as can chloroamine T[260] and bromoamine T.[261] The range of substituted alkenes that react includes acrylate esters.[262]



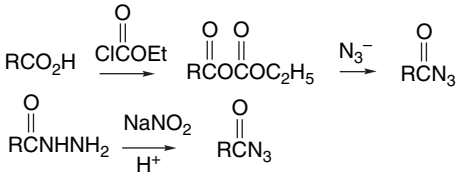
10.2.9. Rearrangements to Electron-Deficient Nitrogen

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 rearrangment 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.

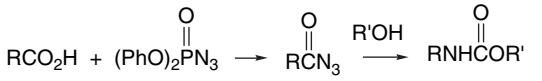
255. D. S. Breslow, M. F. Sloan, N. R. Newburg, and W. B. Renfrow, *J. Am. Chem. Soc.*, **91**, 2273 (1969).
257. R. A. Abramovitch, G. N. Knaus, and V. Uma, *J. Org. Chem.*, **39**, 1101 (1974).
257. D. A. Evans, M. M. Faulk, and M. T. Bilodeau, *J. Am. Chem. Soc.*, **116**, 2742 (1994).
258. P. Mueller, 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).



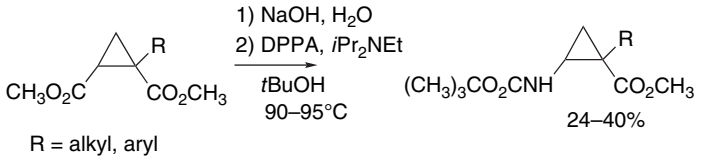
The acyl azide intermediates are prepared either by reaction of sodium azide with a reactive acylating agent or by diazotization of an acyl hydrazide. An especially convenient version of the former process is treatment of the carboxylic acid with ethyl chloroformate to form a mixed anhydride, which then reacts with azide ion.[265]



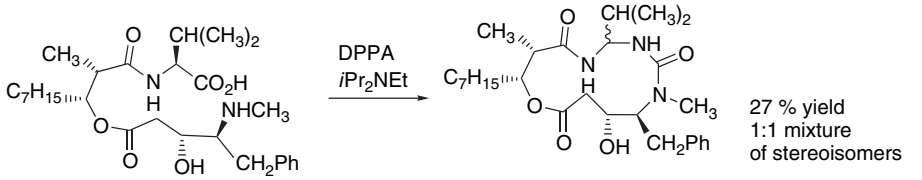
The transformation can also be carried out on the acid using diphenylphosphoryl azide (DPPA).[266]



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]

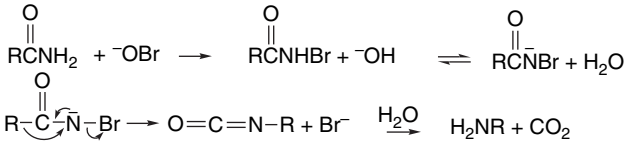


The Curtius reaction has occasionally been used in formation of medium[268] and large[269] rings, usually in modest yield.

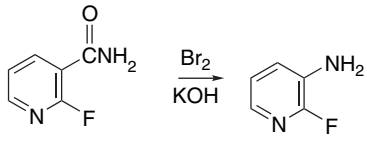


[265] J. Weinstock, *J. Org. Chem.*, **26**, 3511 (1961).
[266] D. Kim and S. M. Weinreb, *J. Org. Chem.*, **43**, 125 (1978).
[267] S. Mangelinckx and N. De Kimpe, *Tetrahedron Lett.*, **44**, 1771 (2003).
[268] C. Hermann, G. C. G. Pais, A Geyer, S. M. Kuhnert, and M. E. Maier, *Tetrahedron*, **56**, 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.

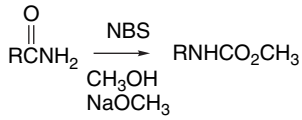


The reaction is useful in the conversion of aromatic carboxylic acids to aromatic amines.

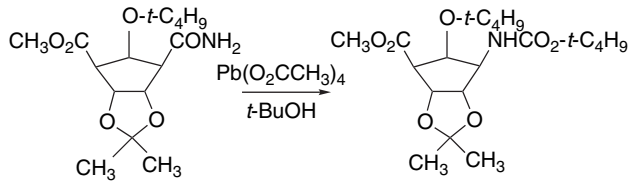


Ref. 270

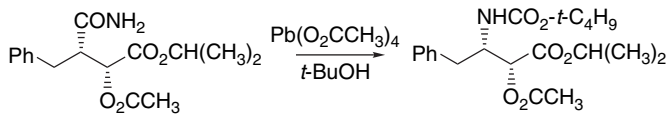
Use of *N*-bromosuccinimide in the presence of sodium methoxide or DBU in methanol traps the isocyanate intermediate as a carbamate.[271]



Direct oxidation of amides can also lead to Hofmann-type rearrangement with formation of amines or carbamates. One reagent that is used is $Pb(O_2CCH_3)_4$.



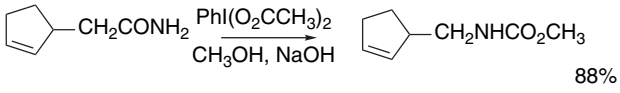
Ref. 272



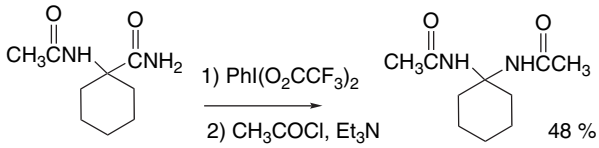
Ref. 273

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).

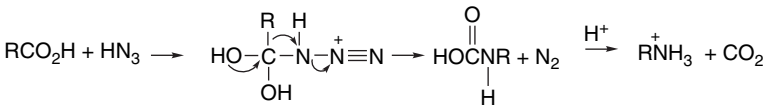
Phenyliodonium diacetate,[274,275] and phenyliodonium *bis*-trifluoroacetate, [276] are also useful oxidants for converting amides to carbamates.



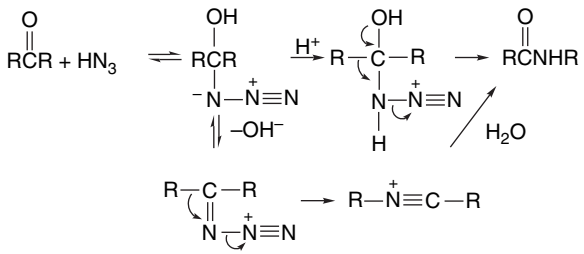
Among the recent applications of the Hofmann reaction has been the preparation of relatively unstable geminal diamides and carbinolamides. For example, 1,1-diacetamidocyclohexane can be prepared in this way.[277]



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.

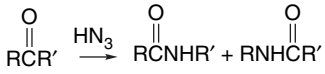
274. R. M. Moriarty, C. J. Chany, II, R. K. Vaid, O. Prakash, and S. M. Tuladar, *J. Org. Chem.*, **58**, 2478 (1993).

275. L.-H. Zhang, G. S. Kaufman, J. A. Pesti, and J. Yin, *J. Org. Chem.*, **62**, 6918 (1997).

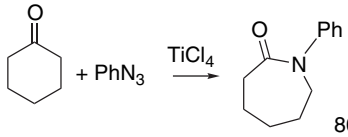
276. G. M. Loudon, A. S. Radhakrishna, M. R. Almond, J. K. Blodgett, and R. H. Boutin, *J. Org. Chem.*, **49**, 4272 (1984).

277. M. C. Davis, D. Stasko, and R. D. Chapman, *Synth. Commun.*, **33**, 2677 (2003).

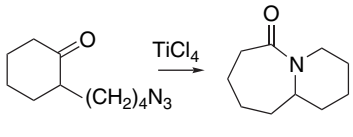
278. H. Wolff, *Org. React.*, **3**, 307 (1946); P. A. S. Smith, in *Molecular Rearrangements*, P. de Mayo ed., Vol. 1, Interscience, New York, 1963, pp. 507–522.



Both inter- and intramolecular variants of the Schmidt reaction in which an alkyl azide effects overall insertion have been observed.

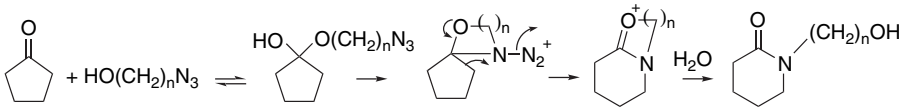


Ref. 279



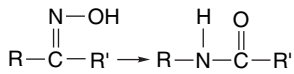
Ref. 280

These reactions are especially favorable for β- and γ-hydroxy azides, where reaction can proceed through a hemiketal intermediate.

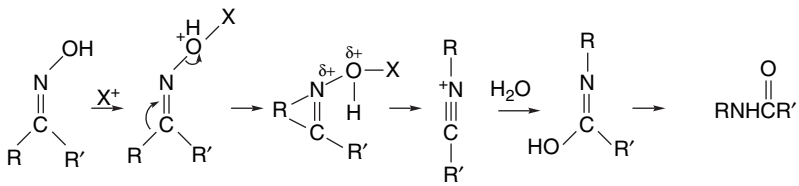


Ref. 281

Another important reaction involving migration to electron-deficient nitrogen is the *Beckmann rearrangement*, in which oximes are converted to amides.[282]



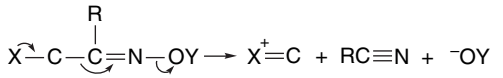
A variety of protic acids, Lewis acids, acid anhydrides, or acyl and sulfonyl halides can cause the reaction to occur. The mechanism involves conversion of the oxime hydroxy group to a leaving group. Ionization and migration then occur as a concerted process, with the group that is *anti* to the oxime leaving group migrating. The migration results in formation of a nitrilium ion, which captures a nucleophile. Eventually hydrolysis leads to the amide.



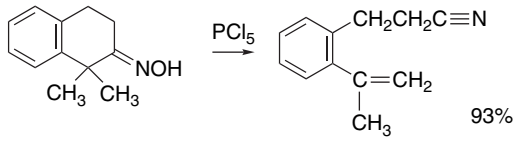
279. J. Aube and G. L. Milligan, *J. Org. Chem.*, **57**, 1635 (1992).
280. J. Aube and G. L. Milligan, *J. Am. Chem. Soc.*, **113**, 8965 (1991).
281. V. Gracias, K. E. Frank, G. L. Milligan, and J. Aube, *Tetrahedron*, **53**, 16241 (1997).
282. L. G. Donaruma and W. Z. Heldt, *Org. React.*, **11**, 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.

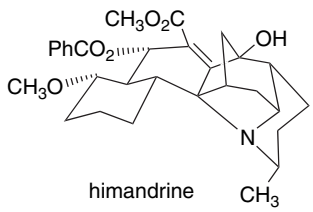


Ref. 284

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.



himandrine

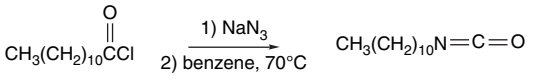
283. R. F. Brown, N. M. van Gulick, and G. H. Schmid, *J. Am. Chem. Soc.*, **77**, 1094 (1955); J. C. Craig and A. R. Naik, *J. Am. Chem. Soc.*, **84**, 3410 (1962).

284. R. T. Conley and R. J. Lange, *J. Org. Chem.*, **28**, 210 (1963).

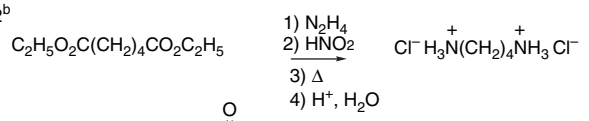
Scheme 10.15. Rearrangement to Electron-Deficient Nitrogen

A. Curtius Rearrangements

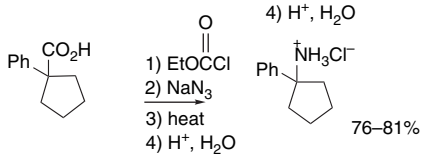
1[a]



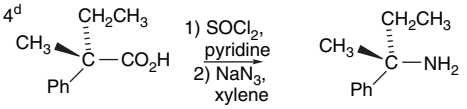
2[b]



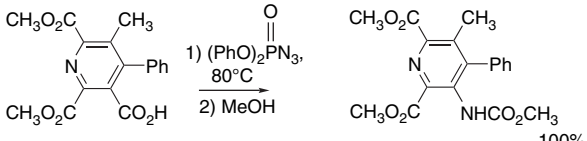
3[c]



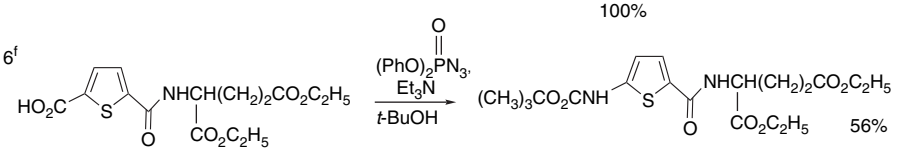
4[d]



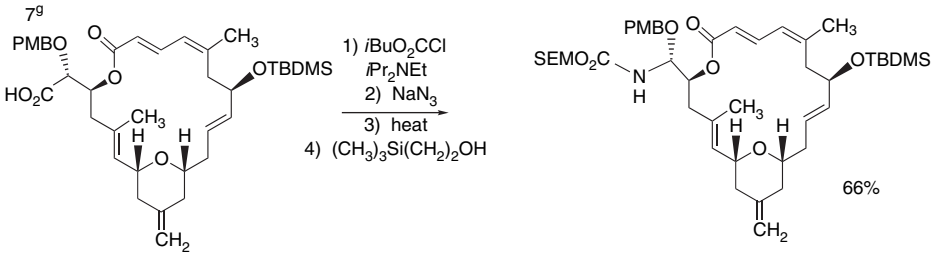
5[e]



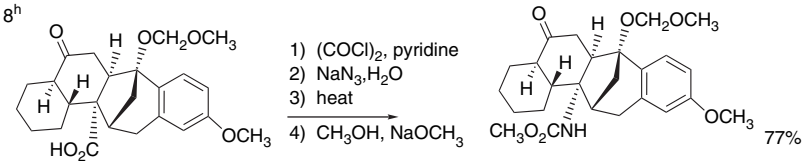
6[f]



7[g]

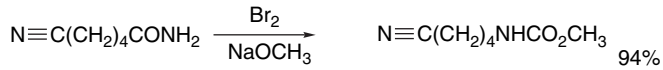


8[h]

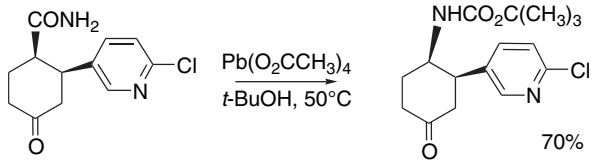


B. Hofmann Rearrangements.

9[i]



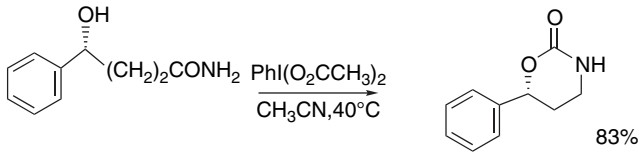
10[j]



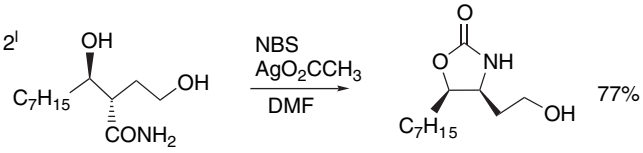
(*Continued*)

Scheme 10.15. (*Continued*)

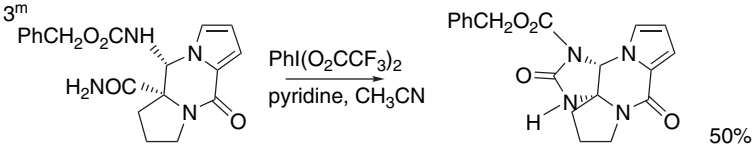
11[k]



12[l]

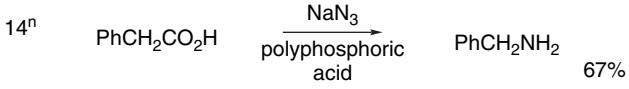


13[m]

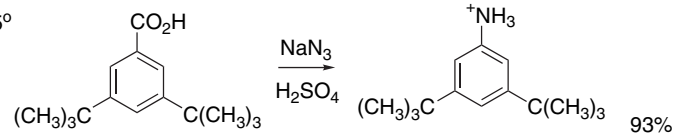


C. Schmidt reactions

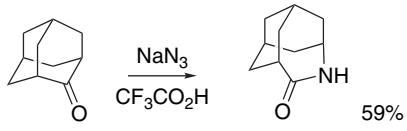
14[n]



15[o]

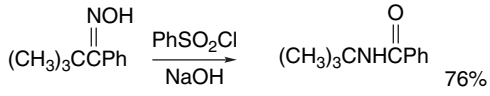


16[p]

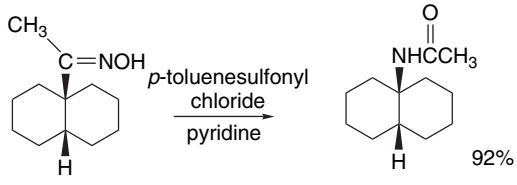


D. Beckmann Rearrangements

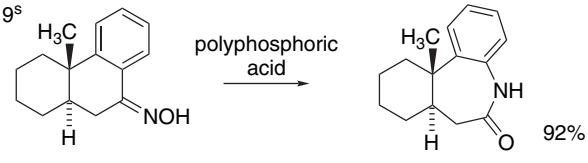
17[q]



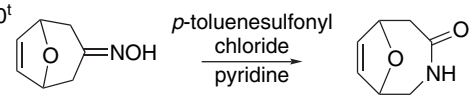
18[r]



19[s]



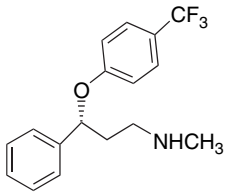
20[t]



(*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 $Pb(OAc)_4$ conditions (see p. 949), was utilized in an enantiospecific synthesis of the naturally occurring analagesic (–)-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.

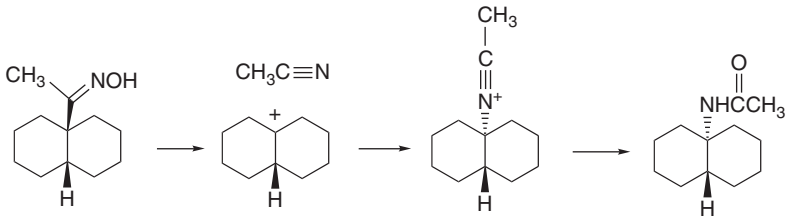


(*R*)-Fluoxetine

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.

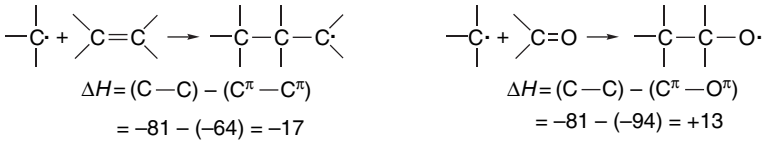
Section D shows some representative Beckmann rearrangements. Entry 17 shows a selective migration of a *t*-butyl group and illustrates the use of oxime sulfonates to control regioselectivity. The opposite regioisomer, resulting from migration of the phenyl group, was observed using HCl in acetic acid. 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.



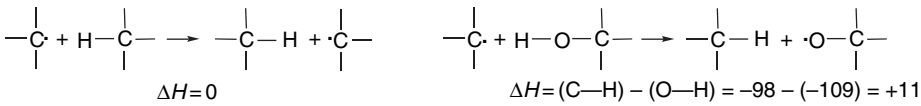
Entries 19 and 20 are examples of lactam formation by ring expansion of cyclic oximes.

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.



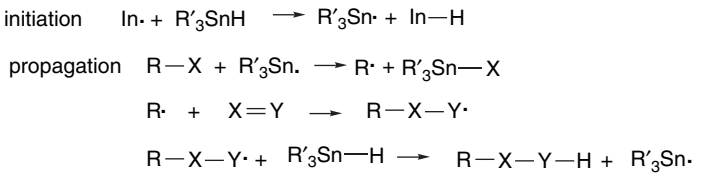
The reaction endothermicity establishes a *minimum* for the activation energy; whereas abstraction of a hydrogen atom from carbon is a feasible step in a chain process, abstraction of a hydrogen atom from a hydroxy group is unlikely. Homolytic cleavage of an O−H bond is likely only if the resulting oxygen 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.

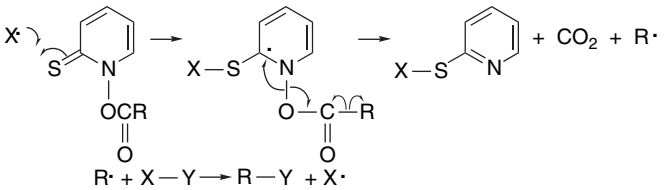
10.3.1. Sources of Radical Intermediates

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 X=Y, and effects addition to the organic radical and a hydrogen atom to the X=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.

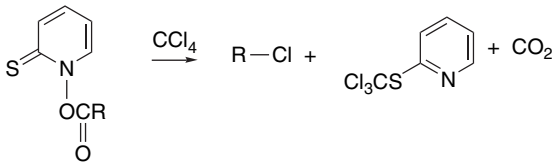


When X−Y is R_3Sn-H the net reaction is decarboxylation and reduction of the original acyloxy group. Halogen atom donors can also participate in such reactions.

[286] D. Crich, *Aldrichimica Acta*, **20**, 35 (1987); D. H. R. Barton, *Aldrichimica Acta*, **23**, 3 (1990).

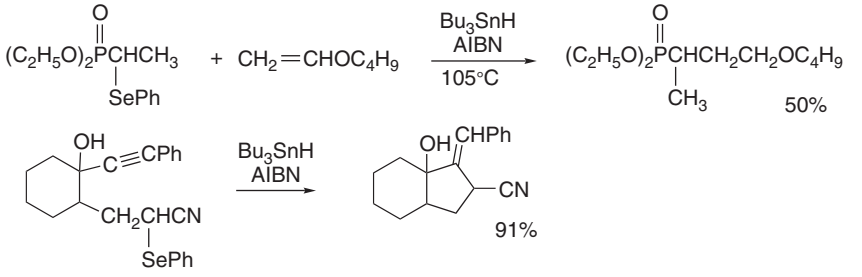
[287] D. H. R. Barton, D. Crich, and W. B. Motherwell, *Tetrahedron*, **41**, 3901 (1985); D. H. R. Barton, D. Crich, and G. Kretzschmar, *J. Chem. Soc., Perkin Trans. 1*, 39 (1986); D. H. R. Barton, D. Bridson, I. Fernandez-Picot, and S. Z. Zard, *Tetrahedron*, **43**, 2733 (1987).

When X−Y is Cl_3C-Cl, the final product is a chloride.[288] Use of Cl_3C-Br gives the corresponding bromide.[289]

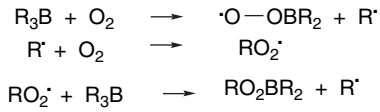


The precise reaction conditions for optimal yields depend upon the specific reagents and both thermal[290] and photochemical[291] conditions have been developed. Phenyl thionocarbonates are easily prepared and are useful in radical generating reactions.[292] A variety of other thiono esters, including 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-selenylphosphonates[295] 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.

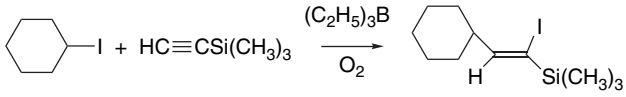


Trialkylboranes, especially triethylborane, are used in conjunction with O_2 to generate radicals.[297] The alkyl radicals are generated by breakdown of a borane-oxygen adduct. An advantage this method has over many other radical initiation systems is that it proceeds at low temperature, e.g., −78°C.



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. Bouivin, 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. 1*, 1574 (1975).
294. J. Pfenninger, C. Heuberger, and W. Graf, *Helv. Chim. Acta*, **63**, 2328 (1980); D. L. Boger and R. J. Mathvink, *J. Org. Chem.*, **53**, 3377 (1988); D. L. Boger and R. J. Mathvink, *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).

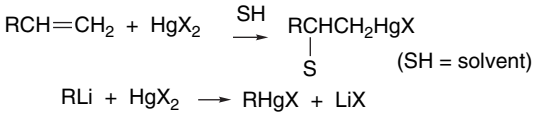
The radicals generated in this way can initiate a variety of chain processes. Alkyl radicals can be generated from alkyl iodides.[298] For example, addition of alkyl radicals to alkynes can be accomplished under these conditions.



Ref. 299

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.

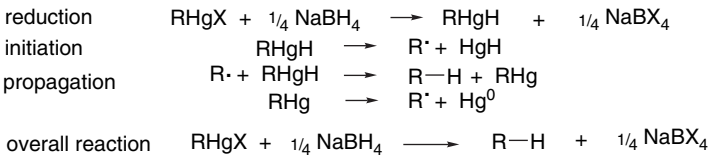
The reductive decomposition of alkylmercury compounds is also a useful source of radicals.[300] The organomercury compounds are available by oxymercuration (see Section 4.1.3) or from organometallic compounds as a result of metal-metal exchange (see Section 7.3.3).



Alkylmercury reagents can also be prepared from alkyl boranes.

Ref. 301

The mercuric hydride formed by reduction undergoes chain decomposition to generate alkyl radicals.



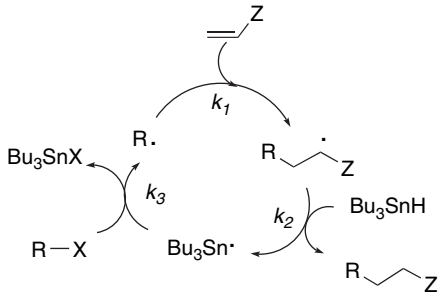
10.3.2. Addition Reactions of Radicals with Substituted Alkenes

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 R· with Bu_3SnH, and (b) between the H abstraction step k_2 and addition to another molecule of the alkene. If

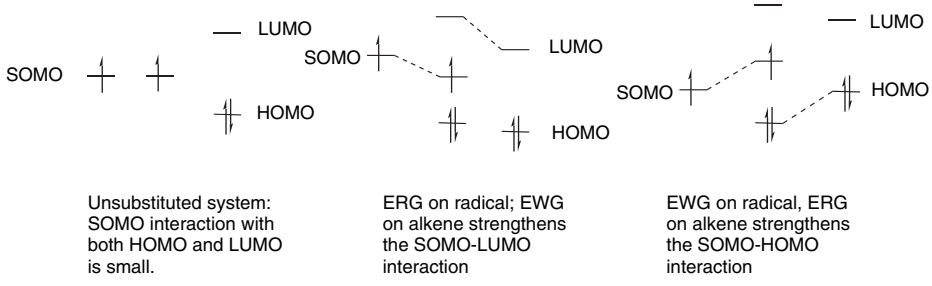
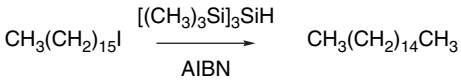


Fig. 10.12. Frontier orbital interpretation of radical substituent effects.

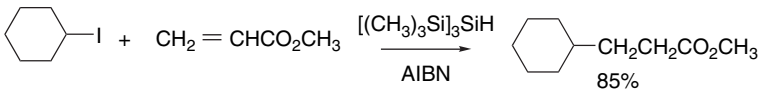
[302] B. Giese, *Angew. Chem. Int. Ed. Engl.*, **22**, 753 (1983); B. Giese, *Angew. Chem. Int. Ed. Engl.*, **24**, 553 (1985).

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 $RCH_2C{\cdot}HZ$ and $RCH_2C{\cdot}HZ$ 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.

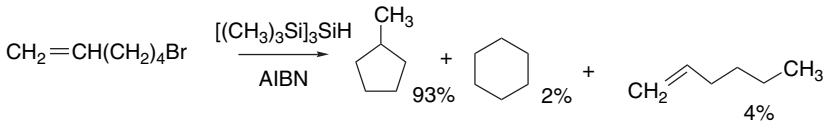
Although most radical reactions involving chain propagation by hydrogen atom transfer can be done using trialkylstannanes, several silanes have been investigated as alternatives.[304] *Tris*-(trimethylsilyl)silane reacts with alkyl radicals at about one-tenth the rate of tri-*n*-butylstannane. The *tris*-(trimethylsilyl)silyl 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. 305



Ref. 306

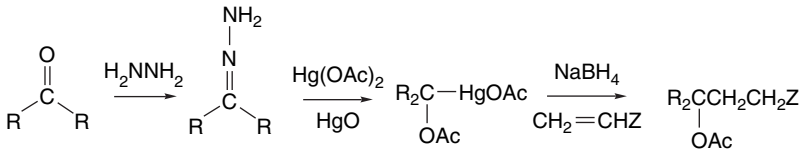


Ref. 306

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).

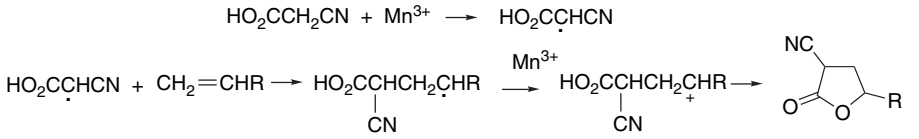
applied to β-hydroxy-,[307] β-alkoxy-,[308] and β-amido-[309] alkylmercury derivatives. α-Acetoxyalkylmercury compounds can be prepared from hydrazones by mercuric oxide and mercuric acetate.



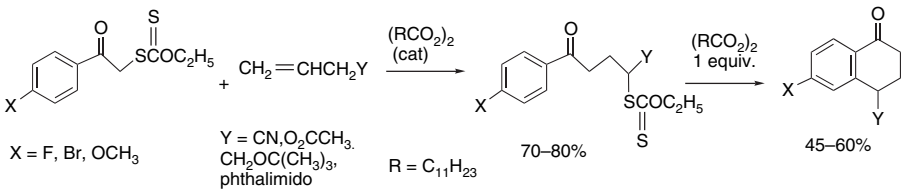
Ref. 310

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.

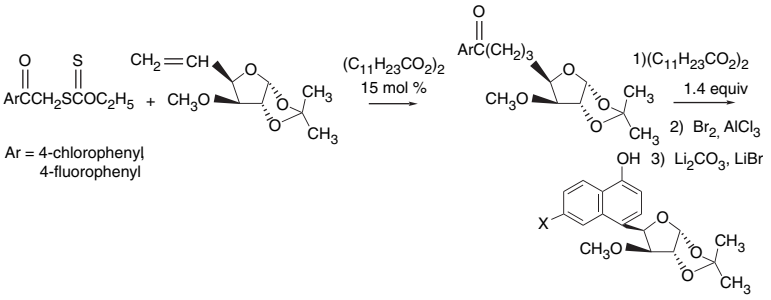


Phenacyl radicals can be generated from the corresponding xanthates and add in good yield to various substituted propenes. The products of the reaction can then be cyclized to tetralones using an equivalent of a peroxide.[313]



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.

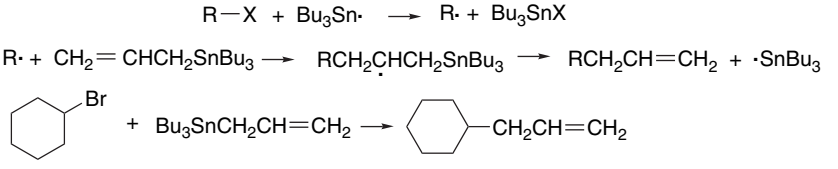


Ref. 314

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 trialkylstannyl radical.[315] The radical source must have some functional group that can be abstracted by trialkylstannyl radicals. In addition to halides, both thiono esters[316] and selenides[317] are reactive.

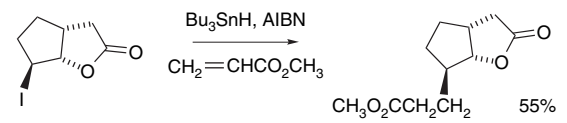


314. A. Cordero-Vargus, B. Quiclet-Sire, and S. Z. Zard, *Tetrahedron Lett.*, **45**, 7335 (2004).
315. G. E. Keck and J. B. Yates, *J. Am. Chem. Soc.*, **104**, 5829 (1982).
316. G. E. Keck, D. F. Kachensky, and E. J. Enholm, *J. Org. Chem.*, **49**, 1462 (1984).
317. R. R. Webb and S. Danishefsky, *Tetrahedron Lett.*, **24**, 1357 (1983); T. Toru, T. Okumura, and Y. Ueno, *J. Org. Chem.*, **55**, 1277 (1990).

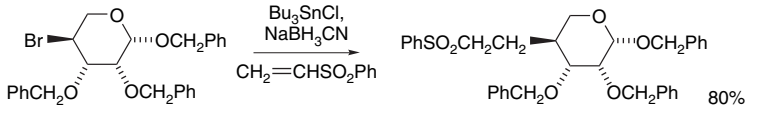
Scheme 10.16. Addition of Alkyl Radicals to Alkenes

A. With radical generation using trisubstituted stannanes

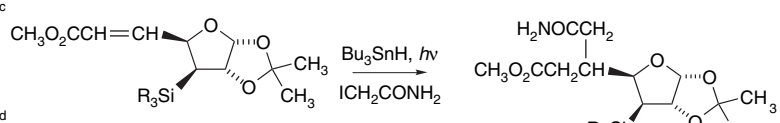
1[a]



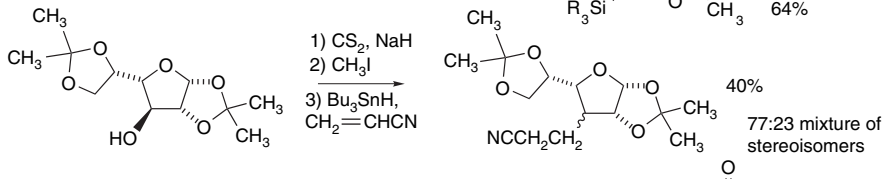
2[b]



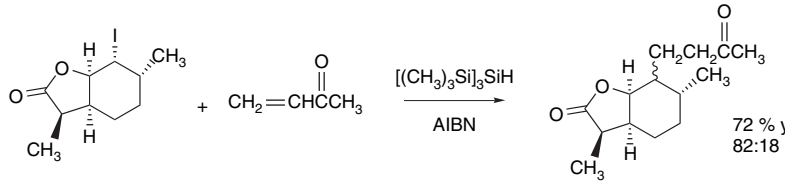
3[c]



4[d]

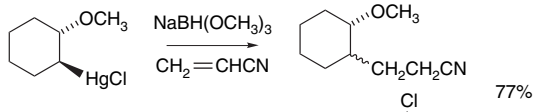


5[e]

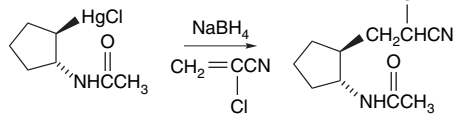


B. Using other methods of radical generation

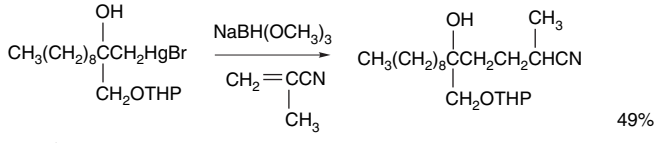
6[f]



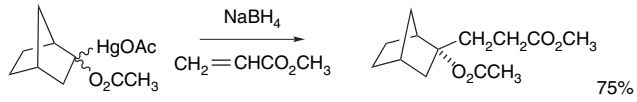
7[g]



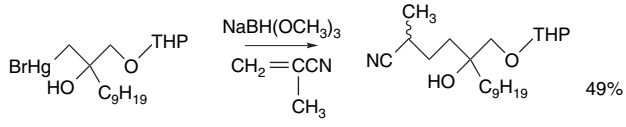
8[h]



9[g]

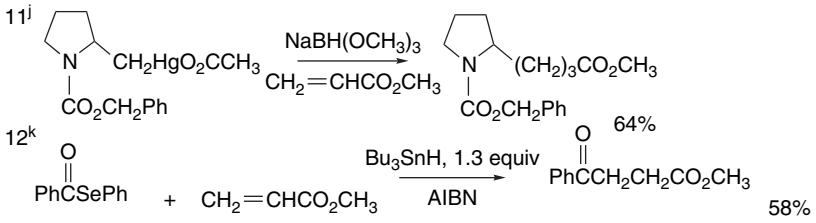


10[i]



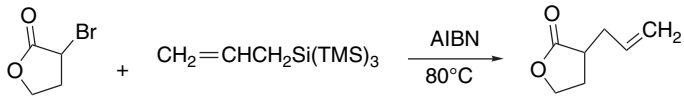
(*Continued*)

Scheme 10.16. (*Continued*)

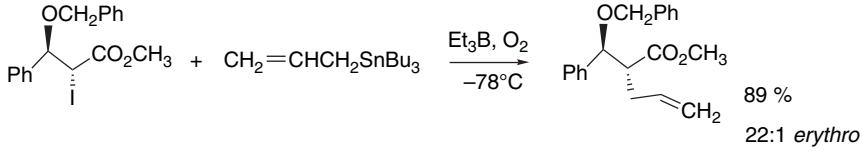


a. S. D. Burke, W. B. Fobare, and D. M. Arminsteadt, *J. Org. Chem.*, **47**, 3348 (1982).
b. M. V. Rao and M. Nagarajan, *J. Org. Chem.*, **53**, 1432 (1988).
c. G. Sacripante, C. Tan, and G. Just, *Tetrahedron Lett.*, **26**, 5643 (1985).
d. B. Giese, J. A. Gonzalez-Gomez, and T. Witzel, *Angew. Chem. 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]



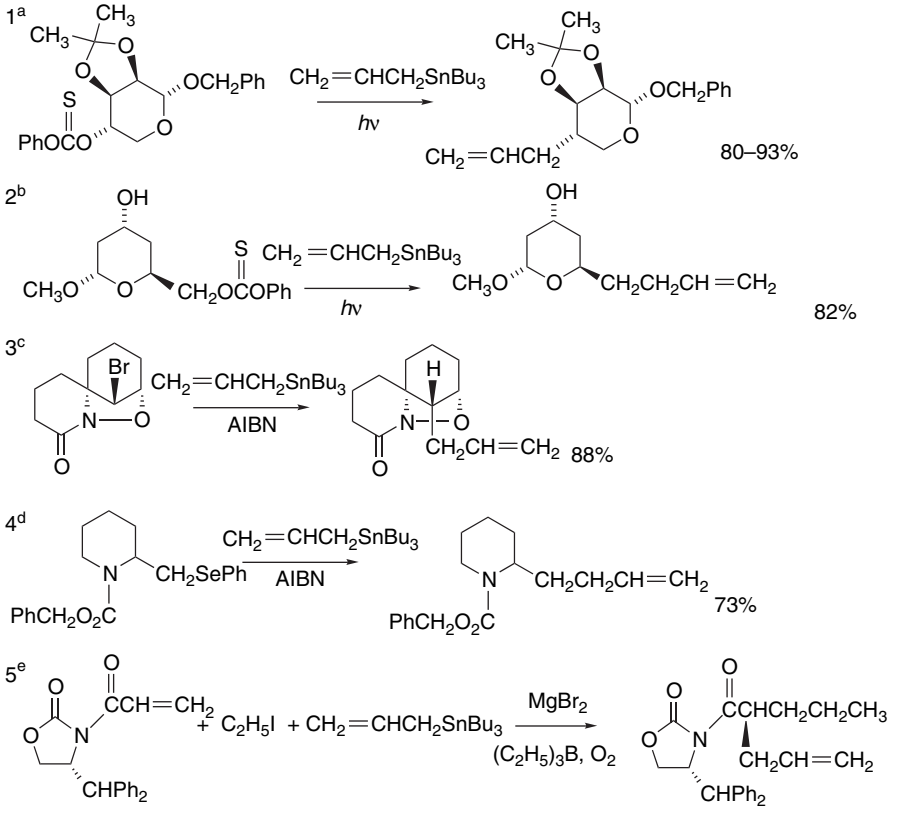
Allylation reactions can be initiated by triethylboron. This procedure has been found to give improved stereoselectivity in acyclic allylations.[319]



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.

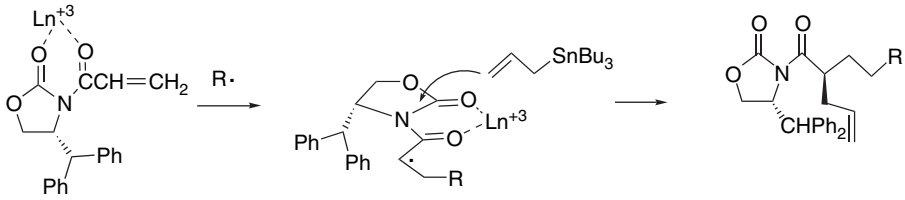
318. C. Chatgilialoglu, C. Ferreri, M. Ballestri, and D. P. Curran, *Tetrahedron Lett.*, **37**, 6387 (1996).
319. Y. Guindon, J. F. Lavallee, L. Boisvert, C. Chabot, D. Delorme, C. Yoakim, D. Hall, R. Lemieux, and B. Simoneau, *Tetrahedron Lett.*, **32**, 27 (1991).

Scheme 10.17. Allylation of Radical Centers



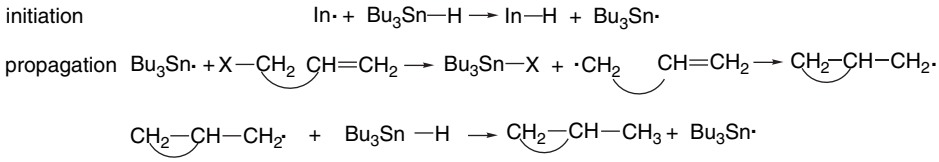
a. G. E. Keck, D. F. Kachensky, and E. J. Enholm, *J. Org. Chem.*, **50**, 4317 (1985).
b. G. E. Keck and D. F. Kachensky, *J. Org. Chem.*, **51**, 2487 (1986).
c. G. E. Keck and J. B. Yates, *J. Org. Chem.*, **47**, 3590 (1982).
d. R. R. Webb, II, and S. Danishefsky, *Tetrahedron Lett.*, **24**, 1357 (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.



10.3.3. Cyclization of Free Radical Intermediates

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°.

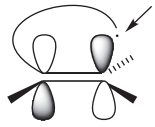


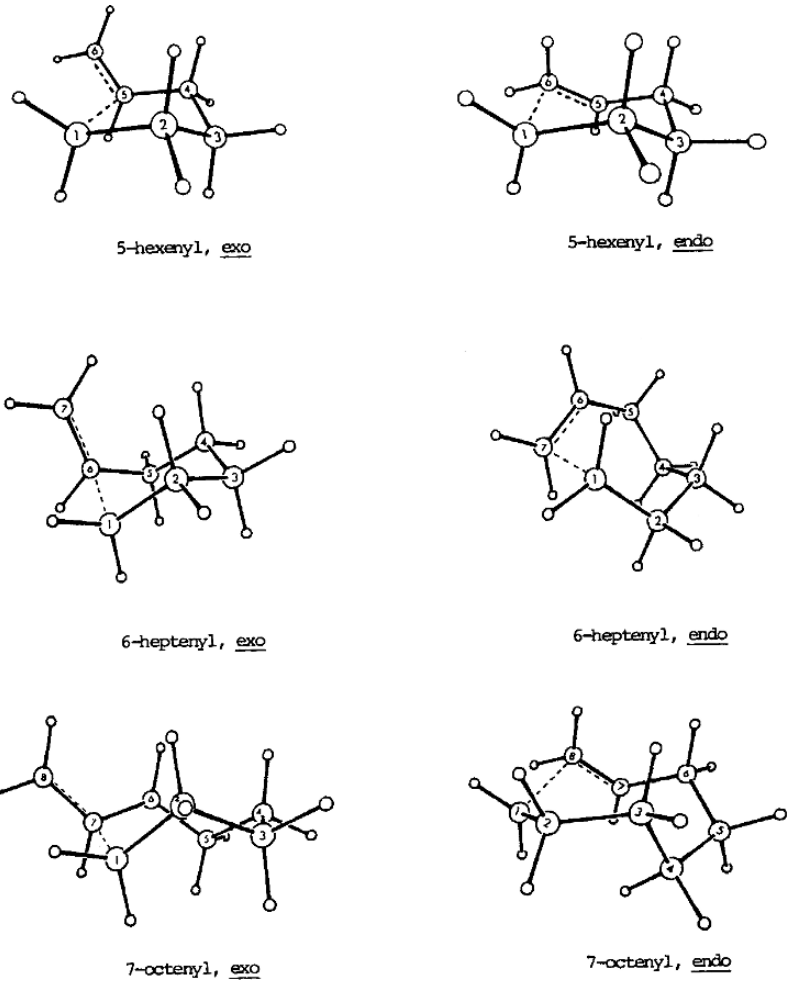
Figure 10.13 shows the preferred geometries and calculated energy differences based on MM2 modeling.

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).

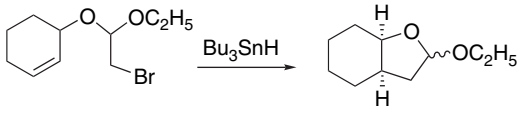


Calculated Energy (kcal/mol) of Transition Structures

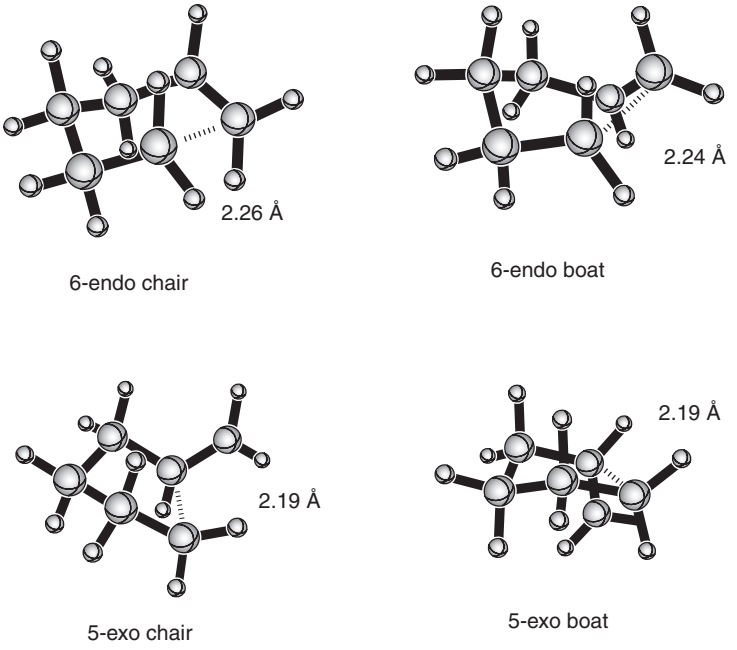
Ring closure	*exo*	*endo*
5/6	7.5	10.3
6/7	9.1	10.8
7/8	15.0	13.0

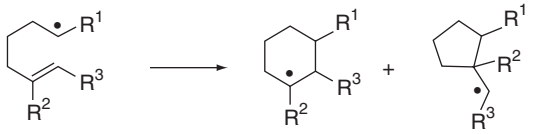
Fig. 10.13. MM2 models of *exo* and *endo* cyclization transition structures for 5-hexenyl, 6-heptenyl, and 7-octenyl radicals. Reproduced from *Tetrahedron*, **41**, 3925 (1985), by permission of Elsevier.

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).



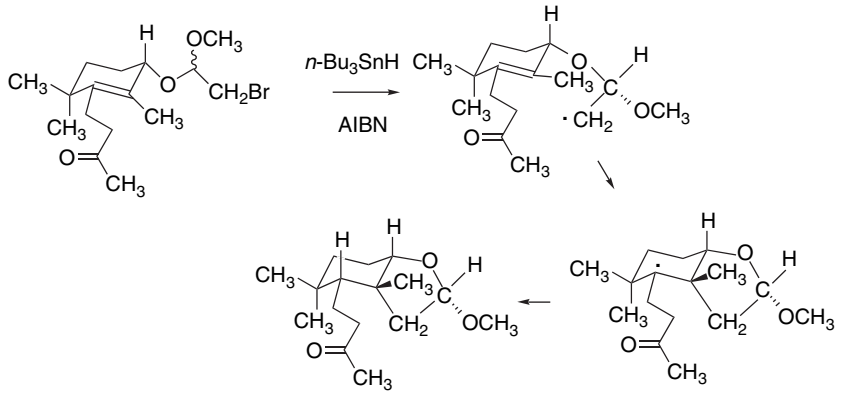


	6-endo pathway		5-exo pathway	
reactant	chair TS	boat TS	chair TS	boat TS
R^1=H, R^2=H, R^3=H,	9.1	11.6	6.4	8.1
R^1=Me, R^2=H, R^3=H,	9.6	12.2	7.0	8.7
R^1=H, R^2=Me, R^3=H,	8.4	10.7	9.1	10.3
R^1=H, R^2=H, R^3=Me,	9.8	12.5	6.5	8.1

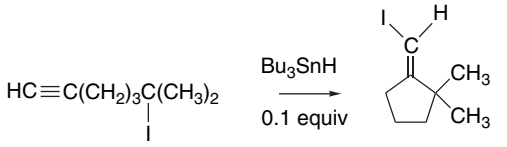
Fig. 10.14. Relative energies of 5-*exo* and 6-*endo* transition structures. Insert shows the effect of methyl substituents. Reproduced from *J. Am. Chem. Soc.*, **125**, 4271 (2003), by permission of the American Chemical Society.

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).

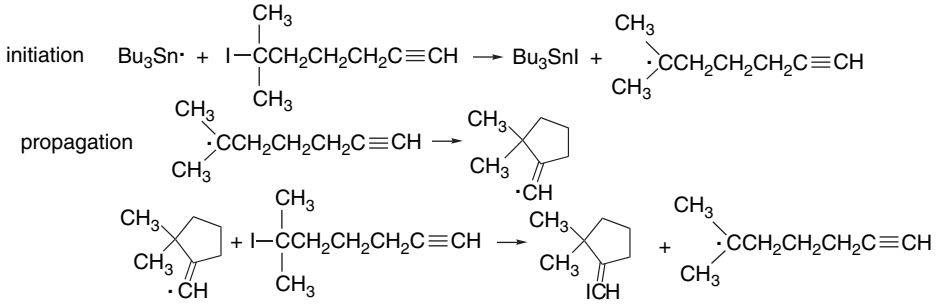


Reaction conditions have been developed in which the cyclized radical can react in some manner other than hydrogen atom abstraction. One such reaction is an iodine atom transfer. The cyclization of 2-iodo-2-methyl-6-heptyne is a structurally simple example.



Ref. 326

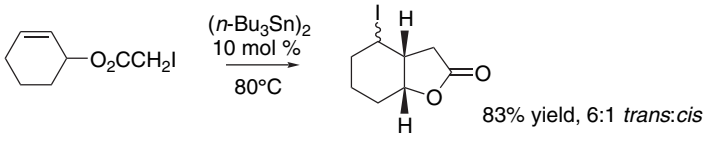
In this reaction, the trialkylstannane serves to initiate the chain sequence but it is present in low concentration to minimize the rate of hydrogen atom abstraction from the stannane. Under these conditions, the chain is propagated by iodine atom abstraction.



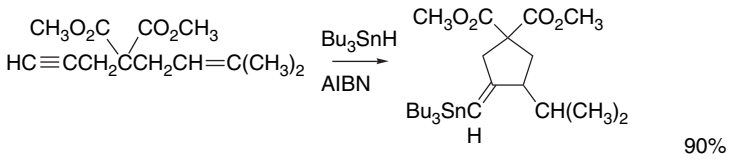
The fact that the cyclization is directed toward an acetylenic group and leads to formation of an alkenyl radical is significant. Formation of a saturated iodide could lead to a more complex product mixture because the cyclized product could undergo iodine atom transfer and proceed to add to a second 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]

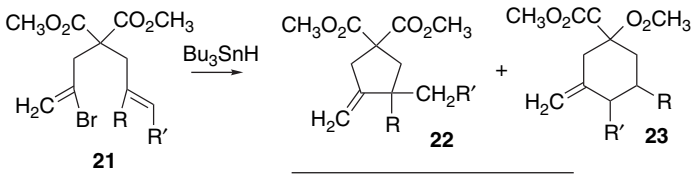


Alkenyl radicals generated by addition of trialkylstannyl radicals to terminal alkynes can undergo cyclization with a nearby double bond.



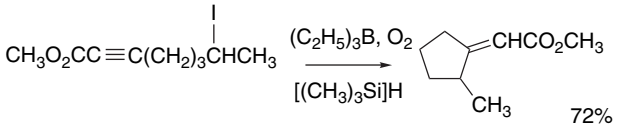
Ref. 328

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.



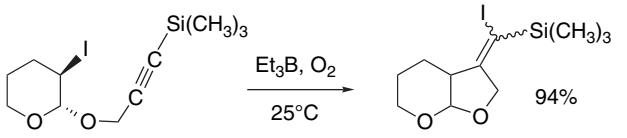
R	R′	Product ratio **22**:**23**
H	H	3:1
CH_3	H	**23** exclusively
H	CH_3	2:1

An alternative system for initiating radical cyclization uses triethylborane and oxygen. Under these conditions, *tris*-(trimethylsilyl)silane is an effective hydrogen donor.[330]



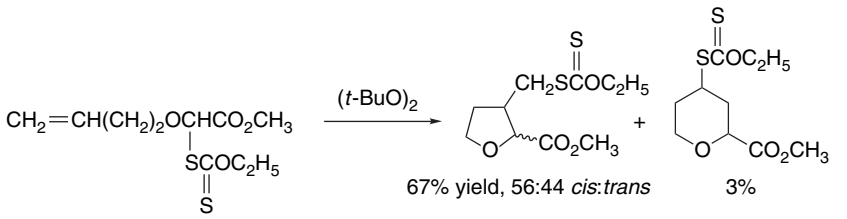
327. D. P. Curran and J. Tamine, *J. Org. Chem.*, **56**, 2746 (1991).
328. G. Stork and R. Mook, Jr., *J. Am. Chem. Soc.*, **109**, 2829 (1987).
329. G. Stork and N. H. Baine, *J. Am. Chem. Soc.*, **104**, 2321 (1982).
330. (a) T. B. Lowinger and L. Weiler, *J. Org. Chem.*, **57**, 6099 (1992); (b) 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.



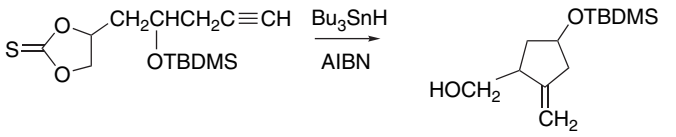
Ref. 332

Intramolecular additions have also been accomplished using xanthate and thionocarbonates.



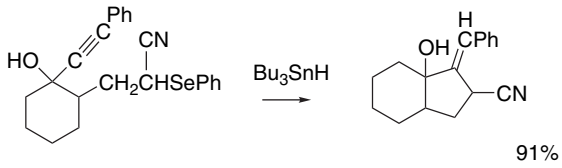
Ref. 333

When a hydrogen donor is present, the product results from reduction.

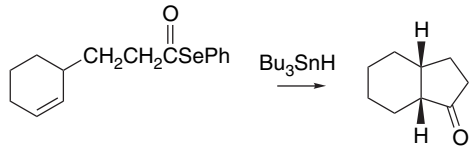


Ref. 334

Cyclization of both alkyl and acyl radicals generated by selenide abstraction have also been observed.



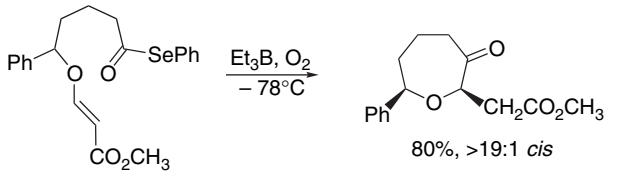
Ref. 335



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. Giesselink, 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).

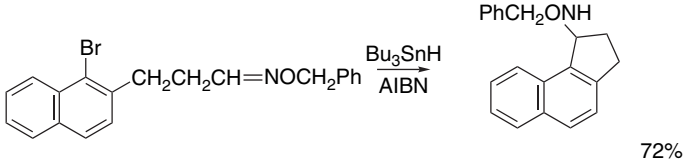
Triethylborane can also be used for radical initiation and the low temperature can lead to improved yields and stereoselectivity.



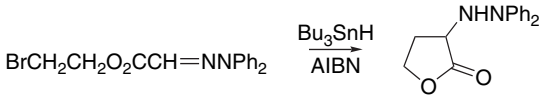
Ref. 330b

10.3.4. Additions to C=N Double Bonds

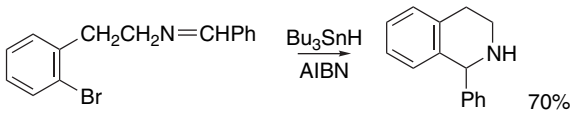
Several functional groups containing carbon-nitrogen double bonds can participate in radical cyclizations. Among these are oxime ethers, imines, and hydrazones.[337] Hydrazones and oximes are somewhat more reactive than imines, evidently because the adjacent substituents can stabilize the radical center at nitrogen.[338] Cyclization at these functional groups leads to amino- substituted products.



Ref. 339



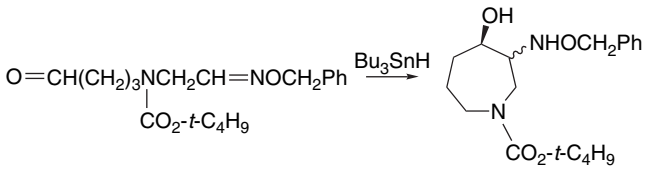
Ref. 340



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.

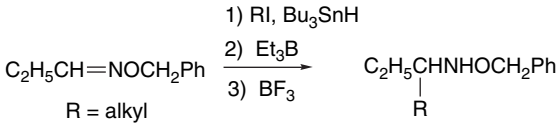
337. G. K. Friestad, *Tetrahedron*, **57**, 5461 (2001).
338. A. G. Fallis and I. M. Brinza, *Tetrahedron*, **53**, 17543 (1997).
339. J. W. Grissom, D. Klingberg, S. Meyenburg, and B. L. Stallman, *J. Org. Chem.*, **59**, 7876 (1994).
340. D. L. J. Clive and J. Zhang, *J. Chem. Soc.,Chem. Commun.*, 549 (1997).
341. M. J. Tomaszewski and J. Warkentin, *Tetrahedron Lett.*, **33**, 2123 (1992).



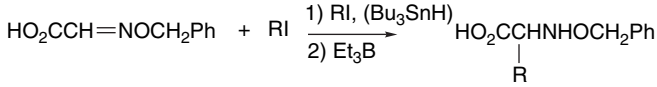
50% 1:2.6 *cis.trans*

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*-benzyloxyamino acids. These reactions have been done in both organic solvents[344] and aqueous mixtures.[345] The reactions can be done with or without Bu_3SnH as a chain carrier.



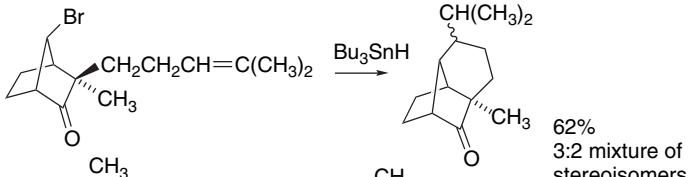
Scheme 10.18 gives some additional examples of cyclization reactions involving radical intermediates. Section A pertains to reactions of alkyl halides. Entry 1 is an early example of the application of a radical cyclization and was used in the synthesis of the terpenes sativene and copacamphene. Entry 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 cylization 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).

Scheme 10.18. Radical Cyclizations

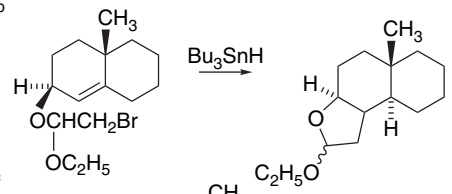
A. Cyclizations of halides terminated by hydrogen atom abstraction or halogen atom transfer

1[a]

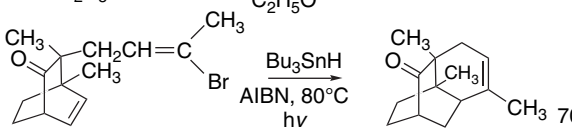


62%
3:2 mixture of stereoisomers

2[b]

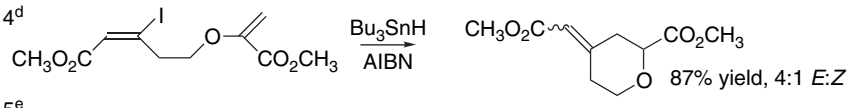


3[c]



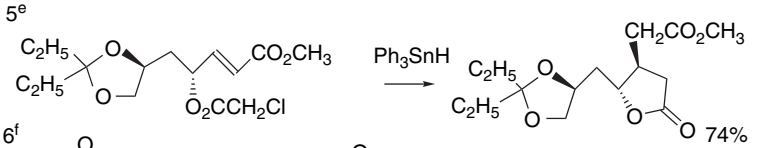
70%

4[d]



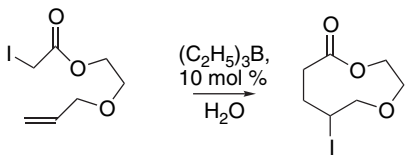
87% yield, 4:1 *E*:*Z*

5[e]



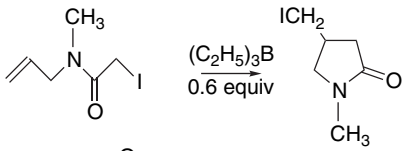
74%

6[f]



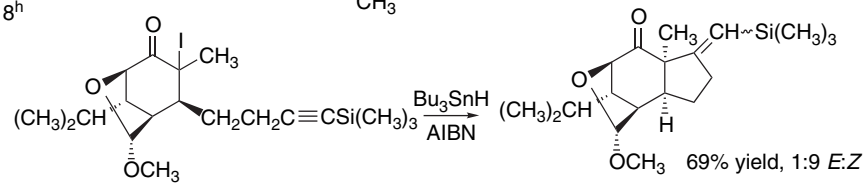
69%

7[g]



71%

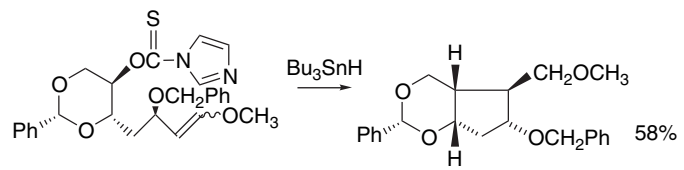
8[h]



69% yield, 1:9 *E*:*Z*

B. Cyclization of thiono esters, sulfides, and selenides

9[i]

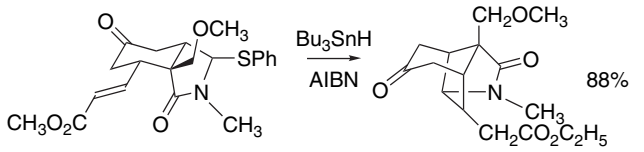


58%

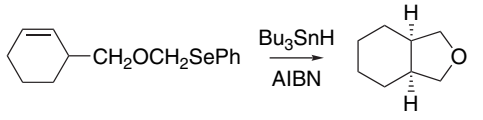
(*Continued*)

Scheme 10.18. (*Continued*)

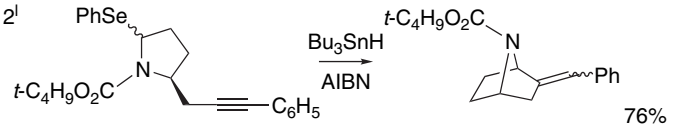
10[j]



11[k]

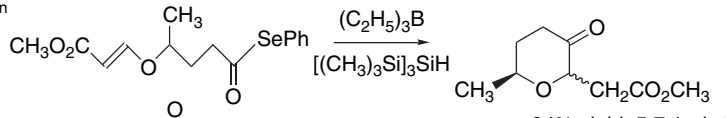


12[l]

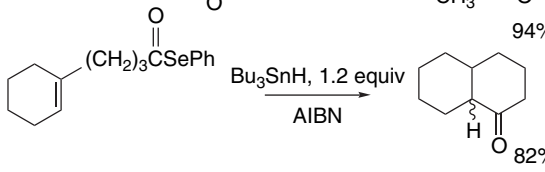


13[m]

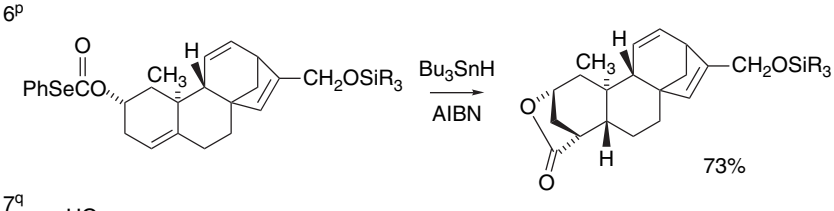
14[n]



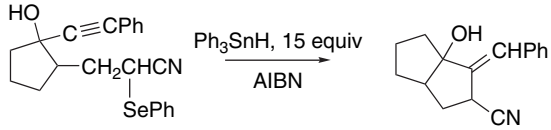
15[o]



16[p]

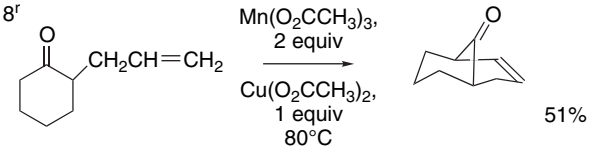


17[q]



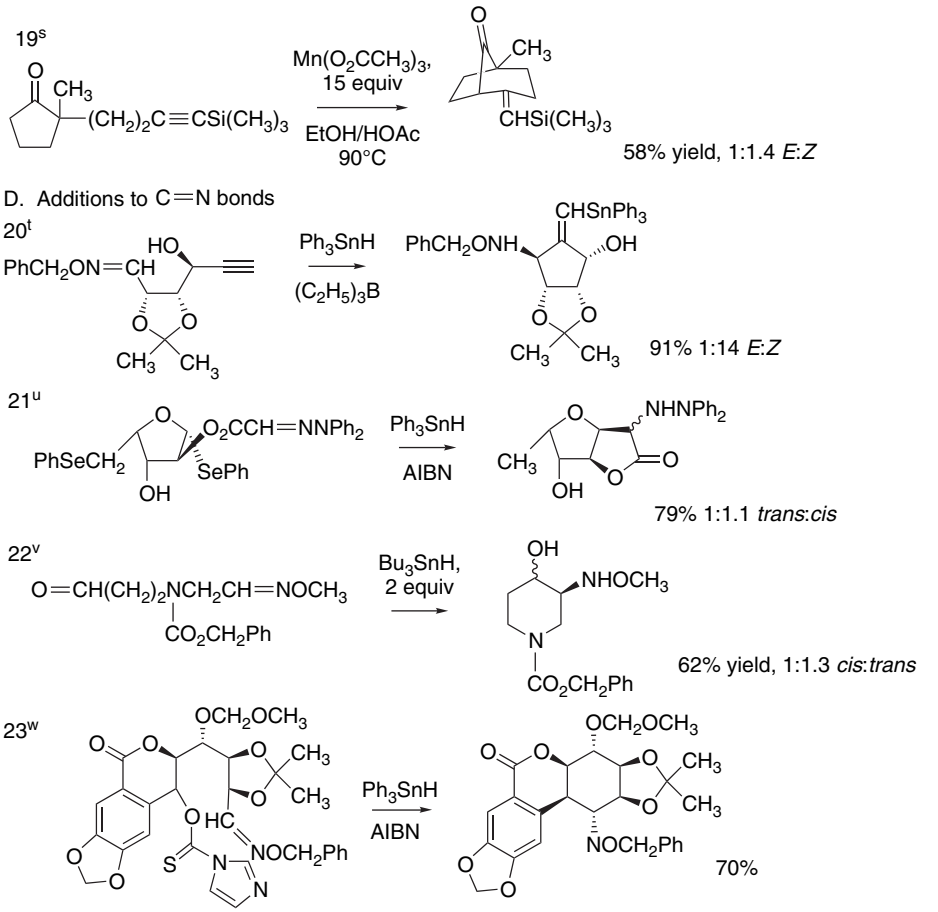
C. Oxidative cyclization with $Mn(O_2CCH_3)_3$

18[r]



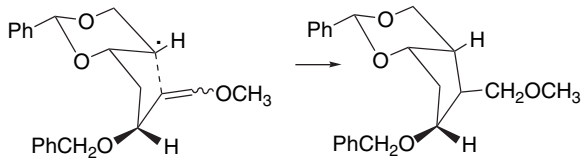
(*continued*)

Scheme 10.18. (***Continued***)

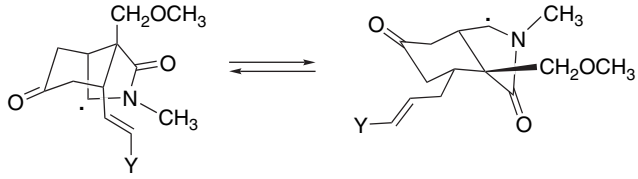


a. P. Bakuzis, O. O. S. Campos, and M. L. F. Bakuzis, *J. Org. Chem.*, **41**, 3261 (1976).
b. G. Stork and M. Kahn, *J. Am. Chem. Soc.*, **107**, 500 (1985).
c. G. Stork and N. H. Baine, *Tetrahedron Lett.*, **26**, 5927 (1985).
d. R. J. Maguire, S. P. Munt, and E. J. Thomas, *J. Chem. Soc., Perkin 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.



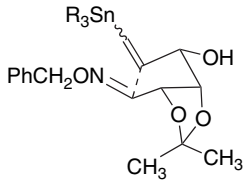
Entry 10 shows the occurrence of 5-*exo* cyclization. The radical in this case is generated from an amino sulfide. This reaction requires a specific, somewhat disfavored conformation of the reactant in order for cyclization to occur. When the unsubstituted vinyl substituent was used, no cyclization occurred. However, increasing the reactivity of the double bond by adding the ester substituent led to successful cyclization.



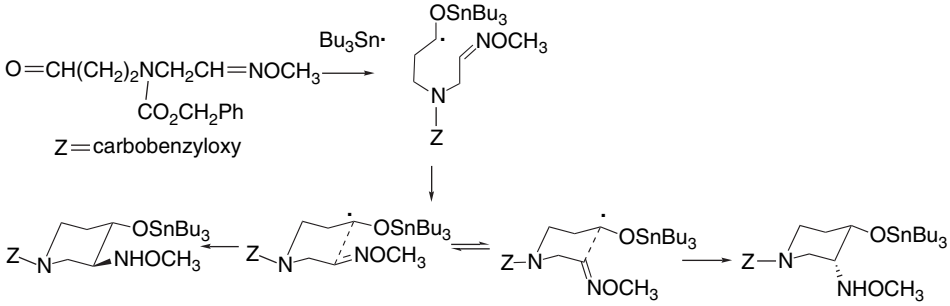
Entry 11 involves generation and cyclization of an alkoxymethyl radical from a selenide. The cyclization mode is the anticipated 5-*exo* with a *cis* ring juncture. This is a case in which the electronic characteristics of the radical are not particularly favorable (ERG oxygen in the radical), but cyclization 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 tetrahydropyranyloxy 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.



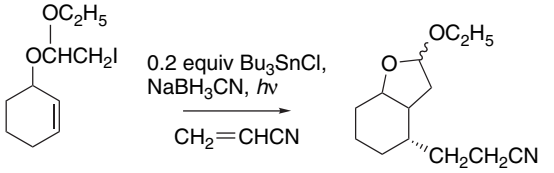
Entry 21 involves addition to a glyoxylic hydrazone and the *cis* ring junction is dictated by strain effects. The primary phenylselenyl group is reductively removed under the reaction conditions. Entry 22 involves generation of a stannyloxy radical by addition of the stannyl radical at the carbonyl *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.

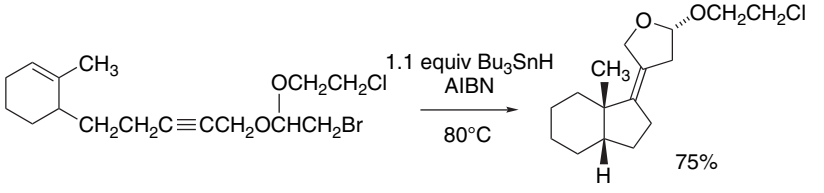
10.3.5. Tandem Radical Cyclizations and Alkylations

The synthetic scope of radical cyclizations can be further extended by tandem trapping by an electrophilic alkene.



Ref.346

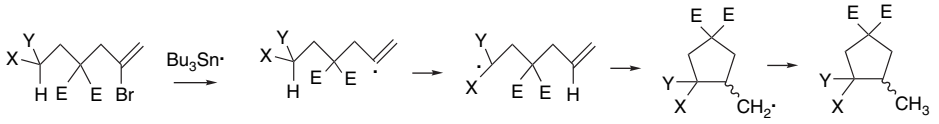
Alkenyl radicals generated by intramolecular addition to a triple bond can add to a nearby double bond, resulting in a tandem cyclization process.



Ref. 347

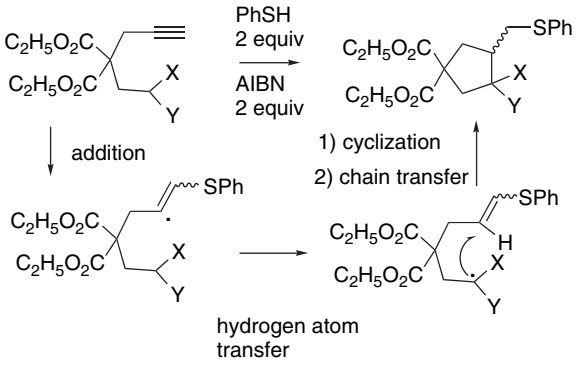
346. G. Stork and P. M. Sher, *J. Am. Chem. Soc*., **108**, 303 (1986).
347. G. Stork and R. Mook, Jr., *J. Am. Chem. Soc*., **105**, 3720 (1983).

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]

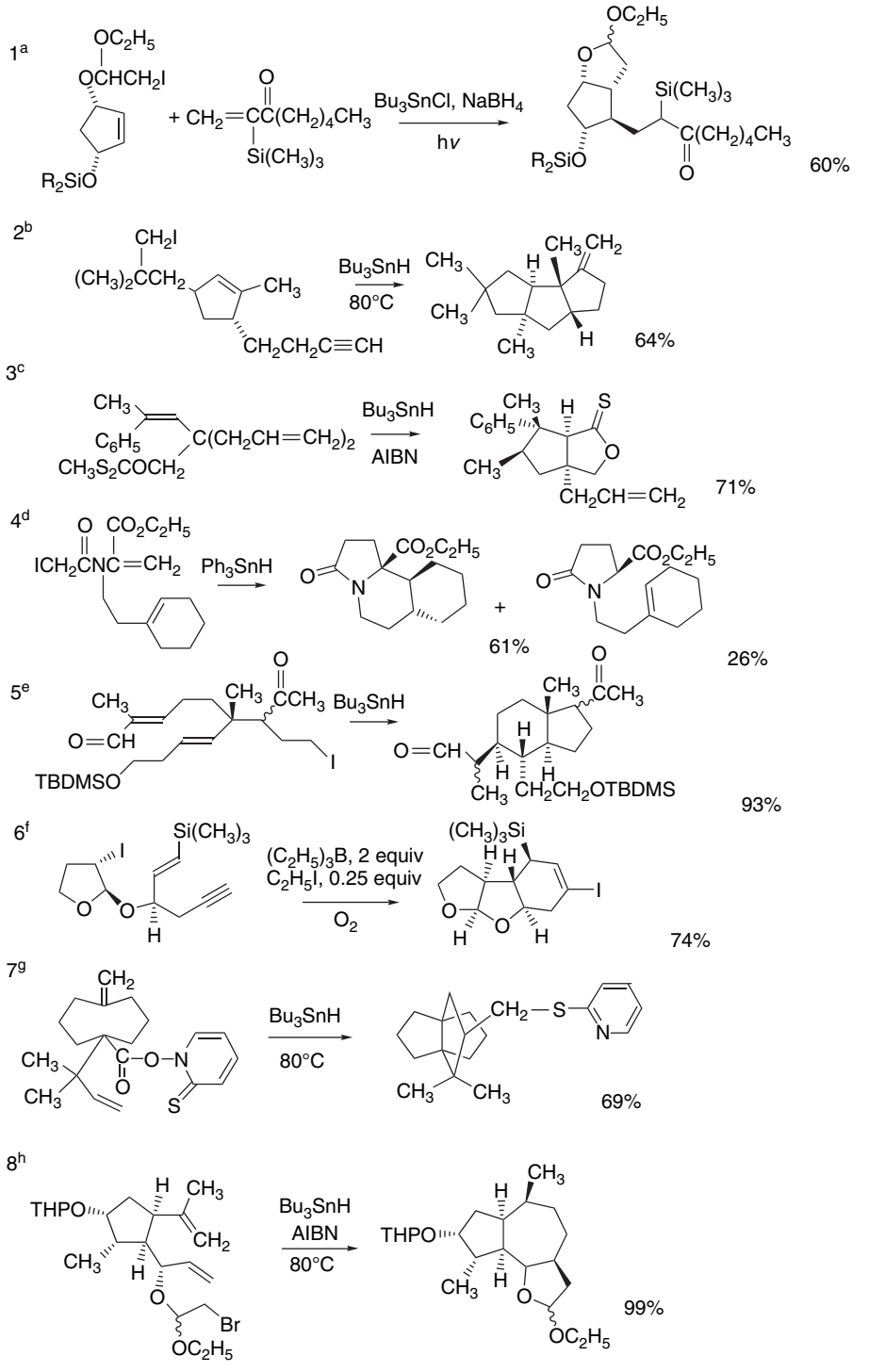


X	Y	% yield
Ph	H	85
CN	H	70
$CO_2C_2H_5$	H	57
TBDMSO	H	89
—O(CH$_2$)$_2$O—		90
CH_3	CH_3	83

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

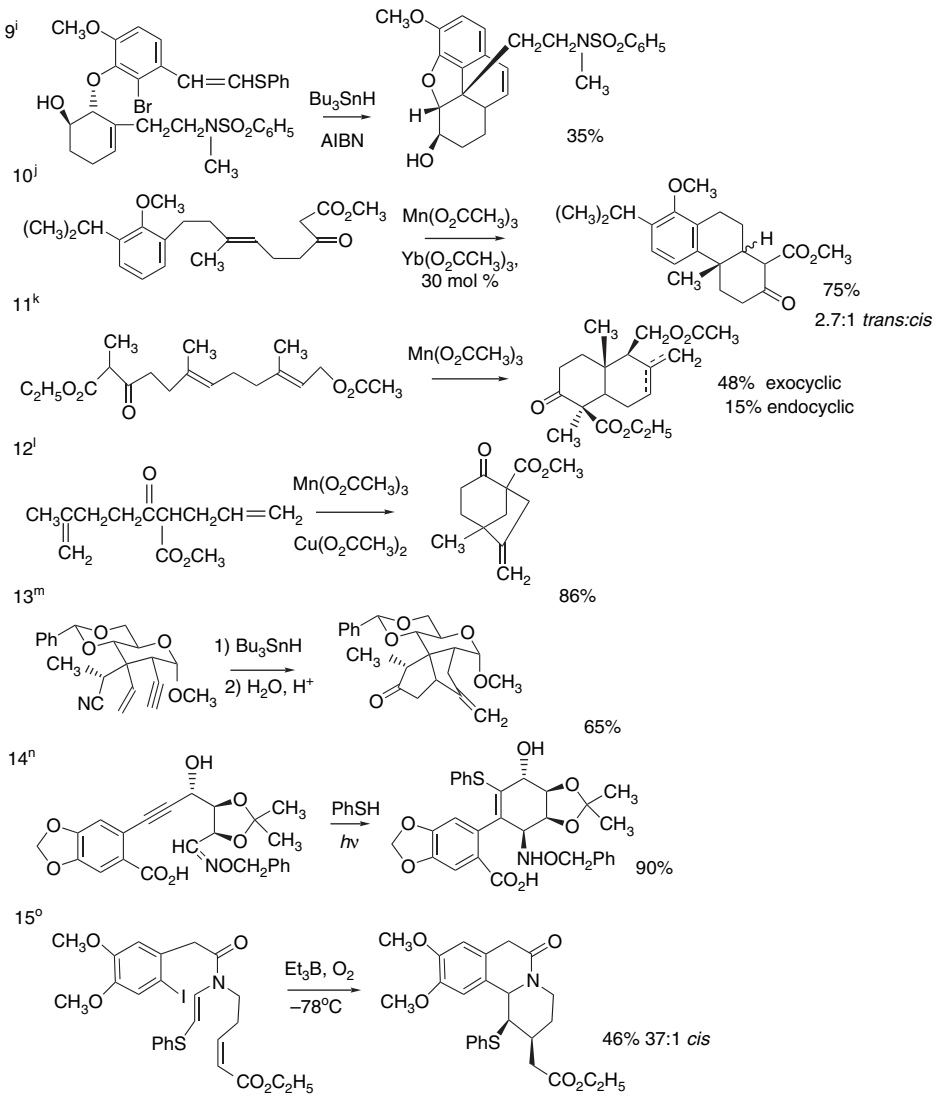
348. D. P. Curran, D. Kim, H. T. Liu, and W. Shen, *J. Am. Chem. Soc.*, **110**, 5900 (1988).
349. F. Beaufils, F. Denes, and P. Renaud, *Org. Lett.*, **6**, 2563 (2004).

Scheme 10.19. Radical Cyclizations with Tandem Alkylation



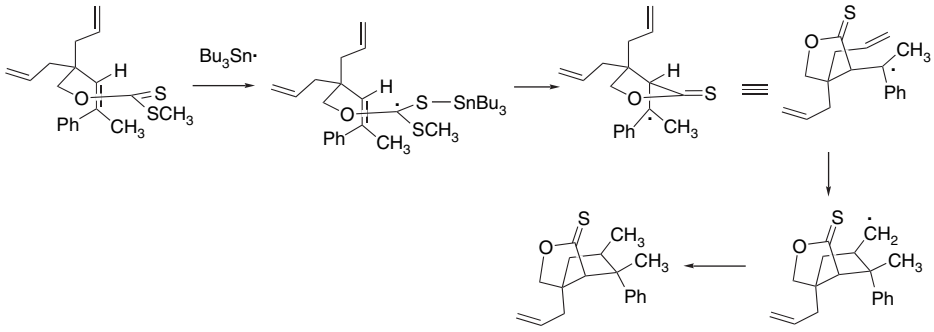
(*Continued*)

Scheme 10.19. (***Continued***)



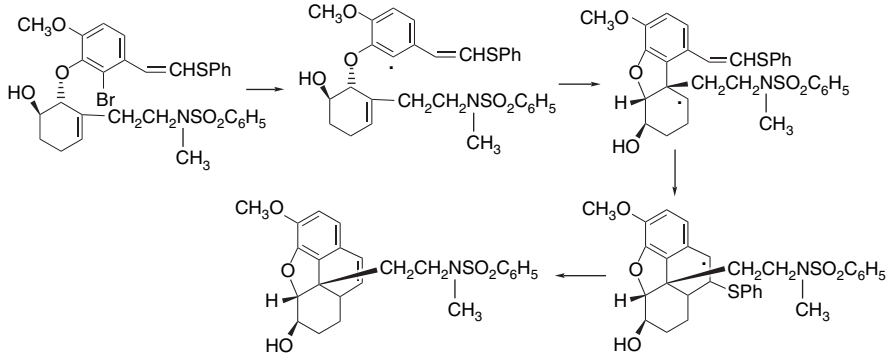
a. G. Stork, P. M. Sher, and H.-L. Chen, *J. Am. Chem. Soc.*, **108**, 6384 (1986).
b. D. P. Curran and D. W. Rakiewicz, *Tetrahedron*, **41**, 3943 (1985).
c. S. Isawa, M. Yamamoto, S. Kohmoto, and K. Yamada, *J. Org. Chem.*, **56**, 2849 (1991).
d. S. R. Baker, A. F. Parsons, J.-F. Pons, and M. Wilson, *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. Rodriquez, *J. Am. Chem. Soc.*, **121**, 5176 (1999).
o. H. Ishibashi, M. Inomata, M Ohba, and M. Ikeda, *Tetrahedron Lett.*, **40**, 1149 (1999).

it fragments. The benzylic radical that is generated by cyclization adds to one of the allyl groups. The chain is then propagated by hydrogen abstraction from the stannane.



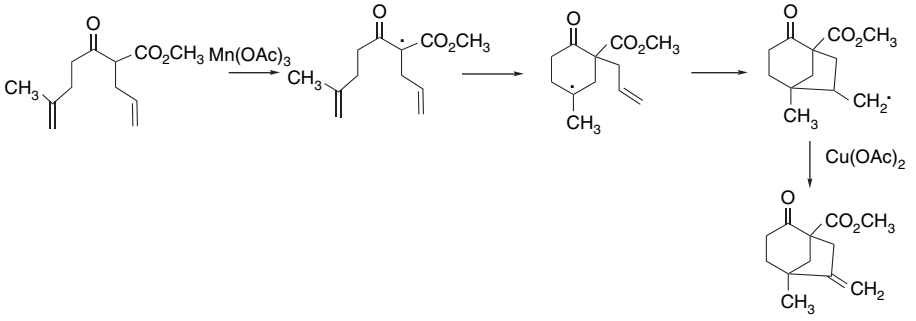
In Entry 4, the initial cyclization is evidently a 5-*endo* process, which in this case is strongly favored by the substitution pattern (capto-dative substituents; see Part A, Section 11.1.6). Most of the cyclized radical then undergoes addition to the cyclohexene ring, generating the major product. 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

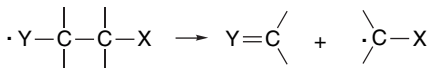
results in the formation of the *trans* decalin product. The by-products of this reaction suggest that the first cyclization is a radical reaction but that oxidation to the tertiary carbocation occurs prior to the second cyclization. Entry 12 involves a tandem process in which the intermediate radical is captured by the second double bond. The presence of Cu(II) results in oxidation of the cyclized radical to an alkene.



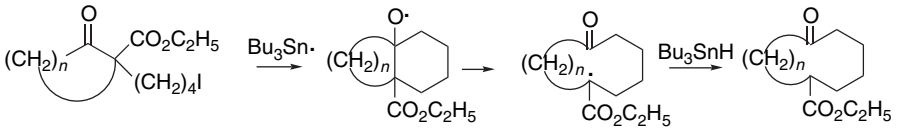
Entries 13 to 15 involve adding to carbon-nitrogen multiple bonds. The reaction in Entry 13 is initiated by addition of the stannyl radical to the terminal alkyne. Cyclization generates a primary radical that adds to the cyano group. Cyano groups are not particularly good radical traps, but in this case 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 stannyl 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.

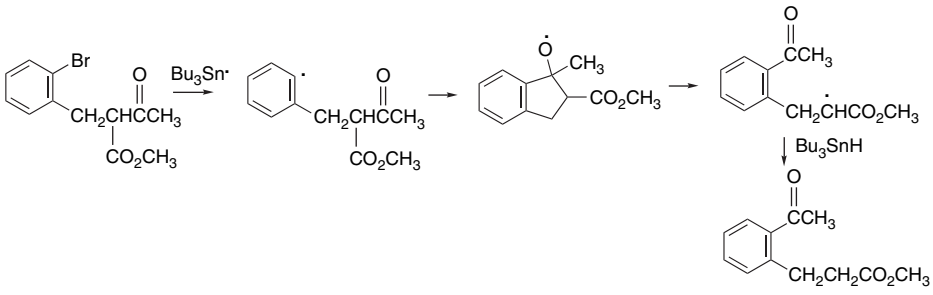


The fragmentation of alkoxyl radicals is especially favorable because the formation of a carbonyl bond makes such reactions exothermic. Rearrangements of radicals frequently occur by a series of addition-fragmentation steps. The following two reactions involve radical rearrangements that proceed through addition-elimination sequences.



Ref. 350

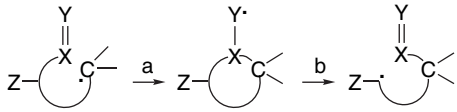
350. P. Dowd and S.-C. Choi, *J. Am. Chem. Soc.*, **109**, 6548 (1987).



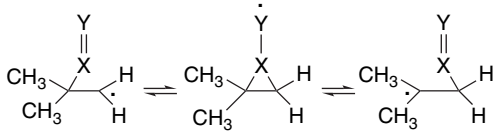
Ref. 351a

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*-Bu_3SnH. 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 alkoxycarbonyl 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 X=Y that is formally "transferred" by the rearrangement process can be C=C, C=O, C=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.

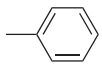


In this system, the overall driving force is the conversion of a primary radical to a tertiary one ($\Delta H \sim -5$ kcal) and the activation barrier incorporates strain associated with formation of the three-membered ring. Rates and activation energies for several migrating groups were determined.[352] A noteworthy feature is the low reactivity of

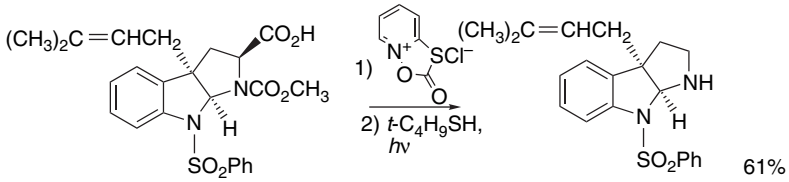
[351] (a) A. L. J. Beckwith, D. M. O'Shea, and S. W. Westwood, *J. Am. Chem. Soc.*, **110** 2565 (1988); (b) R. Tsang, J. K. Pickson, Jr., H. Pak, R. Walton, and B. Fraser-Reid, *J. Am. Chem. Soc.*, **109**, 3484 (1987).

[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.

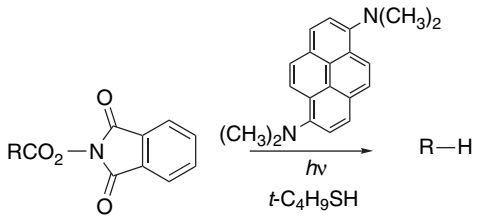
X=Y	$HC{=}CH_2$	$(CH_3)_3C{-}C{=}O$		$-C{\equiv}CC(CH_3)_3$	$C{\equiv}N$
k_r (s^{-1})	10^7	1.7×10^5	7.6×10^3	93	0.9
E_a (kcal/mol)	5.7	7.8	11.8	12.8	16.4

Among the most useful radical fragmentation reactions from a synthetic point of view are decarboxylations and fragmentations of alkoxyl 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

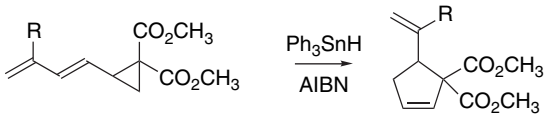
Esters of *N*-hydroxyphthalimide can also be used for decarboxylation. Photolysis in the presence of an electron donor and a hydrogen atom donor leads to decarboxylation. Carboxyl radicals are formed by one-electron reduction of the phthalimide ring.



Ref. 356

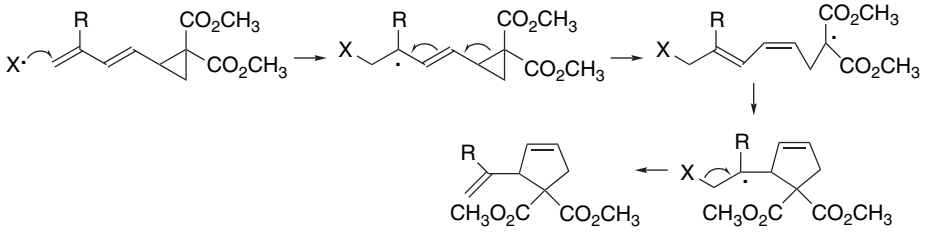
Fragmentation of cyclopropylcarbinyl radicals has been incorporated into several synthetic schemes.[357] For example, 2-dienyl-1,1-(dimethoxycarbonyl)-cyclopropanes undergo ring expansion to cyclopentenes.

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).

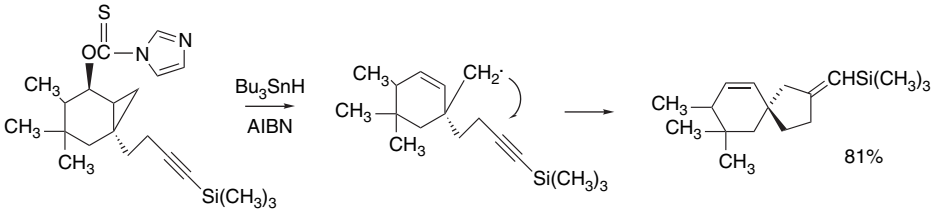


Ref. 358

These reactions presumably involve terminal addition of the chain-carrying radical, followed by fragmentation and recyclization.

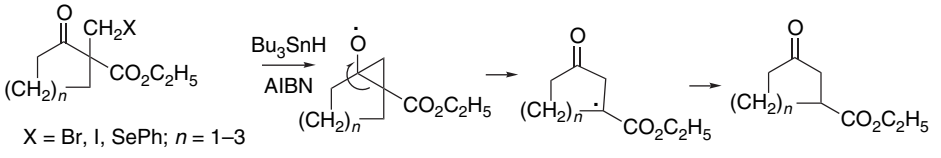


Other intramolecular cyclizations can follow generation and fragmentation of cyclopropylcarbinyl radicals. In the example below, the fragmented radical adds to the alkyne.



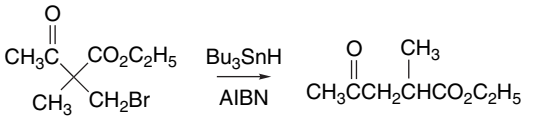
Ref. 359

Cyclic α-halomethyl or α-phenylselenenylmethyl β-ketoesters undergo one-carbon ring expansion via transient cyclopropylalkoxy radicals.[360]

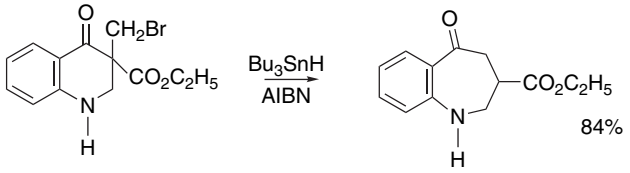


Comparable cyclization-fragmentation sequences have been developed for acyclic and heterocyclic systems.

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).



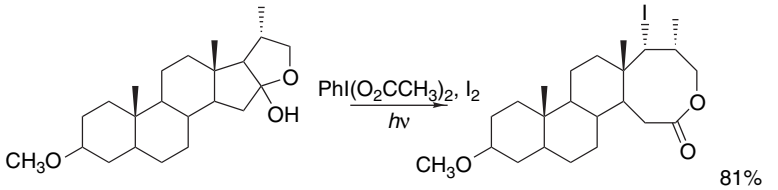
64% Ref. 361



84% Ref. 362

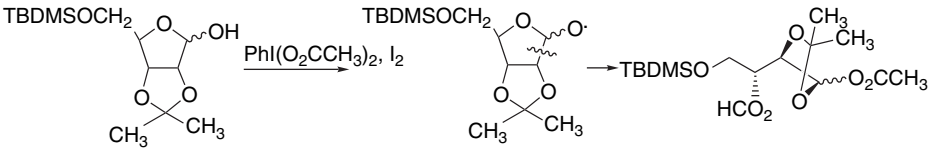
Similar reactions can be conducted using *tris*-(trimethylsilyl)silane as the hydrogen atom donor.[363]

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.



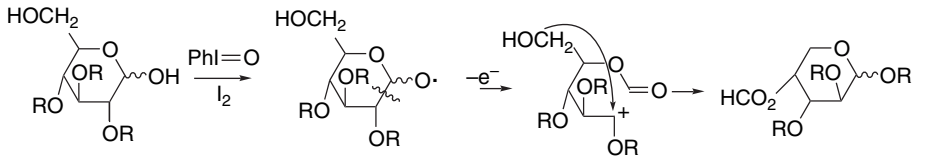
81%

This reagent also can cleave the C(1)−C(2) bond in furanose carbohydrates.

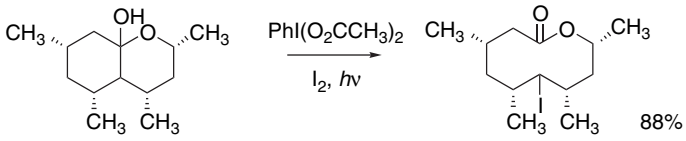


Ref. 366

When the 5-hydroxy group is unprotected, it can capture the fragmented intermediate.[367]

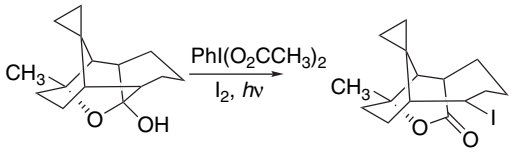


361. P. Dowd and S.-C. Choi, *Tetrahedron*, **45**, 77 (1989).
362. Z. B. Zheng and P. Dowd, *Tetrahedron Lett.*, **34**, 7709 (1993); P. Dowd and S.-C. Choi, *Tetrahedron*, **47**, 4847 (1991).
363. M. Sugi and H. Togo, *Tetrahedron*, **58**, 3171 (2002).
364. L. Yet, *Tetrahedron*, **55**, 9349 (1999).
365. R. Freire, J. J. Marrero, M. S. Rodriquez, 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. Intl. Ed. Engl.*, **31**, 772 (1992).
367. P. de Armas, C. G. Francisco, and E. Suarez, *J. Am. Chem. Soc.*, **115**, 8865 (1993).



Ref. 368

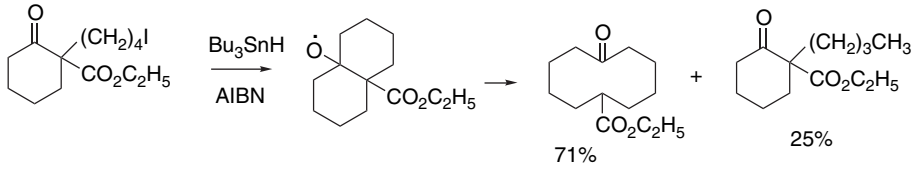
Similarly, bicyclic hemiacetals fragment to medium-size lactones.



Ref. 369

These reactions are believed to proceed through hypoiodite intermediates.

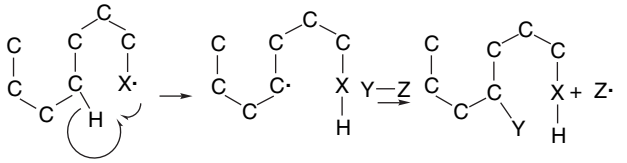
Alkoxy radical fragmentation is also involved in ring expansion of 3- and 4-haloalkyl cyclohexanones. The radical formed by halogen atom abstraction adds to the carbonyl group, after which fragmentation to the carboethoxy-stabilized radical occurs.[370]



The by-product results from competing reduction of the radical by hydrogen atom abstraction.

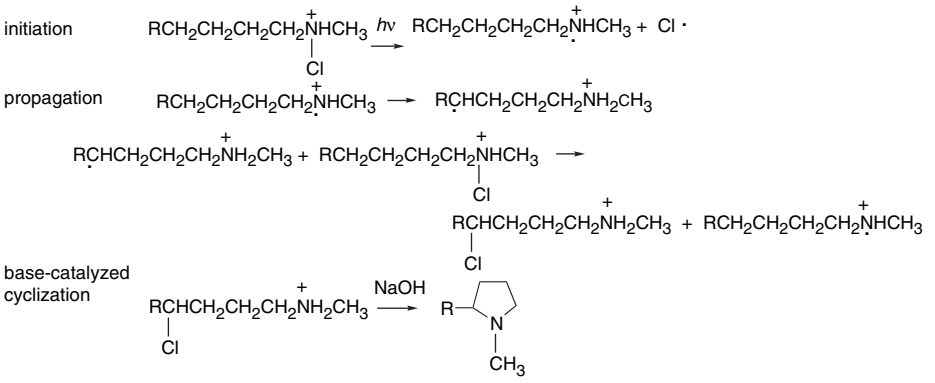
10.3.7. Intramolecular Functionalization by Radical Reactions

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.

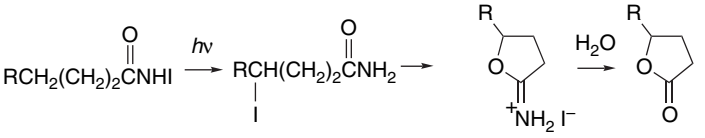


368. M. Kaino, Y. Naruse, K. Ishihara, and H. Yamamoto, *J. Org. Chem.*, **55**, 5814 (1990).
369. J. Lee, J. Oh, S. Jin, J.-R. Choi, J. L. Atwood, and J. K. Cha, *J. Org. Chem.*, **59**, 6955 (1994).
370. P. Dowd and S.-C. Choi, *Tetrahedron*, **45**, 77 (1989); P. Dowd and S.-C. Choi, *J. Am. Chem. Soc.*, **109**, 6548 (1987).

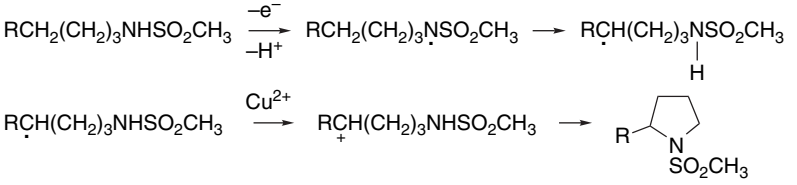
One example of this type of reaction is the photolytically initiated decomposition of *N*-chloroamines in acidic solution, which is known as the *Hofmann-Loeffler-Freytag reaction*.[371] The initial products are δ-chloroamines, but these are usually converted to pyrrolidines by intramolecular nucleophilic substitution.



A closely related procedure results in formation of γ-lactones. Amides are converted to *N*-iodoamides by reaction with iodine and *t*-butyl hypochlorite. Photolysis of the *N*-iodoamides gives lactones via iminolactone intermediates.[372]



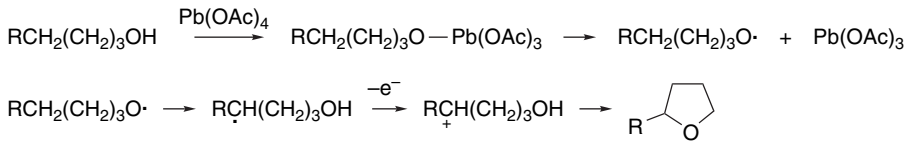
Steps similar to the Hofmann-Loeffler reaction are also involved in cyclization of *N*-alkylmethanesulfonamides by oxidation with $Na_2S_2O_4$ in the presence of cupric ion.[373]



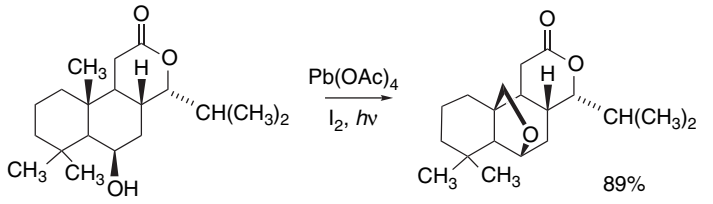
There are also useful intramolecular functionalization methods that involve hydrogen atom abstraction by oxygen radicals. The conditions that were originally developed involved thermal or photochemical dissociation of alkoxy derivative of Pb(IV) generated by exchange with $Pb(OAc)_4$.[374] These decompose, 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).

radicals with reduction to Pb(III). The subsequent oxidation of the radical to a carbocation is effected by Pb(IV) or Pb(III).

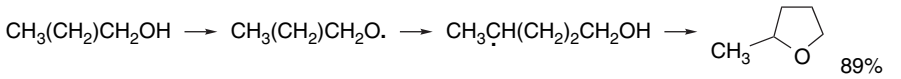


Current procedures include iodine and are believed to involve a hypoiodite intermediate.[375]

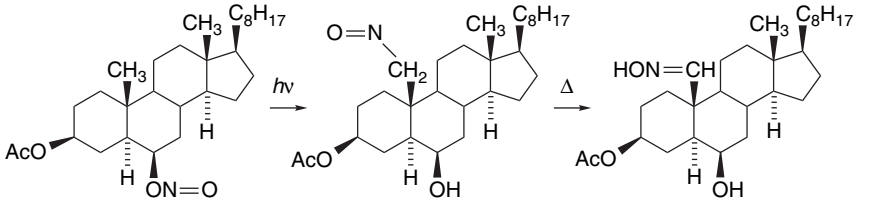


Ref. 376

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]

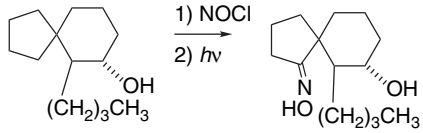


Alkoxy radicals are also the active hydrogen-abstracting species in a procedure that involves photolysis of nitrite esters. This reaction was originally developed as a method for functionalization of methyl groups in steroids. [379]



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).



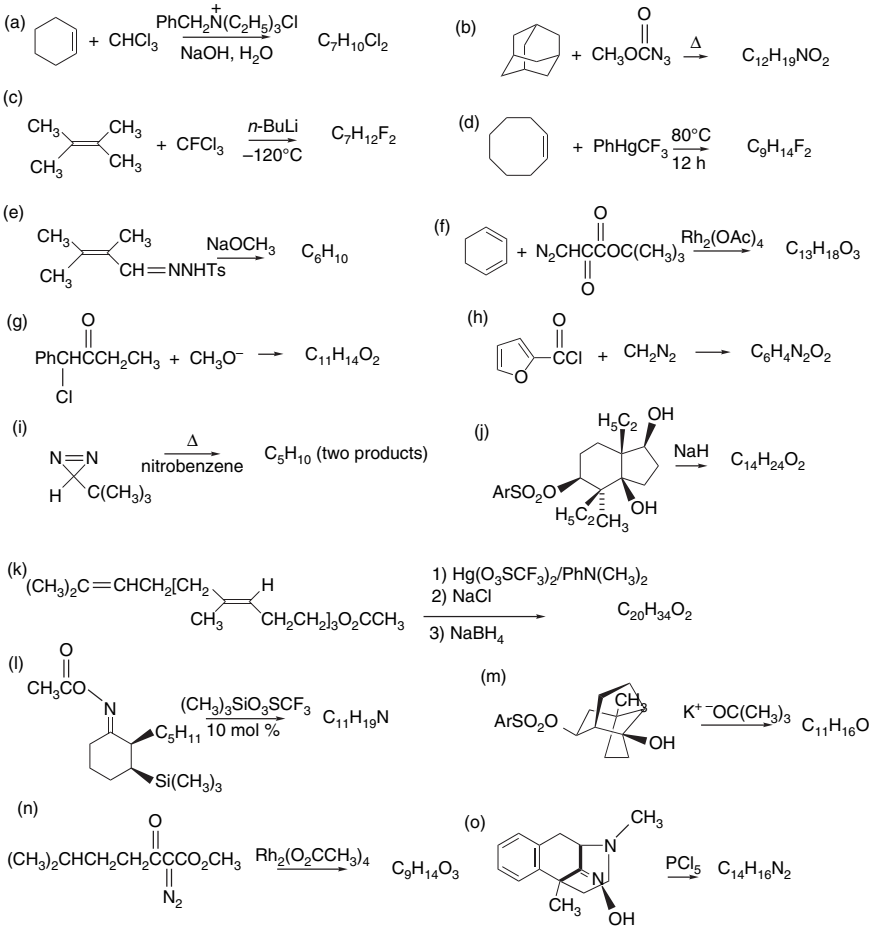
Ref. 380

These reactions depend on the proximity of the alkoxy radical to a particular hydrogen for selectivity.

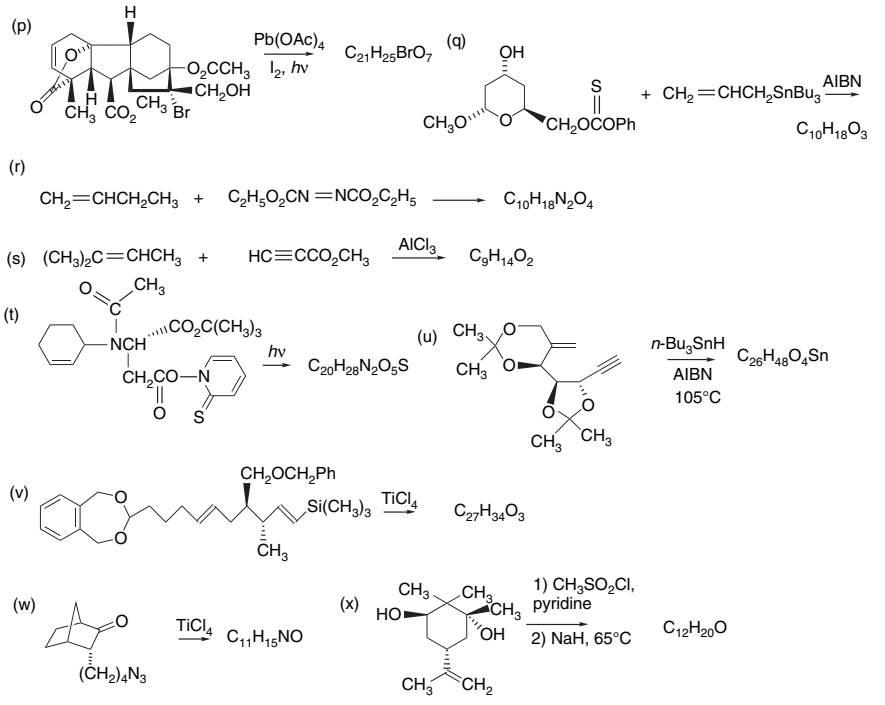
Problems

(*References for these problems will be found on page 1287.*)

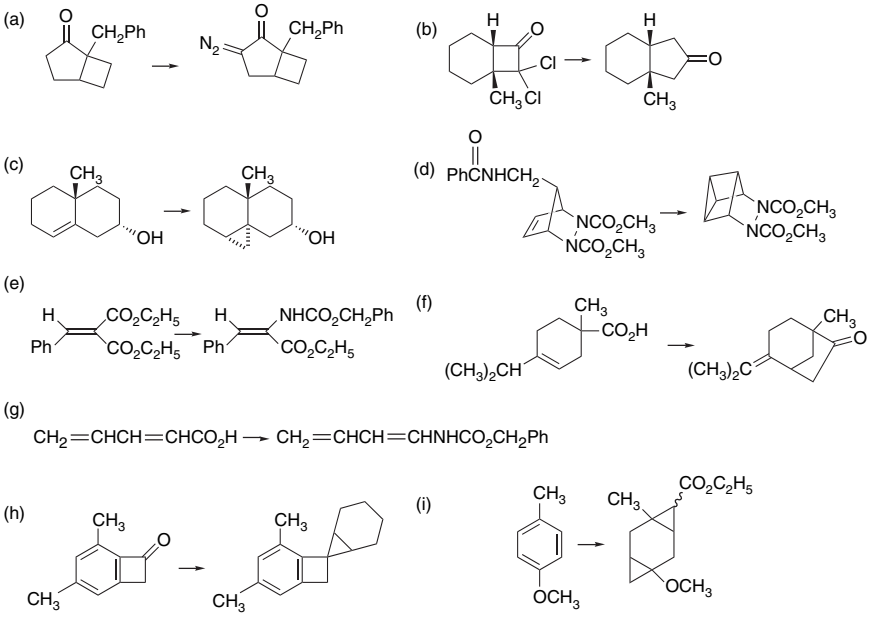
10.1. Indicate the major product to be expected in the following reactions:

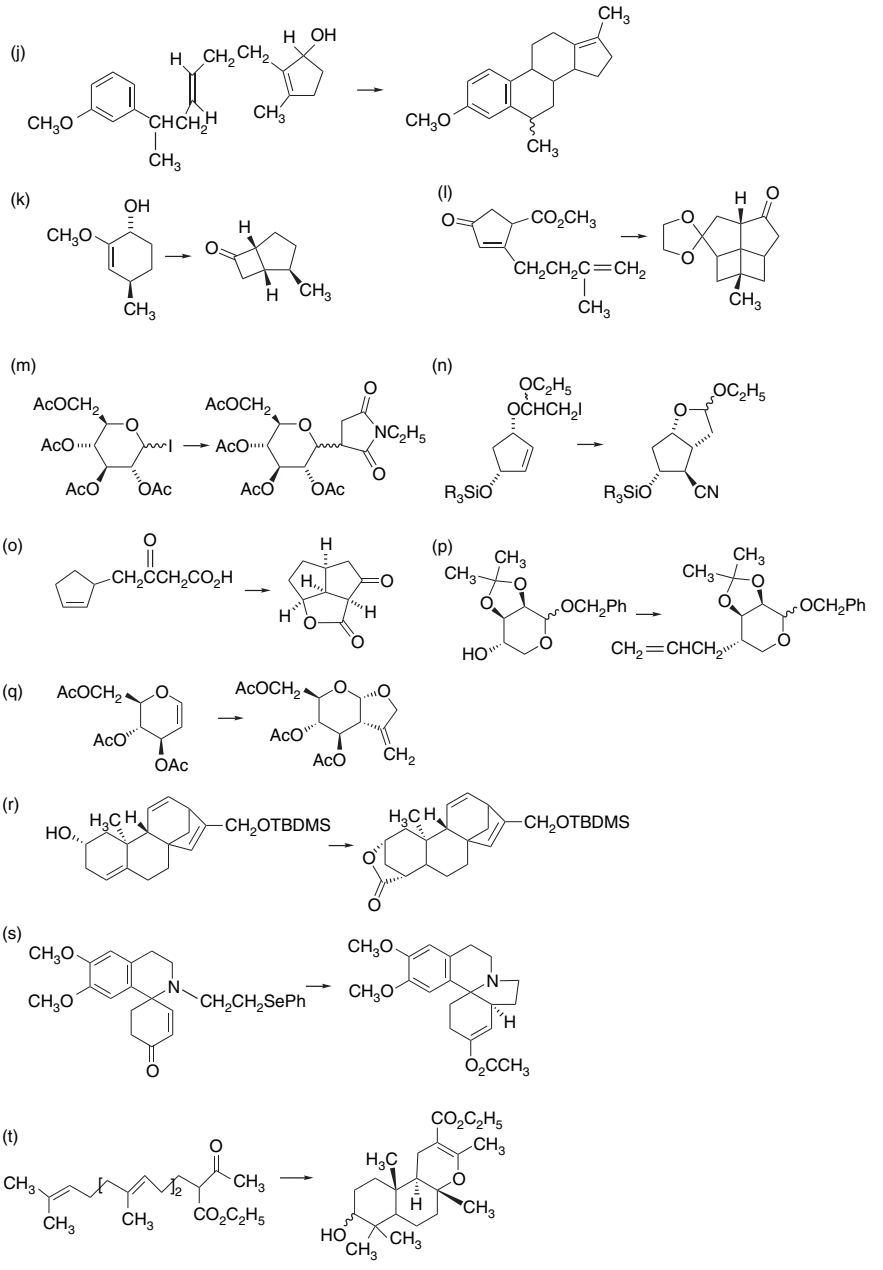


[380] E. J. Corey, J. F. Arnett, and G. N. Widiger, *J. Am. Chem. Soc.*, **97**, 430 (1975).

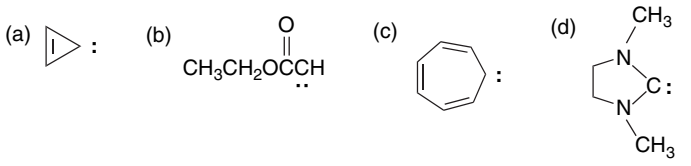


10.2. Indicate appropriate reagents and reaction conditions or a short reaction sequence that could be expected to effect the following transformations:



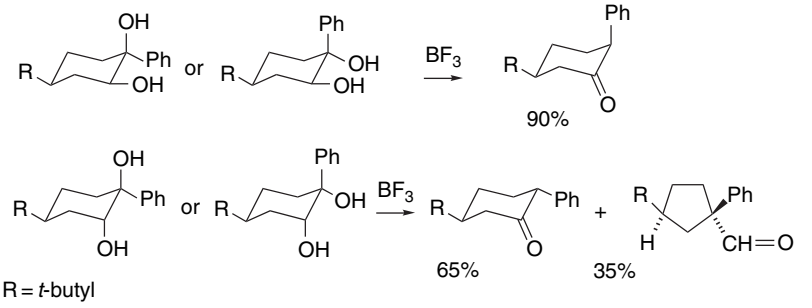


10.3. Each of the following carbenes has been predicted to have a singlet ground state, either as the result of qualitative structural considerations or theoretical calculations. Indicate what structural features might stabilize the singlet state in each case.

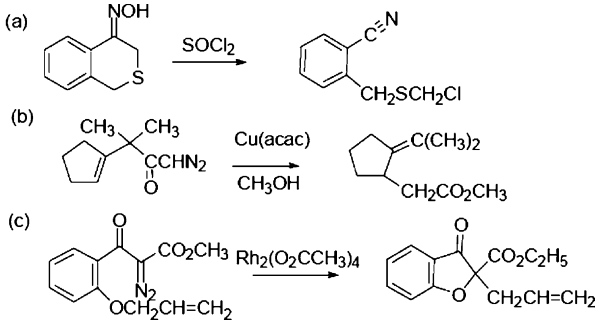


10.4. The hydroxy group in *E*-cycloocten-3-ol determines the stereochemistry of the reaction with the Simmons-Smith reagent. By examining a model, predict the stereochemistry of the product.

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.



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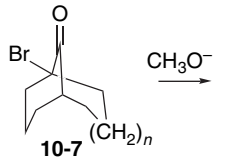
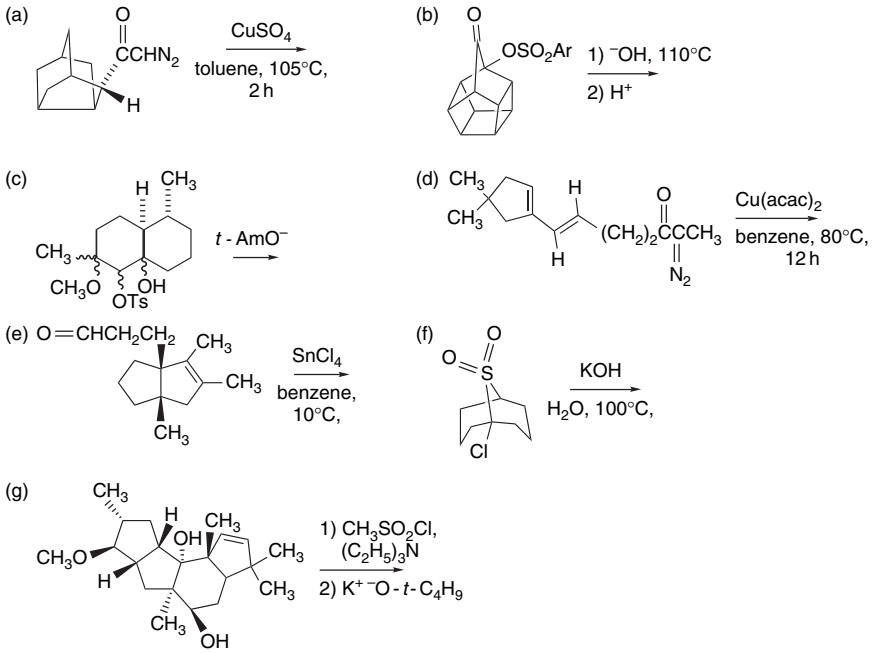
10.7. It has been found that the bromo ketones **10-7a-c** can rearrange by either the cyclopropanone or the semibenzilic mechanism, depending on the size of the ring and the reaction conditions. Suggest two experiments that would permit you to distinguish between the two mechanisms under a given set of circumstances.



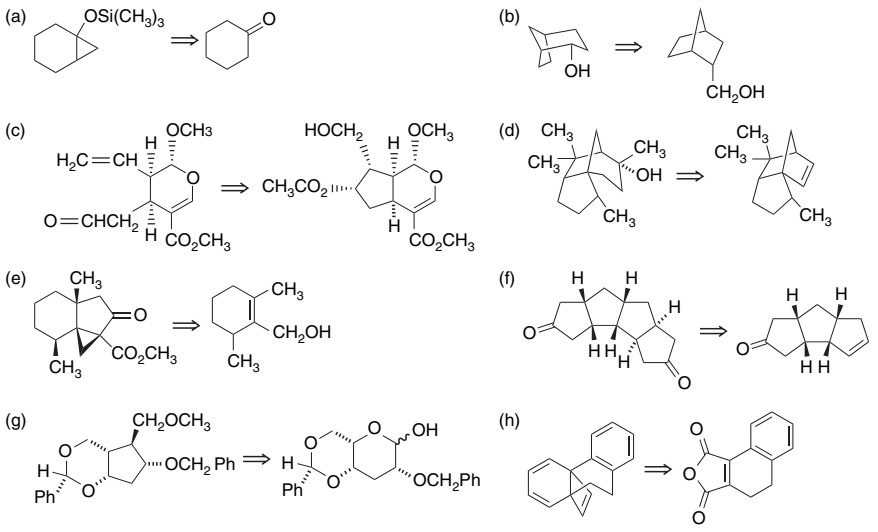
10-7

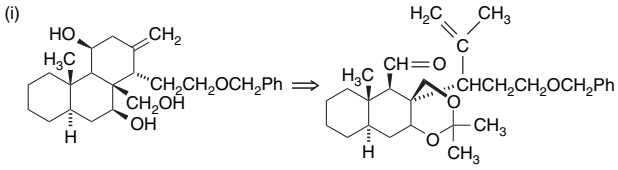
a – c; n = 1–3

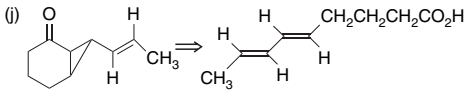
10.8. Predict the major product of the following reactions:

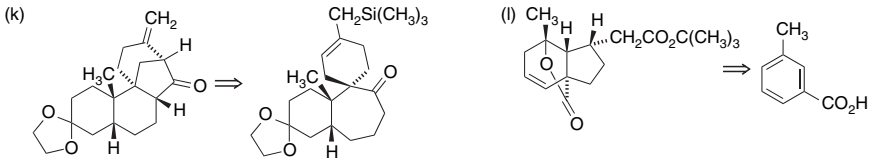


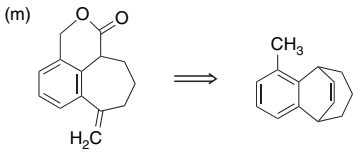
10.9. Short reaction series can effect formation of the desired material on the left from the starting material on the right. Devise an appropriate reaction sequence.



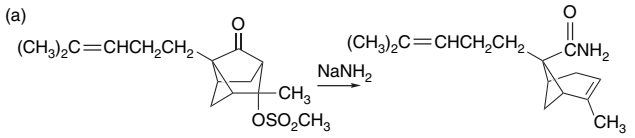


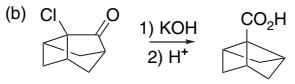


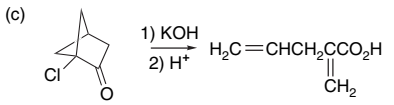


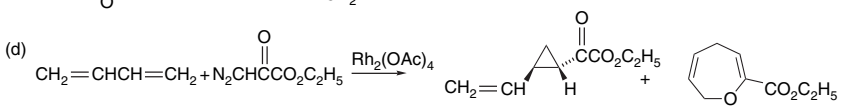


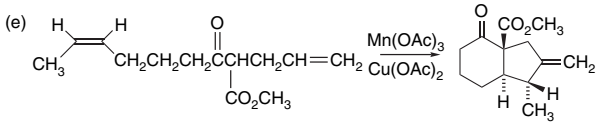
10.10. Formulate mechanisms for the following reactions:

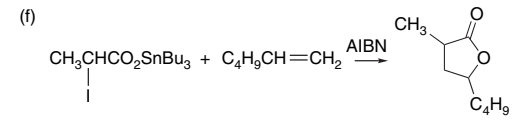


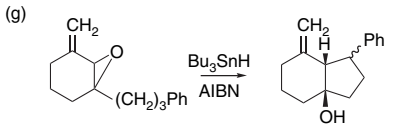




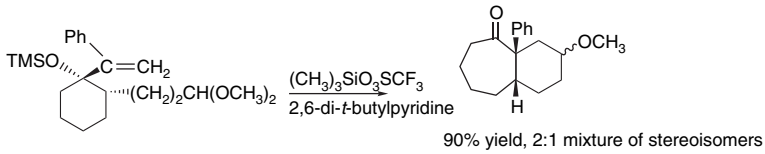






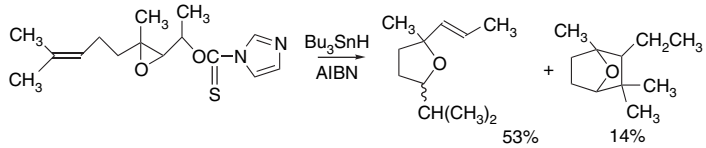


(h)

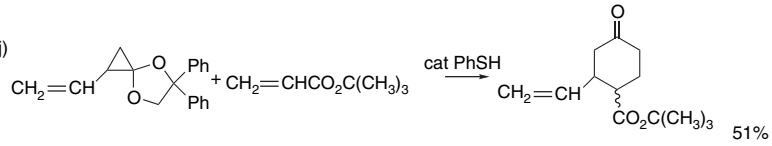


90% yield, 2:1 mixture of stereoisomers

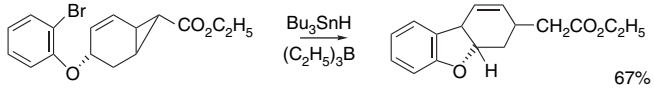
(i)



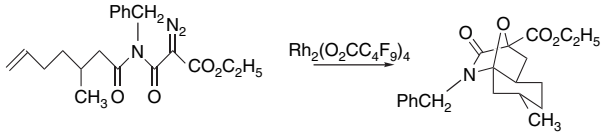
(j)



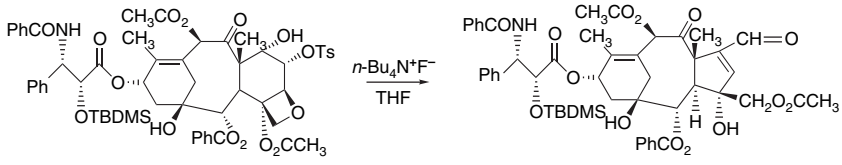
(k)



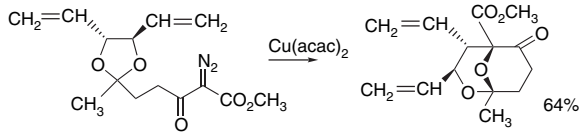
(l)



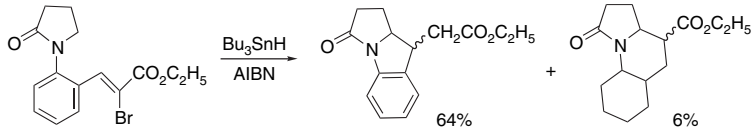
(m)



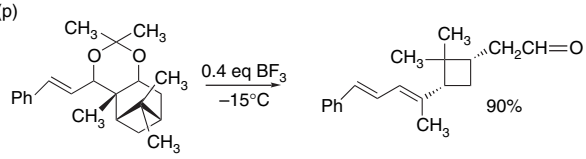
(n)

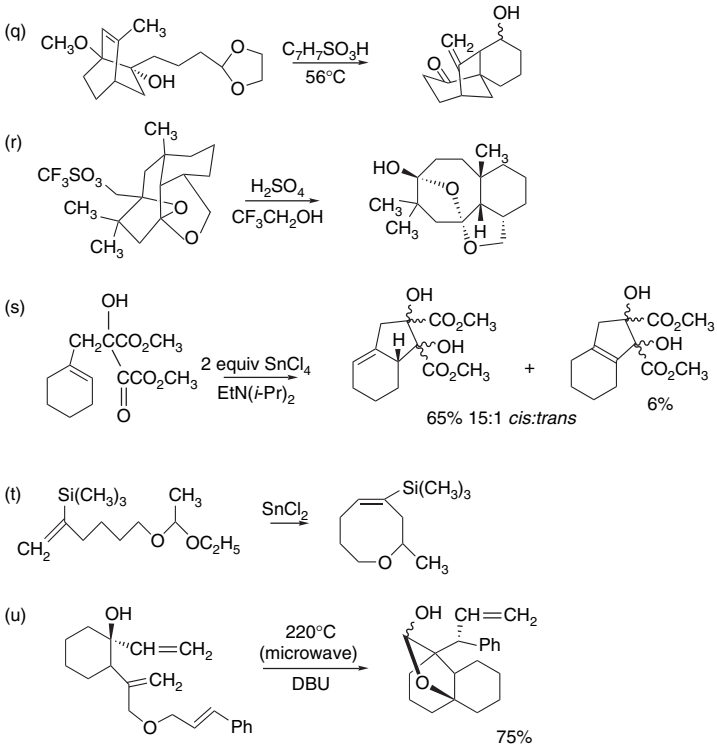


(o)

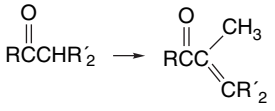


(p)

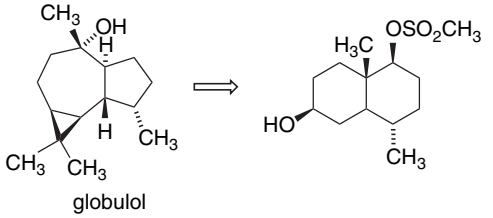




10.11. A sequence of reactions for conversion of acyclic and cyclic ketones into α,β-unsaturated ketones with insertion of a $=CHCH_3$ unit has been developed. The method uses 1-lithio-1,1-dichloroethane as a key carbenoid reagent. The overall sequence involves three steps, one of them before and one after the carbenoid reaction. By analysis of the bonding changes and application of your knowledge of carbene reactions, devise a reaction sequence that would accomplish the transformation.

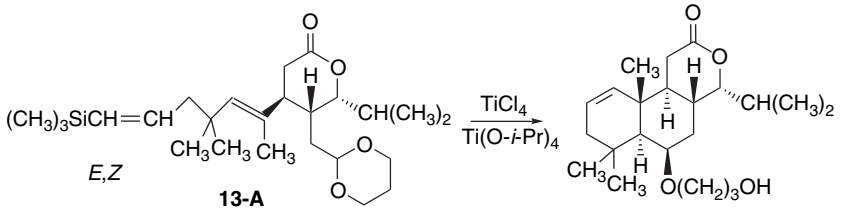


10.12. The synthesis of globulol from the octalin derivative shown proceeds in four stages. These include, not necessarily in sequence, addition of a carbene, a fragmentation reaction, and acid-catalyzed cyclization of a cyclodeca-2,7-dienol. The final step of the synthesis converts a dibromocyclopropane to the dimethylcyclopropane structure using dimethylcuprate. Using retrosynthetic analysis, devise an appropriate sequence of reactions and suggest reagents for each step.

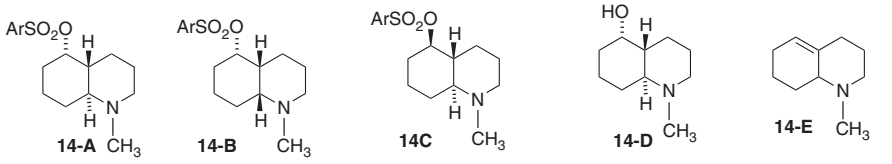


globulol

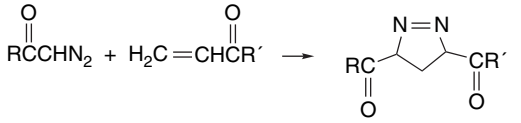
10.13. Both the *E*- and *Z*-isomers of vinylsilane **13-A** have been subjected to polyene cyclization using $TiCl_4$-Ti(O-*i*-Pr)$_4$. Although the *Z*-isomer gives an 85–90% yield, the *E*-isomer affords only a 30–40% yield. Offer an explanation.



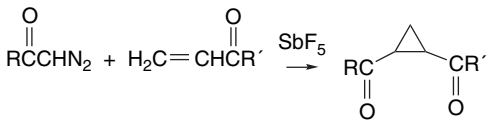
10.14. Each of the three decahydroquinoline sulfonates shown below gives a different product composition on solvolysis. One gives 9-methylamino-*E*-non-5-enal, one gives 9-methylamino-*Z*-non-5-enal, and one gives a mixture of the two quinoline derivatives **14-D** and **14-E**. Deduce which compound 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.

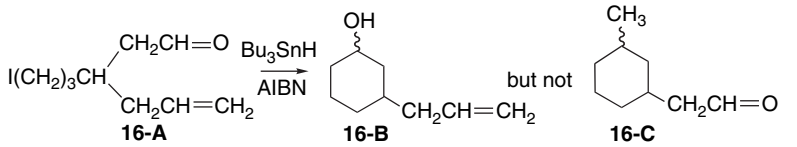


If, however, the reaction is run in the presence of a Lewis acid, particularly SbF_5, the reaction takes a different course, giving a diacyl cyclopropane.



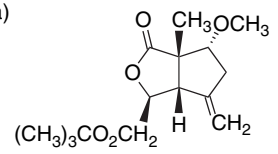
Formulate a mechanism to account for the altered course of the reaction in the presence of SbF_5.

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?

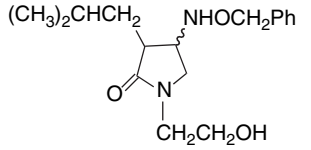


10.17. The following molecules have been synthesized by radical cyclization and tandem radical cyclizations. Identify the bond or bonds that could be formed by radical cyclizations and suggest an appropriate reactant and reaction conditions that would lead to the specified products.

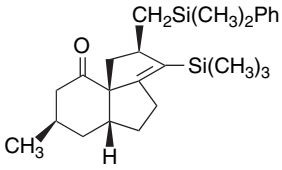
(a)



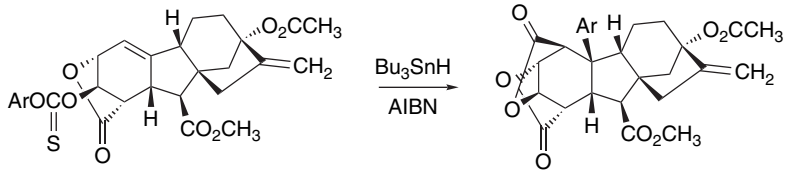
(b)



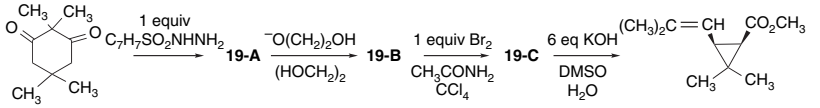
(c)



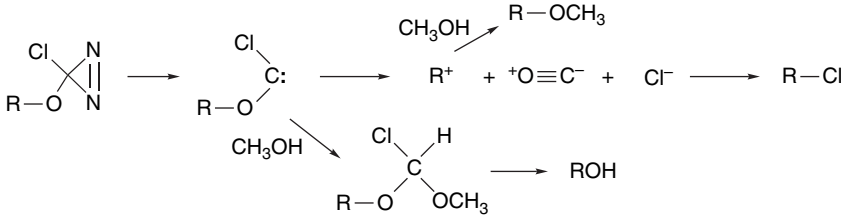
10.18. Attempted deoxygenation of several β-aryl thiono carbonates gave the unexpected product shown. In contrast, the corresponding α-isomers gave the desired deoxygenation product. Account for the formation of the observed products, and indicate why these products are not formed from the α-stereoisomers.



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?

	pentane			CH_2Cl_2		
[MeOH]	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.