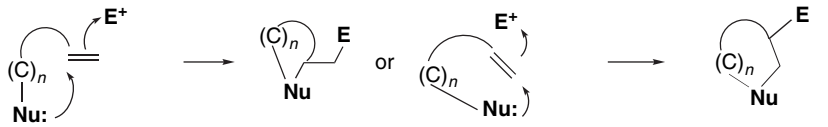
4

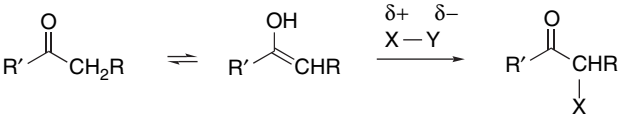
Electrophilic Additions to Carbon-Carbon Multiple Bonds

Introduction

Addition of electrophilic reagents is one of the most general and useful reactions of alkenes and alkynes. This chapter focuses on reactions that proceed through polar intermediates or transition structures. We discuss the fundamental mechanistic characteristics of this class of reactions in Chapter 5 of Part A, including proton-catalyzed additions of water and alcohols and the addition of hydrogen halides. Other electrophilic reagents that we consider there are the halogens and positive halogen compounds, electrophilic sulfur and selenium reagents, and mercuric salts. Hydroboration is another important type of electrophilic addition to alkenes. In the present chapter, we emphasize synthetic application of these reactions. For the most part, electrophilic additions are used to introduce functionality at double and triple bonds. When the nucleophile addition step is intramolecular, a new heterocyclic ring is formed, and this is a very useful synthetic method.



Carbonyl compounds can react with electrophiles via their enol isomers or equivalents, and these reactions result in α-substitution.

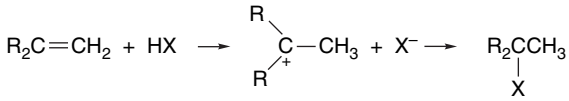


Several other types of addition reactions of alkenes are also of importance and these are discussed elsewhere. Nucleophilic additions to electrophilic alkenes are covered in Section 2.6 and cycloadditions involving concerted mechanisms are encountered in Sections 6.1 to 6.3. Free radical addition reaction are considered in Chapter 11.

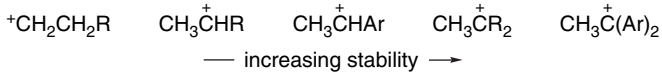
4.1. Electrophilic Addition to Alkenes

4.1.1. Addition of Hydrogen Halides

Hydrogen chloride and hydrogen bromide react with alkenes to give addition products. In early work, it was observed that addition usually takes place to give the product with the halogen atom attached to the more-substituted carbon of the double bond. This behavior is sufficiently general that the name *Markovnikov's rule* was given to the statement describing this mode of addition. The term *regioselective* is used to describe addition reactions that proceed selectively in one direction with unsymmetrical alkenes.[1] A rudimentary picture of the reaction mechanism indicates the basis of Markovnikov's rule. The addition involves either protonation or a partial transfer of a proton to the double bond. The relative stability of the two possible carbocations from an unsymmetrical alkene favors formation of the more-substituted intermediate. Addition is completed when the carbocation reacts with a halide anion.



Markovnikov's rule describes a specific case of regioselectivity that is based on the stabilizing effect of alkyl and aryl substituents on carbocations.



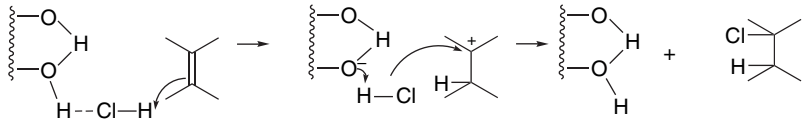
A more complete discussion of the mechanism of addition of hydrogen halides to alkenes is given in Chapter 6 of Part A. In particular, the question of whether or not discrete carbocations are involved is considered there. Even when a carbocation is not involved, the regioselectivity of electrophilic addition is the result of attack of the electrophile at the more *electron-rich* carbon of the double bond. Alkyl substituents increase the electron density of the terminal carbon by hyperconjugation (see Part A, Section 1.1.8).

Terminal and disubstituted internal alkenes react rather slowly with HCl in nonpolar solvents. The rate is greatly accelerated in the presence of silica or alumina in noncoordinating solvents such as dichloromethane or chloroform. Preparatively convenient conditions have been developed in which HCl is generated in situ from $SOCl_2$ or $(ClCO)_2$.[2] These heterogeneous reaction systems also give a Markovnikov orientation.

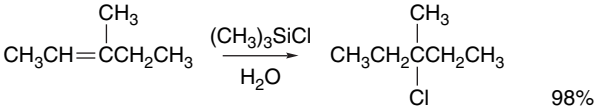
[1] A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

[2] P. J. Kropp, K. A. Daus, M. W. Tubergen, K. D. Kepler, V. P. Wilson, S. L. Craig, M. M. Baillargeon, and G. W. Breton, *J. Am. Chem. Soc.*, **115**, 3071 (1993).

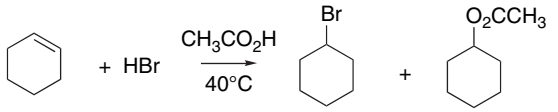
The mechanism is thought to involve an interaction of the silica or alumina surface with HCl that facilitates proton transfer.



Another convenient procedure for hydrochlorination involves adding trimethylsilyl chloride to a mixture of an alkene and water. Good yields of HCl addition products (Markovnikov orientation) are formed.[3] These conditions presumably involve generation of HCl by hydrolysis of the silyl chloride, but it is uncertain if the silicon plays any further role in the reaction.

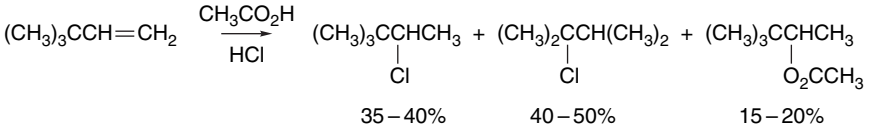


In nucleophilic solvents, products that arise from reaction of the solvent with the cationic intermediate may be formed. For example, reaction of cyclohexene with hydrogen bromide in acetic acid gives cyclohexyl acetate as well as cyclohexyl bromide. This occurs because acetic acid acts as a nucleophile in competition with the bromide ion.

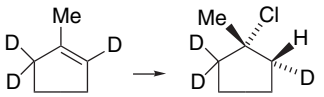


Ref. 4

When carbocations are involved as intermediates, carbon skeleton rearrangement can occur during electrophilic addition reactions. Reaction of *t*-butylethylene with hydrogen chloride in acetic acid gives both rearranged and unrearranged chloride.[5]



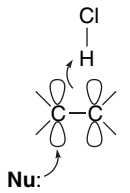
The stereochemistry of addition of hydrogen halides to alkenes depends on the structure of the alkene and also on the reaction conditions. Addition of hydrogen bromide to cyclohexene and to *E*- and *Z*-2-butene is *anti*.[6] The addition of hydrogen chloride to 1-methylcyclopentene is entirely *anti* when carried out at 25° C in nitromethane.[7]



3. P. Boudjouk, B.-K. Kim, and B.-H. Han, *Synth. Commun.*, **26**, 3479 (1996); P. Boudjouk, B.-K. Kim, and B.-H. Han, *J. Chem. Ed.*, **74**, 1223 (1997).
4. R. C. Fahey and R. A. Smith, *J. Am. Chem. Soc.*, **86**, 5035 (1964).
5. R. C. Fahey and C. A. McPherson, *J. Am. Chem. Soc.*, **91**, 3865 (1969).
6. D. J. Pasto, G. R. Meyer, and S. Kang, *J. Am. Chem. Soc.*, **91**, 4205 (1969).
7. Y. Pocker and K. D. Stevens, *J. Am. Chem. Soc.*, **91**, 4205 (1969).

1,2-Dimethylcyclohexene is an example of an alkene for which the stereochemistry of hydrogen chloride addition is dependent on the solvent and temperature. At −78° C in dichloromethane, 88% of the product is the result of *syn* addition, whereas at 0° C in ether, 95% of the product results from *anti* addition.[8] *Syn* addition is particularly common with alkenes having an aryl substituent. Table 4.1 lists several alkenes for which the stereochemistry of addition of hydrogen chloride or hydrogen bromide has been studied.

The stereochemistry of addition depends on the details of the mechanism. The addition can proceed through an ion pair intermediate formed by an initial protonation step. Most alkenes, however, react via a complex that involves the alkene, hydrogen halide, and a third species that delivers the nucleophilic halide. This termolecular mechanism is generally pictured as a nucleophilic attack on an alkene-hydrogen halide complex. This mechanism bypasses a discrete carbocation and exhibits a preference for *anti* addition.



The major factor in determining which mechanism is followed is the stability of the carbocation intermediate. Alkenes that can give rise to a particularly stable carbocation

Table 4.1. Stereochemistry of Addition of Hydrogen Halides to Alkenes

Alkene	Hydrogen halide	Stereochemistry
1,2-Dimethylcyclohexene[a]	HBr	*anti*
1,2-Dimethylcyclohexene[a]	HCl	Solvent and temperature dependent
Cyclohexene[b]	HBr	*anti*
Z-2-Butene[c]	DBr	*anti*
E-2-Butene[c]	DBr	*anti*
1-Methylcyclopentene[d]	HCl	*anti*
1,2-Dimethylcyclopentene[e]	HBr	*anti*
Norbornene[f]	HBr	*syn* and rearrangement
Norbornene[g]	HCl	*syn* and rearrangement
E-1-Phenylpropene[h]	HBr	*syn* (9:1)
Z-1-Phenylpropene[h]	HBr	*syn* (8:1)
Bicyclo[3.1.0]hex-2-ene[i]	DCl	*syn*
1-Phenyl-4-(*t*-butyl)cyclohexene[j]	DCl	*syn*

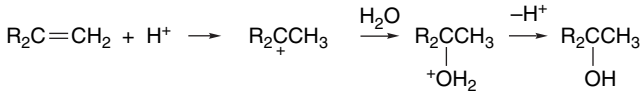
a. G. S. Hammond and T. D. Nevitt, *J. Am. Chem. Soc.*, **76**, 4121 (1954); R. C. Fahey and C. A. McPherson, *J. Am. Chem. Soc.*, **93**, 2445 (1971); K. B. Becker and C. A. Grob, *Synthesis*, 789 (1973).
b. R. C. Fahey and R. A. Smith, *J. Am. Chem. Soc.*, **86**, 5035 (1964).
c. D. J. Pasto, G. R. Meyer, and B. Lepeska, *J. Am. Chem. Soc.*, **96**, 1858 (1974).
d. Y. Pocker and K. D. Stevens, *J. Am. Chem. Soc.*, **91**, 4205 (1969).
e. G. S. Hammond and C. H. Collins, *J. Am. Chem. Soc.*, **82**, 4323 (1960).
f. H. Kwart and J. L. Nyce, *J. Am. Chem. Soc.*, **86**, 2601 (1964).
g. J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *J. Am. Chem. Soc.*, **88**, 4922 (1966).
h. M. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.*, **85**, 3645 (1963).
i. P. K. Freeman, F. A. Raymond, and M. F. Grostic, *J. Org. Chem.*, **32**, 24 (1967).
j. K. D. Berlin, R. O. Lyerla, D. E. Gibbs, and J. P. Devlin, *J. Chem. Soc., Chem. Commun.*, 1246 (1970).

8. K. B. Becker and C. A. Grob, *Synthesis*, 789 (1973).

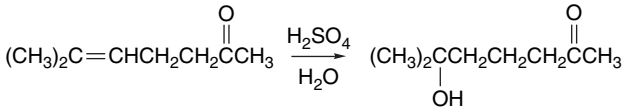
are likely to react via the ion pair mechanism, which is not necessarily stereospecific, as the carbocation intermediate permits loss of stereochemistry relative to the reactant alkene. It might be expected that the ion pair mechanism would lead to a preference for *syn* addition, since at the instant of formation of the ion pair, the halide is on the same side of the alkene as the proton being added. Rapid collapse of the ion pair intermediate would lead to *syn* addition. If the lifetime of the ion pair is longer and the ion pair dissociates, a mixture of *syn* and *anti* addition products can be formed. The termolecular mechanism is expected to give *anti* addition because the nucleophilic attack occurs on the opposite side of the double bond from proton addition. Further discussion of the structural features that affect the competition between the two possible mechanisms can be found in Section 6.1 of Part A.

4.1.2. Hydration and Other Acid-Catalyzed Additions of Oxygen Nucleophiles

Oxygen nucleophiles can be added to double bonds under strongly acidic conditions. A fundamental example is the hydration of alkenes in acidic aqueous solution.



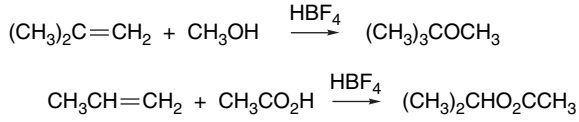
Addition of a proton occurs to give the more-substituted carbocation, so addition is regioselective and in accord with Markovnikov's rule. A more detailed discussion of the reaction mechanism is given in Section 6.2 of Part A. Owing to the strongly acidic and rather vigorous conditions required to effect hydration of most alkenes, these conditions are applicable only to molecules that have no acid-sensitive functional groups. The reaction is occasionally applied to the synthesis of tertiary alcohols.



Ref. 9

Moreover, because of the involvement of cationic intermediates, rearrangements can occur in systems in which a more stable cation can result by aryl, alkyl, or hydrogen migration. *Oxymercuration-reduction*, a much milder and more general procedure for alkene hydration, is discussed in the next section.

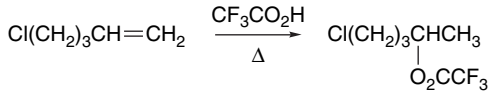
Addition of nucleophilic solvents such as alcohols and carboxylic acids can be effected by using strong acids as catalysts.[10]



[9] J. Meinwald, *J. Am. Chem. Soc.*, **77**, 1617 (1955).

[10] R. D. Morin and A. E. Bearse, *Ind. Eng. Chem.*, **43**, 1596 (1951); D. T. Dalgleish, D. C. Nonhebel, and P. L. Pauson, *J. Chem. Soc. C*, 1174 (1971).

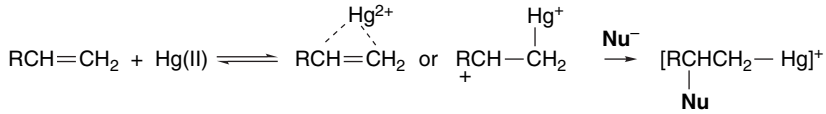
Trifluoroacetic acid (TFA) is strong enough to react with alkenes under relatively mild conditions.[11] The addition is regioselective in the direction predicted by Markovnikov's rule.



Ring strain enhances alkene reactivity. Norbornene, for example, undergoes rapid addition of TFA at 0° C.[12]

4.1.3. Oxymercuration-Reduction

The addition reactions discussed in Sections 4.1.1 and 4.1.2 are initiated by the interaction of a proton with the alkene. Electron density is drawn toward the proton and this causes nucleophilic attack on the double bond. The role of the electrophile can also be played by metal cations, and the mercuric ion is the electrophile in several synthetically valuable procedures.[13] The most commonly used reagent is mercuric acetate, but the trifluoroacetate, trifluoromethanesulfonate, or nitrate salts are more reactive and preferable in some applications. A general mechanism depicts a *mercurinium ion* as an intermediate.[14] Such species can be detected by physical measurements when alkenes react with mercuric ions in nonnucleophilic solvents.[15] The cation may be predominantly bridged or open, depending on the structure of the particular alkene. The addition is completed by attack of a nucleophile at the more-substituted carbon. The nucleophilic capture is usually the rate- and product-controlling step.[13, 16]



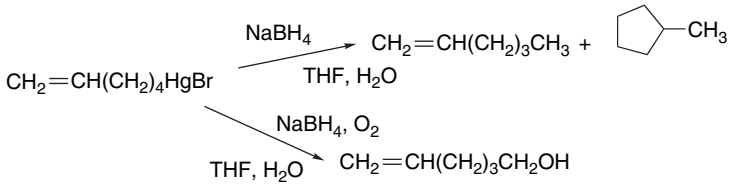
The nucleophiles that are used for synthetic purposes include water, alcohols, carboxylate ions, hydroperoxides, amines, and nitriles. After the addition step is complete, the mercury is usually reductively removed by sodium borohydride, the net result being the addition of hydrogen and the nucleophile to the alkene. The regioselectivity is excellent and is in the same sense as is observed for proton-initiated additions.[17]

11. P. E. Peterson, R. J. Bopp, D. M. Chevli, E. L. Curran, D. E. Dillard, and R. J. Kamat, *J. Am. Chem. Soc.*, **89**, 5902 (1967).
12. H. C. Brown, J. H. Kawakami, and K.-T. Liu, *J. Am. Chem. Soc.*, **92**, 5536 (1970).
13. (a) R. C. Larock, *Angew. Chem. Int. Ed. Engl.*, **17**, 27 (1978); (b) W. Kitching, *Organomet. Chem. Rev.*, **3**, 61 (1968).
14. S. J. Cristol, J. S. Perry, Jr., and R. S. Beckley, *J. Org. Chem.*, **41**, 1912 (1976); D. J. Pasto and J. A. Gontarz, *J. Am. Chem. Soc.*, **93**, 6902 (1971).
15. G. A. Olah and P. R. Clifford, *J. Am. Chem. Soc.*, **95**, 6067 (1973); G. A. Olah and S. H. Yu, *J. Org. Chem.*, **40**, 3638 (1975).
16. W. L. Waters, W. S. Linn, and M. C. Caserio, *J. Am. Chem. Soc.*, **90**, 6741 (1968).
17. H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **35**, 1844 (1970); H. C. Brown, J. T. Kurek, M.-H. Rei, and K. L. Thompson, *J. Org. Chem.*, **49**, 2511 (1984); H. C. Brown, J. T. Kurek, M.-H. Rei, and K. L. Thompson, *J. Org. Chem.*, **50**, 1171 (1985).

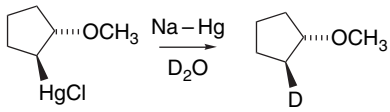
The reductive replacement of mercury using sodium borohydride is a free radical chain reaction involving a mercuric hydride intermediate.[18]

$$RHg^{II}X + NaBH_4 \longrightarrow RHg^{II}H$$
$$In\cdot + RHg^{II}H \longrightarrow In\text{-}H + RHg^{I}$$
$$RHg^{I} \longrightarrow R\cdot + Hg^{0}$$
$$R\cdot + RHg^{II}H \longrightarrow RH + RHg^{I}$$

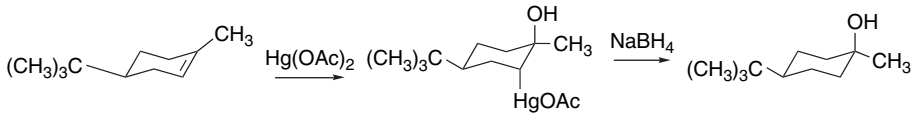
The evidence for the free radical mechanism includes the fact that the course of the reaction can be diverted by oxygen, an efficient radical scavenger. In the presence of oxygen, the mercury is replaced by a hydroxy group. Also consistent with a free radical intermediate is the formation of cyclic products when 5-hexenylmercury compounds are reduced with sodium borohydride.[19] This cyclization reaction is highly characteristic of reactions involving 5-hexenyl radicals (see Part A, Section 11.2.3.3). In the presence of oxygen, no cyclic product is formed, indicating that O_2 traps the radical faster than cyclization occurs.



Tri-*n*-butyltin hydride can also be used for reductive demercuration.[20] An alternative reagent for demercuration is sodium amalgam in a protic solvent. Here the evidence is that free radicals are not involved and the mercury is replaced with retention of configuration.[21]

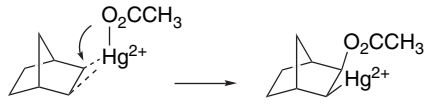


The stereochemistry of oxymercuration has been examined in a number of systems. Conformationally biased cyclic alkenes such as 4-*t*-butylcyclohexene and 4-*t*-butyl-1-methylcyclohexene give exclusively the product of *anti* addition, which is consistent with a mercurinium ion intermediate.[17,22]

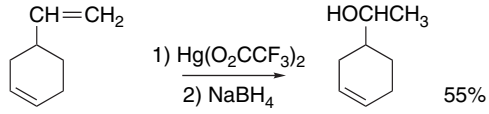


18. C. L. Hill and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 870 (1974).
19. R. P. Quirk and R. E. Lea, *J. Am. Chem. Soc.*, **98**, 5973 (1976).
20. G. M. Whiteside and J. San Fillipo, Jr., *J. Am. Chem. Soc.*, **92**, 6611 (1970).
21. F. R. Jensen, J. J. Miller, S. J. Cristol, and R. S. Beckley, *J. Org. Chem.*, **37**, 434 (1972); R. P. Quirk, *J. Org. Chem.*, **37**, 3554 (1972); W. Kitching, A. R. Atkins, G. Wickham, and V. Alberts, *J. Org. Chem.*, **46**, 563 (1981).
22. H. C. Brown, G. J. Lynch, W. J. Hammar, and L. C. Liu, *J. Org. Chem.*, **44**, 1910 (1979).

Norbornene, in contrast reacts by *syn* addition.[23] This is believed to occur by internal transfer of the nucleophile.

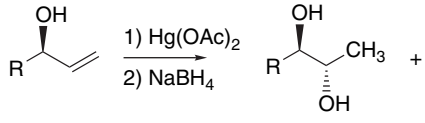


The reactivity of different alkenes toward mercuration spans a considerable range and is governed by a combination of steric and electronic factors.[24] Terminal double bonds are more reactive than internal ones. Disubstituted terminal alkenes, however, are more reactive than monosubstituted cases, as would be expected for electrophilic attack. (See Part A, Table 5.6 for comparative rate data.) The differences in relative reactivities are large enough that selectivity can be achieved with certain dienes.



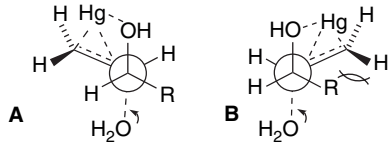
Ref. 24

Diastereoselectivity has been observed in oxymercuration of alkenes having nearby oxygen substituents. Terminal allylic alcohols show a preference for formation of the *anti* 2,3-diols.



R	*anti*	*syn*
Et	76	24
i-Pr	80	20
t-Bu	98	2
Ph	88	12

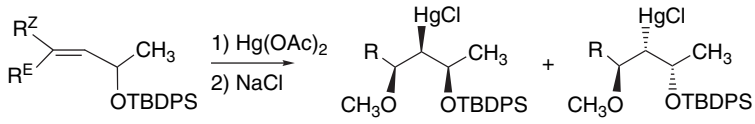
This result can be explained in terms of a steric preference for conformation **A** over **B**. The approach of the mercuric ion is directed by the hydroxy group. The selectivity increases with the size of the substituent R.[25]



The directive effect of allylic silyoxy groups has also been examined. The reactions are completely regioselective for 1,3-oxygen substitution. The reaction of

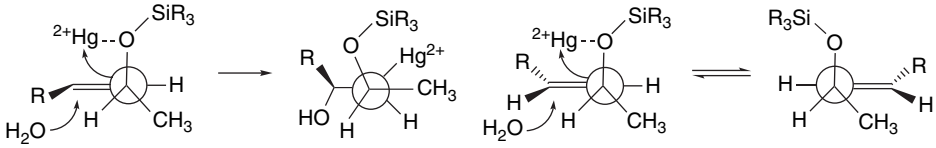
23. T. G. Traylor and A. W. Baker, *J. Am. Chem. Soc.*, **85**, 2746 (1963); H. C. Brown and J. H. Kawakami, *J. Am. Chem. Soc.*, **95**, 8665 (1973).
24. H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **37**, 1937 (1972); H. C. Brown, P. J. Geoghegan, Jr., G. J. Lynch, and J. T. Kurek, *J. Org. Chem.*, **37**, 1941 (1972); H. C. Brown, P. J. Geoghegan, Jr., and J. T. Kurek, *J. Org. Chem.*, **46**, 3810 (1981).
25. B. Giese and D. Bartmann, *Tetrahedron Lett.*, **26**, 1197 (1985).

Z-isomers of 2-pentenyloxy ethers show modest stereoselectivity, but the *E*-ethers show no stereoselectivity.[26] Trisubstituted allylic TBDPS ethers show good stereoselectivity.[27]



R^E	R^Z	*syn*	*anti*
CH_3	H	1	1
H	CH_3	5	1
CH_3	CH_3	20	1

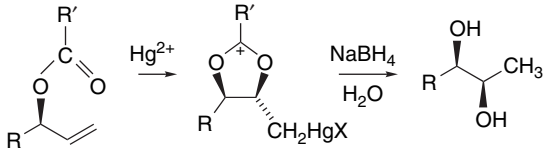
These results are consistent with a directive effect by the silyloxy substituent through the sterically favored conformation of the reactant.



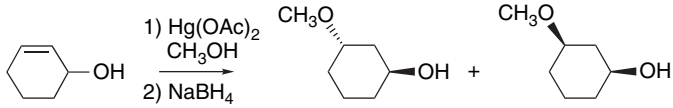
strongly preferred for the *Z*-isomer

no strong conformational preference

With acetoxy derivatives, the 2,3-*syn* isomer is preferred as a result of direct nucleophilic participation by the carbonyl oxygen.



Polar substituents can exert a directing effect. Cyclohexenol, for example, gives high regioselectivity but low stereoselectivity.[28] This indicates that some factor other than hydroxy coordination is involved.

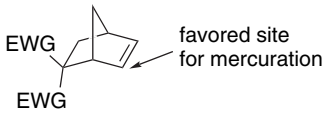


95% 70:30 *trans:cis*

A computational study of remote directing effects was undertaken in substituted norbornenes.[29] It was concluded that polar effects of EWGs favors mercuration at the

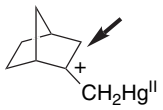
[26] R. Cormick, J. Loefstedt, P. Perlmutter, and G. Westman, *Tetrahedron Lett.*, **38**, 2737 (1997).
[27] R. Cormick, P. Perlmutter, W. Selajarern, and H. Zhang, *Tetrahedron Lett.*, **41**, 3713 (2000).
[28] Y. Senda, S. Takayanagi, T. Sudo, and H. Itoh, *J. Chem. Soc., Perkin Trans. 1*, 270 (2001).
[29] P. Mayo, G. Orlova, J. D. Goddard, and W. Tam, *J. Org. Chem.*, **66**, 5182 (2001).

carbon that is closer to the substituent, which is attributed to a favorable polar effect that stabilizes the negative charge on the mercurated carbon.



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

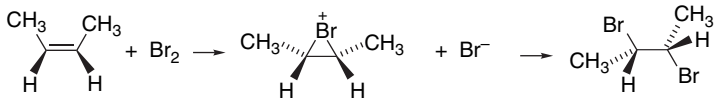
Scheme 4.1 includes examples of oxymercuration reactions. Entries 1 and 2 illustrate the Markovnikov orientation under typical reaction conditions. The high *exo* selectivity in Entry 3 is consistent with steric approach control on a weakly bridged (or open) mercurinium ion. There is no rearrangement, indicating that the intermediate is a localized cation.



Entries 4 and 5 involve formation of ethers using alcohols as solvents, whereas the reaction in Entry 6 forms an amide in acetonitrile. Entries 7 and 8 show use of other nucleophiles to capture the mercurinium ion.

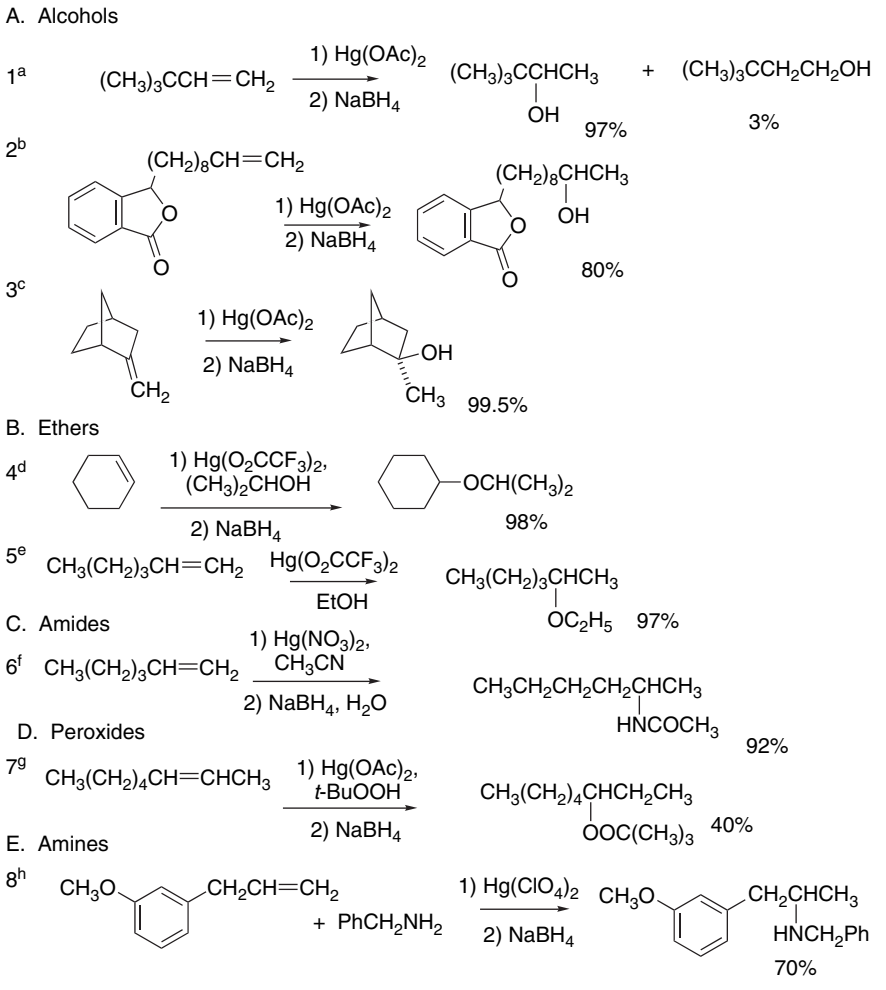
4.1.4. Addition of Halogens to Alkenes

The addition of chlorine or bromine to an alkene is a very general reaction. Section 6.3 of Part A provides a discussion of the reaction mechanism. Bromination of simple alkenes is extremely fast. Some specific rate data are tabulated and discussed in Section 6.3 of Part A. As halogenation involves electrophilic attack, substituents on the double bond that increase electron density increase the rate of reaction, whereas EWG substituents have the opposite effect. Considerable insight into the mechanism of halogen addition has come from studies of the stereochemistry of the reaction. Most simple alkenes add bromine in a stereospecific manner, giving the product of *anti* addition. Among the alkenes that give *anti* addition products are *Z*-2-butene, *E*-2-butene, maleic and fumaric acid, and a number of cycloalkenes.[30] Cyclic, positively charged bromonium ion intermediates provide an explanation for the observed *anti* stereospecificity.



[30] J. H. Rolston and K. Yates, *J. Am. Chem. Soc.*, **91**, 1469, 1477 (1969).

Scheme 4.1. Addition via Mercuration Reactions

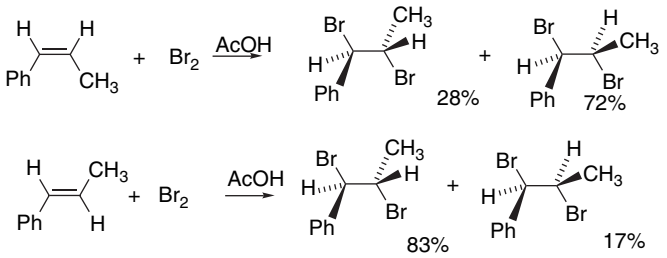


a. H. C. Brown and P. J. Geoghegan, Jr., *J. Org. Chem.*, **35**, 1844 (1970).
b. H. L. Wehrmeister and D. E. Robertson, *J. Org. Chem.*, **33**, 4173 (1968).
c. H. C. Brown and W. J. Hammar, *J. Am. Chem. Soc.*, **89**, 1524 (1967).
d. H. C. Brown and M.-H. Rei, *J. Am. Chem. Soc.*, **91**, 5646 (1969).
e. H. C. Brown, J. T. Kurek, M.-H. Rei, and K. L. Thompson, *J. Org. Chem.*, **50**, 1171 (1985).
f. H. C. Brown and J. T. Kurek, *J. Am. Chem. Soc.*, **91**, 5647 (1969).
g. D. H. Ballard and A. J. Bloodworth, *J. Chem. Soc. C*, 945 (1971).
h. R. C. Griffith, R. J. Gentile, T. A. Davidson, and F. L. Scott, *J. Org. Chem.*, **44**, 3580 (1979).

The bridging by bromine prevents rotation about the remaining bond and back-side nucleophilic opening of the bromonium ion by bromide ion leads to the observed *anti* addition. Direct evidence for the existence of bromonium ions has been obtained from NMR measurements.[31] A bromonium ion salt (with Br_3^- as the counterion) has been isolated from the reaction of bromine with the very hindered alkene adamantylideneadamantane.[32]

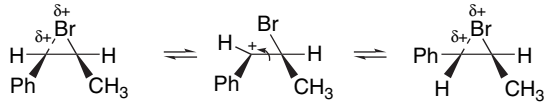
31. G. A. Olah, J. M. Bollinger, and J. Brinich, *J. Am. Chem. Soc.*, **90**, 2587 (1968); G. A. Olah, P. Schilling, P. W. Westerman, and H. C. Lin, *J. Am. Chem. Soc.*, **96**, 3581 (1974).
32. J. Strating, J. H. Wierenga, and H. Wynberg, *J. Chem. Soc., Chem. Commun.*, 907 (1969).

A substantial amount of *syn* addition is observed for *Z*-1-phenylpropene (27–80% *syn* addition), *E*-1-phenylpropene (17–29% *syn* addition), and *cis*-stilbene (up to 90% *syn* addition in polar solvents).



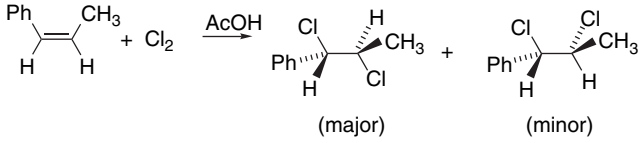
Ref. 30

A common feature of the compounds that give extensive *syn* addition is the presence of a phenyl substituent on the double bond. The presence of a phenyl substituent diminishes the strength of bromine bridging by stabilizing the cationic center. A weakly bridged structure in equilibrium with an open benzylic cation can account for the loss in stereospecificity.



The diminished stereospecificity is similar to that noted for hydrogen halide addition to phenyl-substituted alkenes.

Although chlorination of aliphatic alkenes usually gives *anti* addition, *syn* addition is often dominant for phenyl-substituted alkenes.[33]

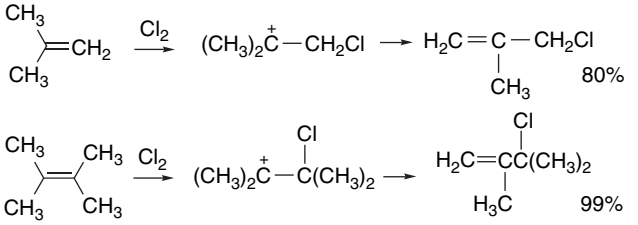


These results, too, reflect a difference in the extent of bridging in the intermediates. With unconjugated alkenes, there is strong bridging and high *anti* stereospecificity. Phenyl substitution leads to cationic character at the benzylic site, and there is more *syn* addition. Because of its smaller size and lesser polarizability, chlorine is not as effective as bromine in bridging for any particular alkene. Bromination therefore generally gives a higher degree of *anti* addition than chlorination, all other factors being the same.[34]

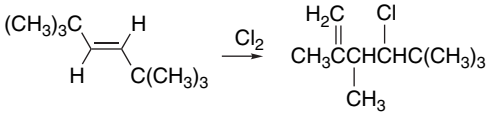
33. M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 2161, 2172 (1965); R. C. Fahey, *J. Am. Chem. Soc.*, **88**, 4681 (1966); R. C. Fahey and C. Shubert, *J. Am. Chem. Soc.*, **87**, 5172 (1965).

34. R. J. Abraham and J. R. Monasterios, *J. Chem. Soc., Perkin Trans. 1*, 1446 (1973).

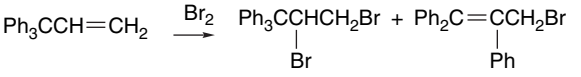
Chlorination can be accompanied by other reactions that are indicative of carbocation intermediates. Branched alkenes can give products that are the result of elimination of a proton from a cationic intermediate.[35]



Skeletal rearrangements are observed in systems that are prone toward migration.

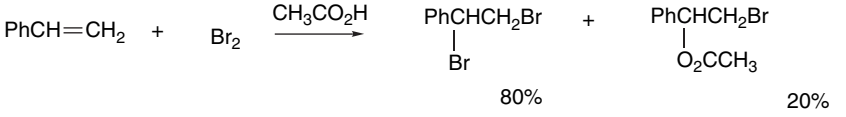


Ref. 35



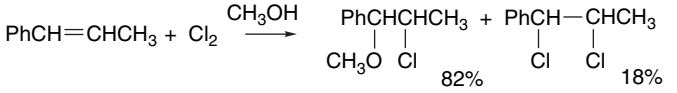
Ref. 36

Nucleophilic solvents can compete with halide ion for the cationic intermediate. For example, the bromination of styrene in acetic acid leads to significant amounts of the acetoxybromo derivative.



Ref. 30

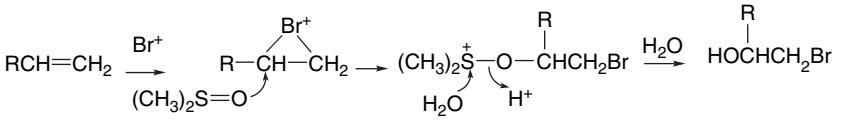
The acetoxy group is introduced exclusively at the benzylic carbon. This is in accord with the intermediate being a weakly bridged species or a benzylic cation. The addition of bromide salts to the reaction mixture diminishes the amount of acetoxy compound formed by shifting the competition for the electrophile in favor of the bromide ion. Chlorination in nucleophilic solvents can also lead to solvent incorporation, as, for example, in the chlorination of 1-phenylpropene in methanol.[37]



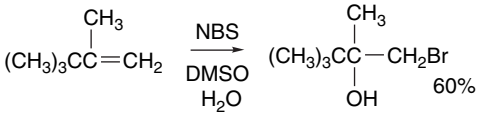
From a synthetic point of view, the participation of water in brominations, leading to bromohydrins, is the most important example of nucleophilic capture of the intermediate by solvent. To favor introduction of water, it is desirable to keep the concentration

35. M. L. Poutsma, *J. Am. Chem. Soc.*, **87**, 4285 (1965).
36. R. O. C. Norman and C. B. Thomas, *J. Chem. Soc. B*, 598 (1967).
37. M. L. Poutsma and J. L. Kartch, *J. Am. Chem. Soc.*, **89**, 6595 (1967).

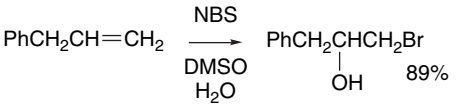
of the bromide ion as low as possible. One method for accomplishing this is to use *N*-bromosuccinimide (NBS) as the brominating reagent.[38,39] High yields of bromohydrins are obtained by using NBS in aqueous DMSO. The reaction is a stereospecific *anti* addition. As in bromination, a bromonium ion intermediate can explain the *anti* stereospecificity. It has been shown that the reactions in DMSO involve nucleophilic attack by the sulfoxide oxygen. The resulting alkoxysulfonium ion intermediate reacts with water to give the bromohydrin.



In accord with the Markovnikov rule, the hydroxy group is introduced at the carbon best able to support positive charge.

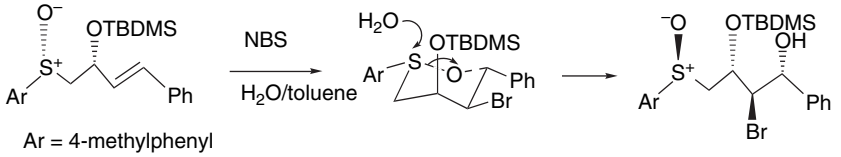


Ref. 40



Ref. 41

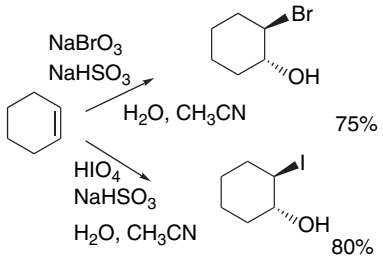
The participation of sulfoxy groups can be used to control the stereochemistry in acyclic systems. In the reaction shown below, the internal sulfoxide captures the bromonium ion and then undergoes inversion at sulfur in the hydrolytic step.



Ref. 42

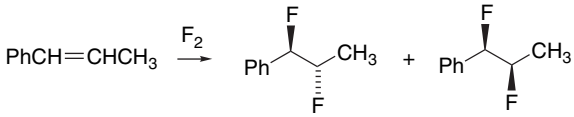
A procedure that is useful for the preparation of both bromohydrins and iodohydrins involves in situ generation of the hypohalous acid from $NaBrO_3$ or $NaIO_4$ by reduction with bisulfite.[43]

38. A. J. Sisti and M. Meyers, *J. Org. Chem.*, **38**, 4431 (1973).
39. C. O. Guss and R. Rosenthal, *J. Am. Chem. Soc.*, **77**, 2549 (1965).
40. D. R. Dalton, V. P. Dutta, and D. C. Jones, *J. Am. Chem. Soc.*, **90**, 5498 (1968).
41. A. W. Langman and D. R. Dalton, *Org. Synth.*, **59**, 16 (1979).
42. S. Raghavan and M. A. Rasheed, *Tetrahedron*, **59**, 10307 (2003).
43. H. Masuda, K. Takase, M. Nishio, A. Hasegawa, Y. Nishiyama, and Y. Ishii, *J. Org. Chem.*, **59**, 5550 (1994).

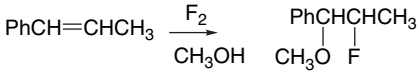


These reactions show the same regioselectivity and stereoselectivity as other reactions that proceed through halonium ion intermediates.

Because of its high reactivity, special precautions must be taken with reactions of fluorine and its use is somewhat specialized.[44] Nevertheless, there is some basis for comparison with the less reactive halogens. Addition of fluorine to *Z*- and *E*-1-propenylbenzene is not stereospecific, but *syn* addition is somewhat favored.[45] This result is consistent with formation of a cationic intermediate.

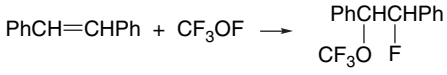


In methanol, the solvent incorporation product is formed, as would be expected for a cationic intermediate.

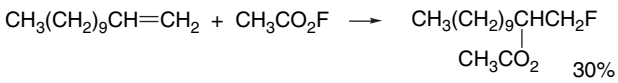


These results are consistent with the expectation that fluorine would not be an effective bridging atom.

There are other reagents, such as CF_3OF and CH_3CO_2F, that transfer an electrophilic fluorine to double bonds. These reactions probably involve an ion pair that collapses to an addition product.



Ref. 46

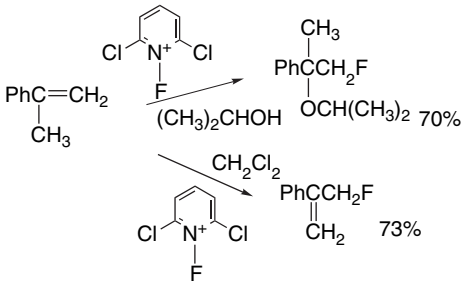


Ref. 47

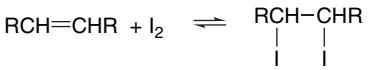
The stability of hypofluorites is improved in derivatives having electron-withdrawing substituents, such as 2,2-dichloropropanoyl hypofluorite.[48] Various other fluorinating agents have been developed and used, including *N*-fluoropyridinium salts such as the

44. H. Vypel, *Chimia*, **39**, 305 (1985).
45. R. F. Merritt, *J. Am. Chem. Soc.*, **89**, 609 (1967).
46. D. H. R. Barton, R. H. Hesse, G. P. Jackman, L. Ogunkoya, and M. M. Pechet, *J. Chem. Soc., Perkin Trans. 1*, 739 (1974).
47. S. Rozen, O. Lerman, M. Kol, and D. Hebel, *J. Org. Chem.*, **50**, 4753 (1985).
48. S. Rozen and D. Hebel, *J. Org. Chem.*, **55**, 2621 (1990).

triflate[49] and heptafluorodiborate.[50] The reactivity of these reagents can be "tuned" by varying the pyridine ring substituents. In contrast to the hypofluorites, these reagents are storable.[51] In nucleophilic solvents such as acetic acid or alcohols, the reagents give addition products, whereas in nonnucleophilic solvents, alkenes give substitution products resulting from deprotonation of a carbocation intermediate.

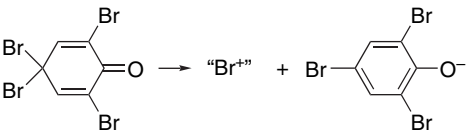


Addition of iodine to alkenes can be accomplished by a photochemically initiated reaction. Elimination of iodine is catalyzed by excess iodine, but the diiodo compounds can be obtained if unreacted iodine is removed.[52]



The diiodo compounds are very sensitive to light and are seldom used in syntheses.

The elemental halogens are not the only sources of electrophilic halogen, and for some synthetic purposes other "positive halogen" compounds may be preferable as electrophiles. The utility of *N*-bromosuccinimide in formation of bromohydrins was mentioned earlier. Both *N*-chlorosuccinimide and *N*-bromosuccinimide transfer electrophilic halogen with the succinimide anion acting as the leaving group. As this anion is subsequently protonated to give the weak nucleophile succinimide, these reagents favor nucleophilic additions by solvent and cyclization reactions because there is no competition from a halide anion. Other compounds that are useful for specific purposes are indicated in Table 4.2. Pyridinium hydrotribromide (pyridinium hydrobromide perbromide), benzyltrimethyl ammonium tribromide, and dioxane-bromine are examples of complexes of bromine in which its reactivity is somewhat attenuated, resulting in increased selectivity. In 2,4,4,6-tetrabromocyclohexadienone is a very mild and selective source of electrophilic bromine; the leaving group is 2,4,6-tribromophenoxide ion.



[49] T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, and K. Tomita, *J. Am. Chem. Soc.*, **112**, 8563 (1990).

[50] A. J. Poss. M. Van Der Puy, D. Nalewajek, G. A. Shia, W. J. Wagner, and R. L. Frenette, *J. Org. Chem.*, **56**, 5962 (1991).

[51] T. Umemoto, K. Tomita, and K. Kawada, *Org. Synth.*, **69**, 129 (1990).

[52] P. S. Skell and R. R. Pavlis, *J. Am. Chem. Soc.*, **86**, 2956 (1964); R. L. Ayres, C. J. Michejda, and E. P. Rack, *J. Am. Chem. Soc.*, **93**, 1389 (1971).

Table 4.2. Other Sources of Electrophilic Halogen

Reagents	Synthetic applications[a]
A. Chlorinating agents	
Sodium hypochlorite solution	Formation of chlorohydrins from alkenes
N-Chlorosuccinimide	Chlorination with solvent participation and cyclization
Chloramine-T[b]	Formation of chlorohydrins in acidic aqueous solution.
B. Brominating agents	
Pyridinium hydrotribromide (pyidinium hydrobromide perbromide)	Mild and selective substitute for bromine
Dioxane bromine complex	Same as for pyridinium hydrotribromide
N-Bromosuccinimide	Used in place of bromine when low bromide concentration is required.
2,4,4,6-Tetrabromocyclohexadienone[c]	Selective bromination of alkenes and carbonyl compounds
Quaternary ammonium tribromides[d]	Similar to pyridinium hydrotribromide
C. Iodinating agents	
bis-(Pyridinium)iodonium[e] tetrafluoroborate	Selective iodination and iodocyclization.

a. For specific examples, consult M. Fieser and L. F. Fieser, *Reagents for Organic Synthesis*, John Wiley & Sons, New York.
b. B. Damin, J. Garapon, and B. Sillion, *Synthesis*, 362 (1981).
c. F. Calo, F. Ciminale, L. Lopez, and P. E. Todesco, *J. Chem. Soc., C*, 3652 (1971) ;Y. Kitahara, T. Kato, and I. Ichinose, *Chem. Lett.*, 283 (1976)
d. S. Kaigaeshi and T. Kakinami, *Ind. Chem. Libr.*, **7**, 29 (1985); G. Bellucci, C. Chiappe, and F. Marioni, *J. Am. Chem. Soc.*, **109**, 515 (1987).
e. J. Barluenga, J. M. Gonzalez, M. A. Garcia-Martin, P. J. Campos, and G. Asensio, *J. Org. Chem.*, **58**, 2058 (1993).

Electrophilic iodine reagents are extensively employed in iodocyclization (see Section 4.2.1). Several salts of pyridine complexes with I^+ such as *bis*-(pyridinium)iodonium tetrafluoroborate and *bis*-(collidine)iodonium hexafluorophosphate have proven especially effective.[53]

4.1.5. Addition of Other Electrophilic Reagents

Many other halogen-containing compounds react with alkenes to give addition products by mechanisms similar to halogenation. A complex is generated and the halogen is transferred to the alkene to generate a bridged cationic intermediate. This may be a symmetrical halonium ion or an unsymmetrically bridged species, depending on the ability of the reacting carbon atoms to accommodate positive charge. The direction of opening of the bridged intermediate is usually governed by electronic factors. That is, the addition is completed by attack of the nucleophile at the more positive carbon atom of the bridged intermediate. The regiochemistry of addition therefore follows Markovnikov's rule. The stereochemistry of addition is usually *anti*, because of the involvement of a bridged halonium intermediate.[54] Several reagents of this type are listed in Entries 1 to 6 of Scheme 4.2. The nucleophilic anions include isocyanate, azide, thiocyanate, and nitrate.

Entries 7 to 9 involve other reagents that react by similar mechanisms. In the case of thiocyanogen chloride and thiocyanogen, the formal electrophile is $[NCS]^+$. The presumed intermediate is a cyanothiairanium ion. The thiocyanate anion is an

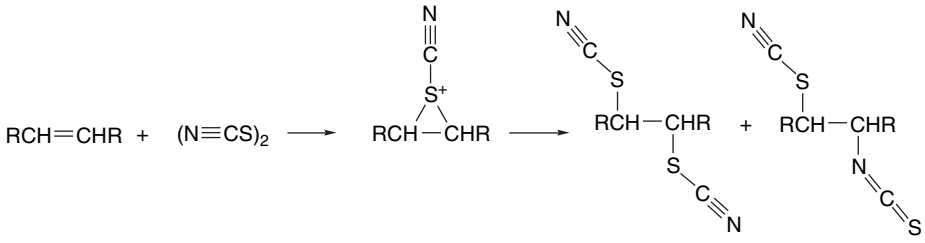
53. Y. Brunel and G. Rousseau, *J. Org. Chem.*, **61**, 5793 (1996).
54. A. Hassner and C. Heathcock, *J. Org. Chem.*, **30**, 1748 (1965).

Scheme 4.2. Addition Reactions of Other Electrophilic Reagents

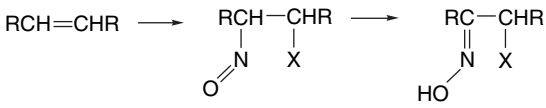
	Reagent	Preparation	Poduct
1[a]	$I-N=C=O$	$AgCNO, I_2$	RCH(I)–CHR(NCO)
2[b]	$Br-N=\overset{+}{N}=N^-$	HN_3, Br_2	RCH(Br)–CHR(N_3)
3[c]	$I-N=\overset{+}{N}=N^-$	NaN_3, ICl	RCH(I)–CHR(N_3)
4[d]	$I-S=C\equiv N$	$(NCS)_2, I_2$	RCH(I)–CHR(S–C≡N)
5[e]	$I-ONO_2$	$AgNO_3$, ICl	RCH(I)–CHR(ONO_2)
6[f]	$Cl-SCN$	$Pb(SCN)_2, Cl_2$	RCH(Cl)–CHR(SCN)
7[g]	$N\equiv CS-SC\equiv N$	$Pb(SCN)_2, Br_2$	RCH(N≡CS)–CHR(SC≡N) and RCH(N≡CS)–CHR(N=C=S)
8[h]	$O=N-Cl$		RC(HON)=CHR(Cl)
9[i]	$O=N-O_2CH$	$C_5H_{11}ONO$ HCO_2H	RC(HON)=CHR(O_2CH)

a. A. Hassner, R. P. Hoblitt, C. Heathcock, J. E. Kropp, and M. Lorber, *J. Am. Chem. Soc.*, **92**, 1326 (1970); A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967).
b. A. Hassner, F. P. Boerwinkle, and A. B. Levy, *J. Am. Chem. Soc.*, **92**, 4879 (1970).
c. F. W. Fowler, A. Hassner, and L. A. Levy, *J. Am. Chem. Soc.*, **89**, 2077 (1967).
d. R. J. Maxwell and L. S. Silbert, *Tetrahedron Lett.*, 4991 (1978).
e. J. W. Lown and A. V. Joshua, *J. Chem. Soc., Perkin Trans. 1*, 2680 (1973).
f. R. G. Guy and I. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 281 (1973); *J. Chem. Soc., Perkin Trans. 2*, 1359 (1973).
g. R. Bonnett, R. G. Guy, and D. Lanigan, *Tetrahedron*, **32**, 2439 (1976); R. J. Maxwell, L. S. Silbert, and J. R. Russell, *J. Org. Chem.*, **42**, 1510 (1977).
h. J. Meinwald, Y. C. Meinwald, and T. N. Baker, III, *J. Am. Chem. Soc.*, **86**, 4074 (1964).
i. H. C. Hamann and D. Swern, *J. Am. Chem. Soc.*, **90**, 6481 (1968).

ambident nucleophile and both carbon-sulfur and carbon-nitrogen bond formation can be observed, depending upon the reaction conditions (see Entry 7 in Scheme 4.2).

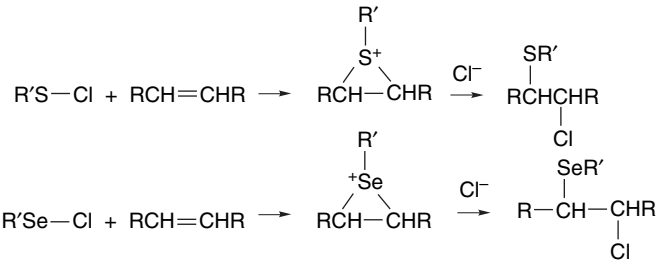


For nitrosyl chloride (Entry 8) and nitrosyl formate (Entry 9), the electrophile is the nitrosonium ion NO^+. The initially formed nitroso compounds can dimerize or isomerize to the more stable oximes.



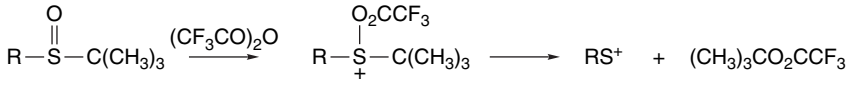
4.1.6. Addition Reactions with Electrophilic Sulfur and Selenium Reagents

Compounds having divalent sulfur and selenium atoms bound to more electronegative elements react with alkenes to give addition products. The mechanism is similar to that in halogenation and involves of bridged cationic intermediates.



In many synthetic applications, the sulfur or selenium substituent is subsequently removed by elimination, as is discussed in Chapter 6.

A variety of electrophilic reagents have been employed and several examples are given in Scheme 4.3. The sulfenylation reagents are listed in Section A. Both aryl and alkyl sulfenyl chlorides are reactive (Entries 1 and 2). Dimethyl(methylthio)sulfonium fluoroborate (Entry 3) uses dimethyl sulfide as a leaving group and can be utilized to effect capture of hydroxylic solvents and anionic nucleophiles, such as acetate and cyanide. Entries 4 and 5 are examples of *sulfenamides*, which normally require a Lewis acid catalyst to react with alkenes. Entry 6 represents application of the *Pummerer rearrangement* for in situ generation of a sulfenylation reagent. Sulfoxides react with acid anhydrides to generate sulfonium salts. When a *t*-alkyl group is present, fragmentation occurs and a sulfenylium ion is generated.[55] TFAA is the preferred anhydride in this application.



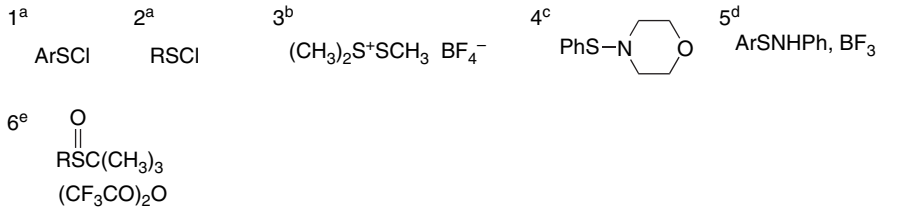
The selenylation reagents include the arylselenenyl chlorides and bromides (Entries 7 and 8), selenylium salts with nonnucleophilic counterions (Entry 9), and selenenyl trifluoroacetates, sulfates, and sulfonates (Entries 10 to 13). Diphenyldiselenide reacts with several oxidation reagents to transfer electrophilic phenylselenenylium ions (Entries 14 to 16). *N*-Phenylselenenylphthalimide is a useful synthetic reagent that has the advantage of the nonnucleophilicity of the phthalimido leaving group (Entry 18). The hindered selenenyl bromide in Entry 19 is useful for selenylcyclizations (see Section 4.2.2).

Selenylation can also be done under conditions in which another nucleophilic component of the reaction captures the selenium-bridged ion. For

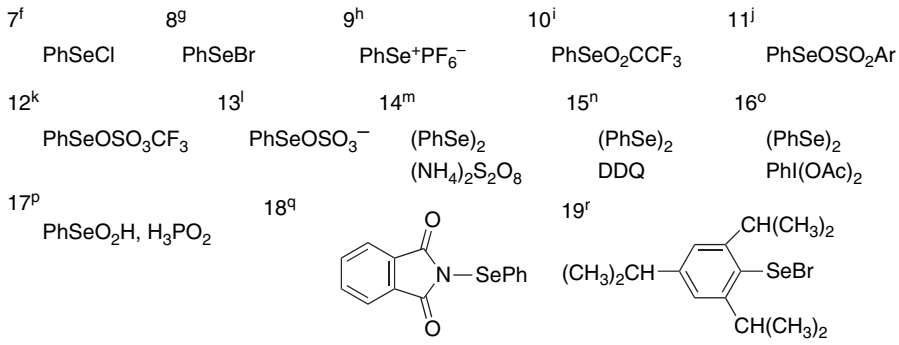
[55] M.-H. Brichard, M. Musick, Z. Janousek, and H. G. Viehe, *Synth. Commun.*, **20**, 2379 (1990).

Scheme 4.3. Sulfur and Selenium Reagents for Electrophilic Addition Reactions

A. Sulfenylation reagents

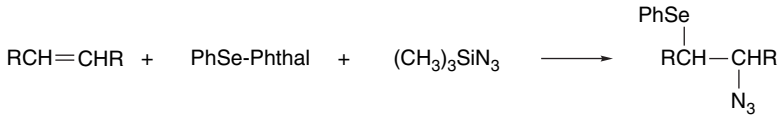


B. Selenenylation reagents



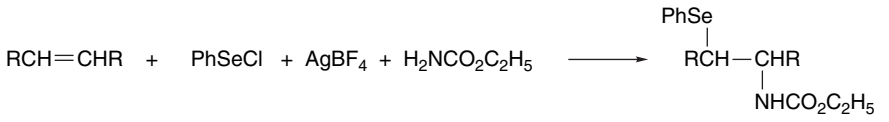
a. G. Capozzi, G. Modena, and L. Pasquato in *The Chemistry of Sulphenic Acids and Their Derivatives*, S. Patai, ed., Wiley, Chichester, 1990, Chap. 10.
b. B. M. Trost, T. Shibata, and S. J. Martin, *J. Am. Chem. Soc.*, **104**, 3228 (1982).
c. P. Brownbridge, *Tetrahedron Lett.*, **25**, 3759 (1984); P. Brownbridge, *J. Chem. Soc. Chem. Commun.*, 1280 (1987); N. S. Zefirov, N. V. Zyk, A. G. Kutateldze, and S. I. Kolbasenko, *Zh. Org. Khim.*, **23**, 227 (1987).
d. L. Benati, P. C. Montevecchi, and P. Spagnolo, *J. Chem. Soc., Perkin Trans. 1*, 1691 (1990).
e. M.-H. Brichard, M. Musick, Z. Janousek, and H. G. Viehe, *Synth. Commun.*, **20**, 2378 (1990).
f. K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **39**, 429 (1974).
g. T. G. Back, *The Chemistry of Organic Selenium and Tellurium Compounds*, S. Patai, ed., Wiley, 1987, pp. 91–312.
h. W. P. Jackson, S. V. Ley, and A. J. Whittle, *J. Chem. Soc.* 1173 (1980).
i. H. J. Reich, *J. Org. Chem.*, **39**, 428 (1974).
j. T. G. Back and K. R. Muralidharan, *J. Org. Chem.* **56**, 2781 (1991).
k. S. Murata and T. Suzuki, *Tetrahedron Lett.*, **28**, 4297, 4415 (1987).
l. M. Tiecco, L. Testaferri, M. Tingoli, L. Bagnoli, and F. Marini, *J. Chem. Soc., Perkin Trans. 1*, 1989 (1993).
m. M. Tiecco, L. Testaferri, M. Tingoli, D. Chianelli, and D. Bartoli, *Tetrahedron Lett.*, **30**, 1417 (1989).
n. M. Tiecco, L. Testaferri, A. Temperinik, L. Bagnoli, F. Marini, and C. Santi, *Synlett*, 1767 (2001).
o. M. Tingoli, M. Tiecco, L. Testaferri, and Temperini, *Synth. Commun.*, **28**, 1769 (1998).
p. D. Labar, A. Krief, and L. Hevesi, *Tetrahedron Lett.*, 3967 (1978).
q. K. C. Nicolaou, N. A. Petasis, and D. A. Claremon, *Tetrahedron*, **41**, 4835 (1985).
r. B. H. Lipshutz and T. Gross, *J. Org. Chem.*, **60**, 3572 (1995).

example, the combination phenylselenylphthalimide and trimethylsilyl azide generates β-azido selenides and phenylselenyl chloride used with $AgBF_4$ and ethyl carbamate give β-carbamido selenides.



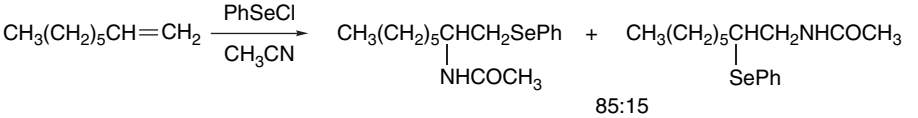
Ref. 56

56. A. Hassner and A. S. Amarasekara, *Tetrahedron Lett.*, **28**, 5185 (1987); R. M. Giuliano and F. Duarte, *Synlett*, 419 (1992).



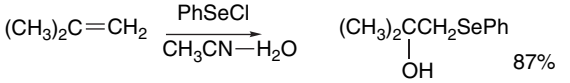
Ref. 57

In the absence of better nucleophiles, solvent can be captured, as in selenenylamidation, which occurs in acetonitrile.

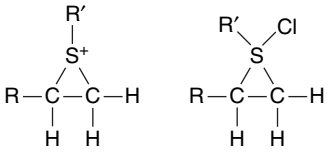


Ref. 58

When reactions with phenylselenenyl chloride are carried out in aqueous acetonitrile solution, β-hydroxyselenides are formed as the result of solvolysis of the chloride.[59]

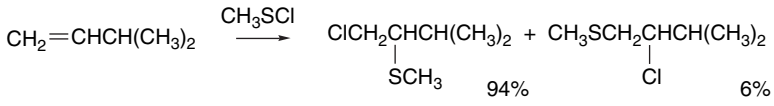


Mechanistic studies have been most thorough with the sulfenyl halides.[60] The reactions show moderate sensitivity to alkene structure, with ERGs on the alkene accelerating the reaction. The addition can occur in either the Markovnikov or anti-Markovnikov sense.[61] The variation in regioselectivity can be understood by focusing attention on the sulfur-bridged intermediate, which may range from being a sulfonium ion to a less electrophilic chlorosulfurane.

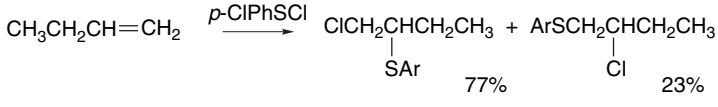


Compared to a bromonium ion, the C−S bonds are stronger and the TS for nucleophilic addition is reached later. This is especially true for the sulfurane structures. Steric interactions that influence access by the nucleophile are a more important factor in determining the direction of addition. For reactions involving phenylsulfenyl chloride or methylsulfenyl chloride, the intermediate is a fairly stable species and ease of approach by the nucleophile is the major factor in determining the direction of ring opening. In these cases, the product has the anti-Markovnikov orientation.[62]

57. C. G. Francisco, E. I. Leon, J. A. Salazar, and E. Suarez, *Tetrahedron Lett.*, **27**, 2513 (1986).
58. A. Toshimitsu, T. Aoai, H. Owada, S. Uemura, and M. Okano, *J. Org. Chem.*, **46**, 4727 (1981).
59. A. Toshimitsu, T. Aoai, H. Owada, S. Uemura, and M. Okano, *Tetrahedron*, **41**, 5301 (1985).
60. W. A. Smit, N. S. Zefirov, I. V. Bodrikov, and M. Z. Krimer, *Acc. Chem. Res.*, **12**, 282 (1979); G. H. Schmid and D. G. Garratt, *The Chemistry of Double-Bonded Functional Groups*, S. Patai, ed., Wiley-Interscience, New York, 1977, Chap. 9; G. A. Jones, C. J. M. Stirling, and N. G. Bromby, *J. Chem. Soc., Perkin Trans.*, **2**, 385 (1983).
61. W. H. Mueller and P. E. Butler, *J. Am. Chem. Soc.*, **90**, 2075 (1968); G. H. Schmid and D. I . Macdonald, *Tetrahedron Lett.*, **25**, 157 (1984).
62. G. H. Schmid, M. Strukelj, S. Dalipi, and M. D. Ryan, *J. Org. Chem.*, **52**, 2403 (1987).

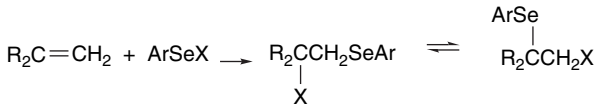


Ref. 61a



Ref. 63

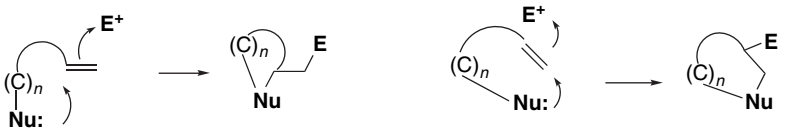
Terminal alkenes react with selenenyl halides with Markovnikov regioselectivity.[64] However, the β-selenyl halide addition products readily rearrange to the isomeric products.[65]



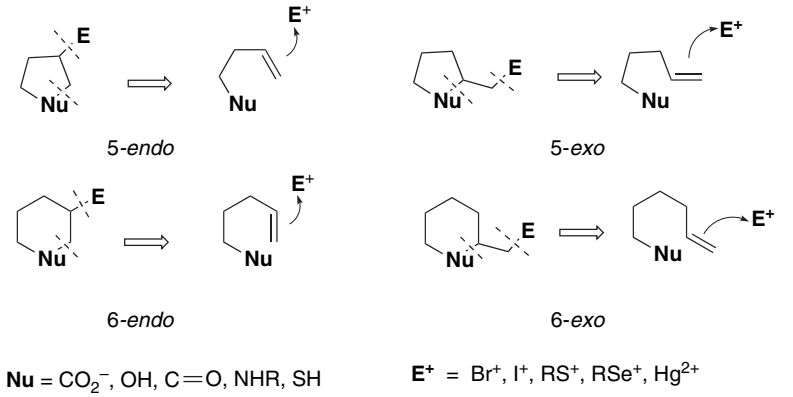
4.2. Electrophilic Cyclization

When unsaturated reactants contain substituents that can participate as nucleophiles, electrophilic reagents frequently bring about cyclizations. Groups that can act as internal nucleophiles include carboxy and carboxylate, hydroxy, amino and amido, as well as carbonyl oxygen. There have been numerous examples of synthetic application of these electrophilic cyclizations.[66] The ring-size preference is usually $5 > 6 > 3 > 4$, but there are exceptions. Both the ring-size preference and the stereoselectivity reactions can usually be traced to structural and conformational features of the cyclization TS. Baldwin called attention to the role of stereoelectronic factors in cyclization reactions.[67] He classified cyclization reactions as *exo* and *endo* and as *tet*, *trig*, and *dig*, according to the hybridization at the cyclization center. The cyclizations are also designated by the size of the ring being formed. For any given separation ($n = 1, 2, 3$, etc.) of the electrophilic and nucleophilic centers, either an *exo* or *endo* mode of cyclization is usually preferred. The preferences for cyclization at trigonal centers are 5-*endo* >> 4-*exo* for $n = 2$; 5-*exo* > 6-*endo* for $n = 3$; and 6-*exo* >> 7-*endo* for $n = 4$. These relationships are determined by the preferred trajectory of the nucleophile to the electrophilic center. Substituents can affect the TS structure by establishing a preferred conformation and by electronic or steric effects.

63. G. H. Schmid, C. L. Dean, and D. G. Garratt, *Can. J. Chem.*, **54**, 1253 (1976).
64. D. Liotta and G. Zima, *Tetrahedron Lett.*, 4977 (1978); P. T. Ho and R. J. Holt, *Can. J. Chem.*, **60**, 663 (1982).
65. S. Raucher, *J. Org. Chem.*, **42**, 2950 (1977).
66. M. Frederickson and R. Grigg, *Org. Prep. Proced. Int.*, **29**, 63 (1997).
67. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734, 738 (1976).



Electrophilic cyclizations are useful for closure of a variety of oxygen-, nitrogen-, and sulfur-containing rings. The product structure depends on the ring size and the *exo-endo* selectivity. The most common cases are formation of five- and six-membered rings.



4.2.1. Halocyclization

Brominating and iodinating reagents effect cyclization of alkenes that have a nucleophilic group situated to permit formation of five-, six-, and, in some cases, seven-membered rings. Hydroxy and carboxylate groups are the most common nucleophiles, but the reaction is feasible for any nucleophilic group that is compatible with the electrophilic halogen source. Amides and carbamates can react at either oxygen or nitrogen, depending on the relative proximity. Sulfonamides are also potential nitrogen nucleophiles. Carbonyl oxygens can act as nucleophiles and give stable products by α-deprotonation.

Intramolecular reactions usually dominate intermolecular addition for favorable ring sizes. Semiempirical (AM1) calculations found the intramolecular TS favorable to a comparable intermolecular reaction.[68] (See Figure 4.1) The intramolecular TS, which is nearly 4 kcal/mol more stable, is quite productlike with a C−O bond distance of 1.6 Å, and a bond order of 0.62. The bromonium ion bridging is unsymmetrical and fairly weak. The bond parameters for the intra- and intermolecular TSs are quite similar.

In general, cyclization can be expected in compounds having the potential for formation of five- or six-membered rings. In addition to the more typical bromination reagents, such as those listed in Table 4.2, the combination of trimethylsilyl bromide, a tertiary amine, and DMSO can effect bromolactonization.

[68] J. Sperka and D. C. Liotta, *Heterocycles*, **35**, 701 (1993).

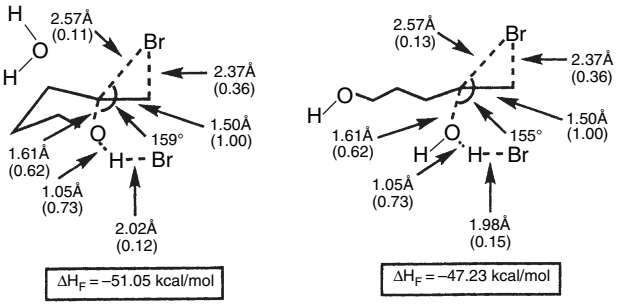
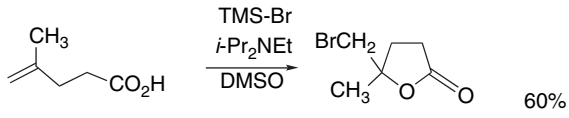
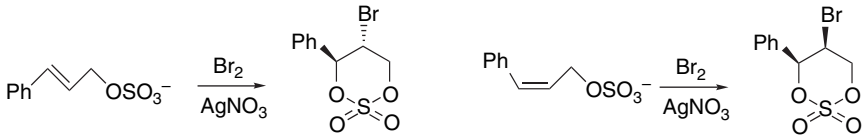


Fig. 4.1. Comparison of intramolecular and intermolecular transition structures for reaction of Br^+, H_2O and 4-penten-1-ol. The numbers in parentheses are bond orders. From *Heterocycles*, **35**, 701 (1993)



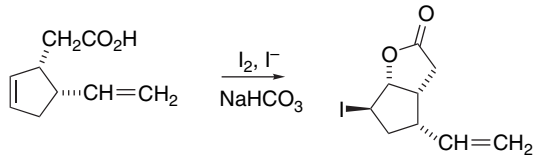
Ref. 69

3-Phenylprop-2-enyl sulfates are cyclized stereospecifically and with Markovnikov regiochemical control. These are 6-*endo* cyclizations.



Ref. 70

Iodine is a very good electrophile for effecting intramolecular nucleophilic addition to alkenes, as exemplified by the *iodolactonization reaction*.[71] Reaction of iodine with carboxylic acids having carbon-carbon double bonds placed to permit intramolecular reaction results in formation of iodolactones. The reaction shows a preference for formation of five- over six-membered[72] rings and is a stereospecific *anti* addition when carried out under basic conditions.



Ref. 73

[69] R. Iwata, A. Tanaka, H. Mizuno, and K. Miyashita, *Hetereocycles*, **31**, 987 (1990).

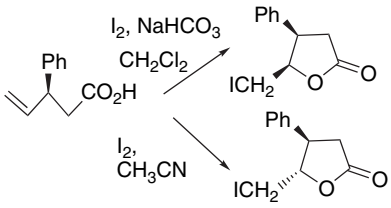
[70] J. G. Steinmann, J. H. Phillips, W. J. Sanders, and L. L. Kiessling, *Org. Lett.*, **3**, 3557 (2001).

[71] M. D. Dowle and D. I. Davies, *Chem. Soc. Rev.*, **8**, 171 (1979); G. Cardillo and M. Orena, *Tetrahedron*, **46**, 3321 (1990); S. Robin and G. Rousseau, *Tetrahedron*, **54**, 13681 (1998); S. Ranganathan, K. M. Muraleedharan, N. K. Vaish, and N. Jayaraman, *Tetrahedron*, **60**, 5273 (2004).

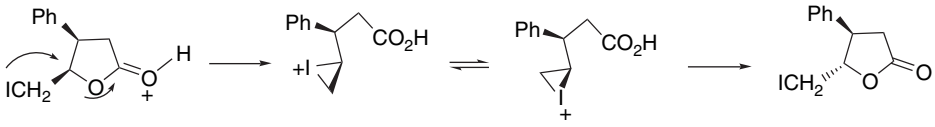
[72] S. Ranganathan, D. Ranganathan, and A. K. Mehrota, *Tetrahedron*, **33**, 807 (1977); C. V. Ramana, K. R. Reddy, and M. Nagarajan, *Ind. J. Chem. B*, **35**, 534 (1996).

[73] L. A. Paquette, G. D. Crouse, and A. K. Sharma, *J. Am. Chem. Soc.*, **102**, 3972 (1980).

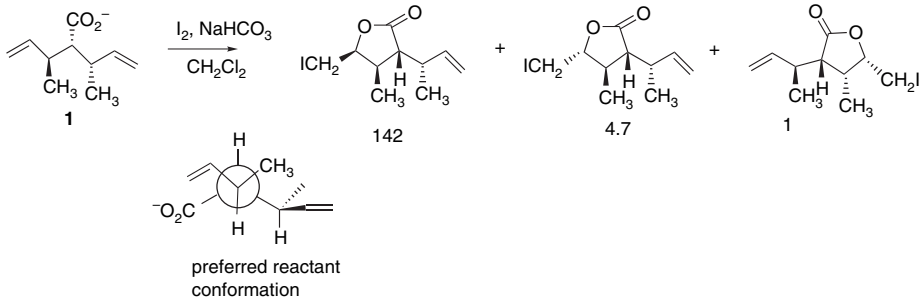
The *anti* addition is a kinetically controlled process that results from irreversible backside opening of an iodonium ion intermediate by the carboxylate nucleophile. Bartlett and co-workers showed that the more stable *trans* product was obtained under acidic conditions in which there is acid-catalyzed equilibration (thermodynamic control).[74]



Ref. 75

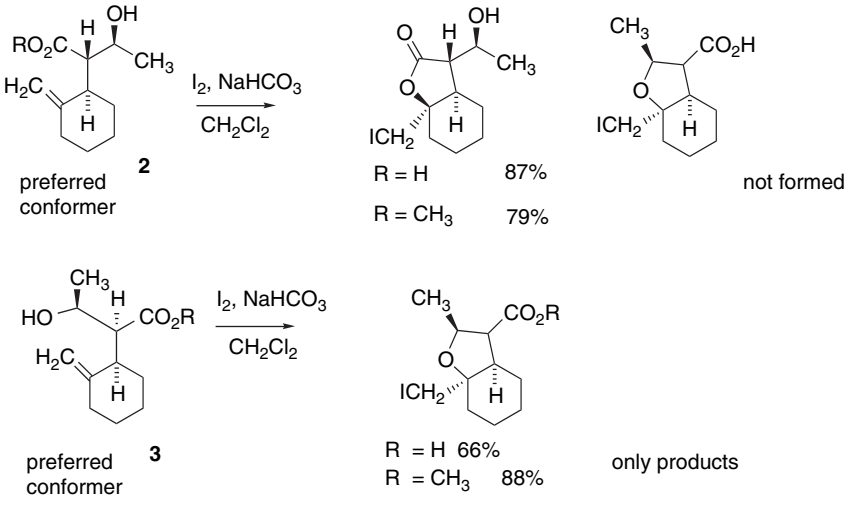


Under kinetic conditions, iodolactonization reflects reactant conformation. Several cases illustrate how the stereoselectivity of iodolactonization can be related to reactant conformation. For example, the high stereoselectivity of **1** corresponds to proximity of the carboxylate group to one of the two double bonds in the preferred reactant conformation.[76]

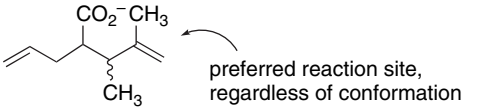


Similarly, with reactants **2** and **3** conformational preference dominates in the selectivity between CO_2^- and CH_2OH as the internal nucleophile. This conformational preference even extends to CO_2CH_3, which can cyclize in preference to CH_2OH when it is in the conformationally preferred position.[77]

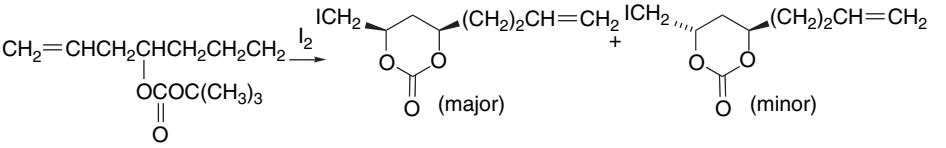
74. P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, **100**, 3950 (1978).
75. F. R. Gonzalez and P. A. Bartlett, *Org. Synth.*, **64**, 175 (1984).
76. M. J. Kurth and E. G. Brown, *J. Am. Chem. Soc.*, **109**, 6844 (1987).
77. M. J. Kurth, R. L. Beard, M. Olmstead, and J. G. Macmillan, *J. Am. Chem. Soc.*, **111**, 3712 (1989).



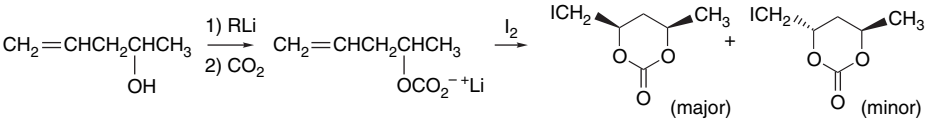
On the other hand, when the competition is between a monosubstituted and a disubstituted double bond, the inherent reactivity difference between the two double bonds overcomes reactant conformational preferences.[78]



Several other nucleophilic functional groups can be induced to participate in iodocyclization reactions. *t*-Butyl carbonate esters cyclize to diol carbonates.[79]



Lithium salts of carbonate monoesters can also be cyclized.[80]

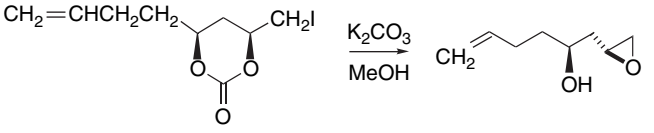


Enhanced stereoselectivity has been found using IBr, which reacts at a lower temperature.[81] (Compare Entries 6 and 7 in Scheme 4.4.) Other reagent systems that generate electrophilic iodine, such as $KI + KHSO_5$,[82] can be used for iodocyclization.

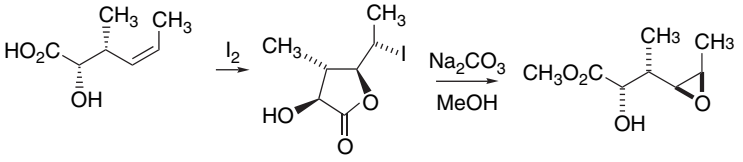
78. M. J. Kurth, E. G. Brown, E. J. Lewis, and J. C. McKew, *Tetrahedron Lett.*, **29**, 1517 (1988).
79. P. A. Bartlett, J. D. Meadows, E. G. Brown, A. Morimoto, and K. K. Jernstedt, *J. Org. Chem.*, **47**, 4013 (1982).
80. A. Bogini, G. Cardillo, M. Orena, G. Ponzi, and S. Sandri, *J. Org. Chem.*, **47**, 4626 (1982).
81. J. J.-W. Duan and A. B. Smith, III, *J. Org. Chem.*, **58**, 3703 (1993).
82. M. Curini, F. Epifano, M. C. Marcotullio, and F. Montanari, *Synlett*, 368 (2004).

Analogous cyclization reactions are induced by brominating reagents but they tend to be less selective than the iodocyclizations.[83] The bromonium ion intermediates are much more reactive and less selective.

The iodocyclization products have a potentially nucleophilic oxygen substituent β to the iodide, which makes them useful in stereospecific syntheses of epoxides and diols.

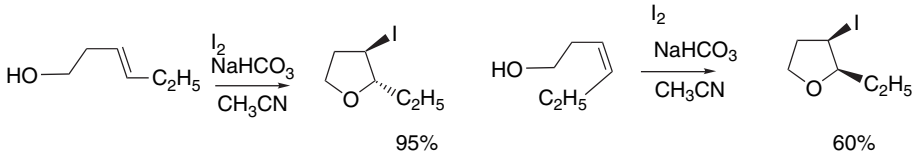


Ref. 79

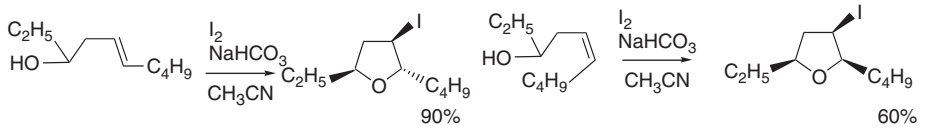


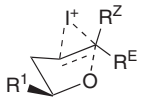
Ref. 84

Positive halogen reagents can cyclize γ- and δ-hydroxyalkenes to tetrahydrofuran and tetrahydropyran derivatives, respectively.[85] Iodocyclization of homoallylic alcohols generates 3-iodotetrahydrofurans when conducted in anhydrous acetonitrile.[86] The reactions are stereospecific, with the *E*-alcohols generating the *trans* and the *Z*-isomer the *cis* product. These are 5-*endo* cyclizations, which are preferred to 4-*exo* reactions.



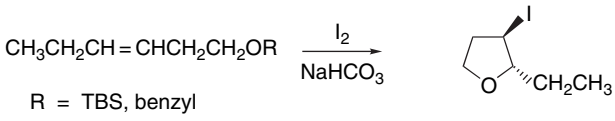
With the corresponding secondary alcohols, the preferred cyclization is via a conformation with a pseudoequatorial conformation.





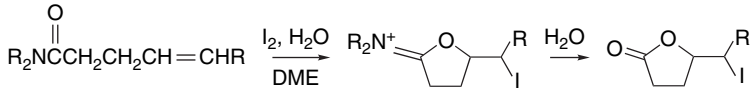
83. B. B. Snider and M. I. Johnston, *Tetrahedron Lett.*, **26**, 5497 (1985).
84. C. Neukome, D. P. Richardson, J. H. Myerson, and P. A. Bartlett, *J. Am. Chem. Soc.*, **108**, 5559 (1986).
85. A. B. Reitz, S. O. Nortey, B. E. Maryanoff, D. Liotta, and R. Monahan, III, *J. Org. Chem.*, **52**, 4191 (1981).
86. J. M. Banks, D. W. Knight, C. J. Seaman, and G. G. Weingarten, *Tetrahedron Lett.*, **35**, 7259 (1994); S. B. Bedford, K. E. Bell, F. Bennett, C. J. Hayes, D. W. Knight, and D. E. Shaw, *J. Chem. Soc., Perkin Trans. 1*, 2143 (1999).

Related *O*-TBS and *O*-benzyl ethers cyclize with loss of the ether substituent.



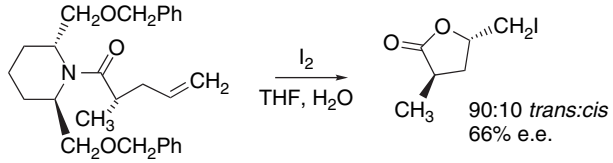
Ref. 87

Other nucleophilic functional groups can participate in iodocyclization. Amides usually react at oxygen, generating imino lactones that are hydrolyzed to lactones.[88]

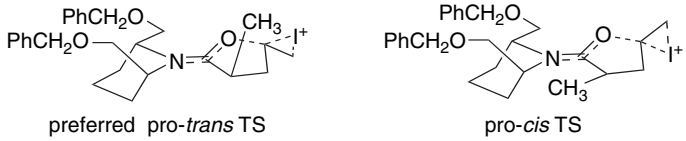


Ref. 89

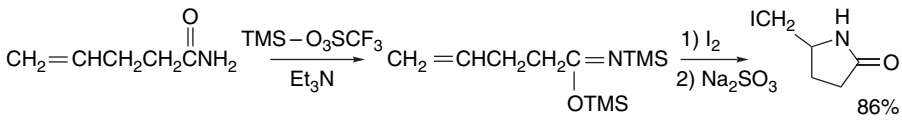
Use of a chiral amide can promote enantioselective cyclization.[90]



The TS preference is influenced by avoidance of $A^{1,3}$ strain between the α-methyl group and the piperidine ring.



Lactams can be obtained by cyclization of *O*,*N*-trimethylsilyl imidates.[91]



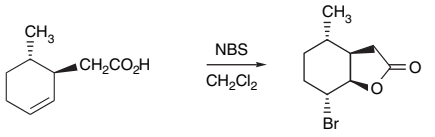
As compared with amides, where oxygen is the most nucleophilic atom, the silyl imidates are more nucleophilic at nitrogen.

Examples of halolactonization and related halocyclizations can be found in Scheme 4.4. The first entry, which involves NBS as the electrophile, demonstrates the *anti* stereospecificity of the reaction, as well as the preference for five-membered rings.

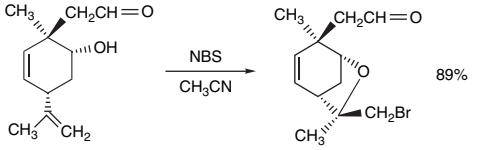
87. S. P. Bew, J. M. Barks, D. W. Knight, and R. J. Middleton, *Tetrahedron Lett.*, **41**, 4447 (2000).
88. S. Robin and G. Rousseau, *Tetrahedron*, **54**, 13681 (1998).
89. Y. Tamaru, M. Mizutani, Y. Furukawa, S. Kawamura, Z. Yoshida, K. Yanagi, and M. Minobe, *J. Am. Chem. Soc.*, **106**, 1079 (1984).
90. S. Najdi, D. Reichlin, and M. J. Kurth, *J. Org. Chem.*, **55**, 6241 (1990).
91. S. Knapp, K. E. Rodriquez, A. T. Levorse, and R. M. Ornat, *Tetrahedron Lett.*, **26**, 1803 (1985).

Scheme 4.4. Iodolactonizations and Other Halocyclizations

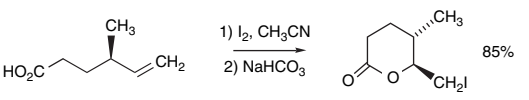
1[a]



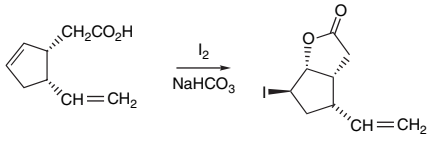
2[b]



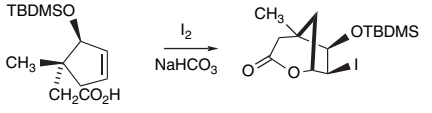
3[c]



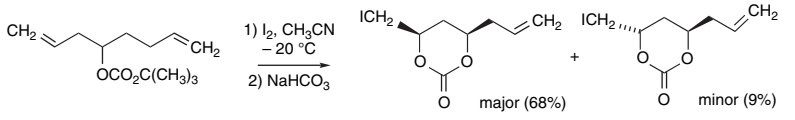
4[d]



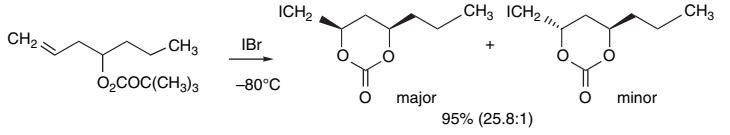
5[f]



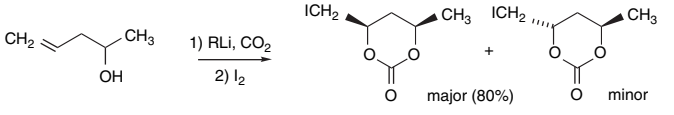
6[g]



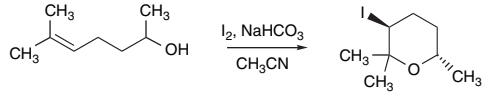
7[h]



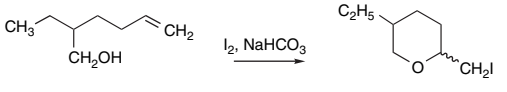
8[i]



9[j]



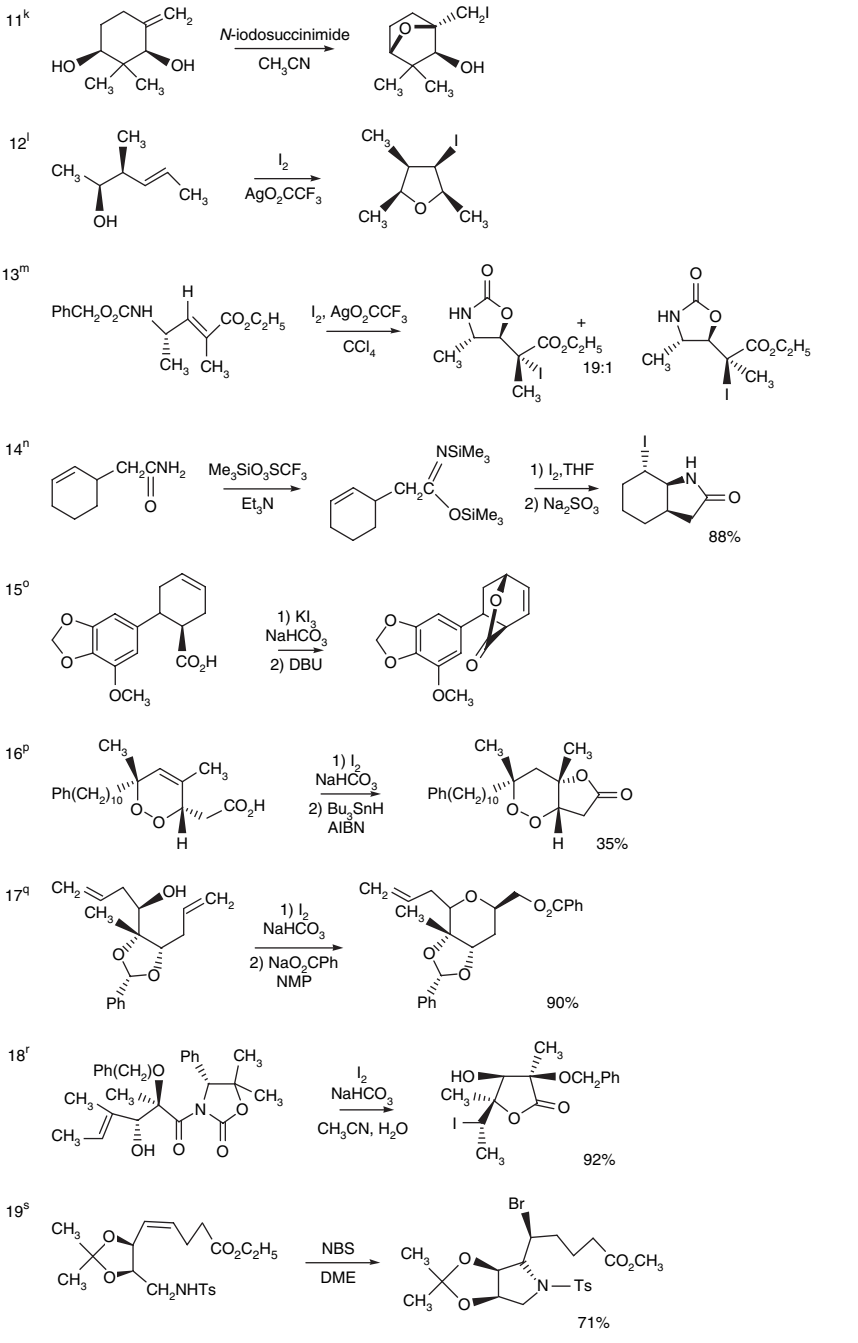
10[k]



92% 2.5 *trans:cis*

(*Continued*)

Scheme 4.4. (*Continued*)

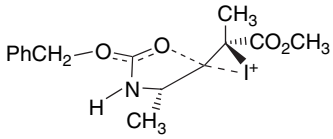


(*Continued*)

a. M. F. Semmelhack, W. R. Epa, A. W. H. Cheung, Y. Gu, C. Kim, N. Zhang, and W. Lew, *J. Am. Chem. Soc.*, **116**, 7455 (1994).
b. M. Miyashita, T. Suzuki, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **111**, 3728 (1989).
c. A. G. M. Barrett, R. A. E. Carr, S. V. Atwood, G. Richardson, and N. D. A. Walshe, *J. Org. Chem.*, **51**, 4840 (1986).
d. L. A. Paquette, G. D. Crouse, and A. K. Sharma, *J. Am. Chem. Soc.*, **102**, 3972 (1980).
e. A. J. Pearson and S.-Y. Hsu, *J. Org. Chem.*, **51**, 2505 (1986).
f. P. A. Bartlett, J. D. Meadows, E. G. Brown, A. Morimoto, and K. K. Jernstedt, *J. Org. Chem.*, **47**, 4013 (1982).
g. J. J.-W. Duan and A. B. Smith, III, *J. Org. Chem.*, **58**, 3703 (1993).
h. L. F. Tietze and C. Schneider, *J. Org. Chem.*, **56**, 2476 (1991).
i. G. L. Edwards and K. A. Walker, *Tetrahedron Lett.*, **33**, 1779 (1992).
j. A. Bongini, G. Cardillo, M. Orena, G. Porzi, and S. Sandri, *J. Org. Chem.*, **47**, 4626 (1982).
k. A. Murai, N. Tanimoto, N. Sakamoto, and T. Masamune, *J. Am. Chem. Soc.*, **110**, 1985 (1988).
l. B. F. Lipshutz and J. C. Barton, *J. Am. Chem. Soc.*, **114**, 1084 (1992).
m. Y. Guindon, A. Slassi, E. Ghiro, G. Bantle, and G. Jung, *Tetrahedron Lett.*, **33**, 4257 (1992).
n. S. Knapp and A. T. Levorse, *J. Org. Chem.*, **53**, 4006 (1988).
o. S. Kim, H. Ko, E. Kim, and D. Kim, *Org. Lett.*, **4**, 1343 (2002).
p. M. Jung, J. Han, and J. Song, *Org. Lett.*, **4**, 2763 (2002).
q. S. H. Kang, S. Y. Kang, H. Choi, C. M. Kim, H.-S. Jun, and J.-H. Youn, *Synthesis*, 1102 (2004).
r. Y. Murata, T. Kamino, T. Aoki, S. Hosokawa, and S. Kobayshi, *Angew. Chem. Int. Ed. Engl.*, **43**, 3175 (2004).
s. Y. G. Kim and J. K. Cha, *Tetrahedron Lett.*, **30**, 5721 (1989).

Entry 2 is a 5-*exo* bromocyclization. The reaction in Entry 3 involves formation of a δ-lactone in an acyclic system. This reaction was carried out under conditions that lead to the thermodynamically favored *trans* isomer. Entry 4 shows typical iodolactonization conditions and illustrates both the *anti* stereoselectivity and preference for formation of five-membered rings. In Entry 5, a six-membered lactone is formed, again with *anti* stereospecificity. Entry 6 is a cyclization of a *t*-butyl carbonate ester. The selectivity between the two double bonds is the result of the relative proximity of the nucleophilic group. Entry 7 is a closely related reaction, but carried out at a much lower temperature by the use of IBr. The *cis*:*trans* ratio was improved to nearly 26:1. The ratio was also solvent dependent, with toluene being the best solvent. Entry 8 is a variation using a lithium carbonate as the nucleophile. Entries 9 and 10 involve hydroxy groups as nucleophiles. Entry 9 is a 6-*endo* iodocyclization. In Entry 10, a primary hydroxy group serves as the nucleophile. Entry 11 is another cyclization involving a hydroxy group, in this case forming a 7-oxabicyclo[2.2.1]heptane structure. Entry 12 is a rather unusual 5-*endo* cyclization.

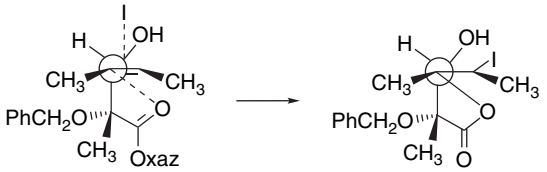
Entry 13 shows cyclization with concomitant loss of the benzyloxycarbonyl group. The TS for this reaction is 5-*exo* with conformation determined by the pseudoequatorial position of the methyl group.



Entry 14 involves formation of a lactam by cyclization of a *bis*-trimethylsilylimidate. The stereoselectivity parallels that of iodolactonization.

Entries 15 to 18 are examples of use of iodocyclization in multistep syntheses. In Entry 15, iodolactonization was followed by elimination of HI from the bicyclic lactone. In Entry 16, a cyclic peroxide group remained unaffected by the standard iodolactonization and subsequent Bu_3SnH reductive deiodination. (See Section 5.5 for

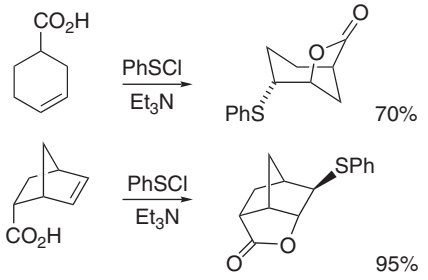
a discussion of this reaction.) In Entry 17, the primary iodo substituent was replaced by a benzoate group. In Entry 18, the reactant was prepared with high *anti* selectivity by an auxiliary-directed aldol reaction. The acyloxazolidinone auxiliary then participated in the iodocyclization and was cleaved in the process.



The reaction in Entry 19 was effected using NBS.

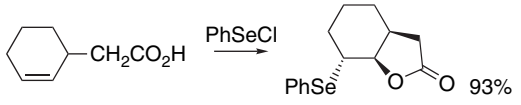
4.2.2. Sulfenylcyclization and Selenenylcyclization

Reactants with internal nucleophiles are also subject to cyclization by electrophilic sulfur reagents, a reaction known as *sulfenylcyclization*.[92] As for iodolactonization, unsaturated carboxylic acids give products that result from *anti* addition.[93]



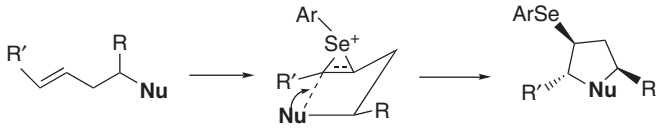
Similarly, alcohols undergo cyclization to ethers.

The corresponding reactions using selenium electrophiles are called selenenylcyclization.[94,95] Carboxylate (selenylactonization), hydroxy (selenyletherification), and nitrogen (selenylamidation) groups can all be captured in appropriate cases.

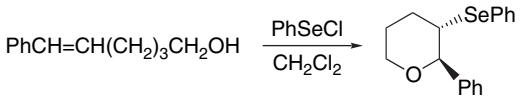


Internal nucleophilic capture of seleniranium ion is governed by general principles similar to those of other electrophilic cyclizations.[96] The stereochemistry of cyclization can usually be predicted on the basis of a cyclic TS with favored pseudoequatorial orientation of the substituents.

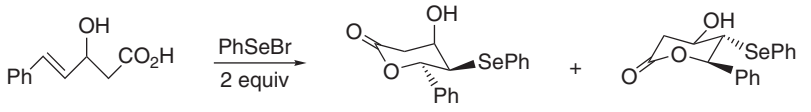
92. G. Capozzi, G. Modena, and L. Pasquato, in *The Chemistry of Sulphenic Acids and Their Derivatives*, S. Patai, ed., Wiley, Chichester, 1990, pp. 446–460.
93. K. C. Nicolaou, S. P. Seitz, W. T. Sipio, and J. F. Blount, *J. Am. Chem. Soc.*, **101**, 3884 (1979).
94. K. Fujita, *Rev. Heteroatom. Chem.*, **16**, 101 (1997).
95. K. C. Nicolaou, S. P. Seitz, W. J. Sipio, and J. F. Blount, *J. Am. Chem. Soc.*, **101**, 3884 (1979); M. Tiecco, *Topics Curr. Chem.*, **208**, 7 (2000); S. Raganathan, K. M. Muraleedharan, N. K. Vaish, and N. Jayaraman, *Tetrahedron*, **60**, 5273 (2004).
96. N. Petragnani, H. A. Stefani, and C. J. Valduga, *Tetrahedron*, **57**, 1411 (2001).



Although *exo* cyclization is usually preferred, there is no strong prohibition of *endo* cyclization and aryl-controlled regioselectivity can override the *exo* preference.



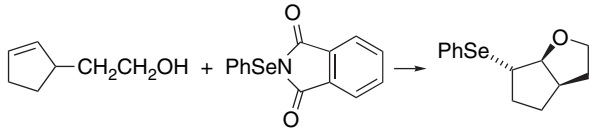
Ref. 97



93:7

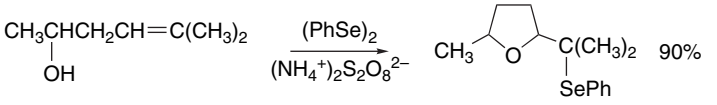
Ref. 98

Various electrophilic selenium reagents such as those described in Scheme 4.3 can be used. *N*-Phenylselenylphthalimide is an excellent reagent for this process and permits the formation of large ring lactones.[99] The advantage of the reagent in this particular application is the low nucleophilicity of phthalimide, which does not compete with the remote internal nucleophile. The reaction of phenylselenenyl chloride or *N*-phenylselenenylphthalimide with unsaturated alcohols leads to formation of β-phenylselenenyl ethers.



Ref. 100

Another useful reagent for selenenylcyclization is phenylselenenyl triflate. This reagent is capable of cyclizing unsaturated acids[101] and alcohols.[102] Phenylselenenyl sulfate can be prepared in situ by oxidation of diphenyl diselenide with ammonium peroxydisulfate.[103]



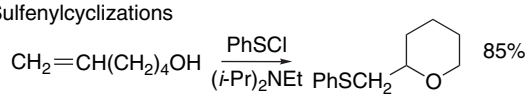
Several examples of sulfenylcyclization are given in Section A of Scheme 4.5. Entry 1 is a *6-exo* sulfenoetherification induced by phenylsulfenyl chloride. Entry 2

97. M. A. Brimble, G. S. Pavia, and R. J. Stevenson, *Tetrahedron Lett.*, **43**, 1735 (2002).
98. M. Gruttadauria, C. Aprile, and R. Noto, *Tetrahedron Lett.*, **43**, 1669 (2002).
99. K. C. Nicolaou, D. A. Claremon, W. E. Barnette, and S. P. Seitz, *J. Am. Chem. Soc.*, **101**, 3704 (1979).
100. K. C. Nicolaou, R. L. Magolda, W. J. Sipio, W. E. Barnette, Z. Lysenko, and M. M. Joullie, *J. Am. Chem. Soc.*, **102**, 3784 (1980).
101. S. Murata and T. Suzuki, *Chem. Lett.*, 849 (1987).
102. A. G. Kutateladze, J. L. Kice, T. G. Kutateladze, N. S. Zefirov, and N. V. Zyk, *Tetrahedron Lett.*, **33**, 1949 (1992).
103. M. Tiecco, L. Testaferri, M. Tingoli, D. Bartoli, and R. Balducci, *J. Org. Chem.*, **5**5, 429 (1990).

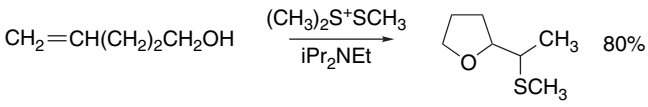
Scheme 4.5. Sulfenyl- and Selenenylcyclization Reactions

A. Sulfenylcyclizations

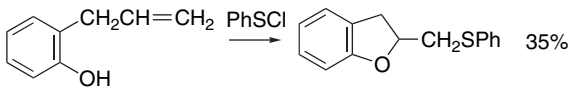
1[a]



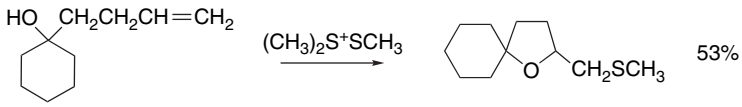
2[b]



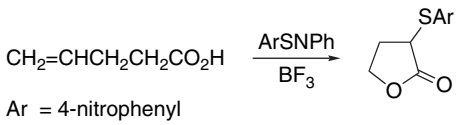
3[c]



4[d]

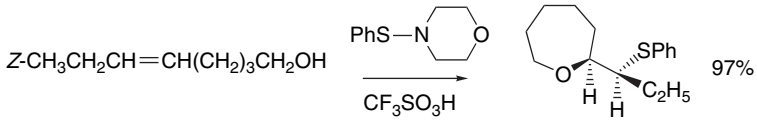


5[e]

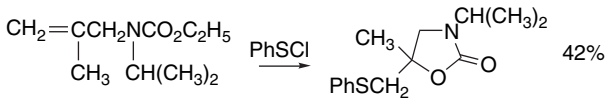


Ar = 4-nitrophenyl

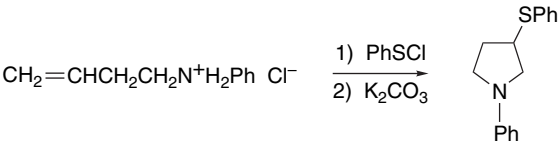
6[f]



7[g]

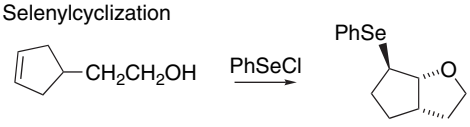


8[h]

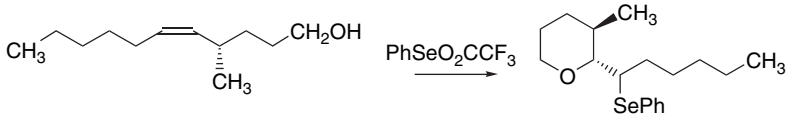


B. Selenylcyclization

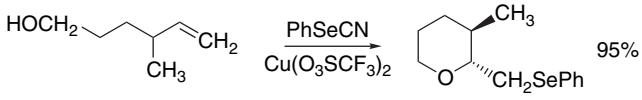
9[i]



10[j]

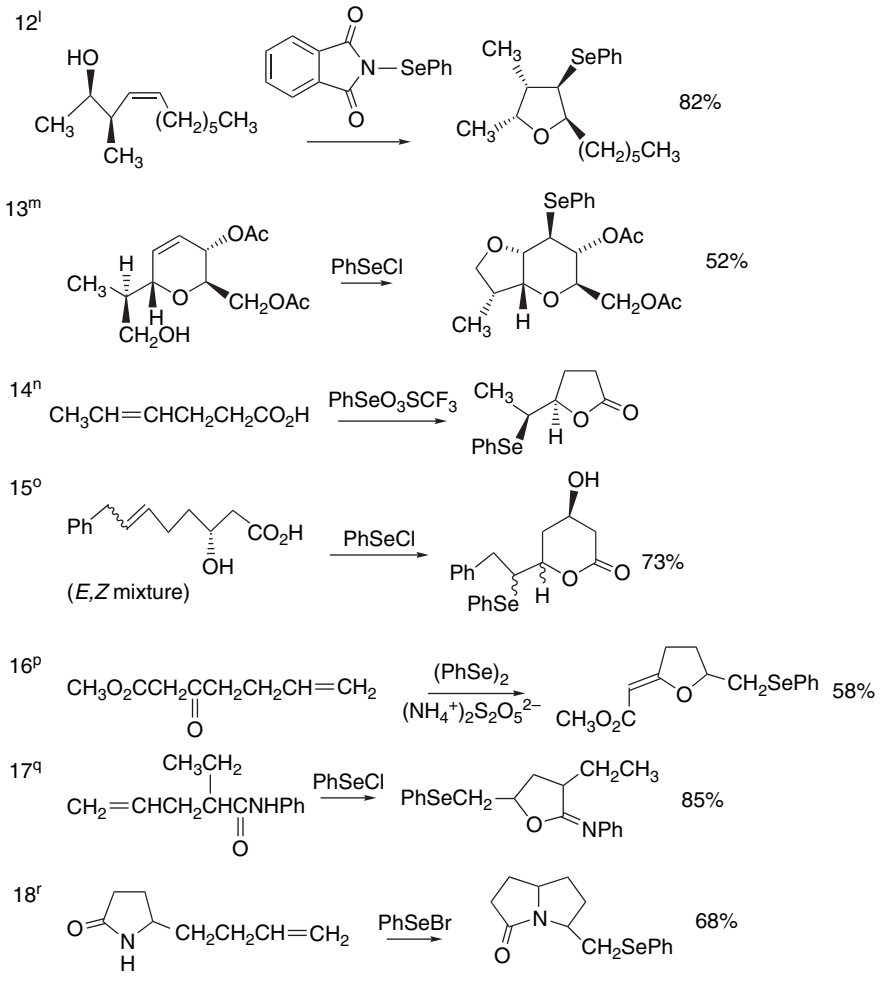


11[k]



(*Continued*)

Scheme 4.5. (***Continued***)

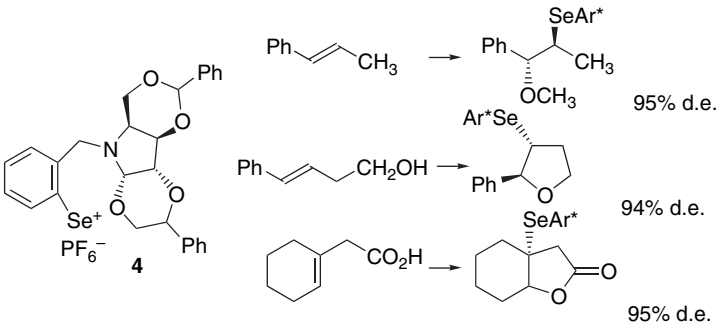


a. S. M. Tuladhar and A. G. Fallis, *Can. J. Chem.*, **65**, 1833 (1987).
b. G. J. O'Malley and M. P. Cava, *Tetrahedron Lett.*, **26**, 6159 (1985).
c. M. Muehlstaedt, C. Shubert, and E. Kleinpeter, *J. Prakt. Chem.*, **327**, 270 (1985).
d. G. Capozzi, S. Menichetti, M. Nicastro, and M. Taddei, *Heterocycles*, **29**, 1703 (1987).
e. L. Benati, L. Capella, P. C. Montevecchi, and P. Spagnolo, *Tetrahedron*, **50**, 12395 (1994).
f. P. Brownbridge, *J. Chem. Soc., Chem. Commun.*, 1280 (1980).
g. M. Muehlstaedt, R. Widera, and B. Olk, *J. Prakt. Chem.*, **324**, 362 (1982).
h. T. Ohsawa, M. Ihara, K. Fukumoto, and T. Kametani, *J. Org. Chem.*, **48**, 3644 (1983).
i. D. L. J. Clive, G. Chittattu, and C. K. Wong, *Can. J. Chem.*, **55**, 3894 (1987).
j. G. Li and W. C. Still, *J. Org. Chem.*, **56**, 6964 (1991).
k. H. Inoue and S. Murata, *Heterocycles*, **45**, 847 (1997).
l. E. D. Mihelich and G. A. Hite, *J. Am. Chem. Soc.*, **114**, 7318 (1992).
m. S. J. Danishefsky, S. DeNinno, and P. Lartey, *J. Am. Chem. Soc.*, **109**, 2082 (1987).
n. S. Murata and T. Suzuki, *Chem. Lett.*, 849 (1987).
o. F. Bennett, D. W. Knight, and G. Fenton, *J. Chem. Soc., Perkin Trans. 1*, 519 (1991).
p. M. Tiecco, L. Testaferri, M. Tingoli, D. Bartoli, and R. Balducci, *J. Org. Chem.*, **55**, 429 (1990).
q. A. Toshimitsu, K. Terao, and S. Uemura, *J. Org. Chem.*, **52**, 2018 (1987).
r. A. Toshimitsu, K. Terao, and S. Uemura, *J. Org. Chem.*, **51**, 1724 (1986).

is mediated by dimethyl(methylthio)sulfonium tetrafluoroborate. Entries 3 and 4 are other examples of 5-*exo* cyclizations. Entries 5 and 6 involve use of sulfenamides as the electrophiles. Entry 7 shows the cyclization of a carbamate involving the carbonyl oxygen. Entry 8 is an 5-*endo* aminocyclization.

Part B of Scheme 4.5 gives some examples of cyclizations induced by selenium electrophiles. Entries 9 to 13 are various selenyletherifications. All exhibit *anti* stereochemistry. Entries 14 and 15 are selenyllactonizations. Entries 17 and 18 involve amido groups as the internal nucleophile. Entry 17 is an 5-*exo* cyclization in which the amido oxygen is the more reactive nucleophilic site, leading to an iminolactone. Geometric factors favor N-cyclization in the latter case.

Chiral selenenylating reagents have been developed and shown to be capable of effecting enantioselective additions and cyclizations. The reagent **4**, for example, achieves more than 90% enantioselectivity in typical reactions.[104]

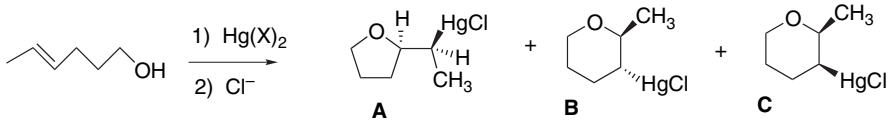


4.2.3. Cyclization by Mercuric Ion

Electrophilic attack by mercuric ion can effect cyclization by intramolecular capture of a nucleophilic functional group. A variety of oxygen and nitrogen nucleophiles can participate in cyclization reactions, and there have been numerous synthetic applications of the reaction. Mechanistic studies have been carried out on several alkenol systems. The ring-size preference for cyclization of 4-hexenol depends on the mercury reagent that is used. The more reactive mercuric salts favor 6-*endo* addition. It is proposed that reversal of formation of the kinetic *exo* product is responsible.[105] Equilibration to favor the thermodynamic addition products occurs using $Hg(O_3SCF_3)_2$ and $Hg(NO_3)_2$. The equilibration does not seem to be dependent on acid catalysis, since the thermodynamically favored product is also formed in the presence of the acid-scavenger TMU.

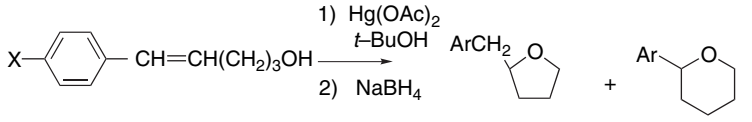
[104] K. Fujita, K. Murata, M. Iwaoka, and S. Tomoda, *Tetrahedron*, **53**, 2029 (1997); K. Fujita, *Rev. Heteroatom Chem.*, **16**, 101 (1997); T. Wirth, *Tetrahedron*, **55**, 1 (1999).

[105] M. Nishizawa, T. Kashima, M. Sakakibara, A. Wakabayashi, K. Takahasi, H. Takao, H. Imagawa, and T. Sugihara, *Heterocycles*, **54**, 629 (2001).



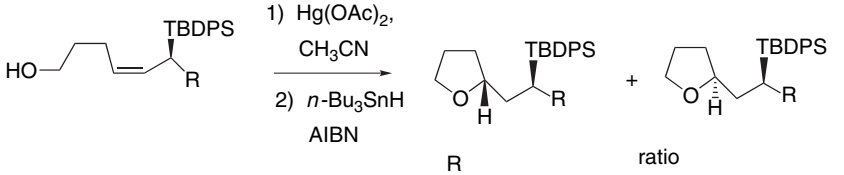
X	A	B	C
O_2CCH_3	92	8	0
O_2CCF_3	13	87	0
O_3SCF_3	0	88	12
O_3SCF_3 (TMU)	0	100	0
NO_3	0	100	0

In 5-aryl-4-hexenols with ERG substituents, electronic factors outweigh the *exo* preference.[106] The ERG substituents increase the cationic character at C(5).

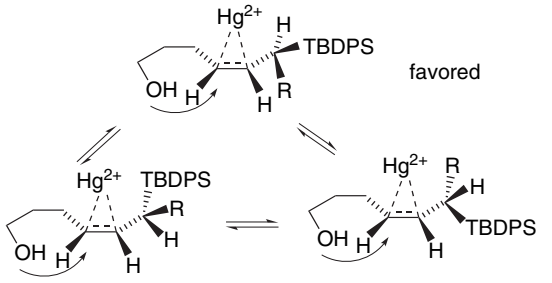


X	
H	81:19
CH_3	47:53
CH_3O	0:100

Cyclization of δ, ε-enols is controlled by a conformation-dependent strain in the *exo* TS.[107] The C(5)–C(6) bond is rotated to minimize $A^{1,3}$ strain.



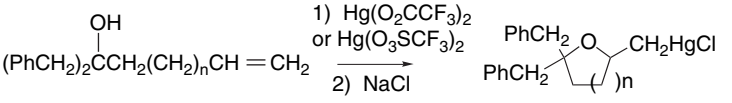
R	ratio
CH_3	19:1
$CH_3CH_2CH_2$	10:1
Ph	10:1



[106] Y. Senda, H. Kanto, and H. Itoh, *J. Chem. Soc., Perkin Trans. 2*, 1143 (1997).
[107] K. Bratt, A. Garavelas, P. Perlmutter, and G. Westman, *J. Org. Chem.*, **61**, 2109 (1996).

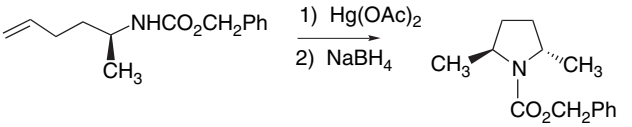
In the corresponding *E*-alkene, where this factor is not present, the cyclization is much less stereoselective. A stabilizing interaction between the siloxy oxygen and the Hg^{2+} center has also been suggested.[108]

Reaction of $Hg(O_2CCF_3)_2$ or $Hg(O_3SCF_3)_2$ with a series of dibenzylcarbinols gave *exo* cyclization for formation of five-, six-, and seven-, but not eight-membered rings.[109]

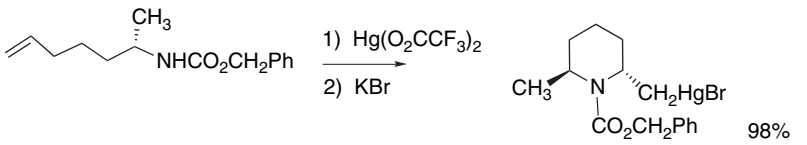


n	ring size	*exo:endo*
1	5	> 99:1
2	6	>99:1
3	7	>99:1
4	8	-

Benzyl carbamates have been used to form both five- and six-membered nitrogen-containing rings. The selectivity for N over O nucleophilicity in these cases is the result of the nitrogen being able to form a better ring size (5 or 6 versus 7 or 8) than the carbonyl oxygen.

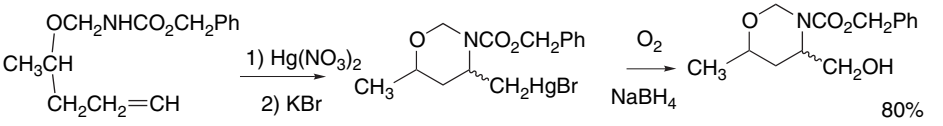


Ref. 110



Ref. 111

The trapping of the radical intermediate in demercuration by oxygen can be exploited as a method for introduction of a hydroxy substituent (see p. 295). The example below and Entries 3 and 4 in Scheme 4.6 illustrate this reaction.

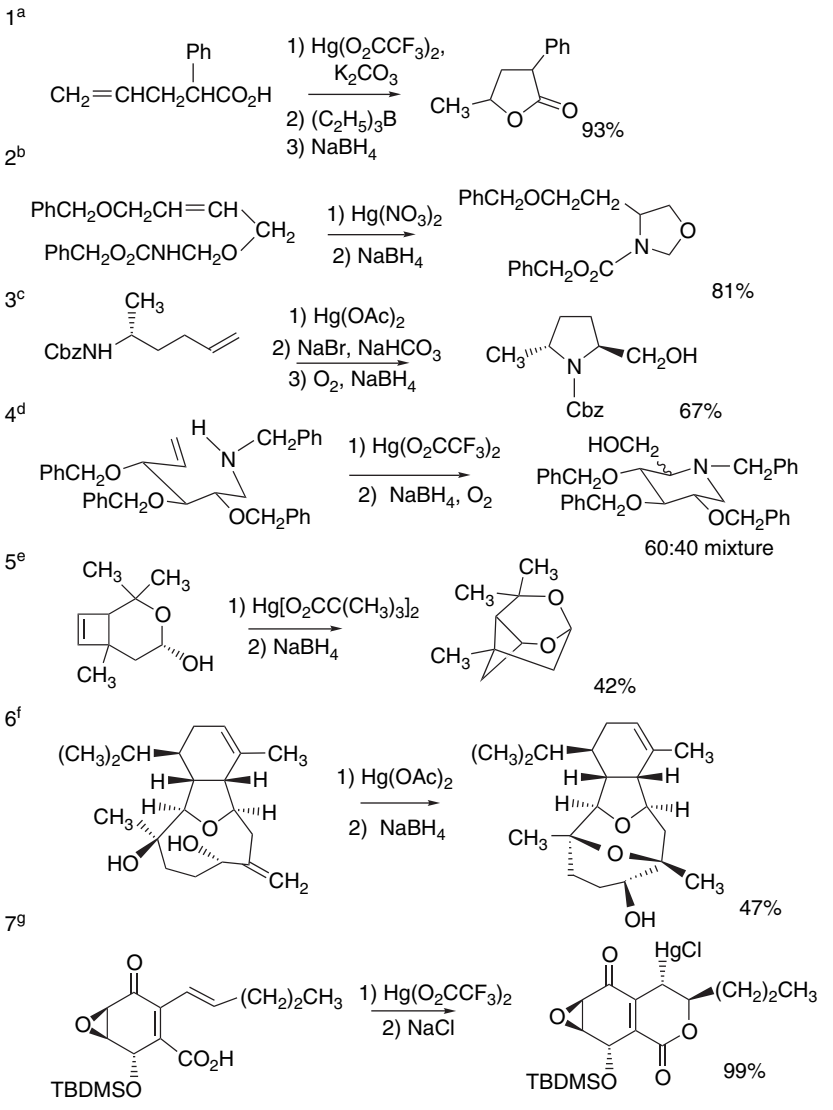


Ref. 112

Cyclization induced by mercuric ion is often used in multistep syntheses to form five- and six-membered hetereocyclic rings, as illustrated in Scheme 4.6. The reactions in Entries 1 to 3 involve acyclic reactants that cyclize to give 5-*exo* products. Entry 4 is an 6-*exo* cyclization. In Entries 1 and 2, the mercury is removed reductively, but in Entries 3 and 4 a hydroxy group is introduced in the presence of oxygen. Inclusion of triethylboron in the reduction has been found to improve yields (Entry 1).[113]

108. A. Garavelas, I. Mavropoulos, P. Permutter, and G. Westman, *Tetrahedron Lett.*, **36**, 463 (1995).
109. H. Imagawa, T. Shigaraki, T. Suzuki, H. Takao, H. Yamada, T. Sugihara, and M. Nishizawa, *Chem. Pharm. Bull.*, **46**, 1341 (1998).
110. T. Yamakazi, R. Gimi, and J. T. Welch, *Synlett*, 573 (1991).
111. H. Takahata, H. Bandoh, and T. Momose, *Tetrahedron*, **49**, 11205 (1993).
112. K. E. Harding, T. H. Marman, and D.-H. Nam, *Tetrahedron Lett.*, **29**, 1627 (1988).
113. S. H. Kang, J. H. Lee, and S. B. Lee, *Tetrahedron Lett.*, **39**, 59 (1998).

Scheme 4.6. Cyclization Effected by Mercuration

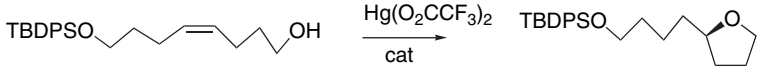


a. S. H. Kang, J. H. Lee, and S. B. Lee, *Tetrahedron Lett.*, **39**, 59 (1998).
b. K. E. Harding and D. R. Hollingsworth, *Tetrahedron Lett.*, **29**, 3789 (1988).
c. H. Takahata, H. Bandoh, and T. Momose, *J. Org. Chem.*, **57**, 4401 (1992).
d. R. C. Bernotas and B. Ganem, *Tetrahedron Lett.*, **26**, 1123 (1985).
e. J. D. White, M. A. Avery and J. P. Carter, *J. Am. Chem. Soc.*, **104**, 5486 (1986).
f. D. W. C. MacMillan, L. E. Overman, and L. D. Pennington, *J. Am. Chem. Soc.*, **123**, 9033 (2001).
g. M. Shoji, T. Uno, and Y. Hayashi, *Org. Lett.*, **6**, 4535 (2004).

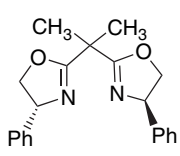
The reaction in Entry 5 was used in the syntheses of linetin, which is an aggregation pheromone of the ambrosia beetle. In Entry 6, a transannular 5-*exo* cyclization occurs. Entry 7 is an example of formation of a lactone by carboxylate capture. In this case, the product was isolated as the mercurochloride.

Some progress has been made toward achieving enantioselectivity in mercuration-induced cyclization. Several *bis*-oxazoline (BOX) ligands have been investigated. The

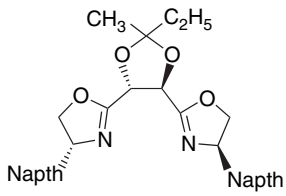
diphenyl BOX ligand, in conjunction with $Hg(O_2CCF_3)_2$, results in formation of tetrahydrofuran rings with 80% e.e. Other *bis*-oxazoline ligands derived from tartaric acid were screened and the best results were obtained with a 2-naphthyl ligand, which gave more than 90% e.e. in several cases.



68% yield, 86% e.e.



PhBOX

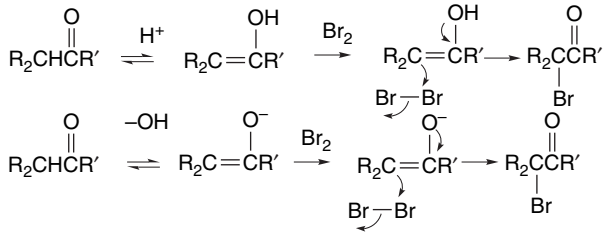


Ref. 114

4.3. Electrophilic Substitution α to Carbonyl Groups

4.3.1. Halogenation α to Carbonyl Groups

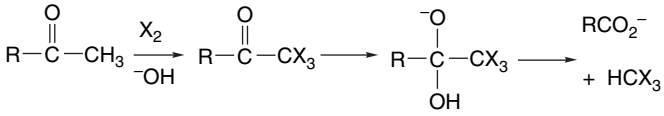
Although the reaction of ketones and other carbonyl compounds with electrophiles such as bromine leads to substitution rather than addition, the mechanism of the reaction is closely related to electrophilic additions to alkenes. An enol, enolate, or enolate equivalent derived from the carbonyl compound is the nucleophile, and the electrophilic attack by the halogen is analogous to that on alkenes. The reaction is completed by restoration of the carbonyl bond, rather than by addition of a nucleophile. The acid- and base-catalyzed halogenation of ketones, which is discussed briefly in Section 6.4 of Part A, provide the most-studied examples of the reaction from a mechanistic perspective.



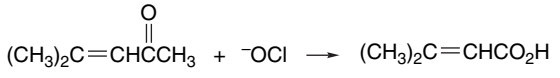
The reactions involving bromine or chlorine generate hydrogen halide and are autocatalytic. Reactions with *N*-bromosuccinimide or tetrabromocyclohexadienone do not form any hydrogen bromide and may therefore be preferable reagents in the case of acid-sensitive compounds. Under some conditions halogenation is faster than enolization. When this is true, the position of substitution in unsymmetrical ketones is governed by the relative rates of formation of the isomeric enols. In general, mixtures are formed with unsymmetrical ketones. The presence of a halogen substituent

[114.] S. H. Kang and M. Kim, *J. Am. Chem. Soc.*, **125**, 4684 (2003).

decreases the rate of acid-catalyzed enolization and thus retards the introduction of a second halogen at the same site, so monohalogenation can usually be carried out satisfactorily. In contrast, in basic solution halogenation tends to proceed to polyhalogenated products because the polar effect of a halogen accelerates base-catalyzed enolization. With methyl ketones, base-catalyzed reaction with iodine or bromine leads ultimately to cleavage to a carboxylic acid.[115] These reactions proceed to the trihalomethyl ketones, which are susceptible to base-induced cleavage.

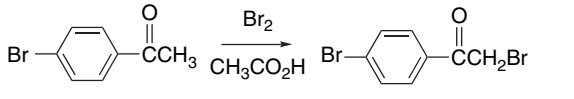


The reaction can also be effected with hypochlorite ion, and this constitutes a useful method for converting methyl ketones to carboxylic acids.

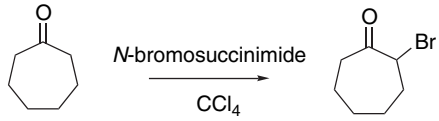


Ref. 116

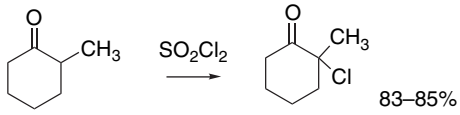
The most common preparative procedures involve use of the halogen, usually bromine, in acetic acid. Other suitable halogenating agents include *N*-bromosuccinimide, tetrabromocyclohexadienone, and sulfuryl chloride.



Ref. 117

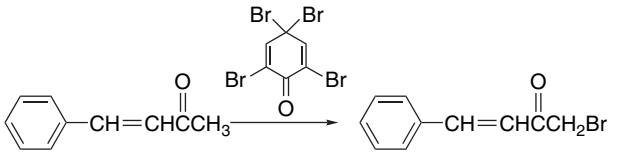


Ref. 118



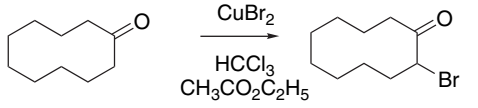
Ref. 119

115. S. J. Chakabartty, in *Oxidations in Organic Chemistry*, Part C, W. Trahanovsky, ed., Academic Press, New York, 1978, Chap. V.
116. L. J. Smith, W. W. Prichard, and L. J. Spillane, *Org. Synth.*, **III**, 302 (1955).
117. W. D. Langley, *Org. Synth.*, **1**, 122 (1932).
118. E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1954).
119. E. W. Warnhoff, D. G. Martin, and W. S. Johnson, *Org. Synth.*, **IV**, 162 (1963).



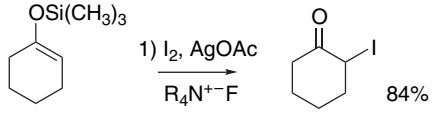
91% Ref. 120

Another preparatively useful procedure for monohalogenation of ketones involves reaction with cupric chloride or cupric bromide.[121]

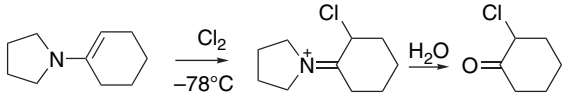


Ref. 122

Instead of direct halogenation of ketones, reactions with more reactive derivatives such as silyl enol ethers and enamines have advantages in certain cases.

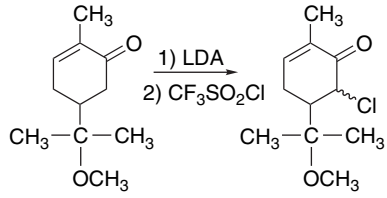


84% Ref. 123



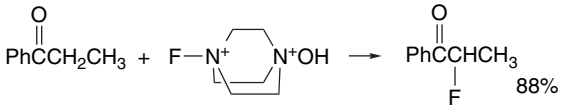
65% Ref. 124

There are also procedures in which the enolate is generated quantitatively and allowed to react with a halogenating agent. Regioselectivity can then be controlled by the direction of enolate formation. Among the sources of halogen that have been used under these conditions are bromine,[125] *N*-chlorosuccinimide,[126] trifluoromethanesulfonyl chloride,[127] and hexachloroethane.[128]



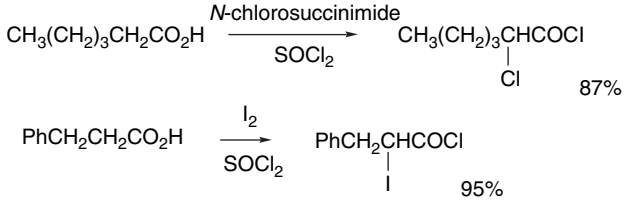
120. V. Calo, L. Lopez, G. Pesce, and P. E. Todesco, *Tetrahedron*, **29**, 1625 (1973).
121. E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963); E. M. Kosower and G.-S. Wu, *J. Org. Chem.*, **28**, 633 (1963).
122. D. P. Bauer and R. S. Macomber, *J. Org. Chem.*, **40**, 1990 (1975).
123. G. M. Rubottom and R. C. Mott, *J. Org. Chem.*, **44**, 1731 (1979); G. A. Olah, L. Ohannesian, M. Arvanaghi, and G. K. S. Prakash, *J. Org. Chem.*, **49**, 2032 (1984).
124. W. Seufert and F. Effenberger, *Chem. Ber.*, **112**, 1670 (1979).
125. T. Woolf, A. Trevor, T. Baille, and N. Castagnoli, Jr., *J. Org. Chem.*, **49**, 3305 (1984).
126. A. D. N. Vaz and G. Schoellmann, *J. Org. Chem.*, **49**, 1286 (1984).
127. P. A. Wender and D. A. Holt, *J. Am. Chem. Soc.*, **107**, 7771 (1985).
128. M. B. Glinski, J. C. Freed, and T. Durst, *J. Org. Chem.*, **52**, 2749 (1987).

α-Fluoroketones are made primarily by reactions of enol acetates or silyl enol ethers with fluorinating agents such as CF_3OF[129], XeF_2,[130] or dilute F_2.[131] Other fluorinating reagents that can be used include *N*-fluoropyridinium salts,[132] 1-fluoro-4-hydroxy-1,4-diazabicyclo[2.2.2]octane,[133] and 1,4-difluoro-1,4-diazabicyclo[2.2.2]octane.[134] These reagents fluorinate readily enolizable carbonyl compounds and silyl enol ethers.

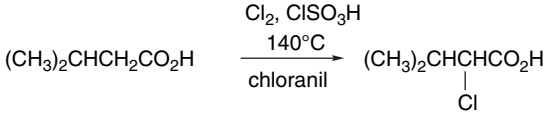


Ref. 135

The α-halogenation of acid chlorides also has synthetic utility. The mechanism is presumed to be similar to ketone halogenation and to proceed through an enol. The reaction can be effected in thionyl chloride as solvent to give α-chloro, α-bromo, or α-iodo acyl chlorides, using, respectively, *N*-chlorosuccinimide, *N*-bromosuccinimide, or molecular iodine as the halogenating agent.[136] Since thionyl chloride rapidly converts carboxylic acids to acyl chlorides, the acid can be used as the starting material.



Direct chlorination can be carried out in the presence of $ClSO_3H$, which acts as a strong acid catalyst. These procedures use various compounds including 1,3-dinitrobenzene, chloranil, and TCNQ to inhibit competing radical chain halogenation.[137]

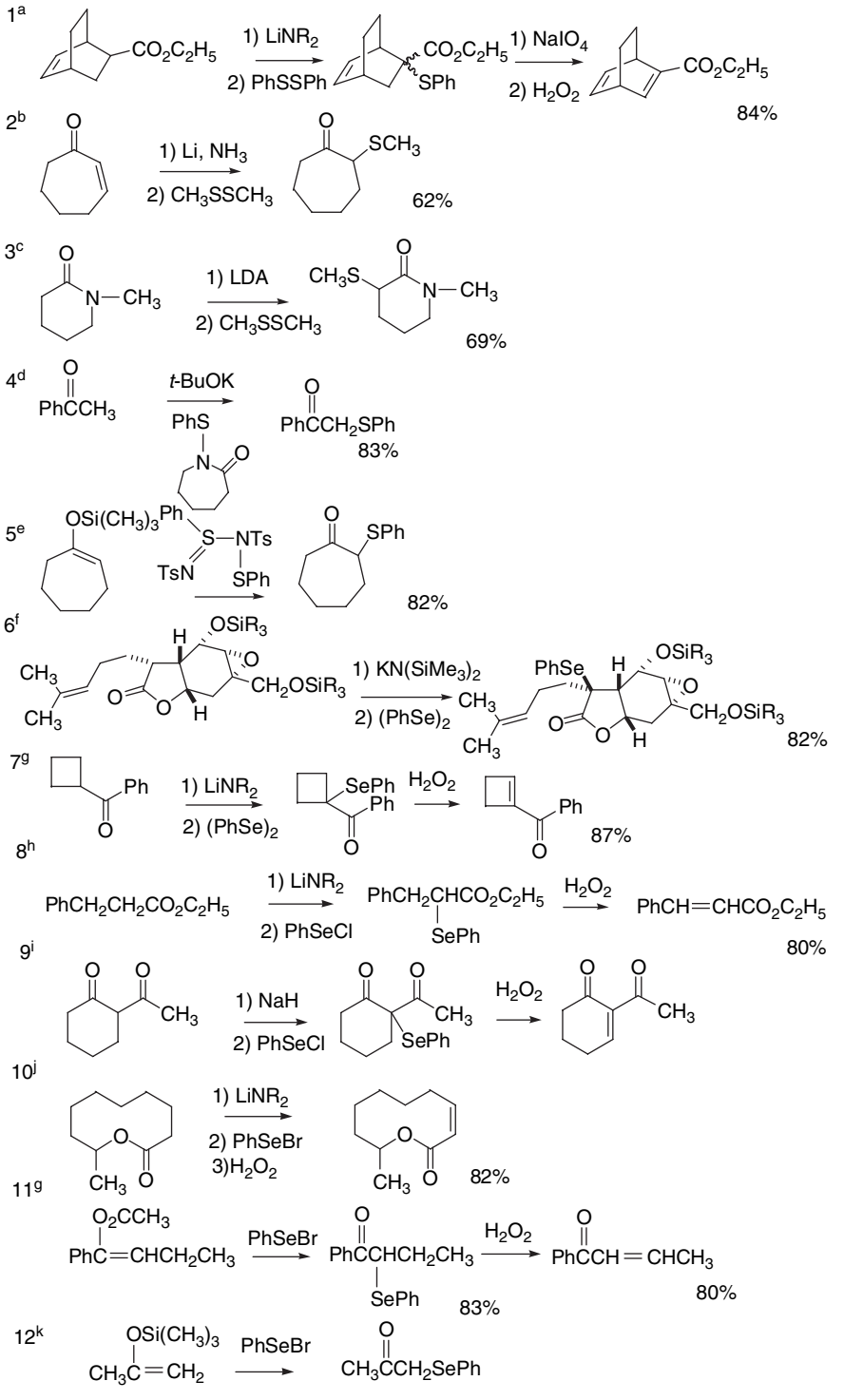


4.3.2. Sulfenylation and Selenenylation *α* to Carbonyl Groups

The α-sulfenylation[138] and α-selenenylation[139] of carbonyl compounds are synthetically important reactions, particularly in connection with the introduction of

129. W. J. Middleton and E. M. Bingham, *J. Am. Chem. Soc.*, **102**, 4845 (1980).
130. B. Zajac and M. Zupan, *J. Chem. Soc., Chem. Commun.*, 759 (1980).
131. S. Rozen and Y. Menahem, *Tetrahedron Lett.*, 725 (1979).
132. T. Umemoto, M. Nagayoshi, K. Adachi, and G. Tomizawa, *J. Org. Chem.*, **63**, 3379 (1998).
133. S. Stavber, M. Zupan, A. J. Poss, and G. A. Shia, *Tetrahedron Lett.*, **36**, 6769 (1995).
134. T. Umemoto and M. Nagayoshi, *Bull. Chem. Soc. Jpn.*, **69**, 2287 (1996).
135. S. Stavber and M. Zupan, *Tetrahedron Lett.*, **37**, 3591 (1996).
136. D. N. Harpp, L. Q. Bao, C. J. Black, J. G. Gleason, and R. A. Smith, *J. Org. Chem.*, **40**, 3420 (1975); Y. Ogata, K. Adachi, and F.-C. Chen, *J. Org. Chem.*, **48**, 4147 (1983).
137. Y. Ogata, T. Harada, K. Matsuyama, and T. Ikejiri, *J. Org. Chem.*, **40**, 2960 (1975); R. J. Crawford, *J. Org. Chem.*, **48**, 1364 (1983).
138. B. M. Trost, *Chem. Rev.*, **78**, 363 (1978).
139. H. J. Reich, *Acc. Chem. Res.*, **12**, 22 (1979); H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).

Scheme 4.7. α-Sulfenylation and α-Selenenylation of Carbonyl Compounds



(*Continued*)

a. B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976).
b. P. G. Gassman, D. P. Gilbert, and S. M. Cole, *J. Org. Chem.*, **42**, 3233 (1977).
c. P. G. Gassman and R. J. Balchunis, *J. Org. Chem.*, **42**, 3236 (1977).
d. G. Foray, A. Penenory, and A. Rossi, *Tetrahedron Lett.*, **38**, 2035 (1997).
e. P. Magnus and P. Rigollier, *Tetrahedron Lett.*, **33**, 6111 (1992).
f. A. B. Smith, III, and R. E. Richmond, *J. Am. Chem. Soc.*, **105**, 575 (1983).
g. H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).
h. J. M. Renga and H. J. Reich, *Org. Synth.*, **59**, 58 (1979).
i. T. Wakamatsu, K. Akasaka, and Y. Ban, *J. Org. Chem.*, **44**, 2008 (1979).
j. H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973).
k. I. Ryu, S. Murai, I. Niwa, and N. Sonoda, *Synthesis*, 874 (1977).

unsaturation. The products can subsequently be oxidized to sulfoxides and selenoxides that readily undergo elimination (see Section 6.8.3), generating the corresponding α,β-unsaturated carbonyl compound. Sulfenylations and selenenylations are usually carried out under conditions in which the enolate of the carbonyl compound is the reactive species. If a regiospecific enolate is generated by one of the methods described in Chapter 1, the position of sulfenylation or selenenylation can be controlled.[140] Disulfides are the most common sulfenylation reagents, whereas diselenides or selenenyl halides are used for selenenylation.

Scheme 4.7 gives some specific examples of these types of reactions. Entry 1 shows the use of sulfenylation followed by oxidation to introduce a conjugated double bond. Entries 2 and 3 are α-sulfenylations of a ketone and lactam, respectively, using dimethyl disulfide as the sulfenylating reagent. Entries 4 and 5 illustrate the use of alternative sulfenylating reagents. Entry 4 uses *N*-phenylsulfenylcaprolactam, which is commercially available. The reagent in Entry 5 is generated by reaction of diphenyldisulfide with chloramine-T. Entries 6 to 10 are examples of reactions of preformed enolates with diphenyl diselenide or phenylselenenyl chloride. As Entries 11 and 12 indicate, the selenenylation of ketones can also be effected by reactions of enol acetates or enol silyl ethers.

4.4. Additions to Allenes and Alkynes

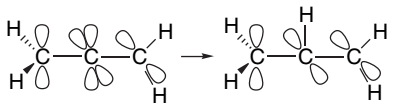
Both allenes[141] and alkynes[142] require special consideration with regard to mechanisms of electrophilic addition. The attack by a proton on allene might conceivably lead to the allyl cation or the 2-propenyl cation.

$$^{+}CH_2-CH=CH_2 \xleftarrow{H^+} CH_2=C=CH_2 \xrightarrow{H^+} CH_3-\overset{+}{C}=CH_2$$

An immediate presumption that the more stable allyl ion will be formed overlooks the stereoelectronic facets of the reaction. Protonation at the center carbon without rotation of one of the terminal methylene groups leads to a primary carbocation

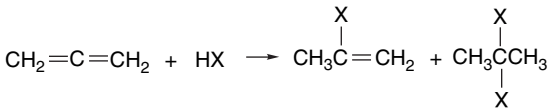
140. P. G. Gassman, D. P. Gilbert, and S. M. Cole, *J. Org. Chem.*, **42**, 3233 (1977).
141. H. F. Schuster and G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, 1984 ; W. Smadja, *Chem. Rev.*, **83**, 263 (1983); S. Ma, in *Modern Allene Chemistry*, N. Krause and A. S. K. Hashmi, eds., Wiley-VCH, Weinheim, 2004, pp. 595–699.
142. W. Drenth, in *The Chemistry of Triple Bonded Functional Groups*, Supplement C2, Vol. 2, S. Patai, ed., John Wiley & Sons, New York, 1994, pp. 873–915.

that is not stabilized by resonance, because the adjacent π bond is orthogonal to the empty *p* orbital.

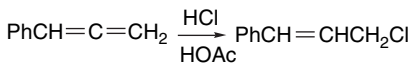


As a result, protonation both in solution[143] and gas phase[144] occurs at a terminal carbon to give the 2-propenyl cation, not the allylic cation.

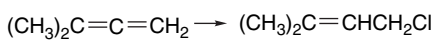
The addition of HCl, HBr, and HI to allene has been studied in some detail.[145] In each case a 2-halopropene is formed, corresponding to protonation at a terminal carbon. The initial product can undergo a second addition, giving rise to 2,2-dihalopropanes. The regiochemistry reflects the donor effect of the halogen. Dimers are also formed, but we have not considered them.



The presence of a phenyl group results in the formation of products from protonation at the center carbon.[146]

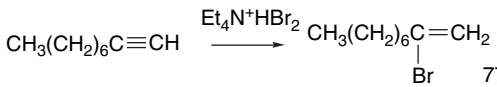


Two alkyl substituents, as in 1,1-dimethylallene, also lead to protonation at the center carbon.[147]



These substituent effects are due to the stabilization of the carbocations that result from protonation at the center carbon. Even if allylic conjugation is not important, the aryl and alkyl substituents make the terminal carbocation more stable than the alternative, a secondary vinyl cation.

Acid-catalyzed additions to terminal alkynes follow the Markovnikov rule.

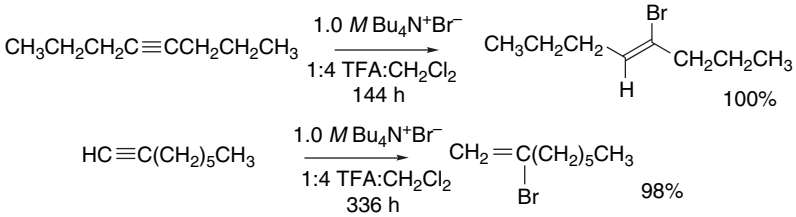


Ref. 148

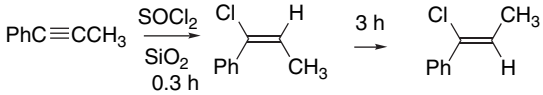
The rate and selectivity of the reaction can be considerably enhanced by using an added quaternary bromide salt in 1:1 TFA:CH_2Cl_2. Note that the reactions are quite

143. P. Cramer and T. T. Tidwell, *J. Org. Chem.*, **46**, 2683 (1981).
144. M. T. Bowers, L. Shuying, P. Kemper, R. Stradling, H. Webb, D. H. Aue, J. R. Gilbert, and K. R. Jennings, *J. Am. Chem. Soc.*, **102**, 4830 (1980); S. Fornarini, M. Speranza, M. Attina, F. Cacace, and P. Giacomello, *J. Am. Chem. Soc.*, **106**, 2498 (1984).
145. K. Griesbaum, W. Naegele, and G. G. Wanless, *J. Am. Chem. Soc.*, **87**, 3151 (1965).
146. T. Okuyama, K. Izawa, and T. Fueno, *J. Am. Chem. Soc.*, **95**, 6749 (1973).
147. T. L. Jacobs and R. N. Johnson, *J. Am. Chem. Soc.*, **82**, 6397 (1960).
148. J. Cousseau, *Synthesis*, 805 (1980).

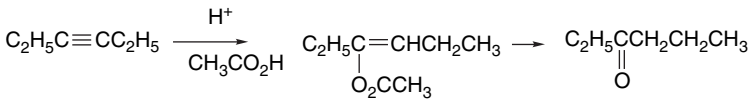
slow, even under these favorable conditions, but there is clean formation of the *anti* addition product.[149]



Surface-mediated addition of HCl or HBr can be carried out in the presence of silica or alumina.[150] The hydrogen halides can be generated from thionyl chloride, oxalyl chloride, oxalyl bromide, phosphorus tribromide, or acetyl bromide. The kinetic products from HCl and 1-phenylpropyne result from *syn* addition, but isomerization to the more stable *Z*-isomer occurs upon continued exposure to the acidic conditions.

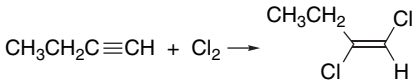


The initial addition products to alkynes are not always stable. Addition of acetic acid, for example, results in the formation of enol acetates, which are converted to the corresponding ketone under the reaction conditions.[151]



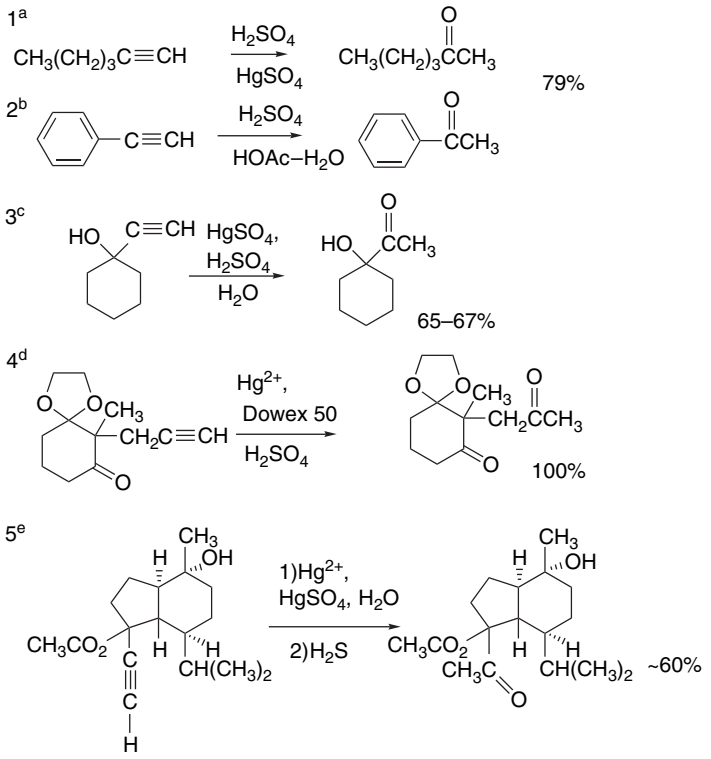
The most synthetically valuable method for converting alkynes to ketones is by mercuric ion–catalyzed hydration. Terminal alkynes give methyl ketones, in accordance with the Markovnikov rule. Internal alkynes give mixtures of ketones unless some structural feature promotes regioselectivity. Reactions with $Hg(OAc)_2$ in other nucleophilic solvents such as acetic acid or methanol proceed to β-acetoxy- or β-methoxyalkenylmercury intermediates,[152] which can be reduced or solvolyzed to ketones. The regiochemistry is indicative of a mercurinium ion intermediate that is opened by nucleophilic attack at the more positive carbon, that is, the additions follow the Markovnikov rule. Scheme 4.8 gives some examples of alkyne hydration reactions.

Addition of chlorine to 1-butyne is slow in the absence of light. When addition is initiated by light, the major product is *E*-1,2-dichlorobutene if butyne is present in large excess.[153]



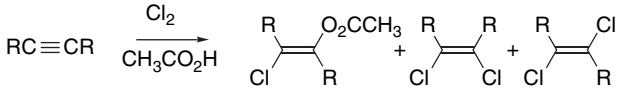
149. H. M. Weiss and K. M. Touchette, *J. Chem. Soc., Perkin Trans. 2*, 1523 (1998).
150. P. J. Kropp and S. D. Crawford, *J. Org. Chem.*, **59**, 3102 (1994).
151. R. C. Fahey and D.-J. Lee, *J. Am. Chem. Soc.*, **90**, 2124 (1968).
152. M. Uemura, H. Miyoshi, and M. Okano, *J. Chem. Soc., Perkin Trans. 1*, 1098 (1980); R. D. Bach, R. A. Woodward, T. J. Anderson, and M. D. Glick, *J. Org. Chem.*, **47**, 3707 (1982); M. Bassetti, B. Floris, and G. Spadafora, *J. Org. Chem.*, **54**, 5934 (1989).
153. M. L. Poutsma and J. L. Kartch, *Tetrahedron*, **22**, 2167 (1966).

Scheme 4.8. Ketones by Hydration of Alkynes



a. R. J. Thomas, K. N. Campbell, and G. F. Hennion, *J. Am. Chem. Soc.*, **60**, 718 (1938).
b. R. W. Bott, C. Eaborn, and D. R. M. Walton, *J. Chem. Soc.*, 384 (1965).
c. G. N. Stacy and R. A. Mikulec, *Org. Synth.*, **IV**, 13 (1963).
d. W. G. Dauben and D. J. Hart, *J. Org. Chem.*, **42**, 3787 (1977).
e. D. Caine and F. N. Tuller, *J. Org. Chem.*, **38**, 3663 (1973).

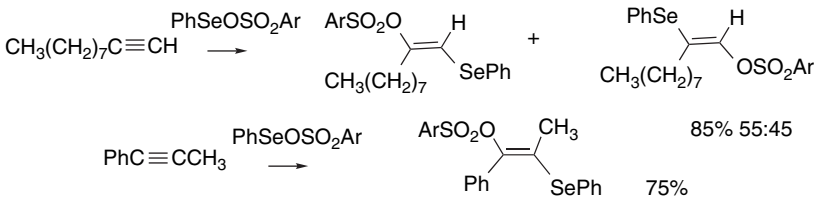
In acetic acid, both 1-pentyne and 1-hexyne give the *syn* addition product. With 2-butyne and 3-hexyne, the major products are β-chlorovinyl acetates of *E*-configuration.[154] Some of the dichloro compounds are also formed, with more of the *E*- than the *Z*-isomer being observed.



The reactions of the internal alkynes are considered to involve a cyclic halonium ion intermediate, whereas the terminal alkynes seem to react by a rapid collapse of a vinyl cation.

Alkynes react with electrophilic selenium reagents such as phenylselenenyl tosylate.[155] The reaction occurs with *anti* stereoselectivity. Aryl-substituted alkynes are regioselective, but alkyl-substituted alkynes are not.

154. K. Yates and T. A. Go, *J. Org. Chem.*, **45**, 2385 (1980).
155. T. G. Back and K. R. Muralidharan, *J. Org. Chem.*, **56**, 2781 (1991).

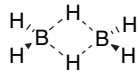


Some of the most synthetically useful addition reactions of alkynes are with organometallic reagents, and these reactions, which can lead to carbon-carbon bond formation, are discussed in Chapter 8.

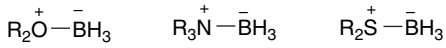
4.5. Addition at Double Bonds via Organoborane Intermediates

4.5.1. Hydroboration

Borane, BH_3, having only six valence electrons on boron, is an avid electron pair acceptor. Pure borane exists as a dimer in which two hydrogens bridge the borons.



In aprotic solvents that can act as electron pair donors such as ethers, tertiary amines, and sulfides, borane forms Lewis acid-base adducts.

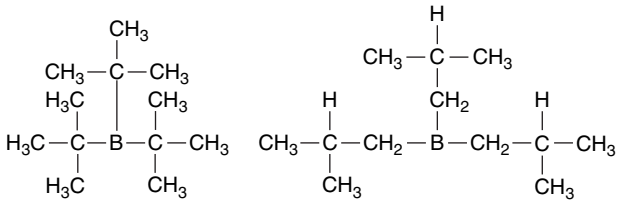


Borane dissolved in THF or dimethyl sulfide undergoes addition reactions rapidly with most alkenes. This reaction, which is known as *hydroboration*, has been extensively studied and a variety of useful synthetic processes have been developed, largely through the work of H. C. Brown and his associates.

Hydroboration is highly *regioselective* and *stereospecific*. The boron becomes bonded primarily to the *less-substituted* carbon atom of the alkene. A combination of steric and electronic effects works to favor this orientation. Borane is an electrophilic reagent. The reaction with substituted styrenes exhibits a weakly negative ρ value (−0.5).[156] Compared with bromination ($\rho^+ = -4.3$),[157] this is a small substituent effect, but it does favor addition of the electrophilic boron at the less-substituted end of the double bond. In contrast to the case of addition of protic acids to alkenes, it is the *boron, not the hydrogen, that is the more electrophilic atom*. This electronic effect is reinforced by steric factors. Hydroboration is usually done under conditions in which the borane eventually reacts with three alkene molecules to give a trialkylborane. The

156. L. C. Vishwakarma and A. Fry, *J. Org. Chem.*, **45**, 5306 (1980).
157. J. A. Pincock and K. Yates, *Can. J. Chem.*, **48**, 2944 (1970).

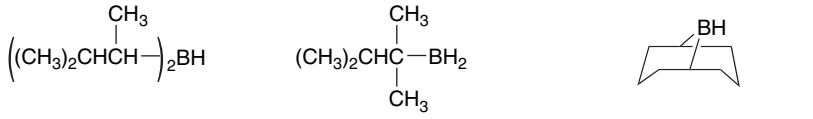
second and third alkyl groups would increase steric repulsion if the boron were added at the internal carbon.



nonbonded repulsions

nonbonded repulsions reduced

Table 4.3 provides some data on the regioselectivity of addition of diborane and several of its derivatives to representative alkenes. Table 4.3 includes data for some mono- and dialkylboranes that show even higher regioselectivity than diborane itself. These derivatives are widely used in synthesis and are frequently referred to by the shortened names shown with the structures.



disiamylborane
bis(1,2-dimethylpropyl) borane

thexylborane
1,1,2-trimethylpropylborane

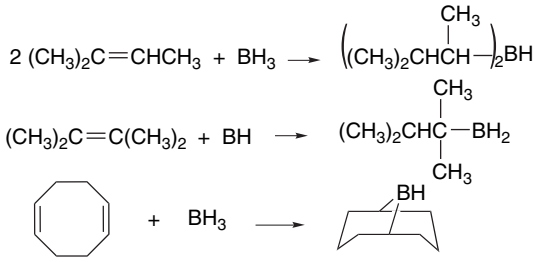
9-BBN
9-borabicyclo[3.3.1]nonane

Table 4.3. Regioselectivity of Diborane and Alkylboranes toward Some Alkenes

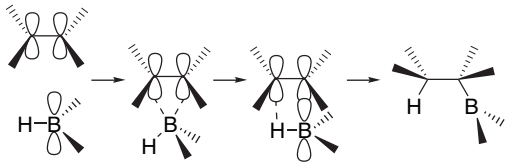
	Percent boron at less substituted carbon			
Hydroborating agent	1-Hexene	2-Methyl-1-butene	4-Methyl-2-pentene	Styrene
Diborane[a]	94	99	57	80
Chloroborane-dimethyl sulfide[b]	99	99.5	–	98
Disiamylborane[a]	99	–	97	98
Thexylborane-dimethyl sulfide[c]	94	–	66	95
Thexylchloroborane-dimethyl sulfide	99	99	97	99
9-Borabicyclo[3.3.1]borane	99.9	99.8[f]	99.3	98.5

a. G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).
b. H. C. Brown, N. Ravindran, and S. U. Kulkarni, *J. Org. Chem.*, **44**, 2417 (1969); H. C. Brown and U. S. Racherla, *J. Org. Chem.*, **51**, 895 (1986).
c. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 4708 (1960).
d. H. C. Brown, J. A. Sikorski, S. U. Kulkarni, and H. D. Lee, *J. Org. Chem.*, **45**, 4540 (1980).
e. H. C. Brown, E. F. Knight, and C. G. Scouten, *J. Am. Chem. Soc.*, **96**, 7765 (1974).
f. Data for 2-methyl-1-pentene.

These reagents are prepared by hydroboration of the appropriate alkene, using control of stoichiometry to terminate the hydroboration at the desired degree of alkylation.



Hydroboration is a stereospecific *syn* addition that occurs through a four-center TS with simultaneous bonding to boron and hydrogen. The new C−B and C−H bonds are thus both formed from the same face of the double bond. In molecular orbital terms, the addition is viewed as taking place by interaction of the filled alkene π orbital with the empty *p* orbital on boron, accompanied by concerted C−H bond formation.[158]



As is true for most reagents, there is a preference for approach of the borane from the less hindered face of the alkene. Because diborane itself is a relatively small molecule, the stereoselectivity is not high for unhindered alkenes. Table 4.4 gives some data comparing the direction of approach for three cyclic alkenes. The products in all cases result from *syn* addition, but the mixtures result from both the low regioselectivity and from addition to both faces of the double bond. Even 7,7-dimethylnorbornene shows only modest preference for *endo* addition with diborane. The selectivity is enhanced with the bulkier reagent 9-BBN.

Table 4.4. Stereoselectivity of Hydroboration of Cyclic Alkenes[a]

	Product composition[b]								
	3-Methyl cyclopentene			4-Methyl cyclohexene				7,7-Dimethylbi-cyclo[2.2.1]heptene	
	trans-2	*cis*-3	*trans*-3	*cis*-2	*trans*-2	*cis*-3	*trans*-3	*exo*	*endo*
Diborane	45	55		16	34	18	32	22	78[c]
Disiamylborane	40	60		18	30	27	25	–	–
9-BBN	25	50	25	0	20	40	40	3	97

a. Data from H. C. Brown, R. Liotta, and L. Brener, *J. Am. Chem. Soc.*, **99**, 3427 (1977), except where otherwise noted.
b. Product composition refers to methylcycloalkanols formed by oxidation.
c. H. C. Brown, J. H. Kawakami, and K.-T. Liu, *J. Am. Chem. Soc.*, **95**, 2209 (1973).

158. D. J. Pasto, B. Lepeska, and T.-C. Cheng, *J. Am. Chem. Soc.*, **94**, 6083 (1972); P. R. Jones, *J. Org. Chem.*, **37**, 1886 (1972); S. Nagase, K. N. Ray, and K. Morokuma, *J. Am. Chem. Soc.*, **102**, 4536 (1980); X. Wang, Y. Li, Y.-D. Wu, M. N. Paddon-Row, N. G. Rondan, and K. N. Houk, *J. Org. Chem.*, **55**, 2601 (1990); N. J. R. van Eikema Hommes and P. v. R. Schleyer, *J. Org. Chem.*, **56**, 4074 (1991).

The haloboranes BH_2Cl, BH_2Br, $BHCl_2$, and $BHBr_2$ are also useful hydroborating reagents.[159] These compounds are somewhat more regioselective than borane itself, but otherwise show similar reactivity. A useful aspect of the chemistry of the haloboranes is the potential for sequential introduction of substituents at boron. The halogens can be replaced by alkoxide or by hydride. When halogen is replaced by hydride, a second hydroboration step can be carried out.

$$R_2BX + NaOR' \longrightarrow R_2BOR'$$

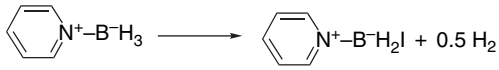
$$R_2BX + LiAlH_4 \longrightarrow R_2BH$$

$$RBX_2 + LiAlH_4 \longrightarrow RBH_2$$

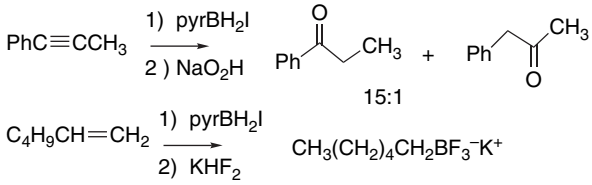
X = Cl, Br

Examples of these transformations are discussed in Chapter 9, where carbon-carbon bond-forming reactions of organoboranes are covered.

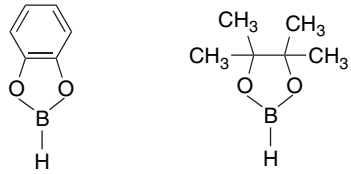
Amine-borane complexes are not very reactive toward hydroboration, but the pyridine complex of borane can be activated by reaction with iodine.[160] The active reagent is thought to be the pyridine complex of iodoborane.



The resulting boranes can be subjected to oxidation or isolated as potassium trifluoroborates.



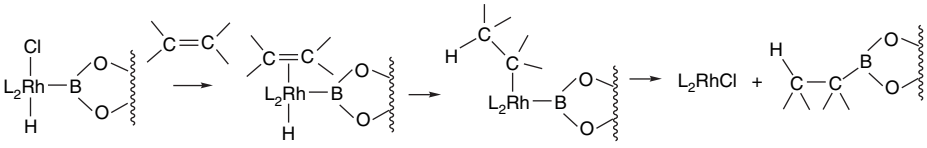
Catecholborane and pinacolborane, in which the boron has two oxygen substituents, are much less reactive hydroborating reagents than alkyl or haloboranes because the boron electron deficiency is attenuated by the oxygen atoms. Nevertheless, they are useful reagents for certain applications.[161] The reactivity of catecholborane has been found to be substantially enhanced by addition of 10–20% of *N*,*N*-dimethylacetamide to CH_2Cl_2.[162]



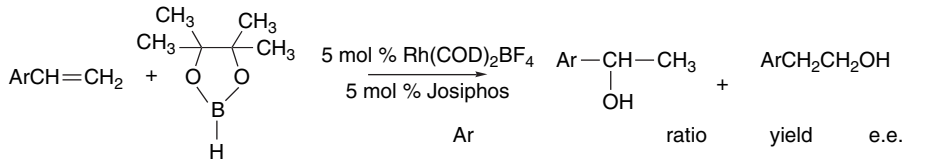
catecholborane pinacolborane

159. H. C. Brown and S. U. Kulkarni, *J. Organomet. Chem.*, **239**, 23 (1982).
160. J. M. Clay and E. Vedejs, *J. Am. Chem. Soc.*, **127**, 5766 (2005).
161. C. E. Tucker, J. Davidson, and P. Knockel, *J. Org. Chem.*, **57**, 3482 (1992).
162. C. E. Garrett and G. C. Fu, *J. Org. Chem.*, **61**, 3224 (1996).

Catecholborane and pinacolborane are especially useful in hydroborations catalyzed by transition metals.[163] Wilkinson's catalyst $Rh(PPh_3)_3Cl$ is among those used frequently.[164] The general mechanism for catalysis is believed to be similar to that for homogeneous hydrogenation and involves oxidative addition of the borane to the metal, generating a metal hydride.[165]

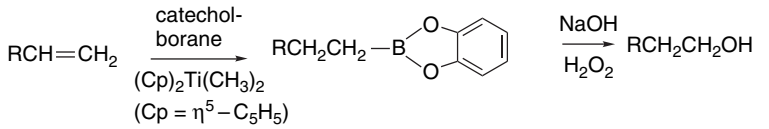


Variation in catalyst and ligand can lead to changes in both regio- and enantioselectivity. For example, the hydroboration of vinyl arenes such as styrene and 6-methoxy-2-vinylnaphthalene can be directed to the internal secondary borane by use of $Rh(COD)_2BF_4$ as a catalyst.[166] These reactions are enantioselective in the presence of a chiral phosphorus ligand.



Ar	ratio	yield	e.e.
Phenyl	83:17	87%	84%
6-Methoxynaphthyl	95:5	83%	88%

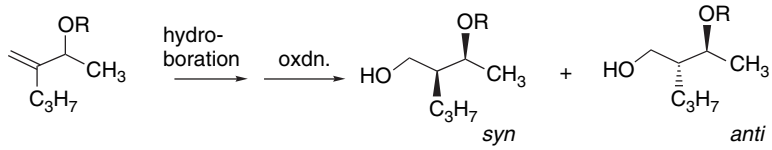
On the other hand, iridium catalysts give very high selectivity for formation of the primary borane.[167] Several other catalysts have been described, including, for example, dimethyltitanocene.[168]



Catalyzed hydroboration has proven to be valuable in controlling the stereoselectivity of hydroboration of functionalized alkenes.[169] For example, allylic alcohols

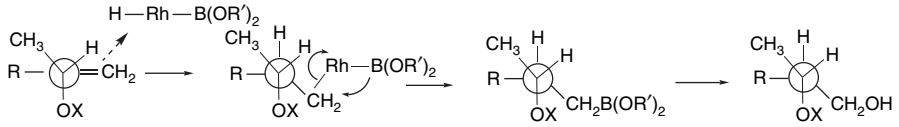
163. I. Beletskaya and A. Pelter, *Tetrahedron*, **53**, 4957 (1997); H. Wadepohl, *Angew. Chem. Int. Ed. Engl.*, **36**, 2441 (1997); K. Burgess and M. J. Ohlmeyer, *Chem. Rev.*, **91**, 1179 (1991); C. M. Crudden and D. Edwards, *Eur. J. Org. Chem.*, 4695 (2003).
164. D. A. Evans, G. C. Fu, and A. H. Hoveyda, *J. Am. Chem. Soc.*, **110**, 6917 (1988); D. Maenning and H. Noeth, *Angew. Chem. Int. Ed. Engl.*, **24**, 878 (1985).
165. D. A. Evans, G. C. Fu, and B. A. Anderson, *J. Am. Chem. Soc.*, **114**, 6679 (1992).
166. C. M. Crudden, Y. B. Hleba, and A. C. Chen, *J. Am. Chem. Soc.*, **126**, 9200 (2004).
167. Y. Yamamoto, R. Fujikawa, T. Unemoto, and N. Miyaura, *Tetrahedron*, **60**, 10695 (2004).
168. X. He and J. F. Hartwig, *J. Am. Chem. Soc.*, **118**, 1696 (1996).
169. D. A. Evans, G. C. Fu, and A. H. Hoveyda, *J. Am. Chem. Soc.*, **114**, 6671 (1992).

and ethers give mainly *syn* product when catalyzed by $Rh(PPh_3)_3Cl$, whereas direct hydroboration with 9-BBN gives mainly *anti* product.

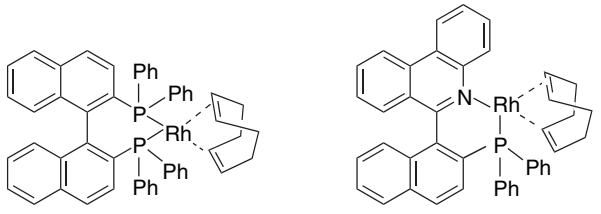


	9-BBN		catecholborane 3 mol % $Rh(PPh_3)_3Cl$	
R	yield	*syn:anti*	yield	*syn:anti*
H	91	17:83	79	81:19
$PhCH_2$	82	25:75	63	80:20
TBDMS	85	13:87	79	93:7

The stereoselectivity of the catalyzed reaction appears to be associated with the complexation step, which is product determining. The preferred orientation of approach of the complex is *anti* to the oxygen substituent, which acts as an electron acceptor and more electronegative groups enhance reactivity. The preferred conformation of the alkene has the hydrogen oriented toward the double bond and this leads to a *syn* relationship between the alkyl and oxygen substituents.[170]



The use of chiral ligands in catalysts can lead to enantioselective hydroboration. Rh-BINAP[171] **C** and the related structure **D**[172] have shown good stereoselectivity in the hydroboration of styrene and related compounds (see also Section 4.5.3).



C **D**

	styrene	indene
C	96% e.e.	13% e.e.
D	67% e.e.	84% e.e.

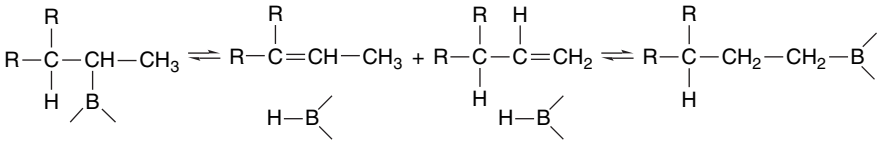
Hydroboration is thermally reversible. B−H moieties are eliminated from alkylboranes at 160° C and above, but the equilibrium still favors of the addition products.

170. K. Burgess, W. A. van der Donk, M. B. Jarstfer, and M. J. Ohlmeyer, *J. Am. Chem. Soc.*, **113**, 6139 (1991).

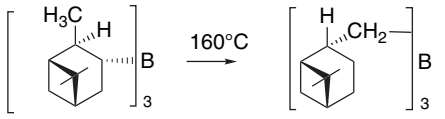
171. T. Hayashi and Y. Matsumoto, *Tetrahedron: Asymmetry*, **2**, 601 (1991).

172. J. M. Valk, G. A. Whitlock, T. P. Layzell, and J. M. Brown, *Tetrahedron: Asymmetry*, **6**, 2593 (1995).

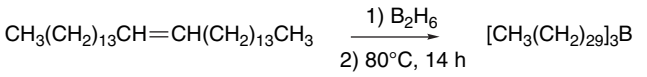
This provides a mechanism for migration of the boron group along the carbon chain by a series of eliminations and additions.



Migration cannot occur past a quaternary carbon, however, since the required elimination is blocked. At equilibrium the major trialkyl borane is the least-substituted terminal isomer that is accessible, since this isomer minimizes unfavorable steric interactions.

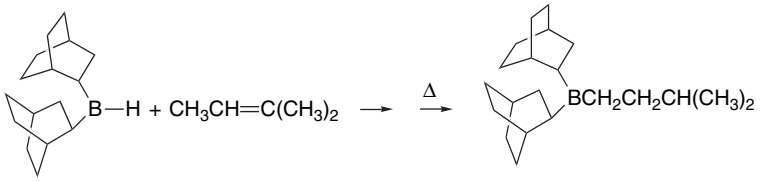


Ref. 173



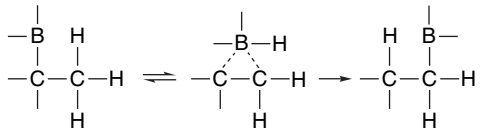
Ref. 174

Migrations are more facile for *tetra*-substituted alkenes and occur at 50°–60° C.[175] Bulky substituents on boron facilitate the migration. *bis*-Bicyclo[2.2.2]octanylboranes, in which there are no complications from migrations in the bicyclic substituent, were found to be particularly useful.



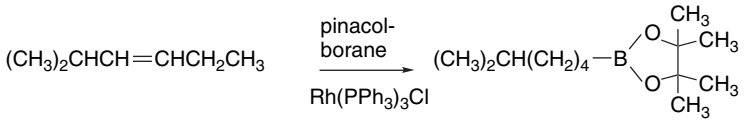
Ref. 176

There is evidence that boron migration occurs intramolecularly.[177] A TS involving an electron-deficient π complex about 20–25 kcal above the trialkylborane that describes the migration has been located computationally.[178]



173. G. Zweifel and H. C. Brown, *J. Am. Chem. Soc.*, **86**, 393 (1964).
174. K. Maruyama, K. Terada, and Y. Yamamoto, *J. Org. Chem.*, **45**, 737 (1980).
175. L. O. Bromm, H. Laaziri, F. Lhermitte, K. Harms, and P. Knochel, *J. Am. Chem. Soc.*, **122**, 10218 (2000).
176. H. C. Brown and U. S. Racherla, *J. Am. Chem. Soc.*, **105**, 6506 (1983).
177. S. E. Wood and B. Rickborn, *J. Org. Chem.*, **48**, 555 (1983).
178. N. J. R. van Eikema Hommes and P. v. R. Schleyer, *J. Org. Chem.*, **56**, 4074 (1991).

Migration of boron to terminal positions is observed under much milder conditions in the presence of transition metal catalysts. For example, hydroboration of 2-methyl-3-hexene by pinacolborane in the presence of $Rh(PPh_3)_3Cl$ leads to the terminal boronate ester.

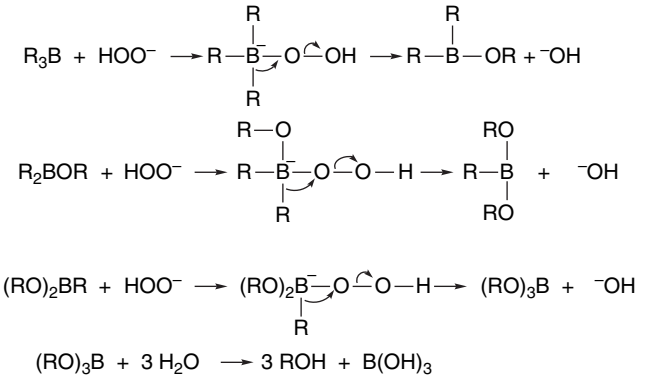


Ref. 179

4.5.2. Reactions of Organoboranes

The organoboranes have proven to be very useful intermediates in organic synthesis. In this section we discuss methods by which the boron atom can be replaced by hydroxy, carbonyl, amino, or halogen groups. There are also important processes that use alkylboranes in the formation of new carbon-carbon bonds. These reactions are discussed in Section 9.1.

The most widely used reaction of organoboranes is the oxidation to alcohols, and alkaline hydrogen peroxide is the reagent usually employed to effect the oxidation. The mechanism, which is outlined below, involves a series of B to O migrations of the alkyl groups. The R−O−B bonds are hydrolyzed in the alkaline aqueous solution, generating the alcohol.

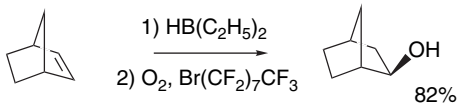


The stereochemical outcome is replacement of the C−B bond by a C−O bond with *retention of configuration*. In combination with stereospecific *syn* hydroboration, this allows the structure and stereochemistry of the alcohols to be predicted with confidence. The preference for hydroboration at the least-substituted carbon of a double bond results in the alcohol being formed with regiochemistry that is complementary to that observed by direct hydration or oxymercuration, that is, anti-Markovnikov.

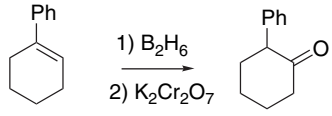
Several other oxidants can be used to effect the borane to alcohol conversion. Oxone® ($2K_2SO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) has been recommended for oxidations done on a

[179.] S. Pereira and M. Srebnik, *J. Am. Chem. Soc.*, **118**, 909 (1996); S. Pereira and M. Srebnik, *Tetrahedron Lett.*, **37**, 3283 (1996).

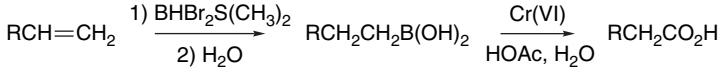
large scale.[180] Conditions that permit oxidation of organoboranes to alcohols using molecular oxygen,[181] sodium peroxycarbonate[182] or amine oxides[183] as oxidants have also been developed. The reaction with molecular oxygen is particularly effective in perfluoroalkane solvents.[184]



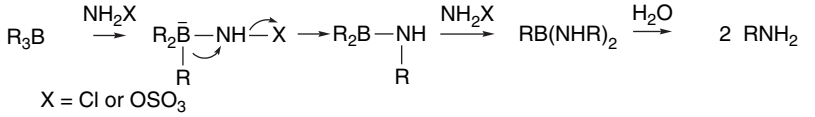
More vigorous oxidants such as Cr(VI) reagents effect replacement of boron and oxidation to the carbonyl level.[185]



An alternative procedure for oxidation to ketones involves treatment of the alkylborane with a quaternary ammonium perruthenate salt and an amine oxide[186] (see Entry 6 in Scheme 4.9). Use of dibromoborane-dimethyl sulfide for hydroboration of terminal alkenes, followed by hydrolysis and Cr(VI) oxidation gives carboxylic acids.[187]

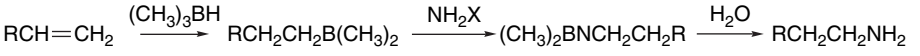


The boron atom can also be replaced by an amino group.[188] The reagents that effect this conversion are chloramine or hydroxylamine-*O*-sulfonic acid, and the mechanism of these reactions is very similar to that of the hydrogen peroxide oxidation of organoboranes. The nitrogen-containing reagent initially reacts as a nucleophile by adding at boron and a B to N rearrangement with expulsion of chloride or sulfate ion follows. Usually only two of the three alkyl groups migrate. As in the oxidation, the migration step occurs with retention of configuration. The amine is freed by hydrolysis.

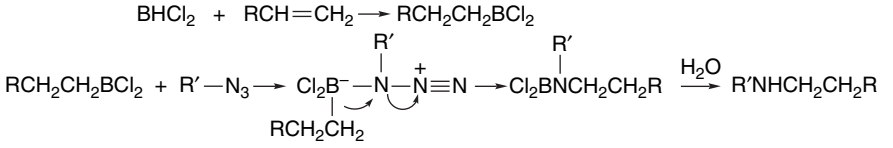


180. D. H. B. Ripin, W. Cai, and S. T. Brenek, *Tetrahedron Lett.*, **41**, 5817 (2000).
181. H. C. Brown, M. M. Midland, and G. W. Kabalka, *J. Am. Chem. Soc.*, **93**, 1024 (1971).
182. G. W. Kabalka, P. P. Wadgaonkar, and T. M. Shoup, *Tetrahedron Lett.*, **30**, 5103 (1989).
183. G. W. Kabalka and H. C. Hedgecock, Jr., *J. Org. Chem.*, **40**, 1776 (1975); R. Koster and Y. Monta, *Liebigs Ann. Chem.*, **704**, 70 (1967).
184. I. Klement and P. Knochel, *Synlett*, 1004 (1996).
185. H. C. Brown and C. P. Garg, *J. Am. Chem. Soc.*, **83**, 2951 (1961); H. C. Brown, C. Rao, and S. Kulkarni, *J. Organomet. Chem.*, **172**, C20 (1979).
186. M. H. Yates, *Tetrahedron Lett.*, **38**, 2813 (1997).
187. H. C. Brown, S. V. Kulkarni, V. V. Khanna, V. D. Patil, and U. S. Racherla, *J. Org. Chem.*, **57**, 6173 (1992).
188. M. W. Rathke, N. Inoue, K. R. Varma, and H. C. Brown, *J. Am. Chem. Soc.*, **88**, 2870 (1966); G. W. Kabalka, K. A. R. Sastry, G. W. McCollum, and H. Yoshioka, *J. Org. Chem.*, **46**, 4296 (1981).

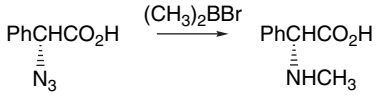
The alkene can be used more efficiently if the hydroboration is done with dimethylborane.[189]



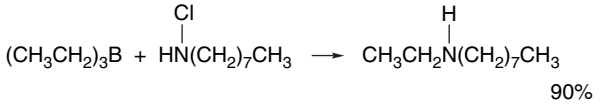
Secondary amines are formed by reaction of trisubstituted boranes with alkyl or aryl azides. The most efficient borane intermediates are monoalkyldichloroboranes, which are generated by reaction of an alkene with $BHCl_2 \cdot Et_2O$.[190] The entire sequence of steps and the mechanism of the final stages are summarized by the equation below.



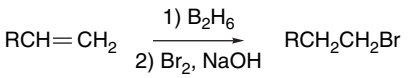
This reaction has been used to prepare α-*N*-methylamino acids using $(CH_3)_2BBr$.[191]



Secondary amines can also be made using the *N*-chloro derivatives of primary amines.[192]

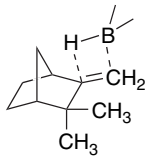


Organoborane intermediates can also be used to synthesize alkyl halides. Replacement of boron by iodine is rapid in the presence of base.[193] The best yields are obtained using sodium methoxide in methanol.[194] If less basic conditions are desirable, the use of iodine monochloride and sodium acetate gives good yields.[195] As is the case in hydroboration-oxidation, the regioselectivity of hydroboration-halogenation is opposite to that observed by direct ionic addition of hydrogen halides to alkenes. Terminal alkenes give primary halides.

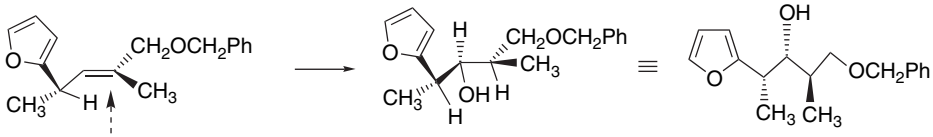


189. H. C. Brown, K.-W. Kim, M. Srebnik, and B. Singaram, *Tetrahedron*, **43**, 4071 (1987).
190. H. C. Brown, M. M. Midland, and A. B. Levy, *J. Am. Chem. Soc.*, **95**, 2394 (1973).
191. R. L. Dorow and D. E. Gingrich, *J. Org. Chem.*, **60**, 4986 (1995).
192. G. W. Kabalka, G. W. McCollum, and S. A. Kunda, *J. Org. Chem.*, **49**, 1656 (1984).
193. H. C. Brown, M. W. Rathke, and M. M. Rogic, *J. Am. Chem. Soc.*, **90**, 5038 (1968).
194. N. R. De Lue and H. C. Brown, *Synthesis*, 114 (1976).
195. G. W. Kabalka and E. E. Gooch, III, *J. Org. Chem.*, **45**, 3578 (1980).

Scheme 4.9 gives some examples of the use of boranes in syntheses of alcohols, aldehydes, ketones, amines, and halides. Entry 1 demonstrates both the regioselectivity and stereospecificity of hydroboration, resulting in the formation of *trans*-2-methylcyclohexanol. Entry 2 illustrates the facial selectivity, with the borane adding *anti* to the *endo* methyl group.



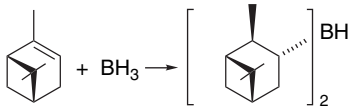
Entry 3 illustrates all aspects of the regio- and stereoselectivity, with *syn* addition occurring *anti* to the dimethyl bridge in the pinene structure. The stereoselectivity in Entry 4 is the result of the preferred conformation of the alkene and approach *syn* to the smaller methyl group, rather than the 2-furyl group.



Entries 5 to 7 are examples of oxidation of boranes to the carbonyl level. In Entry 5, chromic acid was used to obtain a ketone. Entry 6 shows 5 mol % tetrapropylammonium perruthenate with *N*-methylmorpholine-*N*-oxide as the stoichiometric oxidant converting the borane directly to a ketone. Aldehydes were obtained from terminal alkenes using this reagent combination. Pyridinium chlorochromate (Entry 7) can also be used to obtain aldehydes. Entries 8 and 9 illustrate methods for amination of alkenes via boranes. Entries 10 and 11 illustrate the preparation of halides.

4.5.3. Enantioselective Hydroboration

Several alkylboranes are available in enantiomerically enriched or pure form and can be used to prepare enantiomerically enriched alcohols and other compounds available via organoborane intermediates.[196] One route to enantiopure boranes is by hydroboration of readily available terpenes that occur naturally in enantiomerically enriched or pure form. The most thoroughly investigated of these is *bis*-(isopinocampheyl)borane; $(Ipc)_2BH$), which can be prepared in 100% enantiomeric purity from the readily available terpene α-pinene.[197] Both enantiomers are available.

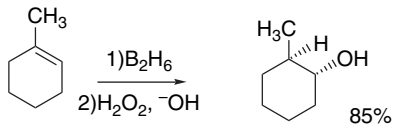


196. H. C. Brown and B. Singaram, *Acc. Chem. Res.*, **21**, 287 (1988); D. S. Matteson, *Acc. Chem. Res.*, **21**, 294 (1988).
197. H. C. Brown, P. K. Jadhav, and A. K. Mandal, *Tetrahedron*, **37**, 3547 (1981); H. C. Brown and P. K. Jadhav, in *Asymmetric Synthesis*, Vol. 2, J. D. Morrison, ed., Academic Press, New York, 1983, Chap. 1.

Scheme 4.9. Synthesis of Alcohols, Aldehydes, Ketones, and Amines from Organoboranes

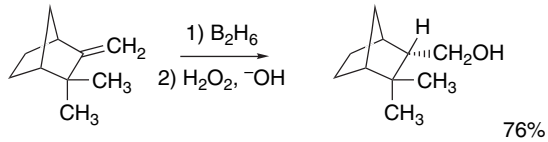
A. Alcohols

1[a]



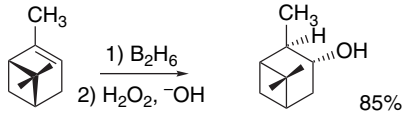
85%

2[b]



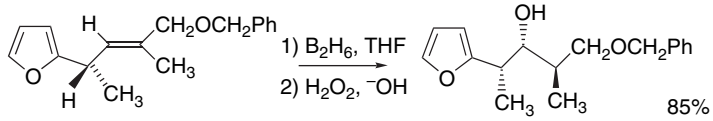
76%

3[c]



85%

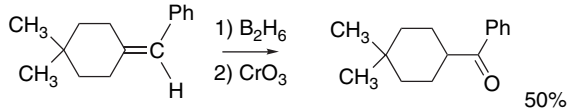
4[d]



85%

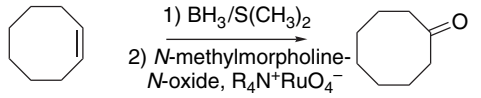
B. Ketones and aldehydes

5[e]

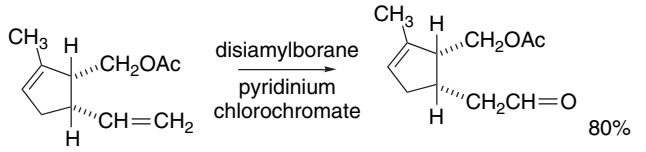


50%

6[f]



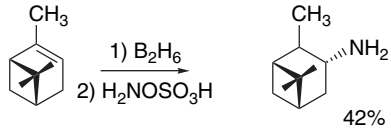
7[g]



80%

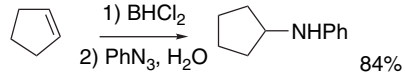
C. Amines

8[h]



42%

9[i]

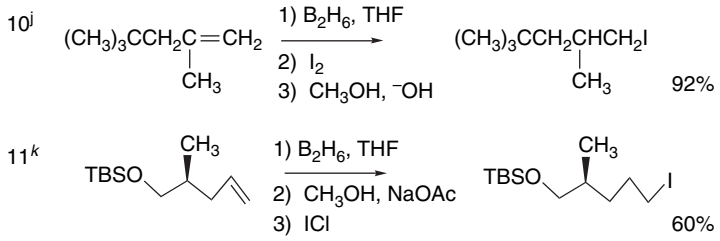


84%

(*Continued*)

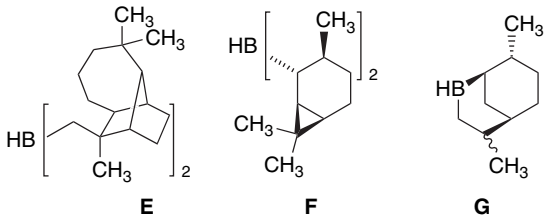
Scheme 4.9. (*Continued*)

D. Halides

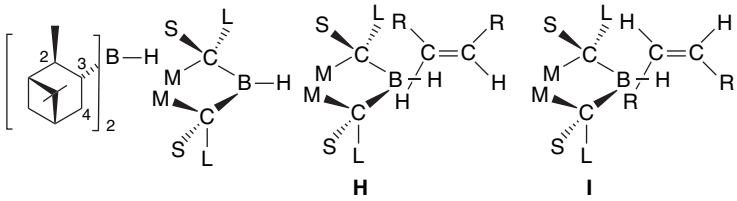


a. H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2544 (1961).
b. R. Dulou, Y. Chretien-Bessiere, *Bull. Soc. Chim. Fr.*, 1362 (1959).
c. G. Zweifel and H. C. Brown, *Org. Synth.*, **52**, 59 (1972).
d. G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.*, **101**, 259 (1979).
e. W. B. Farnham, *J. Am. Chem. Soc.*, **94**, 6857 (1972).
f. M. H. Yates, *Tetrahedron Lett.*, **38**, 2813 (1997).
g. H. C. Brown, S. U. Kulkarni, and C. G. Rao, *Synthesis*, 151 (1980); T. H. Jones and M. S. Blum, *Tetrahedron Lett.*, **22**, 4373 (1981).
h. M. W. Rathke and A. A. Millard, *Org. Synth.*, **58**, 32 (1978).
i. H. C. Brown, M. M. Midland, and A. B. Levy, *J. Am. Chem. Soc.*, **95**, 2394 (1973).
j. H. C. Brown, M. W. Rathke, M. M. Rogic, and N. R. DeLue, *Tetrahedron*, **44**, 2751 (1988).
k. D. Schinzer, A. Bauer, and J. Schreiber, *Chem. Eur. J.*, **5**, 2492 (1999).

Other examples of chiral organoboranes derived from terpenes are **E**, **F**, and **G**, which are derived from longifolene,[198] 2-carene,[199] and limonene,[200] respectively.



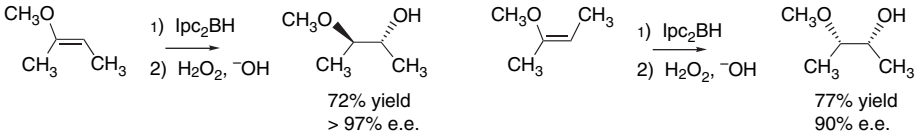
$(Ipc)_2BH$ adopts a conformation that minimizes steric interactions. This conformation can be represented schematically as in **H** and **I**, where the S, M, and L substituents are, respectively, the 3-H, 4-CH_2, and 2-$CHCH_3$ groups of the carbocyclic structure. The steric environment at boron in this conformation is such that *Z*-alkenes encounter less steric encumbrance in TS **I** than in **H**.



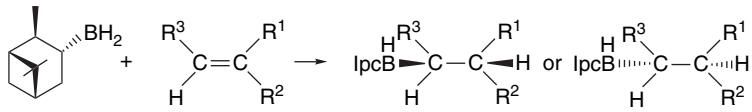
The degree of enantioselectivity of $(Ipc)_2BH$ is not high for all simple alkenes. *Z*-Disubstituted alkenes give good enantioselectivity (75–90%) but *E*-alkenes and

198. P. K. Jadhav and H. C. Brown, *J. Org. Chem.*, **46**, 2988 (1981).
199. H. C. Brown, J. V. N. Vara Prasad, and M. Zaidlewicz, *J. Org. Chem.*, **53**, 2911 (1988).
200. P. K. Jadhav and S. U. Kulkarni, *Heterocylces*, **18**, 169 (1982).

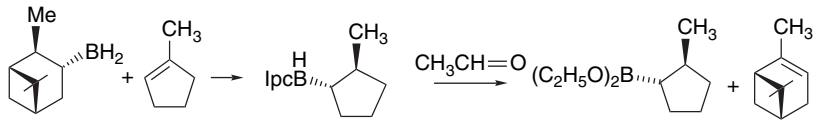
simple cycloalkenes give low enantioselectivity (5–30%). Interestingly, vinyl ethers exhibit good enantioselectivity for both the *E*- and *Z*-isomers.[201]



Monoisocampheylborane ($IpcBH_2$) can be prepared in enantiomerically pure form by separation of a TMEDA adduct.[202] When this monoalkylborane reacts with a prochiral alkene, one of the diastereomeric products is normally formed in excess and can be obtained in high enantiomeric purity by an appropriate separation.[203] Oxidation of the borane then provides the corresponding alcohol having the enantiomeric purity achieved for the borane.



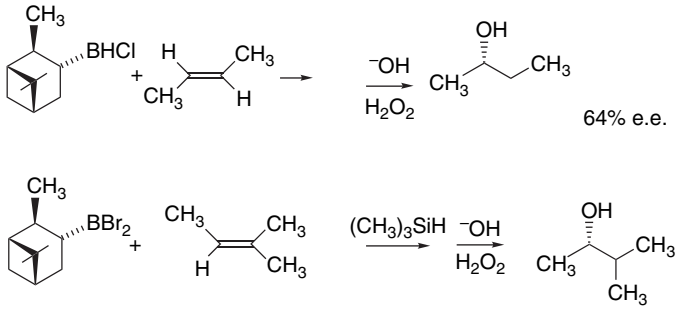
As oxidation also converts the original chiral terpene-derived group to an alcohol, it is not directly reusable as a chiral auxiliary. Although this is not a problem with inexpensive materials, the overall efficiency of generation of enantiomerically pure product is improved by procedures that can regenerate the original terpene. This can be done by heating the dialkylborane intermediate with acetaldehyde. The α-pinene is released and a diethoxyborane is produced.[204]



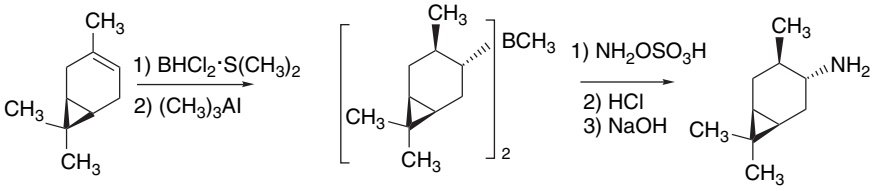
The usual oxidation conditions then convert this boronate ester to an alcohol.[205]

The corresponding haloboranes are also useful for enantioselective hydroboration. Isopinocampheylchloroborane can achieve 45–80% e.e. with representative alkenes.[206] The corresponding bromoborane achieves 65–85% enantioselectivity with simple alkenes when used at −78° C.[207]

201. D. Murali, B. Singaram, and H. C. Brown, *Tetrahedron: Asymmetry*, **11**, 4831 (2000).
202. H. C. Brown, J. R. Schwier, and B. Singaram, *J. Org. Chem.*, **43**, 4395 (1978); H. C. Brown, A. K. Mandal, N. M. Yoon, B. Singaram, J. R. Schwier, and P. K. Jadhav, *J. Org. Chem.*, **47**, 5069 (1982).
203. H. C. Brown and B. Singaram, *J. Am. Chem. Soc.*, **106**, 1797 (1984); H. C. Brown, P. K. Jadhav, and A. K. Mandal, *J. Org. Chem.*, **47**, 5074 (1982).
204. H. C. Brown, B. Singaram, and T. E. Cole, *J. Am. Chem. Soc.*, **107**, 460 (1985); H. C. Brown, T. Imai, M. C. Desai, and B. Singaram, *J. Am. Chem. Soc.*, **107**, 4980 (1985).
205. D. S. Matteson and K. M. Sadhu, *J. Am. Chem. Soc.*, **105**, 2077 (1983).
206. U. P. Dhokte, S. V. Kulkarni, and H. C. Brown, *J. Org. Chem.*, **61**, 5140 (1996).
207. U. P. Dhokte and H. C. Brown, *Tetrahedron Lett.*, **37**, 9021 (1996).

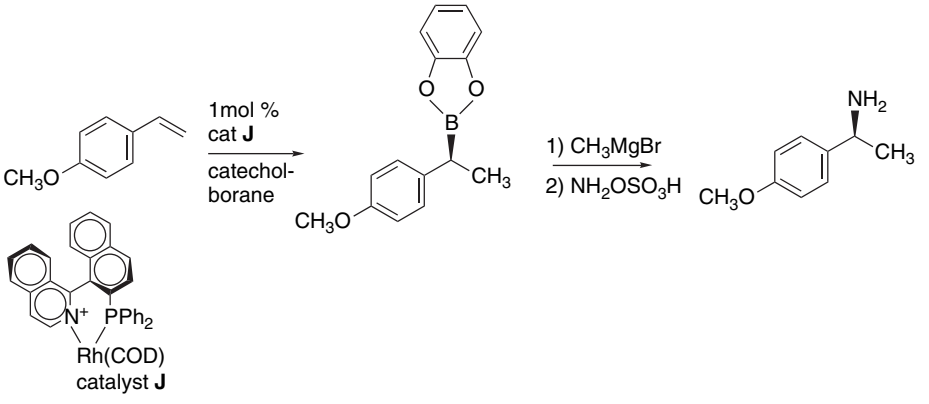


Procedures for synthesis of chiral amines[208] and halides[209] based on chiral alkylboranes involve applying the methods discussed earlier to the enantiomerically enriched organoborane intermediates. For example, enantiomerically pure terpenes can be converted to trialkylboranes and then aminated with hydroxylaminesulfonic acid.



Ref. 210

Combining catalytic enantioselective hydroboration (see p. 342) with amination has provided certain amines with good enantioselectivity. In this procedure the catechol group is replaced by methyl prior to the amination step.

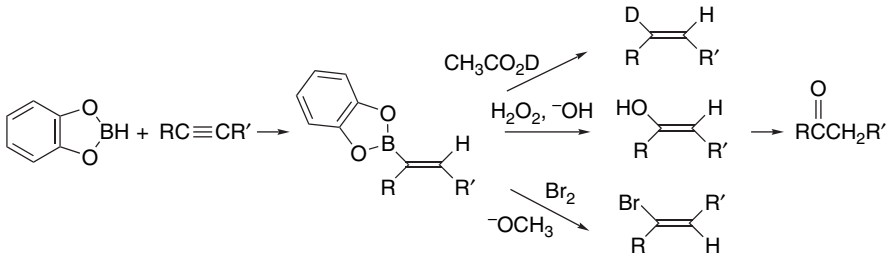


Ref. 211

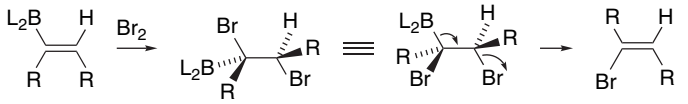
208. L. Verbit and P. J. Heffron, *J. Org. Chem.*, **32**, 3199 (1967); H. C. Brown, K.-W. Kim, T. E. Cole, and B. Singaram, *J. Am. Chem. Soc.*, **108**, 6761 (1986); H. C. Brown, A. M. Sahinke, and B. Singaram, *J. Org. Chem.*, **56**, 1170 (1991).
209. H. C. Brown, N. R. De Lue, G. W. Kabalka, and H. C. Hedgecock, Jr., *J. Am. Chem. Soc.*, **98**, 1290 (1976).
210. H. C. Brown, S. V. Malhotra, and P. V. Ramachandran, *Tetrahedron: Asymmetry*, **7**, 3527 (1996).
211. E. Fernandez, M. W. Hooper, F. I. Knight, and J. M. Brown, *J. Chem. Soc., Chem. Commun.*, 173 (1997).

4.5.4. Hydroboration of Alkynes

Alkynes are reactive toward hydroboration reagents. The most useful procedures involve addition of a disubstituted borane to the alkyne, which avoids complications that occur with borane and lead to polymeric structures. Catechol borane is a particularly useful reagent for hydroboration of alkynes.[212] Protonolysis of the adduct with acetic acid results in reduction of the alkyne to the corresponding *cis*-alkene. Oxidative workup with hydrogen peroxide gives ketones via enol intermediates.

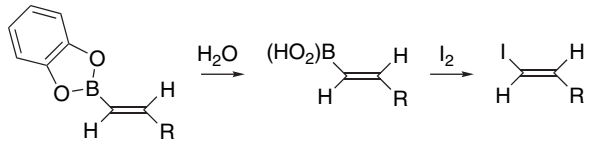


Treatment of the vinylborane with bromine and base leads to vinyl bromides. The reaction occurs with net *anti* addition, and the stereoselectivity is explained on the basis of *anti* addition of bromine followed by a second *anti* elimination of bromide and boron.

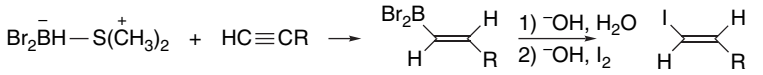


Exceptions to this stereoselectivity have been noted.[213]

The adducts derived from catechol borane are hydrolyzed by water to vinylboronic acids. These materials are useful intermediates for the preparation of terminal vinyl iodides. Since the hydroboration is a *syn* addition and the iodinolysis occurs with retention of the alkene geometry, the iodides have the *E*-configuration.[214]

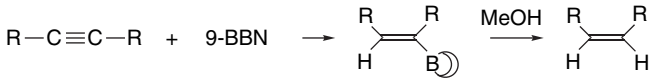


The dimethyl sulfide complex of dibromoborane [215] and pinacolborane[216] are also useful for synthesis of *E*-vinyl iodides from terminal alkynes.



212. H. C. Brown, T. Hamaoka, and N. Ravindran, *J. Am. Chem. Soc.*, **95**, 6456 (1973); C. F. Lane and G. W. Kabalka, *Tetrahedron*, **32**, 981 (1976).
213. J. R. Wiersig, N. Waespe-Sarcevic, and C. Djerassi, *J. Org. Chem.*, **44**, 3374 (1979).
214. H. C. Brown, T. Hamaoka, and N. Ravindran, *J. Am. Chem. Soc.*, **95**, 5786 (1973).
215. H. C. Brown and J. B. Campbell, Jr., *J. Org. Chem.*, **45**, 389 (1980); H. C. Brown, T. Hamaoka, N. Ravindran, C. Subrahmanyam, V. Somayaji, and N. G. Bhat, *J. Org. Chem.*, **54**, 6075 (1989).
216. C. E. Tucker, J. Davidson, and P. Knochel, *J. Org. Chem.*, **57**, 3482 (1992).

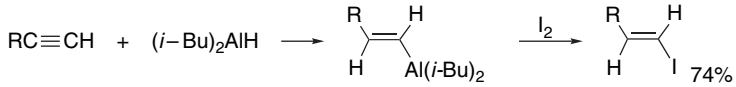
Other disubstituted boranes have also been used for selective hydroboration of alkynes. 9-BBN can be used to hydroborate internal alkynes. Protonolysis can be carried out with methanol and this provides a convenient method for formation of a disubstituted *Z*-alkene.[217]



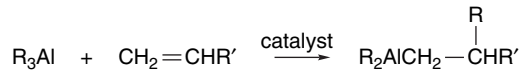
A large number of procedures that involve carbon-carbon bond formation have been developed based on organoboranes. These reactions are considered in Chapter 9.

4.6. Hydroalumination, Carboalumination, Hydrozirconation, and Related Reactions

Aluminum is the immediate congener of boron, and dialkyl and trialkyl aluminum compounds, which are commercially available, have important industrial applications. They also have some similarities with organoboranes that can be exploited for synthetic purposes. Aluminum is considerably less electronegative than boron and as a result the reagents also share characteristics with the common organometallic reagents such as organomagnesium and organolithium compounds. The addition reactions of alkenes and dialkylaluminum reagents occur much less easily than hydroboration. Only terminal or strained alkenes react readily at room temperature.[218] With internal and branched alkenes, the addition does not go to completion. Addition of dialkylalanes to alkynes occurs more readily, and the regiochemistry and stereochemistry are analogous to hydroboration. The resulting vinylalanes react with halogens with *retention of configuration* at the double bond.[219]



With trialkylaluminum compounds, the addition reaction is called *carboalumination*. As discussed below, this reaction requires a catalyst to proceed.

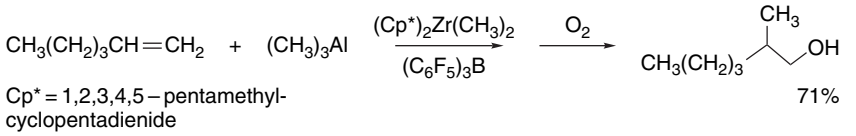


Computational studies of both hydroalumination and carboalumination have indicated a four-center TS for the addition.[220] The aluminum reagents, however, have more nucleophilic character than do boranes. Whereas the TS for hydroboration is primarily electrophilic and resembles that for attack of CH_3^+ on a double bond, the

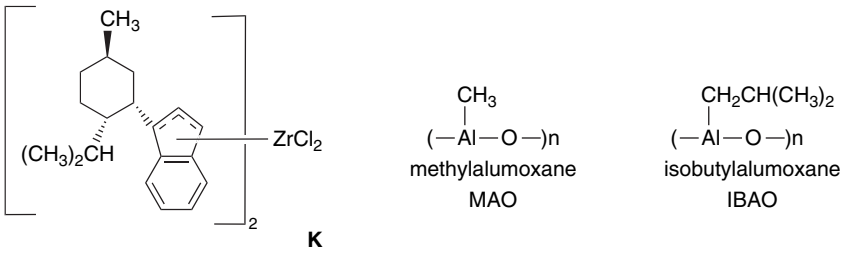
217. H. C. Brown and G. A. Molander, *J. Org. Chem.*, **51**, 4512 (1986); H. C. Brown and K. K. Wang, *J. Org. Chem.*, **51**, 4514 (1986).
218. F. Ansinger, B. Fell, and F. Thiessen, *Chem. Ber.*, **100**, 937 (1967); R. Schimpf and P. Heimbach, *Chem. Ber.*, **103**, 2122 (1970).
219. G. Zweifel and C. C. Whitney, *J. Am. Chem. Soc.*, **89**, 2753 (1967).
220. J. W. Bunders and M. M. Francl, *Organometallics*, **12**, 1608 (1993); J. W. Bunders, J. Yudenfreund, and M. M. Francl, *Organometallics*, **18**, 3913 (1999).

reaction with CH_3AlH_2 has a closer resemblance to reaction of CH_3^- with ethene and the strongest interaction is with the ethene LUMO. This interpretation is consistent with relative reactivity trends in which the reactivity of alkenes decreases with increasing alkyl substitution and alkynes are more reactive than alkenes.

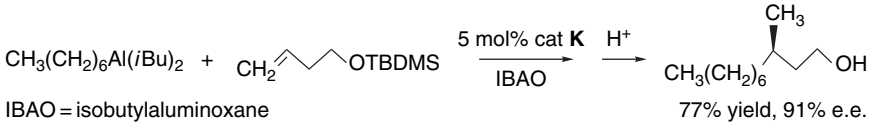
Effective catalysts have recently been developed for the addition of trialkylaluminum reagents to alkenes (carboalumination). *bis*-(Pentamethylcyclopentadienyl) zirconium dimethylide activated by *tris*-(pentafluorophenyl)boron promotes the addition of trimethylaluminum to terminal alkenes.[221]



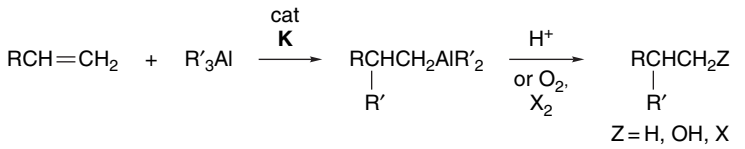
A chiral indene derivative, structure **K**, has been most commonly used.[222] The catalyst interacts with the trialkylaluminum to generate a bimetallic species that is the active catalyst.



The detailed mechanism of the catalysis is not known, but it is believed that the Lewis acid character of the zirconium is critical.[223] The reaction is further accelerated by inclusion of partially hydrolyzed trialkylaluminum reagents known as alumoxanes.[224]

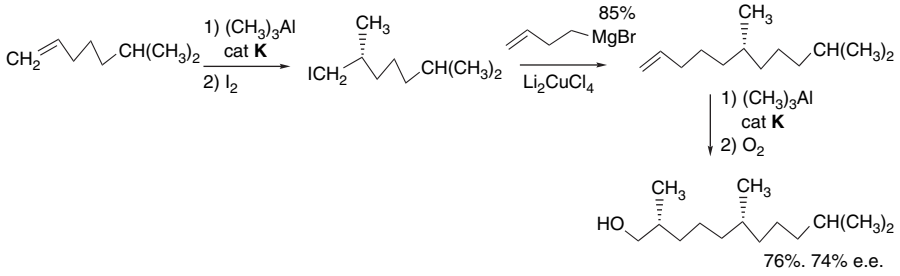


The adducts can be protonolyzed or converted to halides or alcohols.

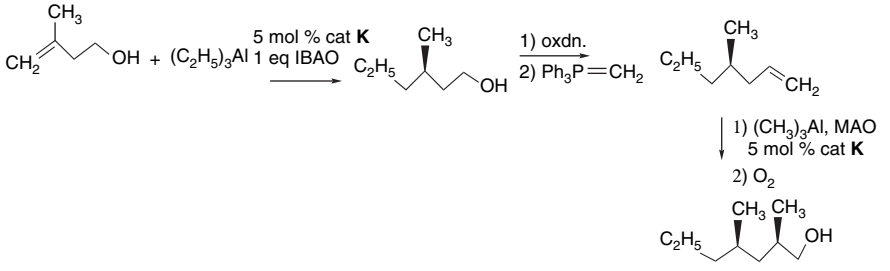


221. K. H. Shaugnessy and R. M. Waymouth, *J. Am. Chem. Soc.*, **117**, 5873 (1995).
222. D. Y. Kondakov and E. Negishi, *J. Am. Chem. Soc.*, **118**, 1577 (1996); K. H. Shaugnessy and R. M. Waymouth, *Organometallics*, **17**, 5738 (1998).
223. E. Negishi, D. Y. Kondakov, D. Choueiry, K. Kasai, and T. Takahashi, *J. Am. Chem. Soc.*, **118**, 9577 (1996); E. Negishi, *Chem. Eur. J.*, **5**, 411 (1999).
224. S. Huo, J. Shi, and E. Negishi, *Angew. Chem. Int. Ed. Engl.*, **41**, 2141 (2002).

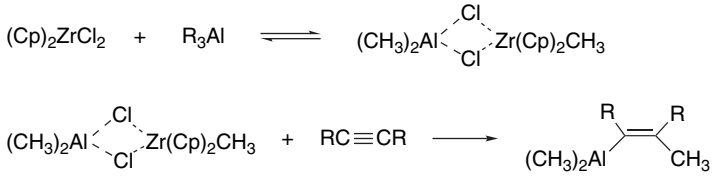
This methodology has been used to create chiral centers in saturated hydrocarbon chains such as those found in vitamin E, vitamin K, and phytol.[225]



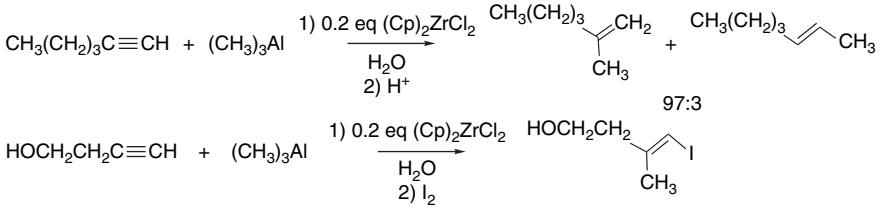
By converting the primary alcohol group to an alkene by oxidation and a Wittig reaction, the reaction can be carried out in iterative fashion to introduce several methyl groups.[226]



At this point in time carboalumination of alkynes has been more widely applied in synthesis. The most frequently used catalyst is $(Cp)_2ZrCl_2$. It is believed that a bimetallic species is formed.[227]

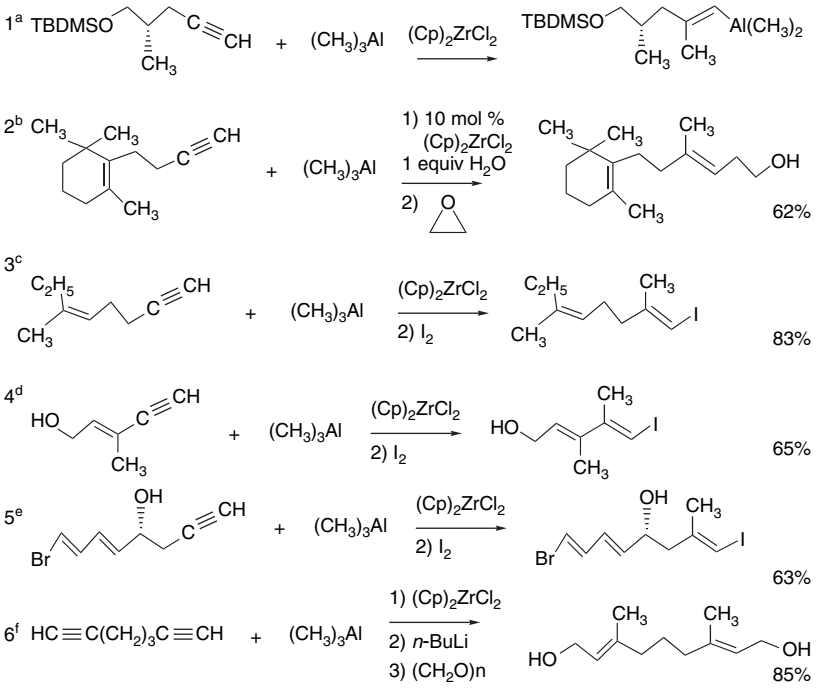


Small amounts of water accelerate carboalumination of alkynes.[228] This acceleration may be the result of formation of aluminoxanes.



225. S. Huo and E. Negishi, *Org. Lett.*, **3**, 3253 (2001).
226. E. Negishi, Z. Tan, B. Liang, and T. Novak, *Proc. Natl. Acad. Sci. USA*, **101**, 5782 (2004); M. Magnin-Lachaux, Z. Tan, B. Liang, and E. Negishi, *Org. Lett.*, **6**, 1425 (2004).
227. E. Negishi and D. Y. Kondakov, *Chem. Soc. Rev.*, **25**, 417 (1996).
228. P. Wipf and S. Lim, *Angew. Chem. Int. Ed. Engl.*, **32**, 1068 (1993).

Scheme 4.10. Carbomethylations of Alkynes



a. R. E. Ireland, L. Liu, and T. D. Roper, *Tetrahedron*, **53**, 13221 (1997).
b. A. Pommier, V. Stephanenko, K. Jarowicki, and P. J. Kocienski, *J. Org. Chem.*, **68**, 4008 (2003).
c. K. Mori and N. Murata, *Liebigs Ann. Chem.*, 2089 (1995).
d. T. K. Chakraborty and D. Thippeswamy, *Synlett*, 150 (1999).
e. M. Romero-Ortega, D. A. Colby, and H. F. Olivo, *Tetrahedron Lett.*, **47**, 6439 (2002).
f. G. Hidalgo-Del Vecchio and A. C. Oehlschlager, *J. Org. Chem.*, **59**, 4853 (1994).

As indicated by the mechanism, carboalumination is a *syn* addition. The resulting vinylalanes react with electrophiles with net retention of configuration. The electrophiles that have been used successfully include iodine, epoxides, formaldehyde, and ethyl chloroformate.[229] We will also see in Chapter 8 that the vinylalanes can undergo exchange reactions with transition metals, opening routes for formation of carbon-carbon bonds.

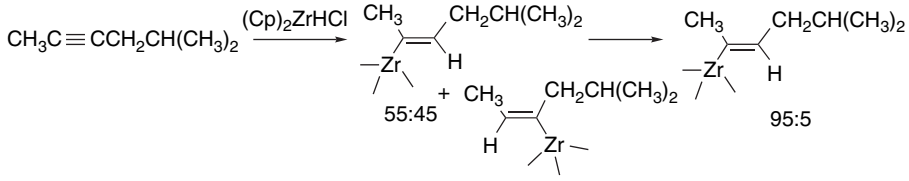
Scheme 4.10 gives some examples of application of alkyne carboalumination in synthesis. The reaction in Entry 1 was carried out as part of a synthesis of the immunosuppressant drug FK-506. The vinyl alane was subsequently transmetallated to a cuprate reagent (see Chapter 8). In Entry 2, the vinyl alane was used as a nucleophile for opening an epoxide ring and extending the carbon chain by two atoms. In Entries 3 to 5, the vinyl alane adducts were converted to vinyl iodides. In Entry 6, the vinyl alane was converted to an "ate" reagent prior to reaction with formaldehyde.

Derivatives of zirconium with a Zr−H bond also can add to alkenes and alkynes. This reaction is known as *hydrozirconation*.[230] The reagent that is used most frequently

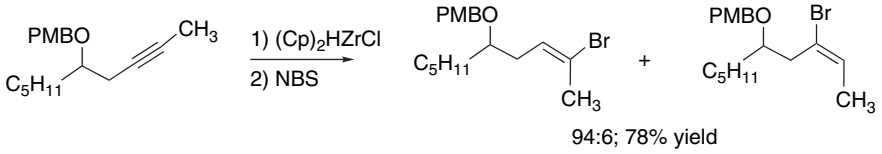
229. N. Okukado and E. Negishi, *Tetrahedron Lett.*, 2357 (1978); M. Kobayashi, L. F. Valente, E. Negishi, W. Patterson, and A. Silveira, Jr., *Synthesis*, 1034 (1980); C. L. Rand, D. E. Van Horn, M. W. Moore, and E. Negishi, *J. Org. Chem.*, **46**, 4093 (1981).

230. P. Wipf and H. Jahn, *Tetrahedron*, **52**, 1283 (1996); P. Wipf and C. Kendall, *Topics Organmetallic Chem.*, **8**, 1 (2004).

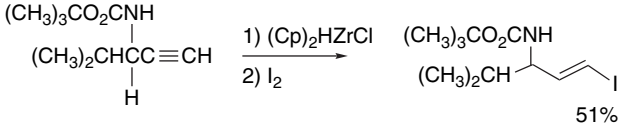
in synthesis is *bis*-(cyclopentadienido)hydridozirconium(IV) chloride. Reduction of $(Cp)_2ZrCl_2$ generates a reactive species that can add to alkenes and alkynes.[231] Various reductants such as $LiAlH_4$[232] and $LiEt_3BH$[233] can be used. Alkynes readily undergo hydrozirconation. With internal alkynes, this reagent initially gives a regioisomeric mixture but isomerization occurs to give the less sterically hindered isomer.



The adducts react with electrophiles such as NCS, NBS, and I_2 to give vinyl halides.

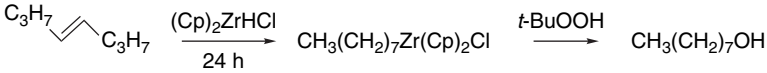


Ref. 234



Ref. 235

Alkenes are less reactive and reactivity decreases with increasing substitution. The adducts from internal alkenes undergo isomerization to terminal derivatives.[236]



Carbon-carbon bond formation from alkyl and alkenyl zirconium reagents usually involves transmetallation reactions and are discussed in Chapter 8.

231. D. W. Hart, T. F. Blackburn, and J. Schwartz, *J. Am. Chem. Soc.*, **97**, 679 (1975); J. Schwartz and J. A. Labinger, *Angew. Chem. Int. Ed. Engl.*, **15**, 333 (1976).
232. S. L. Buchwald, S. J. La Maire, R. B. Nielsen, B. T. Watson, and S. M. King, *Tetrahedron Lett.*, **28**, 3895 (1987).
233. B. H. Lipshutz, R. Kell, and E. L. Ellsworth, *Tetrahedron Lett.*, **31**, 7257 (1990).
234. A. B. Smith, III, S. S.-Y. Chen, F. C. Nelson, J. M. Reichert, and B. A. Salvatore, *J. Am. Chem. Soc.*, **119**, 10935 (1997).
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P. V. Ramachandran and H. C. Brown, *Organoboranes for Synthesis*, American Chemical Society, Washington, 2001.

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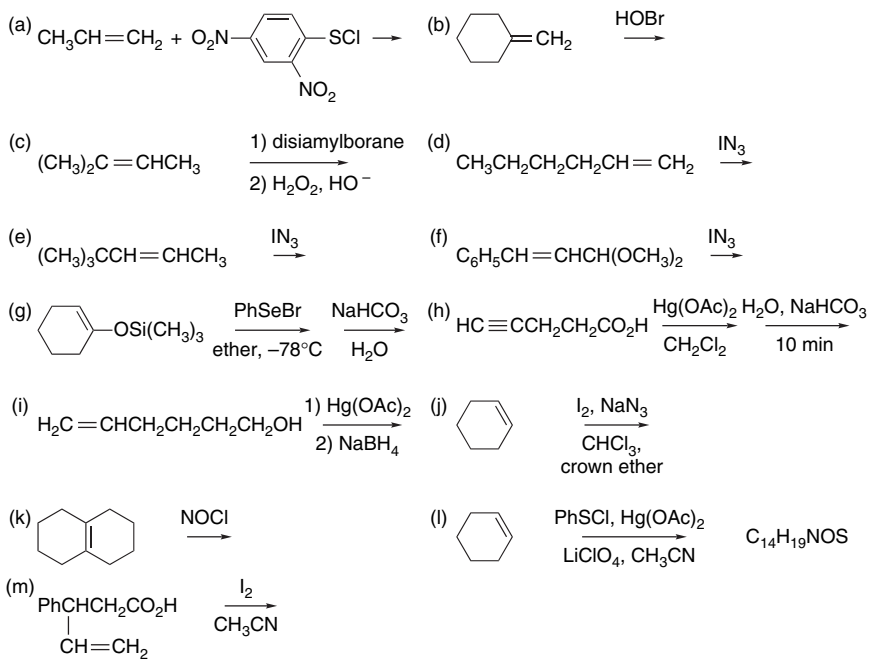
P. J. Stang and F. Diederich, eds., *Modern Acetylene Chemistry*, VCH Publishers, Weinheim, 1995.

Problems

(*References for these problems will be found on page 1277.*)

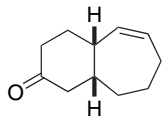
4.1. Predict the products, including regio- and stereochemistry, for the following reactions:



4.2. Bromination of 4-*t*-butylcyclohexene in methanol gives a 45:55 mixture of two compounds, each of composition $C_{11}H_{21}BrO$. Predict the structure and stereochemistry of these two products. How would you confirm your prediction?

4.3. Oxymercuration of 4-*t*-butylcyclohexene, followed by $NaBH_4$ reduction, gives *cis*-4-*t*-butylcyclohexanol and *trans*-3-*t*-butylcyclohexanol in approximately equal amounts. 1-Methyl-4-*t*-butylcyclohexanol under similar conditions gives only *cis*-4-*t*-butyl-1-methylcyclohexanol. Formulate an explanation for these observations.

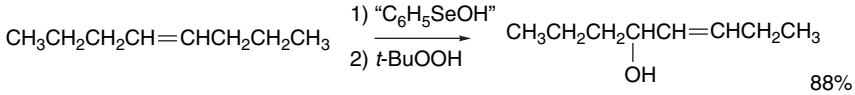
4.4. Treatment of compound **C** with *N*-bromosuccinimide in acetic acid containing sodium acetate gives a product $C_{13}H_{19}BrO_3$. Propose a structure, including stereochemistry, and explain the basis for your proposal.



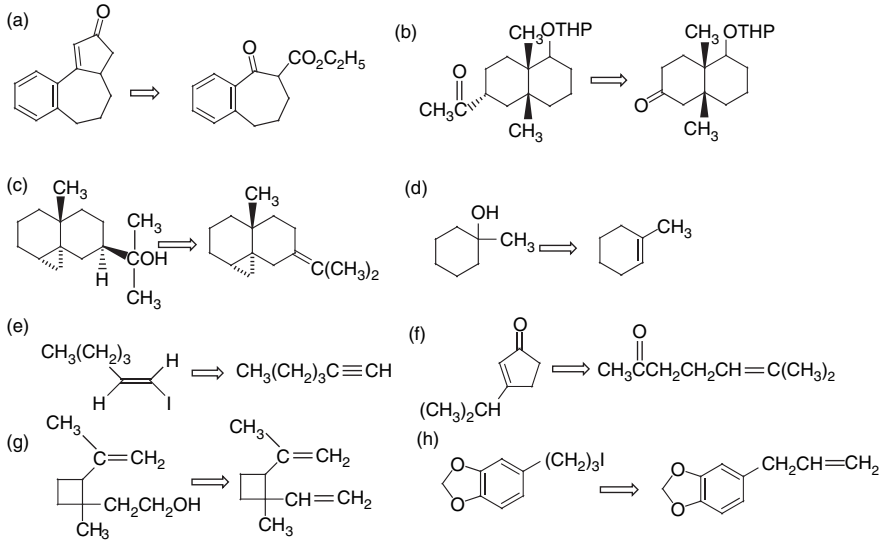
C

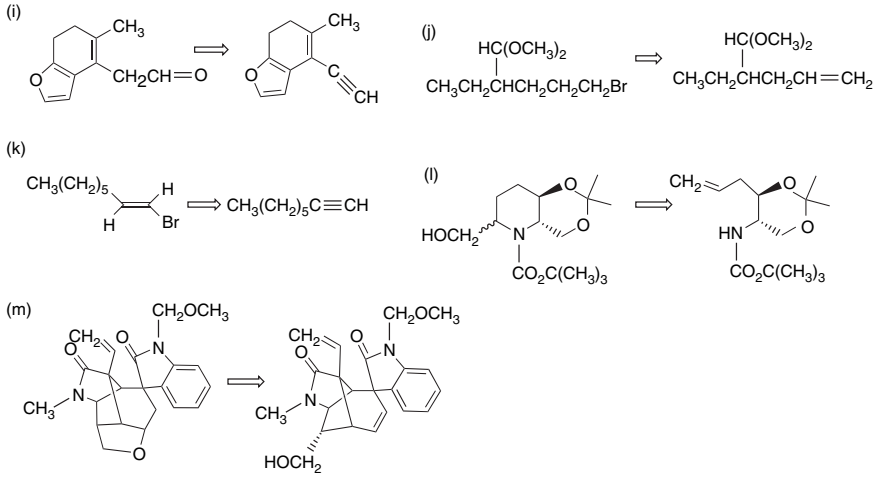
4.5. The hydration of 5-undecyn-2-one with $HgSO_4$ and H_2SO_4 in methanol is regioselective, giving 2,5-undecadione in 85% yield. Suggest an explanation for the high regioselectivity of this internal alkyne.

4.6. A procedure for the preparation of allylic alcohols uses the equivalent of phenylselenenic acid and an alkene. The reaction product is then treated with *t*-butylhydroperoxide. Suggest a mechanistic rationale for this process.

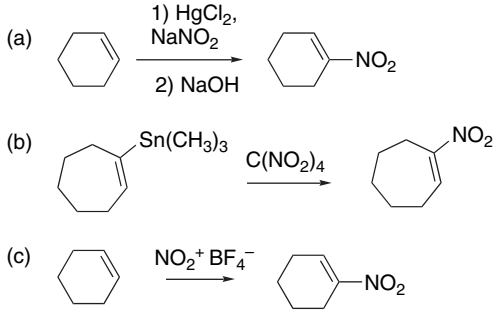


4.7. Suggest reaction conditions or short synthetic sequences that could provide the desired compound from the suggested starting material.





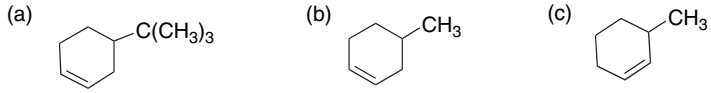
4.8. Three methods for the preparation of nitroalkenes are outlined below. Describe the mechanism by which each of these transformations occurs.



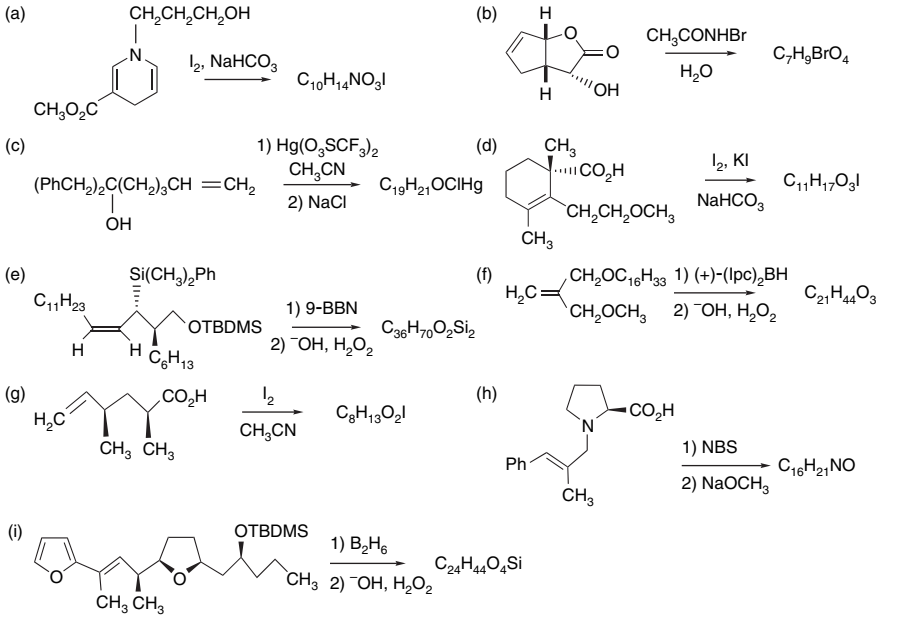
4.9. Hydroboration-oxidation of 1,4-di-*t*-butylcyclohexene gave three alcohols: **9-A** (77%), **9-B** (20%), and **9-C** (3%). Oxidation of **9-A** gave a ketone **9-D** that was readily converted by either acid or base to an isomeric ketone **9-E**. Ketone **9-E** was the only oxidation product of alcohols **9-B** and **9-C**. What are the structures of compounds **9A**–**9E**?

4.10. Show how by using regioselective enolate chemistry and organoselenium reagents, you could convert 2-phenylcyclohexanone to either 2-phenyl-2-cyclohexen-1-one or 6-phenyl-2-cyclohexen-1-one.

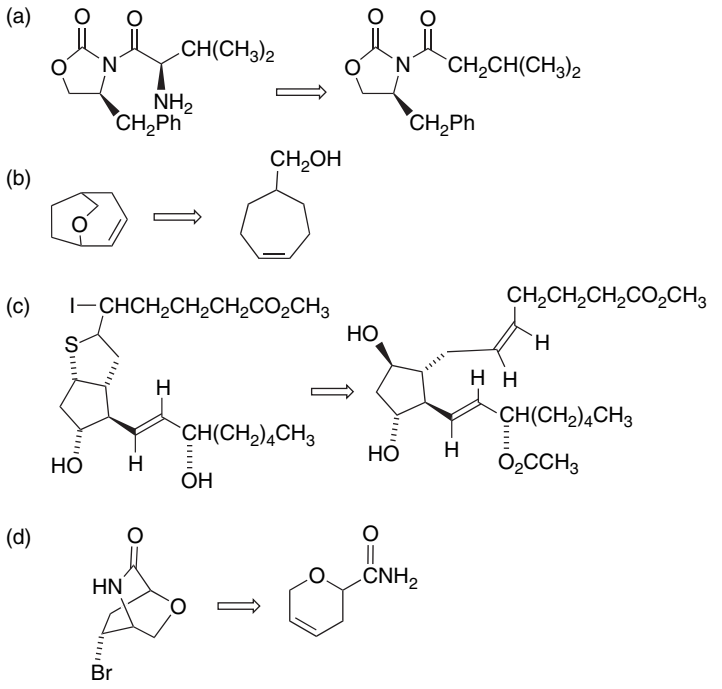
4.11. On the basis of the mechanistic pattern for oxymercuration-demercuration, predict the structure and stereochemistry of the alcohol(s) to be expected by application of the reaction to each of the following substituted cyclohexenes.



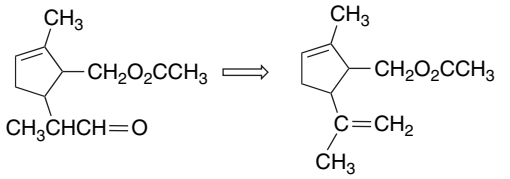
4.12. Give the structure, including stereochemistry, of the expected products of the following reactions. Identify the critical factors that determine the regio- and stereochemistry of the reaction.



4.13. Some synthetic transformations are shown in the retrosynthetic format. Propose a short series of reactions (no more than three steps should be necessary) that could effect each conversion.

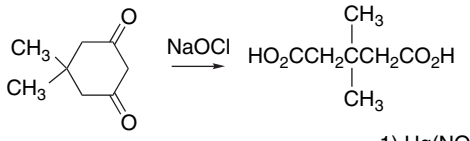


(e)

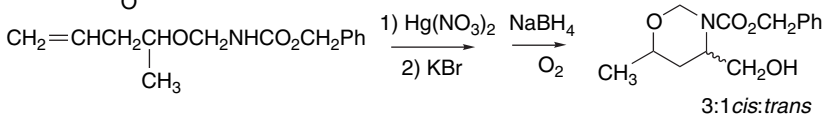


4.14. Write mechanisms for the following reactions:

(a)

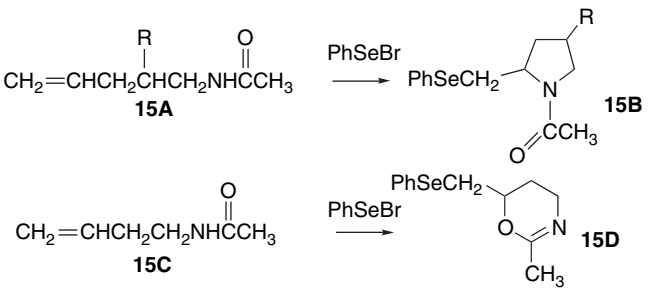


(b)

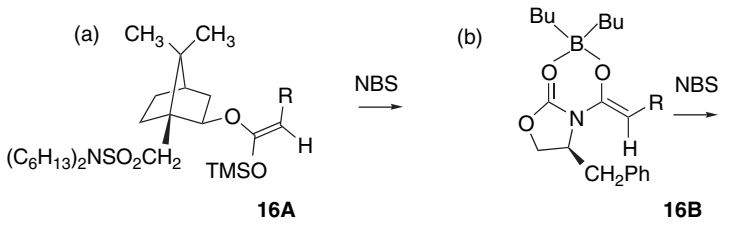


3:1 *cis*:*trans*

4.15. 4-Pentenyl amides such as **15A** cyclize to lactams **15B** on reaction with phenyl selenenyl bromide. The 3-butenyl compound **15C**, on the other hand, cyclizes to an imino ether **15D**. What is the basis for the differing reactions?

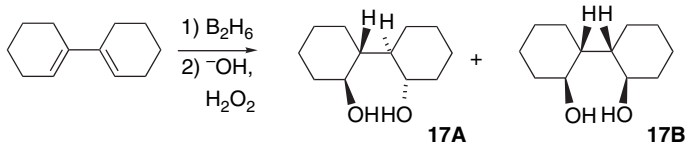


4.16. Procedures for enantioselective preparation of α-bromo acids based on reaction of NBS with enol derivatives **16A** and **16B** have been developed. Predict the absolute configuration of the halogenated compounds produced from both **16A** and **16B**. Explain the basis of your prediction.

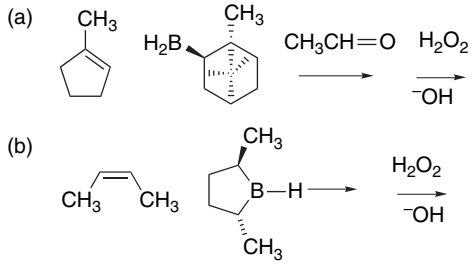


4.17. The stereochemical outcome of the hydroboration-oxidation of 1, 1′-bicyclohexenyl depends on the amount of diborane used. When 1.1 equivalent

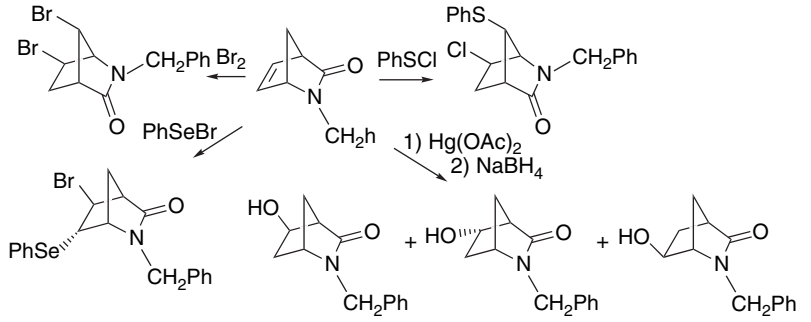
is used, the product is a 3:1 mixture of **17A** and **17B**. When 2.1 equivalent is used, **17A** is formed nearly exclusively. Offer an explanation of these results.



4.18. Predict the absolute configuration of the products obtained from the following enantioselective hydroborations.

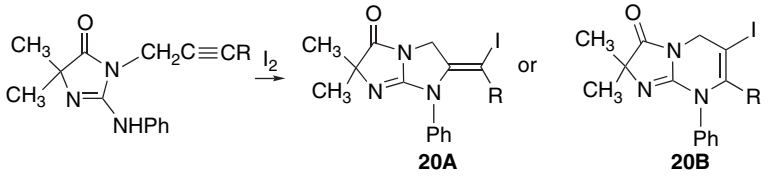


4.19. The regioselectivity and stereoselectivity of electrophilic additions to 2-benzyl-3-azabicyclo[2.2.1]hept-5-en-3-one are quite dependent on the specific electrophile. Discuss the factors that could influence the differing selectivity patterns that are observed.



4.20. Offer mechanistic explanations of the following observations:

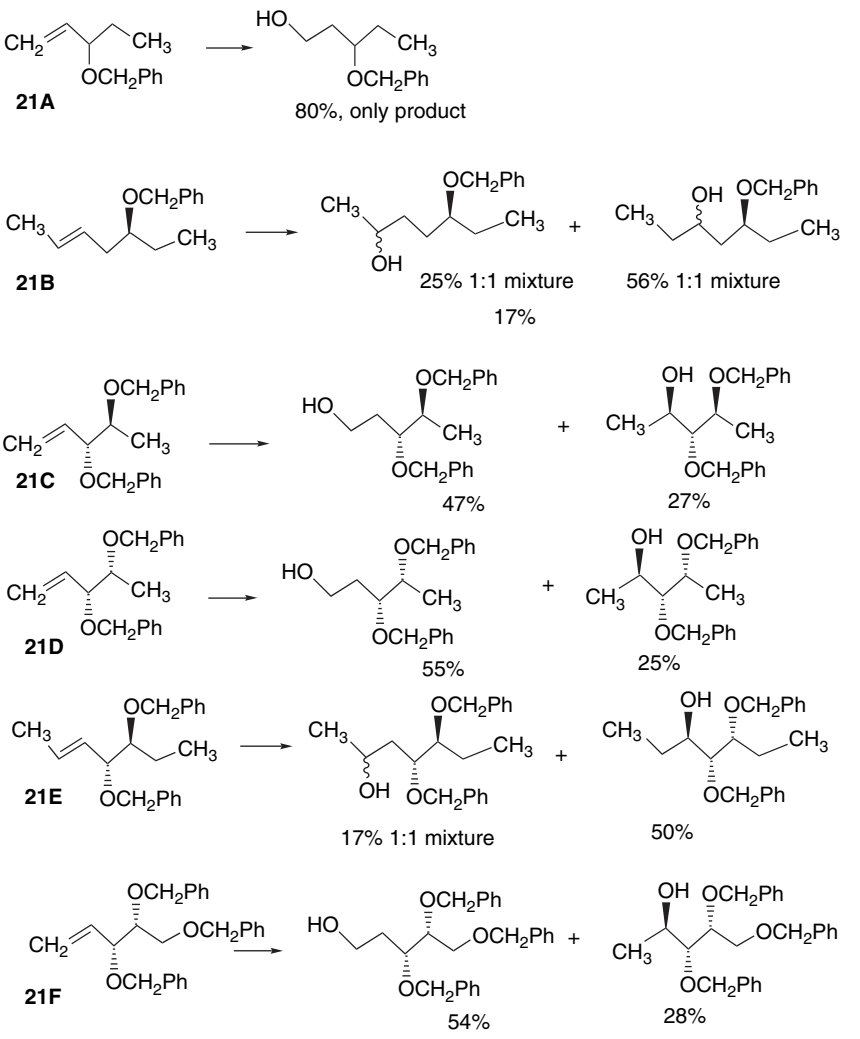
a. In the cyclization reactions shown below, **20A** is the preferred product for R = H, but **20B** is the preferred product for R = methyl or phenyl.



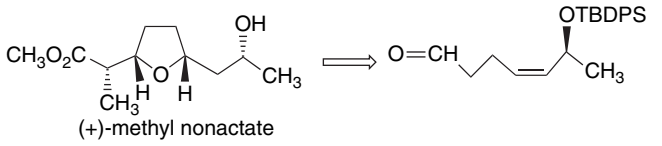
20A **20B**

b. The pent-4-enoyl group has been developed as a protecting group for primary and secondary amines. The conditions for cleavage involve treatment with iodine and a aqueous solution with either THF or acetonitrile as the cosolvent. Account for the mild deprotection under these conditions.

4.21. Analyze the data below concerning the effect of allylic and homoallylic benzyloxy substituents on the regio- and stereoselectivity of hydroboration-oxidation. Propose a TS that is consistent with the results.

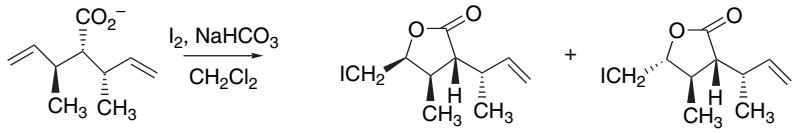


4.22. Propose an enantioselective synthesis of (+) methyl nonactate from the aldehyde shown.

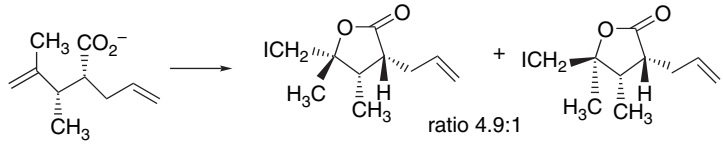


4.23. On page 313, the effect of methyl substitution on the stereoselectivity of α,α-diallylcarboxylic acids under iodolactonization conditions was discussed. Consider the two compounds shown and construct a reaction energy profile for

each compound that illustrates the role of conformational equilibrium, facial selectivity, and substituent effects on $\Delta G^{\ddagger}$ on the stereochemical outcome.

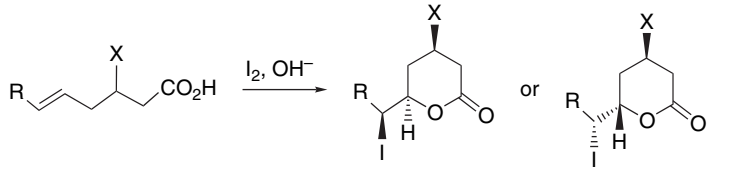


ratio 30:1



ratio 4.9:1

4.24. It has been found that when δ,ε-enolates bearing β-siloxy substituents are subject to iodolactonization, the substituent directs the stereochemistry of cyclization in a manner opposite to an alkyl substituent. Suggest a TS structure that would account for this difference.



major product for X = alkyl

major product for X = trialkylsiloxy