12

Oxidations

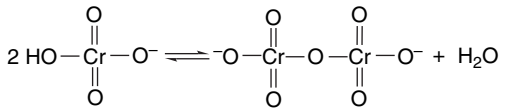
Introduction

This chapter is concerned with reactions that transform a functional group to a more highly oxidized derivative by removal of hydrogen and/or addition of oxygen. There are a great many oxidation methods, and we have chosen the reactions for discussion on the basis of their utility in synthesis. As the reactions are considered, it will become evident that the material in this chapter spans a broader range of mechanisms than most of the previous chapters. Owing to this range, the chapter is organized according to the functional group transformation that is accomplished. This organization facilitates comparison of the methods available for effecting a given synthetic transformation. The major sections consider the following reactions: (1) oxidation of alcohols; (2) addition of oxygen at double bonds; (3) allylic oxidation; (4) oxidative cleavage of double bonds; (5) oxidative cleavage of other functional groups; (6) oxidations of aldehydes and ketones; and (7) oxidation at unfunctionalized positions. The oxidants are grouped into three classes: transition metal derivatives; oxygen, ozone, and peroxides; and other reagents.

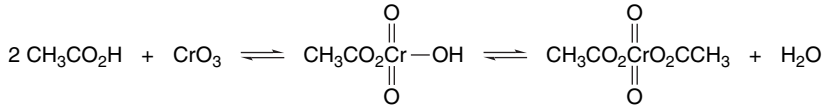
12.1. Oxidation of Alcohols to Aldehydes, Ketones, or Carboxylic Acids

12.1.1. Transition Metal Oxidants

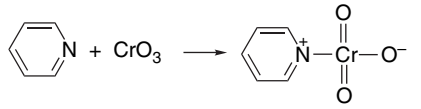
The most widely employed transition metal oxidants for alcohols are based on Cr(VI). The specific reagents are generally prepared from chromic trioxide, CrO_3, or a dichromate salt, $[Cr_2O_7]^{2-}$. The form of Cr(VI) in aqueous solution depends upon concentration and pH; the pK_1 and pK_2 of H_2CrO_4 are 0.74 and 6.49, respectively. In dilute solution, the monomeric acid chromate ion $[HCrO_3]^-$ is the main species present; as concentration increases, the dichromate ion dominates.



In acetic acid, Cr(VI) is present as mixed anhydrides of acetic acid and chromic acid.[1]

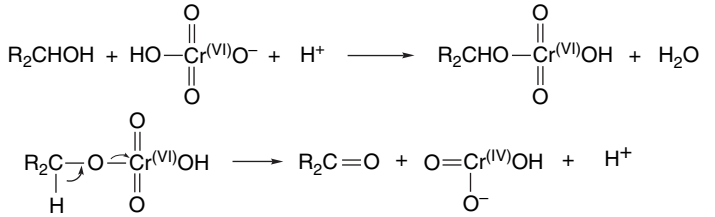


In pyridine, an adduct involving Cr–N bonding is formed.

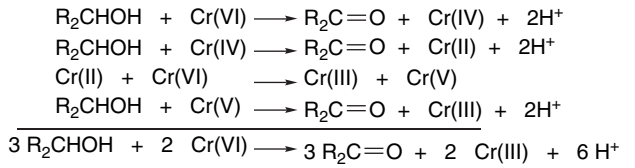


The oxidation state of Cr in each of these species is (VI) and they are all powerful oxidants. The precise reactivity depends on the solvent and the chromium ligands, so substantial selectivity can be achieved by the choice of the particular reagent and conditions.

The general mechanism of alcohol oxidation involves coordination of the alcohol at chromium and a rate-determining deprotonation.



An important piece of evidence for this mechanism is the fact that a primary isotope effect is observed when the α-hydrogen is replaced by deuterium.[2] The Cr(IV) that is produced in the initial step is not stable and is capable of a further oxidation. It is believed that Cr(IV) is reduced to Cr(II), which is then oxidized by Cr(VI) generating Cr(V). This mechanism accounts for the overall stoichiometry of the reaction.[3]

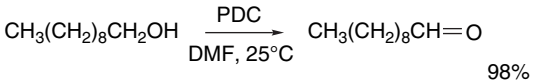


[1] K. B. Wiberg, *Oxidation in Organic Chemistry*, Part A, Academic Press, New York, 1965, pp. 69–72.
[2] F. H. Westheimer and N. Nicolaides, *J. Am. Chem. Soc.*, **71**, 25 (1949).
[3] S. L. Scott, A. Bakac, and J. H. Esperson, *J. Am. Chem. Soc.*, **114**, 4205 (1992); J. F. Perez-Benito and C. Arias, *Can. J. Chem.*, **71**, 649 (1993).

Various experimental conditions have been used for oxidations of alcohols by Cr(VI) on a laboratory scale, and several examples are shown in Scheme 12.1. Entry 1 is an example of oxidation of a primary alcohol to an aldehyde. The propanal is distilled from the reaction mixture as oxidation proceeds, which minimizes overoxidation. For secondary alcohols, oxidation can be done by addition of an acidic aqueous solution containing chromic acid (known as *Jones' reagent*) to an acetone solution of the alcohol. Oxidation normally occurs rapidly, and overoxidation is minimal. In acetone solution, the reduced chromium salts precipitate and the reaction solution can be decanted. Entries 2 to 4 in Scheme 12.1 are examples of this method.

The chromium trioxide-pyridine complex is useful in situations when other functional groups might be susceptible to oxidation or the molecule is sensitive to acid.[4] A procedure for utilizing the CrO_3-pyridine complex, which was developed by Collins,[5] has been widely adopted. The CrO_3-pyridine complex is isolated and dissolved in dichloromethane. With an excess of the reagent, oxidation of simple alcohols is complete in a few minutes, giving the aldehyde or ketone in good yield. A procedure that avoids isolation of the complex can further simplify the experimental operations.[6] Chromium trioxide is added to pyridine in dichloromethane. Subsequent addition of the alcohol to this solution results in oxidation in high yield. Other modifications for use of the CrO_3-pyridine complex have been developed.[7] Entries 5 to 9 in Scheme 12.1 demonstrate the excellent results that have been reported using the CrO_3-pyridine complex in dichloromethane. Entries 5 and 6 involve conversion of primary alcohols to aldehydes, Entry 7 describes preparation of the reagent in situ, and Entry 8 is an example of application of these conditions to a primary alcohol. The conditions described in Entry 9 were developed to optimize the oxidation of sensitive carbohydrates. It was found that inclusion of 4A molecular sieves and a small amount of acetic acid accelerated the reaction.

Another very useful Cr(VI) reagent is pyridinium chlorochromate (PCC), which is prepared by dissolving CrO_3 in hydrochloric acid and adding pyridine to obtain a solid reagent having the composition $CrO_3Cl{\cdot}pyrH$.[8] This reagent can be used in amounts close to the stoichiometric ratio. Entries 10 and 11 are examples of the use of PCC. Reaction of pyridine with CrO_3 in a small amount of water gives pyridinium dichromate (PDC), which is also a useful oxidant.[9] As a solution in DMF or a suspension in dichloromethane, this reagent oxidizes secondary alcohols to ketones. Allylic primary alcohols give the corresponding aldehydes. Depending upon the conditions, saturated primary alcohols give either an aldehyde or the corresponding carboxylic acid.

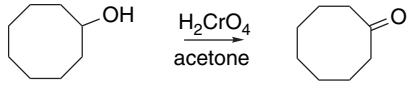


4. G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc*., **75**, 422 (1953); W. S. Johnson, W. A. Vredenburgh, and J. E. Pike, *J. Am. Chem. Soc*., **82**, 3409 (1960); W. S. Allen, S. Bernstein, and R. Little, *J. Am. Chem. Soc*., **76**, 6116 (1954).
5. J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett*., 3363 (1968).
6. R. Ratcliffe and R. Rodehorst, *J. Org. Chem*., **35**, 4000 (1970).
7. J. Herscovici, M.-J. Egron, and K. Antonakis, *J. Chem. Soc., Perkin Trans. 1*, 1967 (1982); E. J. Corey and G. Schmidt, *Tetrahedron Lett*., 399 (1979); S. Czernecki, C. Georgoulis, C. L. Stevens, and K. Vijayakumaran, *Tetrahedron Lett*., **26**, 1699 (1985).
8. E. J. Corey and J. W. Suggs, *Tetrahedron Lett*., 2647 (1975); G. Piancatelli, A. Scettri, and M. D'Auria, *Synthesis*, 245 (1982).
9. E. J. Corey and G. Schmidt, *Tetrahedron Lett*., 399 (1979).

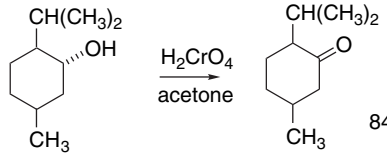
Scheme 12.1. Oxidation with Chromium(VI) Reagents

A. Chromic acid solutions

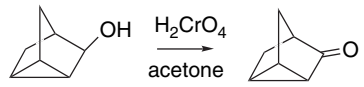
1[a] $CH_3CH_2CH_2OH \xrightarrow[H_2O]{H_2CrO_4} CH_3CH_2CH{=}O$ 45–49%

2[b] 

92–96%

3[c] 

84%

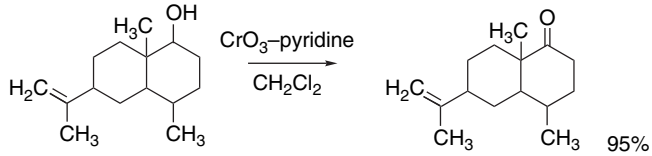
4[d] 

79–88%

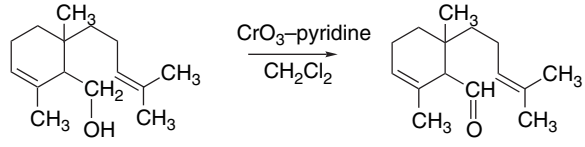
B. Chromium trioxide–pyridine

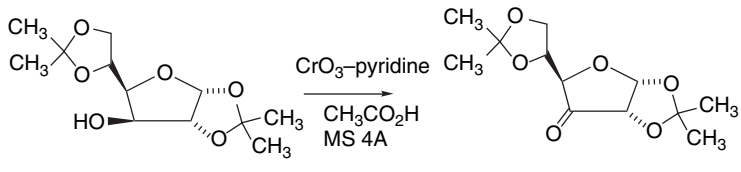
5[e] $CH_3(CH_2)_5CH_2OH \xrightarrow[CH_2Cl_2]{CrO_3\text{–pyridine}} CH_3(CH_2)_5CH{=}O$ 70–84%

6[f] $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}H(CH_2)_4CH_2OH \xrightarrow[CH_2Cl_2]{CrO_3\text{–pyridine}} CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}H(CH_2)_4CH{=}O$ 69%

7[g] 

95%

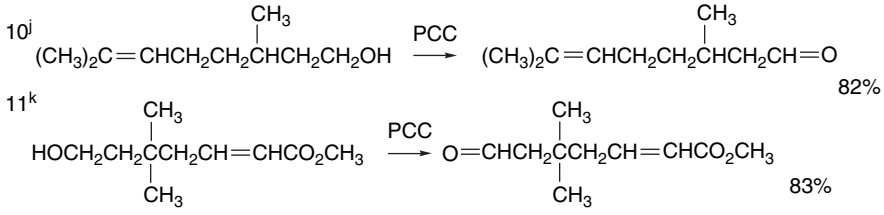
8[h] 

9[i] 

96%

(*Continued*)

C. Pyridinium chlorochromate



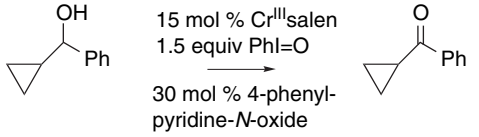
a. C. D. Hurd and R. N. Meinert, *Org. Synth*., **II**, 541 (1943).
b. E. J. Eisenbraun, *Org. Synth*., **V**, 310 (1973).
c. H. C. Brown, C. P. Garg, and K.-T. Liu, *J. Org. Chem*., **36**, 387 (1971).
d. J. Meinwald, J. Crandall, and W. E. Hymans, *Org. Synth*., **V**, 866 (1973).
e. J. C. Collins and W. W. Hess, *Org. Synth*., **52**, 5 (1972).
f. J. I. DeGraw and J. O. Rodin, *J. Org. Chem*., **36**, 2902 (1971).
g. R. Ratcliffe and R. Rodehorst, *J. Org. Chem*., **35**, 4000 (1970).
h. M. A. Schwartz, J. D. Crowell, and J. H. Musser, *J. Am. Chem. Soc*., **94**, 4361 (1972).
i. C. Czernecki, C. Gerogoulis, C. L. Stevens, and K. Vijayakumaran, *Tetrahedron Lett*., **26**, 1699 (1985).
j. E. J. Corey and J. W. Suggs, *Tetrahedron Lett*., 2647 (1975).
k. R. D. Little and G. W. Muller, *J. Am. Chem. Soc*., **103**, 2744 (1981).

Although Cr(VI) oxidants are very versatile and efficient, they have one drawback, which becomes especially serious in larger-scale work: the toxicity and environmental hazards associated with chromium compounds. The reagents are used in stoichiometric or excess amount and the Cr(III) by-products must be disposed of safely.

Potassium permanganate, $KMnO_4$, is another powerful transition metal oxidant, but it has found relatively little application in the oxidation of alcohols to ketones and aldehydes. The reagent is less selective than Cr(VI), and overoxidation is a problem. On the other hand, manganese(IV) dioxide is quite useful.[10] This reagent, which is selective for allylic and benzylic alcohols, is prepared by reaction of $Mn(II)SO_4$ with $KMnO_4$ and sodium hydroxide. The precise reactivity of MnO_2 depends on its mode of preparation and the extent of drying.[11]

Scheme 12.2 shows various types of alcohols that are most susceptible to MnO_2 oxidation. Entries 1 and 2 illustrate the application of MnO_2 to simple benzylic and allylic alcohols. In Entry 2, the MnO_2 was activated by azeotropic drying. Entry 3 demonstrates the application of the reagent to cyclopropylcarbinols. Entry 4 is an application to an acyloin. Entry 5 involves oxidation of a sensitive conjugated system.

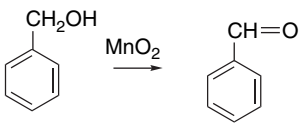
A reagent system that is selective for allylic, benzylic, and cyclopropyl alcohols uses iodosobenzene in conjunction with a Cr(III)(salen) complex.[12]



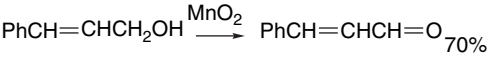
10. D. G. Lee, in *Oxidation*, Vol. 1, R. L. Augustine, ed., Marcel Dekker, New York, 1969, pp. 66–70; A. J. Fatiadi, *Synthesis*, 65 (1976); A. J. Fatiadi, *Synthesis*, 133 (1976).
11. J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, A. B. A. Jansen, and T. Walker, *J. Chem. Soc*., 1094 (1952); I. M. Goldman, *J. Org. Chem*., **34**, 1979 (1969).
12. W. Adam, F. G. Gelacha, C. R. Saha-Moeller, and V. R. Stegmann, *J. Org. Chem*., **65**, 1915 (2000); see also S. S. Kim and D. W. Kim, *Synlett*, 1391 (2003).

Scheme 12.2. Oxidation of Alcohols with Manganese Dioxide

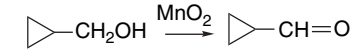
1[a]



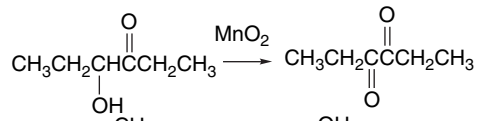
2[b]



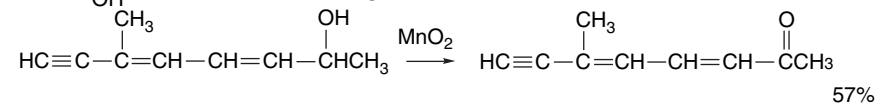
3[c]



4[d]

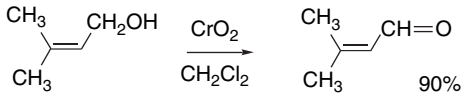


5[e]

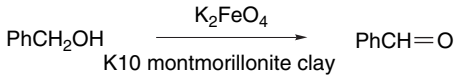


a. E. F. Pratt and J. F. Van De Castle, *J. Org. Chem.*, **26**, 2973 (1961).
b. I. M. Goldman, *J. Org. Chem.*, **34**, 1979 (1969).
c. L. Crombie and J. Crossley, *J. Chem. Soc.*, 4983 (1963).
d. E. P. Papadopoulos, A. Jarrar, and C. H. Issidorides, *J. Org. Chem.*, **31**, 615 (1966).
e. J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Janssen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

Another recently developed oxidant is CrO_2, a solid known as Magtrieve™ that is prepared commercially (for other purposes), which oxidizes allylic and benzylic alcohols in good yield.[13] It is also reactive toward saturated alcohols. Because the solid remains ferromagnetic, it can be recovered by use of a magnet and can be reactivated by exposure to air at high temperature, making it environmentally benign.

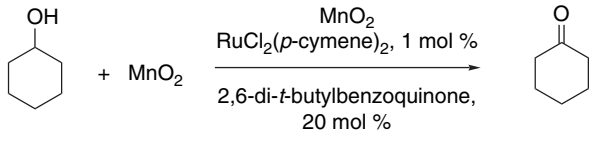


Another possible alternative oxidant that has recently been investigated is an Fe(VI) species, potassium ferrate, K_2FeO_4, supported on montmorillonite clay.[14] This reagent gives clean, high-yielding oxidation of benzylic and allylic alcohols, but saturated alcohols are less reactive.

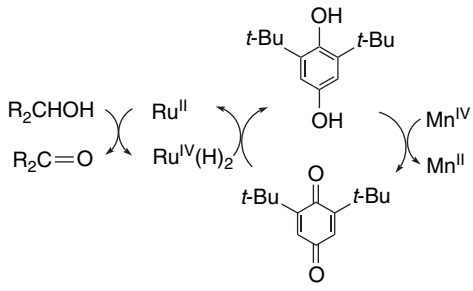


A catalytic system that extends the reactivity of MnO_2 to saturated secondary alcohols has been developed.[15] This system consists of a Ru(II) salt, $RuCl_2(p\text{-cymene})_2$, and 2,6-di-*t*-butylbenzoquinone.

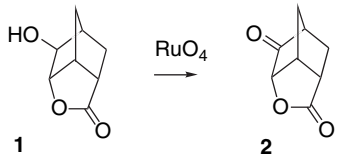
13. R. A. Lee and D. S. Donald, *Tetrahedron Lett.*, **38**, 3857 (1997).
14. L. Delaude and P. Laszlo, *J. Org. Chem.*, **61**, 6360 (1996).
15. U. Karlsson, G. Z. Wang, and J.-E. Backvall, *J. Org. Chem.*, **59**, 1196 (1994).



Ruthenium is the active oxidant and benzoquinone functions as an intermediary hydride transfer agent.

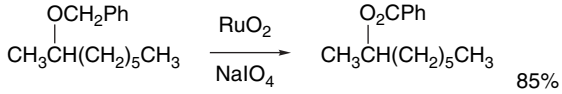


Another reagent that finds application of oxidations of alcohols to ketones is ruthenium tetroxide. The oxidations are typically carried out using a catalytic amount of the ruthenium source, e.g., $RuCl_3$, with $NaIO_4$ or NaOCl as the stoichiometric oxidant.[16] Acetonitrile is a favorable solvent because of its ability to stabilize the ruthenium species that are present.[17] For example, the oxidation of **1** to **2** was successfully achieved with this reagent after a number of other methods failed.



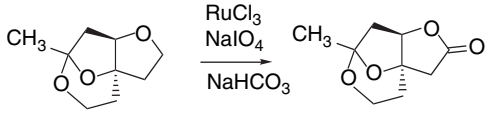
Ref. 18

Ruthenium tetroxide is a potent oxidant, however, and it readily attacks carbon-carbon double bonds.[19] Primary alcohols are oxidized to carboxylic acids, methyl ethers give methyl esters, and benzyl ethers are oxidized to benzoate esters.



Ref. 20

This reagent has been used in multistep syntheses to convert a tetrahydrofuran ring into a γ-lactone.

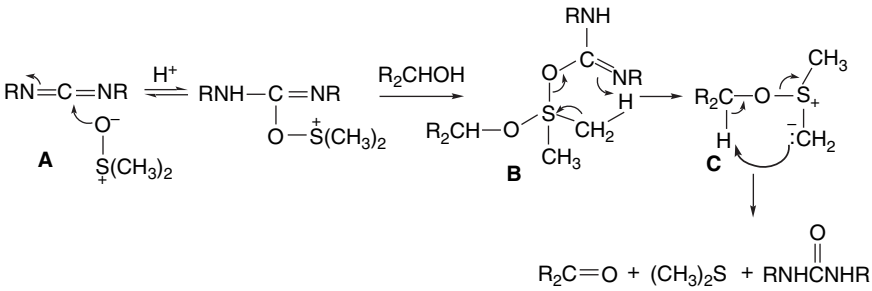


Ref. 21

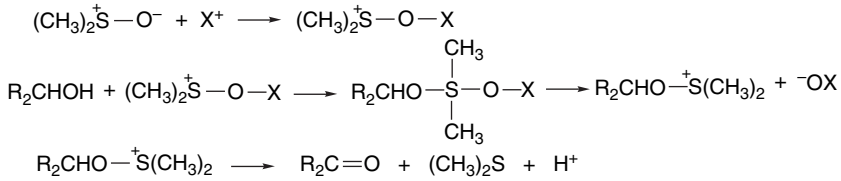
16. P. E. Morris, Jr., and D. E. Kiely, *J. Org. Chem*., **52**, 1149 (1987).
17. P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem*., **46**, 3936 (1981).
18. R. M. Moriarty, H. Gopal, and T. Adams, *Tetrahedron Lett*., 4003 (1970).
19. J. L. Courtney and K. F. Swansborough, *Rev. Pure Appl. Chem*., **22**, 47 (1972); D. G. Lee and M. van den Engh, in *Oxidation*, Part B, W. S. Trahanovsky, ed., Academic Press, New York, 1973, Chap. IV.
20. P. F. Schuda, M. B. Cichowitz, and M. P. Heinmann, *Tetrahedron Lett*., **24**, 3829 (1983).
21. J.-S. Han and T. L. Lowary, *J. Org. Chem*., **68**, 4116 (2003).

12.1.2. Other Oxidants

12.1.2.1. Oxidations Based on Dimethyl Sulfoxide. A very useful group of procedures for oxidation of alcohols to ketones employs dimethyl sulfoxide (DMSO) and any one of several electrophilic reagents, such as dicyclohexylcarbodiimide (DCCI), acetic anhydride, trifluoroacetic anhydride (TFAA), oxalyl chloride, or sulfur trioxide.[22] The original procedure involved DMSO and DCCI.[23] The mechanism of the oxidation involves formation of intermediate **A** by nucleophilic attack by DMSO on the carbodiimide, followed by reaction of the intermediate with the alcohol.[24] A proton transfer leads to an alkoxysulfonium ylide that is converted to product by an intramolecular proton transfer and elimination.



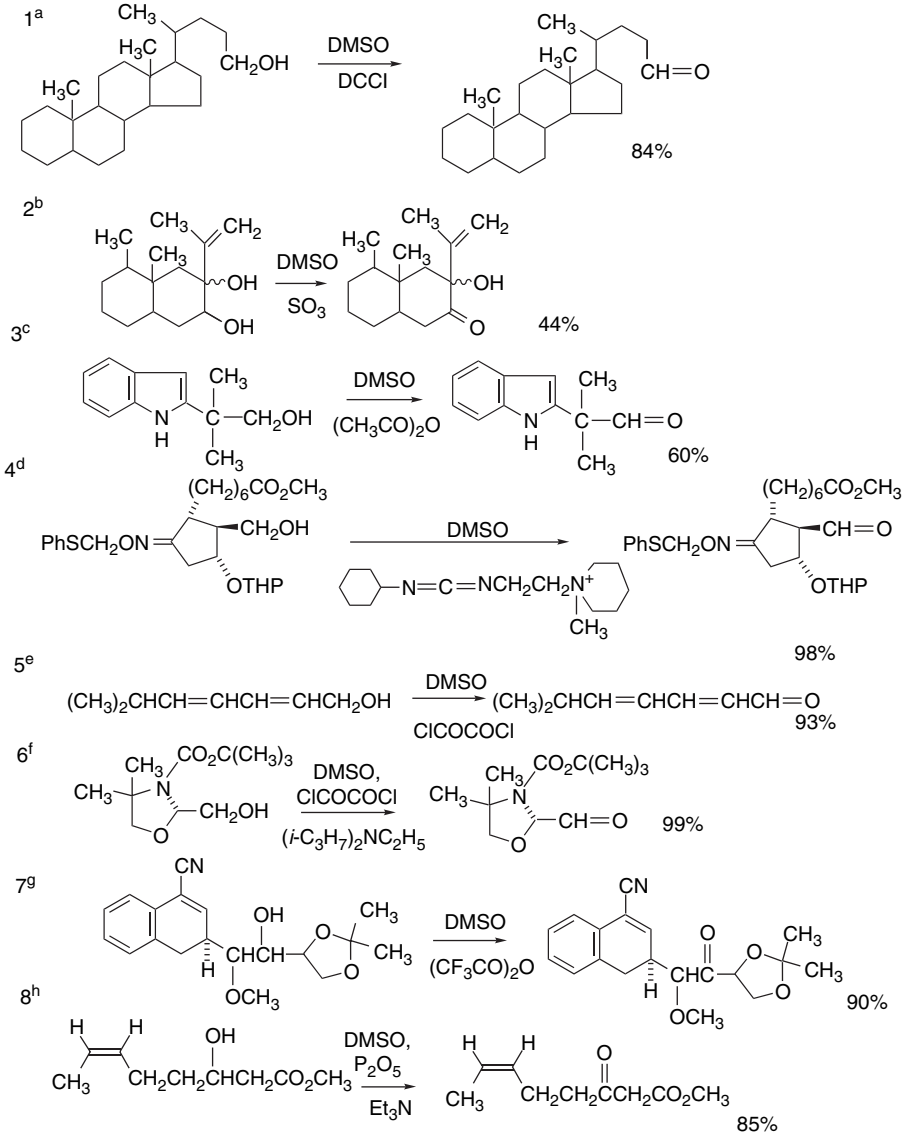
The activation of DMSO toward the addition step can be accomplished by other electrophiles. All of these reagents are believed to form a sulfoxonium species by electrophilic attack at the sulfoxide oxygen. The addition of the alcohol and the departure of the sulfoxide oxygen as part of a leaving group generates an intermediate comparable to **C** in the carbodiimide mechanism.



Preparatively useful procedures based on acetic anhydride,[25] trifluoroacetic anhydride,[26] and oxalyl chloride[27] have been developed. The last method, known as the *Swern oxidation*, is currently the most popular.

Scheme 12.3 gives some representative examples of these methods. Entry 1 is an example of the original procedure using DCCI. Entries 2 and 3 use SO_3 and $(CH_3CO)_2O$, respectively, as the electrophilic reagents. Entry 3 is noteworthy in successfully oxidizing an alcohol without effecting the sensitive indole ring. Entry 4 is

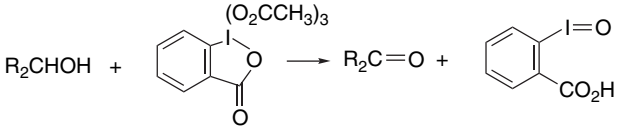
22. A. J. Mancuso and D. Swern, *Synthesis*, 165 (1981); T. T. Tidwell, *Synthesis*, 857 (1990).
23. K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc*., **87**, 5661, 5670 (1965).
24. J. G. Moffatt, *J. Org. Chem*., **36**, 1909 (1971).
25. J. D. Albright and L. Goldman, *J. Am. Chem. Soc*., **89**, 2416 (1967).
26. J. Yoshimura, K. Sato, and H. Hashimoto, *Chem. Lett*., 1327 (1977); K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem*., **41**, 957 (1976); S. L. Huang, K. Omura, and D. Swern, *J. Org. Chem*., **41**, 3329 (1976).
27. A. J. Mancuso, S.-L. Huang, and D. Swern, *J. Org. Chem*., **43**, 2480 (1978).



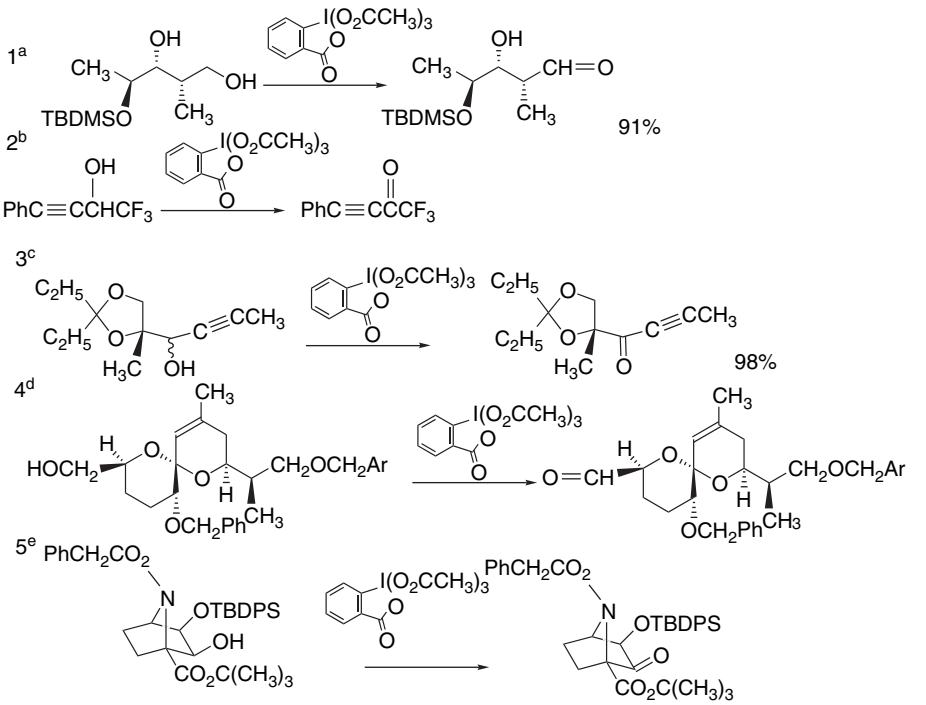
a. J. G. Moffat, *Org. Synth*., **47**, 25 (1967).
b. J. A. Marshall and G. M. Cohen, *J. Org. Chem*., **36**, 877 (1971).
c. E. Houghton and J. E. Saxton, *J. Chem. Soc. C*, 595 (1969).
d. N. Finch, L. D. Veccia, J. J. Fitt, R. Stephani, and I. Vlatta, *J. Org. Chem*., **38**, 4412 (1973).
e. W. R. Roush, *J. Am. Chem. Soc*., **102**, 1390 (1980).
f. A. Dondoni and D. Perrone, *Synthesis*, 527 (1997).
g. R. W. Franck and T. V. John, *J. Org. Chem*., **45**, 1170 (1987).
h. D. F. Taber, J. C. Amedio, Jr., and K.-Y. Jung, *J. Org. Chem*., **52**, 5621 (1987).

an example of the use of a water-soluble carbodiimide as the activating reagent. The modified carbodiimide facilitates product purification by providing for easy removal of the urea by-product. Entries 5 and 6 are examples of the Swern procedure. Entry 7 uses TFAA as the electrophile. Entry 8, which uses the inexpensive reagent P_2O_5 as the electrophile, was conducted on a 60-g scale.

12.1.2.2. Oxidation by the Dess-Martin Reagent. Another reagent that has become important for laboratory synthesis is known as the *Dess-Martin reagent*,[28] which is a hypervalent iodine(V) compound.[29] The reagent is used in inert solvents such as chloroform or acetonitrile and gives rapid oxidation of primary and secondary alcohols. The by-product, *o*-iodosobenzoic acid, can be extracted with base and recycled.



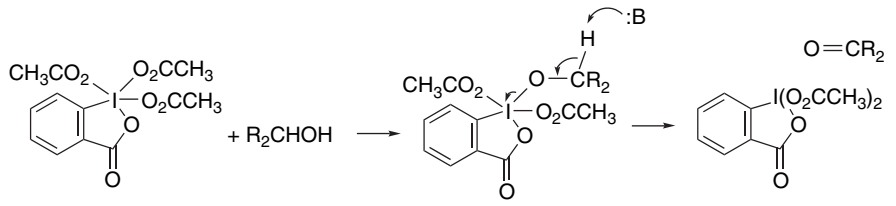
Scheme 12.4. Oxidation by the Dess-Martin Reagent



a. P. R. Blakemore, P. J. Kocienski, A. Morley, and K. Muir, *J. Chem. Soc., Perkin Trans. 1*, 955 (1999).
b. R. J. Linderman and D. M. Graves, *Tetrahedron Lett*., **28**, 4259 (1987).
c. S. D. Burke, J. Hong, J. R. Lennox, and A. P. Mongin, *J. Org. Chem*., **63**, 6952 (1998).
d. S. F. Sabes, R. A. Urbanek, and C. J. Forsyth, *J. Am. Chem. Soc*., **120**, 2534 (1998).
e. B. P. Hart and H. Rapoport, *J. Org. Chem*., **64**, 2050 (1999).

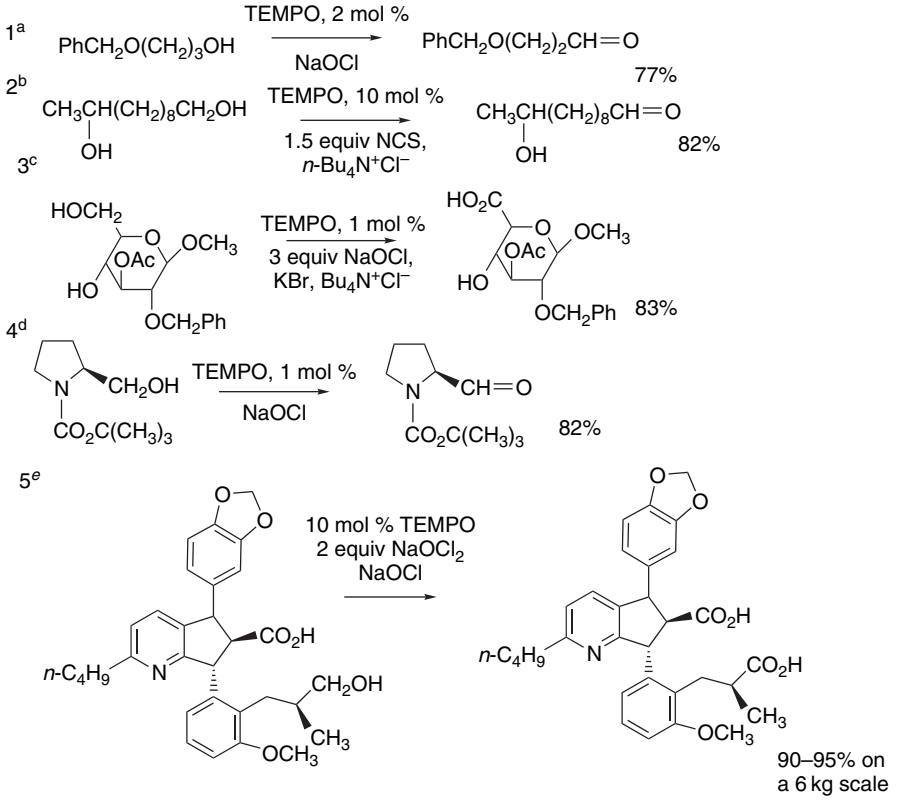
28. D. B. Dess and J. C. Martin, *J. Org. Chem*., **48**, 4155 (1983); R. E. Ireland and L. Liu, *J. Org. Chem*., **58**, 2899 (1993); S. D. Meyer and S. L. Schreiber, *J. Org. Chem*., **59**, 7549 (1994).
29. T. Wirth and U. H. Hirt, *Synthesis*, 471 (1999).

The mechanism of the Dess-Martin oxidation involves exchange of the alcohol for acetate, followed by proton removal.[30]



Scheme 12.4 shows several examples of the use of the Dess-Martin reagent.

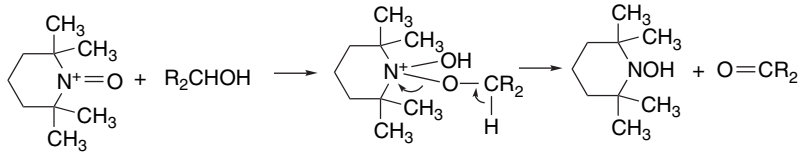
Scheme 12.5. Oxidations Using TEMPO



a. B. G. Szczepankiewicz and C. H. Heathcock, *Tetrahedron*, **53**, 8853 (1997).
b. J. Einhorn, C. Einhorn, F. Ratajczak, and J.-L. Pierre, *J. Org. Chem*., **61**, 7452 (1996).
c. N. J. Davis and S. L. Flitsch, *Tetrahderon Lett*., **34**, 1181 (1993).
d. M. R. Leanna, T. J. Sowin, and H. E. Morton, *Tetrahedron Lett*., **33**, 5029 (1992).
e. Z. J. Song, M. Zhao, R. Desmond, P. Devine, D. M. Tscaen, R. Tillyer, L. Frey, R. Heid, F. Xu, B. Foster, J. Li, R. Reamer, R. Volante, E. J. Grabowski, U. H. Dolling, P. J. Reider, S. Okada, Y. Kato, and E. Mano, *J. Org. Chem*., **64**, 9658 (1999).

30. S. De Munari, M. Frigerio, and M. Santagostino, *J. Org. Chem*., **61**, 9272 (1996).

12.1.2.3. Oxidations Using Oxoammonium Ions. Another oxidation procedure uses an oxoammonium ion, usually derived from the stable nitroxide tetramethylpiperidine nitroxide, TEMPO, as the active reagent.[31] It is regenerated in a catalytic cycle using hypochlorite ion[32] or NCS[33] as the stoichiometric oxidant. These reactions involve an intermediate adduct of the alcohol and the oxoammonium ion.

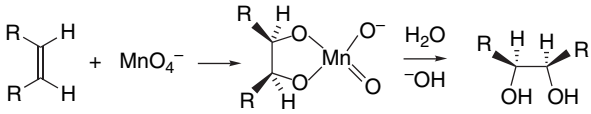


One feature of this oxidation system is that it can selectively oxidize primary alcohols in preference to secondary alcohols, as illustrated by Entry 2 in Scheme 12.5. The reagent can also be used to oxidize primary alcohols to carboxylic acids by a subsequent oxidation with sodium chlorite.[34] Entry 3 shows the selective oxidation of a primary alcohol in a carbohydrate to a carboxylic acid without affecting the secondary alcohol group. Entry 5 is a large-scale preparation that uses $NaClO_2$ in conjunction with bleach as the stoichiometric oxidant.

12.2. Addition of Oxygen at Carbon-Carbon Double Bonds

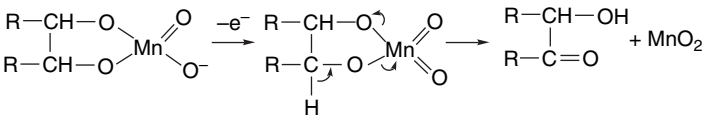
12.2.1. Transition Metal Oxidants

12.2.1.1. Dihydroxylation of Alkenes. The higher oxidation states of certain transition metals, particularly the permanganate ion and osmium tetroxide, are effective reagents for addition of two oxygen atoms at a carbon-carbon double bond. Under carefully controlled reaction conditions, potassium permanganate can effect conversion of alkenes to glycols. However, this oxidant is capable of further oxidizing the glycol with cleavage of the carbon-carbon bond. A cyclic manganese ester is an intermediate in these oxidations. Owing to the cyclic nature of this intermediate, the glycols are formed by *syn* addition.

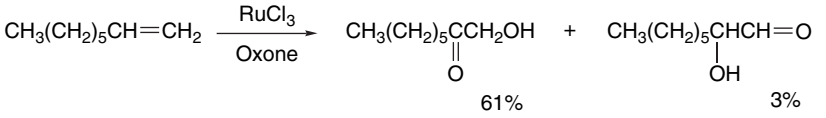


[31] N. Merbouh, J. M. Bobbitt, and C. Brueckner, *Org. Prep. Proced. Int.*, **36**, 3 (2004).
[32] R. Siedlecka, J. Skarzewski, and J. Mlochowski, *Tetrahedron Lett.*, **31**, 2177 (1990); T. Inokuchi, S. Matsumoto, T. Nishiyama, and S. Torii, *J. Org. Chem.*, **55**, 462 (1990); P. L. Anelli, S. Banfi, F. Montanari, and S. Quici, *J. Org. Chem.*, **54**, 2970 (1989); M. R. Leanna, T. J. Sowin, and H. E. Morton, *Tetrahedron Lett.*, **33**, 5029 (1992).
[33] J. Einhorn, C. Einhorn, F. Ratajczak, and J.-L. Pierre, *J. Org. Chem.*, **61**, 7452 (1996).
[34] P. M. Wovkulich, K. Shankaran, J. Kiegel, and M. R. Uskokovic, *J. Org. Chem.*, **58**, 832 (1993).

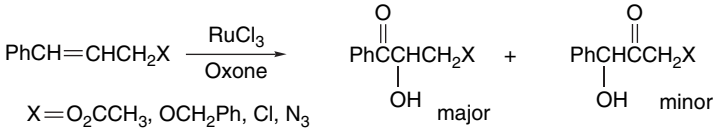
Ketols are also observed as products of permanganate oxidation of alkenes. The ketols are believed to be formed as a result of oxidation of the cyclic intermediate.[35]



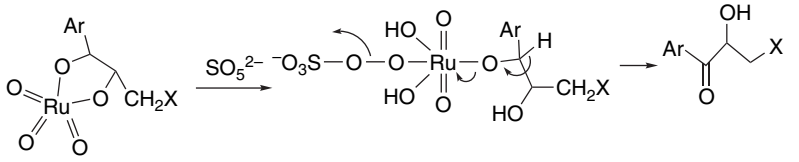
Ruthenium tetroxide can also be used in the oxidation of alkenes. Conditions that are selective for formation of ketols have been developed.[36] Use of 1 mol % of $RuCl_3$ and five equivalents of $KHSO_5$ (Oxone®) in an ethyl acetate-acetonitrile-water mixture gives mainly hydroxymethyl ketones from terminal alkenes.



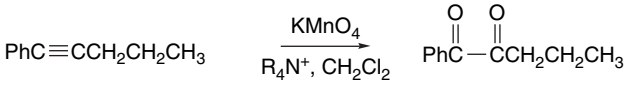
With aryl-substituted alkenes, the aryl ketone is the major product.



The mechanistic basis of this method depends on the use of excess peroxysulfate so that the major pathway leads to ketol rather than diol.

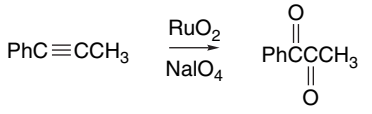


Permanganate ion can be used to oxidize acetylenes to diones.



Ref. 37

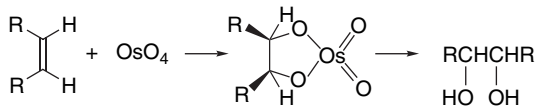
A mixture of $NaIO_4$ and RuO_2 in a heterogeneous solvent system is also effective for this transformation.



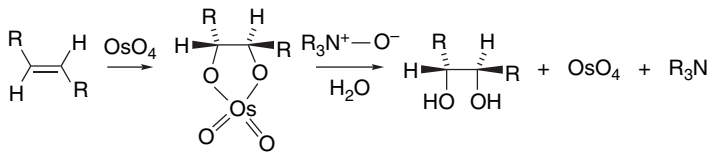
Ref. 38

35. S. Wolfe, C. F. Ingold, and R. U. Lemieux, *J. Am. Chem. Soc*., **103**, 938 (1981); D. G. Lee and T. Chen, *J. Am. Chem. Soc*., **111**, 7534 (1989).
36. B. Plietker, *J. Org. Chem*., **69**, 8287 (2004).
37. D. G. Lee and V. S. Chang, *J. Org. Chem*., **44**, 2726 (1979).
38. R. Zibuck and D. Seebach, *Helv. Chim. Acta*, **71**, 237 (1988).

The most widely used reagent for oxidation of alkenes to glycols is osmium tetroxide. Osmium tetroxide is a highly selective oxidant that gives glycols by a stereospecific *syn* addition.[39] The reaction occurs through a cyclic osmate ester that is formed by a [3 + 2] cycloaddition.[40]



The reagent is toxic and expensive but these disadvantages are minimized by methods that use only a catalytic amount of osmium tetroxide. A very useful procedure involves an amine oxide such as morpholine-*N*-oxide as the stoichiometric oxidant.[41]



t-Butyl hydroperoxide,[42] barium chlorate,[43] or potassium ferricyanide[44] can also be used as oxidants in catalytic procedures.

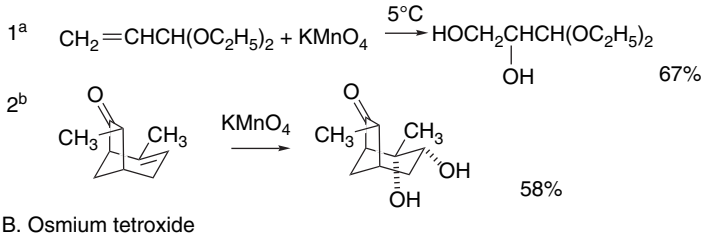
Scheme 12.6 provides some examples of oxidations of alkenes to glycols by both permanganate and osmium tetroxide. The oxidation by $KMnO_4$ in Entry 1 is done in cold aqueous solution. The reaction is very sensitive to the temperature control during the reaction. The reaction in Entry 2 was also done by the catalytic OsO_4 method using *N*-methylmorpholine-*N*-oxide in better (80%) yield. Note that the hydroxy groups are introduced from the less hindered face of the double bond. Entries 3 to 5 illustrate several of the catalytic procedures for OsO_4 oxidation. In each case the reaction is a stereospecific *syn* addition. Note also that in Entries 4 and 5 the double bond is conjugated with an EWG substituent, so the range of the reaction includes deactivated alkenes.

Osmium tetroxide oxidations can be highly enantioselective in the presence of chiral ligands. The most highly developed ligands are derived from the cinchona alkaloids dihydroquinine (DHQ) and dihydroquinidine (DHQD).[45] The most effective

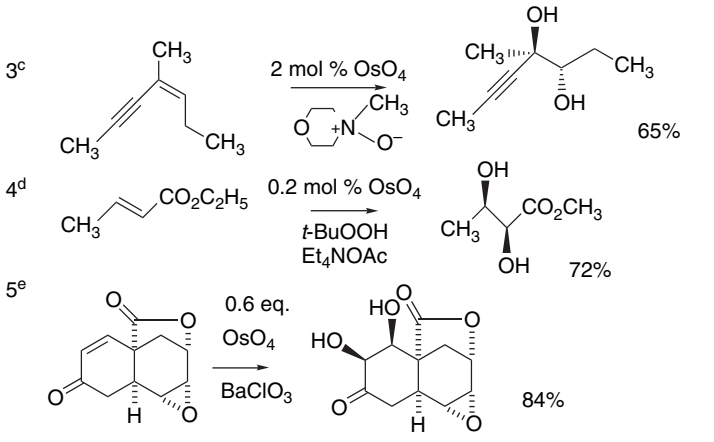
39. M. Schroeder, *Chem. Rev*., **80**, 187 (1980).
40. A. J. DelMonte, J. Haller, K. N. Houk, K. B. Sharpless, D. A. Singleton, T. Strassner, and A. A. Thomas, *J. Am. Chem. Soc*., **119**, 9907 (1997); U. Pidun, C. Boehme, and G. Frenking, *Angew. Chem. Intl. Ed. Engl*., **35**, 2817 (1997).
41. V. Van Rheenen, R. C. Kelly, and D. Y. Cha, *Tetrahedron Lett*., 1973 (1976).
42. K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc*., **98**, 1986 (1976); K. Akashi, R. E. Palermo, and K. B. Sharpless, *J. Org. Chem*., **43**, 2063 (1978).
43. L. Plaha, J. Weichert, J. Zvacek, S. Smolik, and B. Kakac, *Collect. Czech. Chem. Commun*., **25**, 237 (1960); A. S. Kende, T. V. Bentley, R. A. Mader, and D. Ridge, *J. Am. Chem. Soc*., **96**, 4332 (1974).
44. M. Minato, K. Yamamoto, and J. Tsuji, *J. Org. Chem*., **55**, 766 (1990); K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, and X.-L. Zhang, *J. Org. Chem*., **57**, 2768 (1992); J. Eames, H. J. Mitchell, A. Nelson, P. O'Brien, S. Warren, and P. Wyatt, *Tetrahedron Lett*., **36**, 1719 (1995).
45. H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev*., **94**, 2483 (1994).

Scheme 12.6. Examples of *syn* Dihydroxylation of Alkenes

A. Potassium permanganate



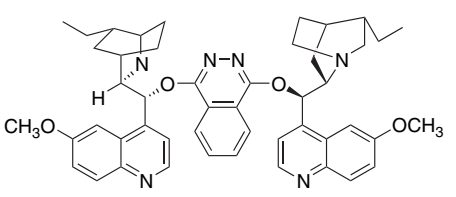
B. Osmium tetroxide

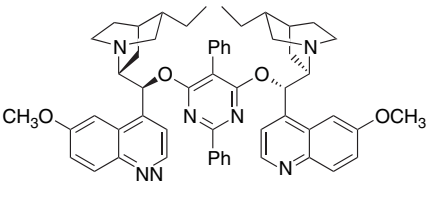


a. E. J. Witzeman, W. L. Evans, H. Haas, and E. F. Schroeder, *Org. Synth*., **II**, 307 (1943).
b. S. D. Larsen and S. A. Monti, *J. Am. Chem. Soc*., **99**, 8015 (1977).
c. E. J. Corey, P. B. Hopkins, S. Kim, S. Yoo, K. P. Nambiar, and J. R. Falck, *J. Am. Chem. Soc*., **101**, 7131 (1979).
d. K. Akashi, R. E. Palermo, and K. B. Sharpless, *J. Org. Chem*., **43**, 2063 (1978).
e. S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, *J. Am. Chem. Soc*., **99**, 6066 (1977).

ligands are dimeric derivatives of these alkaloids.[46] These ligands both induce high enantioselectivity and accelerate the reaction.[47] Potassium ferricyanide is usually used as the stoichiometric oxidant. Optimization of the reaction conditions permits rapid and predictable dihydroxylation of many types of alkenes.[48] The premixed catalysts are available commercially and are referred to by the trade name AD-mix™. Several heterocyclic compounds including phthalazine (PHAL), pyrimidine (PYR), pyridazine (PYDZ), and diphenylpyrimidine (DPPYR) have been used as linking groups for the alkaloids.

46. (a) G. A. Crispino, K. S. Jeong, H. C. Kolb, Z.-M. Wang, D. Xu, and K. B. Sharpless, *J. Org. Chem*., **58**, 3785 (1993); (b) G. A. Crispino, A. Makita, Z.-M. Wang, and K. B. Sharpless, *Tetrahedron Lett*., **35**, 543 (1994); (c) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, and X.-L. Zhang, *J. Org. Chem*., **57**, 2768 (1992); (d) W. Amberg, Y. L. Bennani, R. K. Chadha, G. A. Crispino, W. D. Davis, J. Hartung, K. S. Jeong, Y. Ogino, T. Shibata, and K. B. Sharpless, *J. Org. Chem*., **58**, 844 (1993); (e) H. Becker, S. B. King, M. Taniguchi, K. P. M. Vanhessche, and K. B. Sharpless, *J. Org. Chem*., **60**, 3940 (1995).
47. P. G. Anderson and K. B. Sharpless, *J. Am. Chem. Soc*., **115**, 7047 (1993).
48. T. Gobel and K. B. Sharpless, *Angew. Chem. Int. Ed. Engl*., **32**, 1329 (1993).





Empirical analysis led to the predictive model for enantioselectivity shown in Figure 12.1.[46c,49] The two alkaloids are of opposite chirality and give enantiomeric products. The commercial reagents are designated AD-mix-α and AD-mix-β. The configuration of the products can be predicted by a model based on the relative size of the substituent groups. *E*-Alkenes give the best fit to the binding pocket and give the highest reactivity and enantioselectivity.

There have been two computational studies of the basis for the catalysis and enantioselectivity. A study of the reaction of styrene with the $(DHQD)_2PYDZ$ ligand was done using a hybrid DFT/MM protocol.[50] Two orientations of the styrene molecule were found that were about 3.0 kcal/mol more favorable than any of the others. These TSs are shown in Figure 12.2. Both these structures predict the observed *R*-configuration for the product. Most of the difference among the various structures is found in the MM terms and they are exothermic, that is, there are *net attractive forces involved in the binding of the reactant*. The second study used stilbene as the reactant and $(DHQD)_2PHAL$ as the catalyst ligand.[51] This study arrives at the TS shown in Figure 12.3. The two phenyl groups of stilbene occupy *both* of the sites found for the two low-energy TSs for styrene.

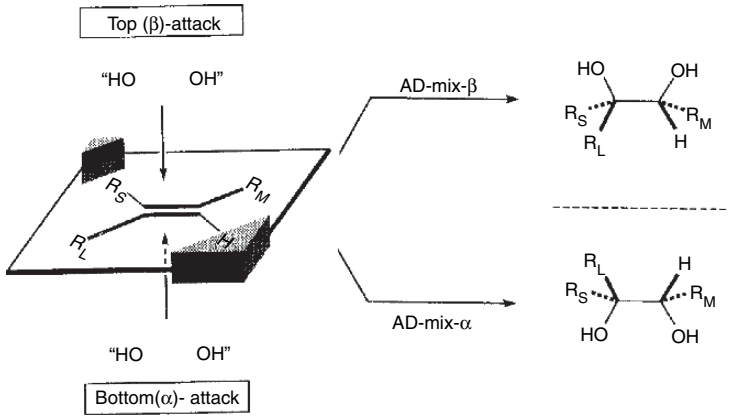


Fig. 12.1. Predictive model for enantioselective dihydroxylation by dimeric alkaloid catalysts. $(DHQD)_2$ catalysts give β-approach; $(DHQ)_2$ catalysts give α-approach. Reproduced from *J. Org. Chem.*, **57**, 2768 (1992), by permission of the American Chemical Society.

49. H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev.*, **94**, 2483 (1994).
50. G. Ujaque, F. Maseras, and A. Lledos, *J. Am. Chem. Soc.*, **121**, 1317 (1999).
51. P.-O. Norrby, T. Rasmussen, J. Haller, T. Strassner, and K. N. Houk, *J. Am. Chem. Soc.*, **121**, 10186 (1999).

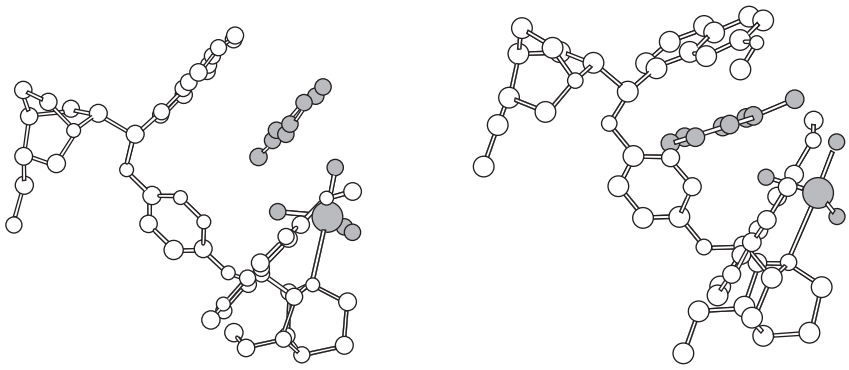


Fig. 12.2. Two lowest-energy transition structures for oxidation of styrene by $(DHQD)_2PYDZ\text{-}OsO_4$ catalysts. The structure on the left is about 0.4 kcal more stable than the one on the right. Both structures predict the formation of *R*-styrene oxide. Reproduced from *J. Am. Chem. Soc*., **121**, 1317 (1999), by permission of the American Chemical Society.

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

Scheme 12.7 gives some examples of enantioselective hydroxylations using these reagents. Entry 1 is an allylic ether with a terminal double bond. *para*-Substituted derivatives also gave high e.e. values, but some *ortho* substituents led to lower e.e. values. Entry 2 is one of several tertiary allylic alcohols that gave excellent results. Entry 3 is a *trans*-substituted alkene with rather large (but unbranched) substituents. The inclusion of methanesulfonamide, as in this example, has been found to be beneficial for di- and trisubstituted alkenes. It functions by speeding the hydrolysis of the osmate ester intermediate. The product in this case goes on to cyclize to the

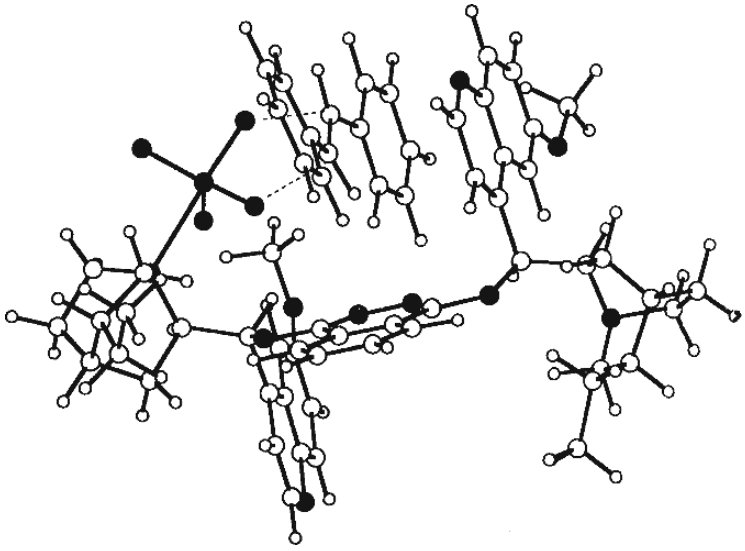
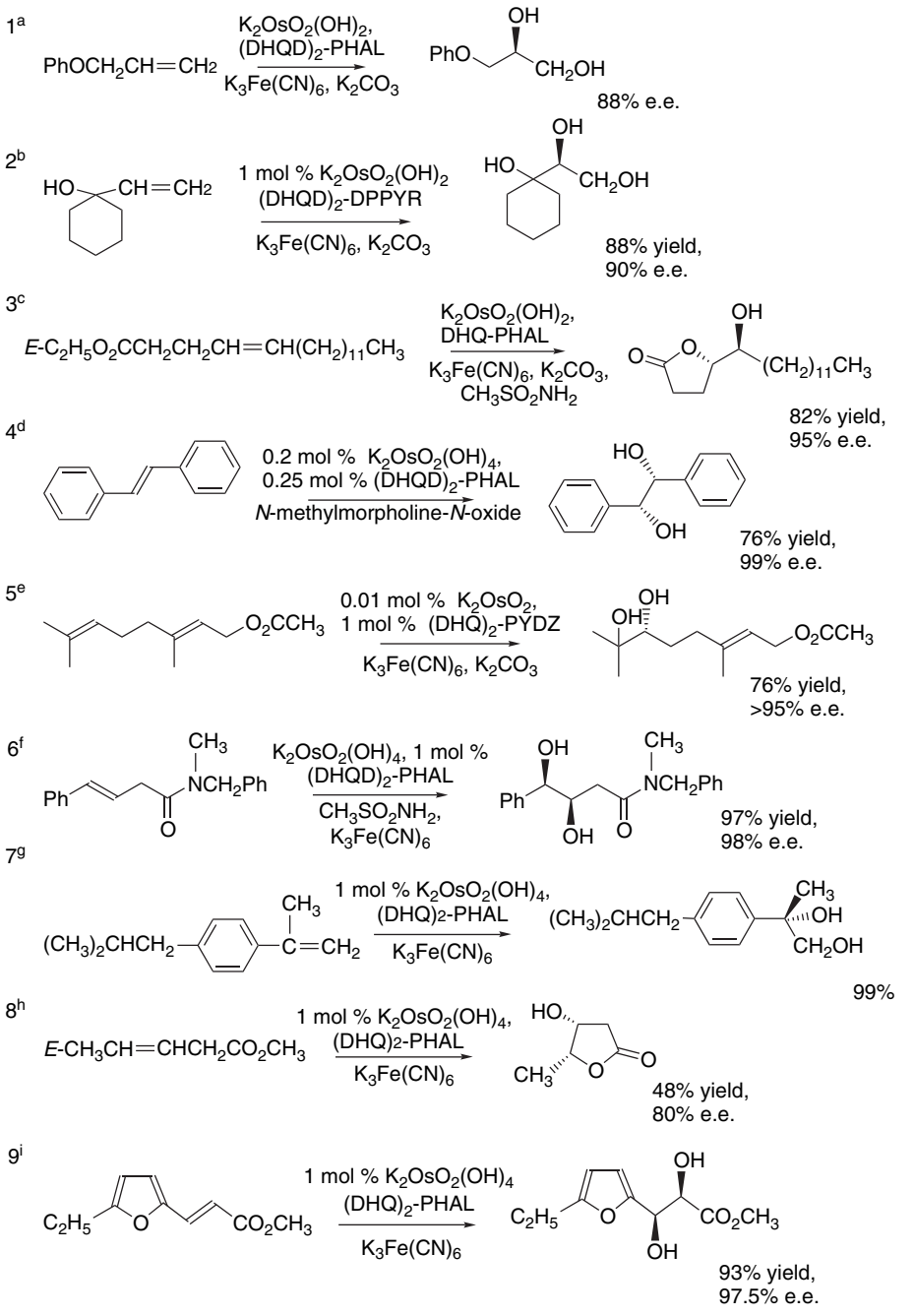


Fig. 12.3. Transition structure for oxidation of stilbene by $(DHQD)_2PHAL\text{-}OsO_4$ catalyst. Reproduced from *J. Am. Chem. Soc*., **121**, 10186 (1999), by permission of the American Chemical Society.

Scheme 12.7. Enantioselective Osmium-Catalyzed Dihydroxylation of Alkenes



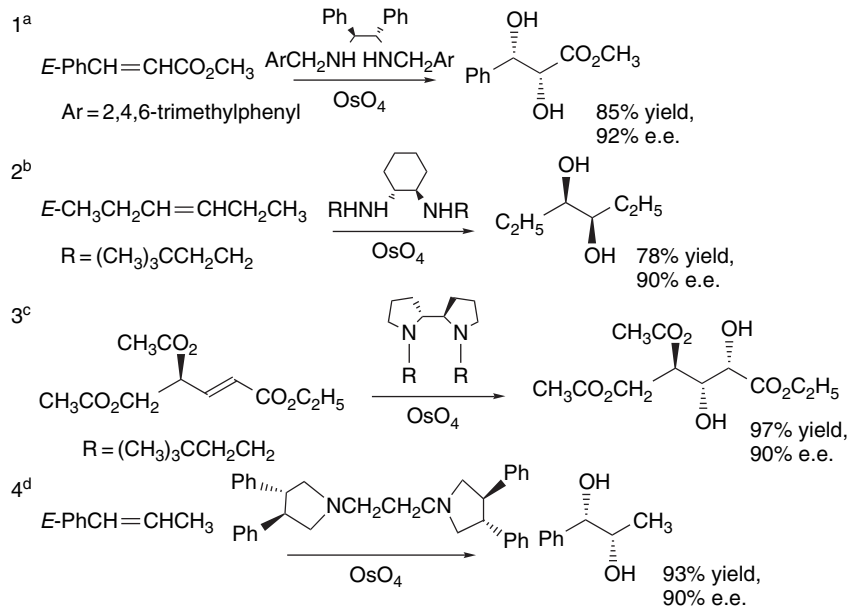
a. Z.-M. Wang, X.-L. Zhang, and K. B. Sharpless, *Tetrahedron Lett*., **34**, 2267 (1993).
b. Z.-M. Wang and K. B. Sharpless, *Tetrahedron Lett*., **34**, 8225 (1993).
c. Z.-M. Wang, X.-L. Zhang, K. B. Sharpless, S. C. Sinha, A. Sinha-Bagchi, and E. Keinan, *Tetrahedron Lett*., **33**, 6407 (1992).
d. H. T. Chang and K. B. Sharpless, *J. Org. Chem*., **61**, 6456 (1996).
e. E. J. Corey, M. C. Noe, and W.-C. Shieh, *Tetrahedron Lett*., **34**, 5995 (1993).
f. Y. L. Bennani and K. B. Sharpless, *Tetrahedron Lett*., **34**, 2079 (1993).
g. H. Ishibashi, M. Maeki, J. Yagi, M. Ohba, and T. Kanai, *Tetrahedron*, **55**, 6075 (1999).
h. T. Berkenbusch and R. Bruckner, *Tetrahedron*, **54**, 11461 (1998).
i. T. Taniguchi, M. Takeuchi, and K. Ogasawara, *Tetrahedron: Asymmetry*, **9**, 1451 (1998).

observed lactone. This particular oxidation was also carried out with $(DHQD)_2$-PHAL, which gave the enantiomeric lactone. Entry 4 is an optimized oxidation of stilbene that was done on a 1-kg scale. Entry 5 is the dihydroxylation of geranyl acetate that shows selectivity for the 6,7-double bond. Entry 6 involves an unsaturated amide and required somewhat higher catalyst loading than normal. Entry 7 provided a starting material for the enantioselective synthesis of *S*-ibuprofen. The reaction in Entry 8 was used to prepare the lactone shown (and its enantiomer) as starting materials for enantioselective synthesis of several natural products. The furan synthesized in Entry 9 was used to prepare a natural material by a route involving eventual oxidation of the furan ring.

Various other chiral diamines have also been explored for use with OsO_4, some of which are illustrated in Scheme 12.8. They presumably function by forming hexacoordinate chelates with OsO_4. The reactant in Entry 3 also raises the issue of diastereoselectivity with respect to the allylic substituent. Normally, the dihydroxylation is *anti* toward such substituents.[52] There are thus matched and mismatched combinations with the chiral osmium ligand. The *R*, *R*-diamine shown gives the matched combination and leads to high diastereoselectivity, as well as high enantioselectivity.

12.2.1.2. Transition Metal–Catalyzed Epoxidation of Alkenes. Other transition metal oxidants can convert alkenes to epoxides. The most useful procedures involve *t*-butyl hydroperoxide as the stoichiometric oxidant in combination with vanadium or

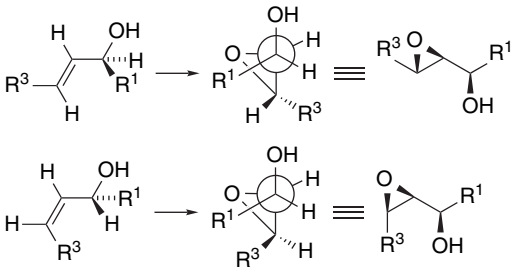
Scheme 12.8. Enantioselective Hydroxylation Using Chiral Diamines



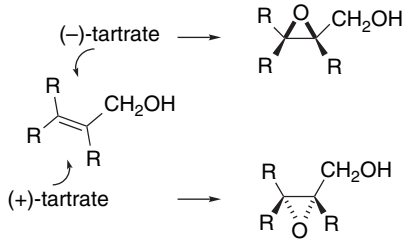
a. E. J. Corey, P. D. Jardine, S. Virgil, P.-W. Yuen, and R. D. Connell, *J. Am. Chem. Soc*., **111**, 9243 (1989).
b. S. Hannessian, P. Meffre, M. Girard, S. Beaudoin, J.-Y. Sanceau, and Y. Bennani, *J. Org. Chem*., **58**, 1991 (1993).
c. T. Oishi, K. Iida, and M. Hirama, *Tetrahedron Lett*., **34**, 3573 (1993).
d. K. Tomioka, M. Nakajima, and K. Koga, *Tetrahedron Lett*., **31**, 1741 (1990).

52. J. K. Cha, W. J. Christ, and Y. Kishi, *Tetrahedron*, **40**, 2247 (1984).

titanium compounds. The most reliable substrates for oxidation are allylic alcohols. The hydroxy group of the alcohol plays both an activating and stereodirecting role in these reactions. *t*-Butyl hydroperoxide and a catalytic amount of VO(acac) convert allylic alcohols to the corresponding epoxides in good yields.[53] The reaction proceeds through a complex in which the allylic alcohol is coordinated to vanadium by the hydroxy group. In cyclic alcohols, this results in epoxidation *cis* to the hydroxy group. In acyclic alcohols the observed stereochemistry is consistent with a TS in which the double bond is oriented at an angle of about 50° to the coordinated hydroxy group. This TS leads to diastereoselective formation of the *syn*-alcohol. This stereoselectivity is observed for both *cis*- and *trans*-disubstituted allylic alcohols.[54]

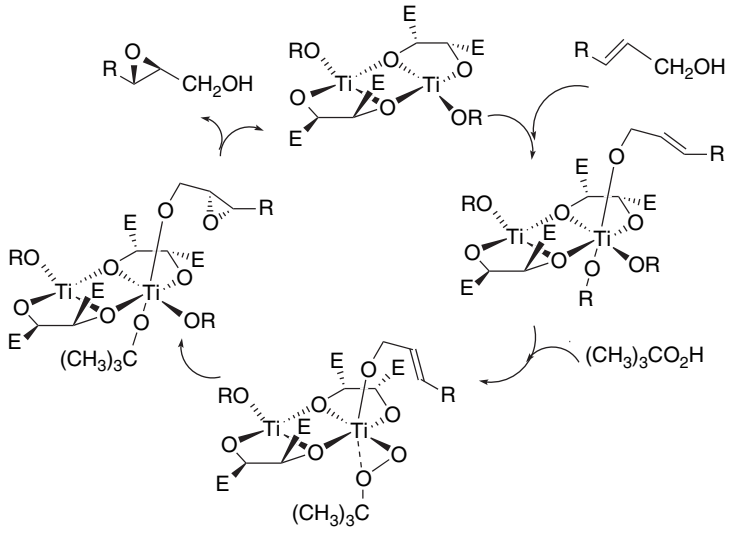


The epoxidation of allylic alcohols can also be effected by *t*-butyl hydroperoxide and titanium tetraisopropoxide. When enantiomerically pure tartrate ligands are included, the reaction is highly enantioselective. This reaction is called the *Sharpless asymmetric epoxidation*.[55] Either the (+) or (−) tartrate ester can be used, so either enantiomer of the desired product can be obtained.



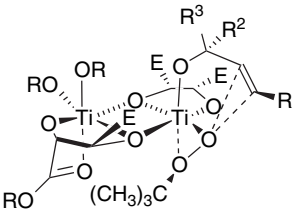
The mechanism by which the enantioselective oxidation occurs is generally similar to that for the vanadium-catalyzed oxidations. The allylic alcohol serves to coordinate the substrate to titanium. The tartrate esters are also coordinated at titanium, creating a chiral environment. The active catalyst is believed to be a dimeric species, and the mechanism involves rapid exchange of the allylic alcohol and *t*-butylhydroperoxide at the titanium ion.

53. K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).
54. E. D. Mihelich, *Tetrahedron Lett.*, 4729 (1979); B. E. Rossiter, T. R. Verhoeven, and K. B. Sharpless, *Tetrahedron Lett.*, 4733 (1979).
55. For reviews, see A. Pfenninger, *Synthesis*, 89 (1986); R. A. Johnson and K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, I. Ojima, ed., VCH Publishers, New York, 1993, pp. 103–158.



This method has proven to be an extremely useful means of synthesizing enantiomerically enriched compounds. Various improvements in the methods for carrying out the Sharpless oxidation have been developed.[56] The reaction can be done with catalytic amounts of titanium isopropoxide and the tartrate ligand.[57] This procedure uses molecular sieves to sequester water, which has a deleterious effect on both the rate and enantioselectivity of the reaction.

The orientation of the reactants is governed by the chirality of the tartrate ligand. In the TS an oxygen atom from the peroxide is transferred to the double bond. The enantioselectivity is consistent with a TS such as that shown below.[58]



There has been a DFT (BLYP/6-31G*) study of the TS and its relationship to the enantioselectivity of the reaction.[59] The strategy used was to build up the model by successively adding components. First the titanium coordination sphere, including an alkene and peroxide group, was modeled (Figure 12.4a). In Figure 12.4b, the diol

[56] J. G. Hill, B. E. Rossiter, and K. B. Sharpless, *J. Org. Chem*., **48**, 3607 (1983); L. A. Reed, III, S. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc*., **104**, 6468 (1982).

[57] R. M. Hanson and K. B. Sharpless, *J. Org. Chem*., **51**, 1922 (1986); Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc*., **109**, 5765 (1987).

[58] V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, and K. B. Sharpless, *J. Am. Chem. Soc*., **103**, 6237 (1981); K. B. Sharpless, S. S. Woodard, and M. G. Finn, *Pure Appl. Chem*., **55**, 1823 (1983); M. G. Finn and K. B. Sharpless, in *Asymmetric Synthesis*, Vol. 5, J. D. Morrison, ed., Academic Press, New York, 1985, Chap 8; M. G. Finn and K. B. Sharpless, *J. Am. Chem. Soc*., **113**, 113 (1991); B. H. McKee, T. H. Kalantar, and K. B. Sharpless, *J. Org. Chem*., **56**, 6966 (1991); For an alternative description of the origin of enantioselectivity, see E. J. Corey, *J. Org. Chem*., **55**, 1693 (1990).

[59] Y.-D. Wu and D. F. W. Lai, *J. Am. Chem. Soc*., **117**, 11327 (1995).

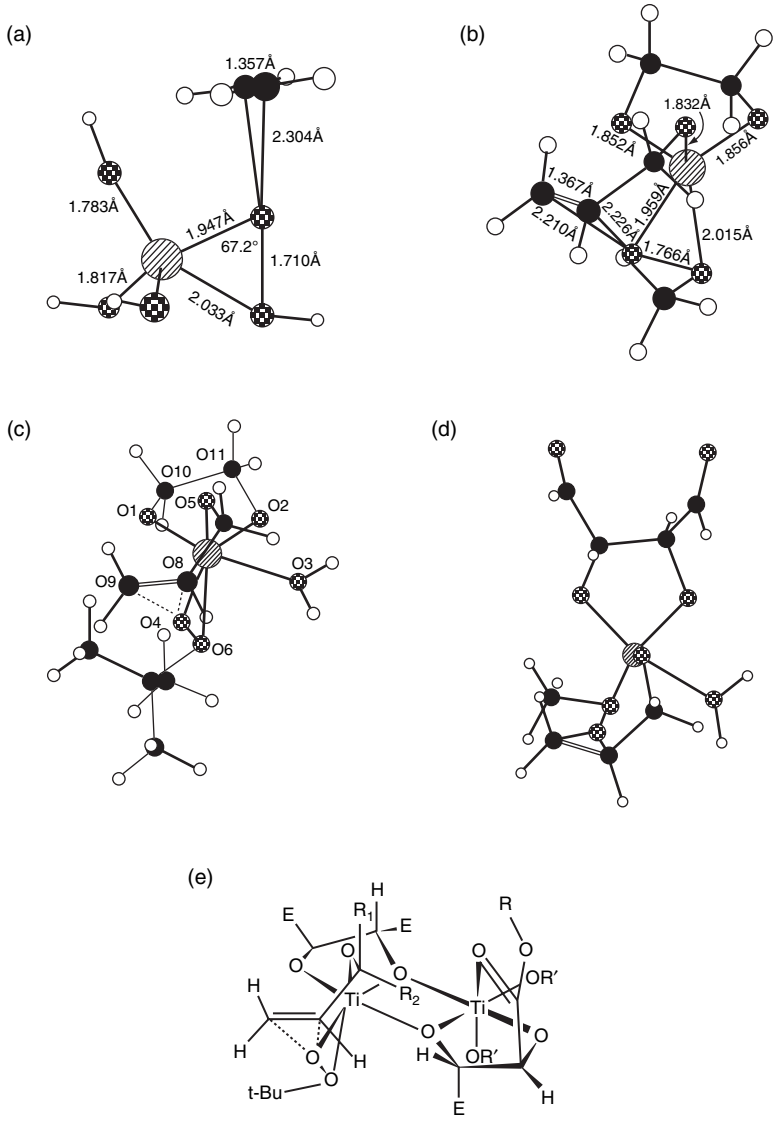


Fig. 12.4. Successive models of the transition state for Sharpless epoxidation. (a) the hexacoordinate Ti core with uncoordinated alkene; (b) Ti with methylhydroperoxide, allyl alcohol, and ethanediol as ligands; (c) monomeric catalytic center incorporating *t*-butylhydroperoxide as oxidant; (d) monomeric catalytic center with formyl groups added; (e) dimeric transition state with chiral tartrate model (E = CH = O). Reproduced from *J. Am. Chem. Soc*., **117**, 11327 (1995), by permission of the American Chemical Society.

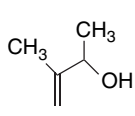
ligand and allylic alcohol were added to the coordination sphere. Then the steric bulk associated with the hydroperoxide was added (Figure 12.4c), and finally the tartrate ligands were added (using formyl groups as surrogates; Figure 12.4d) This led successively to TSs of increasingly detailed structure. The energies were minimized to identify the most stable structure at each step. The key features of the final TS model are the following: (1) The peroxide-titanium interaction has a spiro, rather than

planar, arrangement in the TS for oxygen transfer. (2) The orientation of the alkyl group of the peroxide plays a key role in the enantioselectivity, which is consistent with the experimental observation that less bulky hydroperoxides give much lower enantioselectivity. (3) The C–O bond of the allylic alcohol bisects the Ti–O bond formed by the water and peroxy ligands. (4) The tartrate groups at the active catalytic center are in equatorial positions and do not coordinate to titanium. This implies a conformation flip of the diolate ring as part of the activation process, since the ester groups are in axial positions in the dimeric catalyst.

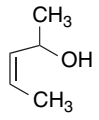
Visual models, additional information and exercises on Sharpless Epoxidation can be found in the Digital Resource available at: Springer.com/carey-sundberg.

Owing to the importance of the allylic hydroxy group in coordinating the reactant to the titanium, the structural relationship between the double bond and the hydroxy group is crucial. Homoallylic alcohols can be oxidized but the degree of enantioselectivity is reduced. Interestingly, the facial selectivity is reversed from that observed with allylic alcohols.[60] Compounds lacking a coordinating hydroxy group are not reactive under the standard reaction conditions.

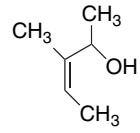
Substituted allylic alcohols also exhibit diastereoselectivity. A DFT study has examined the influence of alkyl substituents in the allylic alcohol on the stereoselectivity.[61] Alcohols **3a, 3b**, and **3c** were studied. The catalytic entity was modeled by $Ti(OH)_4$-CH_3OOH. This approach neglects the steric influence of the *t*-butyl and tartrate ester groups and focuses on the structural features of the allylic alcohols, which are placed on the catalytic core in their minimum energy conformation. Figure 12.5 shows these conformations. The TS structural parameters were derived from the Wu-Lai TS model (see Figure 12.4). The relative energies of the TSs leading to the *erythro* and *threo* products for each alcohol were compared (Figure 12.6). A solvent dielectric chosen to simulate CH_2Cl_2 was used. The general conclusion drawn from this study is that the reactant conformation is the critical feature determining the diastereoselectivity of the epoxidation.



3a



3b

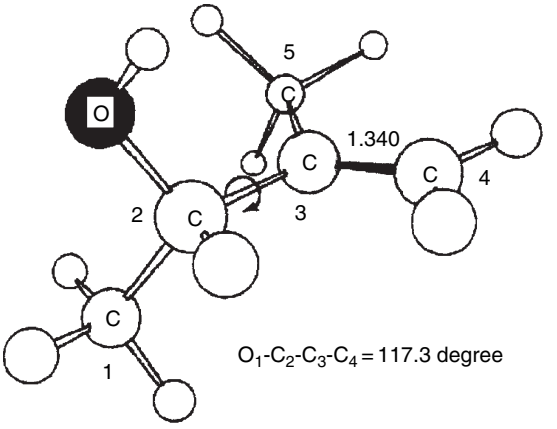


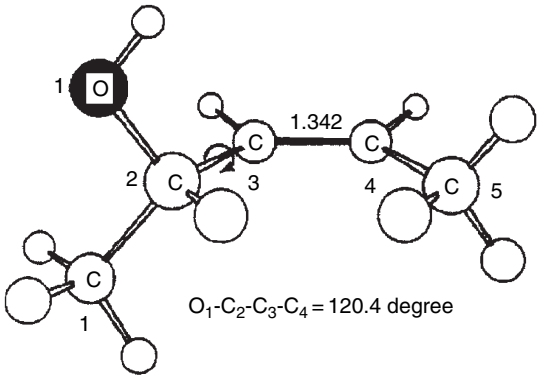
3c

In allylic alcohols with $A^{1,3}$ strain, the main product is *syn*. A methyl substituent at R^4 leads to the methyl group being positioned *anti* to the complexed oxidant. If R^4 is hydrogen, a TS with the methyl group in an "inside" position is favored, as shown in Figure 12.6.

The two TSs for **3a** are shown in Figure 12.7. **TS A** also has a more favorable orientation of the spiro ring structure. The ideal angle is 90°, at which point the two rings are perpendicular. This angle is 78.2° in **TS A** and 36.2° in **TS B**. **TS A** has a O(1)−C(2)−C(3)−C(4) angle of 35.6°, **TS B** has a corresponding angle of 96.1°. Based on the reactant conformational profile, this will introduce about 0.7 kcal more

60. B. E. Rossiter and K. B. Sharpless, *J. Org. Chem.*, **49**, 3707 (1984).
61. M. Cui, W. Adam, J. H. Shen, X. M. Luo, X. J. Tan, K. X. Chen, R. Y. Ji, and H. L. Jiang, *J. Org. Chem.*, **67**, 1427 (2002).





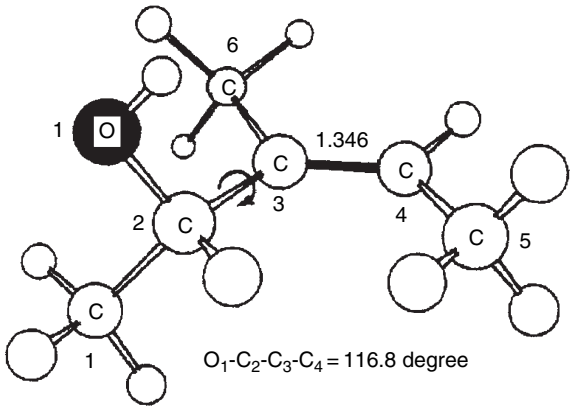


Fig. 12.5. Minimum energy conformations for allylic alcohol. **3a, 3b**, and **3c**. Reproduced from *J. Org. Chem*., **67**, 1427 (2002), by permission of the American Chemical Society.

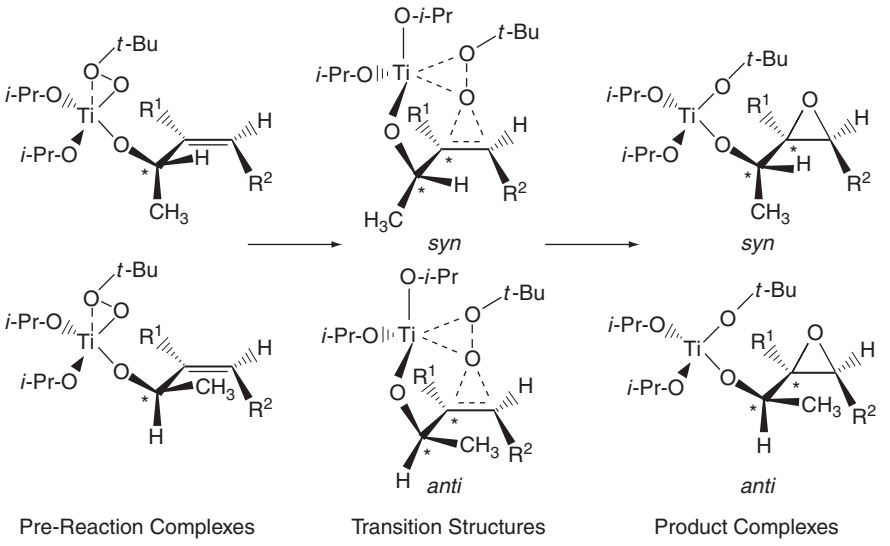


Fig. 12.6. Conformational factors affecting *syn* and *anti* diastereoselectivity in Sharpless epoxidation. If substituent $R^4 > H$, $A^{1,3}$ strain favors the *syn* product. If $R^4 = H$, the preferred transition structure leads to *anti* product. Reproduced from *J. Org. Chem*., **67**, 1427 (2002), by permission of the American Chemical Society.

strain in **TS B** than in **TS A**. Similar analyses were done on the two TSs for **3b** and **3c**. The TS energies were used to compare computational ΔE_a with experimental diastereoselectivity. Whereas **TS A** is favored for **3a, TS B** is favored for **3b** and **3c**, in agreement with the experimental stereoselectivity.

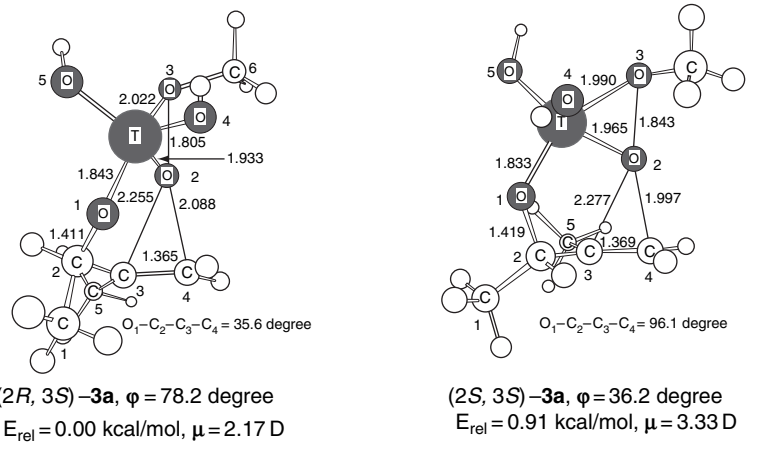
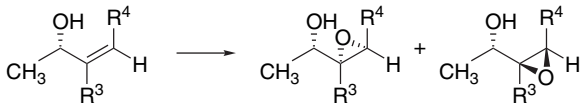


Fig. 12.7. Alternate orientations of 3-methylbut-3-en-1-ol (**3a**) in the transition state for Ti-mediated epoxidation. Angle φ is the inter-ring angle of the spiro rings. Reproduced from *J. Org. Chem*., **67**, 1427 (2002), by permission of the American Chemical Society.

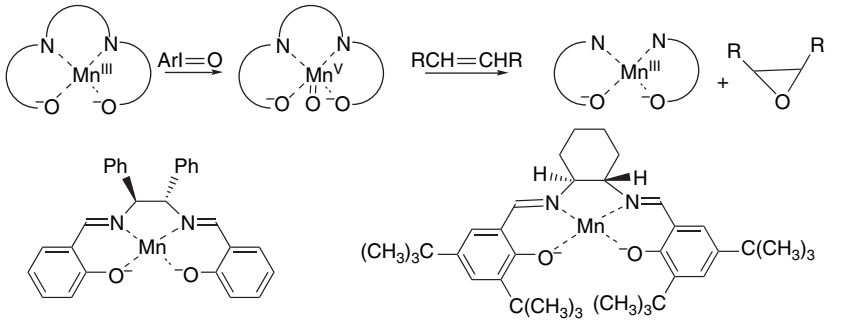


	R^3	R^4	predicted	observed
3a	CH_3	H	12:88	22:78
3b	H	CH_3	92:8	91:9
3c	CH_3	CH_3	77:23	83:17

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

Scheme 12.9 gives some examples of enantioselective oxidation of allylic alcohols. Entry 1 is a representative procedure, as documented in an *Organic Syntheses* preparation. The reaction in Entry 2 was used to prepare a starting material for synthesis of leukotriene C-1. Entry 3 is an example incorporating the use of molecular sieves. The reaction in Entry 4 was the departure point in a synthesis of part of the polyether antibiotic X-206. Entry 5 is another example of the procedure using molecular sieves. The catalyst loading in this reaction is 5%. The reaction in Entry 6 is diastereoselective for the *anti* isomer. Entry 7 also shows a case of diastereoselectivity, in this instance with respect to the 4-methyl group. Note that both of these reactions involve oxidation of the alkene from the same face, although they differ in configuration at C(4). Thus, the enantioselectivity is under reagent control.

Several catalysts that can effect enantioselective epoxidation of unfunctionalized alkenes have been developed, most notably manganese complexes of diimines derived from salicylaldehyde and chiral diamines (salens).[62]

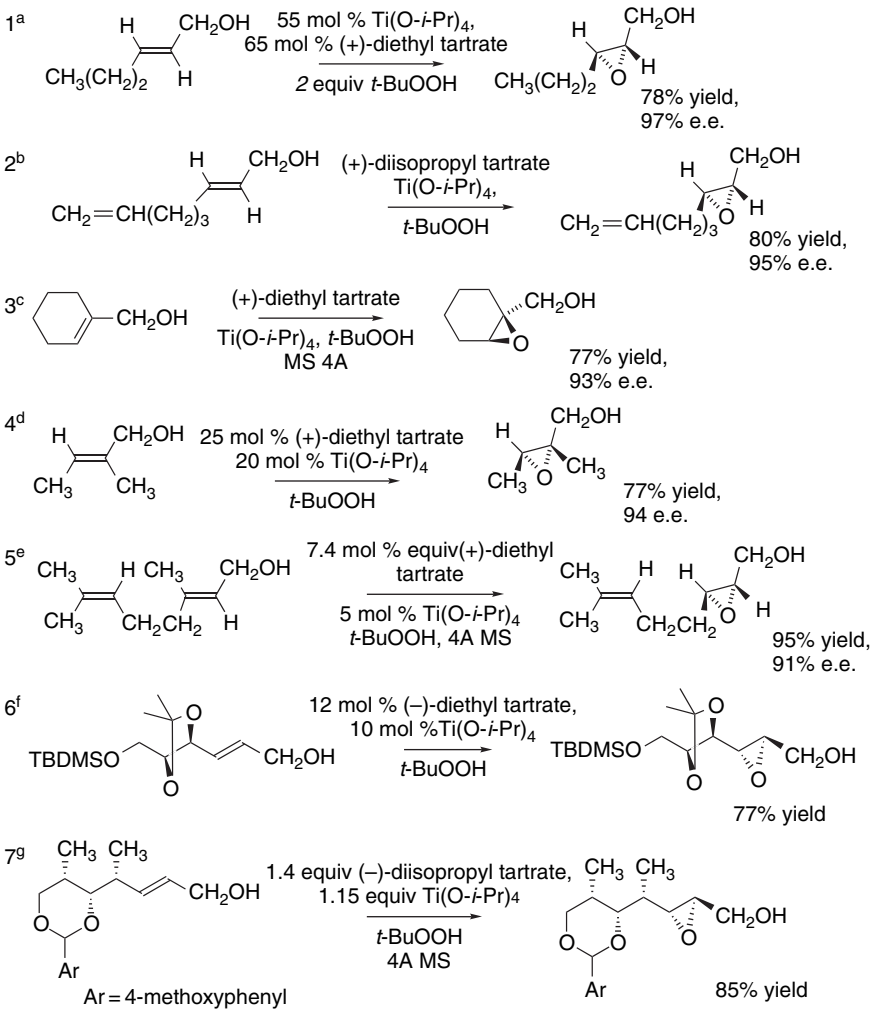


D **E**

These catalysts are used in conjunction with a stoichiometric amount of an oxidant and the active oxidant is believed to be an oxo Mn(V) species. The stoichiometric oxidants that have been used include NaOCl,[63] periodate,[64] and amine oxides.[65] Various other

62. W. Zhang, J. L. Loebach, S. R. Wilson, and E. N. Jacobsen, *J. Am. Chem. Soc*., **112**, 2801 (1990); E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, and L. Deng, *J. Am. Chem. Soc*., **113**, 7063 (1991).
63. W. Zhang and E. N. Jacobsen, *J. Org. Chem*., **56**, 2296 (1991); B. D. Brandes and E. N. Jacobsen, *J. Org. Chem*., **59**, 4378 (1994).
64. P. Pietikainen, *Tetrahedron Lett*., **36**, 319 (1995).
65. M. Palucki, P. J. Pospisil, W. Zhang, and E. N. Jacobsen, *J. Am. Chem. Soc*., **116**, 9333 (1994).

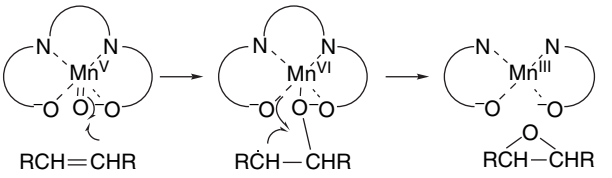
Scheme 12.9. Enantioselective Epoxidation of Allylic Alcohols



a. J. G. Hill and K. B. Sharpless, *Org. Synth*., **63**, 66 (1985).
b. B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *J. Am. Chem. Soc*., **103**, 464 (1981).
c. Y. Gao, R. M. Hanson. J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc*., **109**, 5765 (1987).
d. D. A. Evans, S. L. Bender, and J. Morris, *J. Am. Chem. Soc*., **110**, 2506 (1988).
e. R. M. Hanson and K. B. Sharpless, *J. Org. Chem*., **51**, 1922 (1986).
f. A. K. Ghosh and Y. Wang, *J. Org. Chem*., **64**, 2789 (1999).
g. J. A. Marshall, Z.-H. Lu, and B. A. Johns, *J. Org. Chem*., **63**, 817 (1998).

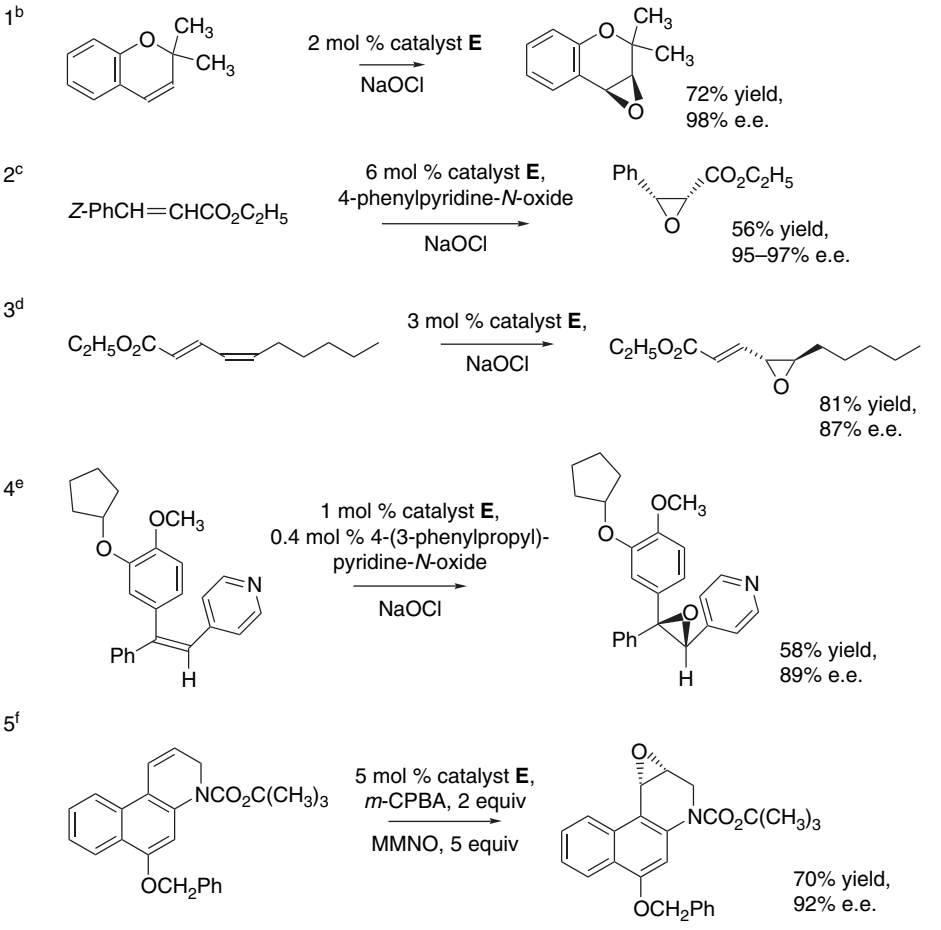
chiral salen-type ligands have also been explored.[66] These epoxidations are not always stereospecific with respect to the alkene geometry, which is attributed to an electron transfer mechanism that involves a radical intermediate.

66. N. Hosoya, R. Irie, and T. Katsuki, *Synlett*, 261 (1993); S. Chang, R. M. Heid, and E. N. Jacobsen, *Tetrahedron Lett*., **35**, 669 (1994).



Scheme 12.10 gives some examples of these oxidations. Entry 1 is one of several aryl-conjugated alkenes that were successfully epoxidized. Entry 2 is a reaction that was applied to enantioselective synthesis of the taxol side chain. Entry 3 demonstrates

Scheme 12.10. Enantioselective Epoxidation with Chiral Manganese Catalysts[a]



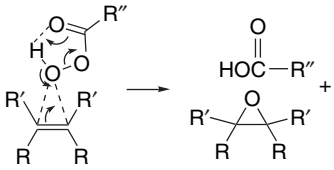
a. The structure of catalyst **E** is shown on p. 1088.
b. E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, and L. Deng, *J. Am. Chem. Soc*., **113**, 7063 (1991).
c. L. Deng and E. N. Jacobsen, *J. Org. Chem*., **57**, 4320 (1992).
d. S. Chang, N. H. Lee, and E. N. Jacobsen, *J. Org. Chem*., **58**, 6939 (1993).
e. J. E. Lynch, W.-B. Choi, H. R. O. Churchill, R. P. Volante, R. A. Reamer, and R. G. Ball, *J. Org. Chem*., **62**, 9223 (1997).
f. D. L. Boger, J. A. McKie, and C. W. Boyce, *Synlett*, 515 (1997).

chemoselectivity for the 4,5-double bond in a dienoate ester. This case also illustrates the occurrence of isomerization during the epoxidation. Entry 4 is a step in the enantioselective synthesis of CDP840, a phosphodiesterase inhibitor. The reaction in Entry 5 provided a starting material for the synthesis of the DNA-alkylating antitumor agent CC-1065.

12.2.2. Epoxides from Alkenes and Peroxidic Reagents

12.2.2.1. Epoxidation by Peroxy Acids and Related Reagents. The most general reagents for conversion of simple alkenes to epoxides are peroxycarboxylic acids.[67] *m*-Chloroperoxybenzoic acid[68] (MCPBA) is a particularly convenient reagent. The magnesium salt of monoperoxyphthalic acid is an alternative.[69] Potassium hydrogen peroxysulfate, which is sold commercially as Oxone®, is a convenient reagent for epoxidations that can be done in aqueous methanol.[70] Peroxyacetic acid, peroxybenzoic acid, and peroxytrifluoroacetic acid have also been used frequently for epoxidation. All of the peroxycarboxylic acids are potentially hazardous materials and require appropriate precautions.

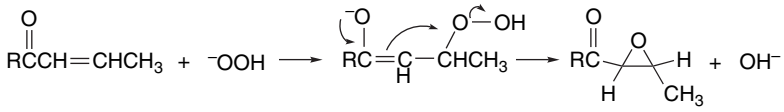
It has been demonstrated that ionic intermediates are not involved in the epoxidation reaction. The reaction rate is not very sensitive to solvent polarity.[71] Stereospecific *syn* addition is consistently observed. The oxidation is therefore believed to be a concerted process. A representation of the transition structure is shown below.



The rate of epoxidation of alkenes is increased by alkyl groups and other ERG substituents and the reactivity of the peroxy acids is increased by EWG substituents.[72] These structure-reactivity relationships demonstrate that the peroxyacid acts as an electrophile in the reaction. Decreased reactivity is exhibited by double bonds that are conjugated with strongly electron-attracting substituents, and more reactive peroxyacids, such as trifluoroperoxyacetic acid, are required for oxidation of such compounds.[73] Electron-poor alkenes can also be epoxidized by alkaline solutions of

67. D. Swern, *Organic Peroxides*, Vol. II, Wiley-Interscience, New York, 1971, pp. 355–533; B. Plesnicar, in *Oxidation in Organic Chemistry*, Part C, W. Trahanovsky, ed., Academic Press, New York, 1978, pp. 211–253.
68. R. N. McDonald, R. N. Steppel, and J. E. Dorsey, *Org. Synth*., **50**, 15 (1970).
69. P. Brougham, M. S. Cooper, D. A. Cummerson, H. Heaney, and N. Thompson, *Synthesis*, 1015 (1987).
70. R. Bloch, J. Abecassis, and D. Hassan, *J. Org. Chem*., **50**, 1544 (1985).
71. N. N. Schwartz and J. N. Blumbergs, *J. Org. Chem*., **29**, 1976 (1964).
72. B. M. Lynch and K. H. Pausacker, *J. Chem. Soc*., 1525 (1955).
73. W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc*., **77**, 89 (1955).

hydrogen peroxide or *t*-butyl hydroperoxide. A quite different mechanism, involving conjugate nucleophilic addition, operates in this case.[74]



There have been a number of computational studies of the epoxidation reaction. These studies have generally found that the hydrogen-bonded peroxy acid is approximately perpendicular to the axis of the double bond, giving a spiro structure.[75] Figure 12.8 shows TS structures and E_a values based on B3LYP/6-31G* computations. The E_a trend is as expected for an electrophilic process: $OCH_3 < CH_3 \sim CH=CH_2 <$ H < CN. Similar trends were found in MP4/6-31G* and QCISD/6-31G* computations.

The stereoselectivity of epoxidation with peroxycarboxylic acids has been well studied. Addition of oxygen occurs preferentially from the less hindered side of the molecule. Norbornene, for example, gives a 96:4 *exo:endo* ratio.[76] In molecules where two potential modes of approach are not very different, a mixture of products is formed.

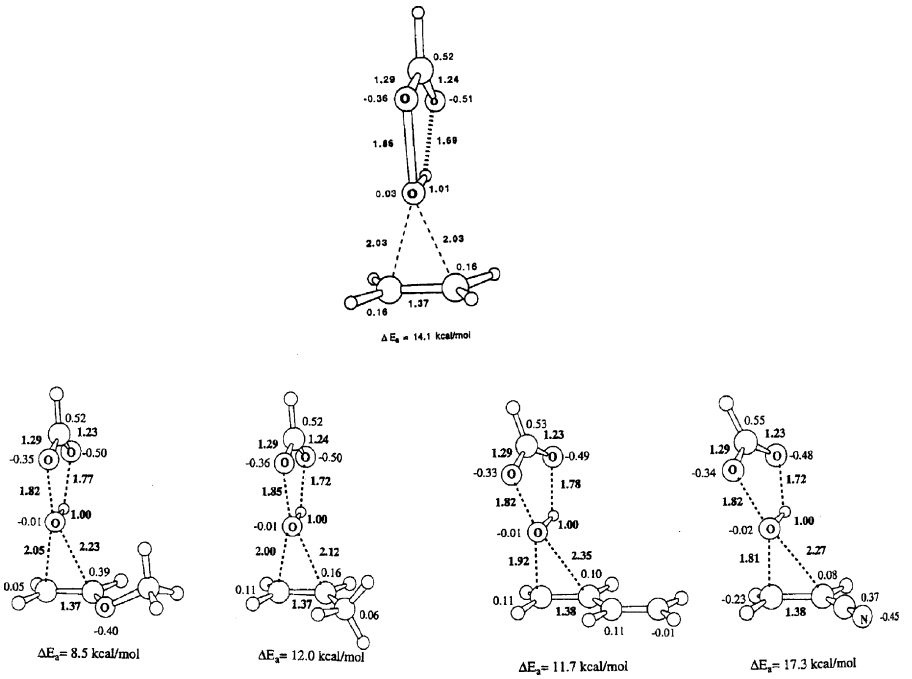
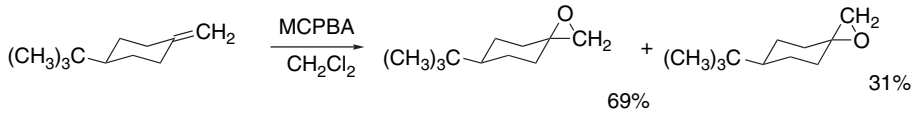


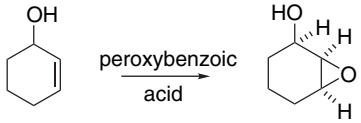
Fig. 12.8. Comparison of epoxidation transition structures and activation energies for ethene and substituted ethenes. Reproduced from *J. Am. Chem. Soc*., **119**, 10147 (1997), by permission of the American Chemical Society.

74. C. A. Bunton and G. J. Minkoff, *J. Chem. Soc*., 665 (1949).
75. R. D. Bach, M. N. Glukhovtsev, and C. Gonzalez, *J. Am. Chem. Soc*., **120**, 9902 (1998); K. N. Houk, J. Liu, N. C. DeMello, and K. R. Condroski, *J. Am. Chem. Soc*., **119**, 10147 (1997).
76. H. Kwart and T. Takeshita, *J. Org. Chem*., **28**, 670 (1963).

For example, the unhindered exocyclic double bond in 4-*t*-butylmethylenecyclohexane gives both stereoisomeric products.[77]



Hydroxy groups exert a directive effect on epoxidation and favor approach from the side of the double bond closest to the hydroxy group.[78] Hydrogen bonding between the hydroxy group and the reagent evidently stabilizes the TS.



This is a strong directing effect that can exert stereochemical control even when steric effects are opposed. Entries 4 and 5 in Scheme 12.11 illustrate the hydroxy-directing effect. Other substituents capable of hydrogen bonding, in particular amides, also can exert a *syn*-directing effect.[79]

The hydroxy-directing effect has been studied computationally, as the hydrogen bond can have several possible orientations.[80] Studies on 2-propen-1-ol show the same preference for the spiro TS as for unfunctionalized alkenes. There is a small preference for hydrogen bonding to a peroxy oxygen, as opposed to the carbonyl oxygen. The TSs for conformations of 2-propen-1-ol that are not hydrogen-bonded are 2–3 kcal/mol higher in energy than the best of the hydrogen-bonded structures. For substituted allylic alcohols, $A^{1,2}$ and $A^{1,3}$ strain comes into play. Figure 12.9 shows the structures and relative energies of the four possible TSs for prop-2-en-1-ol. The *syn,exo* structure with hydrogen-bonding to the transferring oxygen is preferred to the *endo* structure, in which the hydrogen-bonding is to the carbonyl oxygen.

Torsional effects are important in cyclic systems. A PM3 study of the high stereoselectivity of compounds **4a-d** found torsional effects to be the major difference between the diastereomeric TSs.[81] The computed TSs for **4a** are shown in Figure 12.10. The structures all show similar stereoselectivity, regardless of the presence and nature of a 3-substituent.

77. R. G. Carlson and N. S. Behn, *J. Org. Chem.*, **32**, 1363 (1967).
78. H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).
79. F. Mohamadi and M. M. Spees, *Tetrahedron Lett.*, **30**, 1309 (1989); P. G. M. Wuts, A. R. Ritter, and L. E. Pruitt, *J. Org. Chem.*, **57**, 6696 (1992); A. Jemmalm, W. Bets, K. Luthman, I. Csoregh, and U. Hacksell, *J. Org. Chem.*, **60**, 1026 (1995); P. Kocovsky and I. Stary, *J. Org. Chem.*, **55**, 3236 (1990); A. Armstrong, P. A. Barsanti, P. A. Clarke, and A. Wood, *J. Chem. Soc., Perkin Trans. 1*, 1373 (1996).
80. M. Freccero, R. Gandolfi, M. Sarzi-Amade, and A. Rastelli, *J. Org. Chem.*, **64**, 3853 (1999); M. Freccero, R. Gandolfi, M. Sarzi-Amade, and A. Rastelli, *J. Org. Chem.*, **65**, 2030 (2000).
81. M. J. Lucero and K. N. Houk, *J. Org. Chem.*, **63**, 6973 (1998).

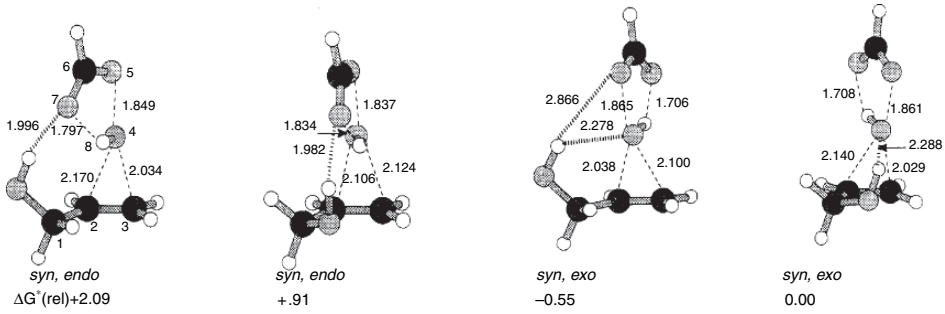
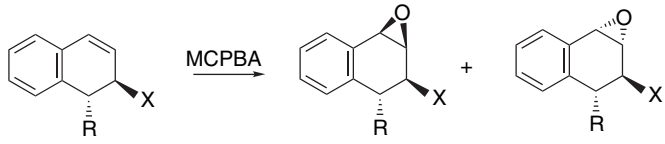


Fig. 12.9. Structure and relative energies of four modes of hydrogen bonding in transition structures for epoxidation of 2-propen-1-ol by peroxyformic acid. Relative energies are from B3LYP/6-311G*-level computations with a solvation model for CH_2Cl_2, $\epsilon = 8.9$. Reproduced from *J. Org. Chem.*, **64**, 3853 (1999), by permission of the American Chemical Society.



	R	X	*anti*	*syn*
4a	CH_3	H	85:15	
4b	Ph	H	high	
4c	Ph	CO_2CH_3	>95:5	
4d	Ph	CH_2OH	>95:5	

Even in the absence of a 3-substituent (**4a, 4b**) and with only a small 4-methyl group (**4a**), the stereoselectivity is high. The preference arises from the staggered relationship between the forming C–O bond and the axial allylic hydrogen.

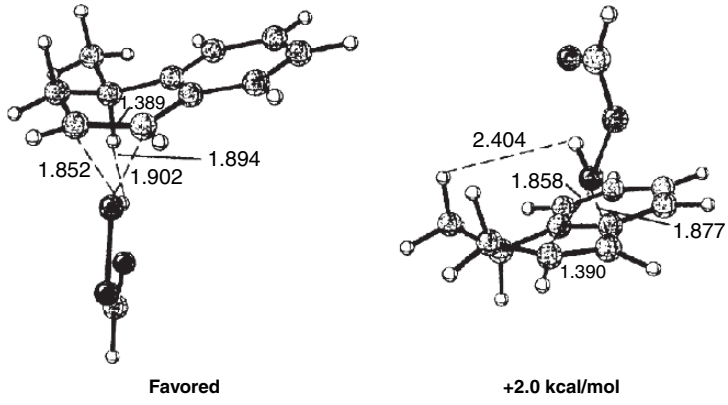
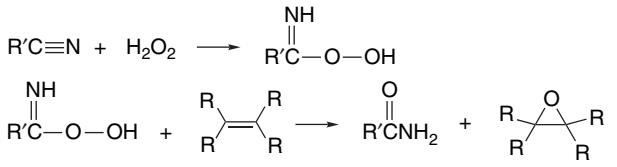
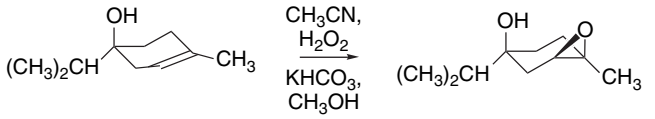


Fig. 12.10. Comparison of *trans*- and *cis*-oriented transition structures for epoxidation of 1-methyl-1,2-dihydronapththalene. Reproduced from *J. Org. Chem.*, **63**, 6973 (1998), by permission of the American Chemical Society.

A process that is effective for epoxidation and avoids acidic conditions involves reaction of an alkene, a nitrile, and hydrogen peroxide.[82] The nitrile and hydrogen peroxide react, forming a peroxyimidic acid, which epoxidizes the alkene, by a mechanism similar to that for peroxyacids. An important contribution to the reactivity of the peroxyimidic acid comes from the formation of the stable amide carbonyl group.



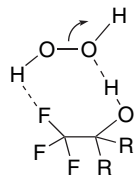
At least in some cases, the hydroxy-directing effect also operates for this version of the reaction.



Ref. 83

Scheme 12.11 gives some examples of epoxidation using peroxyacids and related reagents. Entry 1 shows standard epoxidation conditions applied to styrene. The reaction in Entry 2 uses typical epoxidation conditions and also illustrates the approach from the less hindered face of the molecule. In Entry 3, the selectivity for the more-substituted double bond was used to achieve regioselectivity. Entries 4 and 5 illustrate stereochemical control by hydroxy participation. The reaction in Entry 6 is an example of diastereoselectivity, most likely due to hydrogen bonding by the amide group. Entries 7 and 8 are cases of application of nucleophilic peroxidation conditions to alkenes conjugated with EWG substituents. In Entry 9, the more reactive trifluoroperoxyacetic acid was used to oxidize a deactivated double bond. Entry 10 is an example of use of the peroxyimidic acid conditions.

There is interest in being able to use H_2O_2 directly as an epoxidizing reagent because it is the ultimate source of most peroxides. The reactivity of H_2O_2 is substantially enhanced in hexafluoro-2-propanol (HFIP) and other polyfluorinated alcohols such as nonafluoro-*t*-butanol.[84] Either 30 or 60% H_2O_2 can oxidize alkenes to epoxides in these solvents. The system shows the normal trend of higher reactivity for more-substituted alkenes. The activation is attributed to polarization of the H_2O_2 by hydrogen bonding with the β-fluoroalcohols. The fluoro substituents also increase the acidity of the hydroxy group.

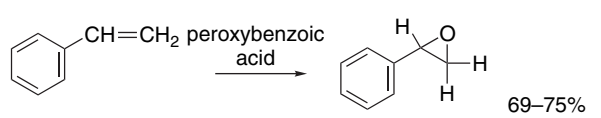


82. G. B. Payne, *Tetrahedron*, **18**, 763 (1962); R. D. Bach and J. W. Knight, *Org. Synth*., **60**, 63 (1981); L. A. Arias, S. Adkins, C. J. Nagel, and R. D. Bach, *J. Org. Chem*., **48**, 888 (1983).
83. W. C. Frank, *Tetrahedron: Asymmetry*, **9**, 3745 (1998).
84. K. Neimann and R. Neumann, *Org. Lett*., **2**, 2861 (2000).

Scheme 12.11. Synthesis of Epoxides from Alkenes Using Peroxy Acids

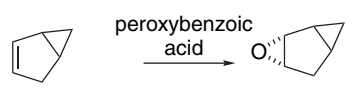
A. Oxidation of alkenes with peroxy acids

1[a]



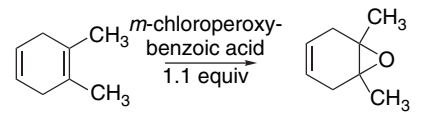
69–75%

2[b]



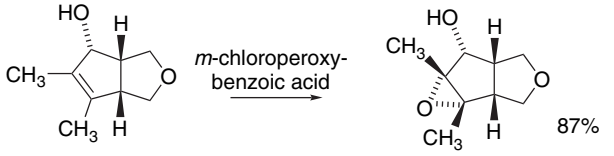
72%

3[c]



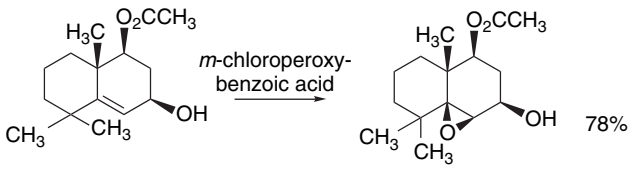
68–78%

4[d]



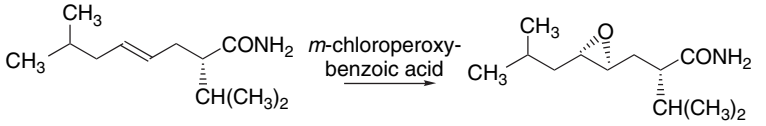
87%

5[e]



78%

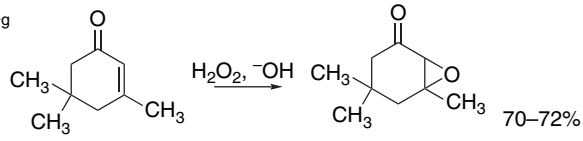
6[f]



12:1 diastereoselectivity

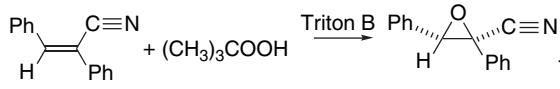
B. Epoxidation of electrophilic alkenes

7[g]



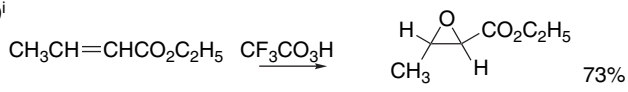
70–72%

8[h]



76%

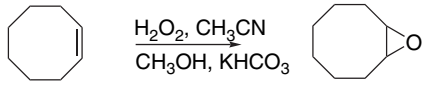
9[i]



73%

C. Epoxidation with peroxyimidic Acids

10[j]

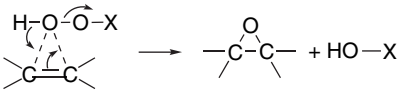


60%

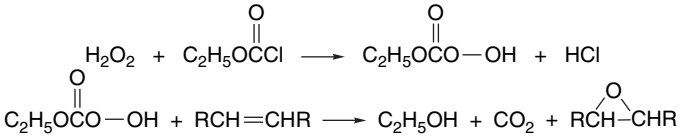
(*Continued*)

a. H. Hibbert and P. Burt, *Org. Synth.*, **I**, 481 (1932).
b. E. J. Corey and R. L. Dawson, *J. Am. Chem. Soc.*, **85**, 1782 (1963).
c. L. A. Paquette and J. H. Barrett, *Org. Synth.*, **49**, 62 (1969).
d. R. M. Scarborough, Jr., B. H. Toder, and A. B. Smith, III, *J. Am. Chem. Soc.*, **102**, 3904 (1980).
e. M. Miyashita and A. Yoshikoshi, *J. Am. Chem. Soc.*, **96**, 1917 (1974).
f. P. G. M. Wuts, A. R. Ritter, and L. E. Pruitt, *J. Org. Chem.*, **57**, 6696 (1992).
g. R. L. Wasson and H. O. House, *Org. Synth.*, **IV**, 552 (1963).
h. G. B. Payne and P. H. Williams, *J. Org. Chem.*, **26**, 651 (1961).
i. W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).
j. R. D. Bach and J. W. Knight, *Org. Synth.*, **60**, 63 (1981).

A variety of electrophilic reagents have been examined with the objective of activating H_2O_2 to generate a good epoxidizing agent. In principle, any species that can convert one of the hydroxy groups to a good leaving group can generate a reactive epoxidizing reagent.

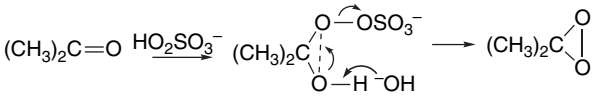


In practice, promising results have been obtained for several systems. For example, fair to good yields of epoxides are obtained when a two-phase system consisting of alkene and ethyl chloroformate is stirred with a buffered basic solution of hydrogen peroxide. The active oxidant is presumed to be *O*-ethyl peroxycarbonic acid.[85]



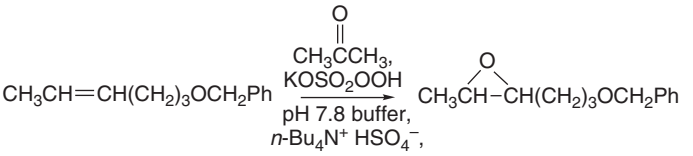
Although these reagent combinations are not as generally useful as the peroxycarboxylic acids, they serve to illustrate that epoxidizing activity is not unique to the peroxyacids.

12.2.2.2. Epoxidation by Dioxirane Derivatives. Another useful epoxidizing agent is dimethyldioxirane (DMDO),[86] which is generated by in situ reaction of acetone and peroxymonosulfate in buffered aqueous solution. Distillation gives about a 0.1 *M* solution of DMDO in acetone.[87]



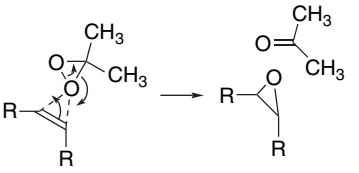
85. R. D. Bach, M. W. Klein, R. A. Ryntz, and J. W. Holubka, *J. Org. Chem.*, **44**, 2569 (1979).
86. R. W. Murray, *Chem. Rev.*, **89**, 1187 (1989); W. Adam and L. P. Hadjiarapoglou, *Topics Current Chem.*, **164**, 45 (1993); W. Adam, A. K. Smerz, and C. G. Zhao, *J. Prakt. Chem., Chem. Zeit.*, **339**, 295 (1997).
87. R. W. Murray and R. Jeyaraman, *J. Org. Chem.*, **50**, 2847 (1985); W. Adam, J. Bialas, and L. Hadjiarapaglou, *Chem. Ber.*, **124**, 2377 (1991).

Higher concentrations of DMDO can be obtained by extraction of a 1:1 aqueous dilution of the distillate by CH_2Cl_2, $CHCl_3$, or CCl_4.[88] Another method involves in situ generation of DMDO under phase transfer conditions.[89]



The yields and rates of oxidation by DMDO under these in situ conditions depend on pH and other reaction parameters.[90]

Various computational models agree that the reaction occurs by a concerted mechanism.[91] Comparison between epoxidation by peroxy acids and dioxiranes suggests that they have similar transition structures.



Kinetics and isotope effects are consistent with this mechanism.[92] The reagent is electrophilic in character and reaction is facilitated by ERG substituents in the alkene. A B3LYP/6-31G* computation found the transition structures and E_a values shown in Figure 12.11.

Similarly to peroxycarboxylic acids, DMDO is subject to *cis or syn* stereoselectivity by hydroxy and other hydrogen-bonding functional groups.[93] However a study of several substituted cyclohexenes in $CH_3CN - H_2O$ suggested a dominance by steric effects. In particular, the hydroxy groups in cyclohex-2-enol and

88. M. Gilbert. M. Farrert, F. Sanchez-Baeza, and A. Messeguer, *Tetrahedron*, **53**, 8643 (1997).
89. S. E. Denmark, D. C. Forbes, D. S. Hays, J. S. DePue, and R. G. Wilde, *J. Org. Chem*., **60**, 1391 (1995).
90. M. Frohn, Z.-X. Wang, and Y. Shi, *J. Org. Chem*., **63**, 6425 (1998); A. O'Connell, T. Smyth, and B. K. Hodnett, *J. Chem. Technol. Biotech*., **72**, 60 (1998).
91. R. D. Bach, M. N. Glukhovtsev, C. Gonzalez, M. Marquez, C. M. Estevez, A. G. Baboul, and H. Schlegel, *J. Phys. Chem*., **101**, 6092 (1997); K. N. Houk, J. Liu, N. C. DeMello, and K. R. Condroski, *J. Am. Chem. Soc*., **119**, 10147 (1997); C. Jenson, J. Liu, K. N. Houk, and W. L. Jorgensen, *J. Am. Chem. Soc*., **119**, 12982 (1987); R. D. Bach, M. N. Glukhovtsev, and C. Canepa, *J. Am. Chem. Soc*., **120**, 775 (1998); M. Freccero, R. Gandolfi, M. Sarzi-Amade, and A. Rastelli, *Tetrahedron*, **54**, 6123 (1998); J. Liu, K. N. Houk, A. Dinoi, C. Fusco, and R. Curci, *J. Org. Chem*., **63**, 8565 (1998); R. D. Bach, O. Dmitrenko, W. Adam, and S. Schambony, *J. Am. Chem. Soc*., **125**, 924 (2003).
92. W. Adam, R. Paredes, A. K. Smerz, and L. A. Veloza, *Liebigs Ann. Chem*., 547 (1997); A. L. Baumstark, E. Michalenabaez, A. M. Navarro, and H. D. Banks, *Heterocycl. Commun*., **3**, 393 (1997); Y. Angelis, X. Zhang, and M. Orfanopoulos, *Tetrahedron Lett*., **37**, 5991 (1996).
93. R. W. Murray, M. Singh, B. L. Williams, and H. M. Moncrief, *J. Org. Chem*., **61**, 1830 (1996); G. Asensio, C. Boix-Bernardini, C. Andreu, M. E. Gonzalez-Nunez, R. Mello, J. O. Edwards, and G. B. Carpenter, *J. Org. Chem*., **64**, 4705 (1999).

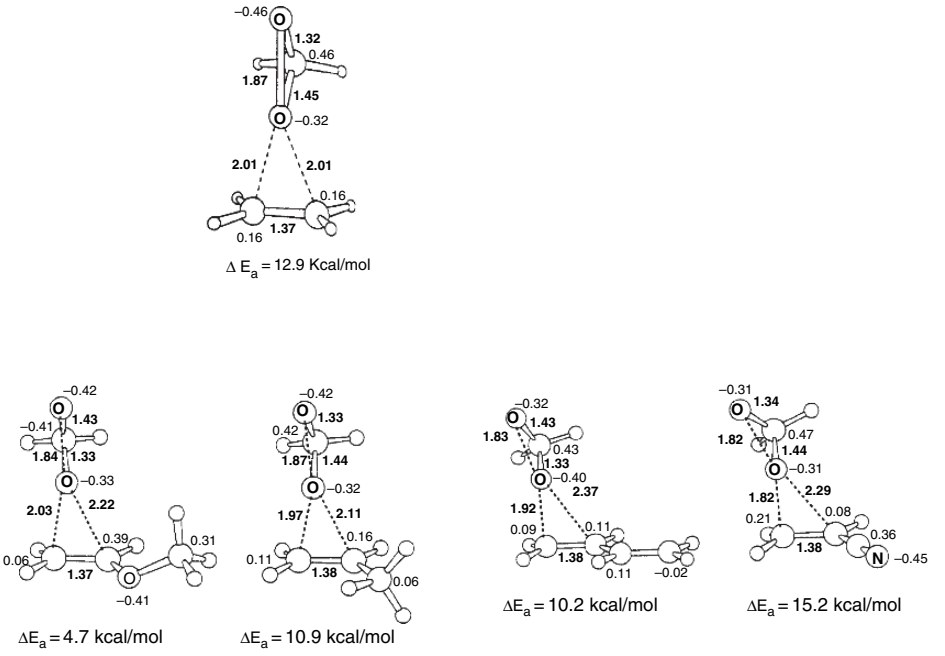
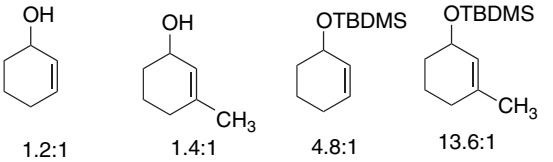
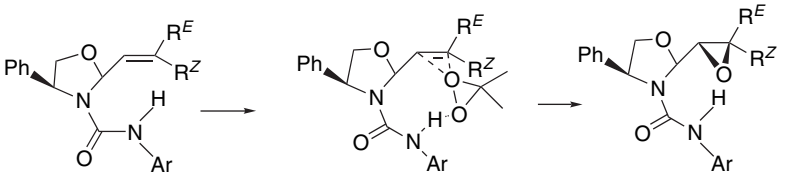


Fig. 12.11. Transition structures and E_a values for epoxidation of ethene and substituted derivatives by dimethyloxirane. Reproduced from *J. Am. Chem. Soc*., **119**, 10147 (1997), by permission of the American Chemical Society.

3-methylcyclohex-2-enol were not very strongly *syn* directing.[94] The hydroxylic solvent may minimize any directive effect by competing hydrogen bonding.[95]



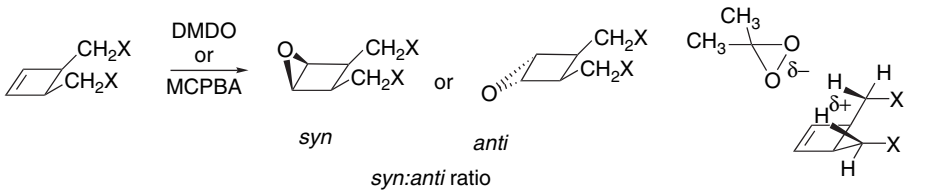
Directing effects have also been attributed to more remote substituents, as, e.g., a urea NH.



Ref. 96

94. D. Yang, G.-S. Jiao, Y.-C. Yip, and M.-K. Wong, *J. Org. Chem*., **64**, 1635 (1999).
95. W. Adam, R. Paredes, A. K. Smerz, and L. A. Veloza, *Eur. J. Org. Chem*., 349 (1998).
96. W. Adam, K. Peters, E.-M. Peters, and S. B. Schambony, *J. Am. Chem. Soc*., **123**, 7228 (2001).

Several disubstituted 3,4-dimethylcyclobutenes show *syn* selectivity. The mesylate groups were strongly *syn* directive, with the hydroxy, methoxy, and acetoxy groups being somewhat less so.[97] The same groups were even more strongly *syn* directing with MCPBA. The effects are attributed to an attractive electrostatic interaction of the relatively positive methylene hydrogens and the oxygens of the dioxirane and peroxy acid.



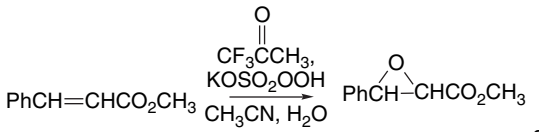
syn *anti*

syn:anti ratio

X	DMDO	MCPBA
OH	67:33	82:18
OCH_3	62:38	76:24
O_2CCH_3	68:32	69:31
OSO_2CH_3	79:21	87:13

For other substituents, both steric and dipolar factors seem to have an influence and several complex reactants have shown good stereoselectivity, although the precise origin of the stereoselectivity is not always evident.[98]

Other ketones besides acetone can be used for in situ generation of dioxiranes by reaction with peroxysulfate or another suitable peroxide. More electrophilic ketones give more reactive dioxiranes. 3-Methyl-3-trifluoromethyldioxirane is a more reactive analog of DMDO.[99] This reagent, which is generated in situ from 1,1,1-trifluoroacetone, can oxidize less reactive compounds such as methyl cinnamate.

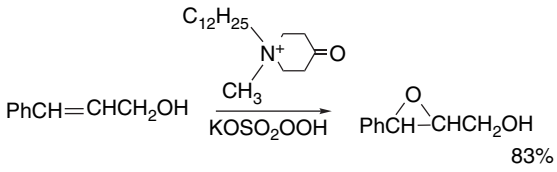


97% Ref. 100

Hexafluoroacetone and hydrogen peroxide in buffered aqueous solution can epoxidize alkenes and allylic alcohols.[101] *N*, *N*-Dialkylpiperidin-4-one salts are also good catalysts for epoxidation.[102] The polar effect of the quaternary nitrogen enhances the

97. M. Freccero, R. Gandolfi, and M. Sarzi-Amade, *Tetrahedron*, **55**, 11309 (1999).
98. R. C. Cambie, A. C. Grimsdale, P. S. Rutledge, M. F. Walker, and A. D. Woodgate, *Austr. J. Chem.*, **44**, 1553 (1991); P. Boricelli and P. Lupattelli, *J. Org. Chem.*, **59**, 4304 (1994); R. Curci, A. Detomaso, T. Prencipe, and G. B. Carpenter, *J. Am. Chem. Soc.*, **116**, 8112 (1994); T. C. Henninger, M. Sabat, and R. J. Sundberg, *Tetrahedron*, **52**, 14403 (1996).
99. R. Mello, M. Fiorentino, O. Sciacevolli, and R. Curci, *J. Org. Chem.*, **53**, 3890 (1988).
100. D. Yang, M.-K. Wong, and Y.-C. Yie, *J. Org. Chem.*, **60**, 3887 (1995).
101. R. P. Heggs and B. Ganem, *J. Am. Chem. Soc.*, **101**, 2484 (1979); A. J. Biloski, R. P. Hegge, and B. Ganem, *Synthesis*, 810 (1980); W. Adam, H.-G. Degen, and C. R. Saha-Moller, *J. Org. Chem.*, **64**, 1274 (1999).
102. S. E. Denmark, D. C. Forbes, D. S. Hays, J. S. DePue, and R. G. Wilde, *J. Org. Chem.*, **60**, 1391 (1995).

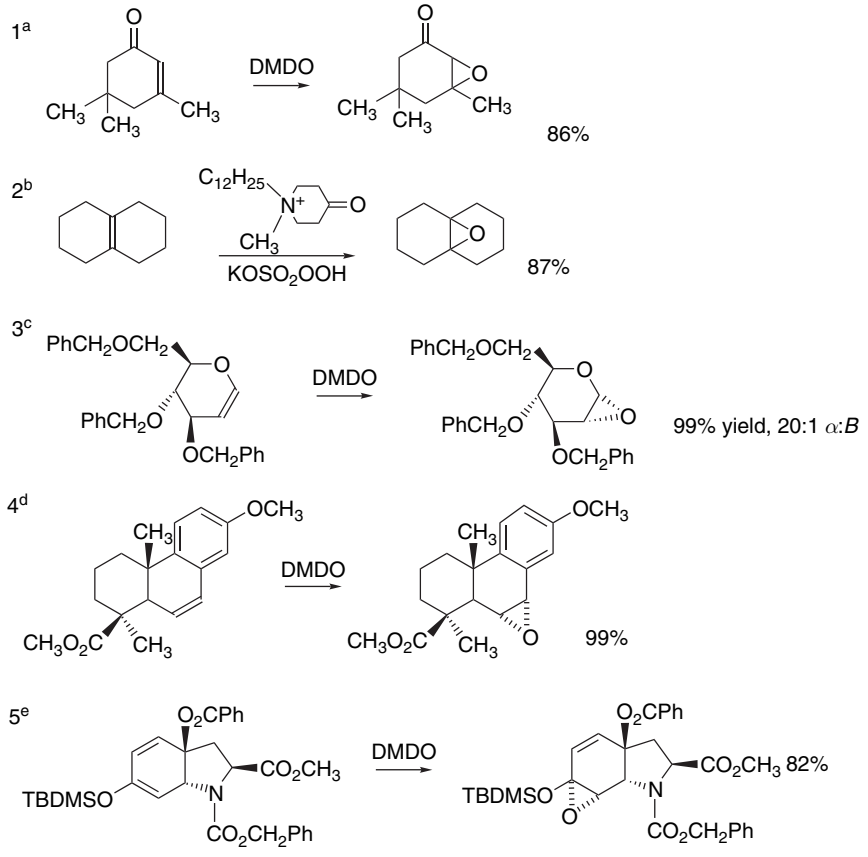
reactivity of the ketone toward nucleophilic addition and also makes the dioxirane intermediate more reactive.



The cyclic sulfone 4-thiopyrone-*S*, *S*-dioxide also exhibits enhanced reactivity as a result of the effect of the sulfone dipole.[103]

Scheme 12.12 gives some examples of epoxidations involving dioxiranes. Entry 1 indicates the ability of the reagent to expoxidize deactivated double bonds. Entry 2

Scheme 12.12. Epoxidation by Dioxiranes



a. W. Adam, L. Hadjarapaglou, and B. Nestler, *Tetrahedron Lett*., **31**, 331 (1990).
b. S. E. Denmark, D. C. Forbes, D. S. Hays, J. S. DePue, and R. G. Wilde, *J. Org. Chem*., **60**, 1391 (1995).
c. R. L. Halcomb and S. J. Danishefsky, *J. Am. Chem. Soc*., **111**, 6661 (1989).
d. R. C. Cambie, A. C. Grimsdale, P. S. Rutledge, M. F. Walker, and P. D. Woodgate, *Aust. J. Chem*., **44**, 1553 (1991).
e. T. C. Henninger, M. Sabat, and R. J. Sundberg, *Tetrahedron*, **52**, 14403 (1996).

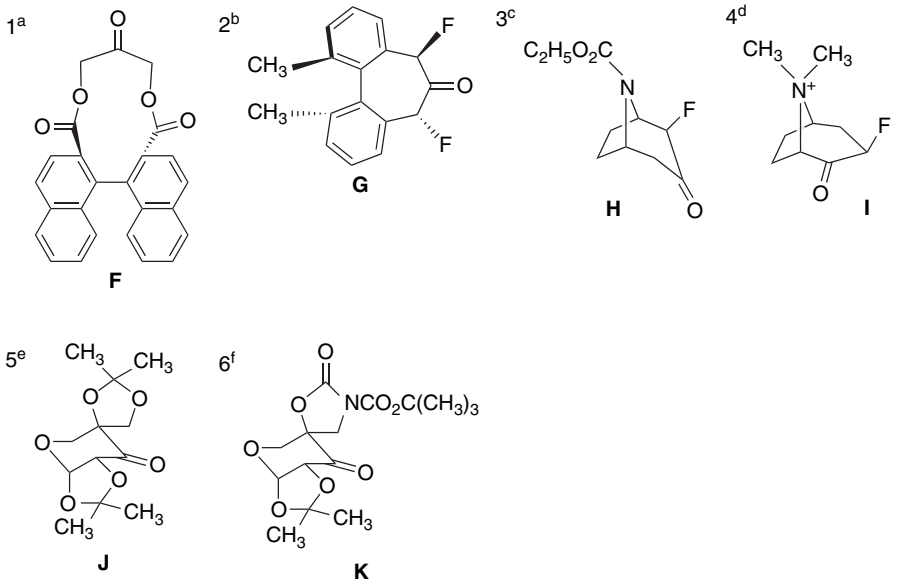
103. D. Yang, Y.-C. Yip, G.-S. Jiao, and M.-K. Wong, *J. Org. Chem*., **63**, 8952 (1998).

illustrates the use of a piperidone salt for in situ generation of a dioxirane. The long alkyl chain imparts phase transfer capability to the ketone. The dioxirane is generated in the aqueous phase but can carry out the epoxidation in the organic phase. Entries 3 to 5 are examples of stereoselective epoxidations. In each case, high stereoselectivity is observed in the presence of nearby functional groups. The exact origins of the stereoselectivity are not clear.

A number of chiral ketones have been developed that are capable of enantioselective epoxidation via dioxirane intermediates.[104] Scheme 12.13 shows the structures of some chiral ketones that have been used as catalysts for enantioselective epoxidation. The BINAP-derived ketone shown in Entry 1, as well as its halogenated derivatives, have shown good enantioselectivity toward di- and trisubstituted alkenes.

Ref. 105

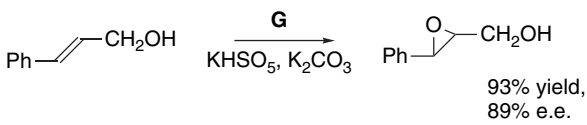
Scheme 12.13. Chiral Ketones Used for Enantioselective Epoxidation



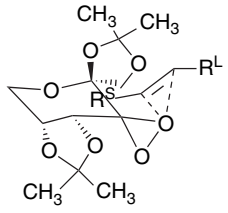
a. D. Yang, M.-K. Wong, Y.-C. Yip, X.-C. Wang, M.-W. Tang, J.-H. Zheng, and K. K. Cheung, *J. Am. Chem. Soc*., **120**, 5943 (1998).
b. S. E. Denmark and Z. C. Wu, *Synlett*, 847 (1999); M. Frohn and Y. Shi, *Synthesis*, 1979 (2000).
c. A. Armstrong, G. Ahmed, B. Dominguez-Fernandez, B. R. Hayter, and J. S. Wailes, *J. Org. Chem*., **67**, 8610 (2002).
d. S. E. Denmark and H. Matsuhashi, *J. Org. Chem*., **67**, 3479 (2002).
e. Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, and Y. Shi, *J. Am. Chem. Soc*., **119**, 11224 (1997).
f. H. Tian, X. She, H. Yu, L. Shu, and Y. Shi, *J. Org. Chem*., **67**, 2435 (2002).

104. D. Yang, *Acc. Chem. Res*., **37**, 497 (2004); Y. Shi, *Acc. Chem. Res*., **37**, 488 (2004).
105. T. Furutani, R. Imashiro, M. Hatsuda, and M. Seki, *J. Org. Chem*., **67**, 4599 (2002).

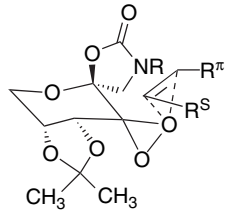
The use of chiral α-fluoro ketone **G** can lead to enantioselective epoxidation.[106]



The fluorinated tropones **H** and **I** also show good reactivity and are enantioselective in favorable cases, but show considerable dependence on reactant structure. The carbohydrate structures **J** and **K** also benefit from a polar effect of the adjacent oxygens and give good enantioselectivity with a variety of *trans* di- and trisubstituted alkenes. The oxazolidinone derivative **K** also shows good enantioselectivity toward *cis*-substituted and terminal alkenes. Transition structures **TS J** and **TS K** have been suggested for epoxidation by these ketones. It has been noted that alkenes with conjugated π systems have a preferred orientation toward the oxazolidinone ring.

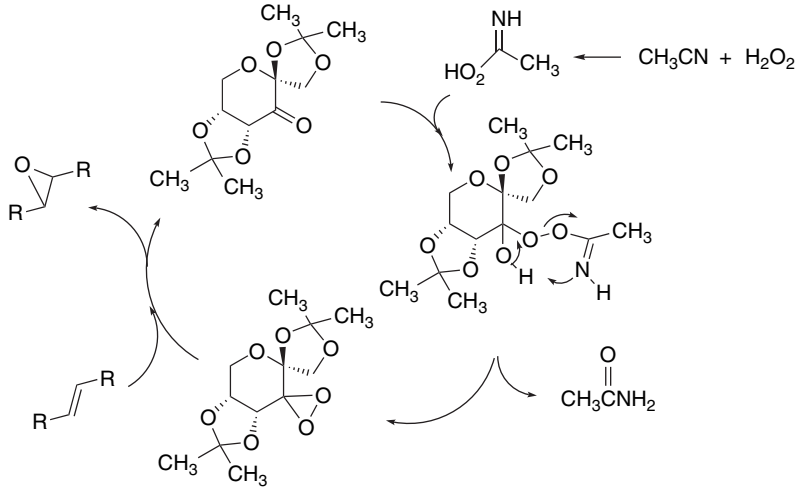


TS – J



TS – K

These ketones can also be used in kinetic resolutions.[107] The carbohydrate-derived ketones have been used in conjunction with acetonitrile and H_2O_2. The reactions are believed to proceed through dioxiranes generated by a catalytic cycle involving a peroxyimidic acid.[108]



106. S. E. Denmark and Z. C. Wu, *Synlett*, 847 (1999); M. Frohn and Y. Shi, *Synthesis*, 1979 (2000).
107. D. Yang, G.-S. Jiao, Y.-C. Yip, T.-H. Lai, and M.-K. Wong, *J. Org. Chem.*, **66**, 4619 (2001); M. Frohn, X. Zhou, J.-R. Zhang, Y. Tang, and Y. Shi, *J. Am. Chem. Soc.*, **121**, 7718 (1999).
108. L. Shu and Y. Shi, *Tetrahedron*, **57**, 5213 (2001).

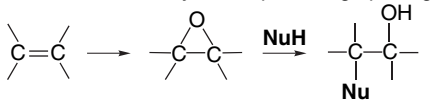
12.2.3. Subsequent Transformations of Epoxides

Epoxides are useful synthetic intermediates and the conversion of an alkene to an epoxide is often part of a more extensive molecular transformation.[109] In many instances advantage is taken of the reactivity of the epoxide ring toward nucleophiles to introduce additional functionality. Since epoxide ring opening is usually stereospecific, such reactions can be used to establish stereochemical relationships between adjacent substituents. Such two- or three-step operations can accomplish specific oxidative transformations of an alkene that may not be easily accomplished in a single step. Scheme 12.14 provides a preview of the type of reactivity to be discussed.

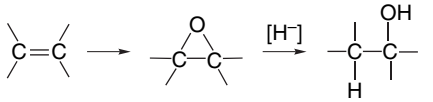
12.2.3.1. Nucleophilic and Solvolytic Ring Opening. Epoxidation may be preliminary to solvolytic or nucleophilic ring opening in synthetic sequences. Epoxides can undergo ring opening under either basic or acidic conditions. Base-catalyzed reactions, in which the nucleophile provides the driving force for ring opening, usually involve breaking the epoxide bond at the less-substituted carbon, since this is the position most accessible to nucleophilic attack.[110] These reactions result in an *anti* relationship between the epoxide oxygen and the nucleophile. The situation in acid-catalyzed reactions is more complex. The bonding of a proton to the oxygen weakens the C−O bonds and facilitates rupture by weak nucleophiles. If the C−O bond is largely intact at the TS, the nucleophile becomes attached to the less-substituted position for the same steric reasons that were cited for nucleophilic ring opening. If, on the other hand, C−O rupture is more complete at the TS, the opposite orientation is observed. This change in regiochemistry results from the ability of the more-substituted carbon to better stabilize the developing positive charge.

Scheme 12.14. Synthetic Transformations of Epoxides

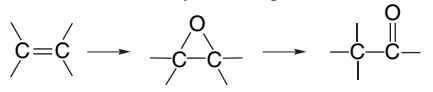
A. Epoxidation followed by nucleophilic ring opening



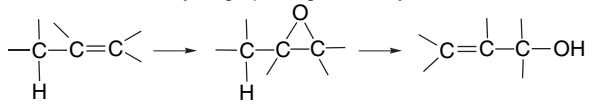
B. Epoxidation followed by reductive ring opening



C. Epoxidation followed by rearrangement to a carbonyl compound

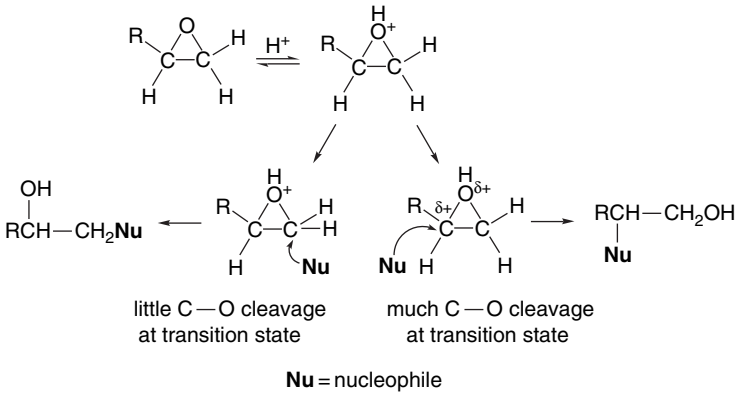


D. Epoxidation followed by ring opening to an allyl alcohol

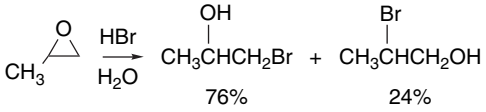


109. J. G. Smith, *Synthesis*, 629 (1984).

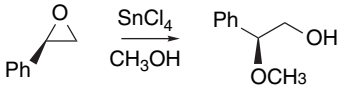
110. R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).



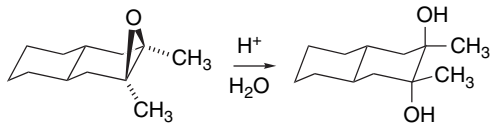
When simple aliphatic epoxides such as propylene oxide react with hydrogen halides, the dominant product has the halide at the less-substituted primary carbon.[111]



Substituents that further stabilize a carbocation intermediate lead to reversal of the mode of addition.[112] The case of styrene oxide hydrolysis has been carefully examined. Under acidic conditions, the bond breaking is exclusively at the benzylic position. Under basic conditions, ring opening occurs at both epoxide carbons.[113] Styrene also undergoes highly regioselective ring opening in the presence of Lewis acids. For example, methanolysis is catalyzed by $SnCl_4$ and occurs with greater than 95% attack at the benzyl carbon and with high inversion.[114] The stereospecificity indicates a concerted nucleophilic opening of the complexed epoxide.



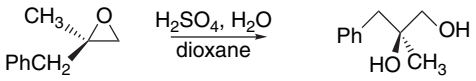
In cyclic systems, ring opening gives the diaxial diol.



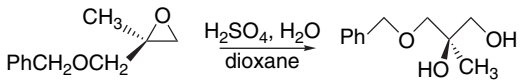
Ref. 115

Under some circumstances, acid-catalyzed ring opening of 2,2-disubstituted epoxides by sulfuric acid in dioxane goes with high *inversion* at the tertiary center.[116]

111. C. A. Stewart and C. A. VanderWerf, *J. Am. Chem. Soc*., **76**, 1259 (1954).
112. S. Winstein and L. L. Ingraham, *J. Am. Chem. Soc*., **74**, 1160 (1952).
113. R. Lin and D. L. Whalen, *J. Org. Chem*., **59**, 1638 (1994); J. J. Blumenstein, V. C. Ukachukwa, R. S. Mohan, and D. Whalen, *J. Org. Chem*., **59**, 1638 (1994).
114. C. Moberg, L. Rakos, and L. Tottie, *Tetrahedron Lett*., **33**, 2191 (1992).
115. B. Rickborn and D. K. Murphy, *J. Org. Chem*., **34**, 3209 (1969).
116. R. V. A. Orru, S. F. Mayer, W. Kroutil, and K. Faber, *Tetrahedron*, **54**, 859 (1998).



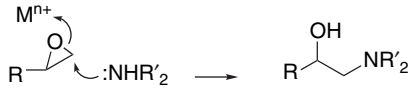
Ref. 117



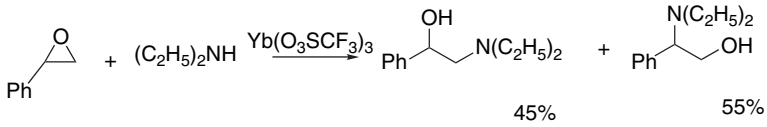
Ref. 118

Under somewhat modified conditions (H_2SO_4 on silica), this reaction has been successfully applied to a complex alkaloid structure.[119]

Recently a number of procedures for epoxide ring opening that feature the oxyphilic Lewis acids, including lanthanides, have been developed. $LiClO_4$, LiO_3SCF_3, $Mg(ClO_4)_2$, $Zn(O_3SCF_3)_2$, and $Yb(O_3SCF_3)_3$ have been shown to catalyze epoxide ring opening.[120] The cations catalyze *anti* addition of amines at the less-substituted carbon, which is consistent with a Lewis acid–assisted nucleophilic ring opening.

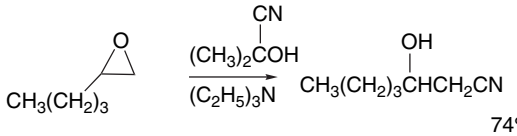


Styrene oxide gives mixtures of C-α and C-β attack, as a result of competition between the activated benzylic site and the primary site.



The same salts can be used to catalyze ring opening by other nucleophiles such as azide ion[121] and cyanide ion.[122]

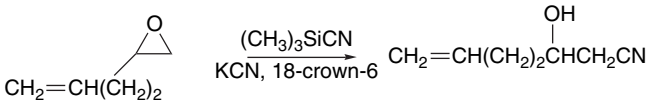
A variety of reaction conditions have been developed for nucleophilic ring opening by cyanide.[123] Heating an epoxide with acetone cyanohydrin (which serves as the cyanide source) and triethylamine leads to ring opening at the less-substituted position.



Ref. 124

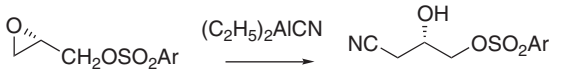
117. R. V. A. Orru, I. Osprian, W. Kroutil, and K. Faber, *Synthesis*, 1259 (1998).
118. A. Steinreiber, H. Hellstrom, S. F. Mayer, R. V. A. Orru, and K. Faber, *Synlett*, 111 (2001).
119. M. E. Kuehne, Y. Qin, A. E. Huot, and S. L. Bane, *J. Org. Chem*., **66**, 5317 (2001).
120. M. Chini, P. Crotti, and F. Macchia, *Tetrahedron Lett*., **31**, 4661 (1990); M. Chini, P. Crotti, L. Favero, F. Macchia, and M. Pineschi, *Tetrahedron Lett*., **35**, 433 (1994); J. Auge and F. Leroy, *Tetrahedron Lett*., **37**, 7715 (1996).
121. M. Chini, P. Crotti, and F. Macchia, *Tetrahedron Lett*., **31**, 5641 (1990); P. Van de Weghe and J. Collin, *Tetrahedron Lett*., **36**, 1649 (1995).
122. M. Chini, P. Crotti, L. Favera, and F. Macchia, *Tetrahedron Lett*., **32**, 4775 (1991).
123. R. A. Smiley and C. J. Arnold, *J. Org. Chem*., **25**, 257 (1960); J. A. Ciaccio, C. Stanescu, and J. Bontemps, *Tetrahedron Lett*., **33**, 1431 (1992).
124. D. Mitchell and T. M. Koenig, *Tetrahedron Lett*., **33**, 3281 (1992).

Trimethylsilyl cyanide in conjunction with KCN and a crown ether also results in nucleophilic ring opening.



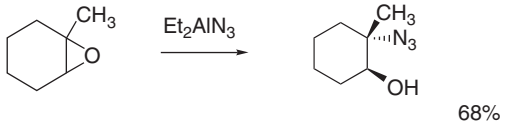
Ref. 125

Diethylaluminum cyanide can also be used for preparation of β-hydroxynitriles.



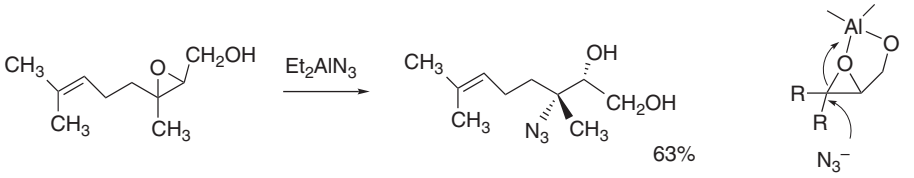
Ref. 126

Similarly, diethylaluminum azide gives β-azido alcohols. The epoxide of 1-methylcyclohexene gives the tertiary azide, indicating that the regiochemistry is controlled by bond cleavage, but with diaxial stereoselectivity.



Ref. 127

Epoxides of allylic alcohols exhibit chelation-controlled regioselectivity.[128]



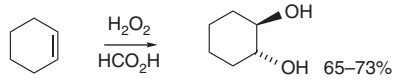
Scheme 12.15 gives some examples of both acid-catalyzed and nucleophilic ring openings of epoxides. Entries 1 and 2 are cases in which epoxidation and solvolysis are carried out without isolation of the epoxide. Both cases also illustrate the preference for *anti* stereochemistry. The regioselectivity in Entry 3 is indicative of dominant bond cleavage in the TS. The reaction in Entry 4 was studied in a number of solvents. The product results from net *syn* addition as a result of phenonium ion participation. The *cis*-epoxide also gives mainly the *syn* product, presumably via isomerization to the

125. M. B. Sassaman, G. K. Surya Prakash, and G. A. Olah, *J. Org. Chem.*, **55**, 2016 (1990).
126. J. M. Klunder, T. Onami, and K. B. Sharpless, *J. Org. Chem.*, **54**, 1295 (1989).
127. H. B. Mereyala and B. Frei, *Helv. Chim. Acta*, **69**, 415 (1986).
128. F. Benedetti, F. Berti, and S. Norbedo, *Tetrahedron Lett.*, **39**, 7971 (1998); C. E. Davis, J. L. Bailey, J. W. Lockner, and R. M. Coates, *J. Org. Chem.*, **68**, 75 (2003).

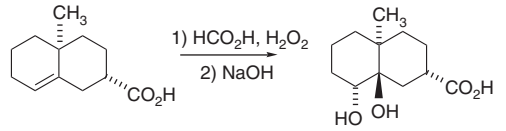
Scheme 12.15. Nucleophilic and Solvolytic Ring Opening of Epoxides

A. Epoxidation with solvolysis of the intermediate epoxide

1[a]

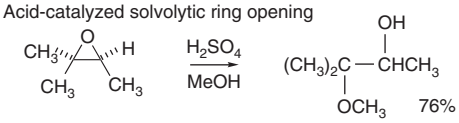


2[b]

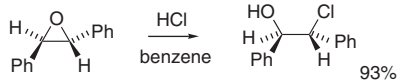


B. Acid-catalyzed solvolytic ring opening

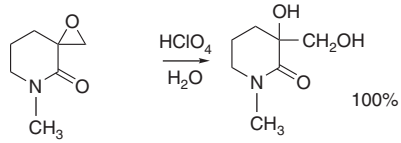
3[c]



4[d]

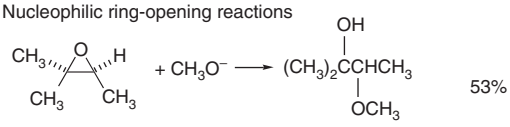


5[e]

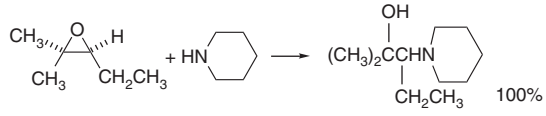


C. Nucleophilic ring-opening reactions

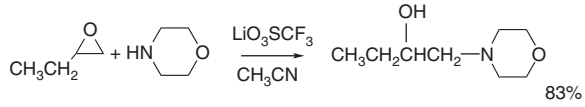
6[c]



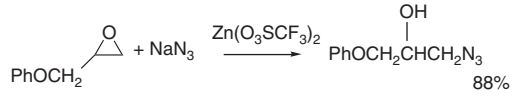
7[f]



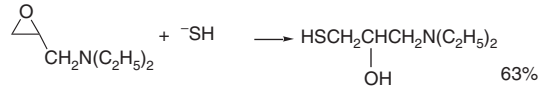
8[g]



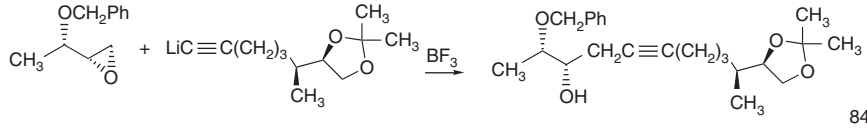
9[h]



10[i]



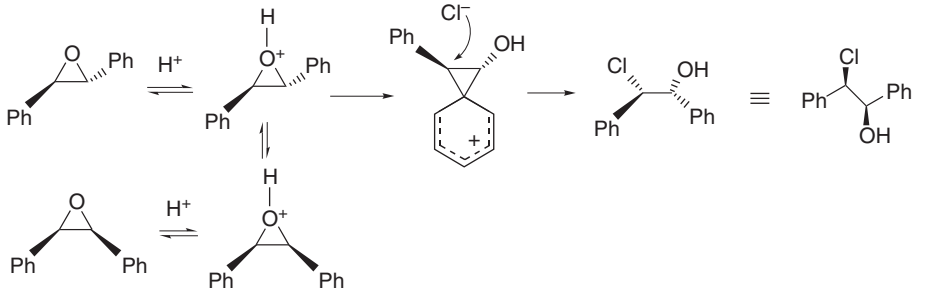
11[j]



(*Continued*)

a. A. Roebuck and H. Adkins, *Org. Synth*., **III**, 217 (1955).
b. T. R. Kelly, *J. Org. Chem*., **37**, 3393 (1972).
c. S. Winstein and L. L. Ingraham, *J. Am. Chem. Soc*., **74**, 1160 (1952).
d. G. Berti, F. Bottari, P. L. Ferrarini, and B. Macchia, *J. Org. Chem*., **30**, 4091 (1965).
e. M. L. Rueppel and H. Rapoport, *J. Am. Chem. Soc*., **94**, 3877 (1972).
f. T. Colclough, J. I. Cunneen, and C. G. Moore, *Tetrahedron*, **15**, 187 (1961).
g. J. Auge and F. Leroy, *Tetrahedron Lett*., **37**, 7715 (1996).
h. M. Chini, P. Crotti, and F. Macchia, *Tetrahedron Lett*., **31**, 5641 (1990).
i. D. M. Burness and H. O. Bayer, *J. Org. Chem*., **28**, 2283 (1963).
j. Z. Liu, C. Yu, R.-F.Wang, and G. Li, *Tetrahedron Lett*., **39**, 5261 (1998).

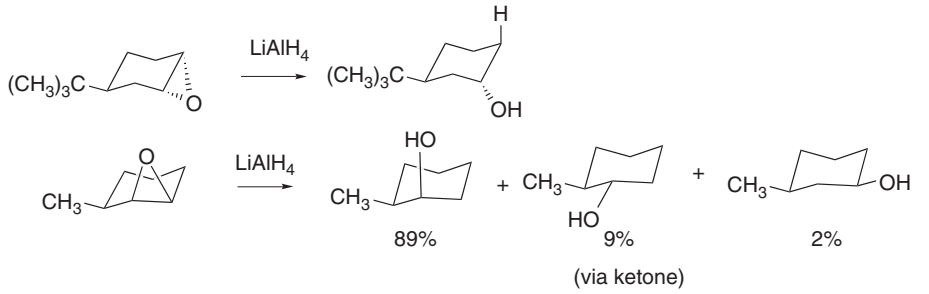
more stable *trans* isomer by reversible ring opening and formation of the more stable *trans*-phenonium ion.



Entry 5 is an example of synthetic application of acid-catalyzed ring opening.

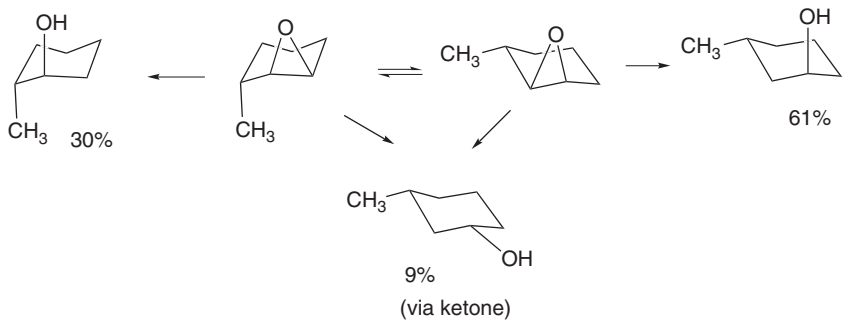
Entries 6 to 11 are examples of nucleophilic ring opening. Each of these entries displays the expected preference for reaction at the less hindered carbon. Entries 8 and 9 involve metal ion catalysis. Entry 11, which involves carbon-carbon bond formation, was part of a synthesis of epothilone A.

12.2.3.2. Reductive Ring Opening. Epoxides can be reduced to saturated alcohols. Lithium aluminum hydride acts as a nucleophilic reducing agent and the hydride is added at the less-substituted carbon atom of the epoxide ring. Substituted cyclohexene oxides prefer diaxial ring opening. A competing process, which accounts for about 10% of the product in the examples shown, involves rearrangement to the cyclohexanone (see below) by hydride shift, followed by reduction.[129]

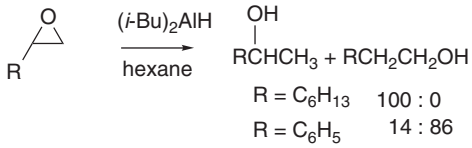


129. B. Rickborn and J. Quartucci, *J. Org. Chem*., **29**, 3185 (1964); B. Rickborn and W. Z. Lamke, II, *J. Org. Chem*., **32**, 537 (1967).

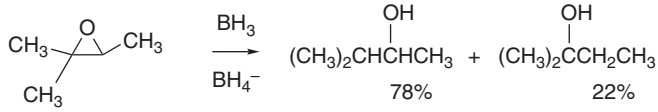
The *trans*-3-methyl isomer appears to react through two conformers, with the axial methyl conformer giving *trans*-2-methylcyclohexanol.



Lithium triethylborohydride is more reactive than $LiAlH_4$ and is superior for epoxides that are resistant to reduction.[130] Reduction by dissolving metals, such as lithium in ethylenediamine,[131] also gives good yields. Di-*i*-butylaluminum hydride also reduces epoxides. 1,2-Epoxyoctane gives 2-octanol in excellent yield, and styrene oxide gives a 1:6 mixture of the secondary and primary alcohols.[132] This relationship indicates that nucleophilic ring opening controls the regiochemistry for 1,2-epoxyoctane but that ring cleavage at the benzylic position is the major factor for styrene oxide.



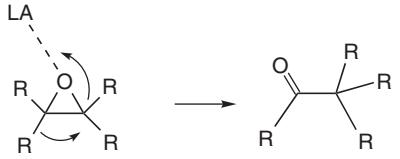
Diborane in THF reduces epoxides, but the yields are low, and other products are formed by pathways that result from the electrophilic nature of diborane.[133] Better yields are obtained when BH_4^- is included in the reaction system, but the electrophilic nature of diborane is still evident because the dominant product results from addition of the hydride at the more-substituted carbon.[134]



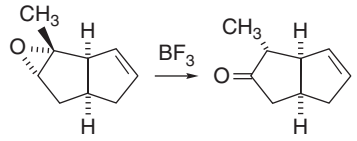
The overall transformation of alkenes to alcohols that is accomplished by epoxidation and reduction corresponds to alkene hydration. Assuming a nucleophilic ring opening by hydride addition at the less-substituted carbon, the reaction corresponds to the Markovnikov orientation. This reaction sequence is therefore an alternative to the hydration methods discussed in Chapter 4 for converting alkenes to alcohols.

130. S. Krishnamurthy, R. M. Schubert, and H. C. Brown, *J. Am. Chem. Soc*., **95**, 8486 (1973).
131. H. C. Brown, S. Ikegami, and J. H. Kawakami, *J. Org. Chem*., **35**, 3243 (1970).
132. J. J. Eisch, Z.-R. Liu, and M. Singh, *J. Org. Chem*., **57**, 1618 (1992).
133. D. J. Pasto, C. C. Cumbo, and J. Hickman, *J. Am. Chem. Soc*., **88**, 2201 (1966).
134. H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc*., **90**, 2686 (1968).

12.2.3.3. Rearrangement of Epoxides to Carbonyl Compounds. Epoxides can be isomerized to carbonyl compounds by Lewis acids.[135] This reaction is closely related to the pinacol rearrangement (see p. 883). The epoxide oxygen functions as the leaving group and becomes the oxygen in the new carbonyl group.

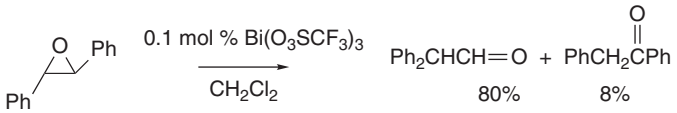


Carbocation intermediates are involved and the structure and stereochemistry of the product are determined by the factors that govern substituent migration in the carbocation. Clean, high-yield reactions can be expected only where structural or conformational factors promote a selective rearrangement. Boron trifluoride is frequently used as the reagent.

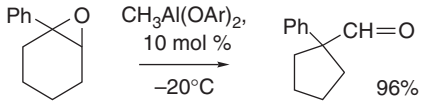


Ref. 136

Catalytic amounts of $Bi(O_3SCF_3)_3$ also promote this rearrangement.[137]



Bulky diaryloxymethylaluminum reagents are also effective for this transformation.

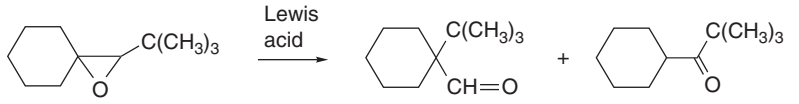


Ar = 2,6-di-*t*-butyl-4-bromophenyl

Ref. 138

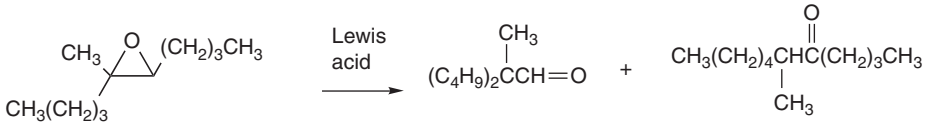
This reagent is selective for rearrangement to aldehydes in cases where BF_3, $SnCl_4$, and SbF_5 give mixtures.[139]

135. J. N. Coxon, M. P. Hartshorn, and W. J. Rae, *Tetrahedron*, **26**, 1091 (1970).
136. J. K. Whitesell, R. S. Matthews, M. A. Minton, and A. M. Helbling, *J. Am. Chem. Soc*., **103**, 3468 (1981).
137. K. A. Bhatia, K. J. Eash, N. M. Leonard, M. C. Oswald, and R. S. Mohan, *Tetrahedron Lett*., **42**, 8129 (2001).
138. K. Maruoka, S. Nagahara, T. Ooi, and H. Yamamoto, *Tetrahedron Lett*., **30**, 5607 (1989).
139. K. Maruoka, T. Ooi, and H. Yamamoto, *Tetrahedron*, **48**, 3303 (1992); K. Maruoka, N. Murase, R. Bureau, T. Ooi, and H. Yamamoto, *Tetrahedron*, **50**, 3663 (1994).



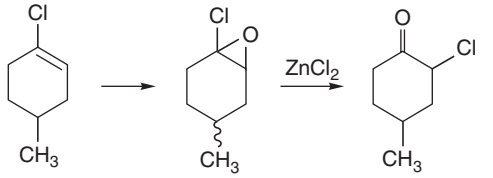
	yield	product ratio
$CH_3Al(OAr)_2$	72%	100:0
BF_3	55%	33:67
$SnCl_4$	72%	50:50
SbF_5	79%	15:85

This selectivity is attributed to the steric bulk of the aluminum reagent favoring the migration of the larger alkyl group. The same selectivity pattern is observed with unbranched substituents.



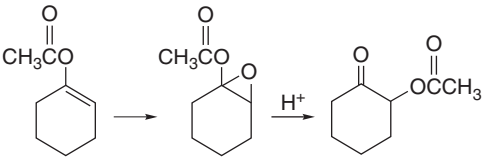
	yield	product ratio
$CH_3Al(OAr)_2$	73%	100:0
BF_3	77%	30:70
SbF_5	86%	82:18

Double bonds having oxygen and halogen substituents are susceptible to epoxidation, and the reactive epoxides that are generated serve as intermediates in some useful synthetic transformations in which the substituent migrates to the other carbon of the original double bond. Vinyl chlorides furnish haloepoxides that can rearrange to α-haloketones.



Ref. 140

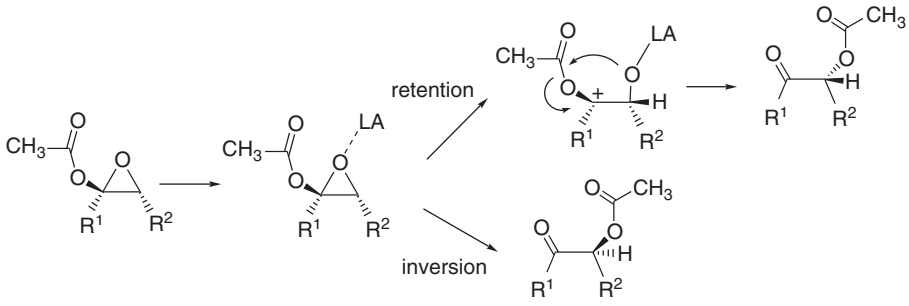
When this reaction sequence is applied to enol esters or enol ethers, the result is α-oxygenation of the starting carbonyl compound. Enol acetates form epoxides that rearrange to α-acetoxyketones.



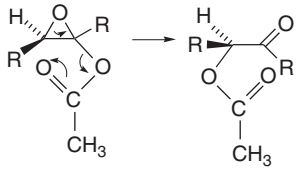
Ref. 141

140. R. N. McDonald and T. E. Tabor, *J. Am. Chem. Soc.*, **89**, 6573 (1967).
141. K. L. Williamson, J. I. Coburn, and M. F. Herr, *J. Org. Chem.*, **32**, 3934 (1967).

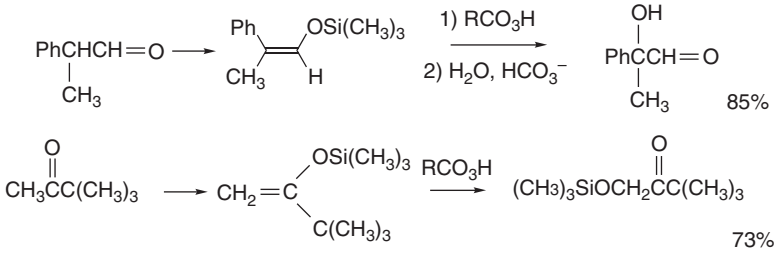
The stereochemistry of the reaction depends on the Lewis acid. Protic acids favor retention of configuration, as does TMSOTf. Most metal halides give mixtures of inversion and retention, but $Al(CH_3)_3$ gives dominant inversion.[142] Inversion is suggestive of direct carbonyl group participation.



The reaction can also be done thermally. The stereochemistry of the thermal rearrangement of the acetoxy epoxides involves inversion at the carbon to which the acetoxy group migrates,[143] and reaction probably proceeds through a cyclic TS.

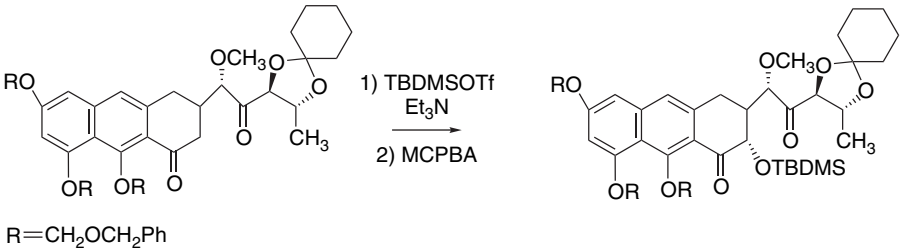


A more synthetically reliable version of this reaction involves epoxidation of silyl enol ethers. Epoxidation of the silyl enol ethers followed by aqueous workup gives α-hydroxyketones and α-hydroxyaldehydes.[144]

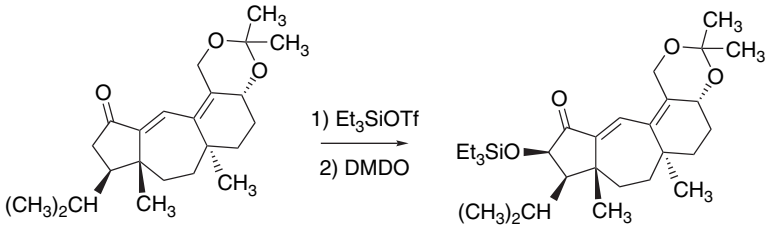


The epoxidation can be done either with peroxy acids or DMDO. In the former case, the rearrangement is catalyzed by the carboxylic acid that is formed, whereas with DMDO, the intermediate epoxides can sometimes be isolated.

142. Y. Zhu, L. Shu., Y. Tu, and Y. Shi, *J. Org. Chem.*, **66**, 1818 (2001).
143. K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).
144. A. Hassner, R. H. Reuss, and H. W. Pinnick, *J. Org. Chem.*, **40**, 3427 (1975).



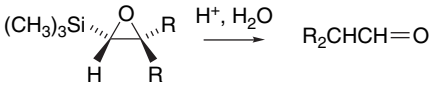
Ref. 145



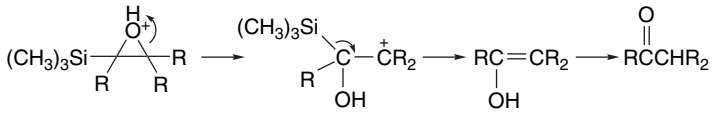
Ref. 146

The oxidation of silyl enol ethers with the osmium tetroxide–amine oxide combination also leads to α-hydroxyketones in generally good yields.[147]

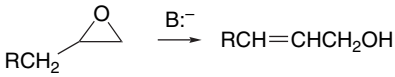
Epoxides derived from vinylsilanes are converted by mildly acidic conditions into ketones or aldehydes.[148]



The regioselective ring opening of the silyl epoxides is facilitated by the stabilizing effect that silicon has on a positive charge in the β-position. This facile transformation permits vinylsilanes to serve as the equivalent of carbonyl groups in multistep synthesis.[149]

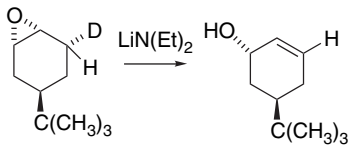


12.2.3.4. Base-Catalyzed Ring Opening of Epoxides. Base-catalyzed ring opening of epoxides provides a route to allylic alcohols.[150]

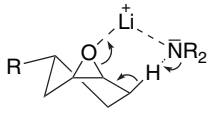


145. W. R. Roush, M. R. Michaelides, D. F. Tai, and W. K. M. Chong, *J. Am. Chem. Soc*., **109**, 7575 (1987).
146. M. Mandal and S. J. Danishefsky, *Tetrahedron Lett*., **45**, 3831 (2004).
147. J. P. McCormick, W. Tomasik, and M. W. Johnson, *Tetrahedron Lett*., 607 (1981).
148. G. Stork and E. Colvin, *J. Am. Chem. Soc*., **93**, 2080 (1971).
149. G. Stork and M. E. Jung, *J. Am. Chem. Soc*., **96**, 3682 (1974).
150. J. K. Crandall and M. Apparu, *Org. React*., **29**, 345 (1983).

Strongly basic reagents, such as the lithium salt of dialkylamines, are required to promote the reaction. The stereochemistry of the ring opening has been investigated by deuterium labeling. A proton *cis* to the epoxide ring is selectively removed.[151]

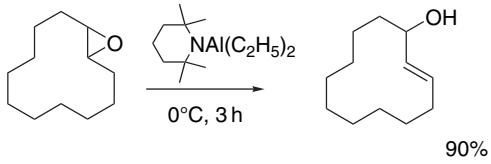


A TS represented by structure **L** accounts for this stereochemistry. Such an arrangement is favored by ion pairing that would bring the amide anion and lithium cation into close proximity. Simultaneous coordination of the lithium ion at the epoxide results in a *syn* elimination.

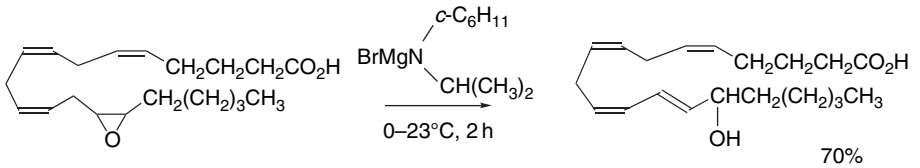


L

Among other reagents that effect epoxide ring opening are diethylaluminum 2,2,6,6-tetramethylpiperidide and magnesium *N*-cyclohexyl-*N*-(*i*-propyl)amide.



Ref. 152

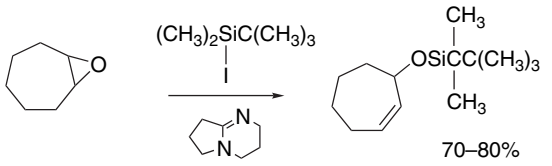


Ref. 153

These reagents are appropriate even for very sensitive molecules. Their efficacy is presumably due to the Lewis acid effect of the aluminum and magnesium ions. The hindered nature of the amide bases also minimizes competition from nucleophilic ring opening.

151. R. P. Thummel and B. Rickborn, *J. Am. Chem. Soc.*, **92**, 2064 (1970).
152. A. Yasuda, S. Tanaka, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **96**, 6513 (1974).
153. E. J. Corey, A. Marfat, J. R. Falck, and J. O. Albright, *J. Am. Chem. Soc.*, **102**, 1433 (1980).

Epoxides can also be converted to allylic alcohols using electrophilic reagents. The treatment of epoxides with trialkyl silyl iodides and an organic base gives the silyl ether of the corresponding allylic alcohols.[154]



Similar ring openings have been achieved using trimethylsilyl triflate and 2,6-di-*t*-butylpyridine.[155]

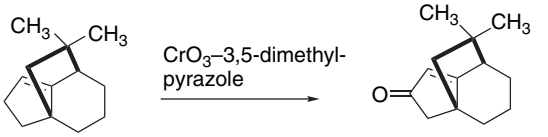
Each of these procedures for epoxidation and ring opening is the equivalent of an allylic oxidation of a double bond with migration of the double bond.

In Section 12.3, other means of effecting this transformation are described.

12.3. Allylic Oxidation

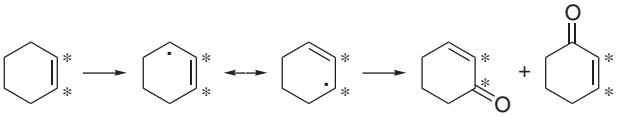
12.3.1. Transition Metal Oxidants

Carbon-carbon double bonds, apart from being susceptible to addition of oxygen or cleavage, can also react at allylic positions. Synthetic utility requires that there be good selectivity between the possible reactions. Among the transition metal oxidants, the CrO_3-pyridine reagent in methylene chloride[156] and a related complex in which 3,5-dimethylpyrazole replaces pyridine[157] are the most satisfactory for allylic oxidation.



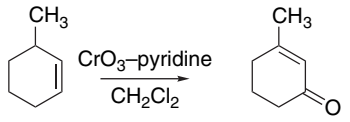
Ref. 158

Several pieces of mechanistic evidence implicate allylic radicals or cations as intermediates in these oxidations. Thus ^{14}C in cyclohexene is distributed in the product cyclohexenone indicating that a symmetrical allylic intermediate is involved at some stage.[159]



154. M. R. Detty, *J. Org. Chem.*, **45**, 924 (1980); M. R. Detty and M. D. Seiler, *J. Org. Chem.*, **46**, 1283 (1981).
155. S. F. Martin and W. Li, *J. Org. Chem.*, **56**, 642 (1991).
156. W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969).
157. W. G. Salmond, M. A. Barta, and J. L. Havens, *J. Org. Chem.*, **43**, 2057 (1978); R. H. Schlessinger, J. L. Wood, A. J. Poos, R. A. Nugent, and W. H. Parson, *J. Org. Chem.*, **48**, 1146 (1983).
158. A. B. Smith, III, and J. P. Konopelski, *J. Org. Chem.*, **49**, 4094 (1984).
159. K. B. Wiberg and S. D. Nielsen, *J. Org. Chem.*, **29**, 3353 (1964).

In many allylic oxidations, the double bond is found in a position indicating that an allylic transposition occurs during the oxidation.



Ref. 156

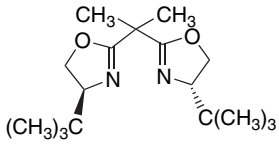
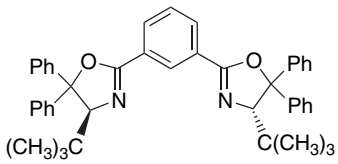
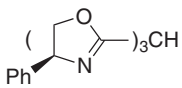
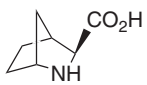
Detailed mechanistic understanding of the allylic oxidation has not been developed. One possibility is that an intermediate oxidation state of Cr, specifically Cr(IV), acts as the key reagent by abstracting hydrogen.[160]

Several catalytic systems based on copper can also achieve allylic oxidation. These reactions involve induced decomposition of peroxy esters (see Part A, Section 11.1.4). When chiral copper ligands are used, enantioselectivity can be achieved. Table 12.1 shows some results for the oxidation of cyclohexene under these conditions.

12.3.2. Reaction of Alkenes with Singlet Oxygen

Among the oxidants that add oxygen at carbon-carbon double bonds is singlet oxygen.[161] For most alkenes this reaction proceeds with the removal of an allylic

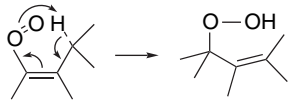
Table 12.1. Enantioselective Copper-Catalyzed Allylic Oxidation of Cyclohexene

	Catalyst	Yield%	e.e.%
1[a]		43	80
2[b]		73	75
3[c]		19	42
4[d]		67	50

a. M. B. Andrus and X. Chen, *Tetrahedron*, **53**, 16229 (1997).
b. G. Sekar, A. Datta Gupta, and V. K. Singh, *J. Org. Chem.*, **62**, 2961 (1998).
c. K. Kawasaki and T. Katsuki, *Tetrahedron*, **53**, 6337 (1997).
d. M. J. Sodergren and P. G. Andersson, *Tetrahedron Lett.*, **37**, 7577 (1996).

160. P. Mueller and J. Rocek, *J. Am. Chem. Soc.*, **96**, 2836 (1974).
161. H. H. Wasserman and R. W. Murray, eds., *Singlet Oxygen*, Academic Press, New York, 1979; A. A. Frimer, *Chem. Rev.*, **79**, 359 (1979); A. Frimer, ed., *Singlet Oxygen*, CRC Press, Boca Raton, FL, 1985; C. S. Foote and E. L. Clennan, in *Active Oxygen in Chemistry*, C. S. Foote, J. S. Valentine, A. Greenberg, and J. F. Liebman, eds., Blackie Academic & Professional, London, 1995, pp. 105–140; M. Prein and W. Adam, *Angew. Chem. Int. Ed. Engl.*, **35**, 477 (1996); M. Orfanopoulos, *Molec. Supramolec. Photochem.*, **8**, 243 (2001).

hydrogen and shift of the double bond to provide an allylic hydroperoxide as the initial product.



The allylic hydroperoxides generated by singlet oxygen oxidation are normally reduced to the corresponding allylic alcohol. The net synthetic transformation is then formation of an allylic alcohol with transposition of the double bond.

A number of methods of generating singlet oxygen are summarized in Scheme 12.16. Singlet oxygen is usually generated from oxygen by dye-sensitized photoexcitation. Porphyrins are also often used as sensitizers. An alternative chemical means of generating $^1O_2$ involves the reaction of hydrogen peroxide with sodium hypochlorite (Entry 2). The method in Entry 3 involves formation of unstable trioxaphosphetane intermediates from O_3 and phosphine or phosphate esters. The adducts are formed at low temperature (−70 °C) and decomposition with generation of singlet oxygen occurs at about −35 °C. The peroxide intermediate in Entry 4 is formed by photolytic addition of oxygen to diphenylanthracene and reacts at around 80 °C to generate $^1O_2$. The method in Entry 5 involves formation of an unstable precursor of $^1O_2$, a trialkylsilyl hydrotrioxide. The half-life of the adduct is roughly 2.5 min at −60 °C.

$$(C_2H_5)_3SiH \quad + \quad O_3 \longrightarrow (C_2H_5)_3SiOOOH \longrightarrow (C_2H_5)_3SiOH \quad + \quad O{=}O$$

Scheme 12.16. Generation of Singlet Oxygen

1[a]

$$\text{Photosensitizer} + h\nu \longrightarrow {}^1[\text{Photosensitizer}]^*$$

$${}^1[\text{Photosensitizer}]^* \longrightarrow {}^3[\text{Photosensitizer}]^*$$

$${}^3[\text{Photosensitizer}]^* + {}^3O_2 \longrightarrow {}^1O_2 + \text{Photosensitizer}$$

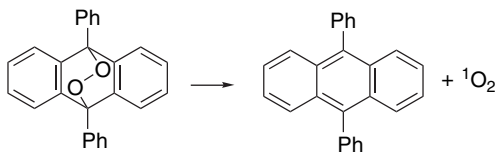
2[b]

$$H_2O_2 + {}^-OCl \longrightarrow {}^1O_2 + H_2O + Cl^-$$

3[c]

$$(RO)_3P + O_3 \longrightarrow (RO)_3P(O_3) \longrightarrow (RO)_3P{=}O + {}^1O_2$$

4[d]

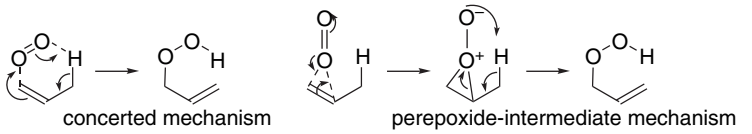


5[e] $(C_2H_5)_3SiH + O_3 \longrightarrow (C_2H_5)_3SiOOOH \longrightarrow (C_2H_5)_3SiOH + {}^1O_2$

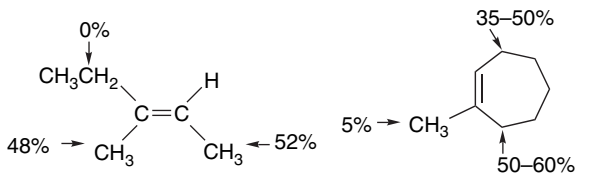
a. C. S. Foote and S. Wexler, *J. Am. Chem. Soc.*, **86**, 3880 (1964).
b. C. S. Foote and S. Wexler, *J. Am. Chem. Soc.*, **86**, 3879 (1964).
c. R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.*, **90**, 537 (1968).
d. H. H. Wasserman, J. R. Sheffler, and J. L. Cooper, *J. Am. Chem. Soc.*, **94**, 4991 (1972).
e. E. J. Corey, M. M. Mehotra, and A. U. Khan, *J. Am. Chem. Soc.*, **108**, 2472 (1986).

Singlet oxygen decays to the ground state triplet at a rate that is strongly dependent on the solvent.[162] Measured half-lives range from about 700 μs in carbon tetrachloride to 2 μs in water. The choice of solvent can therefore have a pronounced effect on the efficiency of oxidation; the longer the singlet state lifetime, the more likely it is that reaction with the alkene can occur.

The reactivity order of alkenes is that expected for attack by an electrophilic reagent. Reactivity increases with the number of alkyl substituents.[163] Terminal alkenes are relatively inert. The reaction has a low $\Delta H^{\ddagger}$ and relative reactivity is dominated by entropic factors.[164] Steric effects govern the direction of approach of the oxygen, so the hydroperoxy group is usually introduced on the less hindered face of the double bond. A key mechanistic issue in singlet oxygen oxidations is whether it is a concerted process or involves an intermediate formulated as a "perepoxide." Most of the available evidence points to the perepoxide mechanism.[165]



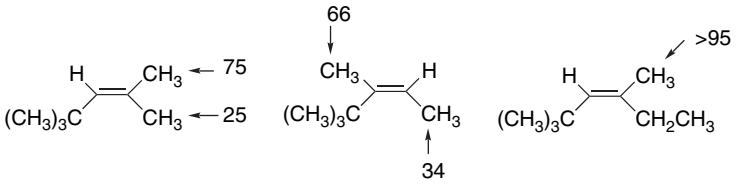
Many alkenes present several different allylic hydrogens, and in this type of situation it is important to be able to predict the degree of selectivity.[166] A useful generalization is that *there is a preference for removal of a hydrogen from the more congested side of the double bond*.[167]



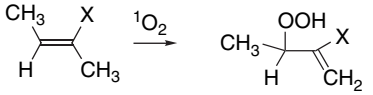
This "*cis* effect" is ascribed to a more favorable TS when the singlet O_2 can interact with two allylic hydrogens. The stabilizing interaction has been described both in FMO[168] and hydrogen-bonding[169] terminology and can be considered an electrostatic effect. The *cis* effect does not apply to alkene having *t*-butyl substituents.[170] There are

162. P. B. Merkel and D. R. Kearns, *J. Am. Chem. Soc*., **94**, 1029, 7244 (1972); P. R. Ogilby and C. S. Foote, *J. Am. Chem. Soc*., **105**, 3423 (1983); J. R. Hurst, J. D. McDonald, and G. B. Schuster, *J. Am. Chem. Soc*., **104**, 2065 (1982).
163. K. R. Kopecky and H. J. Reich, *Can. J. Chem*., **43**, 2265 (1965); C. S. Foote and R. W. Denny, *J. Am. Chem. Soc*., **93**, 5162 (1971); A. Nickon and J. F. Bagli, *J. Am. Chem. Soc*., **83**, 1498 (1961).
164. J. R. Hurst and G. B. Schuster, *J. Am. Chem. Soc*., **104**, 6854 (1982).
165. M. Orfanopoulos, I. Smonou, and C. S. Foote, *J. Am. Chem. Soc*., **112**, 3607 (1990); M. Statakis, M. Orfanopoulos, J. S. Chen, and C. S. Foote, *Tetrahedron Lett*., **37**, 4105 (1996).
166. M. Stratakis and M. Orfanopoulos, *Tetrahedron*, **56**, 1595 (2000).
167. M. Orfanopoulos, M. B. Grdina, and L. M. Stephenson, *J. Am. Chem. Soc*., **101**, 275 (1979); K. H. Schulte-Elte, B. L. Muller, and V. Rautenstrauch, *Helv. Chim. Acta*, **61**, 2777 (1978); K. H. Schulte-Elte and V. Rautenstrauch, *J. Am. Chem. Soc*., **102**, 1738 (1980).
168. L. M. Stephenson, *Tetrahedron Lett*., 1005 (1980).
169. J. R. Hurst, S. L. Wilson, and G. B. Schuster, *Tetrahedron*, **41**, 2191 (1985).
170. M. Stratakis and M. Orfanopoulos, *Tetrahedron Lett*., **36**, 4291 (1995).

probably two reasons for this: the *t*-butyl group does not provide any allylic hydrogens and its steric bulk may interfere with approach by $^1O_2$.



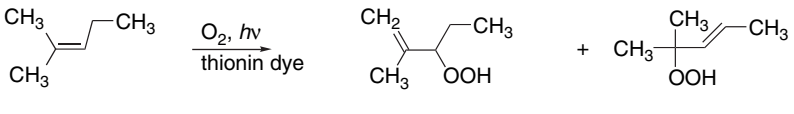
Polar functional groups such as carbonyl, cyano, and sulfoxide, as well as silyl and stannyl groups, exert a strong directing effect, favoring proton removal from the geminal methyl group.[171]



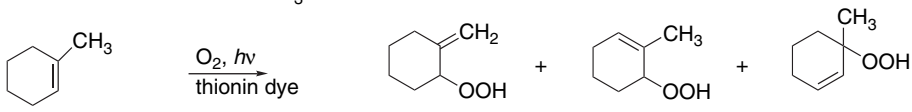
X = CO_2CH_3, CH═O, C≡N, SOPh, $Si(CH_3)_3$, $Sn(CH_3)_3$

Hydroxy[172] and amino[173] groups favor *syn* stereoselectivity. This is similar to the substituent effects observed for peroxy acids and suggests that the substituents may stabilize the TS by hydrogen bonding.

Recently techniques have been developed for $^1O_2$ oxidations in zeolite cavities.[174] The photosensitizer is absorbed in the zeolite and generation of $^1O_2$ and reaction with the alkene occurs within the cavity. The reactions under these conditions show changes in both regiochemistry[175] and stereoselectivity. The *cis* effect is reduced and there is a preference for hydrogen abstraction from methyl groups.



zeolite	100	0
CH_3CN soln	40	60



zeolite	88	2	10
CH_3CN soln	40	15	45

171. E. L. Clennan, X. Chen, and J. J. Koola, *J. Am. Chem. Soc*., **112**, 5193 (1990); M. Orfanopoulos, M. Stratakis, and Y. Elemes, *J. Am. Chem. Soc*., **112**, 6417 (1990); W. Adam and M. J. Richter, *Tetrahedron Lett*., **34**, 8423 (1993).
172. W. Adam and B. Nestler, *J. Am. Chem. Soc*., **114**, 6549 (1992); W. Adam and B. Nestler, *J. Am. Chem. Soc*., **115**, 5041 (1993); M. Stratakis, M. Orfanopoulos, and C. S. Foote, *Tetrahedron Lett*., **37**, 7159 (1996).
173. H.-G. Brunker and W. Adam, *J. Am. Chem. Soc*., **117**, 3976 (1995).
174. X. Li and V. Ramamurthy, *J. Am. Chem. Soc*., **118**, 10666 (1996).
175. J. Shailaja, J. Sivaguru, R. J. Robbins, V. Ramamurthy, R. B. Sunoj, and J. Chandrasekhar, *Tetrahedron*, **56**, 6927 (2000); E. L. Clennan and J. P. Sram, *Tetrahedron*, **56**, 6945 (2000); M. Stratakis, C. Rabalakos, G. Mpourmpakis, and L. G. Froudakis, *J. Org. Chem*., **68**, 2839 (2003).

These changes in regio- and stereochemistry are likely due to conformation changes and electrostatic factors within the cavity. The intrazeolite oxidations can be improved by use of fluorocarbon solvents, owing to an enhanced lifetime of $^1O_2$ and to improved occupancy of the cavity by hydrocarbons in this solvent.[176]

The singlet oxidation mechanism has been subject of a comparative study by kinetic isotope effects and computation of the reaction energy surface.[177] The reaction is described as proceeding through the perepoxide structure, but rather than being a distinct intermediate, this structure occurs at a saddle point on the energy surface; that is, there is no barrier to the second stage of the reaction, the hydrogen abstraction. Figure 12.12 is a representation of such a surface and Figure 12.13 shows the computed geometric characteristics for the perepoxides from *Z*-2-butene and 2,3-dimethyl-2-butene. This study also gives a consistent account for the *cis* effect. The perepoxide structure for engagement of the *cis* hydrogens is of lower energy than the corresponding structure involving the *trans* hydrogens. The *cis* transition structure is attained earlier and retains the synchronous character of the TSs from the symmetrical alkenes, as shown in Figure 12.14.

Scheme 12.17 gives some examples of oxidations by singlet oxygen. The reaction in Entry 1 was used to demonstrate that $^1O_2$ can be generated from H_2O_2 and ClO^-. Similarly, the reaction in Entry 2 was used to verify that the phosphite-ozone adducts

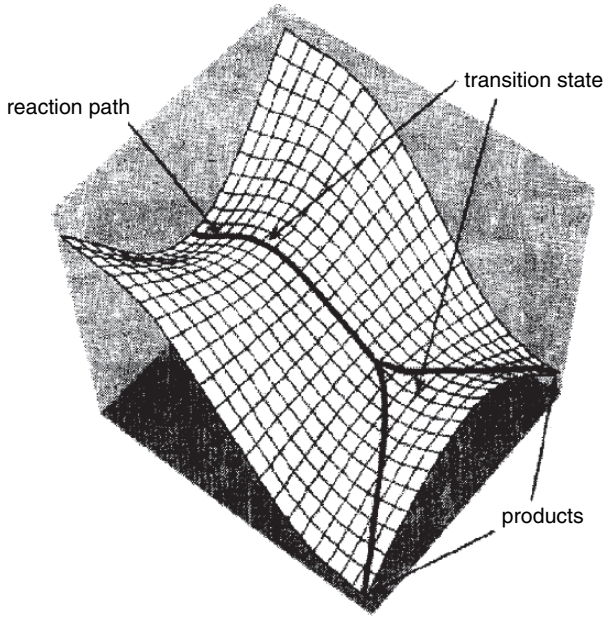


Fig. 12.12. Three-dimensional energy surface showing adjacent transition structures without an intervening intermediate. Reproduced from *J. Am. Chem. Soc*., **125**, 1319 (2003), by permission of the American Chemical Society.

176. A. Pace and E. L. Clennan, *J. Am. Chem. Soc*., **124**, 11236 (2002).
177. D. A. Singleton, C. Hang, M. J. Szymanksi, M. P. Meyer, A. G. Leach, K. T. Kuwata, J. S. Chen, A. Greer, C. S. Foote, and K. N. Houk, *J. Am. Chem. Soc*., **125**, 1319 (2003).

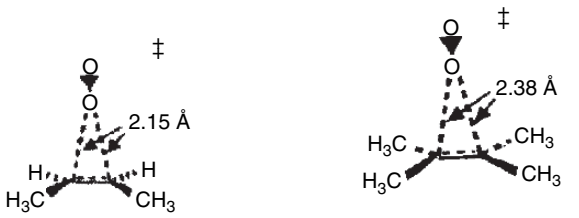
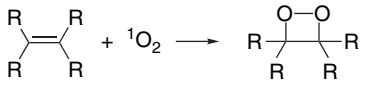


Fig. 12.13. Perepoxide transition structures from *Z*-2-butene and 2,3-dimethyl-2-butene. Reproduced from *J. Am. Chem. Soc*., **125**, 1319 (2003), by permission of the American Chemical Society.

can serve as a $^1O_2$ source. The reactions in Entries 3 and 4 are representative photosensitized procedures with subsequent reduction of the hydroperoxide. Entry 5 used tetra-(perfluorophenyl)phorphyrin as the photosensitizer. This compound, as well as the tetra-(2,6-dichlorophenyl) analog, is reported to have improved stability to degradation under the reaction conditions. In this case the intermediate hydroperoxide was dehydrated to an enone using acetic anhydride. This reaction was carried out on a 25-g scale.

Certain compounds react with singlet oxygen in a different manner, giving dioxetanes as products.[178]



This reaction is not usually a major factor with alkenes bearing only alkyl groups, but is important for vinyl ethers and other alkenes with donor substituents. These

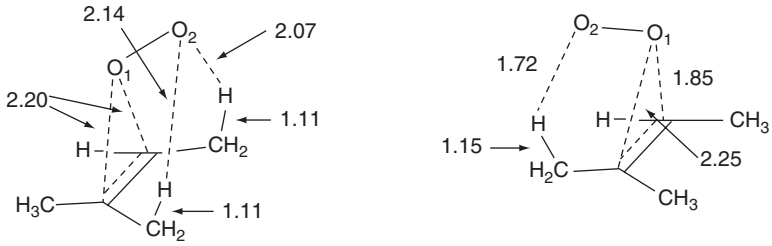
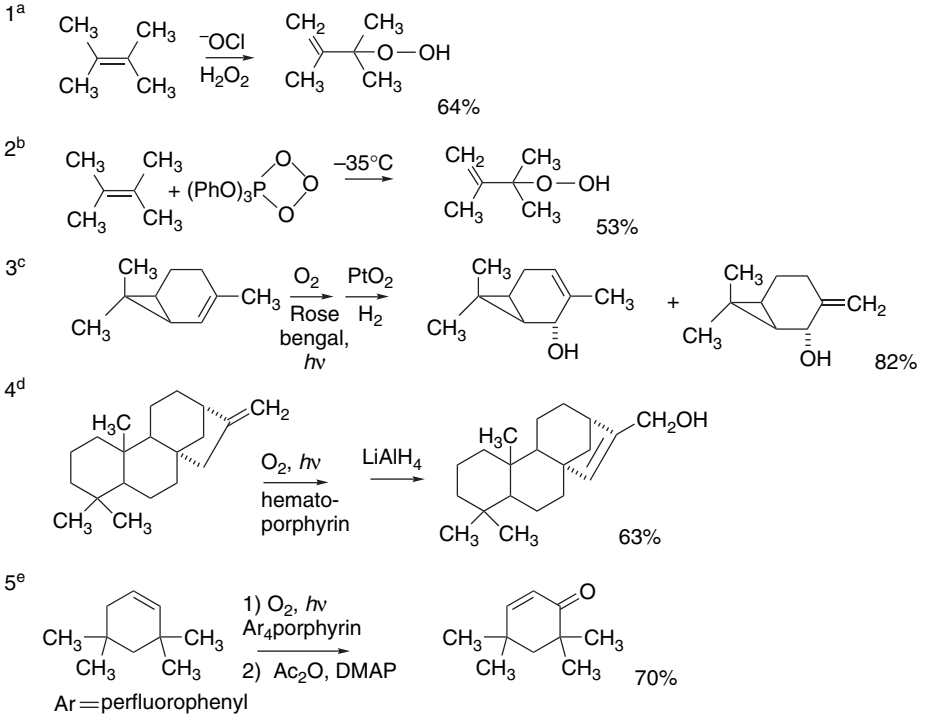


Fig. 12.14. Competing *cis* abstraction and *trans* abstraction transition structures for hydroperoxide formation 2-methyl-2-butene. Adapted *J. Am. Chem. Soc*., **125**, 1319 (2003), by permission of the American Chemical Society.

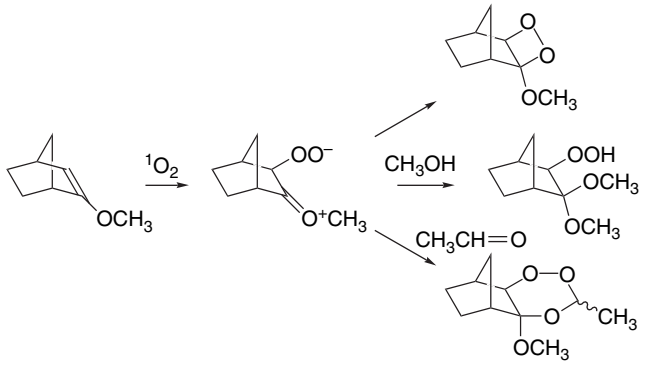
178. W. Fenical, D. R. Kearns, and P. Radlick, *J. Am. Chem. Soc*., **91**, 3396 (1969); S. Mazur and C. S. Foote, *J. Am. Chem. Soc*., **92**, 3225 (1970); P. D. Bartlett and A. P. Schaap, *J. Am. Chem. Soc*., **92**, 3223 (1970).

Scheme 12.17. Oxidation of Alkenes with Singlet Oxygen



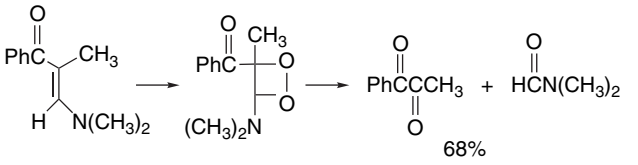
a. C. S. Foote, S. Wexler, W. Ando, and R. Higgins, *J. Am. Chem. Soc*., **90**, 975 (1968).
b. R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc*., **91**, 5358 (1969).
c. K. Gollnick and G. Schade, *Tetrahedron Lett*., 2335 (1966).
d. R. A. Bell, R. E. Ireland, and L. N. Mander, *J. Org. Chem*., **31**, 2536 (1966).
e. H. Quast, T. Dietz, and A. Witzel, *Liebigs Ann. Chem*., 1495 (1995).

reactions are believed to proceed via zwitterionic intermediates that can be diverted by appropriate trapping reagents.[179]

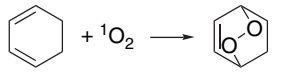


179. C. W. Jefford, S. Kohmoto, J. Boukouvalas, and U. Burger, *J. Am. Chem. Soc*., **105**, 6498 (1983).

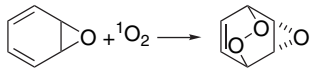
Enaminoketones undergo a clean oxidative cleavage to α-diketones, presumably through a dioxetane intermediate.[180]



Singlet oxygen undergoes [4 + 2] cycloaddition with dienes.



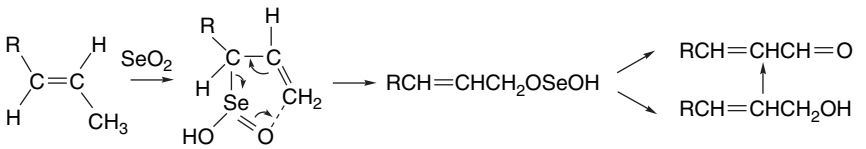
Ref. 181



Ref. 182

12.3.3. Other Oxidants

Selenium dioxide is a useful reagent for allylic oxidation of alkenes. The products can include enones, allylic alcohols, or allylic esters, depending on the reaction conditions. The mechanism consists of three essential steps: (a) an electrophilic "ene" reaction with SeO_2, (b) a [2,3]-sigmatropic rearrangement that restores the original location of the double bond, and (c) solvolysis of the resulting selenium ester.[183]

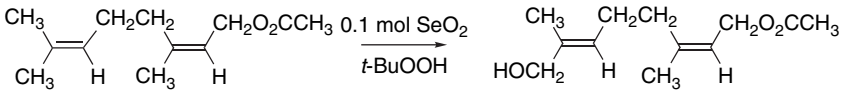


The allylic alcohols that are the initial oxidation products can be further oxidized to carbonyl groups by SeO_2 and the conjugated carbonyl compound is usually isolated. If the alcohol is the desired product, the oxidation can be run in acetic acid, in which case acetate esters are formed.

The mechanism of the reaction has been studied by determining isotope effects for 2-methyl-2-butene and comparing them with predicted values.[184] The isotope effect at the vinyl hydrogen is 0.92 ± 0.01, which is consistent with rehybridization. B3LYP/6-31G* computations located several related TSs with E_a values in the range of 6.0–8.9 kcal/mol. These TSs give calculated isotope effects in good agreement with the experimental values. Although these results are not absolutely definitive, they are consistent with the other evidence for a concerted ene-type mechanism as the first step in SeO_2 oxidation.

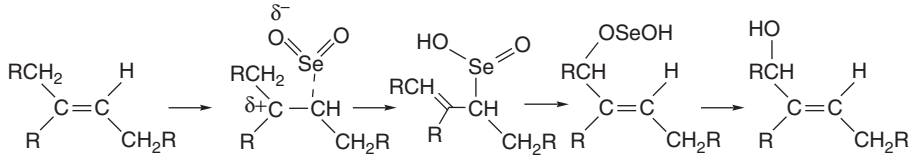
180. H. H. Wasserman and J. L. Ives, *J. Am. Chem. Soc.*, **98**, 7868 (1976).
181. C. S. Foote, S. Wexler, W. Ando, and R. Higgins, *J. Am. Chem. Soc.*, **90**, 975 (1968).
182. C. H. Foster and G. A. Berchtold, *J. Am. Chem. Soc.*, **94**, 7939 (1972).
183. K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **94**, 7154 (1972).
184. D. A. Singleton and C. Hang, *J. Org. Chem.*, **65**, 7554 (2000).

Although the traditional conditions for effecting SeO_2 oxidations involve use of a stoichiometric or excess amount of SeO_2, it is also possible to carry out the reaction with 1.5–2 mol % SeO_2, using *t*-butyl hydroperoxide as a stoichiometric oxidant. Under these conditions, the allylic alcohol is the major product and is obtained in good yields, even from alkenes that are poorly reactive under the traditional conditions.[185]

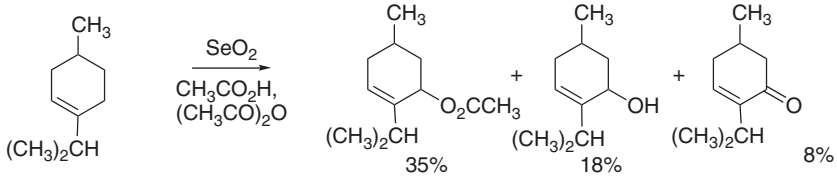


50% + 5% aldehyde

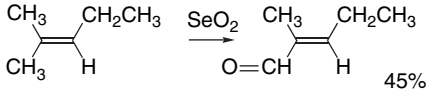
Trisubstituted alkenes are oxidized selectively at the more-substituted end of the carbon-carbon double bond, indicating that the ene reaction step is electrophilic in character.



Ref. 186

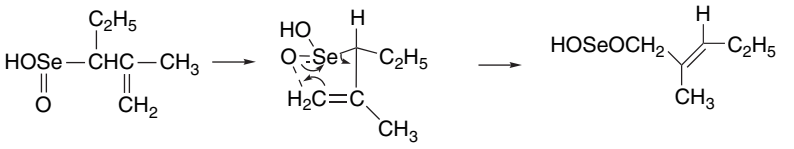


Selenium dioxide reveals a useful stereoselectivity when applied to trisubstituted *gem*-dimethyl alkenes. The products are predominantly the *E*-allylic alcohol or unsaturated aldehyde.[187]

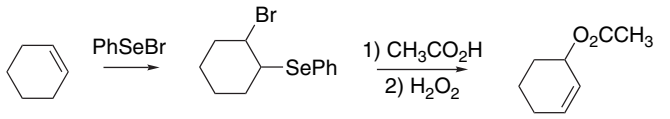


This stereoselectivity can be explained by a five-membered TS for the sigmatropic rearrangement step. The observed *E*-stereochemistry results if the larger alkyl substituent adopts a pseudoequatorial conformation.

185. M. A. Umbreit and K. B. Sharpless, *J. Am. Chem. Soc*., **99**, 5526 (1977).
186. T. Suga, M. Sugimoto, and T. Matsuura, *Bull. Chem. Soc. Jpn*., **36**, 1363 (1963).
187. U. T. Bhalerao and H. Rapoport, *J. Am. Chem. Soc*., **93**, 4835 (1971); G. Buchi and H. Wuest, *Helv. Chim. Acta*, **50**, 2440 (1967).

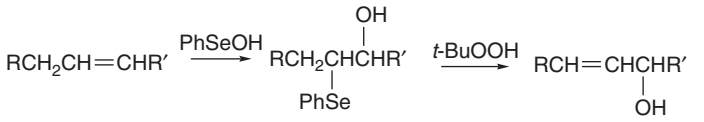


The equivalent to allylic oxidation of alkenes, but with allylic transposition of the carbon-carbon double bond, can be carried out by an indirect oxidative process involving addition of an electrophilic arylselenenyl reagent, followed by oxidative elimination of selenium. In one procedure, addition of an arylselenenyl halide is followed by solvolysis and oxidative elimination.



Ref. 188

This reaction depends upon the facile solvolysis of β-haloselenides and the facile oxidative elimination of a selenoxide, which was discussed in Section 6.6.3. An alternative method, which is experimentally simpler, involves reaction of alkenes with a mixture of diphenyl diselenide and phenylseleninic acid.[189] The two selenium reagents generate an electrophilic selenium species, phenylselenenic acid, PhSeOH.



The elimination is promoted by oxidation of the addition product to the selenoxide by *t*-butyl hydroperoxide. The regioselectivity in this reaction is such that the hydroxy group becomes bound at the more-substituted end of the carbon-carbon double bond. The regioselectivity of the addition step follows Markovnikov's rule with $PhSe^+$ acting as the electrophile. The elimination step specifically proceeds away from the oxygen functionality.

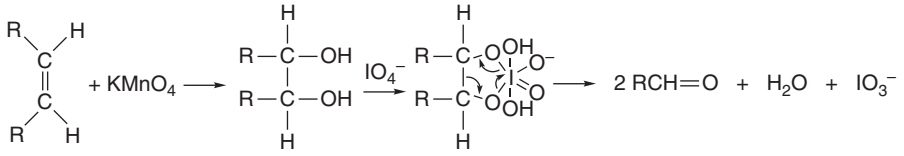
12.4. Oxidative Cleavage of Carbon-Carbon Double Bonds

12.4.1. Transition Metal Oxidants

The most selective methods for cleaving organic molecules at carbon-carbon double bonds involve glycols as intermediates. Oxidations of alkenes to glycols was discussed in Section 12.2.1. Cleavage of alkenes can be carried out in one operation under mild conditions by using a solution containing periodate ion and a catalytic

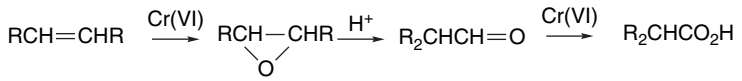
188. K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **39**, 429 (1974); D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 100 (1974).
189. T. Hori and K. B. Sharpless, *J. Org. Chem.*, **43**, 1689 (1978).

amount of permanganate ion.[190] The permanganate ion effects the hydroxylation and the glycol is then cleaved by reaction with periodate. A cyclic intermediate is believed to be involved in the periodate oxidation. Permanganate is regenerated by the oxidizing action of periodate.



Osmium tetroxide used in combination with sodium periodate can also effect alkene cleavage.[191] Successful oxidative cleavage of double bonds using ruthenium tetroxide and sodium periodate has also been reported.[192] In these procedures the osmium or ruthenium can be used in substoichiometric amounts because the periodate reoxidizes the metal to the tetroxide state. Entries 1 to 4 in Scheme 12.18 are examples of these procedures. Entries 5 and 6 show reactions carried out in the course of multistep syntheses. The reaction in Entry 5 followed a 5-*exo* radical cyclization and served to excise an extraneous carbon. The reaction in Entry 6 followed introduction of the allyl group by enolate alkylation. The aldehyde group in the product was used to introduce an amino group by reductive alkylation (see Section 5.3.1.2).

The strong oxidants Cr(VI) and MnO_4^- can also be used for oxidative cleavage of double bonds, provided there are no other sensitive groups in the molecule. The permanganate oxidation proceeds first to the diols and ketols, as described earlier (see p. 1075), and these are then oxidized to carboxylic acids or ketones. Good yields can be obtained provided care is taken to prevent subsequent oxidative degradation of the products. The oxidation of cyclic alkenes by Cr(VI) reagents can be a useful method for formation of dicarboxylic acids. The initial oxidation step appears to yield an epoxide that undergoes solvolytic ring opening to a glycol or glycol monoester, which is then oxidatively cleaved.[193] Two possible complications that can be encountered are competing allylic attack and skeletal rearrangement. Allylic attack can lead to eventual formation of a dicarboxylic acid that has lost one carbon atom. Pinacol-type rearrangements of the epoxide or glycol intermediates can give rise to rearranged products.



Entries 7 to 9 in Scheme 12.18 are illustrative of these oxidative ring cleavages.

[190] R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710 (1955); E. von Rudloff, *Can. J. Chem.*, **33**, 1714 (1955).

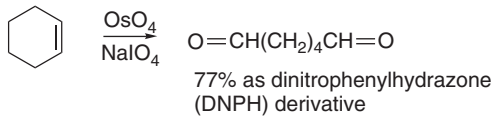
[191] R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956); H. Vorbrueggen and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 2990 (1962).

[192] W. G. Dauben and L. E. Friedrich, *J. Org. Chem.*, **37**, 241 (1972); B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *J. Am. Chem. Soc.*, **103**, 464 (1981); J. W. Patterson, Jr., and D. V. Krishna Murthy, *J. Org. Chem.*, **48**, 4413 (1983).

[193] J. Rocek and J. C. Drozd, *J. Am. Chem. Soc.*, **92**, 6668 (1970); A. K. Awasthy and J. Rocek, *J. Am. Chem. Soc.*, **91**, 991 (1969).

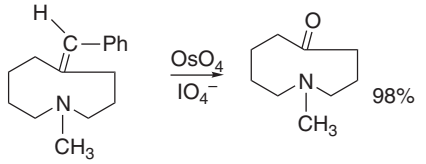
Scheme 12.18. Oxidative Cleavage of Carbon-Carbon Double Bonds Using Transition Metal Oxidants

1[a]



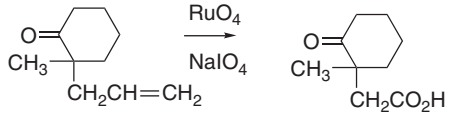
77% as dinitrophenylhydrazone (DNPH) derivative

2[b]

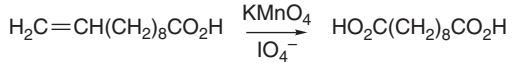


98%

3[c]

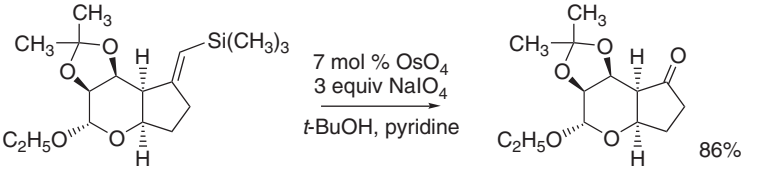


4[d]



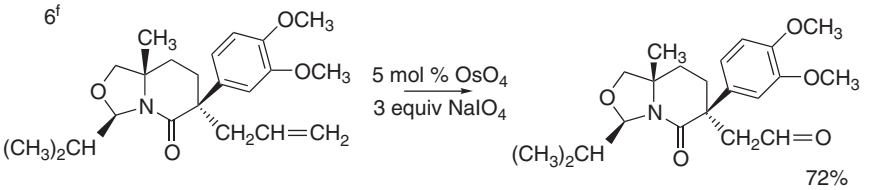
100%

5[e]



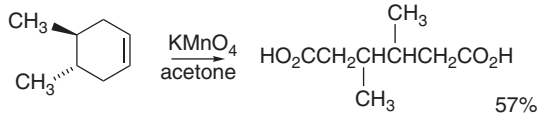
86%

6[f]



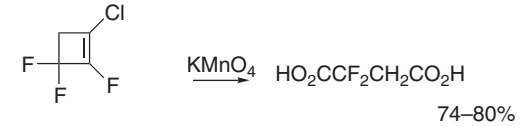
72%

7[g]



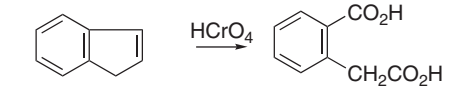
57%

8[h]



74–80%

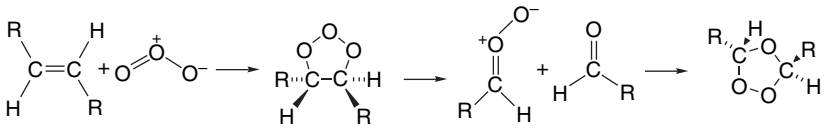
9[i]



66–77%

a. R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).
b. M. G. Reinecke, L. R. Kray, and R. F. Francis, *J. Org. Chem.*, **37**, 3489 (1972).
c. A. A. Asselin, L. G. Humber, T. A. Dobson, J. Komlossy, and R. R. Martel, *J. Med. Chem.*, **19**, 787 (1976).
d. R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).
e. T. Honda, M. Hoshi, K. Kanai, and M. Tsubuki, *J. Chem. Soc., Perkin Trans. 1*, 2091 (1994).
f. A. I. Meyers, R. Hanreich, and K. T. Wanner, *J. Am. Chem. Soc.*, **107**, 7776 (1985).
g. W. C. M. C. Kokke and F. A. Varkvisser, *J. Org. Chem.*, **39**, 1535 (1974).
h. N. S. Raasch and J. E. Castle, *Org. Synth.*, **42**, 44 (1962).
i. O. Grummitt, R. Egan, and A. Buck, *Org. Synth.*, **III**, 449 (1955).

The reaction of alkenes with ozone is a general and selective method of cleaving carbon-carbon double bonds.[194] Application of low-temperature spectroscopic techniques has provided information about the rather unstable intermediates in the ozonolysis process. These studies, along with isotopic-labeling results, have provided an understanding of the reaction mechanism.[195] The two key intermediates in ozonolysis are the 1,2,3-trioxolane, or initial ozonide, and the 1,2,4-trioxolane, or ozonide. The first step of the reaction is a 1,3-dipolar cycloaddition to give the 1,2,3-trioxolane. This is followed by a fragmentation and recombination to give the isomeric 1,2,4-trioxolane. Ozone is a very electrophilic 1,3-dipole because of the accumulation of electronegative oxygen atoms in the ozone molecule. The cycloaddition, fragmentation, and recombination are all predicted to be exothermic on the basis of thermochemical considerations.[196]

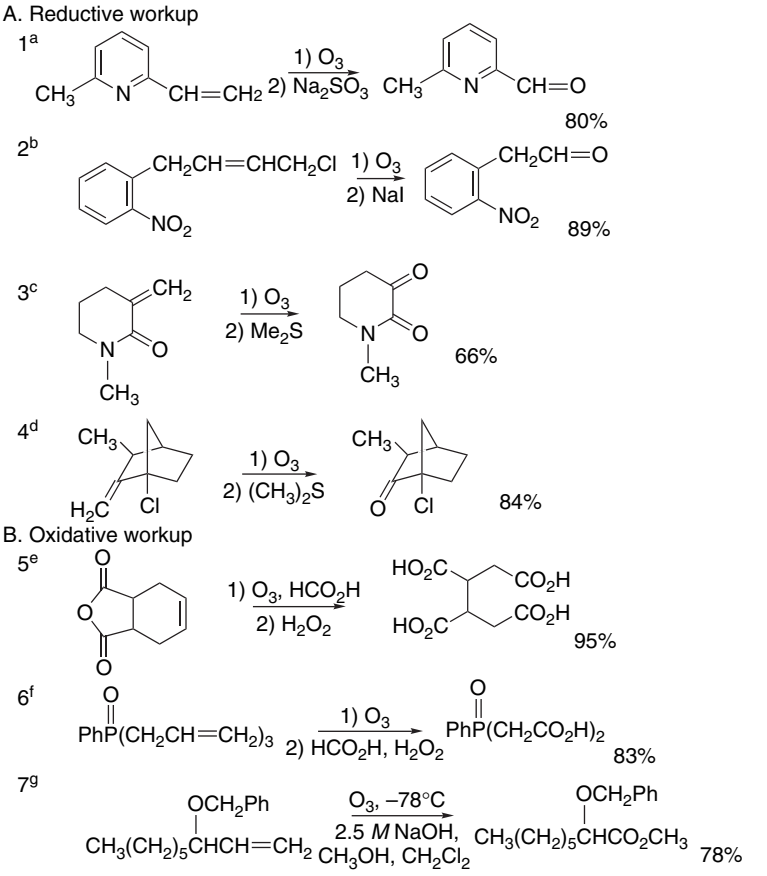


The products isolated after ozonolysis depend upon the conditions of workup. Simple hydrolysis leads to the carbonyl compounds and hydrogen peroxide, and these can react to give secondary oxidation products. It is usually preferable to include a mild reducing agent that is capable of reducing peroxidic bonds. The current practice is to use dimethyl sulfide, though numerous other reducing agents have been used, including zinc,[197] trivalent phosphorus compounds,[198] and sodium sulfite.[199] If the alcohols resulting from the reduction of the carbonyl cleavage products are desired, the reaction mixture can be reduced with $NaBH_4$.[200] Carboxylic acids are formed in good yields from aldehydes when the ozonolysis reaction mixture is worked up in the presence of excess hydrogen peroxide.[201]

Several procedures that intercept the intermediates have been developed. When ozonolysis is done in alcoholic solvents, the carbonyl oxide fragmentation product can be trapped as an α-hydroperoxy ether.[202] Recombination to the ozonide is then prevented, and the carbonyl compound formed in the fragmentation step can also be

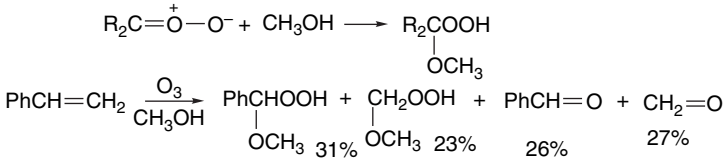
194. P. S. Bailey, *Ozonization in Organic Chemistry*, Vol. 1, Academic Press, New York, 1978.
195. R. P. Lattimer, R. L. Kuckowski, and C. W. Gillies, *J. Am. Chem. Soc*., **96**, 348 (1974); C. W. Gillies, R. P. Lattimer, and R. L. Kuczkowski, *J. Am. Chem. Soc*., **96**, 1536 (1974); G. Klopman and C. M. Joiner, *J. Am. Chem. Soc*., **97**, 5287 (1975); P. S. Bailey and T. M. Ferrell, *J. Am. Chem. Soc*., **100**, 899 (1978); I. C. Histasune, K. Shinoda, and J. Heicklen, *J. Am. Chem. Soc*., **101**, 2524 (1979); J.-I. Choe, M. Srinivasan, and R. L. Kuczkowski, *J. Am. Chem. Soc*., **105**, 4703 (1983). R. L. Kuczkowski, in *1,3-Dipolar Cycloaddition Chemistry*, A. Padwa, ed., Wiley-Interscience, New York, Vol. 2, Chap. 11, 1984; R. L. Kuczkowski, *Chem. Soc. Rev*., **21**, 79 (1992); C. Geletneky and S. Barger, *Eur. J. Chem*., 1625 (1998); K. Schank, *Helv. Chim. Acta*, **87**, 2074 (2004).
196. P. S. Nangia and S. W. Benson, *J. Am. Chem. Soc*., **102**, 3105 (1980).
197. S. M. Church, F. C. Whitmore, and R. V. McGrew, *J. Am. Chem. Soc*., **56**, 176 (1934).
198. W. S. Knowles and Q. E. Thompson, *J. Org. Chem*., **25**, 1031 (1960).
199. R. H. Callighan and M. H. Wilt, *J. Org. Chem*., **26**, 4912 (1961).
200. F. L. Greenwood, *J. Org. Chem*., **20**, 803 (1955).
201. A. L. Henne and P. Hill, *J. Am. Chem. Soc*., **65**, 752 (1943).
202. W. P. Keaveney, M. G. Berger, and J. J. Pappas, *J. Org. Chem*., **32**, 1537 (1967).

Scheme 12.19. Ozonolysis Reactions



a. R. H. Callighan and M. H. Wilt, *J. Org. Chem.*, **26**, 4912 (1961).
b. W. E. Noland and J. H. Sellstedt, *J. Org. Chem.*, **31**, 345 (1966).
c. M. L. Rueppel and H. Rapoport, *J. Am. Chem. Soc.*, **94**, 3877 (1972).
d. J. V. Paukstelis and B. W. Macharia, *J. Org. Chem.*, **38**, 646 (1973).
e. J. E. Franz, W. S. Knowles, and C. Ousch, *J. Org. Chem.*, **30**, 4328 (1965).
f. J. L. Eichelberger and J. K. Stille, *J. Org. Chem.*, **36**, 1840 (1971).
g. J. A. Marshall and A. W. Garofalo, *J. Org. Chem.*, **58**, 3675 (1993).

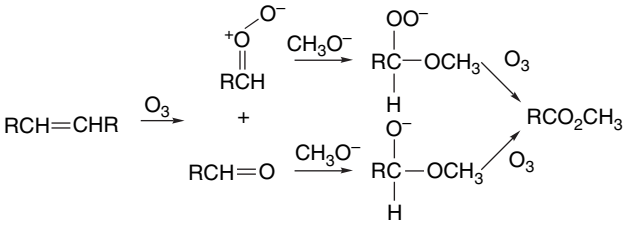
isolated. If the reaction mixture is then treated with dimethyl sulfide, the hydroperoxide is reduced and the second carbonyl compound is also formed in good yield.[203]



Ozonolysis in the presence of NaOH or $NaOCH_3$ in methanol with CH_2Cl_2 as a cosolvent leads to formation of esters. This transformation proceeds by trapping both

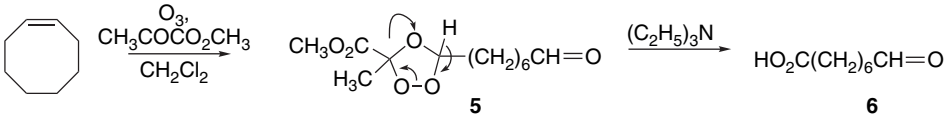
203. J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

the carbonyl oxide and aldehyde products of the fragmentation step.[204] The anionic adducts are then oxidized by O_3.



Cyclooctene gives dimethyl octanedioate under these conditions.

Especially reactive carbonyl compounds such as methyl pyruvate can trap the carbonyl oxide component. For example, ozonolysis of cyclooctene in the presence of methyl pyruvate leads to **5**; when treated with triethylamine **5** is converted to **6**, in which the two carbons of the original double bond have been converted to different functionalities.[205]



5 **6**

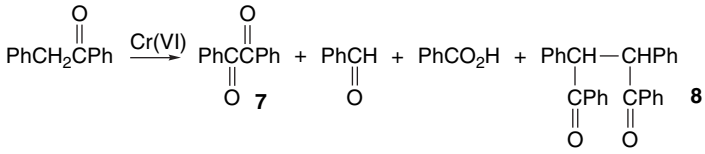
Scheme 12.19 illustrates some cases in which ozonolysis reactions have been used in the course of syntheses. Entries 1 to 4 are examples of use of ozonolysis to introduce carbonyl groups under reductive workup. Entries 5 and 6 involve oxidative workup and give dicarboxylic acid products. The reaction in Entry 7 is an example of direct generation of a methyl ester by methoxide trapping.

12.5. Oxidation of Ketones and Aldehydes

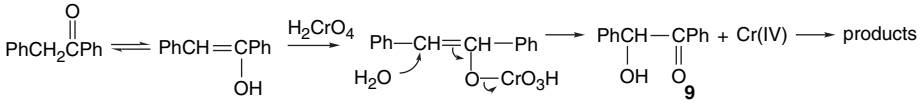
12.5.1. Transition Metal Oxidants

Ketones are oxidatively cleaved by Cr(VI) or Mn(VII) reagents. The reaction is sometimes of utility in the synthesis of difunctional molecules by ring cleavage. The mechanism for both reagents is believed to involve an enol intermediate.[206] A study involving both kinetic data and quantitative product studies has permitted a fairly complete description of the Cr(VI) oxidation of benzyl phenyl ketone.[207] The products include both oxidative-cleavage products and benzil, **7**, which results from oxidation α to the carbonyl. In addition, the dimeric product **8**, which is suggestive of radical intermediates, is formed under some conditions.

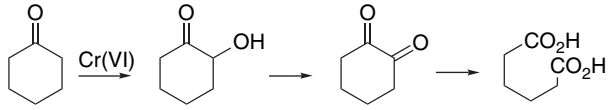
204. J. A. Marshall and A. W. Gordon, *J. Org. Chem.*, **58**, 3675 (1993).
205. Y.-S. Hon and J.-L. Yan, *Tetrahedron*, **53**, 5217 (1997).
206. K. B. Wiberg and R. D. Geer, *J. Am. Chem. Soc.*, **87**, 5202 (1965); J. Rocek and A. Riehl, *J. Am. Chem. Soc.*, **89**, 6691 (1967).
207. K. B. Wiberg, O. Aniline, and A. Gatzke, *J. Org. Chem.*, **37**, 3229 (1972).



Both the diketone and the cleavage products were shown to arise from an α-hydroxyketone intermediate (benzoin) **9**.

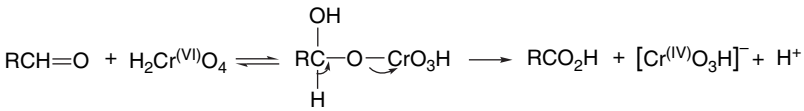


The coupling product is considered to involve a radical intermediate formed by one-electron oxidation, probably effected by Cr(IV). Similarly, the oxidation of cyclohexanone involves 2-hydroxycylohexanone and 1,2-cyclohexanedione as intermediates.[208]



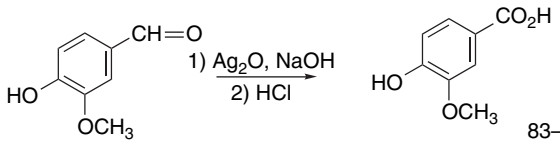
Owing to the efficient oxidation of alcohols to ketones, alcohols can be used as the starting materials in oxidative cleavages. The conditions required are more vigorous than for the alcohol to ketone transformation (see Section 12.1.1).

Aldehydes can be oxidized to carboxylic acids by both Mn(VII) and Cr(VI). Fairly detailed mechanistic studies have been carried out for Cr(VI). A chromate ester of the aldehyde hydrate is believed to be formed, and this species decomposes in the rate-determining step by a mechanism similar to the one that operates in alcohol oxidations.[209]



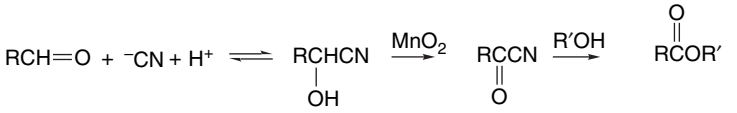
Effective conditions for oxidation of aldehydes to carboxylic acids with $KMnO_4$ involve use of *t*-butanol and an aqueous NaH_2PO_4 buffer as the reaction medium.[210] Buffered sodium chlorite is also a convenient oxidant.[211] Both $KMnO_4$ and $NaClO_2$ can be used in the form of solid-supported materials, using silica and ion exchange resins, respectively,[212] which permits facile workup of the product. Silver oxide is one of the older reagents used for carrying out the aldehyde to carboxylic acid oxidation.

208. J. Rocek and A. Riehl, *J. Org. Chem.*, **32**, 3569 (1967).
209. K. B. Wiberg, *Oxidation in Organic Chemistry*, Part A, Academic Press, New York, 1965, pp. 172–178.
210. A. Abiko, J. C. Roberts, T. Takemasa, and S. Masamune, *Tetrahedron Lett.*, **27**, 4537 (1986).
211. E. Dalcanale and F. Montanari, *J. Org. Chem.*, **51**, 567 (1986); J. P. Bayle, F. Perez, and J. Cortieu, *Bull. Soc. Chim. Fr.*, 565 (1996); E. J. Corey and G. A. Reichard, *Tetrahedron Lett.*, **34**, 6973 (1993); P. M. Wovkulich, K. Shankaran, J. Kiegiel, and M. R. Uskokovic, *J. Org. Chem.*, **58**, 832 (1993); B. R. Babu and K. K. Balasubramaniam, *Org. Prep. Proc. Int.*, **26**, 123 (1994).
212. T. Takemoto, K. Yasuda, and S. V. Ley, *Synlett*, 1555 (2001).

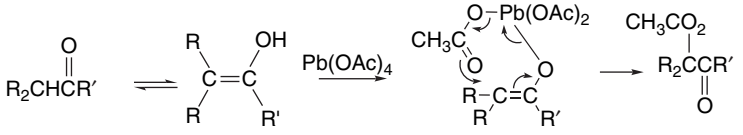


Ref. 213

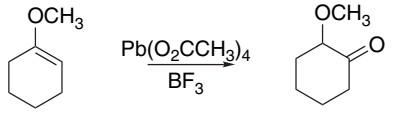
The reaction of aldehydes with MnO_2 in the presence of cyanide ion in an alcoholic solvent is a convenient method of converting aldehydes directly to esters.[214] This reaction involves the cyanohydrin as an intermediate. The initial oxidation product is an acyl cyanide, which is solvolyzed under these reaction conditions.



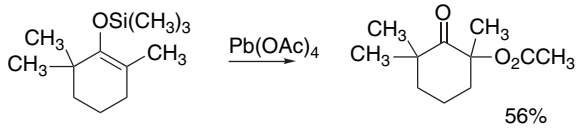
Lead tetraacetate can effect oxidation of carbonyl groups, leading to formation of α-acetoxy ketones,[215] but the yields are seldom high. Boron trifluoride can be used to catalyze these oxidations. It is presumed to function by catalyzing the formation of the enol, which is thought to be the reactive species.[216] With unsymmetrical ketones, products from oxidation at both α-methylene groups are found.[217]



With enol ethers, $Pb(OCCH_3)_4$ gives α-methoxyketones.[218]

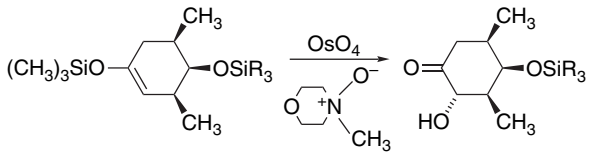


Introduction of oxygen α to a ketone function can also be carried out via the silyl enol ether. Lead tetraacetate gives the α-acetoxy ketone.[219]



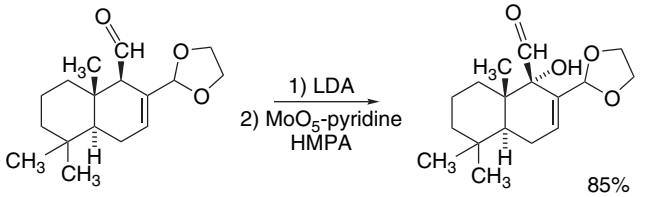
213. I. A. Pearl, *Org. Synth.*, **IV**, 972 (1963).
214. E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Am. Chem. Soc.*, **90**, 5616 (1968).
215. R. Criegee, in *Oxidation in Organic Chemistry*, Part A, K. B. Wiberg, ed., Academic Press, New York, 1965, pp. 305–312.
216. J. D. Cocker, H. B. Henbest, G. H. Philipps, G. P. Slater, and D. A. Thomas, *J. Chem. Soc.*, 6 (1965).
217. S. Moon and H. Bohm, *J. Org. Chem.*, **37**, 4338 (1972).
218. V. S. Singh, C. Singh, and D. K. Dikshit, *Synth. Commun.*, **28**, 45 (1998).
219. G. M. Rubottom, J. M. Gruber, and K. Kincaid, *Synth. Commun.*, **6**, 59 (1976); G. M. Rubottom and J. M. Gruber, *J. Org. Chem.*, **42**, 1051 (1977); G. M. Rubottom and H. D. Juve, Jr., *J. Org. Chem.*, **48**, 422 (1983).

α-Hydroxyketones can be obtained from silyl enol ethers by oxidation using a catalytic amount of OsO_4 with an amine oxide serving as the stoichiometric oxidant.[220]



Ref. 221

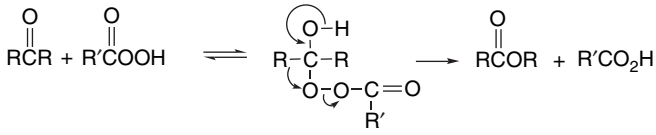
Other procedures for α-oxidation of ketones are based on prior generation of the enolate. Among the reagents used is a molybdenum compound, MoO_5-pyridine-HMPA, which is prepared by dissolving MoO_3 in hydrogen peroxide, followed by addition of HMPA. This reagent oxidizes the enolates of aldehydes, ketones, esters, and lactones to the corresponding α-hydroxy compound.[222]



Ref. 223

12.5.2. Oxidation of Ketones and Aldehydes by Oxygen and Peroxidic Compounds

12.5.2.1. Baeyer-Villiger Oxidation of Ketones. In the presence of acid catalysts, peroxy compounds are capable of oxidizing ketones by insertion of an oxygen atom into one of the carbon-carbon bonds at the carbonyl group. Known as the *Baeyer-Villiger oxidation*,[224] the mechanism involves a sequence of steps that begins with addition to the carbonyl group, followed by peroxide bond cleavage with migration to oxygen.

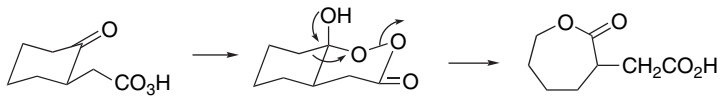


220. J. P. McCormick, W. Tomasik, and M. W. Johnson, *Tetrahedron Lett*., **22**, 607 (1981).
221. R. K. Boeckman, Jr., J. E. Starrett, Jr., D. G. Nickell, and P.-E. Sun, *J. Am. Chem. Soc*., **108**, 5549 (1986).
222. E. Vedejs, *J. Am. Chem. Soc*., **96**, 5945 (1974); E. Vedejs, D. A. Engler, and J. E. Telschow, *J. Org. Chem*., **43**, 188 (1978); E. Vedejs and S. Larsen, *Org. Synth*., **64**, 127 (1985).
223. S. P. Tanis and K. Nakanishi, *J. Am. Chem. Soc*., **101**, 4398 (1979).
224. C. H. Hassall, *Org. React*., **9**, 73 (1957); G. R. Krow, *Org. React*., **43**, 252 (1993); M. Renz and B. Beunier, *Eur. J. Org. Chem*., 737 (1999); G.-J. ten Brink, I. W. C. E. Arends, and R. A. Sheldon, *Chem. Rev*., **104**, 4105 (2004).

The concerted O−O heterolysis-migration is usually the rate-determining step.[225] The reaction is catalyzed by protic and Lewis acids,[226] including $Sc(O_3SCF_3)_3$[227] and $Bi(O_3SCF_3)_3$.[228]

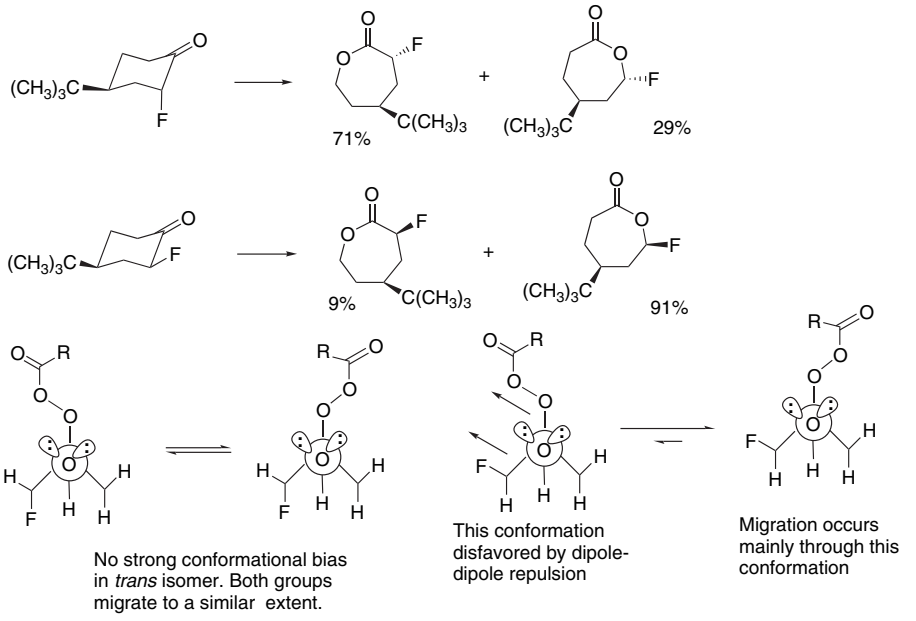
When the reaction involves an unsymmetrical ketone, the structure of the product depends on which group migrates. A number of studies have been directed at ascertaining the basis of migratory preference in the Baeyer-Villiger oxidation, and a general order of likelihood of migration has been established: *tert*-alkyl, *sec*-alkyl>benzyl, phenyl>*pri*-alkyl>cyclopropyl>methyl.[229] Thus, methyl ketones uniformly give acetate esters resulting from migration of the larger group.[230] A major factor in determining which group migrates is the ability to accommodate partial positive charge. In *para*-substituted phenyl groups, ERG substituents favor migration.[231] Similarly, silyl substituents enhance migratory aptitude of alkyl groups.[232] As is generally true of migration to an electron-deficient center, the configuration of the migrating group is retained in Baeyer-Villiger oxidations.

Steric and conformational factors are also important, especially in cyclic systems.[233] There is a preference for the migration of the group that is antiperiplanar with respect to the peroxide bond. In relatively rigid systems, this effect can outweigh the normal preference for the migration of the more branched group.[234]



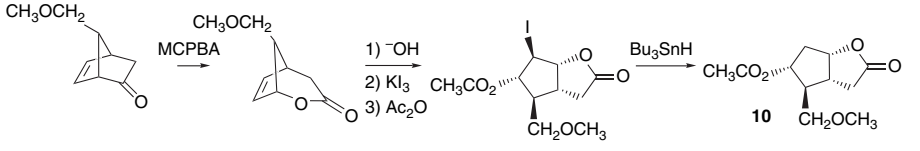
This stereoelectronic effect also explains the contrasting regioselectivity of *cis*- and *trans*-2-fluoro-4-*t*-butylcyclohexanone.[235] As a result of a balance between its polar effect and hyperconjugation, the net effect of a fluoro substituent in acyclic systems is small. However, in 2-fluorocyclohexanones an unfavorable dipole-dipole interaction comes into play for the *cis* isomer and preferential migration of the fluoro-substituted carbon is observed.

225. Y. Ogata and Y. Sawaki, *J. Org. Chem*., **37**, 2953 (1972).
226. G. Stukul, *Angew. Chem. Intl. Ed. Engl*., **37**, 1199 (1998).
227. H. Kotsuki, K. Arimura, T. Araki, and T. Shinohara, *Synlett*, 462 (1999).
228. M. M. Alam, R. Varala, and S. R. Adapa, *Synth. Commun*., **33**, 3035 (2003).
229. H. O. House, *Modern Synthetic Reactions*, 2nd Edition, W. A. Benjamin, Menlo Park, CA, 1972, p. 325.
230. P. A. S. Smith, in *Molecular Rearrangements*, P. de Mayo, ed., Interscience, New York, 1963, pp. 457–591.
231. W. E. Doering and L. Speers, *J. Am. Chem. Soc*., **72**, 5515 (1950).
232. P. F. Hudrlik, A. M. Hudrlik, G. Nagendrappa, T. Yimenu, E. T. Zellers, and E. Chin, *J. Am. Chem. Soc*., **102**, 6894 (1980).
233. M. F. Hawthorne, W. D. Emmons, and K. S. McCallum, *J. Am. Chem. Soc*., **80**, 6393 (1958); J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc*., **82**, 5235 (1960); P. M. Goodman and Y. Kishi, *J. Am. Chem. Soc*., **120**, 9392 (1998).
234. S. Chandrasekhar and C. D. Roy, *J. Chem. Soc., Perkin Trans. 2*, 2141 (1994).
235. C. M. Crudden, A. C. Chen, and L. A. Calhoun, *Angew. Chem. Int. Ed. Engl*., **39**, 2852 (2000).

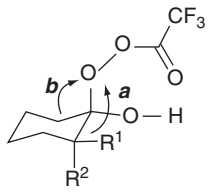


In 2-(trifluoromethyl)cyclohexanone, the methylene group migrates in preference to the trifluoromethylmethine group,[236] owing primarily to the EWG effect of the trifluoromethyl group. The computational energy profile, shown in Figure 12.15, indicates that the reaction proceeds through a minor conformation of the adduct in which the trifluoromethyl group is axial. The same regioselectivity is computed for the adduct having the peroxy substituent in an equatorial position, but this adduct is about 1 kcal/mol higher in energy.

The Baeyer-Villiger reaction has found considerable application in the synthesis of prostaglandins. One common pattern involves the use of bicyclo[2.2.1]heptan-2-one derivatives, which are generally obtained by Diels-Alder reactions. For example, compound **10** is known as the *Corey lactone* and has played a prominent role in the synthesis of prostaglandins.[237] This compound was originally prepared by a Baeyer-Villiger oxidation of 7-(methoxymethyl)bicyclo[2.2.1]hept-5-en-2-one.[238]



236. Y. Itoh, M. Yamanaka, and K. Mikami, *Org. Lett*., **5**, 4803 (2003).
237. R. Bansal, G. F. Cooper, and E. J. Corey, *J. Org Chem*., **56**, 1329 (1991).
238. E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Am. Chem. Soc*., **91**, 5675 (1969).



CP1, TS1: $R^1 = CF_3$, $R^2 = H$, ***a***
CP2, TS2: $R^1 = CF_3$, $R^2 = H$, ***b***
CP3, TS3: $R^1 = H$, $R^2 = CF_3$, ***a***
CP4, TS4: $R^1 = H$, $R^2 = CF_3$, ***b***

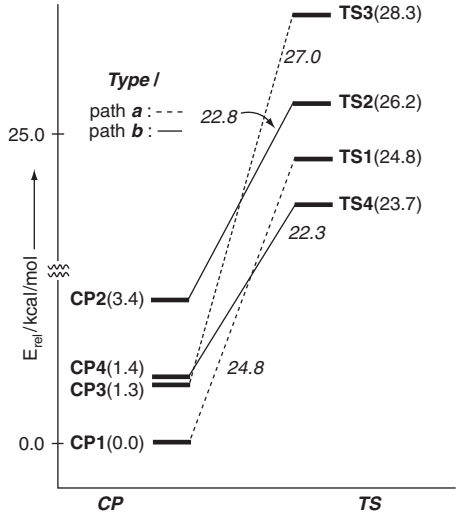


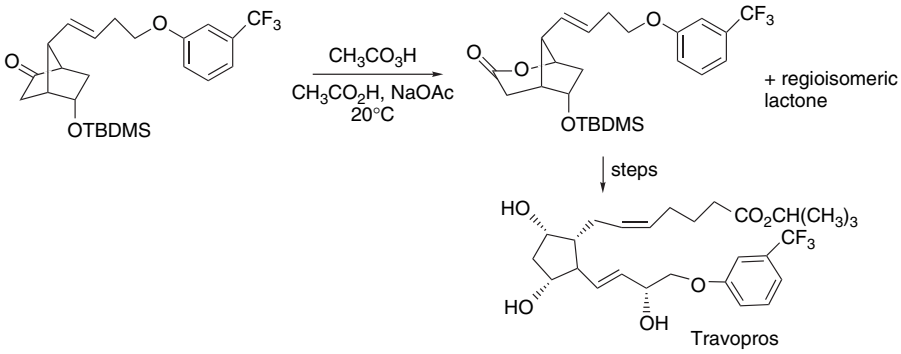
Fig. 12.15. Computational comparison of reactants (adducts) and transition structures for Baeyer-Villiger oxidation of 2-(trifluoromethyl)cyclohexanone by peroxytrifluoroacetic acid. Reproduced from *Org. Lett*., **5**, 4803 (2003), by permission of the American Chemical Society.

This intermediate has the oxygenation and pattern and *trans*-disubstitution pattern found in the prostaglandins. Several syntheses of similar intermediates have been developed.[239]

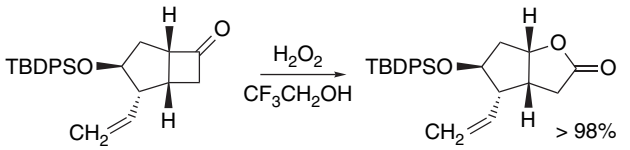
In the synthesis of Travoprost, an antiglaucoma agent, a bicyclo[2.2.1]heptan-2-one is converted to a lactone.[240] The commercial process uses peroxyacetic acid as the oxidant and gives a 40% yield. The regioselectivity in this case is only 3:1 but the unwanted isomer can be removed by selective hydrolysis.

[239] I. Vesely, V. Kozmik, V. Dedek, J. Palecek, J. Mostecky, and I. Stibor, *Coll. Czech. Chem. Commun*., **54**, 1683 (1989); J. S. Bindra, A. Grodski, T. K. Schaaf, and E. J. Corey, *J. Am. Chem. Soc*., **95**, 7522 (1973).

[240] L. T. Boulton, D. Brick, M. E. Fox, M. Jackson, I. C. Lennon, R. McCague, N. Parkin, D. Rhodes, and G. Ruecroft, *Org. Proc. Res. Dev*., **6**, 128 (2002).



A series of 2-vinyl-3-silyloxybicyclo[3.2.0]heptan-6-ones has also been converted to prostanoid lactones in excellent yield but variable regioselectivity. Some of the best regioselectivity was obtained using H_2O_2 in trifluoroethanol (see p. 1097).[241] The strained cyclobutanone ring and the relatively unreactive terminal vinyl group favor the desired reaction in preference to alkene epoxidation.

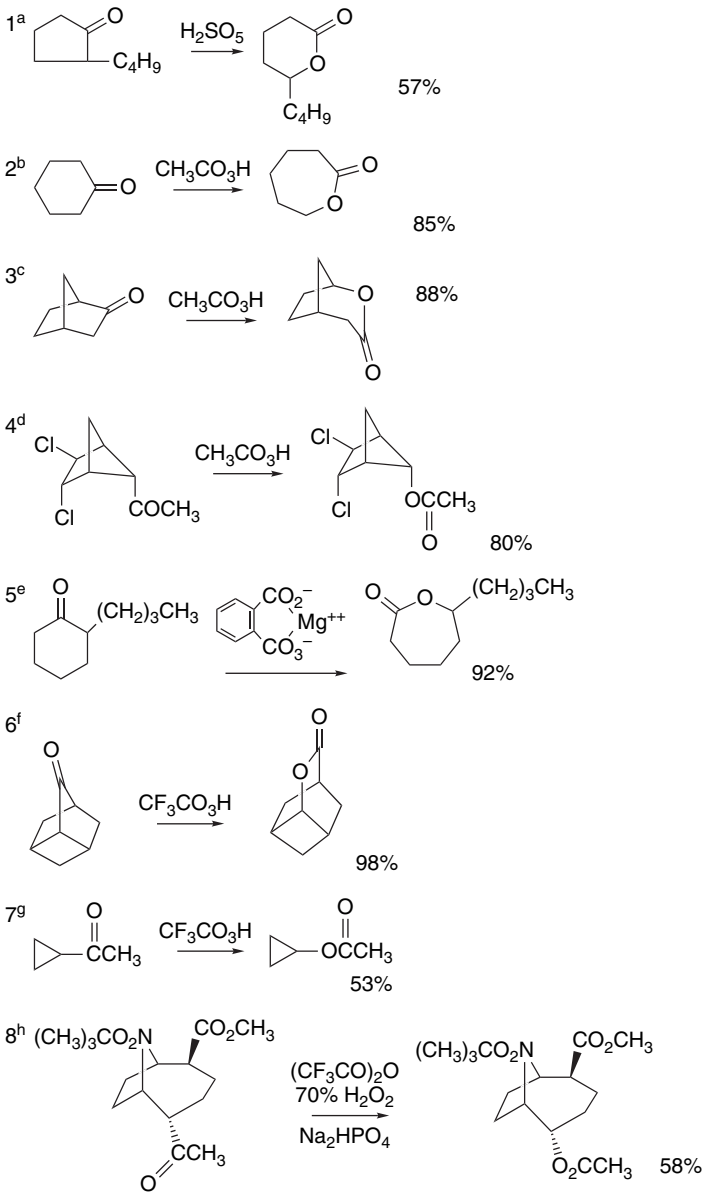


Some typical examples of Baeyer-Villiger oxidations are shown in Scheme 12.20. Entry 1 uses peroxysulfuric acid, the original reagent discovered by Baeyer and Villiger. Entries 2 and 3 generate lactones in good yield from cyclic ketones using peroxyacetic acid. Entry 3 also illustrates the preference for the migration of the more branched group. Entry 4 is a case of formation of an acetate ester from a methyl ketone. Entry 5 illustrates the use of magnesium monoperoxyphthalate and also shows the normal preference for migration of the more branched group. The reaction in Entry 6 exhibits very high regioselectivity. Although this example is consistent with the generalization that the more branched group will migrate, there may be other factors associated with ring geometry that lead to the complete regioselectivity. Entries 7 and 8 use peroxytrifluoroacetic acid and again illustrate the conversion of methyl ketones to acetate esters.

12.5.2.2. Oxidation of Enolates and Enolate Equivalents. Although ketones are essentially inert to molecular oxygen, enolate anions are susceptible to oxidation. The combination of oxygen and a strong base has found some utility in the introduction of an oxygen function at carbanionic sites.[242] Hydroperoxides are the initial products of such oxidations, but when DMSO or some other substance capable of reducing the hydroperoxide is present, the corresponding alcohol is isolated. A procedure that has met with

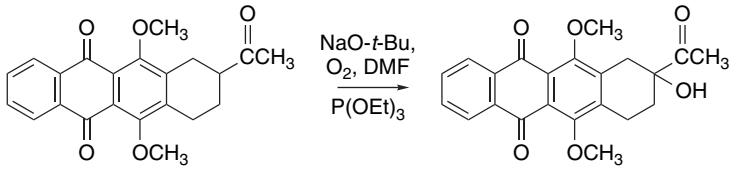
[241] D. Depre, L.-Y. Chen, and L. Ghosez, *Tetrahedron*, **59**, 6797 (2003).
[242] J. N. Gardner, T. L. Popper, F. E. Carlon, O. Gnoj, and H. L. Herzog, *J. Org. Chem.*, **33**, 3695 (1968).

Scheme 12.20. Baeyer-Villiger Oxidation



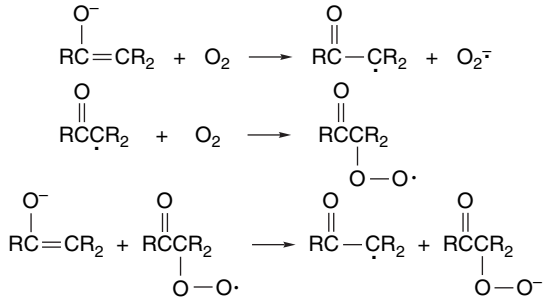
a. T. H. Parliament, M. W. Parliament, and J. S. Fagerson, *Chem. Ind.*, 1845 (1966).
b. P. S. Strarcher and B. Phillips, *J. Am. Chem. Soc*., **80**, 4079 (1958).
c. J. Meinwald and E. Frauenglass, *J. Am. Chem. Soc*., **82**, 5235 (1960).
d. K. B. Wiberg and R. W. Ubersax, *J. Org. Chem*., **37**, 3827 (1972).
e. M. Hirano, S. Yakabe, A. Satoh, J. H. Clark, and T. Morimoto, *Synth. Commun*., **26**, 4591 (1996); T. Mino, S. Masuda, M. Nishio, and M. Yamashita, *J. Org. Chem*., **62**, 2633 (1997).
f. S. A. Monti and S.-S. Yuan, *J. Org. Chem*., **36**, 3350 (1971).
g. W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc*., **77**, 2287 (1955).
h. F. J. Sardina, M. H. Howard, M. Morningstar, and H. Rapoport, *J. Org. Chem*., **55**, 5025 (1990).

considerable success involves oxidation in the presence of a trialkyl phosphite.[243] The intermediate hydroperoxide is efficiently reduced by the phosphite ester.



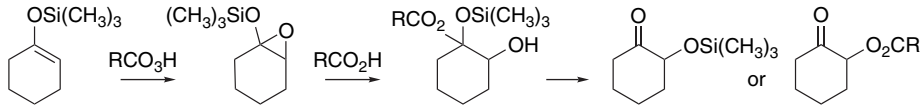
Ref. 144

This oxidative process has been successful with ketones,[244] esters,[245] and lactones.[246] Hydrogen peroxide can also be used as the oxidant, in which case the alcohol is formed directly.[247] The mechanisms for the oxidation of enolates by oxygen is a radical chain autoxidation in which the propagation step involves electron transfer from the carbanion to a hydroperoxy radical.[248]



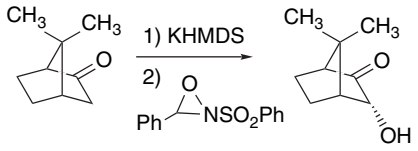
Arguments for a nonchain reaction between the enolate and oxygen to give the hydroperoxide anion directly have been advanced as well.[249]

The silyl enol ethers of ketones are also oxidized to α-hydroxy ketones by *m*-chloroperoxybenzoic acid. If the reaction workup includes acylation, α-acyloxy ketones are obtained.[250] These reactions proceed by initial epoxidation of the silyl enol ether, which then undergoes ring opening. Subsequent transfer of either the *O*-acyl or *O*-TMS substituent occurs, depending on the reaction conditions.

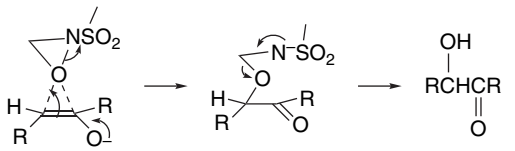


243. J. N. Gardner, F. E. Carlon, and O. Gnoj, *J. Org. Chem*., **33**, 3294 (1968).
244. F. A. J. Kerdesky, R. J. Ardecky, M. V. Lashmikanthan, and M. P. Cava, *J. Am. Chem. Soc*., **103**, 1992 (1981).
245. E. J. Corey and H. E. Ensley, *J. Am. Chem. Soc*., **97**, 6908 (1975).
246. J. J. Plattner, R. D. Gless, and H. Rapoport, *J. Am. Chem. Soc*., **94**, 8613 (1972); R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *J. Am. Chem. Soc*., **93**, 5576 (1971).
247. G. Buchi, K. E. Matsumoto, and H. Nishimura, *J. Am. Chem. Soc*., **93**, 3299 (1971).
248. G. A. Russell and A. G. Bemix, *J. Am. Chem. Soc*., **88**, 5491 (1966).
249. H. R. Gersmann and A. F. Bickel, *J. Chem. Soc. B*, 2230 (1971).
250. G. M. Rubottom, J. M. Gruber, R. K. Boeckman, Jr., M. Ramaiah, and J. B. Medwick, *Tetrahedron Lett*., 4603 (1978); G. M. Rubottom and J. M. Gruber, *J. Org. Chem*., **43**, 1599 (1978); G. M. Rubottom, M. A. Vazquez, and D. R. Pelegrina, *Tetrahedron Lett*., 4319 (1974).

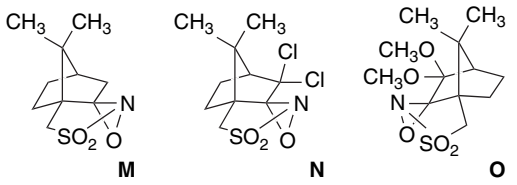
N-Sulfonyloxaziridines are useful reagents for oxidation of enolates to α-hydroxyketones.[251] The best results are frequently achieved by using KHMDS to form the enolate. The hydroxylation occurs preferentially from the less hindered enolate face.



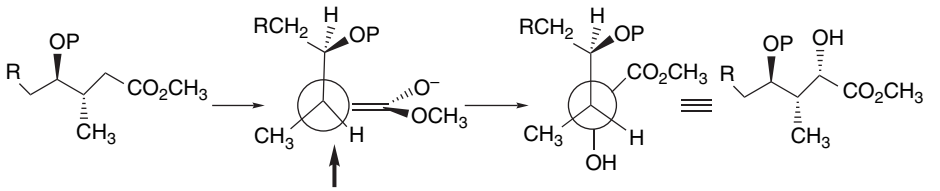
The mechanism of oxygen transfer is believed to involve nucleophilic opening of the oxaziridine, followed by collapse of the resulting *N*-sulfonylcarbinolamine.[252]



These reagents exhibit good stereoselectivity toward chiral reactants, such as acyloxazolidinones.[253] Chiral oxaziridine reagents have been developed that can achieve enantioselective oxidation of enolates to α-hydroxyketones.[254]

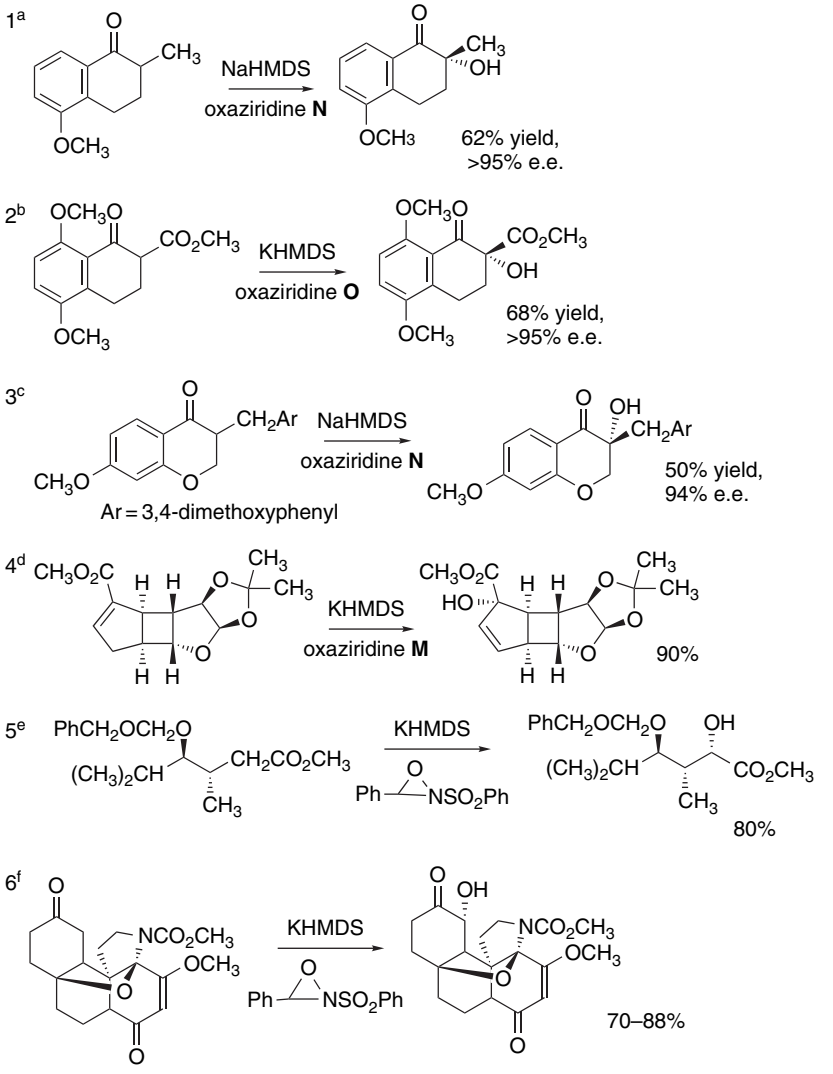


Scheme 12.21 gives some examples of enolate oxidation using *N*-sulfonyloxaziridines. Entries 1 to 3 are examples of enantioselective oxidations using chiral oxaziridines with racemic reactants. In Entry 4, the stereoselectivity is presumably controlled by the reactant shape. The analog with all *cis* stereochemistry at the cyclobutane ring also gave oxidation from the less hindered face of the molecule. Entry 5 is an example of diastereoselective oxidation. The observed *syn* selectivity is consistent with reactant conformation being the controlling factor in reagent approach.



251. F. A. Davis, L. C. Vishwakarma, J. M. Billmers, and J. Finn, *J. Org. Chem.*, **49**, 3241 (1984); L. C. Vishwakarma, O. D. Stringer, and F. A. Davis, *Org. Synth.*, **66**, 203 (1988).
252. F. A. Davis, A. C. Sheppard, B.-C. Chen, and M. S. Haque, *J. Am. Chem. Soc.*, **112**, 6679 (1990).
253. D. A. Evans, M. M. Morrissey, and R. L. Dorow, *J. Am. Chem. Soc.*, **107**, 4346 (1985).
254. F. A. Davis and B.-C. Chen, *Chem. Rev.*, **92**, 919 (1992).

Scheme 12.21. Oxidation of Enolates by Oxaziridines

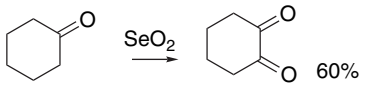


a. F. A. Davis and M. C. Weismiller, *J. Org. Chem*., **55**, 3715 (1990).
b. F. A. Davis, A. Kumar, and B.-C. Chen, *Tetrahedron Lett*., **32**, 867 (1991).
c. F. A. Davis and B.-C. Chen, *J. Org. Chem*., **58**, 1751 (1993).
d. A. B. Smith, III, G. A. Sulikowski, M. M. Sulikowsii, and K. Fujimoto, *J. Am. Chem. Soc*., **114**, 2567 (1992).
e. S. Hanessian, Y. Gai, and W. Wang, *Tetrahedron Lett*., **37**, 7473 (1996).
f. M. A. Tius and M. A. Kerr, *J. Am. Chem. Soc*., **114**, 5959 (1992).

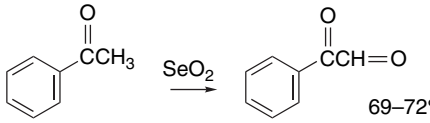
Both the regio- and stereochemistry of Entry 6 are of interest. The regioselectivity is imposed by the rigid ring geometry, which favors enolization at the observed position. Inspection of a molecular model also shows that α-face of the enolate is more accessible.

12.5.3. Oxidation with Other Reagents

Selenium dioxide can be used to oxidize ketones and aldehydes to α-dicarbonyl compounds. The reaction often gives high yields of products when there is a single type of CH_2 group adjacent to the carbonyl group. In unsymmetrical ketones, oxidation usually occurs at the CH_2 that is most readily enolized.[255]

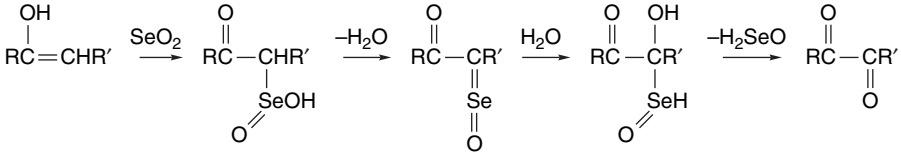


Ref. 256

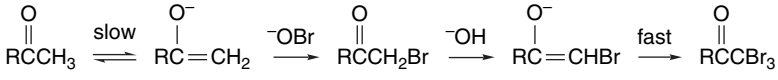


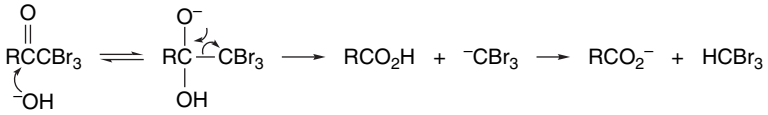
Ref. 257

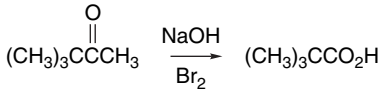
The oxidation is regarded as taking place by an electrophilic attack of selenium dioxide (or selenous acid, H_2SeO_3, the hydrate) on the enol of the ketone or aldehyde. This is followed by hydrolytic elimination of the selenium.[258]



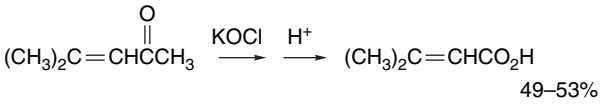
Methyl ketones are degraded to the next lower carboxylic acid by reaction with hypochlorite or hypobromite ions. The initial step in these reactions involves base-catalyzed halogenation. The α-haloketones are more reactive than their precursors, and rapid halogenation to the trihalo compound results. Trihalomethyl ketones are susceptible to alkaline cleavage because of the inductive stabilization provided by the halogen atoms.







Ref. 259



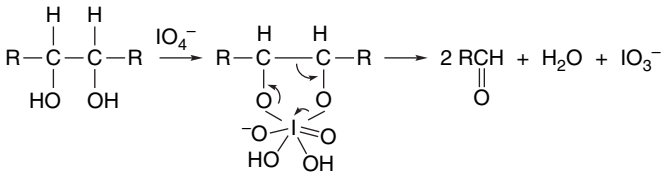
Ref. 260

255. E. N. Trachtenberg, in *Oxidation*, Vol. l, R. L. Augustine, ed., Marcel Dekker, New York, 1969, Chap. 3.
256. C. C. Hach, C. V. Banks, and H. Diehl, *Org. Synth.*, **IV**, 229 (1963).
257. H. A. Riley and A. R. Gray, *Org. Synth.*, **II**, 509 (1943).
258. K. B. Sharpless and K. M. Gordon, *J. Am. Chem. Soc.*, **98**, 300 (1976).
259. L. T. Sandborn and E. W. Bousquet, *Org. Synth.*, **1**, 512 (1932).
260. L. I. Smith, W. W. Prichard, and L. J. Spillane, *Org. Synth.*, **III**, 302 (1955).

12.6. Selective Oxidative Cleavages at Functional Groups

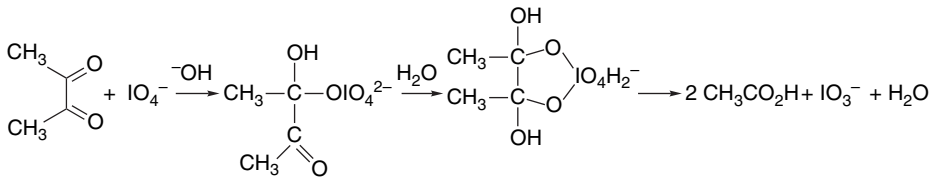
12.6.1. Cleavage of Glycols

As discussed in connection with cleavage of double bonds by permanganate-periodate or osmium tetroxide–periodate (see p. 1127), the glycol unit is susceptible to mild oxidative cleavage. The most commonly used reagent for this oxidative cleavage is the periodate ion.[261] The fragmentation is believed to occur via a cyclic adduct of the glycol and the oxidant.



Structural features that retard formation of the cyclic intermediate decrease the reaction rate. For example, *cis*-1,2-dihydroxycyclohexane is substantially more reactive than the *trans* isomer.[262] Glycols in which the geometry of the molecule precludes the possibility of a cyclic intermediate are essentially inert to periodate.

Certain other combinations of adjacent functional groups are also cleaved by periodate. Diketones are cleaved to carboxylic acids, and it is proposed that a reactive cyclic intermediate is formed by nucleophilic attack on the diketone.[263]

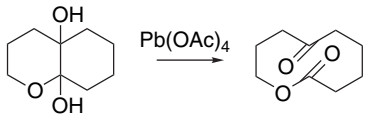


α-Hydroxy ketones and α-amino alcohols are also subject to oxidative cleavage, presumably by a similar mechanism.

Lead tetraacetate is an alternative reagent to periodate for glycol cleavage. It is particularly useful for glycols that have low solubility in the aqueous media used for periodate reactions. A cyclic intermediate is suggested by the same kind of stereochemistry-reactivity relationship discussed for periodate.[264] Unlike periodate, however, glycols that cannot form cyclic intermediates are eventually oxidized. For example, *trans*-9,10-dihydroxydecalin is oxidized, but the rate is 100 times less than for the *cis* isomer.[265] Thus, whereas a cyclic mechanism appears to provide the lowest-energy pathway for this oxidative cleavage, it is not the only possible mechanism. Both

261. C. A. Bunton, in *Oxidation in Organic Chemistry*, Part A, K. B. Wiberg, ed., Academic Press, New York, 1965, pp. 367–388; A. S. Perlin, in *Oxidation*, Vol. 1, R. L. Augustine, ed., Marcel Dekker, New York, 1969, pp. 189–204.
262. C. C. Price and M. Knell, *J. Am. Chem. Soc*., **64**, 552 (1942).
263. C. A. Bunton and V. J. Shiner, *J. Chem. Soc*., 1593 (1960).
264. C. A. Bunton, in *Oxidation in Organic Chemistry*, K. Wiberg, ed., Academic Press, New York, 1965, pp. 398–405; W. S. Trahanovsky, J. R. Gilmore, and P. C. Heaton, *J. Org. Chem*., **38**, 760 (1973).
265. R. Criegee, E. Hoeger, G. Huber, P. Kruck, F. Marktscheffel, and H. Schellenberger, *Liebigs Ann. Chem*., **599**, 81 (1956).

the periodate cleavage and lead tetraacetate oxidation can be applied synthetically to the generation of medium-sized rings when the glycol is at the junction of two rings.



Ref. 266

12.6.2. Oxidative Decarboxylation

Carboxylic acids are oxidized by lead tetraacetate. Decarboxylation occurs and the product may be an alkene, alkane or acetate ester, or under modified conditions a halide. A free radical mechanism operates and the product composition depends on the fate of the radical intermediate.[267] The reaction is catalyzed by cupric salts, which function by oxidizing the intermediate radical to a carbocation (Step 3b in the mechanism). Cu(II) is more reactive than $Pb(OAc)_4$ in this step.

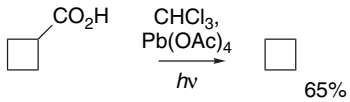
$$Pb(OAc)_4 + RCO_2H \rightleftharpoons RCO_2Pb(OAc)_3 + CH_3CO_2H \quad (1)$$

$$RCO_2Pb(OAc)_3 \longrightarrow R\cdot + CO_2 + Pb(OAc)_3 \quad (2)$$

$$R\cdot + Pb(OAc)_4 \longrightarrow R^+ + Pb(OAc)_3 + CH_3CO_2^- \quad (3a)$$

$$R\cdot + Pb(OAc)_3 \xrightarrow[Cu(II)]{\text{and}} R^+ + Cu(I) \quad (3b)$$

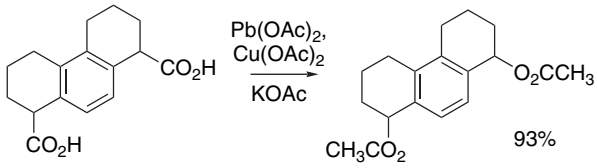
Alkanes are formed when the radical intermediate abstracts hydrogen from solvent faster than it is oxidized to the carbocation. This reductive step is promoted by good hydrogen donor solvents. It is also more prevalent for primary alkyl radicals because of the higher activation energy associated with formation of primary carbocations. The most favorable conditions for alkane formation involve photochemical decomposition of the carboxylic acid in chloroform, which is a relatively good hydrogen donor.



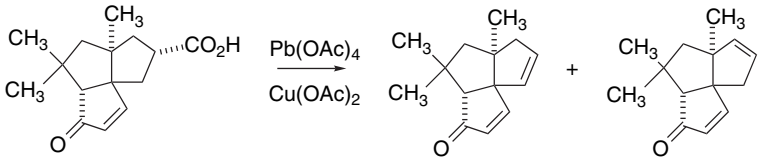
Ref. 268

Normally, the dominant products are the alkene and acetate ester, which arise from the carbocation intermediate by, respectively, elimination of a proton and capture of an acetate ion.[269]

266. T. Wakamatsu, K. Akasaka, and Y. Ban, *Tetrahedron Lett*., 2751, 2755 (1977).
267. R. A. Sheldon and J. K. Kochi, *Org. React*., **19**, 279 (1972).
268. J. K. Kochi and J. D. Bacha, *J. Org. Chem*., **33**, 2746 (1968).
269. J. D. Bacha and J. K. Kochi, *Tetrahedron*, **24**, 2215 (1968).

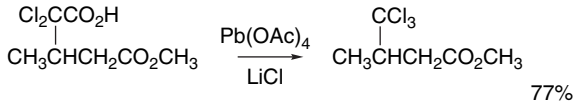


Ref. 270



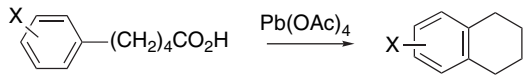
Ref. 271

In the presence of lithium chloride, the product is the corresponding chloride.[272]



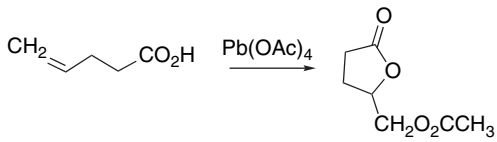
Ref. 273

5-Arylpentanoic acids give tetrahydronaphthalenes, a reaction that is consistent with a radical cyclization.



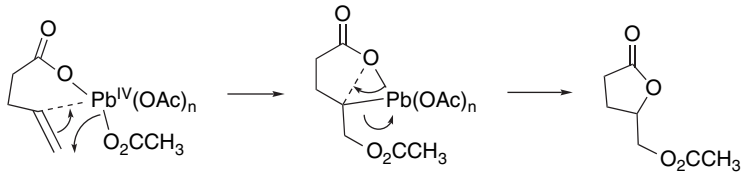
Ref. 274

On the other hand, γ, δ-unsaturated acids give lactones that involve cyclization without decarboxylation.



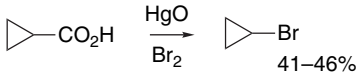
Ref. 275

These products can be formed by a ligand transfer from an intermediate in which the double bond is associated with the Pb.



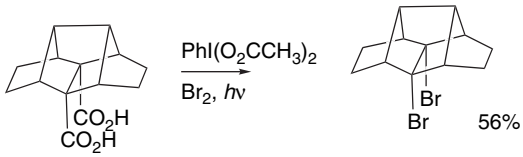
[270] P. Caluwe and T. Pepper, *J. Org. Chem*., **53**, 1786 (1988).
[271] D. D. Sternbach, J. W. Hughes, D. E. Bardi, and B. A. Banks, *J. Am. Chem. Soc*., **107**, 2149 (1985).
[272] J. K. Kochi, *J. Org. Chem*., **30**, 3265 (1965).
[273] S. E. de Laszlo and P. G. Williard, *J. Am. Chem. Soc*., **107**, 199 (1985).
[274] D. I. Davies and C. Waring, *J. Chem. Soc. C*, 1865 (1968).
[275] M. G. Moloney, E. Nettleton, and K. Smithies, *Tetrahedron Lett*., **43**, 907 (2002).

A related method for conversion of carboxylic acids to bromides with decarboxylation is the *Hunsdiecker reaction*.[276] The usual method for carrying out this transformation involves heating the carboxylic acid with mercuric oxide and bromine.

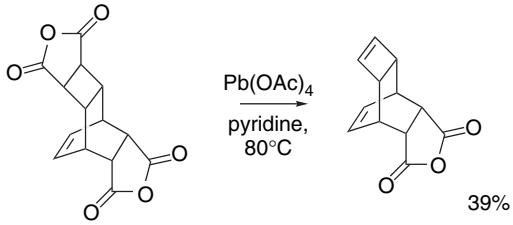


Ref. 277

The overall transformation can also be accomplished by reaction of thallium(I) carboxylate with bromine.[278] Phenyliodonium diacetate and bromine also lead to brominative decarboxylation.[279]

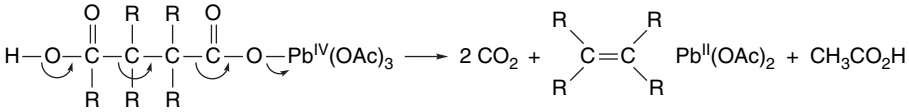


1,2-Dicarboxylic acids undergo *bis*-decarboxylation on reaction with lead tetraacetate to give alkenes. This reaction has been of occasional use for the synthesis of strained alkenes.

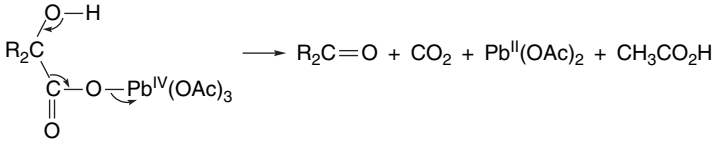


Ref. 280

The reaction can occur by a concerted fragmentation process initiated by a two-electron oxidation.

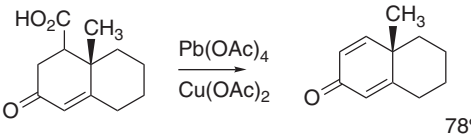


A concerted mechanism is also possible for α-hydroxycarboxylic acids, and these compounds readily undergo oxidative decarboxylation to ketones.[281]



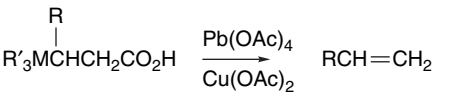
276. C. V. Wilson, *Org. React*., **9**, 332 (1957); R. A. Sheldon and J. Kochi, *Org. React*., **19**, 326 (1972).
277. J. S. Meek and D. T. Osuga, *Org. Synth*., **V**, 126 (1973).
278. A. McKillop, D. Bromley, and E. C. Taylor, *J. Org. Chem*., **34**, 1172 (1969).
279. P. Camps, A. E. Lukach, X. Pujol, and S. Vazquez, *Tetrahedron*, **56**, 2703 (2000).
280. E. Grovenstein, Jr., D. V. Rao, and J. W. Taylor, *J. Am. Chem. Soc*., **83**, 1705 (1961).
281. R. Criegee and E. Büchner, *Chem. Ber*., **73**, 563 (1940).

γ-Ketocarboxylic acids are oxidatively decarboxylated to enones.[282] This reaction is presumed to proceed through the usual oxidative decarboxylation, with the carbocation intermediate being efficiently deprotonated because of the developing conjugation.



78% Ref. 119

Oxidation of β-silyl and β-stannyl acids leads to loss of the substituent and alkene formation.[283]



12.7. Oxidations at Unfunctionalized Carbon

Attempts to achieve selective oxidations of hydrocarbons or other compounds when the desired site of attack is remote from an activating functional group are faced with several difficulties. With powerful transition-metal oxidants, the initial oxidation products are almost always more susceptible to oxidation than the starting material. When a hydrocarbon is oxidized, it is likely to be oxidized to a carboxylic acid, with chain cleavage by successive oxidation of alcohol and carbonyl intermediates. There are a few circumstances under which oxidations of hydrocarbons can be synthetically useful processes. One group involves catalytic industrial processes. Much effort has been expended on the development of selective catalytic oxidation processes and several have economic importance. We focus on several reactions that are used on a laboratory scale.

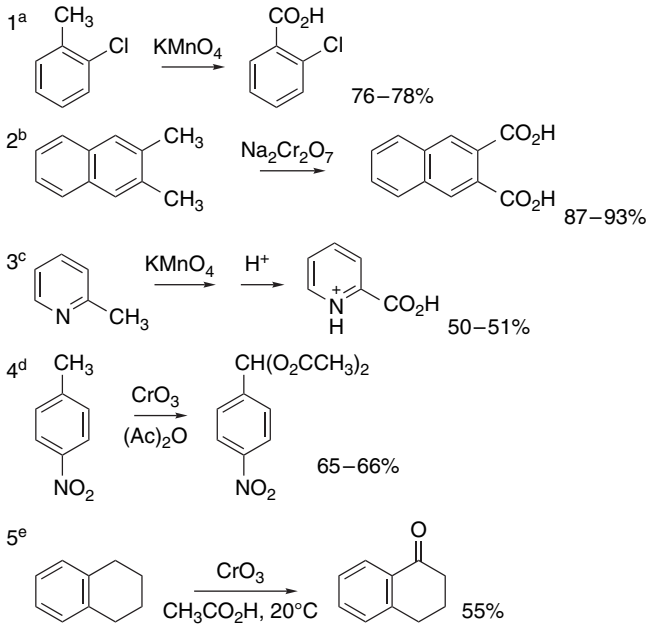
The most general hydrocarbon oxidation is the oxidation of side chains on aromatic rings. Two factors contribute to making this a high-yield procedure, despite the use of strong oxidants. First, the benzylic position is susceptible to hydrogen abstraction by the oxidants.[284] Second, the aromatic ring is resistant to attack by Mn(VII) and Cr(VI) reagents that oxidize the side chain.

Scheme 12.22 provides some examples of the oxidation of aromatic alkyl substituents to carboxylic acid groups. Entries 1 to 3 are typical oxidations of aromatic methyl groups to carboxylic acids. Entries 4 and 5 bring the carbon adjacent to the aromatic ring to the carbonyl oxidation level.

Selective oxidations are possible for certain bicyclic hydrocarbons.[285] Here, the bridgehead position is the preferred site of initial attack because of the order of reactivity of C−H bonds, which is 3° > 2° > 1°. The tertiary alcohols that are the initial oxidation products are not easily further oxidized. The geometry of the bicyclic rings (*Bredt's rule*) prevents both dehydration of the tertiary bridgehead alcohols and further oxidation to ketones. Therefore, oxidation that begins at a bridgehead position

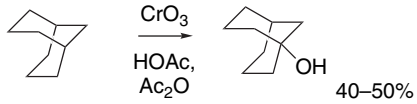
282. J. E. McMurry and L. C. Blaszczak, *J. Org. Chem.*, **39**, 2217 (1974).
283. H. Nishiyama, M. Matsumoto, H. Arai, H. Sakaguchi, and K. Itoh, *Tetrahedron Lett.*, **27**, 1599 (1986).
284. K. A. Gardner, L. L. Kuehnert, and J. M. Mayer, *Inorg. Chem.*, **36**, 2069 (1997).
285. R. C. Bingham and P. v. R. Schleyer, *J. Org. Chem.*, **36**, 1198 (1971).

Scheme 12.22. Side Chain Oxidation of Aromatic Compounds

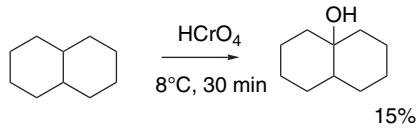


a. H. T. Clarke and E. R. Taylor, *Org. Synth*., **II**, 135 (1943).
b. L. Friedman, *Org. Synth*., **43**, 80 (1963); L. Friedman, D. L. Fishel, and H. Shechter, *J. Org. Chem*., **30**, 1453 (1965).
c. A. W. Singer and S. M. McElvain, *Org. Synth*., **III**, 740 (1955).
d. T. Nishimura, *Org. Synth*., **IV**, 713 (1963).
e. J. W. Burnham, W. P. Duncan, E. J. Eisenbraun, G. W. Keen, and M. C. Hamming, *J. Org. Chem*., **39**, 1416 (1974).

stops at the alcohol stage. Chromic acid oxidation has been the most useful reagent for functionalizing unstrained bicyclic hydrocarbons. The reaction fails for strained bicyclic compounds such as norbornane because the reactivity of the bridgehead position is lowered by the unfavorable energy of radical or carbocation intermediates.



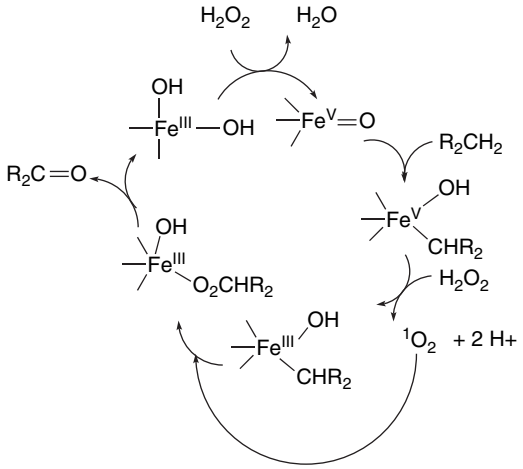
Other successful selective oxidations of hydrocarbons by Cr(VI) have been reported—for example, the oxidation of *cis*-decalin to the corresponding alcohol—but careful attention to reaction conditions is required.



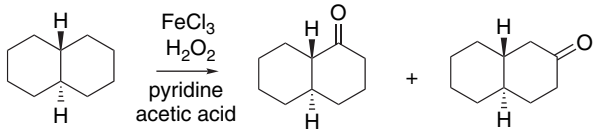
Ref. 286

286. K. B. Wiberg and G. Foster, *J. Am. Chem. Soc*., **83**, 423 (1961).

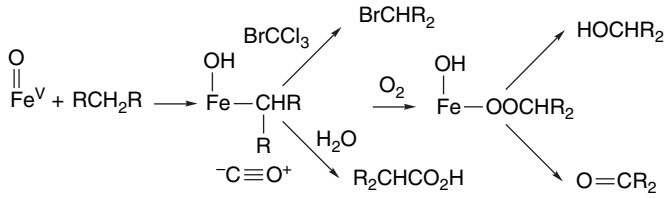
Interesting hydrocarbon oxidations have been observed using Fe(II) catalysts with oxygen or hydrogen peroxide as the oxidant. These catalytic systems have become known as "Gif chemistry" after the location of their discovery in France.[287] An improved system involving Fe(III), picolinic acid, and H_2O_2 has been developed. The reactive species generated in these systems is believed to be at the Fe(V)=O oxidation level.[288] The key step is hydrogen abstraction from the hydrocarbon by this Fe(V)=O intermediate.



Oxidation of *trans*-decalin leads to a mixture of 1- and 2-*trans*-decalone.[289]



The initial intermediates containing C−Fe bonds can be diverted by reagents such as $CBrCl_3$ or CO, among others.[290]



[287] D. H. R. Barton and D. Doller, *Acc. Chem. Res*., **25**, 504 (1992); D. H. R. Barton, *Chem. Soc. Rev*., **25**, 237 (1996); D. H. R. Barton, *Tetrahedron*, **54**, 5805 (1998).

[288] D. H. R. Barton, S. D. Beviere, W. Chavasiri, E. Csuhai, D. Doller, and W. G. Liu, *J. Am. Chem. Soc*., **114**, 2147 (1992).

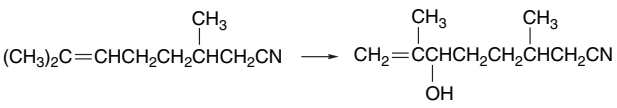
[289] U. Schuchardt, M. J. D. M. Jannini, D. T. Richens, M. C. Guerreiro, and E. V. Spinace, *Tetrahedron*, **57**, 2685 (2001).

[290] D. H. R. Barton, E. Csuhai, and D. Doller, *Tetrahedron Lett*., **33**, 3413 (1992); D. H. R. Barton, E. Csuhai, and D. Doller, *Tetrahedron Lett*., **33**, 4389 (1992).

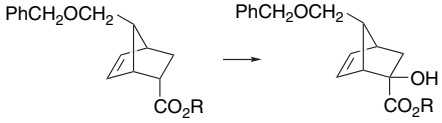
(*References for these problems will be found on page 1290.*)

12.1. Indicate an appropriate oxidant for carrying out the following transformations.

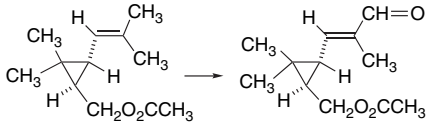
(a)



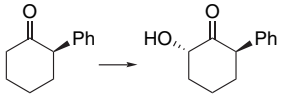
(b)



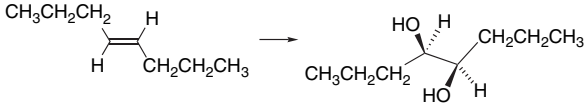
(c)



(d)

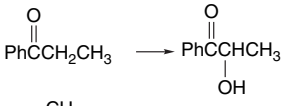


(e)

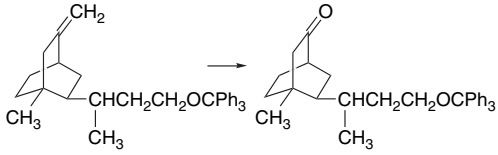


(racemic)

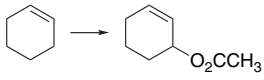
(f)



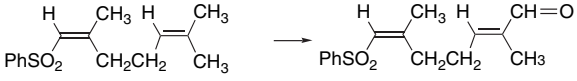
(g)



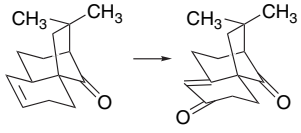
(h)



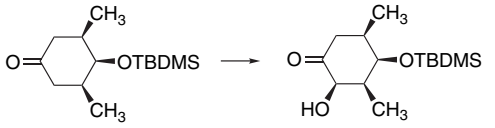
(i)



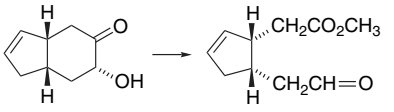
(j)



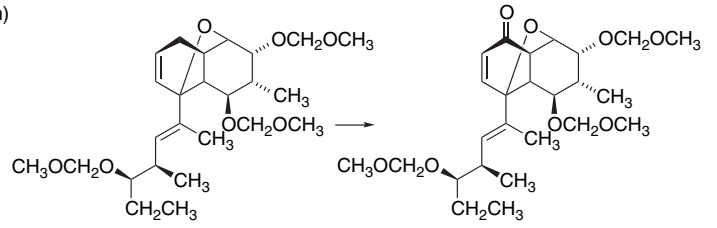
(k)



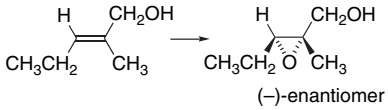
(l)



(m)

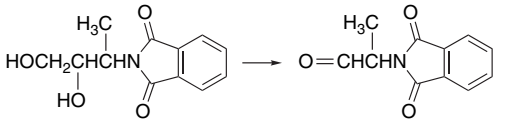


(n)

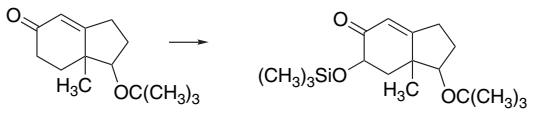


(–)-enantiomer

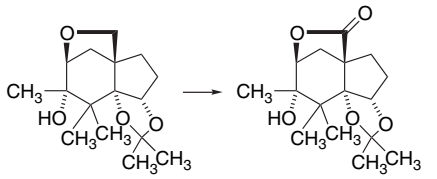
(o)



(p)

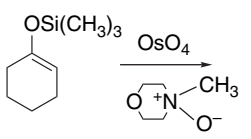


(q)

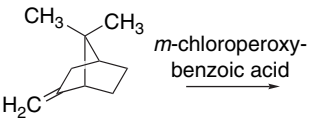


12.2. Predict the products of the following reactions. Be careful to consider all stereochemical aspects.

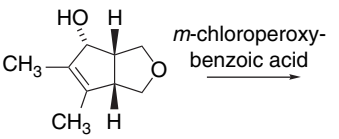
(a)



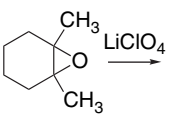
(b)

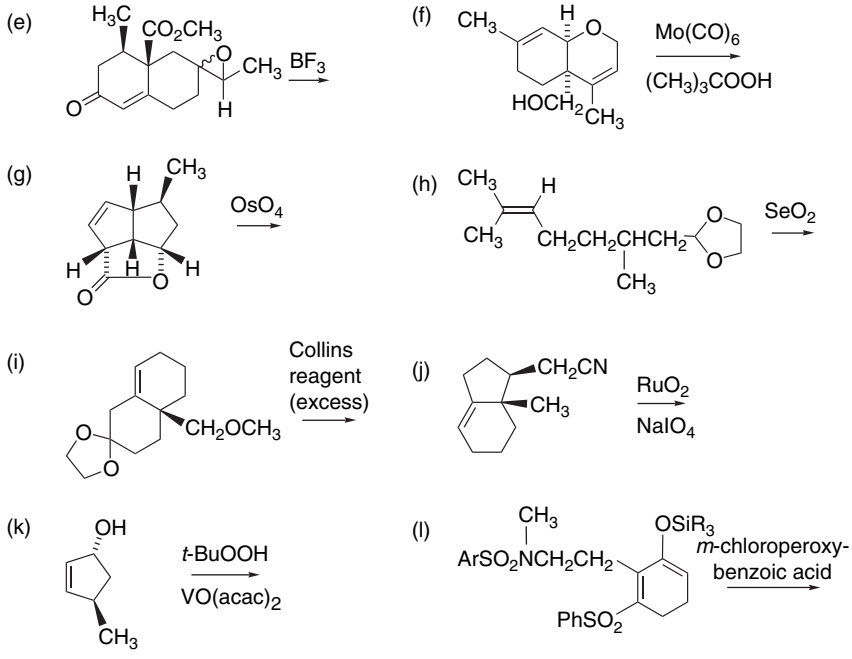


(c)



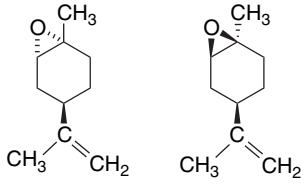
(d)



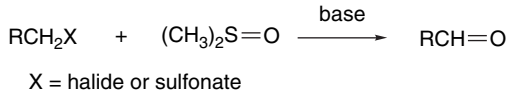


12.3. In chromic acid oxidation of stereoisomeric cyclohexanols, it is usually found that axial hydroxy groups react more rapidly than equatorial groups. For example, *trans*-4-*t*-butylcyclohexanol is less reactive (by a factor of 3.2) than the *cis* isomer. An even larger difference is noted with *cis*- and *trans*-3,3,5-trimethylcyclohexanol. The axial hydroxy in the *trans* isomer is 35 times more reactive than then equatorial hydroxy in the *cis* isomer, even though it is in a more hindered environment. A general relationship is found for pairs of epimeric cyclohexanols in that the ratio of the rates of the isomers is approximately equal to the equilibrium constant for equilibration of the isomers: $k_{ax}/k_{eq} \sim K_{ax/eq}$. Are these data compatible with the mechanism given on p. 1064? What additional details do these data provide about the reaction mechanism? Explain.

12.4. Predict the products from opening of the two stereoisomeric epoxides derived from limonene shown below by reaction with (a) acetic acid and (b) dimethylamine.

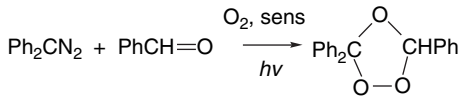


12.5. The direct oxidative conversion of primary halides and sulfonates to aldehydes can be carried out by reaction with DMSO under alkaline conditions. Formulate a mechanism for this reaction.

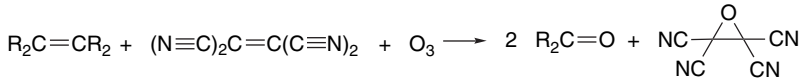


12.6. The following questions pertain to the details of mechanism of ozonolysis under modified conditions.

a. A method for synthesis of ozonides that involves no ozone has been reported. It consists of photosensitized oxidation of diazo compounds in the presence of an aldehyde. Suggest a mechanism for this reaction.

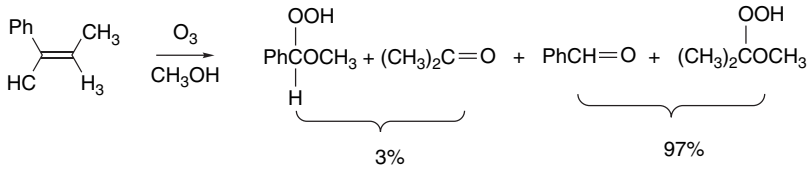


b. Overoxidation of carbonyl products during ozonolysis can be prevented by addition of tetracyanoethylene to the reaction mixture. The stoichiometry of the reaction is then:



Propose a mechanism that would account for the effect of tetracyanoethylene. Does your mechanism suggest that tetracyanoethylene would be a particularly effective alkene for this purpose? Explain.

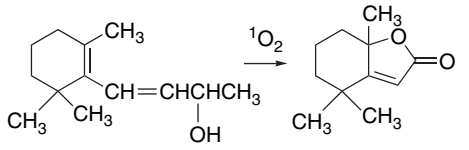
c. It has been found that when unsymmetrical alkenes are ozonized in methanol, there is often a large preference for one cleavage mode of the initial ozonide over the other. For example:



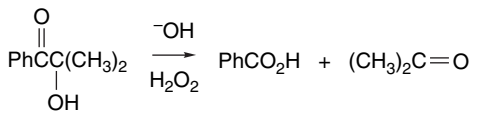
Account for this selectivity.

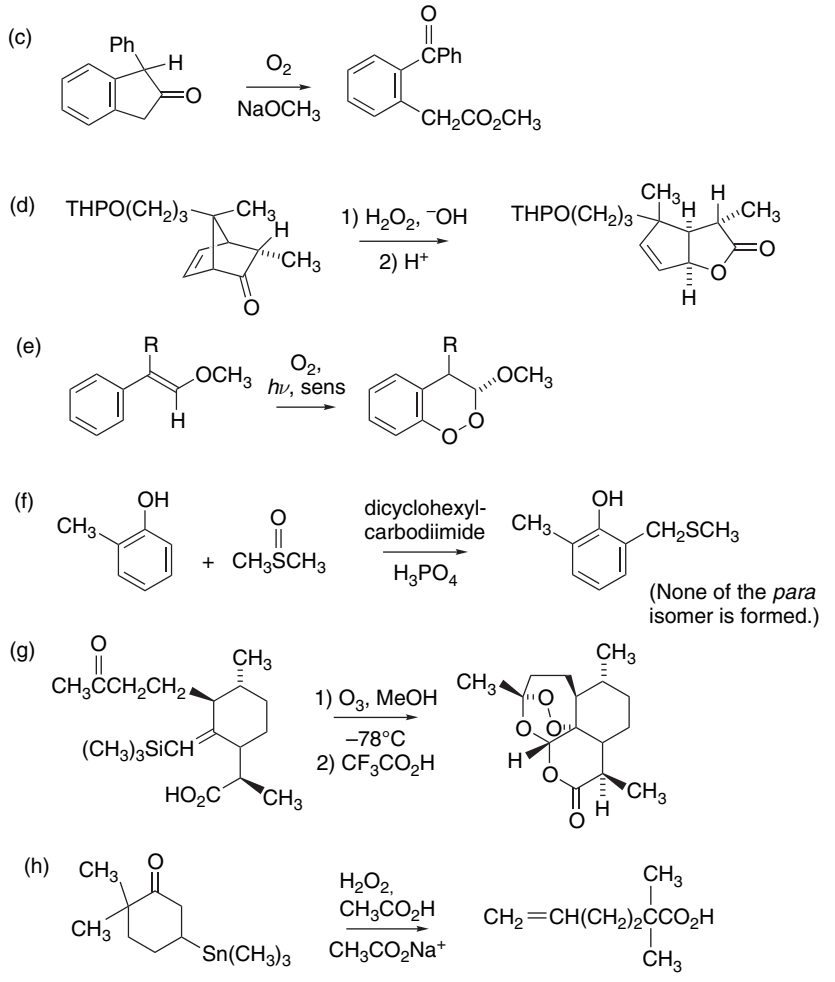
12.7. Suggest mechanisms by which the "abnormal" oxidations shown below could occur.

(a)

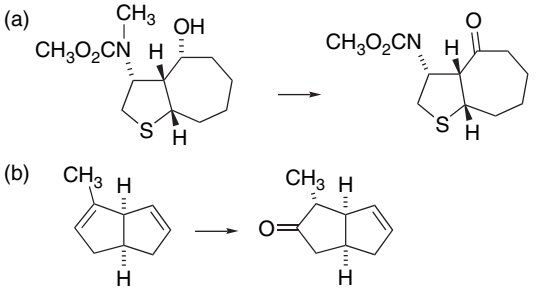


(b)

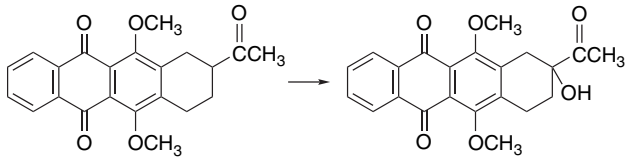




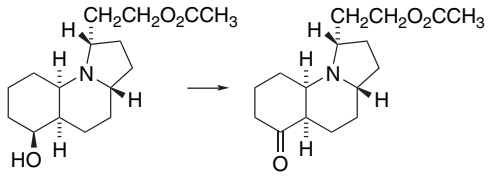
12.8. Indicate one or more satisfactory oxidants for effecting the following transformations. Each molecule poses issues of selectivity or the need to preserve a sensitive functional group. Select oxidants that can avoid the installation of protecting groups. In most cases, a one-pot reaction is possible, and in no case is a sequence of more than three steps required. Explain the reason for your choice of reagent(s).



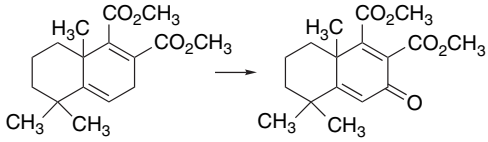
(c)



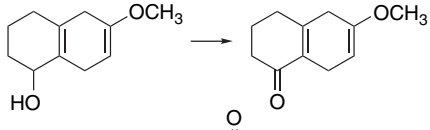
(d)



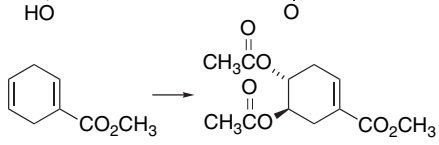
(e)



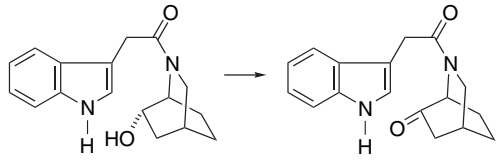
(f)



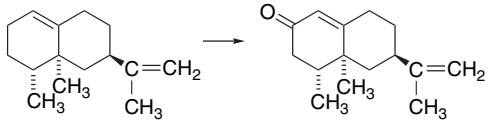
(g)



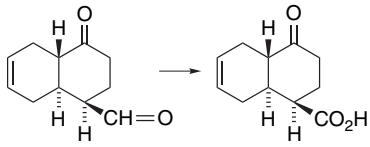
(h)



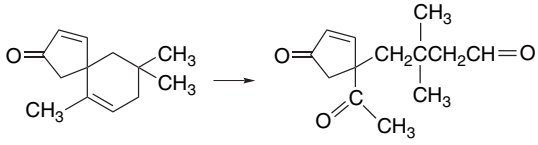
(i)



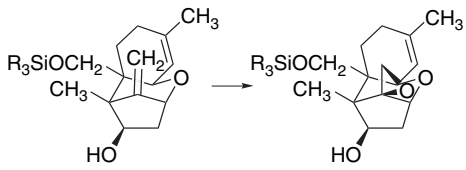
(j)



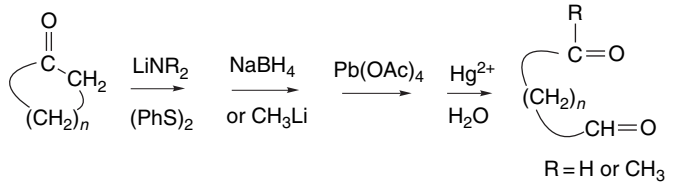
(k)



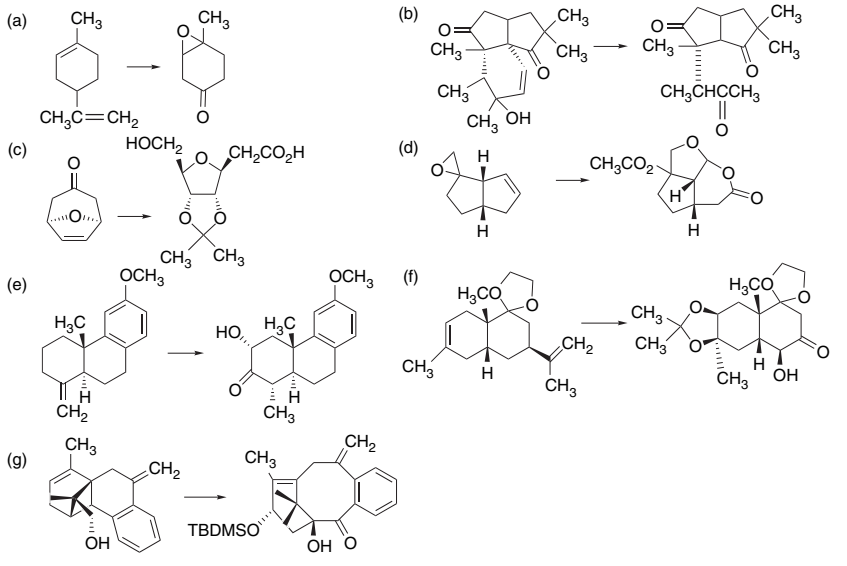
(l)



12.9. A method for oxidative cleavage of cyclic ketones involves a four-stage process. First, the ketone is converted to an α-phenylthio derivative (see Section 4.3.2). The ketone is then converted to an alcohol, either by reduction with $NaBH_4$ or by addition of an organolithium reagent. The alcohol is then treated with $Pb(OAc)_4$ to give an oxidation product in which the hydroxy group has been acetylated and an additional oxygen added to the β-thioalcohol. Aqueous hydrolysis of this intermediate in the presence of Hg^{2+} gives a dicarbonyl compound. Formulate likely structures for the products of each step in this sequence.

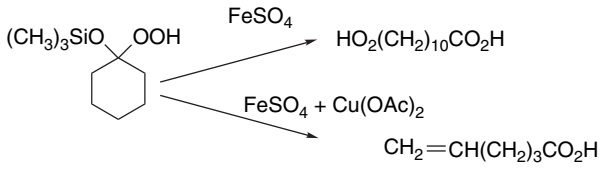


12.10. The transformations shown below have been carried out using reaction sequences involving several oxidation steps. Devise a series of steps that could accomplish these transformations and suggest reagents that would be suitable for each step. Some sequences may also require nonoxidative steps, such as introduction or removal of protecting groups.

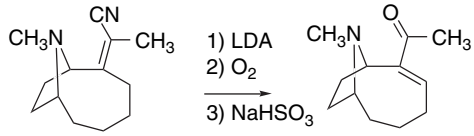


12.11. Provide mechanistic interpretations of the following reactions.

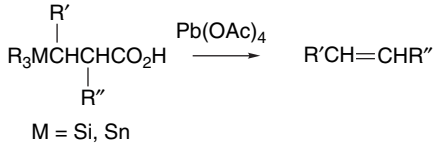
a. Account for the products formed under the following conditions. In particular, why does the inclusion of cupric acetate change the course of the reaction?



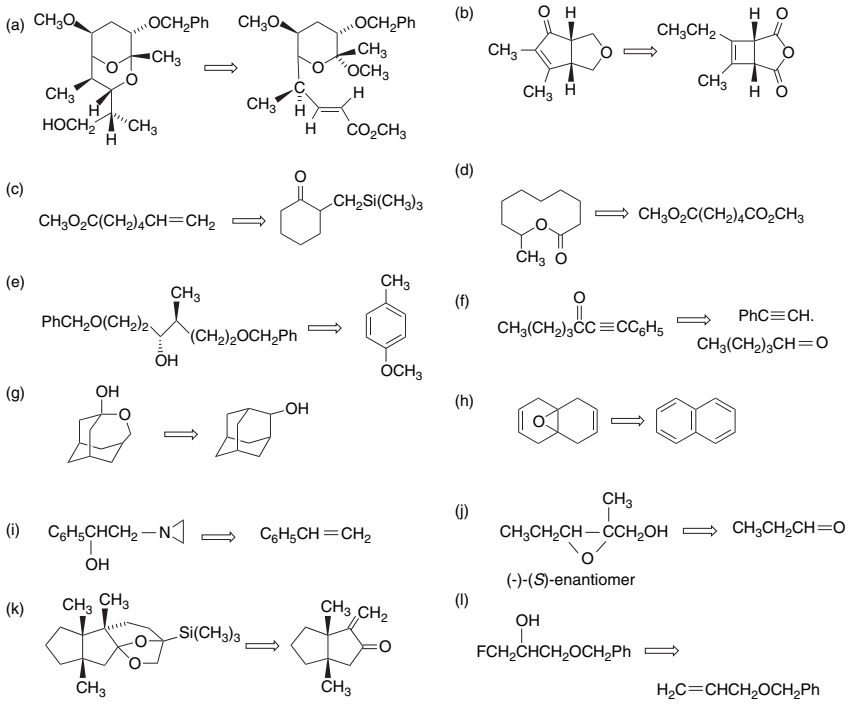
b. Account for this oxidative decyanation.

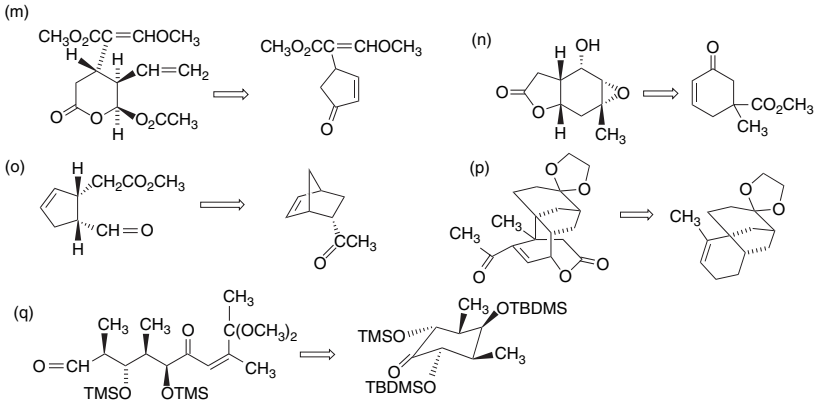


c. It is found that the oxidative decarboxylation of β-silyl and β-stannyl carboxylic acids is substantially accelerated by cupric acetate.

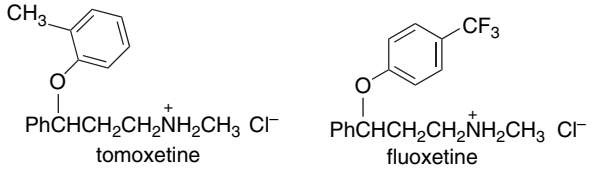


12.12. Use retrosynthetic analysis to devise a sequence of reactions that could accomplish the formation of the structure on the left from the potential precursor on the right.

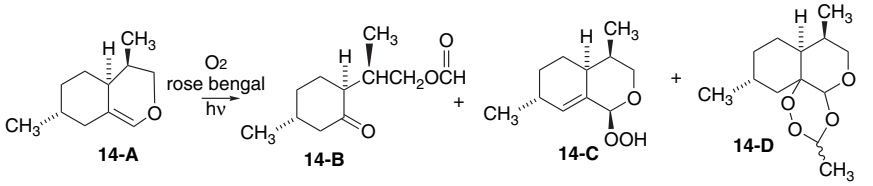




12.13. Tomoxetine and fluoxetine are antidepressants. Both enantiomers of each compound can be prepared enantiospecifically starting from cinnamyl alcohol. Give a reaction sequence that will accomplish this objective.



12.14. The irradiation of **14-A** in the presence of rose bengal and oxygen in methanol gives **14-B** as the only observable product (72% yield). When the irradiation is carried out in acetaldehyde as solvent, the yield of **14-B** is reduced to 54% and two additional products, **14-C** (19%) and **14-D** (17%), are formed. Account for the formation of each product.



12.15. Analyze the following data on the product ratios obtained in the epoxidation of 3-substituted cyclohexenes by dimethyldioxirane. What are the principal factors that determine the stereoselectivity?

Substituent	*trans:cis*[a]
OH	66:34[b]
OH	15:85
OCH_3	85:15
O_2CCH_3	62:38
CO_2CH_3	68:32
CO_2H	84:16

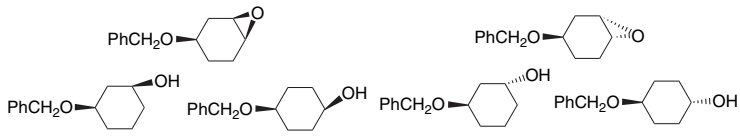
(*Continued*)

Substituent	*trans:cis*[a]
NHCOPh	3:97
Cl	90:10[c]
CF_3	90:10[c]
CH_3	47:53
$(CH_3)_2CHCH_2$	54:46
$(CH_3)_3C$	95:5[c]
Ph	85:15

a. Solvent is 9:1 CCl_4-acetone except as noted otherwise.
b. Solvent is 9:1 methanol-acetone.
c. Solvent is acetone.

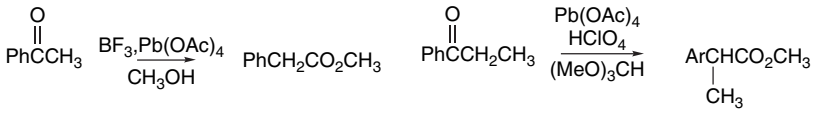
12.16. Offer a mechanistic explanation for the following observations.

a. A change from ether as solvent to pentane with 12-crown-4 reverses the stereoselectivity of $LiAlH_4$ reduction of *cis*-3-benzyloxycyclohexene oxide, but not the *trans* isomer.

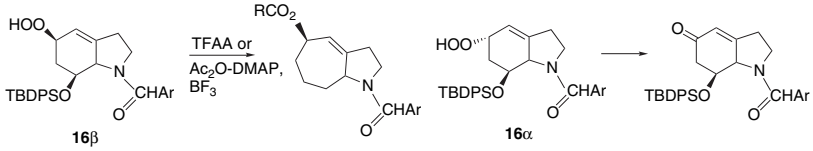


$LiAlH_4$-ether	2	98	97	3
$LiAlH_4$-pentane 12-crown-4	82	18	97	3

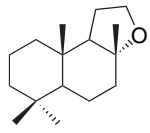
b. In the presence of a strong protic acid or a Lewis acid, acetophenones and propiophenones rearrange to arylalkanoic acid on reaction with $Pb(OAc)_4$.



c. Acylation leads to reaction of the hydroperoxides **16α** and **16β**, but the products are different. In **16β**, the vinyl substituent migrates giving ring expansion, whereas with **16α** an enone is formed.

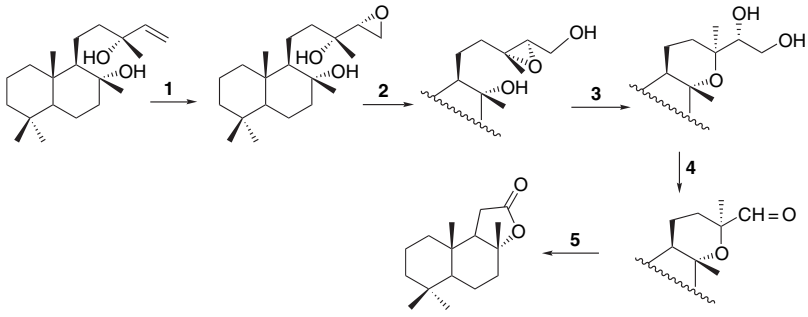


12.17. Various terpene-derived materials are important in the formulation of fragrances and flavors. One example is the tricyclic furan shown below, which is commercially used under the trademark Ambrox.® The synthetic sequences below have been developed to prepare related structures. Suggest reagents for each step in these sequences.

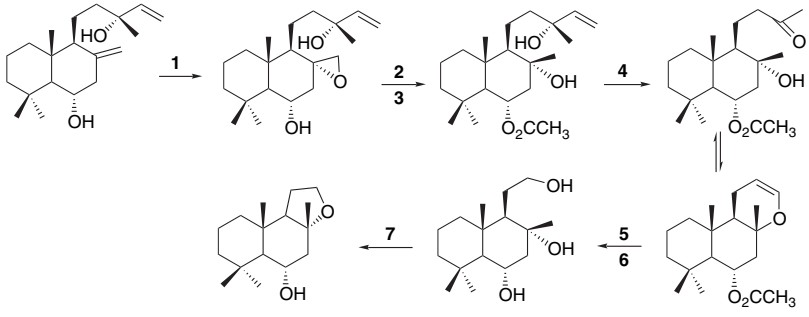


Ambrox^{R}

a. This sequence was developed to avoid the use of transition metal reagents and minimize by-products.



b. The following sequence led to the 6-α–hydroxy derivative.



12.18. The closely related enones **18-A** and **18-B** give different products when treated with $Pb(OAc)_4$ in CH_3CN. Formulate mechanisms to account for both products and identify the factor(s) that lead to the divergent structures.

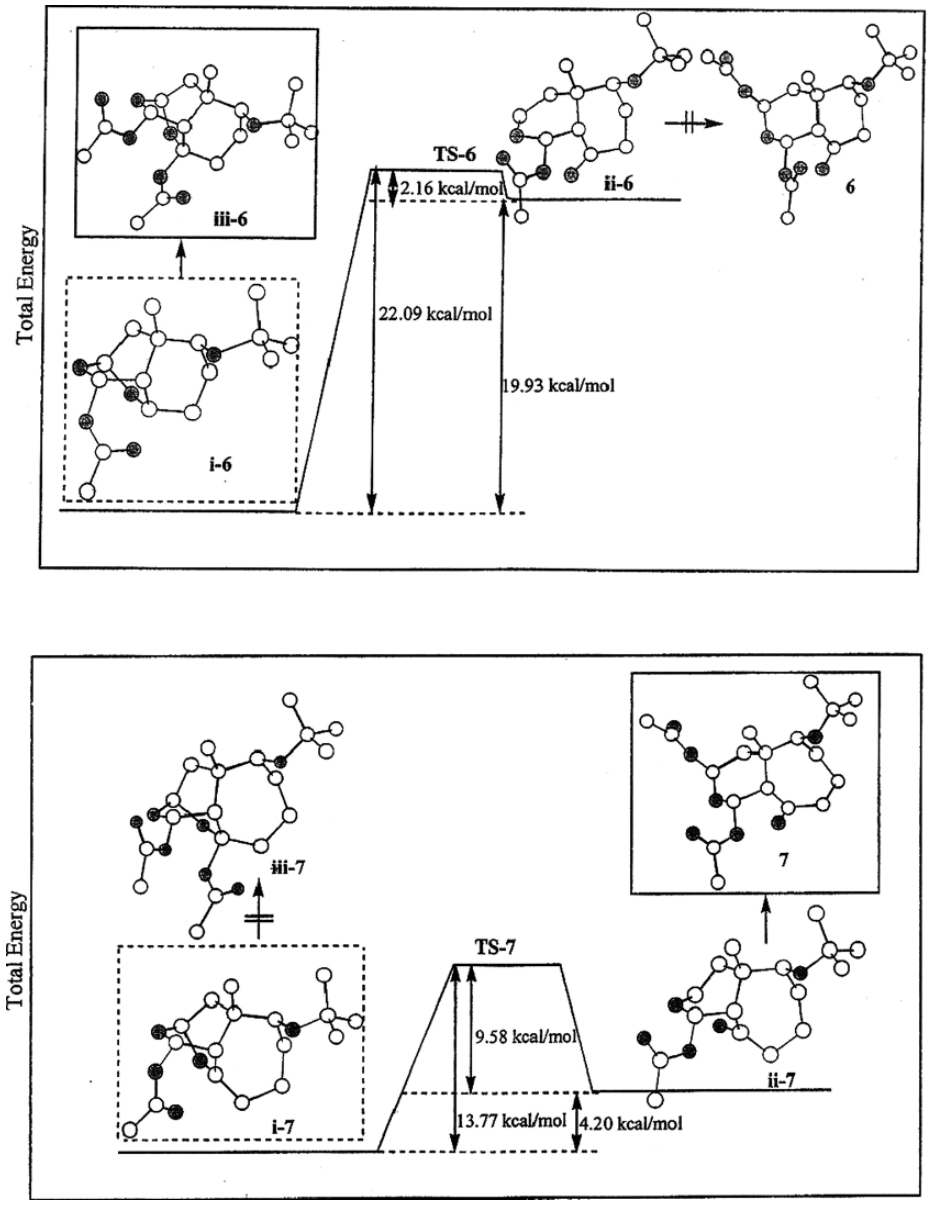
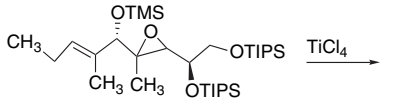


Fig. 12.P18. Comparison of the computed energy profiles for **18-A** and **18-B**. Reproduced from *J. Org. Chem*., **67**, 2447 (2002), by permission of the American Chemical Society.

12.19. Predict the structure and stereochemistry of the Lewis acid–catalyzed rearrangement of the following epoxides.

a.



b.