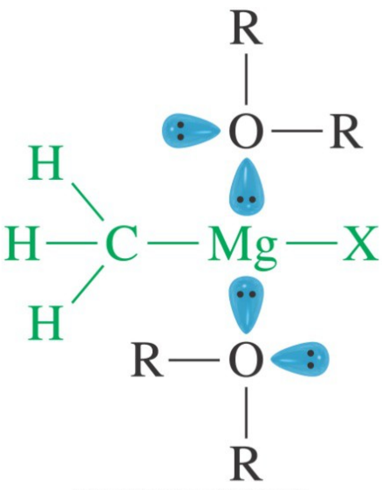
Organic Chemistry, 7th Edition
L. G. Wade, Jr.



Chapter 14

Ethers, Epoxides, and Sulfides

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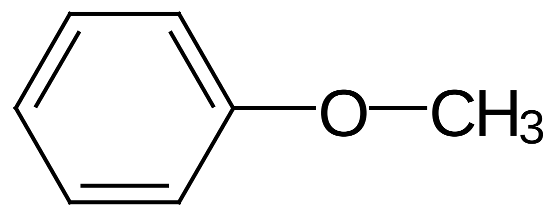
Ethers

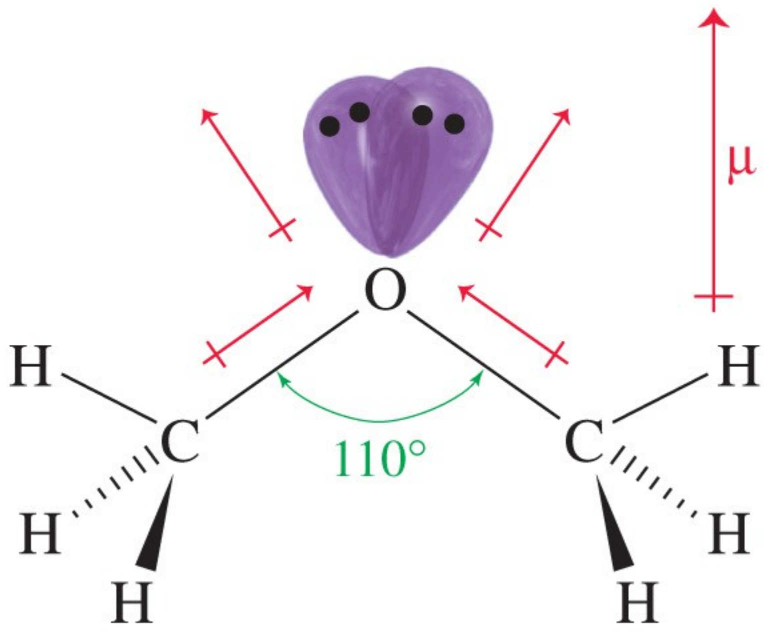
- Formula is R—O—R   where R and R are alkyl or aryl.
- Symmetrical or unsymmetrical

$CH_3—O—CH_3$



Structure and Polarity

- Oxygen is *sp*^{3} hybridized.
- Bent molecular geometry.
- C—O—C angles is 110°.
- Polar C—O bonds.
- Dipole moment of 1.3 D.

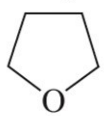


Boiling Points

Similar to alkanes of comparable molecular weight.

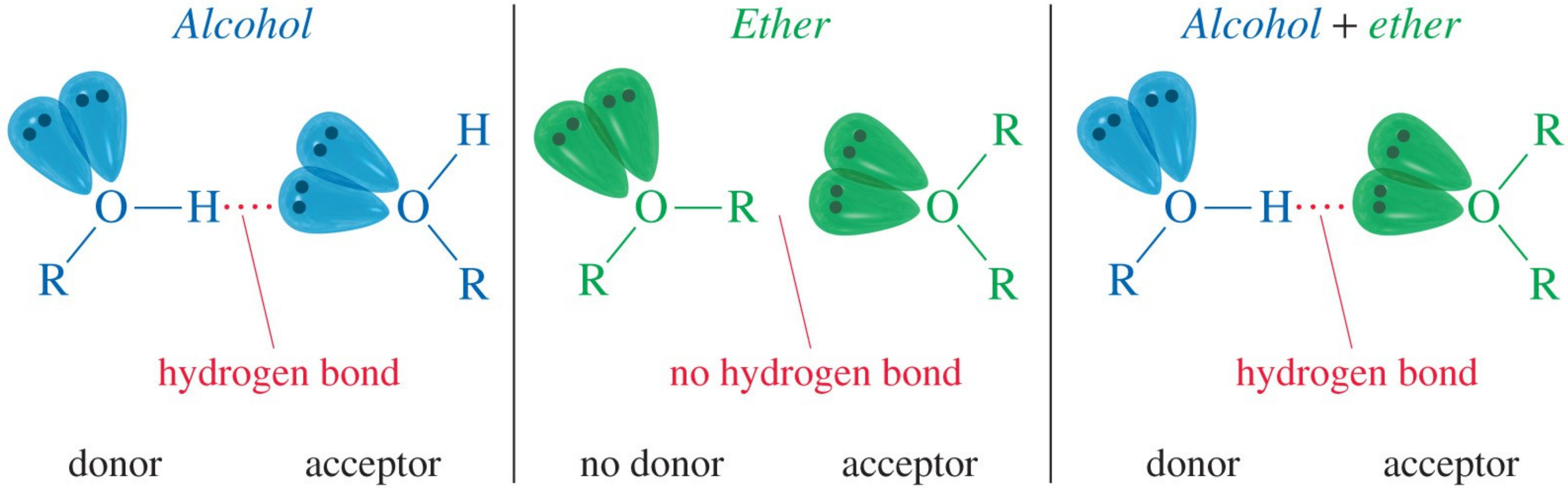
TABLE 14-1

Comparison of the Boiling Points of Ethers, Alkanes, and Alcohols of Similar Molecular Weights

Compound	Formula	MW	bp (°C)	Dipole Moment (D)
water	H_2O	18	100	1.9
ethanol	$CH_3CH_2—OH$	46	78	1.7
dimethyl ether	$CH_3—O—CH_3$	46	−25	1.3
propane	$CH_3CH_2CH_3$	44	−42	0.1
n-butanol	$CH_3CH_2CH_2CH_2—OH$	74	118	1.7
tetrahydrofuran		72	66	1.6
diethyl ether	$CH_3CH_2—O—CH_2CH_3$	74	35	1.2
pentane	$CH_3CH_2CH_2CH_2CH_3$	72	36	0.1

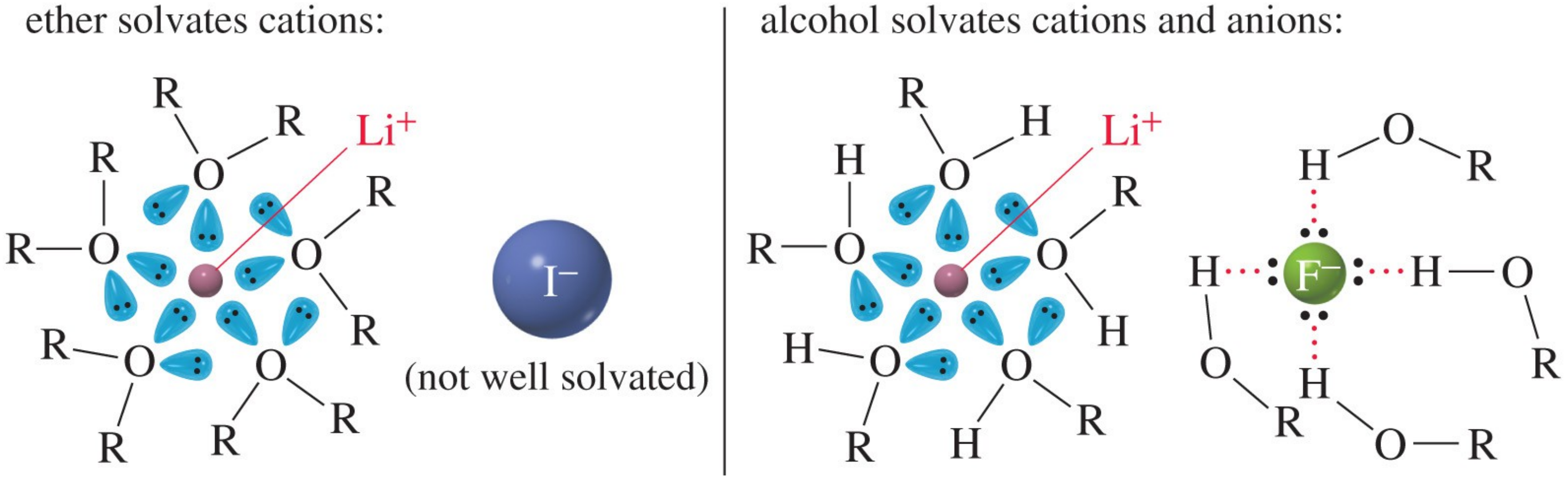
Note: The alcohols are hydrogen bonded, giving them much higher boiling points. The ethers have boiling points that are closer to those of alkanes with similar molecular weights.

Hydrogen Bond Acceptor



- Ethers cannot hydrogen-bond with other ether molecules.
- Molecules that cannot hydrogen-bond intermolecularly have a lower boiling point.
- Ether molecules can hydrogen-bond with water and alcohol molecules.

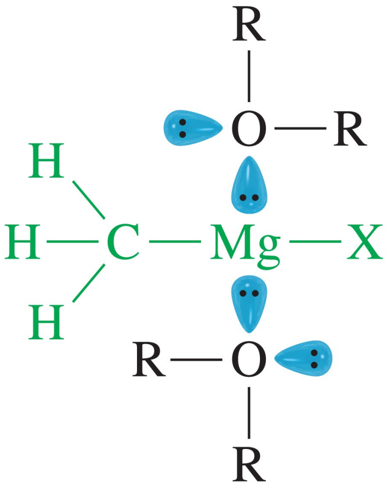
Solvation of Ions with Ether



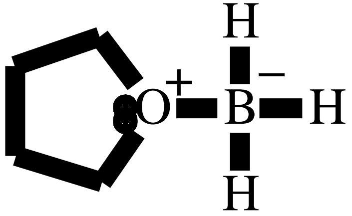
- An ionic substance such as lithium iodide is moderately soluble in ethers because the small lithium cation is strongly solvated by the ether's lone pairs of electrons.
- Unlike alcohols, ether cannot serve as hydrogen-bond donors, so they do not solvate small anions well.

Ether Complexes

- Grignard reagents: Complexation of an ether with a Grignard reagent stabilizes the reagent and helps keep it in solution.

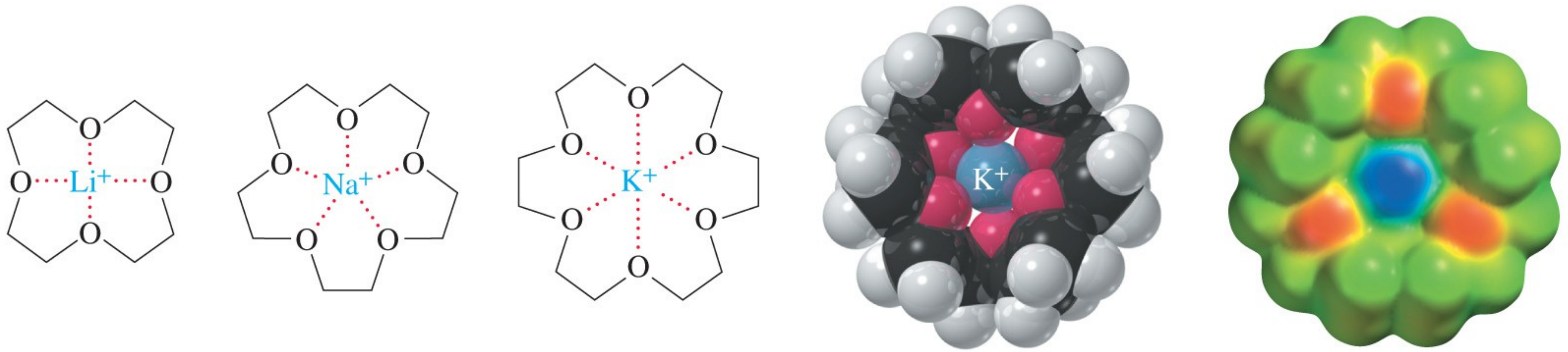


- Electrophiles: The ethers nonbonding electrons stabilize the borane (BH_3).



$BH_3 \bullet THF$

Crown Ether Complexes



12-crown-4 solvates Li^+ | 15-crown-5 solvates Na^+ | 18-crown-6 solvates K^+ | 18-crown-6 with K^+ solvated | EPM of 18-crown-6

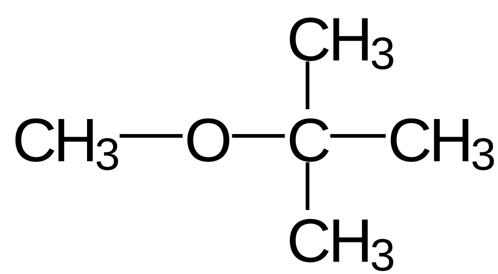
- Crown ethers can complex metal cations inside the ring.
- The size of the cation will determine the size of the ring needed.
- Complexation by crown ethers often allows polar inorganic salts to dissolve in nonpolar organic solvents.

Common Names of Ethers

- Name the two alkyl groups attached to the oxygen and add the word *ether*.
- Name the groups in alphabetical order
- Symmetrical: Use dialkyl or just alkyl.

$$CH_3CH_2—O—CH_2CH_3$$

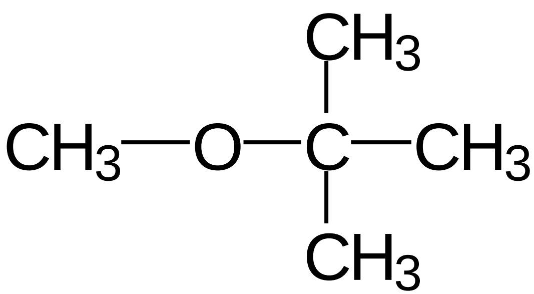
diethyl ether or
ethyl ether



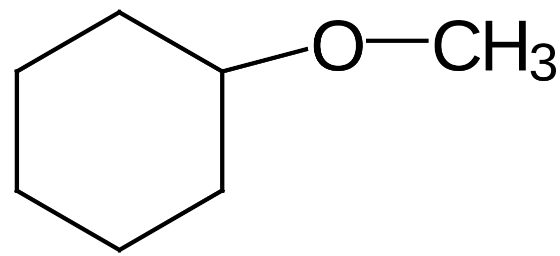
t-butyl methyl ether or
methyl *t*-butyl ether

IUPAC Names

- The more complex alkyl group is the alkane name. The small group (with the oxygen) becomes an "alkoxy" group.

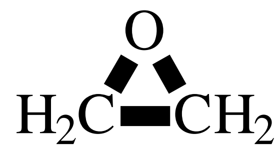


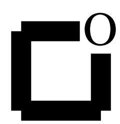
2-methyl-2-methoxypropane

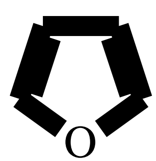


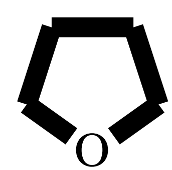
Methoxycyclohexane

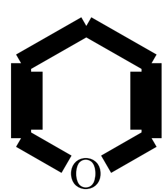
Cyclic Ethers

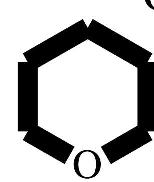
- Heterocyclic: Oxygen is part of the ring.
- Epoxides (oxiranes) 

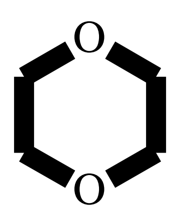
- Oxetanes 

- Furans 

(Oxolanes 

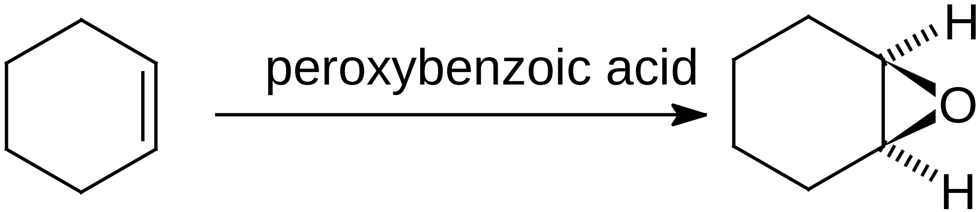
)
- Pyrans 

(Oxanes 

)
- Dioxanes 

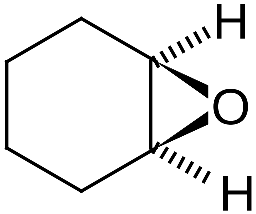
Epoxide Nomenclature

- Name the starting alkene and add “oxide”.



cyclohexene oxide

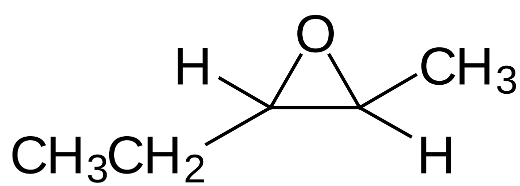
- The oxygen can be treated as a substituent (epoxy) on the compound. Use numbers to specify position.



1,2-epoxycyclohexane

Epoxide Nomenclature (Continued)

- The three-membered oxirane ring is the parent (oxygen is 1, the carbons are 2 and 3). Substituents are named in alphabetical order.

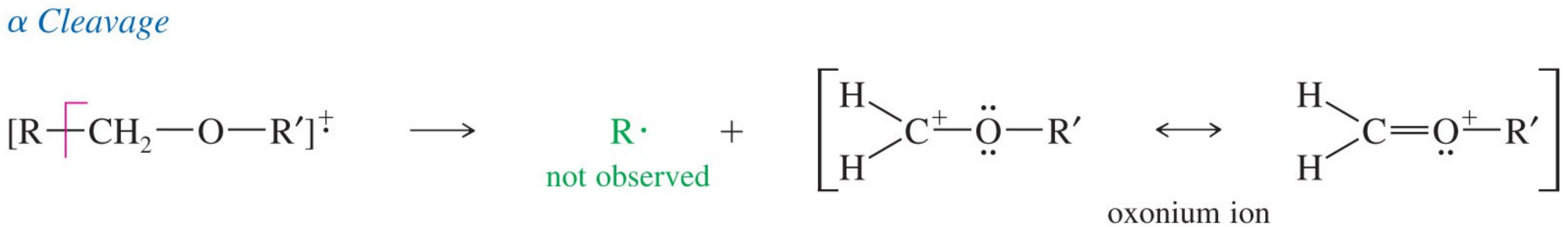


trans-2-ethyl-3-methyloxirane

IR Spectroscopy of Ethers

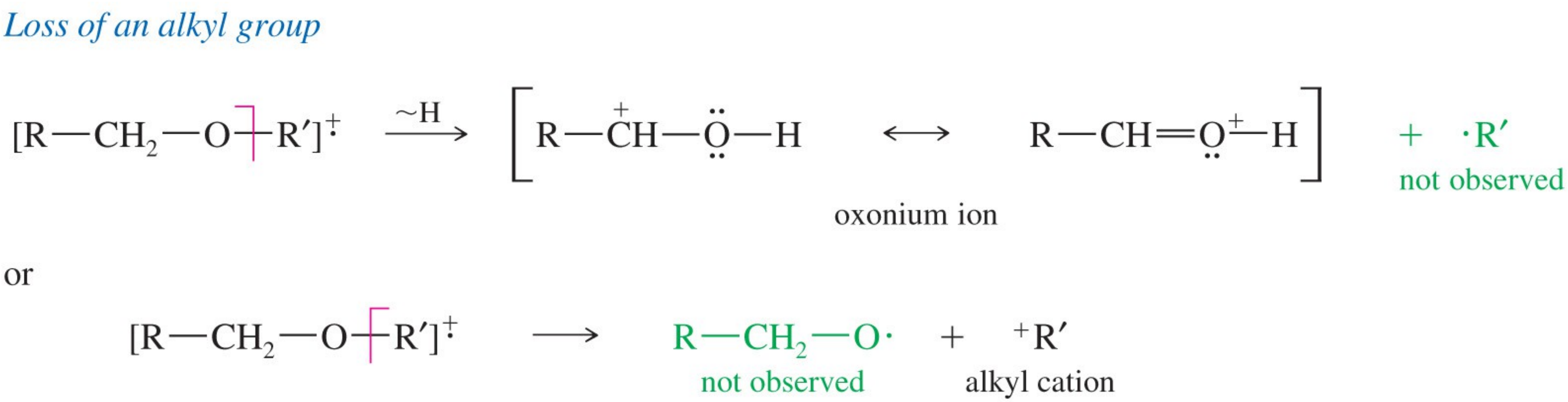
- IR: The C—O stretch is in the fingerprint region around 1000–1200 cm^{-1}.
- Many compounds have the C—O stretch.
- If the IR spectrum has the C—O stretch but does not have a C=O or an OH stretch, then the compound is most likely an ether.

MS Spectrometry of Ethers



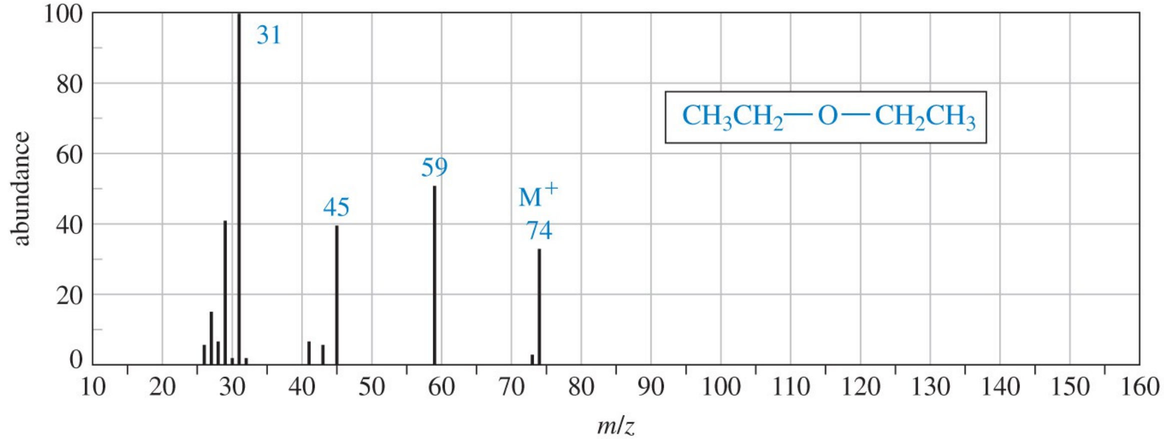
- Main fragmentation is the -cleavage to form the resonance-stabilized oxonium ion.
- Either alkyl group can be cleaved this way.

Loss of an Alkyl Group



- The C—O bond can be cleaved to produce a carbocation.

MS Spectra of Diethyl Ether



Loss of an ethyl group

$$[CH_3-CH_2 \mid O-CH_2-CH_3]^{+\cdot} \longrightarrow H-\overset{+}{O}=CH-CH_3 + \cdot CH_2CH_3$$

45 (cleavage label); m/z 74 → m/z 45; loss of 29

α Cleavage

$$[CH_3-CH_2-O-CH_2 \mid CH_3]^{+\cdot} \longrightarrow CH_3-CH_2-\overset{+}{O}=CH_2 + \cdot CH_3$$

59 (cleavage label); m/z 74 → m/z 59; loss of 15

α Cleavage combined with loss of an ethylene molecule

$$CH_3-CH_2-\overset{+}{O}=CH_2 \longrightarrow H-\overset{+}{O}=CH_2 + CH_2=CH_2$$

m/z 59 → m/z 31; loss of 28

NMR Spectroscopy of Ethers

- The typical chemical shift for ethers in NMR are:

  ^{13}C—O signal between 65– 90.

  ^{1}H—C—O signal between 3.5– 4.

Williamson Ether Synthesis

- This method involves an S_N2 attack of the alkoxide on an unhindered primary halide or tosylate.

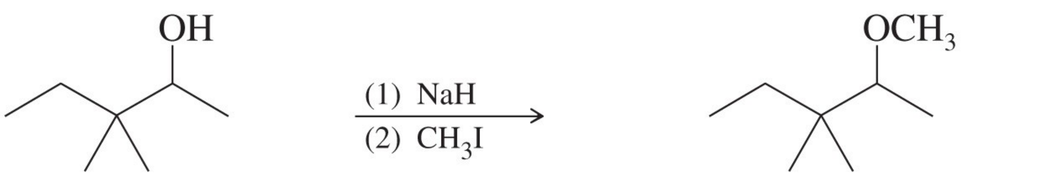
Examples of the Williamson Synthesis

The alkoxide is commonly made by adding Na, K, or NaH to the alcohol (Section 11-14).

Examples

cyclohexanol

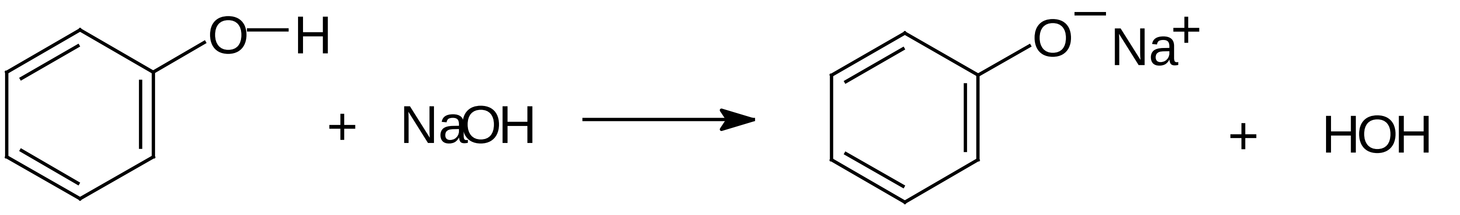
ethoxycyclohexane
(92%)



3,3-dimethyl-2-pentanol

2-methoxy-3,3-dimethylpentane
(90%)

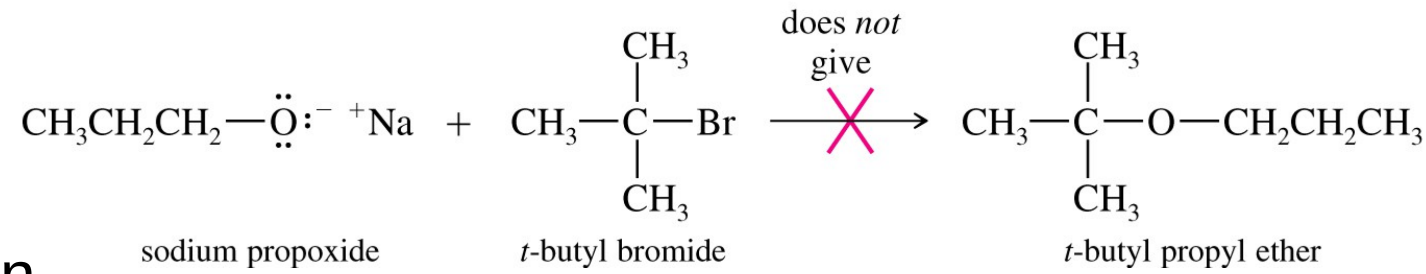
Phenyl Ethers



- Phenoxide ions are easily produced for because the alcohol proton is acidic.
- Phenyl halides or tosylates <u>cannot</u> be used in this synthesis method.

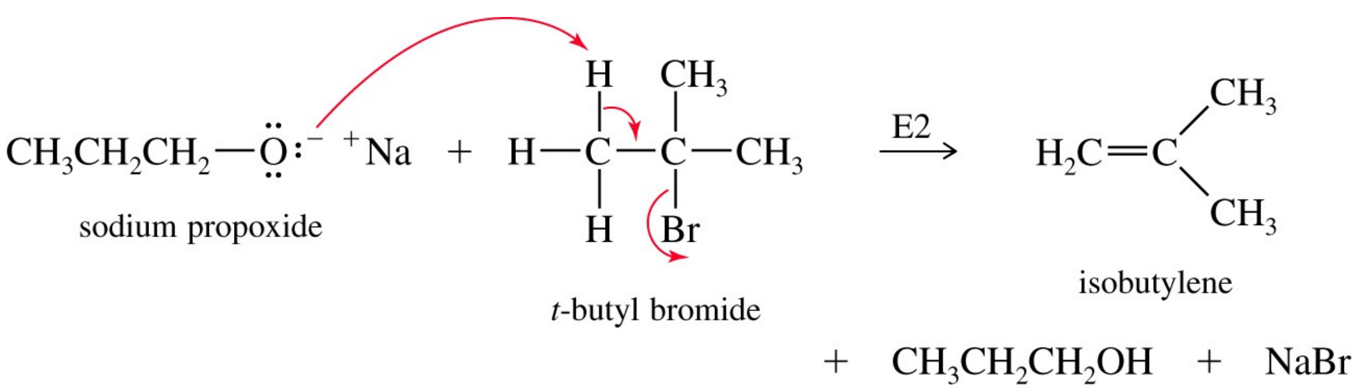
Solved Problem 1

(a) Why is the following reaction a poor method for the synthesis of *t*-butyl propyl ether?
(b) What would be the major product from this reaction?
(c) Propose a better synthesis of *t*-butyl propyl ether.



Solution

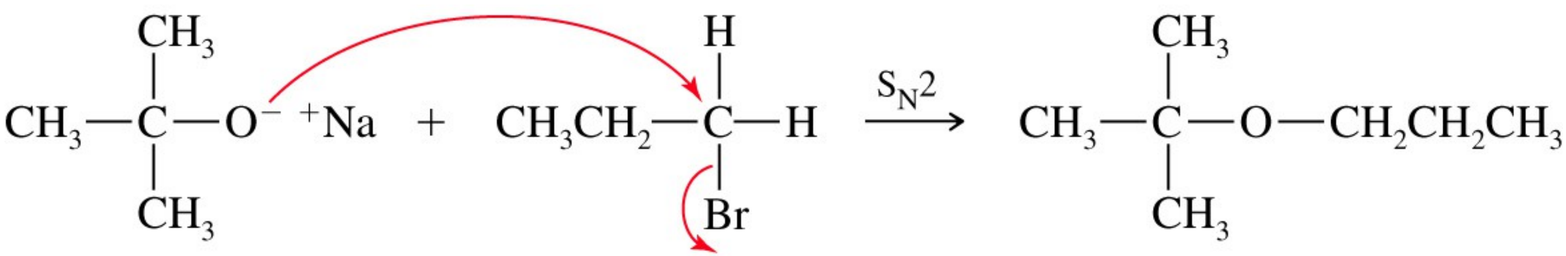
(a) The desired S_N2 reaction cannot occur on the tertiary alkyl halide.
(b) The alkoxide ion is a strong base as well as a nucleophile, and elimination prevails.



Solved Problem 1 (Continued)

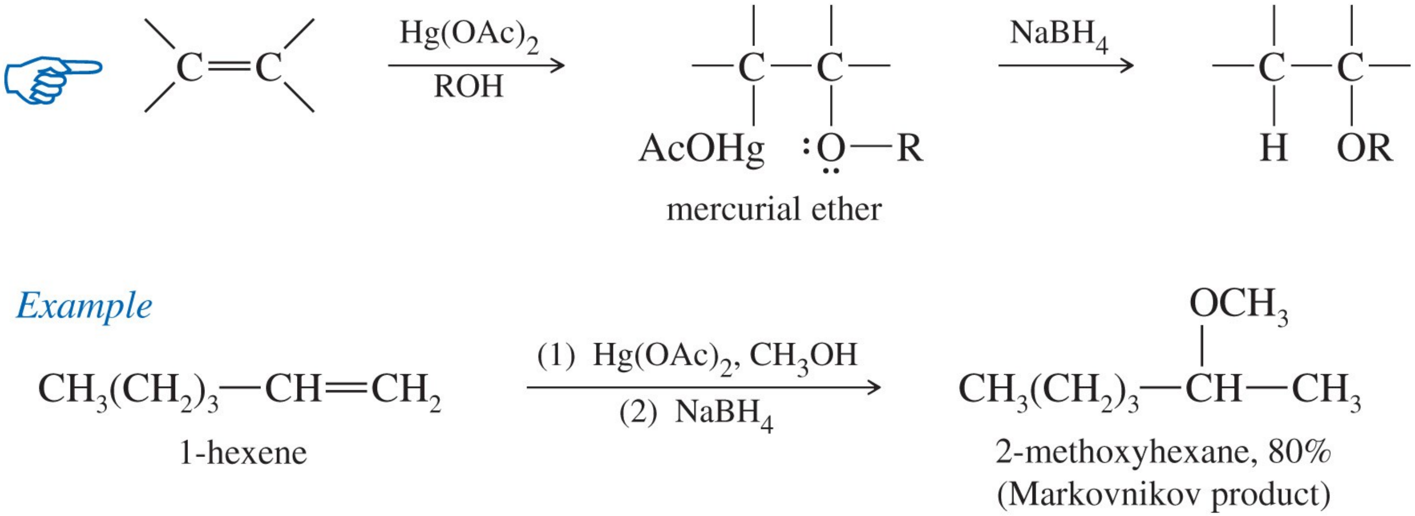
Solution (Continued)

(c) A better synthesis would use the less hindered alkyl group as the S_N2 substrate and the alkoxide of the more hindered alkyl group.



sodium *t*-butoxide   1-bromopropane   *t*-butyl propyl ether

Alkoxymercuration–Demercuration Reaction



- Use mercuric acetate with an alcohol. The alcohol will react with the intermediate mercurinium ion by attacking the more substituted carbon.

Industrial Ether Synthesis

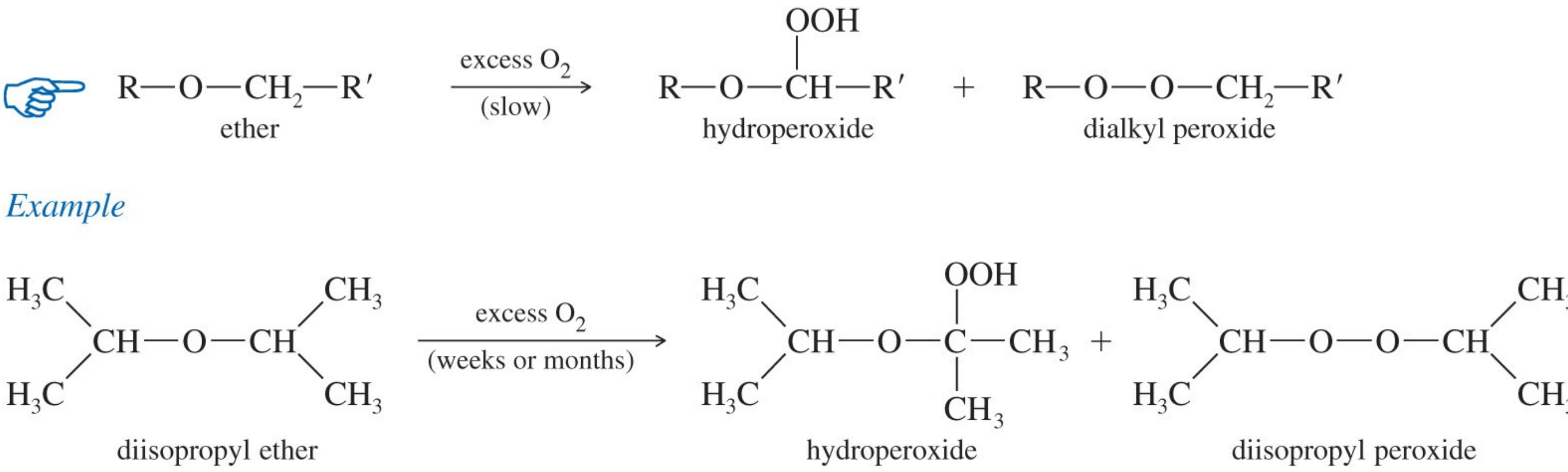
- Industrial method, not good lab synthesis.
- If temperature is too high, alkene forms.

$$CH_3CH_2{-}O{-}H \;+\; H{-}O{-}CH_2CH_3 \xrightarrow[140°C]{H_2SO_4} CH_3CH_2{-}O{-}CH_2CH_3$$

Cleavage of Ethers

- Ethers are unreactive, which makes them ideal solvents for a lot of different reactions.
- They can be cleaved by heating with HBr and HI.
- Reactivity: HI > HBr

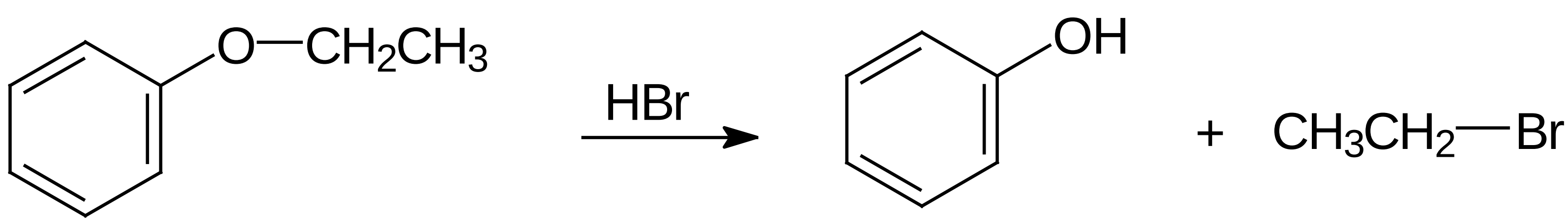
Mechanism of Ether Cleavage



- The acidic conditions will protonate the oxygen.
- The halide will attack the carbon and displace the alcohol (S_N2).
- The alcohol reacts with the acid to form more alkyl halide. This last step will not occur with phenol.

Phenyl Ether Cleavage

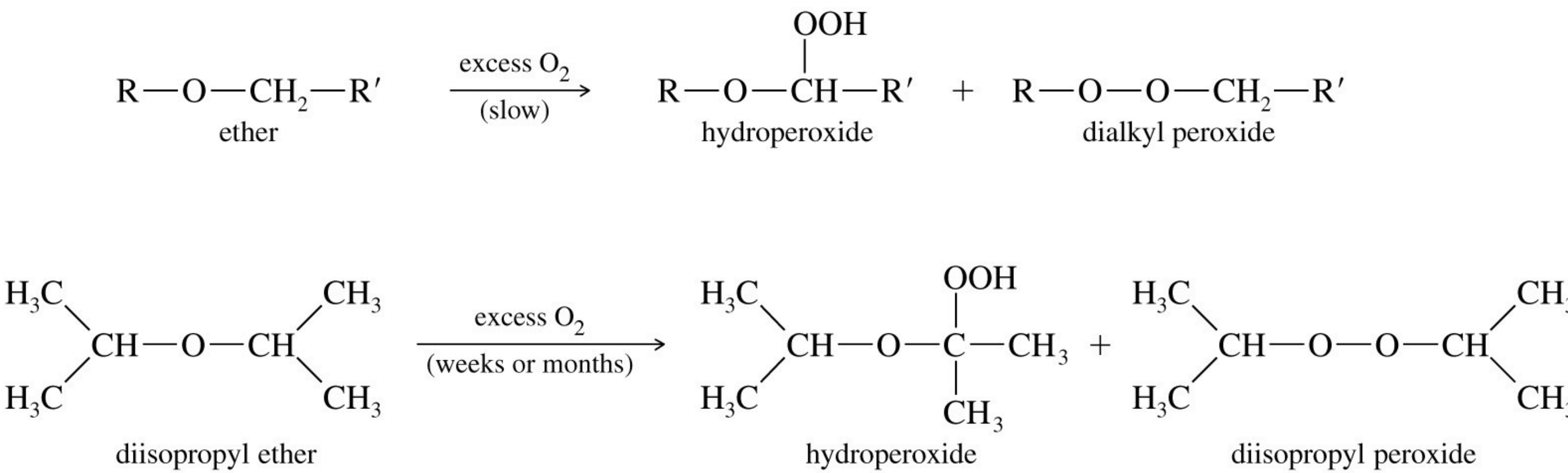
- Phenol cannot react further to become halide because an S_N2 reaction cannot occur on an *sp*^{2} carbon.



Autoxidation of Ethers

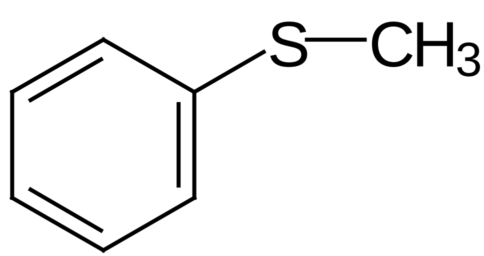
- In the presence of atmospheric oxygen, ethers slowly oxidize to hydroperoxides and dialkyl peroxides.
- Both are highly explosive.
- Precautions:
  - Do not distill to dryness.
  - Store in full bottles with tight caps.

Mechanism of Autoxidation



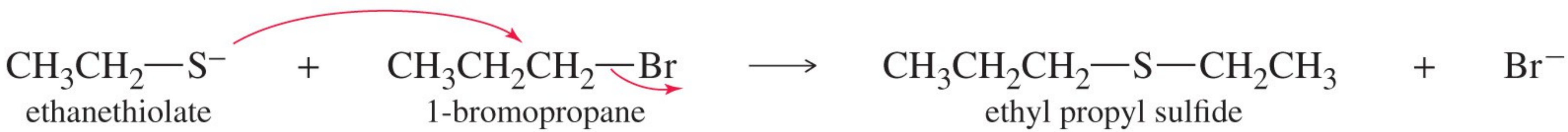
Sulfides (Thioethers)

- R—S—R , analog of ether.
- Name sulfides like ethers, replacing "sulfide" for "ether" in common name, or "alkylthio" for "alkoxy" in IUPAC system.



methyl phenyl sulfide
or
methylthiobenzene

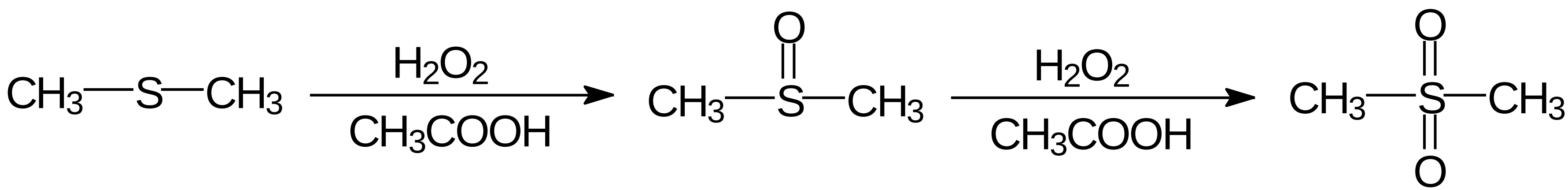
Thiols and Thiolates



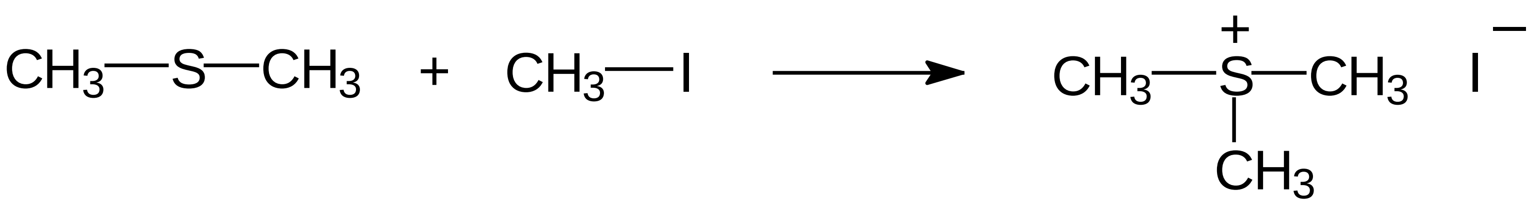
- Thiolates are easily synthesized by the Williamson ether synthesis, using dithiolate as the nucleophile.

Sulfide Reactions

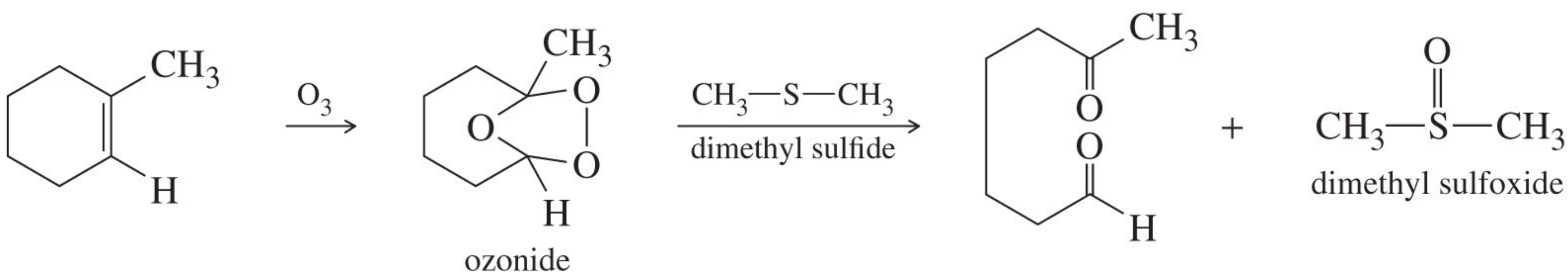
- Sulfides are easily oxidized to sulfoxides and sulfones.



- Sulfides react with unhindered alkyl halides to give sulfonium salts.

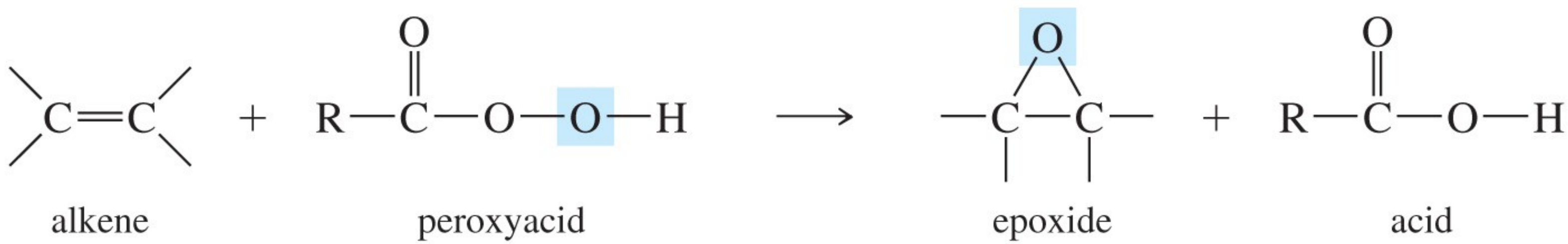


Sulfides as Reducing Agents



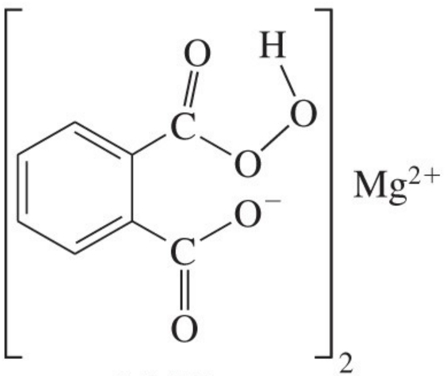
- Because sulfides are easily oxidized, they are often used as mild reducing agents.

Synthesis of Epoxides

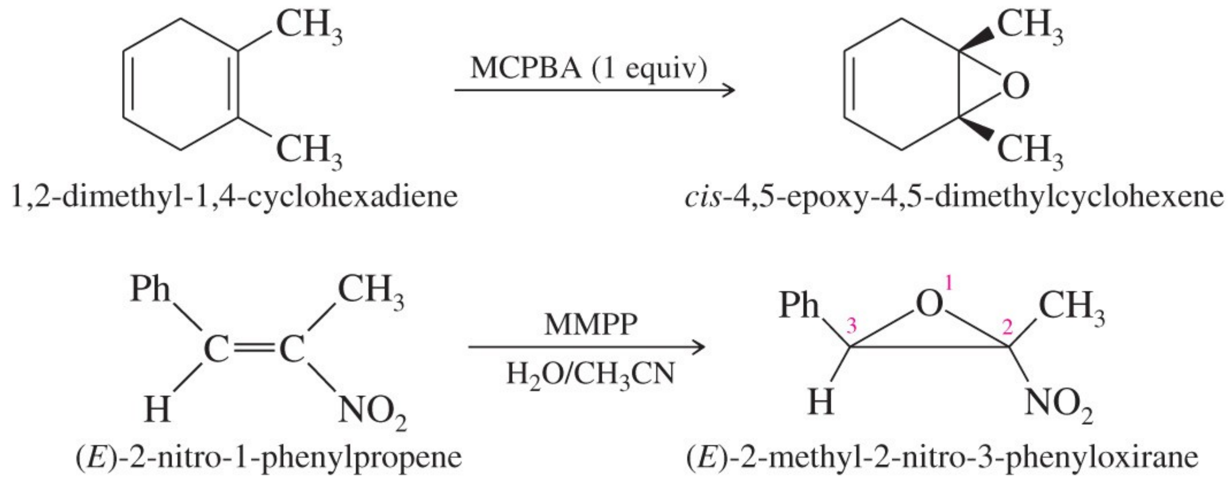


- Peroxyacids are used to convert alkenes to epoxides. Most commonly used peroxyacid is *meta*-chloroperoxybenzoic acid (MCPBA).
- The reaction is carried out in an aprotic acid to prevent the opening of the epoxide.

Selectivity of Epoxidation

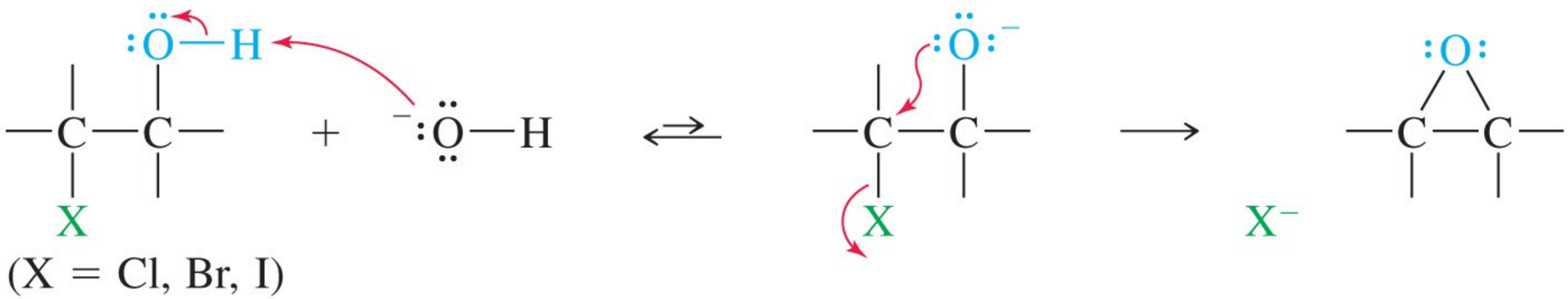


MMPP



- The most electron-rich double bond reacts faster, making selective epoxidation possible.

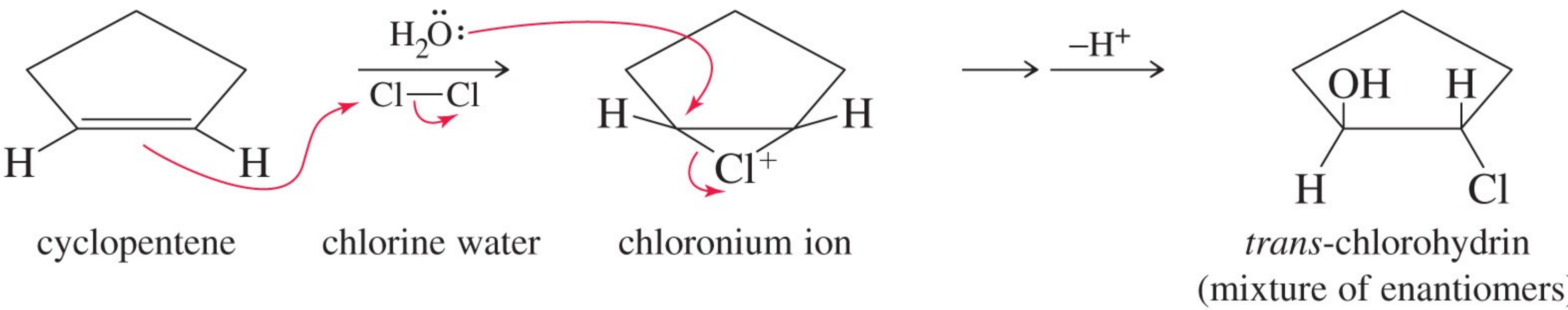
Halohydrin Cyclization



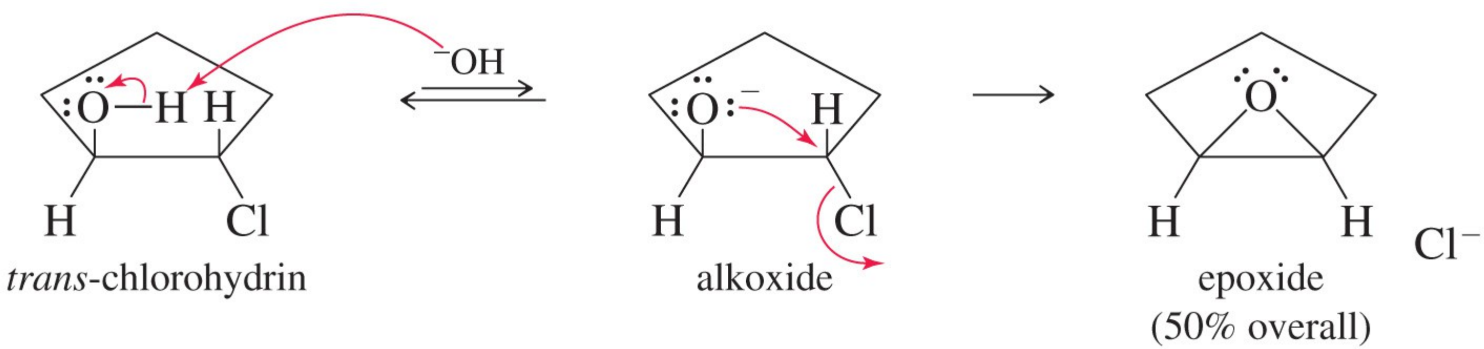
- If an alkoxide and a halogen are located in the same molecule, the alkoxide may displace a halide ion and form a ring.
- Treatment of a halohydrin with a base leads to an epoxide through this internal S_N2 attack.

Epoxides via Halohydrins

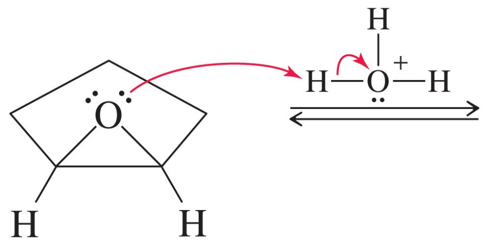
Formation of the chlorohydrin



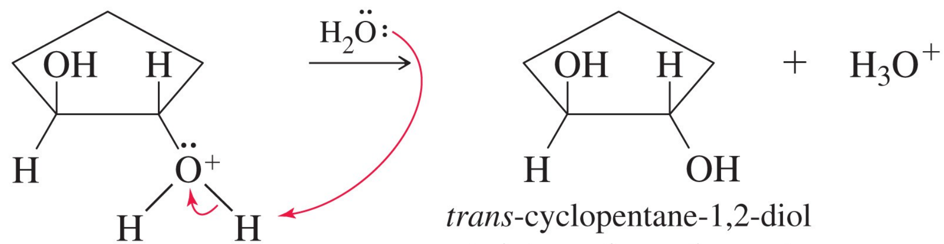
Displacement of the chlorohydrin



Acid-Catalyzed Opening of Epoxides



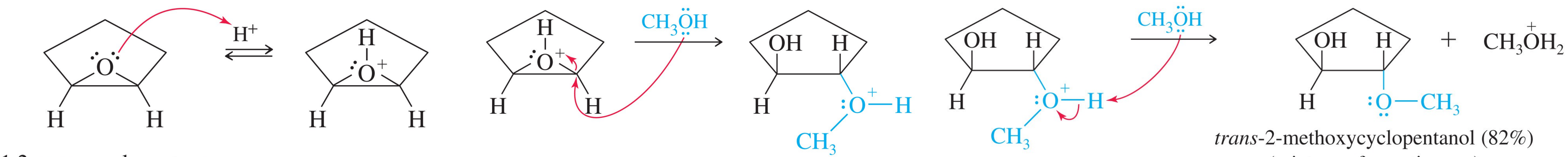
1,2-epoxycyclopentane



trans-cyclopentane-1,2-diol
(mixture of enantiomers)

- Acid-catalyzed hydrolysis of epoxides gives glycols with anti stereochemistry.
- Anti stereochemistry results from the back-side attack of water on the protonated epoxide.

Acid-Catalyzed Opening of Epoxides in Alcohol Solution

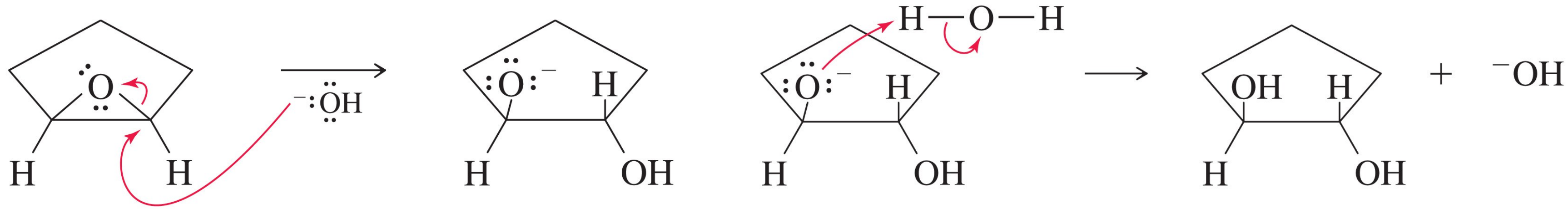


1,2-epoxycyclopentane

trans-2-methoxycyclopentanol (82%)
(mixture of enantiomers)

- A molecule of alcohol acts as the nucleophile and attacks and opens the epoxide.
- This reaction produces an alkoxy alcohol with anti stereochemistry.

Base-Catalyzed Opening of Epoxides

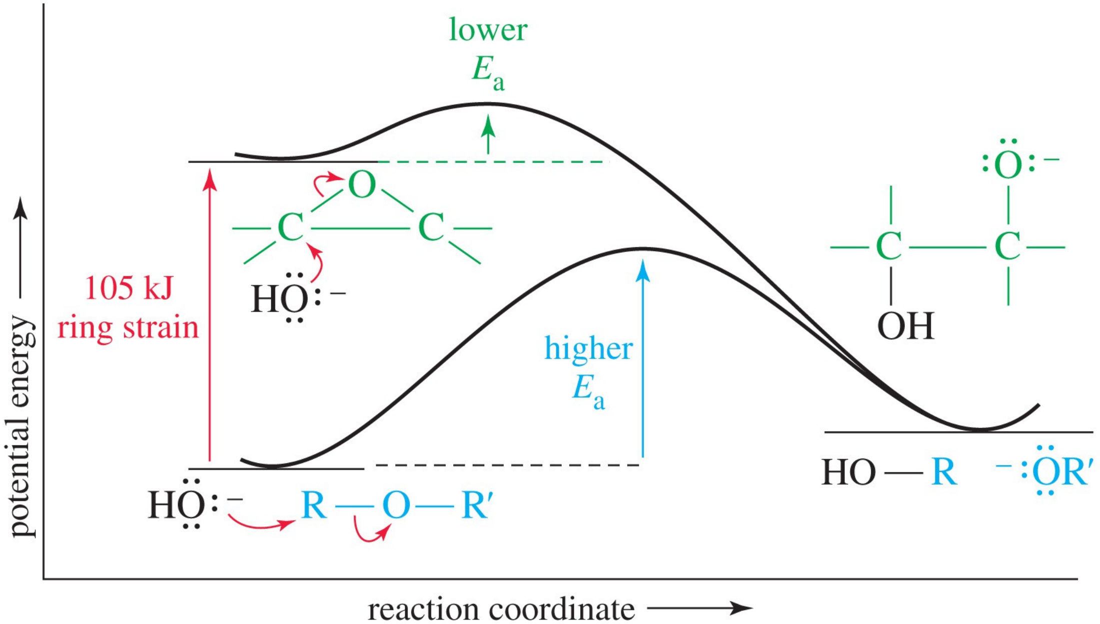


1,2-epoxycyclopentane

trans-cyclopentane-1,2-diol
(mixture of enantiomers)

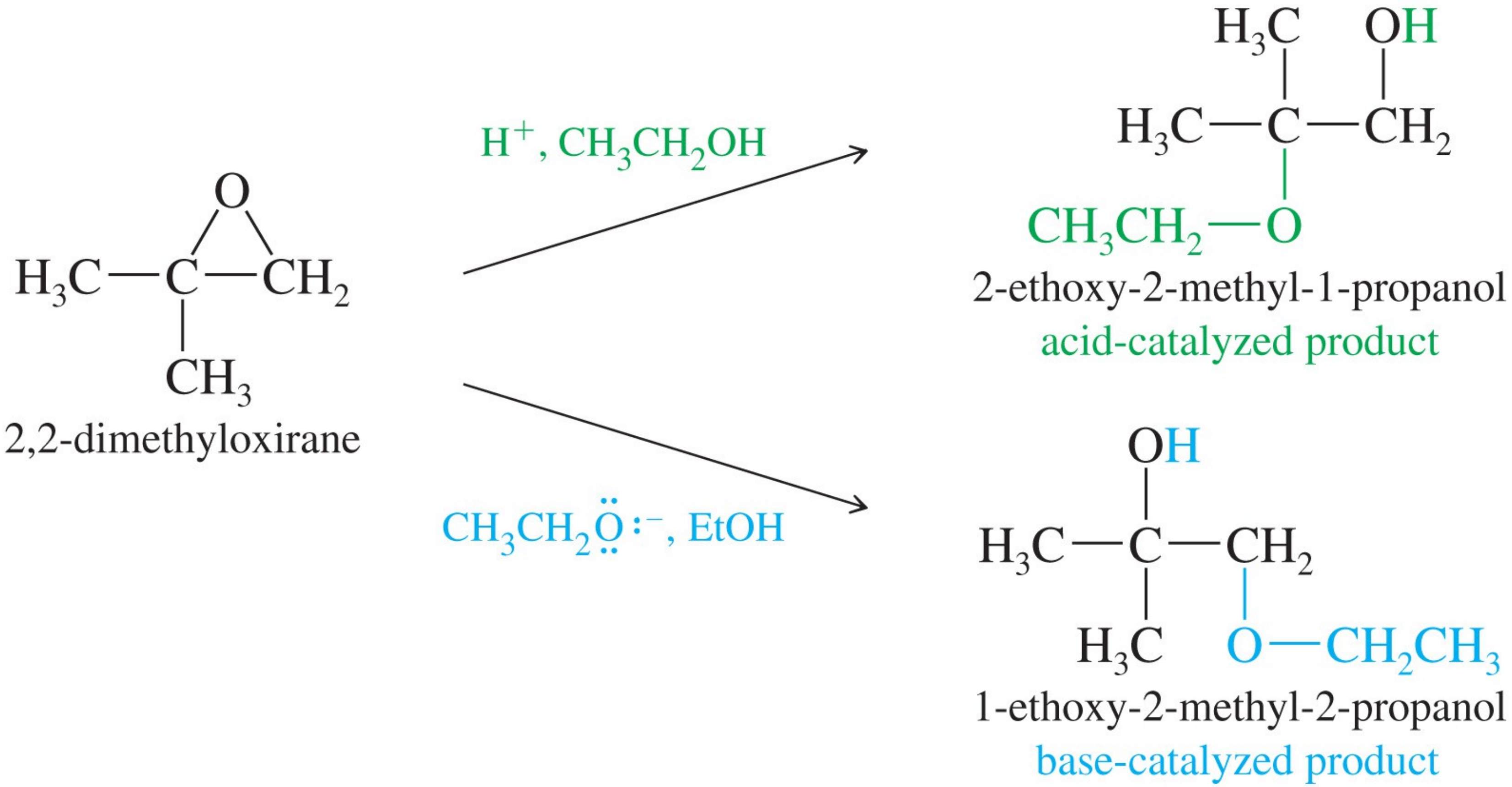
- The hydroxide ion attacks and opens the ring.
- The diol is obtained after protonation of the alkoxide with water.

Ring Opening in Base



- An epoxide is higher in energy than an acyclic ether by about 25 kcal/mol ring strain.
- Release of the ring strain makes the opening of an epoxide thermodynamically favored.

Regioselectivity of Epoxidation

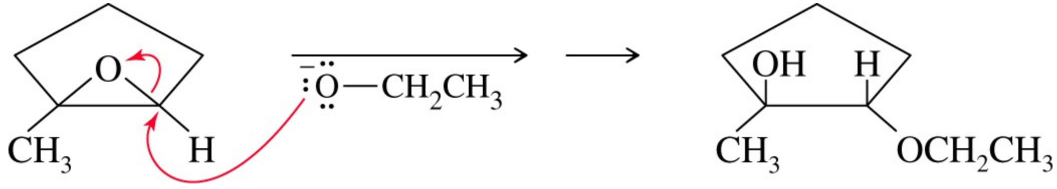


Solved Problem 2

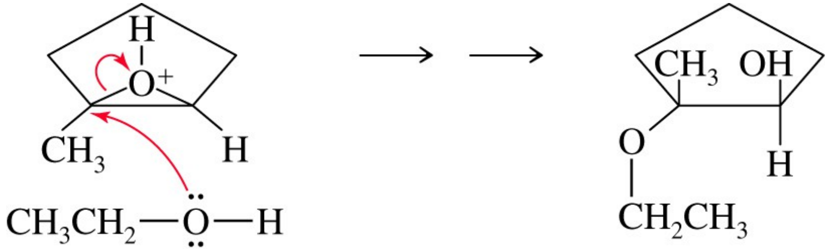
Predict the major products for the reaction of 1-methyl-1,2 epoxycyclopentane with
(a) sodium ethoxide in ethanol
(b) H_2SO_4 in ethanol

Solution

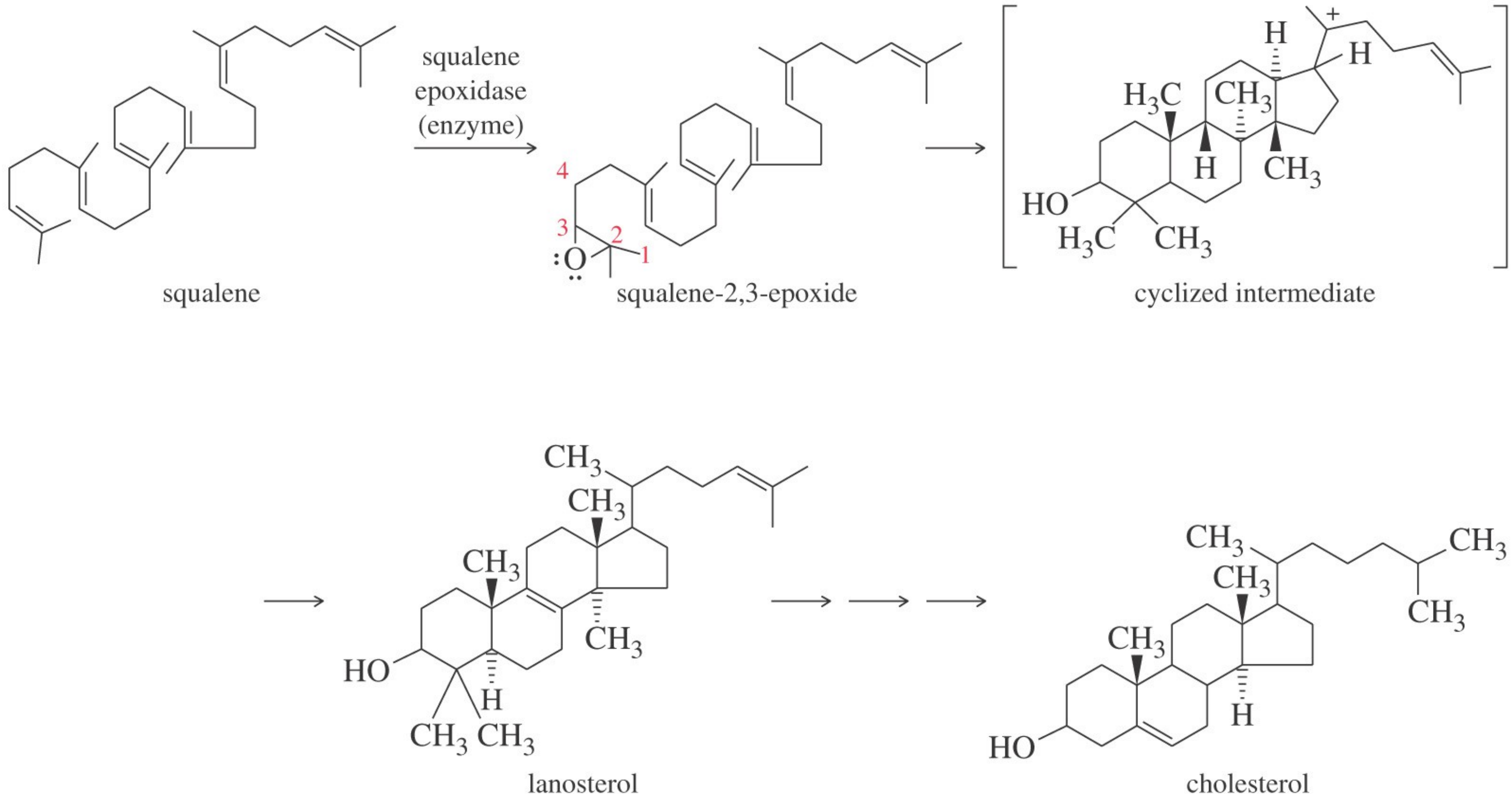
(a) Sodium ethoxide attacks the less hindered secondary carbon to give (E)-2-ethoxy1 methylcyclopentanol.



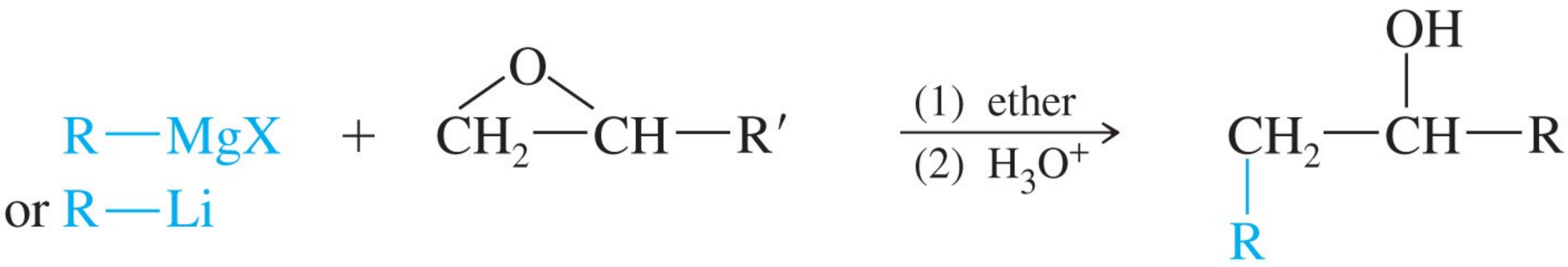
(b) Under acidic conditions, the alcohol attacks the more electrophilic tertiary carbon atom of the protonated epoxide. The product is (E)-2 ethoxy-2-methylcyclopentanol.



Biosynthesis of Steroids



Reaction of Epoxides with Grignard and Organolithiums



- Strong bases, such as Grignards and organolithiums, open the epoxide ring by attacking the less hindered carbon.