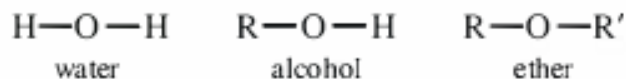
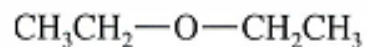


Ethers, Epoxides, and Sulfides

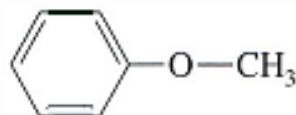
Ethers are compounds of formula $R-O-R'$,



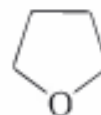
Examples of ethers



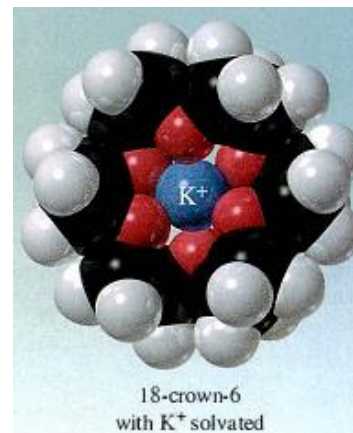
diethyl ether
(a symmetrical ether)



methyl phenyl ether
(an unsymmetrical ether)

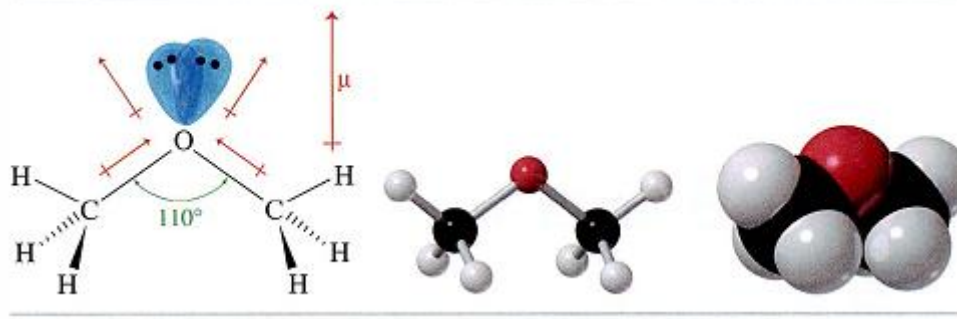


tetrahydrofuran
(a symmetrical, cyclic ether)




Physical Properties of Ethers

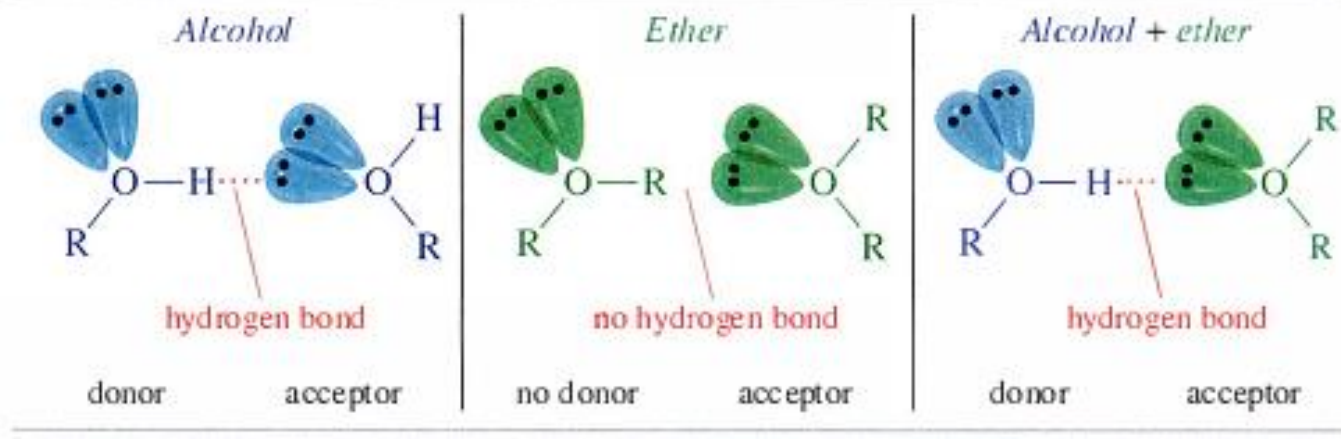
Structure and Polarity of Ethers



Boiling Points of Ethers; Hydrogen Bonding

TABLE 14-1 Comparison of the Boiling Points of Ethers, Alkanes, and Alcohols of Similar Molecular Weights

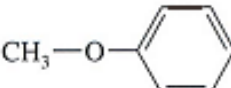
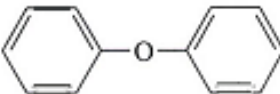


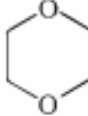
| Compound | Formula | MW | bp (°C) | Dipole Moment (D) |
|-------------------|---|----|---------|-------------------|
| water | H ₂ O | 18 | 100 | 1.9 |
| ethanol | CH ₃ CH ₂ —OH | 46 | 78 | 1.7 |
| dimethyl ether | CH ₃ —O—CH ₃ | 46 | -25 | 1.3 |
| propane | CH ₃ CH ₂ CH ₃ | 44 | -42 | 0.1 |
| <i>n</i> -butanol | CH ₃ CH ₂ CH ₂ CH ₂ —OH | 74 | 118 | 1.7 |
| tetrahydrofuran |  | 72 | 66 | 1.6 |
| diethyl ether | CH ₃ CH ₂ —O—CH ₂ CH ₃ | 74 | 35 | 1.2 |
| pentane | CH ₃ CH ₂ CH ₂ CH ₂ CH ₃ | 72 | 36 | 0.1 |



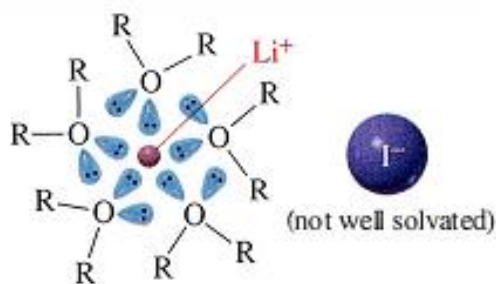
Ethers as Polar Solvents

Ethers are ideally suited as solvents for many organic reactions.

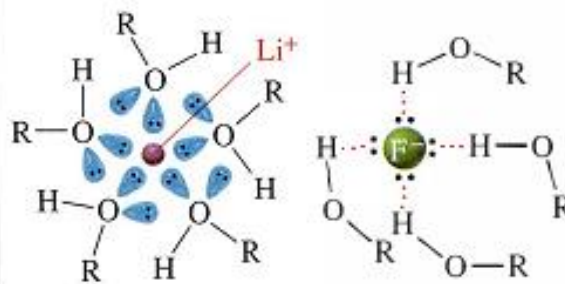
TABLE 14-2 Physical Properties of Some Representative Ethers

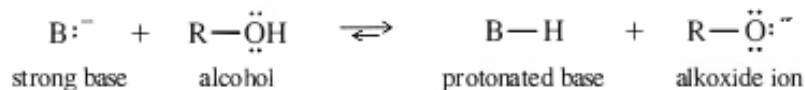
| Name | Structure | mp (°C) | bp (°C) | Density (g/mL) |
|-------------------------------|---|---------|---------|----------------|
| dimethyl ether | $\text{CH}_3\text{—O—CH}_3$ | -140 | -25 | 0.66 |
| ethyl methyl ether | $\text{CH}_3\text{CH}_2\text{—O—CH}_3$ | | 8 | 0.72 |
| diethyl ether | $\text{CH}_3\text{CH}_2\text{—O—CH}_2\text{CH}_3$ | -116 | 35 | 0.71 |
| di- <i>n</i> -propyl ether | $\text{CH}_3\text{CH}_2\text{CH}_2\text{—O—CH}_2\text{CH}_2\text{CH}_3$ | -122 | 91 | 0.74 |
| diisopropyl ether | $(\text{CH}_3)_2\text{CH—O—CH}(\text{CH}_3)_2$ | -86 | 68 | 0.74 |
| 1,2-dimethoxyethane (DME) | $\text{CH}_3\text{—O—CH}_2\text{CH}_2\text{—O—CH}_3$ | -58 | 83 | 0.86 |
| methyl phenyl ether (anisole) |  | -37 | 154 | 0.99 |
| diphenyl ether |  | 27 | 259 | 1.07 |
| furan |  | -86 | 32 | 0.94 |
| tetrahydrofuran (THF) |  | -108 | 65 | 0.89 |
| 1,4-dioxane |  | 11 | 101 | 1.03 |

ether solvates cations:

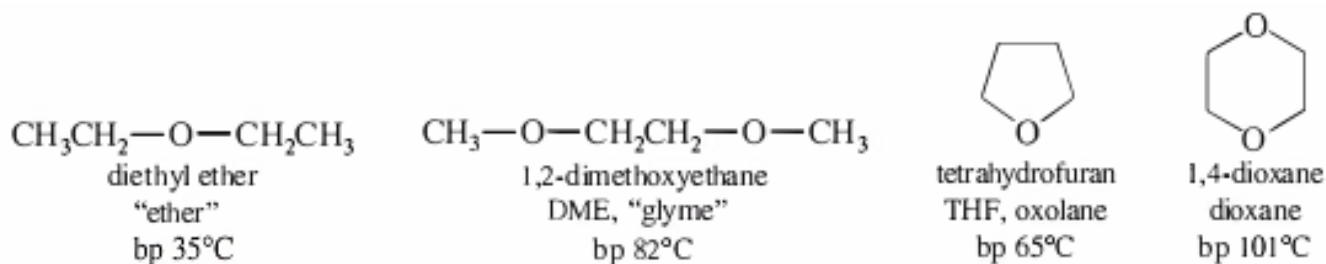


alcohol solvates cations and anions:





DME, THF, and dioxane are miscible with water, and diethyl ether is sparingly soluble in water.



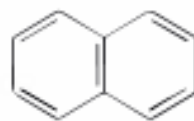
PROBLEM 14-1

Rank the given solvents in decreasing order of their ability to dissolve each compound.

Solutes

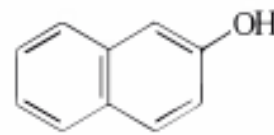
(a) NaOAc

(b)



naphthalene

(c)



2-naphthol

Solvents

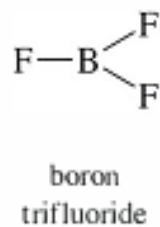
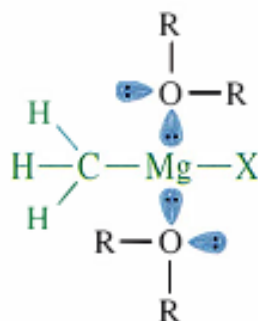
ethyl ether

water

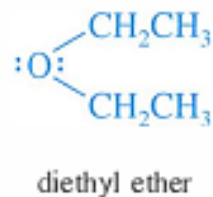
ethanol

dichloromethane

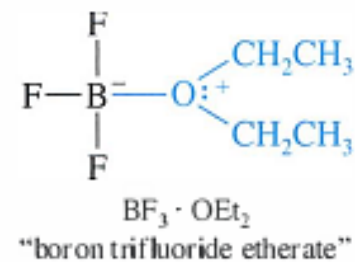
Stable Complexes of Ethers with Reagents



+

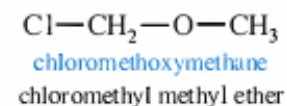
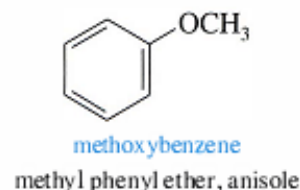
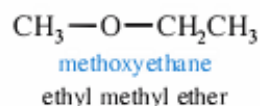


→

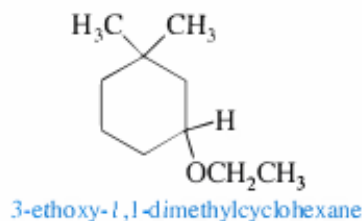


IUPAC Names (Alkoxy Alkane Names)

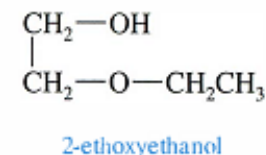
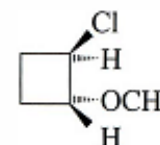
IUPAC name:
common name:



IUPAC name:

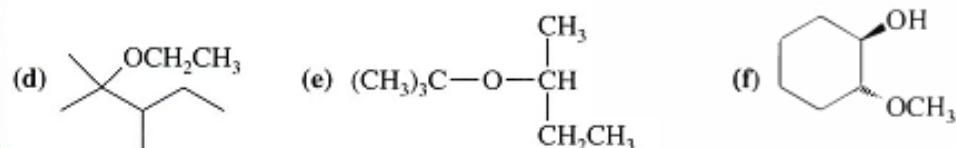
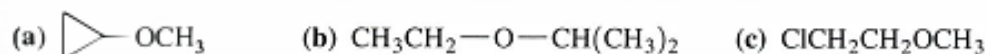


trans-1-chloro-2-methoxycyclobutane



PROBLEM 14-4

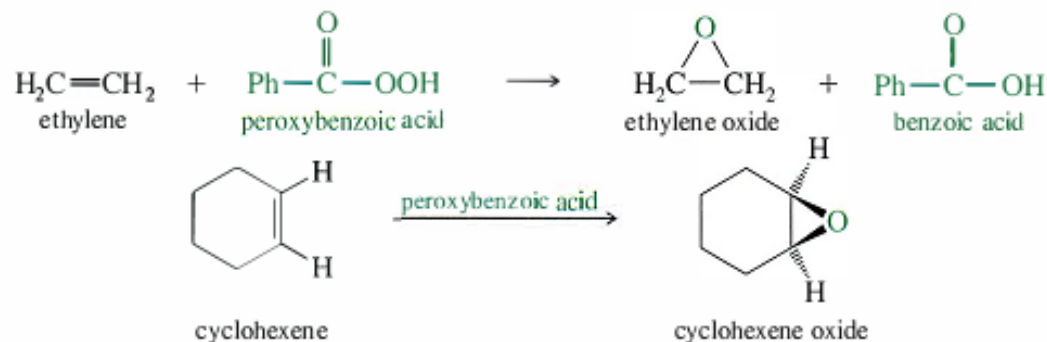
Give a common name and a systematic name for each compound.

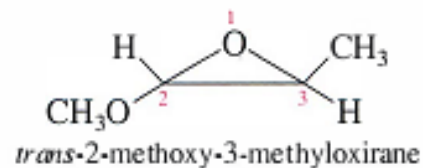
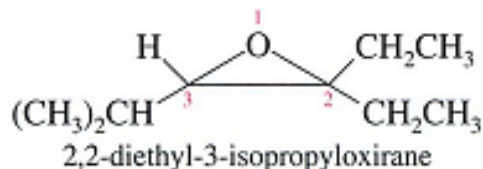
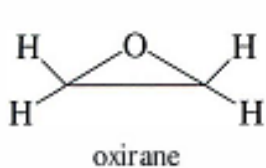


Nomenclature of Cyclic Ethers

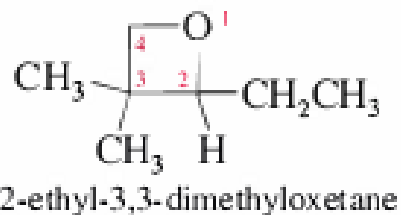
Cyclic ethers are our first examples of **heterocyclic compounds**,

Epoxides (Oxiranes)

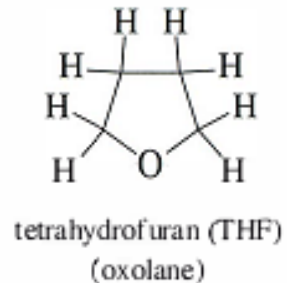
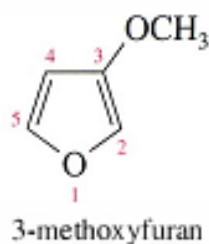
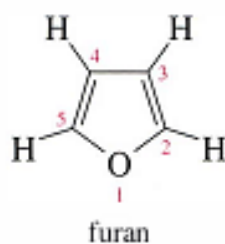




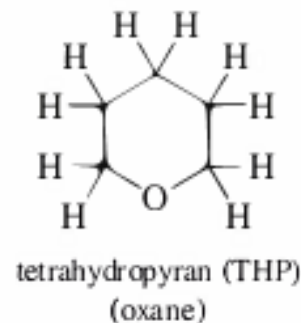
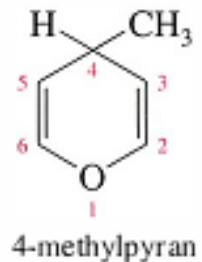
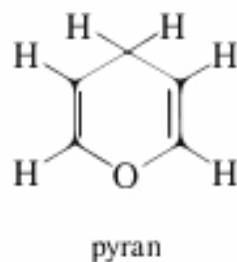
Oxetanes



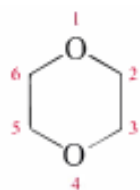
Furans (Oxolanes)



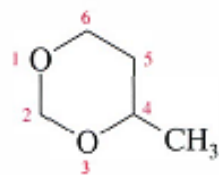
Pyrans (Oxanes)



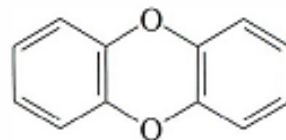
Dioxanes



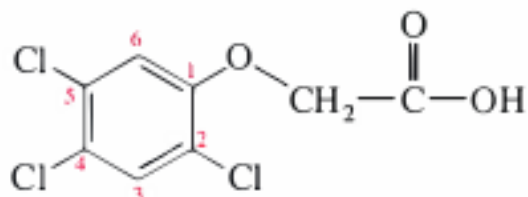
1,4-dioxane



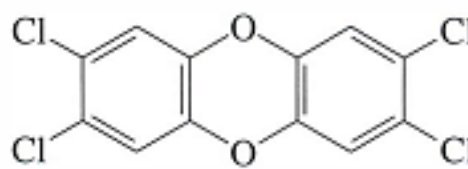
4-methyl-1,3-dioxane



dibenzo-1,4-dioxane (dioxin)



2,4,5-trichlorophenoxyacetic acid
(2,4,5-T or Agent Orange)



2,3,7,8-tetrachlorodibenzodioxin
(TCDD, incorrectly "dioxin")

PROBLEM 14-5

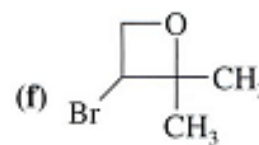
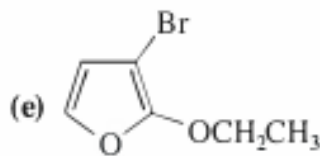
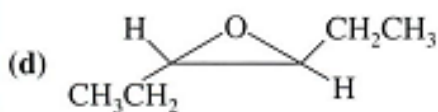
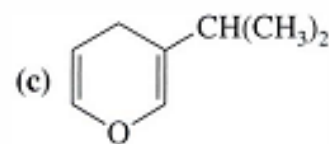
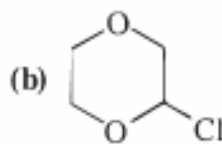
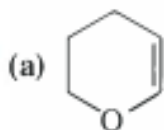
1,4-Dioxane is made commercially by the acid-catalyzed dehydration of an alcohol.

(a) Show what alcohol will dehydrate to give 1,4-dioxane.

(b) Propose a mechanism for this reaction.

PROBLEM 14-6

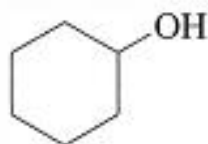
Name the following heterocyclic ethers.



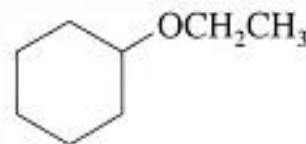
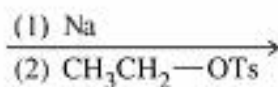
The Williamson Ether Synthesis



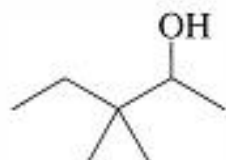
Examples



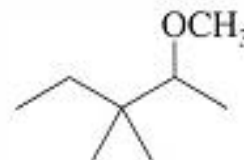
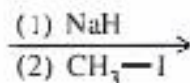
cyclohexanol



ethoxycyclohexane
(92%)



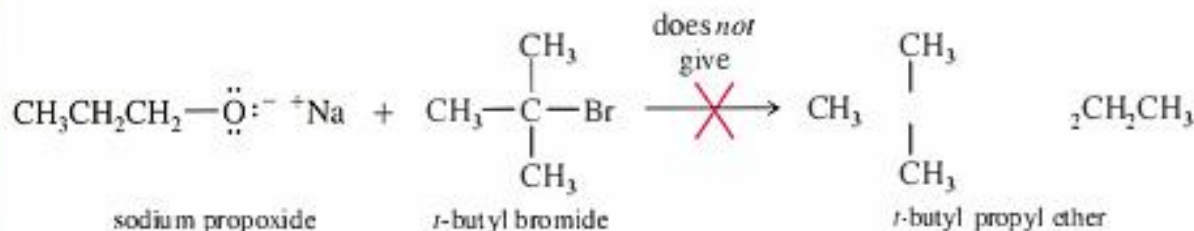
3,3-dimethyl-2-pentanol



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

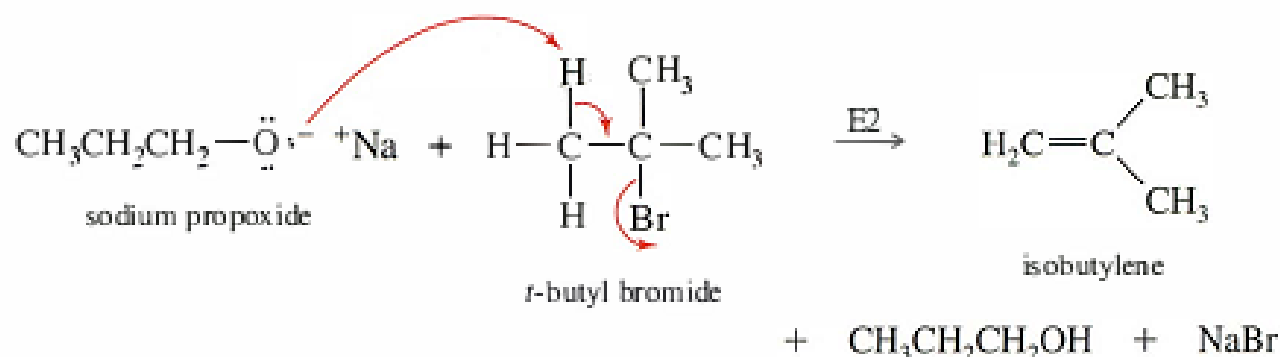
SOLVED PROBLEM 14-1

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

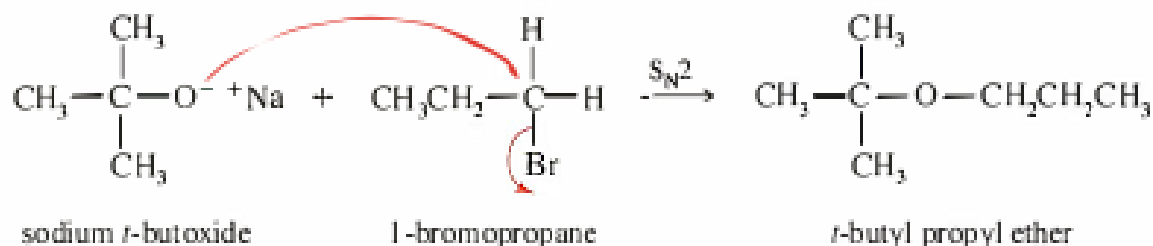


SOLUTION

- (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.



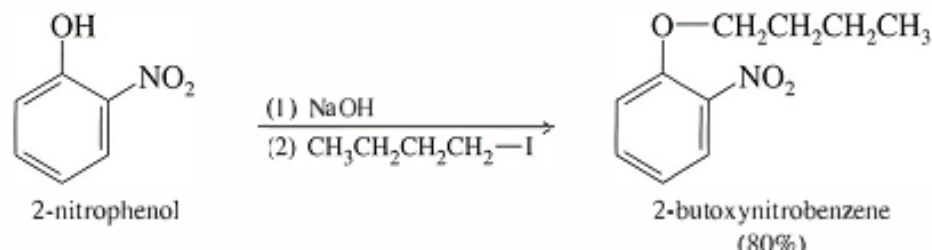
- (c) A better synthesis would use the less hindered alkyl group as the S_N2 substrate and the alkoxide of the more hindered alkyl group.



PROBLEM 14-8

Propose a Williamson synthesis of 3-butoxy-1,1-dimethylcyclohexane from 3,3-dimethylcyclohexanol and butanol.

Synthesis of Phenyl Ethers



PROBLEM 14-9

PROBLEM-SOLVING *Hint*

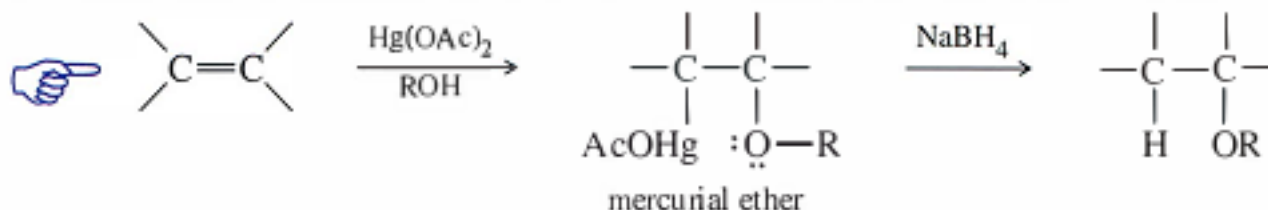
To convert two alcohols to an ether, convert the more hindered alcohol to its alkoxide. Convert the less hindered alcohol to its tosylate (or an alkyl halide). Make sure the tosylate (or halide) is a good S_N2 substrate.

Show how you would use the Williamson ether synthesis to prepare the following ethers. You may use any alcohols or phenols as your organic starting materials.

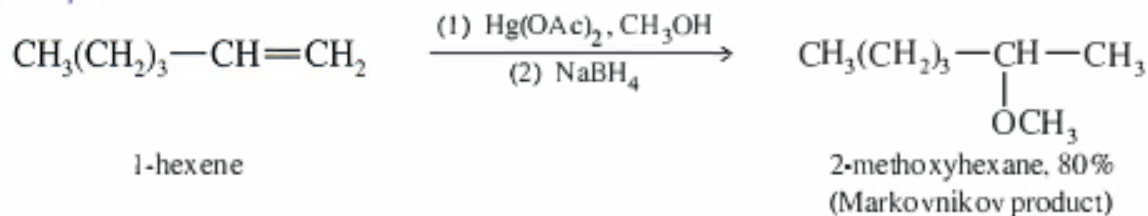
- (a) cyclohexyl propyl ether (b) isopropyl methyl ether
 (c) 1-methoxy-4-nitrobenzene (d) ethyl *n*-propyl ether (two ways)
 (e) benzyl *t*-butyl ether (benzyl = Ph — CH₂ —)

Synthesis of Ethers by Alkoxymercuration–Demercuration

The **alkoxymercuration–demercuration** process adds a molecule of an alcohol across the double bond of an alkene (Section 8-6). The product is an ether, as shown here.



Example



PROBLEM 14-10

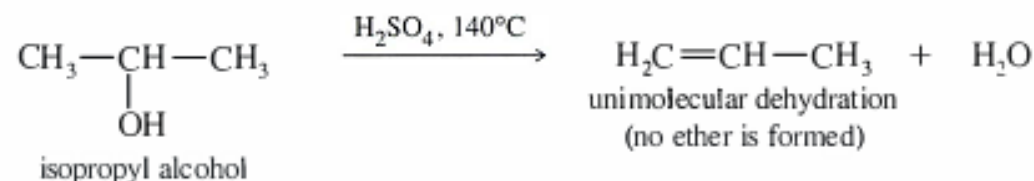
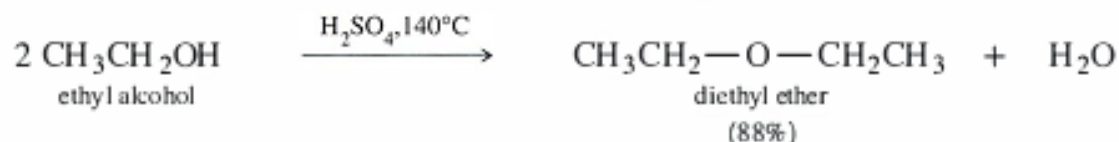
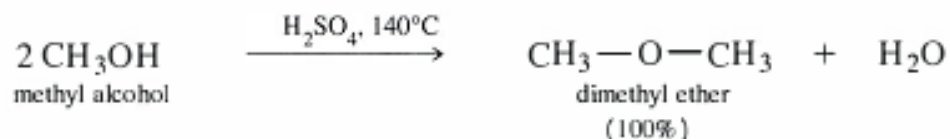
Show how the following ethers might be synthesized using (1) alkoxymercuration-demercuration and (2) the Williamson synthesis. (When one of these methods cannot be used for the given ether, point out why it will not work.)

- | | |
|---------------------------------------|------------------------------------|
| (a) 2-methoxybutane | (b) ethyl cyclohexyl ether |
| (c) 2-methyl-1-methoxycyclopentane | (d) 1-methyl-1-methoxycyclopentane |
| (e) 1-methyl-1-isopropoxycyclopentane | (f) <i>t</i> -butyl phenyl ether |

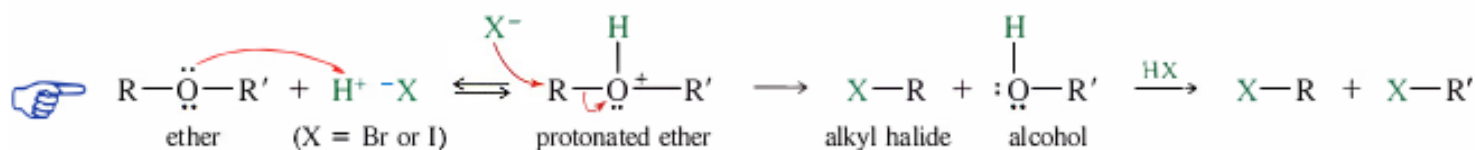
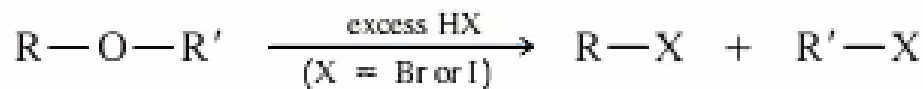
PROBLEM-SOLVING Hint

Alkoxymercuration adds the -OR group of the alcohol to the more substituted carbon atom of the $\text{C}=\text{C}$ double bond.

Industrial Synthesis: Bimolecular Dehydration of Alcohols

Bimolecular dehydration*Examples*

Cleavage of Ethers by HBr and HI

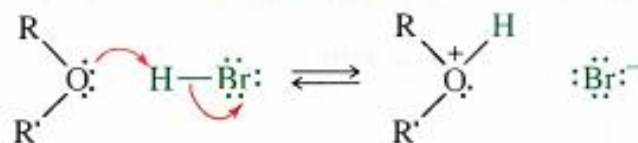


MECHANISM 14-1

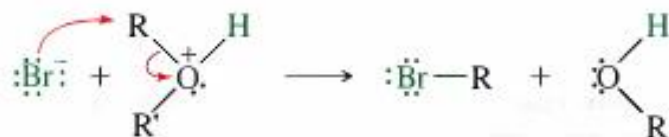
Cleavage of an Ether by HBr or HI

Ethers are cleaved by a nucleophilic substitution of Br^- or I^- on the protonated ether.

Step 1: Protonation of the ether to form a good leaving group.

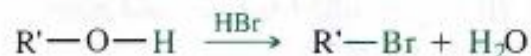


Step 2: $\text{S}_{\text{N}}2$ cleavage of the protonated ether.



Step 3: Conversion of the alcohol fragment to the alkyl halide.

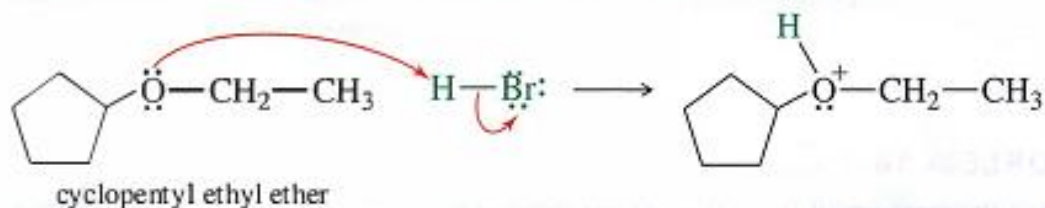
(Does not occur with phenols.)



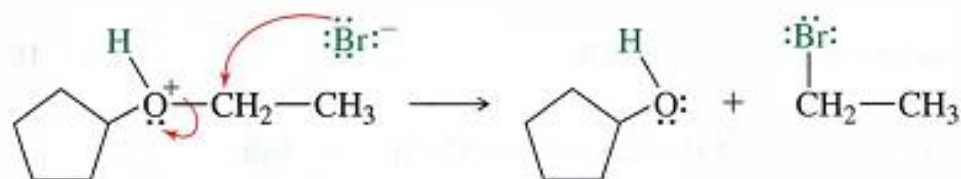
This conversion can occur by either of the two mechanisms shown in Section 11-7, depending on the structure of the alcohol and the reaction conditions. The protonated alcohol undergoes either $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ substitution by bromide ion.

EXAMPLE: Cleavage of cyclopentyl ethyl ether by HBr.

Step 1: Protonation of the ether to form a good leaving group,

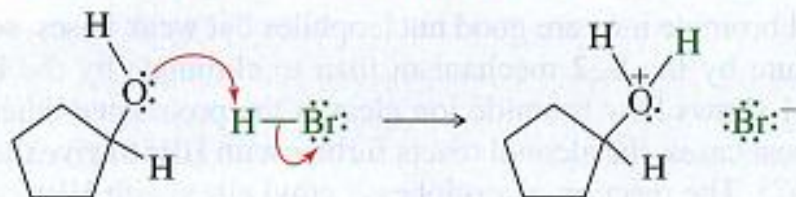


Step 2: Cleavage of the protonated ether

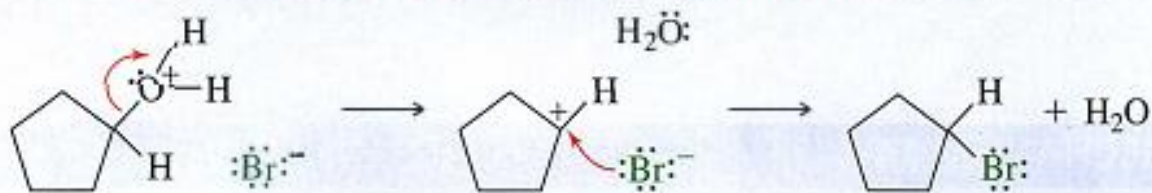


Step 3: Conversion of the alcohol fragment to the alkyl halide.

First, the alcohol is protonated to form a good leaving group.

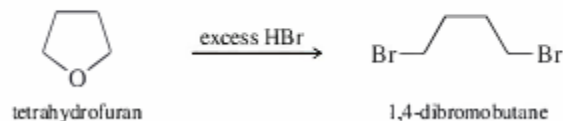
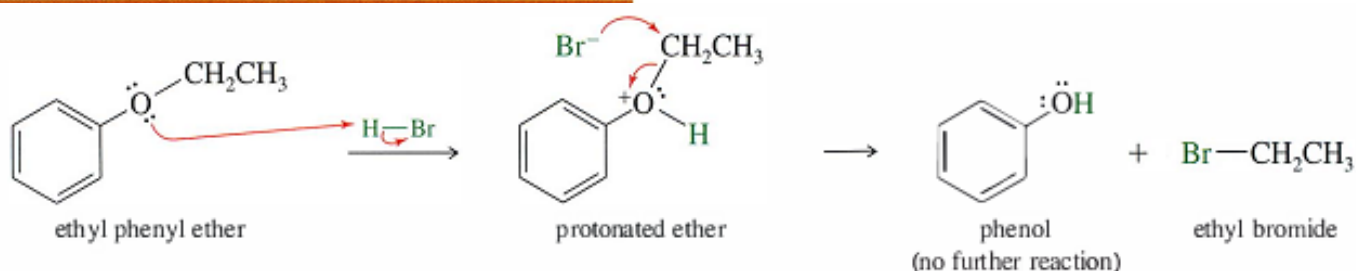


The protonated alcohol undergoes $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ substitution by bromide ion.



PROBLEM 14-14

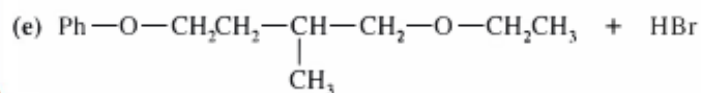
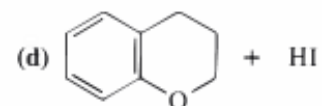
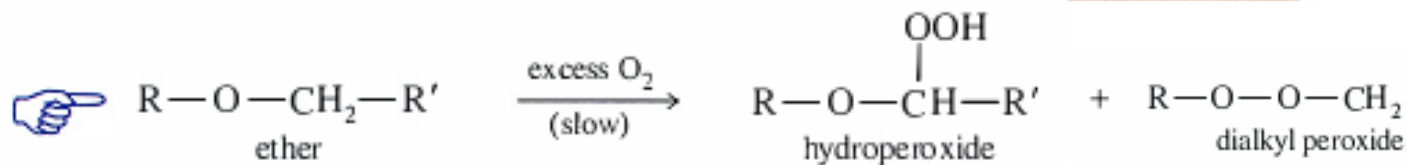
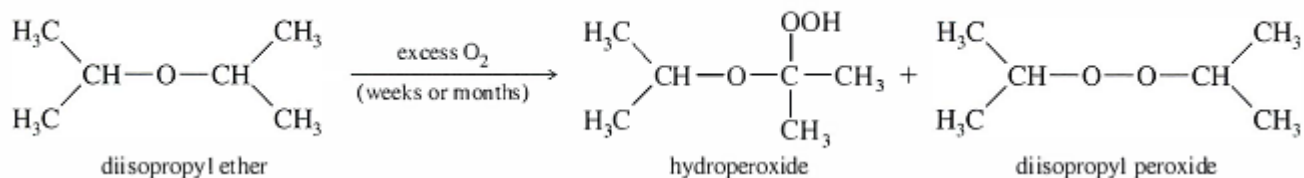
Propose a mechanism for the following reaction.

**Phenyl Ethers****PROBLEM-SOLVING Hint**

HBr and HI convert both alkyl groups (but not aromatic groups) of an ether to alkyl halides; phenols are unreactive, however.

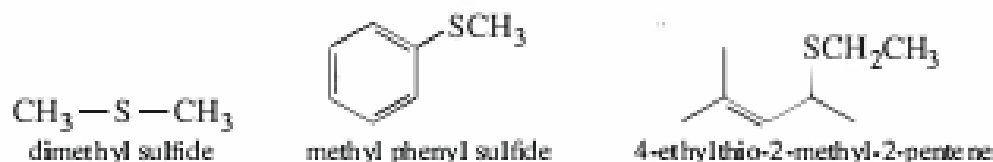
PROBLEM 14-15

Predict the products of the following reactions. An excess of acid is available in each case.

**Autoxidation of Ethers***Example*

Sulfides (Thioethers)

Sulfides are also called **thioethers** because they are the sulfur analogues of ethers.



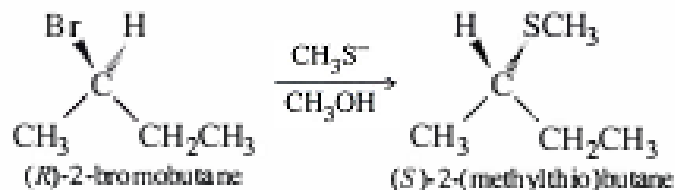
Sulfides are easily synthesized by the Williamson ether synthesis, using a thiolate ion as the nucleophile.



Thiols are more acidic than water. Therefore, thiolate ions are easily generated by treating thiols with aqueous sodium hydroxide.



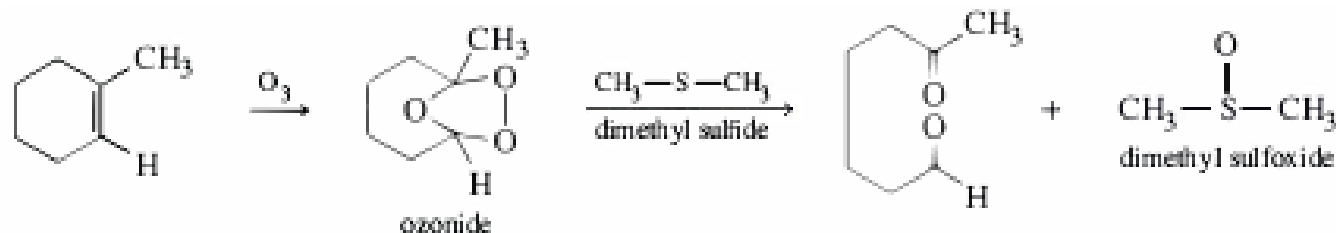
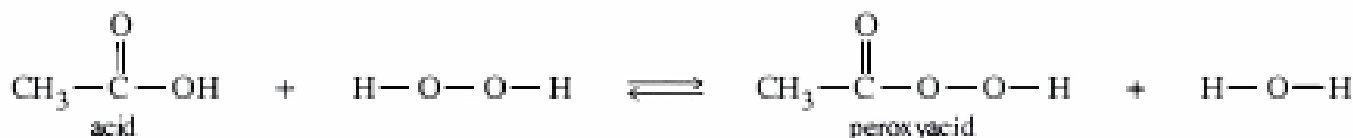
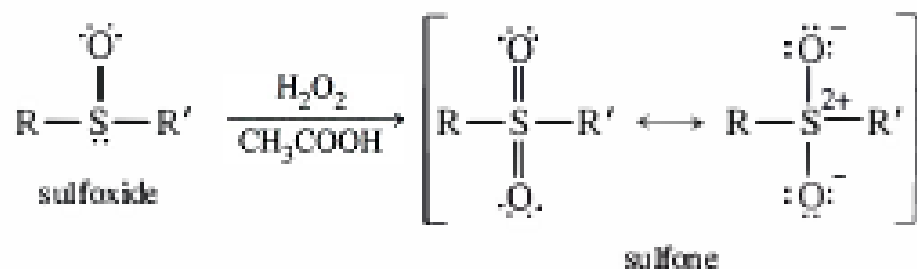
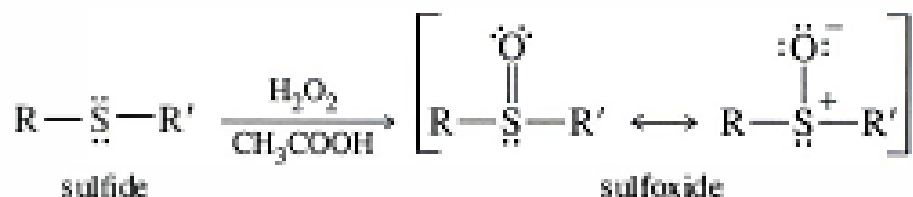
Because sulfur is larger and more polarizable than oxygen, thiolate ions are even better nucleophiles than alkoxide ions. Thiulates are such effective nucleophiles that secondary alkyl halides often react to give good yields of $\text{S}_{\text{N}}2$ products.



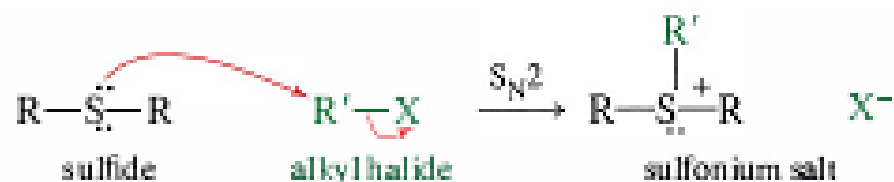
PROBLEM 14-17

Show how you would synthesize butyl isopropyl sulfide using 1-butanol, 2-propanol, and any solvents and reagents you need.

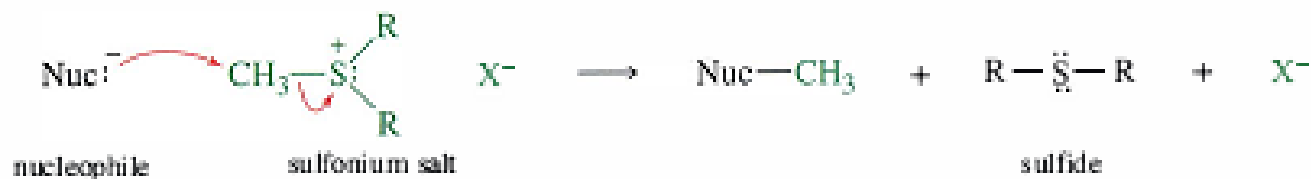
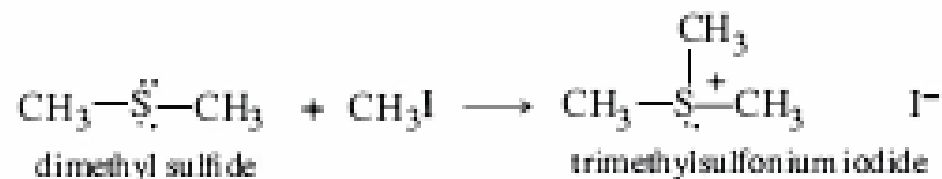
Sulfides are much more reactive than ethers. In a sulfide, sulfur's valence is not necessarily filled: Sulfur can form additional bonds with other atoms. Sulfur forms particularly strong bonds with oxygen, and sulfides are easily oxidized to sulfoxides and sulfones. Sulfoxides and sulfones are drawn using either hypervalent double-bonded structures or formally charged single-bonded structures as shown here.



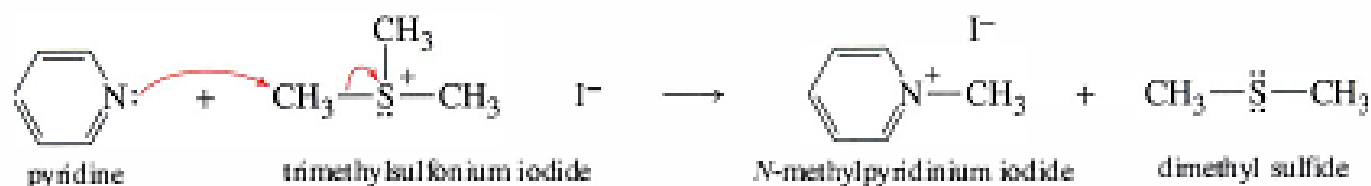
Sulfur compounds are more nucleophilic than the corresponding oxygen com-



Example

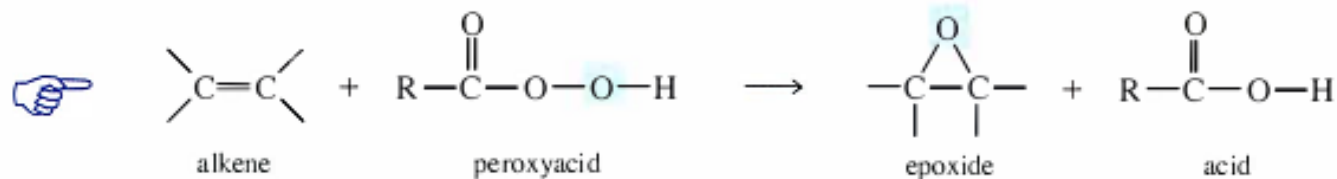


Example

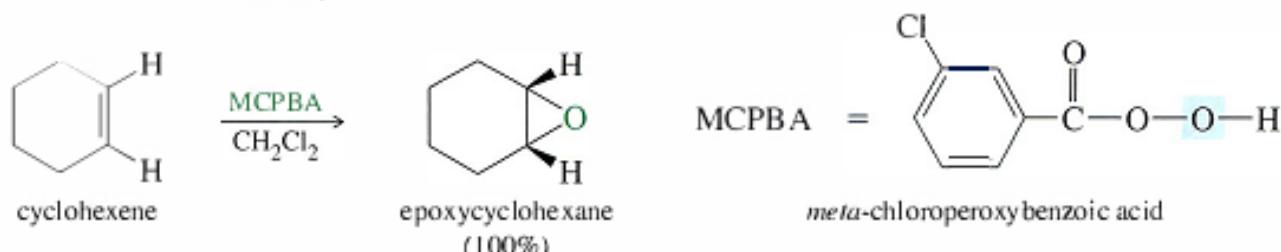


Synthesis of Epoxides

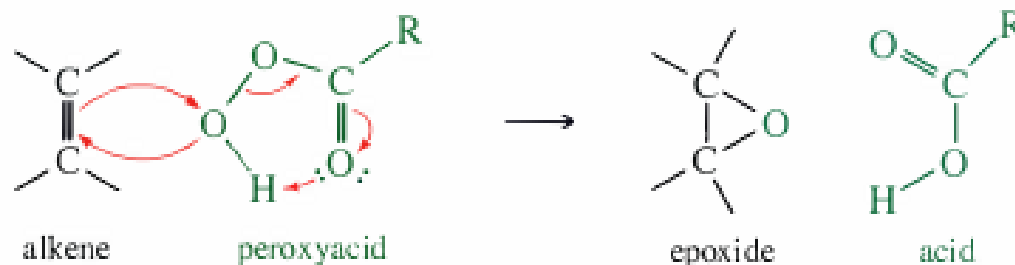
Peroxyacid Epoxidation

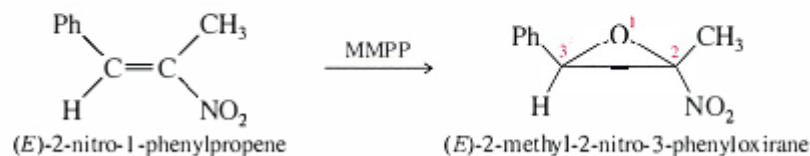
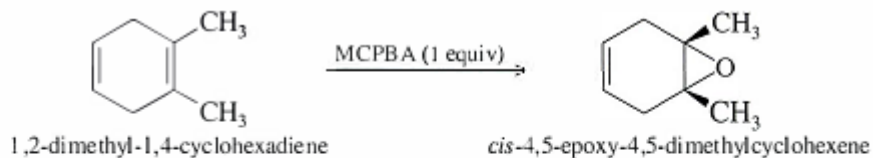
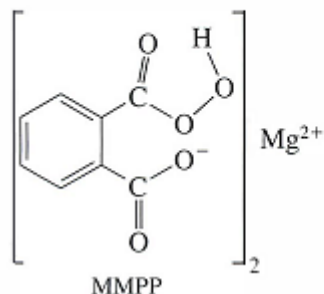


Example

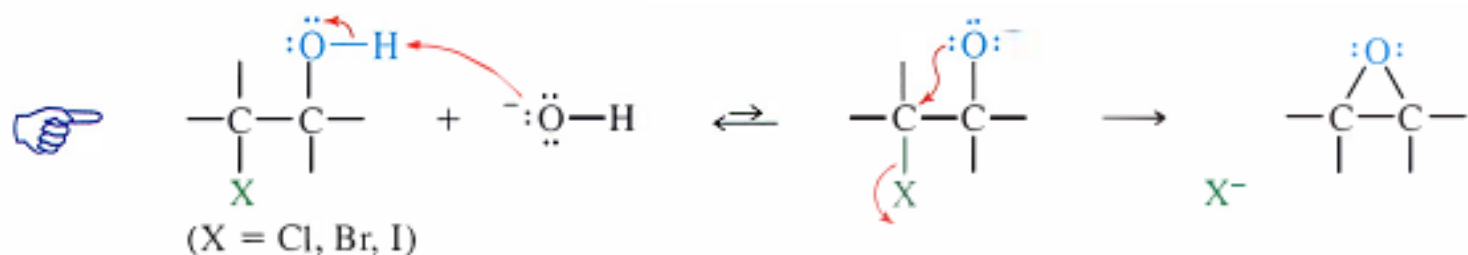


The epoxidation takes place in a one-step, **concerted reaction** that maintains the stereochemistry of any substituents on the double bond.

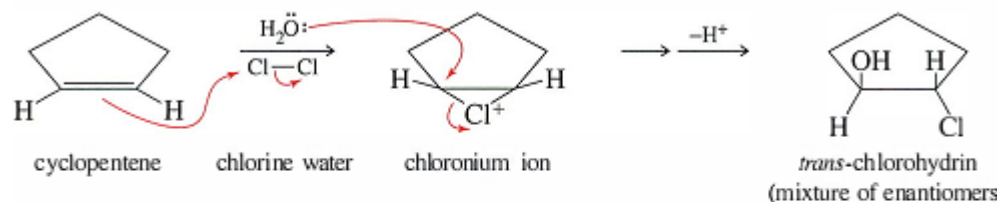




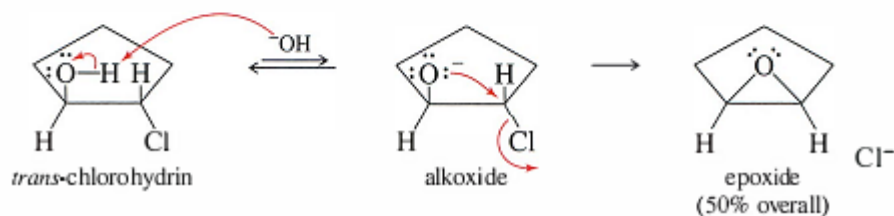
Base-Promoted Cyclization of Halohydrins

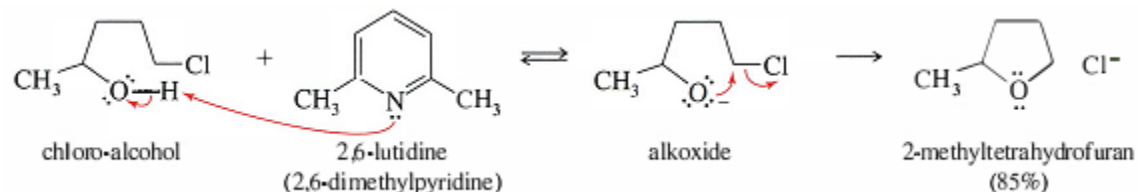


Formation of the chlorohydrin



Displacement of the chlorohydrin





PROBLEM 14-19

Show how you would accomplish the following transformations. Some of these examples require more than one step.

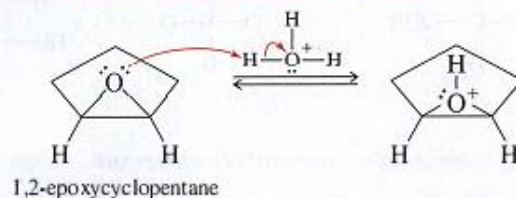
- (a) 2-methylpropene \rightarrow 2,2-dimethyloxirane
- (b) 1-phenylethanol \rightarrow 2-phenyloxirane
- (c) 5-chloro-1-pentene \rightarrow tetrahydropyran
- (d) 5-chloro-1-pentene \rightarrow 2-methyltetrahydrofuran
- (e) 2-chloro-1-hexanol \rightarrow 1,2-epoxyhexane

MECHANISM 14-2

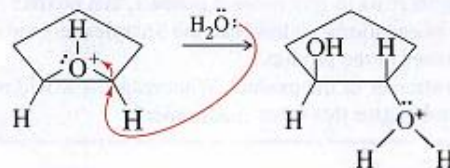
Acid-Catalyzed Opening of Epoxides in Water

Epoxides open in acidic solutions to form glycols.

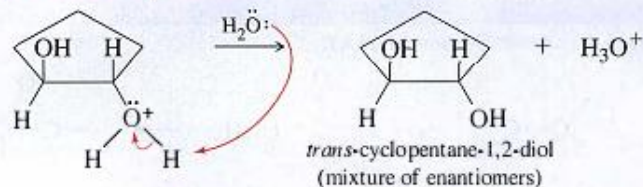
Step 1: Protonation of the epoxide to form a strong electrophile.



Step 2: Water attacks and opens the ring.

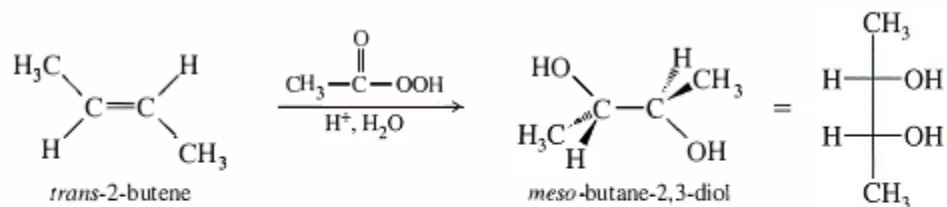


Step 3: Deprotonation to give the diol.



Acid-Catalyzed Ring Opening of Epoxides

In Water



PROBLEM 14-21

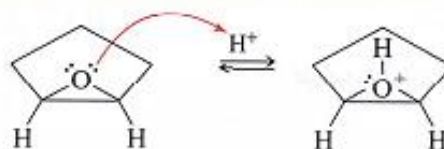
Propose mechanisms for the epoxidation and ring-opening steps of the epoxidation and hydrolysis of *trans*-2-butene shown above. Predict the product of the same reaction with *cis*-2-butene.

MECHANISM 14-3

Acid-Catalyzed Opening of an Epoxide in an Alcohol Solution

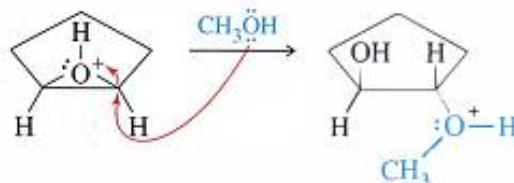
Epoxides open in acidic alcohol solutions to form 2-alkoxy alcohols.

Step 1: Protonation of the epoxide to form a strong electrophile.

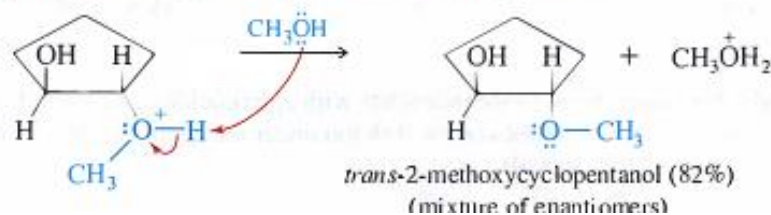


1,2-epoxycyclopentane

Step 2: The alcohol (solvent) attacks and opens the ring.

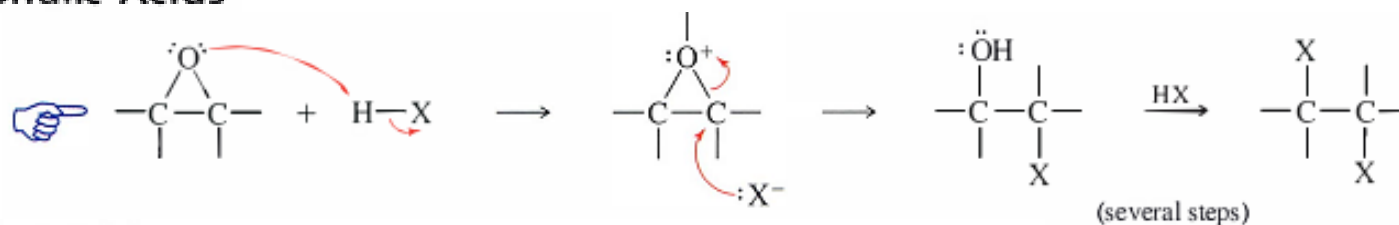


Step 3: Deprotonation to give the product, a 2-alkoxy alcohol.



In Alcohols

Using Hydrohalic Acids



PROBLEM 14-23

When ethylene oxide is treated with anhydrous HBr gas, the major product is 1,2-dibromoethane. When ethylene oxide is treated with concentrated aqueous HBr, the major product is ethylene glycol. Use mechanisms to explain these results.

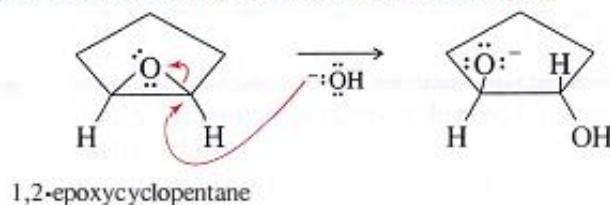
Base-Catalyzed Ring Opening of Epoxides

MECHANISM 14-4

Base-Catalyzed Opening of Epoxides

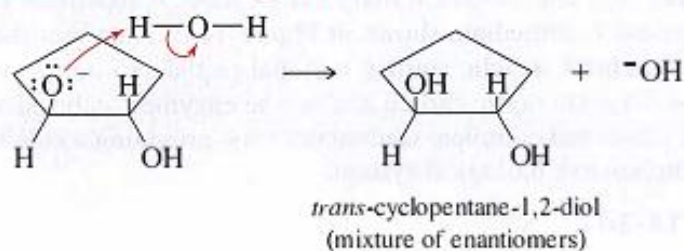
Strong bases and nucleophiles do not attack and cleave most ethers. Epoxides are more reactive, however, because opening the epoxide relieves the strain of the three-membered ring. Strong bases can attack and open epoxides, even though the leaving group is an alkoxide.

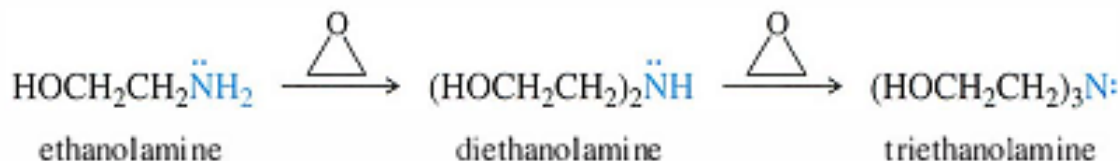
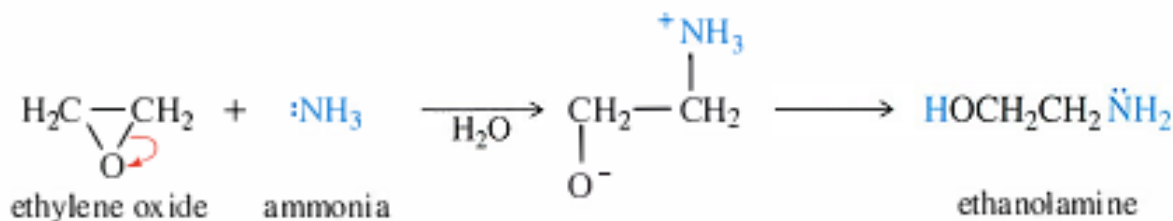
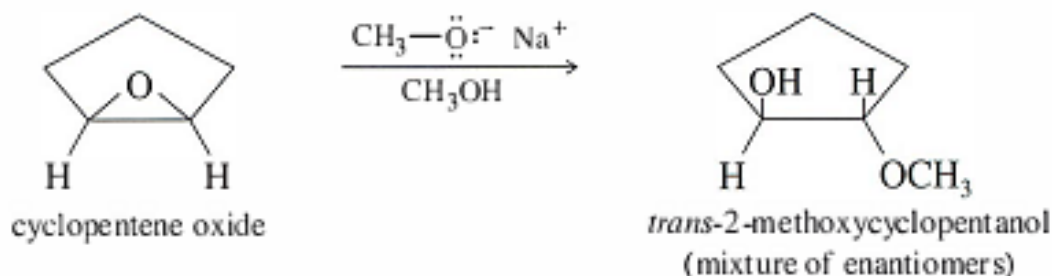
Step 1: A strong base attacks and opens the ring to an alkoxide.



(Continued)

Step 2: Protonation of the alkoxide gives the diol.





PROBLEM 14-25

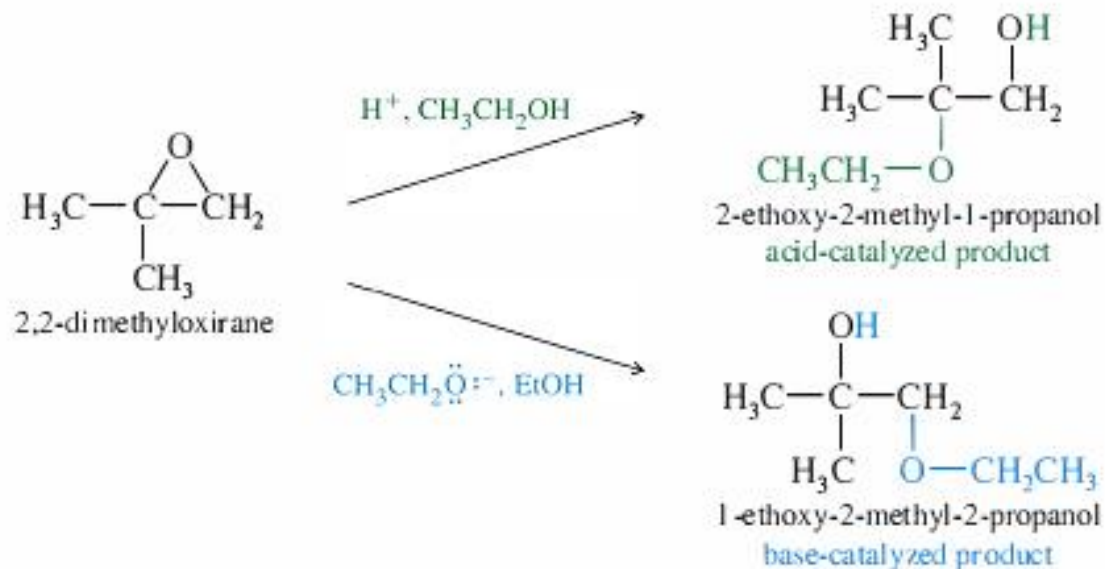
Propose a complete mechanism for the reaction of cyclopentene oxide with sodium methoxide in methanol.

PROBLEM 14-26

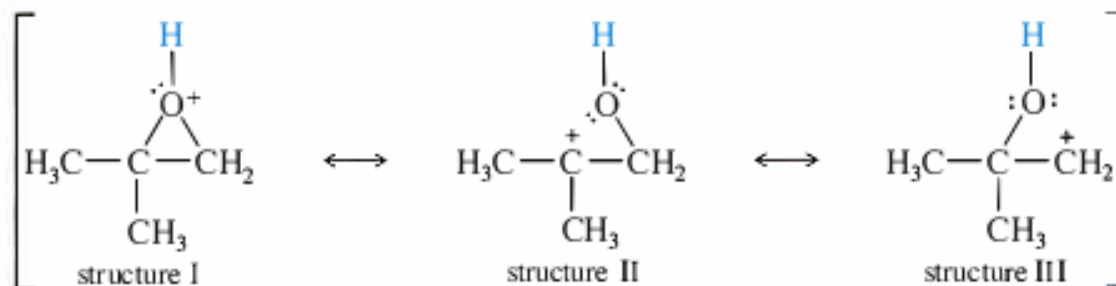
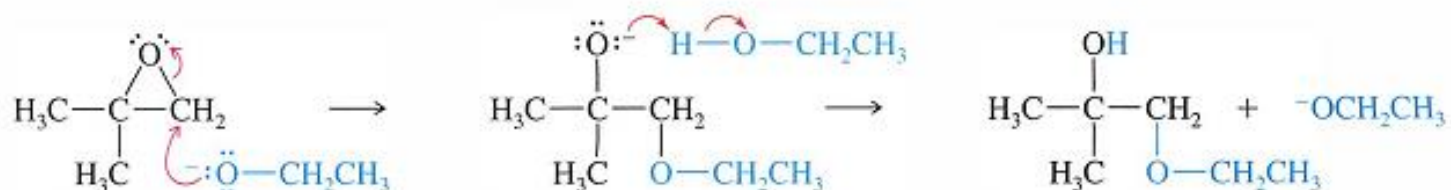
Predict the major product when each reagent reacts with ethylene oxide.

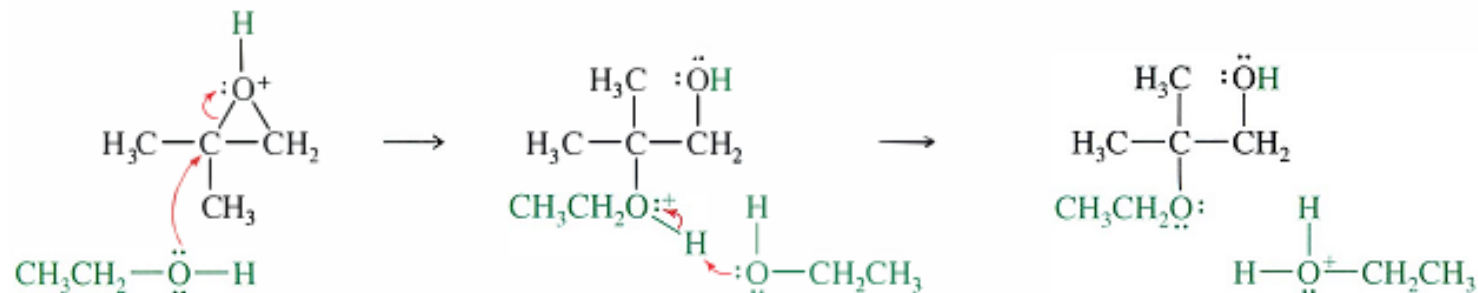
- | | |
|---|------------------------------------|
| (a) $\text{NaOCH}_2\text{CH}_3$ (sodium ethoxide) | (b) NaNH_2 (sodium amide) |
| (c) NaSPh (sodium thiophenoxide) | (d) PhNH_2 (aniline) |
| (e) KCN (potassium cyanide) | (f) NaN_3 (sodium azide) |

Orientation of Epoxide Ring Opening



Under basic conditions, the alkoxide ion simply attacks the less hindered carbon atom in an $\text{S}_{\text{N}}2$ displacement.





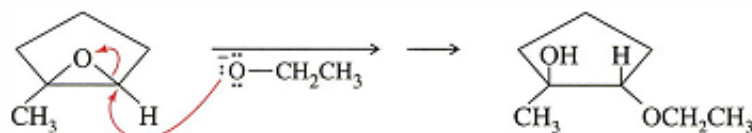
SOLVED PROBLEM 14-2

Predict the major products for the reaction of 1-methyl-1,2-epoxycyclopentane with

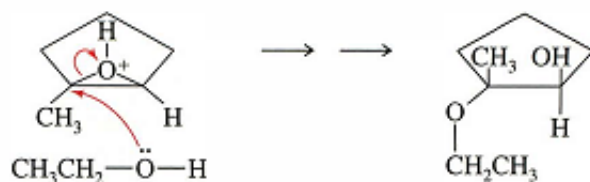
- sodium ethoxide in ethanol
- H_2SO_4 in ethanol

SOLUTION

- Sodium ethoxide attacks the less hindered secondary carbon to give (*E*)-2-ethoxy-1-methylcyclopentanol.



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

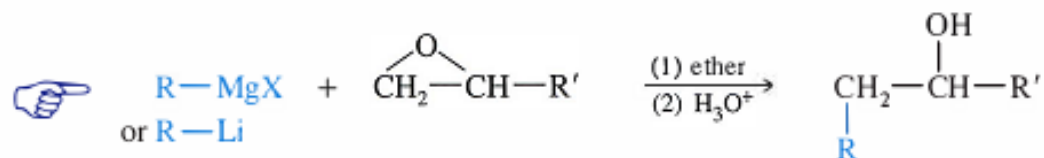


PROBLEM 14-27

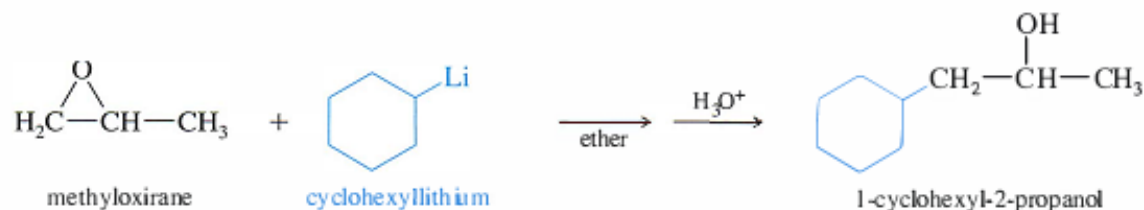
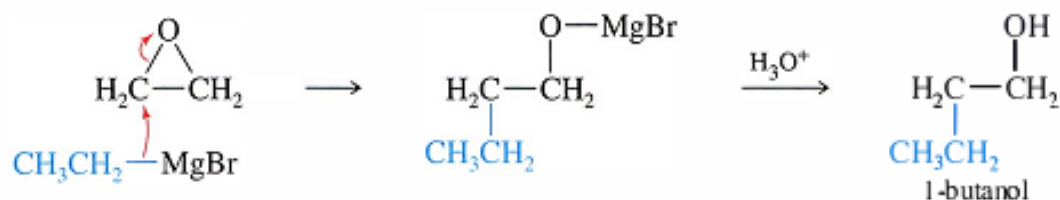
Predict the major products of the following reactions, including stereochemistry where appropriate.

- 2,2-dimethyloxirane + $\text{H}^+/\text{H}_2^{18}\text{O}$ (oxygen-labeled water)
- 2,2-dimethyloxirane + $\text{H}^{18}\text{O}^-/\text{H}_2^{18}\text{O}$
- (*Z*)-2-ethyl-2,3-dimethyloxirane + $\text{CH}_3\text{O}^-/\text{CH}_3\text{OH}$
- (*Z*)-2-ethyl-2,3-dimethyloxirane + $\text{H}^+/\text{CH}_3\text{OH}$

Reactions of Epoxides with Grignard and Organolithium Reagents



For example, ethylmagnesium bromide reacts with oxirane (ethylene oxide) to form the magnesium salt of 1-butanol.



PROBLEM 14-28

Give the expected products of the following reactions. Include a hydrolysis step where necessary.

- ethylene oxide + isopropylmagnesium bromide
- 2,2-dimethyloxirane + methyllithium
- cyclopentylloxirane + ethyllithium