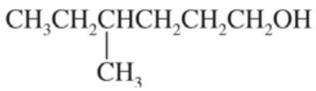
Chapter 11
Alcohols and Ethers

Nomenclature of Alcohols – Systematic names

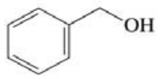
1. **Select the longest chain containing the hydroxyl and change the suffix ending of the parent alkane from -e to -ol**
2. **Number the parent to give the hydroxyl the lowest possible number**
3. **The other substituents take their locations accordingly**



$$CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2CH_2OH$$

4-methyl-1-hexanol

Common alcohols with other groups

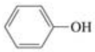


Benzyl alcohol
a benzylic alcohol

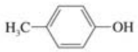
2-Propenol
(or prop-2-en-1-ol,
or allyl alcohol)
an allylic alcohol

2-Propynol
(or prop-2-yn-1-ol,
or propargyl alcohol)

Phenols contain a hydroxy group, but are not classified as an alcohol



Phenol



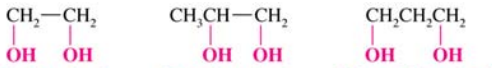
***p*-Methylphenol**
a substituted phenol

Ar—OH

General formula
for a phenol

Common names are still allowed to use

- **Alcohols with two hydroxyls are called diols in nomenclature and glycols in common nomenclature**



$$\underset{\displaystyle OH}{\underset{|}{CH_2}}-\underset{\displaystyle OH}{\underset{|}{CH_2}} \qquad CH_3\underset{\displaystyle OH}{\underset{|}{CH}}-\underset{\displaystyle OH}{\underset{|}{CH_2}} \qquad \underset{\displaystyle OH}{\underset{|}{CH_2}}CH_2\underset{\displaystyle OH}{\underset{|}{CH_2}}$$

Common	Ethylene glycol	Propylene glycol	Trimethylene glycol
IUPAC	1,2-Ethanediol or ethane-1,2-diol	1,2-Propanediol or propane-1,2-diol	1,3-Propanediol or propane-1,3-diol

Nomenclature of Ethers

Common Names

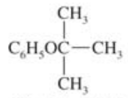
- The groups attached to the oxygen are listed in alphabetical order

$CH_3OCH_2CH_3$

Ethyl methyl ether

$CH_3CH_2OCH_2CH_3$

Diethyl ether

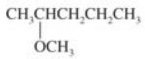


$C_6H_5OC(CH_3)_2-CH_3$

tert-Butyl phenyl ether

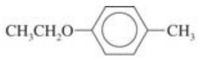
IUPAC

- Ethers are named as having an alkoxyl substituent on the main chain



$CH_3CHCH_2CH_2CH_3$ with OCH_3 on C-2

2-Methoxypentane



1-Ethoxy-4-methylbenzene

$CH_3OCH_2CH_2OCH_3$

1,2-Dimethoxyethane

Cyclic ethers

Cyclic ethers can be named using the prefix oxa-

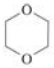
Three-membered ring ethers can be called oxiranes; commonly called epoxides and named as alkene oxides

Four-membered ring ethers can be called oxetanes

Oxacyclopropane
or oxirane
(ethylene oxide)

Oxacyclobutane
or oxetane

Oxacyclopentane
(tetrahydrofuran)

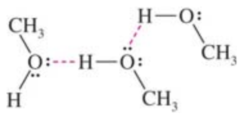


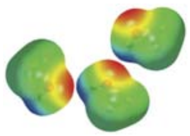
1,4-Dioxacyclohexane
(1,4-dioxane)

THF and dioxane are common solvents

Physical Properties of Alcohols and Ethers

1. Ether boiling points are roughly comparable to hydrocarbons of the same molecular weight
   - Molecules of ethers cannot hydrogen bond to each other
2. Alcohols have considerably higher boiling points
   - Molecules of alcohols hydrogen bond to each other

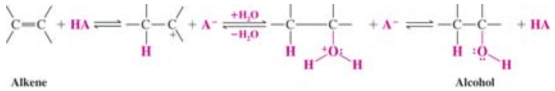




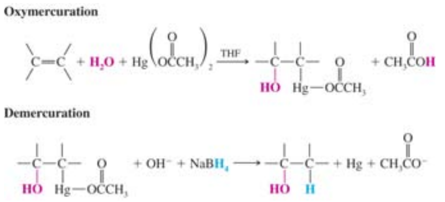
3. Both alcohols and ethers can hydrogen bond to water and have similar solubilities in water (5 C or more insoluble)
   - Diethyl ether and 1-butanol have solubilities of about 8 g per 100 mL in water

Synthesis of Alcohols from Alkenes – all previous

1. Acid-Catalyzed Hydration of Alkenes
   - This is a reversible reaction with Markovnikov regioselectivity

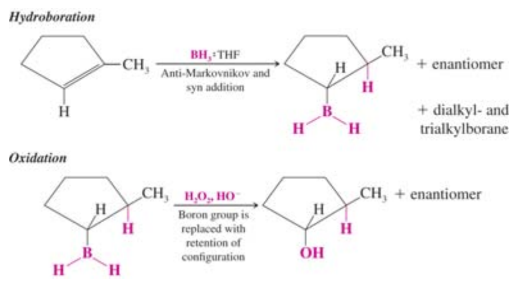


2. Oxymercuration-demercuration
   - This is a Markovnikov addition which occurs without rearrangement



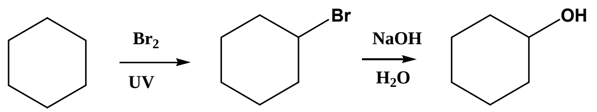
3. Hydroboration-Oxidation

- This addition reaction occurs with anti-Markovnikov regiochemistry and syn stereochemistry



Alcohols from RX

- Alcohols are products of S_N2 and occasionally S_N1 reactions of RX
- Limited usefulness as a synthesis route because RX is usually made from alcohol.



Alcohols as Acids

- Alcohols have acidities similar to water
- Sterically hindered alcohols such as *tert*-butyl alcohol are less acidic (have higher pKa values)
  - Why?: The conjugate base is not well solvated and so is not as stable

Acid	pK_a
CH_3OH	15.5
H_2O	15.74
CH_3CH_2OH	15.9
$(CH_3)_3COH$	18.0

- Alcohols are stronger acids than terminal alkynes and primary or secondary amines

Relative Acidity

$$H_2O > ROH > RC{\equiv}CH > H_2 > NH_3 > RH$$

- An alkoxide can be prepared by the reaction of an alcohol with sodium or potassium metal

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Rough scale of acidities – MEMORIZE!

Acid	Conjugate Base	pKa
Strong (HCl)	NaCl	-5
Organic (RCO_2H)	RCO_2Na	5
Alcohols, water	$NaOCH_3$, NaOH	15
Terminal alkyne	Na C ≡ CR	25
Amine NH, hydrogen	$NaNH_2$, NaH	35 (37)
Alkanes (sp_3 C-H)	BuLi	45-50

Conversion of Alcohols into Leaving Groups

1. Monofunctionalized carbons are critical structures, both for their own purposes and as intermediates
2. Hydroxyl groups are poor leaving groups
3. Several methods are available to convert alcohols into better leaving groups

$$R\text{-}OH \longrightarrow R\text{-}X$$

X= Br, Cl, OSO_2R'

Conversion of Alcohols into Alkyl Halides

Three general methods are available

1. Hydrogen halides
2. Phosphorus tribromide
3. Thionyl chloride

$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-OH + HCl_{(concd)} \xrightarrow{25°C} CH_3-\overset{CH_3}{\underset{CH_3}{C}}-Cl + H_2O$$

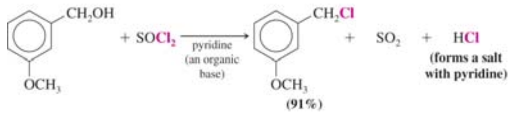
(94%)

$$CH_3CH_2CH_2CH_2OH + HBr_{(concd)} \xrightarrow[\text{reflux}]{} CH_3CH_2CH_2CH_2Br$$

(95%)

$$3\ (CH_3)_2CHCH_2OH + PBr_3 \xrightarrow[4\ h]{-10\ \text{to}\ 0°C} 3\ (CH_3)_2CHCH_2Br + H_3PO_3$$

(55–60%)



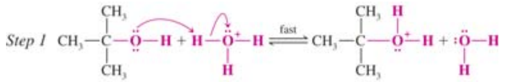
Reaction of Alcohols with Hydrogen Halides

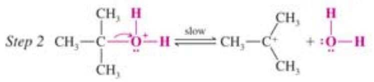
The order of reactivity is as follows

- Hydrogen halide HI > HBr > HCl > HF
- Type of alcohol 3° > 2° > 1° < methyl

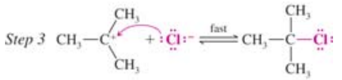
◆ Mechanism of the Reaction of Alcohols with HX

- S_N1 mechanism for 3°, 2°, allylic and benzylic alcohols

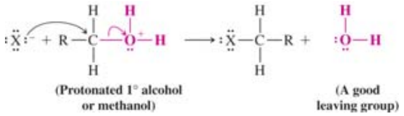




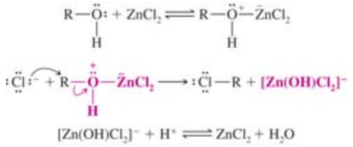
Prone to carbocation rearrange if more stable C+ available!



Primary and methyl alcohols undergo substitution by an S_N2 mechanism



Primary and secondary chlorides can only be made with the assistance of a Lewis acid such as zinc chloride



$$[Zn(OH)Cl_2]^- + H^+ \rightleftharpoons ZnCl_2 + H_2O$$

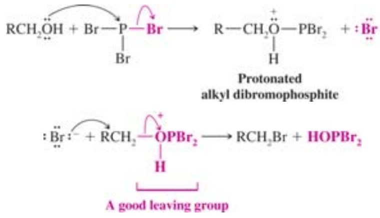
Reaction of Alcohols with PBr_3 and $SOCl_2$

These reagents only react with 1° and 2° alcohols in S_N2 reactions

- Convert the hydroxyl to an excellent leaving group
- No rearrangements

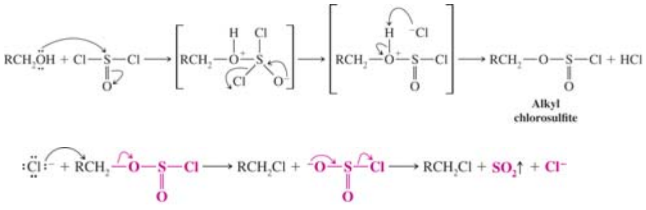
Phosphorus tribromide

$3\ R-OH + PBr_3 \longrightarrow 3\ R-Br + H_3PO_3$ (1° or 2°)



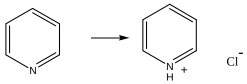
Thionyl chloride

$R-OH + SOCl_2 \xrightarrow{\text{reflux}} R-Cl + SO_2 + HCl$ (1° or 2°)



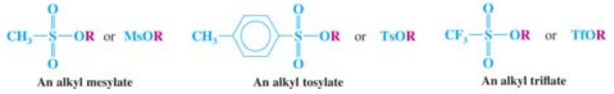
Often an amine is added to react with HCl formed in the reaction

$R_3N: + HCl \longrightarrow R_3NH^+ + Cl^-$



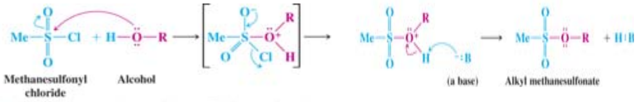
Sulfonate Esters: Tosylates, Mesylates, and Triflates

The hydroxyl group of an alcohol can be converted to a good leaving group by conversion to a sulfonate ester



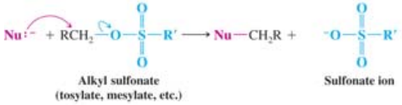
Sulfonyl chlorides are used to convert alcohols to sulfonate esters

- Base is added to react with the HCl generated

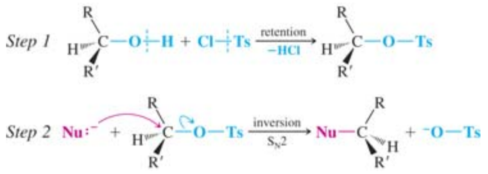


Resume on 11/20

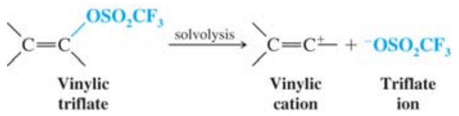
A sulfonate ion (a weak base) is an excellent leaving group

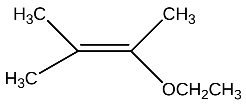


- If the alcohol OH is at a stereogenic center then the overall reaction with the nucleophile proceeds with inversion of configuration
  - Formation of a sulfonate ester proceeds with retention of configuration



Triflate anion is such a good leaving group that even vinyl triflates can undergo S_N1 reaction

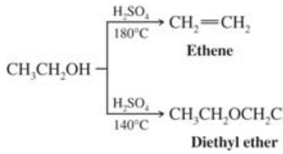




Example of product in ethanol

Synthesis of Ethers

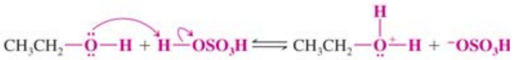
1. **Ethers by Intermolecular Dehydration of Alcohol**
   - **Primary alcohols can dehydrate to ethers**
     - ➔ **This reaction occurs at lower temperature than the competing dehydration to an alkene**
     - ➔ **This method generally does not work with secondary or tertiary alcohols because elimination competes strongly**



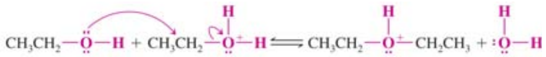
Predict the reaction mechanism!

The mechanism is an S_N2 reaction

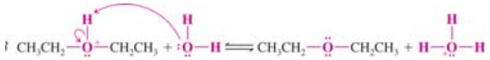
1. protonation



2. Nucleophilic attack by second ROH



3. deprotonation



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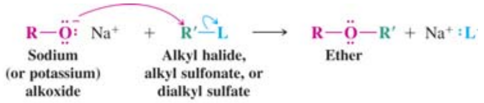
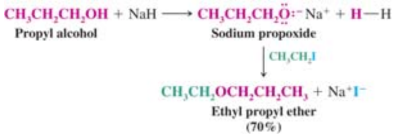
2. Williamson Ether Synthesis

- **This is a good route for synthesis of unsymmetrical ethers**





Limitations?

Alkyl halide or sulfonate should be primary or methyl to avoid E2
If R = t-butyl, R' must be methyl
Modest yields with secondary halides if both substrates unhindered
Substitution is favored over elimination at lower temperatures

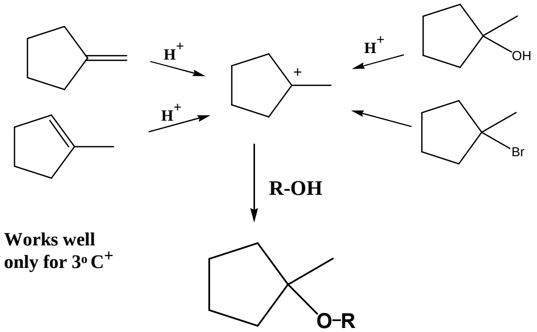
3. Synthesis of Ethers by Alkoxymercuration-Demercuration

Same reaction as used for hydration of alkenes, except using an alcohol as the nucleophile (instead of the water)

(98% Yield)

4. Ethers from carbocations plus alcohols

Generating a carbocation in an alcohol as solvent can lead to ethers



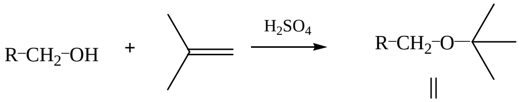
Works well only for 3° C^+

Use of t-butyl ethers as protecting groups

Protecting group: a group added to insulate one sensitive functional group to allow a reaction at another part of the molecule

- Protecting group is later removed

Step 1: Formation of t-butyl ether to protect a hydroxy group



Step 2: reaction elsewhere

||

$R-CH_2-O-$**t-Bu**

Step 3: removal of t-butyl group with dilute aqueous acid

Example: t-butyl ethers as protecting group

Challenge: the alkylation of an alkyne by an alkyl halide that also contains a hydroxy group

$$HOCH_2CH_2CH_2Br \xrightarrow{NaC\equiv CH} HOCH_2CH_2CH_2C\equiv CH$$

4-Pentyn-1-ol

First step fails, Why?

$$HOCH_2CH_2CH_2Br \xrightarrow[(2)\ CH_2=C(CH_3)_2]{(1)\ H_2SO_4} (CH_3)_3COCH_2CH_2CH_2Br \xrightarrow{NaC\equiv CH}$$

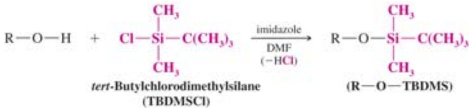
$$(CH_3)_3COCH_2CH_2CH_2C\equiv CH \xrightarrow{H_3O^+/H_2O} HOCH_2CH_2CH_2C\equiv CH + (CH_3)_3COH$$

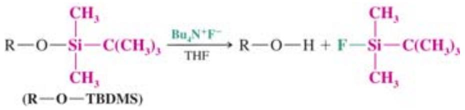
4-Pentyn-1-ol

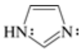
Silyl Ether Protecting Groups

Silyl ethers are widely used protecting groups for alcohols

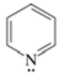
- **The *tert*-butyl dimethysilyl (TBDMS) ether is common**
- **The protecting group is introduced by reaction of the alcohol with the chlorosilane in the presence of an aromatic amine base**
- **The silyl ether protecting group is removed by treatment with fluoride ion (*e.g.* from tetrabutyl ammonium fluoride)**







Imidazole



Pyridine

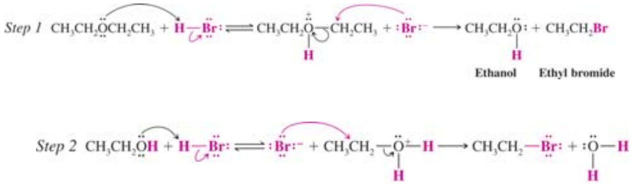
Reactions of Ethers

Acyclic ethers are generally unreactive, except for cleavage by very strong acids to form the corresponding alkyl halides

- **Dialkyl ethers undergo S_N2 reaction to form 2 equivalents of the alkyl bromide**

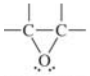
$CH_3CH_2OCH_2CH_3 + 2\ HBr \longrightarrow 2\ CH_3CH_2Br + H_2O$

Cleavage of an ether

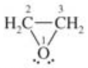


Epoxides: a reactive cyclic ether

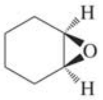
- **Epoxides are three-membered ring cyclic ethers**
  - **These groups are also called oxiranes**



An epoxide



IUPAC name: oxirane
Common name: ethylene oxide

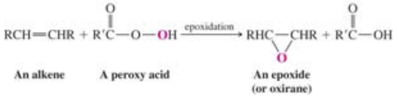


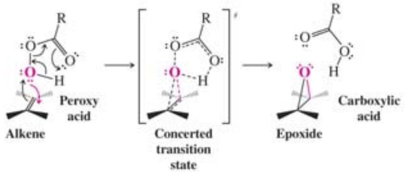
1,2-Epoxycyclohexane
(cyclohexene oxide)

Because of ring strain in the three-membered ring, these ethers are reactive and useful intermediates

Epoxides are formed by reaction of alkenes with peroxy acids

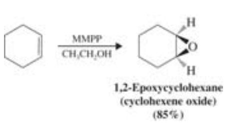
This process is called epoxidation and involves syn addition of oxygen



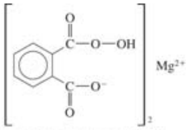


One step transfer of an oxygen atom via a cyclic transition state

Magnesium monoperoxyphthalate (MMPP) is a common and safe peroxy acid for epoxidation



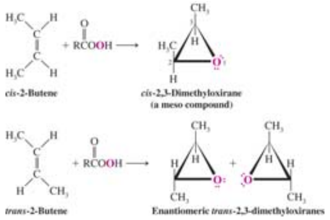
1,2-Epoxycyclohexane (cyclohexene oxide) (85%)



Magnesium monoperoxyphthalate (MMPP)

Epoxidation is stereospecfic

- Epoxidation of *cis*-2-butene gives the meso cis oxirane
- Epoxidation of *trans*-2-butene gives the racemic trans oxirane



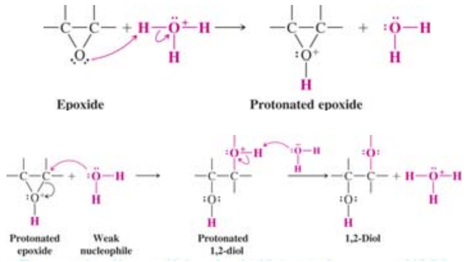
Reaction of Epoxides

Epoxides are much more reactive than regular ethers

- Strain energy is released in opening the three-membered ring

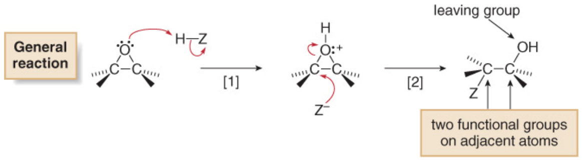
◆ Acid-catalyzed opening of an epoxide occurs by initial protonation of the oxygen, making the epoxide even more reactive

- Acid-catalyzed hydrolysis of an epoxide leads to a 1,2-diol

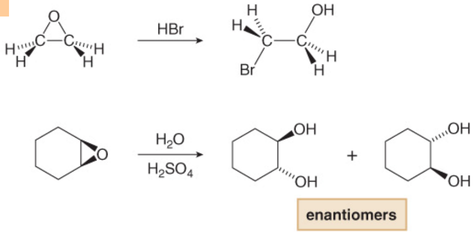


Epoxides + HZ

- Acids that contain a nucleophile Z also open epoxide rings by a two-step sequence.
- HCl, HBr and HI, as well as H_2O and ROH in the presence of acid, all open an epoxide ring in this manner.

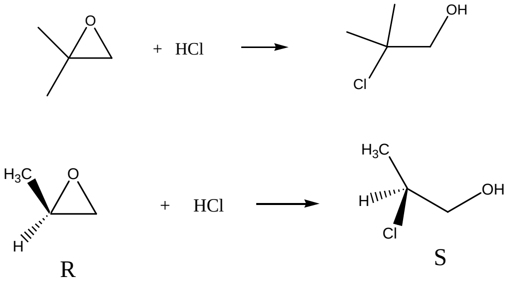


Epoxides + HZ: examples



What does second example tell us abut mechanism?

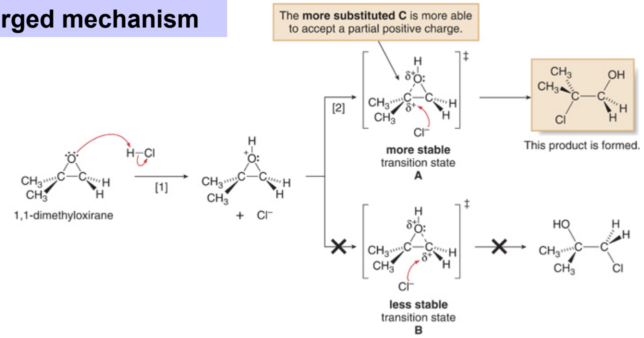
More information about mechanism



Summary of information

- ♦ Not pure S_N1 (no free carbocation):
  - no loss of stereochemistry
  - no rearrangements
- ♦ Not regular S_N2
  - Nucleophile would go to 1°
  - 3°>2°>1°

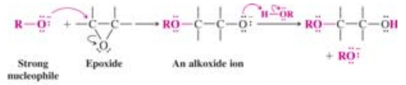
Merged mechanism

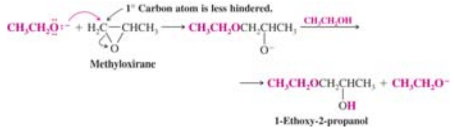


Bridged ion maintains stereochemistry (backside), but directs incoming Nucleophile to more stable carbocation

Base-catalyzed reaction with strong nucleophiles (*e.g.* an alkoxide or hydroxide) occurs by an S_N2 mechanism

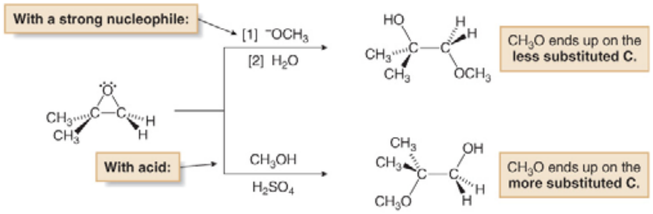
- **The nucleophile attacks at the less sterically hindered carbon of the epoxide**





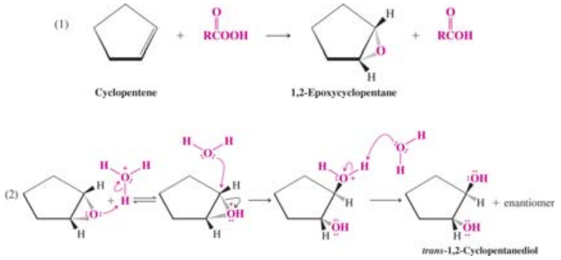
Summary of epoxide openings

- Ring opening of an epoxide with either a strong nucleophile or an acid HZ is regioselective.
- Site selectivity of these two reactions is exactly the opposite!!

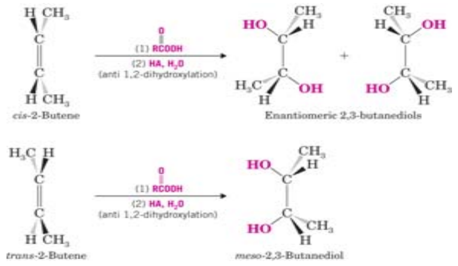


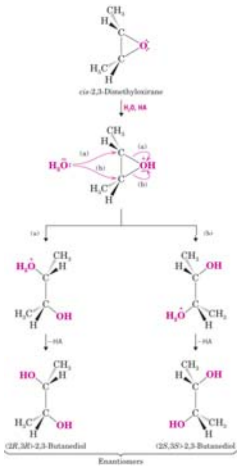
Anti 1,2-Dihydroxylation of Alkenes via Epoxides

Opening of the following epoxide with water under acid catalyzed conditions gives the trans diol

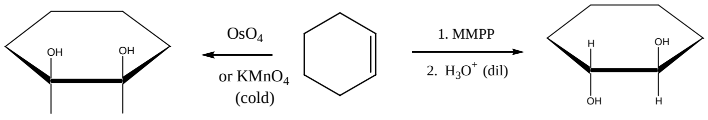


Epoxide ring-opening is a stereospecific process



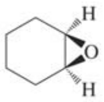


Options for synthesis of diols



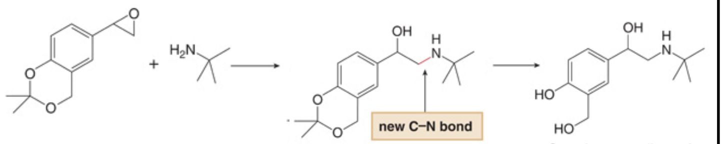
syn addition

Trans product via epoxide



Example in the synthesis of a bronchodilater

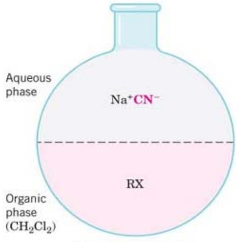
Predict the product



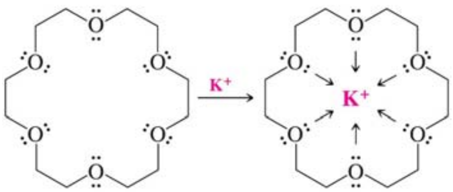
Generic name: albuterol
Trade names: Proventil, Ventolin

Phase Transfer Catalysis

- **General problem: anionic nucleophiles tend to be soluble in water, but not organic solvents**



Crown ethers



18-Crown-6