

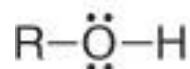
# **Alcohols, Ethers and Epoxides**

## **Chapter 17-18**

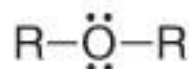
**Organic Chemistry, *8th Edition***

**John McMurry**

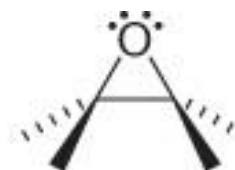
# Introduction—Structure and Bonding



alcohol

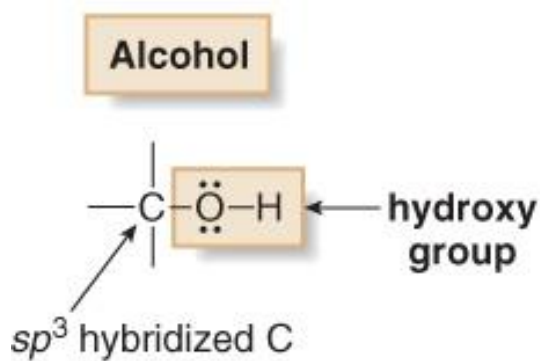


ether

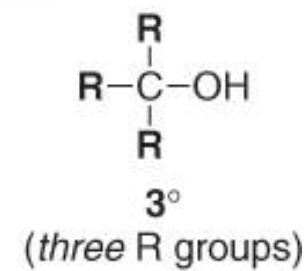
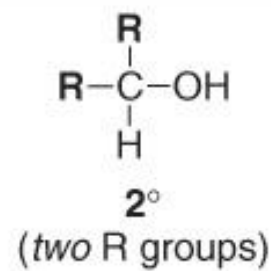
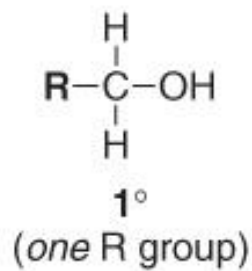


epoxide

- **Alcohols** contain a hydroxy group (OH) bonded to an  $sp^3$  hybridized carbon.

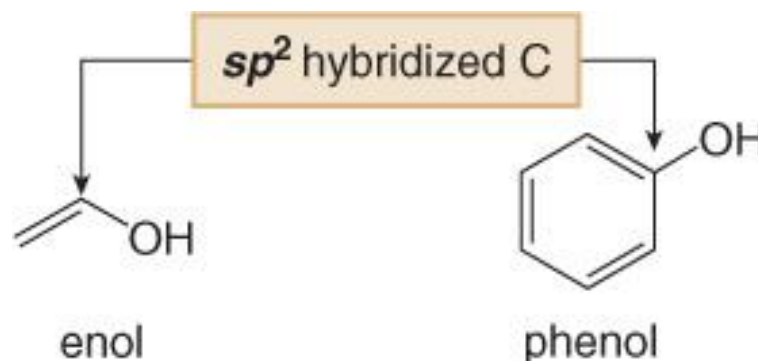


## Classification of alcohols

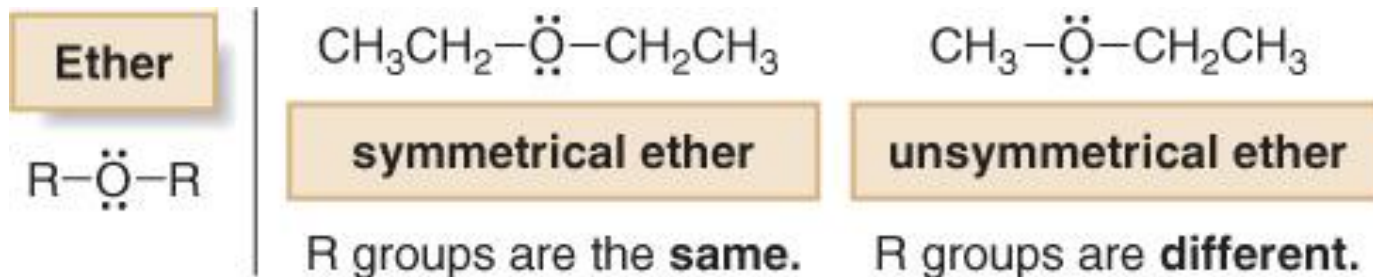


# Introduction—Structure and Bonding

- **enols** and **phenols**—undergo different reactions than alcohols.



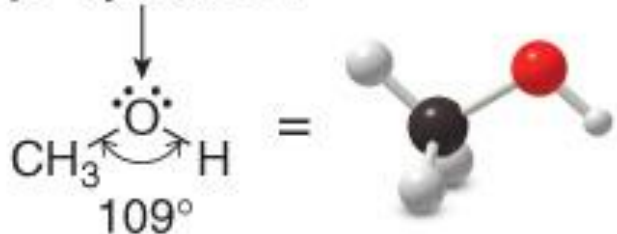
- **Ethers** have two hydrocarbon groups bonded to an oxygen atom.



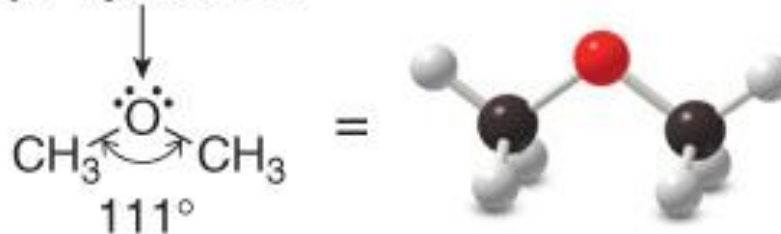
# Introduction—Structure and Bonding

- The oxygen atom in alcohols, ethers and epoxides is  $sp^3$  hybridized. Alcohols and ethers have a bent shape like that in  $H_2O$ .
- The bond angle around the O atom in an alcohol or ether is similar to the tetrahedral bond angle of  $109.5^\circ$ .
- Because the O atom is much more electronegative than carbon or hydrogen, the C—O and O—H bonds are all polar.

$sp^3$  hybridized



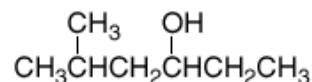
$sp^3$  hybridized



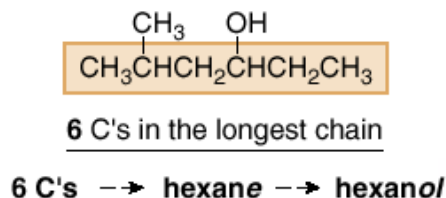
# Nomenclature of Alcohols

## How To Name an Alcohol Using the IUPAC System

**Example** Give the IUPAC name of the following alcohol:



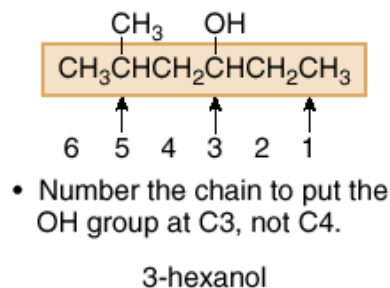
**Step [1]** Find the longest carbon chain containing the carbon bonded to the OH group.



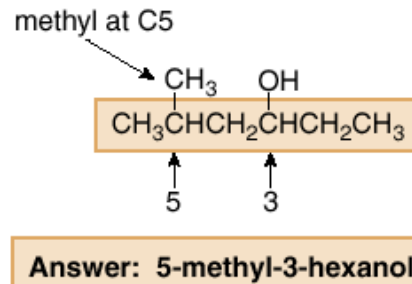
- Change the **-e** ending of the parent alkane to the suffix **-ol**.

**Step [2]** Number the carbon chain to give the OH group the lower number, and apply all other rules of nomenclature.

a. **Number** the chain.

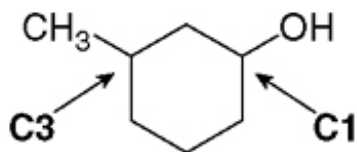


b. **Name** and **number** the substituents.

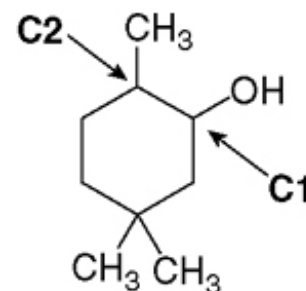


# Nomenclature of Alcohols

- When an OH group is bonded to a ring, the ring is numbered beginning with the OH group.



**3-methylcyclohexanol**

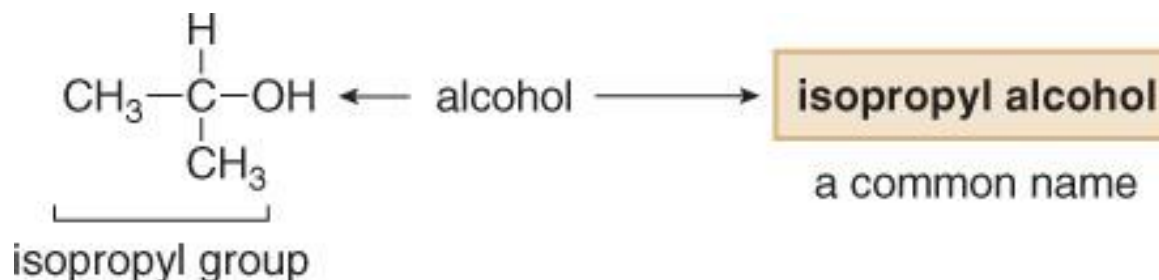


**2,5,5-trimethylcyclohexanol**

[ The OH group is at C1; the second substituent (CH<sub>3</sub>) gets the lower number. ]

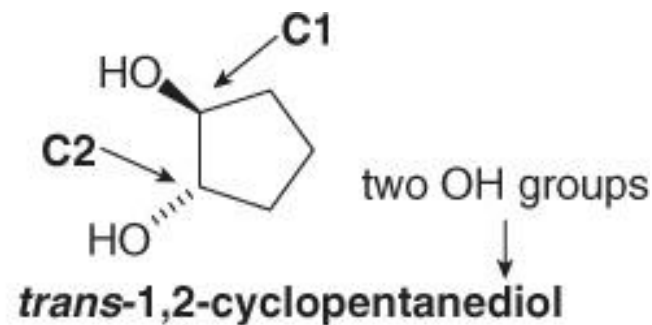
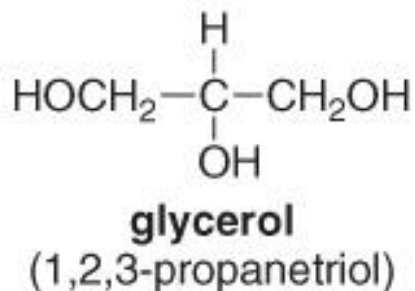
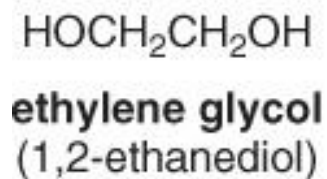
[ The OH group is at C1; the second substituent (CH<sub>3</sub>) gets the lower number. ]

- Common names are often used for simple alcohols.



# Nomenclature of Alcohols

- Compounds with two hydroxy groups are called **diols** or **glycols**. Compounds with three hydroxy groups are called **triols** and so forth.



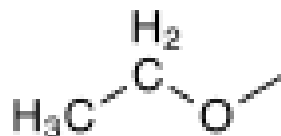
Common names are usually used for these simple compounds.

Numbers are now needed to show the location of **two** OH groups.

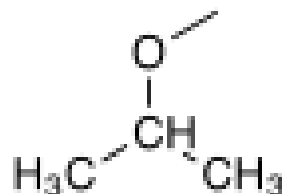
# Nomenclature of Alcohols



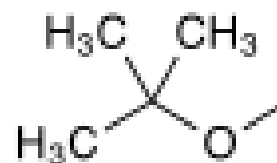
Methoxy



ethoxy



2-propoxy  
isopropoxy

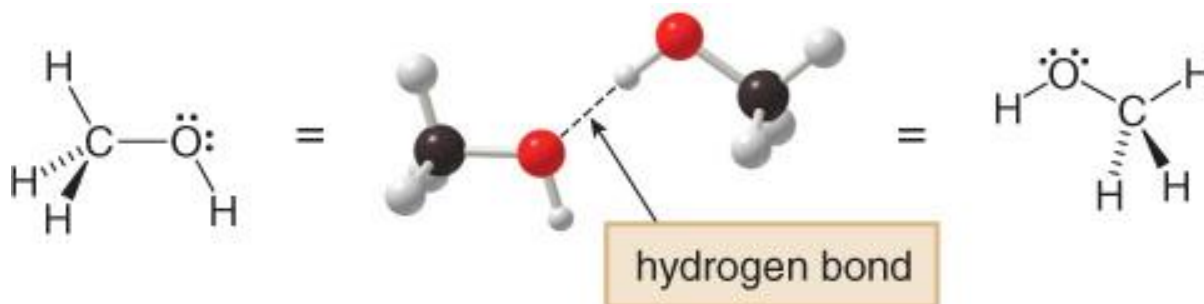


2-methyl-2-propoxy  
tert-butoxy

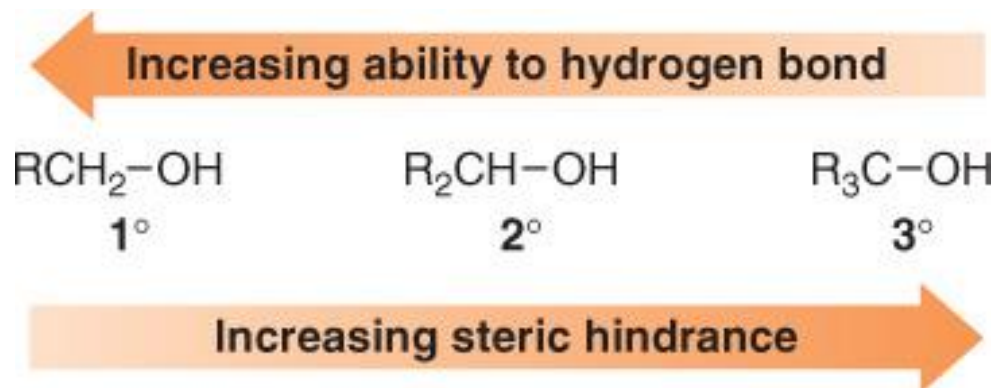


# Physical Properties

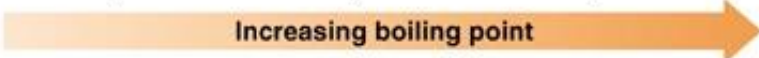

- dipole-dipole interactions.
- intermolecular hydrogen bonding. Alcohols are more polar than ethers and epoxides.



- Steric factors affect hydrogen bonding.

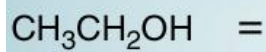


# Physical Properties

Property	Observation
Boiling point (bp) and melting point (mp)	<ul style="list-style-type: none"> <li>For compounds of comparable molecular weight, the <b>stronger</b> the intermolecular forces, the <b>higher</b> the bp or mp.</li> </ul> <div style="text-align: center; margin: 10px 0;"> <math>\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3</math>      <math>\text{CH}_3\text{OCH}_2\text{CH}_3</math>      <math>\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}</math>              VDW                      VDW, DD                      VDW, DD, HB              bp 0 °C                      bp 11 °C                      bp 97 °C         </div> <div style="text-align: center; margin: 10px 0;">  <p><b>Increasing boiling point</b></p> </div> <hr/> <ul style="list-style-type: none"> <li>Bp's <b>increase</b> as the extent of hydrogen bonding <b>increases</b>.</li> </ul> <div style="text-align: center; margin: 10px 0;"> <math>(\text{CH}_3)_3\text{C}-\text{OH}</math>                      <math>\begin{matrix} \text{OH} \\   \\ \text{CH}_3\text{CH}_2\text{CHCH}_3 \end{matrix}</math>                      <math>\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2-\text{OH}</math>              3°    2°    1°              bp 83 °C                                      bp 98 °C                                      bp 118 °C         </div> <div style="text-align: center; margin: 10px 0;">  <p><b>Increasing ability to hydrogen bond</b> <b>Increasing boiling point</b></p> </div>
Solubility	<ul style="list-style-type: none"> <li>Alcohols, ethers, and epoxides having <math>\leq 5</math> C's are <math>\text{H}_2\text{O}</math> soluble because they each have an oxygen atom capable of hydrogen bonding to <math>\text{H}_2\text{O}</math> (Section 3.4C).</li> <li>Alcohols, ethers, and epoxides having <math>&gt; 5</math> C's are <math>\text{H}_2\text{O}</math> insoluble because the nonpolar alkyl portion is too large to dissolve in <math>\text{H}_2\text{O}</math>.</li> <li>Alcohols, ethers, and epoxides of any size are soluble in organic solvents.</li> </ul>

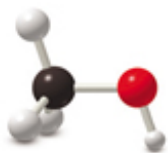
Key: VDW = van der Waals forces; DD = dipole-dipole; HB = hydrogen bonding

# Interesting Alcohols



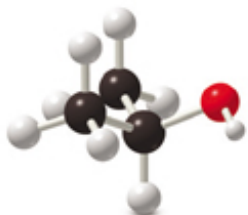
- Ethanol is the alcohol in red wine, obtained by the fermentation of grapes.

# Interesting Alcohols



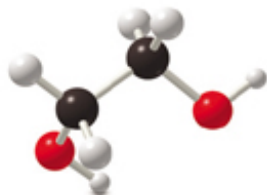
$\text{CH}_3\text{OH}$

- **Methanol ( $\text{CH}_3\text{OH}$ )** is also called wood alcohol, because it can be obtained by heating wood at high temperatures in the absence of air. Methanol is extremely toxic because of the oxidation products formed when it is metabolized in the liver (Section 12.14). Ingestion of as little as 15 mL causes blindness, and 100 mL causes death.
- 



$(\text{CH}_3)_2\text{CHOH}$

- **2-Propanol [ $(\text{CH}_3)_2\text{CHOH}$ ]** is the major component of rubbing alcohol. When rubbed on the skin it evaporates readily, producing a pleasant cooling sensation. Because it has weak antibacterial properties, 2-propanol is used to clean skin before minor surgery and to sterilize medical instruments.
- 

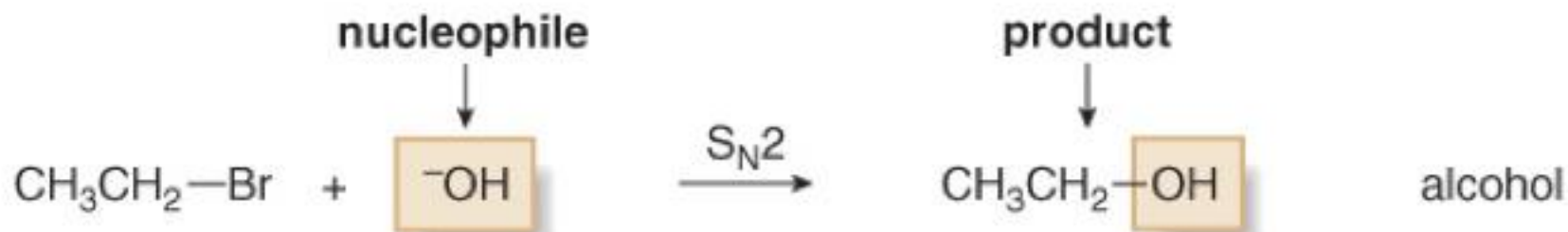


$\text{HOCH}_2\text{CH}_2\text{OH}$

- **Ethylene glycol ( $\text{HOCH}_2\text{CH}_2\text{OH}$ )** is the major component of antifreeze. It is readily prepared from ethylene oxide by reactions discussed in Section 9.15. It is sweet tasting but toxic.

# Preparation of Alcohols

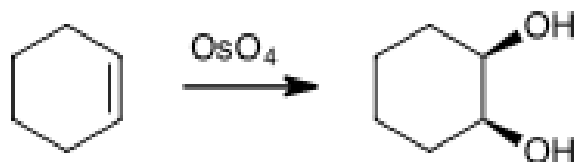
- From alkyl halides



- Hydration/hydroboration of alkenes

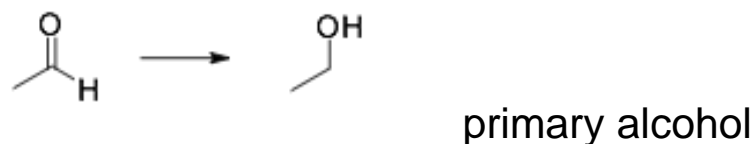


- Dihydroxylation of alkenes



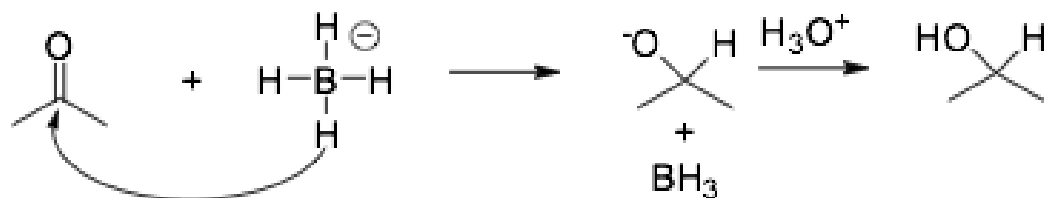
# Preparation of Alcohols

- Reduction of carbonyl compounds



$\text{H}_2/\text{Pd}$  reduces also  $\text{C}=\text{C}$   
 $\text{NaBH}_4, \text{LiAlH}_4$  selective for  $\text{C}=\text{O}$

Mechanism:

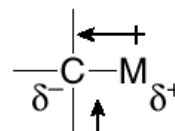


**H is transferred as  $\text{H}^-$**

# Reaction of carbonyl compounds with organometallic reagents

- Organometallic reagents contain a carbon atom bonded to a metal.

Organometallic reagents—  
General structure



=

R—M

M = metal

Most common metals:  
M = Li, Mg, Cu

R—Li

organolithium  
reagents

R—Mg—X

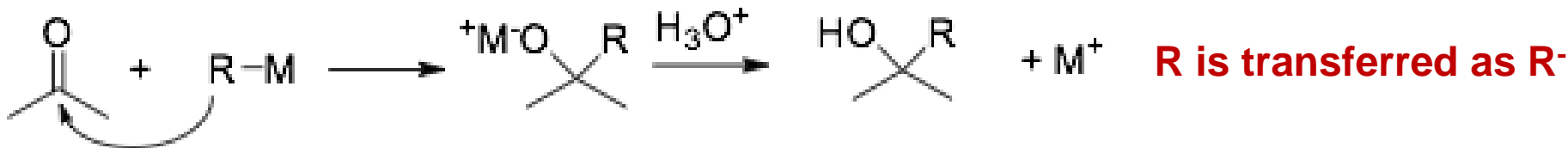
organomagnesium reagents  
or  
Grignard reagents

R  
|  
R—Cu<sup>-</sup> Li<sup>+</sup>

organocopper reagents  
or  
organocuprates

- The more polar the carbon–metal bond, the more reactive the organometallic reagent.

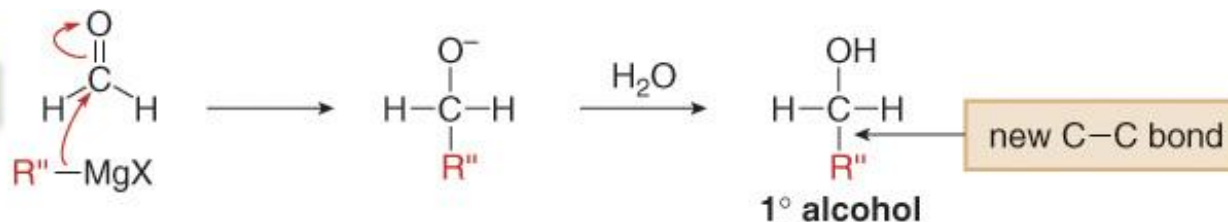
Mechanism:



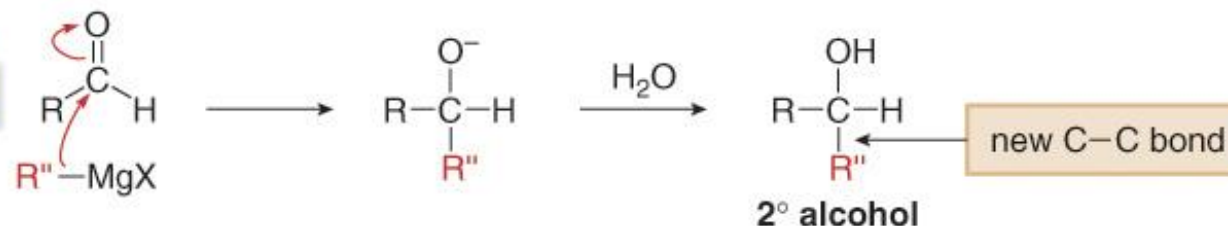


# Reaction of carbonyl compounds with organometallic reagents

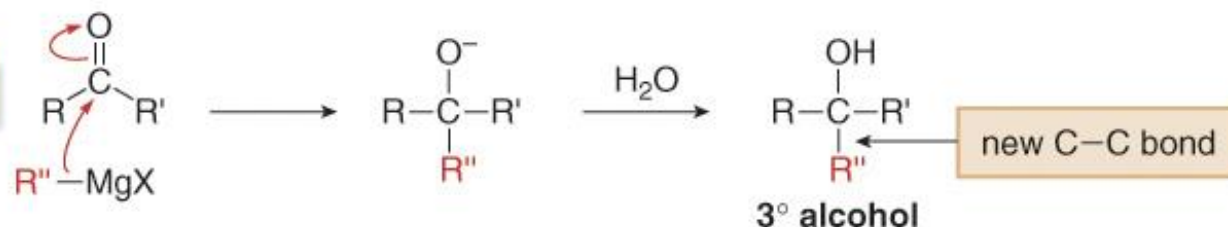
[1] Formaldehyde



[2] Other aldehydes



[3] Ketones



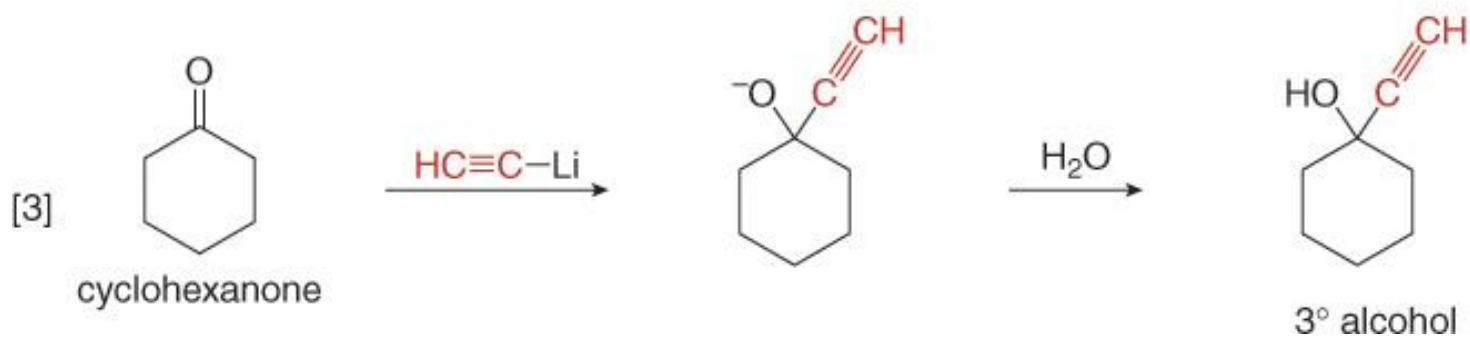
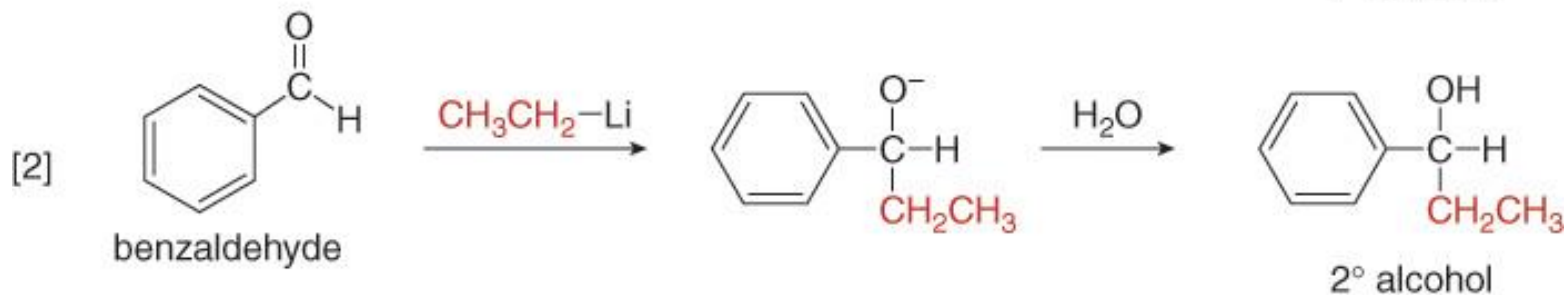
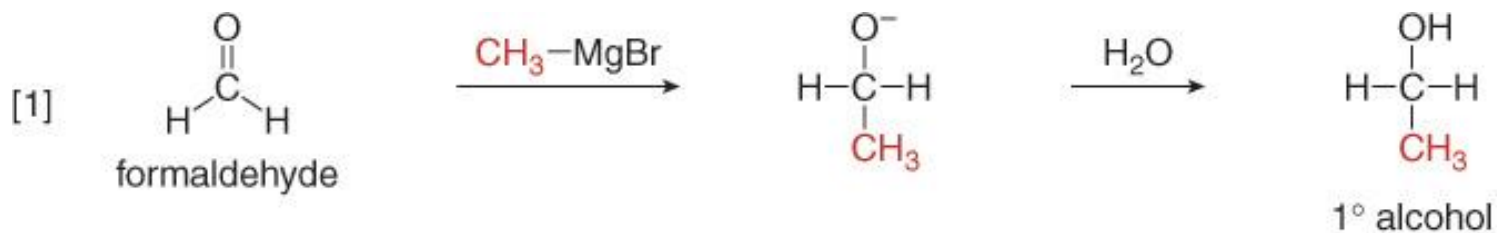
[1] Addition of  $\text{R}''\text{MgX}$  to formaldehyde ( $\text{CH}_2=\text{O}$ ) forms a 1° alcohol.

[2] Addition of  $\text{R}''\text{MgX}$  to all other aldehydes forms a 2° alcohol.

[3] Addition of  $\text{R}''\text{MgX}$  to ketones forms a 3° alcohol.

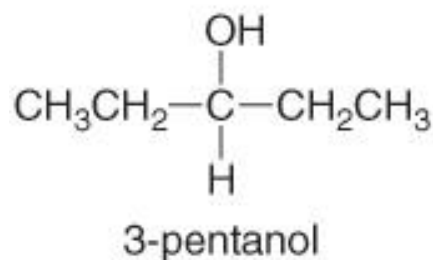


# Reaction of carbonyl compounds with organometallic reagents

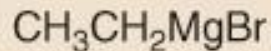
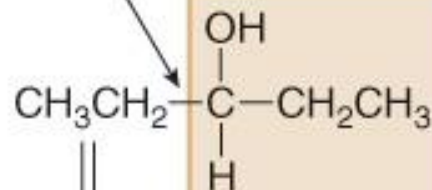


# Reaction of carbonyl compounds with organometallic reagents

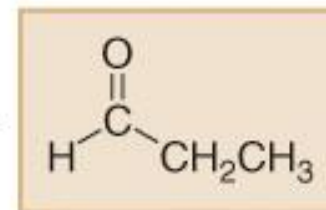
Retrosynthetic analysis for preparing 3-pentanol



Form this new bond by Grignard addition.



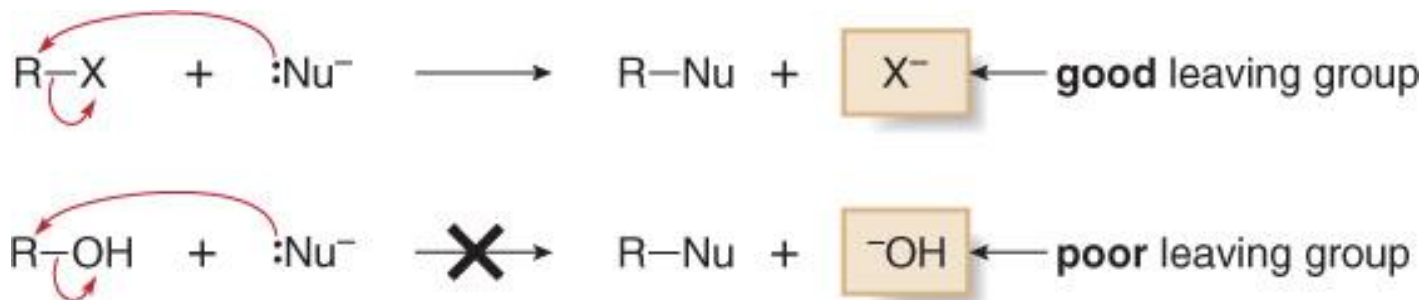
two-carbon  
Grignard reagent



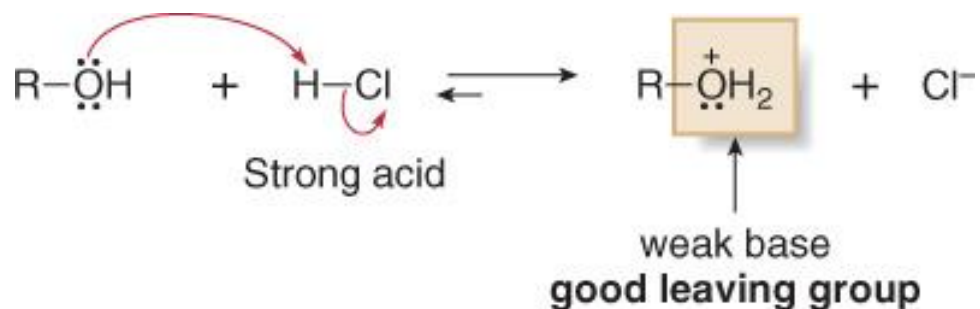
three-carbon aldehyde

# Reactions of Alcohols

- The OH group in alcohols is a very poor leaving group.

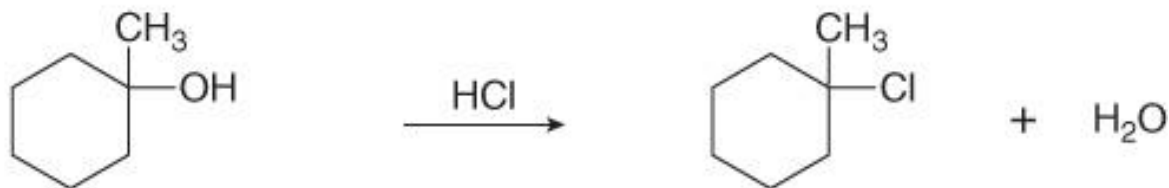


- By using acid, -OH can be converted into  $-\text{OH}_2^+$ , a good leaving group.

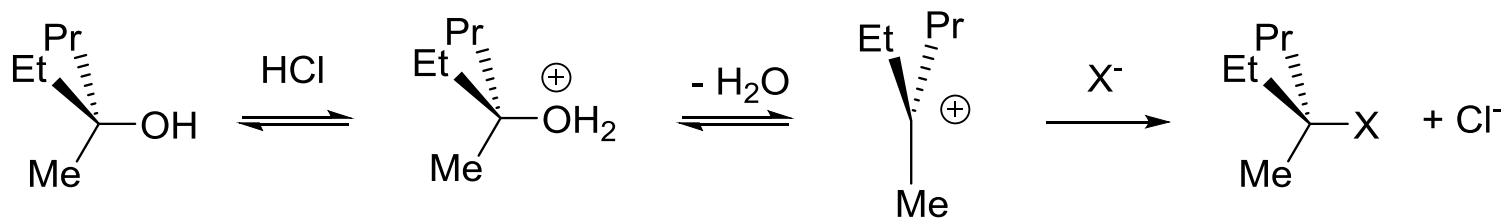


# Conversion of Alcohols to Alkyl Halides with HX

- The reaction of alcohols with HX (X = Cl, Br, I) is a general method to prepare 3° alkyl halides.

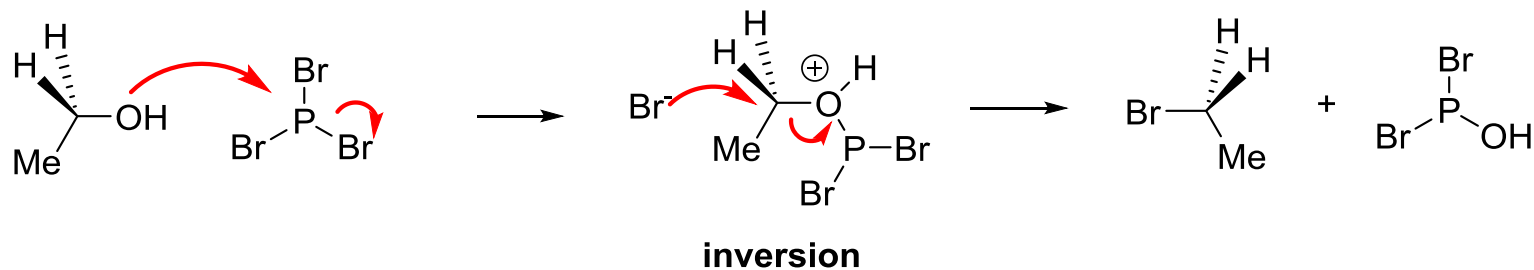
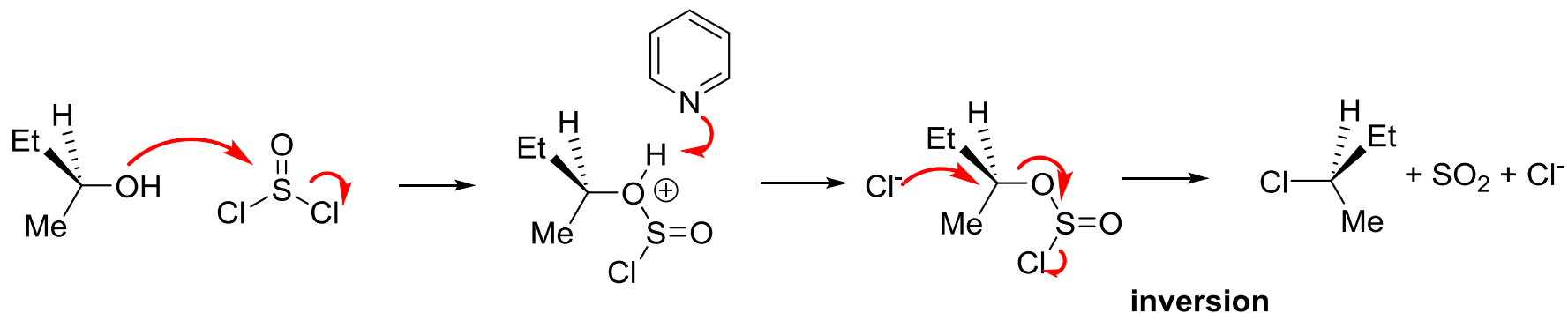


- The mechanism is S<sub>N</sub>1
- Racemization occurs



# Conversion of Alcohols to Alkyl Halides with $\text{SOCl}_2$ and $\text{PBr}_3$

- Primary and secondary alcohols can be converted to alkyl halides using  $\text{SOCl}_2$  (thionyl chloride) and  $\text{PBr}_3$  (phosphorus tribromide)



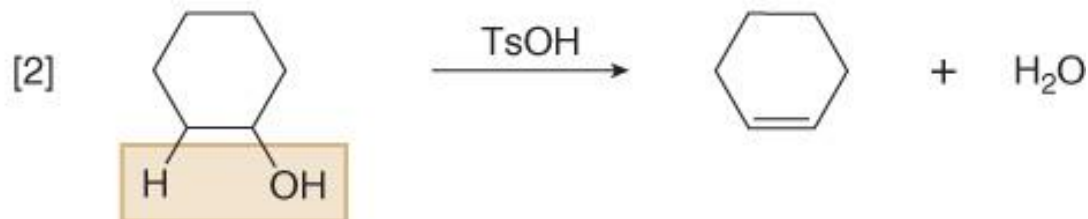
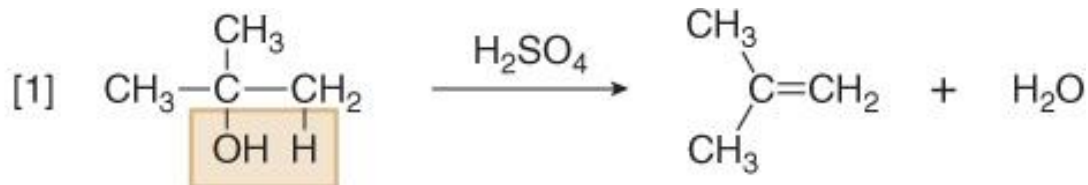
# Conversion of Alcohols to Alkyl Halides

Overall reaction	Reagent	Comment
ROH $\rightarrow$ RCl	HCl	<ul style="list-style-type: none"><li>• Useful for all ROH</li><li>• An S<sub>N</sub>1 mechanism for 2° and 3° ROH; an S<sub>N</sub>2 mechanism for CH<sub>3</sub>OH and 1° ROH</li></ul>
	SOCl <sub>2</sub>	<ul style="list-style-type: none"><li>• Best for CH<sub>3</sub>OH, and 1° and 2° ROH</li><li>• An S<sub>N</sub>2 mechanism</li></ul>
ROH $\rightarrow$ RBr	HBr	<ul style="list-style-type: none"><li>• Useful for all ROH</li><li>• An S<sub>N</sub>1 mechanism for 2° and 3° ROH; an S<sub>N</sub>2 mechanism for CH<sub>3</sub>OH and 1° ROH</li></ul>
	PBr <sub>3</sub>	<ul style="list-style-type: none"><li>• Best for CH<sub>3</sub>OH, and 1° and 2° ROH</li><li>• An S<sub>N</sub>2 mechanism</li></ul>
ROH $\rightarrow$ RI	HI	<ul style="list-style-type: none"><li>• Useful for all ROH</li><li>• An S<sub>N</sub>1 mechanism for 2° and 3° ROH; an S<sub>N</sub>2 mechanism for CH<sub>3</sub>OH and 1° ROH</li></ul>

# Reactions of Alcohols—Dehydration

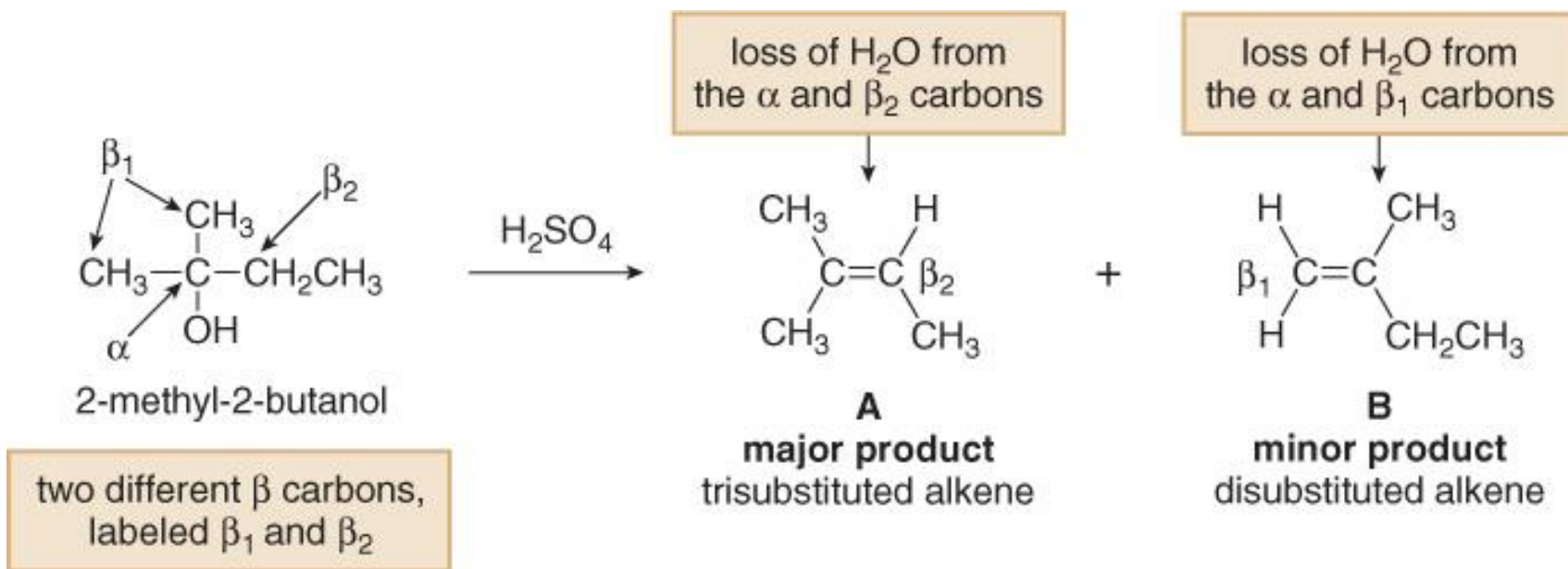
- **Dehydration**, like dehydrohalogenation, is a  $\beta$  elimination reaction in which the elements of OH and H are removed from the  $\alpha$  and  $\beta$  carbon atoms respectively.
- Typical acids used for alcohol dehydration are  $\text{H}_2\text{SO}_4$  or *p*-toluenesulfonic acid (TsOH).

## Examples



# Reactions of Alcohols—Dehydration

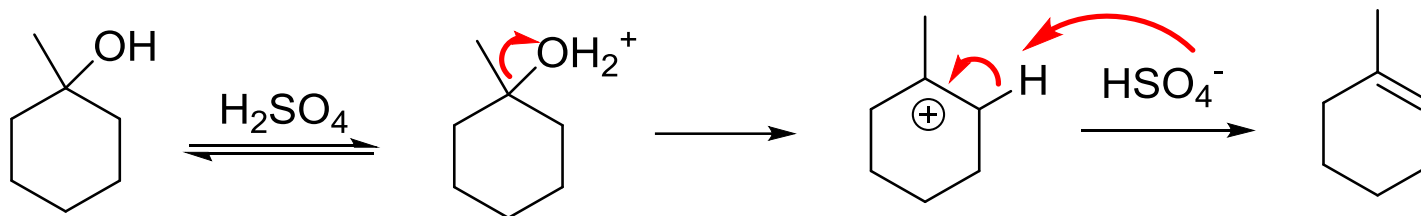
- When an alcohol has two or three  $\beta$  carbons, dehydration is regioselective and follows the Zaitsev rule.



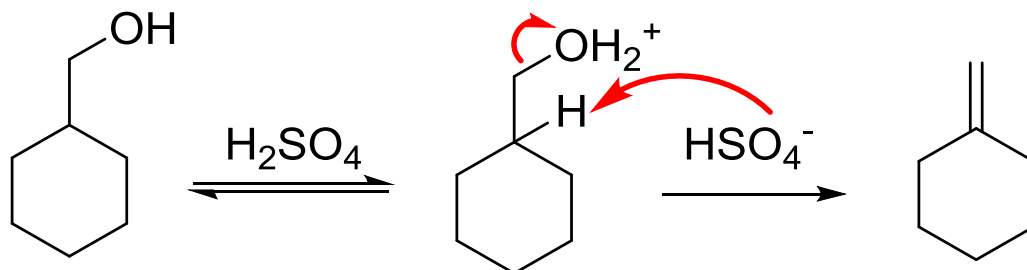


# Reactions of Alcohols—Dehydration

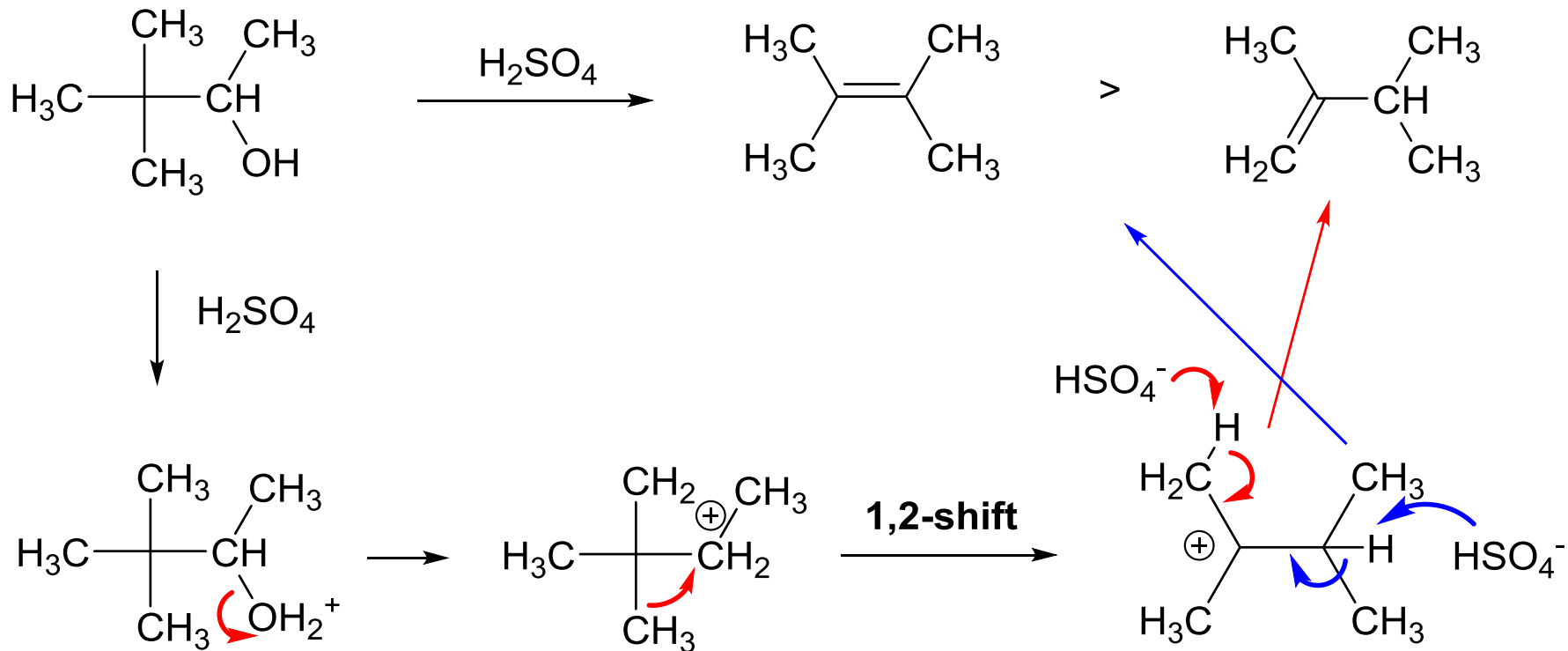
- Tertiary alcohols react by an E1 mechanism.



- 1<sup>ry</sup> alcohols undergo dehydration following an E2 mechanism.



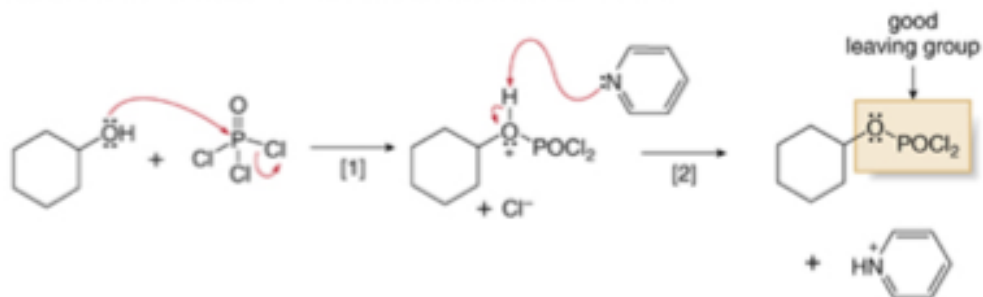
# Carbocation Rearrangements



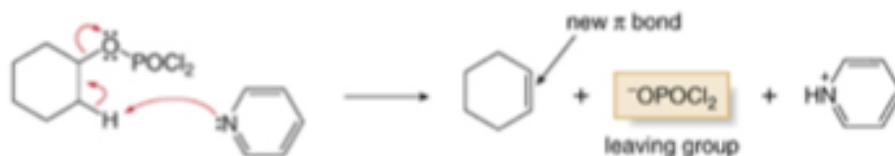
# Dehydration of Alcohols Using $\text{POCl}_3$ and Pyridine

- Some organic compounds decompose in the presence of strong acid, so other methods have been developed to convert alcohols to alkenes.

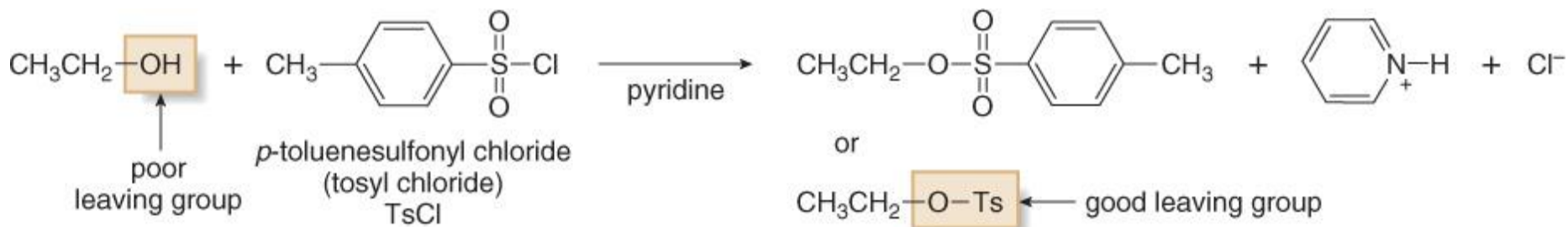
Steps [1] and [2] Conversion of OH to a good leaving group



Step [3] The C-H and C-O bonds are broken and the  $\pi$  bond is formed.

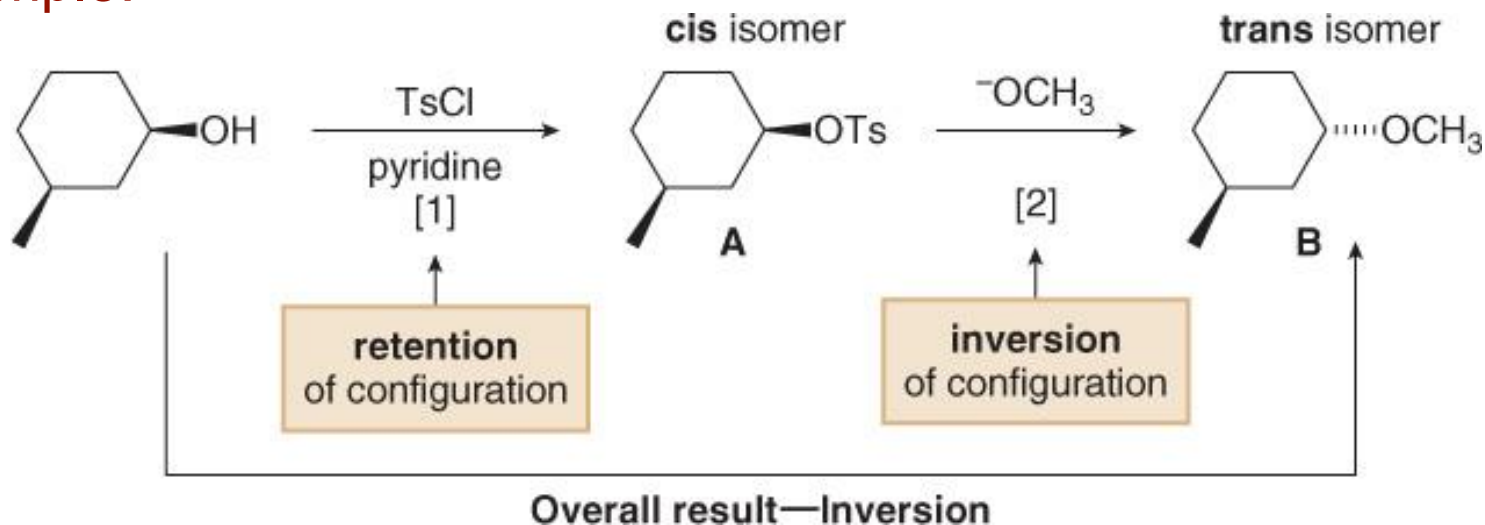


# Tosylate—Another Good Leaving Group

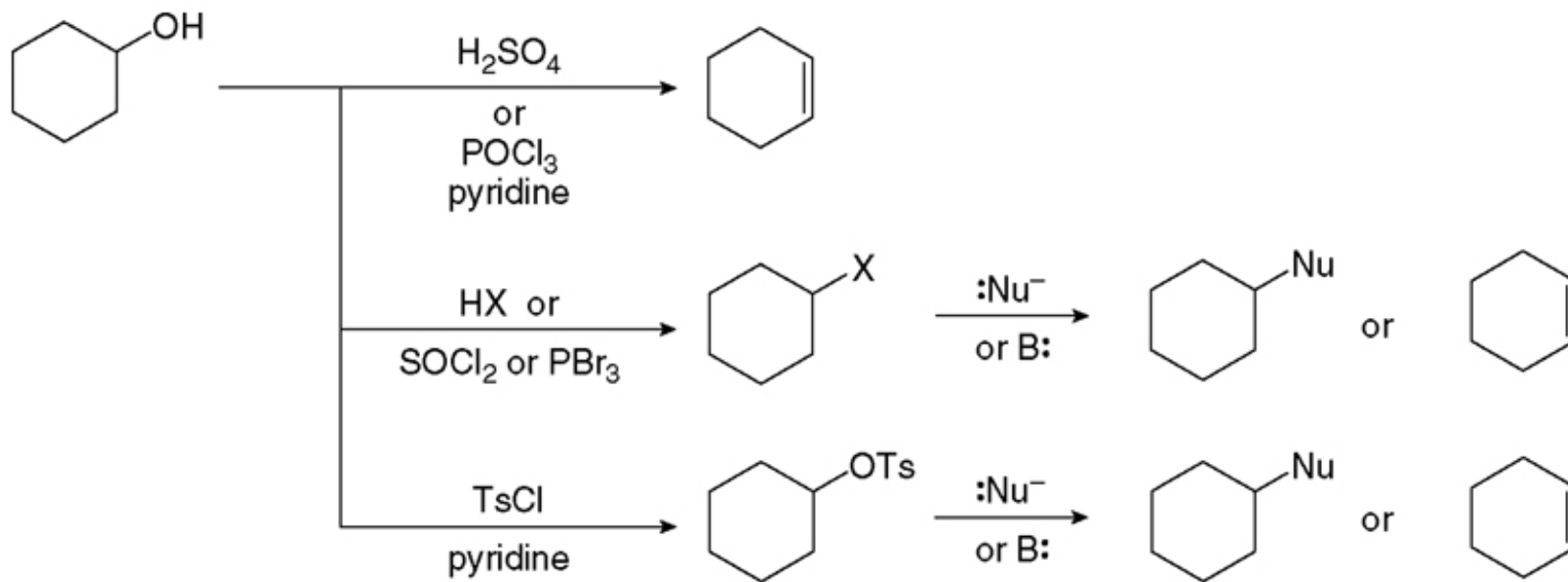


- Tosylate is a good leaving group because its conjugate acid, *p*-toluenesulfonic acid ( $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H}$ , TsOH) is a strong acid ( $\text{pK}_a = -7$ ).

## Example:

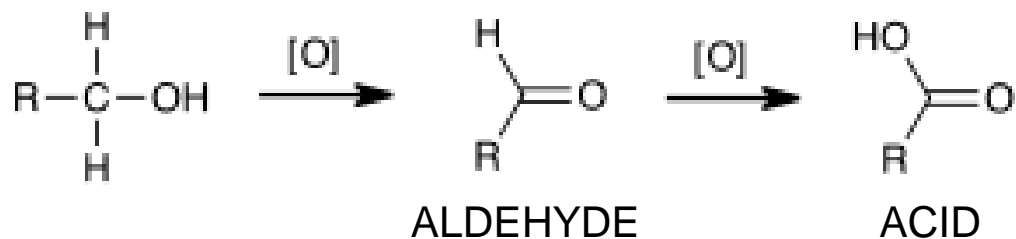


# Nucleophilic substitution and $\beta$ elimination reactions of alcohols

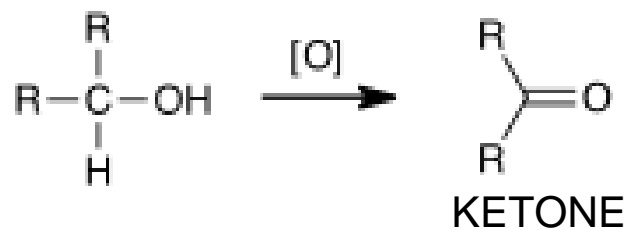


# Oxidation of Alcohols

1° ALCOHOL



2° ALCOHOL

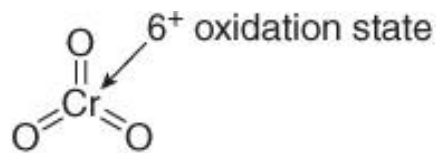


3° ALCOHOL



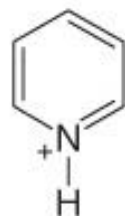
# Oxidation of Alcohols

- The oxidation of alcohols to carbonyl compounds is typically carried out with Cr(VI) oxidants, which are reduced to Cr(III) products.
- $\text{CrO}_3$ ,  $\text{Na}_2\text{Cr}_2\text{O}_7$ , and  $\text{K}_2\text{Cr}_2\text{O}_7$  are strong, nonselective oxidants used in aqueous acid ( $\text{H}_2\text{SO}_4 + \text{H}_2\text{O}$ ).
- PCC is soluble in  $\text{CH}_2\text{Cl}_2$  (dichloromethane) and can be used without strong acid present, making it a more selective, milder oxidant.

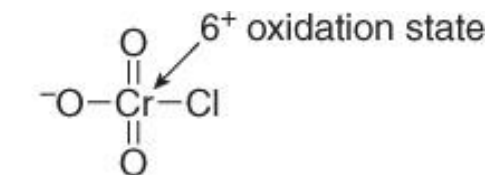


chromium(VI) oxide

$\text{CrO}_3$



pyridinium chlorochromate

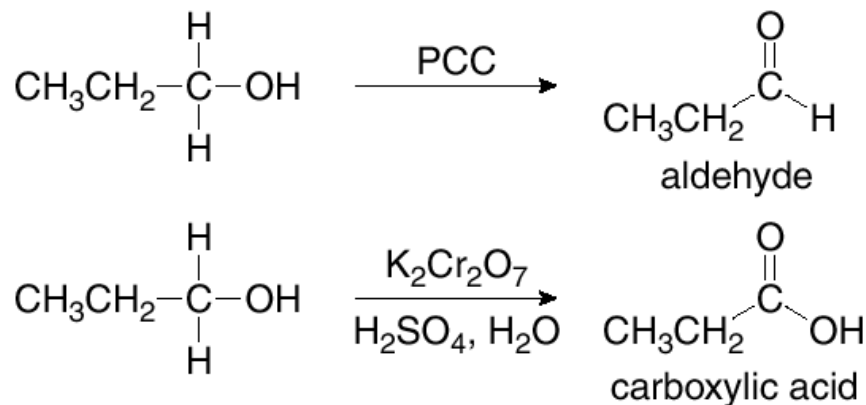


PCC

# Oxidation of Alcohols

- 1° Alcohols are oxidized to aldehydes (RCHO) under mild reaction conditions—using PCC in CH<sub>2</sub>Cl<sub>2</sub>.
- 1° Alcohols are oxidized to carboxylic acids (RCOOH) under harsher reaction conditions: Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>, K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>, or CrO<sub>3</sub> in the presence of H<sub>2</sub>O and H<sub>2</sub>SO<sub>4</sub>.

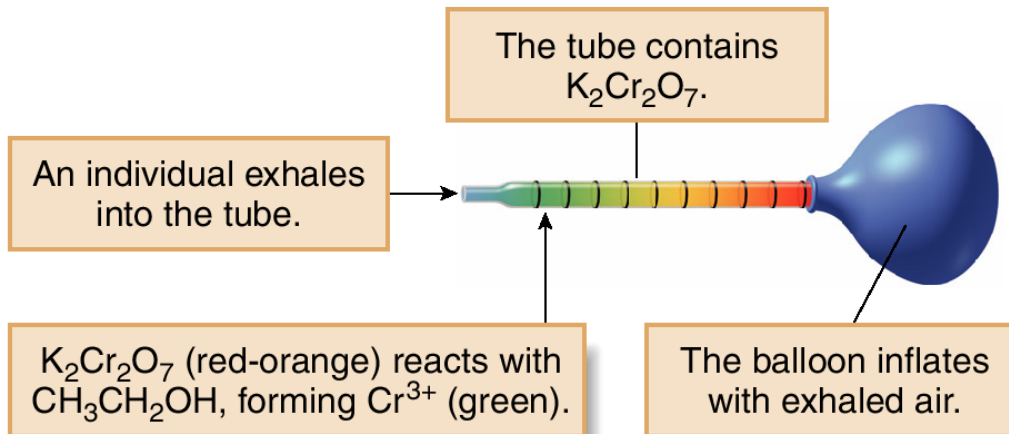
1° Alcohols





# The Alcohol Test

## Schematic of an alcohol testing device



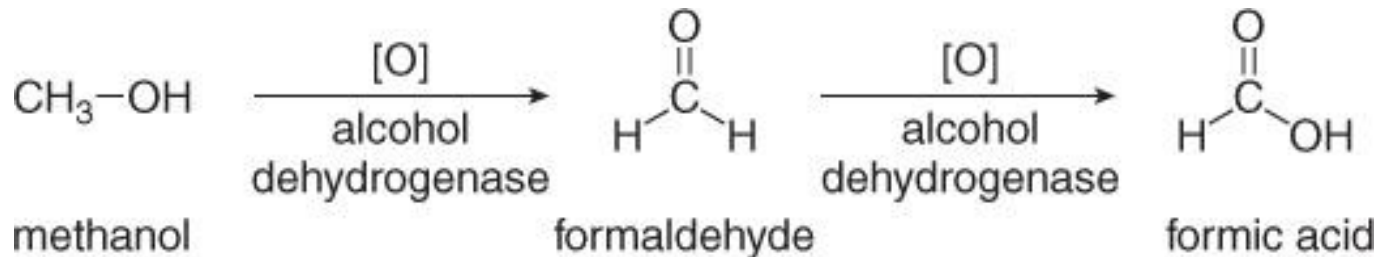
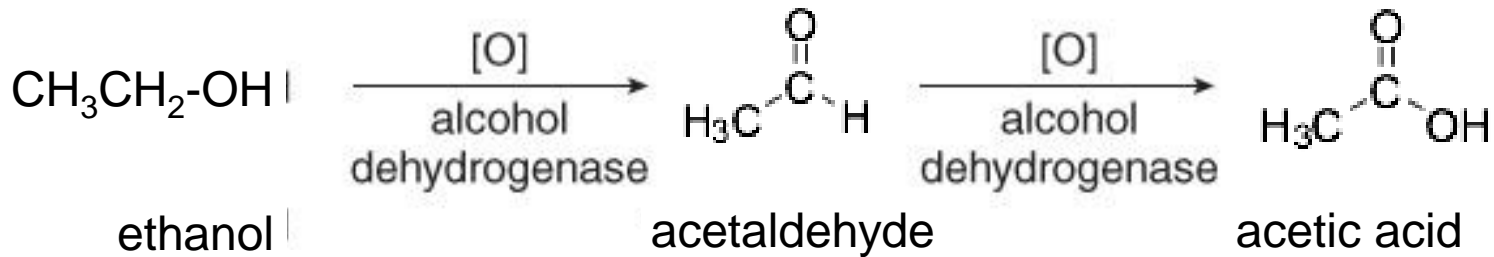
- The oxidation of  $CH_3CH_2OH$  with  $K_2Cr_2O_7$  to form  $CH_3COOH$  and  $Cr^{3+}$  was the first available method for the routine testing of alcohol concentration in exhaled air. Some consumer products for alcohol screening are still based on this technology.

## Consumer product



$K_2Cr_2O_7$

# Ethanol Metabolism

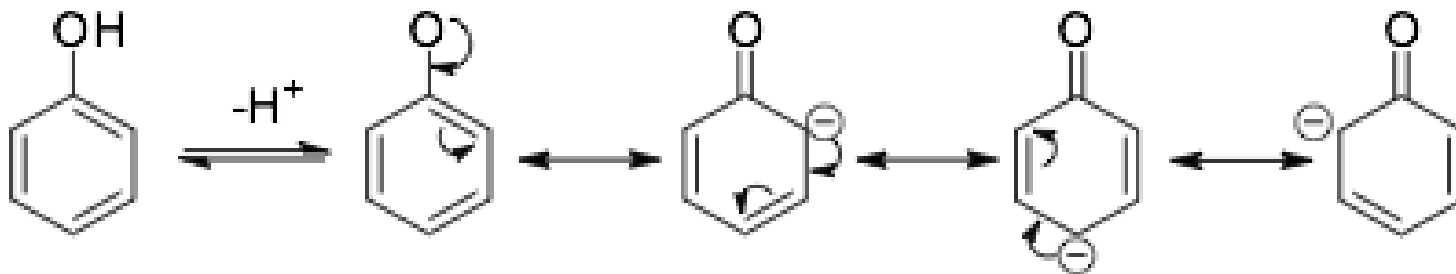


# Acidity of Alcohols

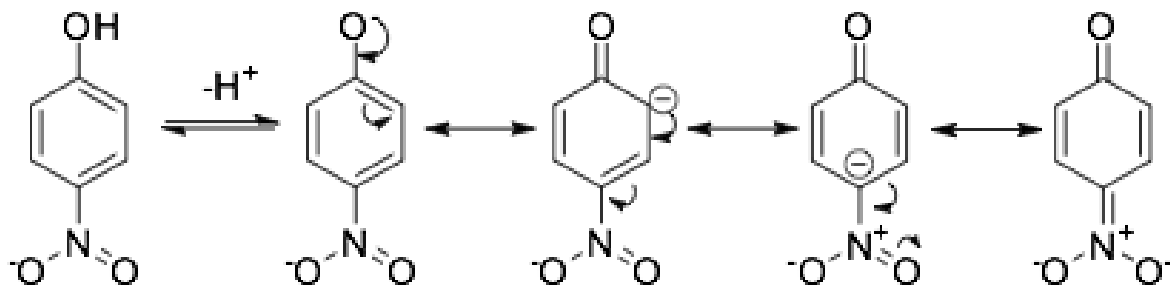
Compound	pK <sub>a</sub>
<i>CH</i> <sub>3</sub> <i>CH</i> <sub>2</sub> <i>OH</i>	16.0
<i>CF</i> <sub>3</sub> <i>CH</i> <sub>2</sub> <i>OH</i>	12.4
<i>C</i> <sub>6</sub> <i>H</i> <sub>5</sub> <i>OH</i>	9.9
<i>p</i> - <i>NH</i> <sub>2</sub> <i>C</i> <sub>6</sub> <i>H</i> <sub>4</sub> <i>OH</i>	10.5
<i>p</i> - <i>NO</i> <sub>2</sub> <i>C</i> <sub>6</sub> <i>H</i> <sub>4</sub> <i>OH</i>	7.2

*CF*<sub>3</sub>*CH*<sub>2</sub>*O*<sup>-</sup>: Inductively stabilized

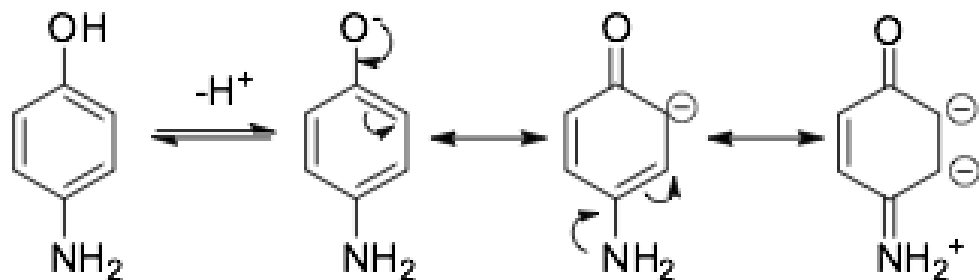
*C*<sub>6</sub>*H*<sub>5</sub>*O*<sup>-</sup>: Resonance stabilized



# Substituent effects on acidity of phenols



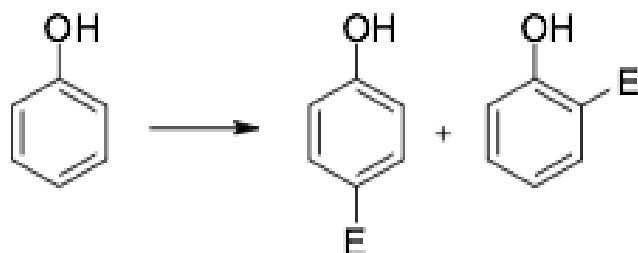
Stabilized by delocalization



Destabilized by delocalization

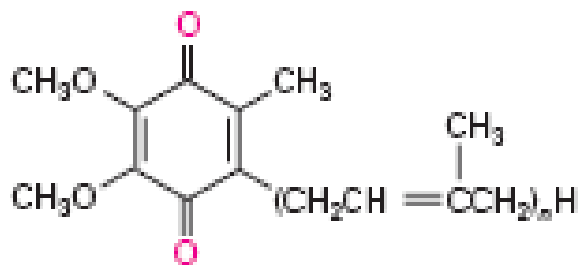
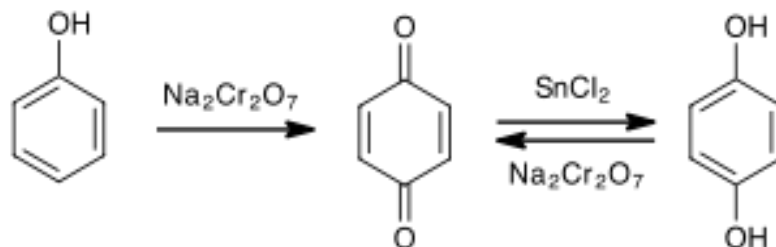
# Reactions of Phenol

$S_EAr$ :



Activated  
(OH: +R > -I)

Oxidation:



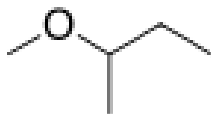
Ubichinoni ( $n = 1-10$ )

# Nomenclature of Ethers

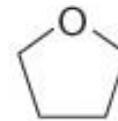
- Common names:



diethyl ether



s-butyl methyl ether



tetrahydrofuran  
**THF**

- IUPAC names:



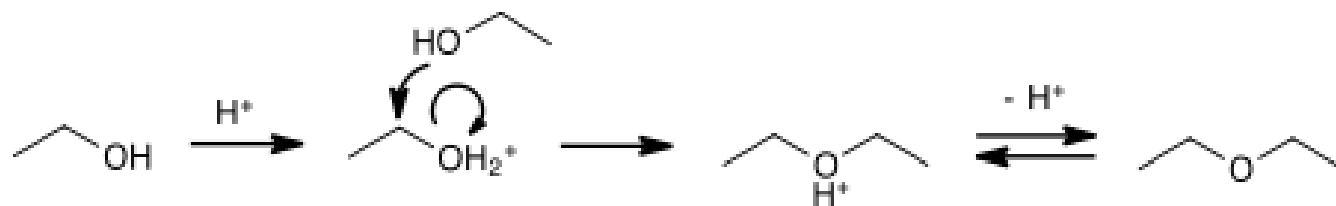
ethoxyethane



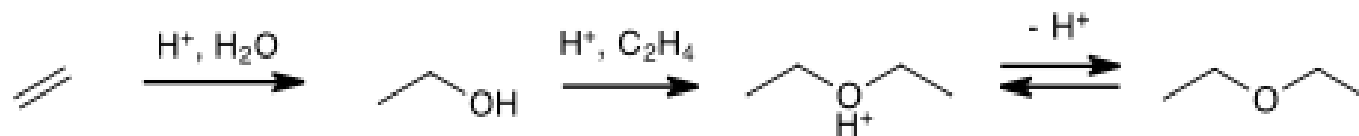
2-methoxybutane

# Preparation of Ethers.

## FROM ALCOHOLS

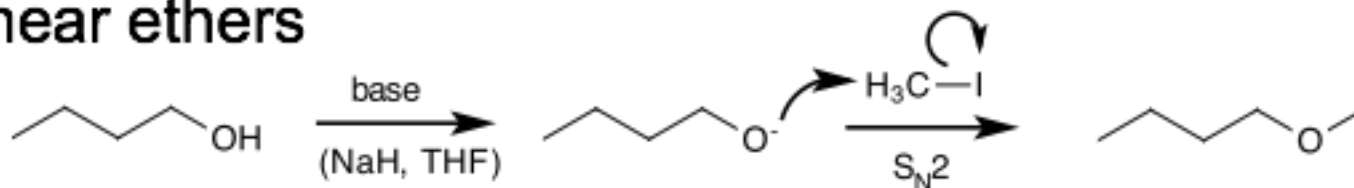


## FROM ALKENES

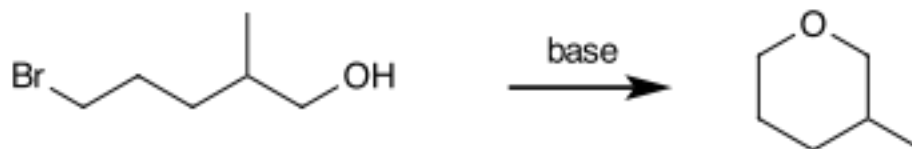


# Preparation of Ethers. Williamson synthesis

## Linear ethers

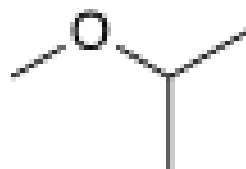


## Cyclic ethers



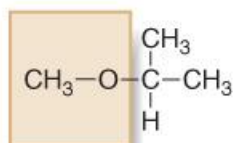


# Preparation of Ethers. Williamson synthesis

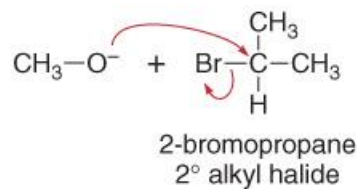


Two possible routes to isopropyl methyl ether

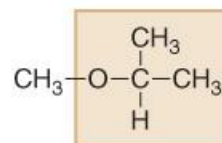
Path [a]



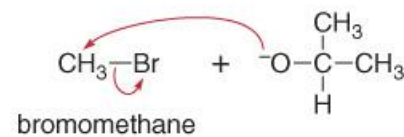
isopropyl methyl ether



Path [b]



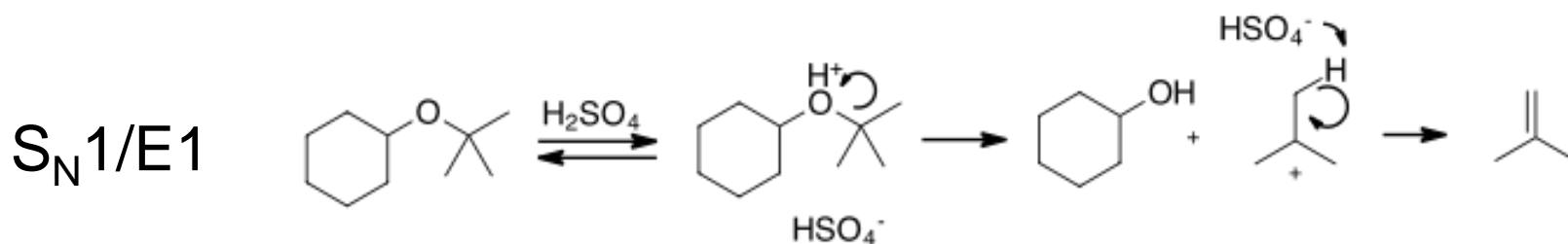
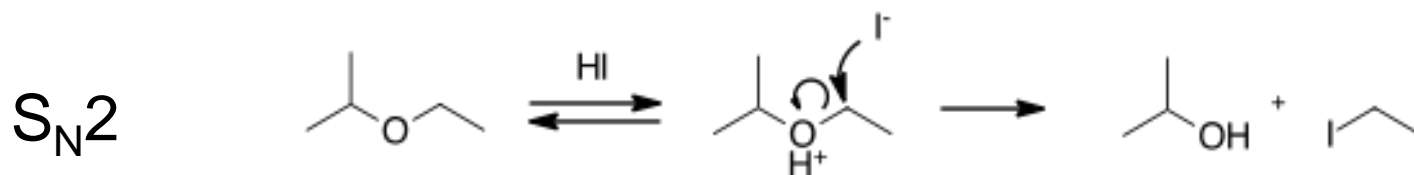
isopropyl methyl ether



less hindered alkyl halide  
**preferred path**

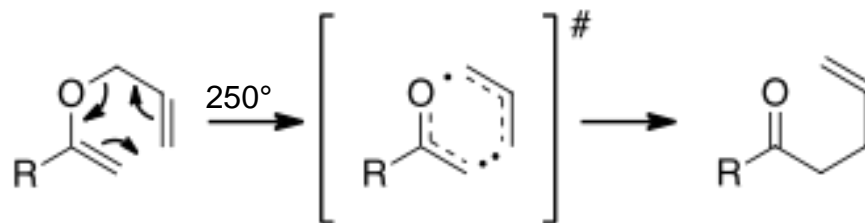
# Reaction of Ethers with Strong Acid

- The ether bond is cleaved with strong acids to give an alcohol and a halide or an alkene

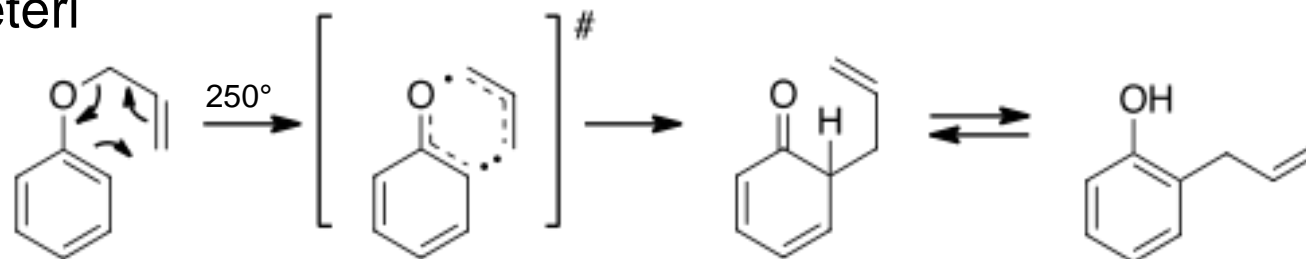


# Claisen Rearrangement

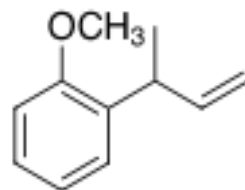
Allilvinileteri



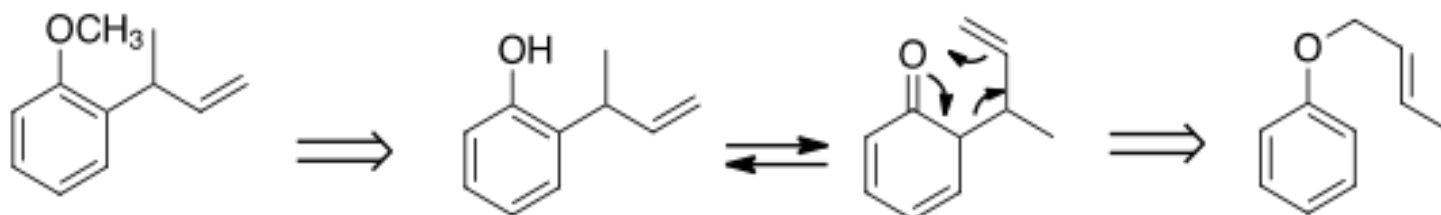
Allilarileteri



# Claisen Rearrangement



Analisi retrosintetica



Sintesi



# Structure of Epoxides

- Epoxides are ethers having the oxygen atom in a three-membered ring. Epoxides are also called **oxiranes**.



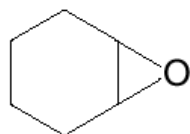
epoxide or oxirane

An epoxide is a special type of ether.

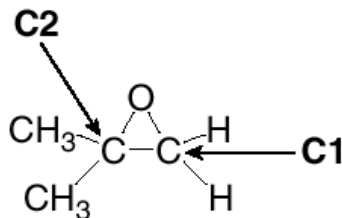
- The C—O—C bond angle for an epoxide must be  $60^\circ$ , a considerable deviation from the tetrahedral bond angle of  $109.5^\circ$ . Thus, epoxides have angle strain, making them more reactive than other ethers.

# Nomenclature of Epoxides

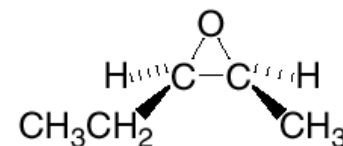
- Epoxyalkanes:



1,2-epoxycyclohexane



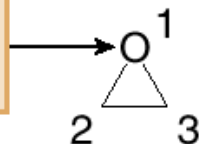
1,2-epoxy-2-methylpropane



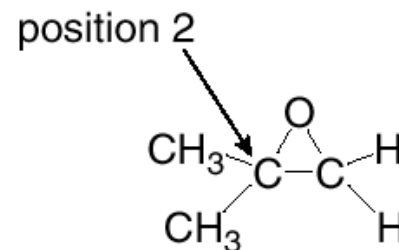
*cis*-2,3-epoxypentane

- Oxiranes:

Number the ring beginning at the O atom.

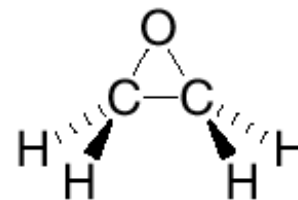
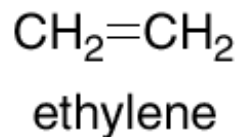


oxirane



2,2-dimethyloxirane

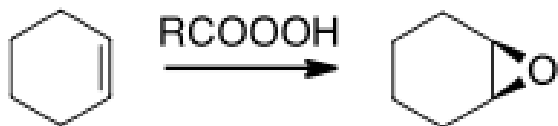
- Alkene oxides:



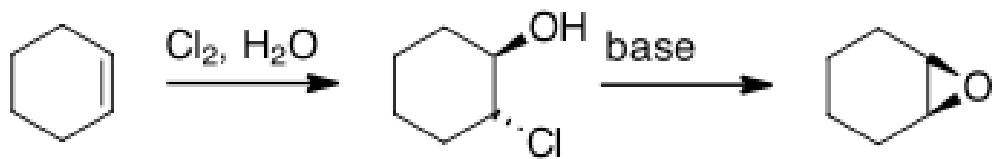
**ethylene oxide**  
oxirane

# Preparation of Epoxides

epoxidation of alkenes

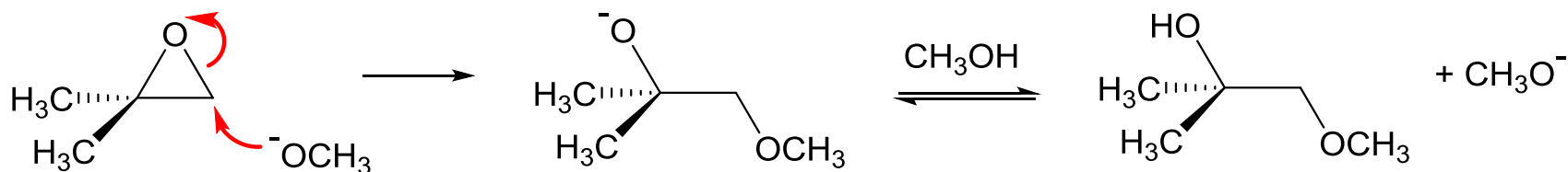


cyclization of halohydrins



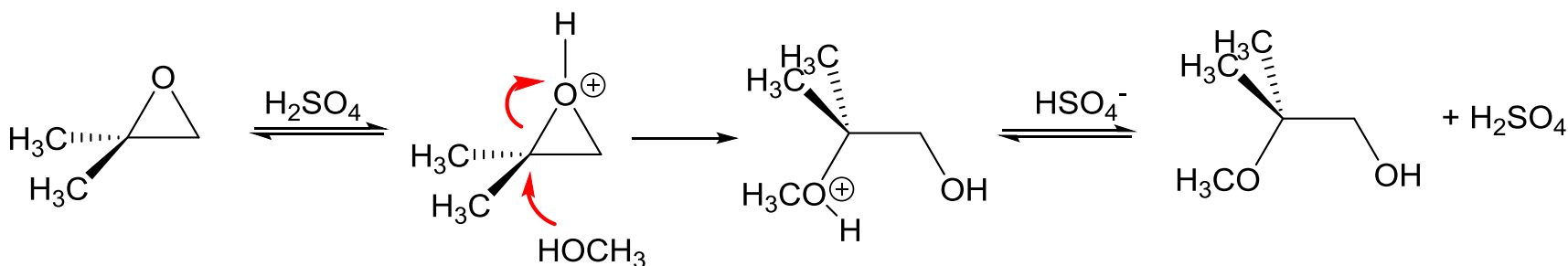
# Reactions of Epoxides

- Nucleophilic attack opens the strained three-membered ring with an S<sub>N</sub>2 mechanism, making it a favourable process even with a poor leaving group.



Backside attack on the less substituted carbon

- Acids catalyse epoxide ring opening by protonating the oxygen:

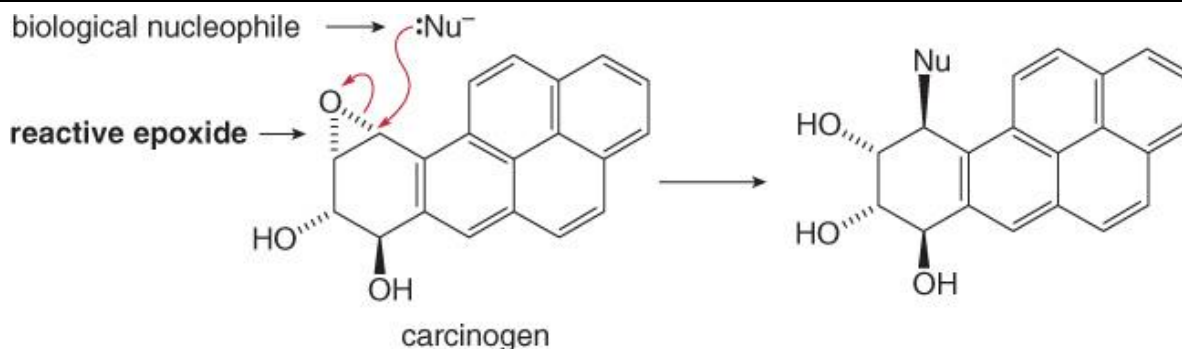
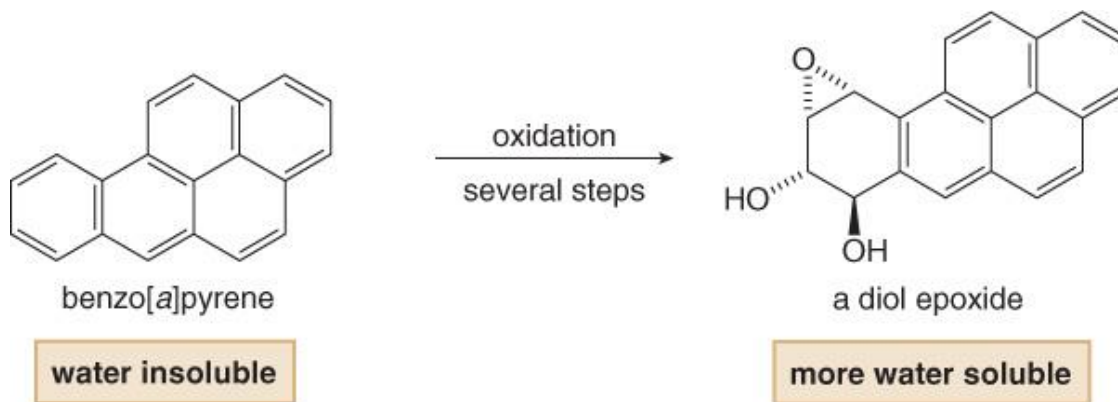


Backside attack on the more substituted carbon



# Reactions of Epoxides

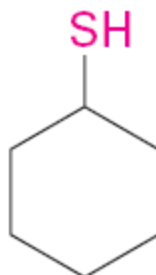
- When polyaromatic hydrocarbons are inhaled or ingested, they are oxidized in the liver to species that often contain a highly reactive epoxide ring.
- The strained three-membered ring reacts readily with biological nucleophiles such as DNA or enzymes, leading to ring-opened products that often disrupt cell function, causing cancer or cell death.



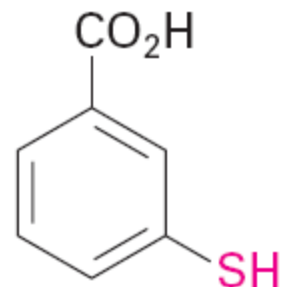
# Thiols and Sulfides



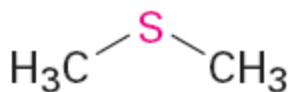
ethanethiol



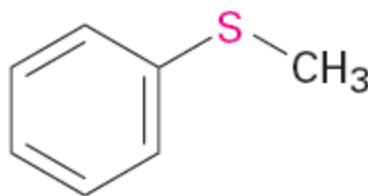
ciclohexanethiol



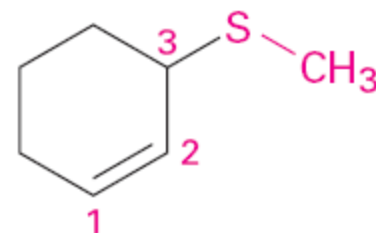
3-mercapto  
benzoic acid



dimethylsulfide

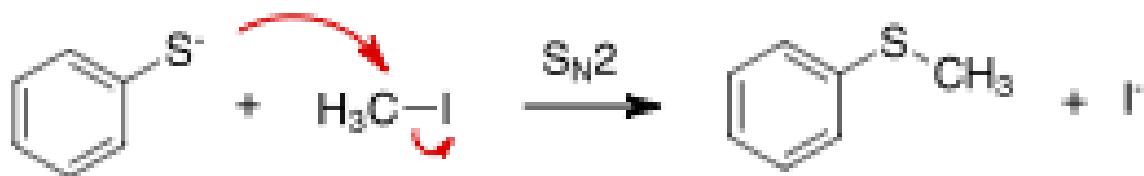


methyl phenyl  
sulfide



3-(methylmercapto)  
cyclohexene

# Thiols and Sulfides: Synthesis



# Thiols and Sulfides: Oxidation



thiol

disulfide

