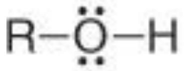
Alcohols, Ethers and Epoxides

Chapter 17-18

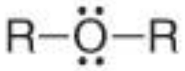
Organic Chemistry, *8th Edition*

John McMurry

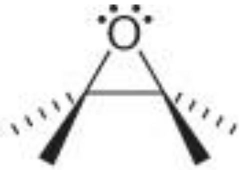
Introduction—Structure and Bonding



alcohol

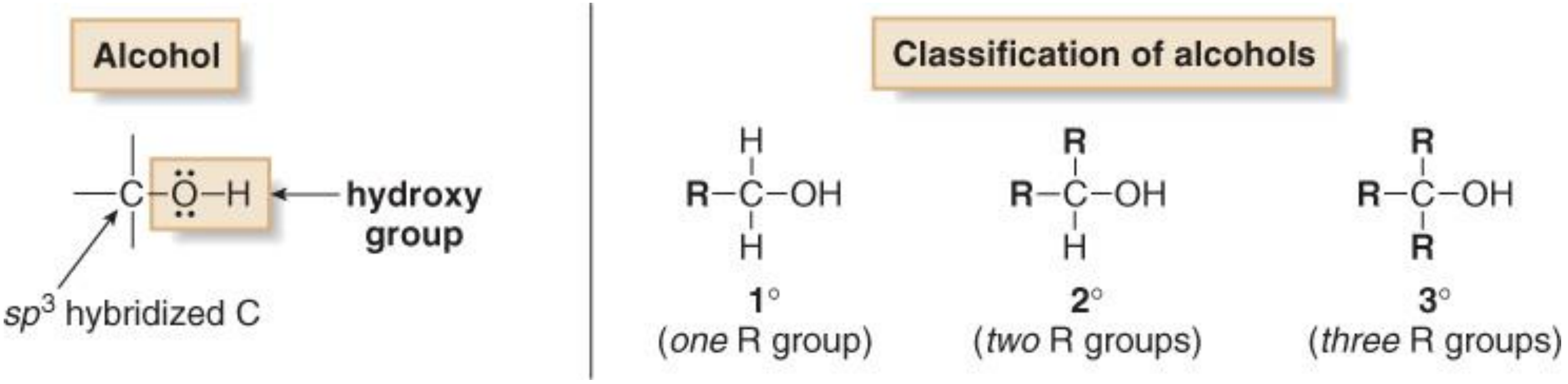


ether



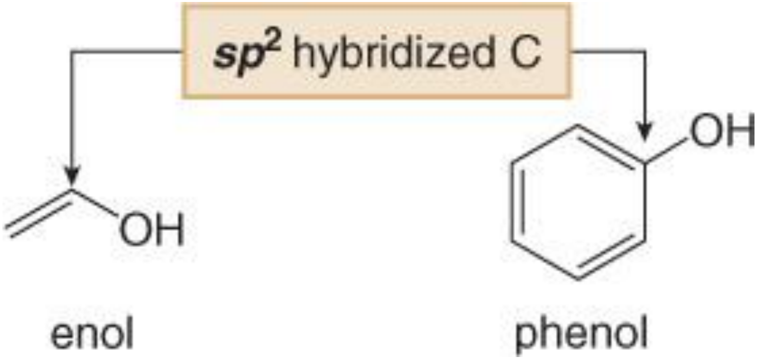
epoxide

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



Introduction—Structure and Bonding

- enols and phenols—undergo different reactions than alcohols.



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

Ether

$\mathrm{R-\ddot{O}-R}$

$\mathrm{CH_3CH_2-\ddot{O}-CH_2CH_3}$

symmetrical ether

R groups are the **same.**

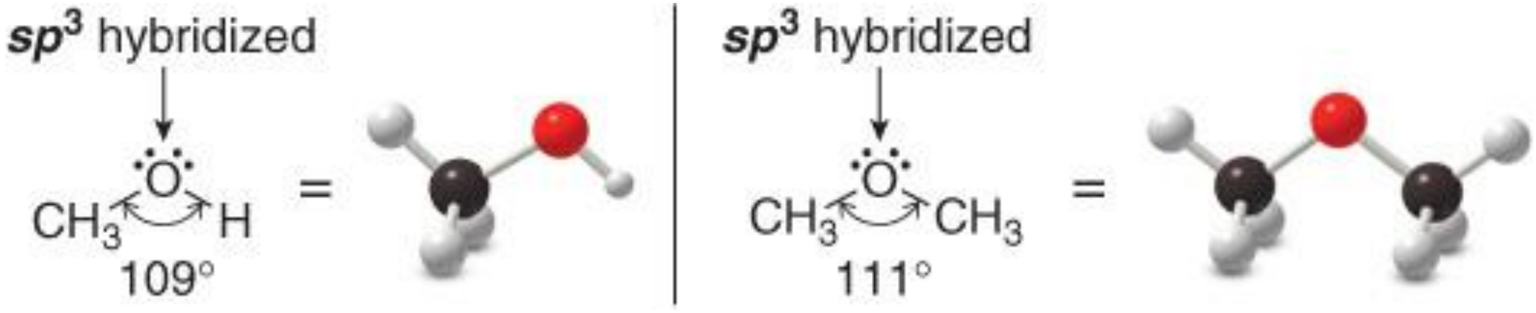
$\mathrm{CH_3-\ddot{O}-CH_2CH_3}$

unsymmetrical ether

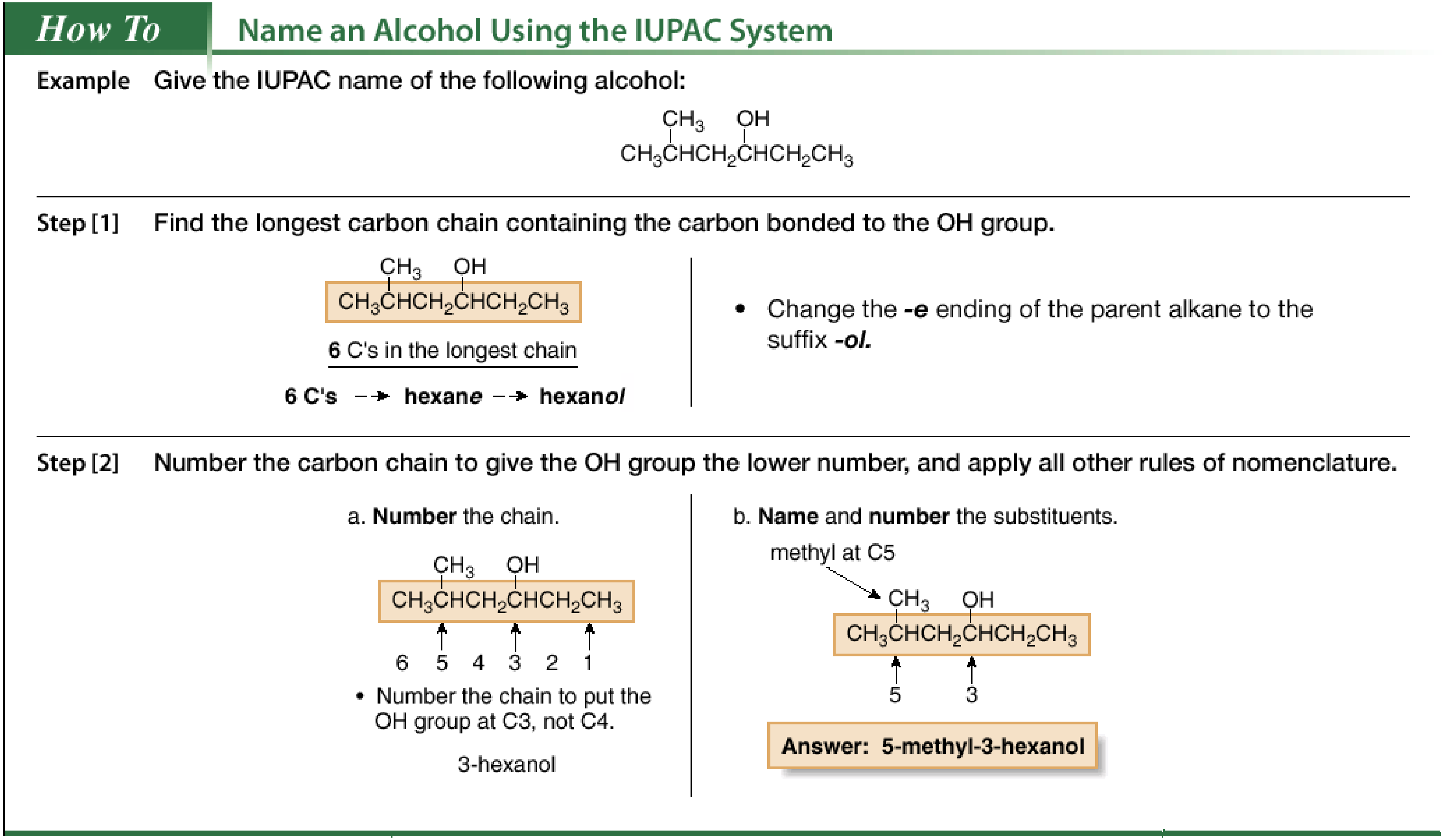
R groups are **different.**

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°.
- Because the O atom is much more electronegative than carbon or hydrogen, the C—O and O—H bonds are all polar.



Nomenclature of Alcohols



How To Name an Alcohol Using the IUPAC System

Example Give the IUPAC name of the following alcohol:

$$CH_3\overset{CH_3}{\overset{|}{C}}HCH_2\overset{OH}{\overset{|}{C}}HCH_2CH_3$$

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

$$\boxed{CH_3\overset{CH_3}{\overset{|}{C}}HCH_2\overset{OH}{\overset{|}{C}}HCH_2CH_3}$$

6 C's in the longest chain

6 C's --> **hexan*e*** --> **hexan*ol***

- 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.

$$\boxed{CH_3\overset{CH_3}{\overset{|}{C}}HCH_2\overset{OH}{\overset{|}{C}}HCH_2CH_3}$$

6 5 4 3 2 1

- Number the chain to put the OH group at C3, not C4.

3-hexanol

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

methyl at C5

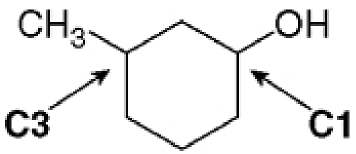
$$\boxed{CH_3\overset{CH_3}{\overset{|}{C}}HCH_2\overset{OH}{\overset{|}{C}}HCH_2CH_3}$$

5 3

Answer: 5-methyl-3-hexanol

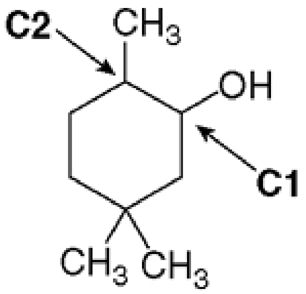
Nomenclature of Alcohols

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



3-methylcyclohexanol

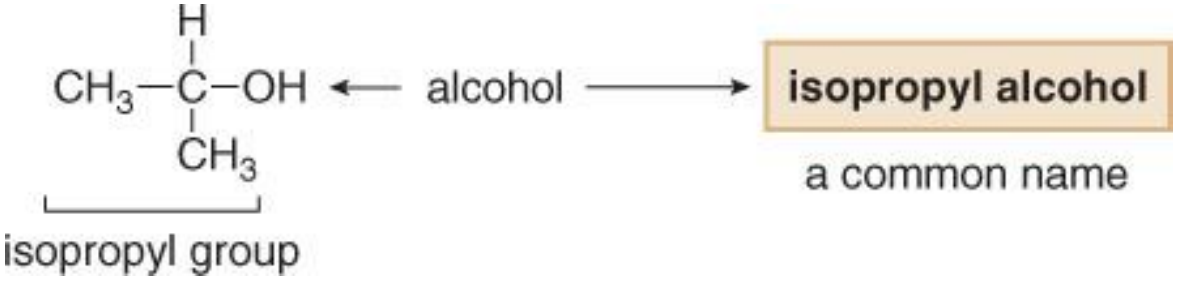
The OH group is at C1; the second substituent (CH_3) gets the lower number.



2,5,5-trimethylcyclohexanol

The OH group is at C1; the second substituent (CH_3) gets the lower number.

- Common names are often used for simple alcohols.



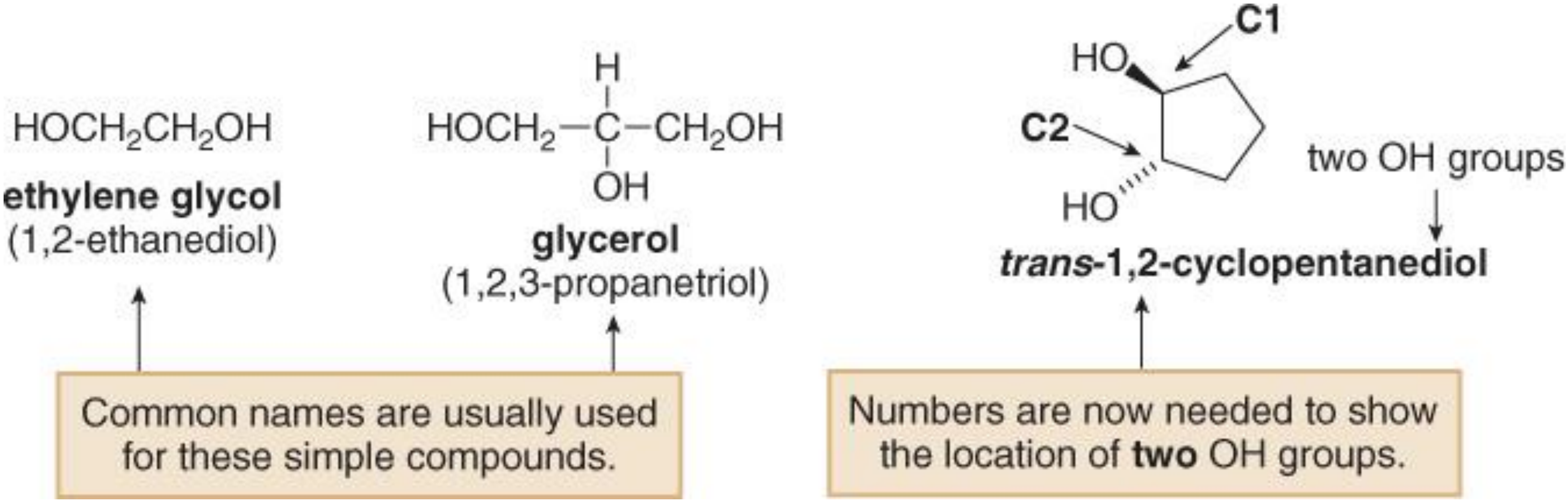
$CH_3-\overset{H}{\underset{CH_3}{C}}-OH$ ← alcohol → **isopropyl alcohol**

isopropyl group

a common name

Nomenclature of Alcohols

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



ethylene glycol
(1,2-ethanediol)

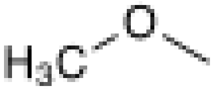
glycerol
(1,2,3-propanetriol)

***trans*-1,2-cyclopentanediol**

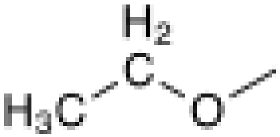
Common names are usually used for these simple compounds.

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

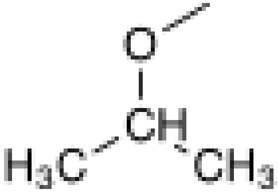
Nomenclature of Alcohols



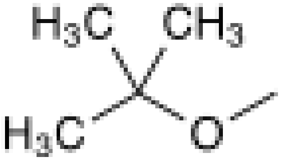
Methoxy



ethoxy



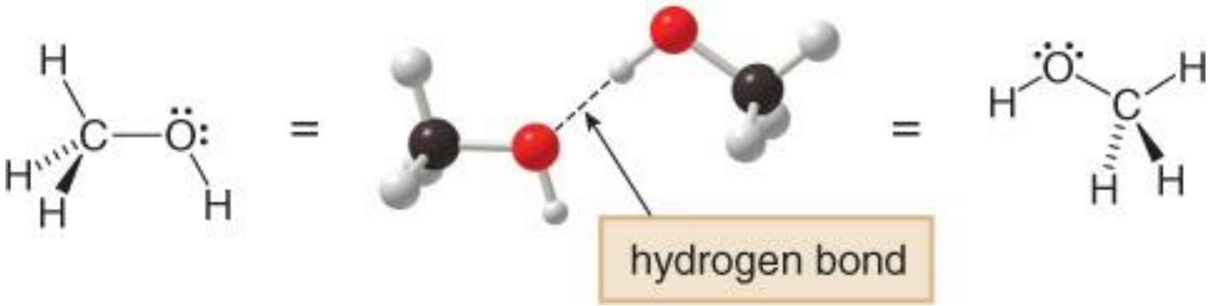
2-propoxy
isopropoxy



2-methyl-2-propoxy
terbutoxy

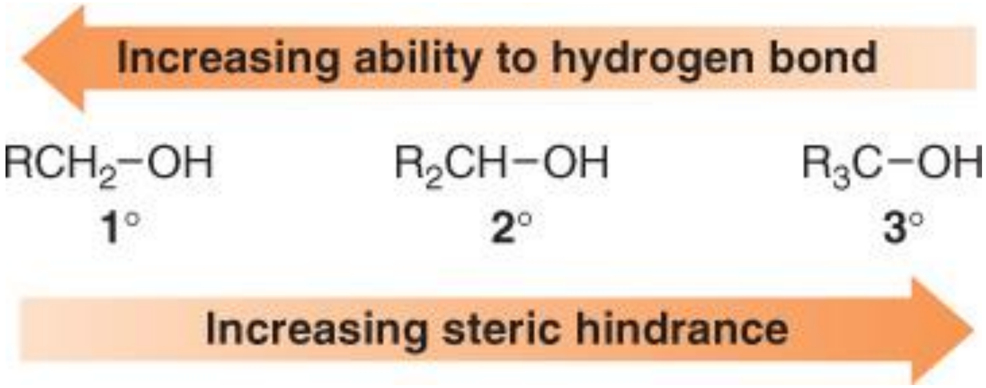
Physical Properties

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



hydrogen bond

- Steric factors affect hydrogen bonding.



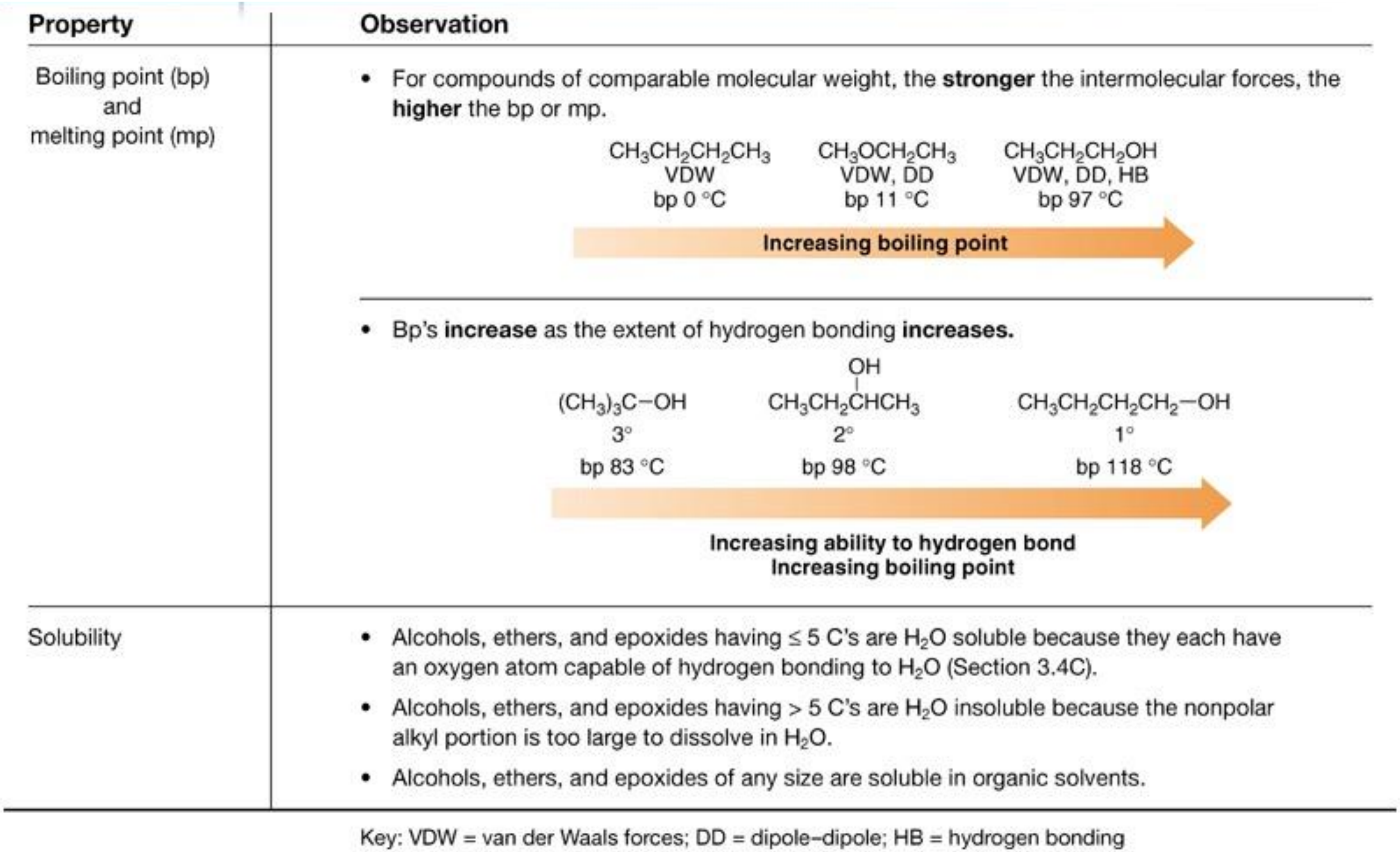
Increasing ability to hydrogen bond

RCH_2-OH R_2CH-OH R_3C-OH

1° 2° 3°

Increasing steric hindrance

Physical Properties



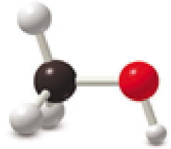
Property	**Observation**
Boiling point (bp) and melting point (mp)	- For compounds of comparable molecular weight, the **stronger** the intermolecular forces, the **higher** the bp or mp. $CH_3CH_2CH_2CH_3$ VDW bp 0 °C $CH_3OCH_2CH_3$ VDW, DD bp 11 °C $CH_3CH_2CH_2OH$ VDW, DD, HB bp 97 °C **Increasing boiling point**
	- Bp's **increase** as the extent of hydrogen bonding **increases.** $(CH_3)_3C{-}OH$ 3° bp 83 °C $CH_3CH_2\overset{\overset{OH}{\vert}}{C}HCH_3$ 2° bp 98 °C $CH_3CH_2CH_2CH_2{-}OH$ 1° bp 118 °C **Increasing ability to hydrogen bond** **Increasing boiling point**
Solubility	- Alcohols, ethers, and epoxides having ≤ 5 C's are H_2O soluble because they each have an oxygen atom capable of hydrogen bonding to H_2O (Section 3.4C). - Alcohols, ethers, and epoxides having > 5 C's are H_2O insoluble because the nonpolar alkyl portion is too large to dissolve in H_2O. - Alcohols, ethers, and epoxides of any size are soluble in organic solvents.

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

Interesting Alcohols

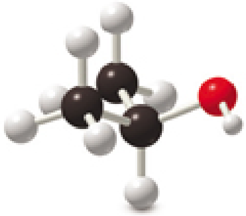
- Ethanol is the alcohol in red wine, obtained by the fermentation of grapes.

Interesting Alcohols



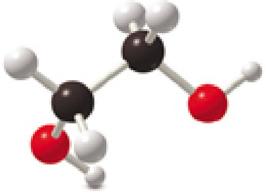
CH_3OH

- **Methanol (CH_3OH)** 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.



$(CH_3)_2CHOH$

- **2-Propanol [$(CH_3)_2CHOH$]** 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.

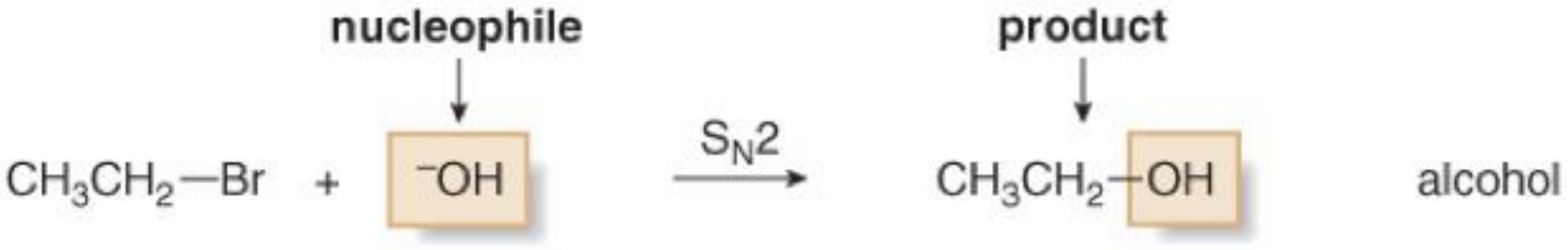


$HOCH_2CH_2OH$

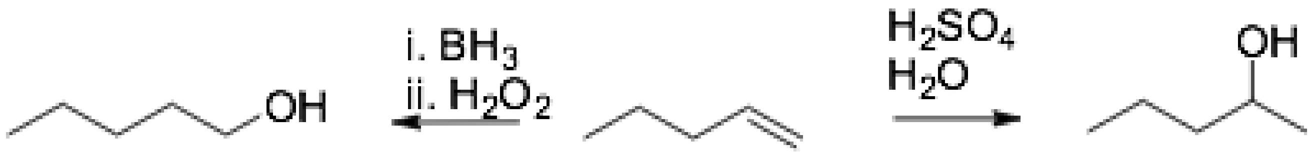
- **Ethylene glycol ($HOCH_2CH_2OH$)** is the major component of antifreeze. It is readily prepared from ethylene oxide by reactions discussed in Section 9.15. It is sweet tasting but toxic.

Preparation of Alcohols

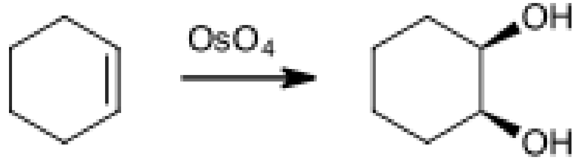
- From alkyl halides



- Hydration/hydroboration of alkenes

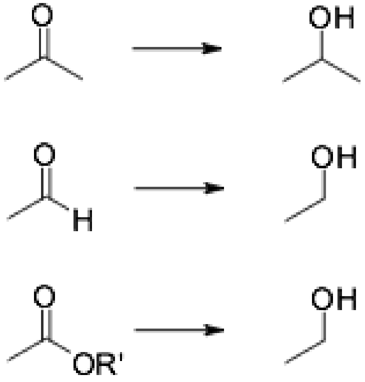


- Dihydroxylation of alkenes



Preparation of Alcohols

- Reduction of carbonyl compounds

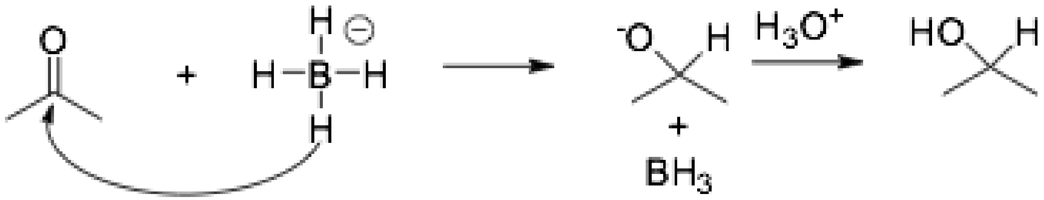


secondary alcohol

primary alcohol

H_2/Pd	reduces also C=C
$NaBH_4$, $LiAlH_4$	selective for C=O

Mechanism:

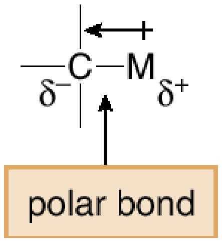


H is transferred as H^-

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

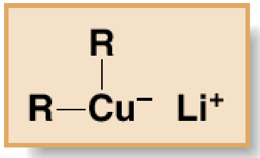
Most common metals:
M = Li, Mg, Cu

R—Li

organolithium reagents

R—Mg—X

organomagnesium reagents
or
Grignard reagents

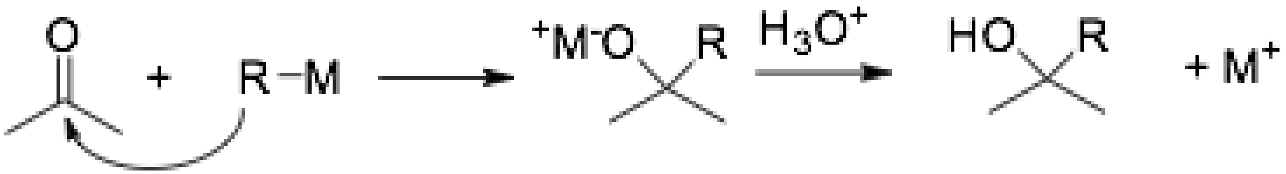


$R_2Cu^- \; Li^+$

organocopper reagents
or
organocuprates

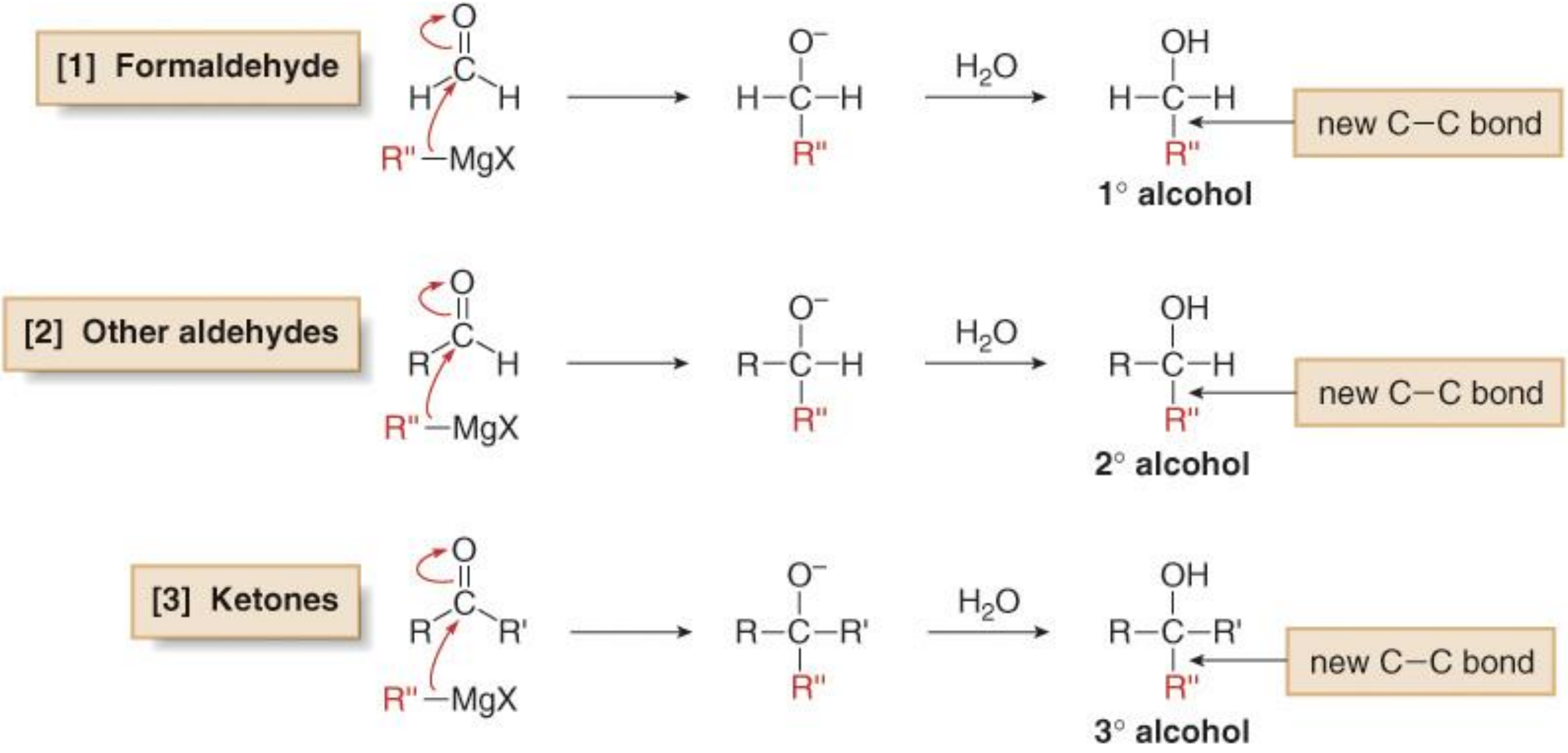
- The more polar the carbon–metal bond, the more reactive the organometallic reagent.

Mechanism:



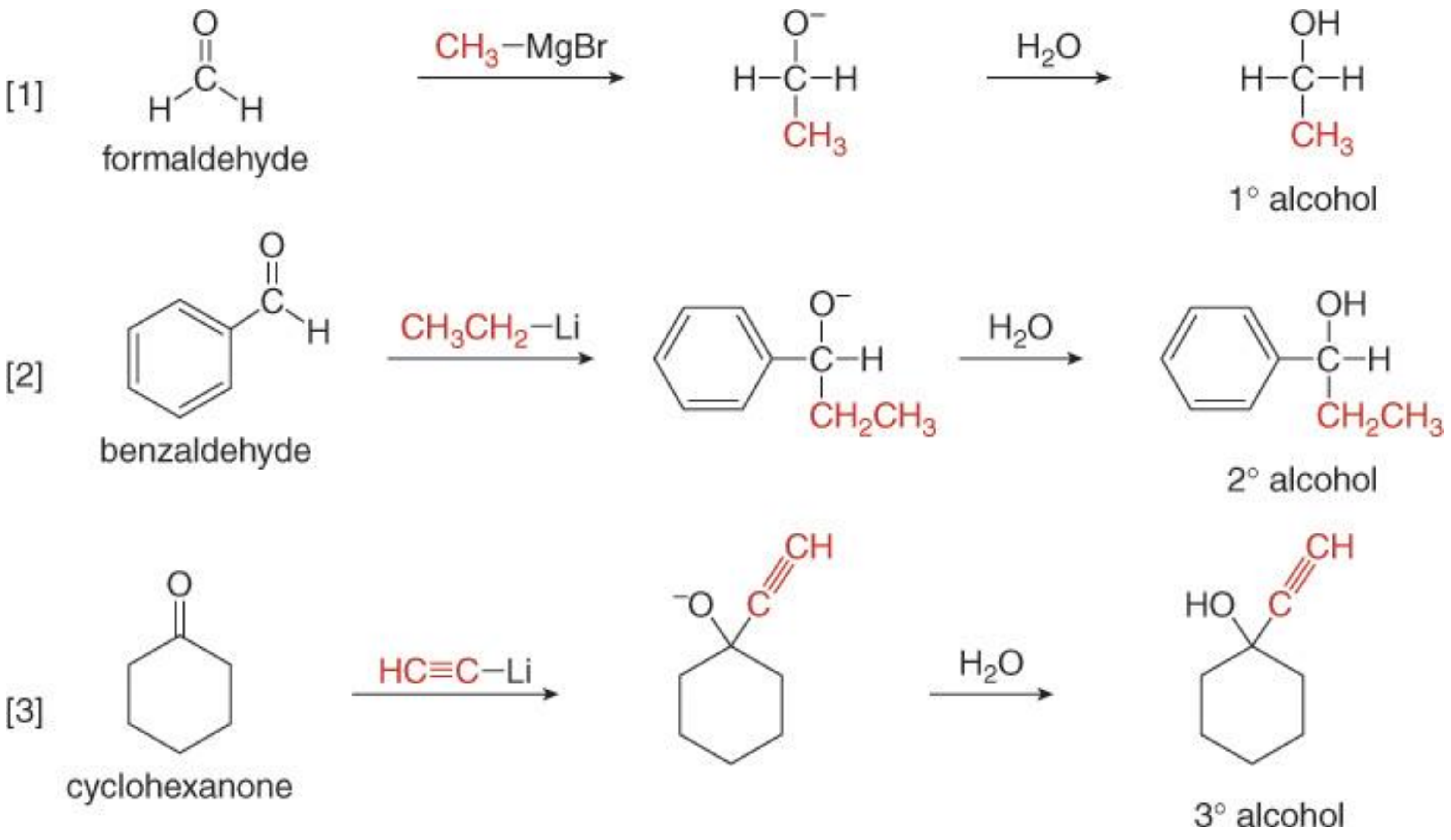
R is transferred as R^-

Reaction of carbonyl compounds with organometallic reagents

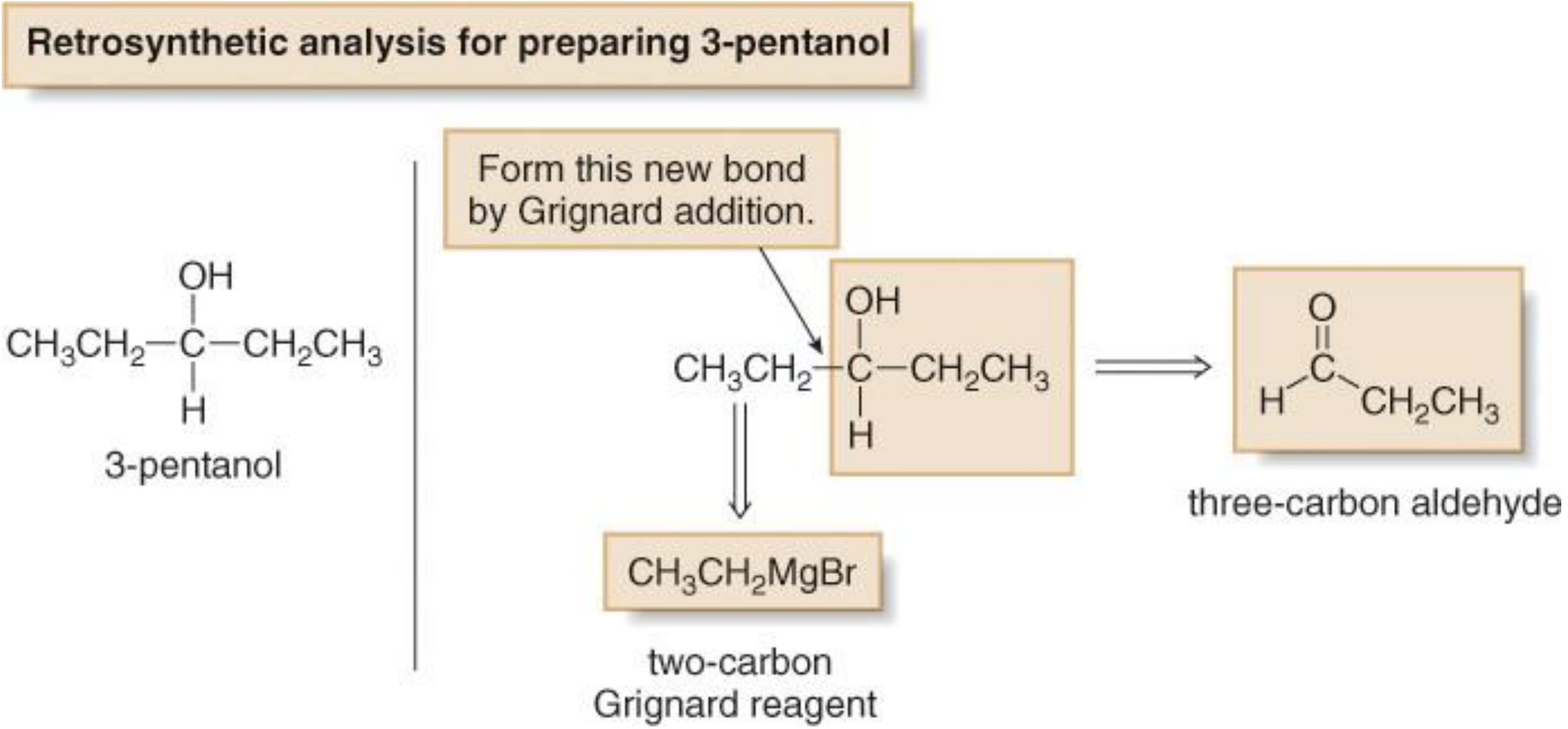


[1] Addition of R"MgX to formaldehyde ($CH_2=O$) forms a 1° alcohol.
[2] Addition of R"MgX to all other aldehydes forms a 2° alcohol.
[3] Addition of R"MgX to ketones forms a 3° alcohol.

Reaction of carbonyl compounds with organometallic reagents



Reaction of carbonyl compounds with organometallic reagents



Retrosynthetic analysis for preparing 3-pentanol

3-pentanol

Form this new bond by Grignard addition.

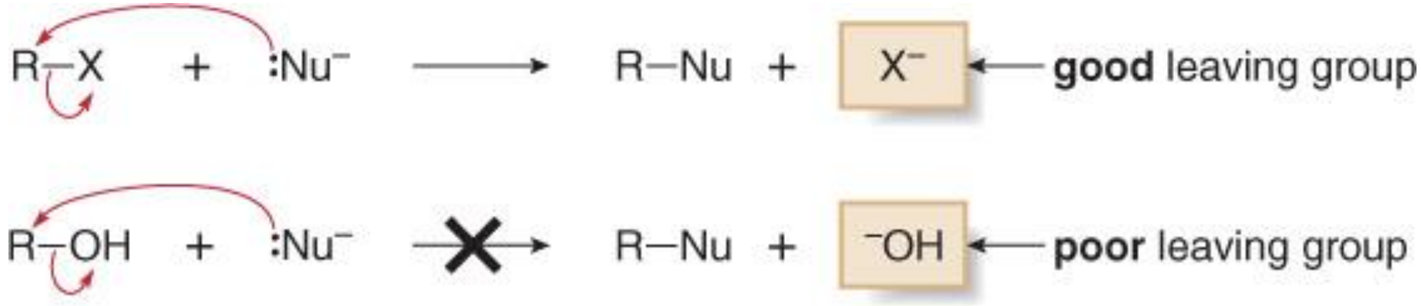
CH_3CH_2MgBr

two-carbon Grignard reagent

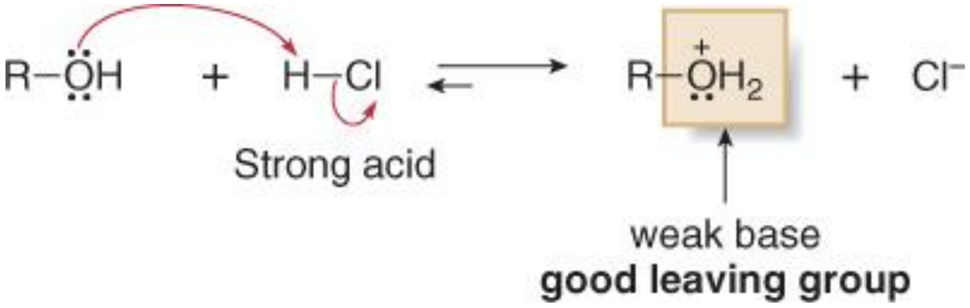
three-carbon aldehyde

Reactions of Alcohols

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

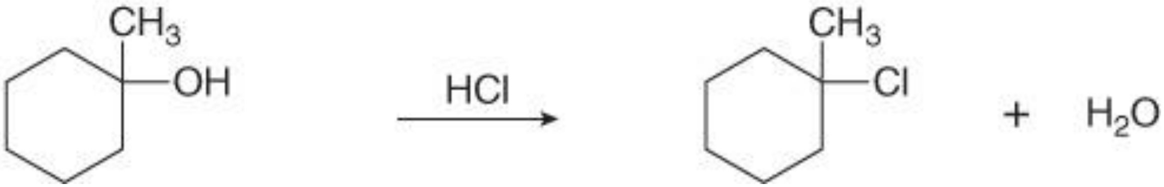


- By using acid, -OH can be converted into $–OH_2^+$, a good leaving group.

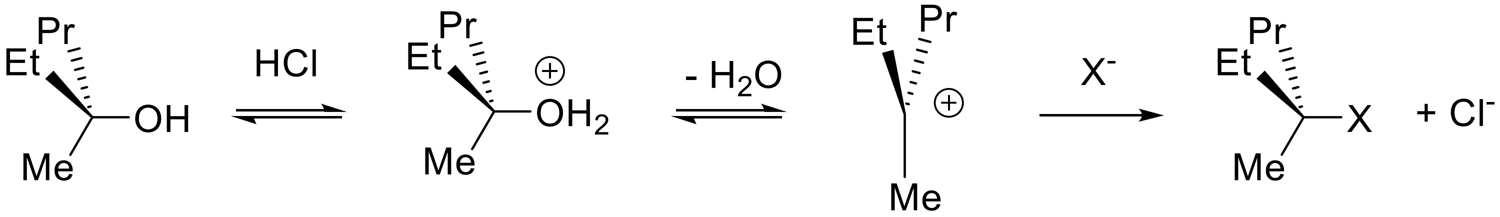


Conversion of Alcohols to Alkyl Halides with HX

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

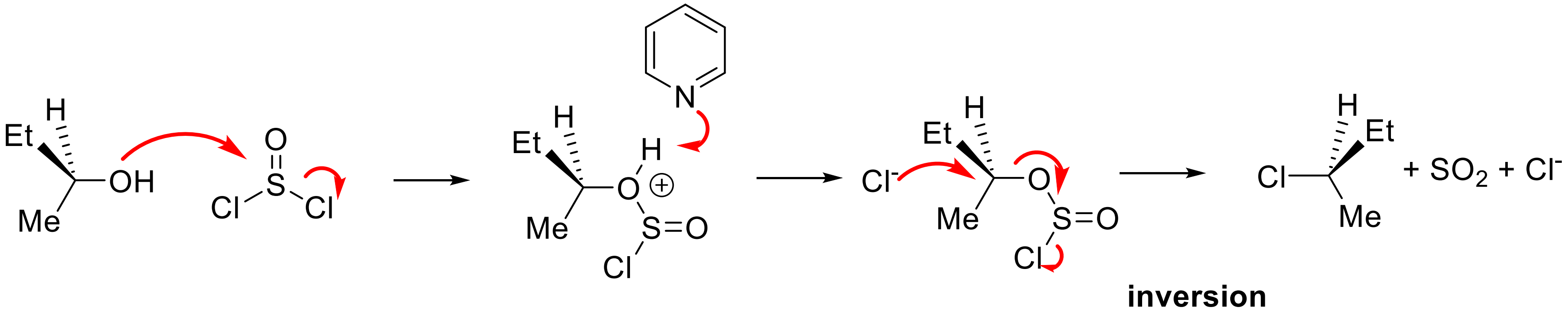


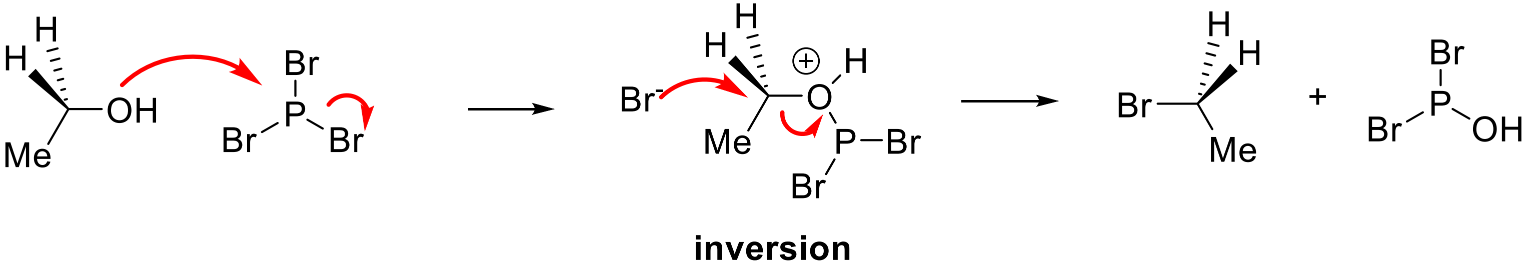
- The mechanism is SN1
- Racemization occurs



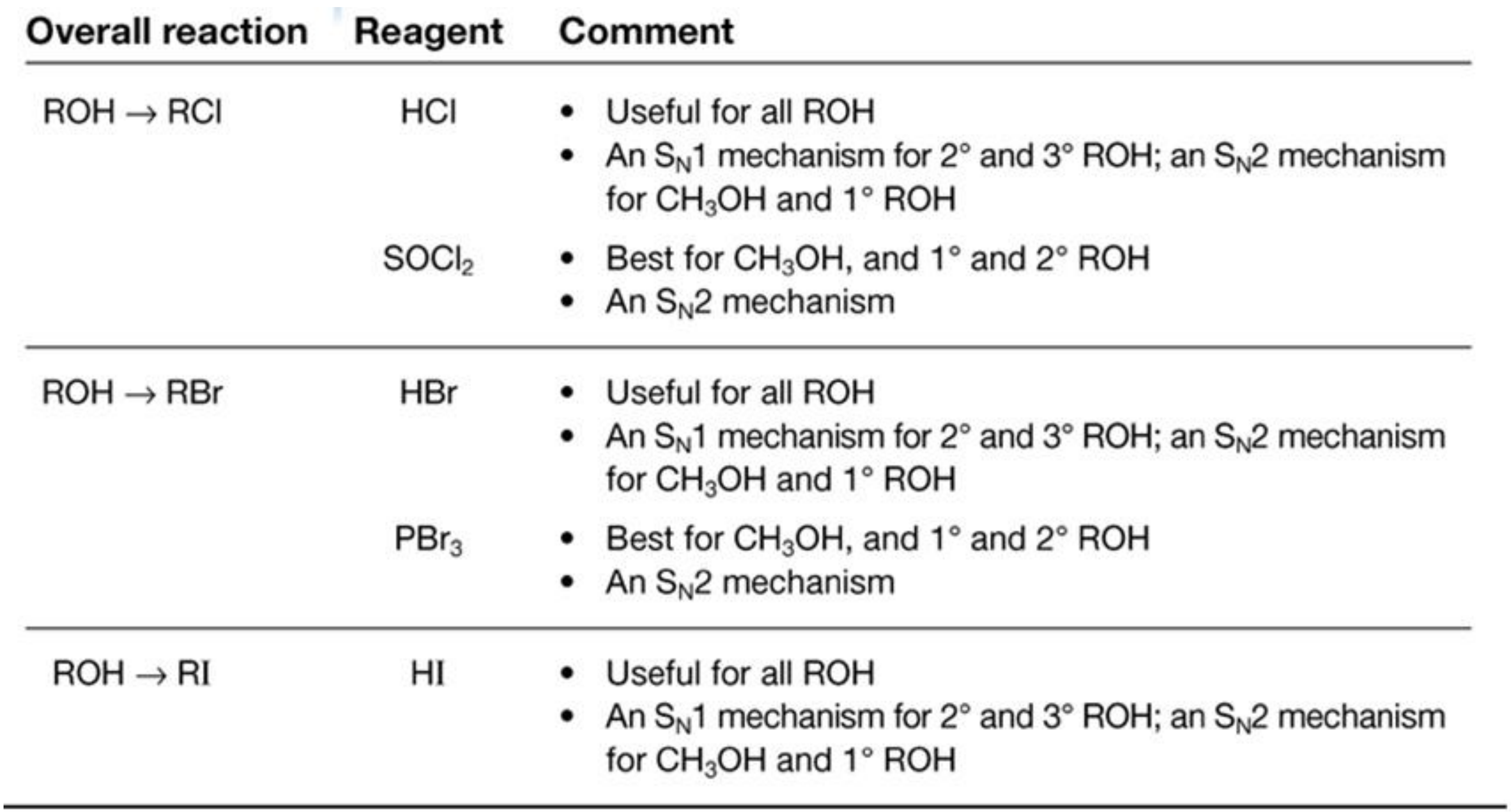
Conversion of Alcohols to Alkyl Halides with $SOCl_2$ and PBr_3

- Primary and secondary alcohols can be converted to alkyl halides using $SOCl_2$ (thionyl chloride) and PBr_3 (phosphorus tribromide)





Conversion of Alcohols to Alkyl Halides

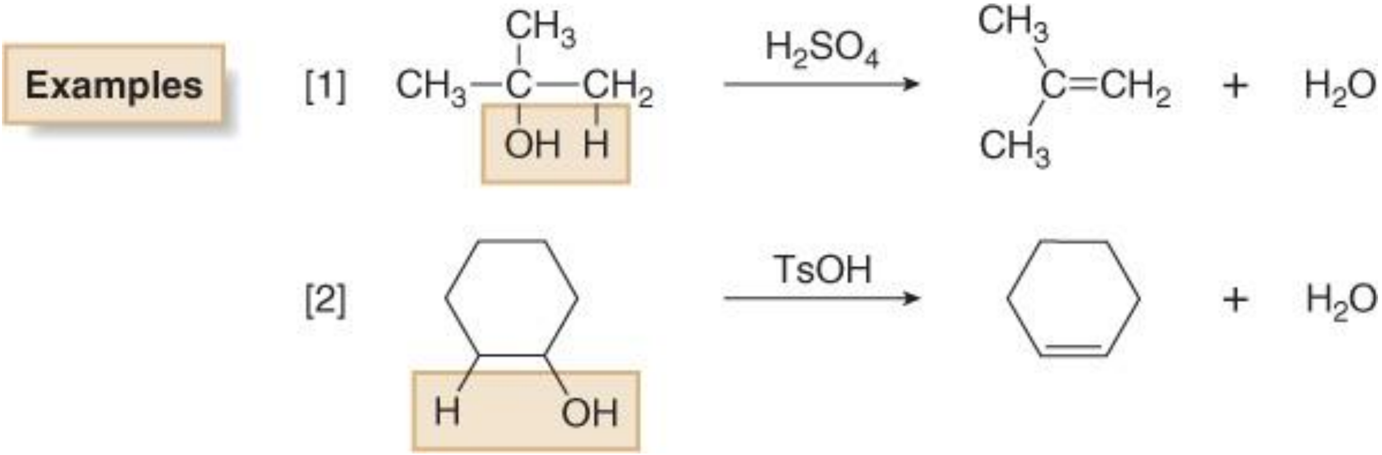


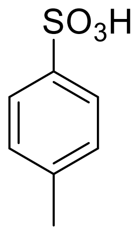
Overall reaction	Reagent	Comment
ROH → RCl	HCl	• Useful for all ROH • An S_N1 mechanism for 2° and 3° ROH; an S_N2 mechanism for CH_3OH and 1° ROH
	$SOCl_2$	• Best for CH_3OH, and 1° and 2° ROH • An S_N2 mechanism
ROH → RBr	HBr	• Useful for all ROH • An S_N1 mechanism for 2° and 3° ROH; an S_N2 mechanism for CH_3OH and 1° ROH
	PBr_3	• Best for CH_3OH, and 1° and 2° ROH • An S_N2 mechanism
ROH → RI	HI	• Useful for all ROH • An S_N1 mechanism for 2° and 3° ROH; an S_N2 mechanism for CH_3OH and 1° ROH

Reactions of Alcohols—Dehydration

- Dehydration, like dehydrohalogenation, is a β elimination reaction in which the elements of OH and H are removed from the α and β carbon atoms respectively.

- Typical acids used for alcohol dehydration are H_2SO_4 or *p*-toluenesulfonic acid (TsOH).

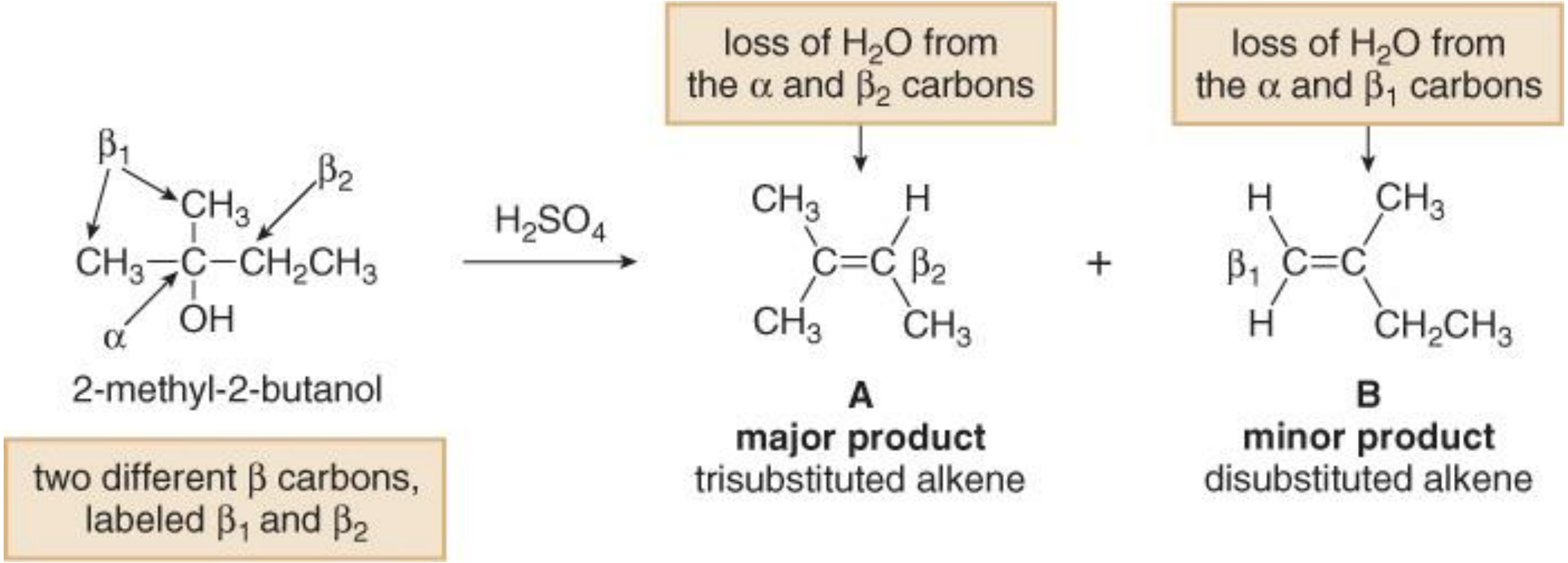




TsOH

Reactions of Alcohols—Dehydration

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



2-methyl-2-butanol

two different β carbons, labeled β_1 and β_2

loss of H_2O from the α and β_2 carbons

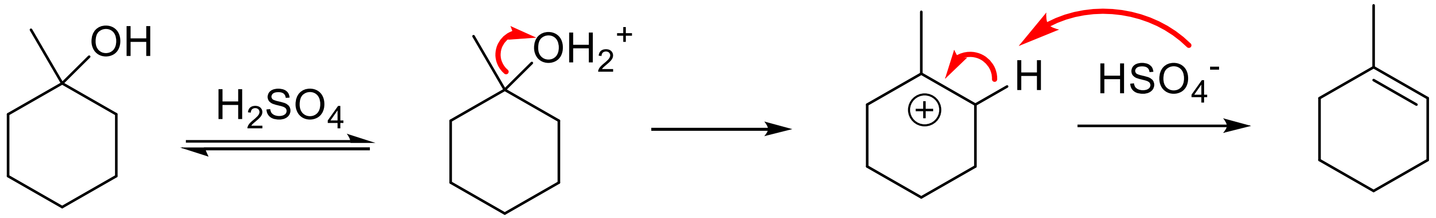
A
major product
trisubstituted alkene

loss of H_2O from the α and β_1 carbons

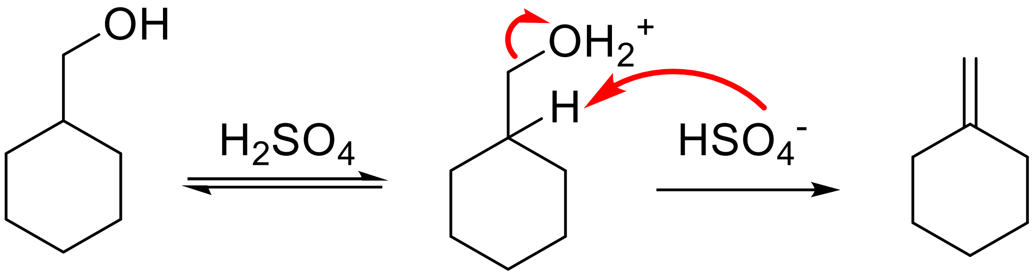
B
minor product
disubstituted alkene

Reactions of Alcohols—Dehydration

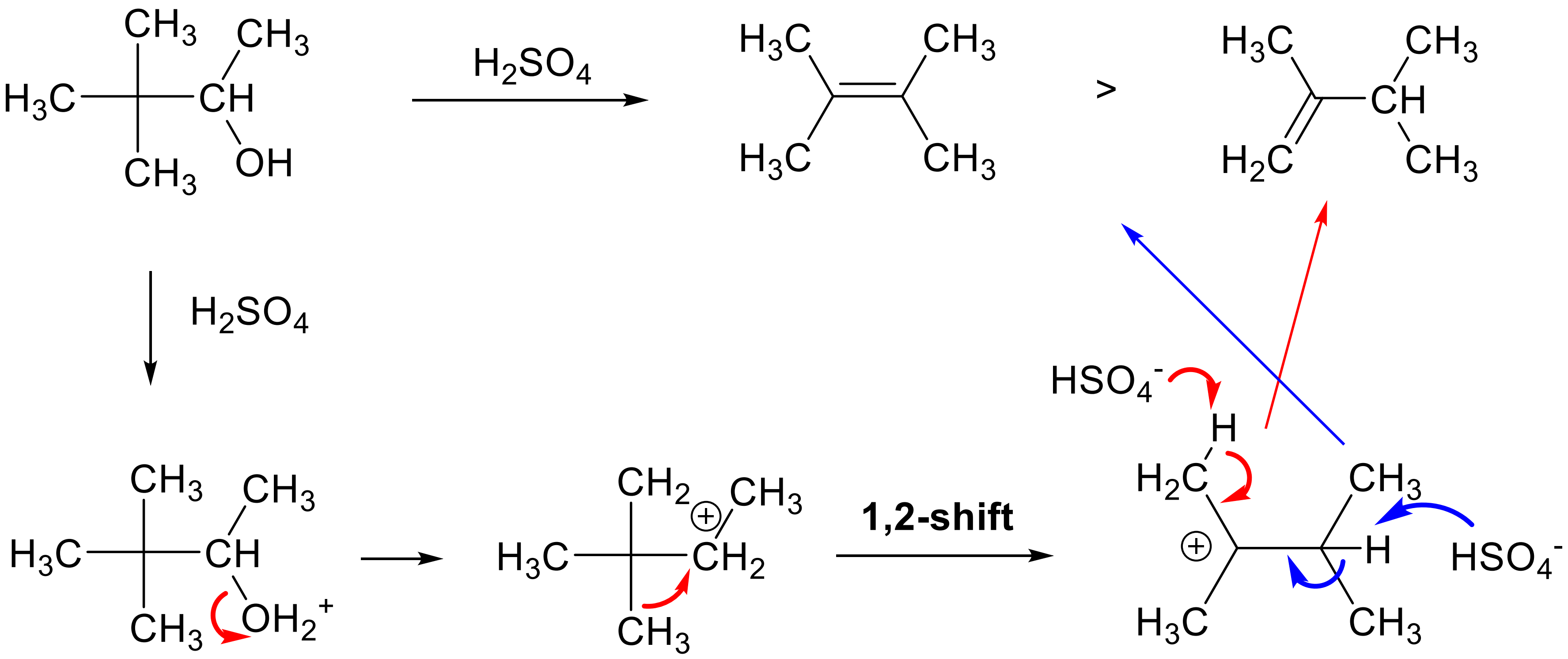
- Tertiary alcohols react by an E1 mechanism.



- 1^{ry} alcohols undergo dehydration following an E2 mechanism.

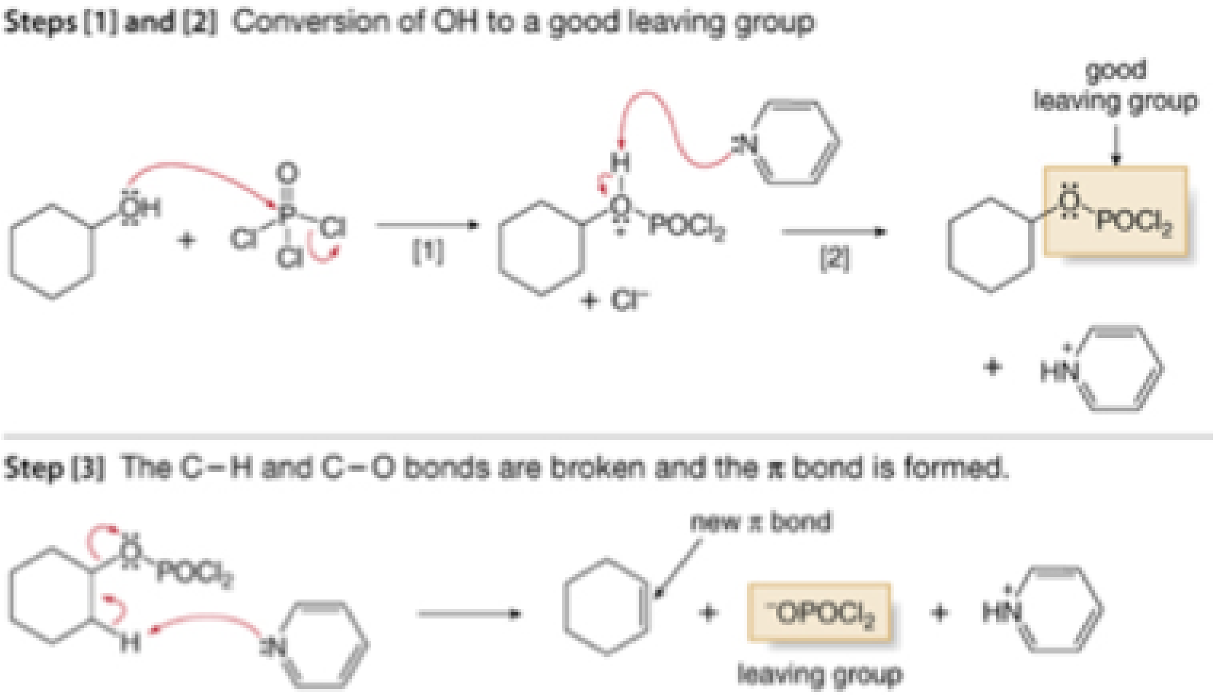


Carbocation Rearrangements

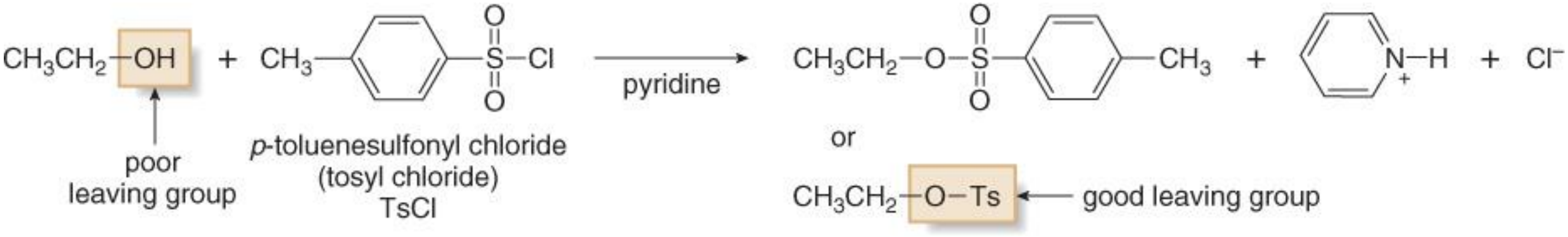


Dehydration of Alcohols Using $POCl_3$ and Pyridine

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

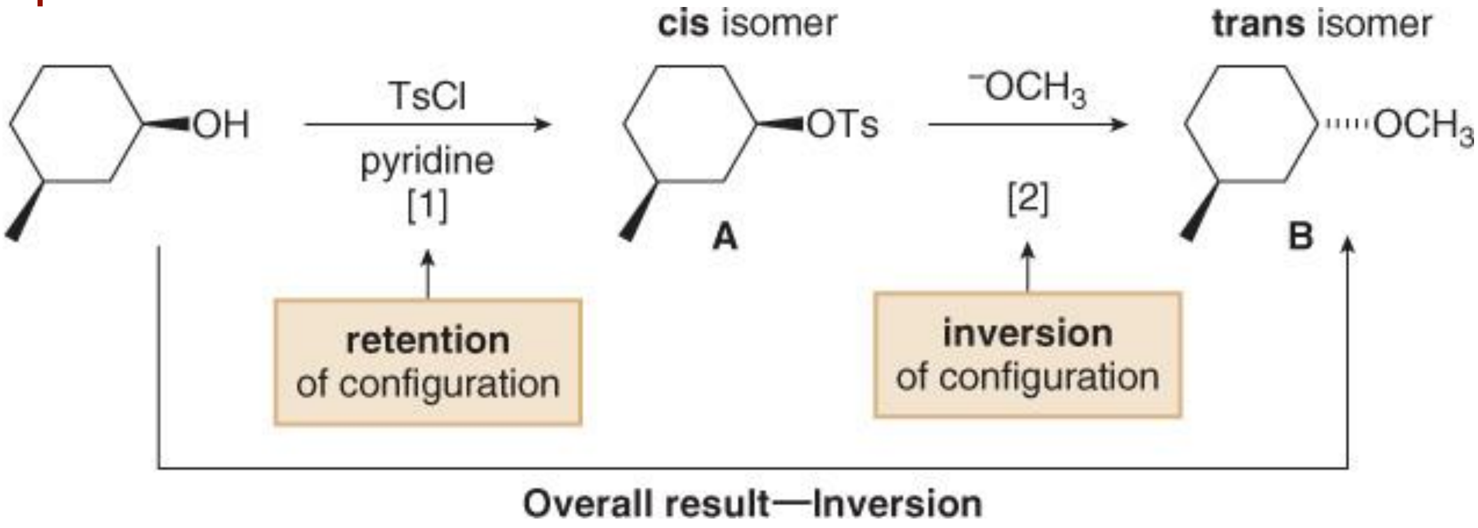


Tosylate—Another Good Leaving Group

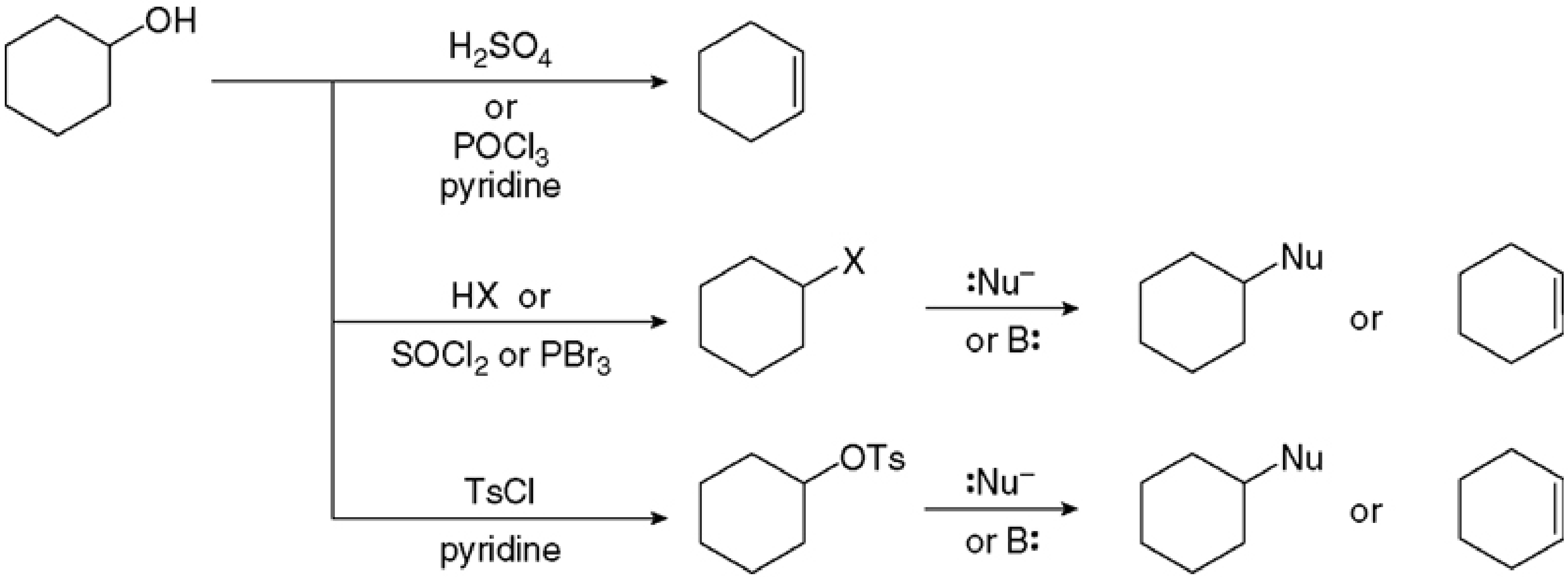


- Tosylate is a good leaving group because its conjugate acid, *p*-toluenesulfonic acid ($CH_3C_6H_4SO_3H$, TsOH) is a strong acid (pK_a = -7).

Example:

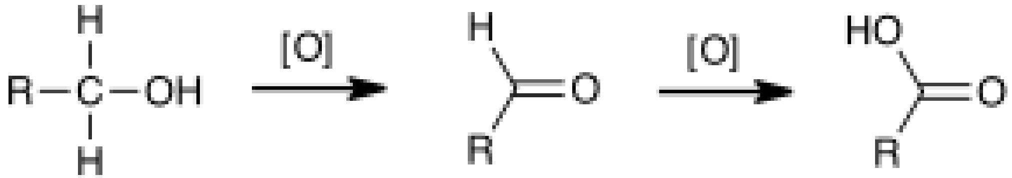


Nucleophilic substitution and β elimination reactions of alcohols



Oxidation of Alcohols

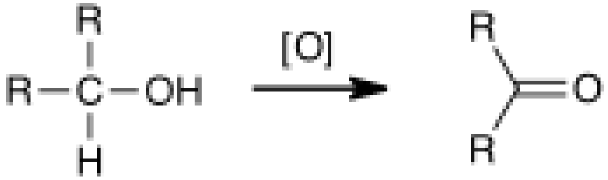
1° ALCOHOL



ALDEHYDE

ACID

2° ALCOHOL

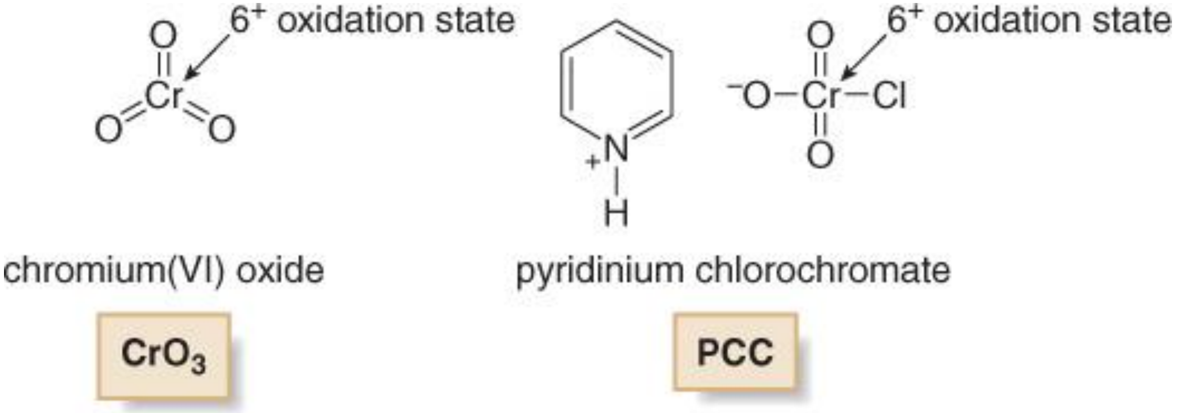


KETONE

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.
- CrO_3, $Na_2Cr_2O_7$, and $K_2Cr_2O_7$ are strong, nonselective oxidants used in aqueous acid ($H_2SO_4 + H_2O$).
- PCC is soluble in CH_2Cl_2 (dichloromethane) and can be used without strong acid present, making it a more selective, milder oxidant.



chromium(VI) oxide

CrO_3

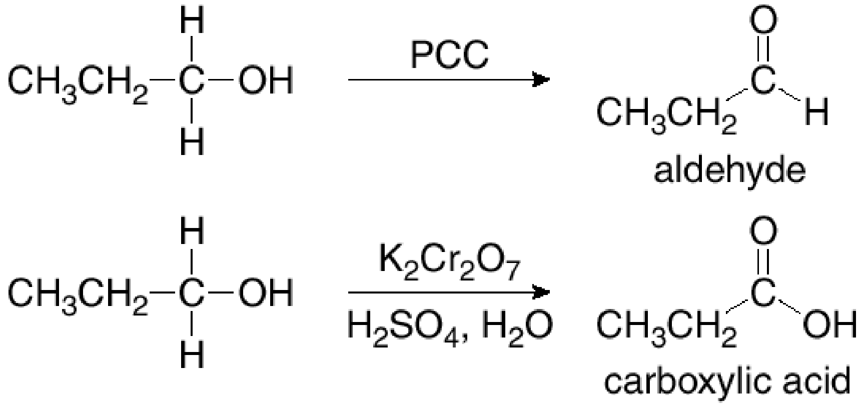
pyridinium chlorochromate

PCC

Oxidation of Alcohols

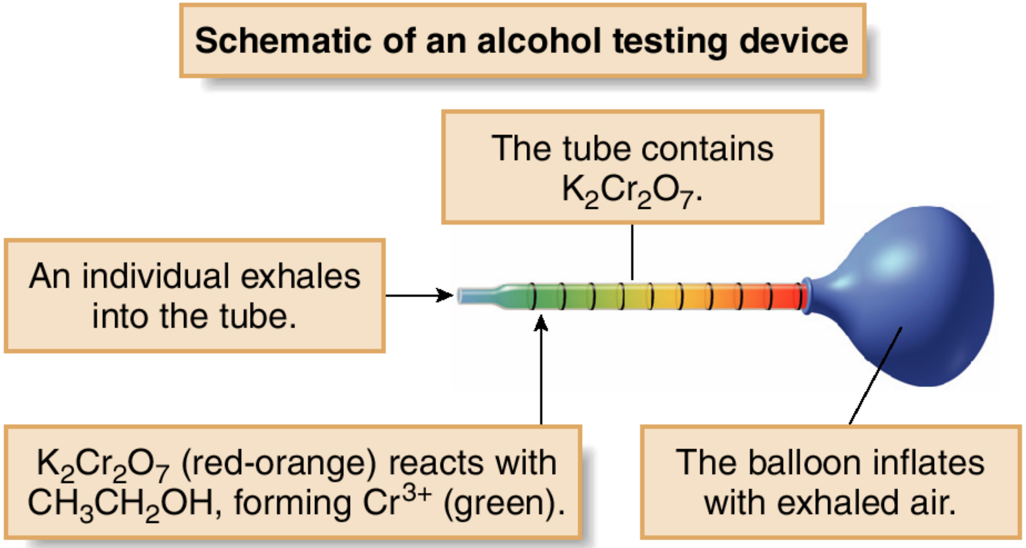
- 1° Alcohols are oxidized to aldehydes (RCHO) under mild reaction conditions—using PCC in CH_2Cl_2.
- 1° Alcohols are oxidized to carboxylic acids (RCOOH) under harsher reaction conditions: $Na_2Cr_2O_7$, $K_2Cr_2O_7$, or CrO_3 in the presence of H_2O and H_2SO_4.

1° Alcohols



The Alcohol Test

- 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.



Schematic of an alcohol testing device

The tube contains $K_2Cr_2O_7$.

An individual exhales into the tube.

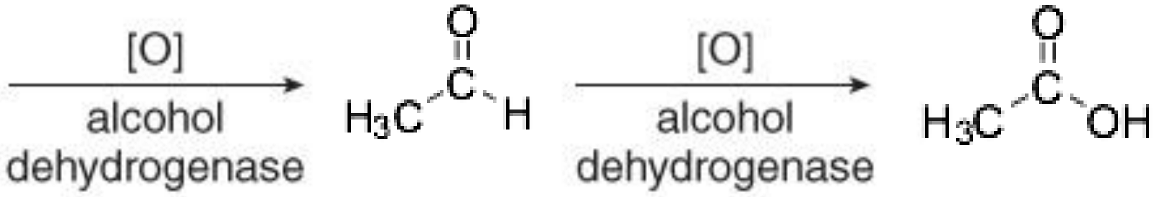
$K_2Cr_2O_7$ (red-orange) reacts with CH_3CH_2OH, forming Cr^{3+} (green).

The balloon inflates with exhaled air.

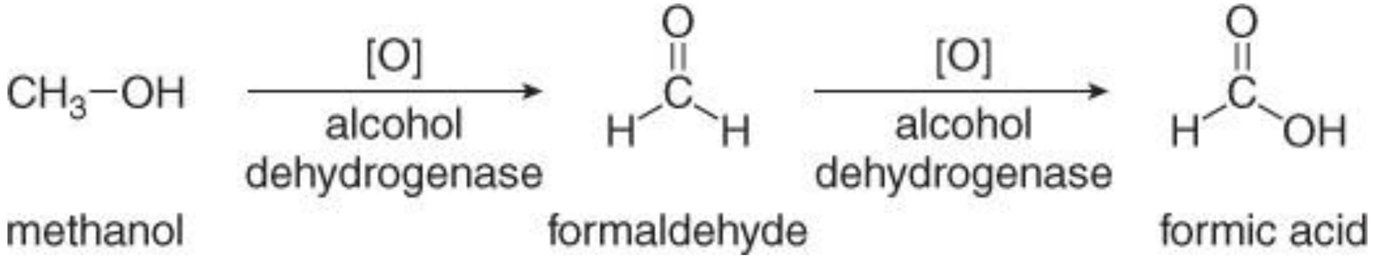
Consumer product

Ethanol Metabolism

CH_3CH_2-OH



ethanol acetaldehyde acetic acid

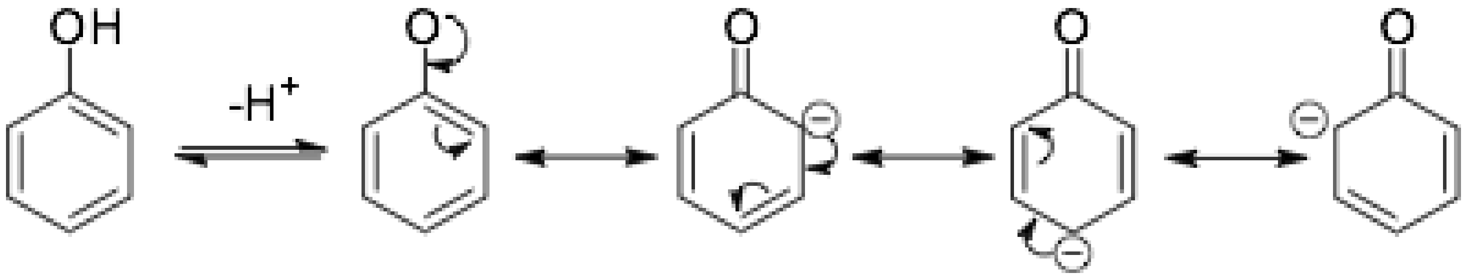


Acidity of Alcohols

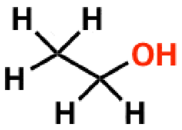
Compound	pK_a
CH_3CH_2OH	16.0
CF_3CH_2OH	12.4
C_6H_5OH	9.9
p-$NH_2C_6H_4OH$	10.5
p-$NO_2C_6H_4OH$	7.2

$CF_3CH_2O^-$: Inductively stabilized

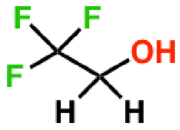
$C_6H_5O^-$: Resonance stabilized



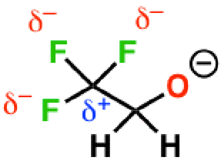
Inductive effect of electron-withdrawing groups increases acidity



Ethanol
pKa = 16



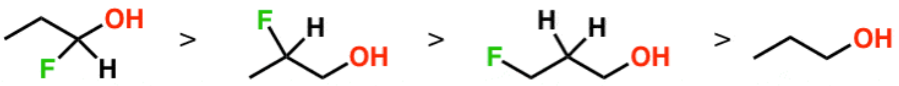
2,2,2-trifluoroethanol
pKa = 12



Conjugate base of trifluoroethanol
(stabilized due to inductive effect)

The highly electronegative fluorine atoms create a strong **inductive effect**, which is transferred through the carbon skeleton and leads to a slightly reduced [and therefore more stabilized] charge on the oxygen

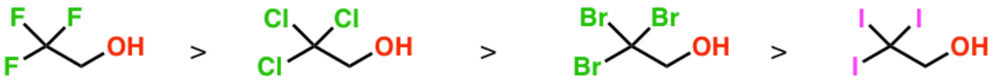
Inductive effect decreases with increasing distance from the acid



most acidic

least acidic

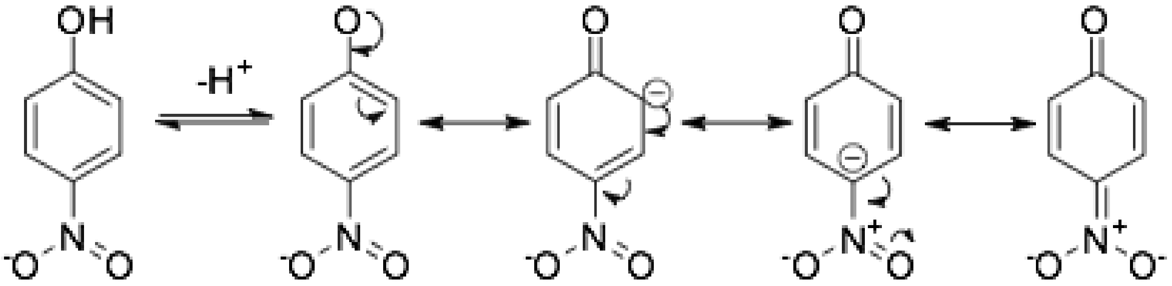
Inductive effect increases with increasing electronegativity



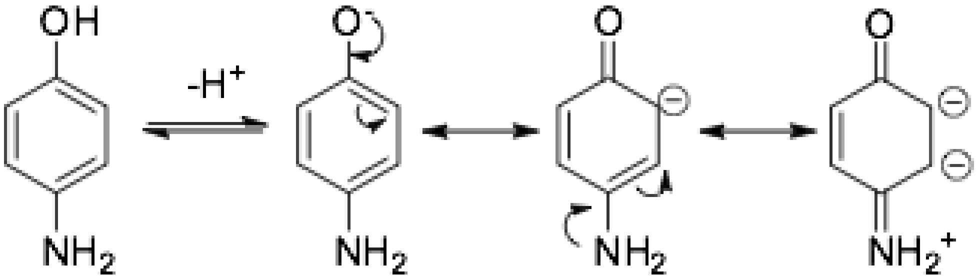
most acidic

least acidic

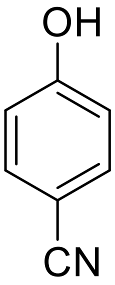
Substituent effects on acidity of phenols



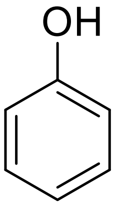
Stabilized by delocalization



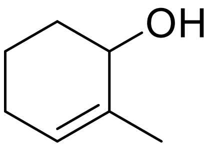
Destabilized by delocalization



1



2



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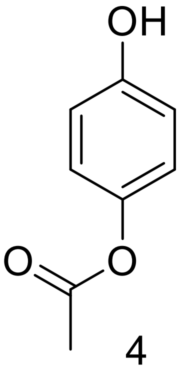

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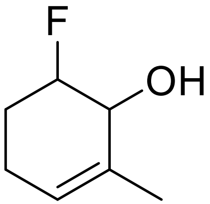

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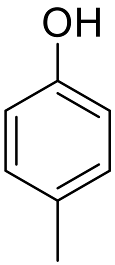
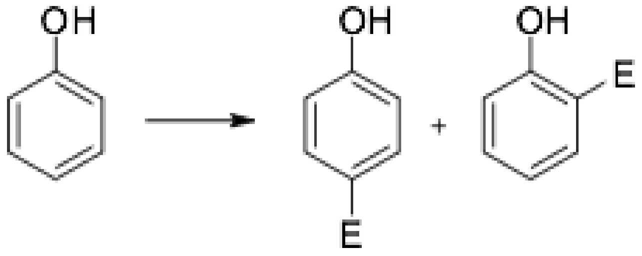


6

3 < 5 < 4 < 6 < 2 < 1

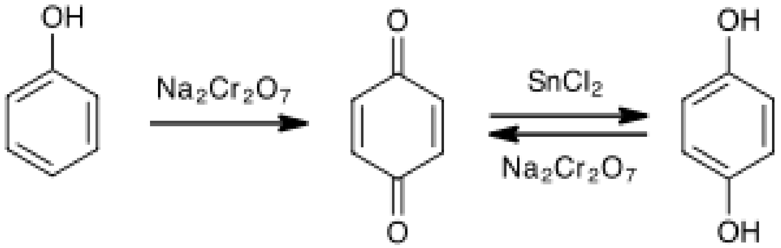
Reactions of Phenol

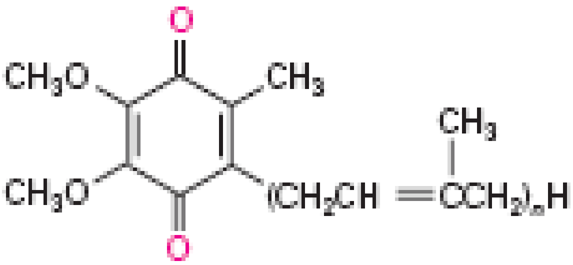
S_EAr:



Activated
(OH: +R > -I)

Oxidation:

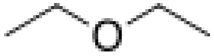




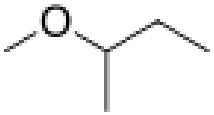
Ubichinoni (*n* = 1–10)

Nomenclature of Ethers

- Common names:



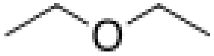
diethyl ether



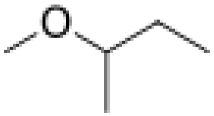
s-butyl methyl ether

tetrahydrofuran
THF

- IUPAC names:

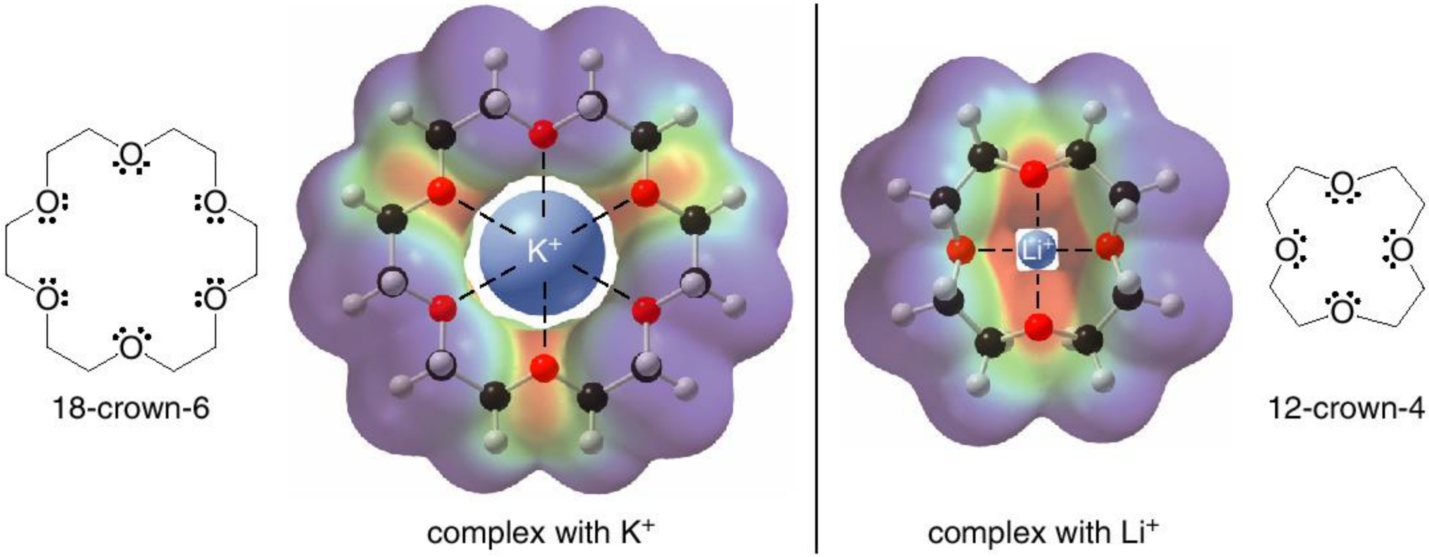


ethoxyethane



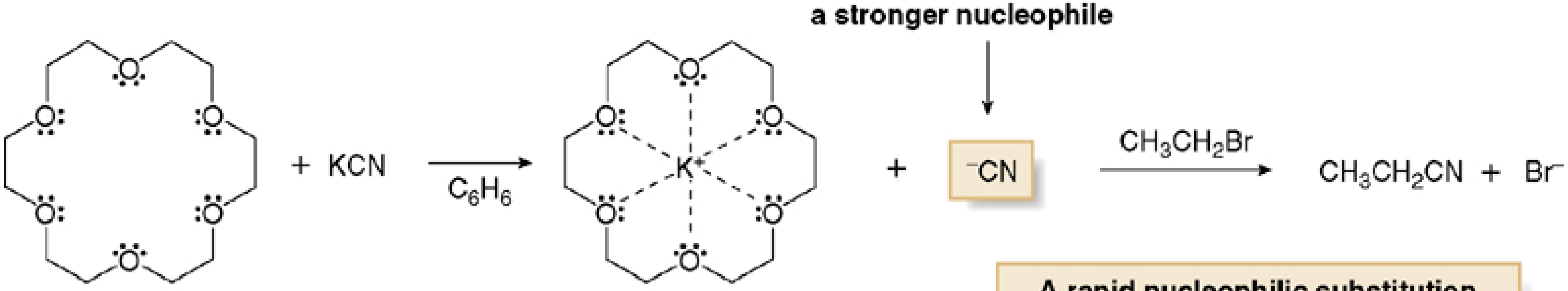
2-methoxybutane

Interesting Ethers



- A crown ether–cation complex is called a *host–guest* complex. The crown ether is the *host* and the cation is the *guest.*
- The ability of a host molecule to bind specific guests is called *molecular recognition.*

KCN is insoluble in nonpolar solvents alone, but with 18-crown-6:



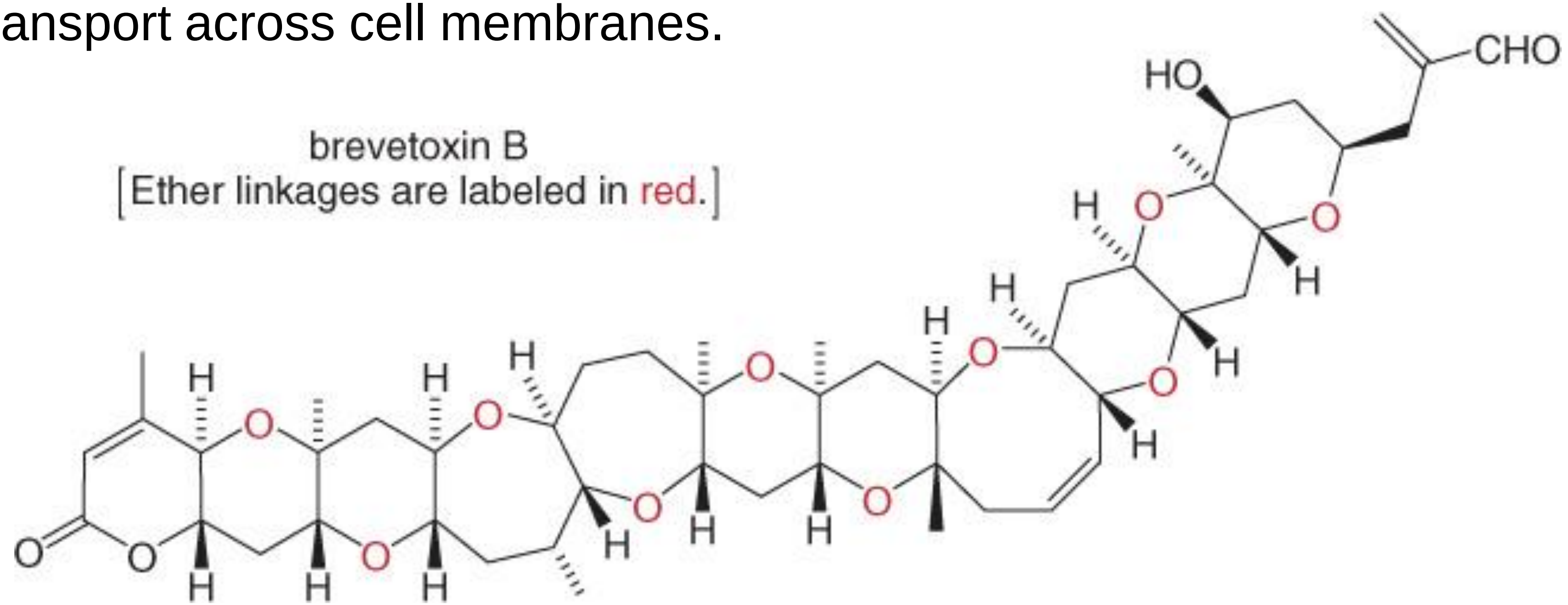
18-crown-6

host–guest complex
soluble in nonpolar solvents

A rapid nucleophilic substitution reaction occurs in nonpolar solvents when a crown ether is added.

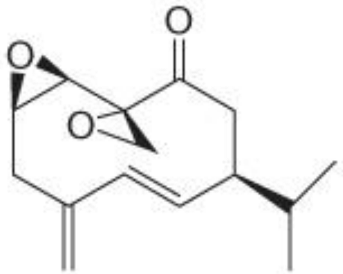
Interesting Ethers and Epoxides

- Brevetoxin B is a naturally occurring polyether that interferes with Na^+ ion transport across cell membranes.

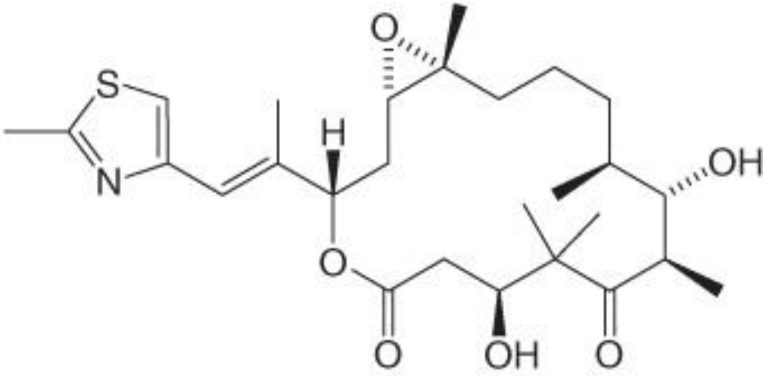


brevetoxin B

[Ether linkages are labeled in red.]



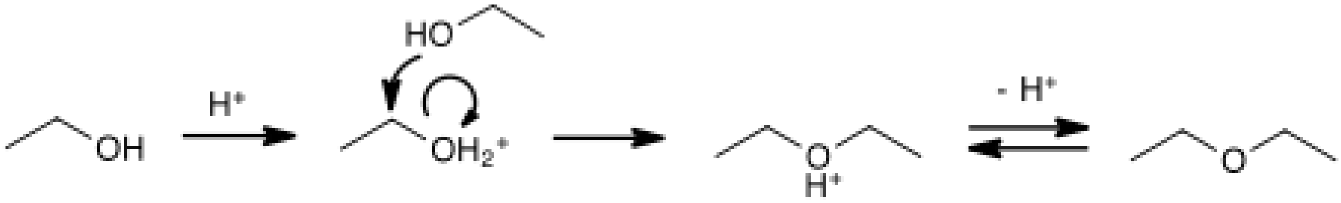
periplanone B
cockroach sex pheromone



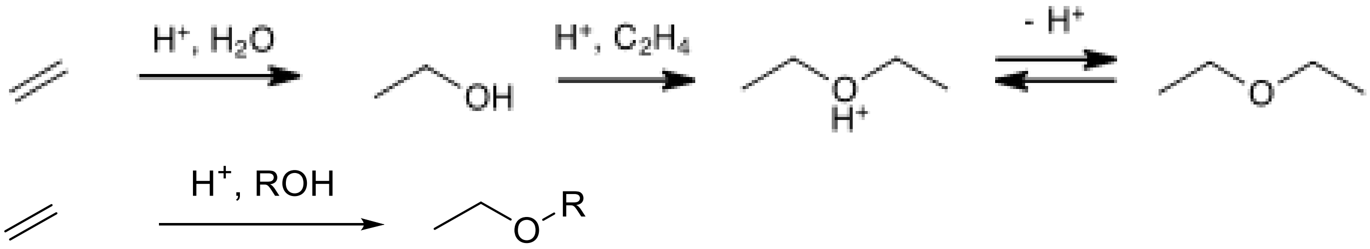
epothilone B
anticancer drug

Preparation of Ethers.

FROM ALCOHOLS

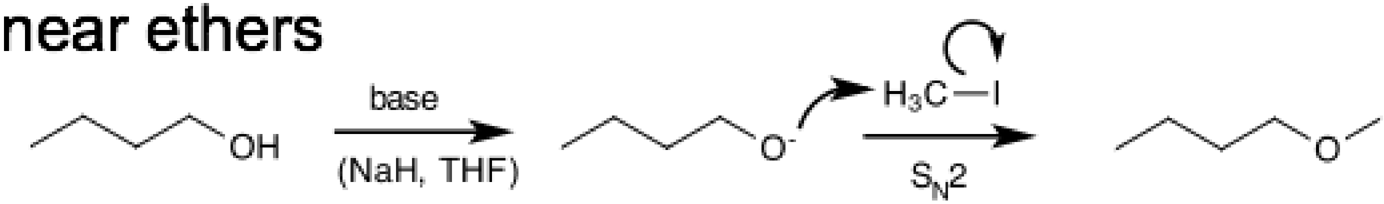


FROM ALKENES



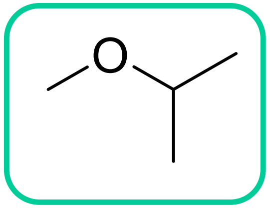
Preparation of Ethers. Williamson synthesis

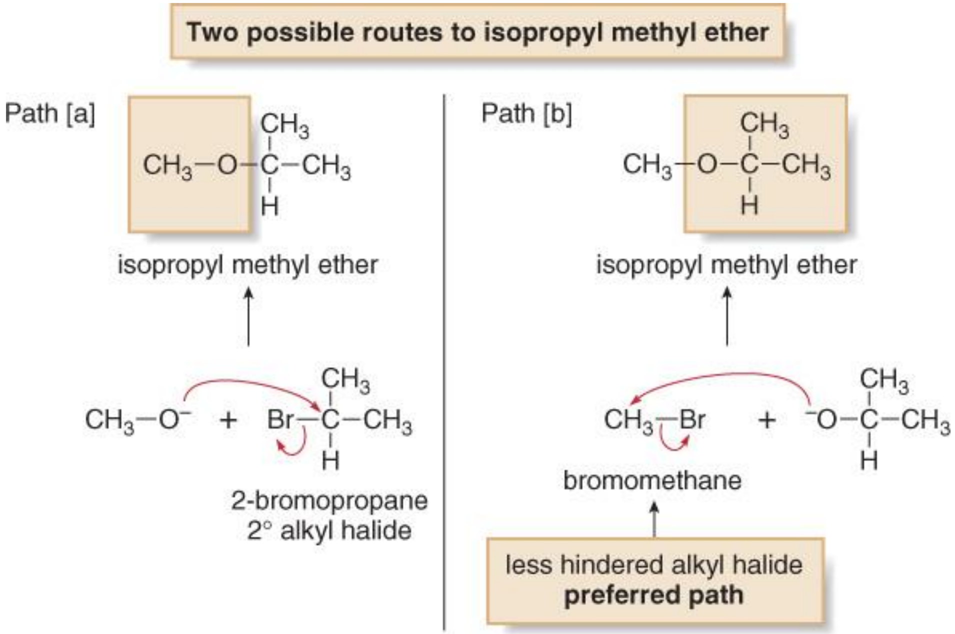
Linear ethers



Cyclic ethers

Preparation of Ethers.
Williamson synthesis

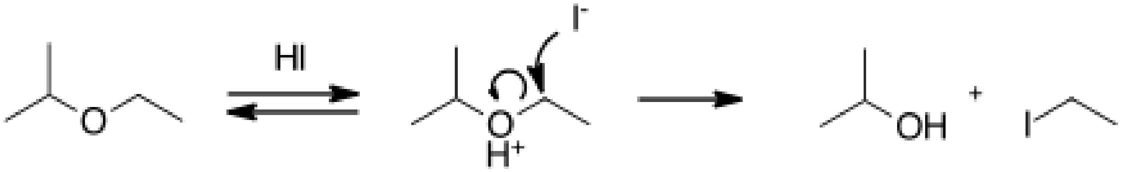



Two possible routes to isopropyl methyl ether

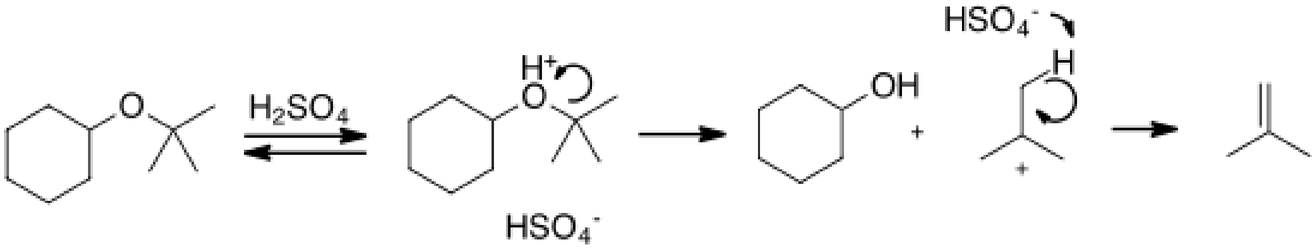
Reaction of Ethers with Strong Acid

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

S_N2

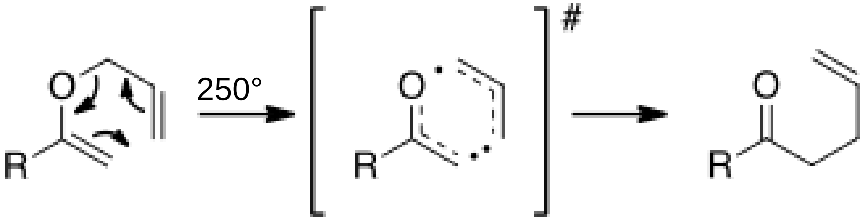


$S_N1/E1$

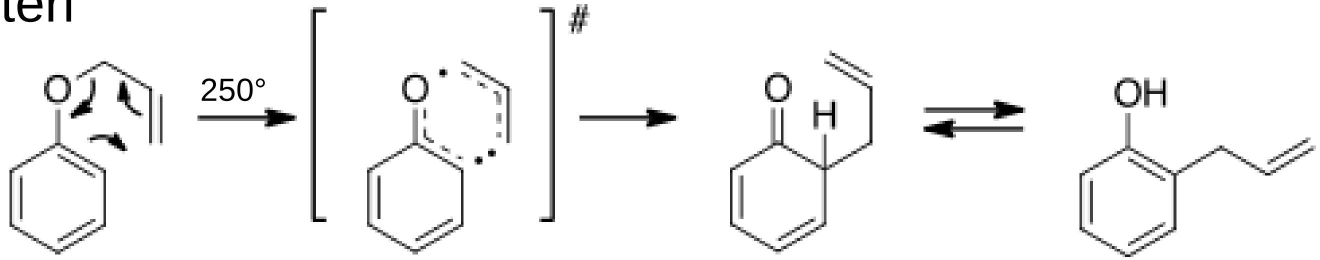


Claisen Rearrangement

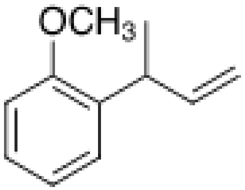
Allilvinileteri



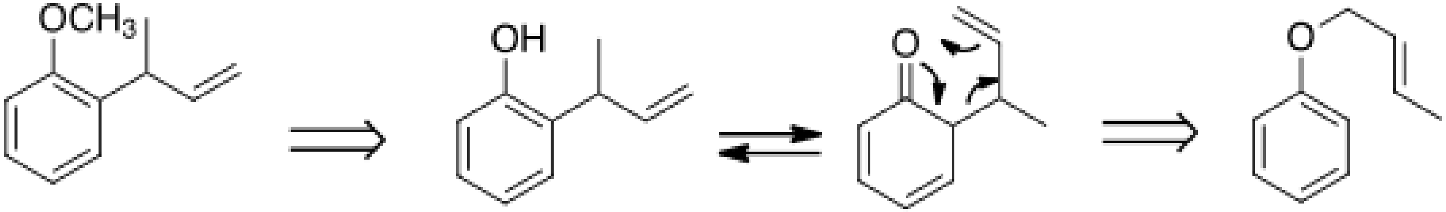
Allilarileteri



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.

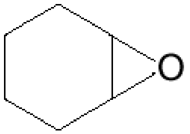
epoxide or **oxirane**

An epoxide is a special type of ether.

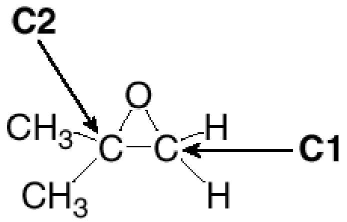
- The C—O—C bond angle for an epoxide must be 60°, a considerable deviation from the tetrahedral bond angle of 109.5°. Thus, epoxides have angle strain, making them more reactive than other ethers.

Nomenclature of Epoxides

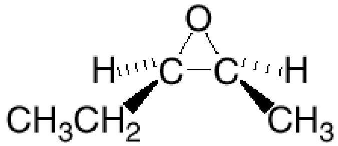
- Epoxyalkanes:



1,2-epoxycyclohexane

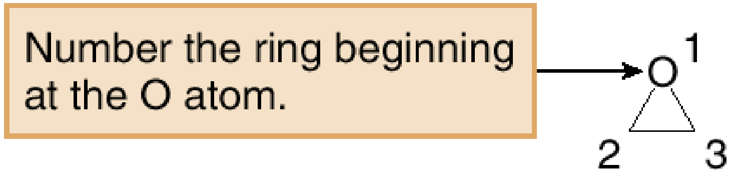


1,2-epoxy-2-methylpropane



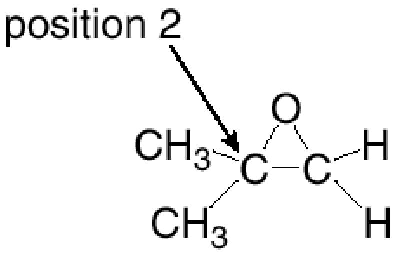
***cis*-2,3-epoxypentane**

- Oxiranes:



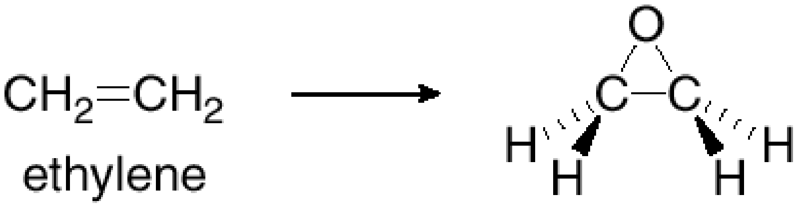
Number the ring beginning at the O atom.

oxirane



2,2-dimethyloxirane

- Alkene oxides:



$CH_2{=}CH_2$

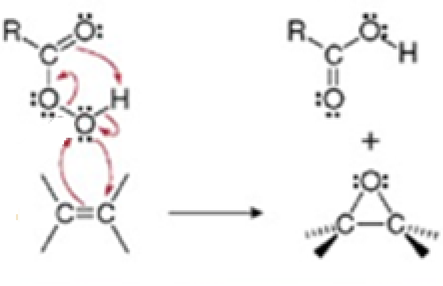
ethylene

ethylene oxide

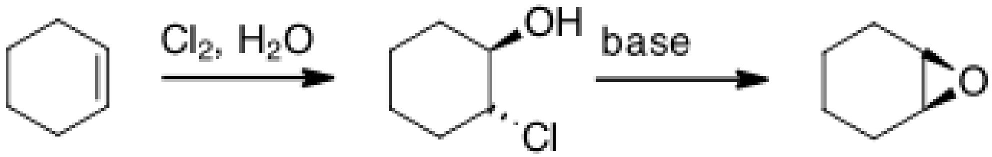
oxirane

Preparation of Epoxides

epoxidation of alkenes

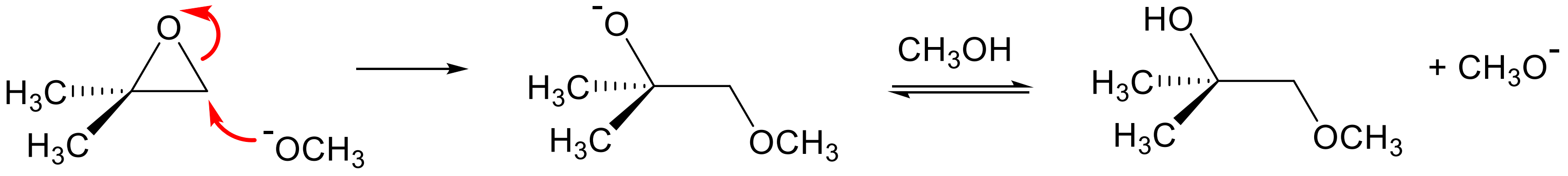


cyclization of halohydrins



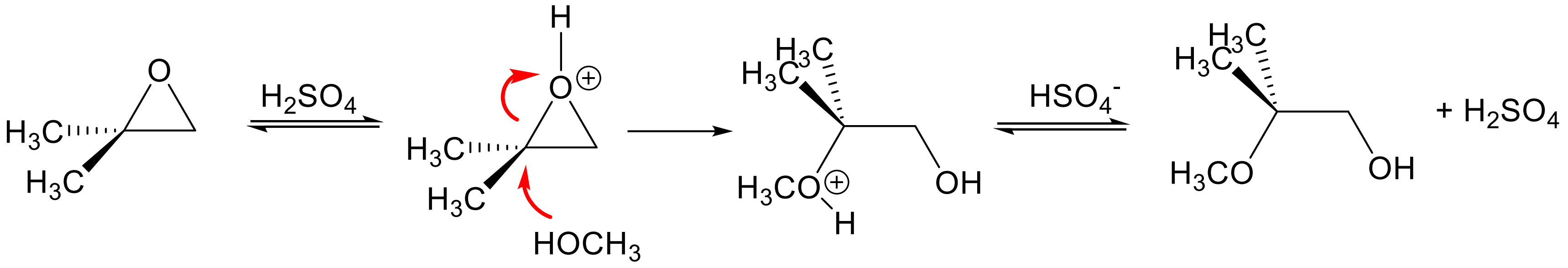
Reactions of Epoxides

- Nucleophilic attack opens the strained three-membered ring with an SN2 mechanism, making it a favorable process even with a poor leaving group.



Backside attack on the
less substituted carbon

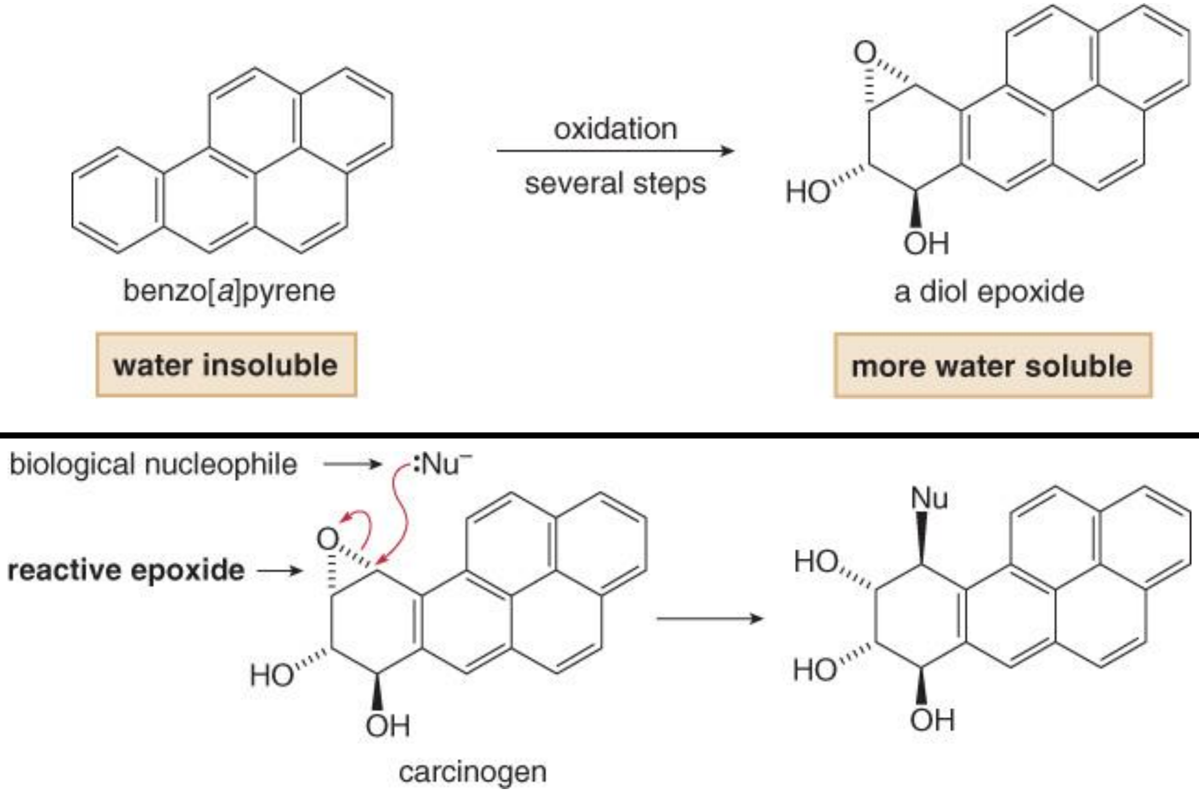
- Acids catalyse epoxide ring opening by protonating the oxygen:



Backside attack on the
more substituted carbon

Reactions of Epoxides

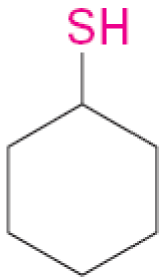
- When polyaromatic hydrocarbons are inhaled or ingested, they are oxidized in the liver to species that often contain a highly reactive epoxide ring.
- The strained three-membered ring reacts readily with biological nucleophiles such as DNA or enzymes, leading to ring-opened products that often disrupt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



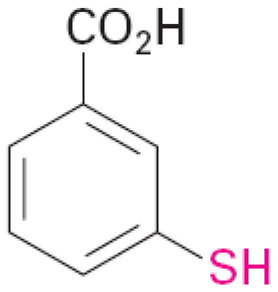
Thiols and Sulfides

CH_3CH_2SH

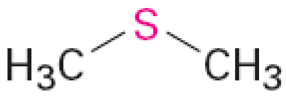
ethanethiol



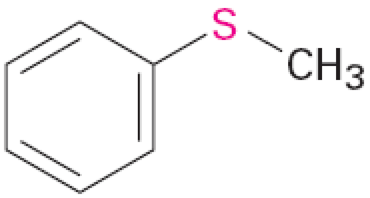
ciclohexanethiol



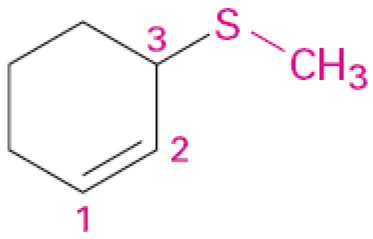
3-mercapto benzoic acid



dimethylsulfide

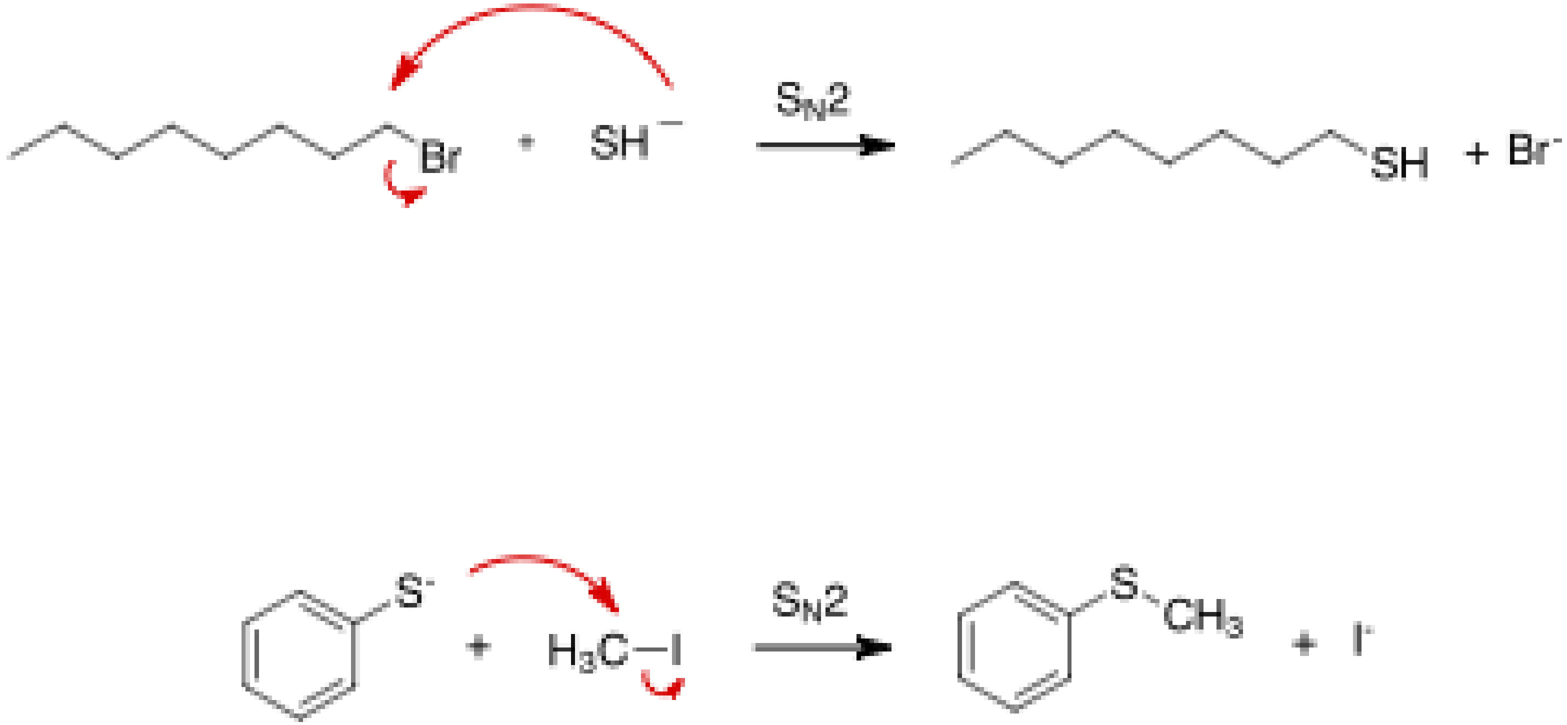


methyl phenyl sulfide

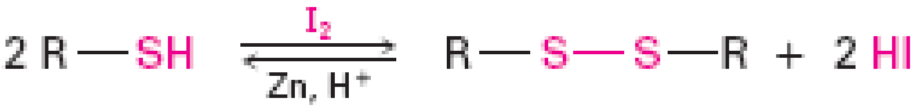


3-(methylmercapto) cyclohexene

Thiols and Sulfides: Synthesis

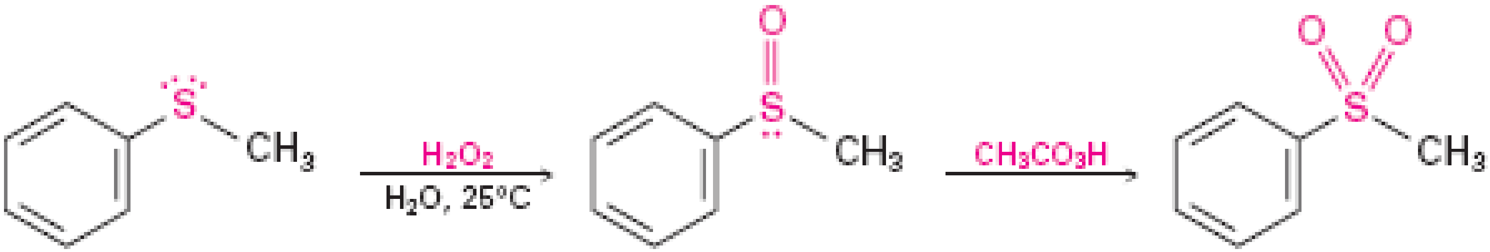


Thiols and Sulfides: Oxidation



$$2\,R{-}SH \underset{Zn,\ H^+}{\overset{I_2}{\rightleftharpoons}} R{-}S{-}S{-}R + 2\,HI$$

thiol disulfide



sulfide sulfoxide sulfone