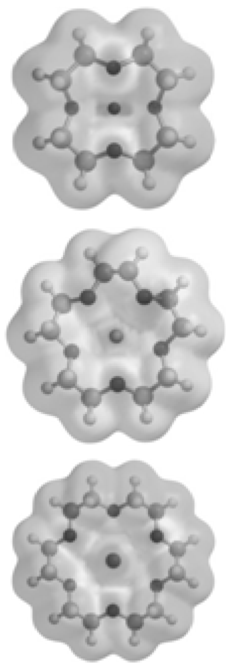
Organic Chemistry
6th Edition
Paula Yurkanis Bruice



Chapter 10

Reactions of Alcohols, Amines, Ethers, Epoxides, and Sulfur-Containing Compounds

Disampaikan oleh : Dr. Sri Handayani
2013

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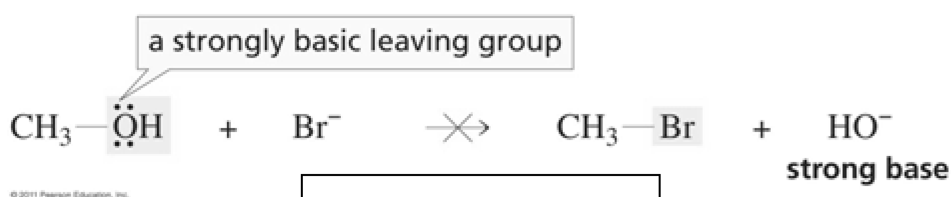
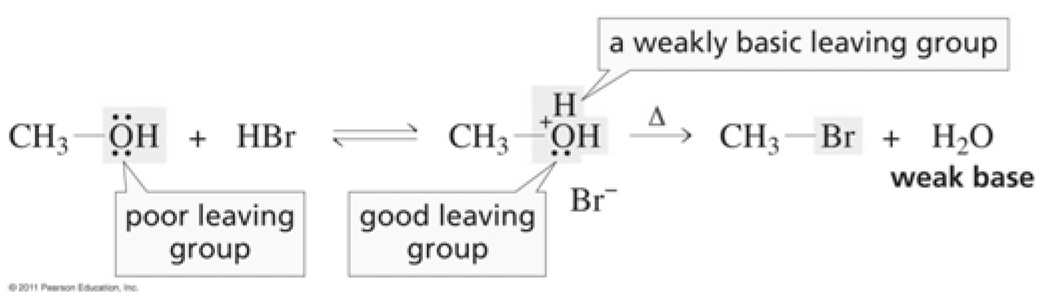
Alcohols and ethers have to be activated before they can undergo a substitution or an elimination reaction:



Convert the strongly basic leaving group (OH^-) into the good leaving group, H_2O (a weaker base):



Only weakly basic nucleophiles can be used

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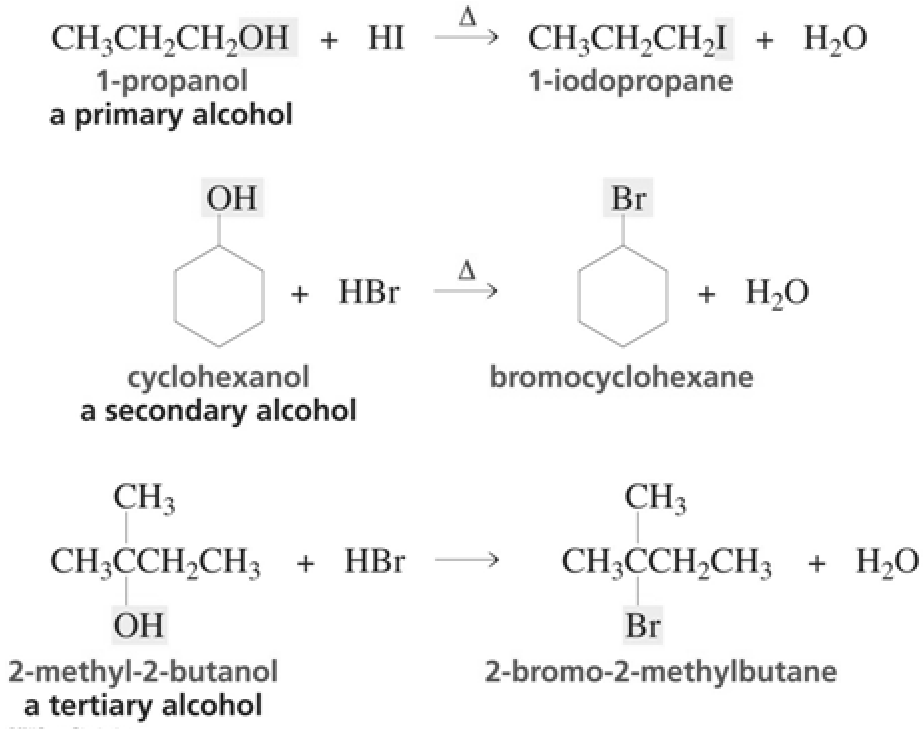
Primary, secondary, and tertiary alcohols all undergo nucleophilic substitution reactions with HI, HBr, and HCl:



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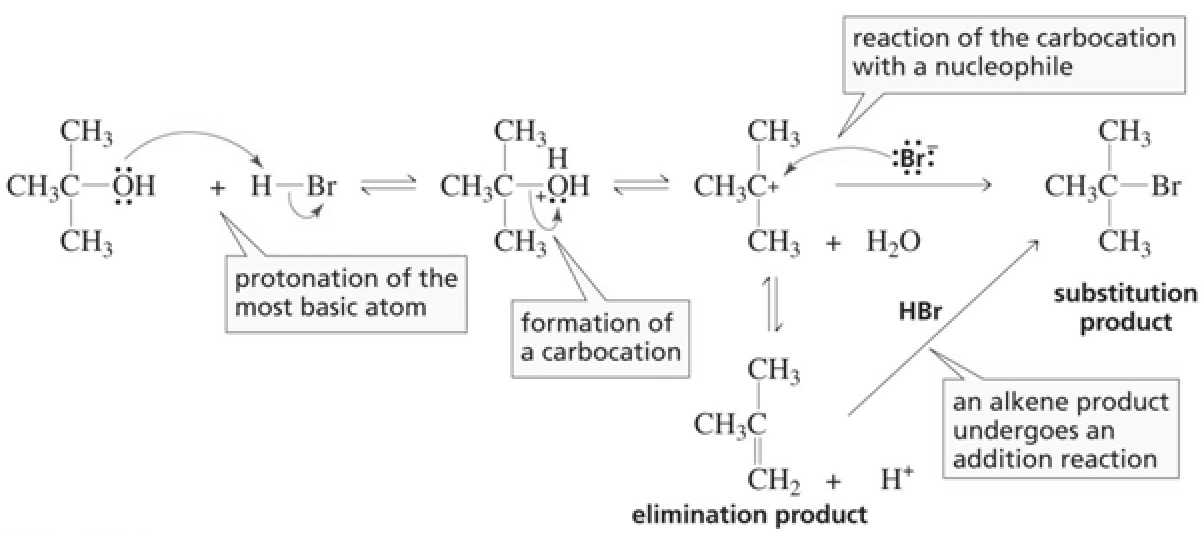
Secondary and tertiary alcohols undergo S_N1 reactions with hydrogen halides:



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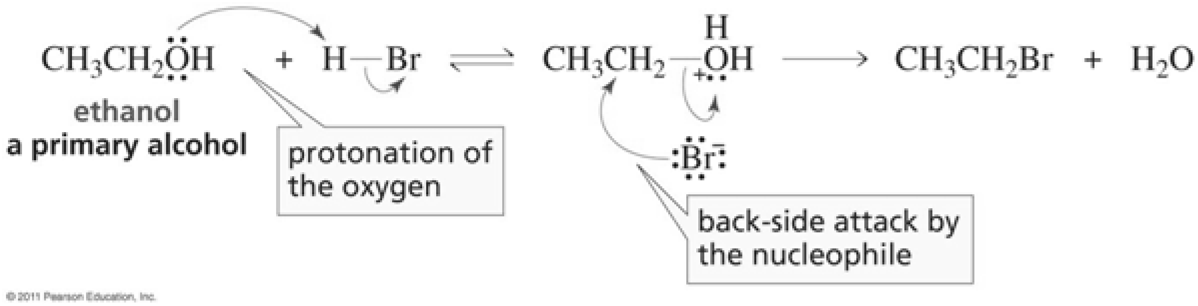
Primary alcohols undergo S_N2 reactions with hydrogen halides:



Reaction carried out in 48% aqueous HBr. Recall that Br^- is an excellent nucleophile in water.

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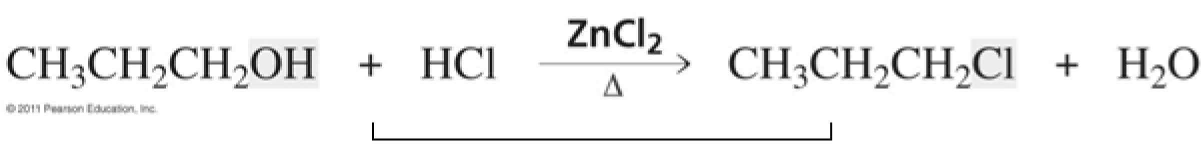
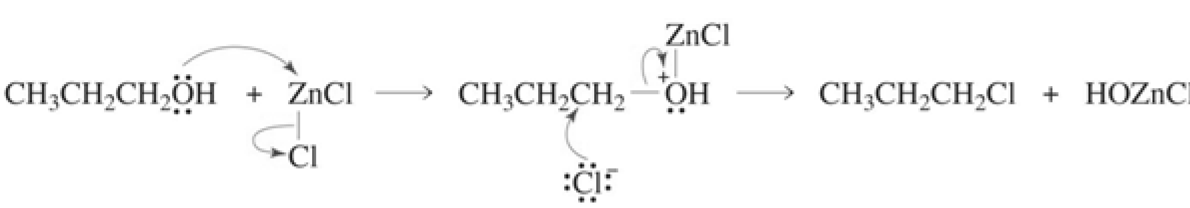
$ZnCl_2$ can be used to catalyze certain S_N2 reactions:



$ZnCl_2$ functions as a Lewis acid that complexes strongly with the lone-pair electrons on oxygen:



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The Lucas Reagent

Anhydrous $ZnCl_2$ in conc HCl

Distinguishes primary, secondary, and tertiary low-molecular-weight alcohols

The Lucas reaction:

$$ROH + HCl \xrightarrow{ZnCl_2} RCl$$

Positive test: Solution becomes cloudy

Test results and mechanisms at room temperature:

- **Primary: No reaction** S_N2
- **Secondary: Reaction in ~5 minutes** S_N2 and S_N1
- **Tertiary, allylic, and benzylic: Reaction immediate** S_N1

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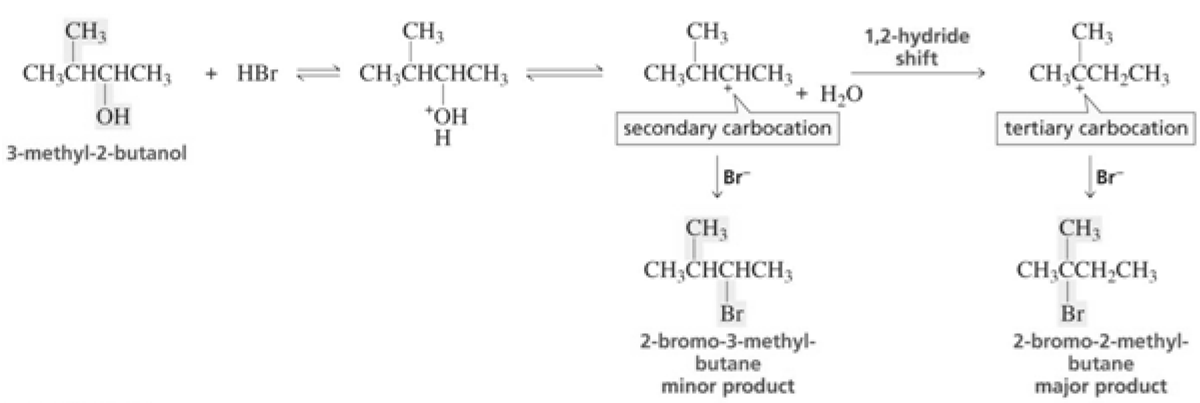
Look out for rearrangement product in the S_N1 reaction of the secondary or tertiary alcohol:



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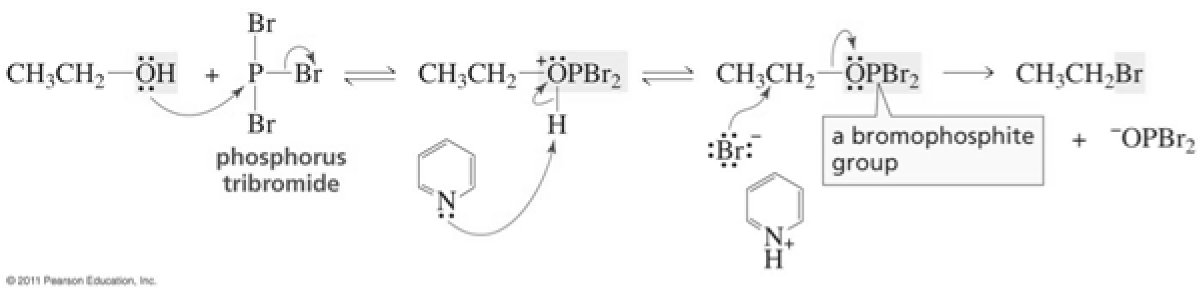
Other Methods for Converting Alcohols into Alkyl Halides

Utilization of phosphorus tribromide:



Other phosphorus reagents can be used:

PBr_3, phosphorus tribromide
PCl_3, phosphorus trichloride
PCl_5, phosphorus pentachloride
$POCl_3$, phosphorus oxychloride

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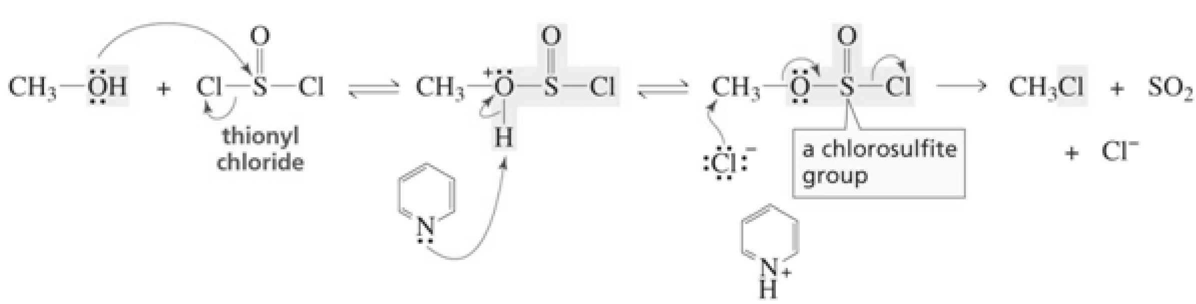
Activation by $SOCl_2$



Pyridine is generally used as a solvent and also acts as a base:

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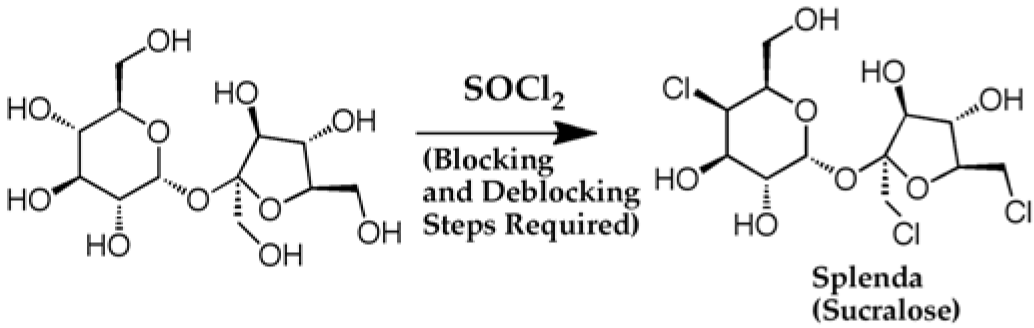
The Artificial Sweetener Splenda (Sucralose)



Could Splenda be a cellular alkylating agent?

No, it is too polar to enter a cell.

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Table 10.1 Commonly Used Methods for Converting Alcohols into Alkyl Halides

ROH	+	HBr	$\xrightarrow{\Delta}$	RBr
ROH	+	HI	$\xrightarrow{\Delta}$	RI
ROH	+	HCl	$\xrightarrow[\Delta]{ZnCl_2}$	RCl
ROH	+	PBr_3	$\xrightarrow[\text{pyridine}]{}$	RBr
ROH	+	PCl_3	$\xrightarrow[\text{pyridine}]{}$	RCl
ROH	+	$SOCl_2$	$\xrightarrow[\text{pyridine}]{}$	RCl

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Summary: Converting of Alcohols to Alkyl Halides

Recommended procedures:

Alcohol	Chloride	Bromide	Iodide
Primary	Thionyl Chloride, PCl_3 , PCl_5, $POCl_3$	PBr_3 , PBr_5, HBr	P / I_2
Secondary	Thionyl Chloride, PCl_3 , PCl_5 , $POCl_3$	PBr_3 , PBr_5,	P / I_2
Tertiary	HCl	HBr	HI

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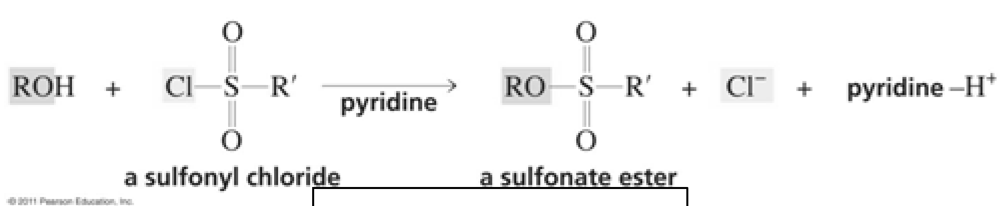
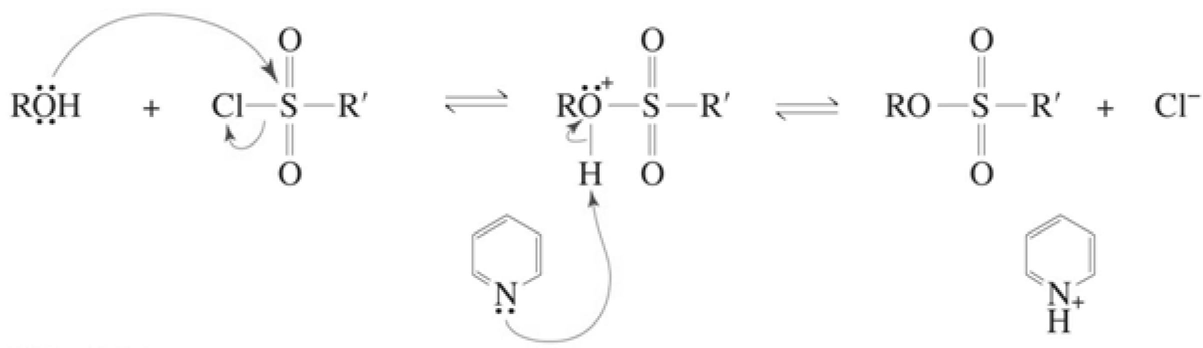
Converting Alcohols into Sulfonate Esters





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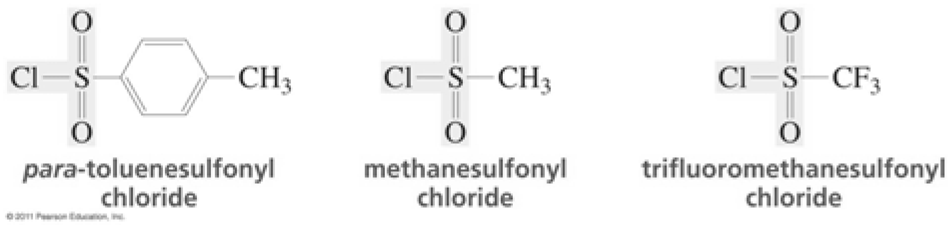
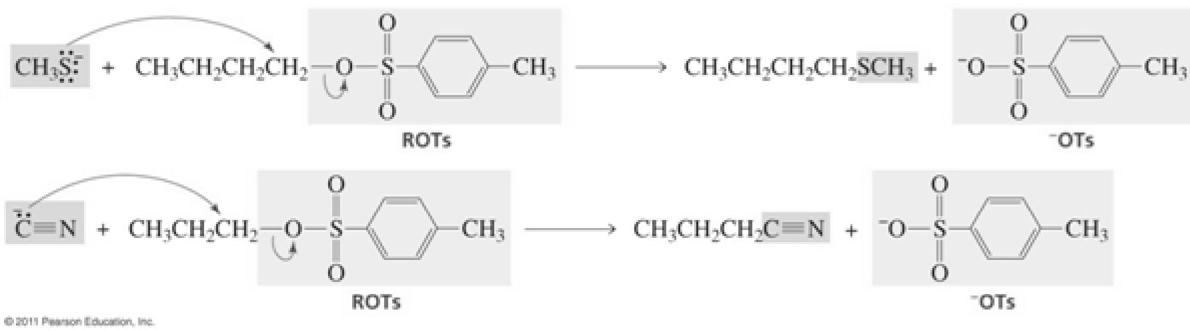
Several sulfonyl chlorides are available to activate OH groups:





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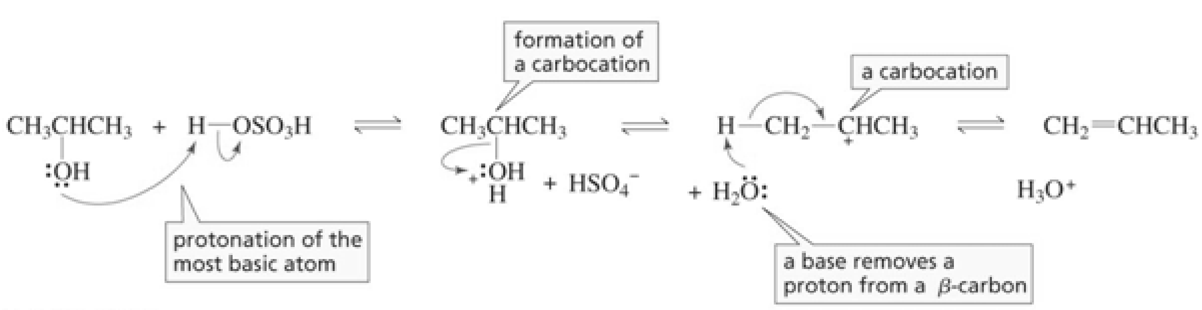
Dehydration of Secondary and Tertiary Alcohols by an E1 Pathway



To prevent the rehydration of the alkene product, one needs to remove the product as it is formed

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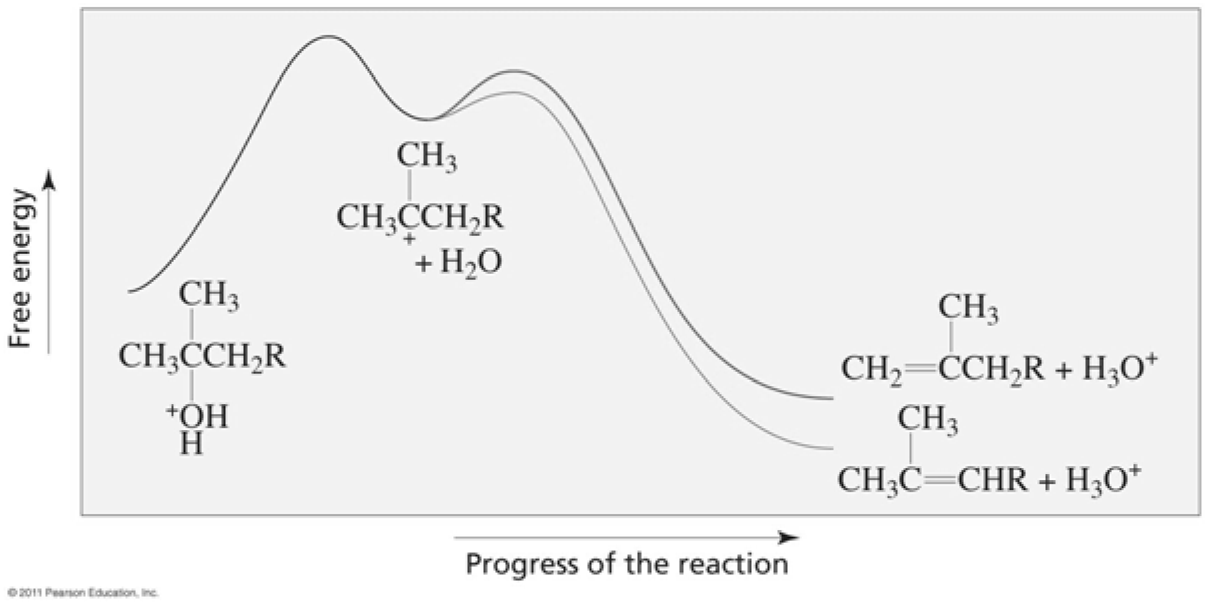
The major product is the most stable alkene product:



The most stable alkene product has the most stable transition state

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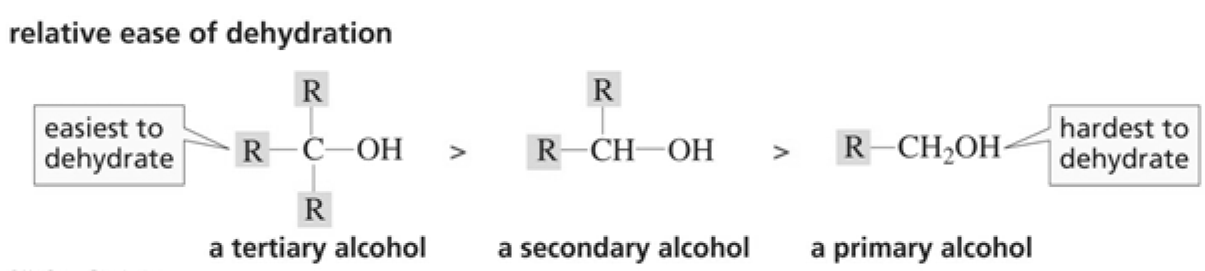
The rate of dehydration reflects the ease with which the carbocation is formed:



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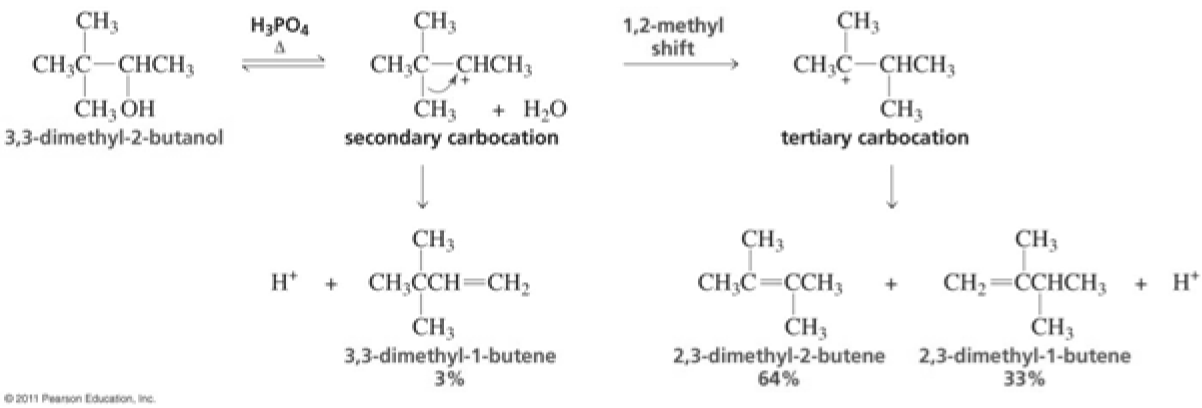
Look out for carbocation rearrangement:



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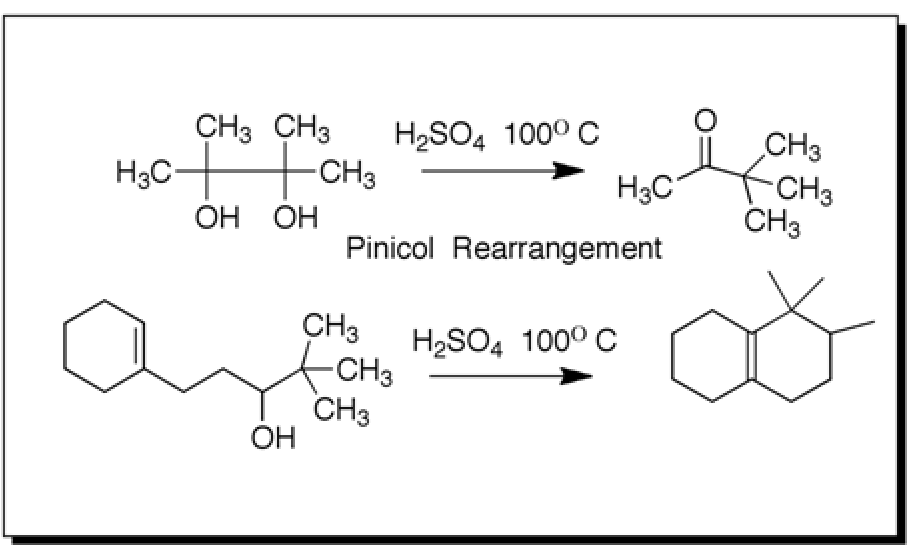
Complex Alcohol Rearrangements in Strong Acid



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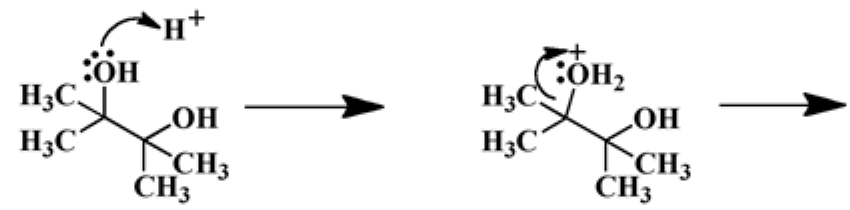
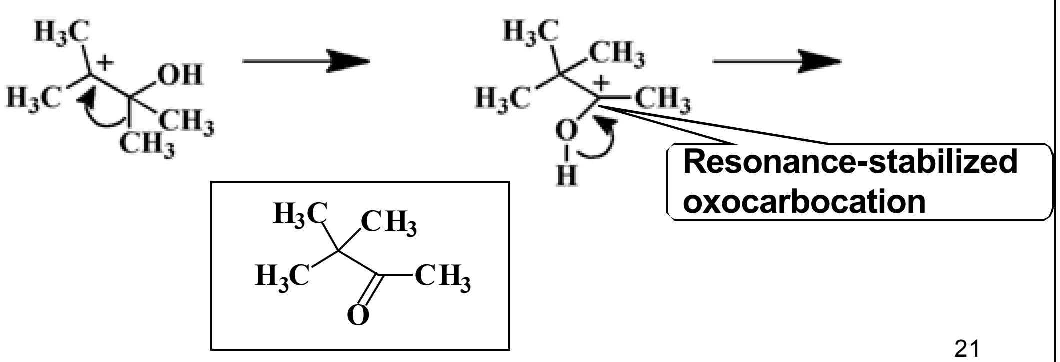
Pinicol Rearrangement

Protonate alcohol: **Eliminate water:**



Rearrange carbocation: **Deprotonate:**



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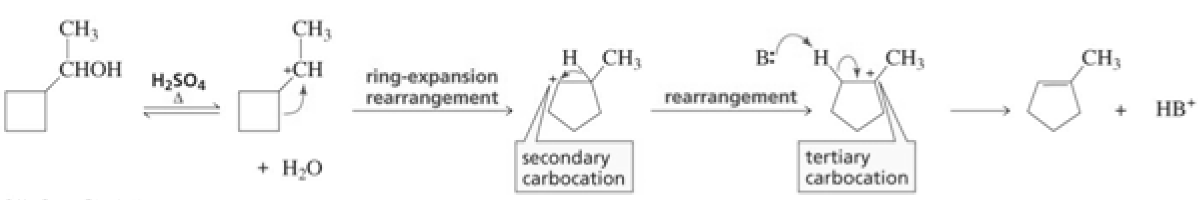
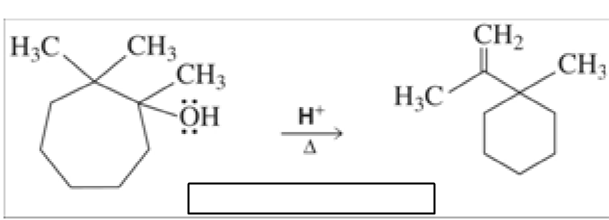
Ring Expansion and Contraction





Show the mechanism for this reaction:
- **Protonate the alcohol.**
- **Eliminate water.**
- **Rearrange carbocation to afford the more stable cyclohexane ring.**
- **Deprotonate.**

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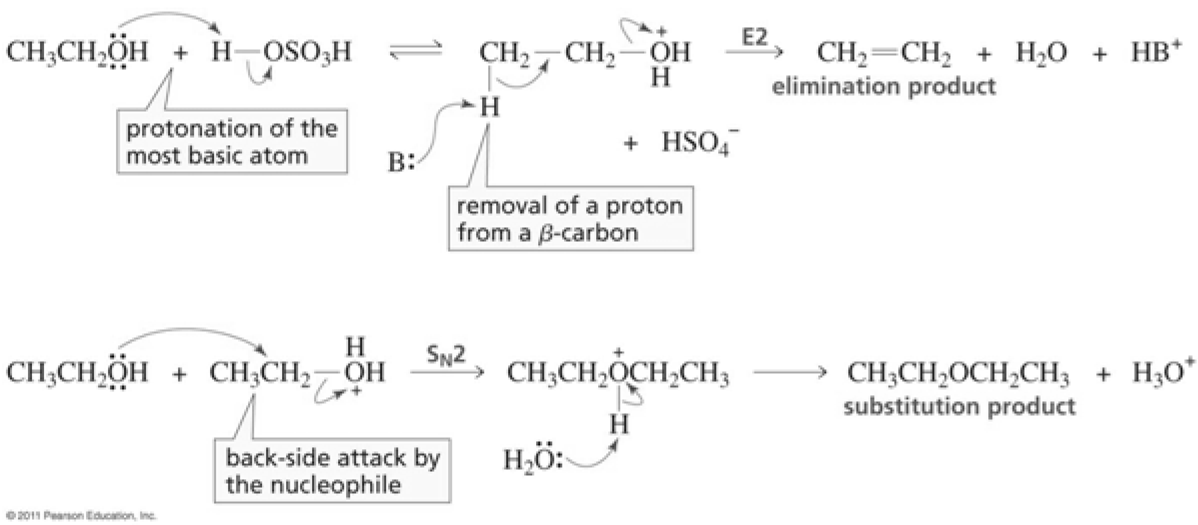
Primary Alcohols Undergo Dehydration by an E2 Pathway



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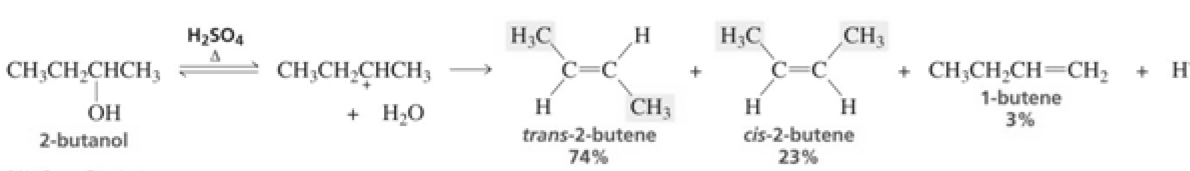
The Stereochemical Outcome of the E1 Dehydration



Alcohols and ethers undergo S_N1/E1 reactions unless they would have to form a primary carbocation

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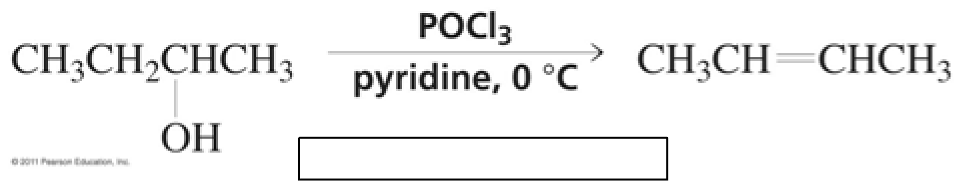
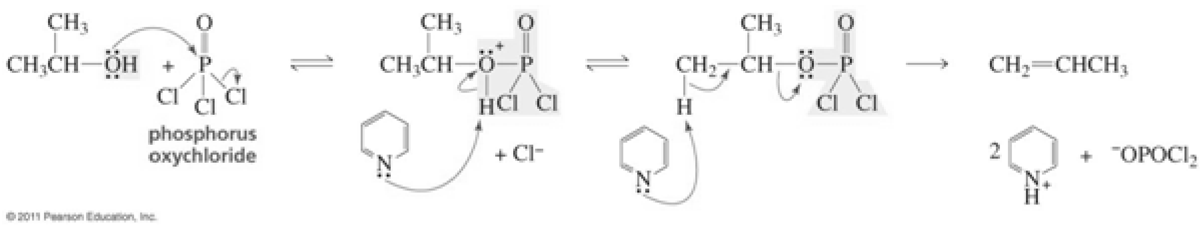
A Milder Way to Dehydrate an Alcohol





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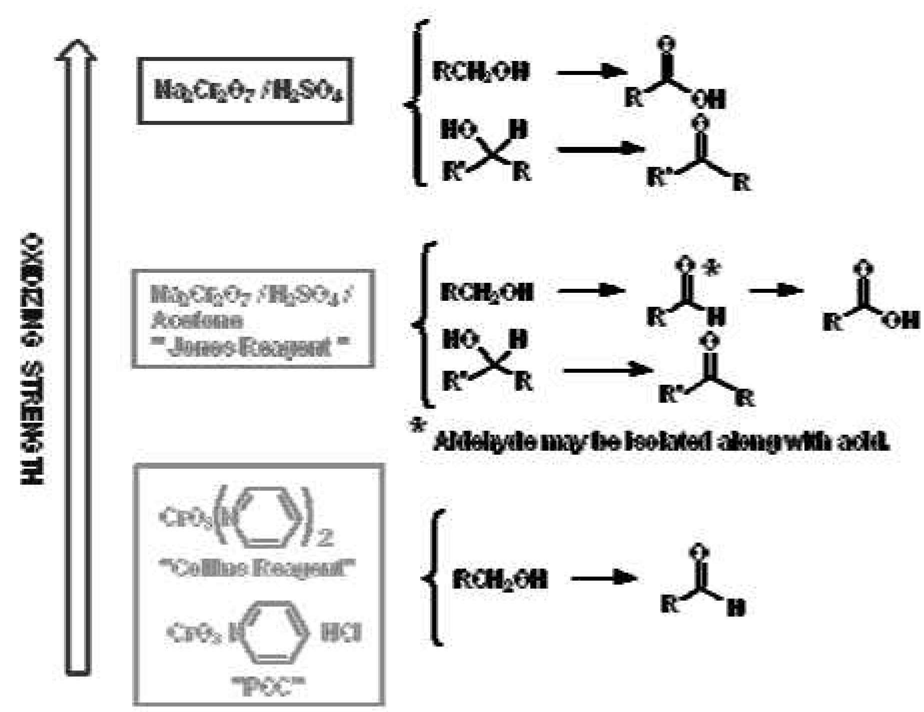
Oxidation by Chromium (VI)



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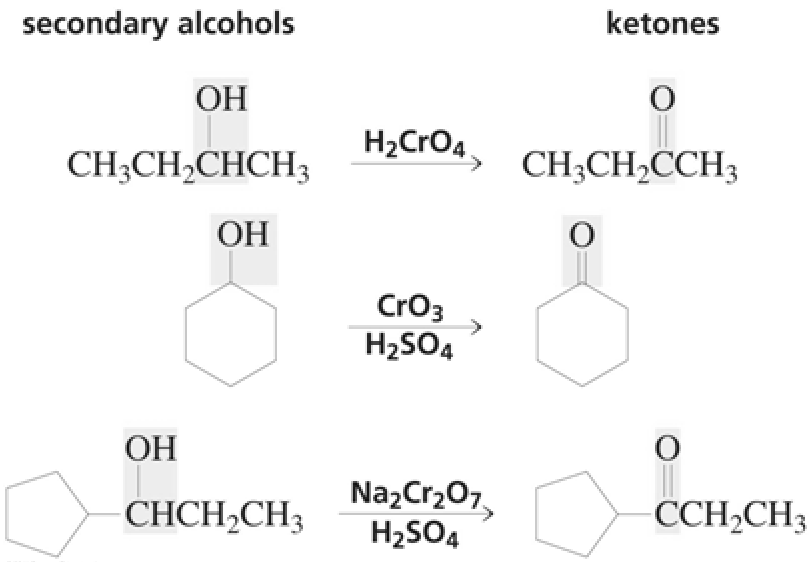
Oxidation of Alcohols

Oxidation by chromic acid:



Secondary alcohols are oxidized to ketones

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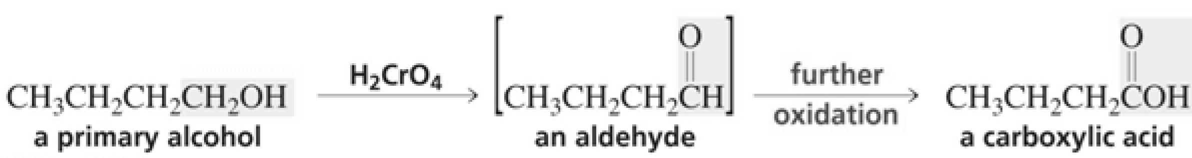
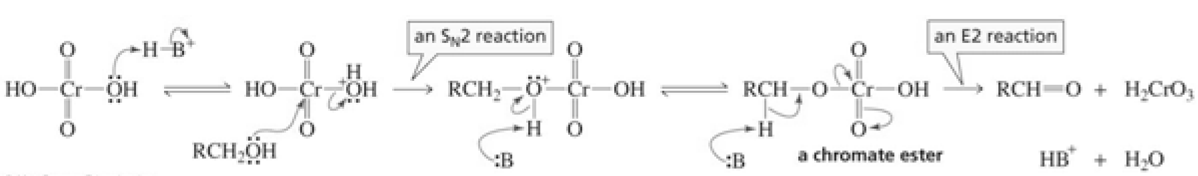
Primary alcohols are oxidized to aldehydes and eventually carboxylic acids:



Mechanism:



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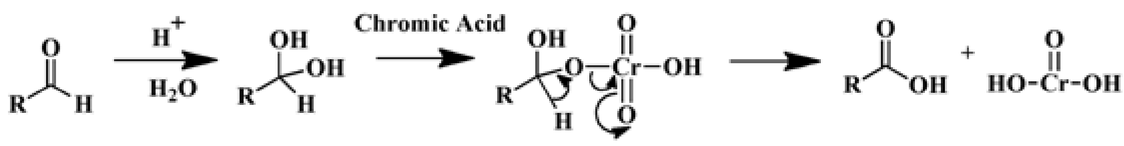
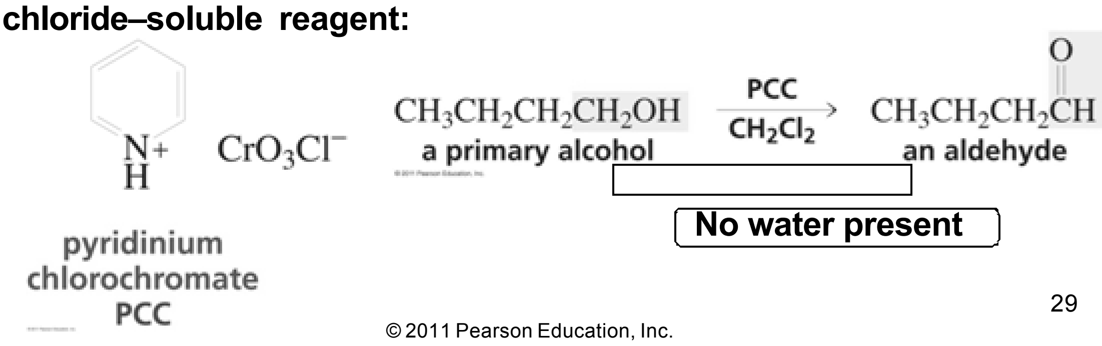
The oxidation of aldehydes to acids requires the presence of water:



In the absence of water, the oxidation stops at the aldehyde:

PCC, a methylene chloride–soluble reagent:



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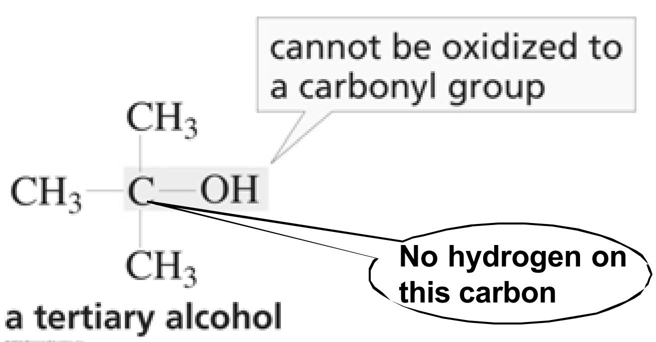
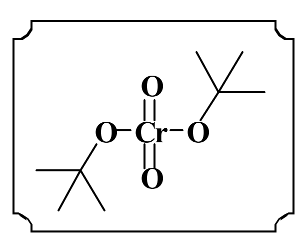
A tertiary alcohol cannot be oxidized and is converted to a stable chromate ester instead:





Di-*tert*-Butyl Chromate

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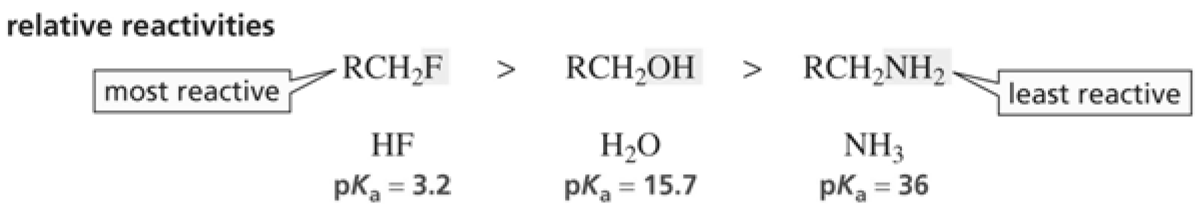
Amines do not undergo substitution reactions because NH_2^- is a very strong base (a very poor leaving group):



Protonation of the amine moiety does not solve the problem:

$$CH_3CH_2\overset{+}{N}H_3 \quad + \quad HO^- \rightleftharpoons CH_3CH_2NH_2 \quad + \quad H_2O$$

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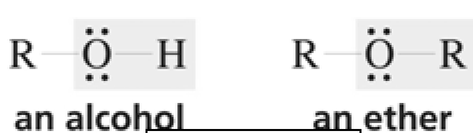
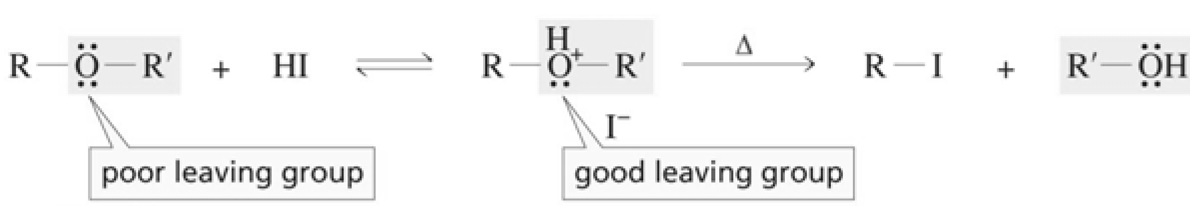
Nucleophilic Substitution Reactions of Ethers



Ethers, like alcohols, can be activated by protonation:



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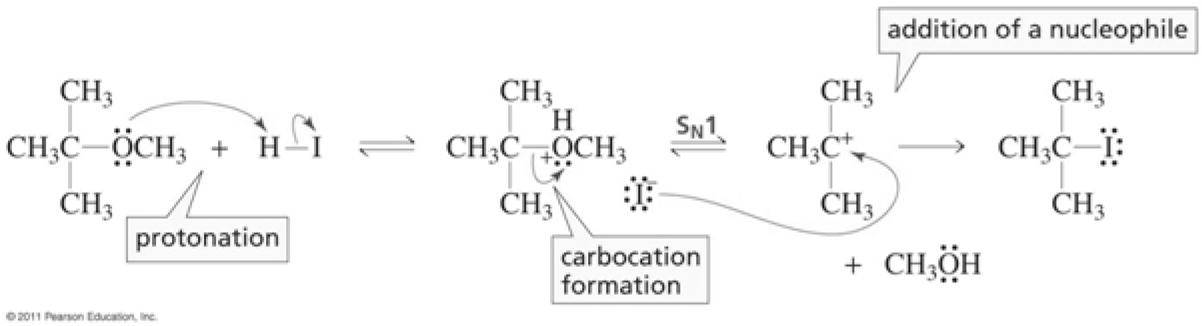
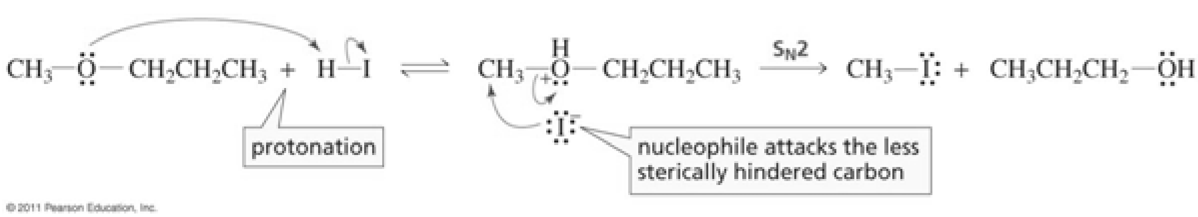
Ether cleavage: an S_N1 reaction:



Ether cleavage: an S_N2 reaction:



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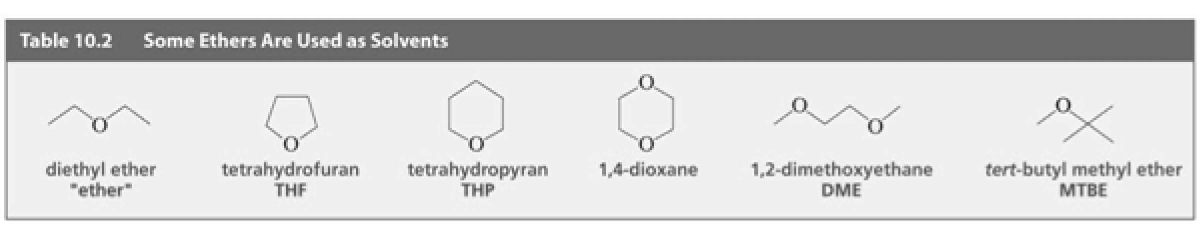
Reagents such as $SOCl_2$ and PCl_3 can activate alcohols but not ethers

Ethers are frequently used as solvents because only they react with hydrogen halides



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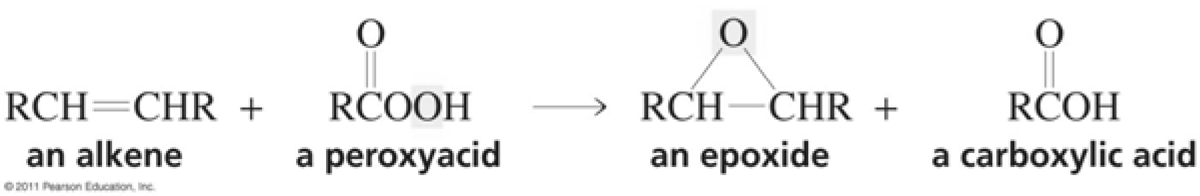
Nucleophilic Substitution Reactions of Epoxides

Recall Section 4.9



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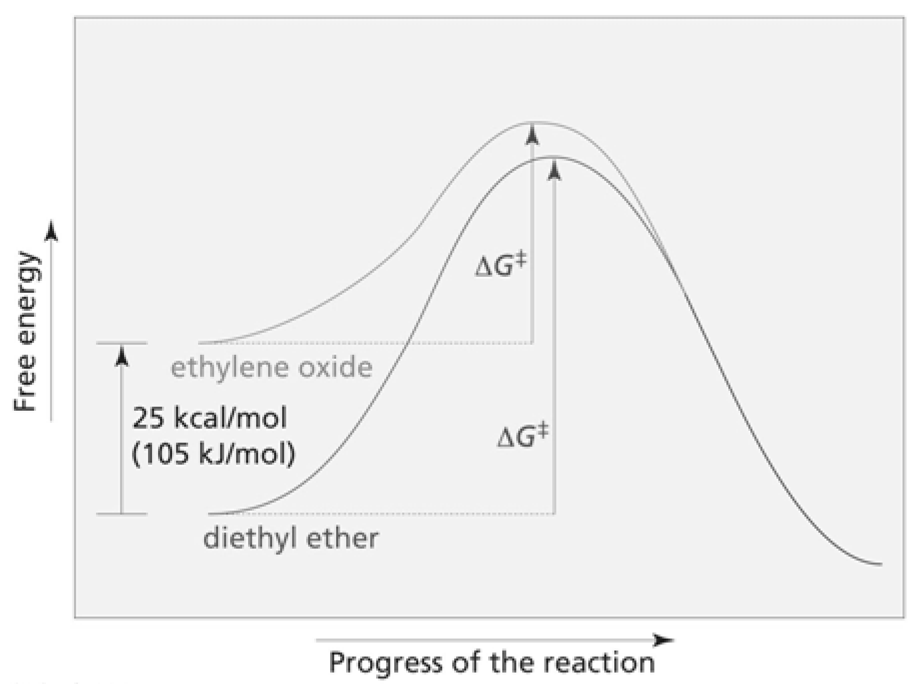
Epoxides are more reactive than ethers in nucleophilic substitution reactions because of ring strain:



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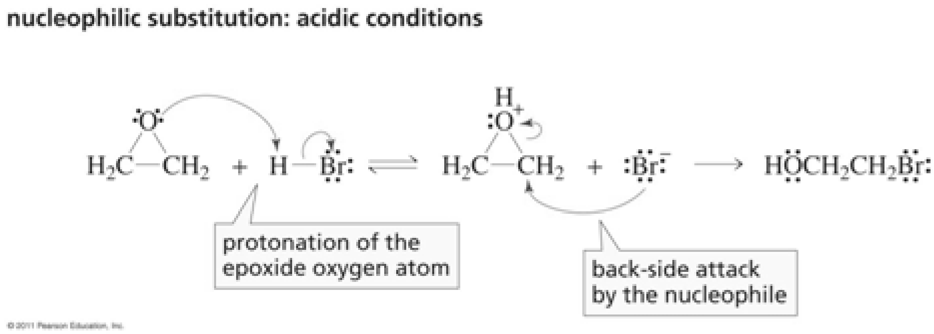
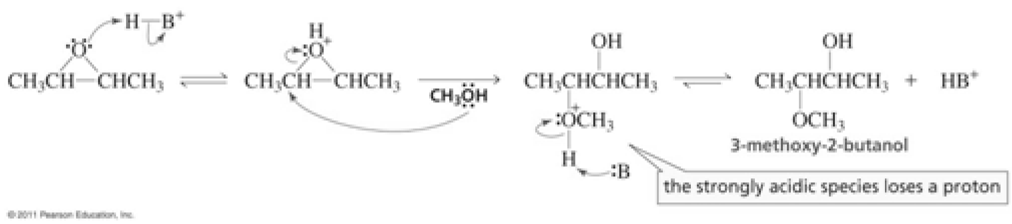
Acid-Catalyzed Epoxide Ring Opening

HBr:



Aqueous acid:



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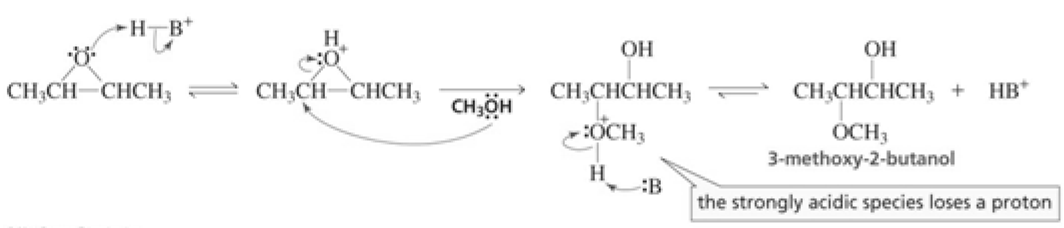
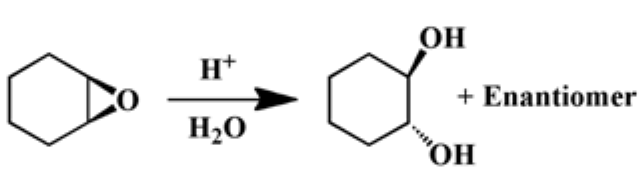
Acidic methanol:

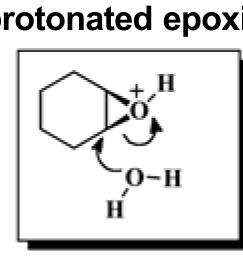


Stereospecificity of epoxide ring opening:

Reason: Back-side attack of water on protonated epoxide:



A trans diol



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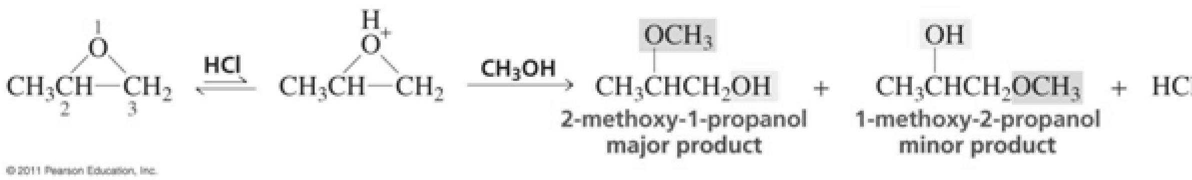
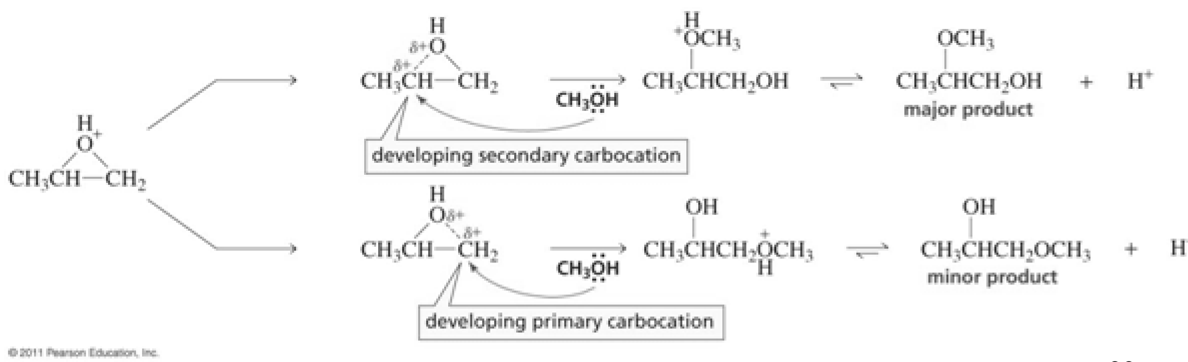
Reaction of an epoxide in the presence of methanol and acid

Regioselectivity:



Mechanism:



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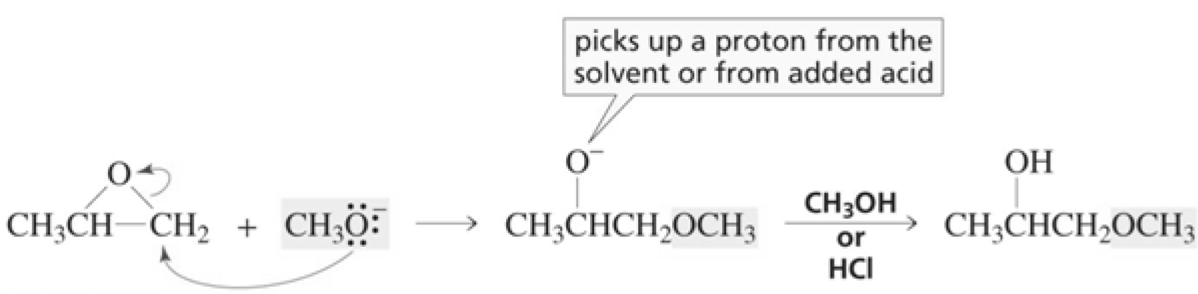
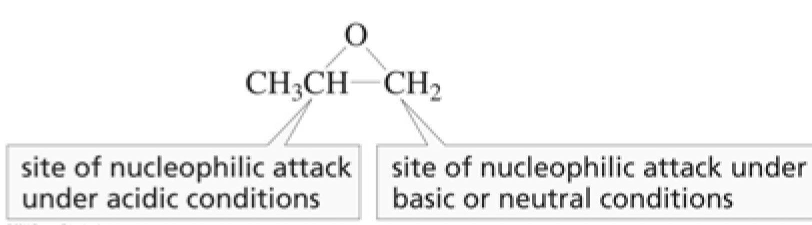
When a nucleophile attacks an unprotonated epoxide, the reaction is a pure S_N2 reaction:



Therefore:



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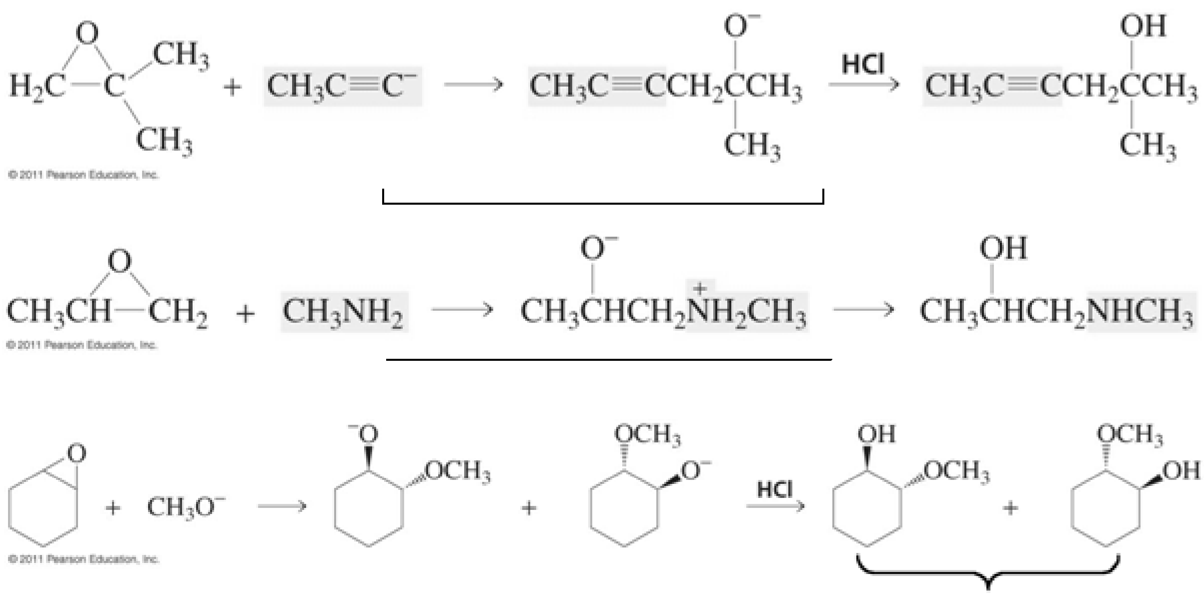
Epoxides Are Synthetically Useful Reagents



Enantiomers

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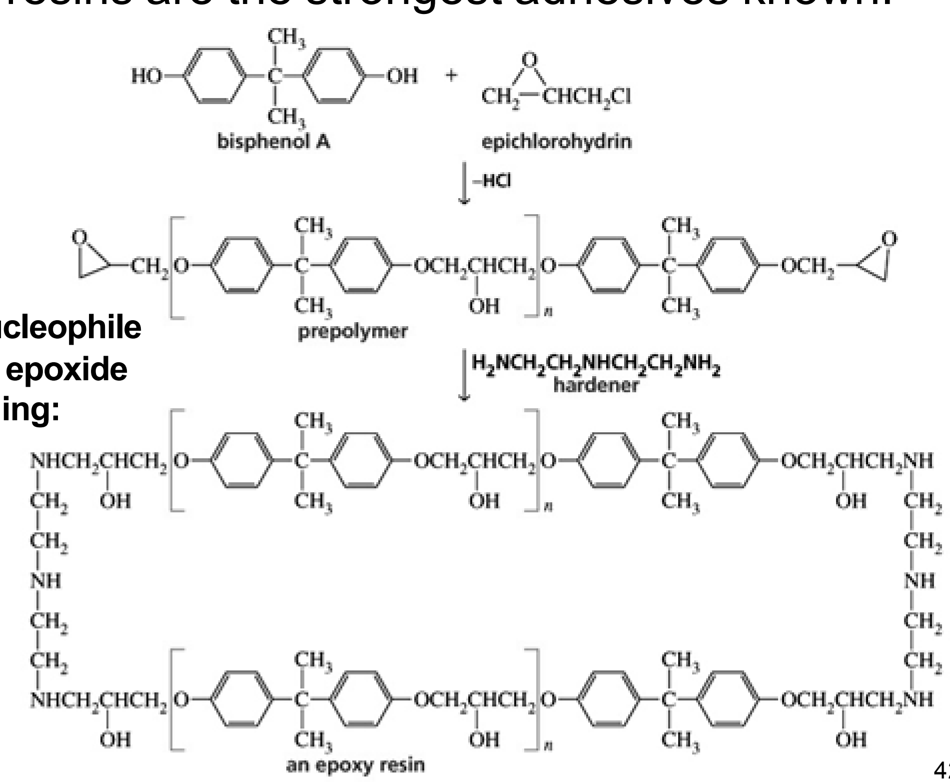
Epoxy resins are the strongest adhesives known:

Amine nucleophile mediated epoxide ring opening:



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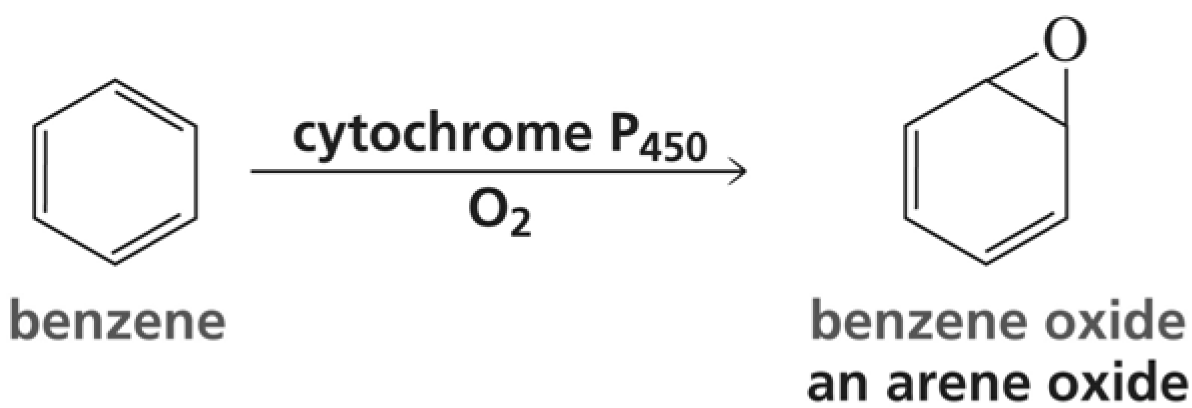
Arene Oxides



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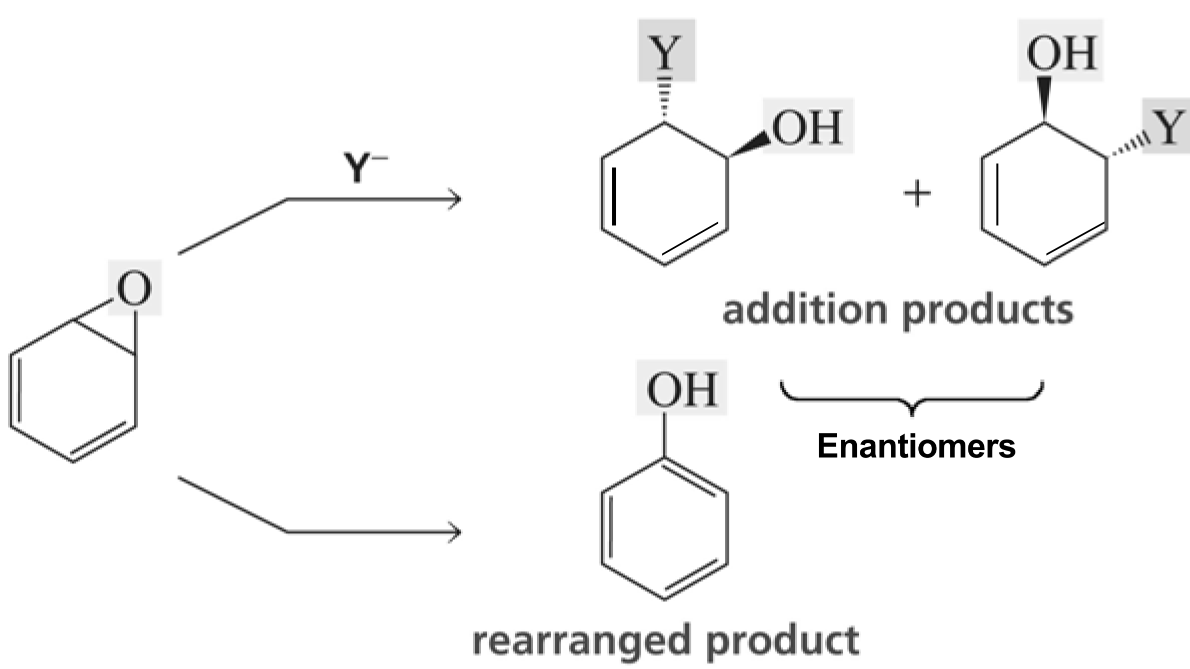
Arene oxide fate:



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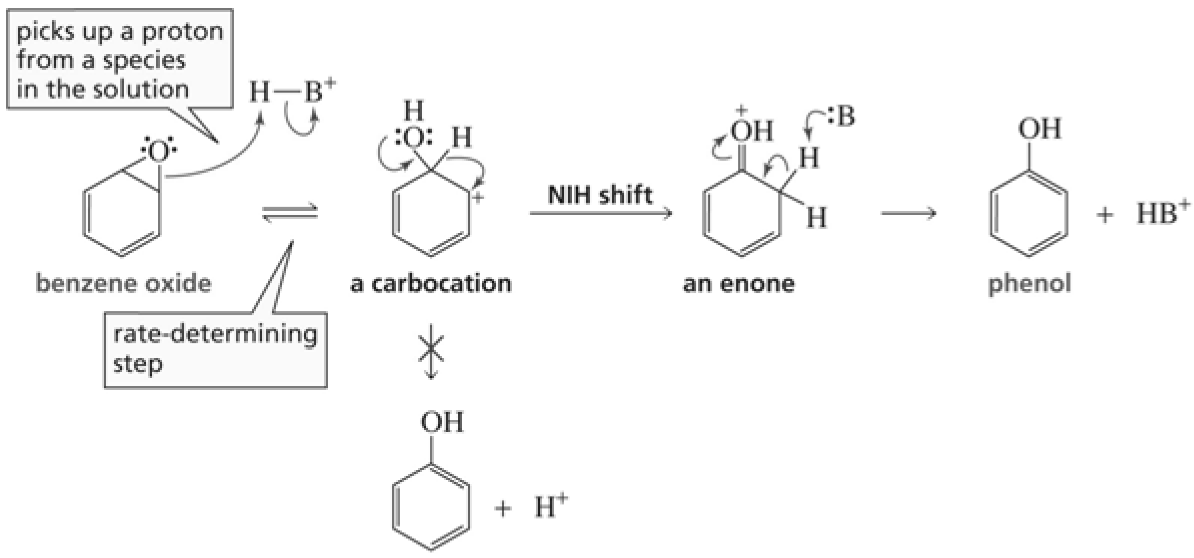
Mechanism for arene oxide rearrangement:



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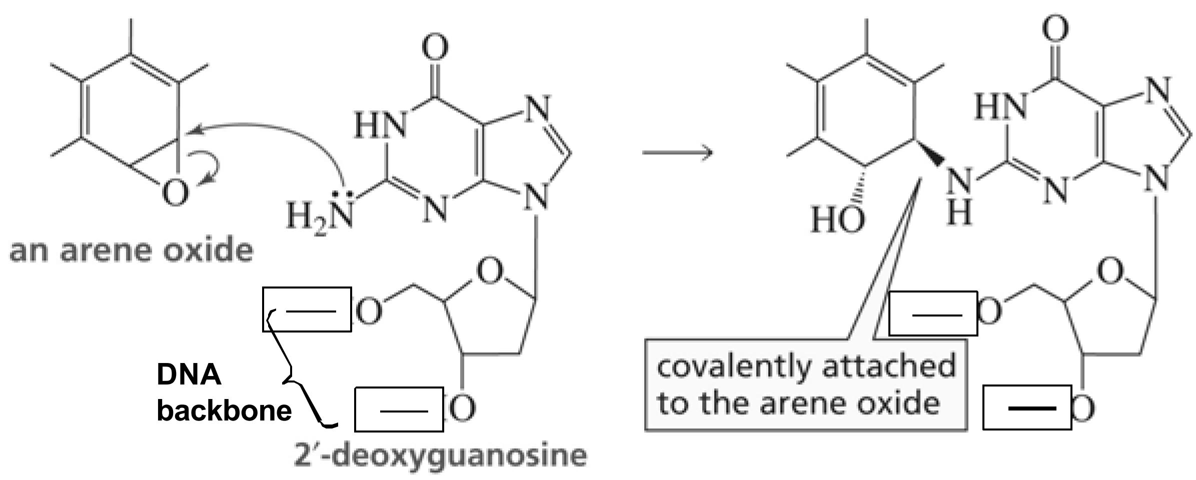
Arene oxides as a carcinogen:



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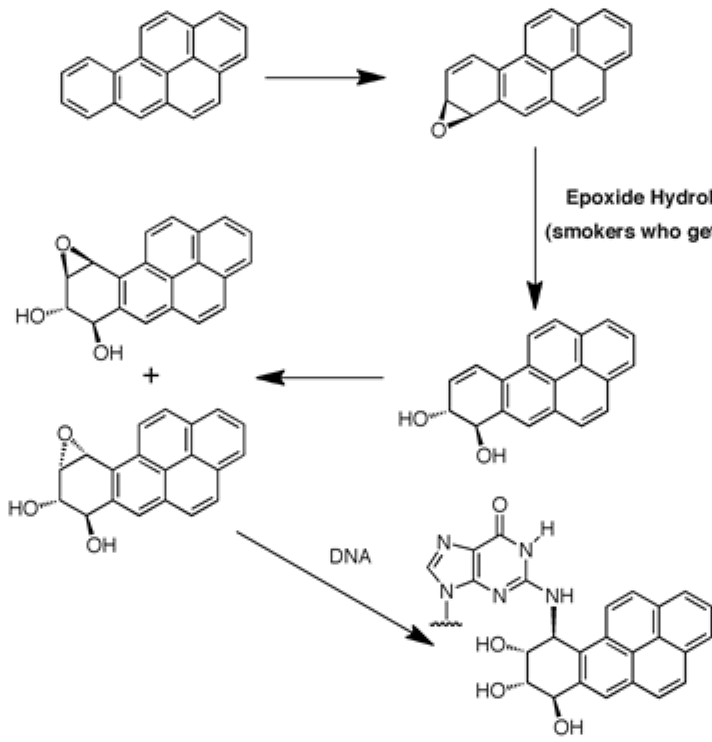
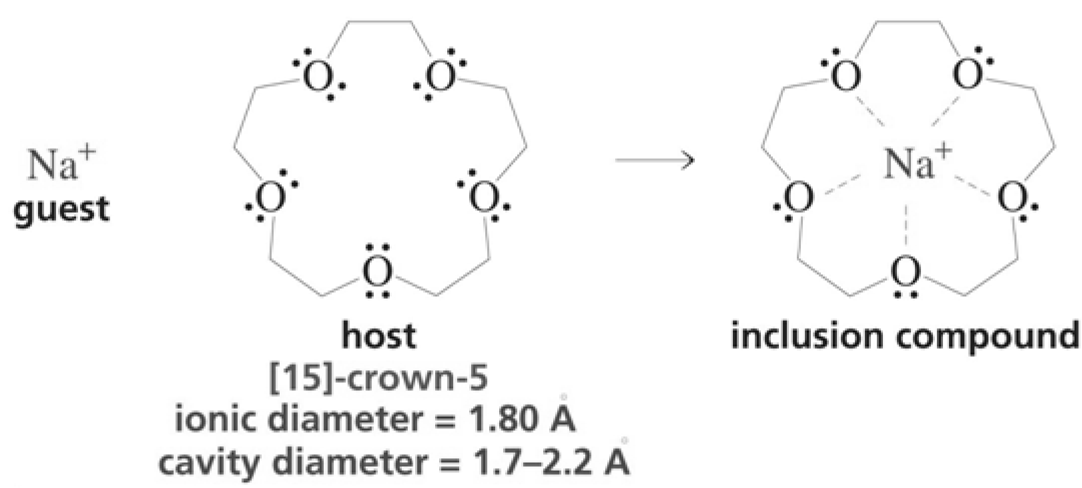
BENZO[a]PYRENE EPOXIDATION



Not all smokers get cancer

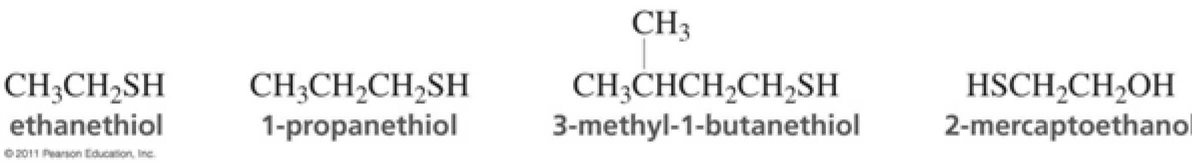
Benzopyrenes in chimneys were responsible for cancer of the scrotum in "chimney-boys." The connection between cancer and chimney soot was made by Percivall Pott in 1775.

Crown Ethers



The ability of a host to bond only certain guests is an example of molecular recognition

Thiols are sulfur analogs of alcohols:



Thiols form strong complexes with heavy metal cations

Thiols are stronger acids (pK_a = 10) than alcohols

Thiols are not good at hydrogen bonding

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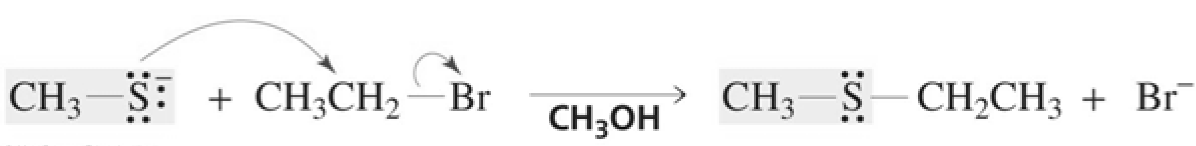
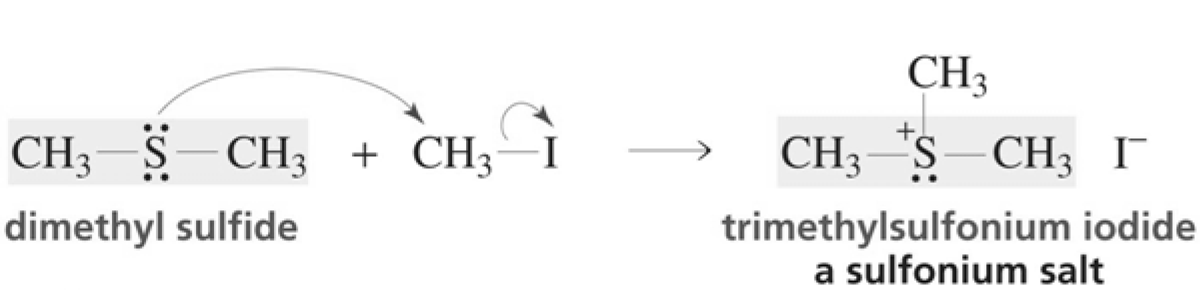
In protic solvent, thiolate ions are better nucleophiles than alkoxide ions:





Sulfur is an excellent nucleophile because its electron cloud is polarized

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