Organic Chemistry, *Fifth Edition*

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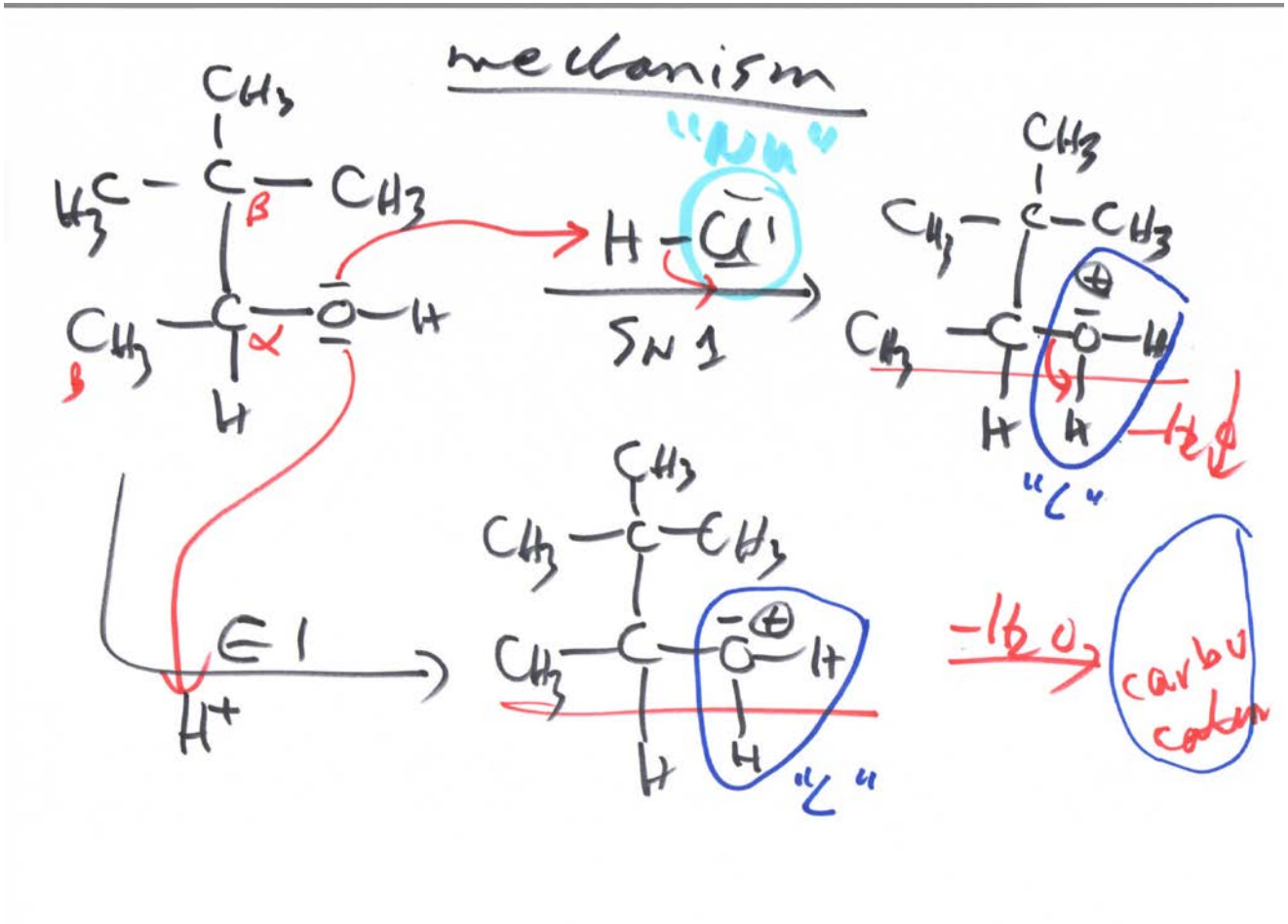
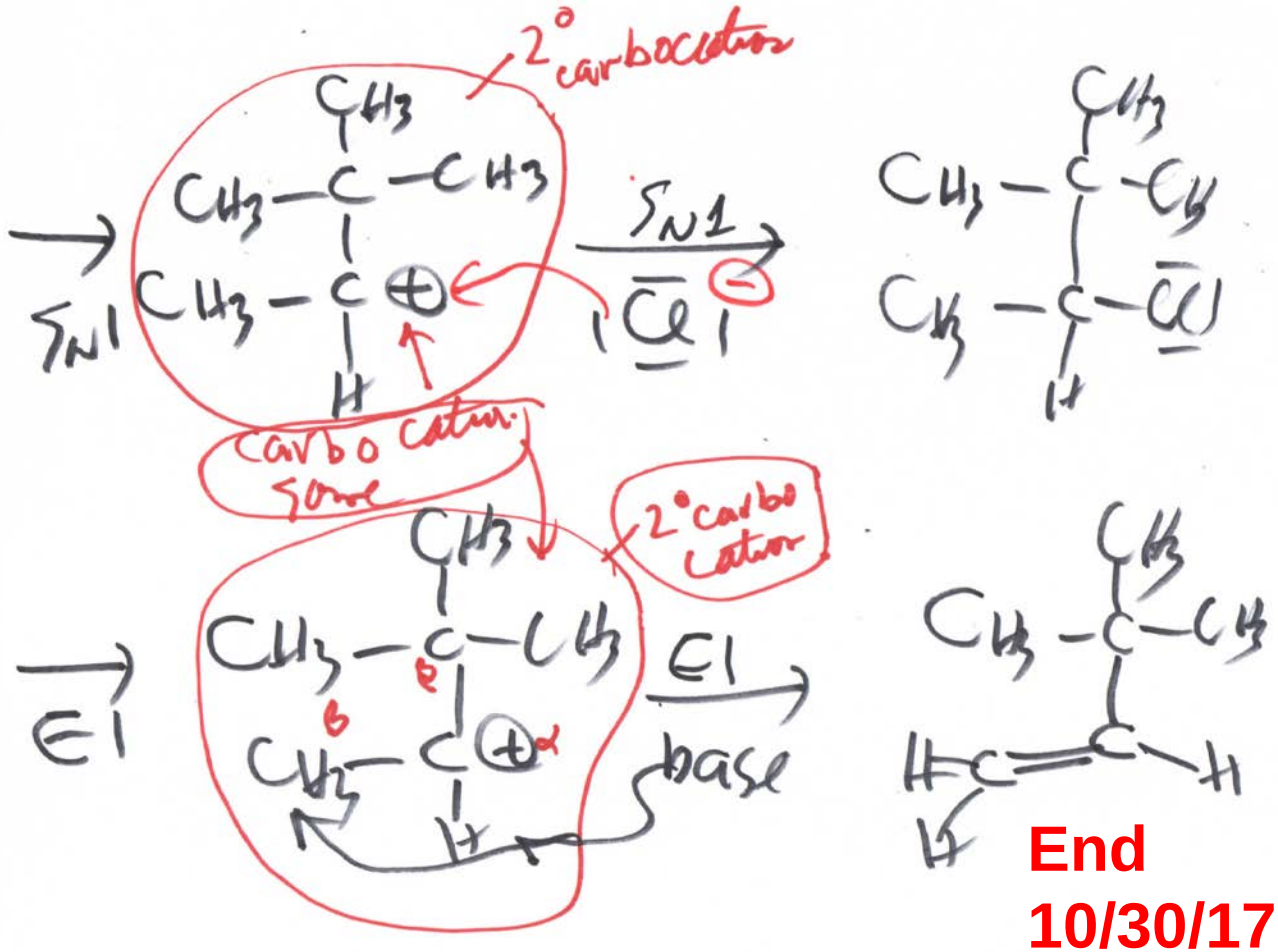
Chapter 9
Alcohol, Ethers, Epoxides

Modified by Dr. Juliet Hahn


mechanism
SN 1
E1
carbocation



End
10/30/17
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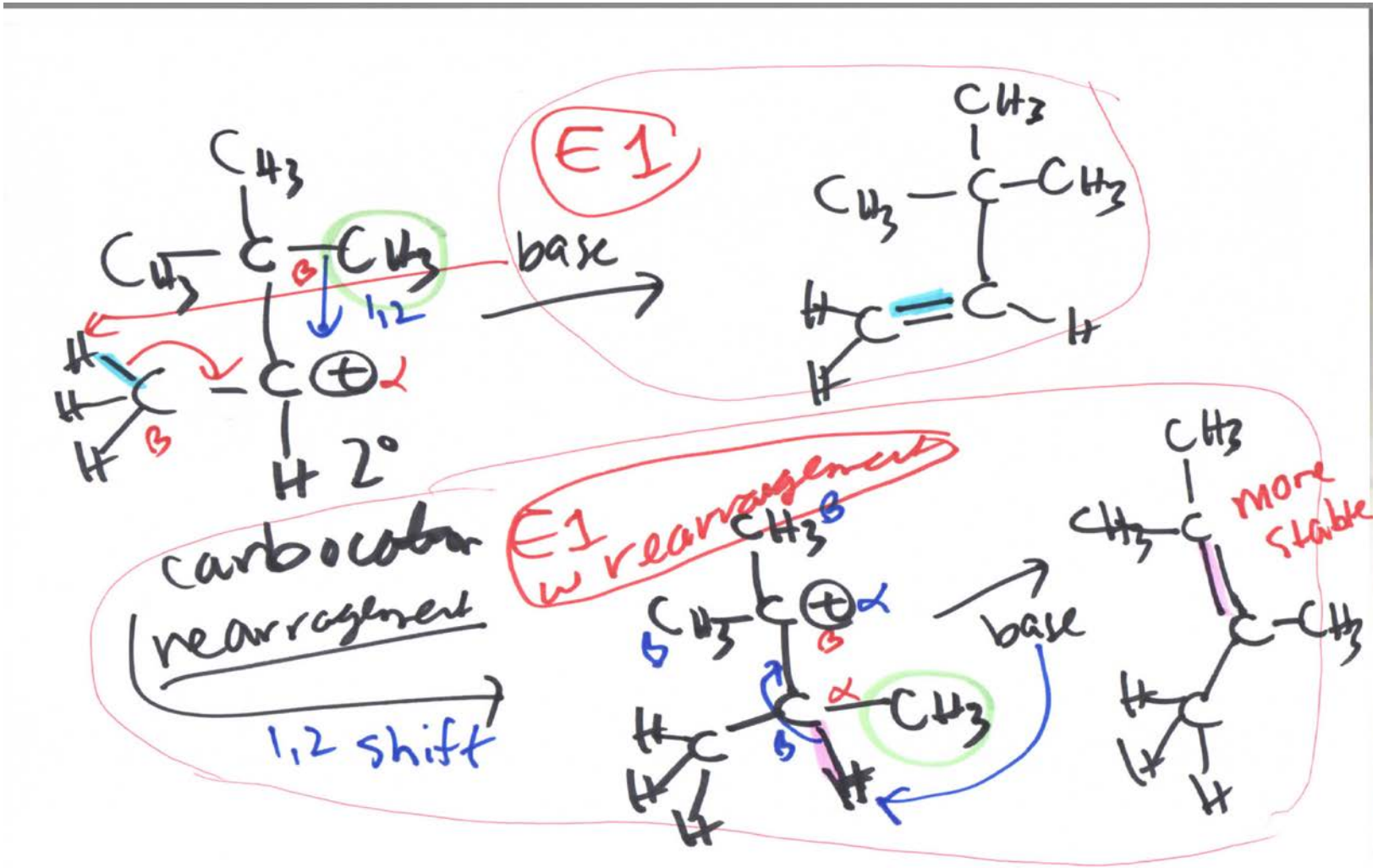
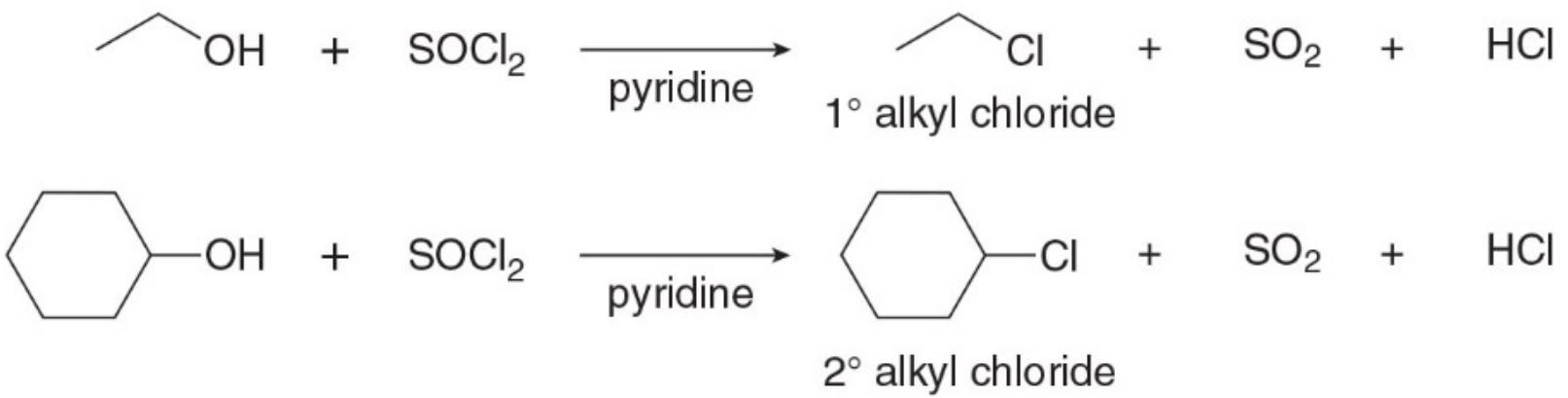

E1
base
1,2
2°
carbocation
rearrangement
1,2 shift
E1
w rearrangement
base
more
stable

(3) Conversion of alcohols to akyl halides with $SOCl_2$ and PBr_3

- **Primary and 2° alcohols can be converted to alkyl halides using $SOCl_2$ and PBr_3. Alcohols to Alkyl Halides with $SOCl_2$**
- **$SOCl_2$ (thionyl chloride) converts alcohols into alkyl chlorides.**
- **PBr_3 (phosphorus tribromide) converts alcohols into alkyl bromides.**

Conversion of Alcohols to Alkyl Chlorides with $SOCl_2$

- **When a 1° or 2° alcohol is treated with $SOCl_2$ and pyridine, an alkyl chloride is formed, with HCl and SO_2 as by-products.**



Conversion of Alcohols to Alkyl Bromides with PBr_3

- **Treatment of a 1º or 2º alcohol with PBr_3 forms an alkyl halide.**

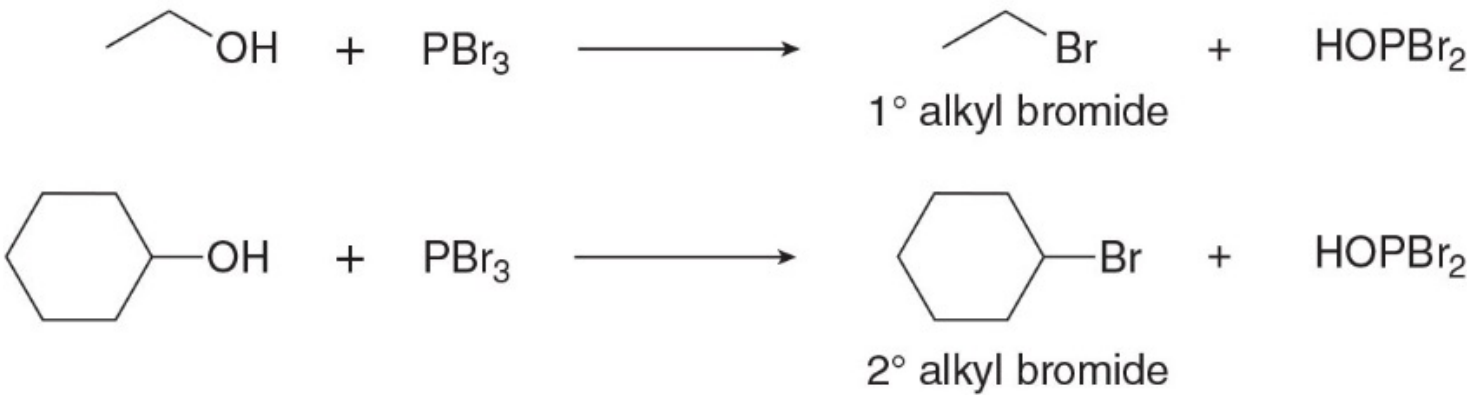
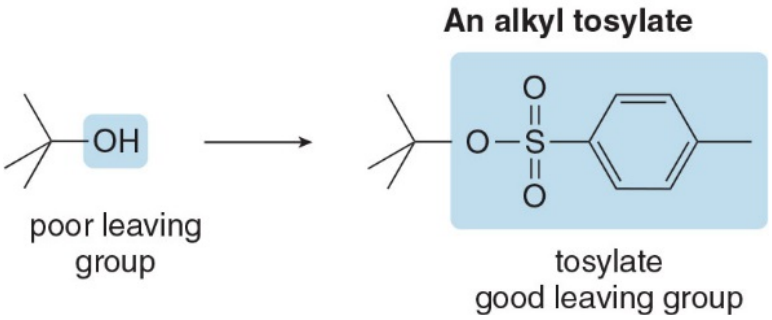


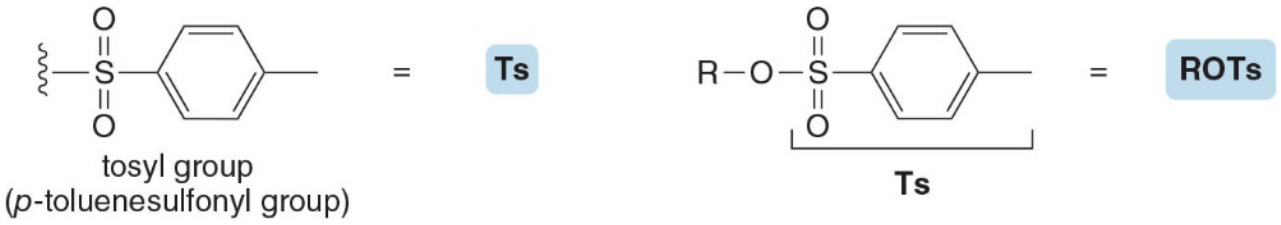
Table 9.2 Summary of Methods for ROH → RX

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

(4) Tosylate as Leaving Group

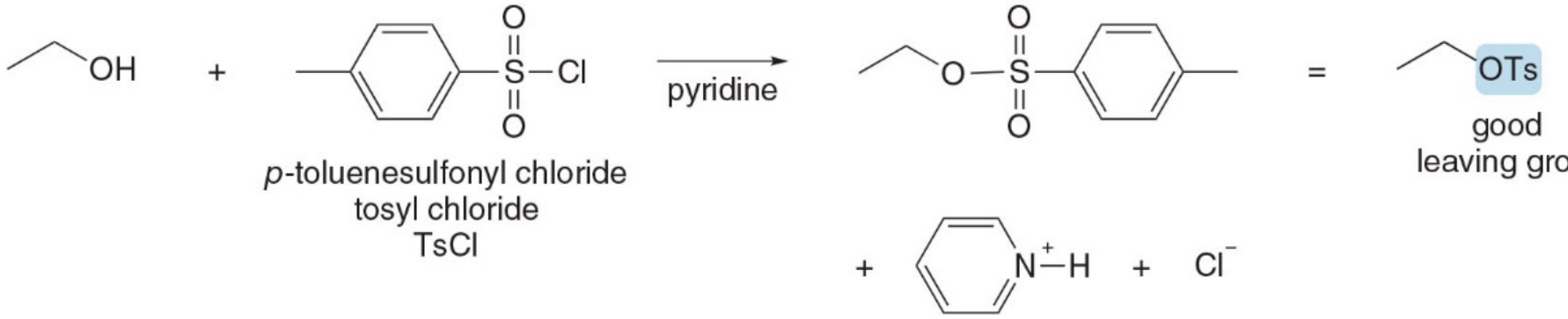
- **Alcohols can be converted into alkyl tosylates.**
- **An alkyl tosylate is composed of two parts: the alkyl group R, derived from an alcohol; and the tosylate (short for *p*-toluenesulfonate), which is a good leaving group.**
- **A tosyl group, $CH_3C_6H_4SO_2^-$, is abbreviated Ts, so an alkyl tosylate becomes ROTs.**





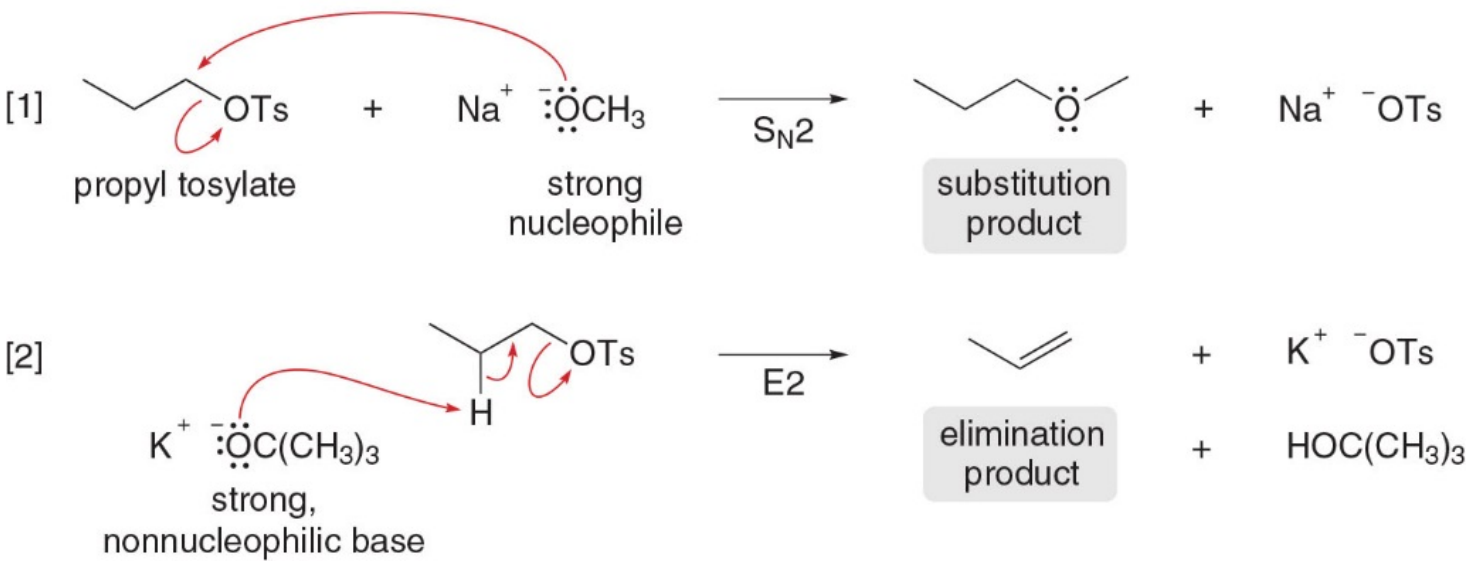
Formation and Use of Tosylates

- **Alcohols are converted to tosylates by treatment with *p*-toluenesulfonyl chloride (TsCl) in the presence of pyridine.**
- **This process converts a poor leaving group ($^-$OH) into a good one ($^-$OTs).**
- **Tosylate is a good leaving group because its conjugate acid, *p*-toluenesulfonic acid ($CH_3C_6H_4SO_3H$, TsOH) is a strong acid ($pK_a = -7$).**



Substitution and Elimination of Tosylates

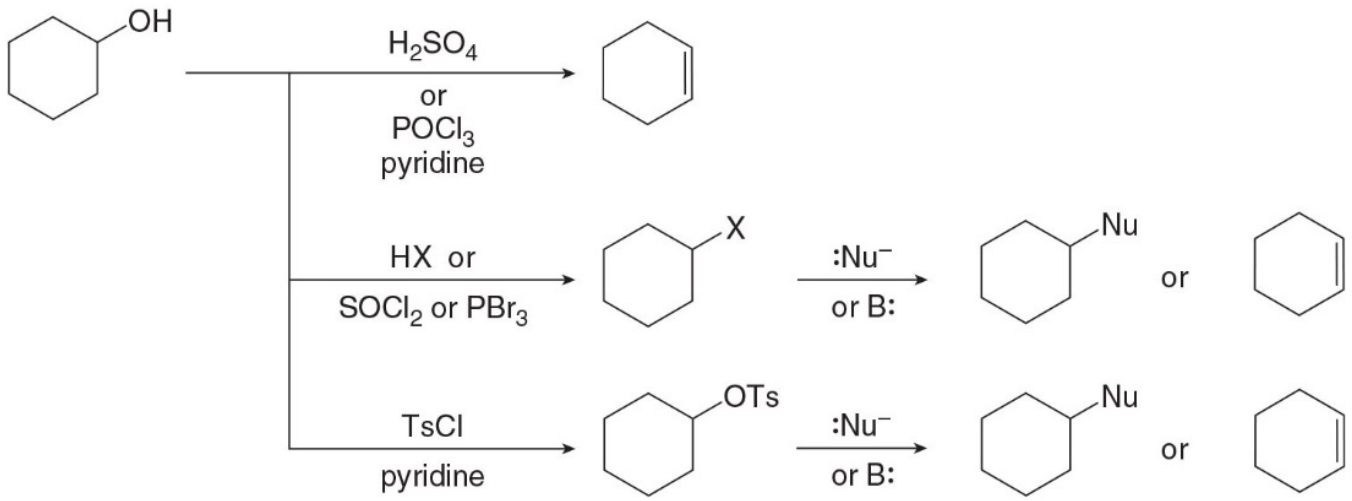
- **Because alkyl tosylates have good leaving groups, they undergo both nucleophilic substitution and β elimination, exactly as alkyl halides do.**
- **Generally, alkyl tosylates are treated with strong nucleophiles and bases, so the mechanism of substitution is S_N2, and the mechanism of elimination is E2.**



Summary of Substitution and Elimination Reactions of Alcohols

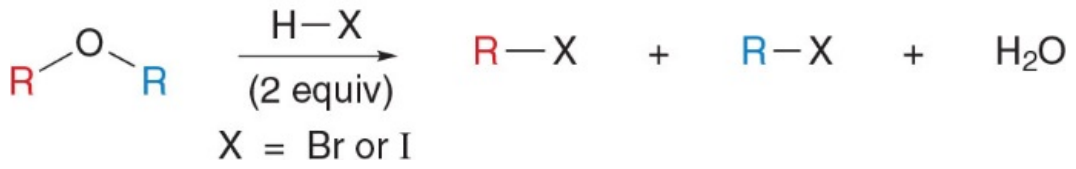
Figure 9.8

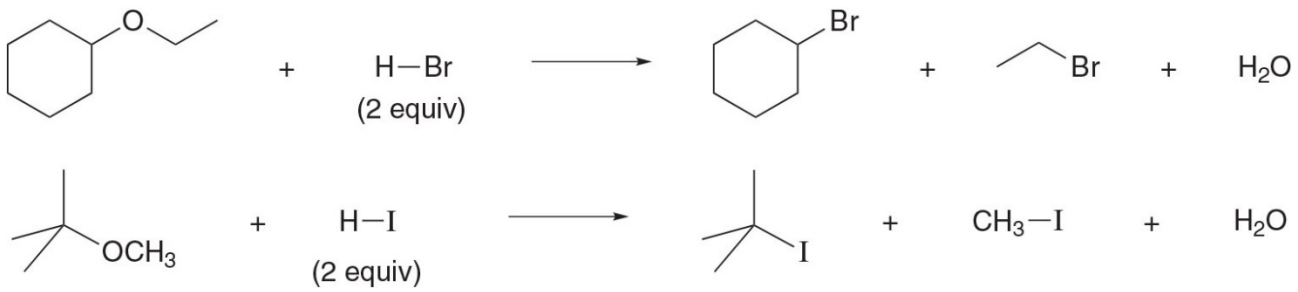
Summary: Nucleophilic substitution and β elimination reactions of alcohols



(4) Reaction of Ethers with Strong Acid

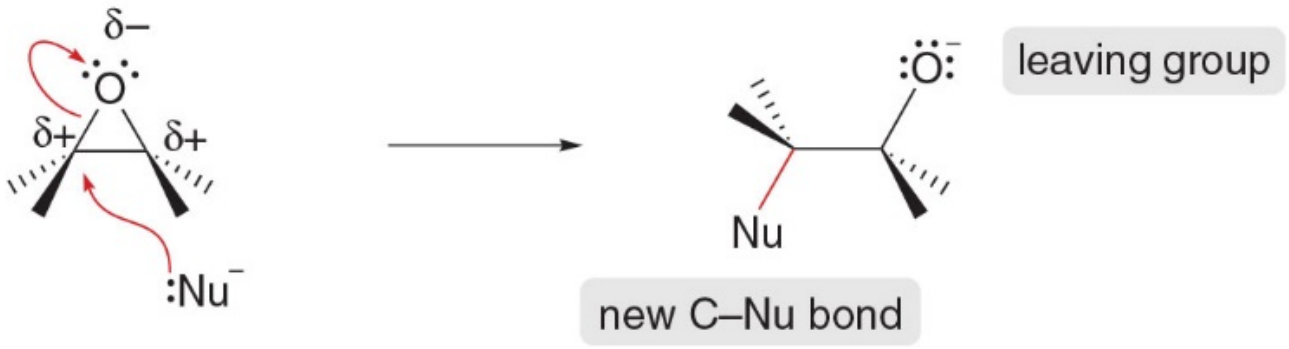
- **In order for ethers to undergo substitution or elimination reactions, their poor leaving group must first be converted into a good leaving group by reaction with strong acids such as HBr and HI.**
- **HBr and HI are strong acids that are also sources of good nucleophiles (Br^- and I^-, respectively).**
- **When ethers react with HBr or HI, both C-O bonds are cleaved and two alkyl halides are formed as products.**





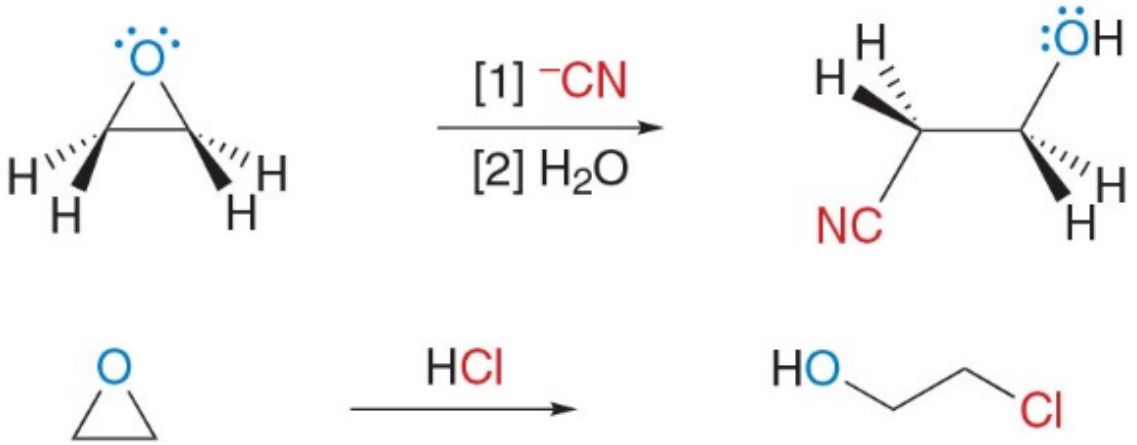
(5) Reactions of Epoxides

- **Epoxides do not contain a good leaving group.**
- **Epoxides do contain a strained three-membered ring with two polar bonds.**
- **Nucleophilic attack opens the strained three-membered ring, making it a favorable process even with a poor leaving group.**



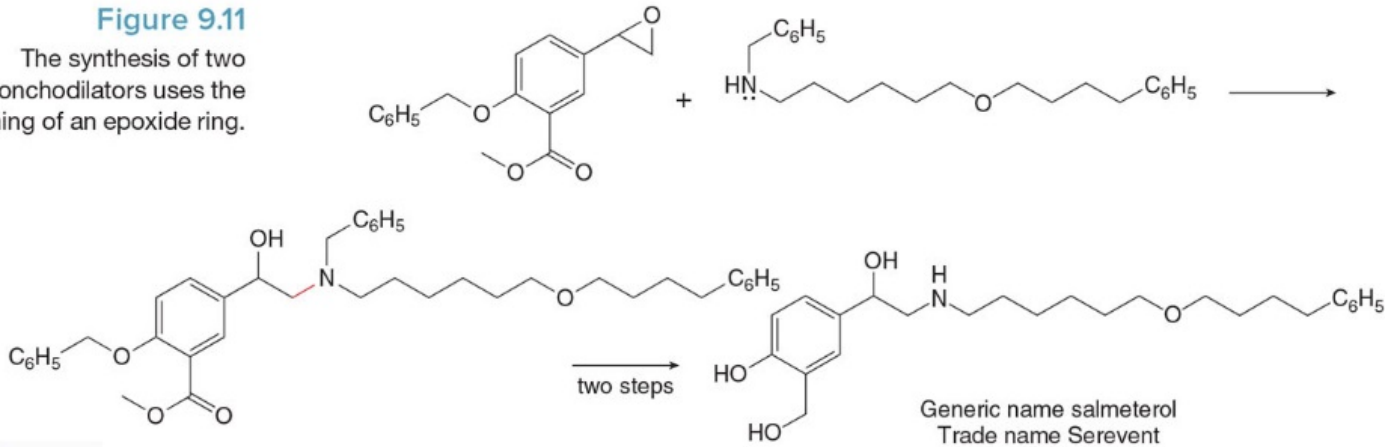
Addition of Nucleophiles to Epoxides

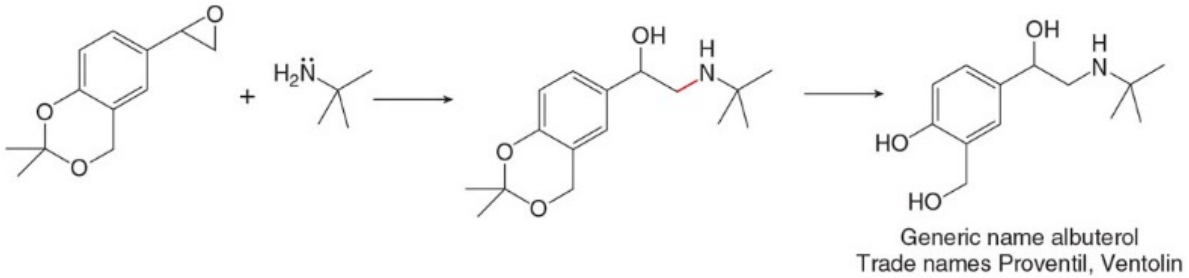
- **Nucleophilic addition to epoxides occurs readily with strong nucleophiles and with acids like HZ, where Z is a nucleophilic atom.**



Synthesis of Bronchodilators from epoxides

Figure 9.11
The synthesis of two bronchodilators uses the opening of an epoxide ring.

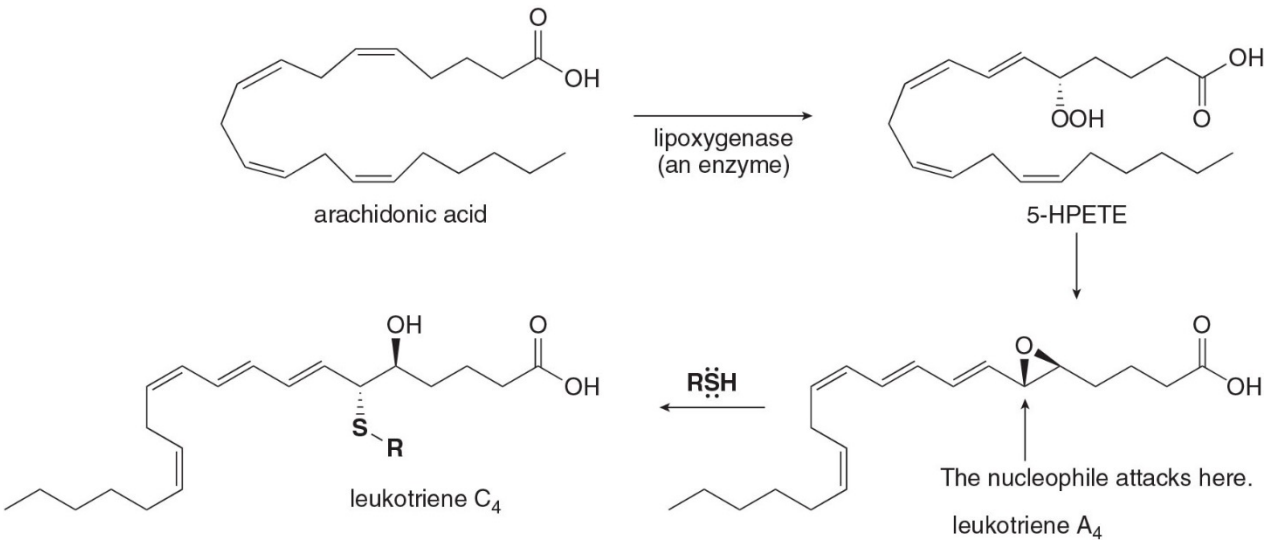


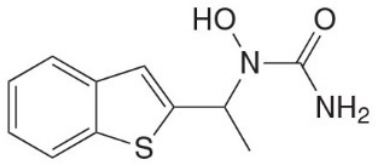


- A key step in each synthesis is the opening of an epoxide ring with a nitrogen nucleophile to form a new C – N bond, shown in red.

Leukotriene synthesis and Asthma drugs

- **Leukotrienes are synthesized in cells by oxidation of arachidonic acid to 5-HPETE.**
- **This is then converted to an epoxide, leukotriene A_4.**
- **Ring opening the epoxide yields leukotriene C_4.**
- **New asthma drugs act by blocking the synthesis of leukotriene C4, for example by inhibiting the enzyme lipoxygenase needed in the biosynthesis.**





Generic name zileuton
Trade name Zyflo CR
anti-asthma drug

Preparation alcohol, ether, epoxide

1. $RX + OH^- \xrightarrow{S_N2} R-O-H$

   $RX + OR'^- \xrightarrow{S_N2} R-O-R'$

2. Williamson Ether Synthesis

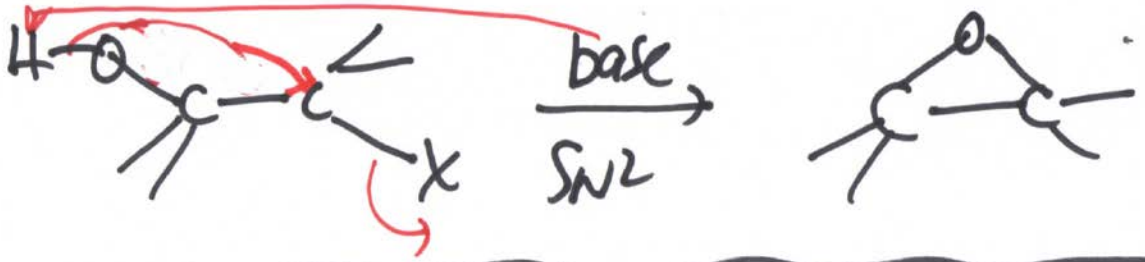
   $R'-OH \xrightarrow{base} R'-O^{\ominus}\ M^{\oplus}$ alkoxide

   ↖ 1°, 2°, 3°

   $R-X + OR' \xrightarrow{S_N2} R-O-R'$

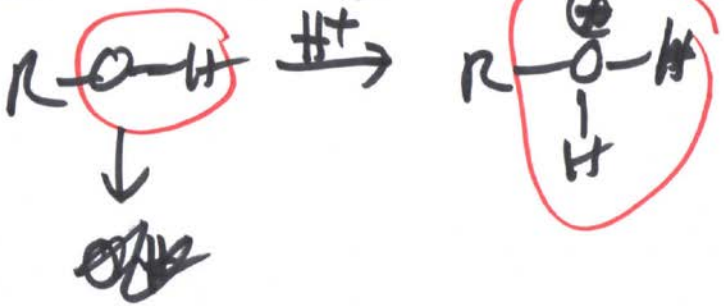
   1° 1°, 2°, 3°

3. epoxide (halohydrin)

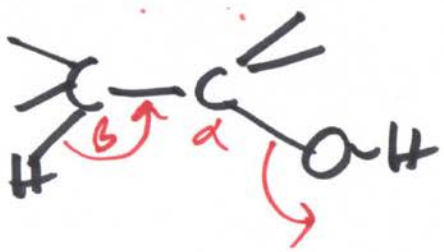


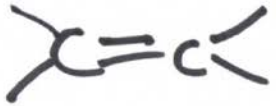
Reactions of Alcohol, Ether, Epoxide

(bad "L" → good "L")



1. **Dehydration:**



$\xrightarrow[H_2SO_4 \text{ or } TsOH]{E1}$  + H_2O

① Zaitsev

② best carbocation

Dehydration:

1° ROH $\xrightarrow[\text{or } SN1 \text{ or } SN2]{E2}$

2. R—OH $\xrightarrow[SN1 \text{ or } SN2]{HX}$ RX

3. R–OH (1°, 2°) $\xrightarrow[\text{or } PBr_3]{SOCl_2}$ RX

4. ROH $\xrightarrow{TsCl}$ ROTs $\xrightarrow[SN2]{\text{"Nu"}}$ R–Nu

5. R–O–R′ $\xrightarrow{HX}$ RX + R′X

6. 

End 11/1/17 W
End Exam IV