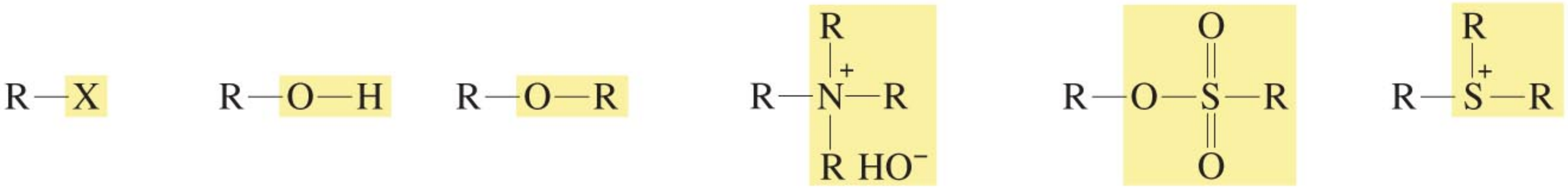
Chapter 10

More substitution and elimination reactions

Reactions of alcohols, ethers, epoxides, amines, and S comp’ds

S_N and E reactions of



an alkyl halide
X = F, Cl, Br, I

an alcohol

an ether

a quaternary ammonium hydroxide ion

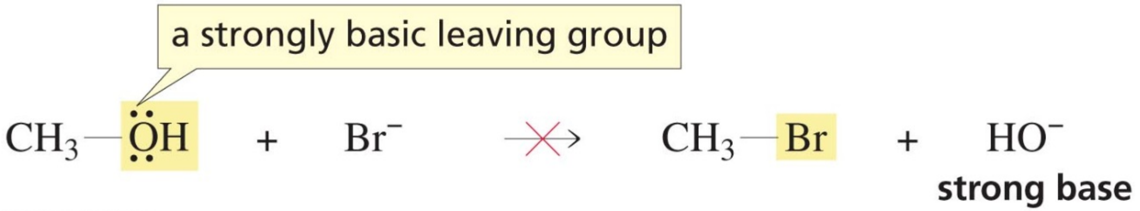
a sulfonate ester

a sulfonium salt

- EWG → LG
  - X^- ~ weak B: ~ good LG
  - ^-OH, ^-OR ~ strong B: ~ poor LG
    - need to be ‘activated’
  - NR_3 ~ medium B:
    - need strong B: and heat
  - RSO_3^-, SR_2 ~ weak B: ~ good LG

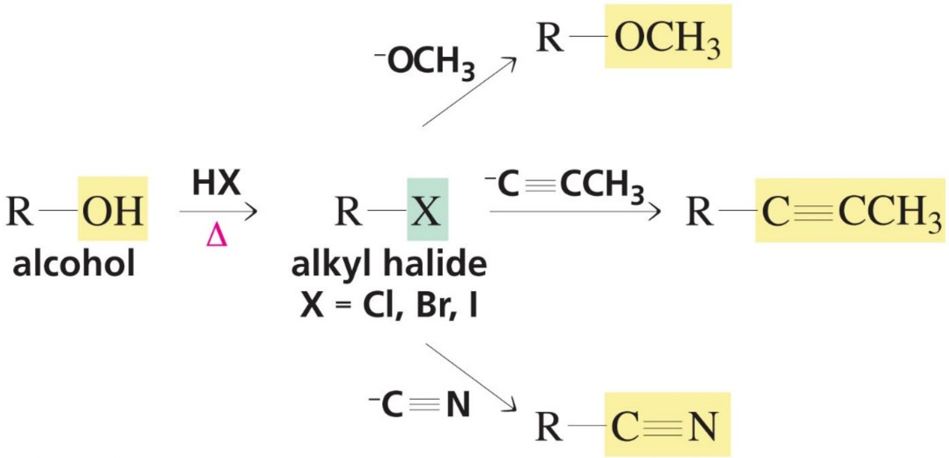
S_N of ROH

- OH is a strongly basic [poor] LG

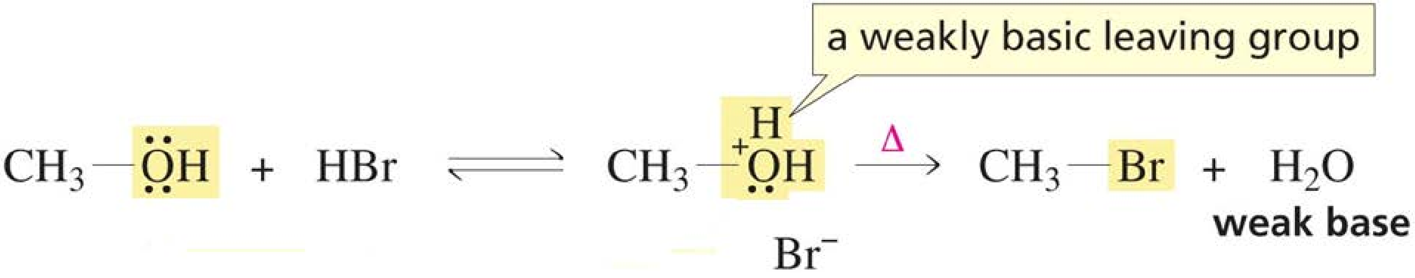


  - ROH is a common and cheap starting material
  - desirable to use ROH in synthesis
  - converting OH to better LG

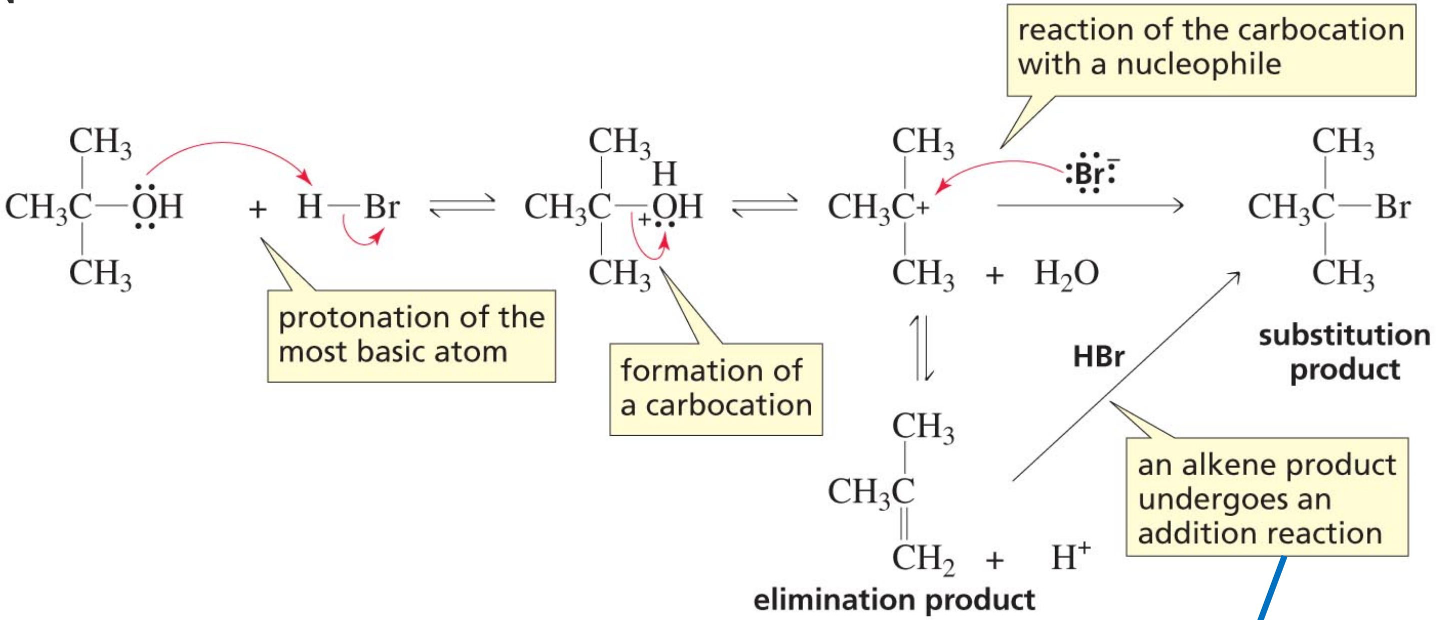
- to OH_2 (and to X)
- (directly) to X
- to OTs, OMs, or OTf



S_N of ROH to form RX through ROH_2



- S_N1 for 2° or 3° alcohol



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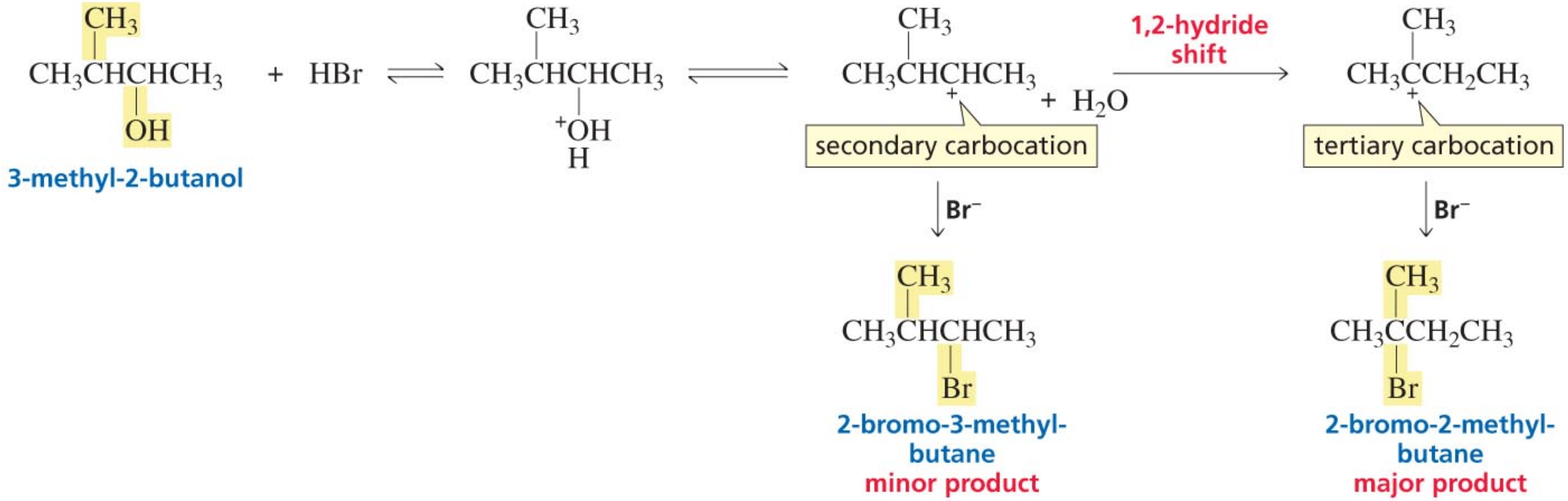
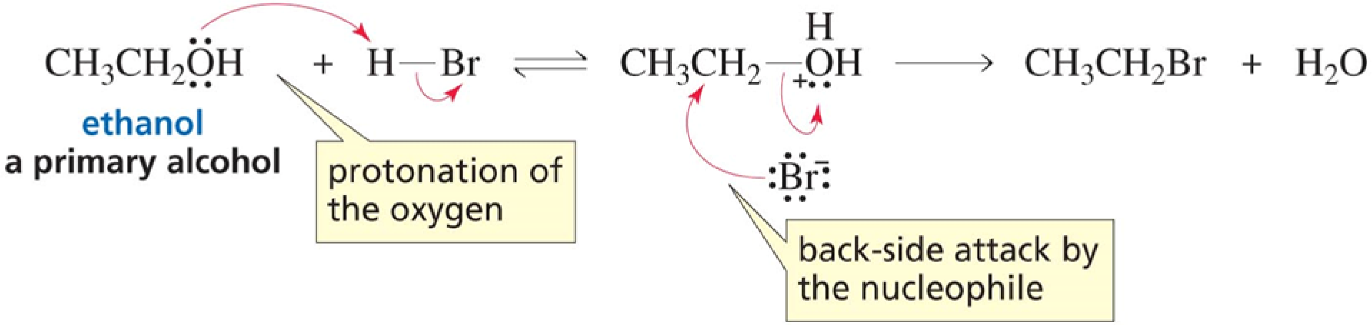
  - predominantly S_N product ← Little E product formed.

- S_N1 for 2° or 3° alcohol (cont'd)
  - why S_N1? X^- is a poor Nu [no good Nu: present]
  - need Δ for 2°
  - C^+ rearrangement



- no S_N2 for 2°?

- S_N2 for 1° alcohol

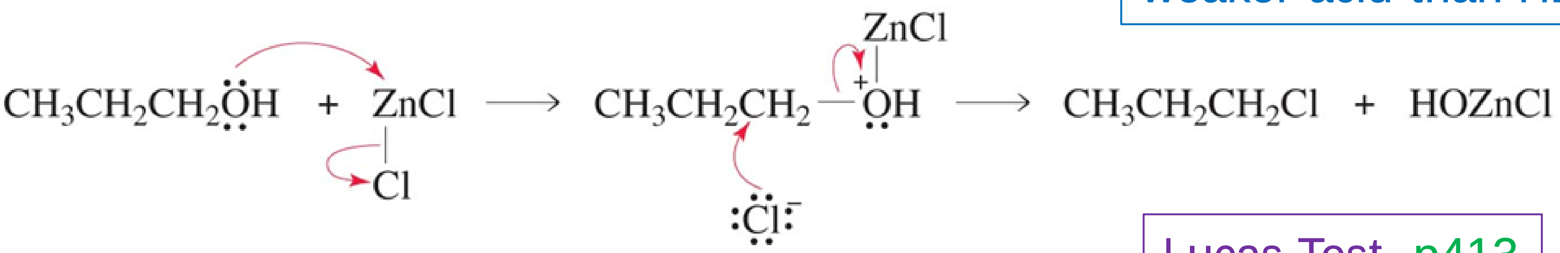


$$CH_3CH_2\ddot{O}H + H{-}Br \rightleftharpoons CH_3CH_2{-}\overset{H}{\overset{|}{\overset{+}{O}}}H \xrightarrow{:\ddot{Br}:^-} CH_3CH_2Br + H_2O$$

  - only S_N, no E product ~ X^- is a weak base

- HBr and HI work alone;
  HCl needs Lewis acid for 1° and 2°.

for 1° ~ Cl^- is a poorer Nu: than Br^- (in H_2O).
for 2° ~ HCl is a weaker acid than HBr.



$$CH_3CH_2CH_2\ddot{O}H + ZnCl{-}Cl \longrightarrow CH_3CH_2CH_2{-}\overset{ZnCl}{\overset{|}{\overset{+}{O}}}H \xrightarrow{:\ddot{Cl}:^-} CH_3CH_2CH_2Cl + HOZnCl$$

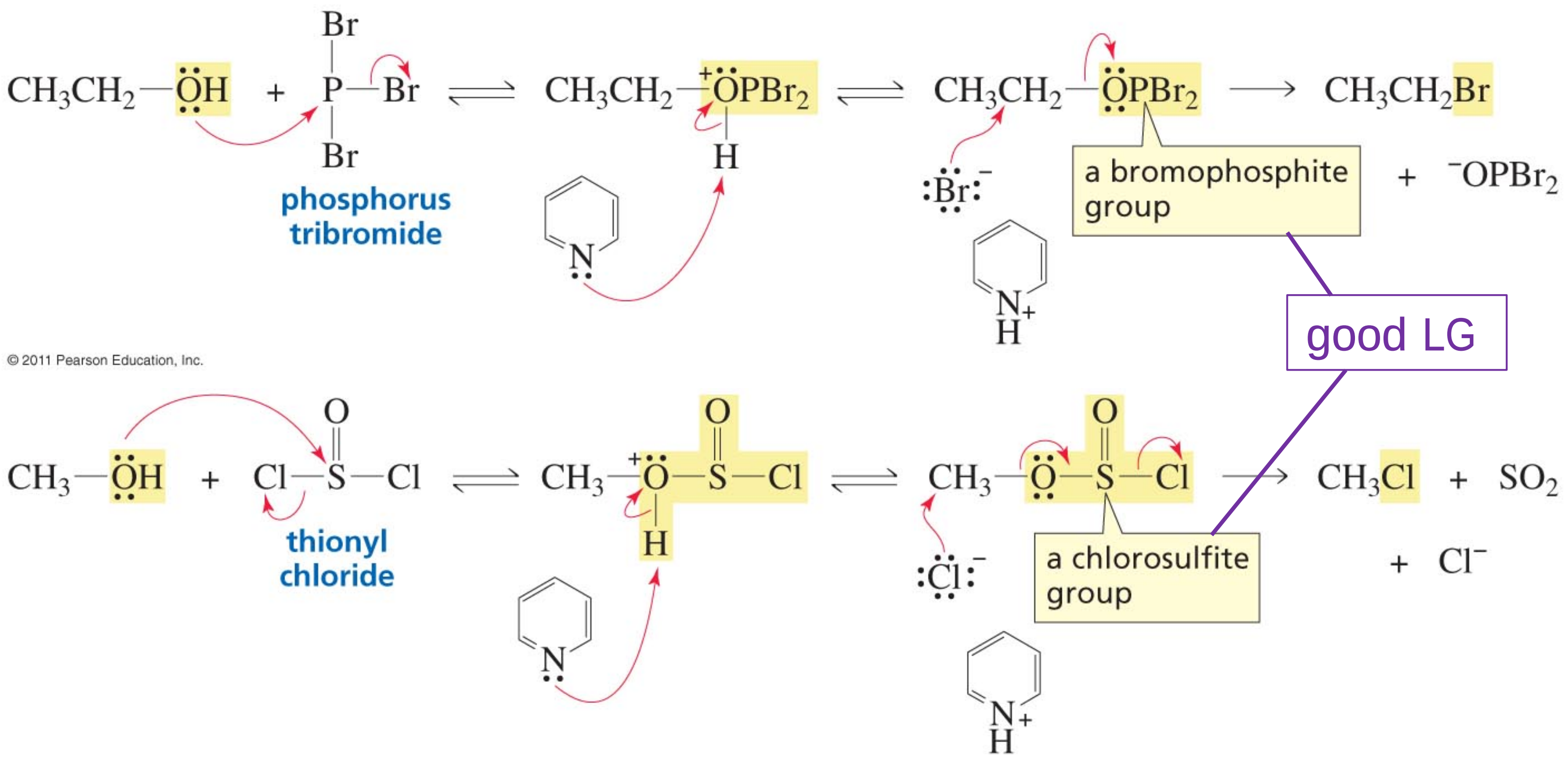
  - LA as H^+ and weakens C–O bond

Lucas Test p413
test of ROH with $HCl/ZnCl_2$

Direct converting ROH to RX

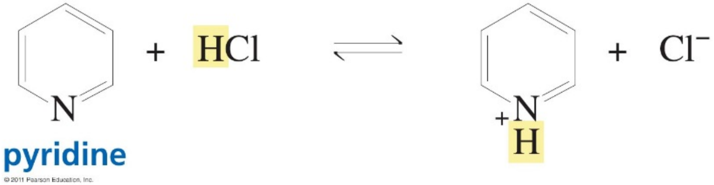
- using $SOCl_2$, PCl_3, PBr_3, or PI_3

$$CH_3CH_2OH + PBr_3 \xrightarrow[\text{pyridine}]{} CH_3CH_2Br$$



condensation or substitution reaction

- pyridine as solvent and acid-acceptor
  - weak base, but accepts H^+



- faster and with high yield than by HX
- works well for 1° or 2°; very low yield for 3° alcohol
  - mechanism must be S_N2?

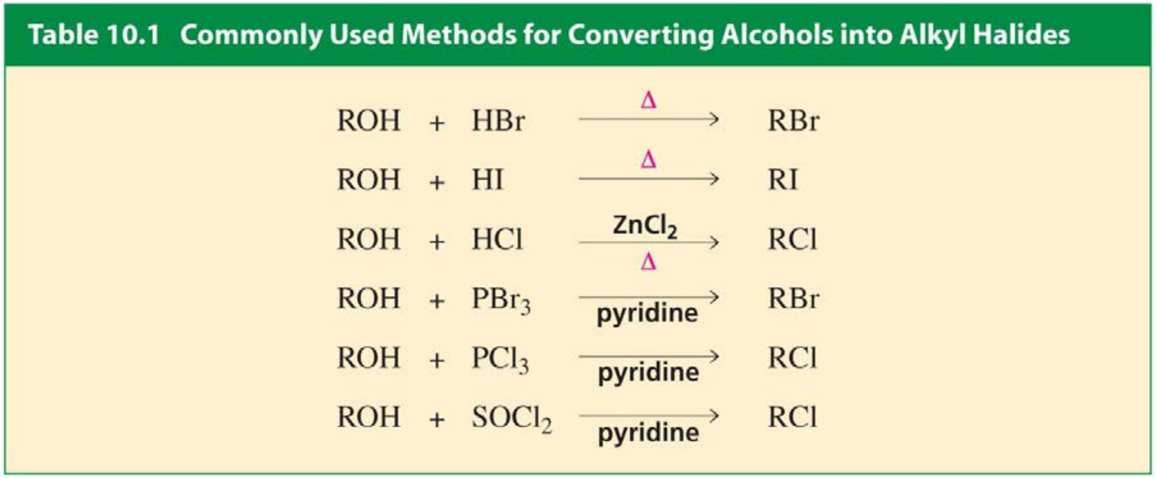
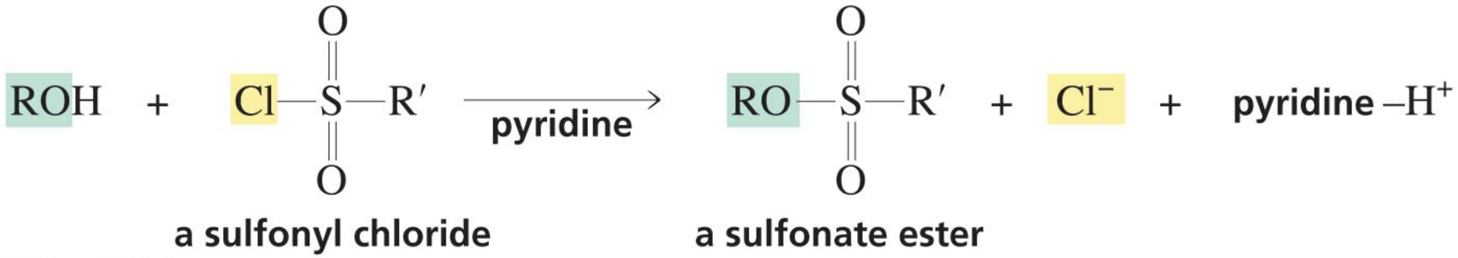


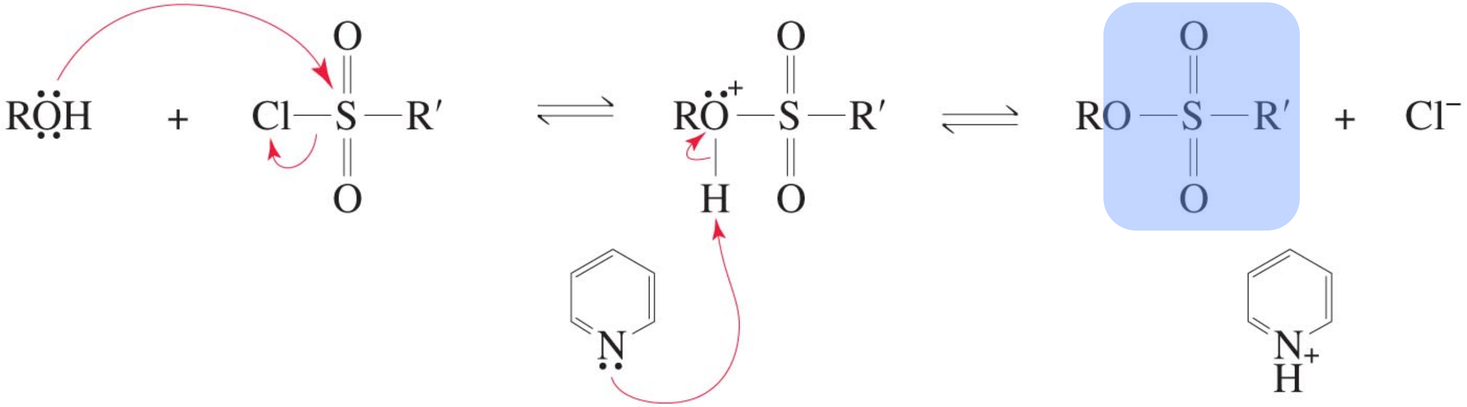
Table 10.1 Commonly Used Methods for Converting Alcohols into Alkyl Halides

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

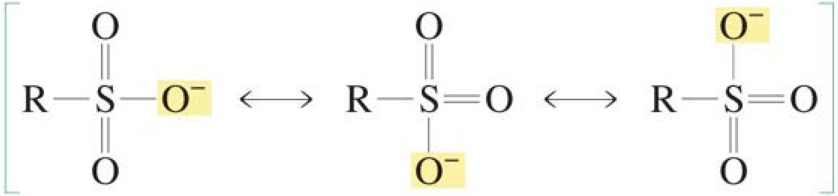
Converting OH to sulfonate esters

- formed by the reaction of ROH with R'SO_2Cl

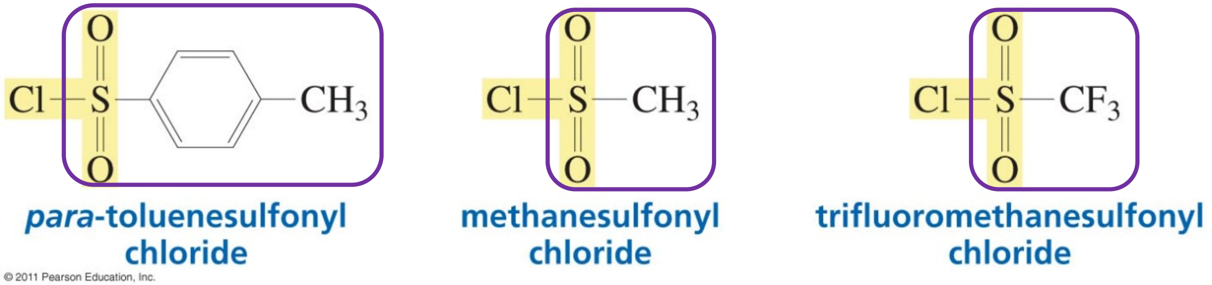




- -OSO_2R is a very good LG.
  - pK_a of $HOSO_2R$ ~ –6.4



- $-OSO_2R$



para-toluenesulfonyl chloride

methanesulfonyl chloride

trifluoromethanesulfonyl chloride

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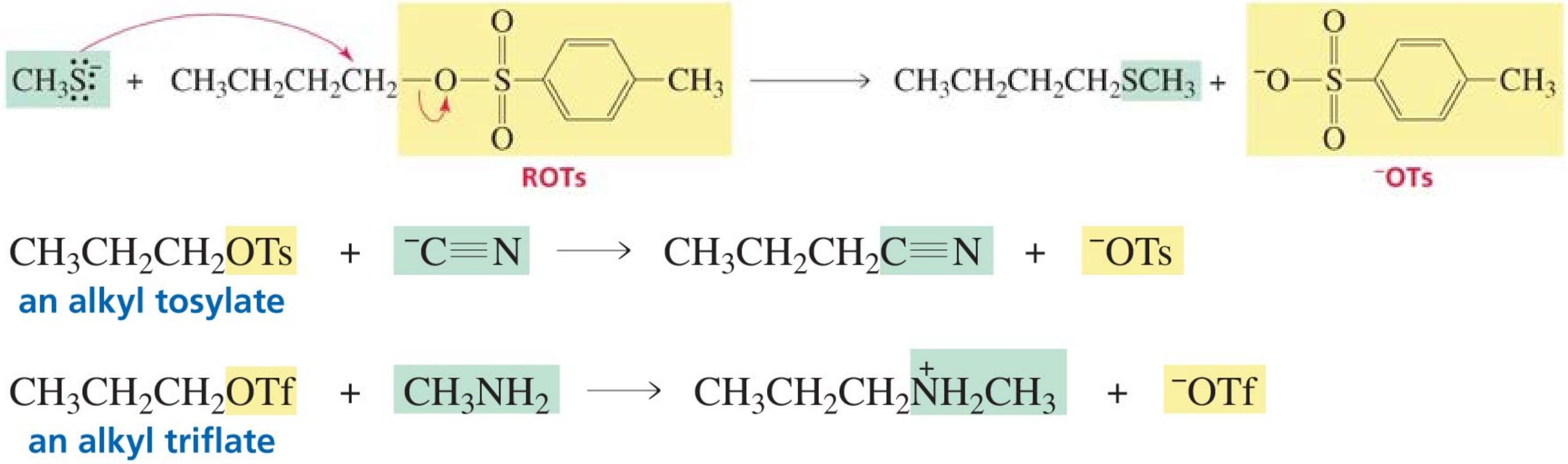
$-SO_2R$ ~	tosyl [Ts]	mesyl [Ms]	trifylyl [Tf]
$-OSO_2R$ ~	tosylate [OTs]	mesylate [OMs]	triflate [OTf]

- useful for substitution rxn



$$CH_3\ddot{S}^- + CH_3CH_2CH_2CH_2{-}OTs \longrightarrow CH_3CH_2CH_2CH_2SCH_3 + {}^-OTs$$

$$CH_3CH_2CH_2OTs + {}^-C{\equiv}N \longrightarrow CH_3CH_2CH_2C{\equiv}N + {}^-OTs$$

$$CH_3CH_2CH_2OTf + CH_3NH_2 \longrightarrow CH_3CH_2CH_2\overset{+}{N}H_2CH_3 + {}^-OTf$$

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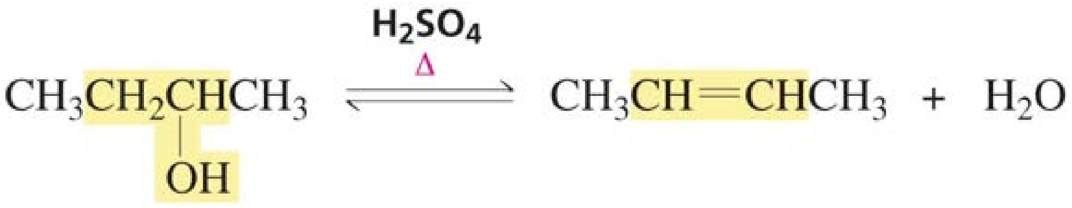
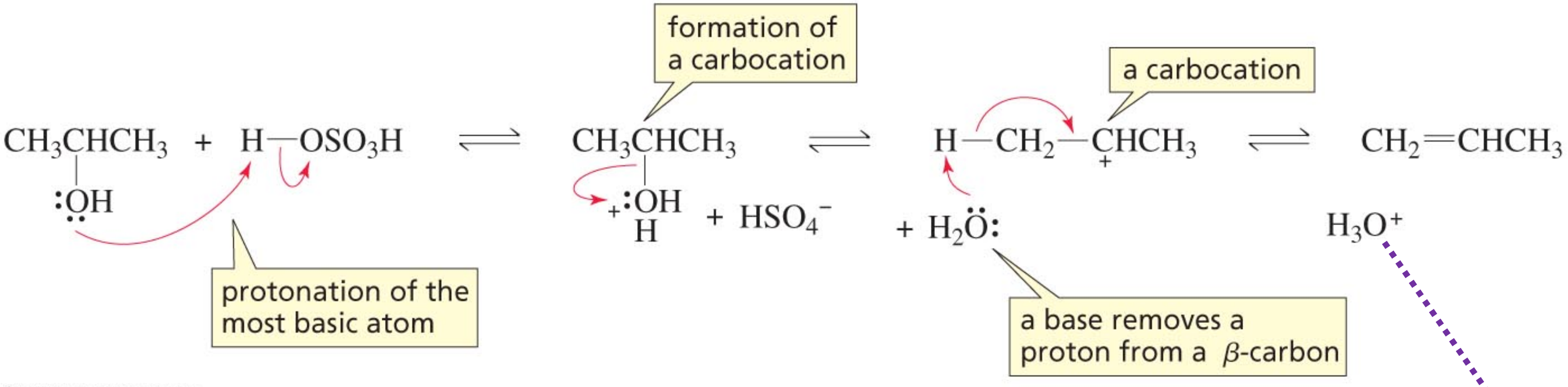
E of ROH: dehydration

- to form alkene



$$CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3 \;\overset{H_2SO_4}{\underset{}{\overset{\Delta}{\rightleftharpoons}}}\; CH_3CH{=}CHCH_3 + H_2O$$

  - need acid catalyst and heat
- E1 for 3° or 2° alcohol



formation of a carbocation

a carbocation

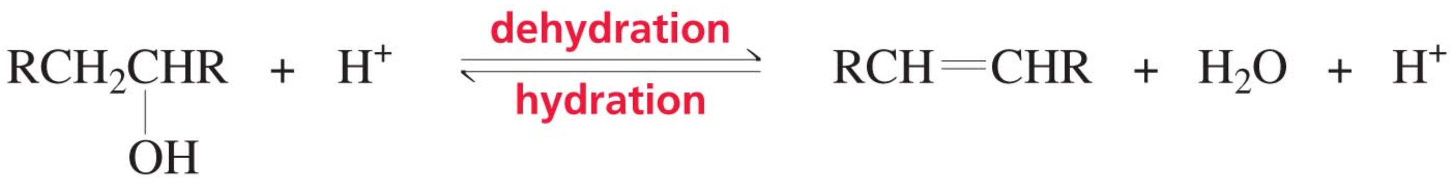
protonation of the most basic atom

a base removes a proton from a β-carbon

acid regenerated

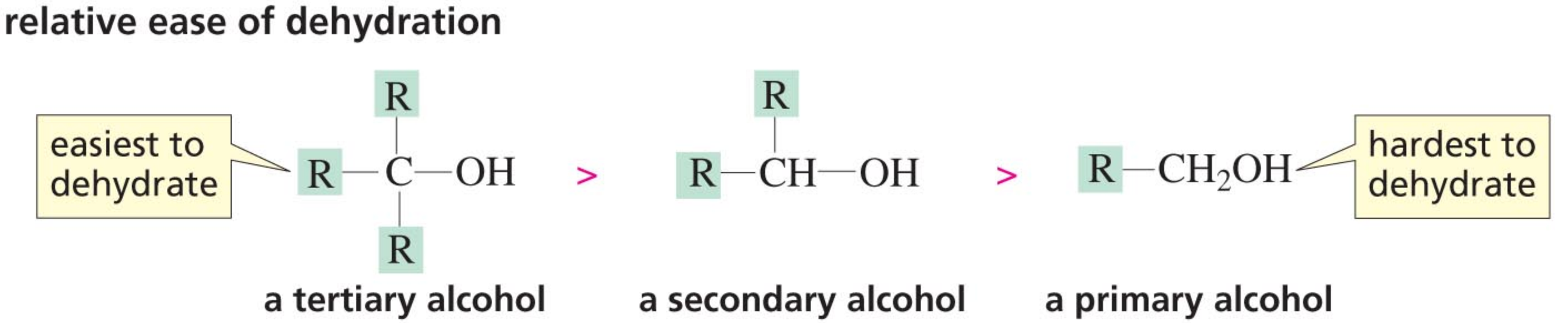
  - catalytic amount of H_2SO_4 or H_3PO_4
  - not HX. why? competition betw S_N1 and E1

- E1 for 3° or 2° (cont'd)
  - Actually, the reverse rxn of hydration of alkene
    - alkene need to be distilled out



$$RCH_2\underset{\displaystyle OH}{\underset{|}{C}}HR + H^+ \underset{\text{hydration}}{\overset{\text{dehydration}}{\rightleftharpoons}} RCH{=}CHR + H_2O + H^+$$

  - reactivity



relative ease of dehydration

a tertiary alcohol

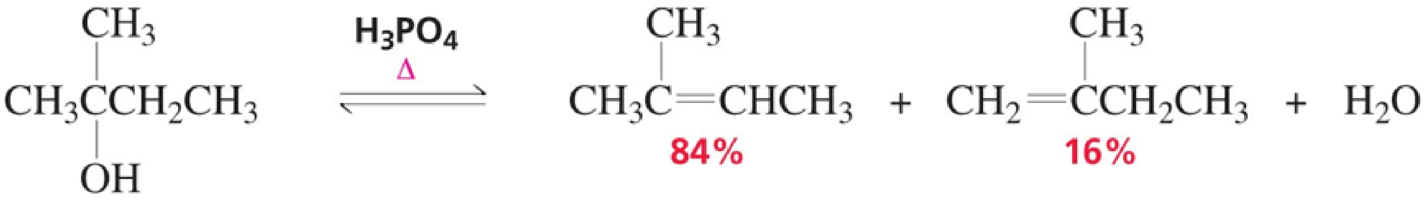
a secondary alcohol

a primary alcohol

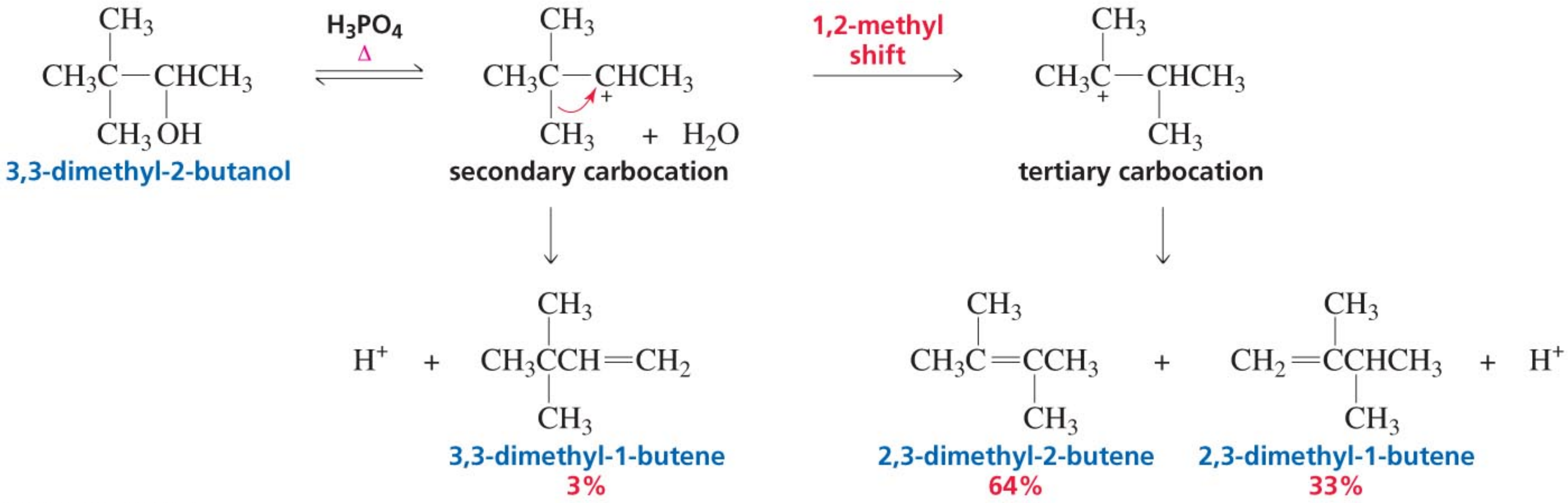
    - need higher Temp and more catalyst for 2° (and 1°)

E1 for 3° or 2° (cont’d)

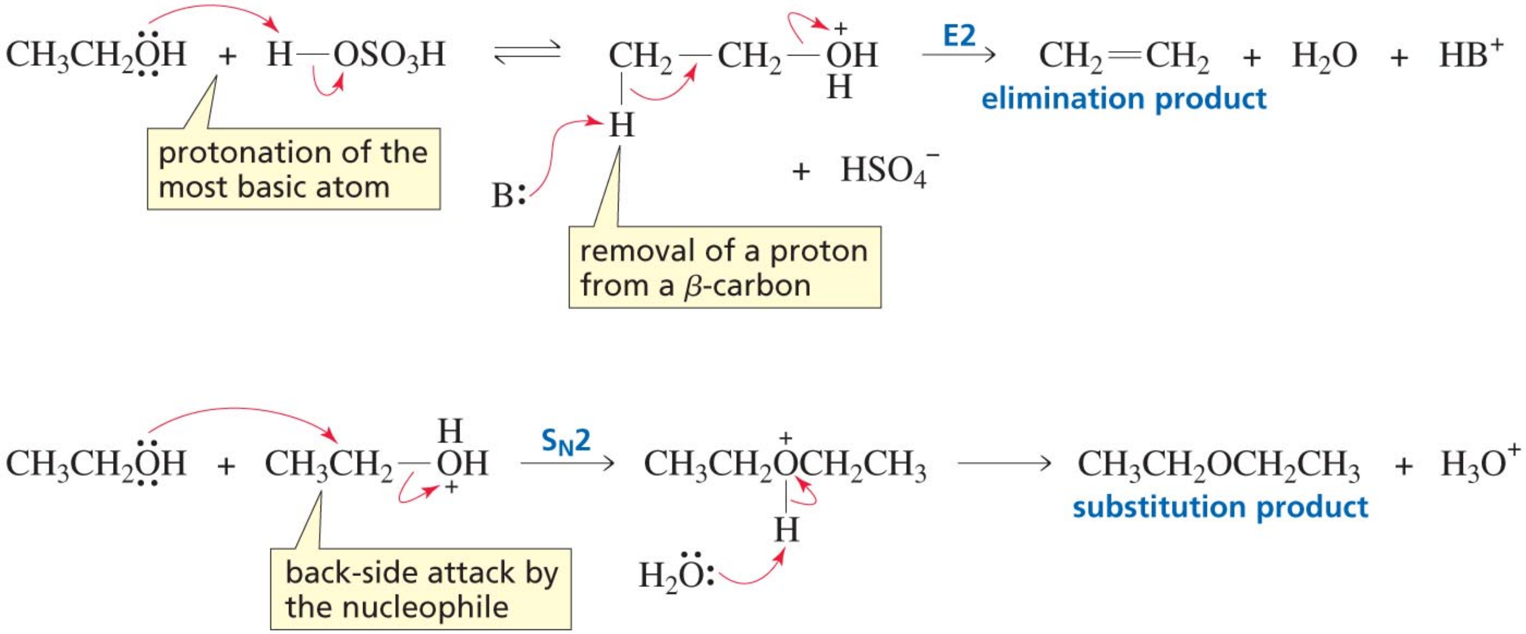
- more substituted alkene major



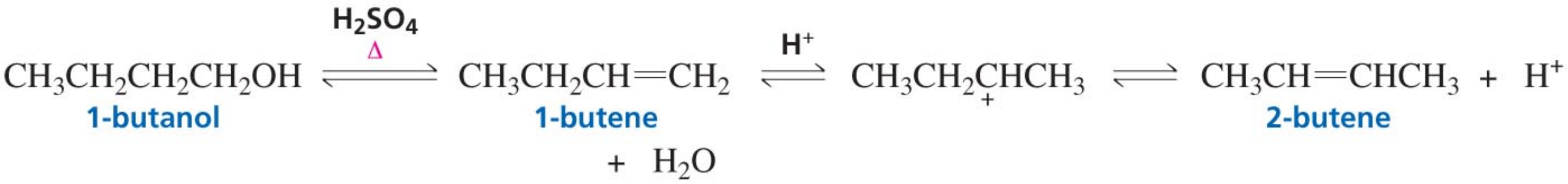
- C^+ rearrangement



- E2 for 1° alcohol
  - even with weak base like HSO_4^-
  - compete with S_N2 (by weak Nu: like ROH)

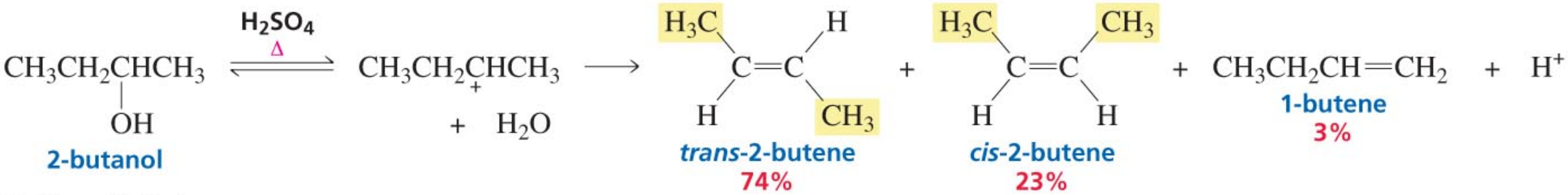


- E2 for 1° (cont'd)
  - Actually, (rearranged) E1 product obtained, when possible.
    - through addition-elimination rxn

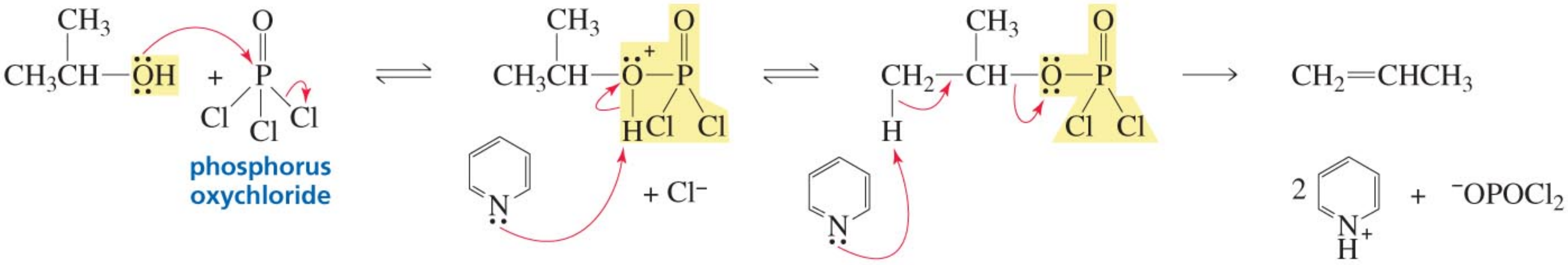


$CH_3CH_2CH_2CH_2OH \xrightleftharpoons[\Delta]{H_2SO_4} CH_3CH_2CH{=}CH_2 + H_2O \xrightleftharpoons{H^+} CH_3CH_2\overset{}{\underset{+}{C}}HCH_3 \rightleftharpoons CH_3CH{=}CHCH_3 + H^+$

- Stereochemistry the same to dehydrohalogenation



- Alternative route
  - under milder condition
  - using $POCl_3$
  - E2 mechanism
    - no C^+ rearrangement



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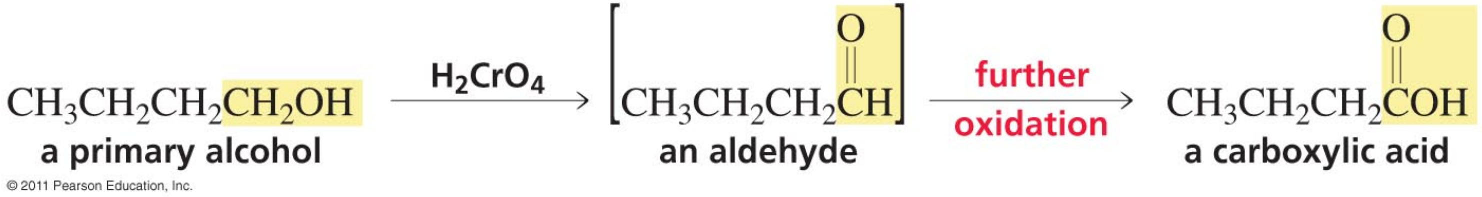
- pyridine takes H^+ and holds HCl (by pyridine:$H^+Cl^–$)

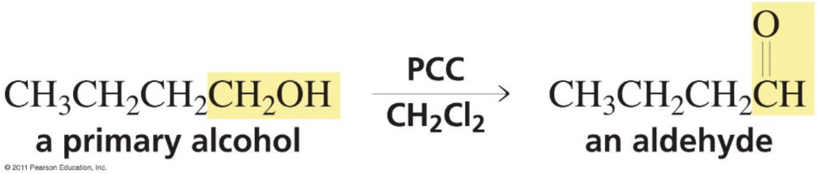
Oxidation of ROH

- 1° ROH to RCHO to RCOOH

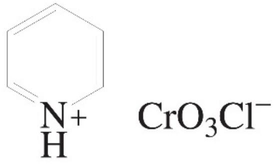


$$CH_3CH_2CH_2CH_2OH \xrightarrow{H_2CrO_4} \left[CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}H\right] \xrightarrow[\text{oxidation}]{\text{further}} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OH$$

  - to stop at aldehyde, use PCC

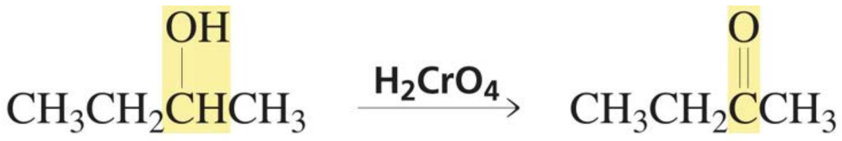


$$CH_3CH_2CH_2CH_2OH \xrightarrow[CH_2Cl_2]{PCC} CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}H$$



pyridinium chlorochromate
PCC

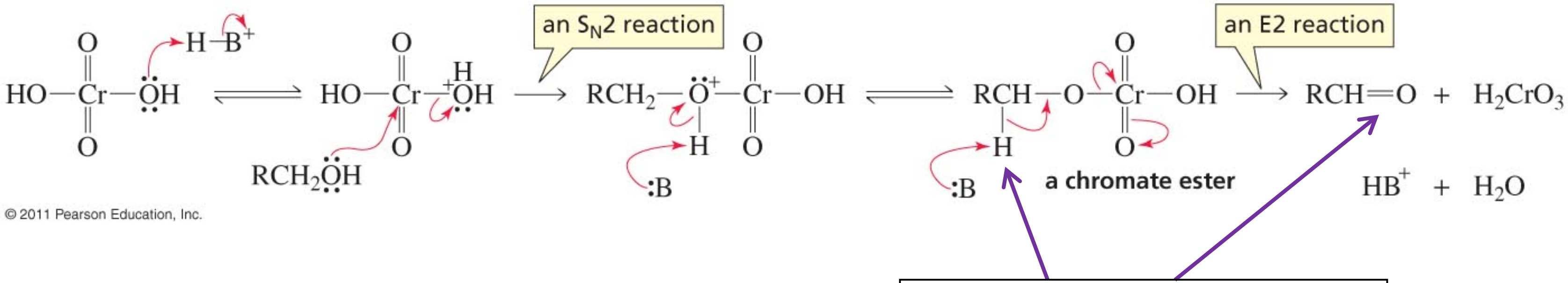
- 2° ROH to ketone



$$CH_3CH_2\overset{OH}{\overset{|}{C}}HCH_3 \xrightarrow{H_2CrO_4} CH_3CH_2\overset{O}{\overset{\|}{C}}CH_3$$

- 3° ROH cannot be oxidized.
  - no α-H

- mechanism
  - H_2CrO_4 from {$Na_2Cr_2O_7$ + H^+ + H_2O}



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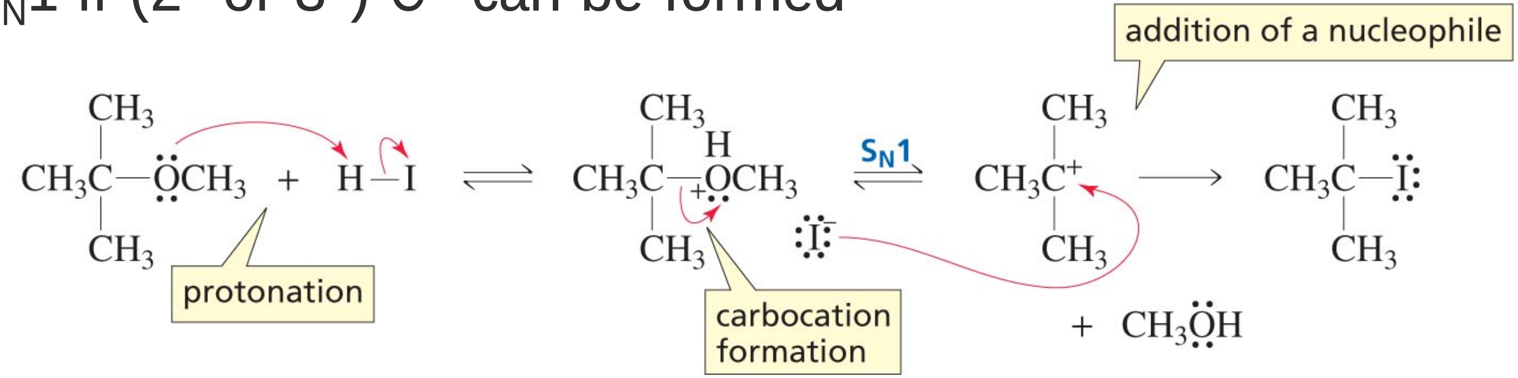
need α-H to form C=O

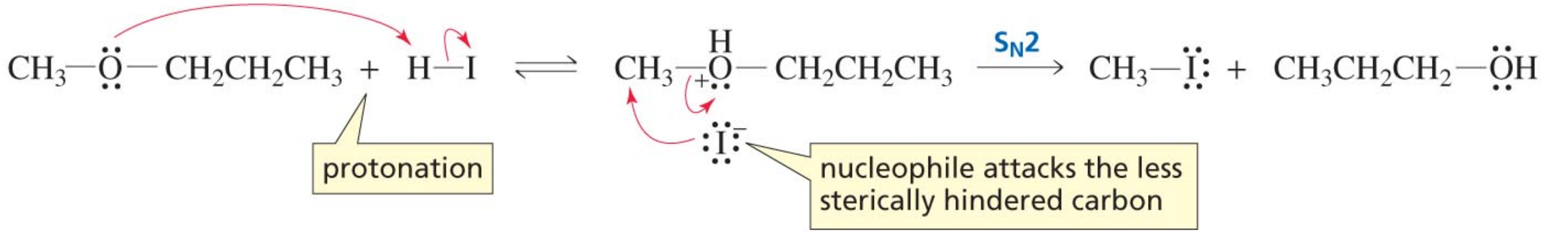
  - S_N2 followed by E2

S_N of ethers

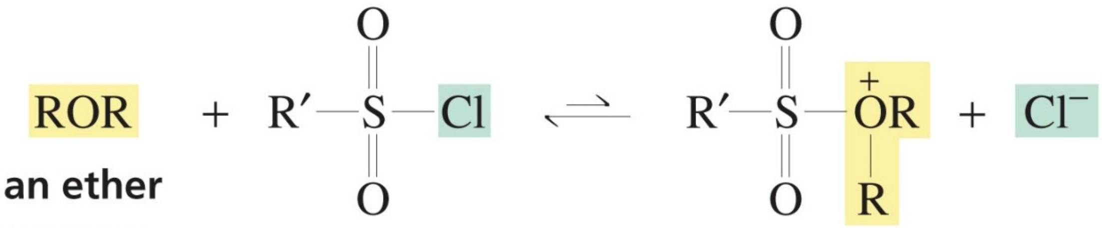
- OR of ether is also a poor LG
    - just like OH of ROH
- activation by protonation with HX
    - S_N1 if (2° or 3°) C^+ can be formed

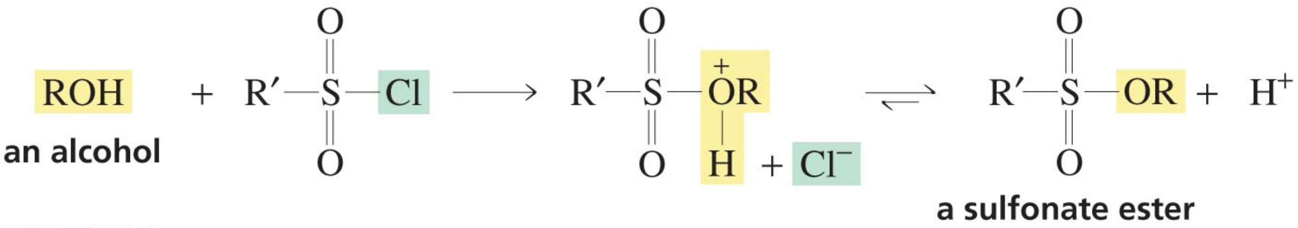


- S_N2 if not



- activation by protonation with HX (cont'd)
  - by HBr or HI, not by HCl ← reason the same to ROH
  - S_N only, no E ← reason the same to ROH
    - weakly basic X + HX addition to E product
- no activation by PBr_3, --- or OTs, ---





  - no H to be dissociated (and accepted by 'acid acceptor')

- Ethers are more useful as solvents.
  - <u>not</u> reactive to most compounds but HX

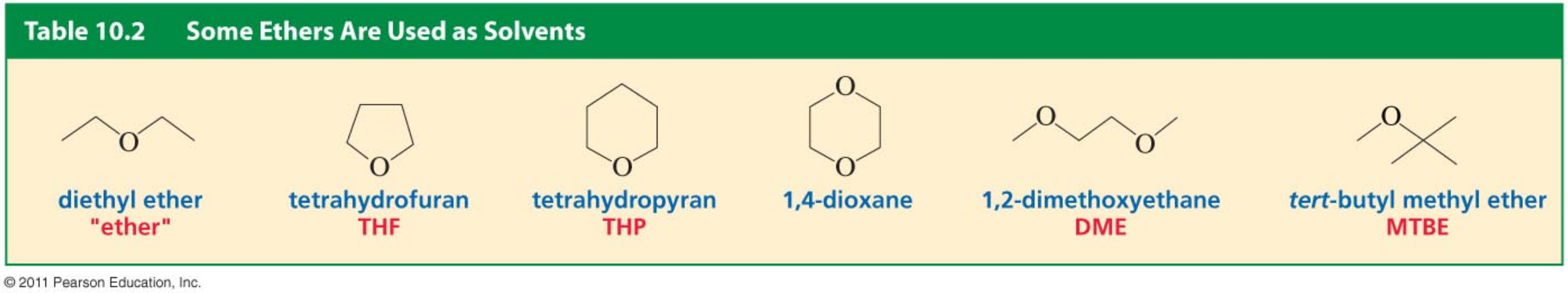


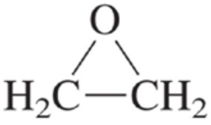
Table 10.2 Some Ethers Are Used as Solvents

diethyl ether	tetrahydrofuran	tetrahydropyran	1,4-dioxane	1,2-dimethoxyethane	*tert*-butyl methyl ether
"ether"	THF	THP		DME	MTBE

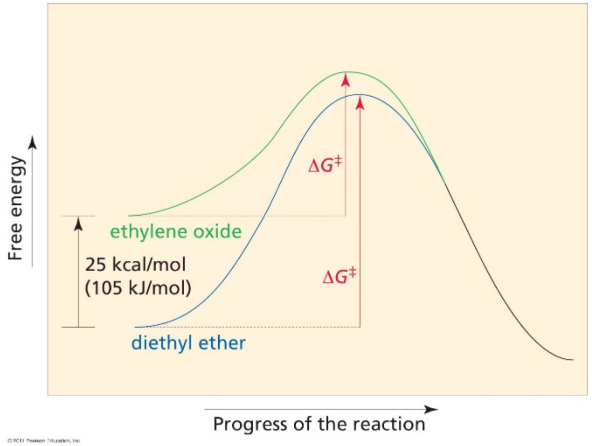
- anesthetics ~ another (once) use of ‘ether’
  - margin of safety = LD1/ED99 Box p429

S_N of epoxides

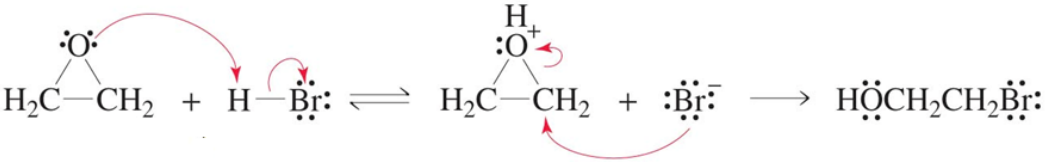
- Epoxides (= 3-membered cyclic ethers)
  - much more reactive than ethers
    - due to (high) ring [angle] strain
  - fast S_N [ring-opening]
    - LG the same ~ OR

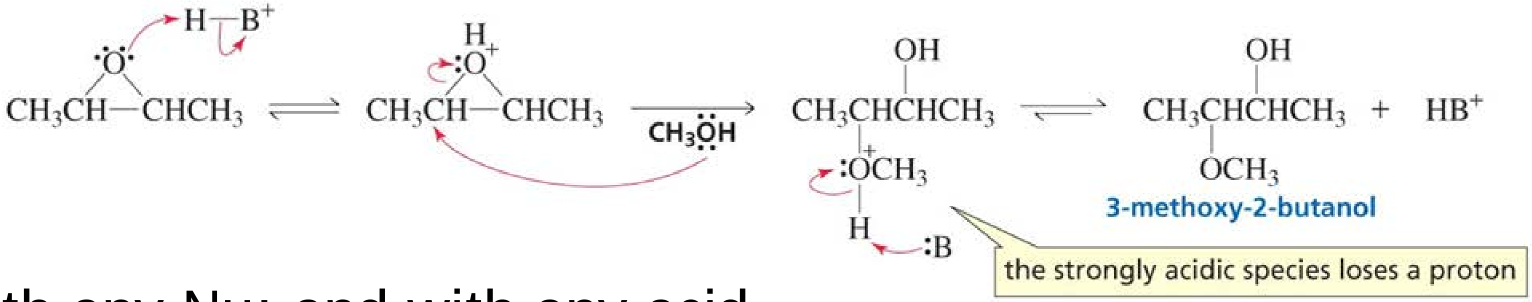


An epoxide



- in acidic condition



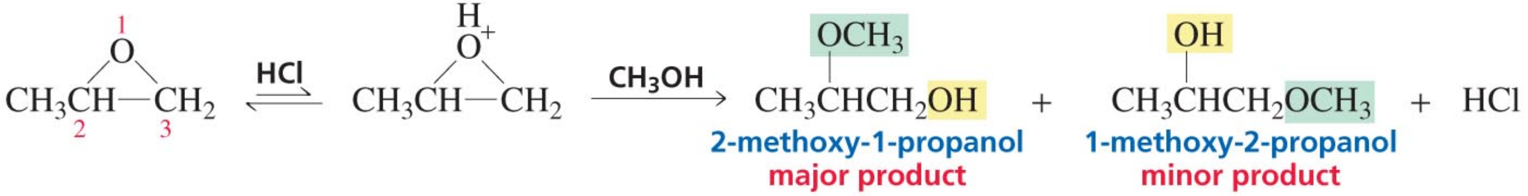


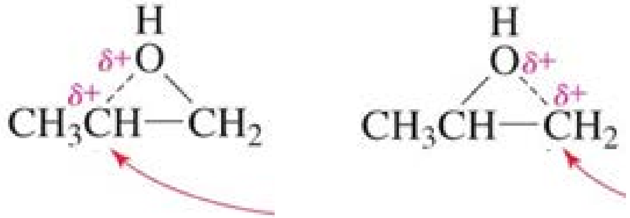
3-methoxy-2-butanol

the strongly acidic species loses a proton

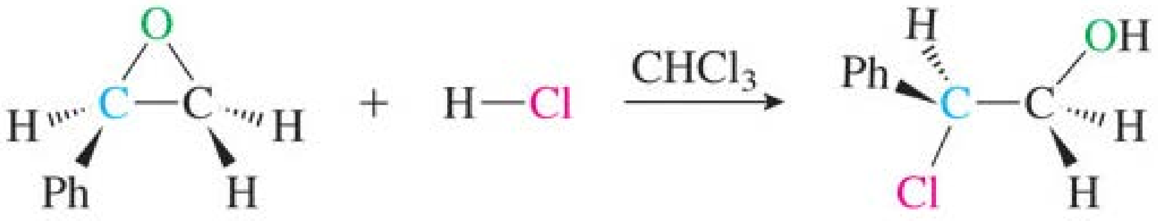
  - with any Nu: and with any acid
    - H_2O OK. ^-OH?

- in acidic condition (cont'd)
  - mechanism ~ $S_N1/2$ [partially S_N1 and partially S_N2]
  - S_N1 regiochemistry



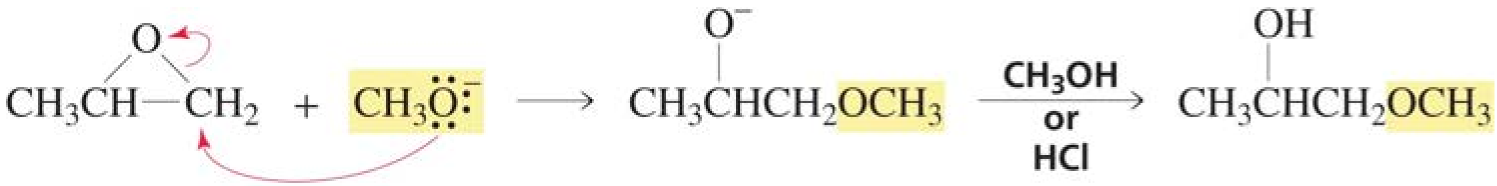


  - S_N2 stereochemistry

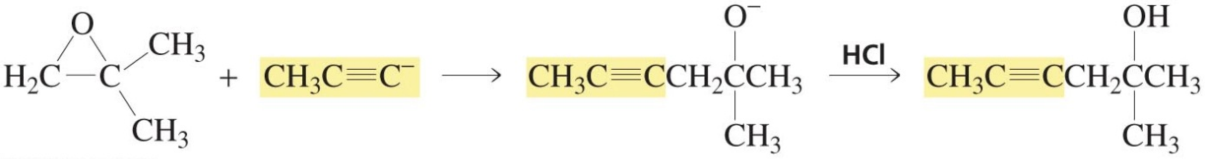


only product

- in neutral or basic condition
  - Epoxides need not be protonated for OR to leave.
  - S_N2



    - Good Nu: attacks less-hindered C.
    - -O^- picks up H^+ from solvent or acid after rxn.



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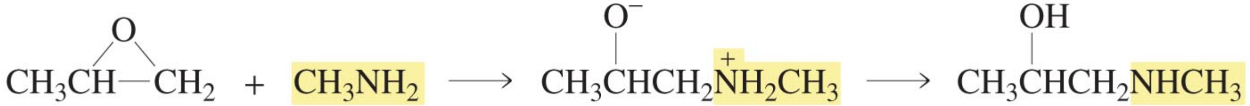

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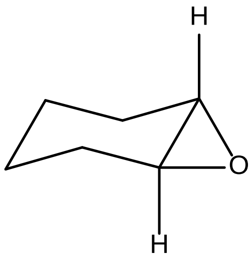

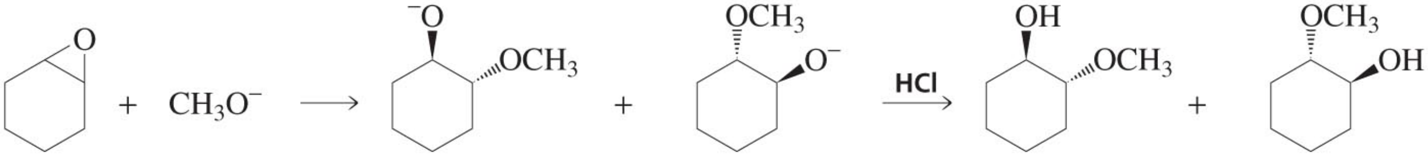

trans

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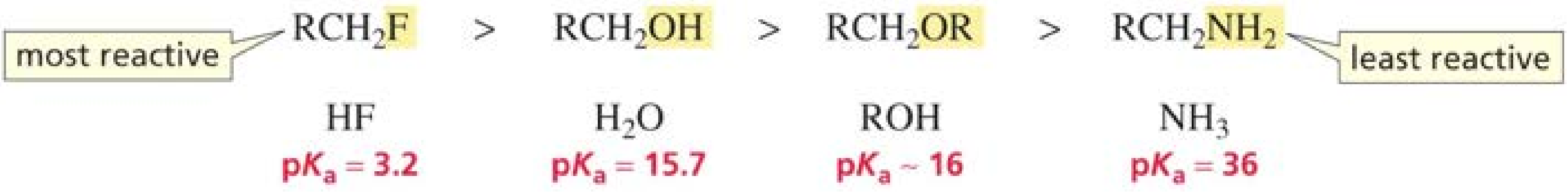
S_N or E of amines?

- Amino group [NH_2] does not leave.



most reactive $RCH_2F > RCH_2OH > RCH_2OR > RCH_2NH_2$ least reactive

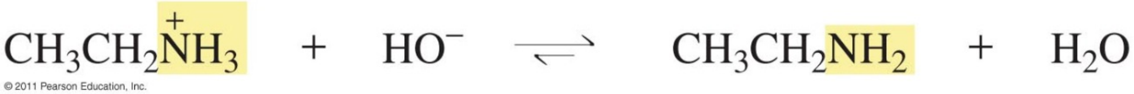
HF	H_2O	ROH	NH_3
$pK_a = 3.2$	$pK_a = 15.7$	$pK_a \sim 16$	$pK_a = 36$

  - NH_2^- is too basic to leave
    - NH_2^- is used when a very strong base is needed, eg, for $RC\equiv C^-$.
- protonated amino group?

$$CH_3CH_2\overset{+}{O}H_2 > CH_3CH_2\overset{+}{N}H_3$$

$pK_a = -2.4$ $\quad$ $pK_a = 11.2$

  - does not leave by X^-
    - ROH or ROR to RX by HX; RNH_2 does <u>not</u>.
  - by strong Nu: like ^-OH? No.



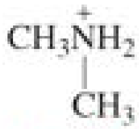
$$CH_3CH_2\overset{+}{N}H_3 + HO^- \rightleftharpoons CH_3CH_2NH_2 + H_2O$$

➢ Amines do not undergo SN or E.

- Amines are most common organic bases.

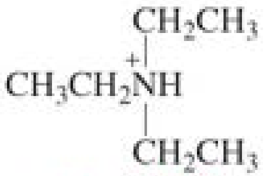
$CH_3CH_2CH_2\overset{+}{N}H_3$

pK_a = 10.8



$CH_3\overset{+}{N}H_2CH_3$

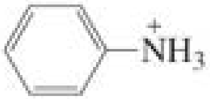
pK_a = 10.9



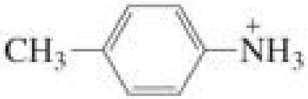
$CH_3CH_2\overset{+}{N}H(CH_2CH_3)_2$

pK_a = 11.1

3.2 3.1 2.9 ~ pK_b of conj base [amine]



pK_a = 4.58



pK_a = 5.07

CH_3NH_2

pK_a = 40

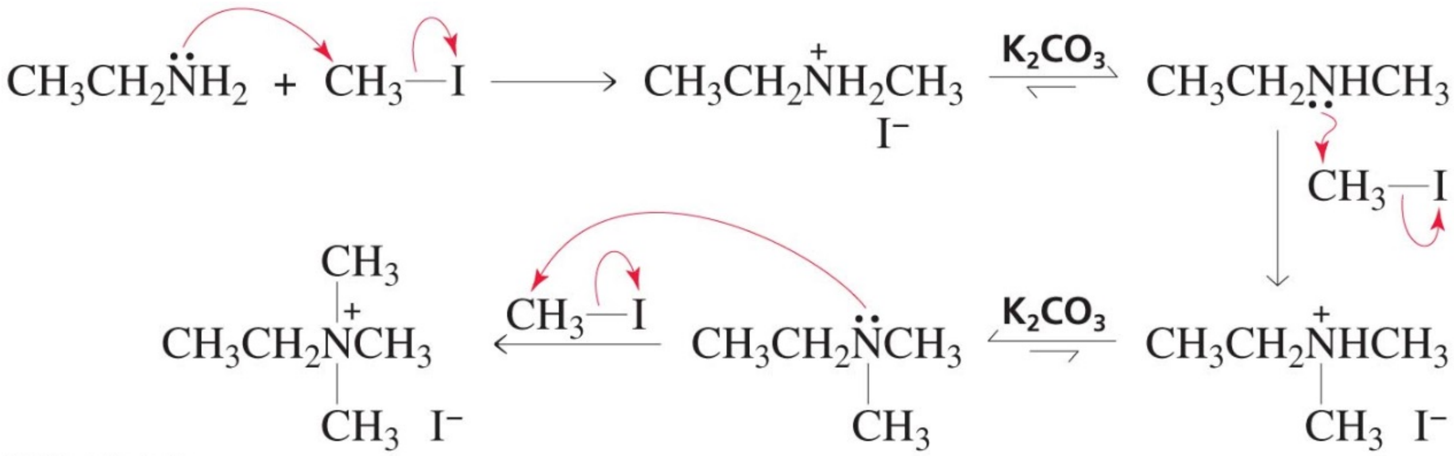
basicity $HO^- < NH_2^- < RN^-H$

acidity $H_2O > NH_3 > RNH_2$

basicity $H_2O < NH_3 < RNH_2 < NR_3$

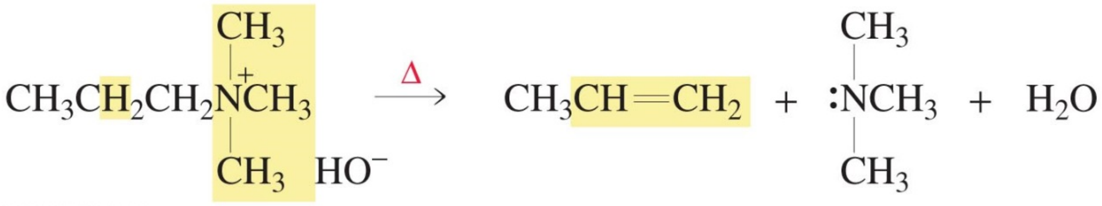
acidity $H_3O^+ > {}^+NH_4 > RN^+H_3 > R_3N^+H$

- Amines are good Nu:.
  - Nu: in S_N2
  - not substrate

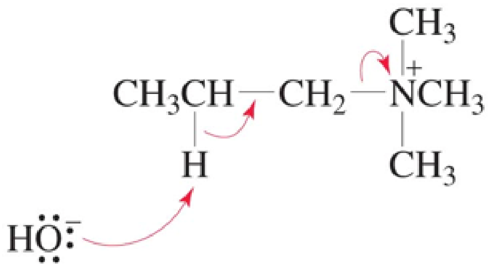


Hoffmann elimination

- 4° ammonium hydroxide [$NR_4^+OH^-$] undergo E.

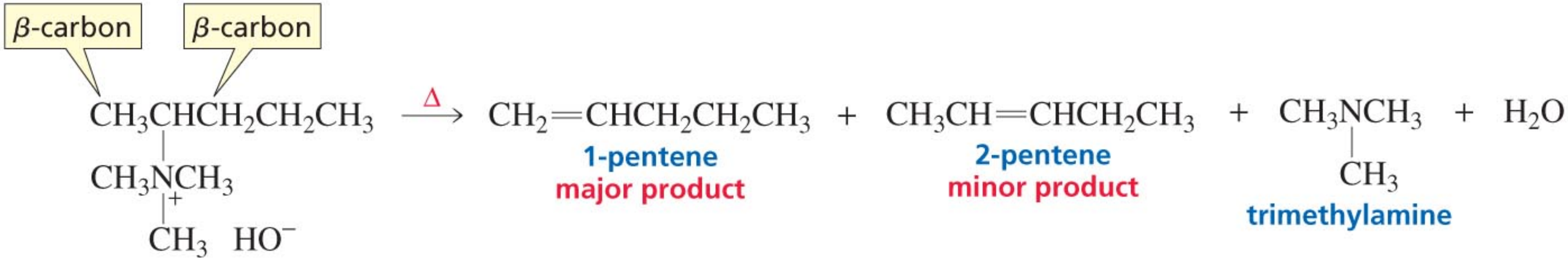


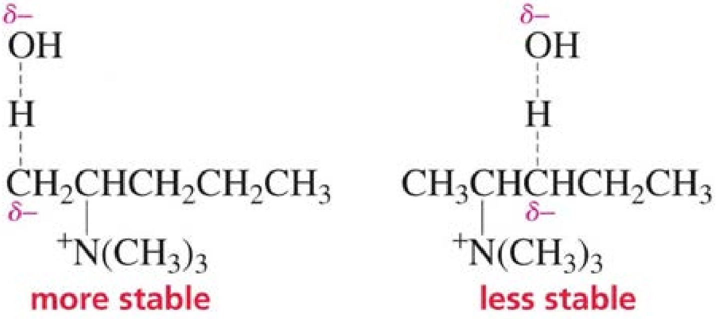
$CH_3CH_2CH_2\overset{+}{N}(CH_3)_3\ HO^- \xrightarrow{\Delta} CH_3CH{=}CH_2 + :N(CH_3)_3 + H_2O$



  - no acidic H to protonate OH^-
  - instead, β-elimination
  - Hoffmann elimination ~ an E2
  - LG is 3° amine [NR_3] ~ not a good LG
    - need heat
  - $NR_4^+OH^-$ only; not $NR_4^+X^-$
    - X^- too weak Nu:

Hoffmann E is an anti-Zaitsev E.





- carbanion-like TS ← NR_3 is not a good LG
- steric effect also

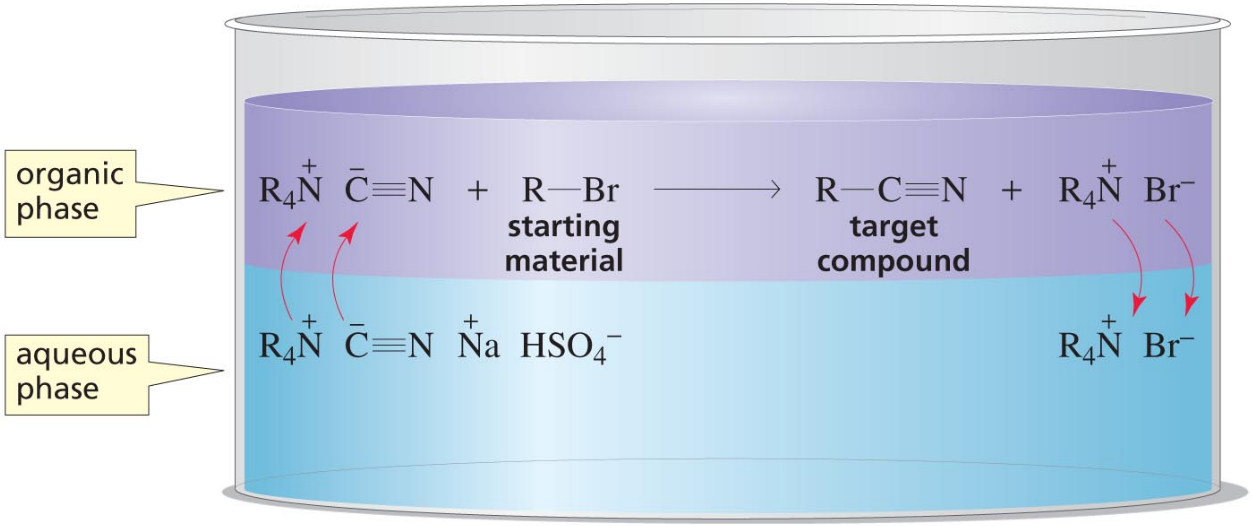
Phase-transfer catalysis

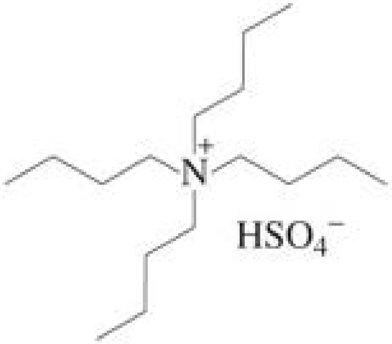
$$CH_3CH_2CH_2CH_2CH_2CH_2Br + {}^{-}C{\equiv}N \xrightarrow{?} CH_3CH_2CH_2CH_2CH_2CH_2C{\equiv}N + Br^{-}$$

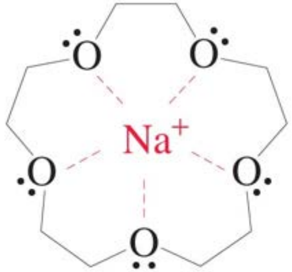
1-bromohexane

soluble only in non-polar solvent organic phase	soluble only in polar solvent aqueous phase

- NR_4^+ is (the most common) phase-transfer catalyst.
- crown ethers also Box p439

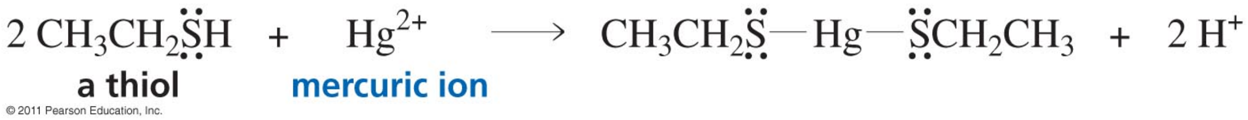




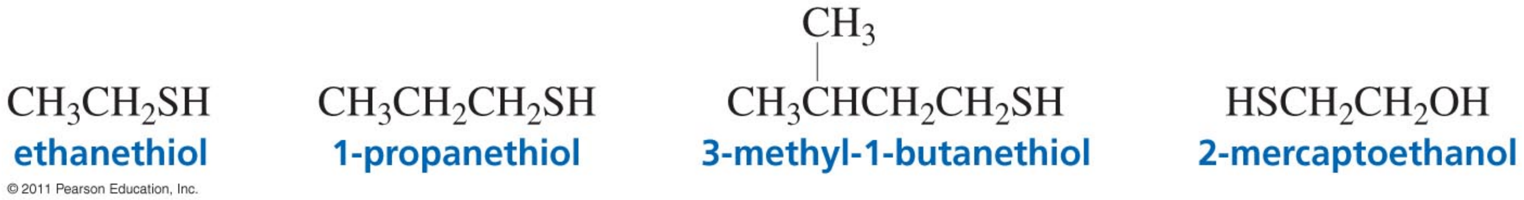


S Nu:

- RSH ~ thiol [mercaptan]



$2\,CH_3CH_2SH + Hg^{2+} \longrightarrow CH_3CH_2S{-}Hg{-}SCH_2CH_3 + 2\,H^+$



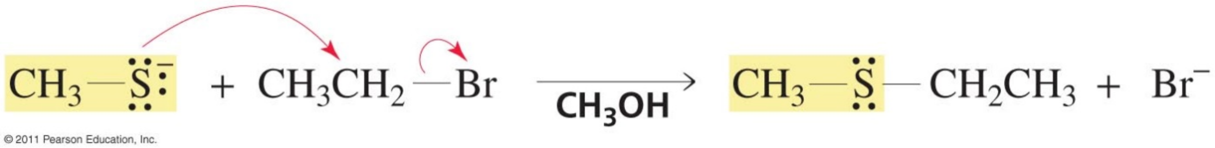
CH_3CH_2SH ethanethiol

$CH_3CH_2CH_2SH$ 1-propanethiol

$CH_3\underset{}{\overset{CH_3}{C}}HCH_2CH_2SH$ 3-methyl-1-butanethiol

$HSCH_2CH_2OH$ 2-mercaptoethanol

  - stronger acid than ROH (pK_a of 10 vs 15)
  - RS^- weaker B: than RO^-
    - better Nu: in protic solvent → more S_N1 and less E1 than RO^-

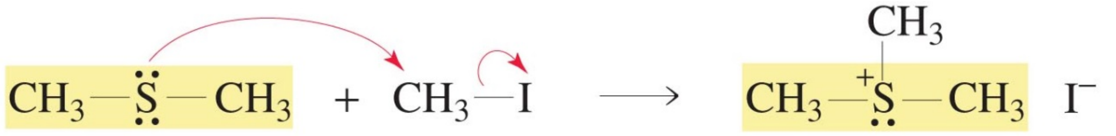


$CH_3{-}S^- + CH_3CH_2{-}Br \xrightarrow[CH_3OH]{} CH_3{-}S{-}CH_2CH_3 + Br^-$

- PR_3 is better Nu: than NR_3.

$Ph_3P: + CH_3{-}Br \xrightarrow{\text{benzene}} Ph_3\overset{+}{P}{-}CH_3\ Br^-\ (99\%)$

- RSR’ ~ thioether [sulfide]
  - (much) better Nu: than ROR’



$$CH_3-\ddot{S}-CH_3 + CH_3-I \longrightarrow CH_3-\overset{CH_3}{\overset{|}{\overset{+}{S}}}-CH_3 \quad I^-$$

dimethyl sulfide

trimethylsulfonium iodide
a sulfonium salt

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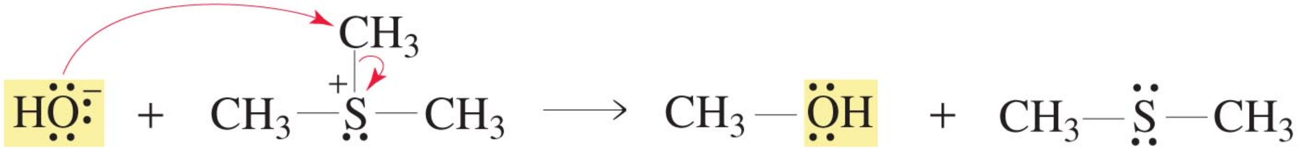
    - Ethers are not reactive to RX.
  - better LG than ROR’



$$H\ddot{O}:^- + CH_3-\overset{CH_3}{\overset{|}{\overset{+}{S}}}-CH_3 \longrightarrow CH_3-\ddot{O}H + CH_3-\ddot{S}-CH_3$$

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