



# Nucleophilic Substitution

Examples of nucleophilic substitution reactions

Nucleophile

Substrate

Leaving group

Table 6.1 ■ Reactions of Common Nucleophiles with Alkyl Halides (Eqs. 6.2 and 6.3)

Nu		R—Nu		Comments
Formula	Name	Formula	Name	
<b>Oxygen nucleophiles</b>				
1. $\text{H}\ddot{\text{O}}:^-$	hydroxide	$\text{R}-\ddot{\text{O}}\text{H}$	alcohol	
2. $\text{R}\ddot{\text{O}}:^-$	alkoxide	$\text{R}-\ddot{\text{O}}\text{R}$	ether	
3. $\text{H}\ddot{\text{O}}\text{H}$	water	$\text{R}-\overset{+}{\text{O}}\begin{matrix} \text{H} \\ \diagup \\ \text{H} \end{matrix}$	alkyloxonium ion	These ions lose a proton and the products are alcohols and ethers. $\xrightarrow{-\text{H}^+} \text{R}\ddot{\text{O}}\text{H}$ (alcohol) $\xrightarrow{-\text{H}^+} \text{R}\ddot{\text{O}}\text{R}$ (ether)
4. $\text{R}\ddot{\text{O}}\text{H}$	alcohol	$\text{R}-\overset{+}{\text{O}}\begin{matrix} \text{R} \\ \diagup \\ \text{H} \end{matrix}$	dialkyloxonium ion	
5. $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\ominus}{\text{O}}\ddot{\text{O}}$	carboxylate	$\text{R}-\overset{\text{O}}{\parallel}{\ddot{\text{O}}}\text{C}-\text{R}$	ester	
<b>Nitrogen nucleophiles</b>				
6. $\ddot{\text{N}}\text{H}_3$	ammonia	$\text{R}-\overset{+}{\text{N}}\text{H}_3$	alkylammonium ion	With a base, these ions readily lose a proton to give amines. $\xrightarrow{-\text{H}^+} \ddot{\text{N}}\text{H}_2$ $\xrightarrow{-\text{H}^+} \text{R}_2\ddot{\text{N}}\text{H}$ $\xrightarrow{-\text{H}^+} \text{R}_3\ddot{\text{N}}:$
7. $\text{R}\ddot{\text{N}}\text{H}_2$	primary amine	$\text{R}-\overset{+}{\text{N}}\text{H}_2\text{R}$	dialkylammonium ion	
8. $\text{R}_2\ddot{\text{N}}\text{H}$	secondary amine	$\text{R}-\overset{+}{\text{N}}\text{HR}_2$	trialkylammonium ion	
9. $\text{R}_3\ddot{\text{N}}$	tertiary amine	$\text{R}-\overset{+}{\text{N}}\text{R}_3$	tetraalkylammonium ion	

### ***Sulfur nucleophiles***

10.  $\text{H}\ddot{\text{S}}:^{-}$  hydrosulfide  $\text{R}-\ddot{\text{S}}\text{H}$  thiol
11.  $\text{R}\ddot{\text{S}}:^{-}$  mercaptide  $\text{R}-\ddot{\text{S}}\text{R}$  thioether (sulfide)
12.  $\text{R}_2\ddot{\text{S}}:$  thioether  $\text{R}-\overset{+}{\text{S}}\text{R}_2$  trialkylsulfonium ion

### ***Halogen nucleophiles***

13.  $:\ddot{\text{I}}:^{-}$  iodide  $\text{R}-\ddot{\text{I}}:$  alkyl iodide

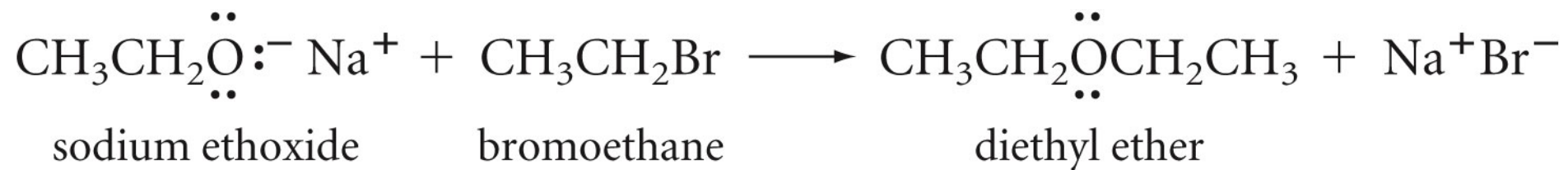
The usual solvent is acetone. Sodium iodide is soluble in acetone, but sodium bromide and sodium chloride are not.

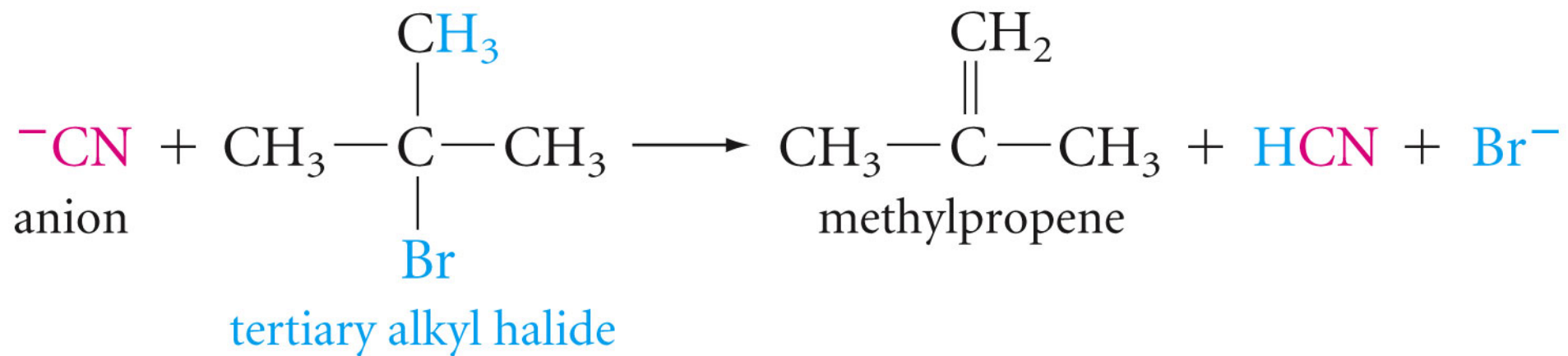
### ***Carbon nucleophiles***

14.  $^{-}:\text{C}\equiv\text{N}:$  cyanide  $\text{R}-\text{C}\equiv\text{N}:$  alkyl cyanide (nitrile)
15.  $^{-}:\text{C}\equiv\text{CR}$  acetylide  $\text{R}-\text{C}\equiv\text{CR}$  alkyne

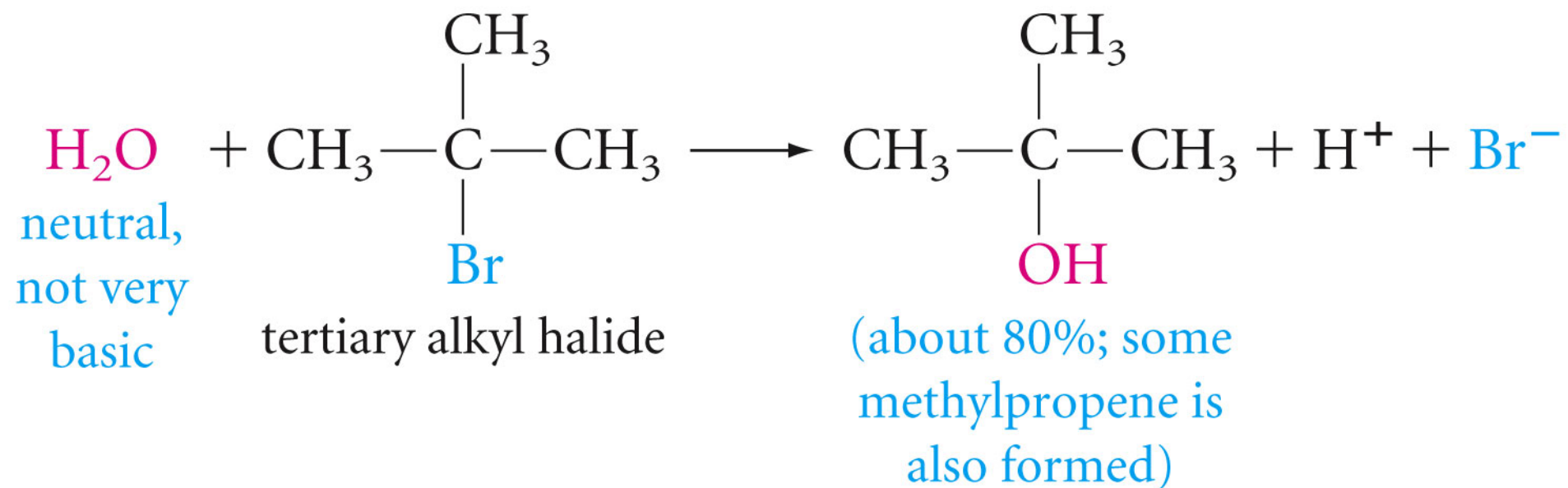
Sometimes the isonitrile,  $\text{R}-\overset{+}{\text{N}}\equiv\overset{-}{\text{C}}:$ , is formed.

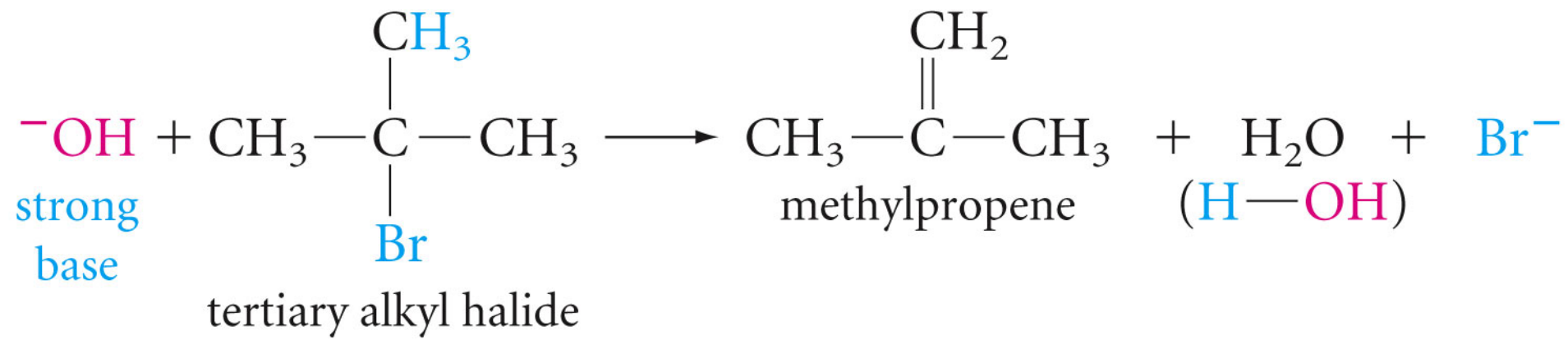
## Reaction of sodium ethoxide with bromoethane







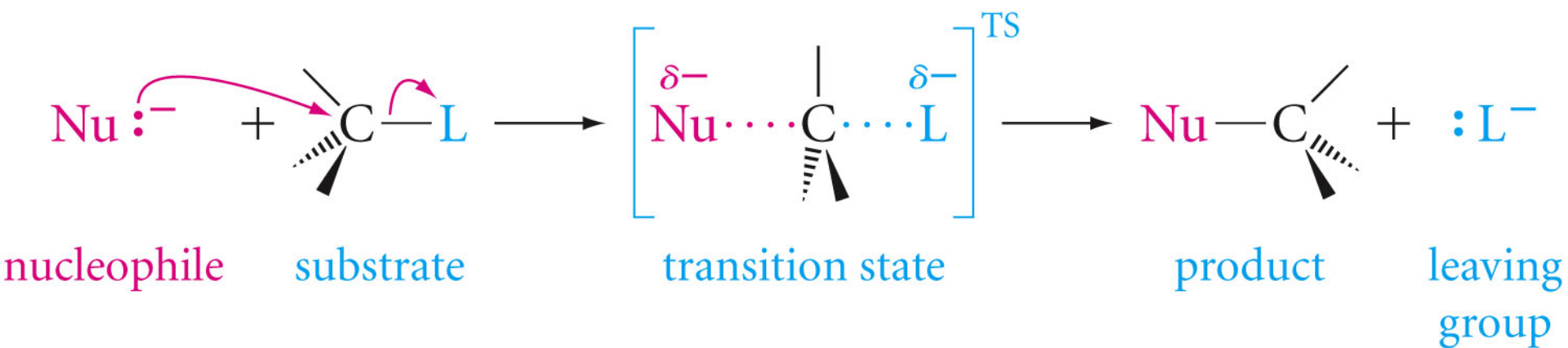


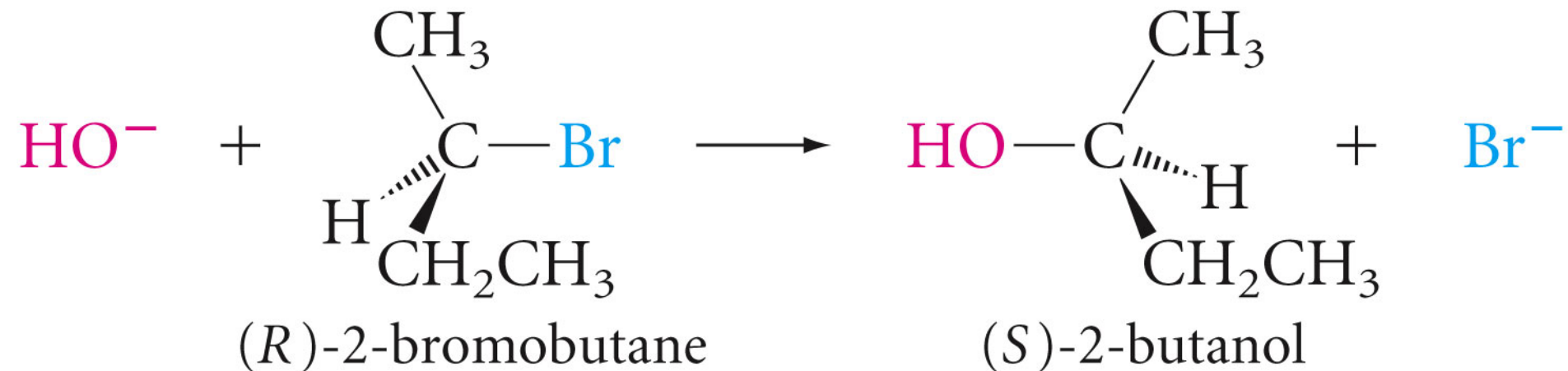




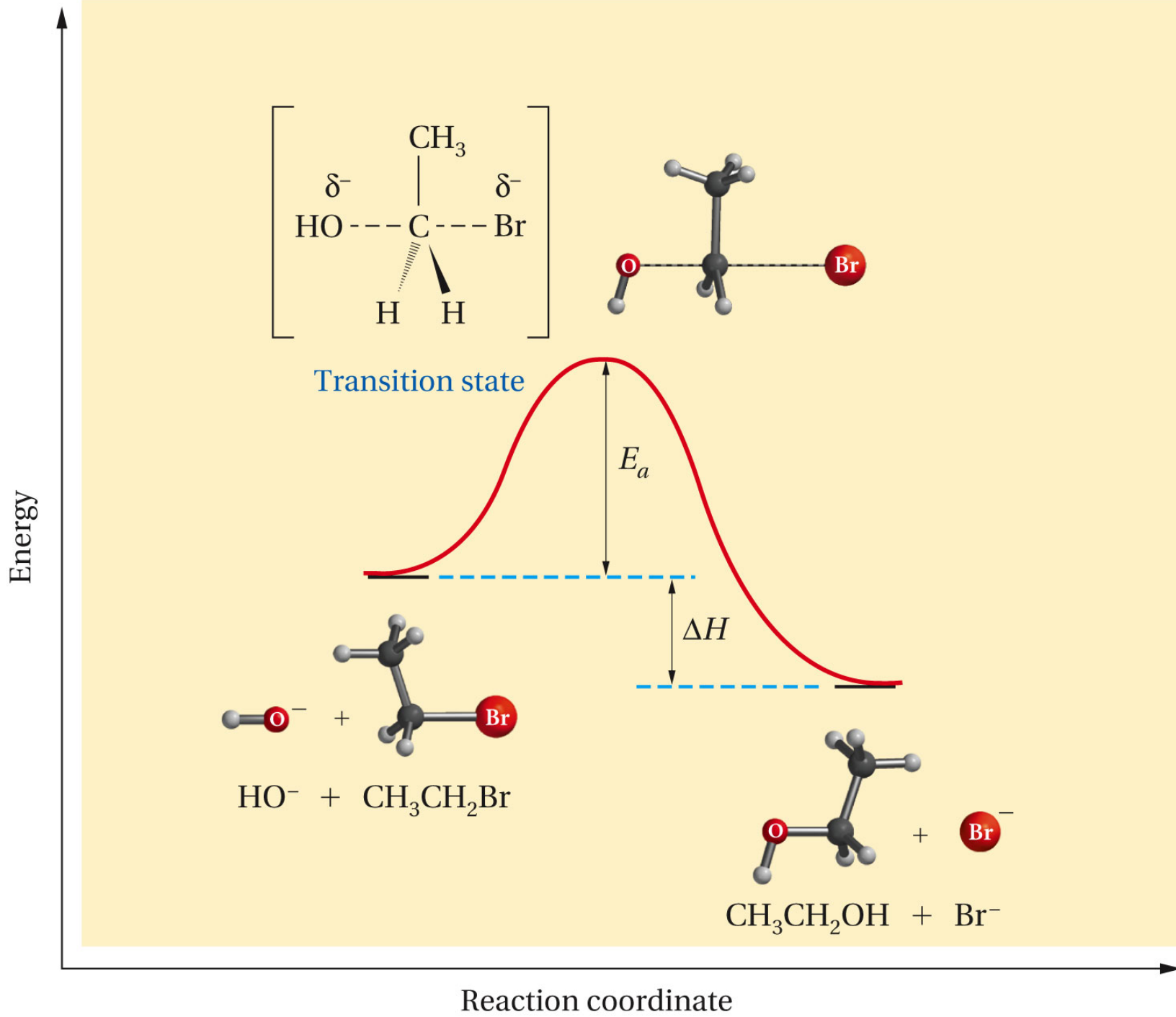
# Nucleophilic Substitution Mechanism

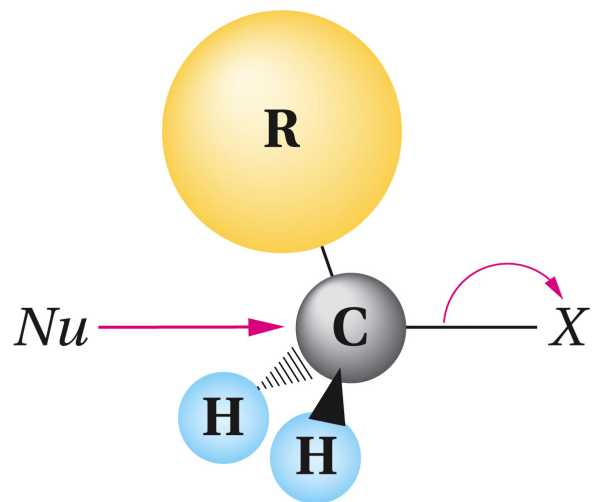
## $S_N2$ Mechanism



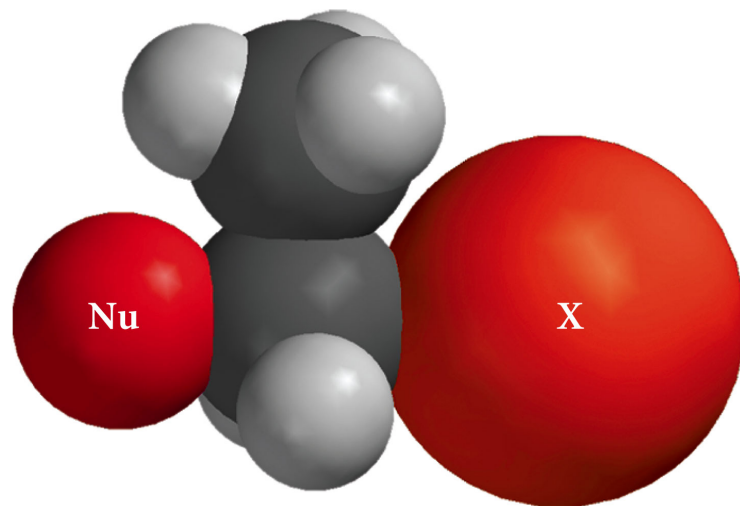


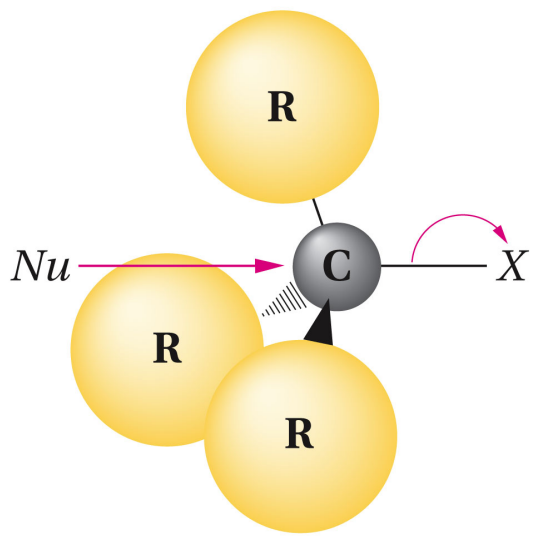
$S_N2$  displacement reactions occurs with inversion of configuration. For example, if we treat *(R)*-2-bromobutane with sodium hydroxide, we obtain *(S)*-2-butanol



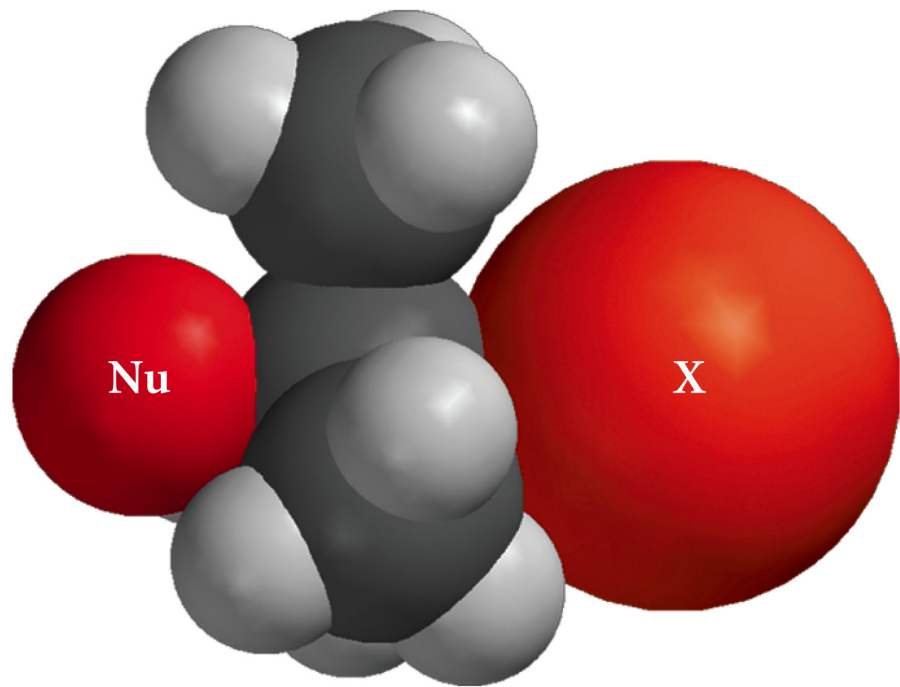


primary alkyl halide  
(rear side not crowded;  $S_N2$  fast)



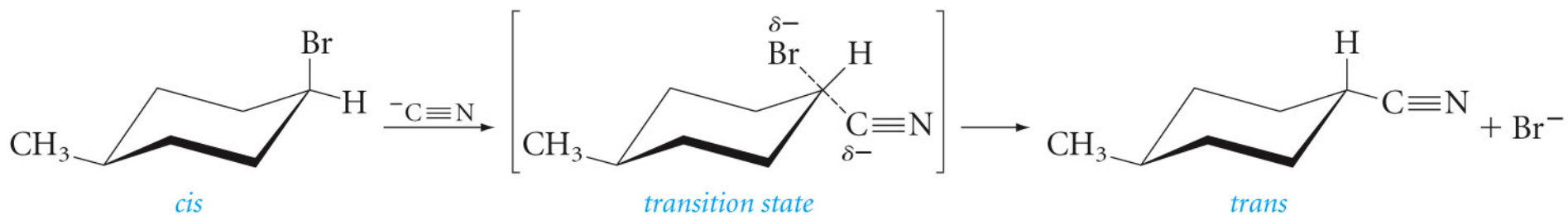


tertiary alkyl halide  
(rear side crowded;  $S_N2$  slow or impossible)

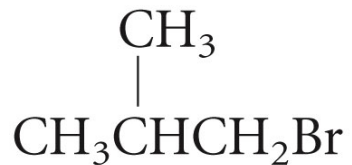
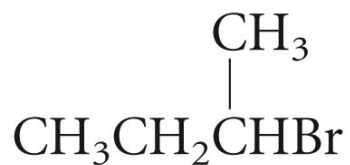


## Example;

Predict the product of the  $S_N2$  reaction of *cis*-4-methylcyclohexyl bromide with cyanide ion

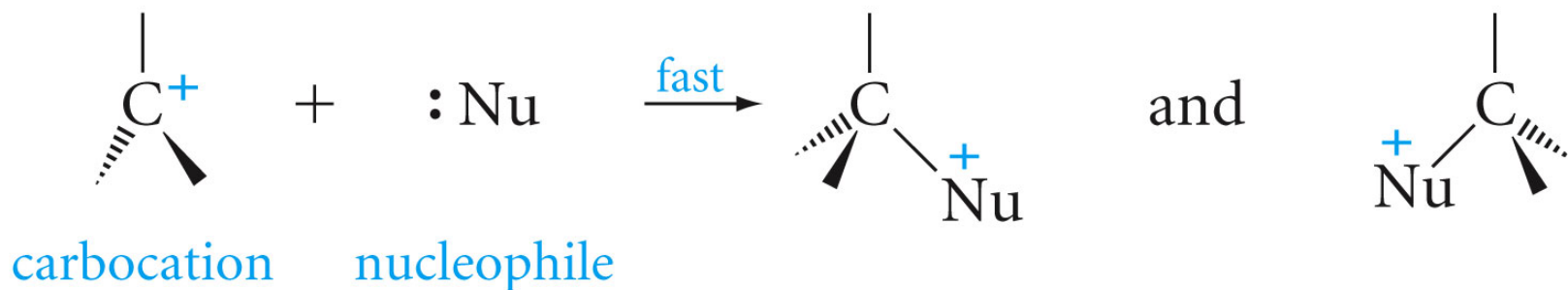
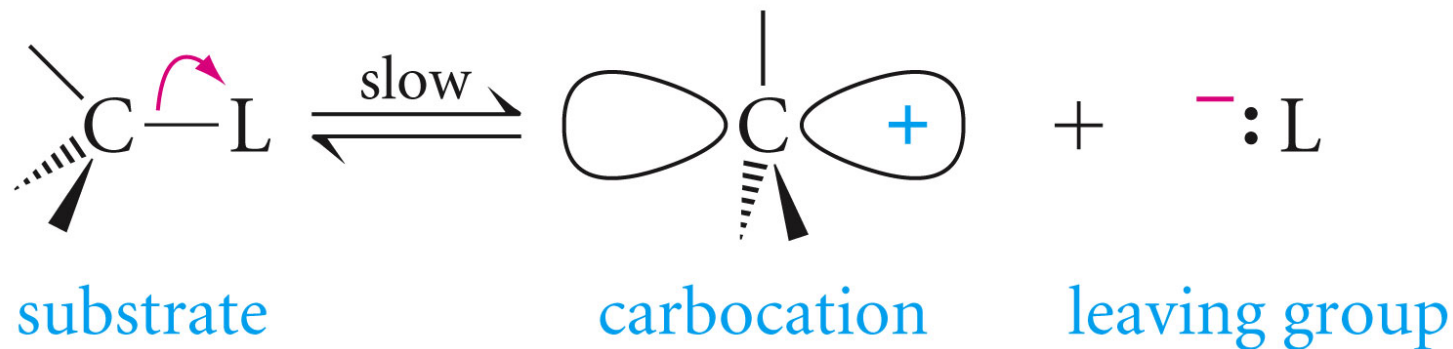


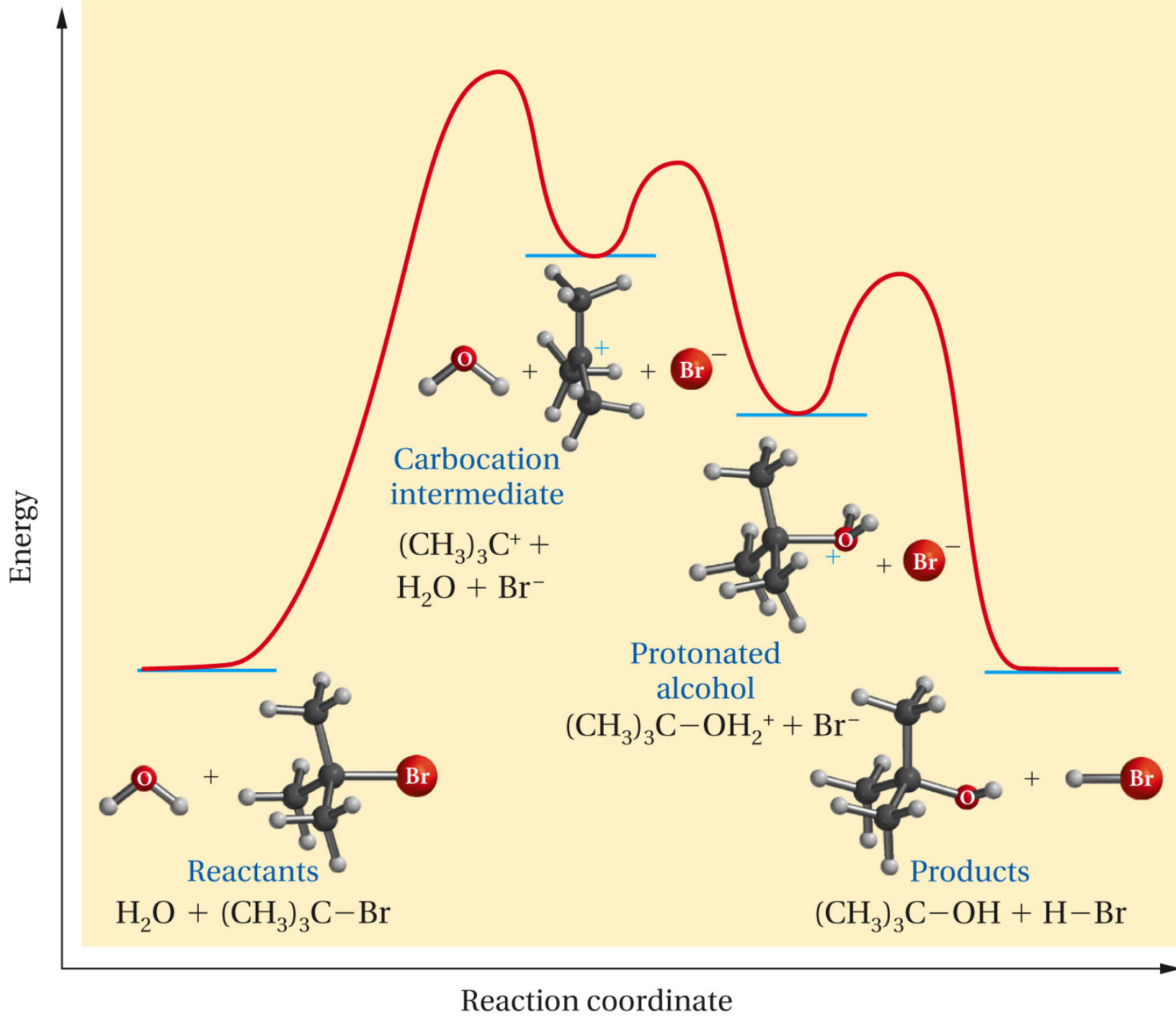
Arrange the following compounds in order of decreasing S<sub>N</sub>2 reactivity toward sodium ethoxide

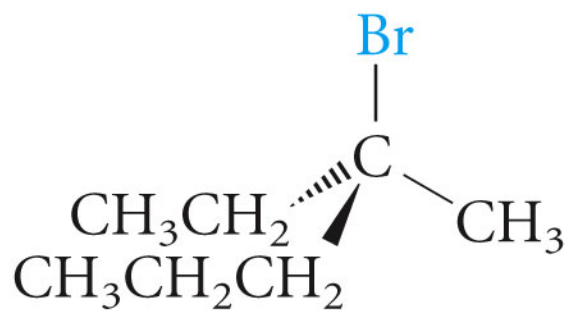




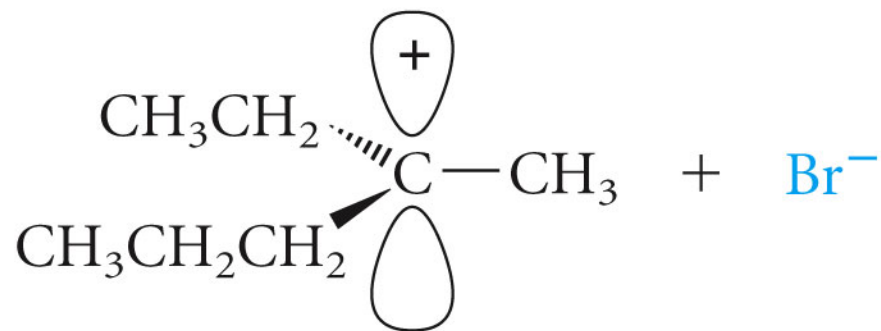
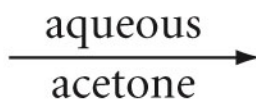
# The S<sub>N</sub>1 Mechanism





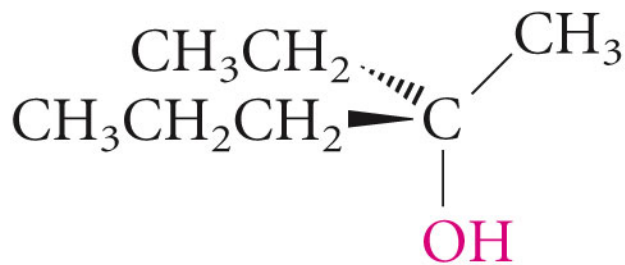


*(R)*-3-bromo-3-methylhexane



carbocation intermediate

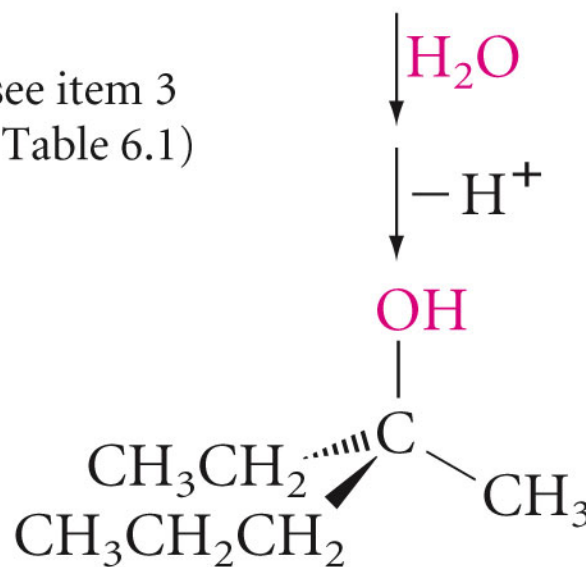
(see item 3  
in Table 6.1)



50% *S*

(product from attack on the  
bottom face of the carbocation)

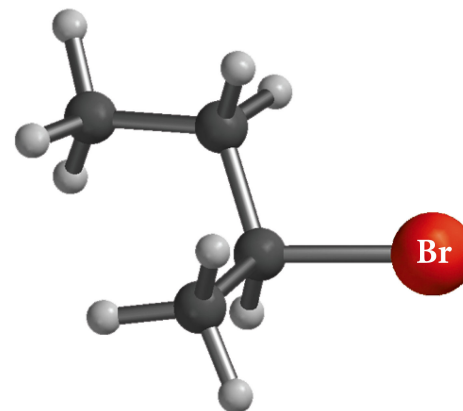
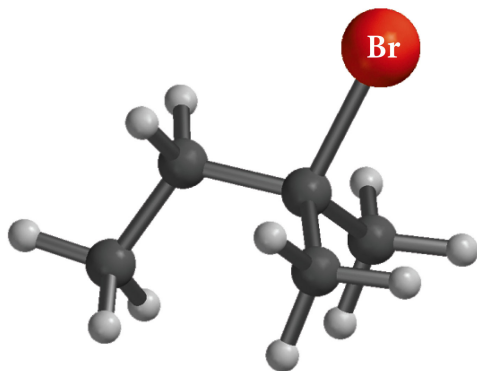
+



50% *R*

(product from attack on the  
top face of the carbocation)

Which of the following bromides will react faster with methanol (via  $S_N1$  reaction)? and what are the reaction products in each case.



**Table 6.2** ■ Comparison of S<sub>N</sub>2 and S<sub>N</sub>1 Substitutions

<b>Variables</b>	<b>S<sub>N</sub>2</b>	<b>S<sub>N</sub>1</b>
<b>Halide structure</b>		
Primary or CH <sub>3</sub>	Common	Rarely*
Secondary	Sometimes	Sometimes
Tertiary	Rarely	Common
<b>Stereochemistry</b>	Inversion	Racemization
<b>Solvent</b>	Rate is retarded by polar protic solvents and increased by polar aprotic solvents	Because the intermediates are ions, the rate is increased by polar solvents
<b>Nucleophile</b>	Rate depends on nucleophile concentration; mechanism is favored when the nucleophile is an anion	Rate is independent of nucleophile concentration; mechanism is more likely with neutral nucleophiles

\*Allyl and benzyl substrates are the common exceptions (see Problem 6.7b).

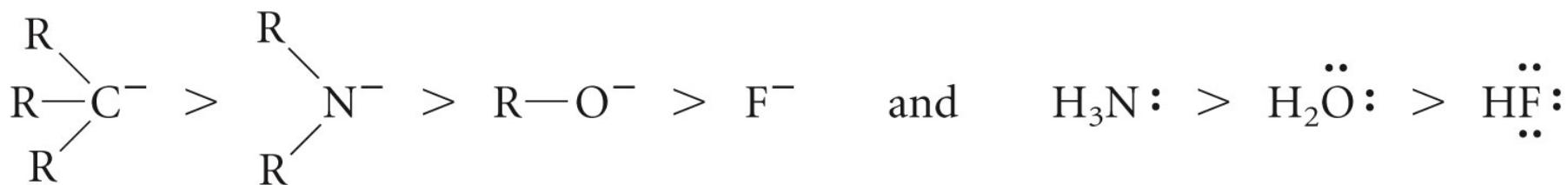
1. Negative ions are more nucleophilic, or better suppliers, than the corresponding neutral molecules.



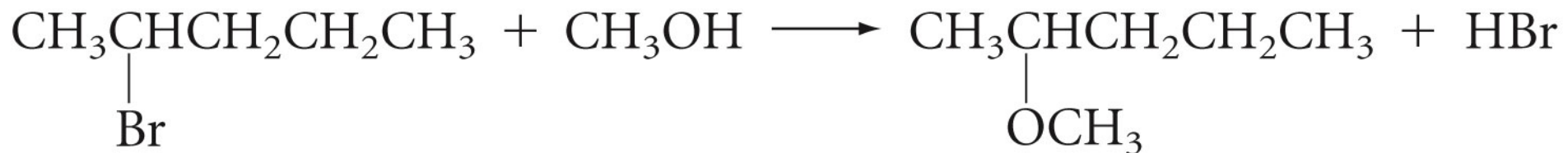
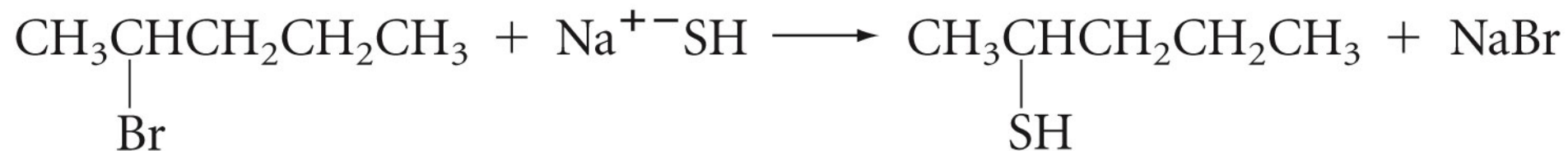
2. Elements low in the periodic table tend to be more nucleophilic than elements above them in the same column



3. Across a row in the periodic table, more electronegative elements (the more tightly an element holds electron to itself) tend to be less nucleophilic.

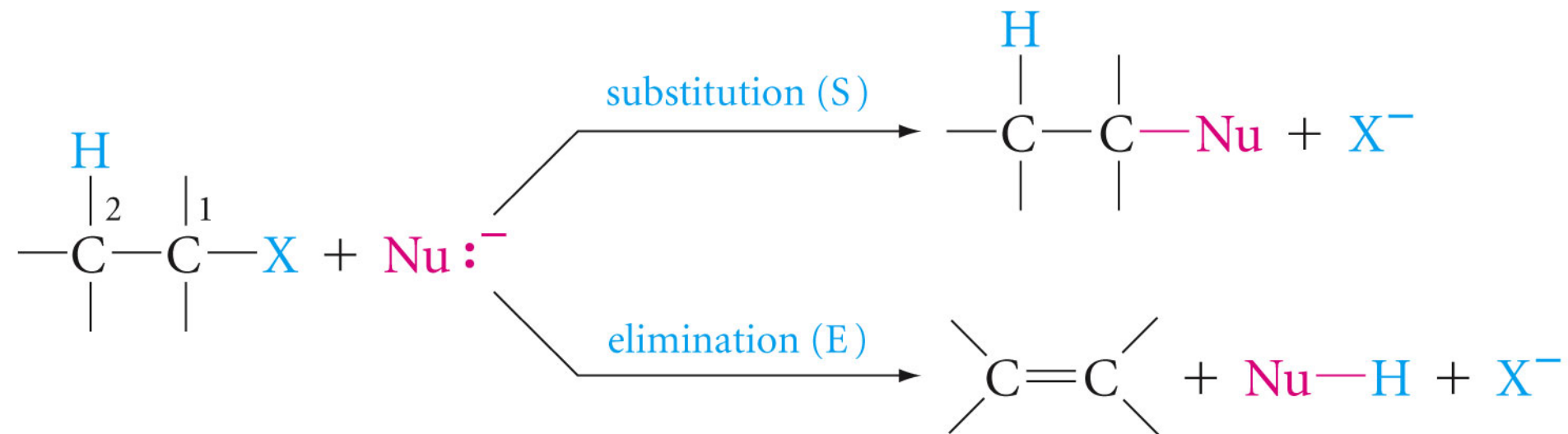


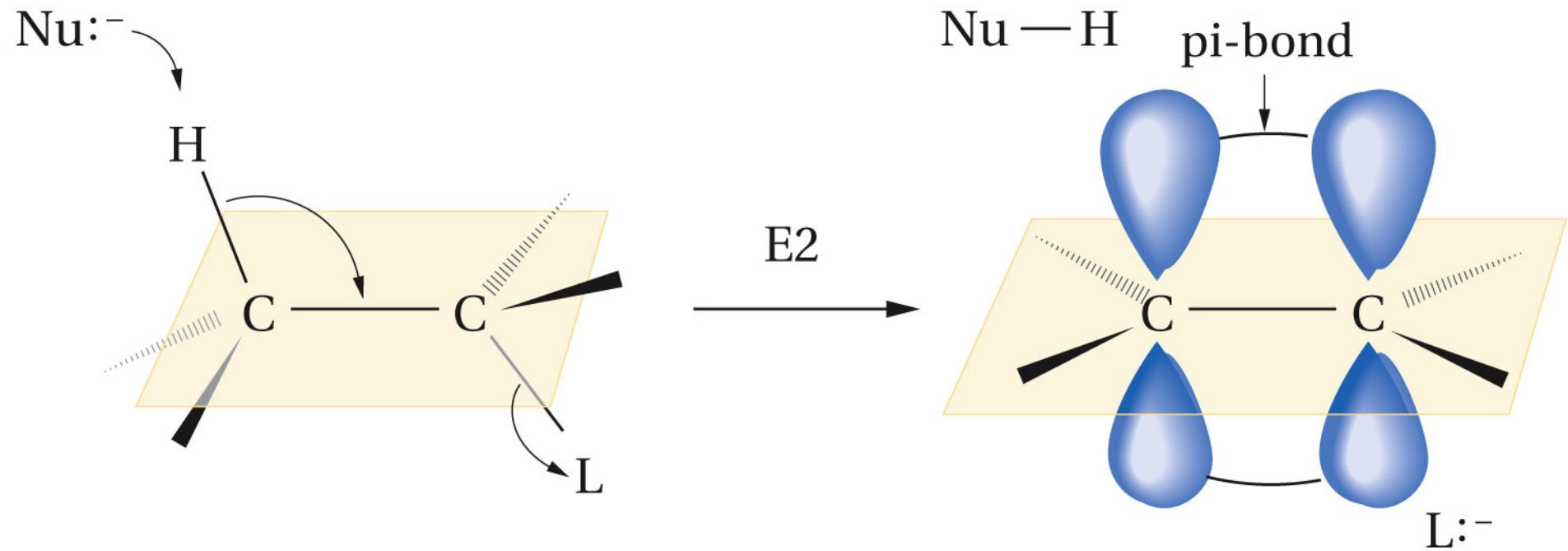
Which mechanism, S<sub>N</sub>1 or S<sub>N</sub>2, would you predict for each of the following reactions?



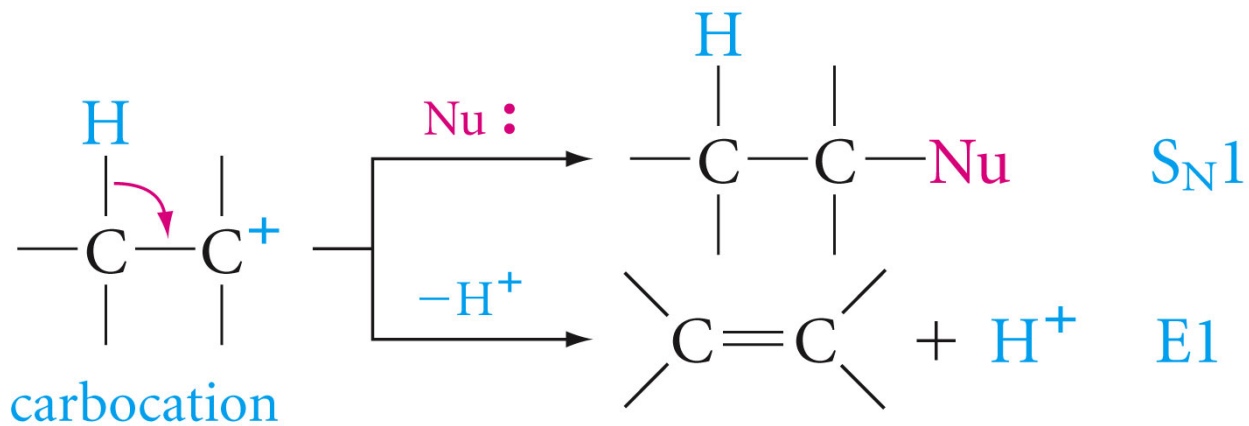
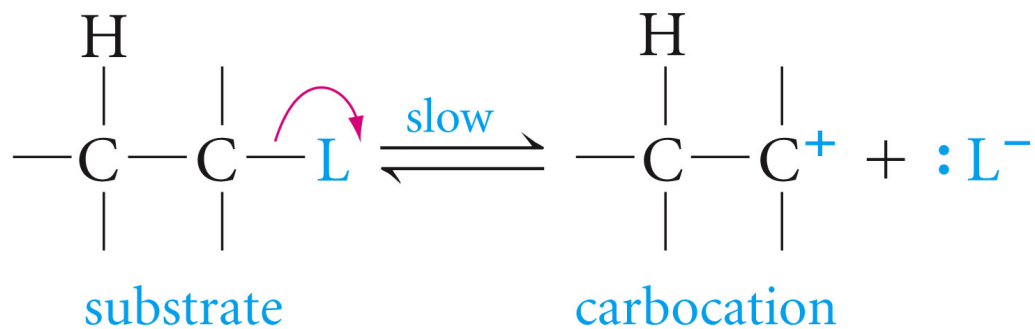


# Dehydrohalogenation, and Elimination Reaction; The E2 and E1 Mechanisms



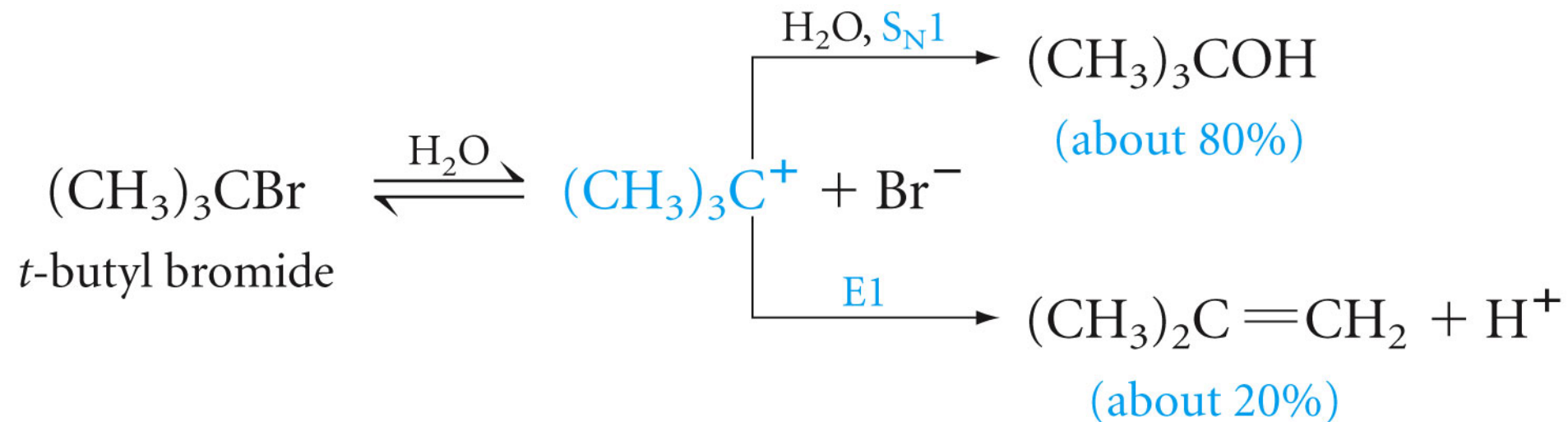


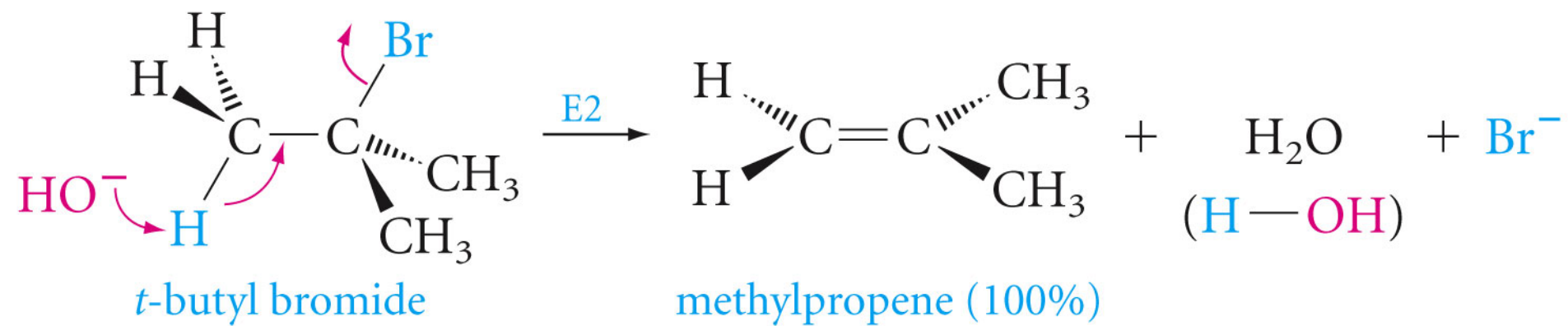
# E1 mechanism



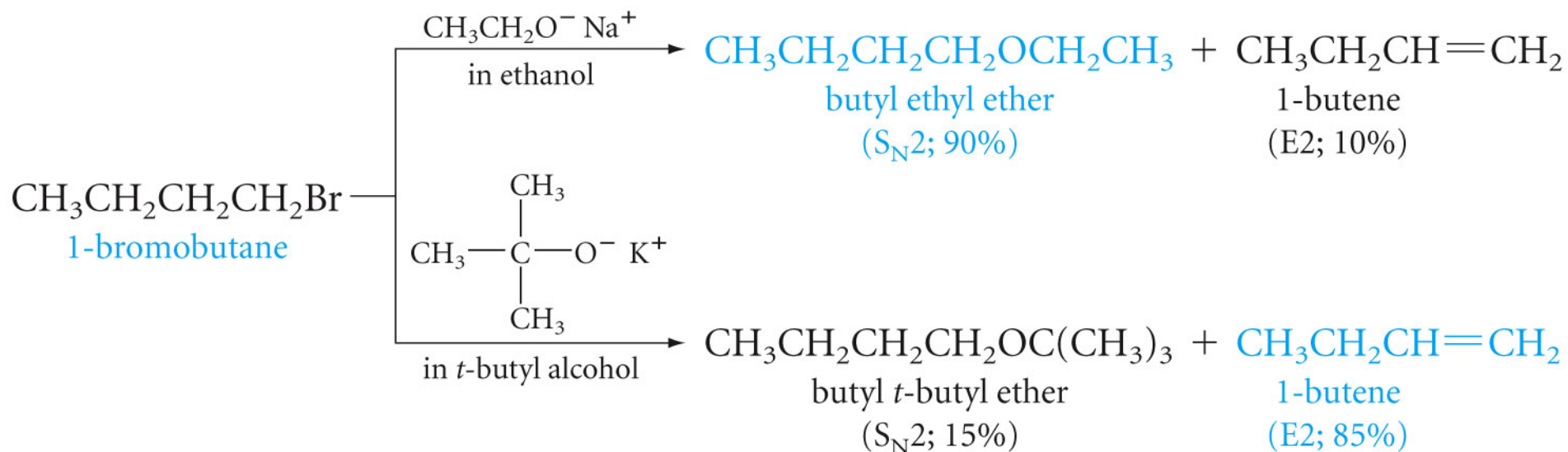
# Substitution and Elimination in Competition

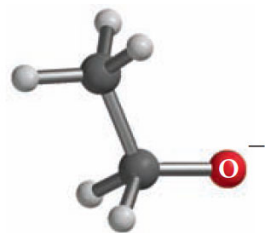
## Tertiary Halides



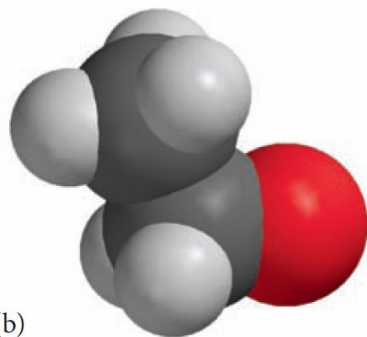


## Primary Halides



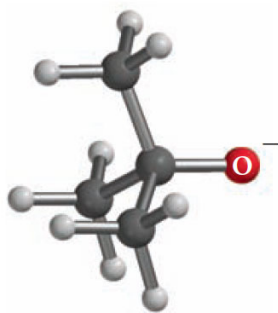


(a)

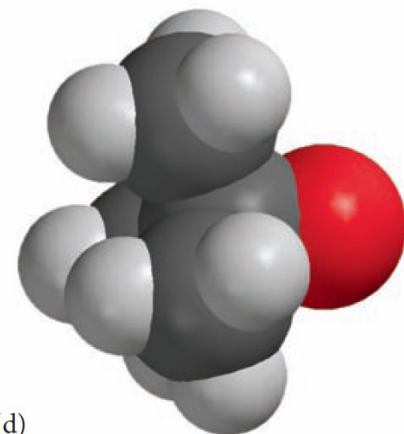


(b)

**Ethoxide**



(c)

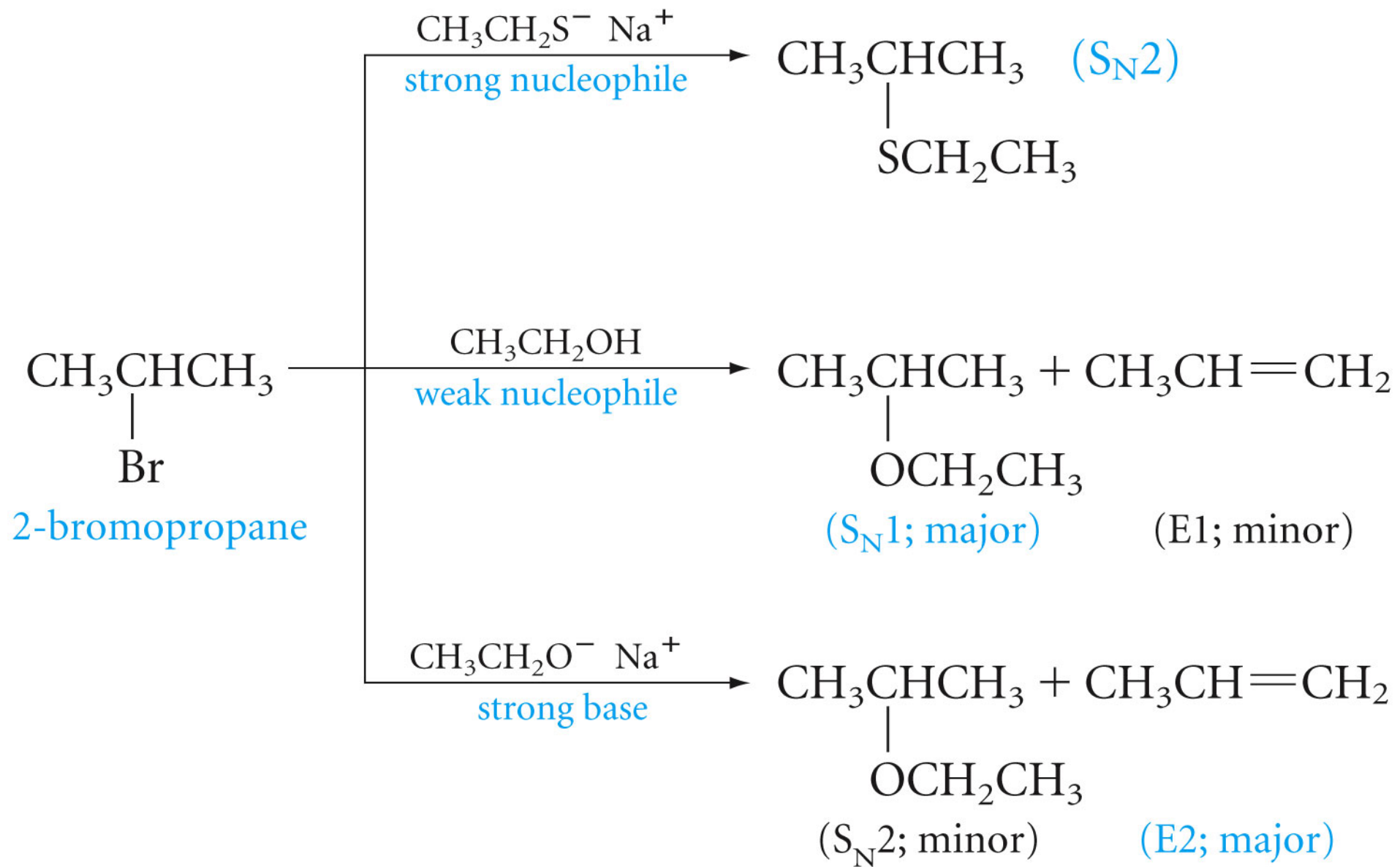


(d)

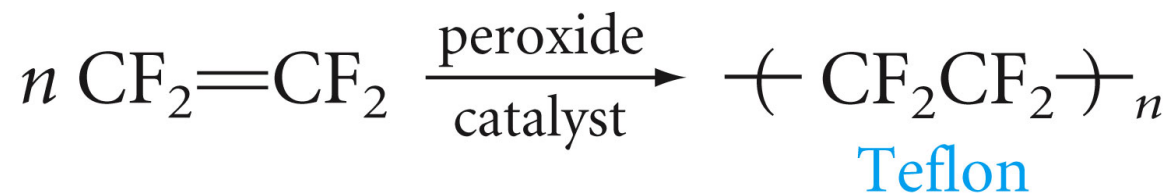
*t*-butoxide



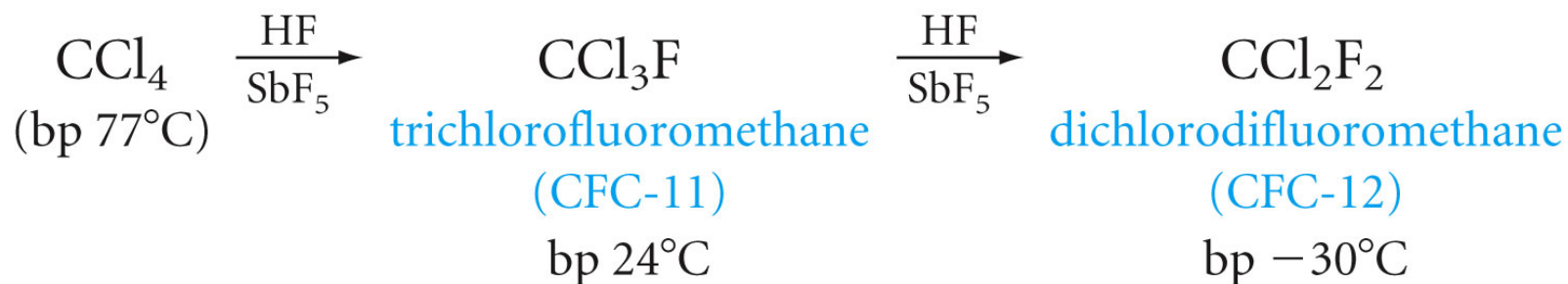
# Secondary Halides



# Polyhalogenated Aliphatic Compounds



# Chlorofluorocarbons (CFCs aka Freons)



# Halons



Bromochlorodifluoromethane  
(Halon-1211)



Bromotrifluoromethane  
Halon-1301