

# **Introduction to Organic Reactions**

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Most organic reactions can be classified into one of five categories:

- 1. Additions reactions**
- 2. Substitution reactions**
- 3. Elimination reactions**
- 4. Rearrangement reactions**
- 5. Oxidation-reduction reactions**

# Overview of Types of Organic Reactions

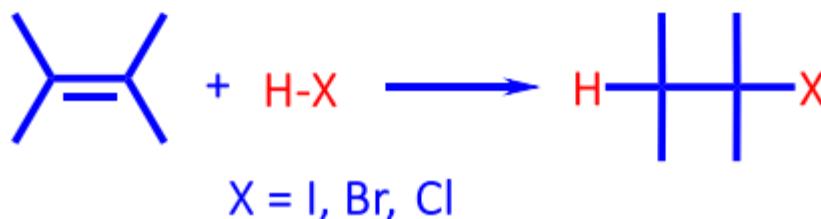
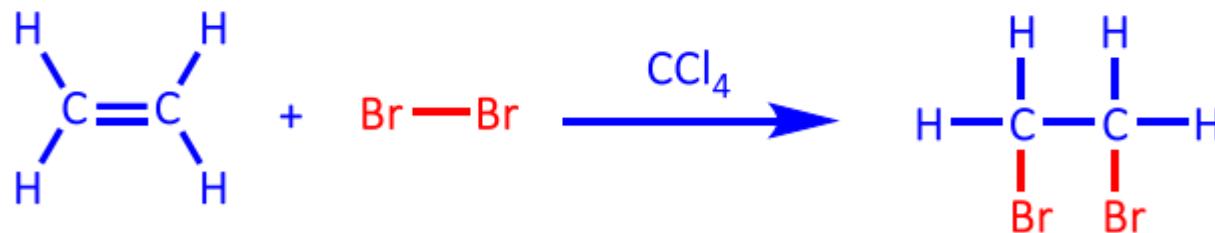
## I. Addition Reactions

Addition reactions occur when two starting materials add together to form only one product with no atoms left over.

$$A + B \longrightarrow A-B$$

In an addition all parts of the adding reagent appear in the product; two molecules become one.

Examples



# Overview of Types of Organic Reactions

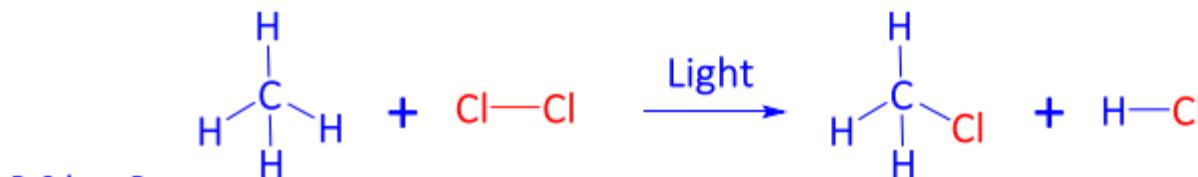
## II. Substitution Reactions

Substitution reactions occur when two starting materials exchange groups to form two new products.



In a substitution, one group replaces another.

Examples



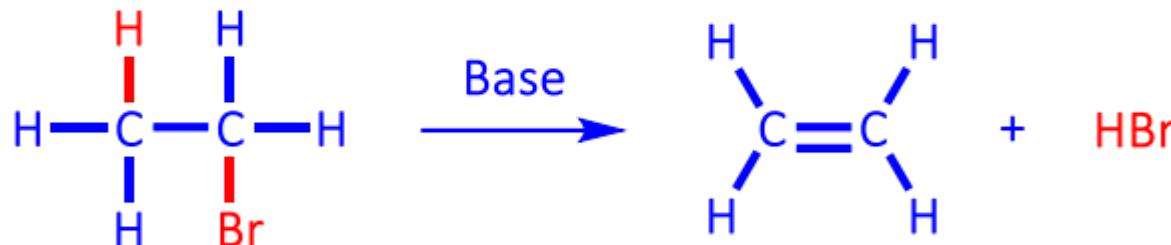
# Overview of Types of Organic Reactions

## III. Elimination Reactions

Elimination reactions are the opposite of addition reactions.



A single reactant is split into two products.



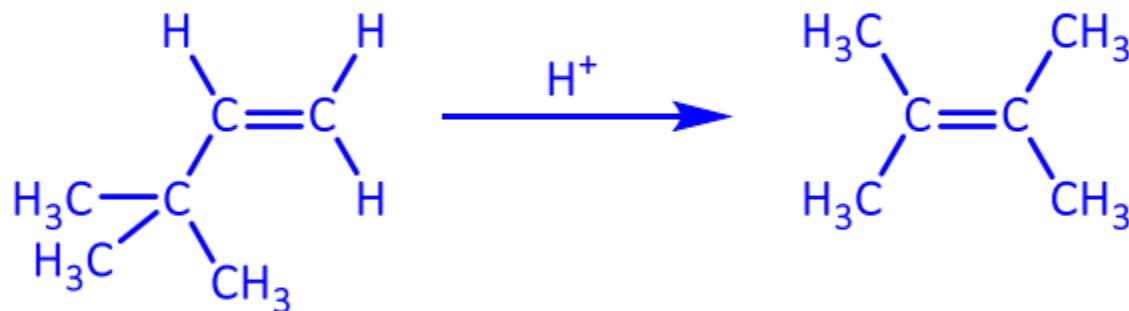
Elimination reactions give us a method for preparing compounds with double and triple bonds.

Two  $\sigma$  bonds are broken, and a  $\pi$  bond is formed between adjacent atoms.

# Overview of Types of Organic Reactions

## IV. Rearrangement Reactions

Rearrangement reactions occur when one starting material forms one product with a different arrangement of atoms and bonds.



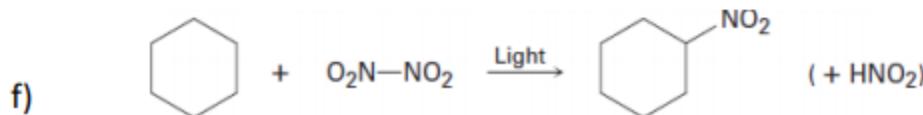
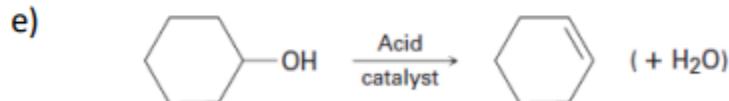
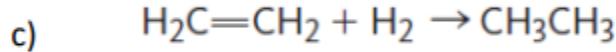
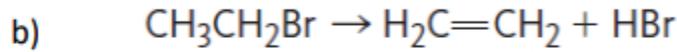
The product is an isomer of the starting material.

We have so far seen the different types of organic reactions, let's now see how reactions occur.

# Overview of Types of Organic Reactions

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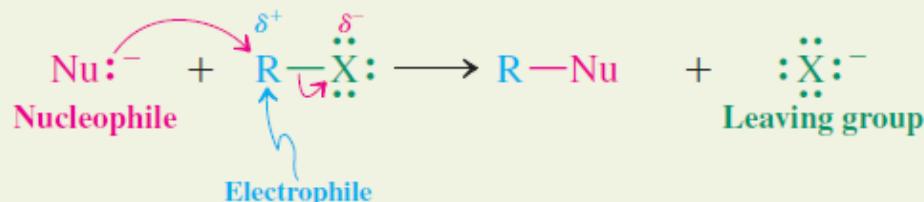
Classify each of the following reactions as addition, elimination, substitution or rearrangement



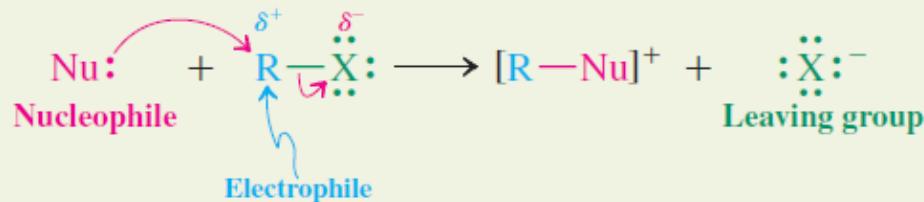
# Substitution reactions

## Nucleophilic Substitutions

Negative nucleophile  
gives neutral product



Neutral nucleophile  
gives positively  
charged product  
(as a salt)



# Substitution reactions

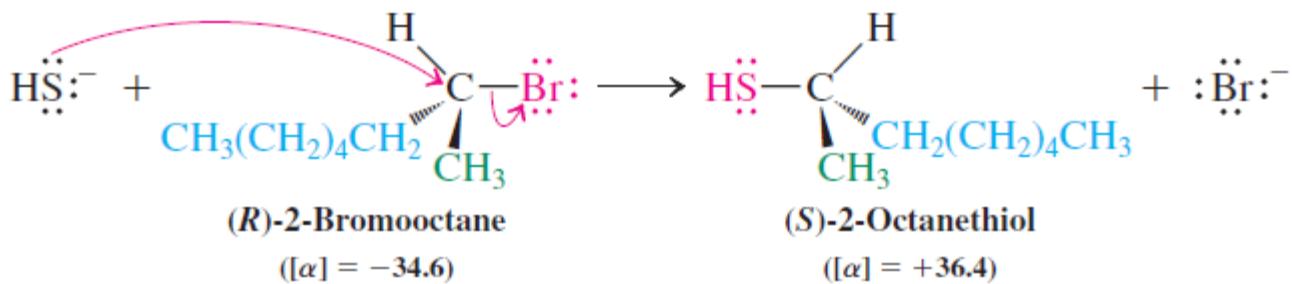
## Nucleophilic Substitution reactions

Mechanisms:

$S_N2$  reaction

$S_N1$  reaction

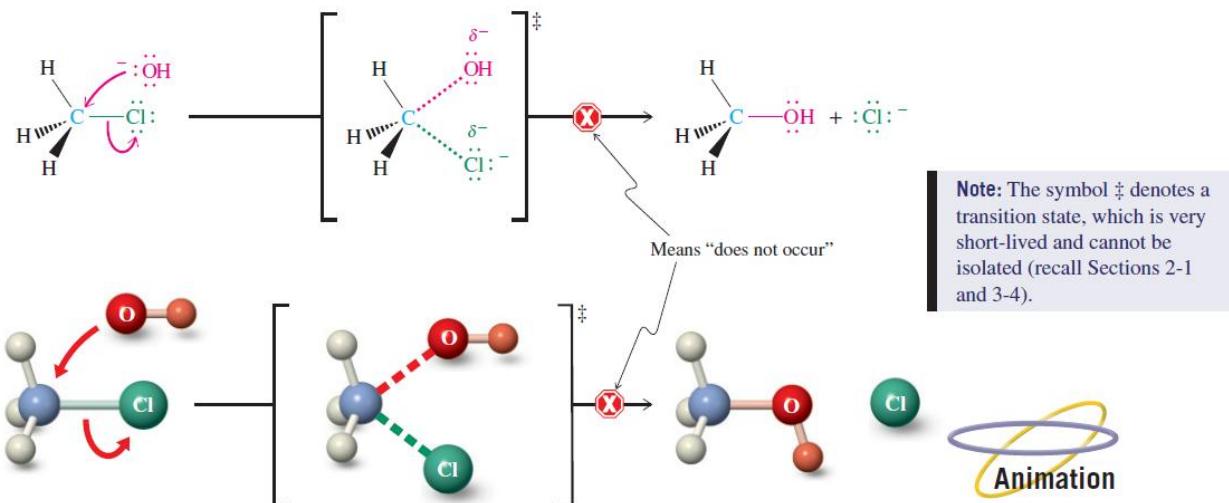
### $S_N2$ reaction



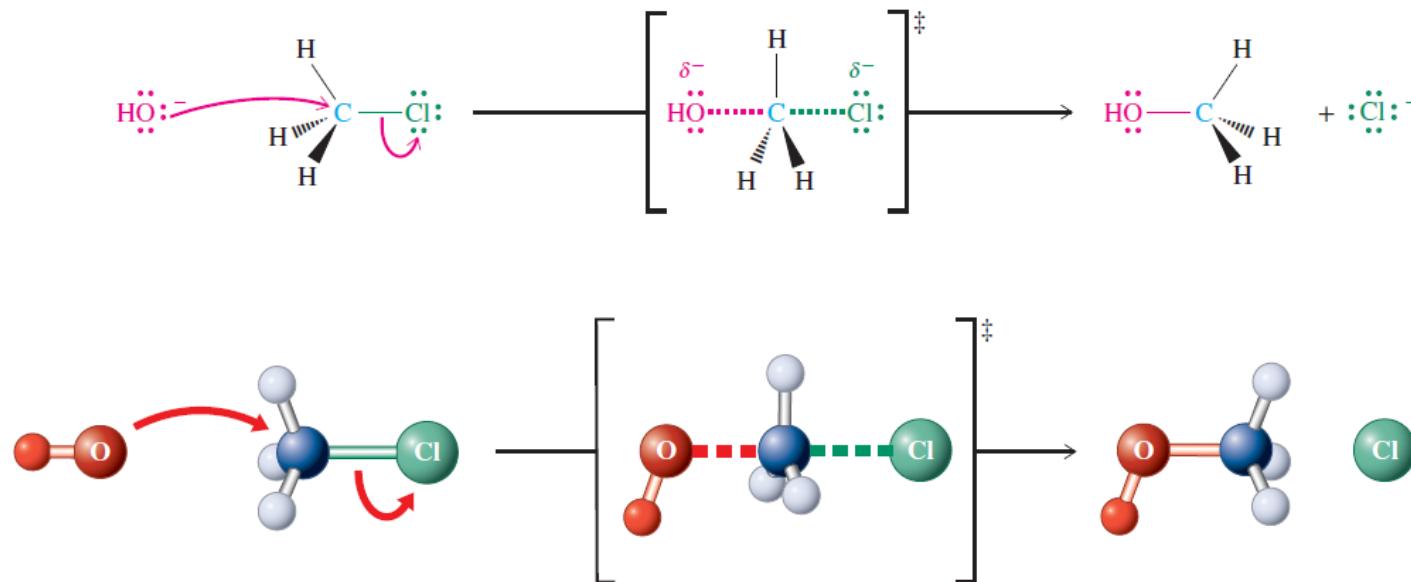
# Substitution reactions

Reaction number	Substrate	Nucleophile	Product	Leaving group
1.	$\text{CH}_3\ddot{\text{Cl}}:$ Chloromethane	$\text{HO}^-$	$\text{CH}_3\ddot{\text{O}}\text{H}$ Methanol	$\text{:Cl}^-$
2.	$\text{CH}_3\text{CH}_2\ddot{\text{I}}:$ Iodoethane	$\text{CH}_3\ddot{\text{O}}^-$	$\text{CH}_3\text{CH}_2\ddot{\text{O}}\text{CH}_3$ Methoxyethane	$\text{:I}^-$
3.	$\begin{array}{c} \text{H} \\   \\ \text{CH}_3\text{CCH}_2\text{CH}_3 \\   \\ :\text{Br}: \end{array}$ 2-Bromobutane	$\text{:I}^-$	$\begin{array}{c} \text{H} \\   \\ \text{CH}_3\text{CCH}_2\text{CH}_3 \\   \\ :\text{I}: \end{array}$ 2-Iodobutane	$\text{:Br}^-$
4.	$\begin{array}{c} \text{H} \\   \\ \text{CH}_3\text{CCH}_2\ddot{\text{I}}: \\   \\ \text{CH}_3 \end{array}$ 1-Iodo-2-methylpropane	$:\text{N}\equiv\text{C}^-$	$\begin{array}{c} \text{H} \\   \\ \text{CH}_3\text{CCH}_2\text{C}\equiv\text{N:} \\   \\ \text{CH}_3 \end{array}$ 3-Methylbutanenitrile	$\text{:I}^-$
5.	$\text{C}_6\text{H}_{11}\ddot{\text{Br}}$ Bromocyclohexane	$\text{CH}_3\ddot{\text{S}}^-$	$\text{C}_6\text{H}_{11}\ddot{\text{SCH}}_3$ Methylthiocyclohexane	$\text{:Br}^-$
6.	$\text{CH}_3\text{CH}_2\ddot{\text{I}}:$ Iodoethane	$:\text{NH}_3$	$\text{CH}_3\text{CH}_2^+\text{NH}_3$ Ethylammonium iodide	$\text{:I}^-$
7.	$\text{CH}_3\ddot{\text{Br}}$ Bromomethane	$:\text{P}(\text{CH}_3)_3$	$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3\text{P}^+(\text{CH}_3)_3 \\   \\ \text{CH}_3 \end{array}$ Tetramethylphosphonium bromide	$\text{:Br}^-$

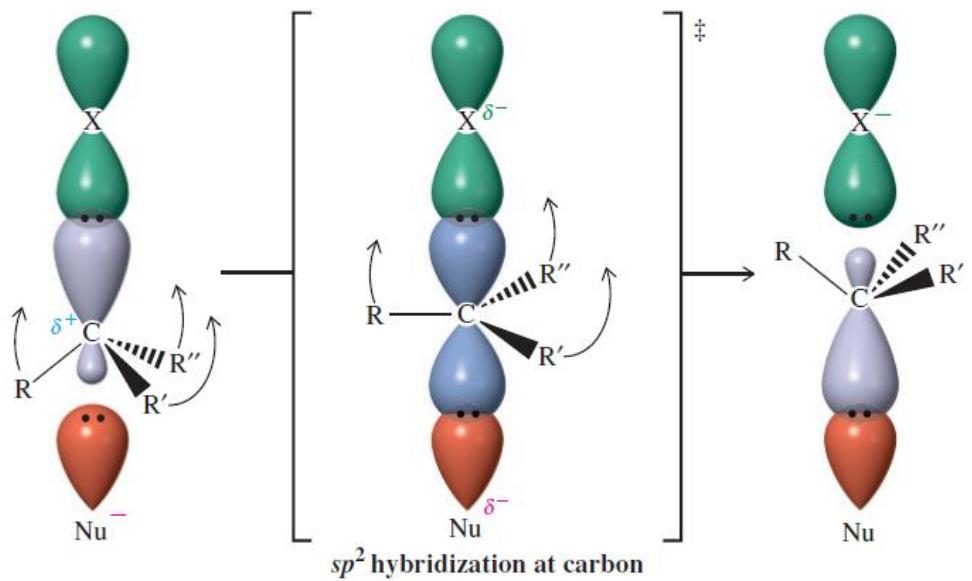
# Substitution reaction Mechanism – S<sub>N</sub>2 reaction



Bimolecular nucleophilic substitution is a concerted, one-step process

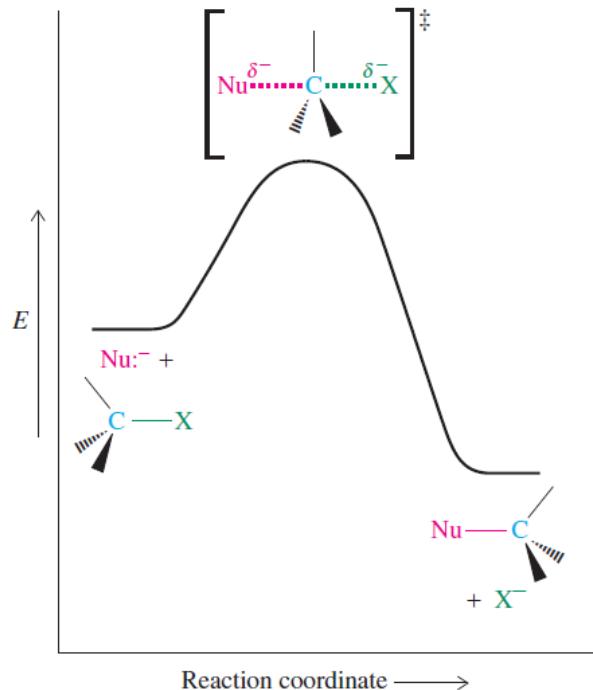


# Transition state - $S_N2$ reaction



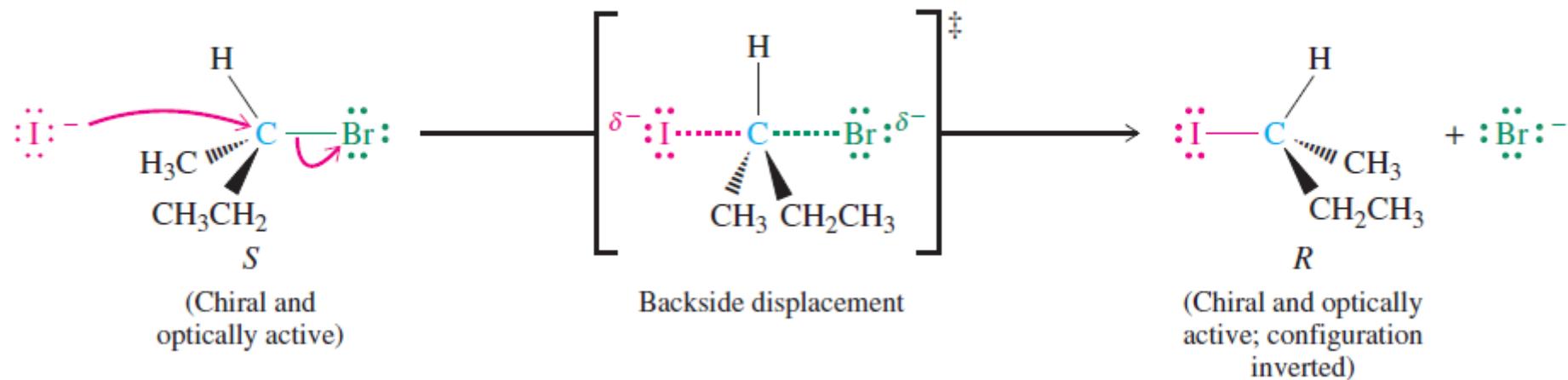
Orbital description of backside attack in the  $S_N2$  reaction.

Potential energy diagram for an  $S_N2$  reaction. The process takes place in a single step, with a single transition state.

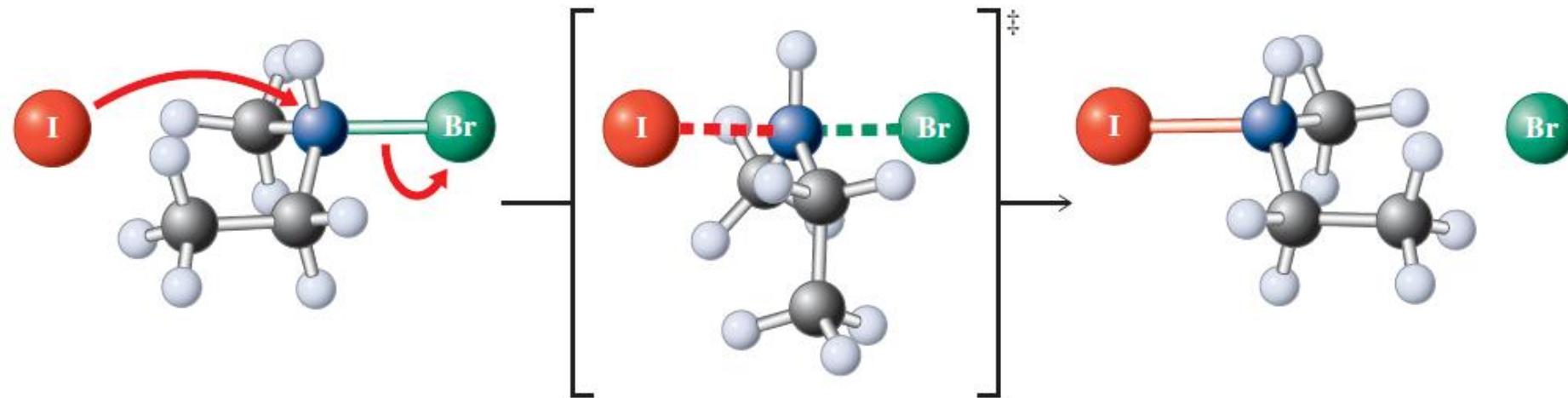


# Substitution reactions - S<sub>N</sub>2 reaction

Stereochemistry of the Backside Displacement Mechanism for S<sub>N</sub>2 Reactions

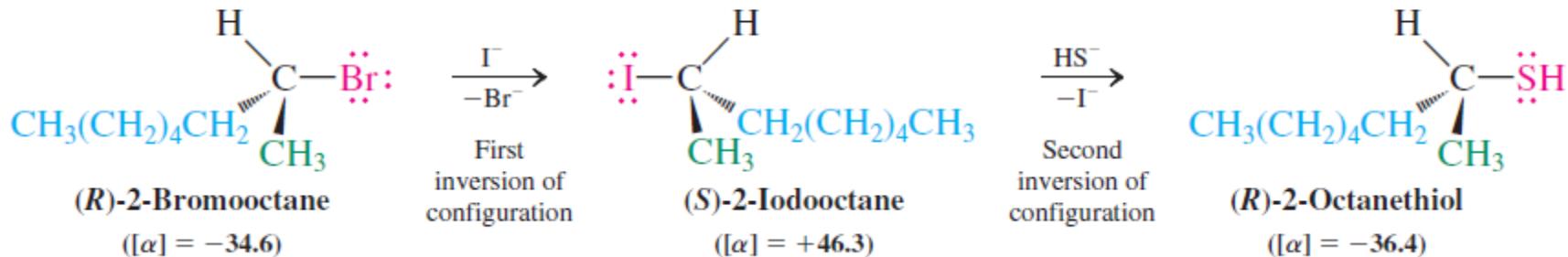


The S<sub>N</sub>2 reaction is stereospecific

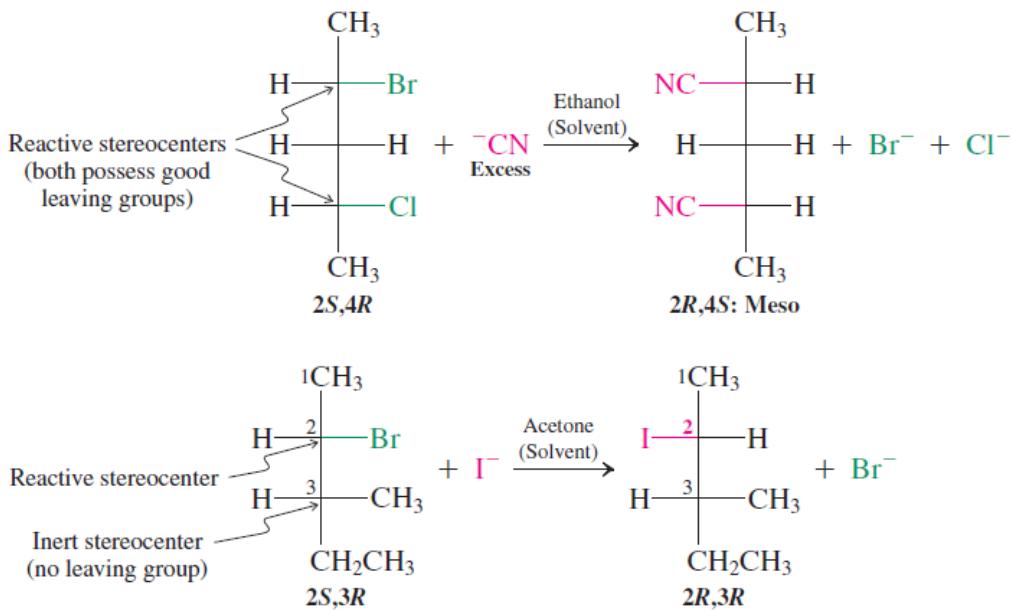


# Substitution reactions - S<sub>N</sub>2 reaction

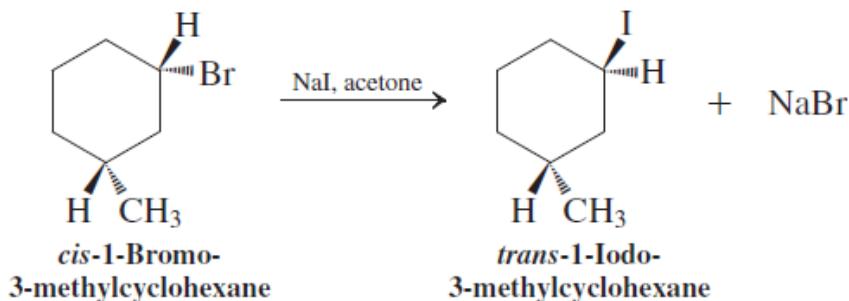
Using Double Inversion to Give Net Retention of Configuration



## S<sub>N</sub>2 Reactions of Molecules with Two Stereocenters



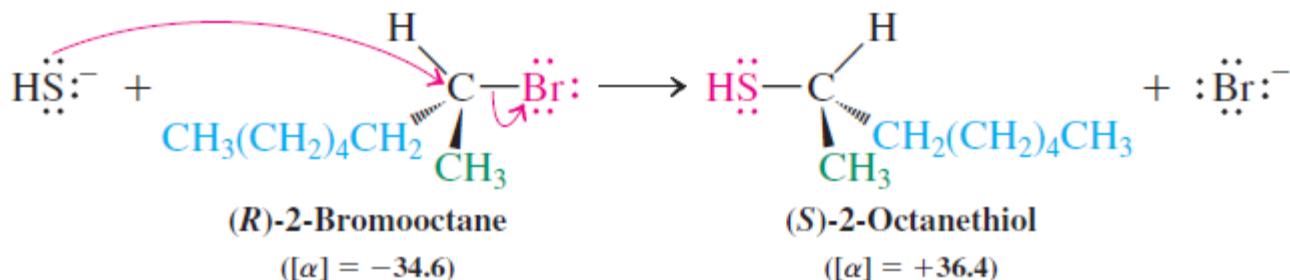
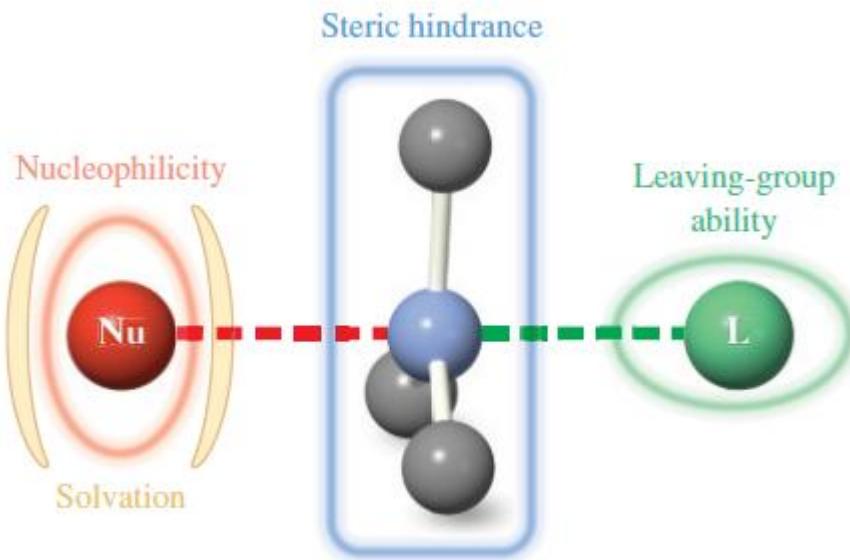
Nucleophilic substitution of a substituted halocycloalkane may change the stereochemical relation between the substituents. For example, in the disubstituted cyclohexane, the stereochemistry changes from cis to trans.



# Substitution reactions - S<sub>N</sub>2 reaction

Variables affecting the S<sub>N</sub>2 reaction mechanism:

1. Nature of leaving group
2. Reactivity of Nucleophile
3. Effect of solvents
4. Structure of substrate



# STRUCTURE AND S<sub>N</sub>2 REACTIVITY: THE LEAVING GROUP

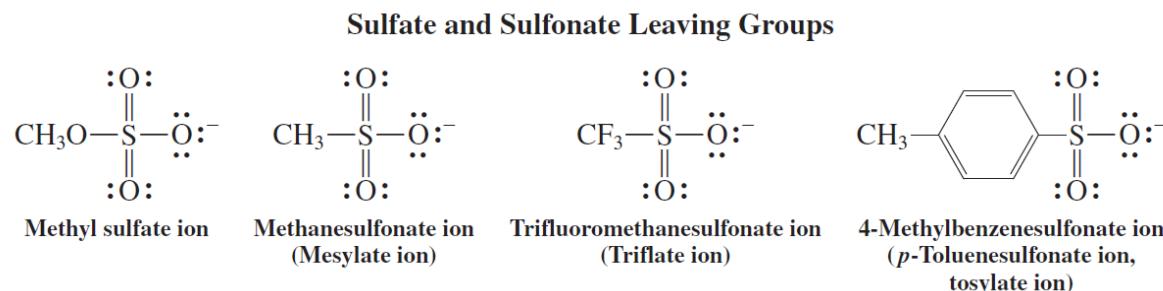
## Leaving-Group Ability



Best

Worst

Increasing



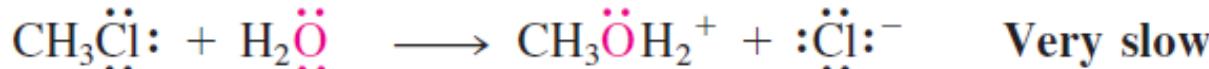
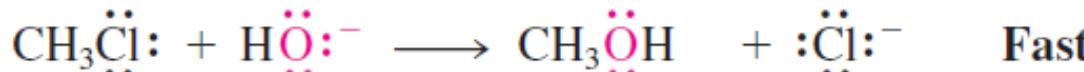
**Weak bases are good leaving groups**

**Table 6-4** Base Strengths and Leaving Groups

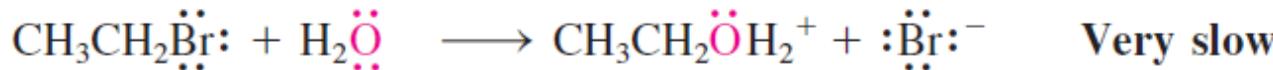
Conjugate acid	Leaving group	Conjugate acid	Leaving group
<i>Strong</i> HI (strongest)	$pK_a = -10.0$	<i>Good</i> $I^-$ (best)	
HBr	$pK_a = -9.0$	$Br^-$	
HCl	$pK_a = -8.0$	$Cl^-$	
$H_2SO_4$	$pK_a = -3.0$	$HSO_4^-$	
$H_3O^+$	$pK_a = -1.7$	$H_2O$	
$CH_3SO_3H$	$pK_a = -1.2$	$CH_3SO_3^-$	
			Better leaving group
		<i>Weak</i>	<i>Poor</i>
		HF	$F^-$
		$CH_3CO_2H$	$CH_3CO_2^-$
		HCN	$NC^-$
		$CH_3SH$	$CH_3S^-$
		$CH_3OH$	$CH_3O^-$
		$H_2O$	$HO^-$
		$NH_3$	$H_2N^-$
		$H_2$ (weakest)	$H^-$ (worst)
			Better leaving group

# STRUCTURE AND S<sub>N</sub>2 REACTIVITY: Nucleophilicity

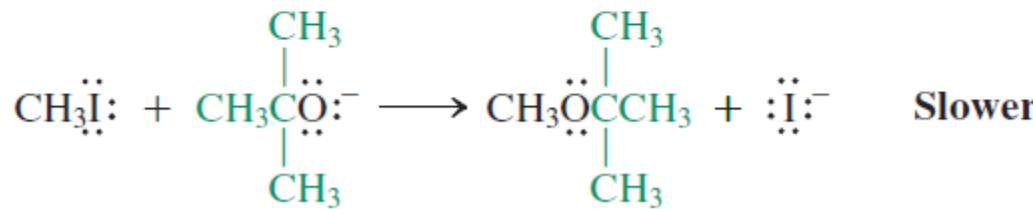
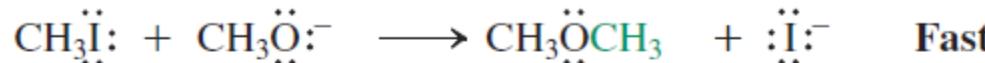
Increasing negative charge increases nucleophilicity



Nucleophilicity decreases to the right in the periodic table



Sterically hindered nucleophiles are poorer reagents

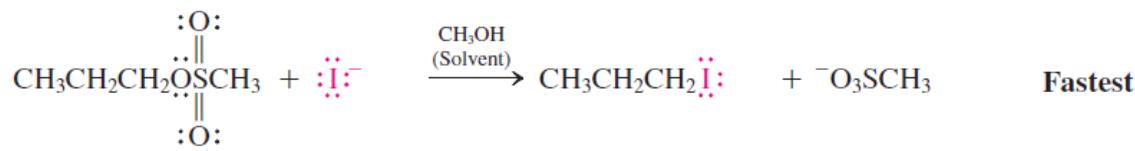
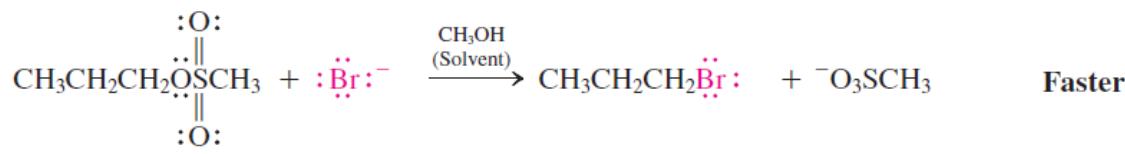
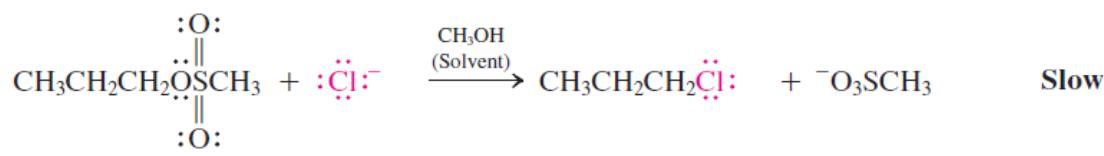


Increasing basicity

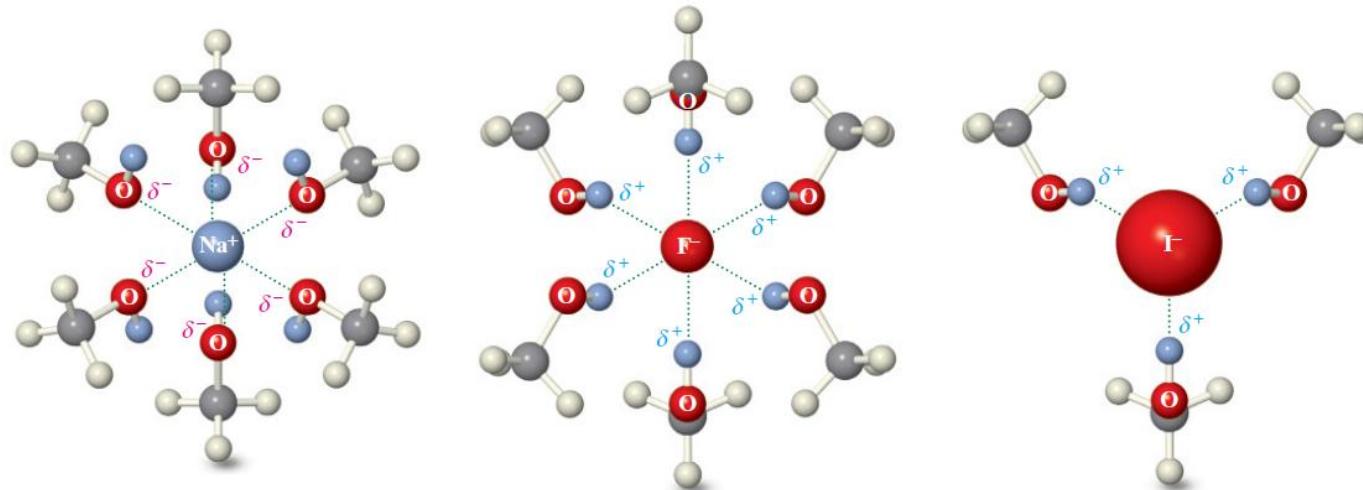


Increasing nucleophilicity

# STRUCTURE AND S<sub>N</sub>2 REACTIVITY: Solvent



Protic polar solvent  
Methanol  
Ethanol



Decreasing solvation by protic solvent →

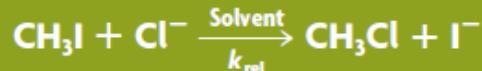


Increasing nucleophilicity →

# STRUCTURE AND S<sub>N</sub>2 REACTIVITY: Solvent

Table 6-6

Relative Rates of S<sub>N</sub>2 Reactions of Iodomethane with Chloride Ion in Various Solvents



Aprotic polar solvent  
Acetone  
Acetonitrile  
DMF  
DMSO

Solvent

Formula	Name	Classification	Relative rate ( $k_{\text{rel}}$ )
CH <sub>3</sub> OH	Methanol	Protic	1
HCONH <sub>2</sub>	Formamide	Protic	12.5
HCONHCH <sub>3</sub>	<i>N</i> -Methylformamide	Protic	45.3
HCON(CH <sub>3</sub> ) <sub>2</sub>	<i>N,N</i> -Dimethylformamide	Aprotic	1,200,000

weaker solvation of anions by aprotic solvents is that the nucleophilicity trend observed in protic solvents inverts

Increasing basicity



Increasing nucleophilicity in aprotic solvents

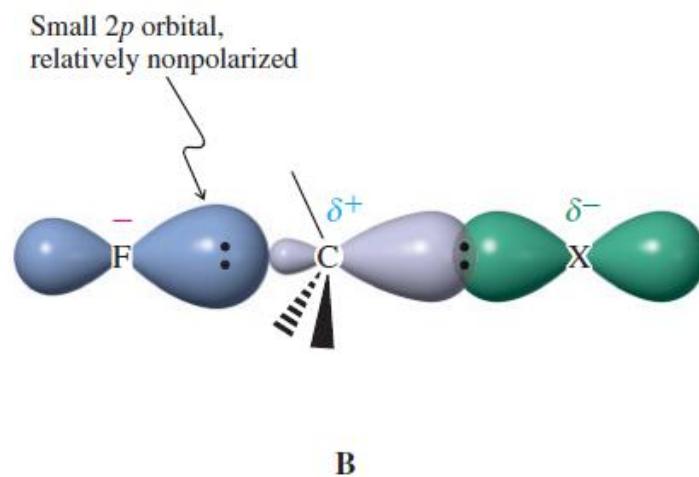
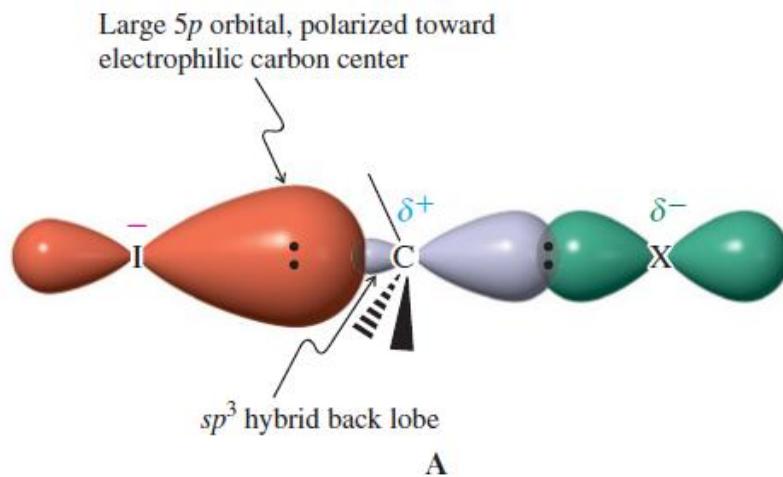
# STRUCTURE AND S<sub>N</sub>2 REACTIVITY: Solvent

## Increasing polarizability improves nucleophilic power

The degree of nucleophilicity increases down the periodic table, even for *uncharged nucleophiles*, for which solvent effects should be much less strong.

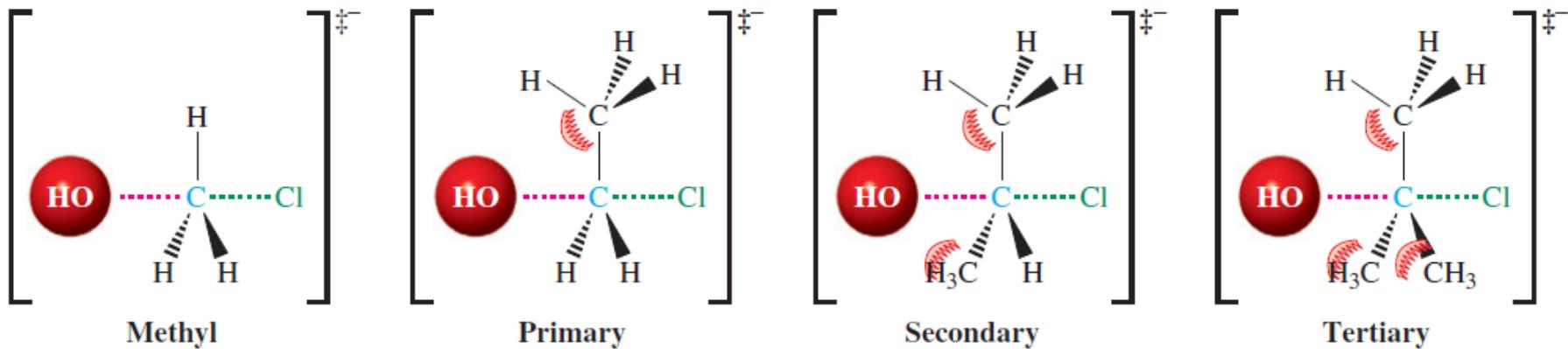


Larger elements have larger, more diffuse, and more polarizable electron clouds. These electron clouds allow for more effective orbital overlap in the S<sub>N</sub>2 transition state. The result is a lower transition-state energy and faster nucleophilic substitution.



# STRUCTURE AND S<sub>N</sub>2 REACTIVITY: Substrate

Branching or Lengthening at the reacting carbon or Branching next to the reacting carbon decreases the rate of the S<sub>N</sub>2 reaction



Replacement of one hydrogen by a methyl group, as in a haloethane, creates substantial steric repulsion with the incoming nucleophile, thereby raising the transition-state energy. This effect significantly retards nucleophilic attack. Lengthening the chain by one or two carbons reduces S<sub>N</sub>2 reactivity.

## Relative S<sub>N</sub>2 Displacement Reactivity of Haloalkanes

Methyl	>	primary	>	secondary	>>	tertiary
Fast		Slower		Very slow		Negligible
Increasing S <sub>N</sub> 2 reactivity						

(Slow reaction: hydrogens on two methyl groups interfere)

Table 6-8

Relative Rates of S<sub>N</sub>2 Reaction of Branched Bromoalkanes with Iodide

Bromoalkane	Rate
CH <sub>3</sub> Br	145
CH <sub>3</sub> CH <sub>2</sub> Br	1
CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> Br	0.0078
CH <sub>3</sub> C(CH <sub>3</sub> ) <sub>2</sub> Br	Negligible

Increasing size of R

Decreasing reactivity in S<sub>N</sub>2 reaction

Table 6-9

Relative Reactivities of Branched Bromoalkanes with Iodide

Bromoalkane	Relative rate
H—C(CH <sub>3</sub> ) <sub>2</sub> Br	1
CH <sub>3</sub> C(CH <sub>3</sub> ) <sub>2</sub> Br	0.8
CH <sub>3</sub> C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> Br	0.03
CH <sub>3</sub> C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub> Br	1.3 × 10 <sup>-5</sup>

Increasing size of R

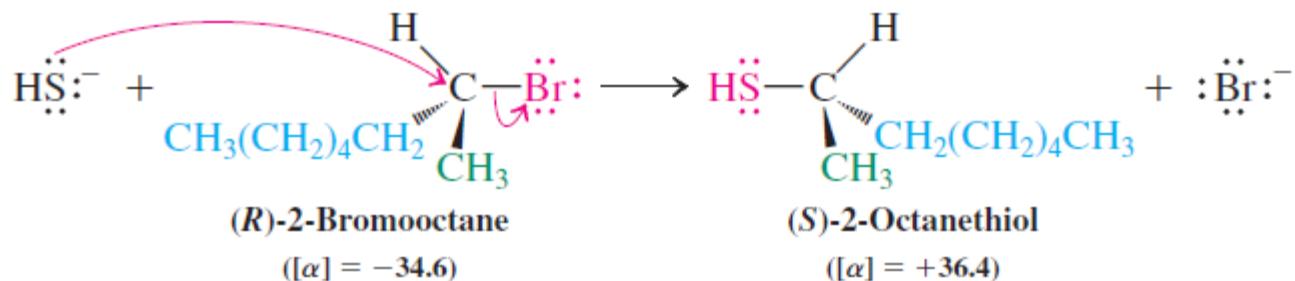
# Substitution reactions – S<sub>N</sub>1 reaction

## S<sub>N</sub>2 reaction

- Has second-order kinetics
- Generates products stereospecifically with inversion of configuration
- Is fastest with halomethanes and successively slower with primary and secondary halides
- Takes place only extremely slowly with tertiary substrates, if at all

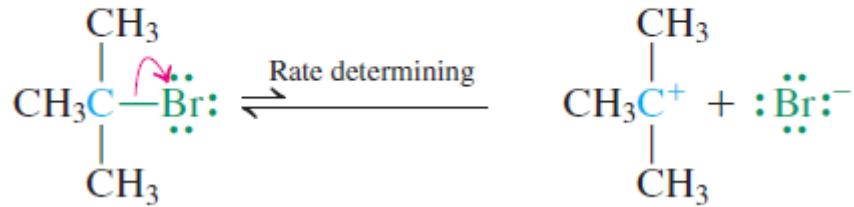
## S<sub>N</sub>1 reaction

- Follow a *first-order* rate law
- Are *not* stereospecific
- Are characterized by the *opposite* order of reactivity

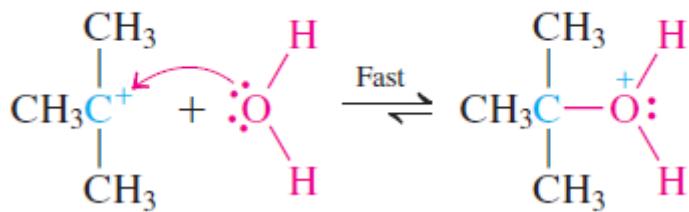


# Substitution reactions – S<sub>N</sub>1 reaction

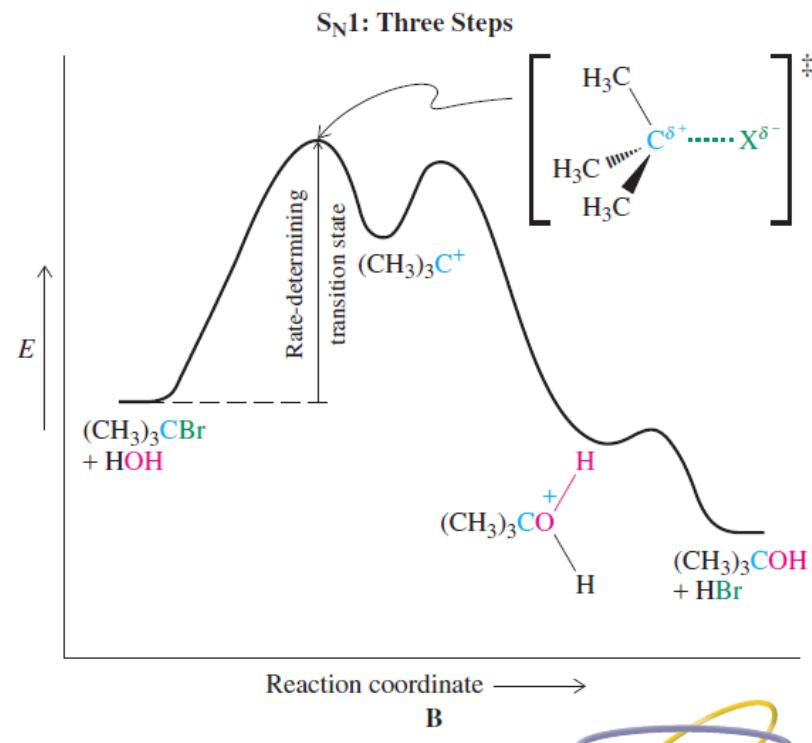
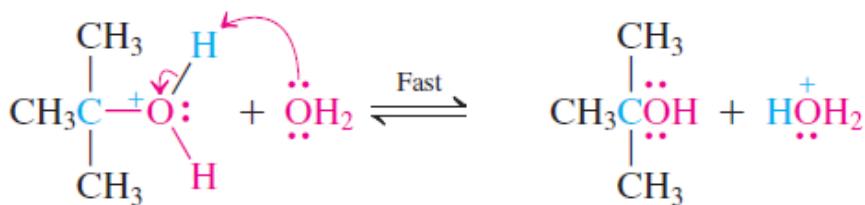
## Dissociation of Halide to Form a Carbocation



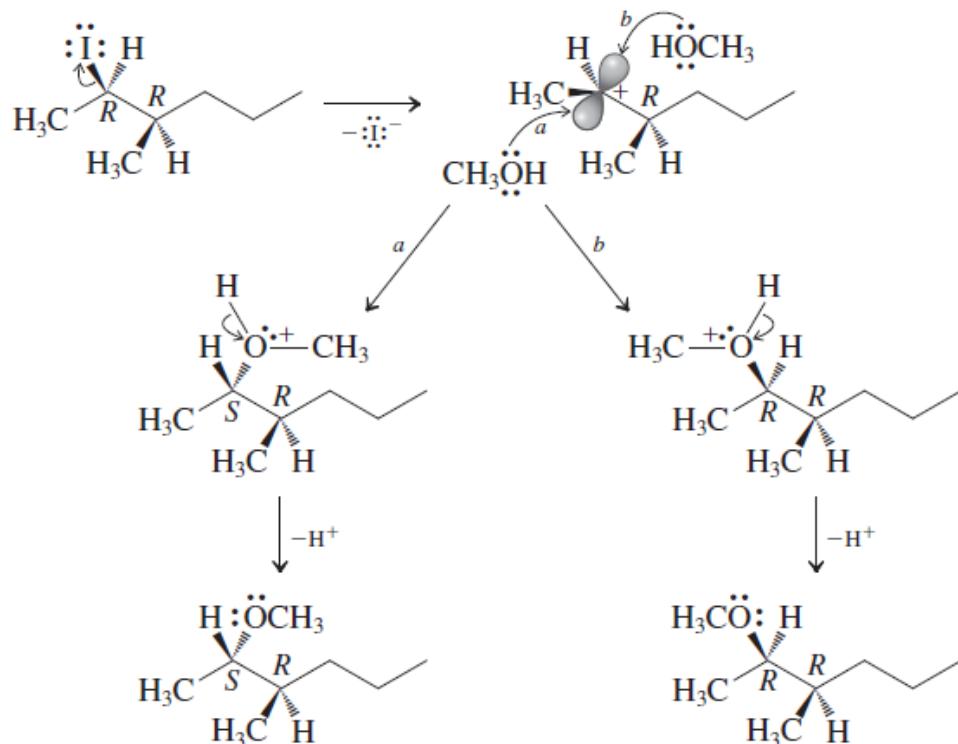
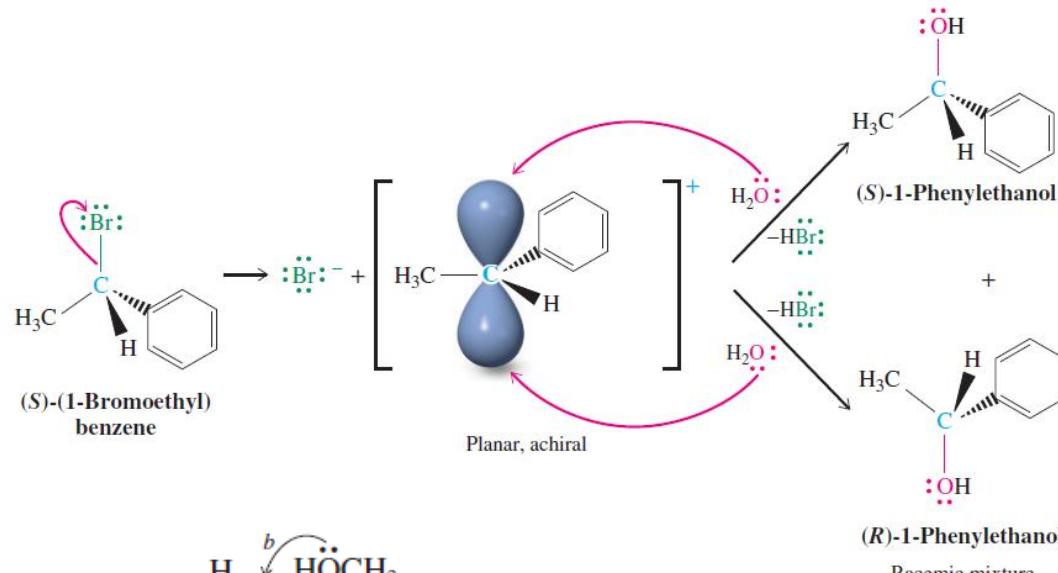
## Nucleophilic Attack by Water



## Deprotonation



# $S_N1$ reaction - Stereochemistry

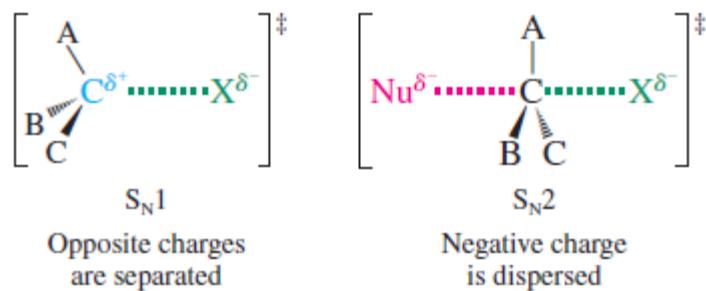


Racemic products obtained when starting with an optically active secondary or tertiary haloalkane in which the stereocenter bears the departing halogen for  $S_N1$  reaction. The formation of racemic products from optically active substrates is strong evidence for the intermediate being a symmetrical, achiral species, such as a carbocation.

# **S<sub>N</sub>1 reaction – Effect of solvent / Leaving Group**

## Polar solvents accelerate the S<sub>N</sub>1 reaction

The rate-determining step of the S<sub>N</sub>1 reaction entails a transition-state structure that is highly polarized, leading eventually to two fully charged ions. In contrast, in a typical S<sub>N</sub>2 transition state, charges are not created; rather, they are dispersed.

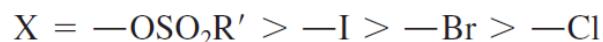


Effect of Solvent on the Rate of an S <sub>N</sub> 1 Reaction		
(CH <sub>3</sub> ) <sub>3</sub> CBr	$\xrightarrow[More\ polar\ solvent]{100\% \ H_2O}$	(CH <sub>3</sub> ) <sub>3</sub> COH + HBr <b>Relative rate 400,000</b>
(CH <sub>3</sub> ) <sub>3</sub> CBr	$\xrightarrow[Less\ polar\ solvent]{90\% \ acetone,\ 10\% \ H_2O}$	(CH <sub>3</sub> ) <sub>3</sub> COH + HBr <b>1</b>

The protic solvent accelerates the S<sub>N</sub>1 reaction because it stabilizes the transition state by hydrogen bonding with the leaving group. In contrast, the S<sub>N</sub>2 reaction is accelerated in polar *aprotic* solvents.

## The S<sub>N</sub>1 reaction speeds up with better leaving groups

### Relative Rate of Solvolysis of RX (R = Tertiary Alkyl)

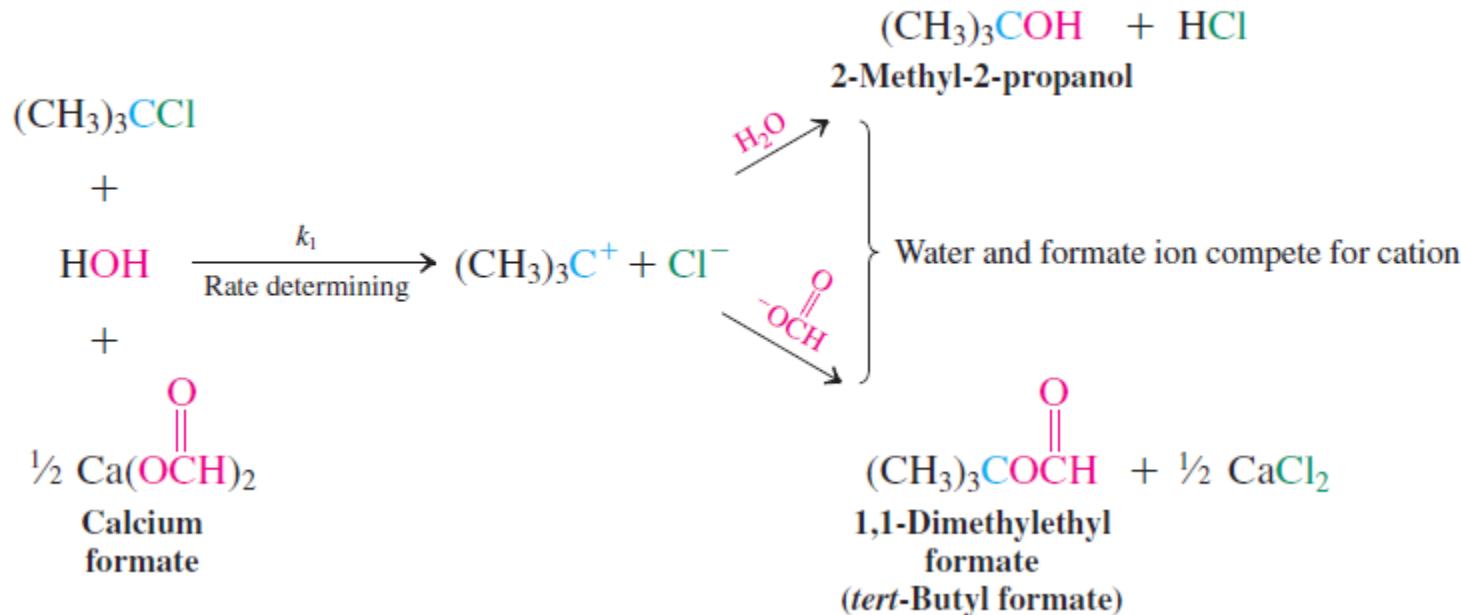


# **S<sub>N</sub>1 reaction – Effect of Nucleophile**

Does changing the nucleophile affect the rate of S<sub>N</sub>1 reaction? The answer is no.

**The strength of the nucleophile affects the product distribution but not the reaction rate**

## Competing Nucleophiles in the S<sub>N</sub>1 Reaction



# $S_N1$ reaction – Effect of Substrate

**Carbocation stability increases from primary to secondary to tertiary**

tertiary halides, whose steric bulk inhibits them from undergoing  $S_N2$  reactions, substitute almost exclusively by the  $S_N1$  mechanism, primary haloalkanes only by  $S_N2$ , and secondary haloalkanes by either route, depending on conditions.

**Why tertiary halides undergo  $S_N1$  reactions?**

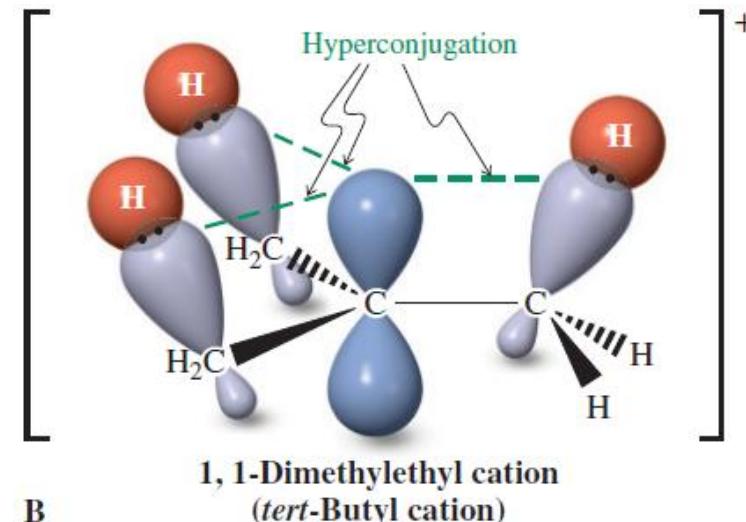
Steric hindrance increases along the series, thereby slowing down  $S_N2$ .

Second, increasing alkyl substitution stabilizes carbocation centers.

## Relative Stability of Carbocations



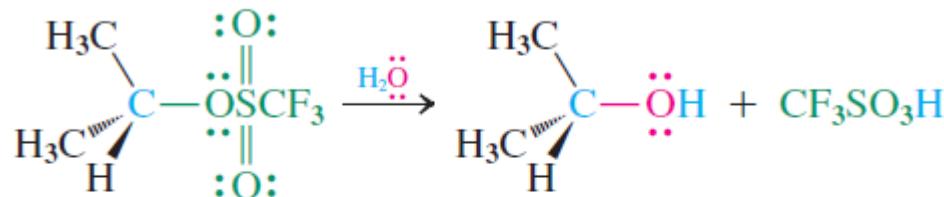
Increasing carbocation stability



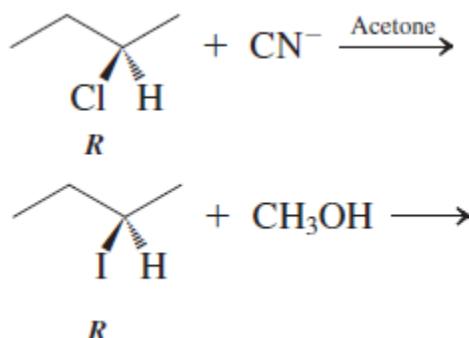
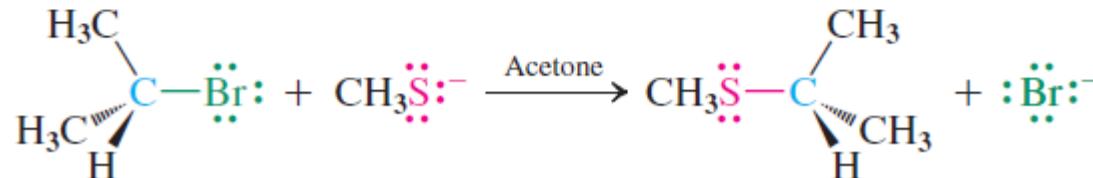
# **S<sub>N</sub>1 reaction – Effect of Substrate**

**Secondary systems undergo both S<sub>N</sub>1 and S<sub>N</sub>2 reactions.** The pathway chosen depends on the reaction conditions: the solvent, the leaving group, and the nucleophile.

## Substitution of a Secondary Substrate Under S<sub>N</sub>1 Conditions

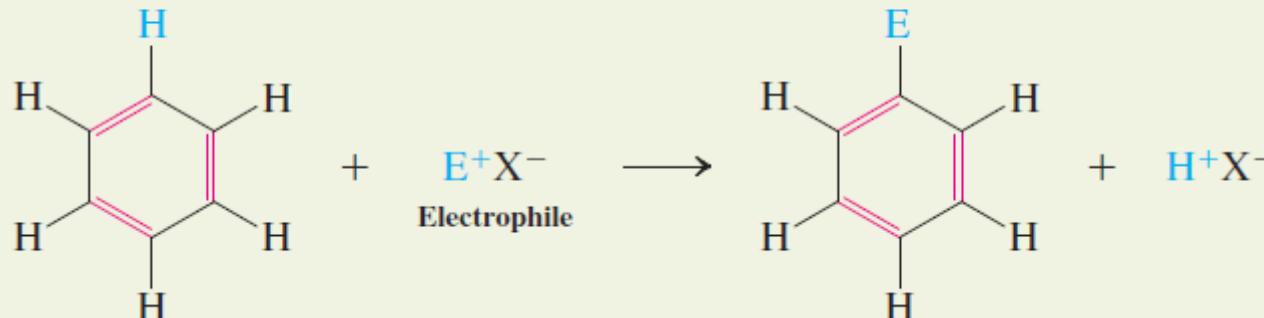


## Substitution of a Secondary Haloalkane Under S<sub>N</sub>2 Conditions



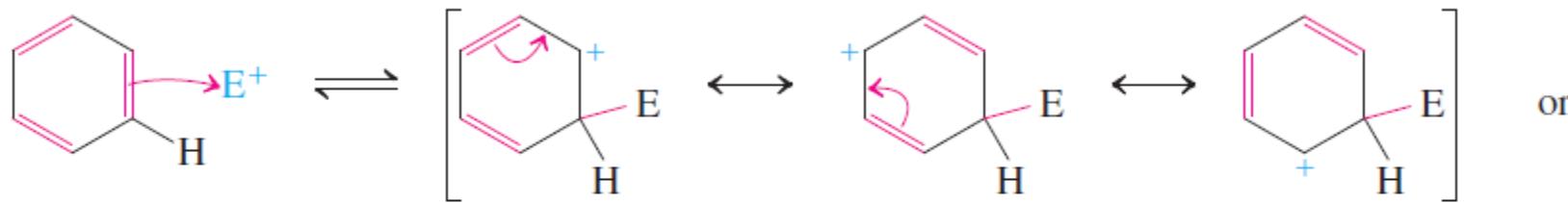
# Electrophilic Aromatic Substitution Reactions

## Electrophilic Aromatic Substitution

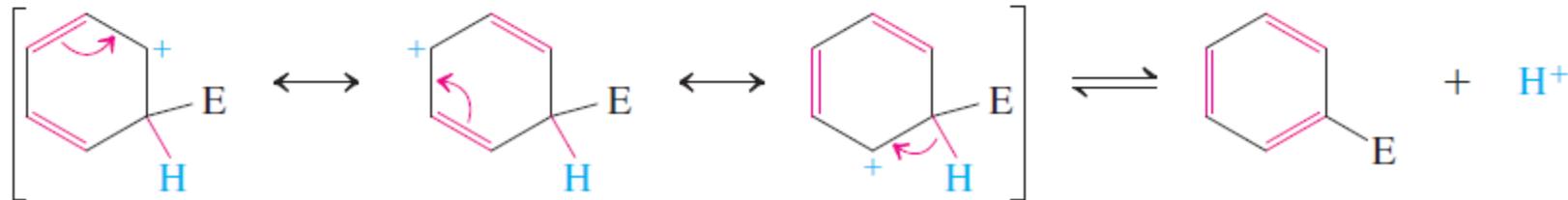


## Mechanism of Electrophilic Aromatic Substitution

### Step 1. Electrophilic attack

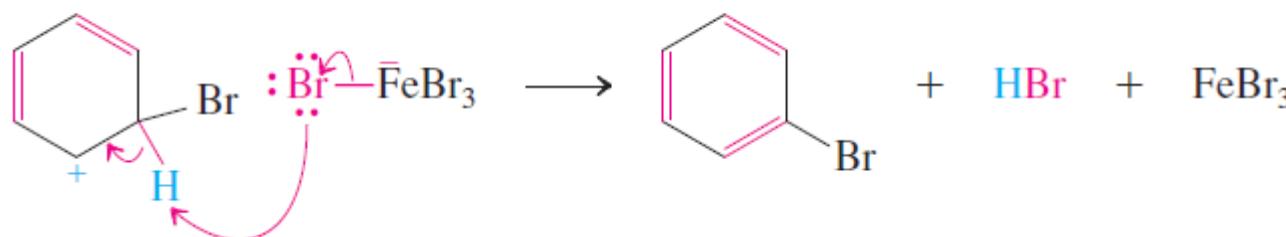
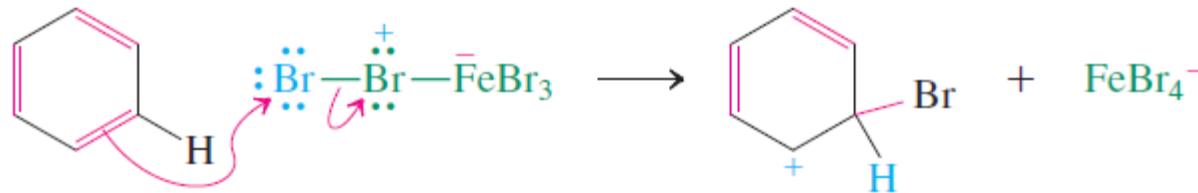


### Step 2. Proton loss

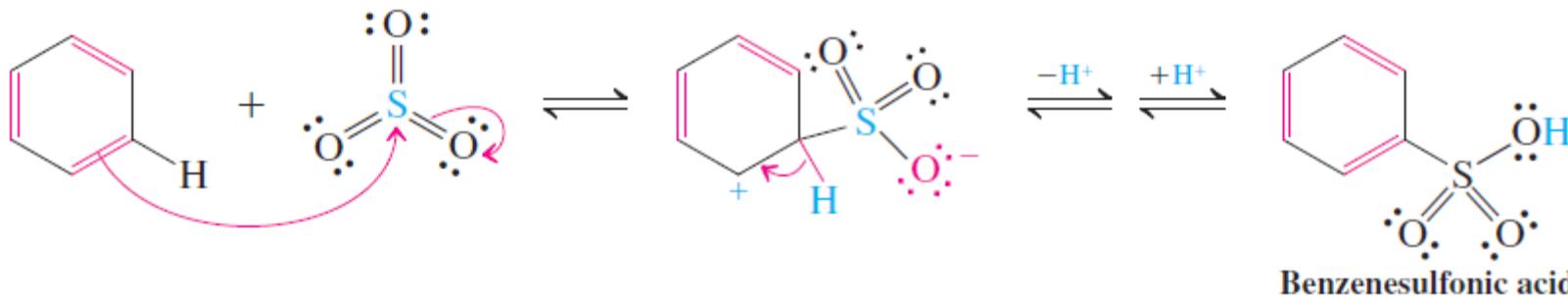


# **Electrophilic Aromatic Substitution Reactions**

# Halogenation



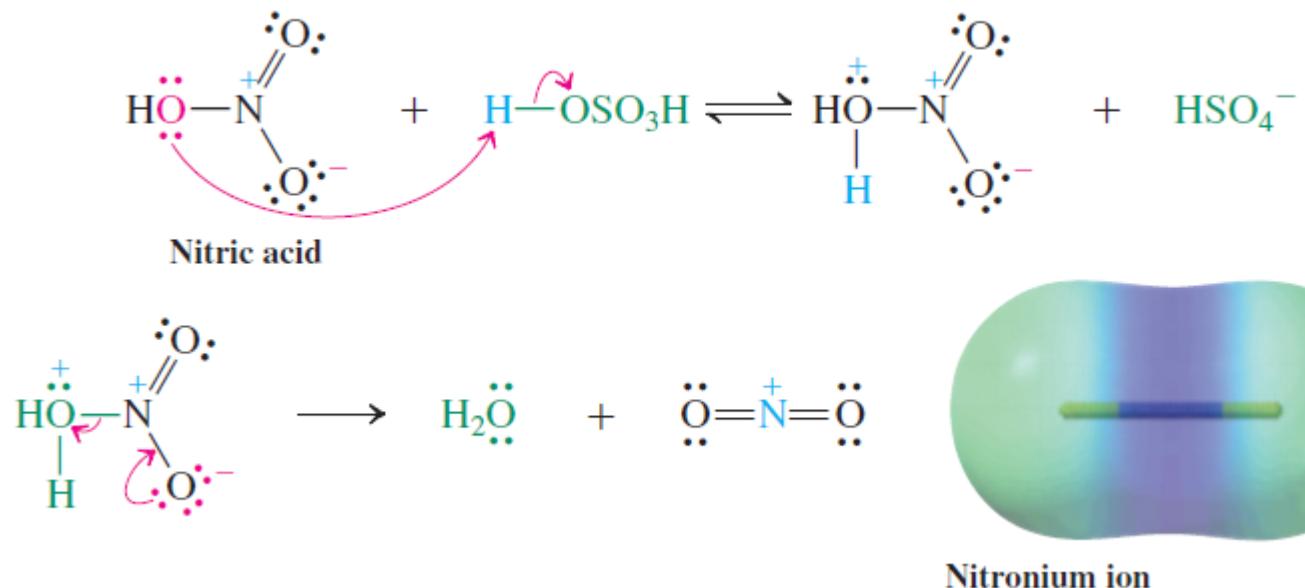
## Sulfonation



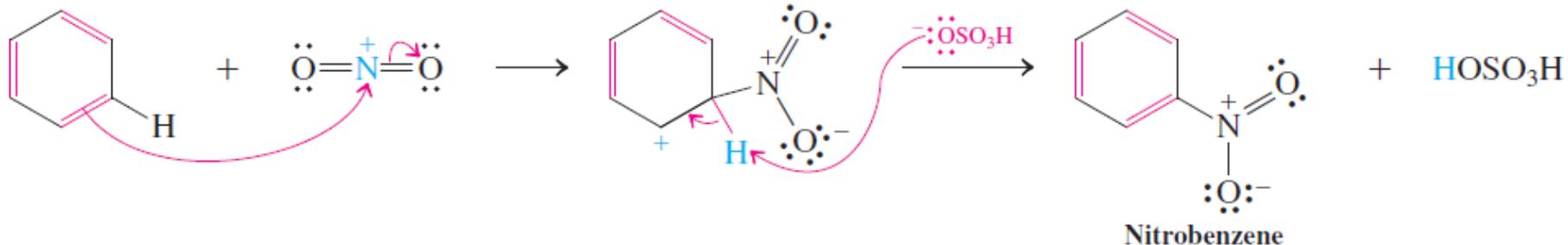
# Substitution Reactions

## Nitration

### Activation of Nitric Acid by Sulfuric Acid

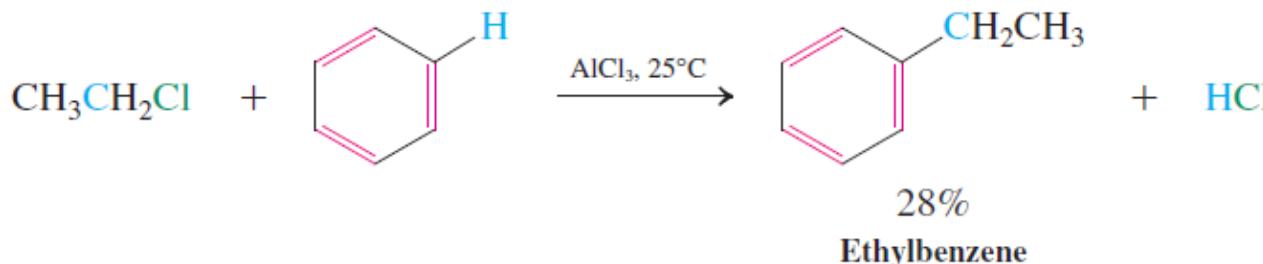


### Mechanism of Aromatic Nitration

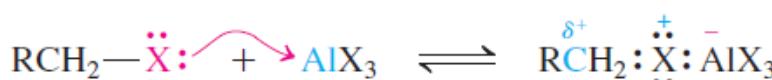


# Substitution Reactions – Friedel crafts alkylation

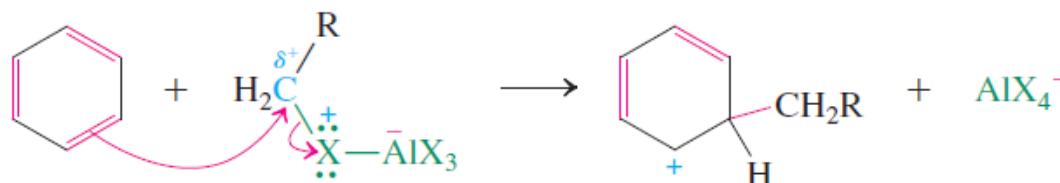
## Friedel-Crafts Alkylation of Benzene with Chloroethane



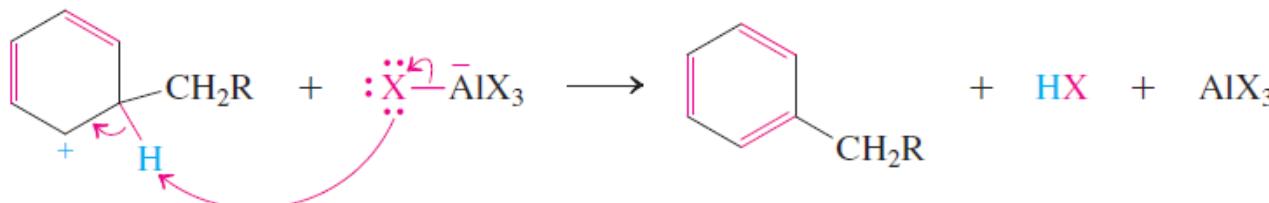
**Step 1.** Haloalkane activation



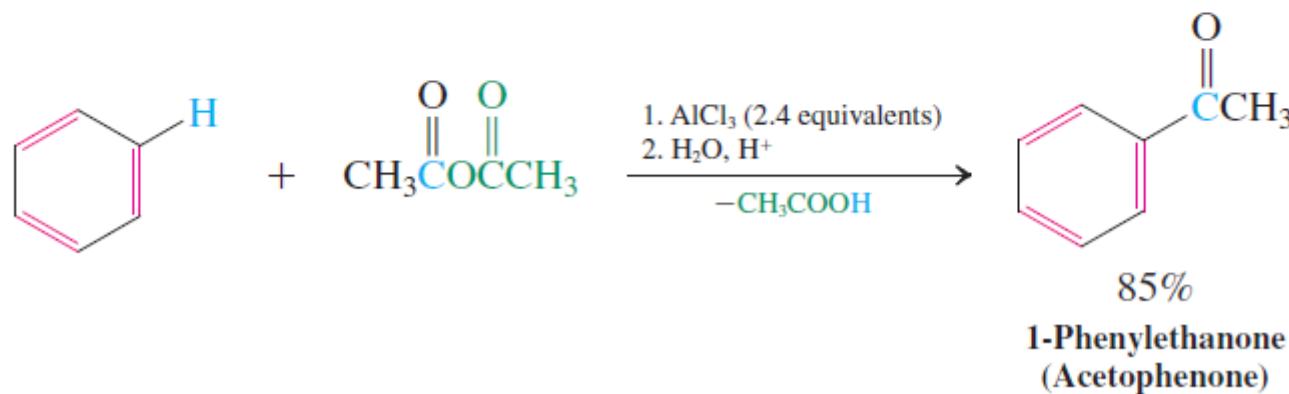
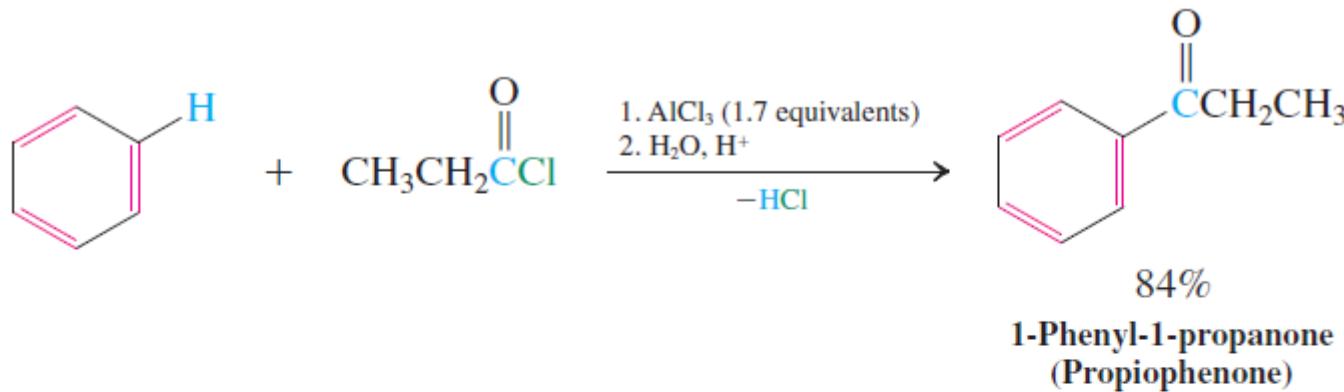
**Step 2.** Electrophilic attack



**Step 3.** Proton loss



# Substitution Reactions – Friedel crafts acylation

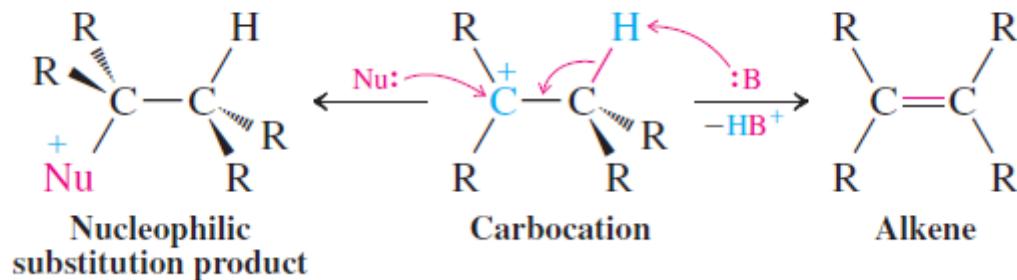


# Elimination Reactions

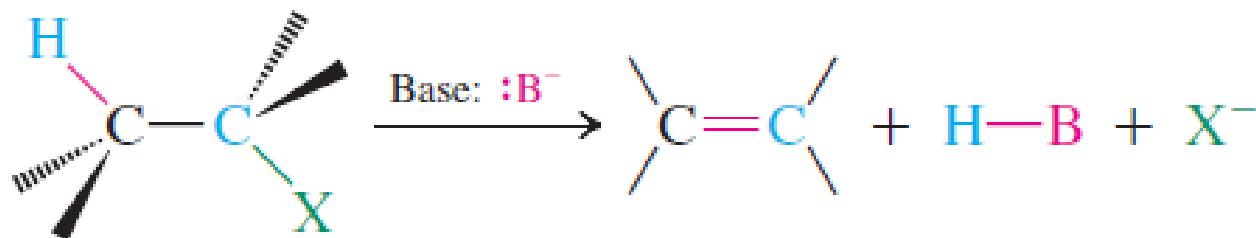
Elimination reaction Mechanism:

1. UNIMOLECULAR ELIMINATION: E1
2. BIMOLECULAR ELIMINATION: E2

Competition Between Nucleophilic and Basic Attack on a Carbocation

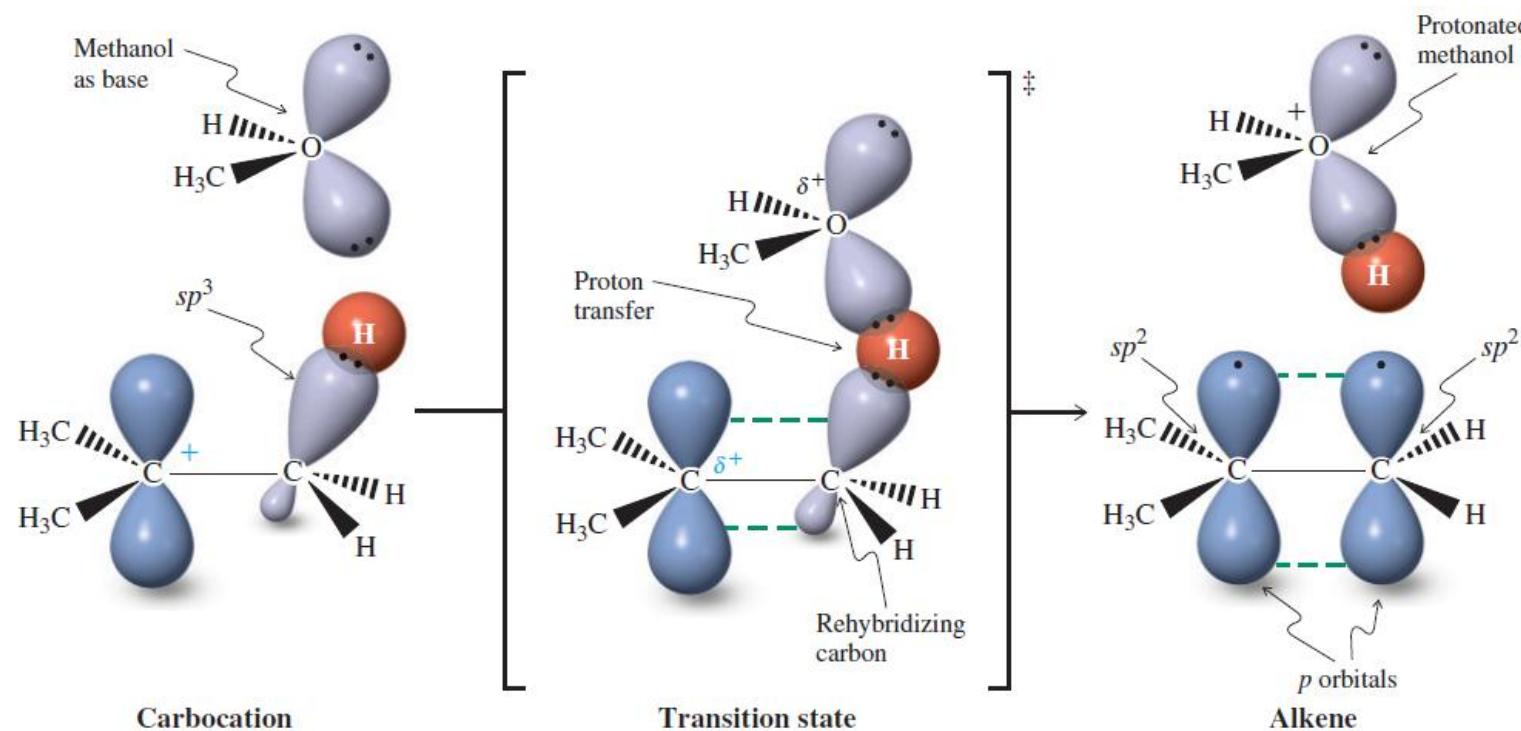
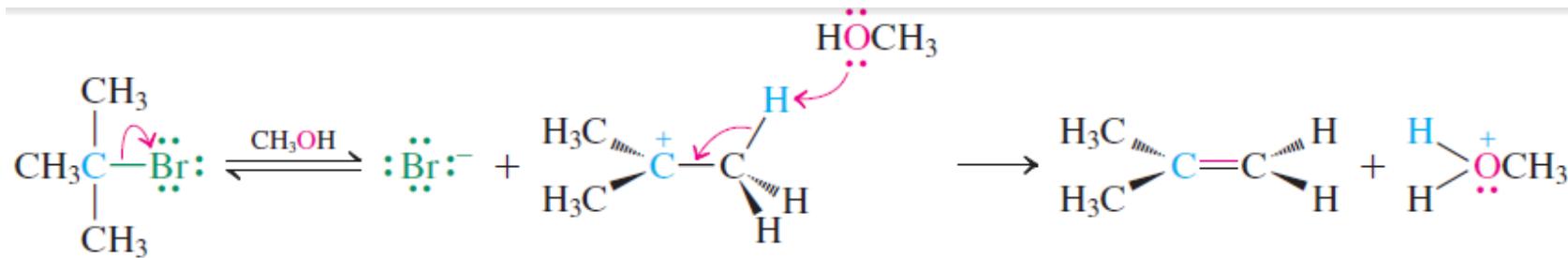


## Elimination



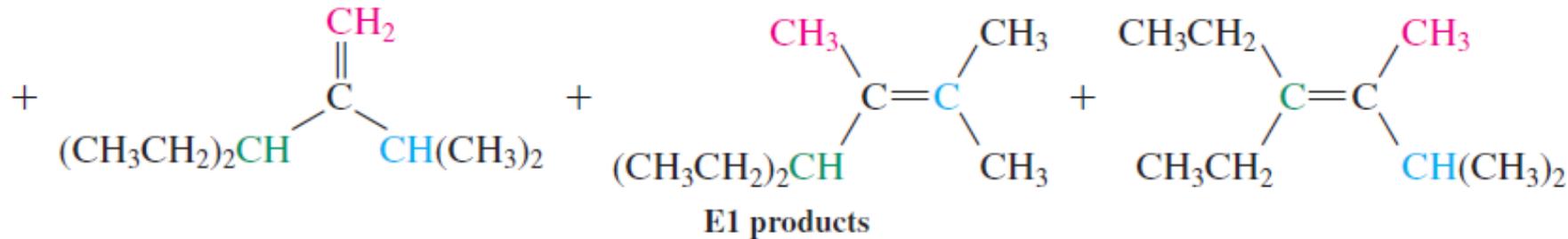
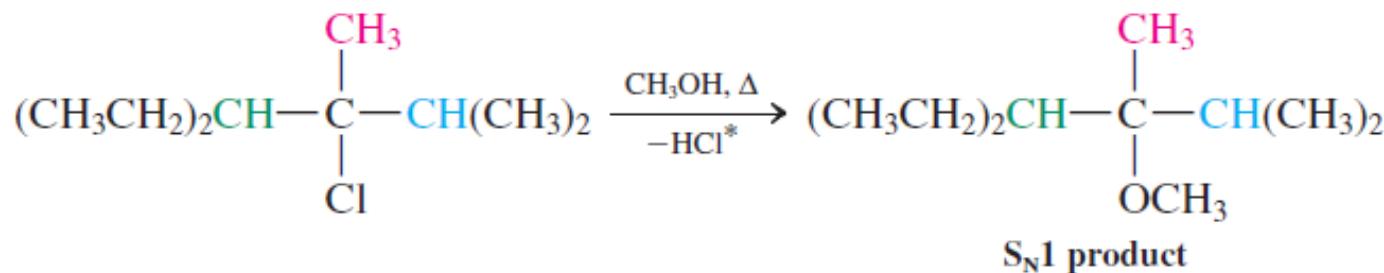
# Unimolecular Elimination: E1

The reaction is first order. They are unimolecular, eliminations of this type are labeled **E1**. The rate-determining step in the E1 process is the same as that in S<sub>N</sub>1 reactions: dissociation to a carbocation followed by loss of a proton from a carbon adjacent to the one bearing the positive charge.



# Unimolecular Elimination: E1

The E1 Reaction Can Give Product Mixtures



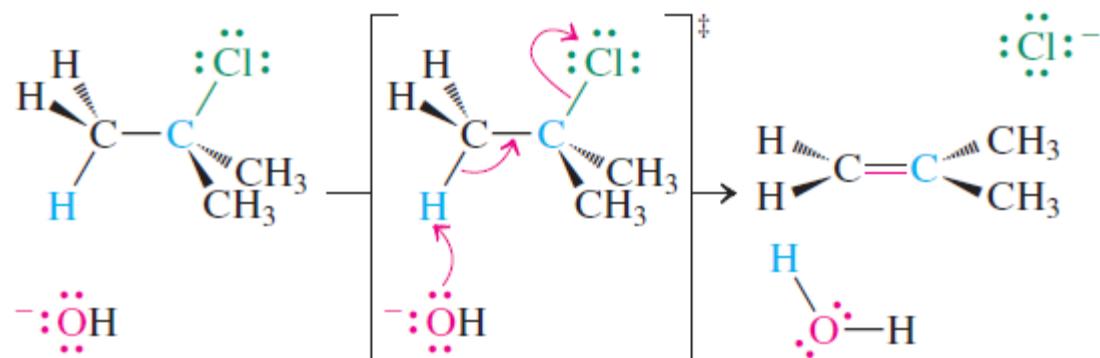
# Bimolecular Elimination: E2

pathway by which haloalkanes may react with nucleophiles *that are strong bases*. Strong bases (such as hydroxide,  $\text{HO}^-$ , and alkoxides,  $\text{RO}^-$ ) can attack haloalkanes before carbocation formation. The target is a hydrogen on a carbon atom next to the one carrying the leaving group.

The bimolecular elimination mechanism consists of a *single step*. Three changes take place:

1. Deprotonation by the base
2. Departure of the leaving group
3. Rehybridization of the reacting carbon centers from  $sp_3$  to  $sp_2$  to furnish the two  $p$  orbitals of the emerging double bond

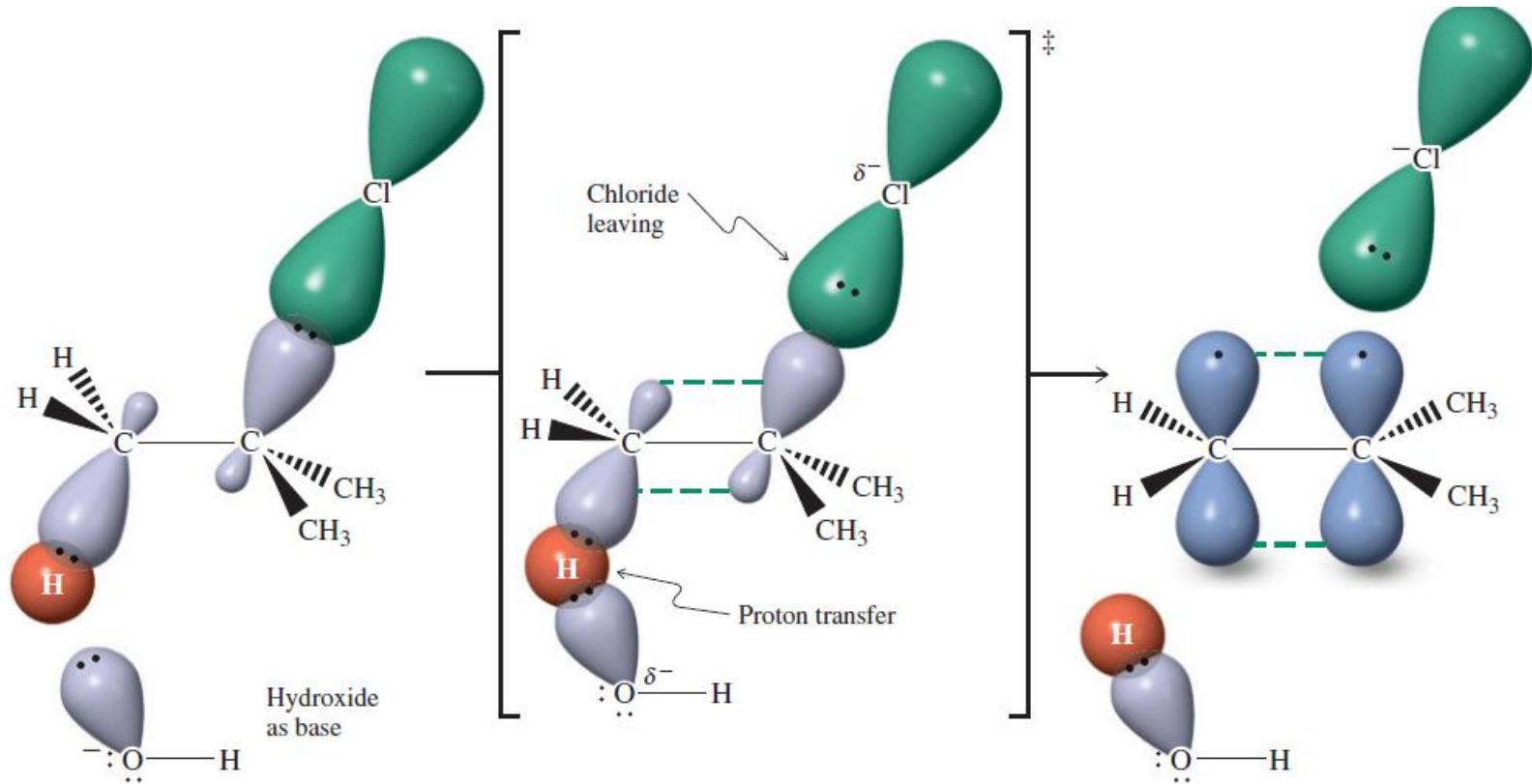
## The E2 Reaction Mechanism



**Strong bases effect  
bimolecular  
elimination**

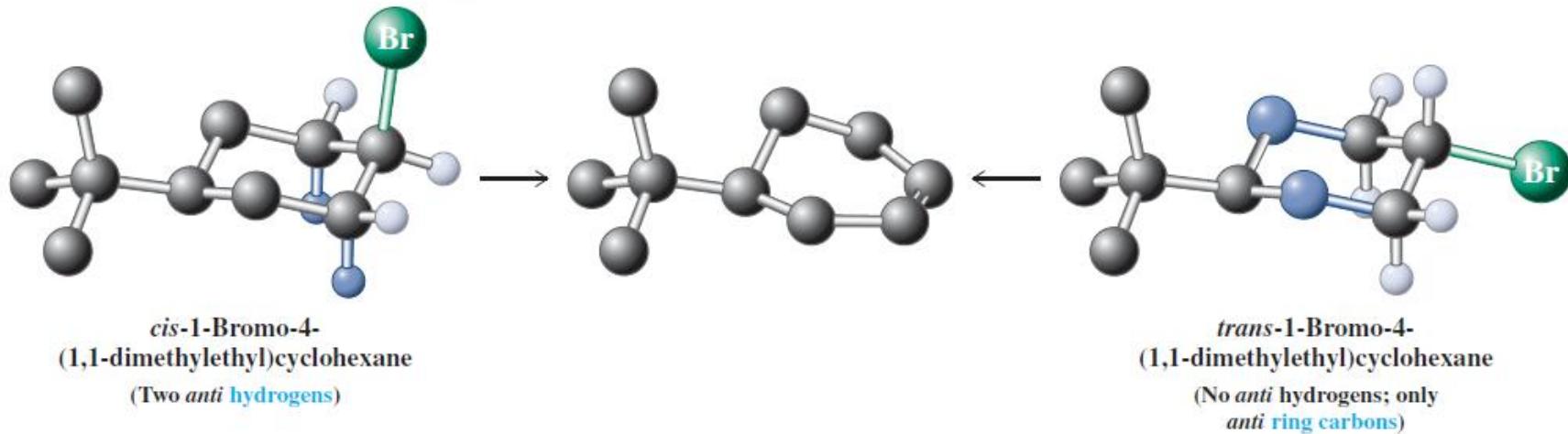
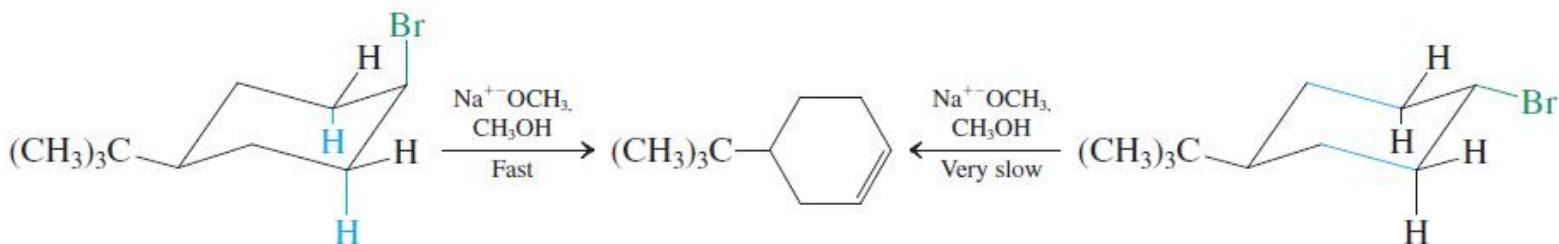
# Bimolecular Elimination: E2

All three changes take place *simultaneously*: The E2 is a one-step, *concerted* process



# Bimolecular Elimination: E2

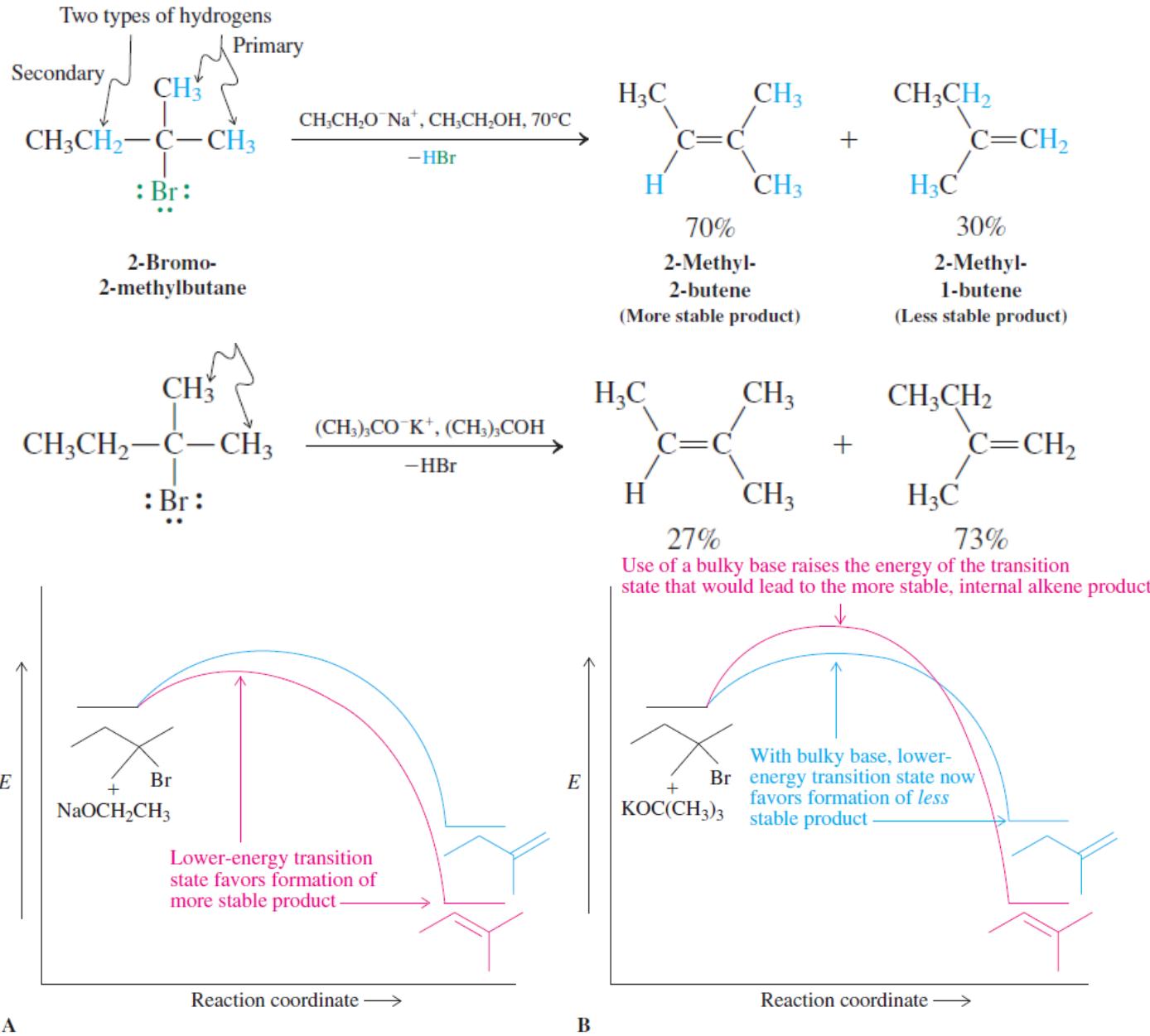
Anti Elimination Occurs Readily for *cis*- but Not for  
*trans*-1-Bromo-4-(1,1-dimethylethyl)cyclohexane



An *anti* transition state is preferred, in which the base abstracts a proton at the same time as the leaving group departs

E2 reactions often favour trans over cis

# Bimolecular Elimination: E2

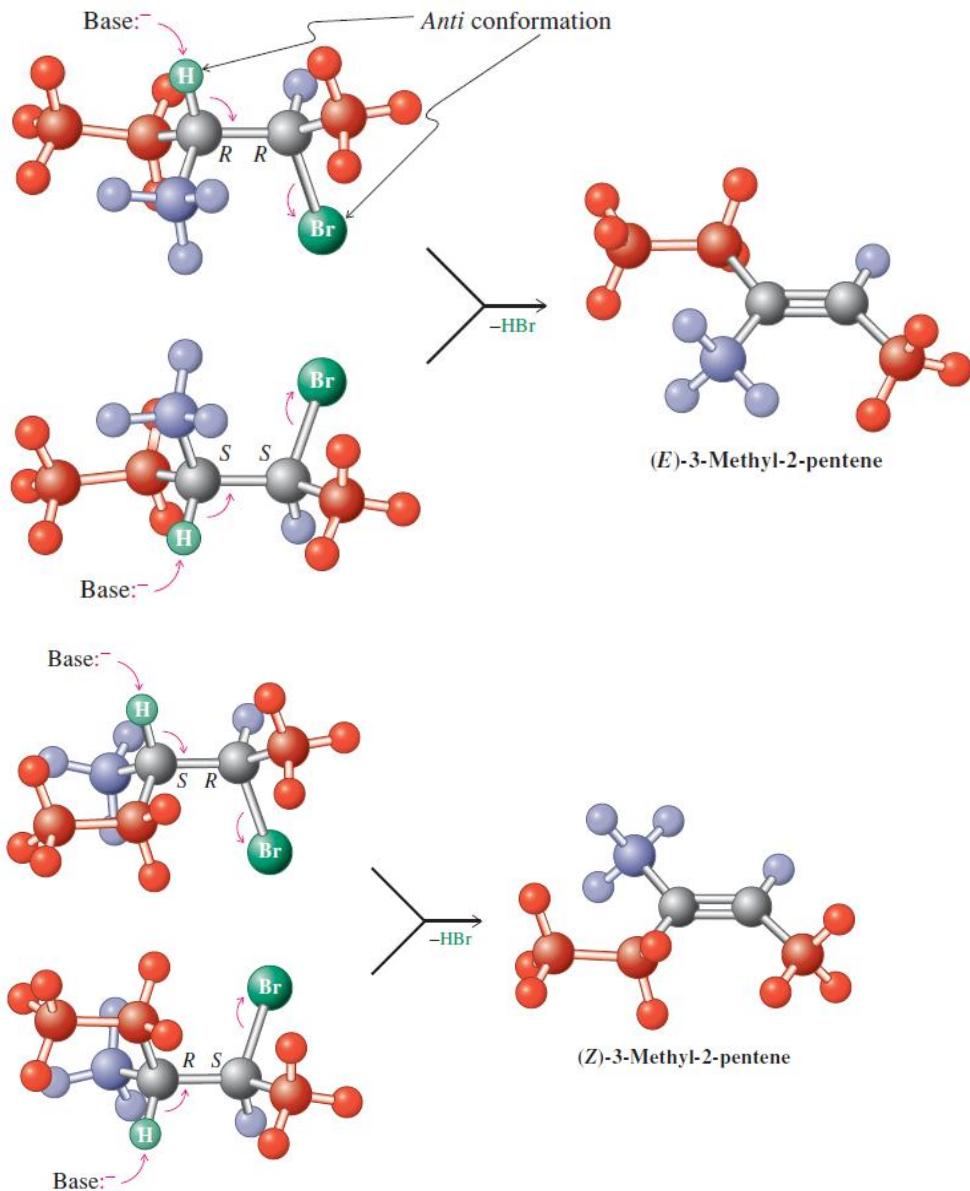


Thermodynamically more stable internal alkenes are formed faster than the terminal isomers.

Bulky bases may favour the formation of the products with thermodynamically less stable (e.g., terminal) double bonds.

# Bimolecular Elimination: E2

Stereospecificity in the E2 Reaction of 2-Bromo-3-methylpentane



Some E2 processes  
are stereospecific

two diastereomers of 2-bromo-3-methylpentane to give 3-methyl-2-pentene is stereospecific.

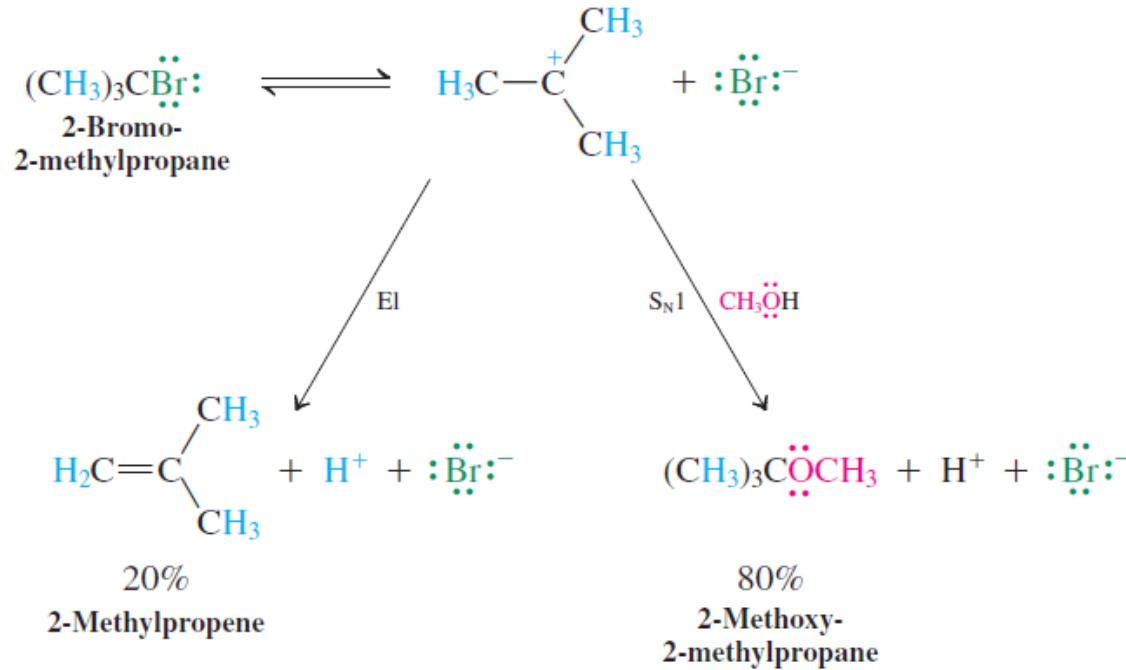
Both the  $(R,R)$  and the  $(S,S)$  isomer yield *exclusively* the  $(E)$  isomer of the alkene.

Conversely, the  $(R,S)$  and  $(S,R)$  diastereomers give only the  $(Z)$  alkene.

# Substitution Vs Elimination

The multiple reaction pathways — S<sub>N</sub>2, S<sub>N</sub>1, E2, and E1

## Competition Between E1 and S<sub>N</sub>1 in the Methanolysis of 2-Bromo-2-methylpropane



Substitution is favored by unhindered substrates and small, less basic nucleophiles.  
Elimination is favored by hindered substrates and bulky, more basic nucleophiles.

# Substitution Vs Elimination

---

The multiple reaction pathways — S<sub>N</sub>2, S<sub>N</sub>1, E2, and E1

## Factor 1. Base strength of the nucleophile

Weak Bases	Strong Bases
H <sub>2</sub> O,* ROH,* PR <sub>3</sub> , halides, RS <sup>-</sup> , N <sub>3</sub> <sup>-</sup> , NC <sup>-</sup> , RCOO <sup>-</sup>	HO <sup>-</sup> , RO <sup>-</sup> , H <sub>2</sub> N <sup>-</sup> , R <sub>2</sub> N <sup>-</sup>
Substitution more likely	Likelihood of elimination increased

## Factor 2. Steric hindrance around the reacting carbon

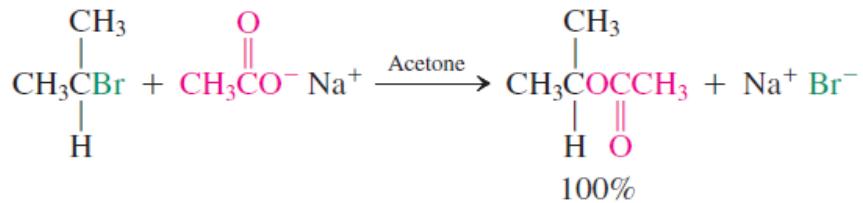
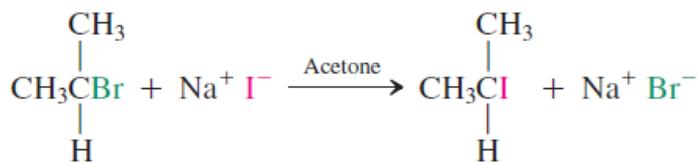
Sterically Unhindered	Sterically Hindered
Primary haloalkanes	Branched primary, secondary, tertiary haloalkanes
Substitution more likely	Likelihood of elimination increased

## Factor 3. Steric hindrance in the nucleophile (strong base)

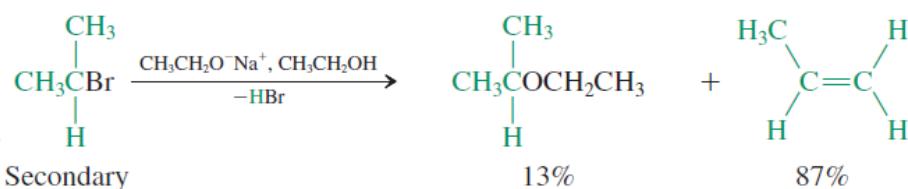
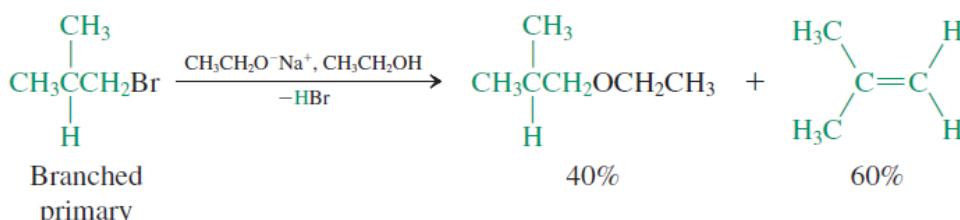
Sterically Unhindered	Sterically Hindered
HO <sup>-</sup> , CH <sub>3</sub> O <sup>-</sup> , CH <sub>3</sub> CH <sub>2</sub> O <sup>-</sup> , H <sub>2</sub> N <sup>-</sup>	(CH <sub>3</sub> ) <sub>3</sub> CO <sup>-</sup> , [(CH <sub>3</sub> ) <sub>2</sub> CH] <sub>2</sub> N <sup>-</sup>
Substitution may occur	Elimination strongly favored

# Substitution Vs Elimination

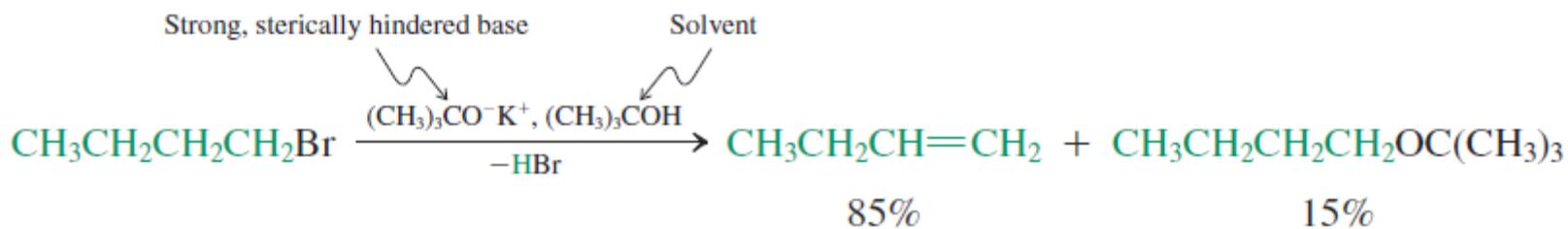
# Weakly basic nucleophiles give substitution



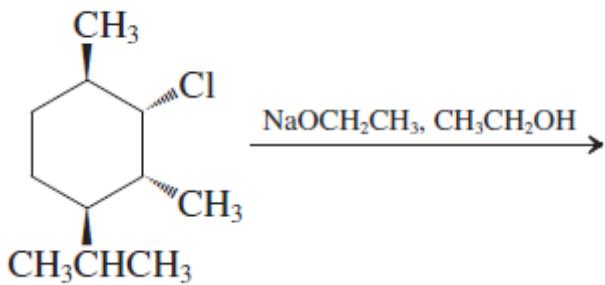
**Strongly basic nucleophiles give more elimination as steric bulk increases**



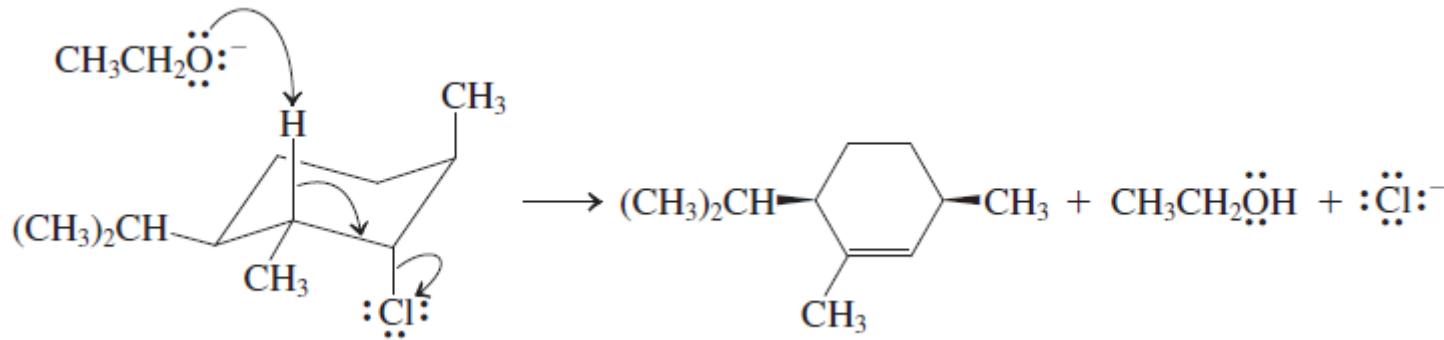
## Sterically hindered basic nucleophiles favour elimination



# Substitution Vs Elimination



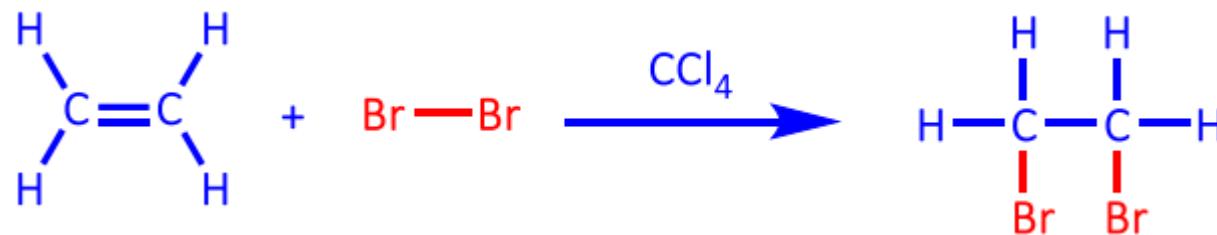
Substitution ?  
or  
Elimination ?



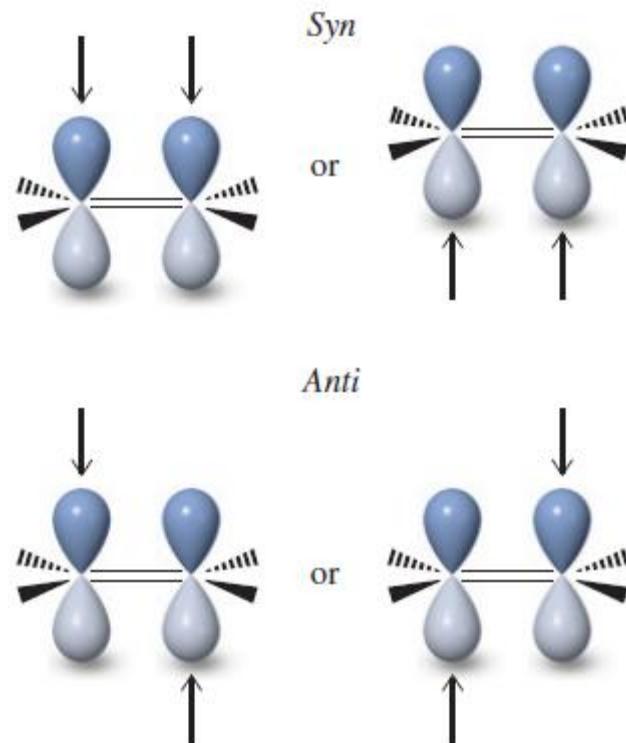
Substitution is favored by unhindered substrates and small, less basic nucleophiles.  
Elimination is favored by hindered substrates and bulky, more basic nucleophiles.

# Addition Reactions

An important feature of addition reactions to alkenes is their potential stereochemistry.

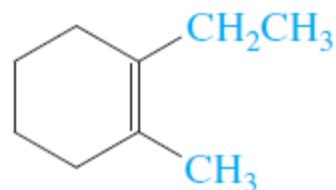
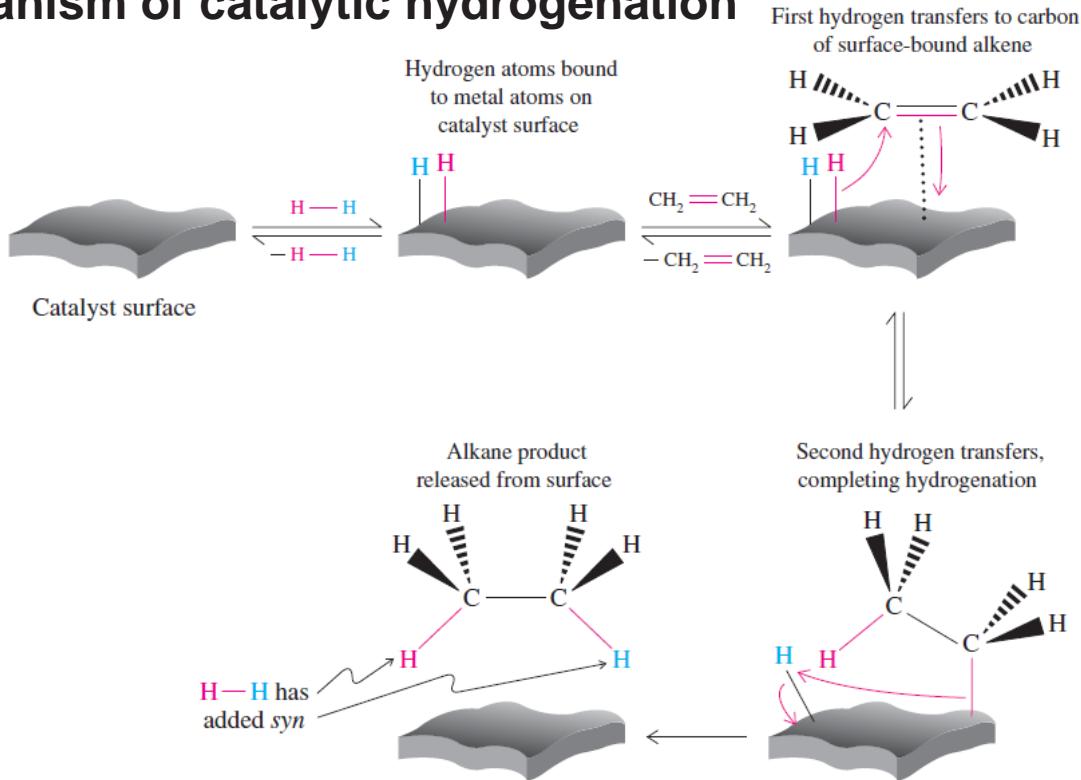


Two Topologies of  
Alkene Addition

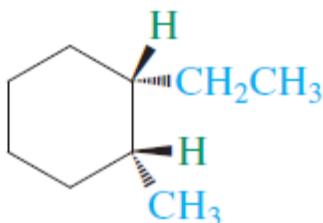


# Addition Reactions - Hydrogenation

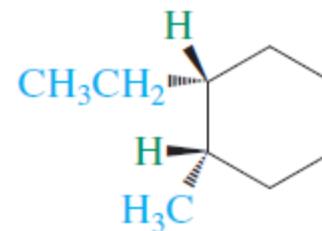
## Mechanism of catalytic hydrogenation



$\text{H}_2$ ,  $\text{PtO}_2$ ,  $\text{CH}_3\text{CH}_2\text{OH}$ ,  $25^\circ\text{C}$



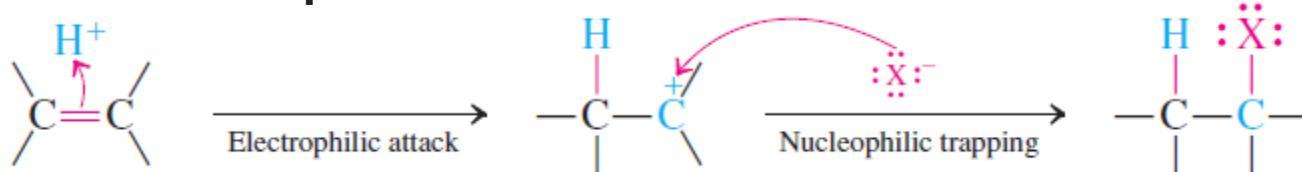
82%



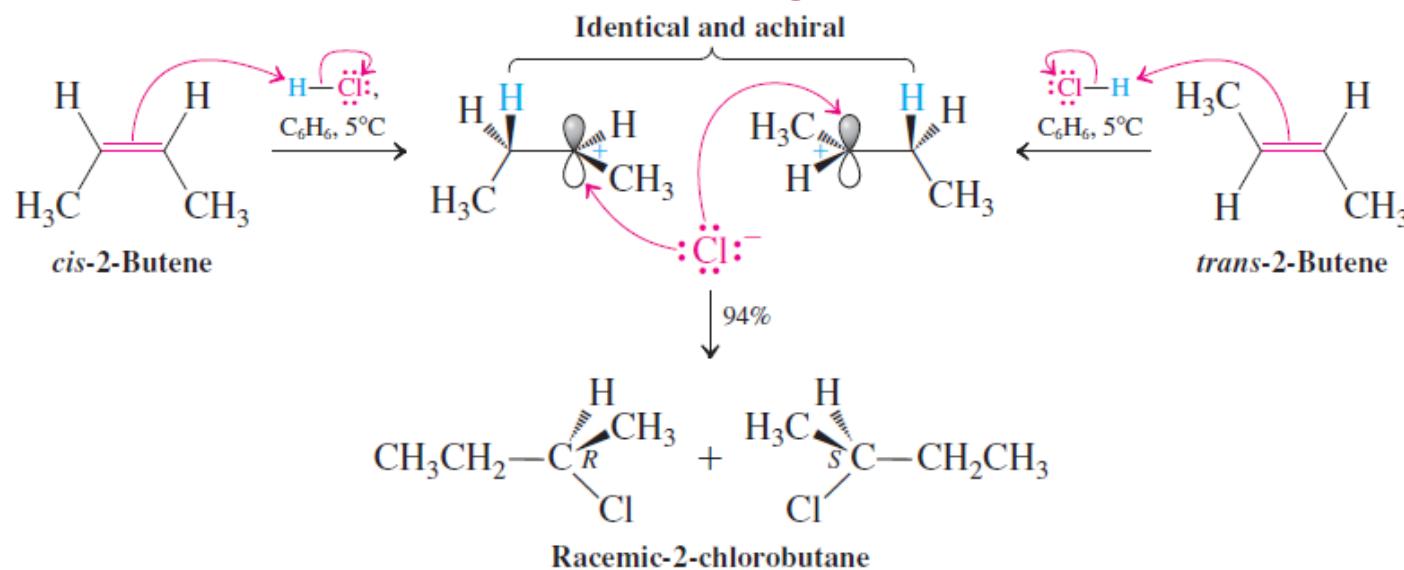
cis-1-Ethyl-2-methylcyclohexane  
(Racemic)

# Addition Reactions – Addition of HX

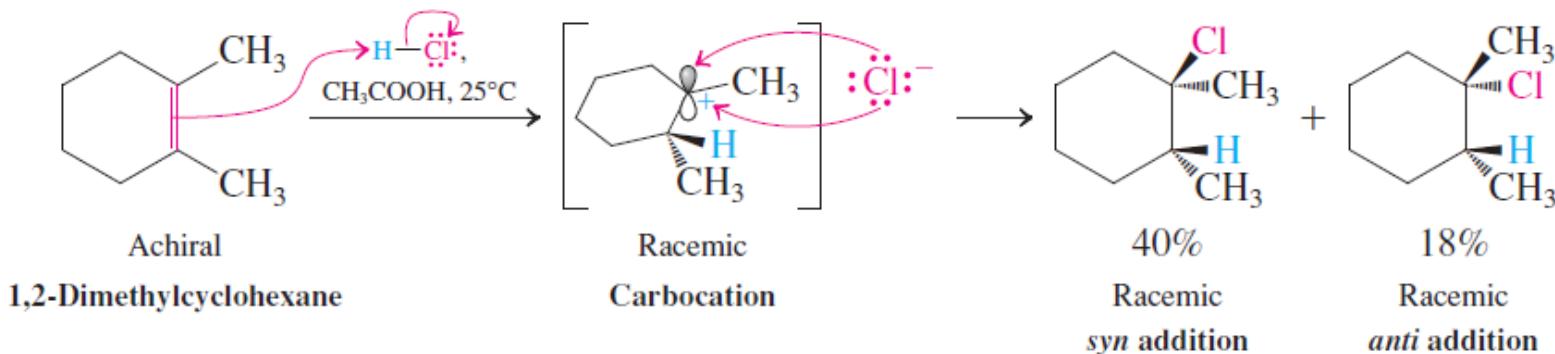
## Mechanism of Electrophilic Addition of HX to Alkenes



Symmetrical alkenes: Nucleophilic trapping of carbocations is nonstereoselective



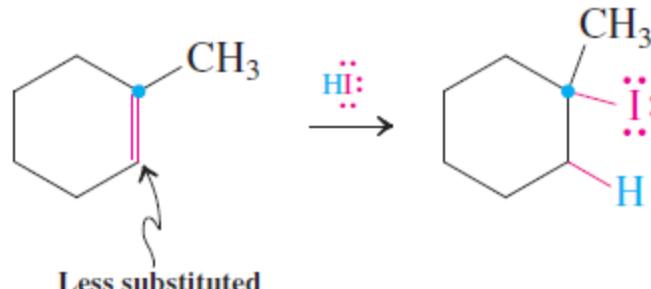
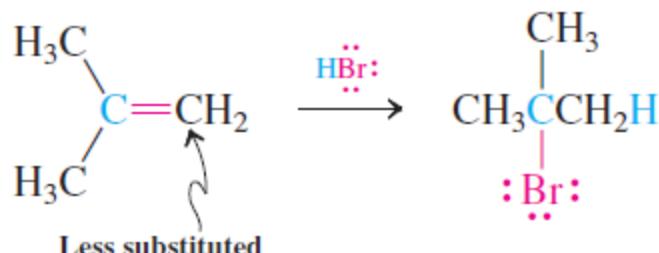
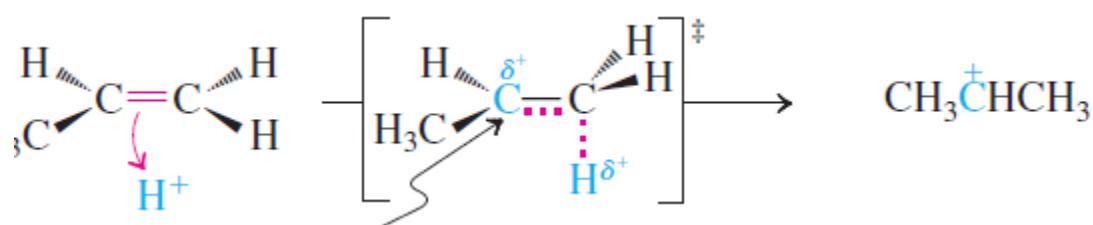
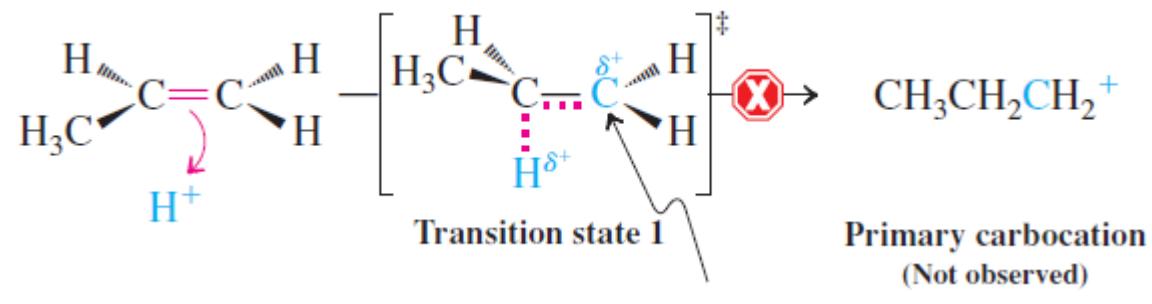
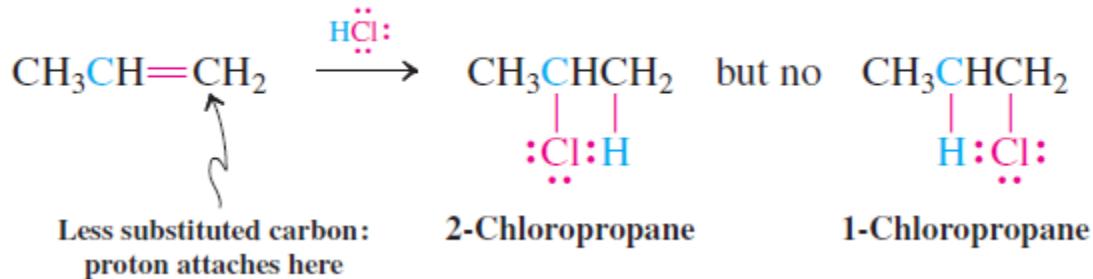
What if two adjacent stereocenters?



# Addition Reactions – Addition of HX

Unsymmetrical alkenes: Markovnikov rule predicts regioselectivity in electrophilic additions

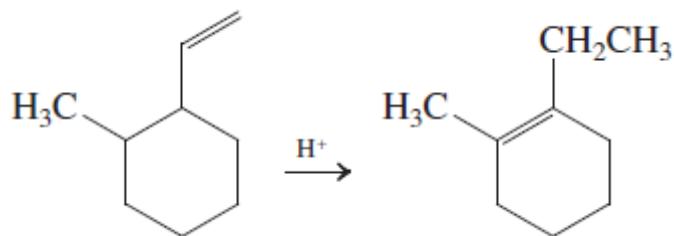
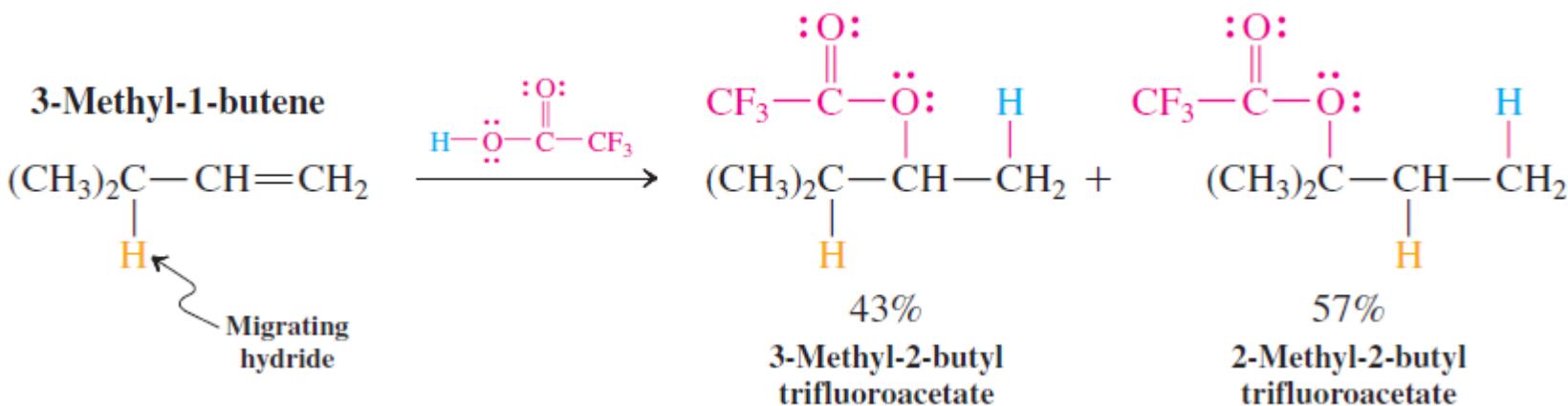
## Regioselective Electrophilic Addition to Propene



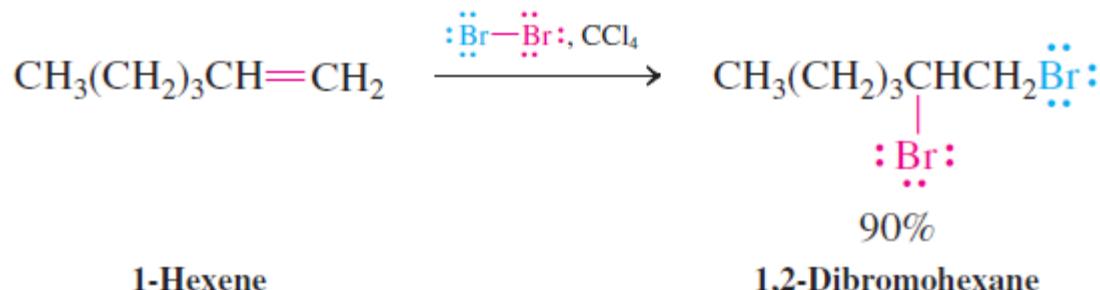
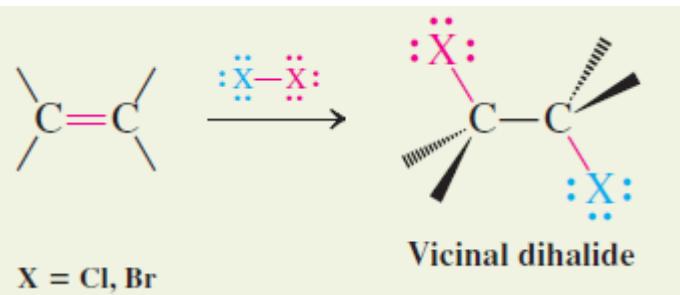
The key is  
the relative stability of the  
resulting carbocation  
intermediates

# Addition Reactions – Addition of HX

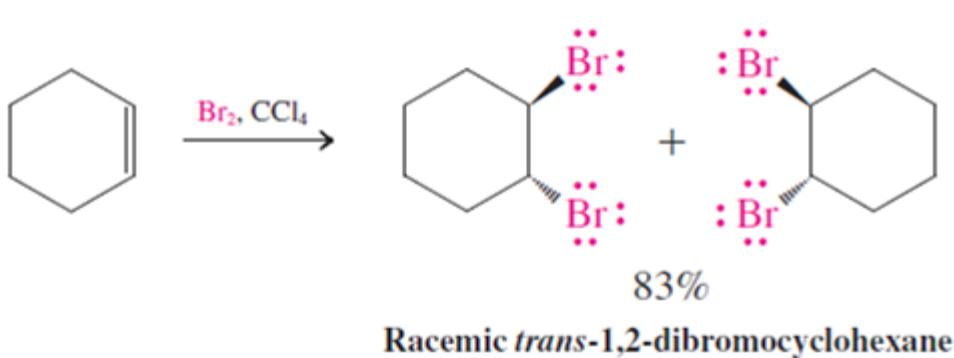
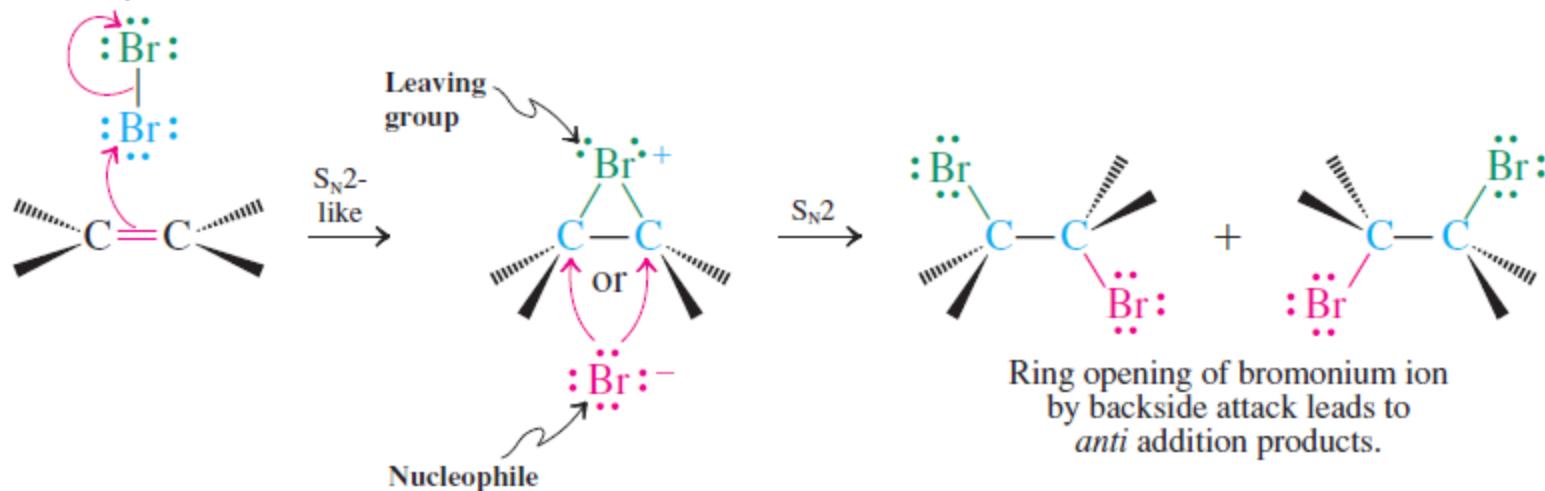
Electrophilic protonation may be followed by carbocation rearrangements



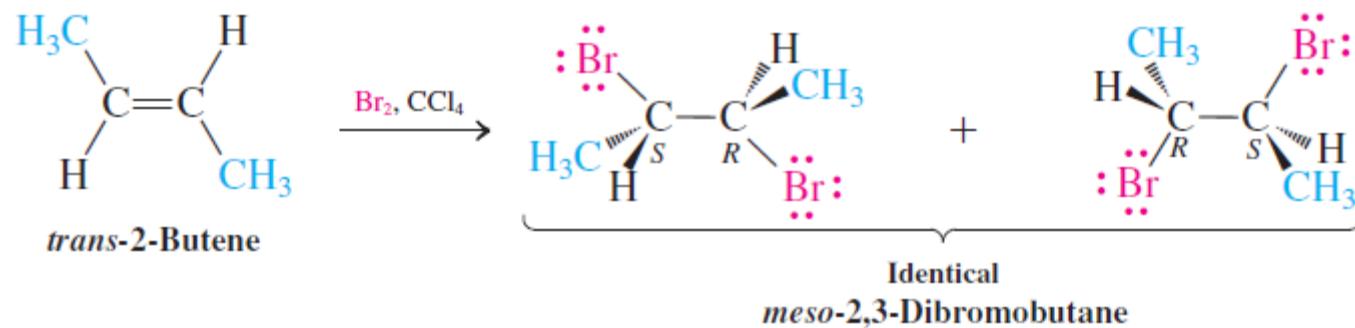
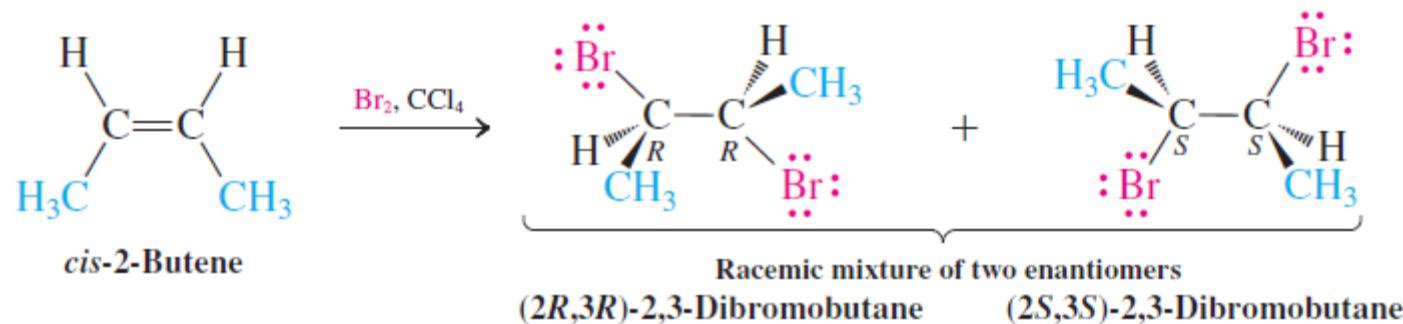
# Addition Reactions – Addition of Halogens



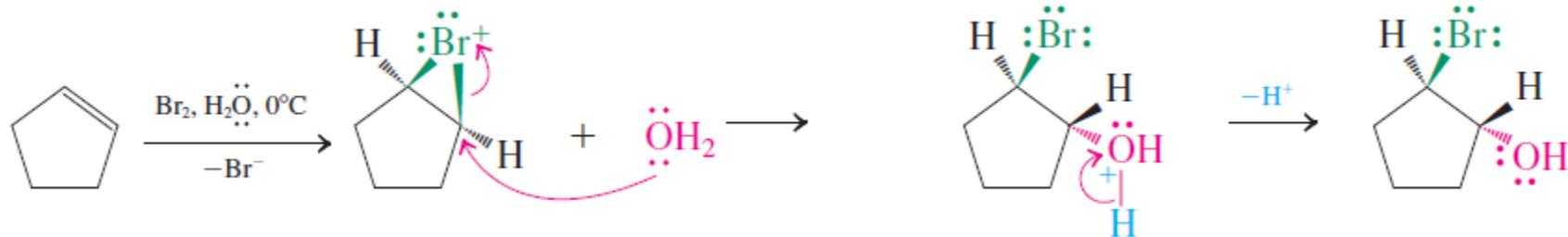
Bromination takes place through *anti* addition, Cyclic bromonium ions explain the stereochemistry



# Addition Reactions – Addition of Halogens

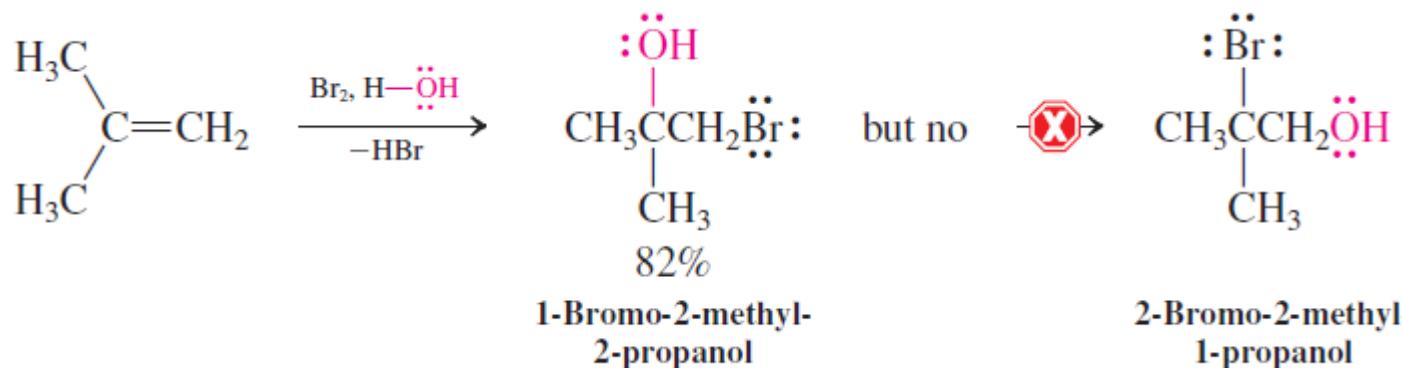


## Bromoalcohol (Bromohydrin) Synthesis

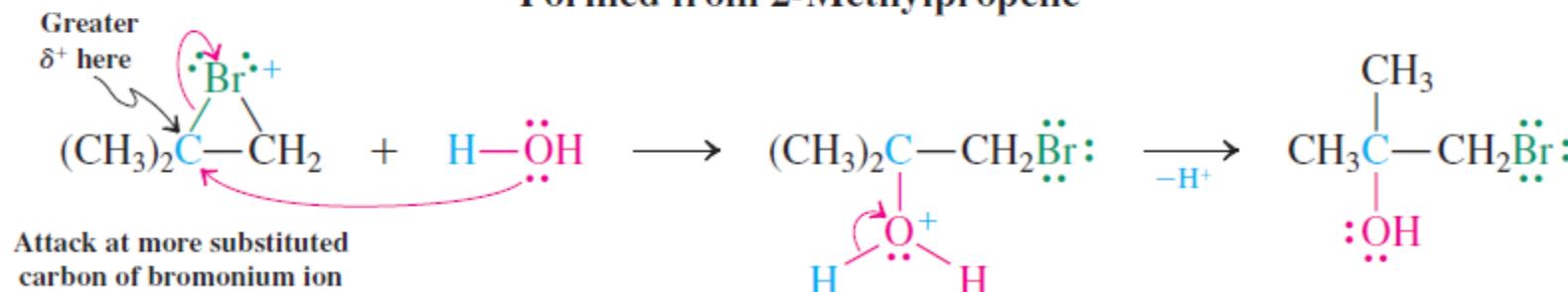


# Addition Reactions – Addition of Halogens

Halonium ion opening can be regioselective



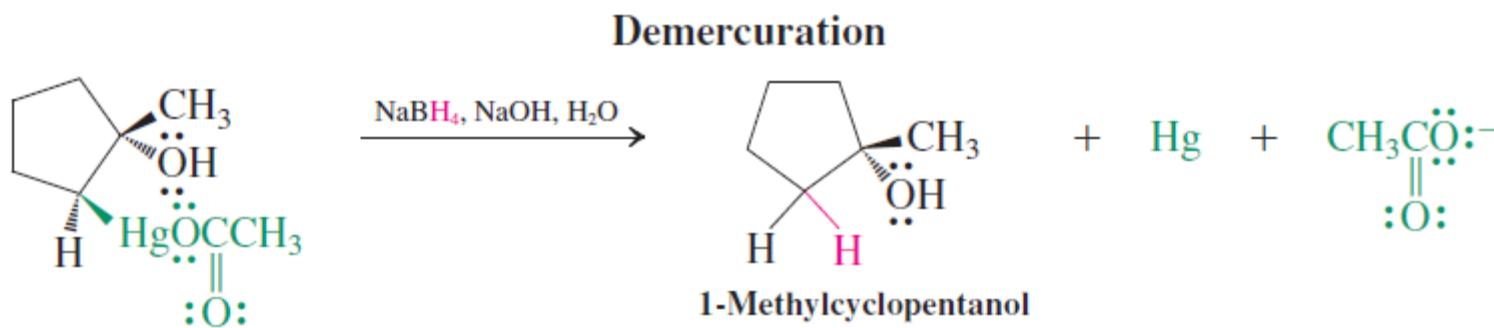
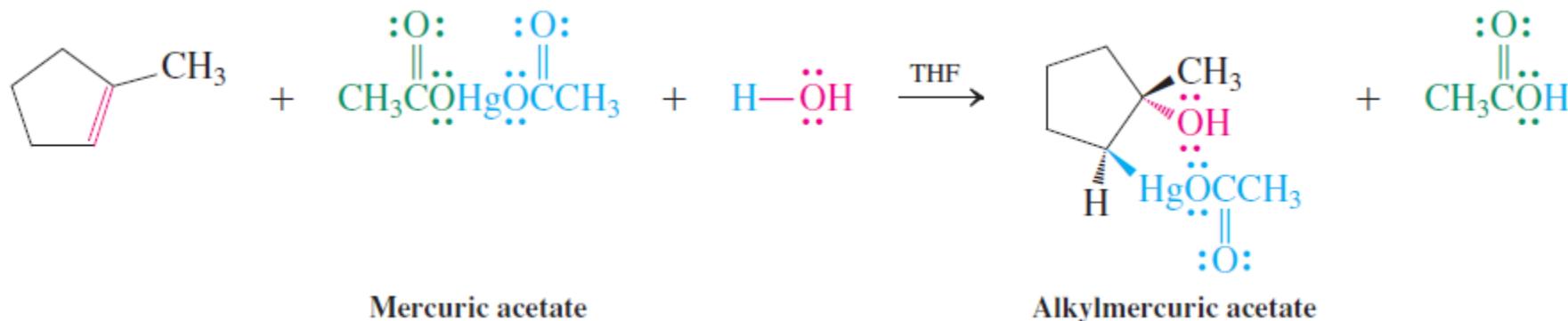
## Regioselective Opening of the Bromonium Ion Formed from 2-Methylpropene



## Addition Reactions – Oxymercuration/demercuration

Electrophilic addition of a mercuric salt to an alkene.

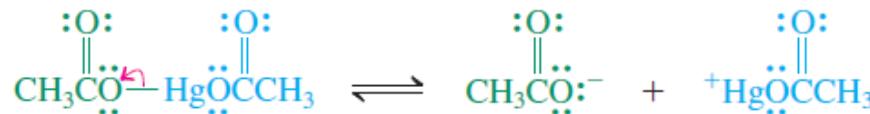
Oxymercuration is anti stereospecific and regioselective



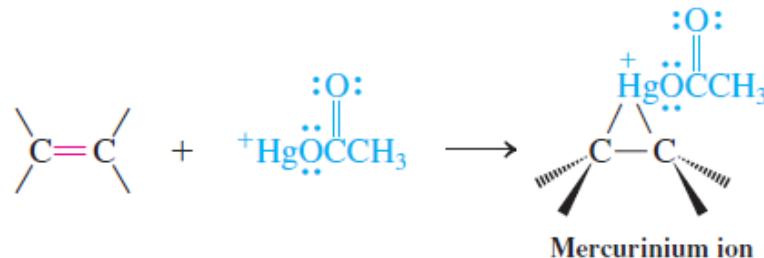
oxymercuration–demercuration is a valuable alternative to acid-catalyzed hydration, because no carbocation is involved; therefore *oxymercuration–demercuration is not susceptible to the rearrangements that commonly occur under acidic conditions*

# Addition Reactions – Oxymercuration/demercuration

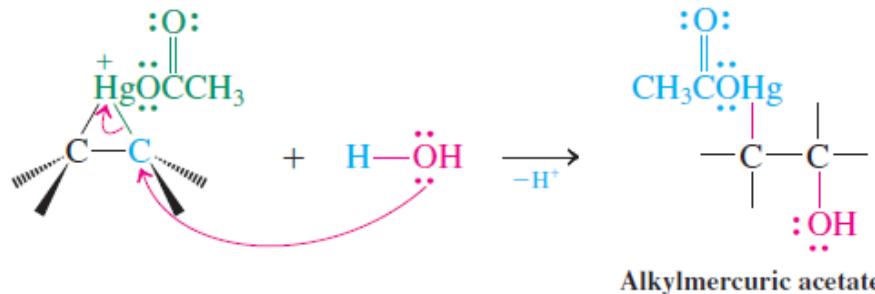
**Step 1.** Dissociation



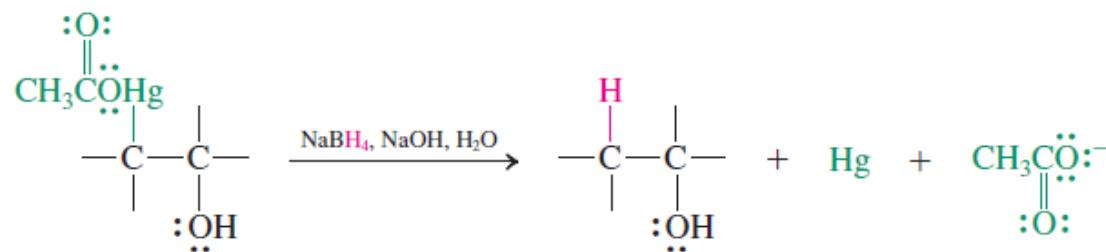
**Step 2.** Electrophilic attack



**Step 3.** Nucleophilic opening (Markovnikov regioselectivity)

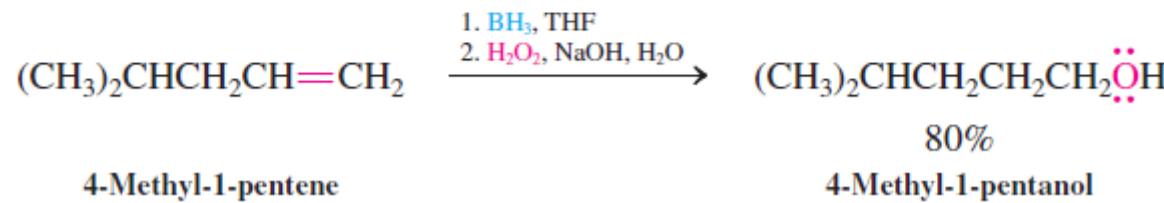
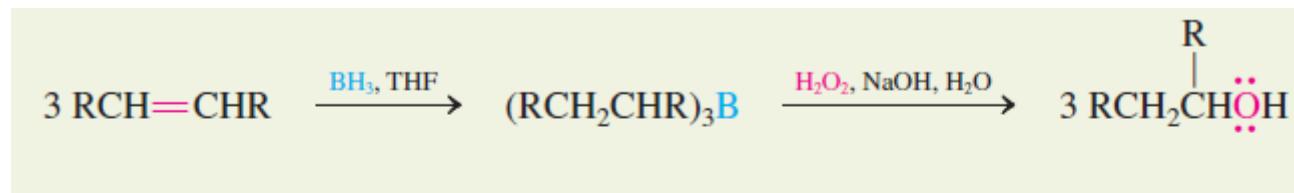


**Step 4.** Reduction

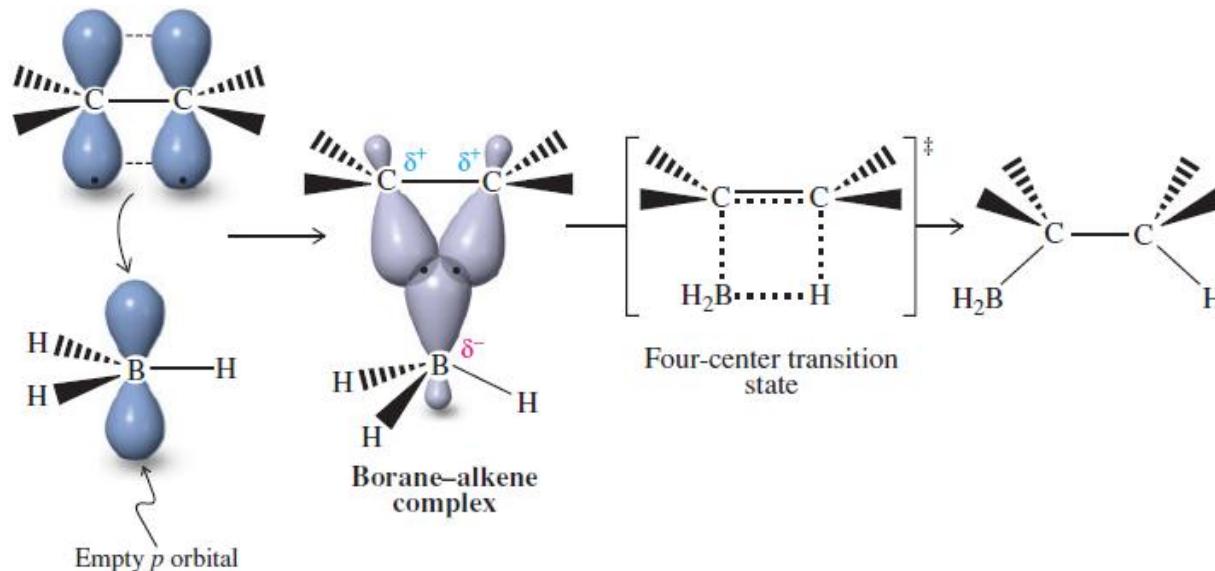


# Addition Reactions - Hydroboration–oxidation

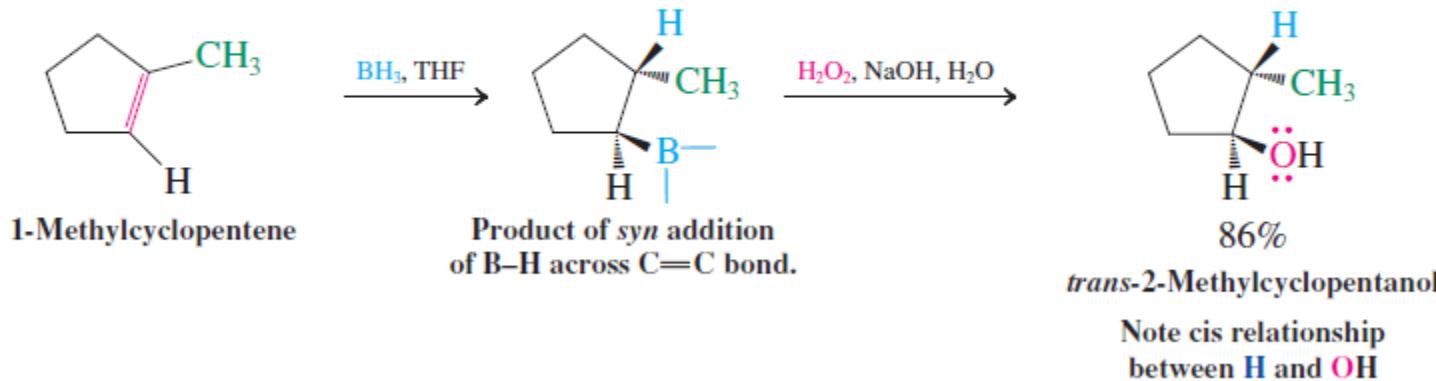
Hydroboration is stereospecific (*syn* addition), it is also regioselective. Hydroboration–oxidation constitutes another method for hydrating alkenes. The initial addition is *syn* and regioselective, the boron shifting to the less hindered carbon. Oxidation of alkyl boranes with basic hydrogen peroxide gives anti-Markovnikov alcohols with retention of configuration of the alkyl group.



# Addition Reactions - Hydroboration–oxidation

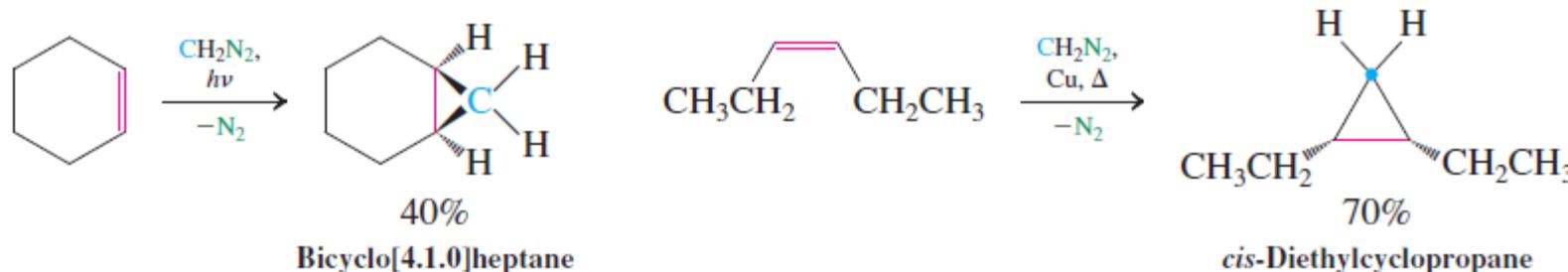
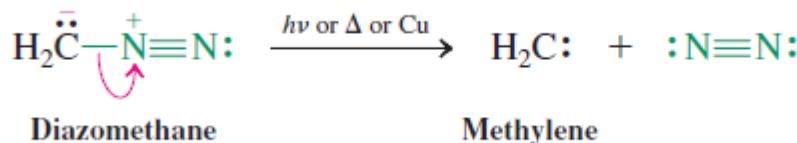


## A Stereospecific and Regioselective Alcohol Synthesis by Hydroboration–Oxidation



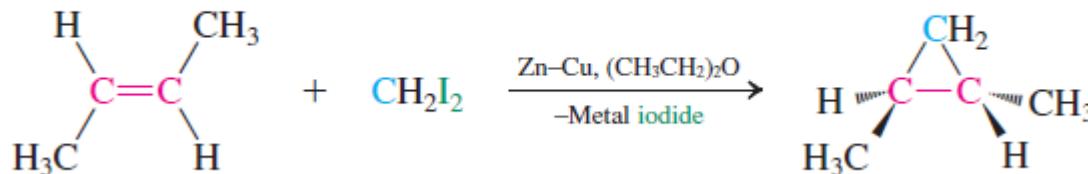
# Addition Reactions - Diazomethane

The unusual substance **diazomethane**,  $\text{CH}_2\text{N}_2$ , is a yellow, highly toxic, and explosive gas. It decomposes on exposure to light, heat, or copper metal by loss of  $\text{N}_2$ . The result is the highly reactive species **methylene**,  $\text{H}_2\text{C:}$ , the simplest carbene.



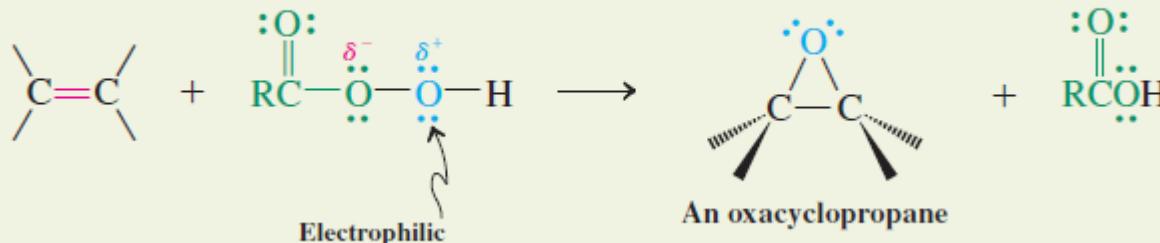
Diiodomethane is treated with zinc powder (usually activated with copper) to generate  $\text{ICH}_2\text{ZnI}$ , called the **Simmons-Smith reagent**. This species is an example of a **carbenoid**, or carbene-like substance, because, like carbenes, it also converts alkenes into cyclopropanes stereospecifically. Use of the Simmons-Smith reagent in cyclopropane synthesis avoids the hazards associated with diazomethane preparation.

## Simmons-Smith Reagent in Cyclopropane Synthesis



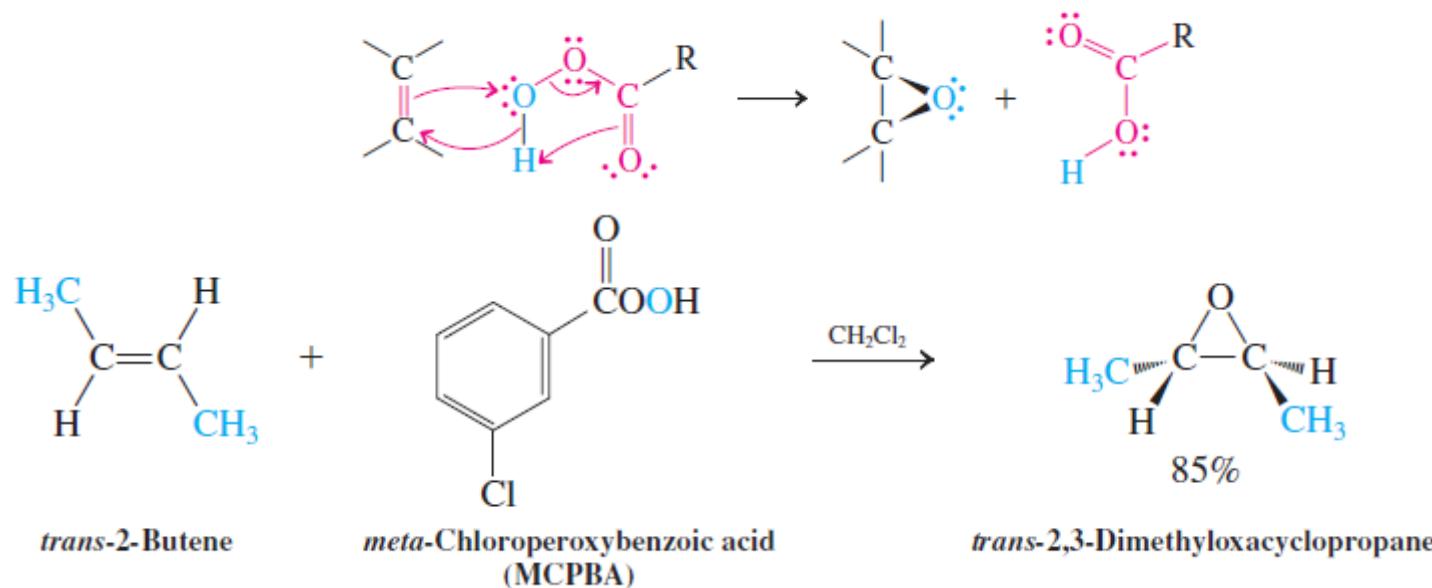
# Addition Reactions - Epoxidation

## Oxacyclopropane Formation: Epoxidation of a Double Bond

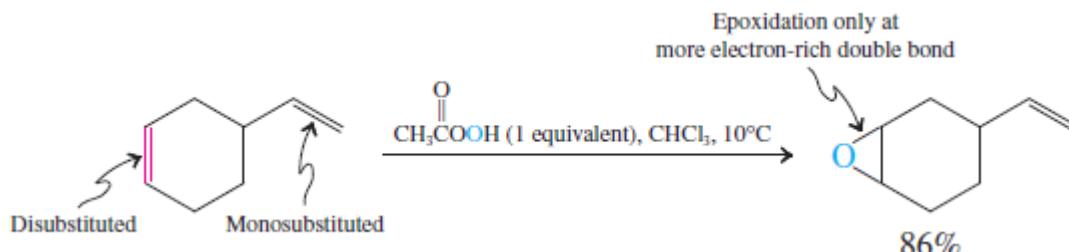


The transfer of oxygen is stereospecifically *syn*, the stereochemistry of the starting alkene being retained in the product. For example, *trans*-2-butene gives *trans*-2,3-dimethyloxacyclopropane; conversely, the *cis*-2-butene yields *cis*-2,3-dimethyloxacyclopropane.

## Mechanism of Oxacyclopropane Formation

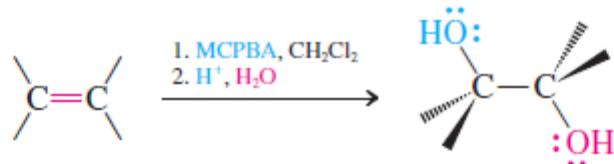


# Addition Reactions - Epoxidation

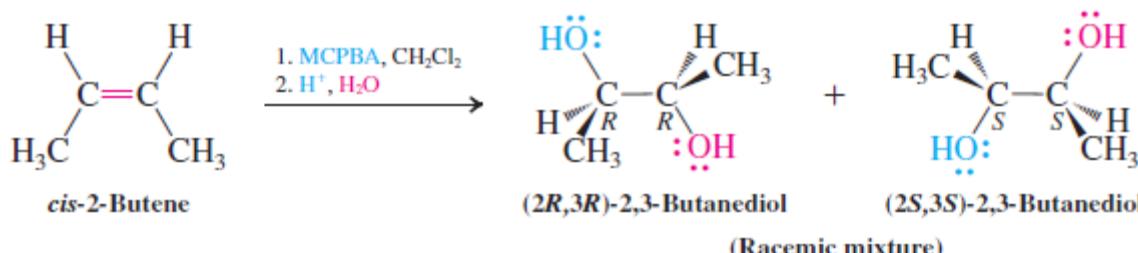
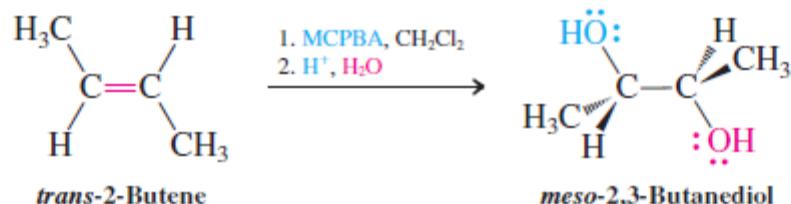


Vicinal *Anti* Diols: The nucleophile (water or hydroxide) attacks the side opposite the oxygen in the three-membered ring, so the net result of the oxidation–hydrolysis sequence constitutes an ***anti* dihydroxylation** of an alkene.

## Vicinal *Anti* Dihydroxylation of Alkenes



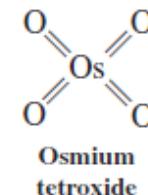
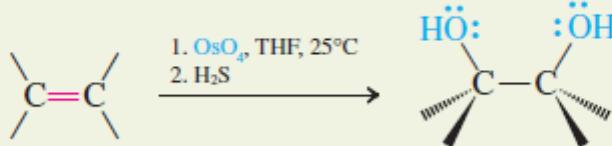
## Synthesis of Isomers of 2,3-Butanediol



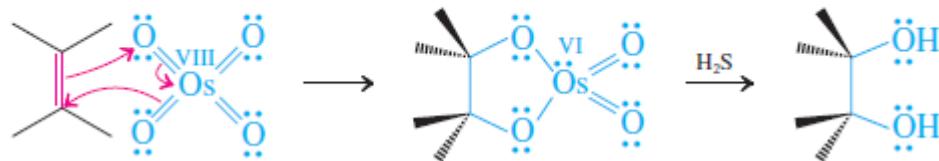
# Addition Reactions – oxidation by OsO<sub>4</sub>

Osmium tetroxide, either stoichiometrically or catalytically together with a second oxidizing agent, converts alkenes into *syn*-1,2-diols.

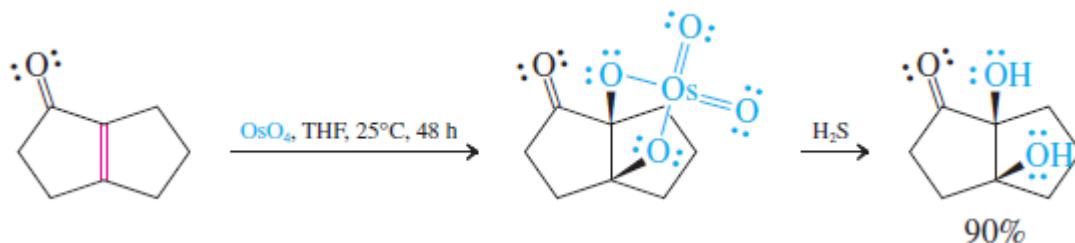
## Vicinal *Syn* Dihydroxylation with Osmium Tetroxide



## Mechanism of the Osmium Tetroxide Oxidation of Alkenes

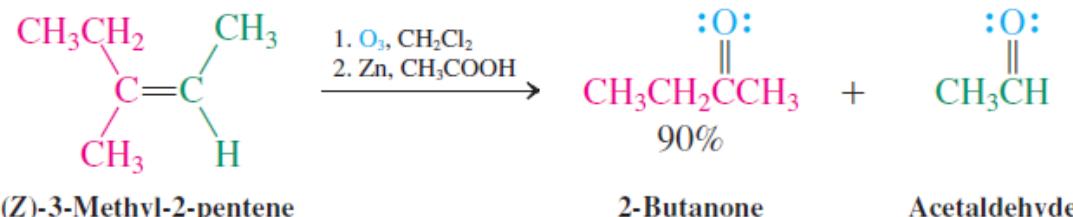
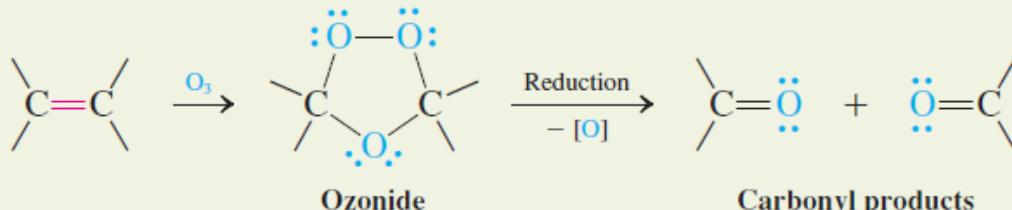


## Vicinal *Syn* Diols



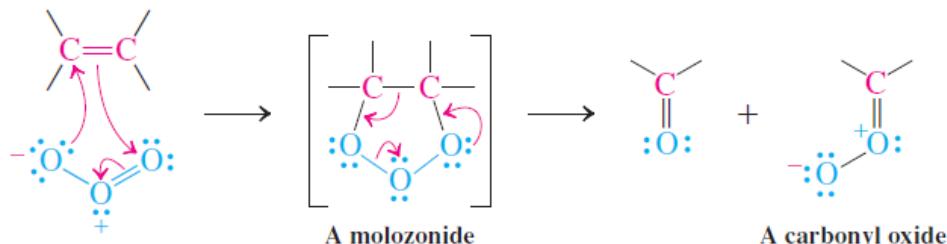
# Addition Reactions - Ozonolysis

## Ozonolysis Reaction of Alkenes



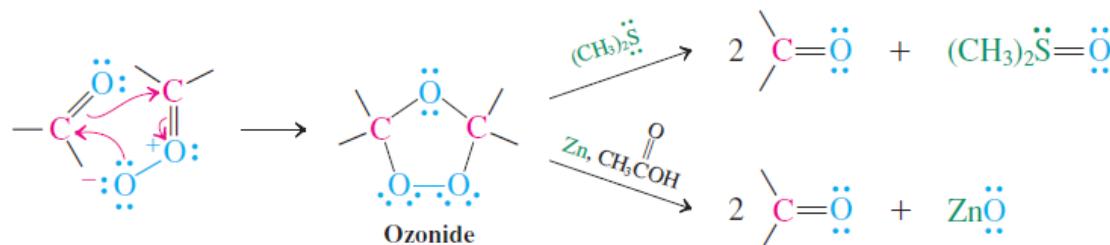
## Mechanism of Ozonolysis

### Step 1. Molozonide formation and cleavage

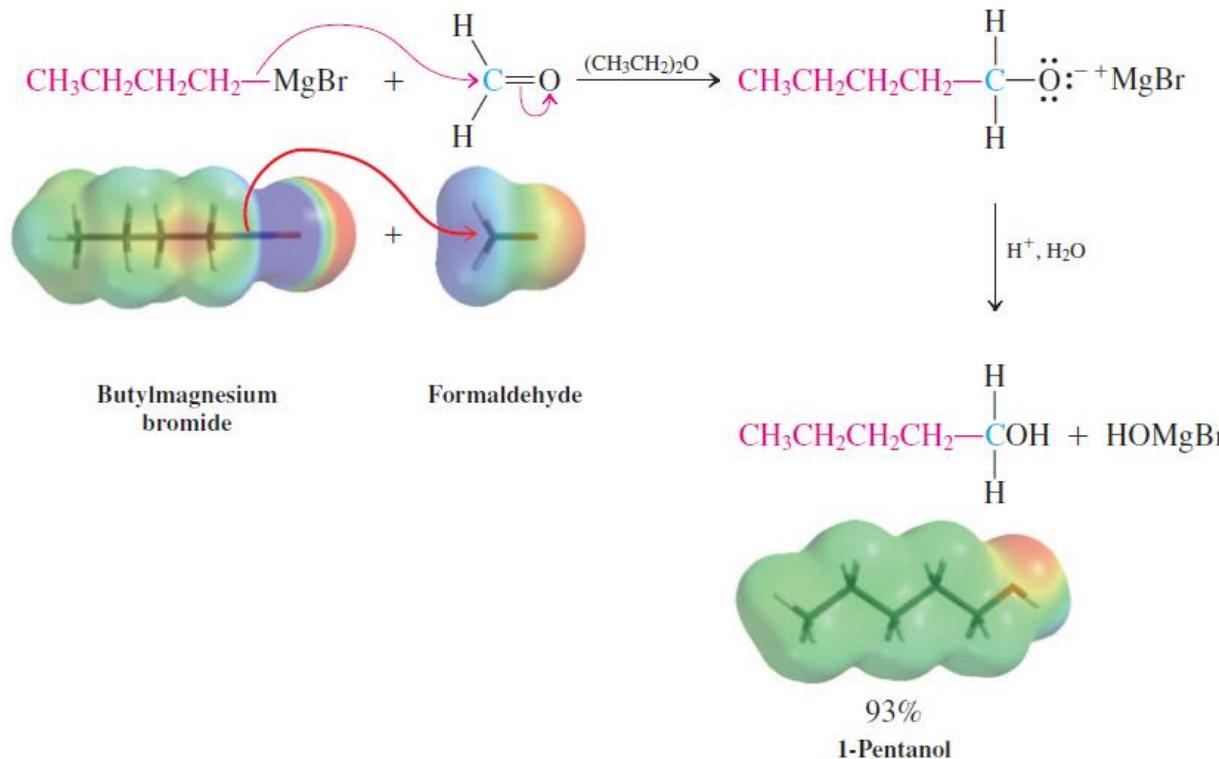
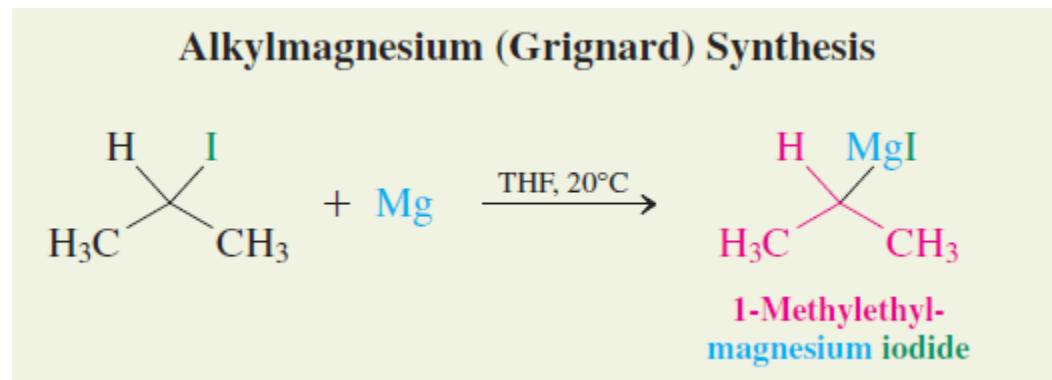


Ozonolysis followed by reduction yields aldehydes and ketones.  
ozonolysis causes cleavage of both the  $\sigma$  and the  $\pi$  bonds.

### Step 2. Ozonide formation and reduction

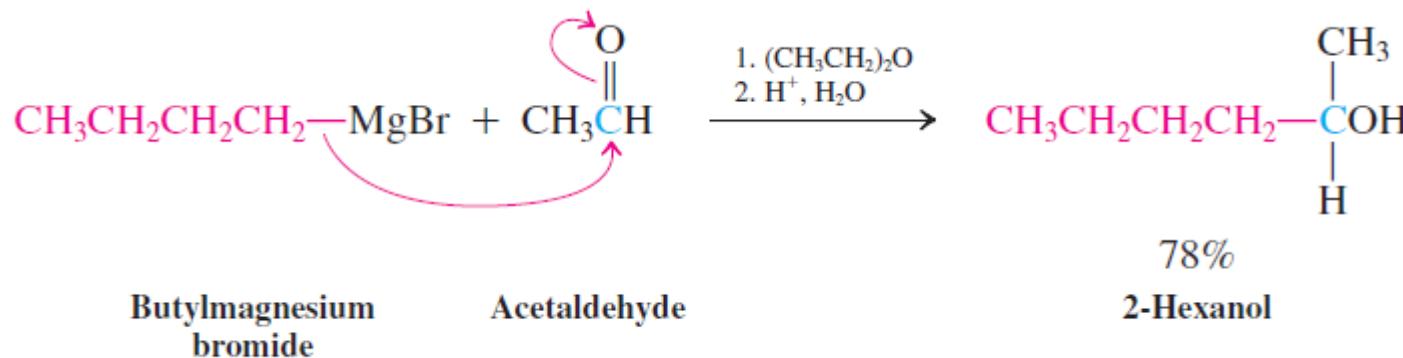


# Addition Reactions - Organometallic Reagents



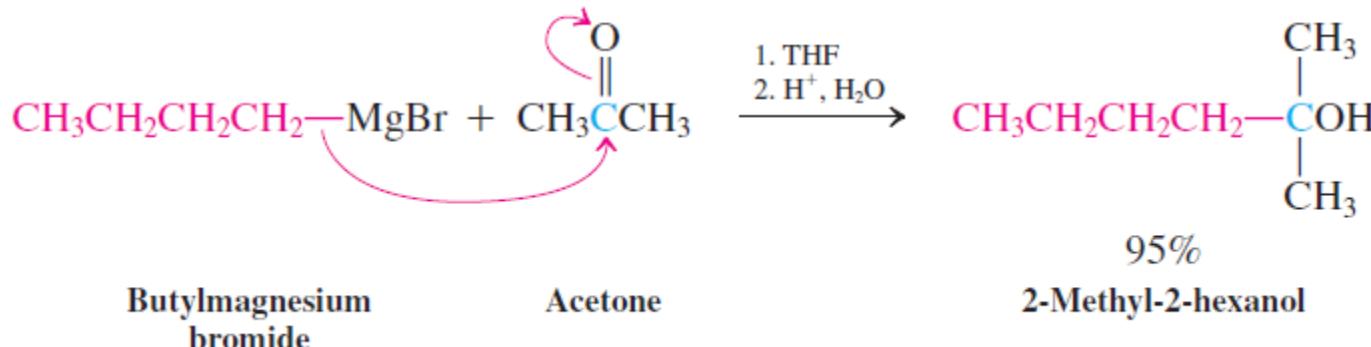
# Addition Reactions

Aldehydes other than formaldehyde convert into secondary alcohols



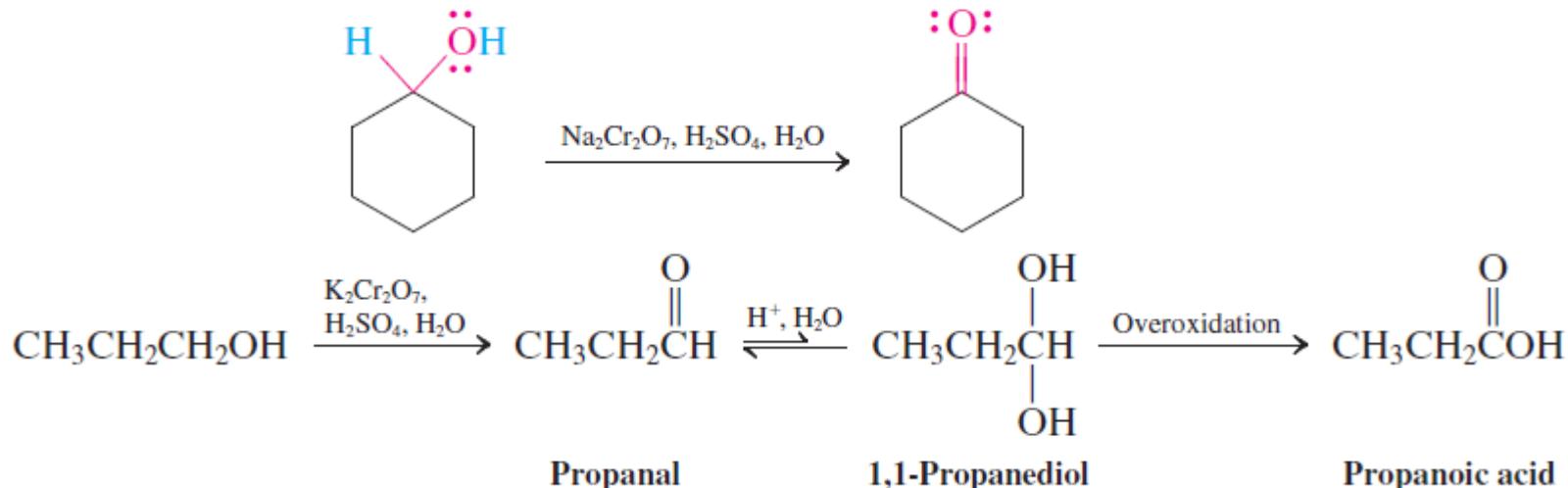
Ketones furnish *tertiary alcohols*.

## Formation of a Tertiary Alcohol from a Grignard Reagent and a Ketone

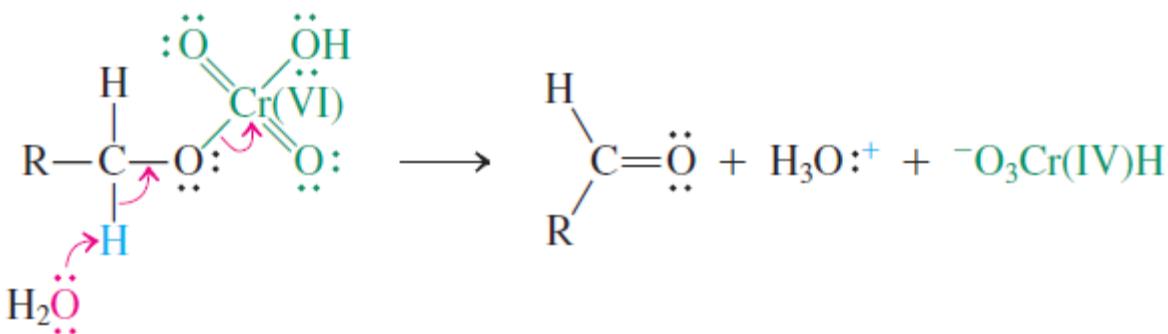
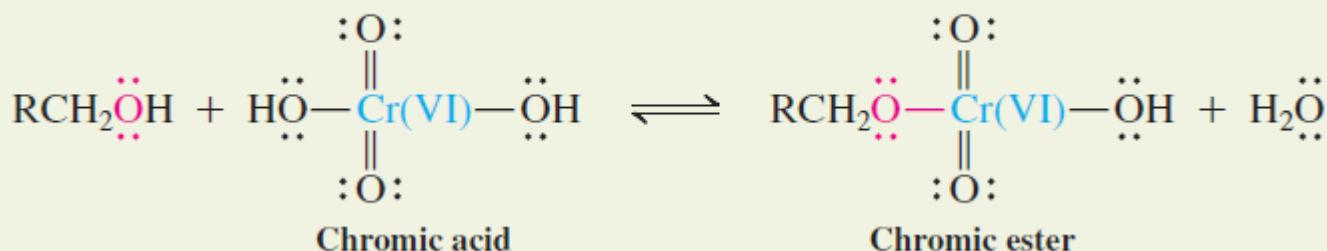


# Oxidation Reactions

## Oxidation of a Secondary Alcohol to a Ketone with Aqueous Cr(VI)

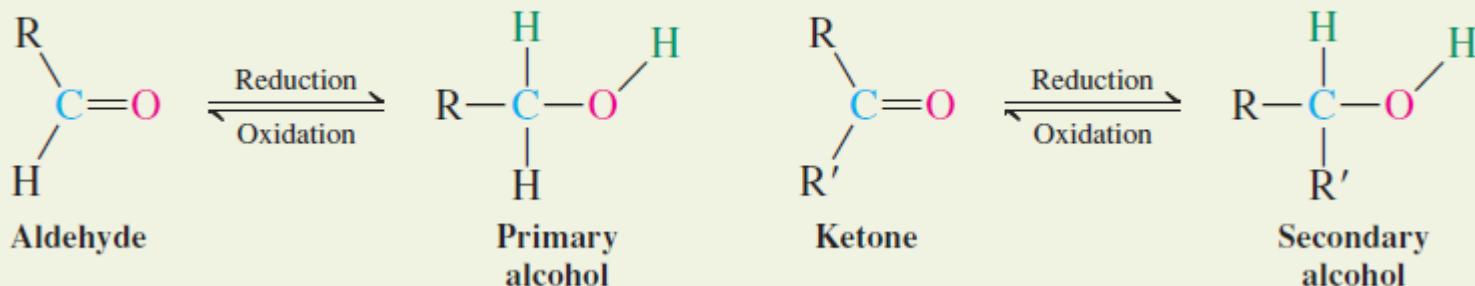


### Chromic Ester Formation from an Alcohol

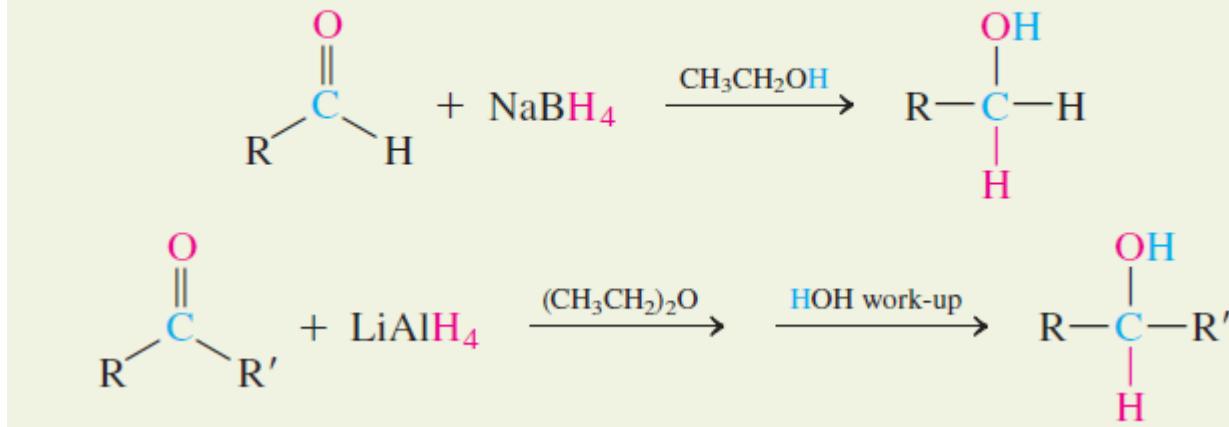


# Reduction Reactions

## The Redox Relation Between Alcohols and Carbonyl Compounds

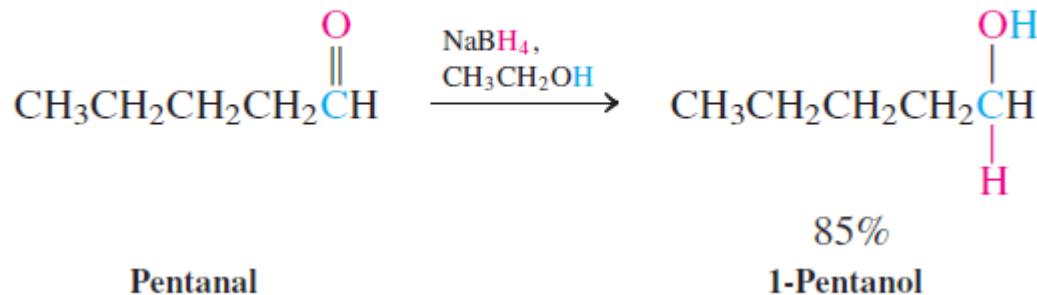


## General Hydride Reductions of Aldehydes and Ketones to Alcohols

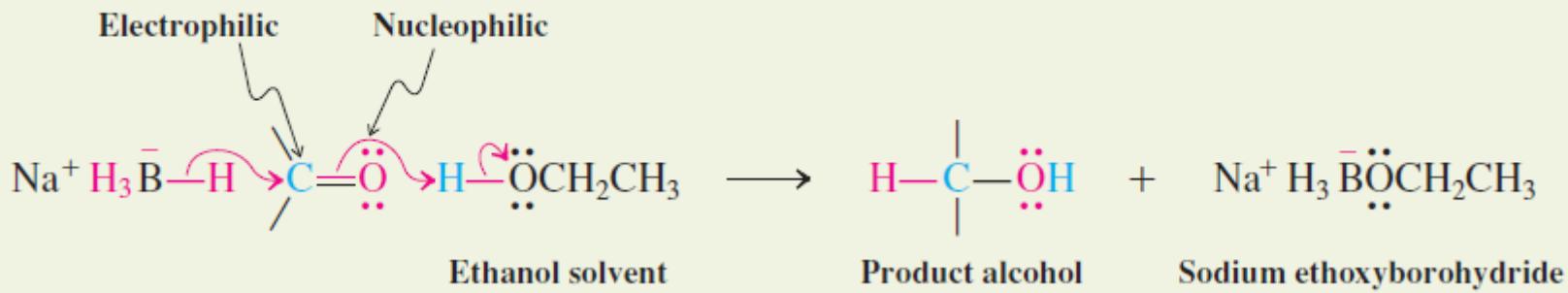


# Reduction Reactions

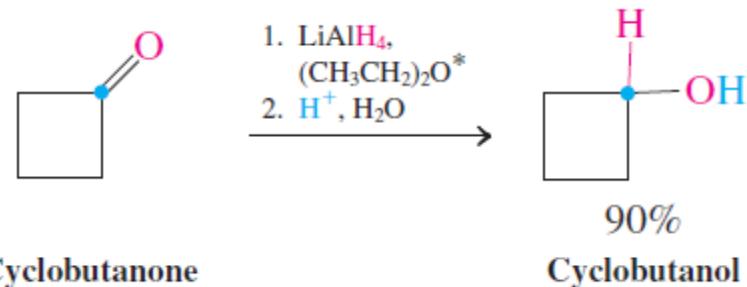
## Examples of Hydride Reductions of Aldehydes and Ketones to Alcohols



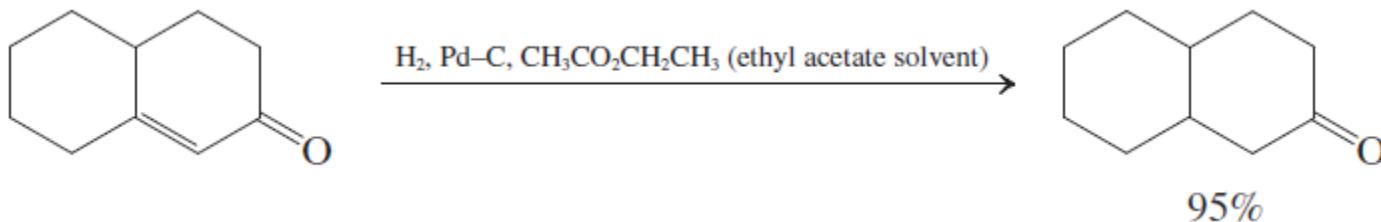
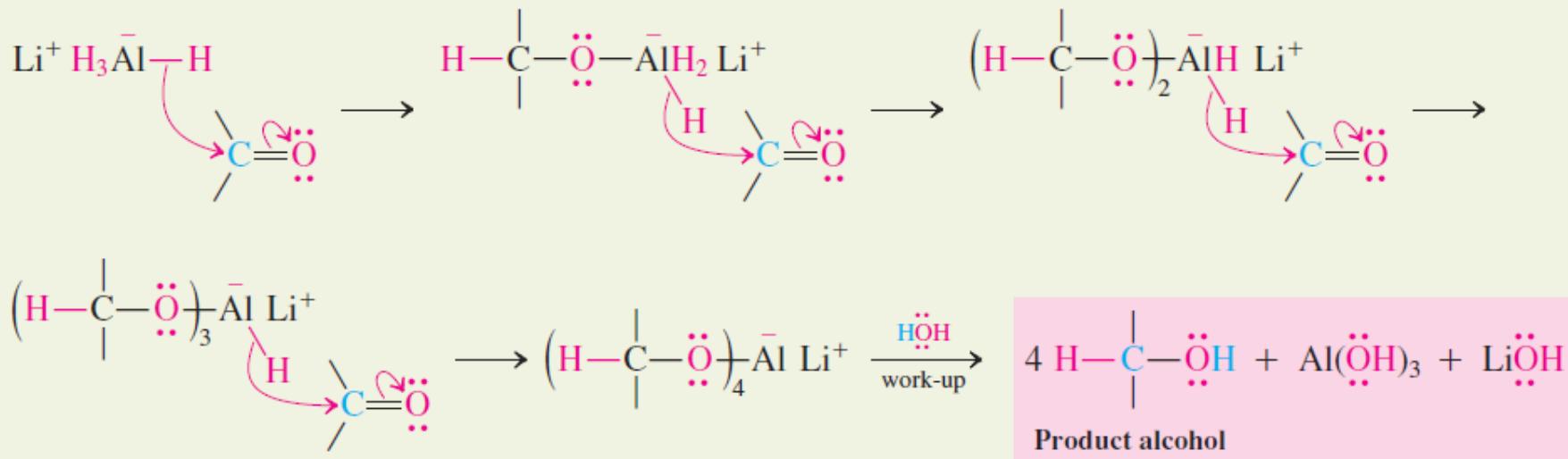
### Mechanism of $\text{NaBH}_4$ Reduction



# Reduction Reactions

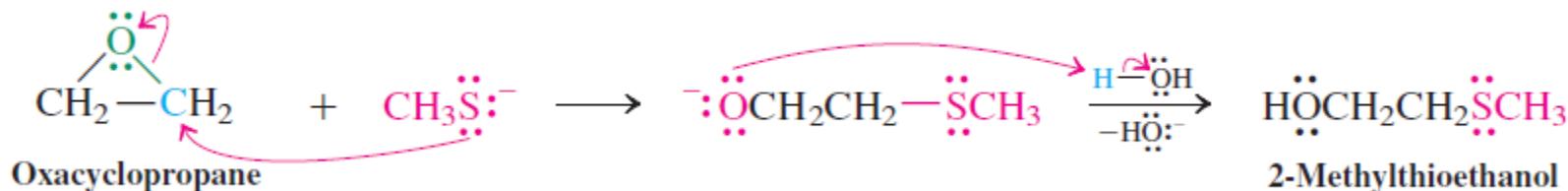


# Mechanism of Lithium Aluminum Hydride Reduction

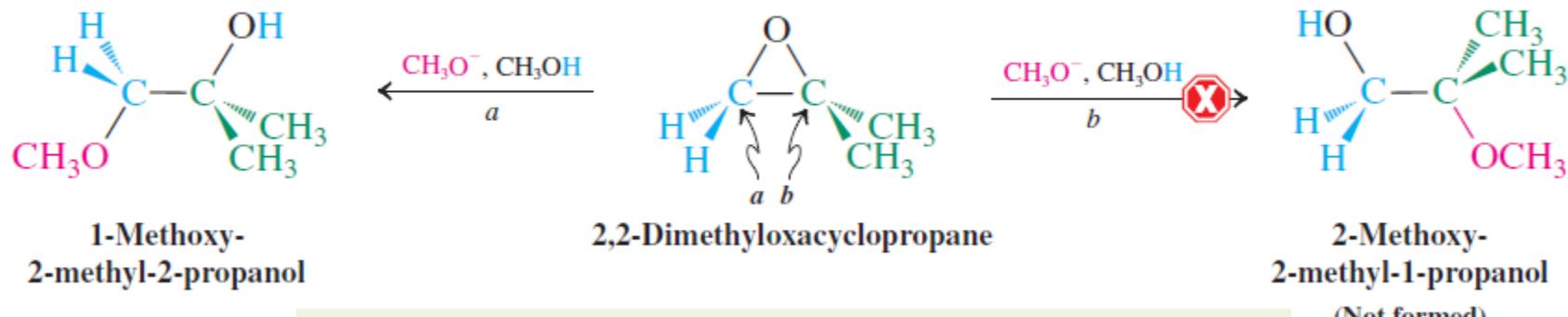


# Ring-opening Reactions

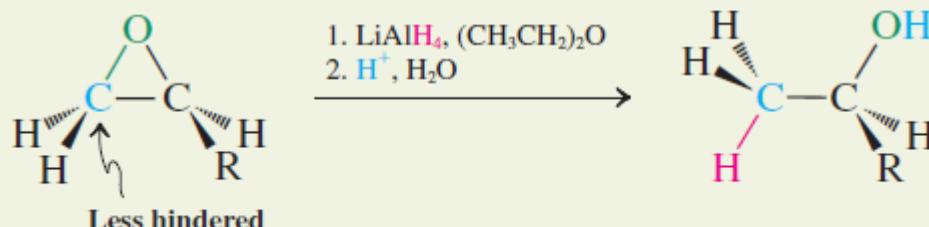
Nucleophilic ring opening of oxacyclopropanes by S<sub>N</sub>2 is regioselective and stereospecific



## Nucleophilic Ring Opening of an Unsymmetrically Substituted Oxacyclopropane

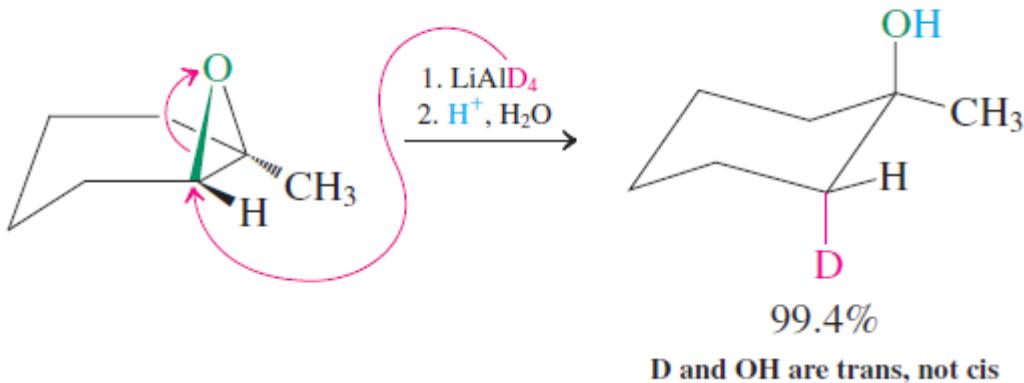


## Ring Opening of an Oxacyclopropane by Lithium Aluminum Hydride

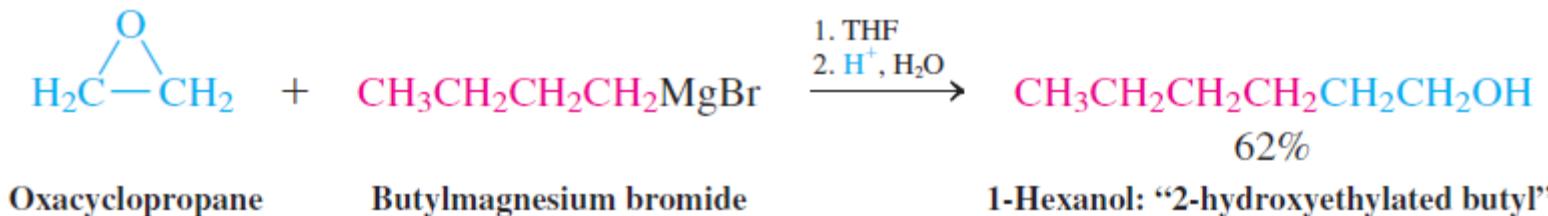


# Ring-opening Reactions

## Inversion on Oxacyclopropane Opening

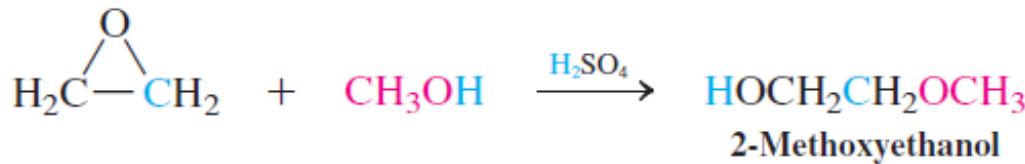


## Oxacyclopropane Ring Opening by a Grignard Reagent: 2-Hydroxyethylation

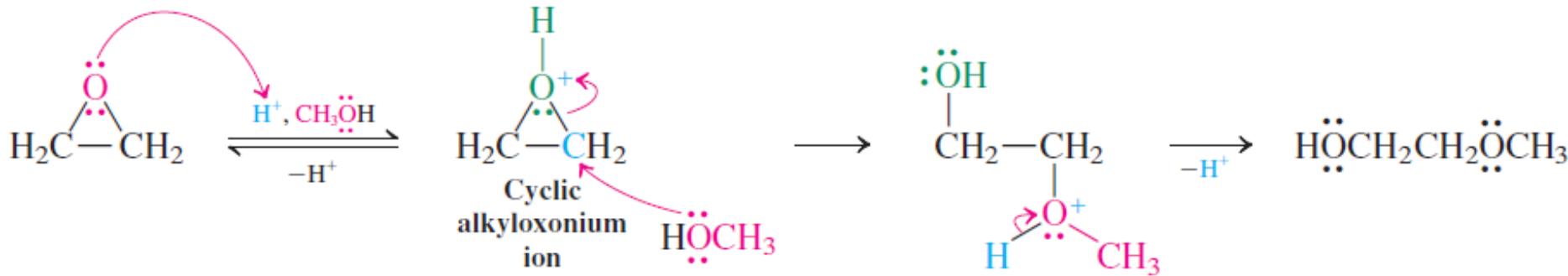


# Ring-opening Reactions

## Acid-Catalyzed Ring Opening of Oxacyclopropane

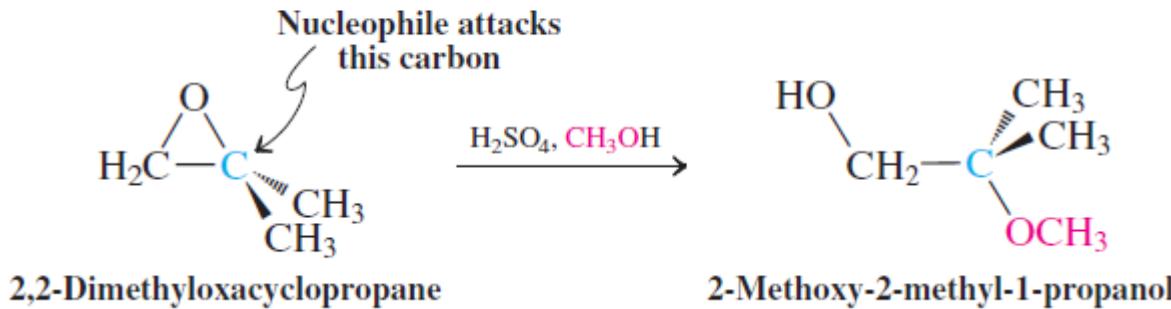


## Mechanism of Acid-Catalyzed Ring Opening

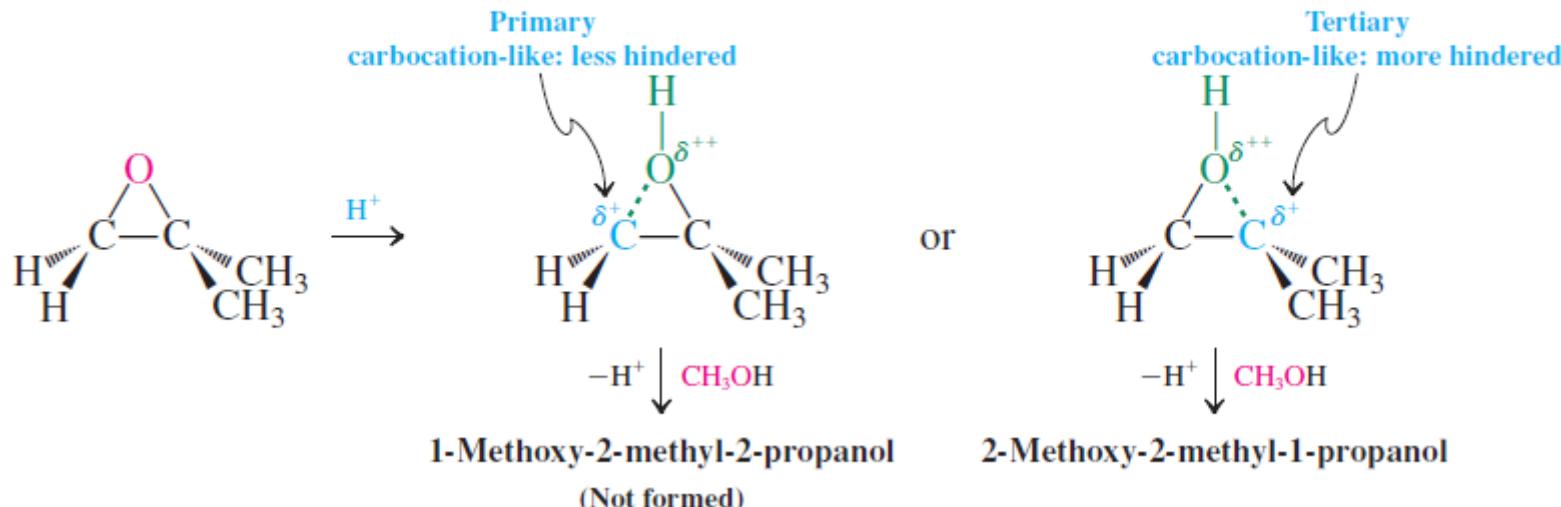


# Ring-opening Reactions

## Acid-Catalyzed Ring Opening of 2,2-Dimethyloxacyclopropane

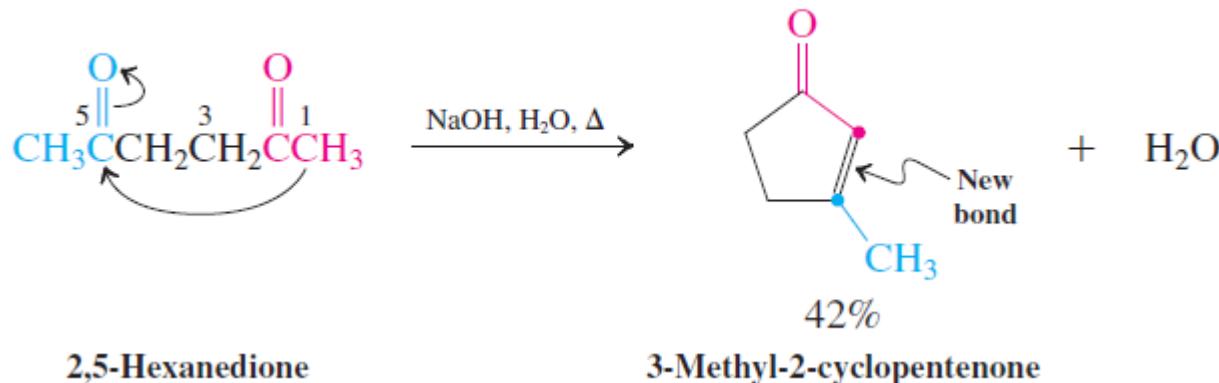


## Mechanism of Acid-Catalyzed Ring Opening of 2,2-Dimethyloxacyclopropane by Methanol

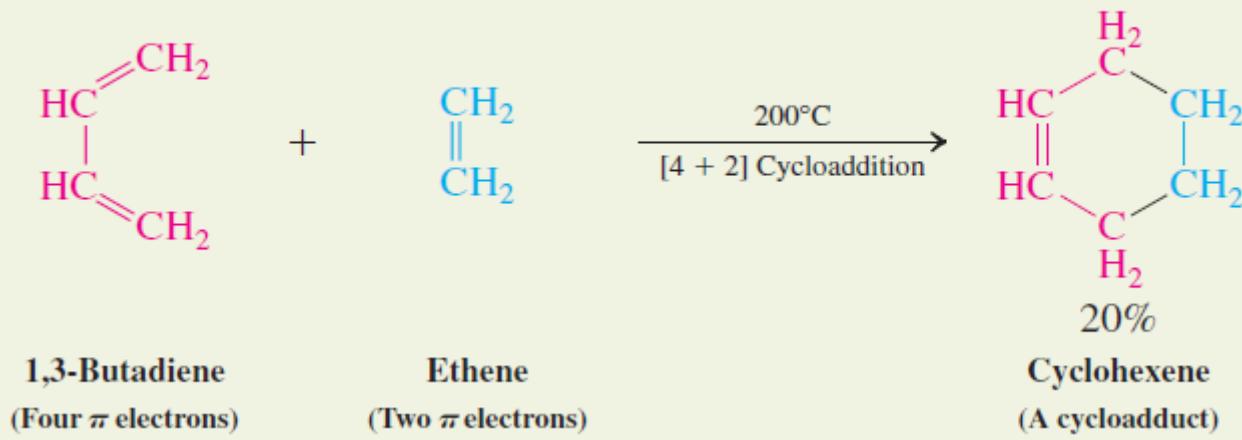


# Cyclization Reactions

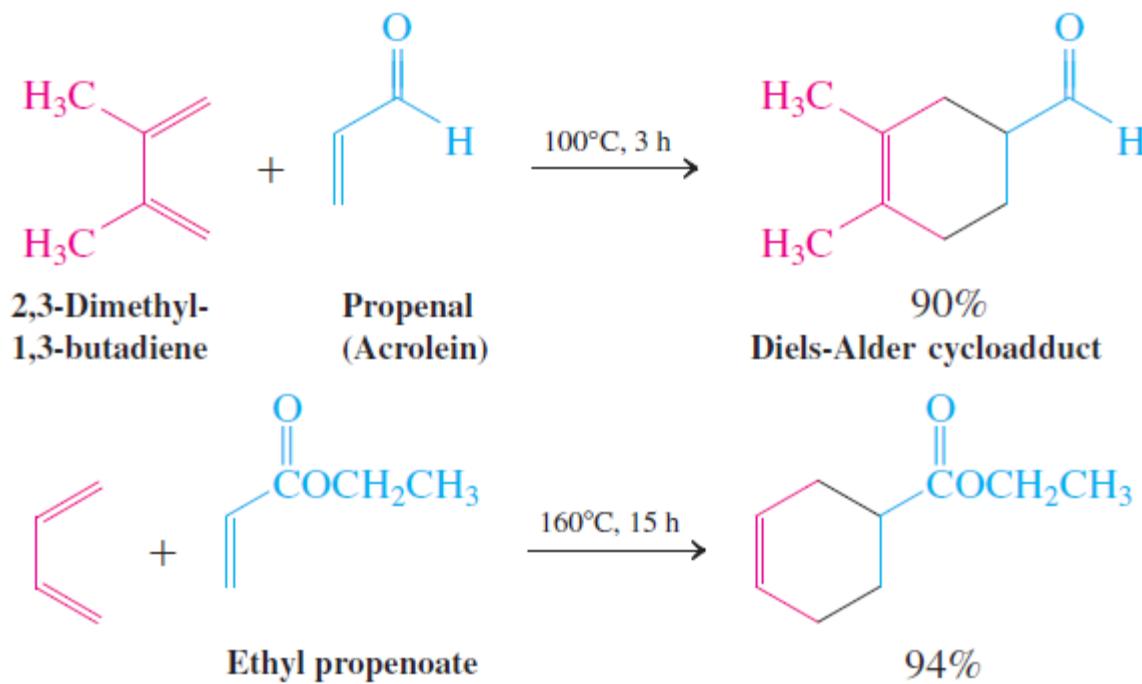
## Intramolecular Aldol Condensation of a Dione



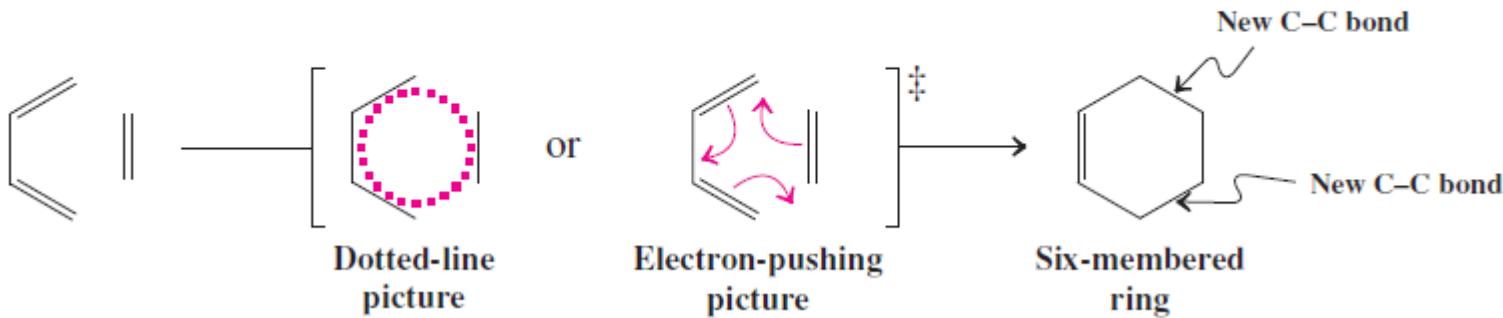
## Diels-Alder Cycloaddition of Ethene and 1,3-Butadiene



# Cyclization Reactions

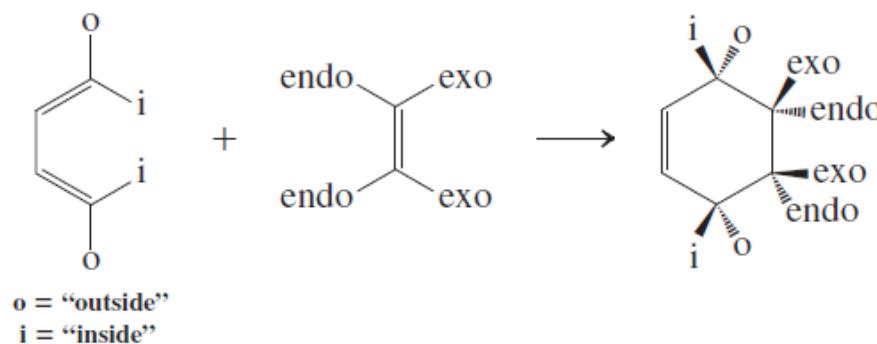
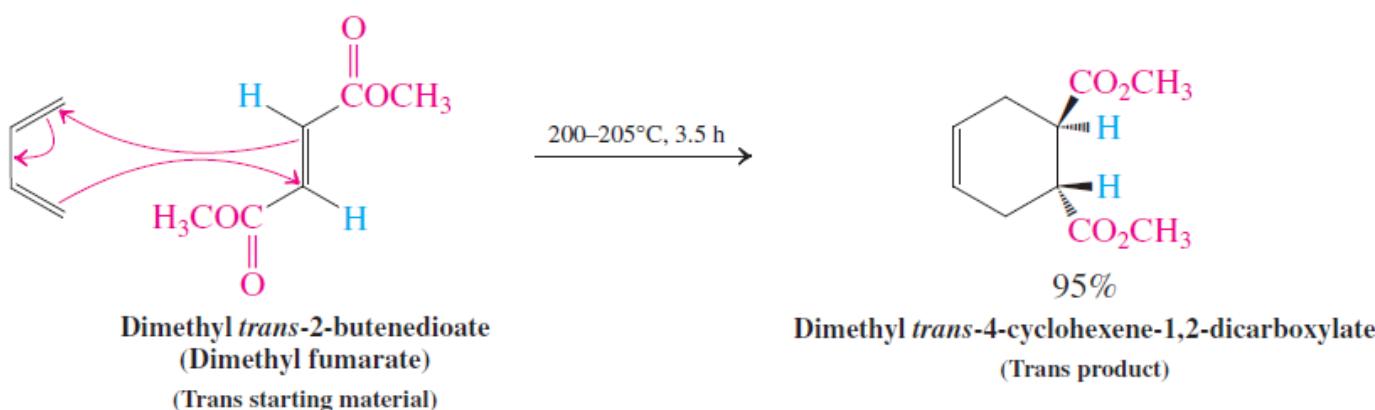
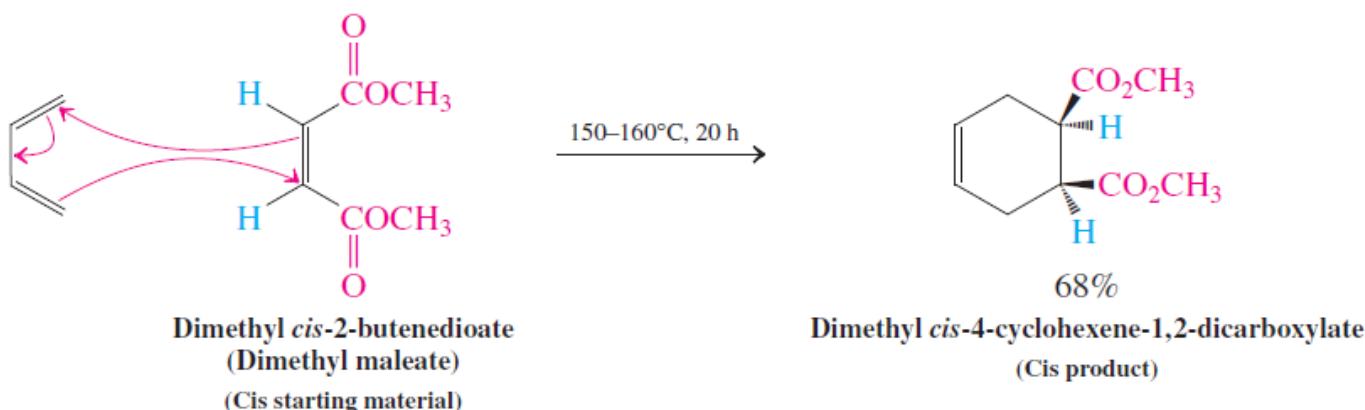


## Two Pictures of the Transition State of the Diels-Alder Reaction

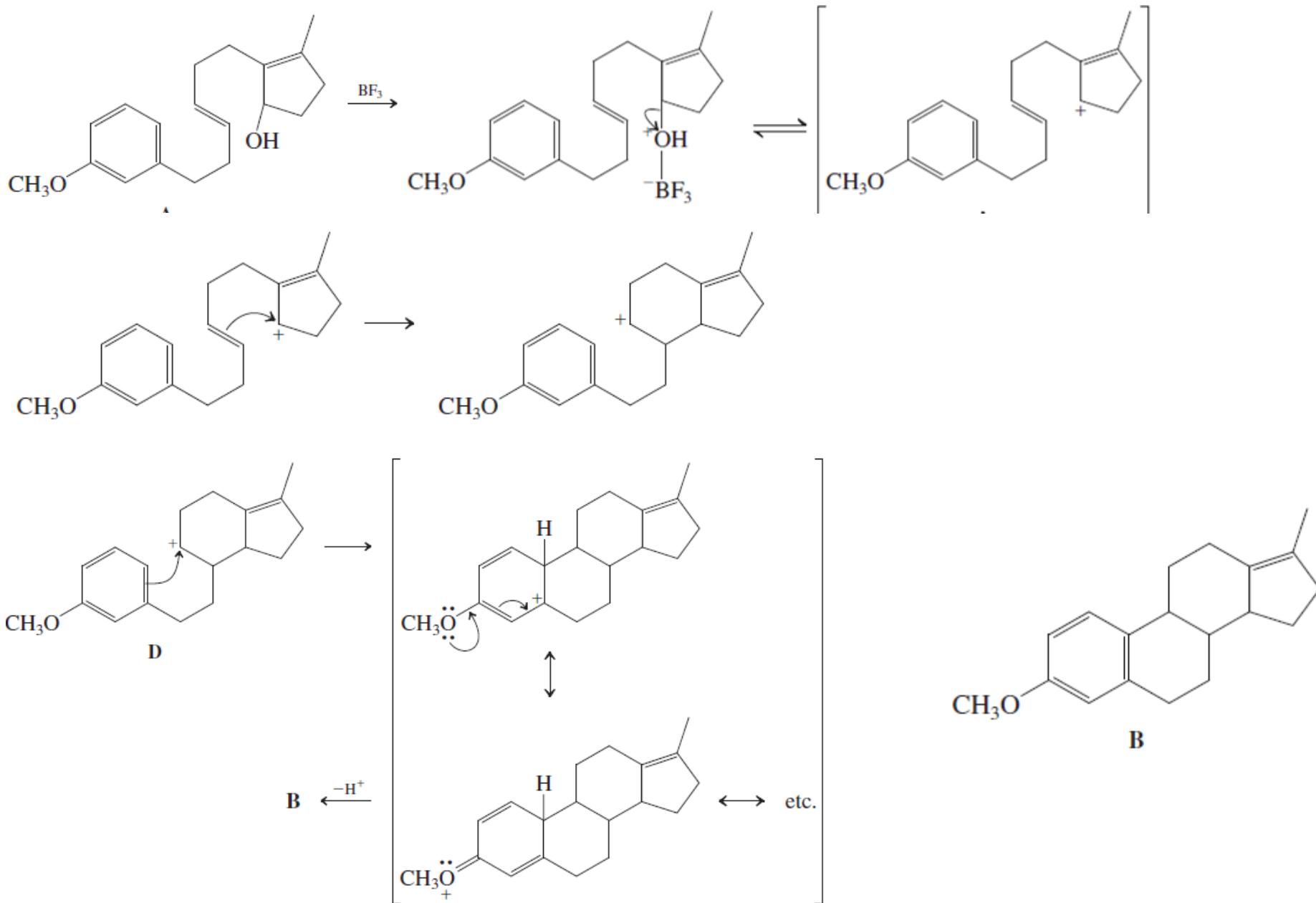


# Cyclization Reactions

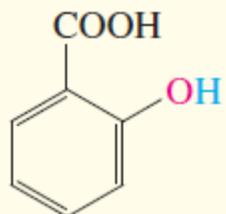
In the Diels-Alder Reaction, the Stereochemistry of the Dienophile and diene is Retained



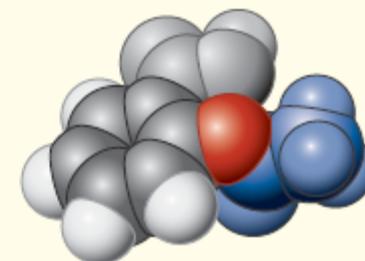
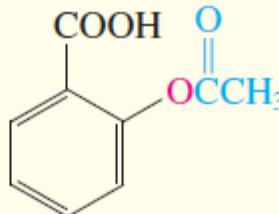
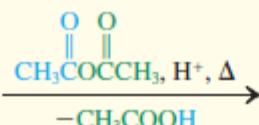
# Cyclization Reactions



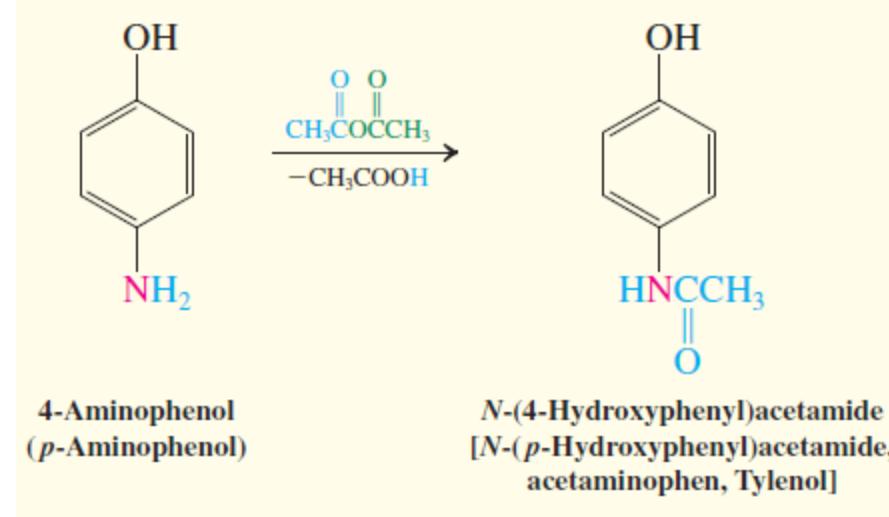
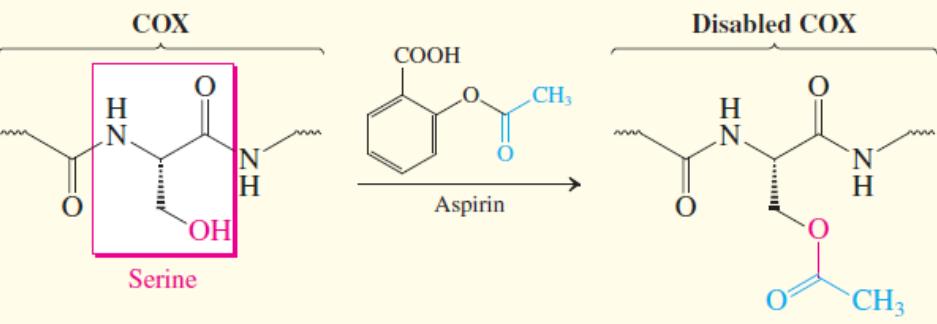
# Aspirin – Acetaminophen: Drug



2-Hydroxybenzoic acid  
(*o*-Hydroxybenzoic acid,  
salicylic acid)



2-Acetoxybenzoic acid  
(*o*-Acetoxybenzoic acid,  
acetylsalicylic acid, aspirin)



Cyclooxygenase mediates the production of prostaglandins molecules that in turn are inflammatory and pain producing. In addition, one of them aggregates blood platelets, necessary for the clotting of blood when injury occurs.

aspirin can have some serious side effects: It is toxic to the liver, prolongs bleeding, and causes gastric irritation. Because of some of these drawbacks, many other drugs compete with aspirin, particularly in the analgesics market, such as naproxen, ibuprofen, and acetaminophen.

# Proparacaine - Anesthetic

Proparacaine is a local anesthetic that is used primarily to numb the eye before minor surgical procedures, such as the removal of foreign objects or stitches.

