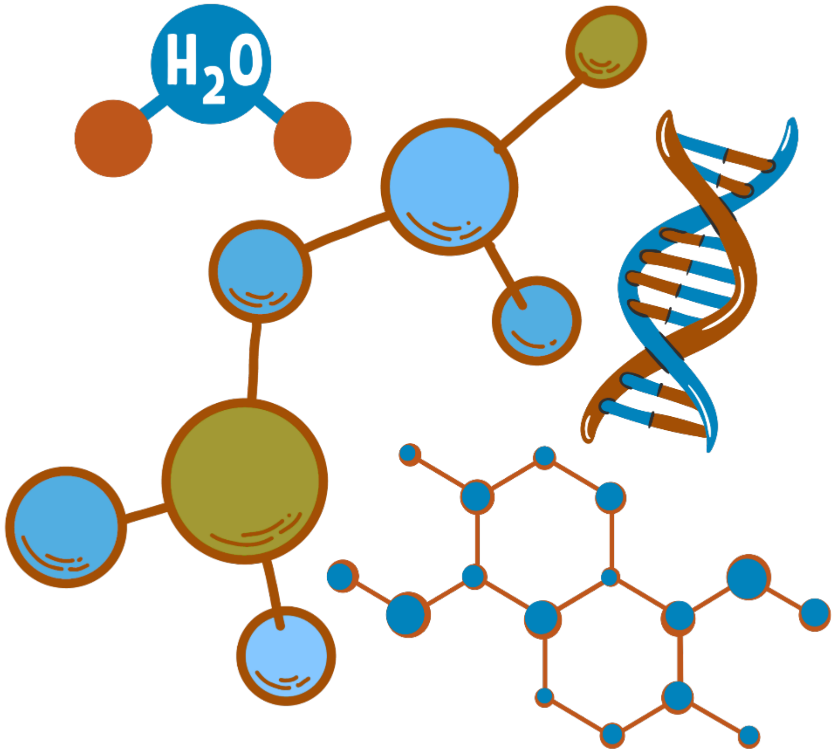
Introduction to Organic Chemistry
CHEM 109

جامعة الملك سعود
King Saud University
COLLEGE OF SCIENCES
CHEMISTRY DEPARTMENT

Chapter 5: Organic Reactions



Acid-Base Reactions

1.Acid-Base Reactions

- Two classes of acid–base reactions are fundamental in organic chemistry;

1.1 Bronsted–Lowry Acids and Base

Brønsted–Lowry acid–base reactions involve the transfer of protons.

- Brønsted–Lowry acid is a substance that can donate (or lose) a proton.

  Example; HCl; donates a proton to H_2O.

- Brønsted–Lowry base is a substance that can accept (or remove) a proton.

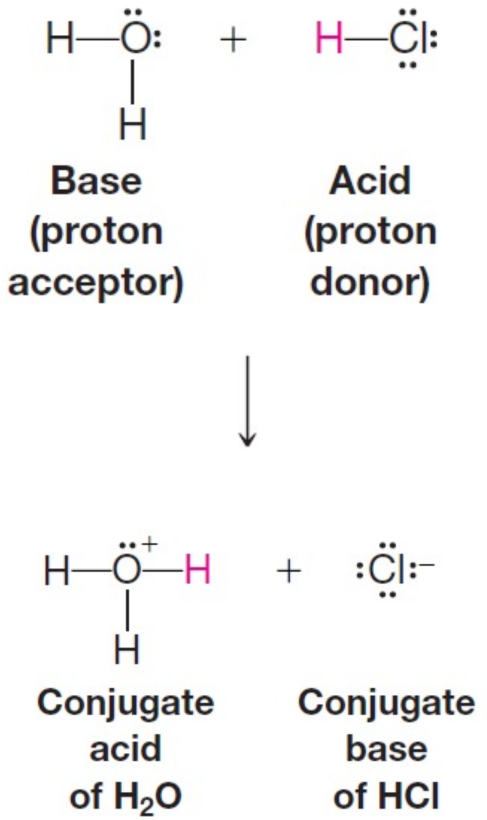
  Example; H_2O; accepts a proton from HCl.

- The products are classified as;
  - Conjugate base (Chloride ion (Cl^-)); it forms when an acid loses its proton.
  - Conjugate acid (Hydronium ion (H_3O^+)); it forms when a base accepts a proton.

- Acid strength;

  Acid strength is a measure of the percentage of ionization and not of concentration.

  Acid strength depends on the extent to which a proton can be separated from it and transferred to a base.



1. Acid-Base Reactions

1.2 Lewis Acids and Bases

In 1923 G. N. Lewis proposed the following definitions for acids and bases.

- **Lewis acid** is electron pair acceptors (i.e. any electron-deficient atom and that have atoms with vacant orbital).

  Example; Aluminum chloride ($AlCl_3$) ; accept electrons.

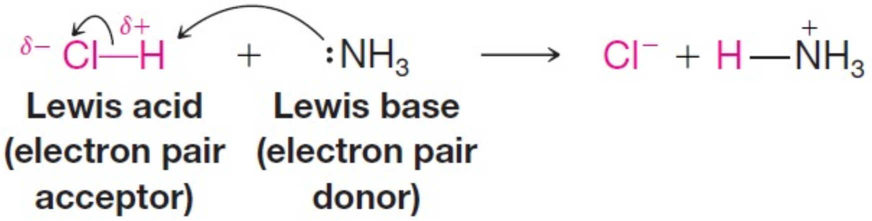
- **Lewis base** is electron pair donors (i.e. Any electron-rich atom).

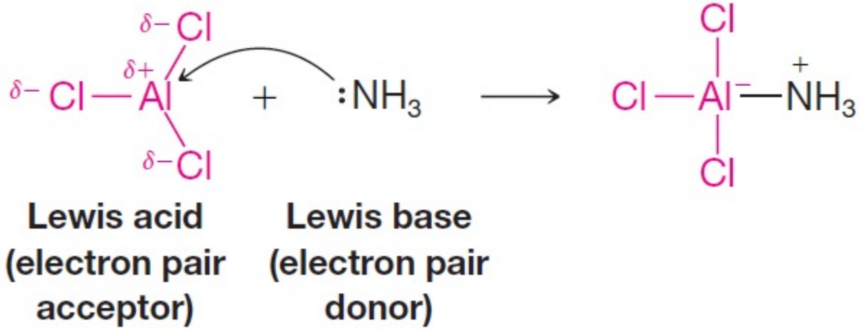
  Example; ammonia (NH_3); donate electrons.

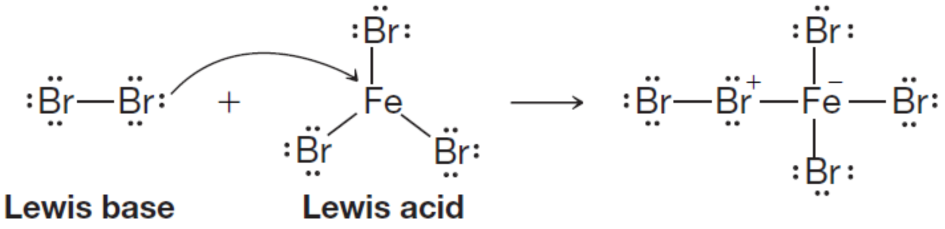
- In Lewis acid–base theory, proton donors are not the only acids

- Example;

  The reaction of Lewis base, bromine (Br_2), with Lewis acid, ferric bromide ($FeBr_3$).







Chapter 5: Organic Reactions

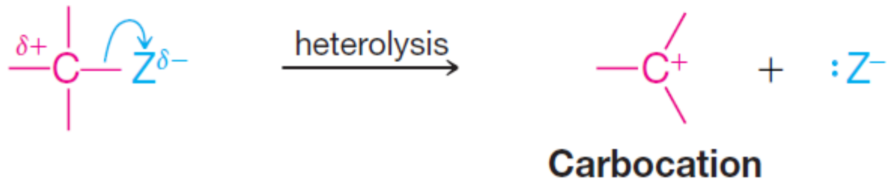
1. Acid-Base Reactions

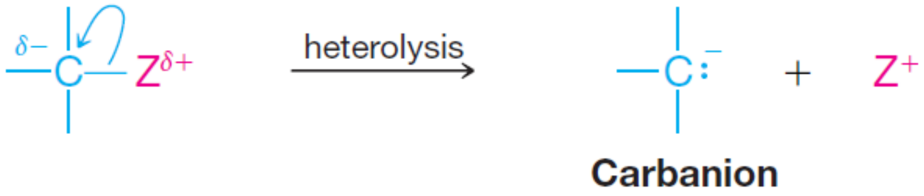
1.3 Heterolysis of Bonds to Carbon: Carbocations and Carbanions

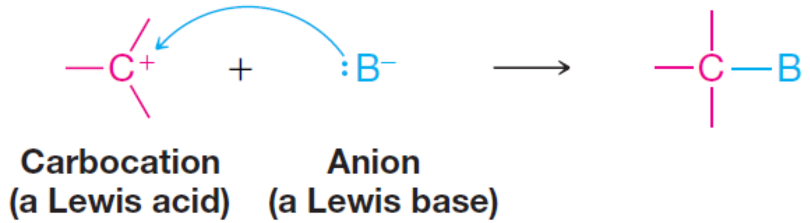
- Heterolysis of a bond to a carbon atom can lead to either of two ions:,

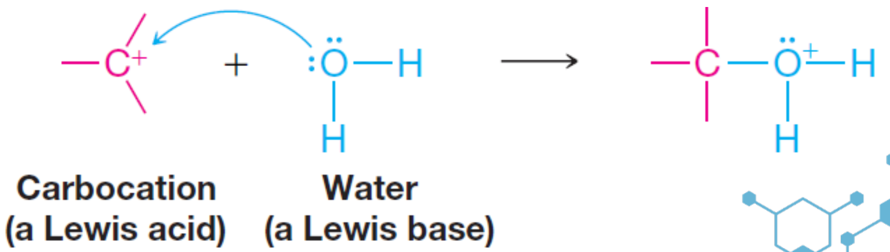
  - A carbocation; an ion with a positive charge on the carbon atom. Example; Carbocations are electron deficient, and therefore carbocations are Lewis acids.

  - A carbanion; an ion with a negatively charged carbon atom. Example; Carbanions are electron rich (have an unshared electron pair) and therefore, carbanions are Lewis bases.









1. Acid-Base Reactions

1.4 Electrophiles and Nucleophiles

- **Electrophiles** are reagents that seek electrons.

  Examples;

  - Lewis acids (electron pair acceptors).
  - Carbocations.
  - Carbon atoms that are electron poor because of bond polarity (i.e. Carbonyl carbon).

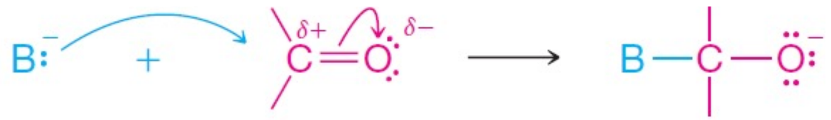
- **Nucleophile** is a Lewis base that seeks a positive center such as a positively charged carbon atom.

  Examples;

  - Lewis bases (electron pair donors).
  - Carbanions

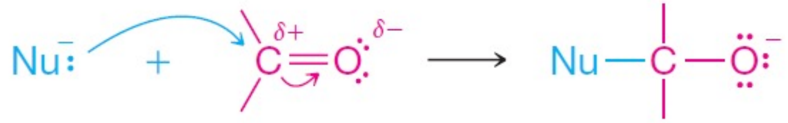
Carbocation
A Lewis acid and electrophile

Lewis base



Lewis base

Lewis acid (electrophile)



Nucleophile

Electrophile

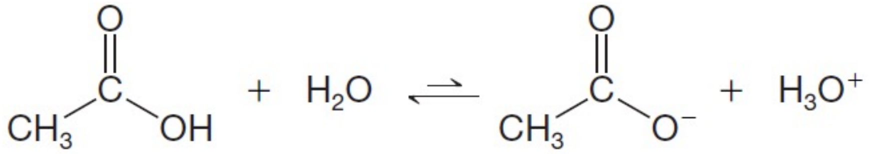
Electrophile

Nucleophile

1. Acid-Base Reactions

1.5 The Strength of Brønsted–Lowry Acids and Bases: K_a and pK_a

- An important consideration, is the relative strengths of compounds that could potentially act as Brønsted–Lowry acids or bases in a reaction.
- Acetic acid, a much weaker acid, when dissolves in water, the following reaction does not proceed to completion:



- acid strength is characterized in terms of acidity constant (*Ka*) or p*Ka* values.

A) The Acidity Constant, Ka

- For any weak acid dissolved in water. Using a generalized hypothetical acid (HA), the reaction in water is:

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

- The expression for the acidity constant is:

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$

- Generally;
  - A large value of K_a means the acid is a strong acid.
  - A small value of K_a means the acid is a weak acid.

Chapter 5: Organic Reactions

1. Acid-Base Reactions

1.5 The Strength of Brønsted–Lowry Acids and Bases: K_a and pK_a

B) Acidity and pKa

- The acidity constant, **Ka**, expressed as its **negative logarithm**, **p*Ka***:

$$pK_a = -\log K_a$$

- This is analogous to expressing the hydronium ion concentration as **pH**:

$$pH = -\log[H_3O^+]$$

- For acetic acid the **p*K_a*** is **4.75** (the **acidity constant** for acetic acid is **1.76 × 10–5**)

$$pK_a = -\log(1.76 \times 10^{-5}) = -(-4.75) = 4.75$$

- The **larger the value** of the *pK_a*, the **weaker** is the acid.

$CH_3CO_2H < CF_3CO_2H < HCl$

pK_a= 4.75 pK_a= 0 pK_a= –7

Weak acid **Very strong acid**

Increasing acid strength

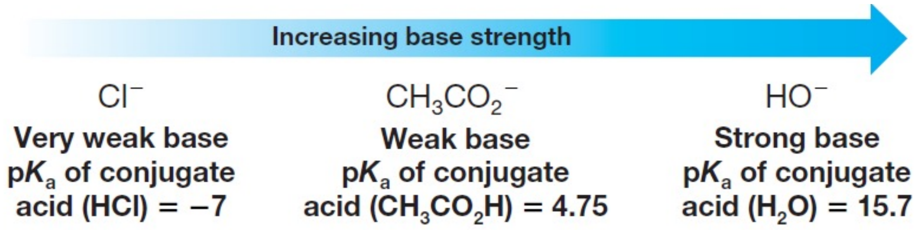
1. Acid-Base Reactions

1.5 The Strength of Brønsted–Lowry Acids and Bases: K_a and pK_a

C) Predicting the Strength of Bases

- **The stronger the acid, the weaker will be its conjugate base.**
- **The larger the pK_a of the conjugate acid, the stronger is the base.**

- Example; **The hydroxide ion is the strongest in this series of three bases because its conjugate acid, water, is the weakest acid (water, largest pK_a).**



Increasing base strength

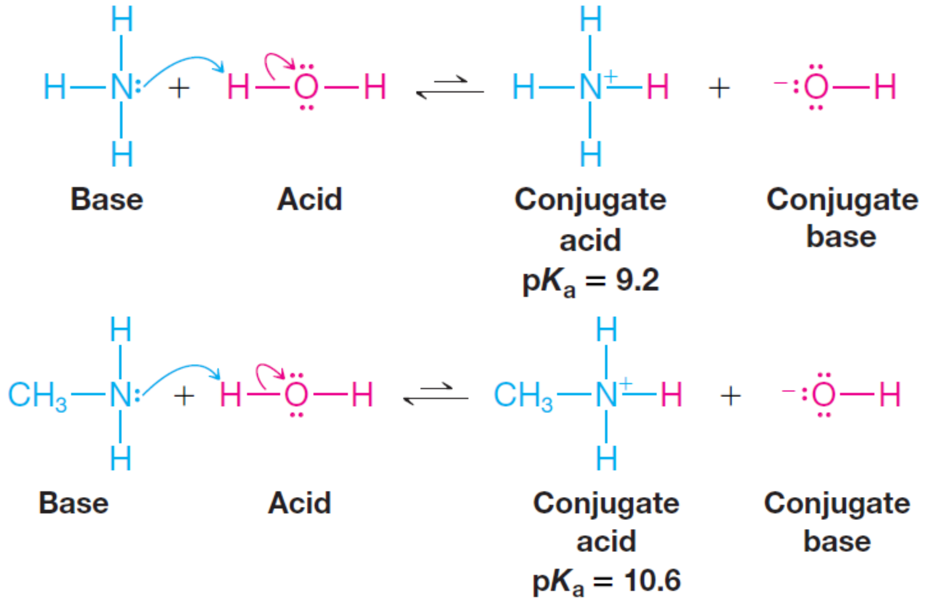
Cl^-	$CH_3CO_2^-$	HO^-
Very weak base	**Weak base**	**Strong base**
pK_a of conjugate acid (HCl) = −7	**pK_a of conjugate acid (CH_3CO_2H) = 4.75**	**pK_a of conjugate acid (H_2O) = 15.7**

1. Acid-Base Reactions

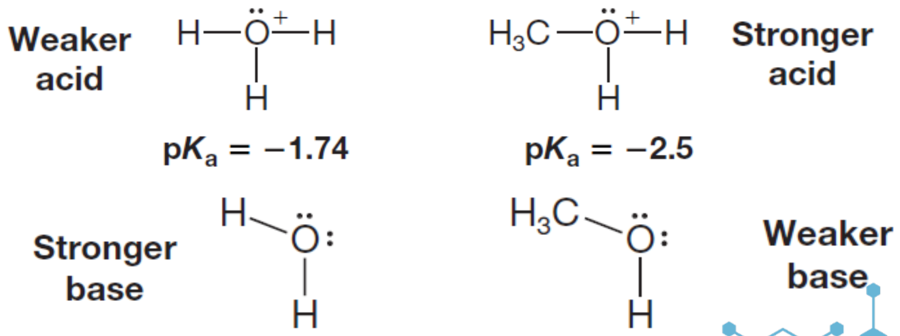
1.5 The Strength of Brønsted–Lowry Acids and Bases: K_a and pK_a

C) Predicting the Strength of Bases

- **Which would be the stronger base, Ammonia and Methylamine?**
  - Dissolving ammonia and methylamine, as weak base, in water.
  - The conjugate acid of ammonia is the ammonium ion NH_4^+, has a p*Ka* = 9.2 and the conjugate acid of methylamine is methylaminium ion $CH_3NH_3^+$, has a p*Ka* = 10.6. Since the conjugate acid of methylamine is a weaker acid than the conjugate acid of ammonia, we can conclude that methylamine is a stronger base than ammonia.



- **Which would be the stronger base, Water or Methanol?**
  - Find the p*Ka* values of the conjugate acids of water and methanol.
  - Because water is the conjugate base of the weaker acid, it is the stronger base.



Chapter 5: Organic Reactions

1. Acid-Base Reactions

1.6 Relationships Between Structure and Acidity

A) Periodic Table Trend

- **Bond Strength To The Proton**

  Acidity increases from top to bottom in a given column with decreasing bond strength.

- **Electronegativity of The Atom Bonded To The Hydrogen**

  Acidity increases from left to right across a given row with increasing electronegativity.

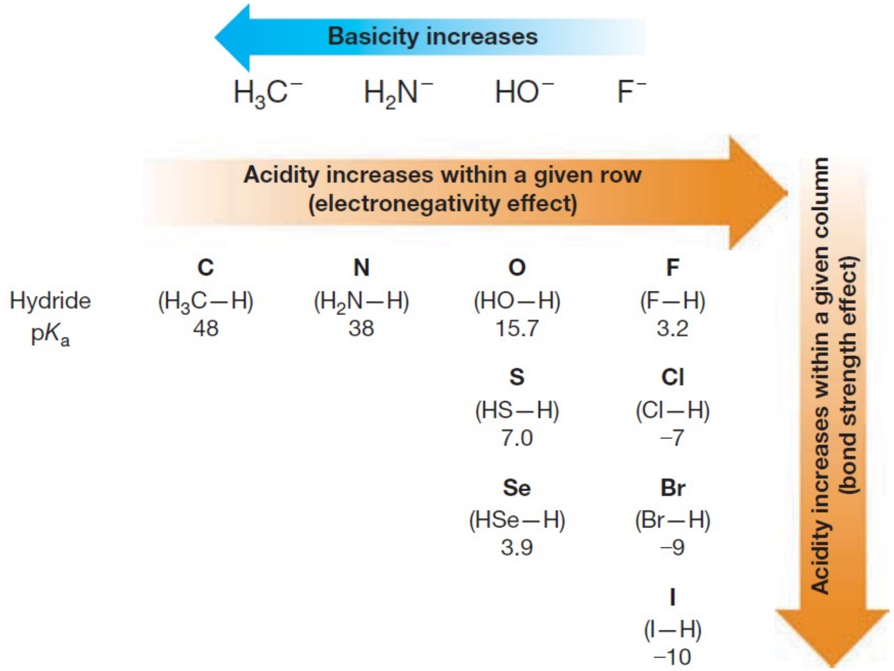
B) The Effect of Hybridization

- An *sp* carbon atom is effectively more electronegative than an *sp*^{2} carbon, which in turn is more electronegative than an *sp*^{3} carbon.

  Alkyne hydrogen is weakly acid and more acidic than alkene and alkane.

C) Inductive Effects

- The electron donating decreases acidity.
- The electron withdrawing increases acidity.



Basicity increases

H_3C^- H_2N^- HO^- F^-

Acidity increases within a given row (electronegativity effect)

Acidity increases within a given column (bond strength effect)

	C	N	O	F
Hydride pK_a	$(H_3C{-}H)$ 48	$(H_2N{-}H)$ 38	$(HO{-}H)$ 15.7	$(F{-}H)$ 3.2
			S $(HS{-}H)$ 7.0	Cl $(Cl{-}H)$ −7
			Se $(HSe{-}H)$ 3.9	Br $(Br{-}H)$ −9
				I $(I{-}H)$ −10

Relative Acidity of the Hydrocarbons

$$HC{\equiv}CH > H_2C{=}CH_2 > H_3C{-}CH_3$$

Relative Basicity of the Carbanions

$$H_3C{-}CH_2{:}^- > H_2C{=}CH{:}^- > HC{\equiv}C{:}^-$$

Chapter 5: Organic Reactions

1. Acid-Base Reactions

1.7 Carboxylic Acids, Phenols and Alcohols as Acids

- Carboxylic acids are weak acids, having pK_a values in the range of 3–5.
- Phenol is weak acid, having pK_a values of 9.89.
- Alcohols, have pK_a values in the range of 15–18, and essentially do not give up a proton unless exposed to a very strong base

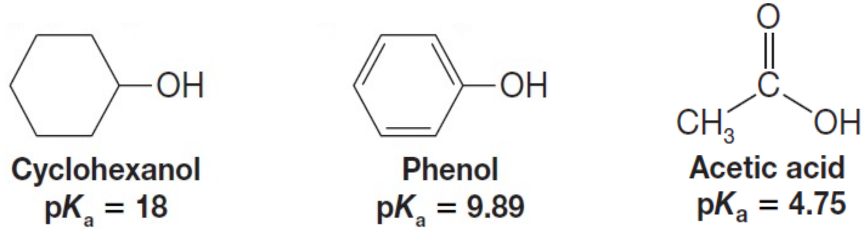
- Example;

  Phenol (pK_a = 9.89) is a weak acid compared with a carboxylic acid such as acetic acid (pK_a = 4.75), and is a much stronger acid than alcohols such as cyclohexanol (pK_a = 18). This due to:

  - Greater stabilization of the carboxylate ion appears to arise from:

    a)delocalization of charge.

    b) an inductive electron-withdrawing effect.
  - The overall resonance hybrid of phenol made by structures 2–4. The hydroxyl group in phenol is *sp*^{2} hybridized, whereas in cyclohexane it is *sp*^{3} hybridized.

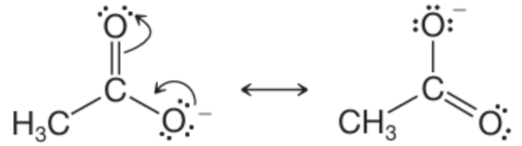


Cyclohexanol
$pK_a = 18$

Phenol
$pK_a = 9.89$

Acetic acid
$pK_a = 4.75$

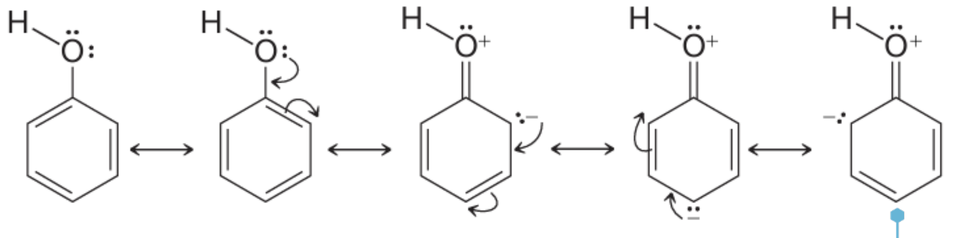
Resonance stabilization in acetate ion



No resonance stabilization in ethanol or ethoxide anion

$$CH_3-CH_2-\ddot{O}-H \; + \; H_2O \; \rightleftharpoons \; CH_3-CH_2-\ddot{O}:^- \; + \; H_3O^+$$

Resonance stabilization in phenol



1a 1b 2 3 4

1. Acid-Base Reactions

1.8 Organic Compounds as Bases

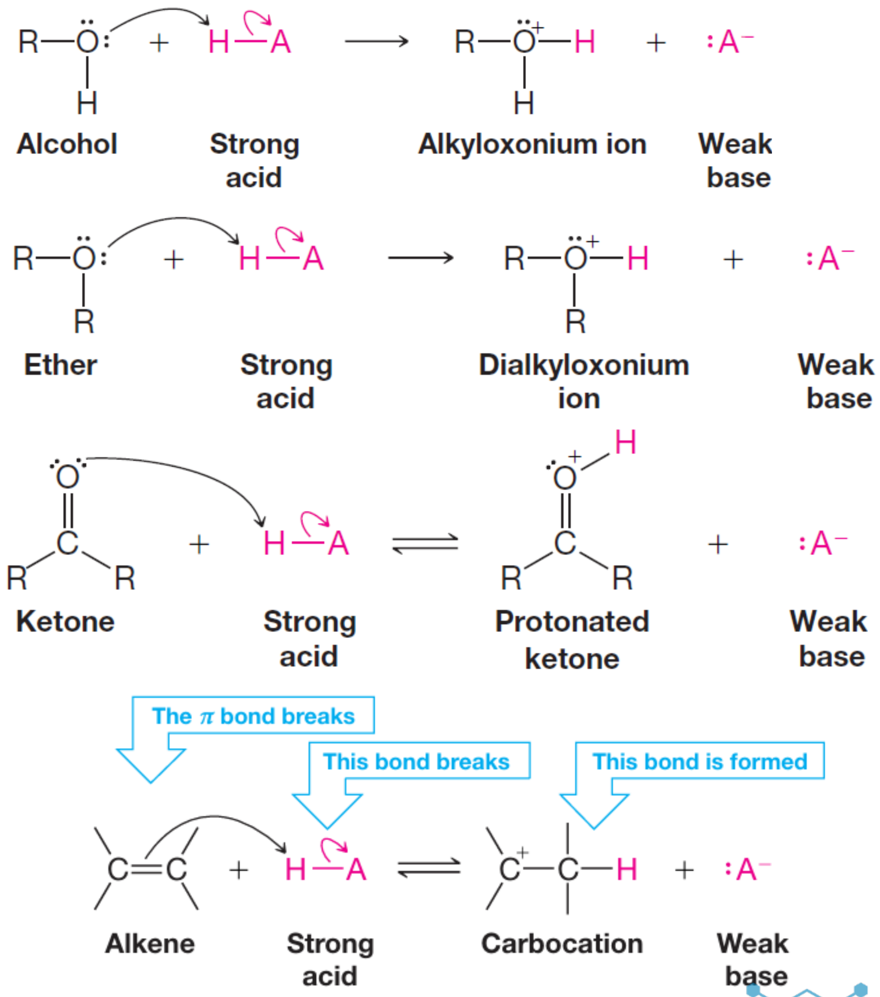
- An organic compound is a potential base if it contains:

(1) an atom with an unshared electron pair

Alcohols, ethers, amines and compounds containing a carbonyl group act as bases in the presence of a strong acid such as HCl and H_2SO_4.

(2) π bond.

Alkenes react with a strong acid by accepting a proton.



1. Acid-Base Reactions

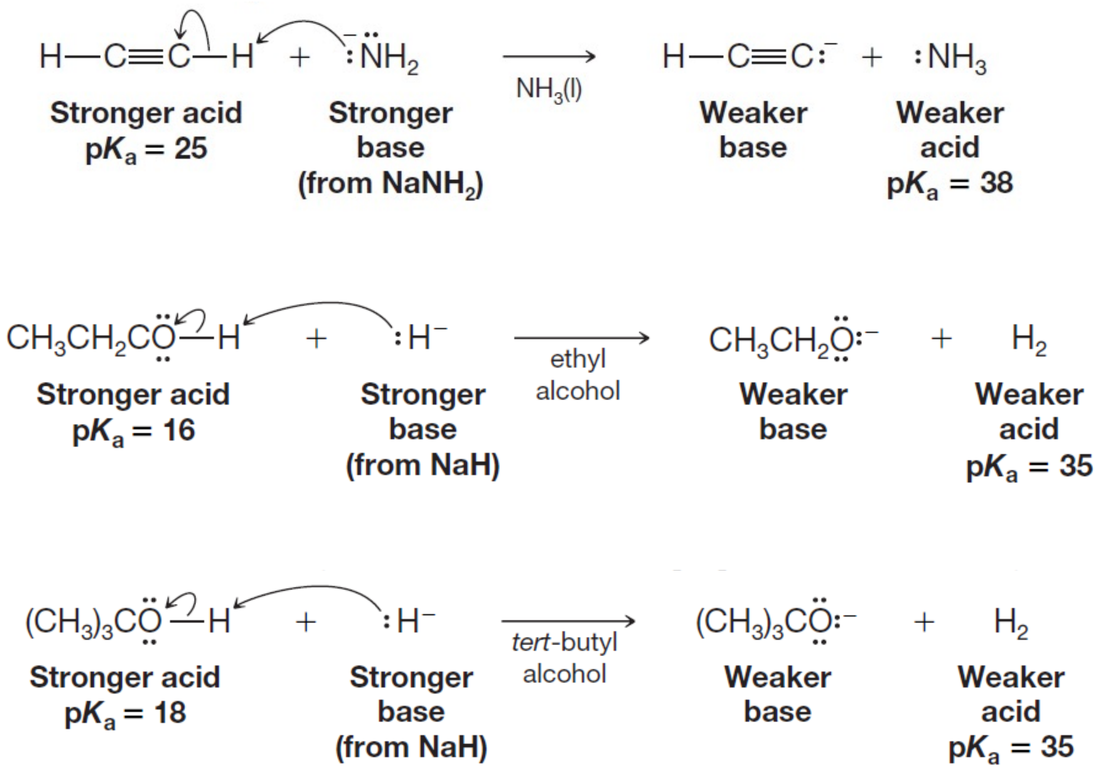
1.9 Acids and Bases in Nonaqueous Solutions

- Most terminal alkynes (alkynes with a proton attached to a triply bonded carbon) have pK_a values of about 25; Therefore, all react with sodium amide in liquid ammonia in the same way that ethyne does.

- Alkoxide ions are stronger bases than hydroxide ions because alcohols are weaker acids than water.

  Example; a solution of sodium ethoxide (CH_3CH_2ONa) in ethyl alcohol can be created by adding sodium hydride (NaH) to ethyl alcohol.

- The *tert*-butoxide ion, $(CH_3)_3CO^-$, in *tert*-butyl alcohol, $(CH_3)_3COH$, is a stronger base than the ethoxide ion in ethyl alcohol, and it can be prepared in a similar way.



Radical Reactions

2. Radical Reactions

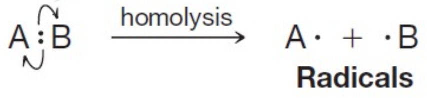
2.1 Production of Radicals

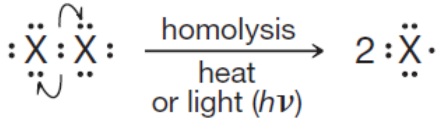
- Homolytic bond cleavage leads to the formation of radicals (or free radicals).
- Radicals are highly reactive, and short-lived species.

- Example;

Homolysis of relatively weak bonds such as X-X bonds can occur with addition of energy in the form of heat or light.

Each atom takes one electron from the covalent bond that joined them.





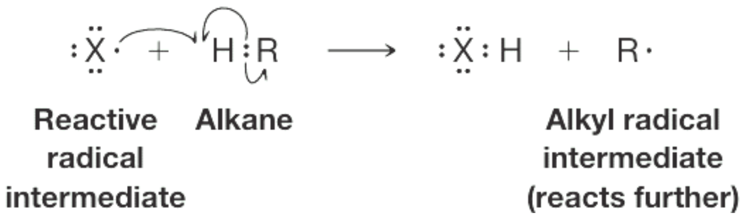
Homolysis of a halogen molecule

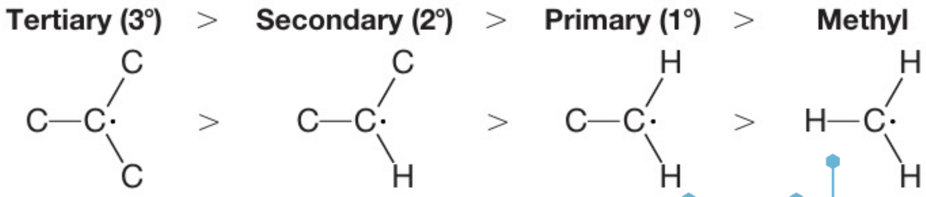
2.2 Reactions of Radicals

- Radicals tend to react in ways that lead to pairing of their unpaired electron.

  Hydrogen abstraction is one way a halogen radical can react to pair its unshared electron.

- The relative stabilities of radicals are $3^\circ > 2^\circ > 1^\circ >$ methyl, follows the same trend as for carbocations. Radicals are electron deficient, as are carbocations, and the most substituted radical is most stable





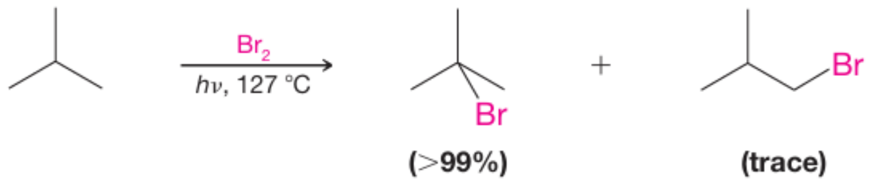
2. Radical Reactions

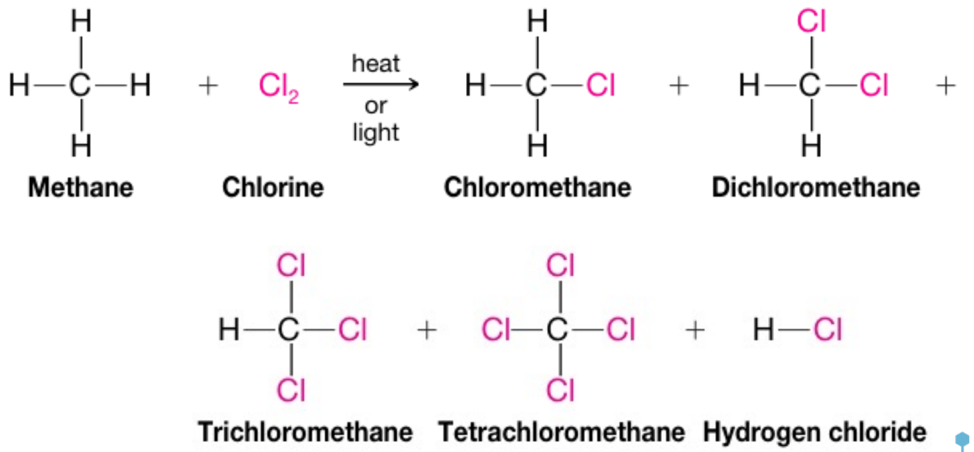
2.3 Reactions of Alkanes with Halogens

- *Radical halogenation;* **alkanes react with molecular halogens to produce alkyl halides by a substitution reaction.**
- **Alkanes undergo substitution reactions with halogens, fluorine, bromine and chlorine, in the presence of *heat or light*.**
- **A halogen atom replaces one or more of the hydrogen atoms of the alkane.**
- **Monosubstitution can be achieved by using a large excess of the alkane to give some selectivity.**
- **Tertiary hydrogens are more reactive than secondary hydrogens which are more reactive than primary hydrogens.**

- **Radical halogenation can yield a mixture of halogenated compounds by substitution of all hydrogen atoms in alkane.**

$$R{-}H + X_2 \longrightarrow R{-}X + HX$$





$$CH_4 + Cl_2 \xrightarrow[\text{light}]{\text{heat or}} CH_3Cl + CH_2Cl_2 + CHCl_3 + CCl_4 + HCl$$

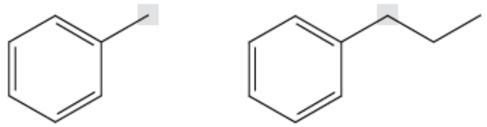
2. Radical Reactions

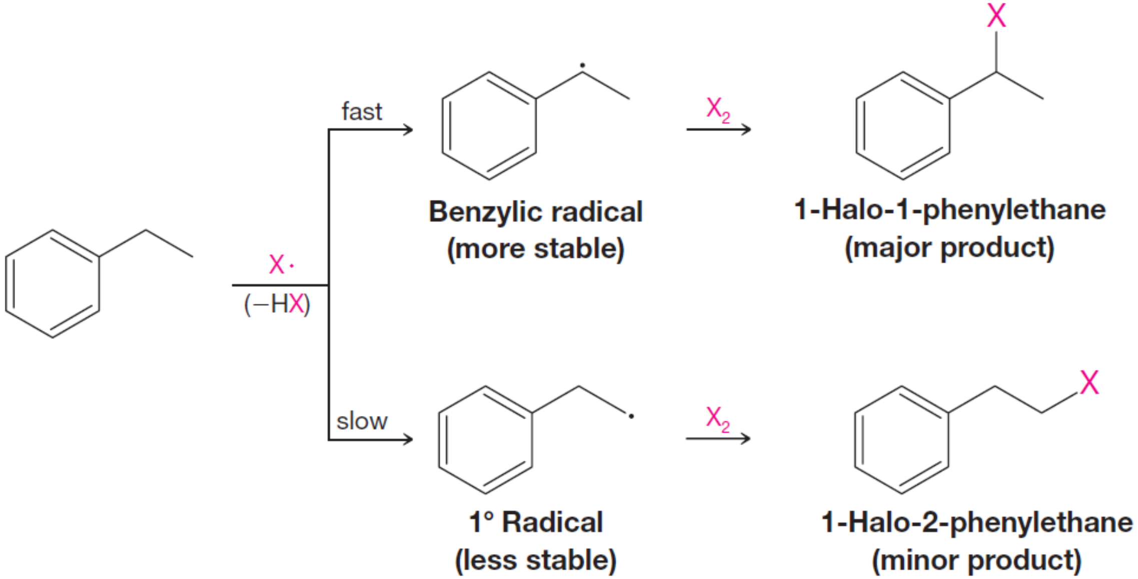
2.4 Benzylic Substitution and Benzylic Radicals

- An atom or group bonded to an *sp3*-hybridized carbon adjacent to a benzene ring is called a benzylic group.

- Example;
- Halogenation of ethylbenzene.
  - The major product is the 1-halo-1-phenylethane.
  - The benzylic radical is formed much faster than the 1° radical due to the greater stability of benzylic radicals.

The hydrogen atoms bonded at the highlighted carbons are benzylic hydrogens





Benzylic radical (more stable)

1-Halo-1-phenylethane (major product)

1° Radical (less stable)

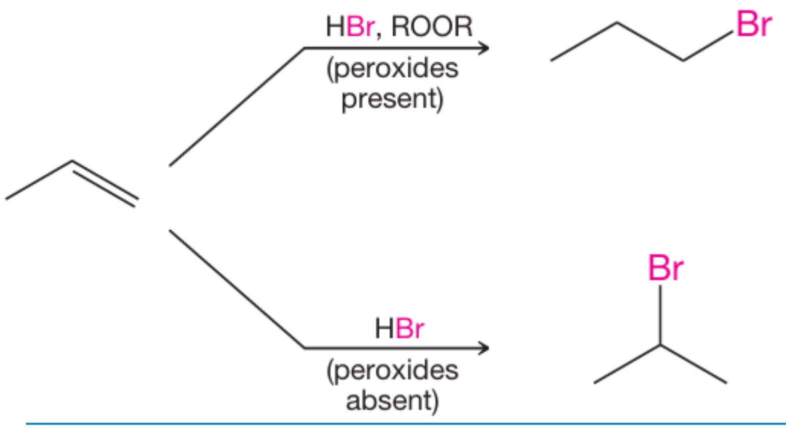
1-Halo-2-phenylethane (minor product)

Chapter 5: Organic Reactions

2. Radical Reactions

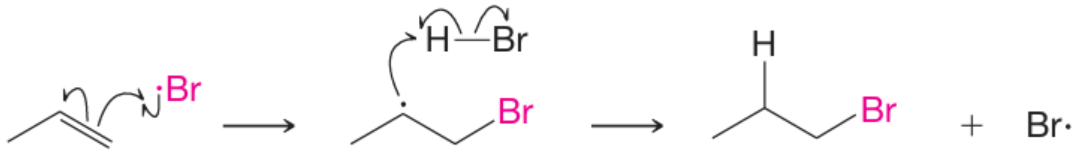
2.5 Radical Addition to Alkenes: Anti-Markovnikov Addition of Hydrogen Bromide

- **Ionic Addition**; The result is **Markovnikov addition**
- **Radical Addition**; In the presence of **peroxides (R-O-O-R)**, The result is **anti-Markovnikov addition**.
- **Hydrogen bromide** is the only hydrogen halide that gives **anti-Markovnikov addition** when peroxides are present.
- **Hydrogen fluoride**, **hydrogen chloride**, and **hydrogen iodide** do not give anti-Markovnikov addition even with peroxides.



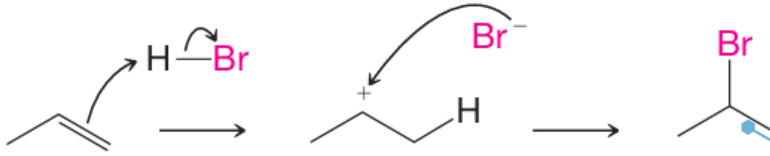
Anti-Markovnikov addition

Markovnikov addition



Addition to form the more stable alkyl radical

Anti-Markovnikov product



Addition to form the more stable carbocation

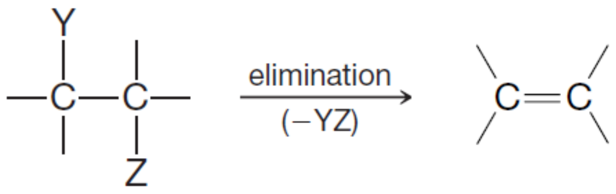
Markovnikov product

Elimination Reactions

3. Elimination Reactions

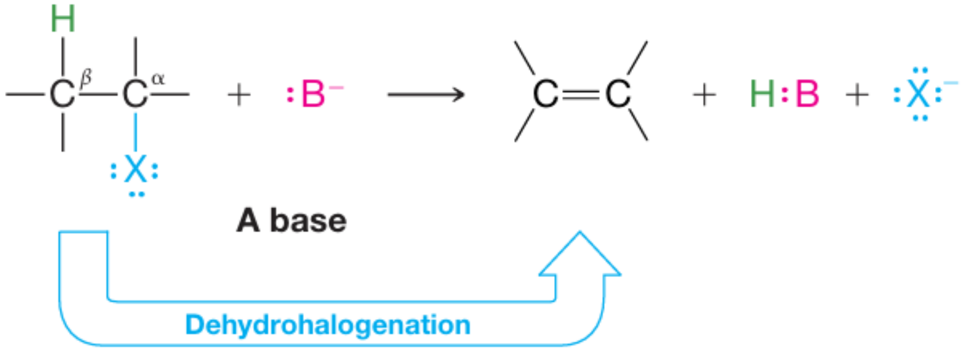
3.1 Synthesis of Alkenes: Elimination Reactions

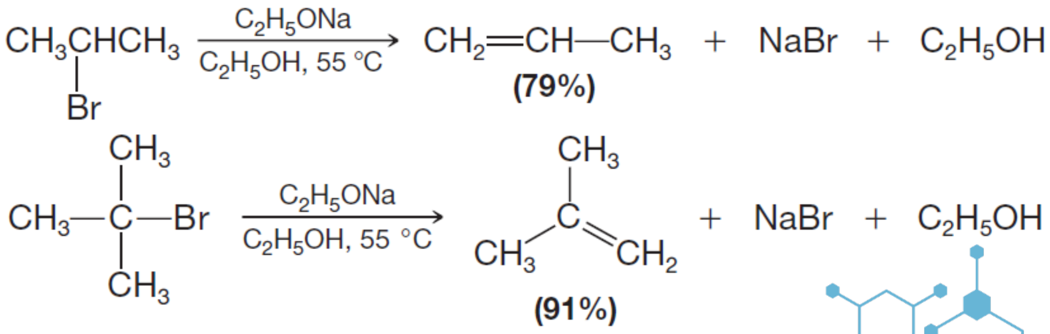
- **Elimination reactions** are the most important means for synthesizing alkenes.



3.2 Dehydrohalogenation; Elimination of Alkyl Halide

- **Heating** the **alkyl halide** with a **strong base** causes the reaction to take place. **Examples;**





$$CH_3CH(Br)CH_3 \xrightarrow[C_2H_5OH,\ 55\ ^\circ C]{C_2H_5ONa} CH_2{=}CH{-}CH_3 + NaBr + C_2H_5OH$$

$$(CH_3)_3C{-}Br \xrightarrow[C_2H_5OH,\ 55\ ^\circ C]{C_2H_5ONa} (CH_3)_2C{=}CH_2 + NaBr + C_2H_5OH$$

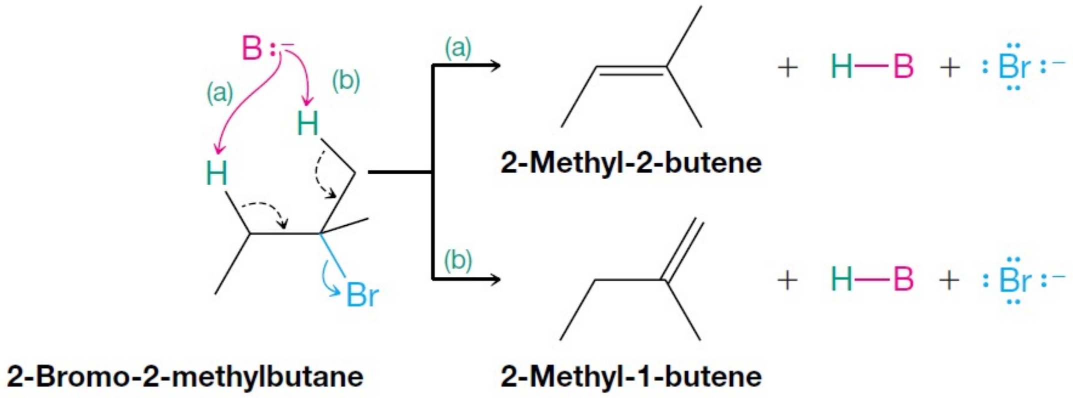
3. Elimination Reactions

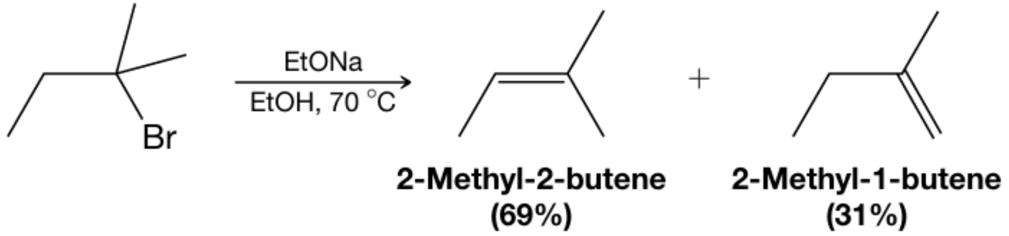
3.2 Dehydrohalogenation; Elimination of Alkyl Halide

- *Zaitsev's Rule: Formation of the More Substituted Alkene is Favored with a Small Base*

- Dehydrohalogenation of alkyl halides, can often yield more than one product. For example; dehydrohalogenation of 2-bromo-2-methylbutane:

- Whenever an elimination occurs to give the more stable, more highly substituted alkene, chemists say that the elimination follows Zaitsev's rule.





Trisubstituted: more stable

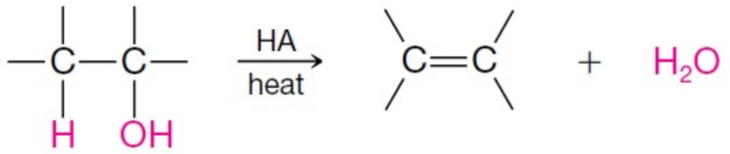
Disubstituted: less stable

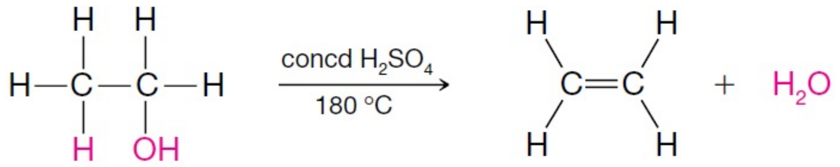
3. Elimination Reactions

3.3 Elimination of Alcohols: Acid-catalyzed Dehydration

- Most alcohols undergo dehydration (*lose a molecule of water*) to form an alkene when heated with a strong acid.

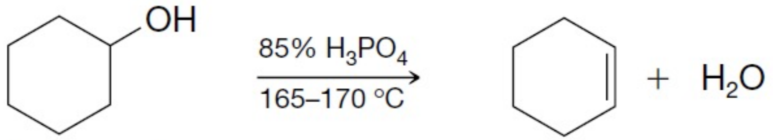
- The temperature and concentration of acid required to dehydrate an alcohol depend on the structure of the alcohol substrate.
  - Dehydration of ethanol (primary alcohol) requires concentrated sulfuric acid and a temperature of 180 °C.
  - Cyclohexanol (secondary alcohol) dehydrates in 85% phosphoric acid at 165–170 °C.
  - *tert*-Butyl alcohol (tertiary alcohol) dehydrates in 20% aqueous sulfuric acid at a temperature of 85 °C.





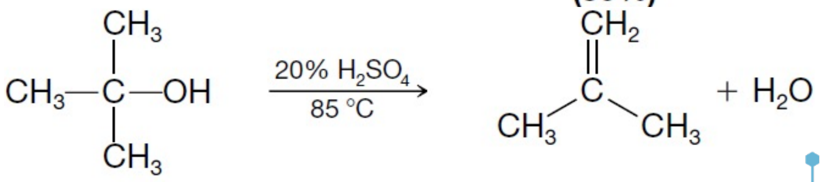
Ethanol
(a 1° alcohol)

Ethene



Cyclohexanol

Cyclohexene
(80%)



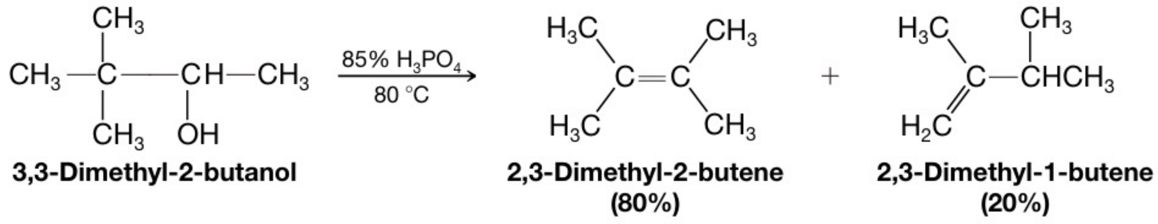
***tert*-Butyl**
alcohol

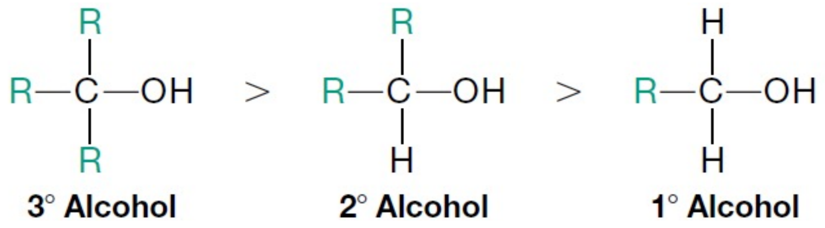
2-Methylpropene
(84%)

3. Elimination Reactions

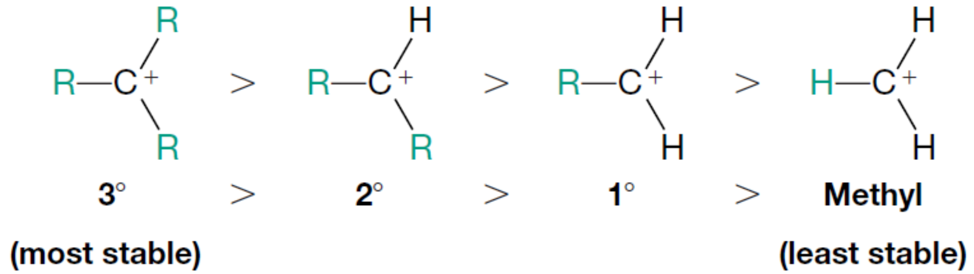
3.3 Elimination of Alcohols: Acid-catalyzed Dehydration

- Some primary and secondary alcohols also undergo rearrangements of their carbon skeletons during dehydration. Such a rearrangement occurs in the dehydration of 3,3-dimethyl-2-butanol.





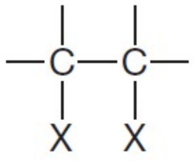
- The relative ease with which alcohols undergo dehydration is 3° > 2° > 1°.



- This behavior is related to the relative stabilities of carbocations.

3. Elimination Reactions

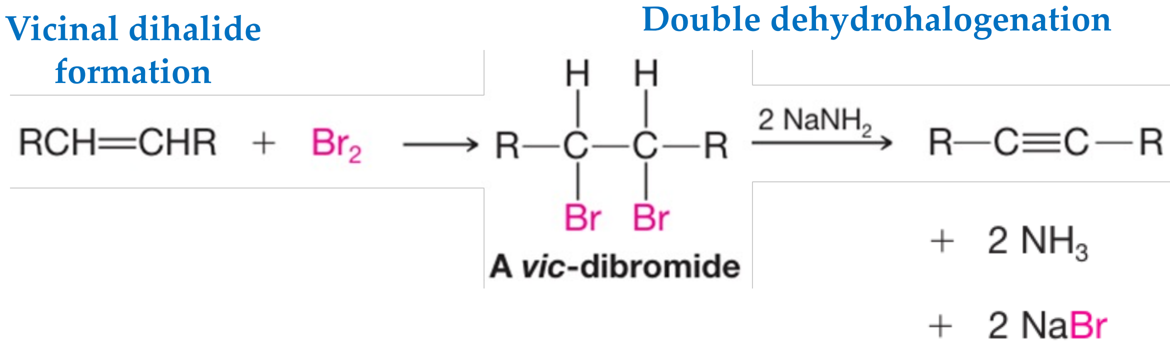
3.4 Synthesis of Alkynes by Elimination Reactions



A *vic*–dihalide

- Alkynes can be synthesized from alkenes via compounds called vicinal dihalides.

- The *vic*-dibromide can be subjected to a double dehydrohalogenation reaction with a strong base to yield an alkyne.

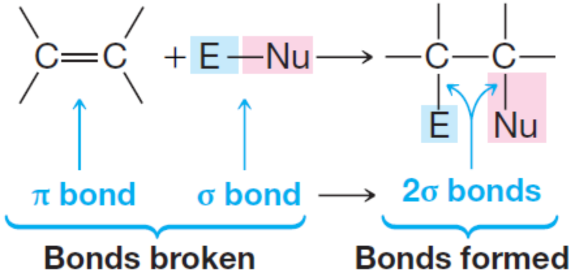


Electrophilic Addition Reactions

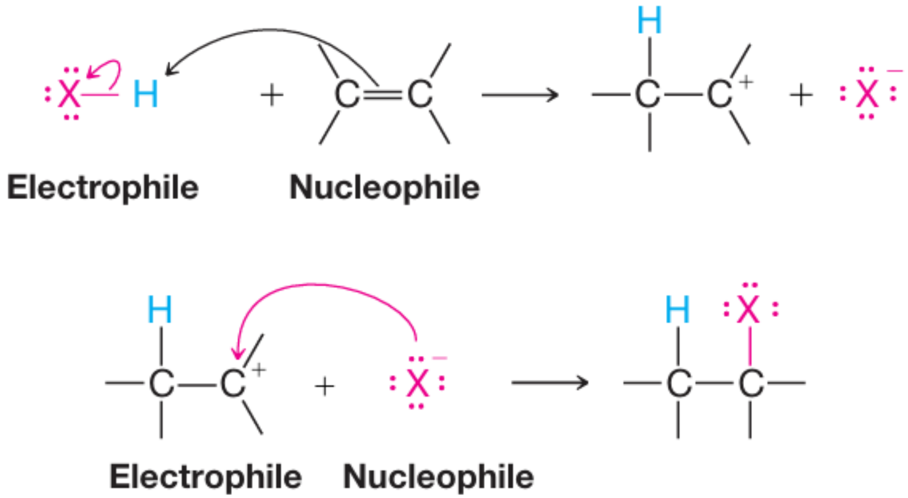
4. Electrophilic Addition Reactions

4.1 Electrophilic Addition to an Alkene

- **Generally the reaction is exothermic because one π and one σ bond are converted to two σ bonds.**



- **In addition reactions the alkene changes from a nucleophile in the first step to an electrophile in the second.**

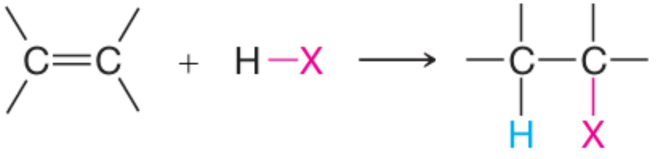


4. Electrophilic Addition Reactions

4.1 Electrophilic Addition to an Alkene

A) Addition of Hydrogen Halides (Hydrohalogenation) to Alkenes: Markovnikov's Rule

- **Hydrogen halides (HI, HBr, HCl, and HF) add to the double bond of alkenes:**

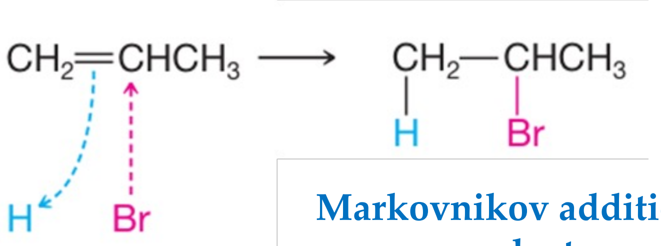


- **The order of reactivity of the hydrogen halides in alkene addition is: HI > HBr > HCl > HF**

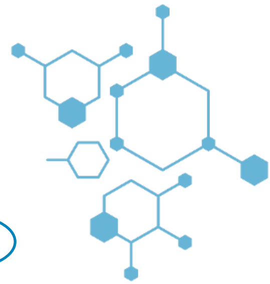
- **The addition of HX to an unsymmetrical alkene could occur in two ways.**

- **One way to state Markovnikov's rule is to say that in the addition of HX to an alkene, the hydrogen atom adds to the carbon atom of the double bond that already has the greater number of hydrogen atoms.**

The alkene carbon atom with the greater number of hydrogen atoms receives the hydrogen.



Markovnikov addition product

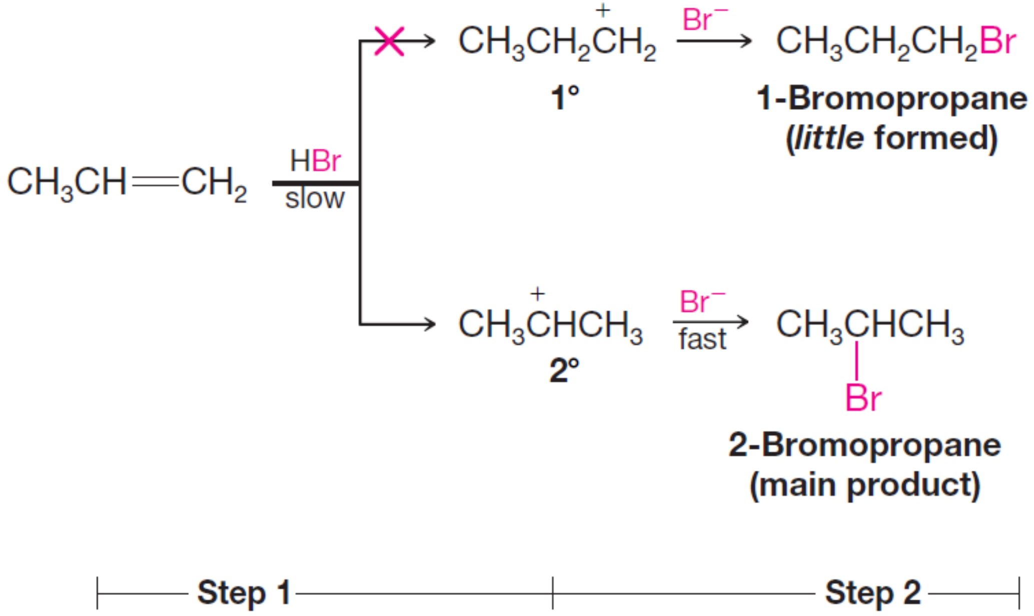


4. Electrophilic Addition Reactions

4.1 Electrophilic Addition to an Alkene

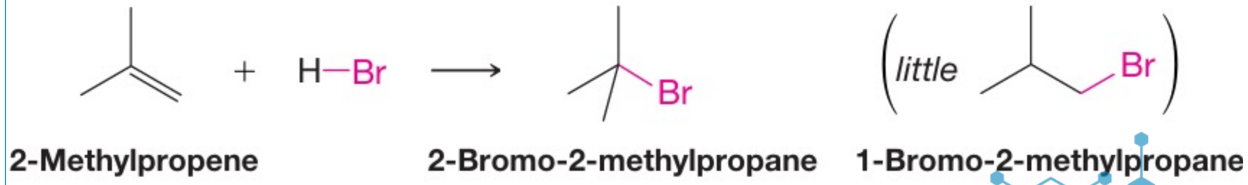
A) Addition of Hydrogen Halides (Hydrohalogenation) to Alkenes: Markovnikov's Rule

- Theoretical Explanation of Markovnikov's Rule
    - These two carbocations are not of equal stability.



- Example; Addition of HBr to 2-methylpropene;

The main product is 2-bromo-2-methylpropane, not 1-bromo-2-methylpropane.



- Anti-Markovnikov Addition of HBr in the Presence of Peroxides (see Section 2.5).

4. Electrophilic Addition Reactions

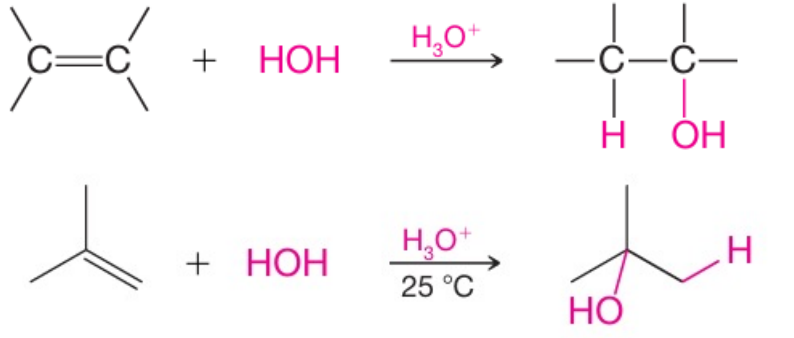
4.1 Electrophilic Addition to an Alkene

B) Acid-Catalyzed Hydration; Addition of Water to Alkenes

- The reaction of alkenes with dilute aqueous acid leads to Markovnikov addition of water.
- Example; the hydration of 2-methylpropene:
- Because the reactions follow Markovnikov's rule, acid-catalyzed hydrations of alkenes do not yield primary alcohols except in the special case of the hydration of ethene:

C) Alcohols from Alkenes through Hydroboration–Oxidation: Anti-Markovnikov Syn Hydration

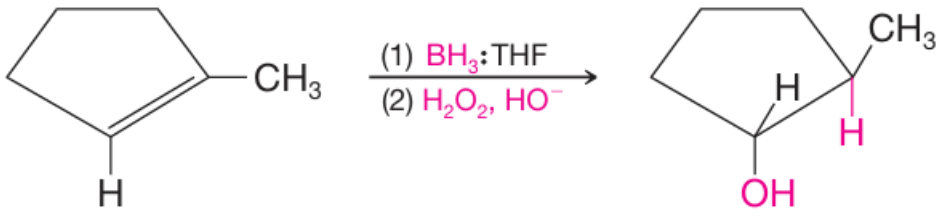
- Hydroboration–oxidation takes place as anti-Markovnikov.
- Example; the hydroboration of 1-methylcyclopentene:



2-Methylpropene (isobutylene)

2-Methyl-2-propanol (*tert*-butyl alcohol)

$$CH_2{=}CH_2 + HOH \xrightarrow[300\ ^\circ C]{H_3PO_4} CH_3CH_2OH$$



1-Methylcyclopentene

2-Methylcyclopentanol

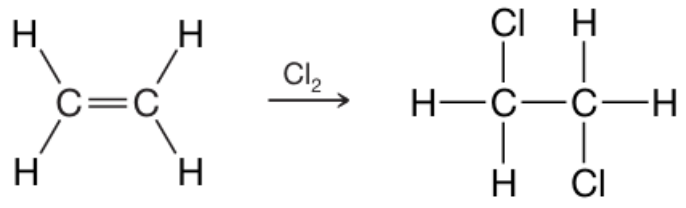
4. Electrophilic Addition Reactions

4.1 Electrophilic Addition to an Alkene

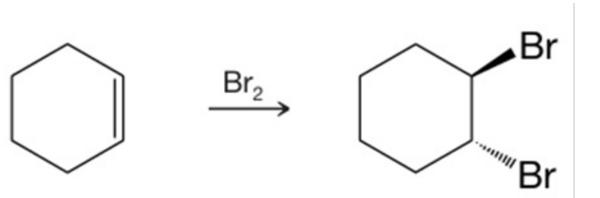
D) Addition of Bromine and Chlorine (Halogenation) to Alkenes

- **Alkenes react rapidly with bromine and chlorine to form vicinal dihalides.**
- **The addition of halogens is an anti addition to the double bond.**

- **Examples;**



Ethene **1,2-Dichloroethane**



Cyclohexene ***trans*-1,2-Dibromocyclohexane**

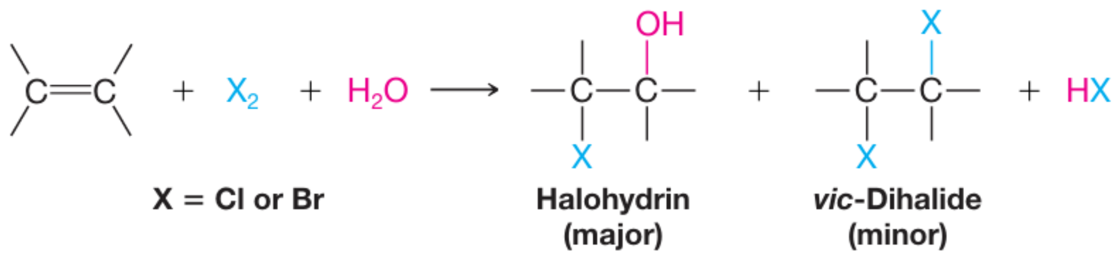
4. Electrophilic Addition Reactions

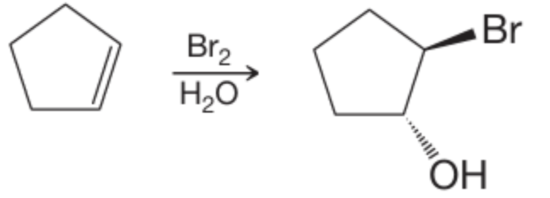
4.1 Electrophilic Addition to an Alkene

E) Halohydrin Formation

- **Halogenation of an alkene in aqueous solution, the major product is a halohydrin (halo alcohol)**
- **If the halogen is bromine, it is called a bromohydrin.**
- **If the halogen is chlorine, it is called a chlorohydrin.**

- **Example;**





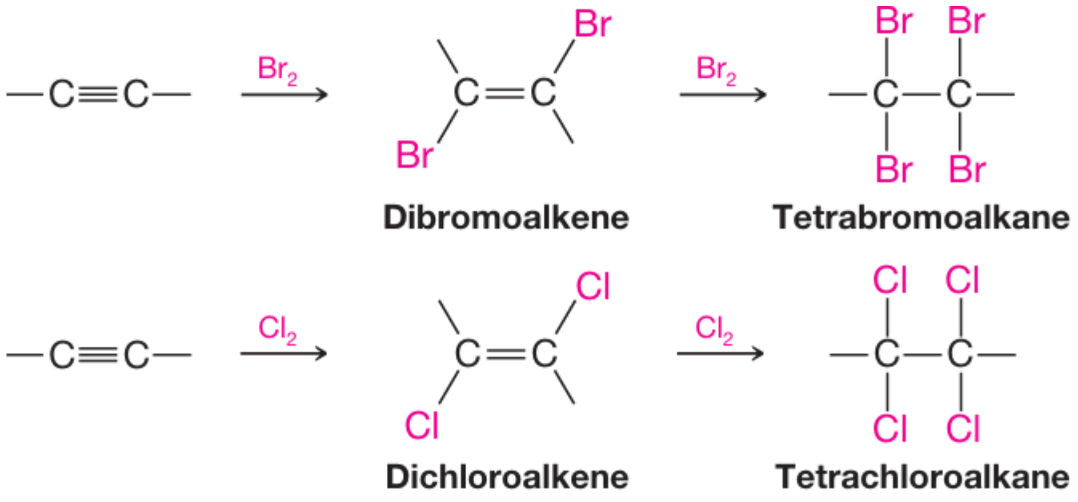
Cyclopentene **2-Bromocyclopentanol**

4. Electrophilic Addition Reactions

4.2 Electrophilic Addition to an Alkyne

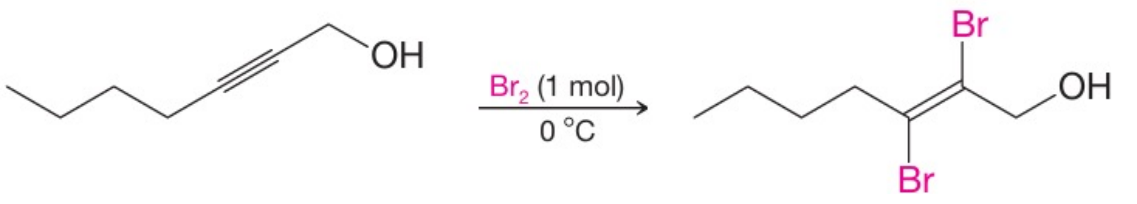
A) Addition of Bromine and Chlorine (Halogenation) to Alkynes

- Alkynes show the same kind of addition reactions with chlorine and bromine that alkenes do.
- With alkynes the addition may occur once or twice, depending on the number of molar equivalents of halogen added.



- Addition of one molar equivalent of chlorine o bromine to an alkyne generally results in anti addition and yields a *trans*-dihaloalkene.

- Example; Addition of bromine to 2-heptyn-1-ol gives the trans isomer.



2-Heptyn-1-ol

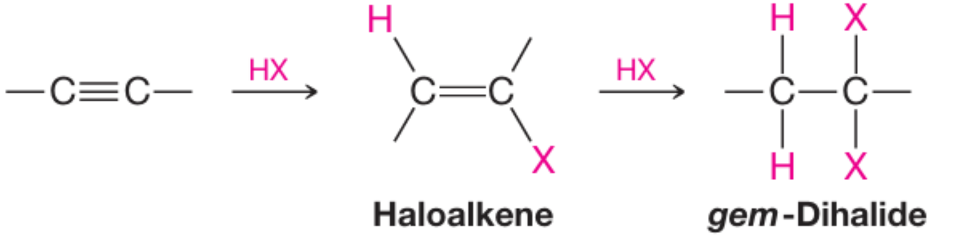
***trans*-2,3-Dibromo-2-Hepten-1-ol**

4. Electrophilic Addition Reactions

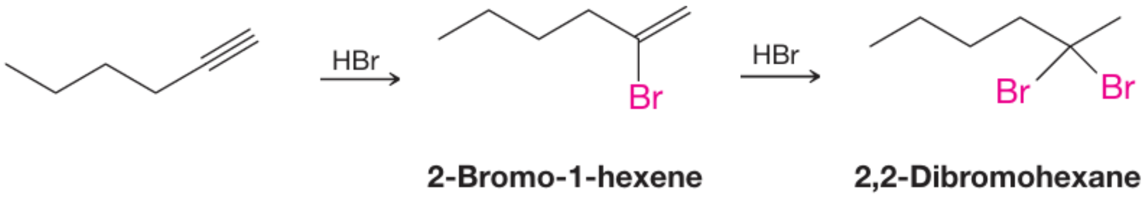
4.2 Electrophilic Addition to an Alkyne

B) Addition of Hydrogen Halides (Hydrohalogenation) to Alkynes

- Alkynes react with one molar equivalent of hydrogen chloride or hydrogen bromide to form haloalkenes, and with two molar equivalents to form geminal dihalides and follow Markovnikov's rule.



- Example;



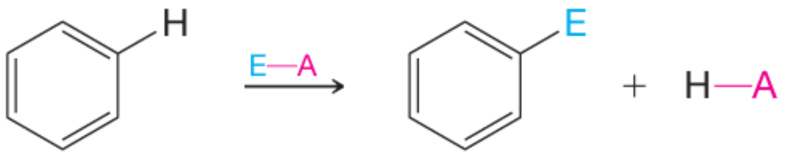
- Anti-Markovnikov addition of HBr occurs in the presence of peroxide (see Section 2.5).

Electrophilic Aromatic Substitution

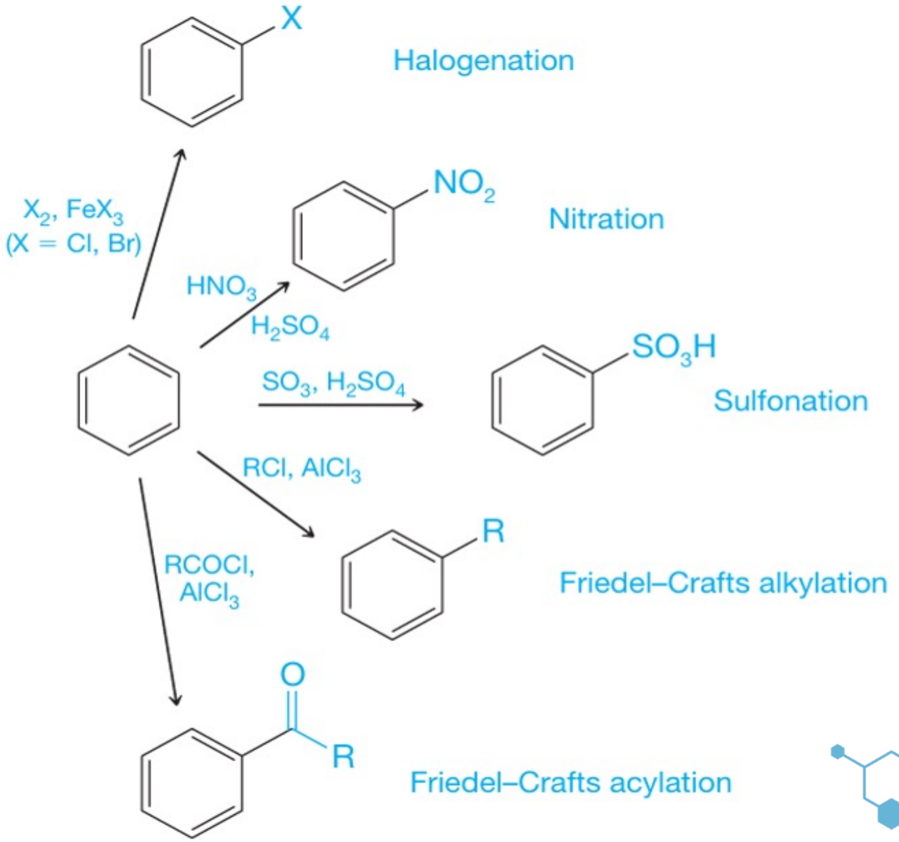
5. Electrophilic Aromatic Substitution Reactions

- Some of the most important reactions of aromatic compounds are those in which an electrophile replaces one of the hydrogen atoms of the ring.
- These reactions, called electrophilic aromatic substitutions (EAS)

- Five different types of electrophilic aromatic substitutions including carbon–carbon bond-forming reactions and halogenations.



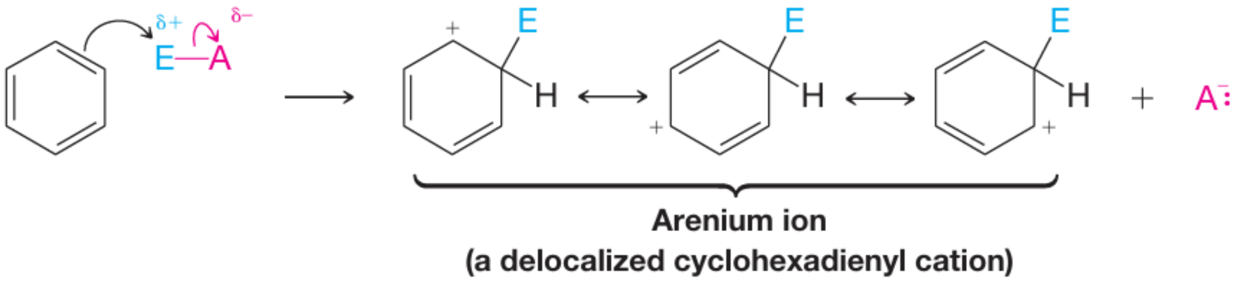
(E—A is an electrophilic reactant)



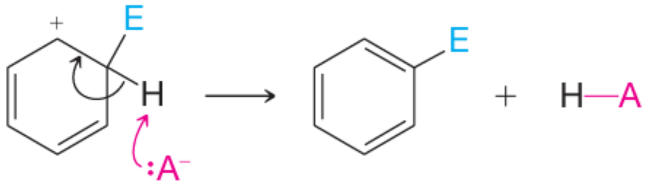
5. Electrophilic Aromatic Substitution Reactions

5.1 A General Mechanism for Electrophilic Aromatic Substitution

- Step 1;
  - The electrophile attacked by the π system to form a σ bond to one carbon atom of the benzene ring.
  - The arenium ion is stabilized by resonance which delocalizes the charge.



- Step 2; A proton is removed, restoring aromaticity to the ring.



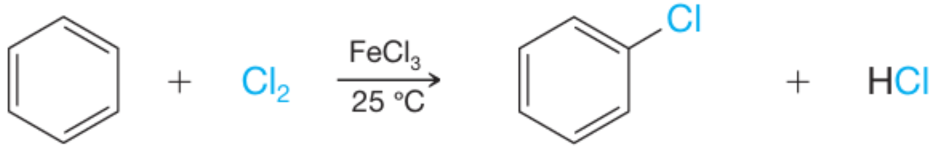
5. Electrophilic Aromatic Substitution Reactions

5.2 A Halogenation of Benzene

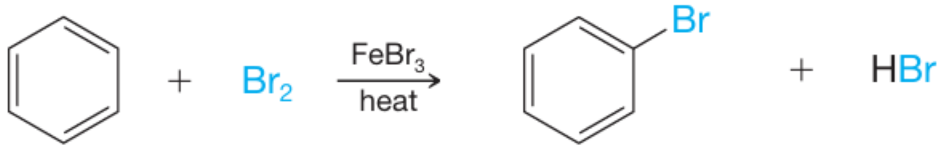
- **Benzene** reacts with **bromine and chlorine** in the presence of **Lewis acids** to give halogenated substitution products.

- **Fluorine** reacts so rapidly with benzene and it is difficult to limit the reaction to monofluorination.

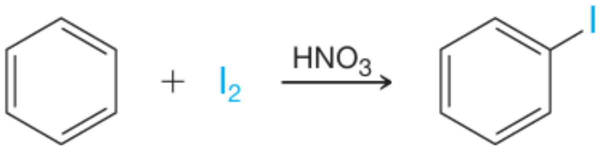
- **Iodine** is so unreactive; the reaction has to be carried out in the presence of an oxidizing agent such as nitric acid.



Chlorobenzene (90%)



Bromobenzene (75%)



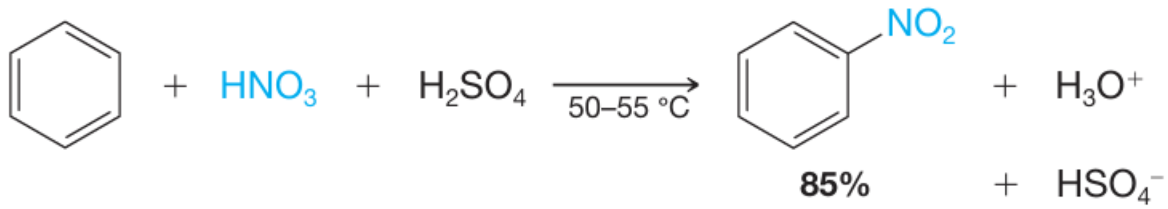
86%

5. Electrophilic Aromatic Substitution Reactions

5.3 Nitration of Benzene

- **Benzene undergoes nitration on reaction with a mixture of concentrated nitric acid and concentrated sulfuric acid.**
- **The electrophile for the reaction is the nitronium ion (NO_2^+).**

$$HNO_3 + 2H_2SO_4 \longrightarrow NO_2^+ + 2HSO_4^- + H_3O^+$$

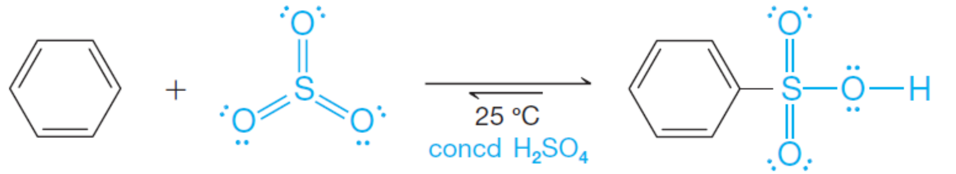


85%

5.4 Sulfonation of Benzene

- **Benzene reacts with fuming sulfuric acid (sulfuric acid contains added sulfur trioxide (SO_3)) at room temperature to produce benzenesulfonic acid.**

$$SO_3 + H_2SO_4 \longrightarrow SO_3H^+ + HSO_4^-$$



Sulfur trioxide

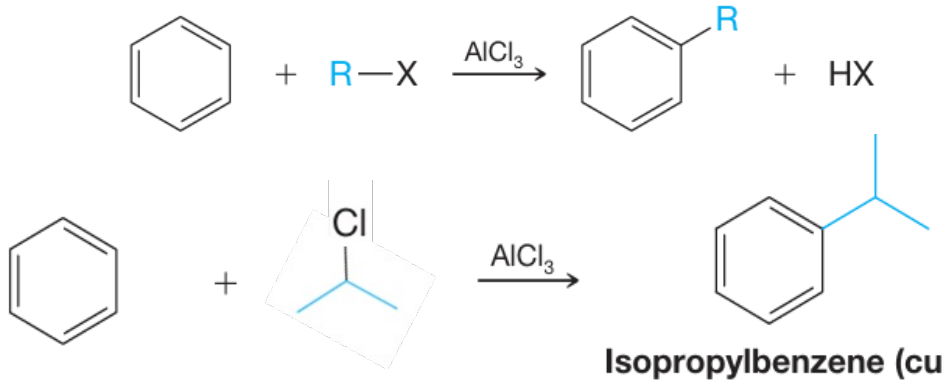
Benzenesulfonic acid (56%)

5. Electrophilic Aromatic Substitution Reactions

5.5 Friedel–Crafts Alkylation

$$RCl + AlCl_3 \longrightarrow R^+ + AlCl_4^-$$

- An aromatic ring can be alkylated by an alkyl halide in the presence of a Lewis acid.
- The Lewis acid serves to generate a carbocation electrophile.



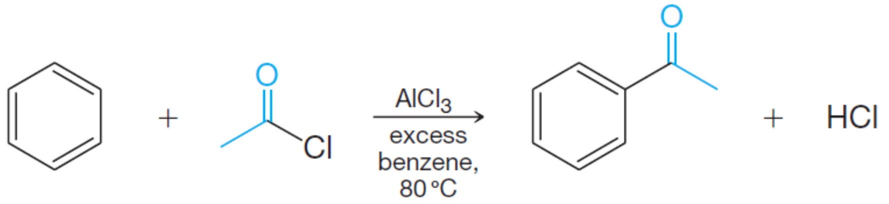
Isopropylbenzene (cumene)
(84%)

5.6 Friedel–Crafts Acylation

- An acyl group has a carbonyl attached to some R group
- Friedel-Crafts acylation requires reaction of an acid chloride with a Lewis acid such as aluminum chloride.

Acetyl group (ethanoyl group)

Benzoyl group



Acetyl chloride

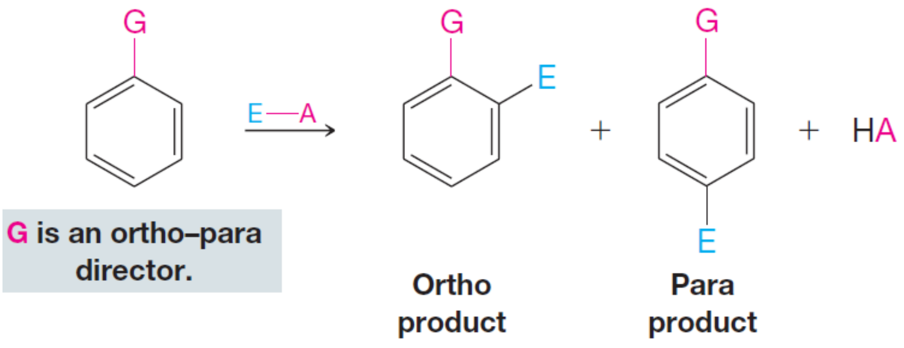
Acetophenone (methyl phenyl ketone) (97%)

5. Electrophilic Aromatic Substitution Reactions

5.7 Existing Substituents Direct the Position of Electrophilic Aromatic Substitution

- *Effects of Substituents on Reactivity and Orientation*

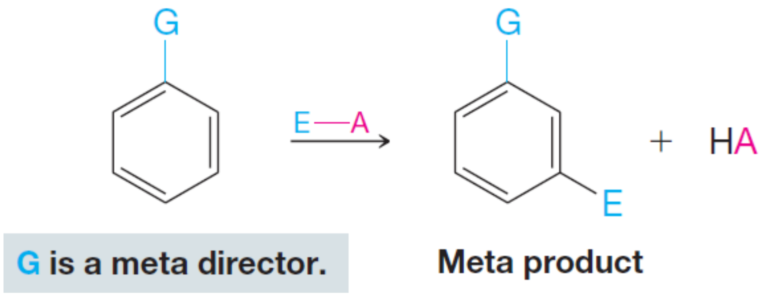
- The nature of groups already on an aromatic ring affect both the reactivity and orientation of future substitution.
  - Activating groups cause the aromatic ring to be more reactive than benzene.
  - Deactivating groups cause the aromatic ring to be less reactive than benzene.
  - *Ortho-para* directors direct future substitution to the *ortho* and *para* positions.
  - *Meta* directors direct future substitution to the *meta* position.



G is an ortho–para director.

Ortho product

Para product



G is a meta director.

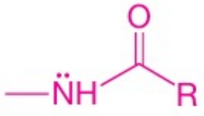
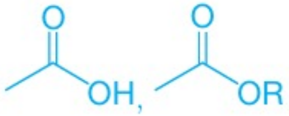
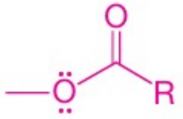
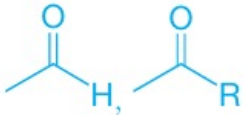
Meta product

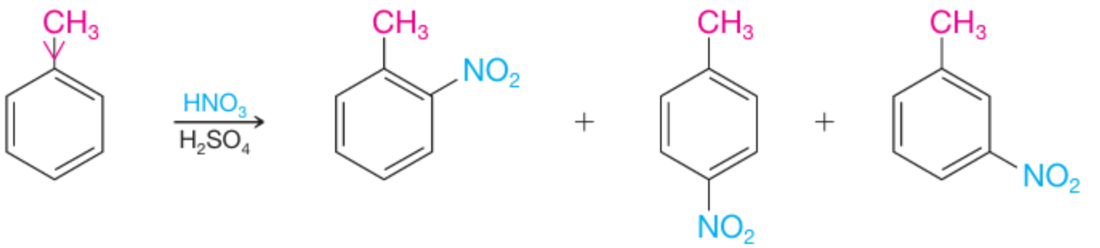
5. Electrophilic Aromatic Substitution Reactions

5.7 Existing Substituents Direct the Position of Electrophilic Aromatic Substitution

- *Effects of Substituents on Reactivity and Orientation*

Effects of Substituents on Electrophilic Aromatic Substitution

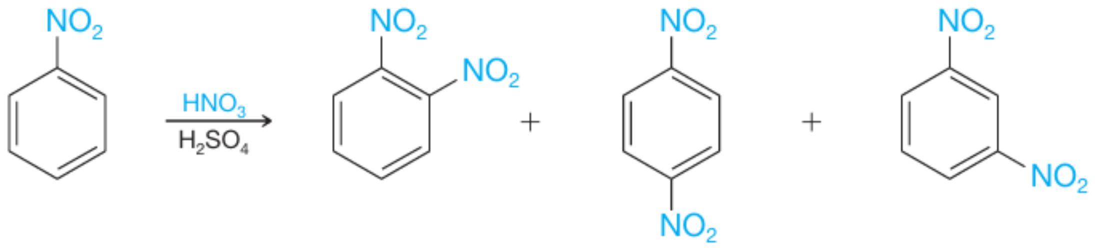
Ortho–Para Directors	**Meta Directors**
Strongly Activating	**Moderately Deactivating**
$-\ddot{N}H_2$, $-\ddot{N}HR$, $-\ddot{N}R_2$	$-C{\equiv}N$
$-\ddot{\underset{..}{O}}H$, $-\ddot{\underset{..}{O}}:^-$, $-\ddot{\underset{..}{O}}R$	$-SO_3H$
Moderately Activating	
	
	
Weakly Activating	**Strongly Deactivating**
$-R$ (alkyl)	$-NO_2$
$-C_6H_5$ (phenyl)	$-NR_3^+$
Weakly Deactivating	$-CF_3$, CCl_3
$-\ddot{\underset{..}{F}}:$, $-\ddot{\underset{..}{Cl}}:$, $-\ddot{\underset{..}{Br}}:$, $-\ddot{\underset{..}{I}}:$	



o-Nitrotoluene (59%)

p-Nitrotoluene (37%)

m-Nitrotoluene (4%)



6%

1%

93%

5. Electrophilic Aromatic Substitution Reactions

5.8 Reactions of Primary Arylamines with Nitrous Acid

- **Reaction of primary arylamines with nitrous acid results in the formation of relatively stable arenediazonium salts.**

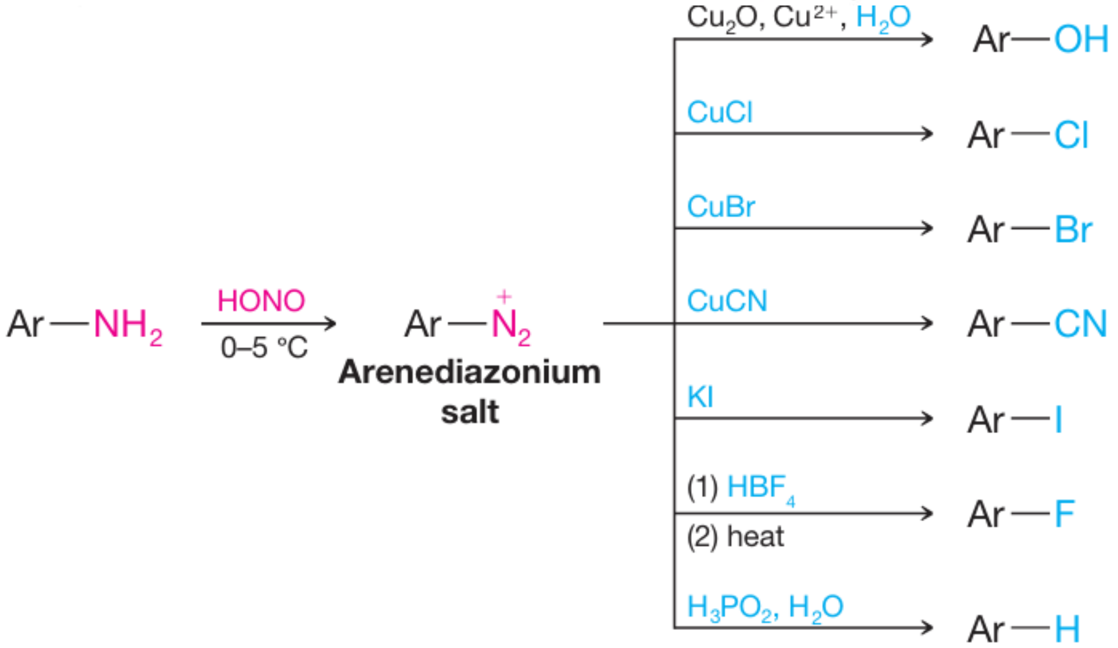
$$Ar{-}NH_2 + NaNO_2 + 2\ HX \longrightarrow Ar{-}\overset{+}{N}{\equiv}N{:}\ X^- + NaX + 2\ H_2O$$

Primary arylamine

Arenediazonium salt (stable if kept below 5 °C)

5.9 Replacement Reactions of Arenediazonium Salts

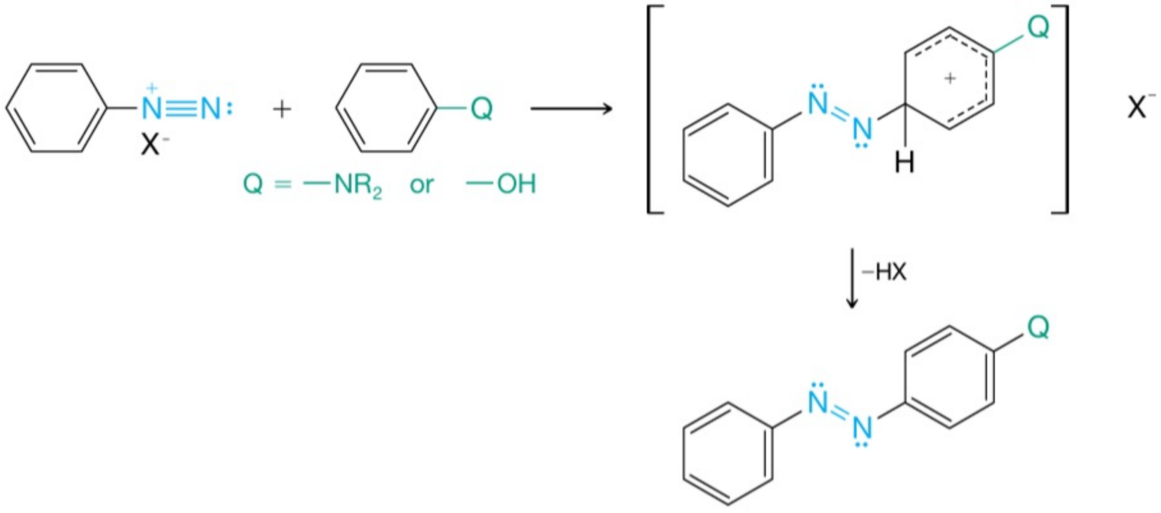
- **Arenediazonium salts are highly useful intermediates in the synthesis of aromatic compounds, because the diazonium group can be replaced by any one of a number of other atoms or groups, including –F, –Cl, –Br, –I, –CN, –OH, and –H.**



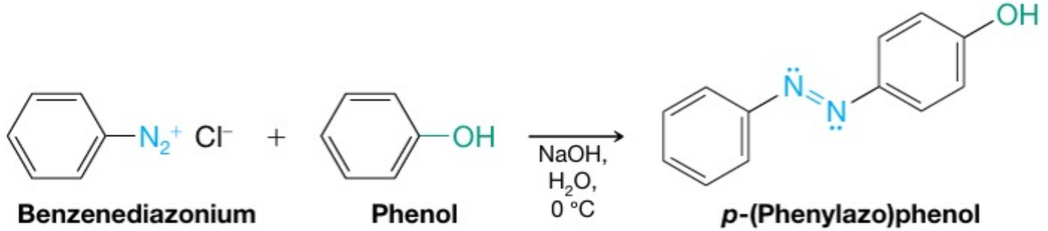
5. Electrophilic Aromatic Substitution Reactions

5.10 coupliNg reActioNs of AreNediAzoNium sAlts

- **Arenediazonium ions** are weak electrophiles; they react with highly reactive aromatic compounds—with phenols and *tertiary* arylamines—to yield **azo compounds**.
- This electrophilic aromatic substitution is often called a **diazo coupling reaction**.



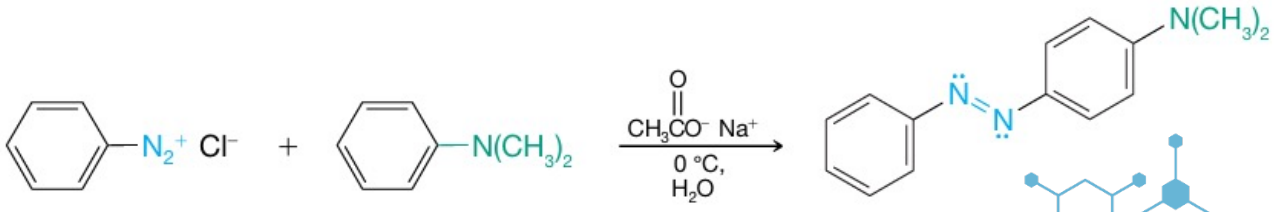
An azo compound



Benzenediazonium chloride

Phenol

***p*-(Phenylazo)phenol (orange solid)**



Benzenediazonium chloride

***N,N*-Dimethylaniline**

***N,N*-Dimethyl-*p*-(phenylazo)aniline (yellow solid)**

Nucleophilic Reactions

6. Nucleophilic Reactions

- **Nucleophilic substitution reactions** are among the most fundamental types of organic reactions. In a nucleophilic substitution reaction a **nucleophile** (**Nu:**) displaces a **leaving group** (**LG**) in the molecule that undergoes the substitution.

$$Nu:^{-} \quad + \quad R{-}LG \longrightarrow R{-}Nu \quad + \quad {}^{-}\!:LG$$

6.1 *Nucleophilic Substitution Reactions of Alcohols*

A) Conversion of Alcohols into Alkyl halides

- **The most commonly used reagents for conversion of alcohols to alkyl halides are the following:**
  - **Hydrogen halides (HCl, HBr, HI)**
  - **Phosphorus tribromide (PBr_3)**
  - **Thionyl chloride ($SOCl_2$)**

6. Nucleophilic Reactions

6.1 Nucleophilic Substitution Reactions of Alcohols

- *Conversion of Alcohols into Alkyl halides*

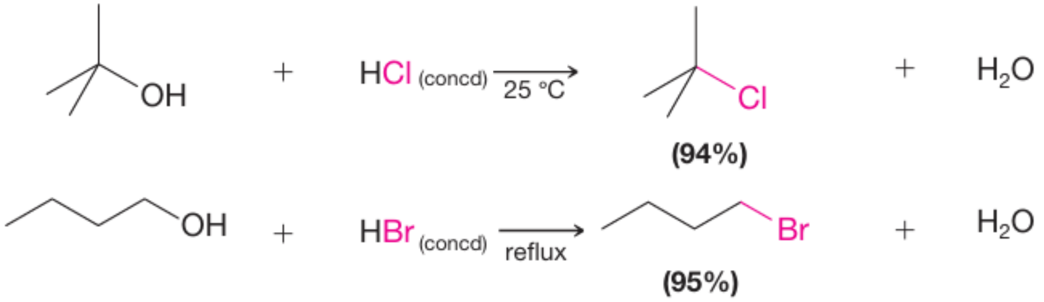
A) Alkyl halides from the reaction of Alcohols with Hydrogen halides

- **When alcohols react with a hydrogen halide, a substitution takes place producing an alkyl halide and water:**

$$R{-}OH + HX \longrightarrow R{-}X + H_2O$$

- **The order of reactivity of alcohols is 3° > 2° > 1°.**
- **The order of reactivity of the hydrogen halides is**

  HI > HBr > HCl (HF is generally unreactive).



6. Nucleophilic Reactions

6.1 Nucleophilic Substitution Reactions of Alcohols

- *Conversion of Alcohols into Alkyl halides*

B) Alkyl halides from the reaction of Alcohols with PBr_3 or $SOCl_2$

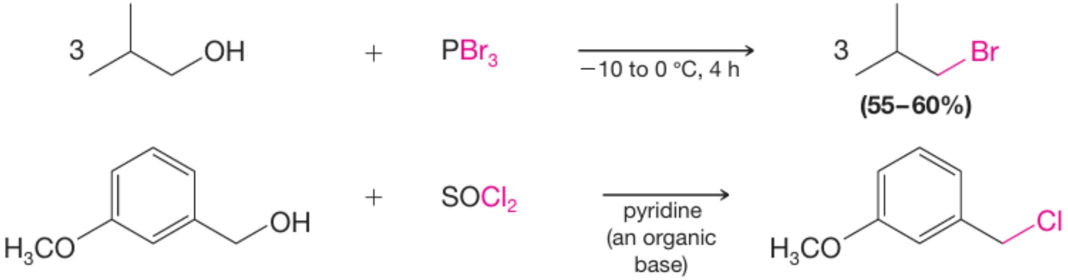
- **Primary and secondary alcohols react with phosphorus tribromide (PBr_3) to yield alkyl bromides.**
- **Thionyl chloride ($SOCl_2$) converts primary and secondary alcohols to alkyl chlorides.**

$$3\ R\text{—}OH + PBr_3 \longrightarrow 3\ R\text{—}Br + H_3PO_3$$

(1° or 2°)

$$R\text{—}OH + SOCl_2 \longrightarrow R\text{—}Cl + SO_2 + HCl$$

(1° or 2°)



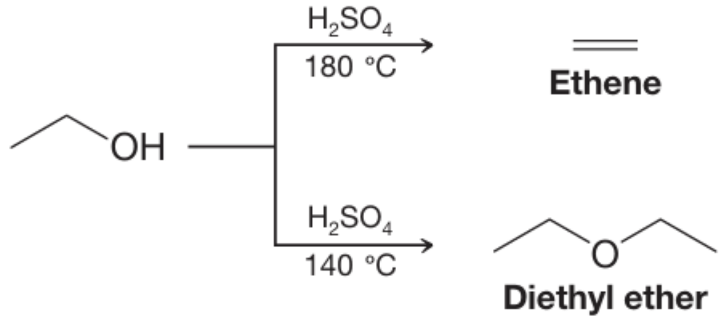
6. Nucleophilic Reactions

6.2 Nucleophilic Substitution Reactions: Synthesis of Ethers

A) Ethers by Intermolecular Dehydration of Alcohols

- **Two alcohol molecules can form an ether by loss of water through an acid-catalyzed substitution reaction.**
- **This reaction occurs at lower temperature than the competing dehydration to an alkene at high temperature.**
- **This method generally does not work with secondary or tertiary alcohols because elimination competes strongly.**

$$R{-}OH + HO{-}R \xrightarrow[-H_2O]{HA} R{-}O{-}R$$



- **Complications of Intermolecular Dehydration**

Intermolecular dehydration is not useful for the preparation of unsymmetrical ethers from primary alcohols because the reaction leads to a mixture of products.

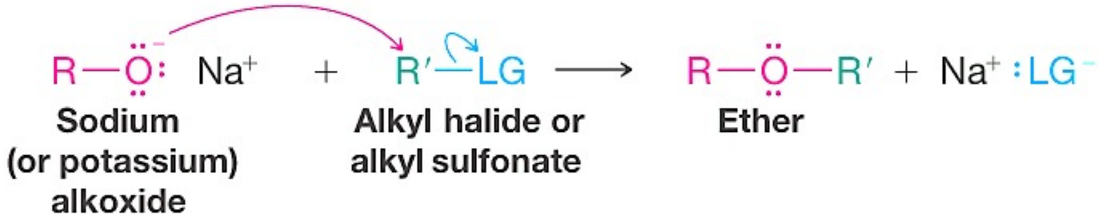
$$\underbrace{ROH + R'OH}_{1°\ \text{Alcohols}} \overset{H_2SO_4}{\rightleftharpoons} ROR + ROR' + R'OR' + H_2O$$

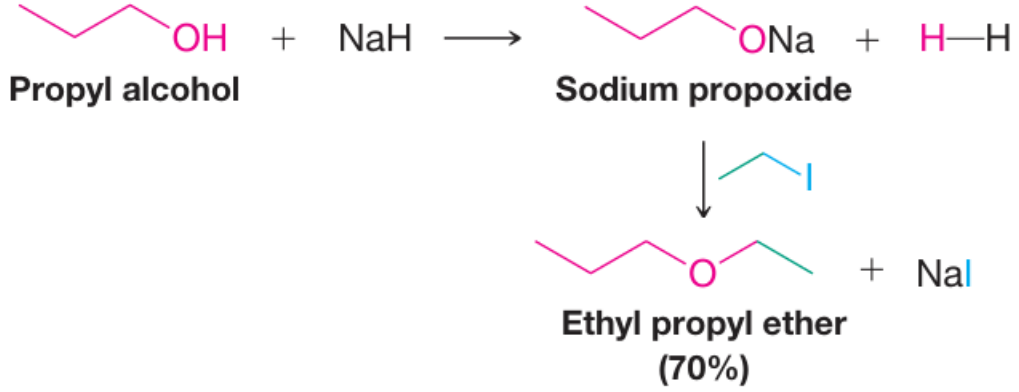
6. Nucleophilic Reactions

6.2 Nucleophilic Substitution Reactions: Synthesis of Ethers

B) The Williamson Ether Synthesis

- This is a good route for synthesis of unsymmetrical ethers.
- Best results are obtained when the alkyl halide is primary (or methyl).
- If the substrate is tertiary, elimination is the exclusive result.
- Substitution is also favored over elimination at lower temperatures.
- Example;





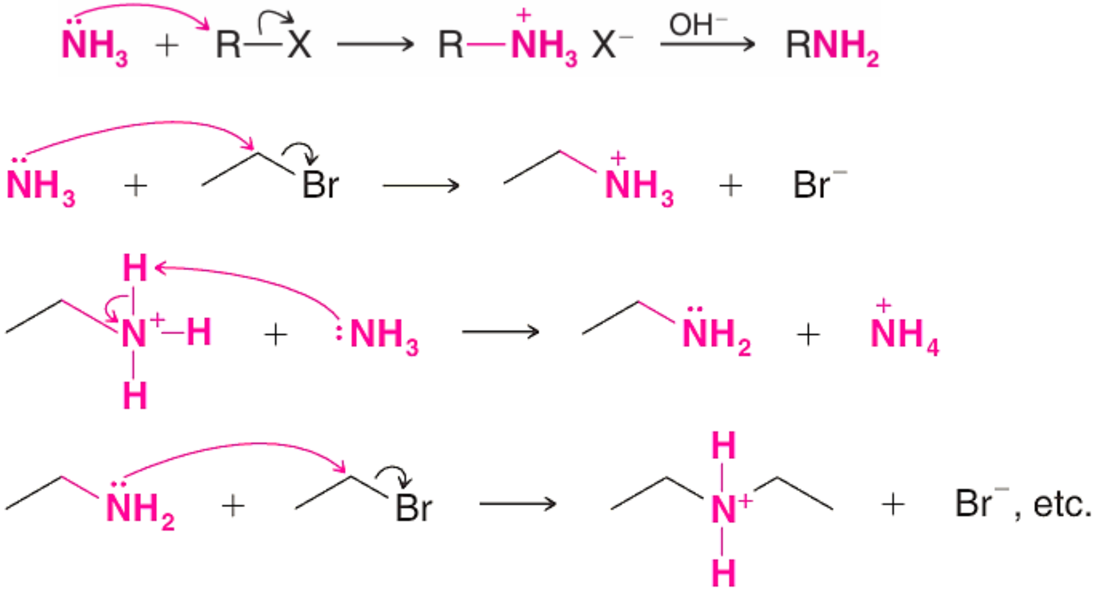
6. Nucleophilic Reactions

6.3 Nucleophilic Substitution Reactions: Preparation of Amines

Alkylation of Ammonia

- **Reaction of ammonia with an alkyl halide leads to an ammonium salt. Subsequent treatment of the resulting aminium salts with a base gives primary amines.**

- **The method is very limited because multiple alkylation usually occur.**



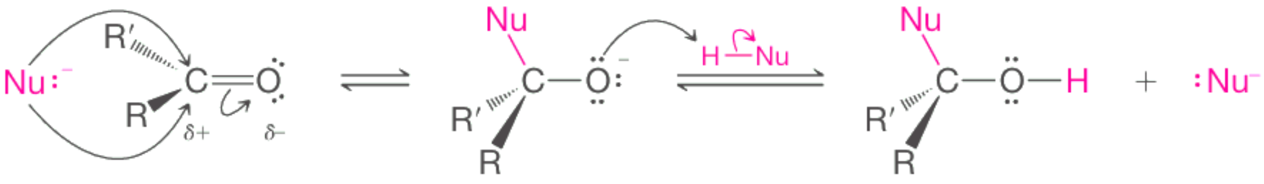
6. Nucleophilic Reactions

6.4 Nucleophilic Addition to Aldehyde or Ketone

- The most characteristic reaction of aldehydes and ketones is nucleophilic addition to the carbon–oxygen double bond.

- *addition of a Strong Nucleophile to an aldehyde or Ketone;*

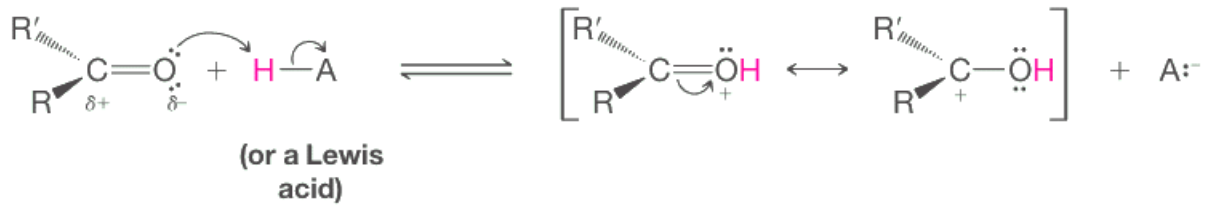
  When the reagent is a strong nucleophile (Nu:⁻)



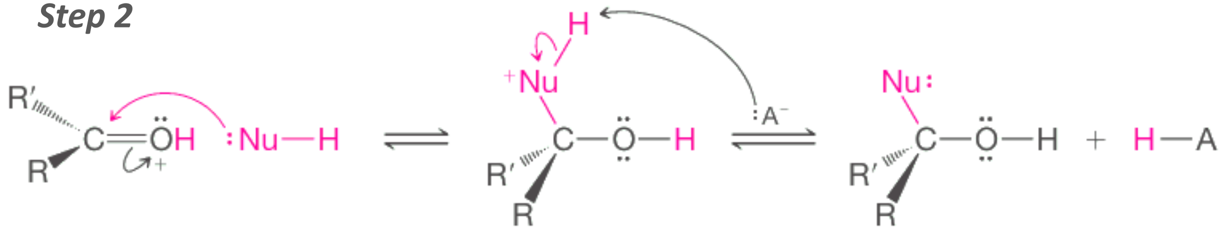
- *Acid-Catalyzed Nucleophilic Addition to an Aldehyde or Ketone;*

  When an acid catalyst is present and the nucleophile is weak.

Step 1



Step 2



Chapter 5: Organic Reactions

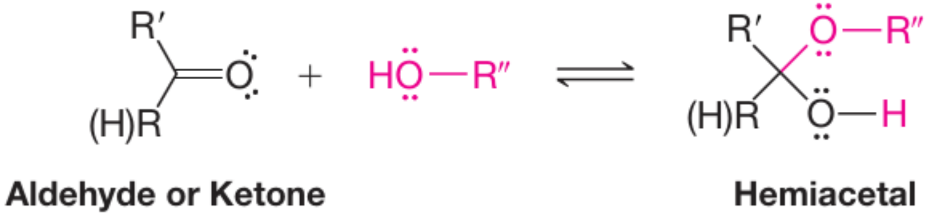
6. Nucleophilic Reactions

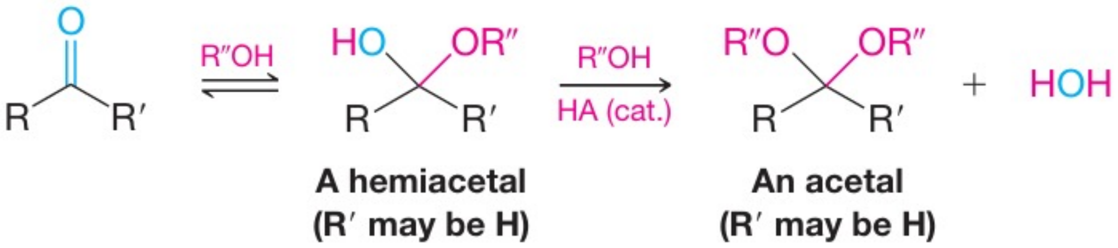
6.4 Nucleophilic Addition to Aldehyde or Ketone

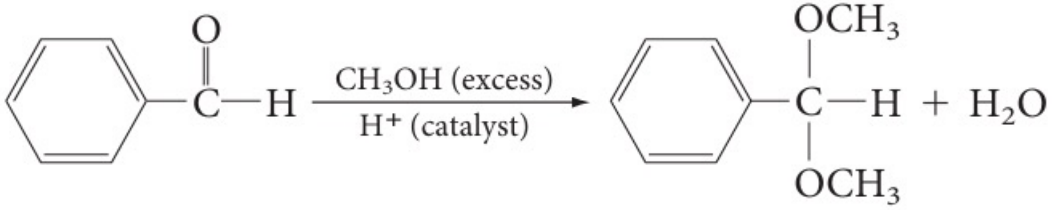
A) The Addition of Alcohols: Hemiacetals and Acetals

- **Hemiacetals;** an –OH and an –OR group attached to the same carbon atom.
- A **hemiacetal** results by nucleophilic addition of an alcohol oxygen to the carbonyl carbon of an aldehyde or ketone.

- **Acetals;** has two –OR groups attached to the same carbon atom.
- An **acetal** forms when an aldehyde or ketone is treated with an excess of alcohol in the presence of an acid catalyst. Although a **hemiacetal is an intermediate**, it usually cannot be isolated because it continues on to become an acetal.







6. Nucleophilic Reactions

6.4 Nucleophilic Addition to Aldehyde or Ketone

B) The Addition of Primary Amines : Imine formation

- **Imine formation** is acid catalyzed, and the product can form from a primary amine and an aldehyde or ketone.

C) Reaction with hydroxylamine : Oxime formation

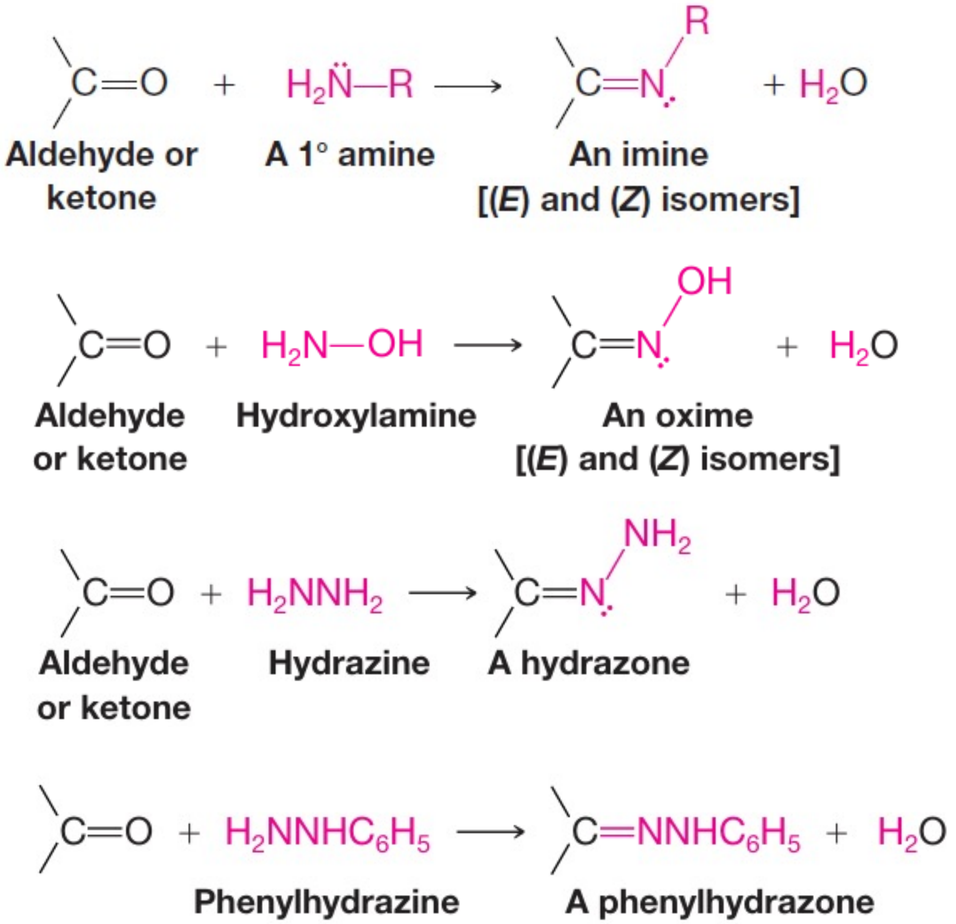
- **Oximes** are formed when aldehydes or ketones react with hydroxylamine (H_2N-OH).

D) Reactions with hydrazine: Hydrazone formation

- **Hydrazone** can formed when aldehydes or ketones react with hydrazine (H_2N-NH_2).

E) Reactions with phenylhydrazine : Phenylhydrazone formation

- **Hydrazone** can formed when aldehydes or ketones react with hydrazine (H_2N-NHC_6H_5).



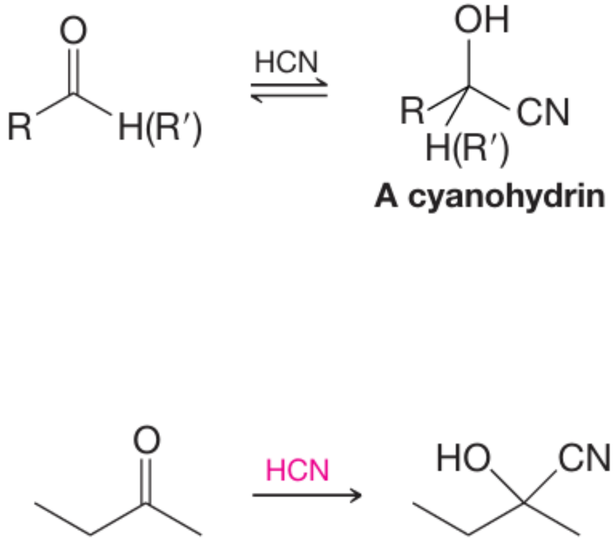
Chapter 5: Organic Reactions

6. Nucleophilic Reactions

6.4 Nucleophilic Addition to Aldehyde or Ketone

F) The Addition of Hydrogen Cyanide: Cyanohydrins

- **Hydrogen cyanide adds to the carbonyl groups of aldehydes and most ketones to form compounds called cyanohydrins.**
- **Cyanohydrins form fastest under conditions where cyanide anions are present to act as the nucleophile.**

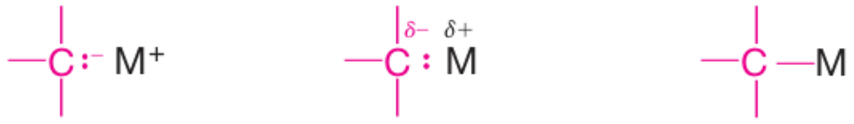


Chapter 5: Organic Reactions

6. Nucleophilic Reactions

6.5 Nucleophilic Addition Grignard Reagents

- Compounds that contain carbon–metal bonds are called organometallic compounds.



Primarily ionic **($M = Na^+$ or K^+)**

($M = Mg$ or Li)

Primarily covalent **($M = Pb, Sn, Hg,$ or Tl)**

$$\left.\begin{array}{l} RX + Mg \xrightarrow{Et_2O} RMgX \\ ArX + Mg \xrightarrow{Et_2O} ArMgX \end{array}\right\}\ \textbf{Grignard reagents}$$

- Grignard reagents are prepared by the reaction of an organic halide with magnesium metal in an anhydrous ether solvent.

$$CH_3I + Mg \xrightarrow[35°C]{Et_2O} CH_3MgI$$

Methylmagnesium iodide (95%)

- The order of reactivity of halides with magnesium is also

  RI > RBr > RCl.

$$C_6H_5Br + Mg \xrightarrow[35°C]{Et_2O} C_6H_5MgBr$$

Phenylmagnesium bromide (95%)

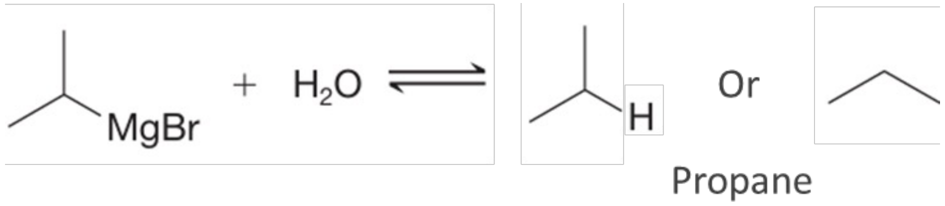
6. Nucleophilic Reactions

6.5 Nucleophilic Addition Grignard Reagents

- *Reactions of Organomagnesium Compounds*

A) Reactions with Compounds Containing Acidic Hydrogen Atoms

- Grignard reagents are very strong bases.
- They react with any compound that has a hydrogen atom attached to an electronegative atom such as oxygen, nitrogen, or sulfur.



6. Nucleophilic Reactions

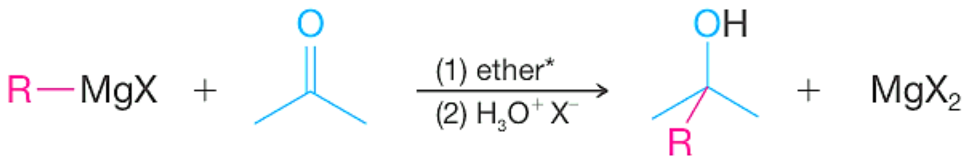
6.5 Nucleophilic Addition Grignard Reagents

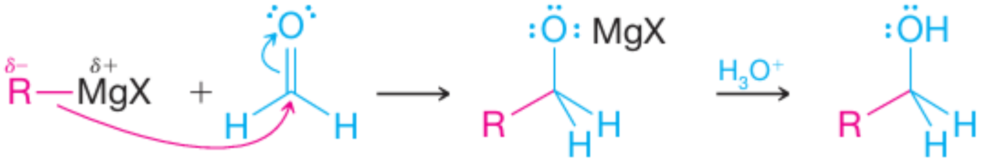
- *Reactions of Organomagnesium Compounds*

B) Reactions with Carbonyl Compounds

- **Grignard reagents react as nucleophiles and attack an unsaturated carbon—the carbon of a carbonyl group (aldehyde and ketone) to prepare primary, secondary, or tertiary alcohols.**

- **Grignard Reagents React with Formaldehyde to Give a Primary Alcohol.**





Formaldehyde **1° Alcohol**

Phenylmagnesium bromide **Formaldehyde** **Benzyl alcohol (90%)**

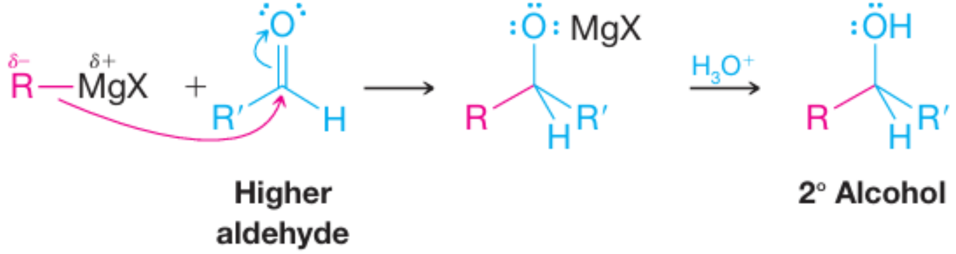
6. Nucleophilic Reactions

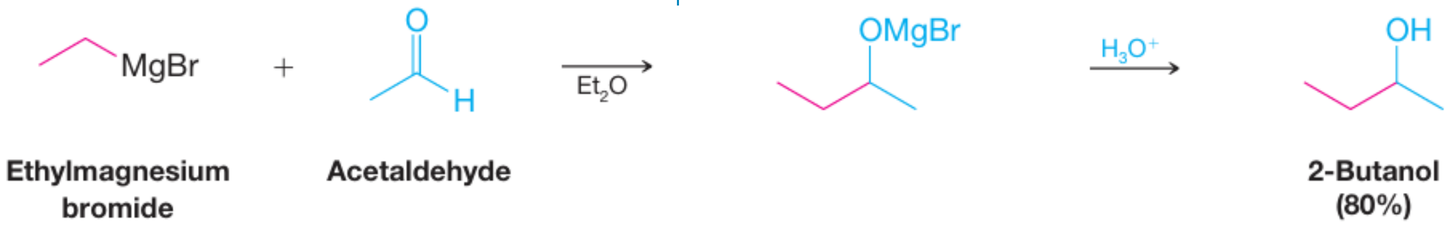
6.5 Nucleophilic Addition Grignard Reagents

- *Reactions of Organomagnesium Compounds*

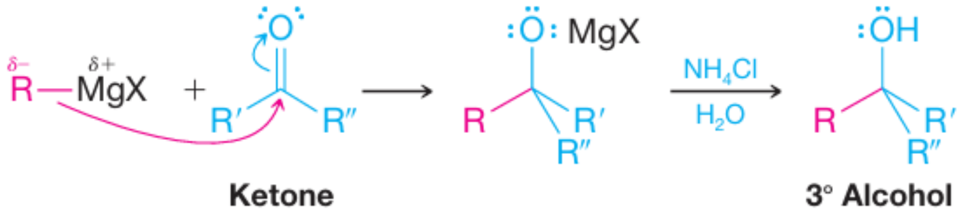
B) Reactions with Carbonyl Compounds

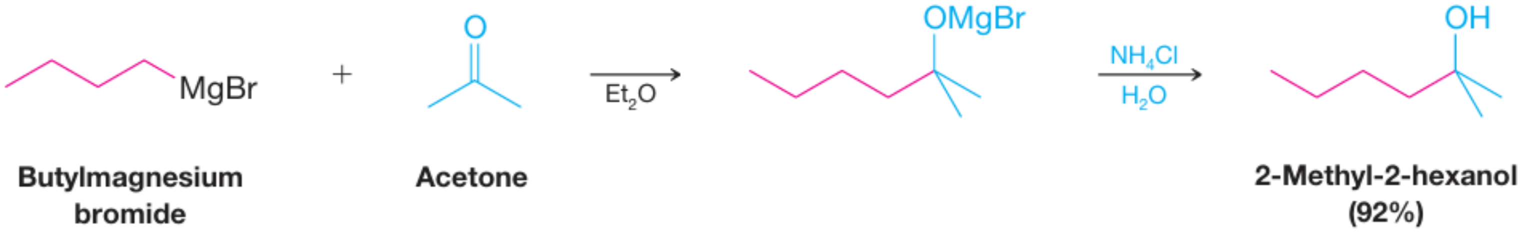
- **Grignard Reagents React with All Other Aldehydes to Give Secondary Alcohols.**





- **Grignard Reagents React with Ketones to Give Tertiary Alcohols.**





6. Nucleophilic Reactions

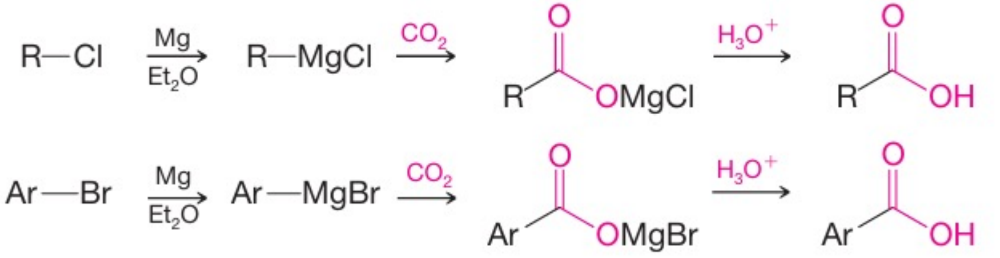
6.5 Nucleophilic Addition Grignard Reagents

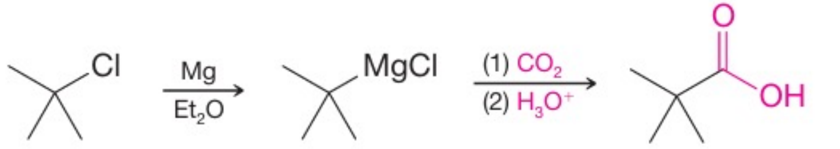
- *Reactions of Organomagnesium Compounds*

C) Carboxylic Acids from Grignard Reagents (Carbonation of Grignard Reagents)

- **Grignard reagents react with carbon dioxide to yield magnesium carboxylates. Acidification produces carboxylic acids.**

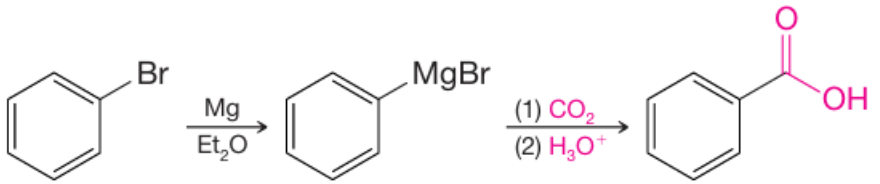
- **This synthesis of carboxylic acids is applicable to primary, secondary, tertiary, allyl, benzyl, and aryl halides.**





***tert*-Butyl chloride**

2,2-Dimethylpropanoic acid (79–80% overall)



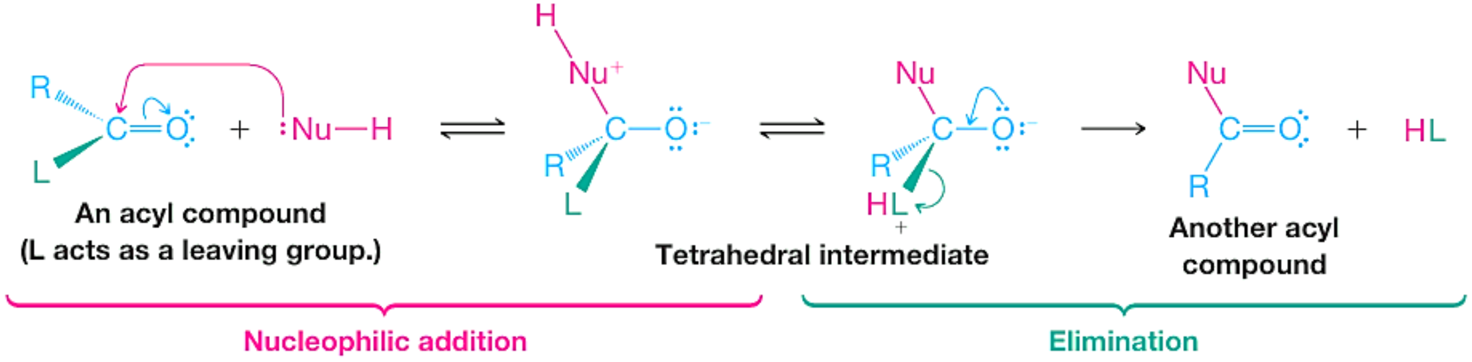
Bromobenzene

Benzoic acid (85%)

6. Nucleophilic Reactions

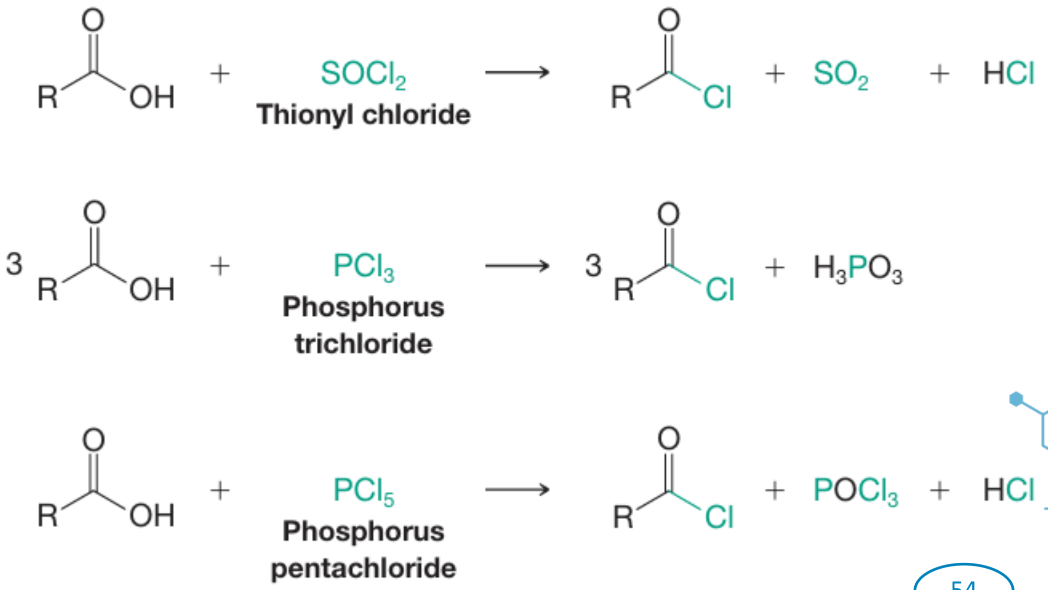
6.6 Substitution by Nucleophilic Addition-Elimination Reaction

- **The reactions of carboxylic acids and their derivatives are characterized by nucleophilic addition–elimination at their acyl (carbonyl) carbon atoms. The result is a substitution at the acyl carbon.**



A) Synthesis of Acyl Chlorides

- **Acid chlorides are made from the reaction of carboxylic acids with thionyl chloride, phosphorus trichloride or phosphorus pentachloride.**

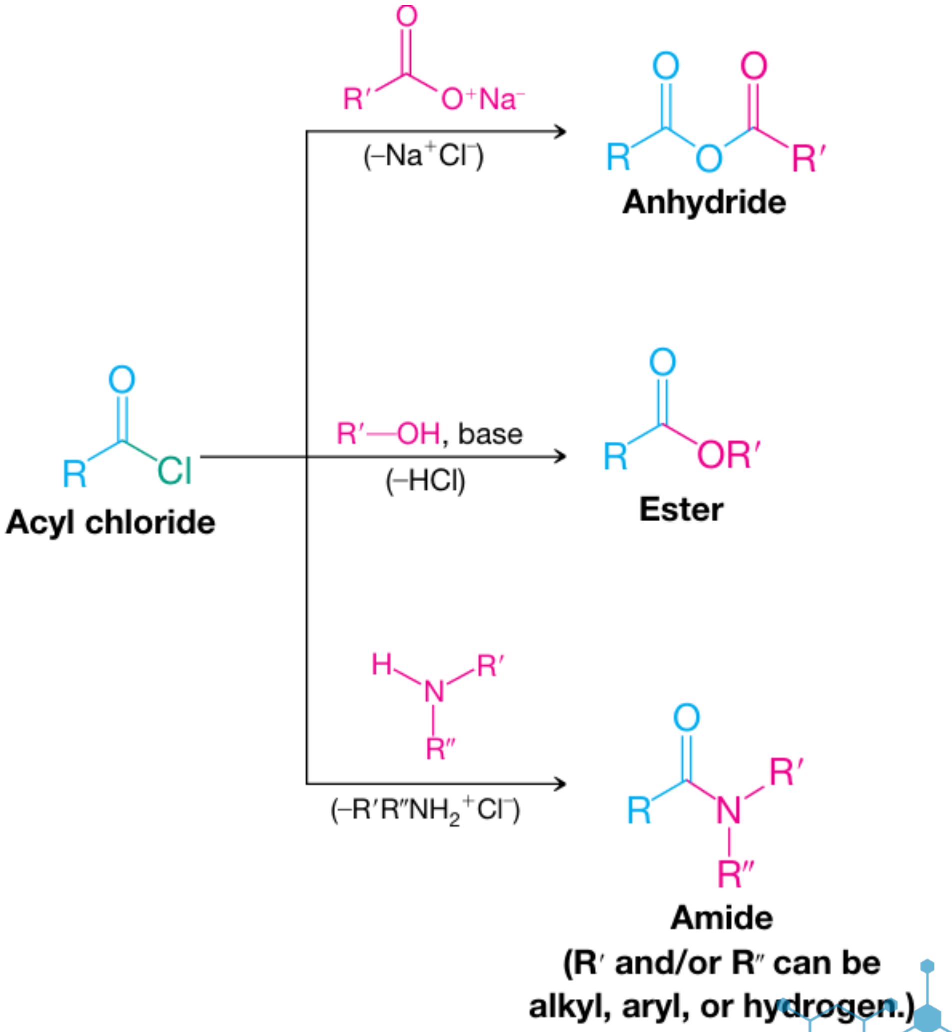


6. Nucleophilic Reactions

6.6 Substitution by Nucleophilic Addition-Elimination Reaction

B) Reactions of Acyl Chlorides

- **Because acyl chlorides are the most reactive of the acyl derivatives, they are easily converted to less reactive ones.**

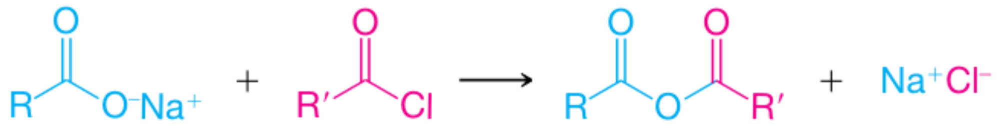


6. Nucleophilic Reactions

6.6 Substitution by Nucleophilic Addition-Elimination Reaction

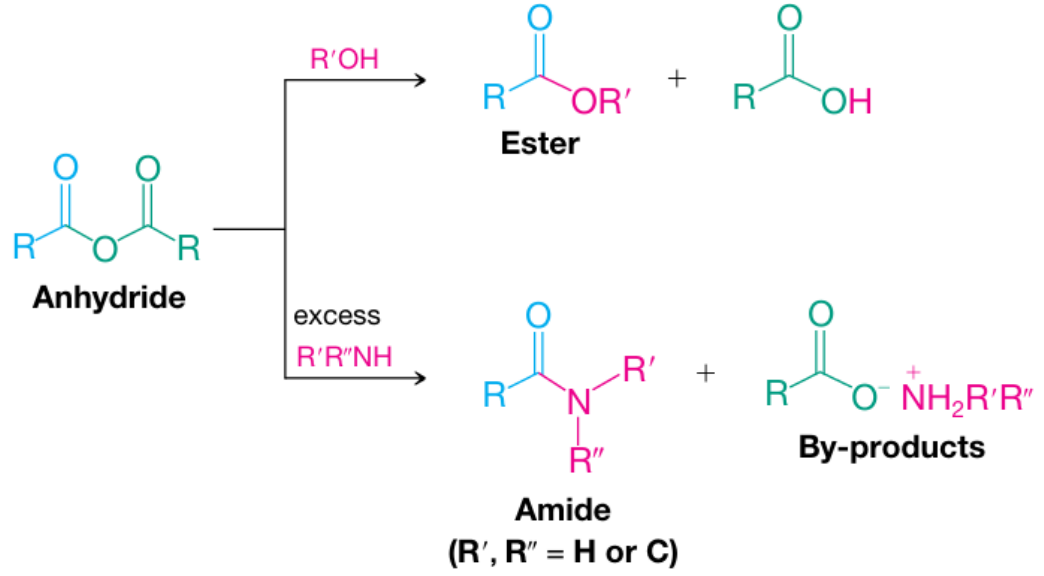
C) Synthesis of Carboxylic Acid Anhydrides

- Sodium salts of carboxylic acids also react with acyl chlorides to give anhydrides.

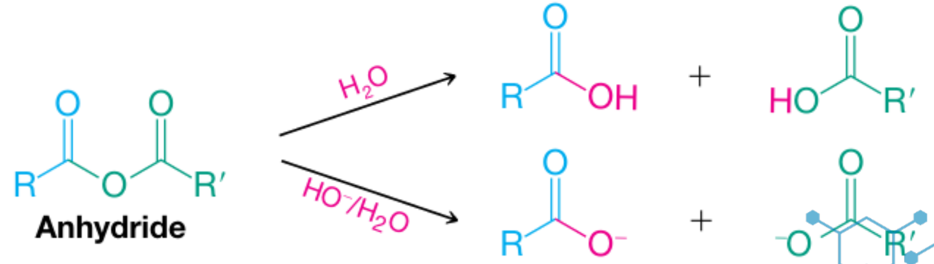


D) Reactions of Carboxylic Acid Anhydrides

- Carboxylic acid anhydrides are very reactive and can be used to synthesize esters and amides.



- Hydrolysis of an anhydride yields the corresponding carboxylic acids.



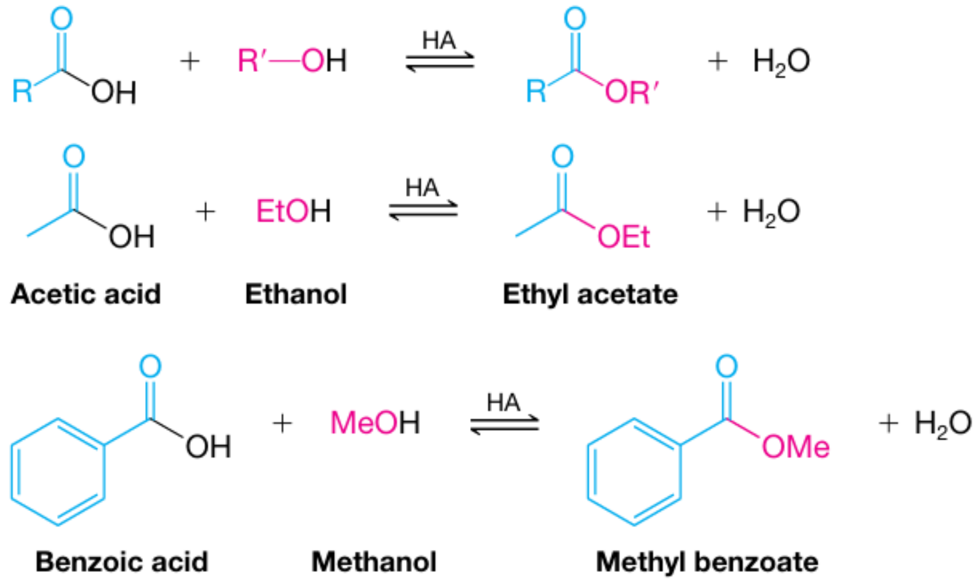
6. Nucleophilic Reactions

6.6 Substitution by Nucleophilic Addition-Elimination Reaction

E) Synthesis of Esters: Esterification

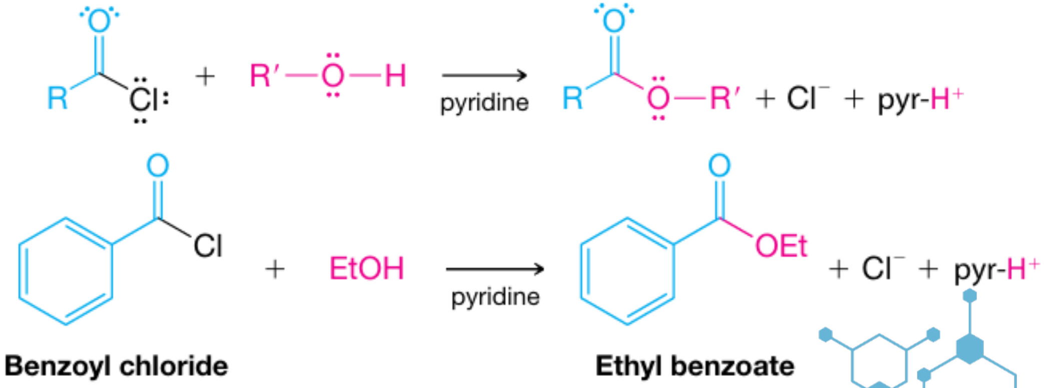
- **Acid-Catalyzed Esterification:**

  Esterification is the formation of an ester by reaction of a carboxylic acid, acid chloride, or carboxylic acid anhydride with an alcohol or phenol. This method is often called **Fischer esterification**.



- **Esters from Acyl Chlorides:**

  The reaction of acyl chlorides with an alcohol or a phenol is one of the best ways to synthesize an ester.



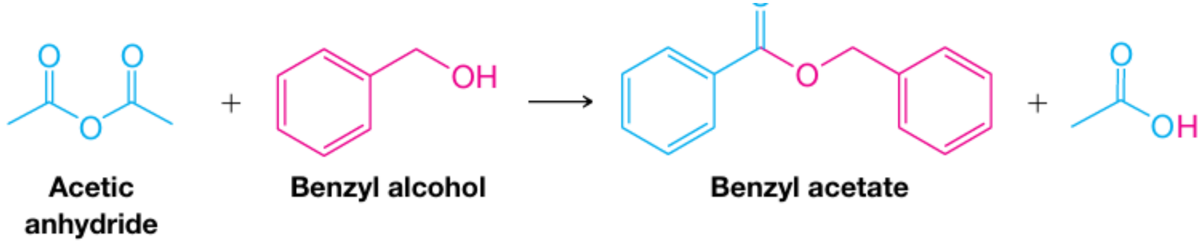
6. Nucleophilic Reactions

6.6 Substitution by Nucleophilic Addition-Elimination Reaction

E) Synthesis of Esters: Esterification

- **Esters from Carboxylic Acid Anhydrides**

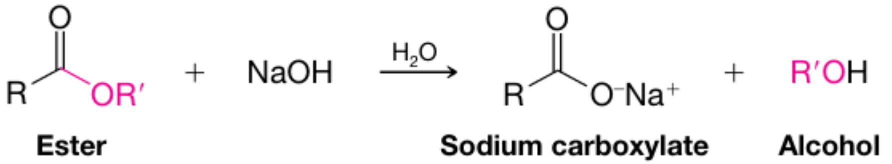
  Carboxylic acid anhydrides react with alcohols and phenols to form esters in the absence of acid catalyst.



F) Reactions of Esters

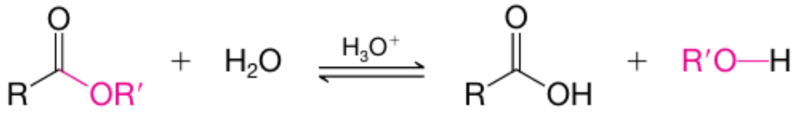
- **Base-Promoted Hydrolysis of Esters: Saponification**

  Reaction of an ester with sodium hydroxide results in the formation of a sodium carboxylate and an alcohol.



- **Acid-Catalyzed Ester Hydrolysis**

  Reaction of an ester with a large excess of water and dilute aqueous HCl or dilute aqueous H_2SO_4.



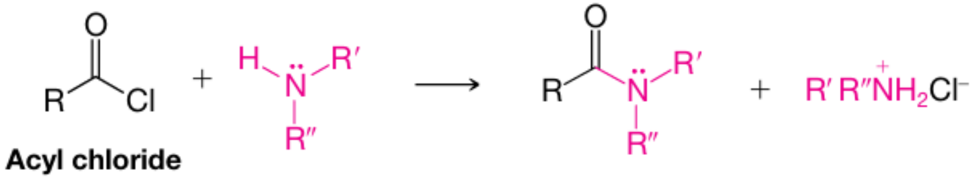
6. Nucleophilic Reactions

6.6 Substitution by Nucleophilic Addition-Elimination Reaction

G) Synthesis of Amides

- **From Acyl Chlorides**

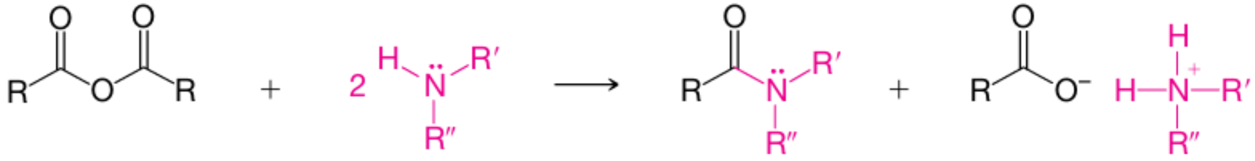
  Ammonia, primary or secondary amines react with acid chlorides to form amides. An excess of amine is added to neutralize the HCl formed in the reaction.



R′, R″ can be H, alkyl, or aryl.

- **From Carboxylic Anhydrides**

  Acid anhydrides react with 2 equivalents of amine to produce an amide and an ammonium carboxylate.



R′, R″ can be H, alkyl, or aryl.

6. Nucleophilic Reactions

6.6 Substitution by Nucleophilic Addition-Elimination Reaction

G) Synthesis of Amides

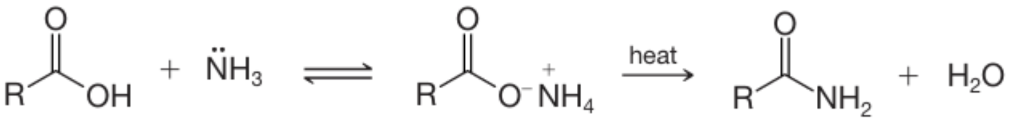
- **Amides from Esters**

  Esters react with ammonia (called ammonolysis) or with primary and secondary amines to produce an amide and an alcohol.

R′ and/or R″ may be H.

- **From Carboxylic Acids and Ammonium Carboxylates**

  Carboxylic acids react with aqueous ammonia to form ammonium salts. Some ammonium salts of carboxylic acids can be dehydrated to the amide at high temperatures



An ammonium carboxylate

6. Nucleophilic Reactions

6.6 Substitution by Nucleophilic Addition-Elimination Reaction

H) Reactions of Amides

- **Hydrolysis of Amides**

  Amides undergo hydrolysis when they are heated with aqueous acid or aqueous base.

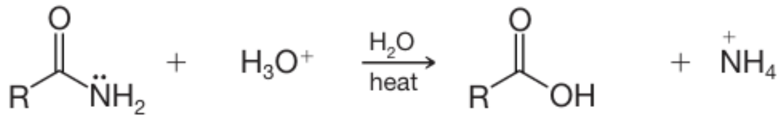
- **Nitriles from the Dehydration of Amides**

  Amides react with boiling acetic anhydride to form nitriles.

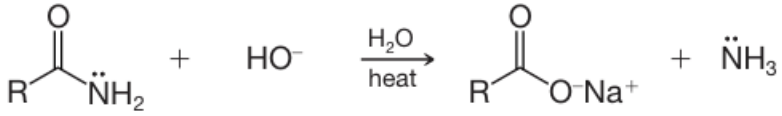
- **Hydrolysis of Nitriles**

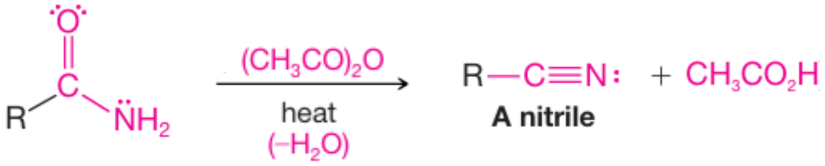
  Complete hydrolysis of a nitrile produces a carboxylic acid or a carboxylate anion.

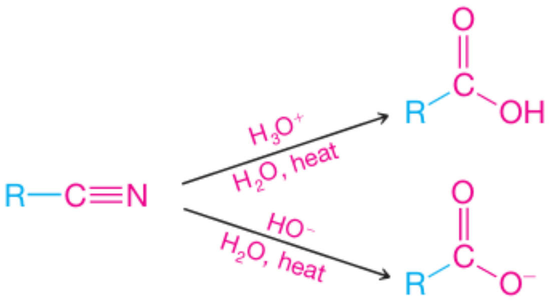
Acidic Hydrolysis



Basic Hydrolysis







Oxidation and Reduction Reactions

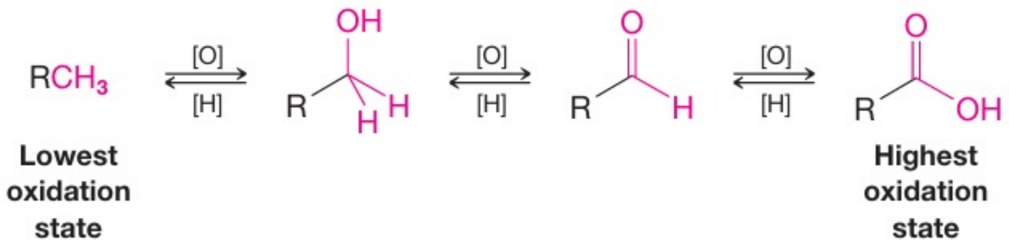
7. Oxidation and Reduction Reactions

- Reduction; increasing the hydrogen content or decreasing the oxygen content of an organic molecule.
- A general symbol for reduction is [H].

- Oxidation; increasing the oxygen content of an organic molecule or decreasing its hydrogen content.
- A general symbol for oxidation is [O].

- Oxidation can also be defined as a reaction that increases the content of any element more electronegative than carbon.

- when an organic compound is reduced, something else the reducing agent must be oxidized.
- And when an organic compound is oxidized, something else the oxidizing agent is reduced.
- These oxidizing and reducing agents are often inorganic compounds.



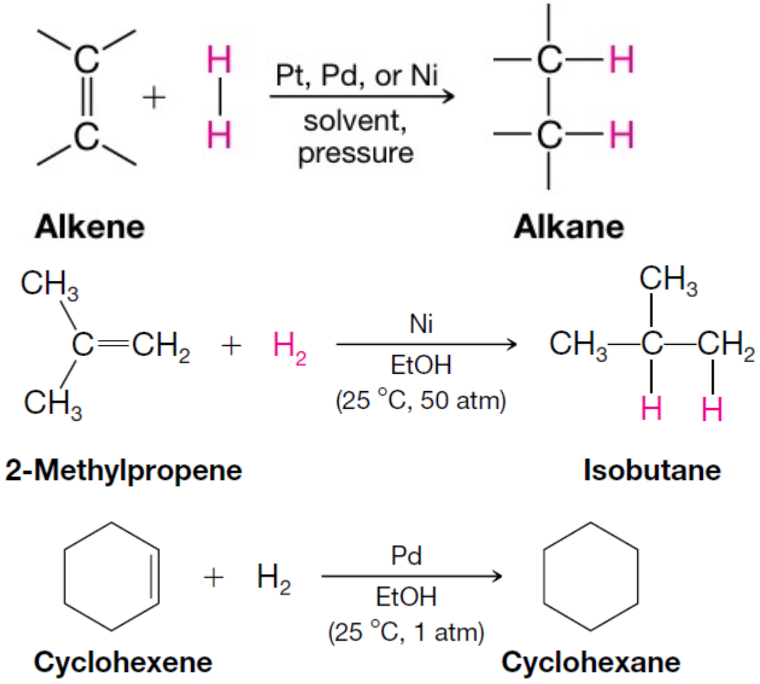
$$Ar{-}CH_3 \underset{[H]}{\overset{[O]}{\rightleftarrows}} Ar{-}CH_2Cl \underset{[H]}{\overset{[O]}{\rightleftarrows}} Ar{-}CHCl_2 \underset{[H]}{\overset{[O]}{\rightleftarrows}} Ar{-}CCl_3$$

7. Oxidation and Reduction Reactions

7.1 Hydrogenation of Alkenes: Synthesis of Alkanes and Cycloalkanes

- **Heterogeneous catalysts:** insoluble platinum, palladium or nickel catalysts that are not soluble in the reaction mixture.
- **Homogeneous catalysts:** soluble catalyst include rhodium or ruthenium complexes; Wilkinson's catalyst ($Rh[(C_6H_5)_3P]_3Cl$) that is soluble in the reaction mixture.

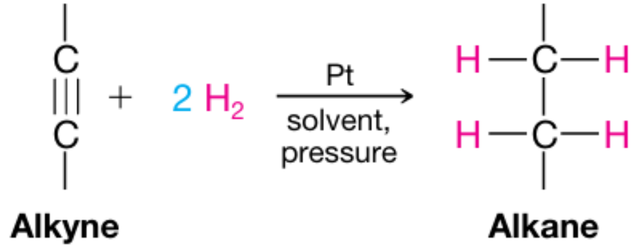
- An unsaturated compound becomes a saturated (with hydrogen) compound.



7. Oxidation and Reduction Reactions

7.2 Hydrogenation of Alkynes: Synthesis of Alkanes and Cycloalkanes

- When a platinum catalyst is used, the alkyne reacts with two molar equivalents of hydrogen to give an alkane.



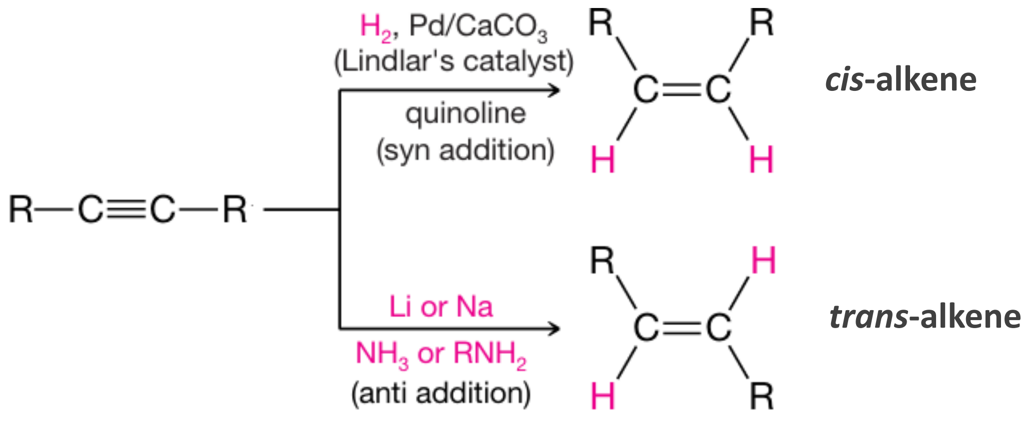
$CH_3C\equiv CCH_3 \xrightarrow{Pt,\ H_2} [CH_3CH{=}CHCH_3] \xrightarrow{Pt,\ H_2} CH_3CH_2CH_2CH_3$

- **Syn Addition of Hydrogen: Synthesis of *cis*-Alkenes**

  Metallic palladium deposited on calcium carbonate (Lindlar's catalyst) can be used to prepare *cis*-alkenes.

- **Anti Addition of Hydrogen: Synthesis of *trans*-Alkenes**

  Treatment of alkynes with lithium or sodium metal in ammonia or ethylamine at low temperatures prepare *trans*-alkene.

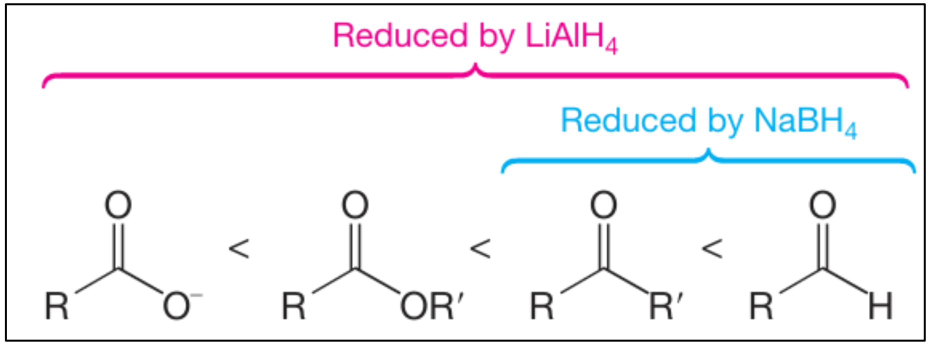


7. Oxidation and Reduction Reactions

7.3 Reduction of Carbonyl Compounds; Synthesis of Alcohols

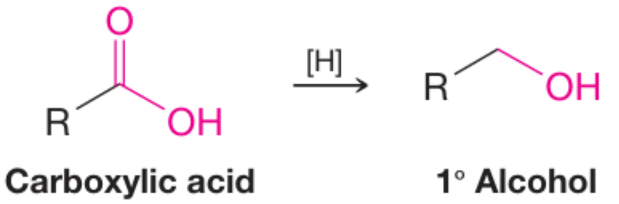
- **Lithium Aluminum Hydride ($LiAlH_4$)**

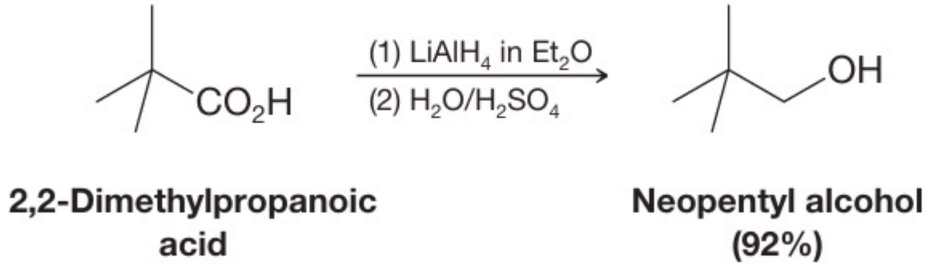
  Carboxylic acids and esters can be reduced to primary alcohols.

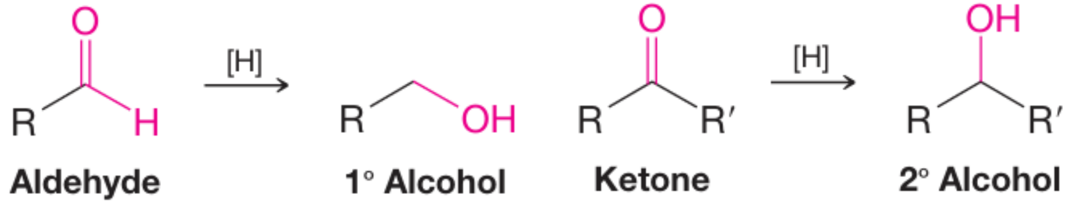


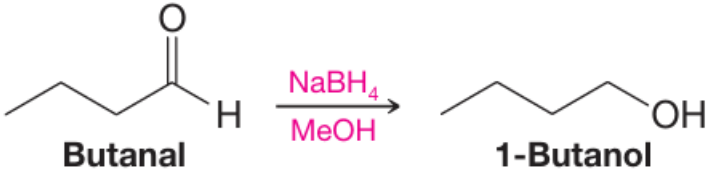
- **Sodium Borohydride ($NaBH_4$)**

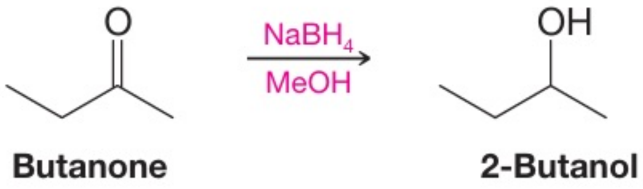
  Aldehydes and ketones are reduced by mild reducing agent sodium borohydride ($NaBH_4$) to 1° and 2° alcohols, respectively.







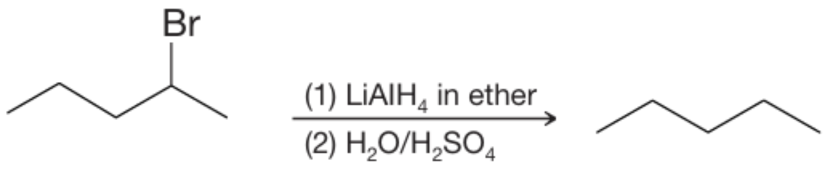




7. Oxidation and Reduction Reactions

7.4 Reduction of Alkyl Halides to Hydrocarbons: RX to RH

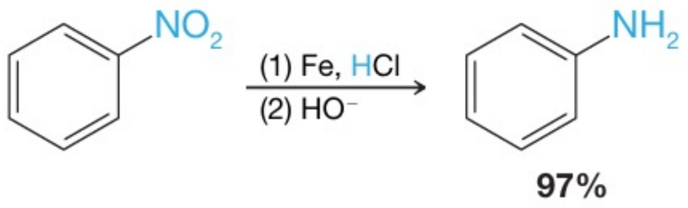
- Replacement of the halogen atom of an alkyl halide by hydrogen can be accomplished by treating the alkyl halide with lithium aluminum hydride.



7.5 Reduction of Nitro Compounds: Preparation of Aromatic Amines

- Aromatic amines can be synthesized by reduction of the corresponding nitro compound.

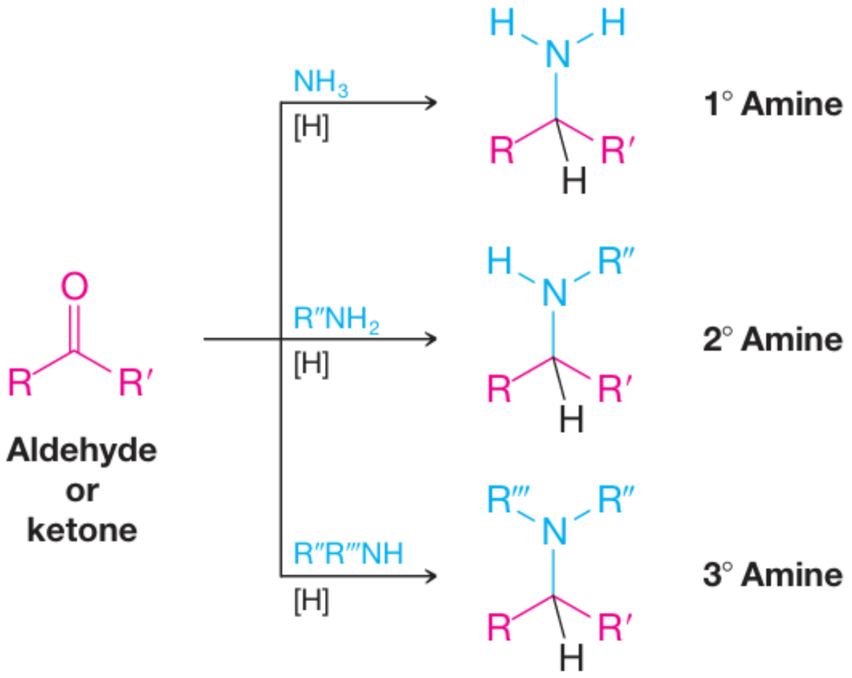
$$Ar{-}NO_2 \xrightarrow[\text{or (1) Fe, HCl (2) HO}^-]{H_2\text{, catalyst}} Ar{-}NH_2$$

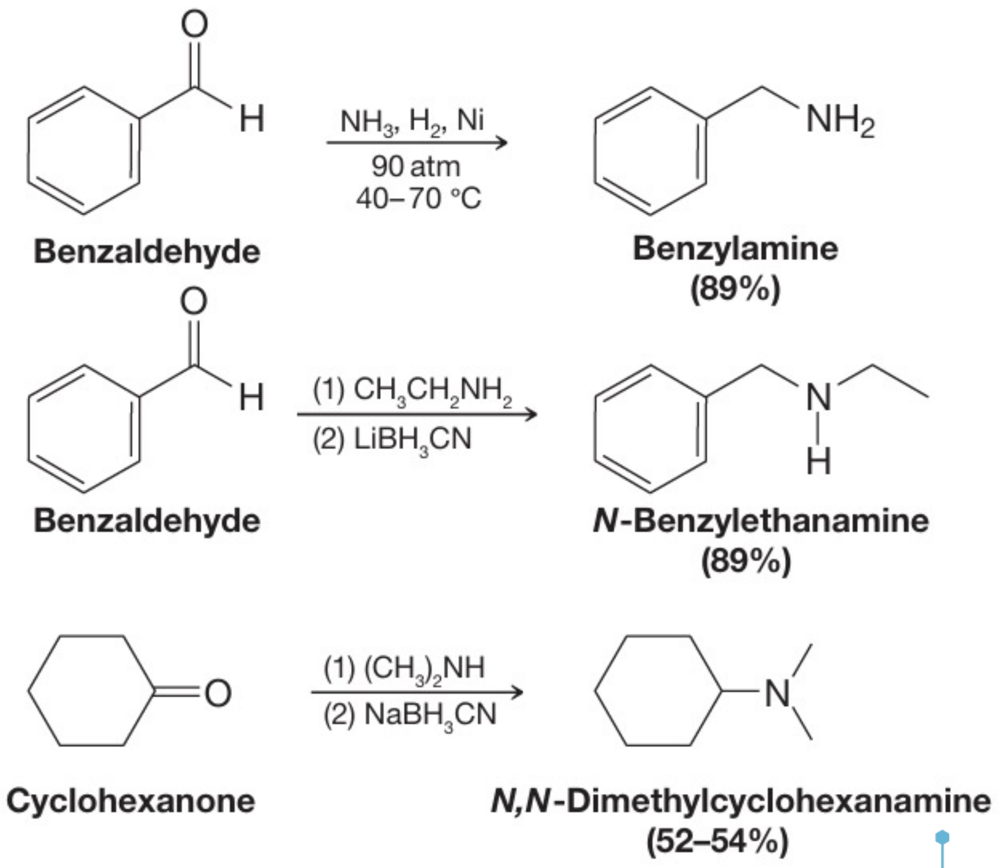


7. Oxidation and Reduction Reactions

7.6 Reductive Amination of aldehyde or ketone: Preparation of Primary, Secondary, and Tertiary Amines

- **Aldehydes and ketones can be converted to amines through catalytic or chemical reduction in the presence of ammonia or an amine.**

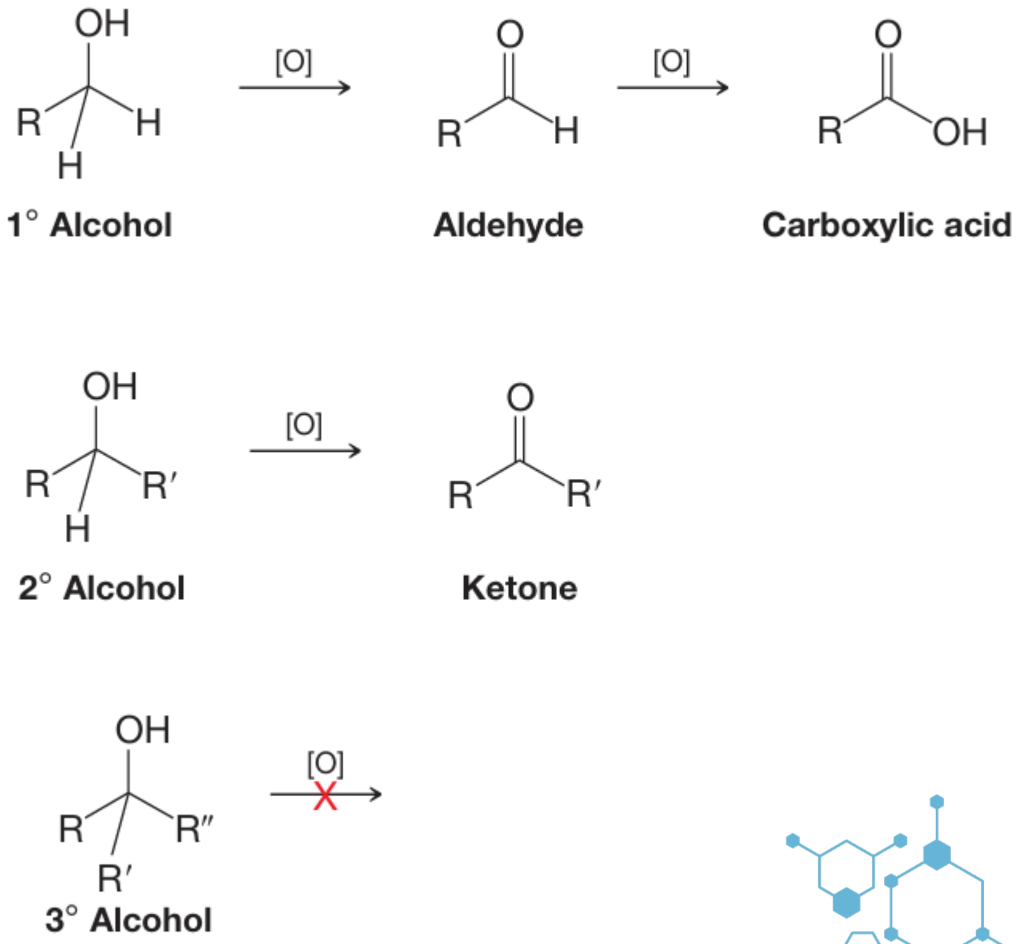




7. Oxidation and Reduction Reactions

7.7 Oxidation of Alcohols: *Preparation of Aldehydes, Ketones, and Carboxylic Acids*

- Primary alcohols can be oxidized to aldehydes, and aldehydes can be oxidized to carboxylic acids.
- Secondary alcohols can be oxidized to ketones.
- Tertiary alcohols cannot be oxidized to carbonyl compounds.



Chapter 5: Organic Reactions

7. Oxidation and Reduction Reactions

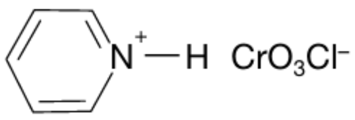
7.7 Oxidation of Alcohols: *Preparation of Aldehydes, Ketones, and Carboxylic Acids*

A) Oxidation by Chromic acid (H_2CrO_4)

- Oxidations involving chromium (VI) reagents such as Jones reagent H_2CrO_4 (CrO_3 in H_2SO_4).
- Primary alcohols are oxidized to carboxylic acids.
- Secondary alcohols are oxidized to ketones.

B) Oxidation by Pyridinium Chlorochromate (PCC)

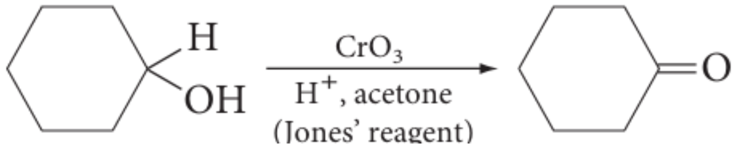
Pyridinium chlorochromate (PCC) is formed between pyridine (C_6N_5N), HCl, and CrO_3. PCC is soluble in dichloromethane. Thus, it can be used under conditions that exclude water, allowing for the oxidization of primary alcohols to aldehydes and secondary alcohols to ketones.



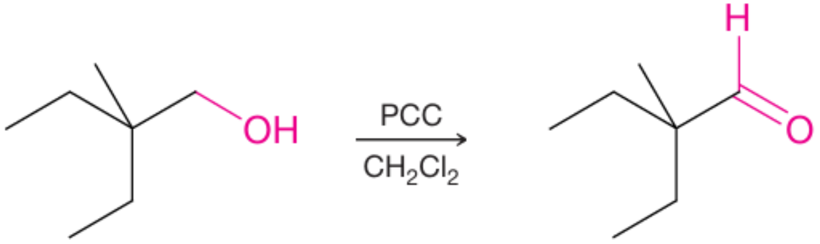
Pyridinium chlorochromate (PCC)

$$CH_3(CH_2)_6CH_2OH \xrightarrow[\text{reagent}]{\text{Jones'}} CH_3(CH_2)_6CO_2H$$

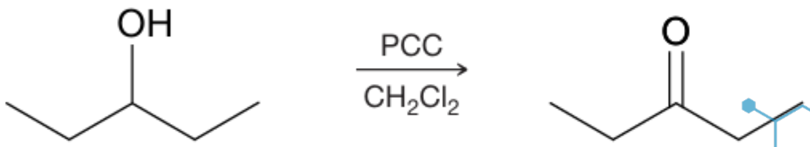
1-Octanol **Octanoic acid**



Cyclohexanol **Cyclohexanone**



2-Ethyl-2-methyl-1-butanol **2-Ethyl-2-methylbutanal**

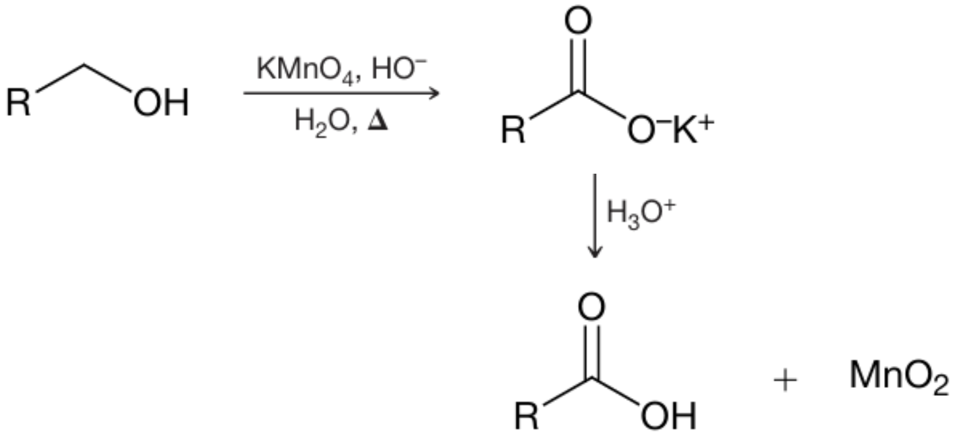


7. Oxidation and Reduction Reactions

7.7 Oxidation of Alcohols; *Preparation of Aldehydes, Ketones, and Carboxylic Acids*

C) Oxidation by Potassium Permanganate ($KMnO_4$)

Primary alcohols and aldehydes can be oxidized by potassium permanganate ($KMnO_4$) to the corresponding carboxylic acids. Secondary alcohols can be oxidized to ketones. The reaction is usually carried out in basic aqueous solution.



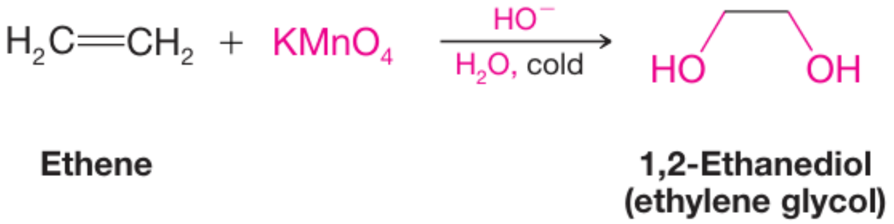
Chapter 5: Organic Reactions

7. Oxidation and Reduction Reactions

7.8 Oxidation of Alkenes

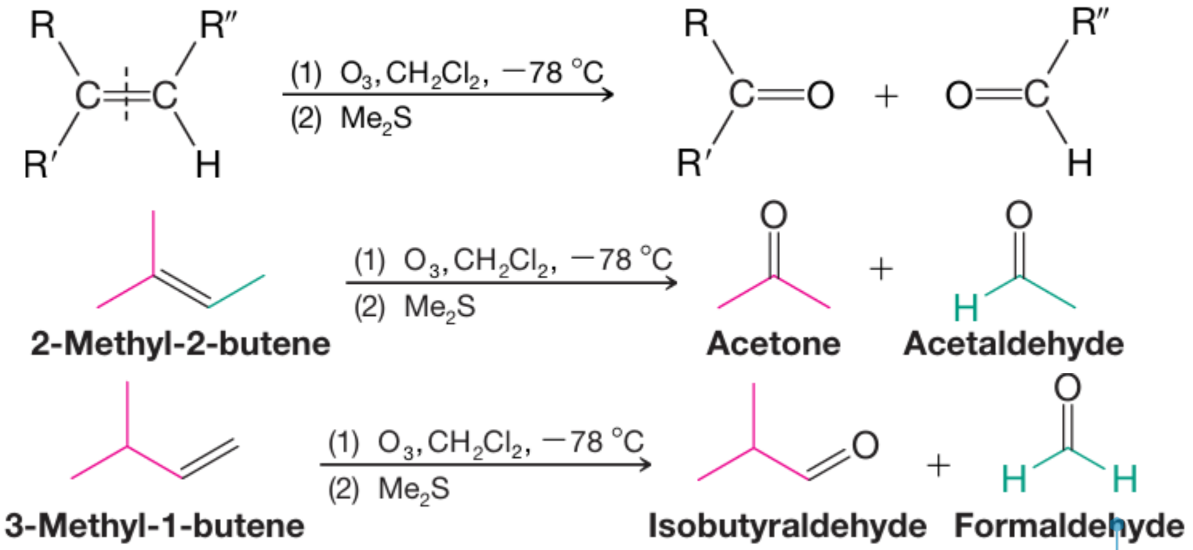
A) Oxidation of Alkenes: Syn 1,2-Dihydroxylation with Cold Basic Potassium Permanganate

Alkenes can be dihydroxylated using dilute solution of potassium permanganate under basic conditions with a cold to form a *cis*-diol (glycol).



B) Oxidative Cleavage OF Alkenes: Cleavage with Ozone

The most useful method for cleaving alkenes is to use ozone (O_3). Unsubstituted carbons are oxidized to formaldehyde, monosubstituted carbons are oxidized to aldehydes and disubstituted carbons are oxidized to ketones



7. Oxidation and Reduction Reactions

7.9 Oxidation of the Side Chain of Aromatic Compounds

- **Alkyl and unsaturated side chains of aromatic rings can be oxidized to the carboxylic acid using hot $KMnO_4$.**