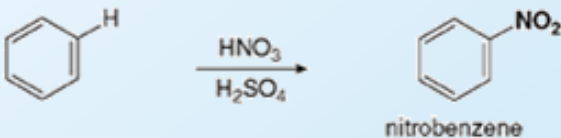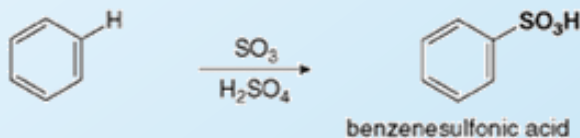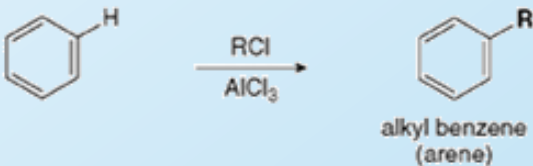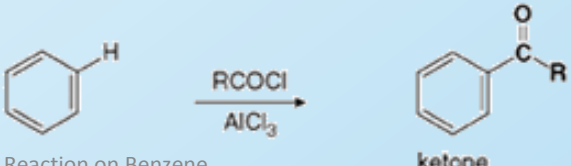# Electrophilic Reactions on Aromatic Compounds Monosubstitution

Dr. Sapna Gupta

Electrophilic Aromatic Substitution

- Arene (Ar-H) is the generic term for an aromatic hydrocarbon
  - The aryl group (Ar) is derived by removal of a hydrogen atom from an arene
- Aromatic compounds undergo electrophilic aromatic substitution (EAS)
  - The electrophile has a full or partial positive charge
  - The benzene ring is the nucleophile.

| Reaction	Electrophile
[1] Halogenation—Replacement of H by X (Cl or Br) $\xrightarrow[\text{FeX}_3]{X_2}$ aryl halide, $X = Cl$, $X = Br$	$E^+ = Cl^+$ or Br^+
[2] Nitration—Replacement of H by NO_2 $\xrightarrow[\text{H}_2\text{SO}_4]{\text{HNO}_3}$ nitrobenzene	$E^+ = \overset{+}{N}O_2$
[3] Sulfonation—Replacement of H by SO_3H $\xrightarrow[\text{H}_2\text{SO}_4]{\text{SO}_3}$ benzenesulfonic acid	$E^+ = \overset{+}{S}O_3H$
[4] Friedel–Crafts alkylation—Replacement of H by R $\xrightarrow[\text{AlCl}_3]{\text{RCl}}$ alkyl benzene (arene)	$E^+ = R^+$
[5] Friedel–Crafts acylation—Replacement of H by RCO $\xrightarrow[\text{AlCl}_3]{\text{RCOCl}}$ ketone	$E^+ = R\overset{+}{C}O$

General Mechanism

Regardless of the electrophile used, all electrophilic aromatic substitution reactions occur by the same two-step mechanism—addition of the electrophile E^+ to form a resonance-stabilized carbocation, followed by deprotonation with base, as shown below:

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Mechanism 18.1   General Mechanism—Electrophilic Aromatic Substitution

Step [1] Addition of the electrophile (E^+) to form a carbocation

resonance-stabilized carbocation
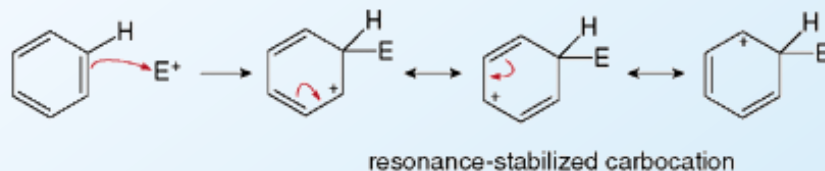
- Addition of the electrophile (E^+) forms a new C−E bond using two π electrons from the benzene ring, and generating a carbocation. This carbocation intermediate is not aromatic, but it is resonance stabilized—**three resonance structures can be drawn.**
- Step [1] is rate-determining because the aromaticity of the benzene ring is lost.

Step [2] Loss of a proton to re-form the aromatic ring
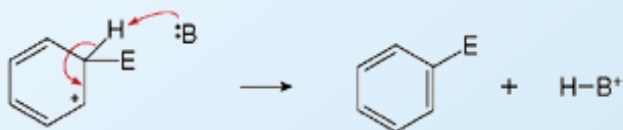
- In Step [2], a base (B:) removes the proton from the carbon bearing the electrophile, thus re-forming the aromatic ring. This step is fast because the aromaticity of the benzene ring is restored.
- Any of the three resonance structures of the carbocation intermediate can be used to draw the product. The choice of resonance structure affects how curved arrows are drawn, but not the identity of the product.

General Mechanism, contd....

- The energy diagram of this reaction shows that the first step is highly endothermic and has a large $\Delta G^{\ddagger}_{(1)}$
  - The first step requires the loss of aromaticity of the very stable benzene ring, which is highly unfavorable
  - The first step is rate-determining

- The second step is highly exothermic and has a small $\Delta G^{\ddagger}_{(2)}$
  - The ring regains its aromatic stabilization, which is a highly favorable process
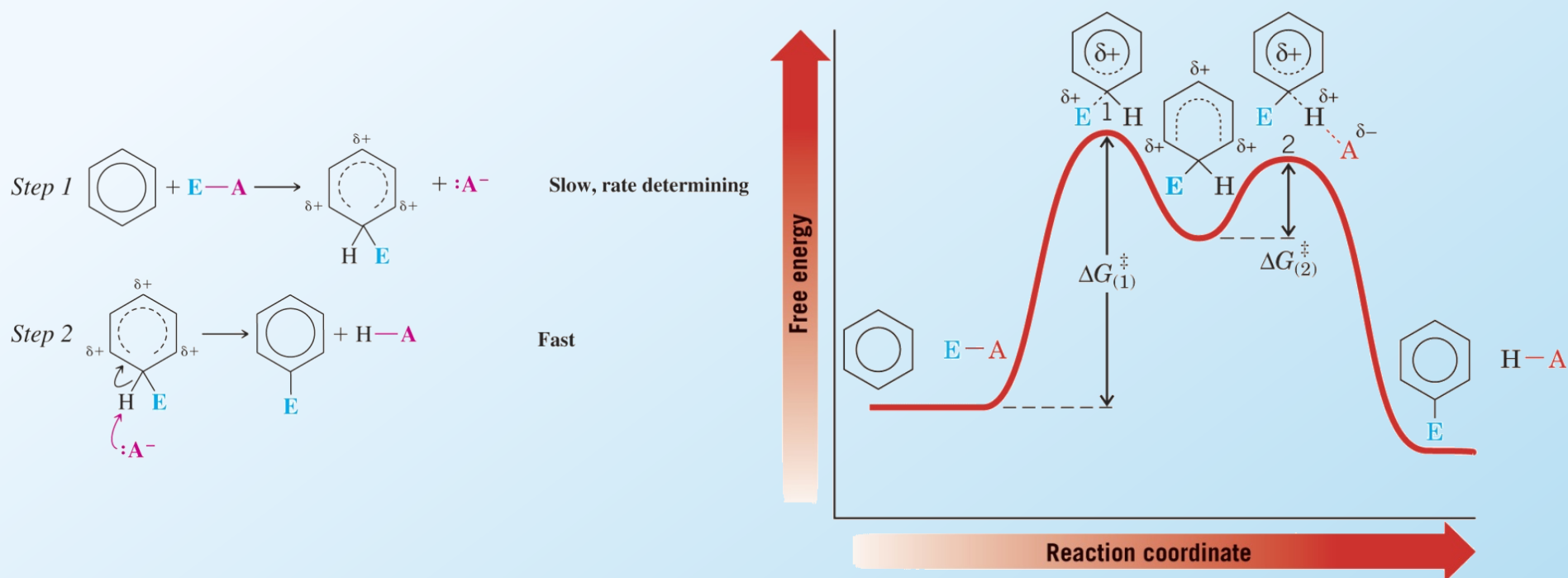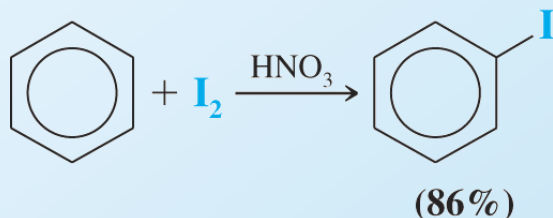
Halogenation of Benzene

- Halogenation of benzene requires the presence of a Lewis acid

Chlorobenzene (90%)

Bromobenzene (75%)
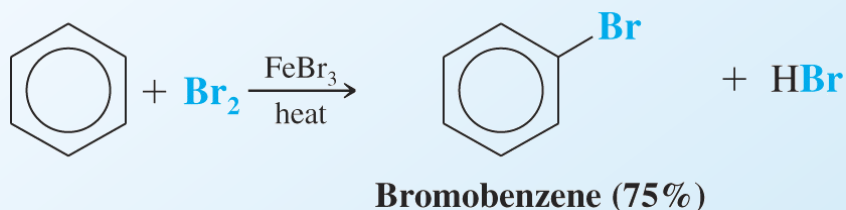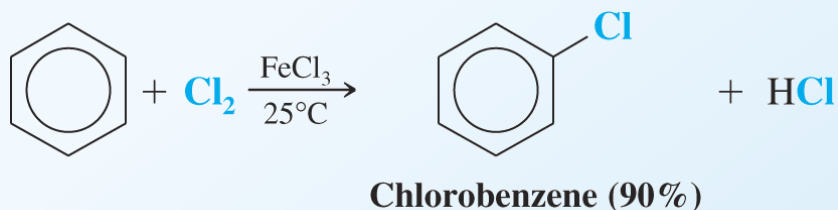
- Fluorination occurs so rapidly it is hard to stop at monofluorination of the ring
  - A special apparatus is used to perform this reaction
- Iodine is so unreactive that an alternative method must be used

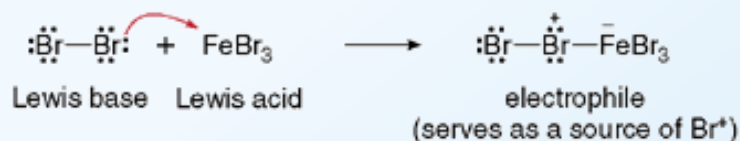

(86%)

Mechanism - Halogenation

- Below is the general mechanism of halogenation using bromine.

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Mechanism 18.2 **Bromination of Benzene**

Step [1] Generation of the electrophile

$:\ddot{B}r-\ddot{B}r: + FeBr_3 \longrightarrow :\ddot{B}r-\overset{+}{\ddot{B}r}-\overset{-}{FeBr_3}$

Lewis base   Lewis acid   electrophile
(serves as a source of Br⁺)

- Lewis acid–base reaction of Br_2 with $FeBr_3$ forms a species with a weakened and polarized $Br-Br$ bond. This adduct serves as a source of Br^+ in the next step.

Step [2] Addition of the electrophile to form a carbocation

resonance-stabilized carbocation
+ $FeBr_4^-$
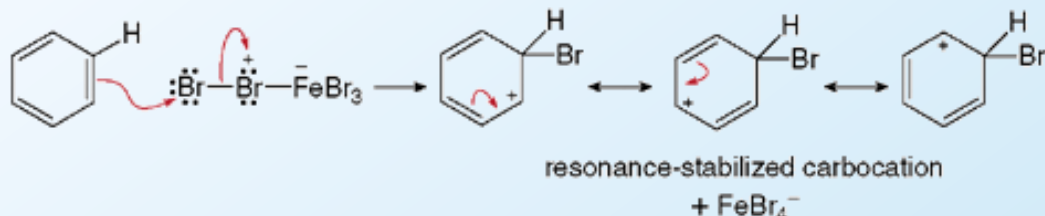
- Addition of the electrophile forms a new $C-Br$ bond and generates a carbocation. This carbocation intermediate is resonance stabilized—**three resonance structures can be drawn.**
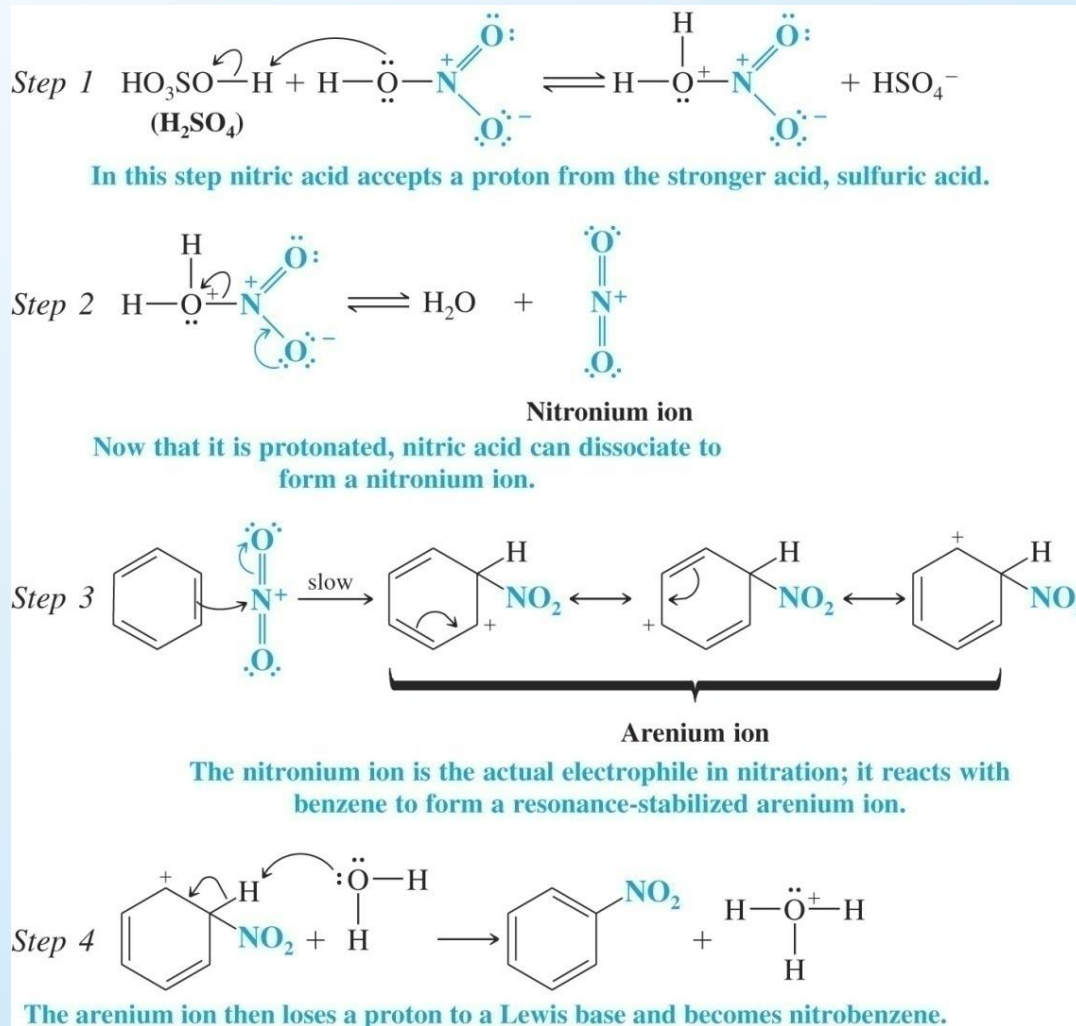- The $FeBr_4^-$ also formed in this reaction is the base used in Step [3].

Step [3] Loss of a proton to re-form the aromatic ring

+ HBr + $FeBr_3$

The catalyst is regenerated.
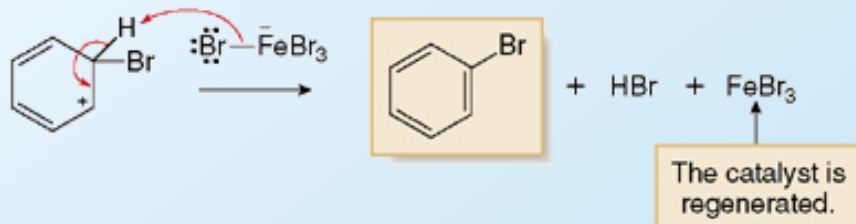
- $FeBr_4^-$ removes the proton from the carbon bearing the Br, thus re-forming the aromatic ring.
- $FeBr_3$, a catalyst, is also regenerated for another reaction cycle.

Nitration of Benzene

- Nitration of benzene occurs with a mixture of concentrated nitric and sulfuric acids
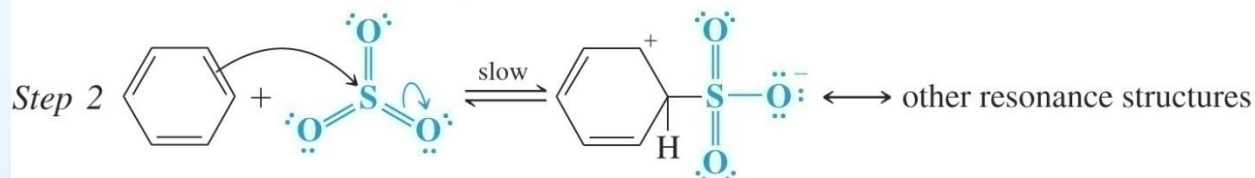 - The electrophile for the reaction is the nitronium ion (NO_2^+)

Step 1 $HO_3SO-H + H-\overset{..}{\underset{..}{O}}-\overset{+}{N}\overset{\overset{\overset{..}{O}:}{\parallel}}{\underset{\underset{..}{O}:^-}{}}$ $\rightleftharpoons$ $H-\overset{H}{\underset{..}{\overset{|}{O}}}{}^{+}-\overset{+}{N}\overset{\overset{\overset{..}{O}:}{\parallel}}{\underset{\underset{..}{O}:^-}{}} + HSO_4^-$
(H_2SO_4)

In this step nitric acid accepts a proton from the stronger acid, sulfuric acid.

Step 2 $H-\overset{H}{\underset{..}{\overset{|}{O}}}{}^{+}-\overset{+}{N}\overset{\overset{..}{O}:}{\underset{..}{O}:^-}$ $\rightleftharpoons$ $H_2O + \overset{..}{\underset{..}{O}}\equiv\overset{+}{N}\overset{+}{\underset{.\overset{..}{O}.}{}}$

Nitronium ion

Now that it is protonated, nitric acid can dissociate to form a nitronium ion.

Step 3 (benzene) $+$ $\overset{..}{\underset{.\overset{..}{O}.}{\overset{\parallel}{N}}}{}^{+}$ $\xrightarrow{\text{slow}}$ arenium ion resonance structures with NO_2

Arenium ion

The nitronium ion is the actual electrophile in nitration; it reacts with benzene to form a resonance-stabilized arenium ion.

Step 4 (arenium ion with NO_2 + H) $+ :\overset{..}{O}-H$ with H $\longrightarrow$ (nitrobenzene) NO_2 $+ H-\overset{..}{\underset{H}{O}}{}^{+}-H$

The arenium ion then loses a proton to a Lewis base and becomes nitrobenzene.
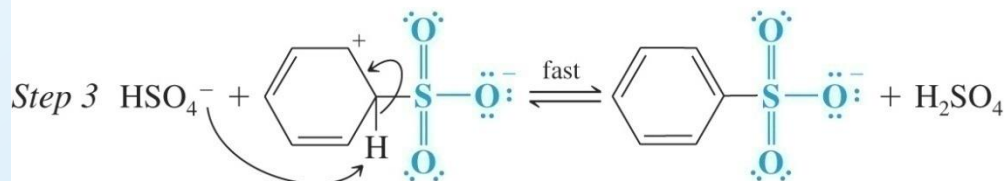
Sulfonation of Benzene

- Sulfonation occurs most rapidly using fuming sulfuric acid (concentrated sulfuric acid that contains SO_3)
    - The reaction also occurs in conc. sulfuric acid, which generates small quantities of SO_3, as shown in step 1 below
    - Sulfonation is an equilibrium reaction; all steps involved are equilibria
        - The sulfonation product is favored by use of concentrated or fuming sulfuric acid
        - Desulfonation can be accomplished using dilute sulfuric acid (*i.e.* with a high concentration of water), or by passing steam through the reaction and collecting the volatile desulfonated compound as it distils with the steam

Step 1 $2\,H_2SO_4 \rightleftharpoons SO_3 + H_3O^+ + HSO_4^-$
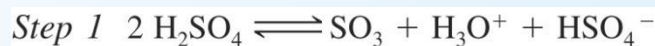
This equilibrium produces SO_3 in concentrated H_2SO_4.

Step 2 ... slow ... other resonance structures

SO_3 is the actual electrophile that reacts with benzene to form an arenium ion.

Step 3 HSO_4^- + ... fast ... + H_2SO_4

A proton is removed from the arenium ion to form the benzenesulfonate ion.
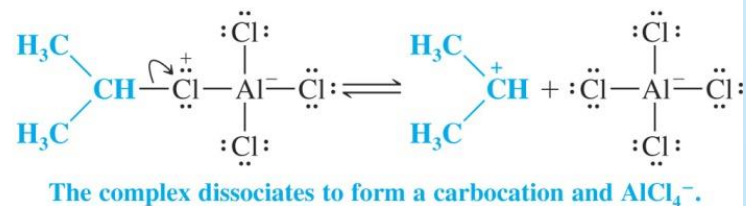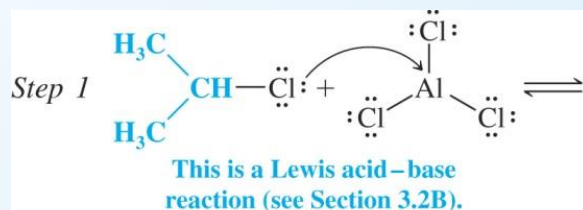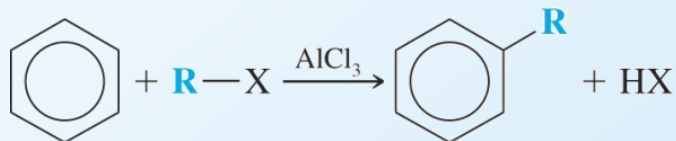
Step 4 ... fast ... + H_2O
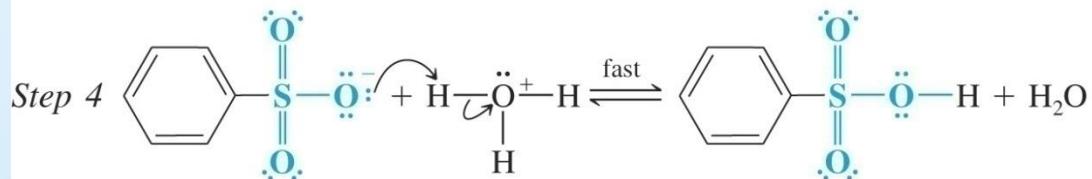
The benzenesulfonate ion accepts a proton to become benzenesulfonic acid.
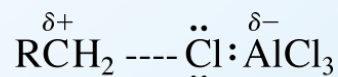
Friedal-Craft Alkylation

An aromatic ring can be alkylated by an alkyl halide in the presence of a Lewis acid

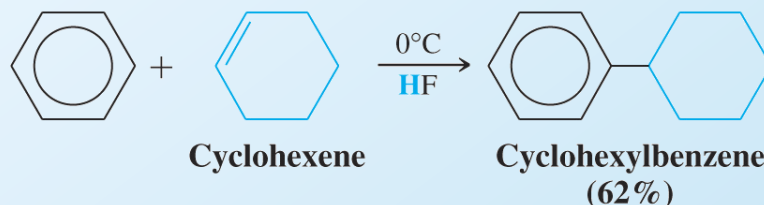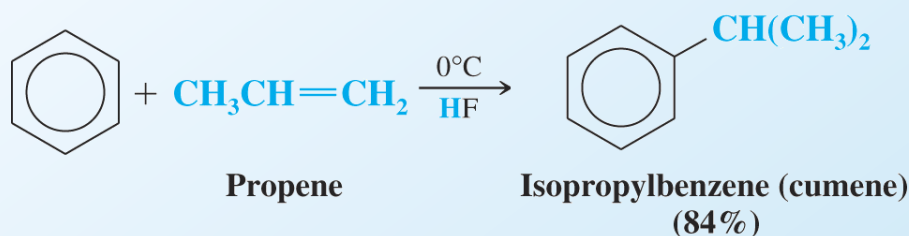(The Lewis acid serves to generate a carbocation electrophile)
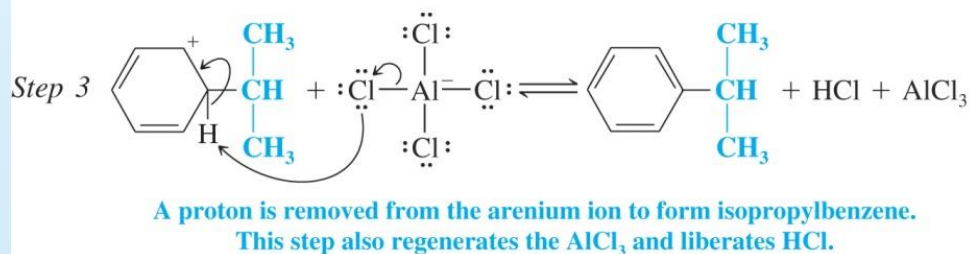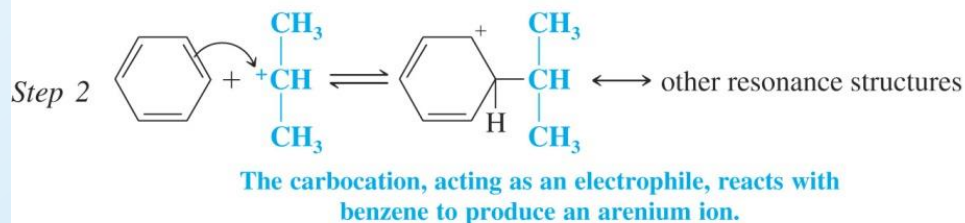
Friedal-Craft Alkylation, contd…

- Primary alkyl halides probably do not form discreet carbocations but the primary carbon in the complex develops considerable positive charge
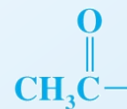
$$\overset{\delta+}{R CH_2} ---- \overset{\cdot\cdot}{\underset{\cdot\cdot}{Cl}} \colon \overset{\delta-}{AlCl_3}$$

- Any compound that can form a carbocation can be used to alkylate an aromatic ring

Propene   Isopropylbenzene (cumene)
(84%)

Cyclohexene   Cyclohexylbenzene
(62%)
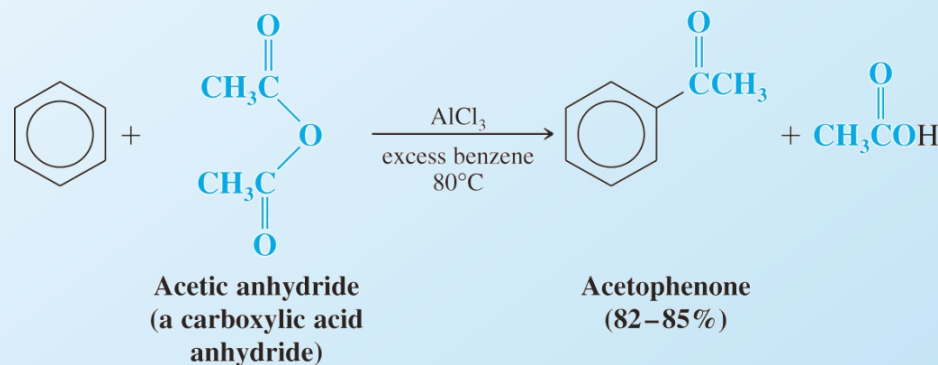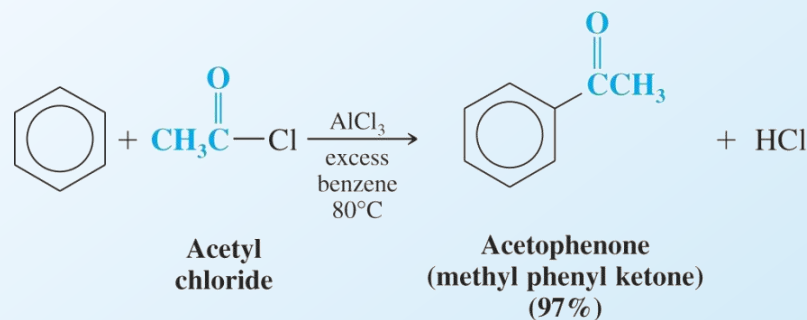
Friedal-Craft Acylation

- An acyl group has a carbonyl attached to some R group

- Friedel-Crafts acylation requires reaction of an acid chloride or acid anhydride with a Lewis acid such as aluminium chloride
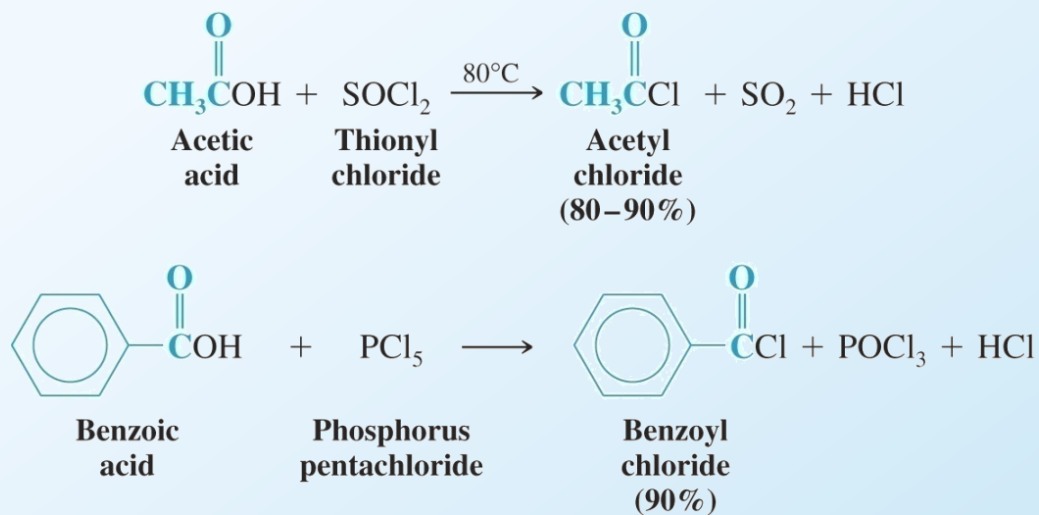

Acetyl group (ethanoyl group)

Benzoyl group

Acetyl chloride

Acetophenone (methyl phenyl ketone) (97%)

Acetic anhydride (a carboxylic acid anhydride)

Acetophenone (82−85%)
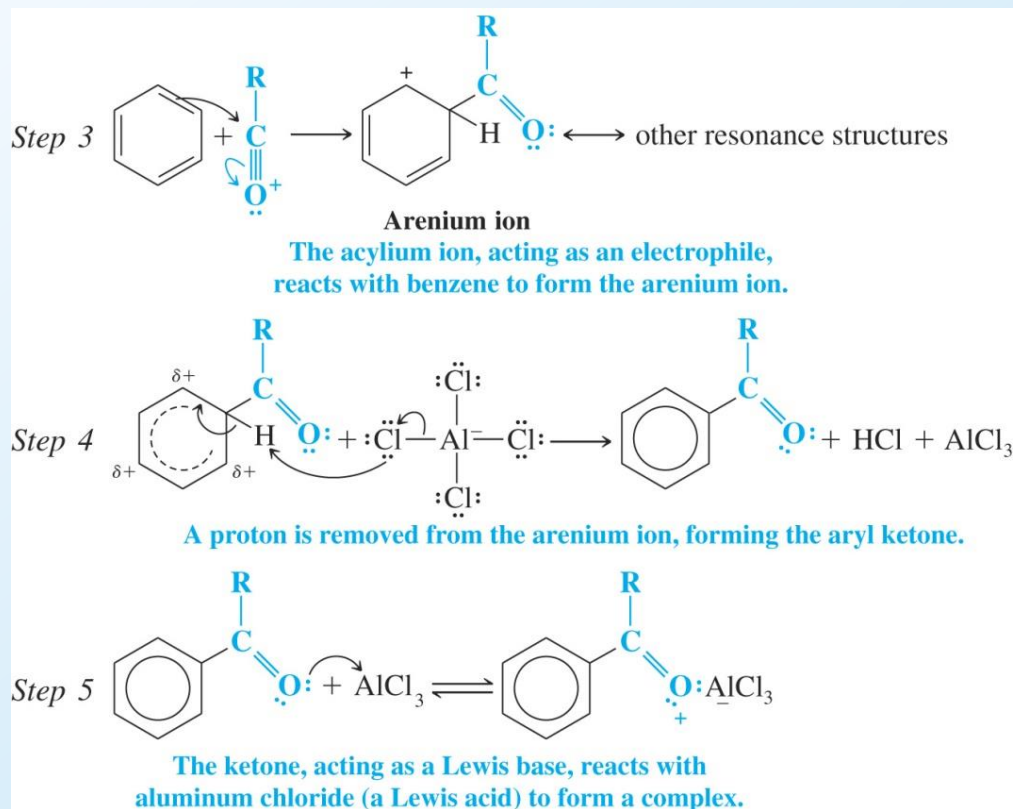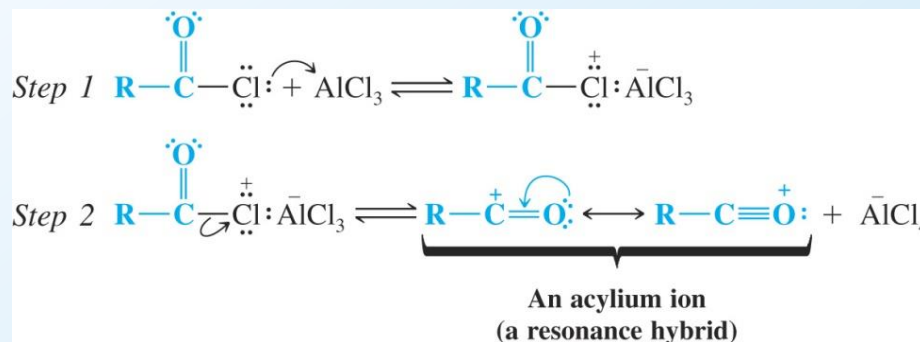
Formation of Acyl Chlorides

Acid chlorides are made from carboxylic acids

# Friedal-Craft Acylation Mechanism

The electrophile in Friedel-Crafts acylation is an acylium ion

*(The acylium ion is stabilized by resonance)*

Limitations of Friedal-Craft Reaction

1) <u>In FC alkylation, the alkyl carbocation intermediate may rearrange</u> to a more stable carbocation prior to alkylation

Butylbenzene
(32−36% of mixture)

***sec*-Butylbenzene**
(64−68% of mixture)
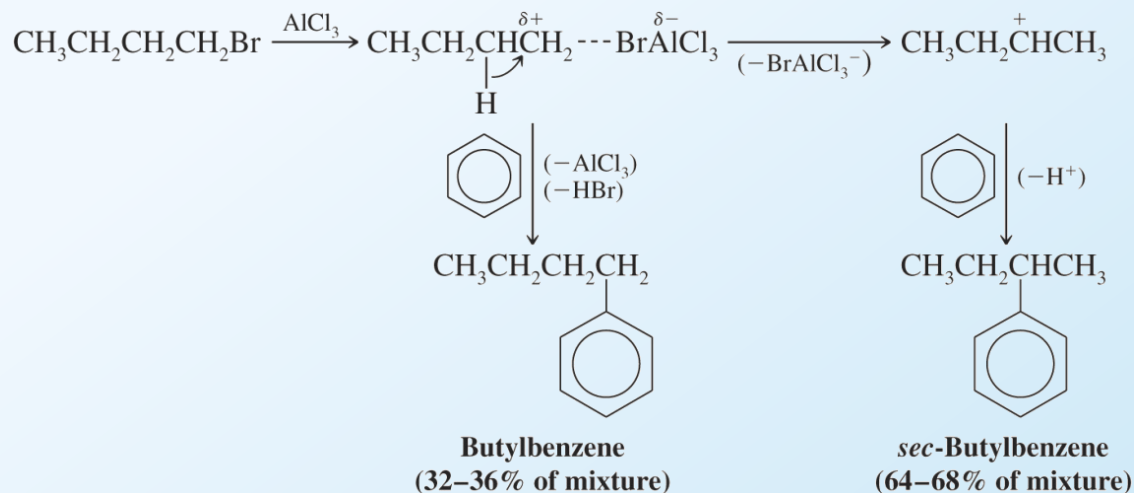
2) <u>Powerful electron-withdrawing groups make an aromatic ring much less reactive</u> toward Friedel-Crafts alkylation or acylation

➔ Amino groups also make the ring less reactive to Friedel-Crafts reaction because they become electron-withdrawing groups upon Lewis acid-base reaction with the Lewis acid catalyst


These usually give poor yields in
Friedel−Crafts reactions.
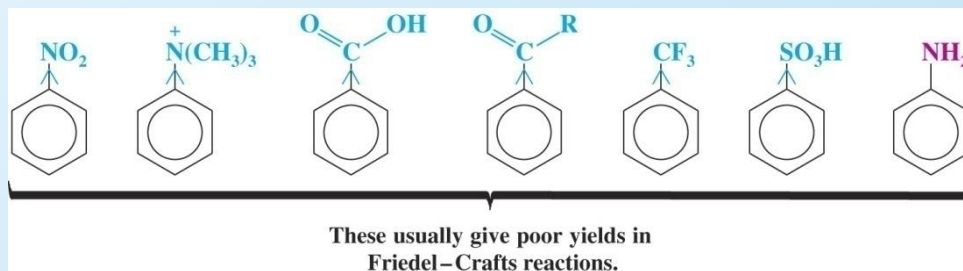
Limitations of Friedal-Craft Reaction

3) <u>Aryl and vinyl halides cannot be used</u> in Friedel-Crafts reactions because they do not form carbocations readily
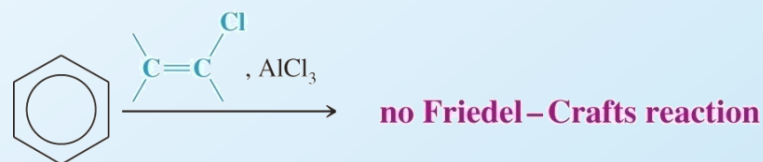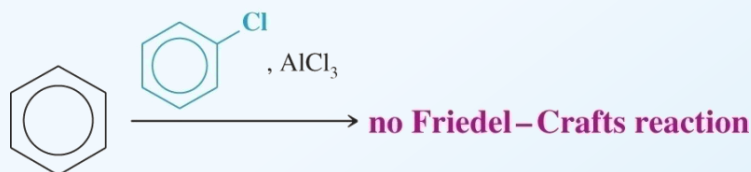
4) <u>Polyalkylation occurs</u> frequently with Friedel-Crafts alkylation because the first alkyl group introduced activates the ring toward further substitution

> ➔ Polyacylation does not occur because the acyl group deactivates the aromatic ring to further substitution
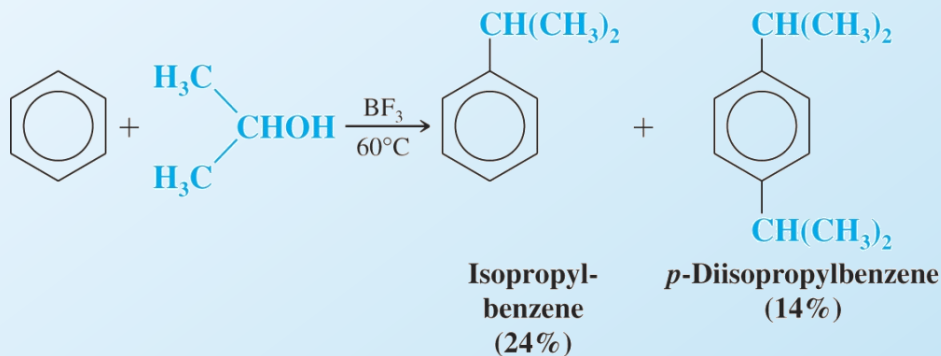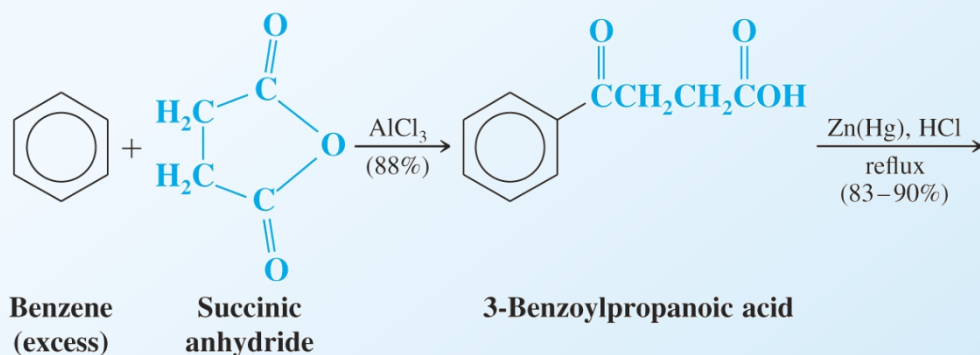
Synthetic Applications of FC-Acylation

Primary alkyl halides often yield rearranged products in Friedel-Crafts alkylation which is a major limitation of this reaction

1. The Clemmensen reduction— uses zinc and mercury in the presence of strong acid.

2. The Wolff-Kishner reduction—uses hydrazine (NH_2NH_2) and strong base (KOH).
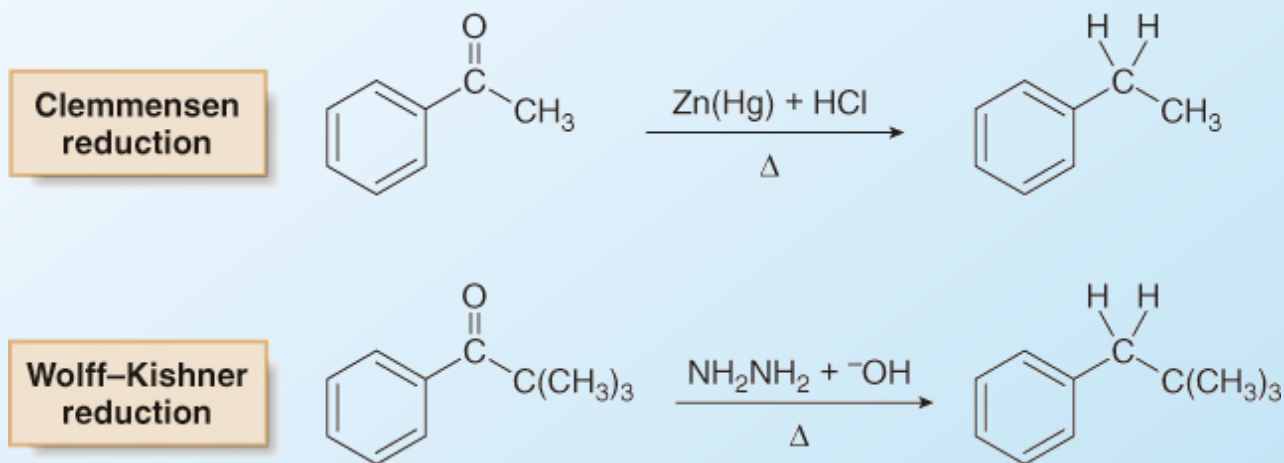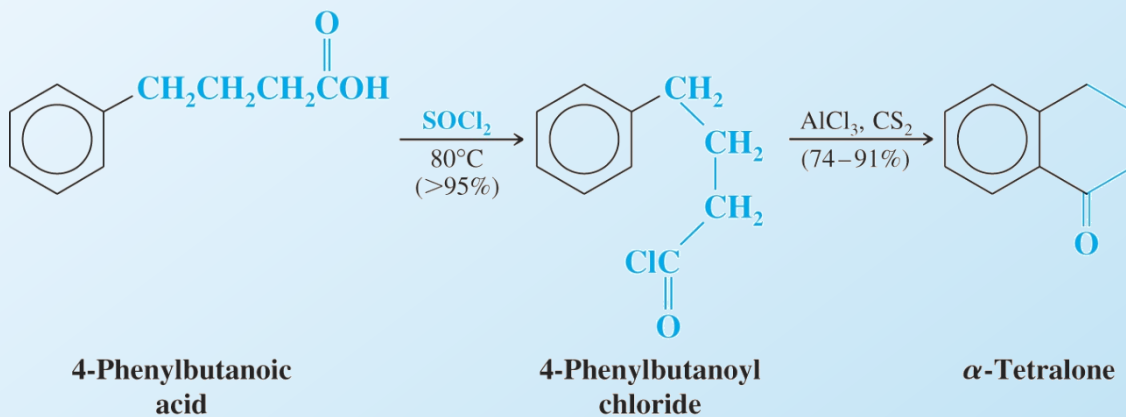
Examples

- This method can be used to add a ring to an aromatic ring starting with a cyclic anhydride (Note that the Clemmensen reagents do not reduce the carboxylic acid)

- Using Anhydrides

Benzene (excess) + **Succinic anhydride** → (AlCl$_3$, 88%) → **3-Benzoylpropanoic acid** → (Zn(Hg), HCl, reflux, 83–90%)

- Intramolecular Cyclization

4-Phenylbutanoic acid → (SOCl$_2$, 80°C, >95%) → **4-Phenylbutanoyl chloride** → (AlCl$_3$, CS$_2$, 74–91%) → **α-Tetralone**

Key Concepts

- Electrophilic substitution
- Nitration
- Sulfonation
- Friedal Craft Alkylation
- Friedal Craft Acylation
- Drawbacks of FC alkylation
- Synthetic applications