Chapter Number	Week
15	7, 8
16	9, 10, 11
18	12, 13
20	14

Chapter 15
Reactions of Aromatic Compounds

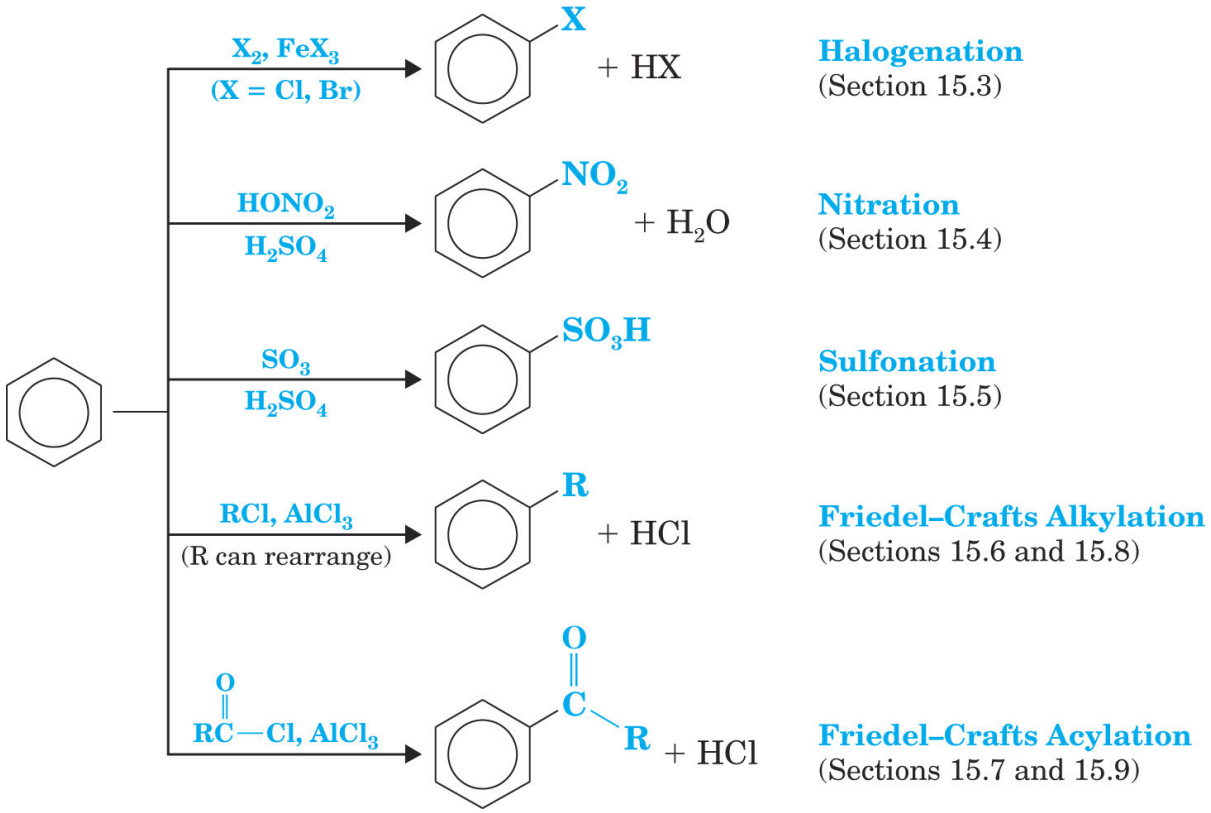
♦ Electrophilic Aromatic Substitution

➔ **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**



♦ A General Mechanism for Electrophilic Aromatic Substitution: Arenium Ion Intermediates

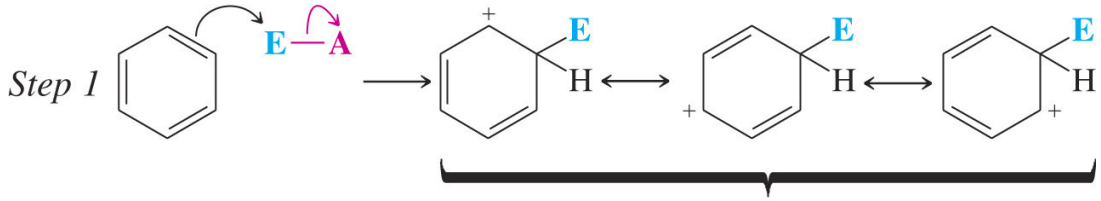
➔ **Benzene reacts with an electrophile using two of its π electrons**

- **This first step is like an addition to an ordinary double bond**

➔ **Unlike an addition reaction, the benzene ring reacts further so that it may regenerate the very stable aromatic system**

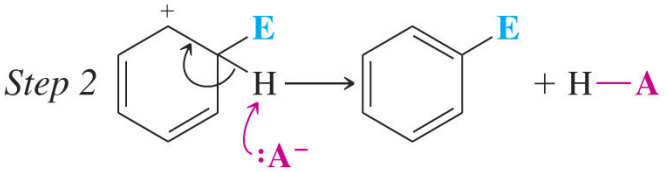
➔ **In step 1 of the mechanism, the electrophile reacts with two π electrons from the aromatic ring to form an arenium ion**

- **The arenium ion is stabilized by resonance which delocalizes the charge**



Arenium ion
(a delocalized cyclohexadienyl cation)

➔ **In step 2, a proton is removed and the aromatic system is regenerated**

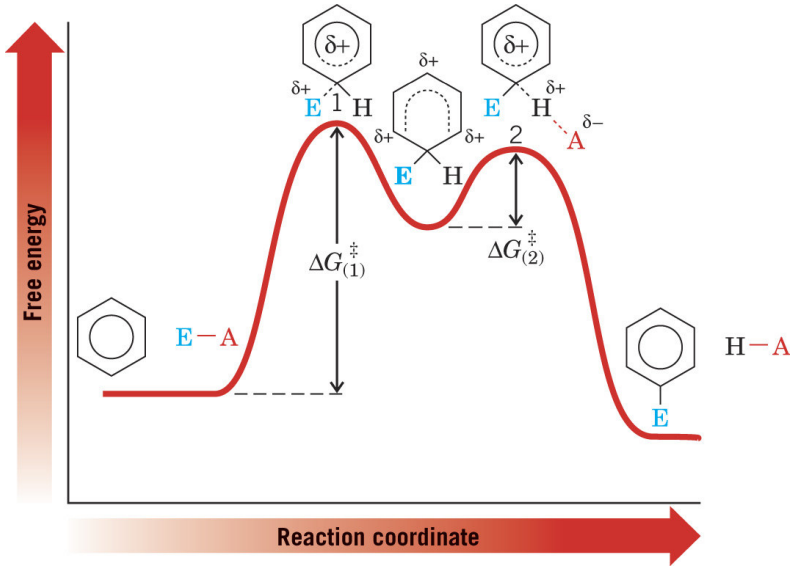


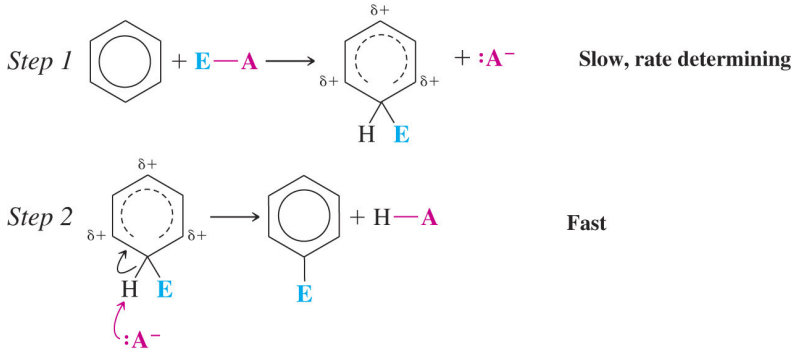
➔ **The energy diagram of this reaction shows that the first step is highly endothermic and has a large $\Delta G^{\ddagger}_{(1)}$**

- **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 $\Delta G^{\ddagger}_{(2)}$**

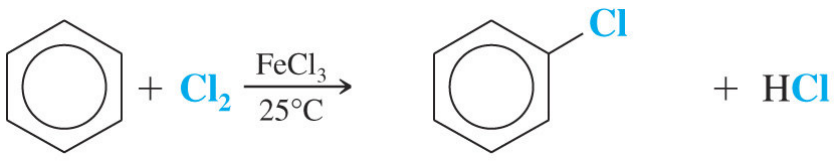
- **The ring regains its aromatic stabilization, which is a highly favorable process**



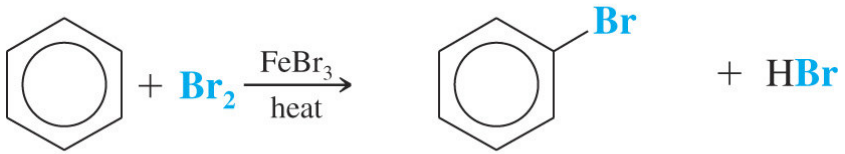


♦ Halogenation of Benzene

➔ **Halogenation of benzene requires the presence of a Lewis acid**



Chlorobenzene (90%)

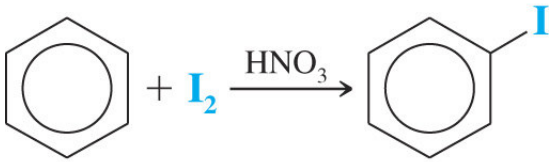


Bromobenzene (75%)

➔ **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%)

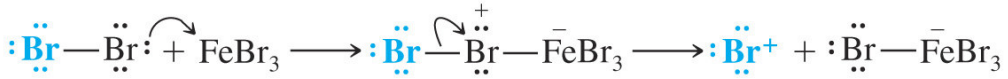
➔ **In the step 1 of the mechanism, bromine reacts with ferric bromide to generate an electrophilic bromine species**

➔ **In step 2, the highly electrophilic bromine reacts with π electrons of the benzene ring, forming an arenium ion**

➔ **In step 3, a proton is removed from the arenium ion and aromaticity is regenerated**

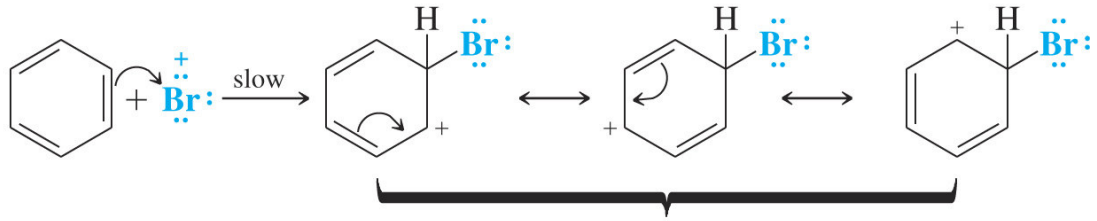
- **The $FeBr_3$ catalyst is regenerated**

Step 1



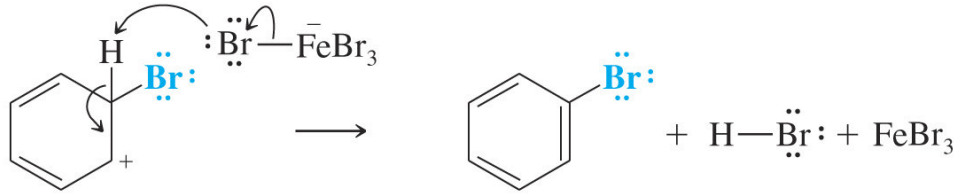
Bromine combines with $FeBr_3$ to form a complex that dissociates to form a positive bromine ion and $FeBr_4^-$.

Step 2



The positive bromine ion attacks benzene to form an arenium ion.

Step 3



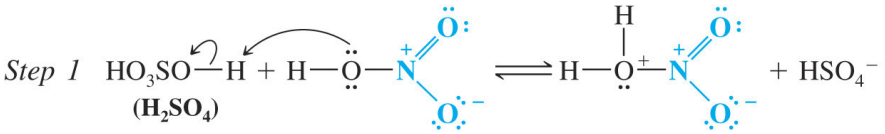
A proton is removed from the arenium ion to become bromobenzene.

♦ Nitration of Benzene

➔Nitration of benzene occurs with a mixture of concentrated nitric and sulfuric acids

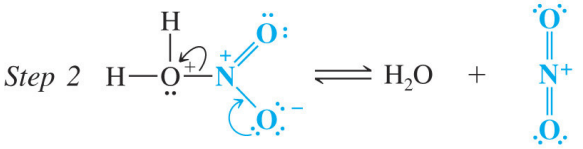
- **The electrophile for the reaction is the nitronium ion (NO_2^+)**

Step 1



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

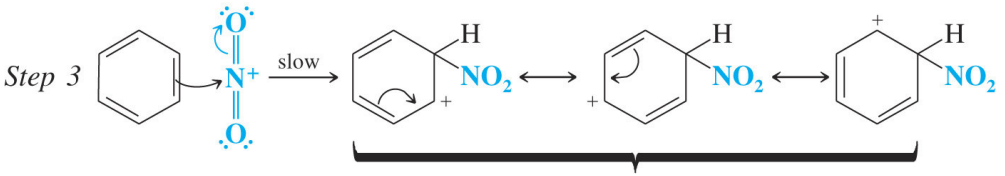
Step 2



Nitronium ion

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

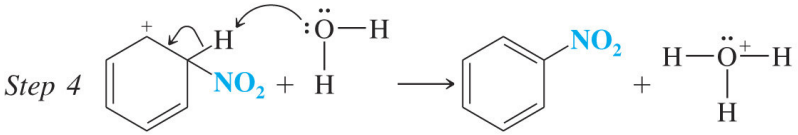
Step 3



Arenium ion

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

Step 4



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

♦ Sulfonation of Benzene

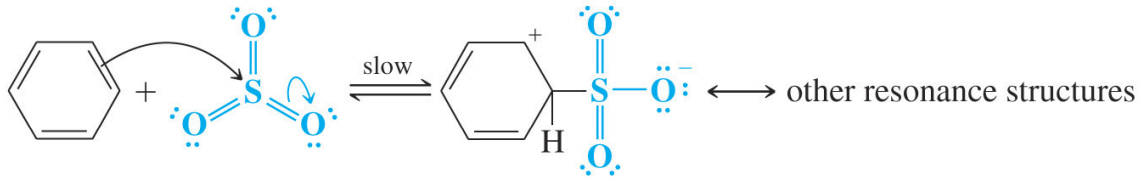
➔Sulfonation occurs most rapidly using fuming sulfuric acid (concentrated sulfuric acid that contains SO_3)

- **The reaction also occurs in conc. sulfuric acid, which generates small quantities of SO_3, as shown in step 1 below**

Step 1 $2\ H_2SO_4 \rightleftharpoons SO_3 + H_3O^+ + HSO_4^-$

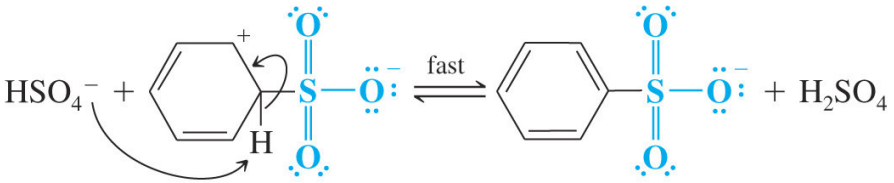
This equilibrium produces SO_3 in concentrated H_2SO_4.

Step 2



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

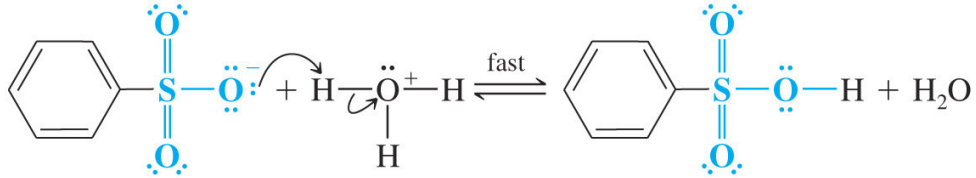
Step 3



$+ H_2SO_4$

A proton is removed from the arenium ion to form the benzenesulfonate ion.

Step 4

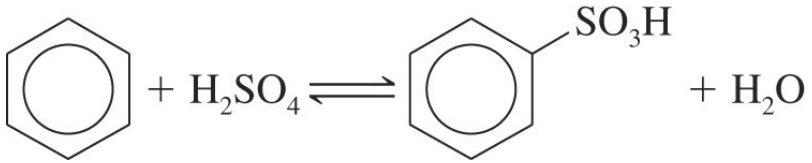


$+ H_2O$

The benzenesulfonate ion accepts a proton to become benzenesulfonic acid.

➔Sulfonation is an equilibrium reaction; all steps involved are equilibria

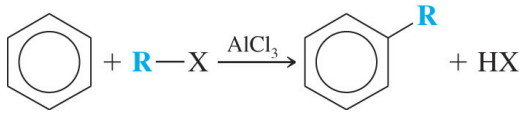
- **The sulfonation product is favored by use of concentrated or fuming sulfuric acid**
- **Desulfonation can be accomplished using dilute sulfuric acid (*i.e.* with a high concentration of water), or by passing steam through the reaction and collecting the volatile desulfonated compound as it distils with the steam**

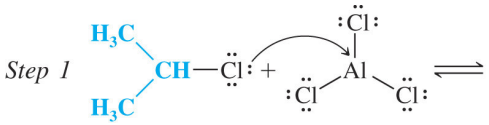


♦ Friedel-Crafts Alkylation

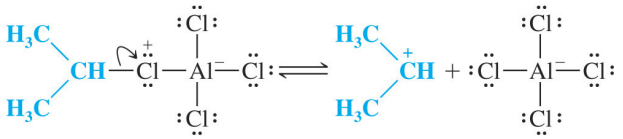
➔ An aromatic ring can be alkylated by an alkyl halide in the presence of a Lewis acid

- The Lewis acid serves to generate a carbocation electrophile

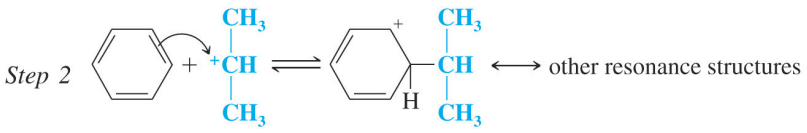




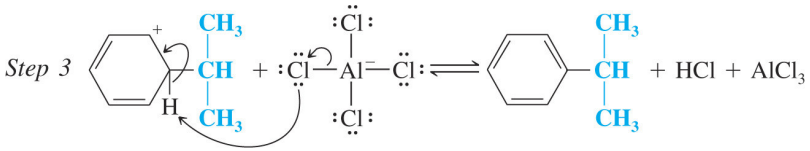
This is a Lewis acid–base reaction (see Section 3.2B).



The complex dissociates to form a carbocation and $AlCl_4^-$.



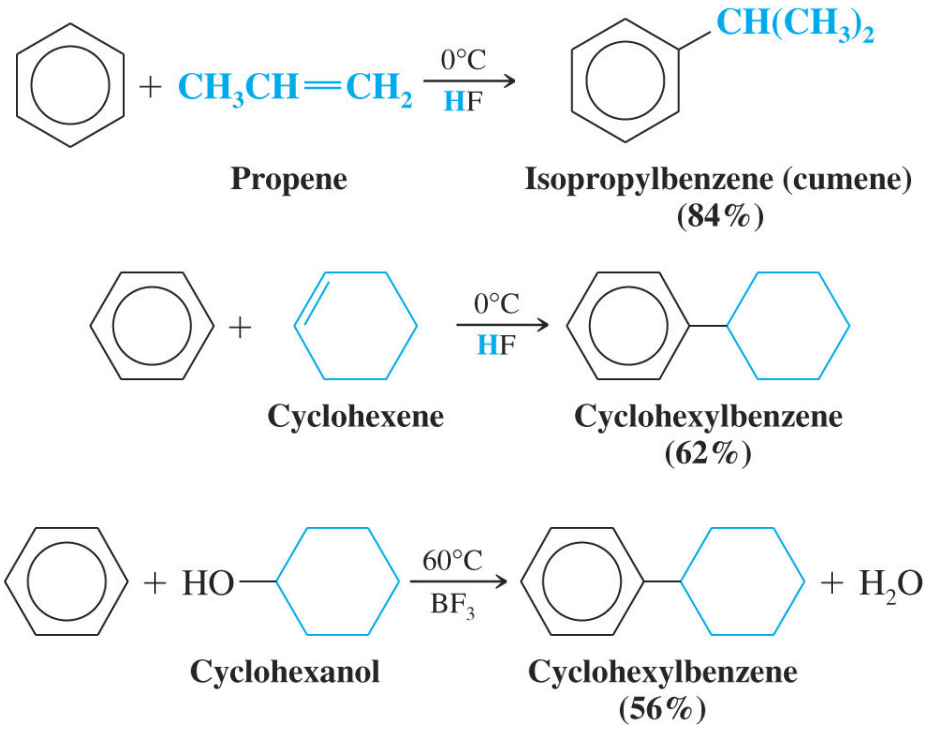
The carbocation, acting as an electrophile, reacts with benzene to produce an arenium ion.



A proton is removed from the arenium ion to form isopropylbenzene. This step also regenerates the $AlCl_3$ and liberates HCl.

➔ **Primary alkyl halides probably do not form discreet carbocations but the primary carbon in the complex develops considerable positive charge**

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



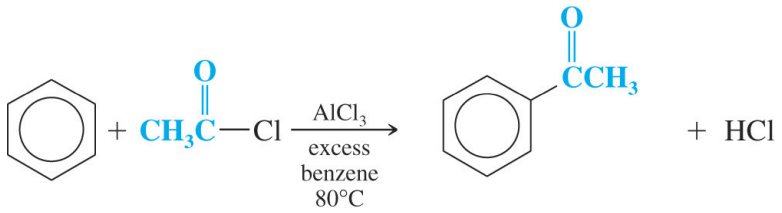
♦ Friedel-Crafts Acylation

➔ **An acyl group has a carbonyl attached to some R group**

Acetyl group (ethanoyl group)

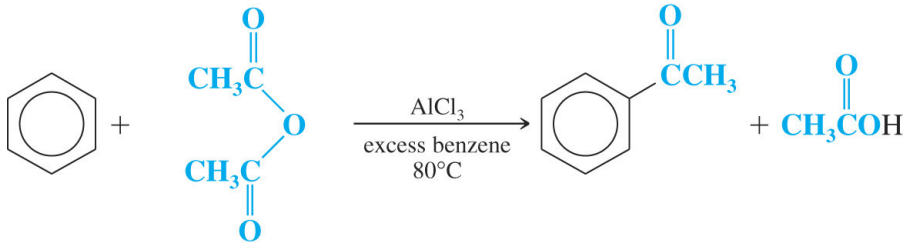
Benzoyl group

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



Acetyl chloride

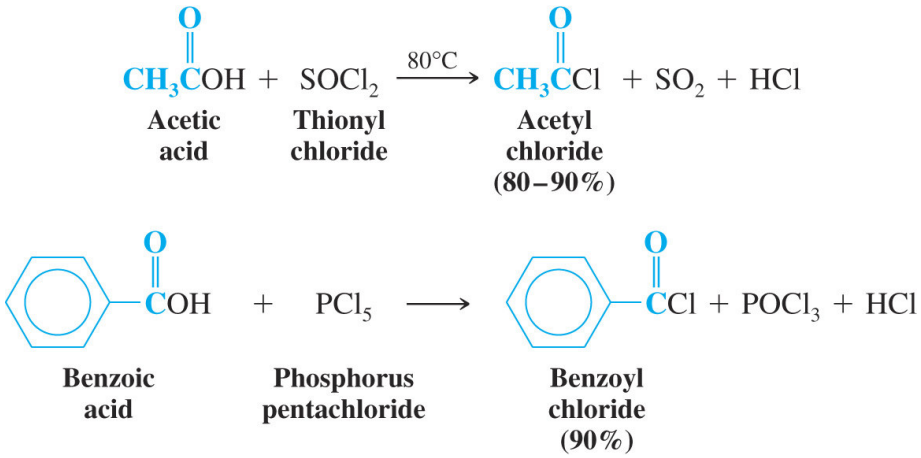
Acetophenone (methyl phenyl ketone) (97%)



Acetic anhydride (a carboxylic acid anhydride)

Acetophenone (82–85%)

➔ **Acid chlorides are made from carboxylic acids**



December 2007

Sat	Sun	Mon	Tue	Wed	Thr	Fri
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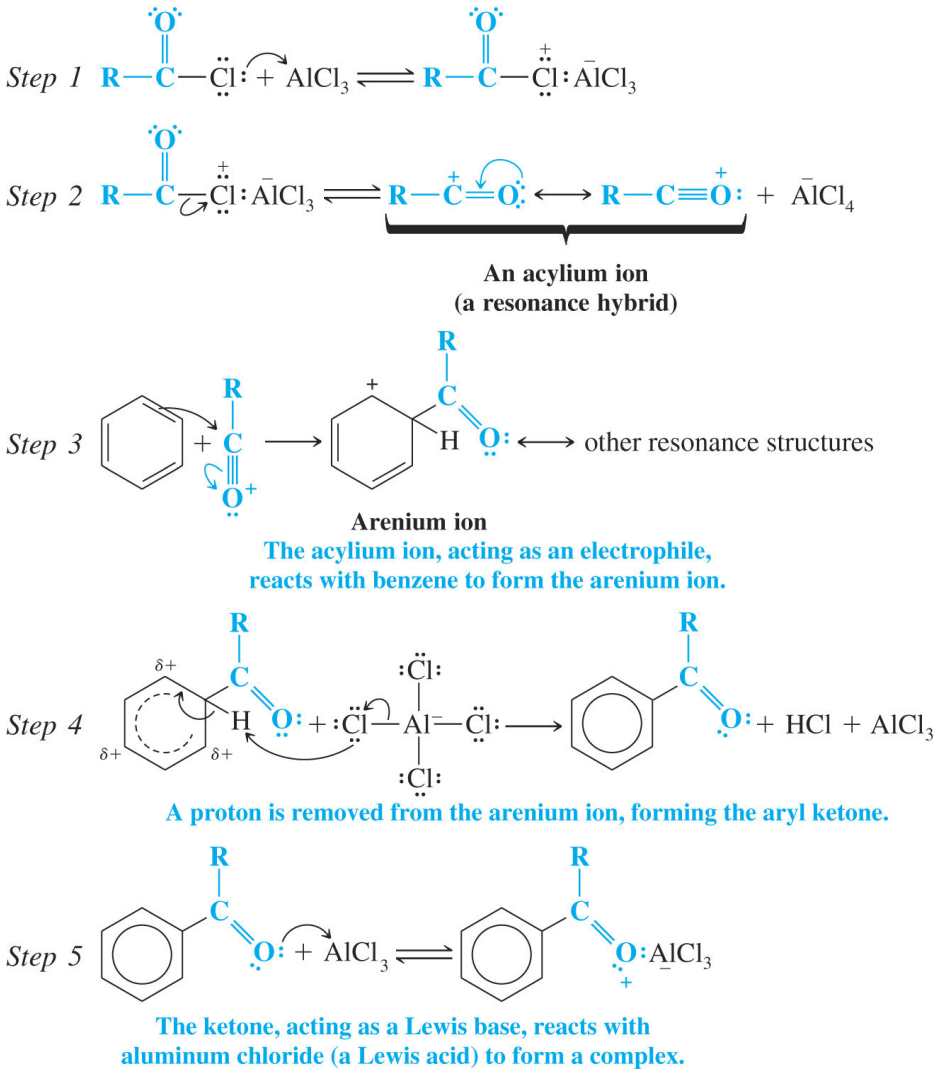
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28

➔The electrophile in Friedel-Crafts acylation is an acylium ion

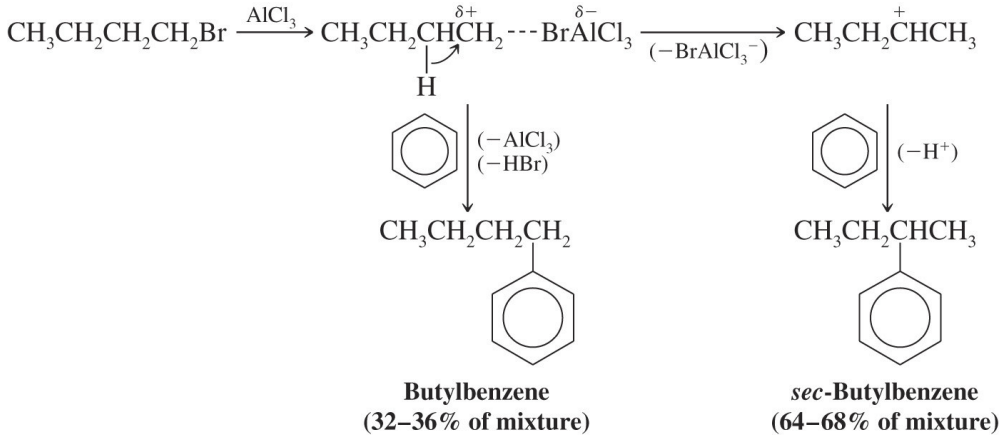
- **The acylium ion is stabilized by resonance**



♦ Limitations of Friedel-Crafts Reactions

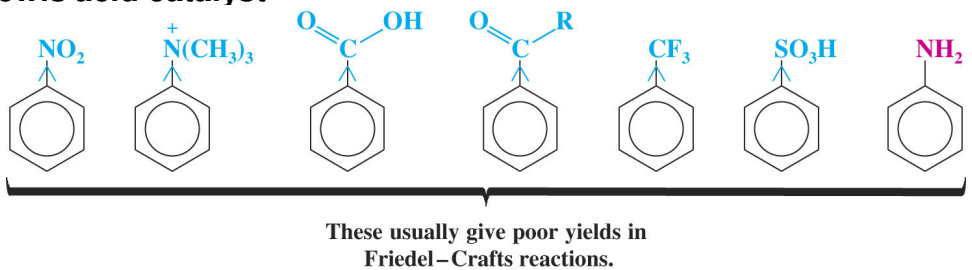
➔In Friedel-Crafts alkylation, the alkyl carbocation intermediate may rearrange to a more stable carbocation prior to alkylation

- The reaction of n-butyl bromide leads to a mixture of products derived from primary and secondary carbocations

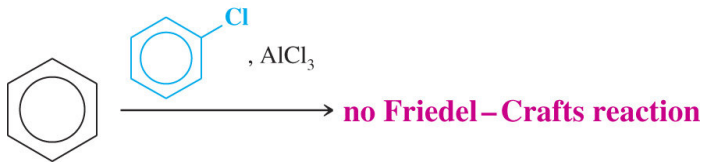


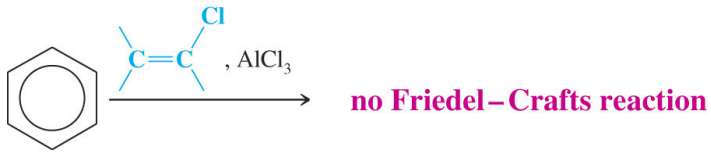
➔Powerful electron-withdrawing groups make an aromatic ring much less reactive toward Friedel-Crafts alkylation or acylation

- 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



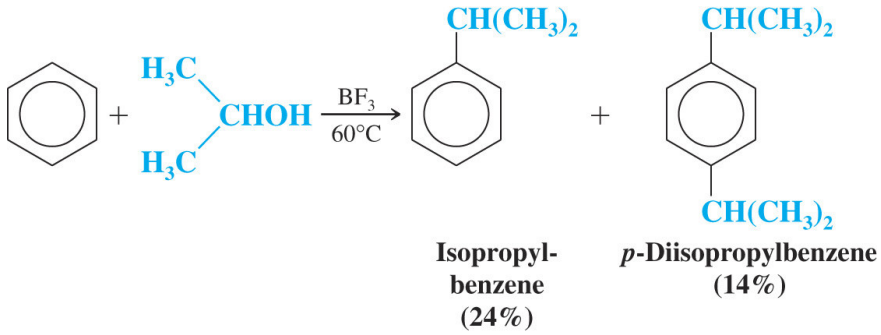
➔ **Aryl and vinyl halides cannot be used in Friedel-Crafts reactions because they do not form carbocations readily**





➔ **Polyalkylation occurs 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**

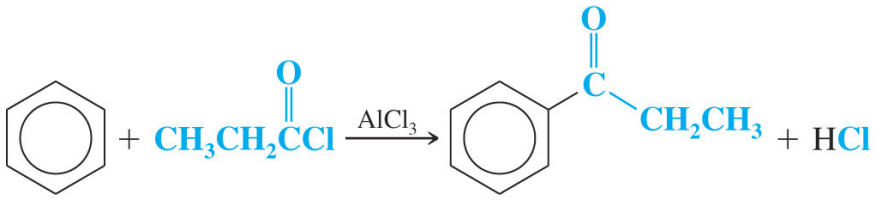


♦ Synthetic Applications of Friedel-Crafts Acylations: The Clemmensen Reduction

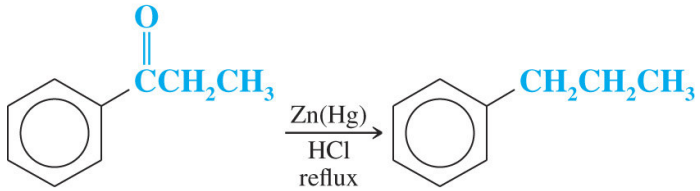
➔ **Primary alkyl halides often yield rearranged products in Friedel-Crafts alkylation which is a major limitation of this reaction**

➔ **Unbranched alkylbenzenes can be obtained in good yield by acylation followed by Clemmensen reduction**

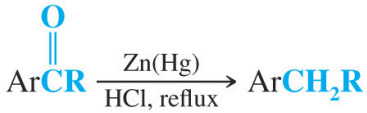
- **Clemmensen reduction reduces phenyl ketones to the methylene (CH_2) group**



Propanoyl chloride — **Ethyl phenyl ketone (90%)**

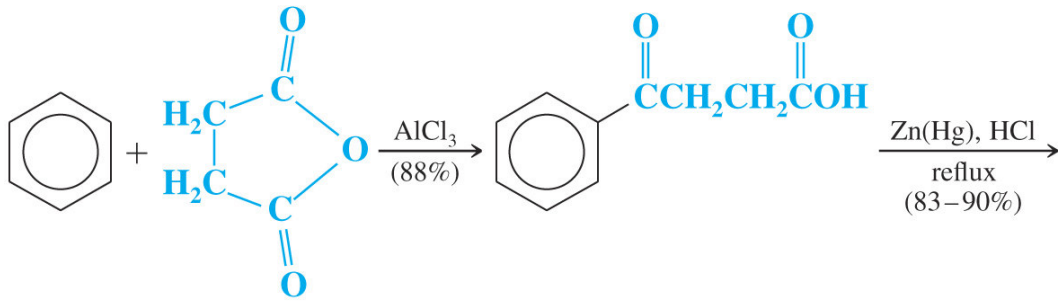


Ethyl phenyl ketone — **Propylbenzene (80%)**

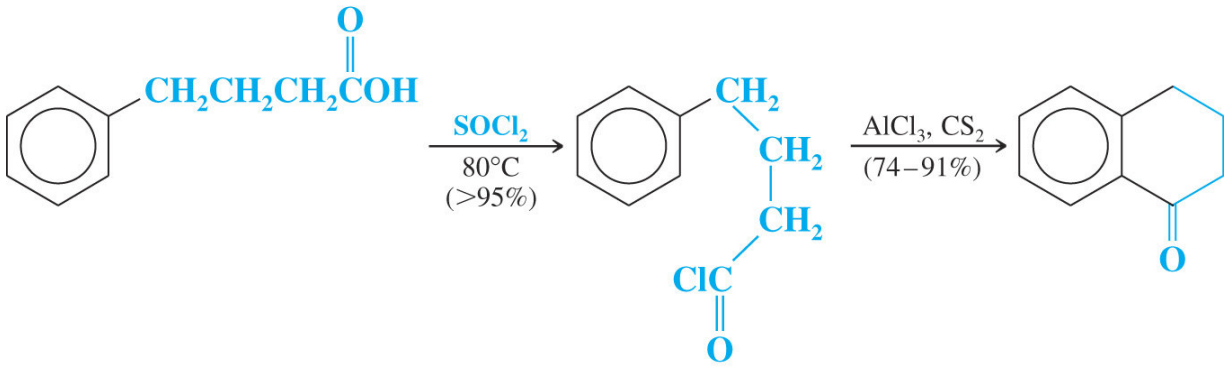


➔ **This method can be used to add a ring to an aromatic ring starting with a cyclic anhydride**

- **Note that the Clemmensen reagents do not reduce the carboxylic acid**



Benzene (excess) **Succinic anhydride** **3-Benzoylpropanoic acid**



4-Phenylbutanoic acid **4-Phenylbutanoyl chloride** **α-Tetralone**

♦ 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

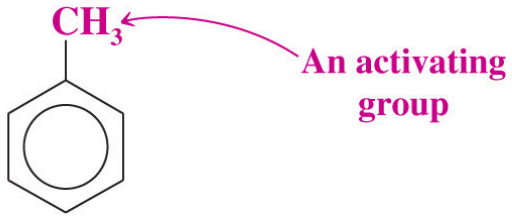
● Activating Groups: Ortho-Para Directors

➔ All activating groups are also ortho-para directors

- The halides are also ortho-para directors but are mildly deactivating

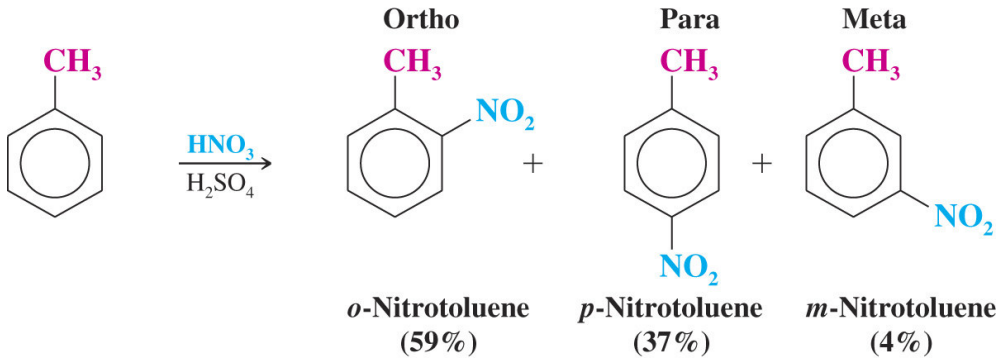
➔ The methyl group of toluene is an ortho-para director

- Toluene reacts more readily than benzene, *e.g.* at a lower temperatures than benzene



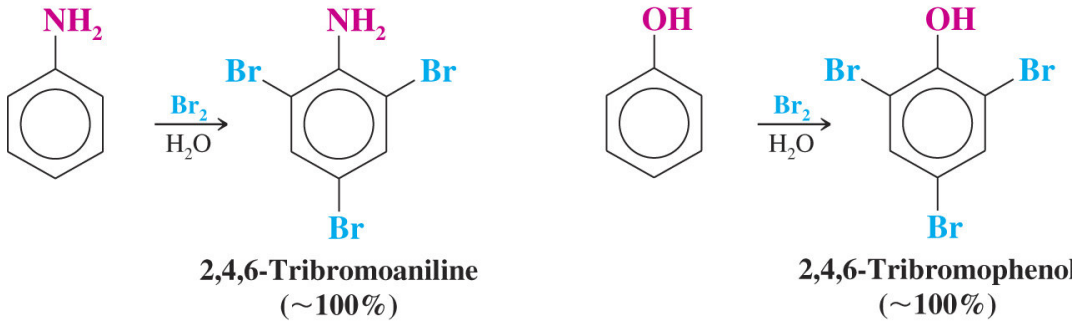
More reactive than benzene
toward electrophilic substitution

➔ **The methyl group of toluene is an ortho-para director**



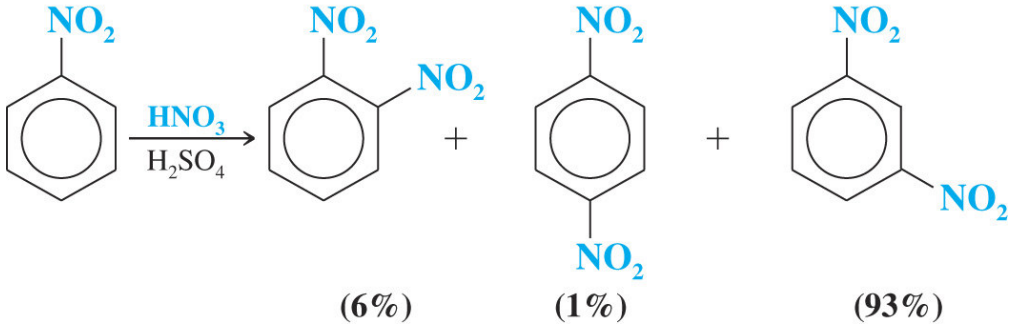
➔ **Amino and hydroxyl groups are also activating and ortho-para directors**

- **These groups are so activating that catalysts are often not necessary**



➔ **Alkyl groups and heteroatoms with one or more unshared electron pairs directly bonded to the aromatic ring will be ortho-para directors.**

- **Deactivating Groups: Meta Directors**
  - ➔ **Strong electron-withdrawing groups such as nitro, carboxyl, and sulfonate are deactivators and meta directors**



- **Halo Substitutents: Deactivating Ortho-Para Directors**
  - ➔ **Chloro and bromo groups are weakly deactivating but are also ortho, para directors**
    - **In electrophilic substitution of chlorobenzene, the ortho and para products are major:**

Reaction	Ortho Product (%)	Para Product (%)	Total Ortho and Para (%)	Meta Product (%)
Chlorination	39	55	94	6
Bromination	11	87	98	2
Nitration	30	70	100	
Sulfonation		100	100	

♦ Classification of Substitutents

Ortho–Para Directors	Meta Directors
Strongly Activating $-\ddot{N}H_2$, $-\ddot{N}HR$, $-\ddot{N}R_2$ $-\ddot{O}H$, $-\ddot{O}:^-$	**Moderately Deactivating** $-C\equiv N$ $-SO_3H$ $-CO_2H$, $-CO_2R$ $-CHO$, $-COR$
Moderately Activating $-\ddot{N}HCOCH_3$, $-\ddot{N}HCOR$ $-\ddot{O}CH_3$, $-\ddot{O}R$	**Strongly Deactivating** $-NO_2$ $-NR_3^+$ $-CF_3$, $-CCl_3$
Weakly Activating $-CH_3$, $-C_2H_5$, $-R$ $-C_6H_5$	
Weakly Deactivating $-\ddot{F}:$, $-\ddot{C}l:$, $-\ddot{B}r:$, $-\ddot{I}:$	

♦ Theory of Substituent Effects on Electrophilic Substitution

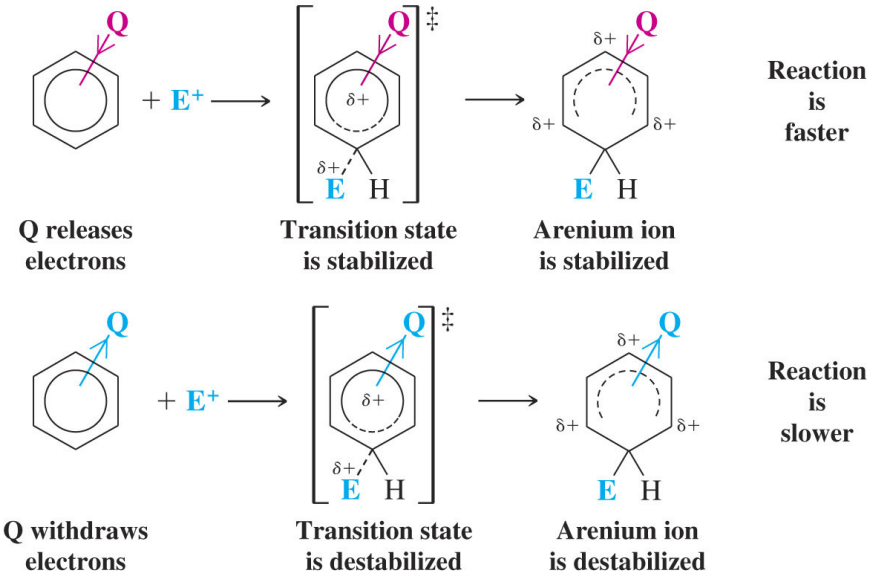
● Reactivity: The Effect of Electron-Releasing and Electron-Withdrawing Groups

➔ Electron-releasing groups activate the ring toward further reaction

- Electron-releasing groups stabilize the transition state of the first step of substitution and lead to lower $\Delta G^{\ddagger}$ and faster rates of reaction

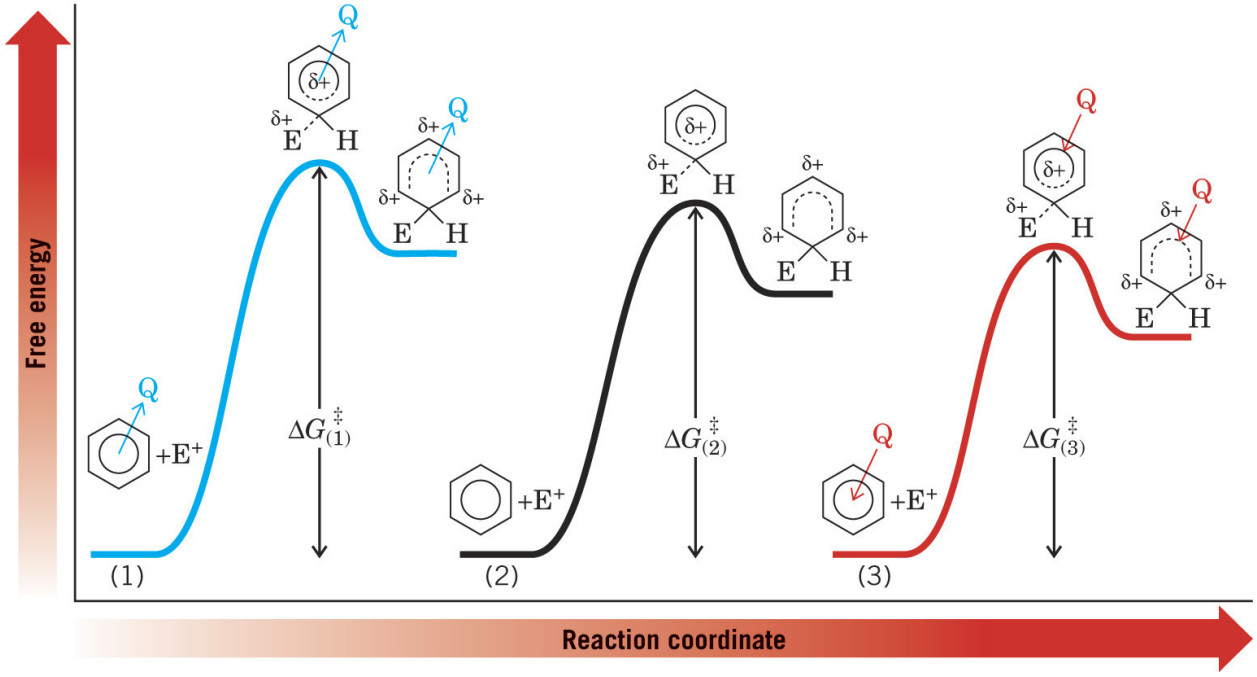
➔ Electron-withdrawing groups deactivate the ring toward further reaction

- Electron-withdrawing groups destabilize the transition state and lead to higher $\Delta G^{\ddagger}$ and slower rates of reaction

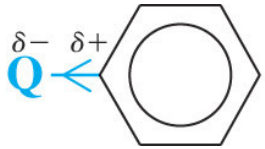


➔ **The following free-energy profiles compare the stability of the first transition state in electrophilic substitution when various types of substitutents are already on the ring**

- **These substitutents are electron-withdrawing, neutral (e.g., H), and electron-donating**

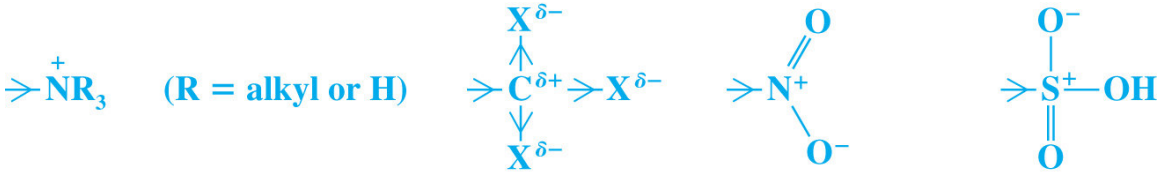


- **Inductive and Resonance Effects: Theory of Orientation**
  - ➔ **The inductive effect of some substituent Q arises from the interaction of the polarized bond to Q with the developing positive charge in the ring as an electrophile reacts with it**
    - **If Q is an electron-withdrawing group then attack on the ring is slowed because this leads to additional positive charge on the ring**



(e.g., Q = F, Cl, or Br)

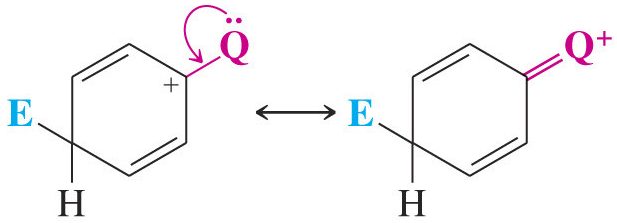
  - ➔ **The following are some other groups that have an electron-withdrawing effect because the atom directly attached to the ring has a partial or full positive charge**



Electron-withdrawing groups with a full or partial charge on the atom attached to the ring

➔ **The resonance effect of Q refers to its ability to increase or decrease the resonance stabilization of the arenium ion**

- **When Q has a lone pair on the atom directly attached to the ring it can stabilize the arenium by contributing a fourth resonance form**

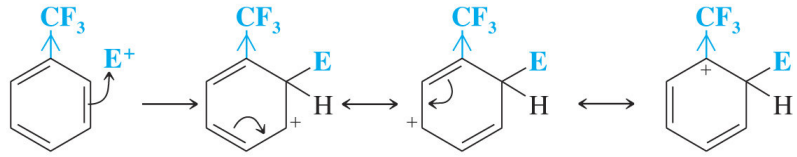


➔ **Electron-donating resonance ability is summarized below**

Most electron donating —NH$_2$, —NR$_2$ > —OH, —OR > —X: Least electron donating

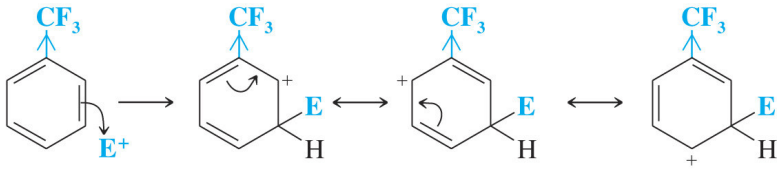
- **Meta-directing Groups**
  - ➔ **All meta-directing groups have either a partial or full positive charge on the atom directly attached to the aromatic ring**
  - ➔ **The trifluoromethyl group destabilizes the arenium ion intermediate in ortho and para substitution pathways**
    - **The arenium ion resulting from meta substitution is not so destabilized and therefore meta substitution is favored**

Ortho Attack

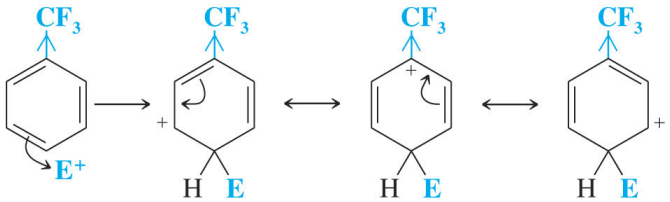


Highly unstable contributor

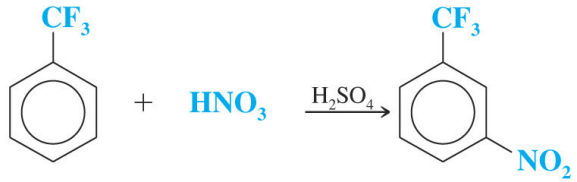
Meta Attack



Para Attack

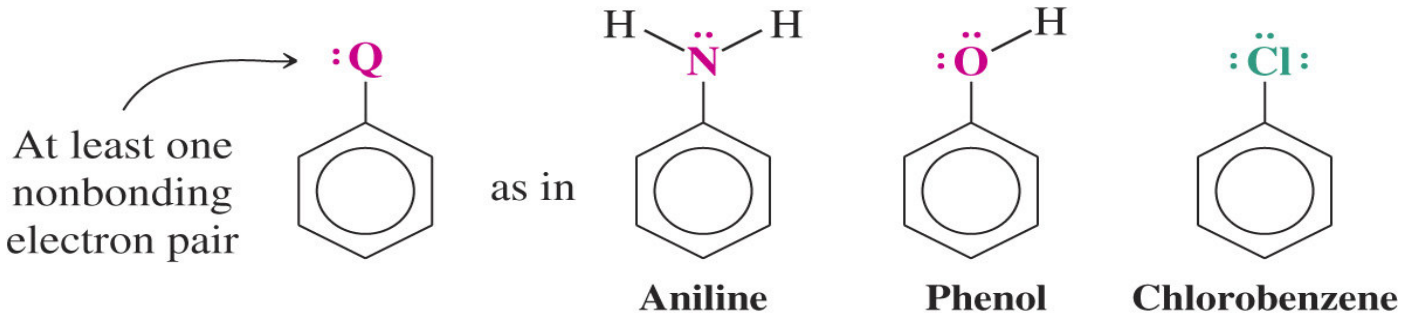


Highly unstable contributor



Trifluoromethylbenzene **(~100%)**

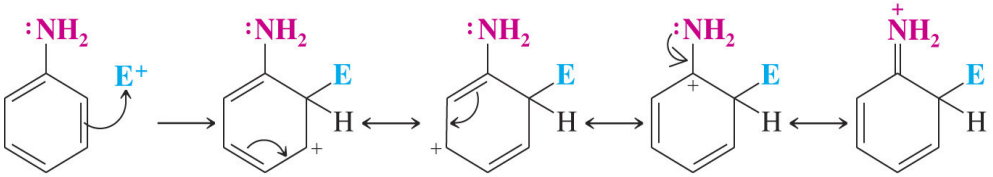
- **Ortho-Para Directing Groups**
  - ➔ **Many ortho-para directors are groups that have a lone pair of electrons on the atom directly attached to the ring**



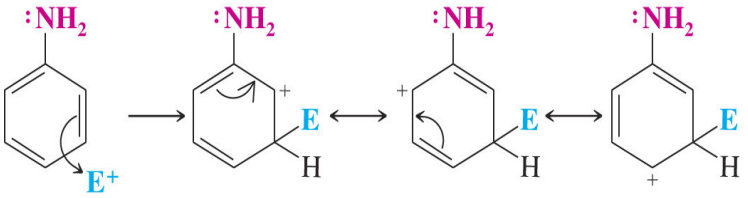
➔ **Activating groups having unshared electrons on the atom bonded to the ring exert primarily a resonance effect**

- **The aromatic ring is activated because of the resonance effect of these groups**
- **They are ortho-para directors because they contribute a fourth important resonance form which stabilizes the arenium ion in the cases of ortho and para substitution only**
- **The fourth resonance form that involves the heteroatom is particularly important because the octet rule is satisfied for all atoms in the arenium ion**

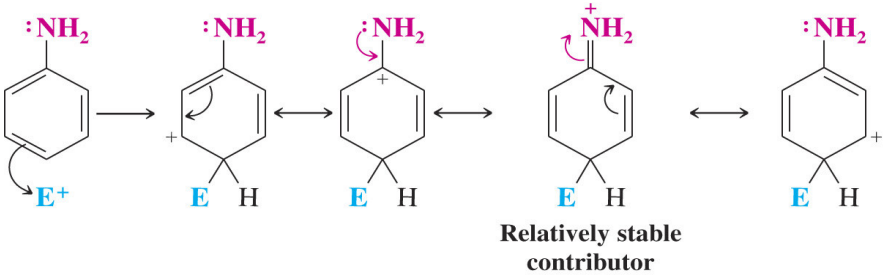
Ortho Attack



Meta Attack

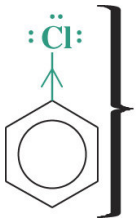


Para Attack

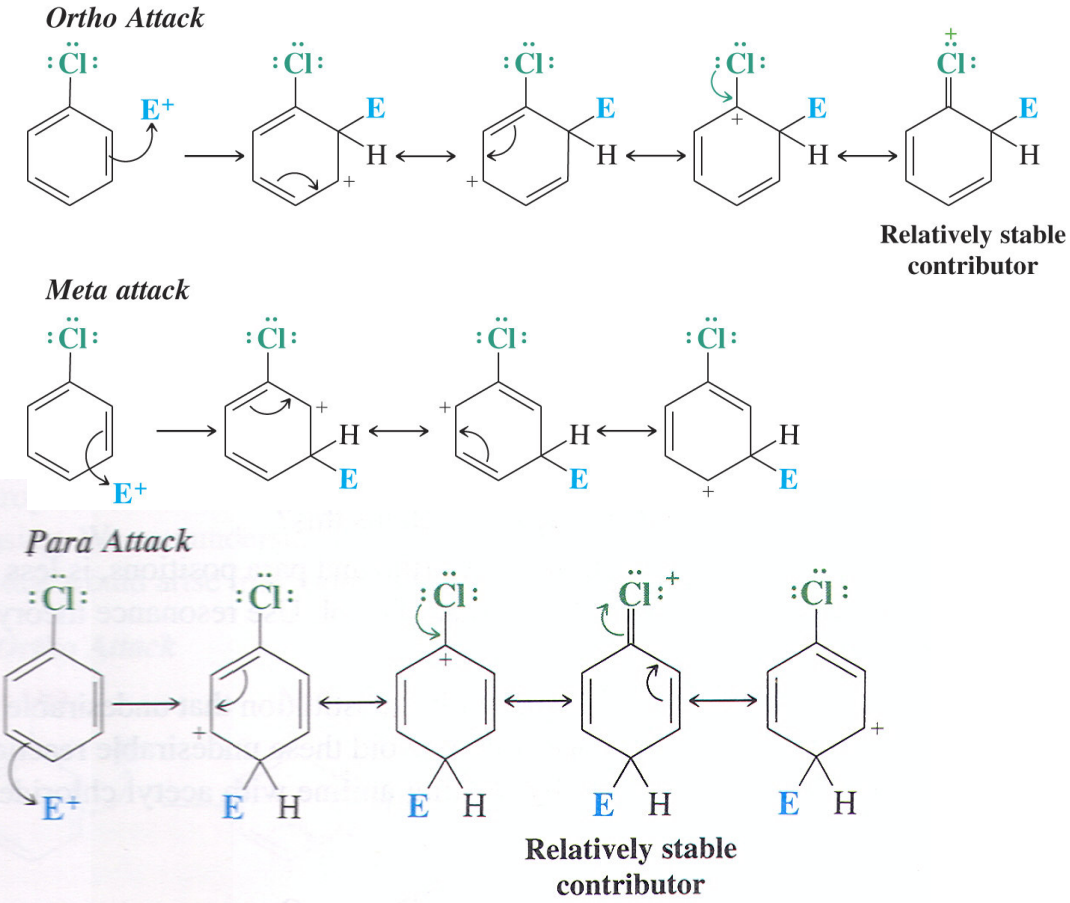


➔Halo groups are ortho-para directors but are also deactivating

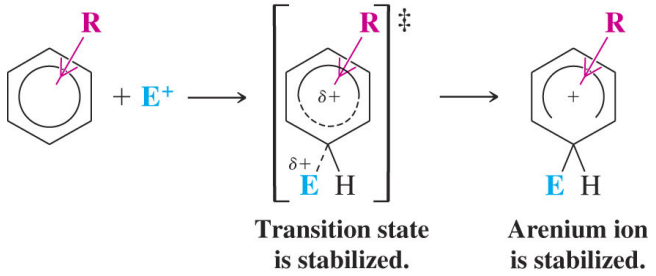
- **The electron-withdrawing inductive effect of the halide is the primary influence that deactivates haloaromatic compounds toward electrophilic aromatic substitution**
- **The electron-donating resonance effect of the halogen's unshared electron pairs is the primary ortho-para directing influence**

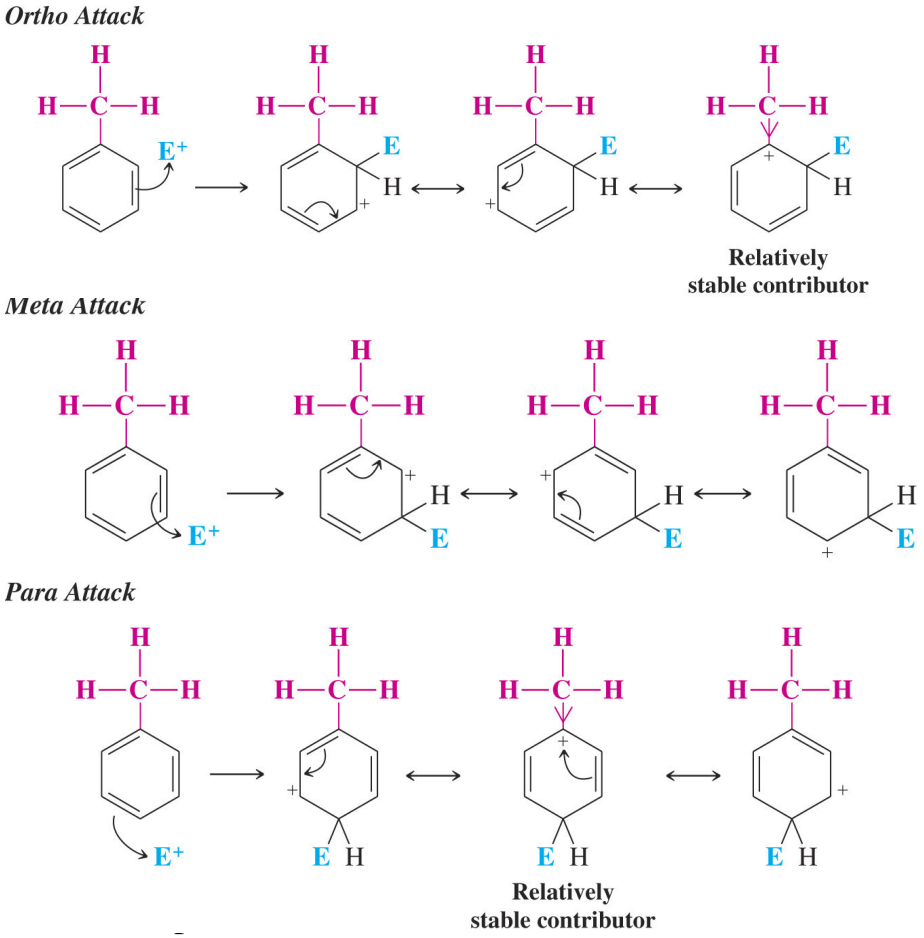


Inductive effect of chlorine atom deactivates ring.



- **Ortho-Para Direction and Reactivity of Alkylbenzenes**
  - ➔ **Alkyl groups activate aromatic rings by inductively stabilizing the transition state leading to the arenium ion**
  - ➔ **Alkyl groups are ortho-para directors because they inductively stabilize one of the resonance forms of the arenium ion in ortho and para substitution**



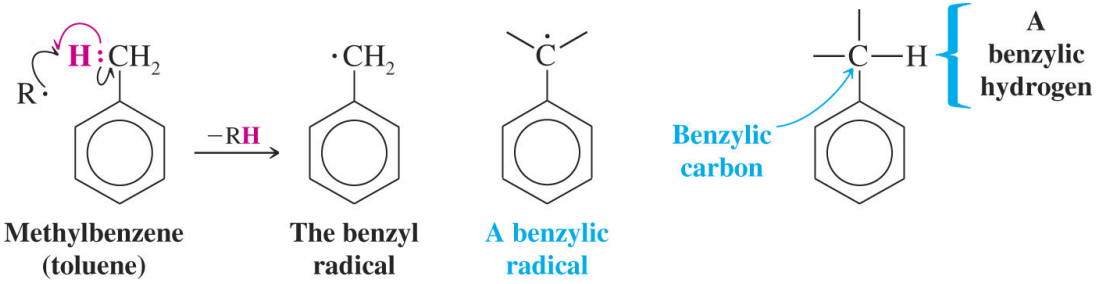


♦ Reactions of the Side Chain of Alkylbenzenes

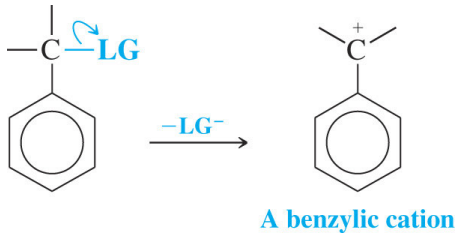
● Benzylic Radicals and Cations

➔ When toluene undergoes hydrogen abstraction from its methyl group it produces a benzyl radical

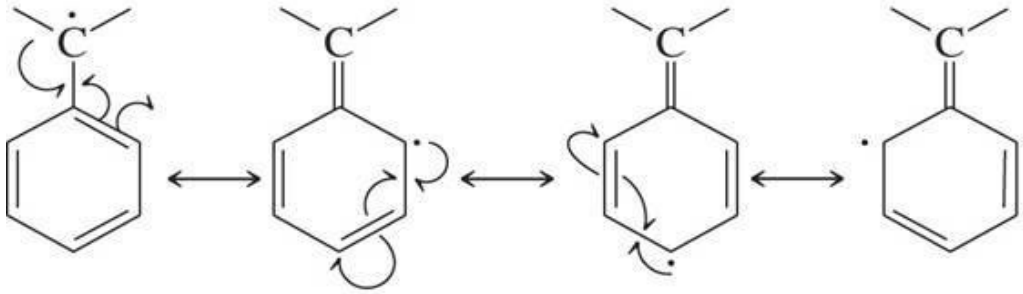
- A benzylic radical is a radical in which the carbon bearing the unpaired electron is directly bonded to an aromatic ring



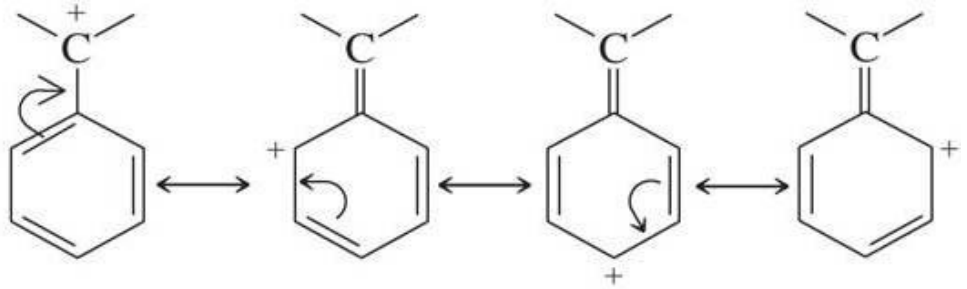
➔ Departure of a leaving group by an S_N1 process from a benzylic position leads to formation of a benzylic cation



➔ **Benylic radicals and cations are stabilized by resonance delocalization of the radical and positive charge, respectively**

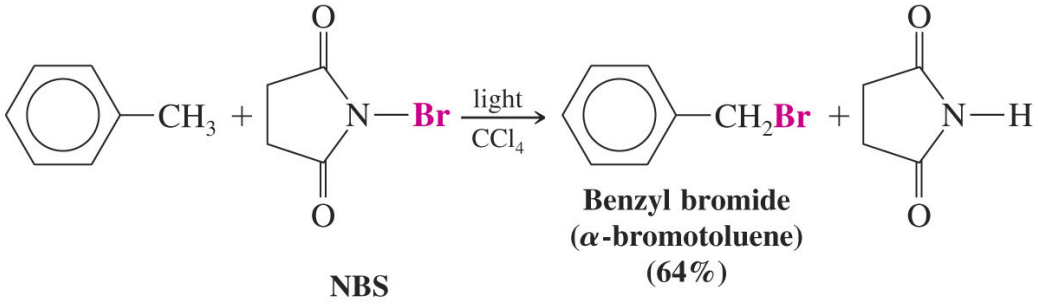


Benzylic radicals are stabilized by resonance.

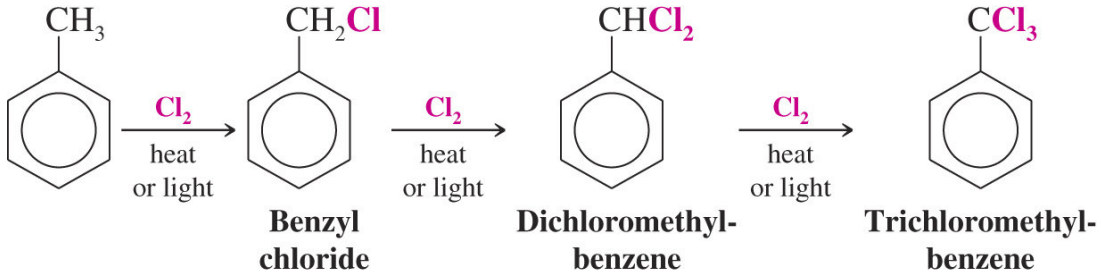


Benzylic cations are stabilized by resonance.

- **Halogenation of the Side Chain: Benzylic Radicals**
  - ➔ **Benzylic halogenation takes place under conditions which favor radical reactions**
  - ➔ **Reaction of *N*-bromosuccinamide with toluene in the presence of light leads to allylic bromination**
    - **Recall *N*-bromosuccinamide produces a low concentration of bromine which favors radical reaction**



  - ➔ **Reaction of toluene with excess chlorine can produce multiple benzylic chlorinations**

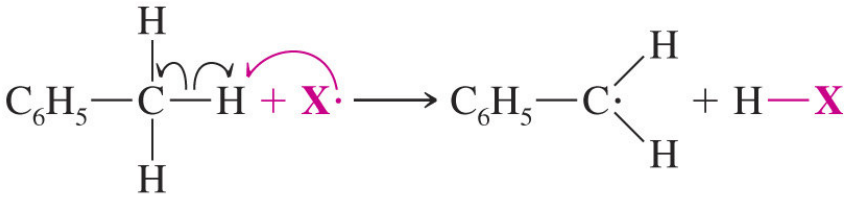


Chain Initiation

Step 1: $X{-}X \xrightarrow[\text{or light}]{\text{peroxides, heat}} 2\,X\cdot$

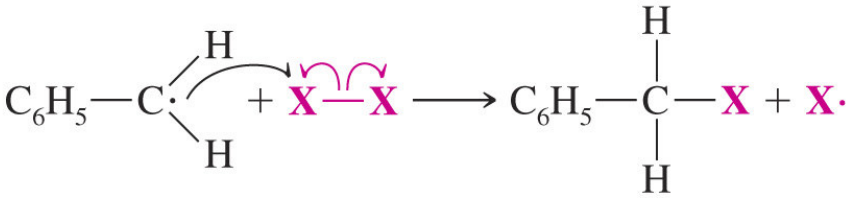
Chain Propagation

Step 2:



Benzyl radical

Step 3:



Benzyl radical **Benzyl halide**

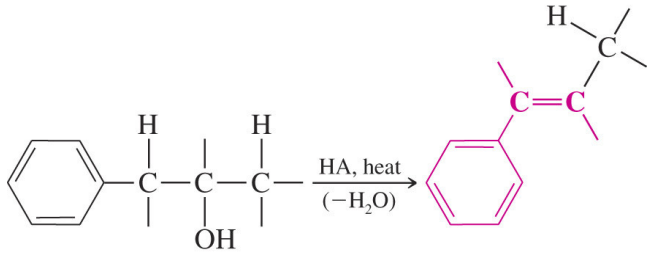
➔ **When ethylbenzene or propylbenzene react under radical conditions, halogenation occurs primarily at the benzylic position**

♦ Alkenylbenzenes

● Stability of Conjugated Alkenylbenzenes

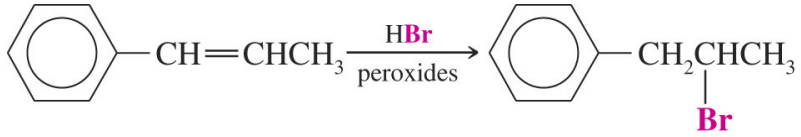
➔ **Conjugated alkenyl benzenes are more stable than nonconjugated alkenylbenzenes**

- **Dehydration of the alcohol below yields only the more stable conjugated alkenyl benzene**

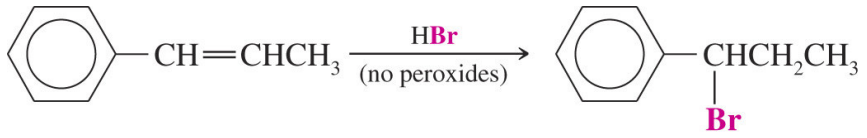


● Additions to the Double Bond of Alkenylbenzenes

➔ **Additions proceed through the most stable benzylic radical or benzylic cation intermediates**

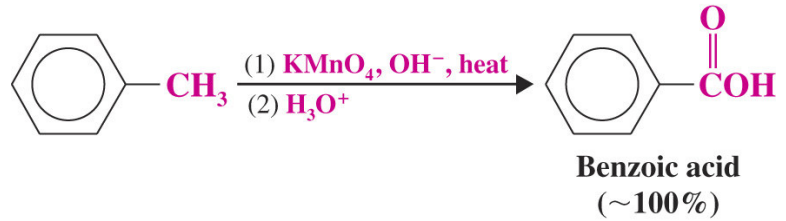


1-Phenylpropene **2-Bromo-1-phenylpropane**

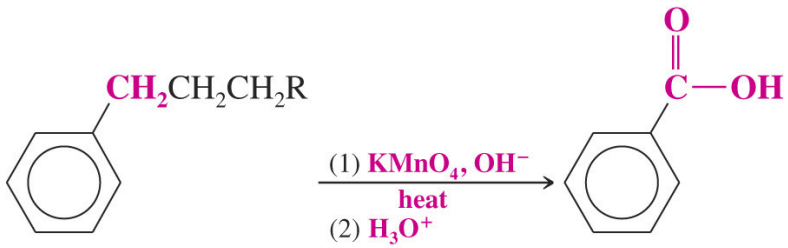


1-Phenylpropene **1-Bromo-1-phenylpropane**

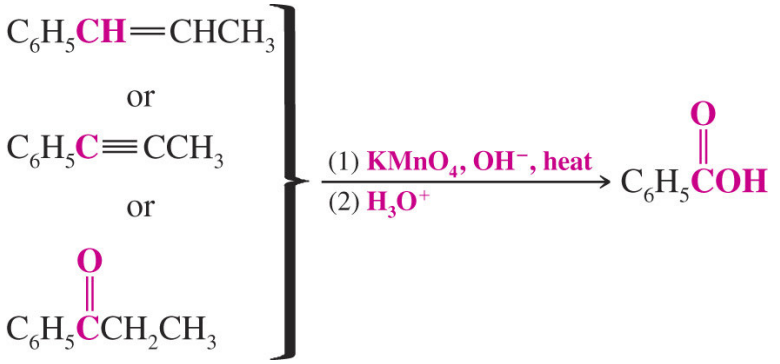
- **Oxidation of the Side Chain**
  - ➔ **Alkyl and unsaturated side chains of aromatic rings can be oxidized to the carboxylic acid using hot $KMnO_4$**



Benzoic acid
(~100%)



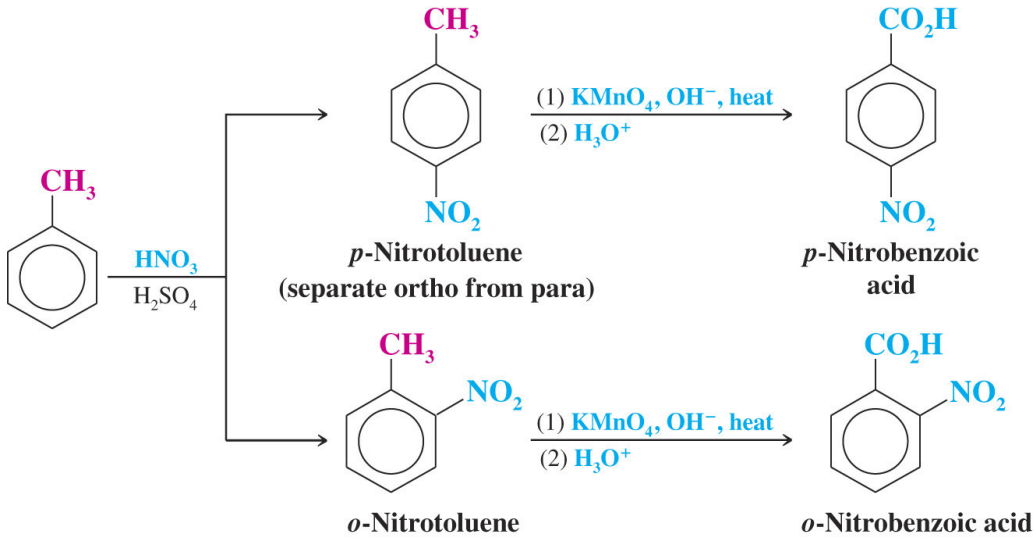
An alkylbenzene **Benzoic acid**

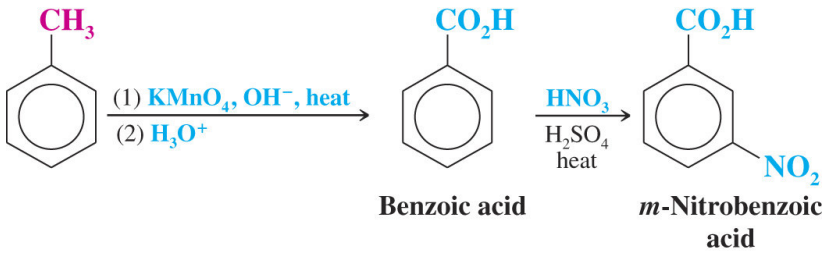


♦ Synthetic Applications

➔ When designing a synthesis of substituted benzenes, the order in which the substituents are introduced is crucial

➔ Example: Synthesize ortho-, meta-, and para-nitrobenzoic acid from toluene

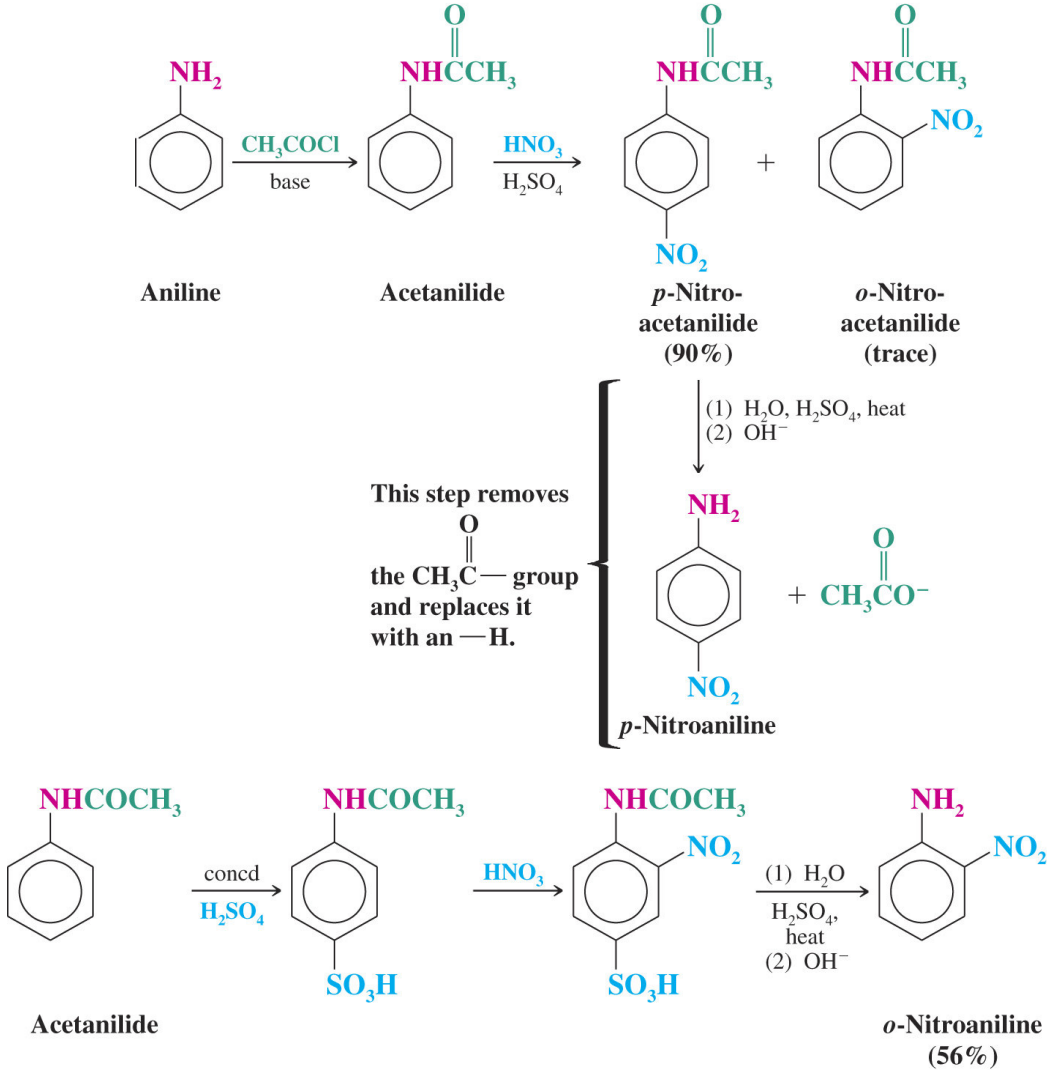




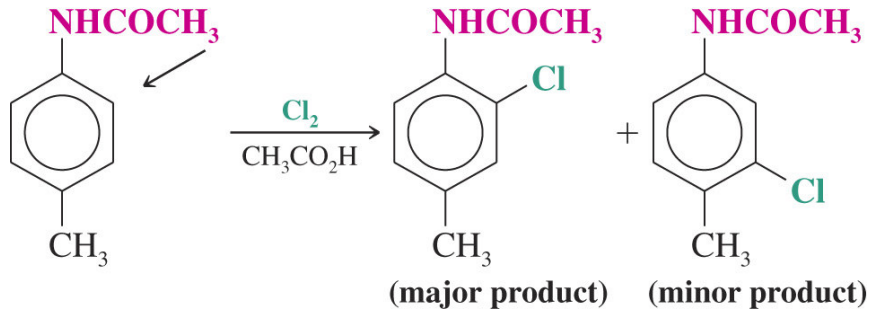
- **Use of Protecting and Blocking Groups**
  - **➔Strong activating groups such as amino and hydroxyl cause the aromatic ring to be so reactive that unwanted reactions can take place**
    - **These groups activate aromatic rings to oxidation by nitric acid when nitration is attempted; the ring is destroyed**
    - **An amino group can be protected (and turned into a moderately activating group) by acetylation**

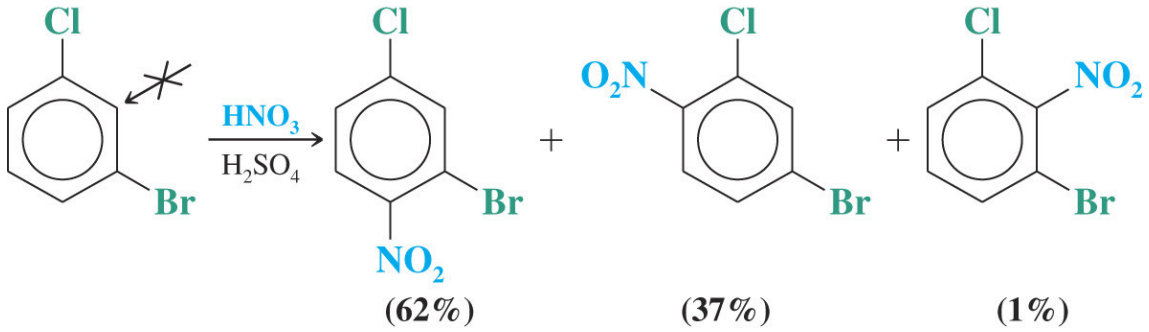
➔ Example: The synthesis of *p*- and *o*-nitroaniline from aniline

- **A sulfonic acid group is used as a blocking group to force ortho substitution**



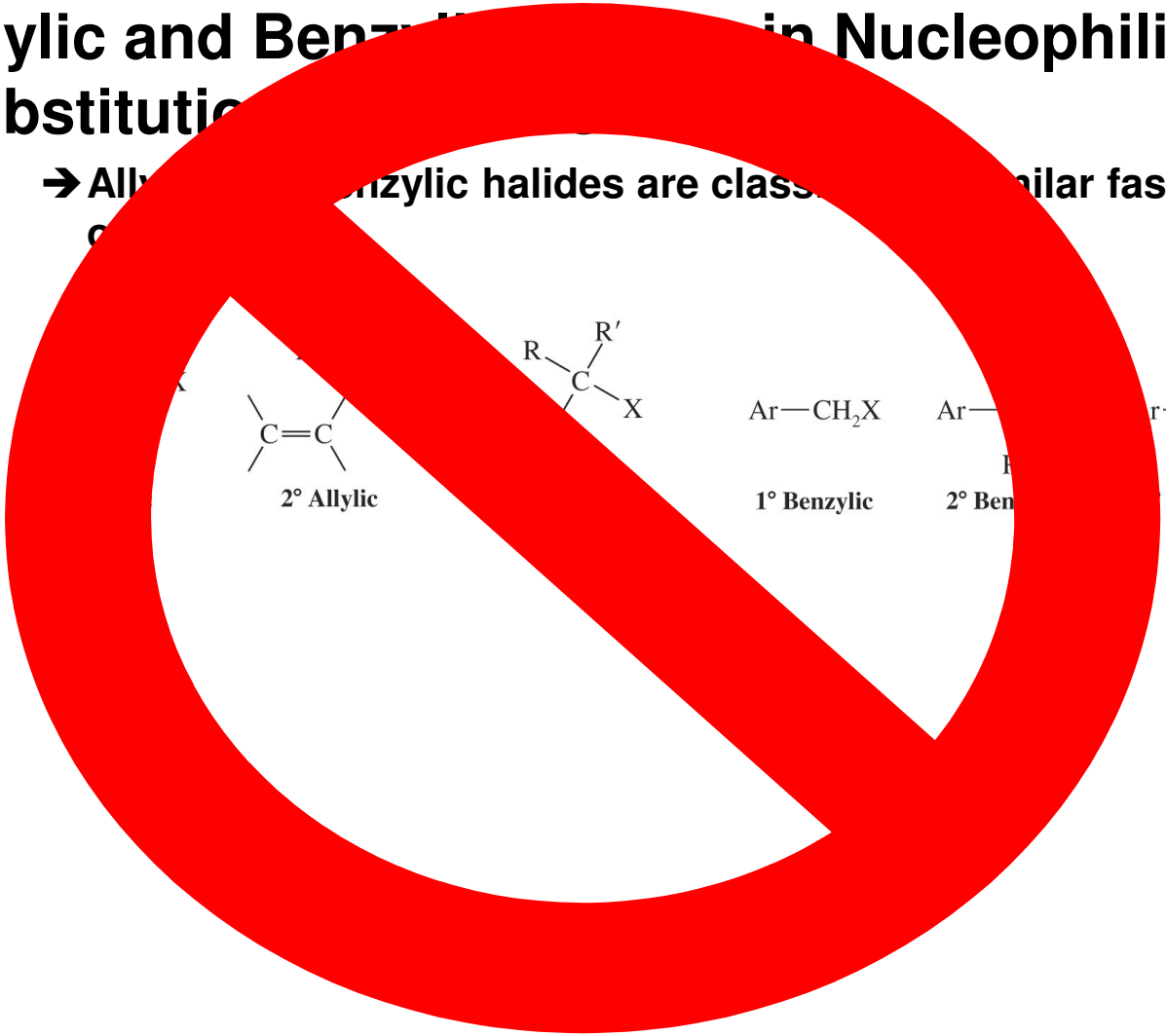
- **Orientation in Disubstituted Benzenes**
  - **➔When two substituents are present on the ring initially, the more powerful activating group generally determines the orientation of subsequent substitution**
    - **Ortho-para directors determine orientation over meta directors**
    - **Substitution does not occur between meta substituents due to steric hindrance**





♦ **Allylic and Benz… in Nucleophilic Substitutio…**

➔ **All… …nzylic halides are class… …ilar fashion to …**



➔ **Both primary [illegible] benzylic halides can undergo [illegible]**

- **[illegible]halides are able to unde[illegible] because of the added the allylic and benzylic carbocat[illegible]**

➔ **T[illegible] and benzylic halides can u[illegible]rgo S_N1 reaction**