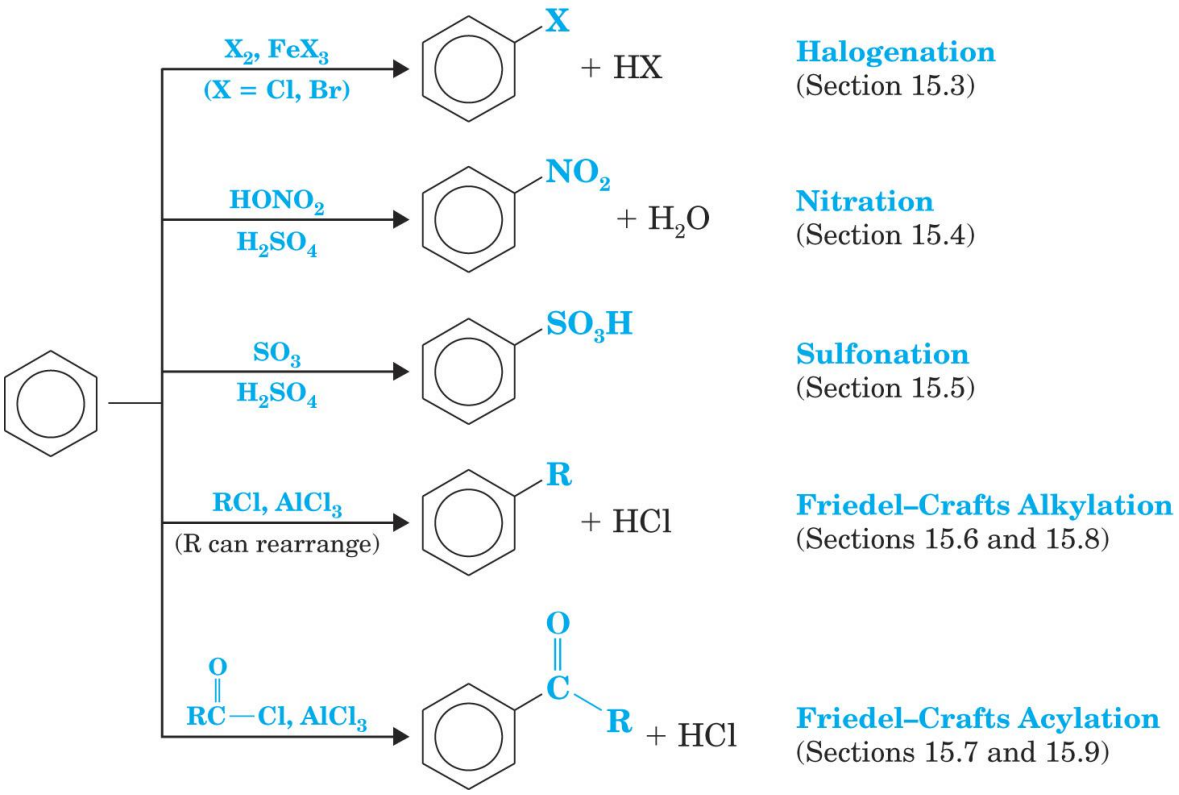
Chapter 15
Reactions of Aromatic Compounds

15.1) Electrophilic Aromatic Substitution:

§**Arene (Ar-H) is the generic term for an aromatic hydrocarbon**

- **The aryl group (Ar) is derived by removal of a H atom from an arene**

Aromatic compounds undergo electrophilic aromatic substitution (EAS) and the electrophile has a full or partial positive charge.



15.2) 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.**

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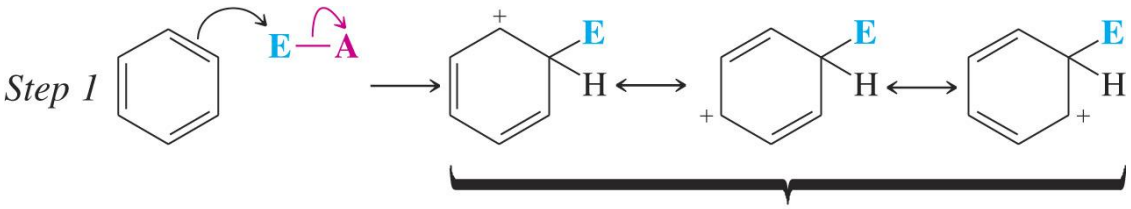
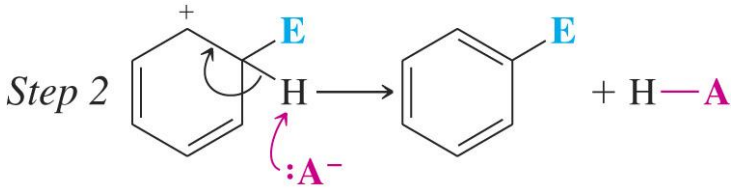
In step 1: the electrophile reacts with two π electrons from the aromatic ring

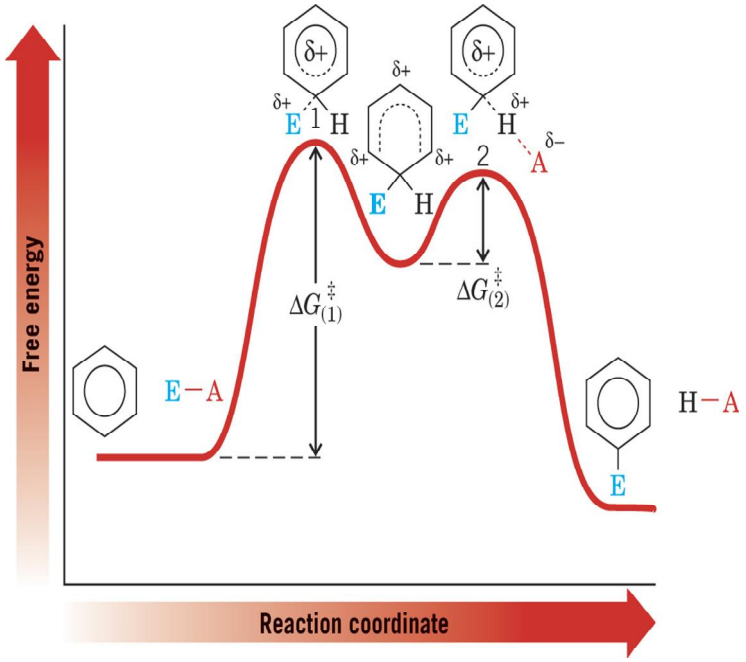


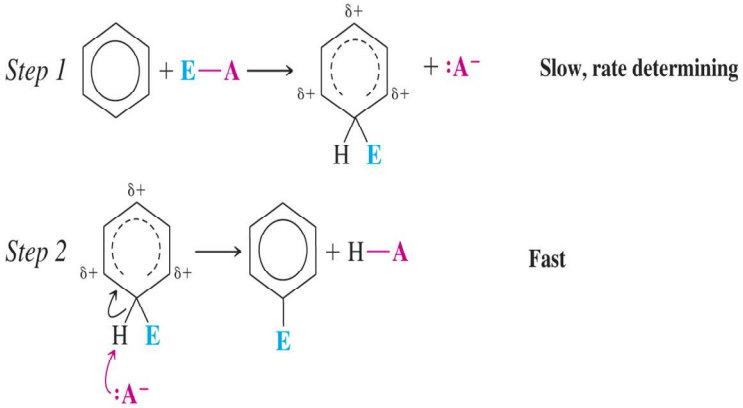
The arenium ion is stabilized by resonance which delocalizes the charge

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 second step is highly exothermic and has a small $\Delta G\ddagger_{(2)}$.





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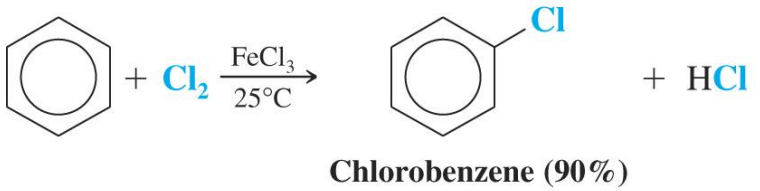
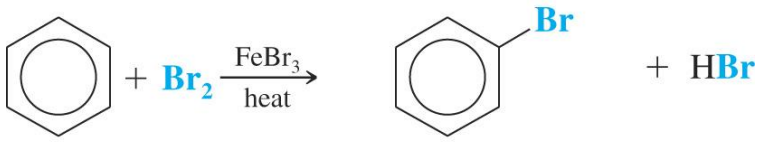
15.3) Halogenation of Benzene:



Chlorobenzene (90%)

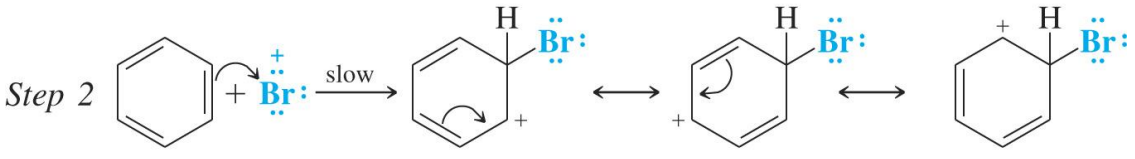


Bromobenzene (75%)

Halogenation of benzene requires the presence of a Lewis acid.

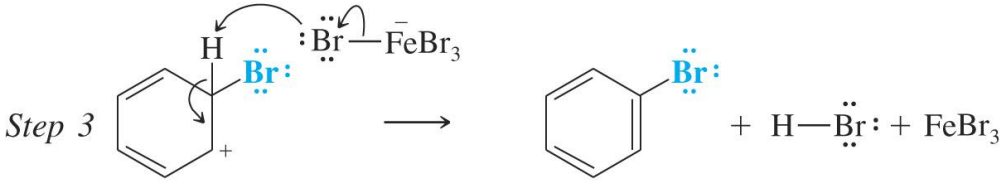
Mechanism

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



Arenium ion

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



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

- **Fluorination occurs so rapidly it is hard to stop at mono-fluorination of the ring (A special apparatus is used to perform this reaction).**
- **Iodine is so unreactive that an alternative method must be used**

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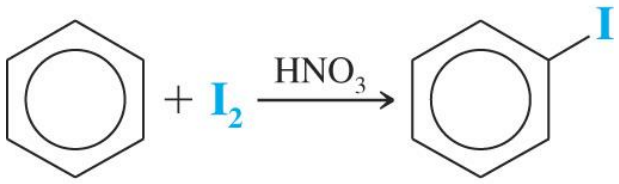
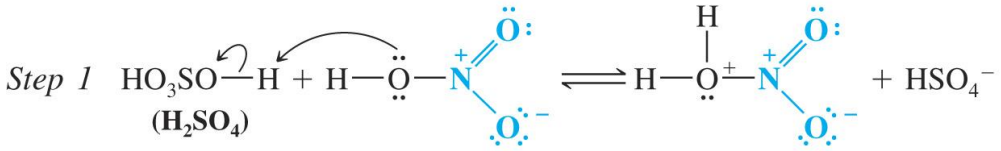
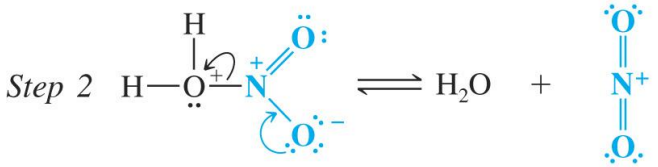


15.4) Nitration of Benzene:

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

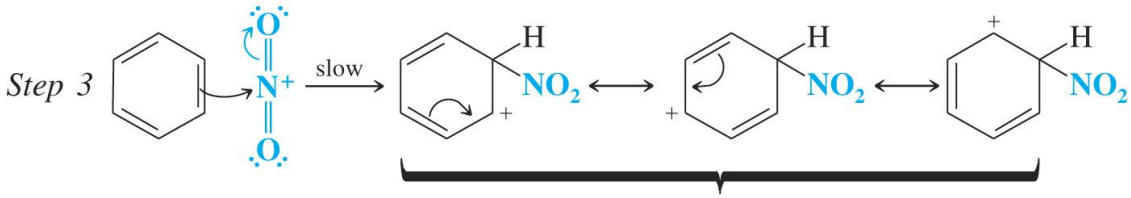


In this step nitric acid accepts a proton from the stronger acid, sulfuric acid.



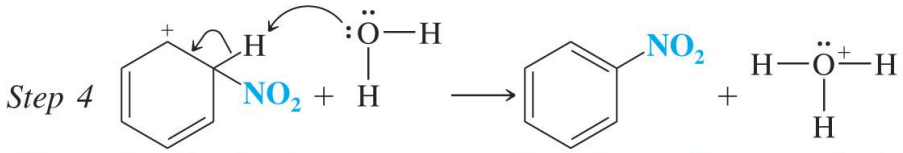
Nitronium ion

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



Arenium ion

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



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

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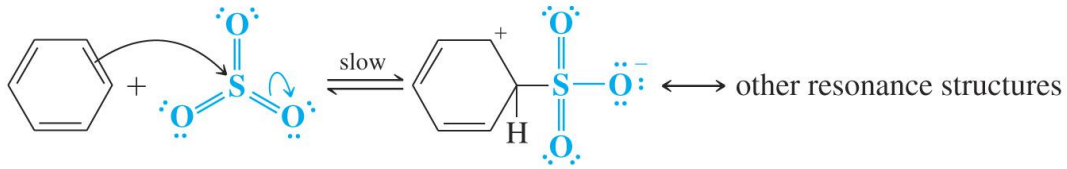
15.5) Sulfonation of Benzene:

§**Sulfonation occurs most rapidly using fuming sulfuric acid (concentrated sulfuric acid that contains SO_3). Sulfonation also occurs in conc. sulfuric acid, which contains small quantities of SO_3, as shown in step 1 below, but more slowly.**

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

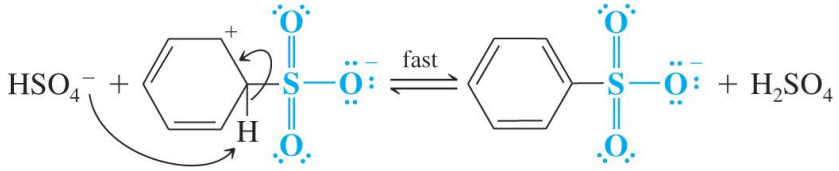
This equilibrium produces SO_3 in concentrated H_2SO_4.

Step 2



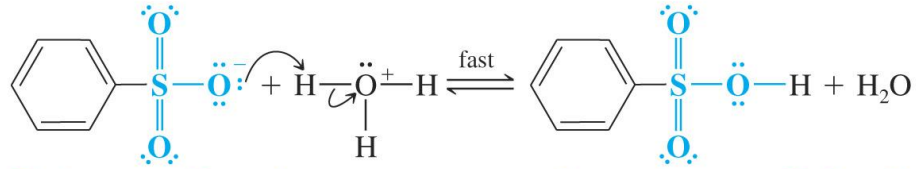
SO_3 is the actual electrophile that reacts with benzene to form an arenium ion.

Step 3



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

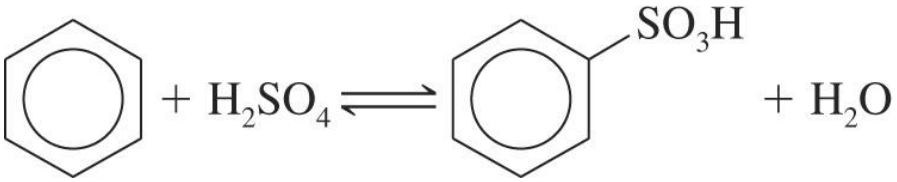
Step 4



The benzenesulfonate ion accepts a proton to become benzenesulfonic acid.

§**Sulfonation is an equilibrium reaction; all steps involved are equilibria.**

§**Desulfonation can be accomplished using dilute sulfuric acid (*i.e.* with a high concentration of water)**



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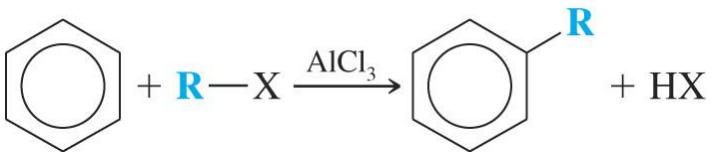
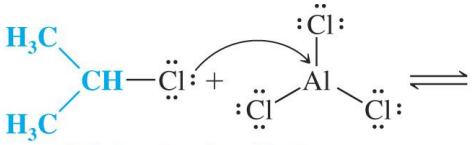
15.6) Friedel-Crafts Alkylation:

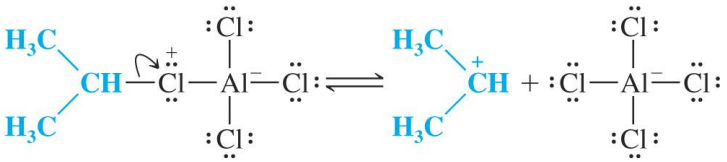
§ **An aromatic ring can be alkylated by an alkyl halide in the presence of a Lewis acid (The Lewis acid serves to generate a carbocation electrophile)**



Step 1

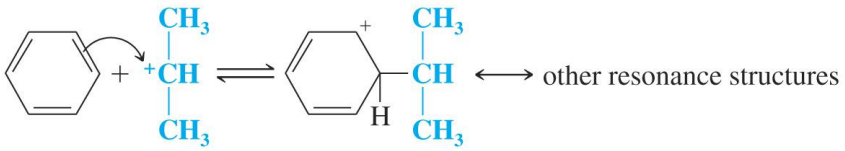


This is a Lewis acid–base reaction (see Section 3.2B).



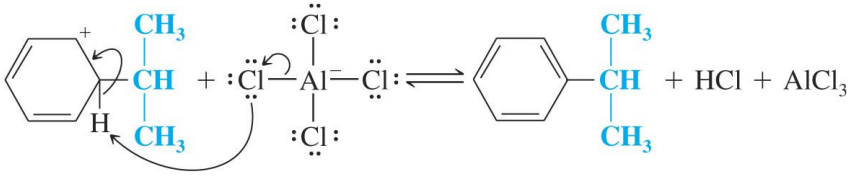
The complex dissociates to form a carbocation and $AlCl_4^-$.

Step 2



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

Step 3



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

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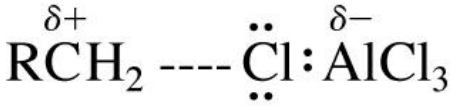
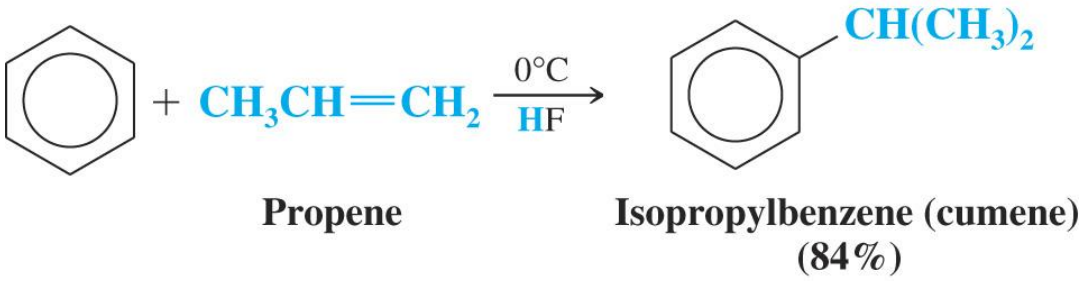
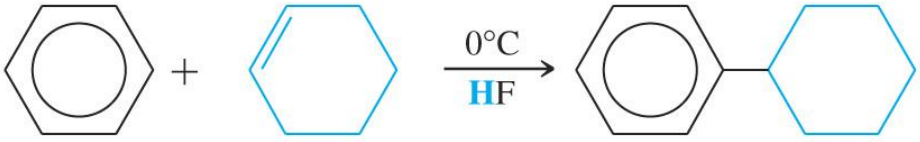
§**Primary alkyl halides probably do not form discreet carbocations but the primary carbon in the complex develops considerable positive charge**



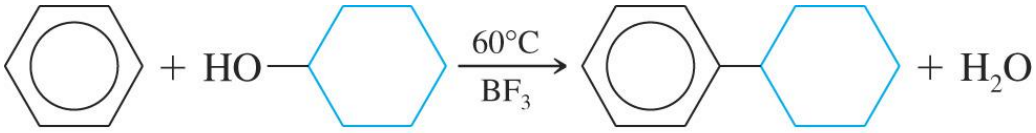
§**Any compound that can form a carbocation can be used to alkylate an aromatic ring**



Propene **Isopropylbenzene (cumene) (84%)**



Cyclohexene **Cyclohexylbenzene (62%)**



Cyclohexanol **Cyclohexylbenzene (56%)**

15.7) Friedel-Crafts Acylation:

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

Acetyl group (ethanoyl group) **Benzoyl group**

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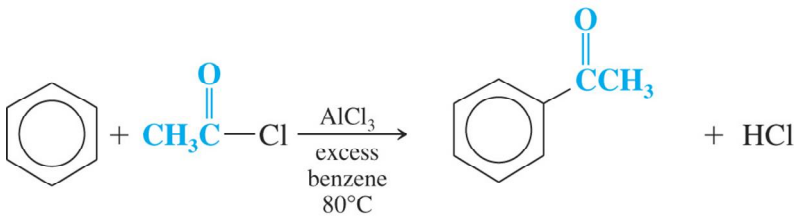
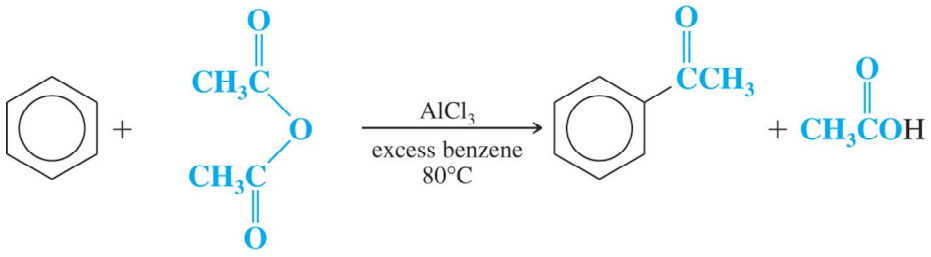
§ **Friedel-Crafts acylation requires reaction of an acid chloride or acid anhydride with a Lewis acid such as aluminium chloride**



Acetyl chloride

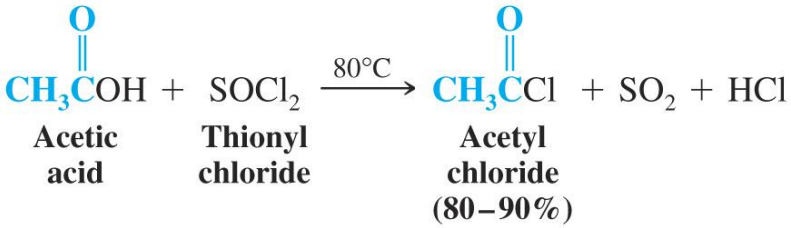
Acetophenone (methyl phenyl ketone) (97%)



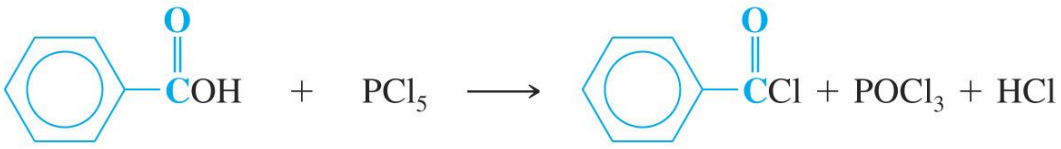
Acetic anhydride (a carboxylic acid anhydride)

Acetophenone (82–85%)

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



Acetic acid **Thionyl chloride** **Acetyl chloride (80–90%)**



Benzoic acid **Phosphorus pentachloride** **Benzoyl chloride (90%)**

§ **The electrophile in Friedel-Crafts acylation is an acylium ion**

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

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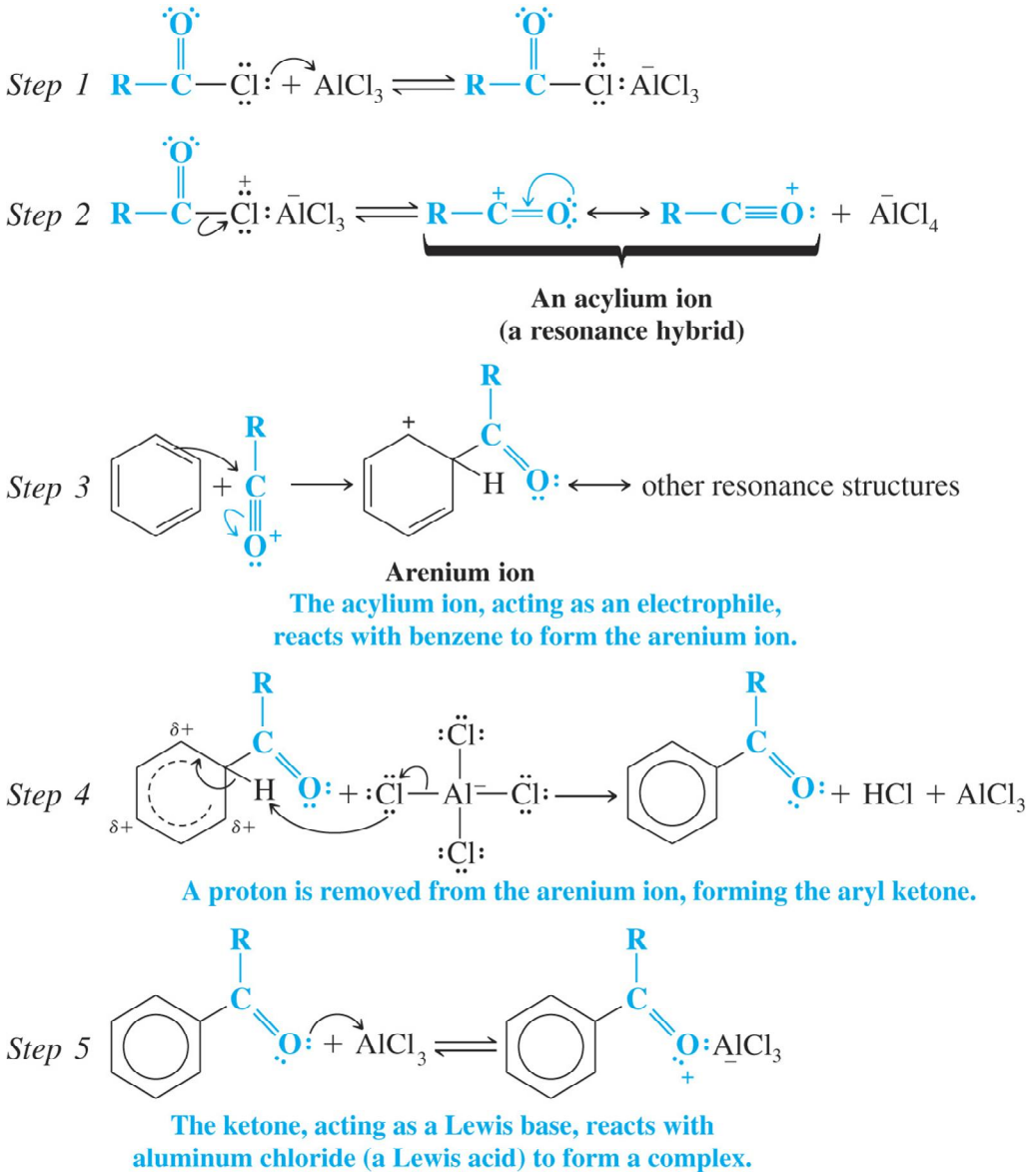
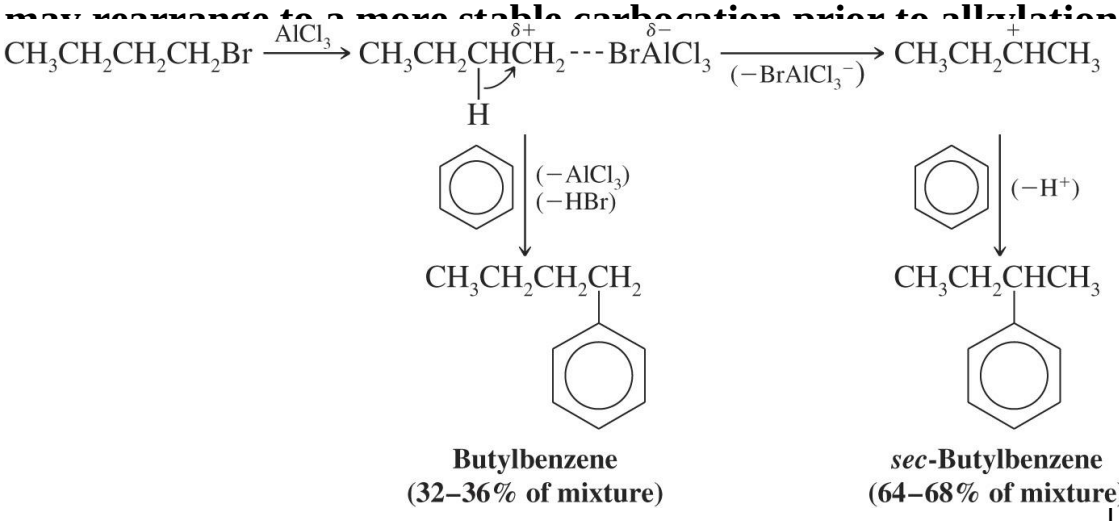


15.8) Limitations of Friedel-Crafts Reactions:

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



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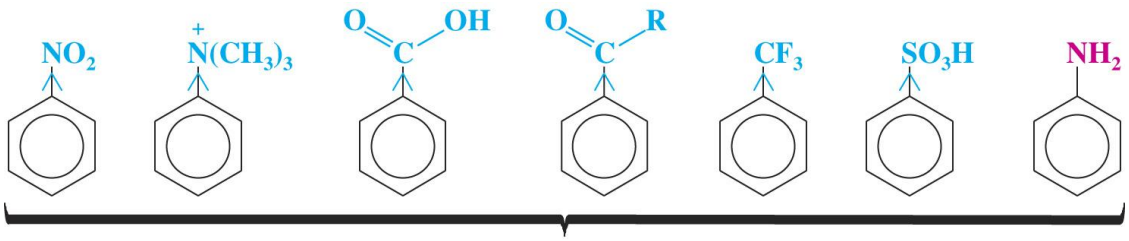
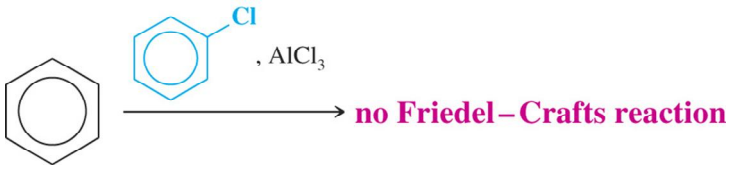
§ **Powerful electron-withdrawing groups make an aromatic ring much less reactive toward Friedel-Crafts alkylation or acylation**

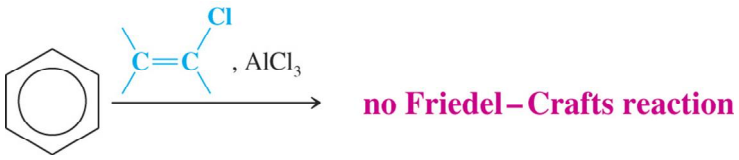


These usually give poor yields in Friedel–Crafts reactions.

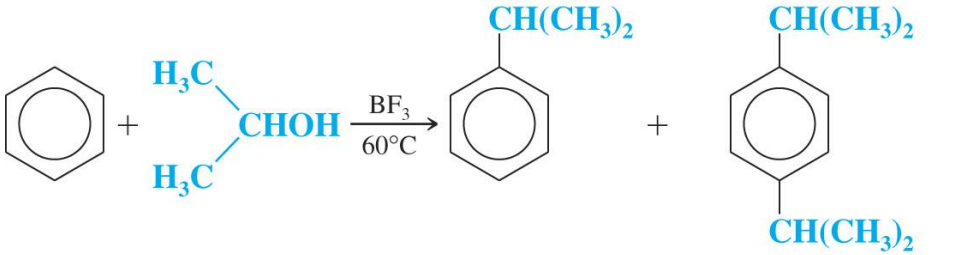
Amino groups also make the ring less reactive to Friedel-Crafts reaction because they become electron-withdrawing groups upon Lewis acid-base reaction with the Lewis acid catalyst

§ **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).**



Isopropyl-benzene (24%)

p-Diisopropylbenzene (14%)

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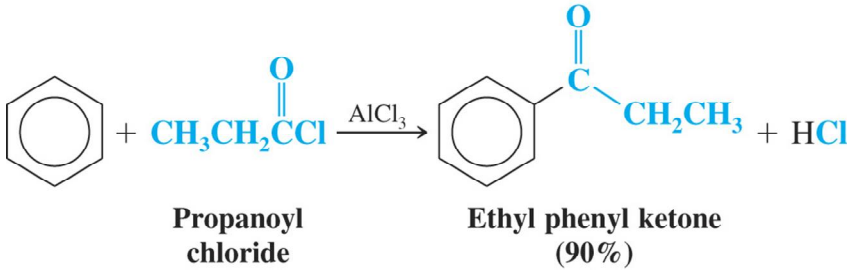
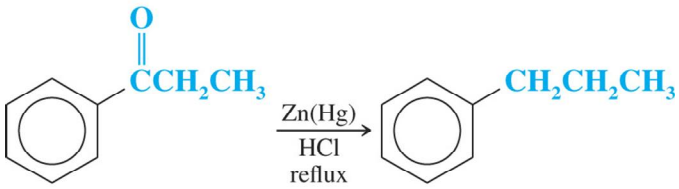
15.9) Synthetic Applications of Friedel-Crafts Acylations: The Clemmensen Reduction:

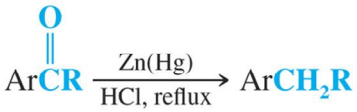
- **Primary alkyl halides often yield rearranged products in Friedel-Crafts alkylation which is a major limitation of this reaction.**
- **Unbranched alkylbenzenes can be obtained in good yield by acylation followed by Clemmensen reduction. (Clemmensen reduction reduces phenyl ketones to the methylene (CH_2) group**



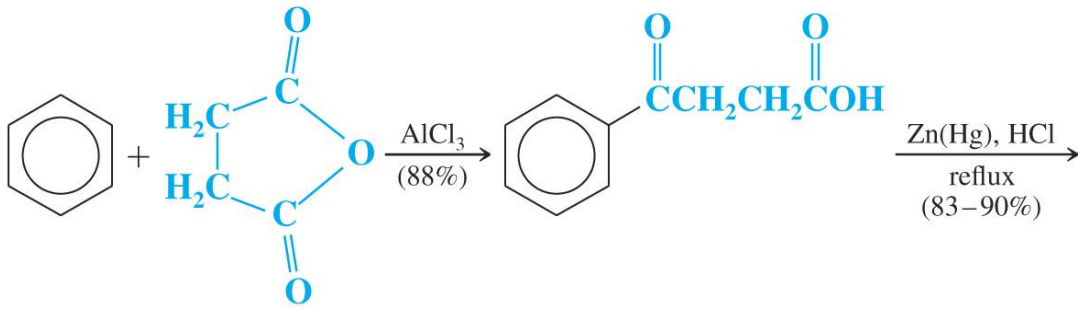
Propanoyl chloride — **Ethyl phenyl ketone (90%)**



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**

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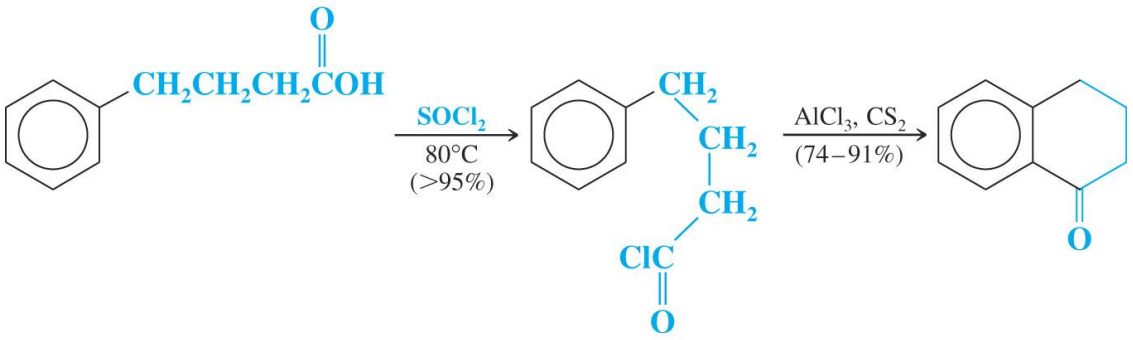


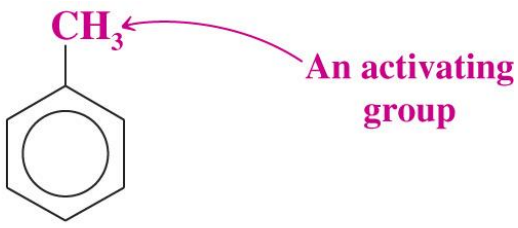
4-Phenylbutanoic acid | 4-Phenylbutanoyl chloride | α-Tetralone

15.10) 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

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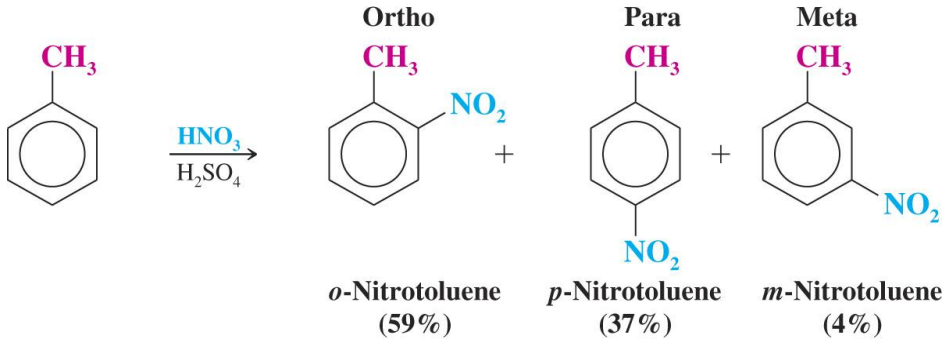
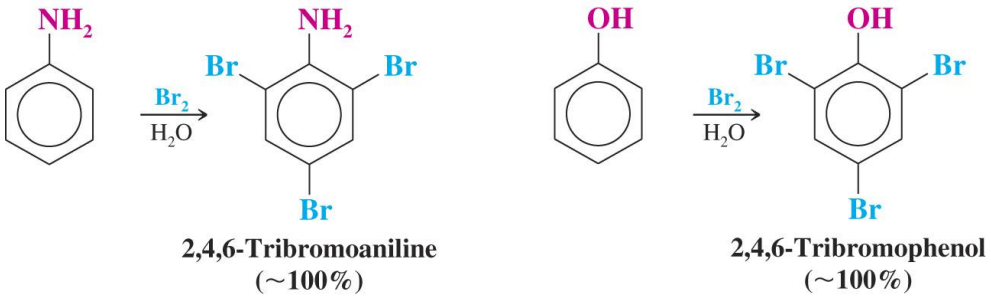
§**The methyl group of toluene is an ortho-para director**



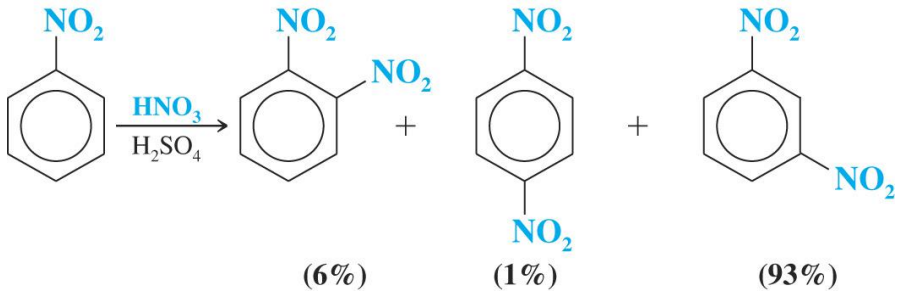
§**Amino and hydroxyl groups are also activating and ortho-para directors. (These groups are so activating that catalysts are often not necessary)**



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

l **<u>Deactivating Groups: Meta Directors:</u>**

§**Strong electron-withdrawing groups such as nitro, carboxyl, and sulfonate are deactivators and meta directors**



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l 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 $-\ddot{F}:$, $-\ddot{C}l:$, $-\ddot{B}r:$, $-\ddot{I}:$	

15.11) Theory of Substituent Effects on Electrophilic Substitution:

l 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**

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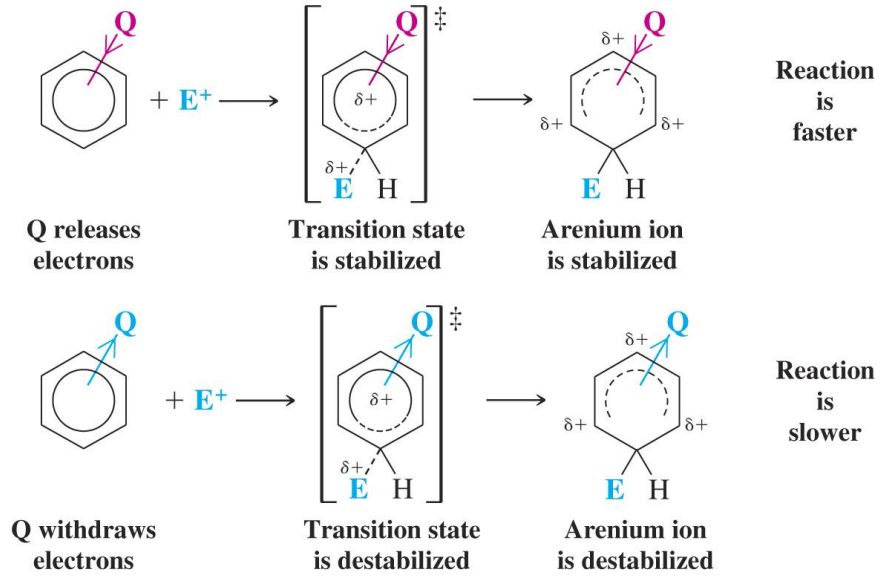
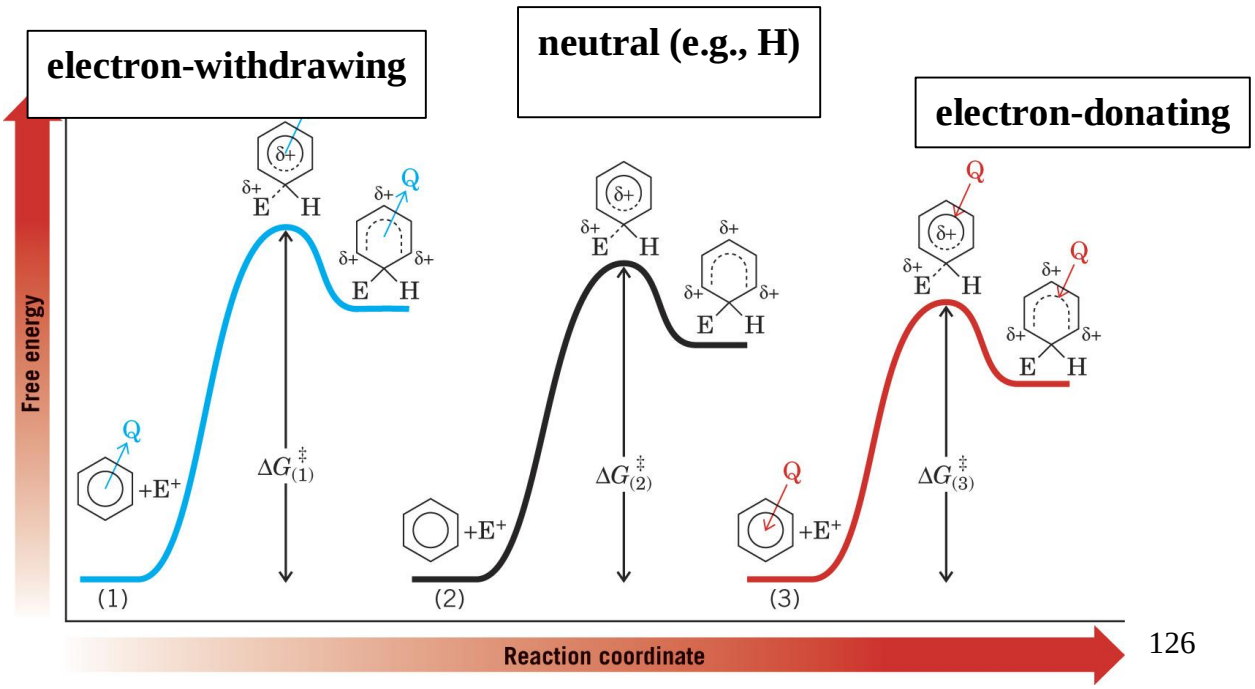
the first step of substitution and lead to lower $\Delta G^{\ddagger}$ and faster rates of reaction

§ **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.**



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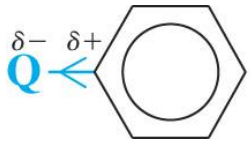
Inductive and Resonance Effects: Theory of Orientation:

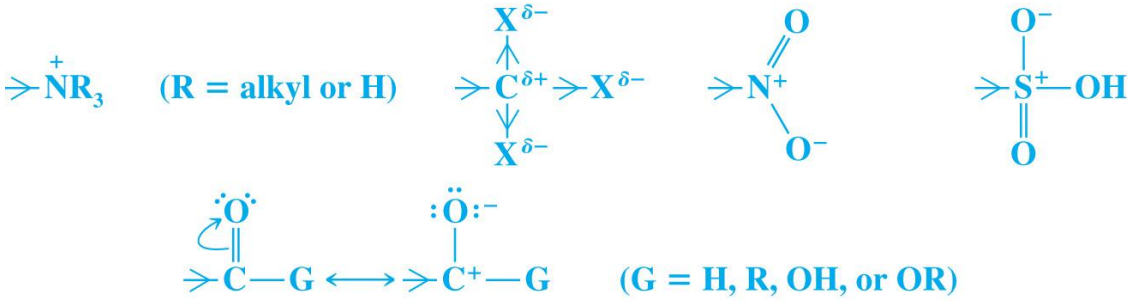
- **The inductive effect of some substituent Q arises from the interaction of the polarized bond to Q with the developing positive charge in the ring as an electrophile reacts with it**



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

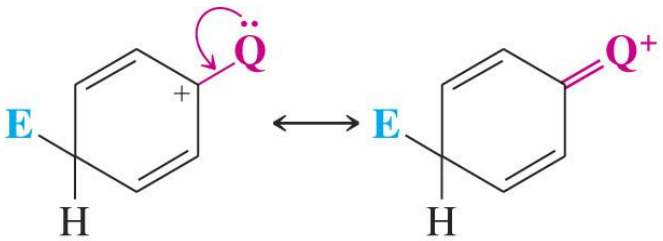
If Q is an electron-withdrawing group then attack on the ring is slowed because this leads to additional positive charge on the ring

- **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

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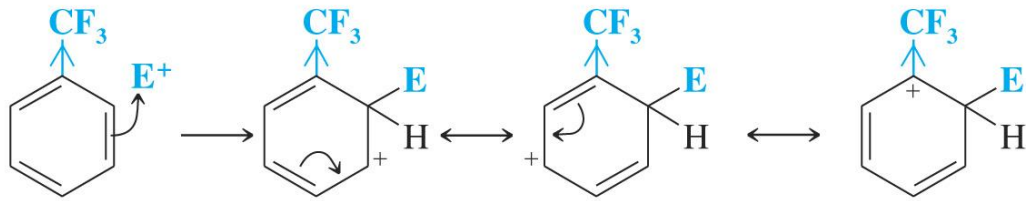
§ **Electron-donating resonance ability is summarized below**

l Meta-directing Groups:

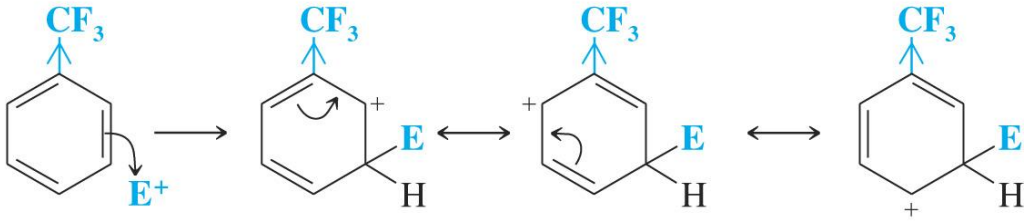
§ **All meta-directing groups have either a partial or full positive charge on the atom directly attached to the aromatic ring.**

§ **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)**

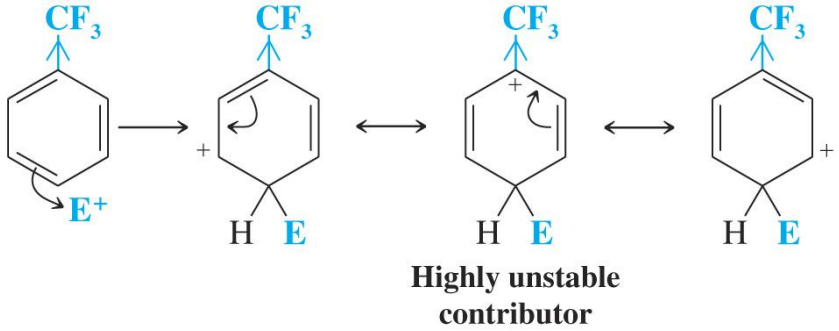
Ortho Attack



Meta Attack



Para Attack



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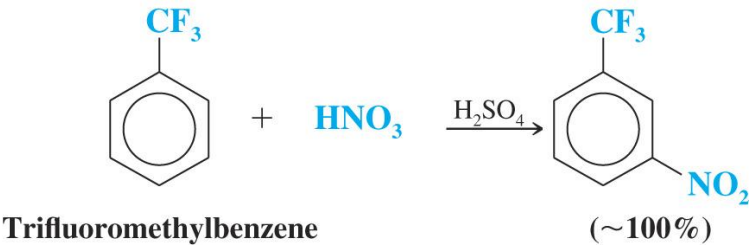
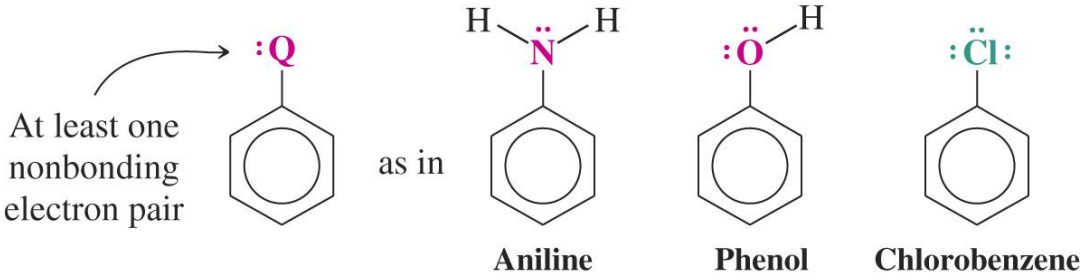


Trifluoromethylbenzene (~100%)

Ortho-Para Directing Groups:

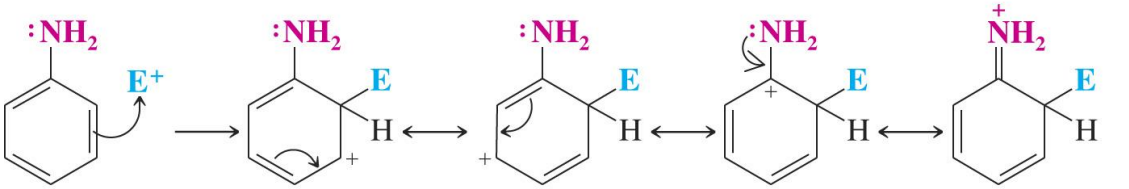
§ **Many ortho-para directors are groups that have a lone pair of electrons on the atom directly attached to the ring**



§ **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



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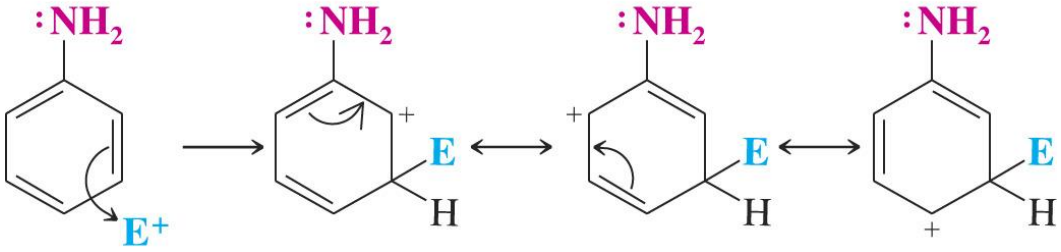
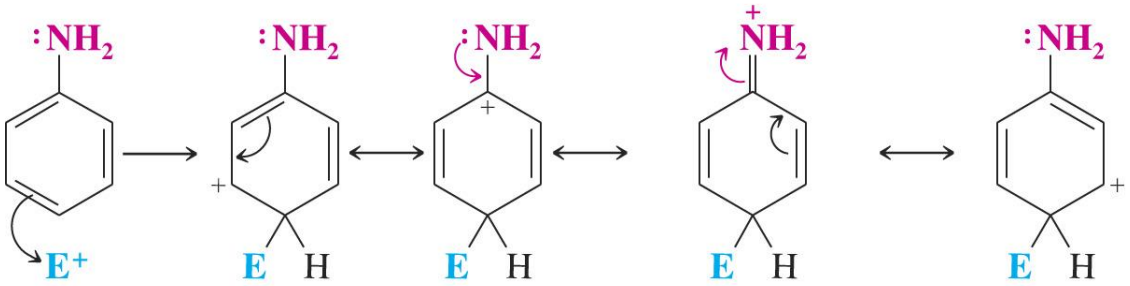
Meta Attack

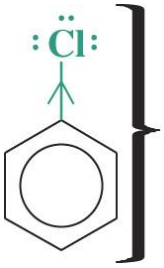


Para Attack



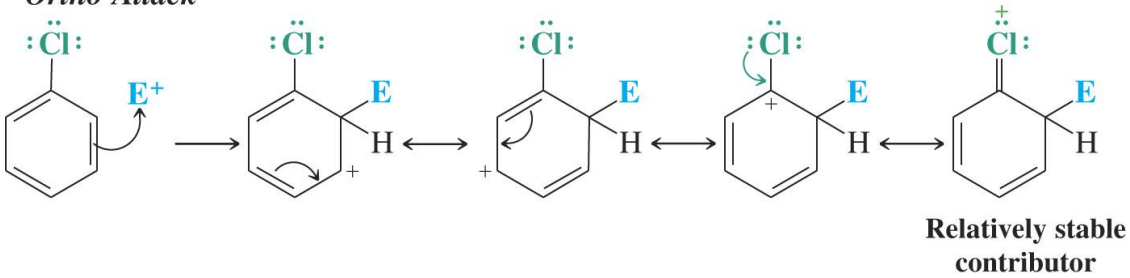
§Halo groups are ortho-para directors but are also deactivating

- **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 Attack



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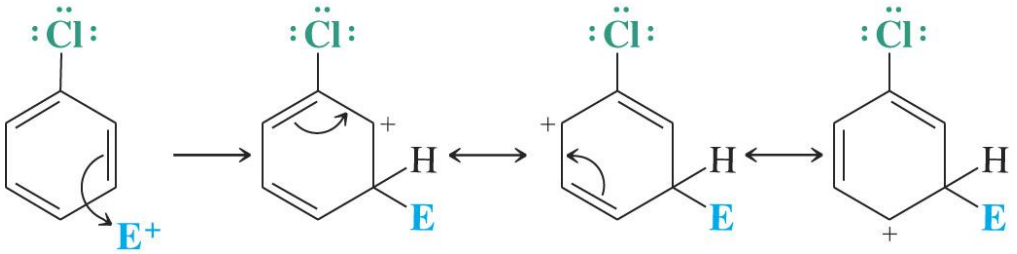
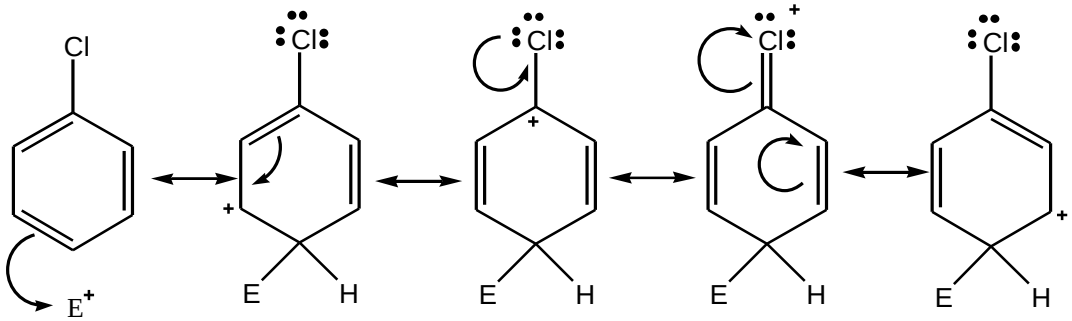
Meta attack



Para attack

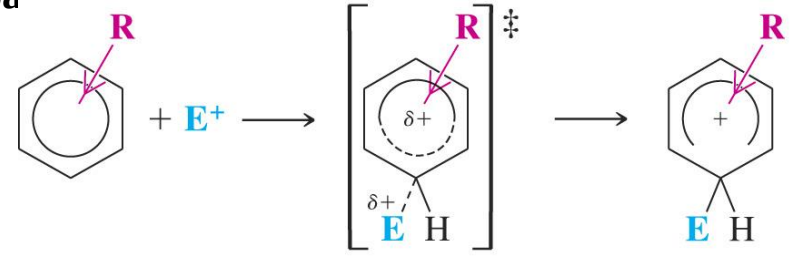


Relatively stable contributor

l Ortho-Para Direction and Reactivity of Alkylbenzenes:

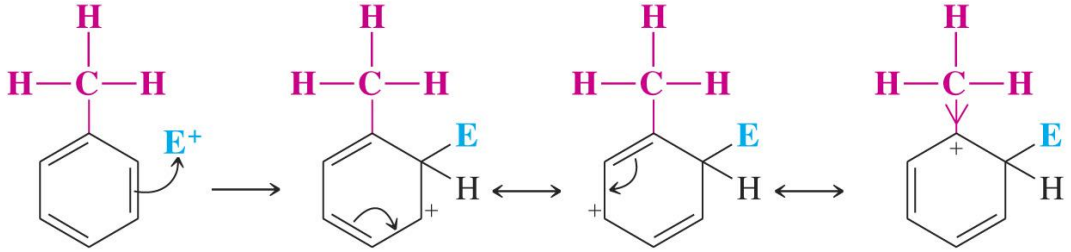
§ **Alkyl groups activate aromatic rings by inductively stabilizing the transition state leading to the arenium ion.**

§ **Alkyl groups are ortho-para directors because they inductively stabilize one of the resonance forms of the arenium ion in ortho and para substitution**



Transition state is stabilized. **Arenium ion is stabilized.**

Ortho Attack



Relatively stable contributor

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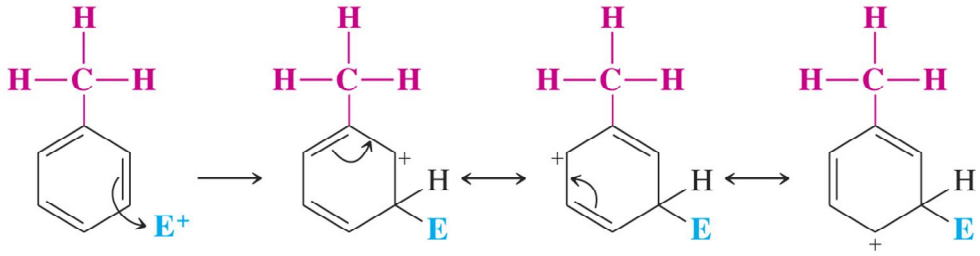
Meta Attack



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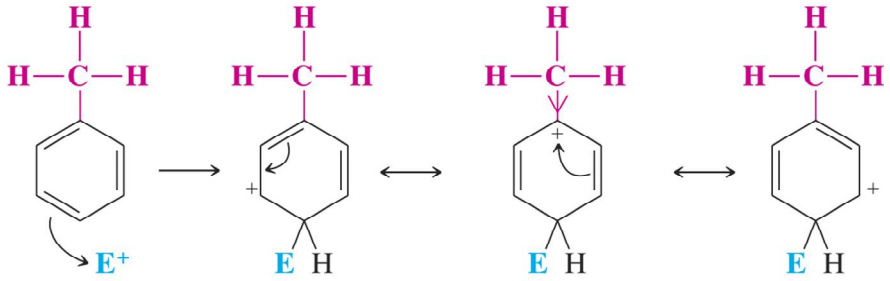
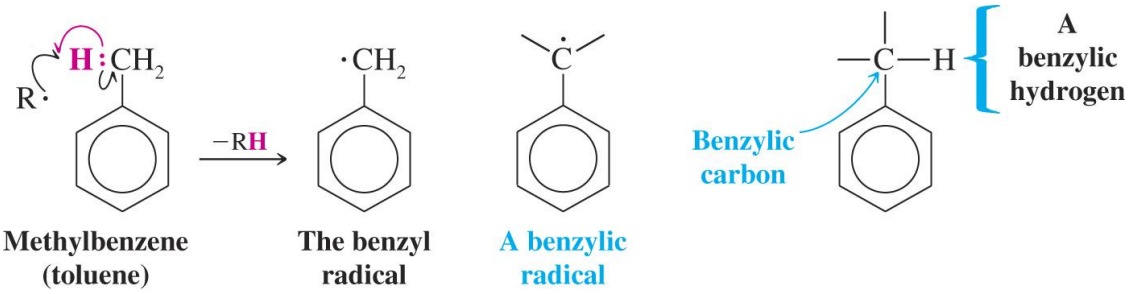


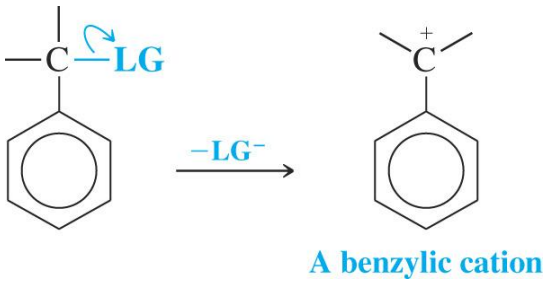
15.12) Reactions of the Side Chain of Alkylbenzenes:

l Benzylic Radicals and Cations:

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



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



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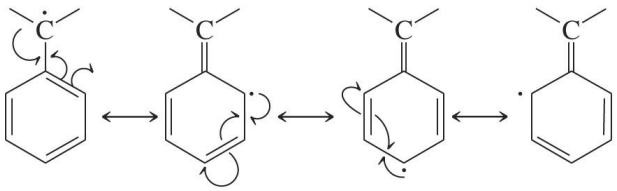
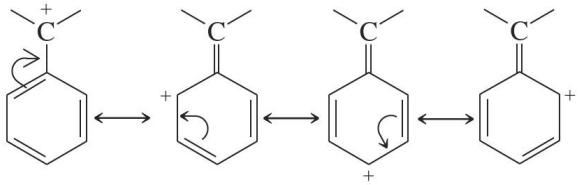
§**Benylic radicals and cations are stabilized by resonance delocalization of the radical and positive charge, respectively**



Benzylic radicals are stabilized by resonance.



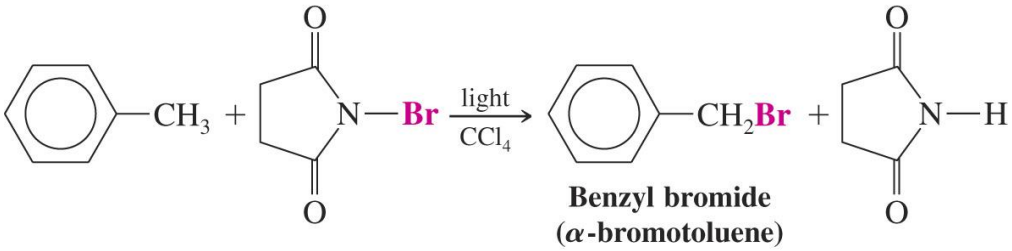
Benzylic cations are stabilized by resonance.

l 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**

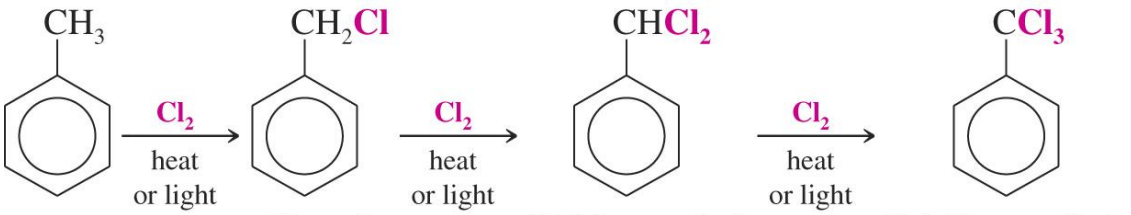
H **Recall *N*-bromosuccinamide produces a low concentration of bromine which favors radical reaction**



NBS

Benzyl bromide (α-bromotoluene) (64%)

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



Benzyl chloride

Dichloromethyl-benzene

Trichloromethyl-benzene

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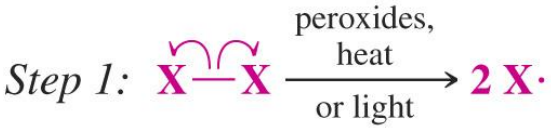
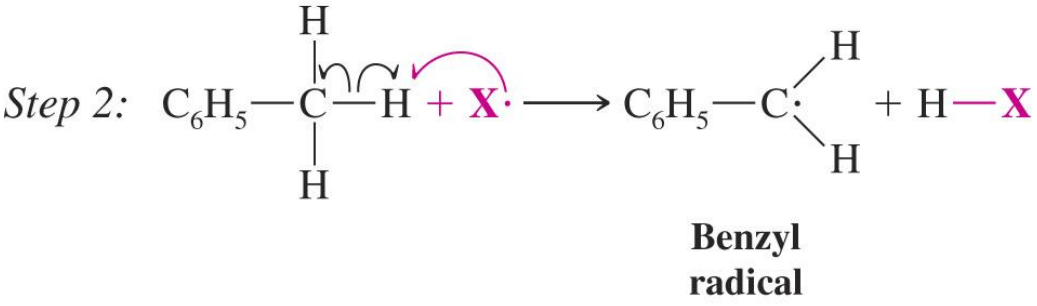
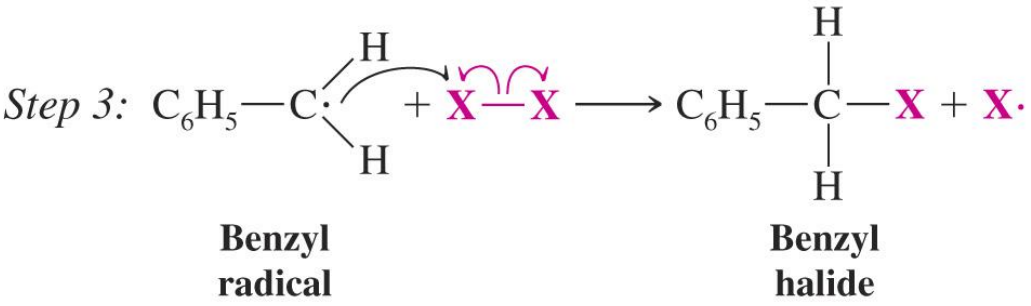
Chain Initiation



Chain Propagation

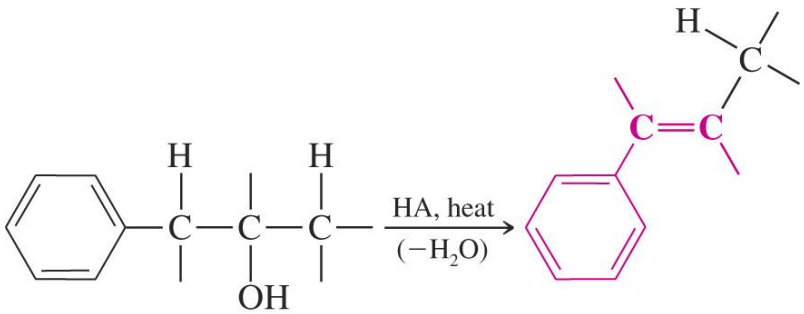




When ethylbenzene or propylbenzene react under radical conditions, halogenation occurs primarily at the benzylic position

15.13) Alkenylbenzenes:

- **Stability of Conjugated Alkenylbenzenes:**
  - **Conjugated alkenyl benzenes are more stable than nonconjugated alkenylbenzenes**



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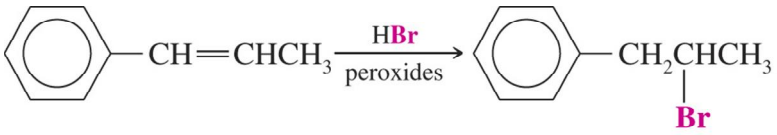
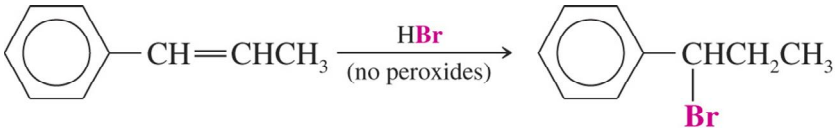
§**Additions proceed through the most stable benzylic radical or benzylic cation intermediates**



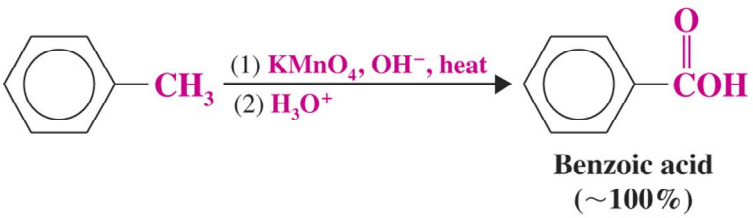
1-Phenylpropene **2-Bromo-1-phenylpropane**



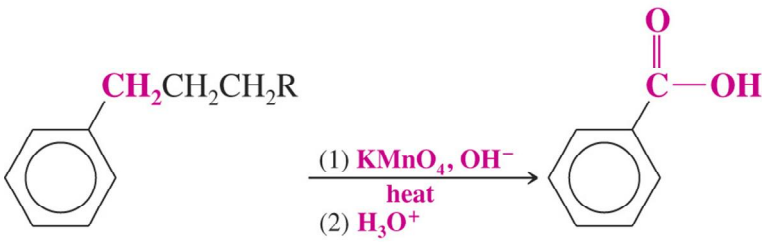
1-Phenylpropene **1-Bromo-1-phenylpropane**

l Oxidation of the Side Chain:

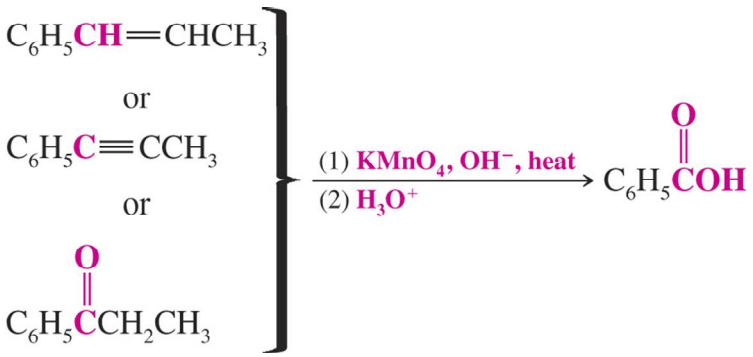
§**Alkyl and unsaturated side chains of aromatic rings can be oxidized to the carboxylic acid using hot $KMnO_4$.**



Benzoic acid (~100%)



An alkylbenzene **Benzoic acid**



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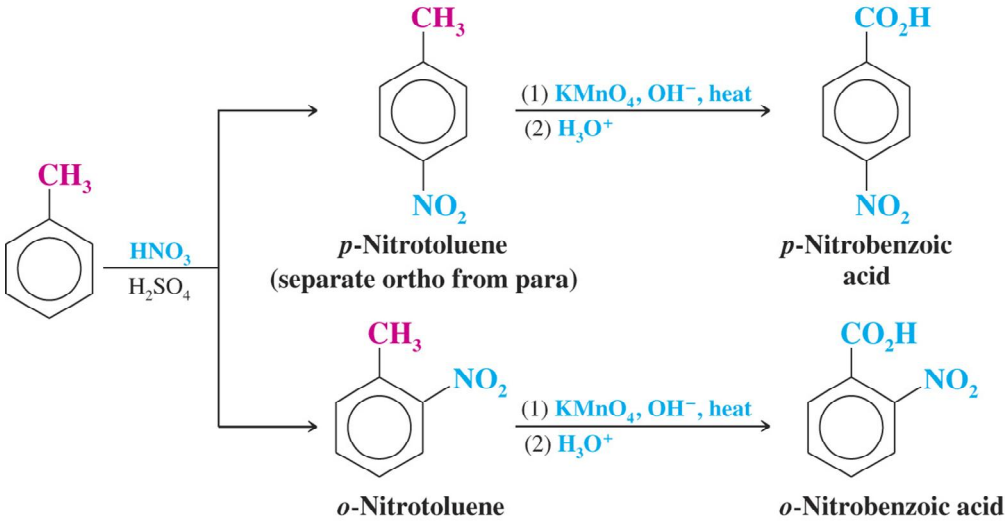
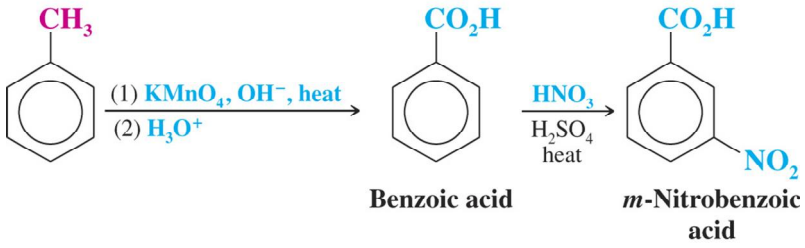
15.14) Synthetic Applications:

§ **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**





l 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**

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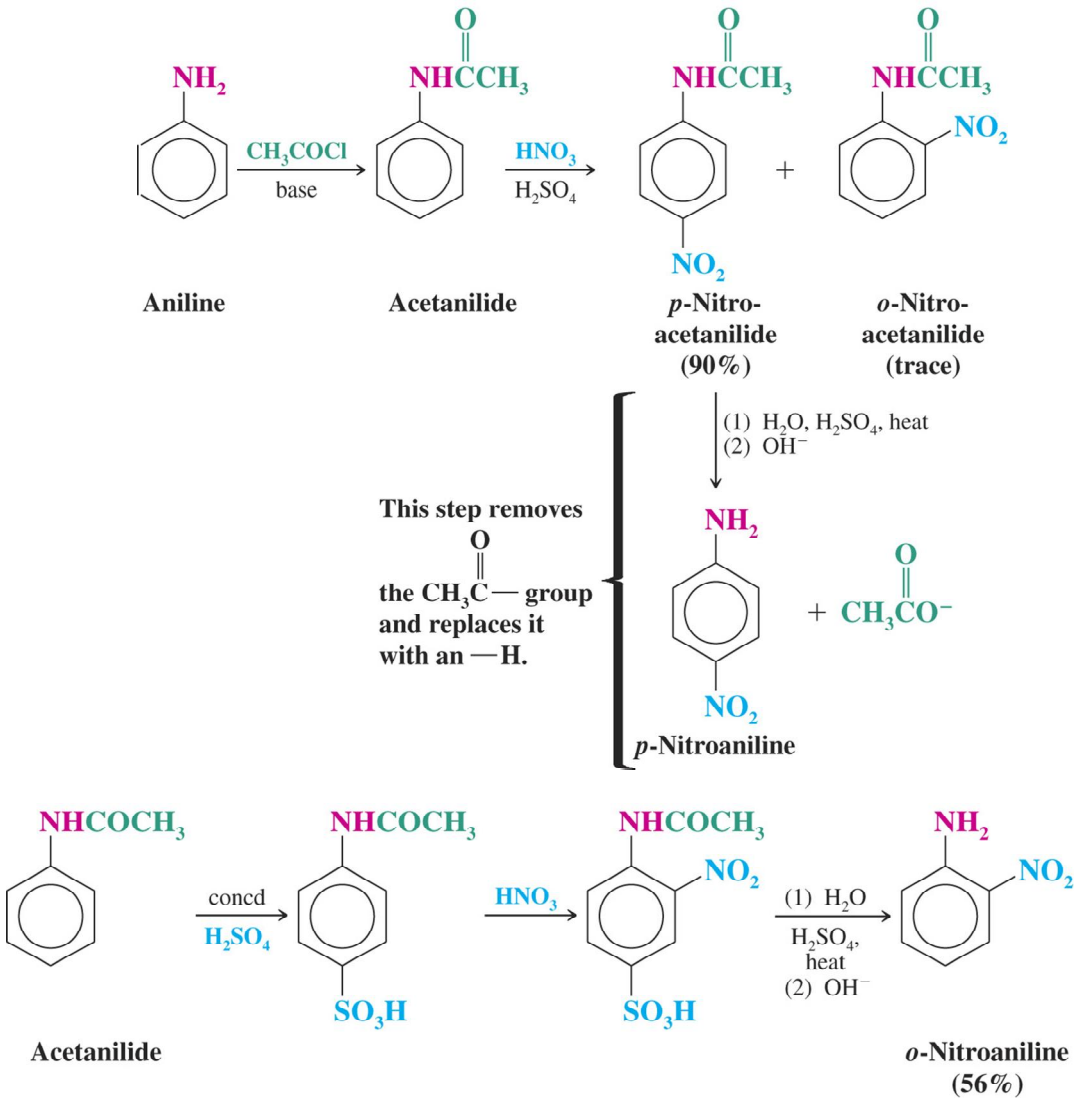
§**Example: The synthesis of *p*- and *o*-nitroaniline from aniline**

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



l 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.**

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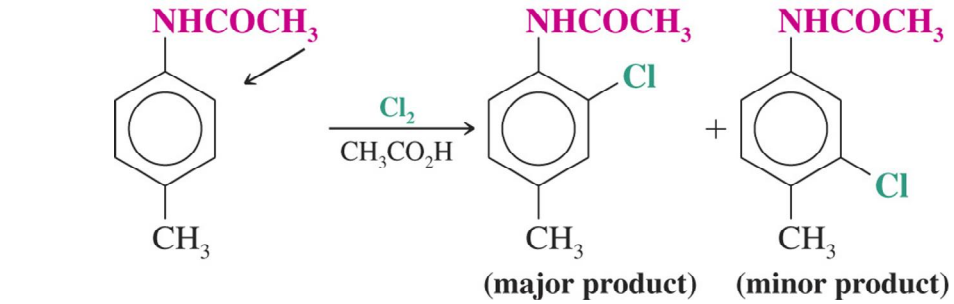
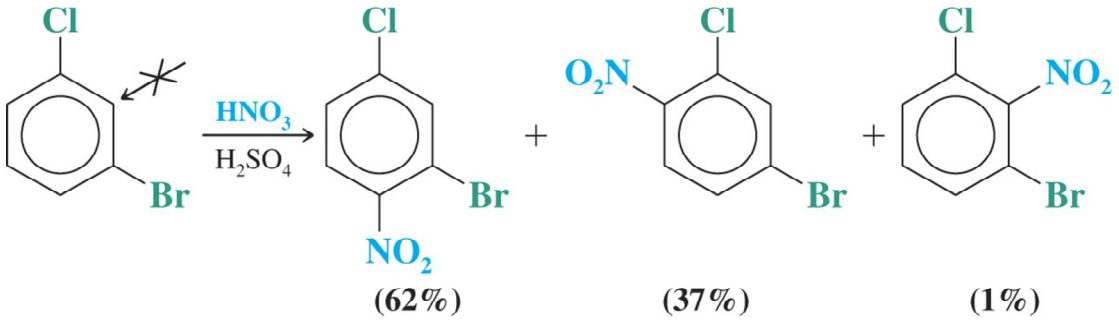
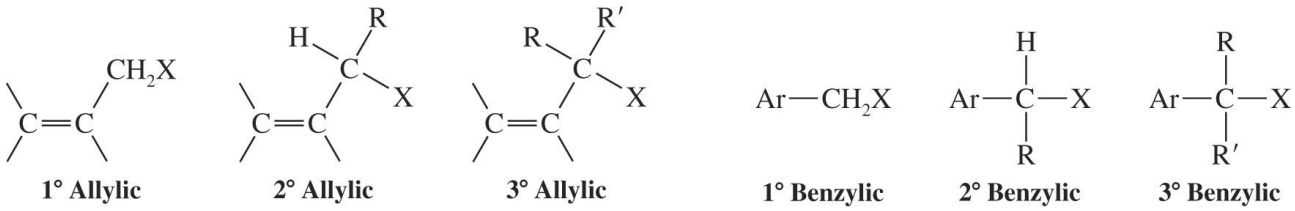
- **Ortho-para directors determine orientation over meta directors**
- **Substitution does not occur between meta substituents due to steric hindrance**





15.15) Allylic and Benzylic Halides in Nucleophilic Substitution Reactions:

Allylic and benzylic halides are classified in similar fashion to other halides



§**Both primary and secondary allylic and benzylic halides can undergo S_N1 or S_N2 reaction. (These primary halides are able to**

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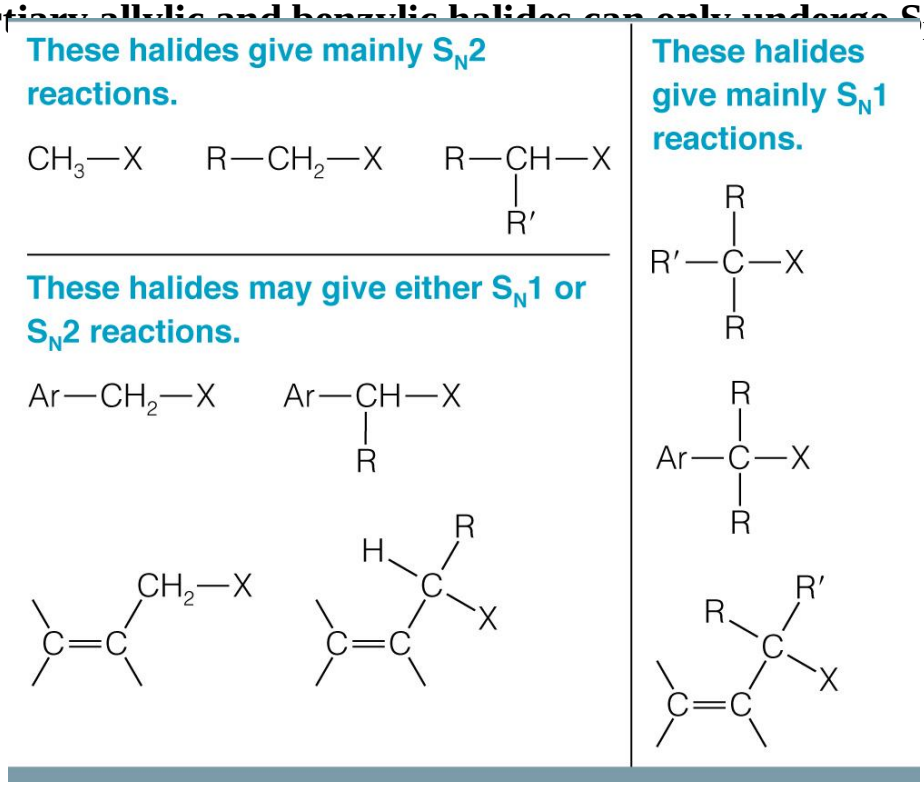
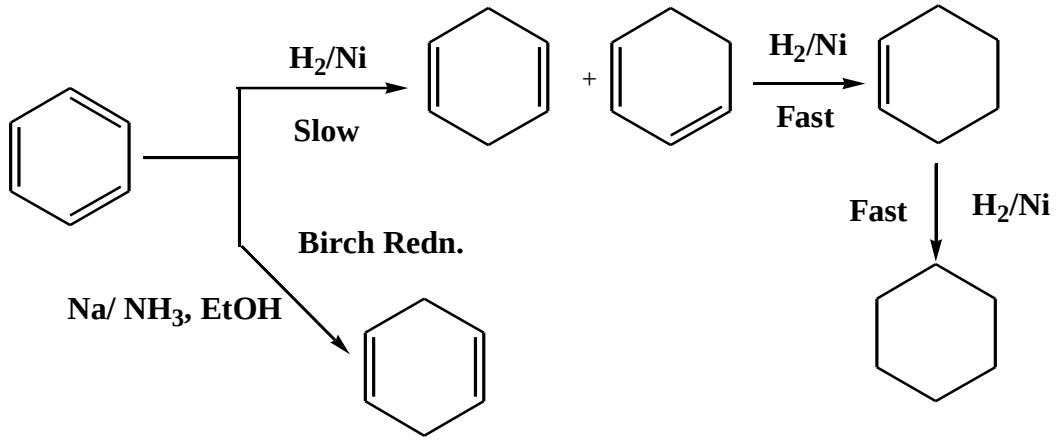
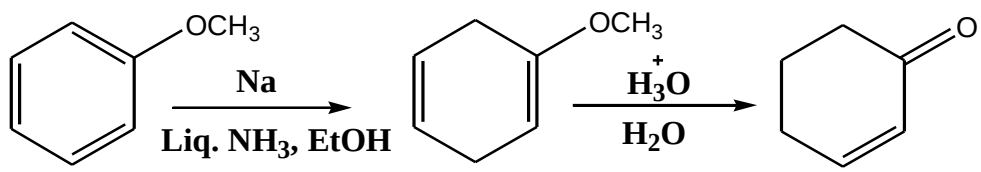
undergo S_N1 reaction because of the added stability of the allylic and benzylic carbocation)

§Tertiary allylic and benzylic halides can only undergo S_N1 rxn.



15.16) Reduction of Aromatic Compounds:





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