Chapter 16
Chemistry of Benzene: Electrophilic Aromatic Substitution

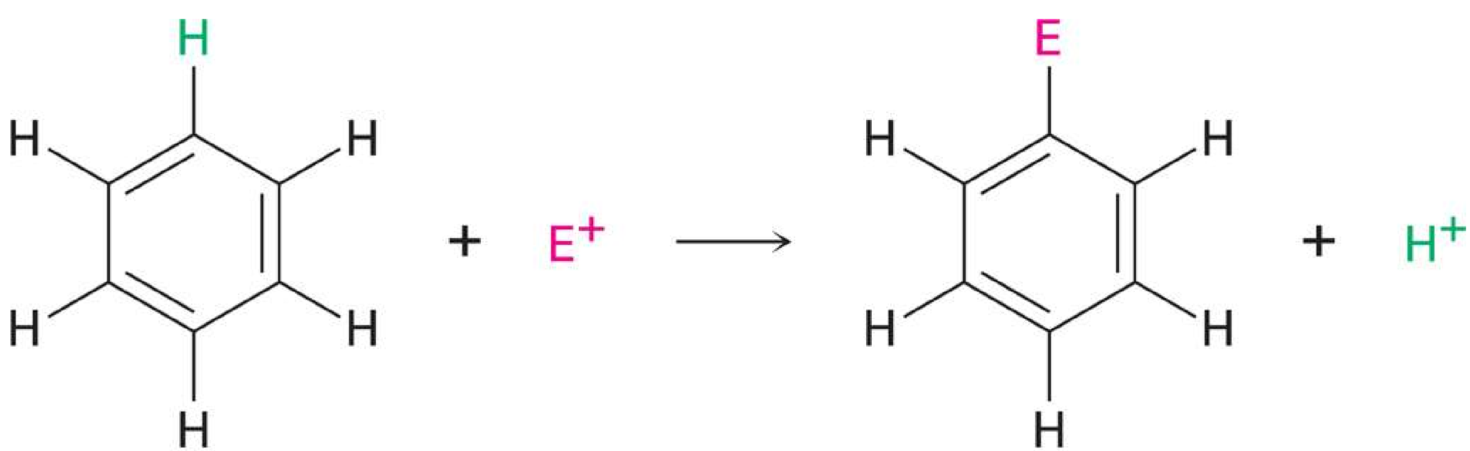
Aromatic Compounds: Hückel Rule

- States that a molecule can be aromatic only if:
  - It has a planar, monocyclic system of conjugation
  - It contains a total of $4n + 2$ π electrons
    - $n = 0,1,2,3\ldots$
- Antiaromatic if $4n$ π electrons are considered

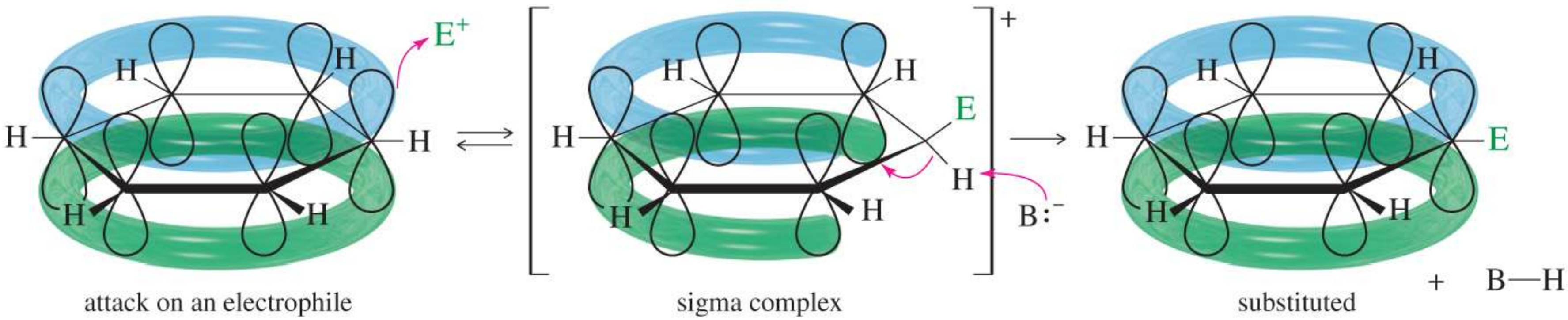
ELECTROPHILIC AROMATIC SUBSTITUTION

Electrophilic Aromatic Substitution

- Electrophilic aromatic substitution
  - Most common reaction of aromatic compounds
  - An electrophile substitutes for an hydrogen in an aromatic ring
  - Used to test for aromaticity



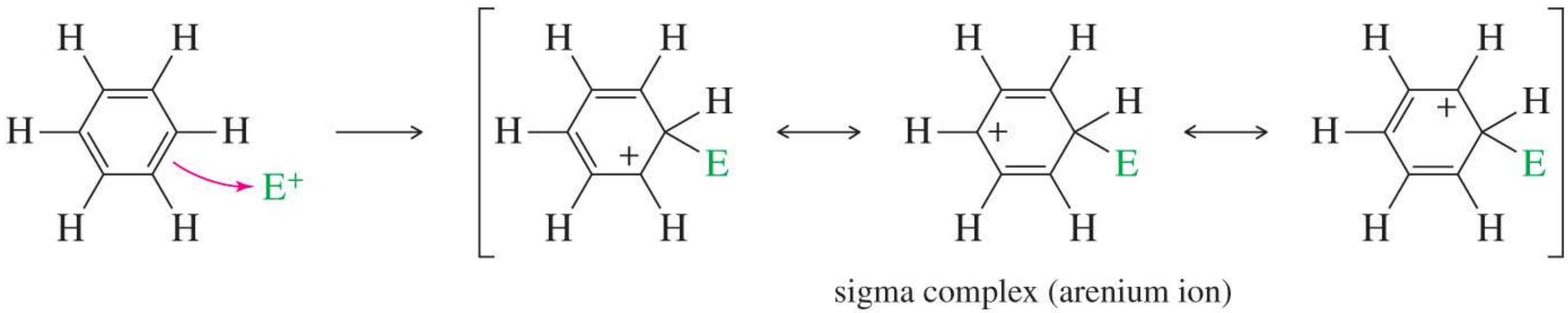
Electrophilic Aromatic Substitution



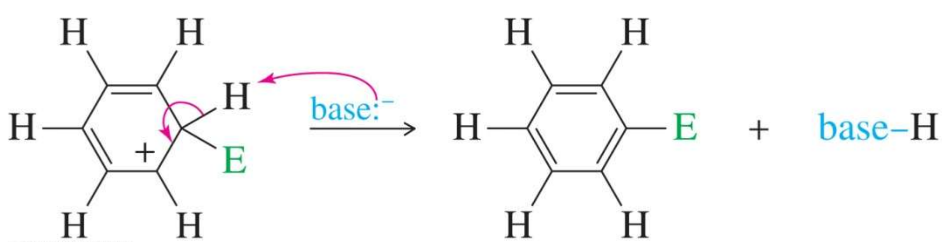
- benzene's pi electrons are available to attack a strong electrophile to give a carbocation
- Resonance-stabilized carbocation is called a ***sigma complex*** because the electrophile is joined to the benzene ring by a new sigma bond
- Aromaticity is regained by loss of a proton

Electrophilic Aromatic Substitution: Mechanism

Step 1: Attack on the electrophile forms the sigma complex.



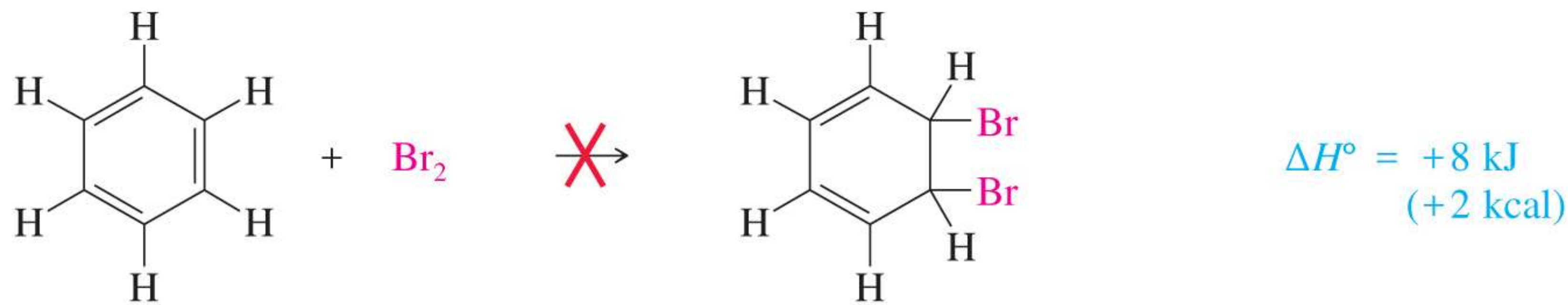
Step 2: Loss of a proton gives the substitution product.



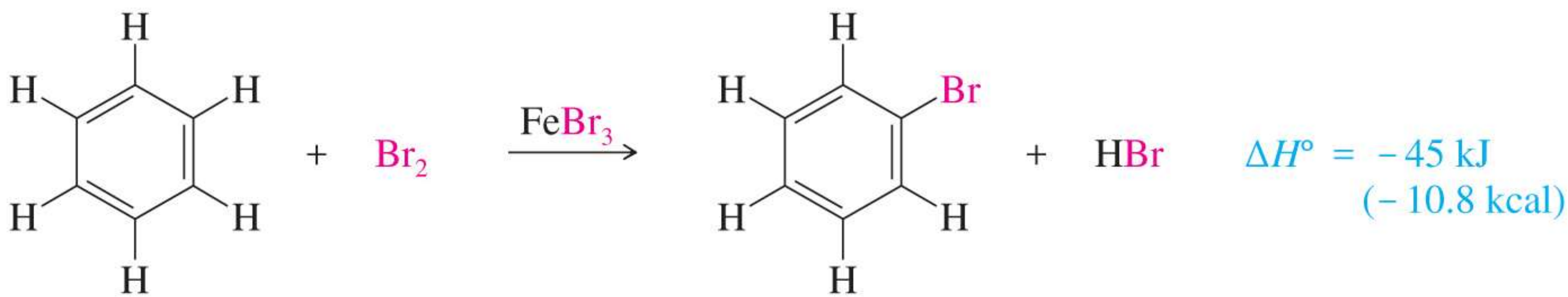
Electrophilic Aromatic Substitution: Halogenation

- Bromine, chlorine, iodine, and fluorine can produce aromatic substitution with the addition of other reagents to promote the reaction

Electrophilic Aromatic Substitution: Bromination

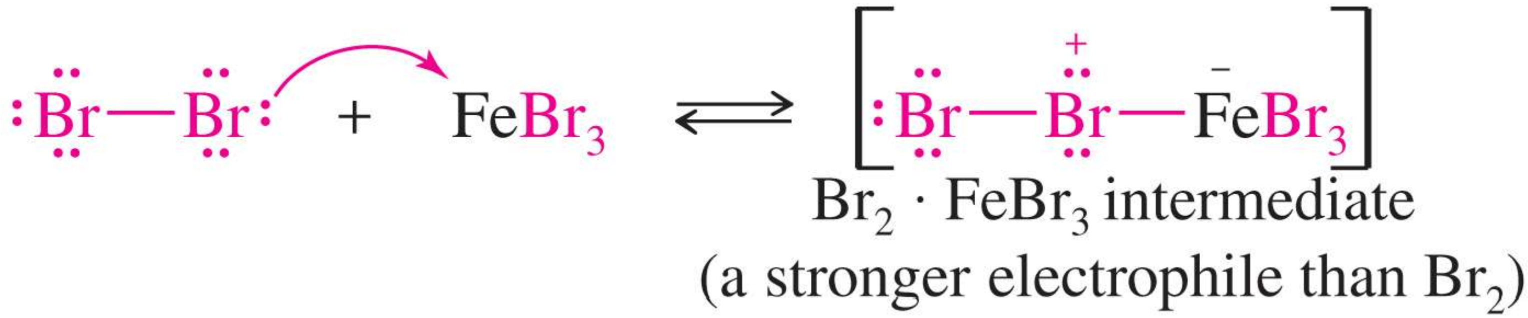


In the bromination of benzene a catalyst, such as $FeBr_3$, is used



bromobenzene
(80%)

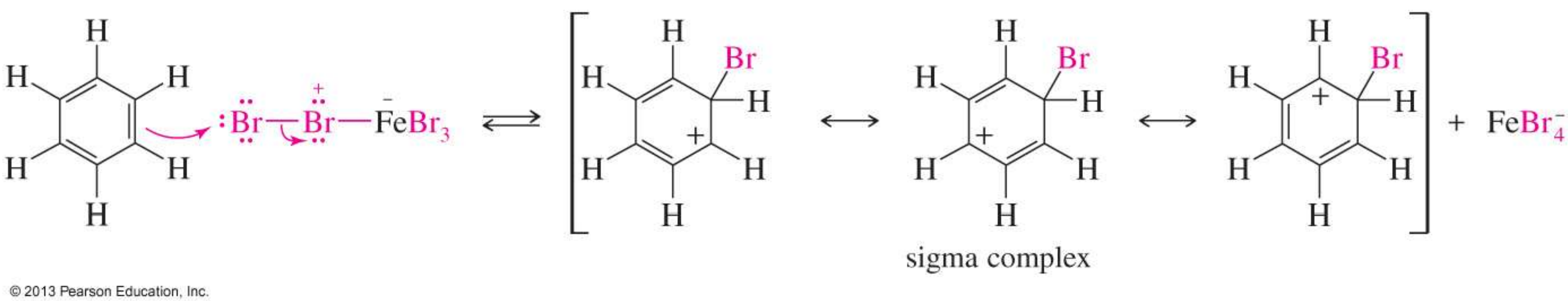
Electrophilic Aromatic Substitution: Bromination Preliminary Step



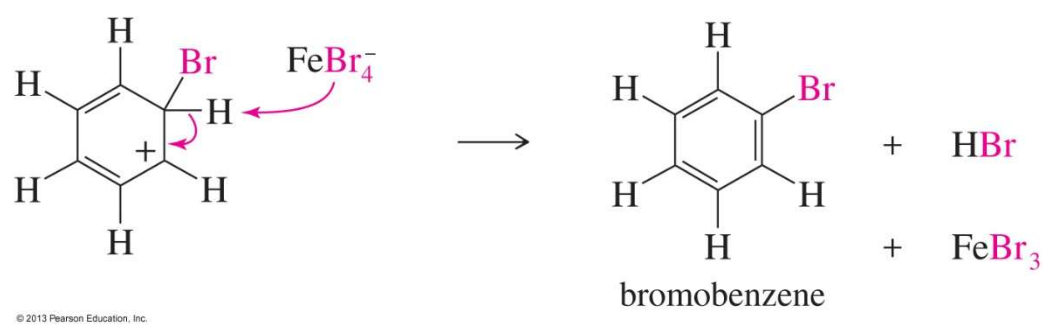
- Electrophile must be activated before electrophilic aromatic substitution can occur
- A strong Lewis acid catalyst, such as $FeBr_3$, should be used

Electrophilic Aromatic Substitution: Bromination Mechanism

Step 1: Electrophilic attack and formation of the sigma complex.



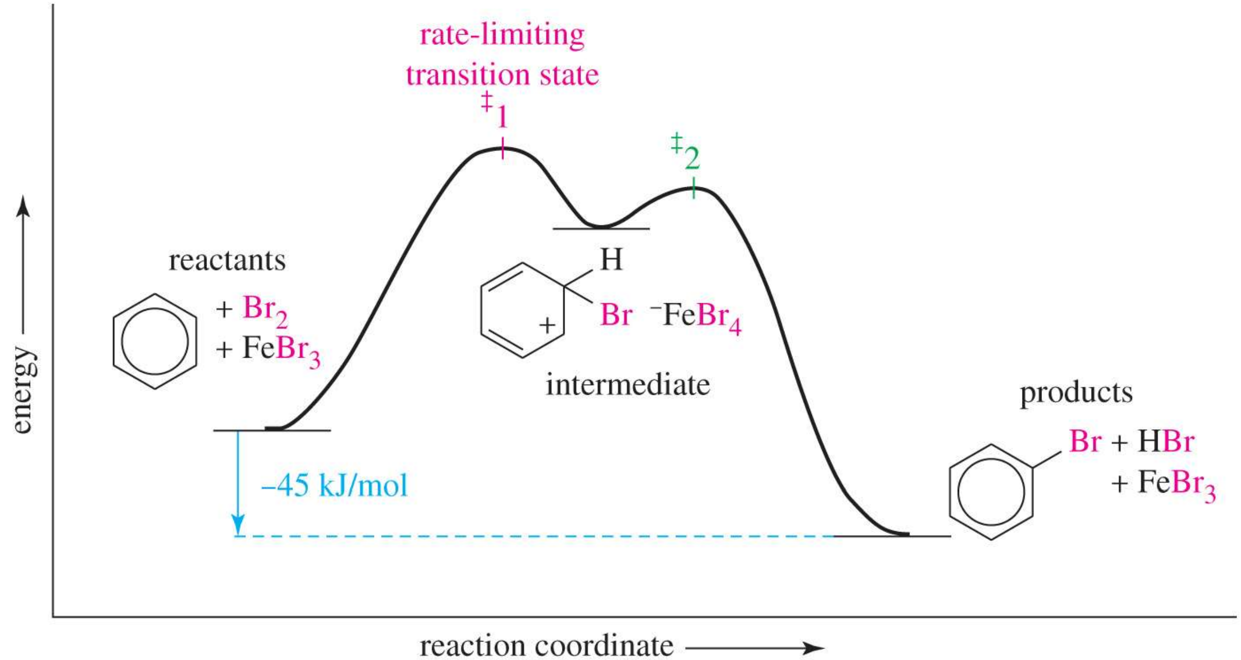
Step 2: Loss of a proton to give the products.



REMEMBER

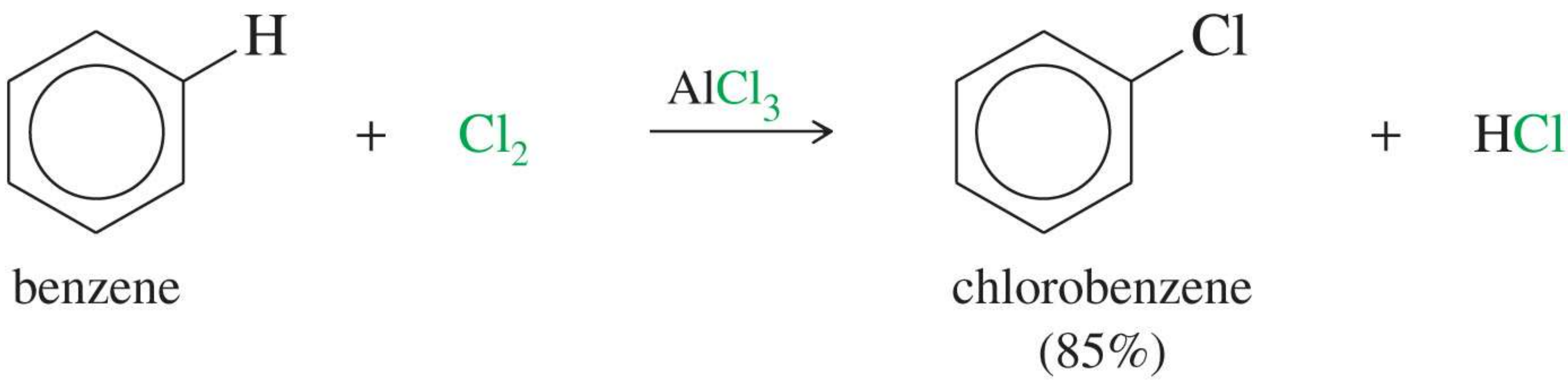
Note that the three resonance forms of the sigma complex show the positive charge on the three carbon atoms ortho and para to the site of substitution.

Electrophilic Aromatic Substitution: Bromination



- Stability of the intermediate in electrophilic aromatic substitution is lesser than that of the starting benzene ring
  - ***Reaction of an electrophile is endergonic, possesses substantial activation energy, and comparatively slow***

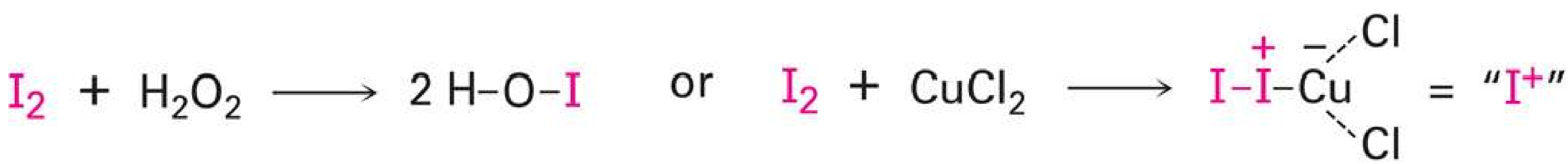
Electrophilic Aromatic Substitution: Chlorination

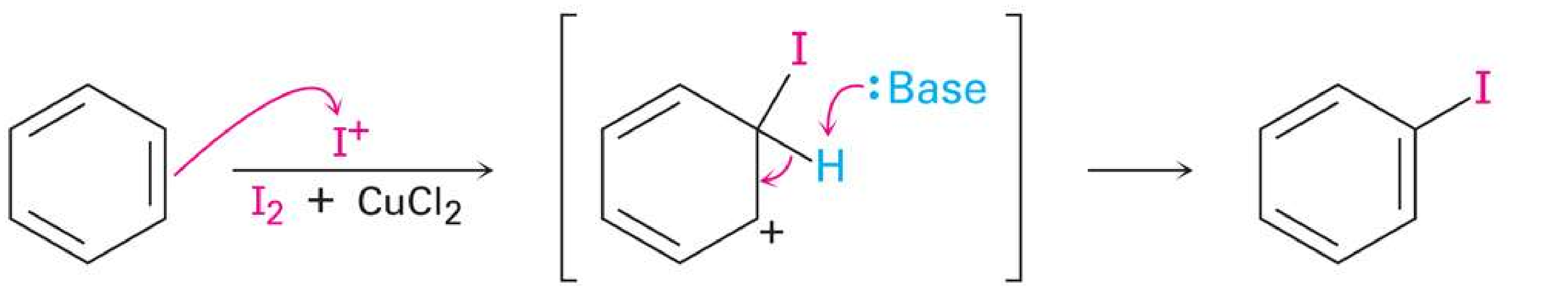


- Chlorination is similar to bromination
- Catalyst that can be used
  - $AlCl_3$ is most often used
  - $FeCl_3$ is used often
- Reaction used in numerous pharmaceutical agents

Electrophilic Aromatic Substitution: Iodination

- Iodination requires an acidic oxidizing agent to produce iodide cation
  - Nitric acid, to produce iodide cation.



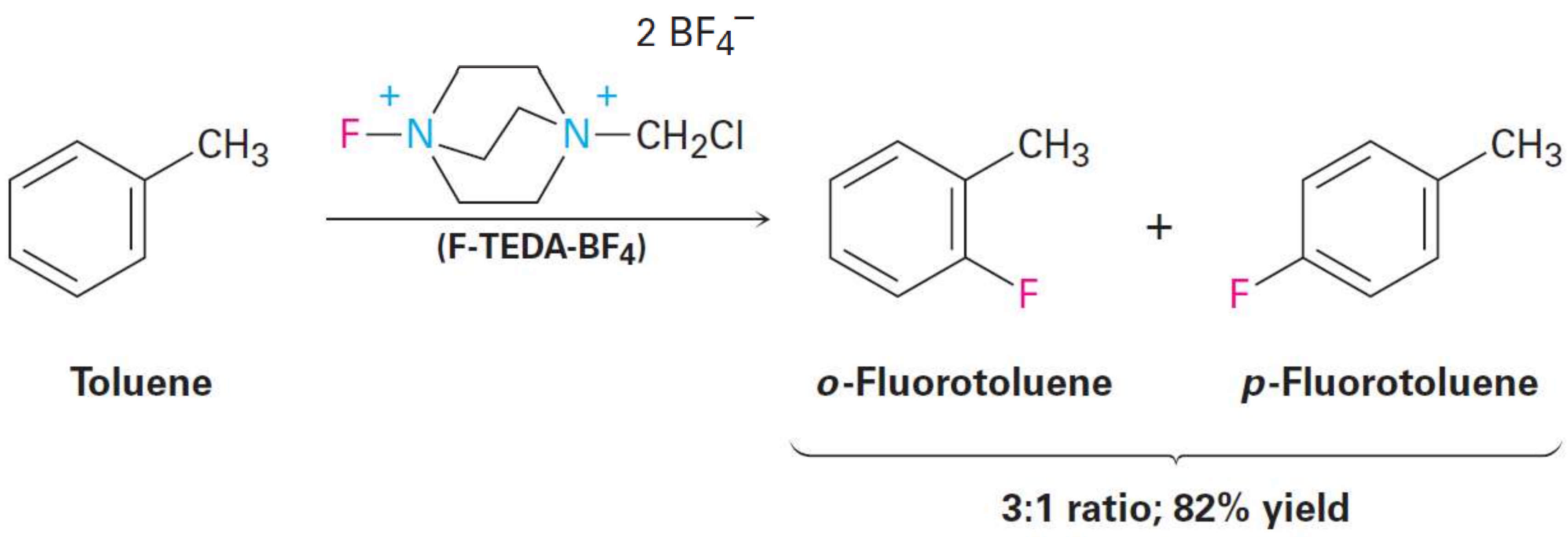


Benzene

Iodobenzene (65%)

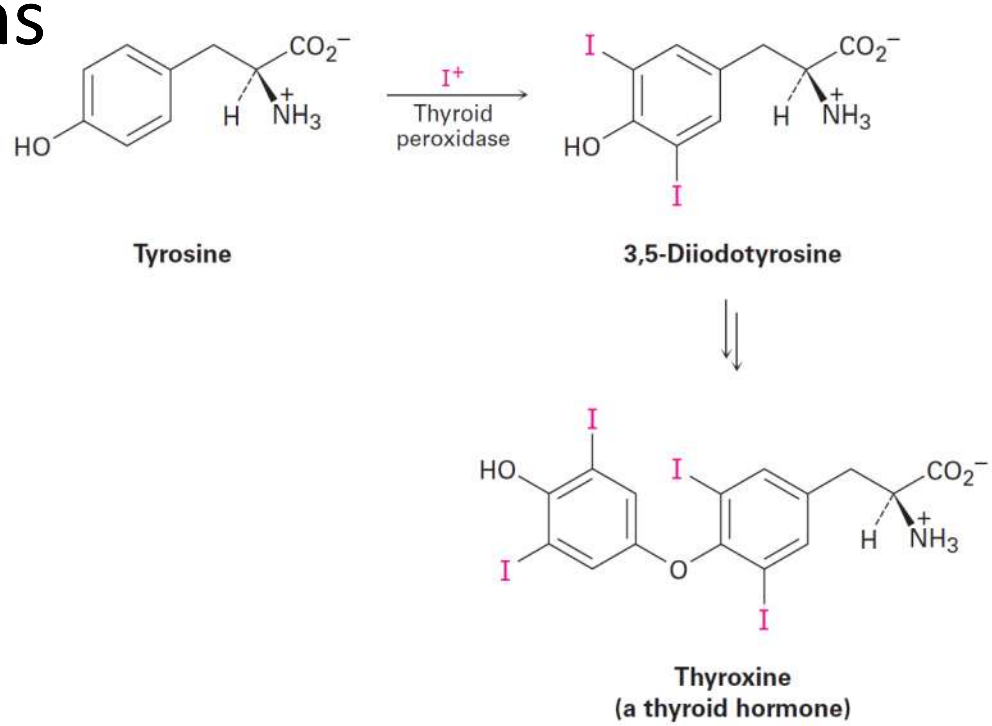
Electrophilic Aromatic Substitution: Fluorination

- Fluorination requires F^+ bonded to TEDA-BF_4 with a coordinate covalent bond



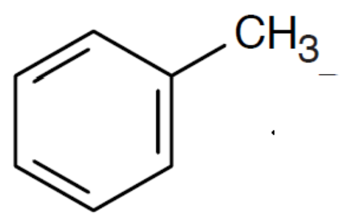
Electrophilic Aromatic Substitution: Natural Halogenations

- Widely found in marine organisms
- Occurs in the biosynthesis of thyroxine in humans

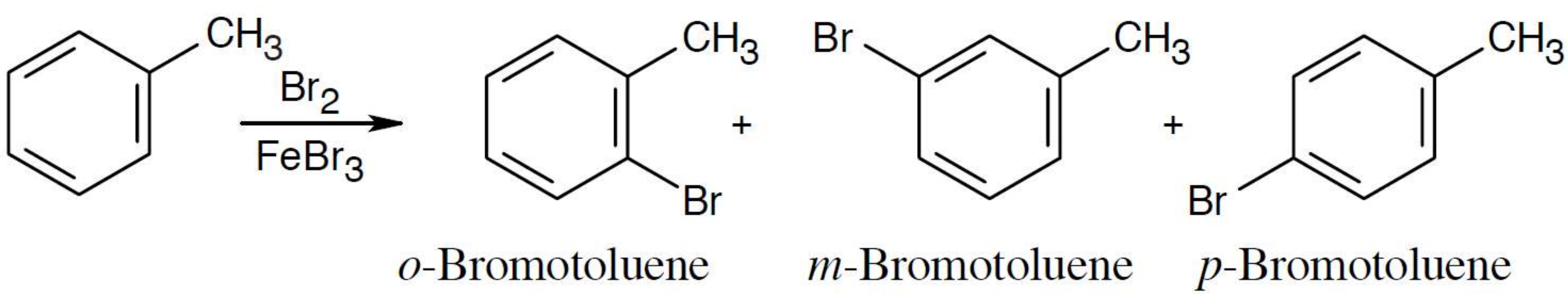


Worked Example

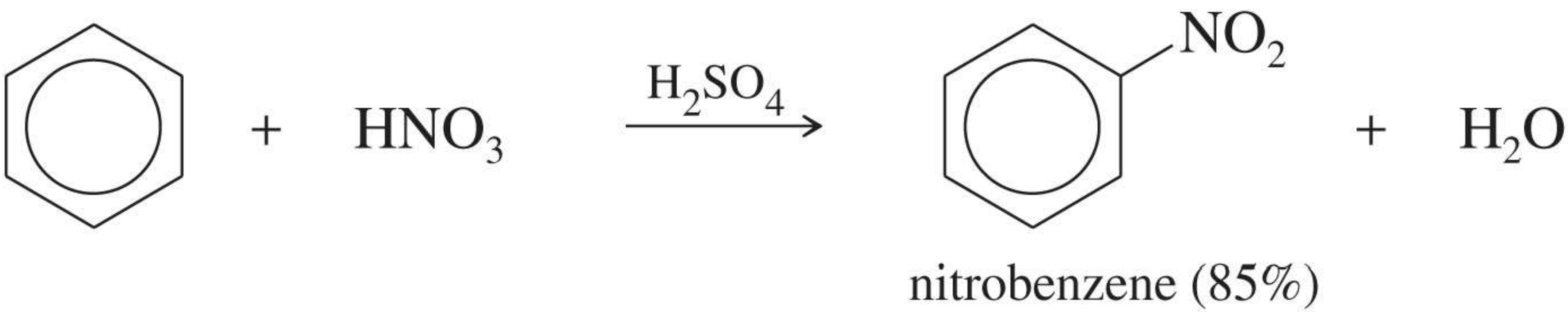
- Monobromination of toluene gives a mixture of three bromotoluene products
  - Draw and name them



- Solution:

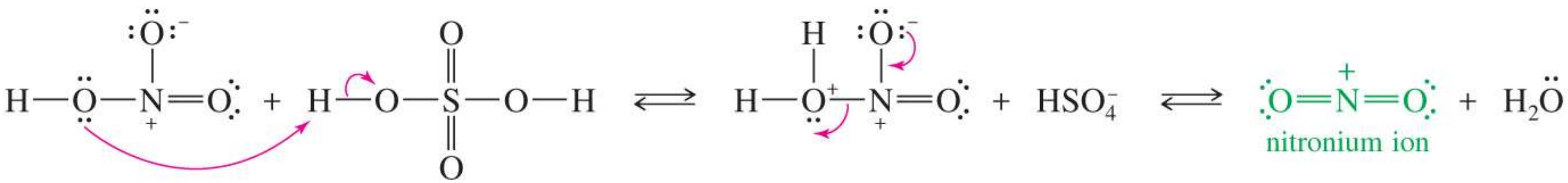


Electrophilic Aromatic Substitution: Nitration



- Sulfuric acid acts as a catalyst, allowing the reaction to be faster and at lower temperatures.
- HNO_3 and H_2SO_4 react together to form the electrophile of the reaction: nitronium ion (NO_2^+).

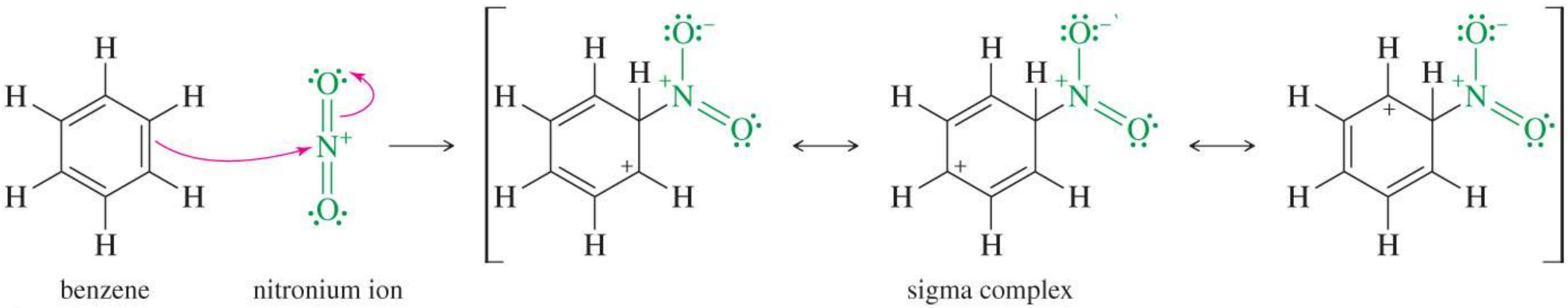
Electrophilic Aromatic Substitution: Preliminary Step of Nitration



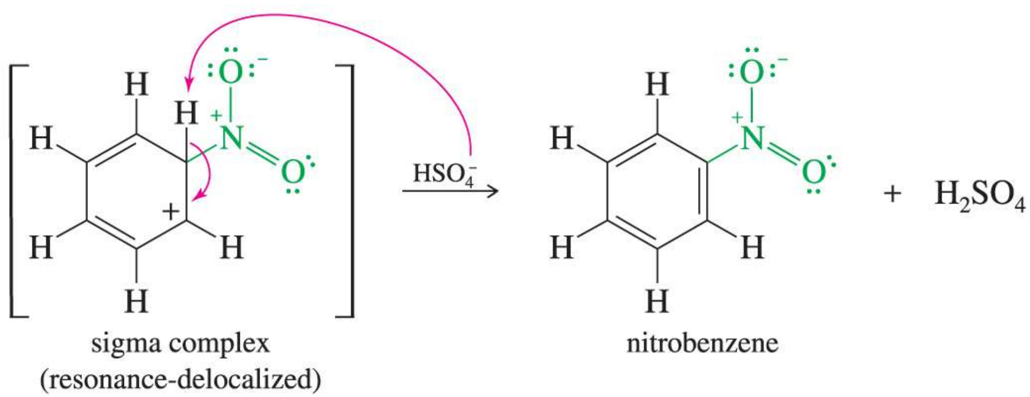
- Preliminary step is formation of the nitronium ion

Electrophilic Aromatic Substitution: Nitration Mechanism

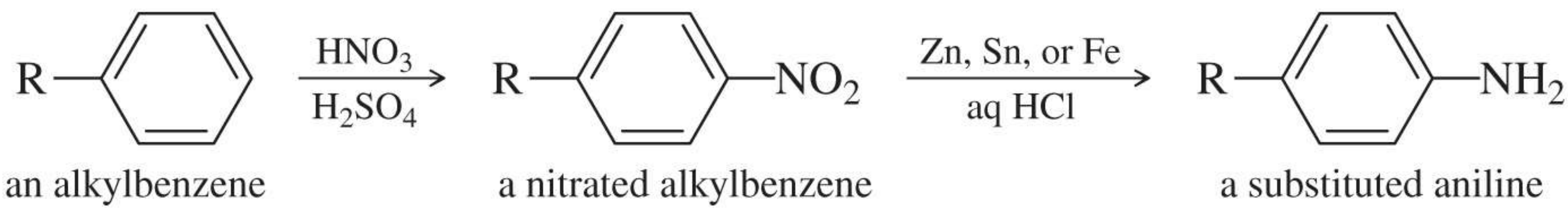
Step 1: Formation of the sigma complex.



Step 2: Loss of a proton gives nitrobenzene.

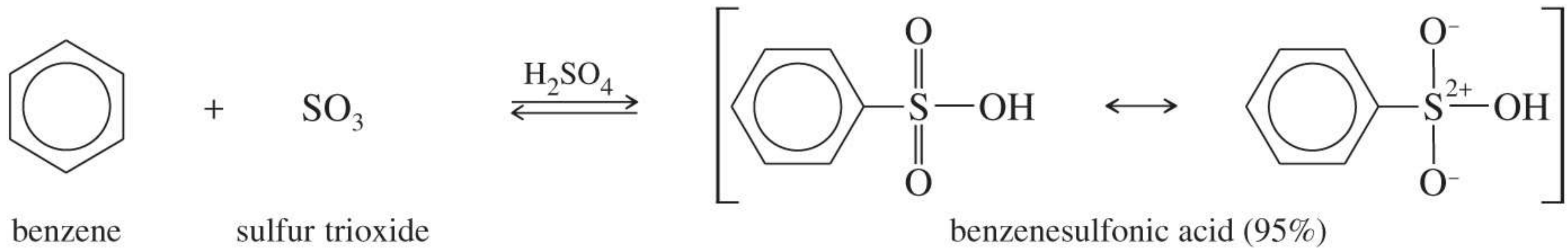


Electrophilic Aromatic Substitution: Reduction of the Nitro Group



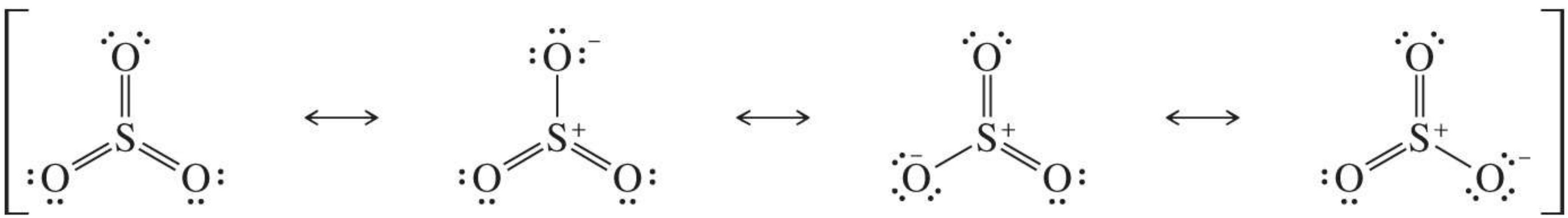
- Reduce the nitro to an amino group
  - Treat with zinc, tin, or iron in dilute acid
- Best method for adding an amino group to a aromatic ring

Electrophilic Aromatic Substitution: Sulfonation



- Sulfur trioxide (SO_3) is the electrophile in the reaction.
- A 7% mixture of SO_3 and H_2SO_4 is commonly referred to as "fuming sulfuric acid."
- The —SO_3H group is called a *sulfonic acid*.

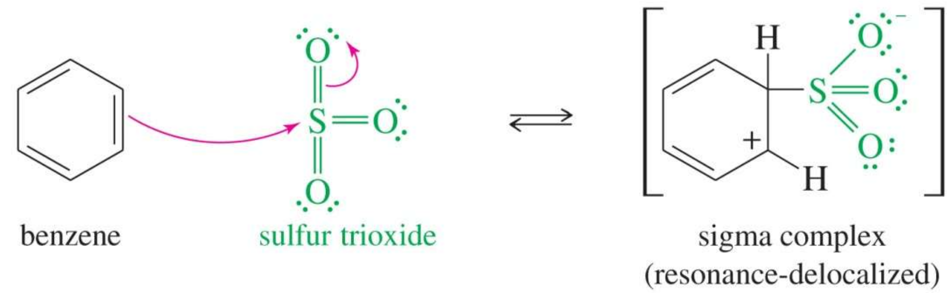
Electrophilic Aromatic Substitution: Sulfonation

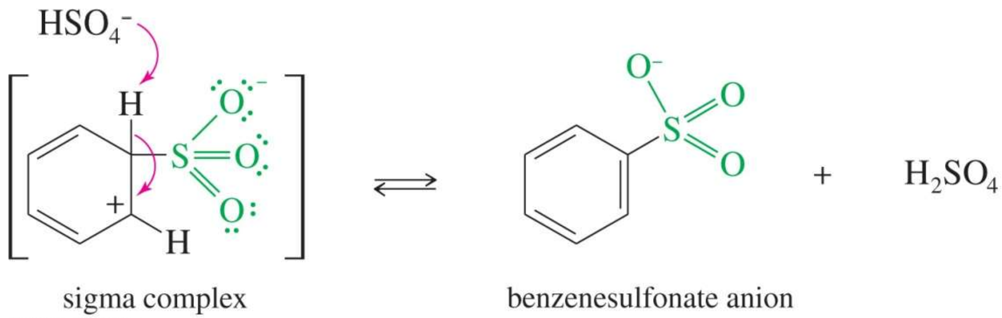


sulfur trioxide, a powerful electrophile

- Sulfur trioxide
  - Strong electrophile
  - In resonance with three sulfonyl bonds
    - Draws electron density away from the sulfur atom

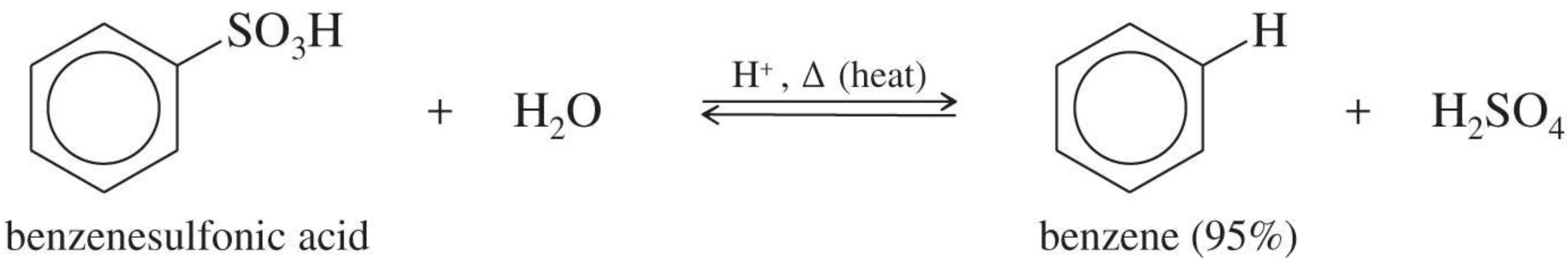
Electrophilic Aromatic Substitution: Sulfonation Mechanism





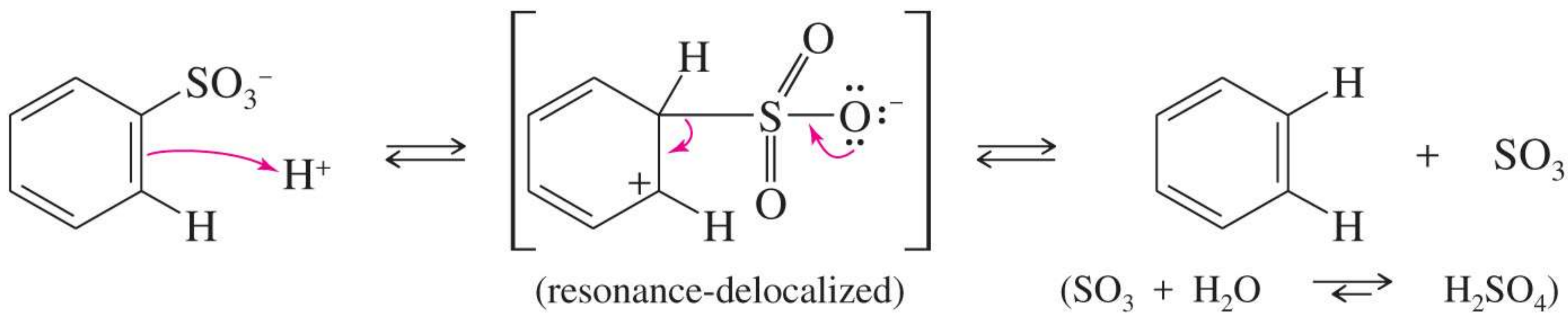
- Benzene attacks sulfur trioxide, forming a sigma complex
- Loss of a proton on the tetrahedral carbon and reprotonation of oxygen gives benzenesulfonic acid

Electrophilic Aromatic Substitution: Desulfonation



- Sulfonation is reversible
- Sulfonic acid group is removed from an aromatic ring by heating in dilute sulfuric acid

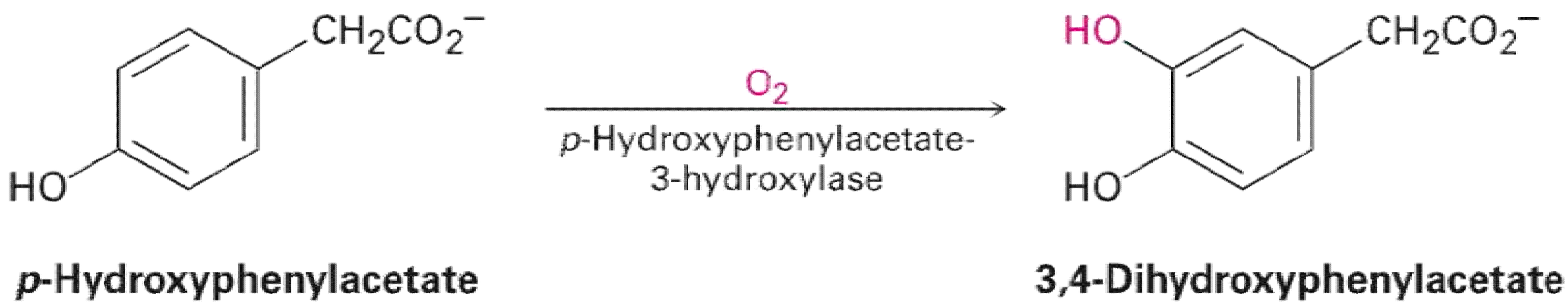
Electrophilic Aromatic Substitution: Desulfonation Mechanism



- Desulfonation reaction
  - A proton adds to the ring (the electrophile)
  - Loss of sulfur trioxide gives back benzene

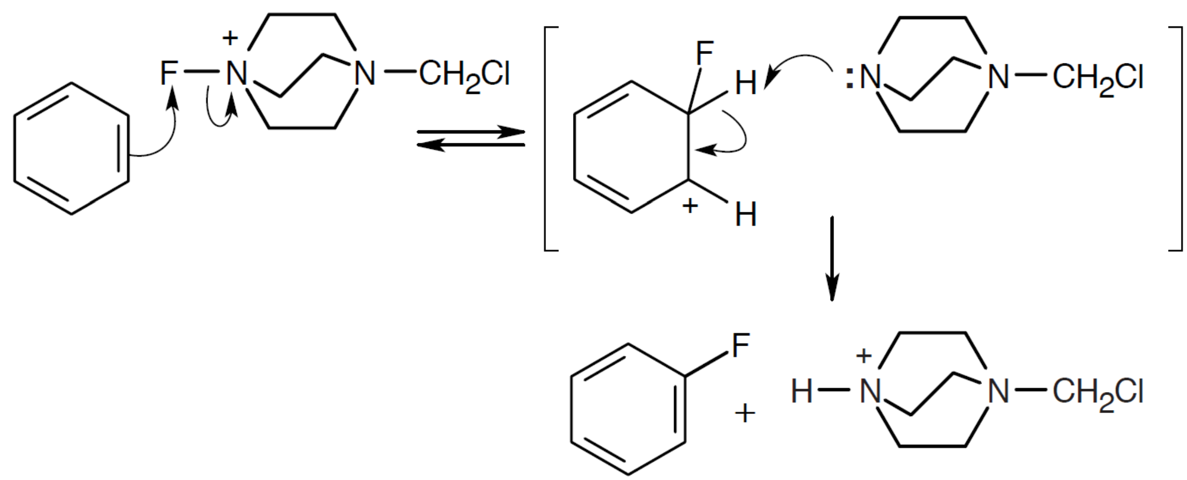
Electrophilic Aromatic Substitution: Hydroxylation

- Direct hydroxylation of an aromatic ring is difficult in the laboratory
- Usually occurs in biological pathways



Worked Example

- Propose a mechanism for the electrophilic fluorination of benzene with F-TEDA-BF_4
- Solution:

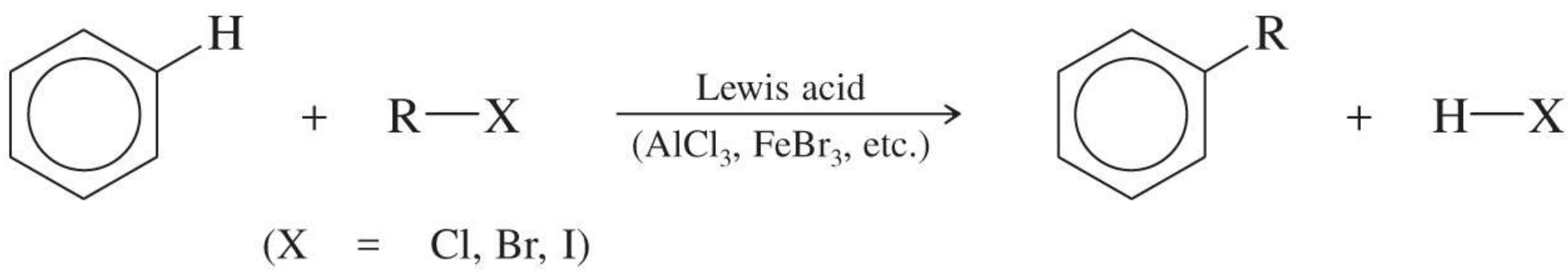


  – The pi electrons of benzene attack the fluorine of F-TEDA-BF_4
    - The nonaromatic intermediate loses –H to give the fluorinated product

ALKYLATION AND ACYLATION OF AROMATIC RINGS

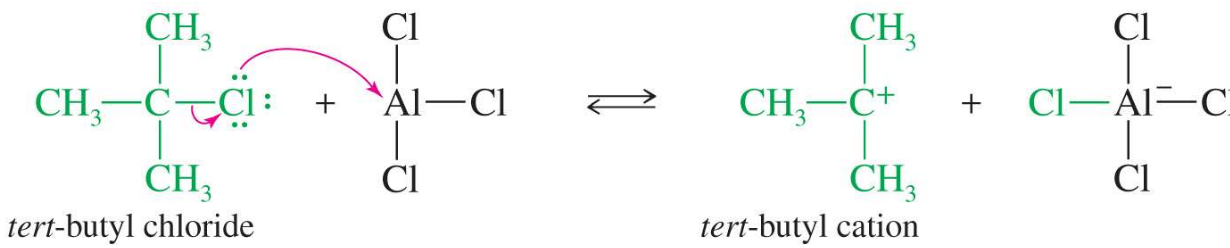
Alkylation of Aromatic Rings: Friedel-Crafts Reaction

- **Alkylation**: Introducing an alkyl group onto the benzene ring
  - Also called the **Friedel-Crafts reaction**
  - Aromatic compound is treated with an alkyl chloride and a Lewis acid
    - Alkyl halide reacts with a Lewis acid and produces a carbocation which is the electrophile

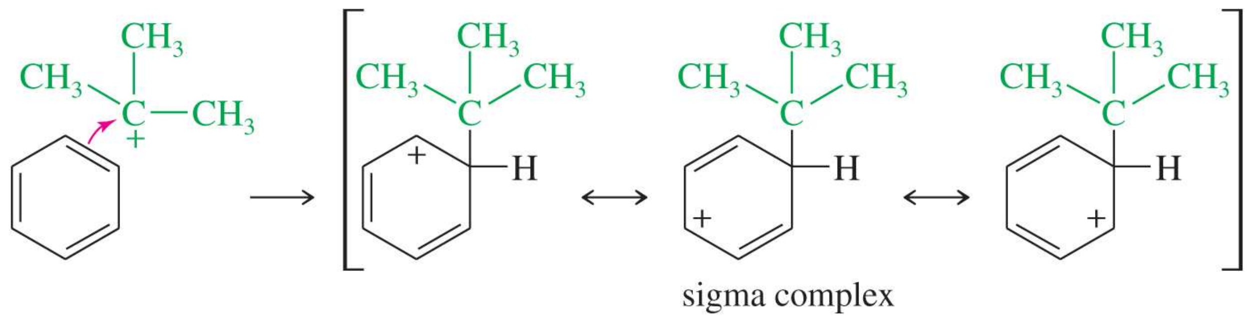


Alkylation of Aromatic Rings: Friedel-Crafts Reaction Mechanism

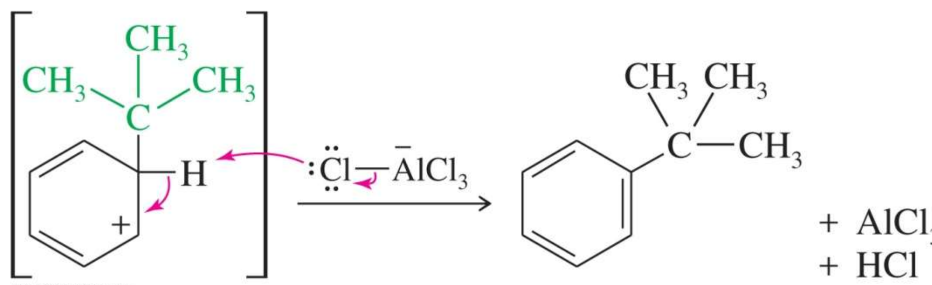
Step 1



Step 2

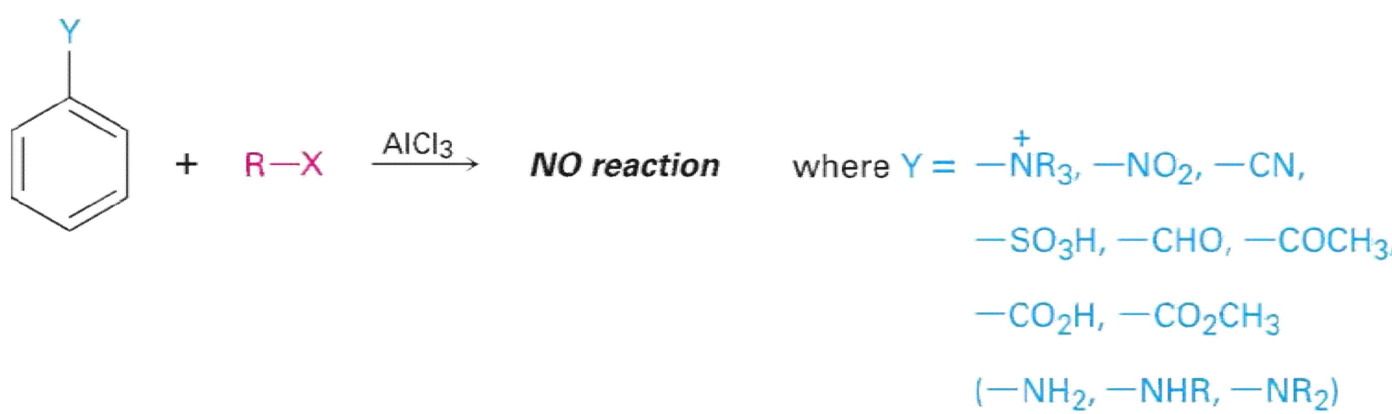


Step 3



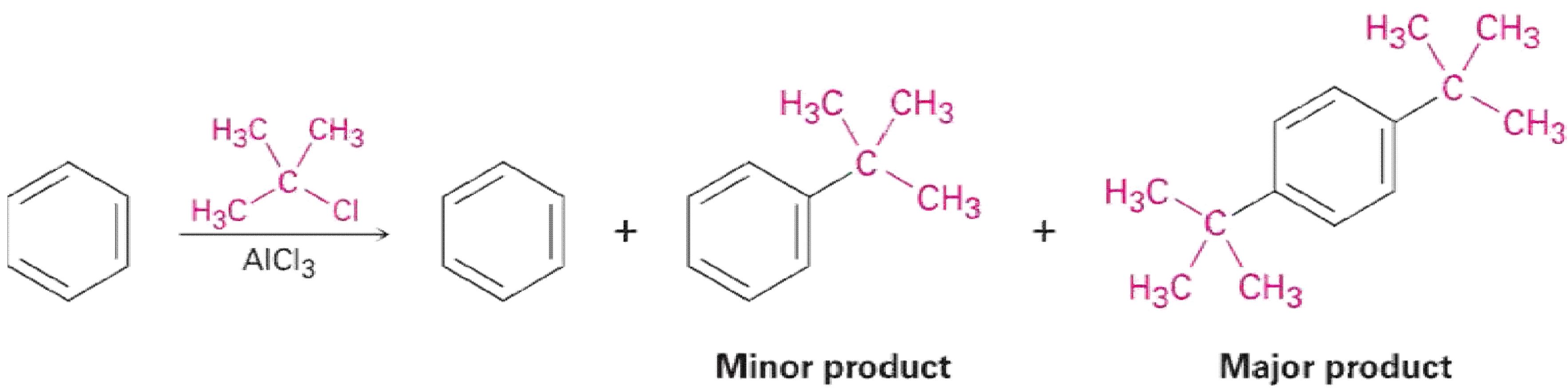
Alkylation of Aromatic Rings: Friedel-Crafts Reaction Limitations

1. Only alkyl halides can be used (F, Cl, I, Br)
   – High energy levels of aromatic and vinylic halides are not suitable to Friedel-Crafts requirements
2. Not feasible on rings containing an amino group substituent or a strong electron-withdrawing group



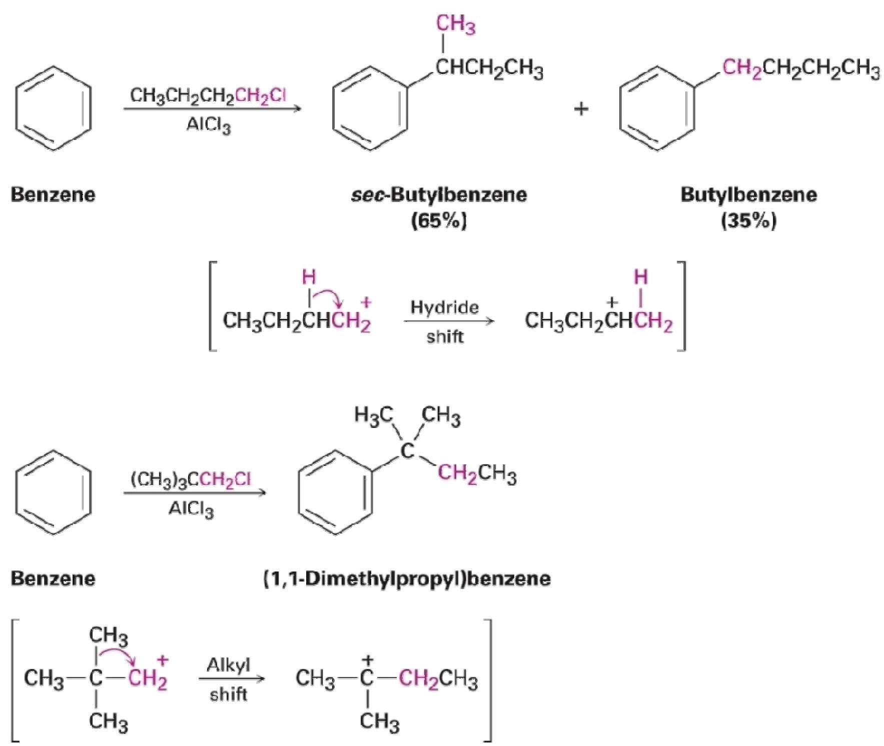
Alkylation of Aromatic Rings: Friedel-Crafts Reaction Limitations

3. Termination of the reaction allowing a single substitution is difficult
   - Polyalkylation occurs



Alkylation of Aromatic Rings: Friedel-Crafts Reaction Limitations

4. Occasional skeletal rearrangement of the alkyl carbocation electrophile
   - Occurs more often with the use of a primary alkyl halide

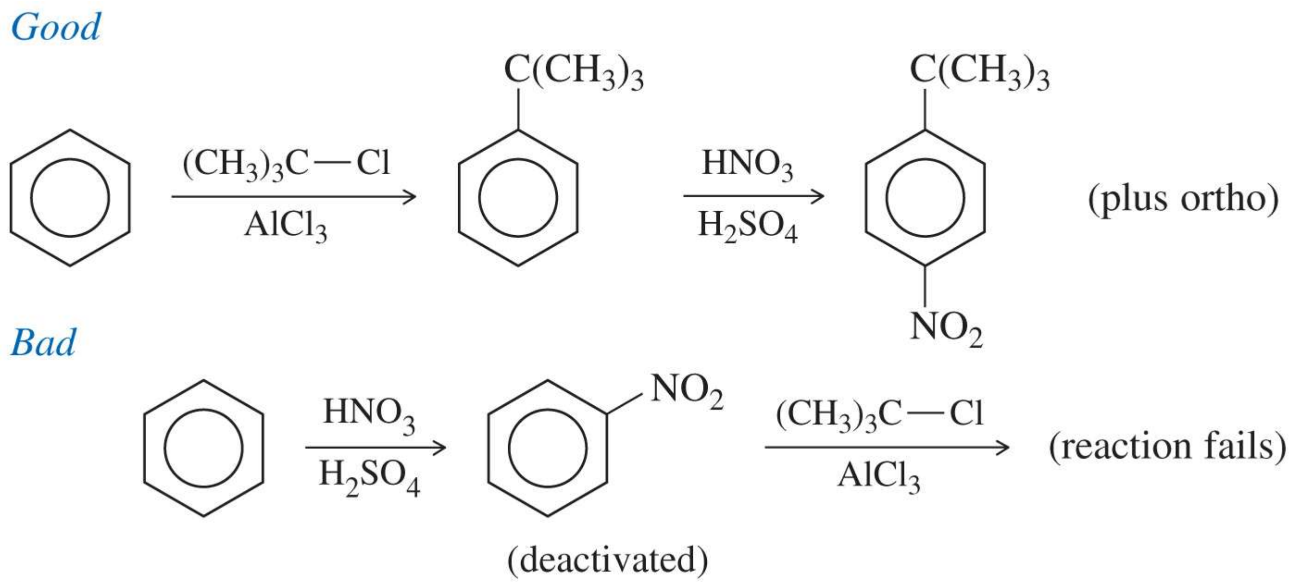


Solved Problem 2

Devise a synthesis of *p*-nitro-*t*-butylbenzene from benzene.

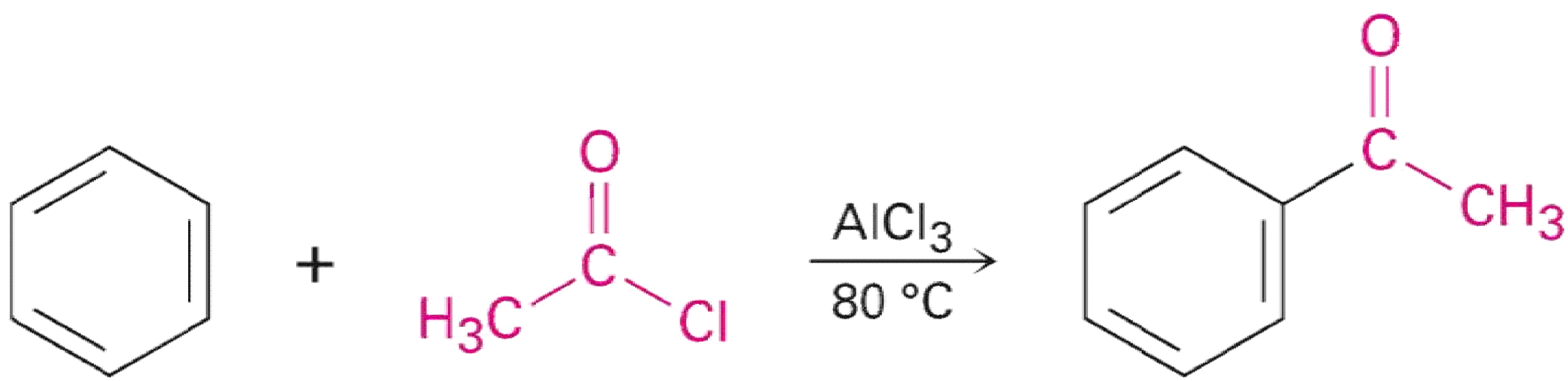
Solution

To make *p*-nitro-*t*-butylbenzene, we would first use a Friedel–Crafts reaction to make *t*-butylbenzene. Nitration gives the correct product. If we were to make nitrobenzene first, the Friedel–Crafts reaction to add the *t*-butyl group would fail.



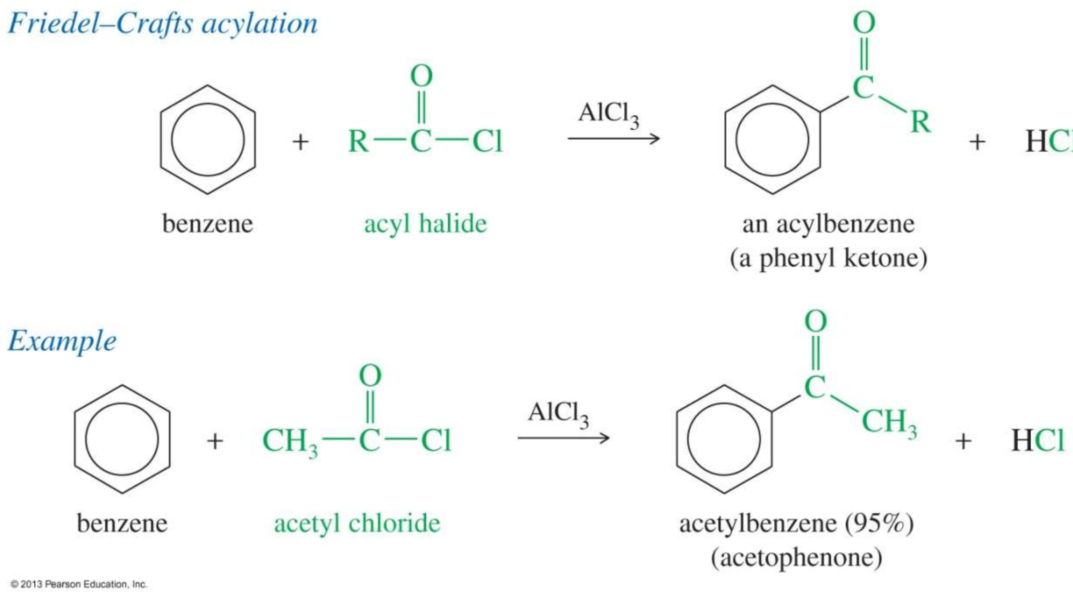
Acylation of Aromatic Rings: Friedel-Crafts Reaction

- Acylation: An acyl group substitiution
  - Created by reacting an aromatic ring, a carboxylic acid chloride and $AlCl_3$



Benzene Acetyl chloride Acetophenone (95%)

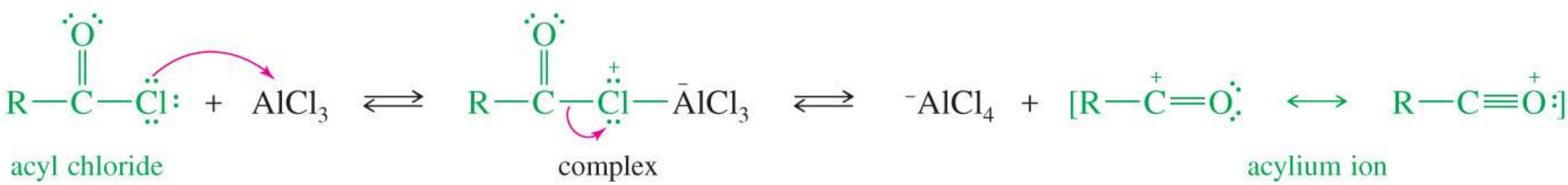
Acylation of Aromatic Rings: Friedel-Crafts Reaction



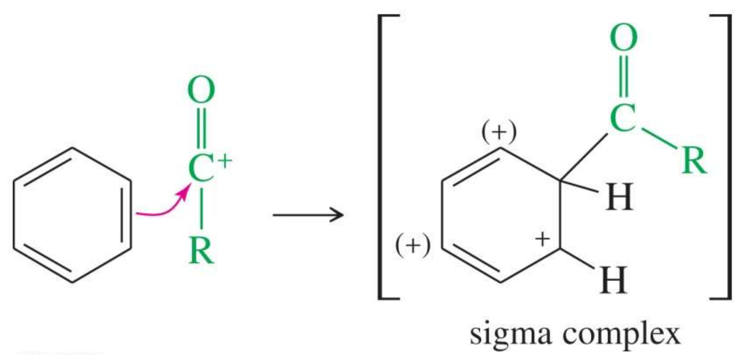
- Acyl chloride is used in place of alkyl chloride.
- The product is a phenyl ketone that is less reactive than benzene.

Acylation of Aromatic Rings: Friedel-Crafts Reaction Mechanism

Step 1: Formation of the acylium ion (resonance of carbocation prevents rearrangements)

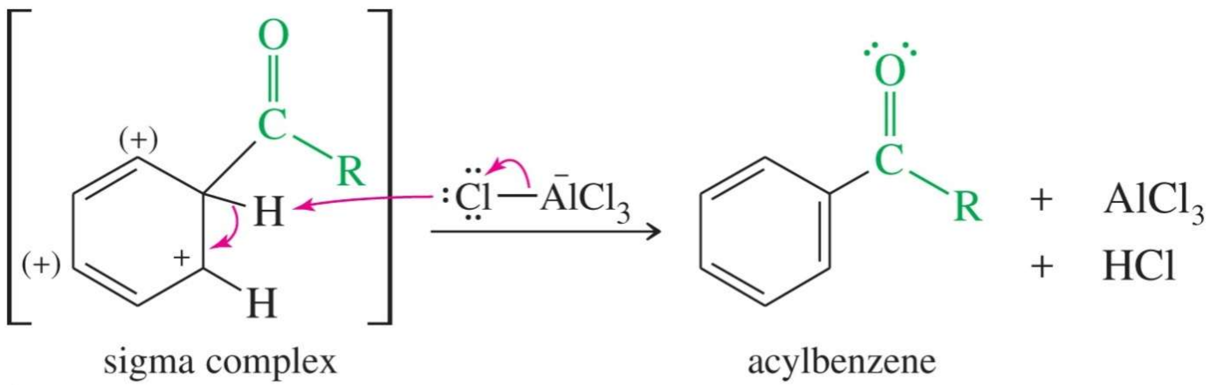


Step 2: Electrophilic attack to form the sigma complex



Acylation of Aromatic Rings: Friedel-Crafts Reaction Mechanism (Continued)

Step 3: Loss of a proton to form the product



Acylation of Aromatic Rings: Friedel-Crafts Reaction Mechanism

- Have the same limitations on the aromatic substrate

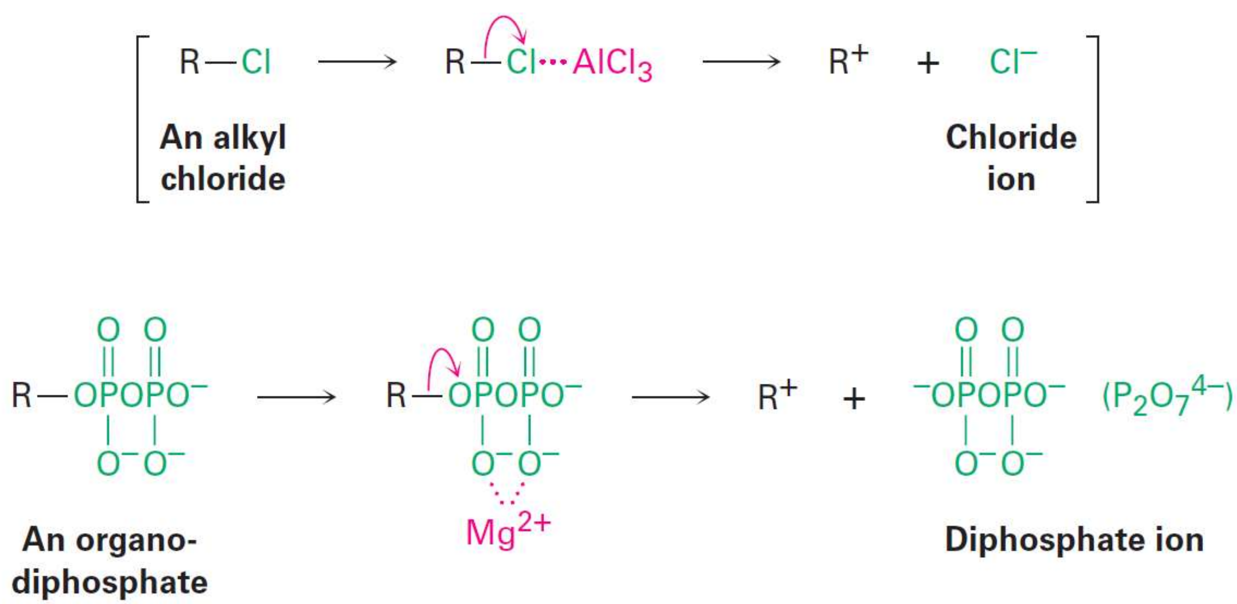
where Y = $-\overset{+}{N}R_3$, $-NO_2$, $-CN$,
$-SO_3H$, $-CHO$, $-COCH_3$,
$-CO_2H$, $-CO_2CH_3$
($-NH_2$, $-NHR$, $-NR_2$)

REMEMBER

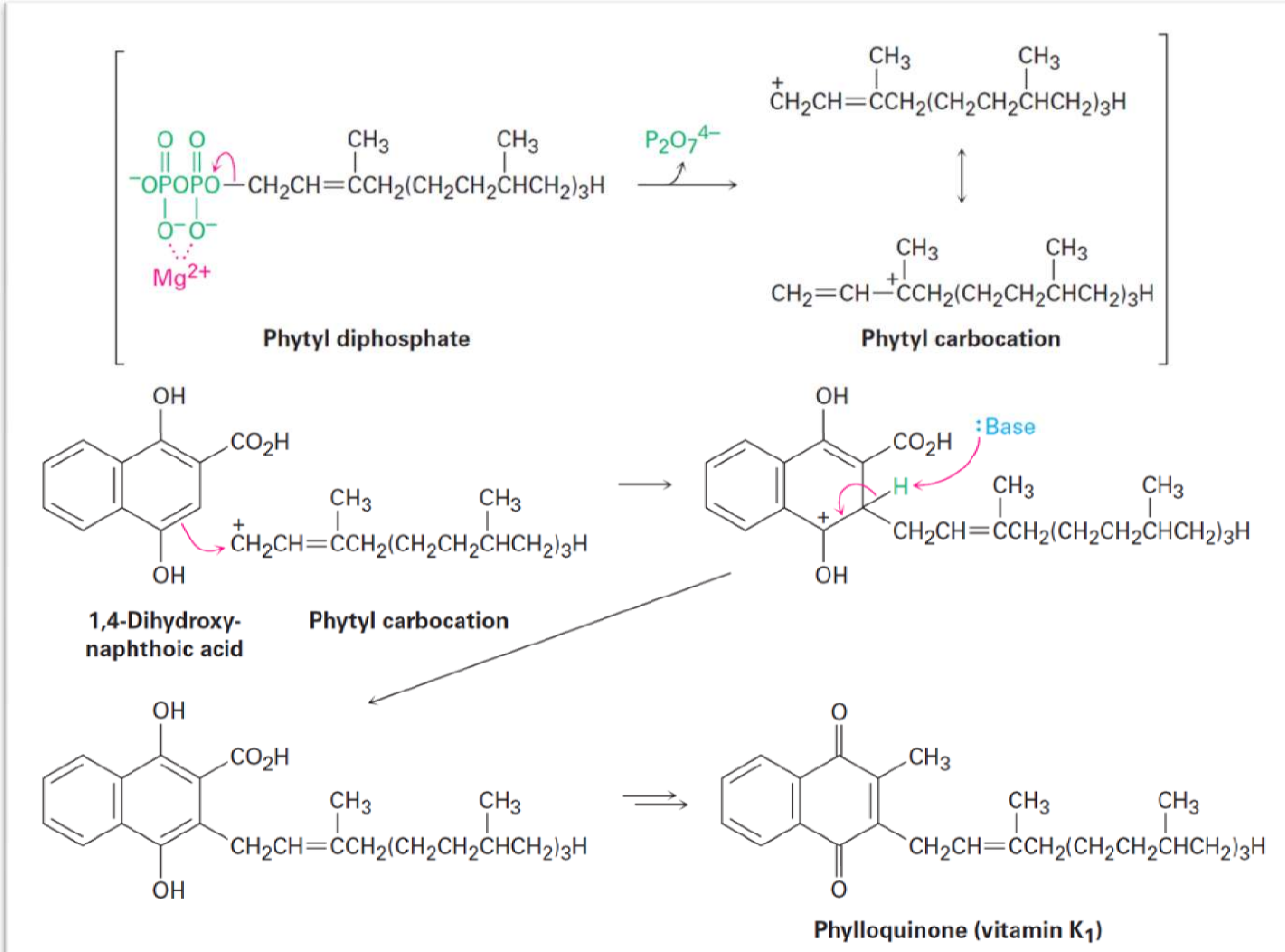
Friedel–Crafts acylations are generally free from rearrangements and multiple substitution. They do not go on strongly deactivated rings, however.

Alkylation of Aromatic Rings: Natural Friedel-Crafts Reaction

- Natural aromatic alkylations are a part of many biological pathways
  - Catalyzing effect of $AlCl_3$ is replaced by organidiphosphate dissociation



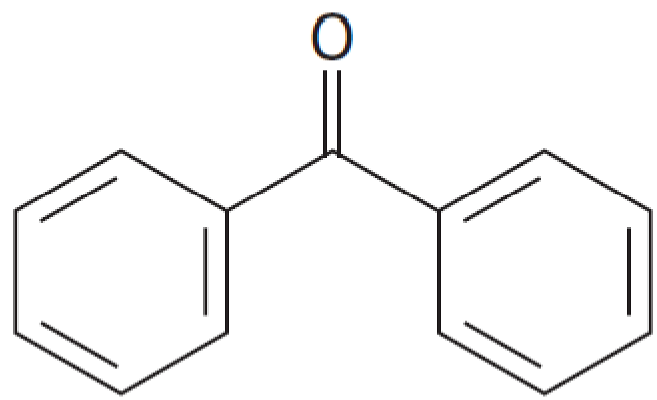
Alkylation of Aromatic Rings: Natural Friedel-Crafts Reaction Example



Biosynthesis of Phylloquinone from 1,4-dihydroxynaphthoic Acid

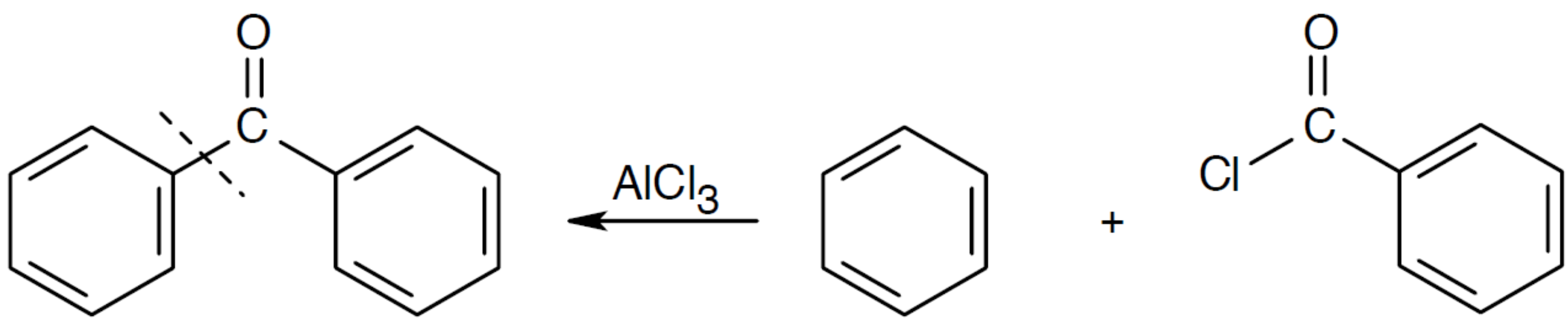
Worked Example

- Identify the carboxylic acid that might be used in a Friedel-Crafts acylation to prepare the following acylbenzene



Worked Example

- Solution:
  - Identification of the carboxylic acid chloride used in the Friedel-Crafts acylation of benzene involves:
    - Breaking the bond between benzene and the ketone carbon
    - Using a –Cl replacement



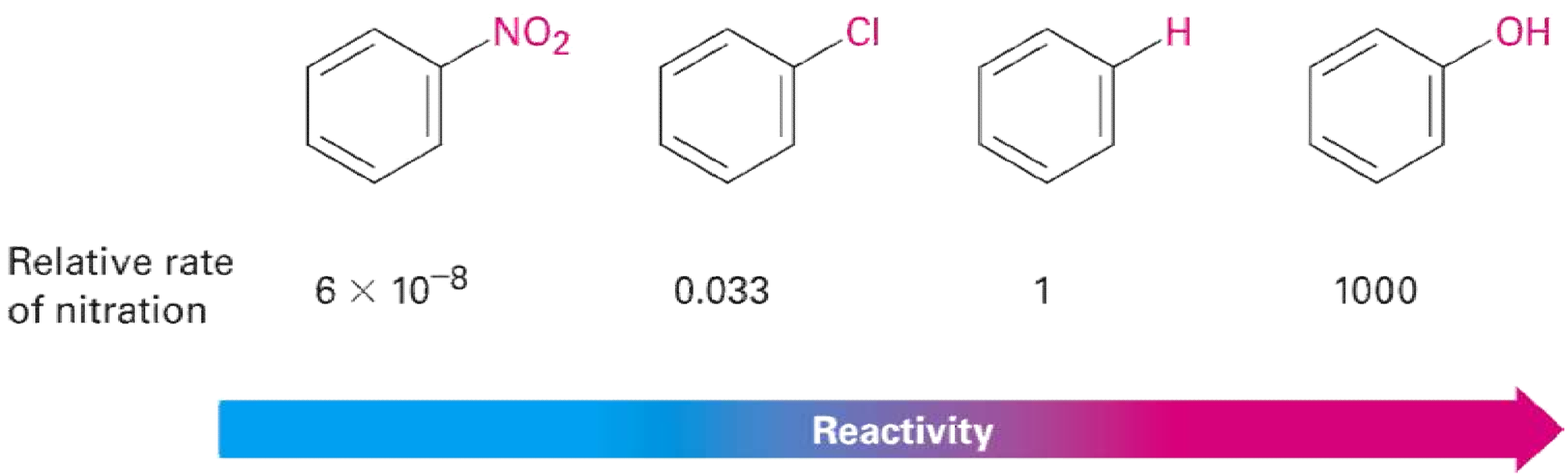
SUBSTITUENT EFFECTS IN ELECTROPHILIC SUBSTITUTIONS

Substituent Effects in Electrophilic Substitutions

- Substituents affect
  - Reactivity of the aromatic ring

Substituent Effects in Electrophilic Substitutions

- Reactivity of the aromatic ring is affected
  - Substitution can result in an aromatic ring with a higher or a lower reactivity than benzene



Substituent Effects in Electrophilic Substitutions

- Substituents affect
  - Reactivity of the aromatic ring
  - Orientation of the reaction
    - Initial substituent on ring determines placement of latter substituents

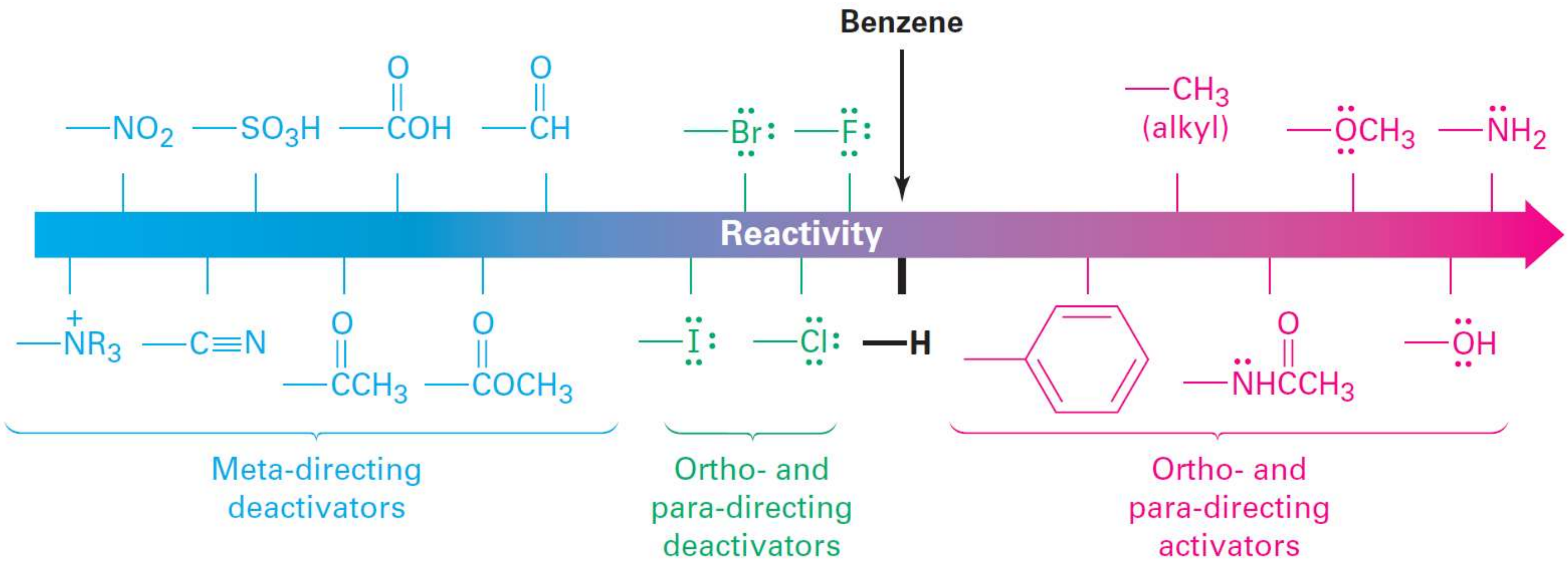
Substituent Effects in Electrophilic Substitutions

- Substituent initially present on benzene ring
  - Activating groups
    - Speed up the reaction
    - Groups that donate electron density to the ring
    - Direct substituents to ortho/para positions
    - Three types of ortho/para directors
      - Alkyl groups stabilize the aromatic ring by providing electron density
      - Pi bonds stabilize the aromatic ring by providing electron density through resonance
      - Lone pairs stabilize the aromatic ring by providing resonance
    - -OH group is an ortho- and para- directing activator

Substituent Effects in Electrophilic Substitutions

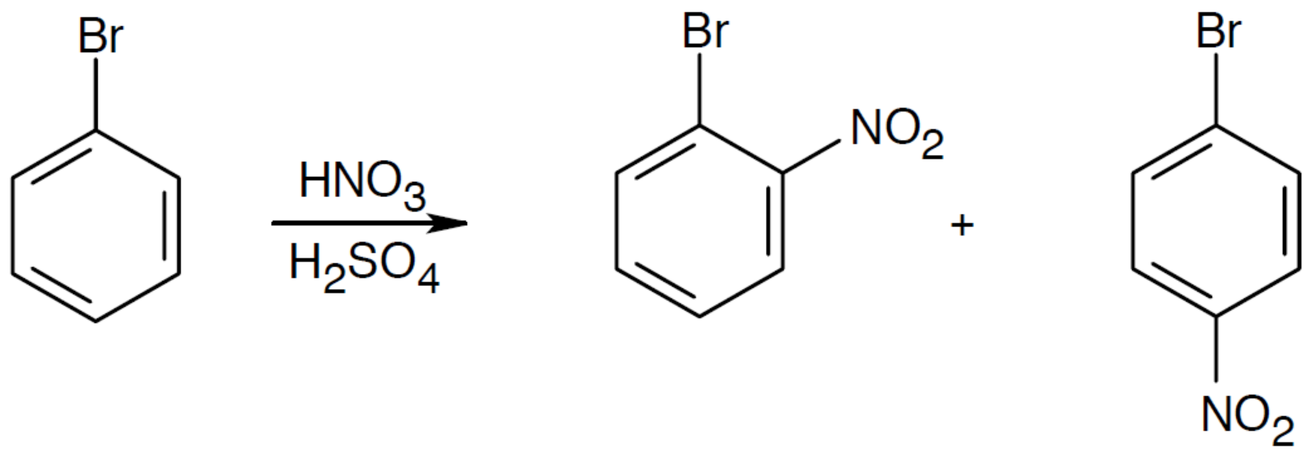
- Substituent initially present on benzene ring
  - Deactivating groups
    - Slow down the reaction
    - Groups that withdraw electron density from the ring
    - Direct substituents to
      - Ortho/para positions: only halogens
        - » Weakly deactivating
      - Meta positions
        - » Groups are strongly deactivating
        - » -CHO (carbonyl group)

Substituent Effects in Electrophilic Substitutions



Worked Example

- Predict the major product in the nitration of bromobenzene
- Solution:



  – Even though bromine is a deactivator, it is used as an ortho-para director

ACTIVATING OR DEACTIVATING EFFECTS

Activating or Deactivating Effects

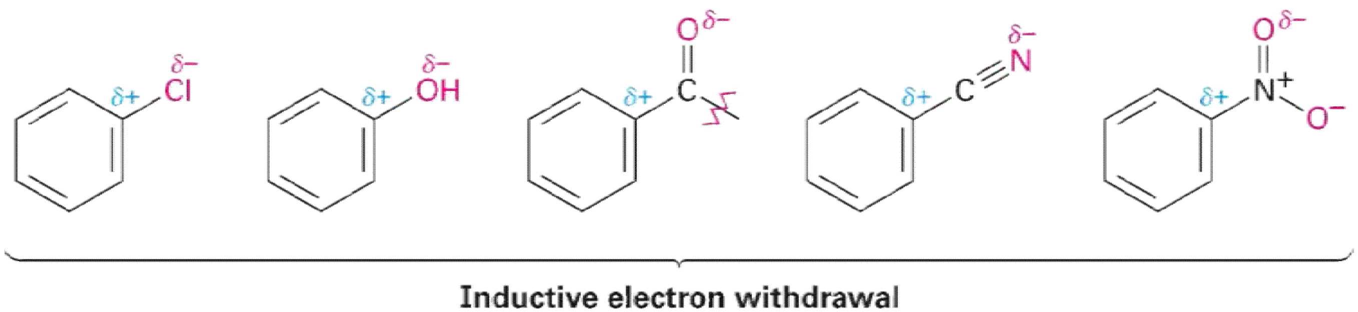
- Activating groups contribute electrons to the aromatic ring
  - The ring possesses more electrons
  - The carbocation intermediate is stabilized
  - Activation energy is lowered
- Deactivating groups withdraw electrons from the aromatic ring
  - The ring possesses lesser electrons
  - The carbocation intermediate is destabilized
  - Activation energy is increased

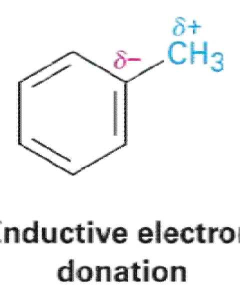
Activating or Deactivating Effects

- Electron withdrawal or donation by a substituent group is controlled by
  - **Inductive effects**

Origins of Substituent Effects

- **Inductive effect**: Withdrawal or donation of electrons by a sigma bond due to electronegativity
  - Prevalent in halobenzenes and phenols



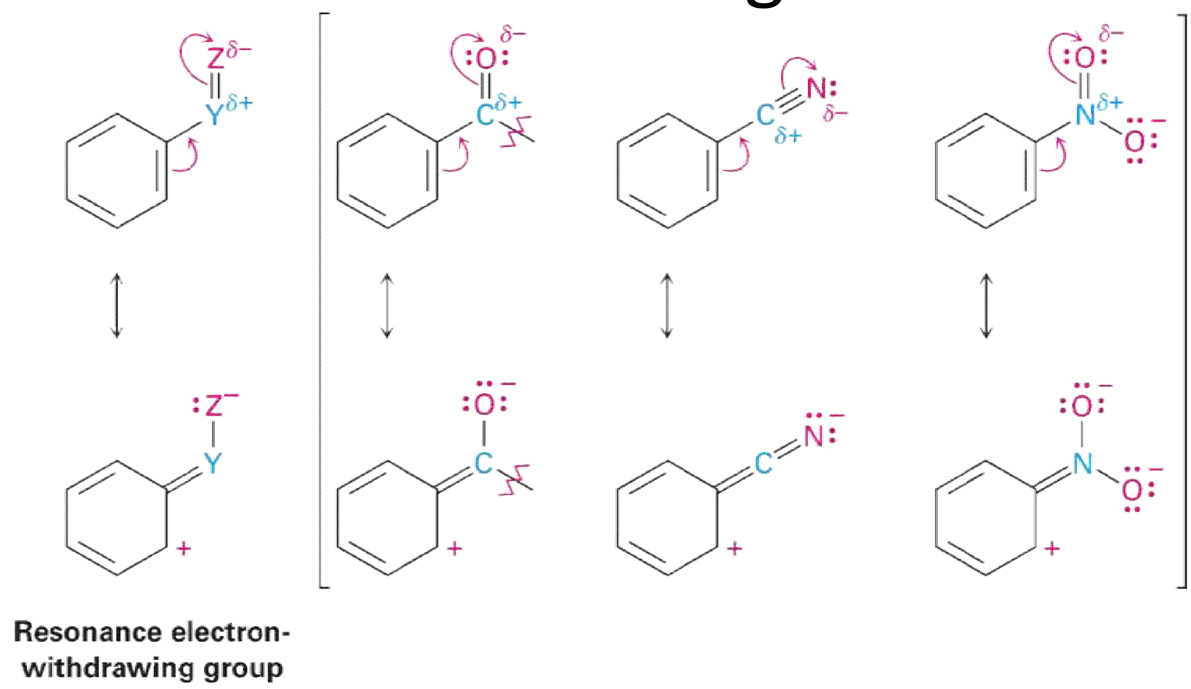


Activating or Deactivating Effects

- Electron withdrawal or donation by a substituent group is controlled by
  - Inductive effects
  - **Resonance effects**

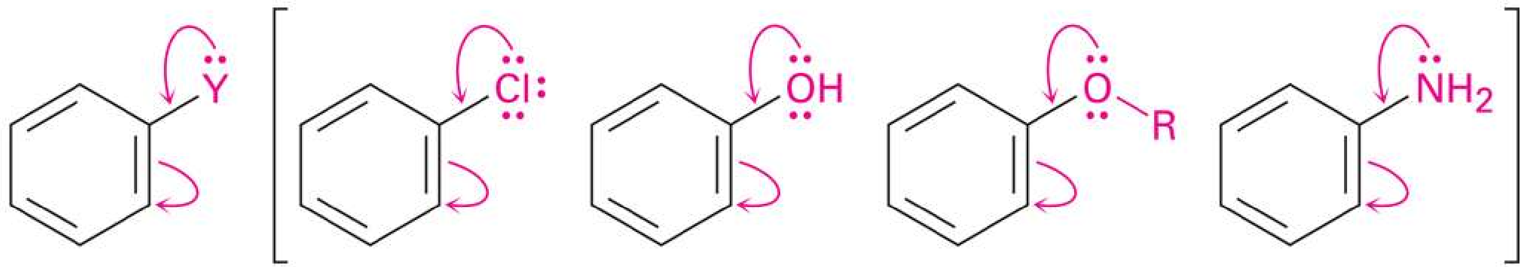
Resonance Effects - Electron Withdrawal

- **Resonance effect**: Withdrawal or donation of electrons through a π bond due to the overlap of a *p* orbital on the substituent with a *p* orbital on the aromatic ring



Resonance Effects - Electron Withdrawal

- **Resonance effect**: Withdrawal or donation of electrons through a π bond due to the overlap of a *p* orbital on the substituent with a *p* orbital on the aromatic ring



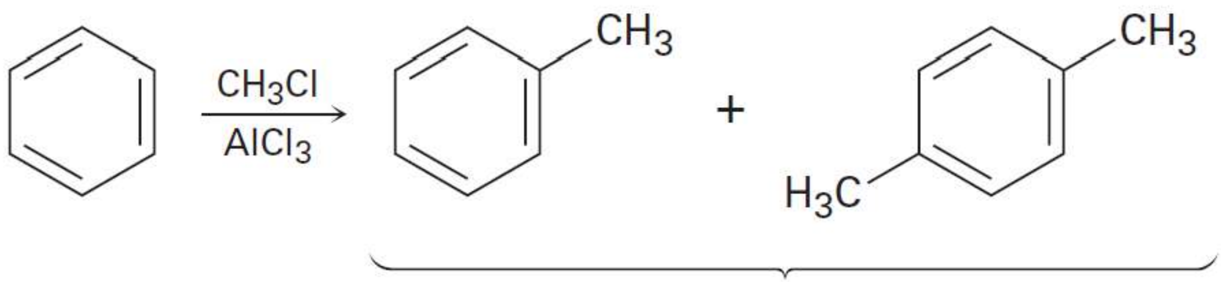
Resonance electron-donating groups

Activating or Deactivating Effects

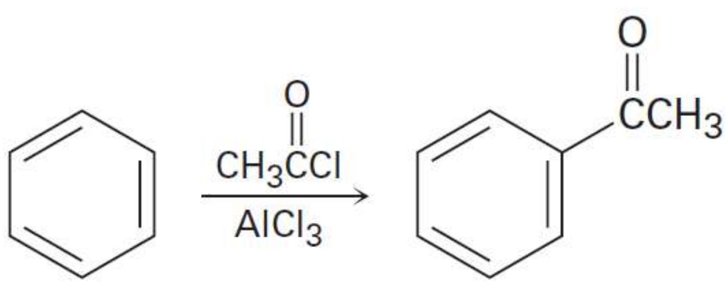
- Electron withdrawal or donation by a substituent group is controlled by
  - Inductive effects
  - Resonance effects
- If the two effects act in opposite direction, the stronger on dominates
  - Hydroxyl, alkoxyl and amino groups are activators because they have a stronger electron-donating resonance as compared to their weak inductive effect
  - Halogens are deactivators because their stronger inductive effect as compared to their resonance effects

Worked Example

- Explain why Freidel-Crafts alkylations often give polyalkylation substitution but Freidel-Crafts acylations do not



(Product mixture)



(Sole product)

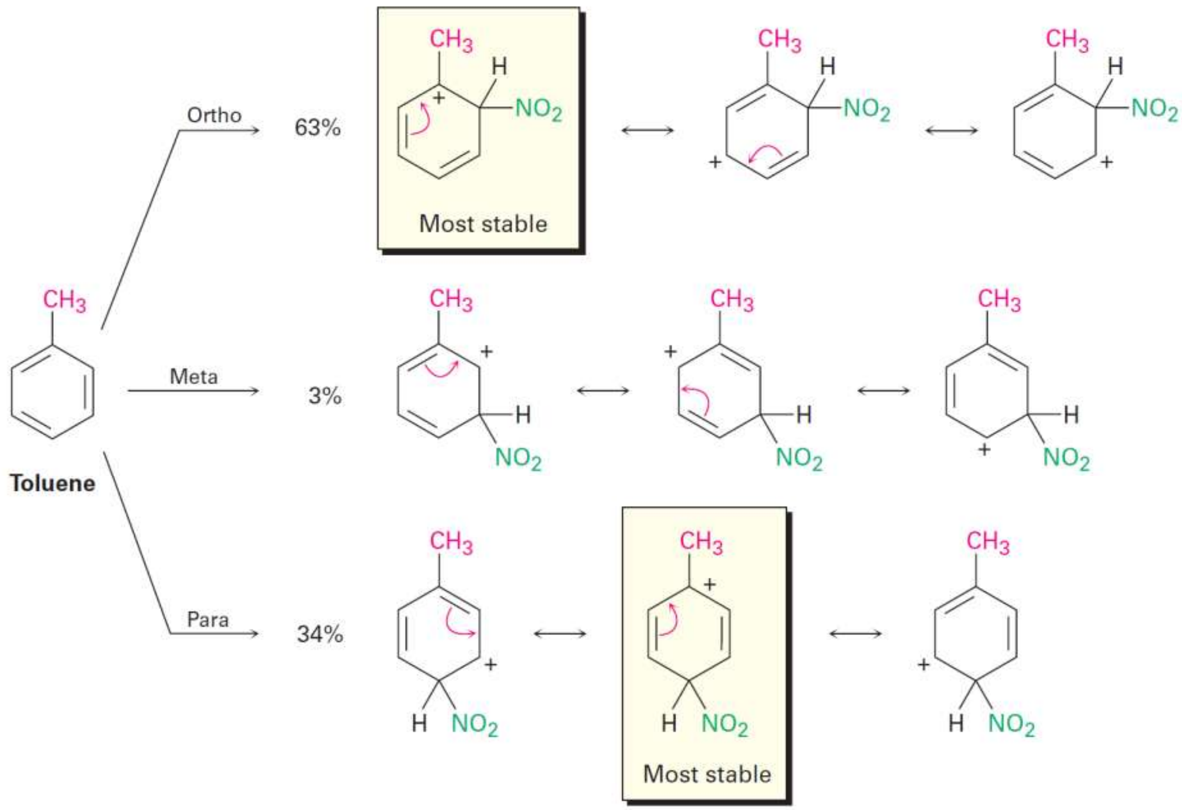
Worked Example

- Solution
  - An acyl substituent is deactivating
    - Once an aromatic ring has been acylated, it is less reactive to further substitution
  - An alkyl substituent is activating, however, an alkyl-substituted ring is more reactive than an unsubstituted ring
    - Polysubstitution occurs readily

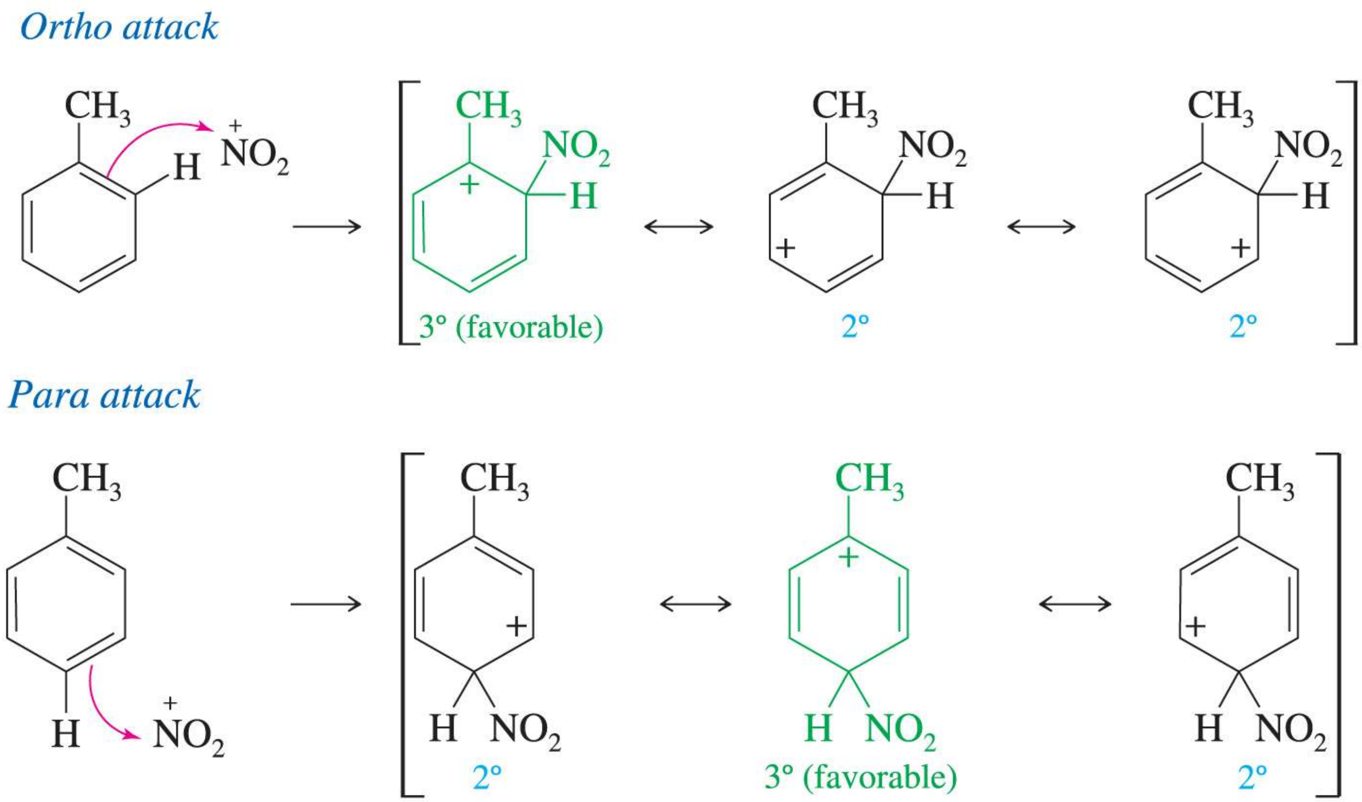
ORTHO- AND PARA-DIRECTING ACTIVATORS

Ortho- and Para-Directing Activators: Alkyl Groups

- Alkyl groups possess an electron-donating inductive effect

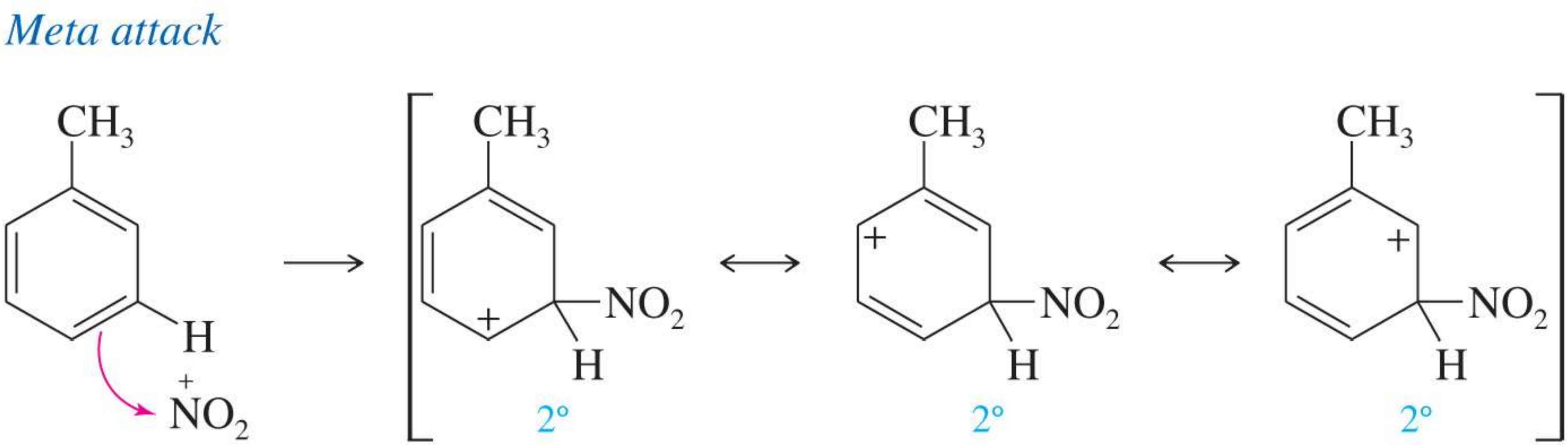


Ortho- and Para-Directing Activators: Alkyl Groups



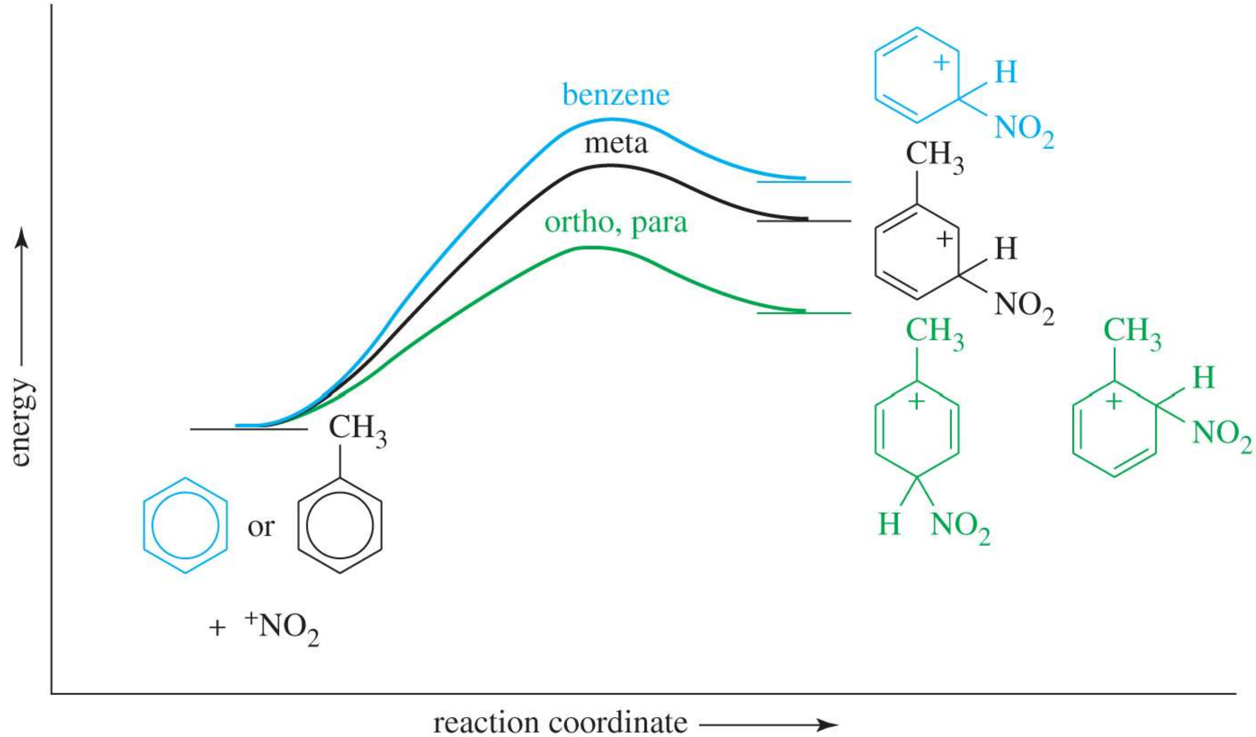
- *Ortho* and *para* attacks are preferred because their resonance structures include one tertiary carbocation

Ortho- and Para-Directing Activators: Alkyl Groups



- When substitution occurs at the meta position, the positive charge is not delocalized onto the tertiary carbon, and the methyl group has a smaller effect on the stability of the sigma complex

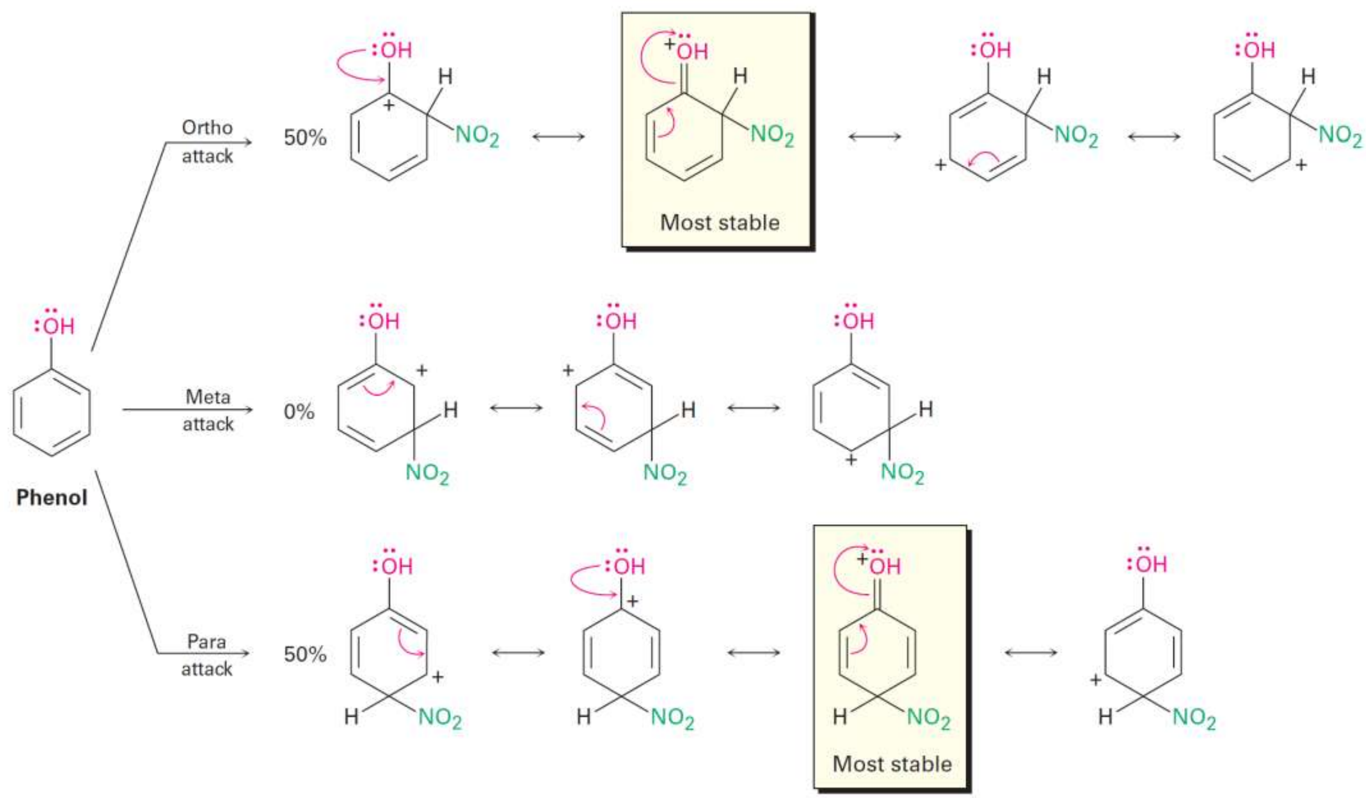
Ortho- and Para-Directing Activators: Alkyl Groups



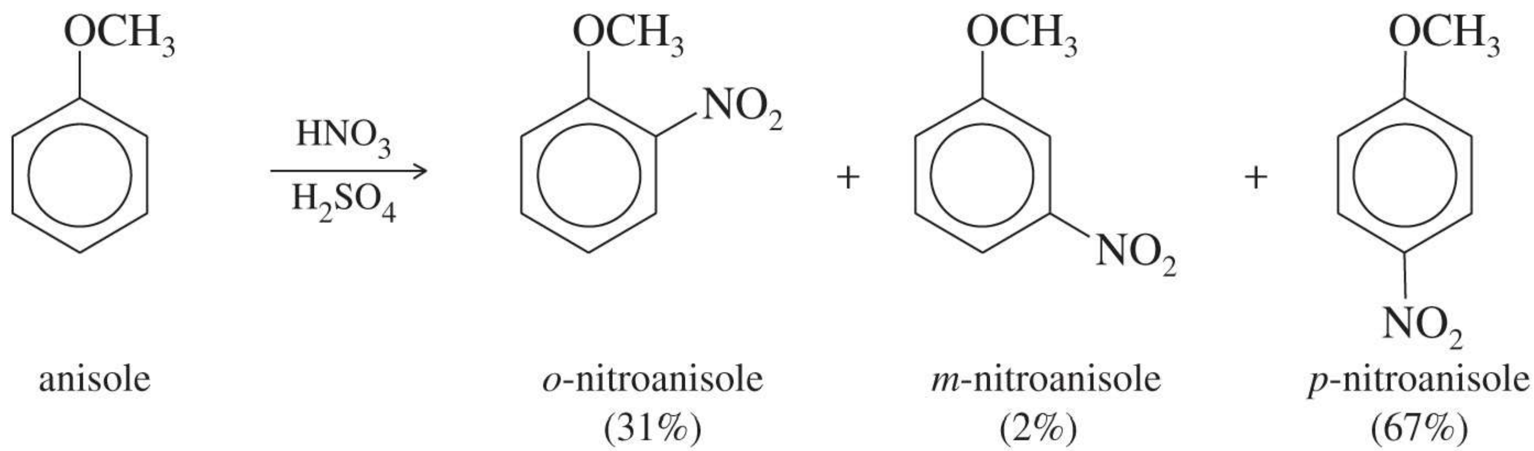
- Carbocation in ortho and para position are stabilized by inductive effect of the methyl group and form faster and are more stable than the meta group

Ortho- and Para-Directing Activators: OR, OH and NH_2

- Hydroxyl, alkoxyl, and amino groups possess a strong, electron-donating resonance effect

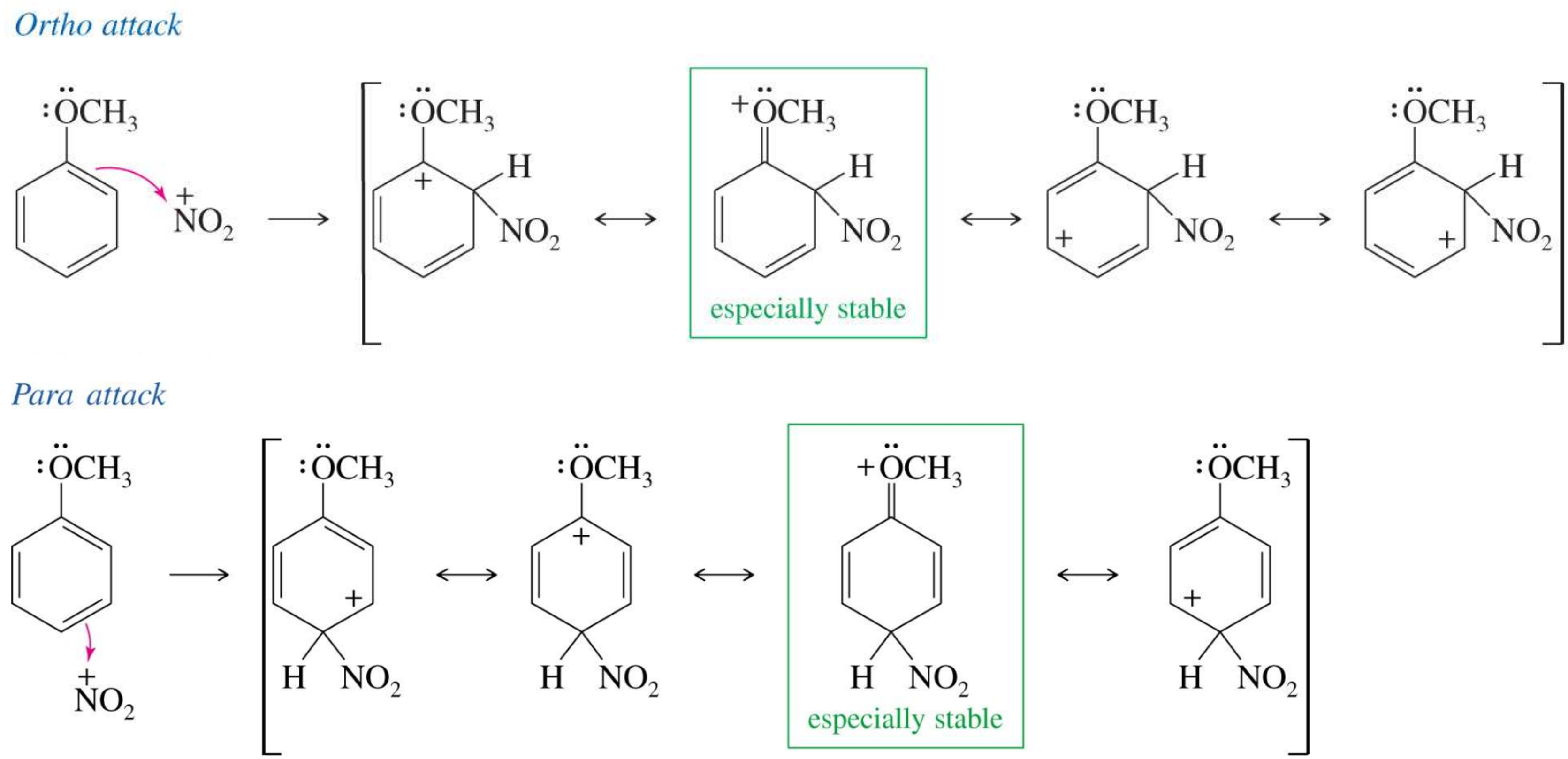


Ortho- and Para-Directing Activators: OR, OH and NH_2



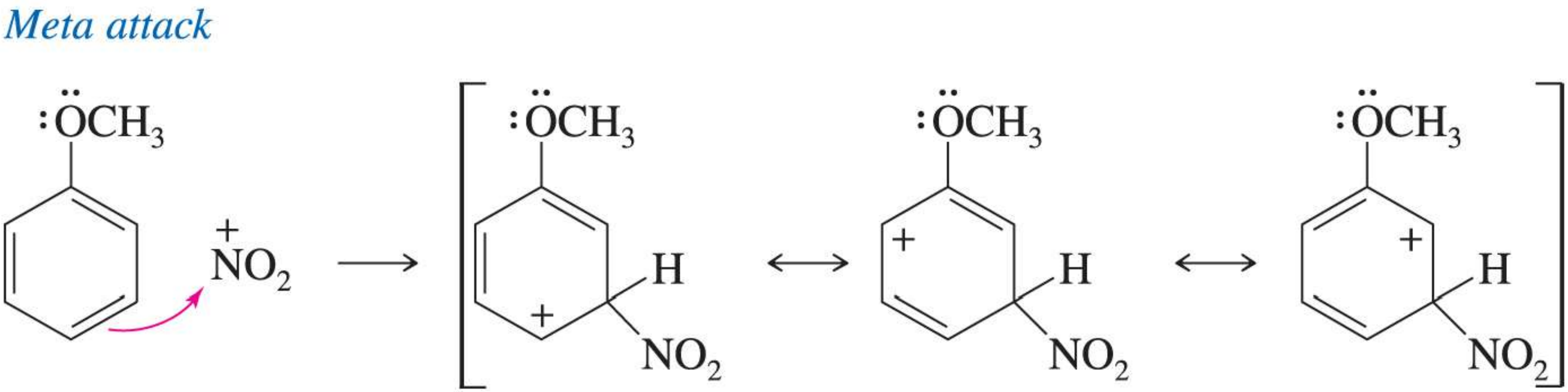
- Anisole undergoes nitration about 10,000 times faster than benzene and about 400 times faster than toluene
- This result seems curious because oxygen is a strongly electronegative group, yet it donates electron density to stabilize the transition state and the sigma complex

Ortho- and Para-Directing Activators: OR, OH and NH_2



Resonance stabilization is provided by a pi bond between the $—OCH_3$ substituent and the ring

Ortho- and Para-Directing Activators: OR, OH and NH_2

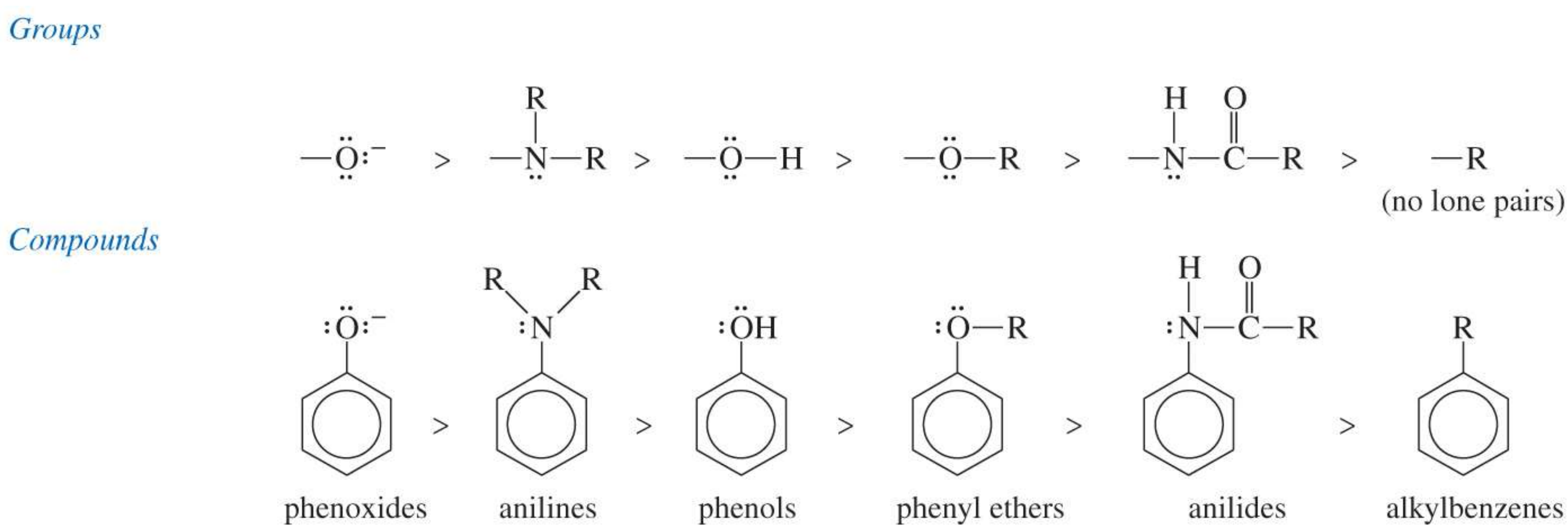


- Resonance forms show that the methoxy group cannot stabilize the sigma complex in the meta substitution.

Ortho- and Para-Directing Activators: OR, OH and NH_2

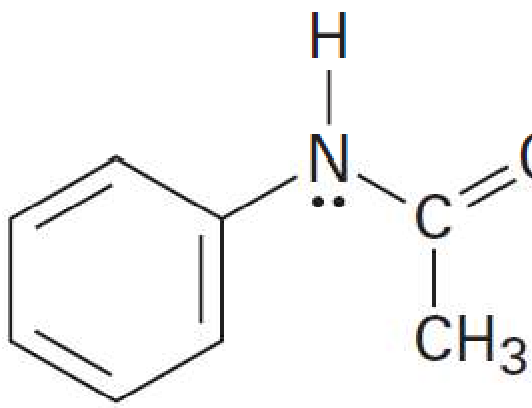
- The ortho and para intermediates are lower in energy than the meta intermediate and form faster

Summary of Activators

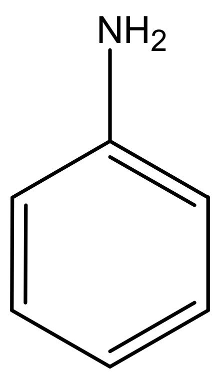


Worked Example

- Explain why acetanilide is less reactive than aniline toward electrophilic substitution



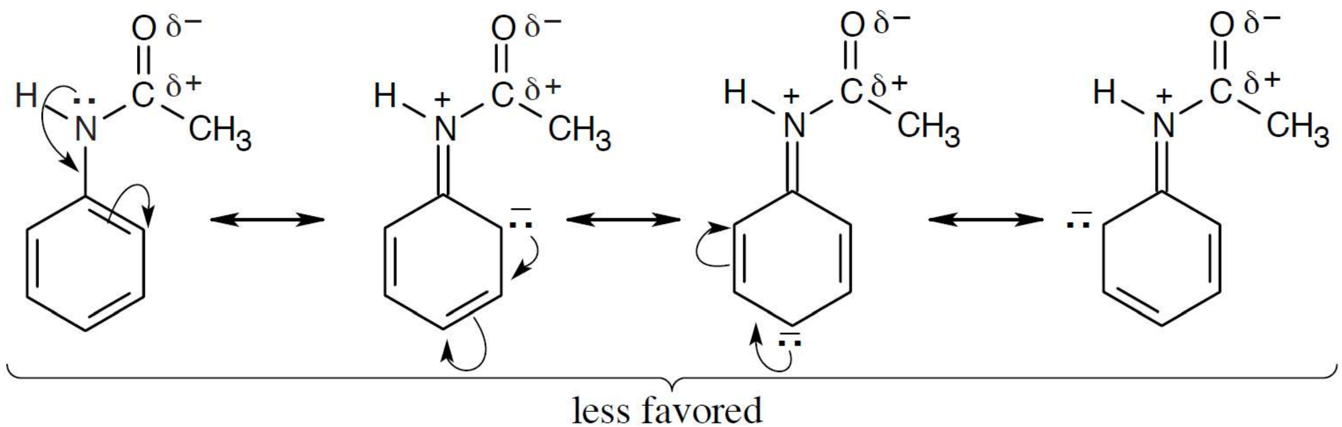
Acetanilide

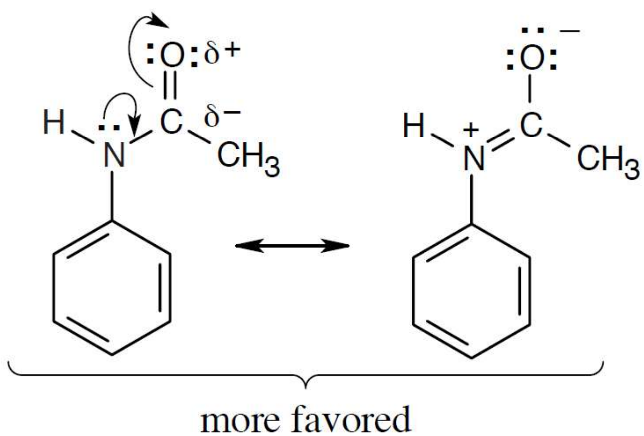


Aniline

Worked Example

- Solution:

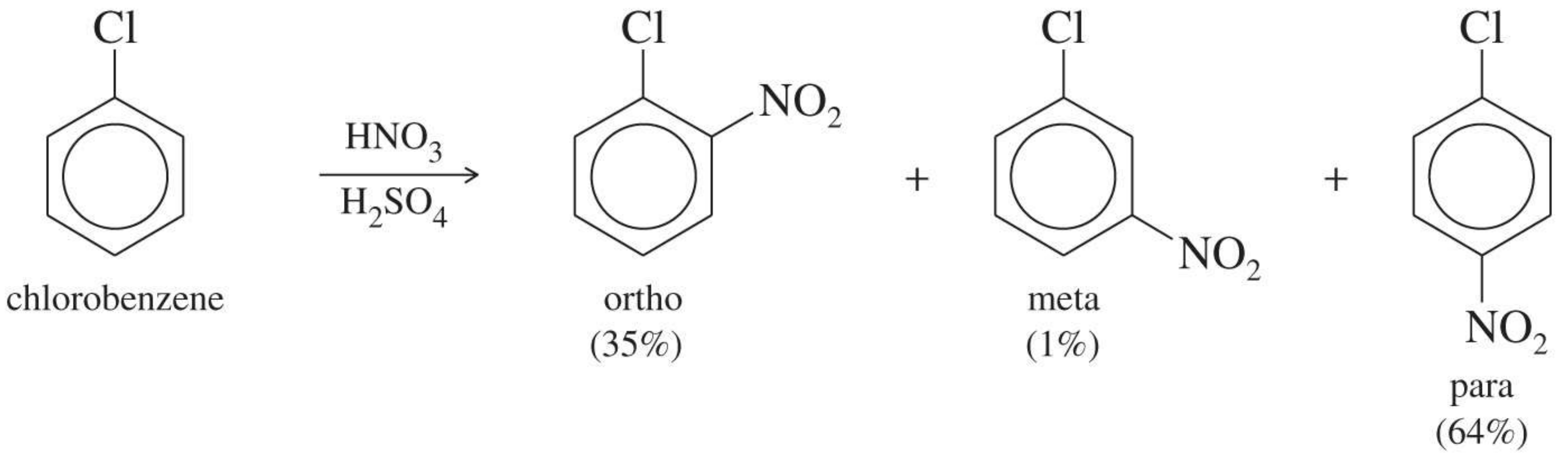




The decreased availability of nitrogen lone pair electrons results in decreased reactivity of the ring toward electrophilic substitution

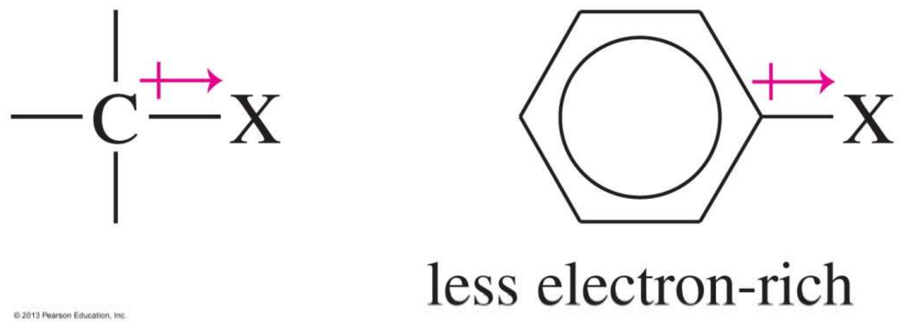
ORTHO- AND PARA-DIRECTING DEACTIVATORS

Ortho- and Para-Directing Deactivators: Halogens



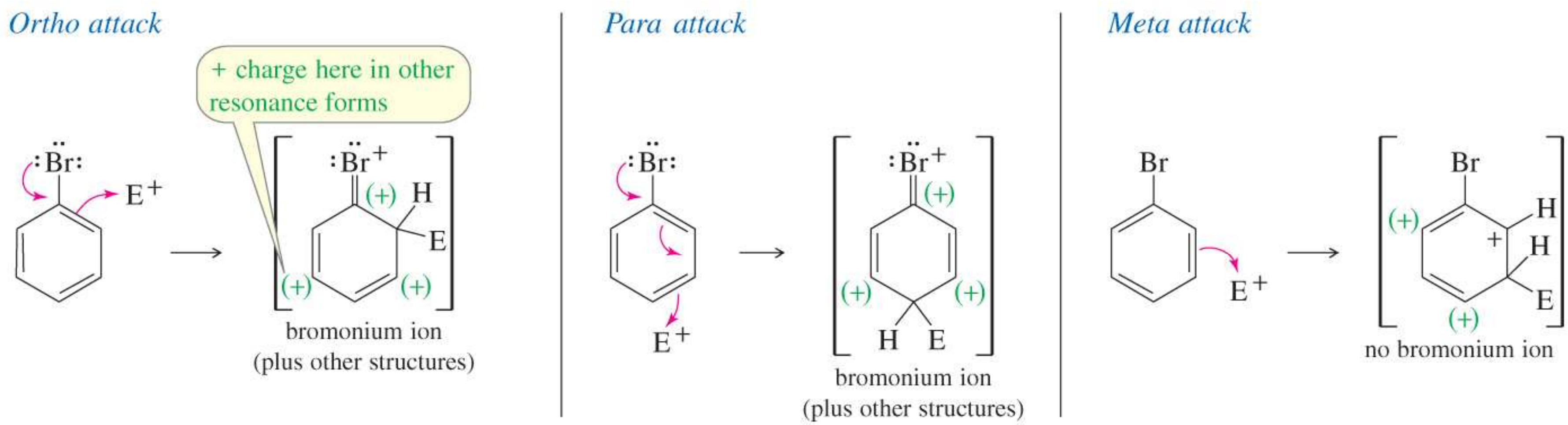
- Halogens are deactivators since they react slower than benzene
- Halogens are ortho, para-directors because the halogen can stabilize the sigma complex

Ortho- and Para-Directing Deactivators: Halogens



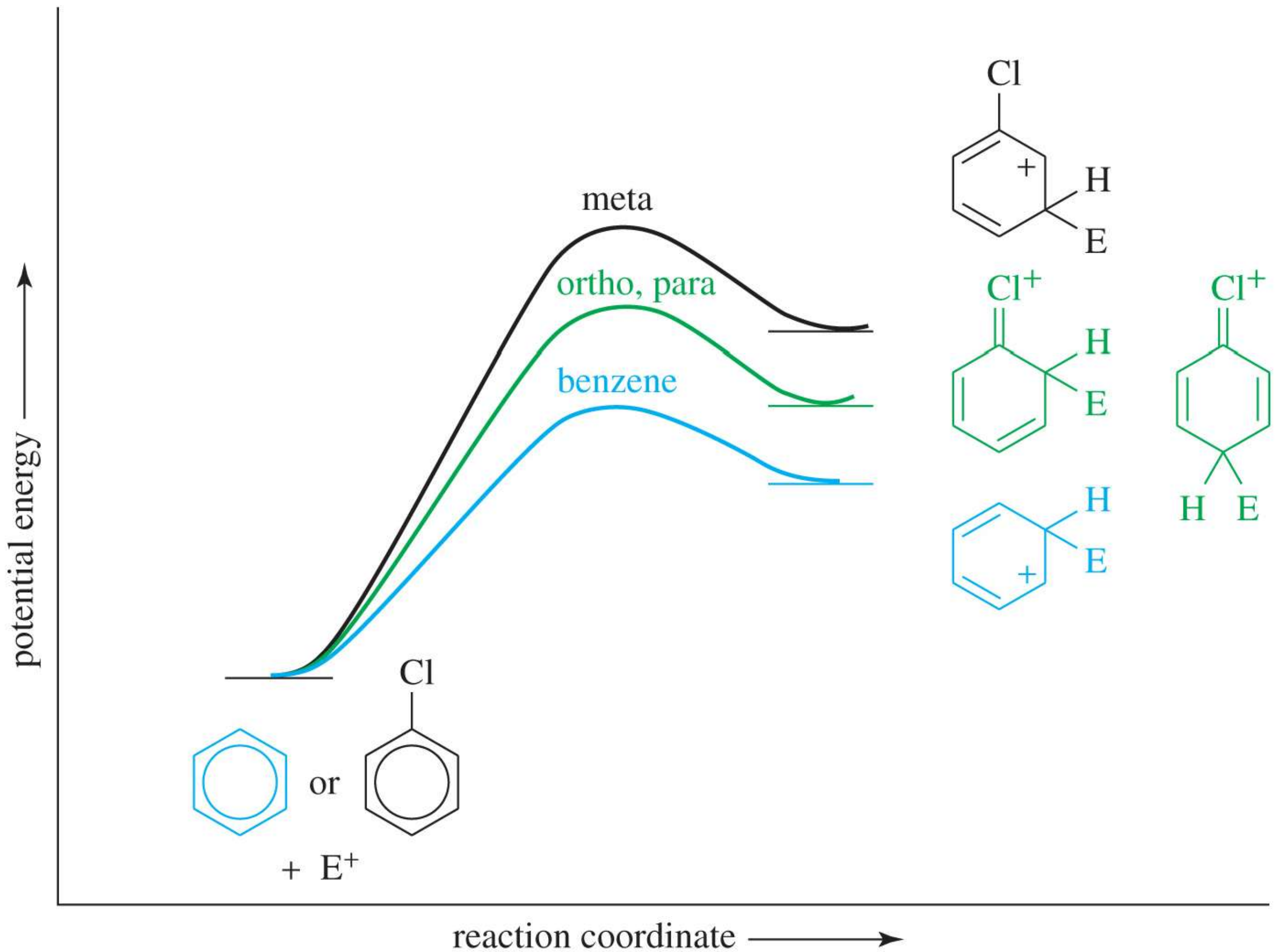
- ***Inductive effect***: Halogens are deactivating because they are electronegative and can withdraw electron density from the ring along the sigma bond

Ortho- and Para-Directing Deactivators: Halogens



- ***Resonance effect***: The lone pairs on the halogen can be used to stabilize the sigma complex by resonance

Ortho- and Para-Directing Deactivators: Halogens



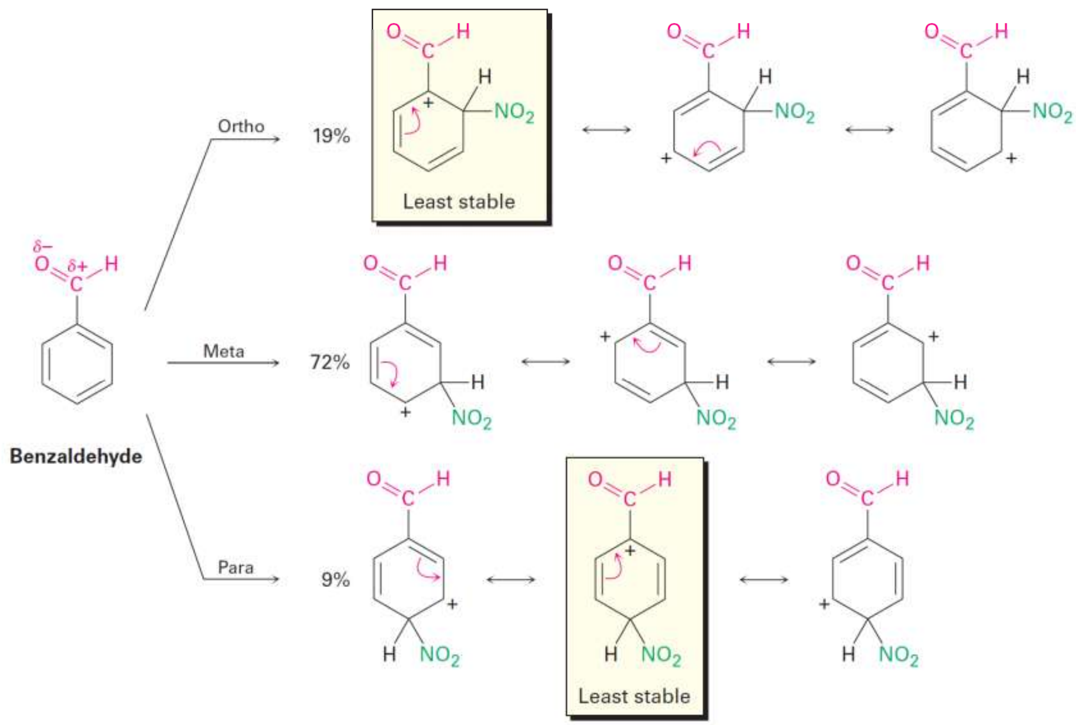
Ortho- and Para-Directing Deactivators: Halogens

- Caused by the dominance of the stronger electron-withdrawing inductive effect over their weaker electron-donating resonance effect
  - Electron donating resonance effect is present only at the ortho and para positions

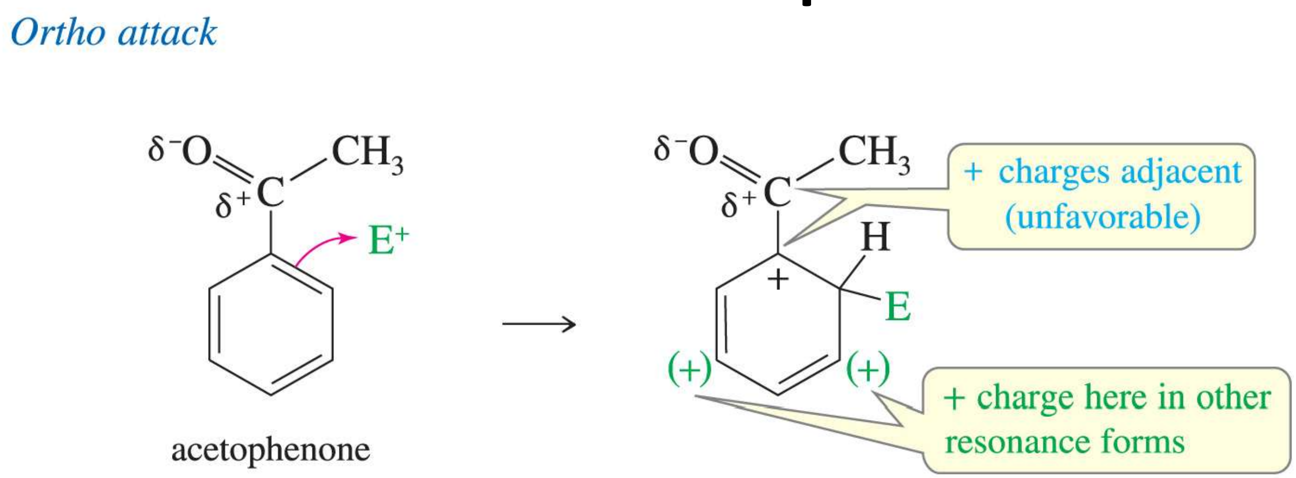
META-DIRECTING DEACTIVATORS

Meta-Directing Deactivators

- The meta intermediate possesses three favourable resonance forms
  - Ortho and para intermediates possess only two

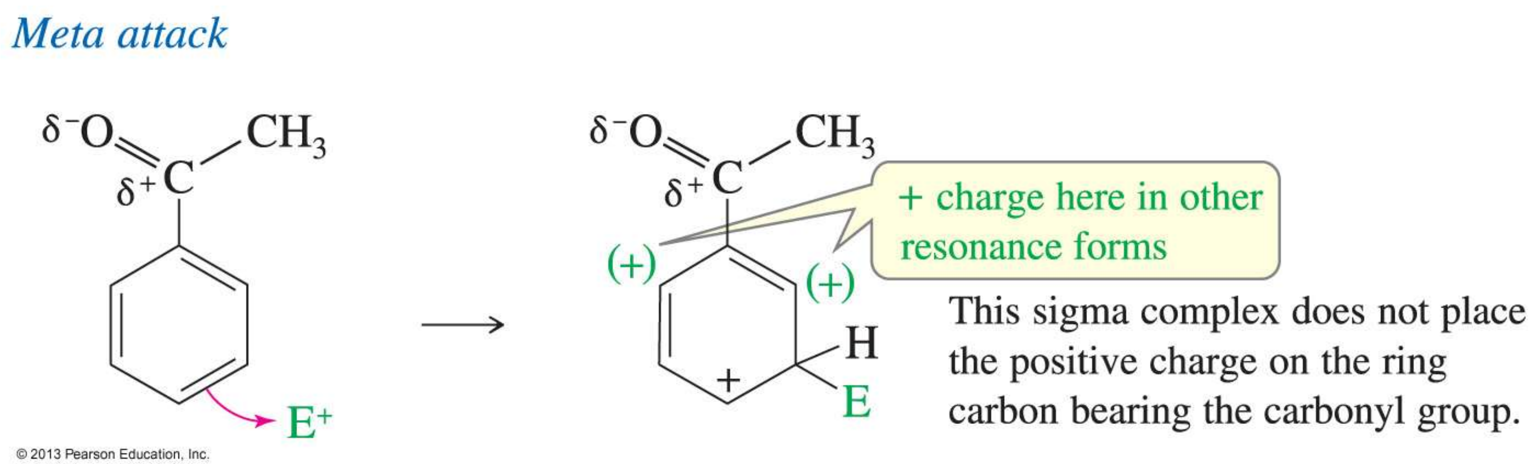


Meta-Directing Deactivators: Ortho Attack of Acetophenone



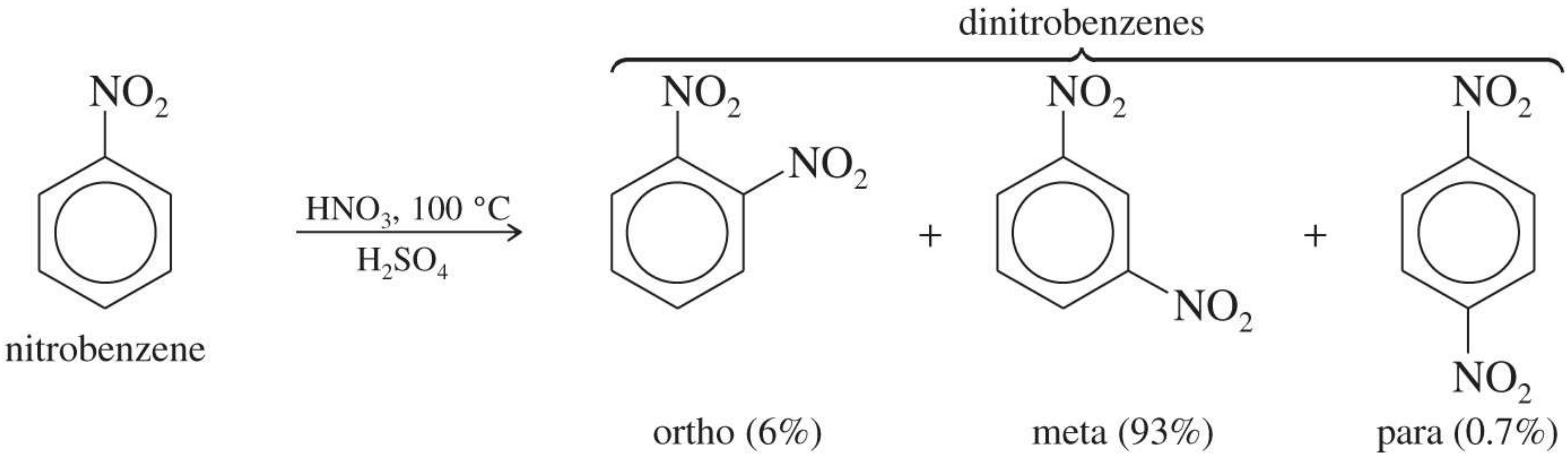
- In ortho and para substitution of acetophenone, one of the carbon atoms bearing the positive charge is the carbon attached to the partial positive carbonyl carbon.
- Since like charges repel, this close proximity of the two positive charges is especially unstable

Meta-Directing Deactivators: Meta Attack on Acetophenone



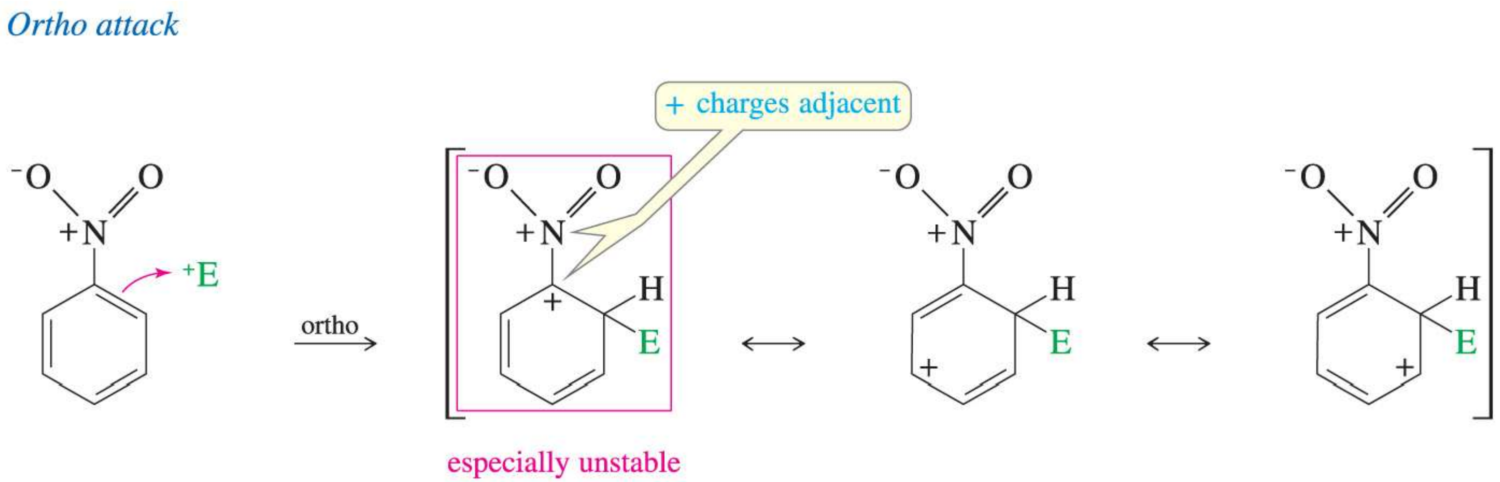
- The meta attack on acetophenone avoids bearing the positive charge on the carbon attached to the partial positive carbonyl

Meta-Directing Deactivators: Nitration of Nitrobenzene



- Electrophilic substitution reactions for nitrobenzene are 100,000 times <u>slower</u> than for benzene
- The product mix contains mostly the meta isomer, and only small amounts of the ortho and para isomers

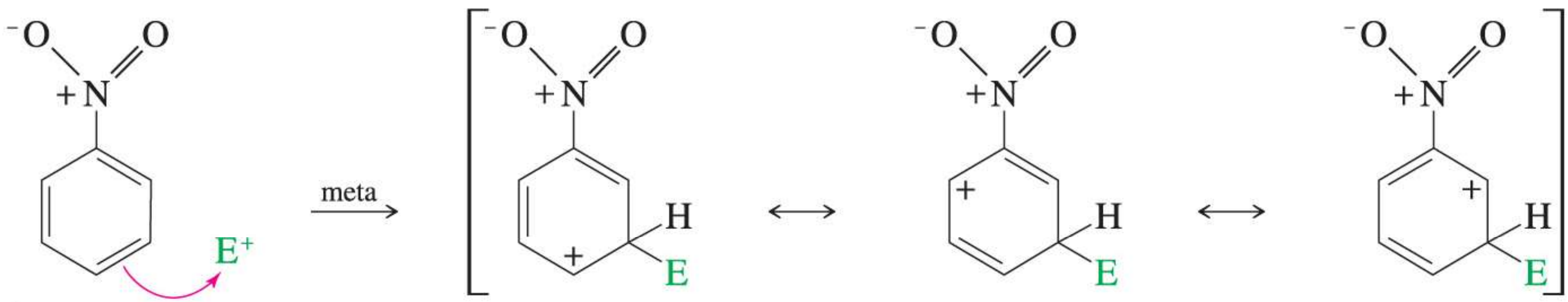
Meta-Directing Deactivators: Ortho Substitution of Nitrobenzene



- The nitro group is a strongly deactivating group when considering its resonance forms
- The nitrogen always has a formal positive charge
- Ortho or para addition will create an especially unstable intermediate

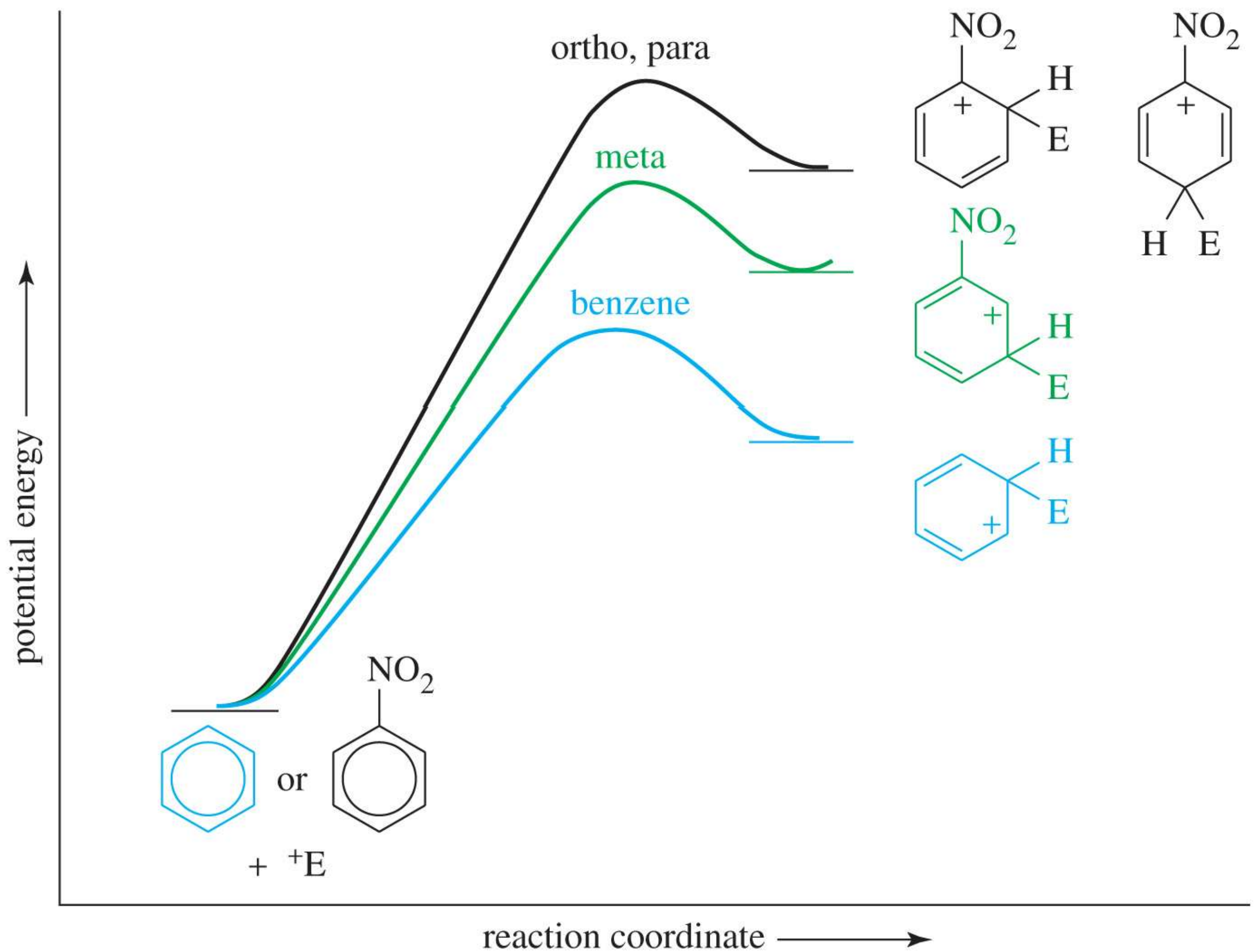
Meta-Directing Deactivators: Meta Substitution on Nitrobenzene

Meta attack



- Meta substitution will not put the positive charge on the same carbon that bears the nitro group

Meta-Directing Deactivators: Energy Diagram



Meta-Directing Deactivators

- Most electron-withdrawing groups are deactivators and meta-directors
- The atom attached to the aromatic ring has a positive or partial positive charge
- Electron density is withdrawn inductively along the sigma bond, so the ring has less electron density than benzene, and will be slower to react

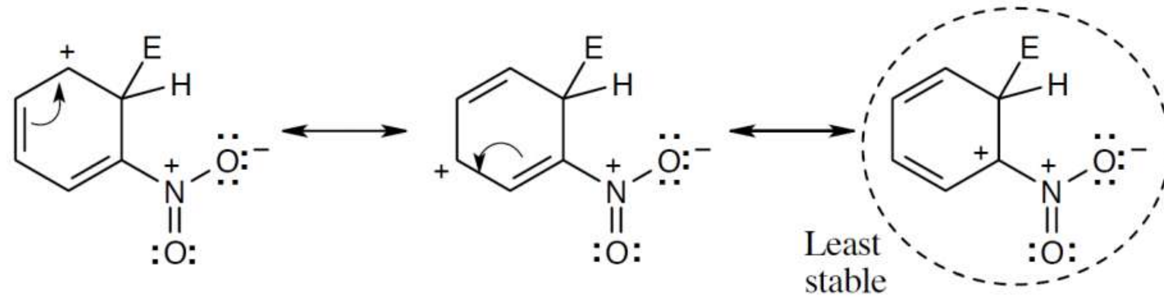
Worked Example

- Draw resonance structures for the intermediates from the reaction of an electrophile at the ortho, meta, and para positions of nitrobenzene
  - Determine which intermediates are most stable

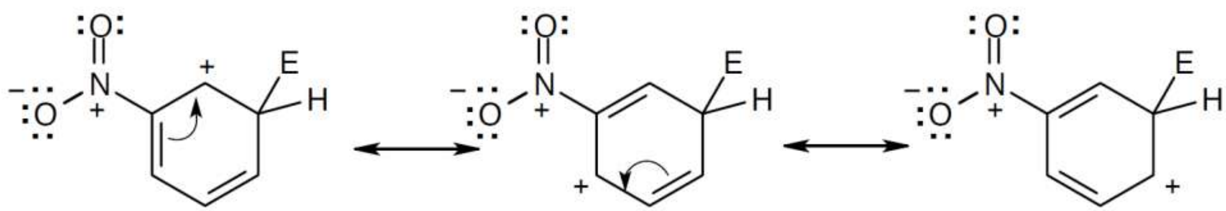
Worked Example

- Solution:

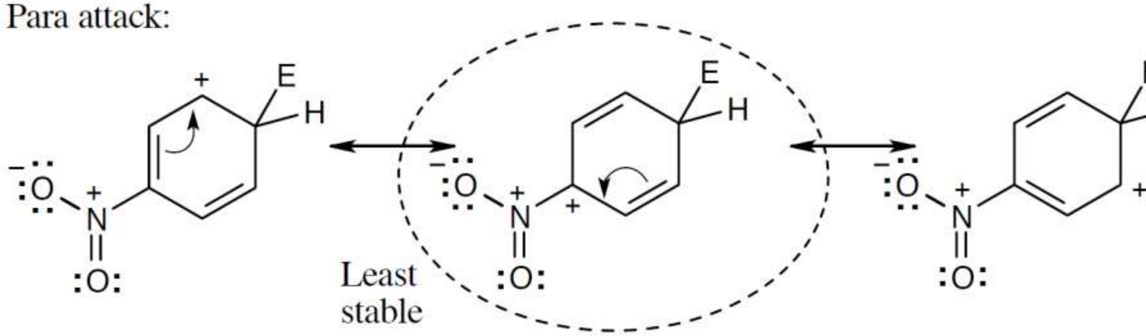
Ortho attack:



Meta attack:



Para attack:



Substituent Effects in Electrophilic Aromatic Substitution

Substituent	Reactivity	Orienting effect	Inductive effect	Resonance effect
$-CH_3$	Activating	Ortho, para	Weak donating	—
$-OH$, $-NH_2$	Activating	Ortho, para	Weak withdrawing	Strong donating
$-F$, $-Cl$, $-Br$, $-I$	Deactivating	Ortho, para	Strong withdrawing	Weak donating
$-NO_2$, $-CN$, $-CHO$, $-CO_2R$, $-COR$, $-CO_2H$	Deactivating	Meta	Strong withdrawing	Strong withdrawing

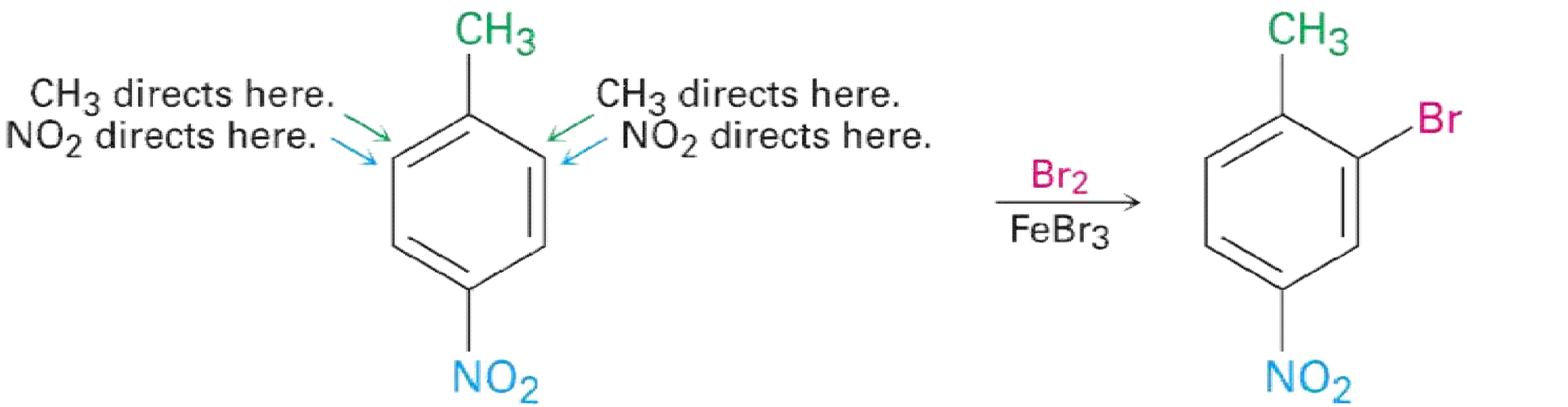
REMEMBER

Remember which substituents are activating and which are deactivating. Activators are ortho, para-directing, and deactivators are meta-directing, except for the halogens.

TRISUBSTITUTED BENZENES

Trisubstituted Benzenes: Additivity of Effects

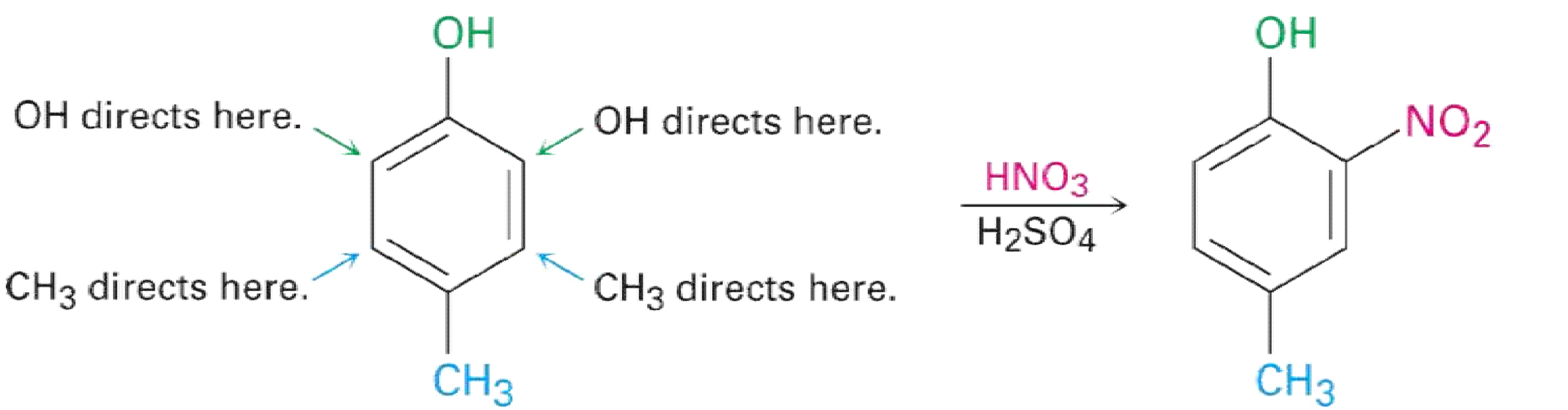
- Additivity effects are based on three rules:
  - The situation is straightforward if the directing effects of the groups reinforce each other



***p*-Nitrotoluene** **2-Bromo-4-nitrotoluene**

Trisubstituted Benzenes: Additivity of Effects

– If the directing effects of two groups oppose each other, the more powerful activating group decides the principal outcome
  - Usually gives mixtures of products

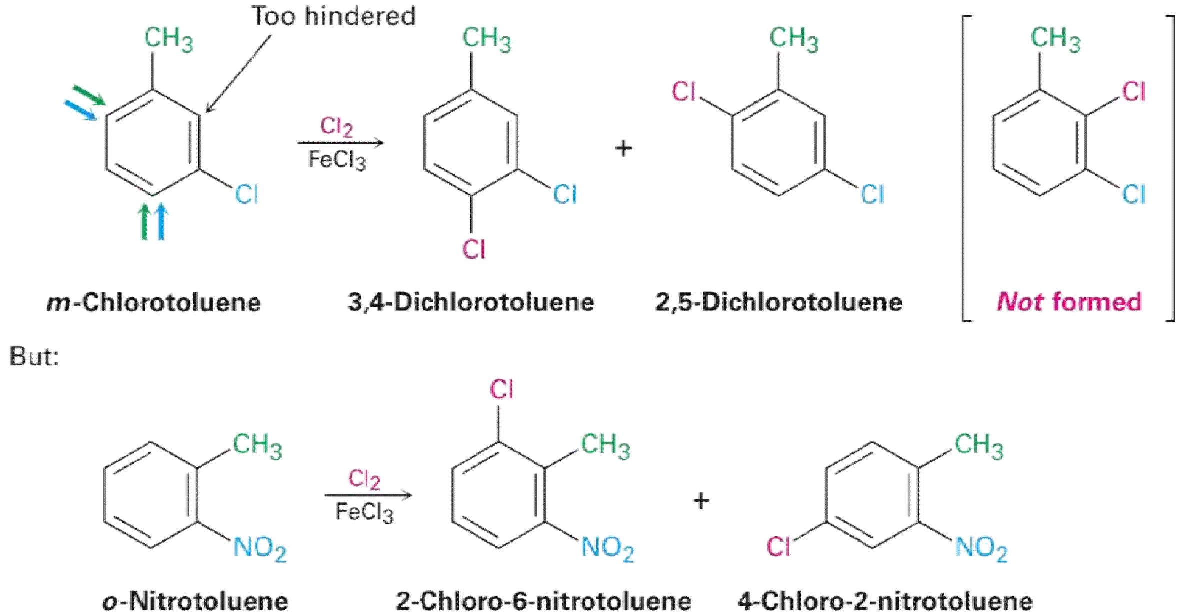


p-Methylphenol

4-Methyl-2-nitrophenol

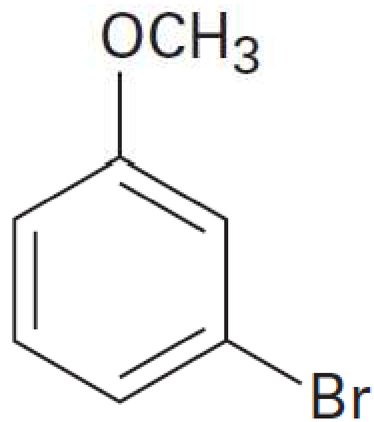
Trisubstituted Benzenes: Additivity of Effects

– Further substitution is rare when two groups are in a meta-disubstituted compound as the site is too hindered
    - An alternate route must be taken in the preparation of aromatic rings with three adjacent substituents



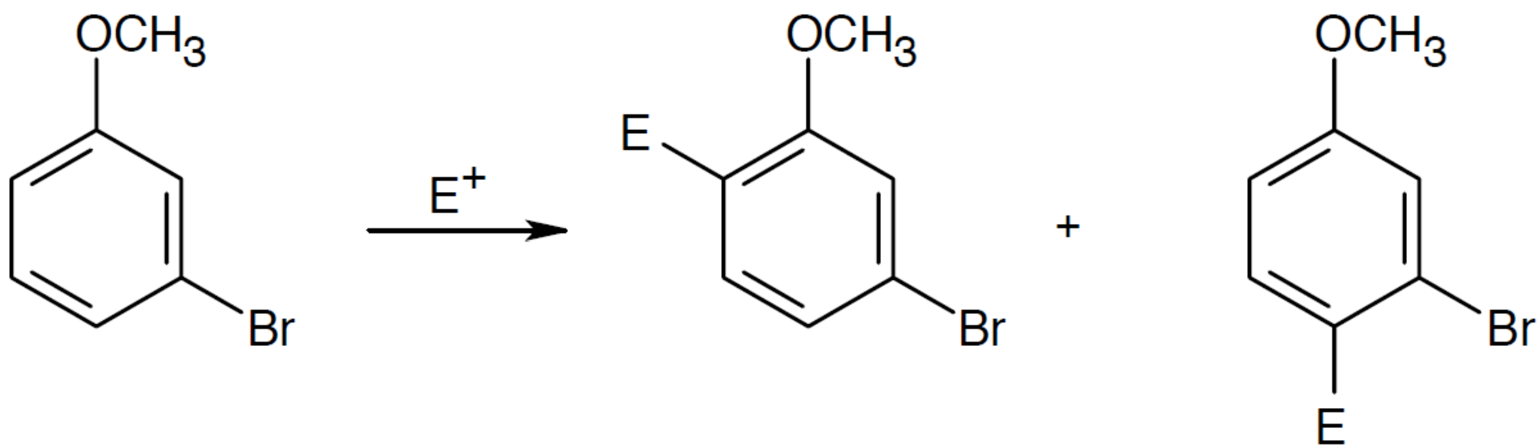
Worked Example

- Determine the position at which electrophilic substitution occurs in the following substance



Worked Example

- Solution:

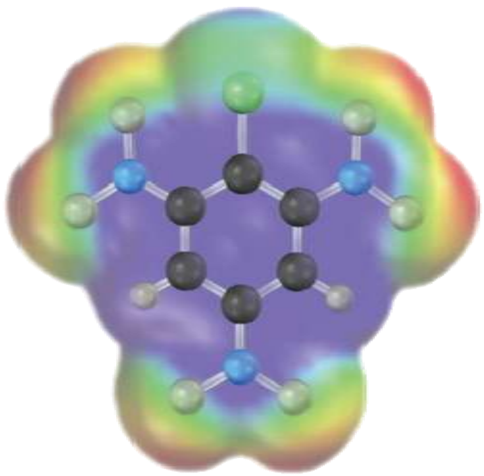


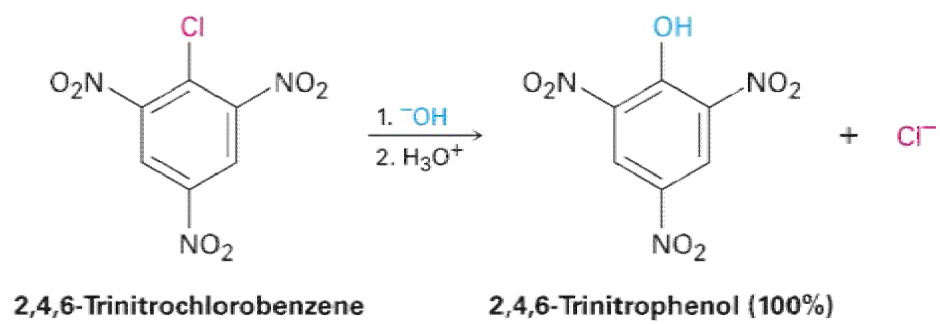
  - Both groups are ortho-para directors and direct substitution to the same positions
    - Attack does not occur between the two groups for steric reasons

NUCLEOPHILIC AROMATIC SUBSTITUTION

Nucleophilic Aromatic Substitution

- Aryl halides with electron-withdrawing substituents can also undergo a nucleophilic substitution reaction





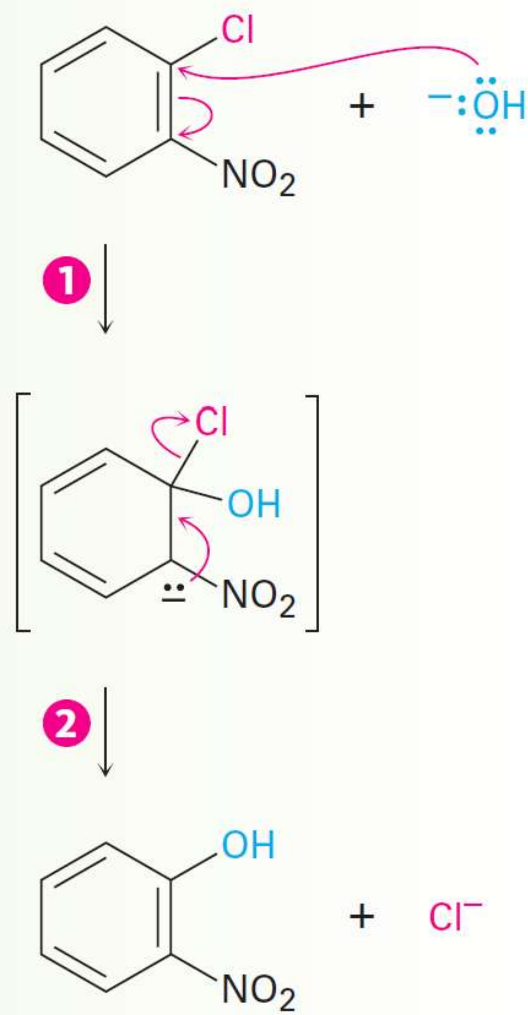
Nucleophilic Aromatic Substitution

- Not very common
- Uses
  - Reaction of proteins with Sanger's reagent results in a label being attached to one end of the protein chain
  - Reaction is superficially similar to the S_N1 and S_N2 nucleophilic substitutions
    - Aryl halides are inert to both S_N1 and S_N2 conditions

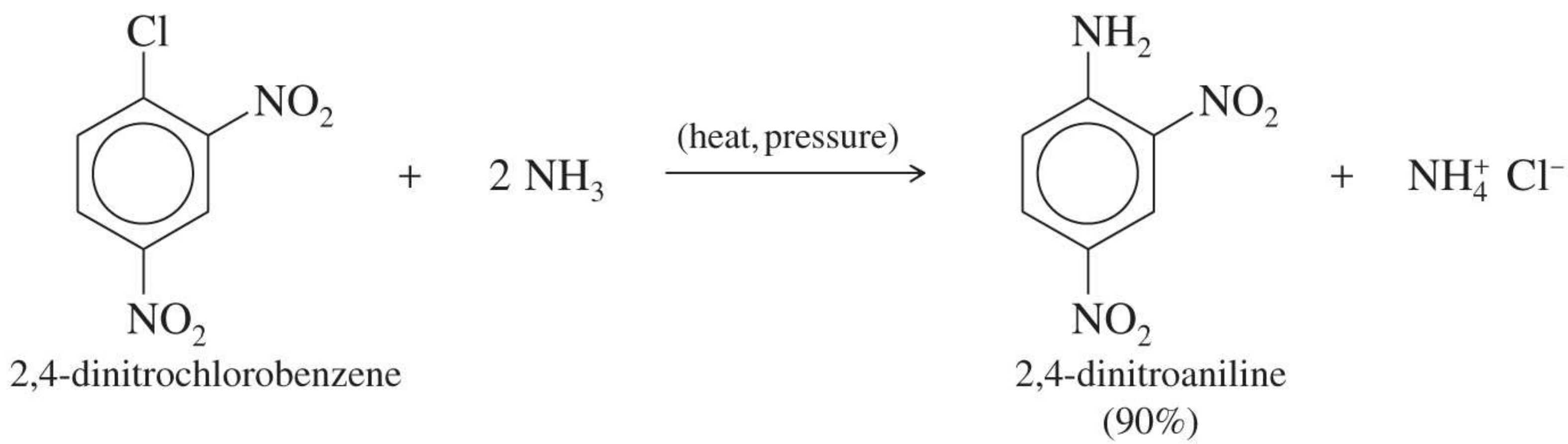
Nucleophilic Aromatic Substitution: Mechanism

1. Nucleophilic addition of hydroxide ion to the electron-poor aromatic ring takes place, yielding a stabilized carbanion intermediate.

2. The carbanion intermediate undergoes elimination of chloride ion in a second step to give the substitution product.



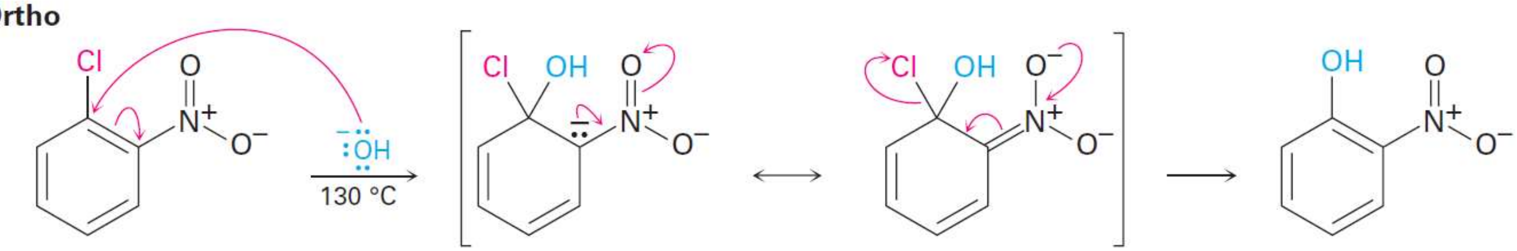
Nucleophilic Aromatic Substitution



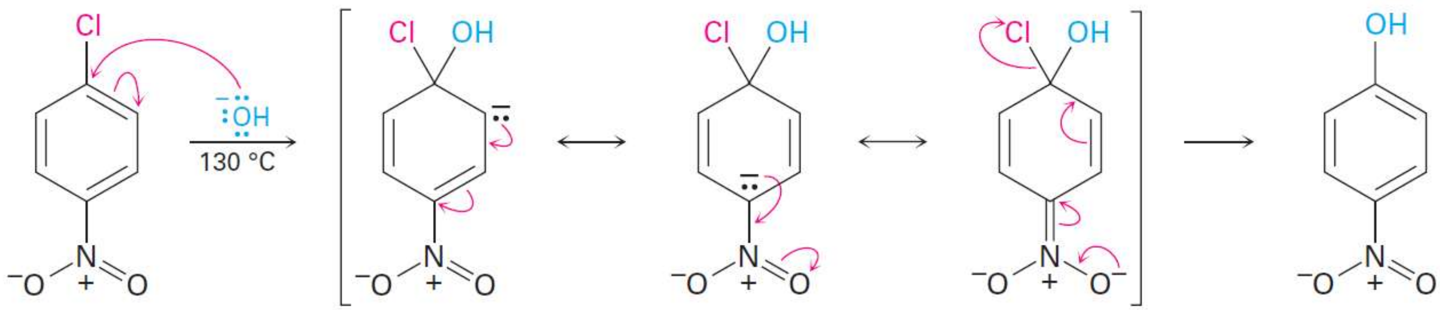
- A nucleophile replaces a leaving group on the aromatic ring
- This is an addition–elimination reaction
- Electron-withdrawing substituents activate the ring for nucleophilic substitution

Nucleophilic Aromatic Substitution: Nitrochlorobenzenes

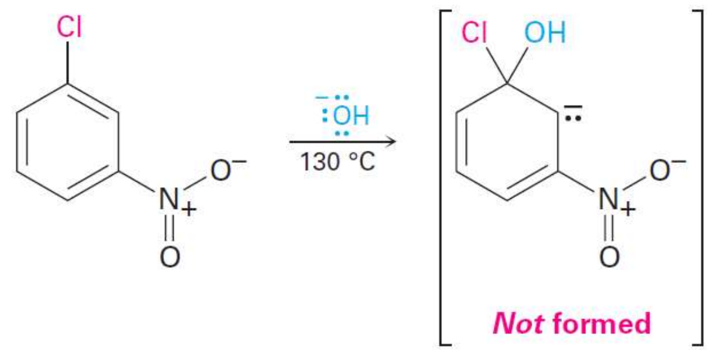
Ortho



Para



Meta



Differences Between Electrophilic and Nucleophilic Aromatic Substitutions

Electrophilic substitutions

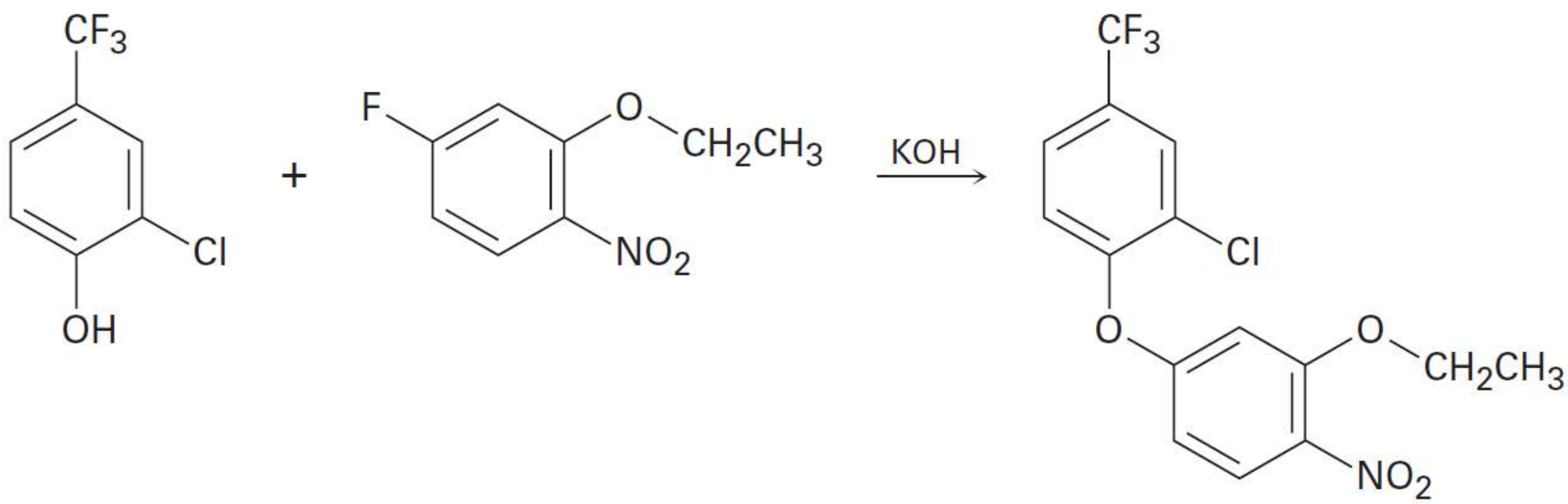
- Favored by electron-donating substituents
- Electron-withdrawing groups cause ring deactivation
  - Electron-withdrawing groups are meta directors
- Replace hydrogen on the ring

Nucleophilic substitutions

- Favored by electron-withdrawing substituents
- Electron-withdrawing groups cause ring activation
  - Electron withdrawing groups are ortho-para directors
- Replace a leaving group

Worked Example

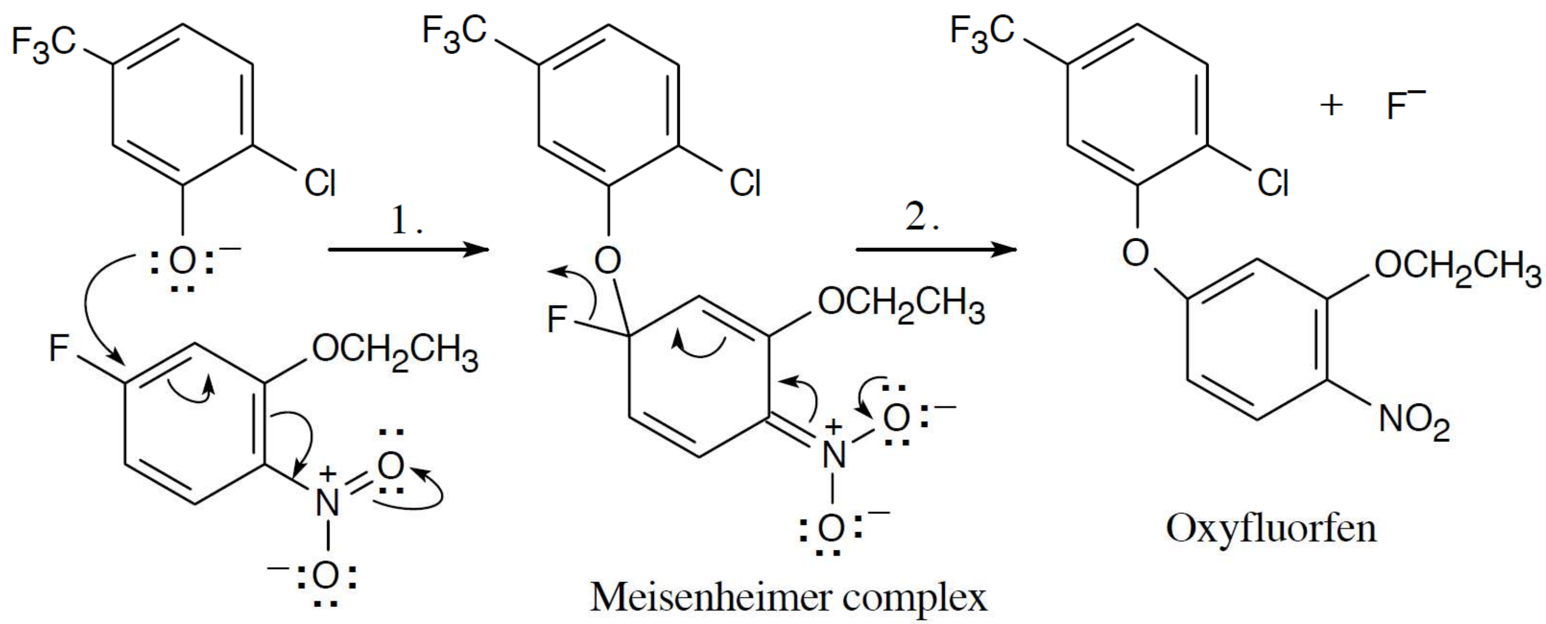
- Propose a mechanism for the preparation of oxyfluorfen, a herbicide, through the reaction between phenol and an aryl fluoride



Oxyfluorfen

Worked Example

- Solution:

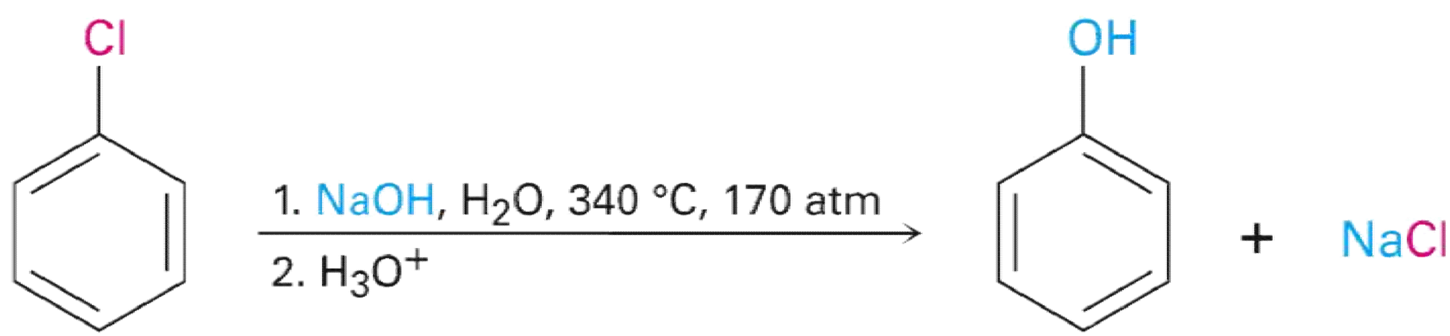


  - Step 1: Addition of the nucleophile
  - Step 2: Elimination of the fluoride ion

BENZYNE

Benzyne

- On a general basis, there are no reactions between nucleophiles and halobenzenes that do not have electron withdrawing substituents
  - High temperatures can be used to make chlorobenzene react

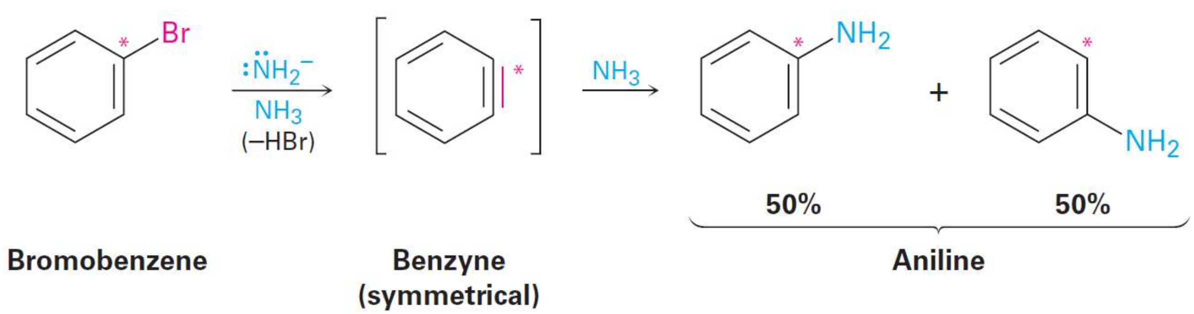


Chlorobenzene

Phenol

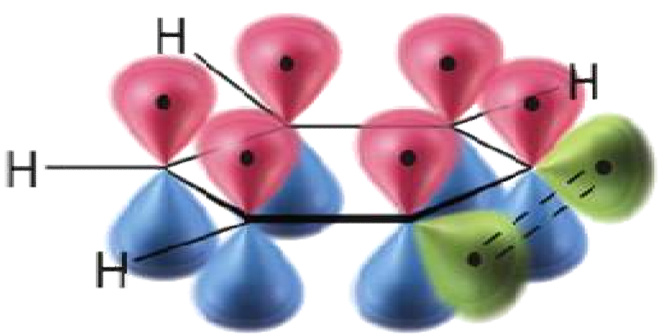
Benzyne

- A Diels-Adler reaction occurs when bromobenzene reacts with KNH_2 in the presence of a conjugated diene, such as furan
  - Elimination of HBr from bromobenzene forms a **benzyne** as the chemical intermediate

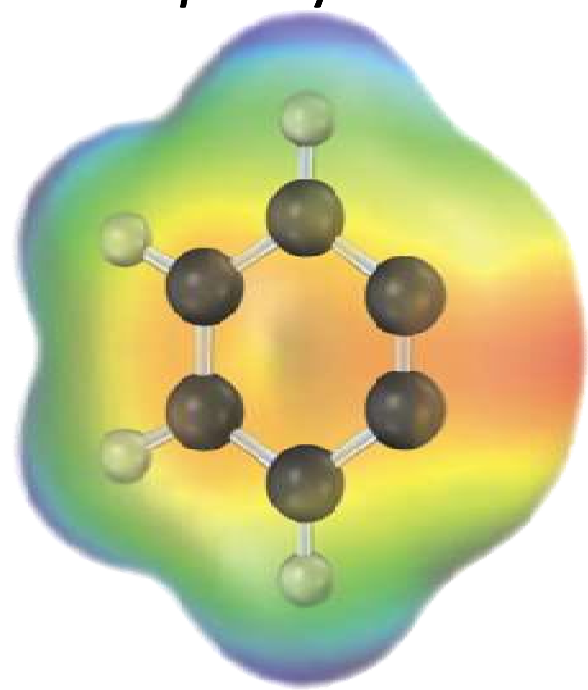


Benzyne

- Benzyne has the electronic structure of a highly distorted alkyne
  - The benzyne triple bond uses *sp*^{2}-hybridized carbon atoms

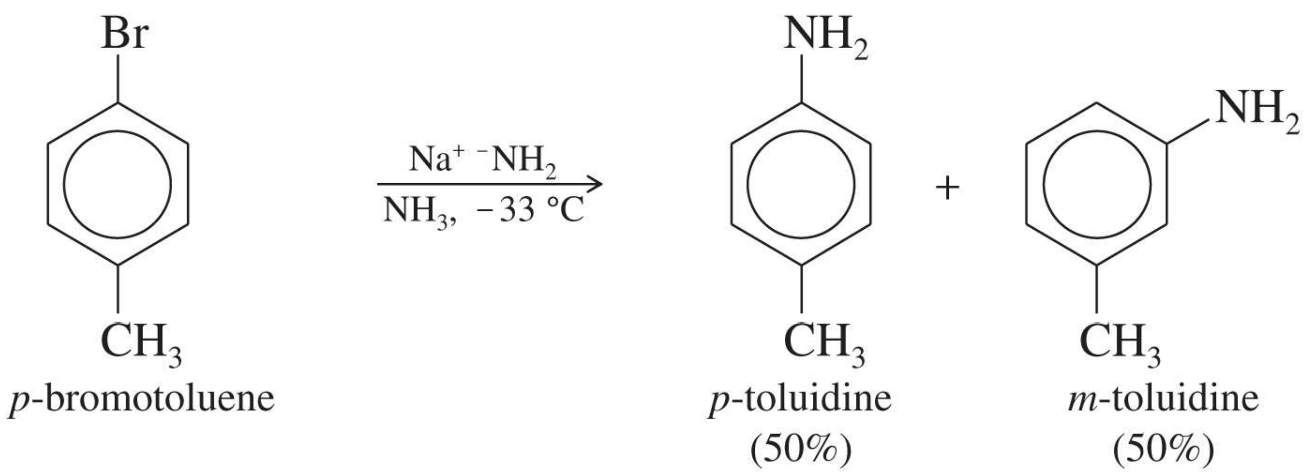


Side view



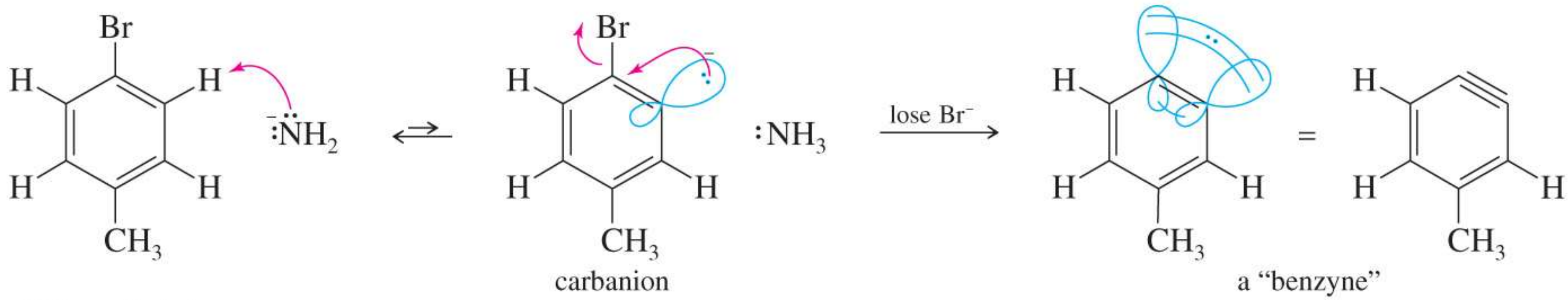
Benzyne

Benzyne Reaction: Elimination–Addition



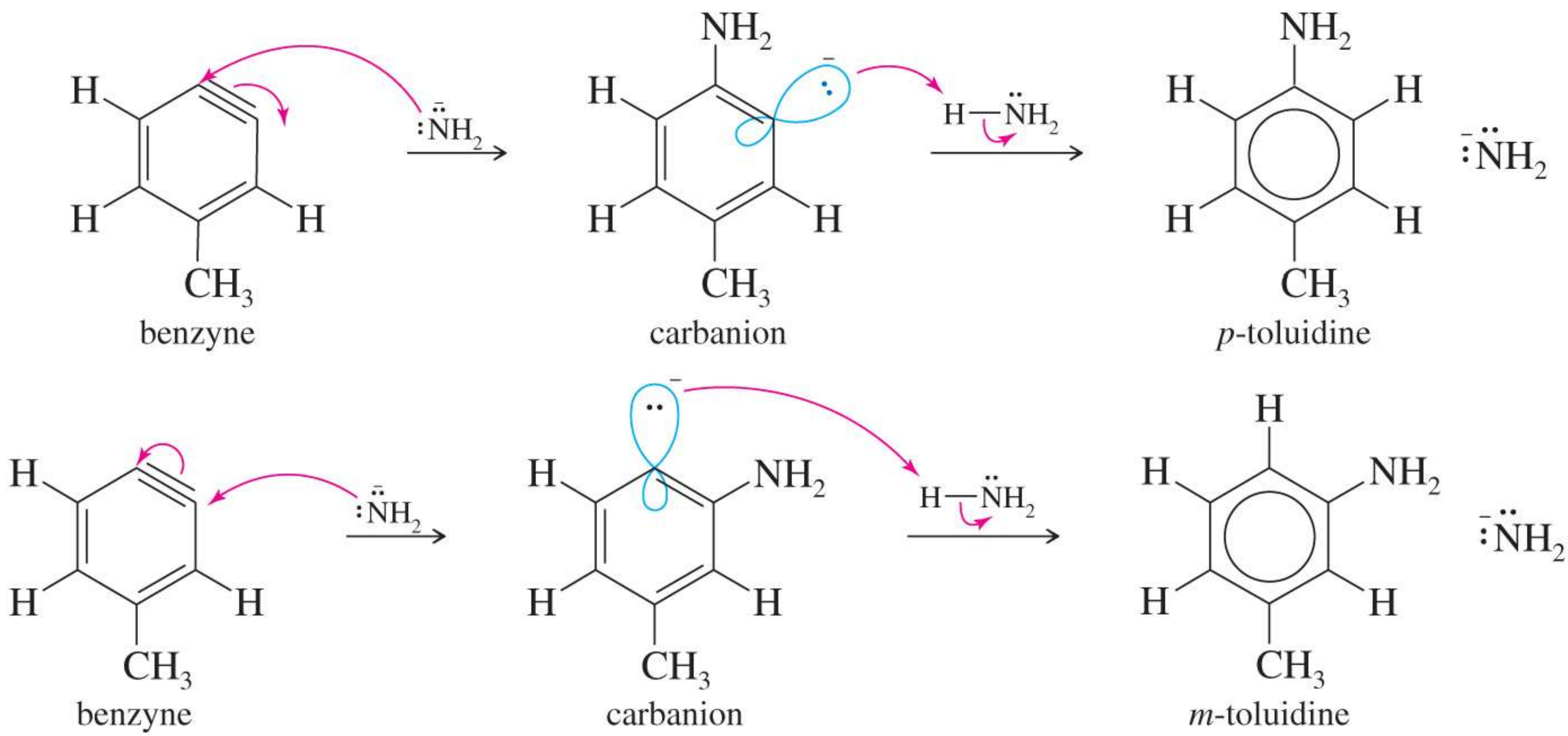
- Reactant is halobenzene with no electron-withdrawing groups on the ring
- Use a very strong base like $NaNH_2$

Benzyne: Mechanism



- Sodium amide abstracts a proton.
- The benzyne intermediate forms when the bromide is expelled and the electrons on the *sp*^{2} orbital adjacent to it overlap with the empty *sp*^{2} orbital of the carbon that lost the bromide.
- Benzynes are very reactive species due to the high strain of the triple bond

Benzyne: Mechanism Intermediate



REMEMBER

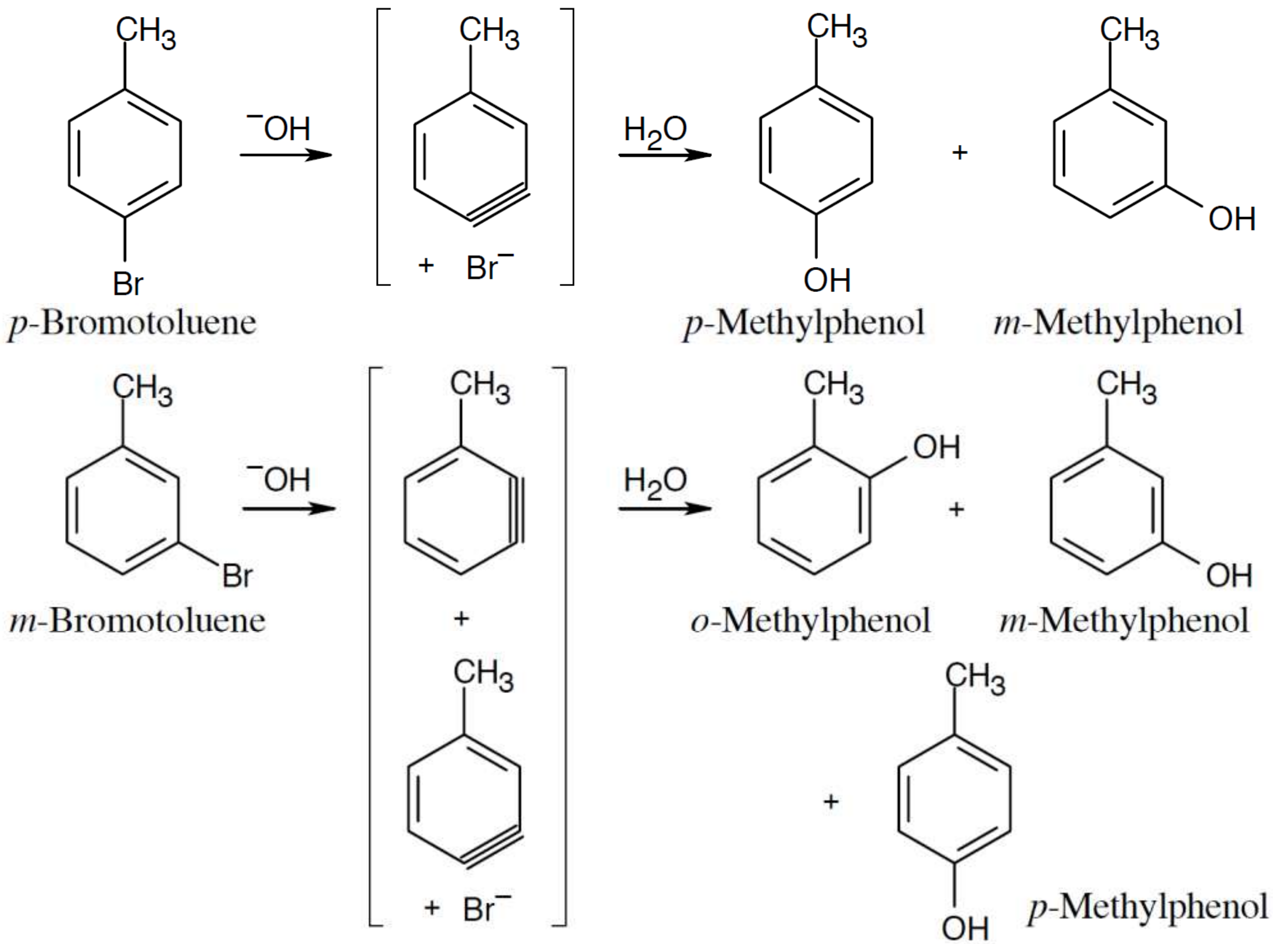
With strong electron-withdrawing groups ortho or para, the nucleophilic aromatic substitution is more likely. Without these activating groups, stronger conditions are required, and the benzyne mechanism is likely.

Worked Example

- Explain why the treatment of *p*-toluene with NaOH at 300°C yields a mixture of two products, but treatment of *m*-bromotoluene with NaOH yields a mixture of two or three products

Worked Example

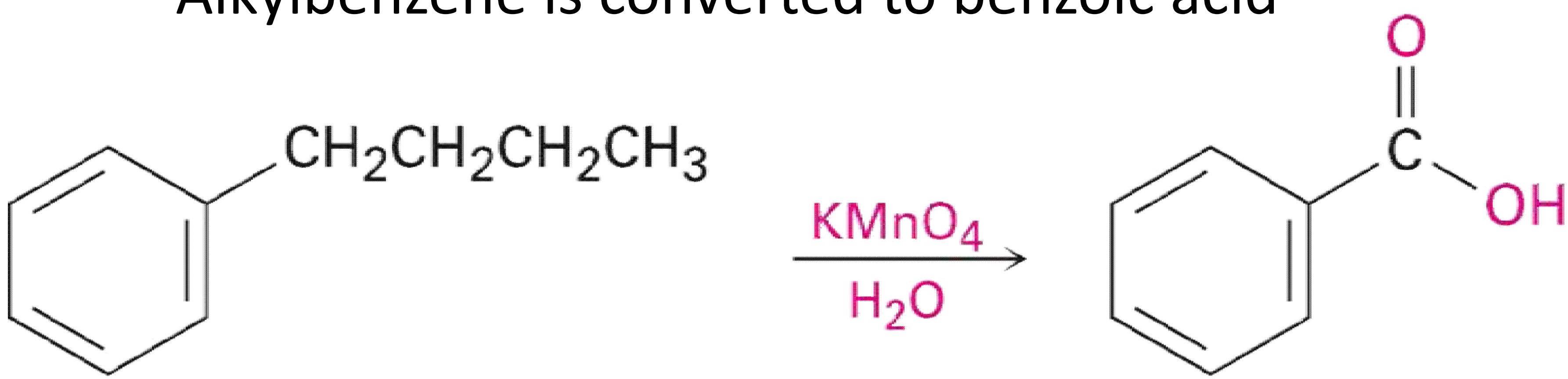
- Solution:



OXIDATION OF AROMATIC COMPOUNDS

Oxidation of Aromatic Compounds: Alkyl Side Chains

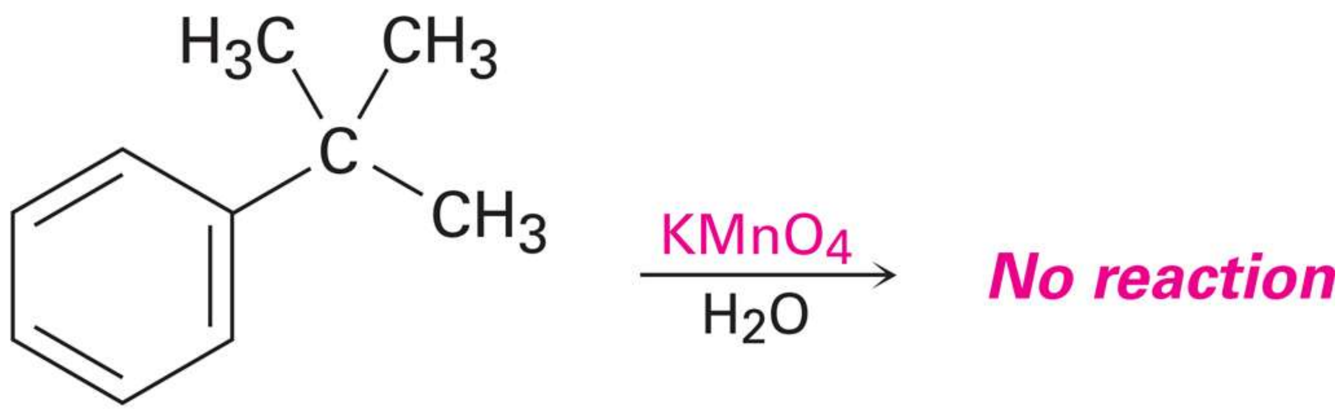
- In the presence of an aromatic ring, alkyl side chains are converted to carboxyl groups through oxidation
  - Alkylbenzene is converted to benzoic acid



Butylbenzene **Benzoic acid (85%)**

Oxidation of Aromatic Compounds: Alkyl Side Chains

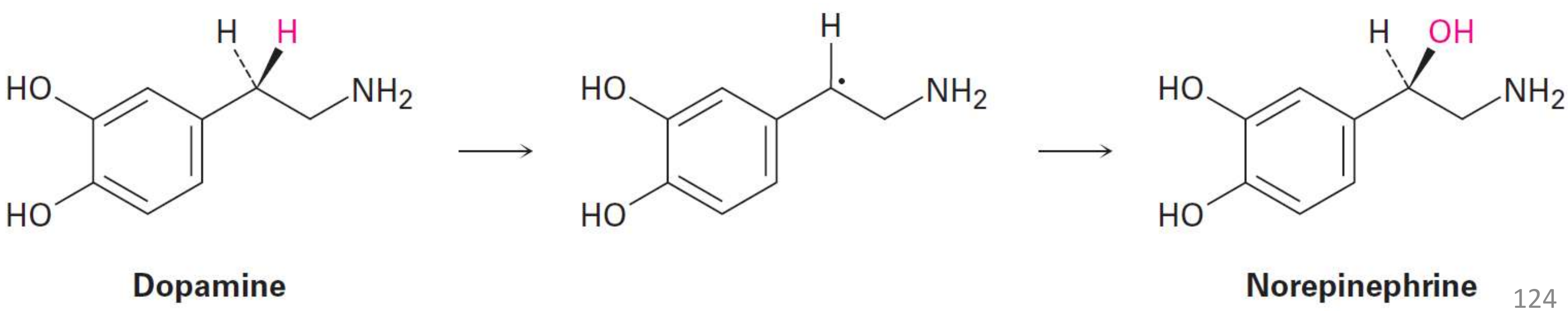
- Mechanism involves reaction of benzylic C-H bond
  - **No Benzylic Hydrogens, No Reaction**



tert-Butylbenzene

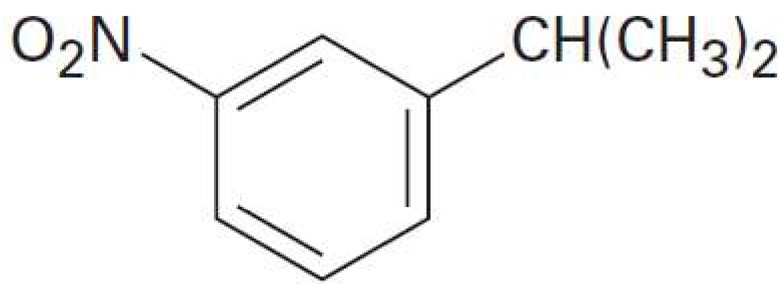
Oxidation of Aromatic Compounds : Alkyl Side Chains

- Side-chain oxidation involves a complex mechanism wherein C–H bonds next to the aromatic ring react to form intermediate benzylic radicals
- Analogous side-chain reactions are a part of many biosynthetic pathways



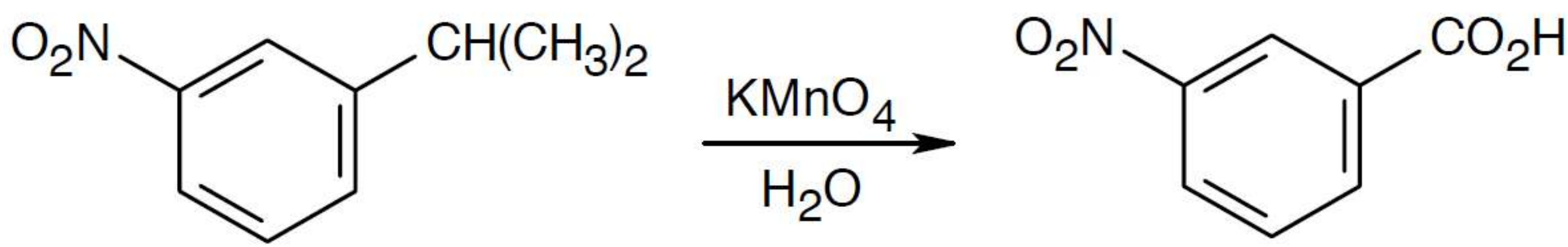
Worked Example

- Mention the aromatic substance that is obtained if $KMnO_4$ undergoes oxidation with the following substance

(a) 

Worked Example

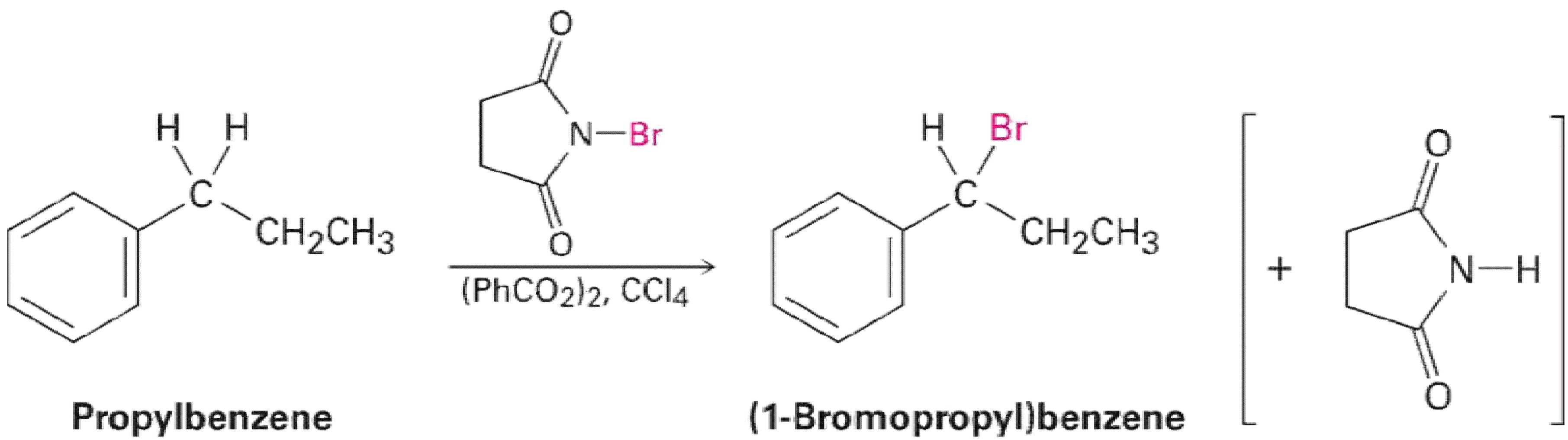
- Solution:
  - Oxidation takes place at the benzylic position



m-Nitrobenzoic acid

Oxidation of Aromatic Compounds: Alkylbenzene Side Chain Bromination

- Occurs when an alkylbenzene is treated with *N*-bromosuccinimide (NBS)

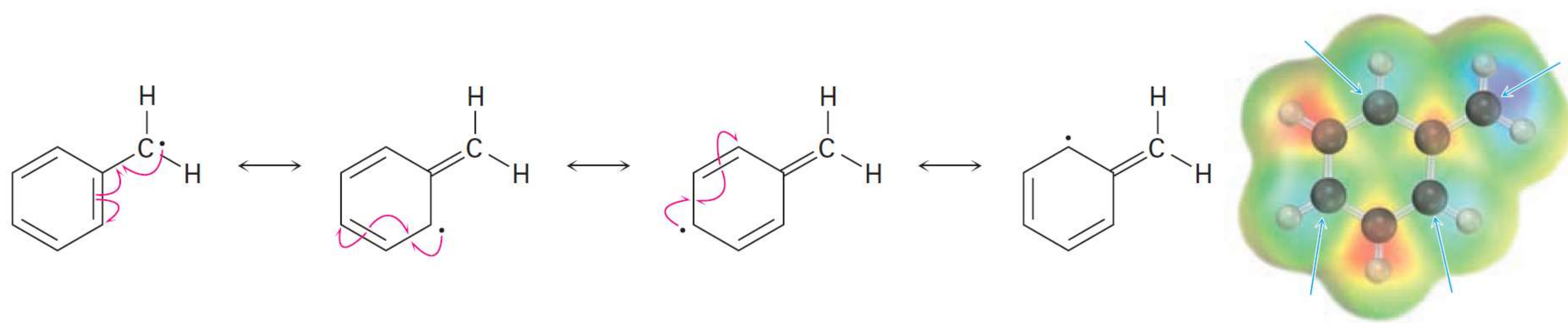


Propylbenzene

(1-Bromopropyl)benzene (97%)

Oxidation of Aromatic Compounds: Alkylbenzene Side Chain Bromination

- The reaction of HBr with NBS occurs only at the benzylic position
  - The benzylic radical intermediate is stabilized by resonance
    - The *p* orbital of the benzyl radical overlaps with the ringed π electron system



Oxidation of Aromatic Compounds: Alkylbenzene Side Chain Bromination Mechanism

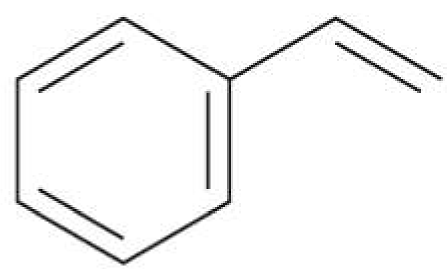
- Mechanism
  - Abstraction of a benzylic hydrogen atom generate an intermediate benzylic radical
  - Benzylic radical reacts with Br_2 to yield product and a Br^- radical
  - Br^- radical cycles back into reaction to carry on the chain
  - Br_2 is produced when HBr reacts with NBS

REMEMBER

In predicting reactions on side chains of aromatic rings, consider resonance forms that delocalize a charge or a radical electron onto the ring.

Worked Example

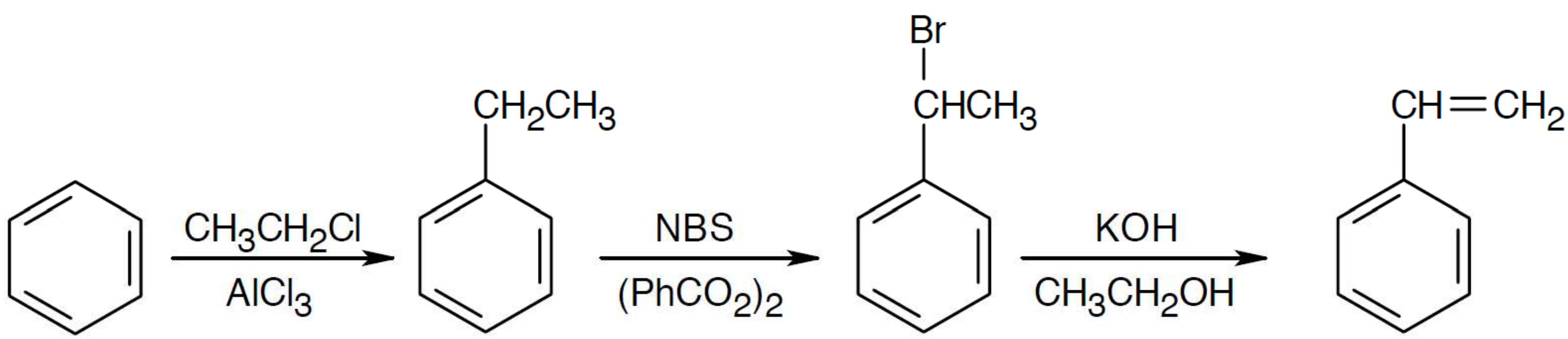
- Styrene, the simplest alkenylbenzene, is prepared for commercial use in plastics manufacture by catalytic dehydrogenation of ethylbenzene
  - Prepare styrene from benzene



Styrene

Worked Example

- Solution:

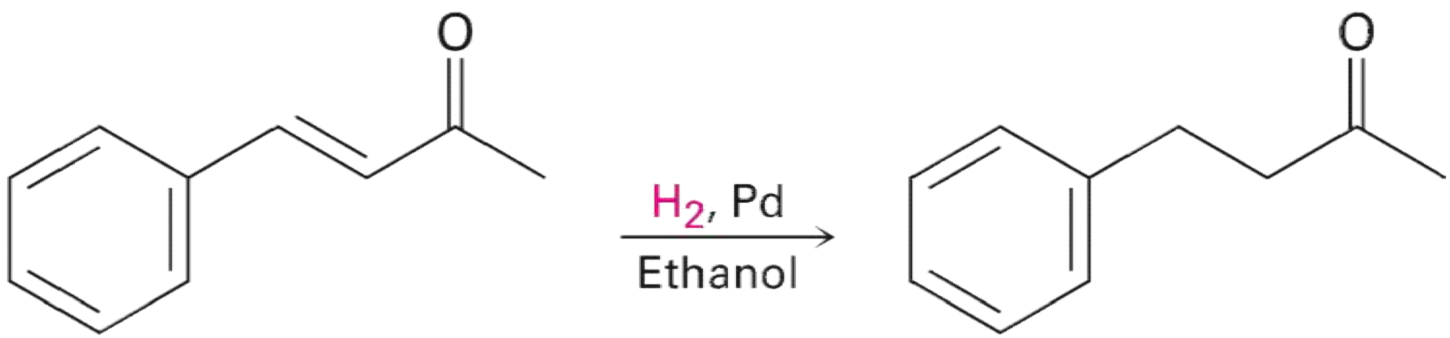


Styrene

REDUCTION OF AROMATIC COMPOUNDS

Aromatic Ring Reduction: Catalytic Hydrogenation

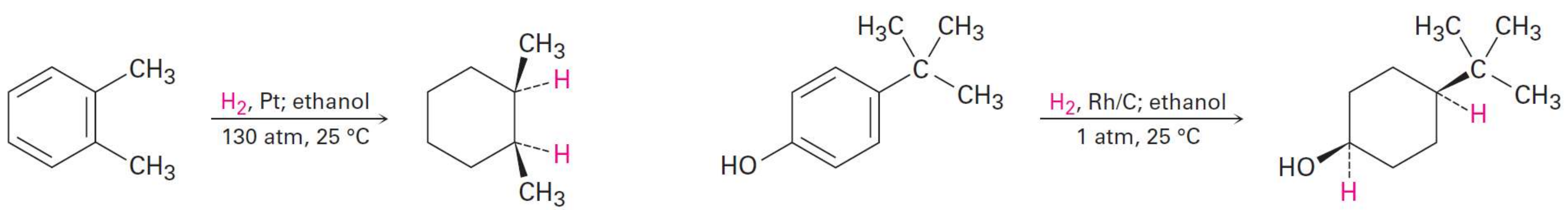
- Aromatic rings are inert to catalytic hydrogenation under conditions that reduce alkene double bonds
  - Selectively reduce an alkene double bond in the presence of an aromatic ring



4-Phenyl-3-buten-2-one → **4-Phenyl-2-butanone (100%)**

Aromatic Ring Reduction: Catalytic Hydrogenation

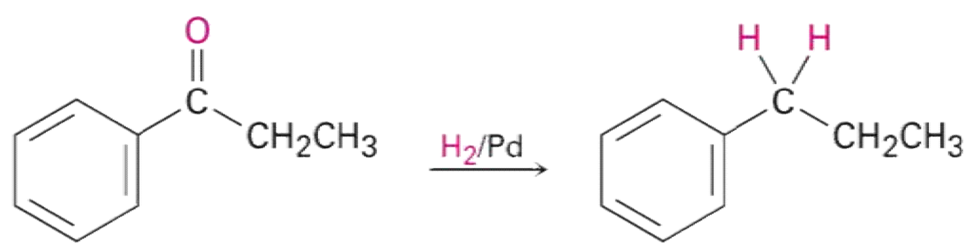
- Reduction of an aromatic ring requires either:
  - A platinum catalyst and a pressure of several hundred atmospheres
  - A catalyst such as rhodium or carbon
- Reduction cannot be stopped at an intermediate stage



***o*-Xylene** **_cis_-1,2-Dimethyl-cyclohexane** **4-_tert_-Butylphenol** **_cis_-4-_tert_-Butyl-cyclohexanol**

Aromatic Ring Reduction: Aryl Alkyl Ketones

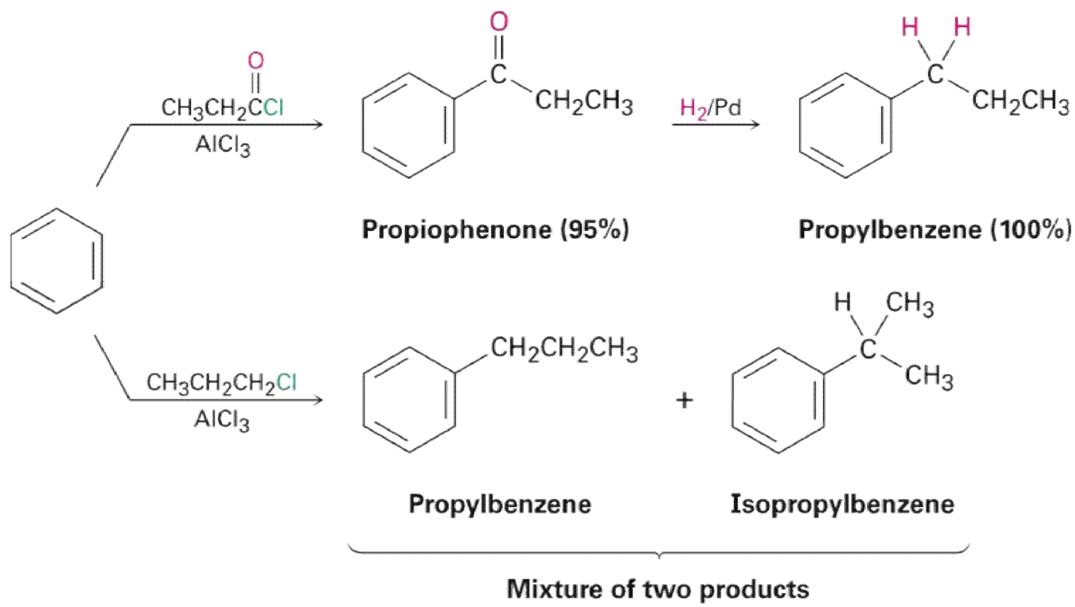
- An aromatic ring can activate neighboring carbonyl group toward reduction
  - An aryl alkyl ketone can be converted into an alkylbenzene by catalytic hydrogenation over a palladium catalyst



Propiophenone (95%) Propylbenzene (100%)

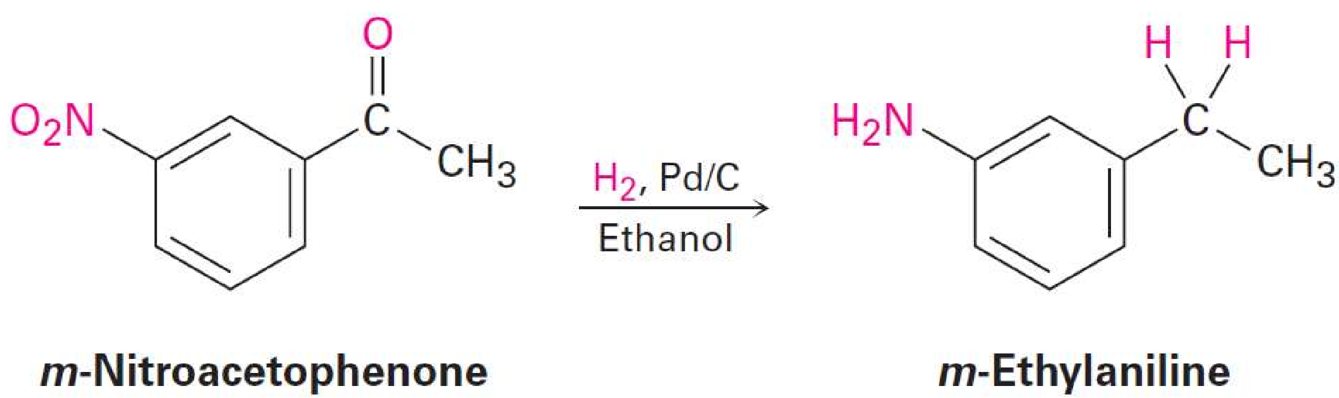
Aromatic Ring Reduction: Aryl Alkyl Ketones

- Aryl alkyl ketone prepared by Friedel-Crafts acylation can be converted into an alkylbenzene
  - Circumvents carbocation rearrangement problems that occur with Friedel-Crafts alkylation



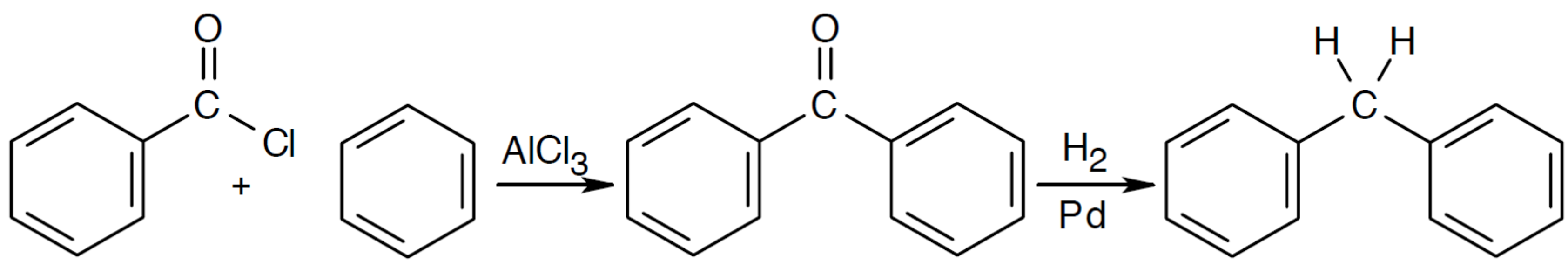
Aromatic Ring Reduction: Aryl Alkyl Ketones

- Only aryl alkyl ketones can be converted into a methylene group by catalytic hydrogenation
- Nitro substituents hinder the catalytic reduction of aryl alkyl ketones
  - Nitro group undergoes reduction to form an amino group



Worked Example

- Prepare diphenylmethane, $(Ph)_2CH_2$, from benzene and an acid chloride
- Solution:



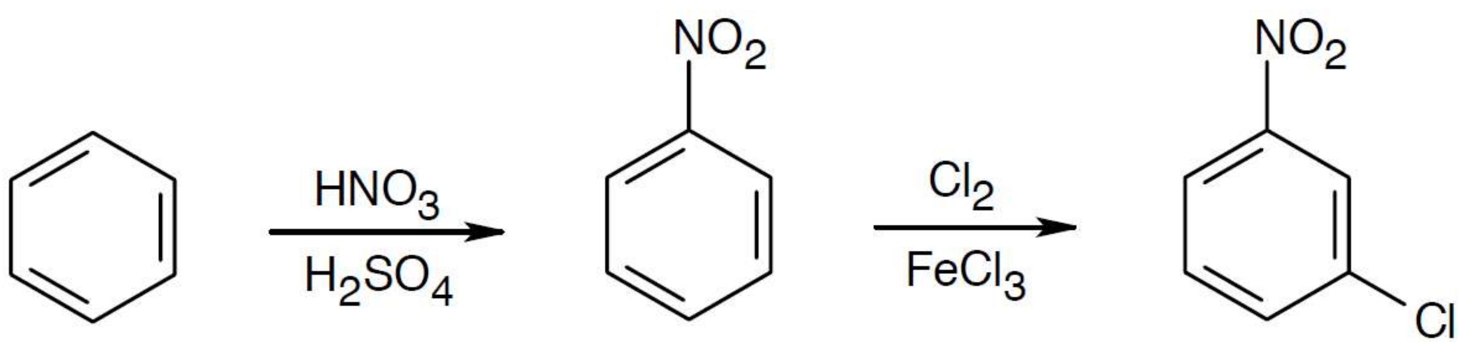
SYNTHESIS OF POLYSUBSTITUTED BENZENES

Synthesis of Polysubstituted Benzenes

- Working synthesis reactions is one of the best ways to learn organic chemistry
- Knowledge on using the right reactions at the right time is vital to a successful scheme
- Ability to plan a sequence of reactions in right order is valuable to synthesis of substituted aromatic rings

Worked Example

- Synthesize *m*-Chloronitrobenzene from benzene
- Solution:
  - In order to synthesize the product with the correct orientation of substituents, benzene must be nitrated before it is chlorinated



m-Chloronitrobenzene

Summary

- There are two phases in an electrophilic aromatic substitution reaction:
  - Initial reaction of an electrophile E^+
  - Loss of H^+ from the resonance-stabilized carbocation intermediate
- The Friedel-Crafts alkylation and acylation reactions are important electrophilic aromatic substitution reactions that involve the reaction of an aromatic ring with carbocation electrophiles

Summary

- Resonance and inductive effects are the means by which substituents influence aromatic rings
- Nucleophilic aromatic substitution is a reaction that halobenzenes go through and involve an addition of a nucleophile to the ring
- In halobenzenes that are not activated by electron-withdrawing substituents, nucleophilic aromatic substitutions occur by elimination of HX which yields a benzene