# Organic Chemistry, *Fourth Edition*

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# Chapter 18
# Lecture Outline

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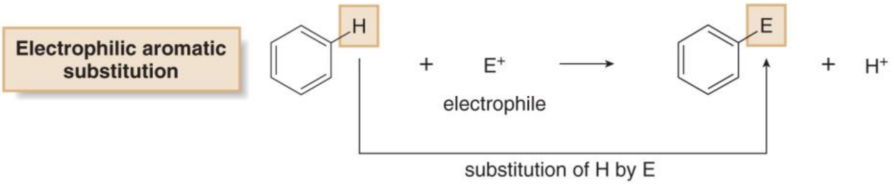
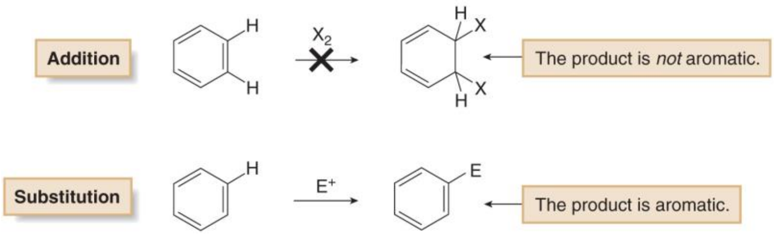
## Electrophilic Aromatic Substitution

- **The characteristic reaction of benzene is electrophilic aromatic substitution—a hydrogen atom is replaced by an electrophile.**
- **Since benzene is especially stable, reactions that keep the aromatic ring intact are favored.**



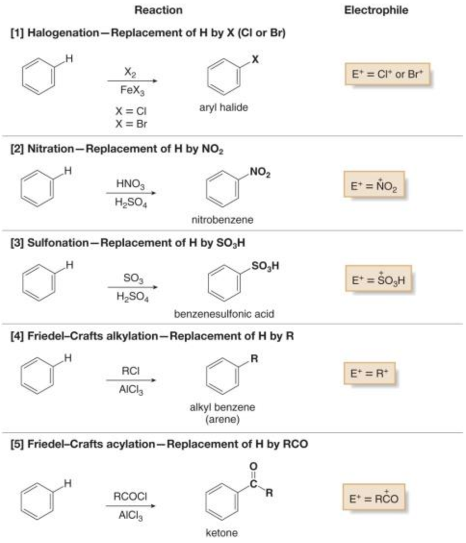
# Substitution Instead of Addition

- Benzene does not undergo addition reactions like other unsaturated hydrocarbons, because addition would yield a product that is not aromatic.
- Substitution of a hydrogen keeps the aromatic ring intact.
- There are several common examples of electrophilic aromatic substitution.



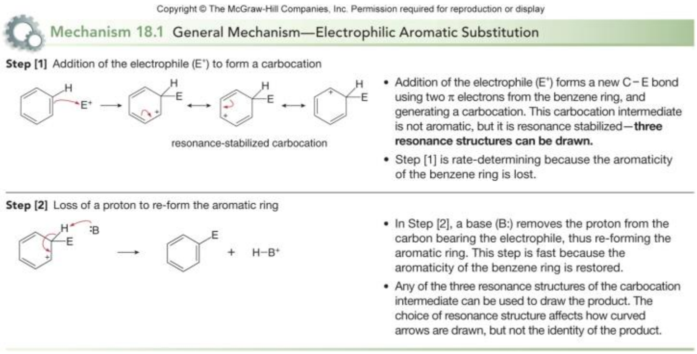
# Examples of Electrophilic Aromatic Substitution

Figure 18.1



# Mechanism of Substitution

- **Regardless of the electrophile used, all electrophilic aromatic substitution reactions occur by the same two-step mechanism:**
    1. **addition of the electrophile $E^+$ to form a resonance-stabilized carbocation,**
    2. **followed by deprotonation with base.**



**Mechanism 18.1** General Mechanism—Electrophilic Aromatic Substitution

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

resonance-stabilized carbocation

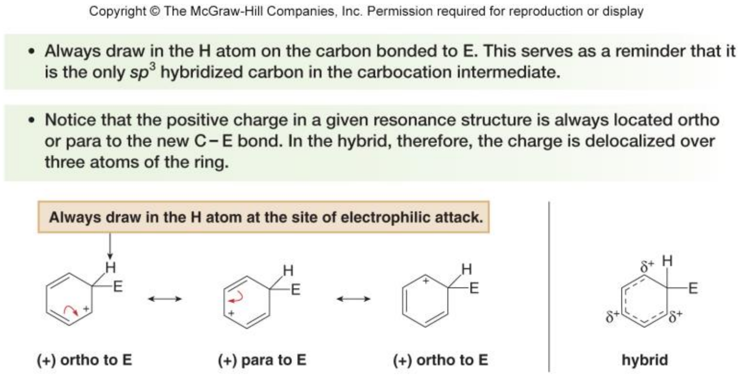
- Addition of the electrophile ($E^+$) forms a new C–E bond using two π electrons from the benzene ring, and generating a carbocation. This carbocation intermediate is not aromatic, but it is resonance stabilized—**three resonance structures can be drawn.**
- Step [1] is rate-determining because the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

**Step [2]** Loss of a proton to re-form the aromatic ring

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

# Resonance-Stabilized Aromatic Carbocation

- **The first step in electrophilic aromatic substitution forms a carbocation, for which three resonance structures can be drawn.**
- **To help keep track of the location of the positive charge:**



- Always draw in the H atom on the carbon bonded to E. This serves as a reminder that it is the only $sp^3$ hybridized carbon in the carbocation intermediate.

- Notice that the positive charge in a given resonance structure is always located ortho or para to the new C–E bond. In the hybrid, therefore, the charge is delocalized over three atoms of the ring.

**Always draw in the H atom at the site of electrophilic attack.**

**(+) ortho to E**

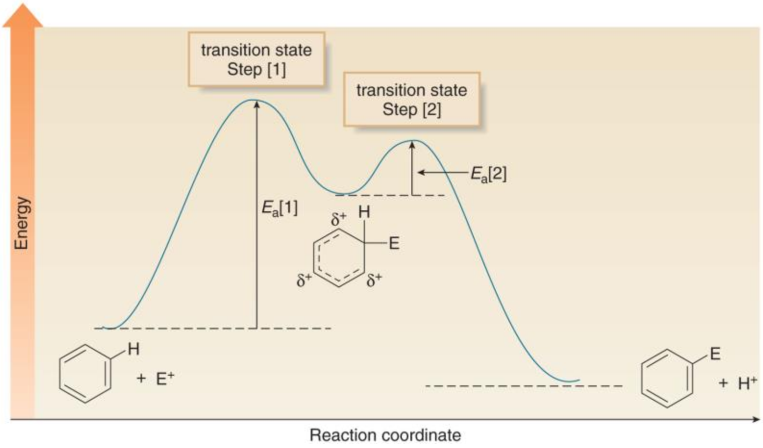
**(+) para to E**

**(+) ortho to E**

**hybrid**

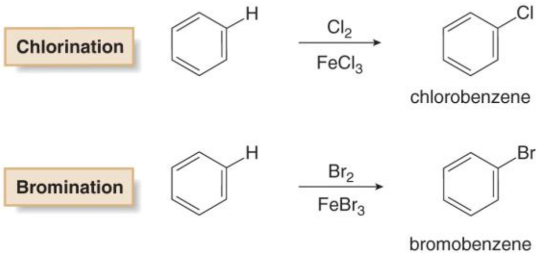
# Energy Diagram for Electrophilic Aromatic Substitution

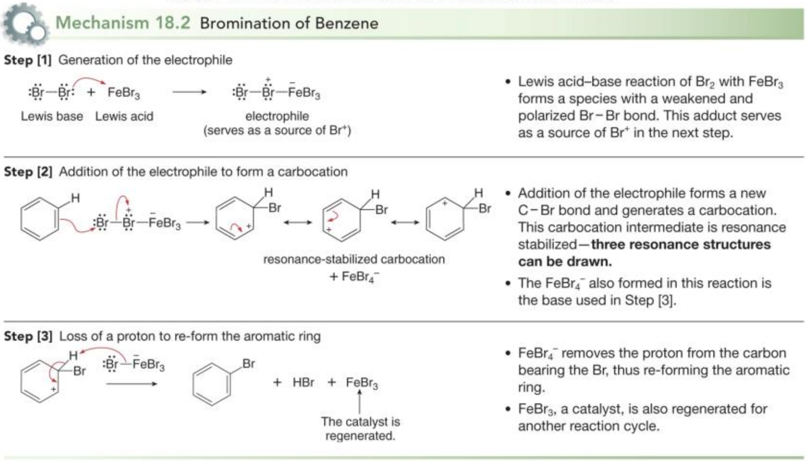
Figure 18.2



# Halogenation

- In **halogenation**, benzene reacts with $Cl_2$ or $Br_2$ in the presence of a Lewis acid catalyst, such as **$FeCl_3$** or **$FeBr_3$**, to give the aryl halides chlorobenzene or bromobenzene, respectively.
- Analogous reactions with $I_2$ and $F_2$ are not synthetically useful because $I_2$ is too unreactive and $F_2$ reacts too violently.





**Step [1]** Generation of the electrophile

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

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

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

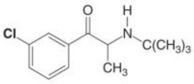
**Step [3]** Loss of a proton to re-form the aromatic ring

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

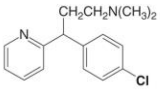
- **Chlorination proceeds by a similar mechanism.**

# Biologically Active Alkyl Chlorides

Figure 18.3

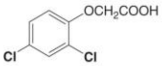


Generic name: **bupropion**
Trade names: **Wellbutrin, Zyban**
antidepressant,
also used to reduce nicotine cravings

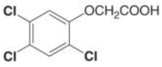


**chlorpheniramine**
antihistamine

Herbicides were used extensively during the Vietnam War to defoliate dense jungle areas. The concentration of certain herbicide by-products in the soil remains high today.



**2,4-D**
2,4-dichlorophenoxy-acetic acid
herbicide

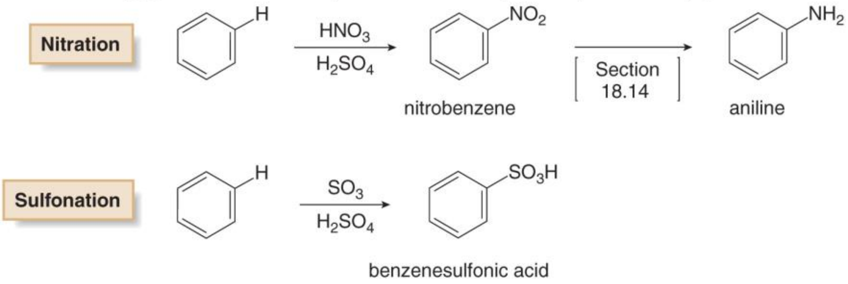


**2,4,5-T**
2,4,5-trichlorophenoxy-acetic acid
herbicide

the active components in **Agent Orange**,
a defoliant used in the Vietnam War

# Nitration and Sulfonation

- **Nitration and sulfonation introduce two different functional groups into the aromatic ring.**
- **Nitration is especially useful because the nitro group can be reduced to an $NH_2$ group.**



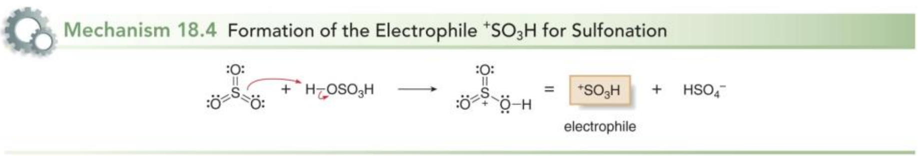
# Nitration Mechanism

- **Generation of the electrophile in nitration requires strong acid.**


Mechanism 18.3 Formation of the Nitronium Ion ($^+NO_2$) for Nitration

# Sulfonation Mechanism

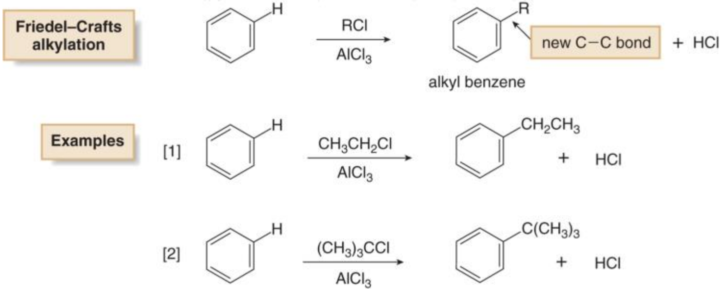
- **Generation of the electrophile in sulfonation requires strong acid.**



Mechanism 18.4 Formation of the Electrophile $^{+}SO_3H$ for Sulfonation

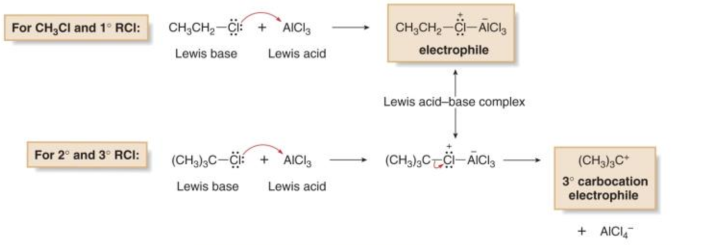
# Friedel–Crafts Alkylation

- **In Friedel–Crafts alkylation, treatment of benzene with an alkyl halide and a Lewis acid ($AlCl_3$) forms an alkyl benzene.**



# Electrophiles in Friedel–Crafts Alkylation

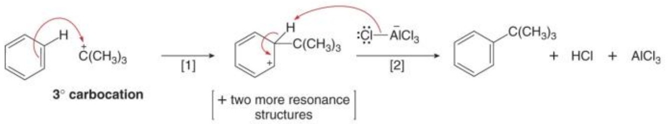
**Mechanism 18.5** Formation of the Electrophile in Friedel–Crafts Alkylation—Two Possibilities



- For $CH_3Cl$ and 1° RCl, the Lewis acid–base complex itself serves as the electrophile for electrophilic aromatic substitution.
- With 2° and 3° RCl, the Lewis acid–base complex reacts further to give a 2° or 3° carbocation, which serves as the electrophile. Carbocation formation occurs only with 2° and 3° alkyl chlorides, because they afford more stable carbocations.

# Friedel–Crafts Alkylation with 3º Carbocation

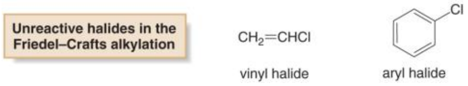
**Mechanism 18.6** Friedel–Crafts Alkylation Using a 3° Carbocation



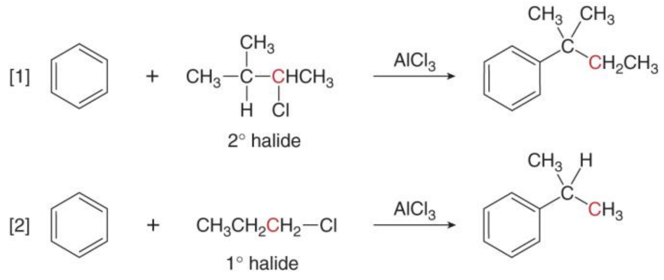
- Addition of the electrophile (a 3° carbocation) forms a new carbon–carbon bond in Step [1].
- $AlCl_4^-$ removes a proton on the carbon bearing the new substituent, thus re-forming the aromatic ring in Step [2].

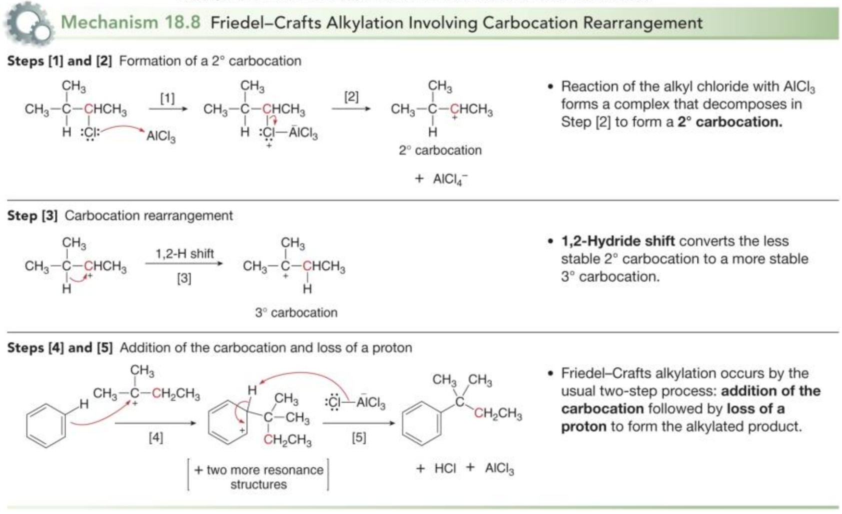
# Other Facts About Friedel–Crafts Alkylation

[1] **Vinyl halides and aryl halides do not react in Friedel–Crafts alkylation.**



[2] **Rearrangements can occur.**



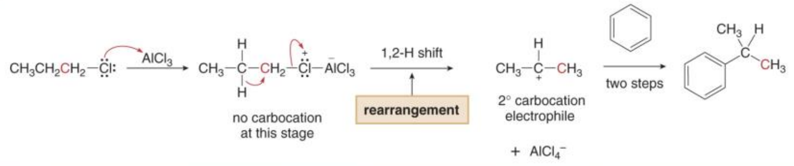


- Reaction of the alkyl chloride with $AlCl_3$ forms a complex that decomposes in Step [2] to form a **2° carbocation.**
- **1,2-Hydride shift** converts the less stable 2° carbocation to a more stable 3° carbocation.
- Friedel–Crafts alkylation occurs by the usual two-step process: **addition of the carbocation** followed by **loss of a proton** to form the alkylated product.

# Rearrangements of 1º Alkyl Halides

- **Rearrangements can occur even when no free carbocation is formed initially.**

**Mechanism 18.9** A Rearrangement Reaction Beginning with a 1° Alkyl Chloride

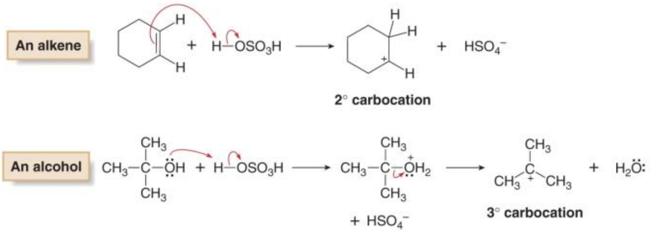


# Other Carbocations in Friedel–Crafts Alkylation

**[3] Other functional groups that form carbocations can also be used as starting materials.**

- Protonation of an alkene forms a carbocation, which can then serve as an electrophile in a Friedel–Crafts alkylation.

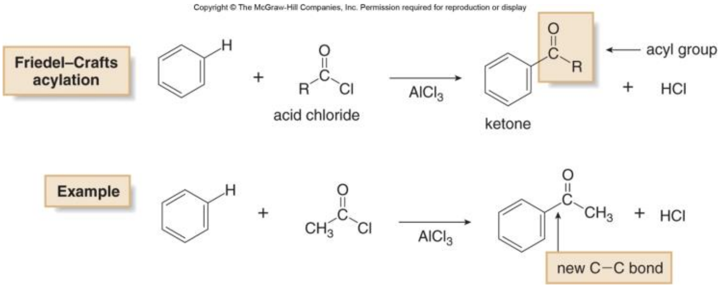
- Protonation of an alcohol, followed by loss of water, likewise forms a carbocation.



- **Carbocations formed in the presence of benzene can then substitute onto the ring by the usual mechanism.**

# Friedel–Crafts Acylation

- In **Friedel–Crafts acylation**, a benzene ring is treated with an acid chloride (**RCOCl**) and $AlCl_3$ to form a ketone.
- Because the new group bonded to the benzene ring is called an **acyl group**, the transfer of an acyl group from one atom to another is an acylation.



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# Friedel–Crafts Acylation

- In Friedel–Crafts acylation, the Lewis acid $AlCl_3$ ionizes the carbon–halogen bond of the acid chloride, thus forming a positively charged carbon electrophile called an **acylium ion**, which is resonance stabilized.
- The positively charged carbon atom of the acylium ion then goes on to react with benzene in the two-step mechanism of electrophilic aromatic substitution.

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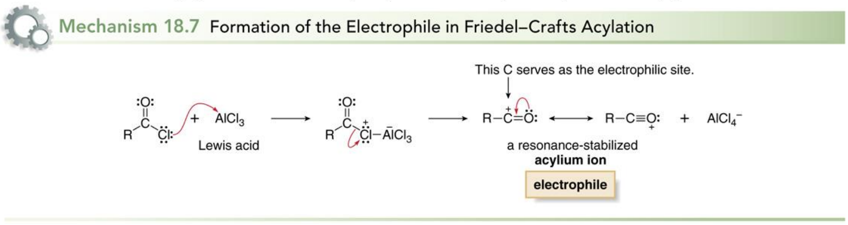
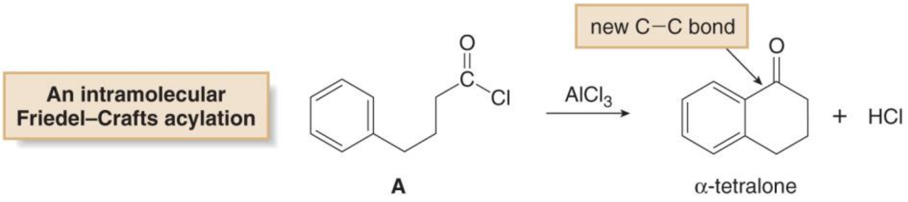


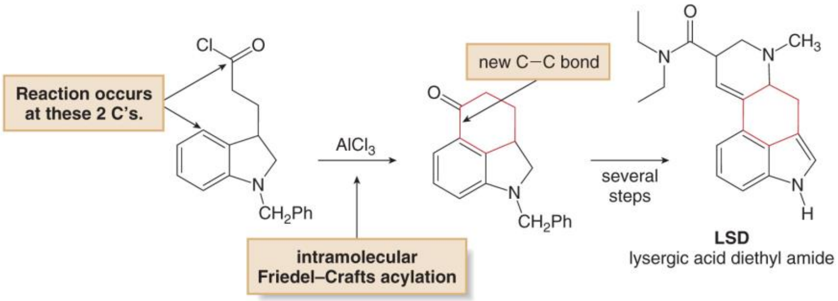
# Intramolecular Friedel–Crafts Reactions

- **Starting materials that contain both a benzene ring and an electrophile are capable of intramolecular Friedel–Crafts reactions.**



# Intramolecular Friedel–Crafts Reactions

Figure 18.4
Synthesis of LSD

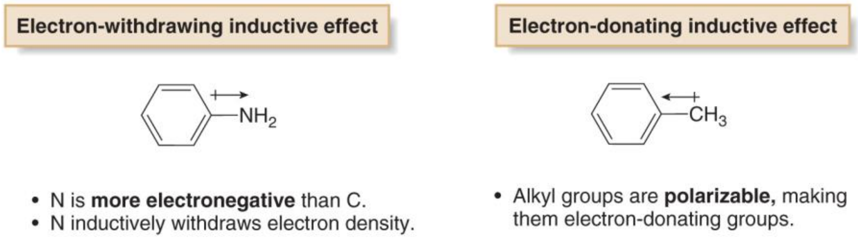


## Substituent Effects of Substituted Benzenes

- **Many substituted benzene rings undergo electrophilic aromatic substitution.**
- **Each substituent either increases or decreases the electron density in the benzene ring, and this affects the course of electrophilic aromatic substitution.**
  - **Donation of electron density to the ring makes benzene more electron rich.**
  - **Withdrawal of electron density from the ring makes benzene less electron rich.**
- **Electrophilic substitution on an already substituted benzene produces isomers, some of which are favored over others.**

## Inductive Effects

- **Considering inductive effects only, the $NH_2$ group withdraws electron density and $CH_3$ donates electron density.**



- N is **more electronegative** than C.
- N inductively withdraws electron density.

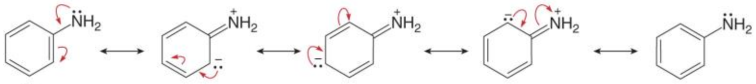
- Alkyl groups are **polarizable,** making them electron-donating groups.

# Resonance Effects

- **Resonance effects are only observed with substituents containing lone pairs or π bonds.**

- A resonance effect is electron donating when resonance structures place a negative charge on carbons of the benzene ring.
- A resonance effect is electron withdrawing when resonance structures place a positive charge on carbons of the benzene ring.

- **An electron-donating resonance effect is observed whenever an atom Z having a lone pair of electrons is directly bonded to a benzene ring.**

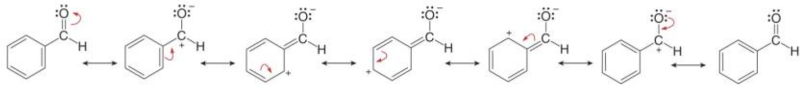


aniline

Three resonance structures place a (–) charge on atoms in the ring.

# Electron-Withdrawing Resonance Effects

- **An electron-withdrawing resonance effect is observed in substituted benzenes having the general structure $C_6H_5$-Y=Z, where Z is more electronegative than Y.**
- **Seven resonance structures can be drawn for benzaldehyde ($C_6H_5CHO$).**
- **Because three of them place a positive charge on a carbon atom of the benzene ring, the CHO group withdraws electrons from the benzene ring by a resonance effect.**

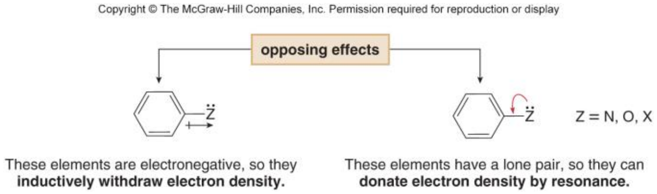


benzaldehyde

Three resonance structures place a (+) charge on atoms in the ring.

# Inductive and Resonance Effects

- To predict whether a substituted benzene is more or less electron rich than benzene itself, we must consider the net balance of both the inductive and resonance effects.
- Alkyl groups donate electrons by an inductive effect, but they have no resonance effect because they lack nonbonded electron pairs or $\pi$ bonds.
- Thus, any alkyl-substituted benzene is more electron rich than benzene itself.
- The same analysis can be done with groups other than alkyl.

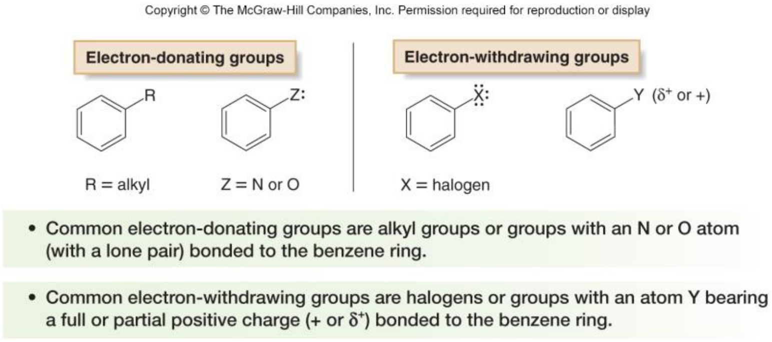


These elements are electronegative, so they **inductively withdraw electron density.**

These elements have a lone pair, so they can **donate electron density by resonance.**

# Electron-Donating and Electron-Withdrawing Groups

- These compounds represent examples of the general structural features in electron-donating and electron-withdrawing substituents.

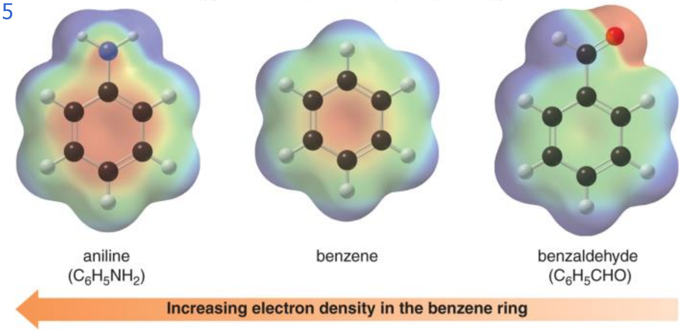


- Common electron-donating groups are alkyl groups or groups with an N or O atom (with a lone pair) bonded to the benzene ring.
- Common electron-withdrawing groups are halogens or groups with an atom Y bearing a full or partial positive charge (+ or $\delta^+$) bonded to the benzene ring.

# Electron-Donating and Electron-Withdrawing Groups

- The $NH_2$ group donates electron density making the benzene ring more electron rich.
- The CHO group withdraws electron density, making the benzene ring less electron rich.

Figure 18.5

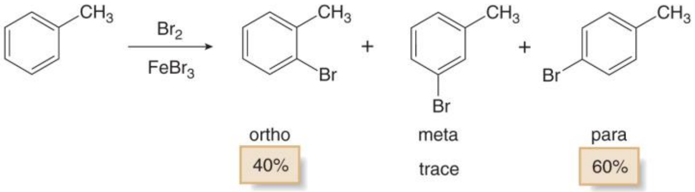


# Substituent Effects on Electrophilic Aromatic Substitution

- Electrophilic aromatic substitution is a general reaction of all aromatic compounds, including polycyclic aromatic hydrocarbons, heterocycles, and substituted benzene derivatives.
- A substituent affects two aspects of the electrophilic aromatic substitution reaction:
  1. The rate of the reaction: A substituted benzene reacts faster or slower than benzene itself.
  2. The orientation: The new group is located either ortho, meta, or para to the existing substituent.
     - The identity of the first substituent determines the position of the second incoming substituent.

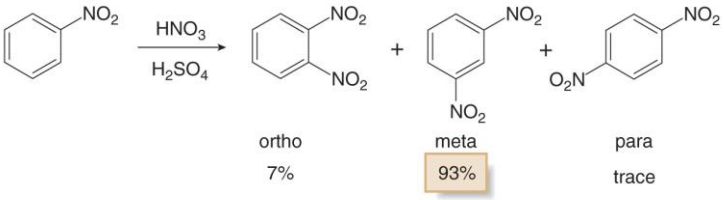
# Ortho, Para Directors—Activators

- **Toluene reacts faster than benzene in all substitution reactions.**
- **The electron-donating $CH_3$ group activates the benzene ring to electrophilic attack.**
- **Ortho and para products predominate.**
- **The $CH_3$ group is called an ortho, para director.**



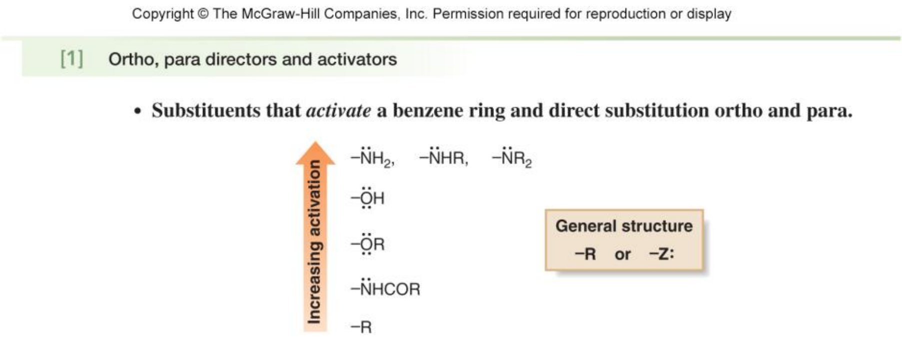
# Meta Directors—Deactivators

- **Nitrobenzene reacts more slowly than benzene in all substitution reactions.**
- **The electron-withdrawing $NO_2$ group deactivates the benzene ring to electrophilic attack.**
- **The meta product predominates.**
- **The $NO_2$ group is called a meta director.**



# Categorizing Directors and Activators

- **All substituents can be divided into three general types:**



[1] Ortho, para directors and activators

- **Substituents that *activate* a benzene ring and direct substitution ortho and para.**

$-\ddot{N}H_2$, $-\ddot{N}HR$, $-\ddot{N}R_2$

$-\ddot{\underset{\cdot\cdot}{O}}H$

$-\ddot{\underset{\cdot\cdot}{O}}R$

$-\ddot{N}HCOR$

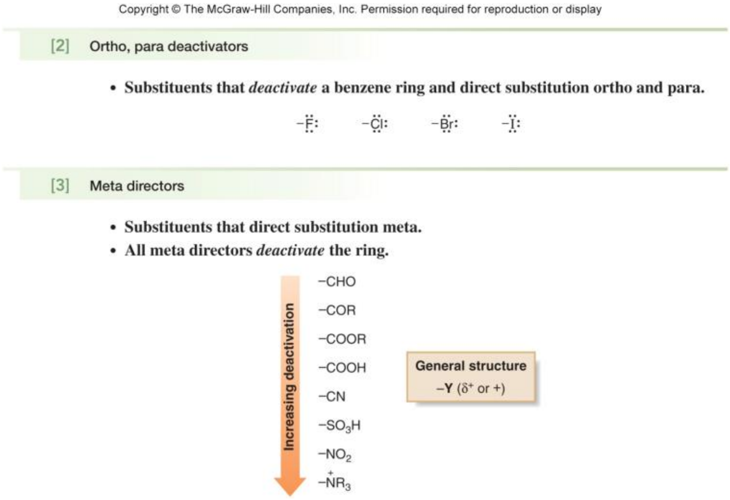
$-R$

**General structure**

**$-R$ or $-Z:$**

# Categorizing Directors and Activators

- **Halogens are in a class by themselves.**



[2] Ortho, para deactivators

- **Substituents that *deactivate* a benzene ring and direct substitution ortho and para.**

$-\ddot{\underset{\cdot\cdot}{F}}:$ $-\ddot{\underset{\cdot\cdot}{Cl}}:$ $-\ddot{\underset{\cdot\cdot}{Br}}:$ $-\ddot{\underset{\cdot\cdot}{I}}:$

[3] Meta directors

- **Substituents that direct substitution meta.**
- **All meta directors *deactivate* the ring.**

$-CHO$

$-COR$

$-COOR$

$-COOH$

$-CN$

$-SO_3H$

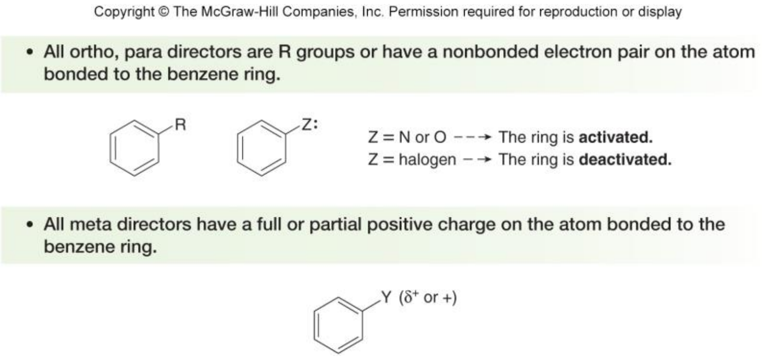
$-NO_2$

$-\overset{+}{N}R_3$

**General structure**

**$-Y$** ($\delta^+$ or $+$)

# Characteristics of Ortho and Para Directors and Meta Directors



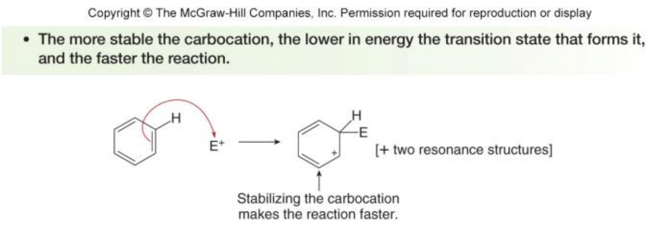
- All ortho, para directors are R groups or have a nonbonded electron pair on the atom bonded to the benzene ring.

Z = N or O ‑‑→ The ring is **activated.**
Z = halogen ‑→ The ring is **deactivated.**

- All meta directors have a full or partial positive charge on the atom bonded to the benzene ring.

# Mechanism of Activation/Deactivation

- To understand how substituents activate or deactivate the ring, we must consider the first step in electrophilic aromatic substitution.
- The first step involves addition of the electrophile ($E^+$) to form a resonance-stabilized carbocation.
- The Hammond postulate makes it possible to predict the relative rate of the reaction by looking at the stability of the carbocation intermediate.

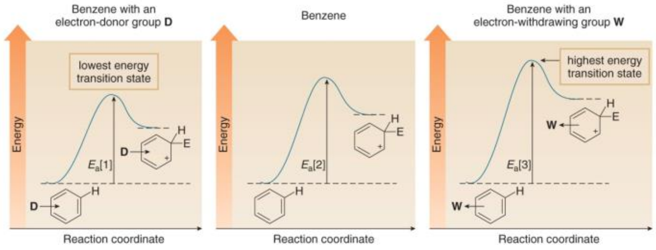


- The more stable the carbocation, the lower in energy the transition state that forms it, and the faster the reaction.

# Energy Diagrams Comparing Substitution Rates

- **The energy diagrams below illustrate the effect of electron-withdrawing and electron-donating groups on the transition state energy of the rate-determining step.**

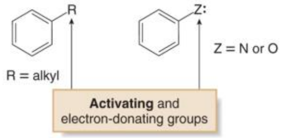
Figure 18.6 Energy diagrams comparing the rate of electrophilic substitution of substituted benzenes



- Electron-donor groups **D** stabilize the carbocation intermediate, lower the energy of the transition state, and increase the rate of reaction.
- Electron-withdrawing groups **W** destabilize the carbocation intermediate, raise the energy of the transition state, and decrease the rate of reaction.

# Summary: Activators and Deactivators

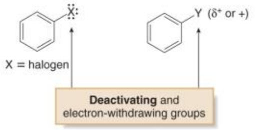
- All activators are either R groups or they have an N or O atom with a lone pair bonded directly to the benzene ring. These are the electron-donor groups of Section 18.6.



**Activating groups:**

$-\ddot{N}H_2$ $-\ddot{N}HR$ $-\ddot{N}R_2$
$-\ddot{\underset{\cdot\cdot}{O}}H$ $-\ddot{\underset{\cdot\cdot}{O}}R$
$-\ddot{N}HCOR$
$-R$

- All deactivators are either halogens or they have an atom with a partial or full positive charge bonded directly to the benzene ring. These are the electron-withdrawing groups of Section 18.6.



**Deactivating groups:**

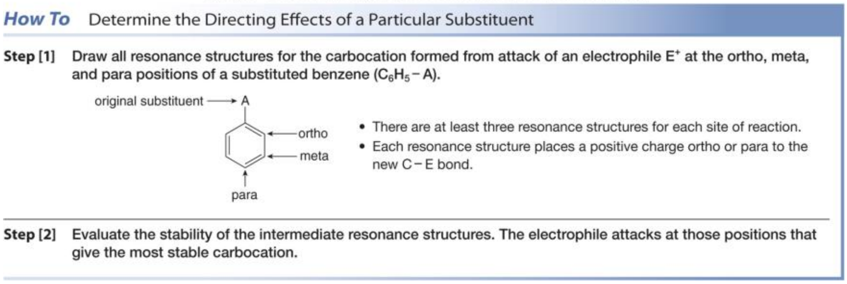
$-\ddot{\underset{\cdot\cdot}{F}}:$ $-\ddot{\underset{\cdot\cdot}{Cl}}:$ $-\ddot{\underset{\cdot\cdot}{Br}}:$ $-\ddot{\underset{\cdot\cdot}{I}}:$
$-CHO$ $-COR$
$-COOR$ $-COOH$
$-CN$ $-SO_3H$ $-NO_2$ $-\overset{+}{N}R_3$

# Orientation Effects in Substituted Benzenes

- **There are two general types of ortho, para directors and one general type of meta director.**
- **All ortho, para directors are R groups or have a nonbonded electron pair on the atom bonded to the benzene ring.**
- **All meta directors have a full or partial positive charge on the atom bonded to the benzene ring.**

# Determining Directing Effects

- **To evaluate the effects of a given substituent, we can use the following stepwise procedure:**



***How To*** Determine the Directing Effects of a Particular Substituent

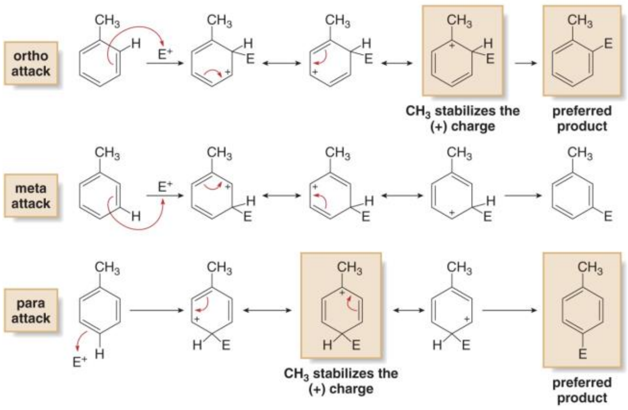
**Step [1]** Draw all resonance structures for the carbocation formed from attack of an electrophile $E^+$ at the ortho, meta, and para positions of a substituted benzene ($C_6H_5-A$).

- There are at least three resonance structures for each site of reaction.
- Each resonance structure places a positive charge ortho or para to the new C – E bond.

**Step [2]** Evaluate the stability of the intermediate resonance structures. The electrophile attacks at those positions that give the most stable carbocation.

# Methyl Carbocation Stabilization

- **A $CH_3$ group directs electrophilic attack ortho and para to itself because an electron-donating inductive effect stabilizes the carbocation intermediate.**



CH3 stabilizes the (+) charge

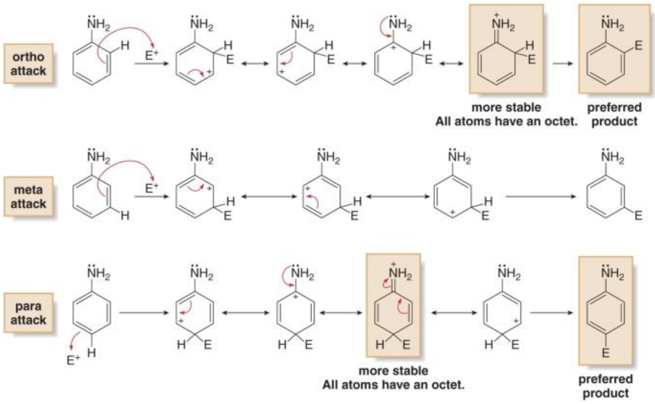
preferred product

CH3 stabilizes the (+) charge

preferred product

# Amine Carbocation Stabilization

- **An $NH_2$ group directs electrophilic attack ortho and para to itself because the carbocation intermediate has additional resonance stabilization.**



more stable
All atoms have an octet.

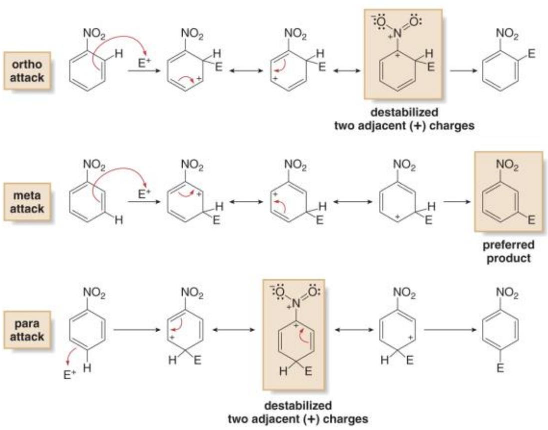
preferred product

more stable
All atoms have an octet.

preferred product

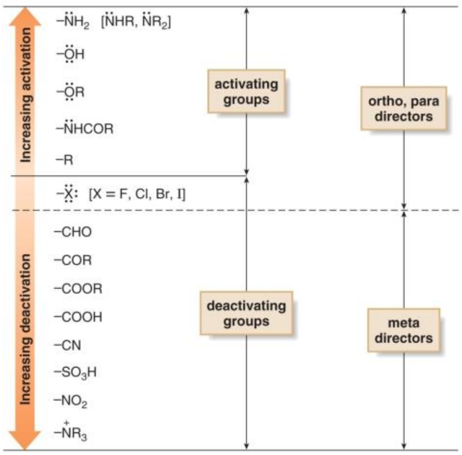
# Nitro Carbocation Stabilization

- With the $NO_2$ group (and all meta directors) meta attack occurs because attack at the ortho and para position gives a destabilized carbocation intermediate.



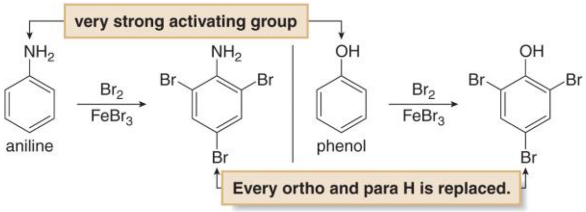
# Summary of Reactivity and Directing Effects

Figure 18.7

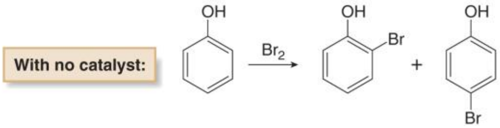


# Reactions of Activated Rings

- **Benzene rings activated by strong electron-donating groups—OH, $NH_2$, and their derivatives (OR, NHR, and $NR_2$)—undergo polyhalogenation when treated with $X_2$ and $FeX_3$.**

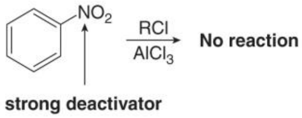


**Monosubstitution** of H by Br occurs with $Br_2$ *alone* without added catalyst to form a mixture of ortho and para products.

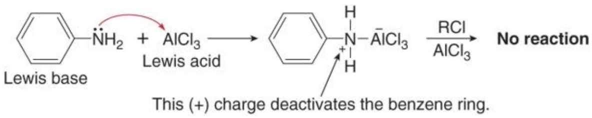


# Reactions of Deactivated Rings

- **A benzene ring deactivated by strong electron-withdrawing groups (i.e., any of the meta directors) is not electron rich enough to undergo Friedel–Crafts reactions.**

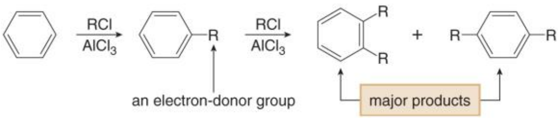


- **Friedel–Crafts reactions also do not occur with $NH_2$ groups because the complex that forms between the $NH_2$ group and the $AlCl_3$ catalyst deactivates the ring towards Friedel–Crafts reactions.**

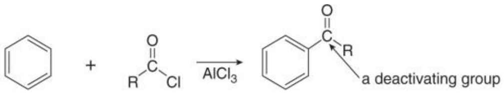


## Friedel–Crafts Reactions and Ring Activation

- Treatment of benzene with an alkyl halide and $AlCl_3$ places an electron-donor R group on the ring.
- Since R groups activate the ring, the alkylated product ($C_6H_5R$) is now more reactive than benzene itself towards further substitution, and it reacts again with RCl to give products of polyalkylation.

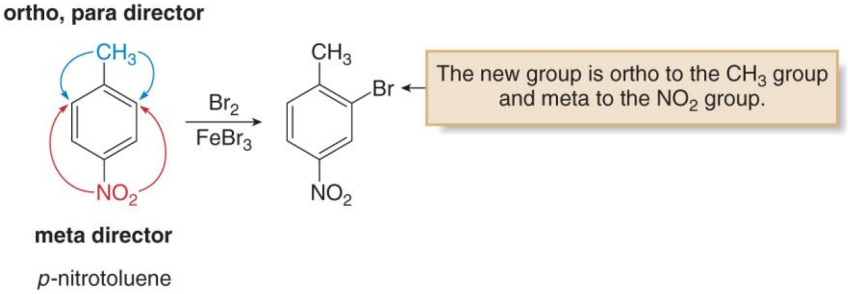


- Polysubstitution does not occur with Friedel–Crafts acylation.



## Reinforcing Directing Effects

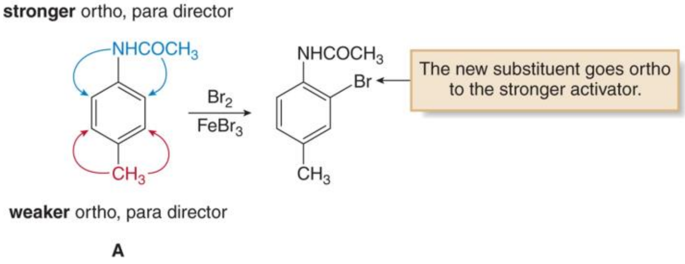
1. When the directing effects of two groups reinforce, the new substituent is located on the position directed by both groups.



The new group is ortho to the $CH_3$ group and meta to the $NO_2$ group.

# Opposing Directing Effects

2. If the directing effects of two groups oppose each other, the more powerful activator "wins out."

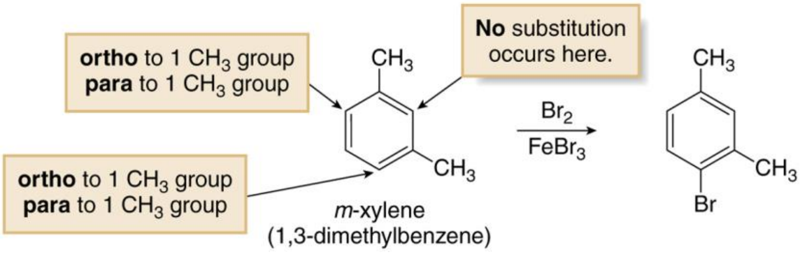


The new substituent goes ortho to the stronger activator.

**A**

# Steric Limitations to Directing Effects

3. No substitution occurs between two meta substituents because of crowding.



**ortho** to 1 $CH_3$ group
**para** to 1 $CH_3$ group

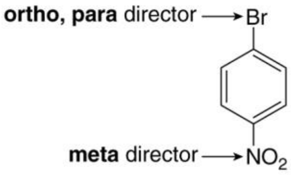
**No** substitution occurs here.

**ortho** to 1 $CH_3$ group
**para** to 1 $CH_3$ group

*m*-xylene
(1,3-dimethylbenzene)

## Synthesis of Benzene Derivatives

- **In a disubstituted benzene, the directing effects indicate which substituent must be added to the ring first.**



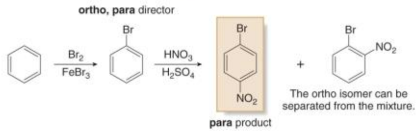
*p*-bromonitrobenzene

Because the two groups are para to each other, **add the ortho, para director first.**

## Synthesis of Benzene Derivatives

- **Pathway 1, in which bromination precedes nitration, yields the desired product.**
- **Pathway 2 yields the undesired meta isomer.**

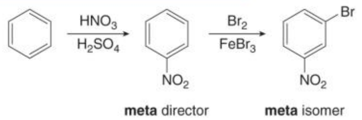
**Pathway [1]: Bromination before nitration**



The ortho isomer can be separated from the mixture.

This pathway gives the desired product.

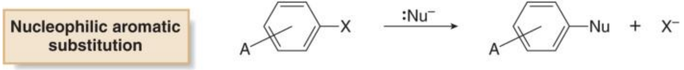
**Pathway [2]: Nitration before bromination**



This pathway does NOT form the desired product.

# Nucleophilic Aromatic Substitution

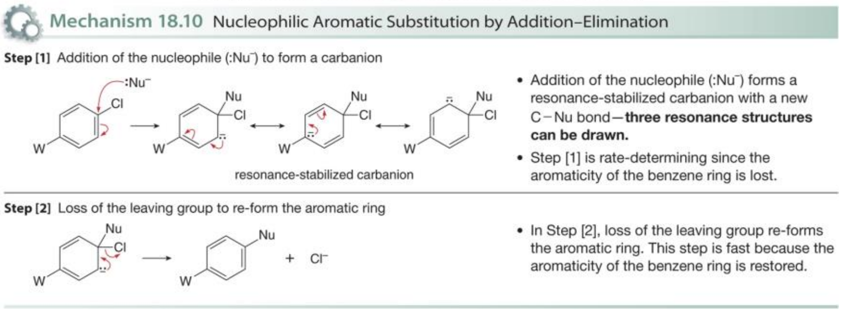
- Nucleophilic aromatic substitution results in the substitution of a halogen on a benzene ring by a nucleophile.



X = F, Cl, Br, I
A = H or electron-withdrawing group

- Two different mechanisms are proposed to explain the result of the reaction.
  - Addition-elimination
  - Elimination-addition

# Nucleophilic Aromatic Substitution by Addition-Elimination



**Mechanism 18.10** Nucleophilic Aromatic Substitution by Addition–Elimination

**Step [1]** Addition of the nucleophile (:Nu⁻) to form a carbanion

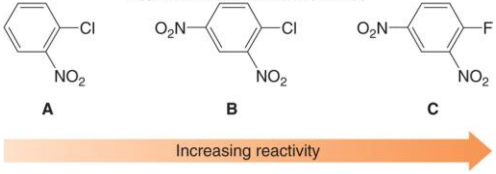
- Addition of the nucleophile (:Nu⁻) forms a resonance-stabilized carbanion with a new C−Nu bond—**three resonance structures can be drawn.**
- Step [1] is rate-determining since the aromaticity of the benzene ring is lost.

**Step [2]** Loss of the leaving group to re-form the aromatic ring

- In Step [2], loss of the leaving group re-forms the aromatic ring. This step is fast because the aromaticity of the benzene ring is restored.

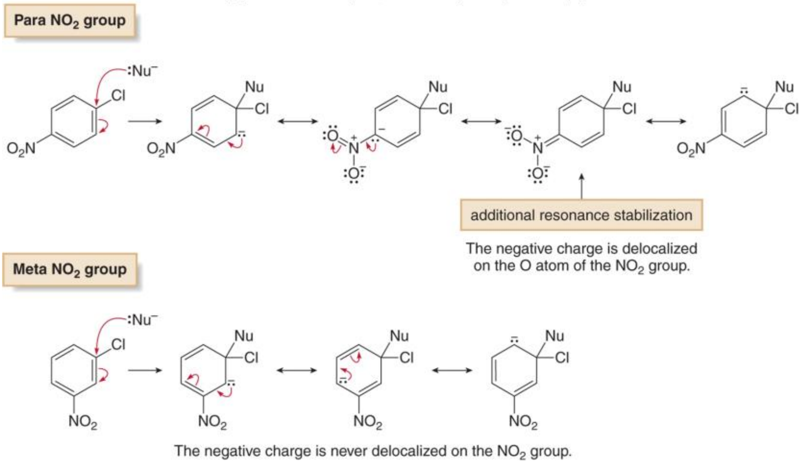
## Reactivity Trends in Nucleophilic Aromatic Substitution

- Increasing the number of electron-withdrawing groups increases the reactivity of the aryl halide.
  - Electron-withdrawing groups stabilize the intermediate carbanion.
- Increasing the electronegativity of the halogen increases the reactivity of the aryl halide.
  - A more electronegative halogen stabilizes the intermediate carbanion by an inductive effect.



## Orientation for Addition-Elimination

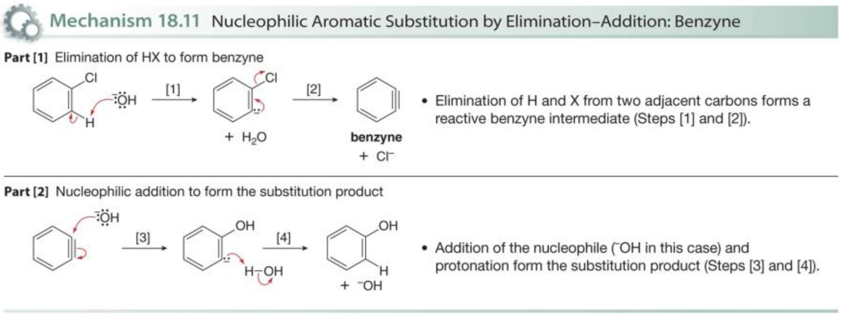
- Nucleophilic aromatic substitution only occurs by an addition-elimination mechanism with aryl halides that contain ortho or para electron-withdrawing substituents.



The negative charge is delocalized on the O atom of the $NO_2$ group.

The negative charge is never delocalized on the $NO_2$ group.

# Nucleophilic Aromatic Substitution by Elimination-Addition



**Mechanism 18.11** Nucleophilic Aromatic Substitution by Elimination–Addition: Benzyne

**Part [1]** Elimination of HX to form benzyne

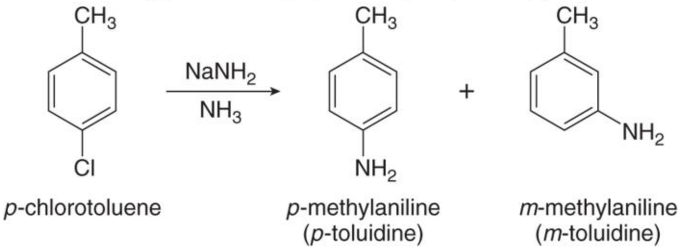
- Elimination of H and X from two adjacent carbons forms a reactive benzyne intermediate (Steps [1] and [2]).

**Part [2]** Nucleophilic addition to form the substitution product

- Addition of the nucleophile ($^-$OH in this case) and protonation form the substitution product (Steps [3] and [4]).

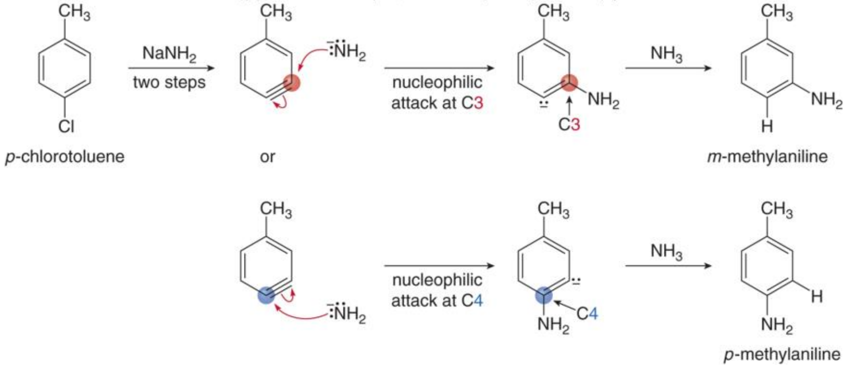
# Products of Elimination-Addition

- **Formation of a benzyne intermediate explains why substituted aryl halides form mixtures of products.**
- **Nucleophilic aromatic substitution by an elimination-addition mechanism affords substitution on the carbon directly bonded to the leaving group and the carbon adjacent to it.**



# Products of Elimination-Addition

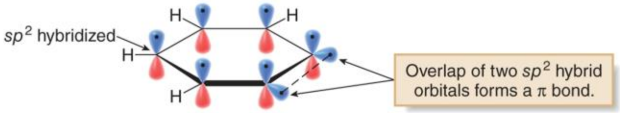
- **Nucleophilic attack on the benzyne intermediate may occur at C3 to form *m*-methylaniline, or C4 to form *p*-methylaniline.**



# Products of Elimination-Addition

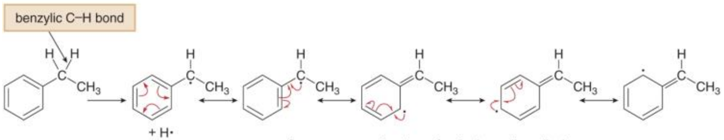
- **The second $\pi$ bond of benzyne is different from all other $\pi$ bonds seen thus far:**
  - **It is formed by the side-by-side overlap of *sp*$^2$ hybrid orbitals, not *p* orbitals.**
  - **Therefore, it is extremely weak.**

- The $\sigma$ bond is formed by overlap of two *sp*$^2$ hybrid orbitals.
- One $\pi$ bond is formed by overlap of two *p* orbitals perpendicular to the plane of the molecule.
- The second $\pi$ bond is formed by overlap of two *sp*$^2$ hybrid orbitals.



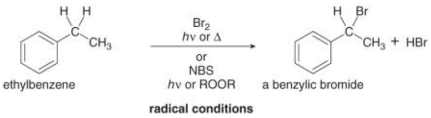
# Halogenation of Alkyl Benzenes

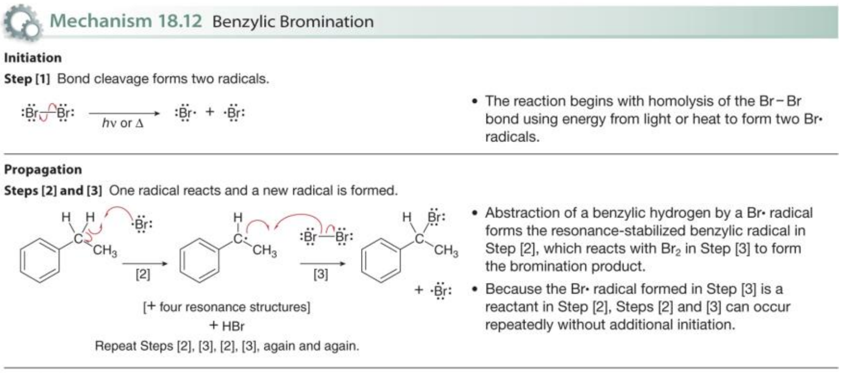
- **Benzylic C–H bonds are weaker than most other *sp*$^3$ hybridized C–H bonds, because homolysis forms a resonance-stabilized benzylic radical.**



five resonance structures for the benzylic radical

- **As a result, alkyl benzenes undergo selective bromination at the weak benzylic C–H bond under radical conditions to form the benzylic halide.**





**Mechanism 18.12** Benzylic Bromination

**Initiation**

**Step [1]** Bond cleavage forms two radicals.

- The reaction begins with homolysis of the Br – Br bond using energy from light or heat to form two Br• radicals.

**Propagation**

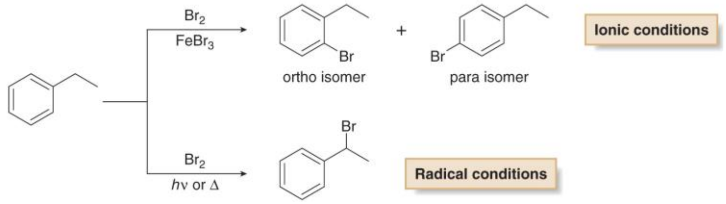
**Steps [2] and [3]** One radical reacts and a new radical is formed.

[+ four resonance structures]
+ HBr
Repeat Steps [2], [3], [2], [3], again and again.

- Abstraction of a benzylic hydrogen by a Br• radical forms the resonance-stabilized benzylic radical in Step [2], which reacts with $Br_2$ in Step [3] to form the bromination product.
- Because the Br• radical formed in Step [3] is a reactant in Step [2], Steps [2] and [3] can occur repeatedly without additional initiation.

# Ionic and Radical Halogenation

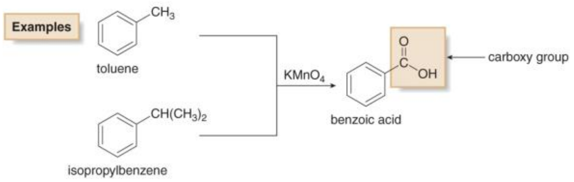
- Alkyl benzenes undergo two different reactions depending on the reaction conditions:



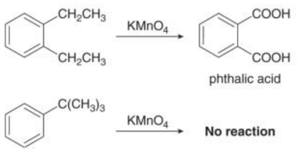
- With $Br_2$ and $FeBr_3$ (ionic conditions), electrophilic aromatic substitution occurs, resulting in replacement of H by Br on the aromatic ring to form ortho and para isomers.
- With $Br_2$ and light or heat (radical conditions), substitution of H by Br occurs at the benzylic carbon of the alkyl group.

# Oxidation of Alkyl Benzenes

- Arenes containing at least one benzylic C–H bond are oxidized with $KMnO_4$ to benzoic acid.



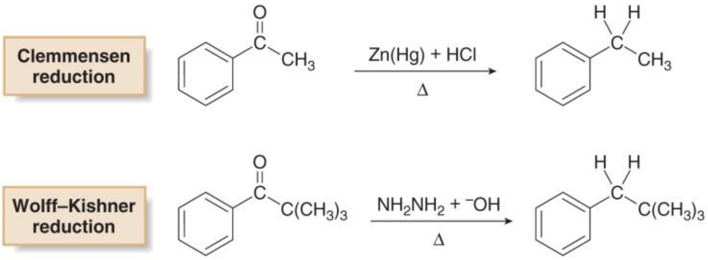
- Substrates with more than one alkyl group are oxidized to dicarboxylic acids.
- Compounds without a benzylic hydrogen are inert to oxidation.



# Reduction of Acyl Benzenes

- **Ketones formed as products of Friedel–Crafts acylation can be reduced to alkyl benzenes by two different methods:**

1. **The Clemmensen reduction—uses zinc and mercury in the presence of strong acid.**
2. **The Wolff–Kishner reduction—uses hydrazine ($NH_2NH_2$) and strong base (KOH).**

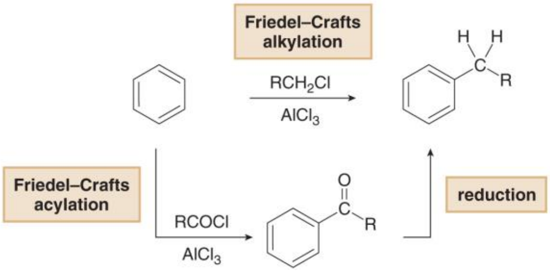


# Synthesis of Alkyl Benzenes

- **We now know two different ways to introduce an alkyl group on a benzene ring:**

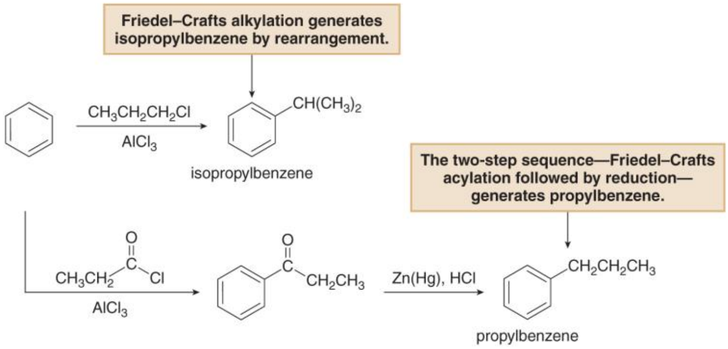
1. **A one-step method using Friedel–Crafts alkylation.**
2. **A two-step method using Friedel–Crafts acylation to form a ketone, followed by reduction.**

Figure 18.8



# Synthesis of Alkyl Benzenes

- Although the two-step method seems more roundabout, it must be used to synthesize certain alkyl benzenes that cannot be prepared by the one-step Friedel–Crafts alkylation because of rearrangements.

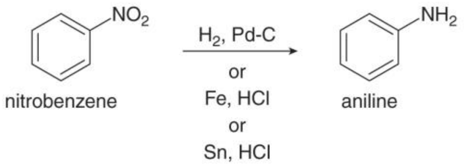


Friedel–Crafts alkylation generates isopropylbenzene by rearrangement.

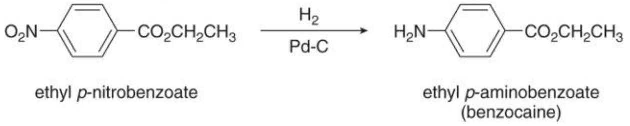
The two-step sequence—Friedel–Crafts acylation followed by reduction—generates propylbenzene.

# Reduction of Nitro Benzenes

- A nitro group ($NO_2$) that has been introduced on a benzene ring by nitration with strong acid can readily be reduced to an amino group ($NH_2$) under a variety of conditions.

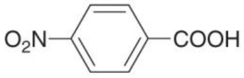


- Reduction of ethyl *p*-nitrobenzoate with $H_2$ and a palladium catalyst forms ethyl *p*-aminobenzoate, a local anesthetic commonly called benzocaine.



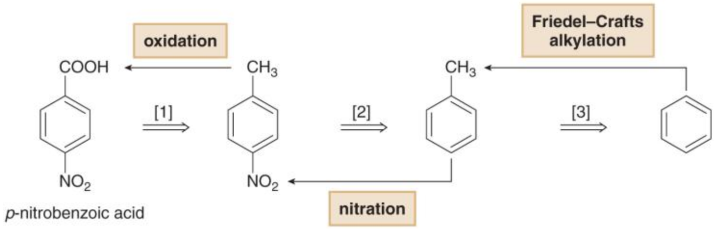
# Multistep Synthesis

- Write out a synthesis of *p*-nitrobenzoic acid from benzene.



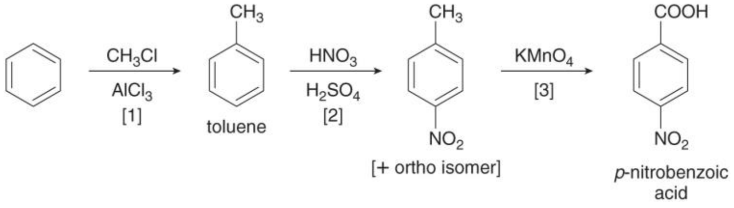
*p*-nitrobenzoic acid

- First, perform retrosynthetic analysis.



# Multistep Synthesis

- Then, write out the synthesis from starting material to product.



- Make sure you put the methyl group on first as nitro is a meta director and deactivator.
- Do not oxidize the methyl group until after adding the nitro as a carboxylic acid is a meta director and deactivator.