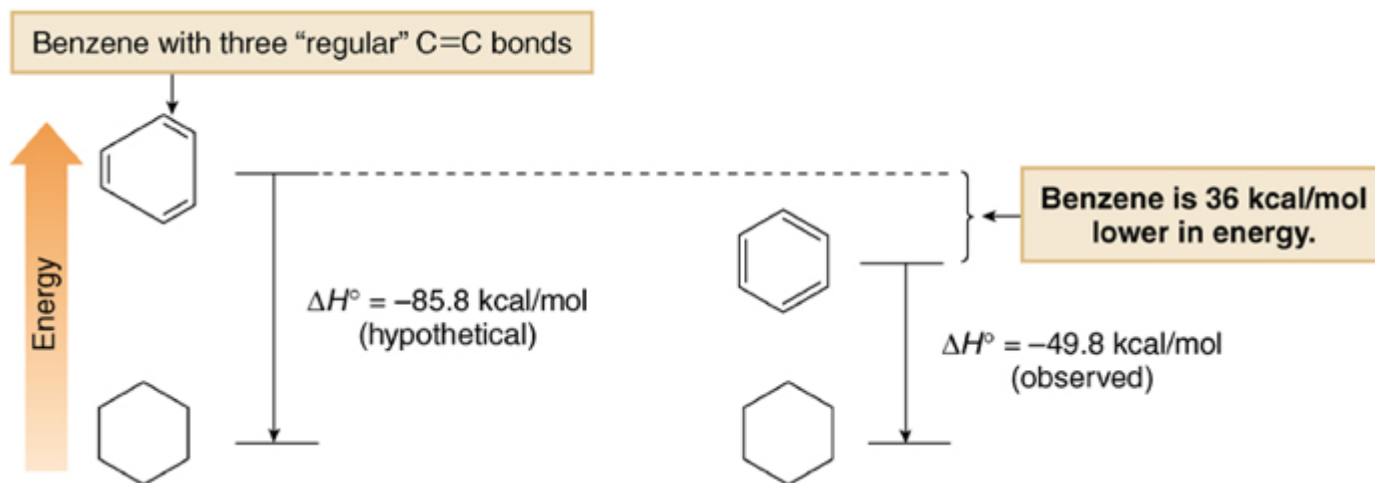
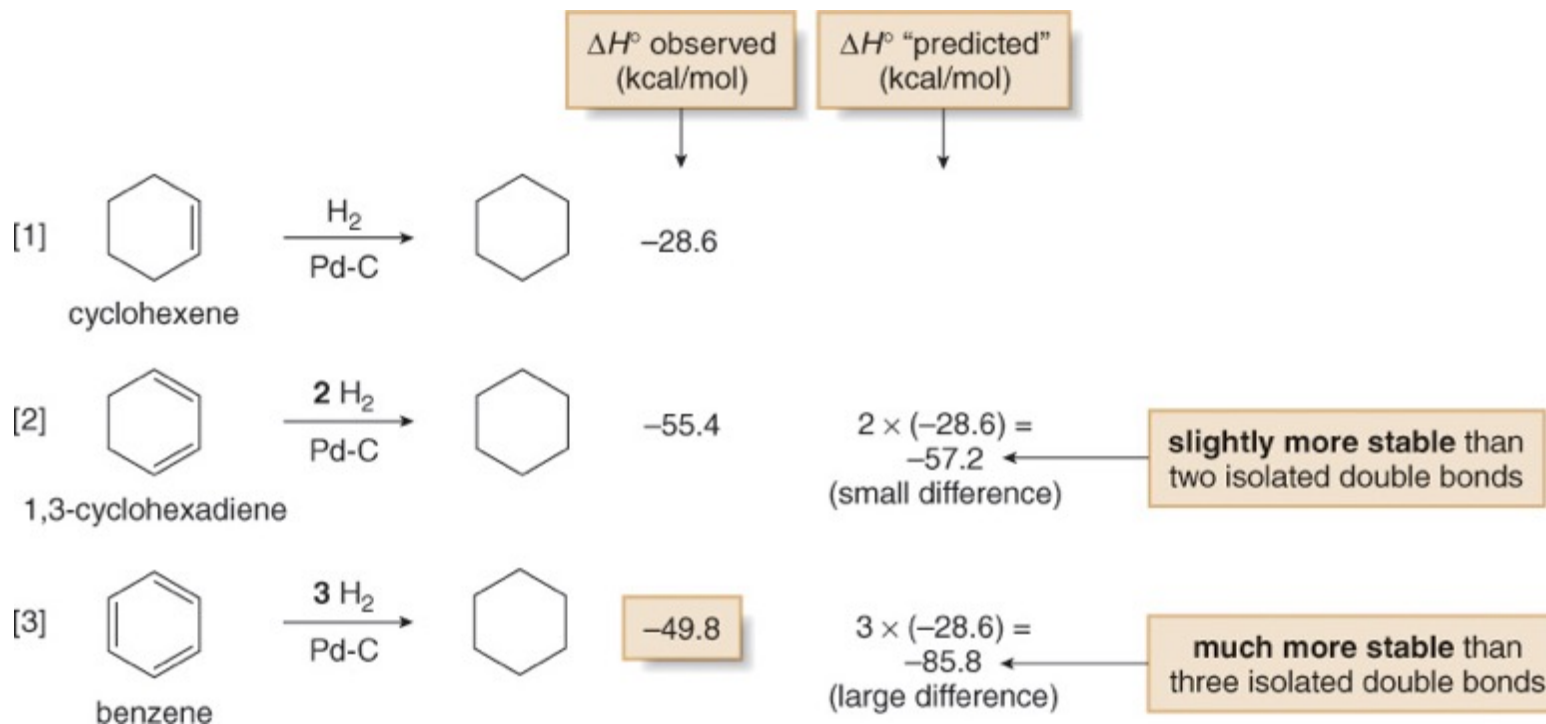


# Electrophilic Aromatic Substitution

Chapter 16  
Organic Chemistry, *8<sup>th</sup> Edition*  
John McMurry

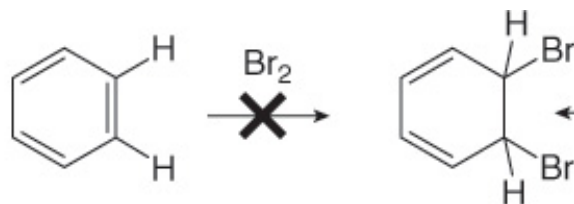
# Aromaticity – Resonance Energy



# Stability of Benzene - Aromaticity

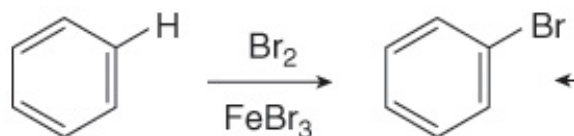
Benzene does not undergo addition reactions typical of other highly unsaturated compounds, including conjugated dienes.

Addition does *not* occur.



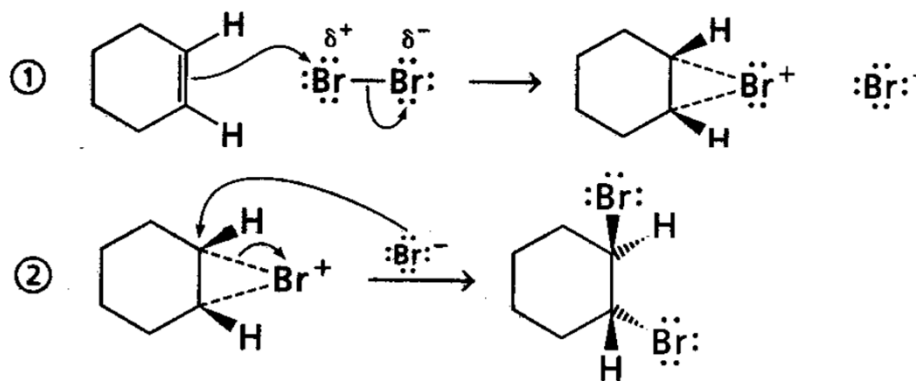
An addition product would no longer contain a benzene ring.

Substitution occurs.



A substitution product still contains a benzene ring.

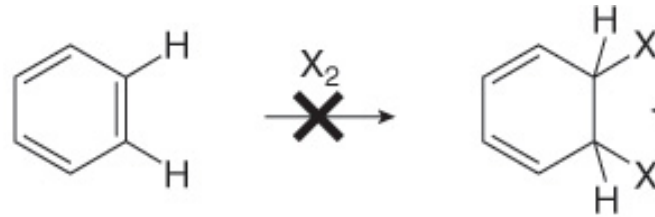
meccanismo



*trans*-1,2-Dibromocyclohexane

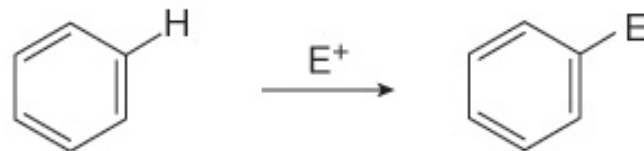
# Introduction

Addition

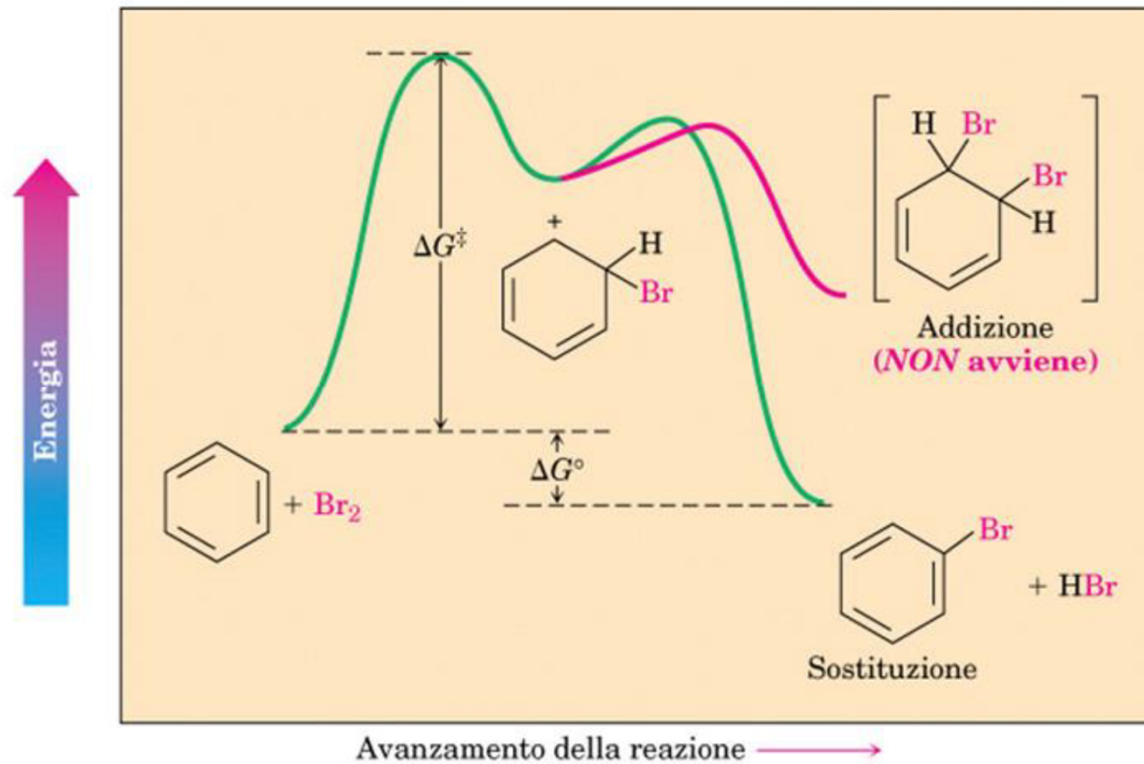


The product is *not* aromatic.

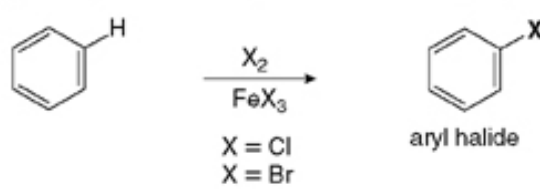
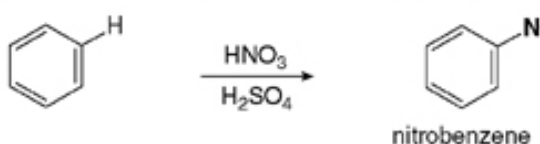
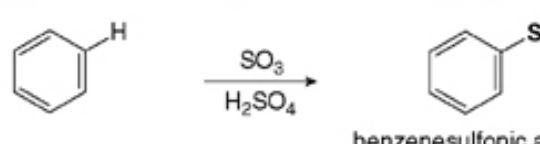
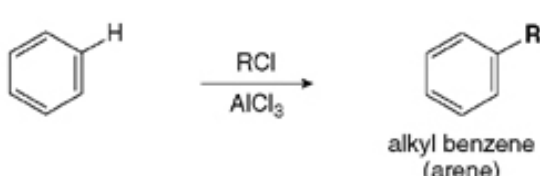
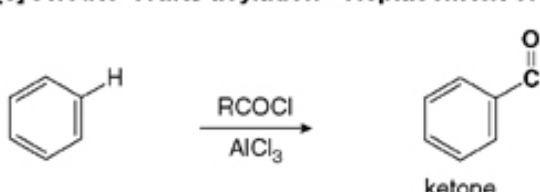
Substitution



The product is aromatic.



# Introduction

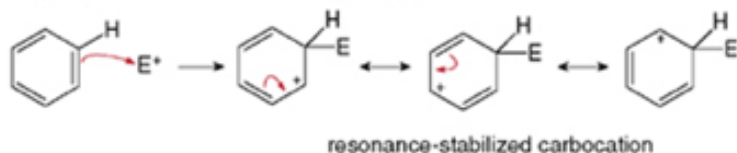
Reaction	Electrophile
<p><b>[1] Halogenation—Replacement of H by X (Cl or Br)</b></p>  <p><math>\text{C}_6\text{H}_6 \xrightarrow[\text{FeX}_3]{\text{X}_2} \text{C}_6\text{H}_5\text{X}</math> X = Cl X = Br</p> <p>aryl halide</p>	$\text{E}^+ = \text{Cl}^+ \text{ or } \text{Br}^+$
<p><b>[2] Nitration—Replacement of H by <math>\text{NO}_2</math></b></p>  <p><math>\text{C}_6\text{H}_6 \xrightarrow[\text{H}_2\text{SO}_4]{\text{HNO}_3} \text{C}_6\text{H}_5\text{NO}_2</math></p> <p>nitrobenzene</p>	$\text{E}^+ = \overset{+}{\text{N}}\text{O}_2$
<p><b>[3] Sulfonation—Replacement of H by <math>\text{SO}_3\text{H}</math></b></p>  <p><math>\text{C}_6\text{H}_6 \xrightarrow[\text{H}_2\text{SO}_4]{\text{SO}_3} \text{C}_6\text{H}_5\text{SO}_3\text{H}</math></p> <p>benzenesulfonic acid</p>	$\text{E}^+ = \overset{+}{\text{S}}\text{O}_3\text{H}$
<p><b>[4] Friedel-Crafts alkylation—Replacement of H by R</b></p>  <p><math>\text{C}_6\text{H}_6 \xrightarrow[\text{AlCl}_3]{\text{RCl}} \text{C}_6\text{H}_5\text{R}</math></p> <p>alkyl benzene (arene)</p>	$\text{E}^+ = \text{R}^+$
<p><b>[5] Friedel-Crafts acylation—Replacement of H by <math>\text{RCO}</math></b></p>  <p><math>\text{C}_6\text{H}_6 \xrightarrow[\text{AlCl}_3]{\text{RCOCl}} \text{C}_6\text{H}_5\text{COR}</math></p> <p>ketone</p>	$\text{E}^+ = \overset{+}{\text{C}}\text{O}$

# Mechanism



## Mechanism 18.1 General Mechanism—Electrophilic Aromatic Substitution

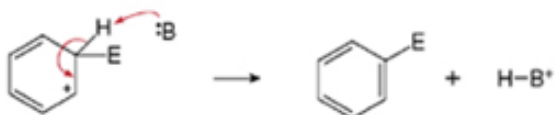
Step [1] Addition of the electrophile ( $E^+$ ) to form a carbocation



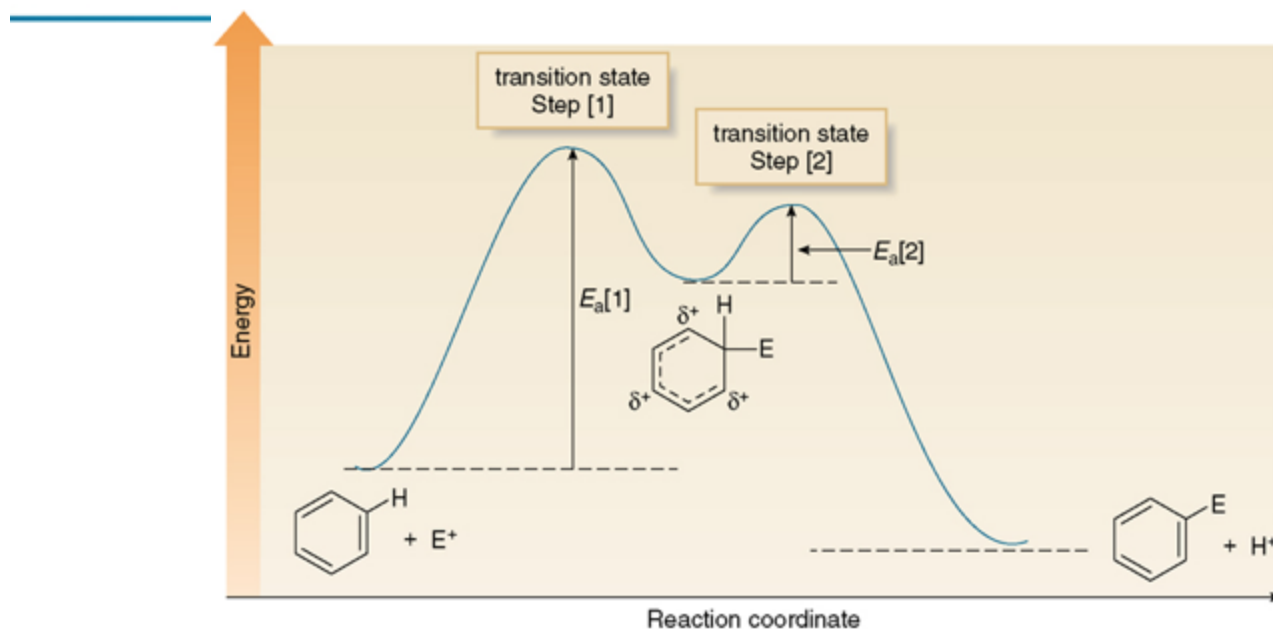
**intermedio di Wheland**

- Addition of the electrophile ( $E^+$ ) forms a new C–E bond using two  $\pi$  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.

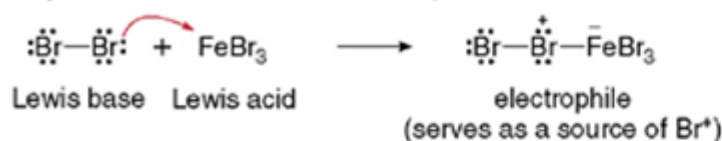


# Halogenation



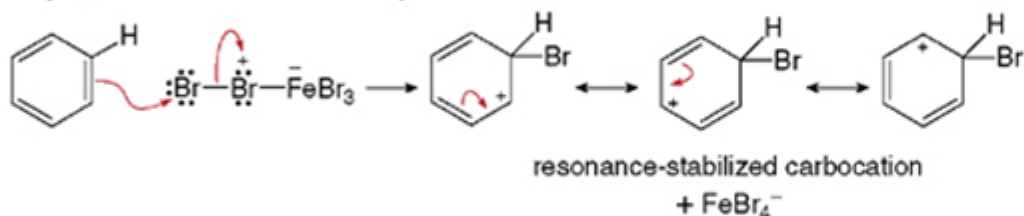
## Mechanism 18.2 Bromination of Benzene

Step [1] Generation of the electrophile



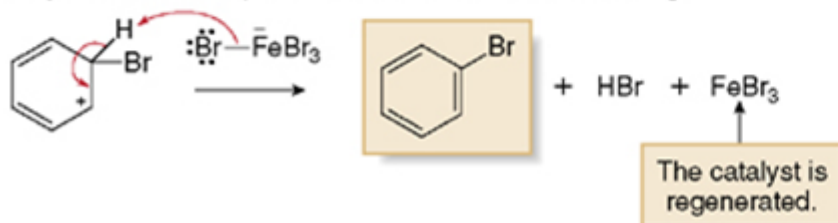
- Lewis acid–base reaction of  $\text{Br}_2$  with  $\text{FeBr}_3$  forms a species with a weakened and polarized  $\text{Br}-\text{Br}$  bond. This adduct serves as a source of  $\text{Br}^+$  in the next step.

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



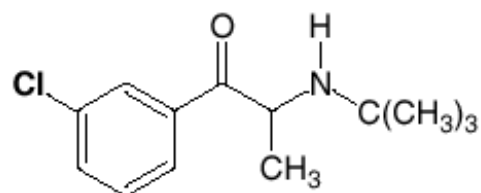
- Addition of the electrophile forms a new  $\text{C}-\text{Br}$  bond and generates a carbocation. This carbocation intermediate is resonance stabilized—**three resonance structures can be drawn**.
- The  $\text{FeBr}_4^-$  also formed in this reaction is the base used in Step [3].

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

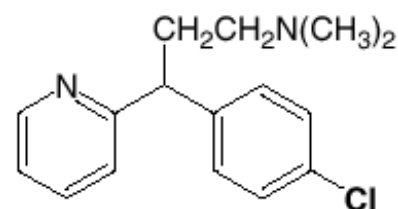


- $\text{FeBr}_4^-$  removes the proton from the carbon bearing the  $\text{Br}$ , thus re-forming the aromatic ring.
- $\text{FeBr}_3$ , a catalyst, is also regenerated for another reaction cycle.

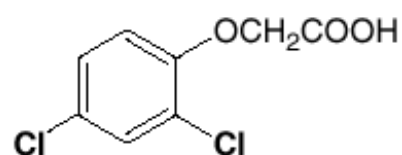
# Halogenation



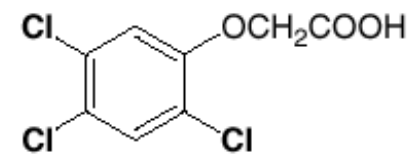
Generic name: **bupropion**  
Trade names: **Wellbutrin, Zyban**  
antidepressant,  
also used to reduce nicotine cravings



**chlorpheniramine**  
antihistamine



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



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

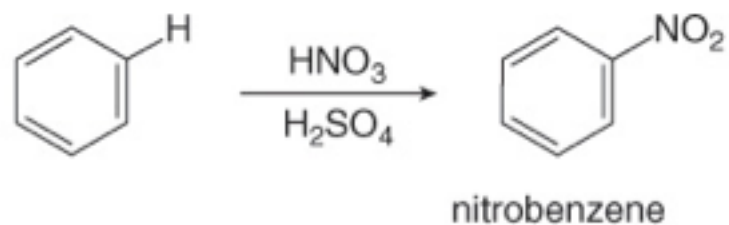
Herbicides were used extensively during the Vietnam War to defoliate dense jungle areas. The concentration of certain herbicide by-products in the soil remains high today.



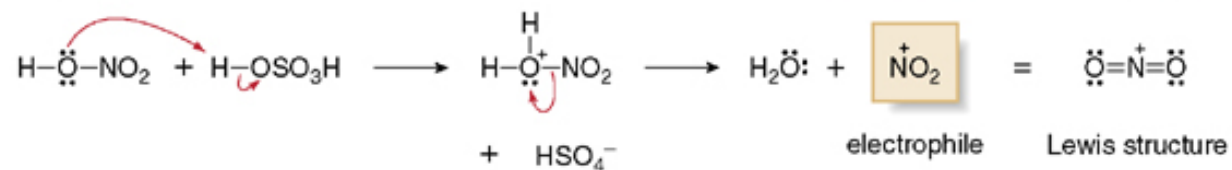
the active components in **Agent Orange**,  
a defoliant used in the Vietnam War



# Nitration

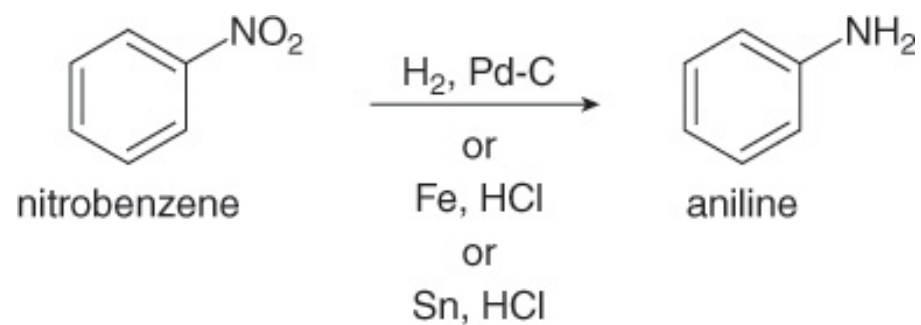


## Mechanism 18.3 Formation of the Nitronium Ion ( $^+\text{NO}_2$ ) for Nitration

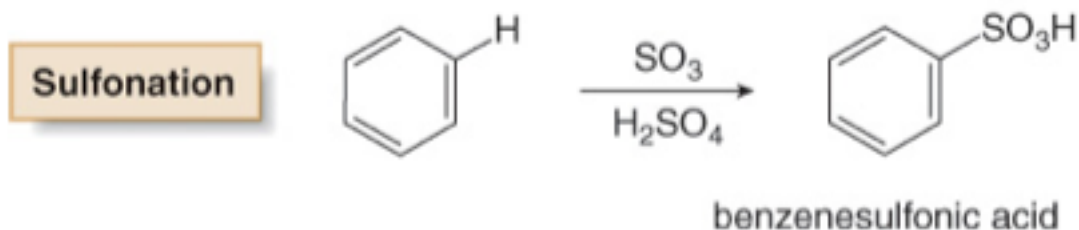


# Nitro Group Reduction

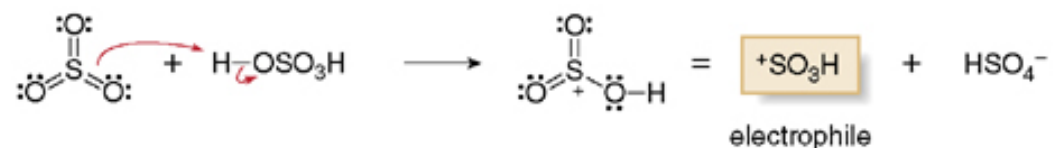
Aromatic nitro groups ( $\text{NO}_2$ ) can readily be reduced to amino groups ( $\text{NH}_2$ ) under a variety of conditions.



# Sulfonation



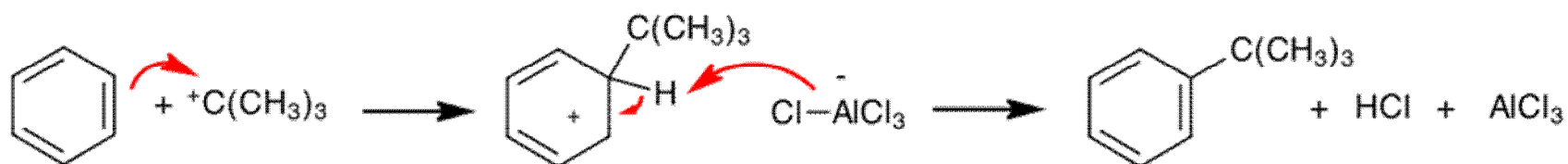
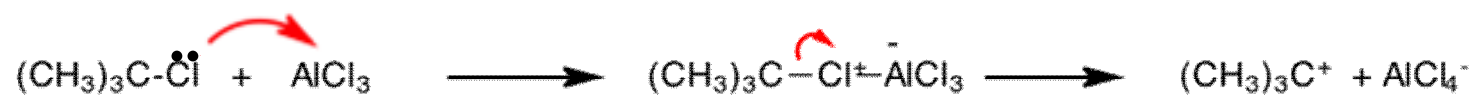
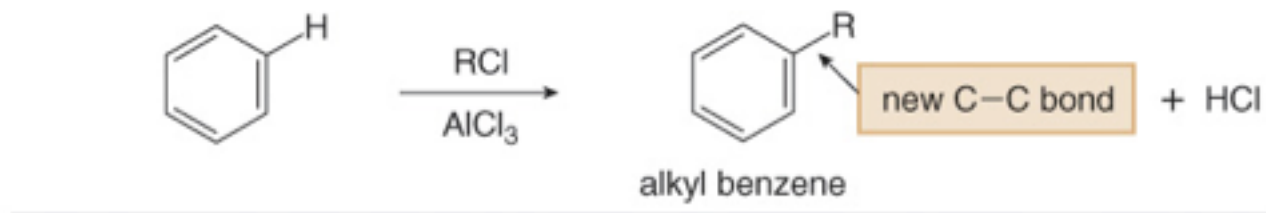
## Mechanism 18.4 Formation of the Electrophile $^+\text{SO}_3\text{H}$ for Sulfonation



$\text{SO}_3$ , anidride solforica, è un potente elettrofilo, presente in acido solforico fumante

**La solfonazione, diversamente dalle altre reazioni, è reversibile alle alte temperature.**

# Friedel-Crafts Alkylation

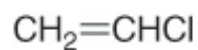


Best with 2ry and 3ry halides

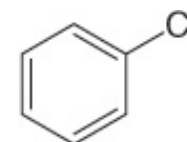
# Limitations

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

Unreactive halides in the Friedel-Crafts alkylation

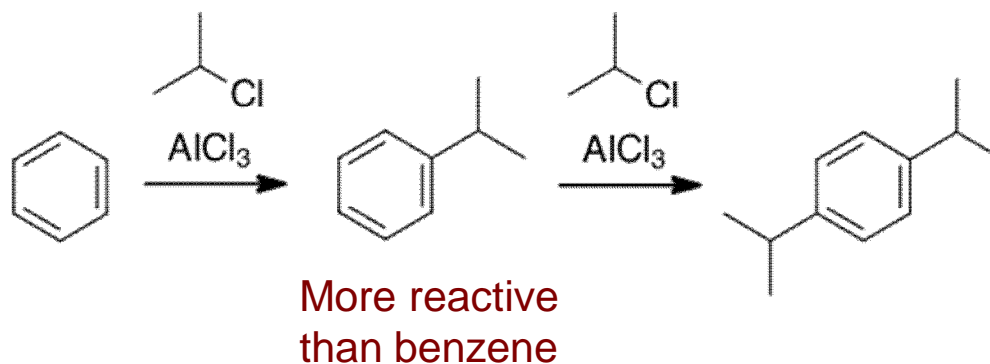


vinyl halide



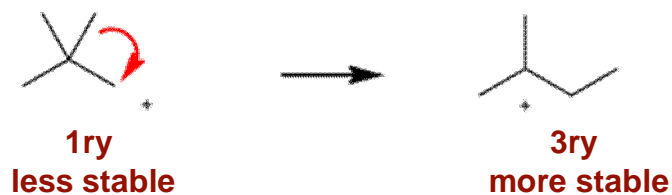
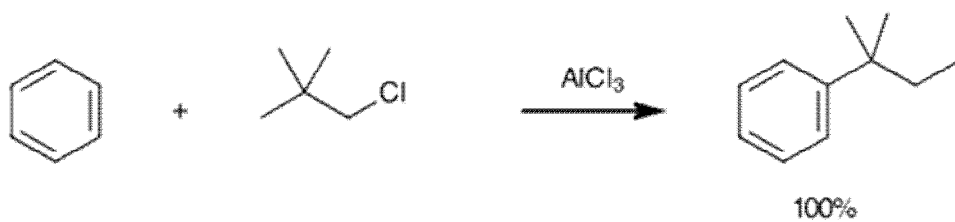
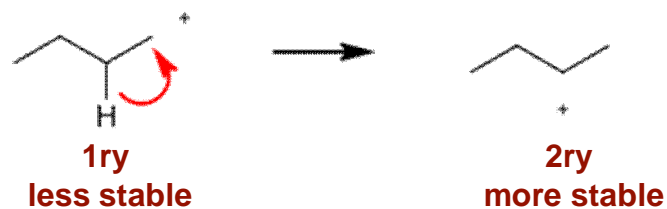
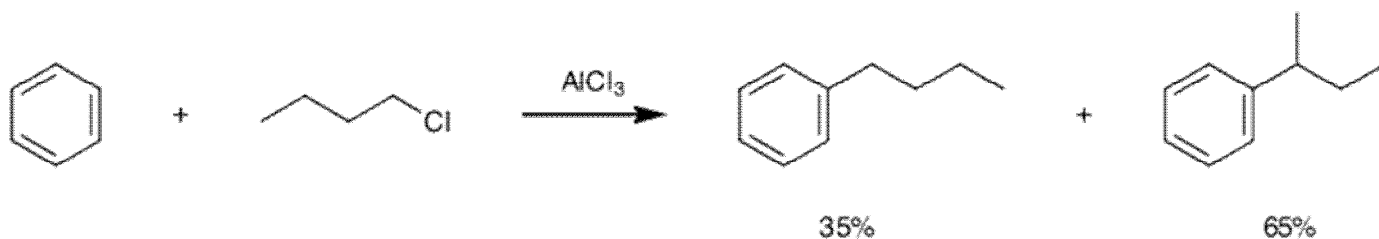
aryl halide

[2] Disubstituted products are obtained in F.-C. alkylations, but not in acylations.



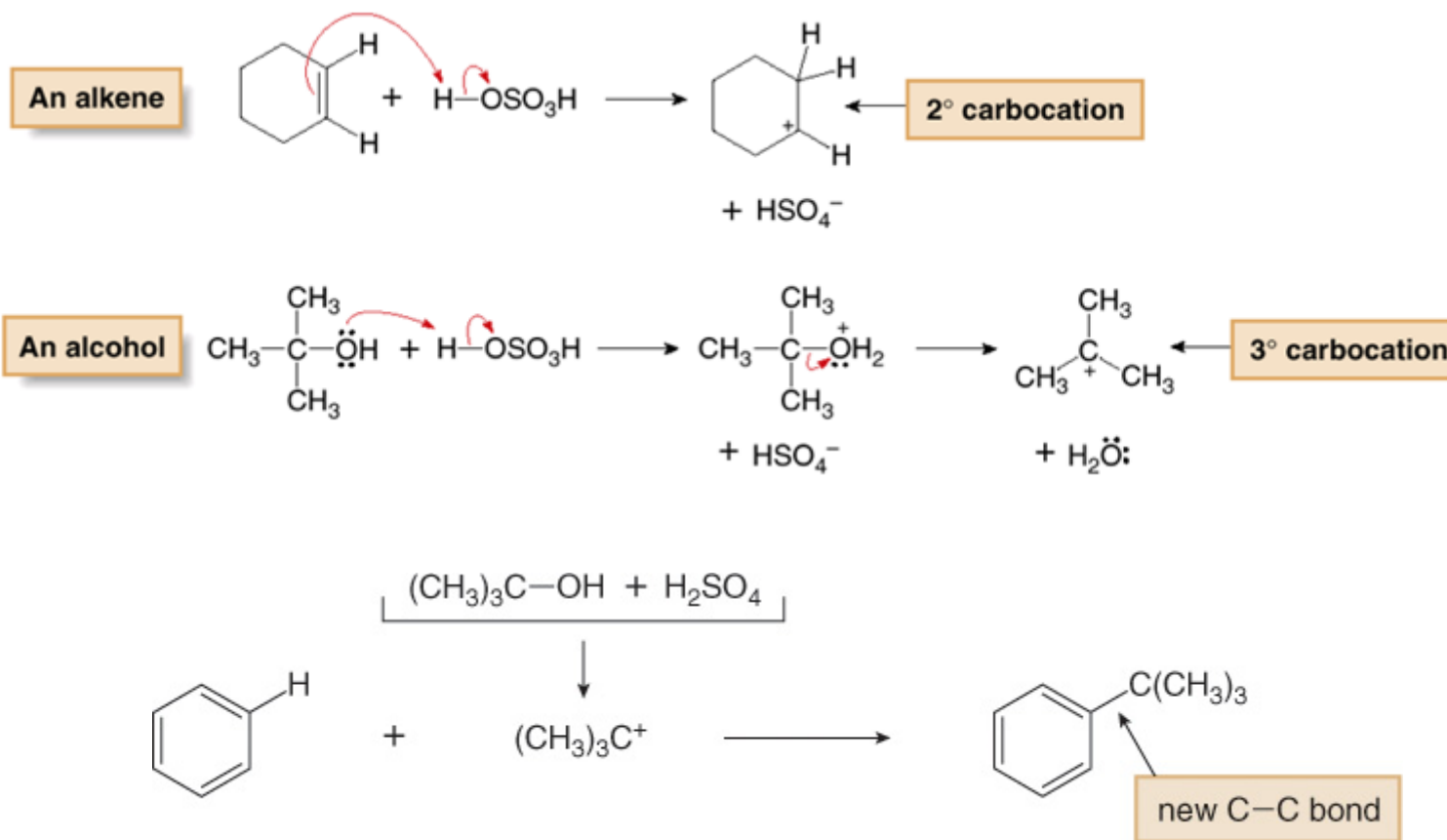
# Limitations

[3] Rearrangements can occur.



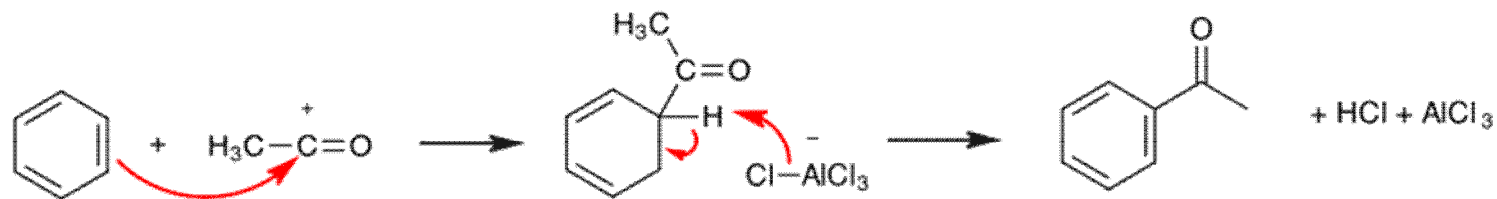
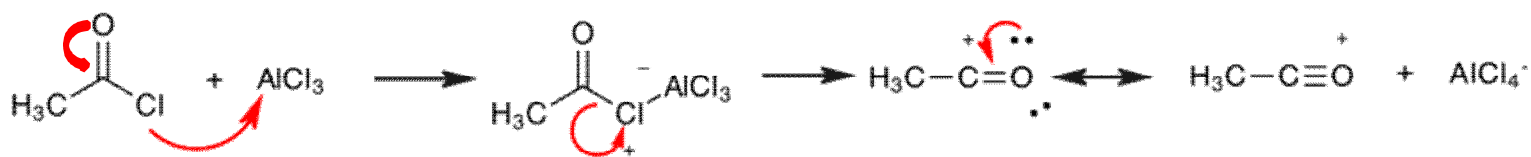
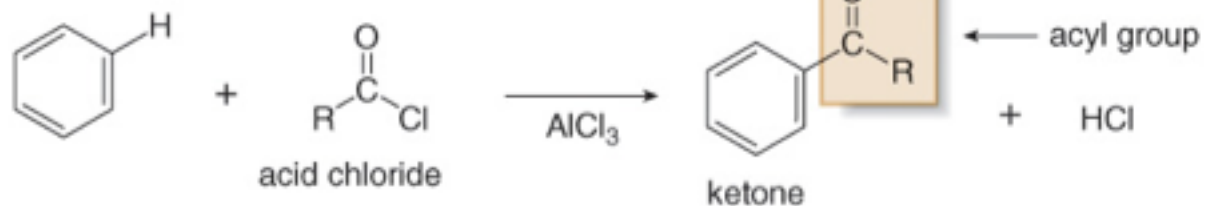
# Friedel-Crafts Alkylation

Other functional groups that form carbocations can also be used as starting materials.



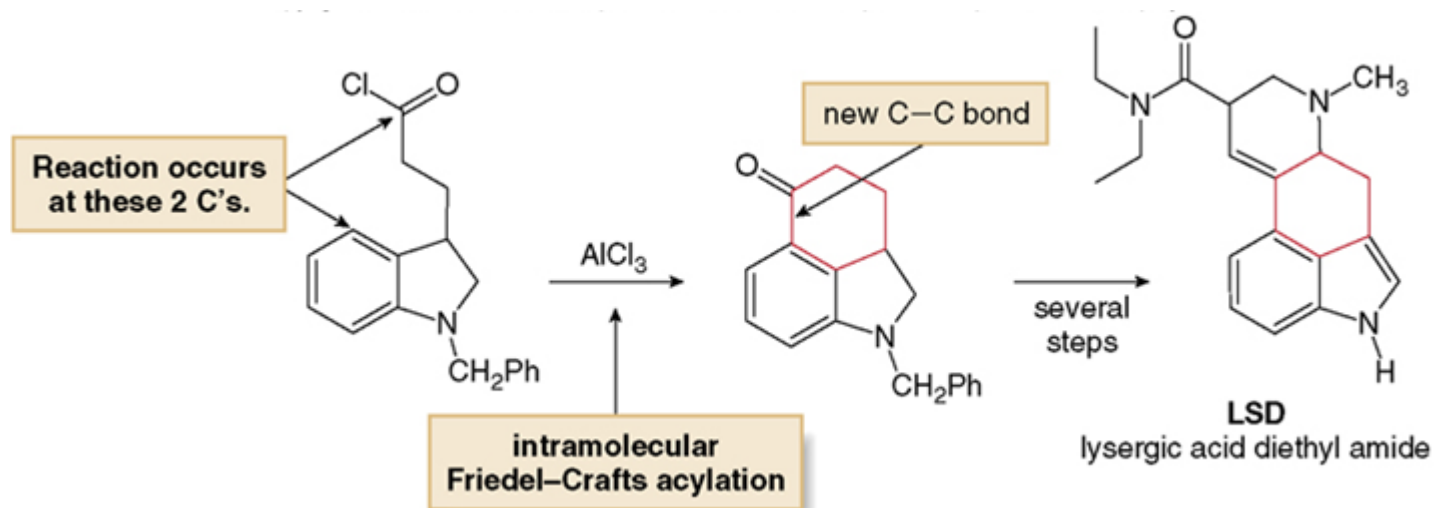
# Friedel-Crafts Acylation

Friedel-Crafts acylation—  
General reaction

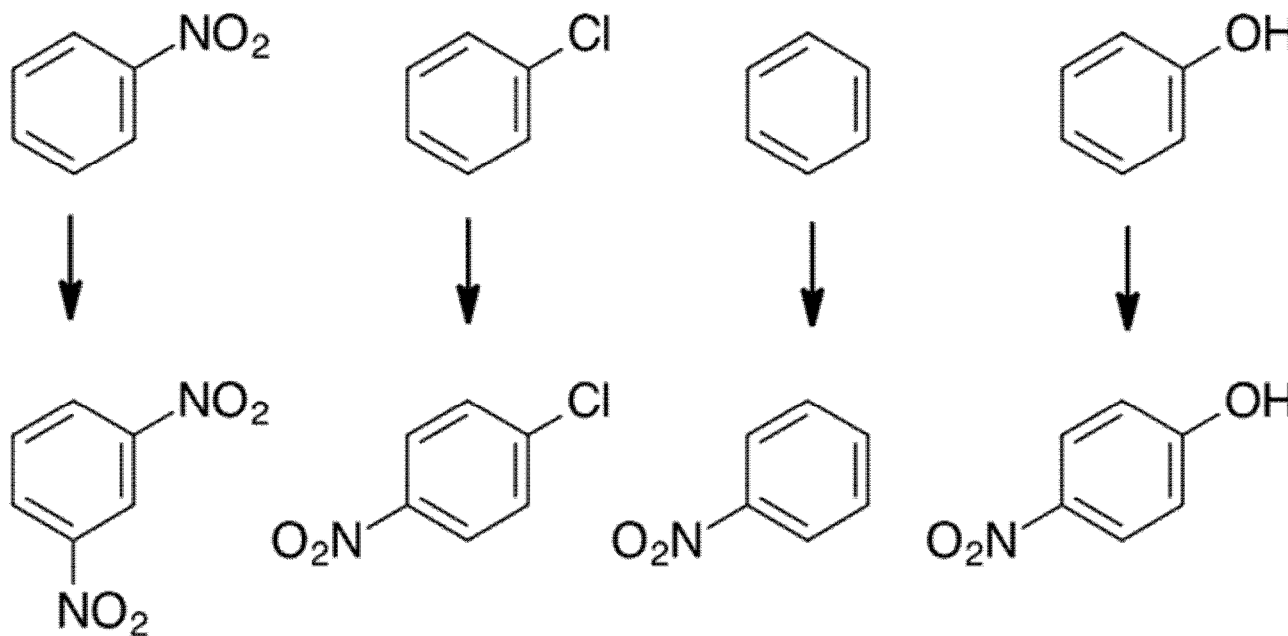




# Intramolecular Friedel-Crafts reactions.



# Nitration of Substituted Benzenes



Relative  
rates

$6 \times 10^{-8}$

0.033

1

1000

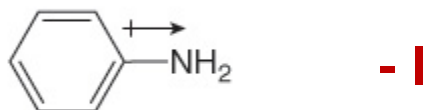
Substituents modify the electron density in the benzene ring, and this affects the course of electrophilic aromatic substitution.

# Substituted Benzenes

## Inductive effects (through $\sigma$ bonds):

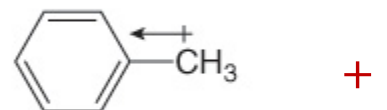
- Atoms more electronegative than carbon—including N, O, and X—pull electron density away from carbon and thus exhibit an electron-withdrawing inductive effect.
- Polarizable alkyl groups donate electron density, and thus exhibit an electron-donating inductive effect.

### Electron-withdrawing inductive effect



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

### Electron-donating inductive effect



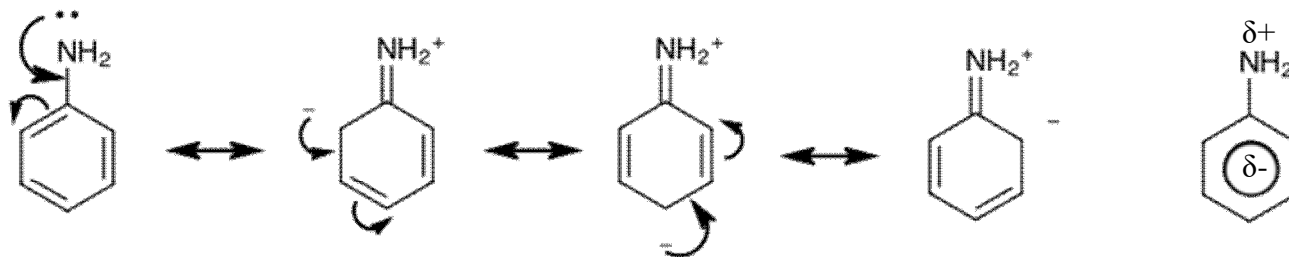
- Alkyl groups are **polarizable**, making them electron-donating groups.

- /	-NH <sub>3</sub> <sup>+</sup>	-NH <sub>2</sub> ,	-OH	-F	-CHO	-CN	SO <sub>3</sub> H	-NO <sub>2</sub>
	-CF <sub>3</sub>	-NHR	-OR	-Cl	-COR		SO <sub>2</sub> R	
		-NR <sub>2</sub>		-Br	-COOH			
				-I	-COOR			
+ /	-CH <sub>3</sub>							
	-Alkyl							
	-SiR <sub>3</sub>							
	SiR <sub>3</sub>							

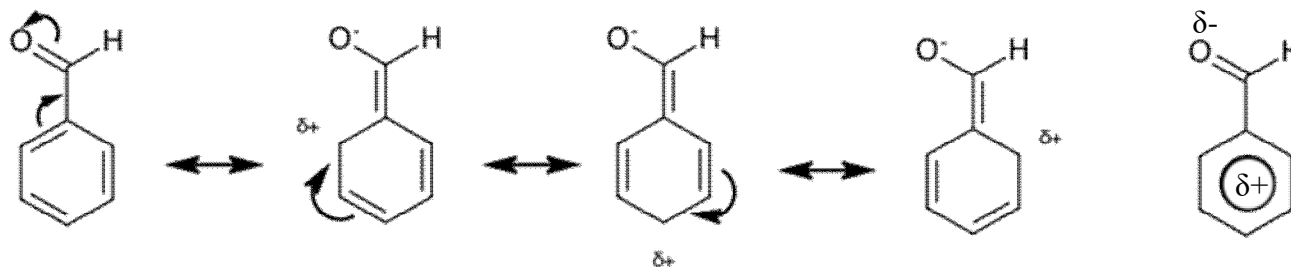
# Substituted Benzenes

**Resonance effects** (through  $\pi$  bonds) are only observed with substituents containing lone pairs or  $\pi$  bonds.

- Substituents containing lone pairs are electron donating (**+ R**)



- Substituents  $-\text{Y} = \text{Z}$  ( $\text{C}_6\text{H}_5-\text{Y} = \text{Z}$ ), where Z is more electronegative than Y are electron accepting (**- R**)

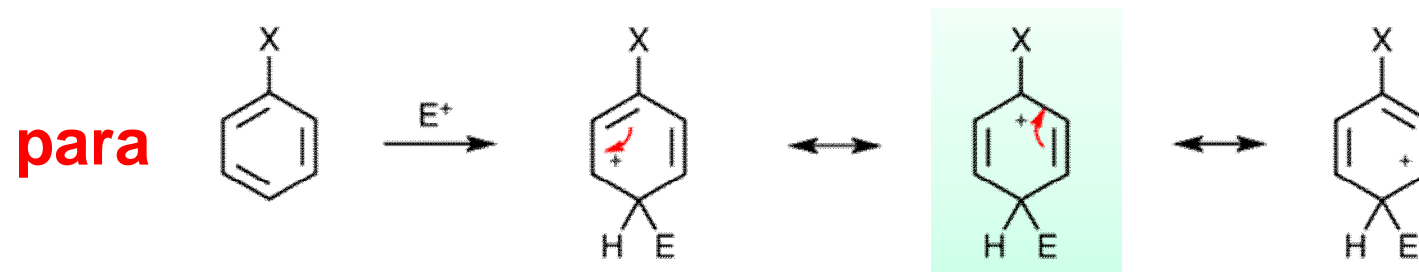
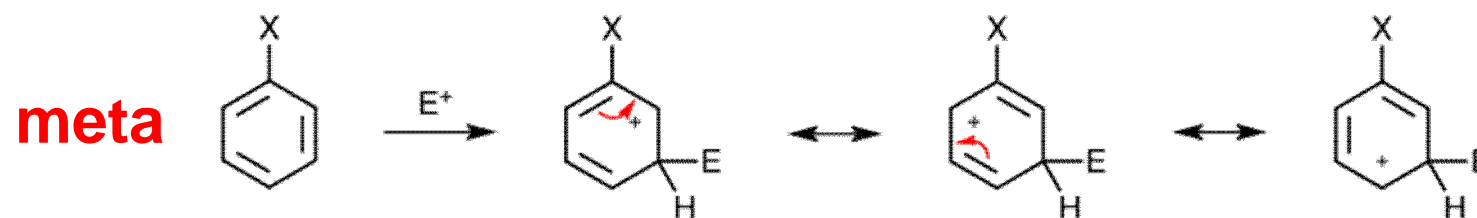
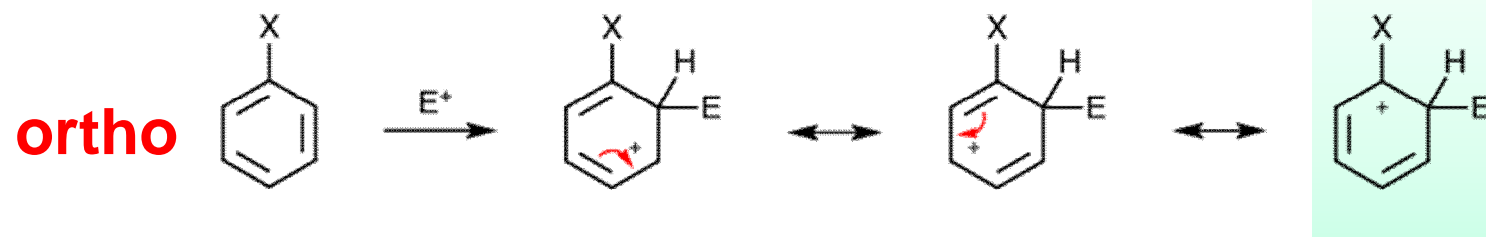


# Substituted Benzenes: Activation

		+ R			- R			
		+R > -I		-I > +R				
- /	-NR <sub>3</sub> <sup>+</sup> CF <sub>3</sub>	-NH <sub>2</sub> , -NHR -NR <sub>2</sub>	-OH -OR	-F -Cl -Br -I	-CHO -COR -COOH -COOR	CN	SO <sub>3</sub> H SO <sub>2</sub> R	-NO <sub>2</sub>
+ /	-CH <sub>3</sub> -Alkyl -SiR <sub>3</sub>							

- Substituents that increase the electron density on the ring activate the ring towards electrophiles. Substituents that decrease the electron density on the ring deactivate the ring towards electrophiles.
- 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**.

# Substituted Benzenes: Orientation

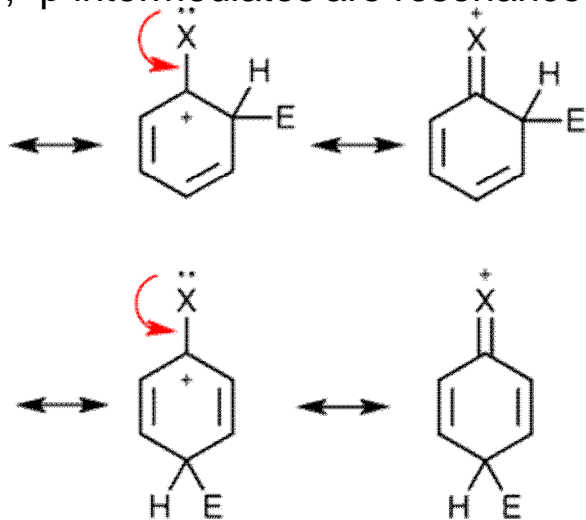


If the reaction takes place in the ortho or para positions a positive charge develops on the carbon atom adjacent to the substituent. 22

# Substituted Benzenes: Orientation

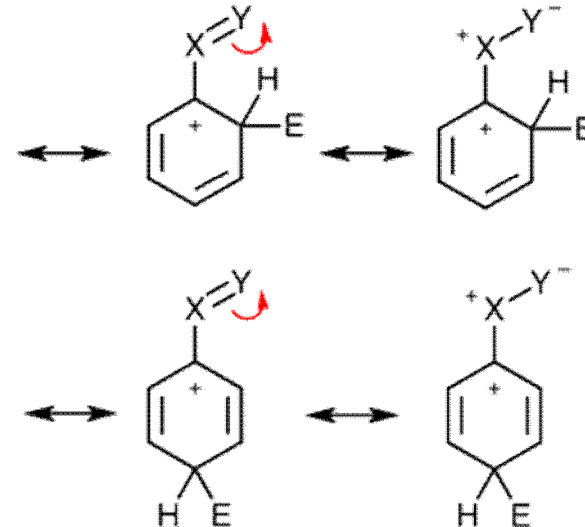
+ R

-o, -p intermediates are resonance stabilised



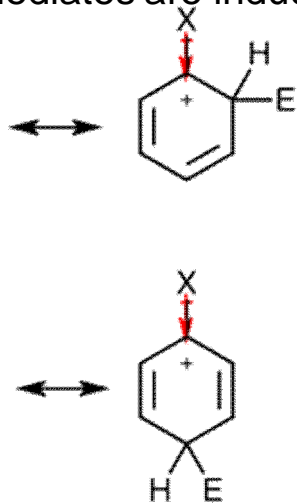
- R

-o, -p intermediates are resonance destabilised



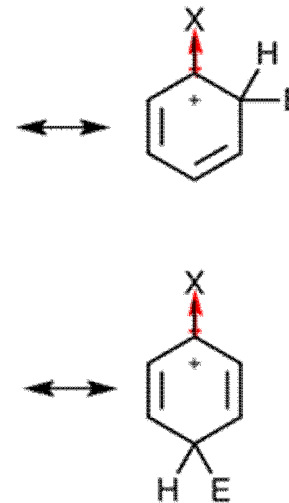
+ I

-o, -p intermediates are inductively stabilised



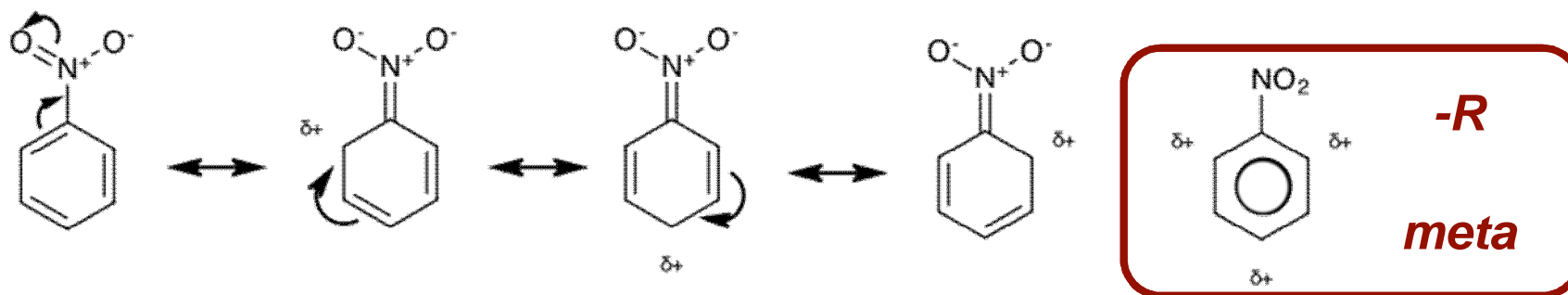
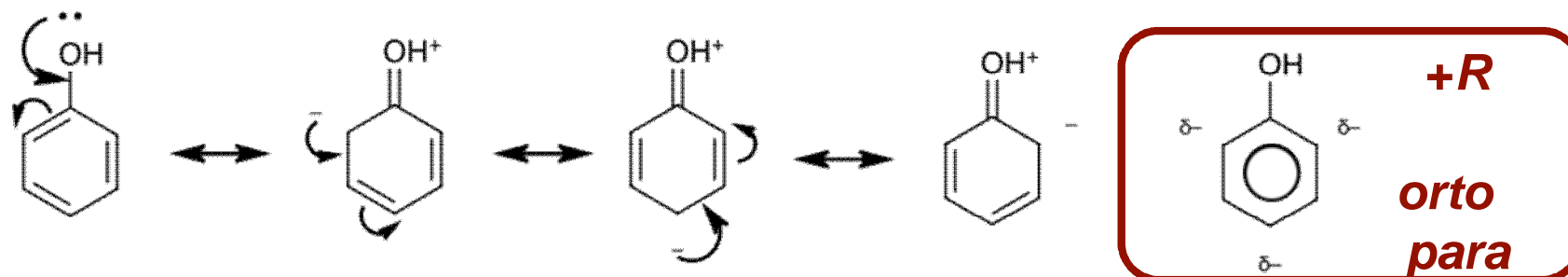
- I

-o, -p intermediates are inductively destabilised



# Substituted Benzenes: Orientation

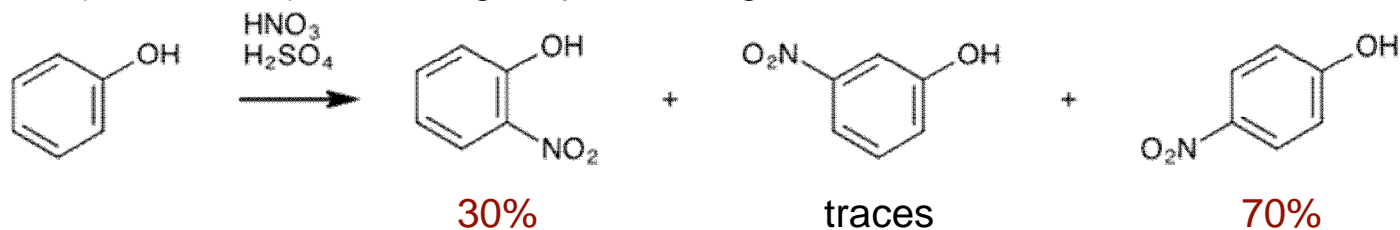
The new group is located either ortho, meta, or para to the existing substituent. The resonance effect of the first substituent determines the position of the second incoming substituent



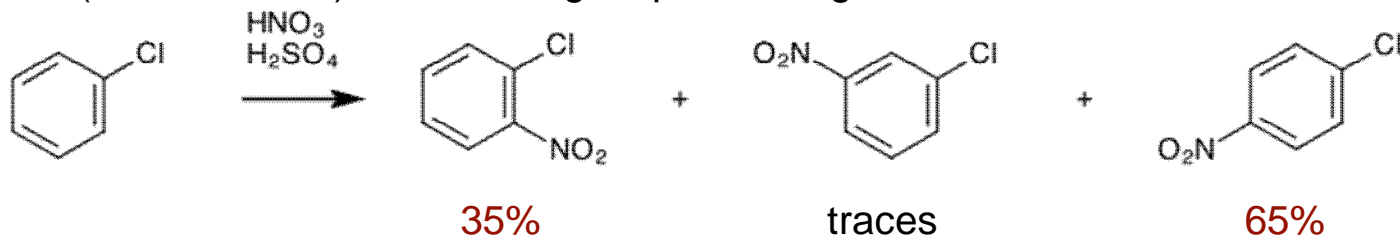


# Substituted Benzenes: Orientation

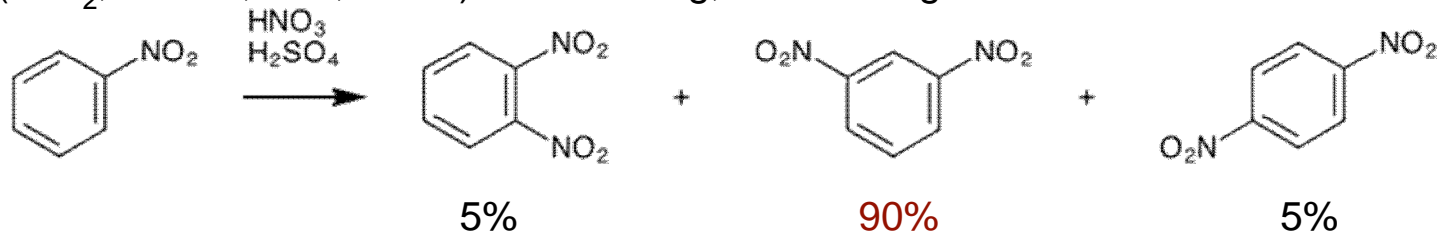
**+R > -I** (-OR, -NR<sub>2</sub>): activating, o- p- directing



**-I > +R** (-F, -Cl, -Br, -I): deactivating, o- p- directing

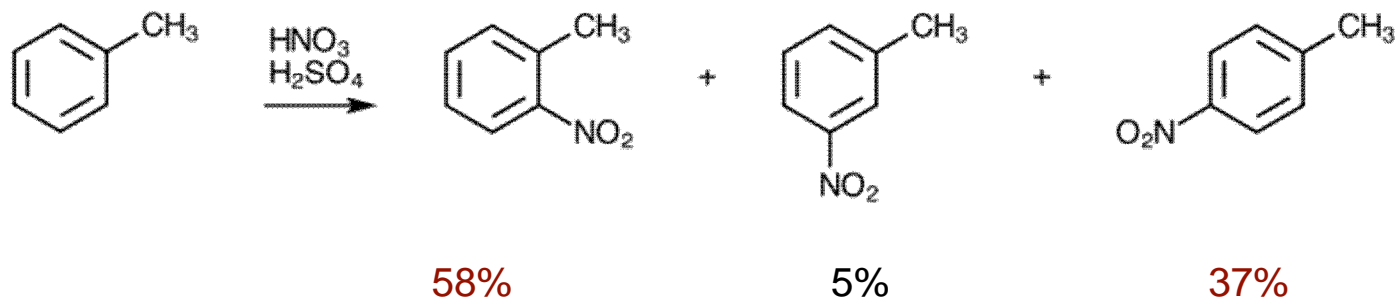


**-I, -R** (-NO<sub>2</sub>, -SO<sub>3</sub>H, -CN, -COR): deactivating, m- directing.

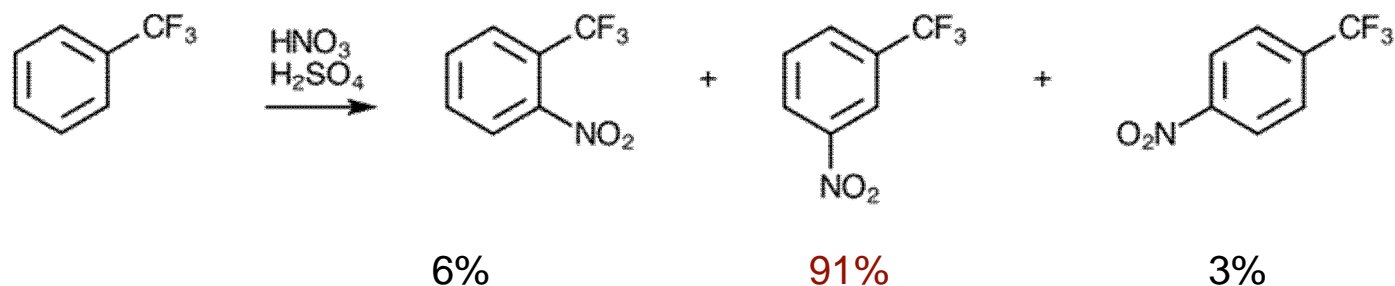


# Substituted Benzenes: Orientation

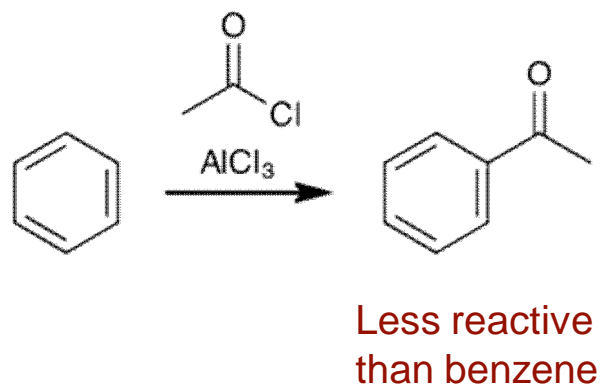
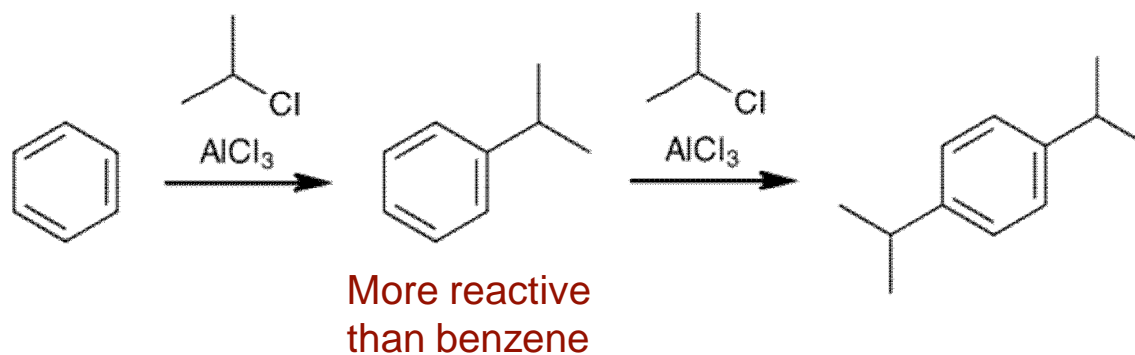
+ I: activating, -o -p directing (same as + R)



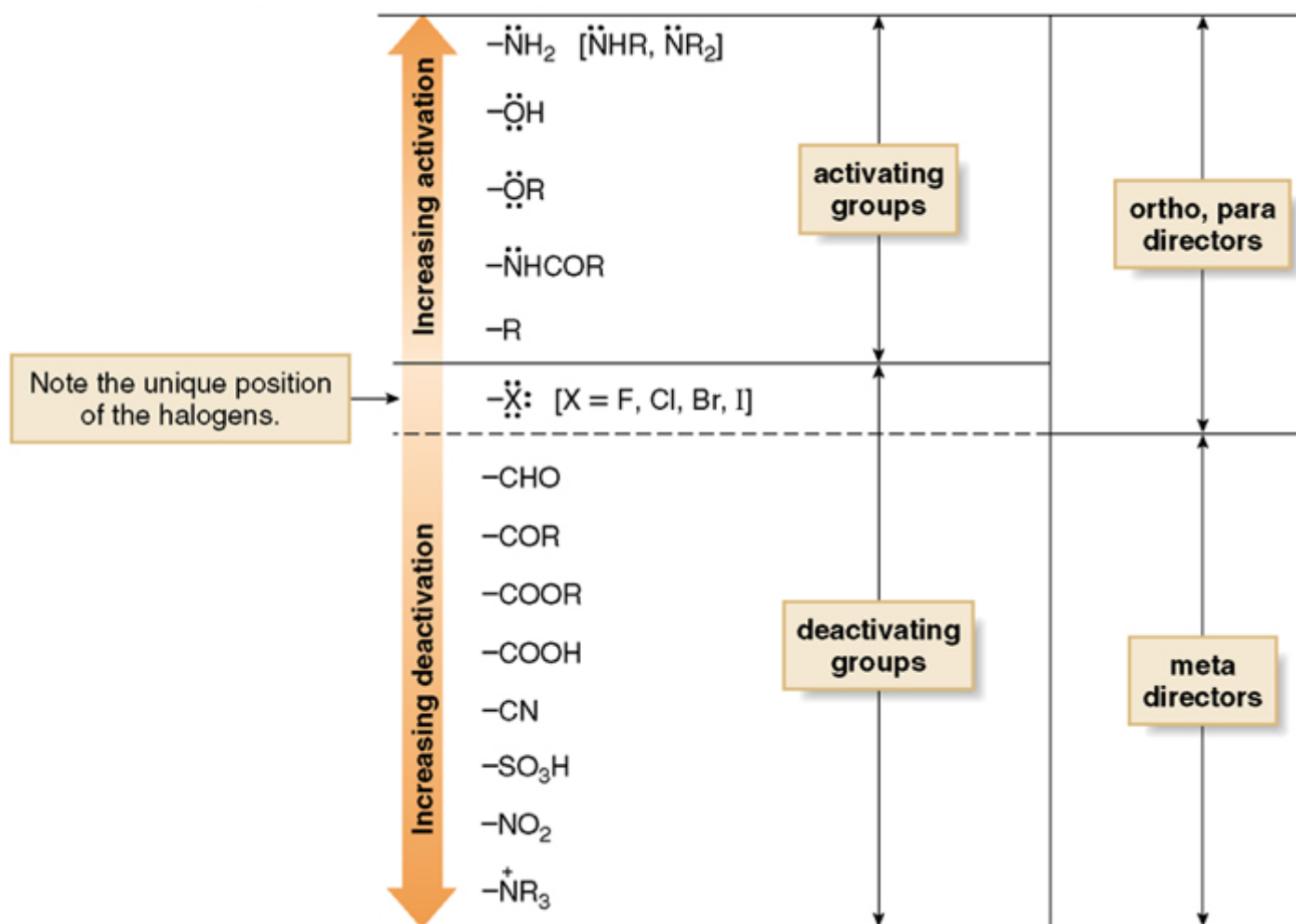
- I: deactivating, -m directing (same as - R)



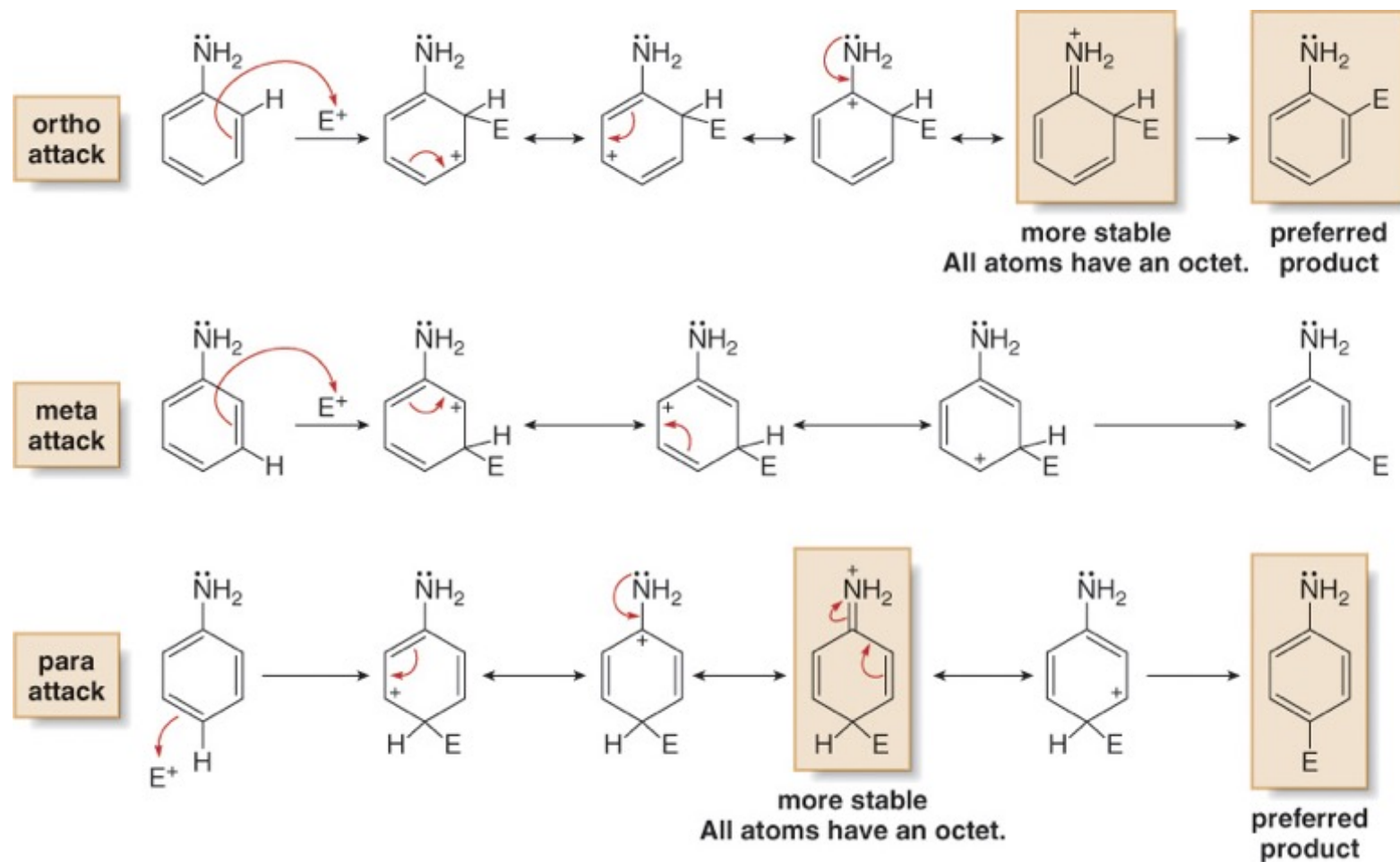
# Substituted Benzenes: Activation



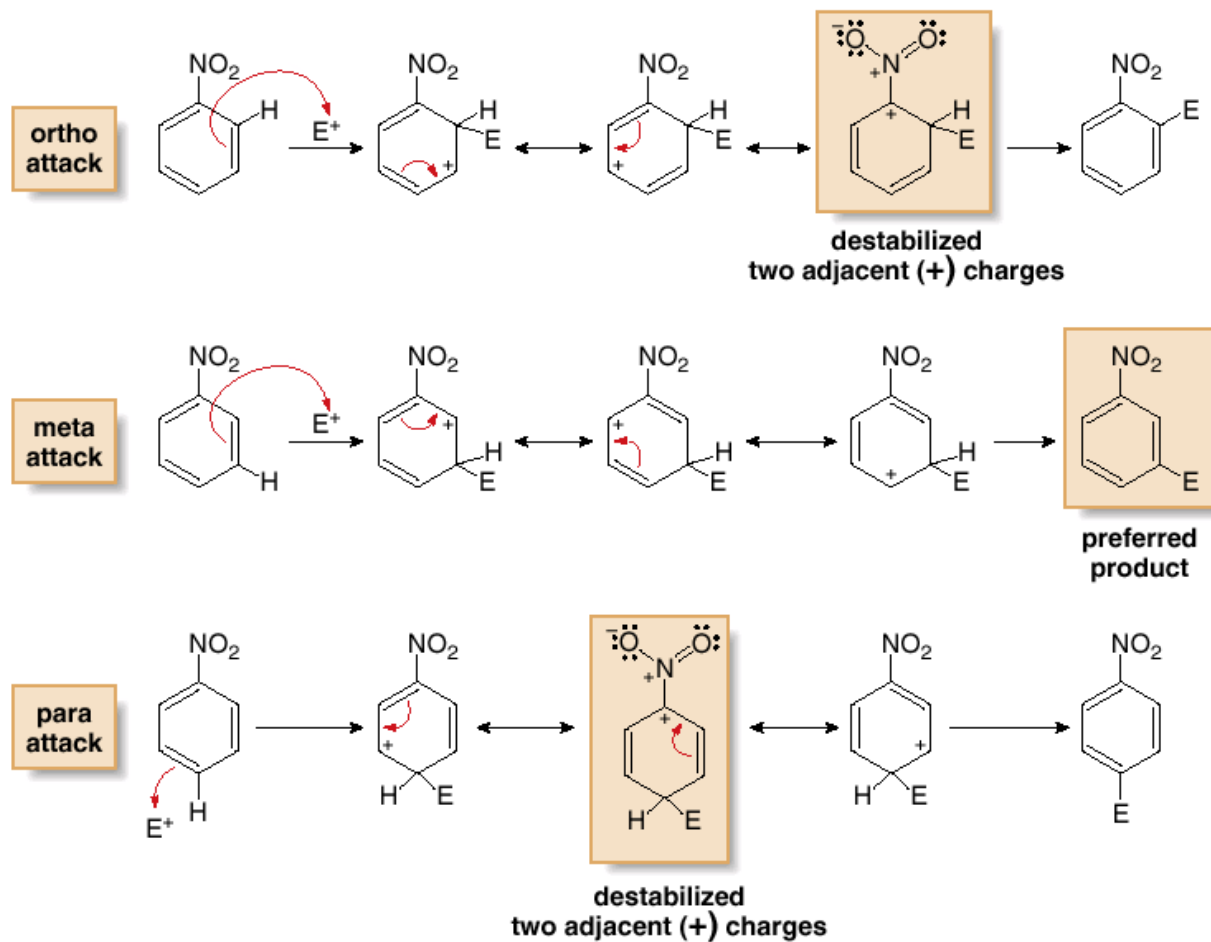
# Substituent Effects. Summary



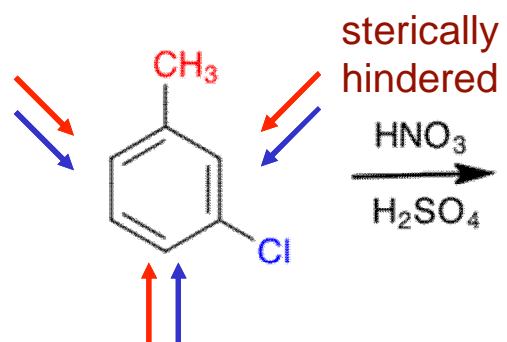
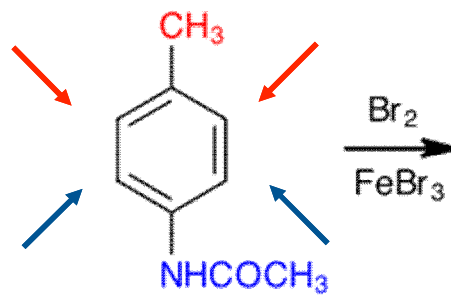
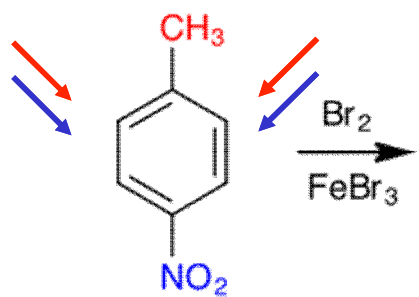
# Substituent Effects. Alternative Explanation



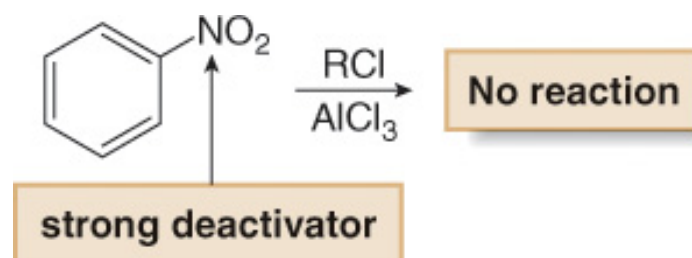
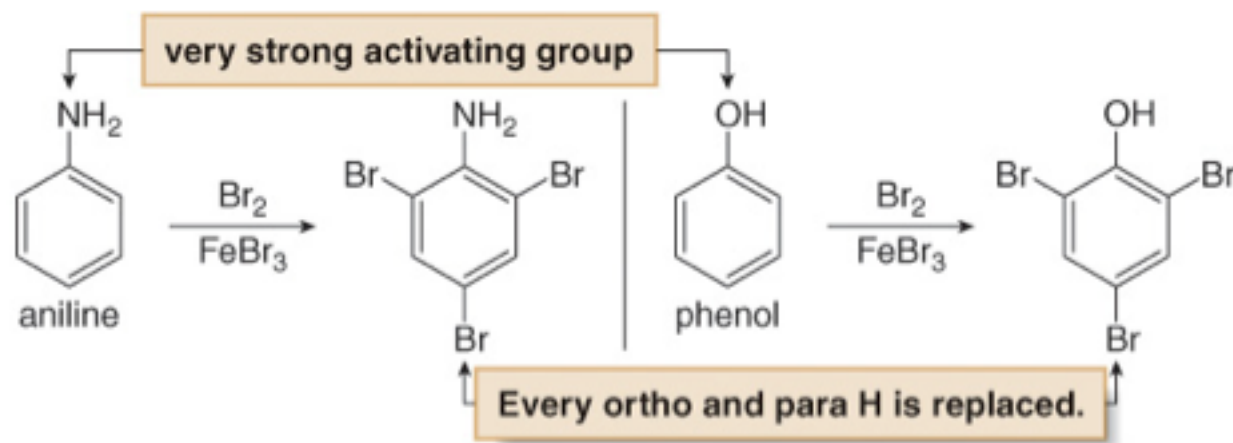
# Substituent Effects. Alternative Explanation



# Disubstituted Benzenes

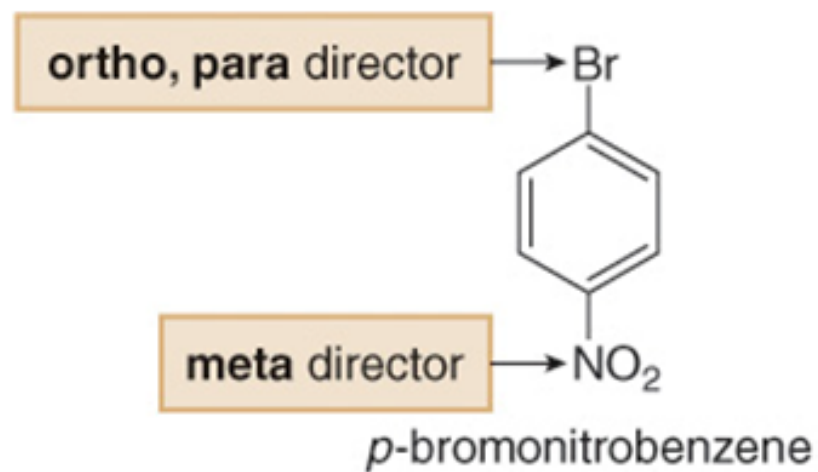


# Further Examples



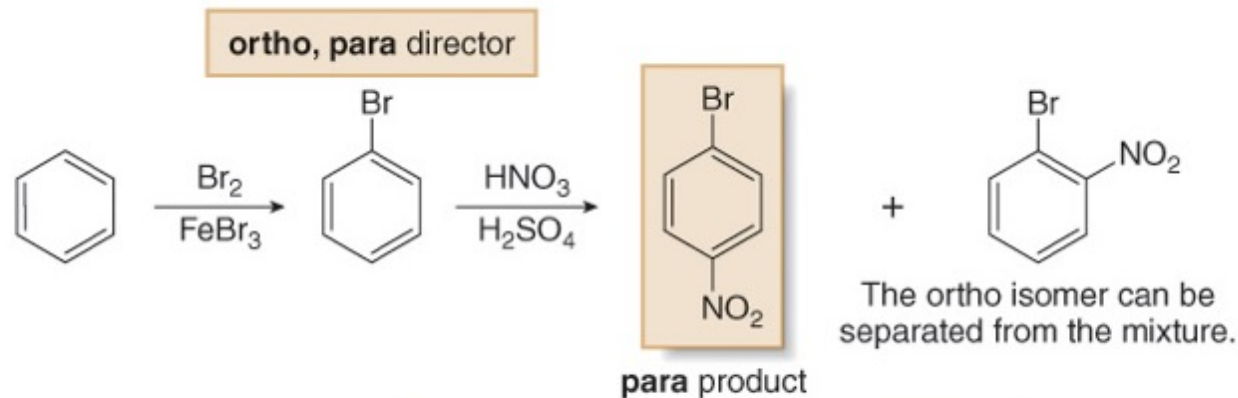


# Synthesis of Polysubstituted Benzenes



# Synthesis of Polysubstituted Benzenes

## Pathway [1]: Bromination before nitration

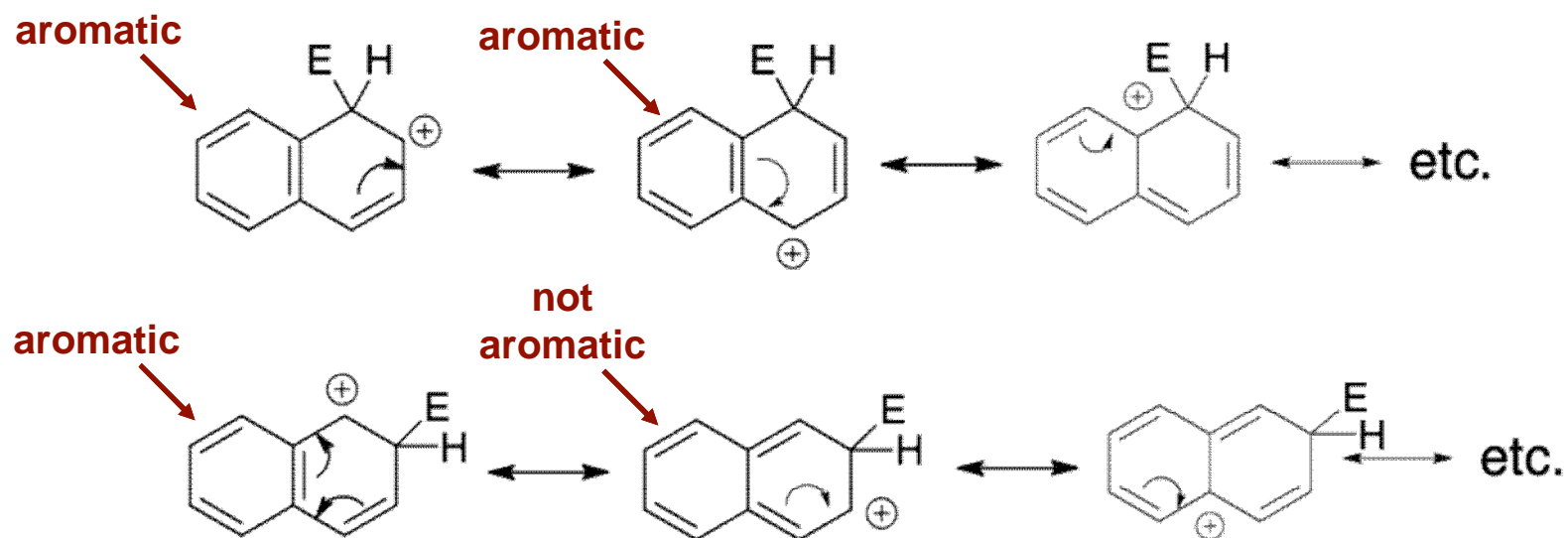
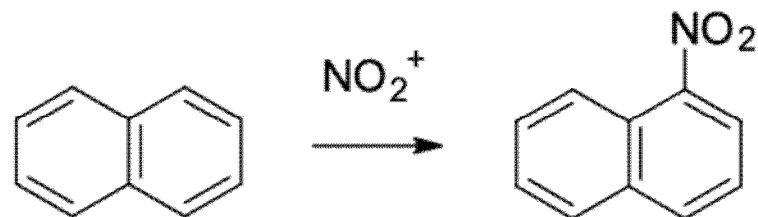


This pathway gives the desired product.

## Pathway [2]: Nitration before bromination

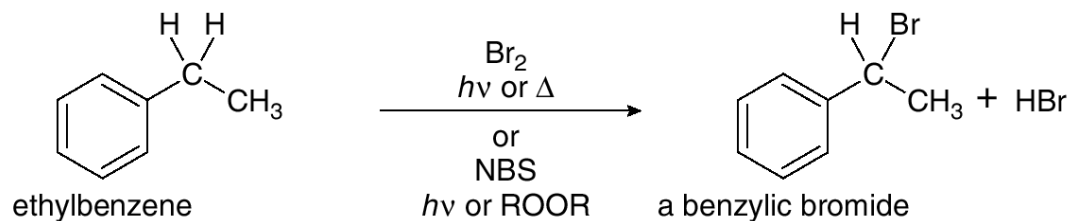
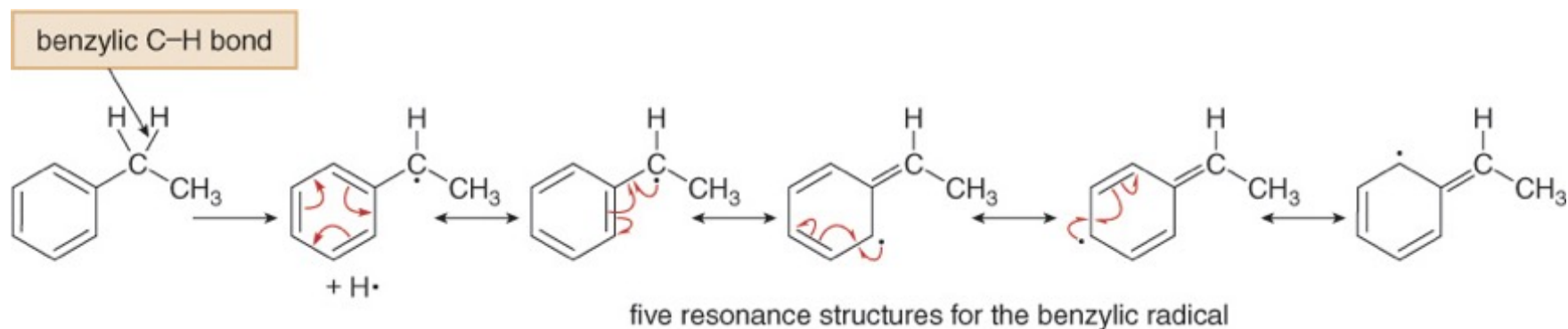


# $S_EAr$ in Polycyclic Aromatic Compounds



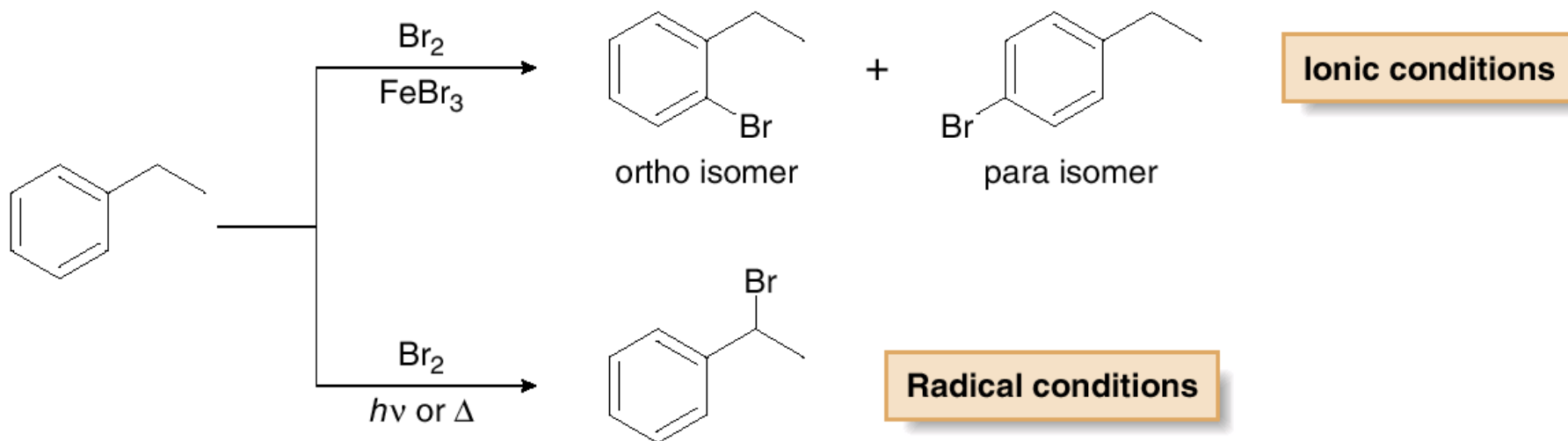
# Side Chain Reactivity: Radical Halogenation

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

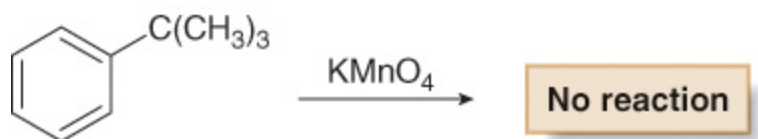
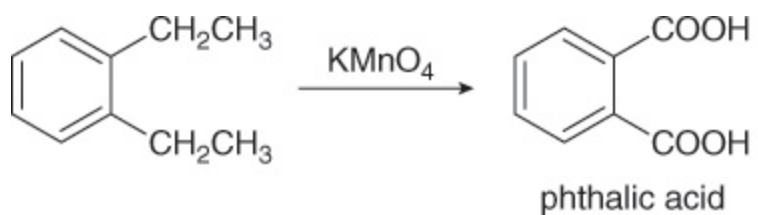
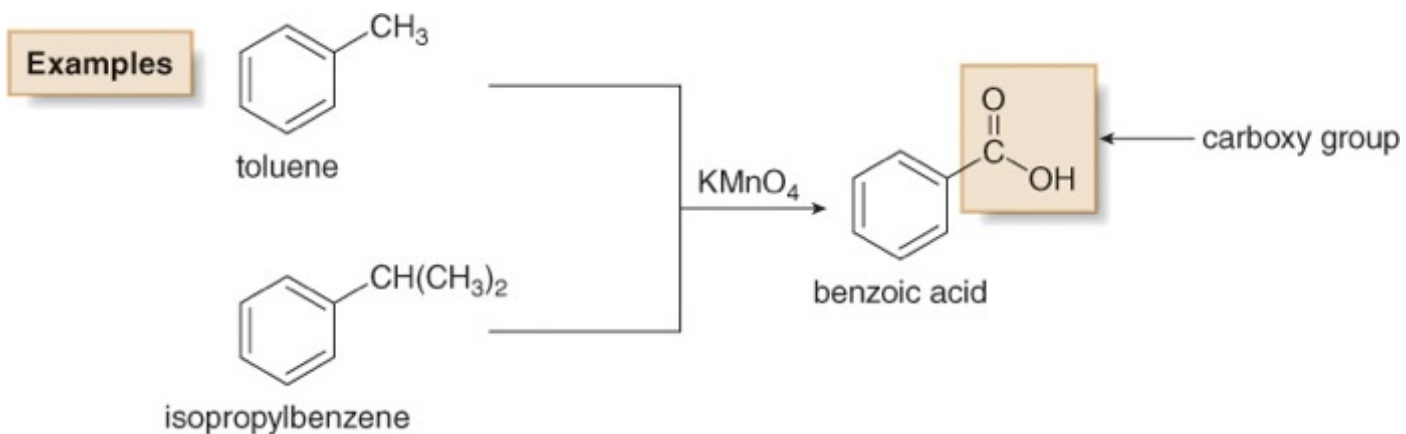


radical conditions

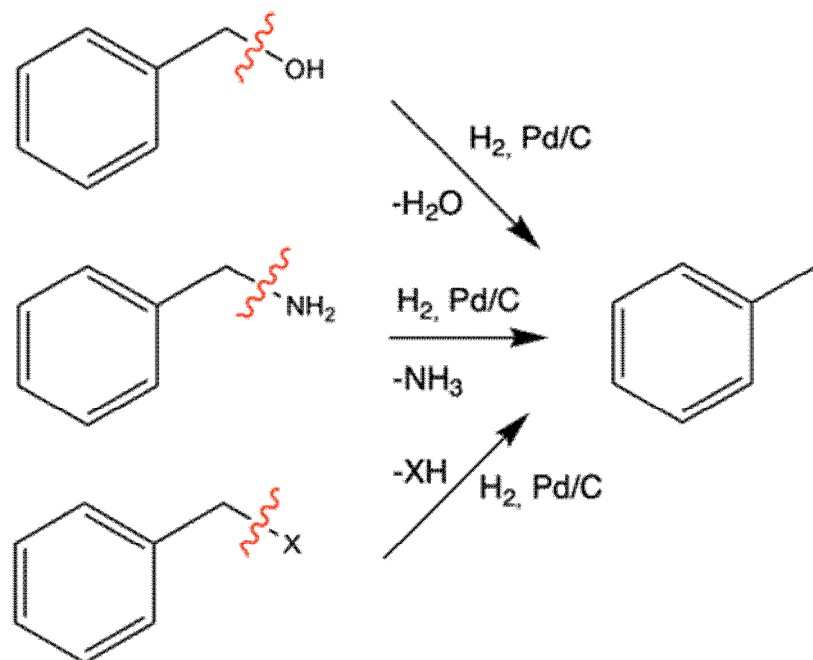
# Side Chain Reactivity



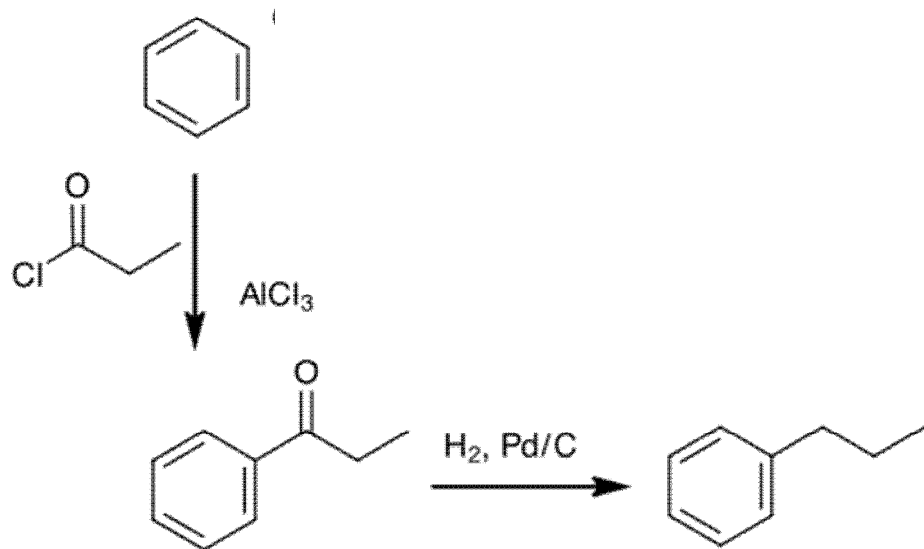
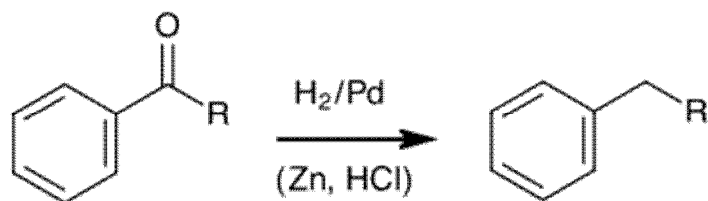
# Side Chain Reactivity: Oxidation



# Side Chain Reactivity: Reduction



# Side Chain Reactivity: Reduction





# Side Chain Reactivity: Reduction

