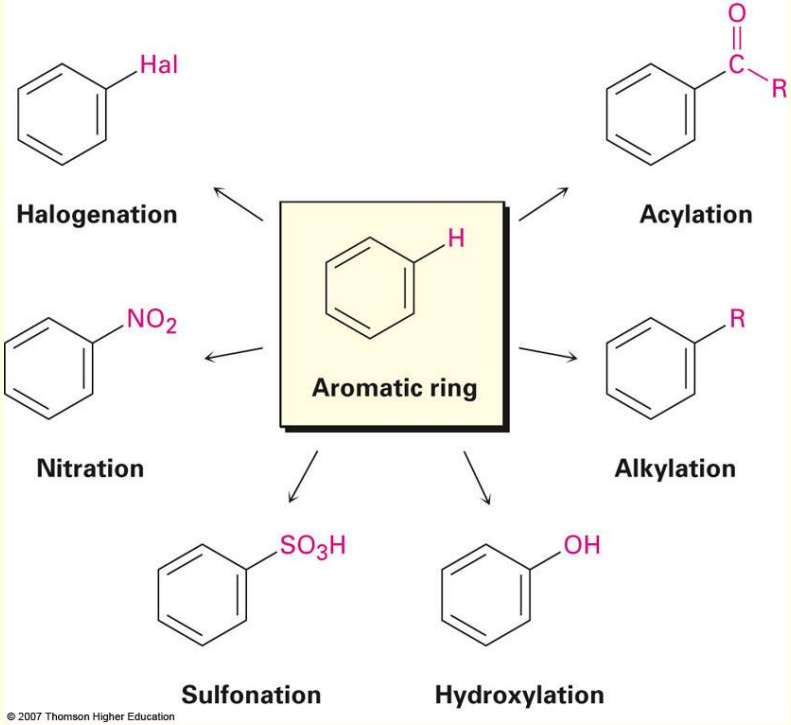
15. Chemistry of Benzene: Electrophilic Aromatic Substitution

Based on McMurry's *Organic Chemistry*, 7th edition

Substitution Reactions of Benzene and Its Derivatives

- Benzene is aromatic: a cyclic conjugated compound with 6 π electrons
- Reactions of benzene lead to the retention of the aromatic center



Why this Chapter?

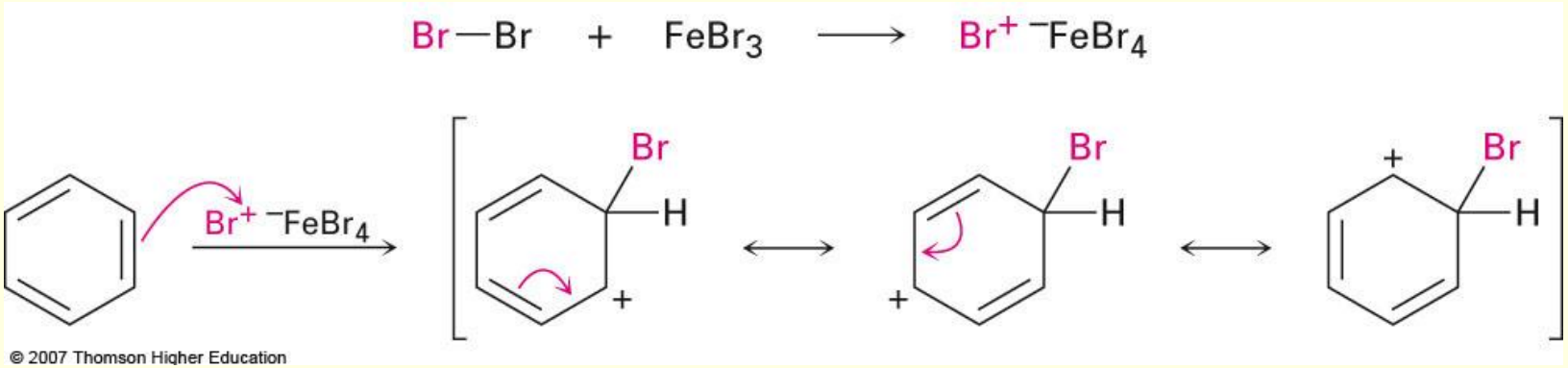
- Continuation of coverage of aromatic compounds in preceding chapter…focus shift to understanding reactions
- Study relationship between aromatic structure and reactivity
- To understanding of how biological molecules/pharmaceutical agents are synthesized

16.1 Electrophilic Aromatic Substitution Reactions: Bromination

- Benzene's π electrons play a part as a Lewis base in reactions with Lewis acids
- The product is formed by loss of a proton, which is replaced by bromine
- $FeBr_3$ is added as a catalyst to polarize the bromine reagent

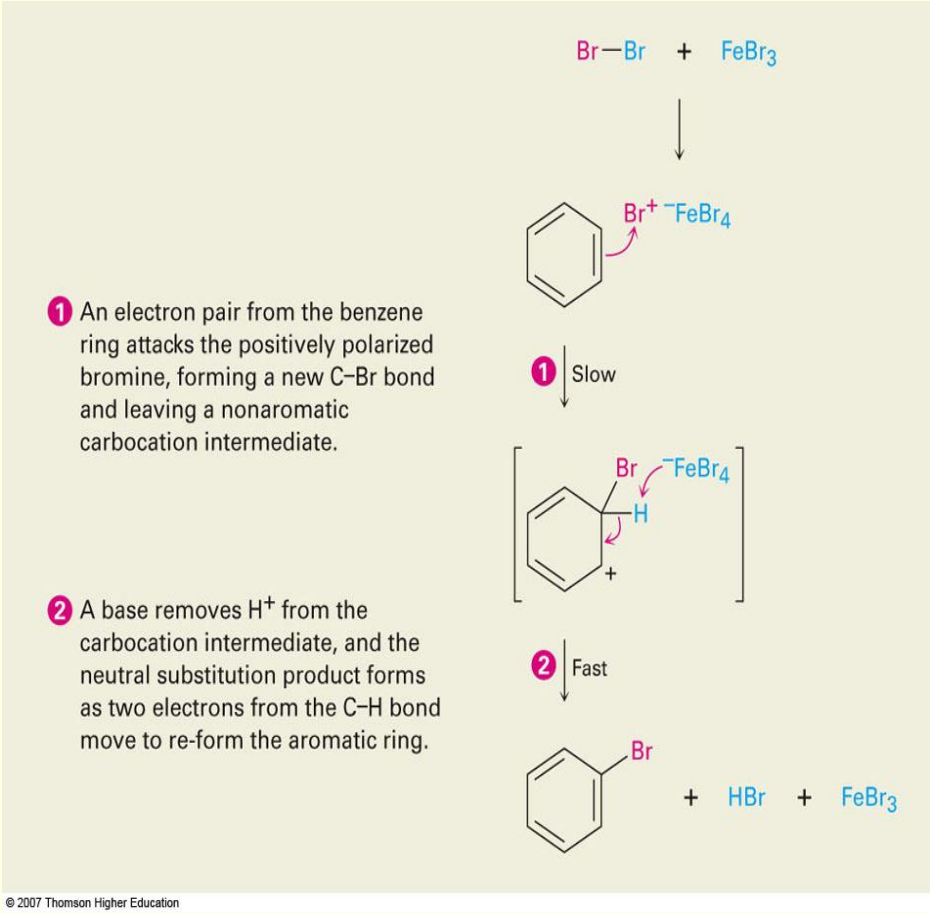
Addition Intermediate in Bromination

- The addition of bromine occurs in two steps
- In the first step the π electrons act as a nucleophile toward Br_2 (in a complex with $FeBr_3$) make the Br_2 more electrophilic by polarizing it.
- The polarized Br_2 reacts with the nuclephilic benzene ring
- This forms a cationic addition intermediate from benzene and a bromine cation
- The intermediate is not aromatic carbocation intermediate has three resonance forms.



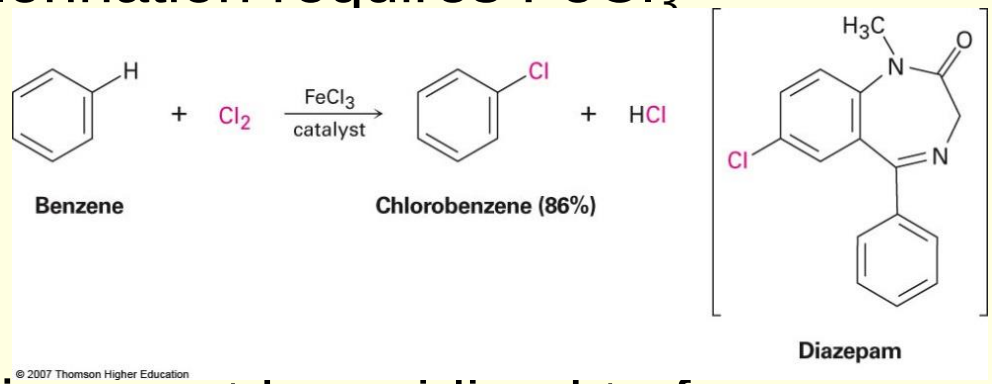
Formation of Product from Intermediate

- The cationic addition intermediate transfers a proton to $FeBr_4^-$ (from Br^- and $FeBr_3$)
- The reaction occure in two steps and involves a resonance-stabilized carbocation intermediate
- The addition occur after the carbocation intermediate has formed.

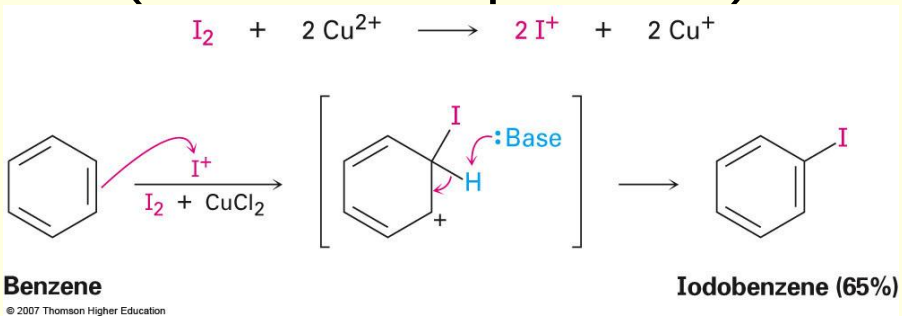


16.2 Other Aromatic Substitutions

- Chlorine and iodine (but not fluorine, which is too reactive) can produce aromatic substitution with the addition of other reagents to promote the reaction
- Chlorination requires $FeCl_3$

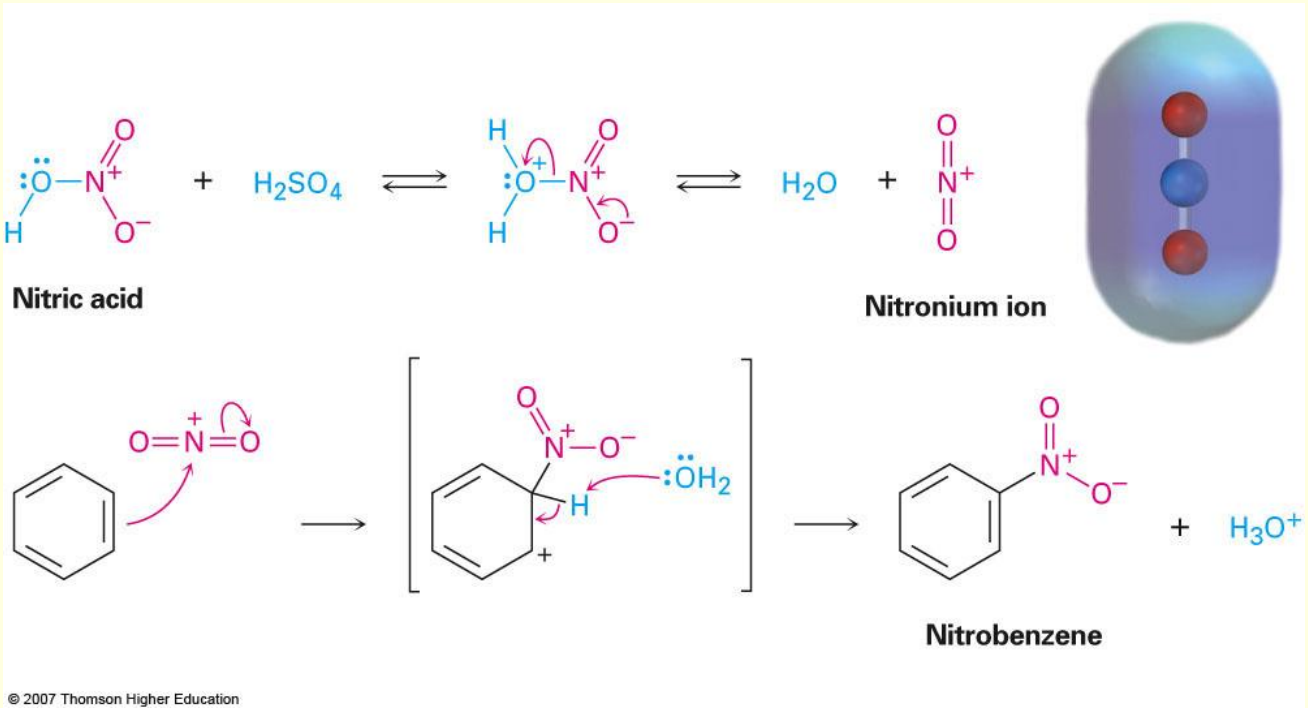


- Iodine must be oxidized to form a more powerful I^+ species (with Cu^+ or peroxide)

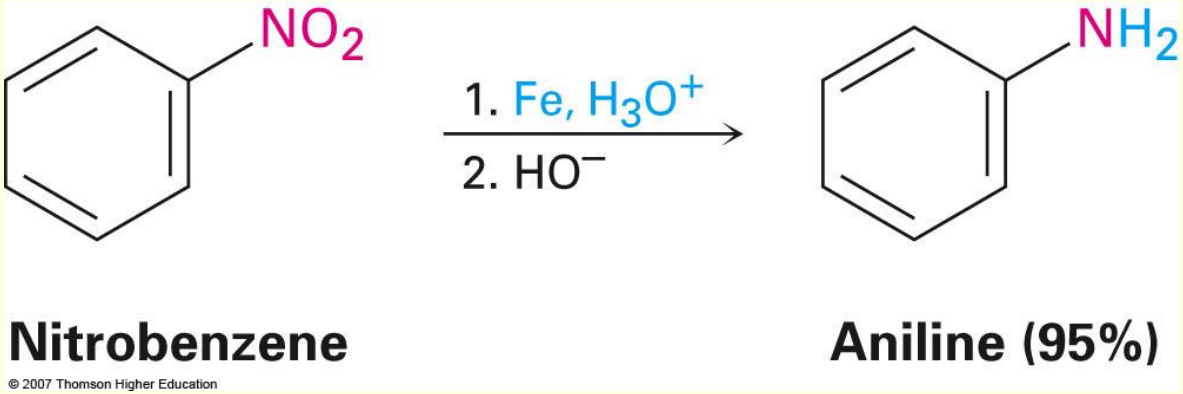


Aromatic Nitration

- Aromatic rings can be nitrated by reaction with a mixture of concentrated nitric and sulfuric acids
- The combination of nitric acid and sulfuric acid produces NO_2^+ (nitronium ion)
- The reaction with benzene produces nitrobenzene

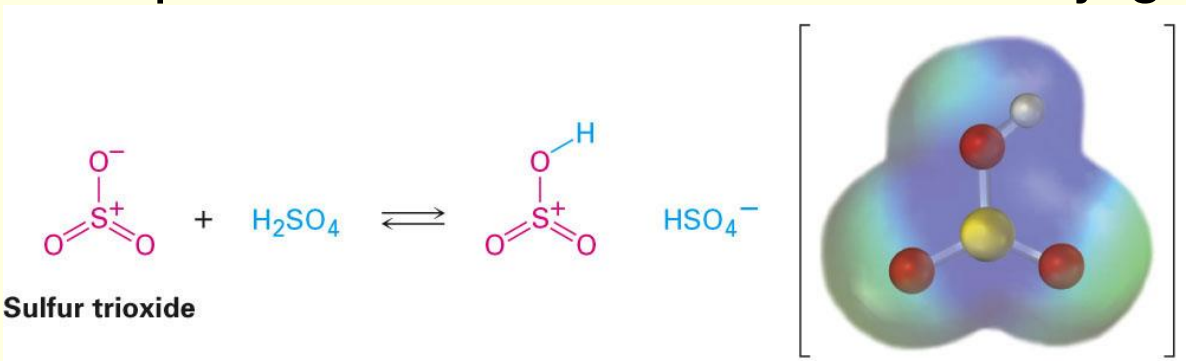


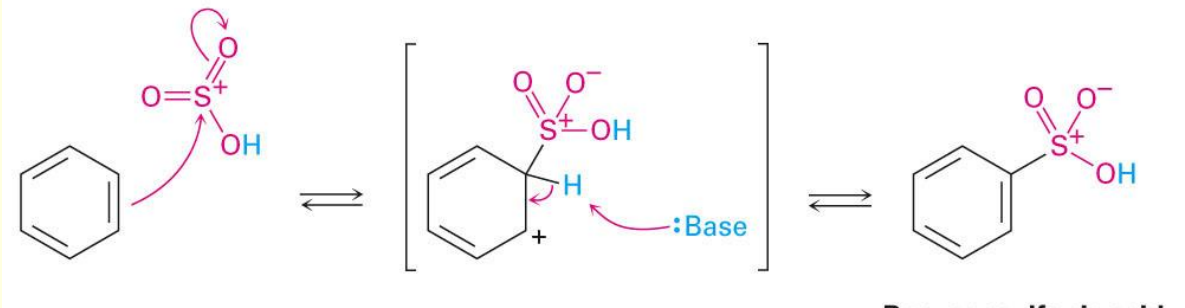
- The nitro-substituted product can be reduced by reagent such as iron, tin or SnCl2 to yield an arylamine.



Aromatic Sulfonation

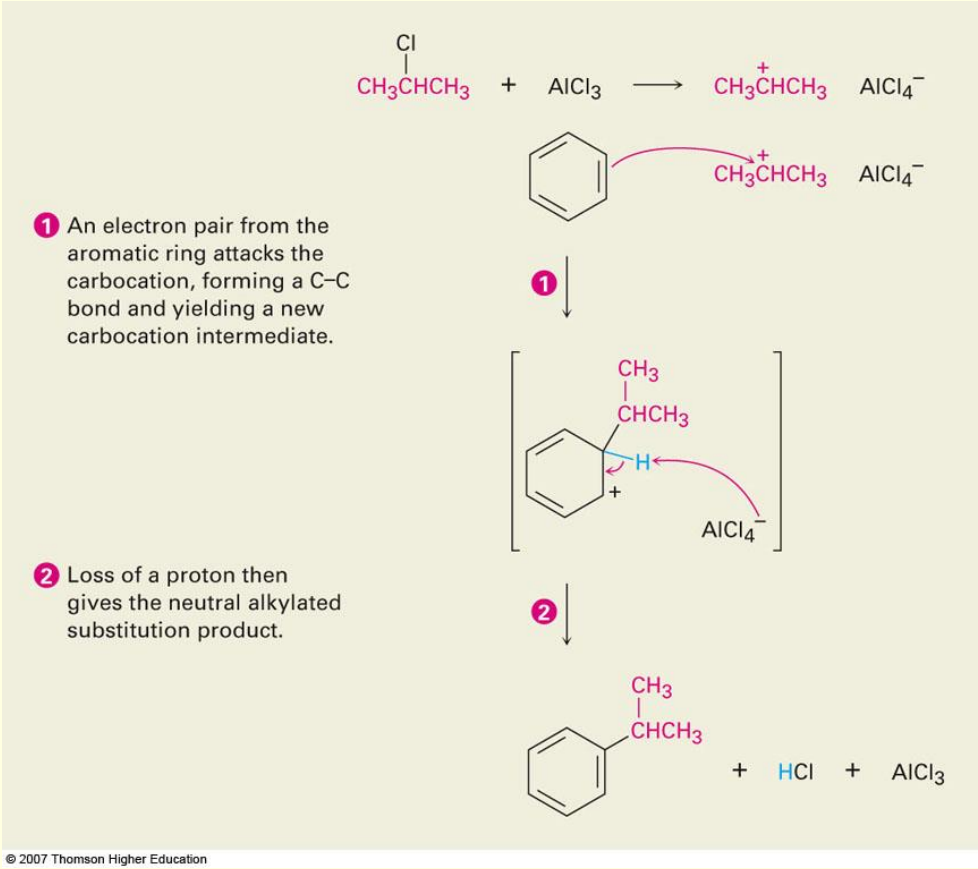
- Aromatic ring can be sulfonated by Substitution of H by SO_3
- Reaction with a mixture of sulfuric acid and sulfur trioxide SO_3
- Reactive species is sulfur trioxide or its conjugate acid





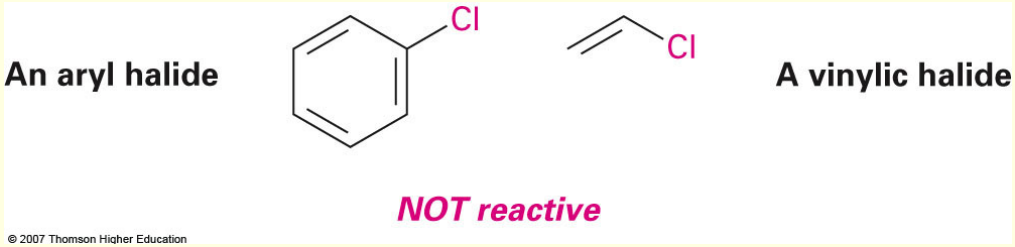
16.3 Alkylation of Aromatic Rings: The Friedel–Crafts Reaction

- Alkylation among most useful electrophilic aromatic subsitution reactions
- Aromatic substitution of R^+ for H^+
- Aluminum chloride catalyzes the reaction by the formation of the carbocation

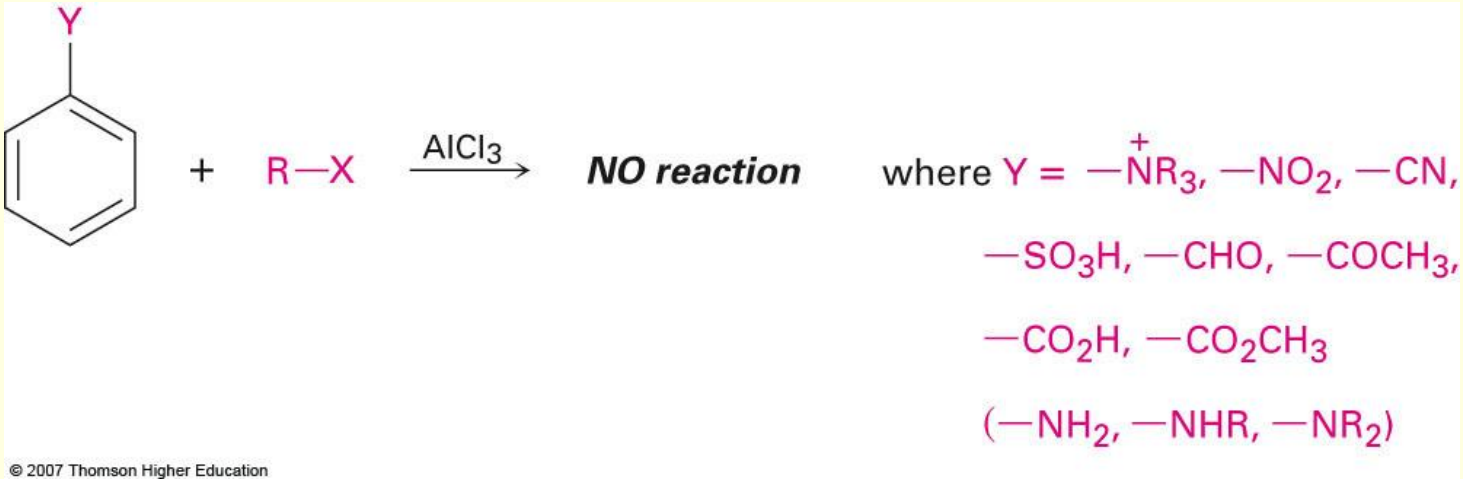


Limitations of the Friedel-Crafts Alkylation

- Only *alkyl* halides can be used (F, Cl, I, Br)
- *Aryl* halides and *vinylic* halides do not react (their carbocations are too hard to form)

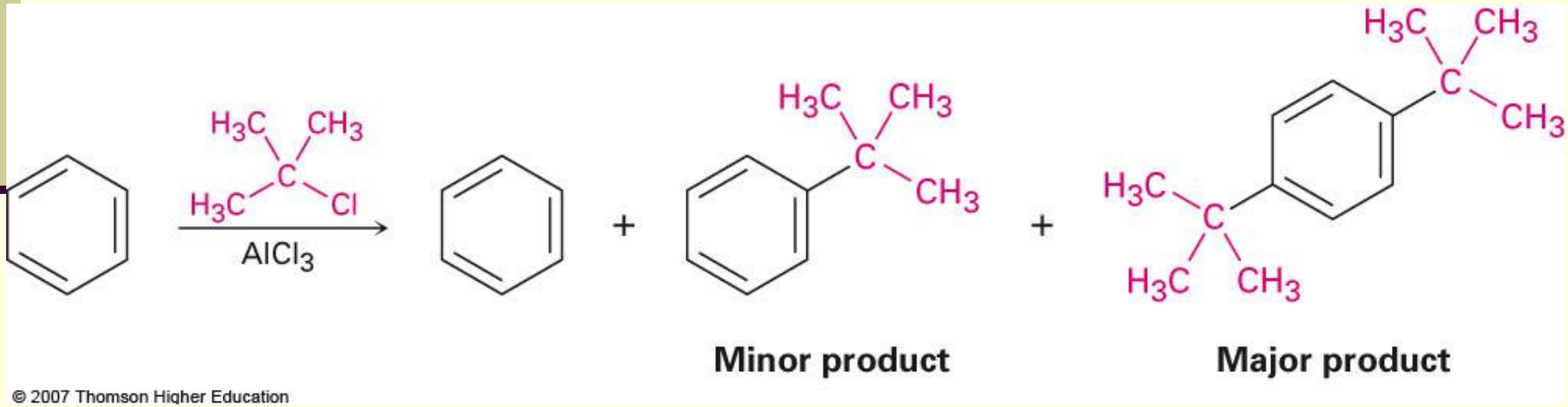


- Will not work with rings containing an amino group substituent or a strongly electron-withdrawing group



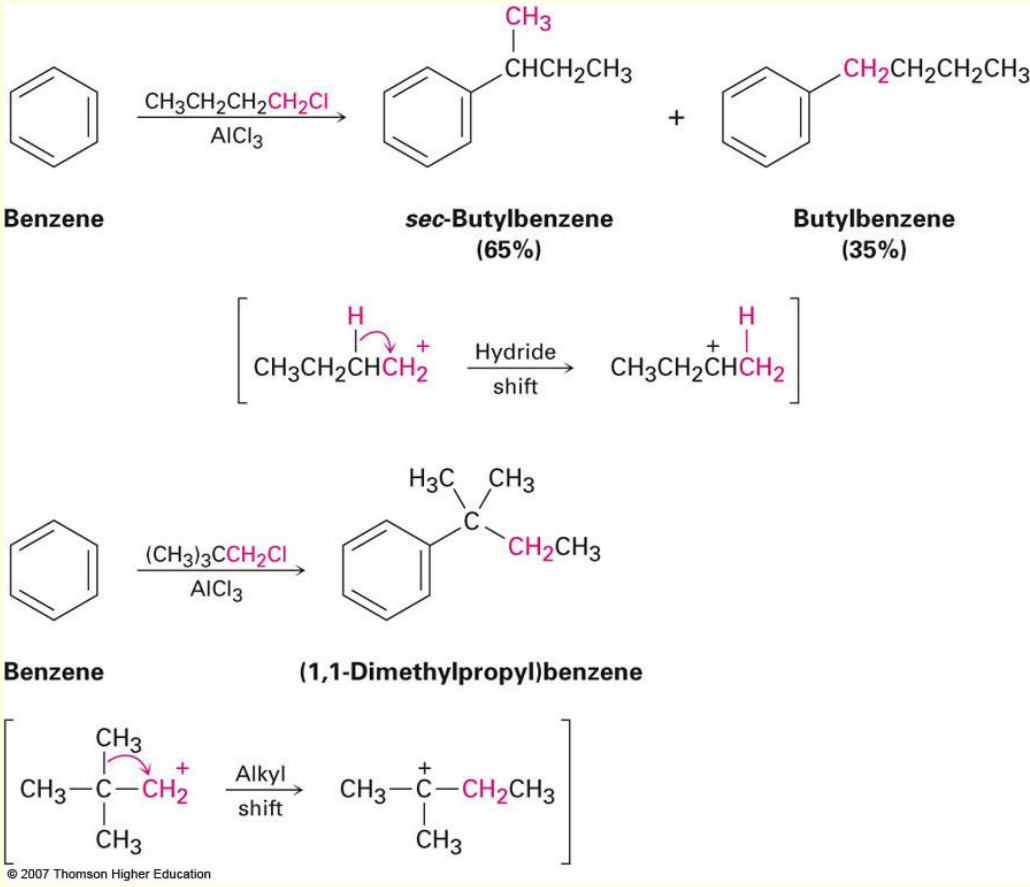
Control Problems

- Multiple alkylations (polyalkylation)can occur because the first alkylation is activating
- Reaction of benzene with 2-chloro -2-methylpropane,yields p-di-tert-butylbenzene ,tert-buty benzene and benzene.



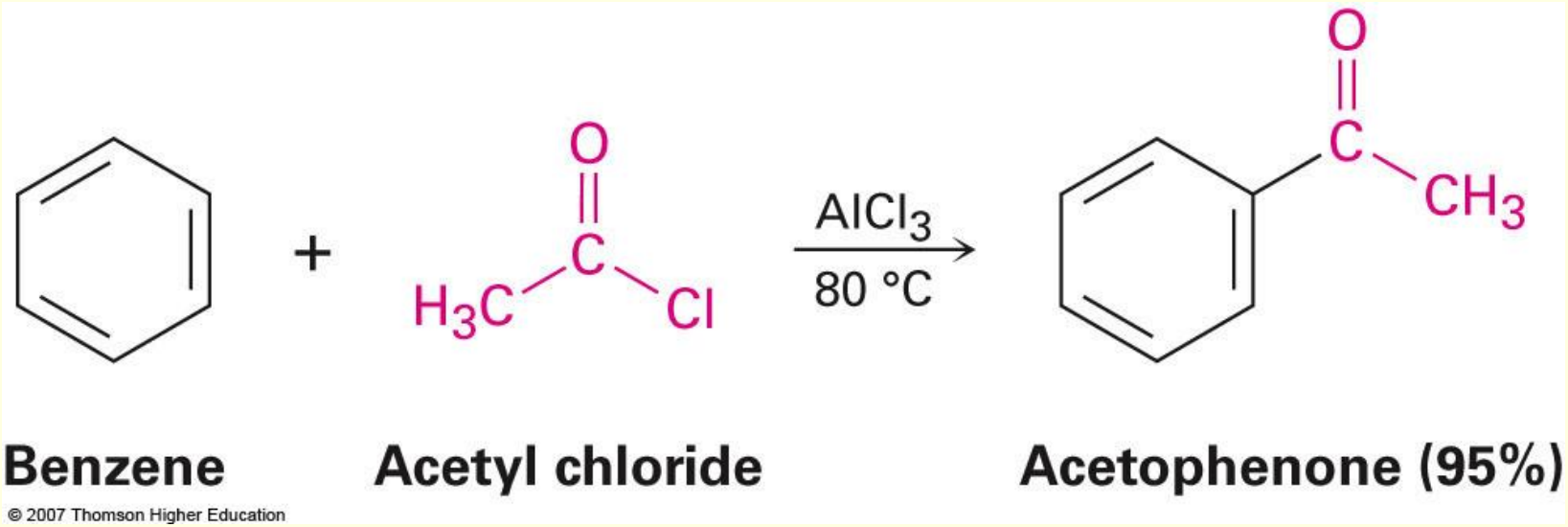
Carbocation Rearrangements During Alkylation

- Similar to those that occur during electrophilic additions to alkenes
- Can involve H in
- (1-chlorobutane) or alkyl in
- (1-chloro,2,2-dimethulpropane) shifts



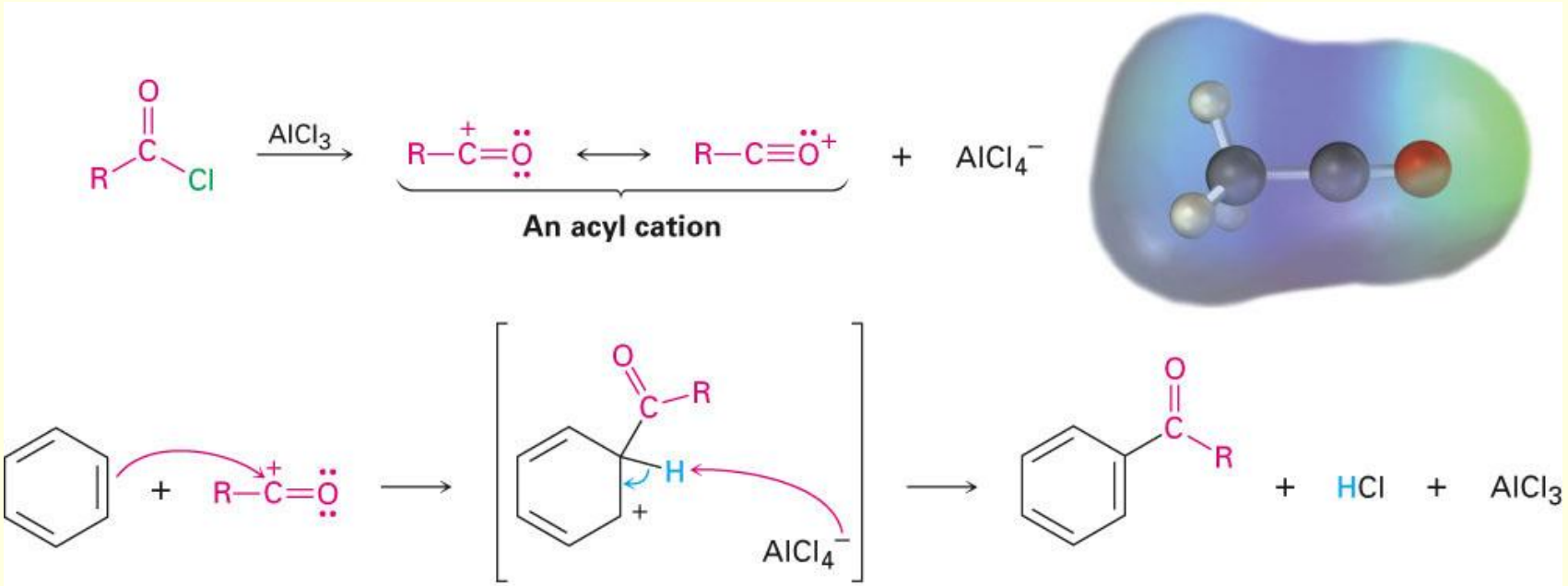
Acylation of Aromatic Rings

- Reaction of an acid chloride (RCOCl) and an aromatic ring in the presence of $AlCl_3$ introduces **acyl group**, —COR
  - Benzene with acetyl chloride yields acetophenone



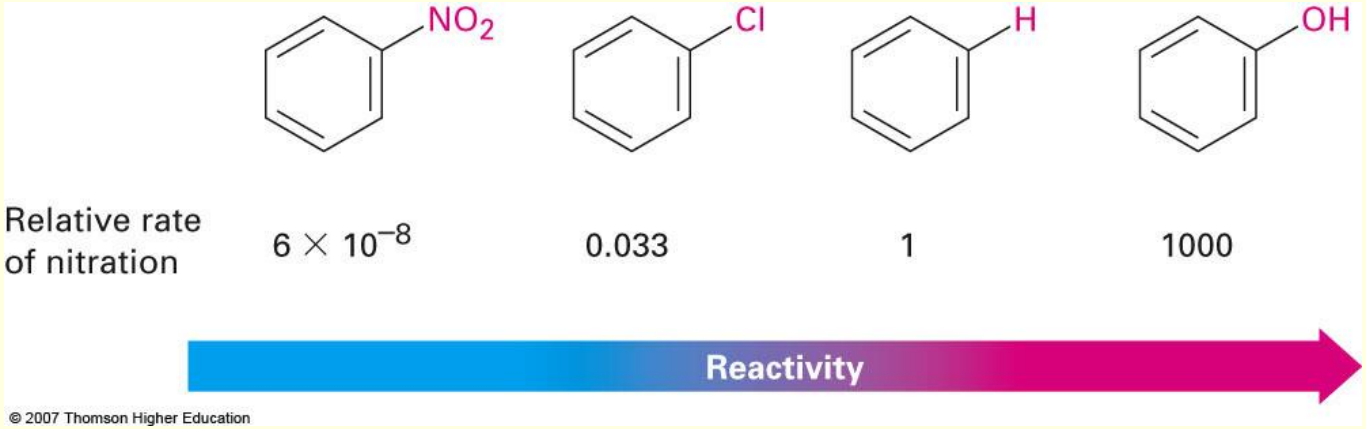
Mechanism of Friedel-Crafts Acylation

- Similar to alkylation
- Reactive electrophile: resonance-stabilized acyl cation
- An acyl cation is stabilized,no carbocation rearrangement occurs during acylation.



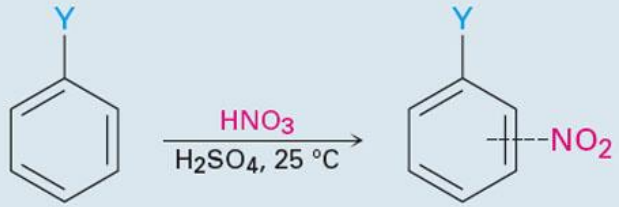
16.4 Substituent Effects in Aromatic Rings

- Substituents can cause a compound to be (much) more or (much) less reactive than benzene

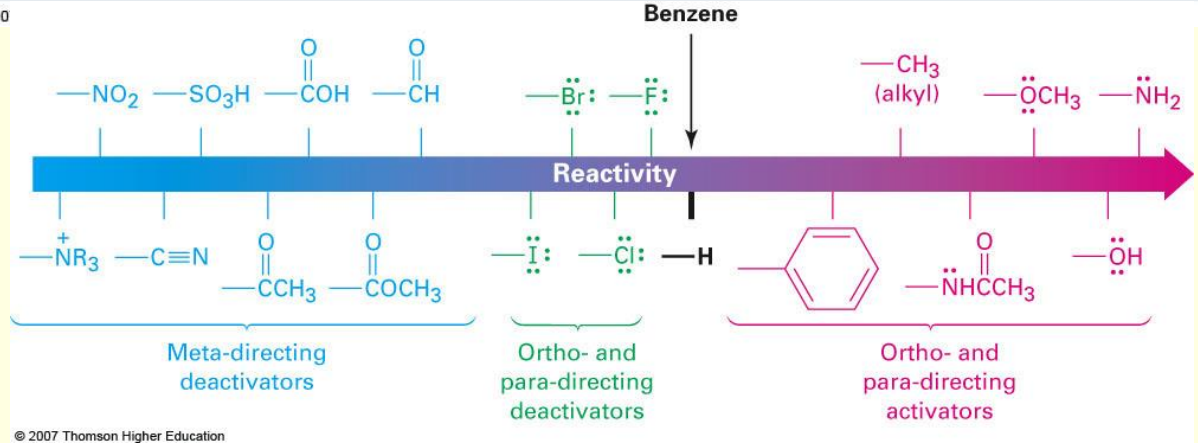


  - The nature of the substituent already present on the benzene ring determines the position of the second substitution.
  - ortho- and para-directing activators, ortho- and para-directing deactivators, and meta-directing deactivators (Table 16.1)

Table 16.1 Orientation of Nitration in Substituted Benzenes



	Product (%)				Product (%)		
	Ortho	Meta	Para		Ortho	Meta	Para
Meta-directing deactivators				**Ortho- and para-directing deactivators**			
$-\overset{+}{N}(CH_3)_3$	2	87	11	$-F$	13	1	86
$-NO_2$	7	91	2	$-Cl$	35	1	64
$-CO_2H$	22	76	2	$-Br$	43	1	56
$-CN$	17	81	2	$-I$	45	1	54
$-CO_2CH_3$	28	66	6	**Ortho- and para-directing activators**			
$-COCH_3$	26	72	2	$-CH_3$	63	3	34
$-CHO$	19	72	9	$-OH$	50	0	50
				$-NHCOCH_3$	19	2	79

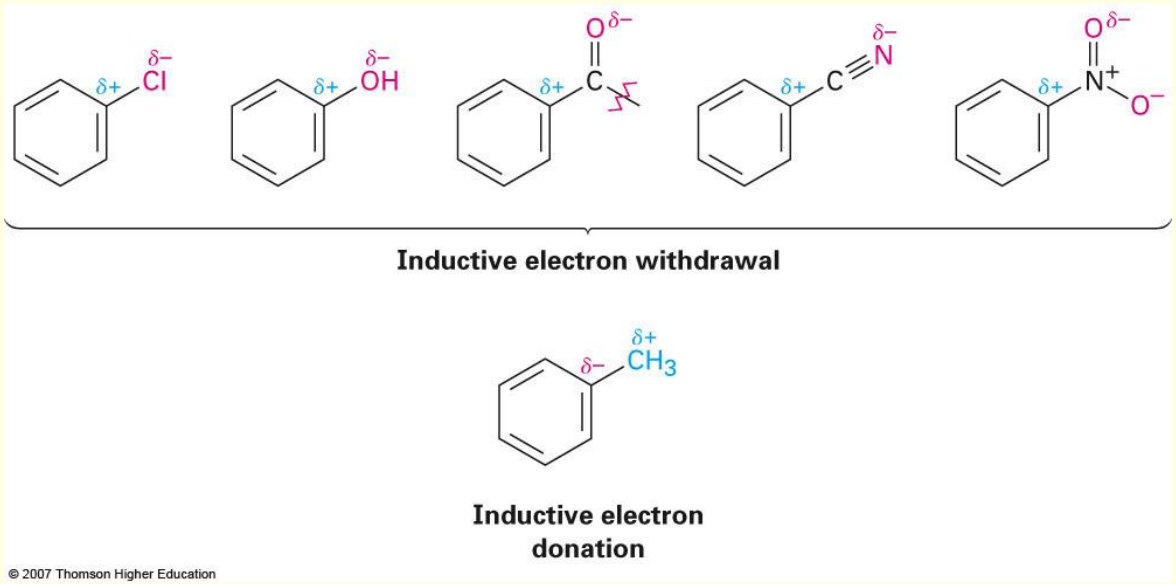


Origins of Substituent Effects

- An interplay of *inductive effects* and *resonance effects*
- Inductive effect - withdrawal or donation of electrons through a σ bond due to electronegativily.OH-,X-,CO-CN-,NO2-
- Alkyl groups, inductively donate electrons.
- 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

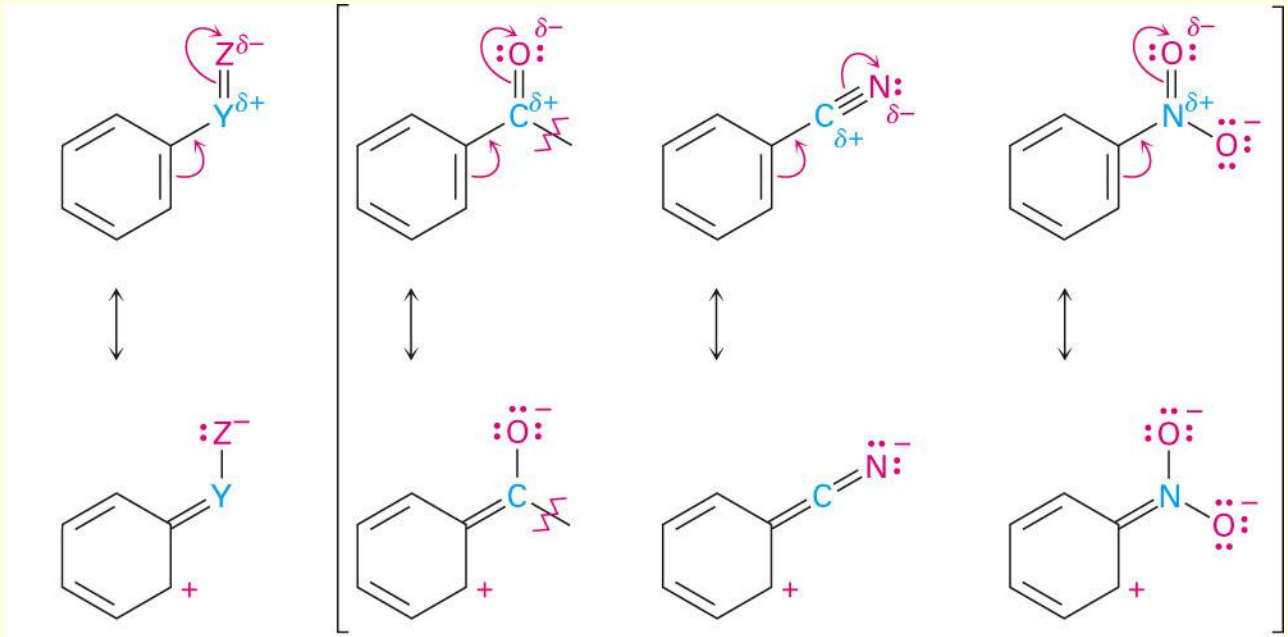
Inductive Effects

- Controlled by electronegativity and the polarity of bonds in functional groups
- Halogens, C=O, CN, and NO_2 *withdraw* electrons through σ bond connected to ring
- Alkyl groups *donate* electrons



Resonance Effects – Electron Withdrawal

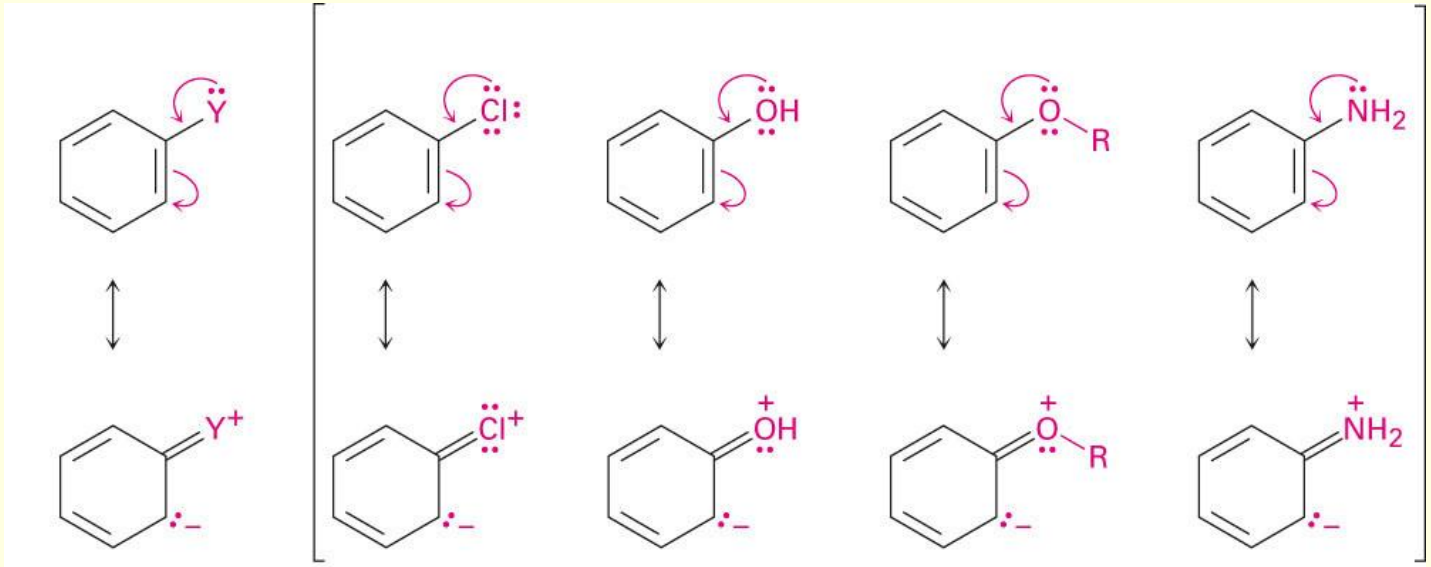
- C=O, CN, NO_2 substituents *withdraw* electrons from the aromatic ring by resonance
- π electrons flow from the rings to the substituents



Resonance electron-withdrawing group

Resonance Effects – Electron Donation

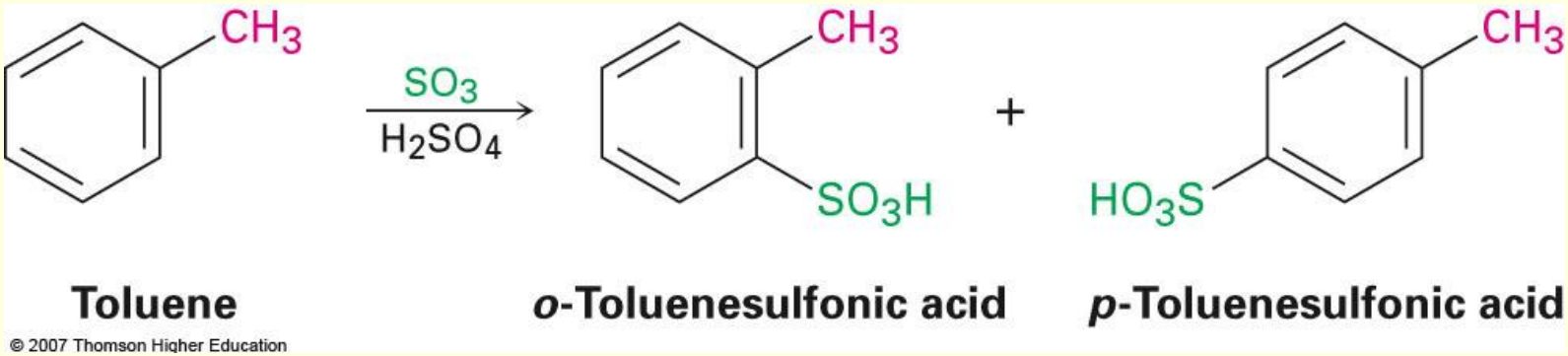
- Halogen, OH, alkoxyl (OR), and amino substituents *donate* electrons
- π electrons flow from the substituents to the ring
- Effect is greatest at ortho and para



Resonance electron-donating group

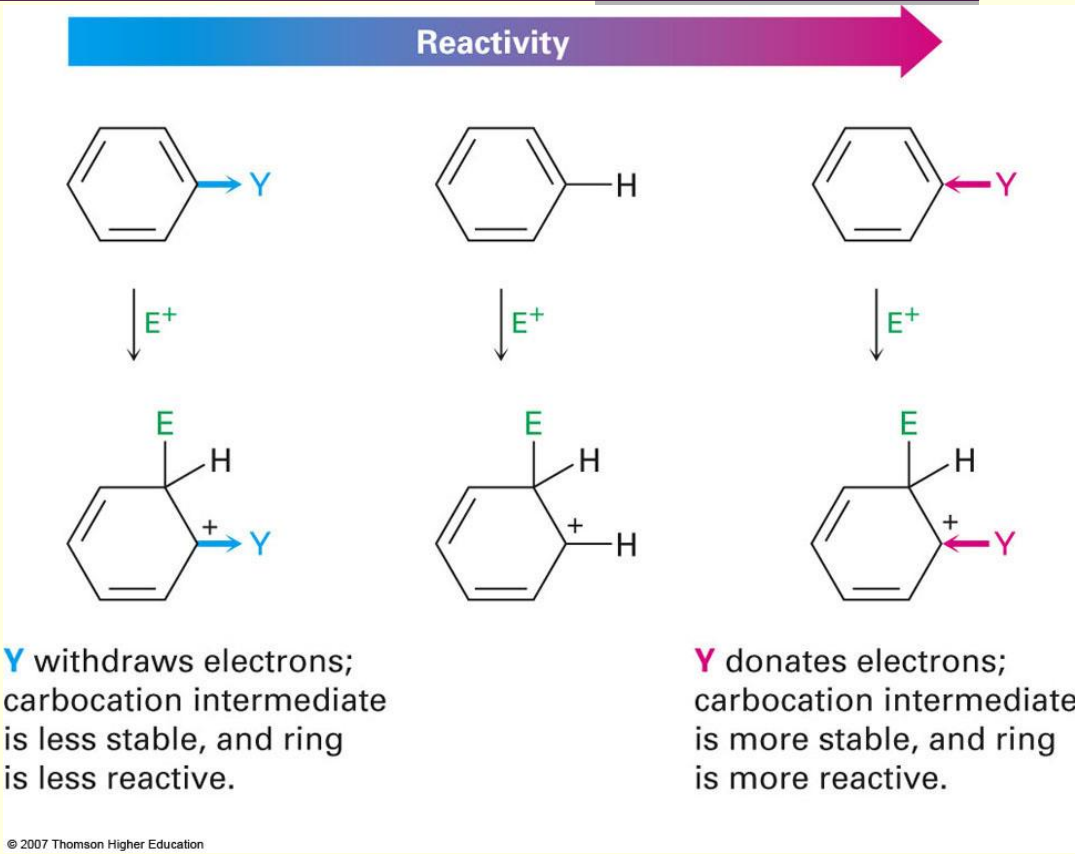
Predicting the product of an Electrophilic aromatic subsitution reaction

- The sulfonation of toluene will give primarily amixture of O-toluenesulfonic acid and p-toluenesulfonic acid. (–CH3 Ortho- and para –directing activators)



16.5 An Explanation of Substituent Effects

- Activating groups donate electrons to the ring, stabilizing the intermediate (carbocation)
- Deactivating groups withdraw electrons from the ring, destabilizing the intermediate

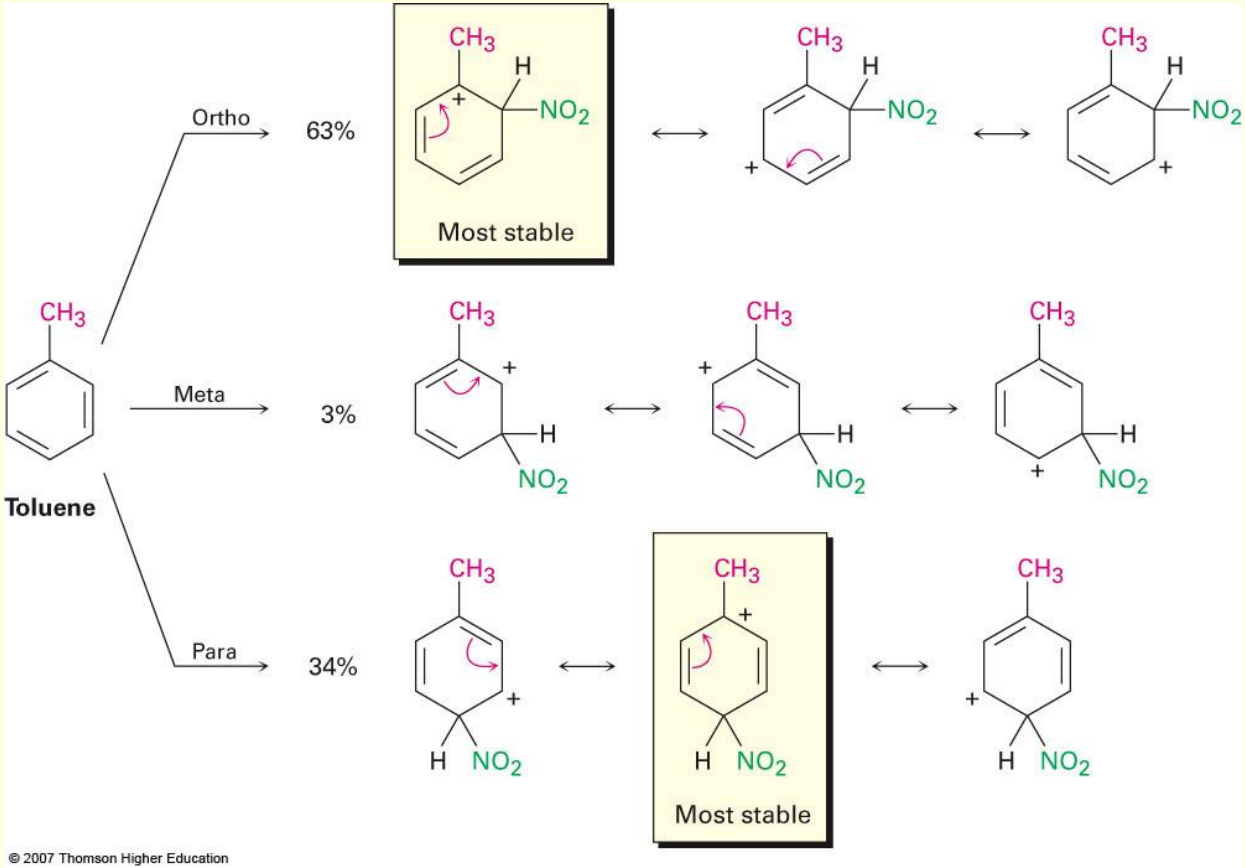


Carbonyl,cyano ,nitro goups.

Halogen, OH, alkoxyl (OR), and amino

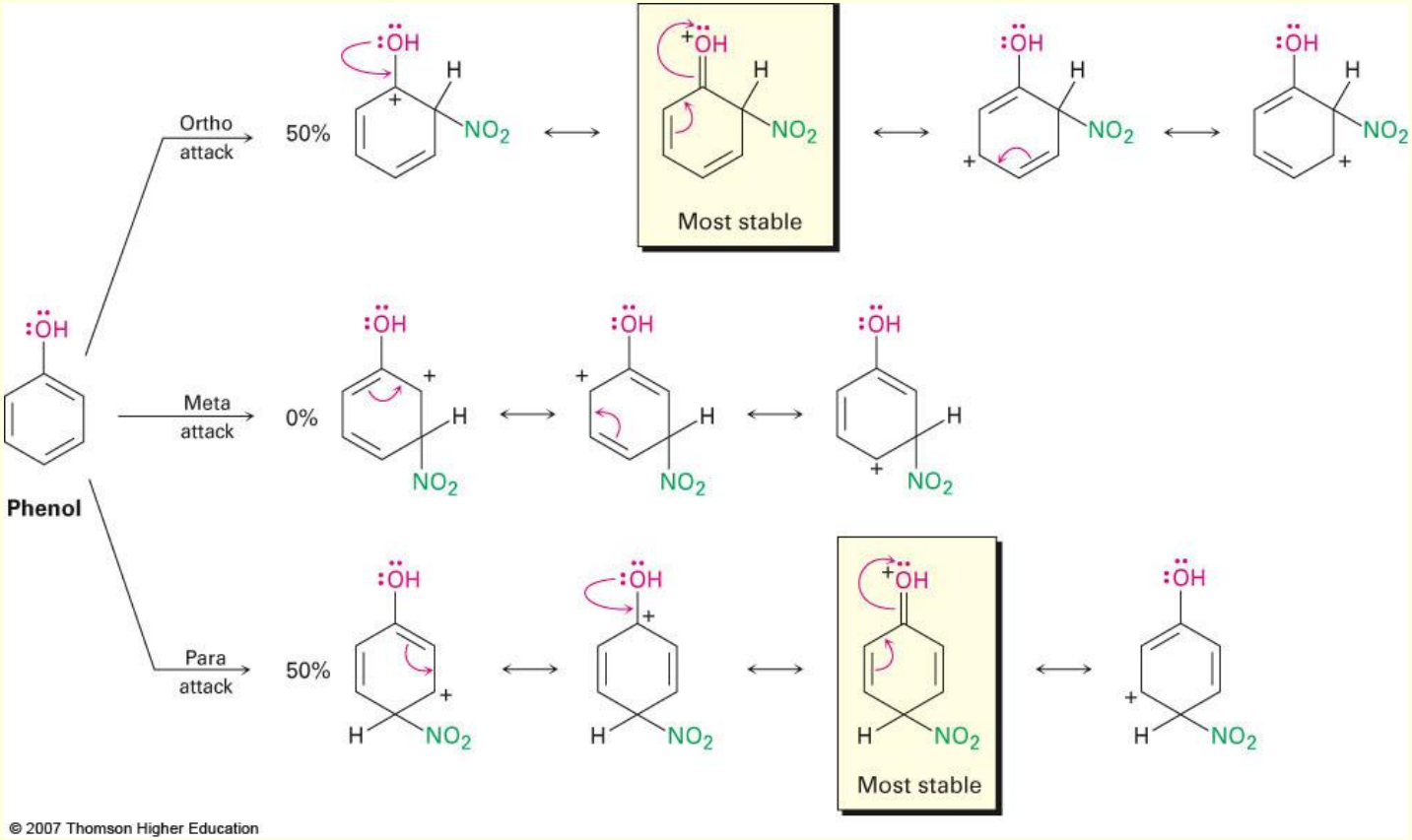
Ortho- and Para-Directing Activators: Alkyl Groups

- Alkyl groups activate: direct more substitution to positions ortho and para to themselves
- Alkyl group is most effective in the ortho and para positions



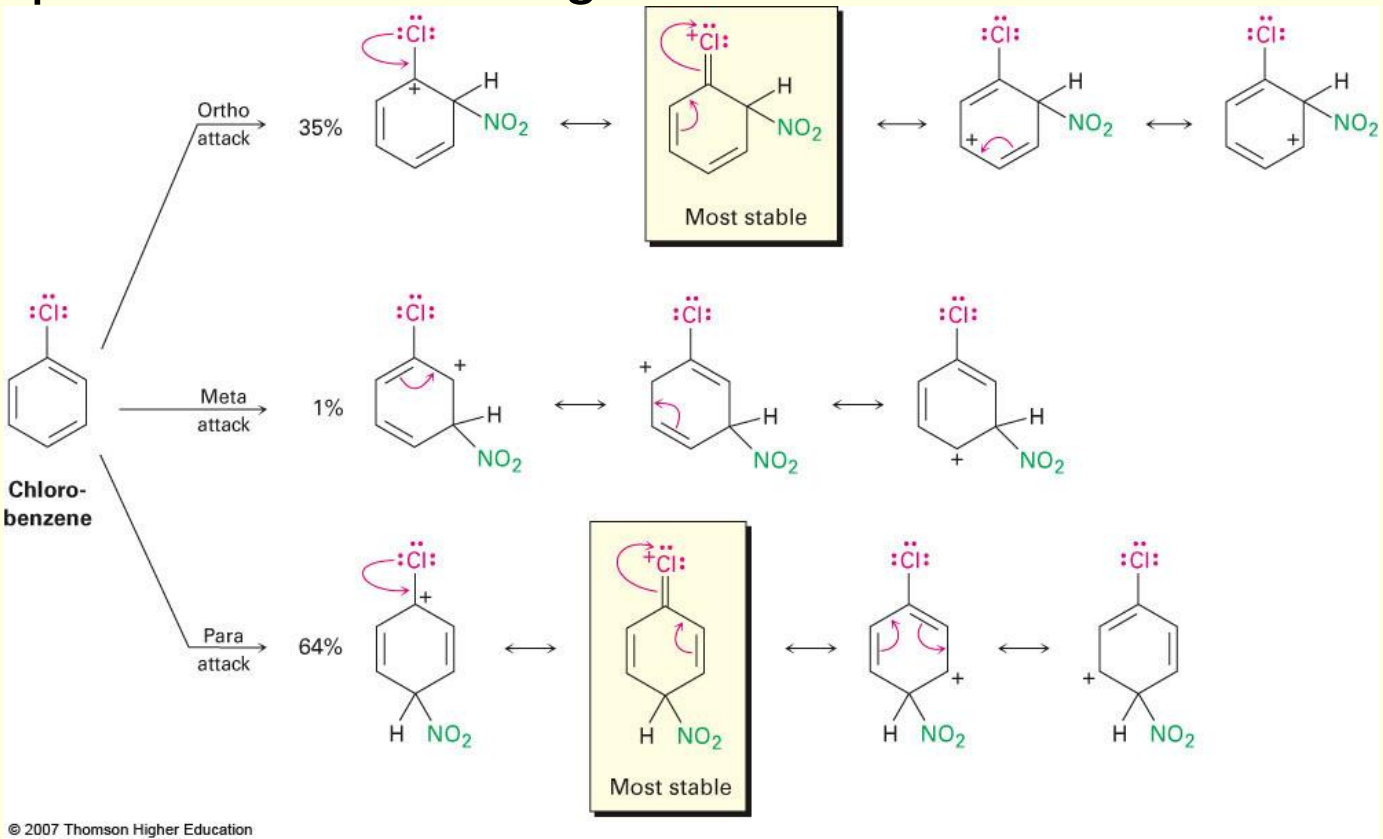
Ortho- and Para-Directing Activators: OH and NH_2

- Alkoxyl, and amino groups have a strong, electron-donating resonance effect
- Most pronounced at the ortho and para positions



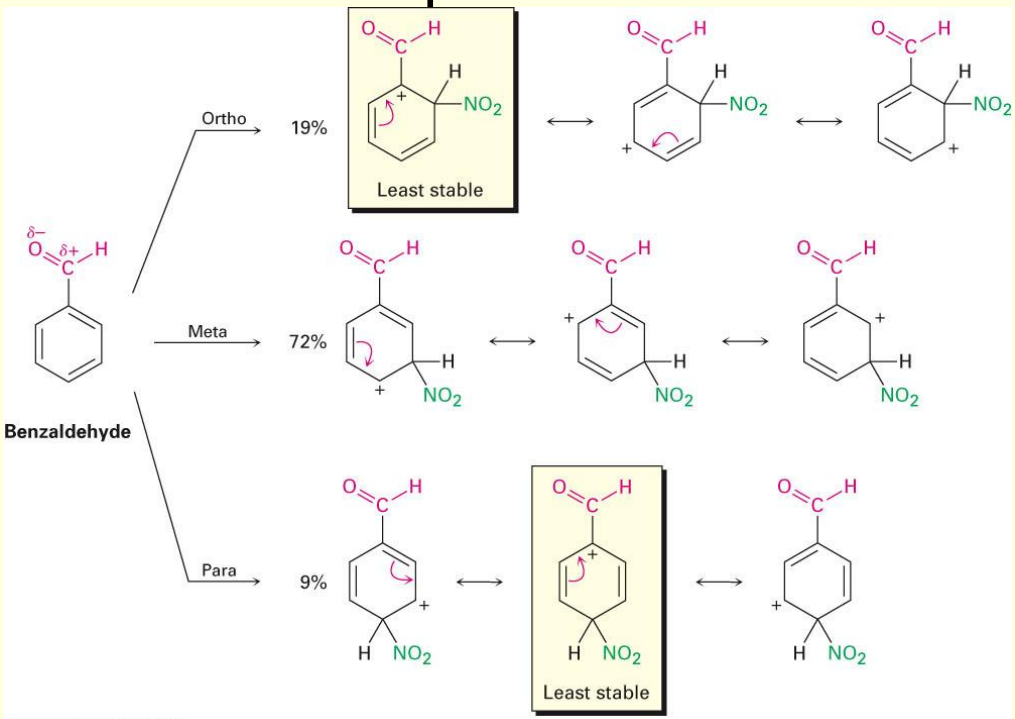
Ortho- and Para-Directing Deactivators: Halogens

- Electron-withdrawing inductive effect outweighs weaker electron-donating resonance effect
- Resonance effect is only at the ortho and para positions, stabilizing carbocation intermediate



Meta-Directing Deactivators

- Inductive and resonance effects add force to each other
- Ortho and para intermediates destabilized by deactivation of carbocation intermediate
- Resonance cannot produce stabilization



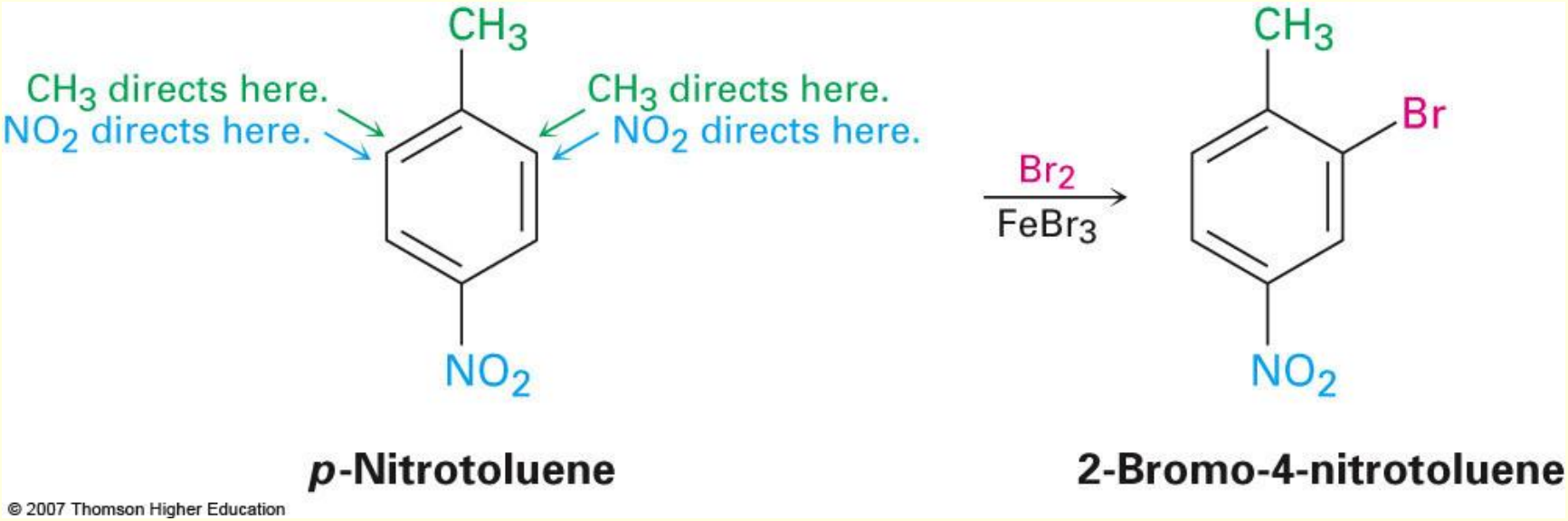
Summary Table: Effect of Substituents in Aromatic Substitution

Table 16.2 | 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

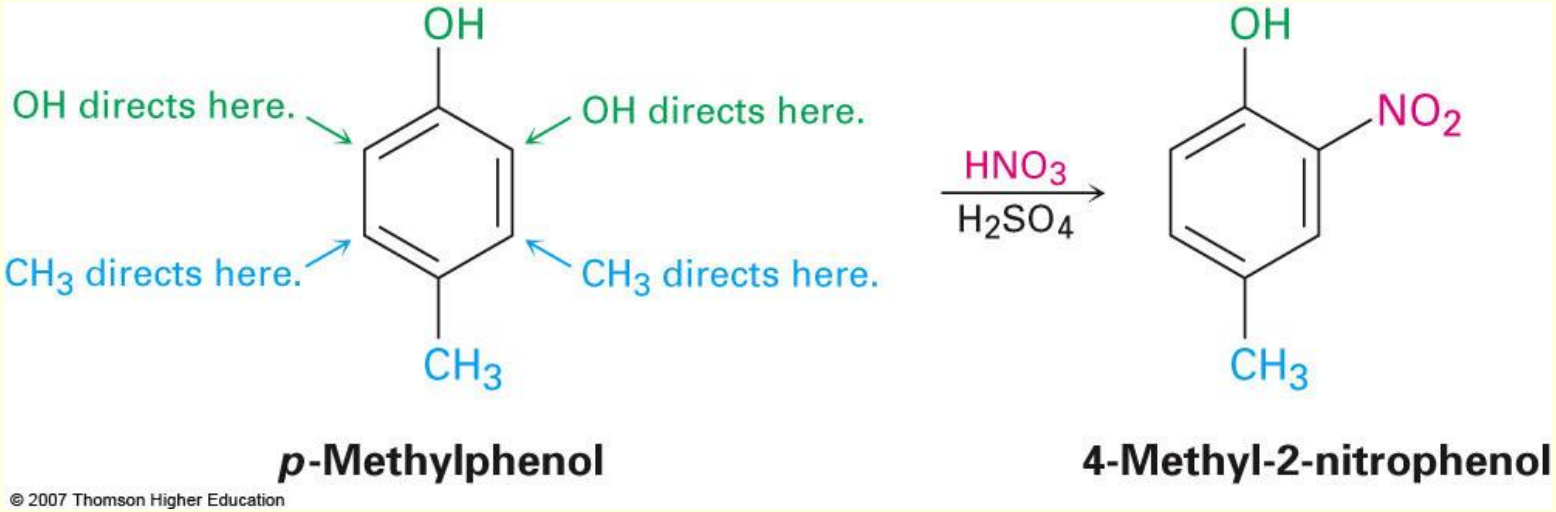
16.6 Trisubstituted Benzenes: Additivity of Effects

- If the directing effects of the two groups are the same, the result is additive



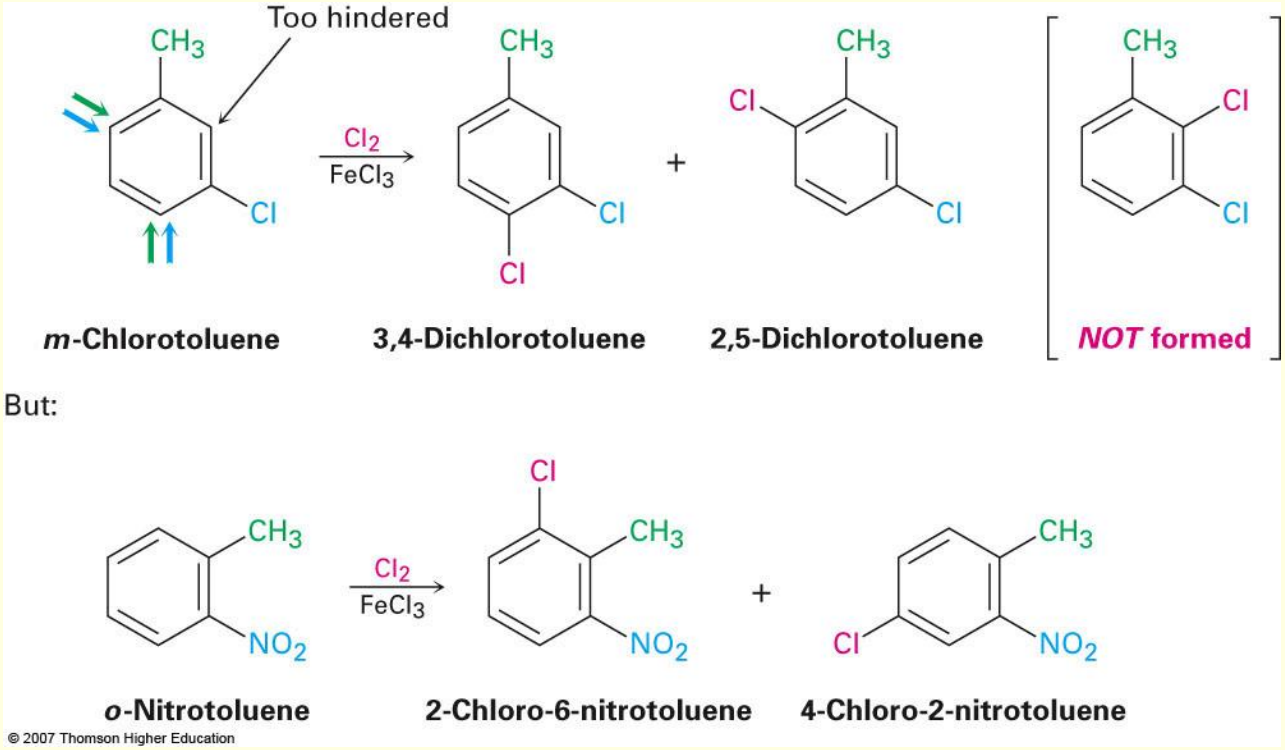
Substituents with Opposite Effects

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



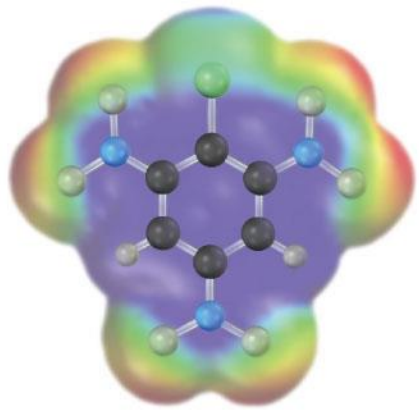
Meta-Disubstituted Compounds

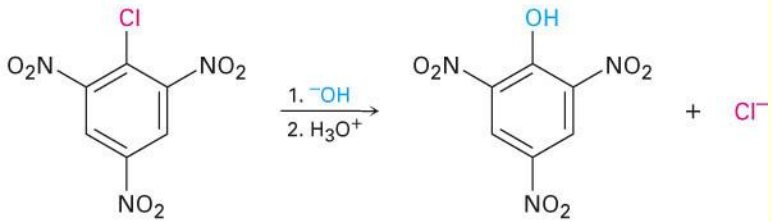
- The reaction site is too hindered
- To make aromatic rings with three adjacent substituents, it is best to start with an ortho-disubstituted compound



16.7 Nucleophilic Aromatic Substitution

- Nucleophilic Aromatic Substitution occurs only if the aromatic ring has anelectron-withdrawing substituent in position ortho or para to the leaving group.
- P-cloronitrobenzene and 0-chloronitrobenzene react with hydroxide ion at 130 c° to yield substitution products , but m-chloronitrobenzene is inert to OH

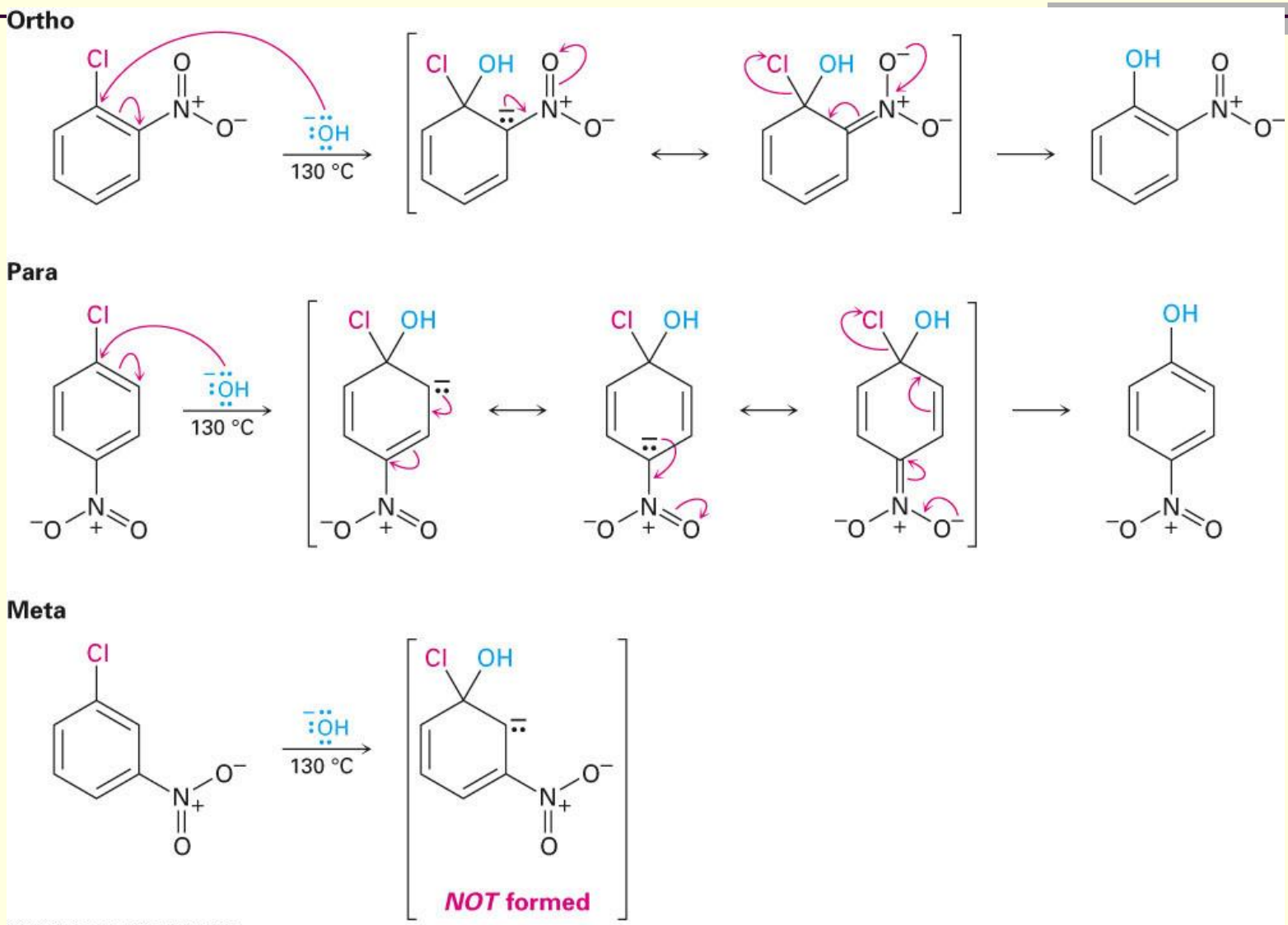




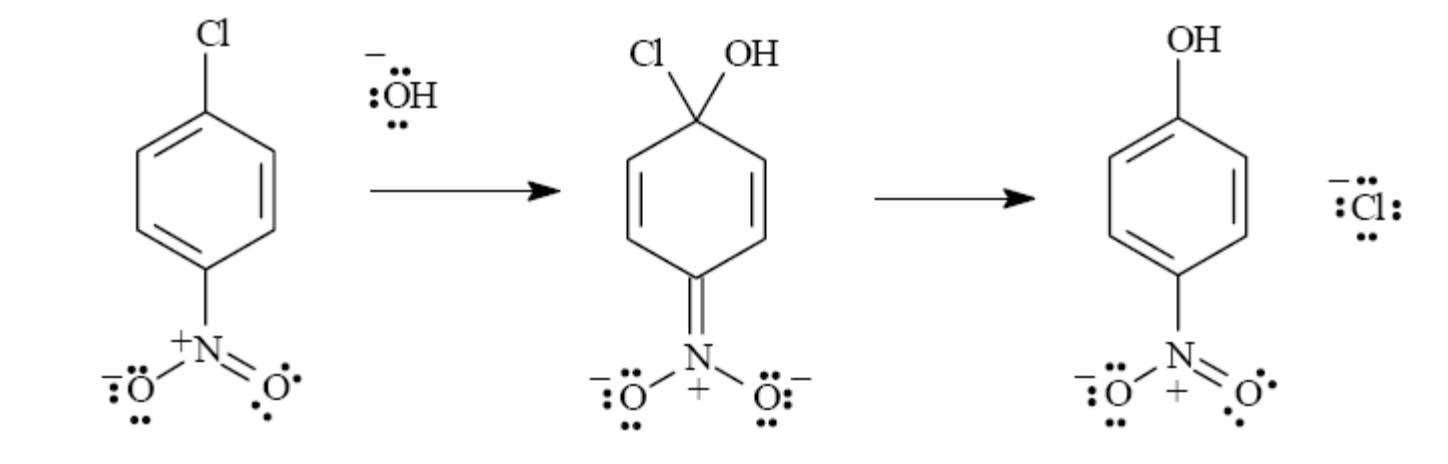
2,4,6-Trinitrochlorobenzene

2,4,6-Trinitrophenol (100%)

16.7 Nucleophilic Aromatic Substitution



show all electron flow with arrows for the nucleophilic aromatic subsitution reaction of *p-nitrochlorobenzene with KOH?*



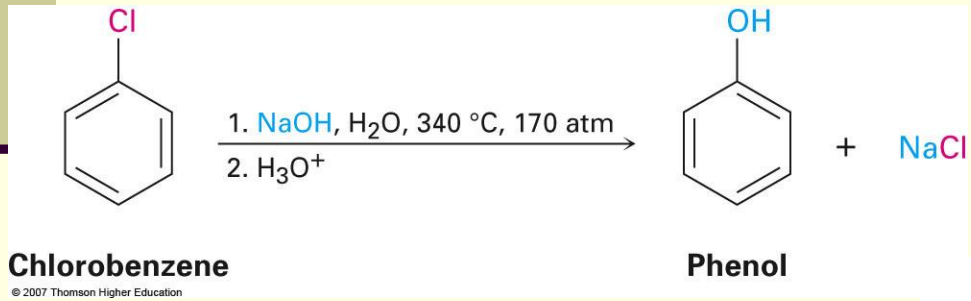
The differences between electrophilic and nucleophilic aromaticsubstitution

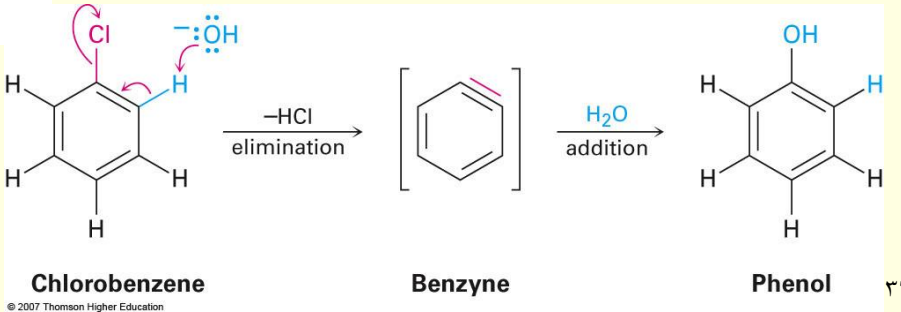
- The electrophilic substitutions are favored by electron-donating substituents which stabilize the carbocation intermediate.
  and replace hydrogen on the ring.
- The nucleophilic substitutions are favored by electron-withdrawing substitutions, which stabilize a carbanion intermediate.

  and replace a leaving group, usually halide ion.

16.8 Benzyne

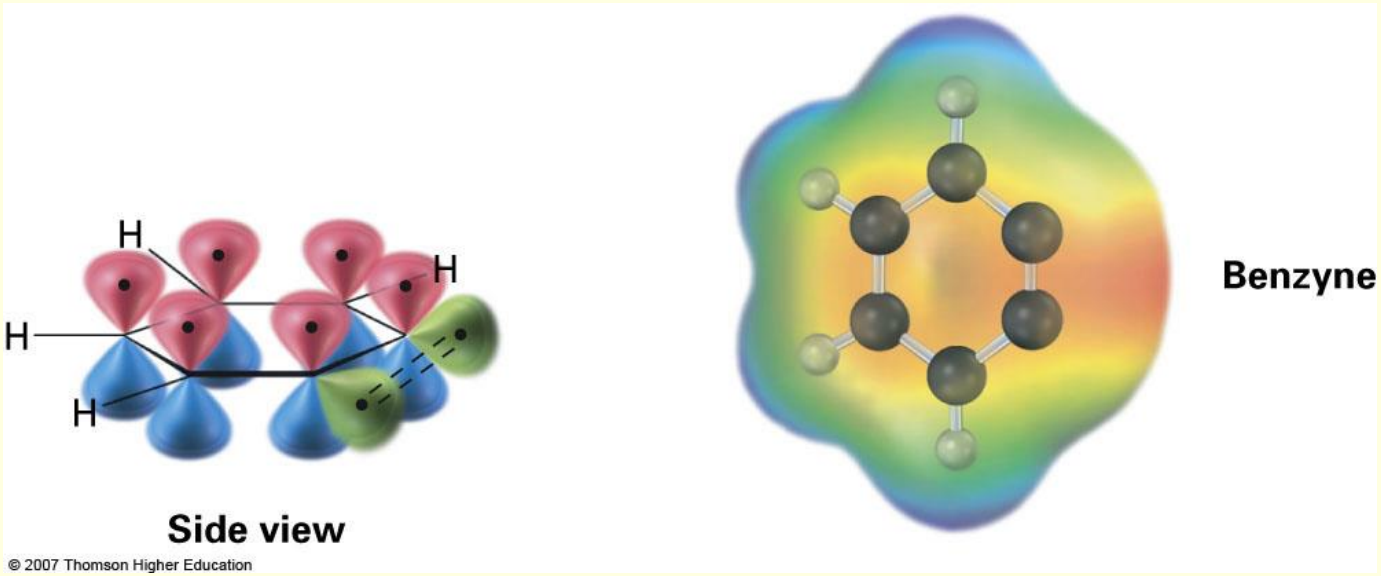
- Phenol is prepared on an industrial scale by treatment of chlorobenzene with dilute aqueous NaOH at 340°C under high pressure
- The reaction involves an elimination reaction that gives a triple bond
- The intermediate in the elimination-addition mechanism of nucleophilic aromatic substitution is called benzyne





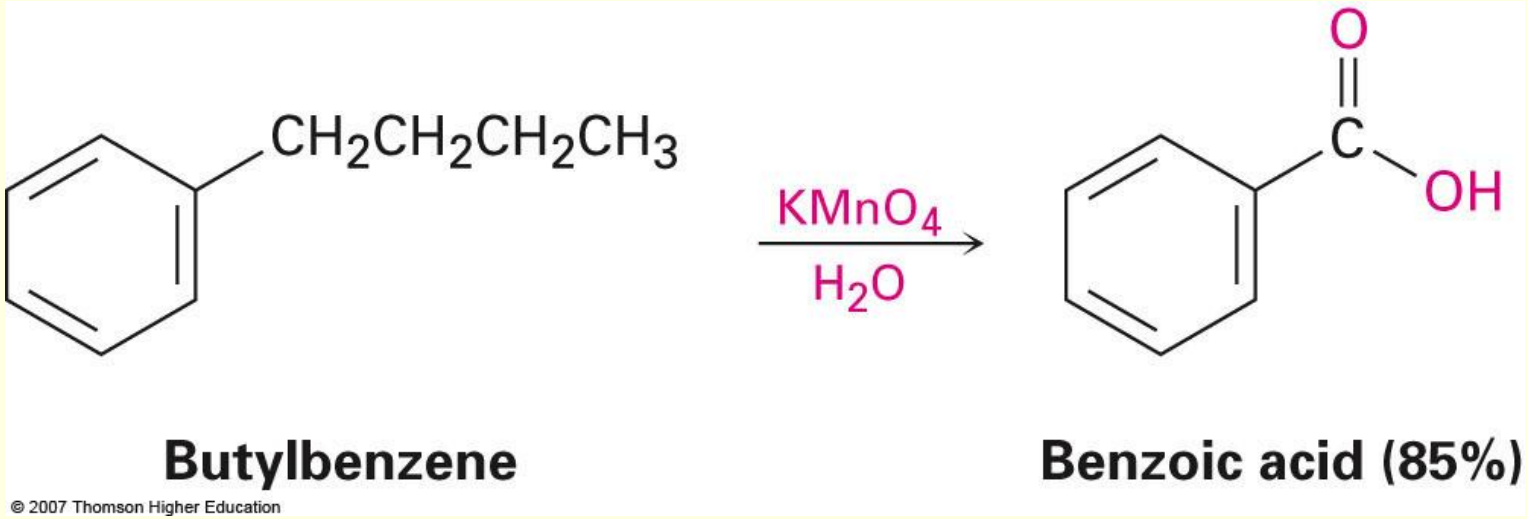
Structure of Benzyne

- Benzyne is a highly distorted alkyne
- The triple bond uses sp^2-hybridized carbons, not the usual sp
- The triple bond has one π bond formed by p–p overlap and another by weak sp^2–sp^2 overlap



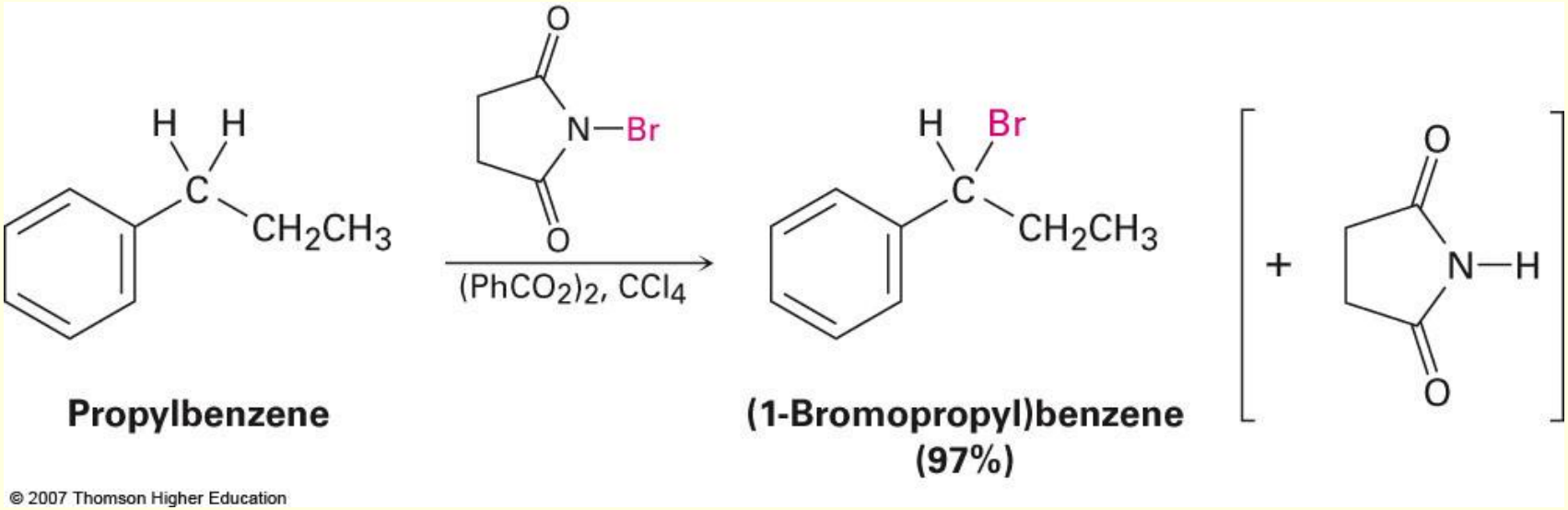
16.9 Oxidation of Aromatic Compounds

- Alkyl side chains can be oxidized to —CO_2H by strong reagents such as $KMnO_4$ and $Na_2Cr_2O_7$ if they have a C-H next to the ring
- Converts an alkylbenzene into a benzoic acid, Ar—R $\rightarrow$ Ar—CO_2H



Bromination of Alkylbenzene Side Chains

- Reaction of an alkylbenzene with *N*-bromo-succinimide (NBS) and benzoyl peroxide (radical initiator) introduces Br into the side chain

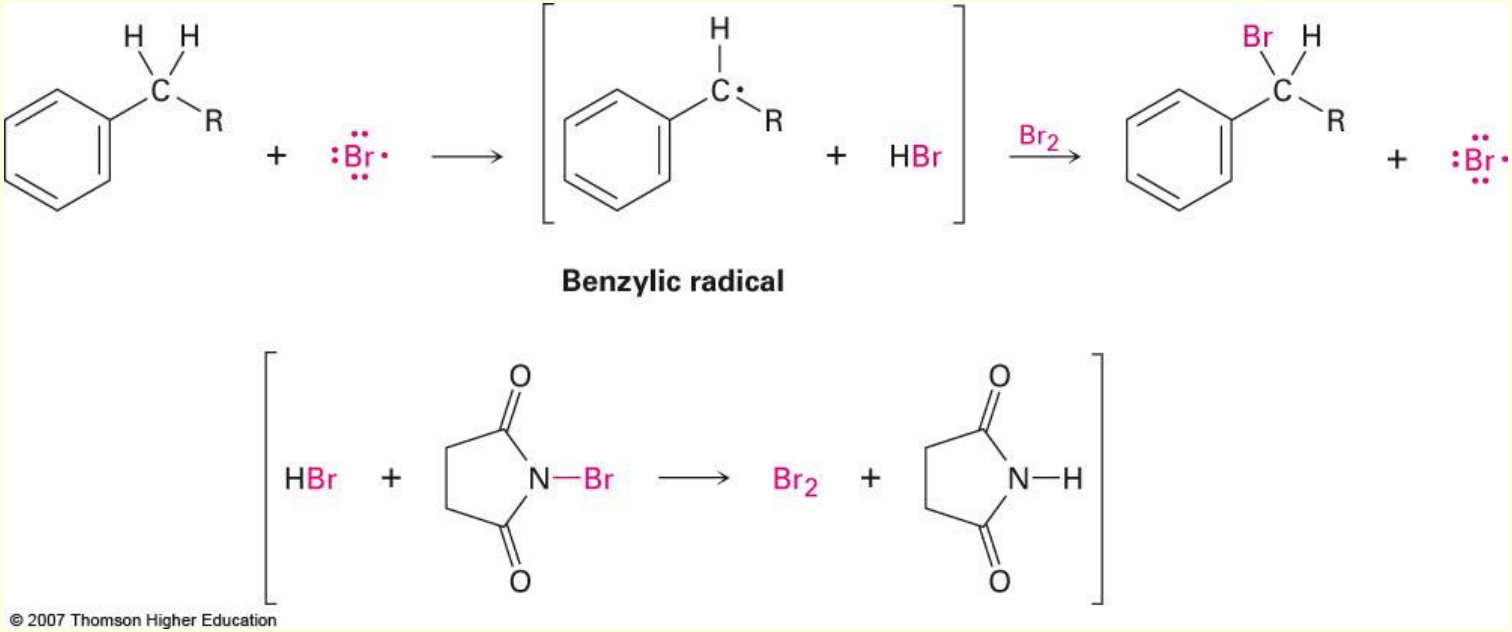


Propylbenzene

(1-Bromopropyl)benzene (97%)

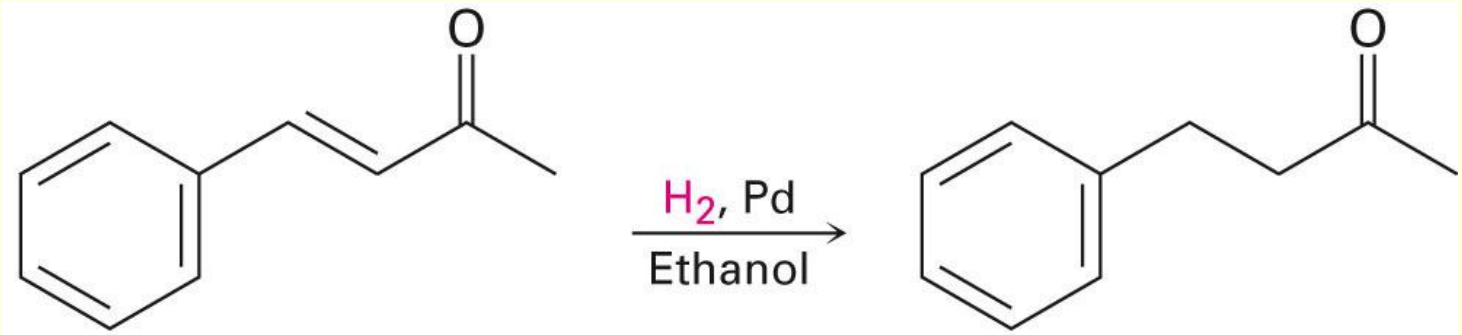
Mechanism of NBS (Radical) Reaction

- Abstraction of a benzylic hydrogen atom generates an intermediate benzylic radical
- Reacts with Br_2 to yield product
- Br· radical cycles back into reaction to carry chain



16.10 Reduction of Aromatic Compounds

- Aromatic rings are inert to catalytic hydrogenation under conditions that reduce alkene double bonds
- Can selectively reduce an alkene double bond in the presence of an aromatic ring
- Reduction of an aromatic ring requires more powerful reducing conditions (high pressure or anather catalysts)

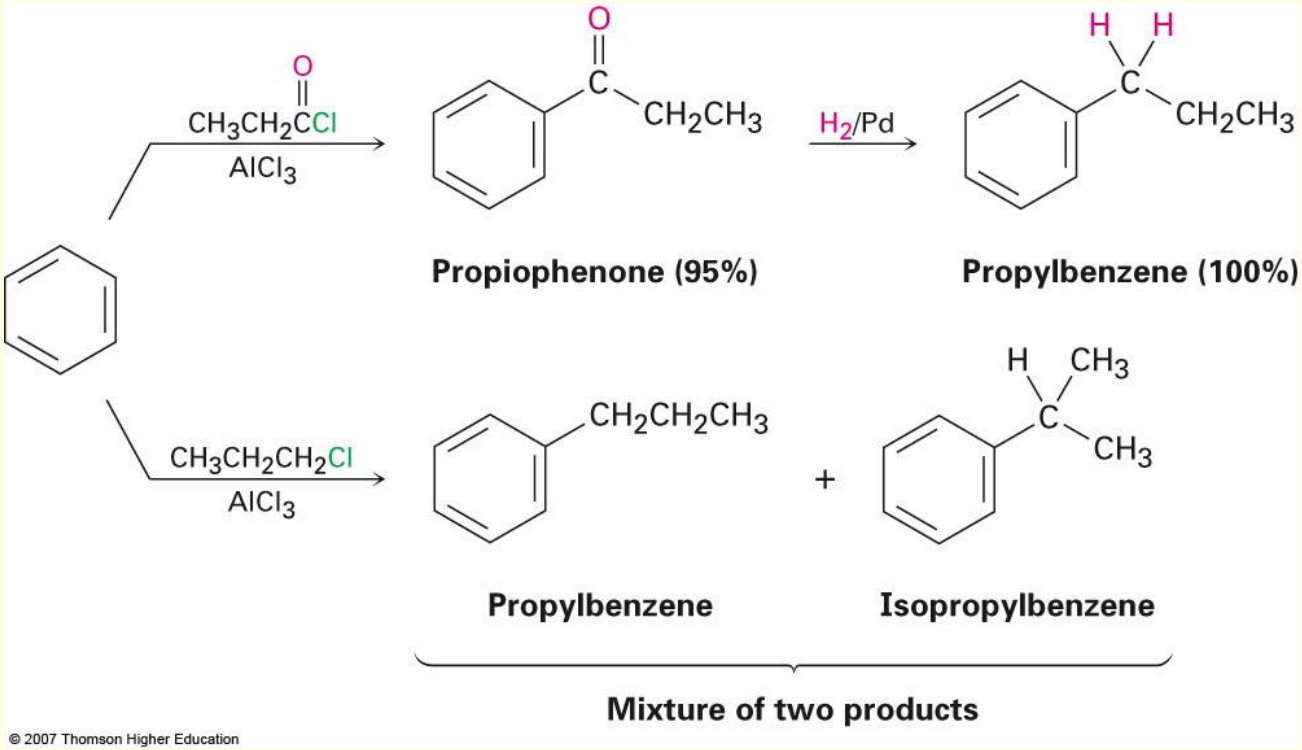


4-Phenyl-3-buten-2-one

4-Phenyl-2-butanone (100%)

Reduction of Aryl Alkyl Ketones

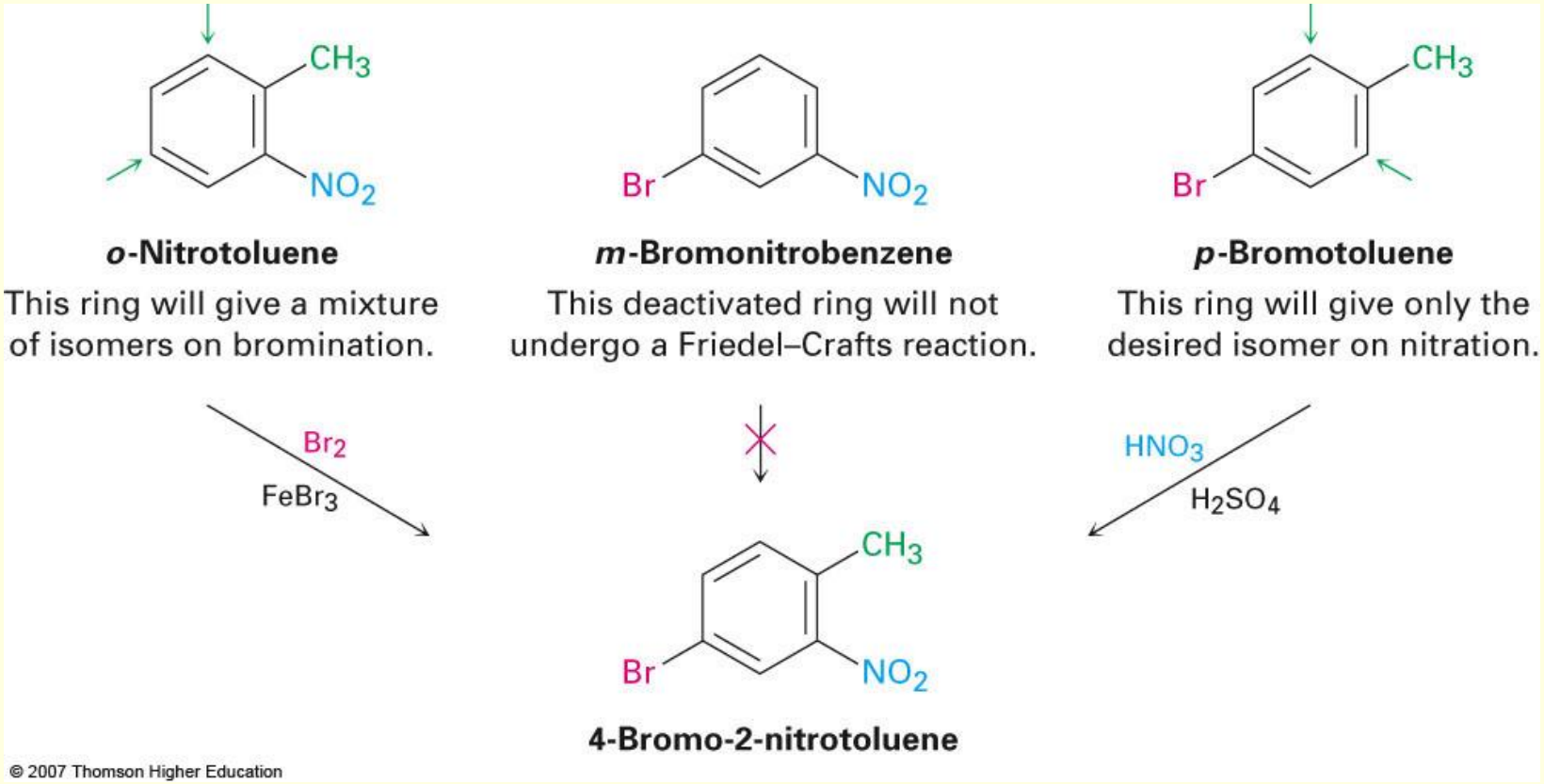
- Aromatic ring activates neighboring carbonyl group toward reduction
- Ketone is converted into an alkylbenzene by catalytic hydrogenation over Pd catalyst



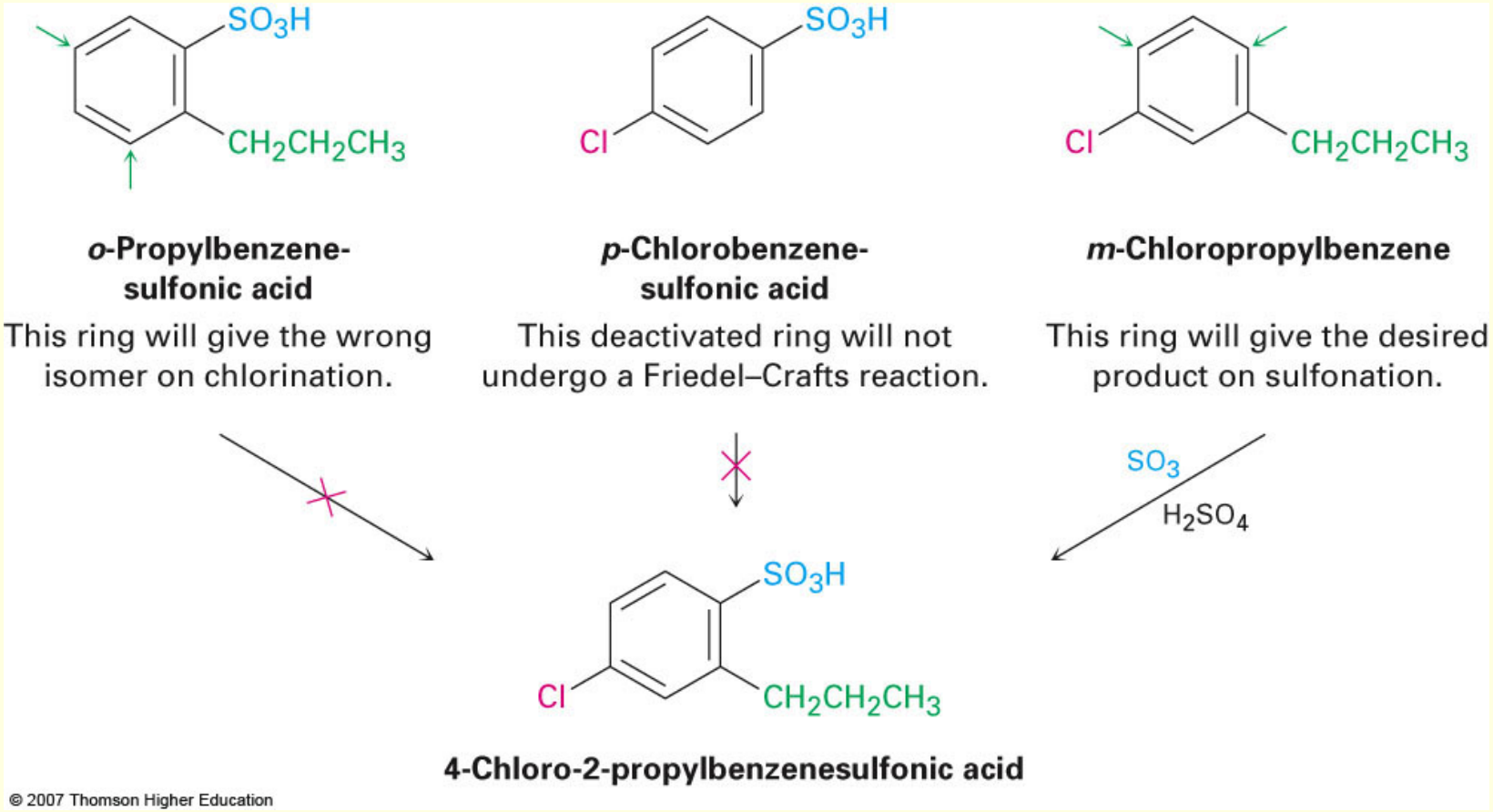
16.11 Synthesis of Trisubstituted Benzenes

- These syntheses require planning and consideration of alternative routes
- Ability to plan a sequence of reactions in right order is valuable to synthesis of substituted aromatic rings

Synthesizie 4-bromo-2-nitrotoluene from benzene.



Synthesize 4-chloro-2propylbenzenesulfonic acid from benzene.



The -NH2 group is listed in our textbook as the strongest *o,p-directing activator in electrophilic aromatic* substitution reactions.

However, when aniline is subjected to standard nitration conditions poor yields of *m-nitroaniline result.*