Chemistry of Benzene: Electrophilic Aromatic Substitution

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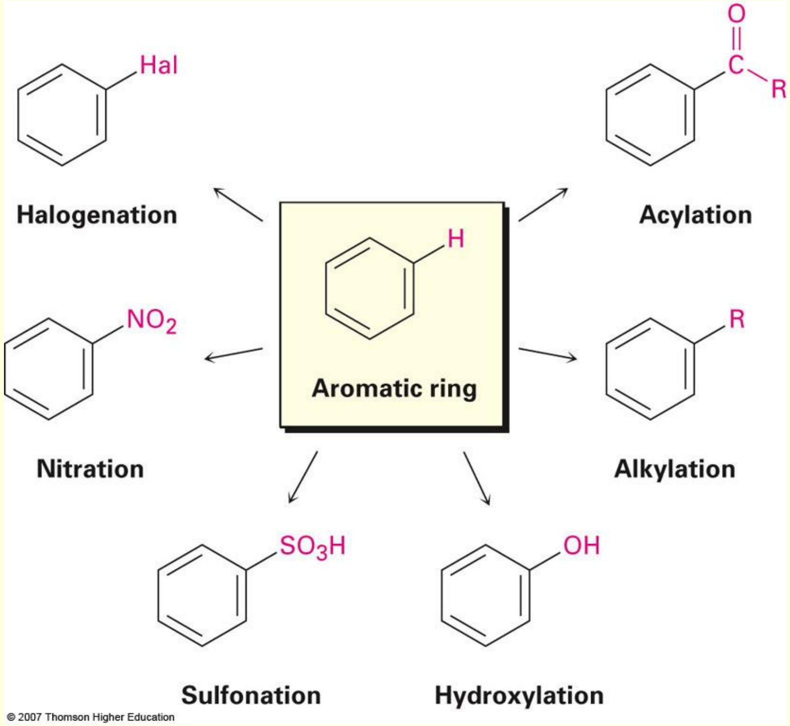
Substitution Reactions of Benzene and Its Derivatives

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



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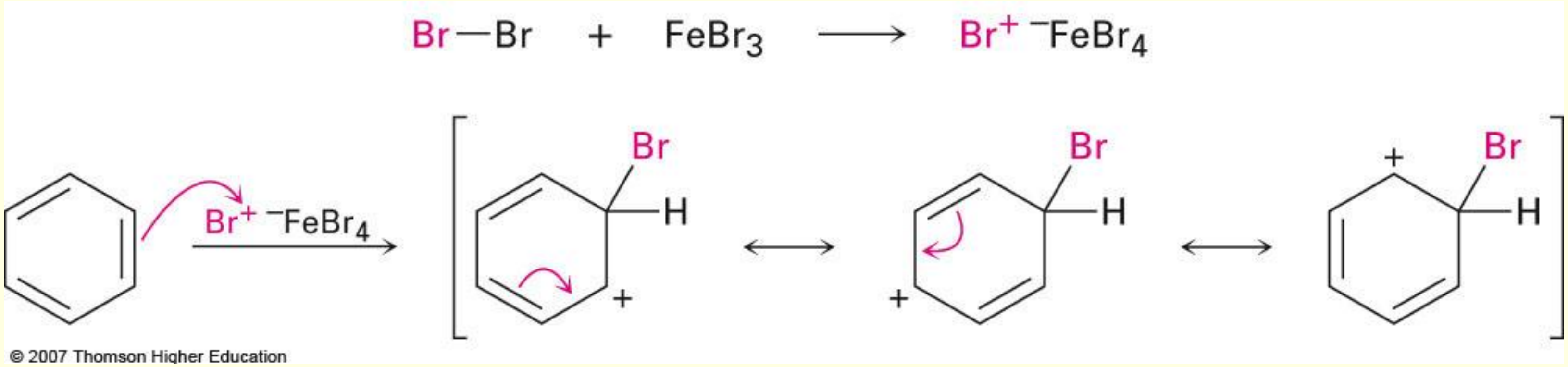
Why this Chapter?

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

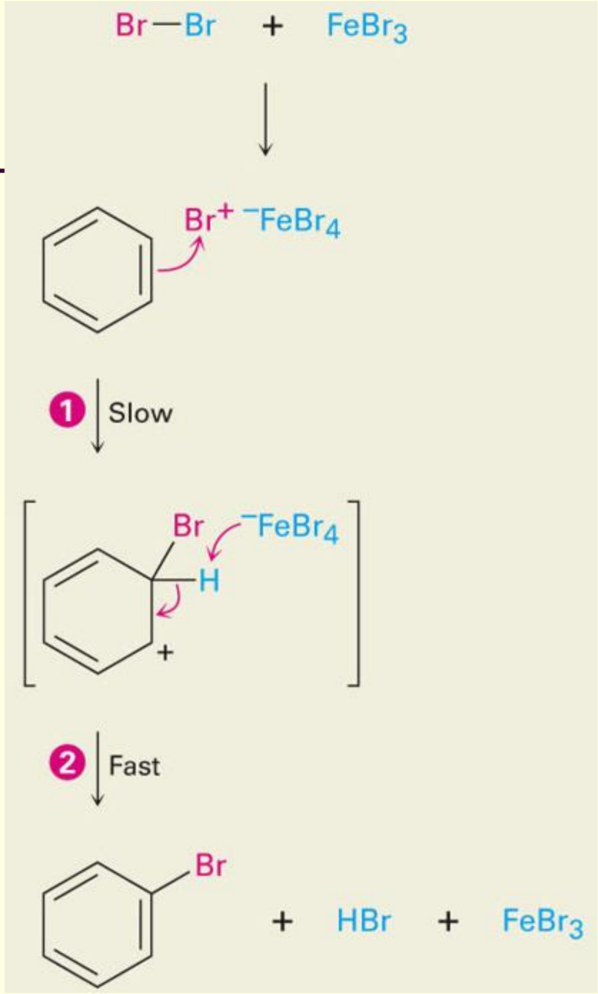
Electrophilic Aromatic Bromination

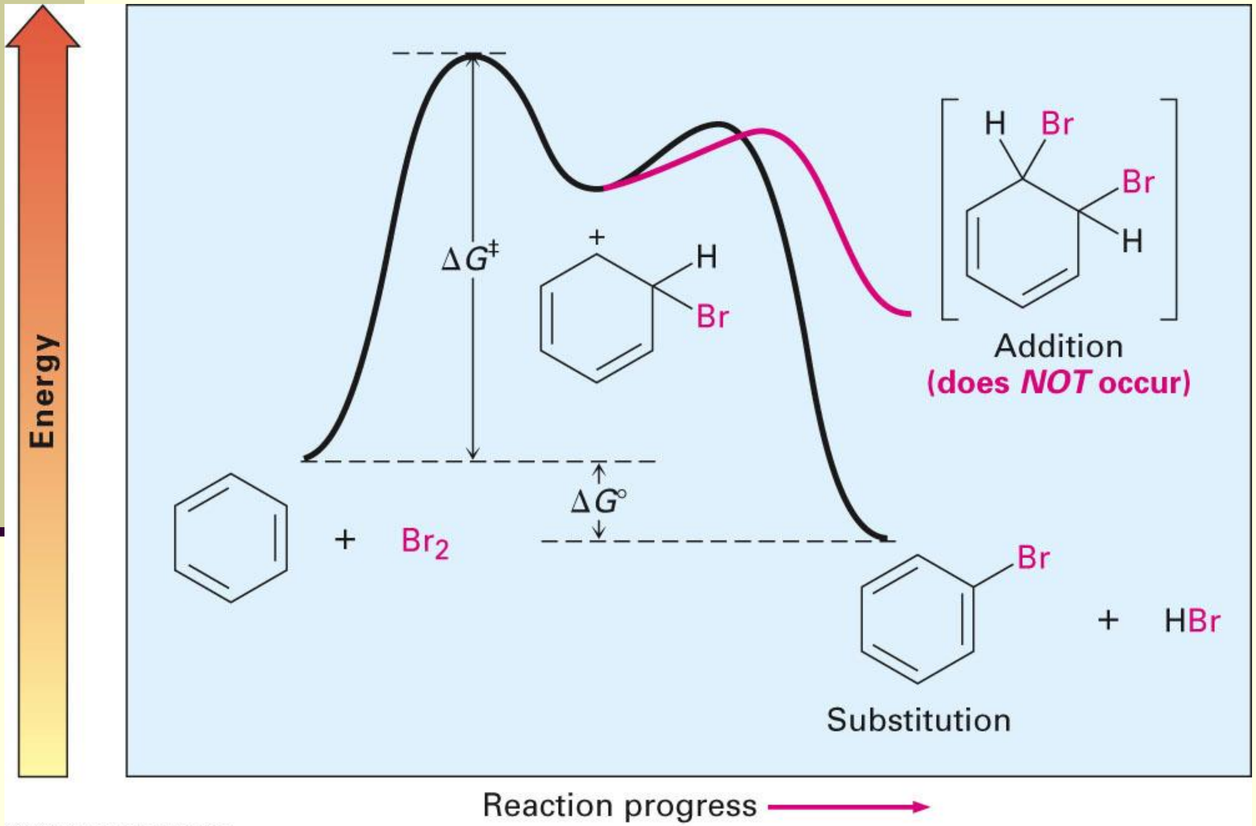
- Benzene's π electrons participate as a Lewis base in reactions with Lewis acids
- The product is formed by loss of a proton, which is replaced by bromine
- $FeBr_3$ is added as a catalyst to polarize the bromine reagent
- In the first step the π electrons act as a nucleophile toward Br_2 (in a complex with $FeBr_3$)
- This forms a cationic addition intermediate from benzene and a bromine cation
- The intermediate is not aromatic and therefore high in energy



Formation of Product from Intermediate

- The cationic addition intermediate transfers a proton to $FeBr_4^-$ (from Br^- and $FeBr_3$)
- This restores aromaticity (in contrast with addition in alkenes)





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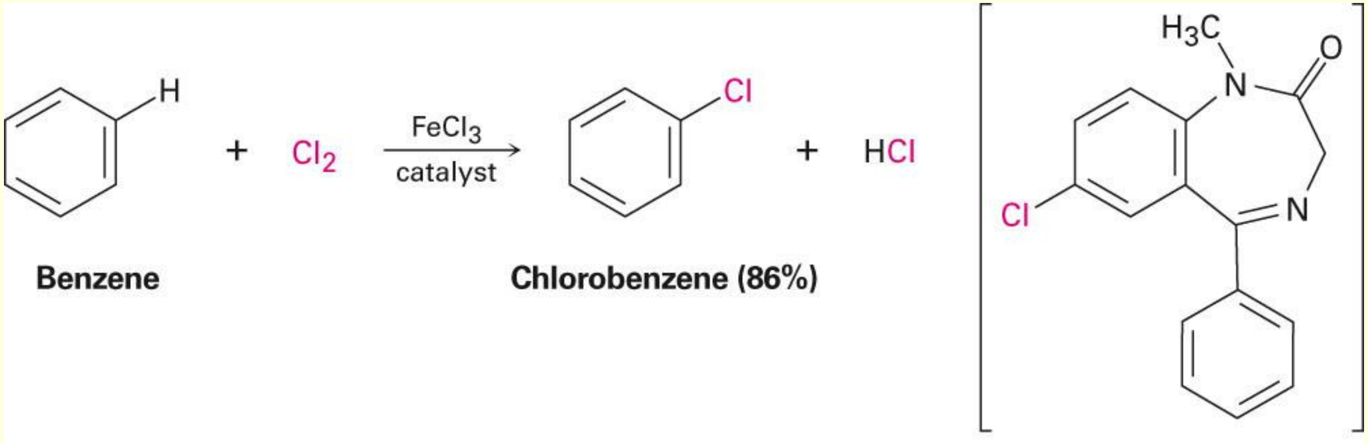
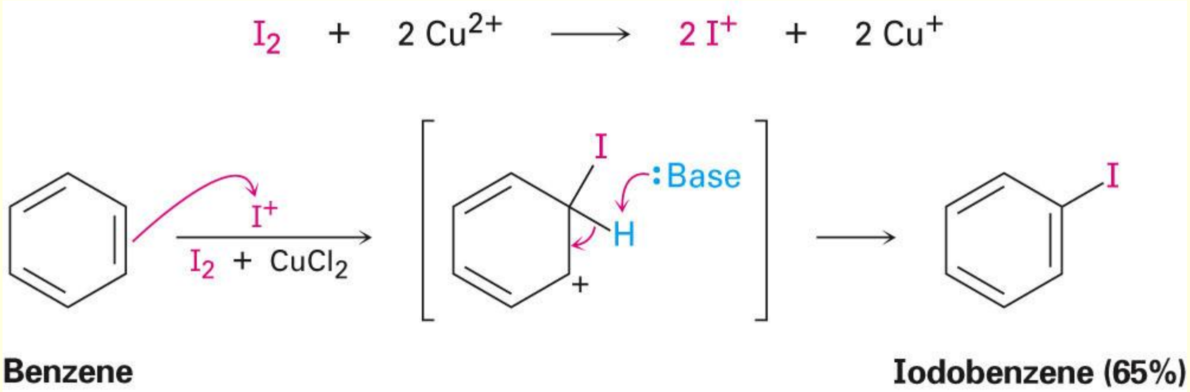
Other Aromatic Halogenations

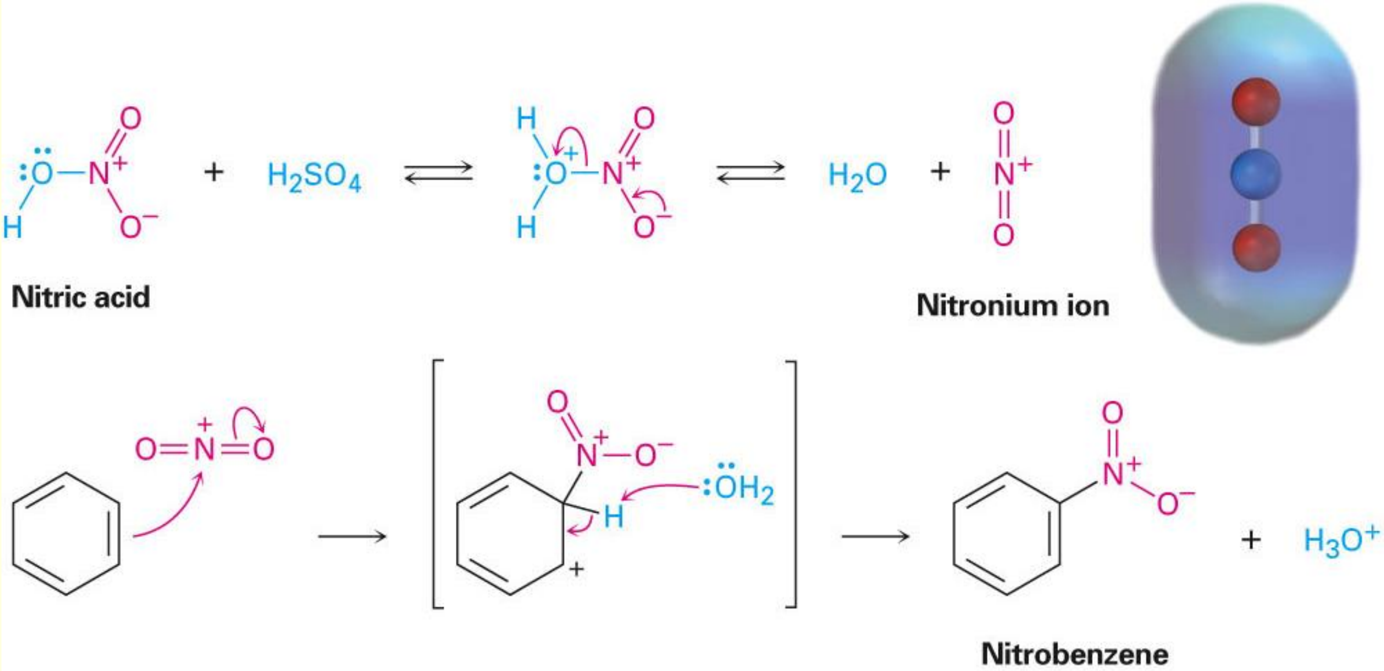
- Chlorine and iodine (but not fluorine, which is too reactive) can produce aromatic substitution with the addition of other reagents to promote the reaction
- Chlorination requires $FeCl_3$
- Iodine must be oxidized to form a more powerful I^+ species (with Cu^{2+} from $CuCl_2$)



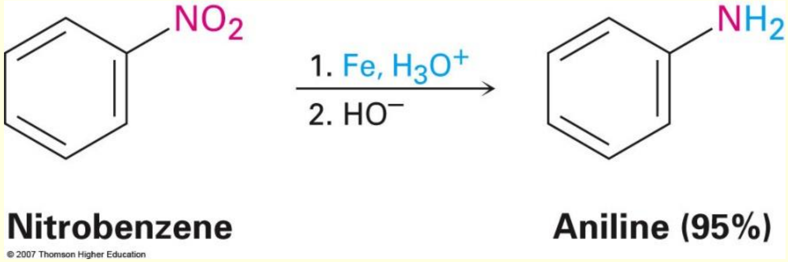


Aromatic Nitration

- The combination of nitric acid and sulfuric acid produces NO_2^+ (nitronium ion)
- The reaction with benzene produces nitrobenzene

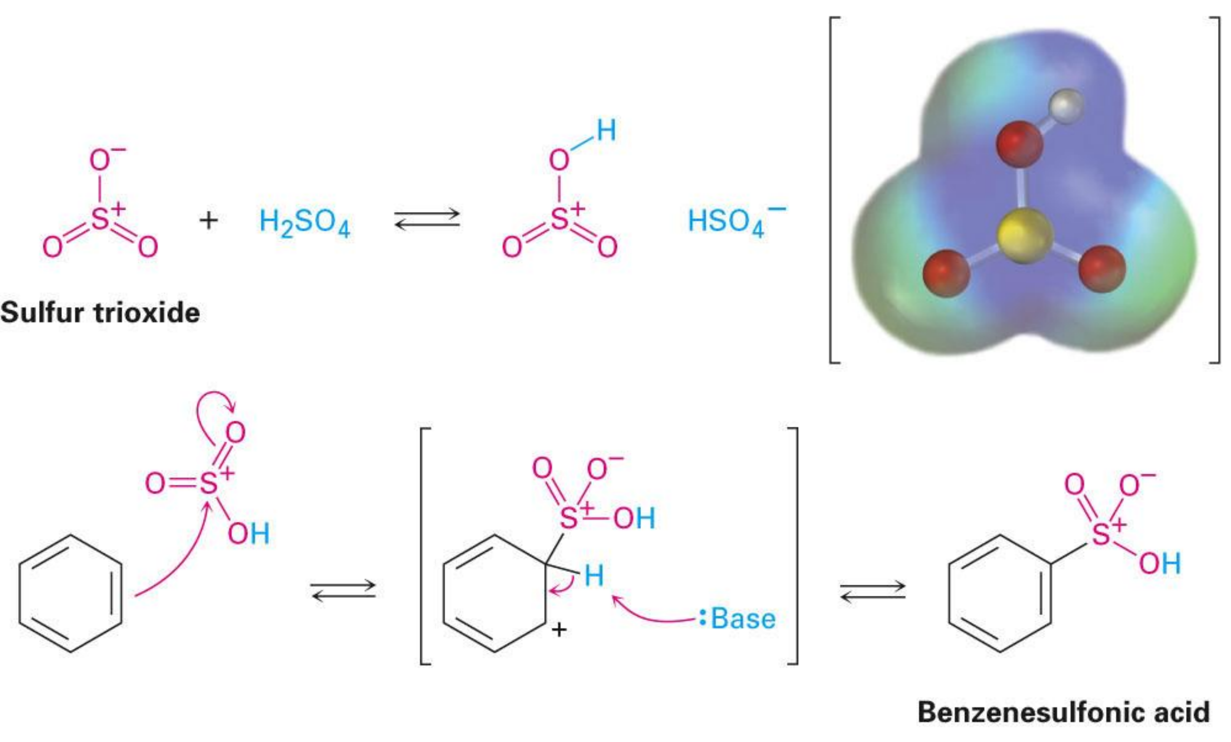


- The Nitro group can be reduced to an Amino group if needed



Aromatic Sulfonation

- Substitution of H by SO_3 (sulfonation)
- Reaction with a mixture of sulfuric acid and SO_3 (“Fuming H_2SO_4)
- Reactive species is sulfur trioxide or its conjugate acid



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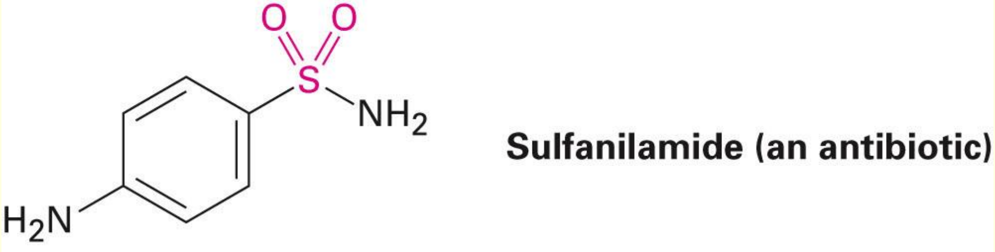
- Sulfonamides are “sulfa drug” antibiotics



Sulfanilamide (an antibiotic)

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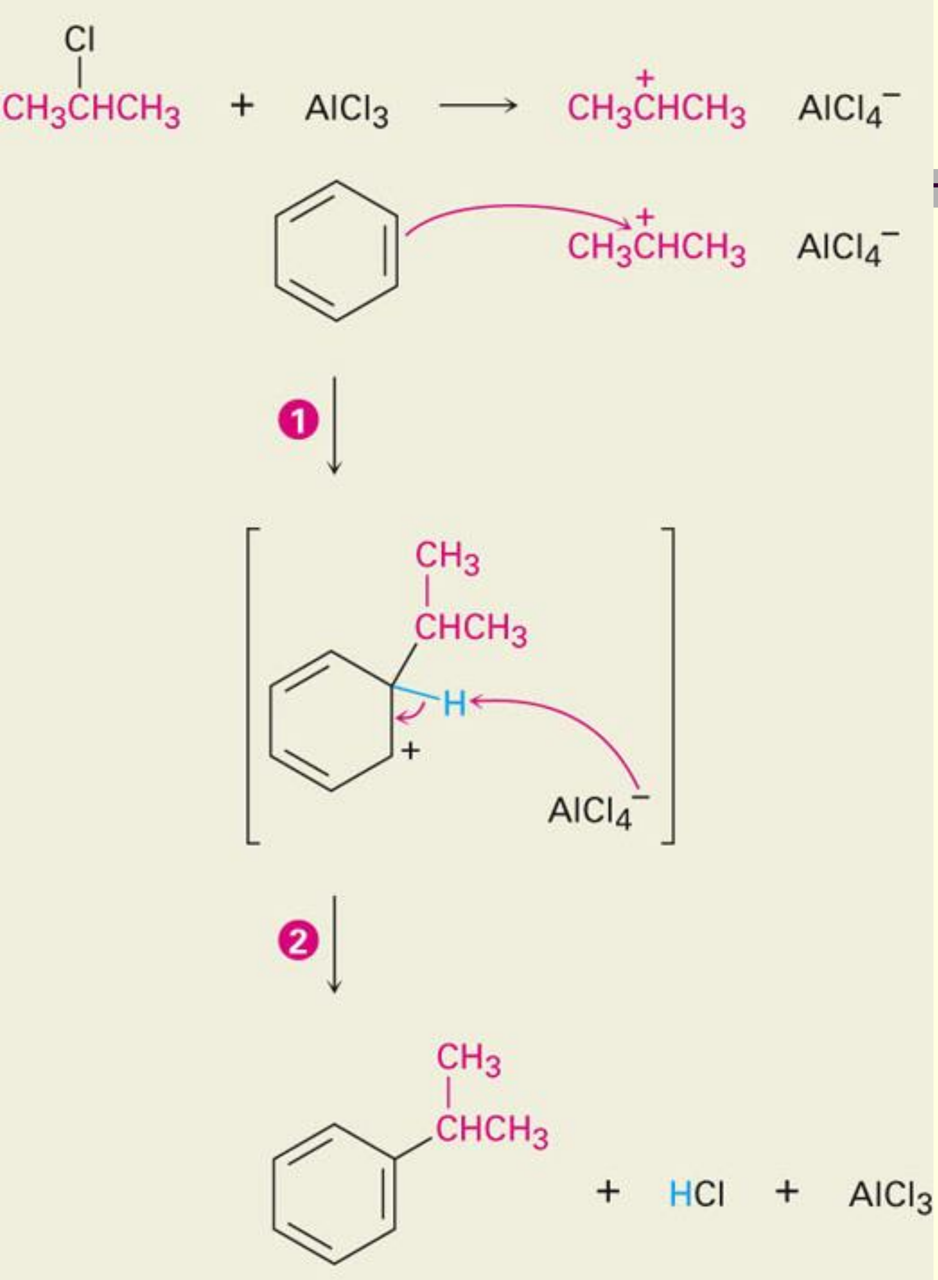
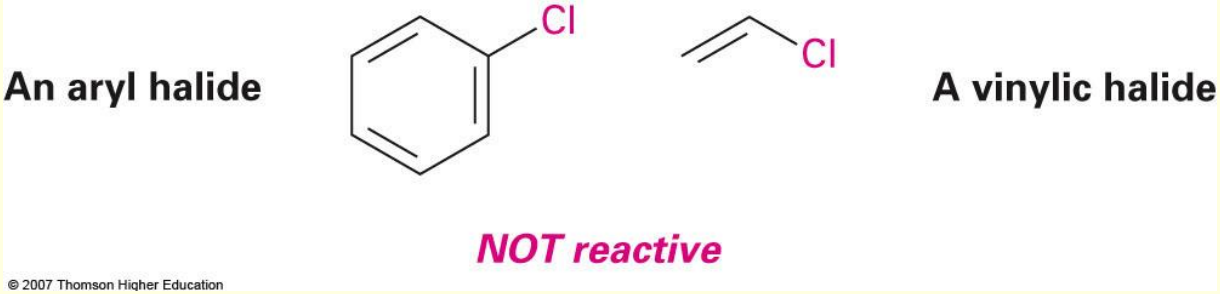
Alkylation of Aromatic Rings: The Friedel–Crafts Reaction

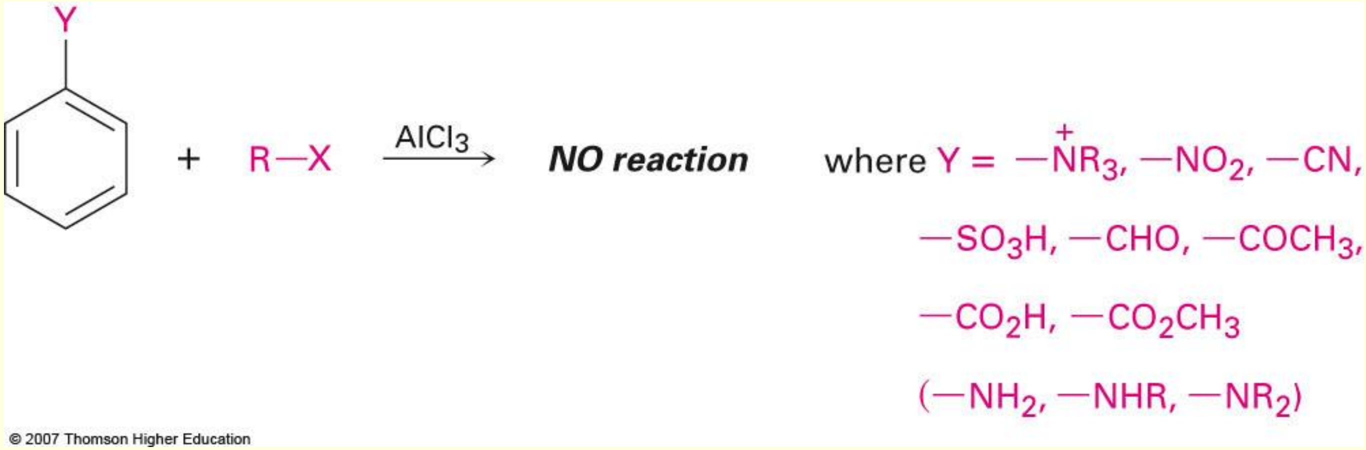
- Alkylation among most useful electrophilic aromatic substitution reactions
- Aromatic substitution of R^+ for H^+
- Aluminum chloride promotes the formation of the carbocation



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





Other Problems with Alkylation

- Multiple alkylations can occur because the first alkylation is activating

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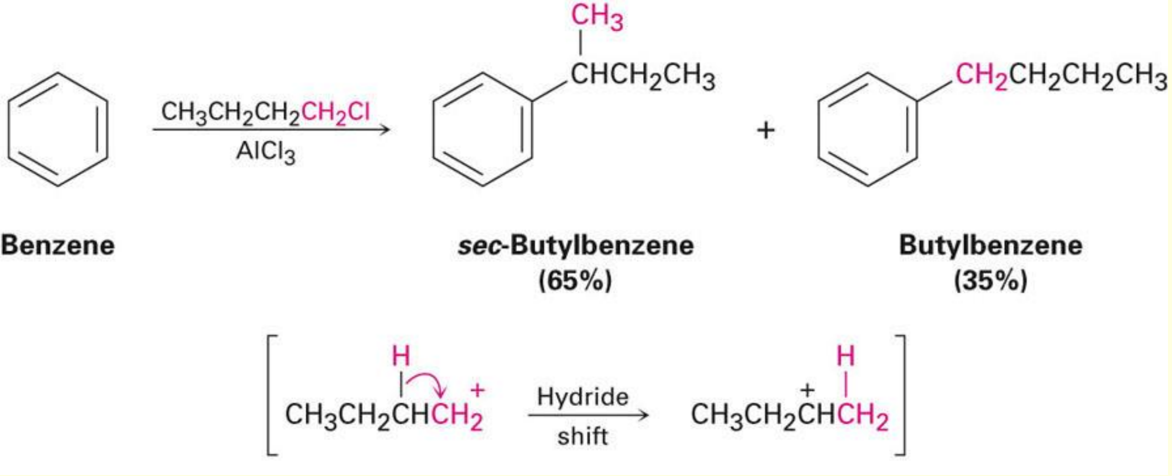
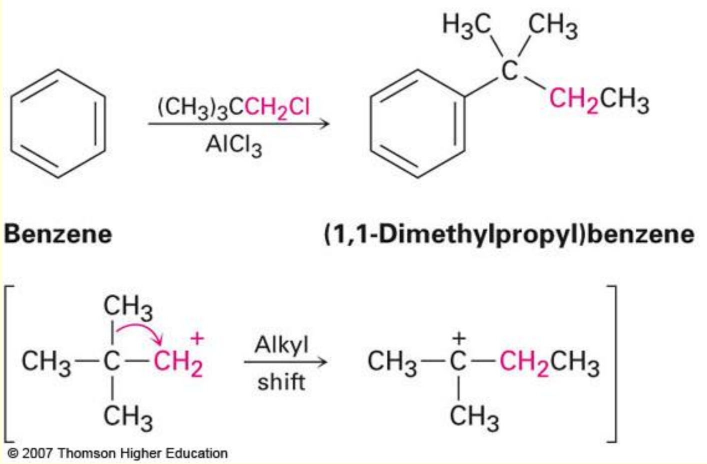
- Carbocation Rearrangements Occur During Alkylation
  - Similar to those occuring during electrophilic additions to alkene
  - Can involve H or alkyl shifts





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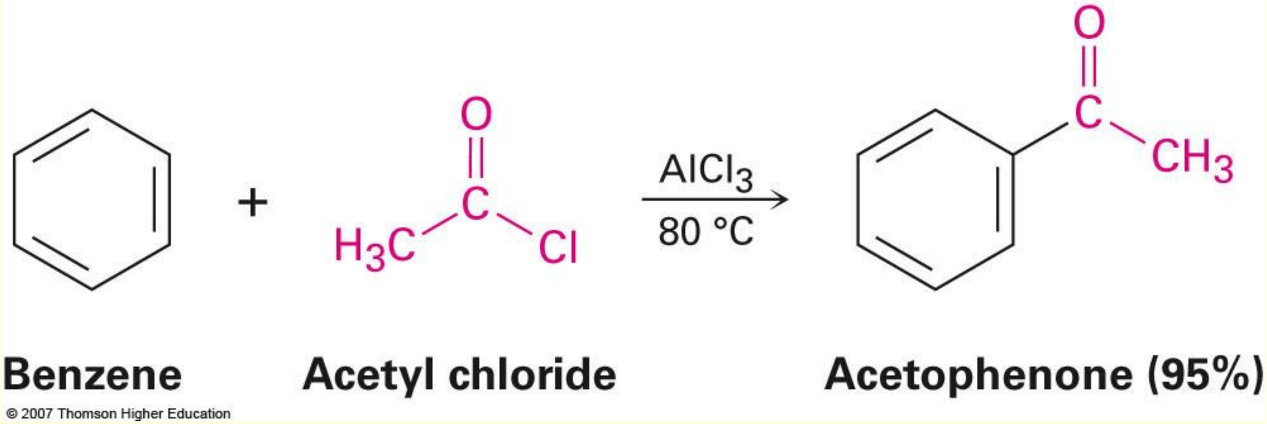
Acylation of Aromatic Rings

- 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
  - 

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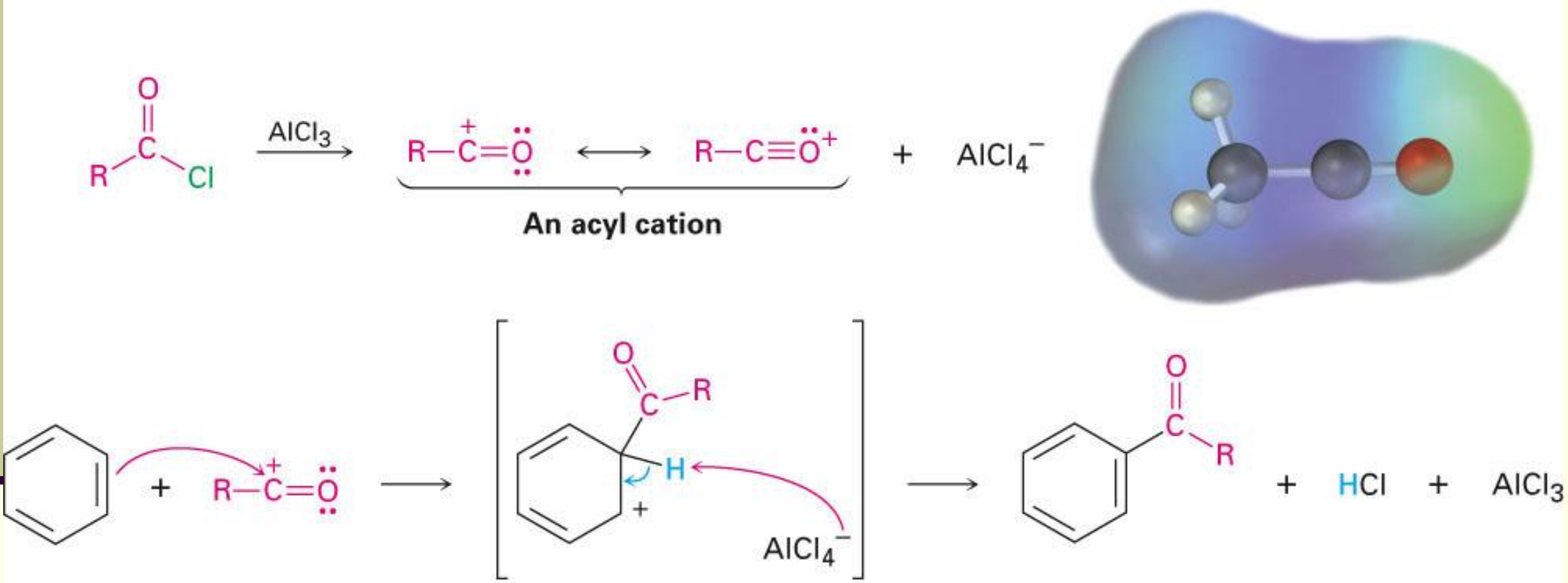
- Avoids many of the problems of alkylation
  - Only substitutes once, because acyl group is deactivating
  - No rearrangement because of resonance stabilized cation

Mechanism of Friedel-Crafts Acylation

- Similar to alkylation
- Reactive electrophile: resonance-stabilized acyl cation
- An acyl cation does not rearrange



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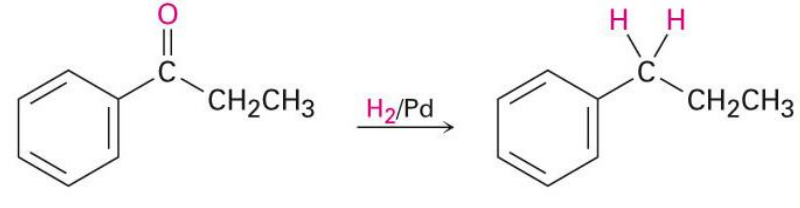
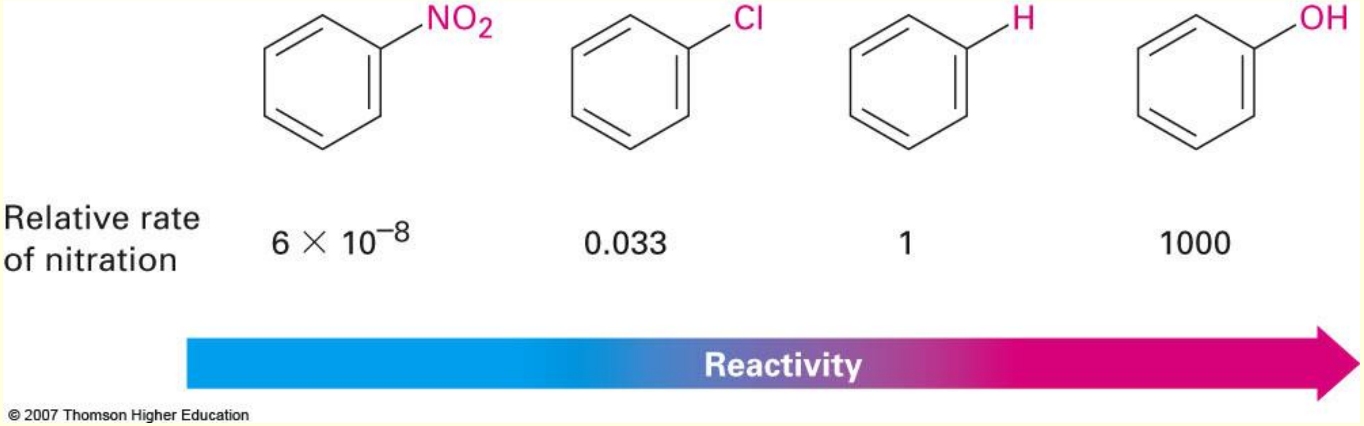
- Can reduce carbonyl to get alkyl product



Substituent Effects in Aromatic Rings

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



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- Substituents affect the orientation of the reaction – the positional relationship is controlled

- ortho- and para-directing activators, ortho- and para-directing deactivators, and meta-directing deactivators.

Origins of Substituent Effects

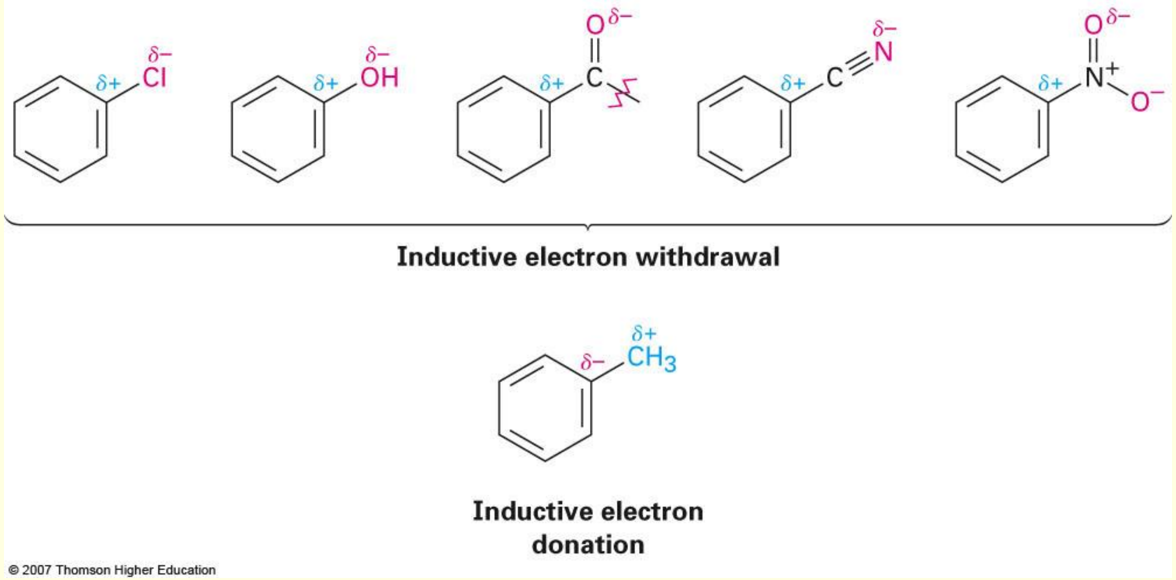
- An interplay of *inductive effects* and *resonance effects*

- Inductive effect - withdrawal or donation of electrons ***through a σ bond*** = Polar Covalent Bonds

- 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



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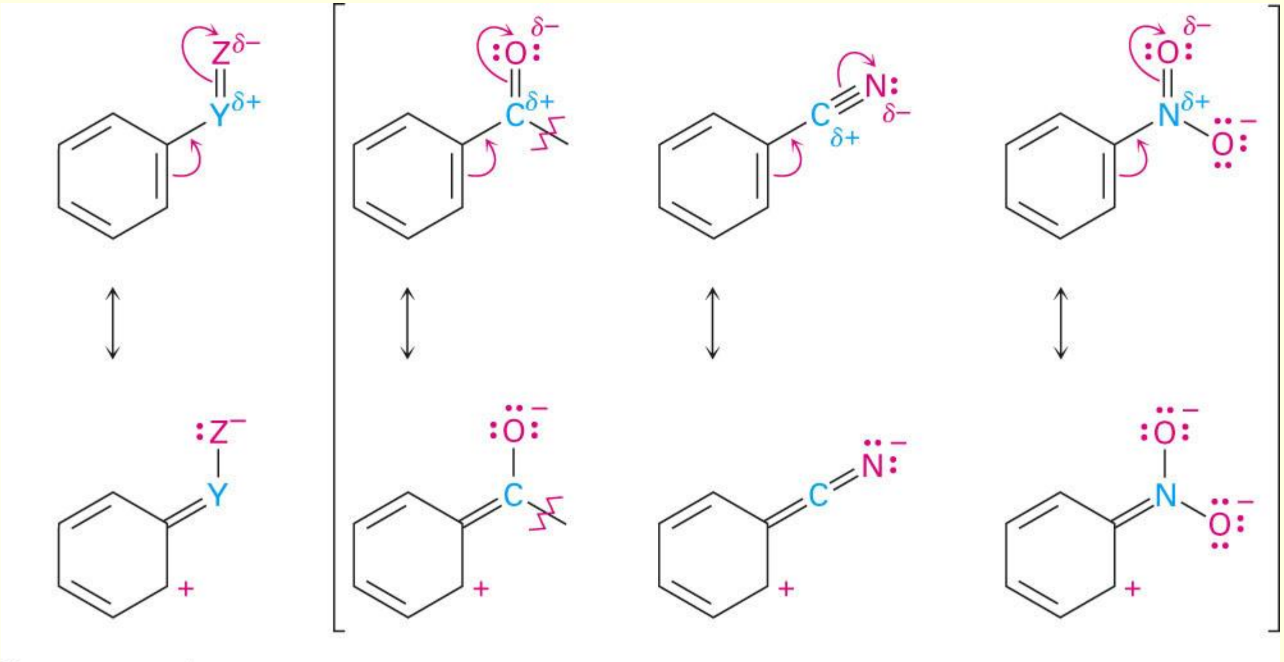
Resonance Effects – Electron Withdrawal

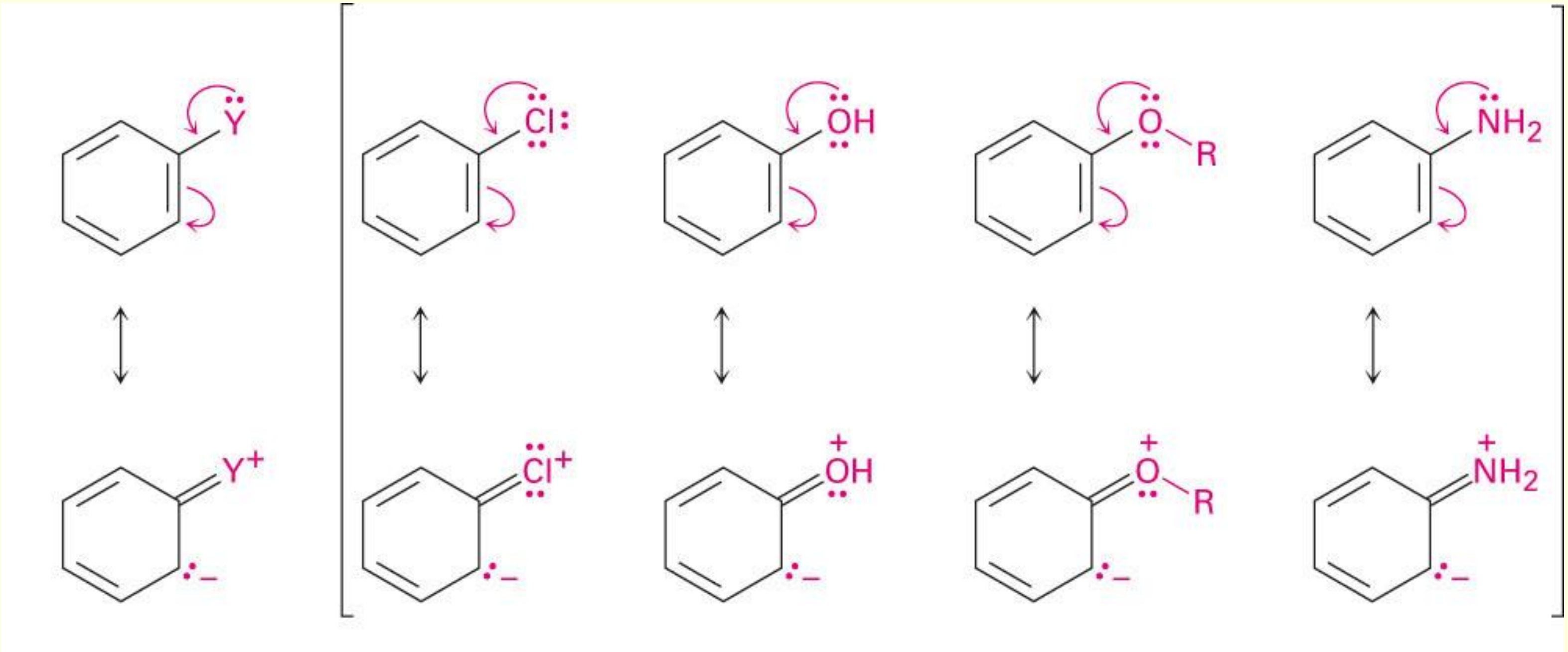
- C=O, CN, NO_2 substituents *withdraw* electrons from the aromatic ring by resonance
- π electrons flow from the rings to the substituents
- ***Look for a double (or triple) bond connected to the ring by a single bond***



Resonance electron-withdrawing group

Resonance Effects – Electron Donation

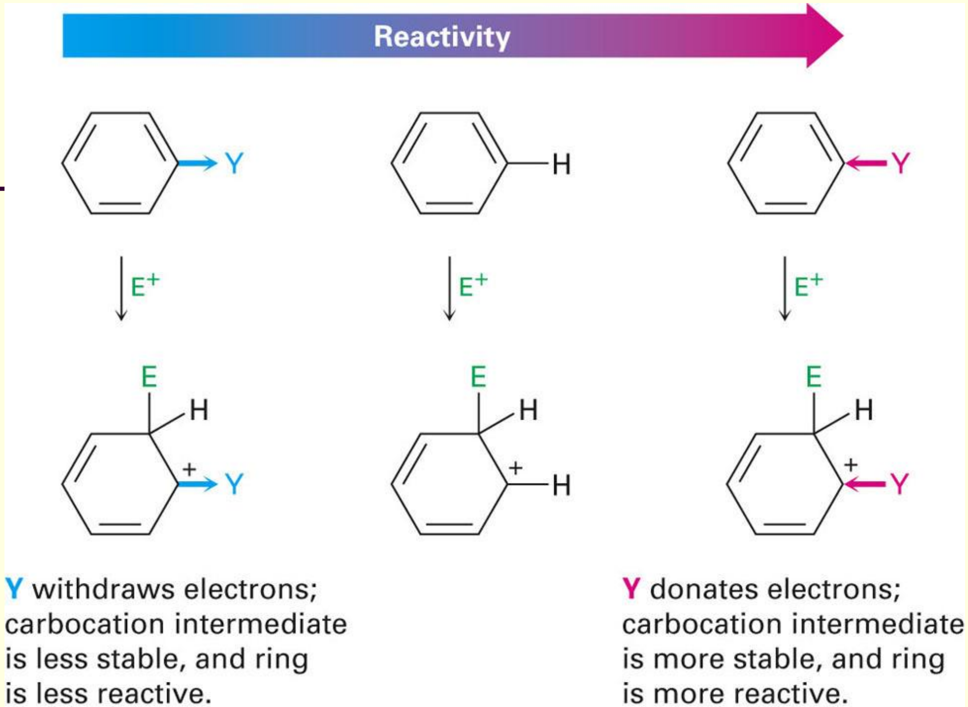
- Halogen, OH, alkoxyl (OR), and amino substituents *donate* electrons
- π electrons flow from the substituents to the ring
- Effect is greatest at ortho and para positions
- ***Look for a lone pair on an atom attached to the ring***



Resonance electron-donating group

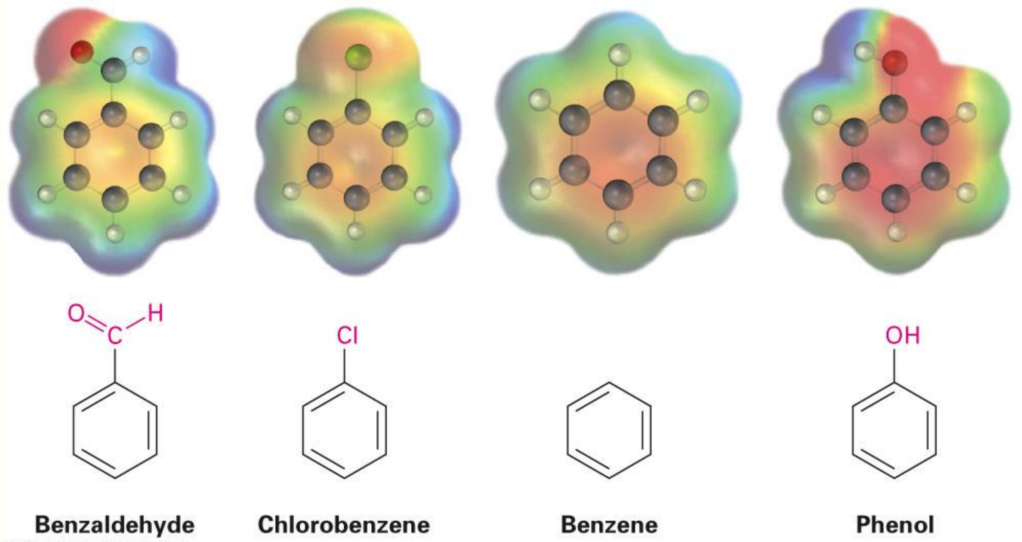
An Explanation of Substituent Effects

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



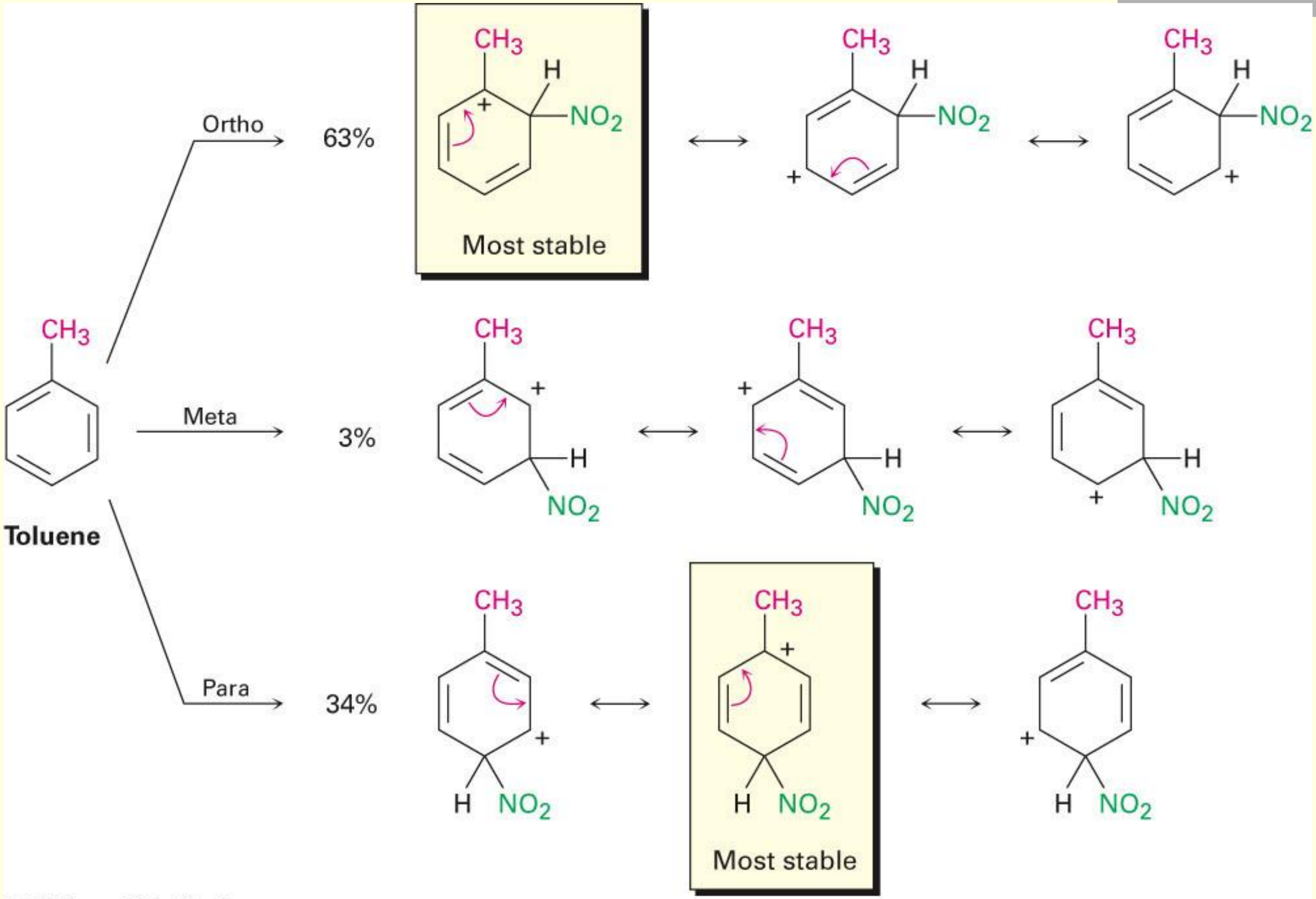
Y withdraws electrons; carbocation intermediate is less stable, and ring is less reactive.

Y donates electrons; carbocation intermediate is more stable, and ring is more reactive.



Ortho/Para-Directing Activators: Alkyl Groups

- Alkyl groups activate by induction: direct further substitution to positions ortho and para to themselves
- Alkyl group has most effect on the ortho and para positions



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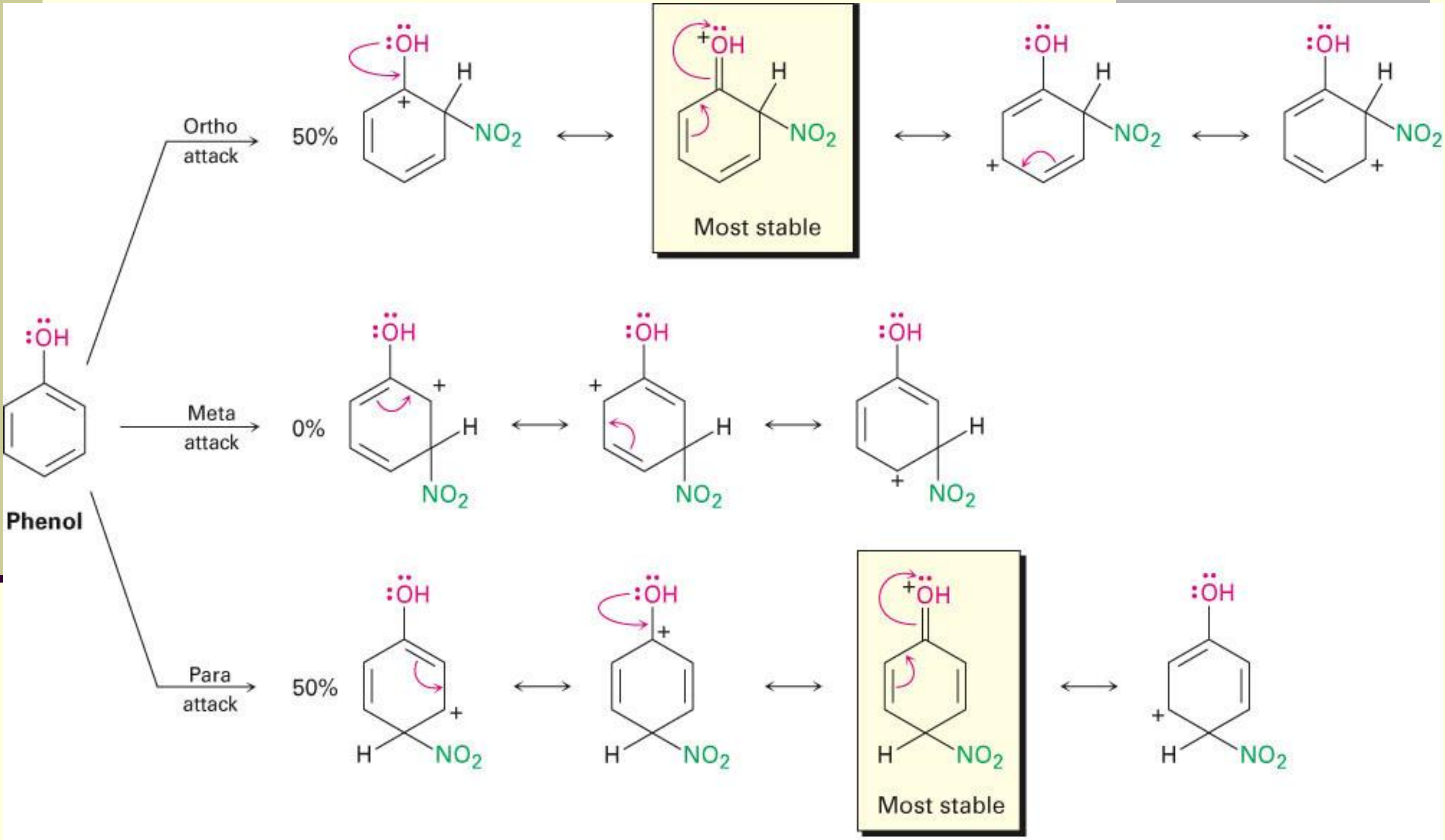
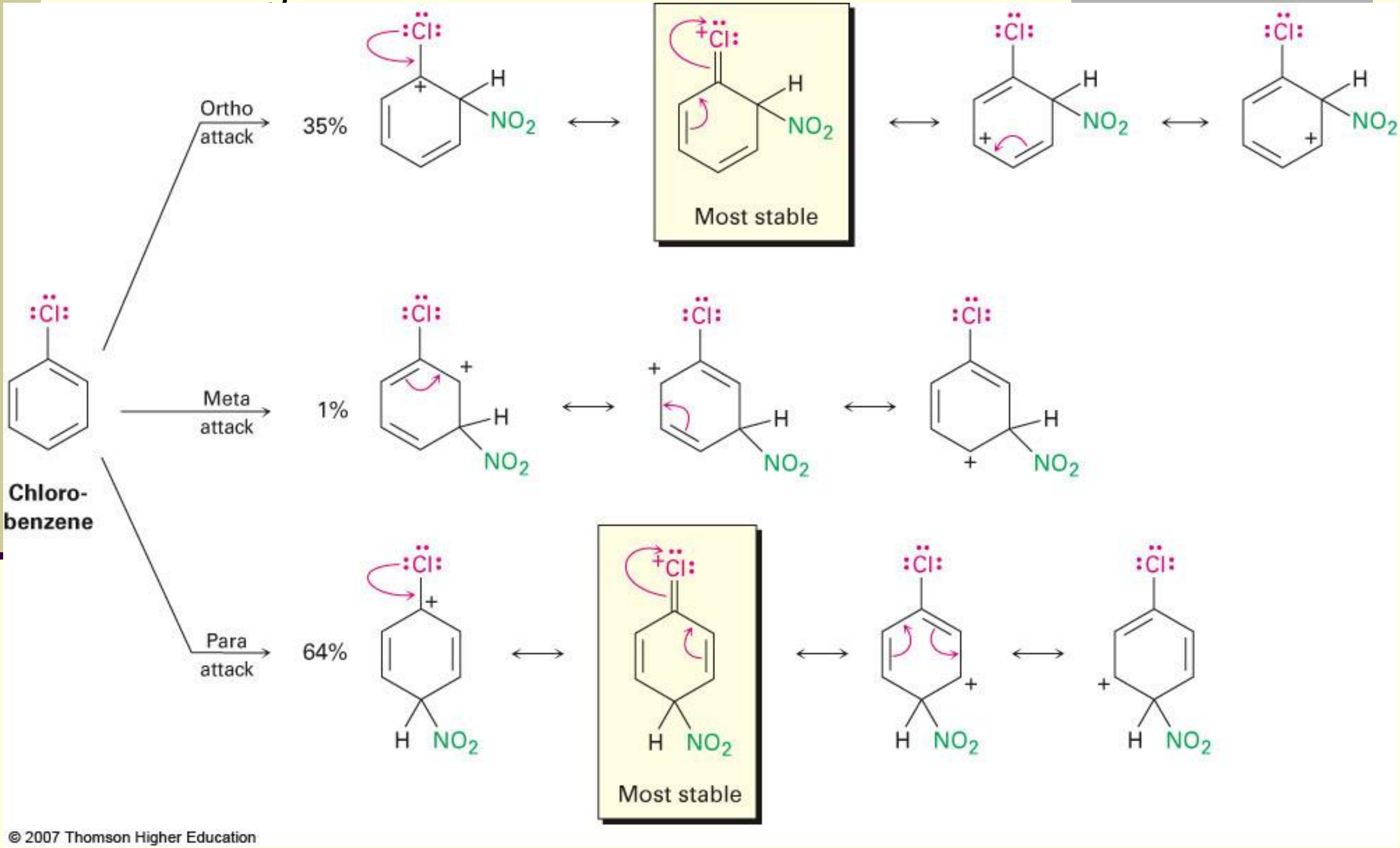
Ortho/Para-Directing Activators: OH and NH_2

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



Ortho/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



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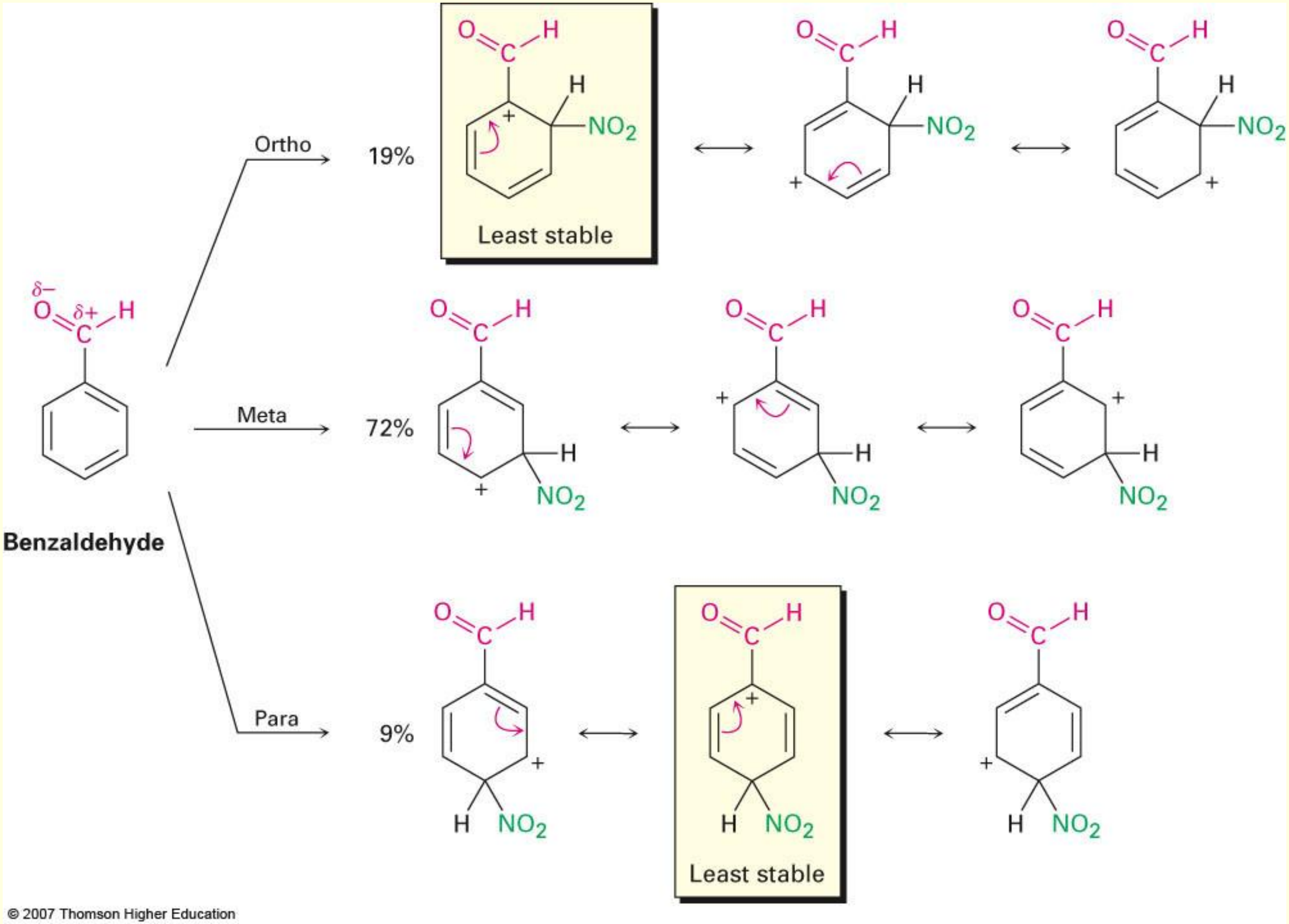
Meta-Directing Deactivators

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



Summary Table: Effect of Substituents in Aromatic Substitution

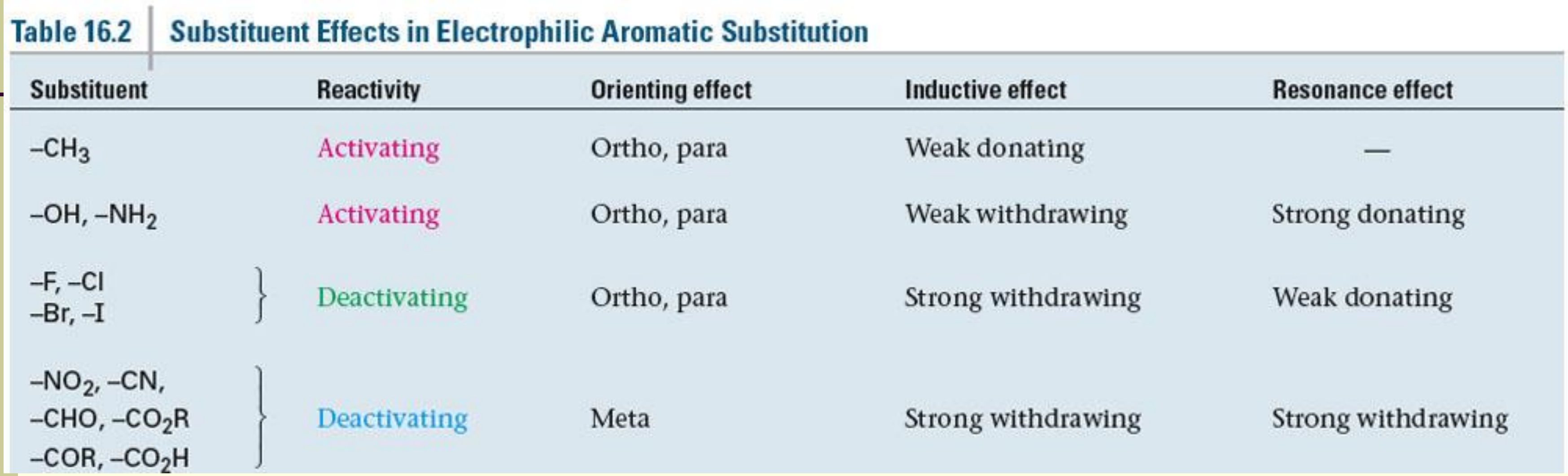
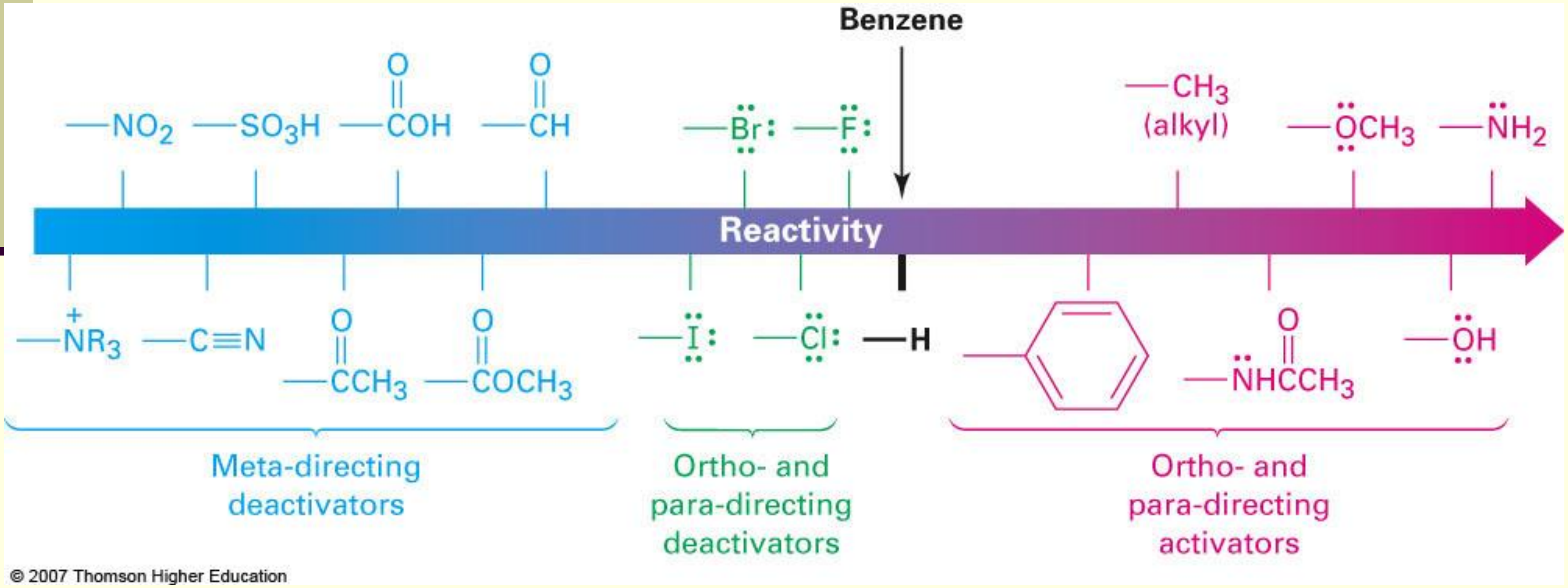


Table 16.2 Substituent Effects in Electrophilic Aromatic Substitution

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



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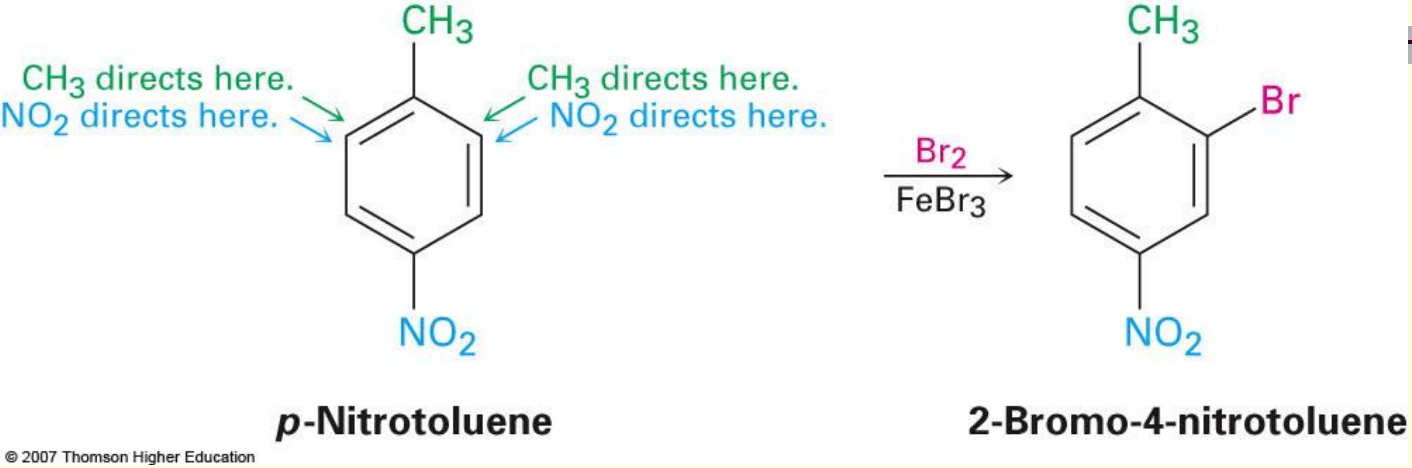
Trisubstituted Benzenes: Additivity of Effects

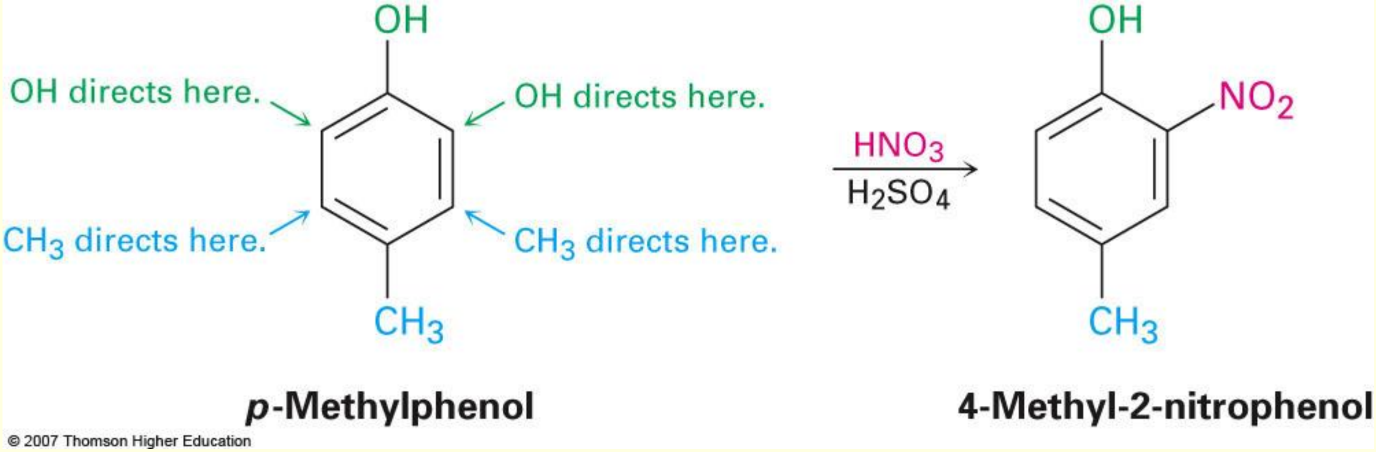
- If the directing effects of the two groups are the same, the result is additive



p-Nitrotoluene

2-Bromo-4-nitrotoluene

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

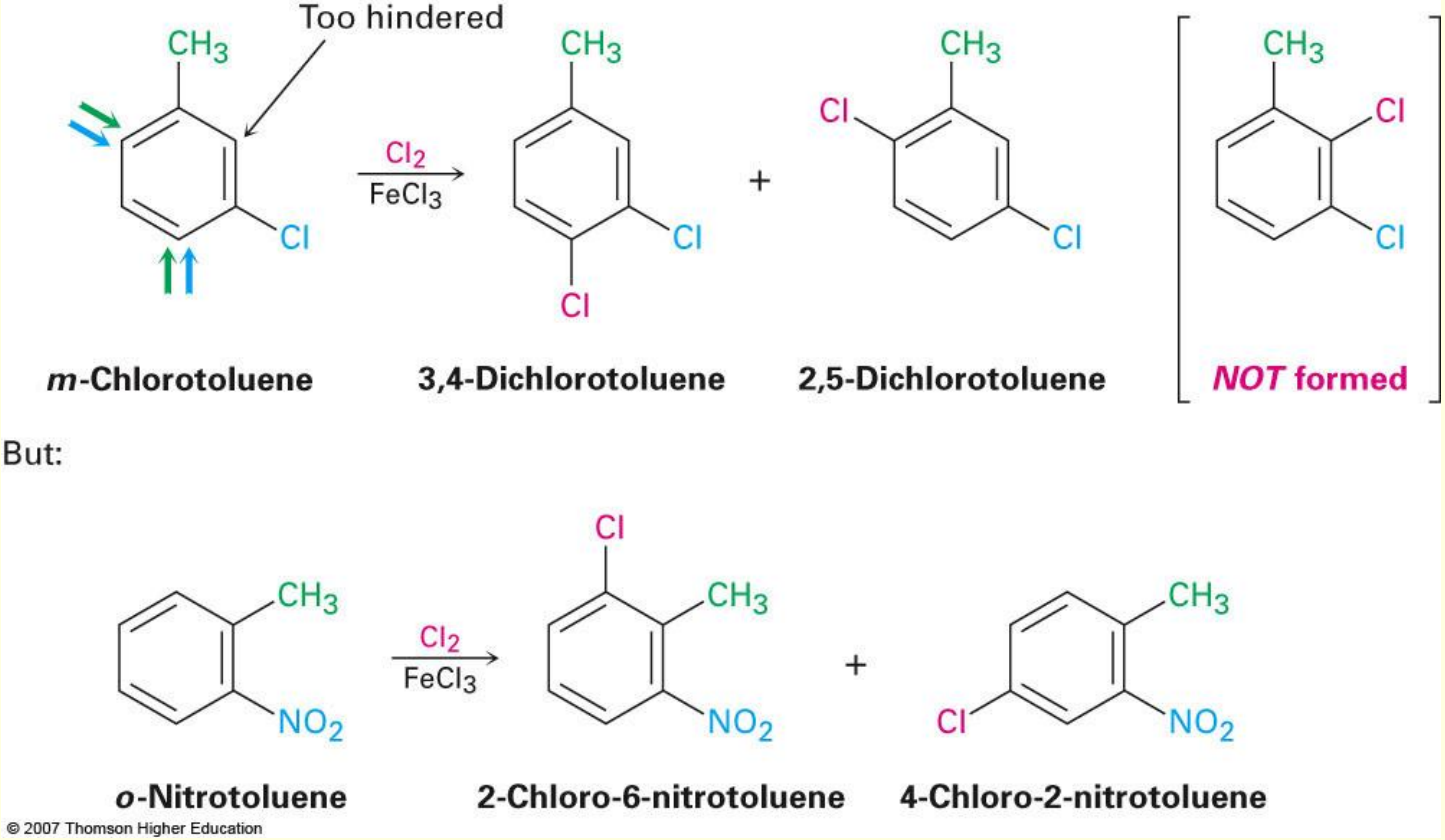


p-Methylphenol

4-Methyl-2-nitrophenol

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



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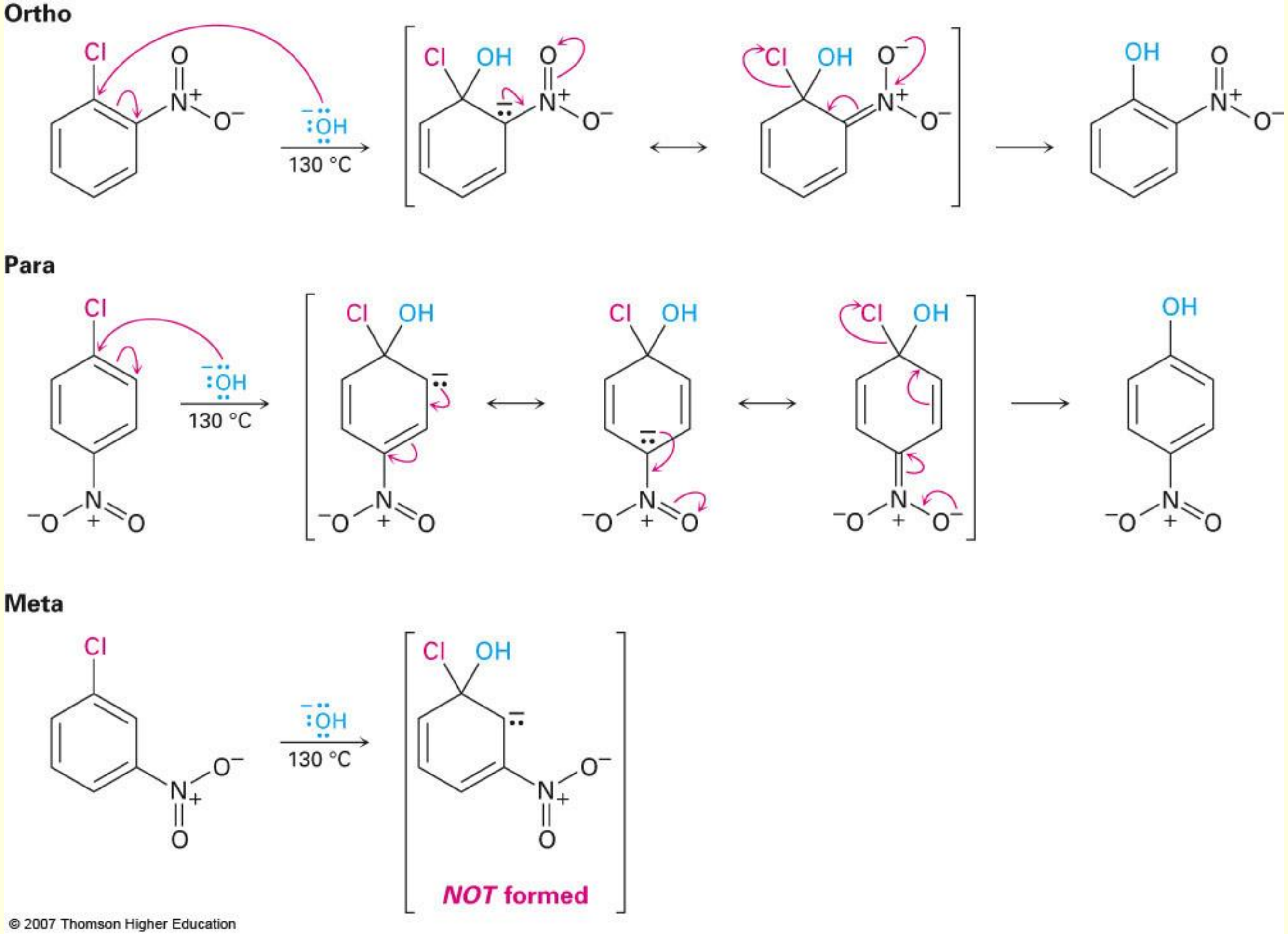
Nucleophilic Aromatic Substitution

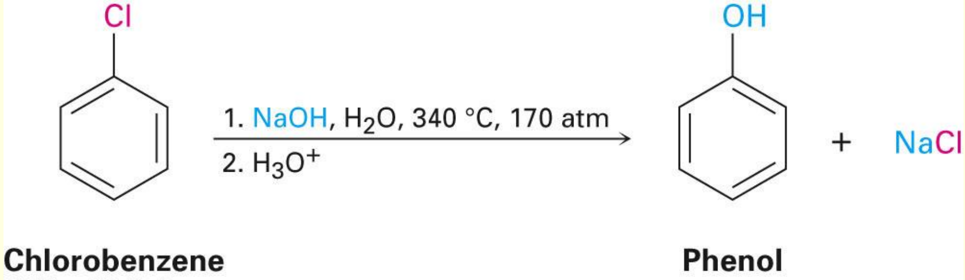
- Aryl halides with electron-withdrawing substituents ortho and para react with nucleophiles (electron withdrawing needed to accept electrons from the nucleophile)

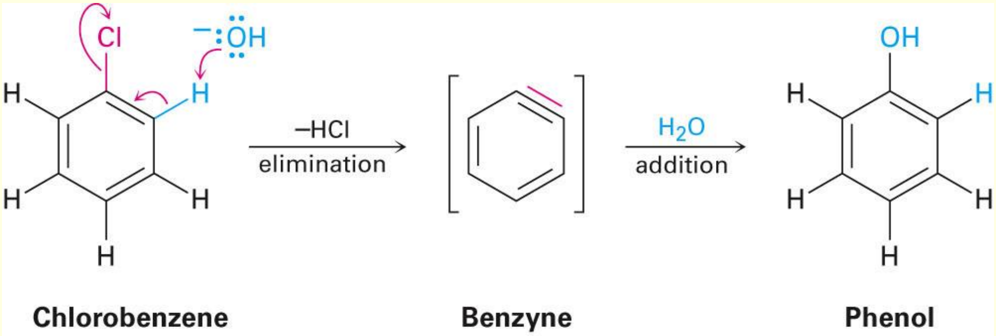
- Form addition intermediate (Meisenheimer complex) that is stabilized by electron-withdrawal. Halide is leaving group.

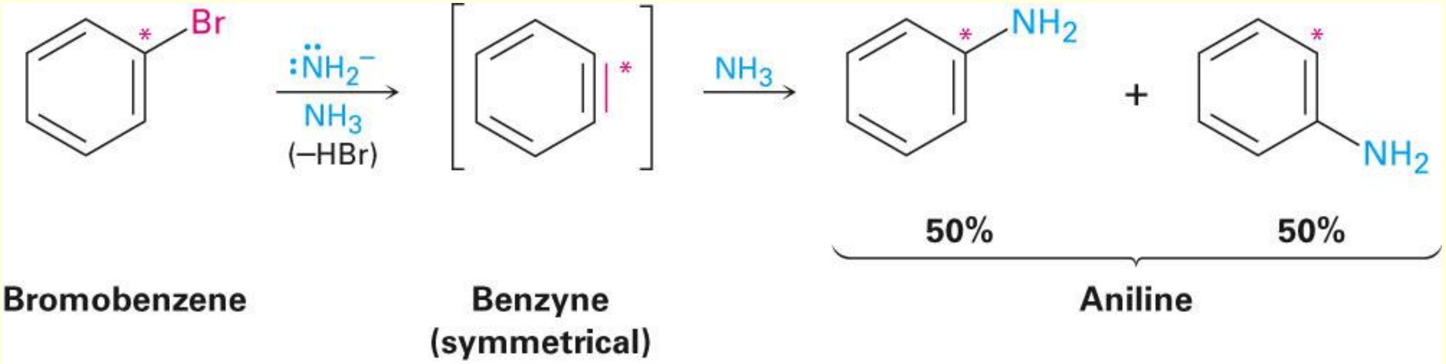


Benzyne: Substitution of Unactivated Aromatics

- Phenol is prepared industrially 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 in the ring: benzyne

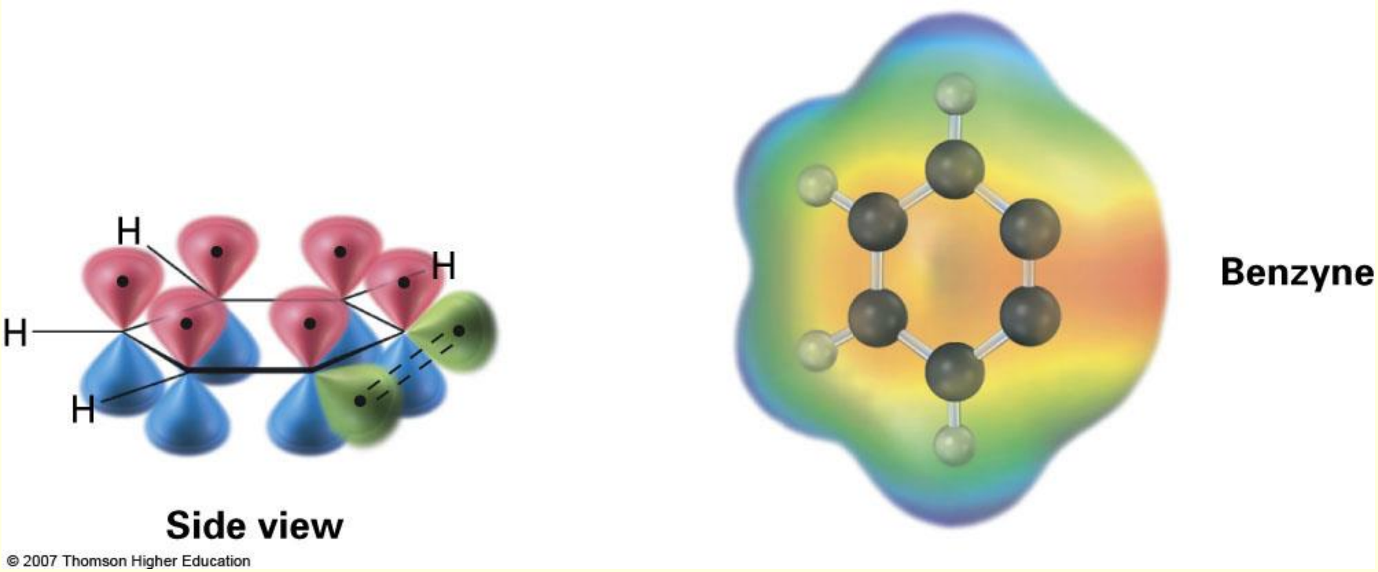






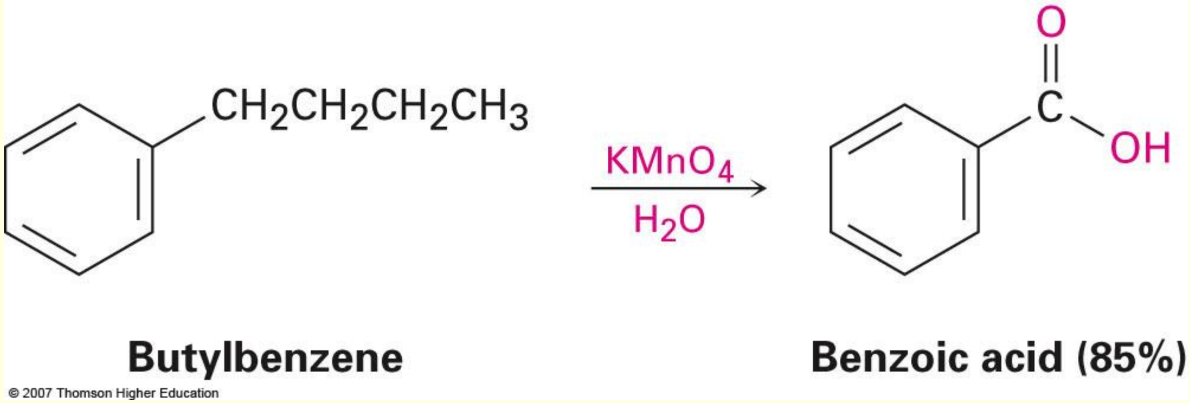
Structure of Benzyne

- 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



Oxidation of Aromatic Compounds

- Alkyl side chains can be oxidized to —CO_2H by strong reagents such as $KMnO_4$ if they have a C-H next to the ring
- Converts an alkylbenzene into a benzoic acid, Ar—R → Ar—CO_2H
- A benzylic C-H bond is required, or no reaction takes place



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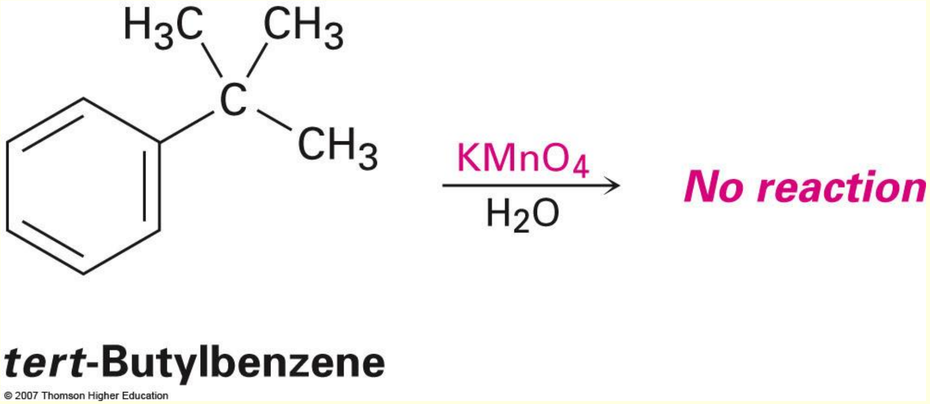

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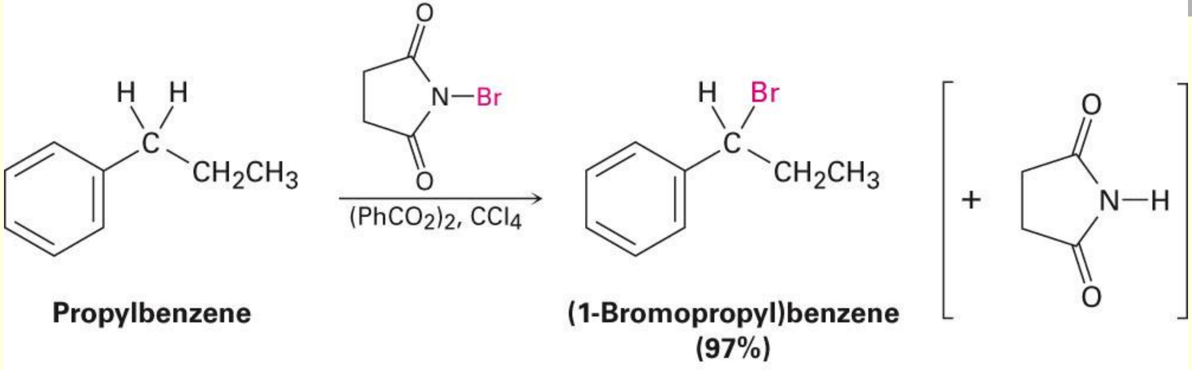
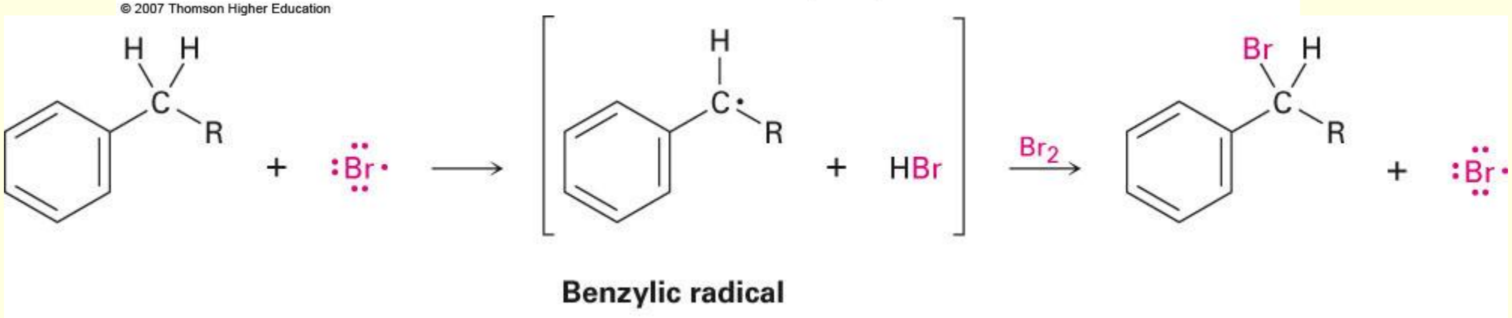
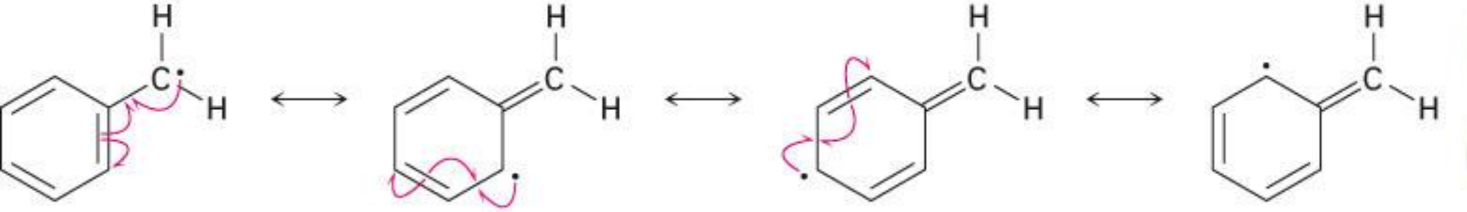
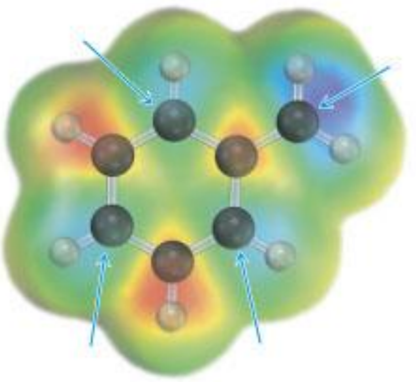
Bromination of Alkylbenzene Side Chains

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



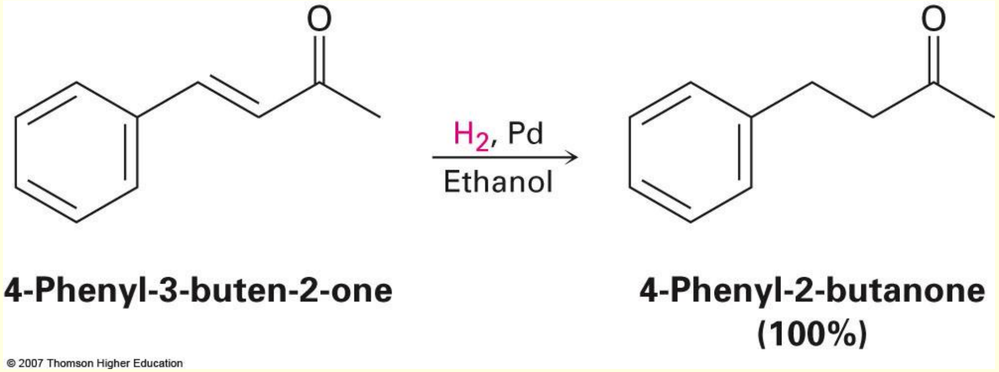






Reduction of Aromatic Compounds

- 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 rhodium catalysts)



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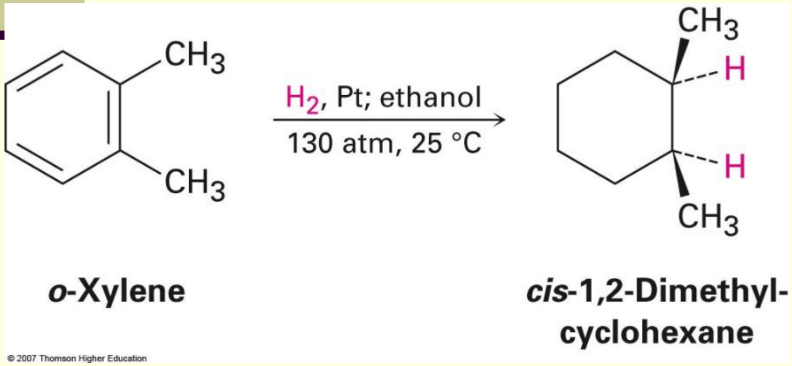

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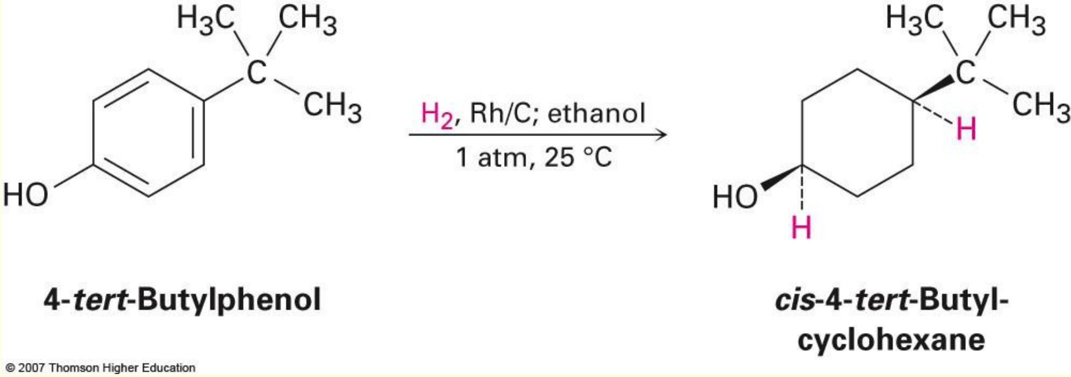

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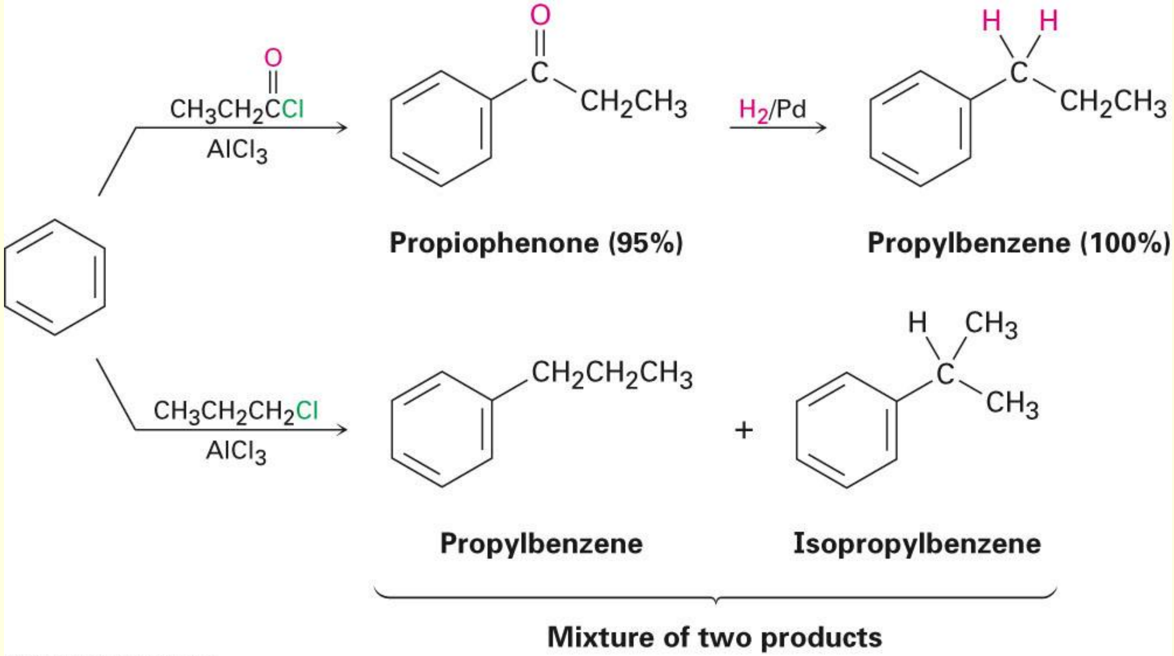
Reduction of Aryl Alkyl Ketones

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



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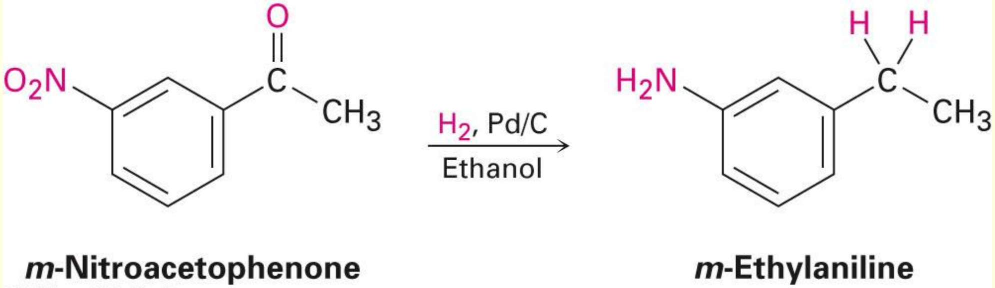

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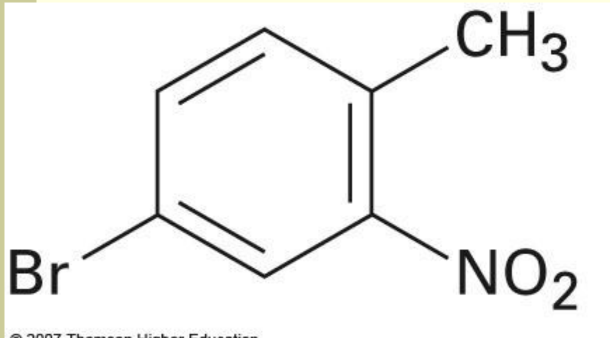
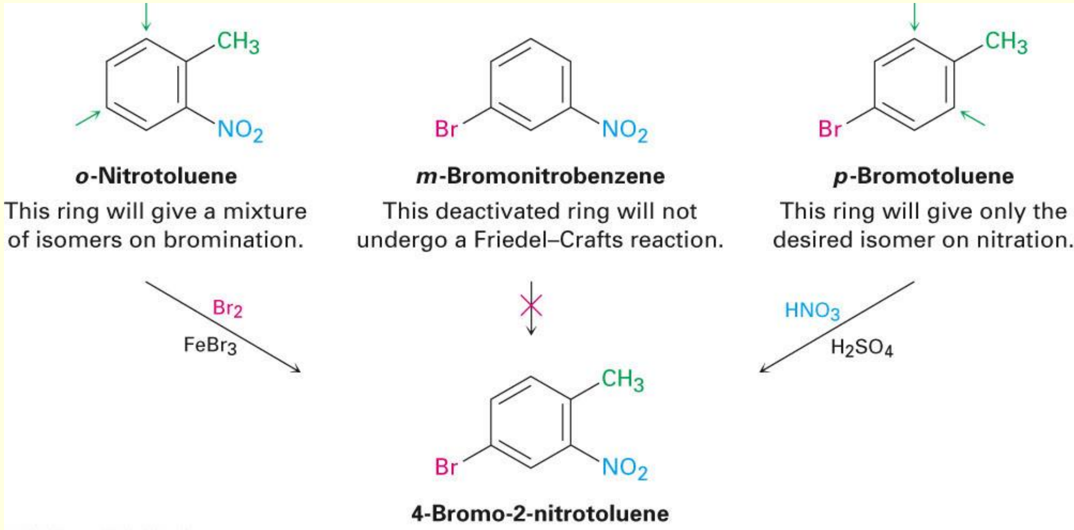
Synthesis of Trisubstituted Benzenes

- 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

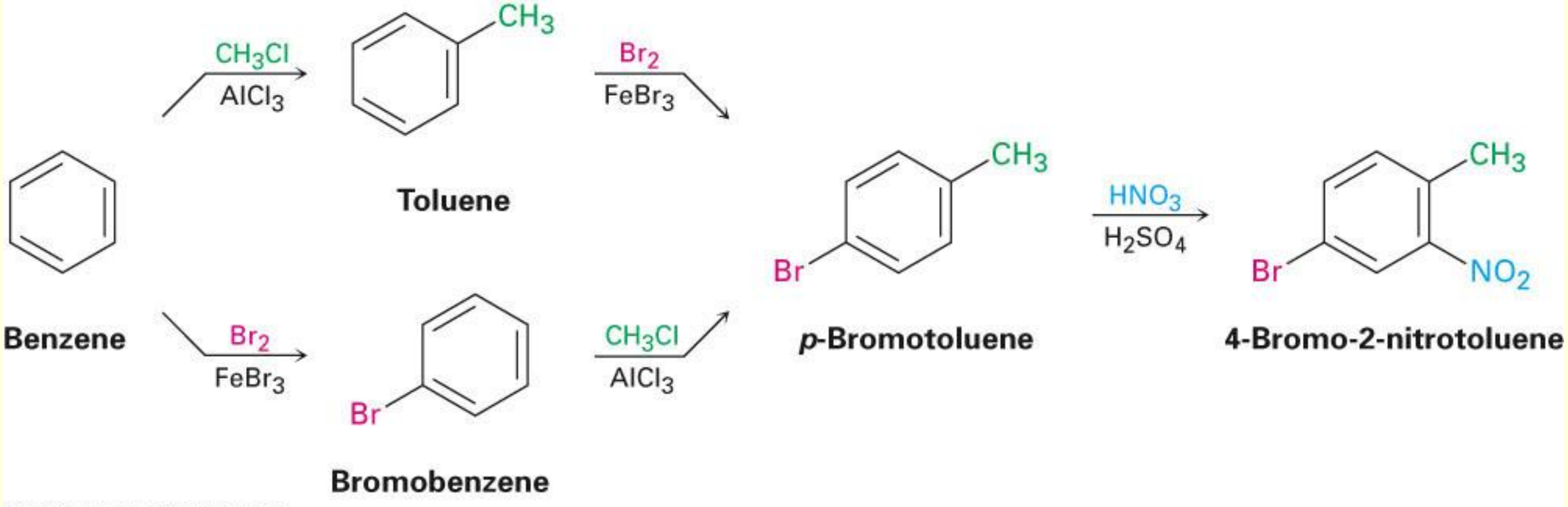


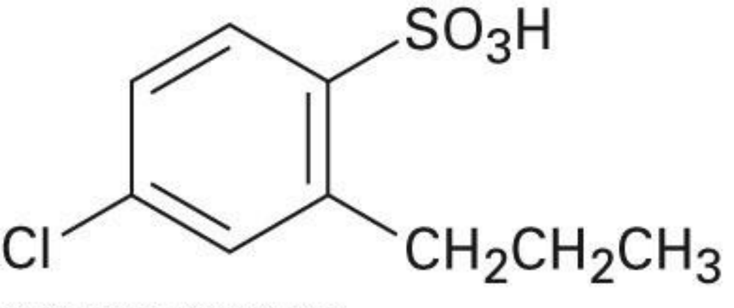


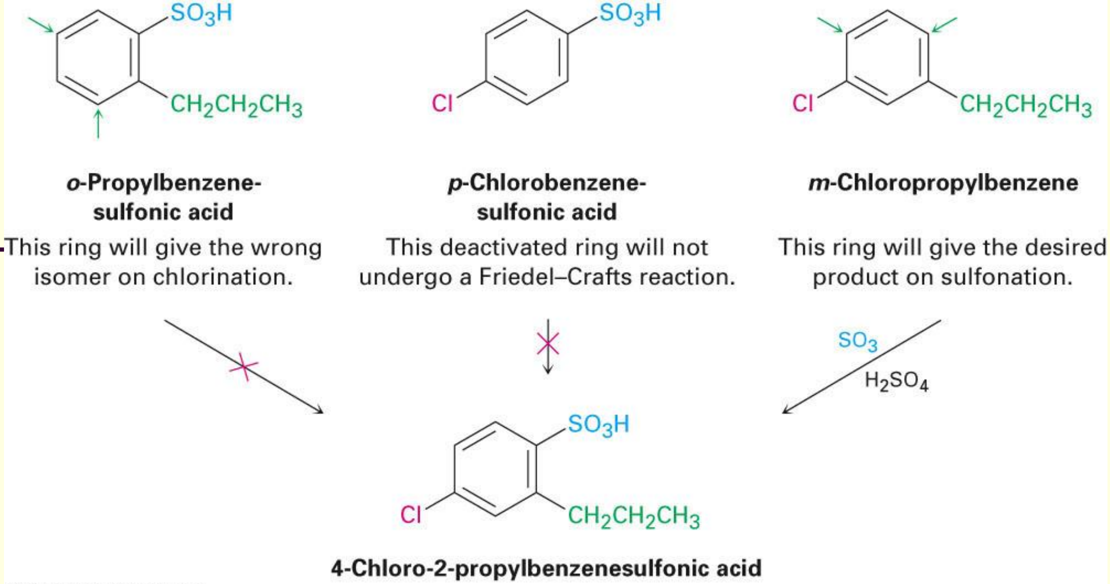
This ring will give a mixture of isomers on bromination.

This deactivated ring will not undergo a Friedel–Crafts reaction.

This ring will give only the desired isomer on nitration.







***o*-Propylbenzene-sulfonic acid**

This ring will give the wrong isomer on chlorination.

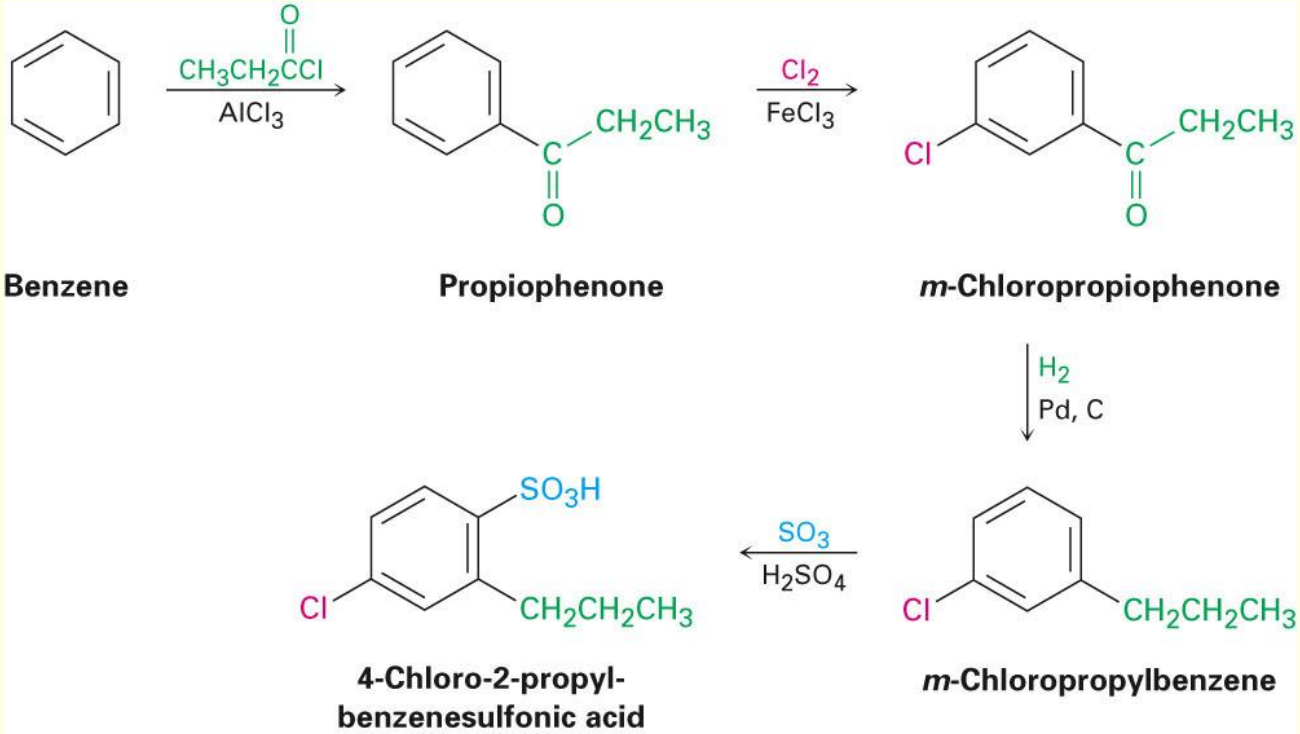
***p*-Chlorobenzene-sulfonic acid**

This deactivated ring will not undergo a Friedel–Crafts reaction.

***m*-Chloropropylbenzene**

This ring will give the desired product on sulfonation.

4-Chloro-2-propylbenzenesulfonic acid



Benzene

Propiophenone

***m*-Chloropropiophenone**

***m*-Chloropropylbenzene**

4-Chloro-2-propyl-benzenesulfonic acid