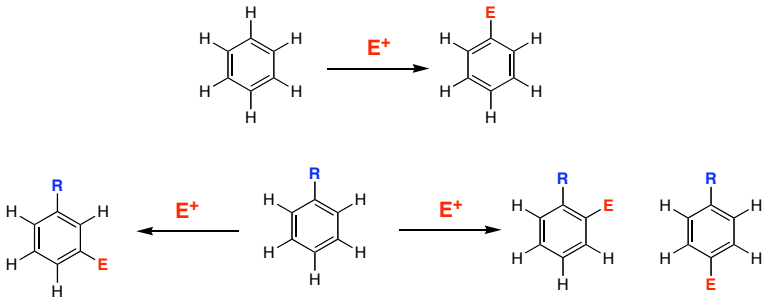
Chapter 16

Chemistry of Benzene: Electrophilic Aromatic Substitution



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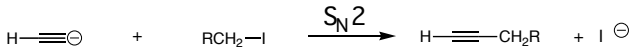
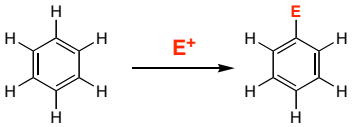
R-X + Y ⟶ R-Y + X

Nucleophilic substitution:



nucleophile electrophile

Electrophilic aromatic substitution:



nucleophile

E= -Cl, -Br, -I (halogenation)
-NO_2 (nitration)
-SO_3H (sulfonation
-R (alkylation)


(acylation)

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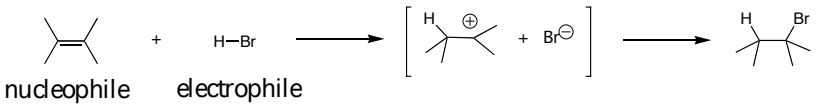
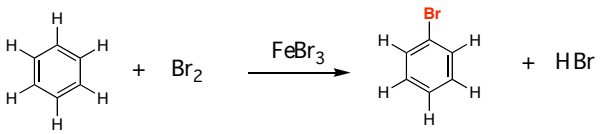
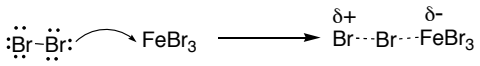
16.1: Bromination:

recall the electophilic addition of HBr (or Br_2) to alkenes



Aromatic rings (benzene) are not sufficiently nucleophilic to react with electrophiles without a catalyst





weak electrophile

strong electrophile

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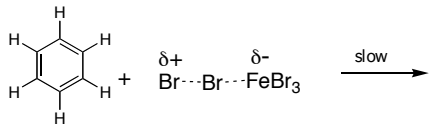
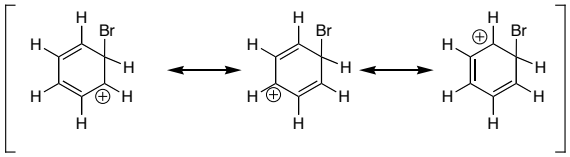
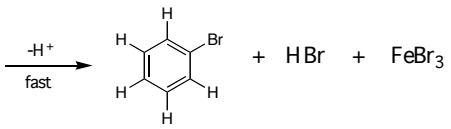
Mechanism: a π-bond of benzene acts as a nucleophile and "attacks" the Br_2•$FeBr_3$ complex (electrophile) leading to a resonance stabilized carbocation. Loss of a proton gives the substitution product and restores aromaticity.







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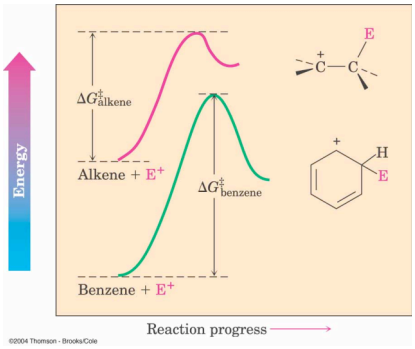
Comparison of electrophilic addition and electrophilic substitution

alkene: more nucleophilic, lower $\Delta G^{\ddagger}$

benzene: less nucleophilc, higher $\Delta G^{\ddagger}$,

resonance stabilized carbocation intermediate



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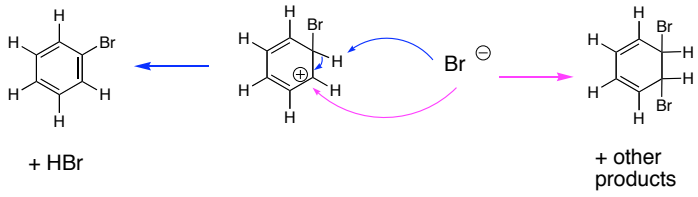


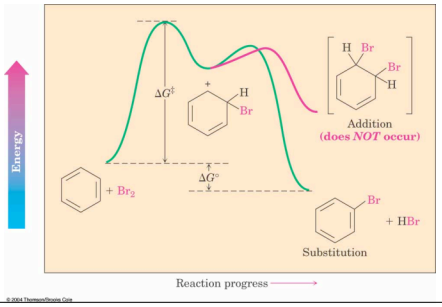
+ HBr

product regains aromatic stabilization

+ other products

products lose aromatic stabilization

Aromaticity is worth ~ 150 KJ/mol



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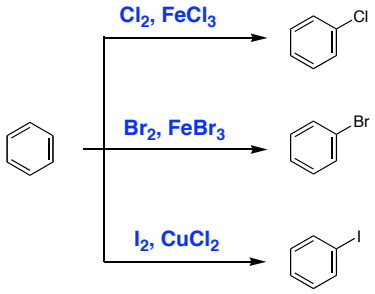
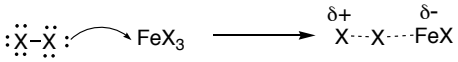
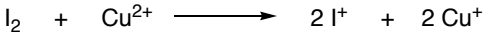
16.2: Other aromatic substitution:

Electrophilic aromatic halogenation:



For X= Cl or Br





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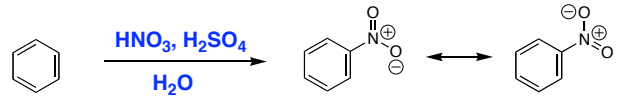
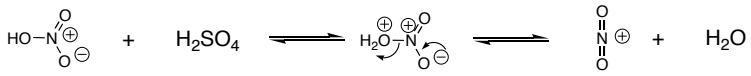
Aromatic nitration:



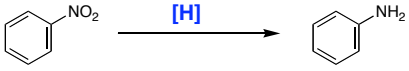


Nitric acid
pK_a~ -1.3

Sulfuric acid
pK_a~ -2.0

Nitronium Ion

Synthesis of anilines (aminobenzenes):



aniline

[H]= a) $SnCl_2$, H_3O^+ b) HO^-
Fe^0 or Sn^0, H_3O^+
H_2, Pd/C
plus many more

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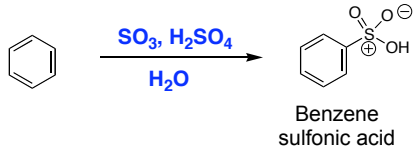
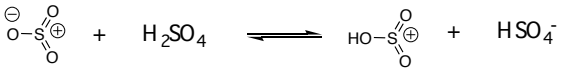
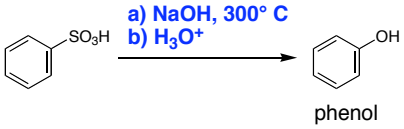
Aromatic sulfonation:



sulfur analogue of a carboxylic acids





alkali fusion reaction

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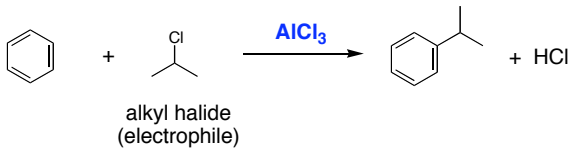
16.3: Alkylation of Aromatic Rings: The Friedel-Crafts Reaction



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alkyl halide:

halide= F, Cl, Br, I

must be an alkyl halide, vinyl and aryl halides do not react

the aromatic substrate:

can not have electron withdrawing substituents, nor an amino group

Y ≠ NO_2, C≡N, $-SO_3H$

(R= ketone, aldehyde, carboxylic acids, ester)

$-NH_2$, NHR, NR_2, $-N^+R_3$,

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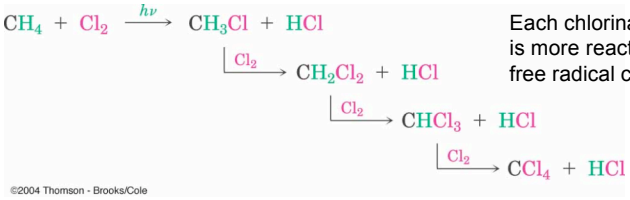
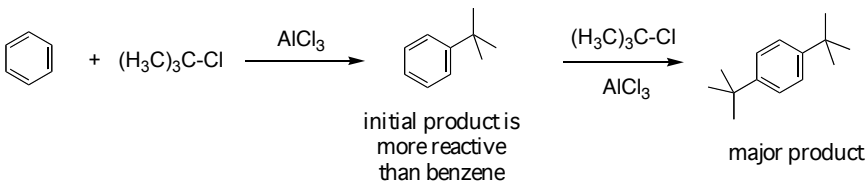
F-C alkylation is often difficult to stop after one alkylation reaction

Recall radical halogenation of methane (Chapter 10.4)



Each chlorination product is more reactive toward free radical chlorination



initial product is more reactive than benzene

major product

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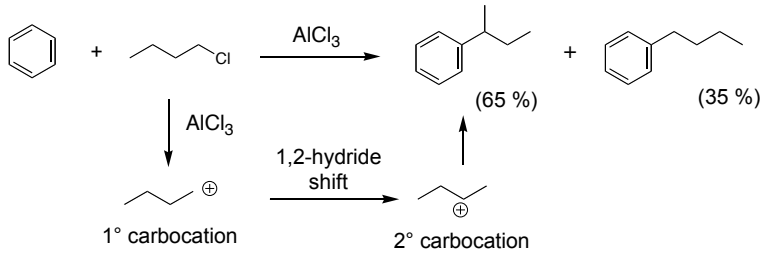
Since the F-C alkylation goes through a carbocation intermediate, skeletal rearrangements of the alkyl halide are common



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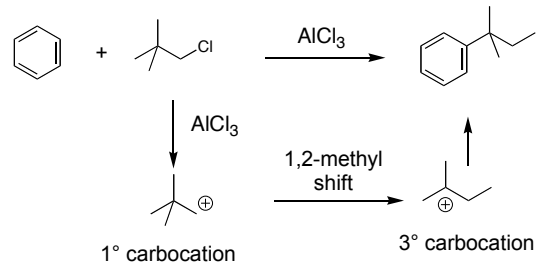

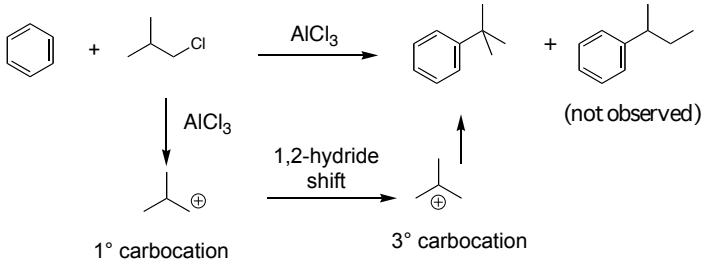

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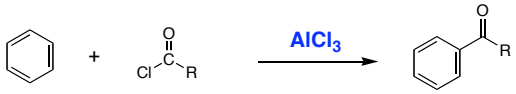
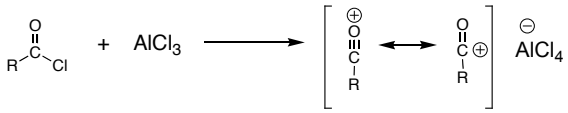
16.4: Acylation of aromatic rings

acyl group





oxacarbenium ion

The acylated product is less reactive than benzene toward electrophilic aromatic substitution. F-C acylation can be stopped after one acyl group is added

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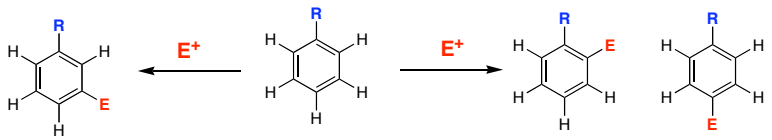
16.5: Substituent Effects in Substituted Aromatic Rings

1. Reactivity
   - activating: more reactive than benzene
   - deactivating: less reactive than benzene
2. Orientation
   - ortho-para directors
   - meta directors



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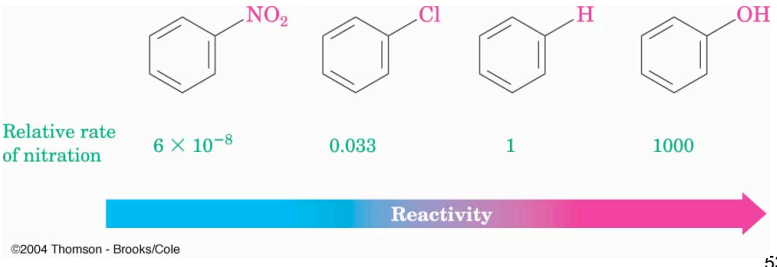
Reactivity of a substituted benzene toward further electrophilic substitution is dependent upon the nature of the substituent

activating substituents : increases reactivity relative to benzene (electron-donating groups)
deactivating substituents: decreases reactivity relative to benzene (electron-withdrawing groups)



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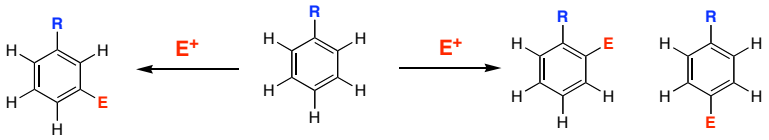
For electrophilic substitution of substituted benzenes, the site of reactivity by the electrophile is not random (statistical) :



Substituents are classified according to their directing effect and influence on reaction rate:

1. ortho-para directing activators
2. meta directing deactivators
3. ortho-para directing deactivator

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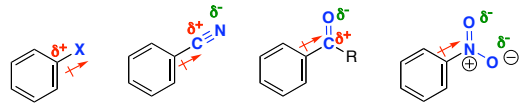
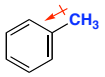
Origin of the activating/deactivating and directing effects

1. Inductive effects: ability of a substituent to donate or withdraw electron density through σ-bonds due to electronegativity differences and bond polarities of a functional group



X= F, Cl, Br, I

Electron-withdrawing groups



Electron-donating groups

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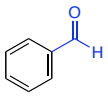
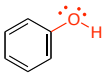
2. Resonance effects: ability of a substituent to donate or withdraw electrons through π-bonds (overlap of π-orbitals)

Resonance effect of an electron withdrawing groups



Benzaldehyde

Resonance effect of an electron donating groups



Phenol

(See page 542)

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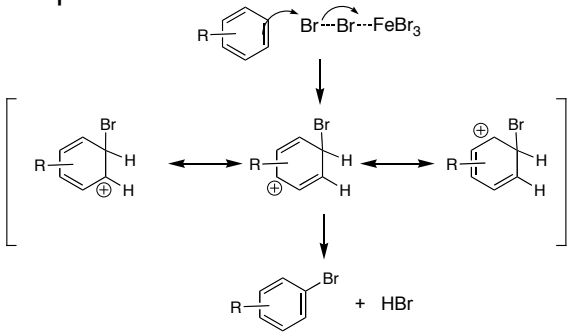
16.6: An explanation of the substituent effects



All activating group can donate electrons, either through inductive effects or resonance. Electron-donating groups stabilize the carbocation intermediate of electrophilic aromatic substitution.

All deactivating groups can withdraw electrons, either through inductive effects or resonance. Withdrawing-electron density destabilizes the carbocation intermediate. 57

Ortho-para directing activators: nitration of toluene

The carbocation intermediate from *o*- or *p*-addition can be stabilized by the substituent through inductive effects and hyperconjugation

(See Fig. 16.12, page 545) 58

Ortho-para directing activators: nitration of phenol (or aniline)

The carbocation intermediate from *o*- or *p*-addition can be stabilized by the substituent through resonance

(See Fig. 16.13, page 546)

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Ortho-para directing deactivators: nitration of chlorobenzene

Halogens are deactivating because they are strong electron-withdrawing groups (inductive effect); however, they have non-bonding pairs of electrons and can also donate electrons (resonance effect)

(See Fig. 16.14, page 547)

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Meta directing deactivators: nitration of nitrobenzene

The charge of the carbocation intermediate can be placed next to the electron-withdrawing group and is destabilized. This destabilization is avoided when *m*-addition occurs

(See Fig. 16.15, page 548)

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Summary of directing and reactivity effect: Table 16.1 (p. 540)

Substituent	Reactivity	Orientation	Inductive effect	Resonance effect
$-CH_3$	Activating	Ortho, para	Weak; electron-donating	None
$-\ddot{O}H$, $-\ddot{N}H_2$	Activating	Ortho, para	Weak; electron-withdrawing	Strong; electron-donating
$-\ddot{F}:$, $-\ddot{Cl}:$, $-\ddot{Br}:$, $-\ddot{I}:$	Deactivating	Ortho, para	Strong; electron-withdrawing	Weak; electron-donating
$-\overset{+}{N}(CH_3)_3$	Deactivating	Meta	Strong; electron-withdrawing	None
$-NO_2$, $-CN$, $-CHO$, $-CO_2CH_3$, $-COCH_3$, $-CO_2H$	Deactivating	Meta	Strong; electron-withdrawing	Strong; electron-withdrawing

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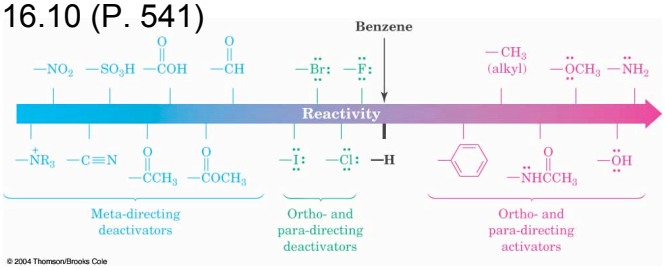
Figure 16.10 (P. 541)



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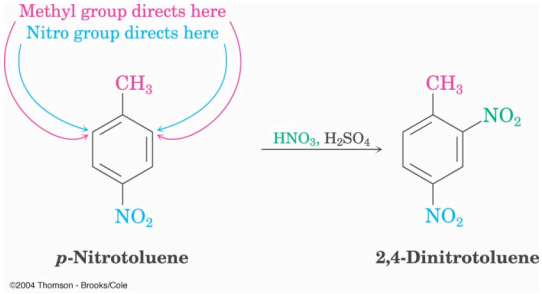
16.7: Trisubstituted Benzenes: Additivity of Effects

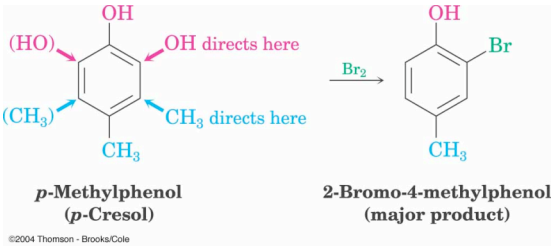
In order to determine the overall directing effect of a disubstitutent benzene toward further electrophilic substitution, you must analyze the individual directing effect of each substituent.

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



63

2. If the directing effects of two groups oppose each other, the stronger activating group has the dominant influence; however, mixtures of products are often produced.



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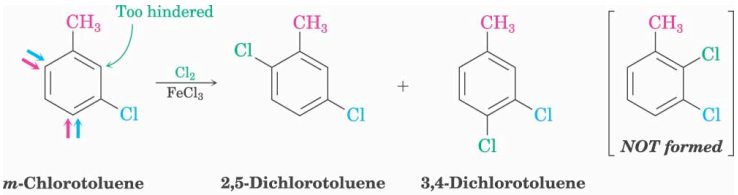
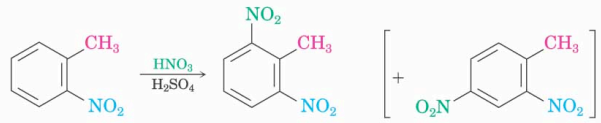
3. Further substitution between two existing substituents rarely occurs. To synthesize aromatic rings with three adjacent substituents, start with an ortho-disubstituted benzene



m-Chlorotoluene 2,5-Dichlorotoluene 3,4-Dichlorotoluene

But:



o-Nitrotoluene 2,6-Dinitrotoluene 2,4-Dinitrotoluene

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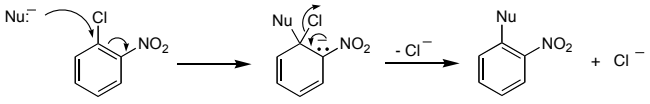
16.8 Nucleophilic Aromatic Substitution (please read)

Aryl halides with electron-withdrawing substituents (nitro groups) in the ortho and/or para positions react with nucleophiles

The mechanism is not an S_N1 or S_N2 reaction,and goes through an anionic intermediate (Meisenheimer complex) that is stabilized by the electron-withdrawing groups

Halide ion then lost from the Meisenheimer complex restoring aromaticity and giving the substitution product



Meisenheimer complex is stablized deolcalization of the negative change into the nitro group. This only occurs when the halogen is *o*- or *p*- to the nitro group

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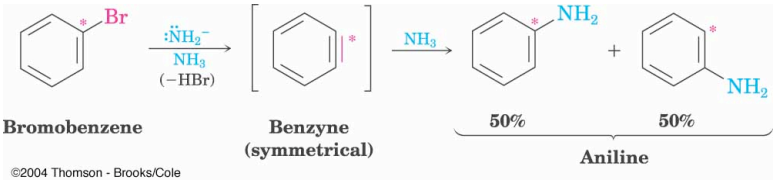
16.9 Benzyne (please read)

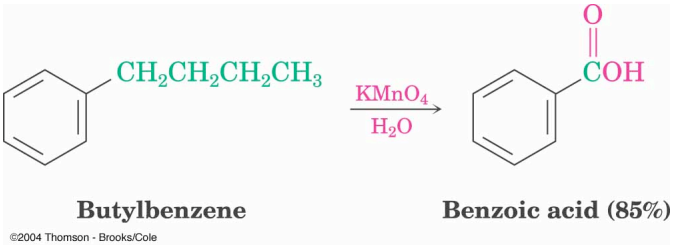
Elimination of HX from a halobenzene can occur under strongly basic conditions to give benzyne. Benzyne is highly reactive and will immediately react with the conjugate acid of the strong base



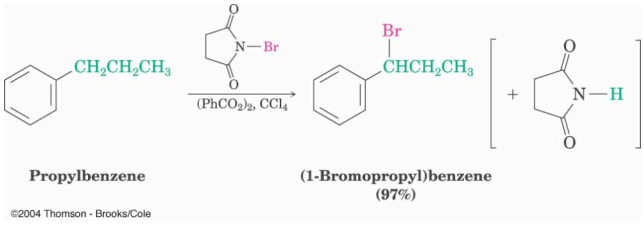
16.10 Oxidation of Aromatic Compounds

Benzene rings do not react with strong oxidants

The benzylic positions of alkylbenzene can be oxidized with strong oxidants such as $KMnO_4$ and $Na_2Cr_2O_7$ to give benzoic acids



Reaction of an alkylbenzene with *N*-bromo-succinimide (NBS) and benzoyl peroxide or light (radical initiator) introduces Br at the benzylic position by a free radical chain reaction



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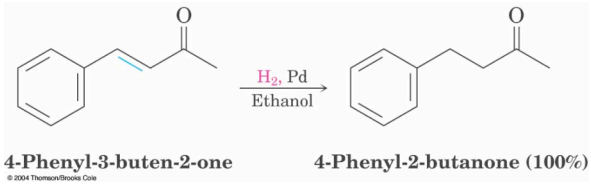
16.11 Reduction of Aromatic Compounds

Aromatic rings are inert to catalytic hydrogenation under conditions that will reduce alkene double bonds

An alkene double bond can therefore be selectively reduced in the presence of an aromatic ring

Reduction of an aromatic ring requires forcing conditions (high pressures of H_2 and special catalysts)



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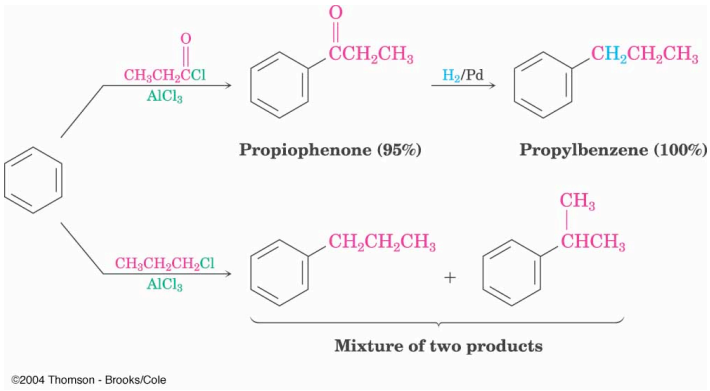
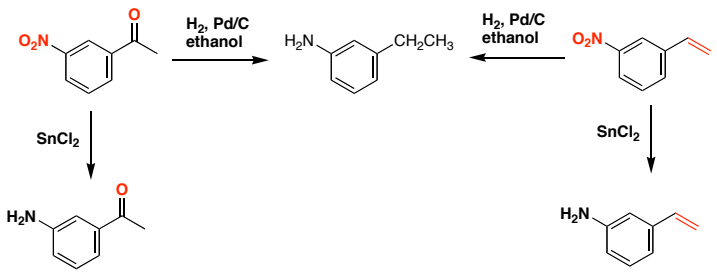
Reduction of Aryl Ketones

An aromatic ring activates carbonyl group at the benzylic position toward reduction. Such ketones are reduced to alkylbenzene by catalytic hydrogenation over Pd catalyst



Nitrobenzenes are reduced to the aminobenzenes at a rate competitive with or faster than alkene reduction or ketone reduction.



The nitro group can be selectively reduced with $SnCl_2$

16.12: Synthesis of trisubstituted benzenes

Work the problem backwards, stepwise from the product to the starting material (retrosynthetic analysis)

Keep in mind functional group compatibility for each step (revise and evaluate)

Keep in mind directing effects of the substituted benzenes

Synthesis should be:

a. as short as possible

b. give as few undesired products as possible

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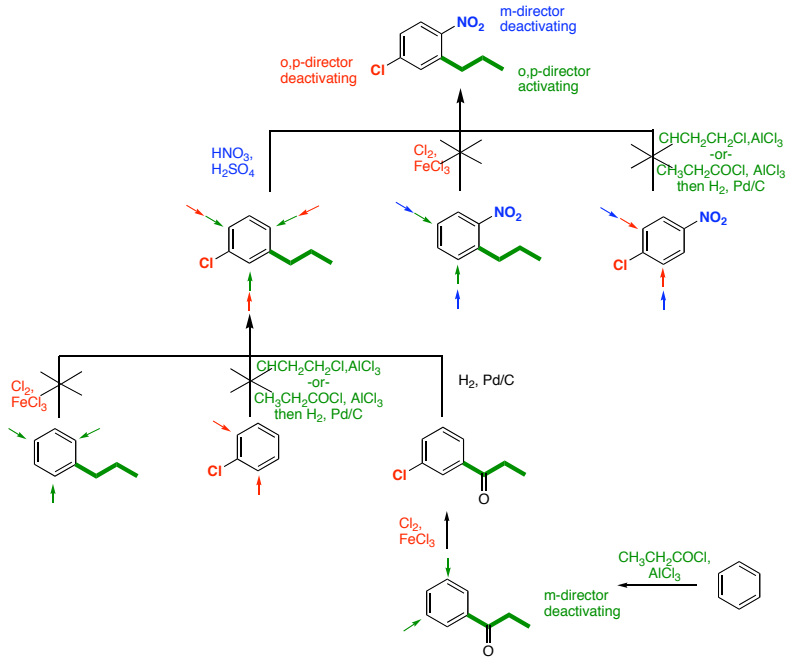
synthesize 4-chloro-1-nitro-2-propylbenzene from benzene



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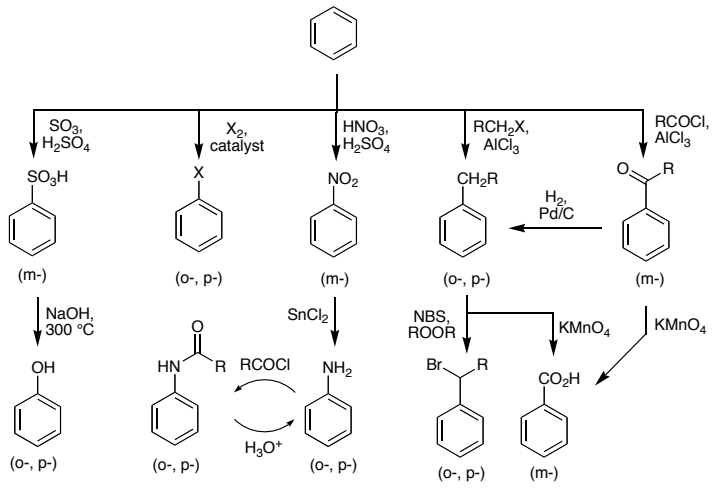
Summary of electrophilic aromatic substitution of benzene

Zanger, M.; Gennaro, A. R.; McKee, J. R. *J. Chem. Ed.* **1993**, *70 (12)* , 985-987



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