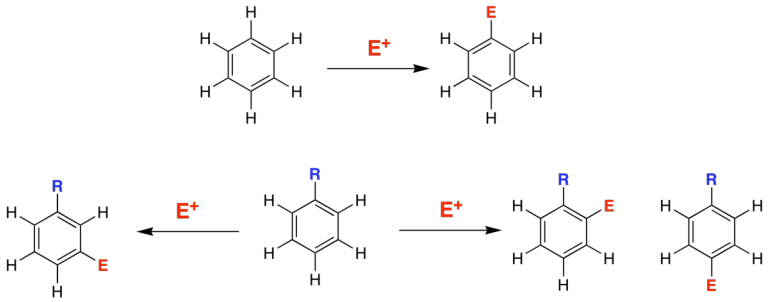
Chapter 12: Reactions of Arenes: Electrophilic Aromatic Substitution

12.1: Representative Electrophilic Aromatic Substitution Reactions of Benzene



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

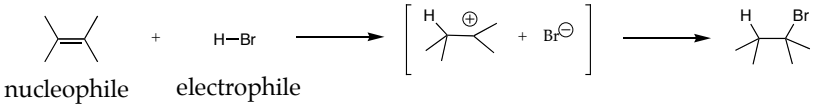
(Table 12.1)


(acylation)

275

12.2: Mechanistic Principles of Electrophilic Aromatic Substitution

Recall the electophilic addition of HBr (or Br_2) to alkenes (Ch. 6)

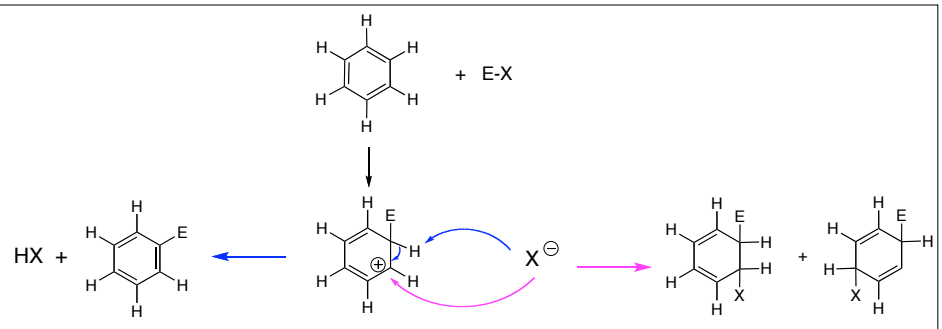


nucleophile electrophile

Most aromatic rings (benzene) are not sufficiently nucleophilic to react with electrophiles. Catalysts are often needed to increase the reactivity of the electrophiles.

Mechanism: a π-bond of benzene acts as a nucleophile and "attacks" the electrophile leading to a resonance stabilized cyclohexadienyl carbocation. Loss of a proton gives the substitution product and restores aromaticity.

276



Electrophilic substitution: product regains aromatic stabilization

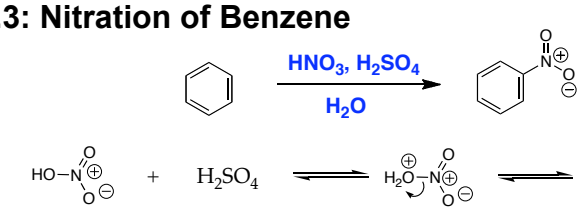
Resonance stabilized cyclohexadienyl cation intermediate

Electrophilic addition: products lose aromatic stabilization

Aromaticity is worth ~ 130-150 KJ/mol

277

12.3: Nitration of Benzene



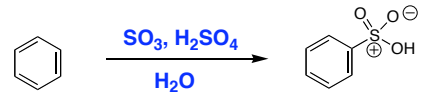
Nitric acid pK_a~ -1.3

Sulfuric acid pK_a~ -2.0

Nitronium Ion

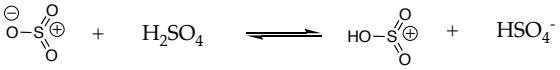
278

12.4: Sulfonation of Benzene



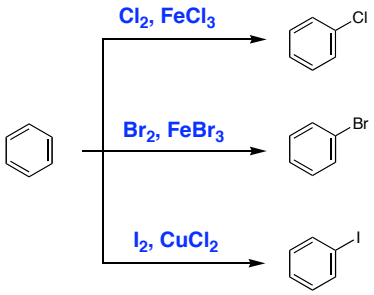
Benzene sulfonic acid

sulfur analogue of a carboxylic acids

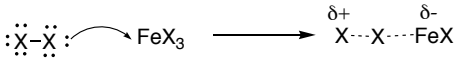


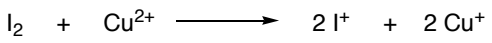
279

12.5: Halogenation of Benzene



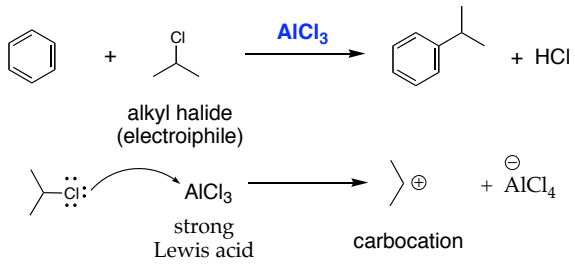
For X= Cl or Br





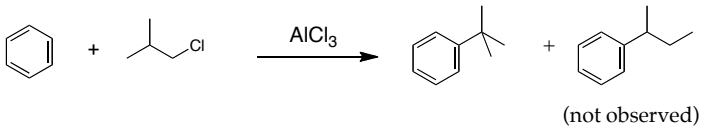
280

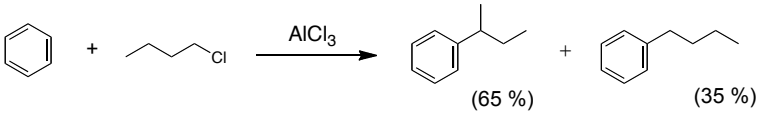
12.6: Friedel-Crafts Alkylation of Benzene



281

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





282

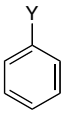
alkyl halide:

halide = F, Cl, Br, I

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

the aromatic substrate:

can not have strong electron withdrawing substituents, nor an amino group

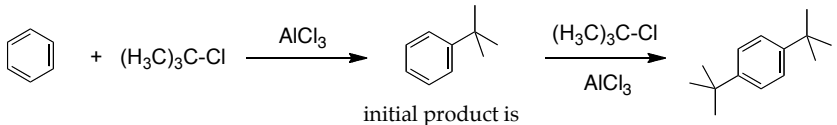


$Y \neq NO_2$, C≡N, $-SO_3H$

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

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

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

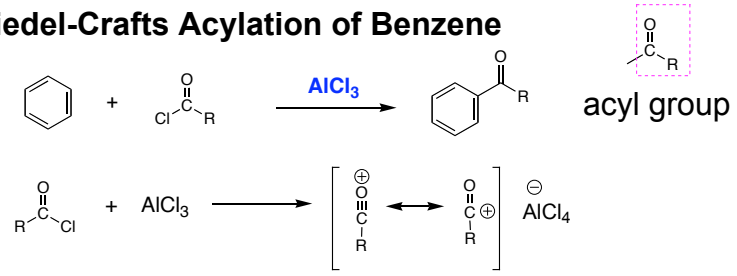


initial product is more reactive than benzene

major product

283

12.7: Friedel-Crafts Acylation of Benzene



acyl group

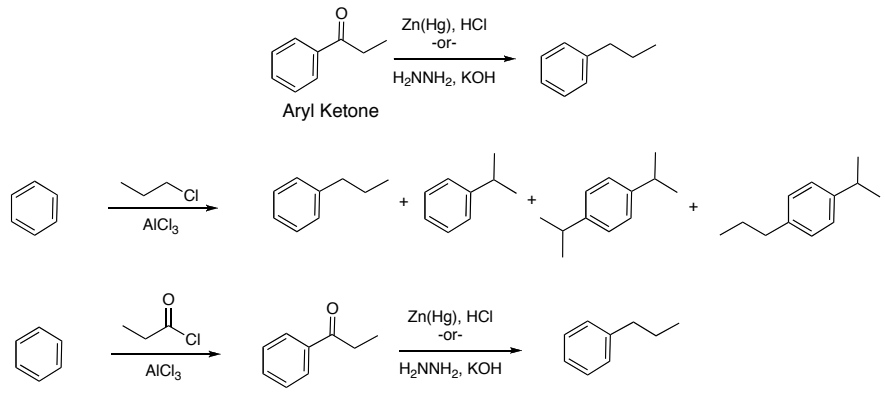
The acylated product is less reactive than benzene toward electrophilic aromatic substitution. F-C acylation can be stopped after one acyl group is added

284

12.8: Synthesis of Alkylbenzenes by Acylation-Reduction
Ketones and aldehydes can be reduced to the alkanes with:

Zn(Hg), HCl (Clemmensen Reduction)

H_2NNH_2, KOH (Wolff-Kishner Reduction)



Rearrangements and multiple alkylations are not observed for the F-C acylation

285

12.9: Rate and Regioselectivity in Electrophilic Aromatic Substitution - The nature of a substituent already present on the benzene ring affects the *rate* and *regioselectivity* (relative position) of electrophilic aromatic substitution.

A substituent (-X) is said to be ***activating*** if the rate of electrophilic aromatic substitution of the substituted benzene (C_6H_5X) is faster than benzene.

A substituent (-X) is said to be ***deactivating*** if the rate of electrophilic aromatic substitution of the substituted benzene (C_6H_5X) is slower than benzene.

Relative rate of nitration:

(trifluoromethyl)benzene

2.5×10^{-5}
deactivating

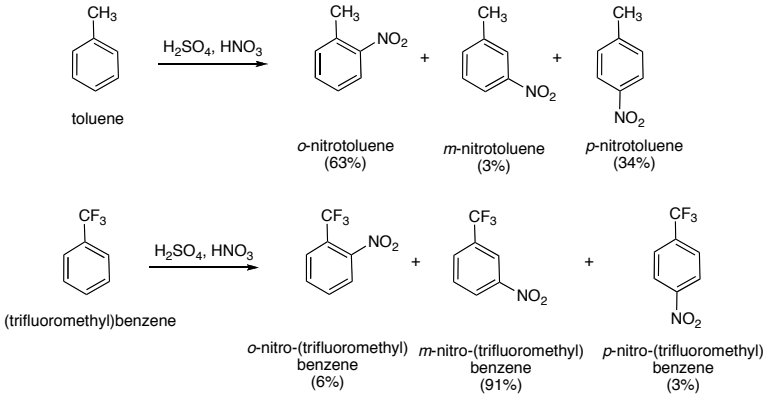
benzene

1

toluene

20-25
activating

286



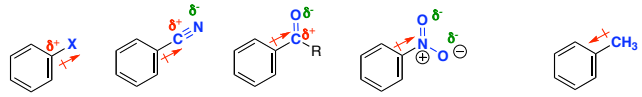
A substituent (-X) is said to be an *ortho-para director* if it directs an incoming electrophile to positions ortho and/or para to itself.

A substituent (-X) is said to be an *meta director* if it directs an incoming electrophile to position meta to itself.

287

Substituents are characterized as either electron-donating or electron-withdrawing and alter the electron density of the aromatic ring through:

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

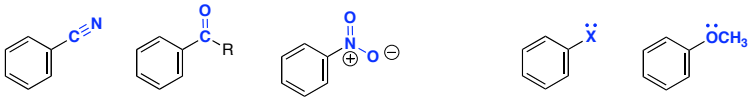


X= F, Cl, Br, I

Electron-withdrawing groups

Electron-donating group

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



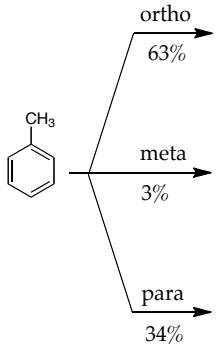
Electron-withdrawing groups

Electron-donating groups

288

The rate (activating or deactivating) and regiochemistry (ortho-para vs meta directing) can be understood by examining the influence of the substituent on the stability of the cyclohexa-dienyl cation intermediate.

12.10: Rate and Regioselectivity in the Nitration of Toluene: Regioselectivity: The carbocation intermediate from *o*- or *p*-addition can be stabilized by the substituent through inductive effects and hyperconjugation.



289

Activating groups increase the rate of electrophilic aromatic substitution at all positions of the ring.

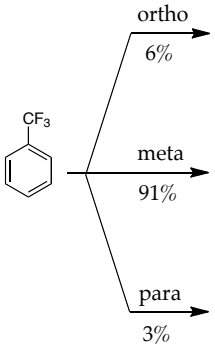
Partial rate factors - relative rate of electrophilic aromatic substitution compared to benzene

Electron rich aromatic rings are more nucleophlic.

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

290

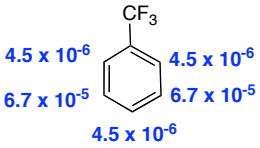
12.11: Rate and Regioselectivity in the Nitration of (Trifluoromethyl)benzene - Regioselectivity: The carbocation intermediate from *o*- or *p*-addition is destabilized by the electron-withdrawing substituent. This directs addition to the *m*-position.



291

Dactivating groups decrease the rate of electrophilic aromatic substitution at all positions of the ring.

Partial rate factors - relative rate of electrophilic aromatic substitution compared to benzene



Electron deficient aromatic rings are less nucleophlic.

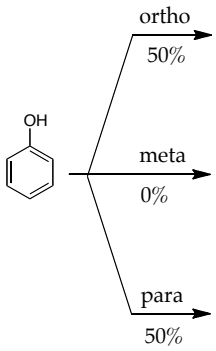
All deactivating group withdraw electrons through inductive effects and/or resonance. Electron-withdrawing groups destabilize the carbocation intermediate of electrophilic aromatic substitution.

292

12.12: Substituent Effects in Electrophilic Aromatic Substitution: Activating Substituents

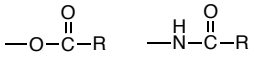
All activating substituents increase the rate of electrophilic aromatic substitution and are ortho-para directors.

Nitration of phenol: the -OH is a very strong activating group



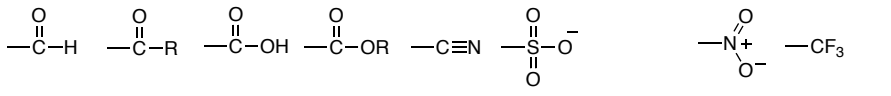
293

Substituents that have an O or N atom directly attached to the aromatic ring are strong activators. Phenol, anisole, and anilines are very strong activators and do not require strong Lewis Acid catalysts to undergo electrophilic aromatic substutution.

-alkyl, -vinyl, -aryl		-OH, -OCH_3, -NH_2
activators	strong activators	very strong activators

12.13: Substituent Effects in Electrophilic Aromatic Substitution: Strongly Deactivating Substituents

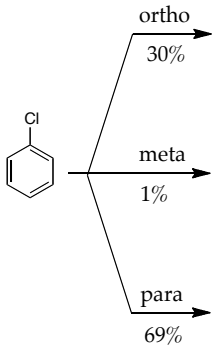
Strong deactivators are meta directors



strong deactivators	very strong deactivators

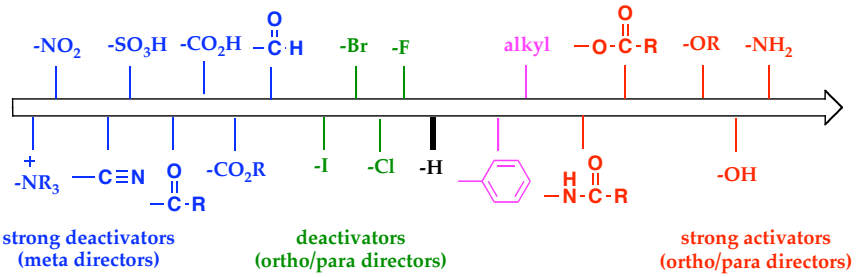
294

12.14: Substituent Effects in Electrophilic Aromatic Substitution: Halogens - 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), and are ortho-para directors.



295

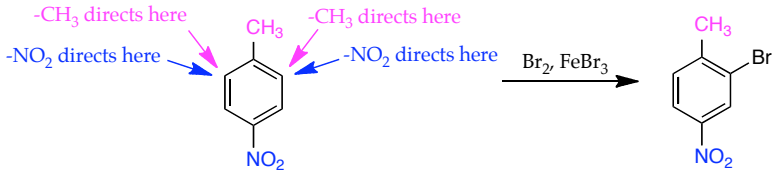
Table 12.2, p. 491



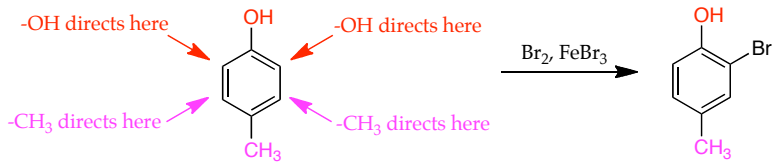
12.15: Multiple Substituent Effects - The individual directing effect of each substituent must be considered in order to determine the overall directing effect of a disubstituted benzene toward further electrophilic substitution.

296

1. When the individual directing effects of the two groups reinforce, further electrophilic substitution is directed to the common position.

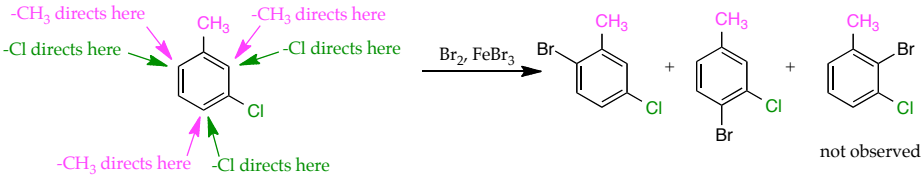


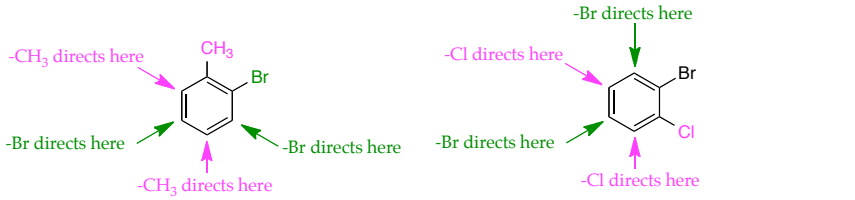
2. When the individual directing effects of two groups oppose, the stronger activating group has the dominant influence; however, mixtures of products are often produced.

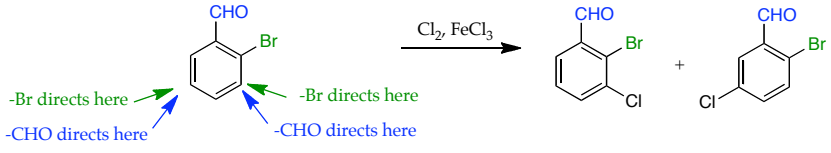


297

3. Further substitution between two existing substituents rarely occurs. Start with an ortho-disubstituted benzene to synthesize 1,2,3-trisubstituted benzenes







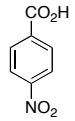
298

12.16: Regioselective Synthesis of Disubstituted Aromatic Compounds

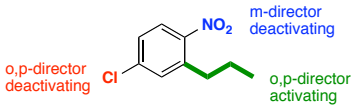
Consider the directing effects of the substituents to determine the order of their introduction to ensure the correct orientation

Friedel-Crafts reactions (alkylation, acylation) cannot be carried out on strongly deactivated aromatics

Sometimes electrophilic aromatic substitution must be combined with a functional group transformation



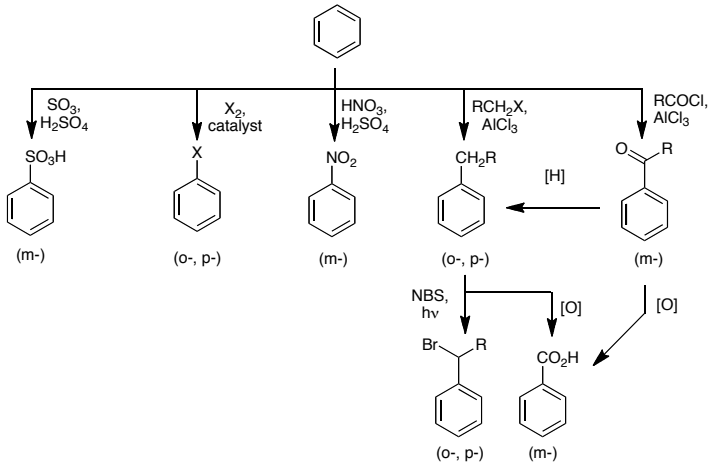
299



300

Summary of electrophilic aromatic substitution of benzene

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



12.17: Substitution in Naphthalene (please read)
12.18: Substitution in Heterocyclic Aromatic Compounds (please read)

301