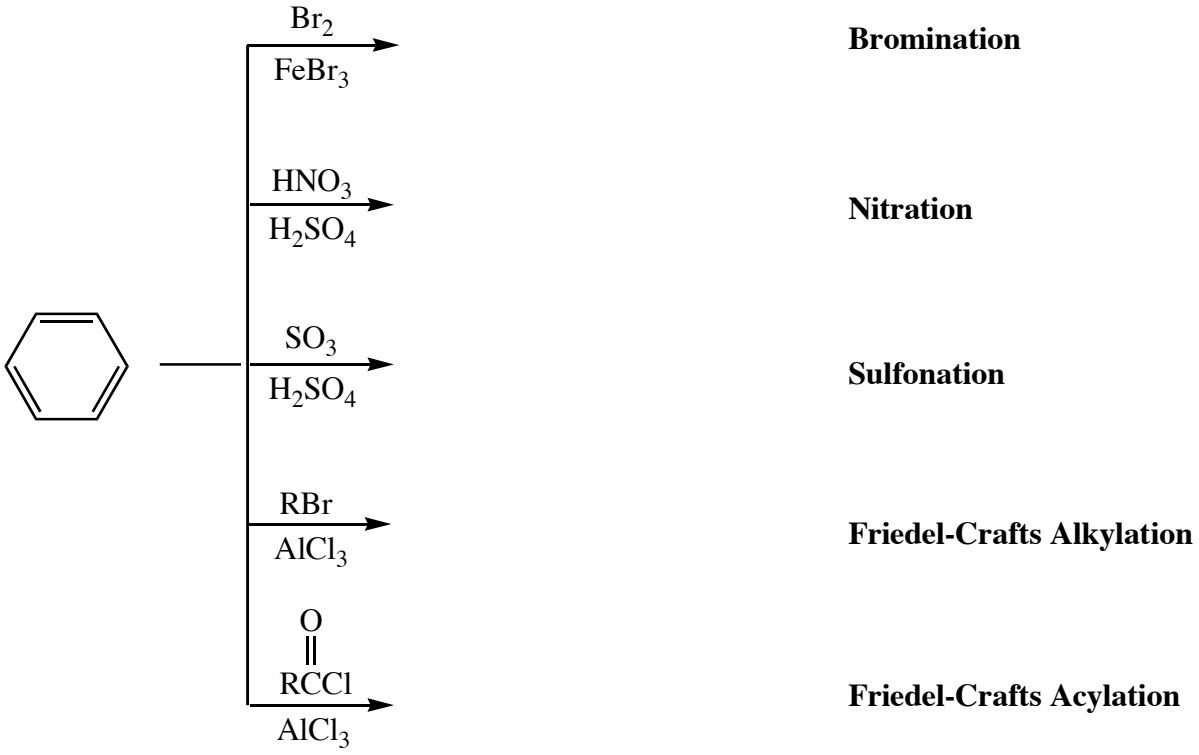
Lecture Notes
Chem 51B
S. King

Chapter 18 Electrophilic Aromatic Substitution

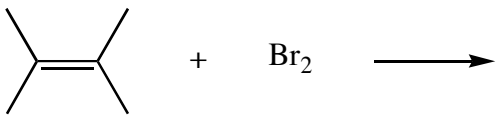
I. Electrophilic Aromatic Substitution

The most characteristic reaction of aromatic compounds is ***electrophilic aromatic substitution***, in which one of the ring hydrogens is substituted by a halogen, nitro group, sulfonic acid group, alkyl or acyl group.

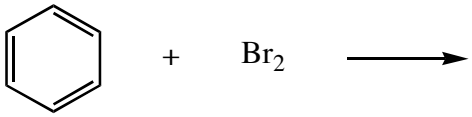


A. Chlorination & Bromination of Benzene

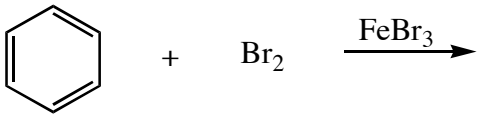
Recall:



With aromatic systems, Electrophilic Addition ***does not*** take place:



If a catalyst and heat is used, **Electrophilic Aromatic Substitution** occurs:



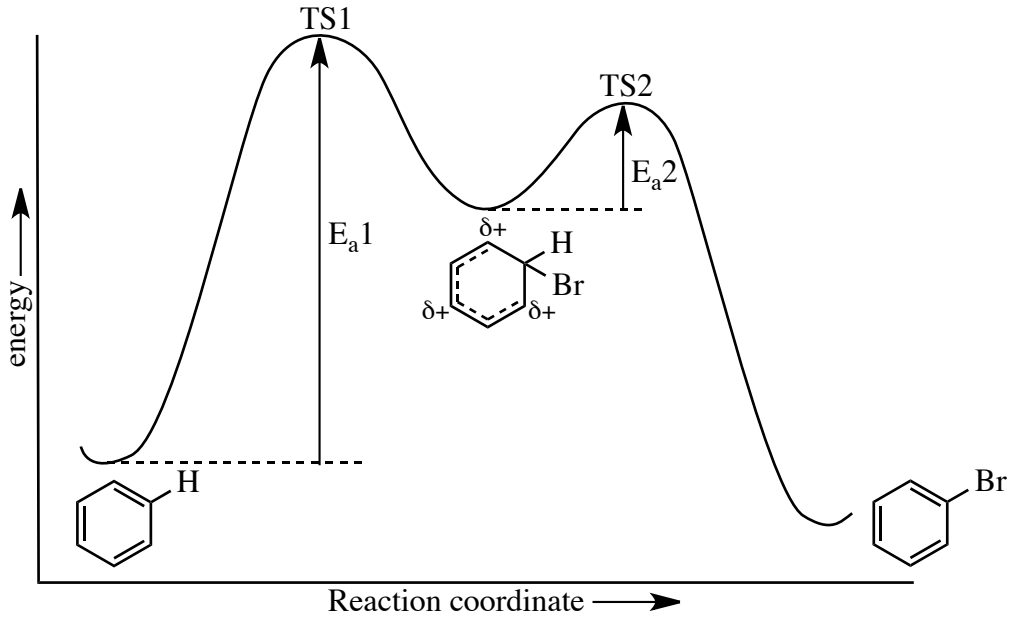
Mechanism:

Step 1: **Make Electrophile**

Step 2: **Benzene attacks electrophile to make a resonance-stabilized carbocation**

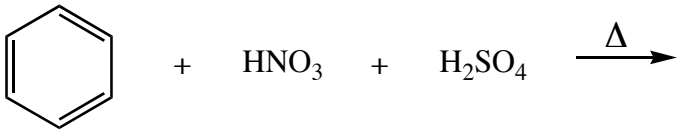
Step 3: **Regenerate Aromatic Ring**

Energy diagram:



B. Nitration of Benzene

Benzene reacts with hot concentrated nitric acid and sulfuric acid to yield nitrobenzene:



- In this reaction the electrophile is nitronium ion, which is created by protonation of HNO_3 by the strong acid sulfuric acid, followed by loss of H_2O.

Mechanism:

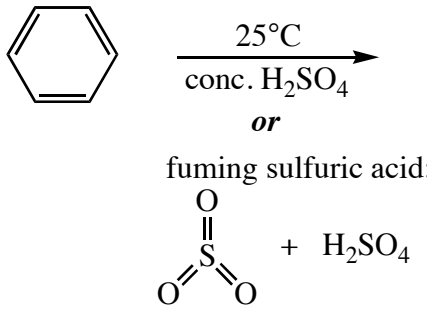
Step 1: **Make electrophile**

Step 2: **Benzene attacks**

Step 3: **Regenerate Aromatic Ring**

C. Sulfonation of Benzene

Benzene reacts with concentrated sulfuric acid or fuming sulfuric acid to produce benzenesulfonic acid.

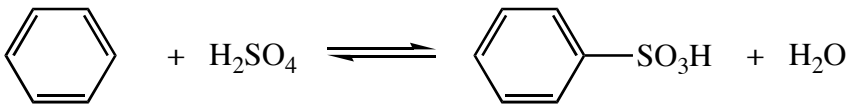


Mechanism:

Step 1: **Make electrophile**

Step 2, 3: **Benzene Attacks & Then Regenerate Aromatic Ring**

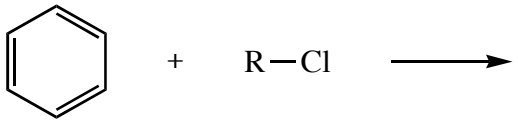
An interesting thing about aromatic sulfonic acids: Formation of an aromatic sulfonic acid is reversible, and can be driven in either direction!



II. Aromatic Substitution with Carbocations as Electrophiles

When carbon is cationic, it can also be an electrophile in aromatic substitution reactions.

A. Friedel-Crafts Alkylation

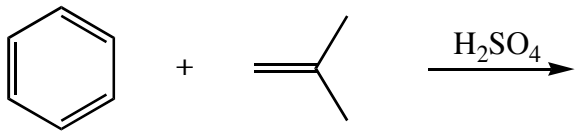


Mechanism:

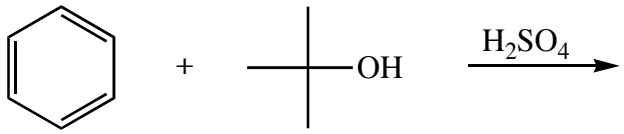
Step 1: **Make electrophile**

Step 2,3: **Benzene Attacks & Regenerate Aromatic Ring**

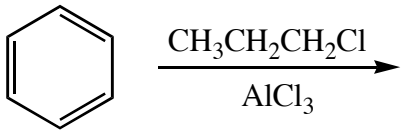
The carbocationic electrophile can also be formed by protonation of an alkene:



The carbocationic electrophile can also be formed by starting with an alcohol:



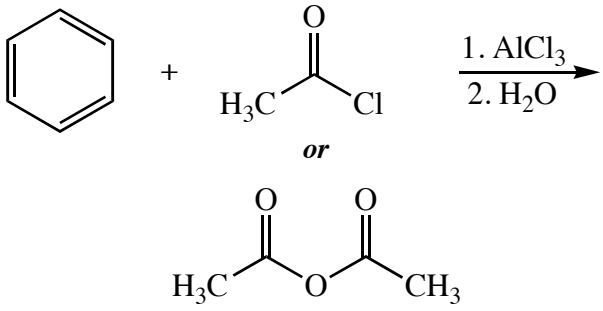
☞ Big Problem: *Carbocations like to rearrange!* Like other reactions involving carbocations, the Friedel-Crafts alkylation is susceptible to carbocationic rearrangement.



Mechanism for carbocation rearrangement:

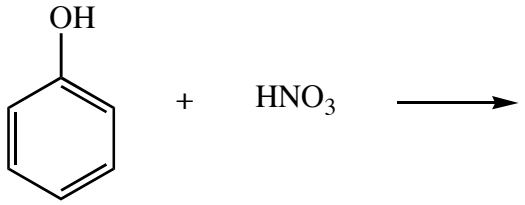
B. Friedel-Crafts Acylation

Acid chlorides and acid anhydrides also serve as sources of electrophiles for Friedel-Crafts reactions.

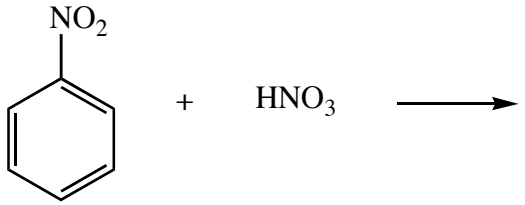


Mechanism:

III. Substituent Effects in Electrophilic Aromatic Substitution



compare with:



✻✻ A group that is already present on a benzene ring may make it ***easier*** or ***harder*** to introduce new substituents, and can ***direct*** where the new substituents will go.

A. Ring Activating: A group that makes it ***easier*** to introduce new substituents is **ring activating**. Ring activating substituents are **<u>ELECTRON DONATING</u>.**

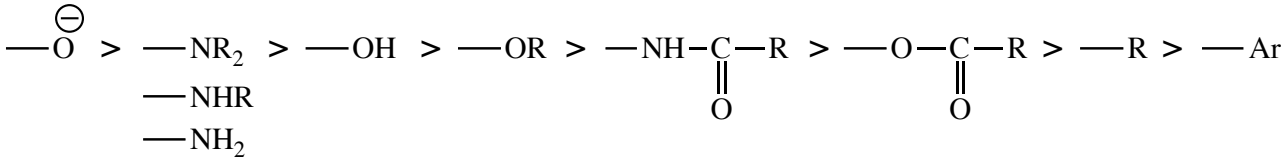
$$-\overset{\ominus}{O} > -NR_2 > -OH > -OR > -NH-\overset{\overset{O}{\|}}{C}-R > -O-\overset{\overset{O}{\|}}{C}-R > -R > -Ar$$
$$-NHR$$
$$-NH_2$$

B. Ring Deactivating: A group that makes it ***harder*** to introduce a second substituent is ring deactivating. Ring deactivating substituents are **<u>ELECTRON WITHDRAWING</u>.**

$$-NO_2 \approx -\overset{+}{N}R_3 > -CF_3 > -CCl_3 > -SO_3H > -C\equiv N > -\overset{\overset{O}{\|}}{C}-R$$
$$-\overset{+}{N}HR_2$$
$$-\overset{+}{N}H_2R$$
$$-\overset{+}{N}H_3$$

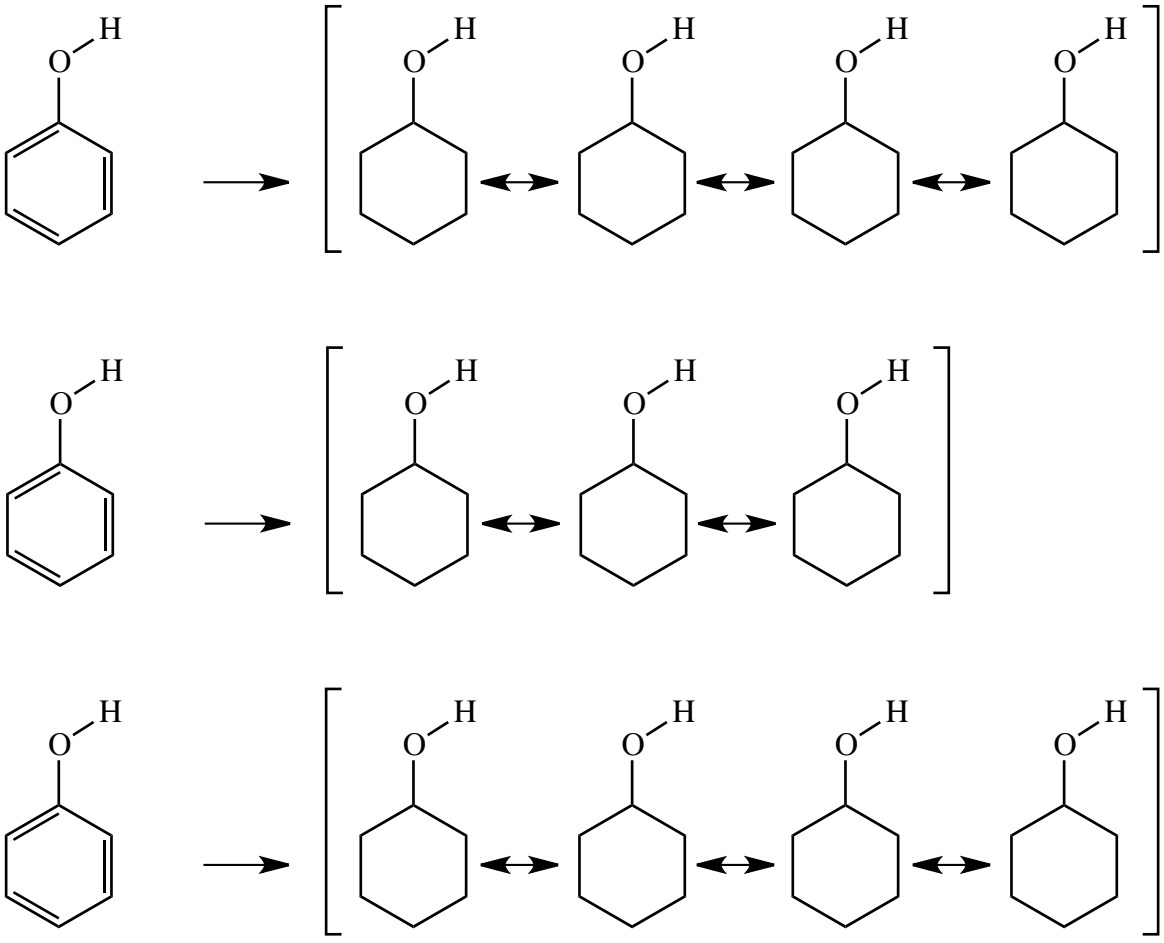
(ketone, aldehydes amides, esters, carboxylic acids)

Rule 1:	**Ring activating substituents** direct incoming substituents into the *o,p-* positions. They are "**ortho, para directing**."

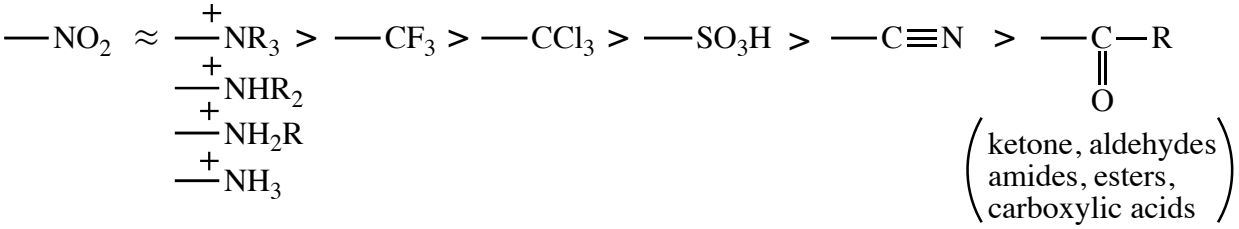


Reasoning: An electron donating group stabilizes the cationic intermediate only when it is *ortho* or *para* to the site of substitution.

Look @ the resonance structures:

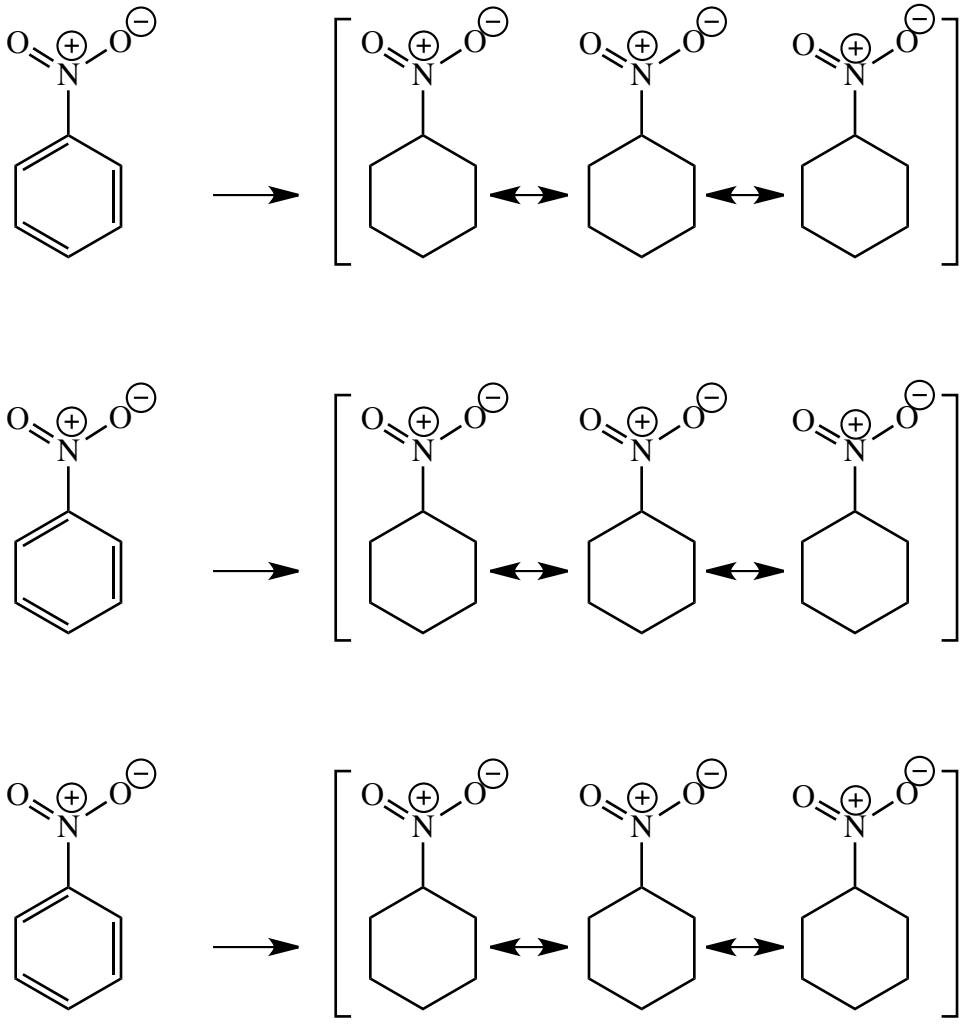


Rule 2:	**Ring deactivating substituents** direct incoming substituents into the *m* -position. They are **"meta directing."**



Reasoning: The meta position is the *least* destabilized**.**

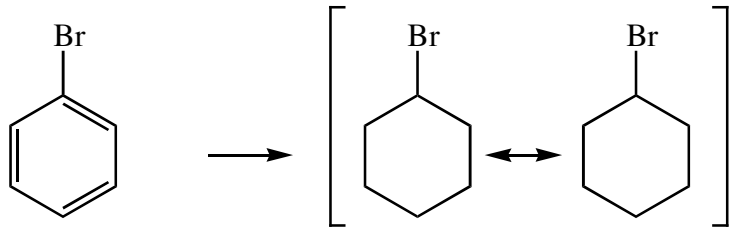
Look @ the resonance structures**:**



Rule 3: **Halogens** are slightly deactivating but **ortho, para directing.**

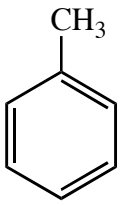
With halogens, there is a strong inductive effect:

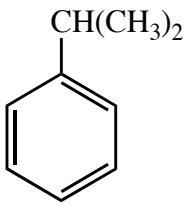
& a weak resonance effect:



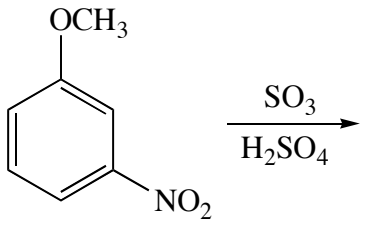
C. Effect of Sterics and More than One Substituent:

1. With *o, p* -directors, *para* will predominate as substituents and incoming reagents get larger:





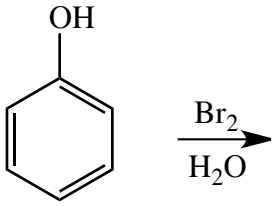
2. When the directing effects of two or more substituents conflict, the one that is ***strongly activating and o,p- directing*** determines the orientation of the new substituent.



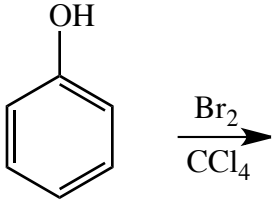
IV. Additional Considerations Regarding Substituent Effects

A. Methoxy, Hydroxy, and Amine Substituents

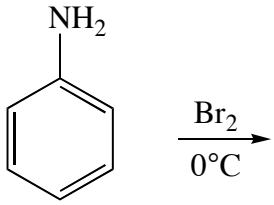
Methoxy, hydroxy, and amine substituents are so strongly activating that halogenation is carried out without the Lewis acid catalyst ($FeBr_3$ or $FeCl_3$). Even without a catalyst, multiple halogenation is observed.



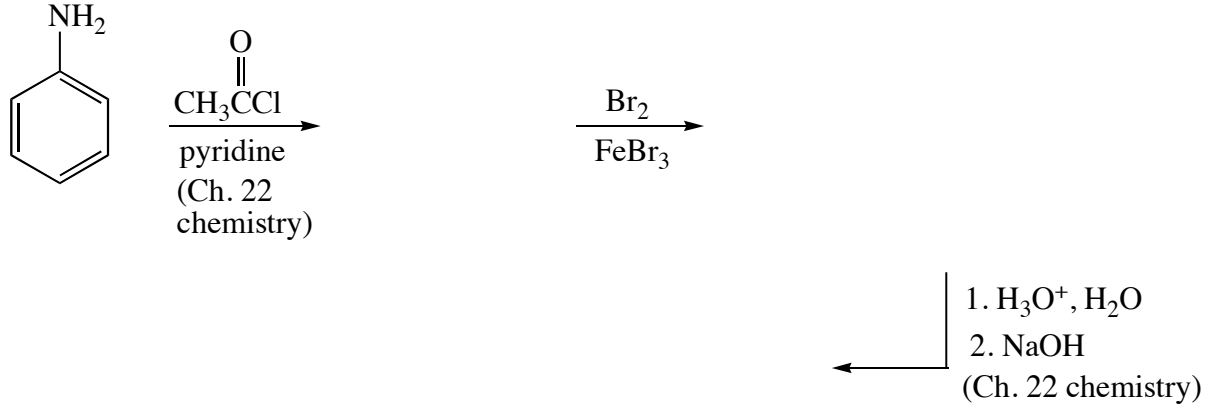
Solution: To monohalogenate phenol, run the reaction in a nonpolar solvent such as CCl_4 without added catalyst:



Amine substituents give multiple halogenation even at low temperature without added catalyst:



Solution: **Acylate the amine.** This turns the ring from strongly activated to moderately activated and allows monohalogenation:

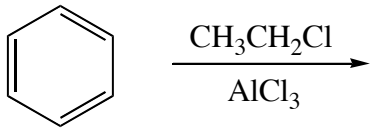


Q. How is the amine converted into an amide?

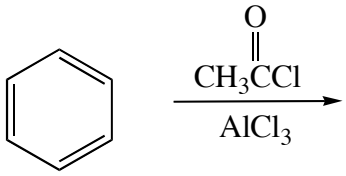
A. An addition/elimination reaction, with a mechanism similar to the mechanism thionyl chloride reacting with an alcohol.

B. Friedel-Crafts Alkylation & Acylation

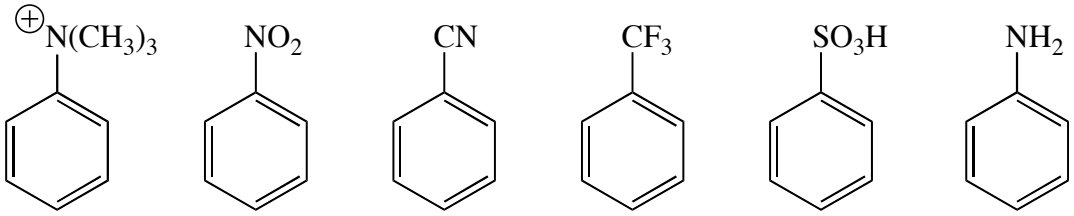
1. In the Friedel-Crafts alkylation reaction, overalkylation is a problem! *(the product is more reactive than the starting material - must use **large excess** benzene to avoid)*.



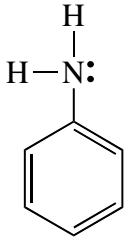
2. Overacylation is not a problem in the Friedel-Crafts acylation reaction.



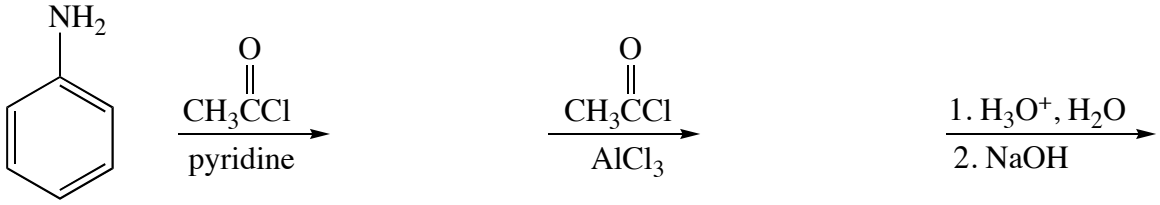
3. Deactivated, meta directing benzene derivatives *and* aniline derivatives give poor yields of Friedel-Crafts products and should not be used in this reaction.



Why aniline derivatives?? The amino groups -NH_2, -NHR, and NR_2 are changed into powerful deactivating groups by the Lewis acids used to catalyze Friedel-Crafts reactions.



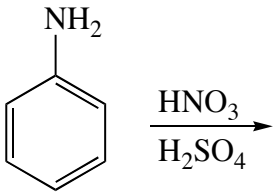
Solution: **Acylate the amine.** This turns the ring from strongly activated to moderately activated and allows Friedel-Crafts reactions to take place:



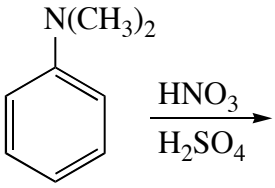
C. Nitration of Aniline Derivatives

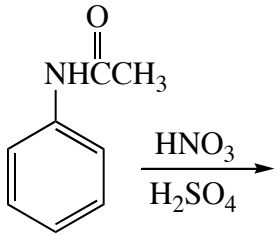
Aniline derivatives cannot be nitrated because nitric acid is an oxidizing agent and primary amines are easily oxidized (nitric acid and aniline can be explosive). Only tertiary aromatic amines and acetamide derivatives can be nitrated.

Don't do this:

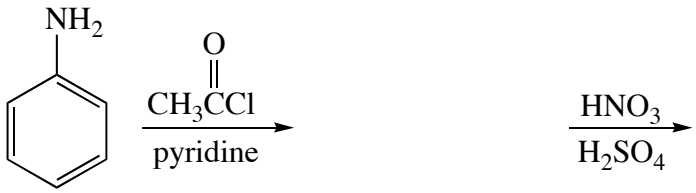


*These **do** work:*



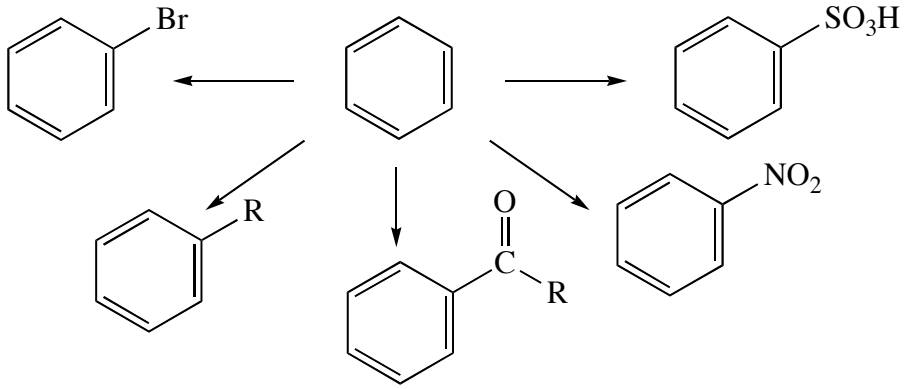


Solution for 1° Amines: **Acylate the amine.**



V. Reactions of Substituents on Benzene

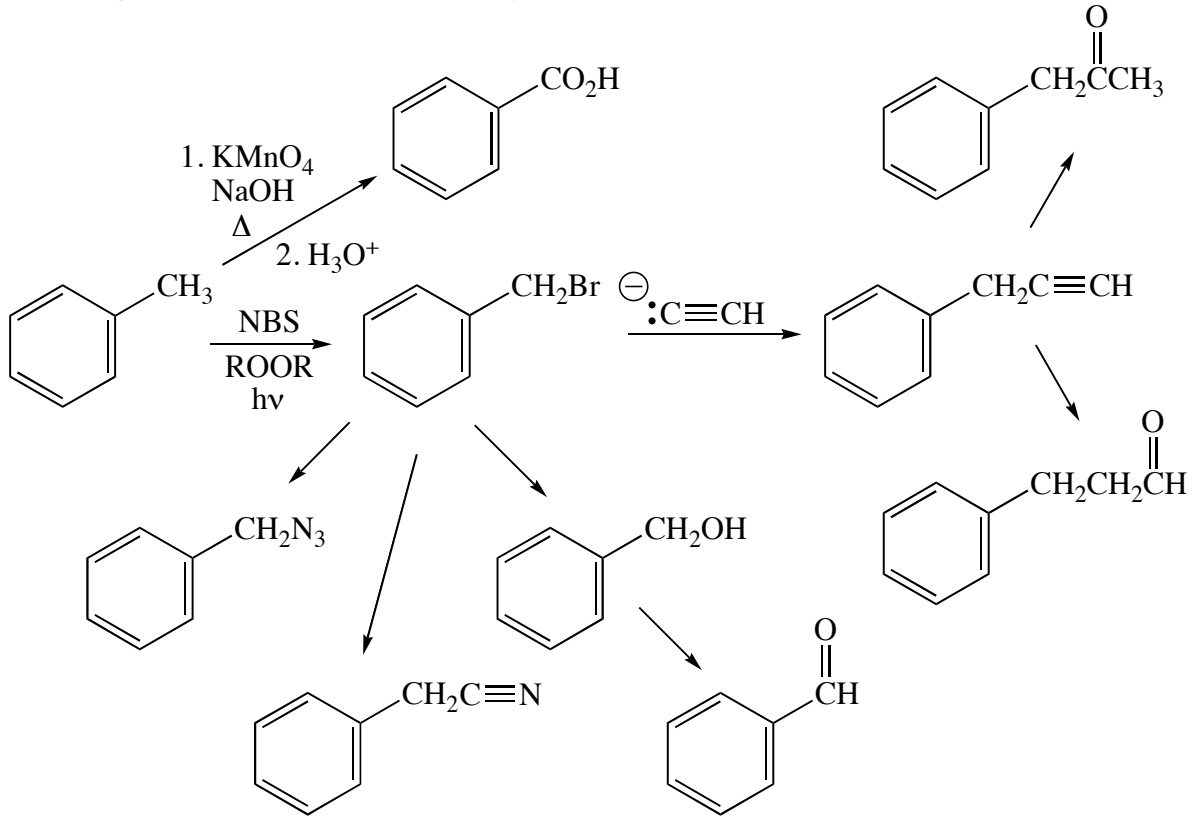
We now know how to convert benzene into a variety of substituted benzene derivatives:

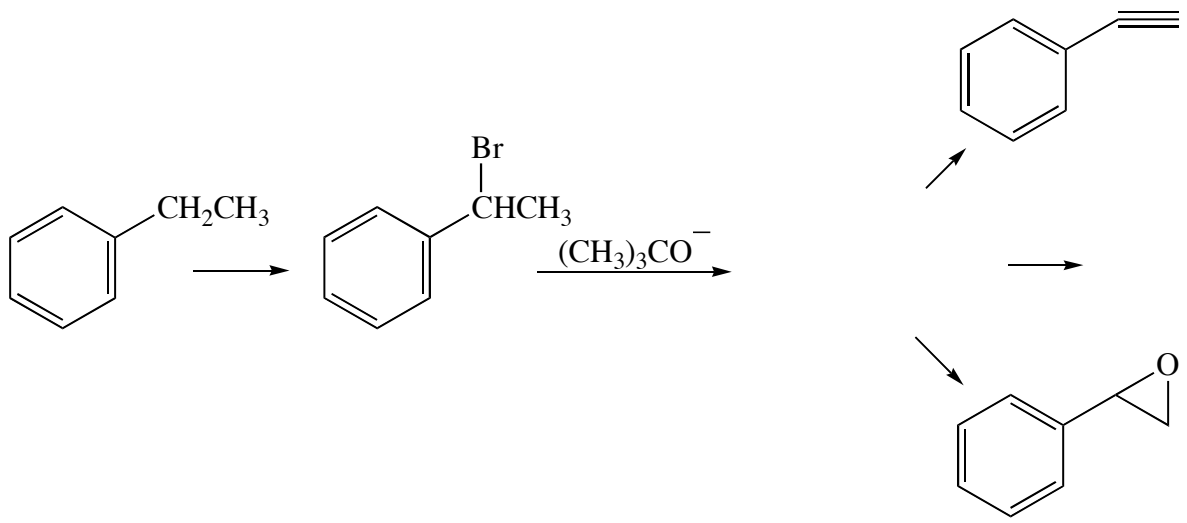


Benzene rings with other substituents can be made by converting these substituted benzene derivatives into other functional groups using chemistry from chapters 7, 8, 9, 10, 11, 12, 15, 16.

A. Reactions of Alkyl Substituents on Benzene

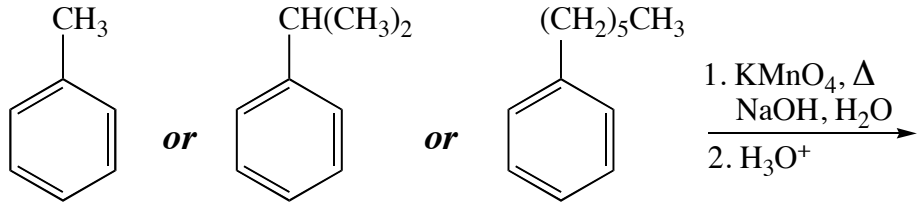
Alkyl substituents on benzene can be converted into many other functional groups using reactions we have already talked about.

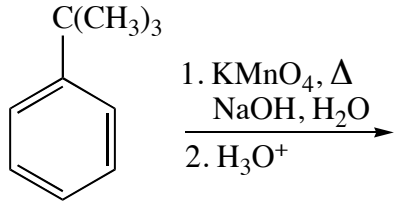




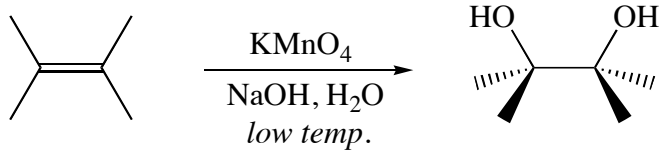
B. Oxidation of Alkyl Groups Bonded to Aromatic Rings

An alkyl group bonded to a benzene ring can be oxidized to a carboxylic acid. commonly used oxidizing agents are $KMnO_4$ or $Na_2Cr_2O_7/H_3O^+$.



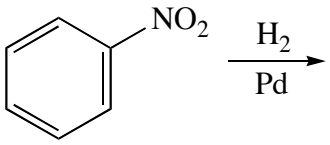


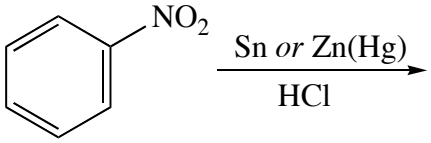
compare with:



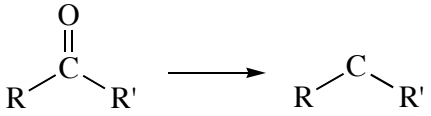
C. Reduction of Substituents Bonded to Benzene

A nitro substituent can be reduced used catalytic hydrogenation or by using a metal *(tin, iron or zinc)* plus HCl. The product is aniline.

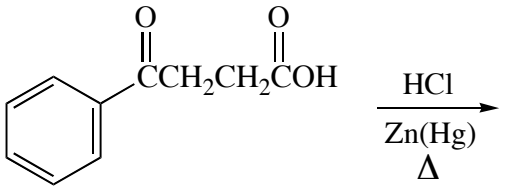




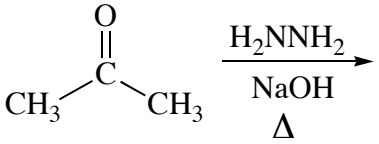
A ketone or aldehyde can be reduced used **Clemmensen** or **Wolff-Kishner** reduction. *These reagents **do not** reduce esters, carboxylic acids, amides or acid chlorides.*



1. Clemmensen Reduction (HCl, Zn/Hg):



2. Wolff-Kishner Reduction (H_2NNH_2, KOH):



Q. Why 2 ways to do the same reduction?
A. Sometimes you have acid sensitive or base sensitive groups elsewhere in the molecule.

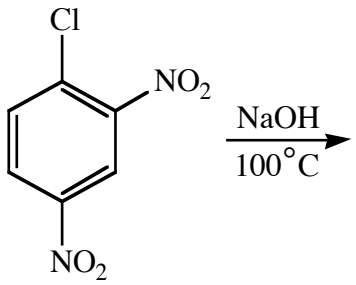
Clemmensen Reduction:

Wolff-Kishner Reduction:

Both methods <u>ONLY WORK FOR ALDEHYDES AND KETONES</u>!!!! You cannot use these methods with esters or other carboxylic acid derivatives!!!!

VI. Nucleophilic Aromatic Substitution *via* Addition/Elimination

Aromatic rings do not react easily with nucleophiles. Nucleophiles ***can*** displace aryl halides in ***highly deactivated benzene derivatives*** via an addition/elimination mechanism.



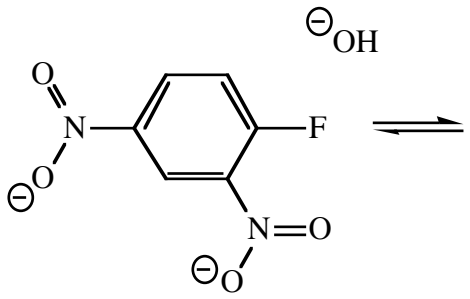
Characteristics of Reaction:

- Strong nucleophile required.
- Reaction ***cannot*** proceed by S_N1 (formation of an aryl cation) because the EWG would destabilize this intermediate.

- Reaction ***cannot*** proceed by S_N2: Like vinyl halides, aryl halides cannot achieve the correct geometry for backside displacement (aromatic ring blocks approach of the nucleophile to the back of the carbon bearing the L.G

- Fluoride is a much better L.G. than iodide ion in this reaction.

Mechanism: Addition Elimination:



Q. Why is fluoro a better L.G. in this reaction?

A. Two reasons:

1. **F** is more electronegative than **I**.

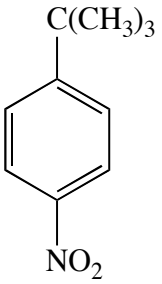
2. **F** is much smaller ∴ there is less steric hindrance to the approaching nucleophile that will bond to carbon and give a tetrahedral intermediate.

VI. Synthetic Applications of Electrophilic Aromatic Substitution

When planning a synthesis involving Electrophilic Aromatic Substitution, a couple of things need to be kept in mind:

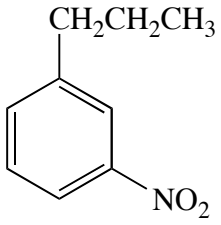
1. Careful attention must be paid to the order in which the reactions are carried out!

Example: Synthesize the following compound from benzene:



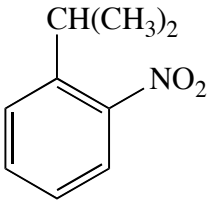
2. *Functional group manipulation can convert substituents on benzene into other functional groups that have the desired directing properties.*

Example: Synthesize the following compound from benzene:



3. The sulfonyl group can be used as a blocking or directing group, which can be easily removed once it has served its purpose.

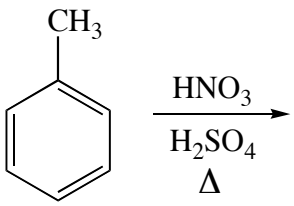
Example: Synthesize the following compound from benzene:



☞ *To add multiple NO_2 groups to the ring, use more HNO_3, H_2SO_4, and increase Δ!*

Q: Why is extra heat needed?
A:

Example:



4. Consider multiple pathways when more complicated syntheses are desired.

Example: Synthesize the following compound from benzene: