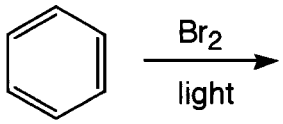
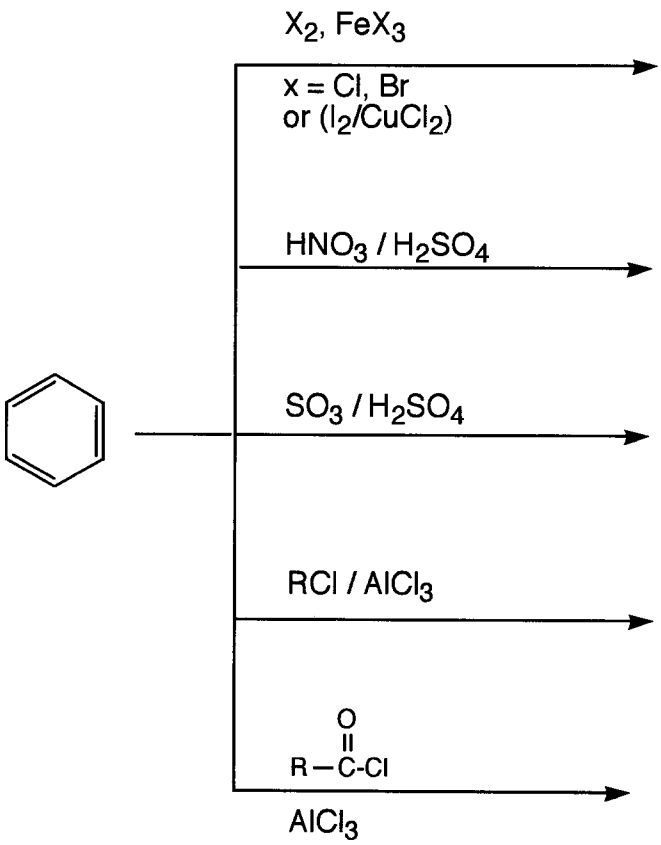
Bean 5
chem 3332

Chapter 17: Reactions of Aromatic Compounds

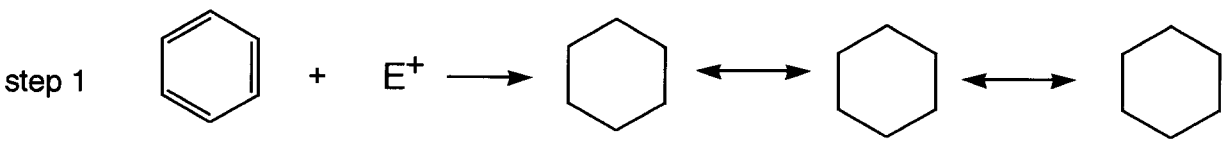
Benzene resists the electrophilic addition reactions common to alkenes and alkynes.

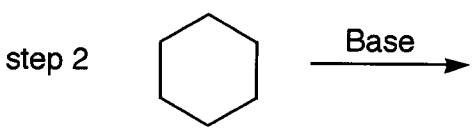


Electrophilic Aromatic Substitution: Benzene does react with electrophiles.



General Mechanism:





Electrophilic Aromatic Substitution Reactions of Benzene

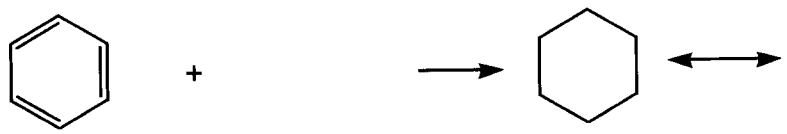
I. Halogenation

A. Catalyst -

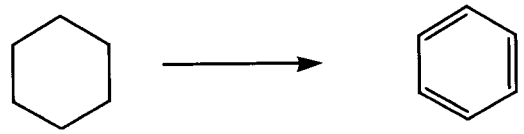
B. Mechanism:

step 1 (generation of electrophile, E^+):

step 2



step 3



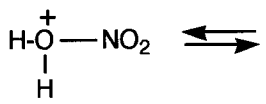
II. Nitration

A. Catalyst -

B. Mechanism:

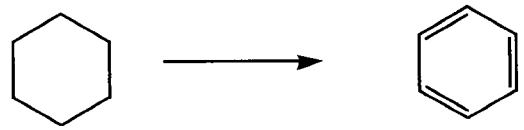
step 1 (generation of E^+)

step 2



step 3

step 4

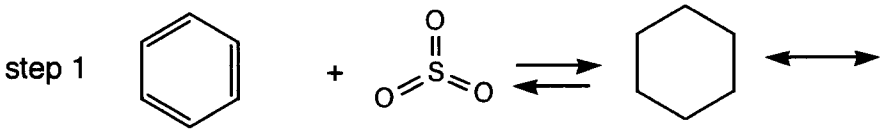


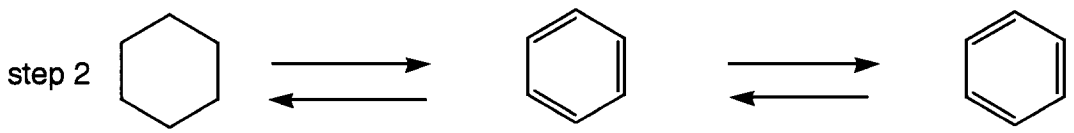
III. Sulfonation

A. $E^+ = SO_3$

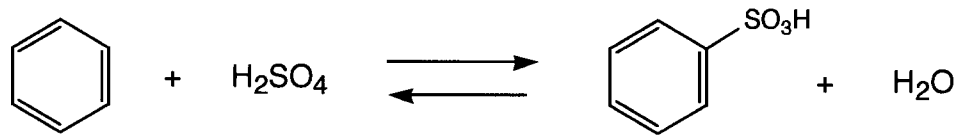
Pure H_2SO_4 contains a small amount of SO_3:

B. Mechanism:



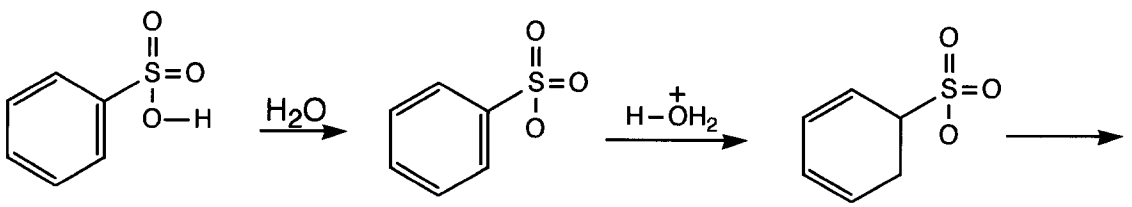


C. Desulfonation - All steps of sulfonation are reversible.
- Position of EQ can be influenced by reaction conditions.

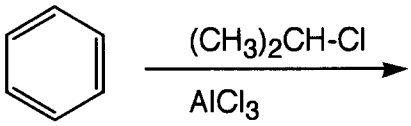


sulfonation:

desulfonation:



IV. Friedel-Crafts Alkylation

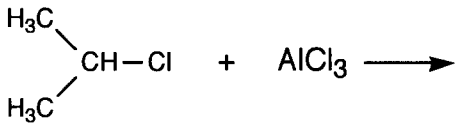


A. Catalyst -

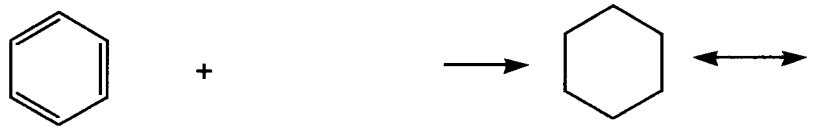
B. E^+ is a carbocation or carbocation-like species.

C. Mechanism:

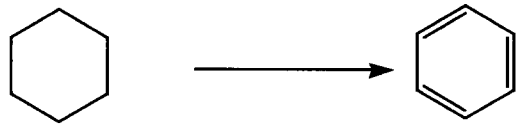
step 1 (generation of E^+)



step 2

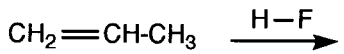


step 3



D. Other methods of generating the carbocation

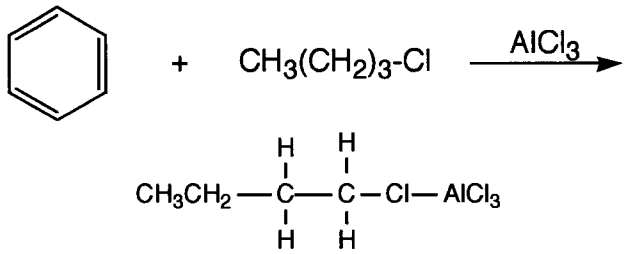
1. alkene + hydrohalic acid (HF is best)



2. alcohol + BF_3

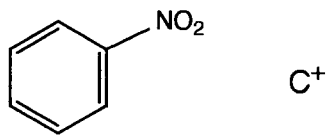
E. Limitations of F-C Alkylation

1. Carbocations that can rearrange, will!

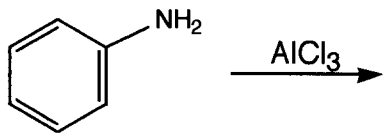


2. F-C reactions will not occur if strong electron withdrawing (deactivating) groups of either of two types are on the ring.

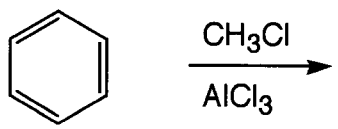
a. any deactivating group stronger than halogen (-NO_2, -SO_3H, -CO_2H, -CN, -$\overset{O}{\overset{\|}{C}}$-R, -$\overset{O}{\overset{\|}{C}}$-H, -$\overset{+}{N}R_3$)



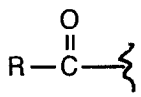
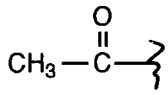
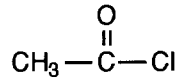
b. Lewis acid-base adduct formed from amino groups (-NH_2, -NHR, -NR_2)

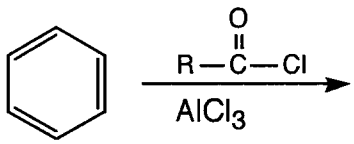


3. Polyalkylation is difficult to control, because alkyl groups are activators.

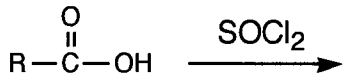


V. Friedel-Crafts Acylation - solves some problems with F-C alkylation

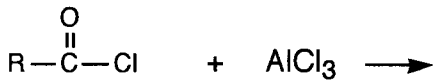






A. Synthesis of a necessary reagent - the acyl chloride

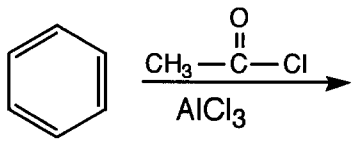


B. Generation of E^+

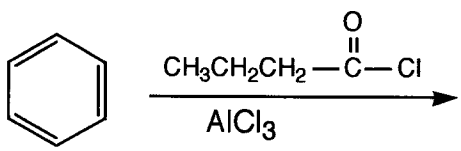


C. Advantages of acylation over alkylation

1. Polyacylation is not a problem.

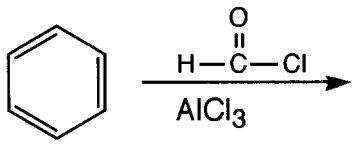


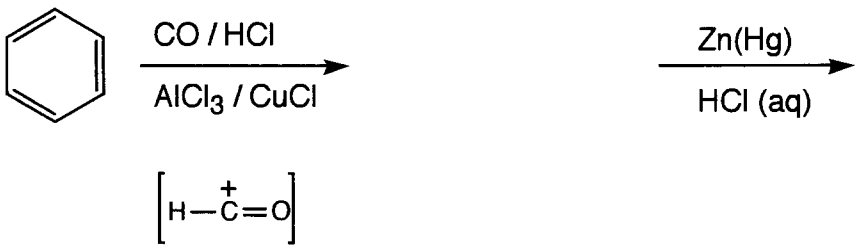
2. No C^+ rearrangement, so F-C acylation is the best method for synthesizing unbranched alkylbenzenes.



F-C Acylation, continued

D. Gatterman-Koch Formylation: The **Proper** Synthesis of Benzaldehyde





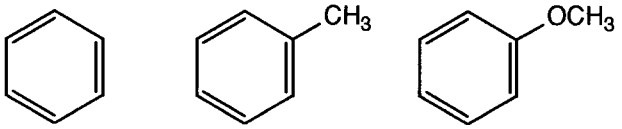
REACTIONS OF SUBSTITUTED BENZENES

How does a substituent on the benzene ring affect the 5 EAS reactions?

I. Reactivity (reaction rate): 2 types of substituents

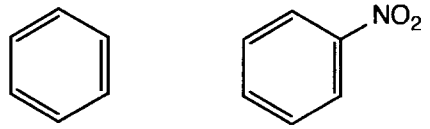
Activating

causes ring to be more reactive than benzene



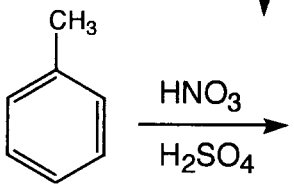
Deactivating

causes ring to be less reactive than benzene

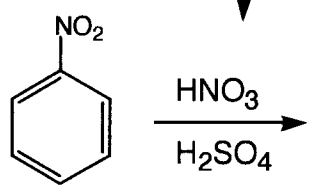


II. Orientation of the incoming group: 2 types of substituents

ortho/para directors

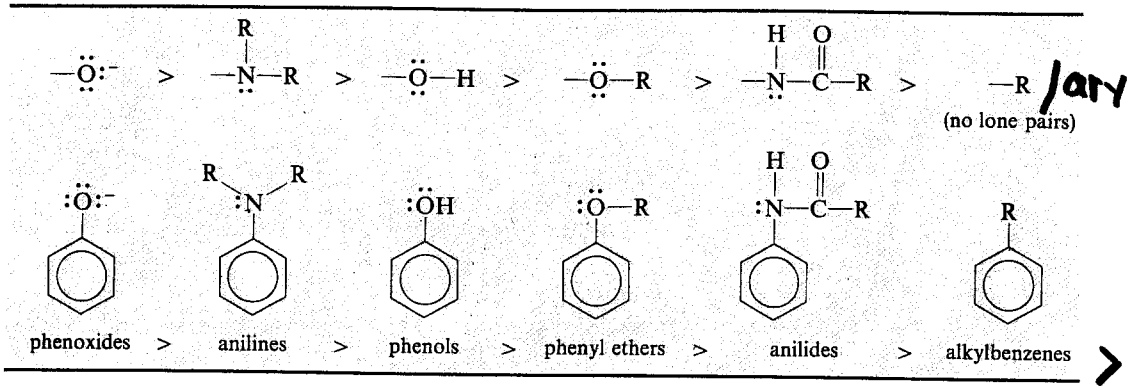


meta directors



Exception:

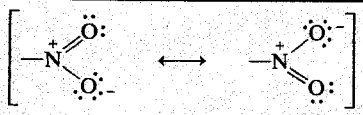
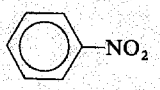
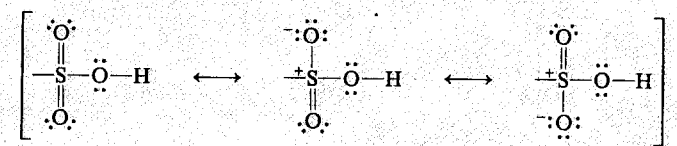
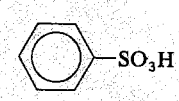
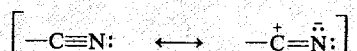
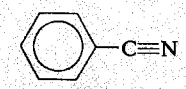
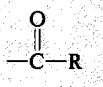
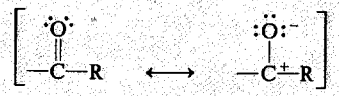
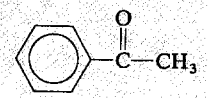
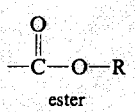
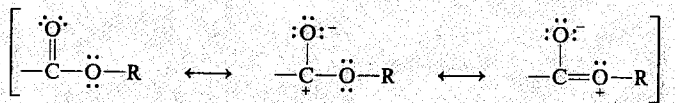
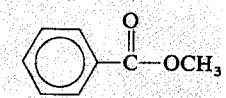
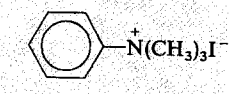
ACTIVATING ORTHO, PARA DIRECTORS T94



aryl / C=C / C≡C

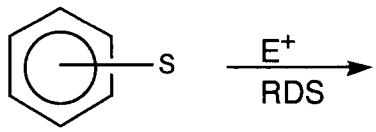
halogens > -C(=O)-H > -C(=O)-OR > -C(=O)-OH > -C(=O)-R > -SO3H > -C≡N > -NO2 > -NR3+

DEACTIVATING META-DIRECTORS

Group	*Resonance Structures*	*Example*
$-NO_2$ nitro		 nitrobenzene
$-SO_3H$ sulfonic acid		 benzenesulfonic acid
$-C{\equiv}N$: cyano		 benzonitrile
 ketone or aldehyde		 acetophenone
 ester		 methyl benzoate
$-\overset{+}{N}R_3$ quaternary ammonium		 trimethylanilinium iodide

Substituents as Activators / Deactivators

How do substituents affect reactivity?



an electron releasing substituent:

an electron withdrawing substituent:

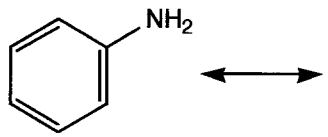
The electron release or withdrawl takes place in two ways.

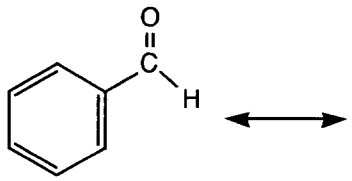
I. Inductive: differences in the electronegativities of the atoms

—CH_3

—Cl

II. Resonance:

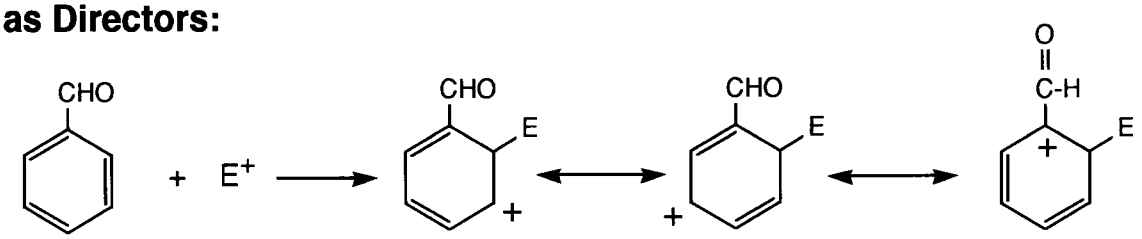
activator 

deactivator 

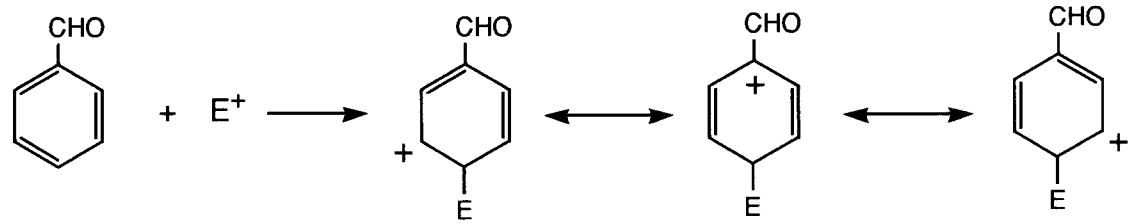
Substituents as Directors:

Meta Directors:

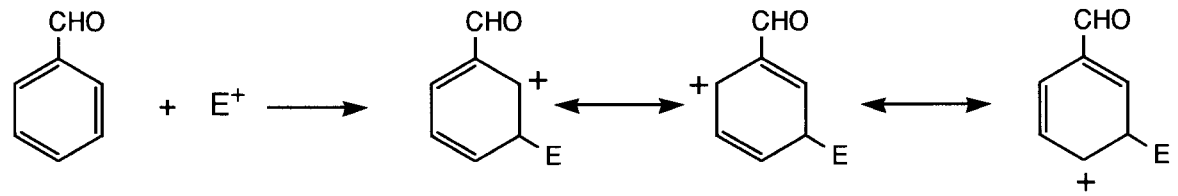
Ortho result



Para result

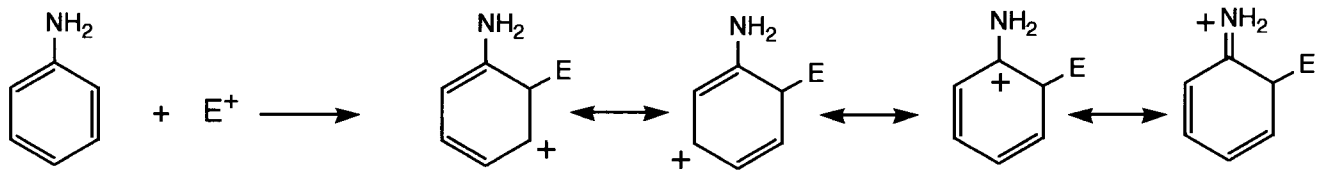


Meta result

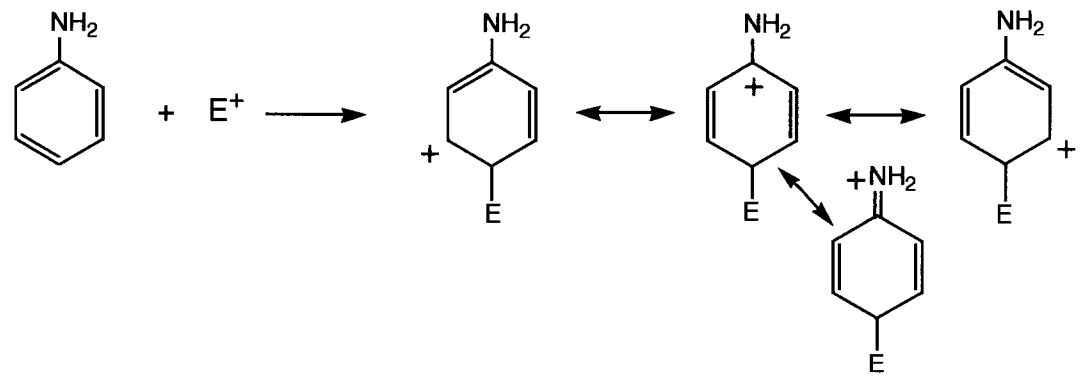


Ortho/Para Directors:

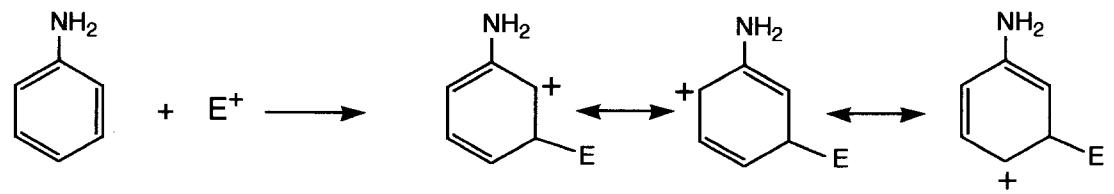
Ortho result



Para result

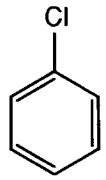


Meta result

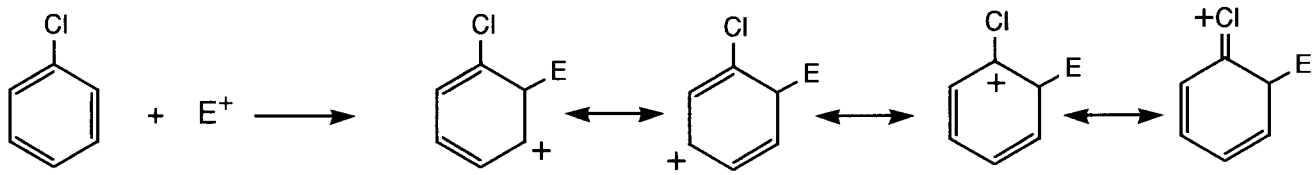


The Special Case of the Halogens:

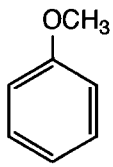
Deactivating:



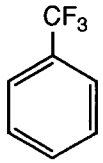
Ortho / Para Directing:



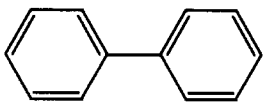
Examples:

1. 

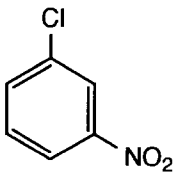
$\xrightarrow[H_2SO_4]{HNO_3}$

2. 

$\xrightarrow{\text{fuming } H_2SO_4}$

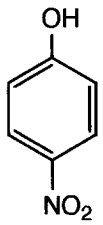
3. 
$\xrightarrow[AlCl_3 \,/\, CuCl]{HCl \,/\, CO}$

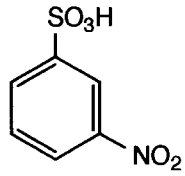
Synthetic Applications:



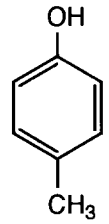
Orientation in Disubstituted Benzenes

I. The "No Brainer" Case:

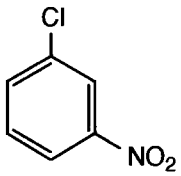




II. A Bigger Challenge:

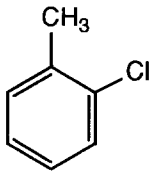


SO_3 / H_2SO_4 →

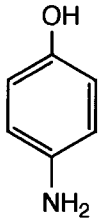


SO_3 / H_2SO_4 →

III. The Biggest Challenge:

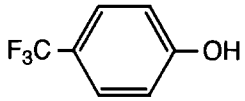


SO_3 / H_2SO_4 →

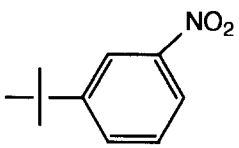


$Br_2 / FeBr_3$ →

Examples:

1. 

$Br_2 / FeBr_3$ →

2. 

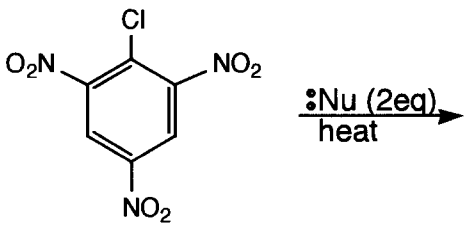
HNO_3 / H_2SO_4 →

NUCLEOPHILIC AROMATIC SUBSTITUTION OF ARYL HALIDES

- NO S_N2 on sp^2!!! (or S_N1 either!)

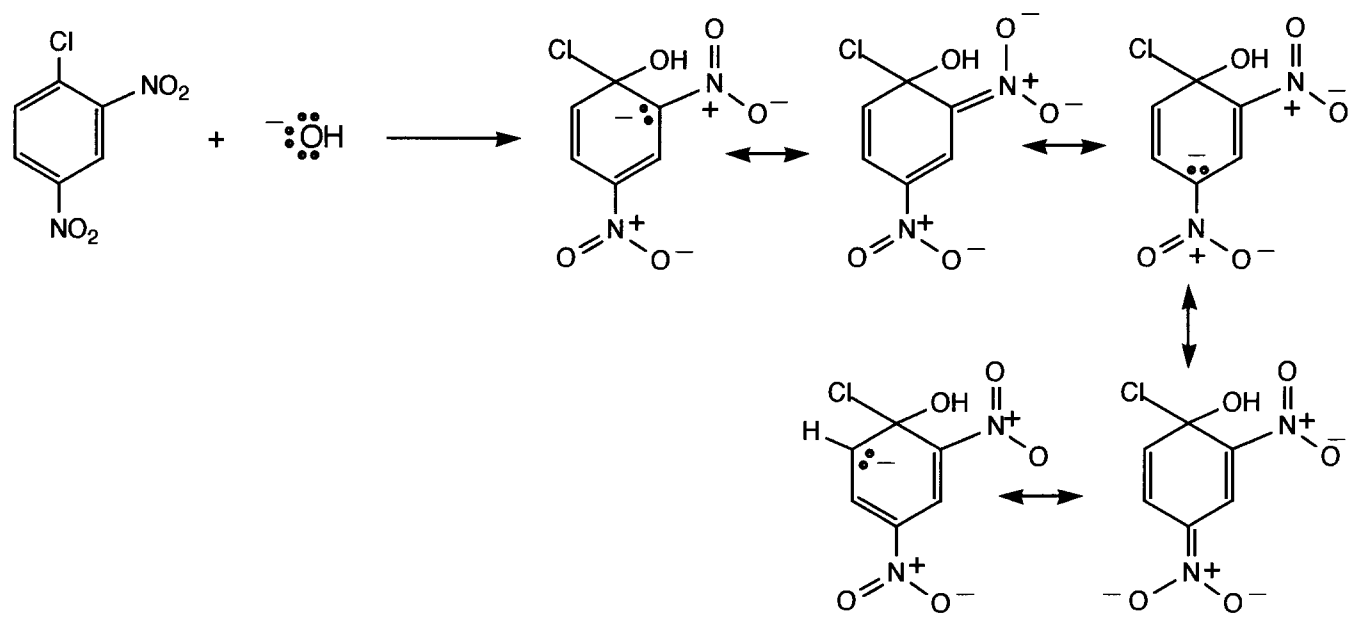
Two pathways:

I. **Addition / Elimination Mechanism** - takes place if strong electron withdrawing (deactivating) groups are ortho and/or para to the halide; the more deactivators, the faster the reacton rate

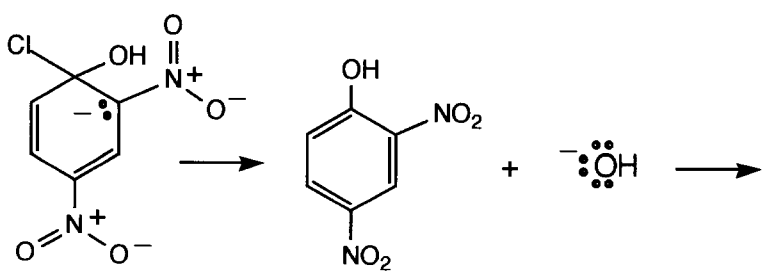


Nu =

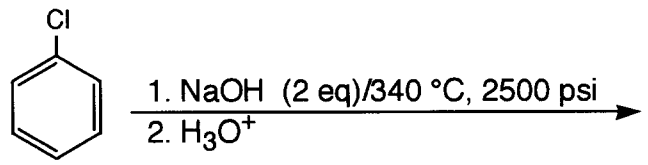
addition:



elimination:



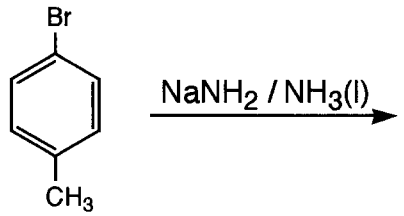
II. Elimination / Addition - takes place when there are **NO** strong electron withdrawing (deactivating) groups **ortho or para** to the halide; requires harsh conditions



Nu =

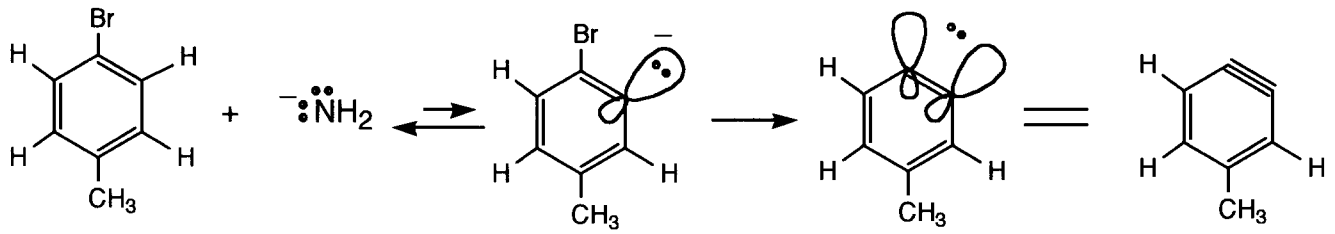
unusual intermediate:

evidence:

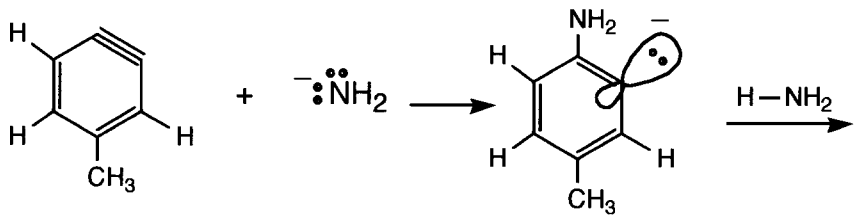


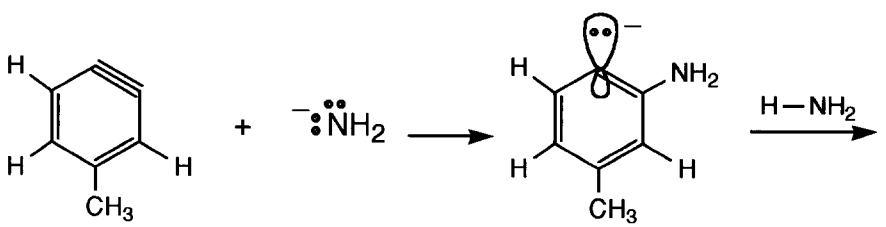
Mechanism:

elimination:



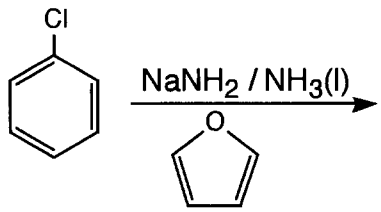
addition:





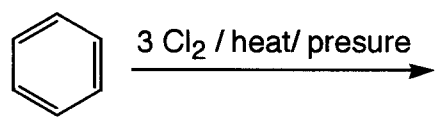
Evidence for Benzyne Existence:

Add furan to reaction mixture:

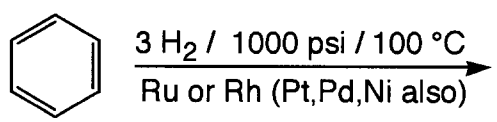


ADDITION REACTIONS OF BENZENE

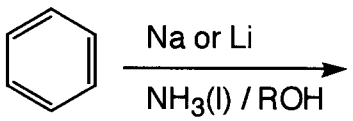
I. Chlorination of Benzene



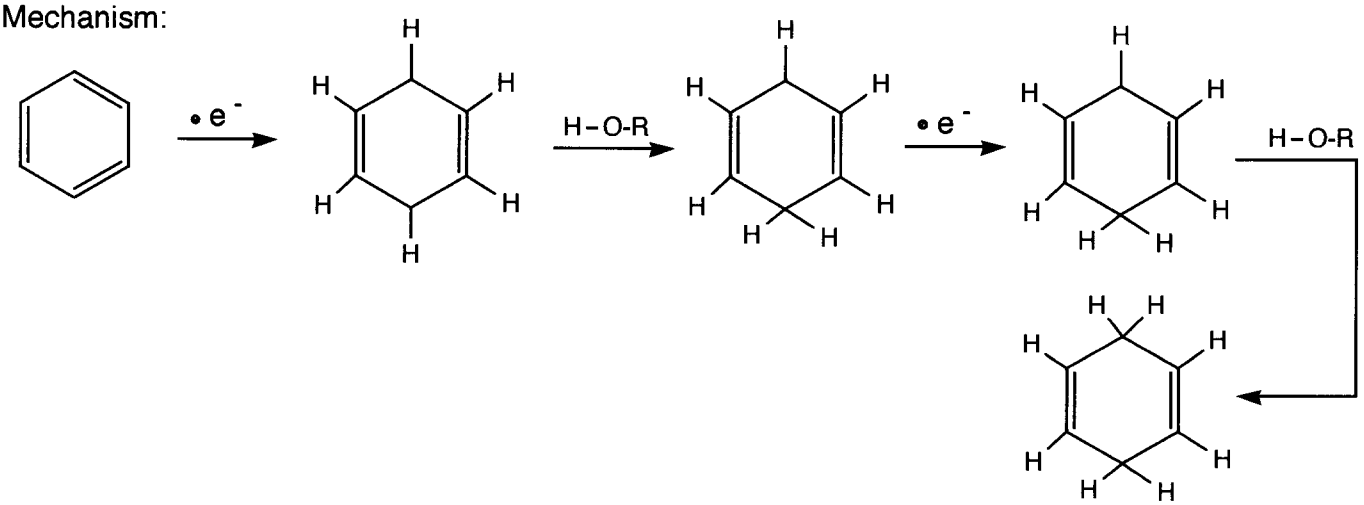
II. Catalytic Hydrogenation



III. Birch Reduction



Mechanism:

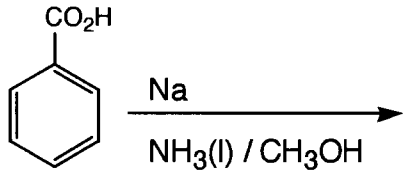


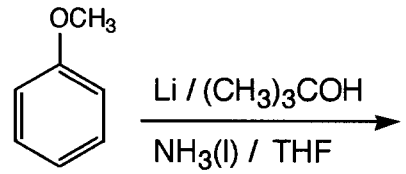
Birch Reduction of Subtituted Benzenes:

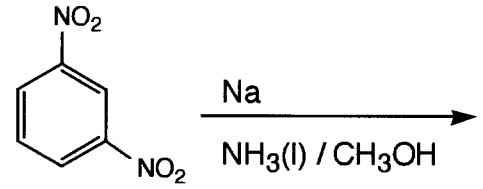
- electron **withdrawing groups activate** a carbon for reduction because the carbanion is stabilized

- electron **donating groups deactivate** a carbon for reduction because the carbanion is destabilized

Examples:

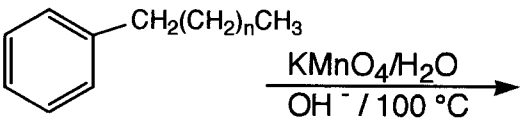
1. 

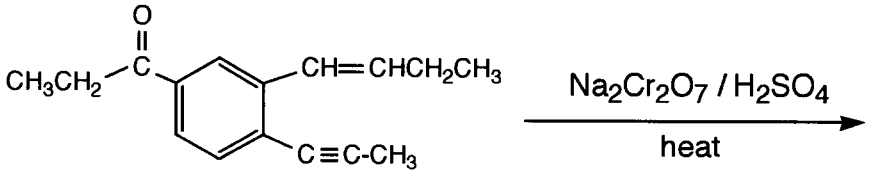
2. 

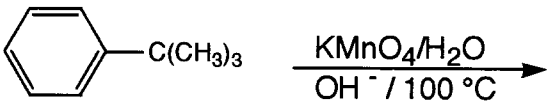
3. 

SIDE CHAIN REACTIONS OF BENZENE DERIVATIVES

I. Oxidation - the benzene ring and the bond to the first carbon of a side chain can survive harsh oxidizing conditions

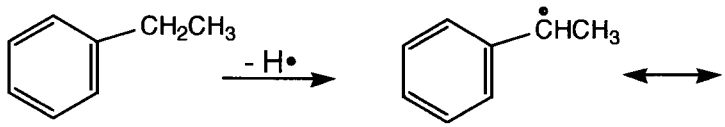
1. 

2. 

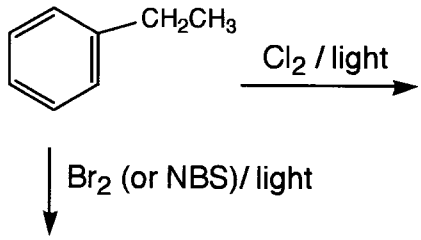
3. 

II. Halogenation of Side Chains

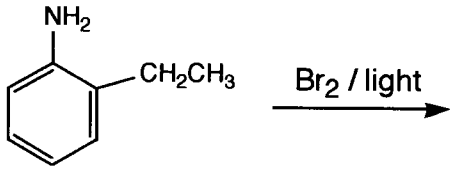
- Benzylic position is similar to allylic position - abstraction of hydrogen on benzylic position gives resonance stabilized radical.

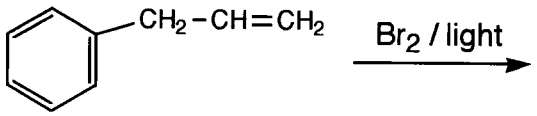


Chlorination vs Bromination:



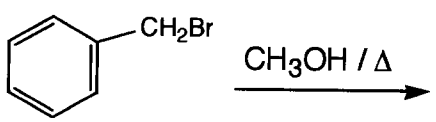
Caution:

1. 

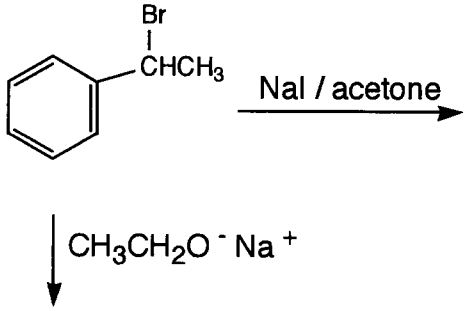
2. 

III. Nucleophilic Substitution of Benzylic Halides

- S_N1 or S_N2 readily occurs - which one? - depends on the reaction conditions

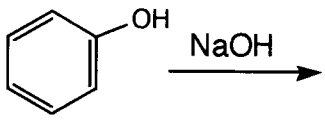


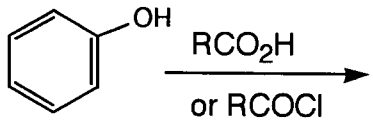
Substitution of benzylic halides, continued

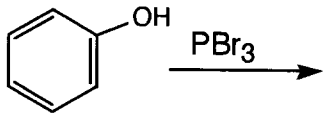


REACTIONS OF PHENOLS

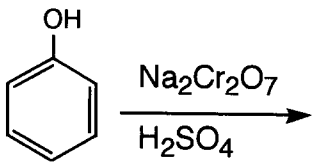
- some similarities to previously studied reactions of aliphatic alcohols / some differences

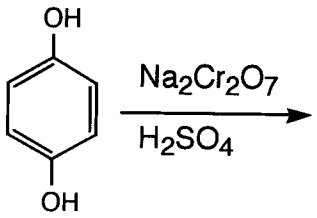
I. 

II. 

III. 

IV.Oxidation of Phenols to Quinones

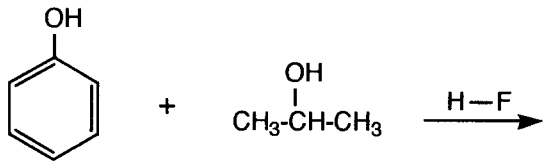




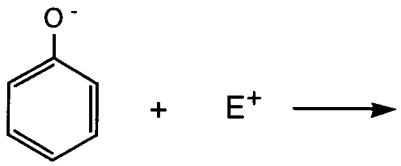
V. Electrophilic Aromatic Substitution of Phenol

- readily undergoes halogenation, nitration, sulfonation and Friedel-Crafts reactions

- need less reactive catalyst for Friedel-Crafts reactions:



VI. Electrophilic Aromatic Substitution of Phenoxide anion



strongly activated - can use weak electrophiles like CO_2