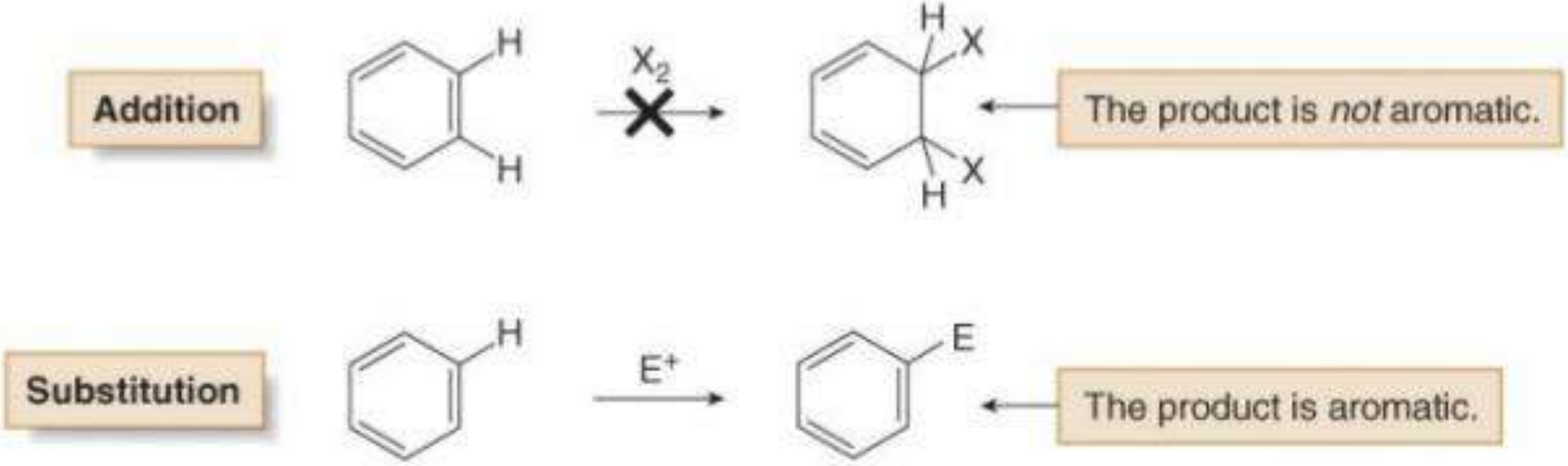
Reactions of Benzene: Electrophilic & Nucleophilic Aromatic Substitution

Part 1

Background

- Benzene does not undergo addition reactions like other unsaturated hydrocarbons, because addition would yield a product that is not aromatic.
- Substitution of a hydrogen keeps the aromatic ring intact.
- There are five main examples of electrophilic aromatic substitution.

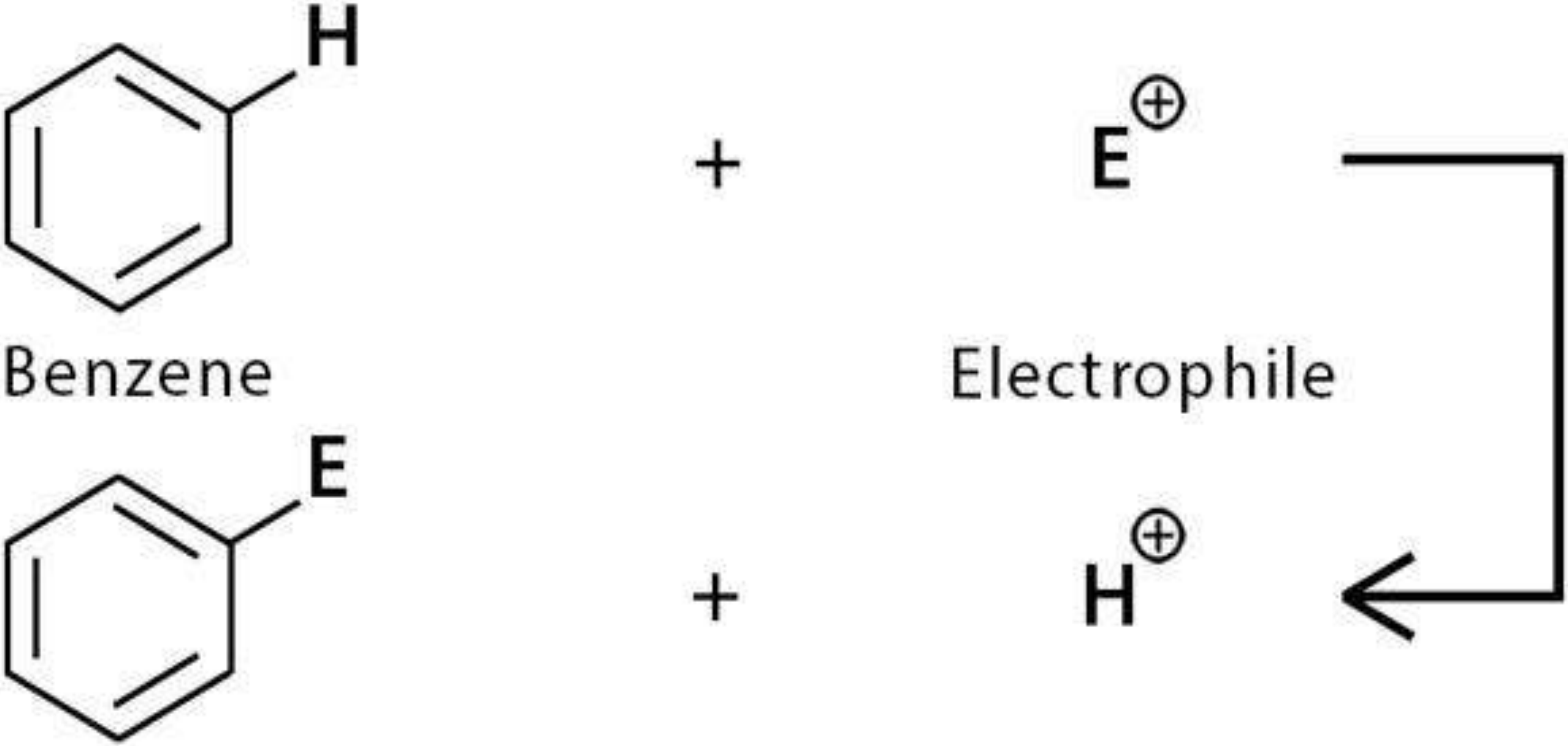

Addition

The product is *not* aromatic.

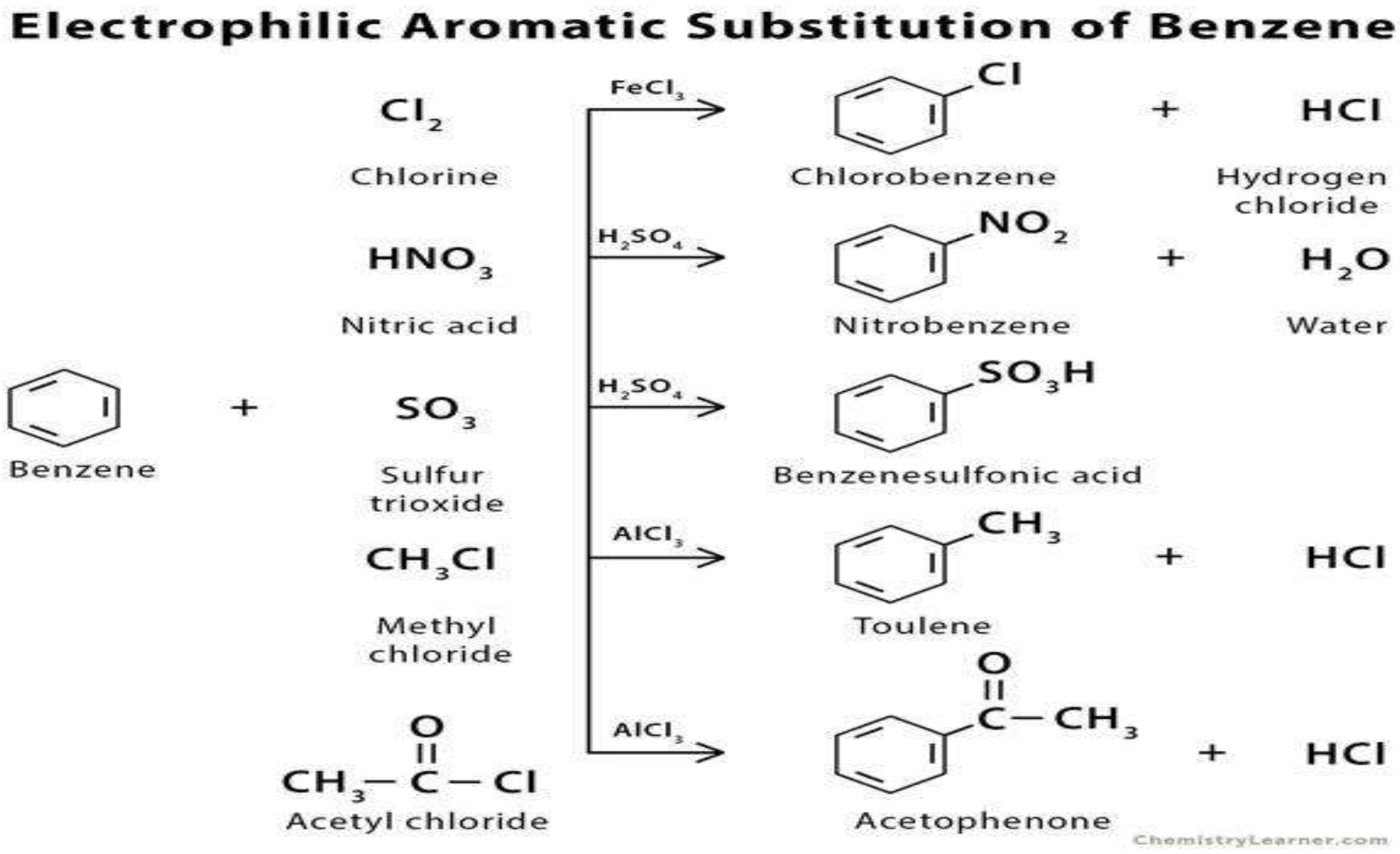
Substitution

The product is aromatic.

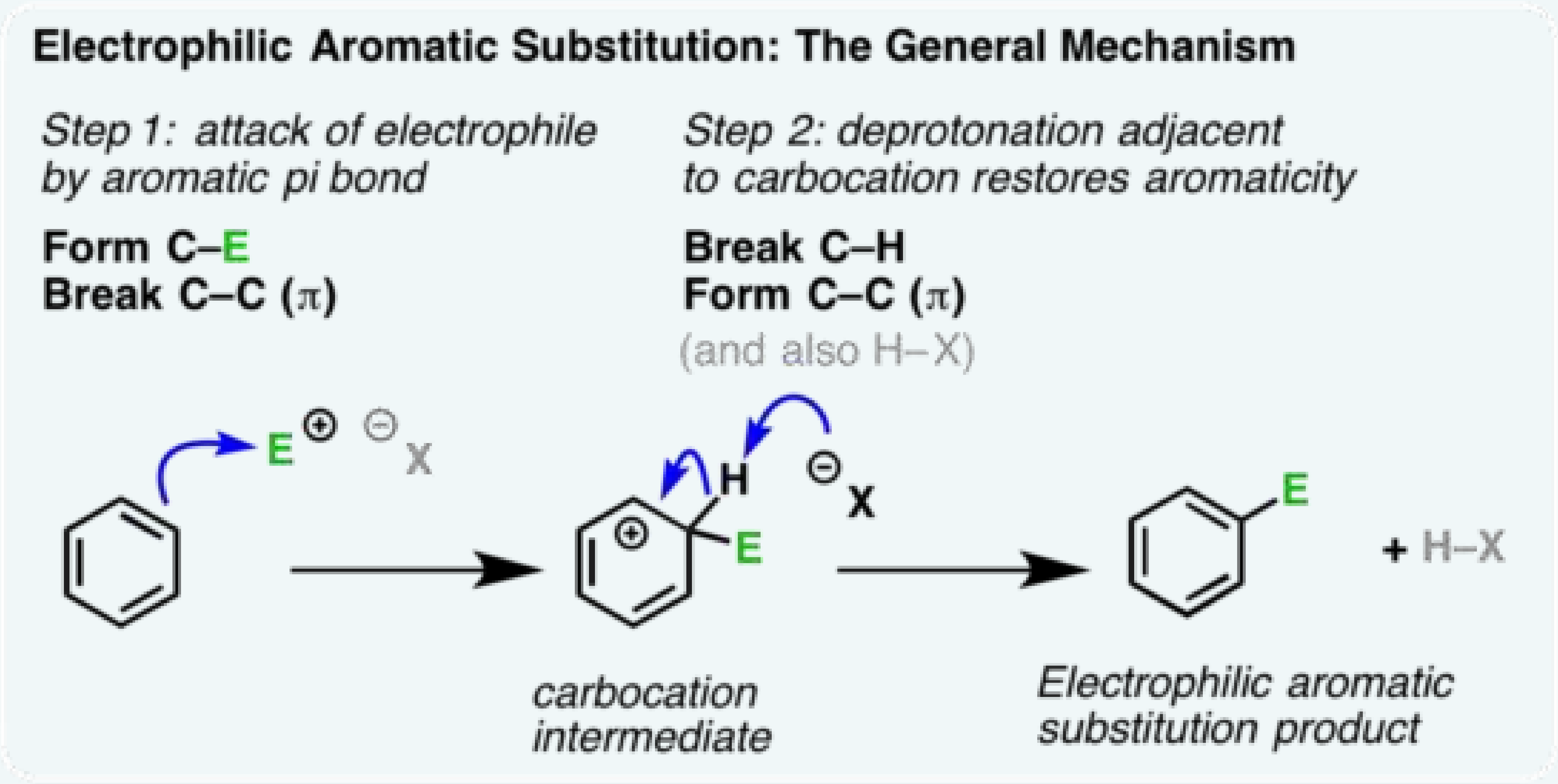
Electrophilic Aromatic Substitution



1] Electrophilic Aromatic Substitution Reaction



General mechanism of Electrophilic aromatic substitution



Electrophilic Aromatic Substitution: The General Mechanism

Step 1: attack of electrophile by aromatic pi bond

Form C–E
Break C–C (π)

Step 2: deprotonation adjacent to carbocation restores aromaticity

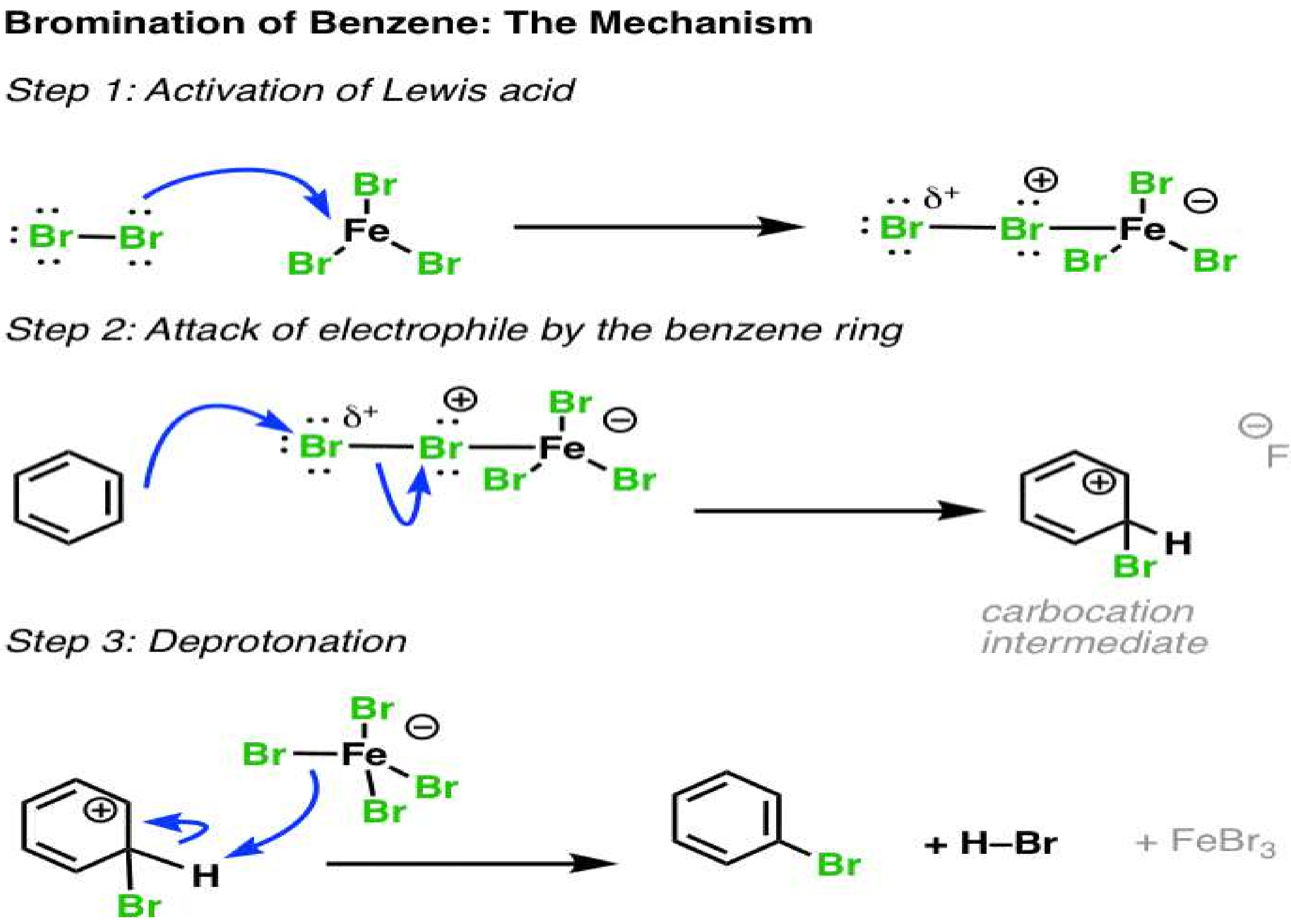
Break C–H
Form C–C (π)
(and also H–X)

carbocation intermediate

Electrophilic aromatic substitution product

1] Halogenation

Bromination or chlorination



Bromination of Benzene: The Mechanism

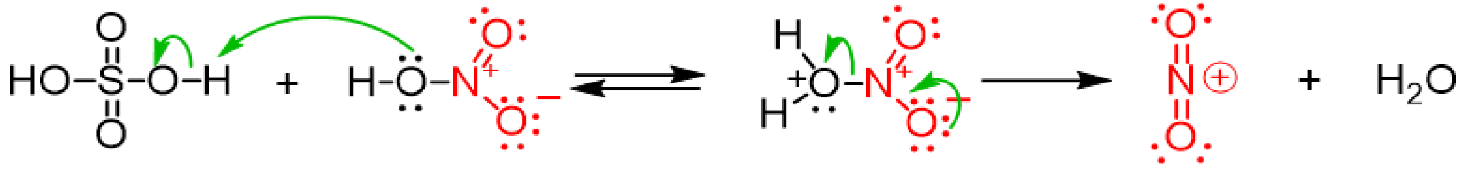
Step 1: Activation of Lewis acid

Step 2: Attack of electrophile by the benzene ring

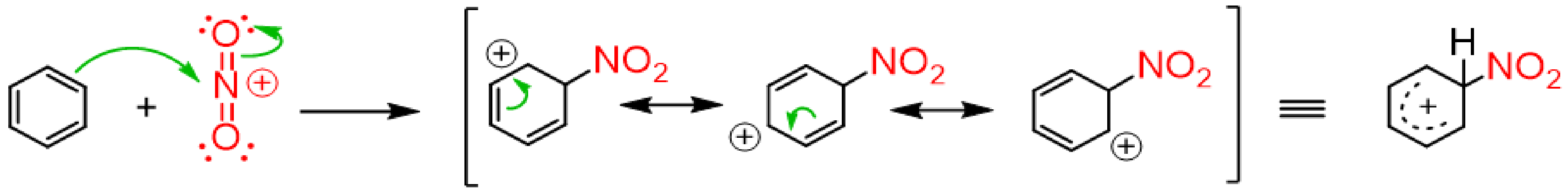
Step 3: Deprotonation

2-Nitration

The stronger sulfuric acid protonates the nitric acid to form $^{+}NO_2$ electrophile



Nitronium ion

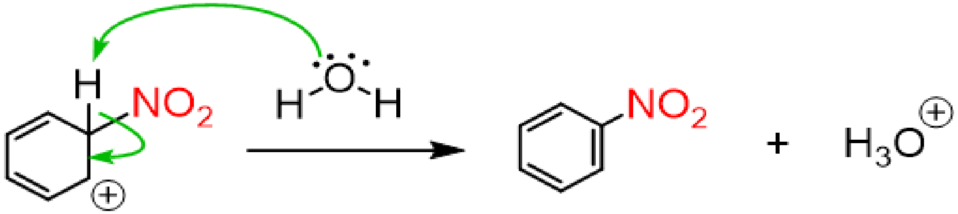


Addition of the electrophile

Sigma Complex

hybrid

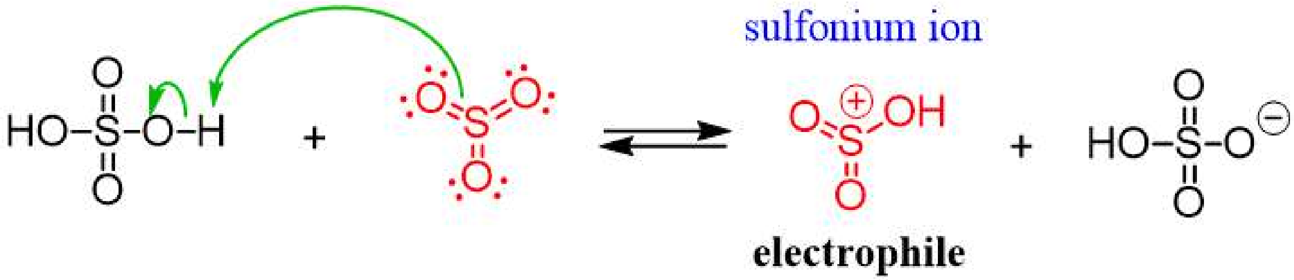
Loss of a proton - restoring the aromaticity

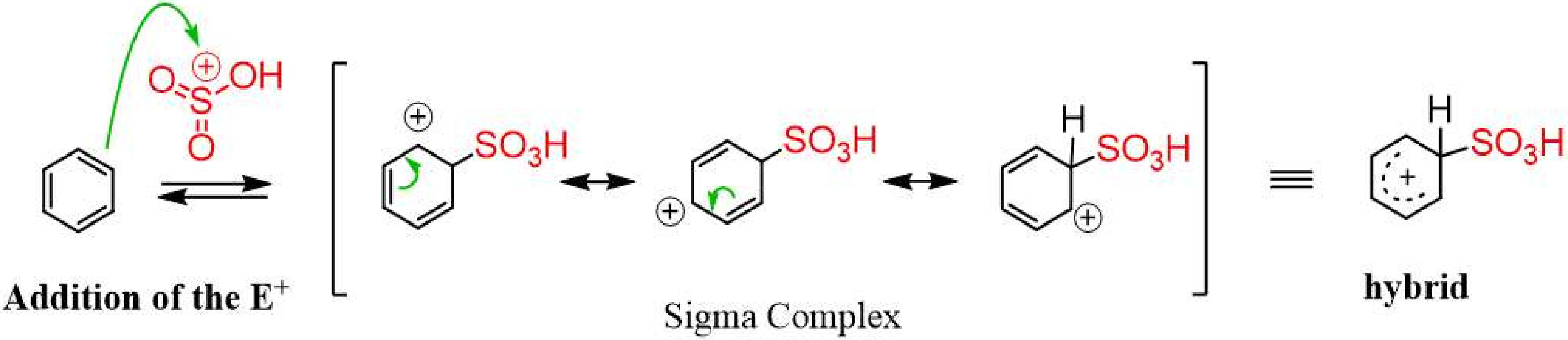


nitrobenzene

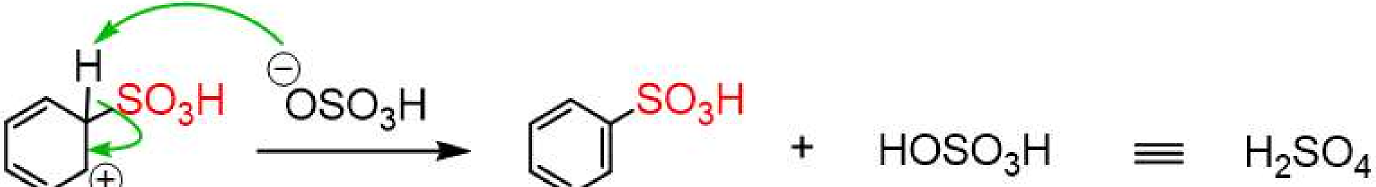
3-Sulfonation

The $^+SO_3H$ strong electrophile is from by protonation of SO_3





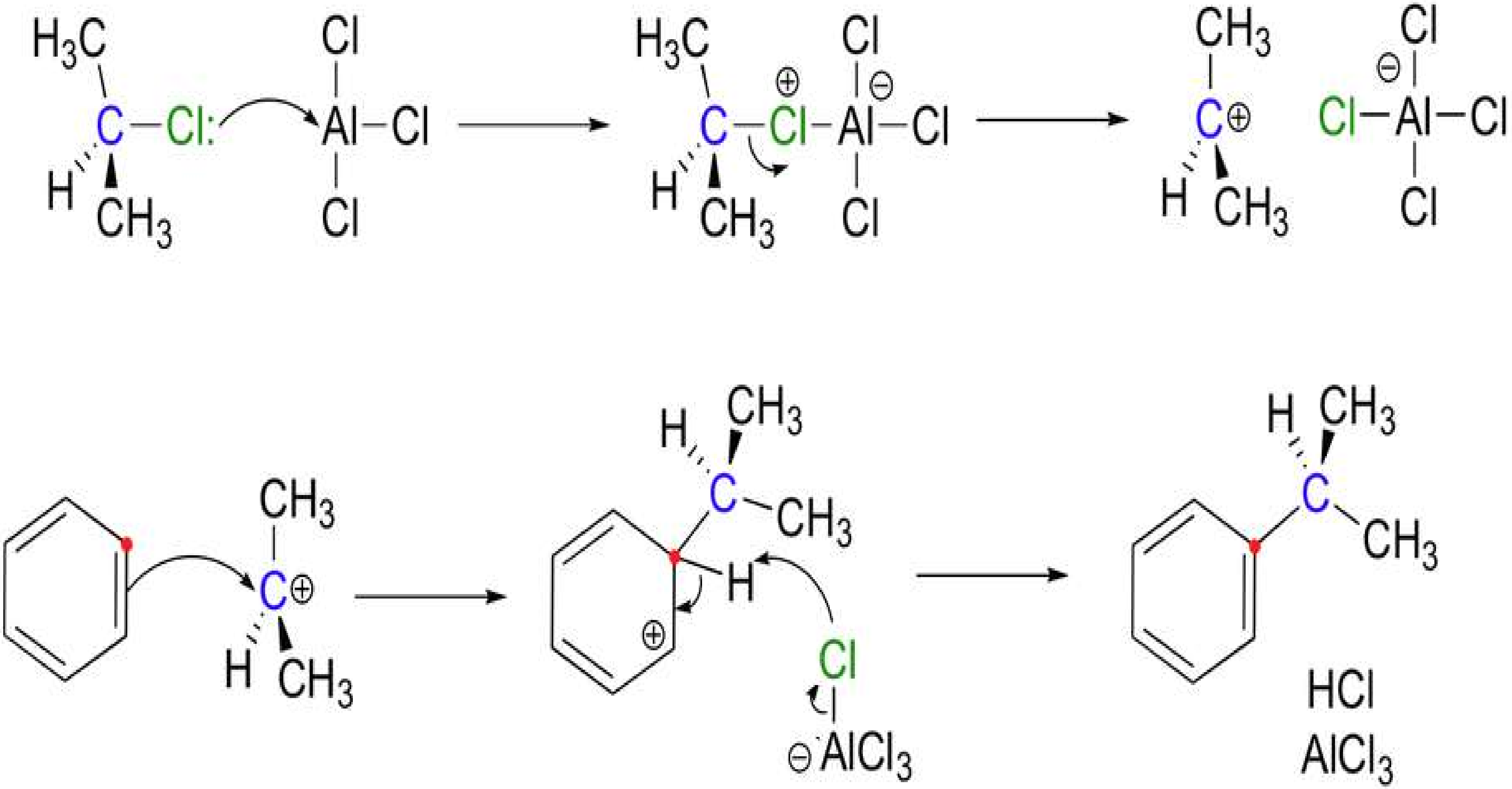
Loss of a proton - restoring the aromaticity



4-Friedel-Crafts Alkylation

Introducing an alkyl group via RX/ AlCl3

Mechanism of the Friedel-Crafts Alkylation



Limitations of the Friedel-Crafts Alkylation

1. **Reaction limited to alkyl halides; aryl or vinyl halides do not react.**
2. **Reaction does not occur on rings containing strong electron withdrawing substituents.**

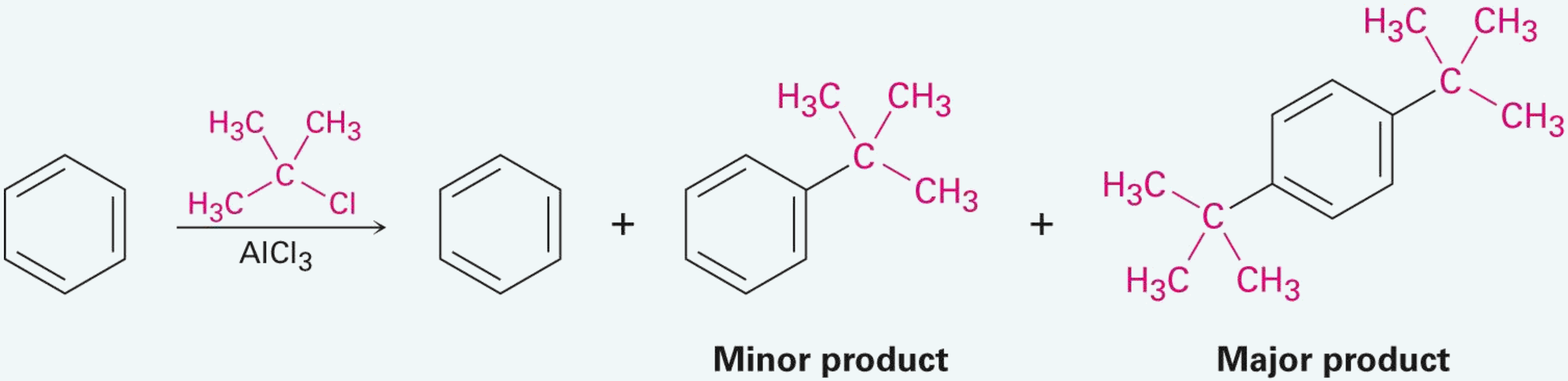
   $-NO_2$ $-CN$ $-SO_3H$ $-CHO$ $-COR$

   $-COOH$ $-COOR$ $-NR_3^+$

3. **Multiple substitutions often occur.**
4. **Carbocation rearrangements can occur, particularly with 1° alkyl halides.**

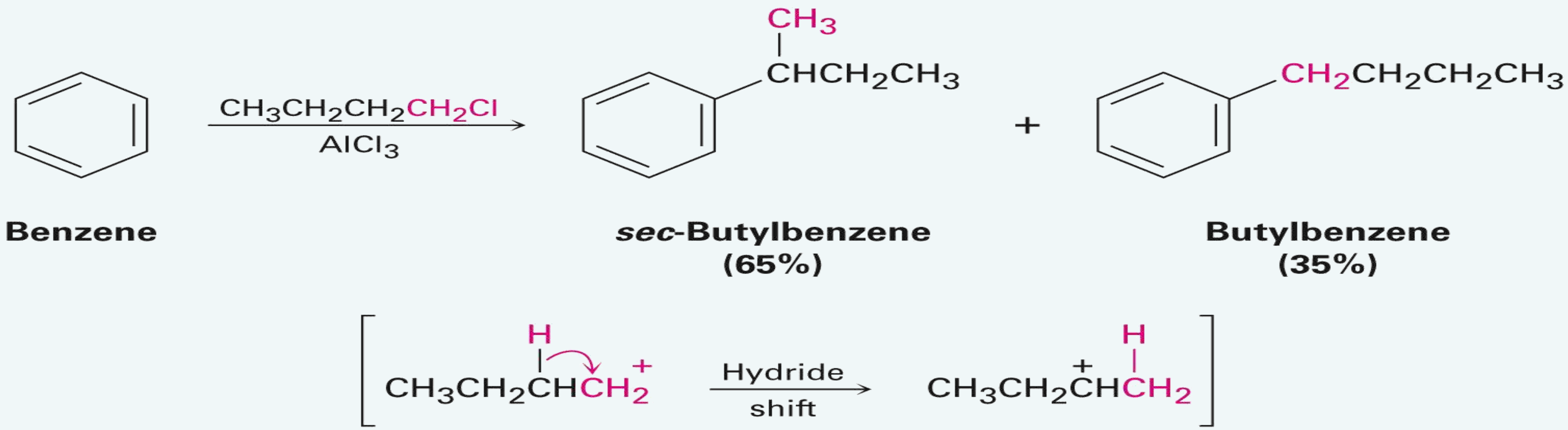
Limitations of the Friedel-Crafts Reaction

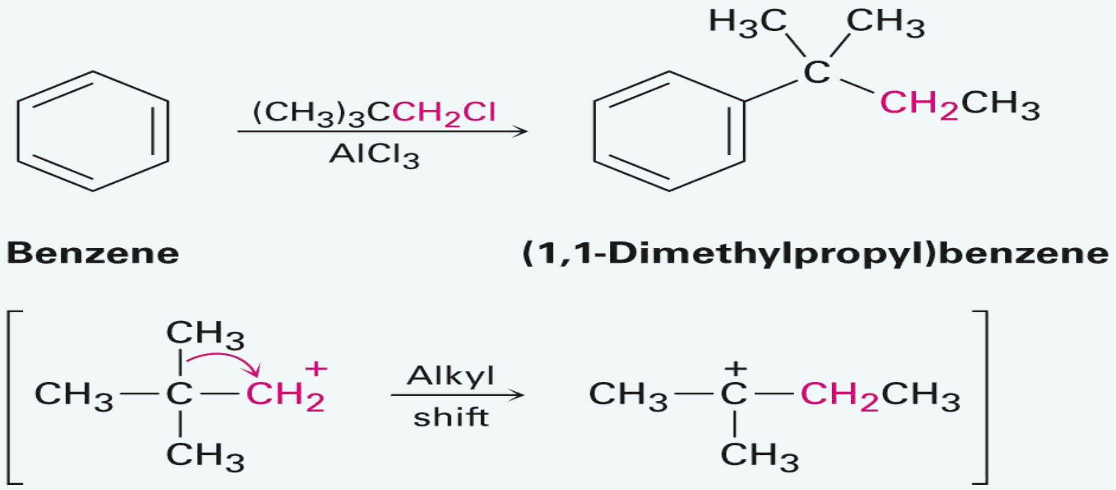
- **Polyalkylation**



Limitations of the Friedel-Crafts Reaction

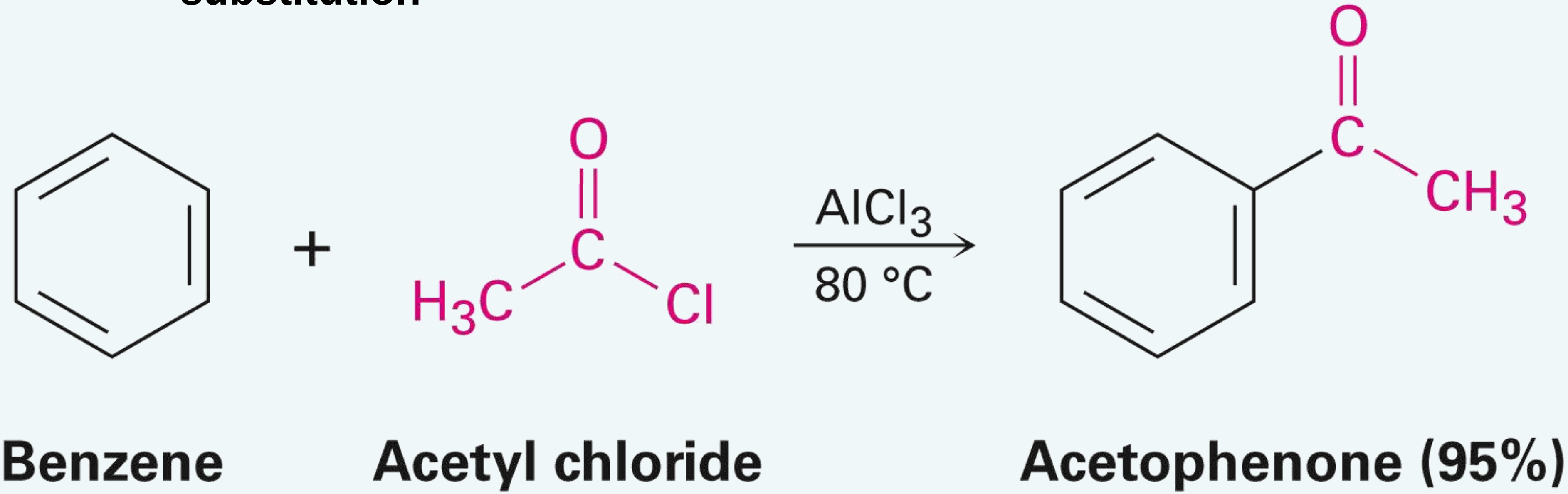
- **Rearrangement**





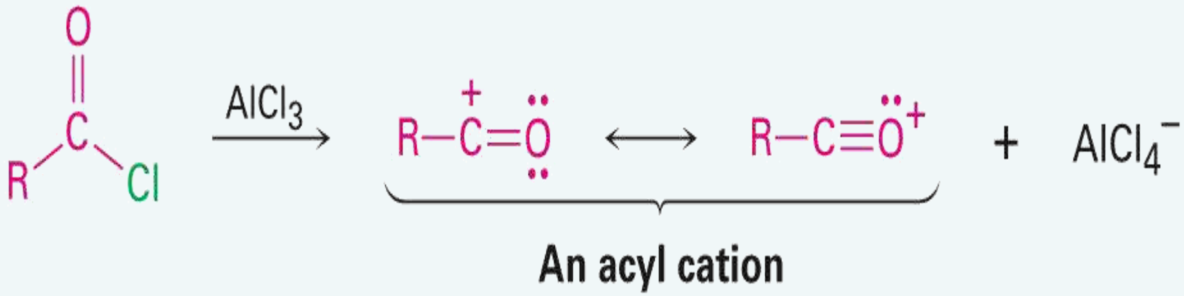
5- Freiedel-Crafts Acylation

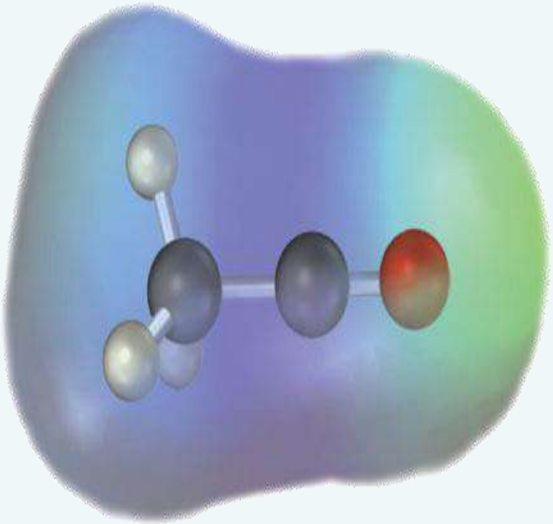
- **Acylation: Reaction of an aromatic ring with a carboxylic acid chloride in the presence of $AlCl_3$ resulting in an acyl group substitution**

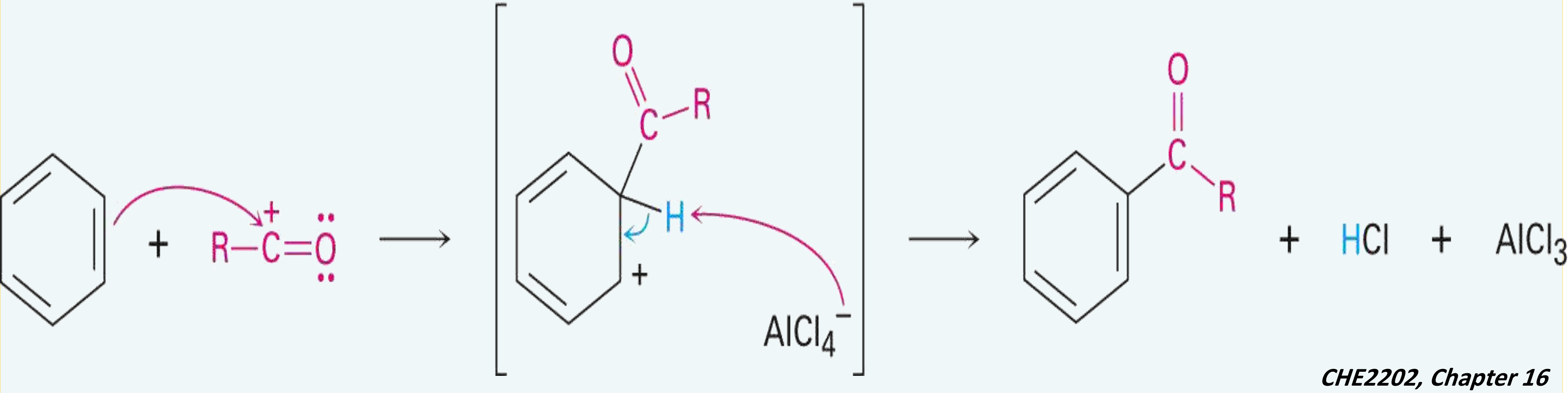


Mechanism of Friedel-Crafts Acylation

- **Similar to Freidel-Crafts alkylation and also possesses the same limitations on the aromatic substrate**





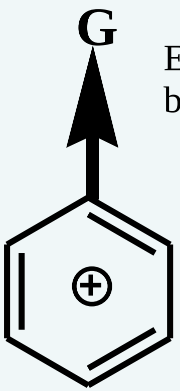


Substituent Effects in Substituted Aromatic Rings

1. **Reactivity** of the aromatic ring is affected
   - Substitution can result in an aromatic ring with a higher or a lower reactivity than benzene.
2. **Orientation** of the reaction
   - Some substituents direct reactions at ortho and para positions
   - Some substituents direct reactions at meta positions

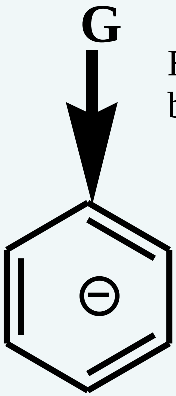
Reactivity

The ring activity to attack electrophile through E.Ar. Sub depends up on what does this ring hold??!!!



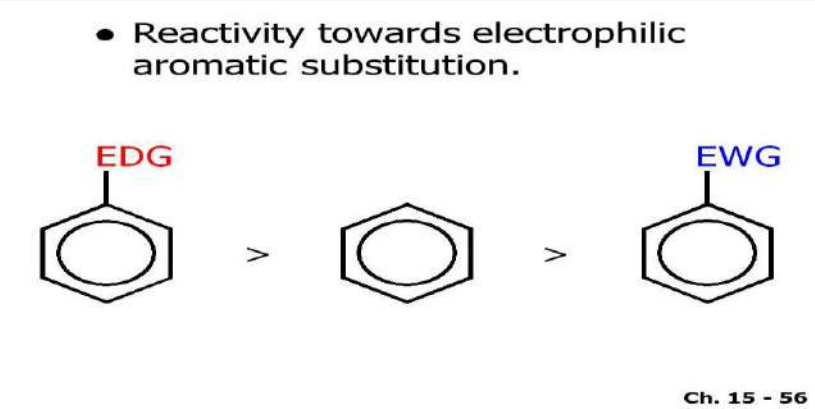
Electron withdrawing group
by I or M effect

Deactivated ring towards
E.Ar. Substitution



Electron donating group
by I or M effect

Activated ring towards
E.Ar. Substitution

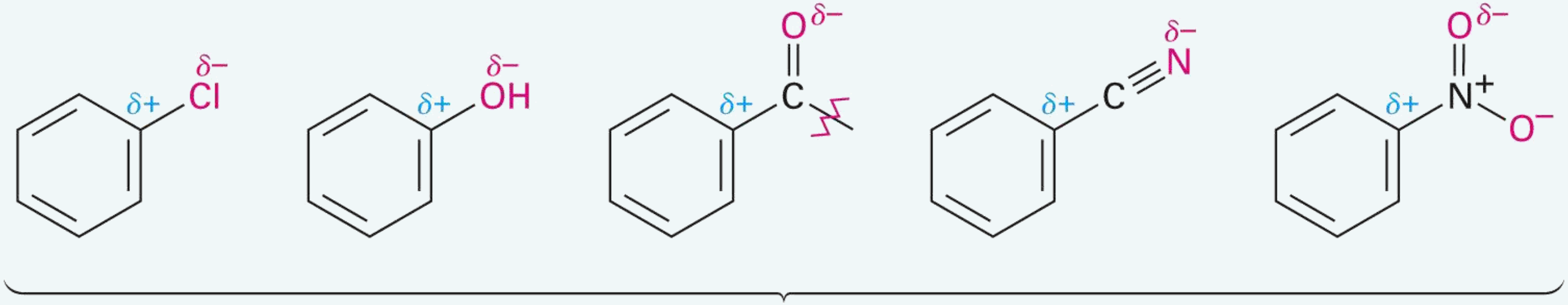


- Reactivity towards electrophilic aromatic substitution.

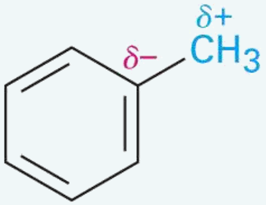
Ch. 15 - 56

Origins of Substituent Effects

- **Inductive effect**: Withdrawal or donation of electrons through a sigma bond due to electronegativity



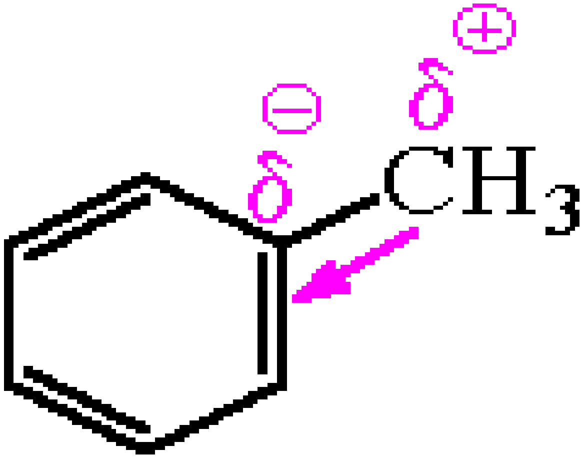
Inductive electron withdrawal



Inductive electron donation

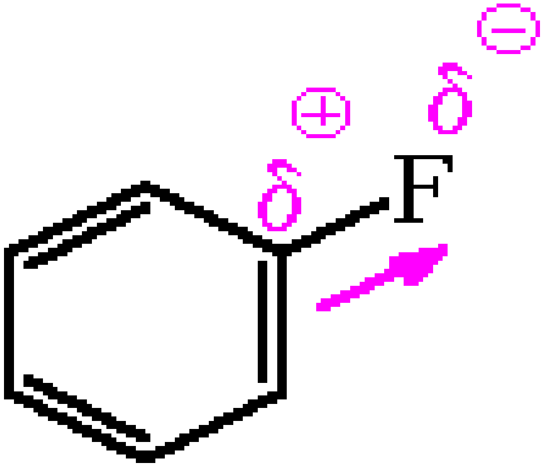
Inductive Effects

Activating Effect



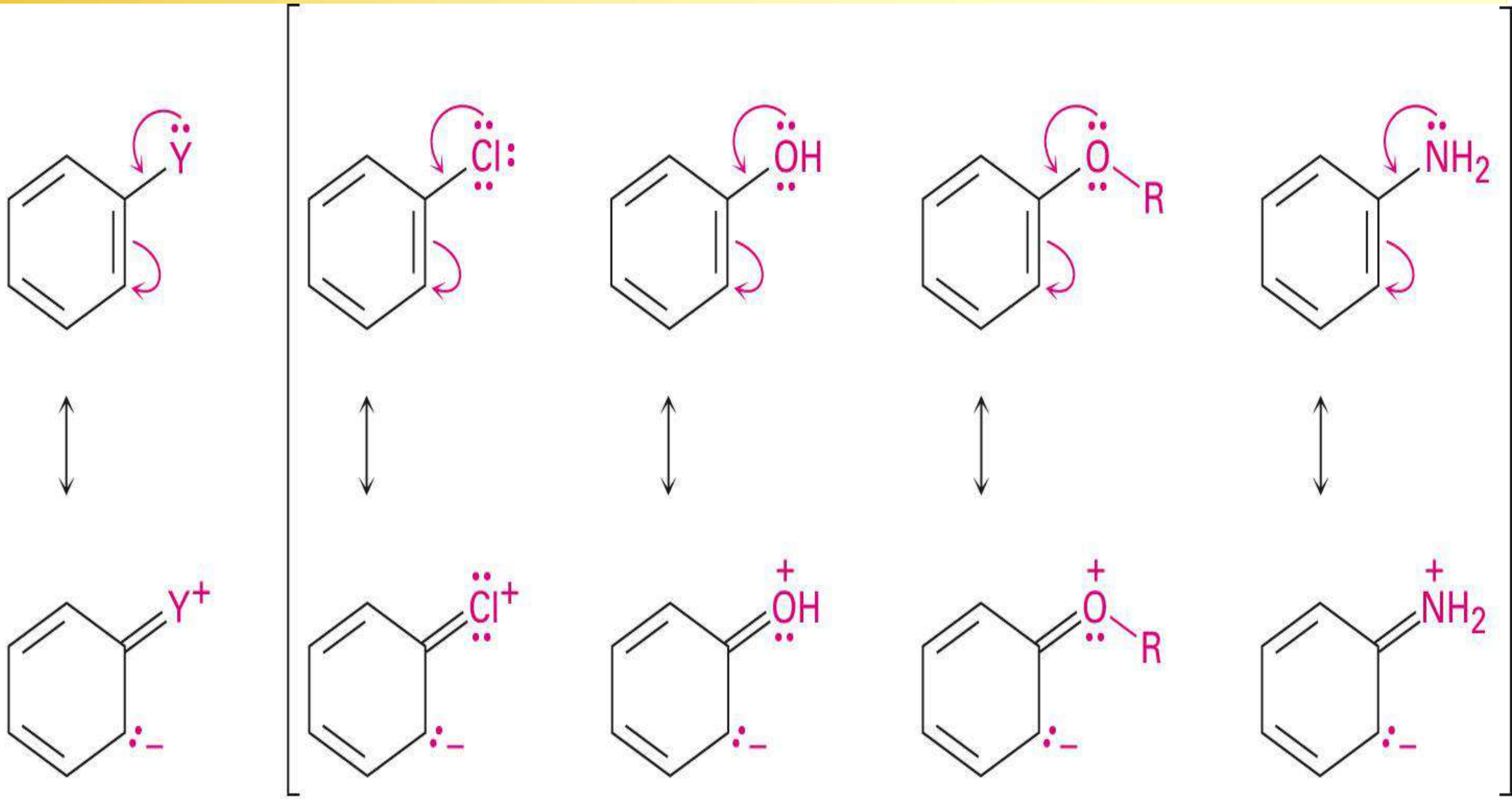
A negative ring is more likely to react with an electrophile (positive).

Deactivating Effect



A positive ring is less likely to react with an electrophile (positive).

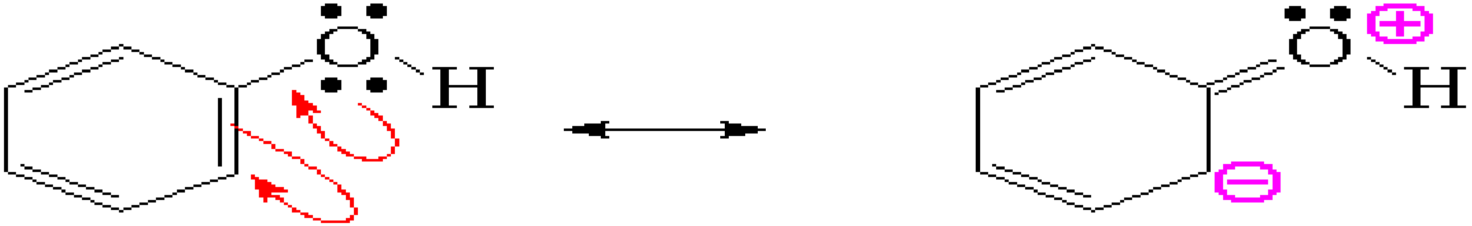
Resonance Effects - Electron Donation



Resonance electron-donating group

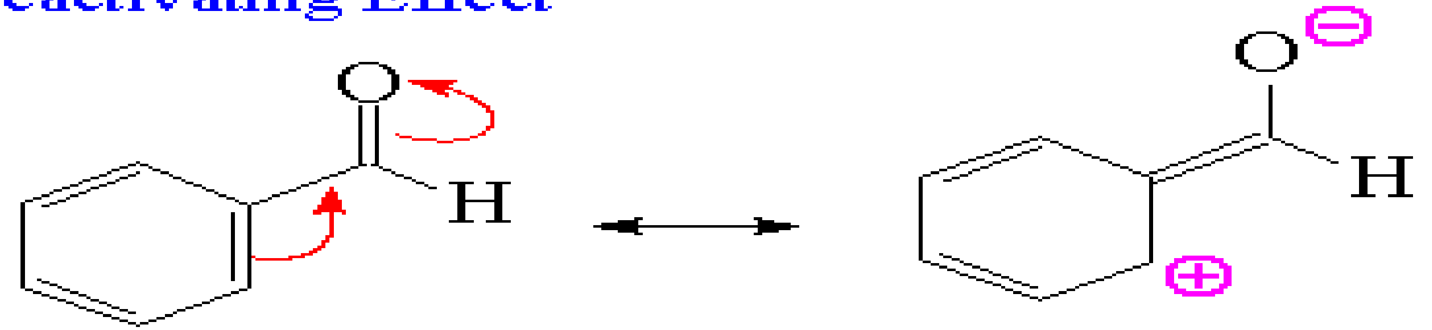
Resonance Effects

Activating Effect



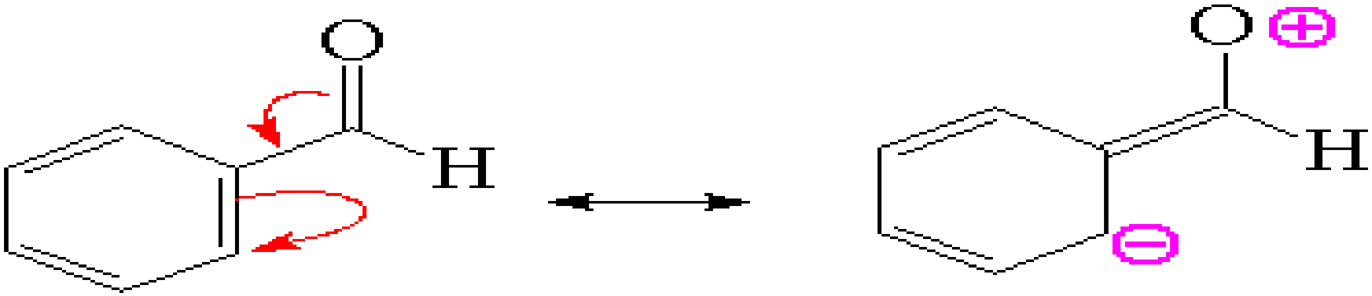
A negative ring is more likely to react with an electrophile (positive).

Deactivating Effect



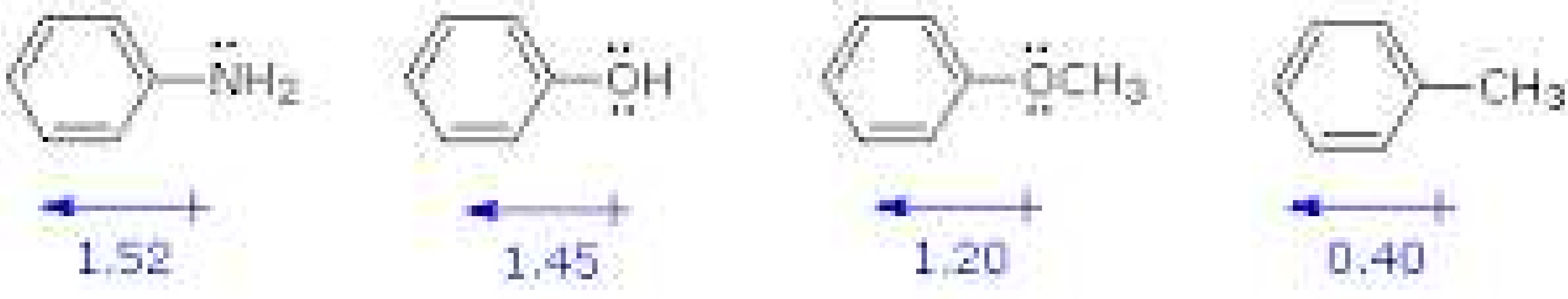
A positive ring is less likely to react with an electrophile (positive).

Note: The contributor below is not significant! Why?

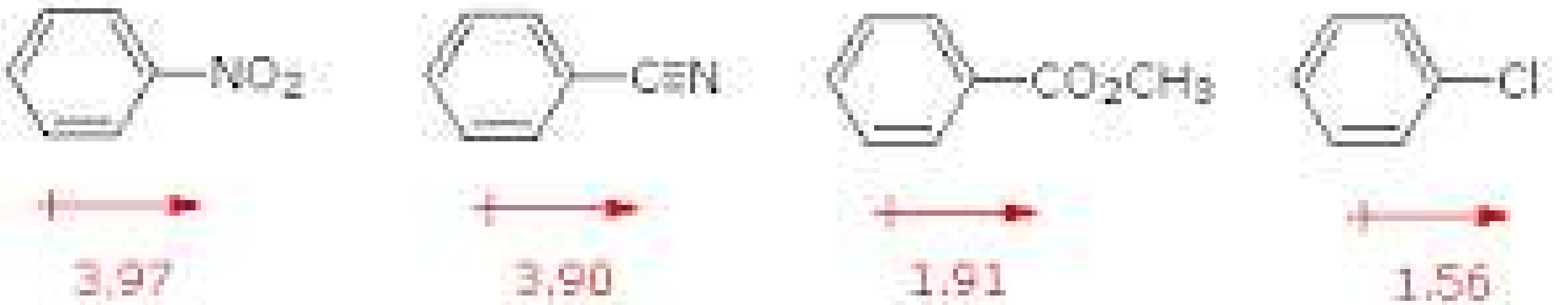


Examples

Activating Substituents

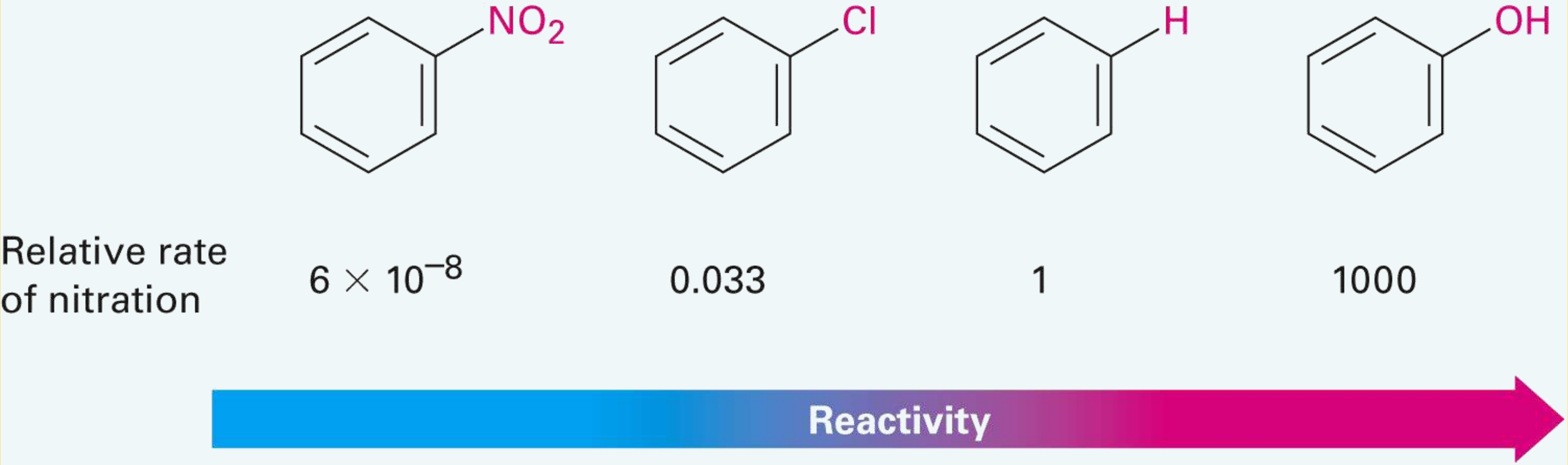


Deactivating Substituents

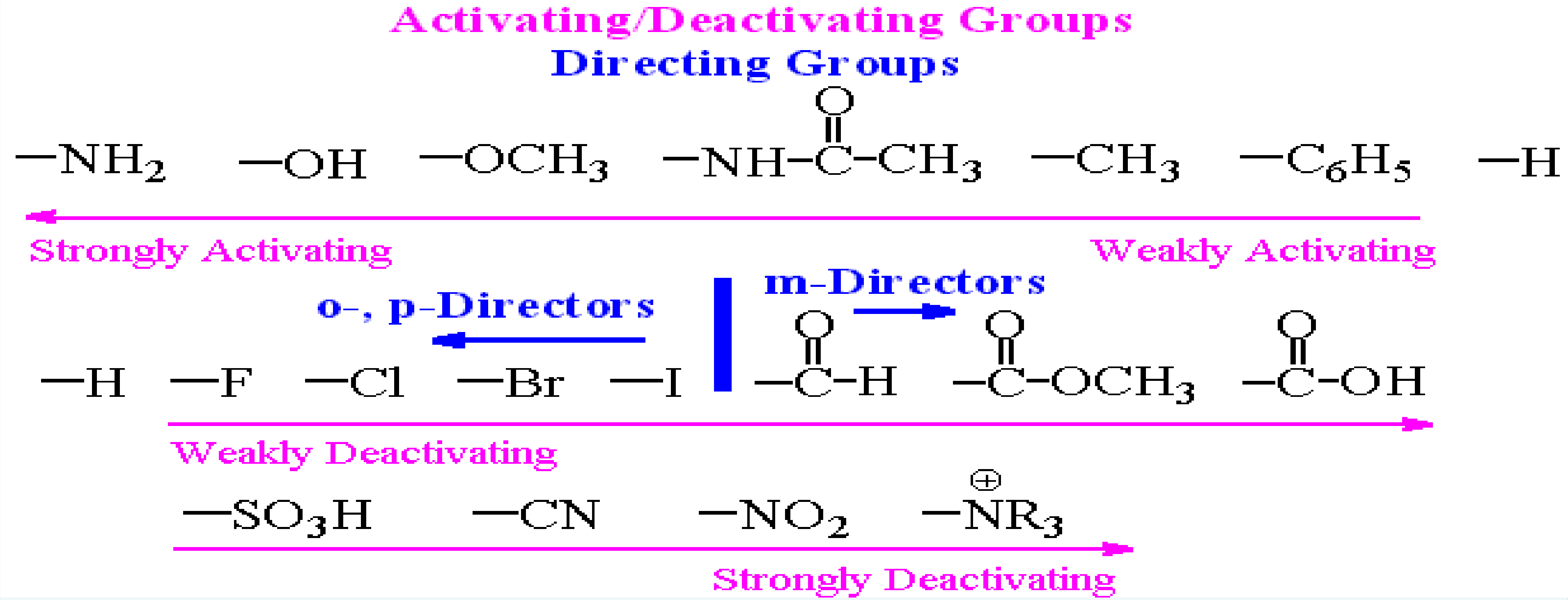


Substituent Effects in Substituted Aromatic Rings

- **Reactivity of the aromatic ring is affected**
  - **Substitution can result in an aromatic ring with a higher or a lower reactivity than benzene**



The general principle of reactivity towards electrophilic aromatic substitution



Activating/Deactivating Groups

Directing Groups

$-NH_2$ $-OH$ $-OCH_3$ $-NH-\overset{O}{\overset{\|}{C}}-CH_3$ $-CH_3$ $-C_6H_5$ $-H$

Strongly Activating

Weakly Activating

o-, p-Directors

m-Directors

$-H$ $-F$ $-Cl$ $-Br$ $-I$ $-\overset{O}{\overset{\|}{C}}-H$ $-\overset{O}{\overset{\|}{C}}-OCH_3$ $-\overset{O}{\overset{\|}{C}}-OH$

Weakly Deactivating

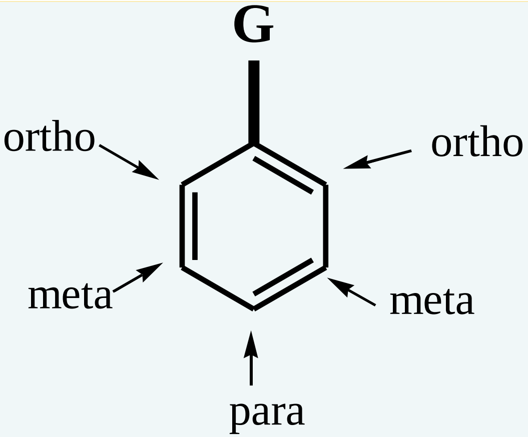
$-SO_3H$ $-CN$ $-NO_2$ $-\overset{\oplus}{N}R_3$

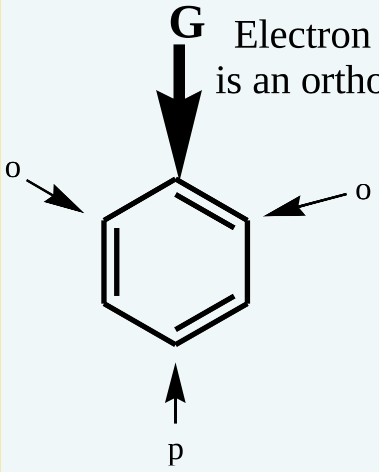
Strongly Deactivating

Part 2

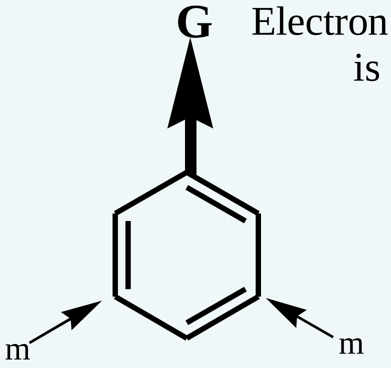
Orientation of substitution

(ortho, meta and para)





Electron donating group
is an ortho or para director

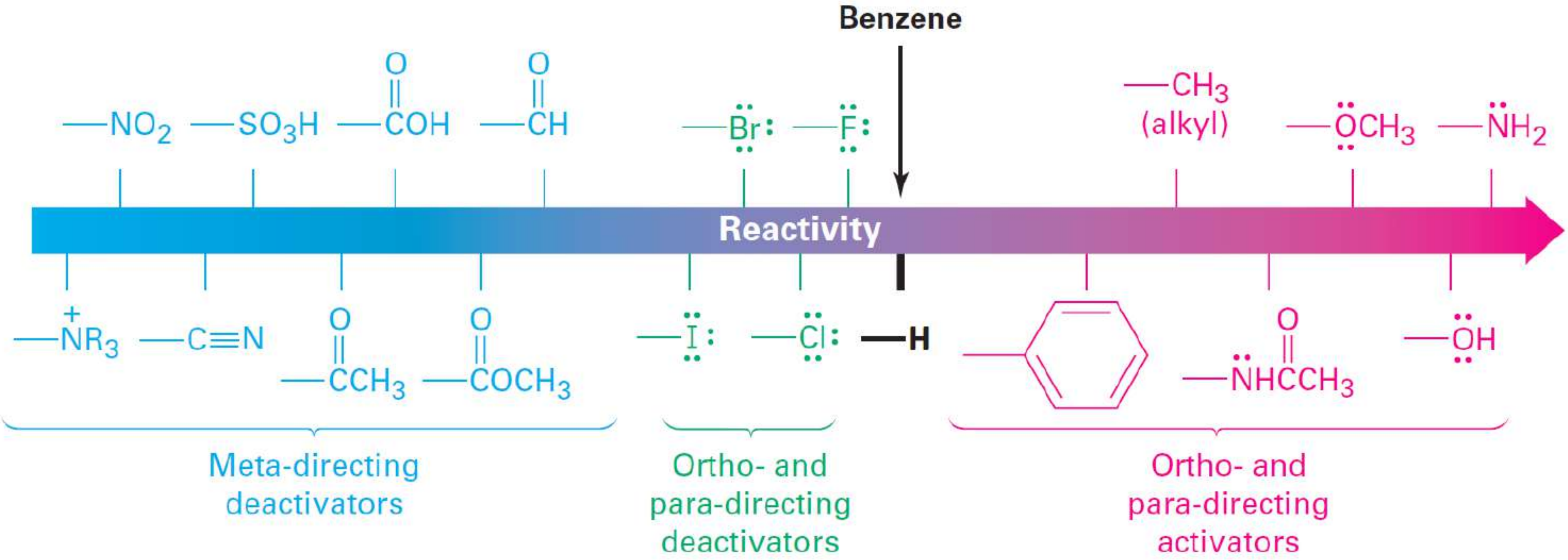


Electron withdrawing group
is meta director

Rule:-

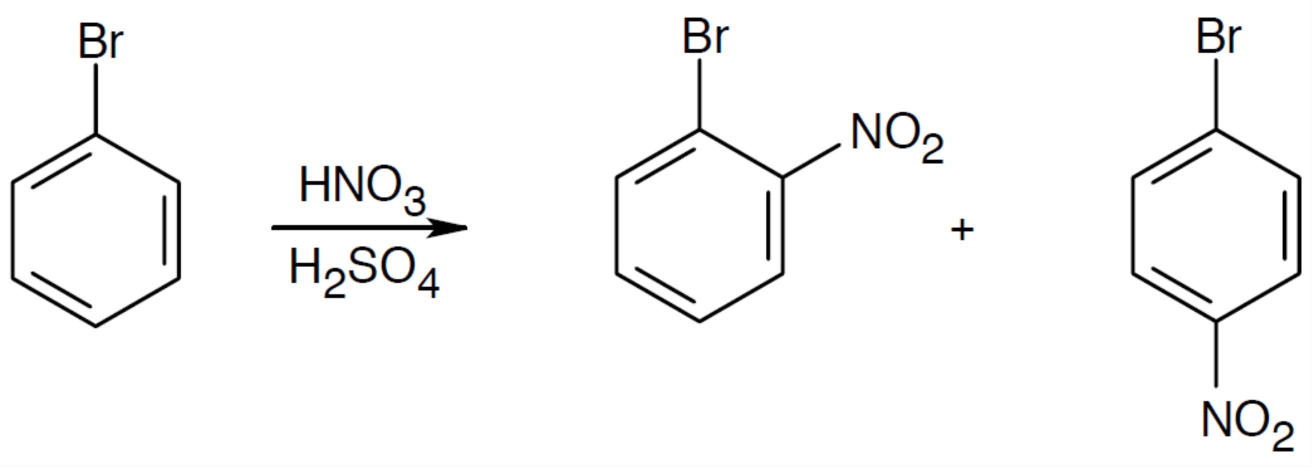
In general; Activating groups are ortho, para directors while deactivating groups are meta directors.

Classification of Substituent Effects in Electrophilic Aromatic Substitution



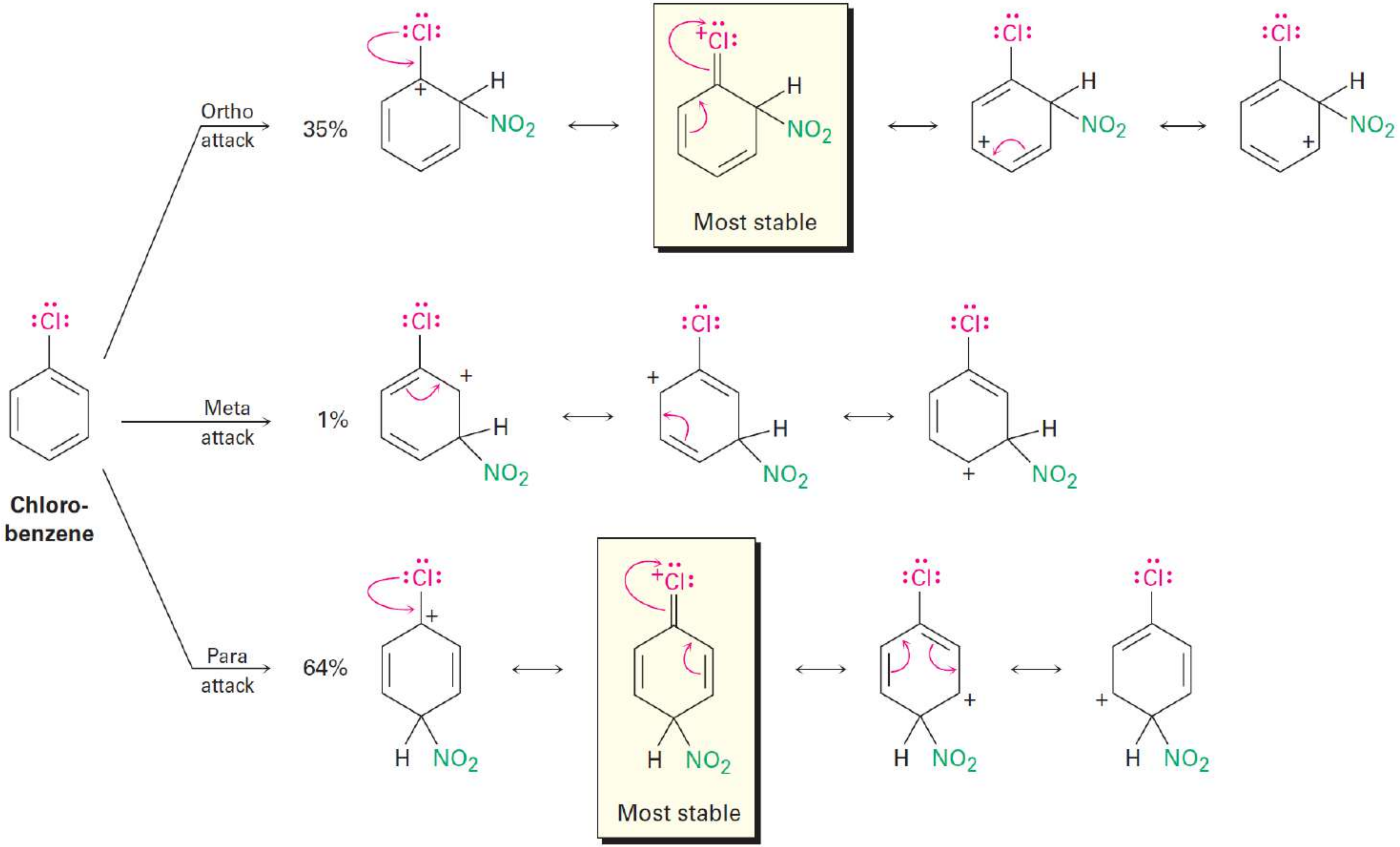
Worked Example

- Predict the major product in the nitration of bromobenzene
- Solution:



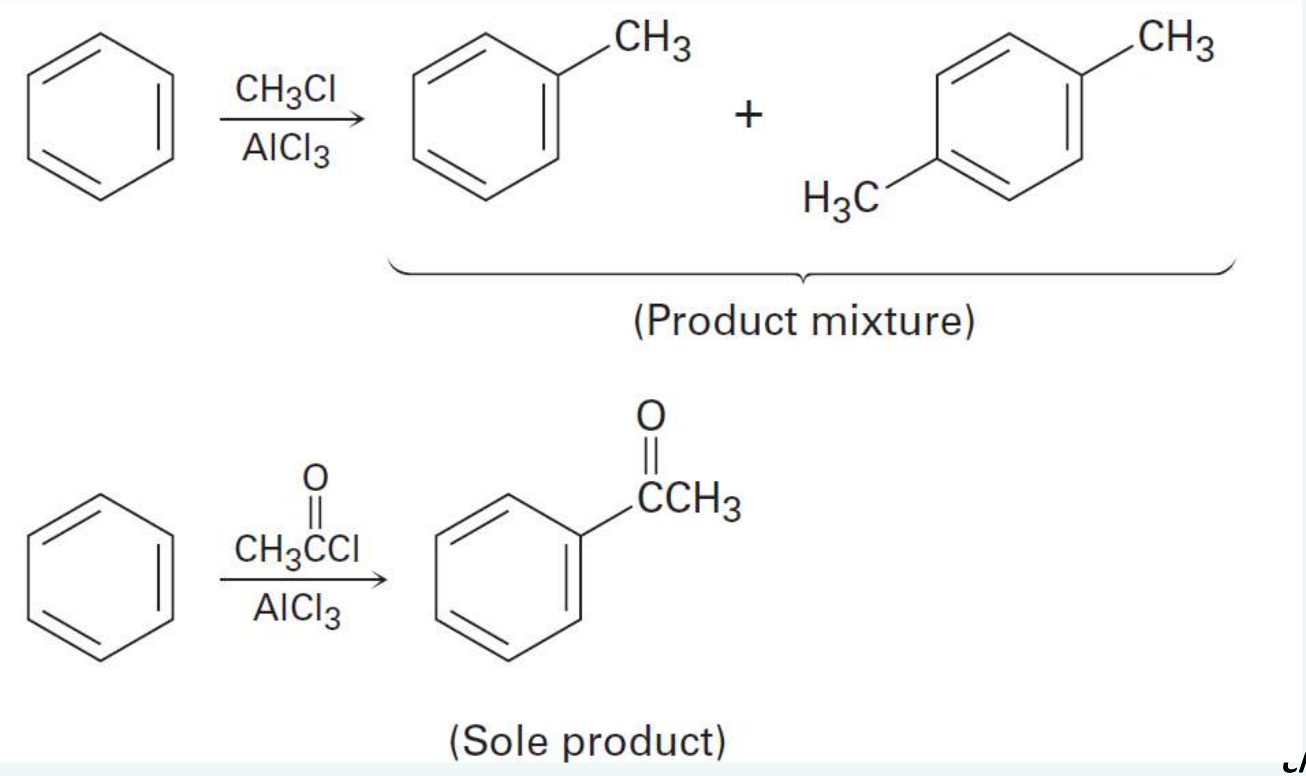
  - Even though bromine is a deactivator, it is used as an ortho-para director.

In spite of its classification as deactivating group halogens are ortho, para directors

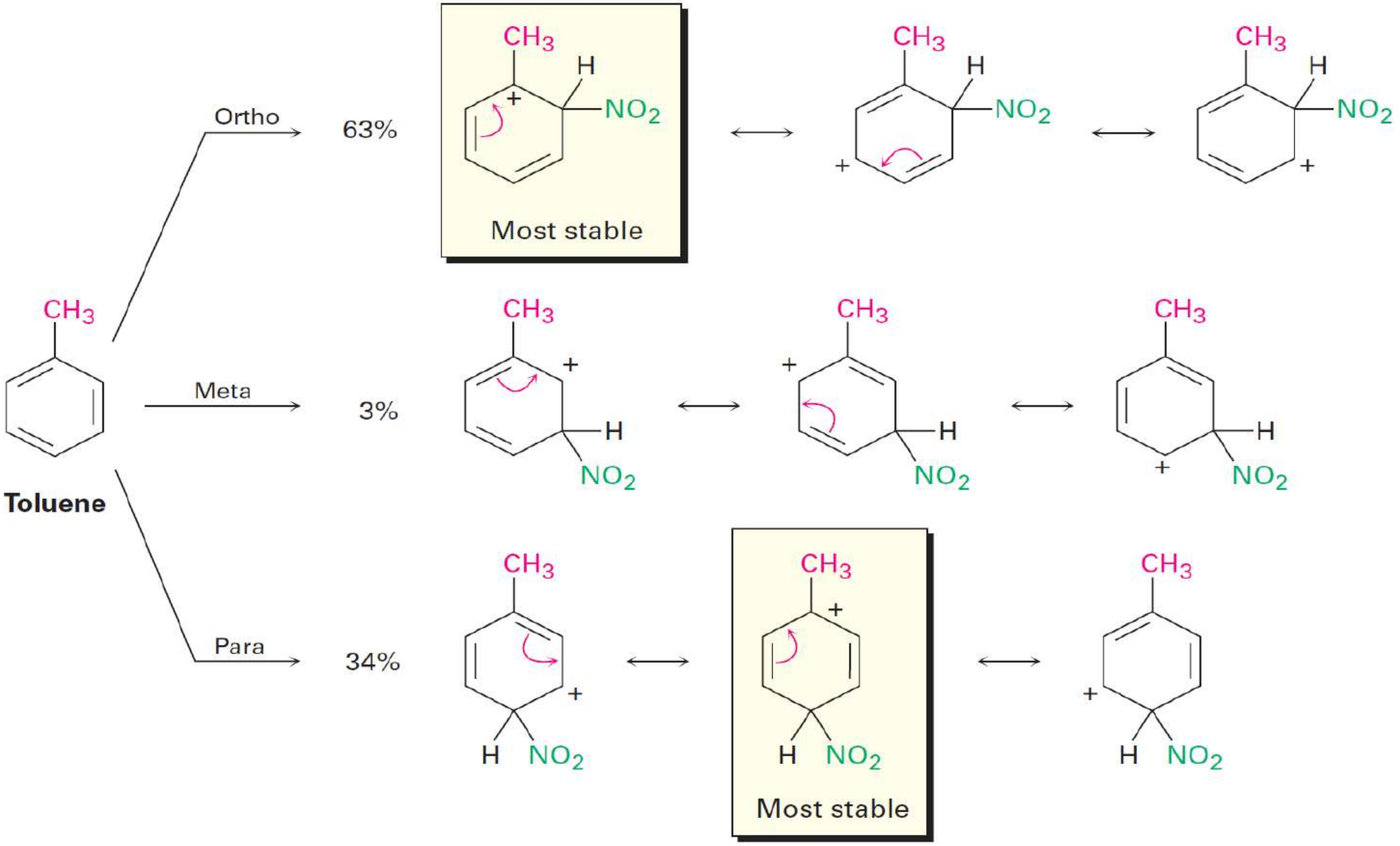


Worked Example

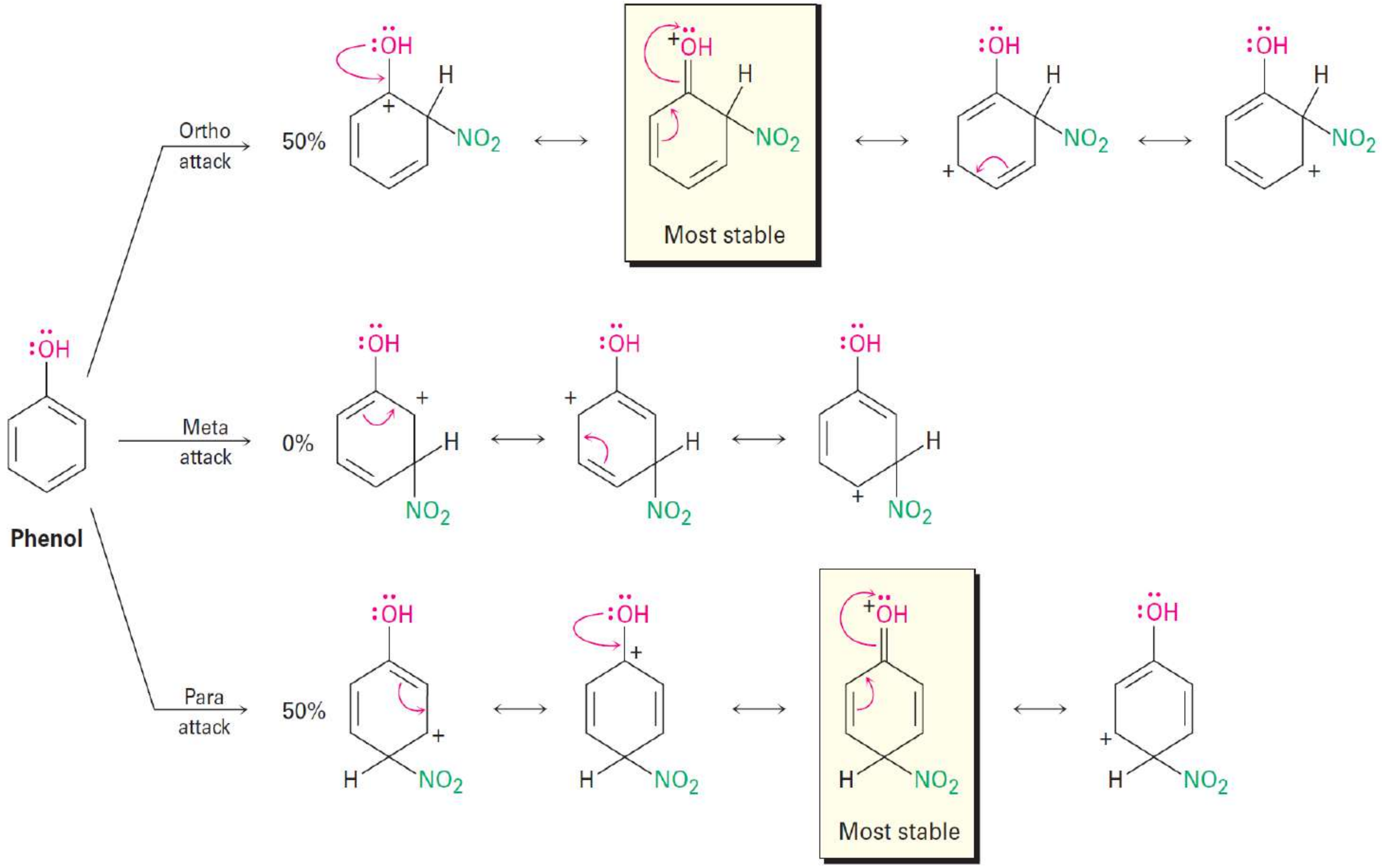
- Why Freidel-Crafts alkylations often give poly-substitution reactions but Freidel-Crafts acylations do not?



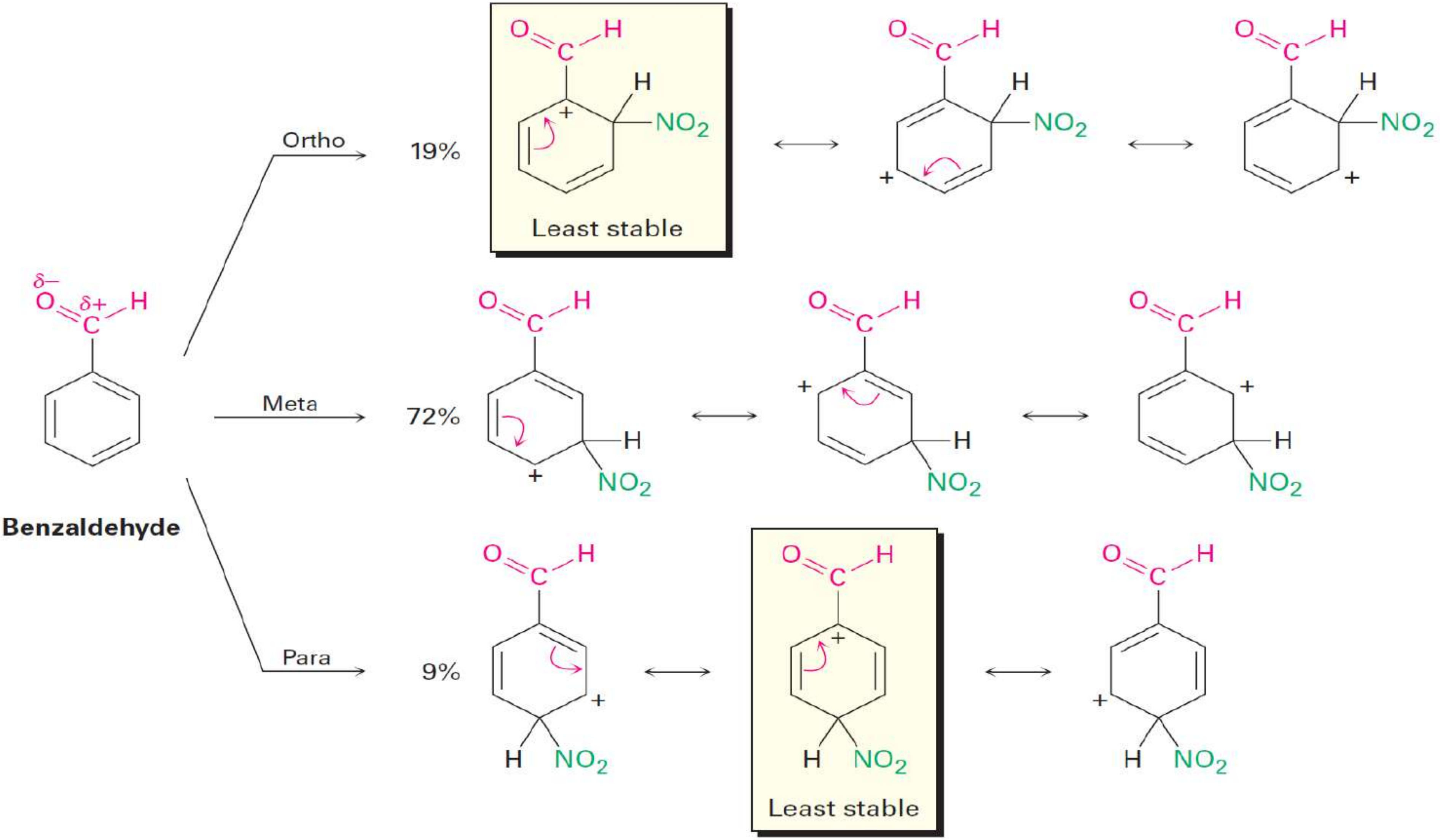
Ortho- and Para-Directing Activators: Alkyl Groups



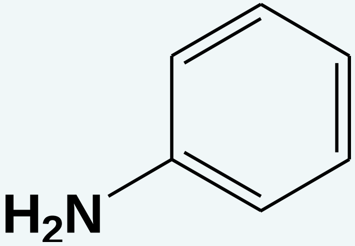
Ortho- and Para-Directing Activators: OH and NH_2



Meta-Directing Deactivators

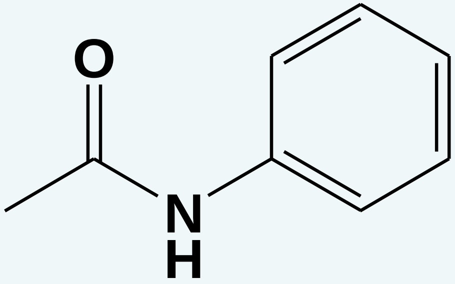


Explain why acetanilide is less reactive than aniline toward electrophilic substitution



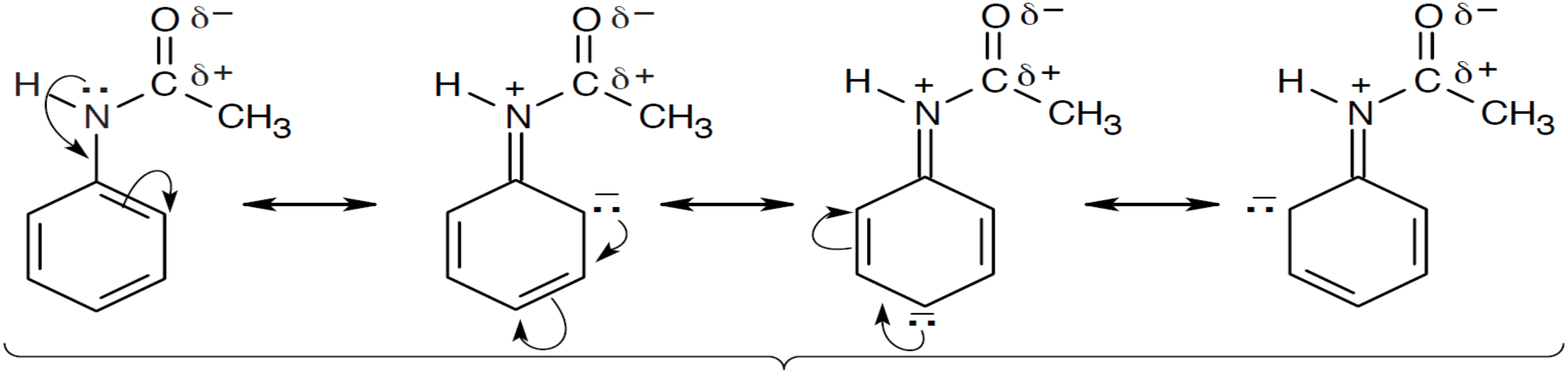
Aniline

>

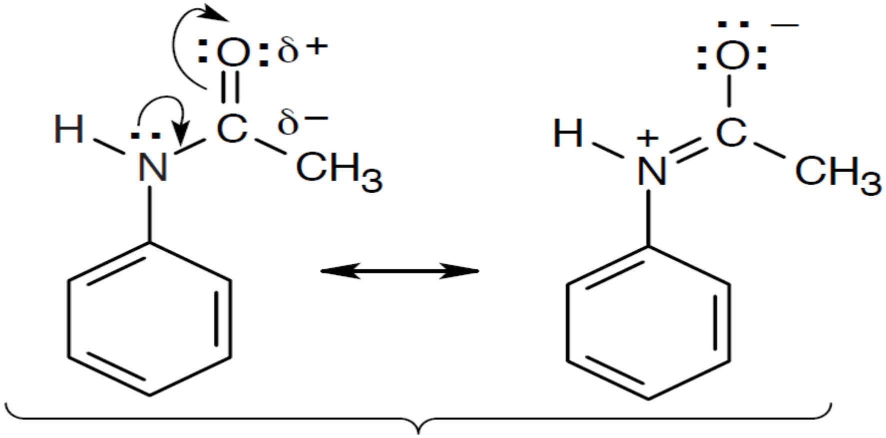


Acetanilide

Solution

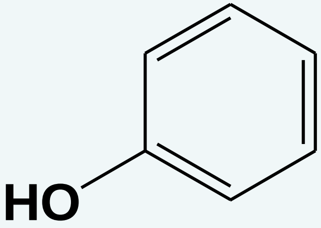


less favored

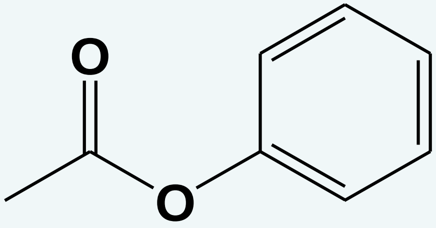


more favored

Explain why Phenylacetate is less reactive than phenol towards electrophilic substitution



>

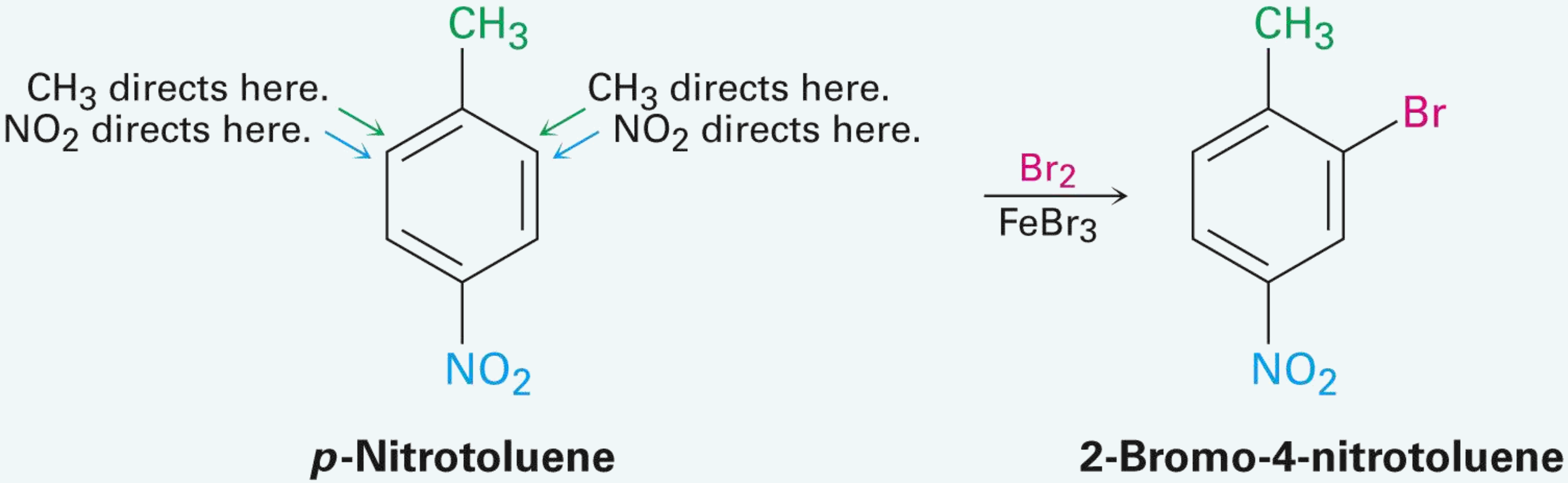


?

Trisubstituted Benzenes: Additivity of Effects

- **Additivity effects are based on three rules:**

  1] The situation is straightforward if the directing effects of the groups reinforce each other

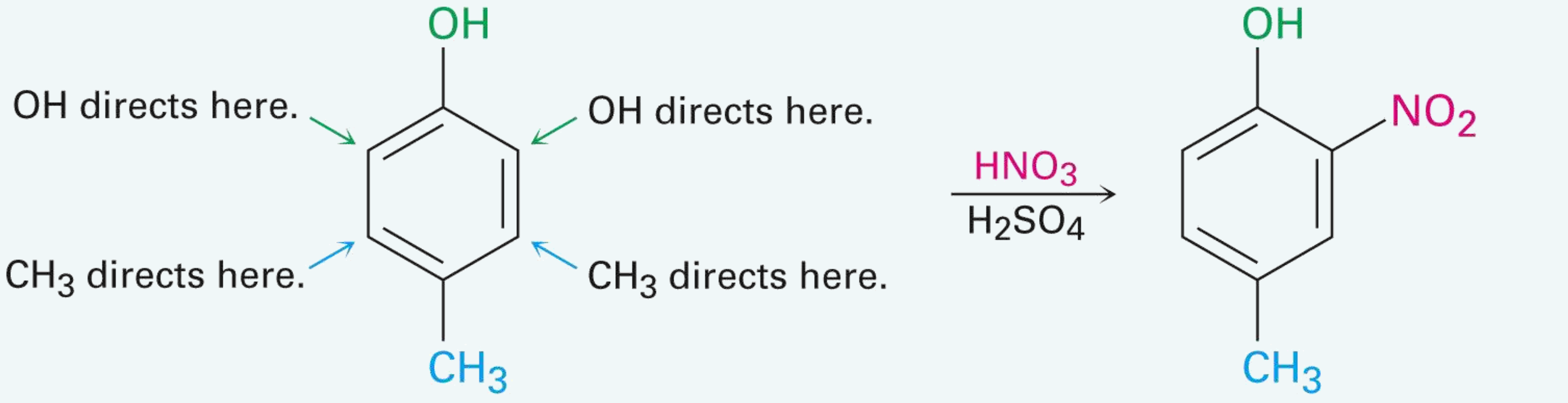


***p*-Nitrotoluene** → **2-Bromo-4-nitrotoluene**

Trisubstituted Benzenes: Additivity of Effects

2] If the directing effects of two groups oppose each other, the more powerful activating group decides the principal outcome

- Usually gives mixtures of products



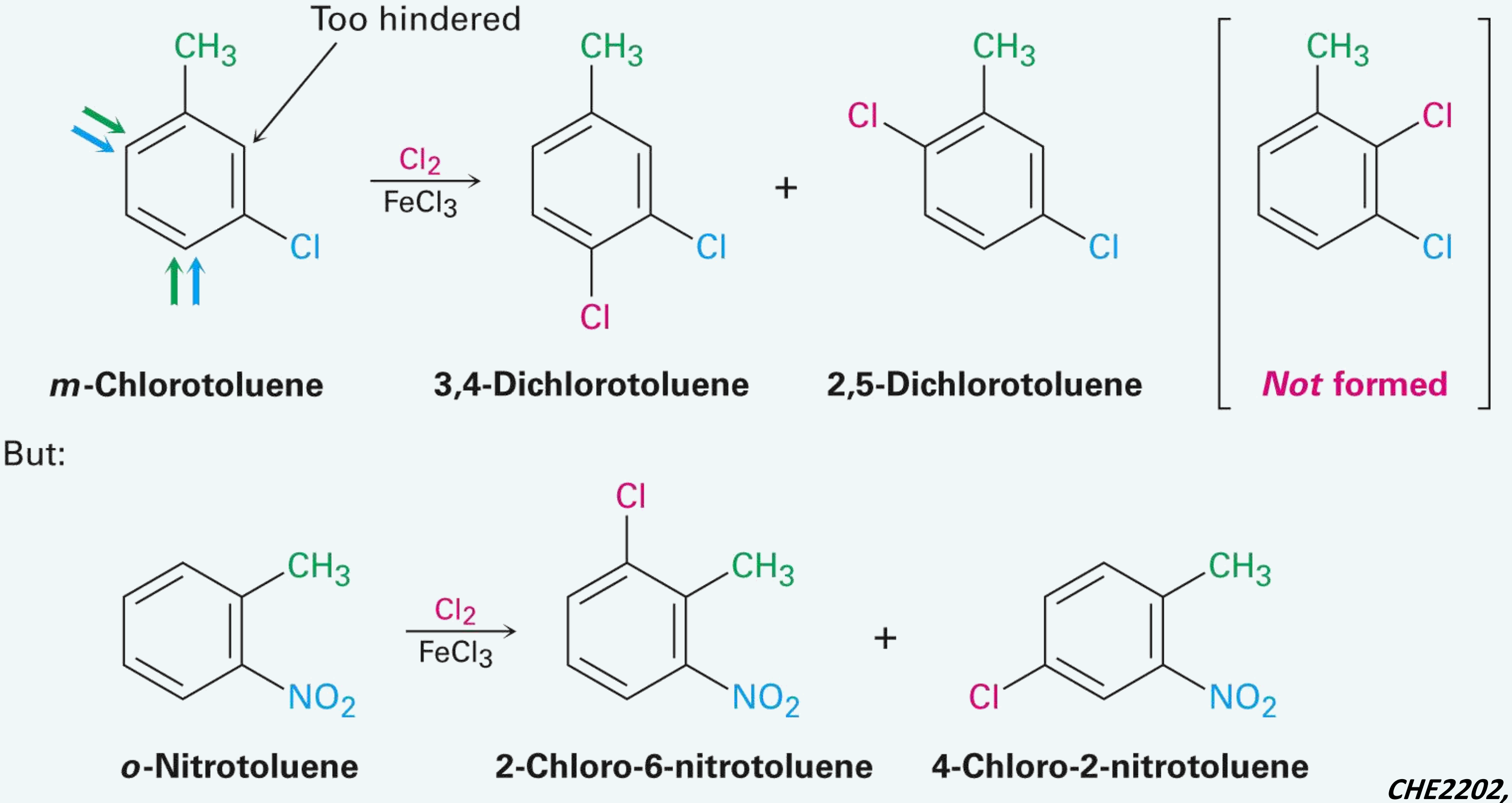
***p*-Methylphenol**

4-Methyl-2-nitrophenol

Trisubstituted Benzenes: Additivity of Effects

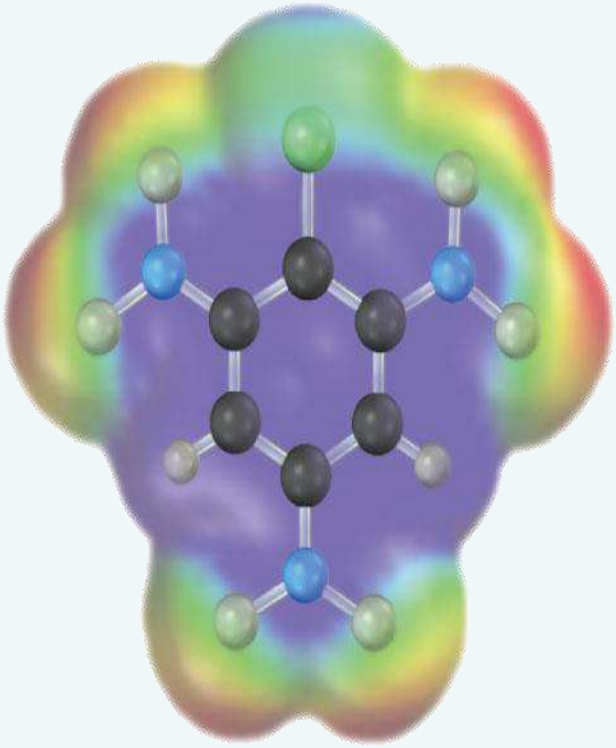
3] Substitution between two groups is rare when they are in a meta-disubstituted compound as the site is too hindered

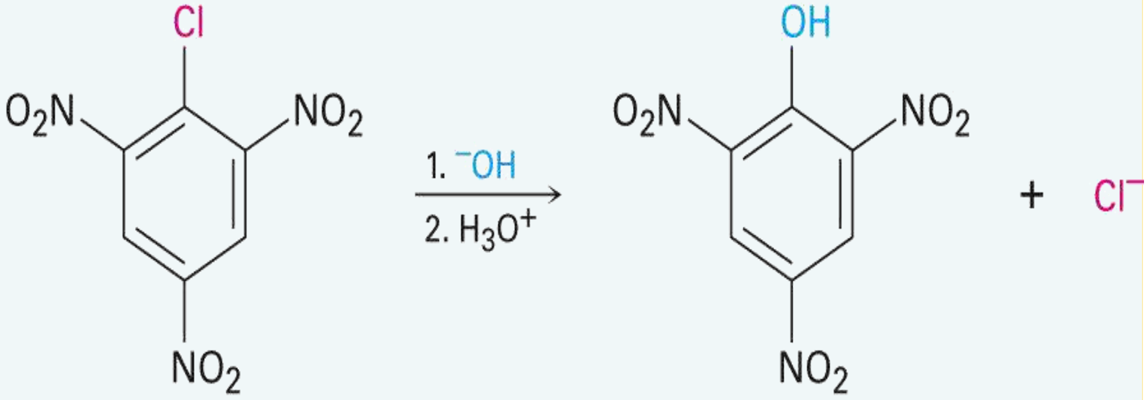
- **An alternate route must be taken in the preparation of aromatic rings with three adjacent substituents**



Nucleophilic Aromatic Substitution

- Aryl halides with electron-withdrawing substituents can also undergo a nucleophilic substitution reaction



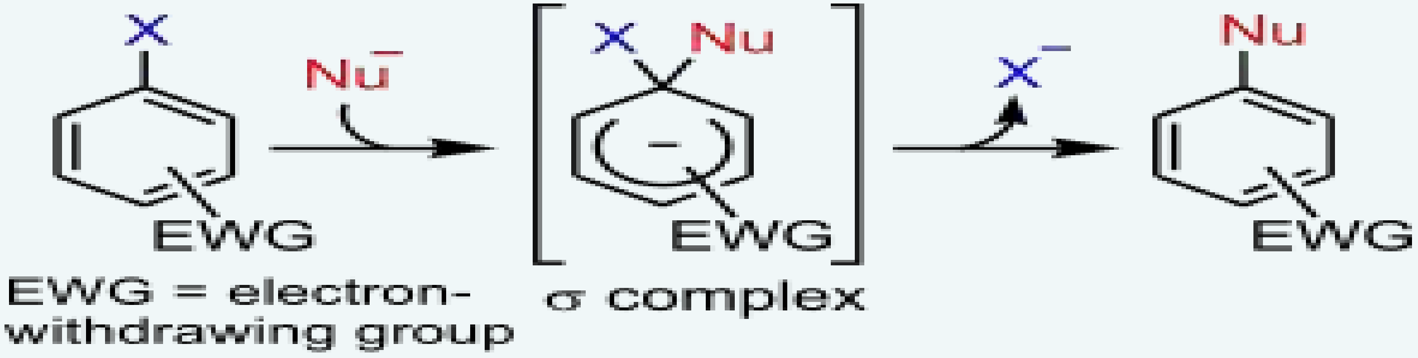


2,4,6-Trinitrochlorobenzene

2,4,6-Trinitrophenol (100%)

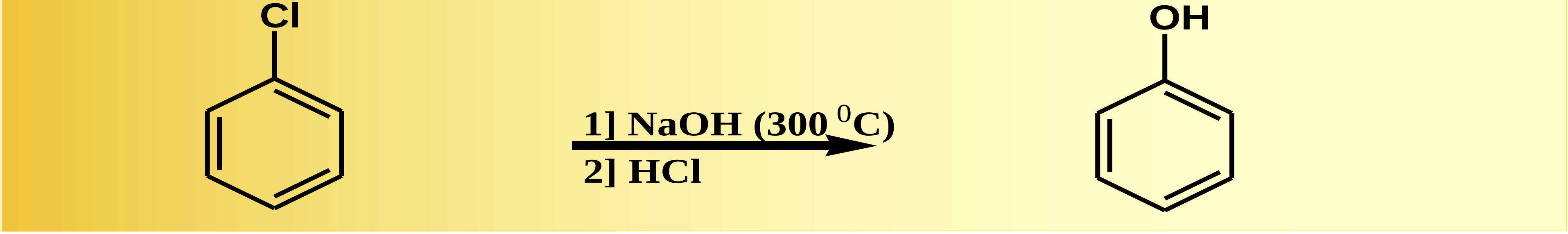
Picric acid

General mechanism of Nucleophilic aromatic substitution

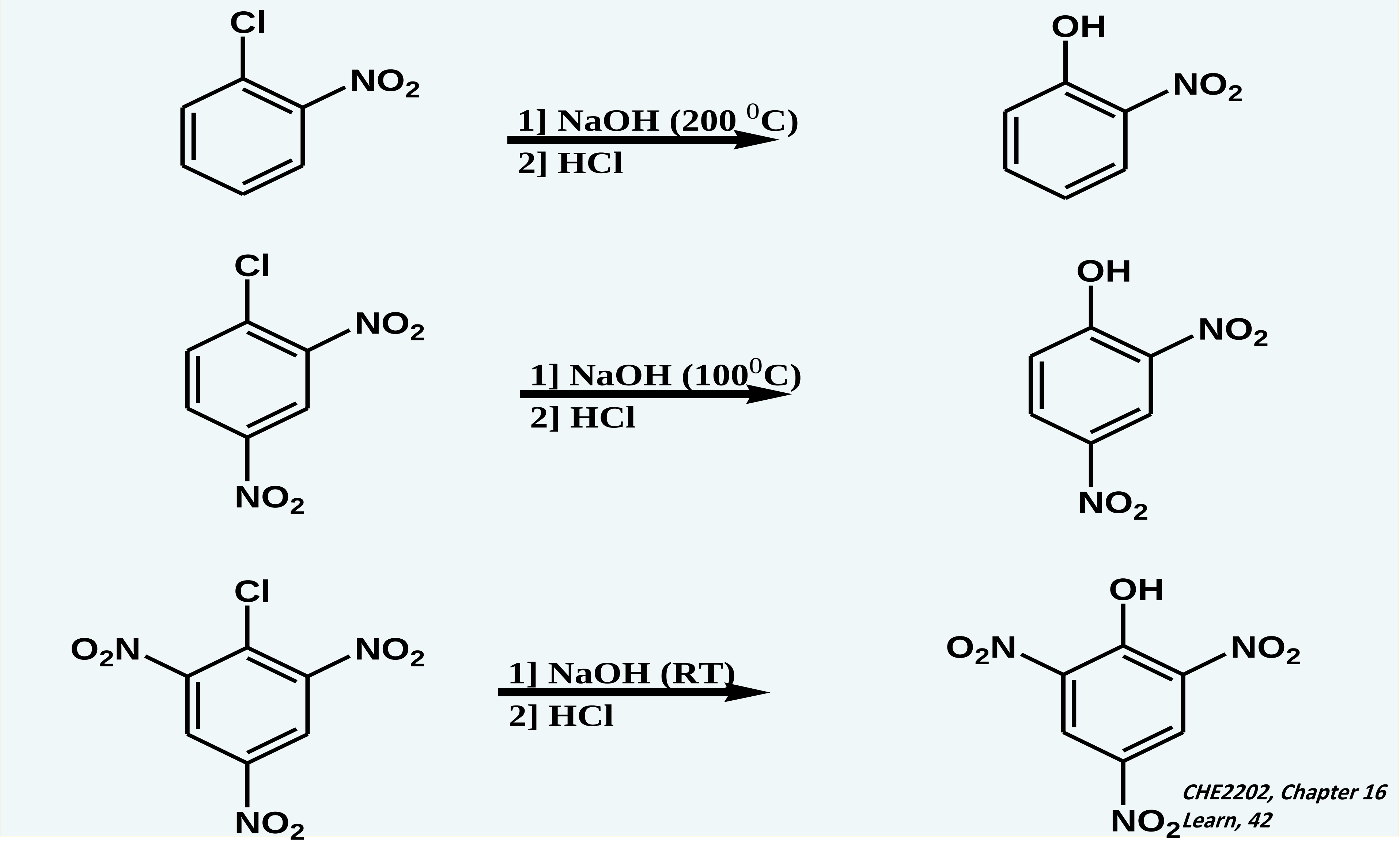


The best conditions for Nu Ar. Sub are:-

1] The availability of Electron withdrawing group.
2] The positions of such groups are orto or para; this is due to stabilization of carbanion intermediates



1] NaOH (300 ^{0}C)
2] HCl

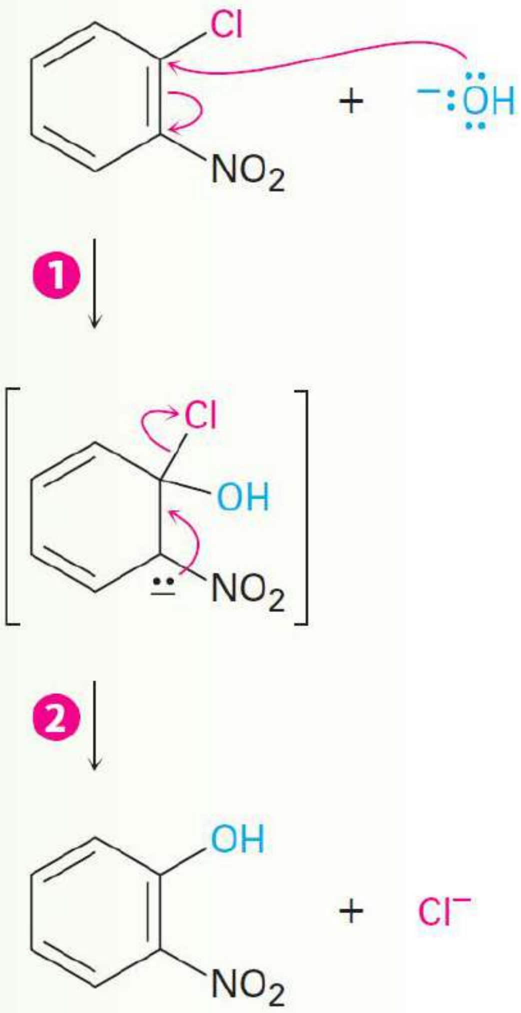


1] NaOH (200 ^{0}C)
2] HCl

1] NaOH (100^{0}C)
2] HCl

1] NaOH (RT)
2] HCl

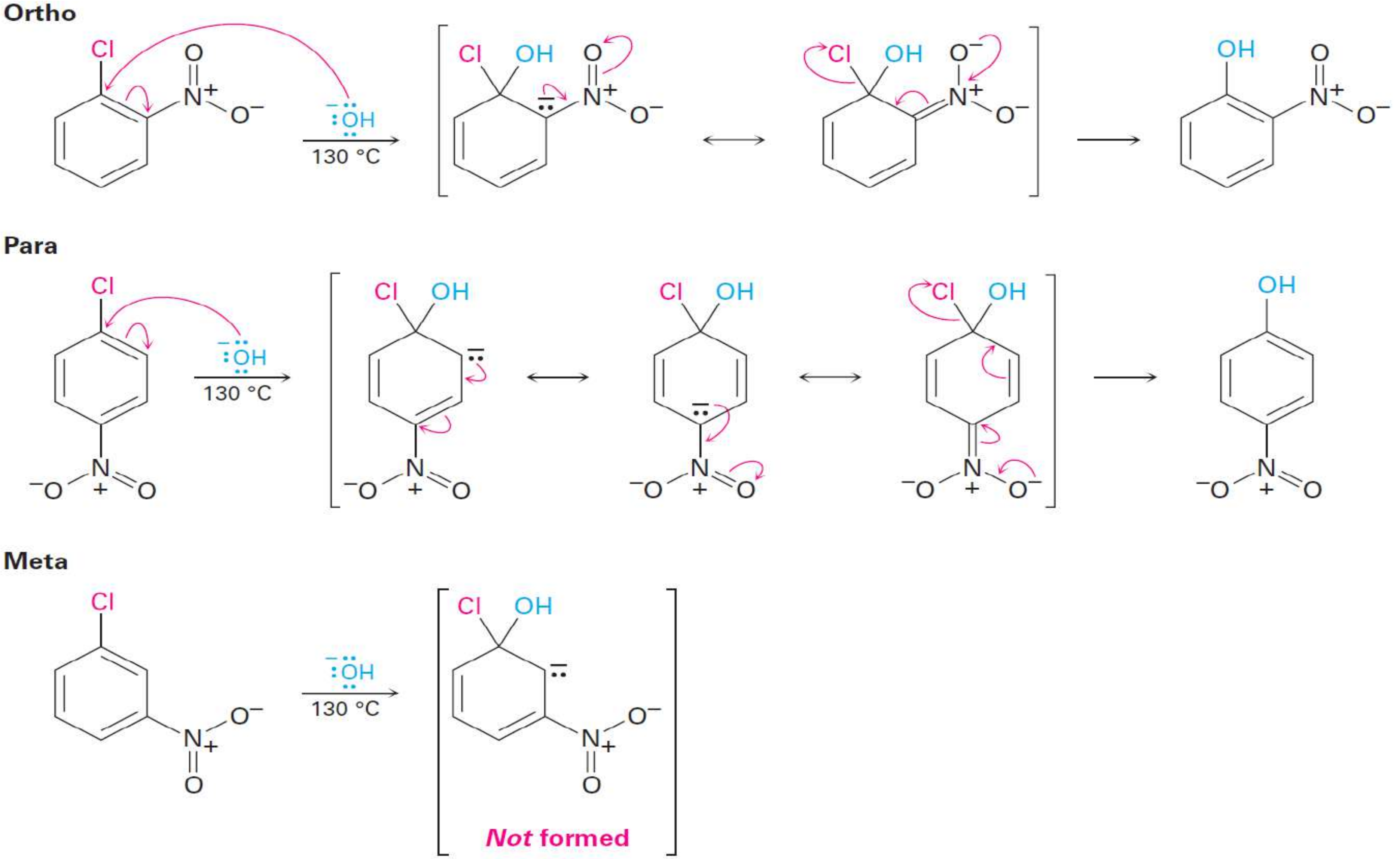
Mechanism of Nucleophilic Aromatic Substitution



① Nucleophilic addition of hydroxide ion to the electron-poor aromatic ring takes place, yielding a stabilized carbanion intermediate.

② The carbanion intermediate undergoes elimination of chloride ion in a second step to give the substitution product.

Nucleophilic Aromatic Substitution of Nitrochlorobenzenes by hydroxide

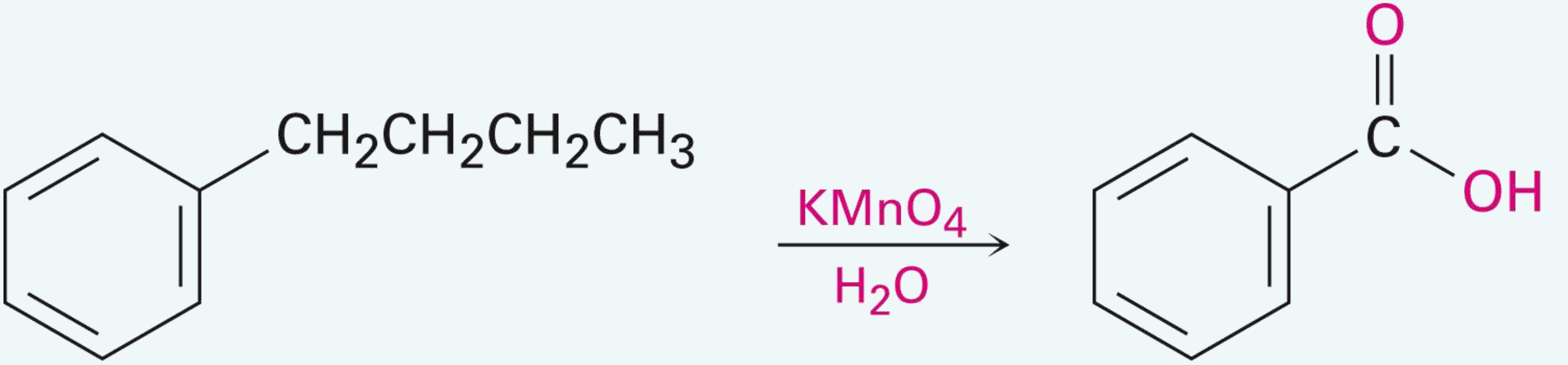


Differences b/w Electrophilic and Nucleophilic Aromatic Substitutions

Electrophilic substitutions	**Nucleophilic substitutions**
• Favored by electron-donating substituents	• Favored by electron-withdrawing substituents
• Electron-withdrawing groups cause ring deactivation	• Electron-withdrawing groups cause ring activation
• Replace hydrogen on the ring	• Replace a leaving group Mainly halides

Oxidation of Aromatic Compounds

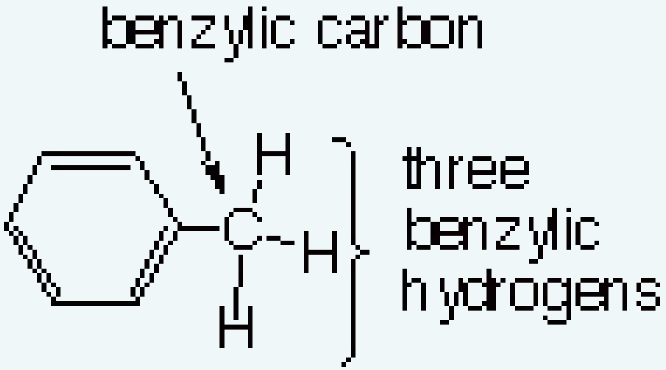
- In the presence of an aromatic ring, alkyl side chains are converted to carboxyl groups through oxidation
  - Alkylbenzene is converted to benzoic acid (**<u>The most important requirement is the availability of benzylic hydrogen)</u>**

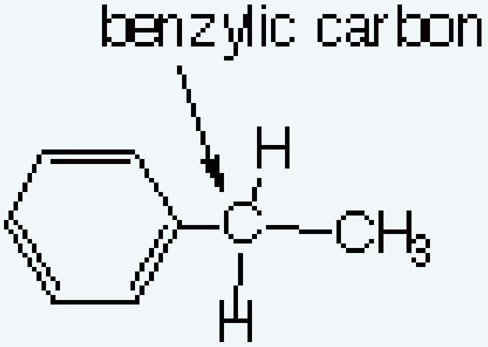


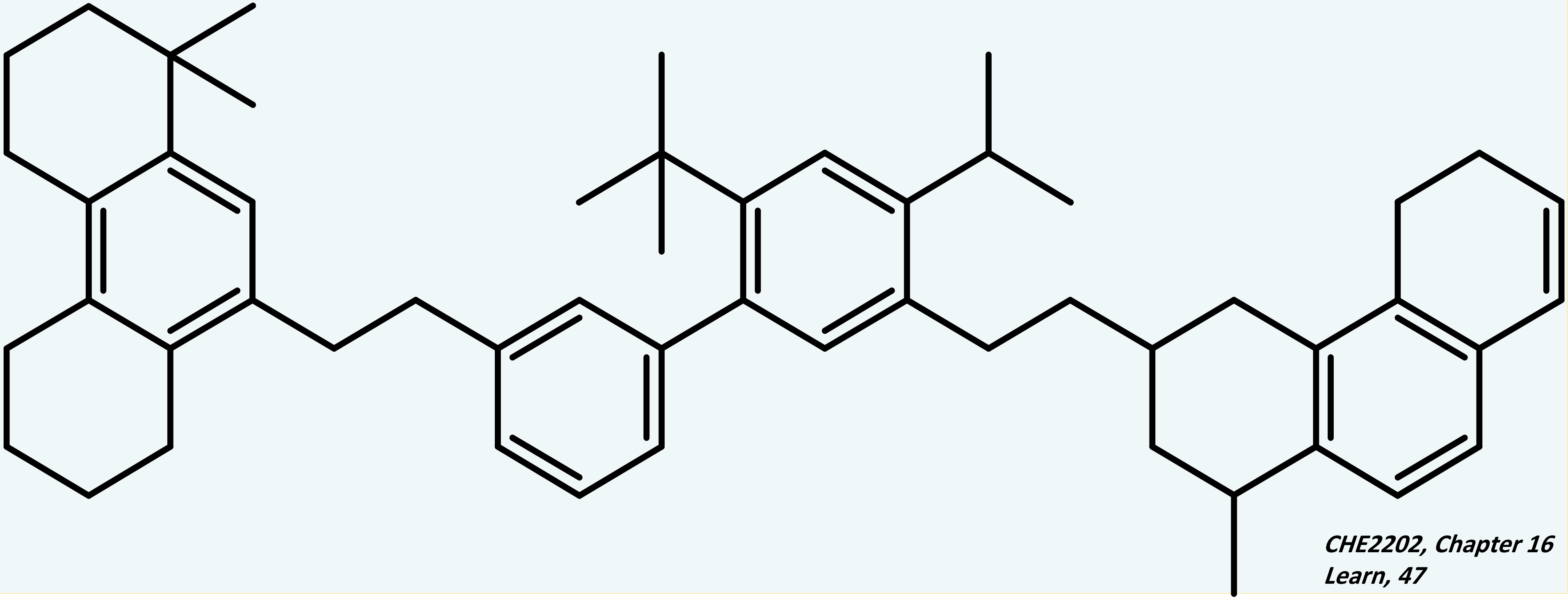
Butylbenzene

Benzoic acid (85%)

Benzylic hydrogen



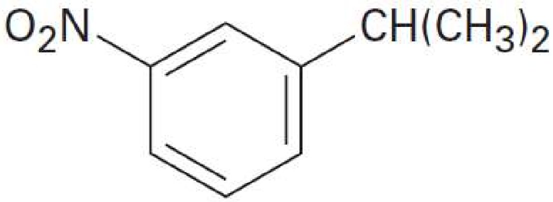




Worked Example

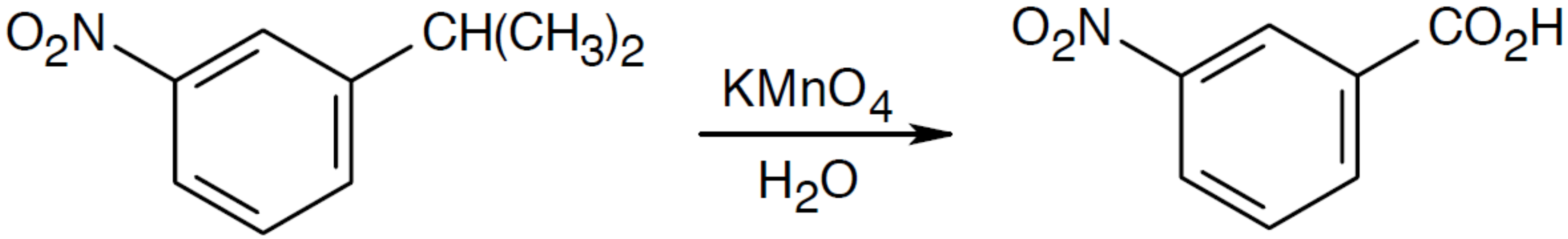
- **Mention the aromatic substance that is obtained if $KMnO_4$ undergoes oxidation with the following substance**

(a)



Solution:

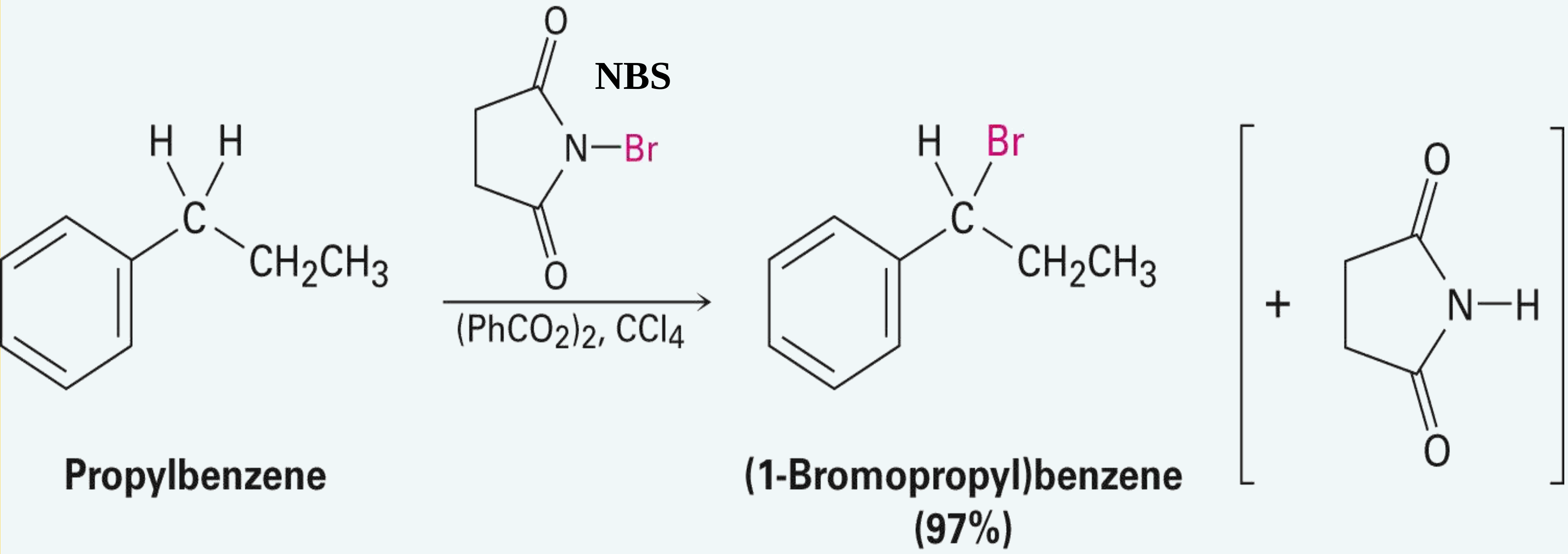
Oxidation takes place at the benzylic position



m-Nitrobenzoic acid

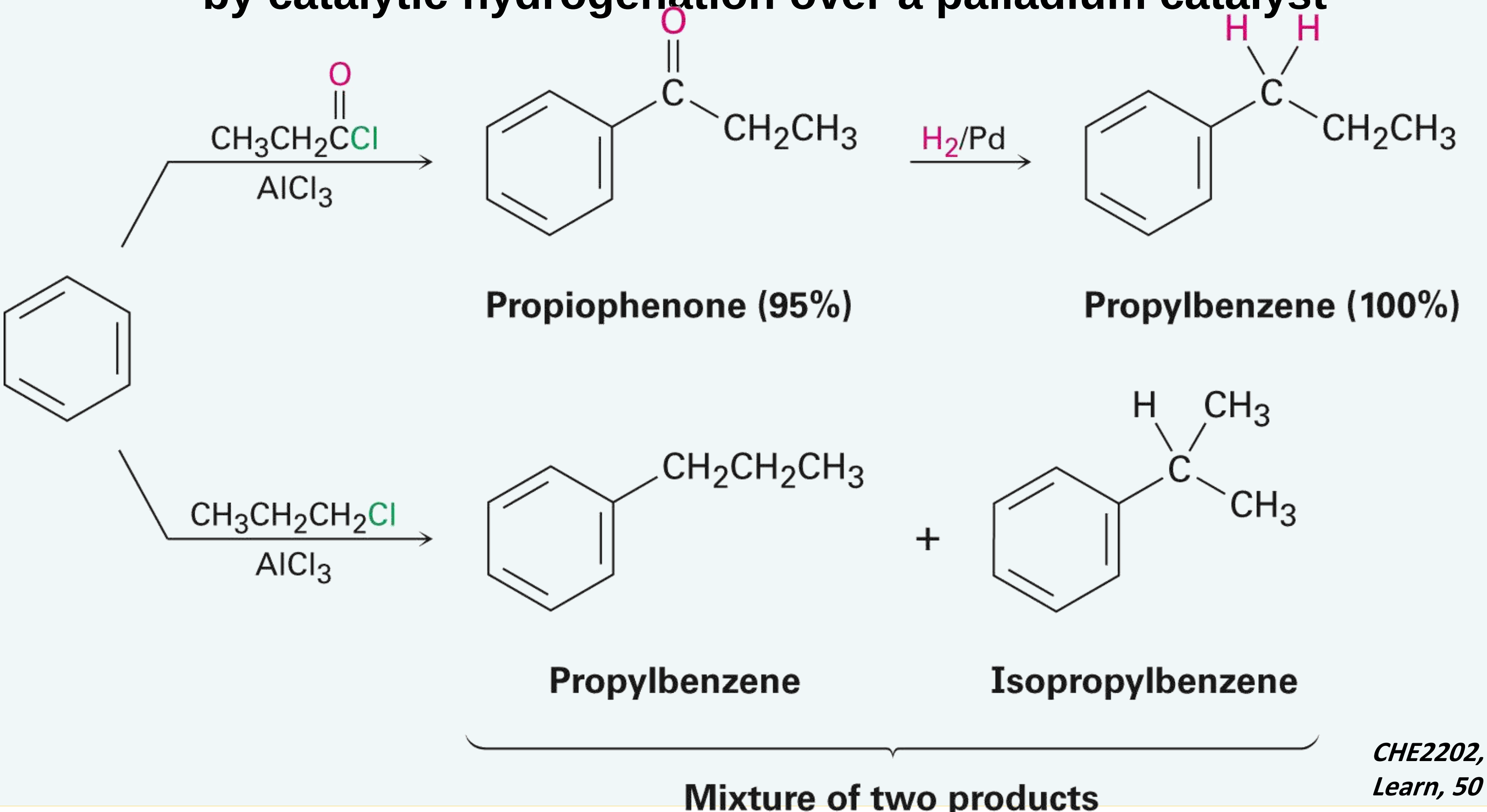
Bromination of Alkylbenzene Side Chains

- Occurs when an alkylbenzene (alo benzylic C-H) is treated with *N*-bromosuccinimide (NBS)

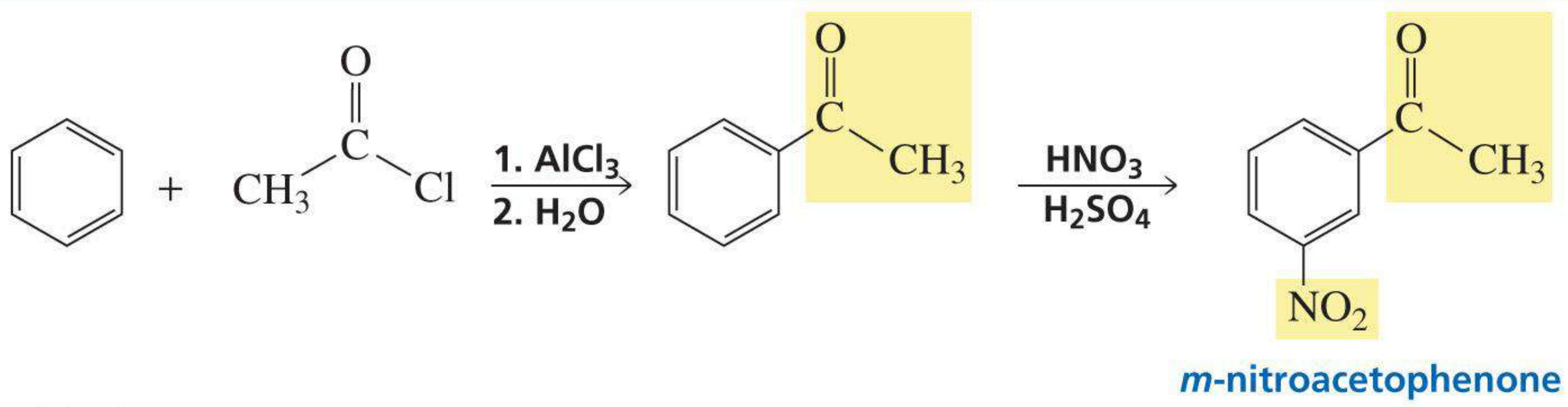


Reduction of Aryl Alkyl Ketones

- **An aromatic ring activates a neighboring carbonyl group toward reduction**
  - **An aryl <u>alkyl ketone</u> can be converted into an alkylbenzene by catalytic hydrogenation over a palladium catalyst**

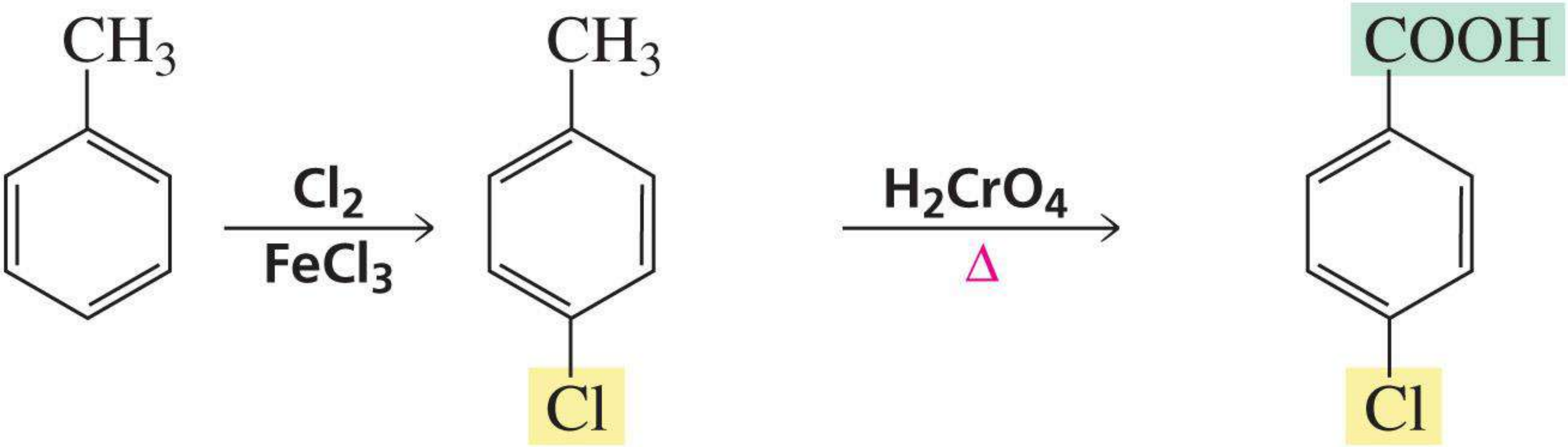


The Order of the Reactions is Important

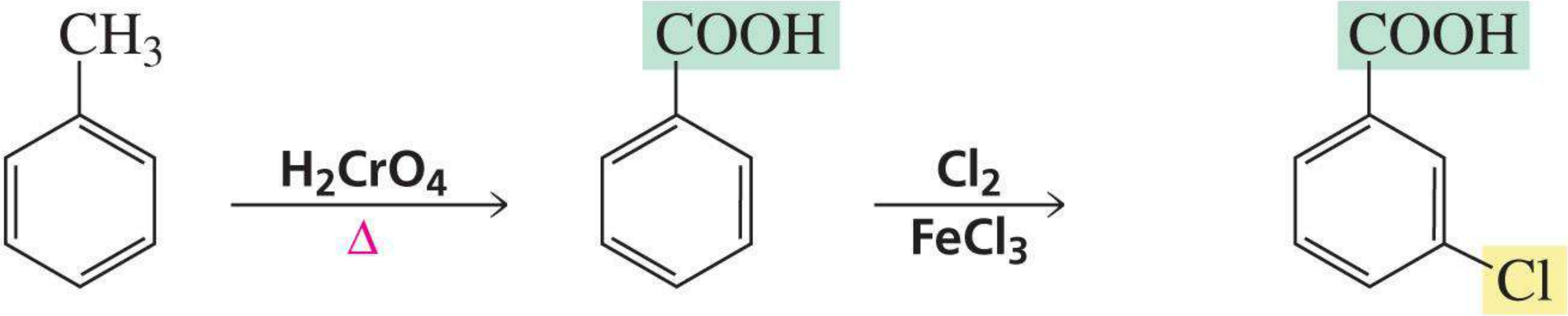


The acetyl group must be added first because a Friedel–Crafts acylation <u>will not occur</u> with a meta director on the ring.

The Order of the Reactions is Important



p-chlorobenzoic acid

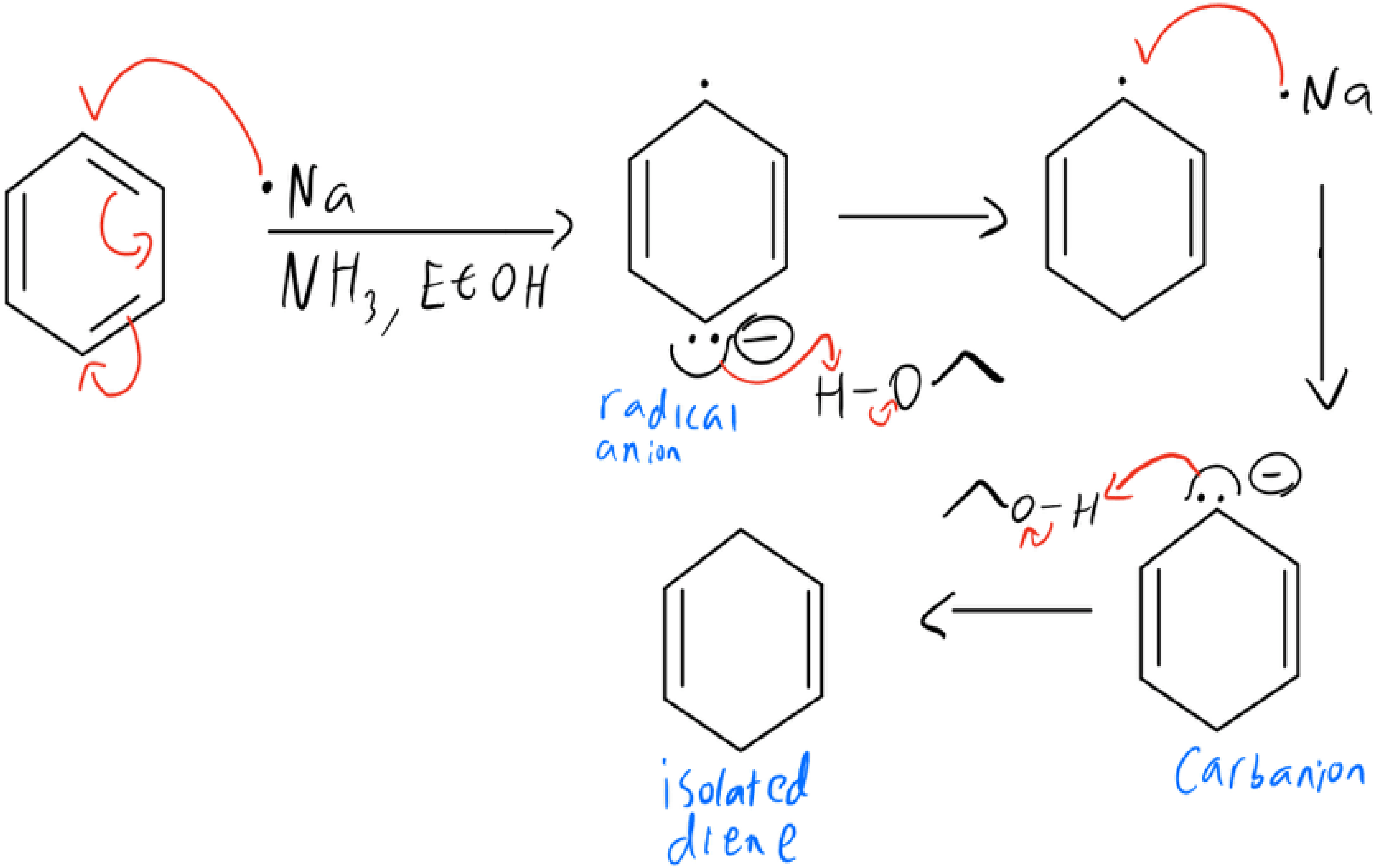


m-chlorobenzoic acid

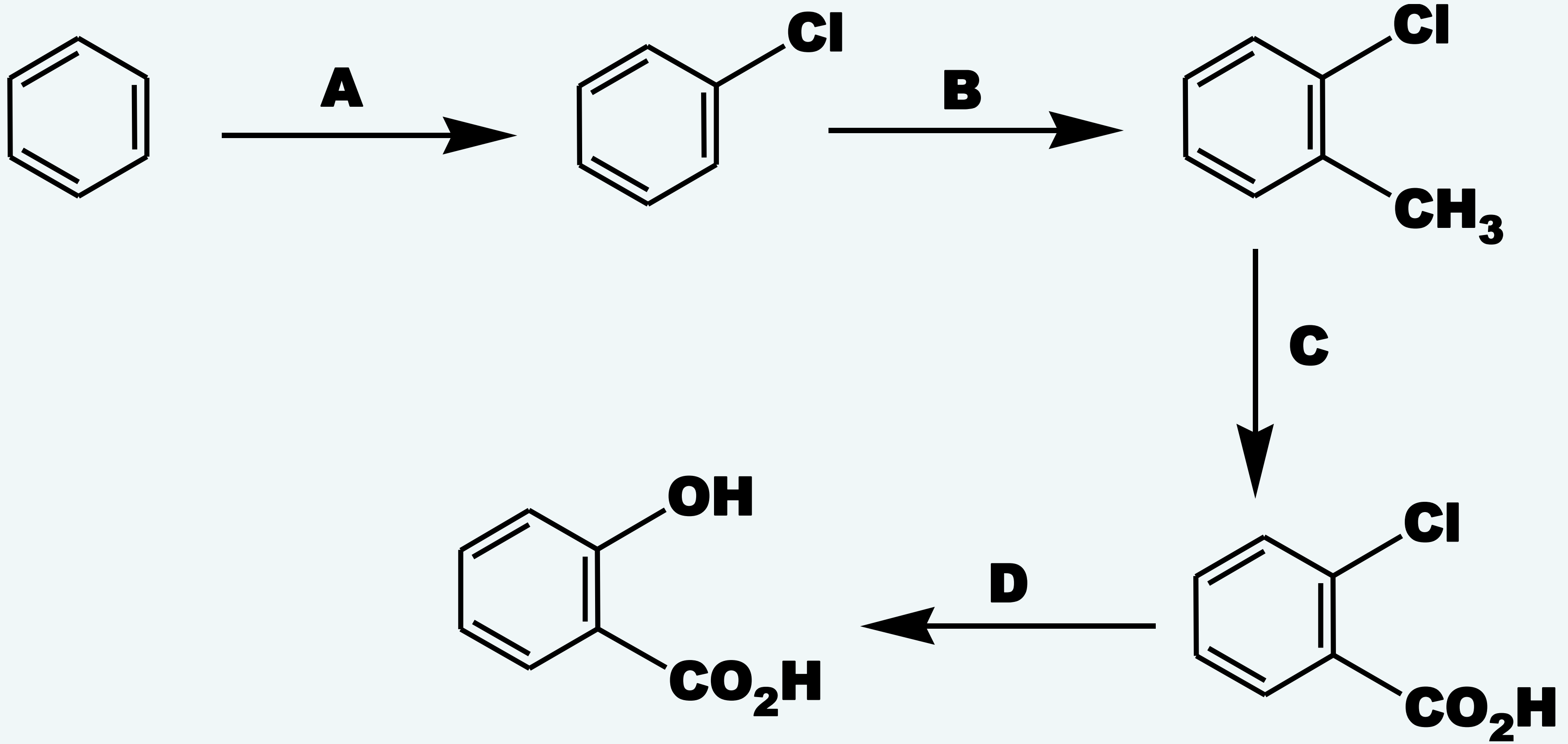
Birch Reduction

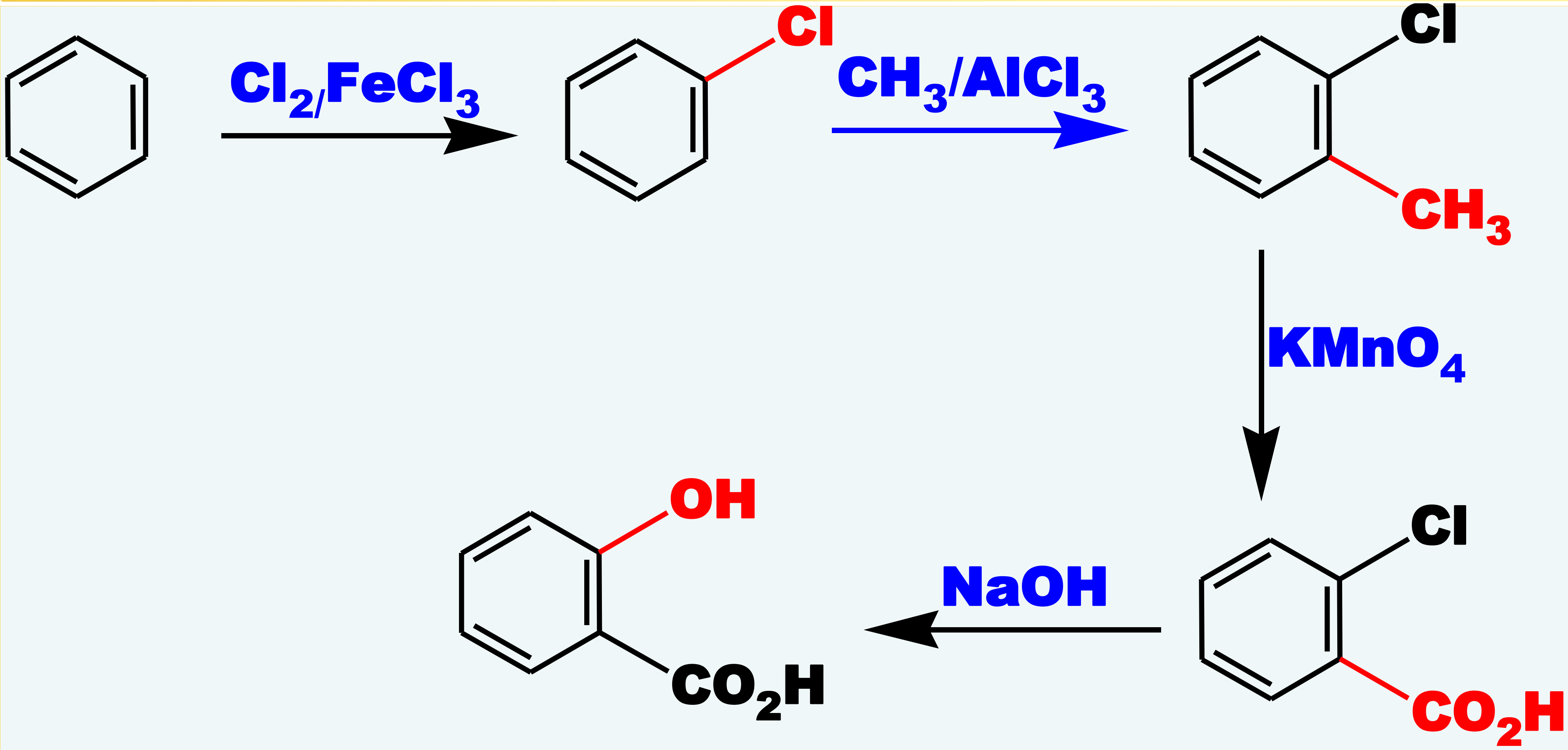
Reduction of benzene to 1,4-cyclohexadiene

$$Na \longrightarrow Na^{\oplus} + e$$



Salicylic acid synthesis




Cl
Cl2/FeCl3
CH3/AlCl3
Cl
CH3
KMnO4
Cl
CO2H
NaOH
OH
CO2H

Discussion

Q1] True or False:-

[ ] Nitrobenzene is easier to be alkylated than benzaldehyde.

[ ] Benzylic C-H can be oxidized easily using $KMnO_4$

[ ] Uncontrolled reaction can be noticed in all E Ar Sub.

[ ] NBS can be used to brominate benzene.

[ ] Aromatic compounds prefer substitution to addition reactions

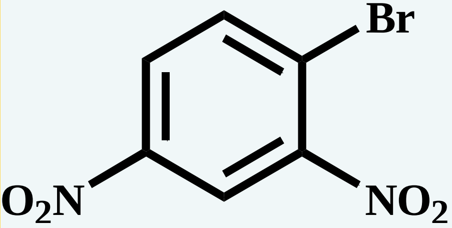
[ ] F.C. Acylation is classified as a controlled reaction

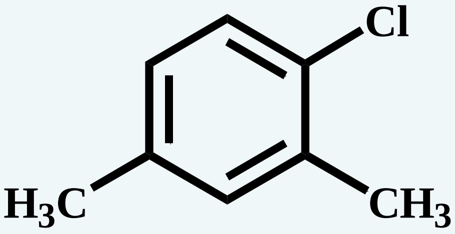
[ ] Birch reduction leads to the formation of 1,3-Cyclohexadiene.

[ ] The best Nu Ar Sub is the one that have EWGs are at meta position to halide.

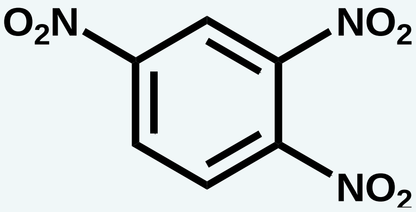
[ ] There is a directly proportional between E. Ar. Sub. and electron donating groups.

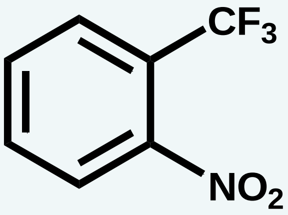
Q5] Circle the compound that is able to undergo easier reaction (according to the given one). Justify your choice in brief.





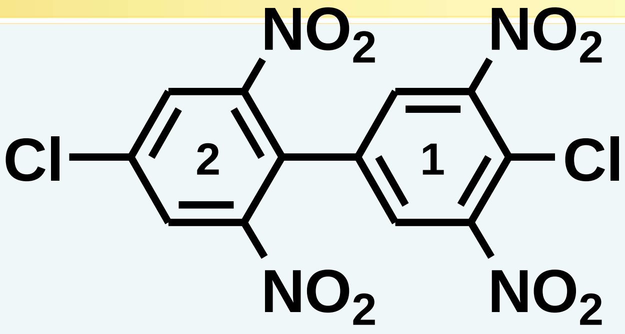
[Nucleophilic aropmatic substitution]





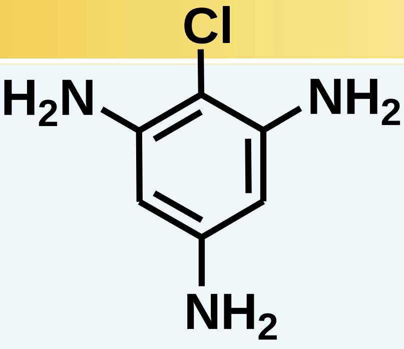
[Sulfonation]

Q6]Circle the ring you expect the NUCLEOPHILIC AROMATIC SUBSTITUTION to occur; Explain briefly.

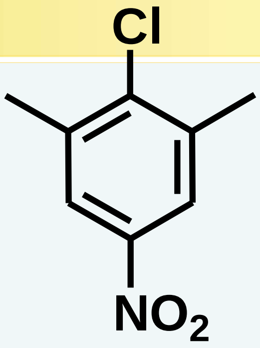


Q7] Arrange the following according to the ease of Nucleophilic aromatic substitution.

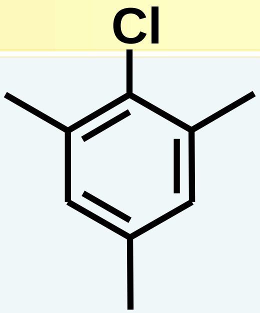
A



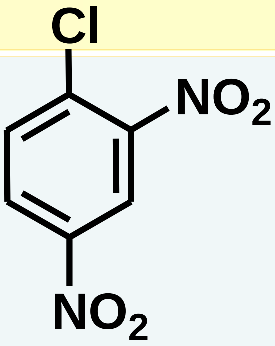
1



2

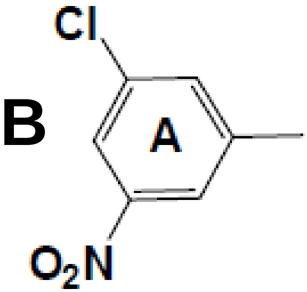


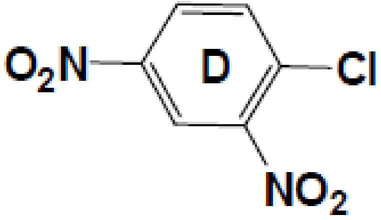
3

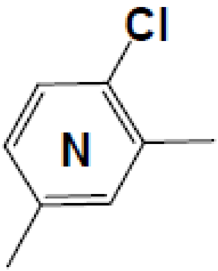


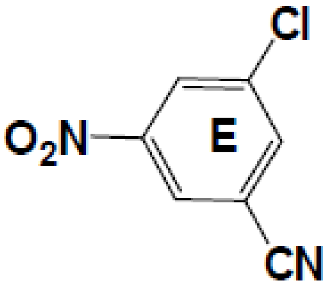
4

B

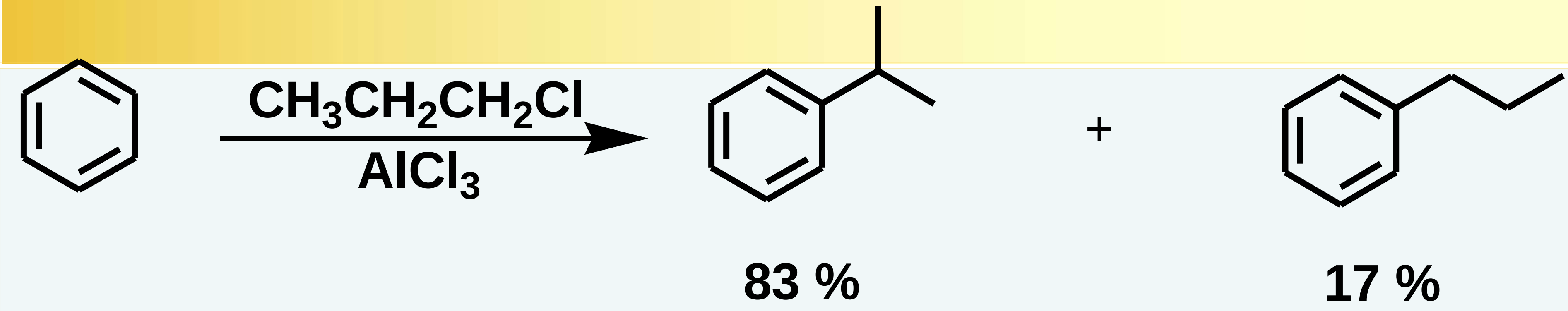




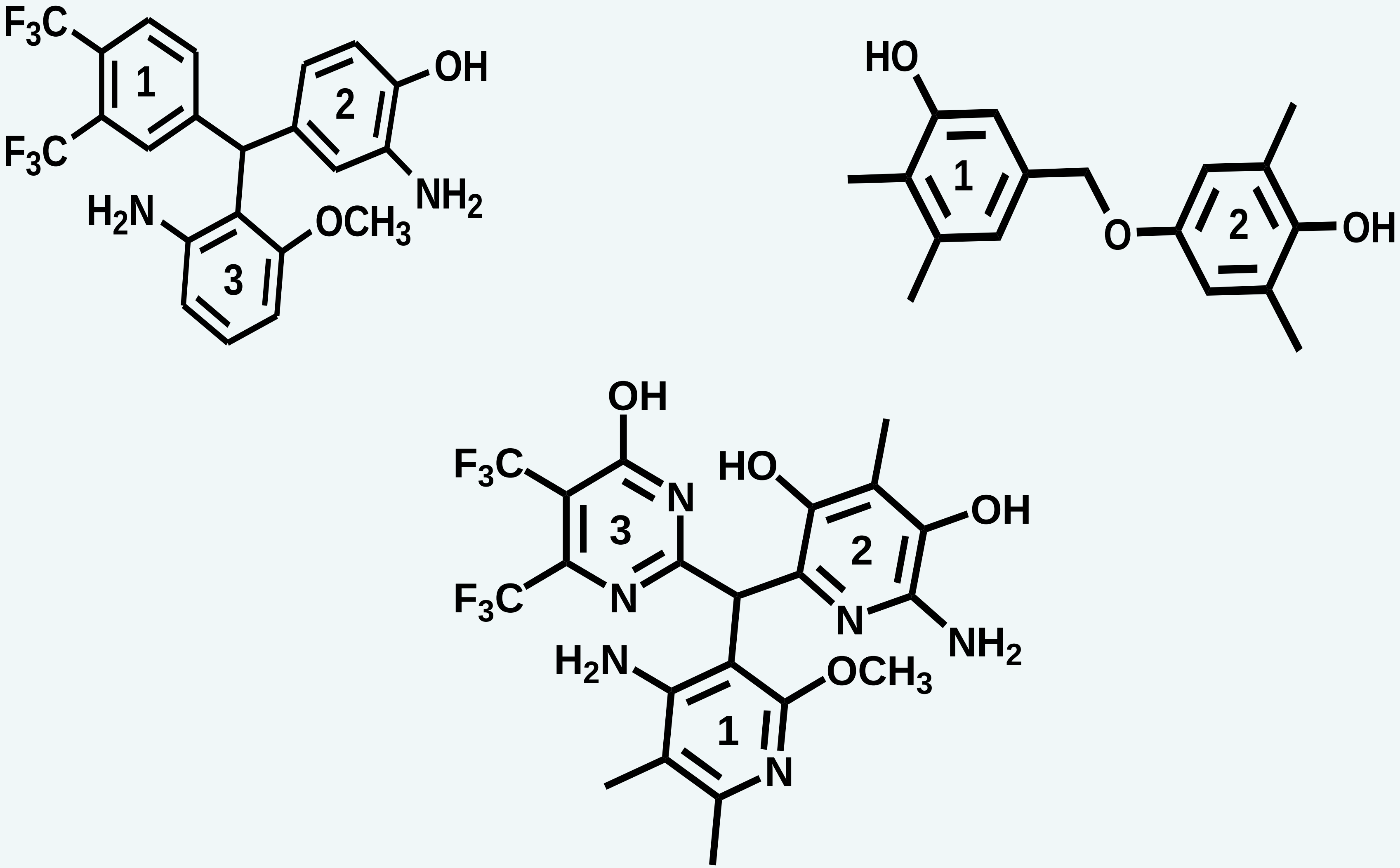




Q8] Discuss the yield percentage in the following reaction

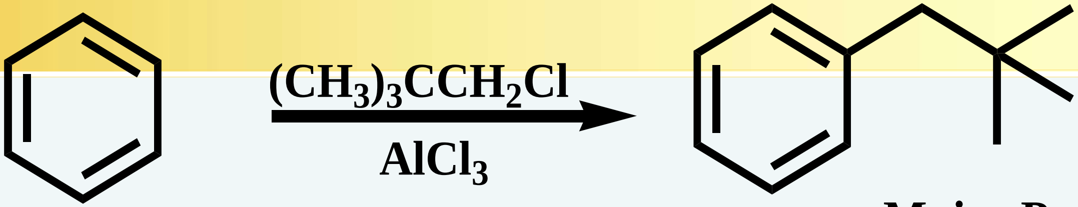


Q9] At which ring would you expect <u>ELECTROPHILIC AROMATIC SUBSTITUTION</u> to occur? Explain briefly.



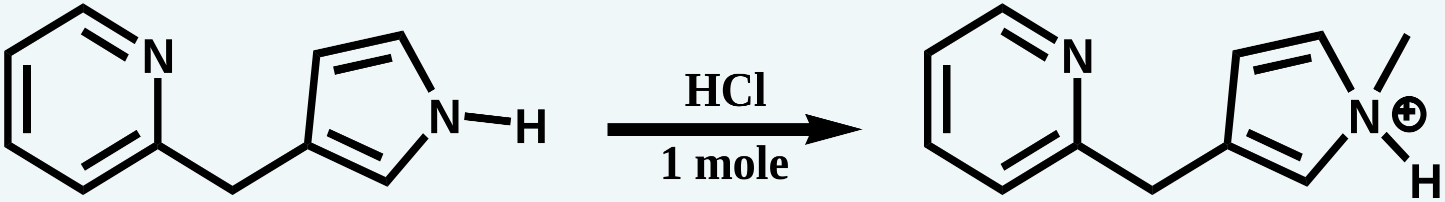
Q10] What is wrong with each of the following reactions?

a]

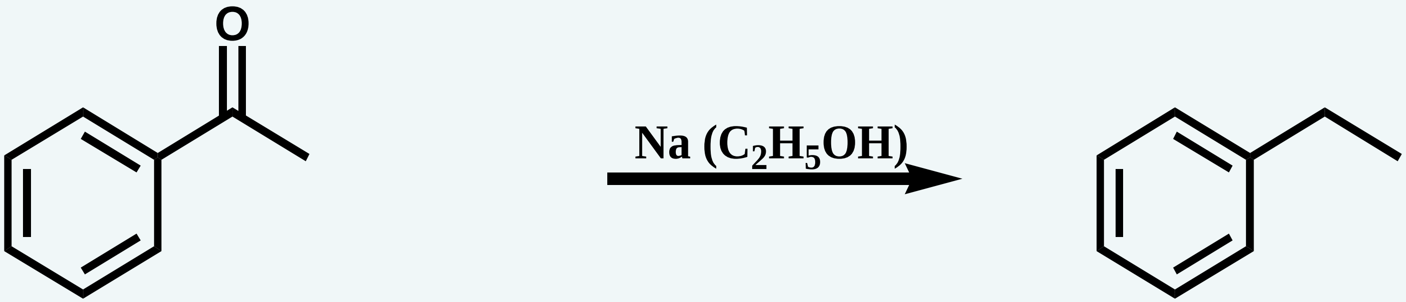


Major Product

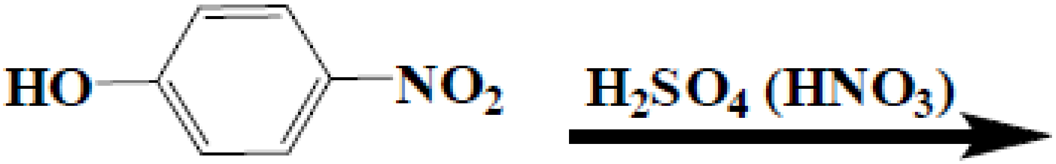
b]

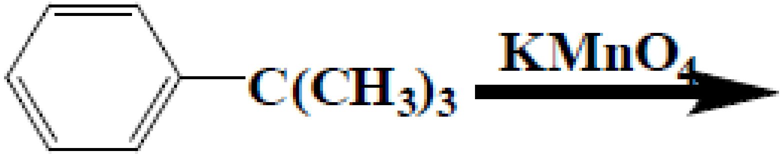


c]



Q 11] Provide the missing





Why

1. **Inspite of its classification as a deactivating atom; chloride is ortho- para dire**

2. **Formyl group is meta director?**

3. **Friedel-Crafts alkylation is accopmpanied with polyalkylation product?**

4. **phenol is more reactive than phenyl acetate towards bromination?**