Topic: Aromatic Electrophilic substitution Reaction

By

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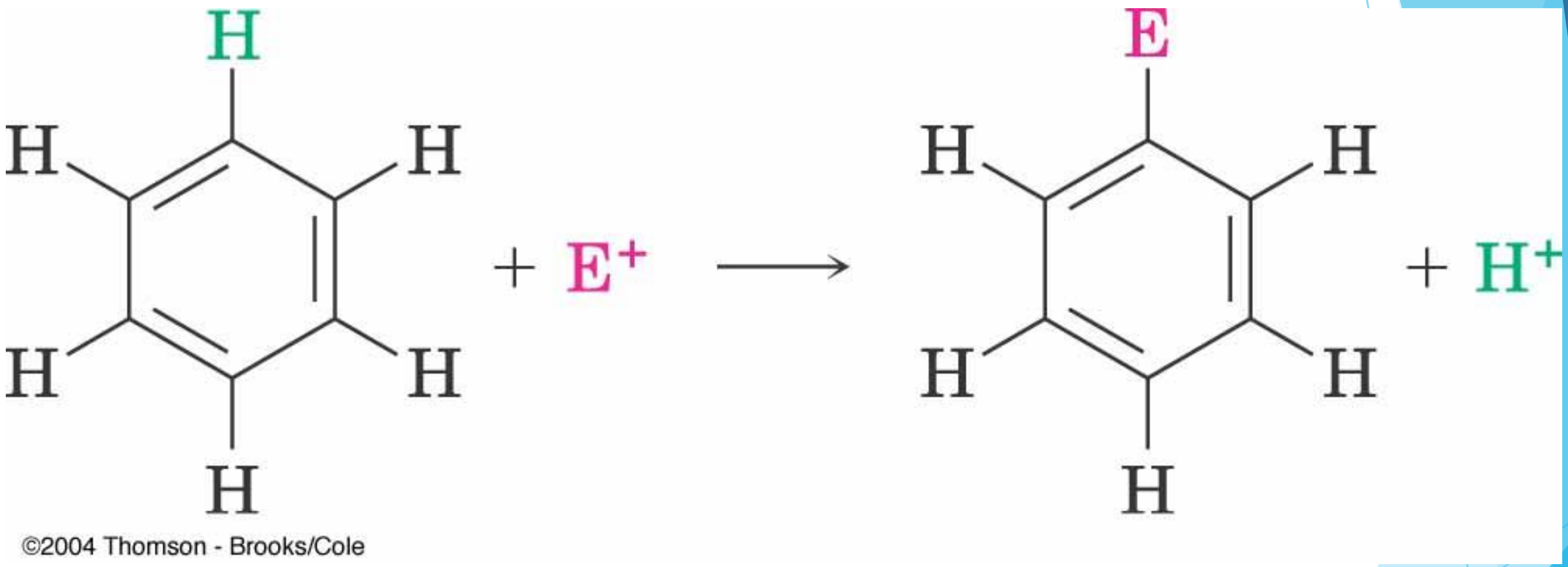
PhD Pursuing)

Contents

Electrophilic Aromatic Substitution



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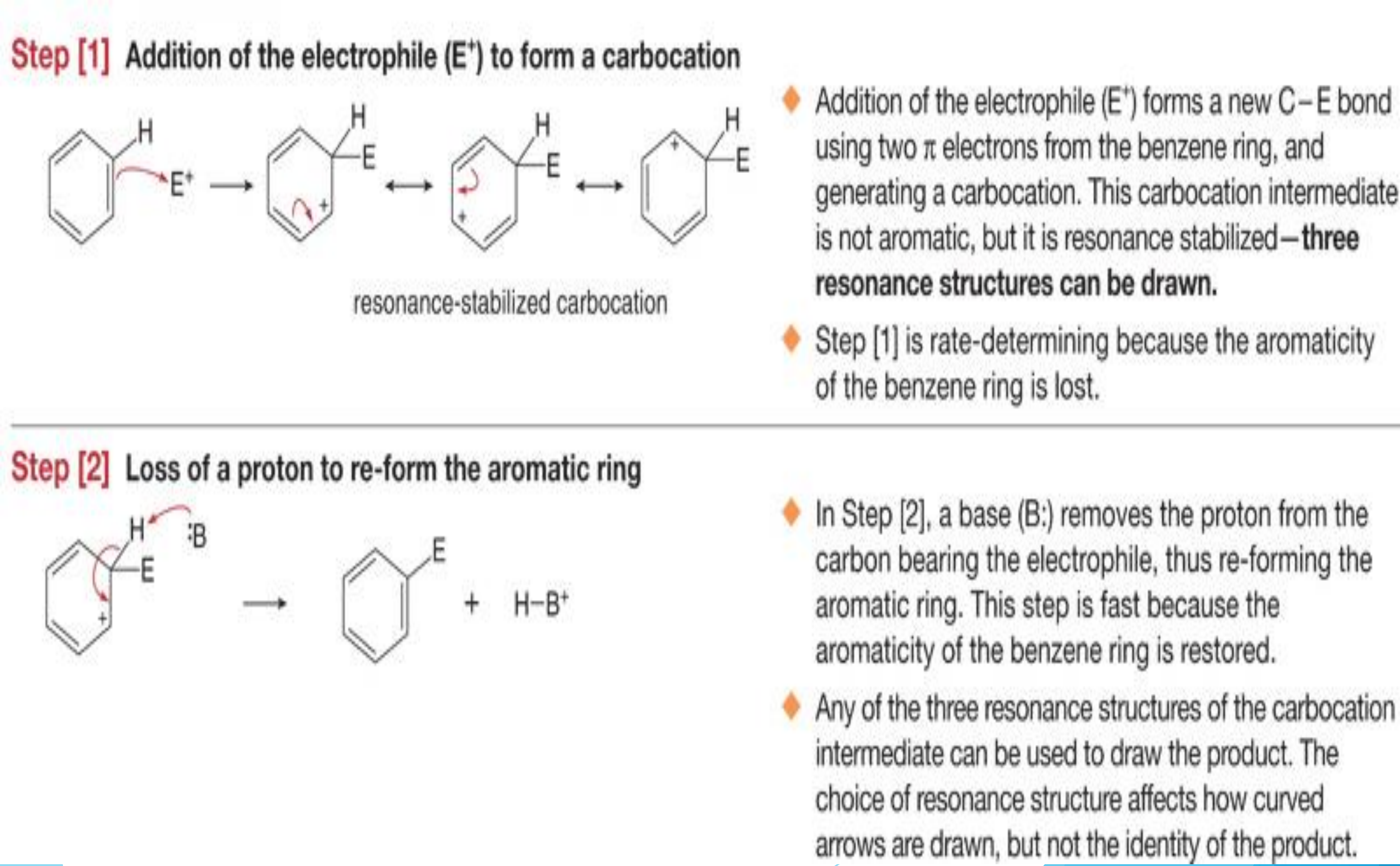
Mechanism of Aromatic



Step [1] **Addition of the electrophile (E^+) to form a carbocation**

resonance-stabilized carbocation

- Addition of the electrophile (E^+) forms a new C–E bond using two π electrons from the benzene ring, and generating a carbocation. This carbocation intermediate is not aromatic, but it is resonance stabilized—**three resonance structures can be drawn.**
- Step [1] is rate-determining because the aromaticity of the benzene ring is lost.

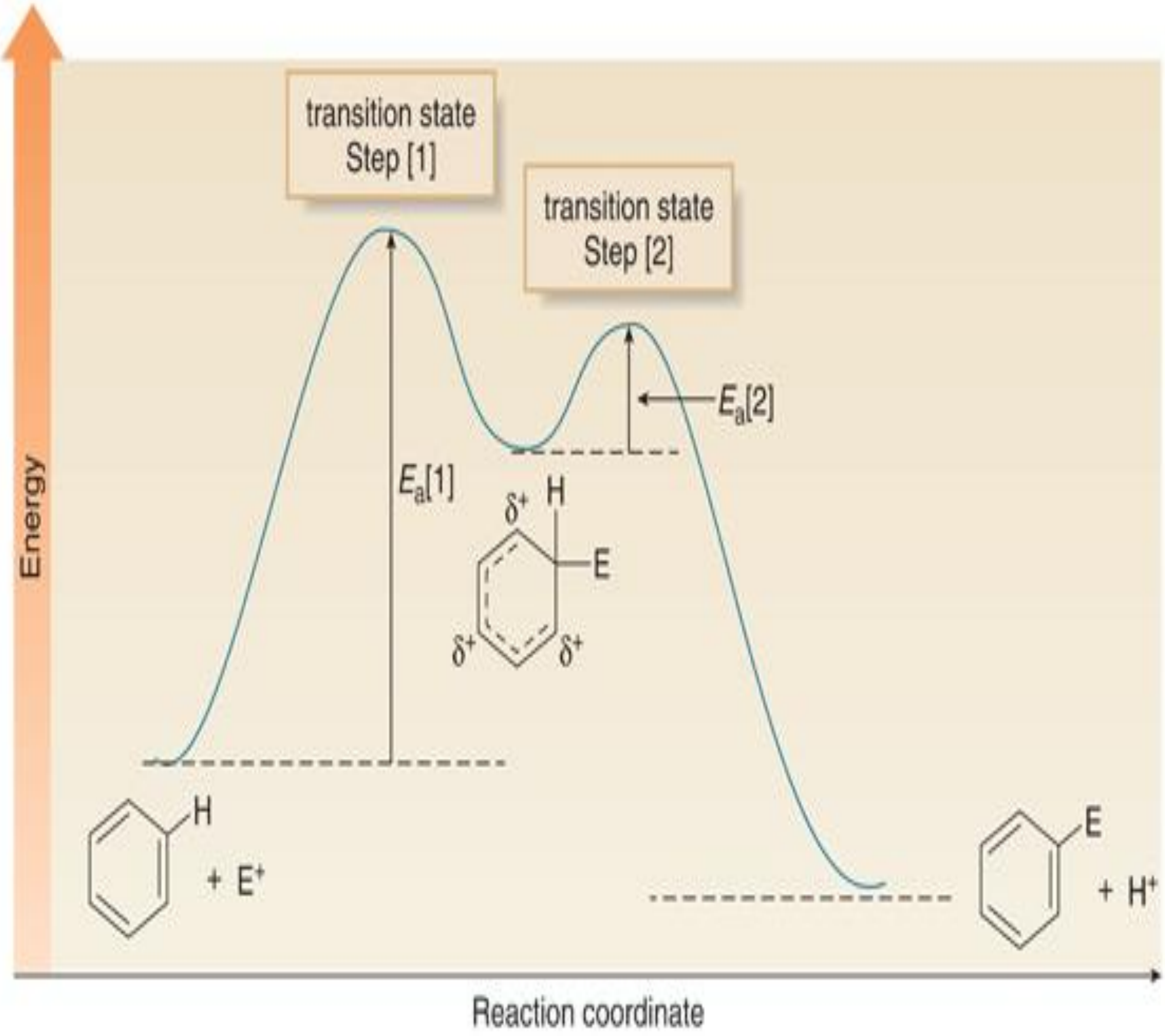
Step [2] **Loss of a proton to re-form the aromatic ring**

- In Step [2], a base (B:) removes the proton from the carbon bearing the electrophile, thus re-forming the aromatic ring. This step is fast because the aromaticity of the benzene ring is restored.
- Any of the three resonance structures of the carbocation intermediate can be used to draw the product. The choice of resonance structure affects how curved arrows are drawn, but not the identity of the product.

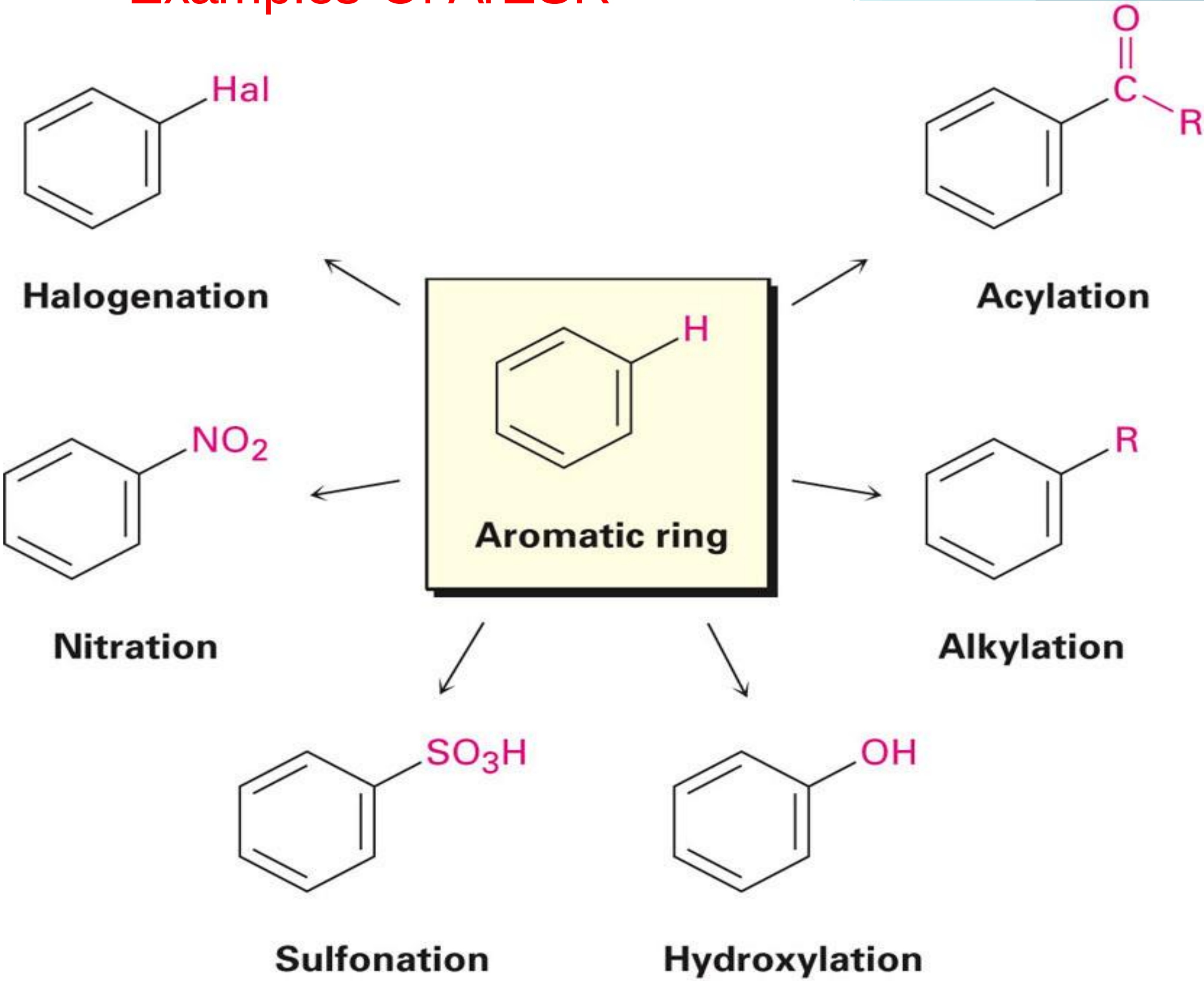
Energy Profile diagram

Figure 18.2 Energy diagram for electrophilic aromatic substitution: $PhH + E^+ \rightarrow PhE + H^+$

- The mechanism has two steps so there are two energy barriers.
- Step [1] is rate-determining; its transition state is at higher energy.



Examples Of ArESR



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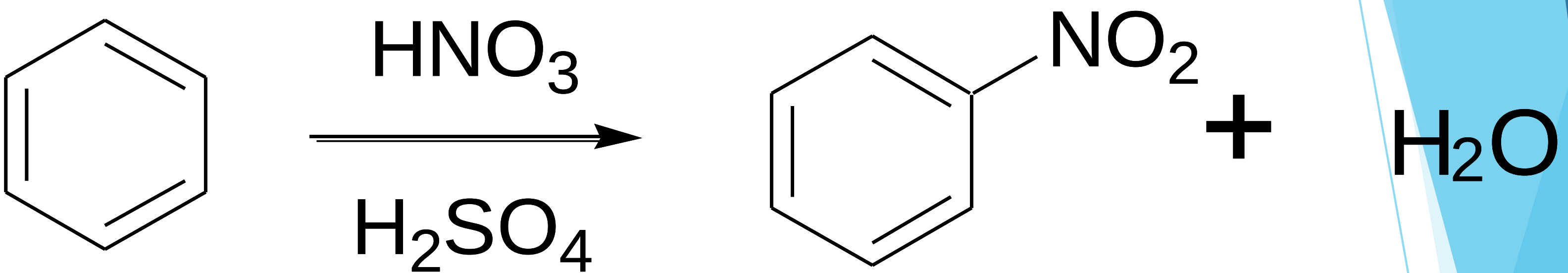
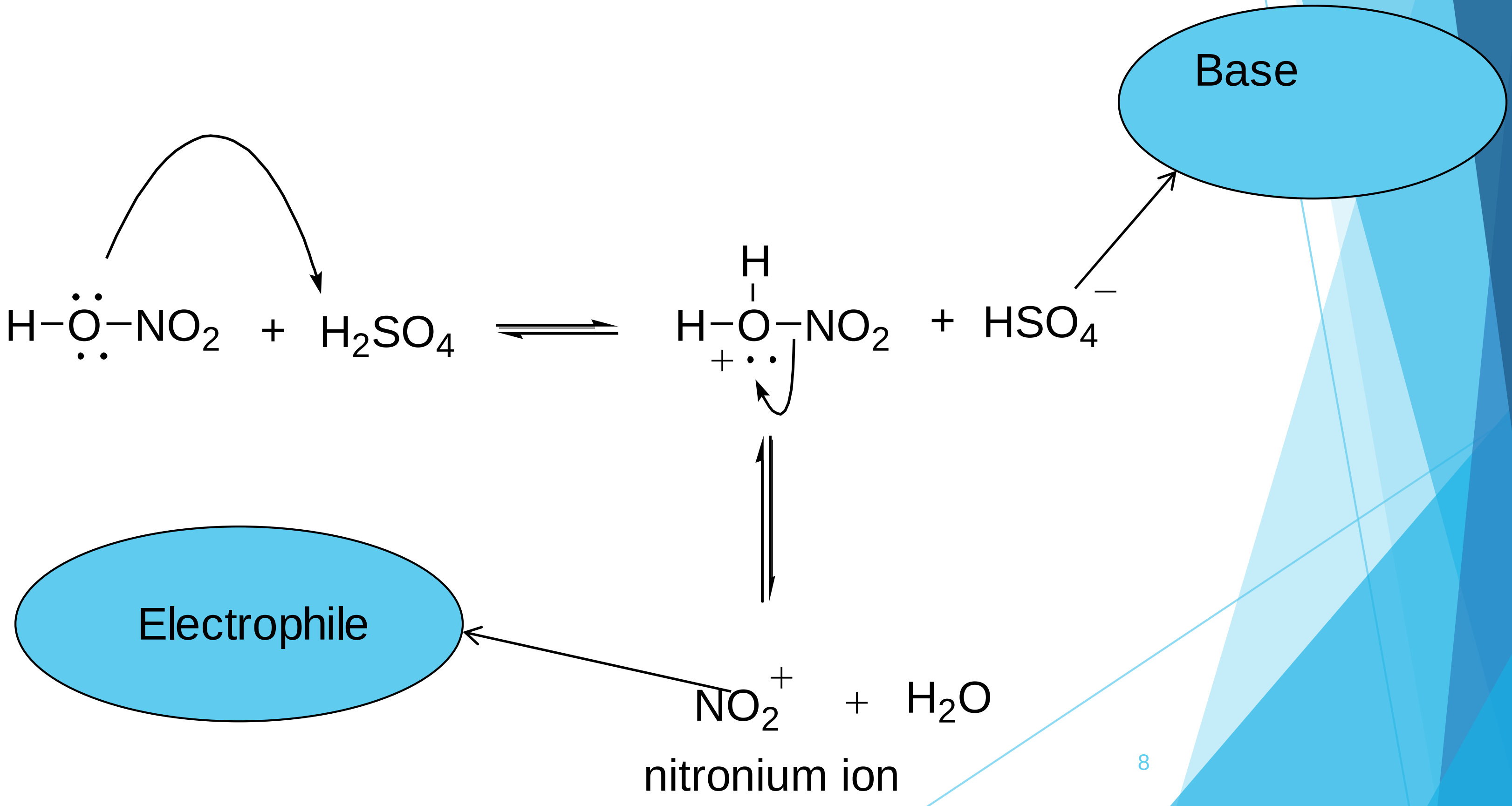
Nitration of Aromatic Rings



Electrophile is the nitronium ion (NO_2^+) Generated from HNO_3 by protonation and loss of water

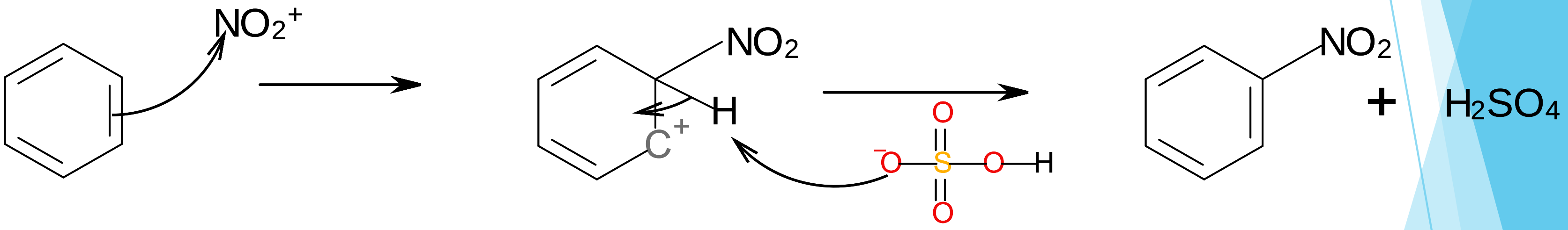
Mechanism: Nitration of Aromatic Rings

- An electrophile must first be generated by treating concentrated nitric acid with concentrated sulfuric acid

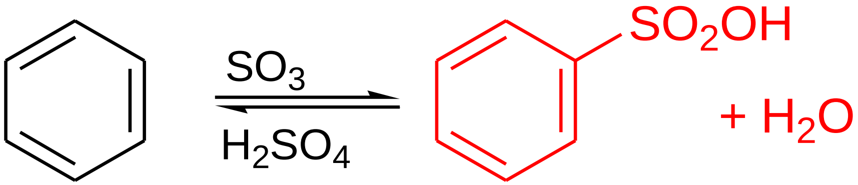


Mechanism: Nitration of Aromatic Rings

- The nitronium electrophile is attacked by the benzene ring (nucleophile)



Sulfonation of Aromatic Rings



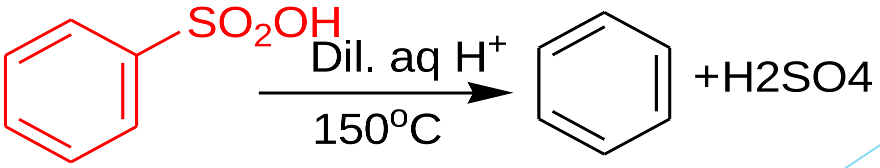
Fuming sulfuric acid – combination of SO_3 and H_2SO_4

Electrophile is HSO_3^+ or SO_3

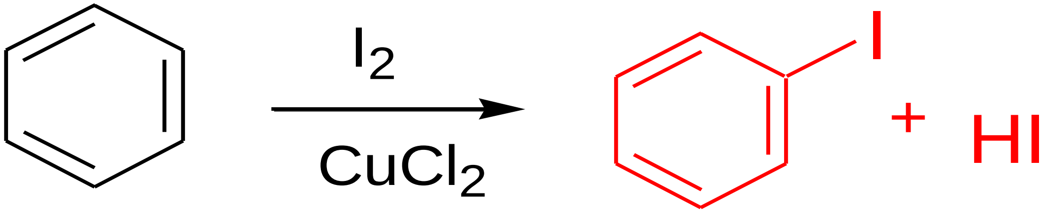
Reaction is reversible

Favored in forward direction with strong acid

Favored in reverse direction with hot dilute aqueous acid under pressure



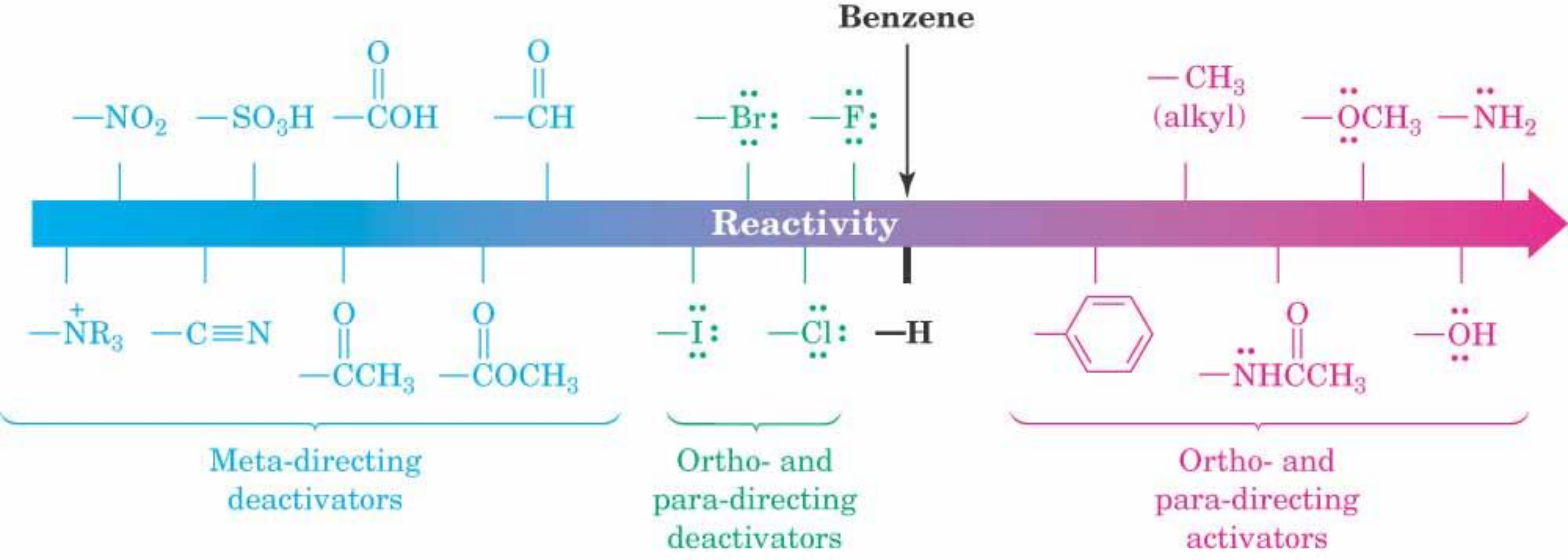
Iodination of Aromatic Rings



- Iodine is unreactive towards aromatic rings
- Oxidizing agents must be added to make reaction go (H_2O_2 or $CuCl_2$)
- Oxidizing agents oxidize I_2 to a usable form (electrohphillic) that reacts as if it were I^+

Substituent Effects in Aromatic Rings

- Substituents can cause a compound to be (much) more or (much) less reactive than benzene
- Substituents affect the orientation of the reaction – the positional relationship is controlled
  - ortho- and para-directing activators, ortho- and para-directing deactivators, and meta-directing deactivators



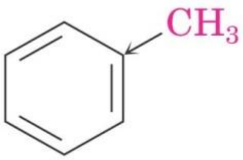
Origins of Substituent Effects

- An interplay of *inductive effects* and *resonance effects*

- Inductive effect - withdrawal or donation of electrons through a sigma bond (comparative electronegativity)

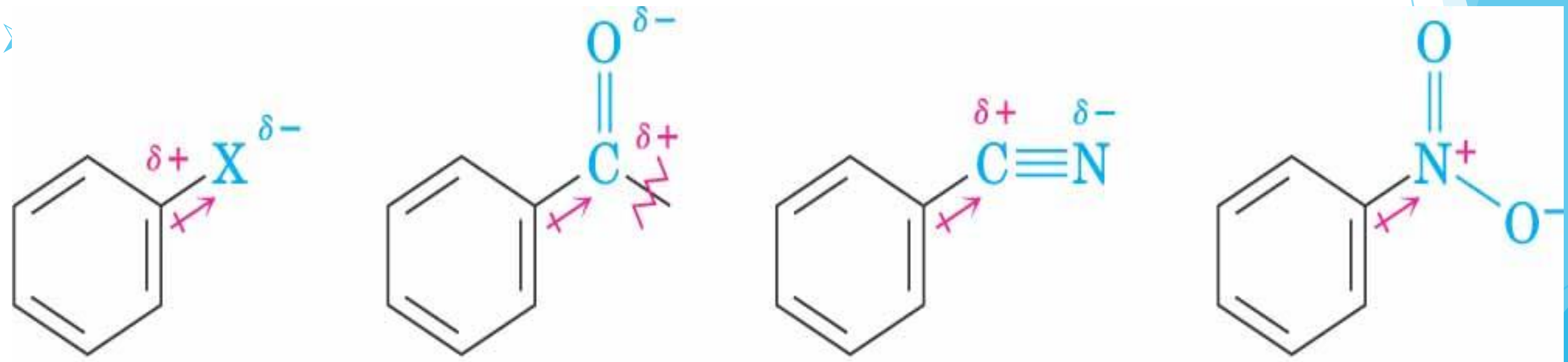
- Resonance effect - withdrawal or donation of electrons through a π bond due to the overlap of a p orbital on the substituent with a p orbital on the aromatic ring

Inductive Effects



Alkyl group; inductively electron-donating

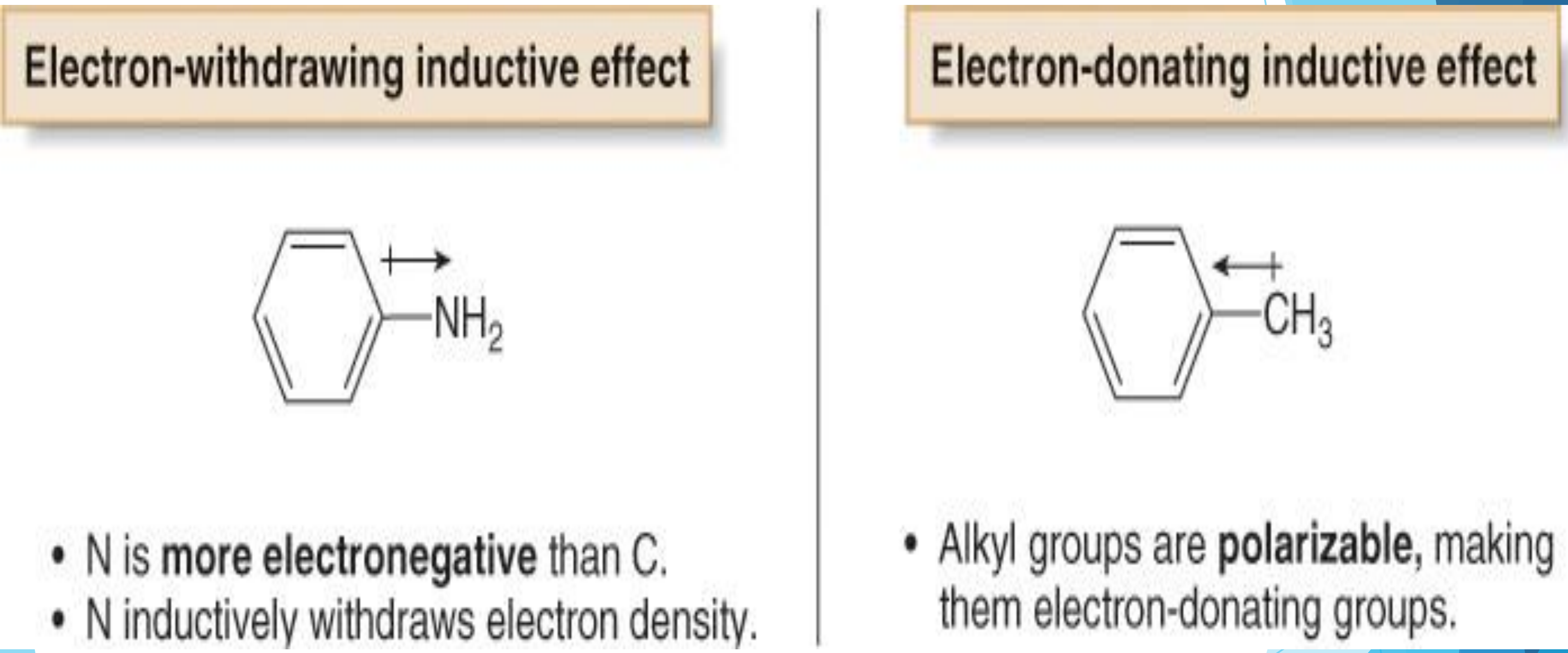
- Controlled by electronegativity and the polarity of bonds in functional groups
- Halogens, C=O, CN, and NO$_2$ *withdraw* electrons through σ bond connected to ring



(X = F, Cl, Br, I)

The groups attached to the aromatic rings are inductively electron-withdrawing because of the polarity of their bonds.

Considering inductive effects only, the NH_2 group withdraws electron density and CH_3 donates electron density.



Electron-withdrawing inductive effect

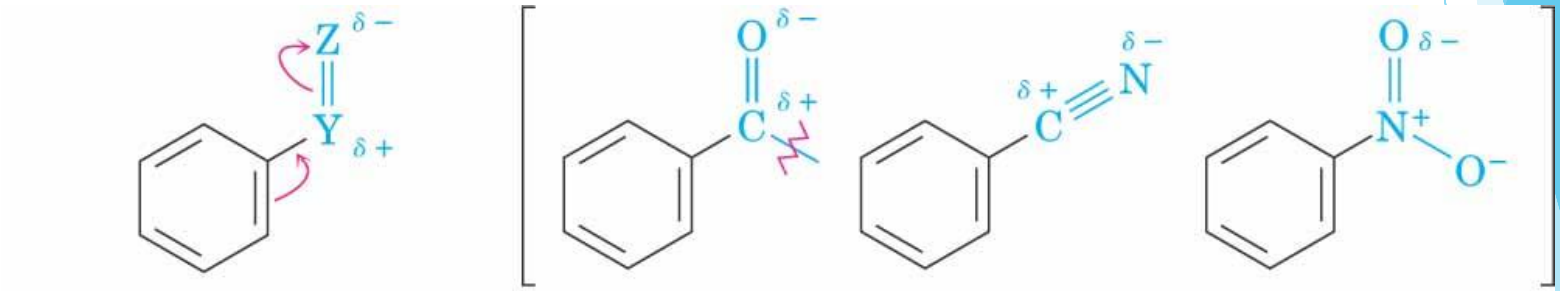
- N is **more electronegative** than C.
- N inductively withdraws electron density.

Electron-donating inductive effect

- Alkyl groups are **polarizable,** making them electron-donating groups.

Resonance Effects – Electron Withdrawal

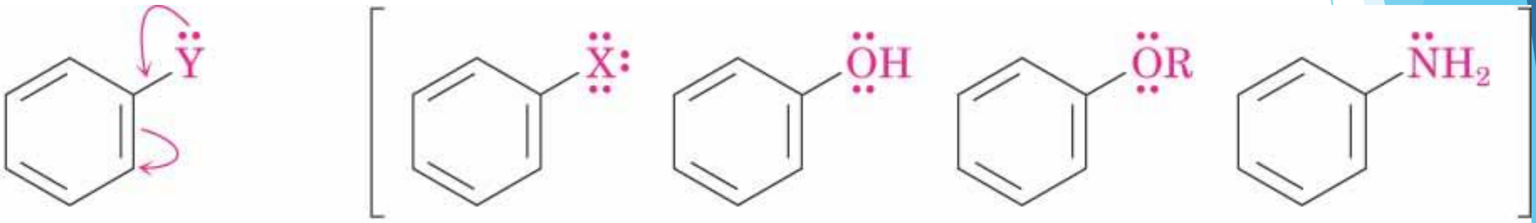
- $C{=}O$, CN, NO_2 substituents *withdraw* electrons from the aromatic ring by resonance
- **π electrons flow from the rings to the substituents**



Rings substituted by a group with an electron-withdrawing resonance effect have this general structure.

Resonance Effects – Electron Donation

- Halogen, OH, alkoxyl (OR), and amino substituents donate electrons
- π electrons flow from the substituents to the ring
- Effect is greatest at ortho and para



Rings substituted by a group with an electron-donating resonance effect have this general structure.

X = Halogen

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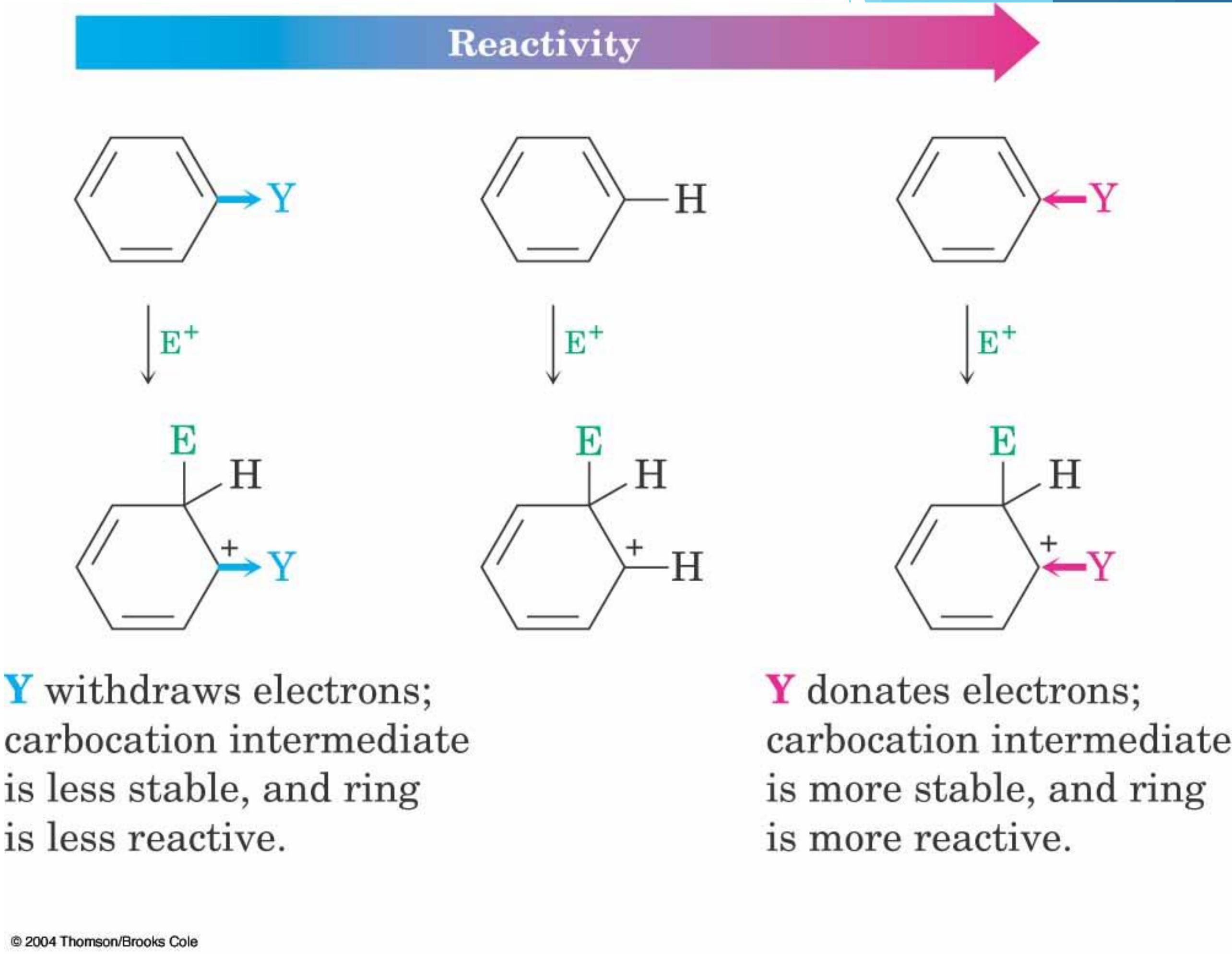
An Explanation of Substituent Effects

- Activating groups donate electrons to the ring, stabilizing the Wheland intermediate (carbocation)
- Deactivating groups withdraw electrons from the ring, destabilizing the Wheland intermediate

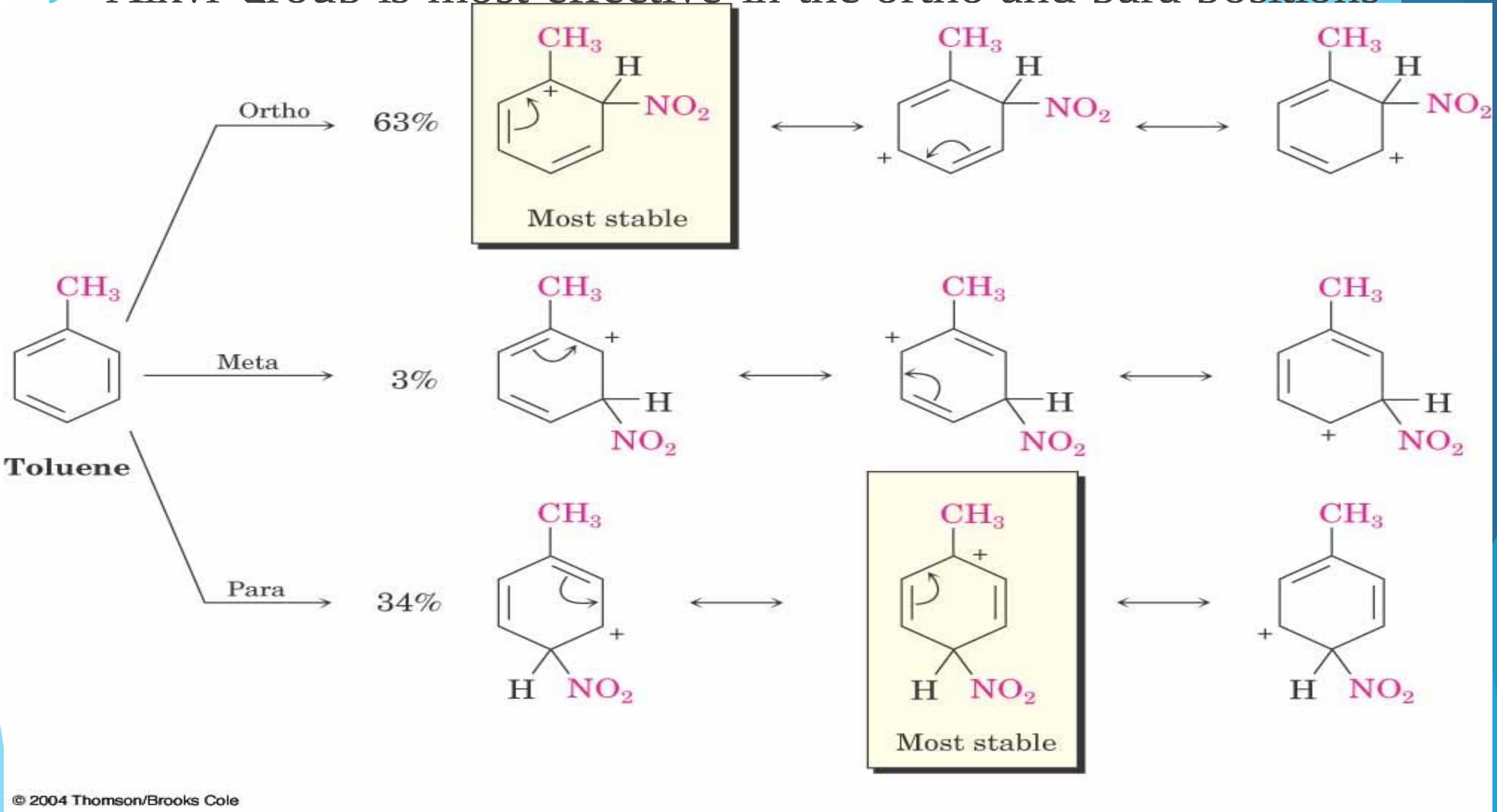


Y withdraws electrons; carbocation intermediate is less stable, and ring is less reactive.

Y donates electrons; carbocation intermediate is more stable, and ring is more reactive.

Ortho- and Para-Directing Activators: Alkyl Groups

- Alkyl groups activate: direct further substitution to positions ortho and para to themselves
- Alkyl group is most effective in the ortho and para positions



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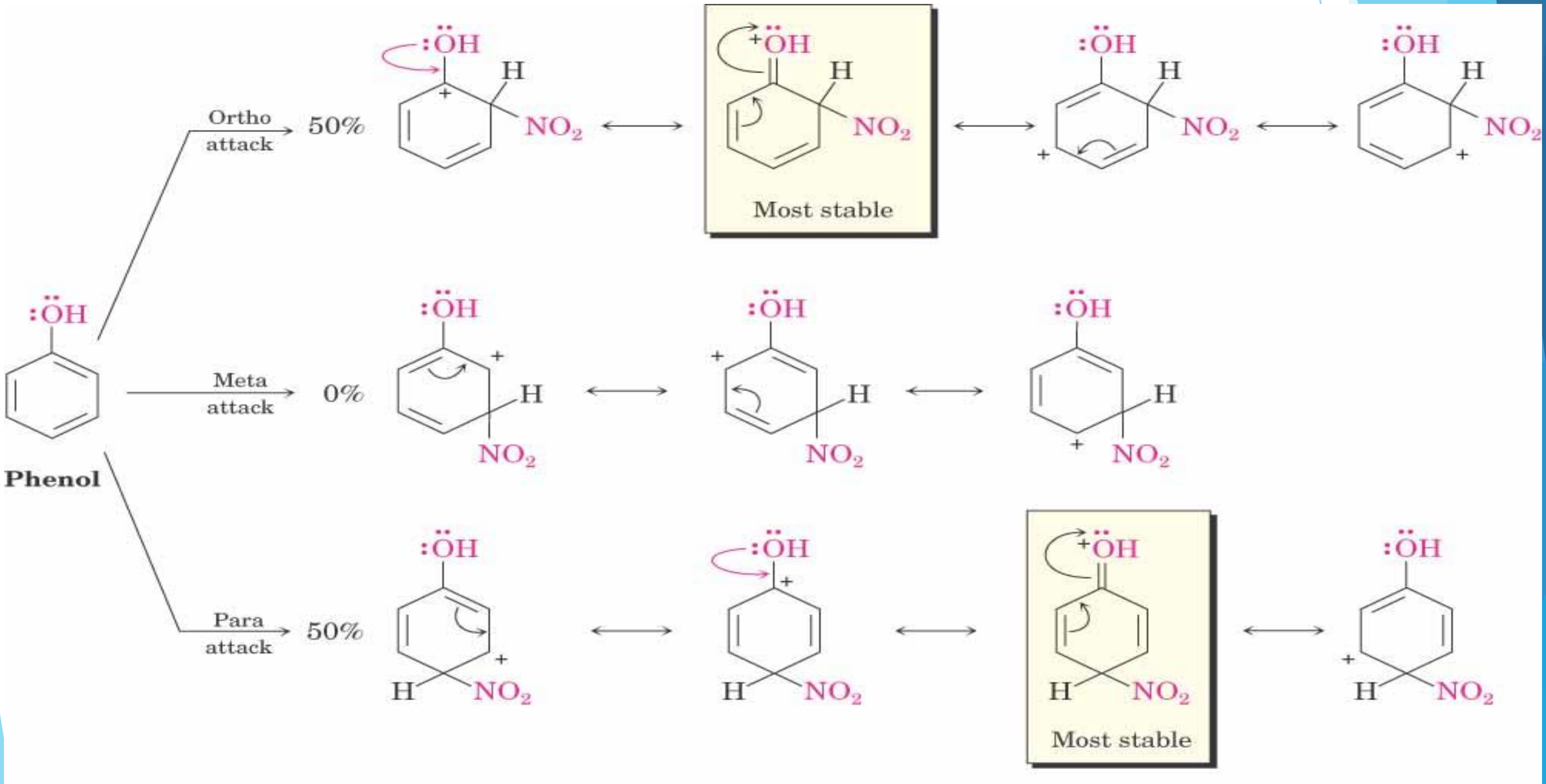
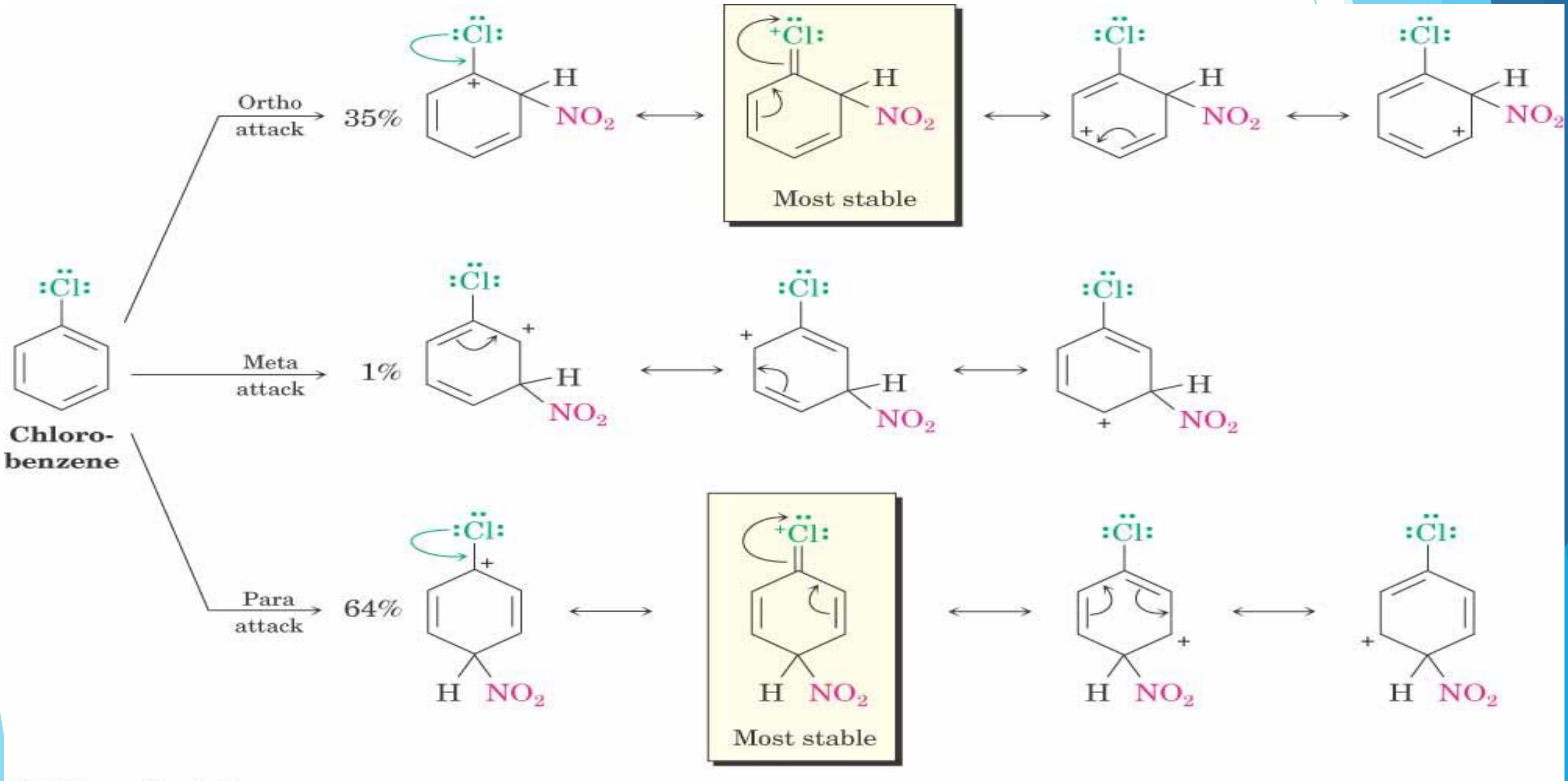
Ortho- and Para-Directing Activators: OH and NH_2

- Alkoxyl, and amino groups have a strong, electron-donating resonance effect
- Most pronounced at the ortho and para positions



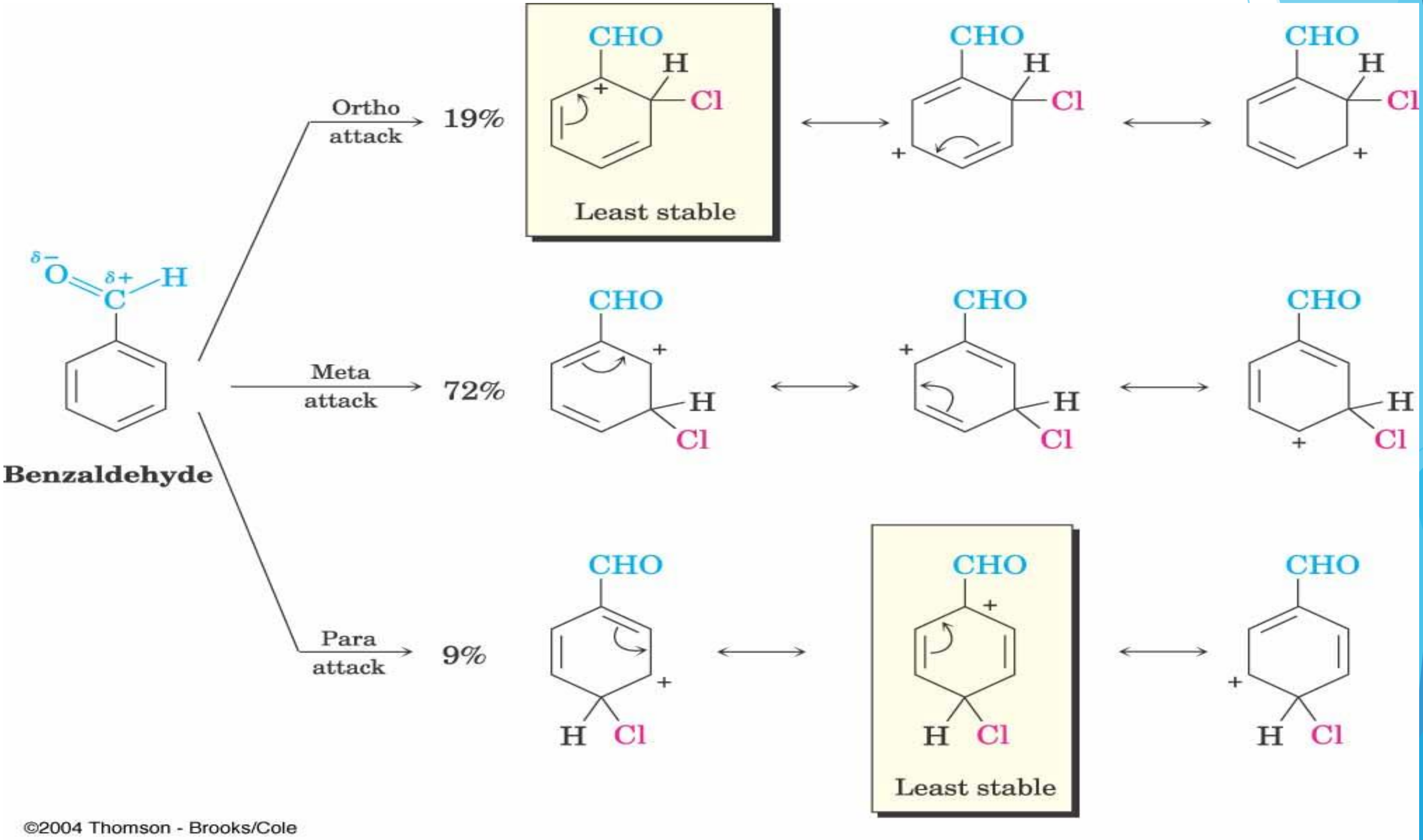
Ortho- and Para-Directing Deactivators: Halogens

- Electron-withdrawing inductive effect outweighs weaker electron-donating resonance effect
- Resonance effect is only at the ortho and para positions, stabilizing carbocation intermediate



Meta-Directing Deactivators

- Ortho and para intermediates destabilized by deactivation from carbocation intermediate
- Resonance cannot produce stabilization



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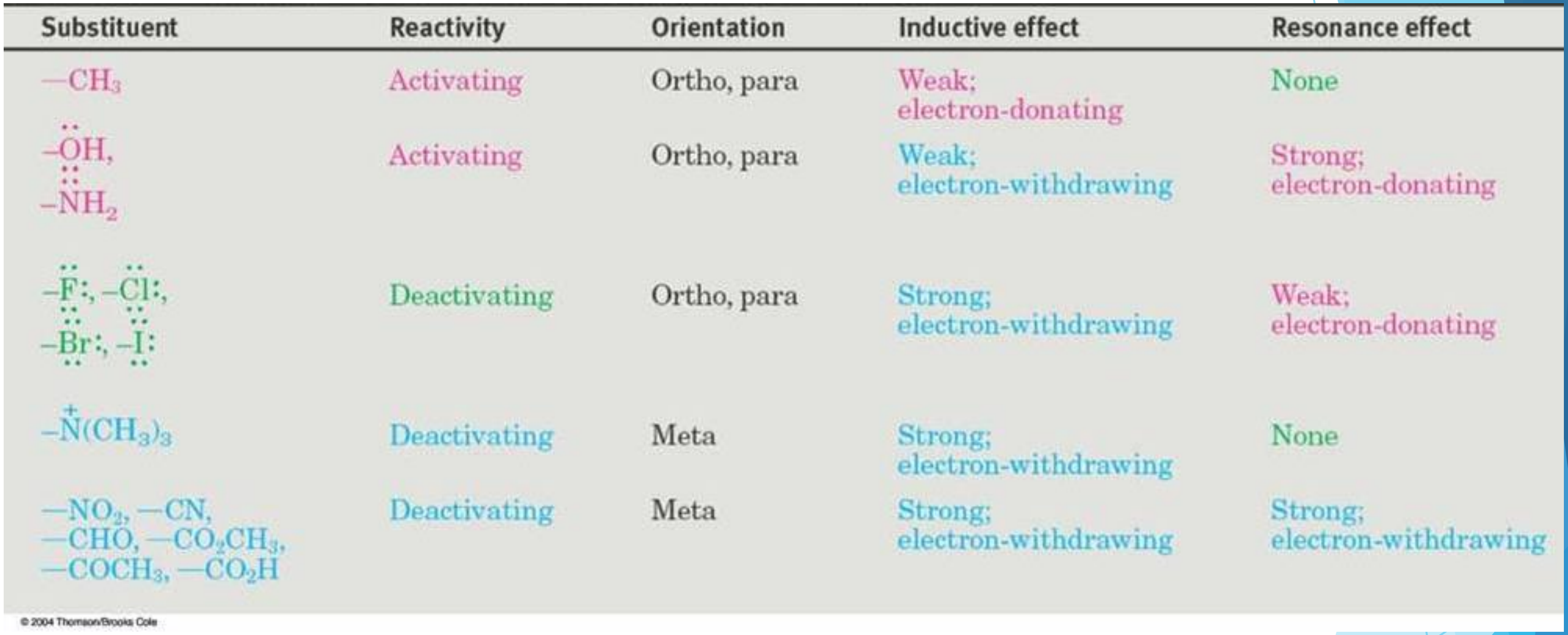
Summary Table: Effect of Substituents in Aromatic Substitution



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

Is it ortho/para or meta directing?????

- All ortho- and para- directors have a lone pair of electrons on the atom directly attached to the ring (with the exception of alkyl, aryl, and CH=CHR groups).

- All meta- directors have a positive charge or a partial positive charge on the atom attached to the ring.

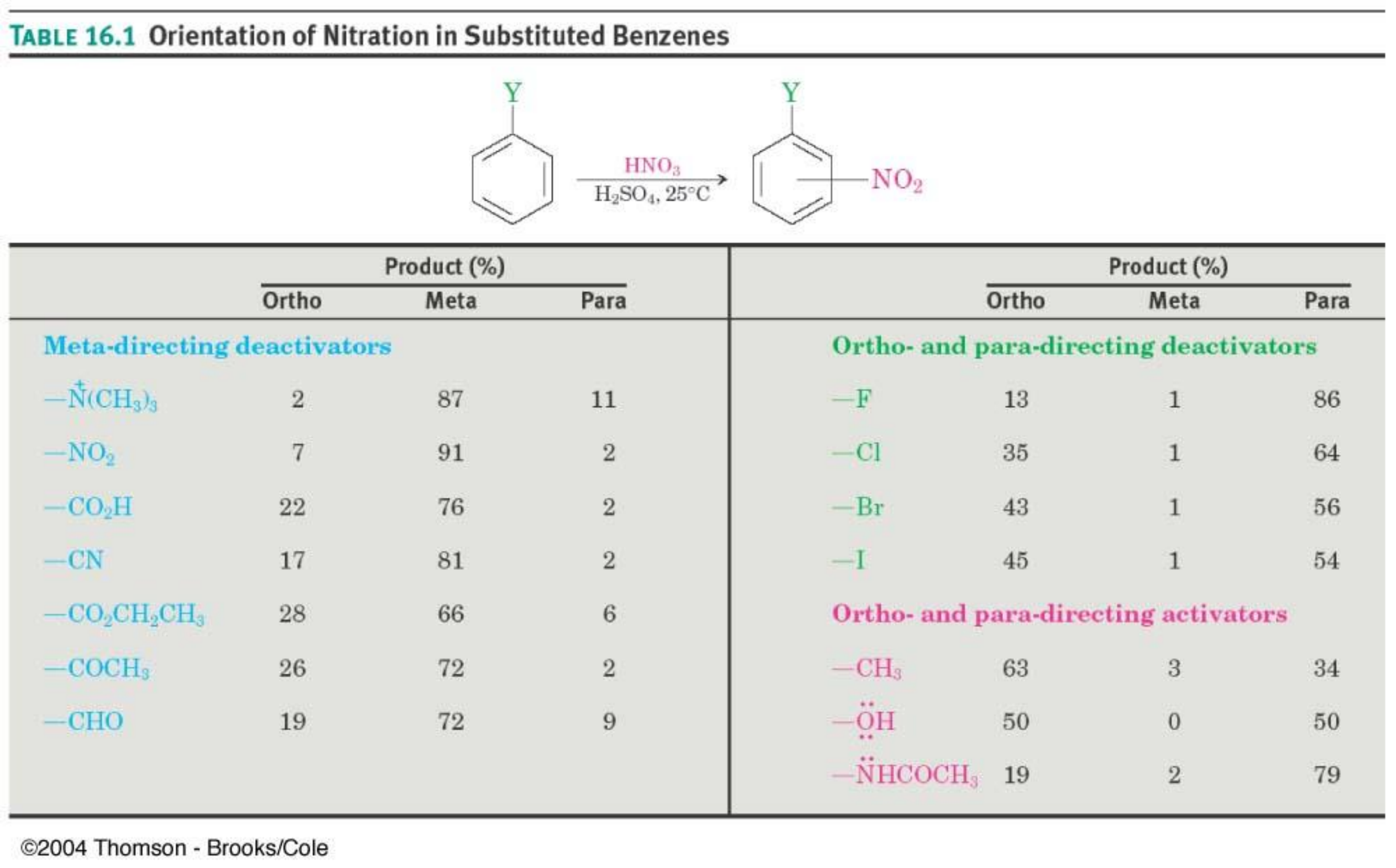


TABLE 16.1 Orientation of Nitration in Substituted Benzenes

	Product (%)				Product (%)		
	Ortho	Meta	Para		Ortho	Meta	Para
Meta-directing deactivators				**Ortho- and para-directing deactivators**			
$-\overset{+}{N}(CH_3)_3$	2	87	11	$-F$	13	1	86
$-NO_2$	7	91	2	$-Cl$	35	1	64
$-CO_2H$	22	76	2	$-Br$	43	1	56
$-CN$	17	81	2	$-I$	45	1	54
$-CO_2CH_2CH_3$	28	66	6	**Ortho- and para-directing activators**			
$-COCH_3$	26	72	2	$-CH_3$	63	3	34
$-CHO$	19	72	9	$-\ddot{\underset{..}{O}}H$	50	0	50
				$-\ddot{N}HCOCH_3$	19	2	79

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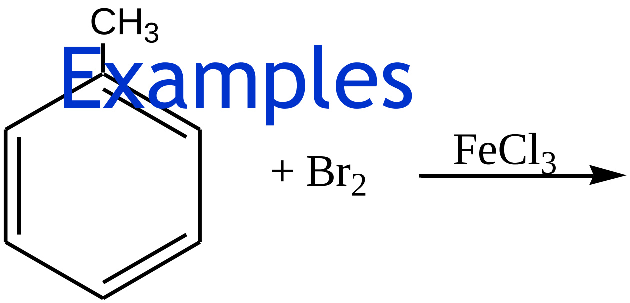
In Summary:

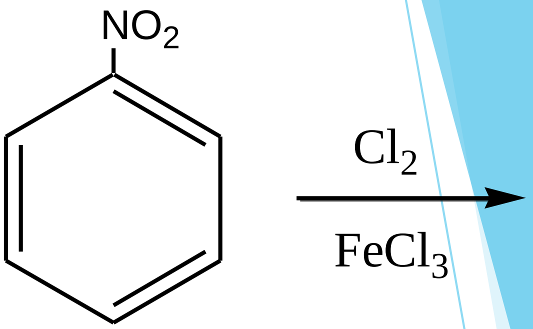
- All activating substituents are ortho/para directors
- The weakly deactivating halogens are ortho/para directors
- All other deactivating substituents are meta directors

Examples



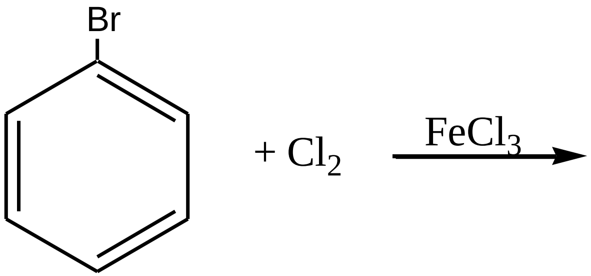
$\text{toluene} + Br_2 \xrightarrow{FeCl_3}$

toluene



$\xrightarrow[FeCl_3]{Cl_2}$

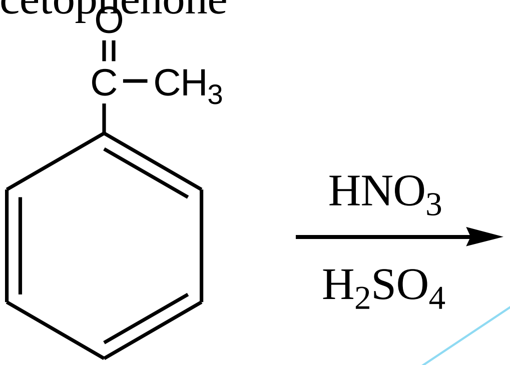
nitrobenzene



$\text{bromobenzene} + Cl_2 \xrightarrow{FeCl_3}$

bromobenzene

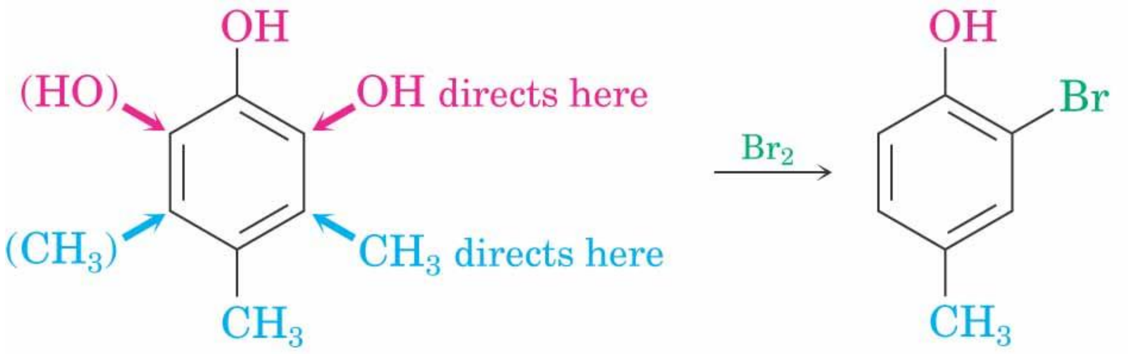
Acetophenone



$\xrightarrow[H_2SO_4]{HNO_3}$

Substituents with Opposite Effects

- If the directing effects of two groups oppose each other, the more powerful activating group decides the principal outcome
- Usually gives mixtures of products

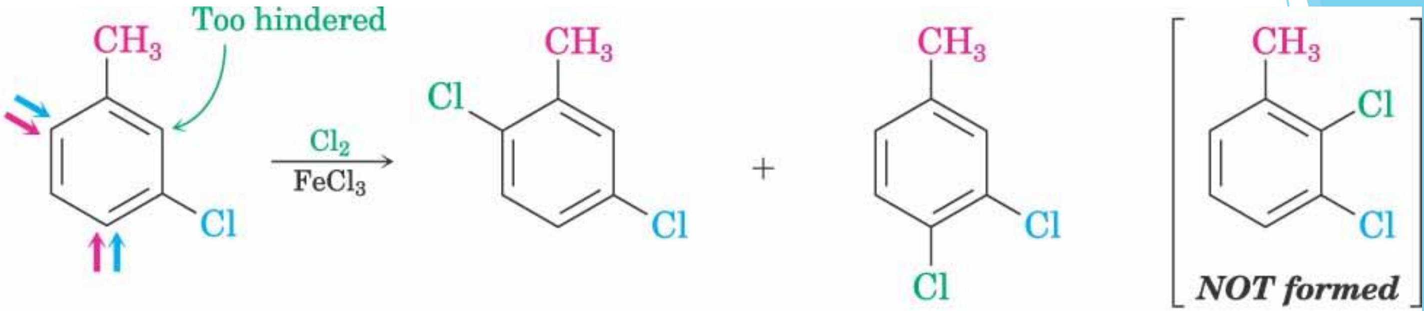


***p*-Methylphenol**
(*p*-Cresol)

2-Bromo-4-methylphenol
(major product)

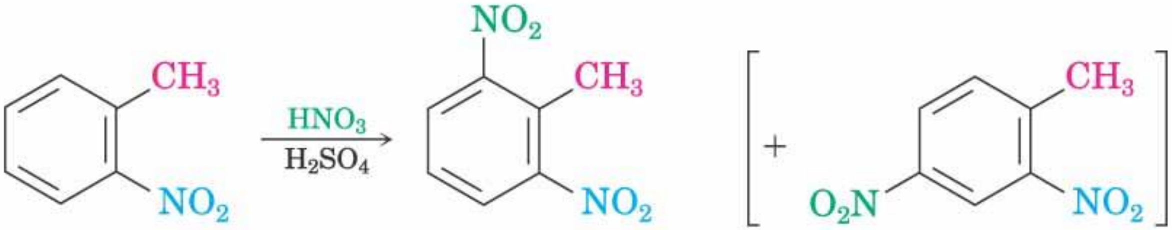
Meta-Disubstituted Compounds Are Unreactive

- The reaction site is too hindered
- To make aromatic rings with three adjacent substituents, it is best to start with an ortho-disubstituted compound



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

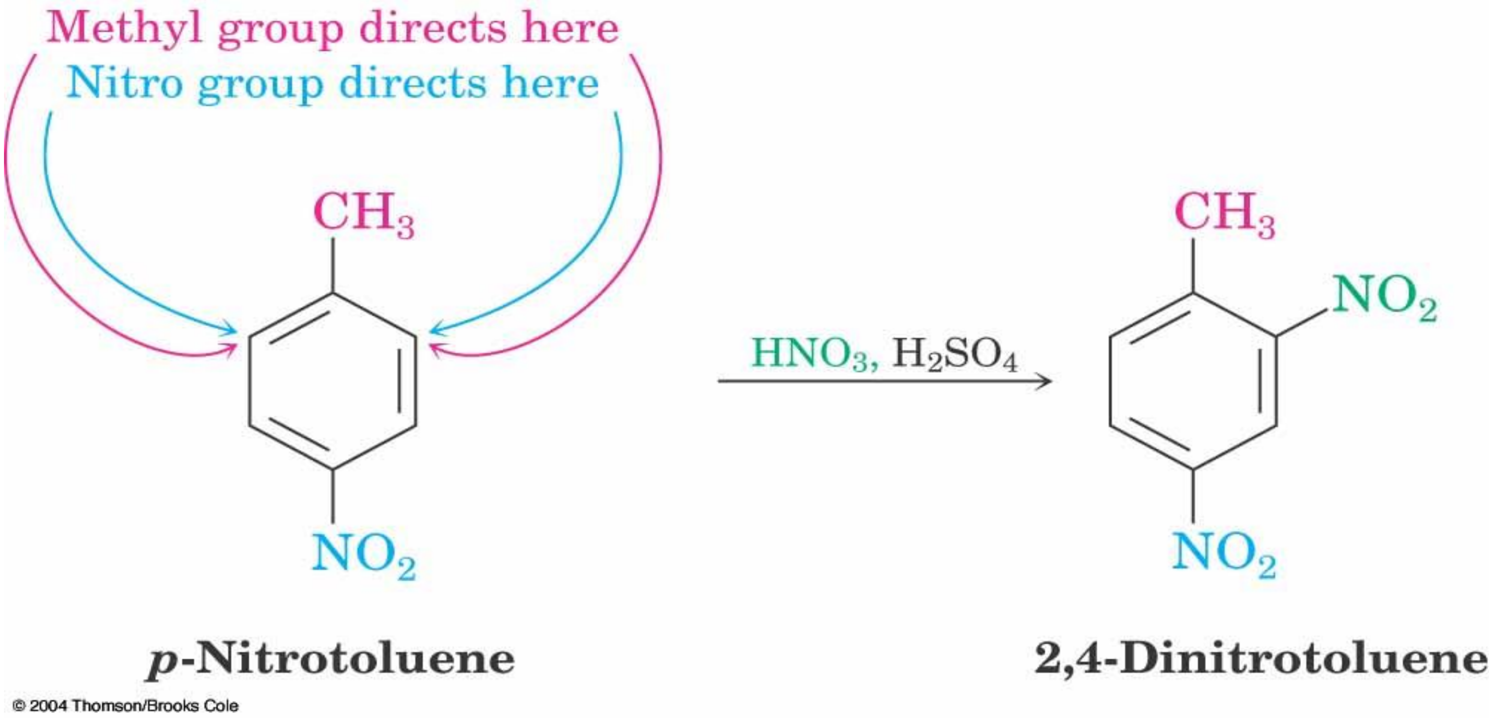
But:



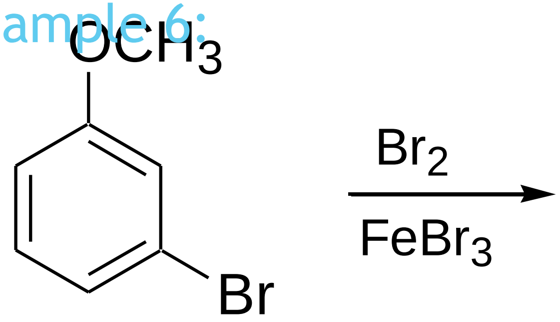
o-Nitrotoluene **2,6-Dinitrotoluene** **2,4-Dinitrotoluene**

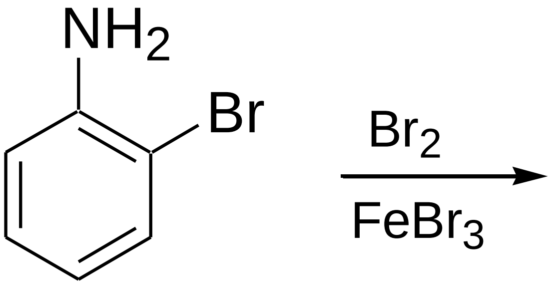
Orientation in benzene ring with more than one substituents

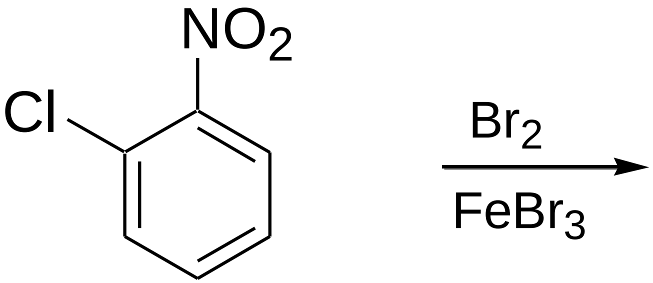
- If the directing effects of the two groups are the same, the result is additive



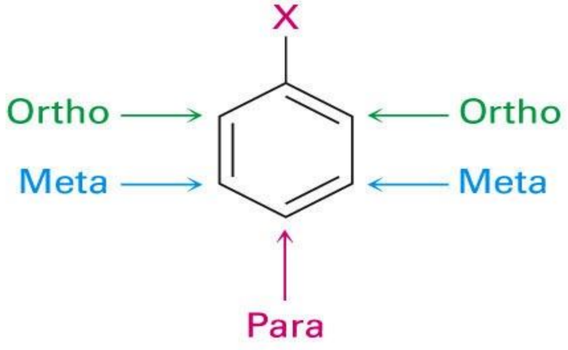
Example 6:







The Ortho, Para Ratio

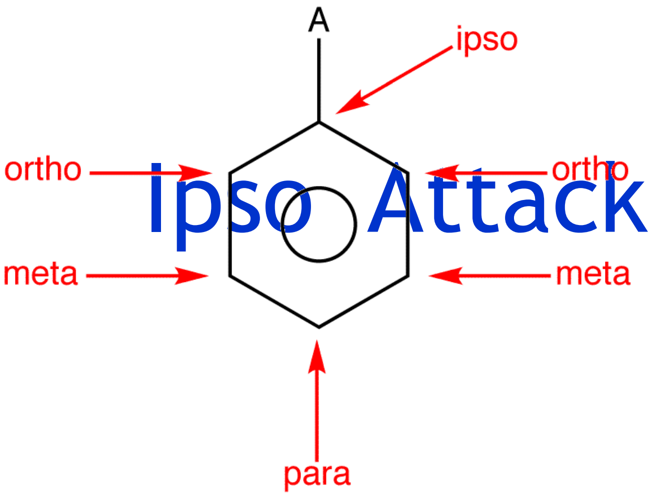


- Ratio of ortho to para products = 2:1?
- Ortho and para isomer should be formed in 2:1 ratio, However in actual practice this O/P ratio is less
- Factors affecting O/P ratio

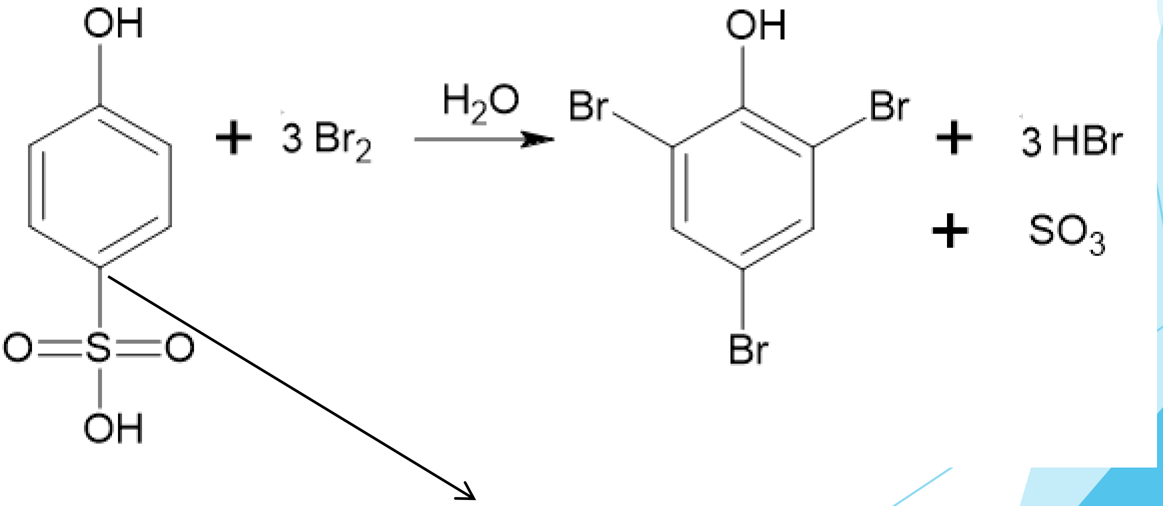
1. Polar Effect (Inductive and Resonance effect)
2. Stearic Hinderance
3. Solvent effect
4. Temperature etc

Fortunately, ortho and para products often have different physical properties and can be separated

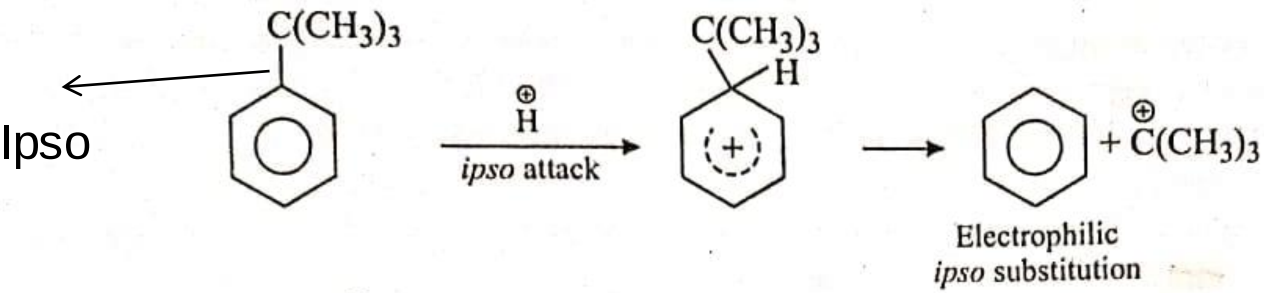
Ipso Attack



The attachment of an entering group to a position in an aromatic compound already carrying a substituent group-A (other than hydrogen).

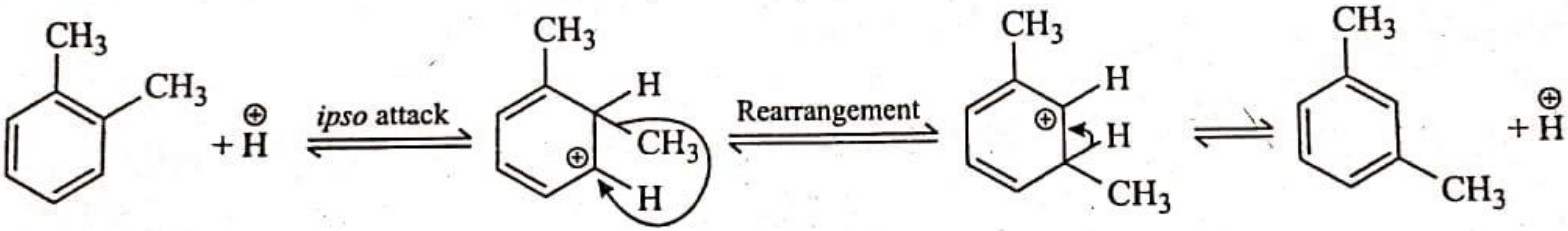


Ipso



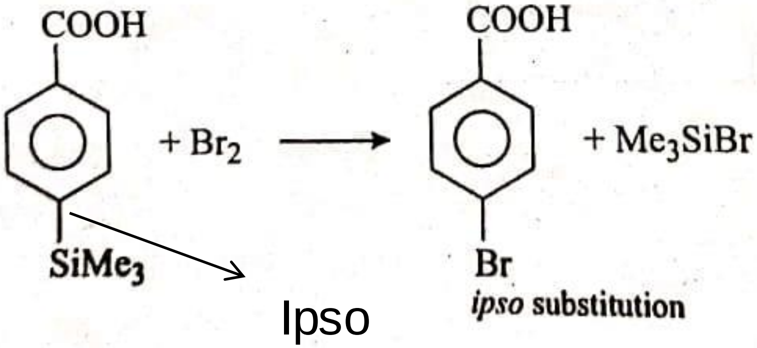
$$(CH_3)_3\overset{\oplus}{C} \longrightarrow (CH_3)_2C{=}CH_2 + H^{\oplus}$$

The rearrangement of alkylbenzenes leading to their isomerisation also involves *ipso* attack. For example, *o*-xylene isomerises to *m*-xylene as follows :



Silyl group has a strong tendency to direct the entering electrophile to the position occupied by it, *i.e.*, *ipso* position. This is due to the strong stabilisation of cationic centre β to the silicon.

Bromodesilylation :

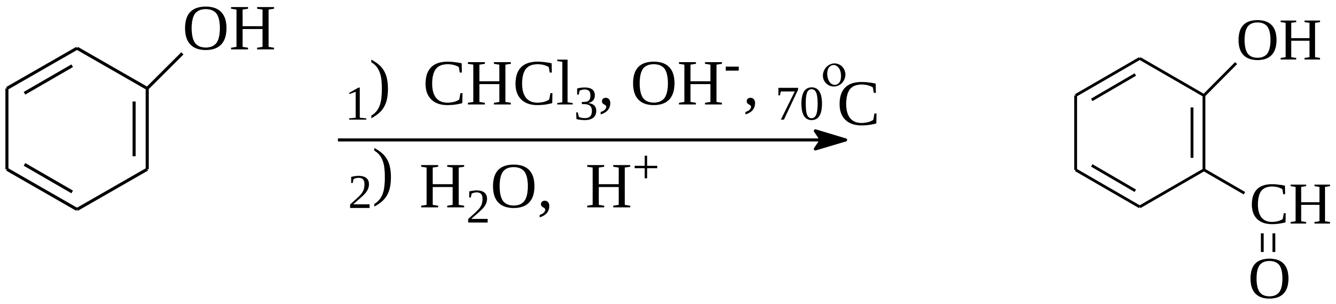


Name Reactions Involving Aromatic electrophilic substitution Reaction

1. Reimer-Tiemann Reaction
2. Vilsmeir-Haack Reaction
3. Diazonium Coupling
4. Gattermann-Koch Reaction
5. Friedel craft Reaction

1. The Reimer-Tiemann Reaction

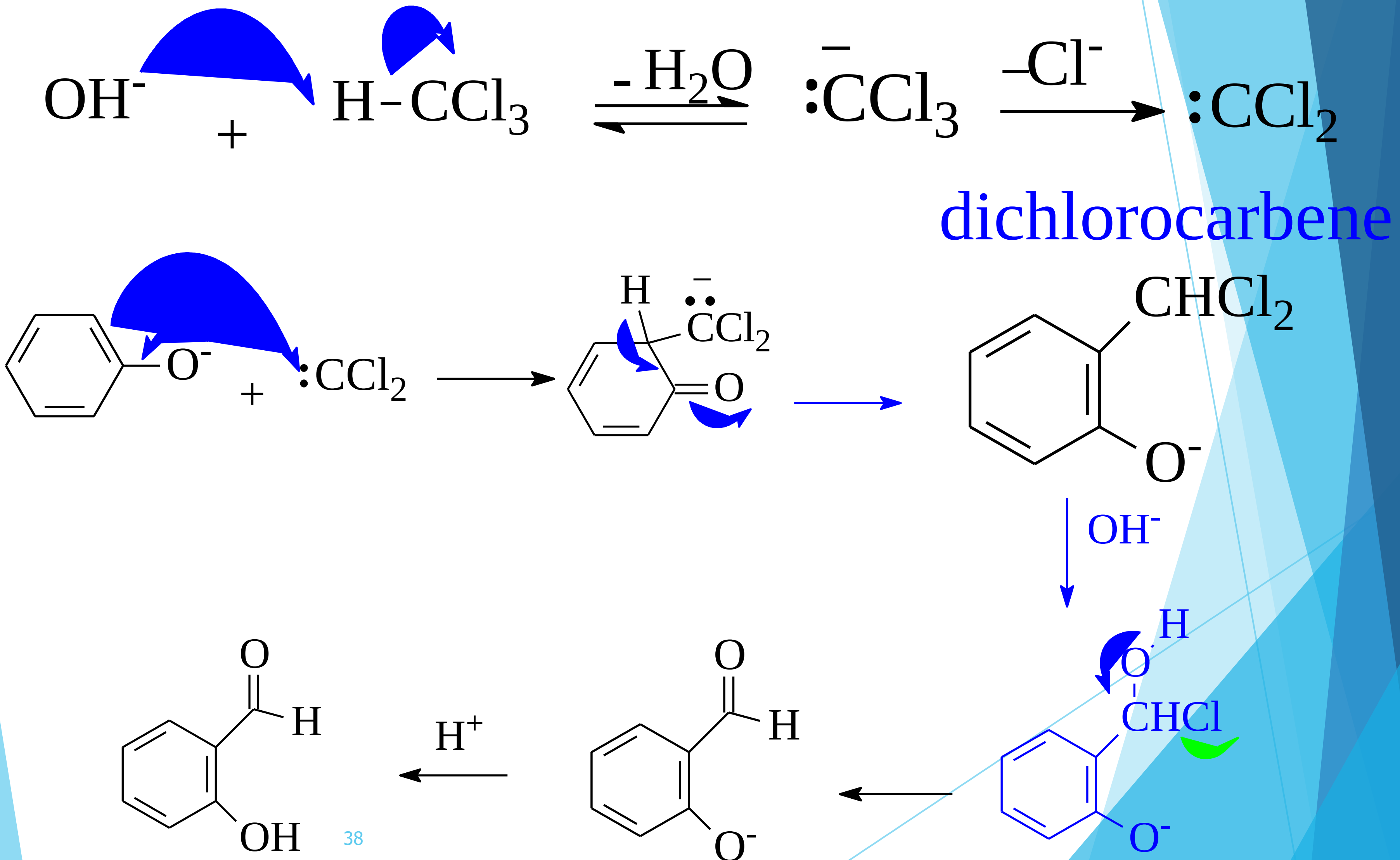
- The formylation of phenol with chloroform and aqueous hydroxide is known as Reimer-Tiemann reaction.
- Dichlorocarbene is an intermediate



Phenol

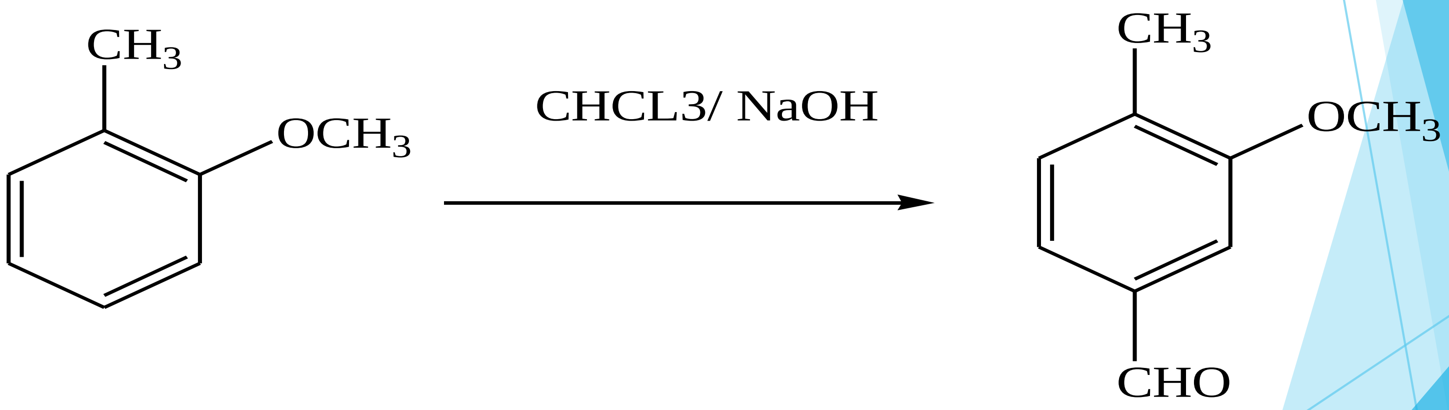
Salicylaldehyde

1.1 Mechanism: Reimer-Tiemann Reaction



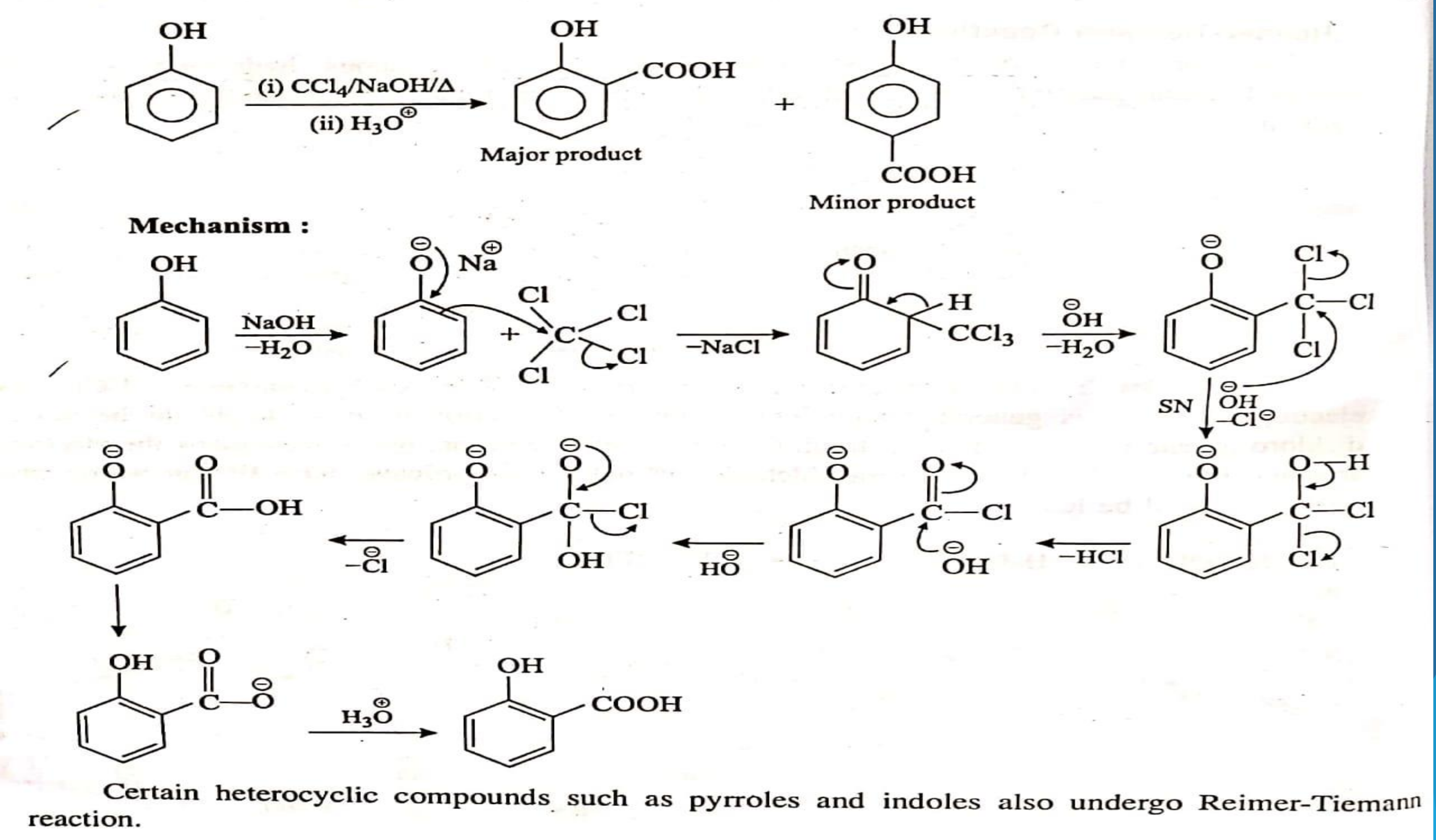
The Reimer-Tiemann Reaction

- If one of the ortho position is occupied, the formylation tends to occur at the para position



1.2 The Reimer-Tiemann Reaction

CCl is used in place of CHCl salicylic acid is the product

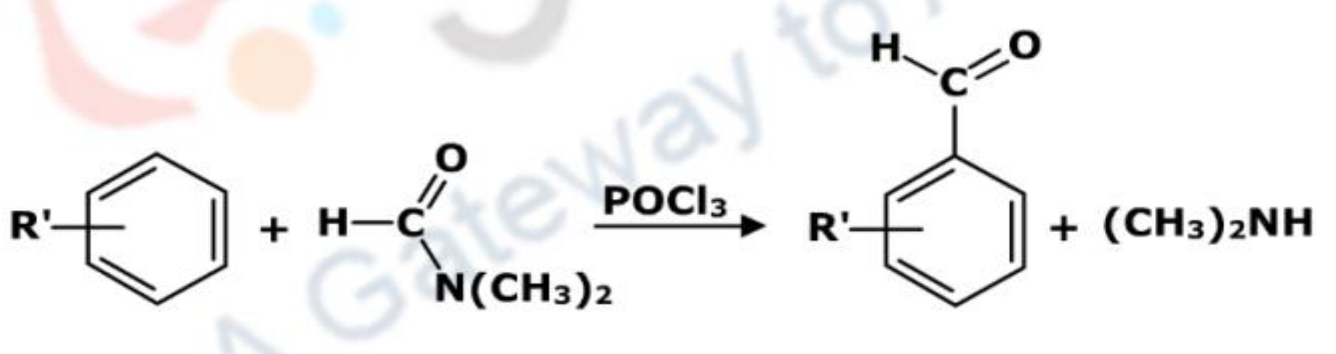


Mechanism :

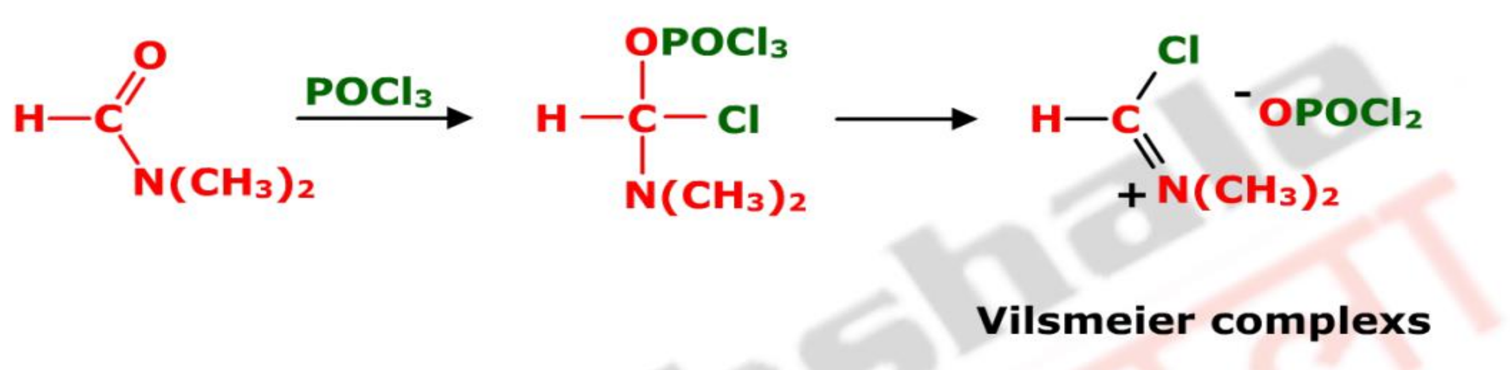
Certain heterocyclic compounds such as pyrroles and indoles also undergo Reimer-Tiemann reaction.

2. Vilsmeir-Haack Reaction

- The reaction of electron rich aromatic compounds with N,N dimethylformamide (DMF) and phosphorus oxychloride (POCl3) to yield an aromatic aldehyde is called the VilsmeierHaack reaction
- V-H reaction is applicable only to electron rich aromatic compounds such as amines and phenols.

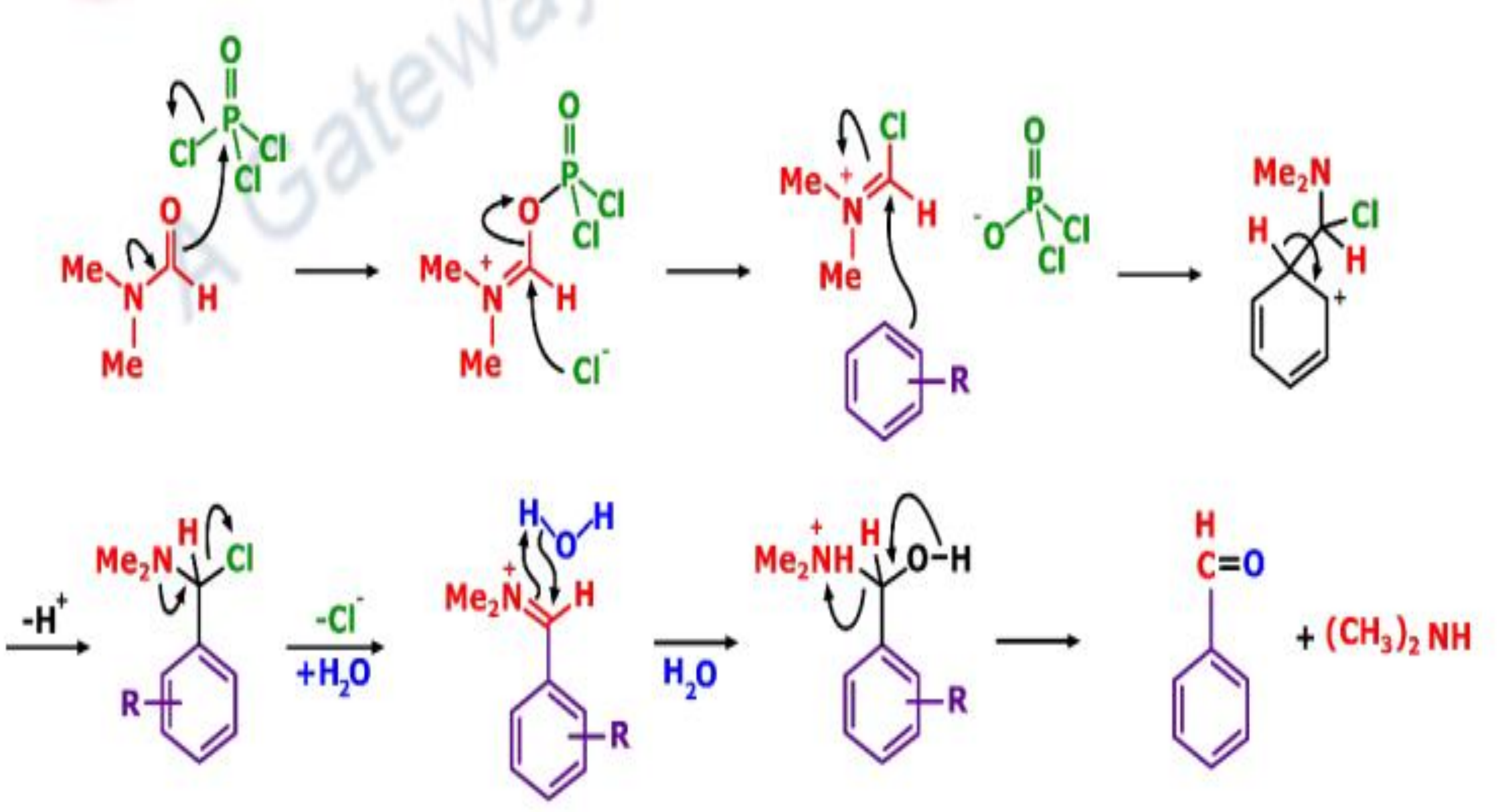


Vilsmeier-Haack Complex



Vilsmeier complexs

2. 1 Mechanism of Vilsmeier-



2.2 Reagents used in Vilsmeier–Haack reaction

- The Vilsmeier complexes employed in the formylation reactions are usually derived from N,N-disubstituted amide and $POCl_3$.

N,N-disubstituted amides:

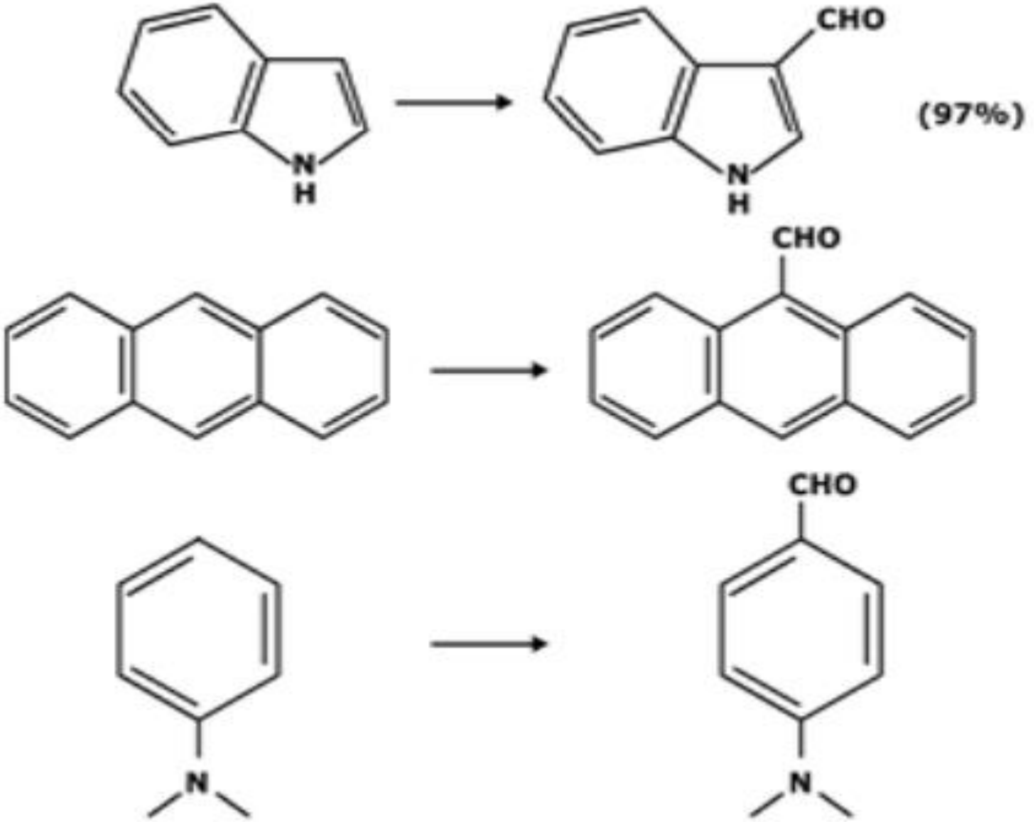
- N-Methyl formamide
- N,N-dimethyl formamide
- N-formylpiperidine and N-formylindeline have also been used other than DMF.

Other amides such as N, N-dimethyl acetamide, N-methyl acetamide, N, N-dimethyl benzamide, etc. have been employed in the presence of POCl3 but these amides are prone to undergo self condensation.

- **Acid chlorides**: Acid chlorides other than POCl3 have also been used in carrying out the Vilsmeier reactions. Some of these are PCl5,SOCl2, COCl2, R/ArCOCl, ArSO2Cl, , Me2NSO2Cl.

- **Solvents**: When liquid amides are used as solvents, excess can be used, e.g DMF, dimethyl acetamide, N-methyl pyrrolidone, etc. Other solvents have also been used like benzene, toluene, chloroform, methylchloride, o-dichlorobenzene, dioxane and tetrahydrofuran.

V-H reaction is applicable only to electron rich aromatic compounds such as amines and phenols. Benzene and naphthalene are unreactive but anthracene gives 1-aldehyde (85%). N, N-dimethyl aniline gives 4-dimethyl amino benzaldehyde (80%). The method is particularly effective for compounds such as benzopyrroles which are not formylated by other procedures.



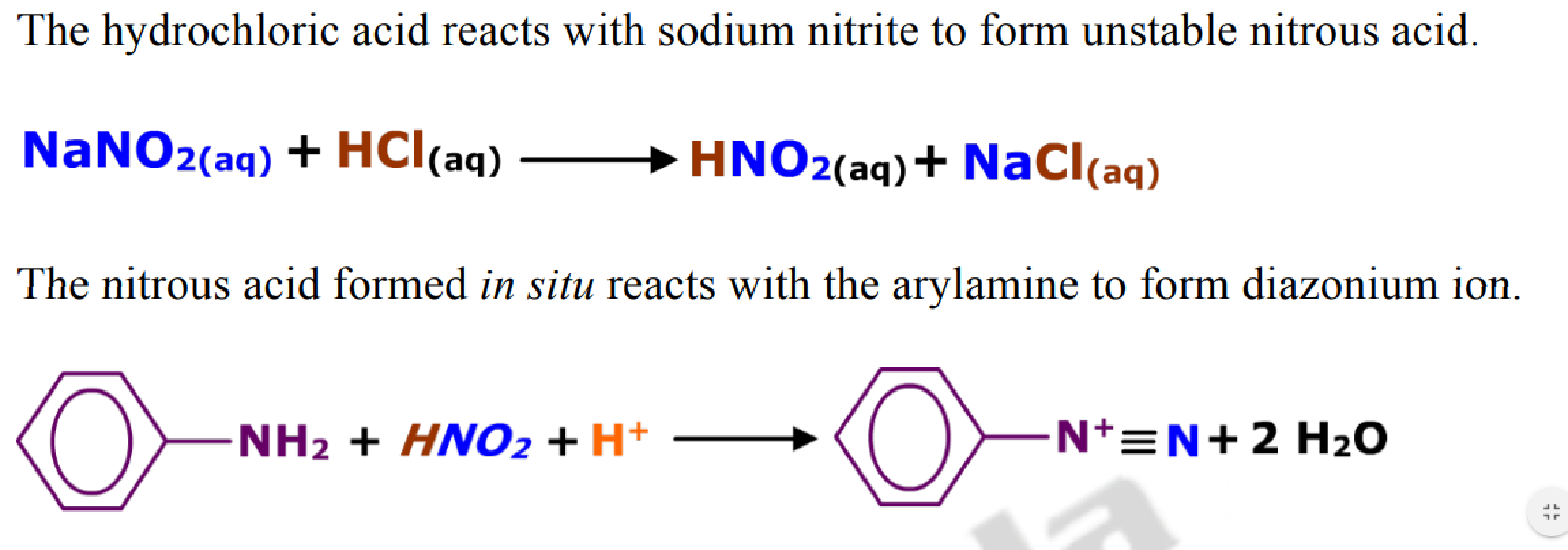
3. Diazonium Coupling

3.1 Diazo Compounds

- Compounds containing -N=N- group are known as diazo compounds. Their general structure is R-N=N-R’
- Here R and R’ are preferably arene groups and the azo group is thus stabilised by becoming part of extended delocalised system. They are prepared by coupling reaction between a diazonium salt and a coupling reagent.

3.2 Diazonium Salt

Diazonium salts are prepared by adding cold solution of sodium nitrite (NaNO2) to arylamine solution in dilute acid below 5^{o}C temperature. **This process is called diazotisation**. The diazonium salts are prepared fresh and used immediately.

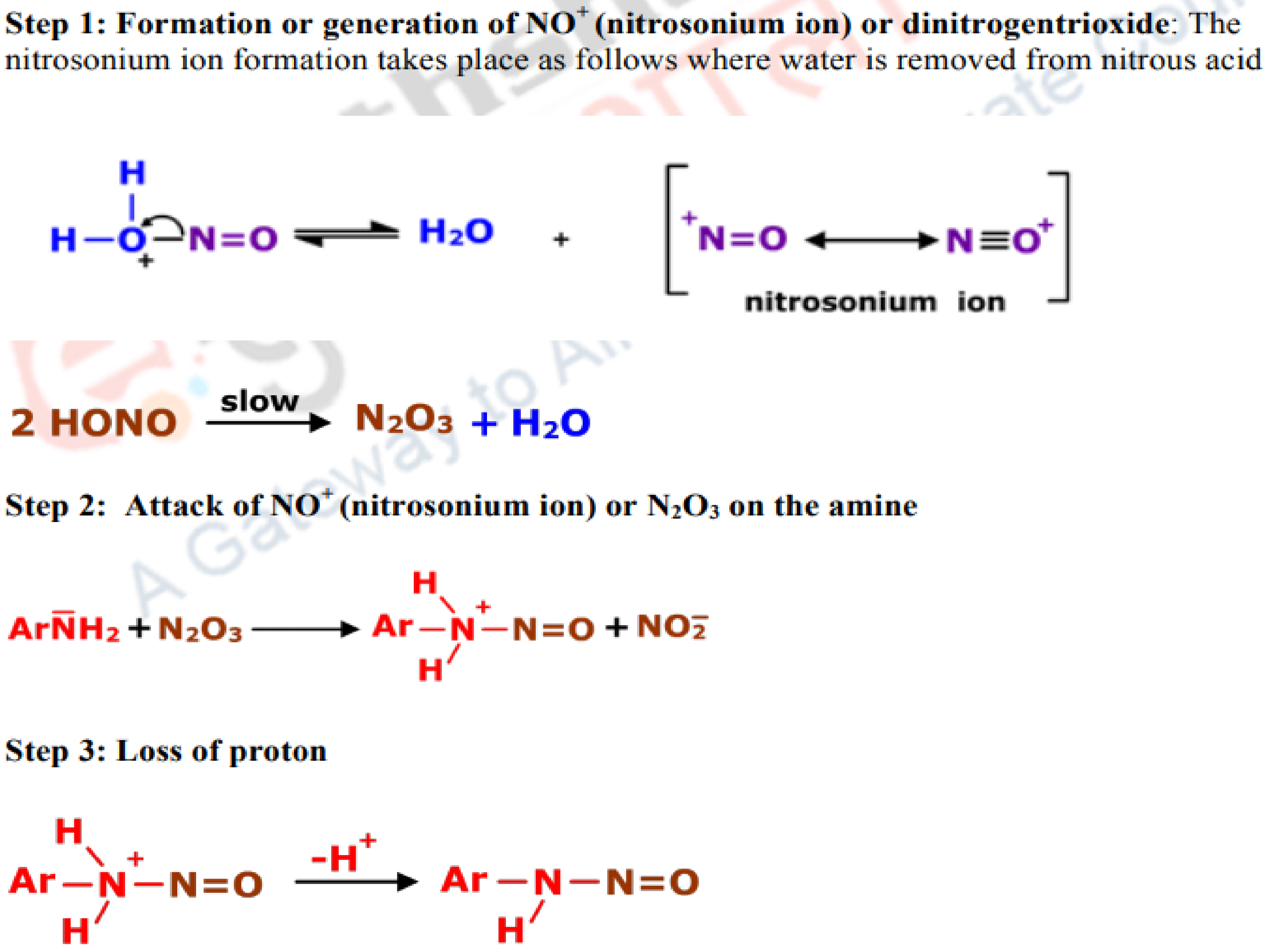


The hydrochloric acid reacts with sodium nitrite to form unstable nitrous acid.

$$NaNO_{2(aq)} + HCl_{(aq)} \longrightarrow HNO_{2(aq)} + NaCl_{(aq)}$$

The nitrous acid formed *in situ* reacts with the arylamine to form diazonium ion.

3.3 Mechanism of



Step 1: Formation or generation of NO^+ (nitrosonium ion) or dinitrogentrioxide: The nitrosonium ion formation takes place as follows where water is removed from nitrous acid

$$H-\overset{H}{\overset{|}{O^+}}-N=O \rightleftharpoons H_2O + \left[{}^+N=O \longleftrightarrow N\equiv O^+\right]$$

$$2\,HONO \xrightarrow{slow} N_2O_3 + H_2O$$

Step 2: Attack of NO^+ (nitrosonium ion) or N_2O_3 on the amine

$$Ar\bar{N}H_2 + N_2O_3 \longrightarrow Ar-\overset{+}{N}H_2-N=O + NO_2^-$$

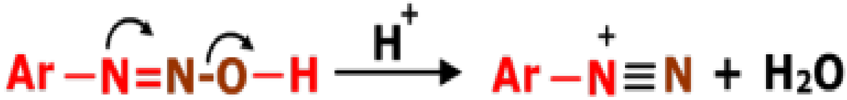
Step 3: Loss of proton

$$Ar-\overset{+}{N}H_2-N=O \xrightarrow{-H^+} Ar-NH-N=O$$

Step 4: Tautomerisation

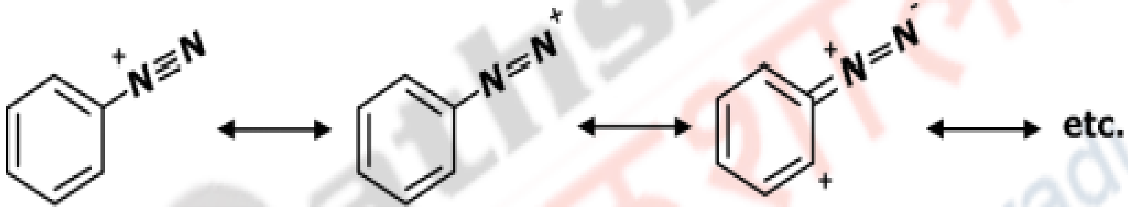
$$Ar-\underset{H}{N}-N=O \xrightleftharpoons{\text{tautom.}} Ar-N=N-O-H$$

Step 5: Loss of water and formation or generation of diazonium ion



$$Ar-N=N-O-H \xrightarrow{H^+} Ar-\overset{+}{N}\equiv N + H_2O$$

Stability of diazonium ion: The aromatic diazonium salts are relatively more stable than aliphatic diazonium salts, as the electron rich benzene ring stabilises the $-N^+\equiv N$ group. If the temperature rises above 5°C, the benzenediazonium chloride decomposes to form phenol and nitrogen gas is given off. The aromatic groups present stabilise the diazonium ion through donating electrons via delocalisation in comparison to aliphatic groups, as shown below.

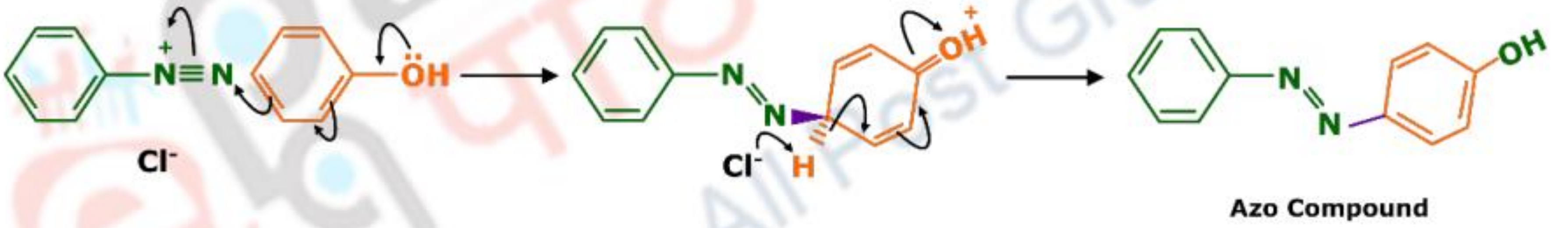


3.4 Coupling Reaction

- If the benzenediazonium chloride is reacted with another compound containing a benzene ring, called a coupling agent (such as phenol or aromatic amine), an azo compound is produced.
- **<u>The diazonium salt acts as an electrophile</u>** in a coupling reaction. Many of the products of coupling reactions are important dyes. A coloured precipitate of azo compound is formed immediately on reaction of diazonium salt with amines or phenols.

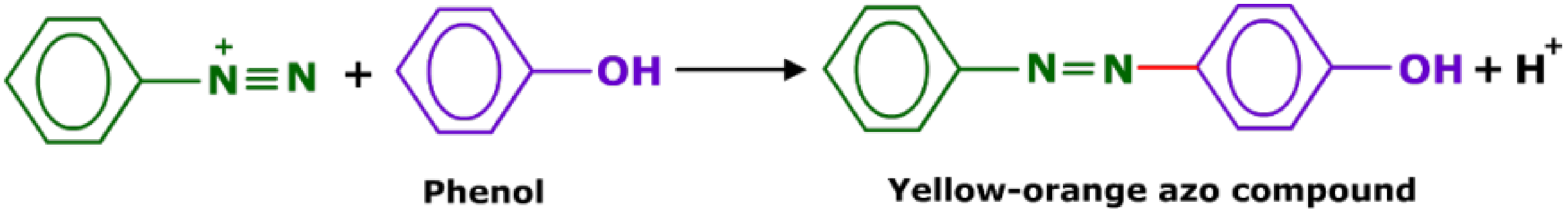
2.4.1 Mechanism of coupling reaction:

The mechanism involves an initial attack of coupling agent (phenols or anilines) on an electrophilic diazonium ion, followed by loss of a proton. The product is normally a trans-diazo compound rather than cis.

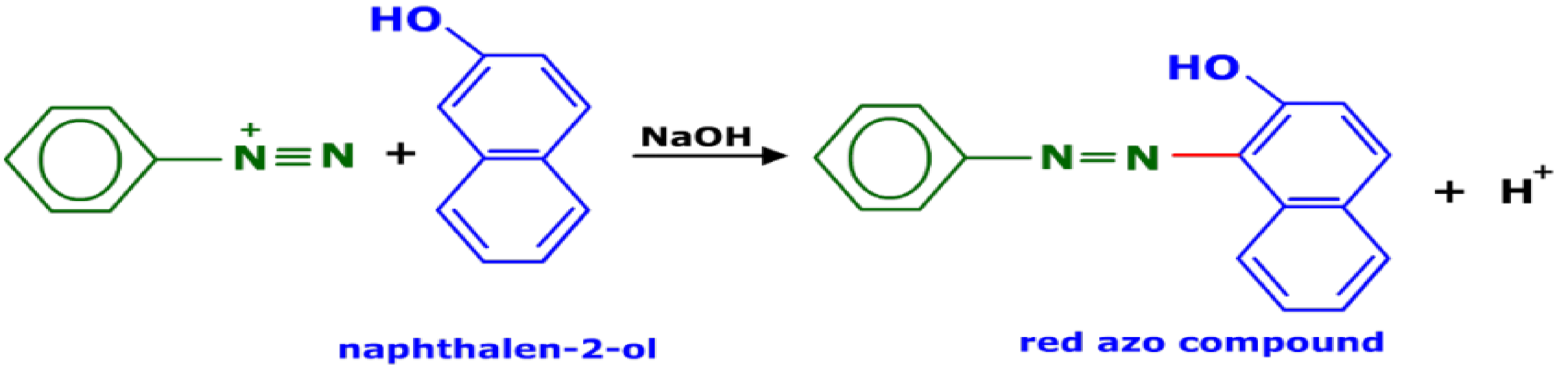


3.5 Examples of coupling reactions:

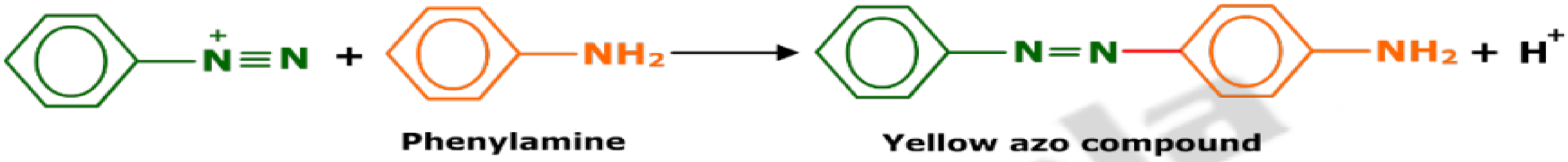
(a) Benzenediazonium salt and alkaline phenol gives a yellow orange azo compound



(b) Benzenediazonium salt and alkaline naphthalen-2-ol gives a red azo compound.

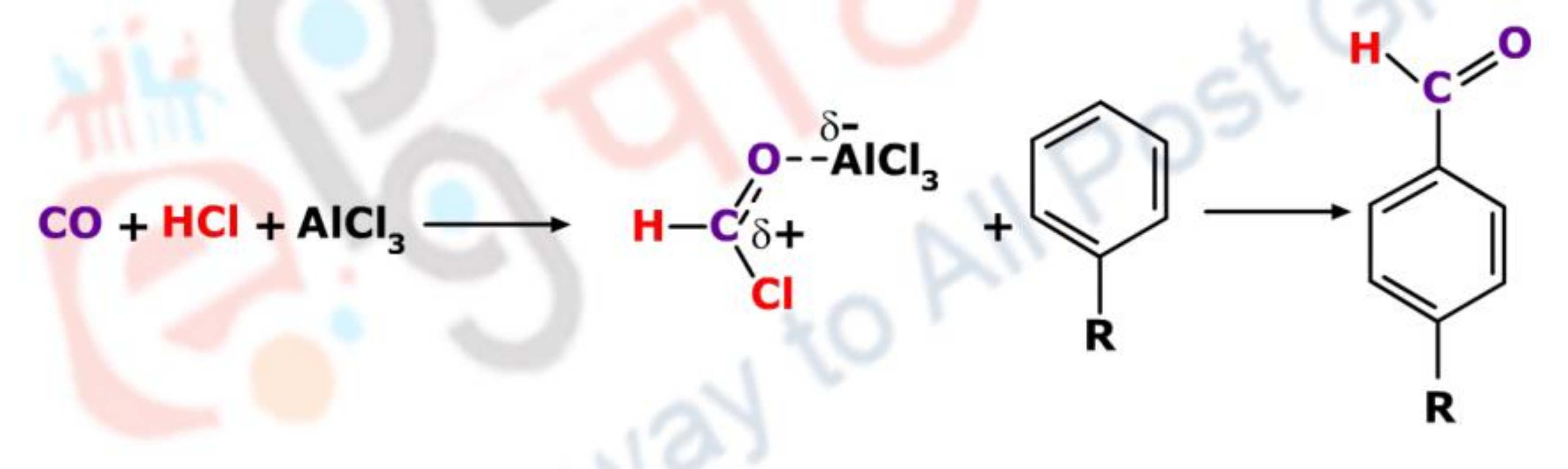


(c) Benzenediazonium salt and phenylamine gives a yellow azo compound.



4. Gattermann-Koch Reaction

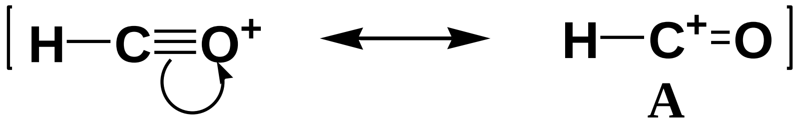
Gattermann-Koch is the name given to the reaction of an aromatic substrate with carbon monoxide and hydrogen chloride (gas) in the presence of a Lewis acid catalyst to form aromatic aldehyde. It is used for formylation of aromatic compounds. The reaction is carried out either under pressure or in the presence of CuCl.



4.1 Mechanism of Gattermann-Koch reaction

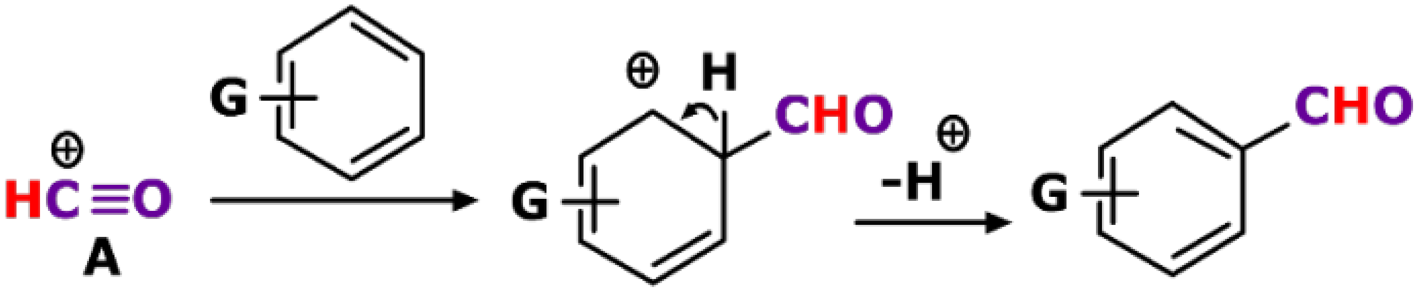
- The reaction proceeds via generation of electrophile by the combination of carbon monoxide and AlCl3. The electrophile HCO+ generated then reacts with the aromatic substrate in an electrophilic aromatic substitution reaction to yield the formylated aromatic compound

$$HCl + CO + AlCl_3 \longrightarrow [HCO^+] + AlCl_4^-$$



$$\left[H-C\equiv O^+ \longleftrightarrow H-C^+=O \right]$$

A

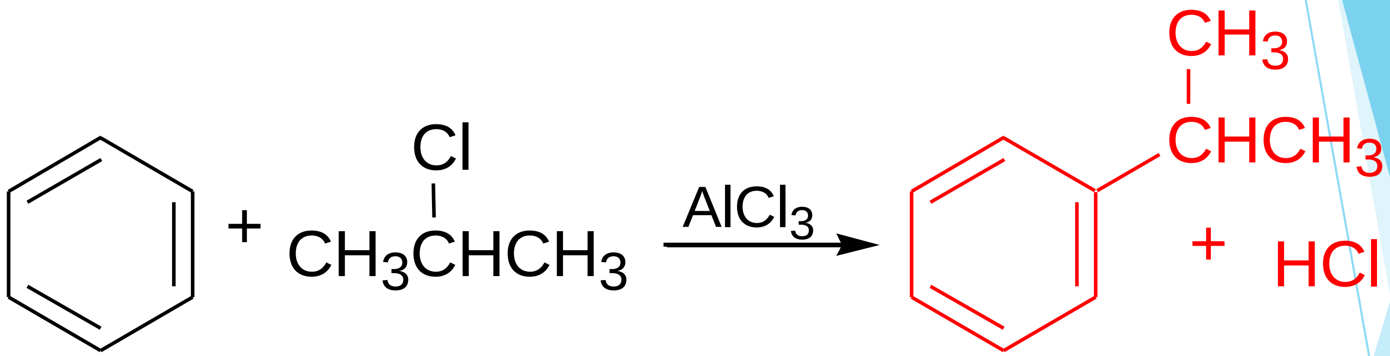


Under high pressure conditions high yields are obtained in this reaction. To overcome the limitation of high pressure requirements, super-acidic catalysts have been developed, For example super acid generated from trifluoromethanesulfonic acid, hydrogen fluoride and boron trifluoride

4.2 Limitations of Gattermann-Koch reaction:

- The role of CuCl is not clear. It is known that CuCl combines with CO and this adduct may aid the reaction between HCl and CO. Gattermann-Koch formylation method has many limitations. There are many other methods available for the formylation of aromatic compounds.
- The reaction is limited to benzene and akylbenzene.
- It does not takes place with phenol, phenolic ethers, amines and ring containing meta -directing substituent's

5. Friedel-Crafts Reaction (Alkylation of Aromatic Rings)

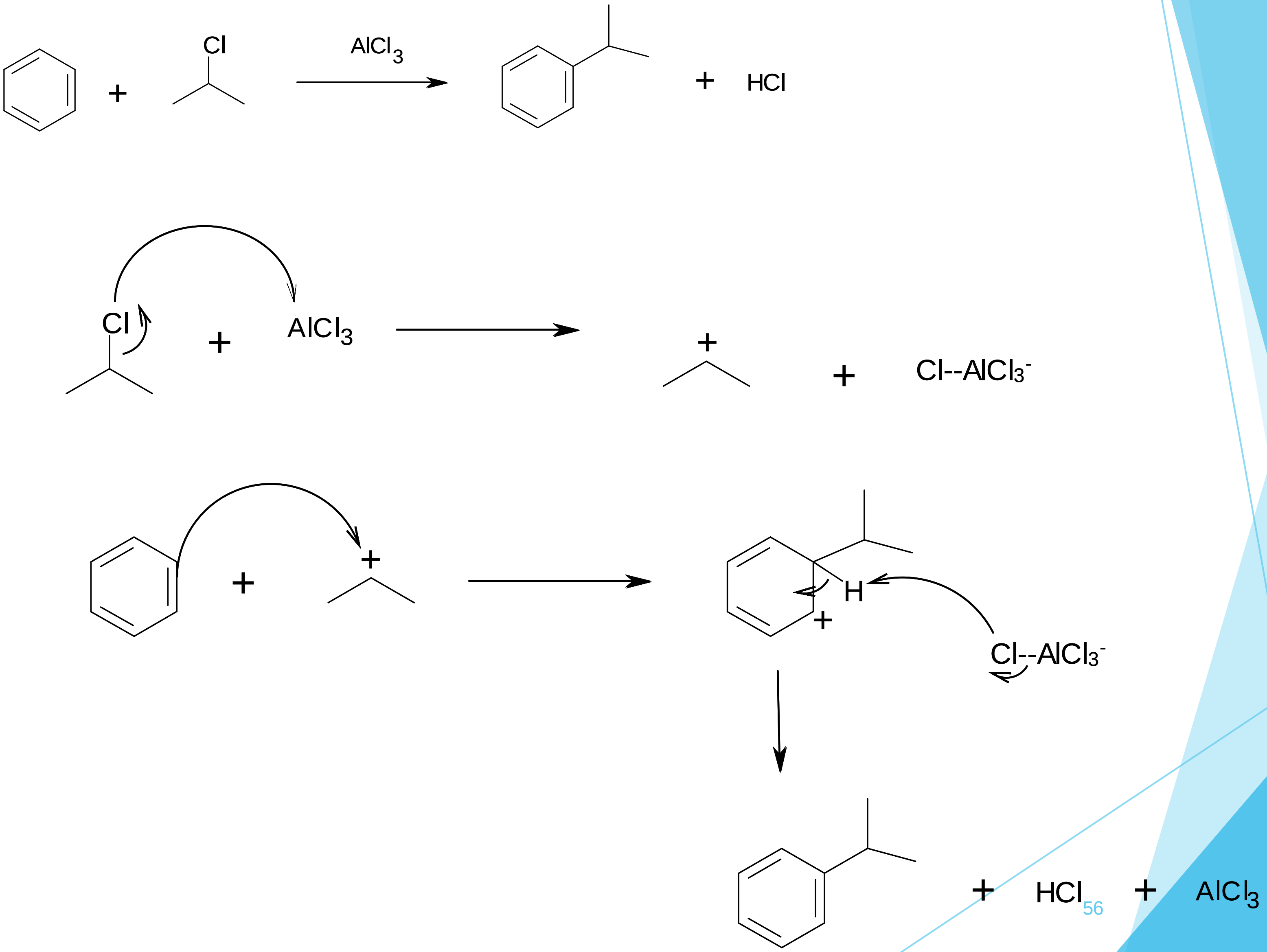


benzene

2-chloropropane

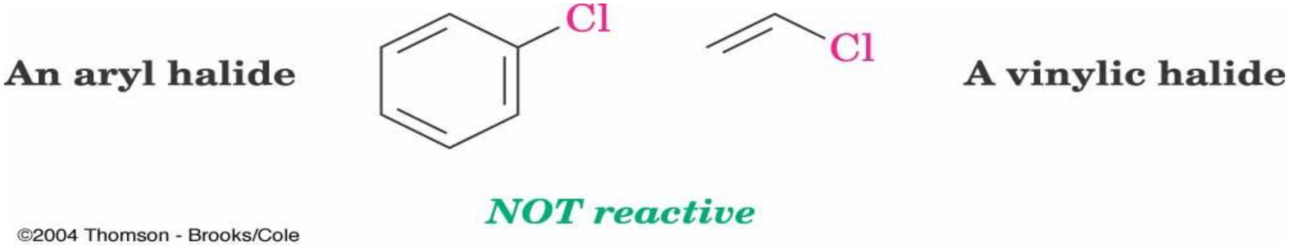
isopropylbenzene

5.1 Mechanism:Friedel-Crafts Reaction



Friedel-Crafts Reaction (Alkylation of Aromatic Rings)

- The electrophile is a carbocation, R^+
- Only alkyl halides can be used
  - **Aryl halides and vinylic halides do not react.**



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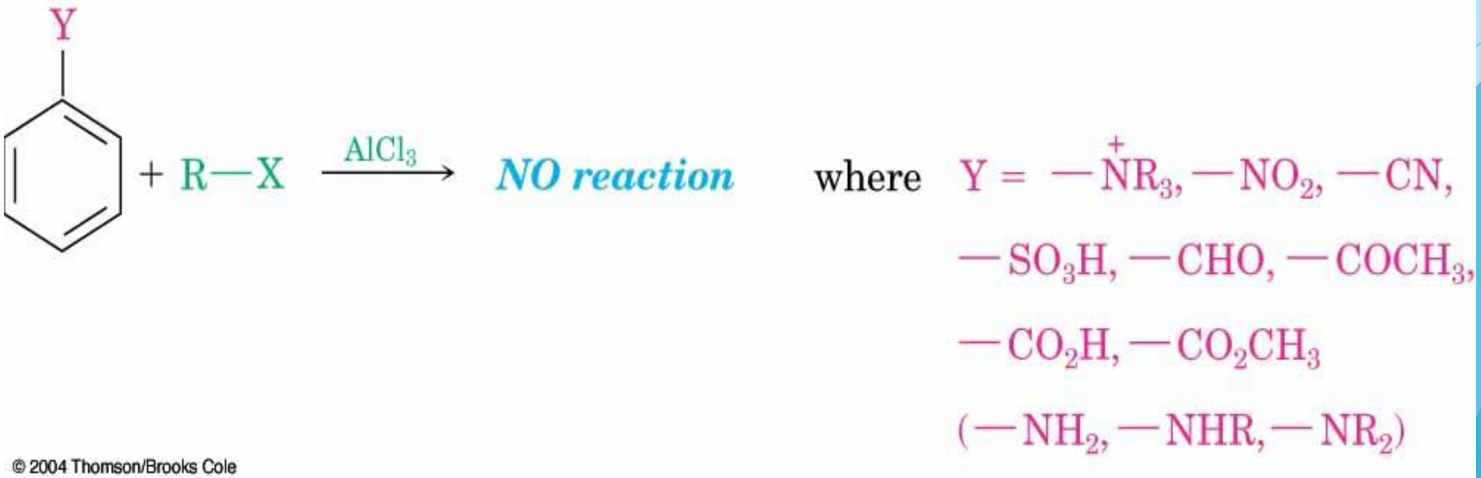
- will not occur on aromatic rings substituted by electron



where $Y = -\overset{+}{N}R_3, -NO_2, -CN, -SO_3H, -CHO, -COCH_3, -CO_2H, -CO_2CH_3$

$(-NH_2, -NHR, -NR_2)$

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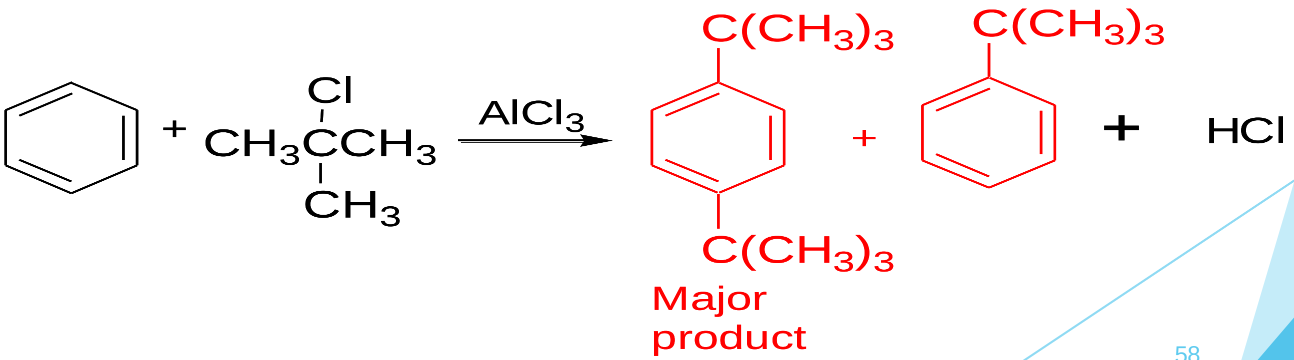
Friedel-Crafts Reaction

- can’t eat just one! It’s hard to stop after one substitution
- skeletal rearrangements of the alkyl group often occur when using tertiary alkyl halides

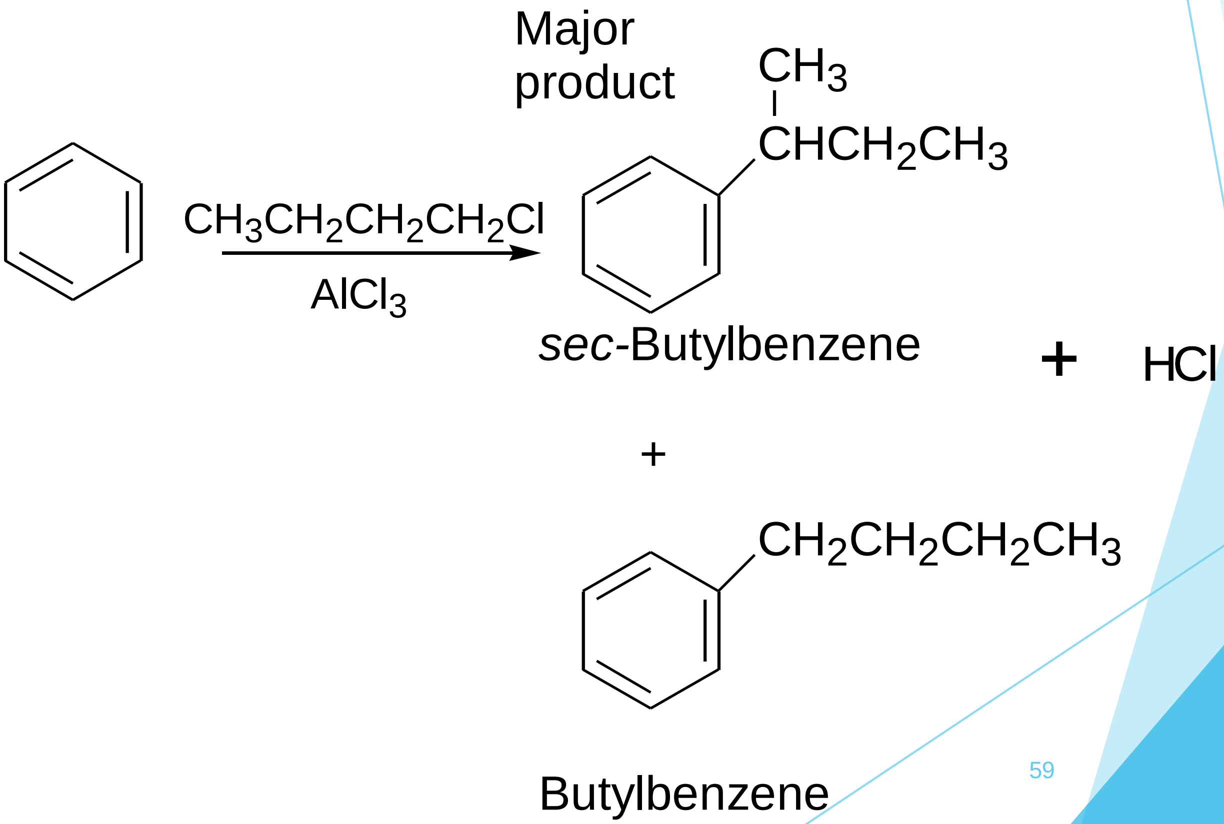
Multiple substitutions:

- Reaction of benzene with 2-chloro-2methylpropane.
- Polyalkylation



Friedel-Crafts Reaction

- Skeletal rearrangements in Friedel-Crafts reactions (hydride shift):
  - Will rearrange to form more stable carbocation intermediates



Friedel-Crafts Reaction

- Skeletal rearrangements in Friedel-Crafts reactions (alkyl shift):
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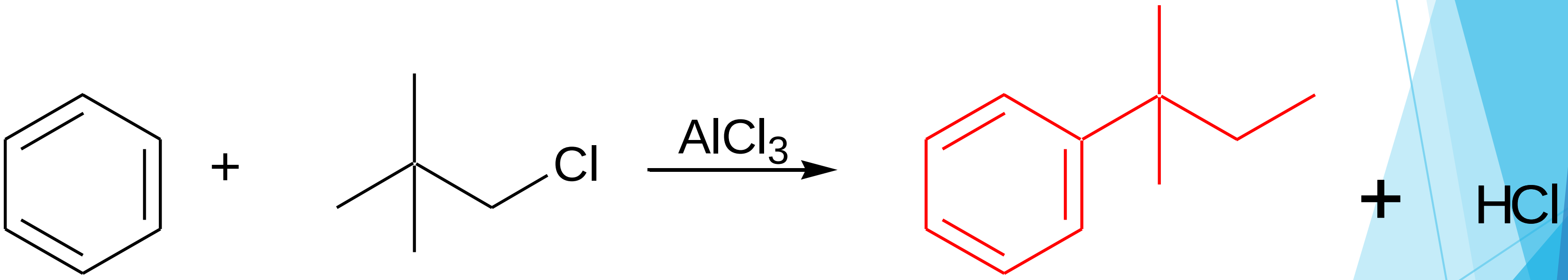


1-Chloro-2,2-dimethylpropane

(1,1-Dimethylpropyl)-benzene

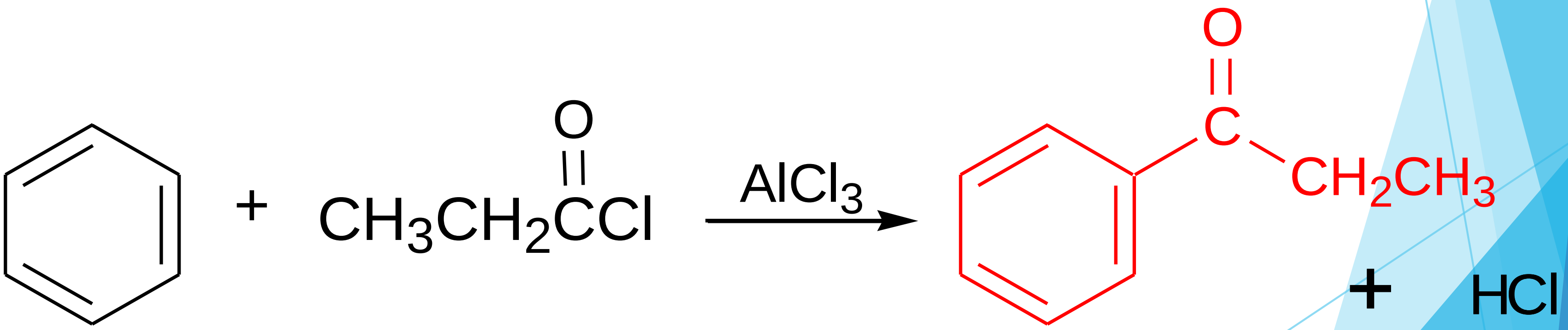
Friedel-Crafts Alkylation Summary

- Only alkyl halides can be used!!
- Will not occur on aromatic rings substituted by electron withdrawing substituents
  - Carbonyl and amino groups
- Will have polyalkylation
- Will have rearrangement to form more stable carbocation intermediate
  - Hydride shift or methyl shift

Friedel-Crafts Acylation

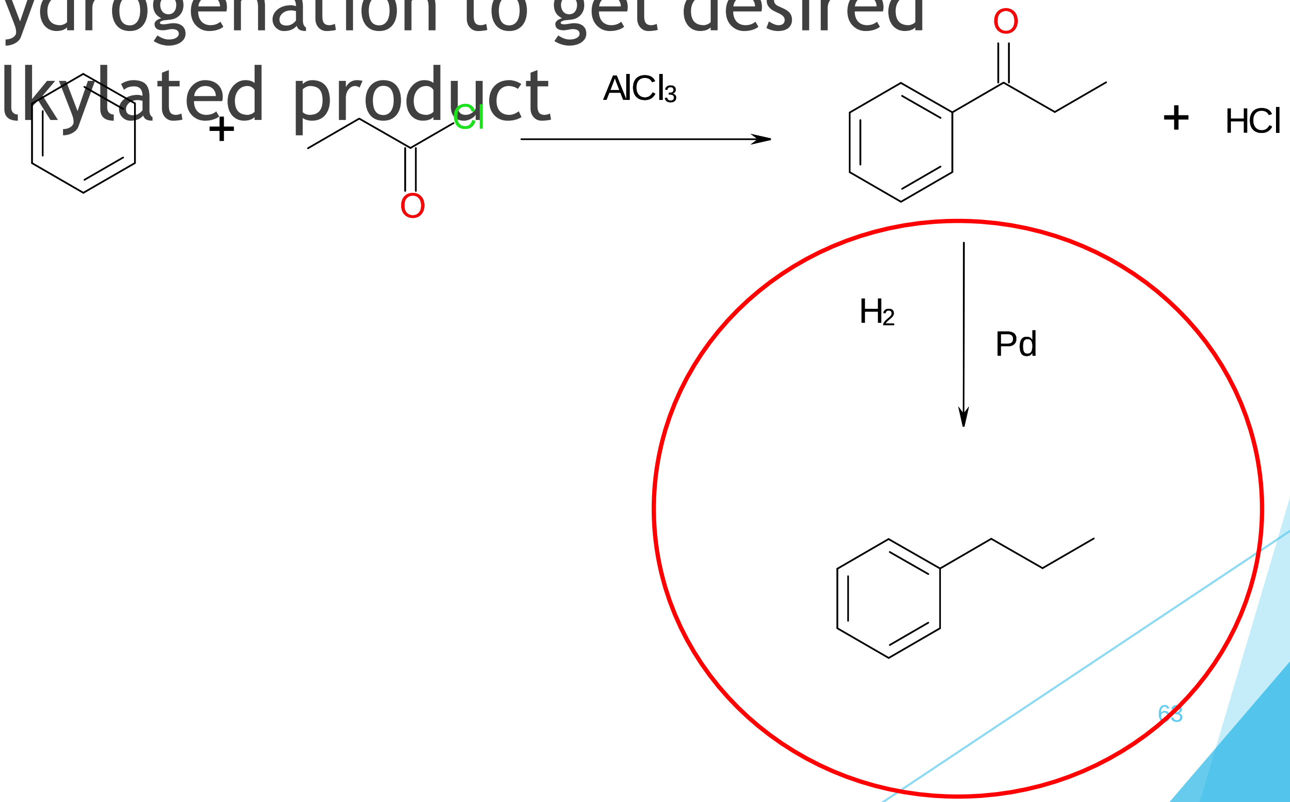
- Reaction of benzene with a carboxylic acid chloride, RCOCl in the presence of $AlCl_3$

- Note: the acyl cation **does not** undergo rearrangement. It also is **not** prone to multiple substitutions.

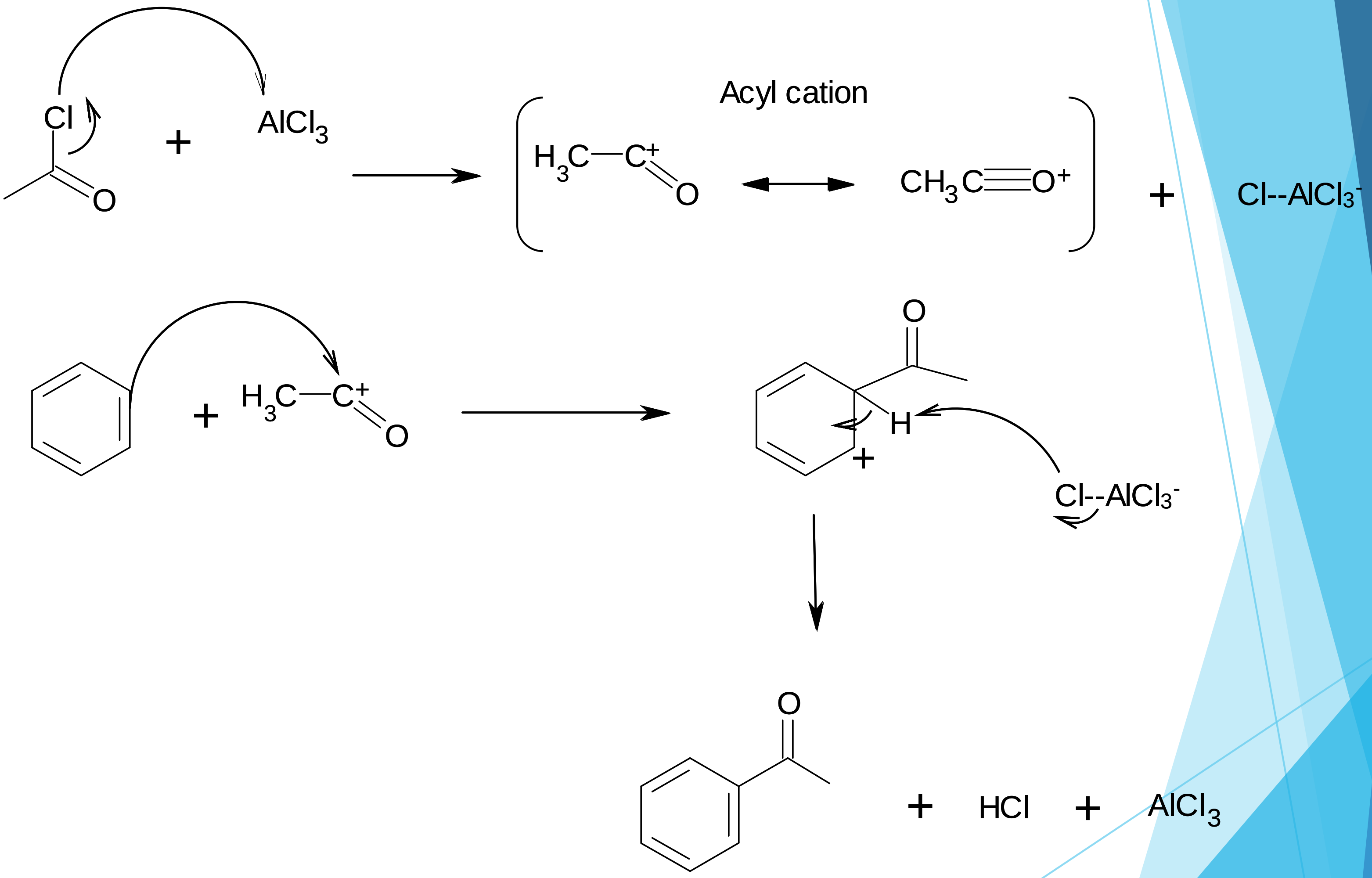


Friedel-Crafts Acylation

- After acylation we can do a hydrogenation to get desired alkylated product



Mechanism:Friedel-Crafts Acylation



Electrophilic and Nucleophilic Substitution

- Electrophilic Sub
  - Favored by electron donating substituents
    - Stabilize carbocation intermediate
- Nucleophilic Sub
  - Favored by electron withdrawing substituents
    - Stabilize carbanion intermediate