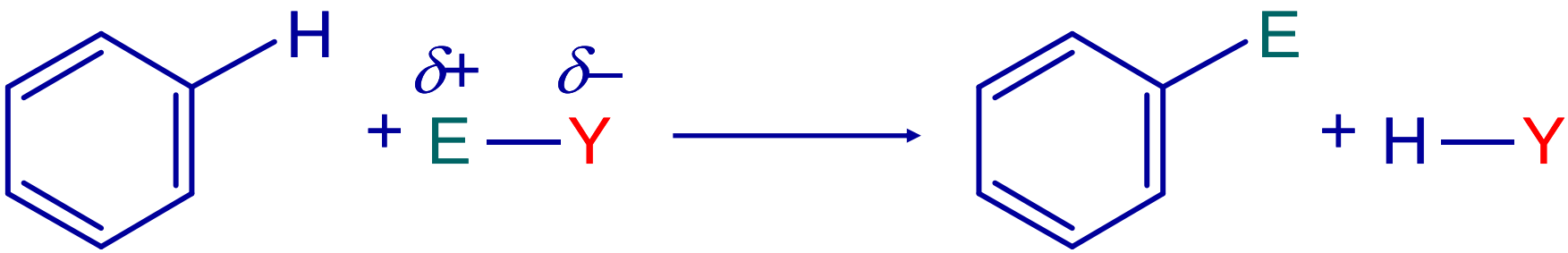
Chapter 12
Reactions of Arenes: Electrophilic and Nucleophilic Aromatic Substitution



Electrophilic aromatic substitutions include:

Nitration

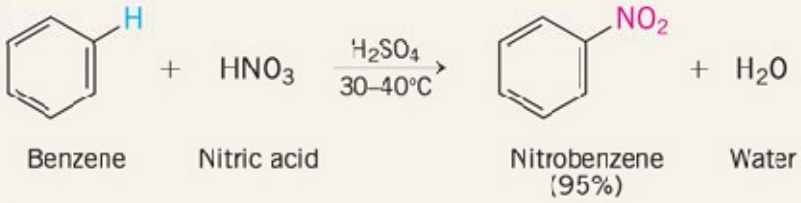
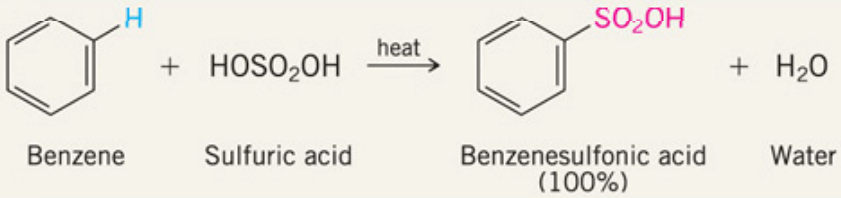
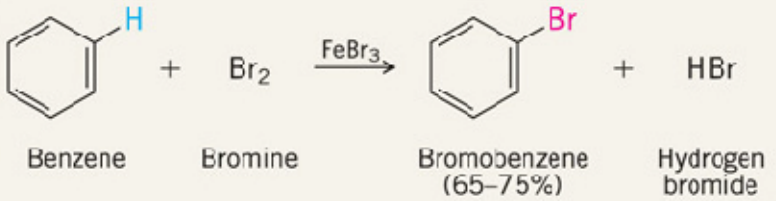
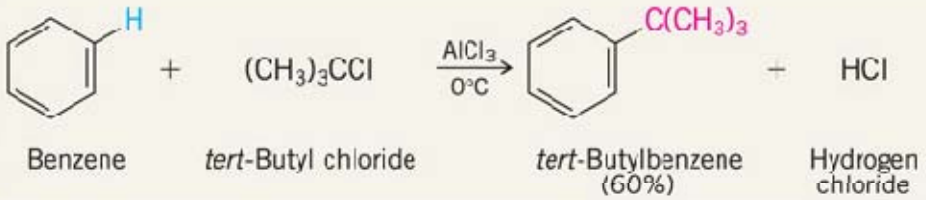
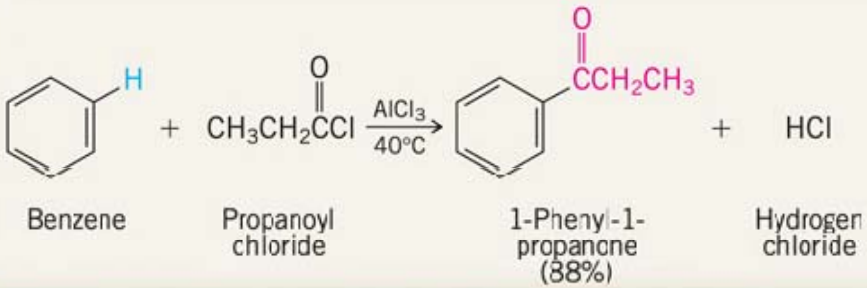
Sulfonation

Halogenation

Friedel-Crafts Alkylation

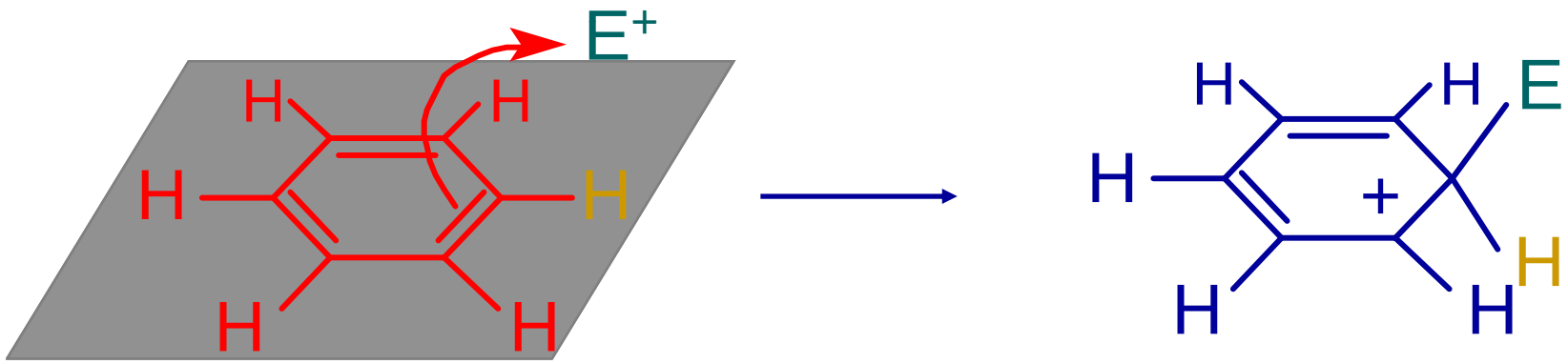
Friedel-Crafts Acylation

TABLE 12.1 Representative Electrophilic Aromatic Substitution Reactions of Benzene

Reaction and comments	Equation
1. Nitration Warming benzene with a mixture of nitric acid and sulfuric acid gives nitrobenzene. A nitro group ($—NO_2$) replaces one of the ring hydrogens.	
2. Sulfonation Treatment of benzene with hot concentrated sulfuric acid gives benzenesulfonic acid. A sulfonic acid group ($—SO_2OH$) replaces one of the ring hydrogens.	
3. Halogenation Bromine reacts with benzene in the presence of iron(III) bromide as a catalyst to give bromobenzene. Chlorine reacts similarly in the presence of iron(III) chloride to give chlorobenzene.	
4. Friedel–Crafts alkylation Alkyl halides react with benzene in the presence of aluminum chloride to yield alkylbenzenes.	
5. Friedel–Crafts acylation An analogous reaction occurs when acyl halides react with benzene in the presence of aluminum chloride. The products are aryl ketones.	

12.2. Mechanistic Principles of Electrophilic Aromatic Substitution

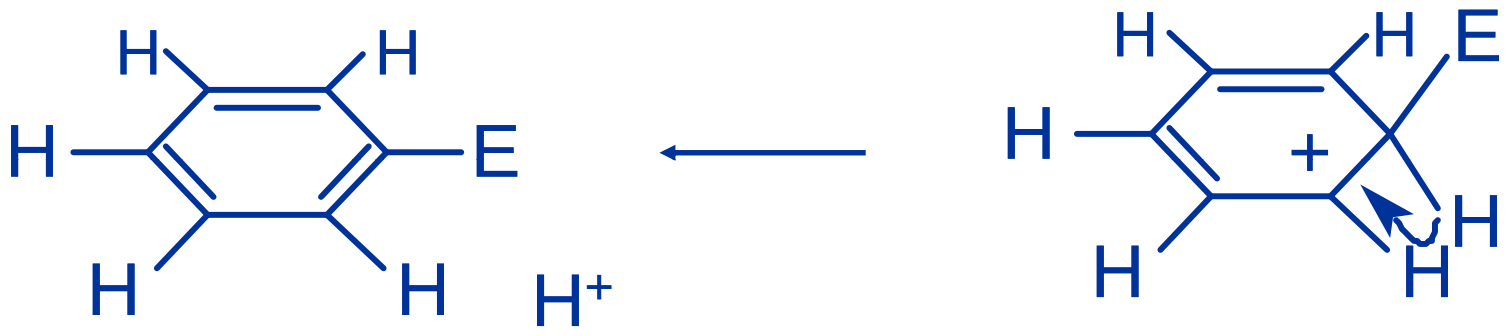
Step 1: attack of electrophile on π-electron system of aromatic ring.



Highly endothermic.

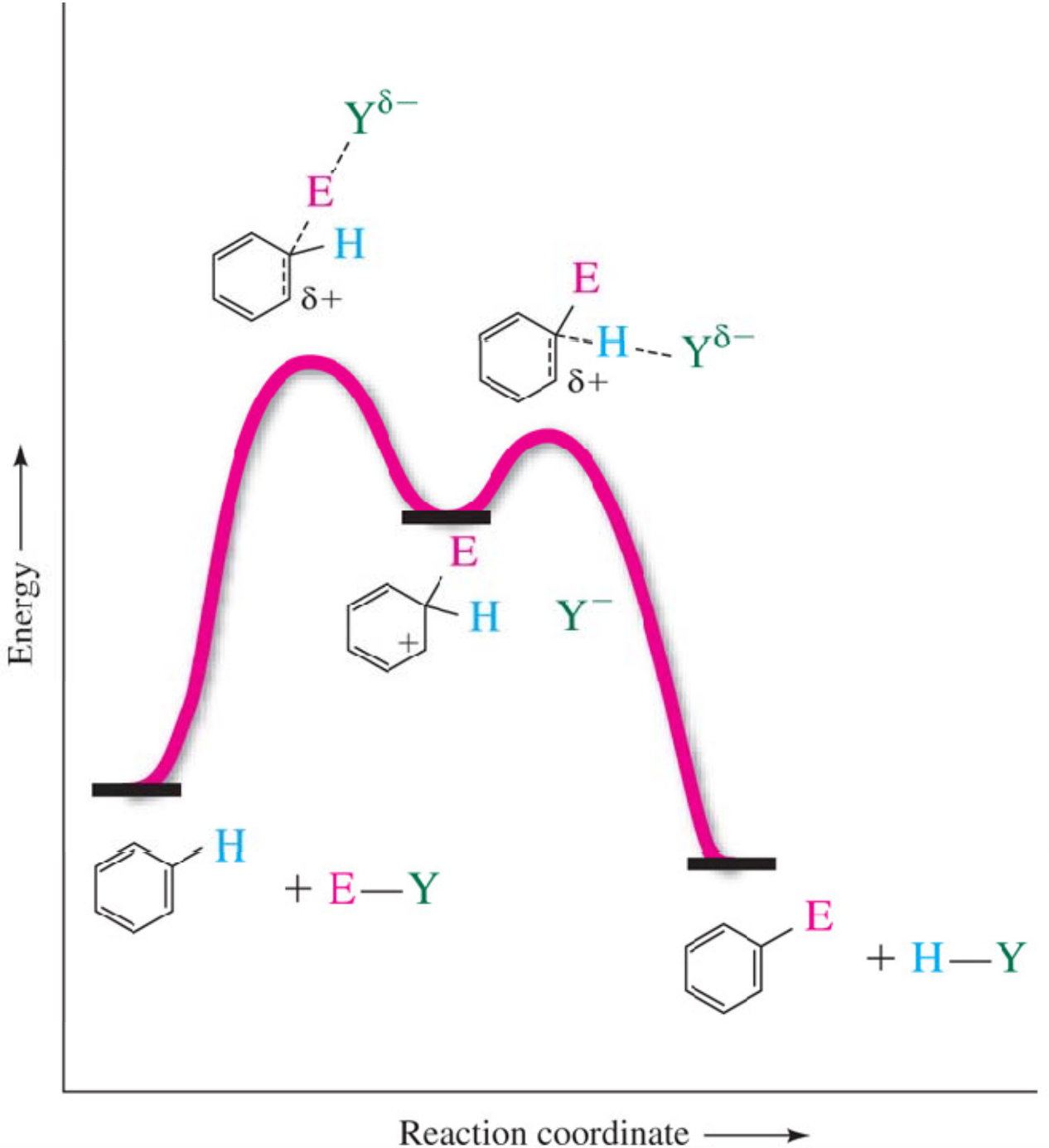
Carbocation is allylic, but not aromatic.

Step 2: loss of a proton from the carbocation intermediate



Highly exothermic.

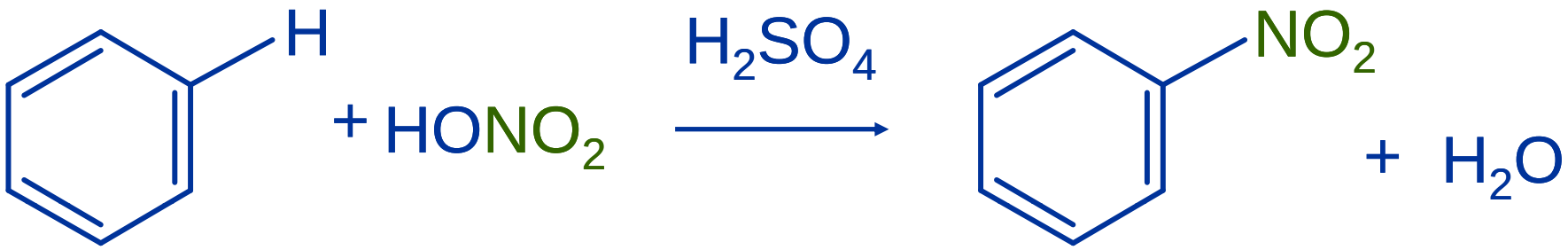
This step restores aromaticity of ring.


Energy
Reaction coordinate
Y^δ−
E
H
δ+
E
H
Y^δ−
δ+
E
H
Y−
H
+ E—Y
E
+ H—Y

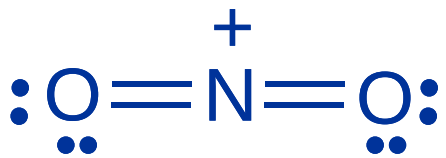
Based on this general mechanism:

- What remains is to identify the electrophile in nitration, sulfonation, halogenation, Friedel-Crafts alkylation, and Friedel-Crafts acylation to establish the mechanism of specific electrophilic aromatic substitutions.

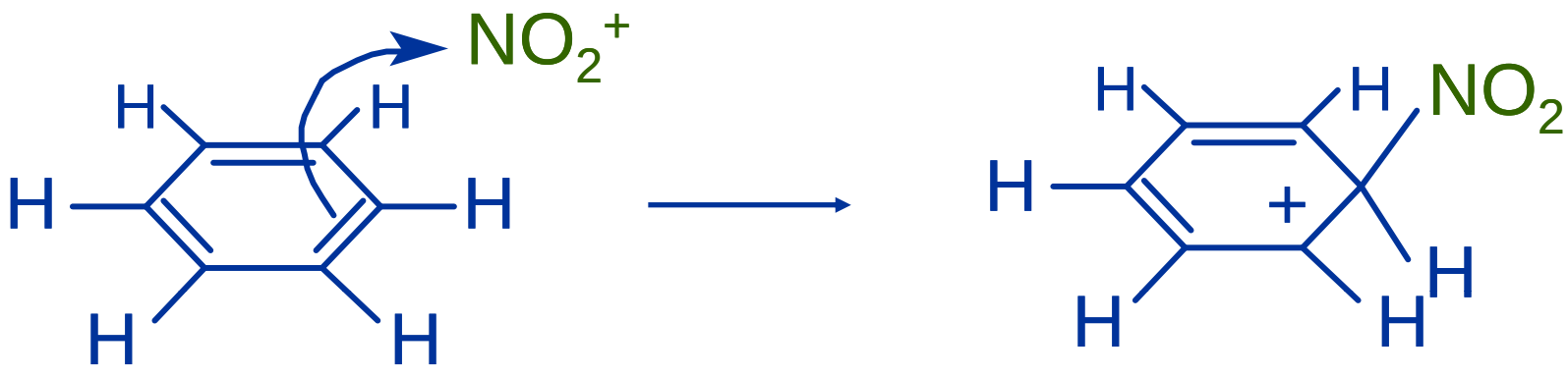
12.3. Nitration of Benzene



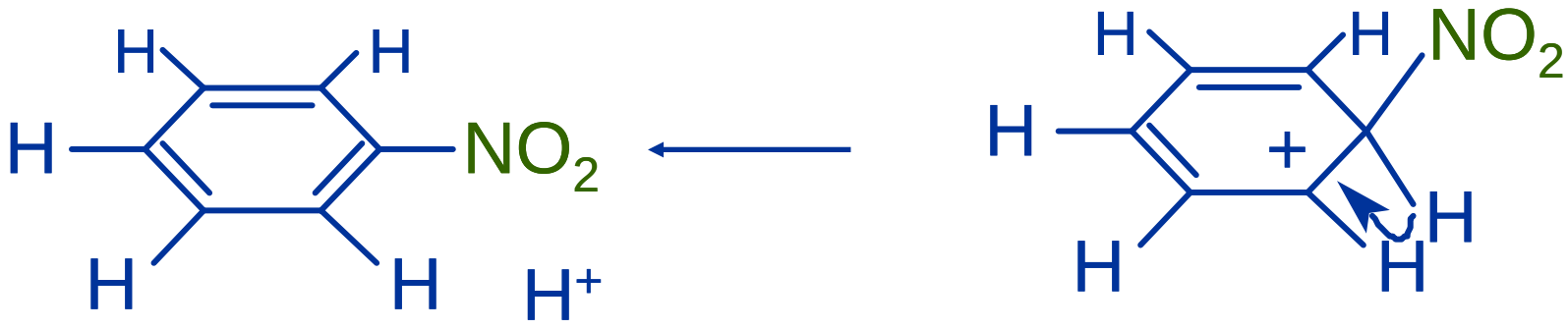
Electrophile is nitronium ion



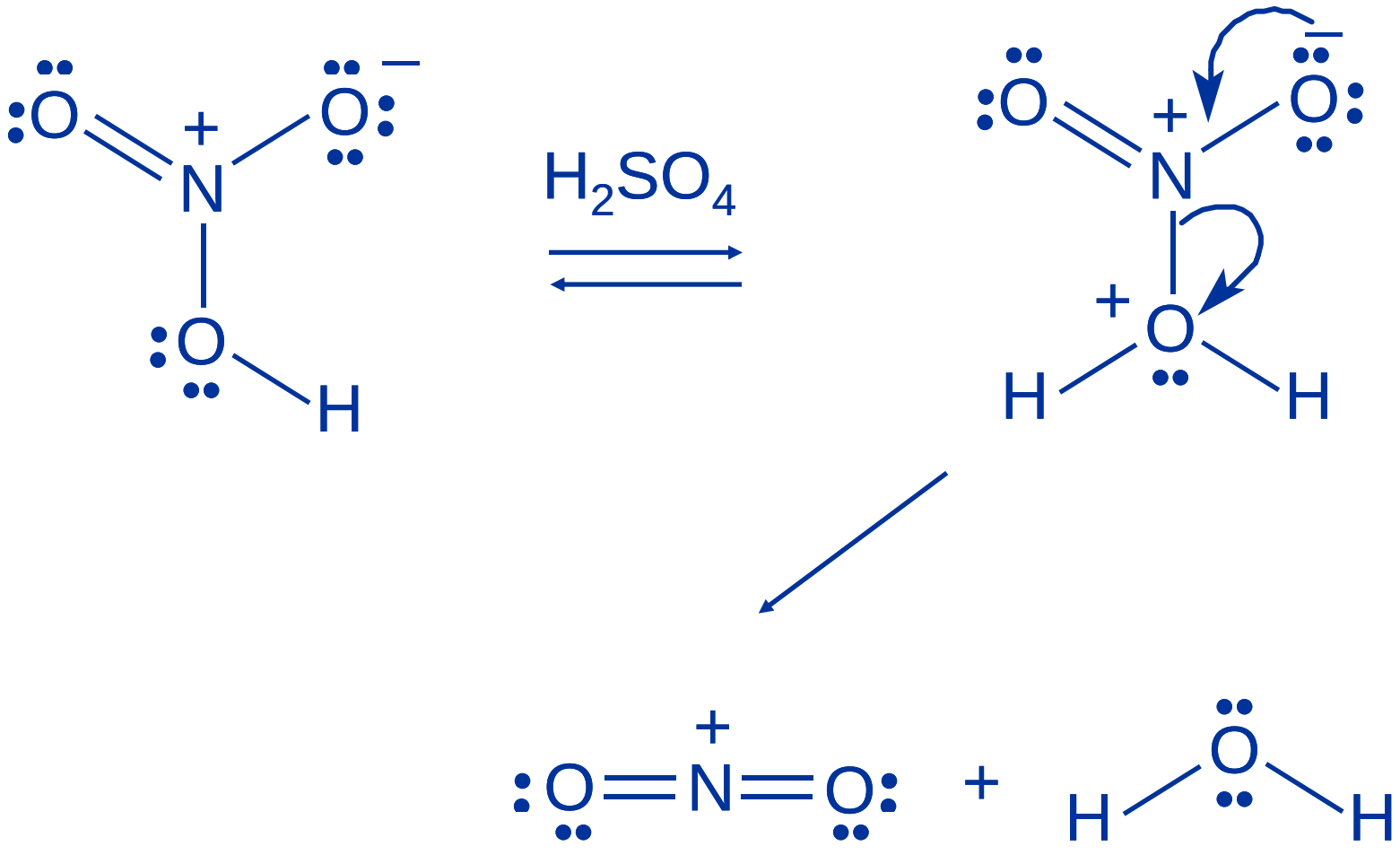
Step 1: attack of nitronium cation on π-electron system of aromatic ring



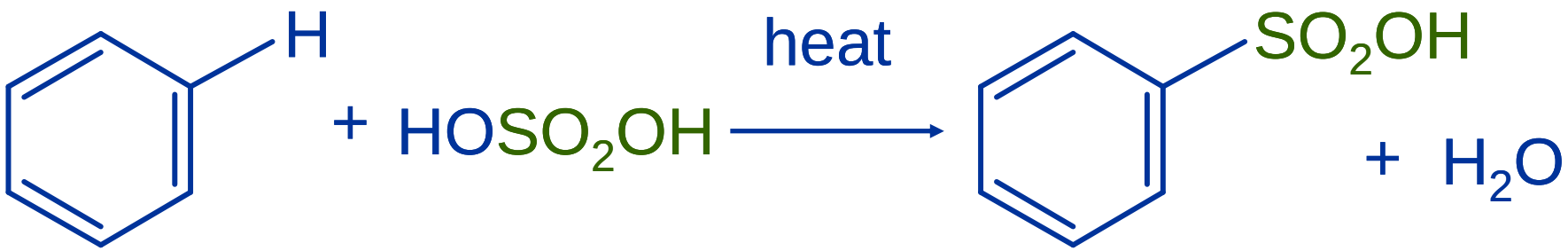
Step 2: loss of a proton from the carbocation intermediate

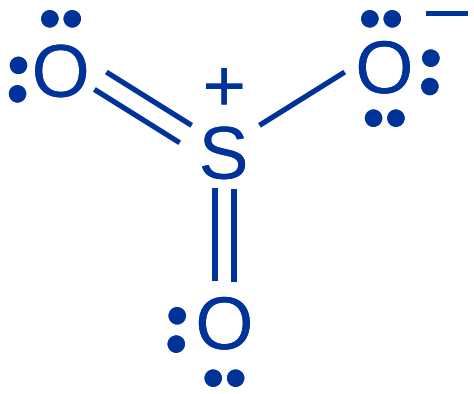


Where does nitronium ion come from?



12.4. Sulfonation of Benzene

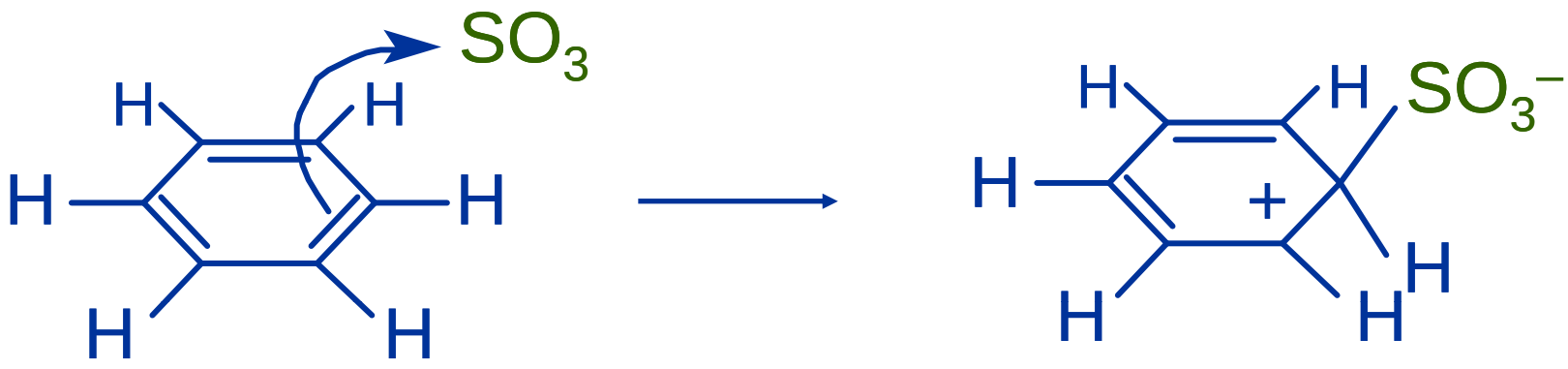




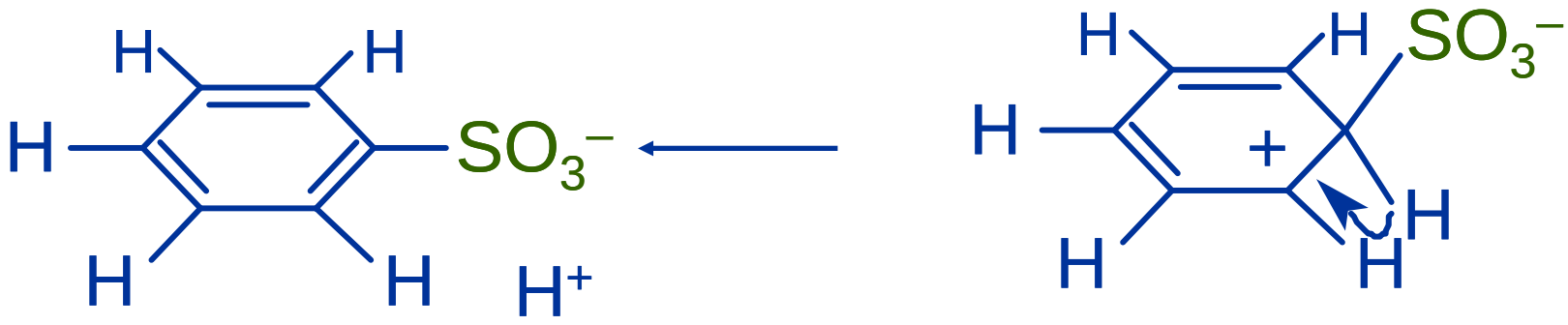
- Several electrophiles present:

a major one is sulfur trioxide.

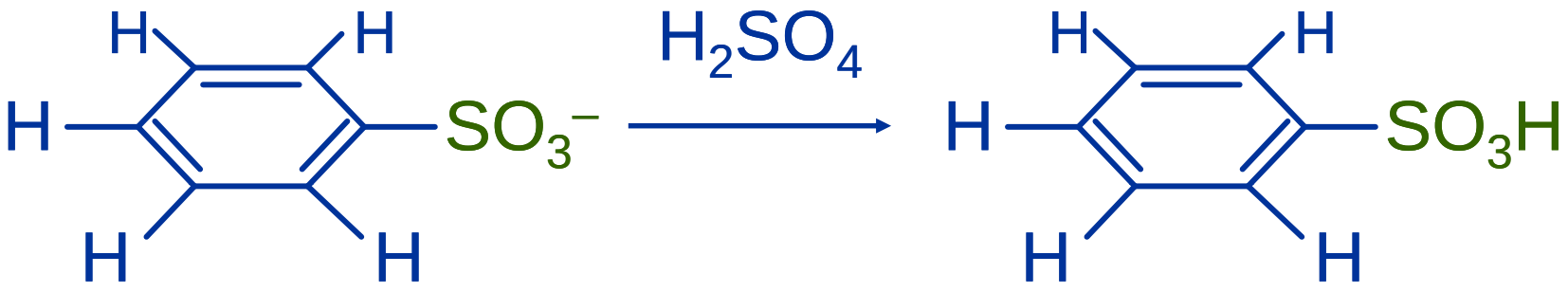
Step 1: attack of sulfur trioxide on π-electron system of aromatic ring



Step 2: loss of a proton from the carbocation intermediate

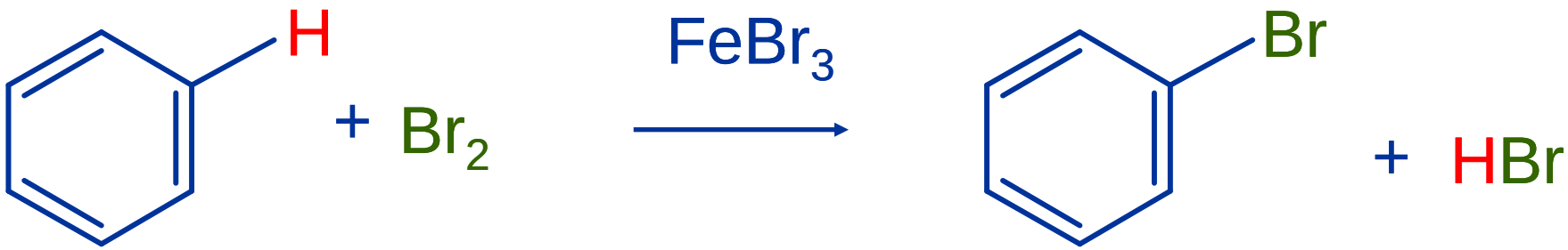


Step 3: protonation of benzenesulfonate ion



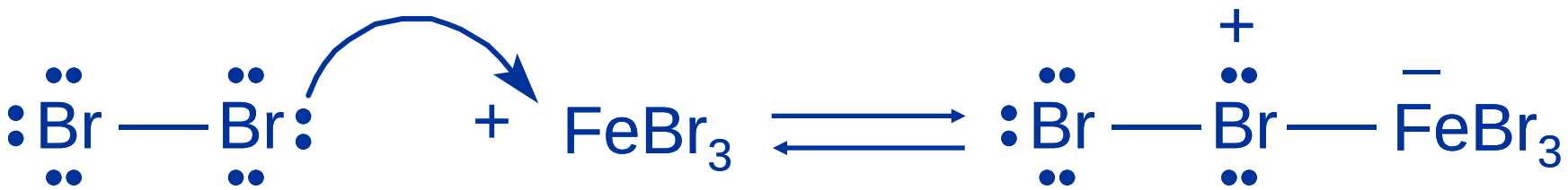
Benzenesulfonic acid

12.5. Halogenation of Benzene



- Electrophile is a Lewis acid-Lewis base. It is a complex between $FeBr_3$ and Br_2.

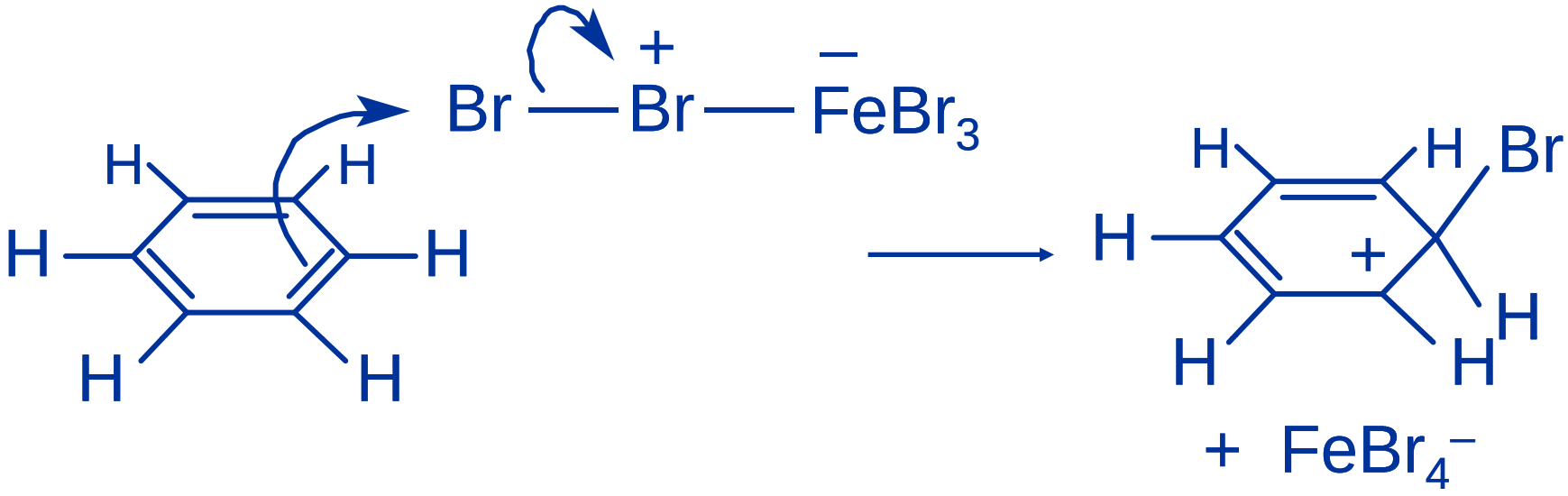
The Br_2-$FeBr_3$ Complex



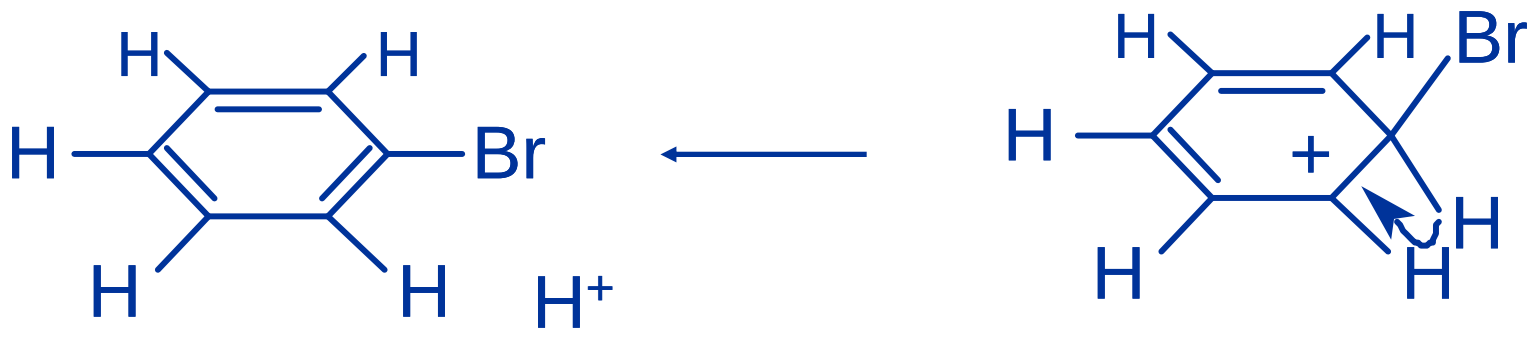
Lewis base Lewis acid Complex

➢ The Br_2-$FeBr_3$ complex is more electrophilic than Br_2 alone.

Step 1: attack of Br_2-$FeBr_3$ complex on π-electron system of aromatic ring

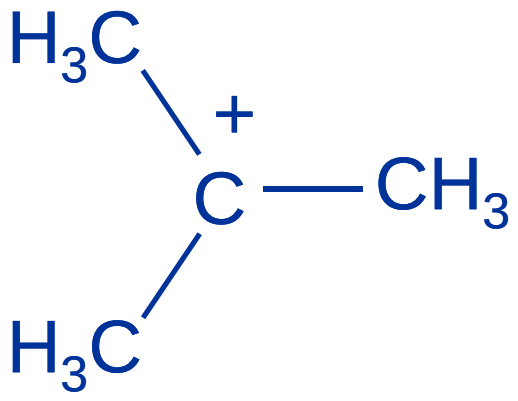


Step 2: loss of a proton from the carbocation intermediate



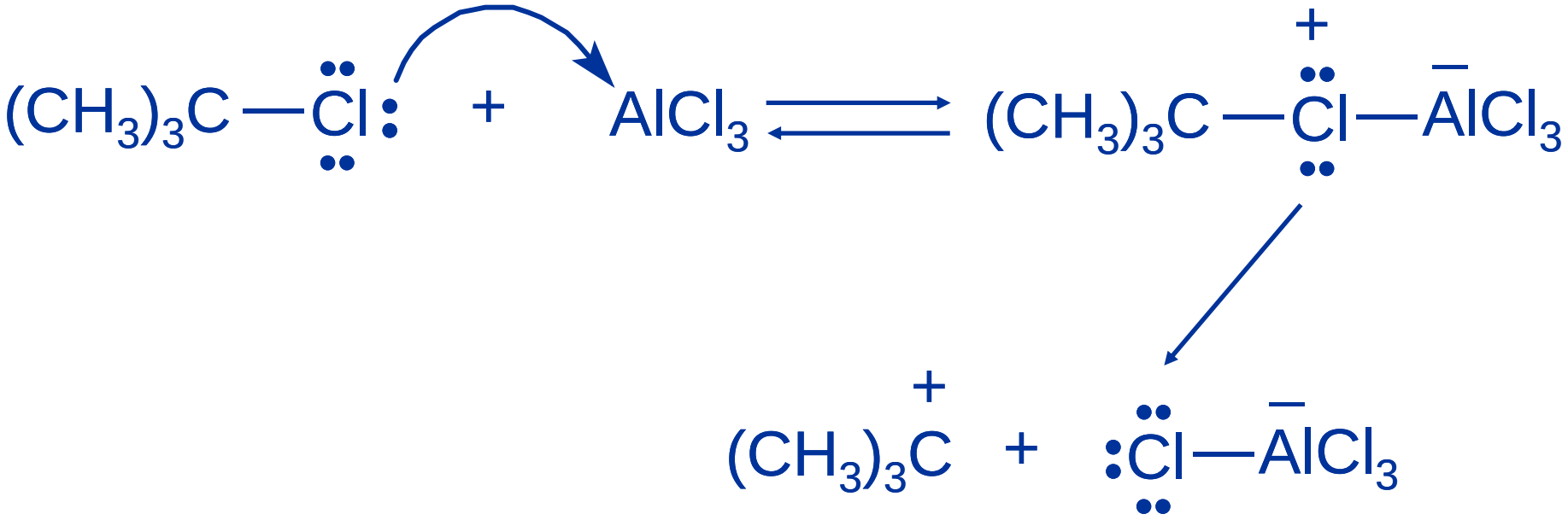
12.6. Friedel-Crafts Alkylation of Benzene

Electrophile is
tert-butyl cation

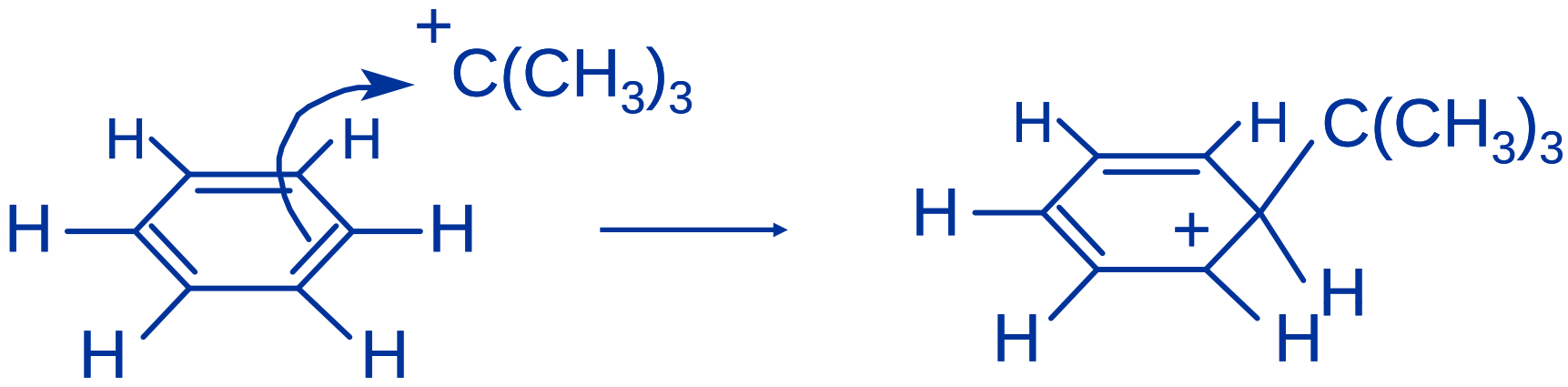


Role of $AlCl_3$

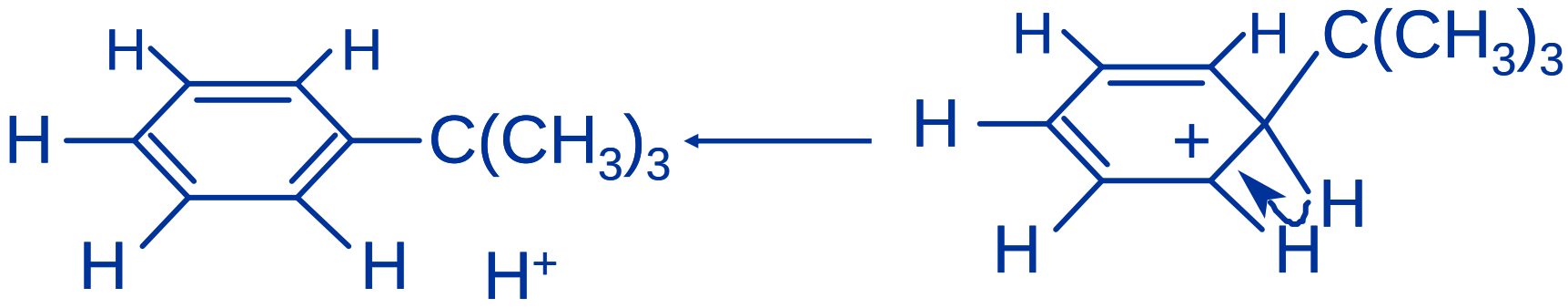
- $AlCl_3$ acts as a Lewis acid to promote ionization of the alkyl halide.



Step 1: attack of tert-butyl cation on π-electron system of aromatic ring

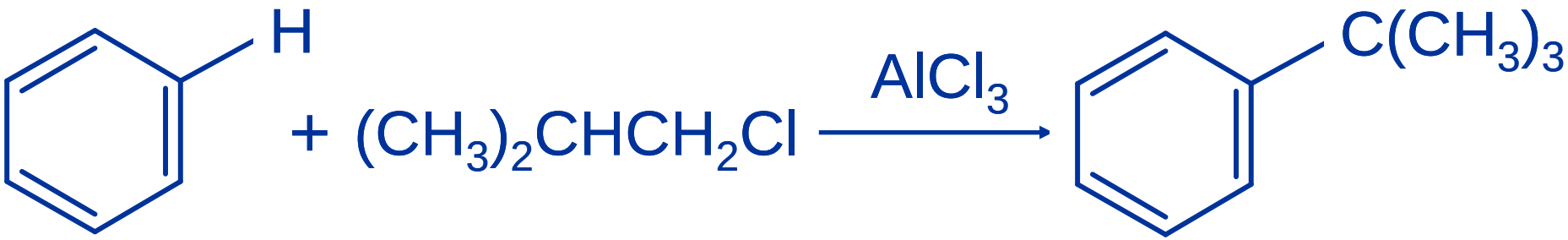


Step 2: loss of a proton from the carbocation intermediate



Rearrangements in Friedel-Crafts Alkylation

➢ Carbocations are intermediates. Therefore, rearrangements can occur!

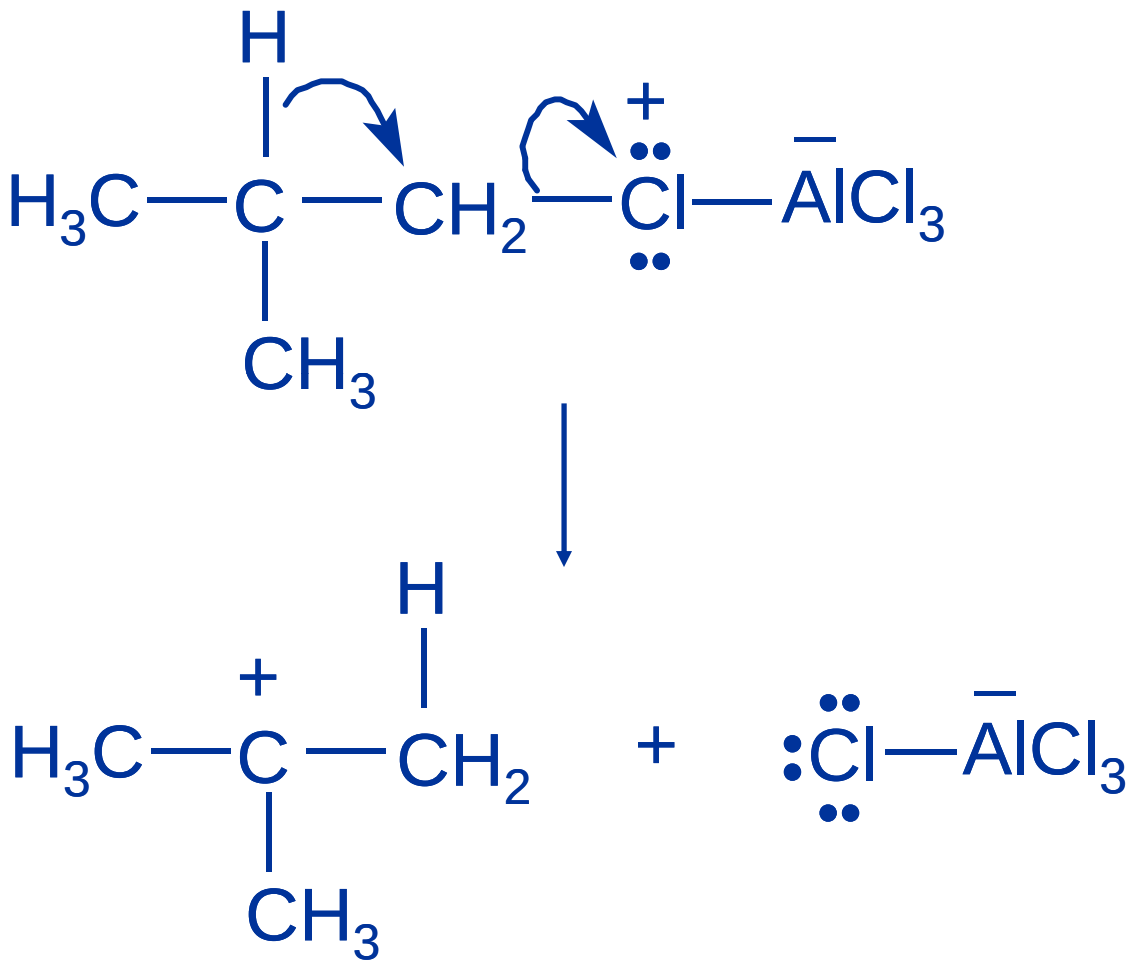


Isobutyl chloride

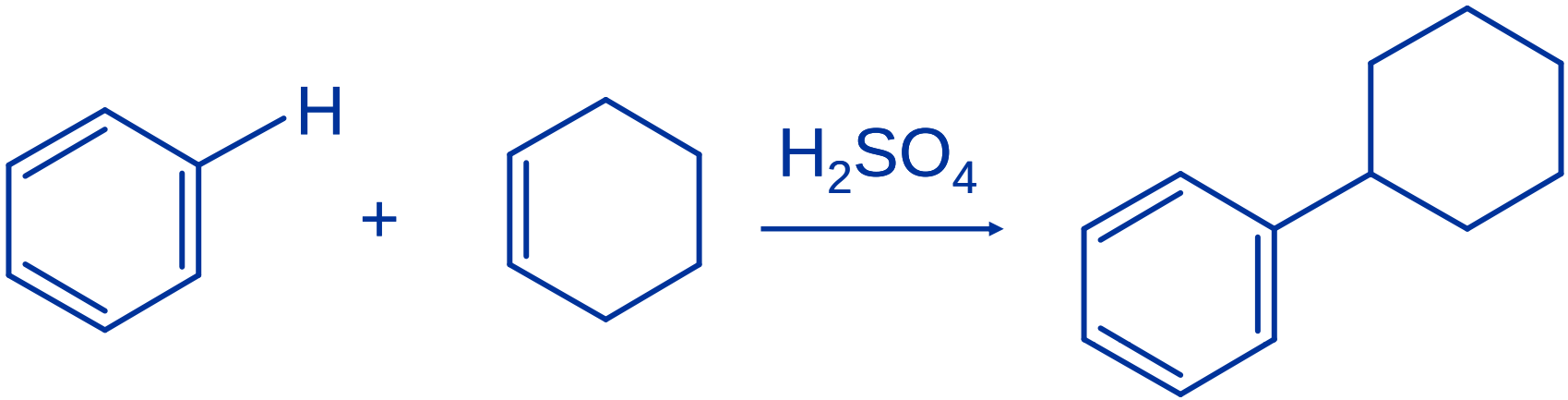
tert-Butylbenzene (66%)

➢ Isobutyl chloride is the alkyl halide. But *tert*-butyl cation is the electrophile.

Rearrangements in Friedel-Crafts Alkylation



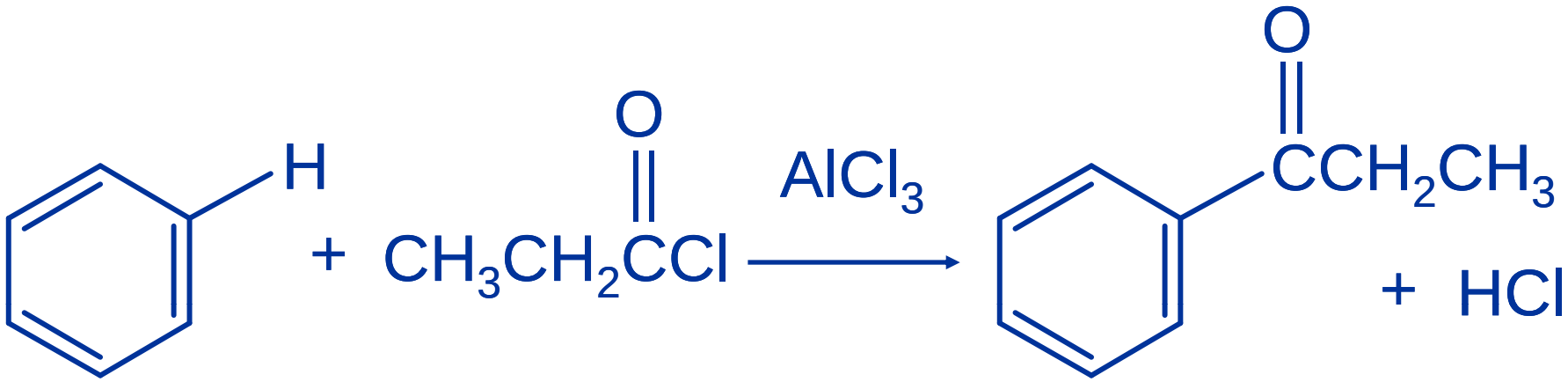
Reactions Related to Friedel-Crafts Alkylation



Cyclohexylbenzene
(65-68%)

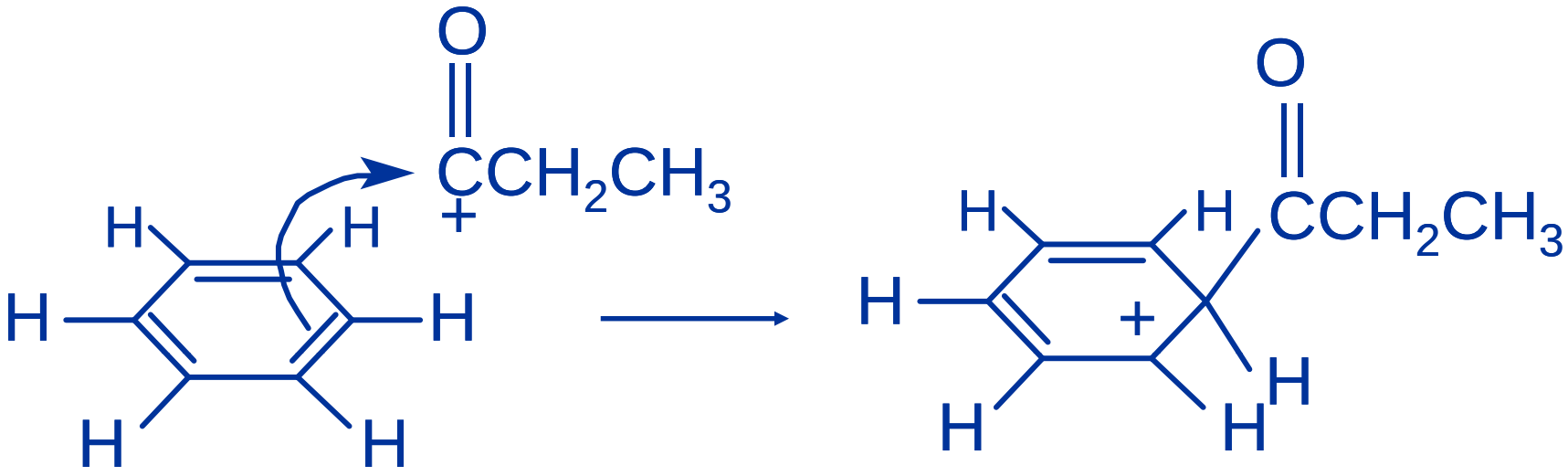
➢ Cyclohexene is protonated by sulfuric acid, giving cyclohexyl cation which attacks the benzene ring.

12.7. Friedel-Crafts Acylation of Benzene

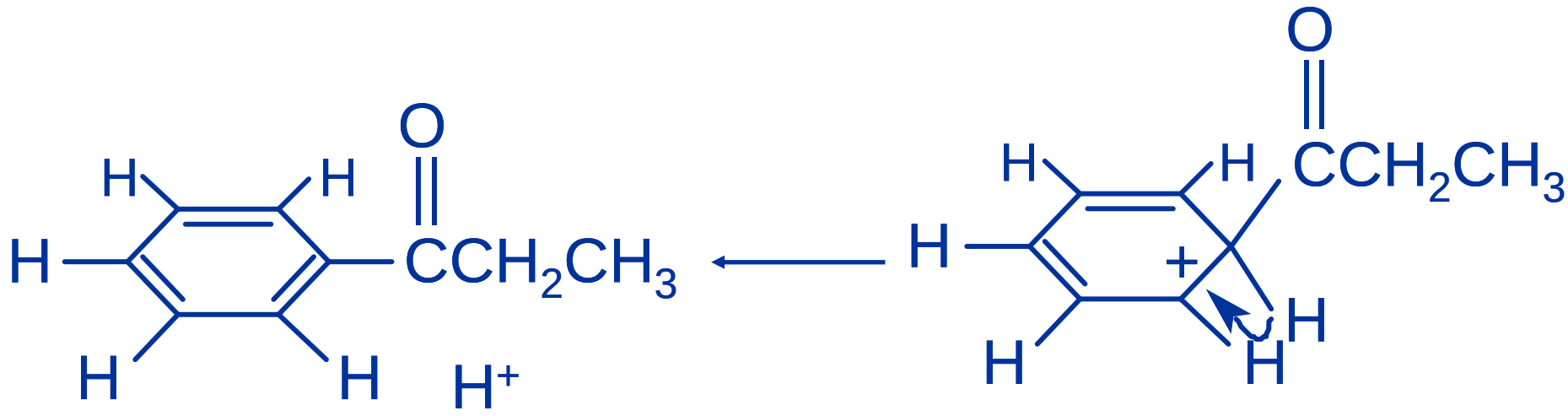


Electrophile is an acyl cation

Step 1: attack of the acyl cation on π-electron system of aromatic ring

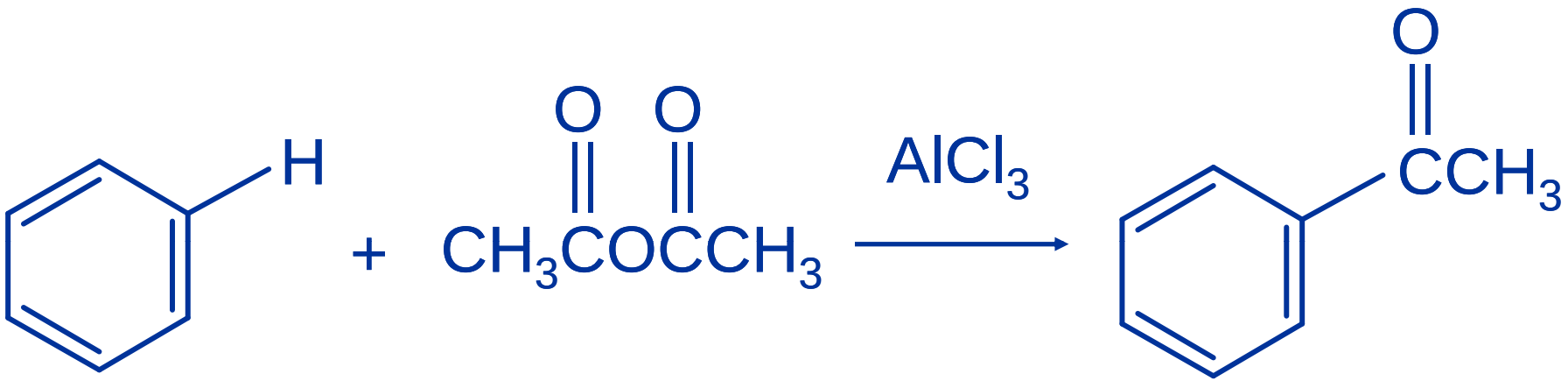


Step 2: loss of a proton from the carbocation intermediate

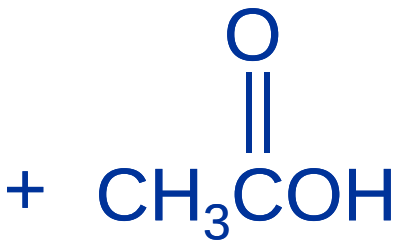


Acid Anhydrides

- Acid Anhydrides can be used instead of acyl chlorides.

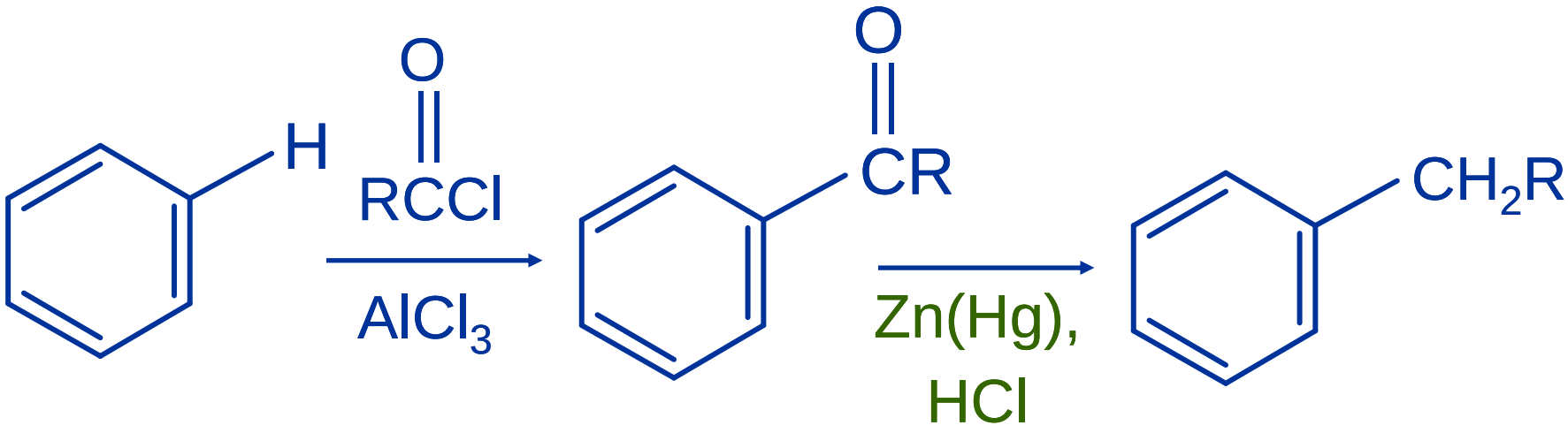


Acetophenone
(76-83%)



12.8. Synthesis of Alkylbenzenes by Acylation-Reduction

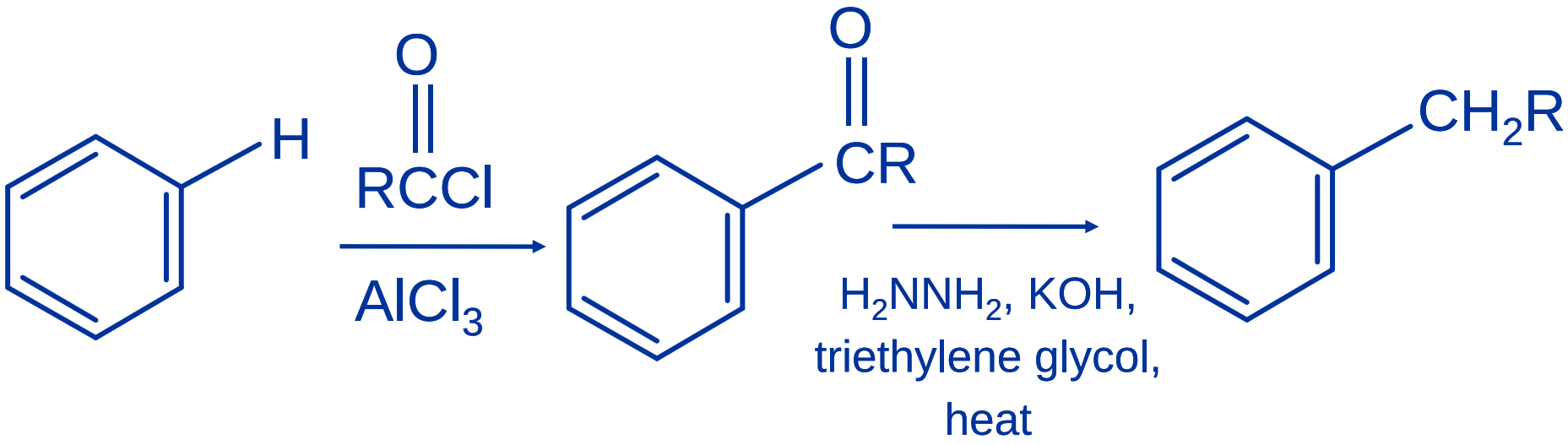
➢ Acylation-Reduction permits primary alkyl groups to be attached to an aromatic ring.



➢ Reduction of aldehyde and ketone carbonyl groups using Zn(Hg) and HCl is called the *Clemmensen reduction*.

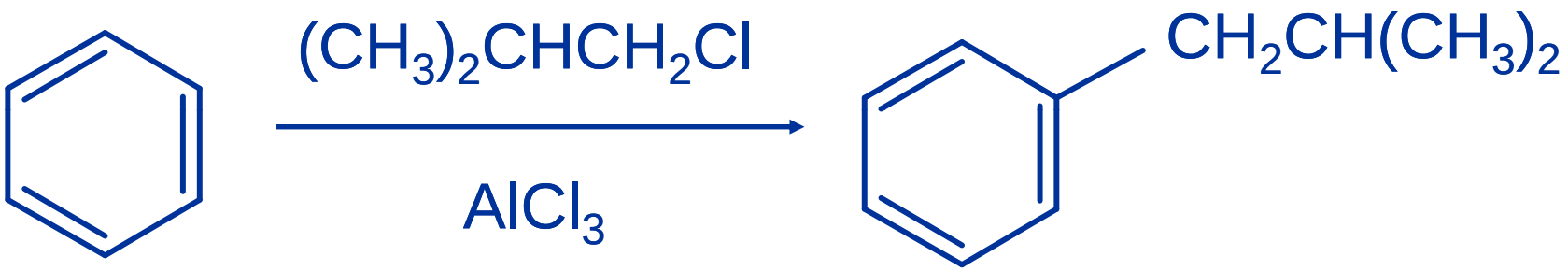
Acylation-Reduction

➢ Acylation-Reduction permits primary alkyl groups to be attached to an aromatic ring.



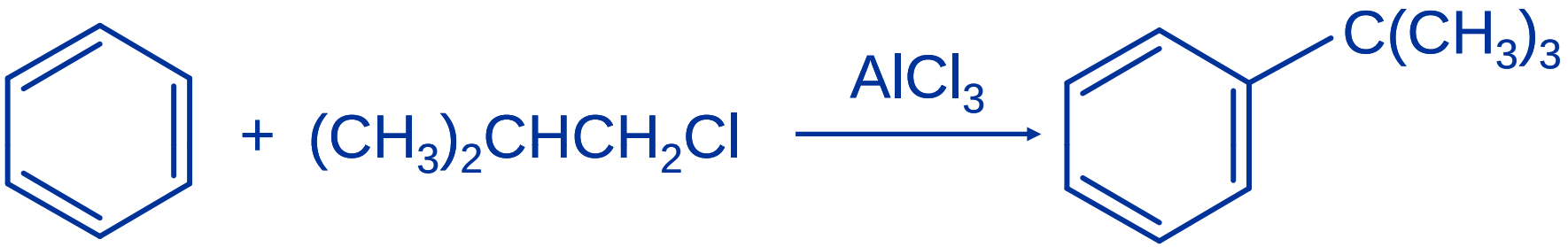
➢ Reduction of aldehyde and ketone carbonyl groups by heating with H_2NNH_2 and KOH is called the *Wolff-Kishner reduction*.

Example: Prepare isobutylbenzene



No! Friedel-Crafts alkylation of benzene using isobutyl chloride fails because of rearrangement.

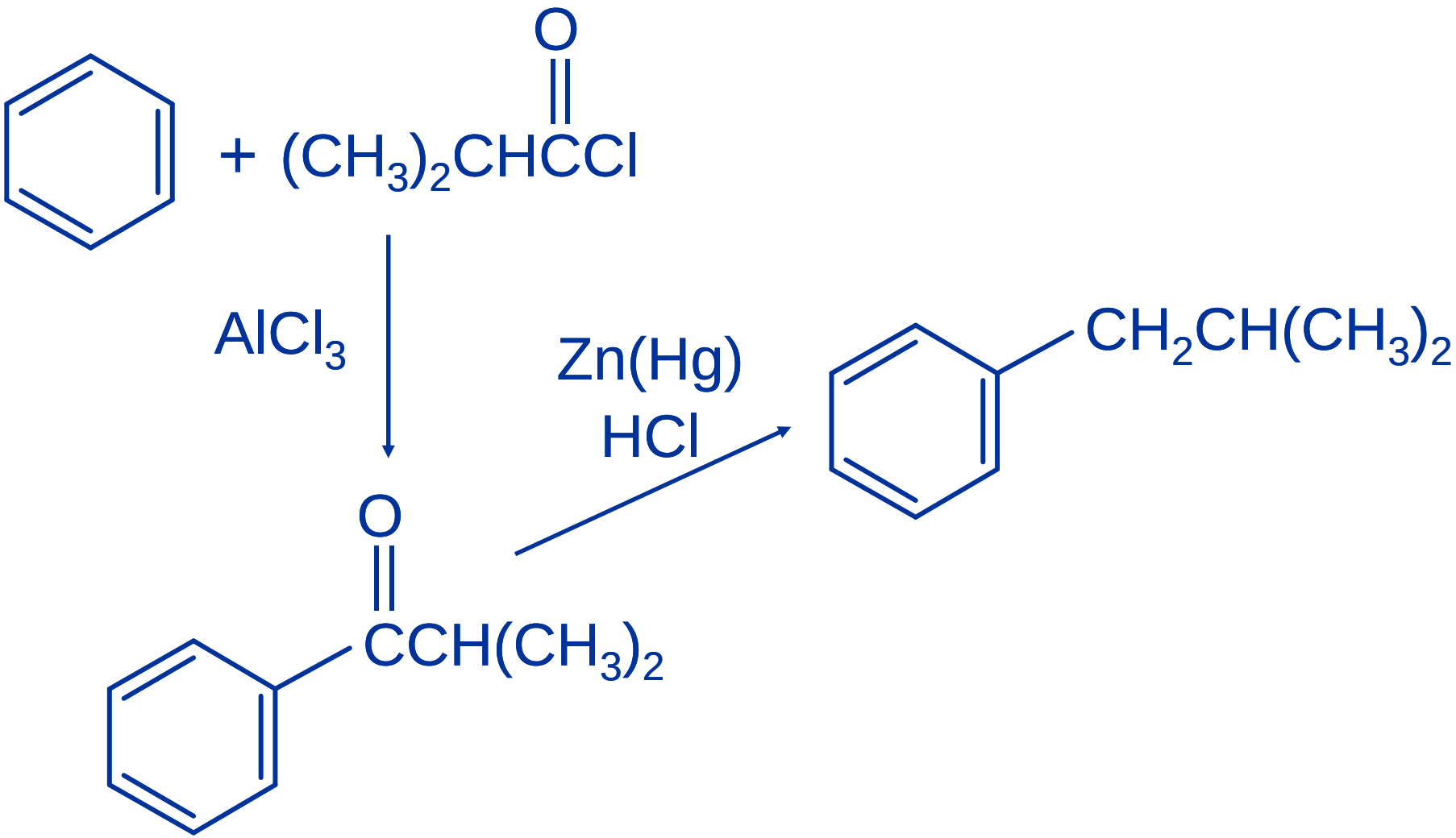
Recall



Isobutyl chloride

tert-Butylbenzene
(66%)

Use Acylation-Reduction Instead



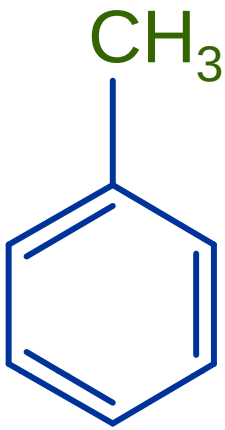
12.9 Rate and Regioselectivity in Electrophilic Aromatic Substitution

- A substituent already present on the ring can affect both the *rate* and *regioselectivity* of electrophilic aromatic substitution.

Effect on Rate

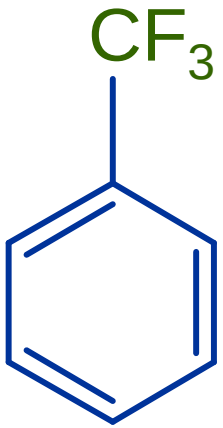
- Activating substituents increase the rate of EAS compared to that of benzene.
- Deactivating substituents decrease the rate of EAS compared to benzene.

Methyl Group



- Toluene undergoes nitration 20-25 times faster than benzene. A methyl group is an activating substituent.

Trifluoromethyl Group



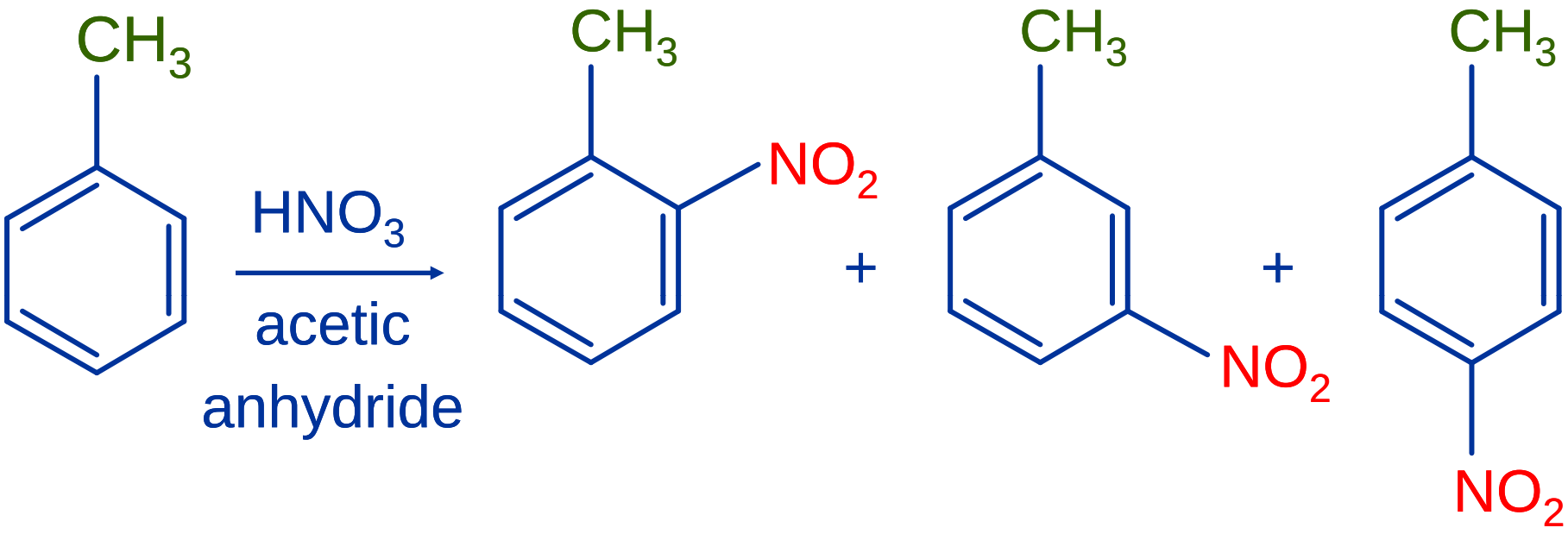
- (Trifluoromethyl)benzene undergoes nitration 40,000 times more slowly than benzene. A trifluoromethyl group is a deactivating substituent.

Effect on Regioselectivity

- *Ortho-para directors* direct an incoming electrophile to positions *ortho* and/or *para* to themselves.

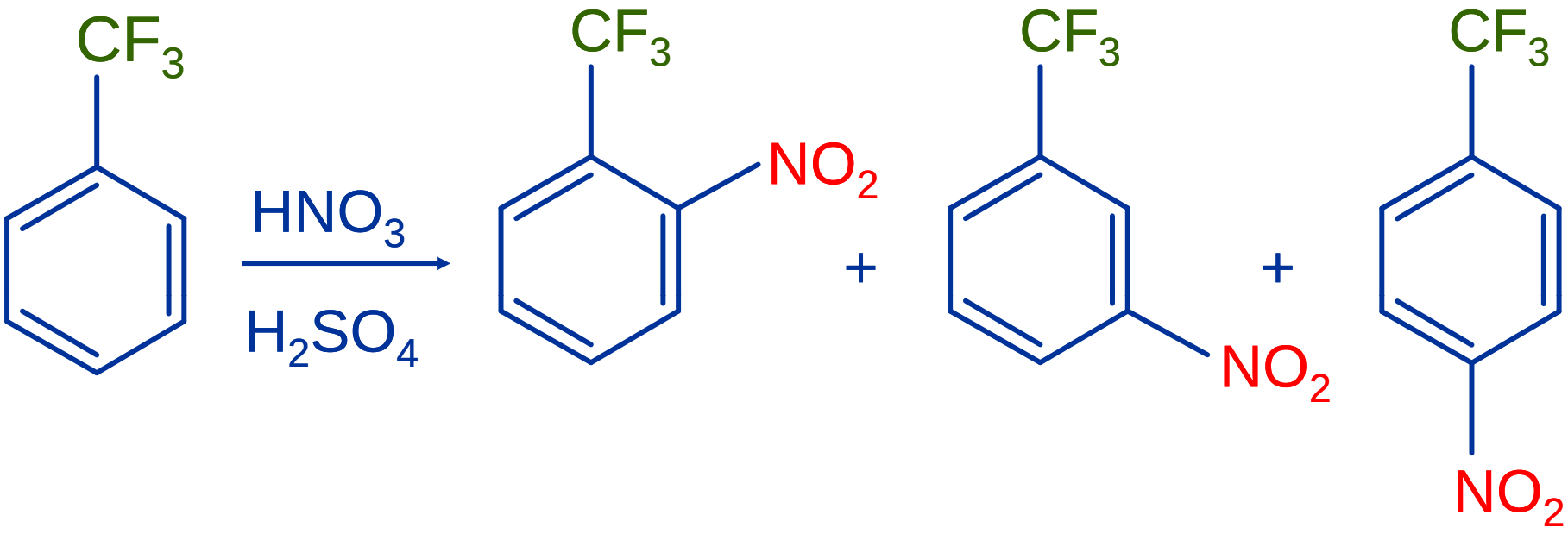
- *Meta directors* direct an incoming electrophile to positions *meta* to themselves.

Nitration of Toluene



- *o*- and *p*-nitrotoluene together comprise 97% of the product.
- A methyl group is an *ortho*-*para* director.

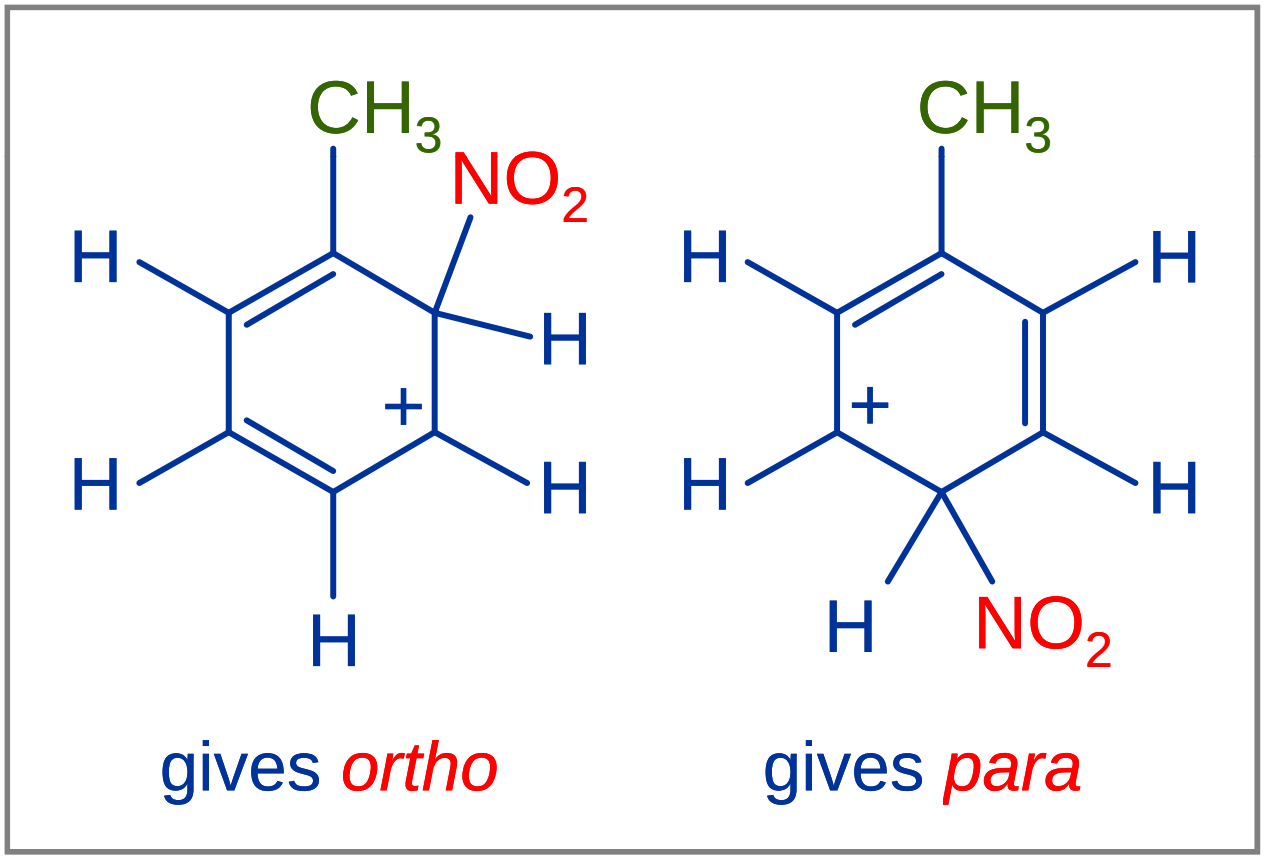
Nitration of (Trifluoromethyl)benzene



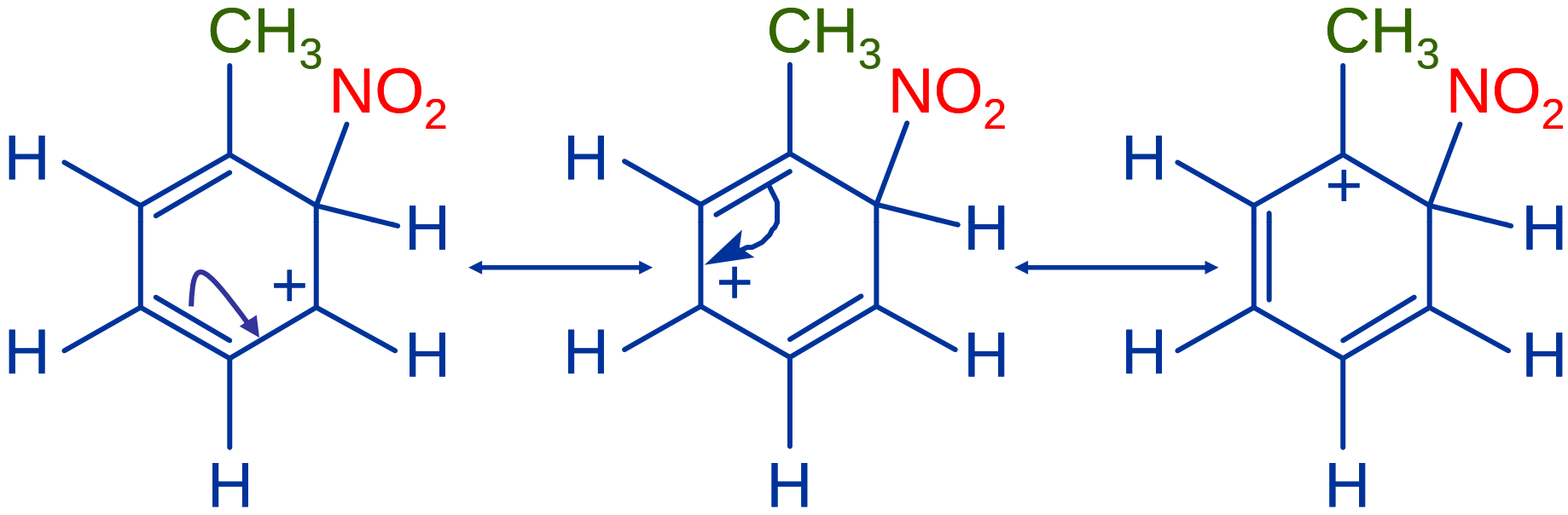
- *m*-nitro(trifluoromethyl)benzene comprises 91% of the product.
- A trifluoromethyl group is a *meta* director.

12.10. Rate and Regioselectivity in the Nitration of Toluene

Carbocation Stability Controls Regioselectivity

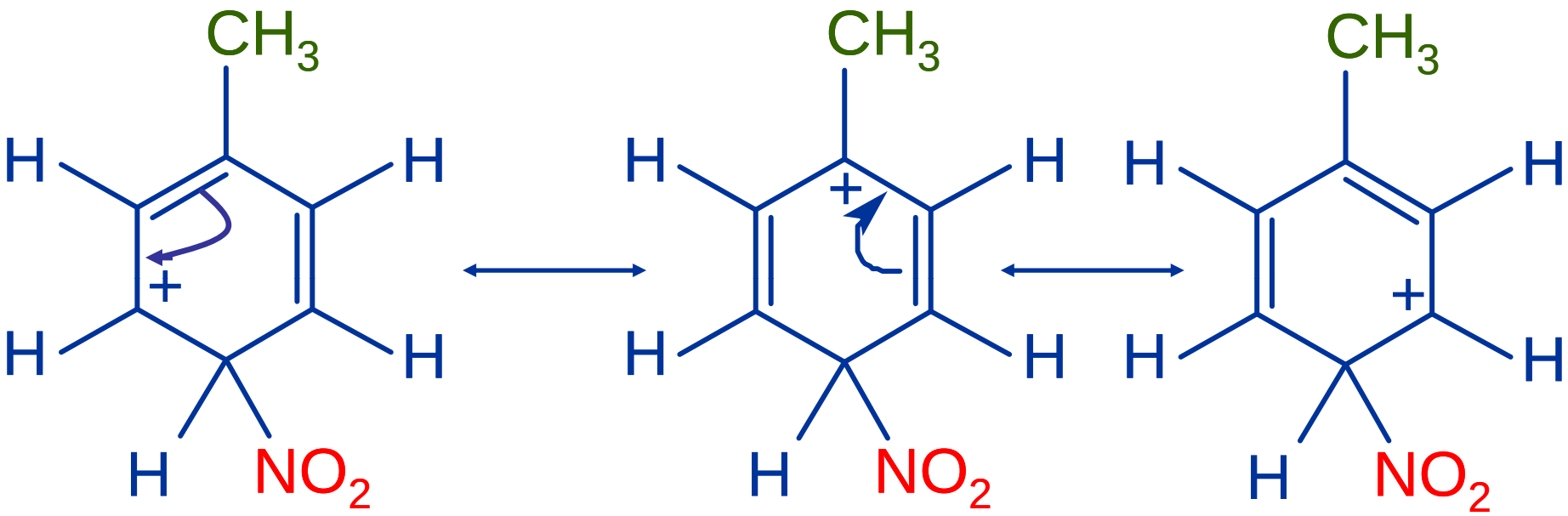


ortho Nitration of Toluene



➢ The rate-determining intermediate in the *ortho* nitration of toluene has tertiary carbocation character.

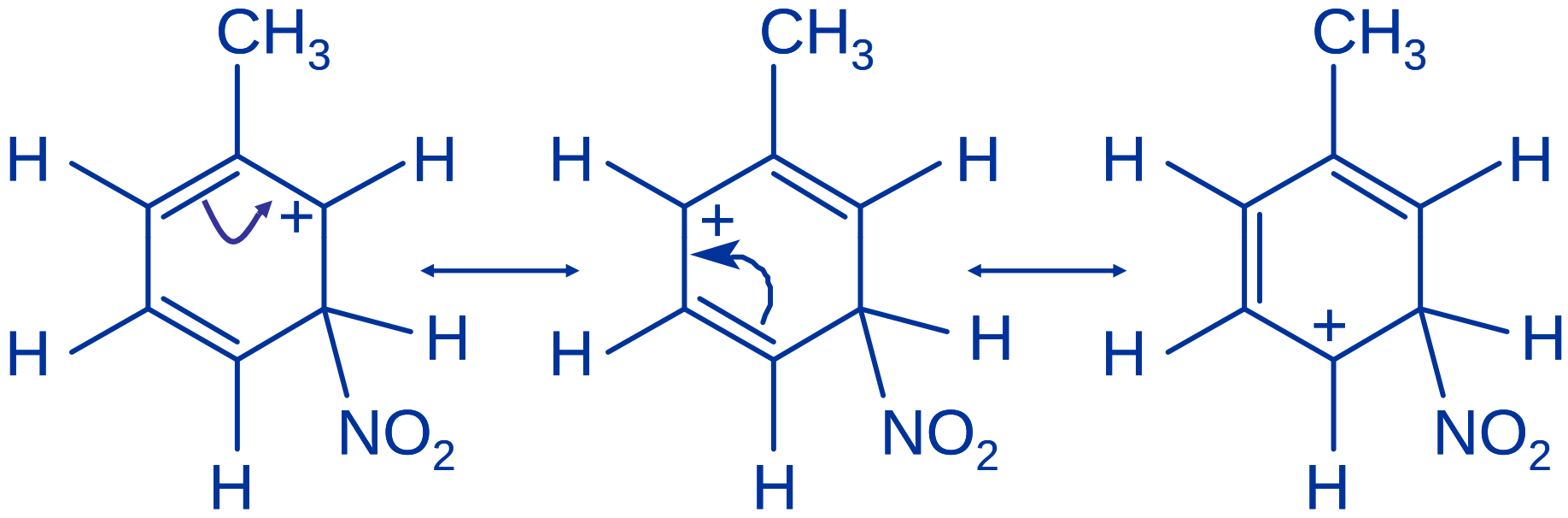
para Nitration of Toluene



This resonance form is a tertiary carbocation

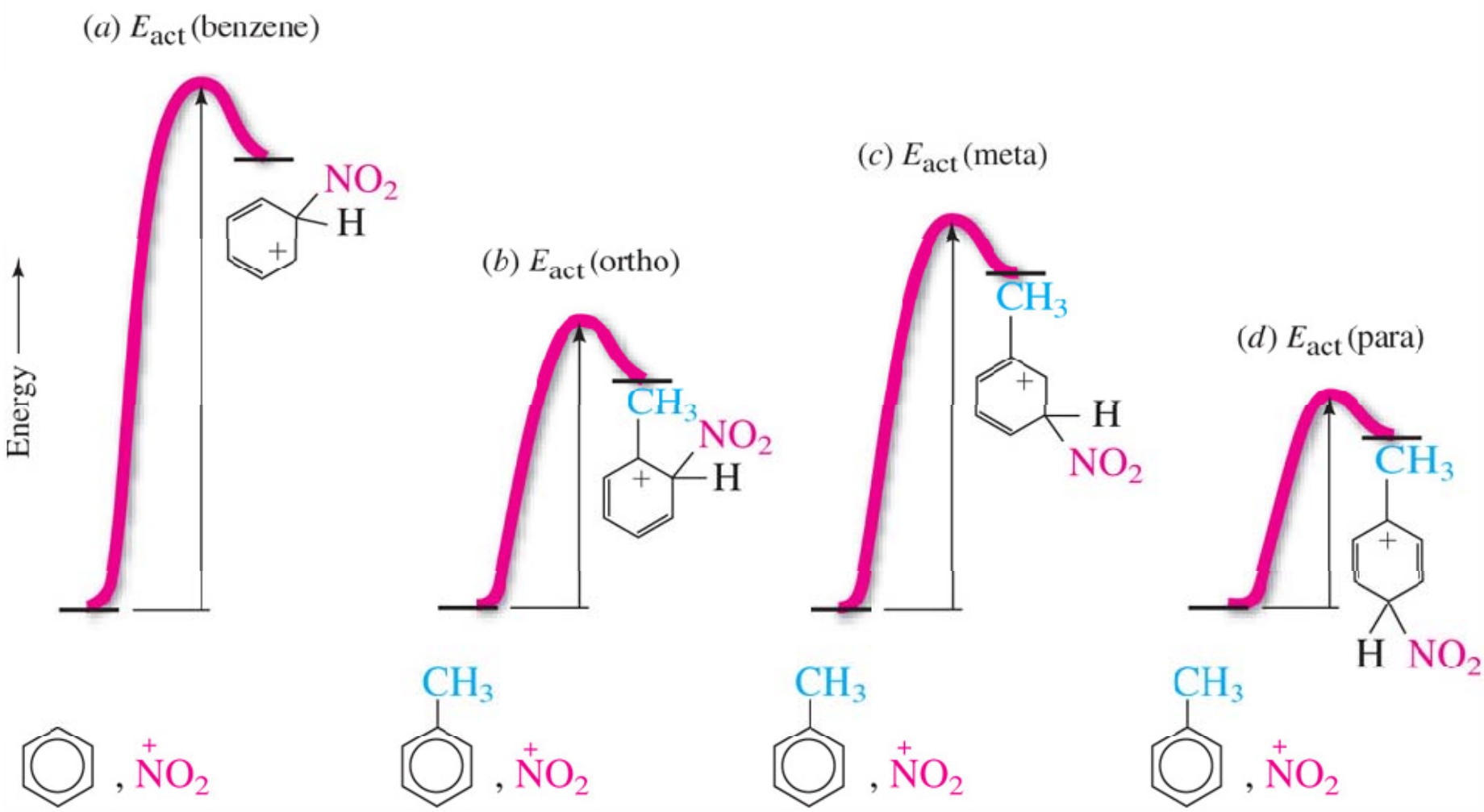
- The rate-determining intermediate in the *para* nitration of toluene has tertiary carbocation character.

meta Nitration of Toluene

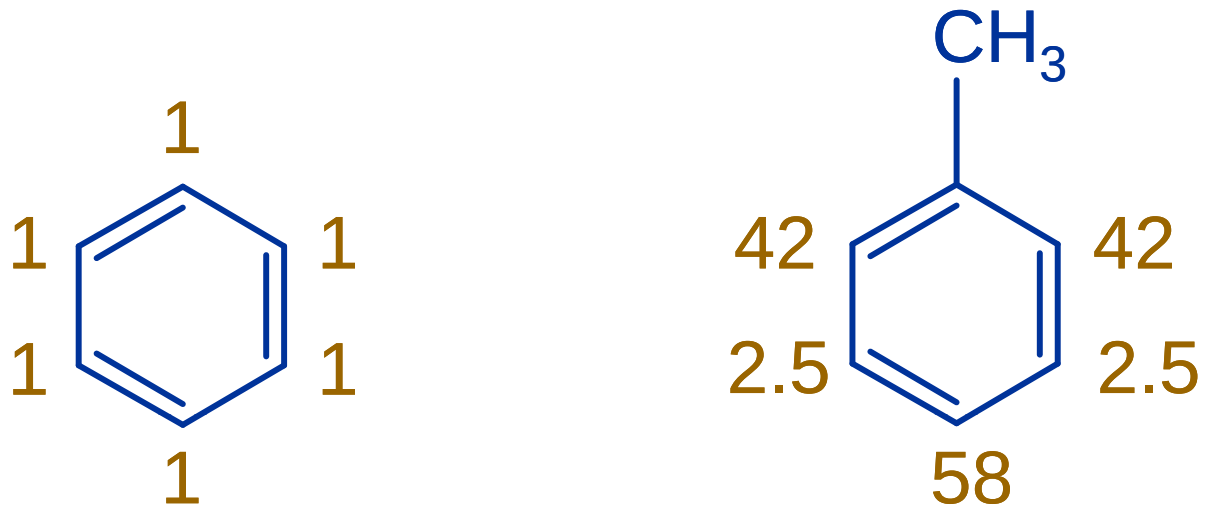


➢ All the resonance forms of the rate-determining intermediate in the *meta* nitration of toluene have their positive charge on a secondary carbon.

Figure 12.4: Comparative Energy Diagrams for Reaction of Nitronium Ion with Benzene and Toluene



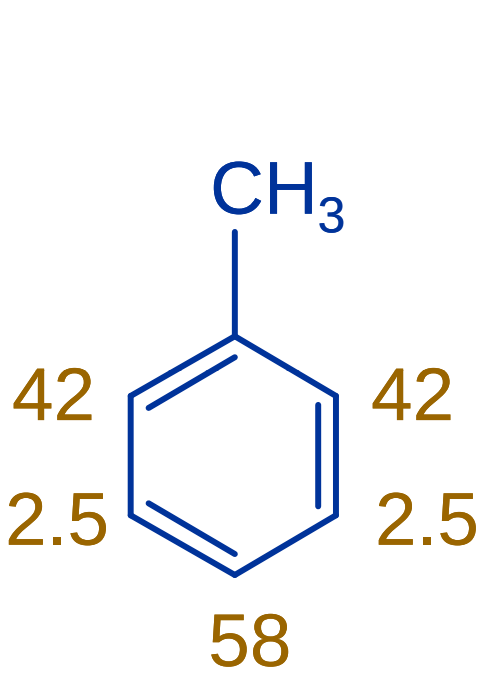
Nitration of Toluene: Partial Rate Factors

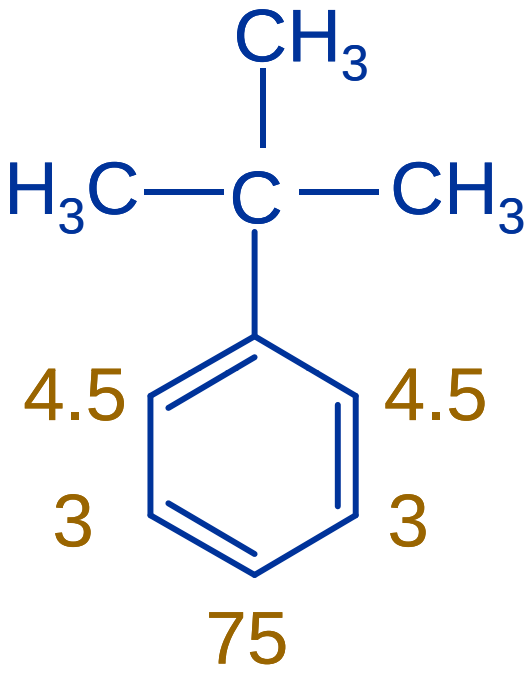


- All of the available ring positions in toluene are more reactive than a single position of benzene.

- A methyl group activates all of the ring positions but the effect is greatest at the *ortho* and *para* positions. Steric hindrance by the methyl group makes each *ortho* position slightly less reactive than *para*.

Nitration of Toluene vs. *tert*-Butylbenzene





- *tert*-Butyl is activating and *ortho*-*para* directing.

- *tert*-Butyl crowds the *ortho* positions and decreases the rate of attack at those positions.

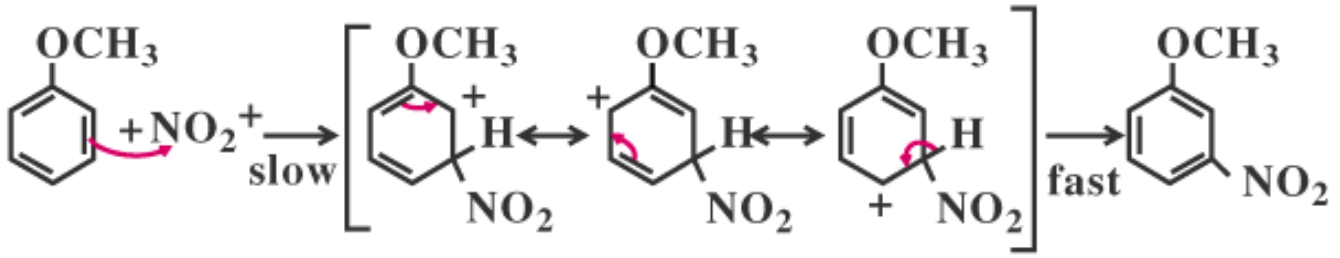
Generalization

- All alkyl groups are activating and *ortho-para* directing.

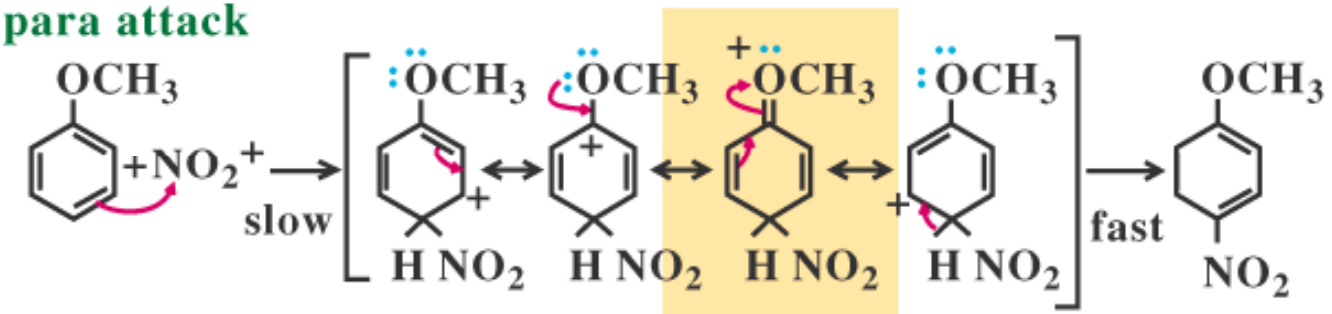
Theory of Directing Effects

Nitration of anisole

meta attack



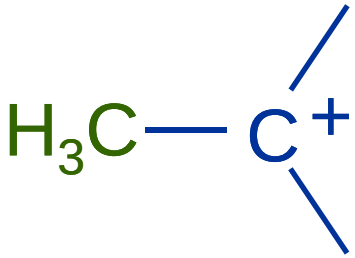
para attack

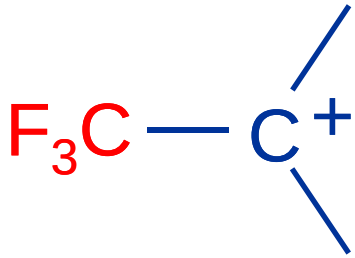


The most important contributing structure

12.11. Rate and Regioselectivity in the Nitration of (Trifluoromethyl)benzene

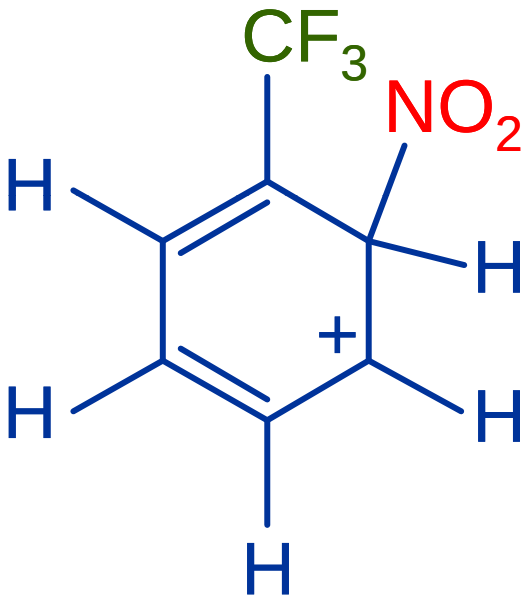
A Key Point



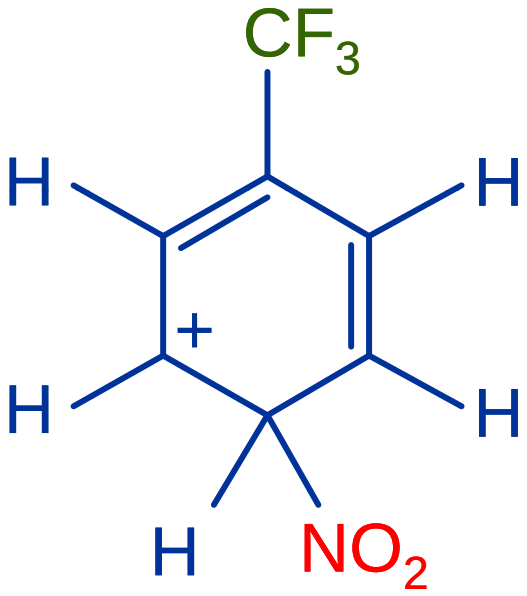


- A methyl group is electron-donating and stabilizes a carbocation.
- Because F is so electronegative, a CF_3 group destabilizes a carbocation.

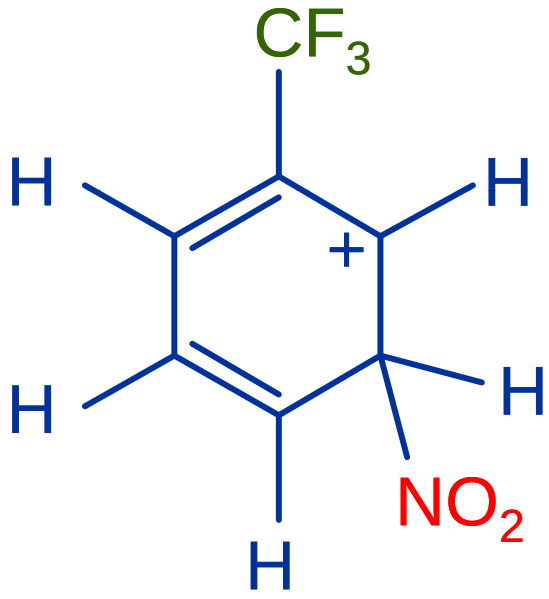
Carbocation Stability Controls Regioselectivity



gives *ortho*



gives *para*

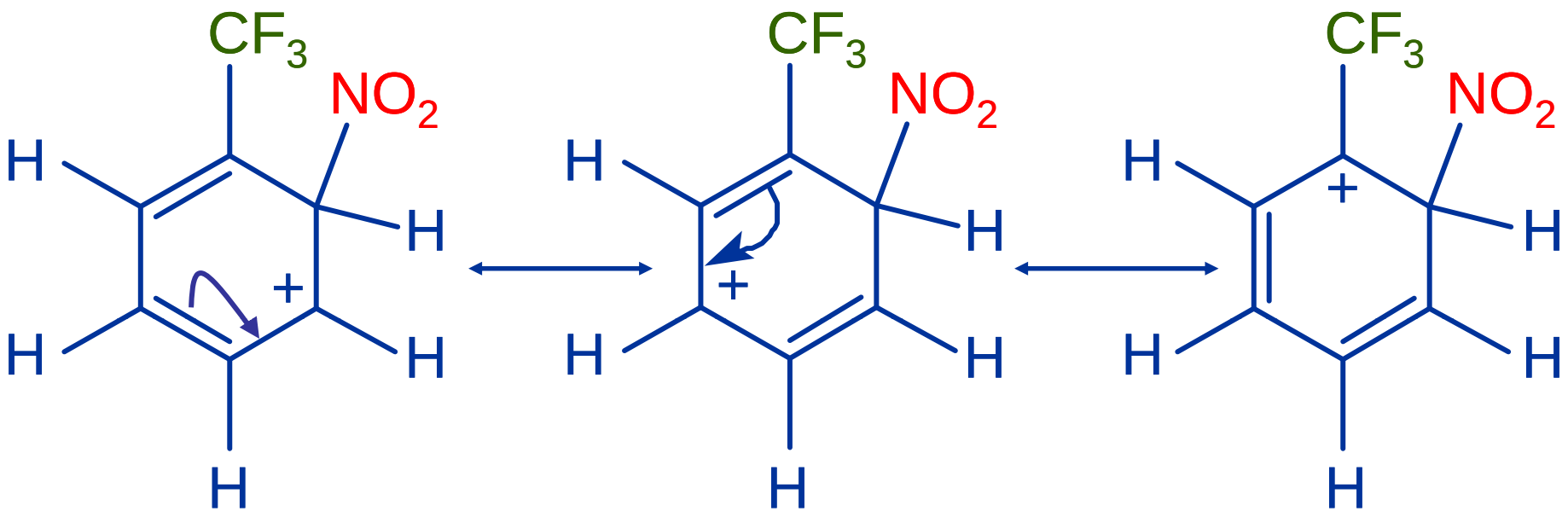


gives *meta*

less stable

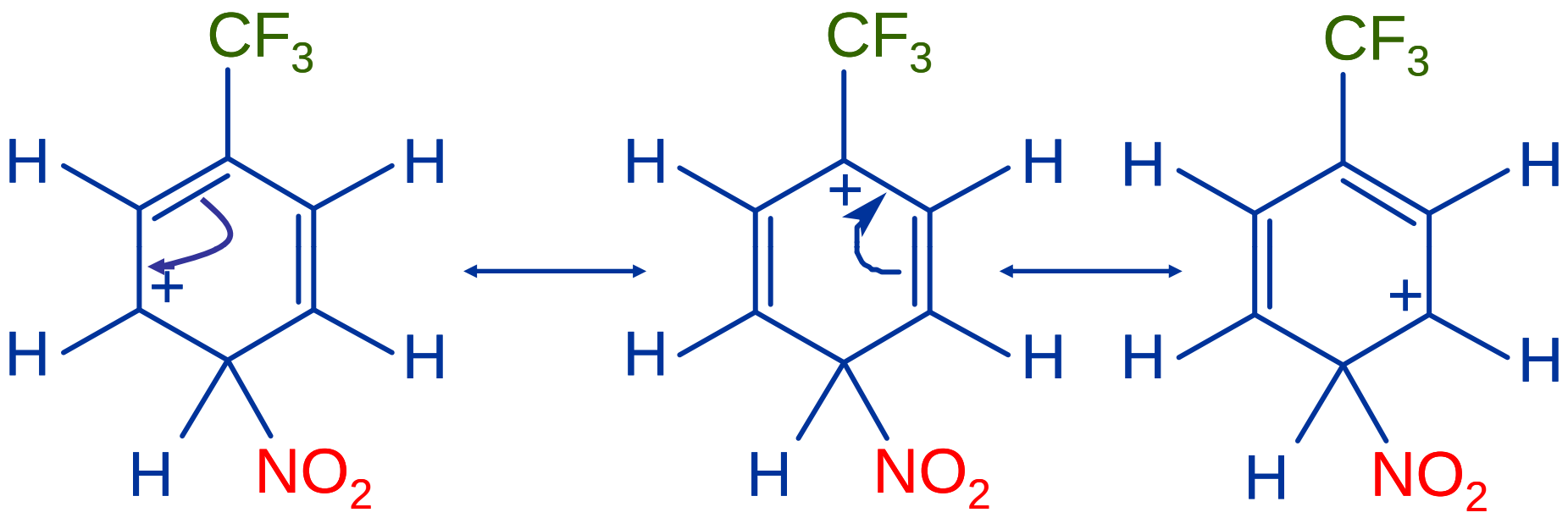
more stable

ortho Nitration of (Trifluoromethyl)benzene



➢ One of the resonance forms of the rate-determining intermediate in the *ortho* nitration of (trifluoromethyl)-benzene is strongly destabilized.

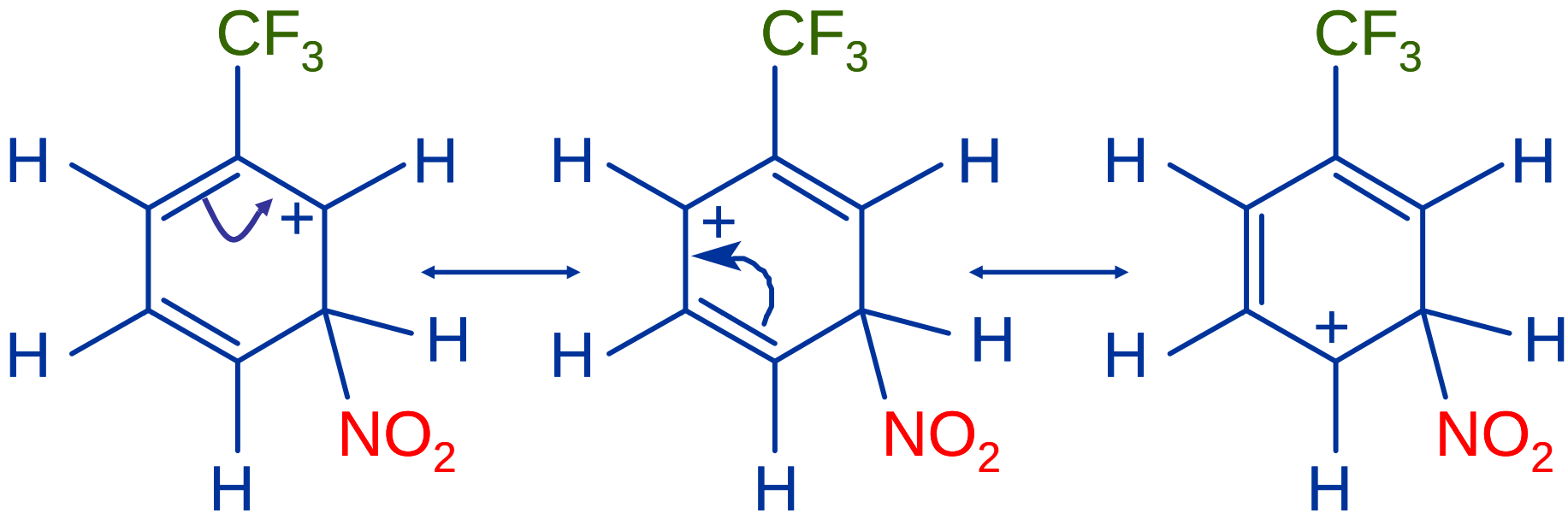
para Nitration of (Trifluoromethyl)benzene



This resonance form is destabilized

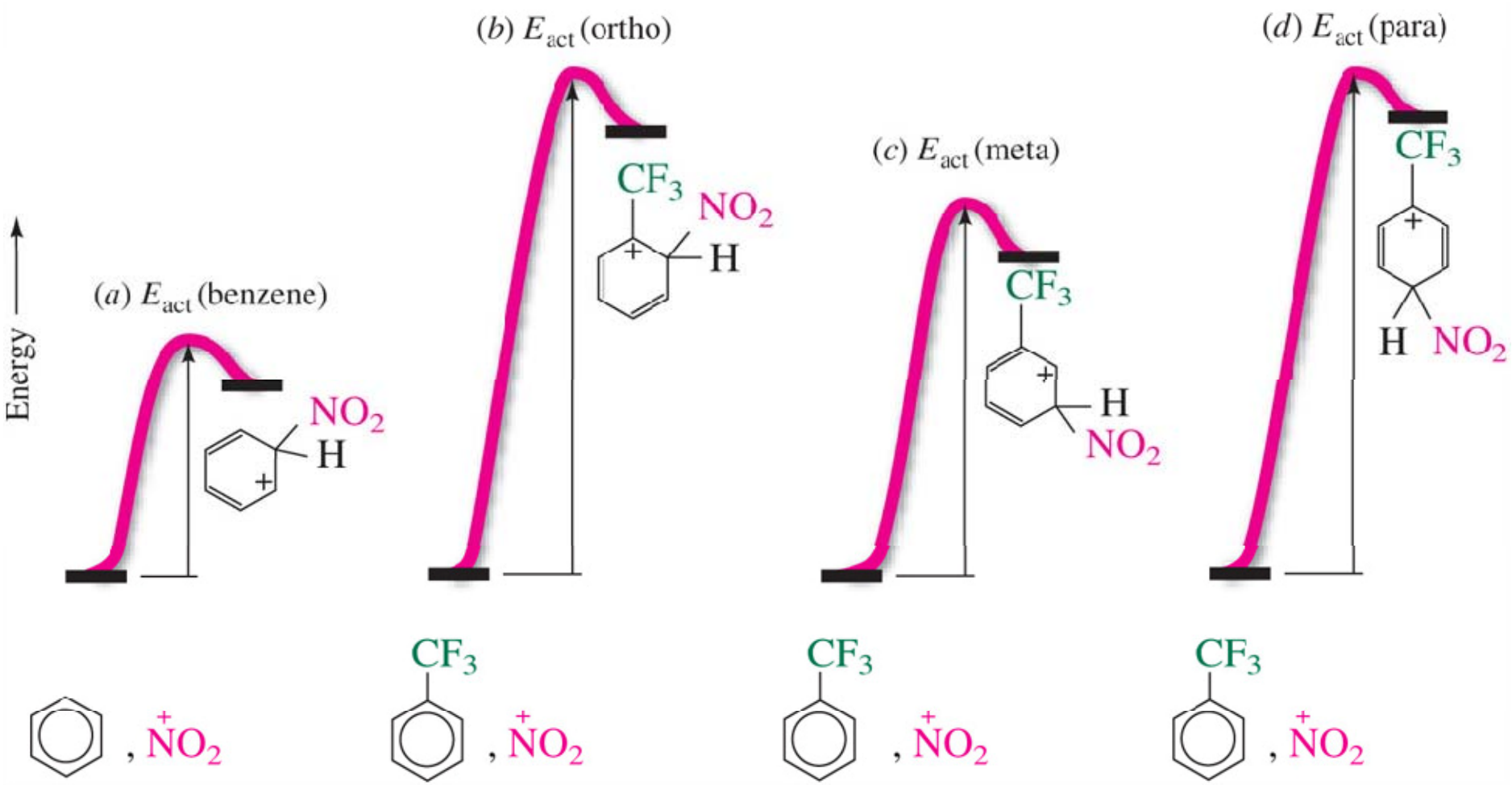
➢ One of the resonance forms of the rate-determining intermediate in the *para* nitration of (trifluoromethyl)-benzene is strongly destabilized.

meta Nitration of (Trifluoromethyl)benzene

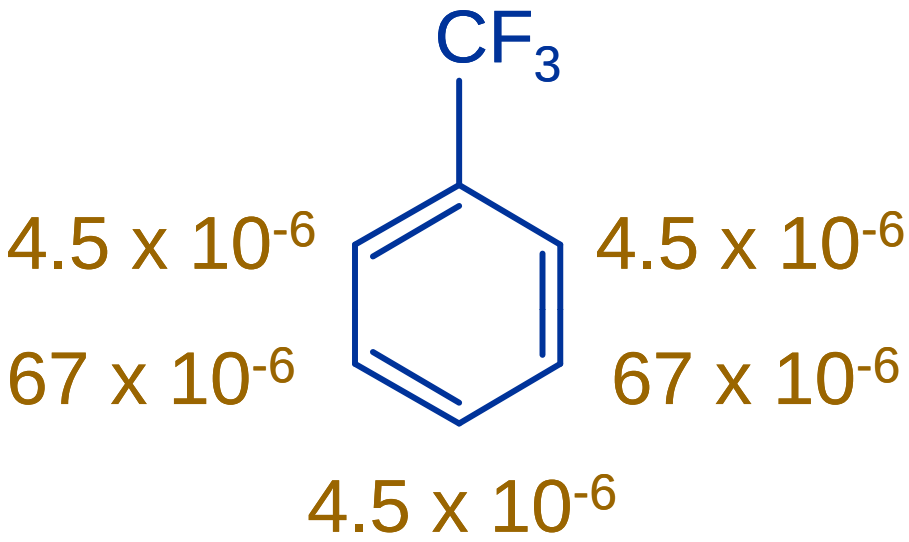


➢ None of the resonance forms of the rate-determining intermediate in the *meta* nitration of (trifluoromethyl)-benzene have their positive charge on the carbon that bears the CF_3 group.

Figure 12.5: Comparative Energy Diagrams for Reaction of Nitronium Ion with Benzene and (Trifluoromethyl)benzene



Nitration of (Trifluoromethyl)benzene: Partial Rate Factors

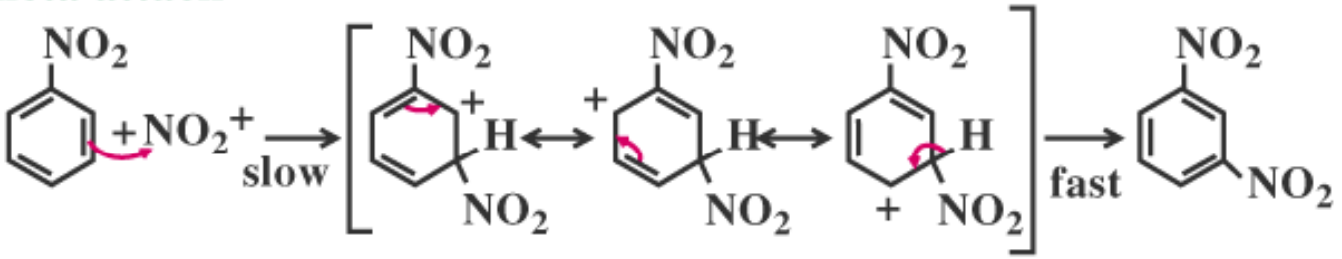


- All of the available ring positions in (trifluoromethyl)-benzene are much less reactive than a single position of benzene.
- A CF_3 group deactivates all of the ring positions but the degree of deactivation is greatest at the *ortho* and *para* positions.

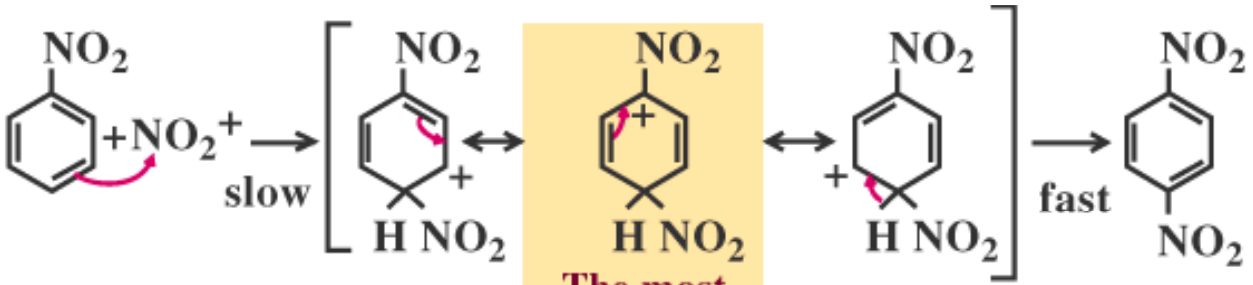
Theory of Directing Effects

Nitration of nitrobenzene

meta attack



para attack



The most disfavored contributing structure

12.12
Substituent Effects in Electrophilic Aromatic Substitution: Activating Substituents

Table 12.2

Classification of Substituents in Electrophilic Aromatic Substitution Reactions

Very strongly activating

Strongly activating

Activating

Standard of comparison is H

Deactivating

Strongly deactivating

Very strongly deactivating

Generalizations

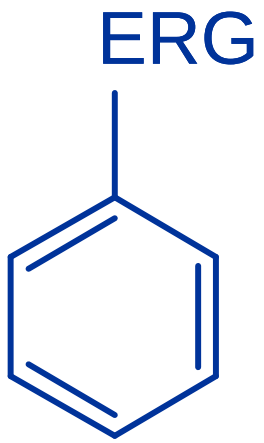
1. All activating substituents are *ortho*-*para* directors.

2. Halogen substituents are slightly deactivating but *ortho*-*para* directing.

3. Strongly deactivating substituents are *meta* directors.

Electron-Releasing Groups (ERGs)

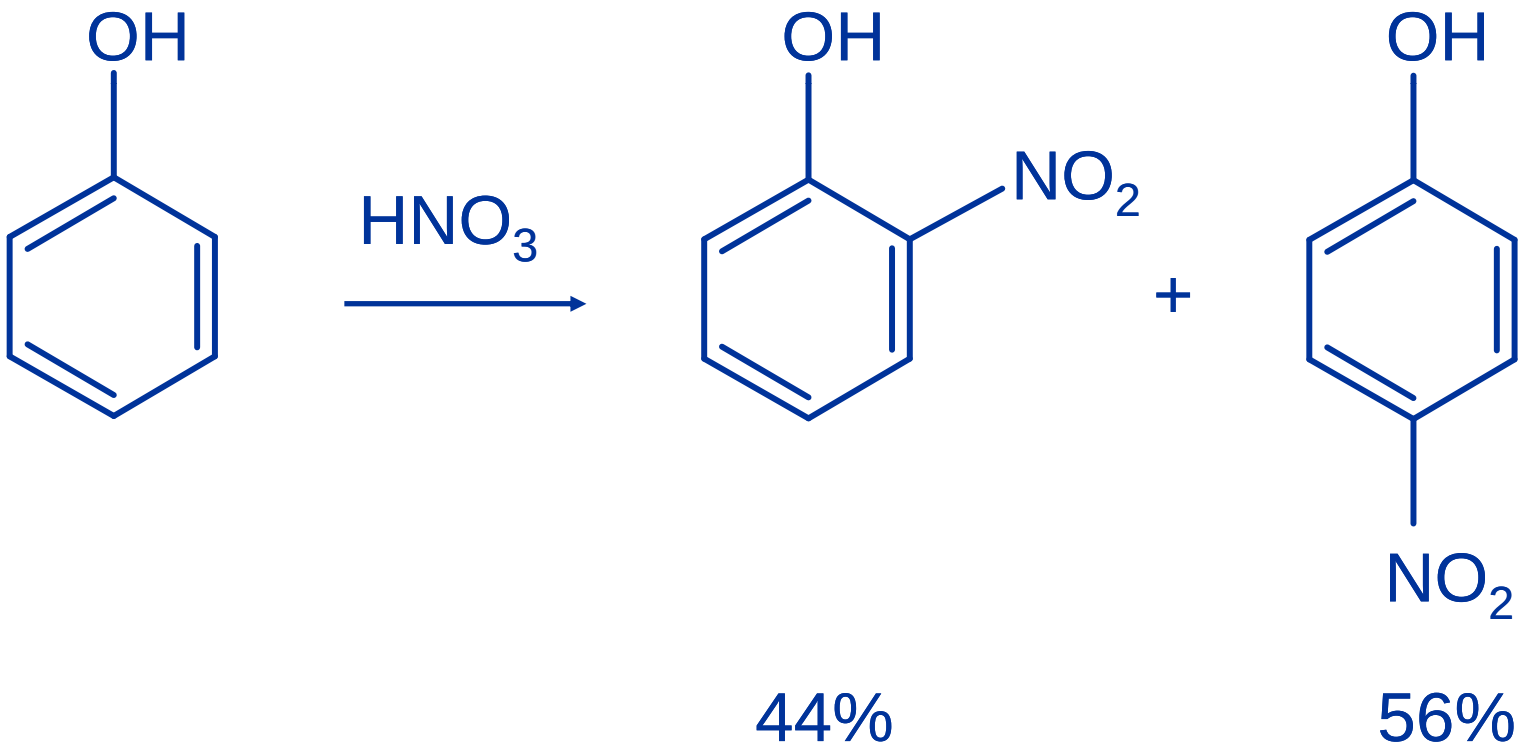
- Electron-Releasing Groups (ERGs) are *ortho*-*para* directing and activating.



- ERGs include —R, —Ar, and —C=C.
- ERGs such as —OH, and —OR are strongly activating.

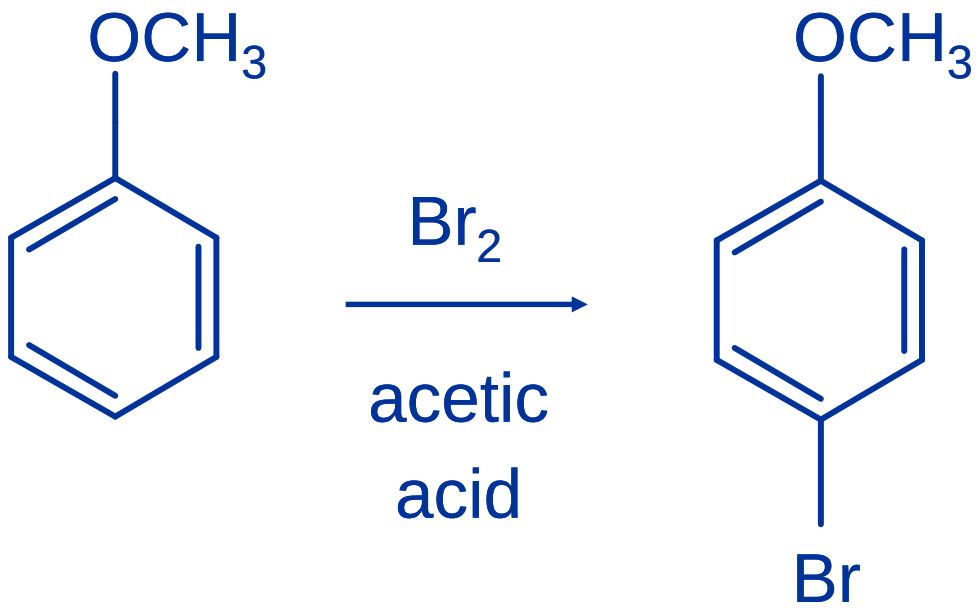
Nitration of Phenol

- Occurs about 1000 times faster than nitration of benzene.



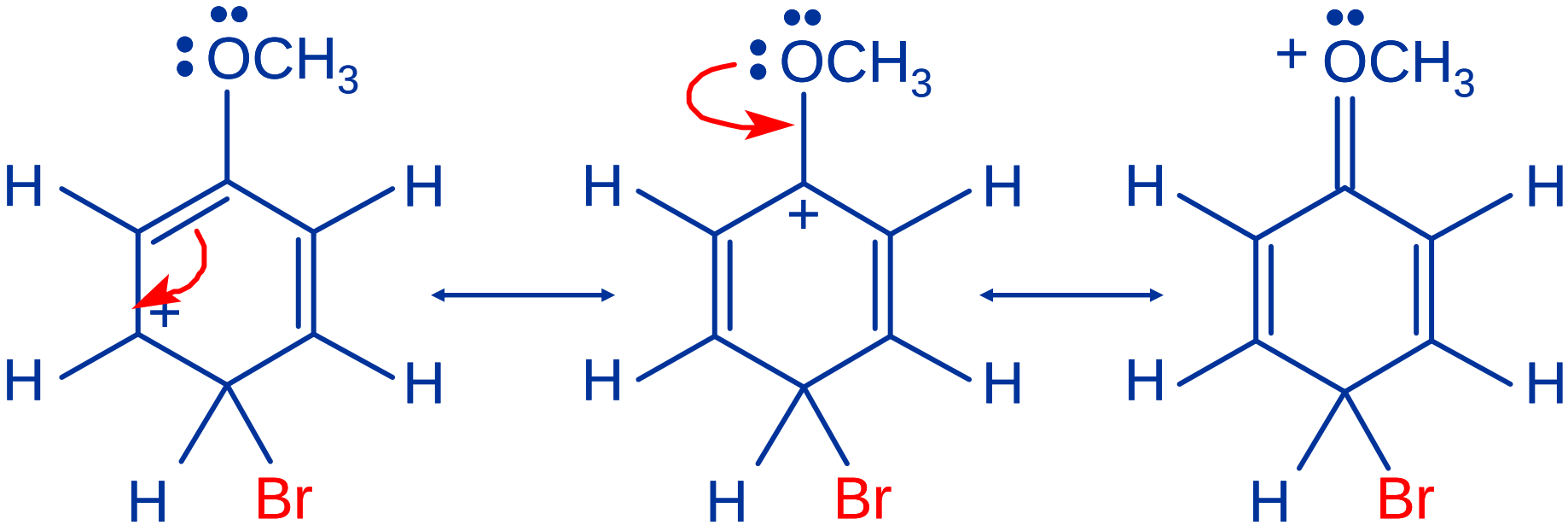
Bromination of Anisole

$FeBr_3$ catalyst is not necessary!



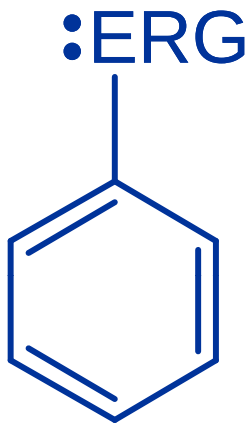
90%

Oxygen Lone Pair Stabilizes Intermediate



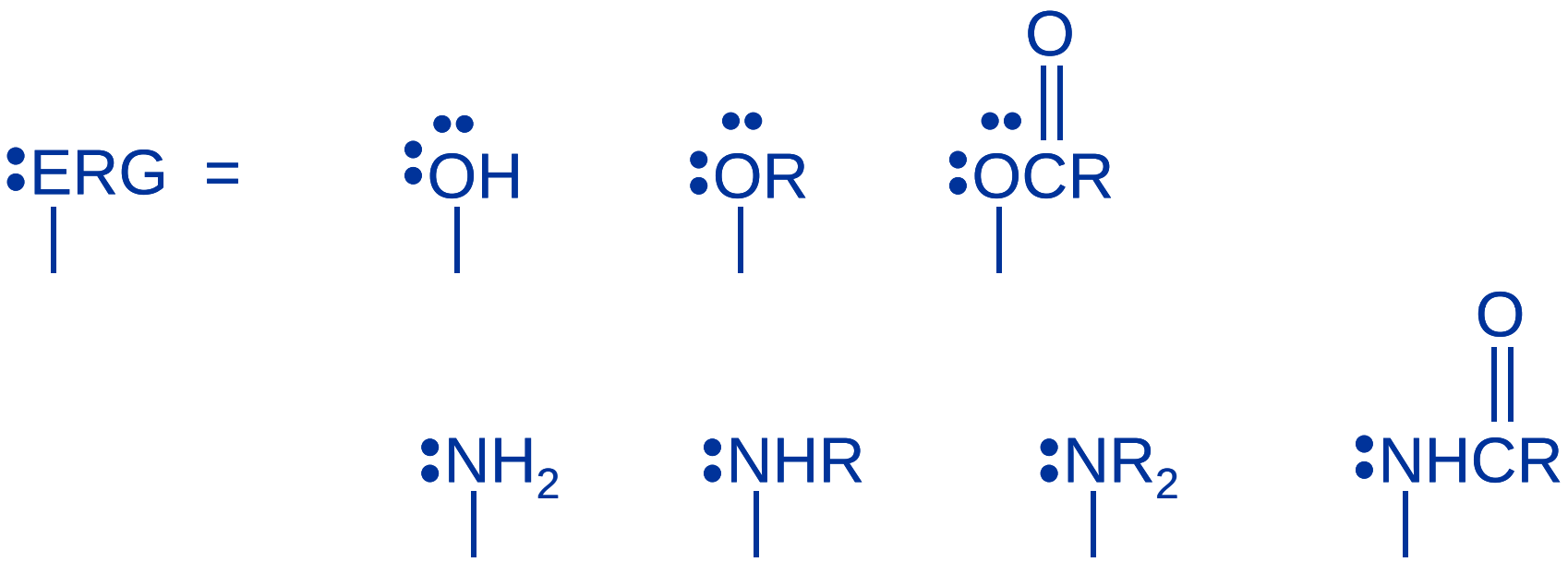
all atoms
have octets

Electron-Releasing Groups (ERGs)



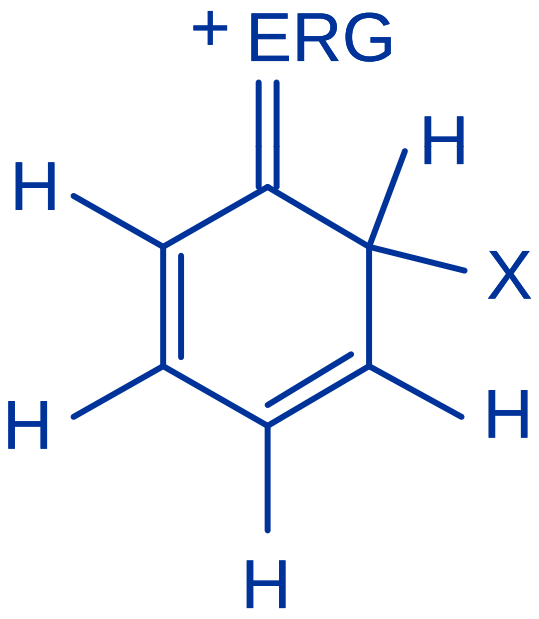
ERGs with a lone pair on the atom directly attached to the ring are *ortho*-*para* directing and strongly activating.

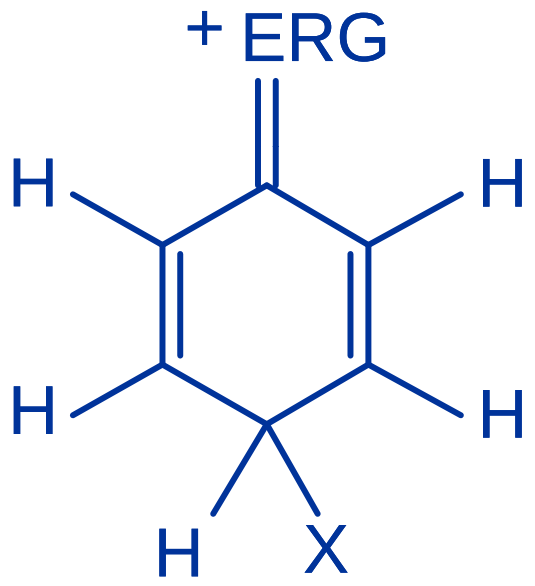
Examples



All of these are *ortho*-*para* directing
and strongly to very strongly activating.

Lone Pair Stabilizes Intermediates for *ortho* and *para* Substitution

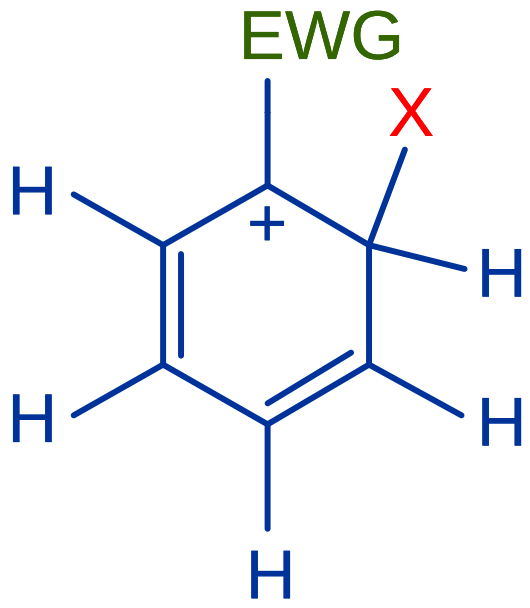


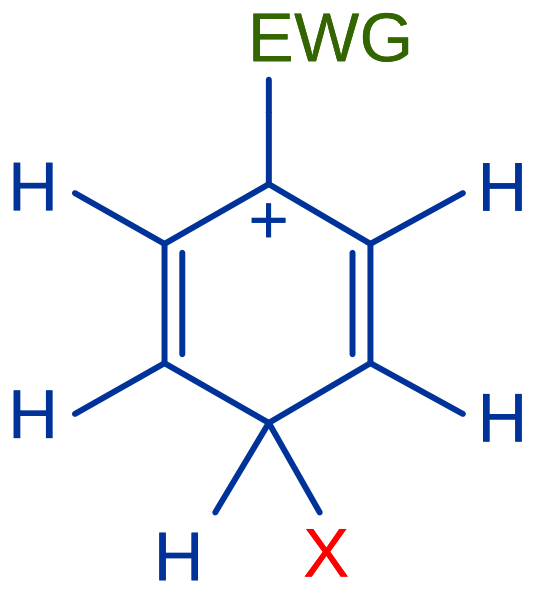


comparable stabilization not possible for intermediate leading to *meta* substitution.

12.13
Substituent Effects in Electrophilic Aromatic Substitution:
Strongly Deactivating Substituents

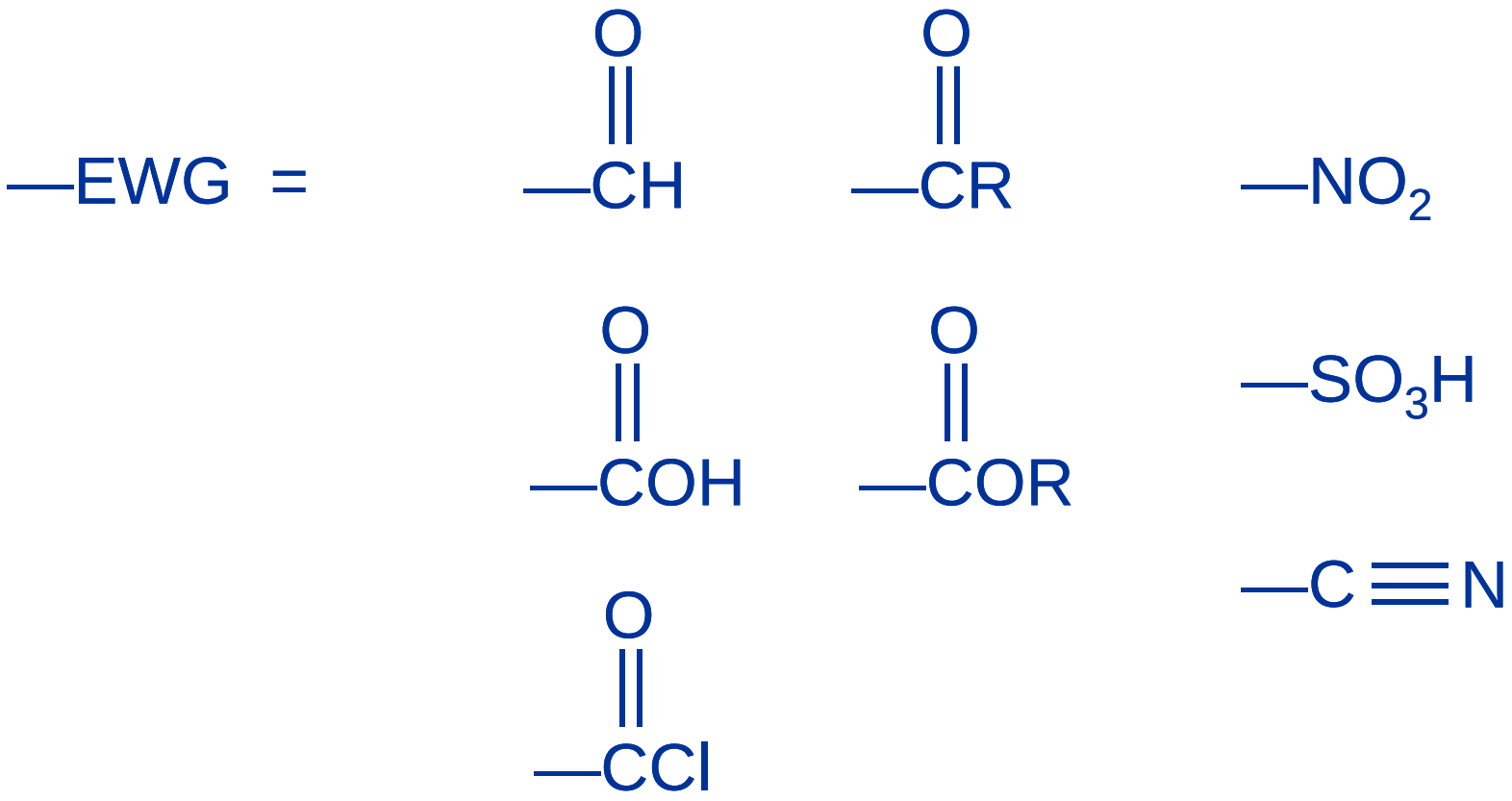
Electron-withdrawing Groups (EWGs) Destabilize Intermediates for *ortho* and *para* Substitution





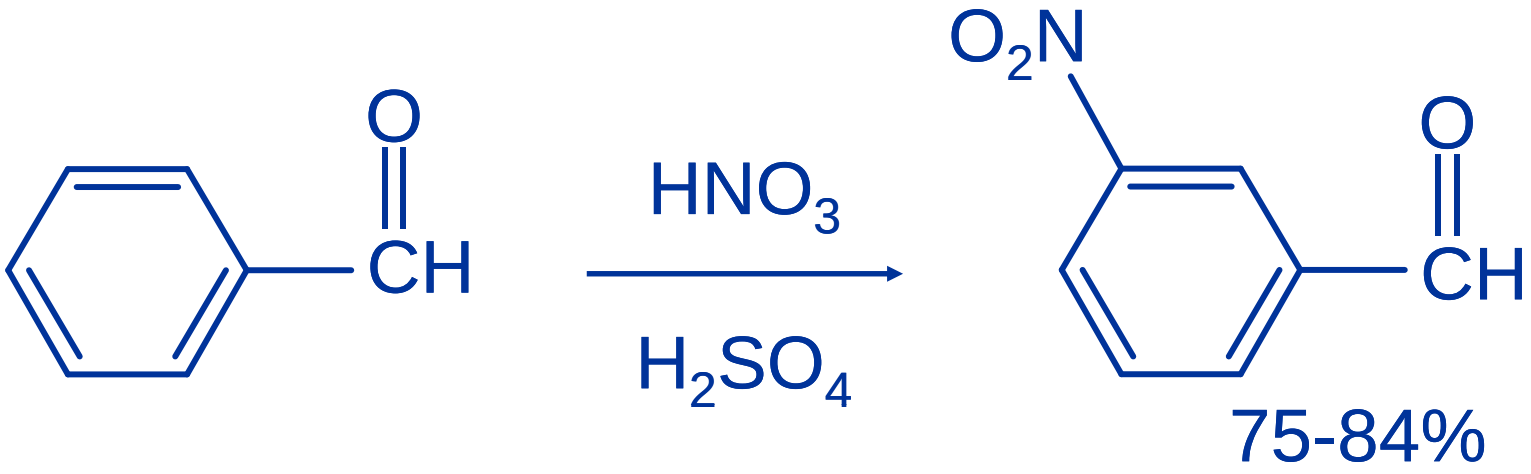
—CF_3 is a powerful EWG. It is strongly deactivating and *meta* directing.

Many EWGs Have a Carbonyl Group Attached Directly to the Ring

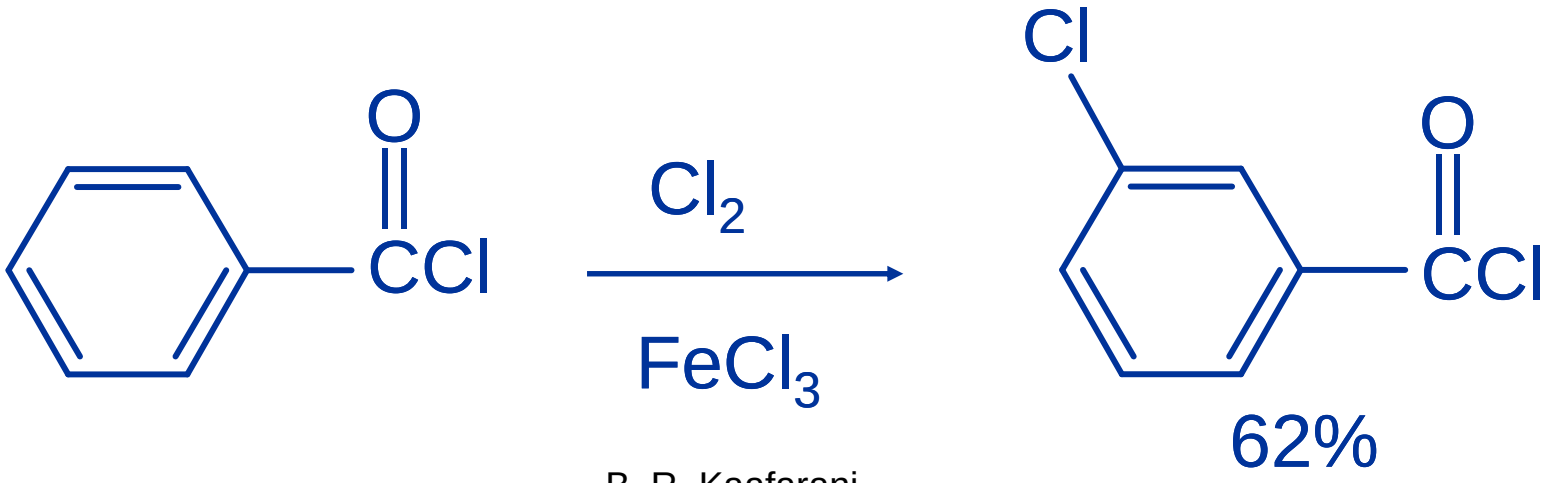


All of these are *meta* directing and strongly deactivating.

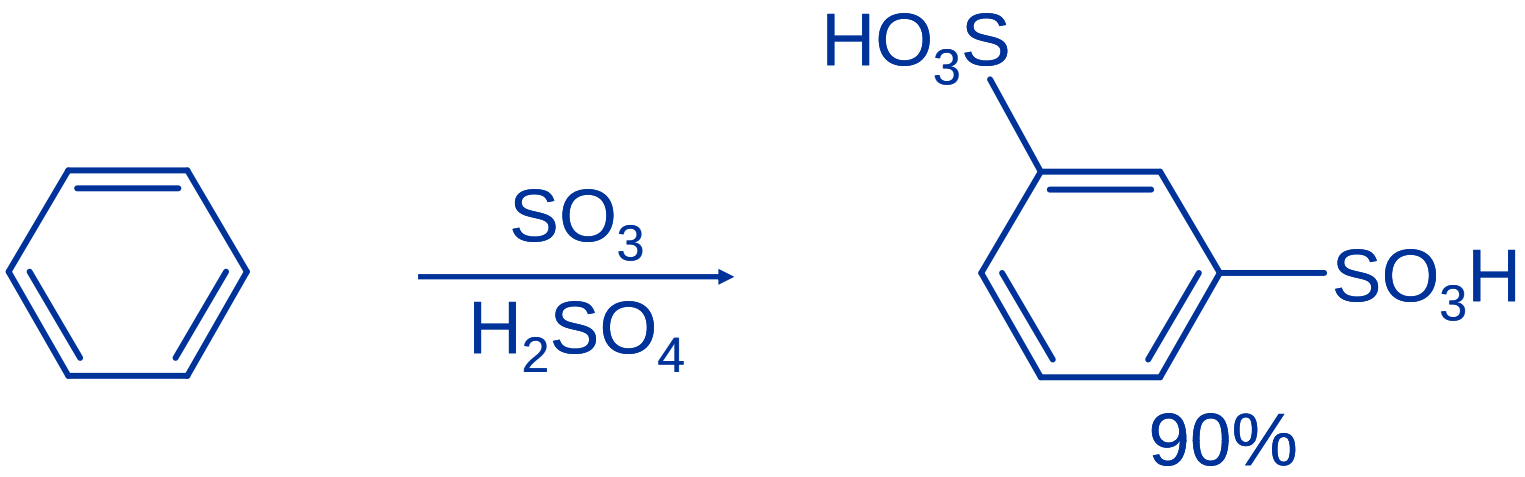
Nitration of Benzaldehyde



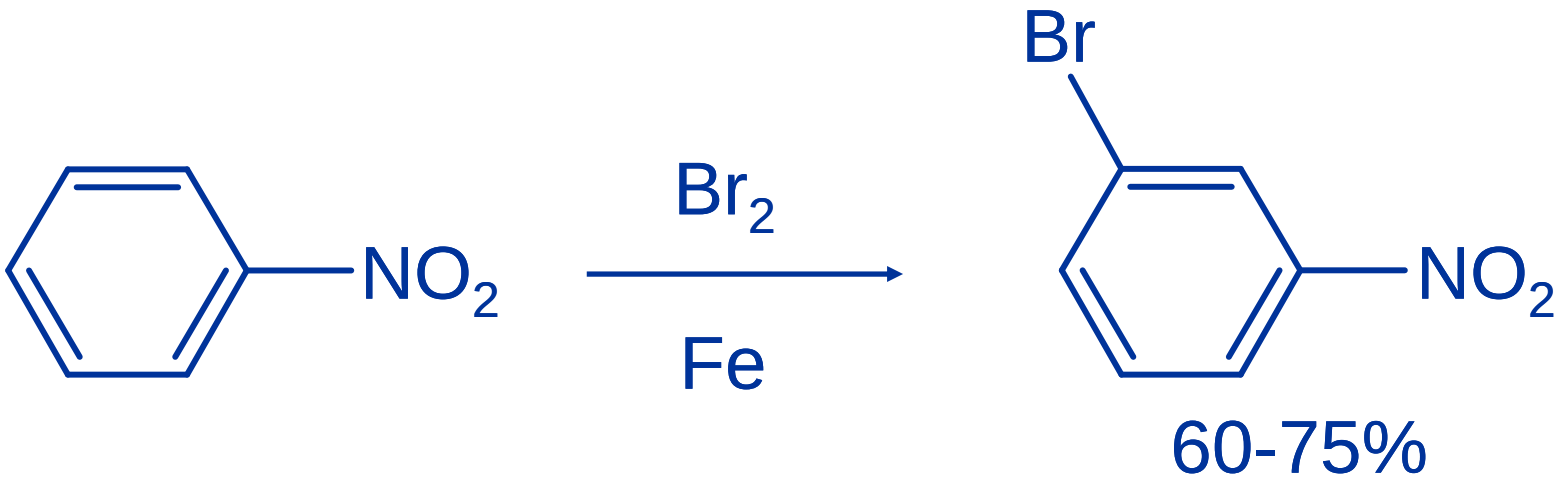
Chlorination of Benzoylchloride



Disulfonation of Benzene



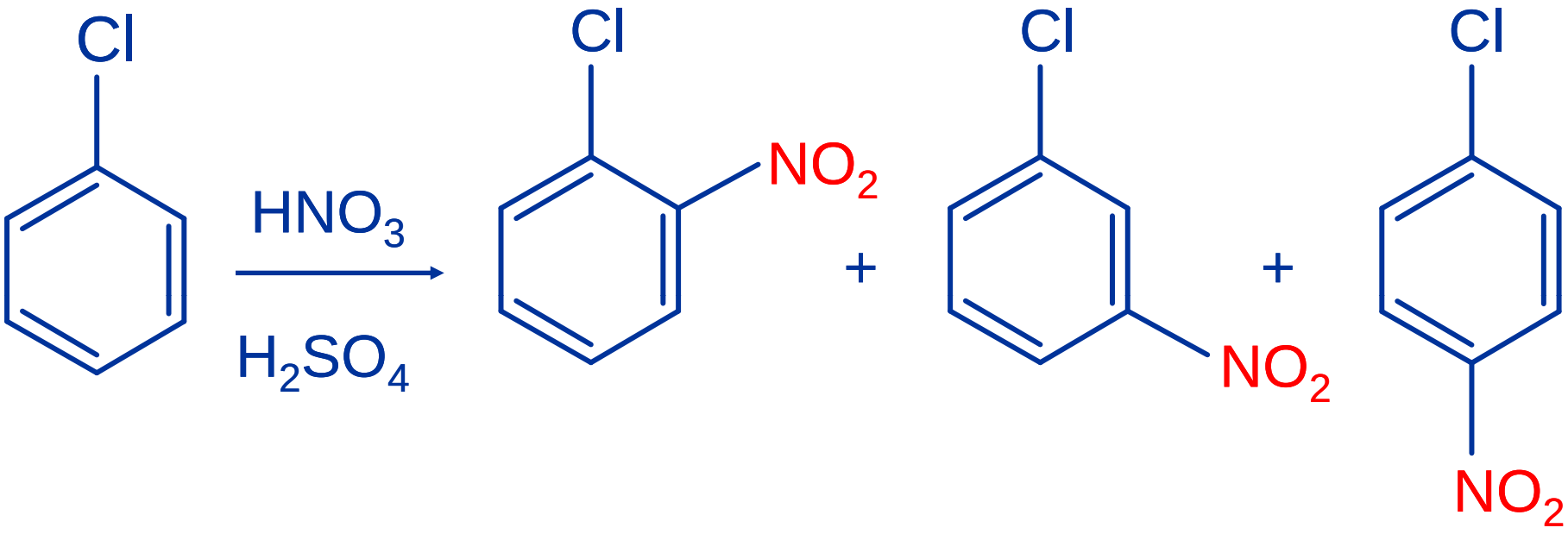
Bromination of Nitrobenzene



12.14
Substituent Effects in Electrophilic Aromatic Substitution: Halogens

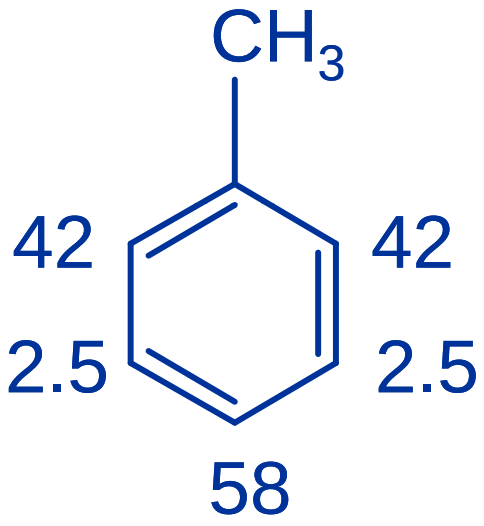
F, Cl, Br, and I are *ortho*-*para* directing,
but deactivating

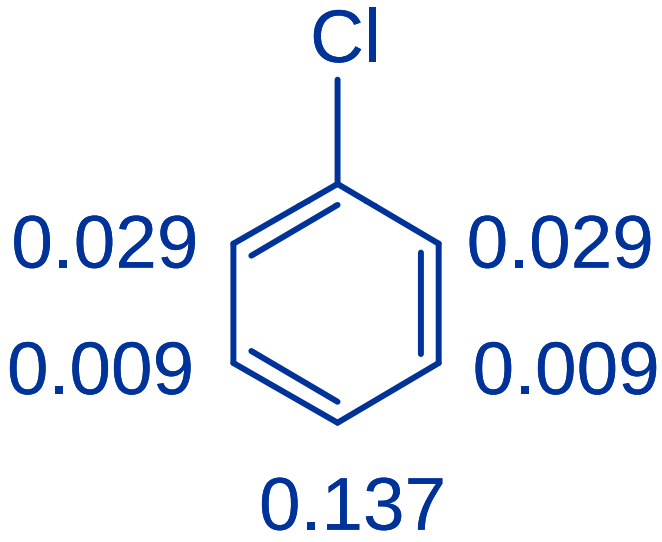
Nitration of Chlorobenzene



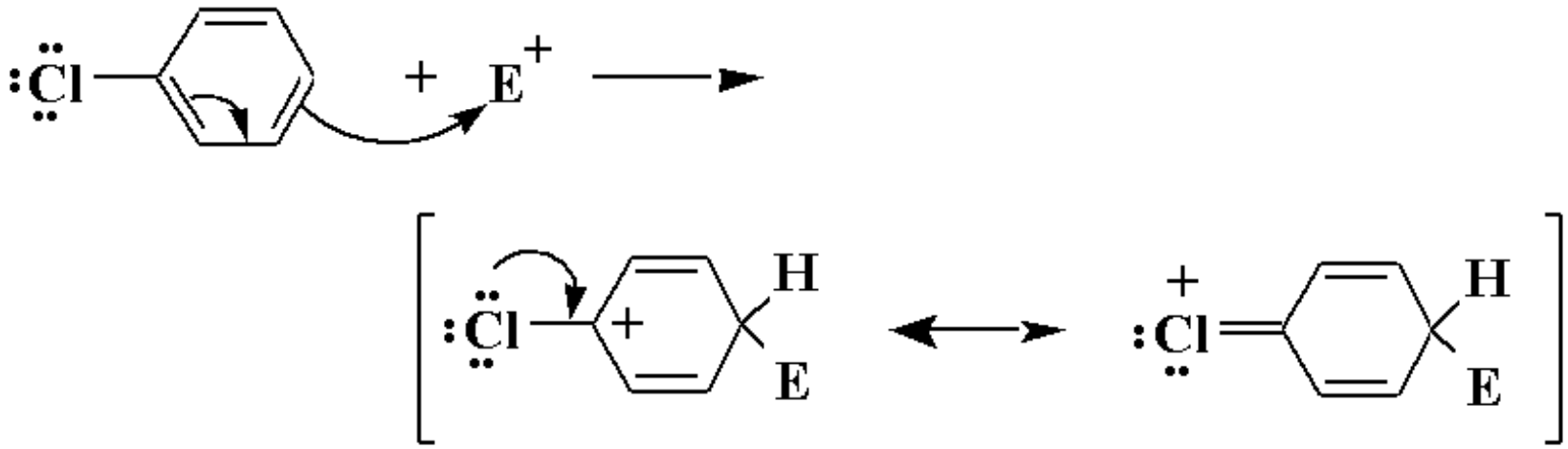
- The rate of nitration of chlorobenzene is about 30 times slower than that of benzene.

Nitration of Toluene vs. Chlorobenzene





Halogens

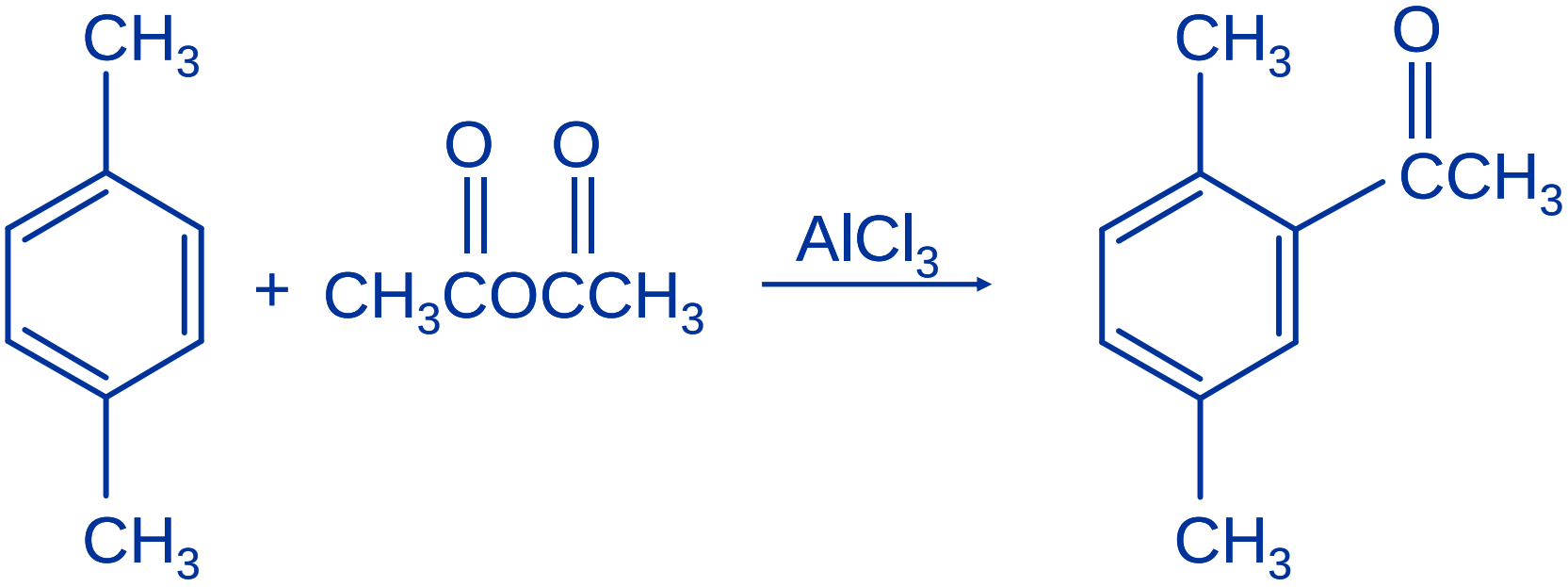


- Thus, for the halogens, the inductive and resonance effects run counter to each other, but the former is somewhat stronger.
- The net effect is that halogens are deactivating but *ortho*-*para* directing.

12.15. Multiple Substituent Effects

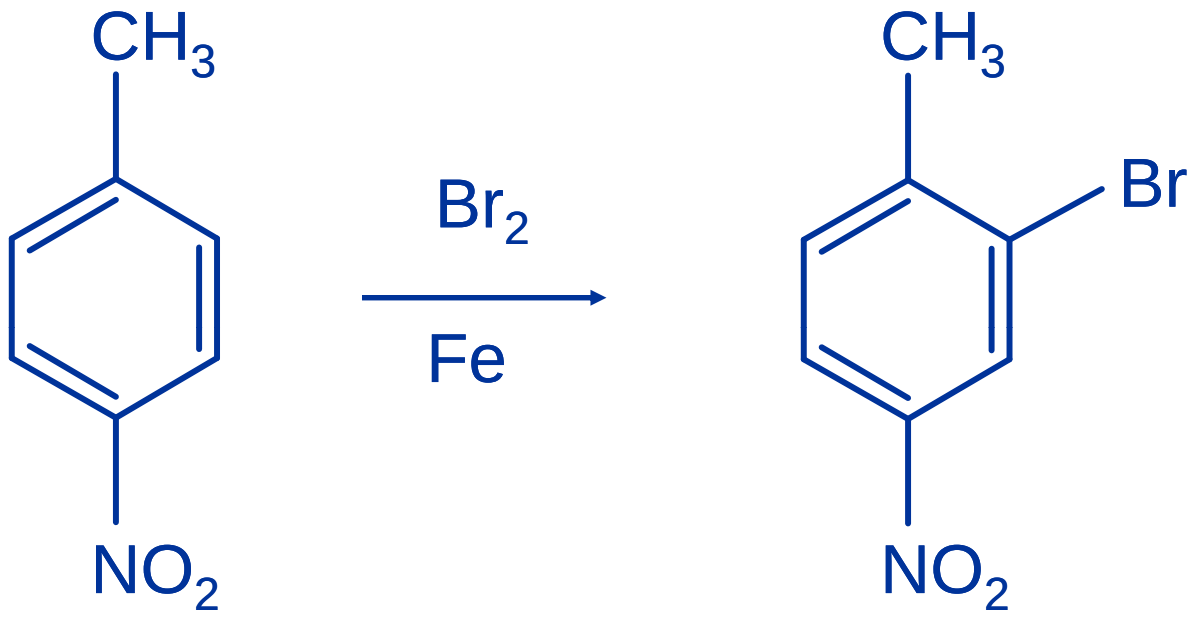
The Simplest Case

All possible EAS sites may be equivalent



99%

Another Straightforward Case



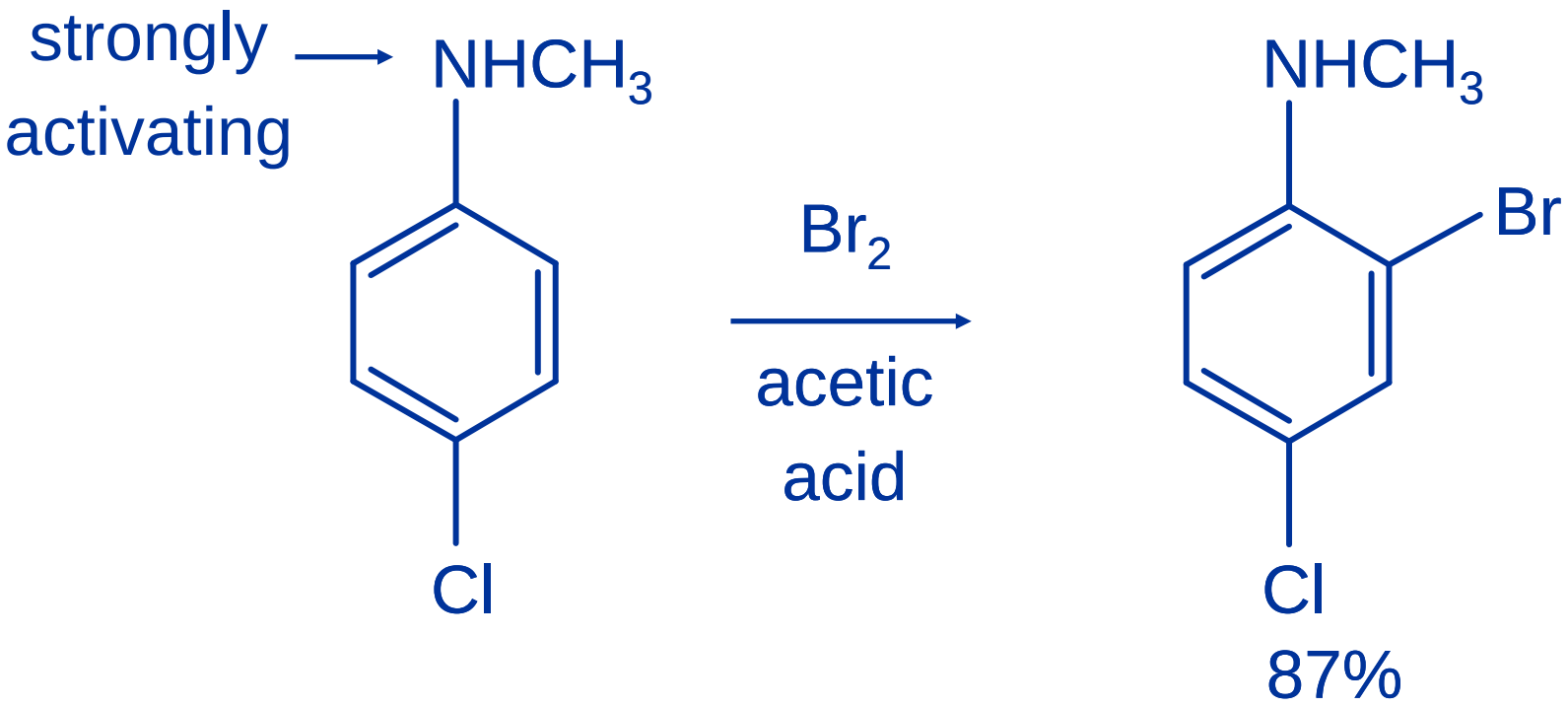
86-90%

➢ Directing effects of substituents reinforce each other; substitution takes place *ortho* to the methyl group and *meta* to the nitro group.

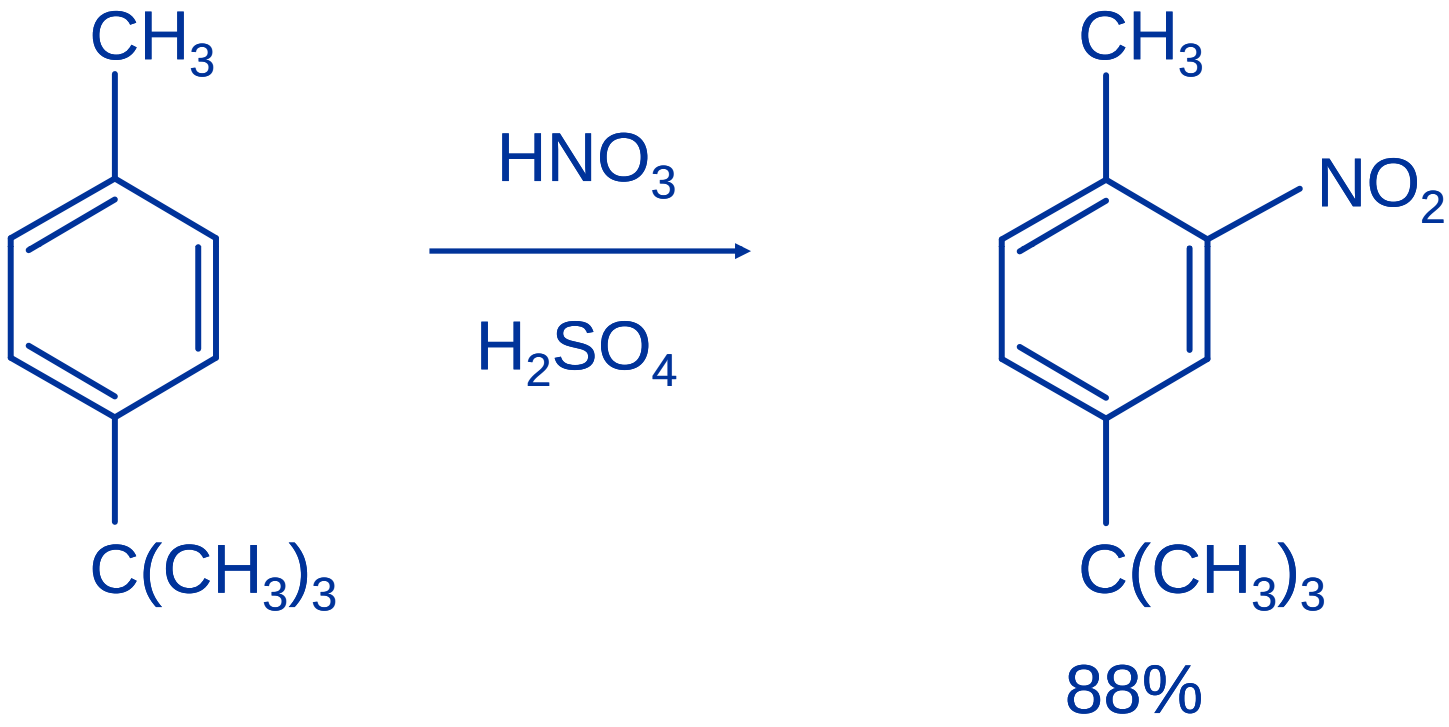
Generalization: Regioselectivity is controlled by the most activating substituent.

The Simplest Case

All possible EAS sites may be equivalent

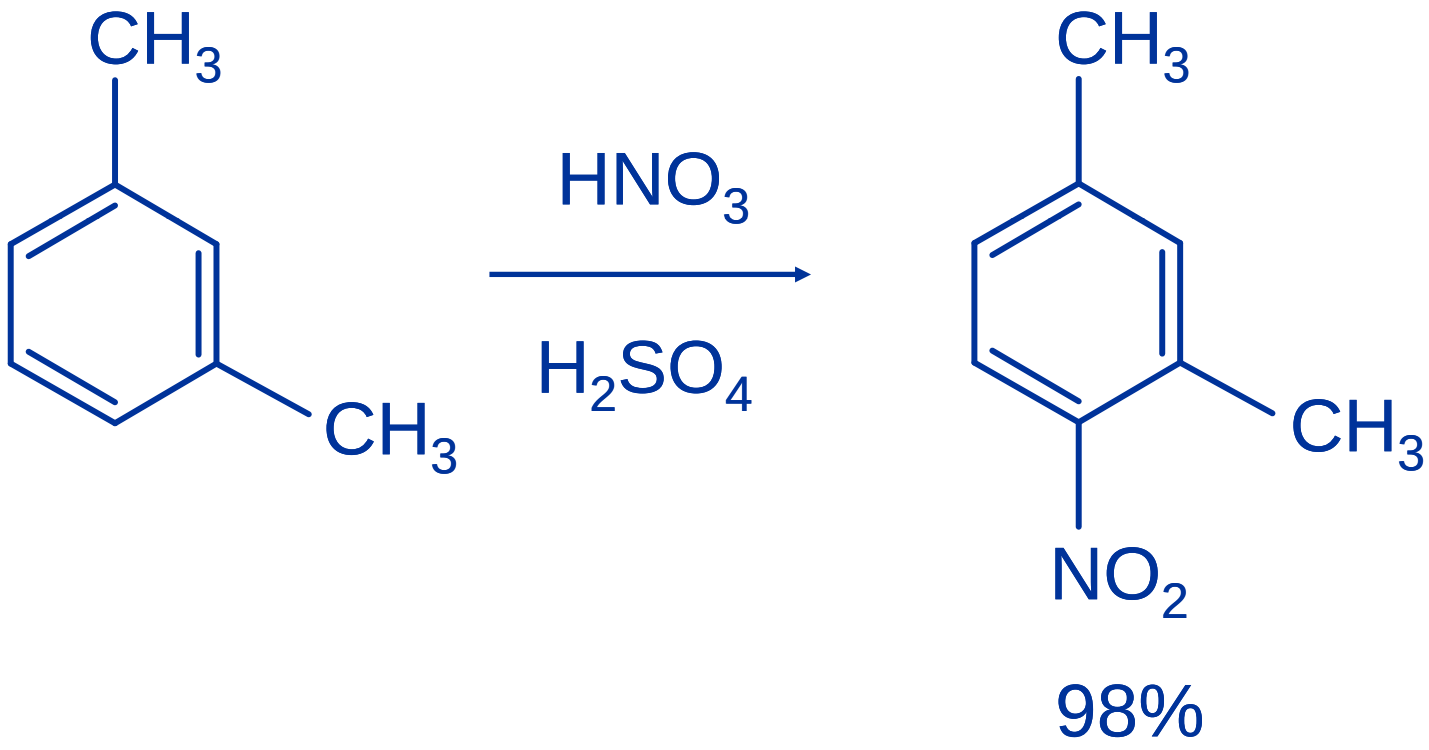


When activating effects are similar...



Substitution occurs *ortho* to the smaller group.

Steric effects control regioselectivity when electronic effects are similar



98%

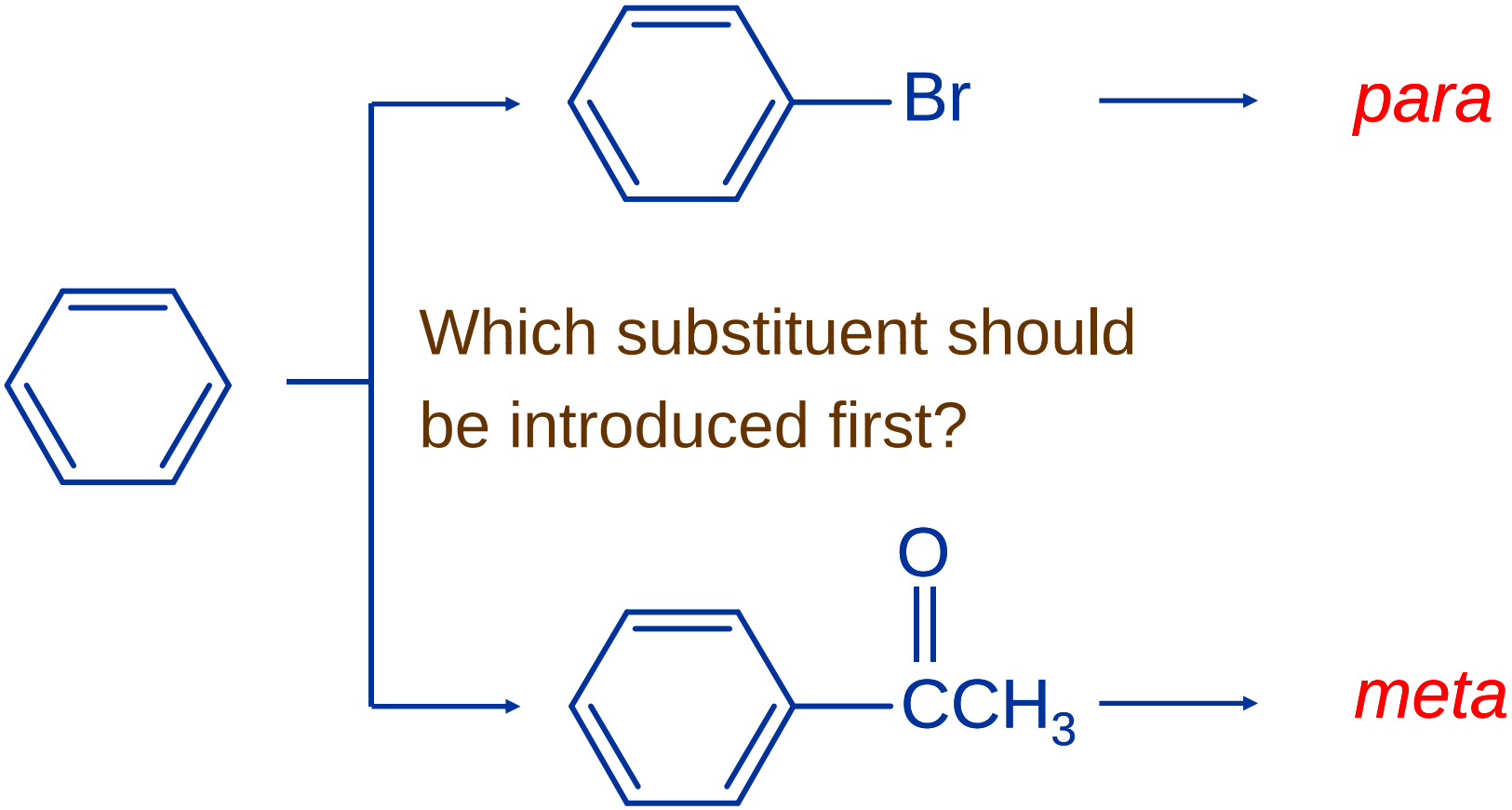
Position between two substituents is last position to be substituted.

12.16
Regioselective Synthesis of Disubstituted Aromatic Compounds

Factors to Consider

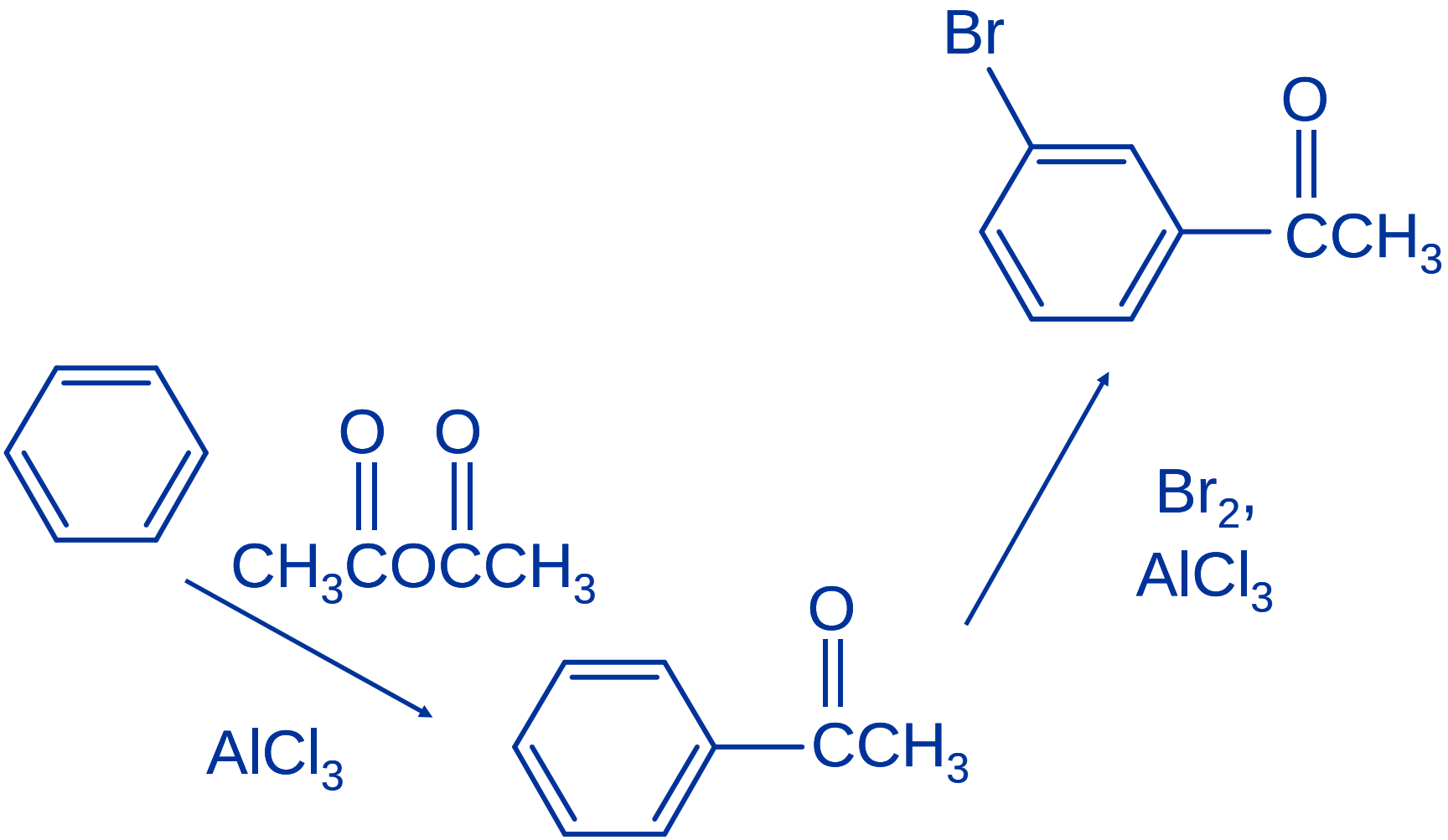
- Order of introduction of substituents to ensure correct orientation.

Synthesis of *m*-Bromoacetophenone



➢ If bromine is introduced first, *p*-bromoacetophenone is major product.

Synthesis of *m*-Bromoacetophenone



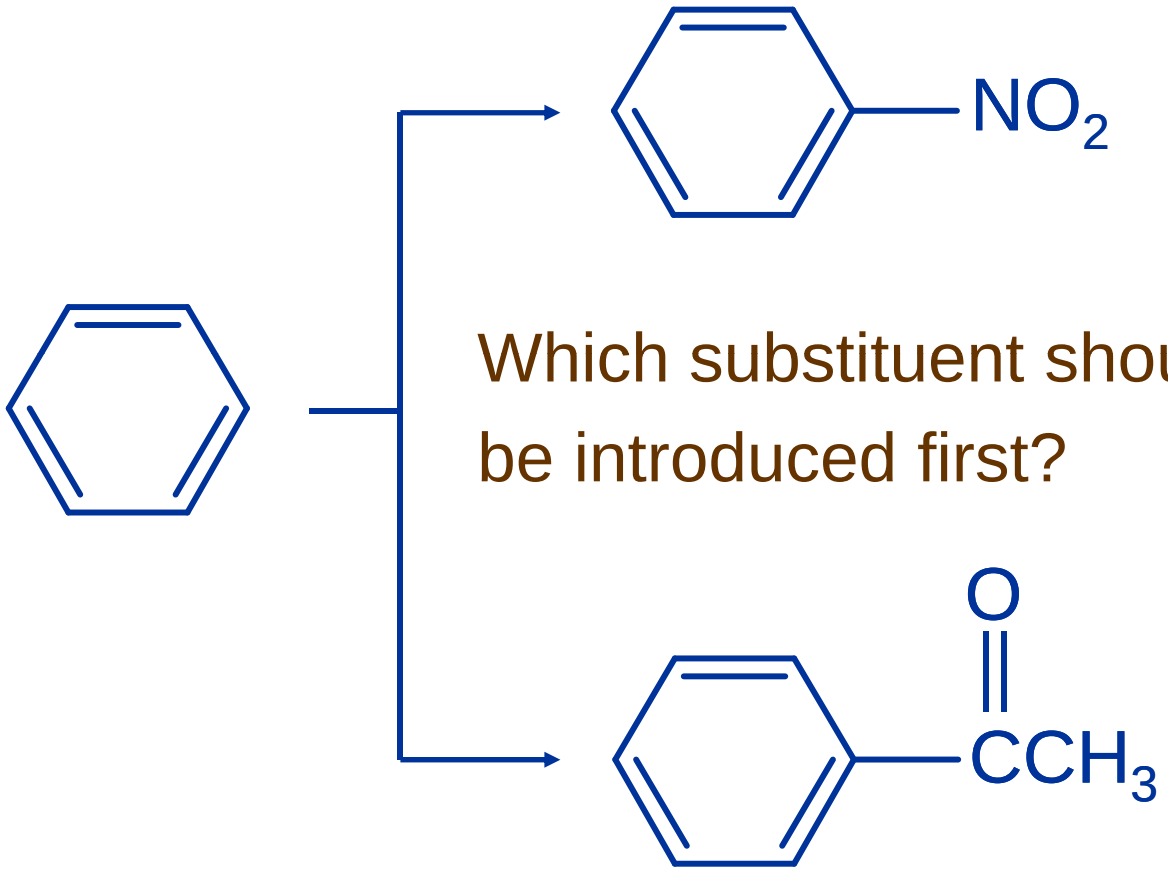
Factors to Consider

- Order of introduction of substituents to ensure correct orientation.

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

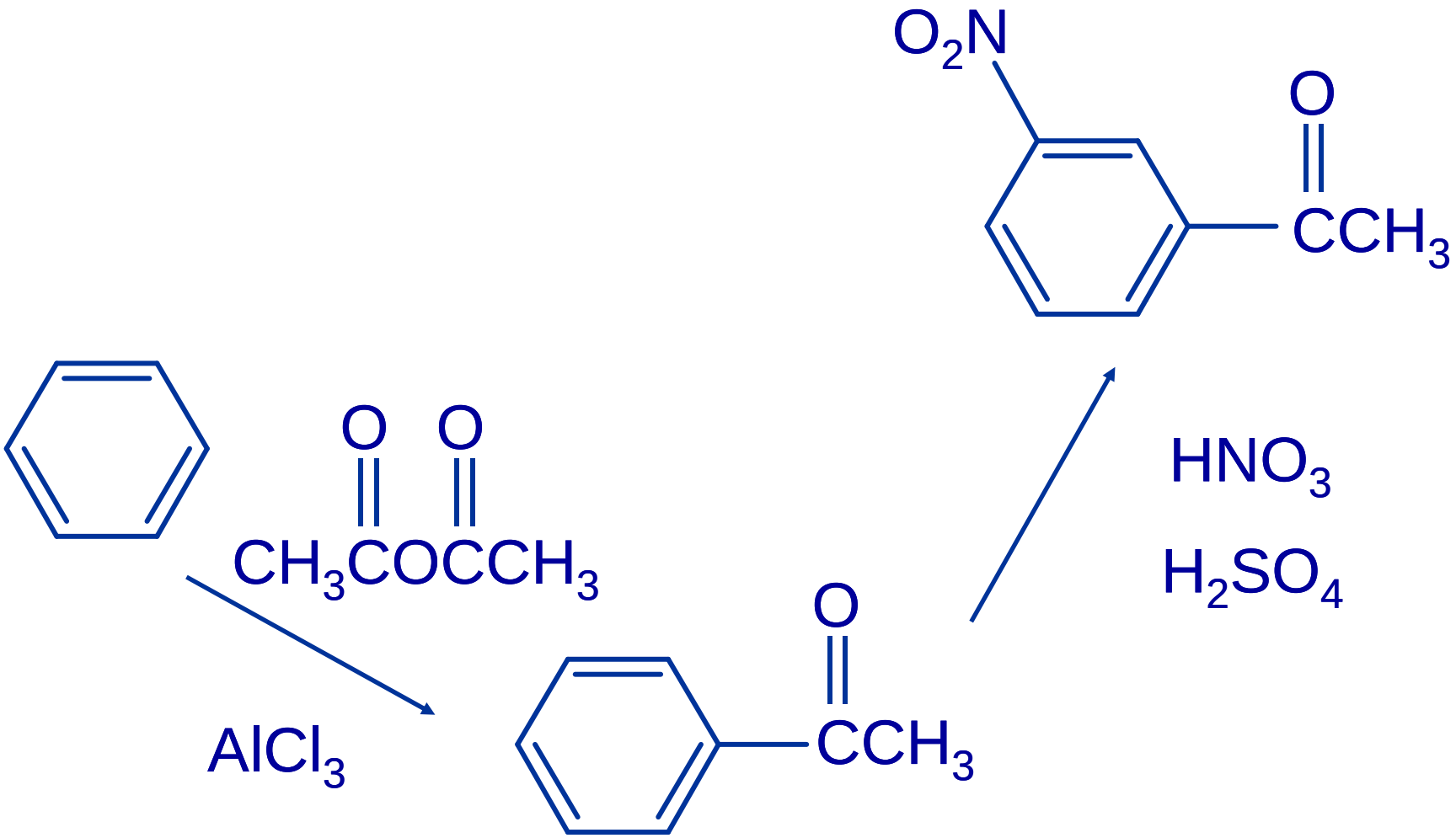
- Sometimes electrophilic aromatic substitution must be combined with a functional group transformation.

Synthesis of *m*-Nitroacetophenone

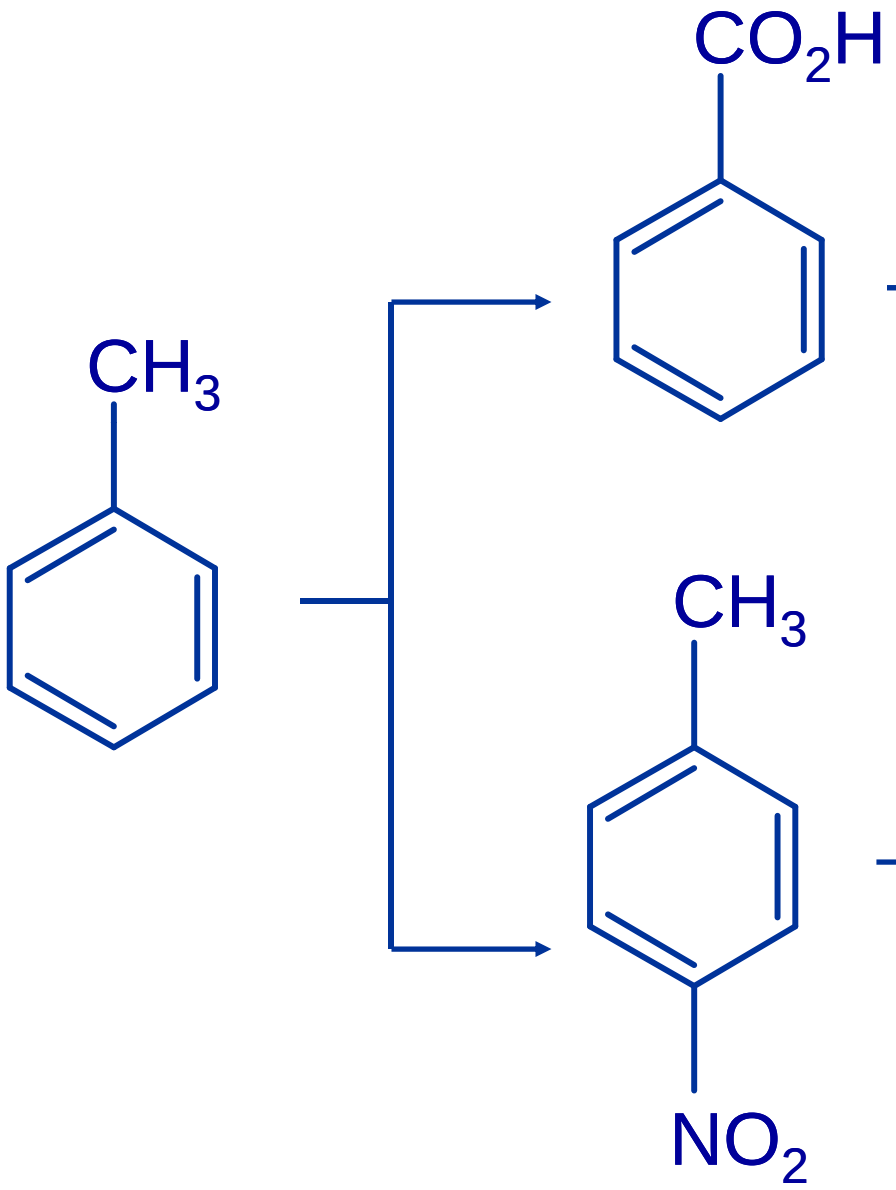


➢ If NO_2 is introduced first, the next step (Friedel-Crafts acylation) fails.

Synthesis of *m*-Nitroacetophenone



Synthesis of *p*-Nitrobenzoic Acid from Toluene

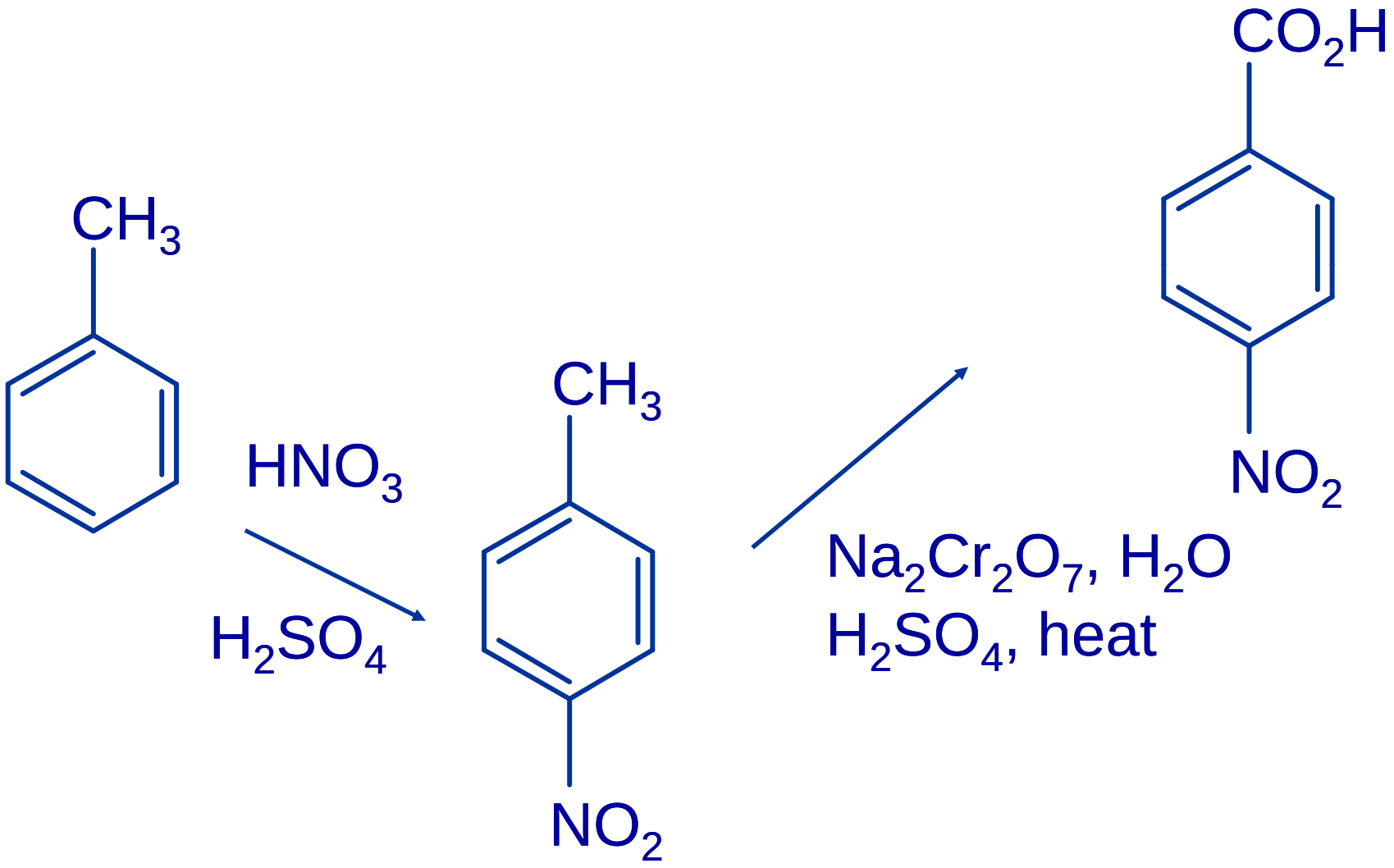


nitration gives *m*-nitrobenzoic acid

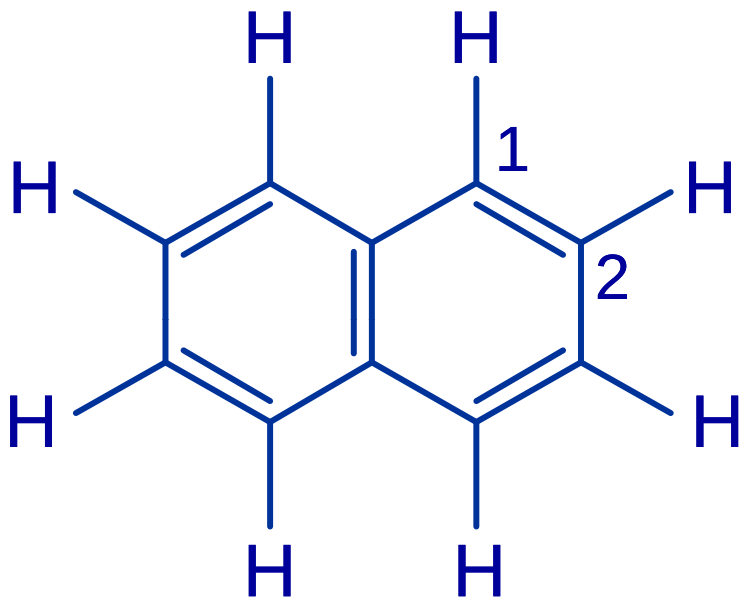
Which first? (oxidation of methyl group or nitration of ring)

oxidation gives *p*-nitrobenzoic acid

Synthesis of *p*-Nitrobenzoic Acid from Toluene

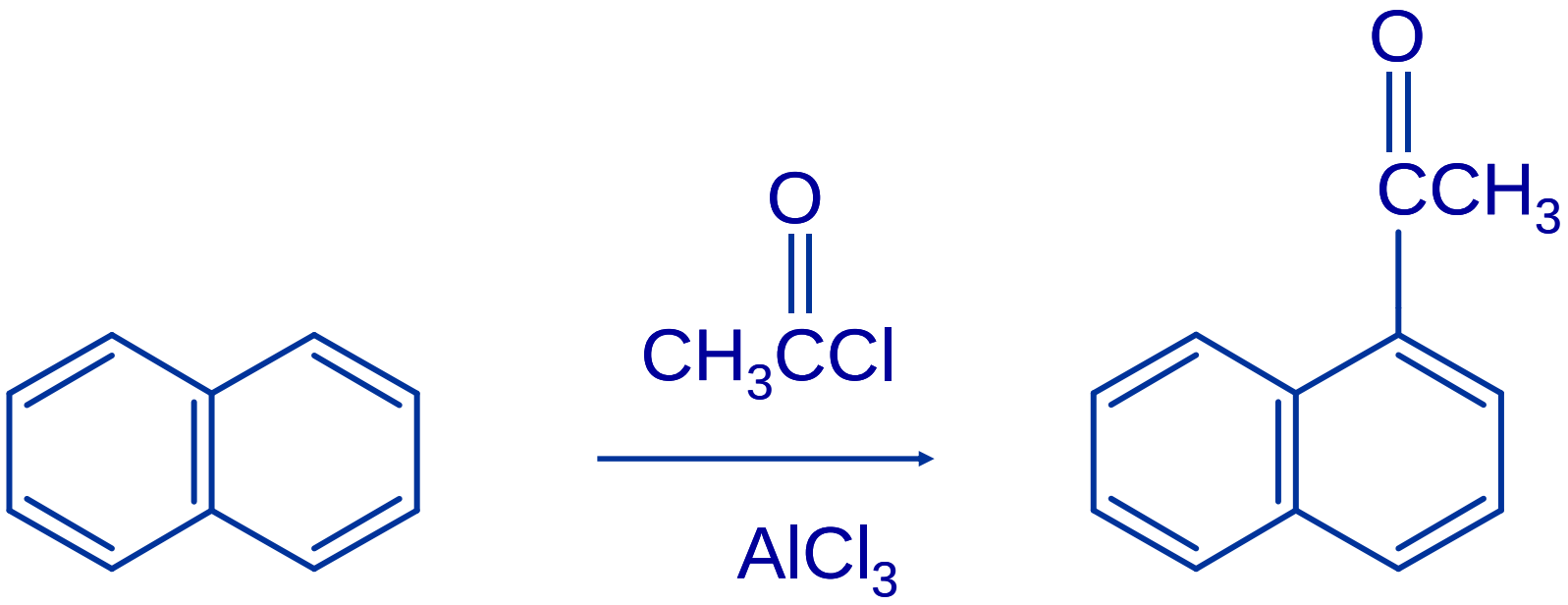


12.17. Substitution in Naphthalene



- Two sites possible for electrophilic aromatic substitution.
- All other sites at which substitution can occur are equivalent to 1 and 2.

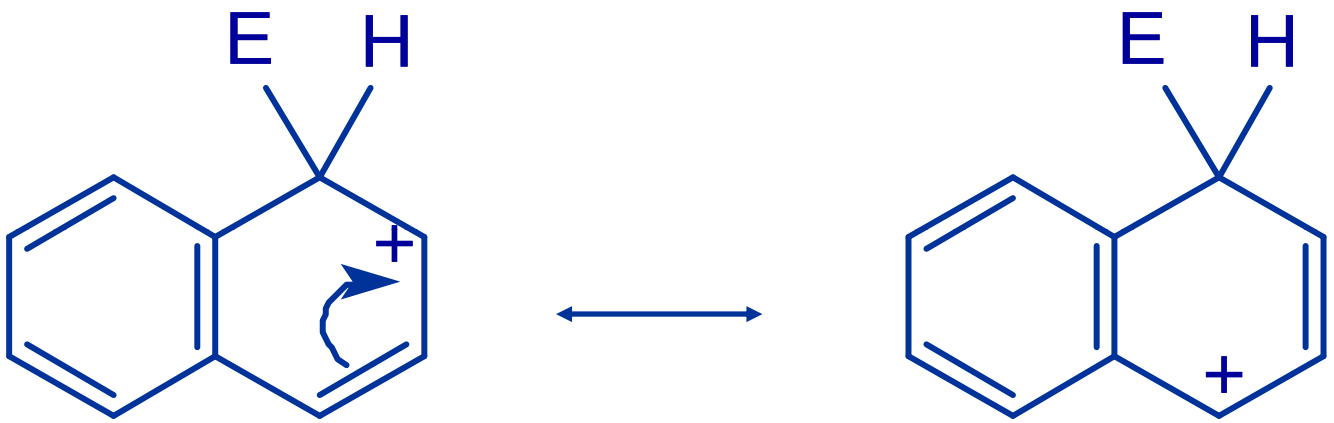
EAS in Naphthalene



90%

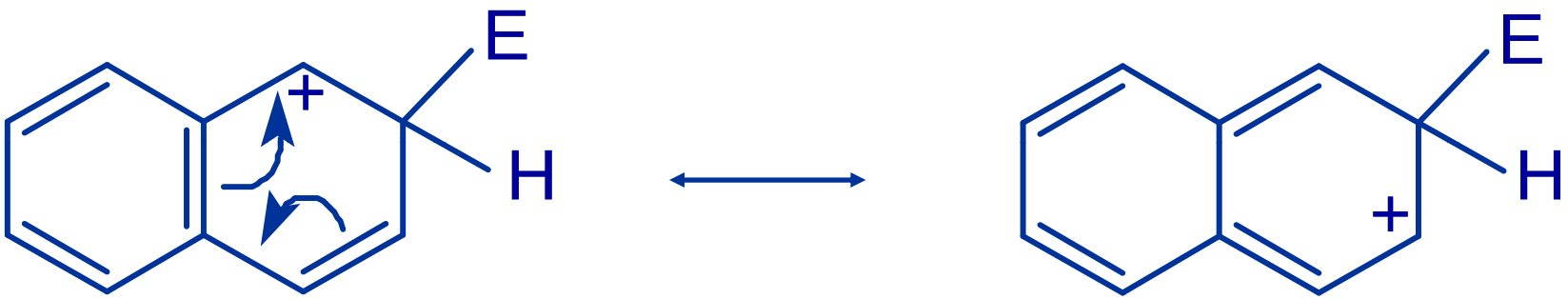
This is faster at C-1 than at C-2.

EAS in Naphthalene



When attack is at C-1, carbocation is stabilized by allylic resonance; benzenoid character of other ring is maintained.

EAS in Naphthalene



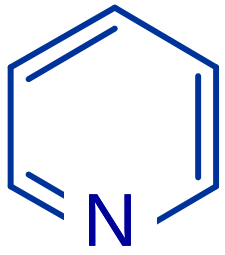
➢ When attack is at C-2, in order for carbocation to be stabilized by allylic resonance, the benzenoid character of the other ring is sacrificed.

12.18. Substitution in Heterocyclic Aromatic Compounds

Generalization

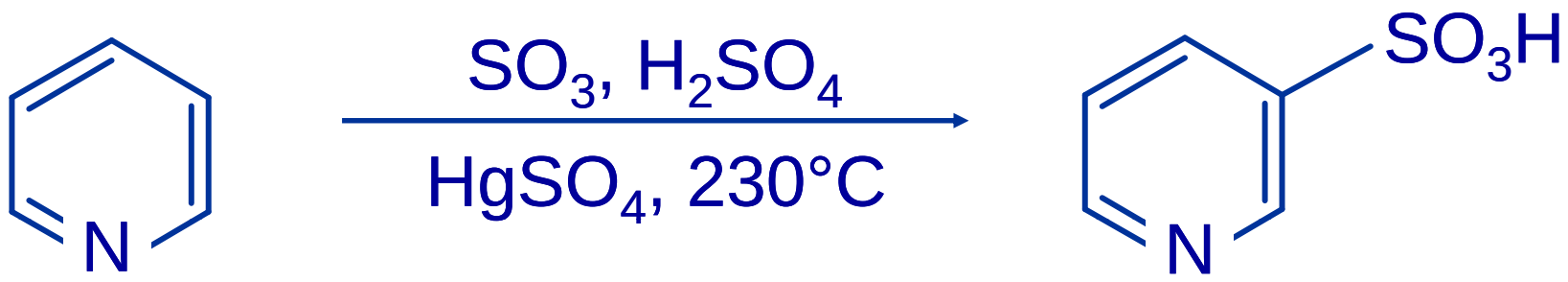
- There is none.
- There are so many different kinds of heterocyclic aromatic compounds that no generalization is possible.
- Some heterocyclic aromatic compounds are very reactive toward electrophilic aromatic substitution, others are very unreactive.

Pyridine



- Pyridine is very unreactive; it resembles nitrobenzene in its reactivity.
- Presence of electronegative atom (N) in ring causes π electrons to be held more strongly than in benzene.

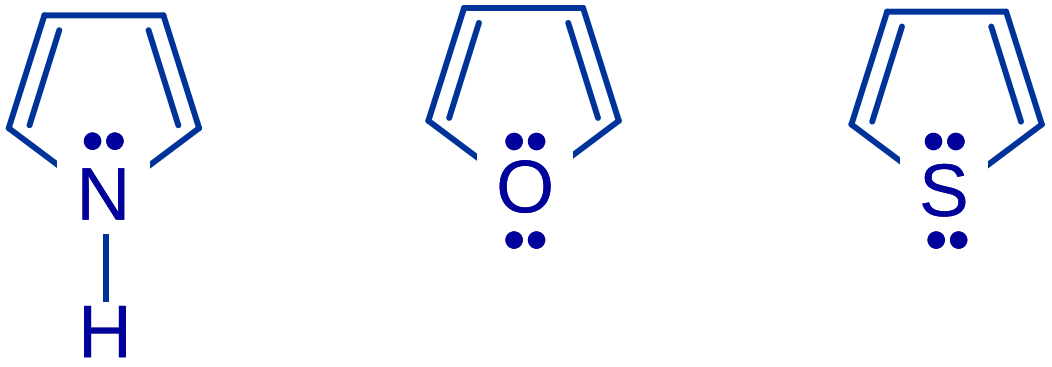
Pyridine



71%

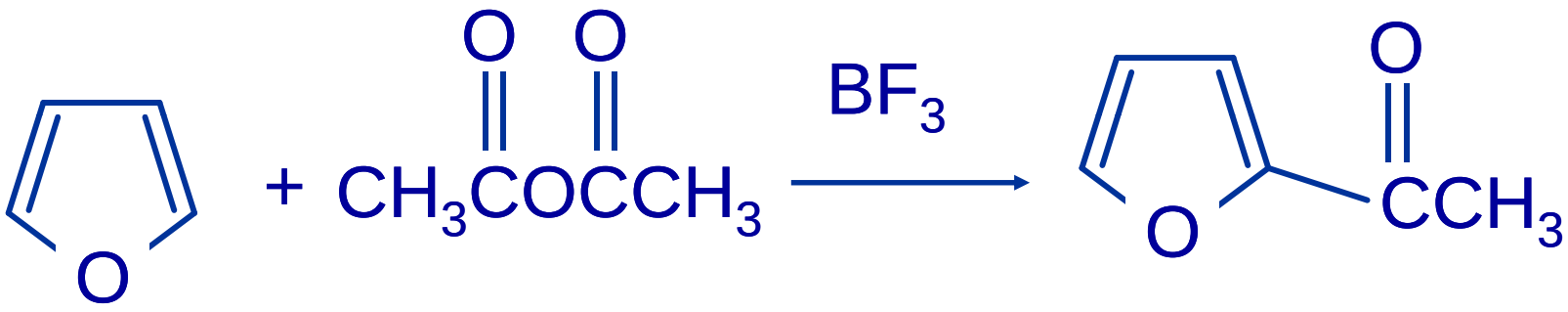
- Pyridine can be sulfonated at high temperature.
- EAS takes place at C-3.

Pyrrole, Furan, and Thiophene



- Have 1 less ring atom than benzene or pyridine to hold same number of π electrons (6).
- π electrons are held less strongly.
- These compounds are relatively reactive toward EAS.

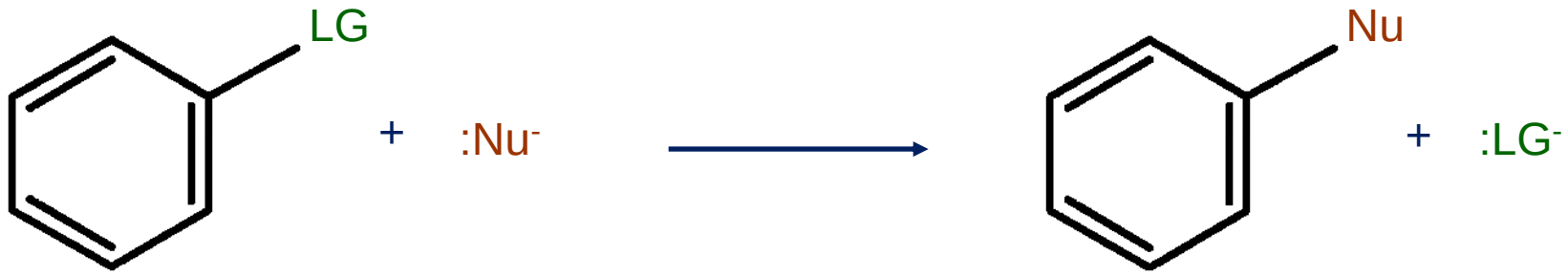
Example: Furan



75-92%

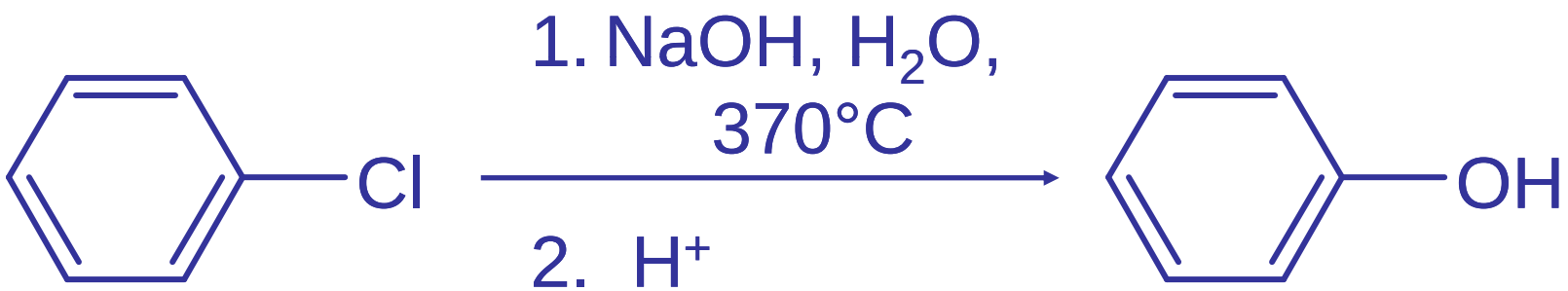
Undergoes EAS readily; C-2 is most reactive position.

12.19. Nucleophilic Aromatic Substitution



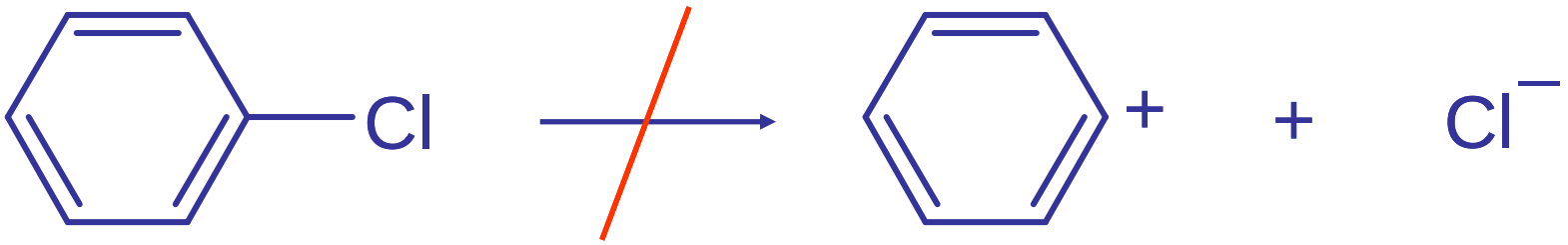
- Aryl halides are halides in which the halogen is attached directly to an aromatic ring.
- Carbon-halogen bonds in aryl halides are shorter and stronger than carbon-halogen bonds in alkyl halides.
- Because the carbon-halogen bond is stronger, aryl halides react more slowly than alkyl halides when carbon-halogen bond breaking is rate determining.

12.20. Nucleophilic Substitution in Nitro-Substituted Aryl Halides



(97%)

Reasons for Low Reactivity



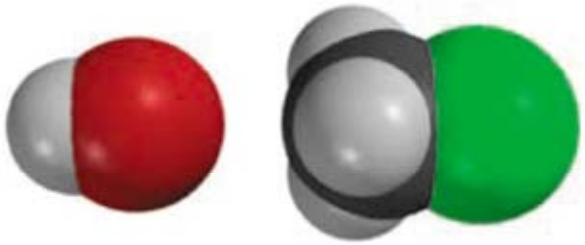
- S_N1 not reasonable because:

  1) C—Cl bond is strong; therefore, ionization to a carbocation is a high-energy process.

  2) Aryl cations are less stable than alkyl cations.

Reasons for Low Reactivity

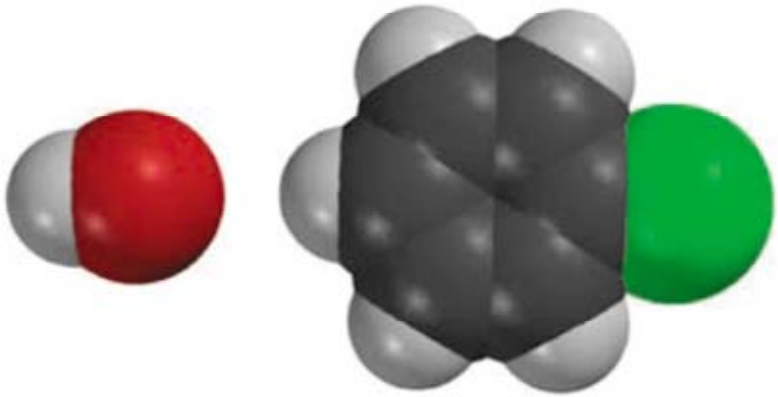
(*a*) Hydroxide ion + chloromethane



Alkyl halide:

- S_N2 possible: Attack of the nucleophile at carbon from the side opposite the bond to the leaving group.

(*b*) Hydroxide ion + chlorobenzene

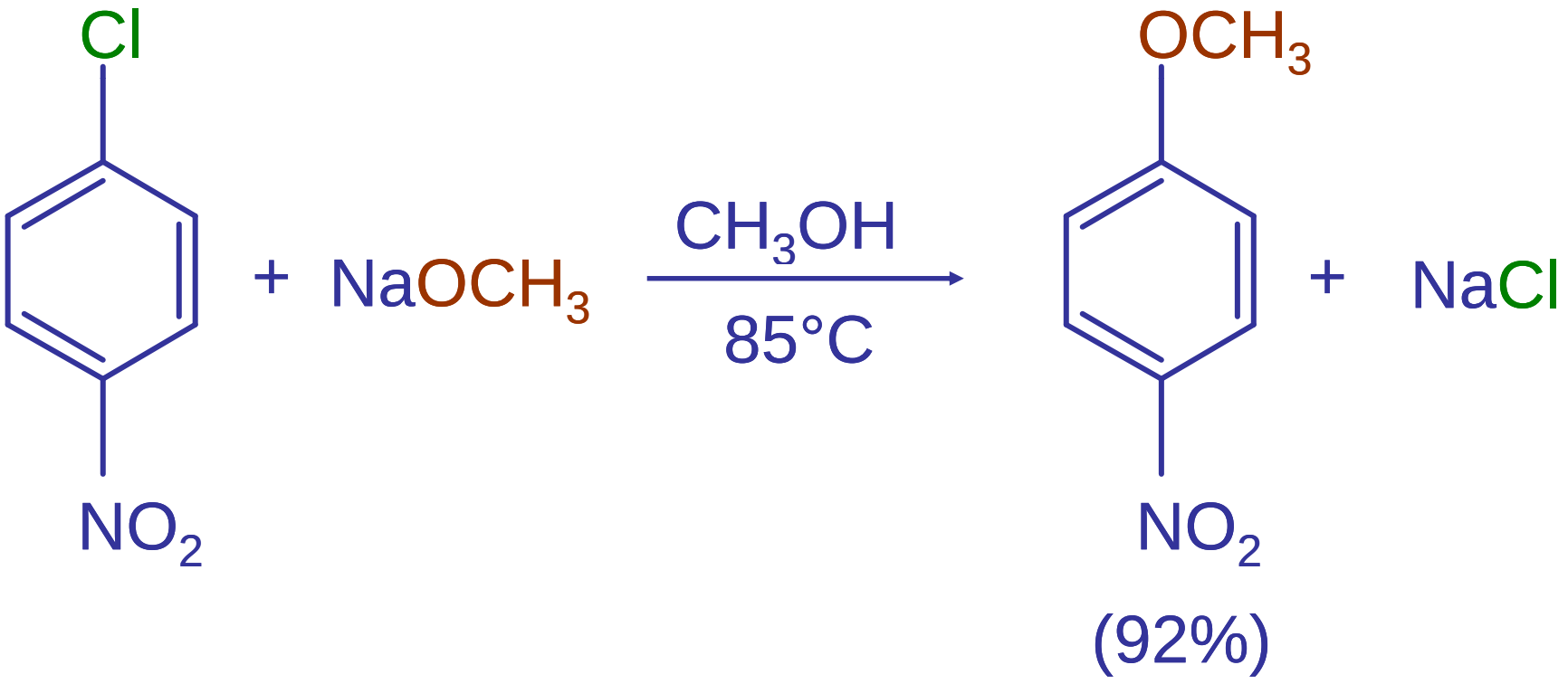


Aryl halide:

- ~~S_N2~~ **not** reasonable because ring blocks attack of nucleophile from side opposite bond to leaving group.

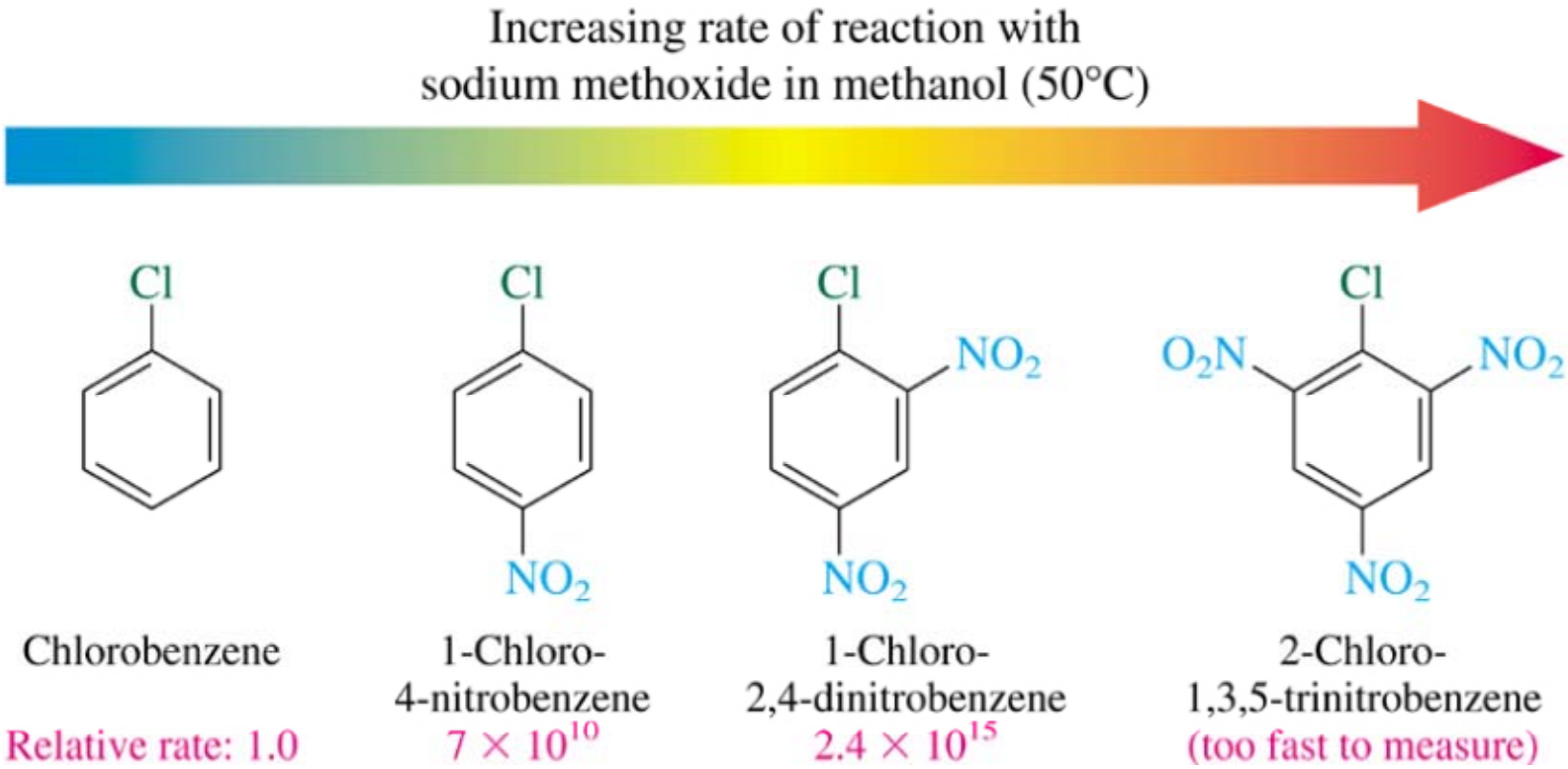
But...

- Nitro-substituted aryl halides **DO** undergo nucleophilic aromatic substitution readily.



Effect of nitro group is cumulative

- Especially when nitro group is *ortho* and/or *para* to leaving group.



Kinetics

- Follows second-order rate law:

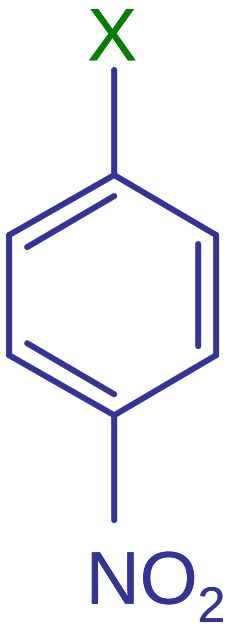
  rate = *k*[aryl halide][nucleophile]

- Inference:

  Both the aryl halide and the nucleophile are involved in rate-determining step.

Effect of leaving group

Unusual order: F > Cl > Br > I



X	Relative Rate*
F	312
Cl	1.0
Br	0.8
I	0.4

*$NaOCH_3$, CH_3OH, 50°C

General Conclusions About Mechanism

- Bimolecular rate-determining step in which nucleophile attacks aryl halide.

- Rate-determining step precedes carbon-halogen bond cleavage.

- Rate-determining transition state is stabilized by electron-withdrawing groups (such as NO_2).

12.21
The Addition-Elimination Mechanism of Nucleophilic Aromatic Substitution

Addition-Elimination Mechanism

- Two step mechanism:

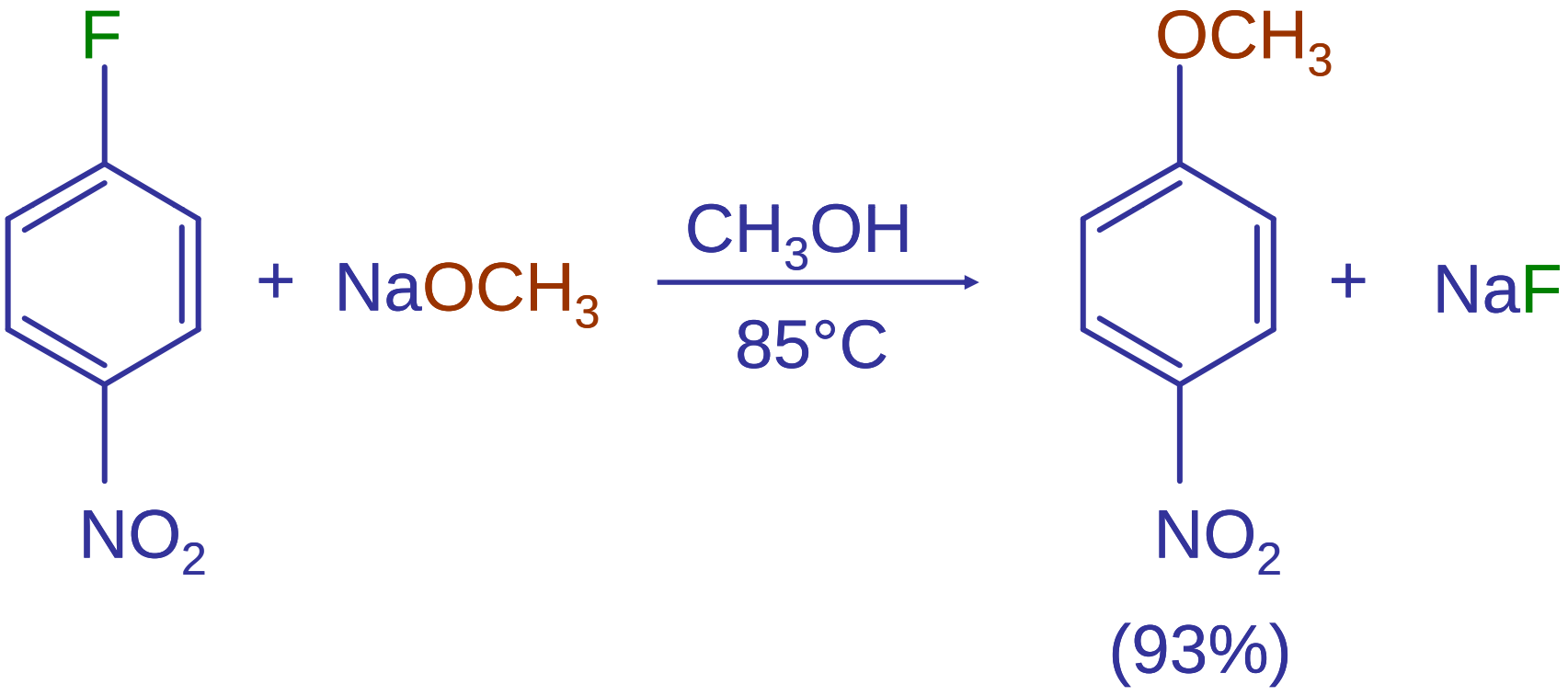
  Step 1. Nucleophile attacks aryl halide and bonds to the carbon that bears the halogen.

  (slow: aromaticity of ring lost in this step)

  Step 2. intermediate formed in first step loses halide.

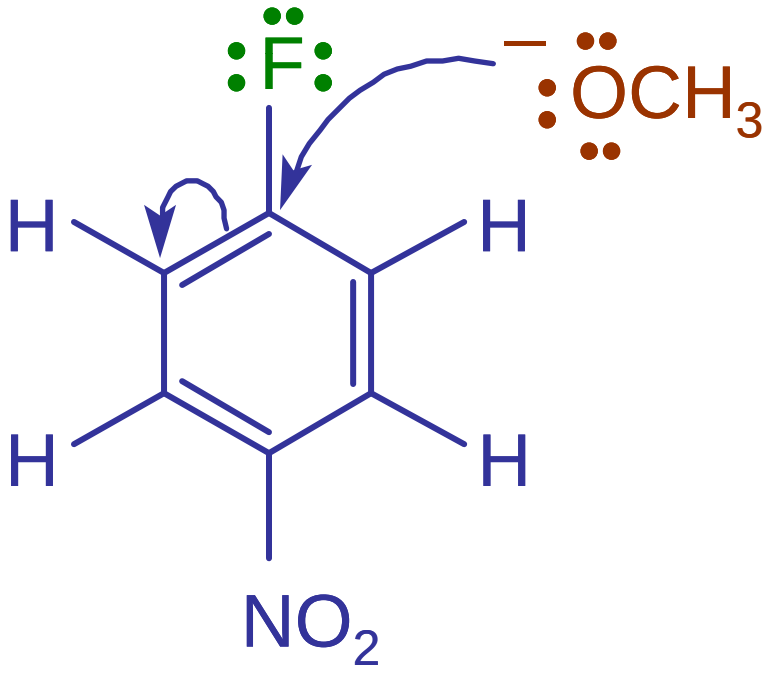
  (fast: aromaticity of ring restored in this step)

Reaction



Mechanism

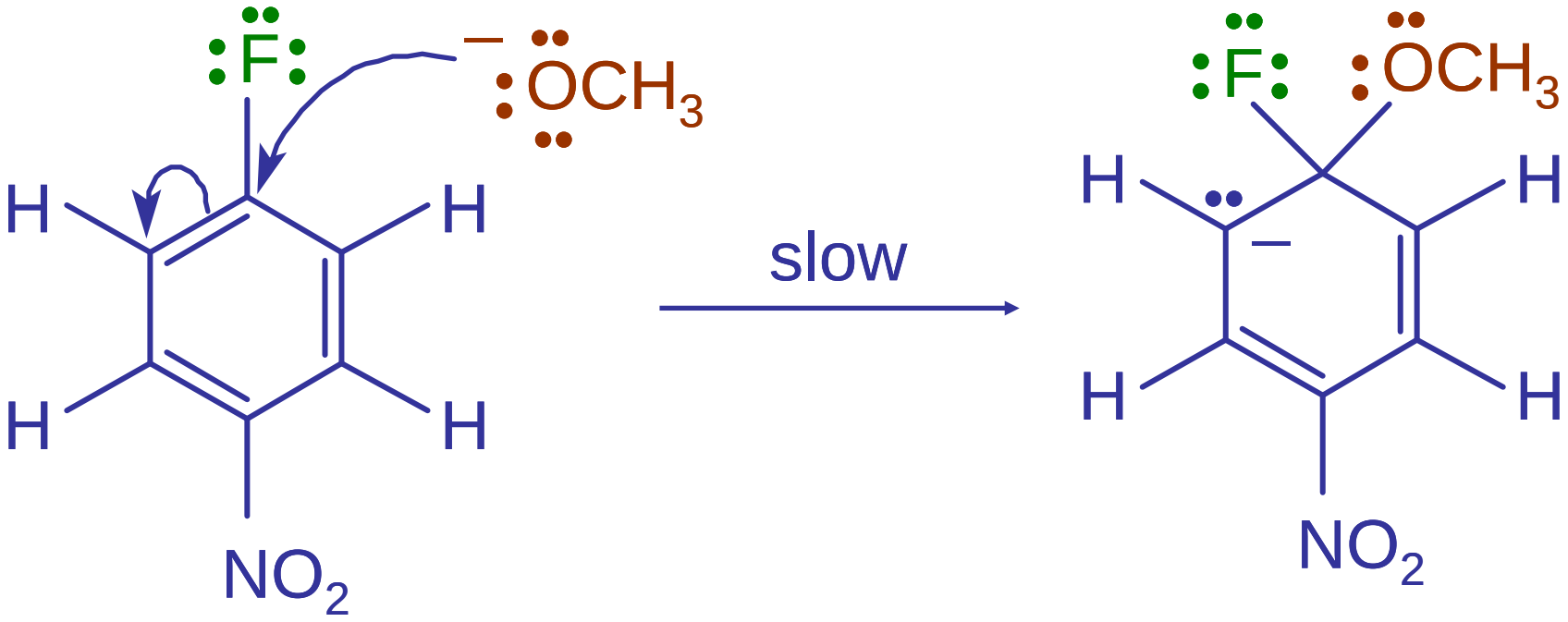
Step 1



- Bimolecular.
- Consistent with second-order kinetics; first order in aryl halide, first order in nucleophile.

Mechanism

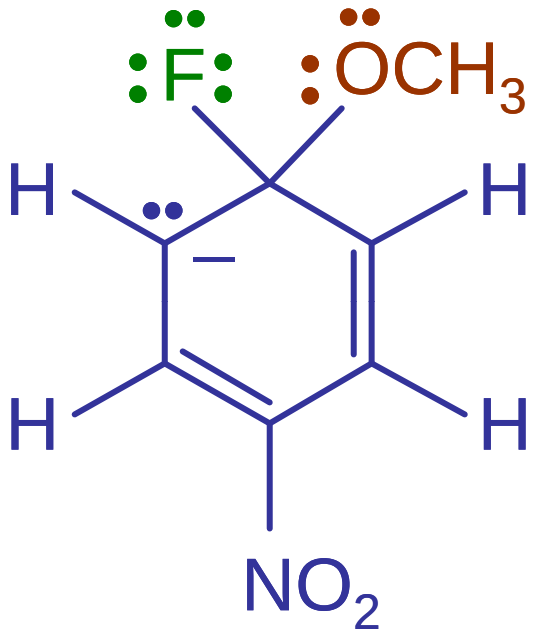
Step 1



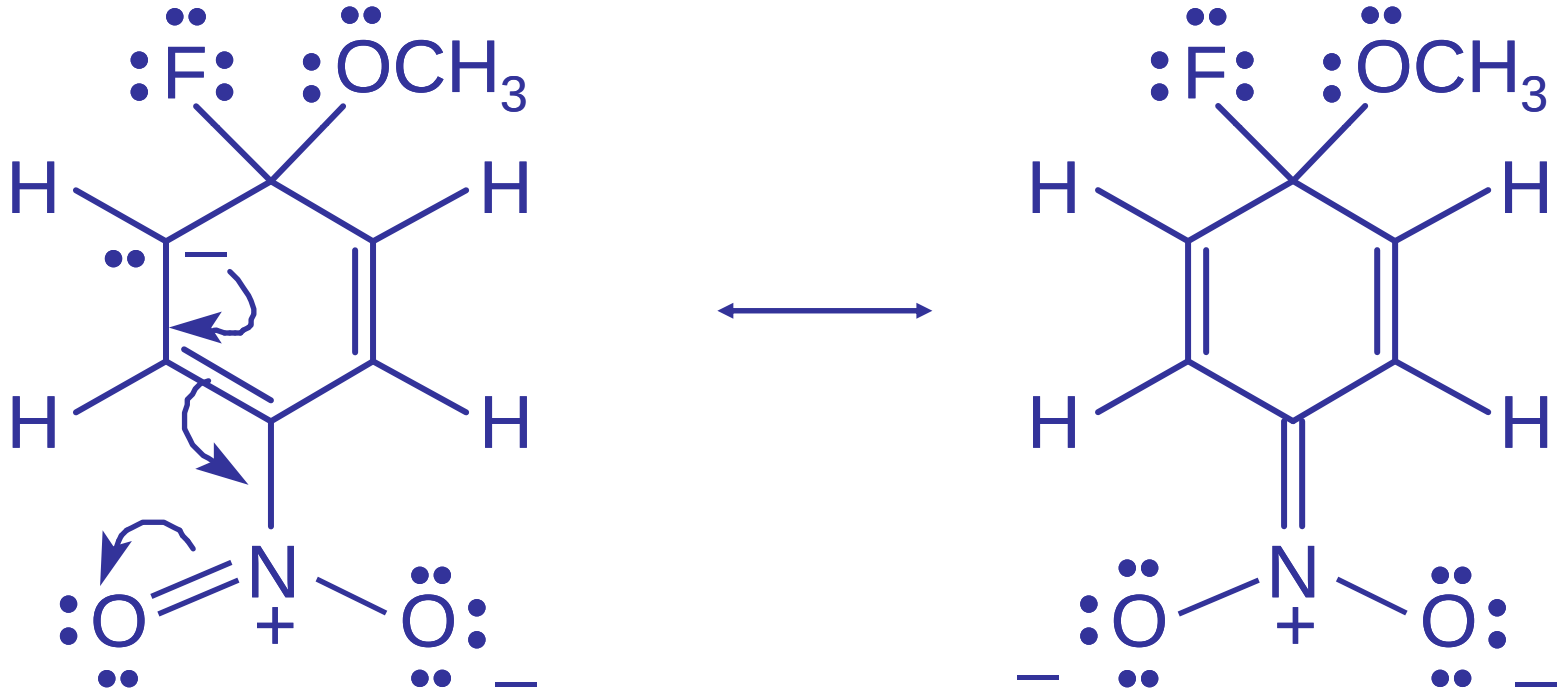
Mechanism

- Intermediate is negatively charged.

- Formed faster when ring bears electron-withdrawing groups such as NO_2.

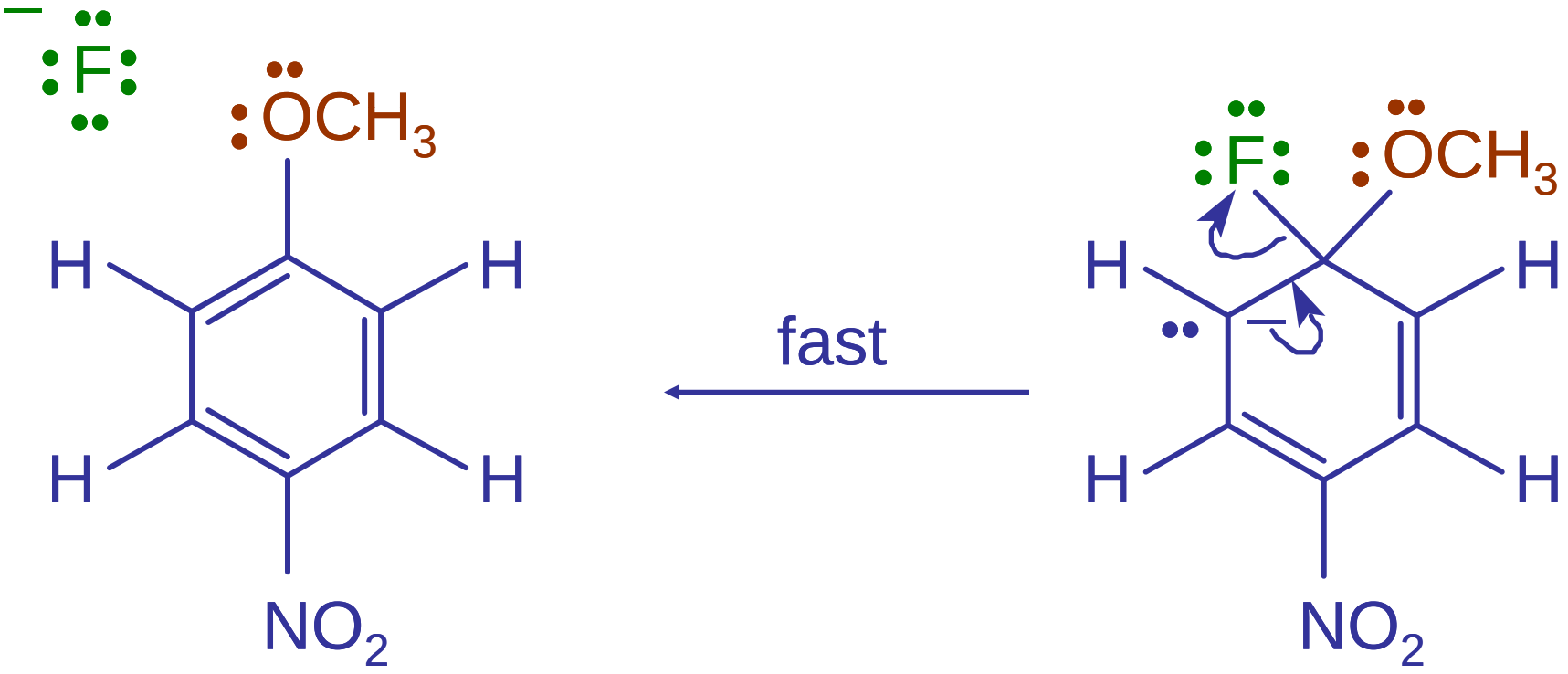


Stabilization of Rate-Determining Intermediate by Nitro Group



Mechanism

Step 2



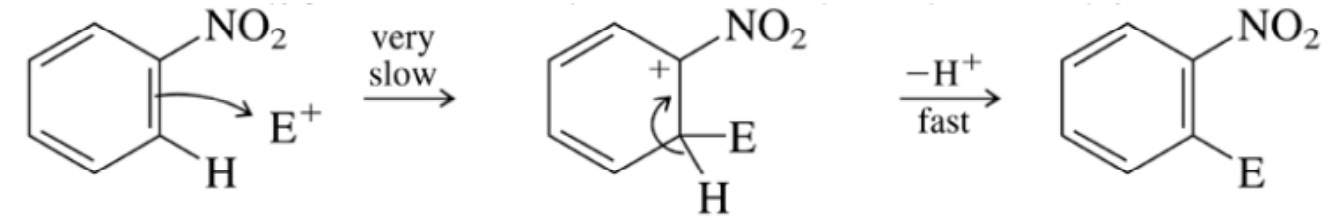
Leaving Group Effects

F > Cl > Br > I is unusual, but consistent with mechanism.

- Carbon-halogen bond breaking does not occur until after the rate-determining step.
- Electronegative F stabilizes negatively charged intermediate.

Contrasting Effect: Always check what reaction you are evaluating!

- **In <u>electrophilic aromatic substitutions</u>, the nitro group acts as a deactivator.**

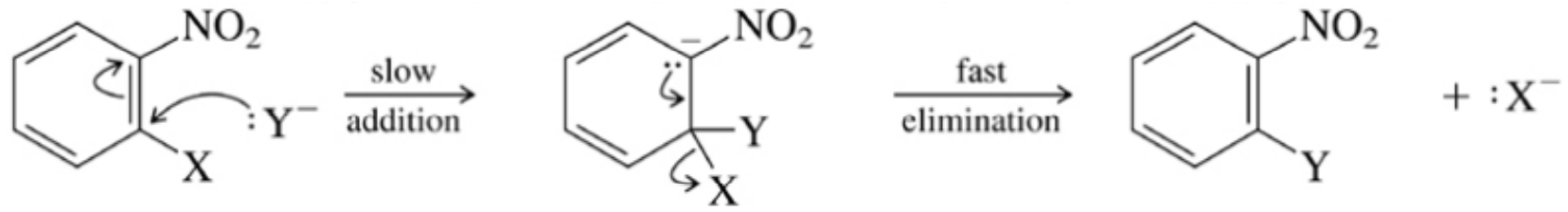


Nitrobenzene and an electrophile

Cyclohexadienyl cation intermediate; nitro group is destabilizing

Product of electrophilic aromatic substitution

- **In <u>nucleophilic aromatic substitutions</u>, the nitro group acts as an activator.**



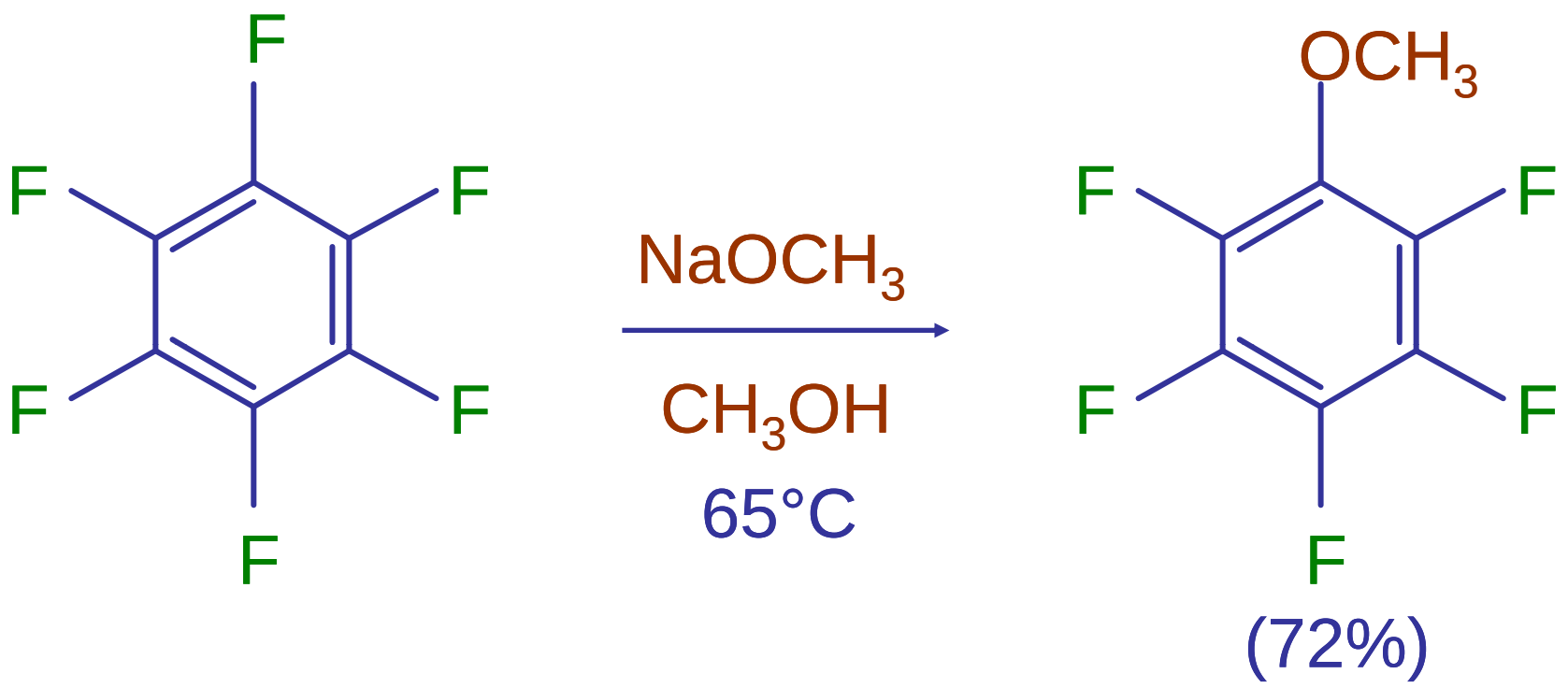
o-Halonitrobenzene (X = F, Cl, Br, or I) and a nucleophile

Cyclohexadienyl anion intermediate; nitro group is stabilizing

Product of nucleophilic aromatic substitution

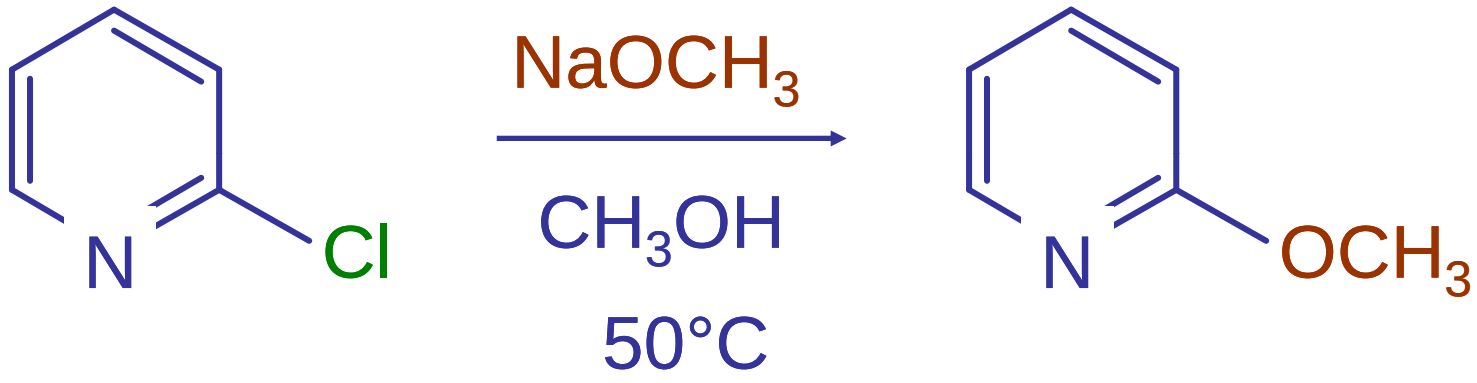
12.22
Related Nucleophilic Aromatic Substitution Reactions

Example: Hexafluorobenzene



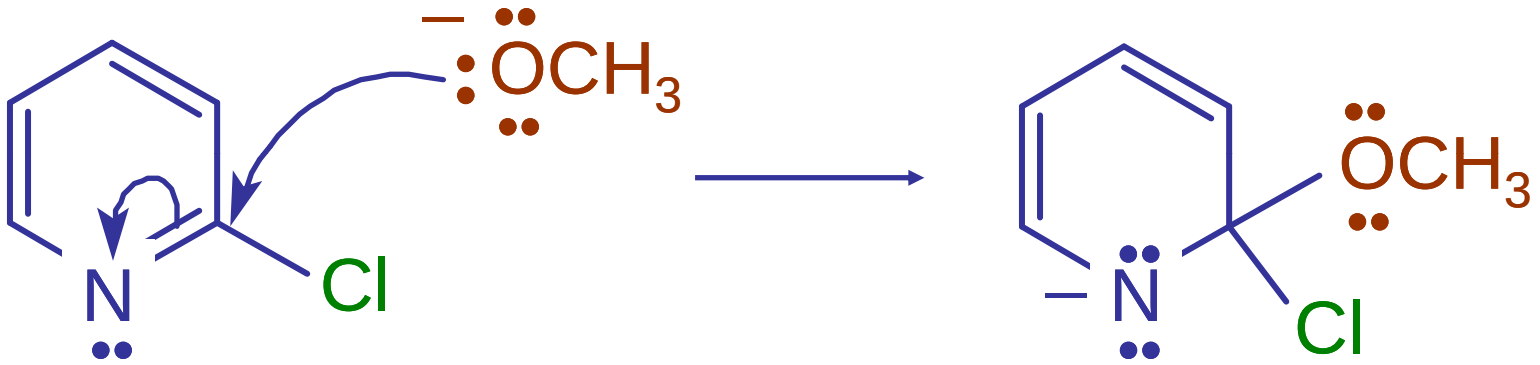
➢ Six fluorine substituents stabilize negatively charged intermediate formed in rate-determining step and increase rate of nucleophilic aromatic substitution.

Example: 2-Chloropyridine



➢ 2-Chloropyridine reacts 230,000,000 times faster than chlorobenzene under these conditions.

Example: 2-Chloropyridine

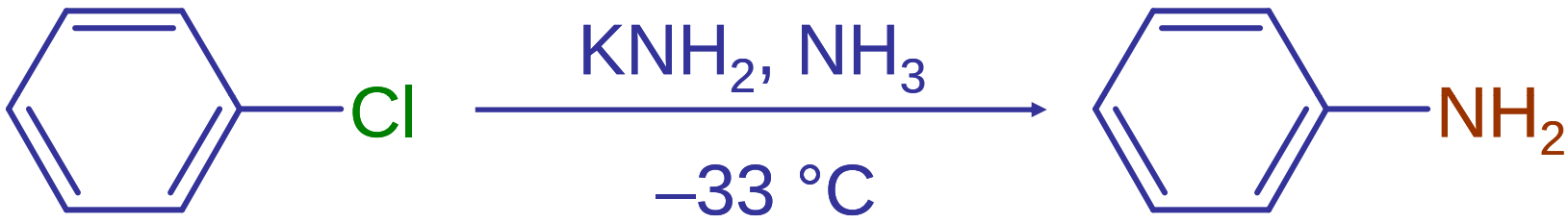


➢ Nitrogen is more electronegative than carbon, stabilizes the anionic intermediate, and increases the rate at which it is formed.

The Elimination-Addition Mechanism of Nucleophilic Aromatic Substitution: Benzyne

*** Presence of a strong base!**

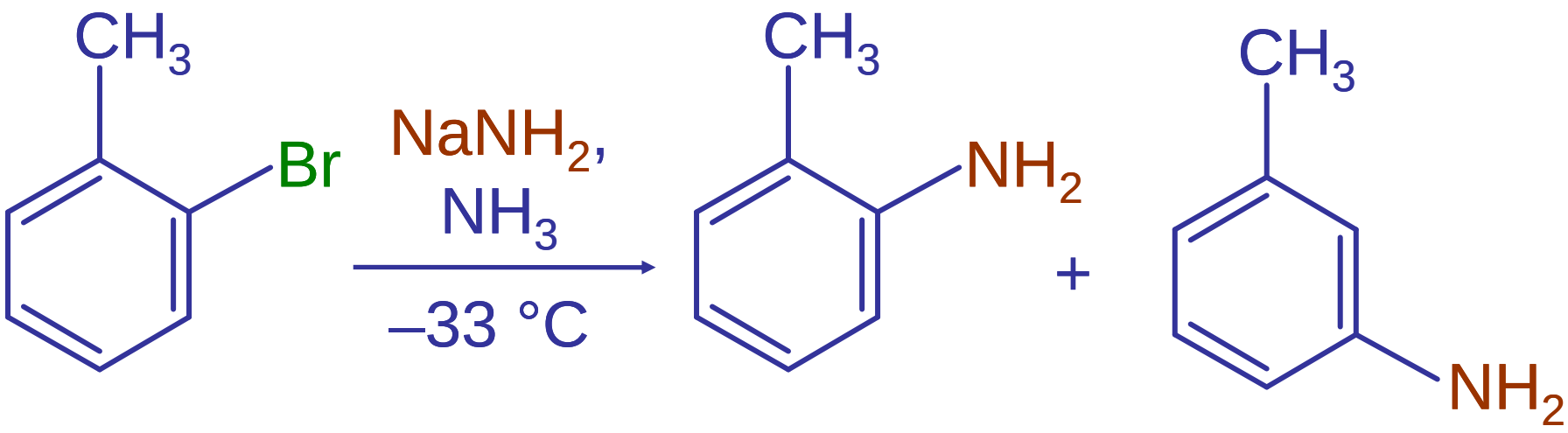
Aryl Halides Undergo Substitution When Treated With Very Strong Bases



(52%)

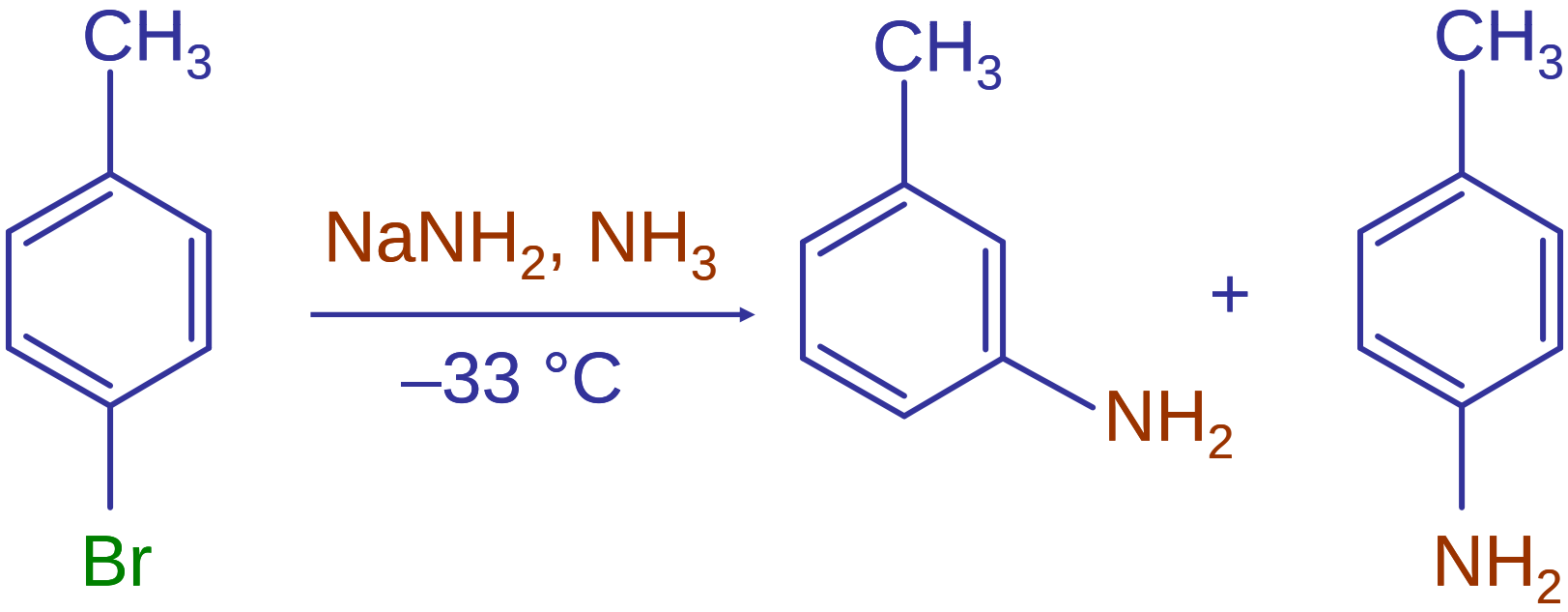
Regiochemistry

➢ New substituent becomes attached to either the carbon that binds to the leaving group or to the carbon adjacent to it.

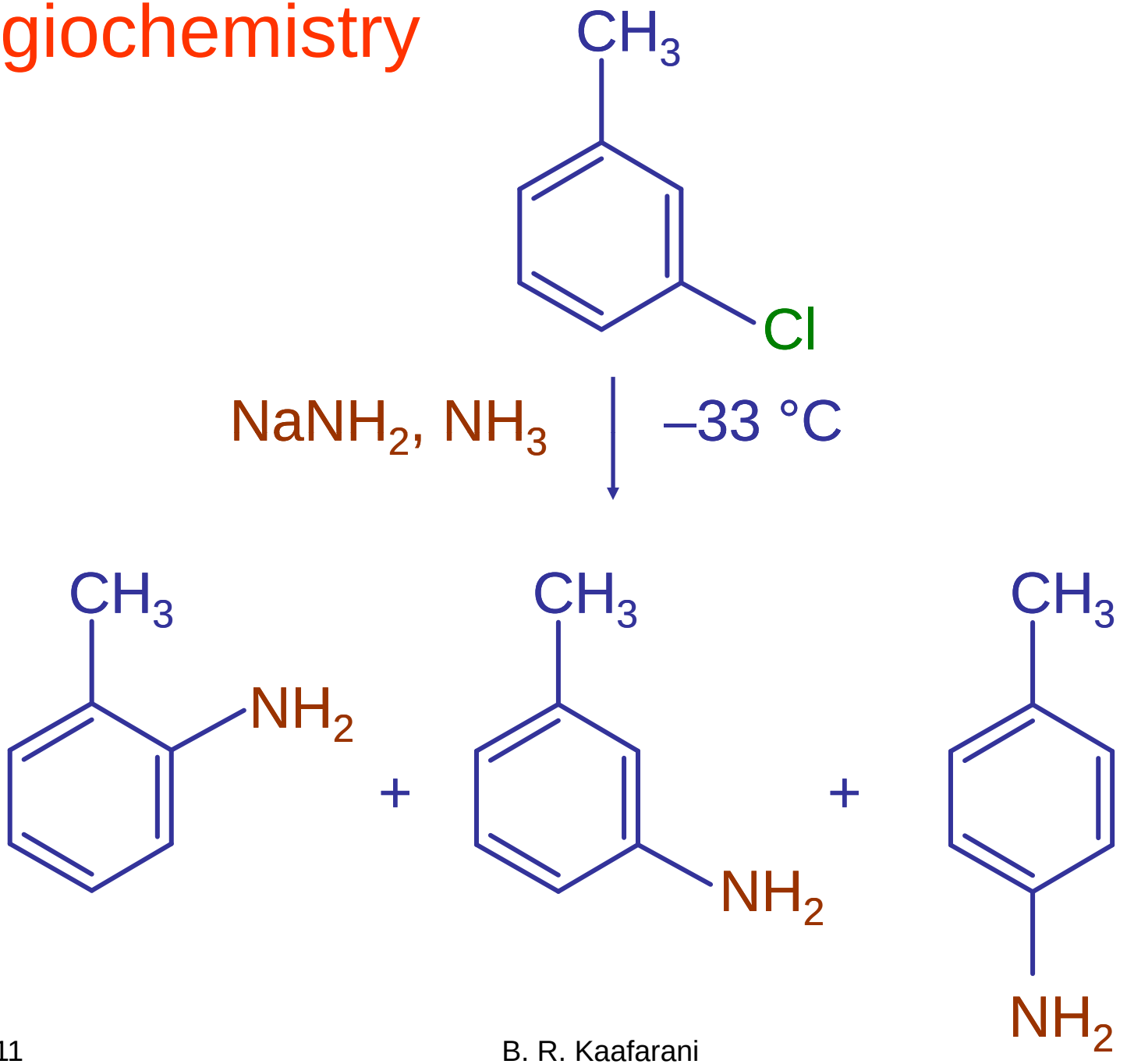


Regiochemistry

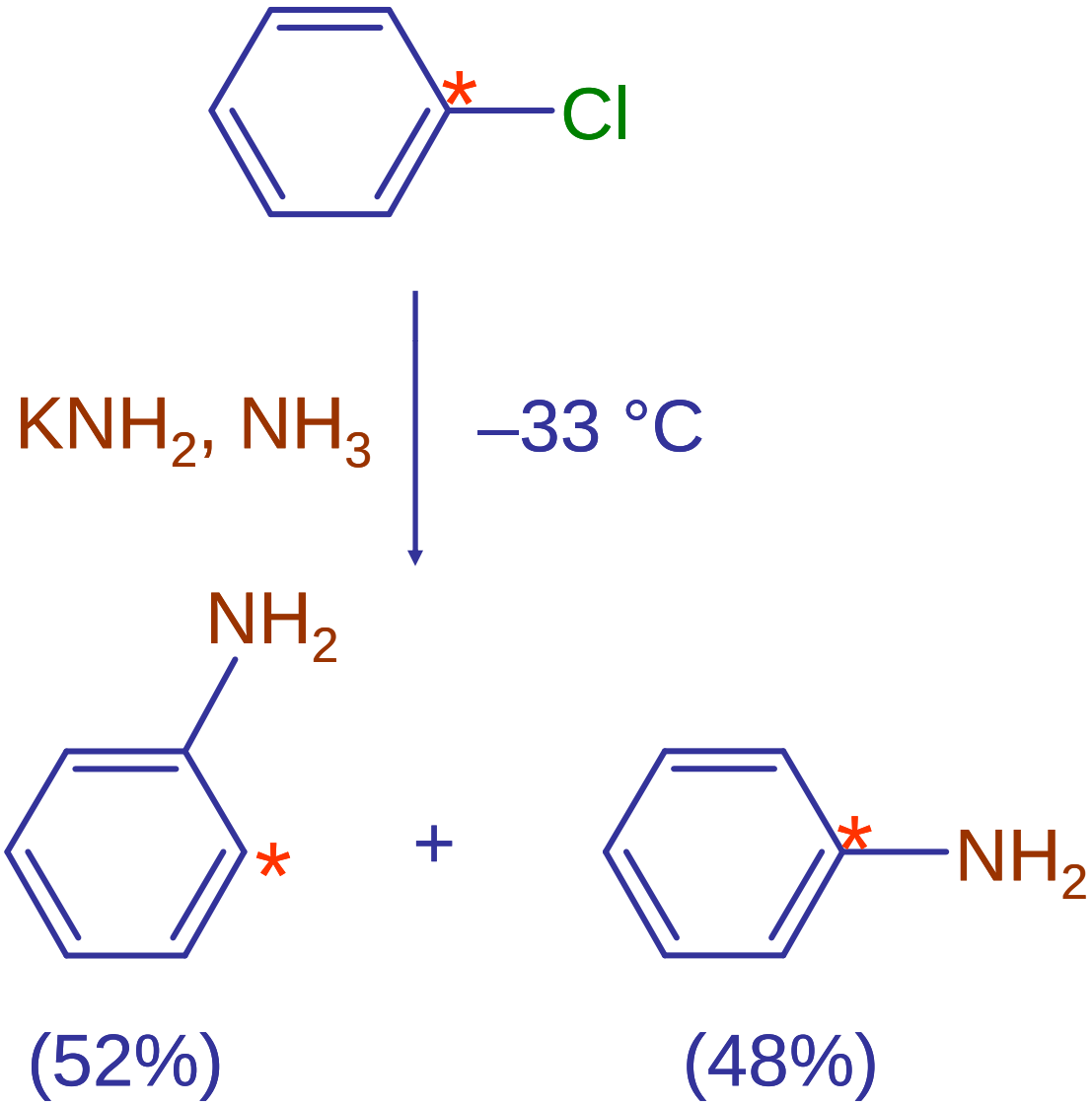
➢ New substituent becomes attached to either the carbon that binds to the leaving group or to the carbon adjacent to it.



Regiochemistry

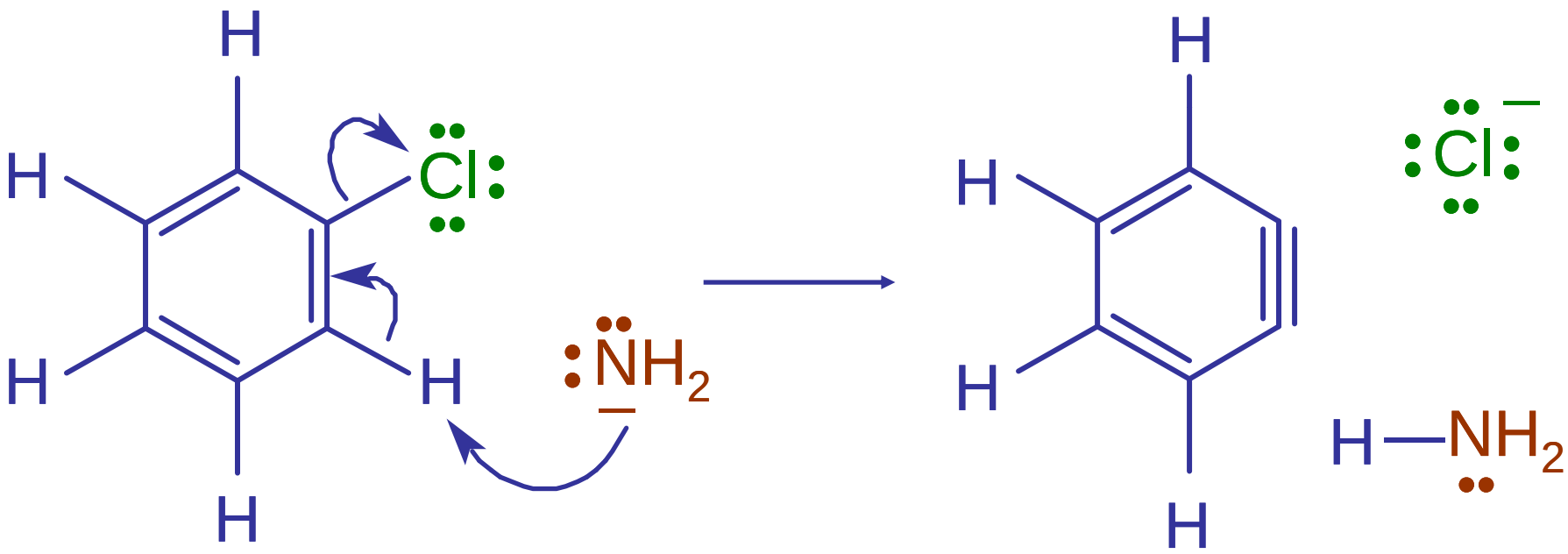


Same result using ^{14}C label



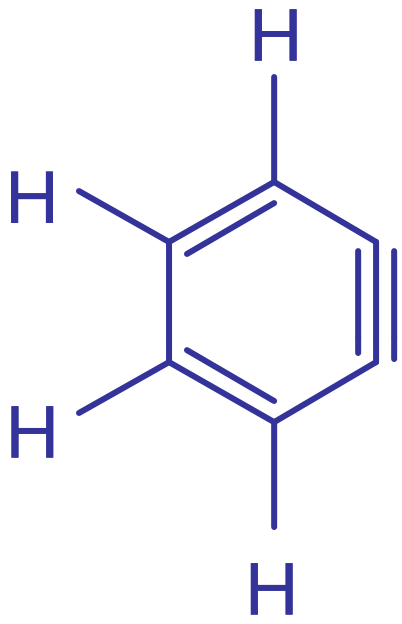
Mechanism

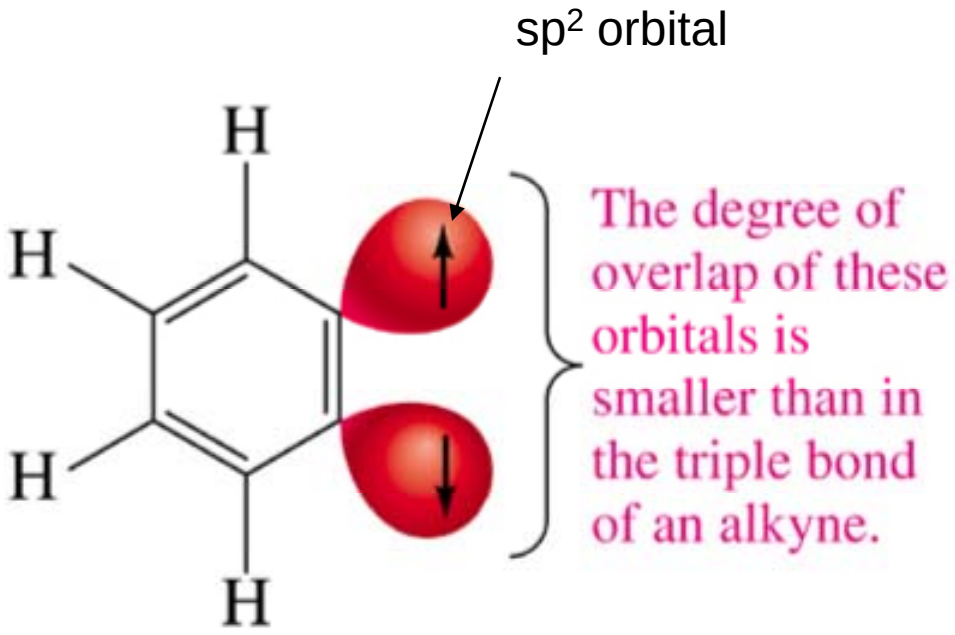
Step 1



- Compound formed in this step is called *benzyne.*

Benzyne

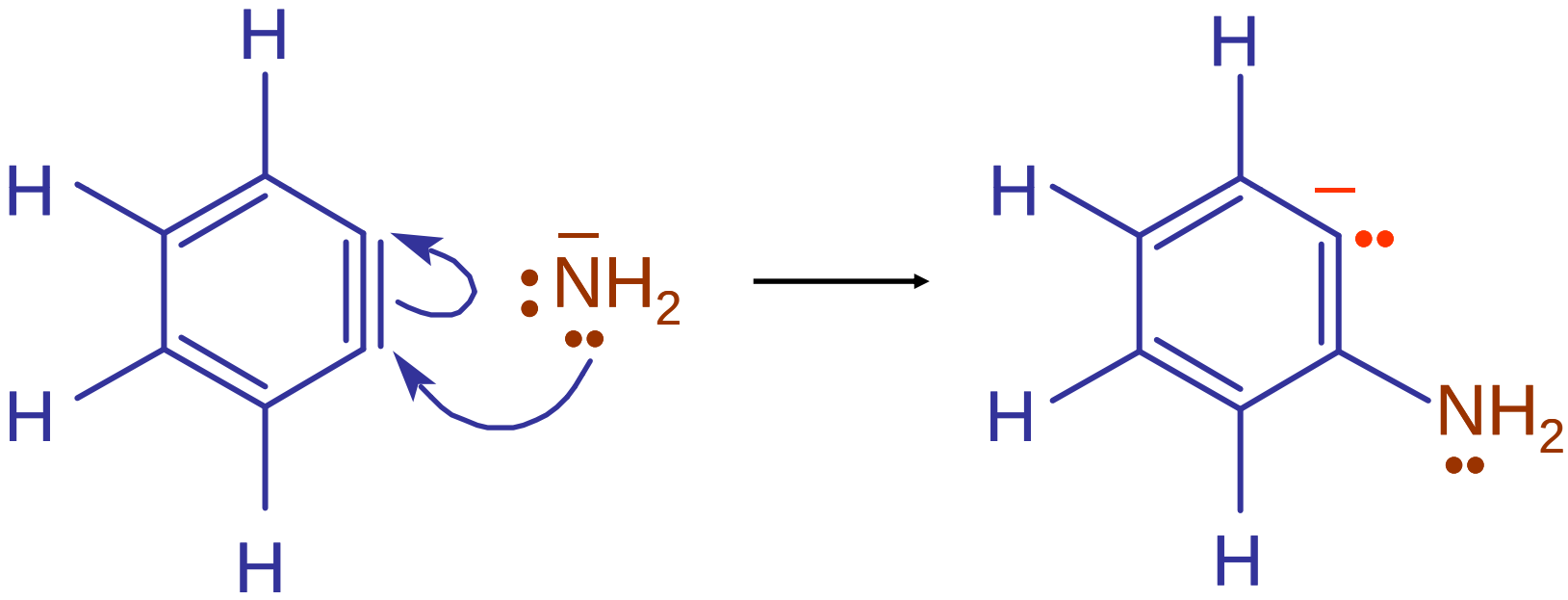




- Benzyne has a strained triple bond.
- It cannot be isolated in this reaction, but is formed as a reactive intermediate.

Mechanism

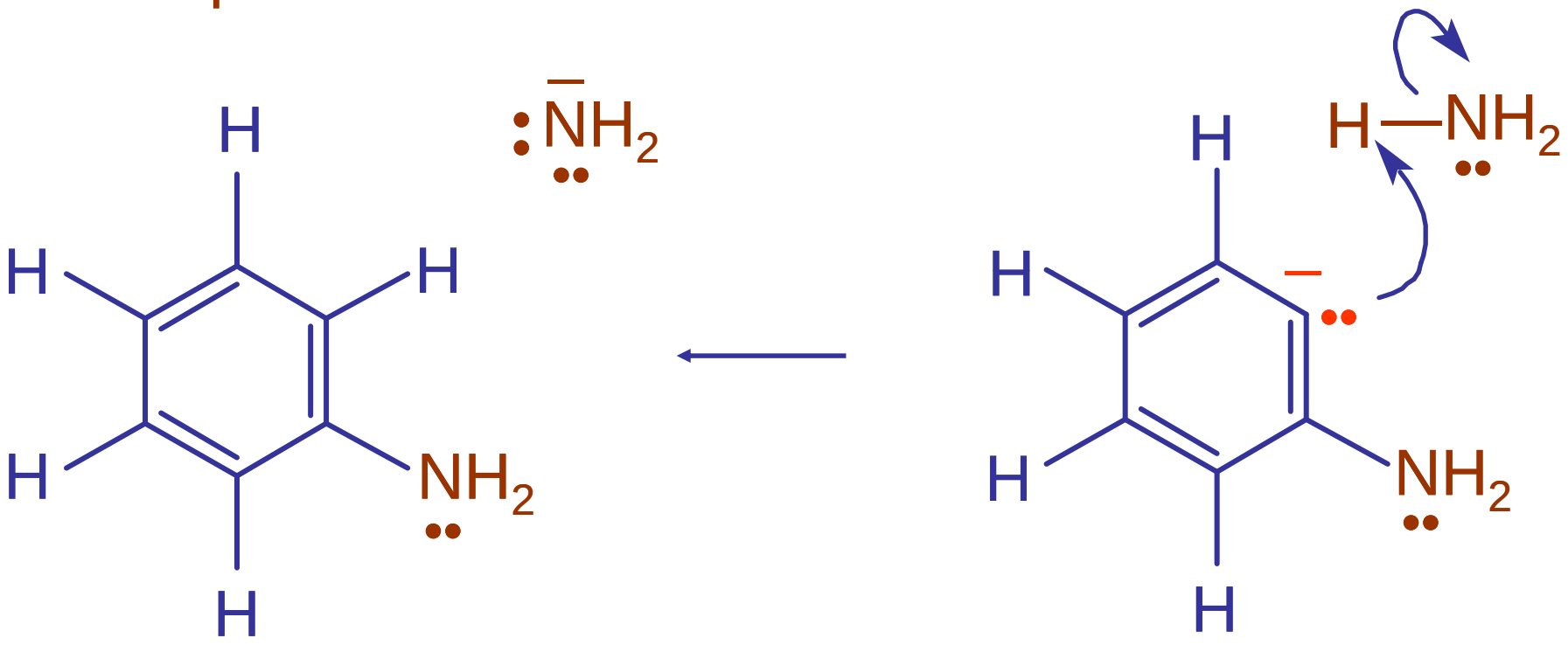
Step 2



- Angle strain is relieved. The two *sp*-hybridized ring carbons in benzyne become sp^2 hybridized in the resulting anion.

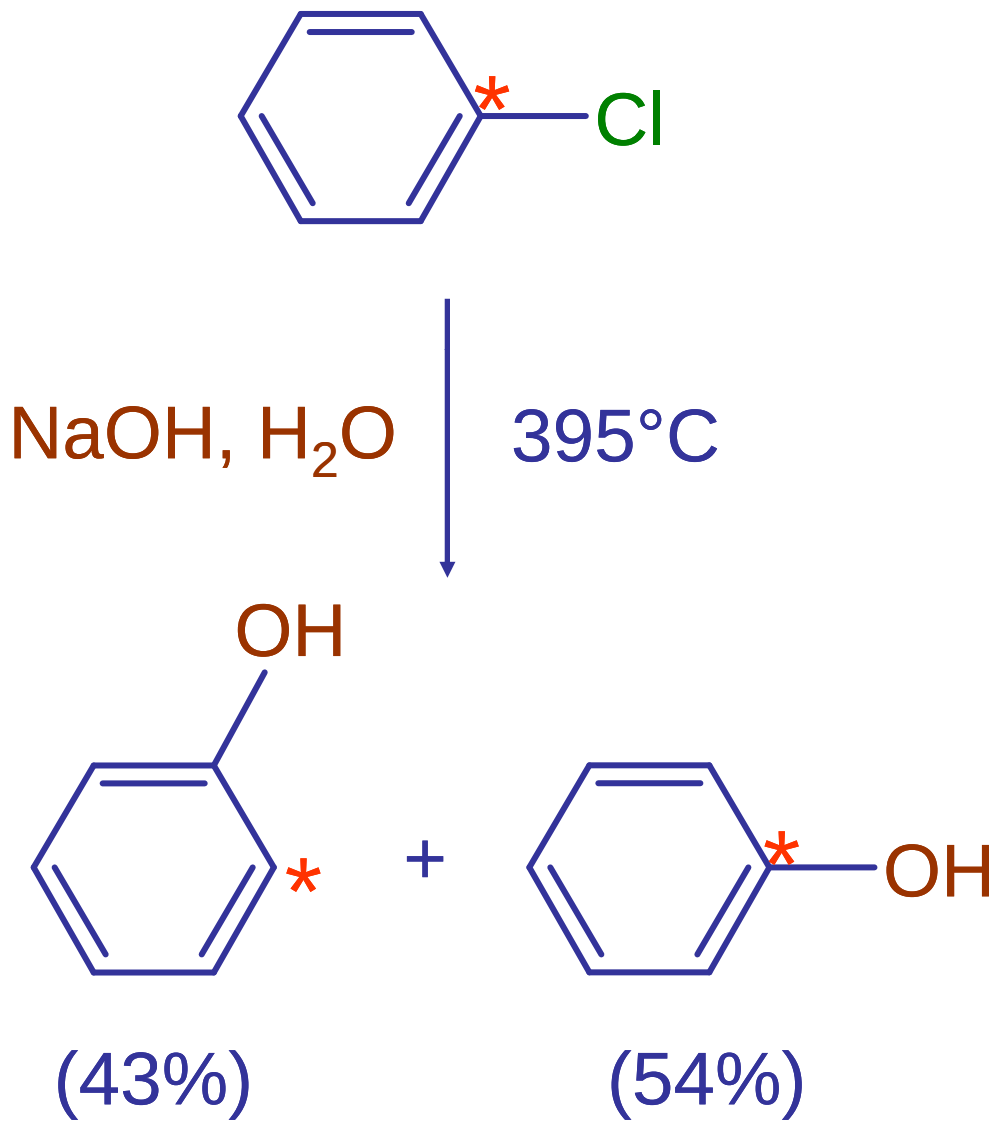
Mechanism

Step 3



Hydrolysis of Chlorobenzene

- ^{14}C labeling indicates that the high-temperature reaction of chlorobenzene with NaOH goes via benzyne.



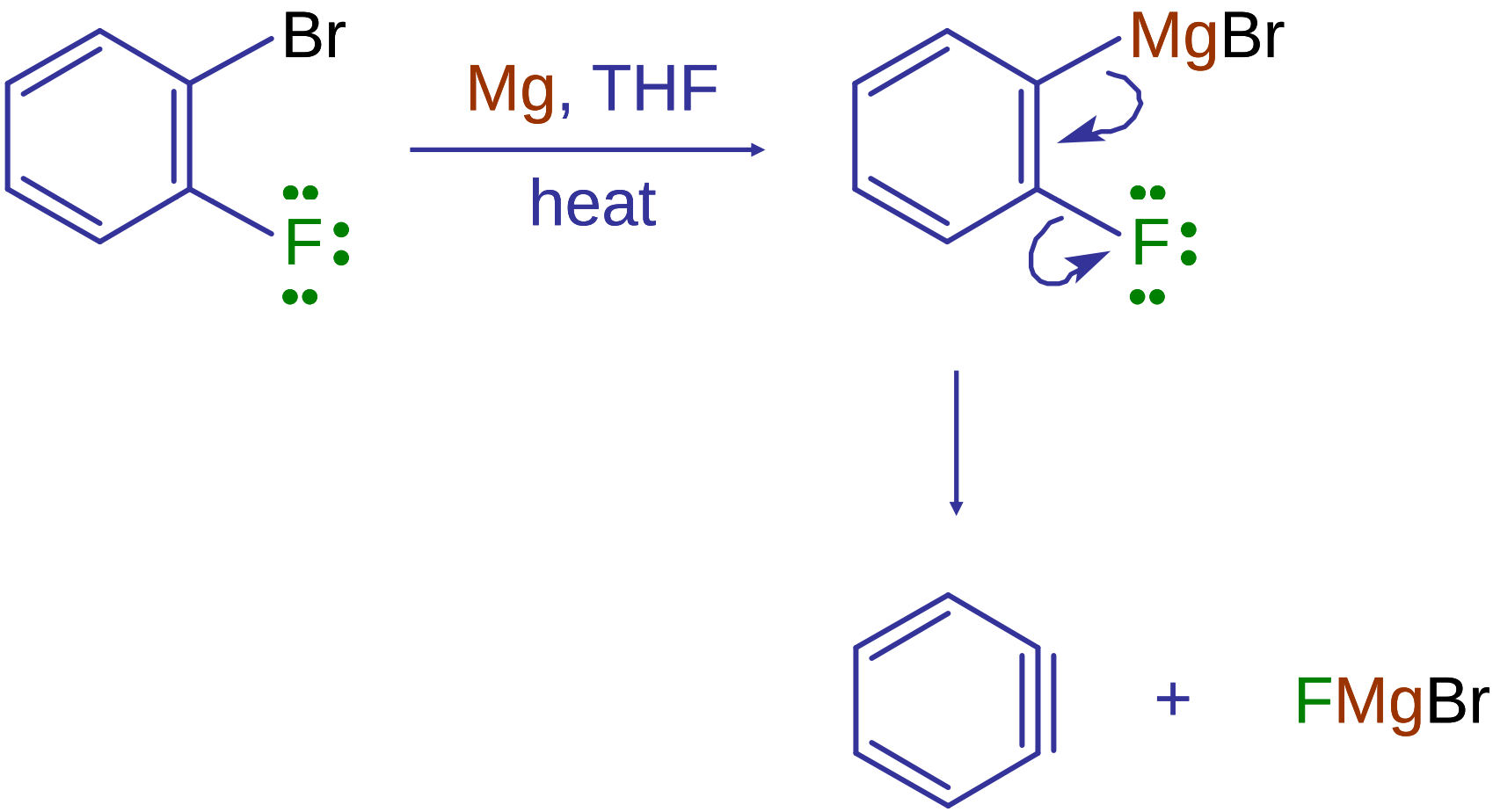
Diels-Alder Reactions of Benzyne

Other Routes to Benzyne

- Benzyne can be prepared as a reactive intermediate by methods other than treatment of chlorobenzene with strong bases.

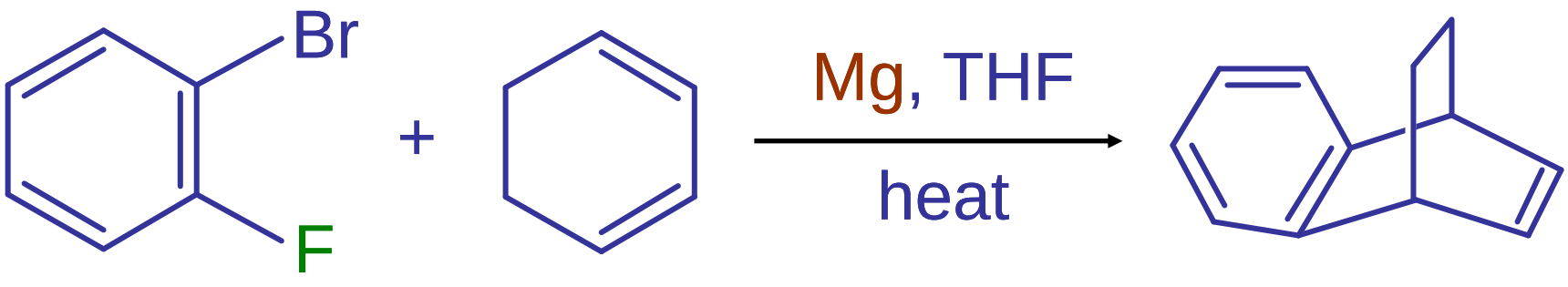
- Another method involves loss of fluoride ion from the Grignard reagent of 1-bromo-2-fluorobenzene.

Other Routes to Benzyne

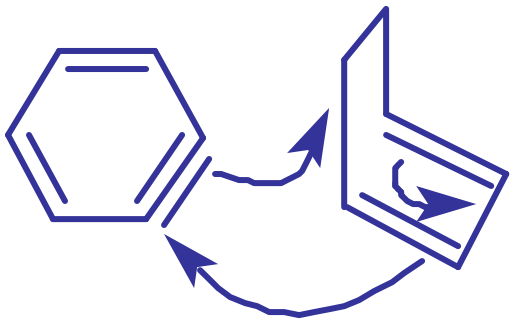


Benzyne as a Dienophile

- Benzyne is a fairly reactive dienophile, and gives Diels-Alder adducts when generated in the presence of conjugated dienes.

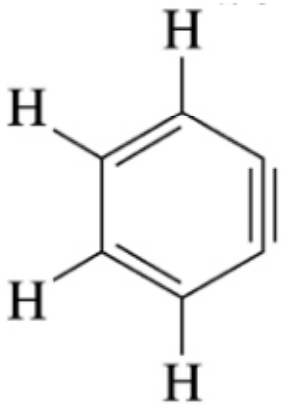


(46%)

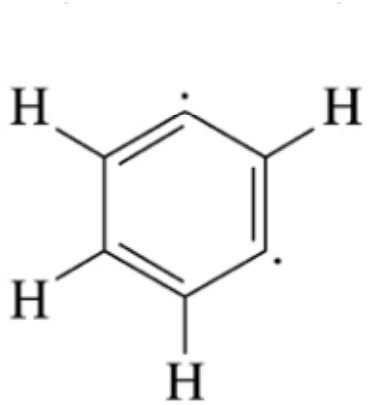


m-Benzyne and *p*-Benzyne

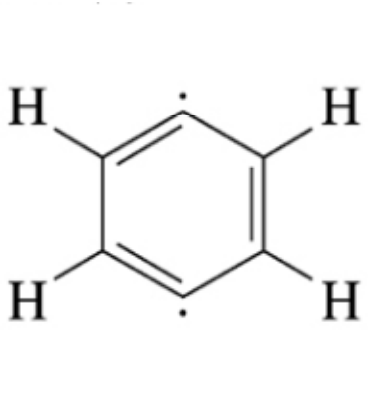
- Benzynes are highly reactive. 1,2-Dehydrobenzene is the most stable in the series compared to 1,3- and 1,4-dehydrobenzene.



1,2-Dehydrobenzene
(*o*-Benzyne)



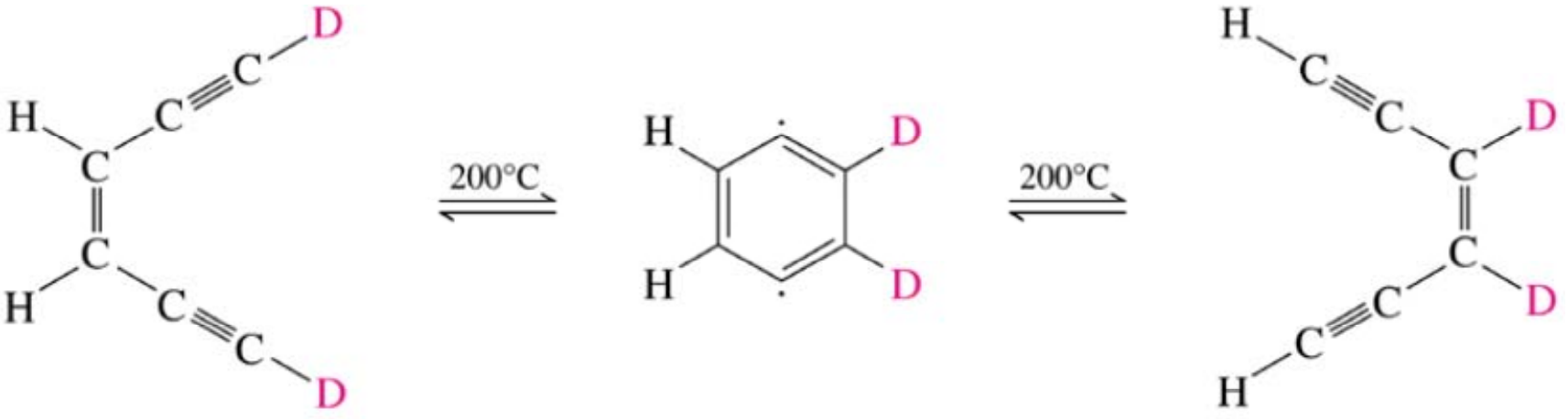
1,3-Dehydrobenzene
(*m*-Benzyne)



1,4-Dehydrobenzene
(*p*-Benzyne)

Dehydrobenzene Intermediate

Bergman Cyclization



1,6-Dideuterio isomer

3,4-Dideuterio isomer

Enediyne antibiotics