

Reactions of Aromatic Compounds 1 - Monosubstitution

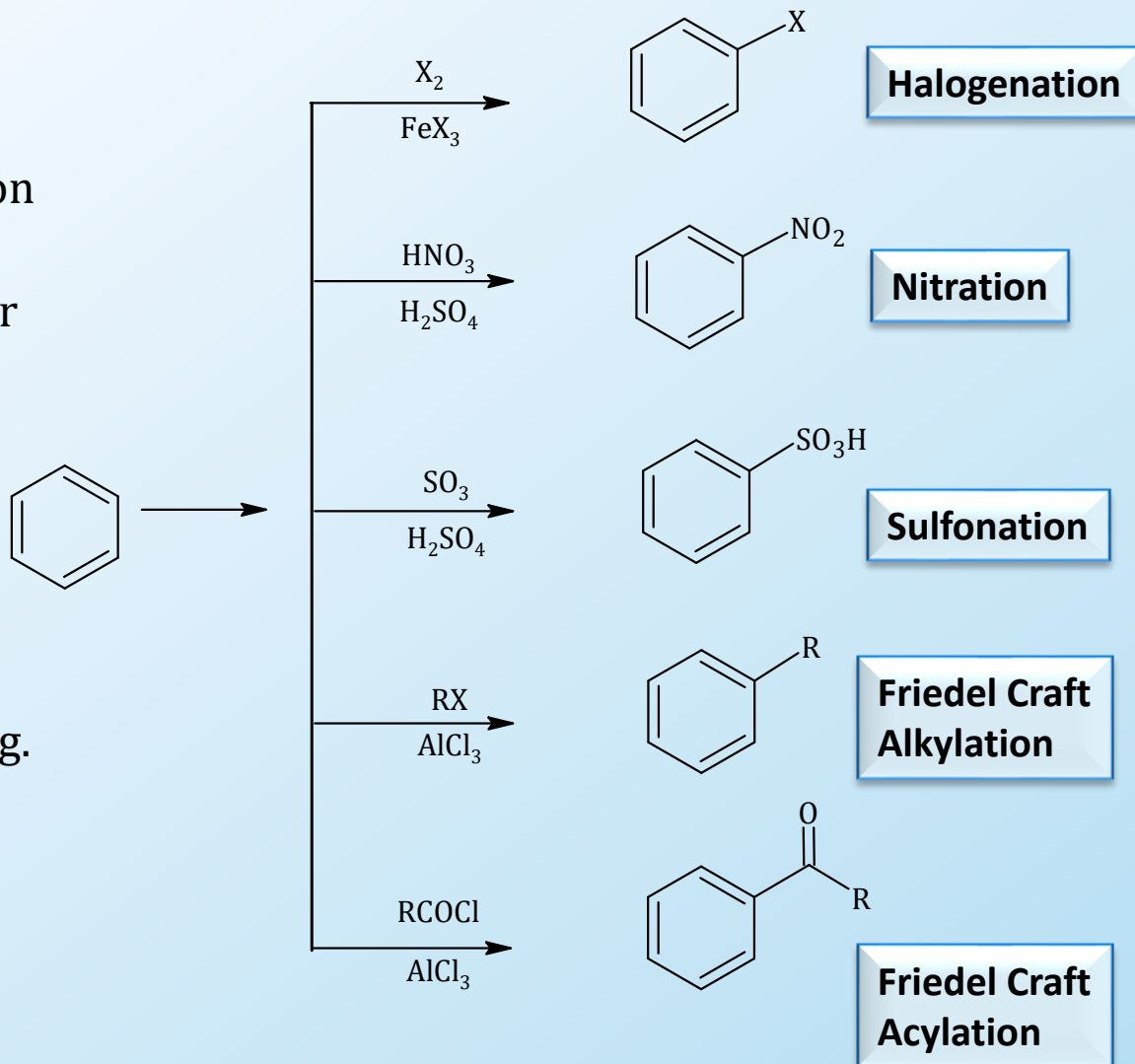
Dr. Sapna Gupta

Electrophilic Aromatic Substitution

Aromatic compounds undergo electrophilic aromatic substitution (EAS)

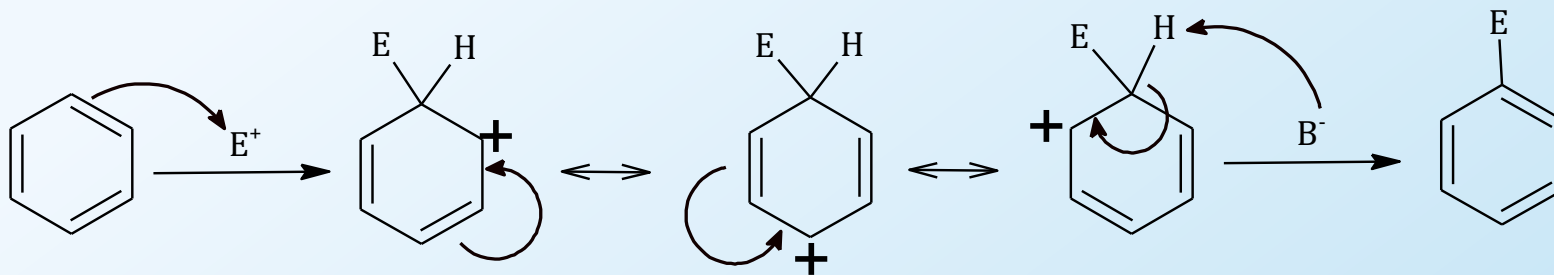
- The electrophile has a full or partial positive charge
- The benzene ring is the nucleophile.

We will cover all the reactions shown on the right. These are all monosubstitution of benzene ring.



General Mechanism

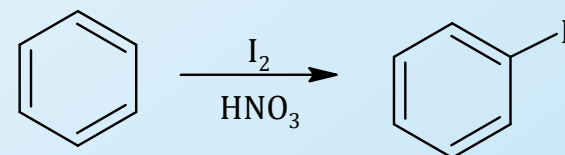
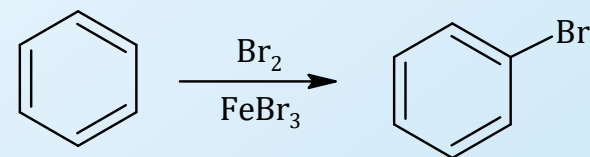
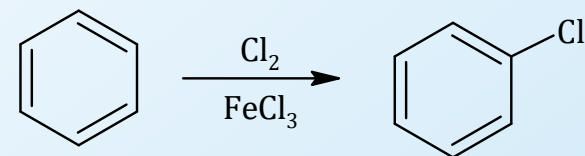
Regardless of the electrophile used, all electrophilic aromatic substitution reactions occur by the same two-step mechanism—addition of the electrophile E^+ to form a resonance-stabilized carbocation, followed by deprotonation with base, as shown below:



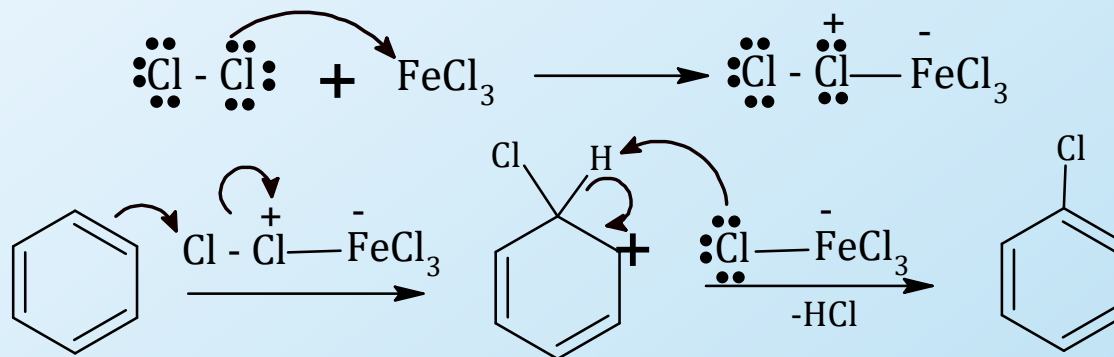
Halogenation of Benzene

Halogenation of benzene requires the presence of a Lewis acid which is generally the iron halide using the same halide as the halogenation needed.

- Fluorination occurs so rapidly it is hard to stop at monofluorination of the ring.
- Iodine is so unreactive that a strong acid must be used for the reaction.

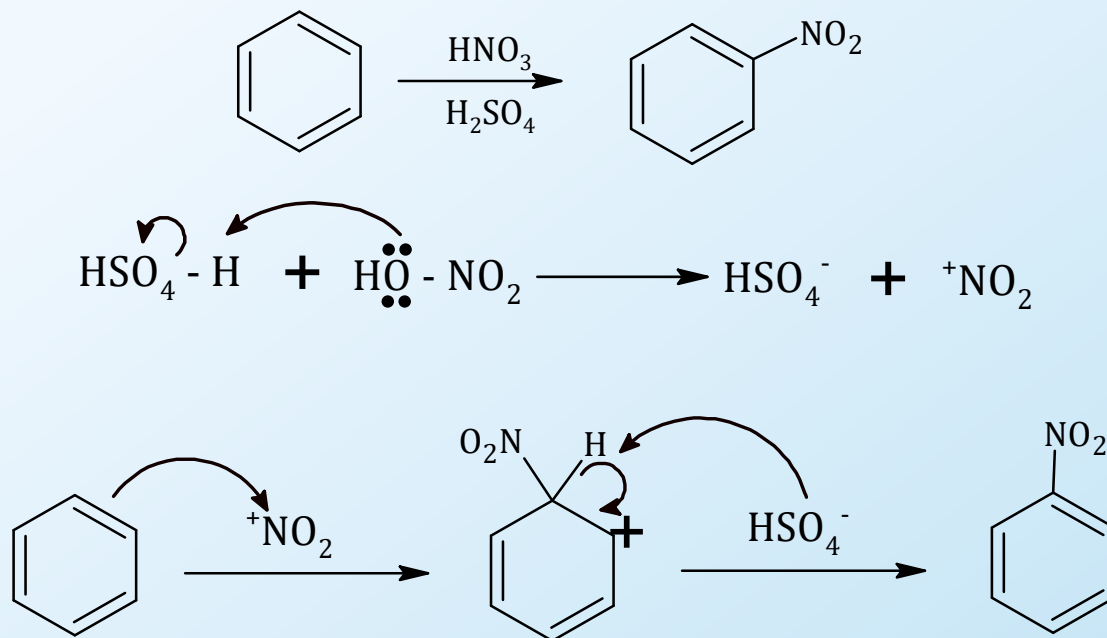


Mechanism of halogenation involves 1) forming the electrophile (Cl^+) using the Lewis acid, 2) the benzene (Nu^-) attacking the Cl^+ and lastly 3) aromaticity is restored by the conjugate base picking up a proton. The catalyst is also regenerated in this step.



Nitration of Benzene

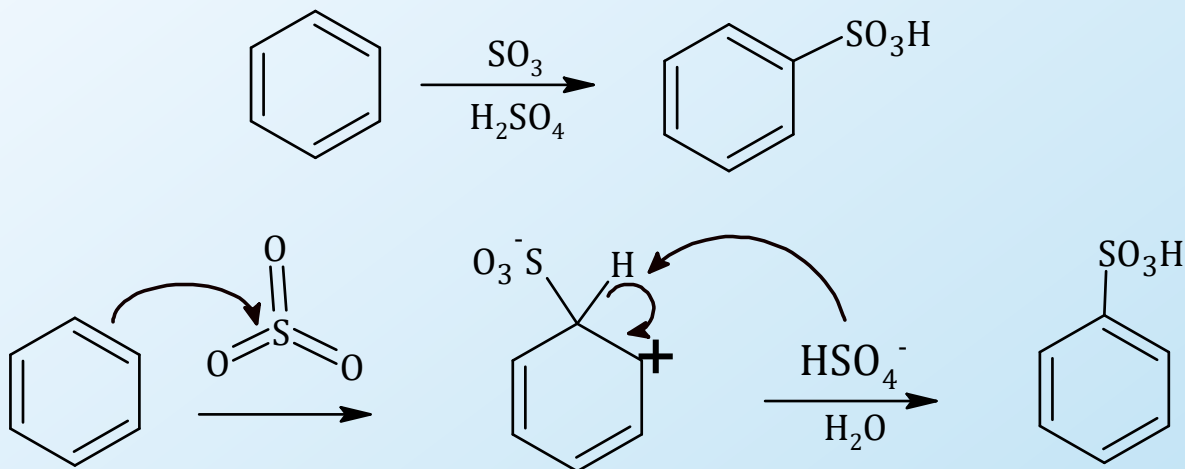
Nitration of benzene occurs with a mixture of concentrated nitric and sulfuric acids. Sulfuric acid is the catalyst that helps to generate the electrophile, the nitronium ion (NO_2^+)



Sulfonation of Benzene

Sulfonation occurs most rapidly using fuming sulfuric acid (concentrated sulfuric acid that contains SO_3). The reaction also occurs in conc. sulfuric acid, which generates small quantities of SO_3 , as shown in step 1 below

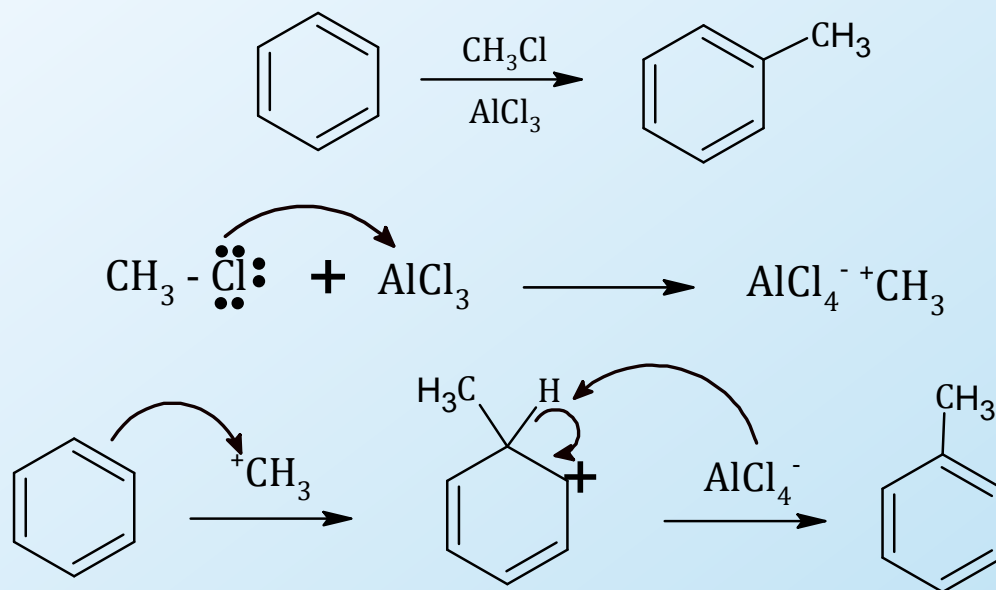
- Sulfonation is an equilibrium reaction; all steps involved are equilibria.
- Sulfonation is favored by using concentrated or fuming sulfuric acid.
- Desulfonation can be accomplished using dilute sulfuric acid (*i.e.* with a high concentration of water).



Friedel-Craft Alkylation

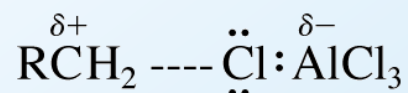
An aromatic ring can be alkylated by an alkyl halide in the presence of a Lewis acid. The Lewis acid serves to generate a carbocation electrophile. This reaction was discovered by Charles Friedel and James Craft in 1877 to add substituents to the benzene ring. Friedel Craft (FC) reaction is a great way of making a C-C bond.

An alkyl halide is used to react with AlCl_3 to generate an electrophile, a carbocation which then reacts with benzene.

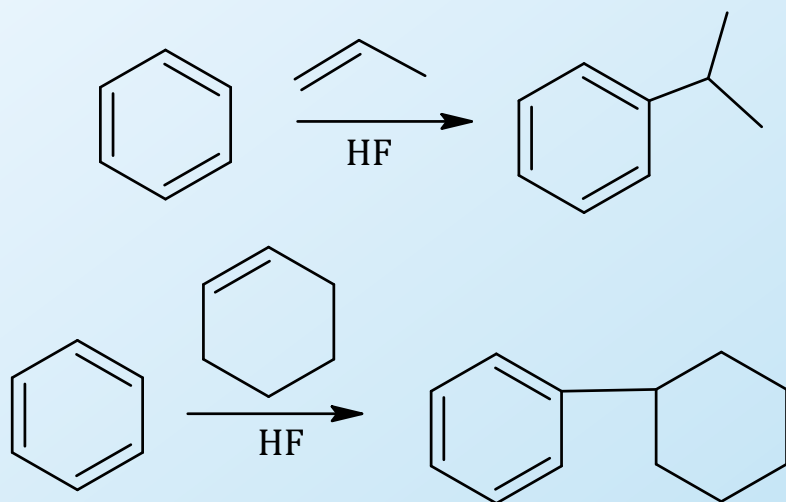


Friedel-Craft Alkylation, contd...

Primary alkyl halides probably do not form discrete carbocations since they are not stable, but the primary carbon in the alkyl group, e.g., methyl and ethyl develops considerable positive charge

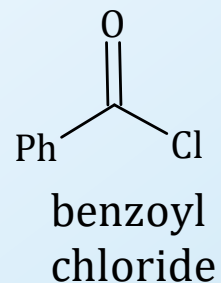
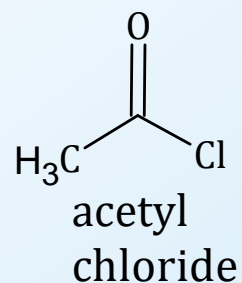
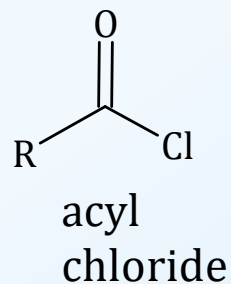


Any compound that can form a carbocation can be used to alkylate an aromatic ring. Alkenes react with benzene where hydrofluoric acid is used as a catalyst.

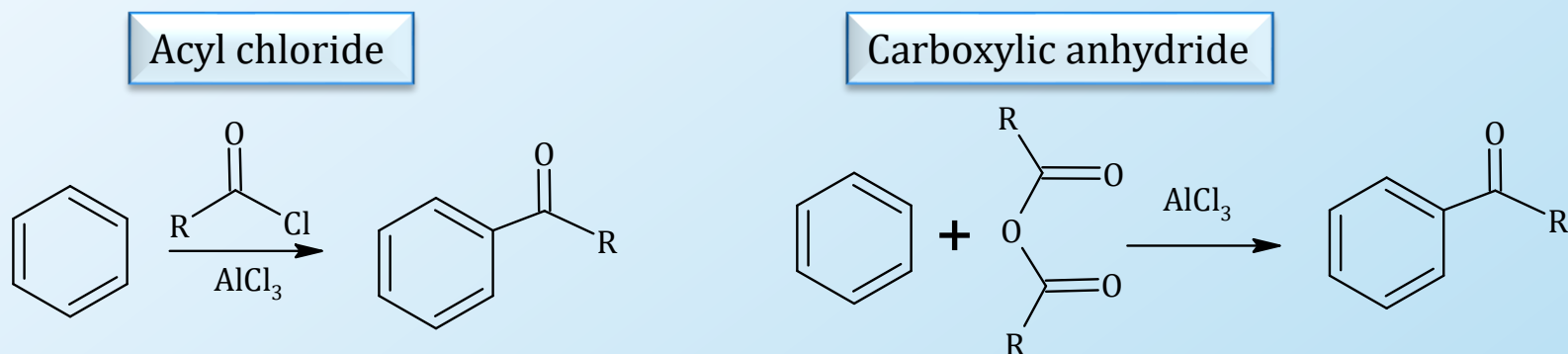


Friedel-Craft Acylation

In FC acylation an acyl group can be substituted on the benzene. An acyl group has a carbonyl (-C=O) attached to some R group. If it is CH₃, the group is called acetyl chloride, if benzene, then benzoyl.

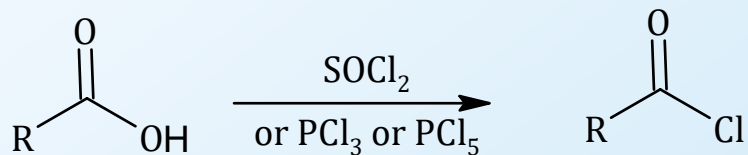


Friedel-Crafts acylation requires reaction of an acid chloride or acid anhydride with a Lewis acid such as aluminum chloride.

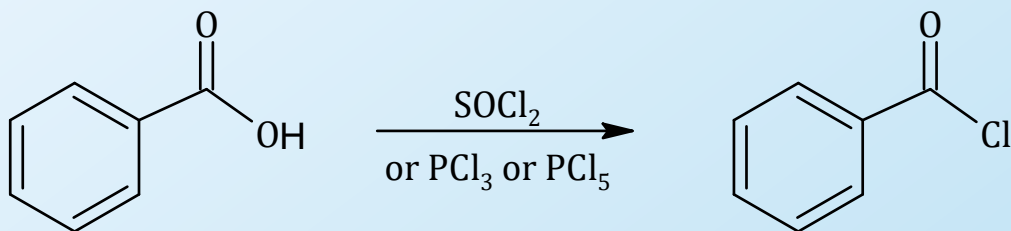
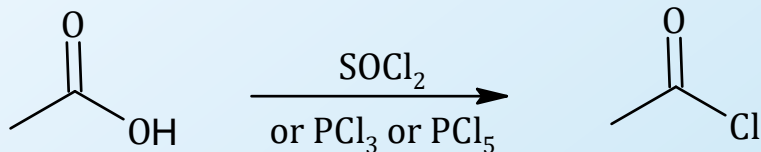


Formation of Acyl Chlorides

Acid chlorides are made from carboxylic acids and thionyl chloride, phosphorous pentachloride or phosphorous trichloride.

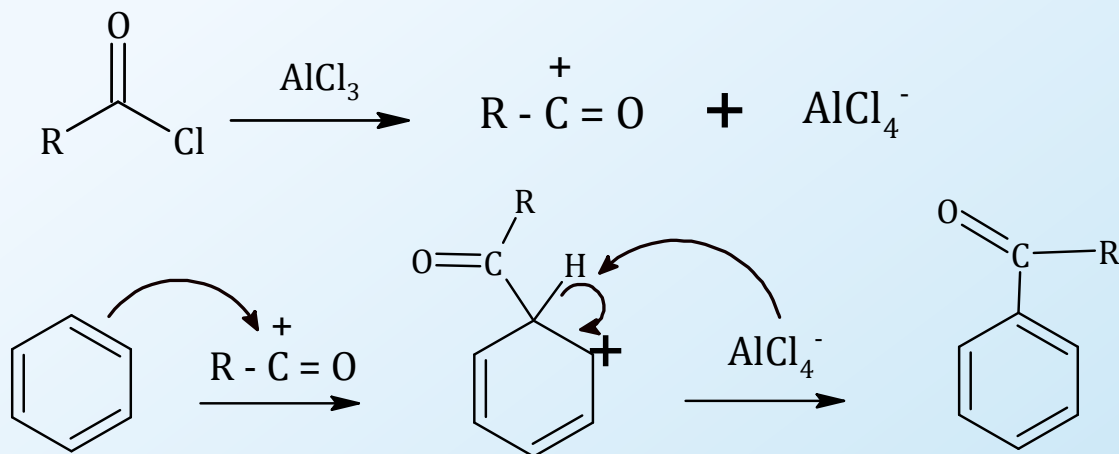


Examples:



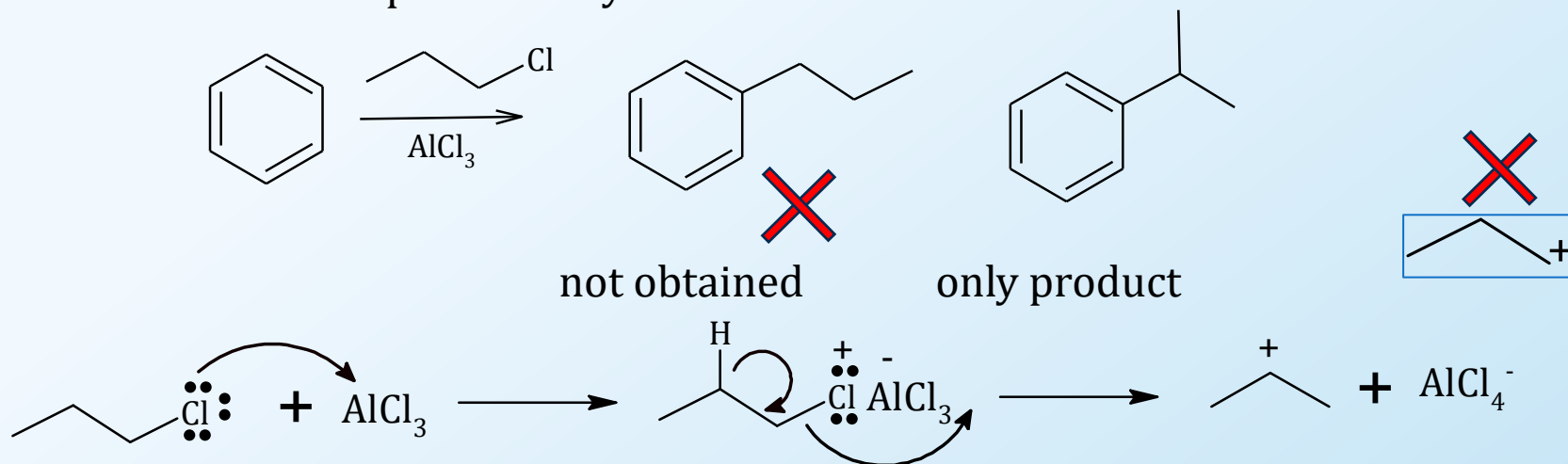
Friedel-Craft Acylation Mechanism

The electrophile in Friedel-Crafts acylation is an acylium ion which is generated by the reaction of acyl chloride and aluminum chloride. The product of the acylation is a ketone.

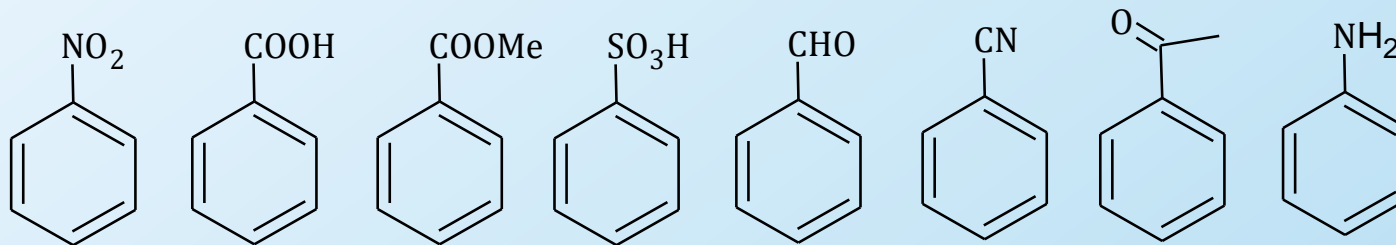


Limitations of Friedel-Craft Reaction

- 1) In FC alkylation, the alkyl carbocation intermediate may rearrange to a more stable carbocation prior to alkylation.

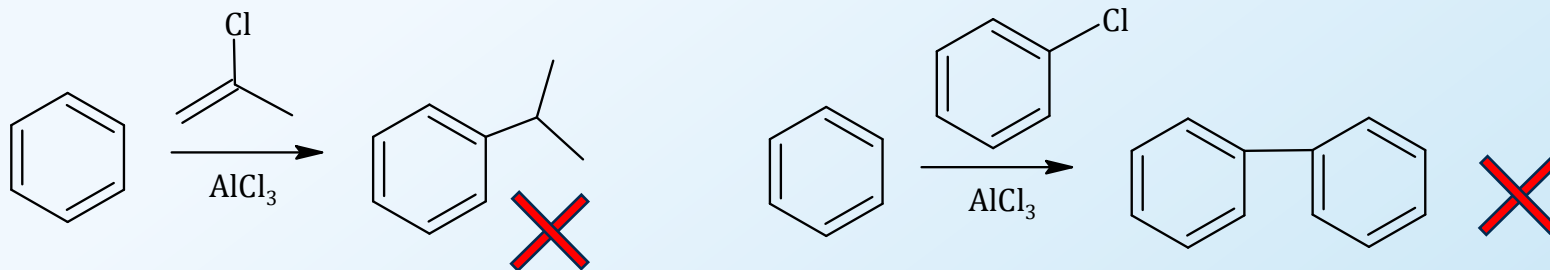


- 2) Powerful electron-withdrawing groups make an aromatic ring much less reactive toward Friedel-Crafts alkylation or acylation. Amino groups also make the ring less reactive to Friedel-Crafts reaction because they become electron-withdrawing groups upon Lewis acid-base reaction with the Lewis acid catalyst.

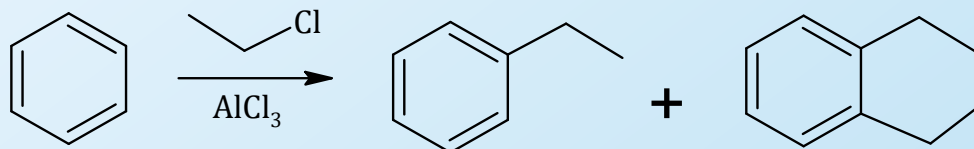


Limitations of Friedel-Craft Reaction

3) Aryl and vinyl halides cannot be used in Friedel-Crafts reactions because they themselves are nucleophilic/electron rich.



4) Polyalkylation occurs frequently with Friedel-Crafts alkylation because the first alkyl group introduced activates the ring toward further substitution. Polyacylation does not occur because the acyl group deactivates the aromatic ring to further substitution.



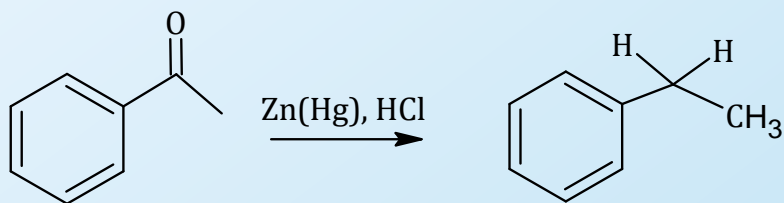
Synthetic Applications of FC-Acylation

Long chain primary alkyl halides carbocation intermediates yield rearranged products in Friedel-Crafts alkylation which is a major limitation of this reaction. This problem can be eliminated by first carrying out the acylation and then reducing the ketone (C=O) to give methylene (CH₂) group.

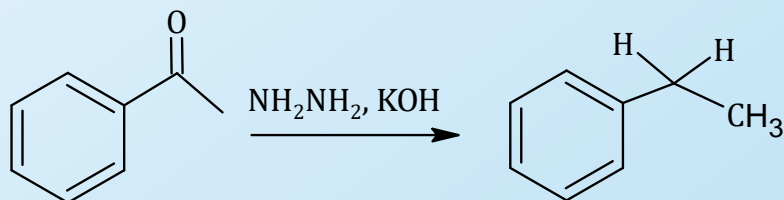
The two reductions commonly used are given below. See next slide for a practical example.

1. The **Clemmensen reduction**— uses zinc and mercury in the presence of strong acid.
2. The **Wolff-Kishner reduction**—uses hydrazine (NH₂NH₂) and strong base (KOH).

**Clemmensen
Reduction**

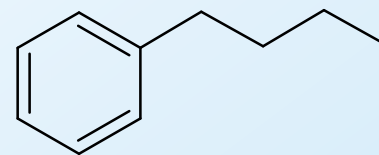


**Wolff-Kishner
Reduction**

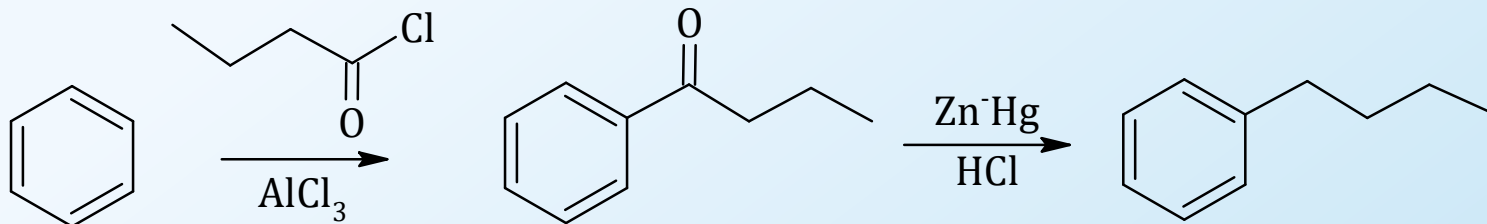


Worked Example

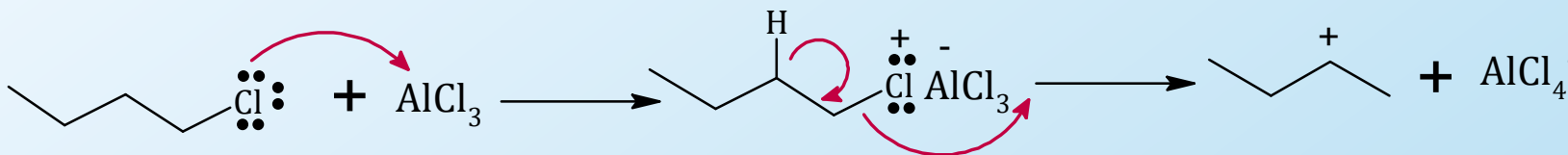
Carry out the following synthesis using appropriate reagents and any organic substances needed.



Answer: We are substituting a long chain alkyl group on benzene. The first step is to make the acylated ring and then reduce it.

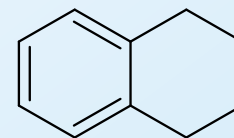


If alkylation was carried out using 1-bromobutane, then rearrangement will occur and sec-butyl benzene will form instead of n-butyl benzene.

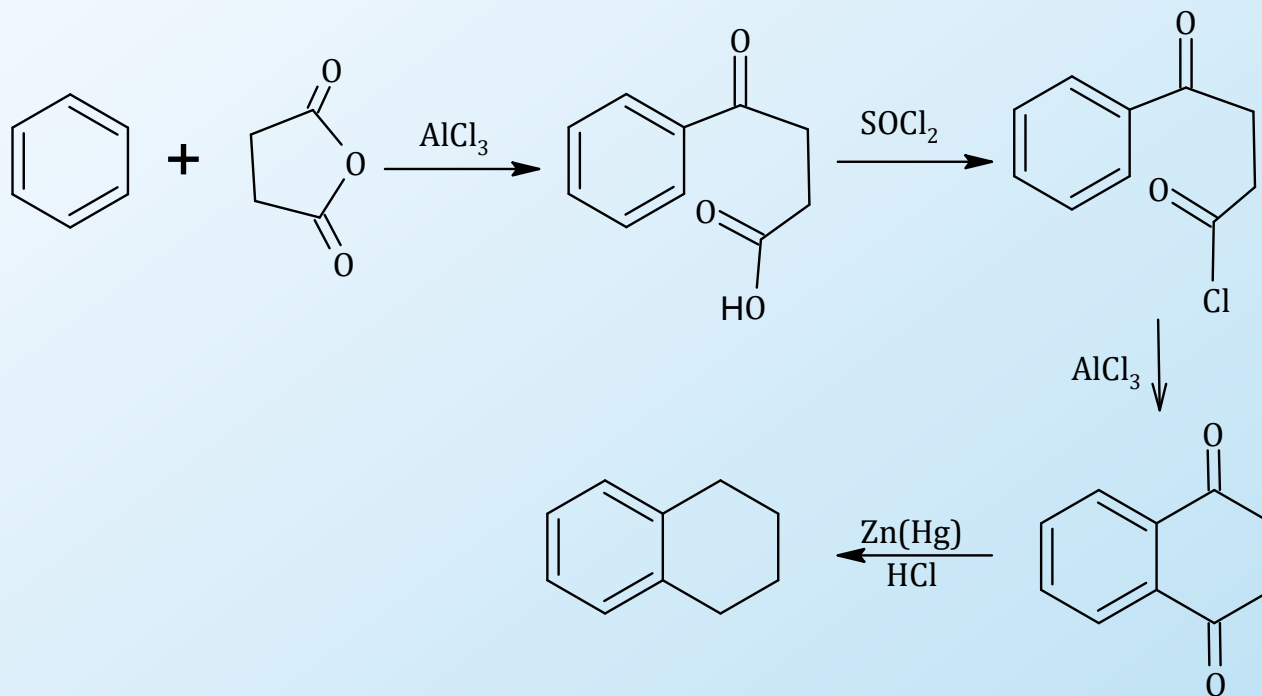


Worked Example

Carry out the following synthesis using appropriate reagents and any organic substances needed.

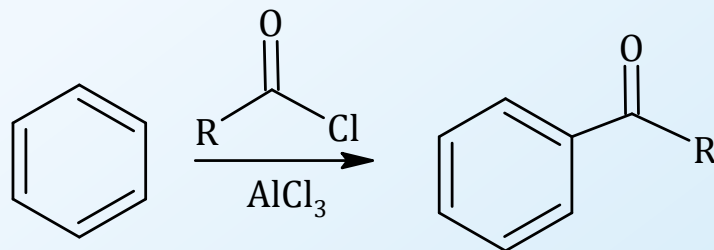


Answer: We are fusing a ring onto benzene by adding 4 carbons. The best way would be to use Friedel Craft reaction using a cyclic anhydride so we will have an acid functional group to carry out the ring fusion in the later steps.. (*Note that the Clemmensen reagents do not reduce the carboxylic acid*).

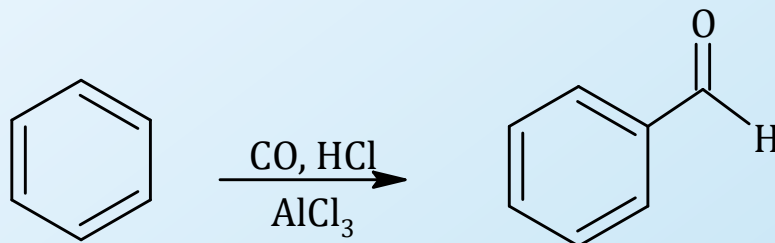


Gatterman Koch Synthesis

This reaction is similar to Friedal Craft synthesis but is used to synthesize benzaldehyde.



To make benzaldehyde, R has to be H. But HCOCl is not stable enough to exist, so it is generated in situ from HCl and CO. The reaction still requires a Lewis acid, aluminum chloride.



Key Concepts

- Electrophilic substitution
- Nitration
- Sulfonation
- Friedel Craft Alkylation
- Friedel Craft Acylation
- Drawbacks of FC alkylation
- Synthetic applications