

# ORGANIC CHEMISTRY II

College of Pharmacy  
2nd Stage/1st semester



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Pharmacognosist

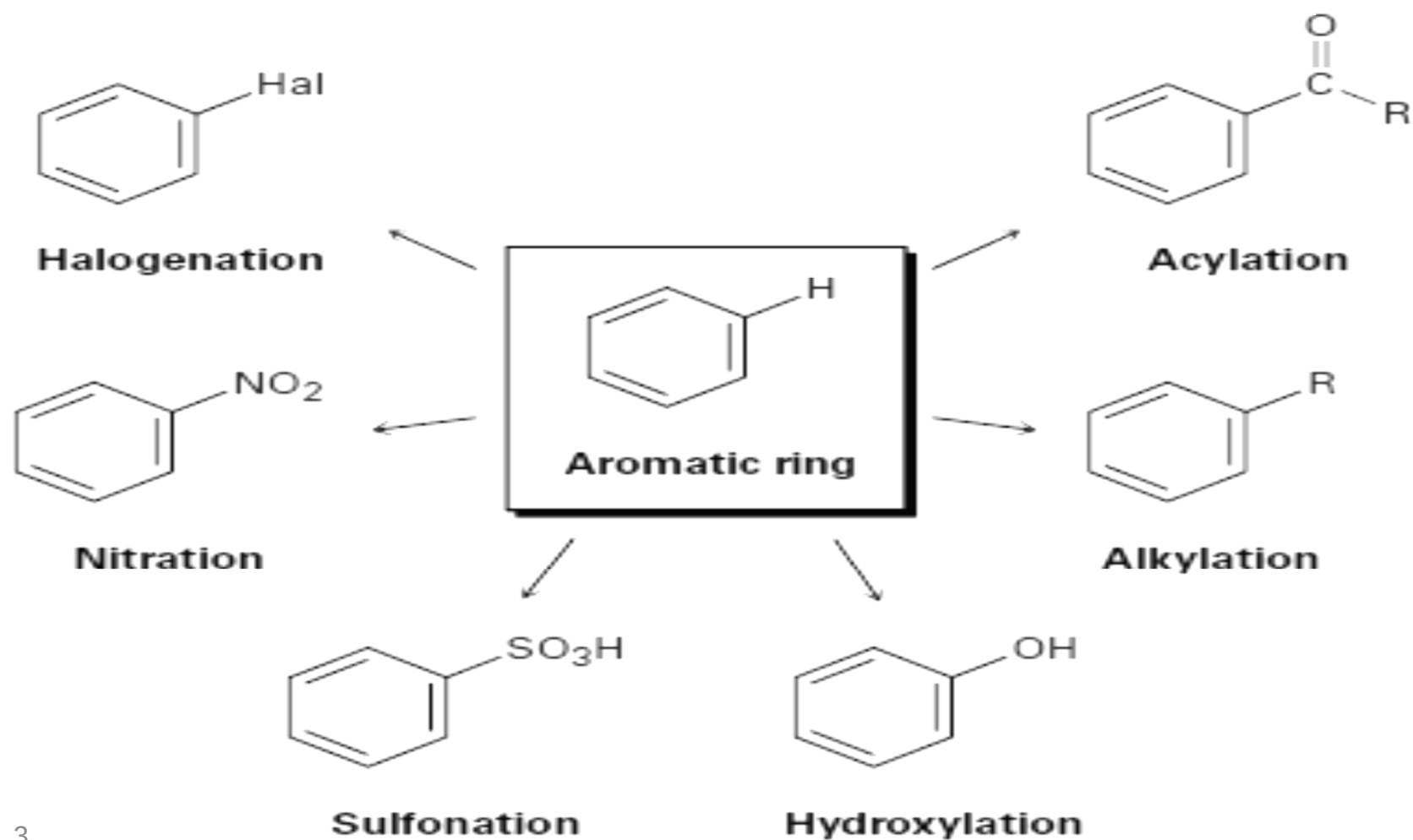
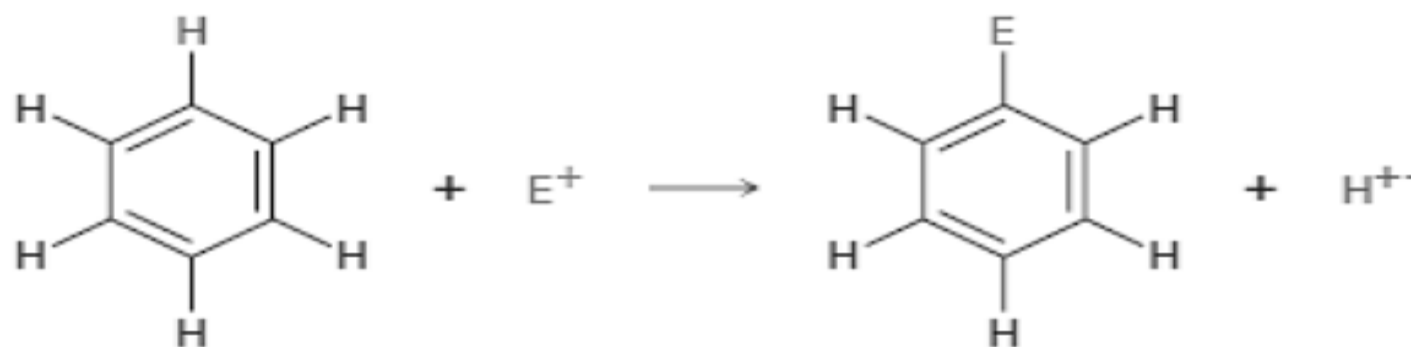
# Reaction of Aromatic Compounds

The most common reaction of aromatic compounds is electrophilic aromatic substitution, in which an electrophile ( $E^+$ ) reacts with an aromatic ring and substitutes for one of the hydrogens. The reaction is characteristic of all aromatic rings, not just benzene and substituted benzenes. In fact, the ability of a compound to undergo electrophilic substitution is a good test of aromaticity.

Many different substituents can be introduced onto an aromatic ring through electrophilic substitution reactions.

1. Halogen ( Cl, Br, I)
2. nitro group (  $NO_2$ ),
3. a sulfonic acid group (  $SO_3H$ ),
4. a hydroxyl group ( OH),
5. an alkyl group ( R),
6. an acyl group ( COR).

**Note** :Starting from only a few simple materials, it's possible to prepare many thousands of substituted aromatic compounds.



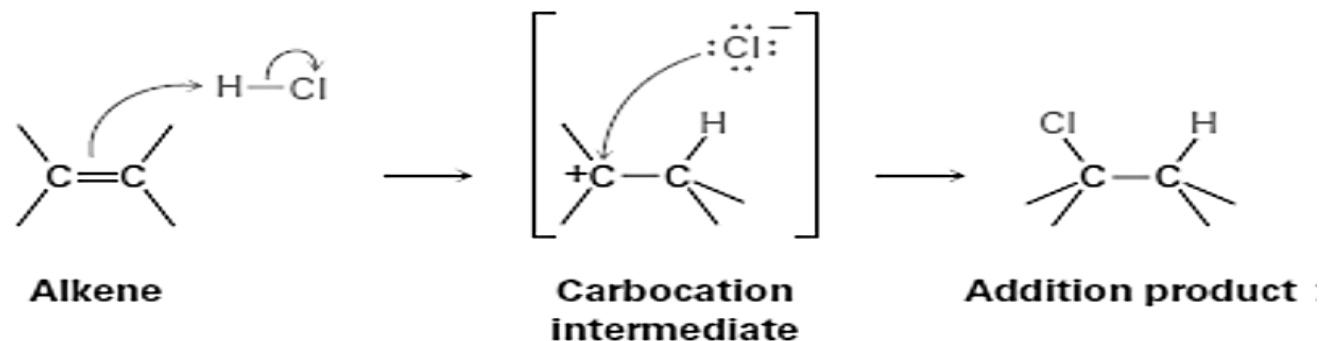
# Substitution Reactions

## 1. Bromination

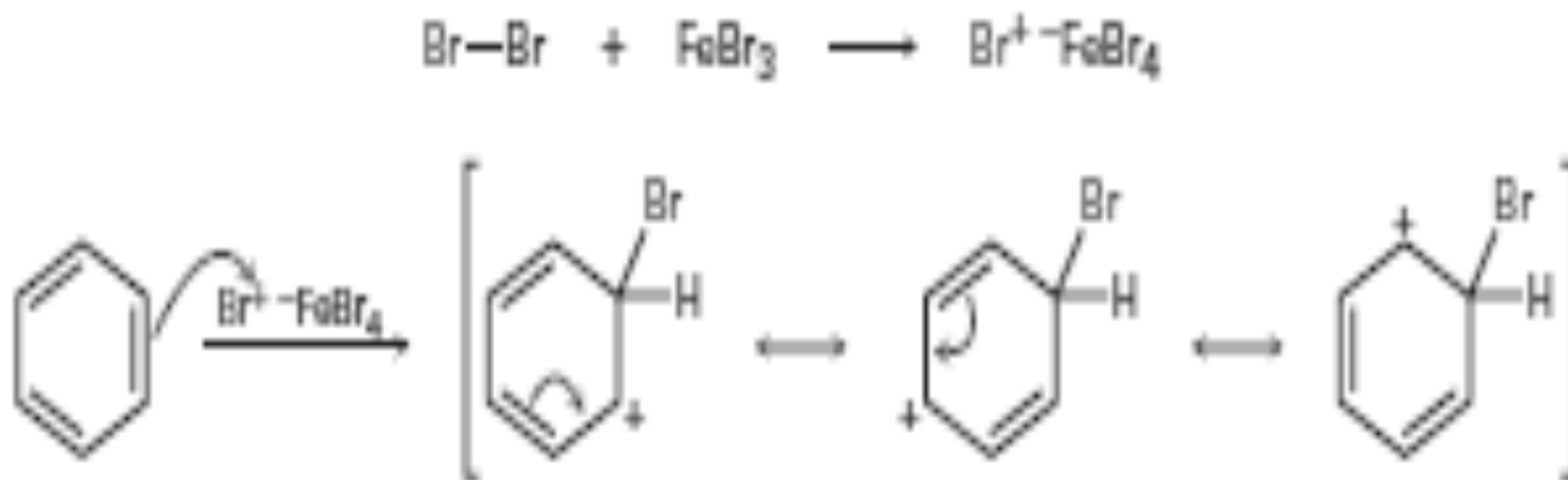
When a reagent such as HCl adds to an alkene, the electrophilic hydrogen approaches the pair of electrons of the double bond and forms a bond to one carbon, leaving a positive charge at the other carbon. This carbocation intermediate then reacts with the nucleophilic Cl<sup>-</sup> ion to yield the addition product.

An electrophilic aromatic substitution reaction begins in a similar way, but there are a number of differences.

1. Aromatic rings are less reactive toward electrophiles than alkenes are. For example, Br<sub>2</sub> reacts instantly with most alkenes but does not react with benzene at room temperature.



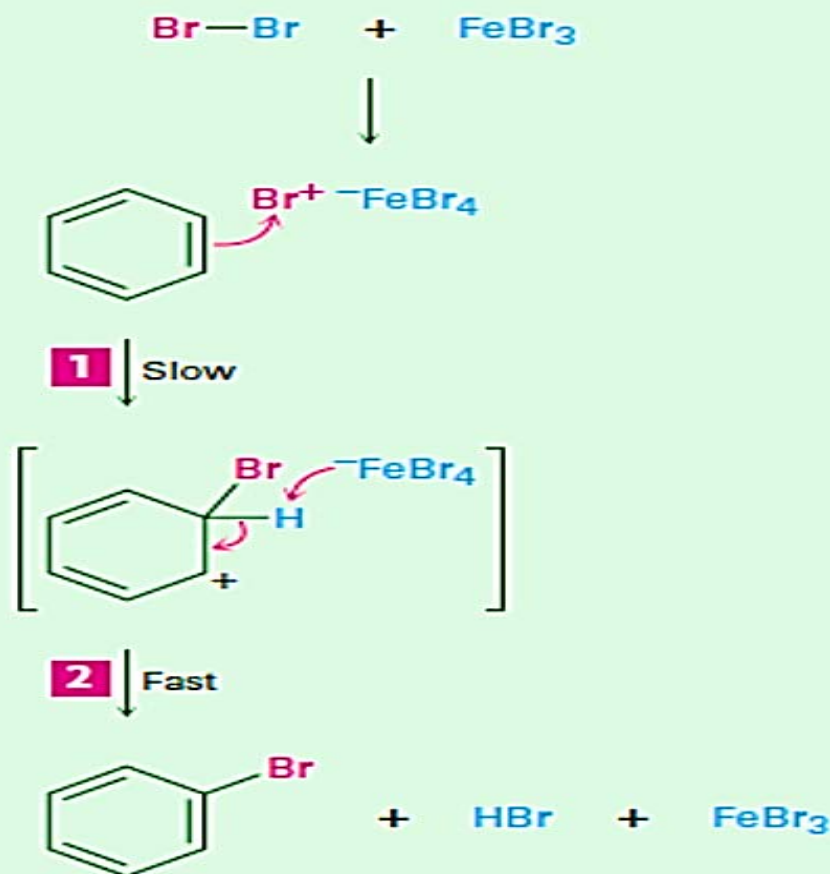
For bromination of benzene to take place, a catalyst such as  $\text{FeBr}_3$  is needed. The catalyst makes the  $\text{Br}_2$  molecule more electrophilic to give an  $\text{FeBr}_4\text{Br}^+$ .  $\text{Br}_2$  molecule then reacts with the nucleophilic benzene ring to yield a nonaromatic carbocation intermediate that has three resonance forms.



2. Another difference between alkene addition and aromatic substitution occurs after the carbocation intermediate has formed. Instead of adding Br<sub>2</sub> to give an addition product, the carbocation intermediate loses H<sup>+</sup> from the bromine-bearing carbon to give a substitution product. Note that this loss of H<sup>+</sup> is similar to what occurs in the second step of an E1 reaction.

**1** An electron pair from the benzene ring attacks the positively polarized bromine, forming a new C–Br bond and leaving a nonaromatic carbocation intermediate.

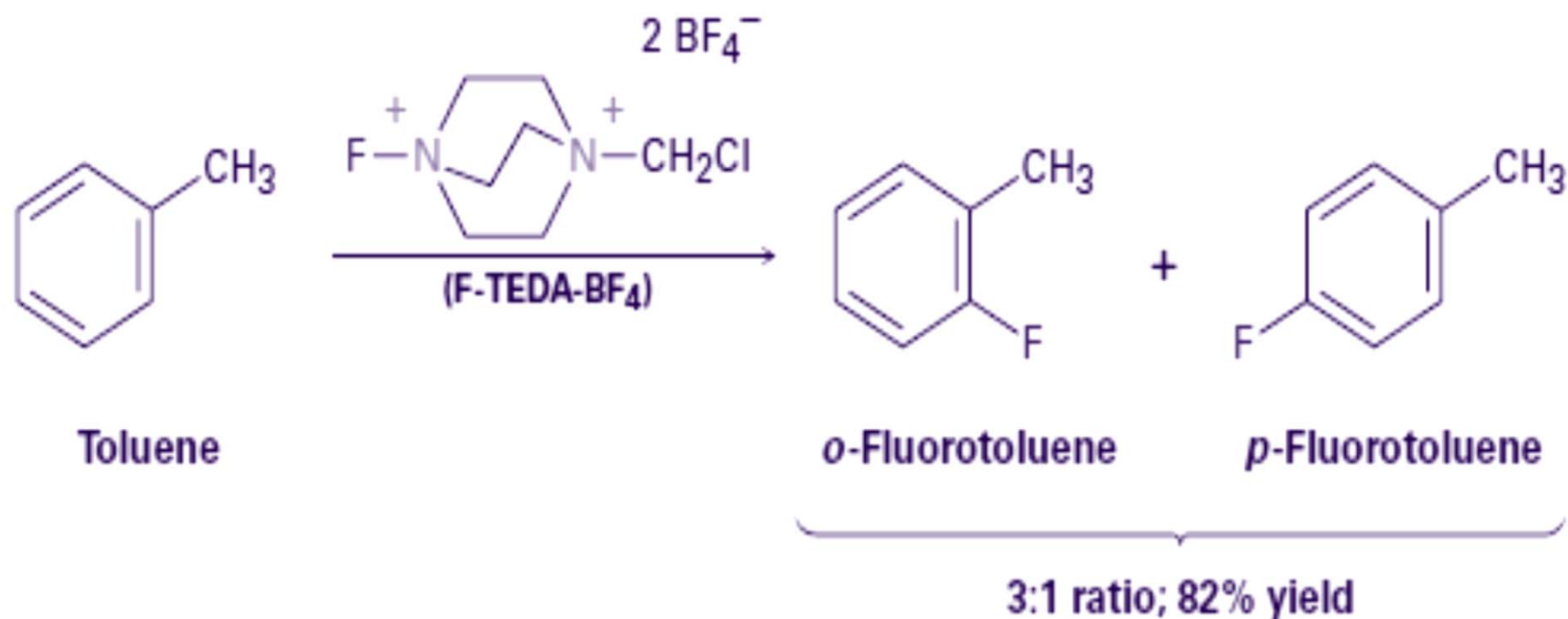
**2** A base removes H<sup>+</sup> from the carbocation intermediate, and the neutral substitution product forms as two electrons from the C–H bond move to re-form the aromatic ring.



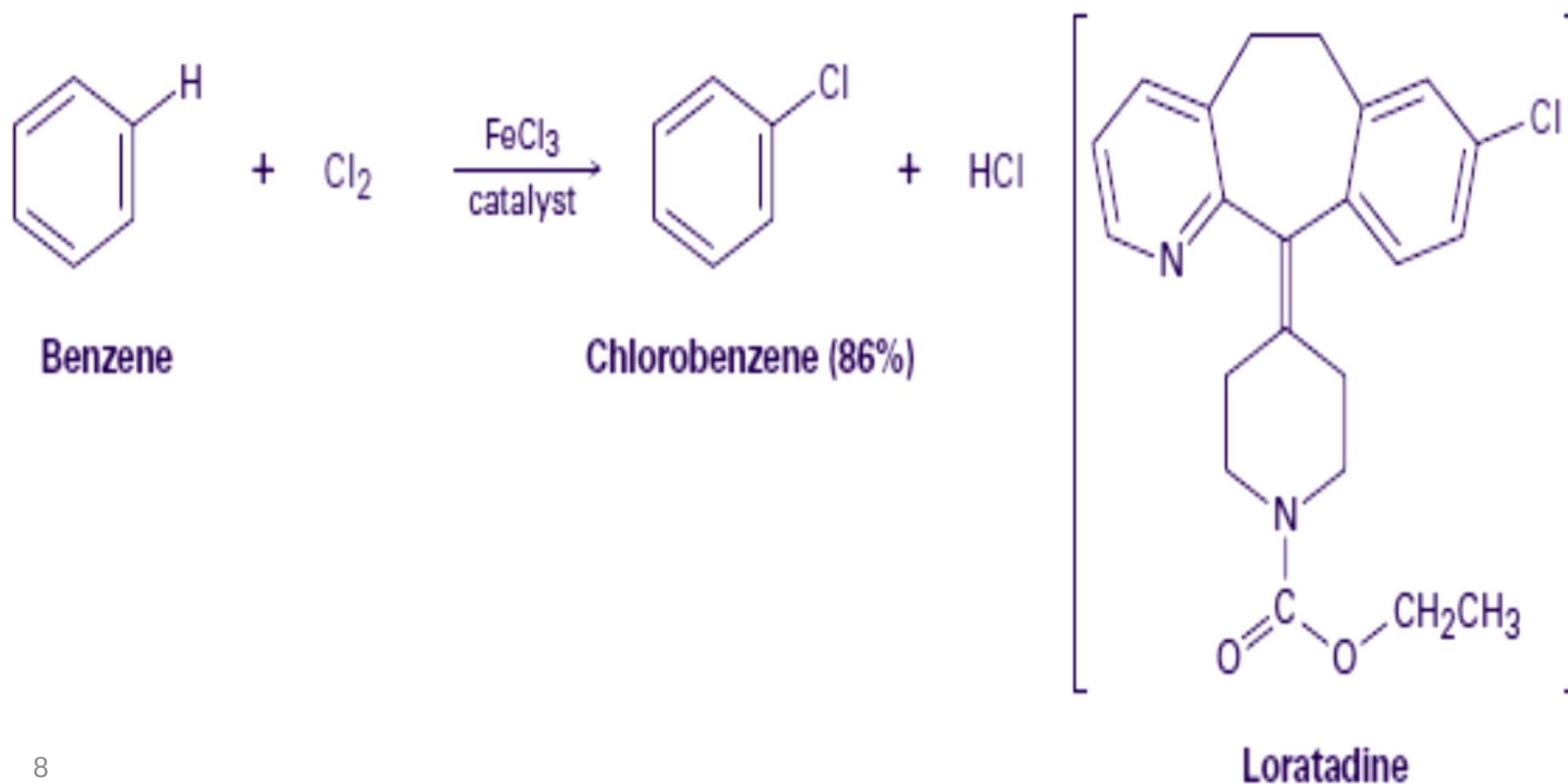
## 2.Aromatic Fluorination, Chlorination, and Iodination

Chlorine and iodine can be introduced into aromatic rings by electrophilic substitution reactions, but fluorine is too reactive and only poor yields of monofluoro aromatic products are obtained by direct fluorination.

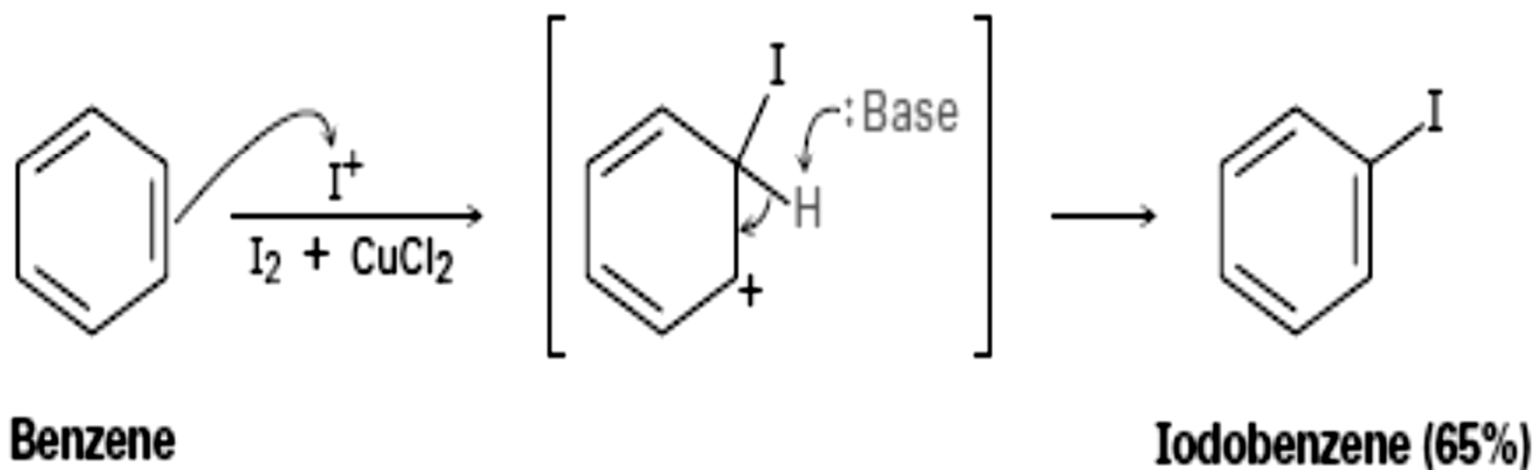
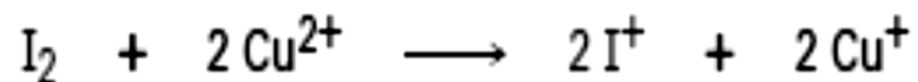
Instead, other sources of “F<sup>+</sup>” are used in which a fluorine atom is bonded to a positively charged nitrogen. One of the most common such reagents goes by the acronym F-TEDA-BF<sub>4</sub> and is sold under the name( Selectfluor).



Aromatic rings react with Cl<sub>2</sub> in the presence of FeCl<sub>3</sub> catalyst to yield chlorobenzenes, just as they react with Br<sub>2</sub> and FeBr<sub>3</sub>. This kind of reaction is used in the synthesis of numerous pharmaceutical agents, including the antiallergy medication loratadine( Claritin).

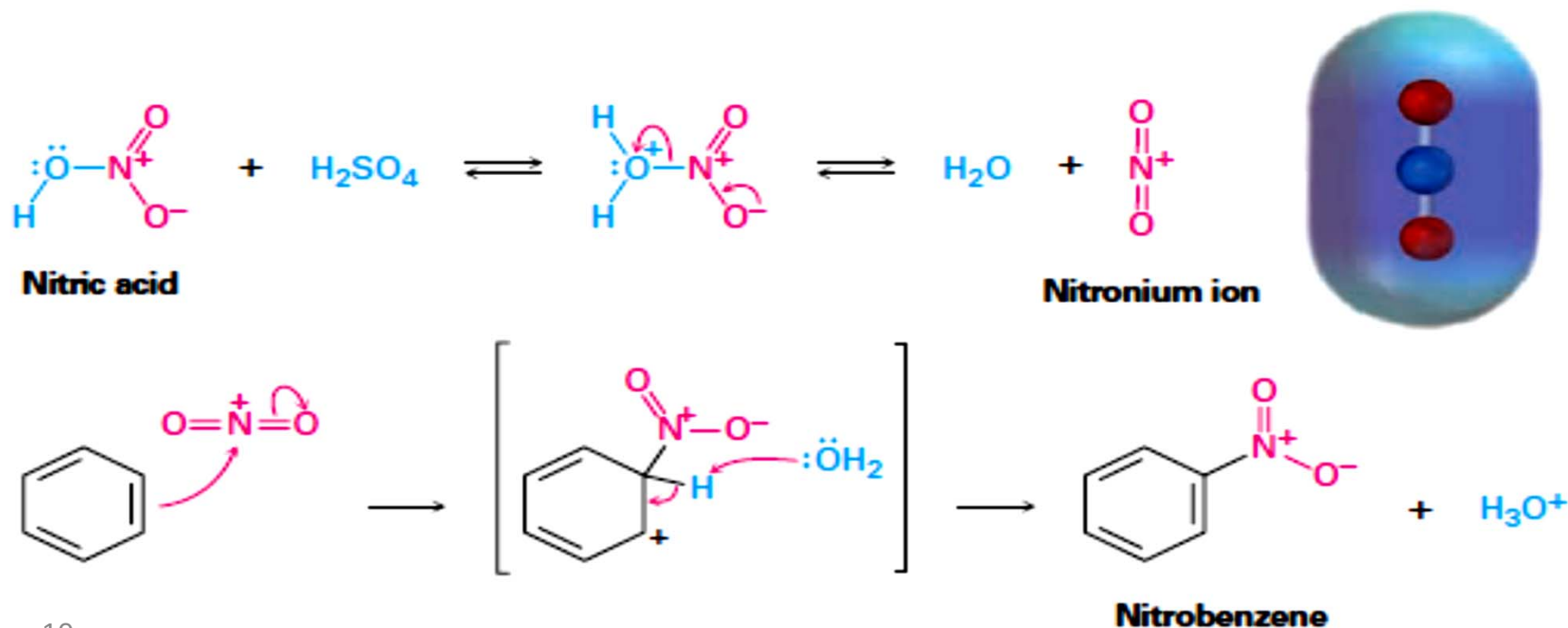


Iodine itself is unreactive toward aromatic rings, so an oxidizing agent such as hydrogen peroxide or a copper salt such as  $\text{CuCl}_2$  must be added to the reaction. These substances accelerate the iodination reaction by oxidizing  $\text{I}_2$  to a more powerful electrophilic species that reacts as if it were  $\text{I}^+$ . The aromatic ring then reacts with  $\text{I}^+$  in the typical way, yielding a substitution product.



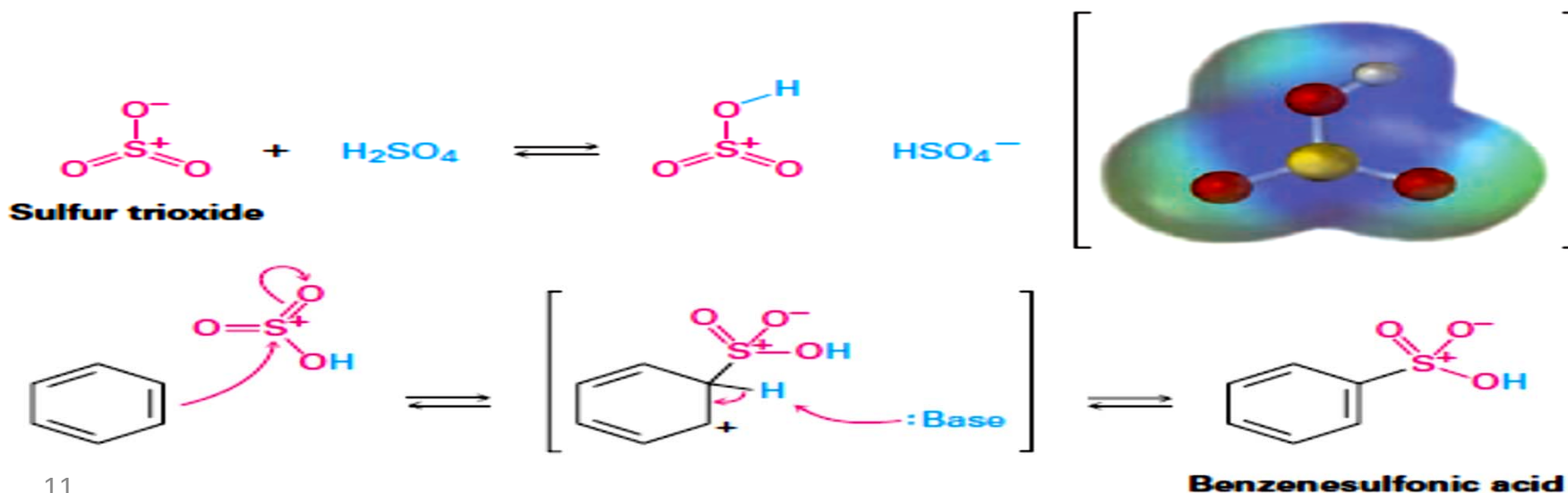
### 3. Aromatic Nitration

Aromatic rings are nitrated by reaction with a mixture of concentrated nitric and sulfuric acids. The electrophile is the nitronium ion,  $\text{NO}_2^+$ , which is formed from  $\text{HNO}_3$  by protonation and loss of water. The nitronium ion reacts with benzene to yield a carbocation intermediate, and loss of  $\text{H}^+$  from this intermediate gives the neutral substitution product (nitrobenzene)

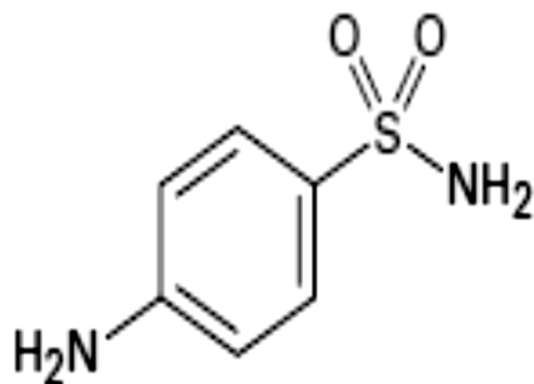


## 4.Aromatic Sulfonation

Aromatic rings can be sulfonated by reaction with fuming sulfuric acid, a mixture of  $\text{H}_2\text{SO}_4$  and  $\text{SO}_3$ . The reactive electrophile is either  $\text{HSO}_3^+$  or neutral  $\text{SO}_3$ , depending on reaction conditions, and substitution occurs by the same two-step mechanism seen previously for bromination and nitration, however, that the sulfonation reaction is readily reversible; it can occur either forward or backward, depending on the reaction conditions. Sulfonation is favored in strong acid, but desulfonation is favored in hot, dilute aqueous acid.



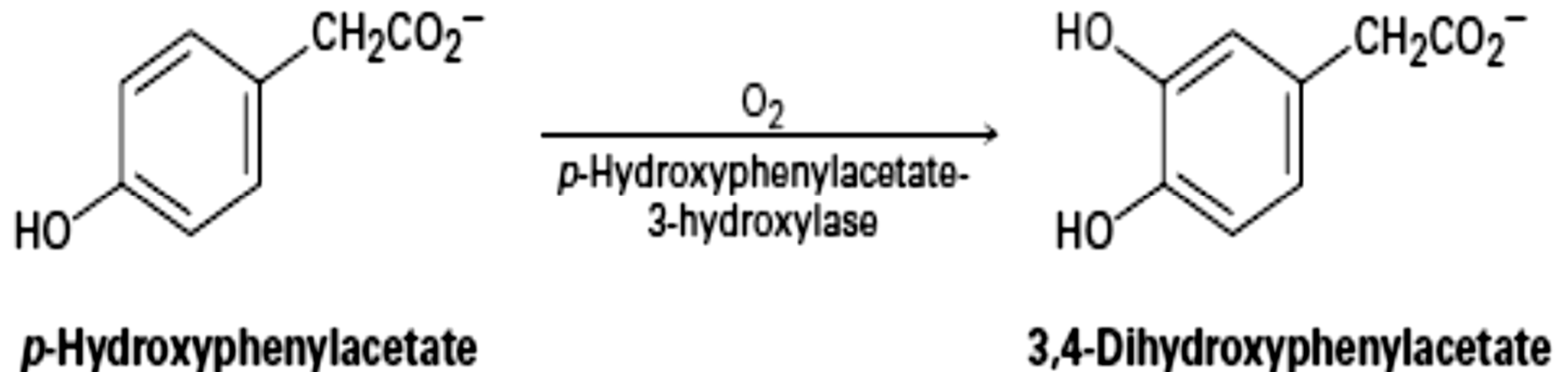
Aromatic sulfonation does not occur naturally but is widely used in the preparation of dyes and pharmaceutical agents. For example, the sulfa drugs, such as sulfanilamide, were among the first clinically useful antibiotics. These drugs are prepared commercially by a process that involves aromatic sulfonation as the key step.



**Sulfanilamide (an antibiotic)**

## 5. Aromatic Hydroxylation

Direct hydroxylation of an aromatic ring to yield a hydroxybenzene (a phenol) is difficult and rarely done in the laboratory but occurs much more frequently in biological pathways. An example is the hydroxylation of *p*-hydroxyphenylacetate to give 3,4- dihydroxyphenylacetate. The reaction is catalyzed by *p*-hydroxyphenylacetate-3-hydroxylase and requires molecular oxygen plus the coenzyme reduced flavin adenine dinucleotide(FADH<sub>2</sub>).

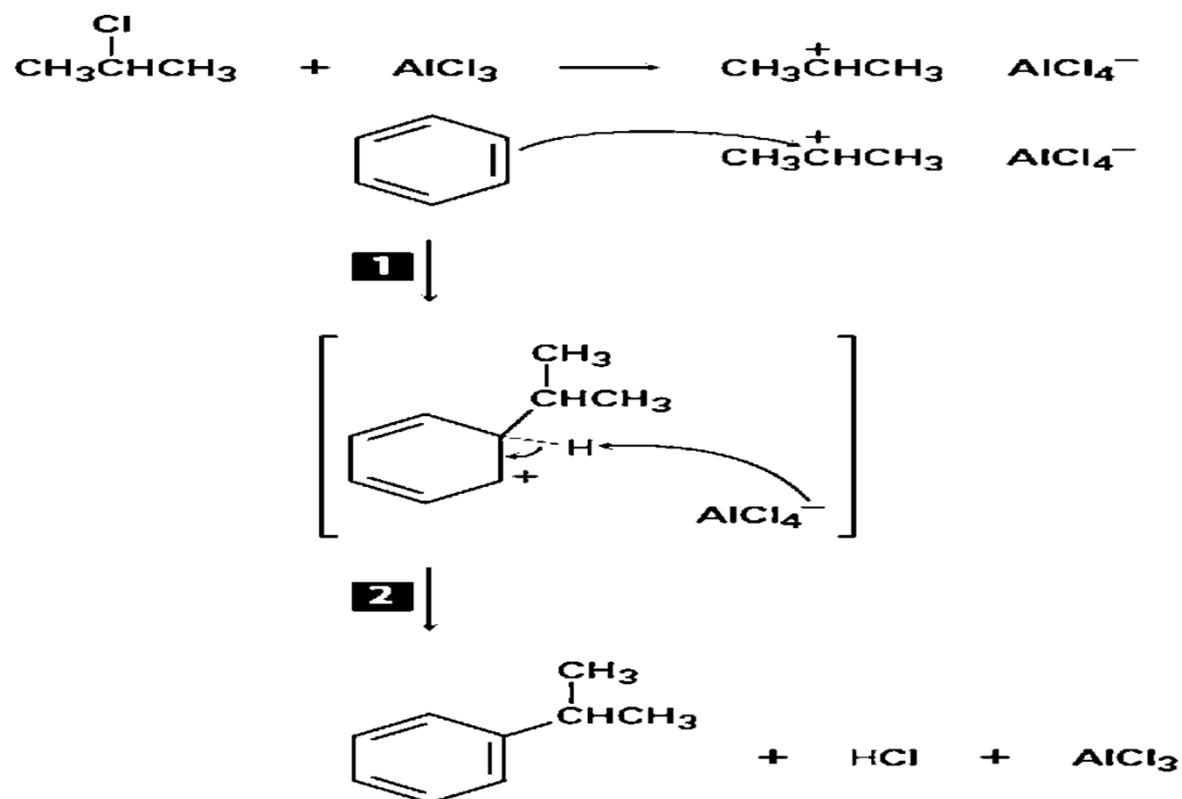


## 6. Alkylation and Acylation of Aromatic Rings: The Friedel-Crafts Reaction

The introduction of an alkyl group onto the benzene ring. Called the Friedel–Crafts reaction, the reaction is carried out by treating the aromatic compound with an alkyl chloride (RCl) in the presence of  $\text{AlCl}_3$  to generate a carbocation electrophile ( $\text{R}^+$ ). Loss of  $\text{H}^+$  then completes the reaction.

**1** An electron pair from the aromatic ring attacks the carbocation, forming a C–C bond and yielding a new carbocation intermediate.

**2** Loss of a proton then gives the neutral alkylated substitution product.



- **Friedel–Crafts alkylation limitations.**

1. only alkyl halides can be used. Aromatic (aryl) halides and vinylic halides don't react because aryl and vinylic carbocations are too high in energy to form under Friedel–Crafts conditions.

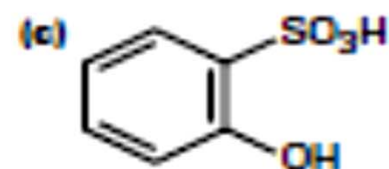
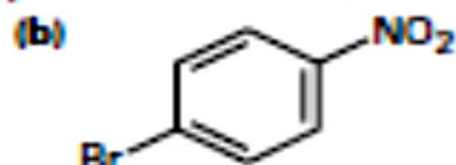
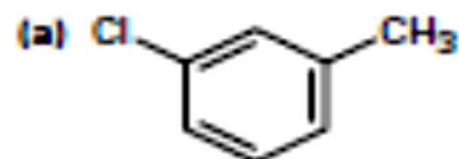
2. that it's often difficult to stop the reaction after a single substitution.

3. Friedel–Crafts reactions don't succeed on aromatic rings that are substituted either by a strongly electron-withdrawing group such as carbonyl or by a basic amino group that can be protonated.

# H.W.

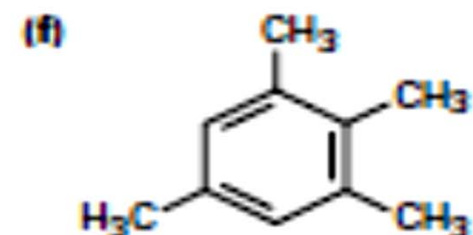
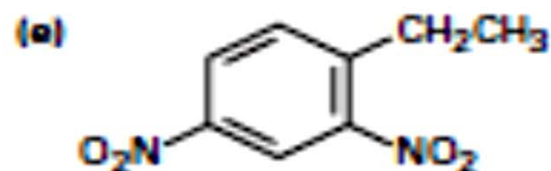
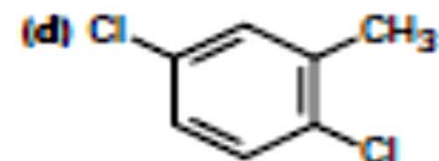
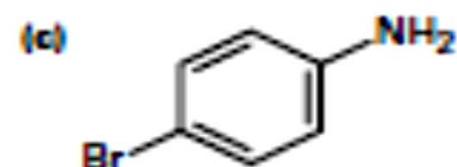
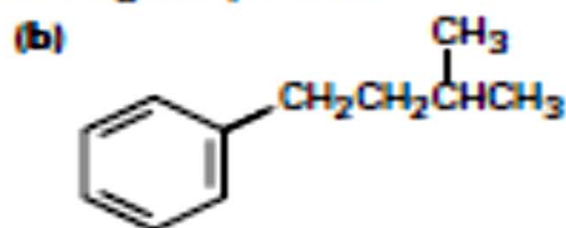
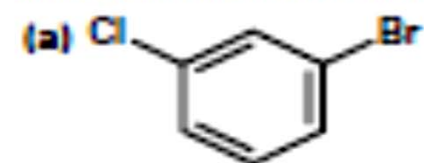
## Problem 15.1

Tell whether the following compounds are ortho-, meta-, or para-disubstituted:



## Problem 15.2

Give IUPAC names for the following compounds:



## Problem 15.3

Draw structures corresponding to the following IUPAC names:

(a) *p*-Bromochlorobenzene

(b) *p*-Bromotoluene

(c) *m*-Chloroaniline

(d) 1-Chloro-3,5-dimethylbenzene