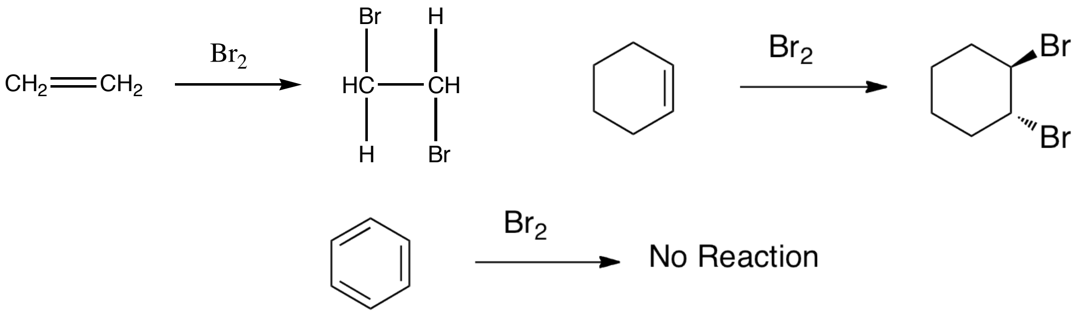
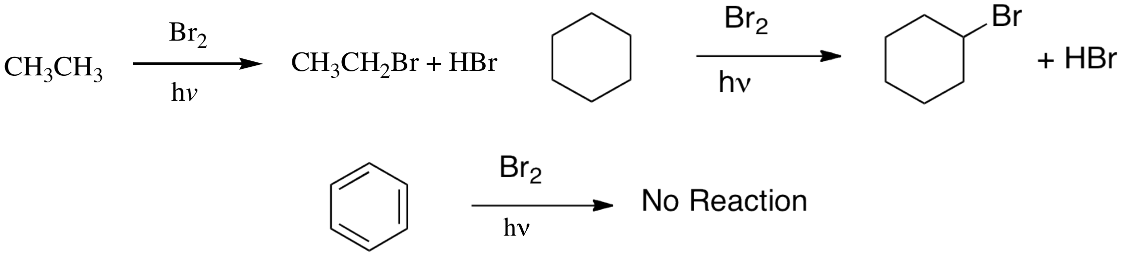
Electrophilic Aromatic Substitution

Benzene appears to be a remarkably stable and unreactive compared to alkenes, such as cyclohexene or ethylene, or even alkanes, such as cyclohexane or ethane.

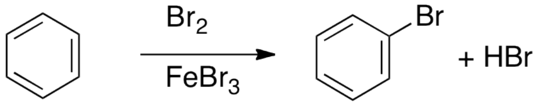


When ethylene or cyclohexene is allowed to react with bromine (an addition reaction), a dibrominated product is formed. However, when benzene is allowed to react with bromine in the absence of catalyst, nothing occurs. It is much less reactive.



In the case of alkanes such as ethane or cyclohexane, light (h*v*) or heat are required for the bromination to occur (this is a substitution). For benzene, there is still no reaction under these conditions.

However, this is not to say that benzene is completely unreactive. Under certain conditions, benzene can be forced to react.

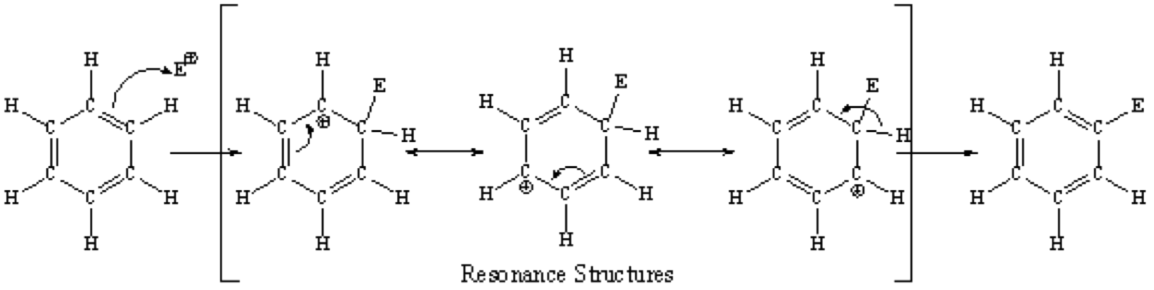


This is an Aromatic Electrophilic Substitution.

In electrophilic aromatic substitution, an electrophile (E^+) is substituted for a hydrogen on the aromatic (e.g. benzene) ring.

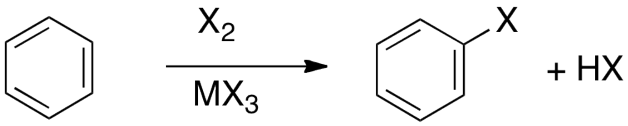
Aromatic compounds are very stable and un-reactive. In this type of reaction, the electrophile must be especially reactive (electron deficient).

The General Mechanism:



The pi system of the benzene ring acts as the nucleophile.
The cation formed in the reaction is resonance stabilized (conjugated with the two double bonds). However, it is not aromatic. Note that the positive charge is ortho and para to the electrophile.
Once the aromatic stabilization is lost, it is easily regained (remember that by staying aromatic, the compound becomes more stable). Hence the last step (loss of proton) is fast to regenerate the aromatic system.

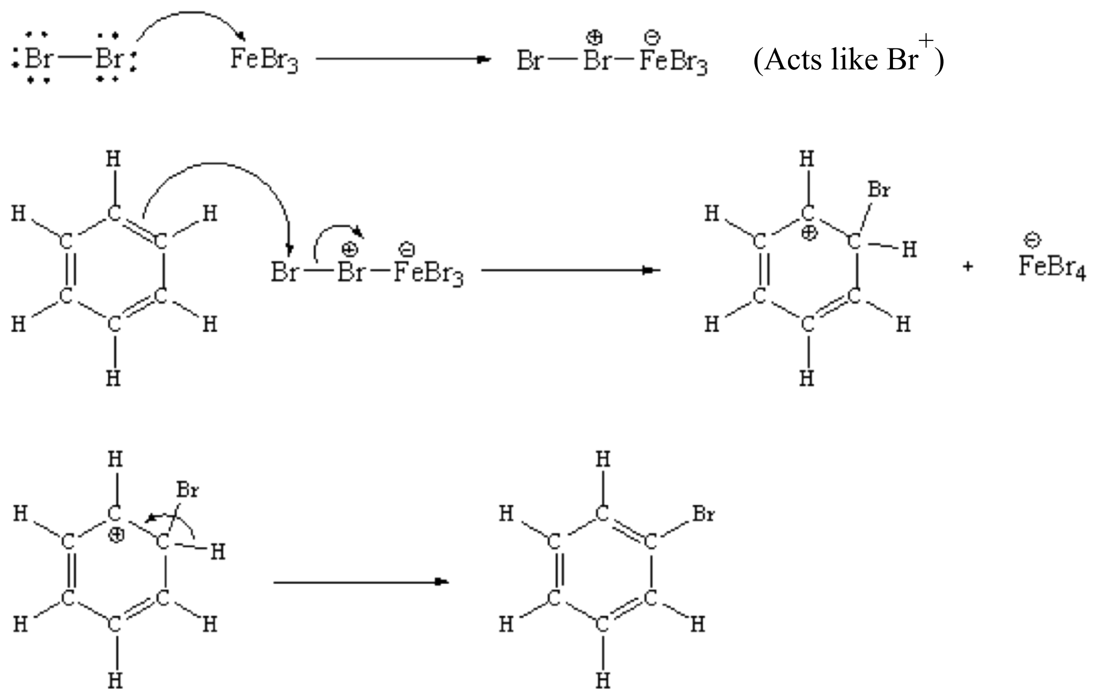
Halogenation (addition of halogen)



Where X = halogen (Cl, Br, and I)
M = metal Fe, B, or Al

In this reaction, MX_3 ($FeBr_3$, $AlCl_3$) is a Lewis Acid catalyst (a Lewis Acid is a substance that can accept a pair of electrons). MX_3 has an empty orbital to accept a pair of electrons. Chlorine or bromine alone are not strong enough electrophiles to react with the weakly nucleophilic benzene by themselves. The catalyst converts the halogen into a stronger electrophile, which can react with benzene.

Mechanism:

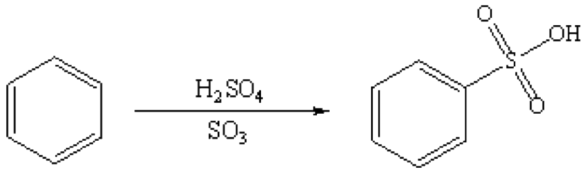


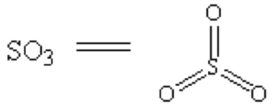
(Acts like Br^{+})

$$H^{\oplus} + FeBr_4^{\ominus} \longrightarrow HBr + FeBr_3$$

In halogenation, the Lewis Acid catalyst is regenerated at the end of the step.

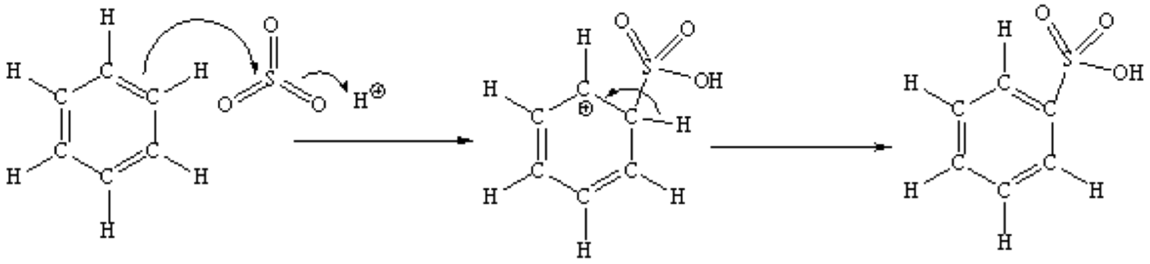
Sulfonation





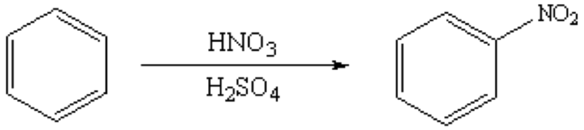
In this reaction, SO$_3$ is the electrophile.

Mechanism:



This reaction of SO_3 is followed by loss of proton from the conjugated cation intermediate (similar to the one we saw in halogenation).

Nitration

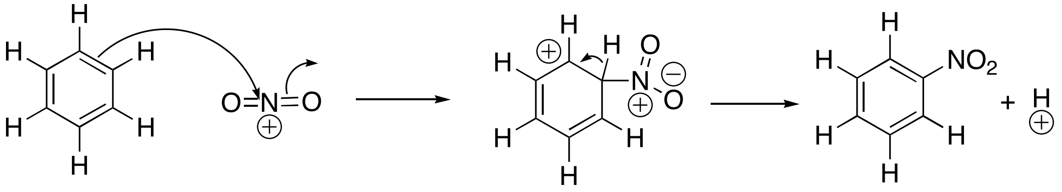


Mechanism:

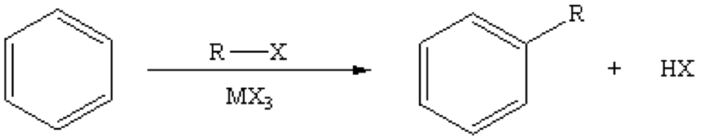
In strong acid, nitric acid is protonated to give $H_2NO_3^+$. Loss of water generates the nitronium ion that acts as an electrophile.

$$HNO_3 + H^{\oplus} \longrightarrow H_2\overset{\oplus}{O}{-}NO_2 + H_2O \rightleftharpoons \underset{\text{nitronium ion}}{{}^{\oplus}NO_2 + H_2O}$$

$$^{\oplus}NO_2 = O{=}\overset{\oplus}{N}{=}O$$

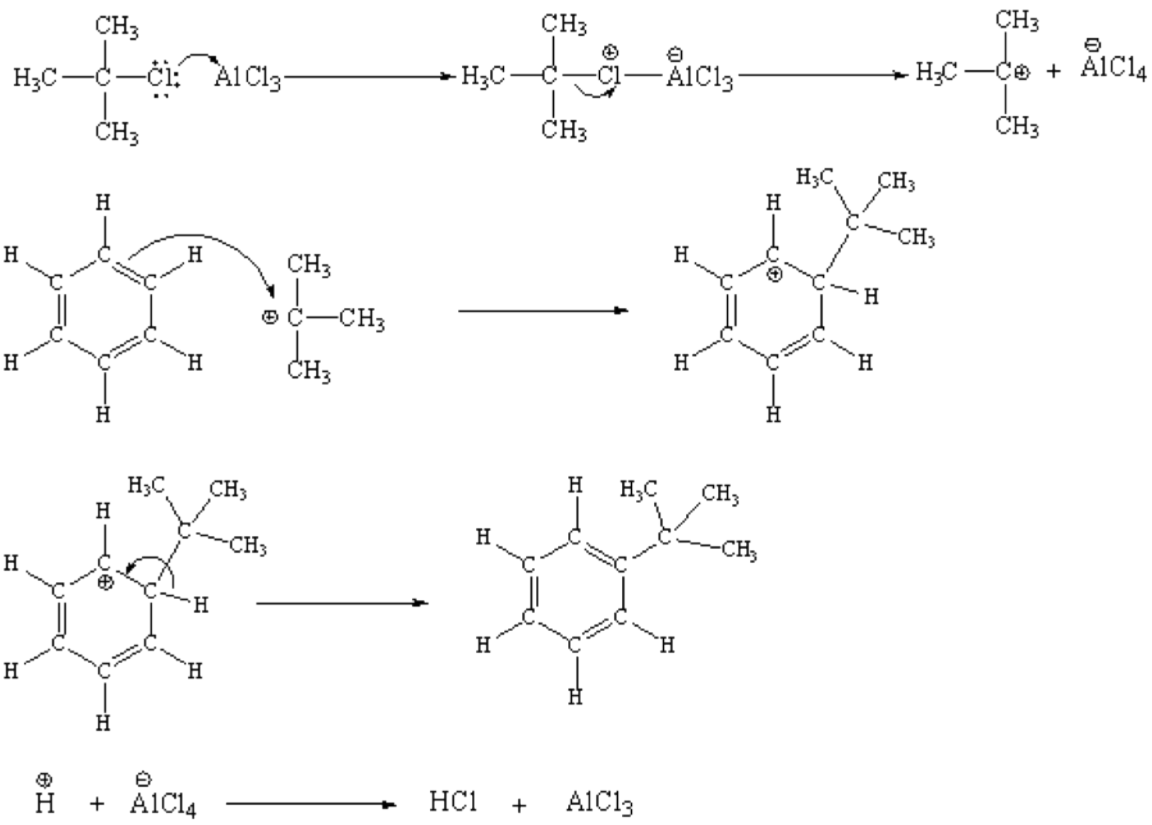


Alkylation (Friedel-Crafts)



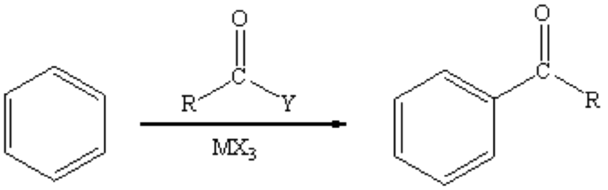
Where R = alkyl (methyl, ethyl, isopropyl, *tert*-butyl, etc)
X = halogen (Cl, Br, and I)
M = metal Fe, B, or Al

Mechanism:

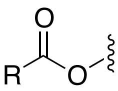


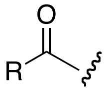
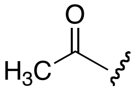
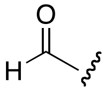
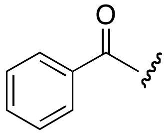
In this reaction, R$^+$ is the electrophile

Friedel-Crafts Acylation:



Where R = alkyl (methyl, ethyl, *tert*-butyl, etc)

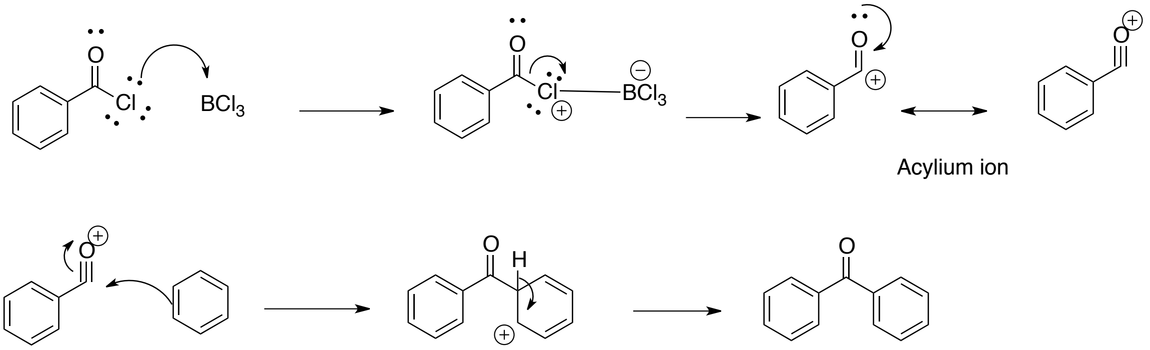
Y = halogen (Cl, Br, and I), or  (an anhydride functionality)
M = metal Fe, B, or Al
X = halogen

An acyl group = . When R=CH$_3$, the group is called acetyl (), when R=H, the group is called formyl (), when R=benzene ring, the group is called benzoyl ().

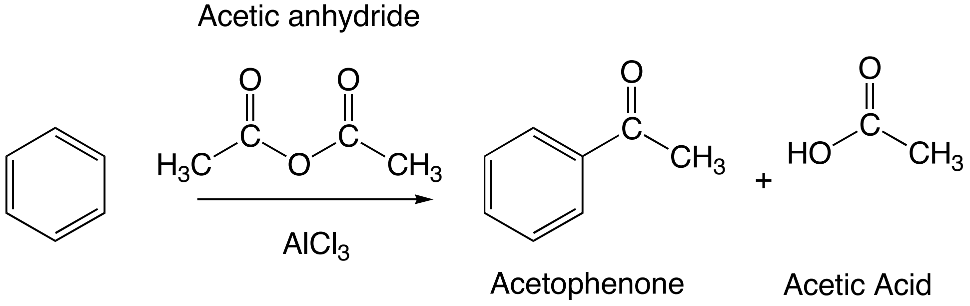
In this reaction, RCO$^+$ is the electrophile.

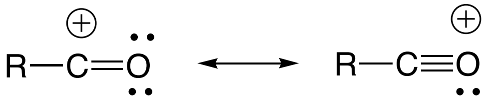
Example:

Mechanism:



Acylation (Friedel Crafts) with Anhydride:





acylium ion

Similar to the above example, this reaction also proceeds through the acylium ion. However, we need one full equivalent of Lewis acid for this reaction. When the acyloxy group (acyl group with another oxygen) reacts with the Lewis acid, the reaction is essentially irreversible and the Lewis acid cannot be regenerated.

Electrophilic Aromatic Substitution for Substituted Benzenes

Substituents already present on the benzene ring determine:
The position of the reaction.
The reactivity of the system.

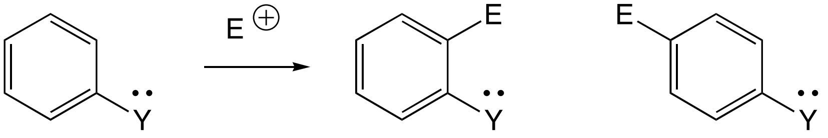
Resonance and Inductive Effects

A substituent can **donate** or **withdraw** electrons from the aromatic ring in 2 ways:
Inductive effects
Resonance effects.

Inductive effects are due to the intrinsic electronegativity of the atoms and to bond polarity in functional groups. These effects operate by donating or withdrawing electrons through the sigma (σ) bonds. An **electron donating group** will direct to the **ortho/para** position while an **electron withdrawing group** will direct to the **meta** position. This effect is considered **weak** compared to resonance effects.

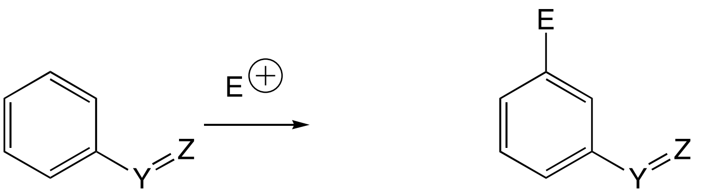
Resonance effects operate by donating or withdrawing electrons through the pi (π) bonds by overlap of the p atomic orbital on the substituent with the p atomic orbitals (π molecular orbital system) on the aromatic ring. An **electron donating group** will direct to the **ortho/para** position while an **electron withdrawing group** will direct to the **meta** position. This effect is considered **strong** compared to inductive effects.

How to determine position and reactivity

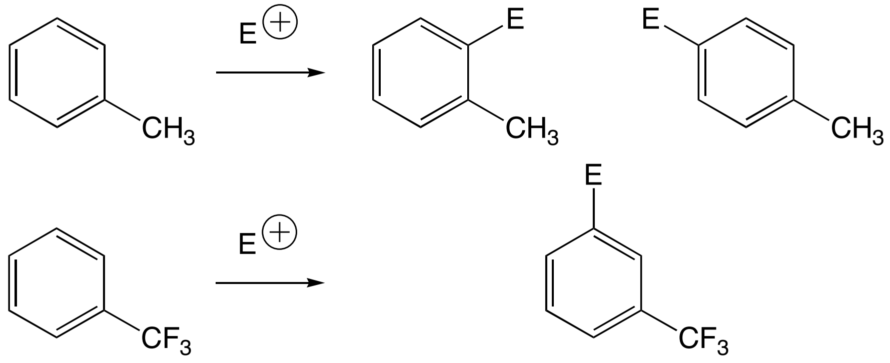


ortho-para
activating

Resonance: strong



meta
deactivating

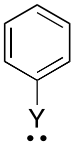


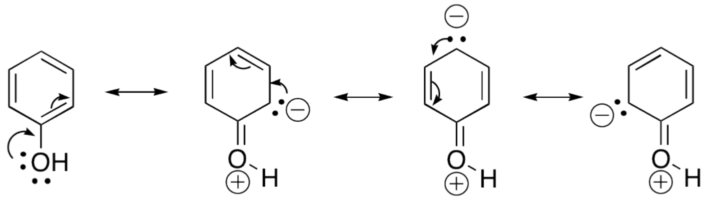
ortho-para
activating

Inductive: weak

meta
deactivating

Aromatic compounds with a heteroatom attached to it with a lone pair of electrons is considered a resonance donating system and will direct the reaction to the *ortho* or *para* positions. This is due to the *ortho* and *para* carbons having higher electron density as seen through the resonance structures





Aromatic compounds with a conjugated double bond conjugated to the aromatic ring are generally resonance withdrawing (especially if Z is electronegative) and will direct aromatic substitution to the *meta* position, where there is no partial positive charge.