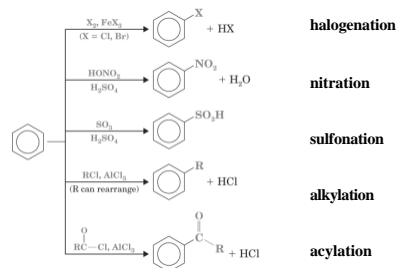


Chapter 15

Reactions of Aromatic Compounds

Electrophilic Aromatic Substitution on Arenes

The characteristic reaction of aromatic rings is substitution initiated by an electrophile

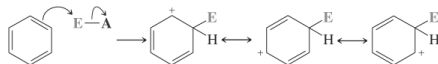


General Mechanism for Electrophilic Aromatic Substitution

1. Benzene uses two of its π electrons to react with an electrophile, forming an arenium ion

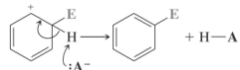
- ➔ This first step is like an addition to an ordinary double bond
- ➔ The arenium ion is stabilized by resonance which delocalizes the charge

Step 1



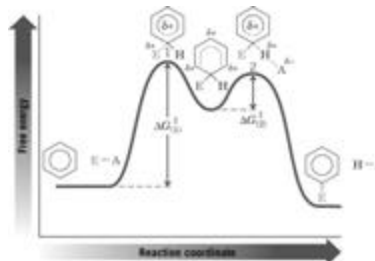
2. The benzene ring reacts further to lose a proton and regenerate the very stable aromatic system

Step 2



The first step is the slow, rate-determining step

- ◆ Step 1: requires loss of aromaticity of the benzene ring
 - Highly endothermic and has a large ΔG^\ddagger
- ◆ Step 2: restores the aromatic stabilization
 - Highly exothermic and has a small ΔG^\ddagger



Halogenation of Benzene

- ◆ Halogenation of benzene requires the presence of a Lewis acid

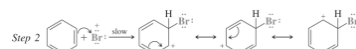


- ◆ Fluorination occurs so rapidly it is hard to stop at monofluorination of the ring
 - A special apparatus is used to perform this reaction

Mechanism of bromination

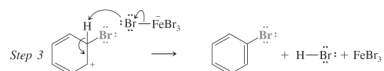
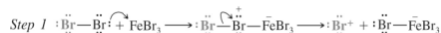
1. Bromine reacts with ferric bromide to generate Br^+
2. In step 2, the highly electrophilic bromine reacts with π electrons of the benzene ring, forming an arenium ion

- ➔ In step 3, a proton is removed from the arenium ion and aromaticity is regenerated
 - The FeBr_3 catalyst is regenerated



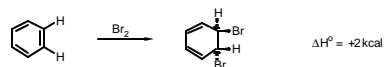
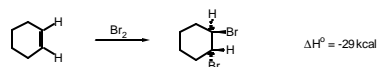
Mechanism of bromination

As in most EAS, there is a preliminary reaction or equilibrium to generate a strong electrophile
Bromine reacts with ferric bromide to generate Br^+

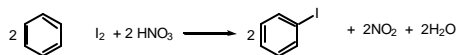
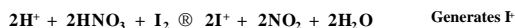
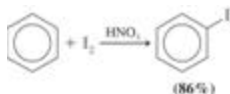


the FeBr_3 catalyst is regenerated

Why bromine substitutes, and doesn't add

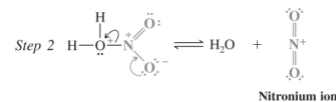
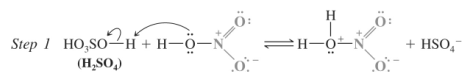


Iodination requires an oxidizing acid



Nitration of Benzene

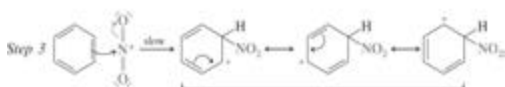
Nitration requires a mixture of concentrated nitric and sulfuric acids
Sulfuric acid is stronger and protonates nitric acid



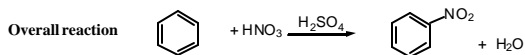
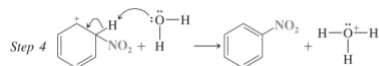
- Protonated nitric acid dissociates to produce the actual electrophile, the nitronium ion (NO_2^+)

Nitration of Benzene

Nitronium ion initiates the attack on benzene

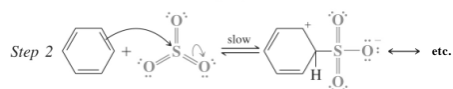
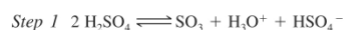


Water (released in step 2, acts as a Lewis base to remove H^+)



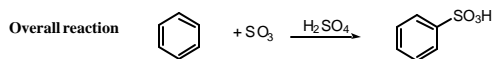
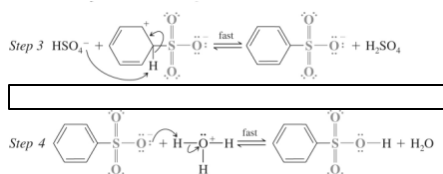
Sulfonation of Benzene

- Sulfonation occurs most rapidly using fuming sulfuric acid (concentrated sulfuric acid that contains SO_3)
 - The reaction also occurs in conc. sulfuric acid, which can generate small quantities of SO_3



Sulfonation of Benzene

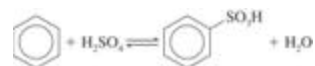
- ◆ Two proton transfers complete the process



Overall sulfonation reaction and its reverse

Sulfonation is reversible; each step is an equilibrium

- ◆ The sulfonation product is favored by use of concentrated or fuming sulfuric acid



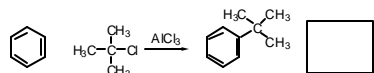
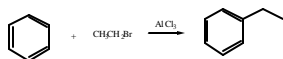
- ◆ Desulfonation can be accomplished

1. using dilute sulfuric acid (i.e. a high concentration of water)
2. or by passing steam through the reaction and collecting the volatile desulfonated compound as it codistills with steam

Friedel-Crafts Alkylation

- ◆ An aromatic ring can be alkylated by an alkyl halide in the presence of a Lewis acid

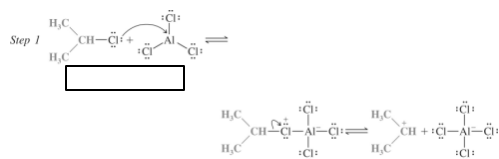
- The Lewis acid serves to generate a carbocation electrophile



Mechanism of Friedel-Crafts Alkylation

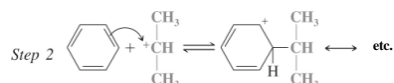
Example: synthesis of isopropylbenzene

Step 1: activation of the alkyl halide by AlCl_3 to produce a carbocation

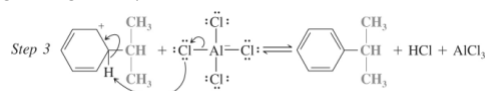


Mechanism of Friedel-Crafts Alkylation

Carbocation acts as the electrophile, seeking the electron rich benzene ring

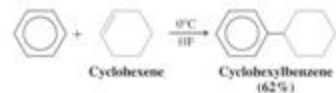


Then proton removed from the arenium ion to form product, also regenerating the catalyst

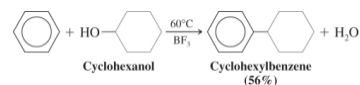


Other carbocations can be used for Friedel-Crafts alkylation

By protonation of alkenes



From alcohols

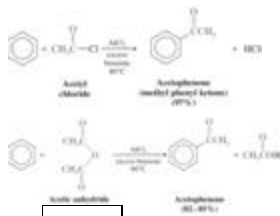


Friedel-Crafts Acylation

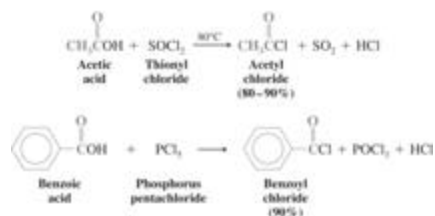
- An acyl group has a carbonyl attached to some R group



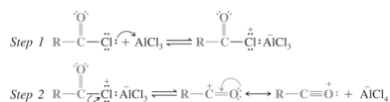
- Friedel-Crafts acylation requires reaction of an acid chloride or acid anhydride with a Lewis acid such as aluminium chloride



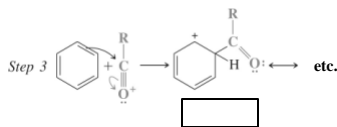
Acid chlorides are readily made from carboxylic acids



The electrophile in Friedel-Crafts acylation is an acylium ion



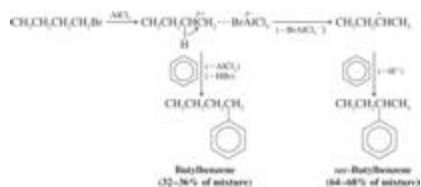
An acylium ion is stabilized by resonance



Followed by loss of proton as in other EAS

Limitations of Friedel-Crafts Reactions

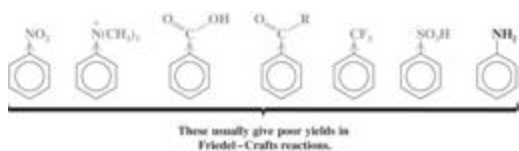
- In FC alkylation, carbocation rearrangements often occur



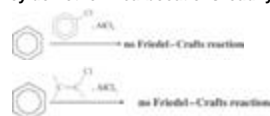
Observing any product from the primary halide means some of the intermediate complex reacts directly

Limitations of Friedel-Crafts Reactions

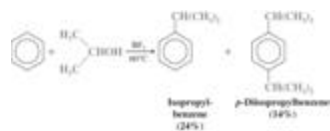
- Powerful electron-withdrawing groups make an aromatic ring non-reactive toward Friedel-Crafts alkylation or acylation
 - Amino groups also make the ring less reactive to Friedel-Crafts reaction because they become electron-withdrawing groups upon Lewis acid-base reaction with the Lewis acid catalyst



- Aryl and vinyl halides cannot be used in Friedel-Crafts reactions because they do not form carbocations readily



- Polyalkylation can occur with F.-C. alkylation because the first alkyl group activates the ring toward further substitution

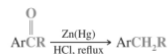


Synthetic Advantages of Friedel-Crafts Acylations

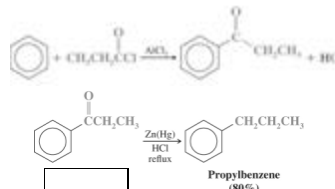
- ◆ Primary alkyl halides usually gives mixtures of rearranged products in Friedel-Crafts alkylation
- ◆ Acylium ions do not rearrange
- ◆ Alkyl benzenes often react further because they are activated
- ◆ Acyl benzenes are deactivated and do not react further
- ◆ Unbranched alkylbenzenes can be obtained in good yield by acylation followed by reduction

Clemmensen Reduction converts acyl benzenes to alkyl benzenes

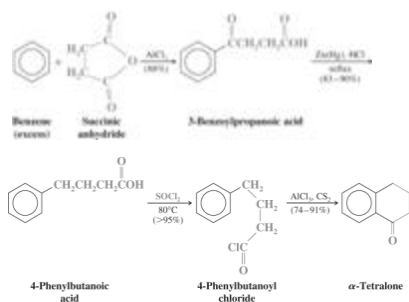
Zinc amalgam and hydrochloric acid reduces phenyl ketones to the methylene(CH₂) group



FC acylation plus Clemmensen reduction gives straight chain alkyl benzenes



- ◆ This method can be used to add a ring to an aromatic ring starting with a cyclic anhydride
 - Note that Clemmensen reagents do not reduce the carboxylic acid

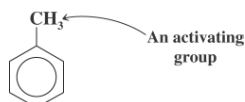


Effects of Ring Substituents

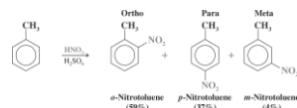
- ◆ Any group already on an aromatic ring affect both the reactivity and orientation of future substitution
 1. Activating groups cause the aromatic ring to be more reactive than benzene
 2. Deactivating groups cause the aromatic ring to be less reactive than benzene
 3. Ortho-para directors direct future substitution to the ortho and para positions
 4. Meta directors direct future substitution to the meta position

Activating Groups: Ortho-Para Directors

- ◆ All activating groups are also ortho-para directors
 - The halides are also ortho-para directors but are mildly deactivating
- ◆ The methyl group of toluene is an ortho-para director
 - Toluene reacts more readily than benzene



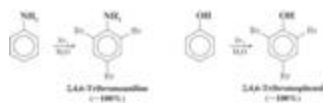
The methyl group of toluene is an ortho-para director



o,p substitution products are found together

Amino and hydroxyl groups are also activating and ortho-para directors

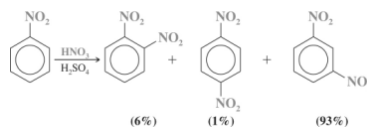
- These groups are so activating that catalysts are often not necessary



- ◆ Alkyl groups and heteroatoms with one or more unshared electron pairs directly bonded to the aromatic ring will be ortho-para directors (see chart on slide 22)

Deactivating Groups: Meta Directors

- ◆ Strong electron-withdrawing groups such as nitro, carbonyl, carboxyl, nitrile, and sulfonate are deactivators and meta directors



Less reactive than benzene

Halogens are the exception

Halo Substituents are weakly deactivating but are also ortho, para directors

- In electrophilic substitution of chlorobenzene, the ortho and para products are major:

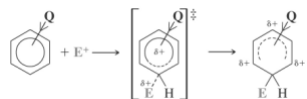
Reaction	Ortho Product (%)	Para Product (%)	Total Ortho and Para (%)	Meta Product (%)
Chlorination	39	55	94	6
Bromination	11	87	98	2
Nitration	30	70	100	0
Sulfonation		100	100	0

Classification of Substituents: a summary

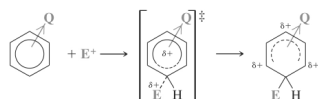
Ortho-Para Directors	Meta Directors
Strongly Activating —NH ₂ , —NHR, —NR ₂ —OH, —O ⁻	Moderately Deactivating —C≡N —SO ₃ H —CO ₂ H, —CO ₂ R —CHO, —COR
Moderately Activating —NHCOCH ₃ , —NHCOR —OCH ₃ , —OR	Strongly Deactivating —NO ₂ —NR ₃ ⁺ —CF ₃ , —CCl ₃
Weakly Activating —CH ₃ , —C ₂ H ₅ , —R —C ₆ H ₅	
Weakly Deactivating —F ⁻ , —Cl ⁻ , —Br ⁻ , —I ⁻	

Why??? - The Effect of Substituents on Reactivity

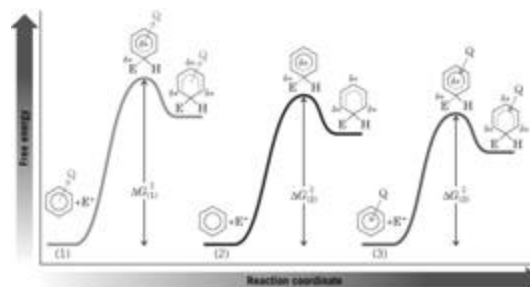
- ◆ Electron-releasing groups activate the ring toward electrophiles
 - Electron-releasing groups stabilize the transition state of the first step of substitution and lead to lower ΔG^\ddagger and faster rates



- ◆ Electron-withdrawing groups deactivate the ring
 - Electron-withdrawing groups destabilize the transition state and lead to higher ΔG^\ddagger and slower rates of reaction



Energy profile of the slow step in electrophilic substitution



With deactivating group

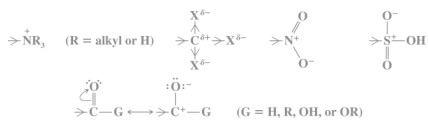
With activating group

Theory of Orientation: Inductive and Resonance Effects

- The inductive effect of substituent Q derives from the interaction of the polarized bond to Q with the developing positive charge in the ring as an electrophile reacts with it
- If Q is an electron-withdrawing group then attack on the ring is slowed because this leads to additional positive charge on the ring

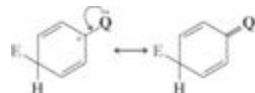


- Other groups that have an electron-withdrawing effect because the atom directly attached to the ring has a partial or full positive charge



Theory of Orientation: Inductive and Resonance Effects

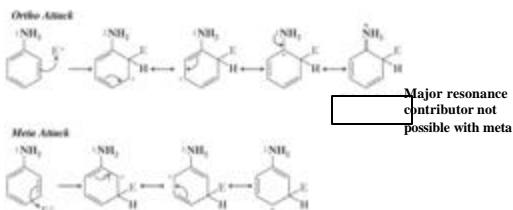
- The resonance effect of Q refers to its ability to increase or decrease the resonance stabilization of the arenium ion
 - When Q has a lone pair on the atom directly attached to the ring it can stabilize the arenium by contributing a fourth resonance form
 - A major contributor because of complete octet on all atoms



- Resonance donating groups

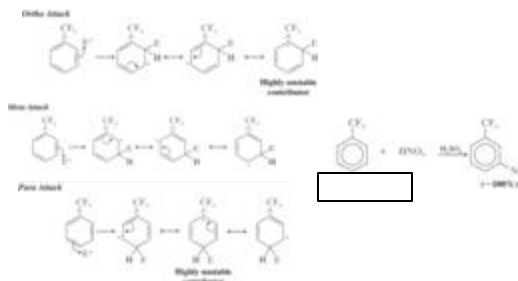


Resonance with an amino group



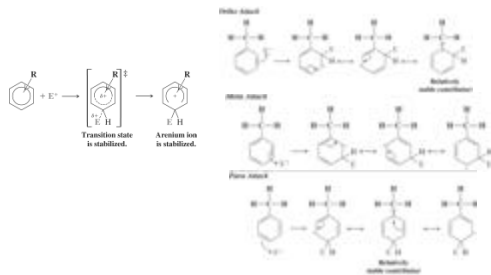
Meta-directing Groups - have either a partial or full positive charge on the atom directly attached to the aromatic ring

- A trifluoromethyl group destabilizes the ortho and para substitution pathways by having one poor resonance contributor in the arenium ion
- The meta intermediate is not as destabilized and is therefore favored



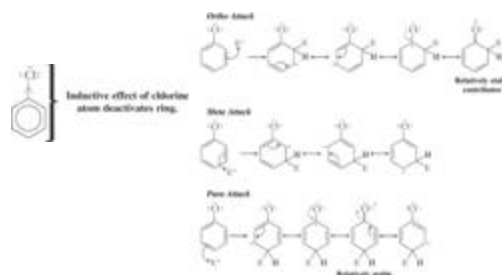
Ortho-Para Direction and Reactivity of Alkylbenzenes

- Alkyl groups activate aromatic rings by inductively stabilizing the transition state leading to the arenium ion
- Alkyl groups are ortho-para directors because they inductively stabilize one of the resonance forms of the arenium ion in ortho, para substitution



Halo groups are ortho-para directors but also deactivating

- The electron-withdrawing inductive effect of the halide deactivates haloaromatic compounds toward electrophiles
- The electron-donating resonance effect of the halogen's unshared electron pairs is the primary ortho-para directing influence



Reactions of the Side Chain of Alkylbenzenes

Benzylic Radicals and Cations

- When toluene undergoes hydrogen abstraction from its methyl group it produces a benzyl radical
 - A benzylic radical is a radical in which the carbon bearing the unpaired electron is directly bonded to an aromatic ring



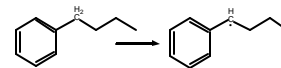
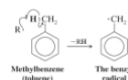
- Departure of a leaving group by an S_N1 process from a benzylic position leads to formation of a benzylic cation



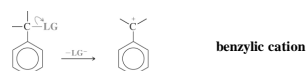
Reactions of the Side Chain of Alkylbenzenes

Benzylic Radicals and Cations

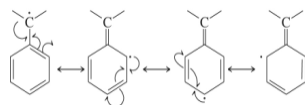
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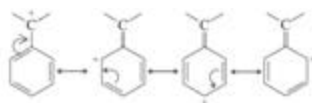
- Departure of a leaving group by an S_N1 process from a benzylic position leads to formation of a benzylic cation



Benzylic radicals and cations are stabilized by resonance



Unpaid electron is delocalized into ring



Positive charge is delocalized into ring

Halogenation of the Side Chain: Benzylic Radicals

- Benzylic halogenation takes place under conditions which favor radical reactions
- Reaction of *N*-bromosuccinimide with toluene in the presence of light leads to allylic bromination
 - Recall *N*-bromosuccinimide produces a low concentration of bromine which favors radical reaction



Halogenation of the Side Chain: Benzylic Radicals

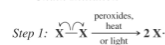
- Benzylic halogenation takes place under conditions which favor radical reactions
- Reaction of toluene with excess chlorine can produce multiple benzylic chlorinations



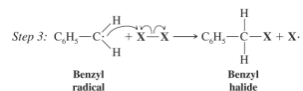
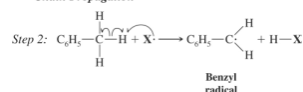
Note that ring substitution does not compete

Mechanism is the standard free radical chain reaction

Chain Initiation



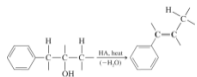
Chain Propagation



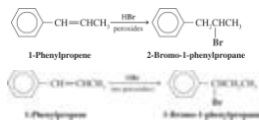
When ethylbenzene or propylbenzene react under radical conditions, halogenation occurs primarily at the benzylic position

Alkenylbenzenes

- ◆ Conjugated alkenyl benzenes are more stable
- ◆ Dehydration of the alcohol below yields only the more stable conjugated alkenyl benzene

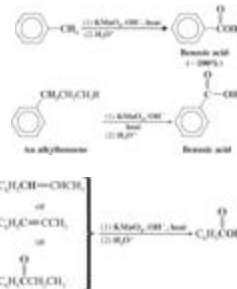


- ◆ Additions to the Double Bond of Alkenylbenzenes
 - Additions proceed through the most stable benzylic radical or benzylic cation intermediates

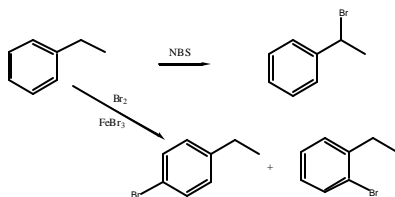


Oxidation of the Side Chain

- ◆ Alkyl and unsaturated side chains of aromatic rings can be oxidized to the carboxylic acid using hot KMnO_4



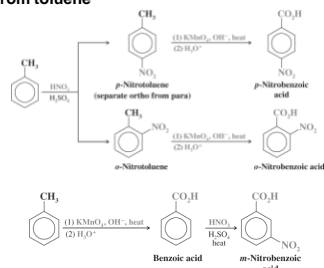
Synthetic applications



o,p always go together, but we also assume we can separate them when needed

Synthetic Applications

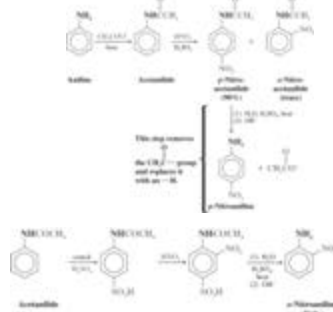
- ◆ When designing a synthesis of substituted benzenes, the order in which the substituents are introduced is crucial
- ◆ Example: Synthesize *ortho*-, *meta*-, and *para*-nitrobenzoic acid from toluene



Use of Protecting and Blocking Groups

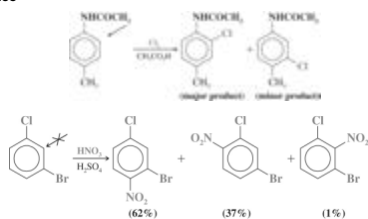
- ◆ Strong activating groups such as amino and hydroxyl cause the aromatic ring to be so reactive that unwanted reactions can take place
 - These groups activate aromatic rings to oxidation by nitric acid when nitration is attempted; the ring is destroyed
 - An amino group can be protected (and turned into a moderately activating group) by acetylation

- ◆ Example: The synthesis of *p*- and *o*-nitroaniline from aniline
 - A sulfonic acid group is used as a blocking group to force *ortho* substitution



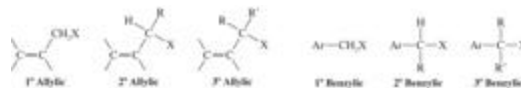
Substitution on Disubstituted Benzenes

- When two substituents are present on the ring initially, the more powerful activating group determines the orientation of subsequent substitution
- Ortho-para directors determine orientation over meta directors
- Substitution does not occur between meta substituents due to steric hindrance

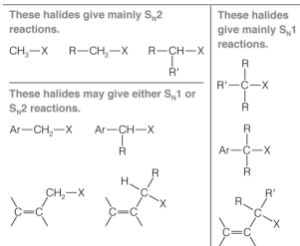


Allylic and Benzylic Halides in Nucleophilic Substitution Reactions

- Allylic and benzylic halides are classified in similar fashion to other halides

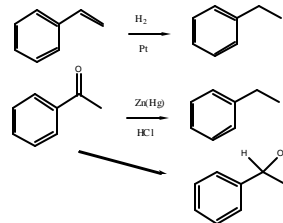


- Both primary and secondary allylic and benzylic halides can undergo $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ reaction
 - These primary halides are able to undergo $\text{S}_{\text{N}}1$ reaction because of the added stability of the allylic and benzylic carbocation
- Tertiary allylic and benzylic halides can only undergo $\text{S}_{\text{N}}1$ reaction



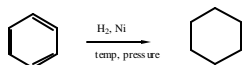
Reduction of aromatic compounds

- Since the benzene ring is very stable, reduction of other functional groups can be carried out



Forceful reductions of benzene

Under vigorous conditions, benzene compounds can be hydrogenated to cyclohexanes (intermediate products not isolable)



Birch reduction: with dissolving metal conditions, the interesting product is the non-conjugated diene

