Week 6

Electrophilic Aromatic Substitution

6.1 Electrophilic Aromatic Substitution 1

2/15:

- Discusses the aromaticity of fluorescein as an example to review from last class.
- Reactions of aromatic compounds are divided into two classes: Electrophilic and nucleophilic aromatic substitutions.
- Example:
  - $C_6H_6 \xrightarrow{H_3O^+} C_6H_6$ means no reaction?
  - $C_6H_6 \xrightarrow{D_3O^+} C_6D_6$; thus, a substitution is occurring.
- Mechanism:

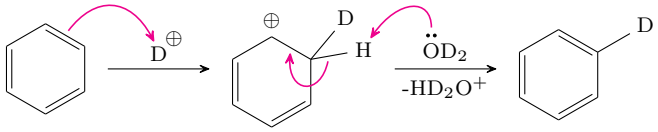


Figure 6.1: Electrophilic aromatic substitution mechanism.

  - To begin, one of the π-bonds of benzene attacks D^+. This causes the loss of aromaticity, but the carbocation is highly resonance delocalized.
  - Although we *could* make an alcohol at this point, this would lead to the loss of aromaticity in the product, so we won't do that.
  - Instead, we do an E1-type reaction.
  - The first step is the RDS.
  - The intermediate in this mechanism is called the **arenium ion**, the **Wheland intermediate**, or the **sigma complex**.
  - Note that the electrophile used in this reaction has to be a very special, very reactive, very strong electrophile in order to make up the energy gap.
- We know that the sigma complex exists because we can trap the intermediate.
- Whether or not we see the product react again depends on whether the product or starting material is more nucleophilic.
- Adding an EDG to the benzene makes the reaction proceed faster.

  - A good EDG will stabilize the arenium ion, lowering the activation barrier of the first step (the RDS).

- Halogenation.
- General form.

$$\mathrm{PhH + Br_2 \xrightarrow{cat.\ FeBr_3} PhBr + HBr}$$

  - Br_2 is too unreactive to have chemistry with benzene on its own.
  - In particular, when we say that Br_2 is too unreactive, we mean that there is not enough Br^+ character, i.e., it is not a good enough electrophile.
  - To overcome the problem, we add Br_2 to $FeBr_3$, a good Lewis acid with an open valence site. It follows that $Br{-}Br^+{-}Fe^-Br_3$ is a super awesome electrophile!

- Mechanism.

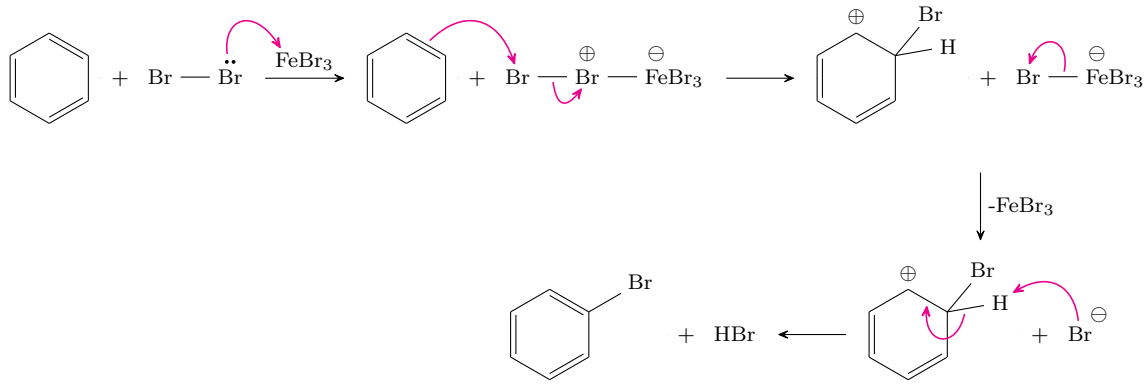


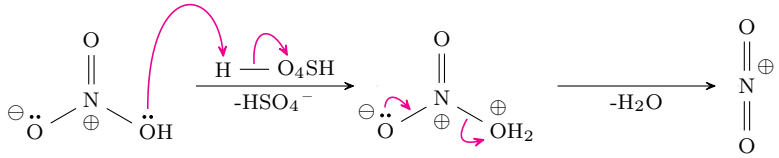
Figure 6.2: EAS halogenation mechanism.

- For chlorination, we use catalytic $AlCl_3$.
- For iodination, we use catalytic CuI_2.
- Nitration.
- General form.

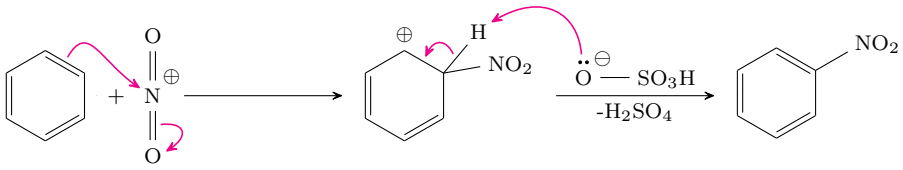
$$\mathrm{PhH + HNO_3 \xrightarrow{cat.\ H_2SO_4} PhNO_2 + H_2O}$$

  - We start with nitric acid, but as before, the nitrogen is not electrophilic enough.
  - Thus, we add catalytic sulfuric acid. Since H_2SO_4 is stronger than HNO_3, it protonates nitric acid to $H_2NO_3^+$, which quickly splits into $H_2O + NO_2^+$, where NO_2^+ is the nitronium ion (a super electrophile!).

- Mechanism.



(a) Nitronium ion formation.



(b) Nitration of benzene.

Figure 6.3: EAS nitration mechanism.

6.2 Electrophilic Aromatic Substitution 2

2/17:

- Problem set 4 posted today.
  - We will have all the material for it by the end of Tuesday.
- Today:
  - We run through a bunch of use cases of EAS (putting different functional groups on an aromatic ring).
  - Regioselectivity, reaction rates, etc. at the end of class.
- Sulfonation.
- General form.

$$\mathrm{PhH} + \mathrm{SO_3} \xrightarrow{\text{cat. } \mathrm{H_2SO_4}} \mathrm{PhSO_3H}$$

  - Important for making detergents — sulfates are highly soluble, so we use them to solvate the constituent lipids.
- Mechanism.

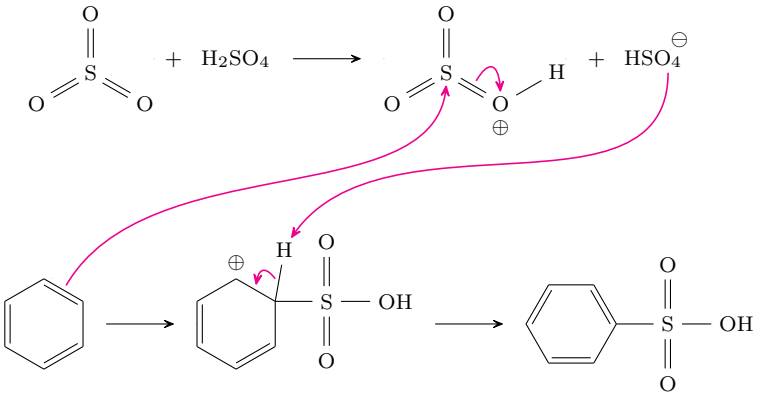


Figure 6.4: EAS sulfonation mechanism.

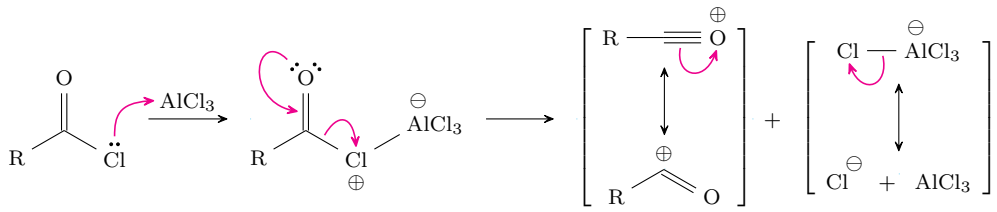
  - As with nitration (Figure 6.3), we use sulfuric acid to protonate a species that will then interact with benzene.
- Friedel-Crafts acylation.
- General form.

$$\mathrm{PhH} + \mathrm{RCOCl} \xrightarrow{\mathrm{AlCl_3}} \mathrm{PhCOR} + \mathrm{HCl}$$

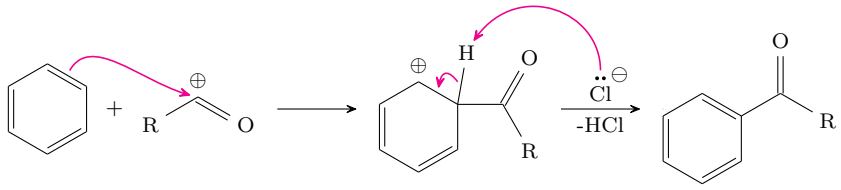
  - The acid chloride is a very strong electrophile, but it needs to be even stronger. We can make it stronger with the $\mathrm{AlCl_3}$ catalyst.

- This reaction is incredibly useful because it forms a new C–C bond.
- Limitation: You cannot have an EWG on the ring (the ring needs to be nucleophilic).

- Mechanism.



(a) Acylium ion formation.



(b) Acylation of benzene.

Figure 6.5: Friedel-Crafts acylation mechanism.

- The reaction with the catalyst makes the carbon center in $O{=}C^{+}{-}R$ extremely electrophilic.

- Friedel-Crafts alkylation.

- General form.

$$PhH + RCl \xrightarrow{AlCl_3} PhR + HCl$$

- Again, F-C alkylation is useful because it forms a C–C bond.

- Mechanism.
  - Mostly analogous to Figure 6.5.
  - Problems:
    - EWGs (you need a nucleophilic aromatic ring as with F-C acylation).
    - Selectivity (you get a mixture of products due to hydride/methyl shifts since the mechanism proceeds through a carbocation intermediate).
  - Additional issue: Over-alkylation. The products are more reactive because the electron-donating alkyl groups increase the nucleophilicity of the aromatic ring. Thus, we get ortho- and para-dialkyl compounds in addition to the monosubstituted products.
    - Note that this is not a problem with the other reactions we've learned so far (everything else added EWGs).
  - Note that since all we need to run the reaction is a carbocation, the other carbocation generation methods we've learned can also lead to F-C alkylation (if an aromatic compound is present in solution).
    - For example, mixing 2-methylpropene and acid generates a tertiary CC+ that can react with benzene to yield *t*-butylbenzene.
    - Intramolecular reactions can also occur this way — if a CC+ is formed on a substituent in an aromatic molecule, it can react with the aromatic ring in a ring-closing mechanism.

- More on the selectivity issue with F-C alkylation.

  - For example, reacting benzene with 1-chloropropane under F-C alkylation conditions will yield isopropylbenzene as the major product and propylbenzene as the minor product.
  - Thus, don't use F-C alkylation for linear *n*-alkyl compounds. It should be reserved for if you want to add a *t*-butyl group or another alkyl group with symmetric hydrogens.
  - If you *do* want to create propylbenzene, make use of the much more controllable F-C acylation reaction. Indeed, react benzene with propionyl chloride under F-C acylation conditions, and then either hydrogenate (H_2/Pd) or perform a **Clemmensen reduction**.

- **Clemmensen reduction**: The selective hydrogenation of a ketone using $Zn(Hg) + HCl$[1].
  - If there is an alkene in the acid chloride added to the benzene that you don't want to hydrogenate, you will have to use the Clemmensen reduction (as it will only hydrogenate the unwanted ketone).

- Example: Ring-closing acylation/alkylation reaction.

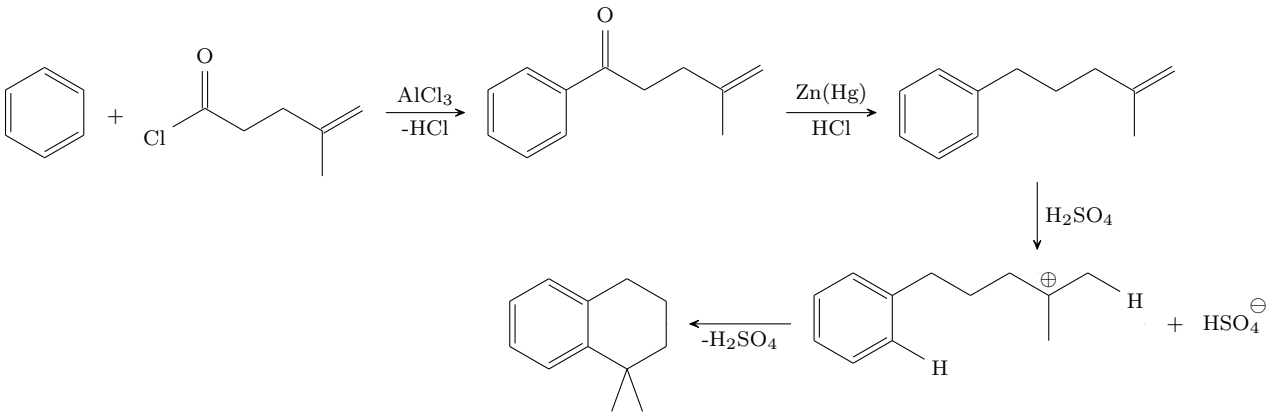


Figure 6.6: Ring-closing Friedel-Crafts mechanism.

  - The acylation product is formed. It can be hydrogenated with the Clemmensen reduction. Then we can turn the alkene into a carbocation with sulfuric acid and subject it to F-C alkylation conditions to yield a ring-closing reaction.

- Forming a benzoic acid.

$$\mathrm{PhR} \xrightarrow[\mathrm{H_2O}]{\mathrm{KMnO_4}} \mathrm{PhCOOH}$$

  - It is necessary to have a benzylic hydrogen for the mechanism to proceed (for example, $PhBu^t$ wouldn't react).
  - It is possible to convert multiple alkyl groups at the same time (for example, $C_6H_4MePr \longrightarrow C_6H_4(COOH)_2$ where the carboxylic acids wind up where the methyl and propyl groups originally were).

- Forming an amine (from a nitro group).

$$\mathrm{PhNO_2} \xrightarrow{\text{reagents}} \mathrm{PhNH_2}$$

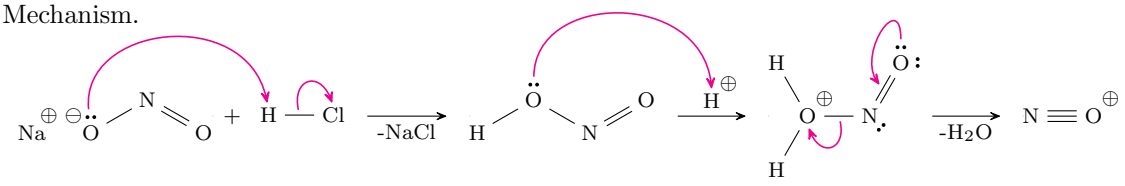
  - A number of reductive reagents can work here. Explicitly, we may use $H_2 + Pd/C$, H^+ (acid), or $SnCl_2 + H_2O$.
  - This reaction takes a strong EWG and turns it into an EDG.
  - The amine is also a gateway to a number of other functional groups, so being able to get one is very helpful.

[1] Note that Zn(Hg) is zinc amalgam.

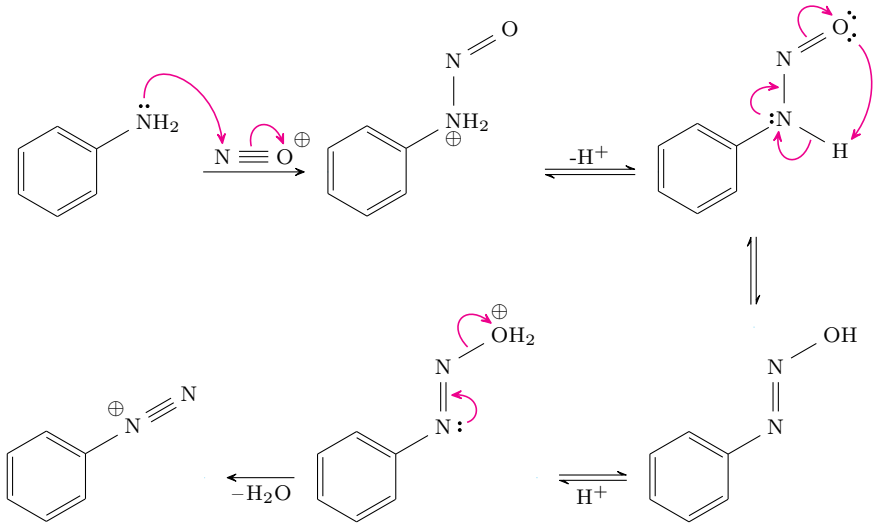
- Diazotization.
- General form.

$$\mathrm{PhNH_2} \xrightarrow{\text{reagents}} \mathrm{PhN_2^+ + X^-}$$

  - We use either $\mathrm{NaNO_2/HCl}$ or $\mathrm{HNO_2}$ as the reagent(s).
  - Note that the product is a diazonium salt.
- Mechanism.



(a) Nitrosonium ion formation.



(b) Diazotization of aniline.

Figure 6.7: EAS diazotization mechanism.

  - Note that the HONO intermediate in Figure 6.7a is called "HONO"[2].
  - Excess strong acid is used here (we need two equivalents of acid at least to form the nitrosonium ion).
  - The nitrosonium ion is very unstable and reacts quickly with the relatively nucleophilic amine.
  - The last step being irreversible serves as the driving force for this reaction.
- **Sandmeyer reaction**: Reacting an aryl diazonium salt with electrophiles in the presence of a copper catalyst substitutes those electrophiles for the diazonium group.
- In particular, mixing $\mathrm{PhN_2^+}$ with...
  - $\mathrm{Cu_2O, H_2O}$ makes PhOH.
  - CuCl makes PhCl.
  - CuBr makes PhBr.

[2] "HOE-NOE"

  - CuI makes PhI.

- Mechanism.
  - Complex; sort-of S_N1-like.
  - The diazonium is a great leaving group, so it leaves, making a phenyl cation and N_2. At this point, a nucleophile can just swoop in and attack the phenyl cation.
  - Note that the phenyl cation intermediate is still aromatic — the electron removed was taken from an sp^2 orbital, not a p orbital.

- We can hydrogenate our diazonium phenyl compound with H_3PO_2.

$$PhN_2^+ \xrightarrow{H_3PO_2} PhH$$

- Why F-C alkylations lead to over-alkylation but others do not.
  - Consider nitration.
  - Nitro groups are strongly electron withdrawing. Thus, they deactivate their host aromatic ring.
    - Over a long time, however, we will see the formation of some meta-dinitrobenzene (not ortho or para).
    - This is because resonance gives us carbocations at the ortho and para positions. Thus, the molecule is 100 000 times less reactive then benzene toward EAS overall, but the molecule is even less reactive (less nucleophilic) at the ortho and para positions.
    - Additionally, if we substitute ortho or para, we will have a resonance structure in the transition state with a carbocation directly adjacent to the positive nitrogen of the nitro group. This is no good, and another reason why EWGs are meta-directing.
  - Same for acyl groups and SO_3H groups.

- With respect to ortho/para selectivity, sterics *may* sometimes make ortho-substitution less likely.

- Activators and deactivators.

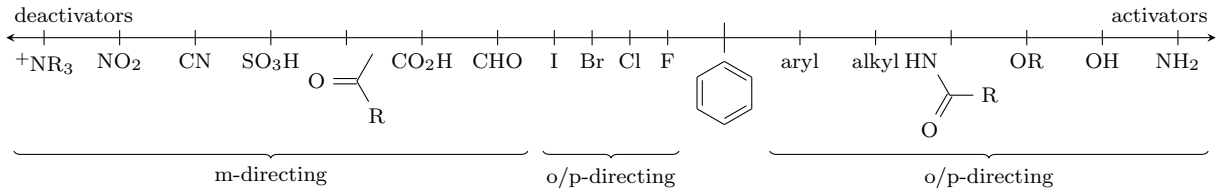


Figure 6.8: Activators and deactivators.

  - Deactivators are meta-directors (the meta position is the most nucleophilic position in a deactivator-substituted molecule).
  - Activators won't break aromaticity as in resonance structures, but said structures can indicate trends. They are ortho/para directors.
    - Convince yourself using resonance structures that ortho/para addition leads to 1 extra resonance structure.
  - Alkyl and aryl groups are ortho/para-directing activators.
    - Ortho/para addition allows us to access a resonance structure where the carbocation intermediate is tertiary.
    - For example, toluene is about 25 times more reactive than benzene, and it is even more reactive at the ortho/para positions.
  - Halogens will be discussed next week.

6.3 Chapter 15: Reactions of Aromatic Compounds

From Solomons et al. [1].

2/23:

- "Kekulé structures are more appropriate for writing mechanisms such as electrophilic aromatic substitution because they permit the use of resonance theory, which, as we shall soon see, is invaluable as an aid to our understanding" [1, p 663].
- Halogenation.
- Bromination and chlorination of benzene are analogous (see Figure 6.2).
  - Flourination of benzene occurs so rapidly that it is hard to limit it to monofluorination. There are indirect methods of producing fluorobenzene, though.
  - Iodination of benzene requires incredibly forcing conditions, and is thus carried out in the presence of a strong oxidizing agent such as nitric acid. Biochemically, iodination of benzene is enzymatically catalyzed.
- Sulfonation.
- **Fuming sulfuric acid**: Sulfuric acid that contains added sulfur trioxide.
- It is the reaction of benzene with fuming sulfuric acid that produces benzenesulfonic acid.
  - Note that since H_2SO_4 partially decomposes into SO_3 over time, the reaction will take place in the presence of concentrated sulfuric acid alone, but much more slowly.
  - The presence of SO_3 is essential to the mechanism.
- Sulfonation is reversible; the equilibrium depends on the conditions.
  - Fuming sulfuric acid promotes sulfonation.
  - Dilute sulfuric acid with steam bubbled through (high $[H_2O]$) promotes desulfonation.
- **Protecting group**: A functional group used to temporarily block a position from electrophilic aromatic substitution.
- Since sulfonation is reversible, sulfonate is often used as a protecting group.
- Friedel-Crafts alkylation.
- For primary halides, an aluminum chloride-alkyl halide complex forms instead of a carbocation. In this case, the C–Cl bond is all but broken, making the carbon atom positive to the point that it acts as if it were a carbocation, but there is still some connecting electron density.
- Any process that creates a carbocation may be used as a precursor to F-C alkylation.
  - A mixture of an alcohol and an acid (e.g., BF_3) can also be used.
- Friedel-Crafts acylation.
- **Acetyl group**: The MeCO group. *Also known as* **ethanoyl group**.
- **Benzoyl group**: The PhCO group.
- **Acyl halide**. *Also known as* **acid halide**.
- Friedel-Crafts acylations can also be carried out using carboxylic acid anhydrides.
- Additional limitation: "Aryl and vinylic halides cannot be used as the halide component because they do not form carbocations readily" [1, p 672].

- Side reaction with the Clemmensen reduction: Zinc and HCl can also reduce nitro groups to amino groups.
- **Wolf-Kishner reduction**: The basic complement of the Clemmensen reduction, which hydrogenates a ketone with hydrazine (H_2NNH_2), KOH, and heat.
- **Arene**: A hydrocarbon that consists of both aliphatic and aromatic groups.
- Covers side-chain reactions, stability, and transmutations.