Week 8

Alcohols, Ethers, and Epoxides

8.1 Office Hours (Salinas)

2/28:

- Does $H_2 + Pd/C$ hydrogenate ketones or not? Conflict between Lecture 11 and 2020 Exam 2A Q1e.
  - Either way.
  - $H_2 + Pd/C$ hydrogenates *benzylic* ketones only; it will leave ketones that are farther away from the benzene ring alone.
  - $Zn(Hg) + HCl$ hydrogenates all ketones, but nothing else.
- When do alkenes in PAHs get hydrogenated?
  - Ones that are added onto the Rocks of Gibraltar molecules.
- Do we have to know that aryl amines present a problem in F-C alkyl/arylations? It seems like there's a lot of content on this exam that BCD never went over.
  - Things like this probably won't show up on the exam.
- Can we use $HCN + NaCN$ to substitute CN?
  - This would work, but Sandmeyer is the go-to.
- How do you indicate you want to do something twice (e.g., bromination on 2020 Exam 2A Q3a)?
  - Write (2x): For example, "Br_2 / $FeBr_3$ (2x)".
- Is it $KMnO_4$ (2020 Exam 2A answer key), $KMnO_4$ / H_2O (class), $KMnO_4$ / $NaOH + \Delta$ (PSet 4 key), or $KMnO_4$ / $NaOH + \Delta$ followed by H_3O^+ (PSet 4 key) for benzoic acid formation?
  - $KMnO_4 + H_2O$ is pretty solid.
- 2020 Exam 2A Q3c: Is it preferable to use S_NAr or a novel Sandmeyer reaction? What are the limits of the Sandmeyer reaction?
  - Note that we can achieve meta addition of an amine when an o/p-director is present by brominating para and then using the benzyne intermediate.
- 2020 Exam 2A Q3d: Is $SnCl_2$ / H_2O selective reduction of nitro groups?
  - Perhaps, Omar will get back to me on whether to use $SnCl_2$ / H_2O or $H_2 + Pd/C$.
- When adding an alkane via F-C alkylation to later be transformed into a benzoic acid, is it preferable to use 2-chloropropane for some reason?

– Anything's fine.

- PSet 4 2021 1f/h:

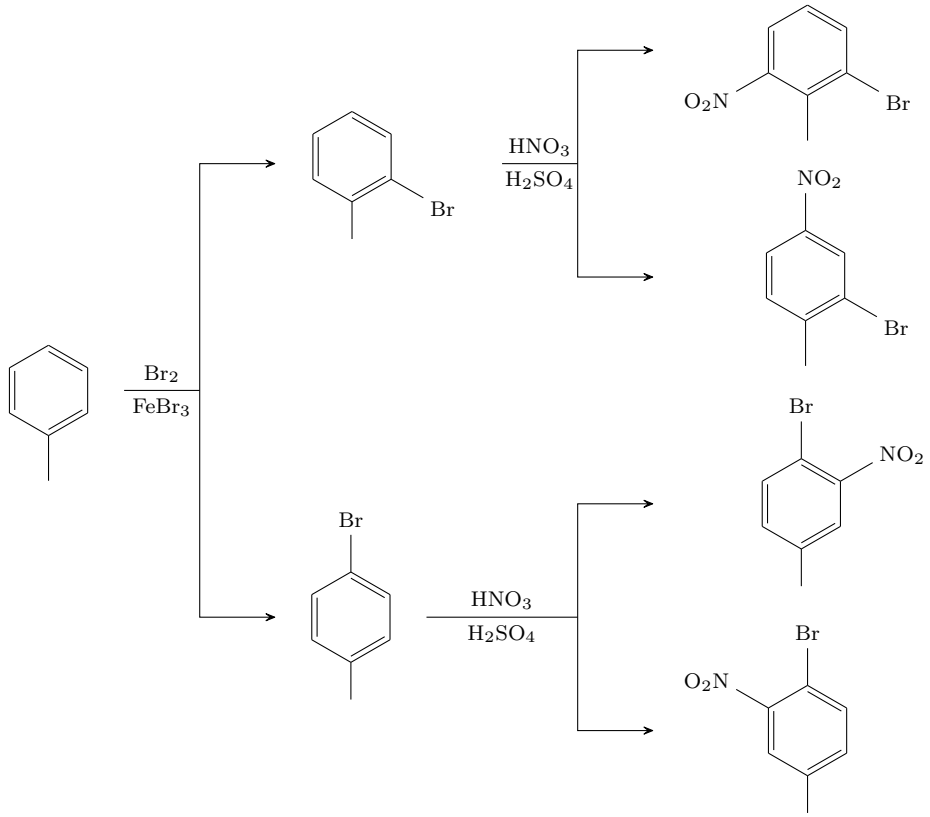


Figure 8.1: Major and minor synthesis products.

– When asked to determine major/minor when it could be kind of ambiguous, assume equimolar concentrations of reactants after the step before the last step.

– In the example above, notice how the two products on the bottom are identical, so they constitute the major product.

8.2 Exam 2 Cheat Sheet

Reactions:

- $C_6H_6 \xrightarrow{D_3O^+} C_6D_6$
- $PhH \xrightarrow[FeBr_3]{Br_2} PhBr$
  - $AlCl_3$, CuI_2.
- $PhH \xrightarrow[H_2SO_4]{HNO_3} PhNO_2$
- $PhH \xrightarrow[H_2SO_4]{SO_3} PhSO_3H$
- $PhH \xrightarrow[AlCl_3]{RCOCl} PhCOR$
- $PhH \xrightarrow[AlCl_3]{RCl} PhR$
- benzylic carbonyl $\xrightarrow[HCl]{Zn(Hg)}$ reduced carbon
- $PhR \xrightarrow[H_2O]{KMnO_4} PhCOOH$
  - Needs benzylic hydrogen.
- $PhNO_2 \xrightarrow{\text{reagents}} PhNH_2$
  - $H_2 + Pd/C$ or $SnCl_2 + H_2O$ (selective).
- $PhNH_2 \xrightarrow[HCl]{NaNO_2} PhN_2^+ + X^-$
  - Mechanism has many equilibrium steps (only first and last are not).
- $PhN_2^+ \xrightarrow[H_2O]{Cu_2O} PhOH$
  - $PhN_2^+ \xrightarrow{CuCl} PhCl$
  - $PhN_2^+ \xrightarrow{CuBr} PhBr$
  - $PhN_2^+ \xrightarrow{CuI} PhI$
  - $PhN_2^+ \xrightarrow{CuCN} PhCN$
- $PhN_2^+ \xrightarrow{D_3PO_2} PhD$
- $PhBr \xrightarrow[NH_3]{NaNH_2} PhNH_2$
- $PhCl \xrightarrow[NuH]{NaNu} PhNu$
- $PhH \xrightarrow[>1000\,\text{psi}]{Pd} CyH$
- benzene $\xrightarrow[NH_3\,/\,EtOH]{2\,Li}$ cyclohexa-1,4-diene $+ 2\,LiOEt$

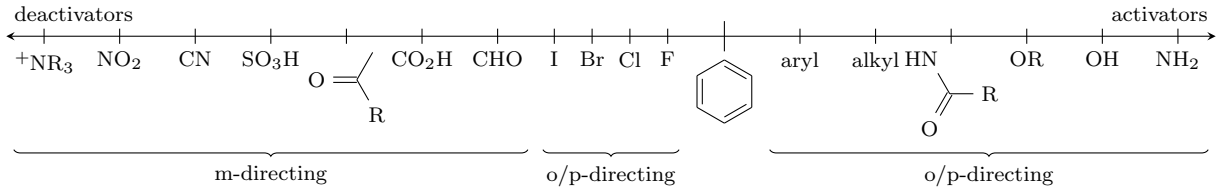
Reminders:

- Aromatic stabilization of benzene: -36.5 kcal/mol.

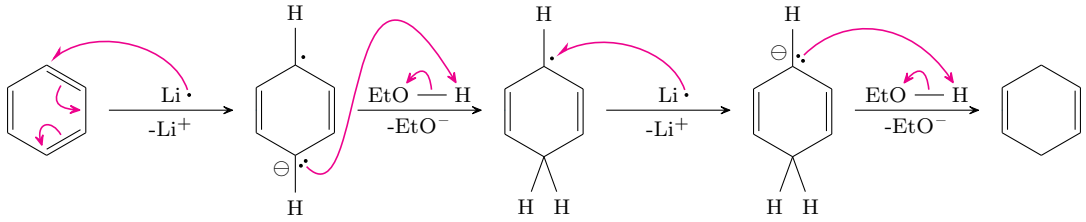
- Frost method: Point down, MOs at the carbons.
  - 5-membered rings: 3 bonding / 2 antibonding. 7-membered: 3 bonding / 4 antibonding.
- Aromaticity checklist: Flat, cyclic, conjugated, uninterrupted flow of p-orbitals, $(4n+2)$-rule.
- $(+/-)$ for Diels-Alder reactions!
- F-C reactions happen ONLY IF there is not an EWG on the ring.
- Add stronger EWGs later.
- Nucleophile strengths.

$$^{-}\text{NRH} > \text{RO}^{-} \,/\, \text{HO}^{-} > \text{Br}^{-} > \text{NR}_3 > \text{Cl}^{-} > \text{F}^{-} > \text{H}_2\text{O} \,/\, \text{ROH} > \text{alkene} > \text{benzene}$$

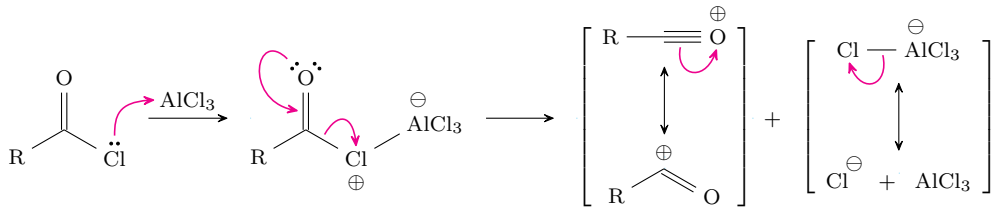
- Breslow (1967), Faraday (1825), Kekulé (1865), Jack Roberts (benzyne).



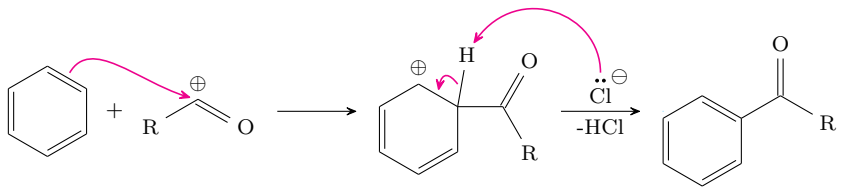
Activators and deactivators.



Birch reduction mechanism.



(a) Acylium ion formation.



(b) Acylation of benzene.

Friedel-Crafts acylation mechanism.