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:

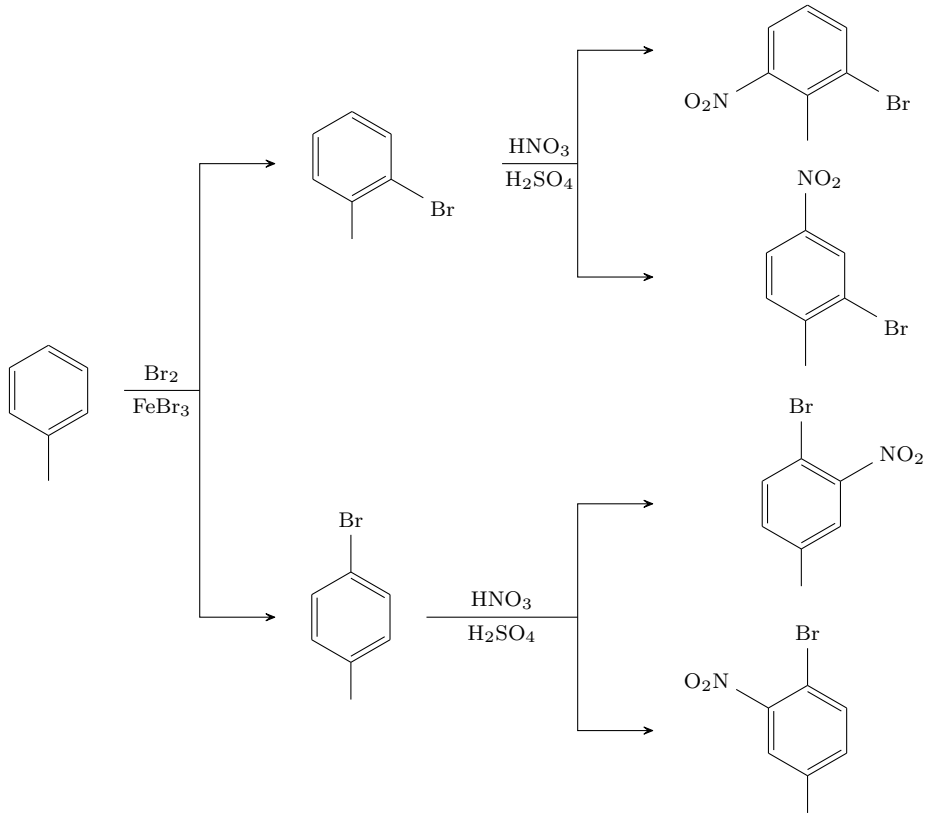


Figure 8.1: Major and minor synthesis products.

– 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 $+ 2\,LiOEt$

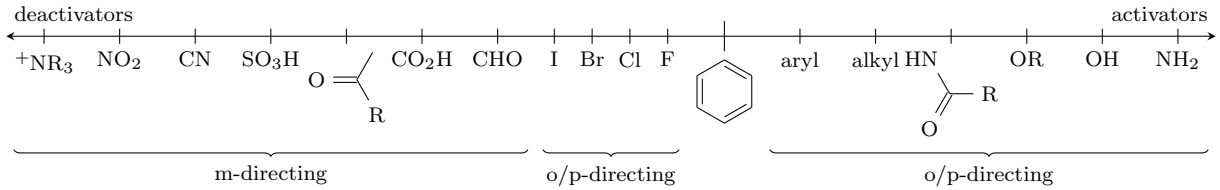
Reminders:

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

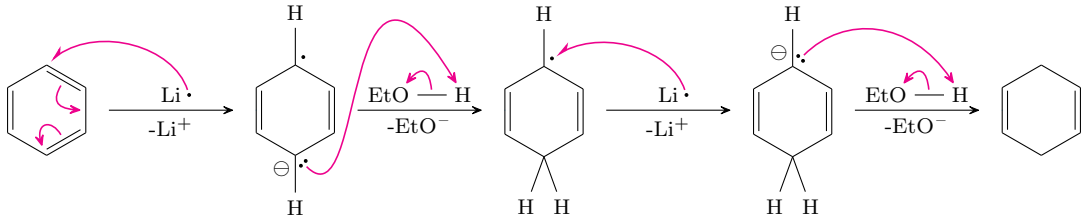
- Frost method: Point down, MOs at the carbons.
  - 5-membered rings: 3 bonding / 2 antibonding. 7-membered: 3 bonding / 4 antibonding.
- Aromaticity checklist: Flat, cyclic, conjugated, uninterrupted flow of p-orbitals, $(4n+2)$-rule.
- $(+/-)$ for Diels-Alder reactions!
- F-C reactions happen ONLY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

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

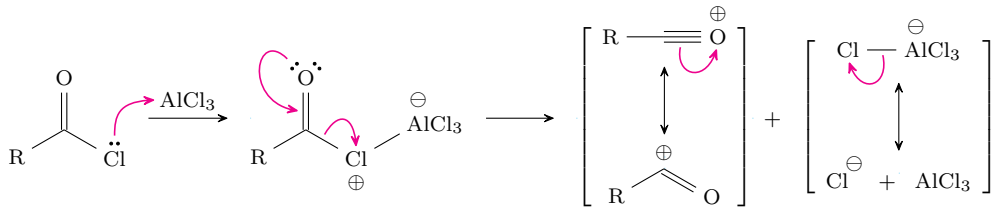
- Breslow (1967), Faraday (1825), Kekulé (1865), Jack Roberts (benzyne).



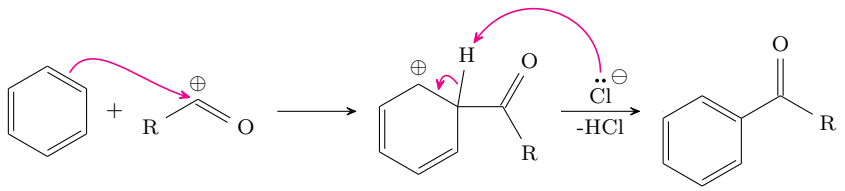
Activators and deactivators.



Birch reduction mechanism.



(a) Acylium ion formation.



(b) Acylation of benzene.

Friedel-Crafts acylation mechanism.

8.3 Alcohols, Ethers, and Epoxides 1

3/3:

- Alcohol chemistry today.
- A fifth optional problem set will be posted today.
- Review of ways to add C−O bonds into molecules.
- **Dihydroxylation**: The treatment of an alkene with OsO_4 followed by $NaHSO_3$, yielding a cis-1,2-diol.
- **Oxidative cleavage**: The treatment of an alkene with $KMnO_4, OH^-, \Delta$ followed by H_3O^+, yielding a ketone.
- Alcohol formation.
  1. Acid-catalyzed hydration.
     - Generally not so useful due to the possibility of rearrangements (CC+ intermediate).
  2. Hydroboration/oxidation.
     - Syn-addition and anti-Markovnikov.
  3. Oxymercuration/demercuration.
     - Markovnikov addition with no rearrangements.
- Now that we know how to make alcohols, we look into what we can do with them.
- Conversion of alcohols into alkyl halides.
- General form.

$$ROH \xrightarrow{HBr} RBr$$

- Mechanism.
  - For a primary alcohol, we use an S_N2 mechanism.
    - Before the main step, however, we need to make the alcohol into a better leaving group. To do so, we protonate the alcohol, converting it into an H_2O^+ group.
  - Secondary, tertiary, benzylic, and allylic alcohols can perform an S_N1 reaction.
    - Hydride shifts are important! They will happen if a 2° CC+ is created next to a 3° carbon, and will make the tertiary product the major one.
    - Additionally, the S_N1 mechanism erases stereochemical information in the reactant.
    - As such, we should avoid reactions in which this mechanism would take place if at all possible.
- Because of the limitations of the above mechanism, we introduce an alternate way to transform alcohols into good leaving groups without passing through a CC+ intermediate.
- Use $SOCl_2$ as a chlorinating reagent.
- General form.

$$ROH + SOCl_2 \xrightarrow{Py} RCl + SO_2 + Cl^- + PyH^+$$

  - There is an inversion of stereochemistry from the alcohol to the alkyl halide.
- Mechanism.
  - The structure of $SOCl_2$.
    - The polar S=O bond makes sulfur electrophilic, which is why the lone pair on the alcohol attacks it in the first step.
    - Chlorine, in addition to being the halogen we are trying to add to our reactant, is a good leaving group, which is necessary for this mechanism to proceed.

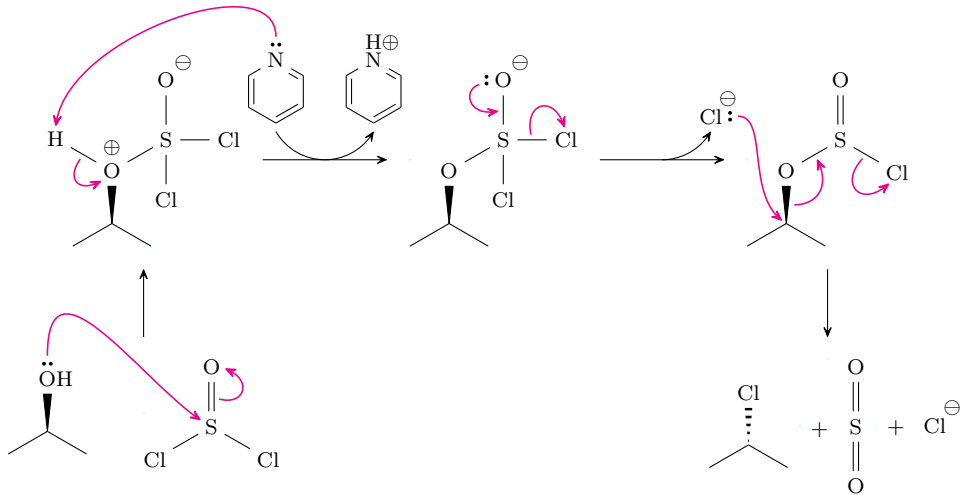


Figure 8.2: Chlorination of an alcohol via the $SOCl_2$ mechanism.

  - The general idea of the reaction is to convert the alcohol into a good leaving group and then perform an S_N2 reaction, thereby avoiding a CC+ intermediate.
  - Indeed, the second-to-last intermediate contains a very good leaving group (SO_2Cl), which is easily pushed out in an S_N2 fashion by Cl^-.

- Use PBr_3 for bromination and PI_3 for iodination.
- The intermediate with the SO_2Cl leaving group is far too reactive to ever be isolated. However, there are mechanisms that can convert an alcohol into a good leaving group without sacrificing stability (i.e., so that the compound can be transformed further at a later date).
- We utilize a 2-step mechanism with tosylate.

$$\mathrm{ROH + Nu} \xrightarrow[\mathrm{NEt_3}]{\mathrm{TsCl}} \mathrm{RNu + HCl}$$

  - This reaction also has an inversion of stereochemistry.

- Mechanism.

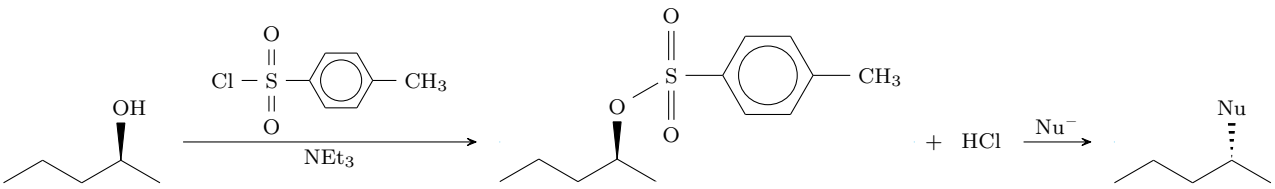
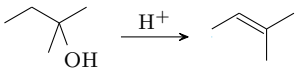


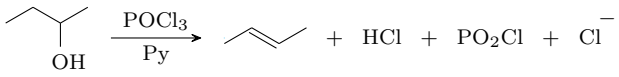
Figure 8.3: Nucleophilation of an alcohol via tosylate mechanism.

  - As before, we begin by using a chlorocompound and a weak base to convert the alcohol into a leaving group. This first step yields an isolable compound.
  - In the second step, which does not need to be performed immediately, we just add the desired nucleophile and S_N2 proceeds.
  - Br^-, I^-, CN^- are all good nucleophiles. Cl^- is not.
  - Note that we can fine tune the aromatic system in tosylate to suit the conditions of a specific reaction better as needed.

- Creating alkenes from alcohols.
- Old way.
- General form.



  - Works only with 3° alcohols.
  - You get a mixture of products.
- These issues are solved the same way as halogenation, i.e., by activating the alcohol, hence avoiding CC+ intermediates and allowing the elimination to proceed in a controlled process.
- New way.
- General form.



  - Uses phosphoryl chloride ($POCl_3$).
  - We use pyridine as our base because it is weak and not very nucleophilic (you want to avoid competition from S_N2).
- The mechanism is analogous to Figure 8.2, except that it ends with E2.
- Having discussed the reactivity of alcohols with respect to substitution and elimination, we now discuss the reactivity of alcohols as nucleophiles.
- Williamson Ether Synthesis.
- General form.

$$\mathrm{ROH} \xrightarrow[\mathrm{MeI}]{\mathrm{NaH}} \mathrm{ROMe} + \mathrm{H_2} + \mathrm{NaI}$$

  - NaH is a very strong base (H does not like to be negative).
- Mechanism.

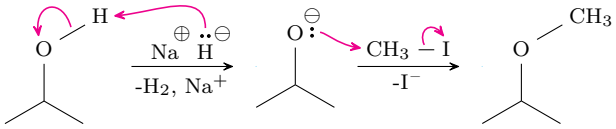


Figure 8.4: Williamson ether synthesis mechanism.

  - S_N2, so use 1° or 2° if needed.
    - For example, t-BuOH + MeI proceeds but t-BuI + MeOH will not proceed.
- The Williamson Ether Synthesis is a reversible process, however.
- Reversal of ethers: Acid-catalyzed cleavage.
- General form.

$$\mathrm{ROR'} \xrightarrow{\mathrm{HBr}} \mathrm{RBr} + \mathrm{R'OH}$$

- Mechanism.

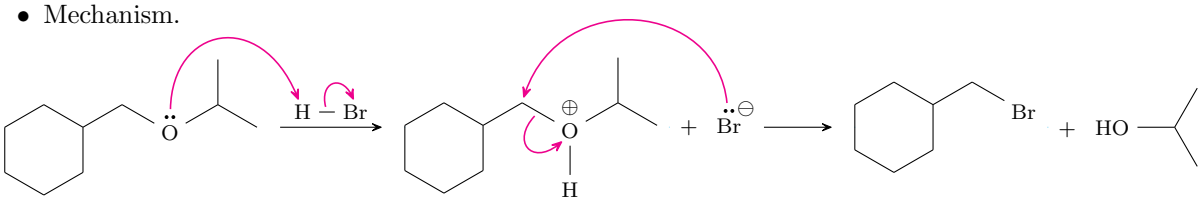


Figure 8.5: Acid-catalyzed cleavage of ethers mechanism.

  - Must have Br^- or I^- to proceed; Cl^- is not nucleophilic enough.

- Protecting groups.
  - Can be added to inactivate reactive sites.
  - For example, you can turn an alcohol ROH into ROPg where Pg is a protecting group. This will inactivate the alcohol so that the rest of the molecule can react under conditions that would usually make the alcohol react. When you are finished tuning the rest of the molecule, you can then remove the protecting group and react the alcohol, if desired.
  - Different protecting groups suit different reactions.
- **Protection**: Adding a protecting group.
- **Deprotection**: Removing a protecting group.
- **Epoxide**: A cyclic ether with a three-atom ring.
- **mCPBA**: meta-Chloroperoxybenzoic acid, the peroxy acid most commonly used to create epoxides from alkenes. *Structure*

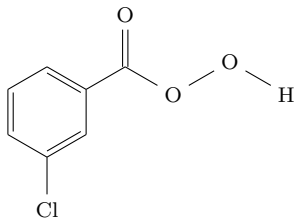
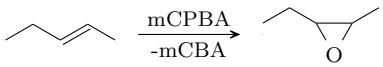


Figure 8.6: meta-Chloroperoxybenzoic acid (mCPBA).

- Creating epoxides from alkenes.
- General form.



  - Epoxides are formed from a reactive carbon-carbon system, e.g., an alkene that interacts with an oxygen donor group.
  - Their formation is formally an oxidation.
  - To add into the carbon-carbon system, the oxygen must be both nucleophilic and electrophilic.
  - A peroxy acid fits the bill because oxygen-oxygen single bonds are good oxidants. In particular, the oxygen further away from the carbonyl is electrophilic, and the ester to which it's bonded is a good leaving group.
  - Relative to peroxy acids, alkenes are nucleophilic.

- Mechanism.

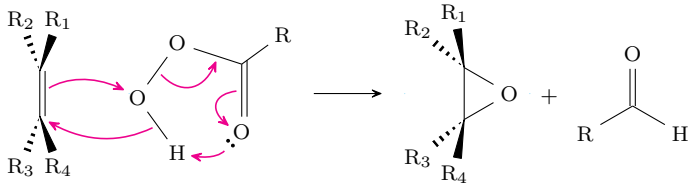
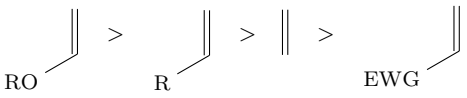
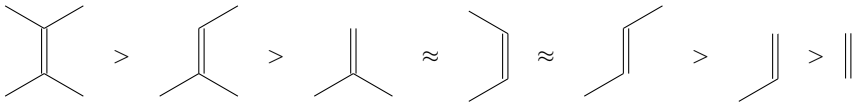


Figure 8.7: Creating epoxides from alkenes mechanism.

  - A concerted mechanism.
  - Stereospecific (chirality is maintained).
  - Note that the most nucleophilic alkenes will react the fastest.



(a) Substituent types.

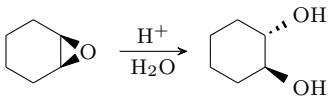


(b) Substitutions.

Figure 8.8: Alkene nucleophilicity.

  - Note that all of the alkenes in Figure 8.8b would rank behind the resonance EDG and ahead of the EWG in Figure 8.8a.
  - Knowing the relative reactivity of alkenes allows us to predict the major/minor products in polyenes. In particular, the more nucleophilic, reactive alkene will be converted into an epoxide more often.

- Creating diols from epoxides.
- General form.



  - Creates a cis-diol.

- Mechanism.

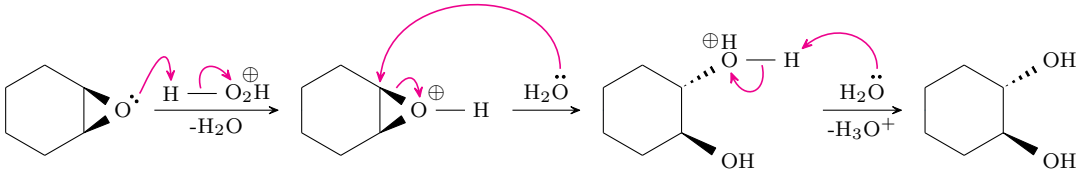


Figure 8.9: Creating diols from epoxides mechanism.

  - 1° or 2° epoxides.
    - The mechanism will primarily be S_N2.
    - Given the choice, the nucleophile will attack the less substituted carbon.
  - Epoxides with at least one 3° carbon.
    - The S_N1 mechanism will be active.
    - Even in this case, though, we will form a cis-product due to the steric bulk of the alcohol group hindering attacks on its face of the molecule.

- We can use the same mechanism with HCl or HBr instead of H_2O to yield a halohydrin with cis stereochemistry.
- Acid- and base-catalyzed ring openings.

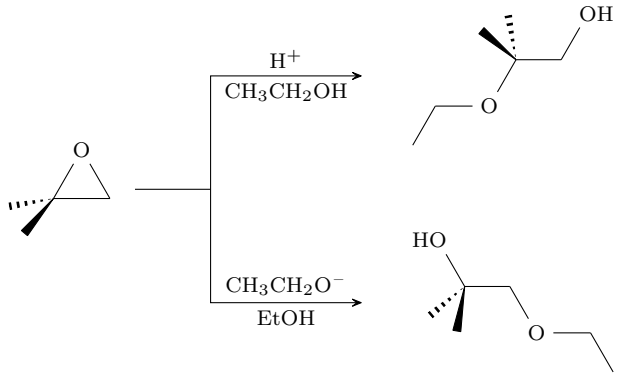


Figure 8.10: Acid- and base-catalyzed epoxide ring openings.

  - Under acidic conditions, carbocation stability drives the reaction.
    - In the acidic reaction in Figure 8.10, we form a formal 3° CC+. This intermediate is subsequently attacked by ethanol, which is then deprotonated.
  - Under basic conditions, the alkoxide ion attacks less hindered carbon via S_N2.
    - In the basic reaction in Figure 8.10, the ethoxide engages in an S_N2 reaction with the 1° epoxide position.
  - If there aren't strong driving forces, though, we can get a mixture of products.

- Epoxide ring openings can be triggered by nucleophiles other than alkoxides, too.
- For example, we can add alkenes into the epoxide with Grignard reagents.

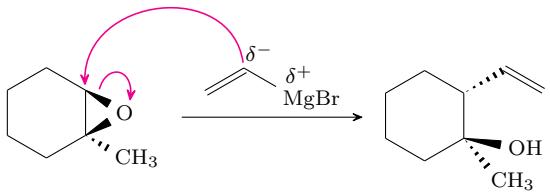
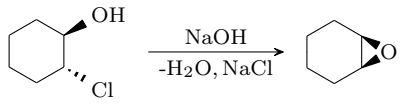


Figure 8.11: Epoxide ring-opening via a Grignard reagent mechanism.

  - This is important as another C−C bond-forming reaction.
  - It is stereoselective, as with the related preceding reactions.
  - It yields a quite complex molecule that can react further in a number of ways.

- Creating epoxides from halohydrins.
- General form.



  - This reaction is not reversible under basic conditions because Cl^- is not nucleophilic enough to attack one of the epoxide carbons without the epoxide oxygen first having been protonated (by an acid).
  - The reactant *must* be a cis-halohydrin because after the alcohol is deprotonated, it reacts with the α-carbon through a backside attack (i.e., in an S_N2 fashion).