6.35 Cationic Rearrangements - 2

11/27:

- Lecture 34 recap.
  - 1,2-hydride shifts are generally favored (all else being equal).
    - This is because shifting a hydride typically produces a more substituted carbocation.
    - 1,2-alkyl shifts will happen if they generate a more stable carbocation.
  - Epoxide openings (Figure 6.18).
    - This is the **Meinwald rearrangement**, named after a Cornell chemist.
  - Pinacol rearrangement (Figure 6.20).
    - Takes a 1,2-diol (also known as a **viscinal** diol) to a ketone.
  - Baeyer-Villiger oxidation (Figure 6.22).
    - Converts a ketone into an ester, or a cyclic ketone into a lactone.
    - Know the migratory aptitudes! Example: In *tert*-butyl methyl ketone, the *tert*-butyl group will migrate first.
- Today: More carbocation rearrangements.
- Lecture outline.

  C. Reactions.
    3) Rearrangements and fragmentations.
       - Beckmann rearrangement.
    4) Neighboring group participation.
       a) Aromatic rings as neighboring groups.
       b) Carbonyls as neighboring groups.
- We now return to Subtopic C.3: Rearrangements and fragmentations.
- The Beckmann rearrangement.

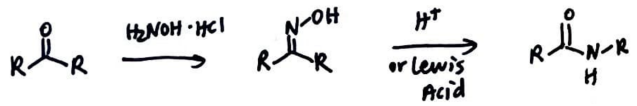


Figure 6.24: Beckmann rearrangement.

  - Take a ketone and add hydroxylamine hydrocholoride (recall from Figure 3.18b) to form an oxime, and then use an acid catalyst to make an amide.
- This reaction is more important at scale than the previous rearrangements we've discussed (not testable content).

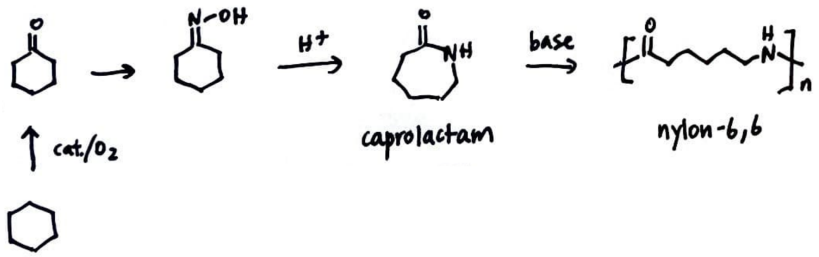


Figure 6.25: Synthesizing nylon!

- This reaction is important because if you want to make a billion of tons of cyclohexanone, start from cyclohexane and subject it to oxygen and a catalyst.
- Then make the oxime.
- Then use your acid catalyst; it used to be a sulfuric acid catalyst, but now they use an acidic clay.
- This yields caprolactam, the polymerization of which makes nylon-6,6 (or nylon!).
- Prof. Buchwald once did some consulting on improving the efficiency of this reaction from 99.83% to 99.84%, which may seem small but means millions of dollars per year in savings.

- Mechanism of the Beckmann rearrangement.

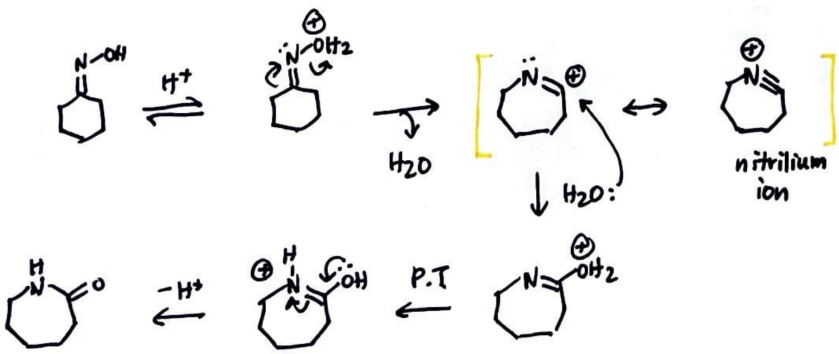
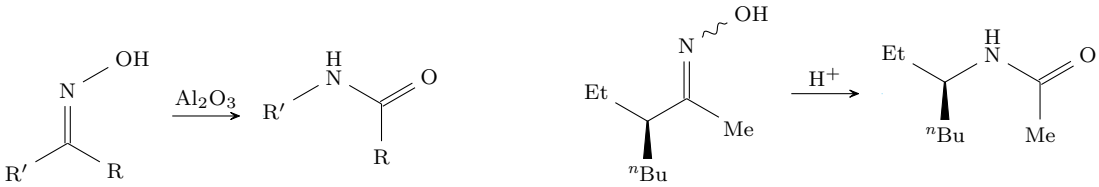


Figure 6.26: Beckmann rearrangement mechanism.

- The nitrogen gets protonated far more often than the oxygen, but every once in a while, the oxygen will be protonated.
- This oxygen protonation allows the rest of the mechanism to proceed, starting with a migration and departure of the leaving group.
- This yields a nitrilium ion, which is very strained.
- The nitrilium ion can then react with water.
- Then, following proton transfer, we get deprotonation to the product.

- Selectivity of the Beckmann rearrangement.



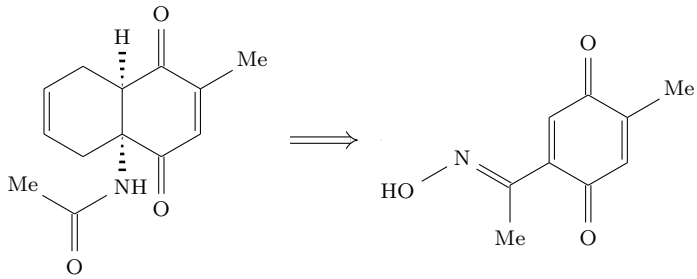
(a) *anti*-migration with weak acid.

(b) Baeyer-Villiger-type migration with strong acid.

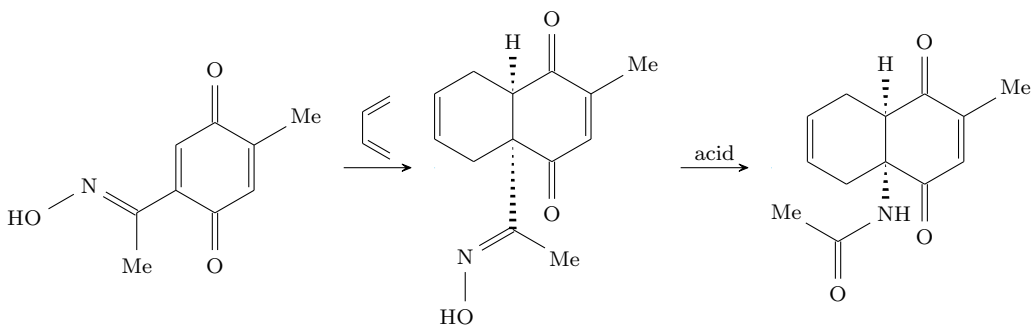
Figure 6.27: Beckmann rearrangement selectivity.

- Only the *anti*-group migrates!
  - This is on full display with the use of a weak Lewis acid like Al_2O_3.
  - Coordination is weak, so you need the *anti*-oriented push.
- However, there is a caveat: If you use a 10 : 1 mixture of oxime isomers that is enantiomerically pure at the α-carbon, you only form a single stereoretentive product.
  - Indeed, the strong acid makes selectivity identical to that of the Baeyer-Villiger.
- Takeaway: Weak Lewis acid catalysis implies that only the *anti*-group migrates, while strong acid catalysis makes selectivity depend on the Baeyer-Villiger migratory aptitude.

- TTQ: Merging Profs. Elkin's and Buchwald's content.



(a) The desired molecule and starting materials.



(b) Retrosynthetic pathway.

Figure 6.28: TTQ: Merging Unit 2 and Unit 6 content.

  - Synthesize the molecule at left in Figure 6.28a from the provided starting material.
  - Looking at the cyclohexene in the product, it seems like we might be able to start with a Diels-Alder reaction!
    - Potential ambiguity: Which enantiomer are we forming? We will indeed form both, but we will only form one diastereomer (from the *endo* transition state, etc.)
    - Potential ambituity: Which side is the stronger dienophile? The left side is because it has the stronger EWG attached.
  - Then we just need a Beckmann rearrangement, which we can cause using acid (either H^+ or Al_2O_3)!

- Recall that we've discussed that substituents can affect reactions, e.g., through steric hindrance or an EWG near a carbonyl. We'll now discuss a topic that's similar to this, but a bit different.

- We now move onto Subtopic C.4: Neighboring group participation.

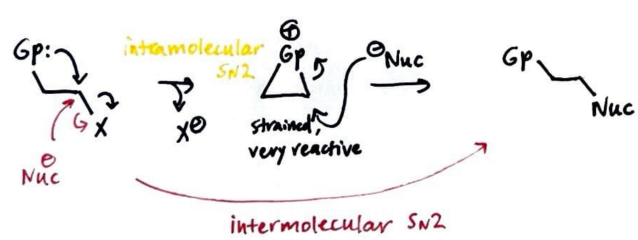
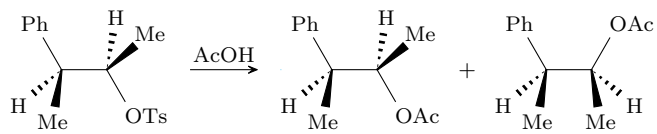


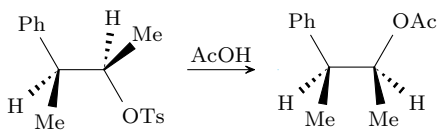
Figure 6.29: Neighboring group participation.

- Consider a group with a lone pair.
- This group can speed up displacement of an adjacent leaving group (because intramolecular chemistry is faster), and speed up subsequent nucleophilic attack because it forms a charged intermediate.
- This wins by $\Delta\Delta G^{\ddagger}$ over direct S_N2-type displacement.

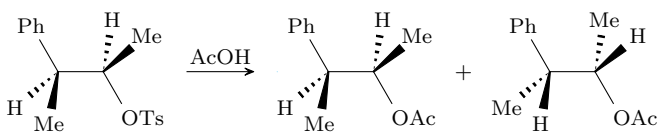
- We now move onto Subtopic C.4.a: Aromatic rings as neighboring groups.



(a) S_N1 products.



(b) S_N2 products.



(c) Actual products.

Figure 6.30: Neighboring group participation provides an alternative to S_N1 and S_N2.

- Consider the above **solvolysis** reaction of a single enantiomer, carried out in acetic acid.
- If tosylate is going to leave, it can do so by either an S_N1 or S_N2 mechanism.
- If S_N1...
  - We should form two diastereomers as products (the left stereocenter is retained, and the right one may or may not be flipped).
- If S_N2...
  - We should form exactly 1 diastereomer (the inverted one) as a product.
- However, when we do the actual experiment, we get two enantiomers as products!

- **Solvolysis** (reaction): A reaction in which the solvent and the reactant are the same.
- How can we explain the result in Figure 6.30c?

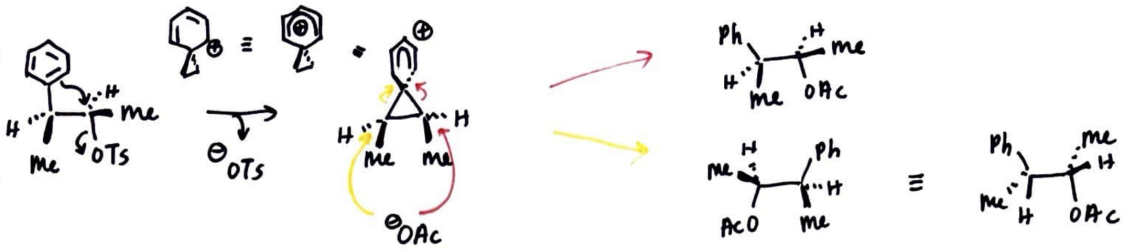


Figure 6.31: Neighboring group participation with aromatic rings.

- The phenyl group attacks the other carbon, pushing out tosylate and forming an intermediate.
  - The positive charge in this intermediate gets spread out over 5 carbons.
  - This intermediate also has a plane of symmetry.
- Because of the plane of symmetry, acetate can add to either the right or left sides, giving our enantiomeric products.
  - Indeed, we have destroyed our asymmetry by going through a symmetric intermediate.
  - Principle: Any reaction that goes through an achiral intermediate will *not* give an enantioenriched product (at least for the purposed of 5.13).

- We now move onto Subtopic C.4.b: Carbonyls as neighboring groups.
- Consider a single enantiomeric starting material, heated in acetic acid.

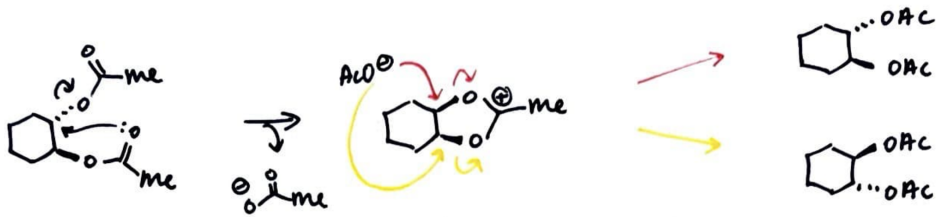


Figure 6.32: Neighboring group participation with carbonyls.

- The result is that we get a racemic mixture of products!
- Thus, we must be going through an achiral intermediate, which we can build with the displacement drawn in Figure 6.32.
- Note that the starting material is **chiral** and **enantiomerically pure**, while the product is chiral and racemic. This subtlety is often missed!

- **Chiral**: You have two hands that are not superimposable.
- **Enantiomerically pure**: You only have one of those hands.
- Recall our discussion of the Hock process (Figure 6.8) from couple of lectures ago.

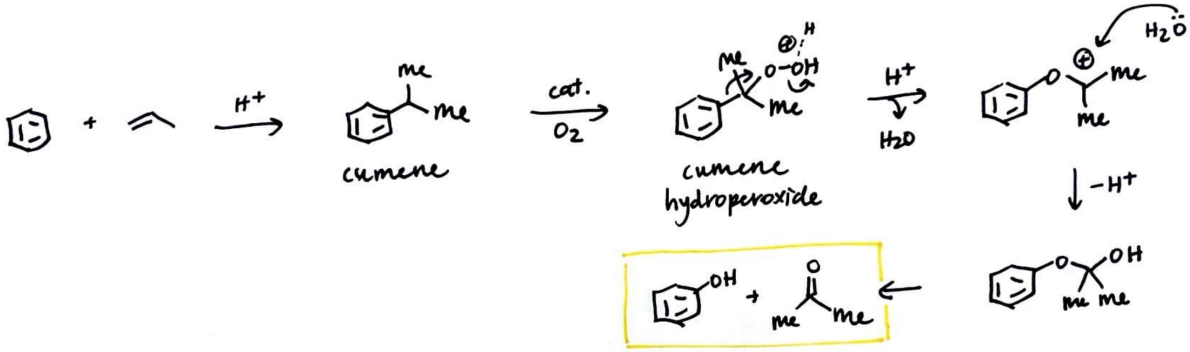


Figure 6.33: Hock process (stages 1-2).

- The Hock process produces phenol (the smell of paste when Prof. Buchwald was a child) and acetone (nail polish remover, and an industrial solvent).
- It does so on an unbelievable scale each year.
- The process works by forming **cumene** in the presence of an acid catalyst.

- We then form **cumene hydroperoxide**, an unstable intermediate, which rearranges and then fragments into the products.
- You would think that there is a simpler way to do this, but because it produces *two* value-added products at scale with cheap starting materials (benzene and propene are both products of petroleum cracking), it is more economical.