  - We assume that this reaction is thermal (even though there is no Δ above the arrow) by default.
    - If we just see acid/reagents and no triangle, assume thermal.
    - If we see $h\nu$, *then* we consider the photochemical pathway.
  - There are 5 atoms and 4 electrons in the π-system, so per the three rules from Lecture 12, there will be five MOs and the lowest two will be filled.
    - Thus, the HOMO is the 2nd energy level, so it will have 1 (symmetric) node.
    - Because this is an odd number of atoms, the middle p-orbital gets deleted!
  - As we have drawn our HOMO, a conrotatory pathway will unite lobes with like shadings.
  - This yields the *trans*-product.

- Example: The product of a Nazarov cyclization after an alternate deprotonation.

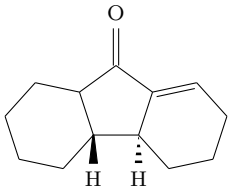


Figure 2.54: Alternate deprotonation sites in Nazarov cyclizations.

  - If we trace through the mechanism that would form this product, we can see that we just deprotonated the post-4π electrocyclization carbocation at a different β-H.
  - Under thermal conditions, we would get the *trans*-product (as drawn).
  - Under photochemical conditions, we would *not* get the molecule in Figure 2.54 but would get the *cis*-product instead.

- There are still a few examples that Prof. Elkin wanted to get through today, but we ran out of time, so they'll be shared in a Canvas announcement.

- Looking ahead.
  - Spend the weekend resting and catching up.
  - Next Wednesday: Sigmatropics.
  - Next Friday: Exam review.

2.17 Sigmatropic Rearrangements

10/16:

- Lecture 16 recap: Considerations for electrocyclizations.
  - Woodward-Hoffmann rules.
    - Prof. Elkin redraws Table 2.1.
  - Conrotatory and disrotatory.
    - To derive this, first draw the HOMO.
    - Then make σ-bonds by rotating the terminal p-orbitals so that the phases match.
  - Misc.
    - Nazarov cyclization (a 4π electrocyclization, not 5π as was accidentally written last lecture).
    - Principle of microscopic reversibility: This helps you understand which product you get in certain retro-electrocyclizations.

- Announcements.
  - Looking ahead: Friday.
    - A review of Unit 2 material.
    - Prof. Elkin will discuss what she believes you should focus on studying!
  - You will learn the most by taking the practice exams timed and closed-book!
- Today: Sigmatropic rearrangements.
  - This is the end of the material for Unit 2; sigmatropics are our last pericyclic reaction!
- Lecture outline.
  - Cope rearrangement: General form, orbital picture, stereochemistry, special types.
  - Claisen rearrangement: General form, examples, stereochemistry.
  - Hydrogen atom shifts: Antarafacial example, suprafacial example, photochemical.
- We'll start with a classic named reaction in the sigmatropic family: The Cope rearrangement.
  - Cope was an MIT alumnus!
- General form.

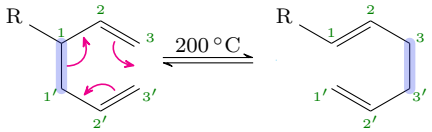
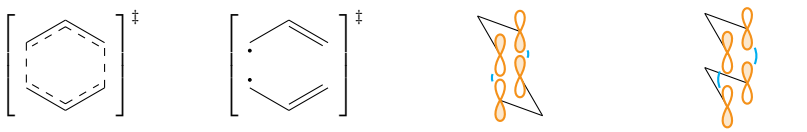


Figure 2.55: Cope rearrangement.

  - The Cope rearrangement proceeds circle arrows, as in any pericyclic reaction.
  - It is reversible.
  - It is thermal, typically occuring around 200 °C.
  - It is classified as a **[3, 3] sigmatropic rearrangement**.
- **[3, 3] sigmatropic rearrangement**: A sigmatropic rearrangement in which the σ-bond moves 3 atoms at one end and 3 atoms at the other end.
  - Numbering our atoms as in Figure 2.55, observe that the σ-bond moves from atoms 1 and $1'$ to atoms 3 and $3'$!
  - This nomenclature is defined another way in Clayden et al. (2012), and another way on Wikipedia and Google, so read a bunch of different definitions and see what sticks :)
  - We're not huge sticklers for nomenclature, but you should learn this!!
- An orbital picture for the Cope rearrangement.



(a) True TS. (b) Radical TS. (c) Chair TS. (d) Boat TS.

Figure 2.56: Cope rearrangement orbitals in 3D space.

- In a pericyclic transition state, all bonds are forming and breaking at the same time (Figure 2.56a).
  - Notice the similarity between Figure 2.56a and the transition state of Figure 2.8!
  - Observe that there is an unchanged "σ-backbone" on the top and bottom.
- Thus, the transition state is kind of like two allyl radicals interacting (Figure 2.56b).
  - Recall the MOs of an allyl radical from Figure 2.16.
  - These MOs tell us that both allyl radicals will interact with their SOMO.
- We can then draw out these SOMOs in 3D, interacting through either a *chair* (Figure 2.56c) or a *boat* (Figure 2.56d) transition state.
  - In each case, we get good overlap at both the bond-breaking and bond-forming positions.
  - However, since chair conformations are usually more stable than boat conformations (as you should recall from 5.12), the chair transition state will usually be more stable than the boat transition state.
  - Note that we mention the boat transition state at all because even though it's less favorable, it can still happen.[13]
- These transition states are super important because they're how we predict stereochemistry!
- Note that we can also split the system into a cation and an anion, and we'll still get good orbital overlap and all the same transition-state stereochemistry.
  - Indeed, splitting into two radicals is more of a convention.
  - You can (and should) try drawing this cation/anion scheme out!!
  - The fact that it works both ways is yet more evidence that MOs are a good, meaningful model.

- Stereochemistry of the Cope rearrangement.

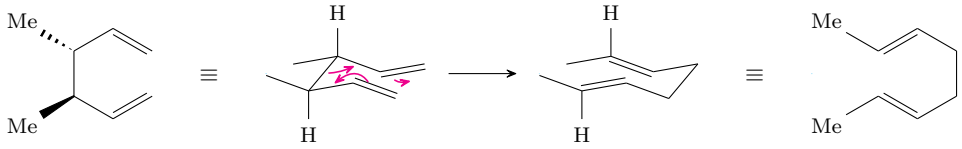
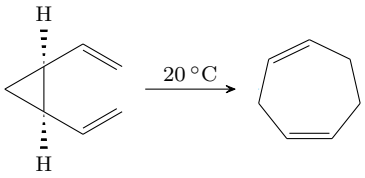


Figure 2.57: Cope rearrangement stereochemistry.

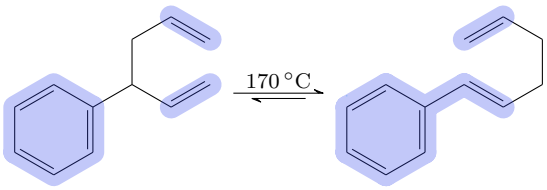
- The Cope rearrangement is stereospecific.
  - Indeed, just like the Diels-Alder (see Figure 2.23), the stereochemistry of the reactant translates directly into whether the product has *cis*- or *trans*-olefins.
- To determine the (major[14]) product, draw the starting material in the most stable chair conformer.
  - In this case, the most stable chair is the one in which both methyl groups are equatorial. This minimizes 1,3-diaxial interactions.
  - The double bonds also point down and up along the lines of the chair.
- Then we draw circle arrows to help us move the bonds.
  - These allow us to draw the product in the chair conformation.
  - Then we must "unfold" the chair into a 2D representation.
- To unfold this structure, first observe that both olefins are *trans*.
  - Then all we need to do is draw a 2D representation that also has two *trans*-olefins, and we're good to go!
- If it helps to draw in the hydrogens, you should feel free to.

[13] Specifically, it can lead to some alternate stereoisomers as minor side products; see Figure 2.57.
[14] We will also have some product formed from the boat transition state, but you are not responsible for this!

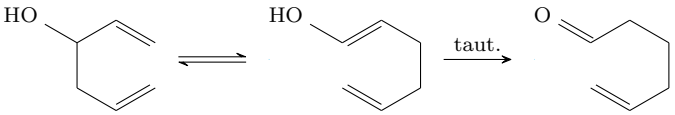
- As mentioned in Figure 2.55, the Cope rearrangement is an equilibrium reaction. But for it to be synthetically useful, we need to be able to drive the equilibrium toward starting materials or products. How can we do this?



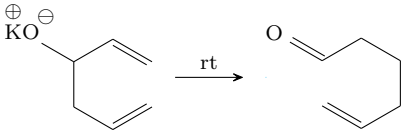
(a) Release of ring strain.



(b) Conjugate a product olefin.



(c) Oxy-Cope rearrangement.

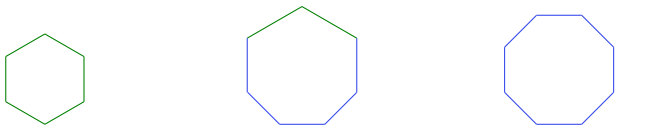


(d) Anionic oxy-Cope rearrangement.

Figure 2.58: Methods to drive the equilibrium in a Cope rearrangement.

1. Release ring strain (Figure 2.58a).
   - If we put a 3-membered ring in our reactant, we get a 7-membered ring in the product that is far more stable.
   - The temperature we need to run this reaction is only about 20 °C!
2. Create a conjugated product (Figure 2.58a).
   - If you can make your product significantly more stable, you'll drive the equilibrium that way.
   - One way to do this is to build a starting material such that one of the new double bonds formed will be conjugated to the *aryl* ring.
     - Note that the newly conjugated olefin will still *not* be conjugated with respect to the product olefin at the other terminal.
   - This is energetically favorable because it's a reduction of the number of independent alkene systems from 3 to 2.
   - The temperature we need to run this reaction is down from the initial 200 °C (Figure 2.55) to about 170 °C.
3. Make it an **oxy-Cope rearrangement** (Figure 2.58c).
   - To do so, add an alcohol to the 1 or 1′ carbon.
   - This way, the product tautomerizes to a ketone (which is far more stable than the starting material).
   - This method is very common and ubiquitous in the chemical literature, hence why it has it's own name.
4. Make it an **anionic oxy-Cope rearrangement** (Figure 2.58d).
   - To do so, start with an oxy-Cope substrate and add a base to solution so that we can form the deprotonated alkoxide.
   - Then the Cope rearrangement and subsequent keto-enol tautomerization will occur at room temperature (rt).
   - Why is this reaction so much faster than the oxy-Cope?
     - The anionic starting material is higher energy than the neutral starting material, so it takes less *additional* energy for the starting materials to reach the transition state.
     - Indeed, this is another example of ground state destabilization! See Figure 2.38b.

- Aside: Drawing 7-membered rings.



(a) 6-membered. (b) 7-membered. (c) 8-membered.

Figure 2.59: Drawing a 7-membered ring.

  - When drawing 7-membered rings on paper, draw an octagon with a hat!
  - This is much easier to draw freehand than the exact angles, as in Figure 2.58a.
  - Drawing 7-membered rings like this on your exam will make your graders' lives easier!
- Tip: If it's been a while since you've drawn chairs, practice this!!
- This concludes our discussion of the Cope; we now move onto another special sigmatropic.
- The Claisen rearrangement.
  - This reaction is like the Cope, but with an oxygen in the ring.
- General form.

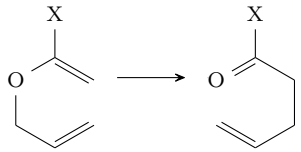


Figure 2.60: Claisen rearrangement.

  - The starting material in Figure 2.60 is called an **allyl vinyl ether**.
  - It does a rearrangement to form a carbonyl.
    - The driving force comes from the fact that carbonyls are more stable than ethers.
  - Like the Cope, this is *also* a $[3,3]$ sigmatropic rearrangement.
- The Claisen rearrangement can be accelerated by adding different substituents in the X position.

X	$\boldsymbol{\Delta H}$ **(kcal/mol)**
H	-16
OR	-28
NHR	-30

Table 2.2: Substituent effects on the Claisen rearrangement.

  - If X = H, the product is an aldehyde.
  - If X = OR, the product is an ester.
  - If X = NHR, the product is an amide.
    - This is the most stable product, so it's the most downhill reaction.
  - Why does stability decrease from amides to esters to aldehydes?
    - We'll cover this in another Unit later this semester!

- Example: Claisen rearrangements in aromatic systems.

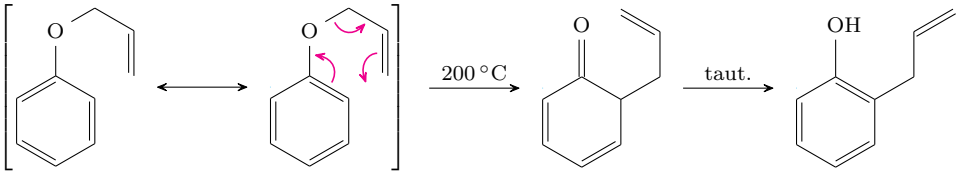


Figure 2.61: Claisen rearrangement of allyl phenyl ether.

  - Claisen rearrangements can occur even with substrates that might not immediately look like they could engage in such reactivity.
  - For example, consider the molecule at left in Figure 2.61.
    - This molecule is aromatic.
    - Indeed, the "vinyl" group is actually part of an aromatic system here!
  - To make it easier to see which aromatic double bond we should engage, we can redraw the starting material as its resonance structure.
    - Then we can push arrows in our Claisen rearrangement to yield a nonaromatic intermediate.
  - This intermediate then tautomerizes into an enol.
    - Enols are usually less stable than ketones, but this enol is aromatic.[15] Therefore, it's favored.
  - This Claisen rearrangement happens at 200 °C because it's not quite as thermodynamically downhill as some others.

- Stereochemistry of the Claisen rearrangement.

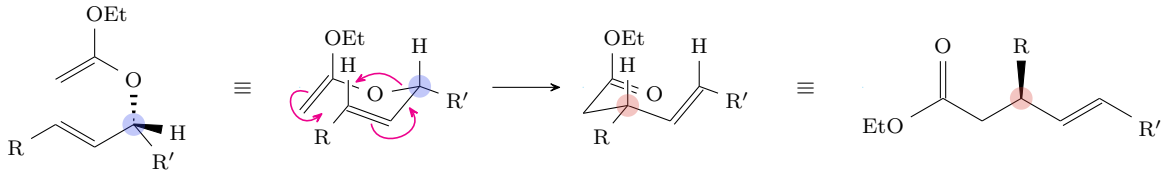


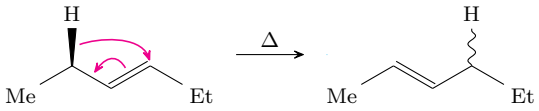
Figure 2.62: Claisen rearrangement stereochemistry.

  - Like the Cope, the Claisen rearrangement is stereospecific.
    - As such, the one stereocenter (blue) in the starting material will determine whether the product has a *cis*- or *trans*-olefin.
  - To determine the product stereochemistry, we once again draw a chair-like transition state.
    - This time, the way to make the most things equatorial is to put the two R groups equatorial and leave the ethoxy group axial.
    - Drawing in hydrogens can help you figure out the substituent positions at the stereocenter!
  - Then we draw circle arrows to help us move the bonds to the product chair.
  - We now unfold the product chair.
    - The new olefin is *trans*.
    - The new stereocenter (red) will be Cahn-Ingold-Prelog (R) if R = Me, for example.
    - Therefore, we can draw the product linearly with a *trans*-olefin and "(R)" stereocenter.

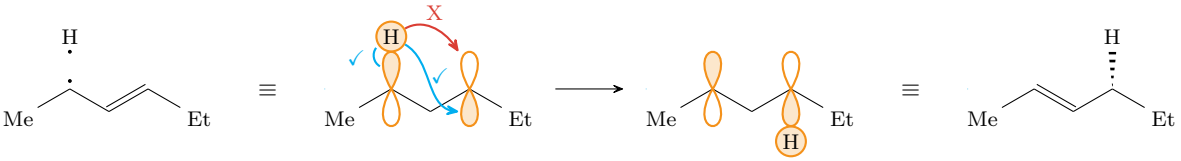
- This concludes our discussion of the Claisen rearrangement.

[15] Technically, we call aromatic enols, "phenols."

- We now move onto sigmatropic hydrogen atom shifts.
  - Note that chemists refer to these reactions interchangeably as "hydrogen atom shifts," "H-atom shifts," "H shifts," etc.
  - We can also have sigmatropic methyl shifts, though we won't discuss these explicitly this lecture.
- Example: A $[1,3]$ H-atom shift.



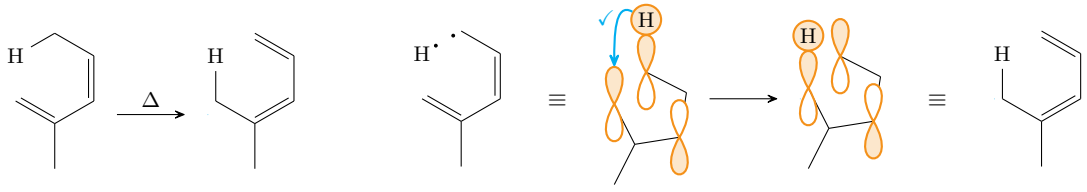
(a) A $[1,3]$ H-shift.



(b) Orbital pathway.

Figure 2.63: $[1,3]$ hydrogen atom shift.

  - This reaction is classified as a **[1, 3] sigmatropic rearrangement**.
  - The general form involves the migration of a hydrogen through a concerted, pericyclic transition state (Figure 2.63a).
  - However, we need orbitals to determine the stereochemistry at the new stereocenter (Figure 2.63b).
    - Treat the transition state as a diradical, like with the Cope (see Figure 2.56).
      - Breaking bonds, we get one allyl radical again (3 p-orbitals and 3 electrons), but we also get a hydrogen radical (1 s-orbital and 1 electron).
      - Draw the reactive MOs for these two radicals.
    - Now for the hydrogen to move, it has to find another lobe with the right shading.
      - In particular, the H can't just jump to the other top orbital because said top orbital has the wrong shading.
  - Takeaway: For H to move, it has to cross to the other face of the molecule.
    - This is called **antarafacial** movement.
      - This contrasts with **suprafacial** movement, which we'll discuss in the next example.
    - Practically speaking, antarafacial moves are rare. But they are possible!
      - See Clayden et al. (2012) for movement in larger systems!!
- **Antarafacial** (movement): Movement of an atom to a position on the *opposite* face of the molecule.
- **Suprafacial** (movement): Movement of an atom to another position on the *same* face of the molecule.
- Example: Consider a $[1,5]$ H-atom shift.



(a) A $[1,5]$ H-shift.

(b) Orbital pathway.

Figure 2.64: $[1,5]$ hydrogen atom shift.

  - This reaction is classified as a **[1, 5] sigmatropic rearrangement**.
    - In fact, it is the same reaction we discussed several lectures ago in Figure 2.11!
  - We predict the product stereochemistry by continuing to use the same method as before.
    - This time, we split into a pentadienyl radical (5 p-orbitals and 5 electrons) to complement our hydrogen radical (1 s-orbital and 1 electron).
    - The HOMO of the pentadienyl radical will be the 3rd energy level, so it will have 2 symmetric nodes.
      - ➢ It may be helpful to draw the HOMO on a straight line first (as in Figure 2.14) and then "wrap it around" onto the intermediate drawn in Figure 2.64b.
    - With the orbitals drawn, we must (once again) move the hydrogen to another lobe with the right shading.
      - ➢ This time, however, the H can just jump directly over from shaded to shaded.
      - ➢ This is suprafacial movement!
  - Practically speaking, suprafacial moves are common.
    - [1, 5] H-atom shifts happen frequently, whether we like it or not!
    - This is a real thing: When we try to make a product in the lab, we often access conditions in which the hydrogen will just dance back and forth.
    - Indeed, there are isotopic labeling studies in which a molecule with deuterium (D) on one position will engage in [1, 5] H/D-shifts to such an extent that the deuterium will become scrambled (i.e., equally distributed between the two possible positions) over time.
    - See Clayden et al. (2012) for more.

- We can do all of these rearrangements photochemically as well, instead of thermally.
  - This will lead to the opposite things from before, because we now have a new HOMO.
  - Implication: Photochemical [1, 3] shifts will be suprafacial and photochemical [1, 5] shifts will be antarafacial.
  - You should try drawing these new orbitals and arrangements out!!

- Note: Clayden et al. (2012) says that [1, 3] suprafacial is thermally forbidden, but practically, there is a small possibility that this will happen.