3. Figure 2.31c: A cool example of an inverse electron-demand Diels-Alder reaction.
   - The heteroatoms (nitrogens) in the ring of the diene should clue us into the fact that this might be an inverse electron-demand Diels-Alder reaction. (See the definition of inverse electron-demand Diels-Alder reaction.)
     - Indeed, this diene is called a **tetrazine**, and it can do inverse electron-demand reactions.
   - The diene within the tetrazine ring is highlighted in red, and the reactive alkene within the dienophile is highlighted in blue.
   - Drawing the product of the first Diels-Alder reaction can be a bit tricky, but Prof. Elkin has a good method for doing it.
     - Begin by stacking the starting materials in a perspective drawing.
     - Add dashed lines between the bonding atoms, yielding a drawing of your transition state.
     - Fill in the dashed lines and rearrange the double bonds to complete the transformation.
   - What's cool about this reaction is that there is an immediate follow-up reaction to the first Diels-Alder.
     - In particular, the product of the first step does a retro-Diels-Alder, releasing N_2 gas.
       - ➢ The release of an extremely stable gas molecule is a driving force for this second reaction.
     - Once N_2 is released, we can redraw the product (now the final product) as a **diazine**.

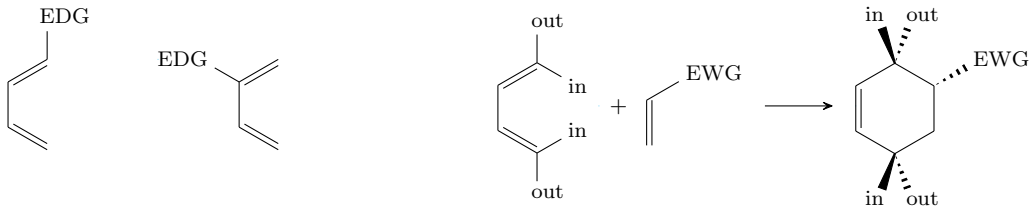
- **Tetrazine**: A molecule with a central six-membered aromatic ring containing four nitrogen atoms.
- **Diazine**: A molecule with a central six-membered aromatic ring containing two nitrogen atoms.

2.15 Cycloadditions

10/9:
- An update on who won this year's Nobel Prize in Chemistry!
  - Awarded for: The computational design and prediction of protein structures.
  - ½ share: David Baker (University of Washington-Seattle).
    - For artificial protein design and synthesis.
    - One of the things he did was design and synthesize a protein to catalyze Diels-Alder reactions, called Diels-Alderase! You can read more about it in Siegel et al. (2010).
      - ➢ Diels-Alderases were hypothesized to exist ever since the discovery of the Diels-Alder reaction, but they were not found in nature until 20 years ago when we isolated the first natural Diels-Alderase from a mango tree.
  - ¼ share, each: Dennis Hassabis and John Jumper (both from Google DeepMind).
    - For building a computer program called AlphaFold.
      - ➢ AlphaFold predicts protein structures from their amino acid sequences.
      - ➢ This largely solves the **protein folding problem**.
      - ➢ Hassabis and Jumper used basically poured all of Google's computational resources into this endeavor and combined it with a lot of machine learning to create a true tour de force of engineering.
      - ➢ When the dust settled, AlphaFold worked pretty well, and it's now used all over the world.
      - ➢ AlphaFold still needs some future development, though.
    - Prof. Elkin is especially interested in this topic because she *researches* the intersection of machine learning and chemistry.
      - ➢ She will give a "special topics" lecture on it later this semester!
      - ➢ If you are curious about machine learning and chemistry, too, come talk to her!!

- **Protein folding problem**: Given a sequence of amino acids, predict the structure of the protein.

- Lecture 14 recap: A cheat sheet for Diels-Alder reactions.



(a) *o*- and *p*-selective dienes. (b) Stereochemistry.

Figure 2.32: Diels-Alder cheat sheet.

  - Reactivity.
    - Normal electron-demand Diels-Alder reactions are accelerated by...
      - EDGs on the diene;
      - EWGs on the dienophile;
      - Promoting the s-*cis* conformation of the diene;
      - Lewis acid catalysts.
    - Inverse electron-demand Diels-Alder reactions are also accelerated by all of these things, except you switch EDGs to the dienophile and EWGs to the diene.
  - Regiochemistry (Figure 2.32a).
    - *ortho*- and *para*-products are preferred.
    - A diene with an EDG on the 1-position (left diene in Figure 2.32a) favors the *ortho*-product.
    - A diene with an EDG on the 2-position (right diene in Figure 2.32a) favors the *para*-product.
  - Stereochemistry (Figure 2.32b).
    - The dienophile's stereochemistry matters.
      - A *cis*-dienophile implies a *cis*-product, and a *trans*-dienophile implies a *trans*-product.
      - See Figure 2.23.
    - The *endo* transition state is preferred.
      - This means that we usually form the sterochemistry shown in Figure 2.32b.
      - In particular, the EWG should be *cis* to the "out" substituents.
  - You *will* need to know the reasons behind all these things and be able to derive them with orbitals on the exam.
    - However, these shortcuts can help us on "predict the product"-type questions.

- Today: Cycloadditions.

- Lecture outline.
  - Dipolar cycloadditions.
    - Examples of dipoles.
    - Example reactions.
    - The molecular orbital picture.
    - Azide as a dipole: Click reactions.
    - Ozone as a dipole: Ozonolysis and ozonide trapping.
  - $[2 + 2]$ cycloadditions.

- **Dipolar** (cycloaddition): A (usually $[3+2]$) cycloaddition between a **dipole** and a **dipolarophile**.
  - These are nice because they make 5-membered rings the same way Diels-Alder reactions make 6-membered rings!
- **Dipole**: A molecule with the following general form. *Structure*

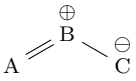


Figure 2.33: Dipole.

  - A, B, and C are atoms.
    - Depending on the specific atoms involved, the double bond may be a triple bond or the single bond may be a double bond.
    - The zwitterion (adjacent positive and negative formal charges) is always present, though; this is the actual dipole within the dipole molecule!
  - Tip from Prof. Elkin: Now is probably a good time to review how to draw Lewis structures, resonance forms, etc. from Gen Chem or 5.12; this content is relevant to how to draw dipoles.
- **Dipolarophile**: The species that reacts with the dipole. *Etymology* from Latin "lover of dipoles."
  - This is usually an alkene or alkyne.
- Mechanism.

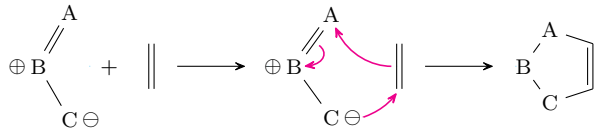
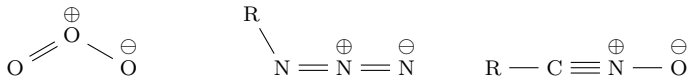


Figure 2.34: Dipolar cycloaddition.

  - Prof. Elkin likes to draw circle arrows starting from the center of electron density.
- Examples of dipoles.



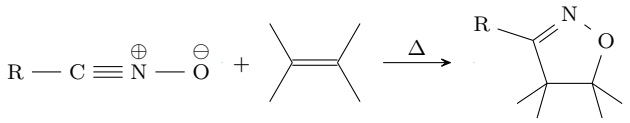
(a) Ozone. (b) Azide. (c) Nitrile oxide.

Figure 2.35: Examples of dipoles.

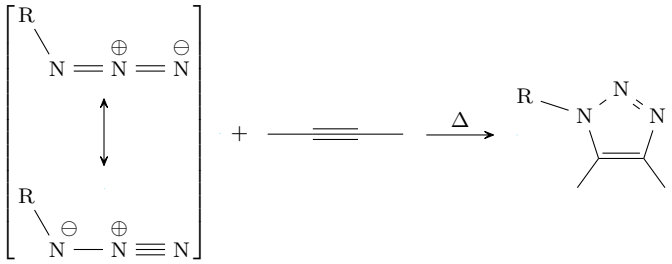
1. **Ozone**.
2. **Azide**.
3. **Nitrile oxide**.

- **Ozone**: The O_3 molecule. *Structure* (see Figure 2.35a.)
- **Azide**: The N_3^- functional group. *Structure* (see Figure 2.35b.)
- **Nitrile oxide**: The CNO^- functional group. *Structure* (see Figure 2.35c.)

- Examples of dipolar cycloadditions.



(a) Reacting a nitrile oxide.



(b) Reacting an azide.

Figure 2.36: Examples of dipolar cycloadditions.

  - Reacting a nitrile oxide with an alkene (Figure 2.36a).
    - Forms the 5-membered ring you'd expect by drawing arrows as in Figure 2.34.
  - Reacting an azide with an alkyne (Figure 2.36b).
    - Note that *both* resonance structures can react with the alkyne.
      - ➢ You will have to draw different arrows, but if you start from the negatively charged atom on the dipole (as Prof. Elkin likes to), you'll get the same product.
      - ➢ Draw both mechanisms out as practice!!
    - Product is aromatic, so this is a very thermodynamically downhill (i.e., favorable) reaction.
    - This is our first example of a **click reaction**.

- Let's now look at the orbitals involved in a dipolar cycloaddition.

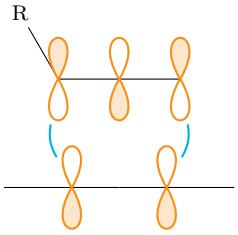


Figure 2.37: Dipolar cycloaddition orbitals in 3D space.

  - As a reference, we can think of the orbitals that would be involved in the azide reaction from Figure 2.36b, but it will be the same orbitals in any dipolar cycloaddition.
  - Something that's new with dipolar cycloadditions vs. the Diels-Alder reaction: It is hard to tell which reactant (dipole or dipolarophile) reacts with its HOMO, and which one reacts with its LUMO.
    - In fact, the choice to draw the HOMO for one and the LUMO for the other is arbitrary!
    - The shading will work out either way, as long as you're reacting a HOMO on one species and a LUMO on the other.

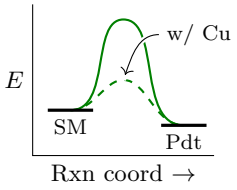
  - So, without loss of generality, let's suppose our dipole reacts with its LUMO.
    - Per Figure 2.35b, the Lewis structure for the azide has two π-bonds (which naturally contain four total electrons) along the three-atom-long dipole.
    - Thus, when we're making molecular orbitals, we should consider the case of 3 p-orbitals with 4 electrons. But this setup is isoelectronic to our allyl MOs (Figure 2.16) from a few lectures ago!
    - Therefore, the LUMO of the dipole will look like the third energy level of Figure 2.16. Indeed, that's what we've drawn in Figure 2.37!
  - If our dipole reacts with its LUMO, then our dipolarophile must react with its HOMO.
    - This time, we recognize a two-atom, two-electron system in each alkyne π-bond.
    - However, the alkyne will only react with one of its π-bonds. Thus, our MOs should align with the case of 2 p-orbitals with 2 electrons, which is analogous to Figure 2.13.
    - Therefore, the HOMO of the dipolarophile will look like the first energy level of Figure 2.13. Indeed, that's what we've drawn in Figure 2.37!
  - With our MOs drawn, we can see that the phases do indeed match between our LUMO and HOMO!
    - Thus, the reaction proceeds and new σ-bonds to begin to form.
  - To reiterate: We could alternatively draw the HOMO of the dipole and the LUMO of the dipolarophile, and the phasing would still work out!
    - Try this yourself for practice!!

- **Click** (reaction): A reaction that joins two molecules quickly and irreversibly.
  - History of click reactions.
    - Etymology: These reactions "click" molecules together like Legos.
    - It's fun that we're talking about them on Nobel Prize day of this year because these reactions won the 2022 Nobel Prize in Chemistry!
  - Defining characteristics.
    - Click reactions have to be very **chemoselective**.
    - Highly reactive (i.e., with a fast rate). We obtain this especially with some modifications.

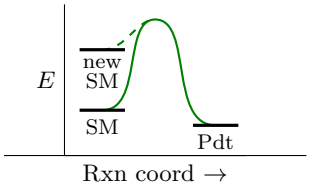
- **Chemoselective** (reaction): A reaction between molecules that only react with each other, even in the presence of related functional groups.
  - Chemoselective reactions are essential for certain biological applications.
    - Imagine you have two molecules in a cell that you want to join together, e.g., you've got a protein and you want to track where it goes by attaching a fluorescent dye to it.
    - To do this, you attach one reactant (e.g., an azide) to the protein and the other (e.g., an alkyne) to the fluorescent dye.
    - Then, once in the cell, the azide and alkyne will react with each other but nothing else in the cell because they're *chemoselective* for each other.
  - Azide-alkyne cycloadditions were great when they were developed because there's not a lot of azides or alkynes in cells, so once you put them in a cell, they'll click together very easily.

- The initial azide-alkyne cycloaddition was good, but it needed improvement in two main areas in order to be biocompatible.
  1. It needed to be able to be run at room temperature, so that it could work at body temperature inside a living cell.
  2. It needed to have nontoxic reactants, so that the reactants wouldn't damage anything else inside a living cell.

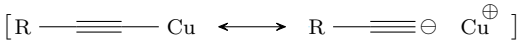
- For the reaction to be able to be run at room temperature, we needed to make the reaction even more highly reactive. There are two approaches that met this goal.



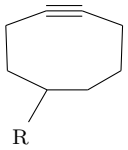
(a) Copper-catalyzed energy diagram.



(b) Cyclooctyne energy diagram.



(c) Copper catalysis.



(d) Cyclooctyne reactant.

Figure 2.38: Accelerating click reactions.

1. Copper catalysis.
   - Approach.
     - When you add copper into solution, it adds into the end of the alkyne (Figure 2.38c).
     - This pushes more electron density into the alkyne via resonance, raising our HOMO.
     - This is exactly the same phenomenon as putting an EDG on the diene in a Diels-Alder reaction!
   - Benefits.
     - This was great because now the reaction proceeds at room temperature!
     - Copper did this by lowering activation energy/transition state barrier (Figure 2.38a).
   - Drawbacks.
     - Cu is toxic, so this accelerated reaction can't be run in cells.
     - Our second approach has to overcome the "copper kills everything in a cell" problem.
2. Strain release with cyclooctyne.
   - Approach.
     - Incorporate our alkyne into an 8-membered ring; this yields a very strained molecule (Figure 2.38d).
     - But when you go from an alkyne to an alkene in the course of the reaction (see Figure 2.36b), you release that strain because an alkene has appropriate bond angles to exist in an 8-membered ring.
     - Essentially, we've added an additional thermodynamic driving force: Strain is released when the reaction occurs, so it is more downhill.
     - This is an approach called **ground state destabilization**.
     - Here's how it looks on an energy diagram (Figure 2.38b): We've lowered the transition state energy *relative* to the starting material by putting more energy into the reactants, specifically energy in the form of potential energy trapped in the strained ring.
   - Benefits.
     - Proceeds at room temperature.
     - No toxic copper.
   - Drawbacks.
     - None!

- So to recap: Two strategies for accelerating a reaction are lowering the transition state barrier and raising the energy of the starting materials.
- Why don't you put an alkyne in a 6-membered ring? Wouldn't that be even more strained and hence better?
  - You can't have your reactant be so strained that it can't even be made; indeed, a six-membered ring with an alkyne is too strained to be synthesized.
  - An 8-membered ring is the "sweet spot" because it is strained enough to react at room temperature but not so strained that it can't be synthesized.[9]
- We now return to ozonolysis, a reaction that you may be familiar with from 5.12. The mechanism of ozonolysis actually involves a dipolar cycloaddition!
- General form.

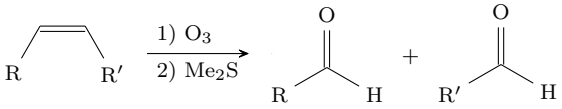
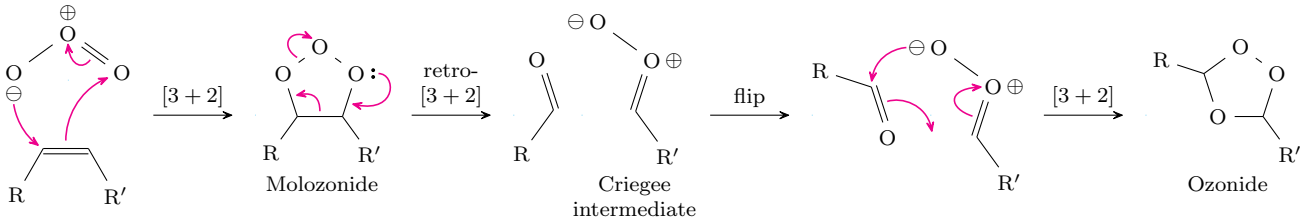
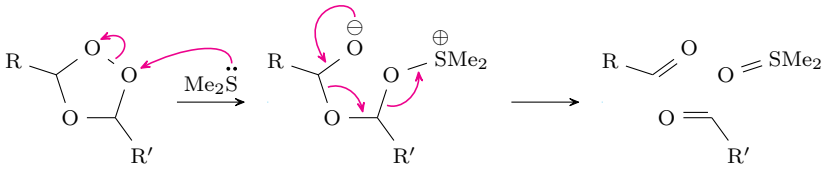


Figure 2.39: Ozonolysis.

  - Fun facts about ozone.
    - It's sky blue; there's a lot of it in the sky!
    - It's also very toxic and explosive; when we work with it in the lab, we do so very carefully.
    - Once upon a time: Chlorofluorocarbons (CFCs) were tearing a huge hole in the atmospheric ozone layer, MIT chemist Dr. Susan Solomon figured out how CFCs did this, the world banned CFCs, and the ozone layer healed! So there was a time when we did solve a climate change issue :)
  - Fun facts about Me_2S.
    - It smells like farts; it's not fun when your labmate is running the reaction.
    - But if your reaction works, the fart smell goes away as the reaction proceeds!
- Mechanism.



(a) First step.



(b) Second step.

Figure 2.40: Ozonolysis mechanism.

[9] If you want to learn more about this type of chemistry, Georgia (one of the TFs) is happy to chat! She studied it in her undergrad research, except that her approach was photochemically synthesizing strained *trans*-cyclooctenes.

  - First step.
    - The alkene reactant does a dipolar $[3+2]$ cycloaddition with ozone to form a **molozonide**.
    - The molozonide does a retro-$[3+2]$, yielding an aldehyde and a **carbonyl oxide** (also known as a **Criegee intermediate**).
    - The aldehyde and Criegee intermediate then rearrange in space.
    - This rearrangement puts partial negative charges near partial positive charges, giving us the right regioselectivity for a *second* dipolar $[3+2]$ cycloaddition. This step yields an **ozonide**.
  - The ozonide is the product of the first step; if you don't add Me_2S, you'll isolate the ozonide.
  - Second step.
    - We introduce a mild reducing agent (Me_2S), which attacks the ozonide.
    - The last step is a final rearrangement splitting.
  - After the second step, we obtain three products: Two aldehydes, and **DMSO**.
  - Note that while we've drawn Figure 2.40 out with a reactant that gives us as aldehydes as products, we could equally well run this reaction with a geminal-, tri-, or tetra-substituted alkene to get some ketones as products!

- **Dimethylsulfoxide**: A common laboratory solvent, which essentially acts like "less polar water" and does not smell like farts. *Also known as* **DMSO**.
- Once we form the ozonide, we don't *have* to break it into ketones/aldehydes with Me_2S.
  - Something else we coud do, for example, is react it with another reagent to get different products!
- Alternate second steps.
  1. Add H_2O_2.
     - This yields carboxylic acids instead of ketones/aldehydes.
  2. Add $NaBH_4$.
     - This yields alcohols instead of ketones/aldehydes.
- Example of an alternate second step: Cyclohexene to a ring-opened diacid.

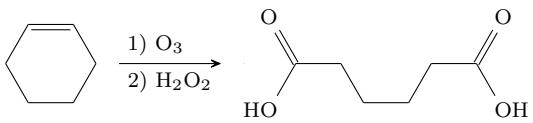


Figure 2.41: An alternate ozonide reaction.

  - Sanity check: Count the carbons in the starting material and product to confirm that there is the same number of carbons in each. Indeed, this chemical reaction only adds oxygens!
- Would adding hydrazone as a second reagent allow us to form the diamide?
  - If we wanted to synthesize an amide or ester, we'd typically form the acid and then do a separate, subsequent amidation.
  - That being said, there are other possible second steps that Prof. Elkin hasn't listed.
- $[2+2]$ cycloadditions.
  - Often photochemical.
  - If we react these with heat, we get no reaction.
  - Just like with dipolar cycloadditions, the stereochemistry of a $[2+2]$ mirrors the Diels-Alder: *cis*-alkenes give *cis*-products, and *trans*-alkenes give *trans*-products.

- General form.

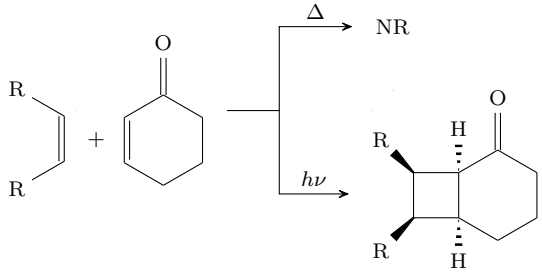
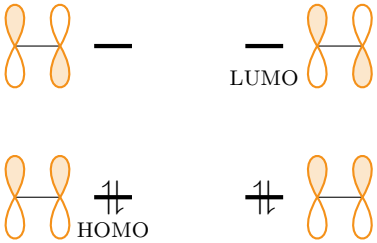
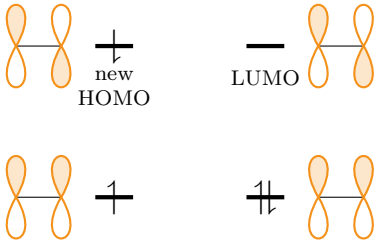


Figure 2.42: $[2+2]$ cycloaddition.

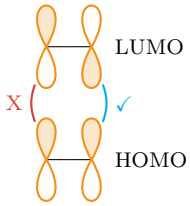
- Why $[2+2]$ cycloadditions *must* be photochemical instead of thermal: MO theory!



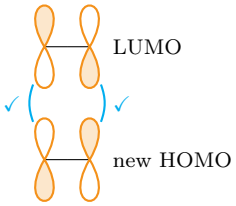
(a) Thermal $[2+2]$ MOs.



(b) Photochemical $[2+2]$ MOs.



(c) Thermal orbitals in 3D space.



(d) Photochemical orbitals in 3D space.

Figure 2.43: $[2+2]$ cycloaddition orbitals.

  - Let's consider a $[2+2]$ cycloaddition between ethylene and itself.
  - Since the reactants are identical, we may choose (arbitrarily and without loss of generality) which molecule reacts with its HOMO. It will then follow that the other molecule reacts with its LUMO.
    - Thus, let the left (Figures 2.43a-2.43b) and bottom (Figures 2.43c-2.43d) molecules react with their HOMO, and let the right/top molecules react with their LUMO.
  - In the thermal case, the HOMO and LUMO don't overlap well (Figure 2.43c).
    - The phasings match on one side, but not on the other.
  - However, in a *photochemical* reaction, we excite an electron up one energy level (Figure 2.43b).
    - Recall that we briefly discussed this phenomenon in Figure 2.15.
    - This excitation gives us a new HOMO.
  - The new HOMO can react with the LUMO (same as thermal) because the phasing now matches!
- In Figure 2.43, we could choose the HOMO and LUMO arbitrarily because the reactants were identical.
  - But in Figure 2.42, the reactants are *not* identical.
  - Moreover, it turns out that there *is* a preference for which of these two species absorbs the photon!

- The species that can form the more stable diradical will absorb the light.

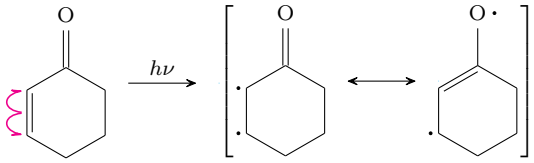


Figure 2.44: Systems with more stable excited states preferentially absorb light.

  - In the context of Figure 2.42, the enone will absorb the photon because its diradical is resonance-stabilized.
  - Thus, the enone will react with its (new) HOMO.
    - Note that this new HOMO is also a SOMO!
    - Per Figure 2.43b, the photoexcited species will actually have *two* SOMOs.
  - For more context, check out Clayden et al. (2012): The textbook actually does an excellent job covering this photochemistry stuff!!

- Looking ahead (Friday).
  - We will begin with a bit more content on cycloadditions that we could not get to today.
  - After that, we will cover electrocyclizations.
  - It's going to be a long lecture, but you'll have the weekend to digest it.

References

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