

- So which product do we actually get?
 - We will determine this by using either *resonance* or *hyperconjugation/partial negative charges* to identify and match the electron-rich and electron-poor sites on our diene and dienophile.^[8]
 - Use whichever method you prefer since they give the same result, but you should learn both!!
 - The resonance analysis (Figures 2.25c-2.25d).
 - As in Figure 2.20, push arrows as far as we can to get the reactive resonance structure.
 - The hyperconjugation analysis (Figures 2.25e-2.25f).
 - Begin with an atom that we *know* will have a partial positive (δ^+) or partial negative (δ^-) charge.
 - For example, we know that oxygen will be δ^- because it is the most electronegative atom in both structures.
 - Thus, we can label it first in both Figures 2.25e and 2.25f.
 - Then expand out over the rest of the conjugated system, alternating δ^+ or δ^- atom-to-atom.
 - So since oxygen is δ^- , the carbon α to it should be δ^+ , the carbon(s) β to it should be δ^- , the carbon(s) γ to it should be δ^+ , etc.
 - Keep track of the partial charges on the termini of the diene and dienophile (i.e., the reactive sites). These are circled in Figures 2.25e-2.25f.
 - Notice the agreement/consistency between the two methods!
 - Indeed, the carbanion in Figure 2.25c corresponds to a δ^- carbon in Figure 2.25e, and the carbocation in Figure 2.25d corresponds to a δ^+ carbon in Figure 2.25f.
 - Once we have performed either analysis, matching up the negatives on the diene to the positives on the dienophile and vice versa predicts our product!
 - Thus, by both analyses, the *para*-product is favored!
 - This matching of positive and negative charges is indicative of the maxim that “organic chemistry is just magnets everywhere.”
 - Exercise: Try drawing the meta-product, which will force you to put positive near positive and negative near negative.
 - “That’s not fun, that’s not how magnets work.”
- **meta-product:** The product of a Diels-Alder reaction in which the substituents would be oriented *meta* to each other on the six-membered ring, if the six-membered ring were aromatic.
 - **para-product:** The product of a Diels-Alder reaction in which the substituents would be oriented *para* to each other on the six-membered ring, if the six-membered ring were aromatic.
 - Prof. Elkin has many more examples, but will go through them on Monday.

2.14 Diels-Alder - 2

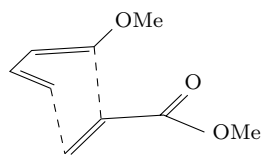
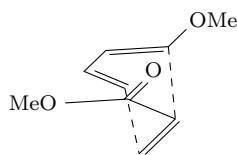
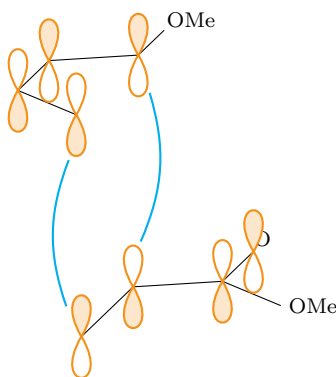
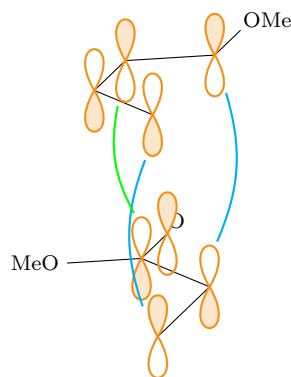
10/7:

- Lecture 13 recap.
 - Corrections to Lecture 13.
 - The word “Diels-Alder” usually has a hyphen; it is *not* written “Diels Alder” with a space.
 - The methyl-activated diene in Figure 2.19c is faster because of *electronics*, not sterics.
 - Indeed, this diene has the same steric preference for *s-trans* as buta-1,3-diene, but it is slightly faster because methyl groups are slightly electron-donating.

⁸Note that there is also a secret third method: MO theory! See Clayden et al. (2012, p. 890) for how to do this. As we would expect, the predictions we get by both resonance and hyperconjugation match the predictions of MO theory. (Note also that you are not required to learn the MO theory method because it was not covered in class; this comment is purely to point out an interesting connection :)

- Definitions of **stereoretentive**, **stereospecific**, and **stereoselective** reactions.
- Recap of regioselectivity.
 - Prof. Elkin redraws Figure 2.25h as a method of predicting the *para*-product (Figure 2.25b).
- **Stereoretentive** (reaction): A reaction in which the stereocenter(s) in the starting material are retained exactly.
 - Example: (*R*)-butan-2-ol reacts and is still an (*R*)-alcohol.
- **Stereospecific** (reaction): A reaction in which the stereocenter(s) of the starting material decide the stereocenter(s) of the product.
 - Example: Figure 2.23.
 - To reiterate: The phenomenon exemplified by Figure 2.23 is an example of stereospecificity, *not* stereoselectivity (as was incorrectly said last lecture).
- **Stereoselective** (reaction): A reaction in which a certain stereoisomer of the product is preferred.
 - Example: Butan-2-one is reduced to (*R*)-butan-2-ol, instead of racemic (\pm)-butan-2-ol.
 - Stereoselective is an “umbrella” term: Both stereoretentive and stereospecific reactions are stereoselective, but not all stereoselective reactions are stereoretentive or stereospecific.
- Today: More on the Diels-Alder reaction.
- Lecture outline.
 - More on regioselectivity.
 - *exo* vs. *endo* transition states.
 - *exo* vs. *endo* products.
 - Lewis acid catalysts for Diels-Alder reactions.
 - Inverse electron-demand Diels-Alder reactions.
 - Example Diels-Alder reactions; relevant to PSet 4!
- We'll begin today by continuing our discussion of regioselectivity.
 - Recap of Figure 2.25.
 - Note that like we have the *meta*-product and *para*-product, we can have the *ortho*-product.
 - General rules (timesavers).
 1. A single EDG on the diene and EWG on the dienophile (usually) leads to the *ortho*-product or the *para*-product, not (usually) the *meta*-product.
 2. If there isn't a clear preference (e.g., weak EDG or EWG only), you get a mixture of products.
 - Example: The methyl-activated diene, penta-1,3-diene (see Figure 2.19c), reacts with propenal to give both the *ortho*- and *meta*-products in an 8:1 ratio. On the other hand, the methoxy-activated diene, 1-methoxybuta-1,3-diene (see Figure 2.19a), reacts with propenal to give 100% of the *ortho*-product.
- Switching subjects, let's finally investigate what determines the full stereochemistry of the product.
 - We have previously discussed the *stereospecificity* implied by *cis* or *trans* starting materials, but we will now discuss a type of *stereoselectivity*.
 - Specifically, we will need to begin our investigation with a slight detour to define and analyze the *endo* and *exo* transition states.
- **endo** (transition state): The Diels-Alder TS in which the dienophile's EWG points *toward* the diene.
- **exo** (transition state): The Diels-Alder TS in which the dienophile's EWG points *away from* the diene.

- *exo* vs. *endo* transition states.

(a) *exo* transition state.(b) *endo* transition state.(c) *exo* orbitals.(d) *endo* orbitals.Figure 2.26: *exo* vs. *endo* transition states in the Diels-Alder.

- Essentially, observe that when the starting materials in a Diels-Alder reaction encounter each other, the dienophile's substituent can either point “out” (Figure 2.26a) or “in” (Figure 2.26b).
 - Remember that per Figure 2.18, the substituents have to encounter each other top-to-bottom.
 - Remember that per regioselectivity, the reactants will encounter each other as drawn so as to form the *ortho*-product.
- The lower energy transition state will lead to more product, so let's compare their relative energies.
- To do this, we will have to consider the “full LUMO” of the dienophile.
 - While we've only considered the dienophile's alkene functional group so far, observe that methyl acrylate also has an adjacent carbonyl π -bond that can conjugate with the alkene functional group just like in a diene!
 - Thus, four p -orbitals will form the “full MOs” of the dienophile.
 - The four dienophile MOs resulting from these four p -orbitals can be drawn using the three rules from Lecture 12, resulting in a picture exactly like Figure 2.14.
 - Since the dienophile will still be reacting with its LUMO, the “full LUMO” of the dienophile will look like the third energy level in Figure 2.14. Indeed, that's what we draw on the dienophile in both Figures 2.26c-2.26d!
- In both the *exo* and *endo* transition states, our “full LUMO” has **primary orbital interactions** with the diene HOMO analogous to Figure 2.18b. This enables the formation of σ -bonds as we'd expect, even (to reiterate) with the “full LUMO.”
- However, there are also some differences between the transition states.
 - *exo* transition state: There is *less steric clash* between the diene/dienophile substituents.
 - *endo* transition state: There is a new **secondary orbital interaction** that is stabilizing.
- This secondary orbital interaction is (usually) more stabilizing than the lack of sterics, so the *endo* transition state is (usually) preferred!
 - This is technically a $\pi_{\text{HOMO}} \rightarrow \pi_{\text{full LUMO}}^*$ interaction.

- **Primary** (orbital interaction): An orbital interaction that leads to bonding.
- **Secondary** (orbital interaction): An orbital interaction that doesn't lead to bonding, but is stabilizing (or destabilizing).
- Let's now connect *endo* and *exo* transition states back to the stereochemistry of the product in a Diels-Alder reaction.

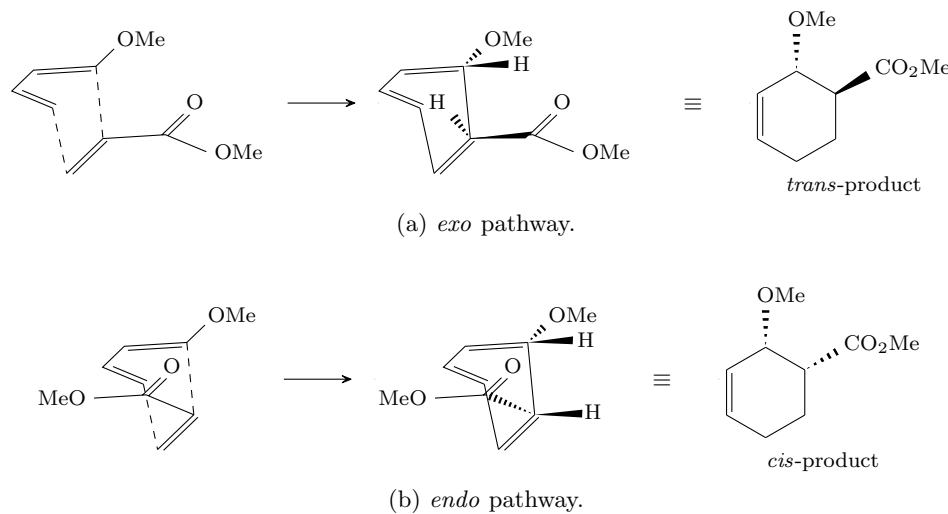


Figure 2.27: The transition state predicts Diels-Alder product stereochemistry.

- In the course of a Diels-Alder reaction, once we form our (*endo* or *exo*) transition state, we will subsequently form bonds and then unfold the structure — like a book — into our product.
 - Consider drawing in the hydrogens to help see how we get from the second to the third picture.
- For the particular Diels-Alder reaction we've considered in both Figures 2.26 and 2.27, the *exo* transition state yields the *trans*-product and the *endo* transition state yields the *cis*-product.
 - Because the *cis*-product arises from the *endo* transition state (which, to reiterate, is the preferred transition state), the *trans*-product will be preferred for this reaction!
 - I.e.: The *cis*-product is the major product, and the *trans*-product is the minor product.
- Since the Diels-Alder is not **enantioselective**, we can draw either enantiomer of the product.
 - In other words: We could switch all wedges and dashes for dashes and wedges, respectively, in Figure 2.27a-2.27b and still have the right answer.
- Help digesting this material: Look for some online visualizations, get a molecular model kit, etc.!!
- **Enantioselective** (reaction): A reaction that favors one enantiomer of the product over another.
- Example: Predicting the proper stereochemistry in the following Diels-Alder reaction.

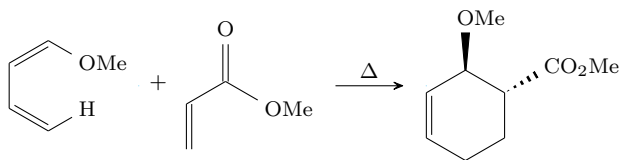


Figure 2.28: Diels-Alder reaction of (*Z*)-1-methoxybuta-1,3-diene and methyl acrylate.

- The rate will be slower than if (*E*)-1-methoxybuta-1,3-diene were used because the diene in Figure 2.28 is *s-cis* destabilized.
 - The *s-cis* destabilization comes from steric clashing between the methoxy group and the hydrogen.
- The regioselectivity will pair the bottom carbon on the diene in Figure 2.28 to the bottom carbon on the dienophile in Figure 2.28, yielding the *ortho*-product.
- The stereoselectivity will favor the *endo* transition state because the dienophile's EWG has a π -system that can participate in secondary orbital interactions with the diene.
 - Thus, we will favor the drawn diastereomer (and its enantiomer!).
 - Note that in this reaction, the *endo* transition state yields the *trans*-product. This is the opposite of Figure 2.27b, in which the *endo* transition state yielded the *cis*-product.
 - This illustrates that it's not always the *cis*-product that's major! Rather, whether *cis* or *trans* is major depends on the transition state (*endo* or *exo*) from which each originates.
- Tip for learning this content: Just practice, esp. drawing the product regio- and stereochemistry.
- This wraps up all we need to say about *endo* and *exo* transition states.
- So, switching topics, let's discuss accelerating Diels-Alder reactions with catalysis.
 - So far, every Diels-Alder reaction we've considered has been thermal.
 - We can accelerate these reactions with a Lewis acid catalyst (such as SnCl_4 , EtAlCl_2 , etc.).
 - This allows us to do our Diels-Alder reactions...
 1. At a lower temperature;
 2. With greater stereoselectivity.
 - Lower temperatures make the *endo* transition state even more preferred.
- Example: How does this Lewis acid catalysis work?

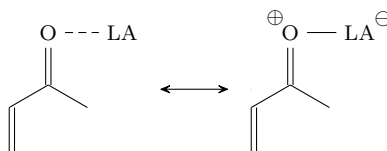


Figure 2.29: Lewis acid catalysis of Diels-Alder reactions.

- Three-step process.
 1. The Lewis acid (LA) coordinates to the dienophile's EWG, making it more electron poor.
 2. This lowers the LUMO even further, which gives you better energy overlap.
 3. Better energy overlap stabilizes the transition state.
- Essentially, Lewis acid catalysts work by making our EWG "better."
- Switching topics again, let's discuss something to which we've alluded a few times: What happens when the diene is super stabilized and the dienophile is super destabilized.
- **Inverse electron-demand** (Diels-Alder reaction): A Diels-Alder reaction in which the HOMO of the dienophile interacts with the LUMO of the diene.
 - Still *ortho*/*para*-directing.
 - Still *endo* TS preferred.
 - Often see this when we have a heteroatom in the ring.

- Example inverse electron-demand Diels-Alder reaction.

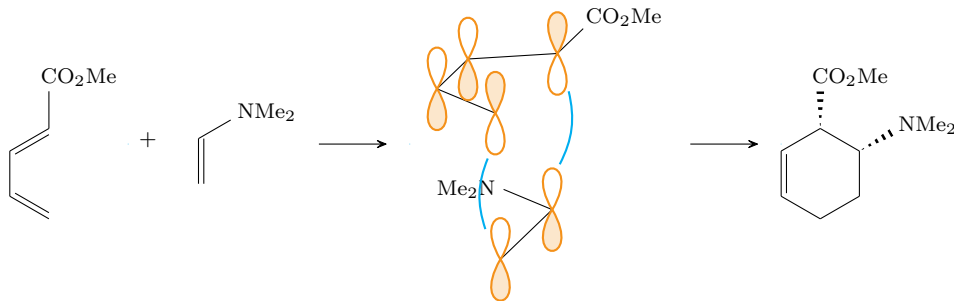
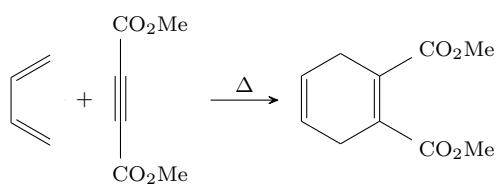
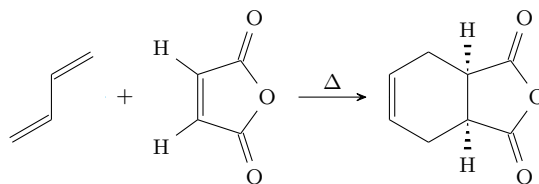
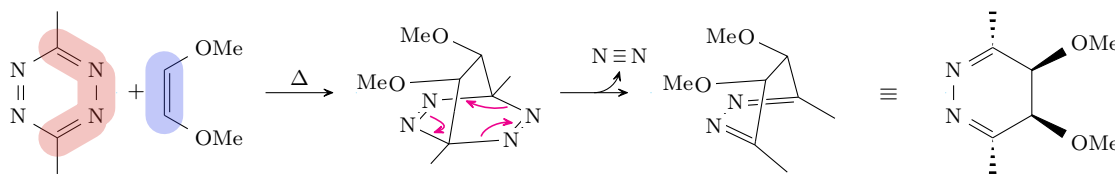


Figure 2.30: Diels-Alder reaction with inverse electron-demand.

- Because of the methyl ester EWG, the diene in Figure 2.30 is now electron-poor.
 - As such, it will react with its LUMO (the third energy level in Figure 2.14).
- Because of the amine EDG, the dienophile in Figure 2.30 is now electron-rich.
 - As such, it will react with its HOMO (the first/lowest energy level in Figure 2.13).
- However, when we draw the HOMO of the dienophile and LUMO of the diene, we still get good orbital overlap. Thus, this reaction can still proceed, forming the *ortho-cis*-product through the *endo* transition state.
- Why is the *endo* TS still preferred?
 - The exact orbital interactions here deal more with coefficients and differently sized orbital lobes, but that is beyond the scope of this class.
 - Take 5.43 and 5.53 if you want to learn more!
- More example Diels-Alder reactions.



(a) Alkynes can be dienophiles.

(b) *cis/trans* dienophiles and *s-cis/s-trans* dienes.

(c) Multistep one-pot inverse electron-demand Diels-Alder.

Figure 2.31: Exotic Diels-Alder reactions.

- Figure 2.31a: Dienophiles can be triple-bonded as well!
 - If a given molecule has at least one double bond, it can (usually) react as a dienophile.
- Figure 2.31b: Don't be fooled by *s-trans* drawing; the diene is still buta-1,3-diene!
 - We will form the *cis*-product because the alkene hydrogens in the dienophile reactant are locked in the *cis*-orientation. (See Figure 2.23 for more context.)

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.