

Organic Chemistry  
Mechanistic Patterns  
(Ogilvie)

Chapter 20

(sections 20.1 to 20.3  
except 20.3.3-20.3.4  
and 20.3.6.2-20.3.6.3)



# CHEMISTRY 2600

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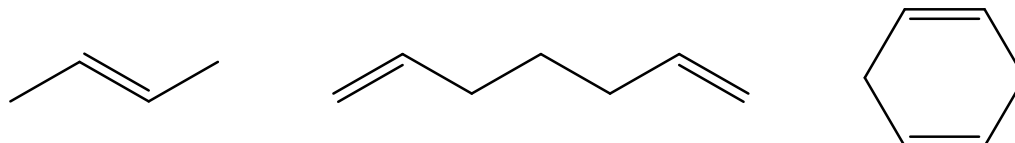
Topic #9: Cycloadditions

Spring 2021

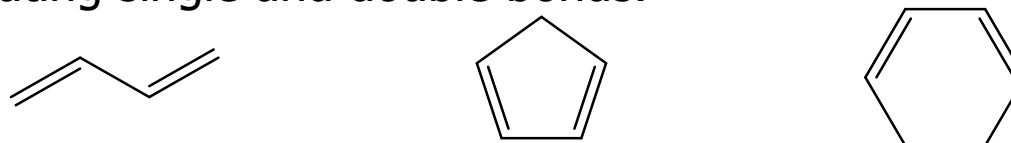
Dr. Susan Findlay

# Different Kinds of Dienes

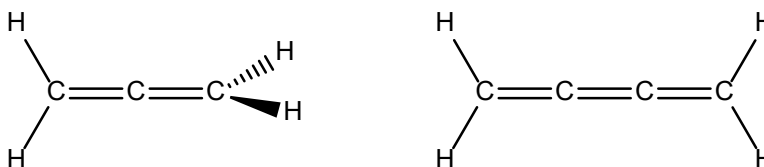
- When a molecule contains multiple  $\pi$ -bonds, its reactivity is dictated in part by their relative locations in the molecule:
  - An **isolated double bond** is separated from all other  $\pi$ -bonds by at least one tetrahedral carbon atom. It is its own  $\pi$ -system and reacts independently of any other  $\pi$ -systems in the molecule.



- A **conjugated double bond** is part of an extended  $\pi$ -system which reacts as a single entity. This is usually characterized by alternating single and double bonds.



- A **cumulated double bond** is one of two double bonds involving the same carbon atom. The two  $\pi$ -systems are perpendicular and react completely independently.





# Molecular Orbitals of Extended Pi Systems

- According to molecular orbital (MO) theory\*, all  $\pi$ -symmetric orbitals in a  $\pi$ -system combine to give a set of  $\pi$ -MOs in which:
  - The number of  $\pi$ -MOs is equal to the number of  $p$  orbitals which combined to make them. This means you have one  $\pi$ -MO per atom in the pi system.
  - In a linear  $\pi$ -system, # energy levels = #  $\pi$ -MOs.
  - In a cyclic  $\pi$ -system, use a Frost circle to predict energy levels; the polygon should always point down.
  - The number of delocalized  $\pi$ -electrons is equal to 2 electrons per double bond + 2 electrons per **lone pair that is part of the  $\pi$ -system**. *We are primarily interested in the HOMO and LUMO of any given  $\pi$ -system, so make sure you count your electrons carefully to correctly identify the HOMO and LUMO!*

\* The shapes of  $\sigma$ -symmetric MOs of nonlinear molecules are not trivial to predict. Fortunately, we rarely need to know what those MOs look like – and, if we do, we just ask HyperChem (or similar software)!  
All we need to know is how the energies of the  $\sigma$ - and  $\pi$ -MOs generally compare:  
 $\sigma$ ,  $\pi$ , nonbonding,  $\pi^*$ ,  $\sigma^*$



# Molecular Orbitals of Extended Pi Systems

- The shape of each MO can be predicted using symmetry and nodes:
  - The lowest energy  $\pi$ -MO has all  $p$  orbitals aligned in phase, giving no nodes perpendicular to the plane of the  $\pi$ -system.
  - The next  $\pi$ -MO will have one node perpendicular to the plane of the  $\pi$ -system, the next  $\pi$ -MO will have two such nodes, etc.
  - The highest energy  $\pi$ -MO will have every  $p$  orbital out-of-phase with the  $p$  orbitals on both neighbouring atoms.
  - As long as the  $\pi$ -system is symmetric, every MO will be either **symmetric** or **antisymmetric** (lobes are symmetric in shape, but phases are opposite).
  - It's usually easiest to
    - 1) Draw the highest and lowest energy  $\pi$ -MOs
    - 2) Count the perpendicular nodes in those  $\pi$ -MOs.
    - 3) Determine how many perpendicular nodes ought to be in each other  $\pi$ -MO.
    - 4) Draw the remaining  $\pi$ -MOs, remembering that the nodes must be spaced evenly if the  $\pi$ -system is symmetric.



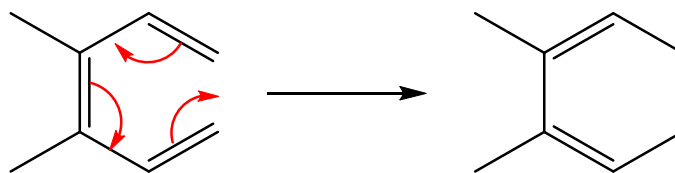
# Molecular Orbitals of Extended Pi Systems

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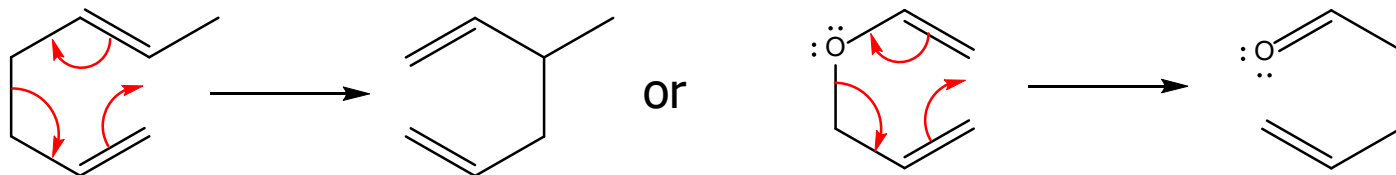
- Draw a valence  $\pi$ -MO energy level diagram and the  $\pi$ -MOs for 1,3-butadiene.

# Pericyclic Reactions

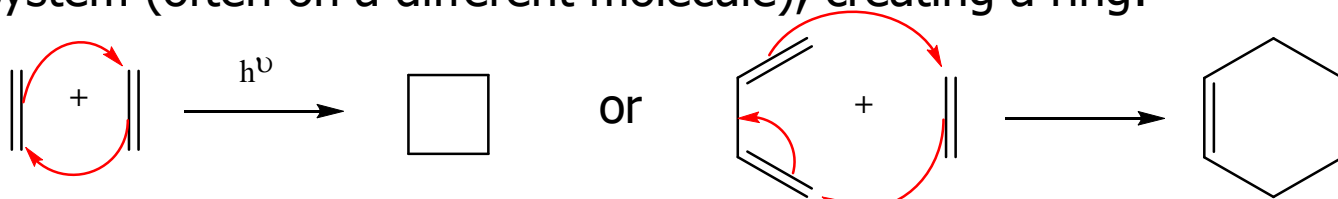
- Polyenes (including dienes) can undergo **pericyclic reactions** in which  $\pi$ -electrons move in cyclic fashion, forming new bonds:
  - In an **electrocyclic reaction**, a single conjugated  $\pi$ -system is used to form a  $\sigma$ -bond connecting the two ends of the former  $\pi$ -system:



- In a **sigmatropic rearrangement**, two  $\pi$ -systems on the same molecule are used to "migrate" a  $\sigma$ -bond:

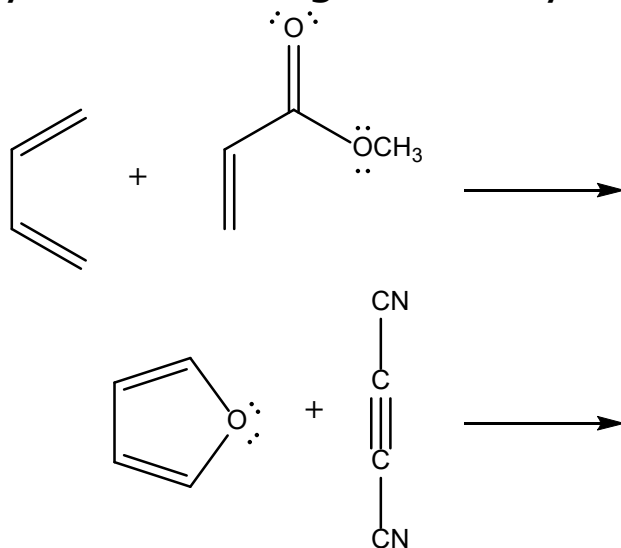


- In a **cycloaddition**, one  $\pi$ -system is "added across" another  $\pi$ -system (often on a different molecule), creating a ring:



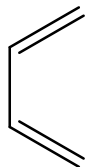
# Diels-Alder Reactions

- One of the most important pericyclic reaction is a type of cycloaddition called the **Diels-Alder reaction**:
  - This is a [4+2] cycloaddition (4-atom pi system reacting with 2-atom pi system).
  - A Diels-Alder reaction therefore must involve a **diene** and an alkene (or alkyne), typically referred to as a **dienophile**.
  - The reaction is concerted. All 6 electrons move at once.
  - A Diels-Alder adduct (addition product) always contains a cyclohexene ring formed by addition of the dienophile to the diene:

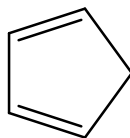


# Diels-Alder Reactions: Dienes and Dienophiles

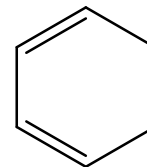
- In order for a diene to react in a Diels-Alder reaction, it must adopt an *s-cis* (short for "sigma cisoid") conformation:



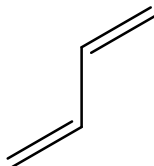
or



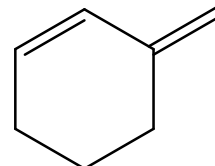
or



NOT



NOT







# Diels-Alder Reactions: Dienes and Dienophiles

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- Many dienes can also act as dienophiles. You can't buy a bottle of pure 1,3-cyclopentadiene; you buy dicyclopentadiene which must be "cracked" to generate the diene via a retro-Diels-Alder reaction:



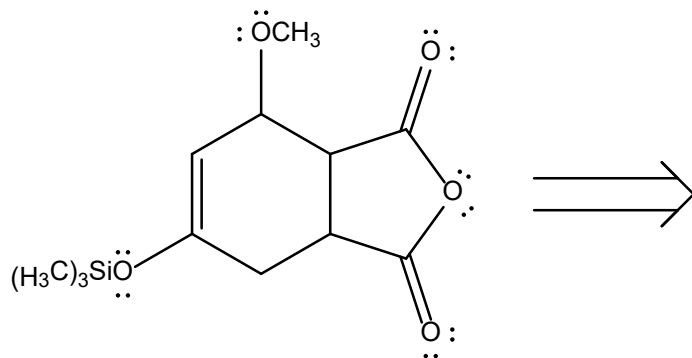
# Diels-Alder Reactions: Dienes and Dienophiles

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- Dienophiles are usually alkenes; however, they may also be alkynes. When the dienophile is an alkyne, only one  $\pi$ -system is involved in the reaction, so only one  $\pi$  bond is broken.
- In this case, the newly formed ring is a 1,4-cyclohexadiene ring (*instead of a cyclohexene*):

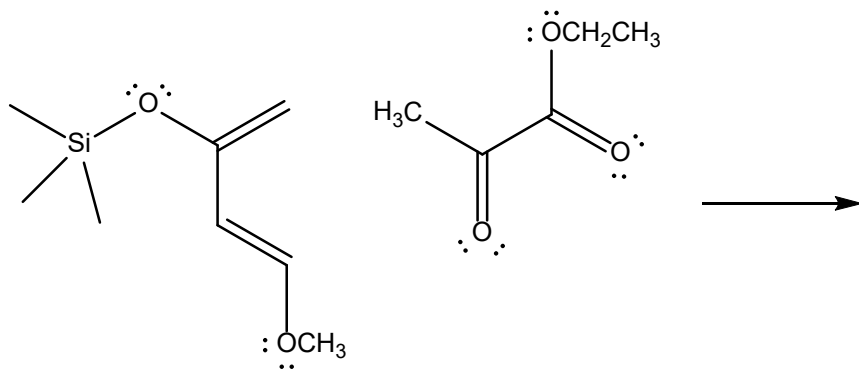
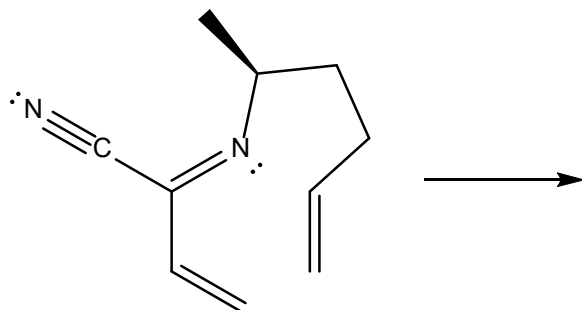
# Diels-Alder Reactions: Dienes and Dienophiles

- To determine what diene and what dienophile reacted to give a Diels-Alder adduct, find the cyclohexene ring and work out which bonds were formed in the reaction:



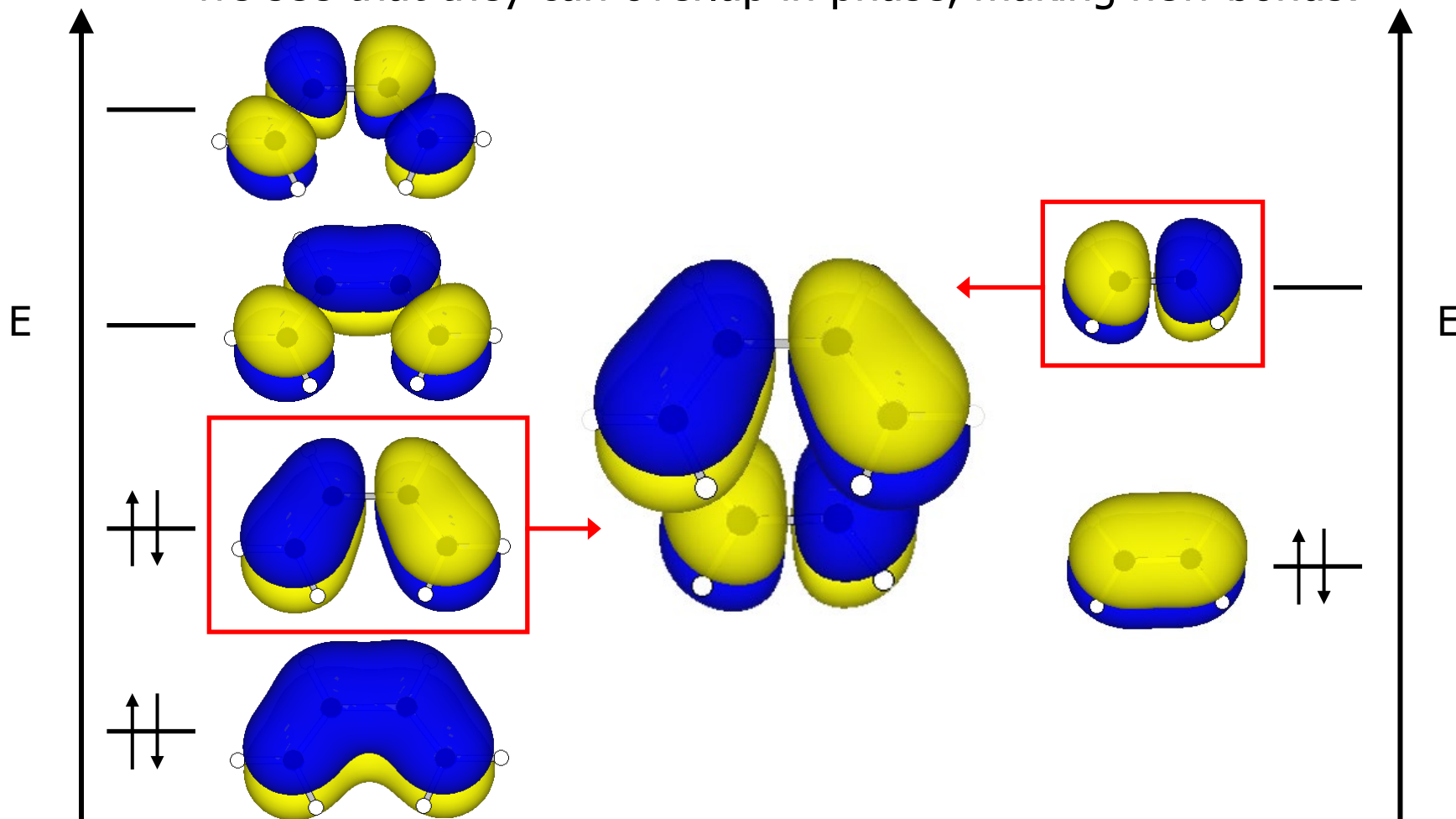
# Diels-Alder Reactions: Dienes and Dienophiles

- If one or more atoms making up the "diene" or "dienophile" is a **heteroatom** ("not carbon or hydrogen"), the cycloaddition is called a **hetero-Diels-Alder reaction**:

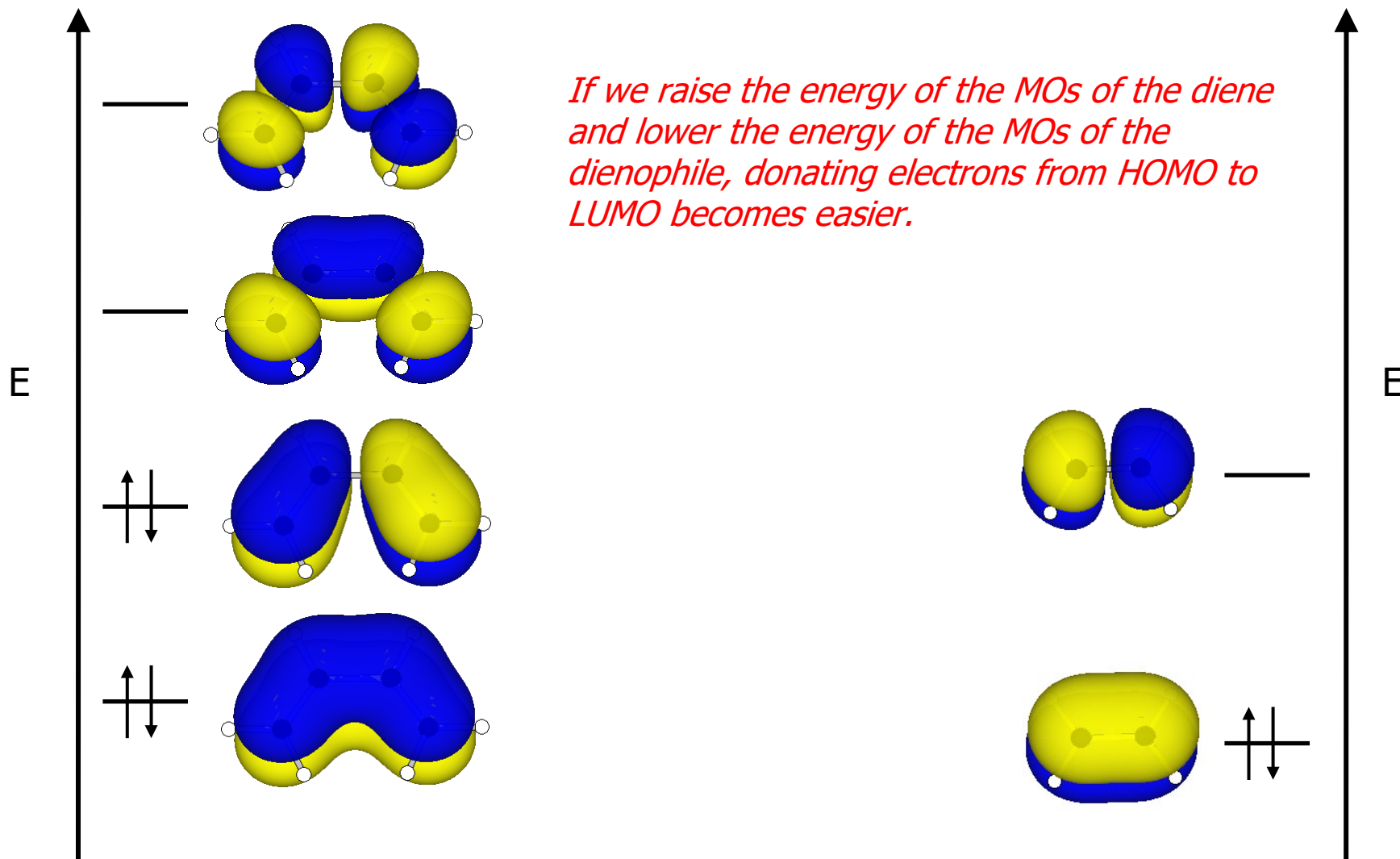


# Diels-Alder Reactions: Substituent Effects

- Looking at the HOMO of a diene and the LUMO of a dienophile, we see that they can overlap in phase, making new bonds:



# Diels-Alder Reactions: Substituent Effects





# Diels-Alder Reactions: Substituent Effects

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- A normal Diels-Alder reaction involves the HOMO of the diene and the LUMO of the dienophile. Since a reaction is easiest when electrons are donated from a high energy MO (HOMO) into a low energy MO (LUMO), we want:
  - A diene with a high-energy HOMO. This means electron-donating groups to make the diene electron-rich!
  - A dienophile with a low-energy LUMO. This means electron-withdrawing groups to make the dienophile electron-poor!



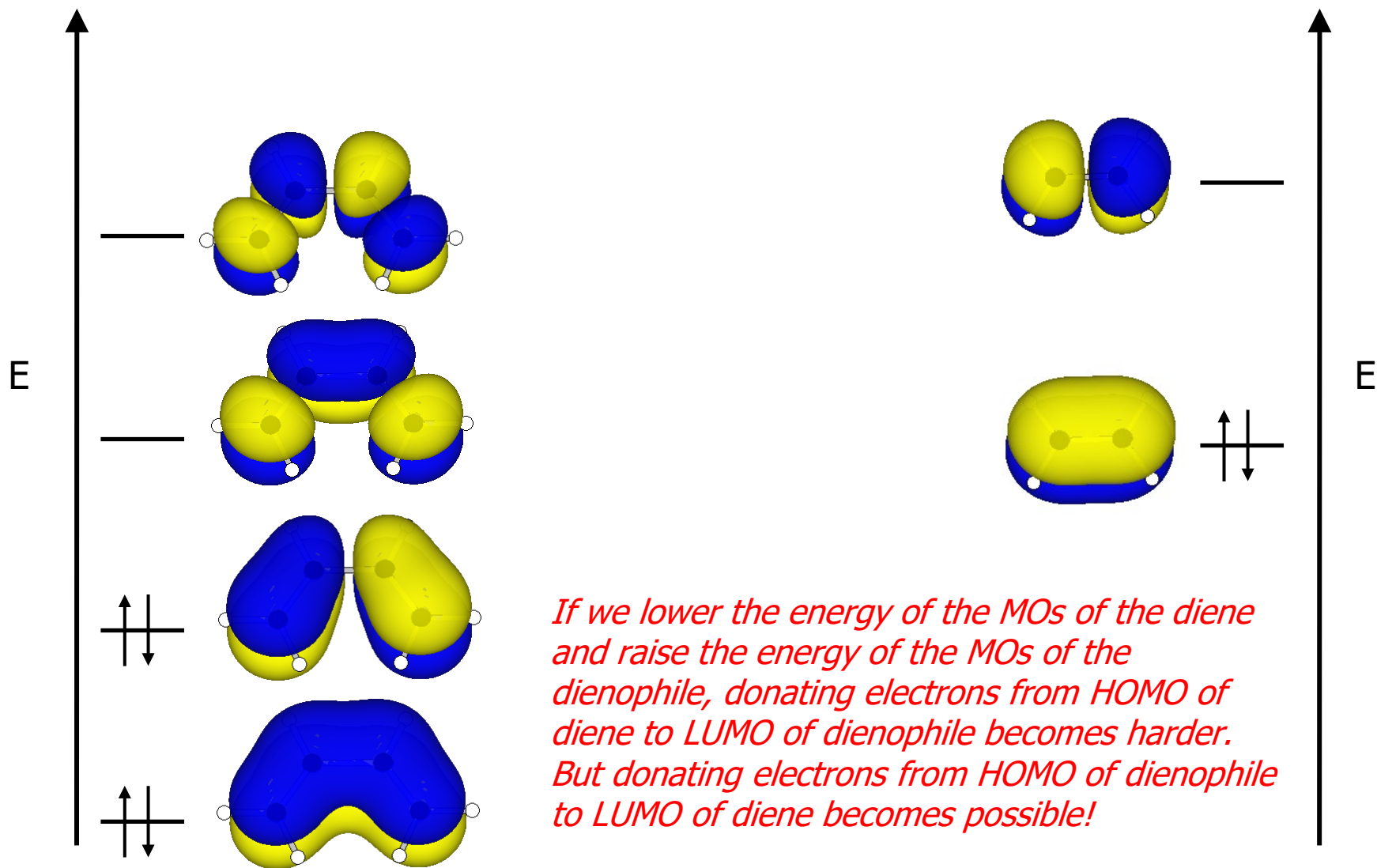
# Diels-Alder Reactions: Substituent Effects

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- Occasionally, a normal Diels-Alder reaction is not feasible so we must switch the roles of diene and dienophile. In these “inverse electron demand” Diels-Alder reactions, the dienophile acts as nucleophile and the diene act as electrophile, so we want:
  - A dienophile with a high-energy HOMO. This means electron-donating groups to make the dienophile electron-rich!
  - A diene with a low-energy LUMO. This means electron-withdrawing groups to make the diene electron-poor!



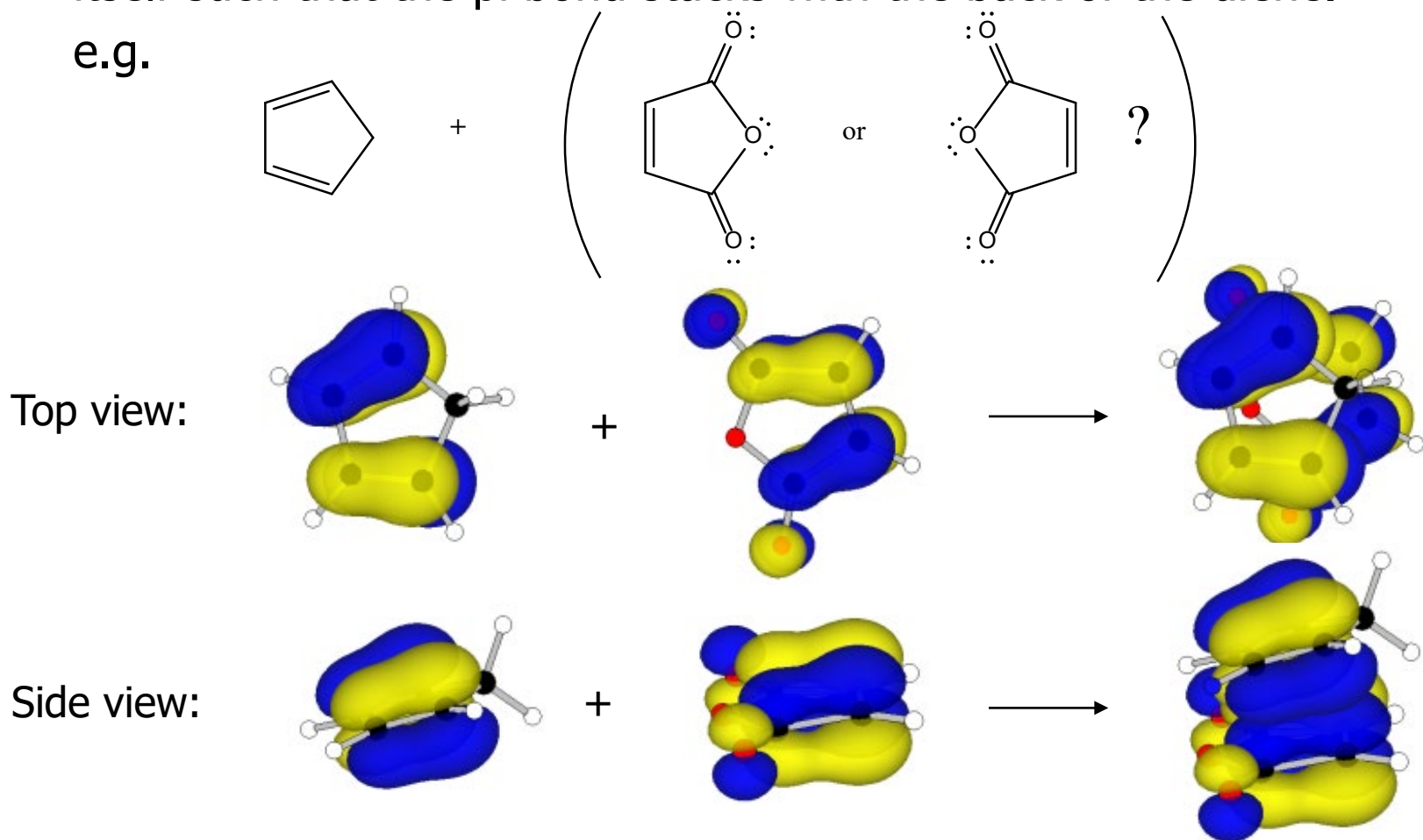
# Diels-Alder Reactions: Substituent Effects



# Diels-Alder Reactions: Stereochemistry

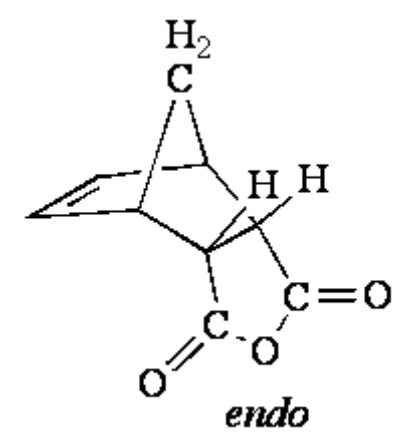
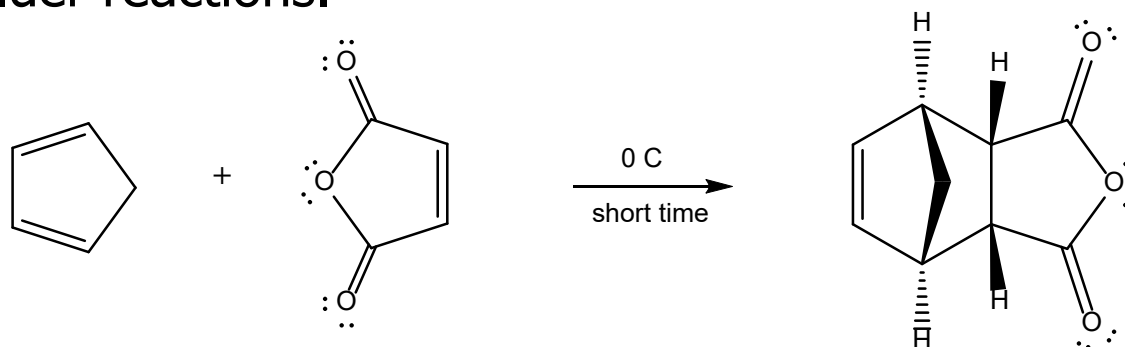
- $\pi$  orbitals can be stabilized by "stacking". If the dienophile has any substituents with double (or triple) bonds, it tends to orient itself such that the pi bond stacks with the back of the diene.

e.g.



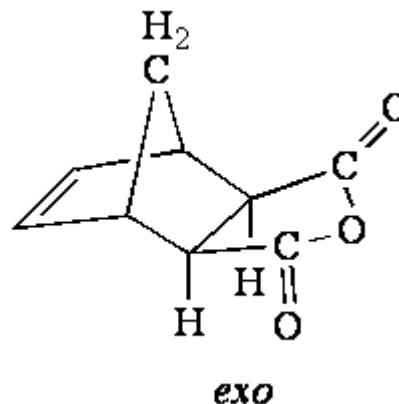
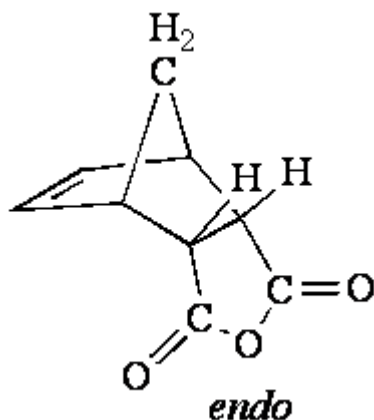
# Diels-Alder Reactions: Stereochemistry

- This gives the *endo* adduct, which is the kinetic product of most Diels-Alder reactions.



# Diels-Alder Reactions: Stereochemistry

- The alternative to the *endo* adduct is the *exo* adduct.
- What is the stereochemical relationship between the *exo* and *endo* adducts which can be produced from the same Diels-Alder reaction?

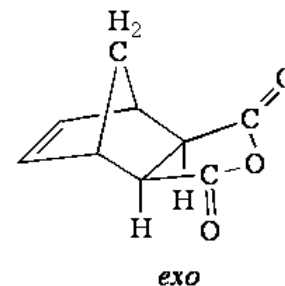


*Note that both adducts are racemic! There is no reason why the dienophile couldn't have approached the diene from above...*

# Diels-Alder Reactions: Stereochemistry

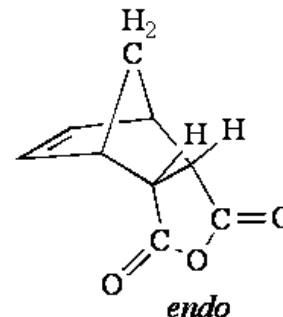
- The *exo* adduct is the thermodynamic product. As such, its formation can be promoted by:

- high temperatures
- long reaction time



- When the *endo* adduct is the kinetic product, its formation can be favoured by:

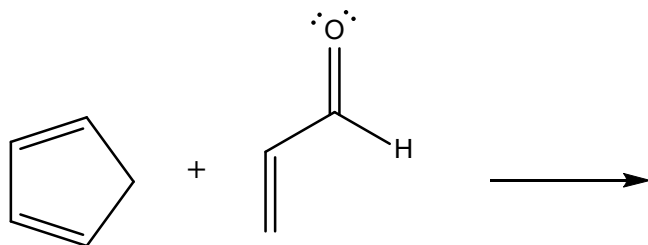
- low temperatures
- short reaction time



- In cases where the *endo* adduct is not the kinetic product, there is no way to favour its formation.

# Diels-Alder Reactions: Stereochemistry

- Draw the *endo* and *exo* products for the following reaction:





# Diels-Alder Reactions: Stereochemistry

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- In which Diels-Alder reactions would the adducts **not** be classified as *endo* or *exo*?



# Diels-Alder Reactions: Stereochemistry

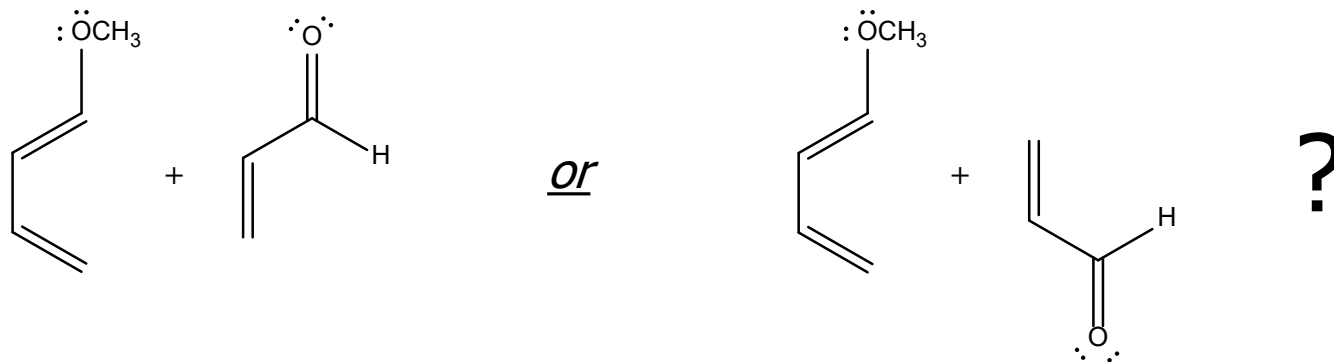
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- Relative stereochemistry of substituents on the dienophile is always preserved in a Diels-Alder reaction.
  - If the dienophile has two substituents that are *cis* to each other, they will also be *cis* in the Diels-Alder adduct:
  
  
  
  
  
  
  
  
  
  
  - If the dienophile has two substituents that are *trans* to each other, they will also be *trans* in the Diels-Alder adduct:



# Diels-Alder Reactions: Regiochemistry

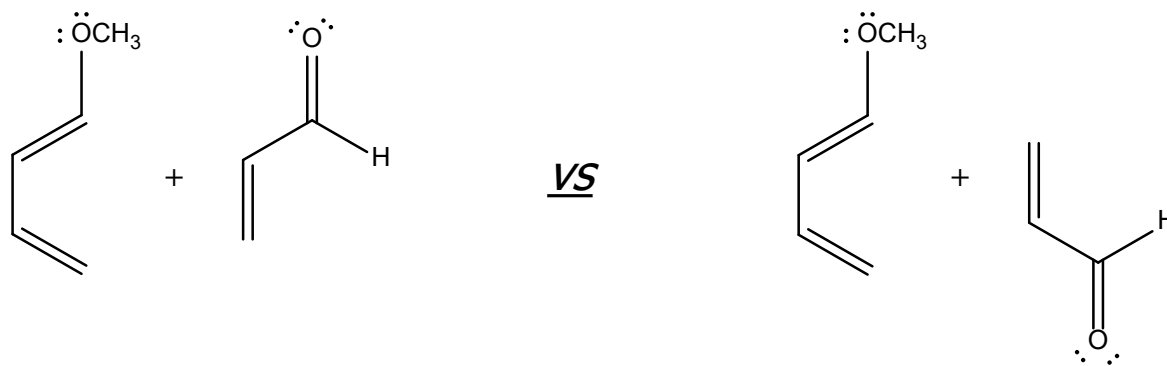
- When both the diene and dienophile in a Diels-Alder reaction are unsymmetrical, we must also consider the regiochemistry of the reaction.



- The rule of thumb is that the strongest EWG on the dienophile and the strongest EDG on the diene will be either 1,2- or 1,4-disubstituted. *You may hear this referred to as the "ortho or para rule" – even though that terminology isn't really appropriate given that the product is not a benzene ring.*

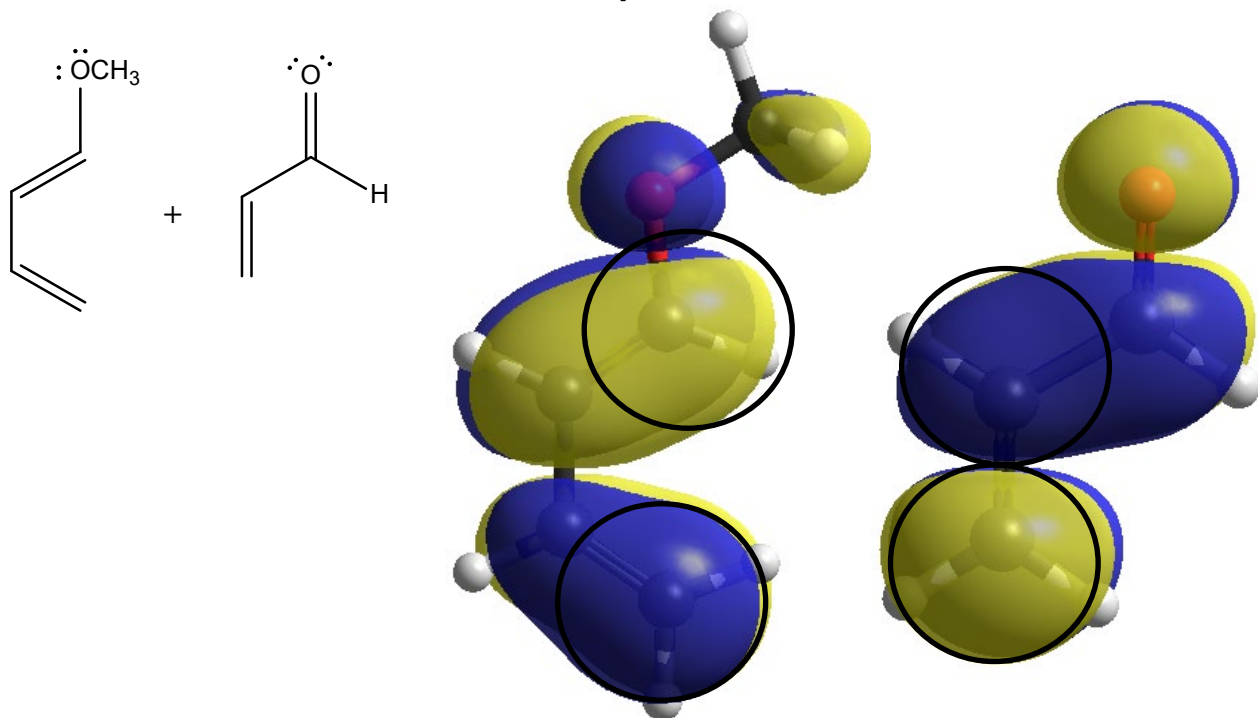
# Diels-Alder Reactions: Regiochemistry

- We can use resonance structures to rationalise the preference for the 1,2-regioisomer over the 1,3-regioisomer:



# Diels-Alder Reactions: Regiochemistry

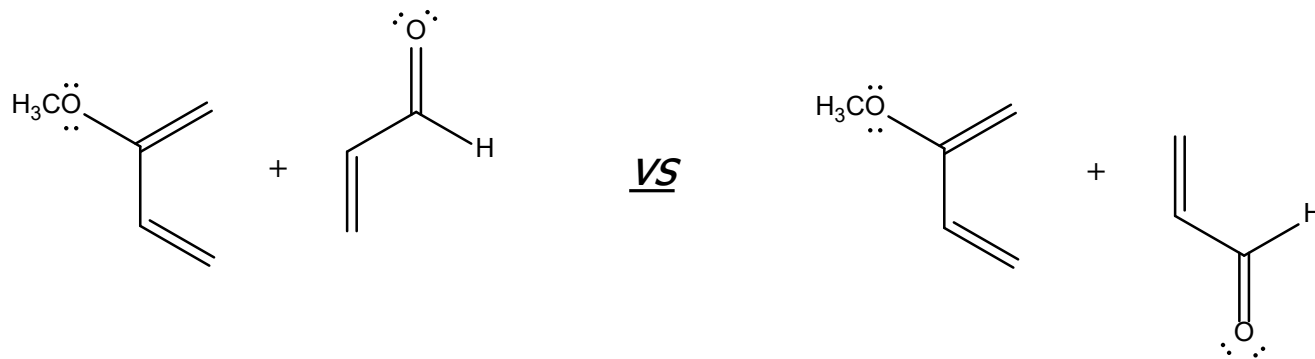
- We can also look at the molecular orbitals to see how to get the largest lobe on the diene's HOMO to overlap with the largest lobe on the dienophile's LUMO:



- The black circles are all the same size – which helps us see which lobes are larger – but it's certainly not immediately obvious. That's why the resonance arguments are still useful. 27

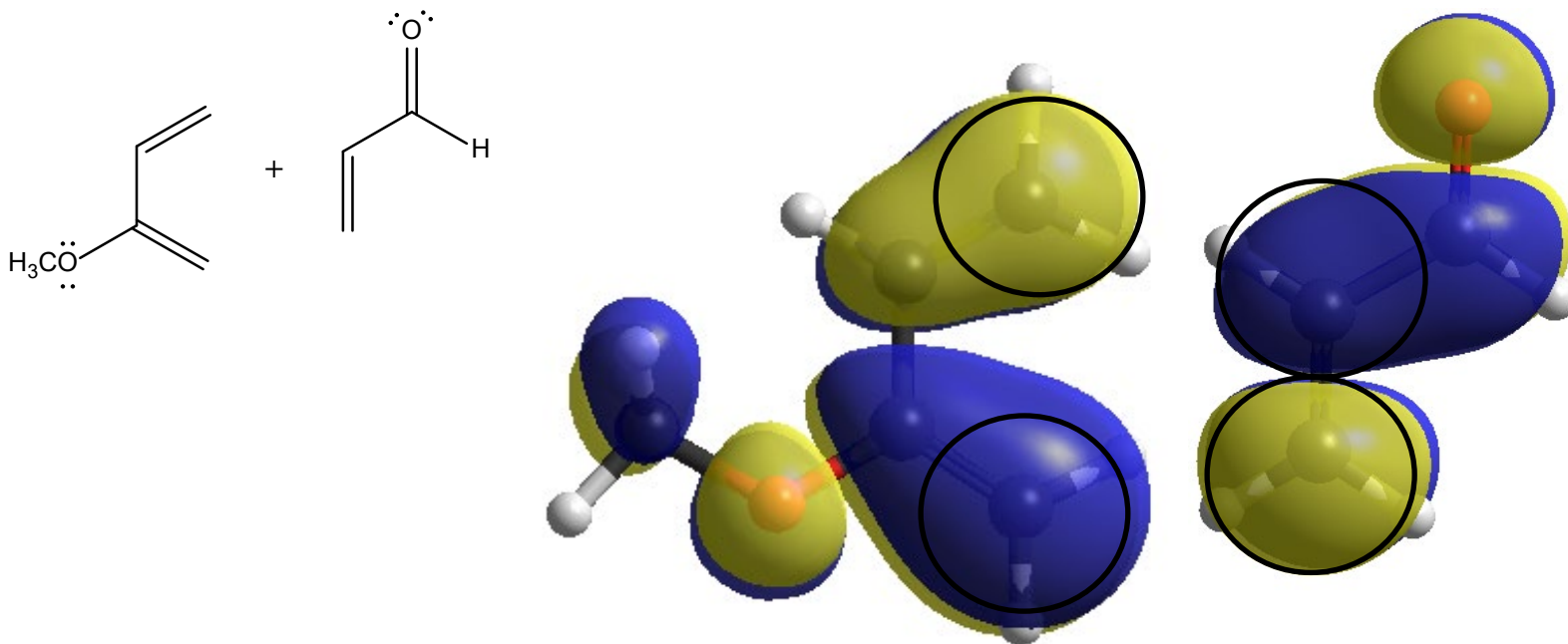
# Diels-Alder Reactions: Regiochemistry

- The same type of resonance argument works to rationalise the preference for the 1,4-regioisomer over the 1,3-regioisomer:



# Diels-Alder Reactions: Regiochemistry

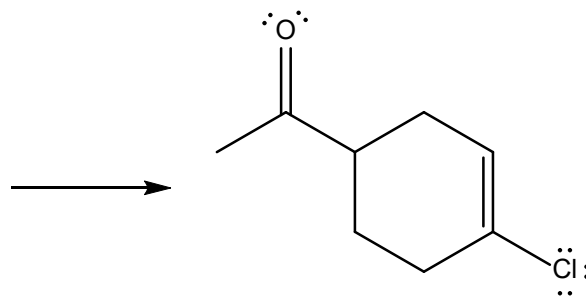
- Again, we can look at the molecular orbitals to see how to get the largest lobe on the diene's HOMO to overlap with the largest lobe on the dienophile's LUMO:



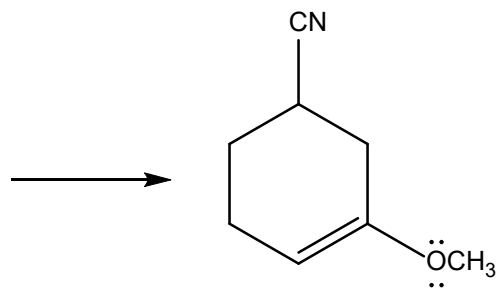
- Again, the black circles are all the same size to help us see which lobes are larger. It's a little more obvious in this case than the last one.

# Diels-Alder Reactions: Putting It All Together

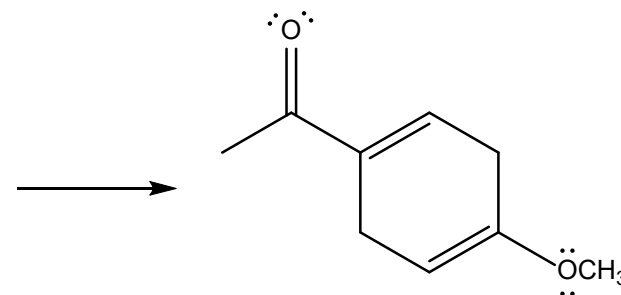
- Which of the following compounds could you prepare via a Diels-Alder reaction? For those that could be made this way, identify the diene and dienophile.



# Diels-Alder Reactions: Putting It All Together



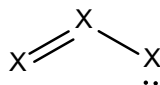
# Diels-Alder Reactions: Putting It All Together



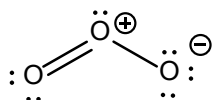


# 1,3-Dipolar Cycloadditions

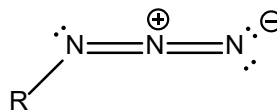
- Dienes are not the only molecules with four-electron pi systems. A four-electron pi system is also formed when one of the atoms in a double bond is attached to a third atom with at least one lone pair:



- 1,3-dipoles fall into this category. A 1,3-dipole has a nucleophilic site and an electrophilic site separated by an atom (usually positively charged) that can serve as an electron acceptor. Common examples include:



ozone



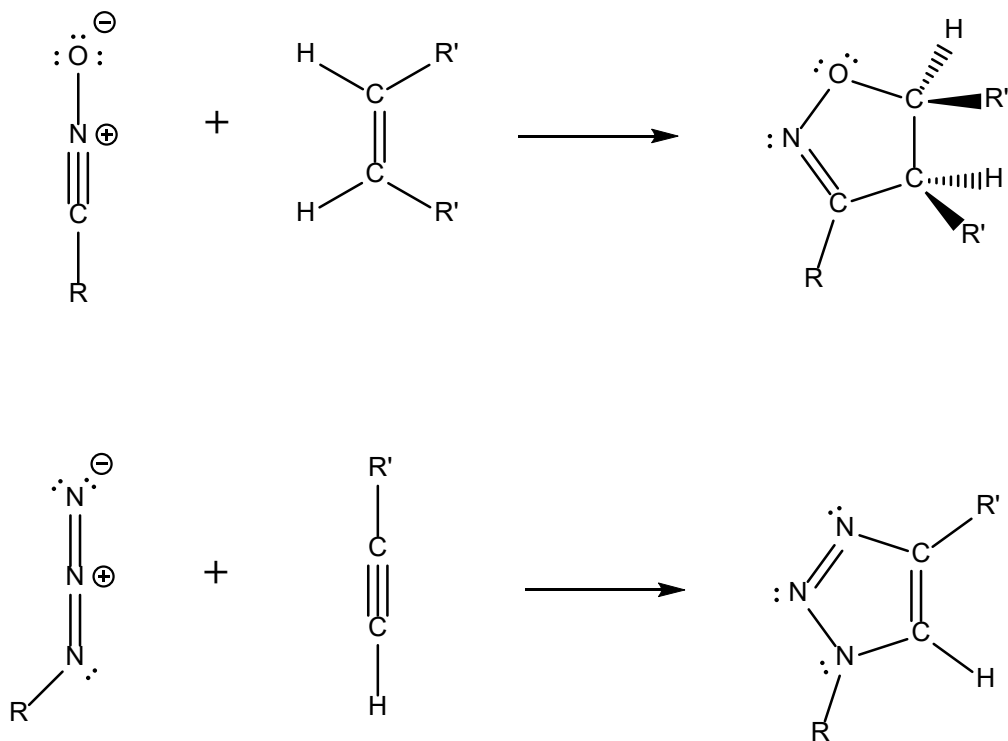
alkyl azide



nitrile oxide

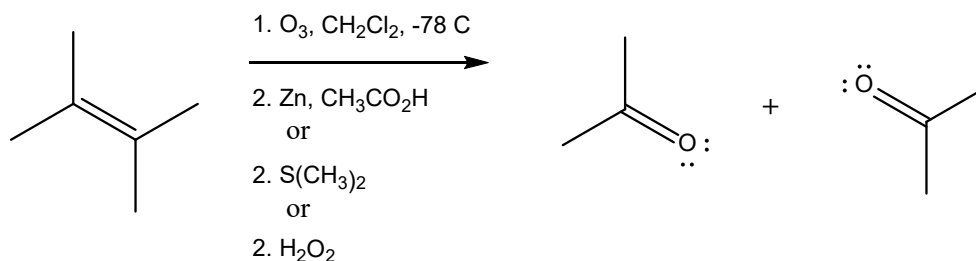
# 1,3-Dipolar Cycloadditions

- A 1,3-dipole can react with a "dipolarophile" (analogous to "dienophile") in a [3+2] cycloaddition (3-atom pi system reacting with 2-atom pi system):



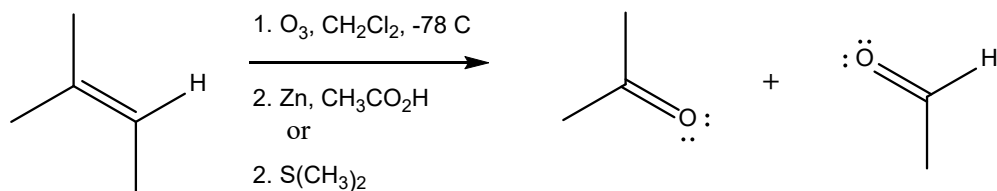
# 1,3-Dipolar Cycloadditions: Ozonolysis

- A particularly useful reaction based on 1,3-dipolar cycloaddition is **ozonolysis**. An alkene is "lysed" (broken) by reacting it with ozone.
- This results in two carbonyl groups, one for each carbon that used to be part of the alkene:

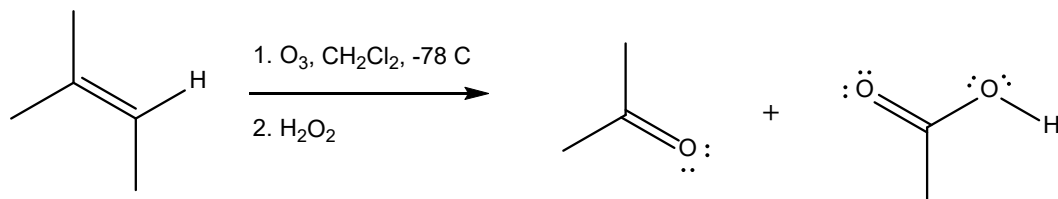


# 1,3-Dipolar Cycloadditions: Ozonolysis

- The three potential work-ups are equivalent when the alkene is tetrasubstituted (four carbon atoms attached to alkene).
- If either vinyl carbon has one or more hydrogens attached, reductive work-up ( $\text{Zn}/\text{CH}_3\text{CO}_2\text{H}$  or  $\text{S}(\text{CH}_3)_2$ ) gives an aldehyde:

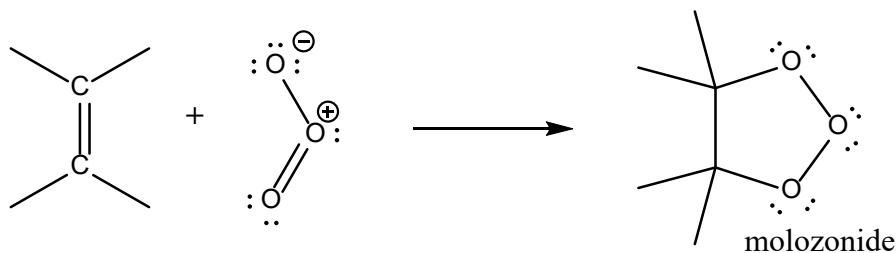


- On the other hand, oxidative work-up ( $\text{H}_2\text{O}_2$ ) inserts an oxygen atom into the C-H bond, giving a carboxylic acid:

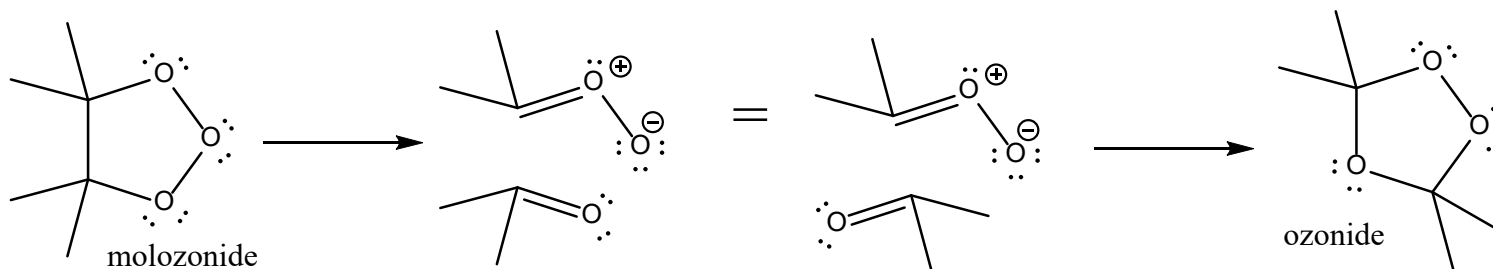


# 1,3-Dipolar Cycloadditions: Ozonolysis

- How does ozonolysis work?
  - Step 1a: 1,3-Dipolar cycloaddition reaction between the alkene and ozone. This gives a very unstable intermediate called a molozonide:

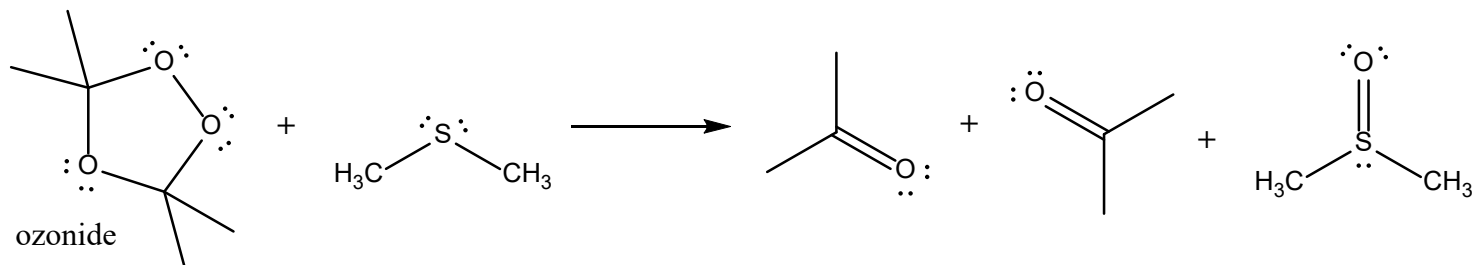


- Step 1b: The molozonide rearranges to a more stable isomer called an ozonide (a kind of cyclic peroxide). This occurs via a retro-1,3-dipolar cycloaddition followed by another 1,3-dipolar cycloaddition!



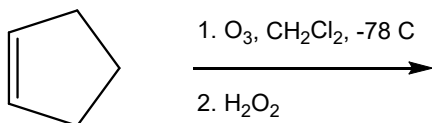
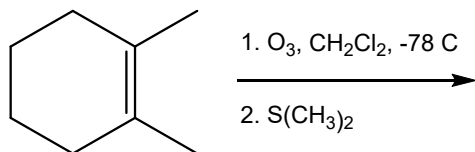
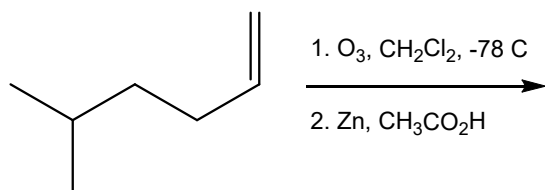
# 1,3-Dipolar Cycloadditions: Ozonolysis

- Step 2: Work-up. At this point, the mechanism depends on the kind of work-up. Oxidative work-up gives ketones and carboxylic acids (though only one H is replaced by OH in the case of a terminal alkene). Reductive work-up gives ketones and aldehydes. e.g.



# 1,3-Dipolar Cycloadditions: Ozonolysis

- Draw the ozonolysis product for each of the following alkenes. Pay attention to whether the work-up is oxidative or reductive!



# 1,3-Dipolar Cycloadditions: Ozonolysis

- Now, we can be very clever when proposing synthetic routes:

