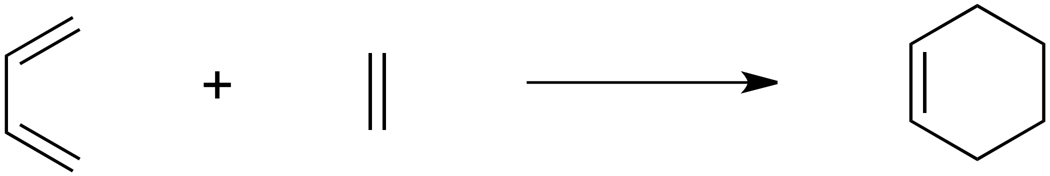
Topic I – Pericyclic and Related Reactions

Pericyclic reactions are **concerted** reactions that take place via a **transition state** that contains a **cyclic array of orbitals**.

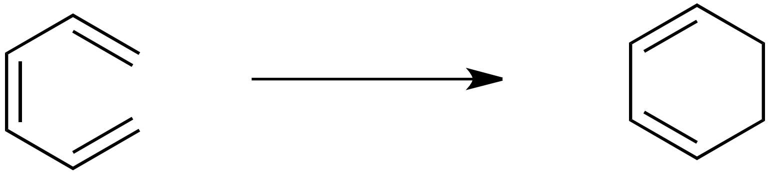
Recall: concerted reactions take place by traversing a single energy barrier whereas step-wise mechanisms involve discrete intermediates (e.g. cations, anions or radicals).

The most important pericyclic reactions are grouped into three classes:

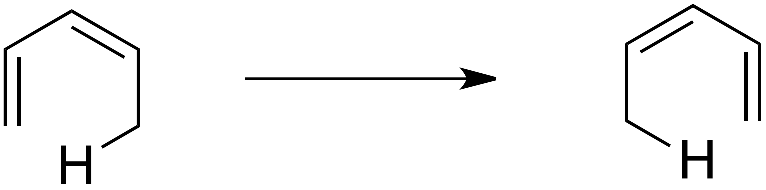
1. Cycloadditions



2. Electrocyclic reactions



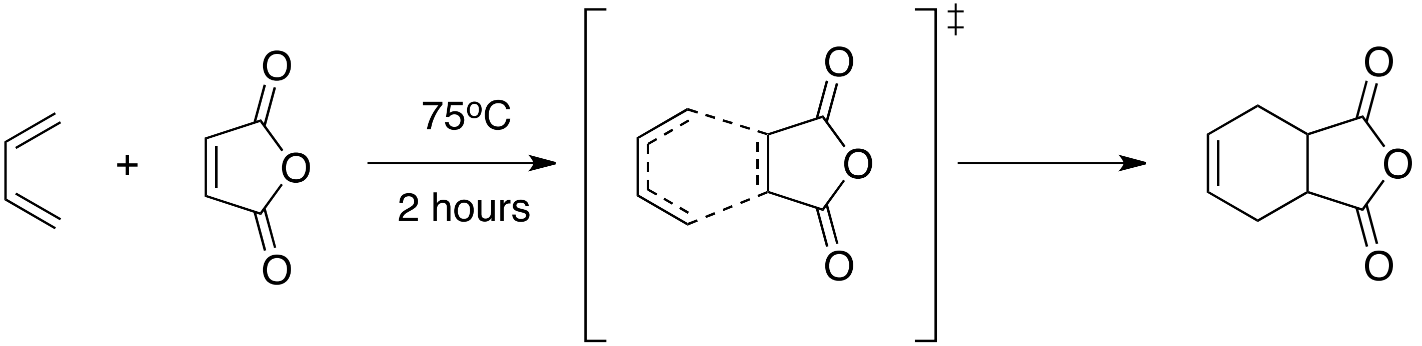
3. Sigmatropic rearrangements



1. Cycloadditions

Bimolecular concerted reactions that take place via a transition state that contains a cyclic array of orbitals – very useful for making complex ring systems.

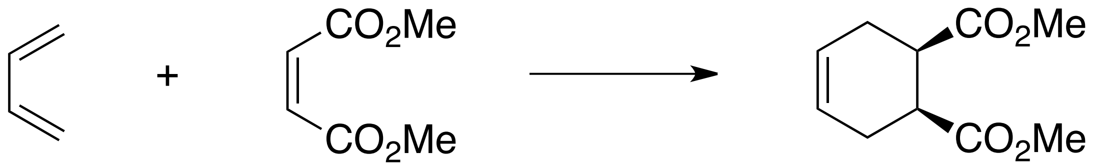
Classic example: the Diels-Alder reaction (1928, Nobel Prize awarded in 1950)

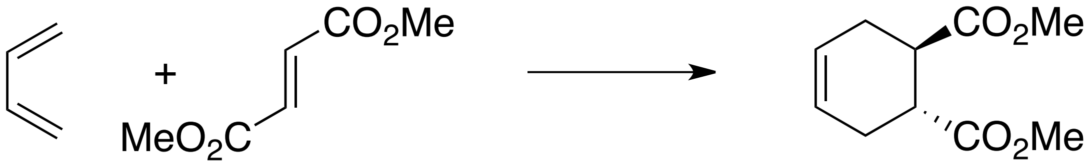


This is an example of a [4+2] cycloaddition. It involves three pairs of electrons: 4 from the two double bonds of one reactant and 2 from the double bond of the other.

These electrons move to make and break bonds in a concerted fashion, i.e. there is no intermediate. The driving force for the reaction is the conversion of 2 π bonds in the reactants to 2 σ bonds in the product.

Since bond formation between the two ends of the diene and dienophile takes place in a concerted fashion, the reactions are stereospecific with respect to the configuration of the dienophile. For example,

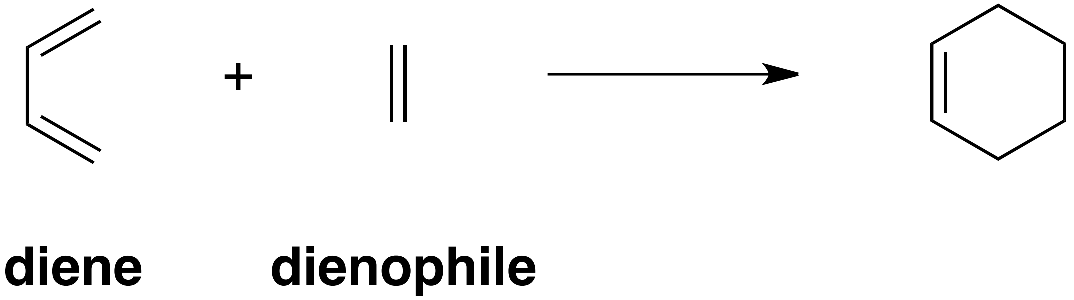




Qualitative MO theory (also known as Frontier Molecular Orbital theory) is extremely useful in understanding these reactions. In particular, the relative rates, regiochemistry and stereochemistry of these reactions.

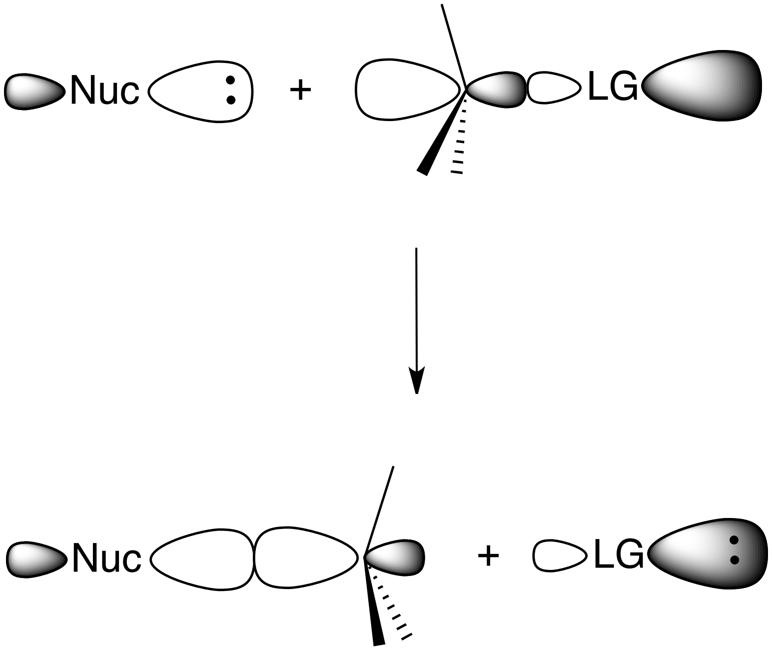
Recall: the frontier molecular orbitals are those between which the electrons move in the nucleophile (the HOMO) and the electrophile (the LUMO).

Usually, in a [4+2] cycloaddition, the diene is the nucleophile and the dienophile is the electrophile. Therefore, it is the HOMO of the diene and LUMO of the dienophile that is important in determining the electronic rearrangement in the TS.



How do we know what the MOs look like?

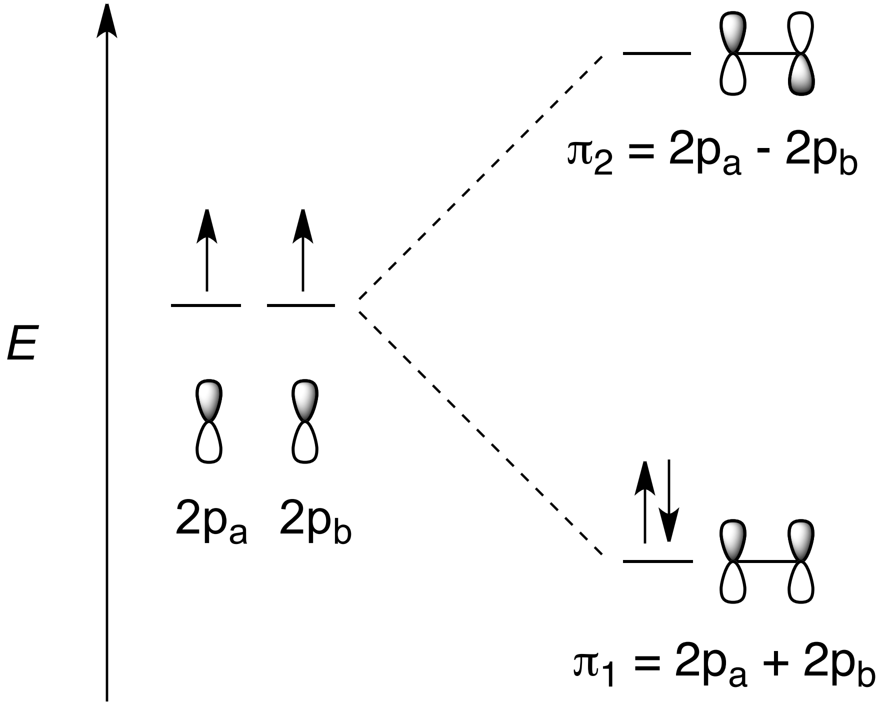
In an S_N2 reaction, it is relatively easy to identify the HOMO and the LUMO. The HOMO is the lone pair of electrons on the nucleophile, and the LUMO is the σ^* of the bond between the carbon and the leaving group:



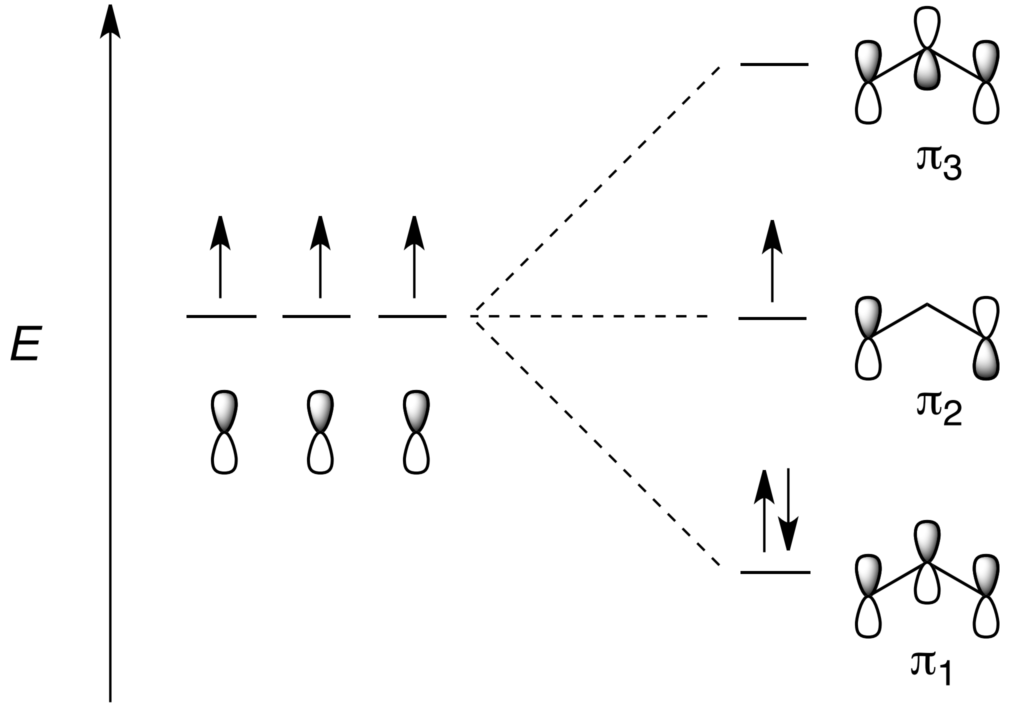
In the case of pericyclic reactions, which involve conjugated systems, the MOs are more complex since they involve contributions of multiple atomic orbitals.

For information on the properties (including molecular orbitals) of conjugated systems, see Chapter 7 in Clayden.

Recall the π-bonding in ethylene:



This can be extended by another 2p orbital to yield the π- MOs for the allyl fragment (shown as the radical):

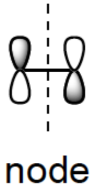


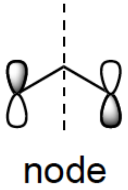
Explicitly, the rules for constructing π-MO’s for conjugated systems is as follows:

1. Number of atomic orbitals = number of molecular orbitals

2. Orbitals of increasing energy have increasing numbers of nodes

N.B. A node is a point where the phase changes between overlapping orbitals; they can be in between atoms or on atoms with no contribution to the MO



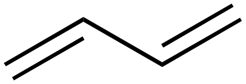


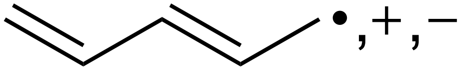
3. Nodes are symmetrically disposed about the centre of symmetry of the **π**-system

4. If n (number of atomic orbitals) is an even number, there are n/2 bonding and n/2 antibonding orbitals

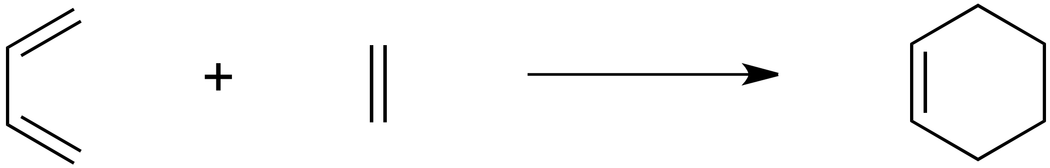
5. If n is an odd number, there are (n-1)/2 bonding and (n-1)/2 antibonding orbitals and one non-bonding orbital

So, for butadiene and pentadiene, respectively:





Consider again the generalized example:



diene **dienophile**

How do we know that it is the HOMO of the diene and the LUMO of the dienophile and not vice versa?

We look at the relative energies of the MOs.

1,3-butadiene	ethylene
LUMO = +1.0 eV	LUMO = +1.5 eV
HOMO = -9.1 eV	HOMO = -10.5 eV

If 1,3-butadiene is the nucleophile and ethylene is the electrophile, the FMO energies differ by:

$$\Delta E = 1.5 - (-9.1) = 10.6 \text{ eV}$$

If 1,3-butadiene is the electrophile and ethylene is the nucleophile, the FMO energies differ by:

$$\Delta E = 1.0 - (-10.5) = 11.5 \text{ eV}$$

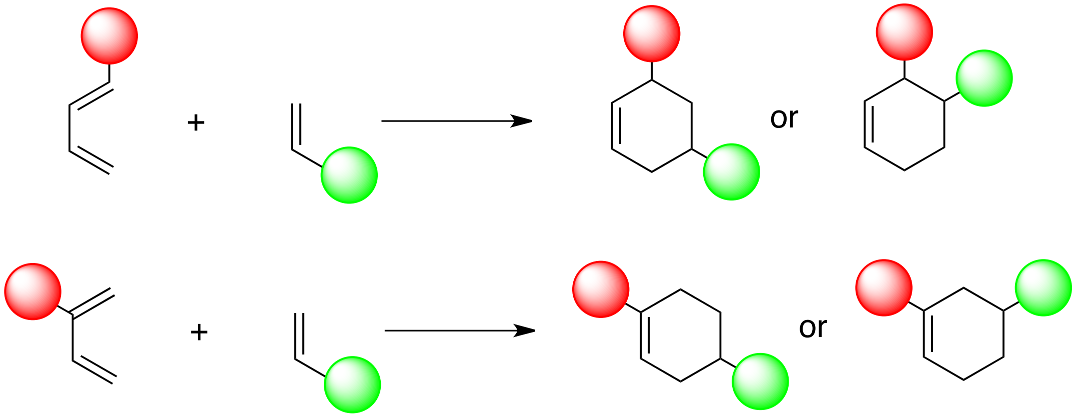
Therefore, the latter is the preferred pathway.

The reality is that this is a very difficult reaction. The reason is because the energy gap between the HOMO of the diene and the LUMO of the dienophile is simply too big – therefore requiring very high temperatures. In fact, another reaction predominates! *Which one???*

In contrast, when ethylene is replaced as the dienophile with maleic anhydride (the Diels-Alder reaction), the ΔE is now 8.5 eV since it is a better electrophile (its LUMO energy is -0.6 eV).

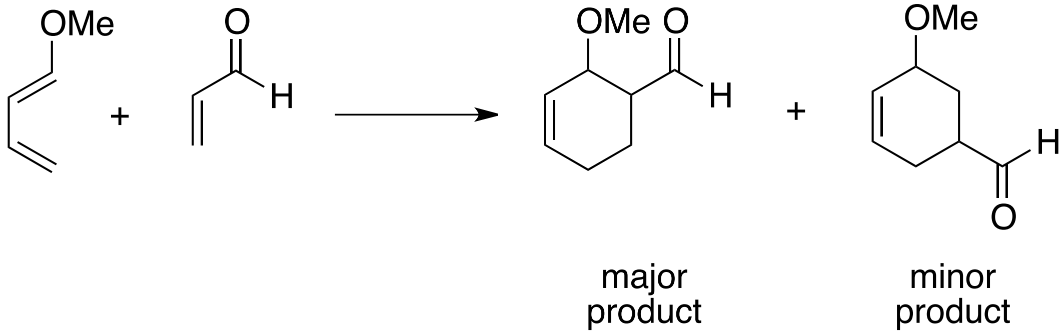
These reactions are referred to as proceeding via **Normal Electron Demand**. If, the diene is very electron-poor and the dienophile is very electron-rich, the reaction may proceed with **Inverse Electron Demand**, that is, via the interaction of the HOMO of the dienophile and the LUMO of the diene. This is far less common.

Knowing which MOs are involved in the reaction are important not only in understanding the relative rates of cycloadditions, but also the regiochemical outcomes of these reactions. Consider when the reactants are substituted in an asymmetric way:



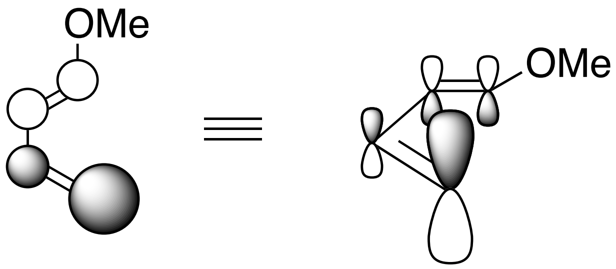
Which product predominates and why?

For example,

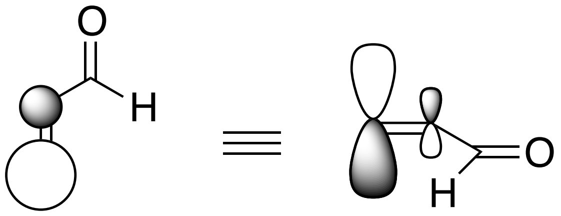


Why? The polarization of the MO’s.

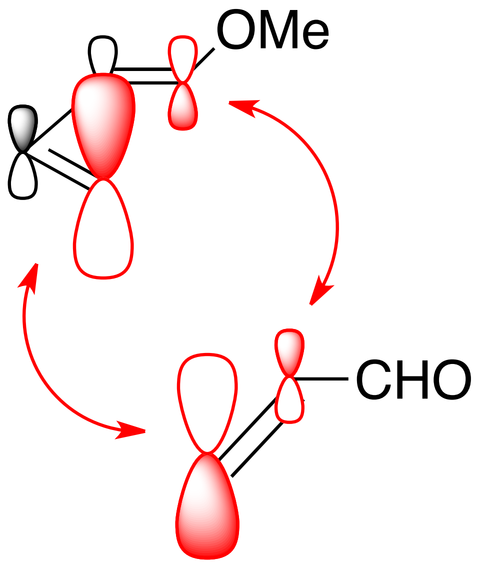
The HOMO of the 1-methoxy-1,3-butadiene is polarized away from the substituent, making the furthest carbon the most nucleophilic:

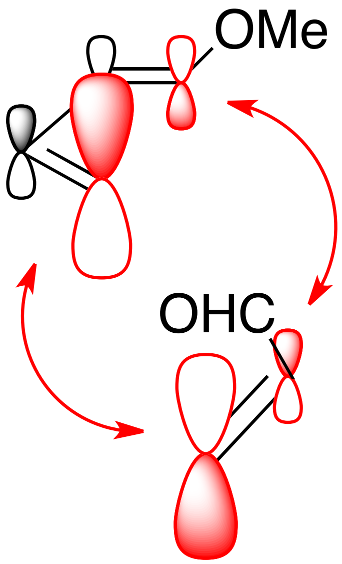


And the LUMO of acrolein is polarized away from the substituent, making the furthest carbon the most electrophilic:



So, the lowest energy transition state is the one that forms a bond between the most nucleophilic and most electrophilic carbons – or those carbons with the largest atomic orbital contributions to the HOMO and LUMO.

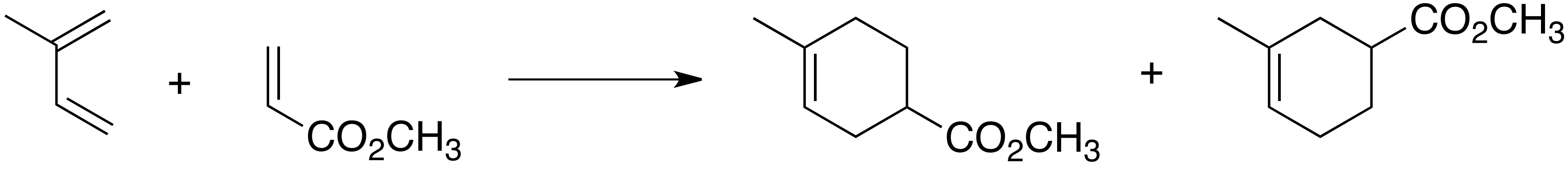




In general, electron-donating groups (e.g. -NR$_2$, -OR, -SR, -R) polarize π-HOMOs away from the substituent and polarize π-LUMOs toward the substituent, and electron-withdrawing groups (e.g. –NO$_2$, -CN, carbonyls, -CF$_3$) polarize π-LUMOs away from the substituent and polarize π-HOMOs toward the substituent.

Polarization via the addition of catalysts…

For example,

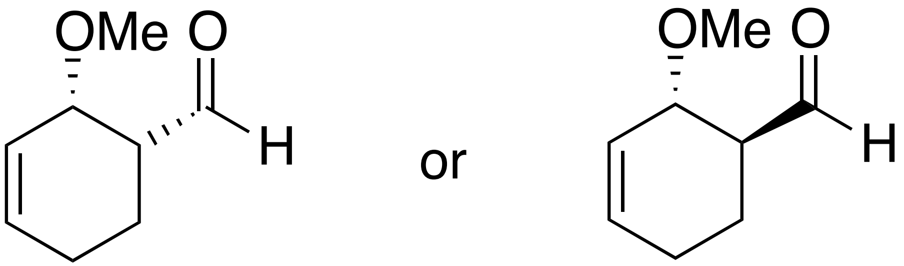


conditions A: 120°C for 6 hours	70%	30%
conditions B: + 1 eq. $AlCl_3$ 20°C for 3 hours	95%	5%

Recommended Reading: Clayden p. 875-891

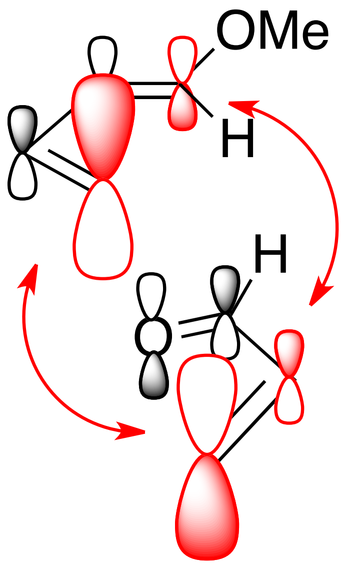
Practice Problems: #1-3 in Chapter 34 of Clayden

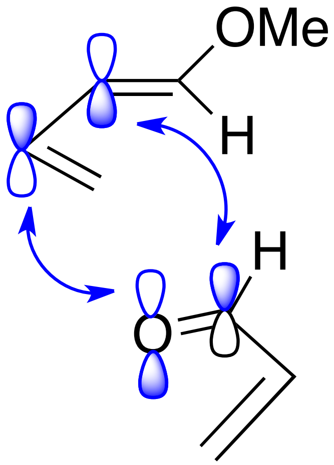
For decades, it had been observed that the *syn* diastereoisomers are the preferred products in [4+2] cycloadditions. For instance, in the example above, while two diastereoisomers (*syn* and *anti*) of the preferred regioisomer are possible, only the product on the left is observed.



This seems counterintuitive since the *syn* product is more sterically congested. Again, we can look at the MO's to understand what is going on.

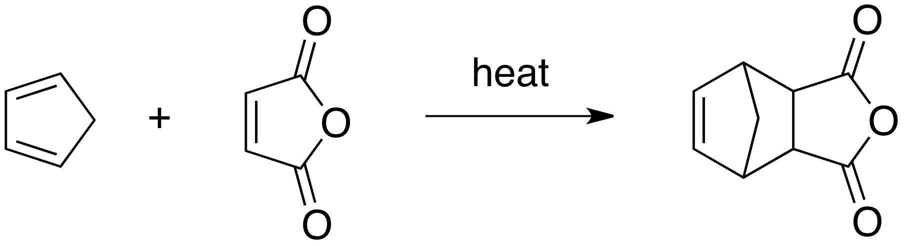
Ignoring the contributions of the atomic orbitals on the carbons between which bonds are being formed (in red, below), we can clearly see the positive interaction between the p orbitals on the carbon atoms between which the double bond is being formed and the p orbitals of the substituent carbonyl group.





This so-called **secondary orbital interaction** arises whenever an unsaturated group is on the dienophile, which happens to be most of the time.

One of the more interesting dienes used in [4+2] cycloadditions is cyclopentadiene, and arguably the most famous [4+2] cycloaddition is between it and maleic anhydride:



Because of the secondary orbital interaction illustrated above, only the *endo* product is formed in this reaction.

The *endo* isomer is so-called because the double bond and the carbonyl groups are on the same side of the newly-formed ring. If they are on the opposite side the isomer is *exo*.

Cyclopentadiene is a much better diene for cycloadditions because its cyclic structure enforces the *s*-cis geometry essential for the reaction to occur. Butadiene exists predominantly in the unreactive *s*-trans geometry at equilibrium.

In general, cyclic dienes are very good substrates for [4+2] cycloadditions.

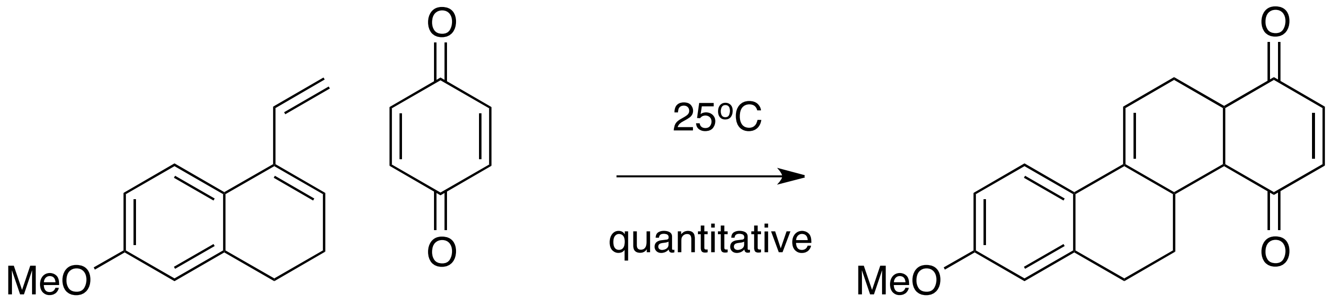
Cyclopentadiene exists itself as a [4+2] cycloadduct of itself at ambient temperature. In order to liberate cyclopentadiene to carry out cycloadditions (or other reactions), it is distilled directly before use (b.p. 42°C).

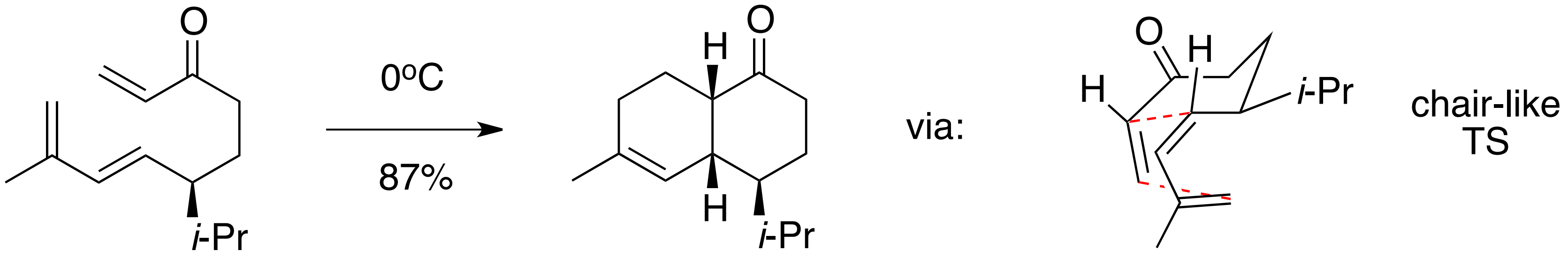
This highlights the reversible nature of the cycloaddition – the backwards reaction is referred to as a cycloreversion.

Running the cycloaddition in reverse generally takes high temperatures, and is usually only successful when ring strain is relieved.

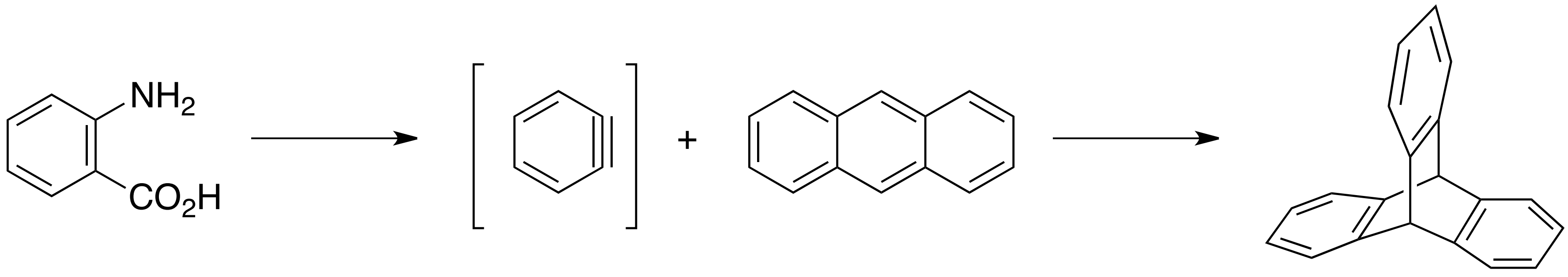
The [4+2] cycloaddition is one of the most synthetically useful reactions for the preparation of bicyclic compounds and polycyclic compounds of well-defined stereochemistry.

Some examples:

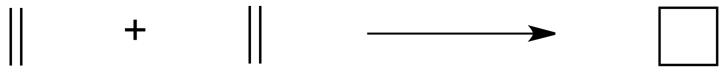




Various combinations of unsaturated reagents can give rise to cycloadditions:



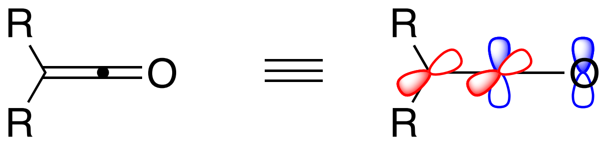
The simplest cycloaddition would be between two alkenes, a formal [2+2] cycloaddition:



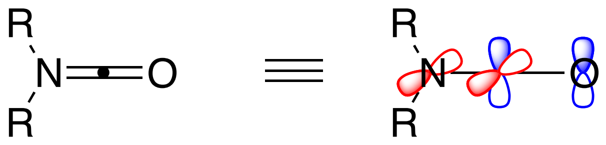
However, if we look at the frontier MO’s we can see that this shouldn’t happen.

In fact, the reaction can happen, but it requires a transition state geometry that is *very* difficult to achieve, thereby requiring lots of energy (very high temperatures).

This only works for *very* electron-poor alkenes: **ketenes** and **isocyanates**.

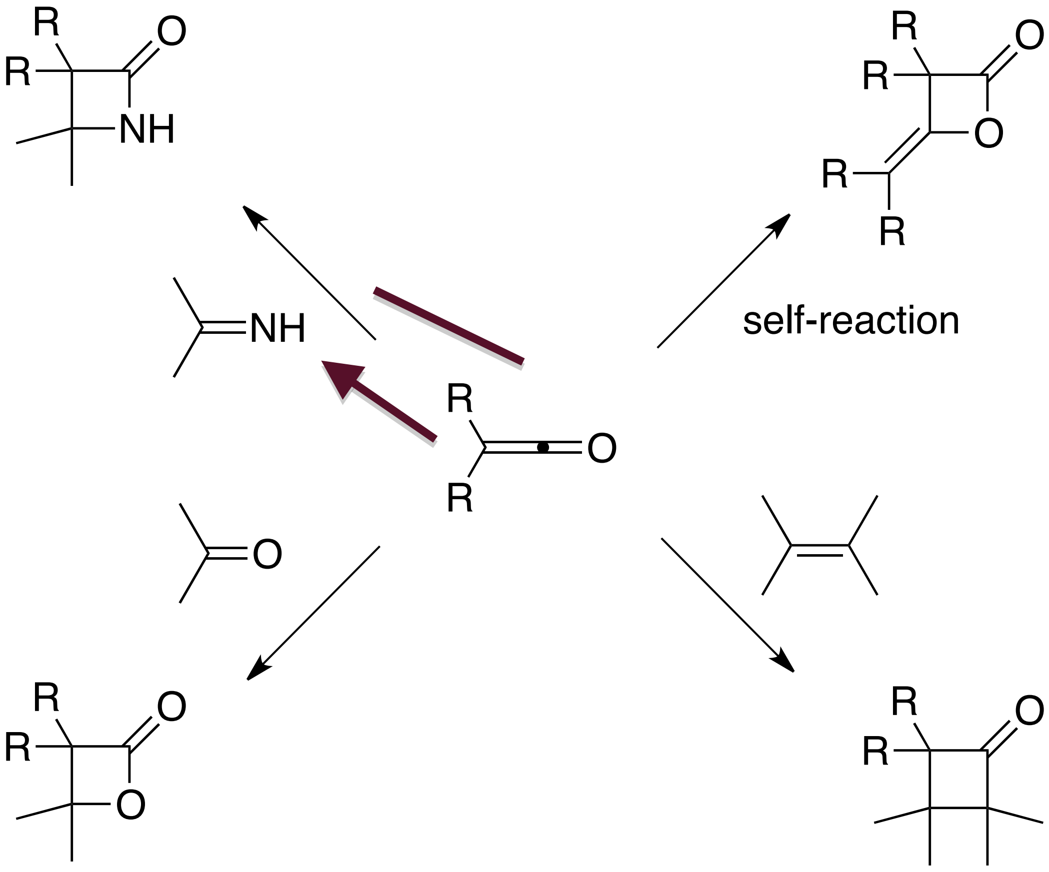


ketene

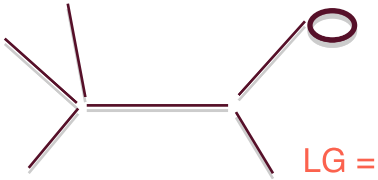


isocyanate

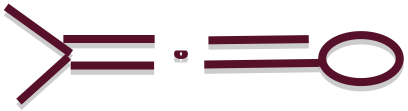
Cycloadditions of ketenes are particularly important synthetic reactions, and are a key strategy for the construction of four-membered rings:



How are ketenes made?

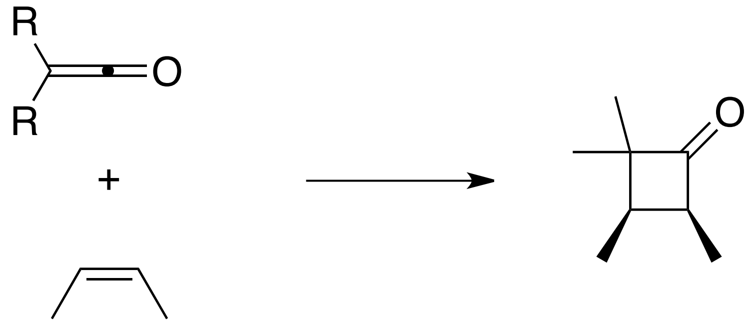


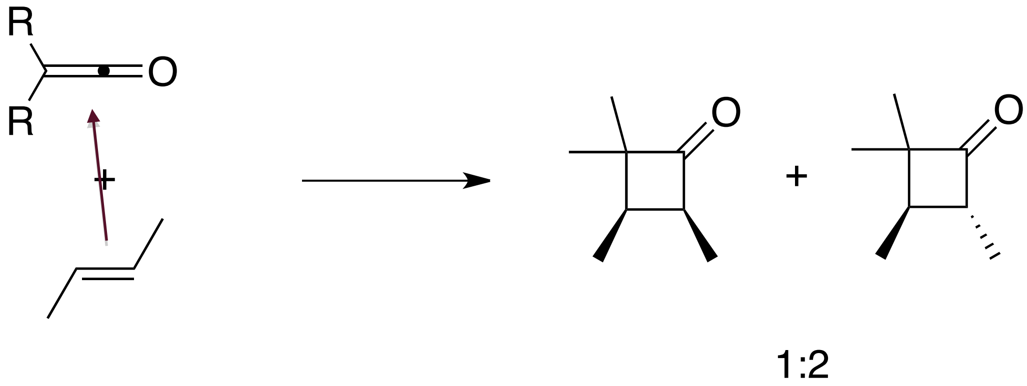
LG = LEAVING GROUP= CL



This is not touched upon in your text, but apparent [2+2] cycloadditions of ketenes often proceed instead by ionic mechanisms:

Consider:

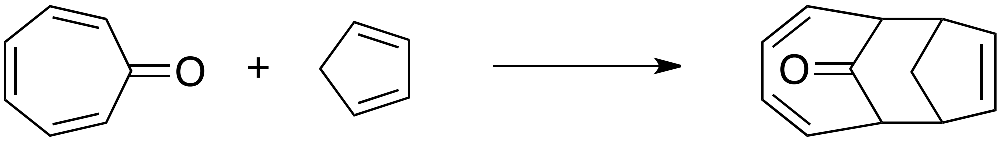


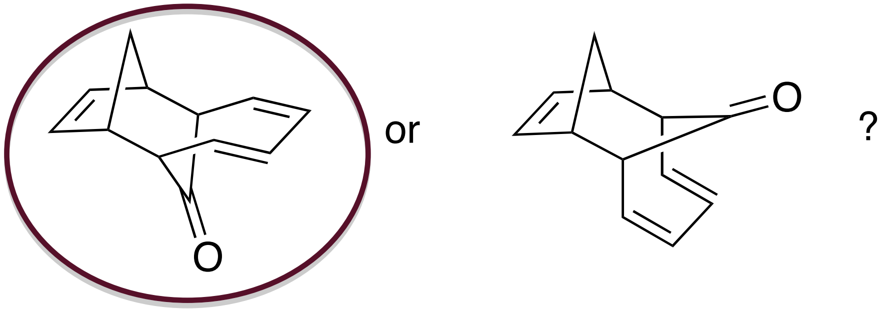


This relatively subtle difference illustrates how difficult it is to achieve the necessary transition state for a [2+2] cycloaddition.

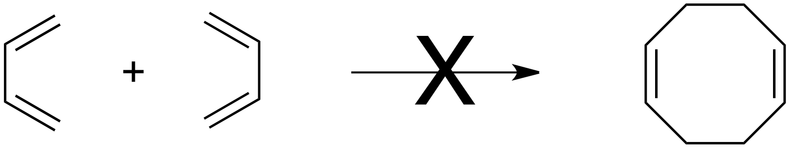
In general, cycloadditions which have **4n+2 mobile electrons** in the transition state occur upon heating whereas those with **4n mobile electrons** do not.

[4+6]



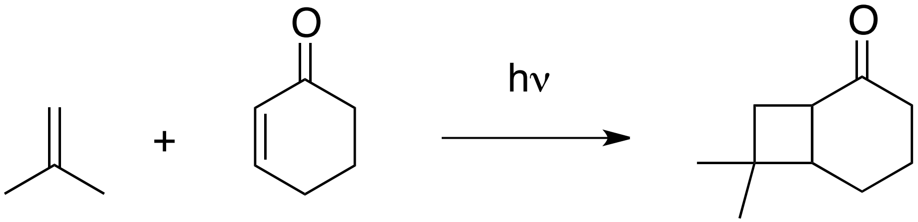


[4+4]

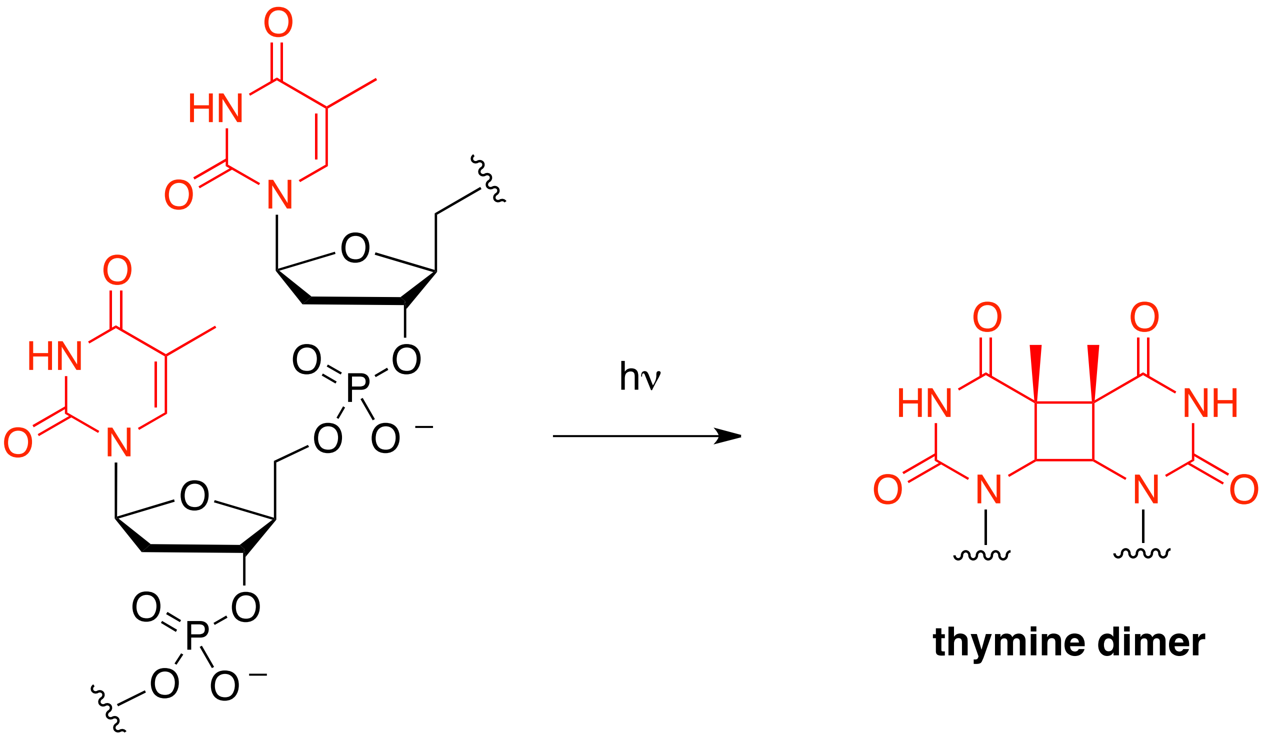


However, cycloadditions with 4n mobile electrons can occur in the presence of UV light; these so-called **photochemical reactions** take place when an electronically excited state of one of the reagents reacts with the ground state of the other. Now, the MO interactions are as follows:

The regiochemical outcome of these reactions is opposite to what is observed for 'normal' thermal processes… it is governed by the interaction of the two LUMO's:



Perhaps the most famous example of a photochemical [2+2] cycloaddition is the formation of thymine dimers in DNA:

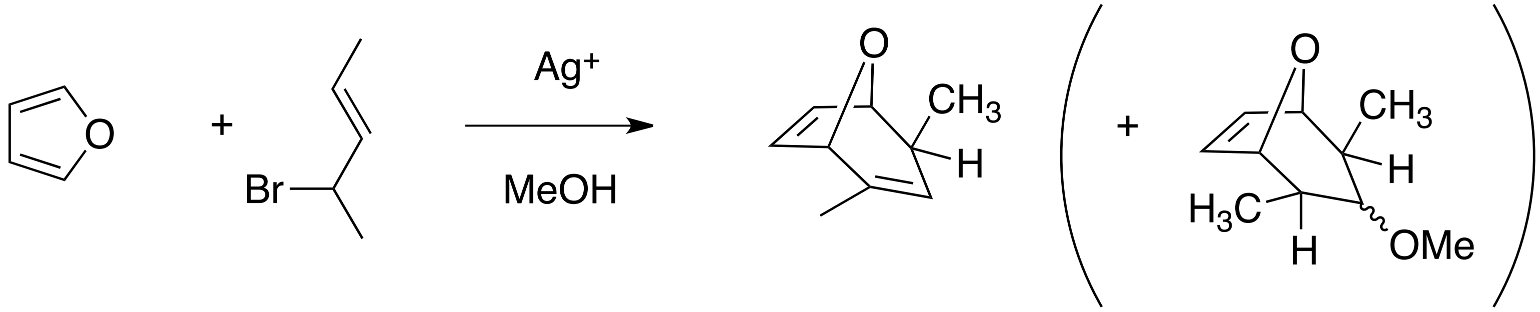


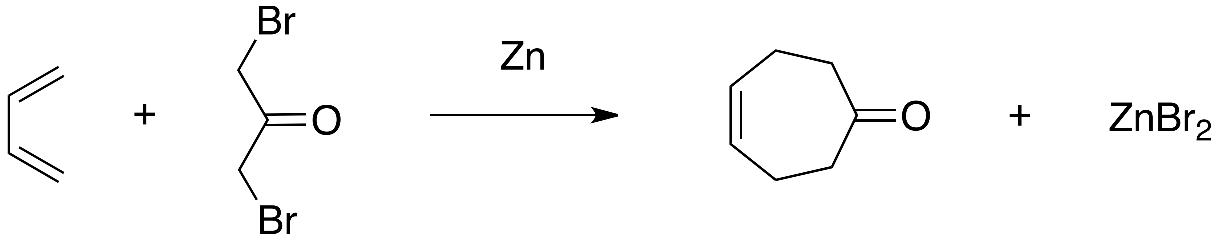
thymine dimer

Can also take place for cytosine, but is less common… Likewise for uridine in double-stranded RNA.

Odd-numbered ring systems are also accessible by cycloadditions, but the reactants must still be conjugated systems with a total of 4n+2 mobile electrons in the transition state.

Allylic cations, which have three carbon atoms but only 2 π electrons, are good dienophiles in formal [4+3] cycloadditions used to make 7-membered rings. They are usually generated *in situ* from allyl bromides or α-bromoenolates:

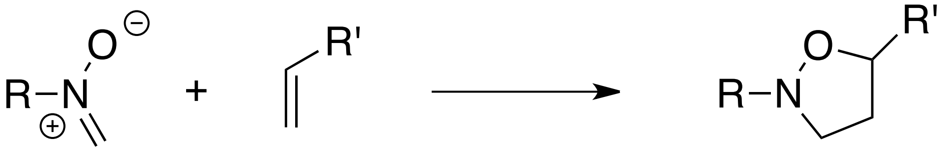




Again, we can understand these reactions using frontier MO theory:

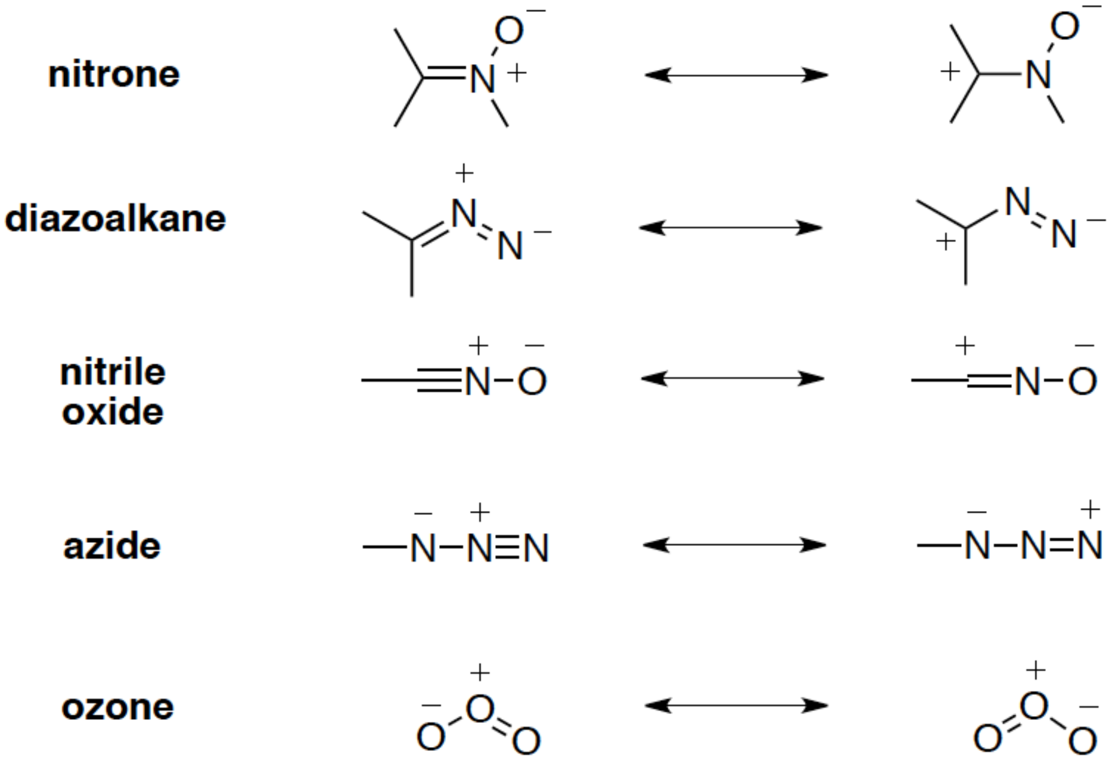
Three-centre, conjugated systems with 4 π electrons (essentially a double bond and a lone pair of electorns in conjugation - isoelectronic with the allyl anion) are generally called **1,3-dipoles** and undergo cycloaddition reactions with 2 π electron systems (often called **dipolarophiles**) to give 5-membered ring systems.

For example,



1,3-dipole **dipolarophile**

Some common 1,3-dipoles that used in dipolar cycloadditions:



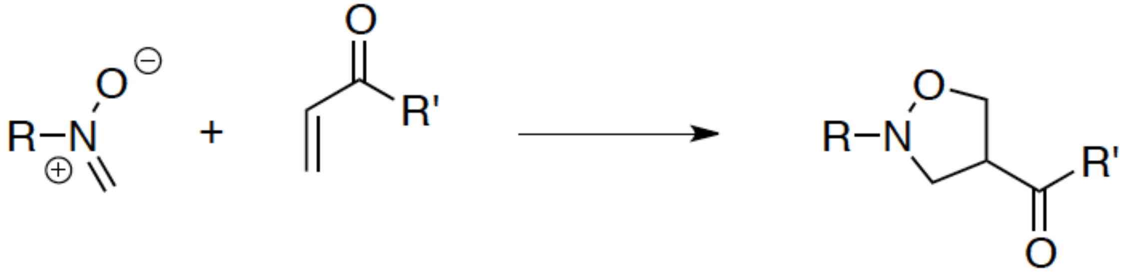
These are all isoelectronic with the allyl anions, so the nodal structure of the HOMO and LUMO are very similar.

We can predict whether the cycloaddition of a 1,3-dipole and dipolarophile will be normal electron demand (dipole HOMO + dipolarophile LUMO) or inverse electron demand (dipole LUMO + dipolarophile HOMO) by looking at the orbital energies.

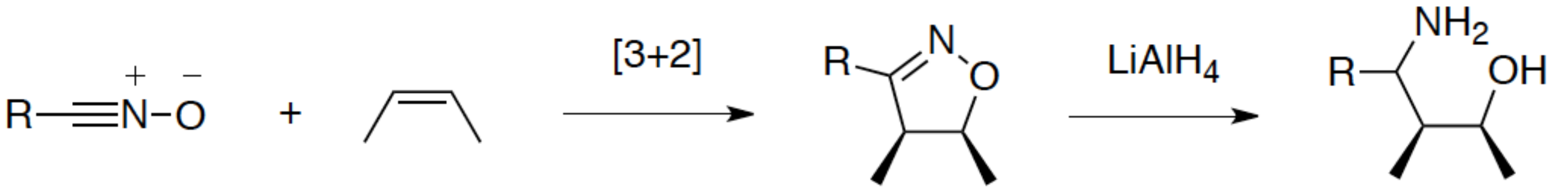
In general, the electronics of the dipolarophile govern the electron demand. If the dipolarophile is electron-rich, it is the nucleophile and reacts with its HOMO. If the dipolarophile is electron-poor, it is the electrophile and reacts with its LUMO.

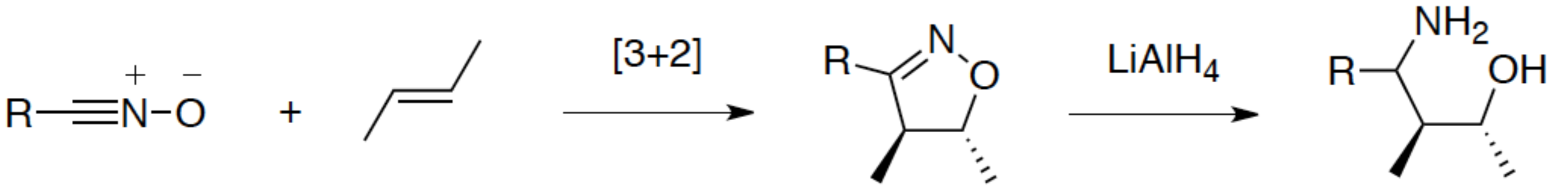
e.g.

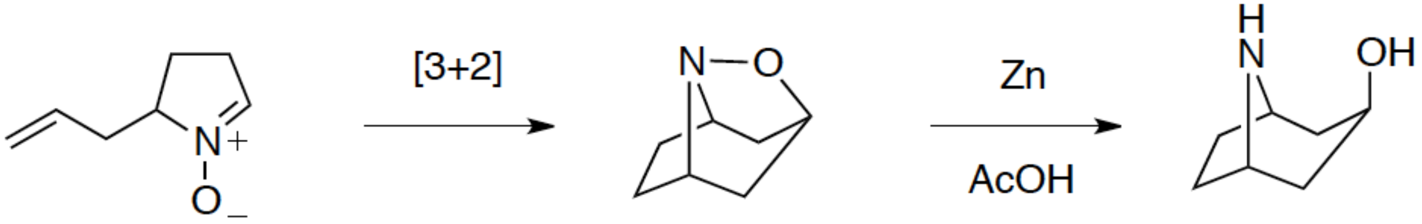
Again, we can predict the regiochemistry by looking at the polarization of the FMO's… this may not always be obvious in the 1,3-dipoles.



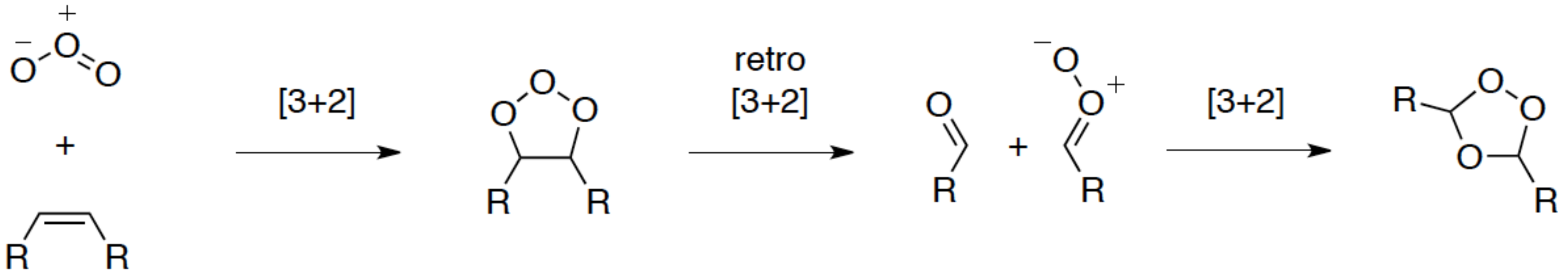
It is important to note that 5-membered heterocyclic ring products of 1,3-dipolar cycloadditions can be important targets in the synthesis of pharmaceuticals, natural products and industrial chemicals, but they can also serve as important intermediates to products that may be otherwise difficult to access.

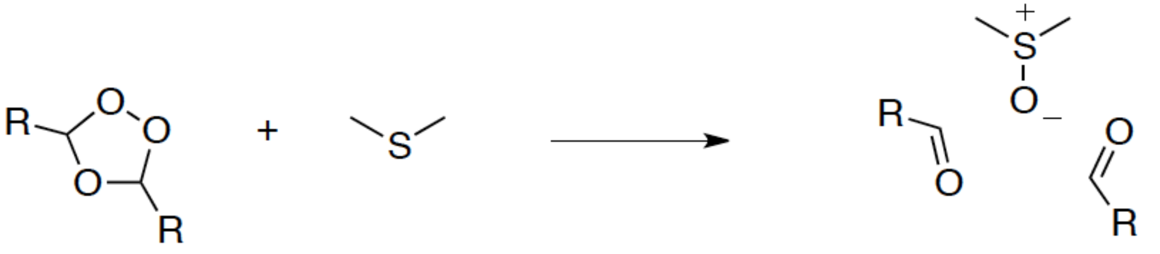






A particularly important 1,3-dipole in this context is ozone. The cycloadduct formed upon reaction with an alkene (called a primary ozonide) is unstable, and undergoes a cycloreversion to give an aldehyde and a carbonyl oxide. The carbonyl oxide itself is a 1,3-dipole, and another dipolar cycloaddition takes place to give a second cycloadduct (called a secondary ozonide). This compound reacts with reducing agents (on work-up), such as Zn or dimethylsulfide to give two aldehydes.





This process is called **ozonolysis**.

Recommended Reading: Clayden p. 893-908

Practice Problems: #4, 6-12 in Chapter 34 of Clayden