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Topic: Pericyclic Reactions

Pericyclic reactions

In pericyclic reactions the breaking and making of bonds occur simultaneously by the way of a single cyclic transition state (concerted reaction). There are no intermediates formed during the reaction.

transitions state
six delocalized π electrons
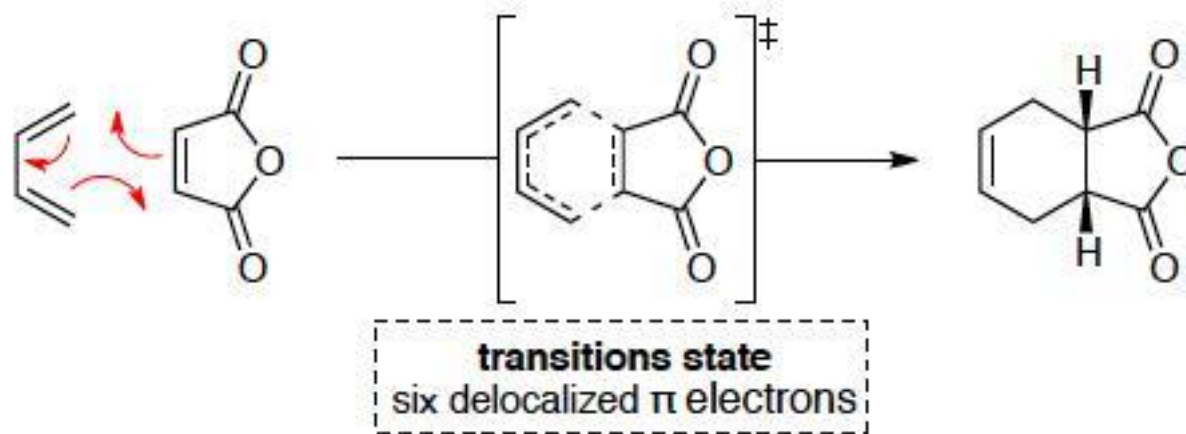
Cycloadditions
Electrocyclic reactions
Sigmatropic rearrangements
Group transfer reactions

Prediction of pericyclic reactions

Several theories have been established in order to predict whether a pericyclic reaction will proceed under given conditions or not (allowed or forbidden reaction).

FMO theory

The FMO theory was proposed by Kenichi Fukui in 1952. The prediction of pericyclic reaction is based on the interaction between frontier molecular orbitals (FMOs). This theory will be discussed more detailed during this class.

Woodward-Hoffmann rules

In 1965, Robert Woodward and Roald Hoffmann introduced a set of rules to predict the outcome of pericyclic reactions. Their concept is based on the assumption that orbital symmetry is conserved during a pericyclic reaction. Despite its brilliance, the application of the Woodward-Hoffmann rules can be tedious and complicated.

Huckel-Möbius theory

The Huckel-Möbius theory provides an alternative to the Woodward-Hoffmann rules. The theory is relatively simple: Pericyclic reactions with an aromatic transition state ($4n+2$ electrons) are thermally allowed, whereas reactions with Möbius topology ($4n$ electrons) are photochemically allowed.
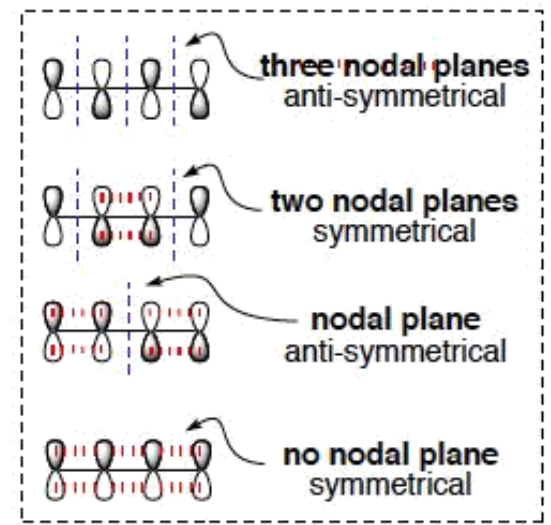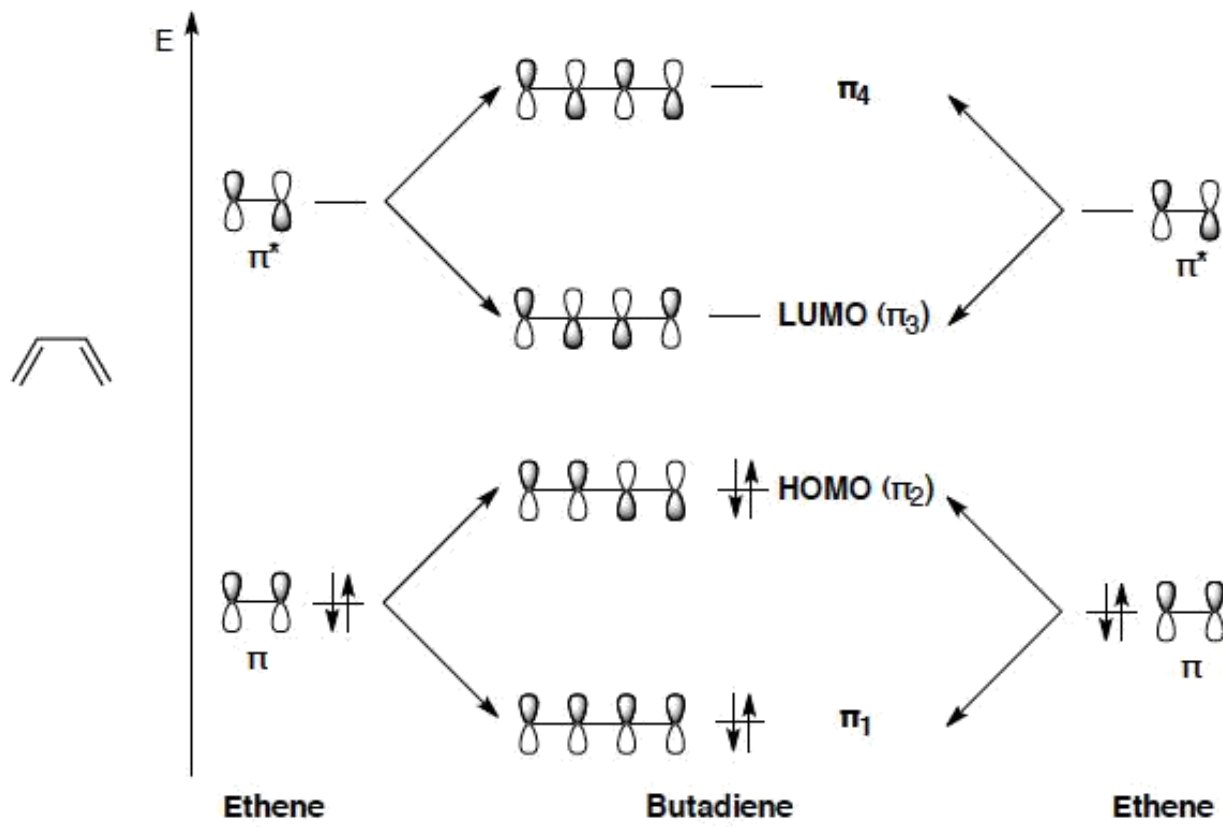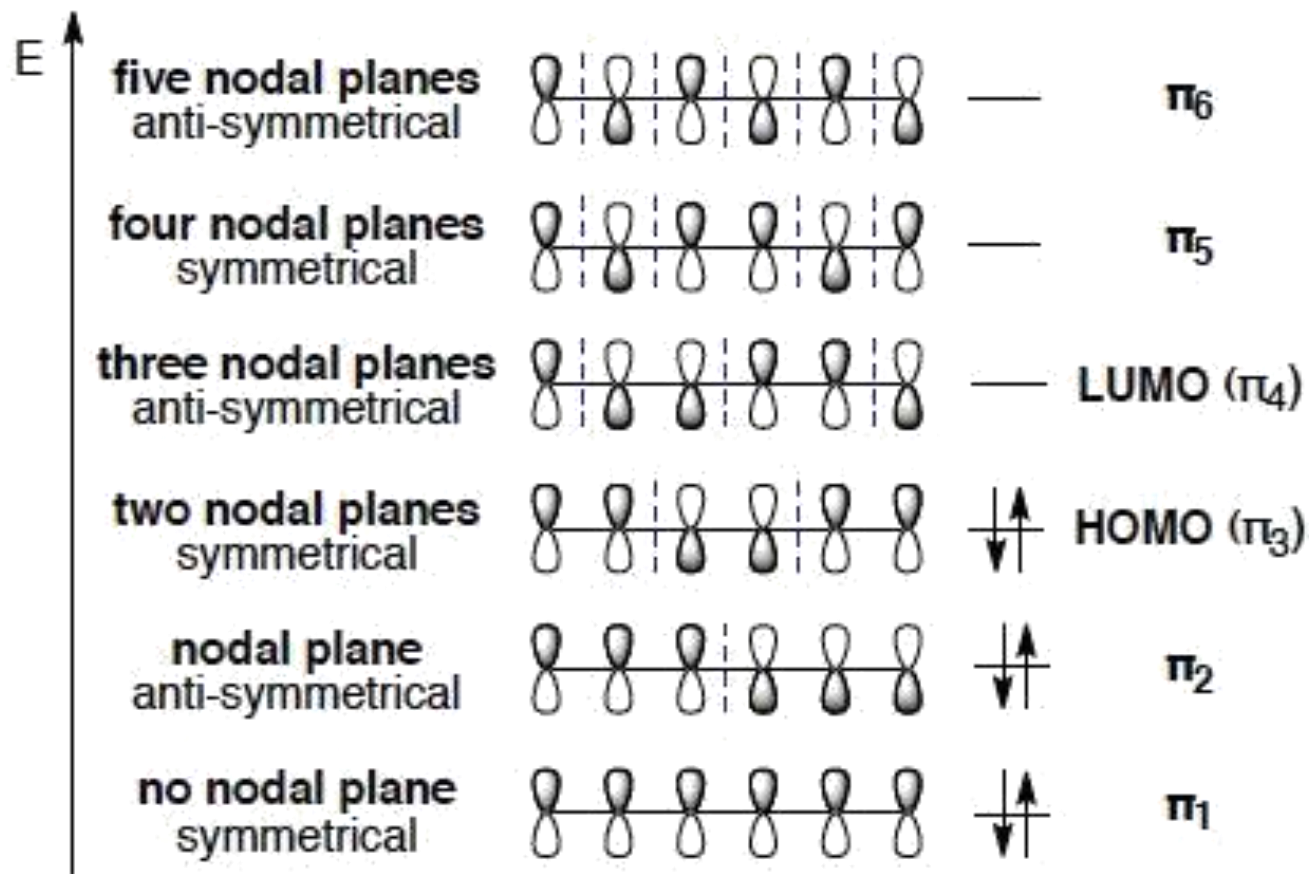
Introduction to FMO theory

Fukui realized that for a good approximation of reactivity it is not necessary to look at all the orbitals, but just at the so called frontier molecular orbitals.
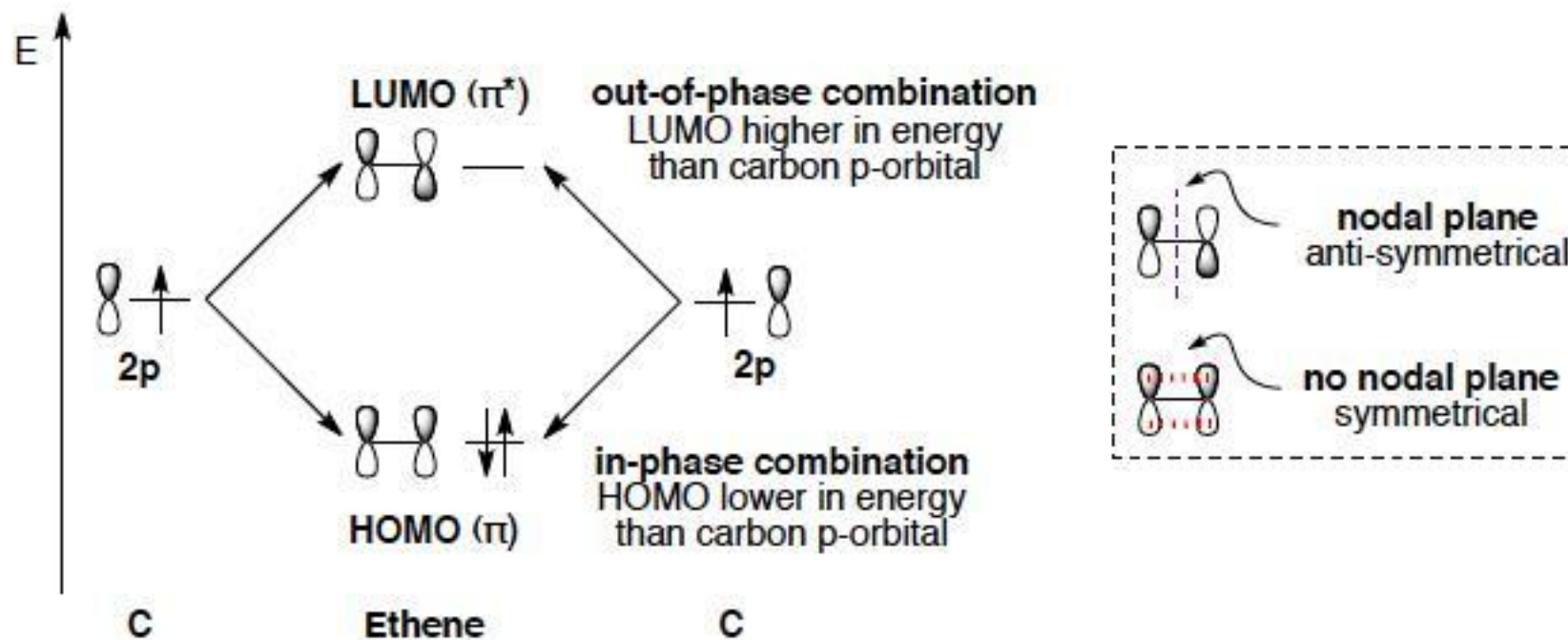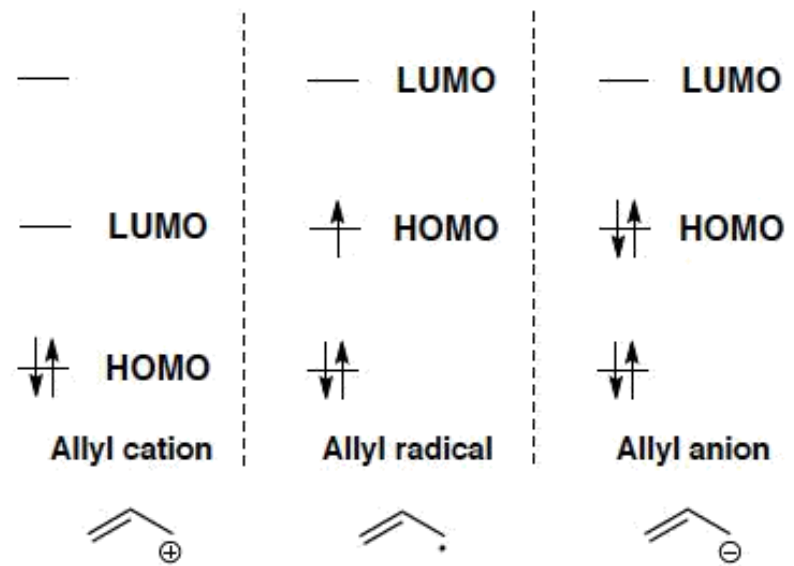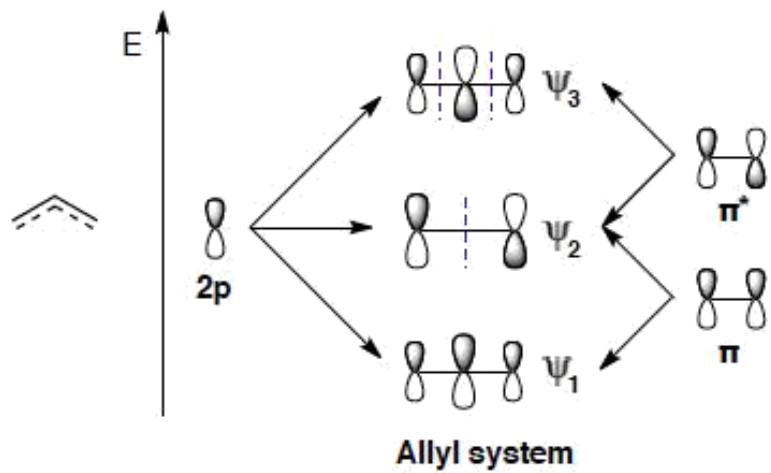

Following rules can be established:

1) The number of molecular orbitals has to be equal to the number of atomic orbital (in the case of ethene: two 2p orbitals form two molecular orbitals)
2) The molecular orbital with the lowest energy has no nodal plane
3) The relative energy of the molecular orbitals increases with the number of nodal planes
4) The molecular orbitals are occupied by two electrons, starting from the energetically lowest one

E

π⁎

π

Ethene

π₄

LUMO (π₃)

HOMO (π₂)

π₁

Butadiene

π⁎

π

Ethene

three nodal planes
anti-symmetrical

two nodal planes
symmetrical

nodal plane
anti-symmetrical

no nodal plane
symmetrical

five nodal planes anti-symmetrical	—	π_6
four nodal planes symmetrical	—	π_5
three nodal planes anti-symmetrical	—	LUMO (π_4)
two nodal planes symmetrical	⇅	HOMO (π_3)
nodal plane anti-symmetrical	⇅	π_2
no nodal plane symmetrical	⇅	π_1

Hexatriene

E

2p

ψ_3

ψ_2

ψ_1

π^*

π

Allyl system

— LUMO

$\uparrow\downarrow$ HOMO

Allyl cation

— LUMO

$\uparrow$ HOMO

$\uparrow\downarrow$

Allyl radical

— LUMO

$\uparrow\downarrow$ HOMO

$\uparrow\downarrow$

Allyl anion

Cycloadditions

Diels-Alder reaction

The Diels-Alder reaction is a [4+2]-cycloaddition between a conjugated diene and an alkene (dienophile) to form a cyclohexene system. As all pericyclic reactions the Diels-Alder reaction proceeds in a single step.
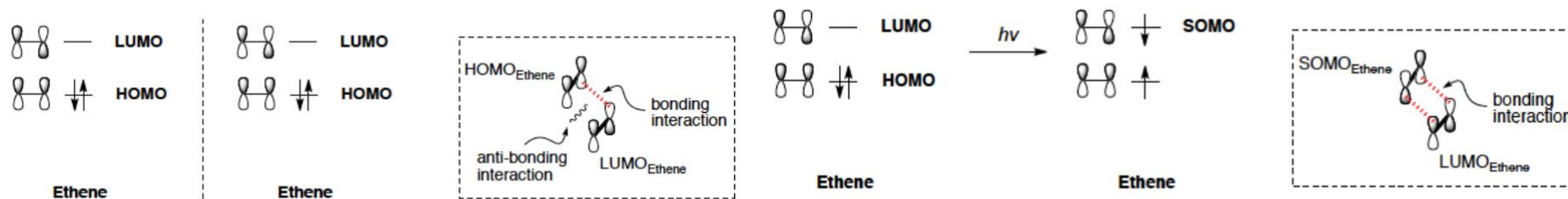

diene
butadiene

dienophile
ethene

heat

product
cyclohexene

Two new σ-bonds are formed at the same time during a Diels-Alder reaction. Therefore two filled p-orbitals and two empty p-orbitals have to be available. Expressed in FMOs this means the interaction between the HOMO of the diene and the LUMO of the dienophile (or vice versa). It is important to note that in cycloadditions the two molecules approach each other in a co-planar way (see below).
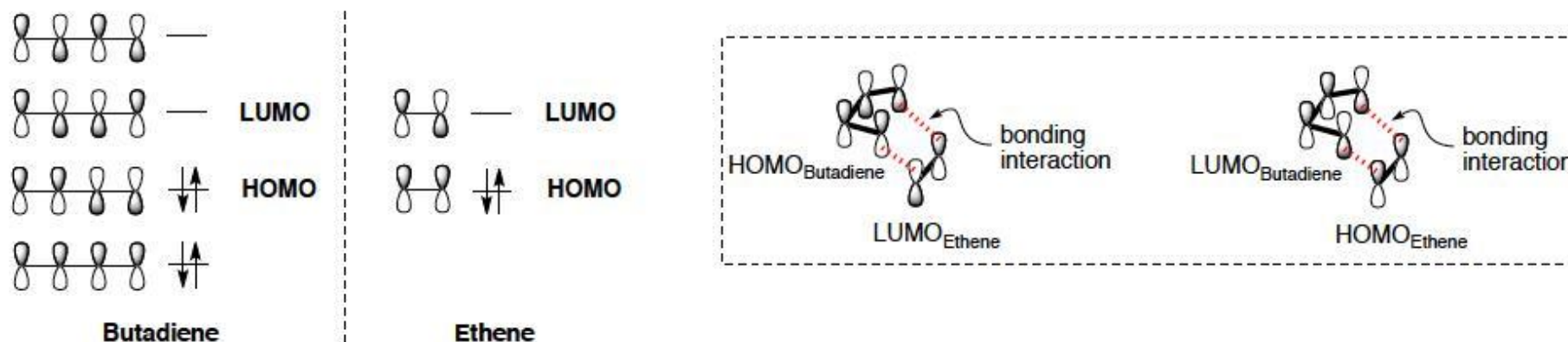
[2+2]-cycloadditions

Despite the Diels-Alder reaction the thermal reaction between two alkenes does not provide any cyclobutane product. However under photochemical conditions cyclobutane is formed.

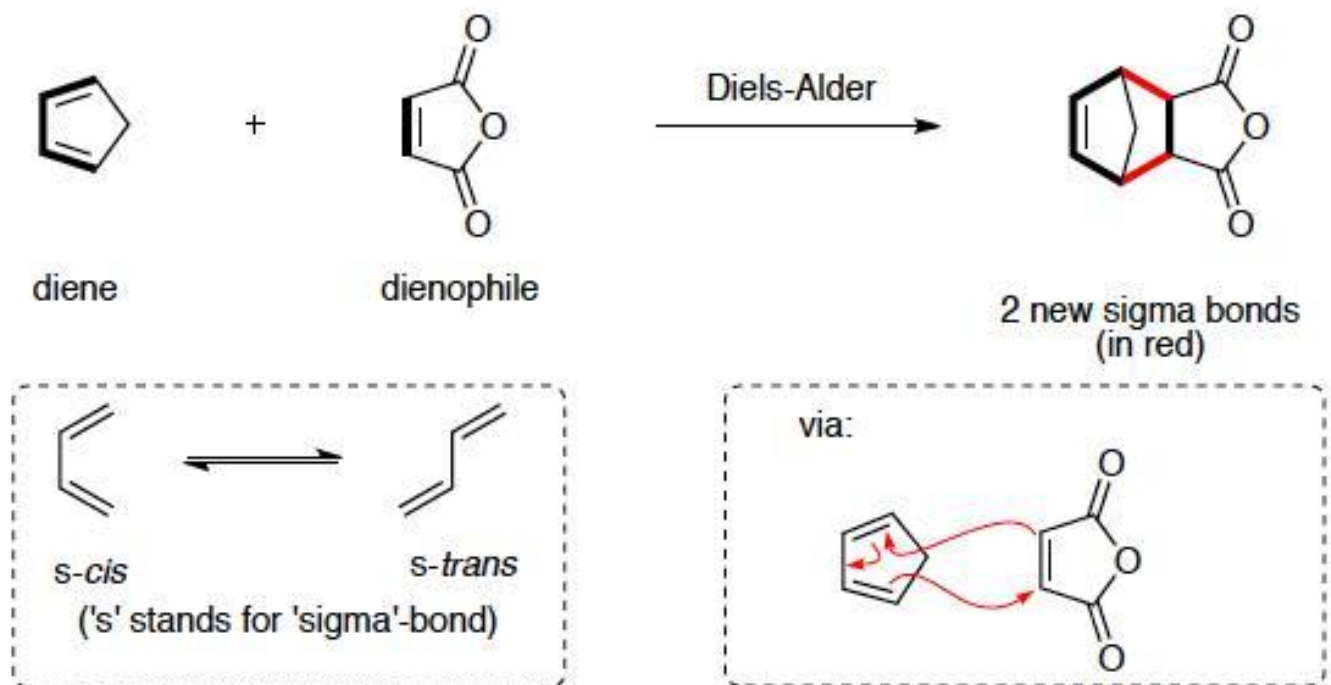**We say [2+2]-cycloadditions are thermally forbidden.**

Diels-Alder Reactions

The Diels-Alder (DA) reaction is a reaction between a diene and a dienophile (an olefin) forming sixmembered ring products.

-the diene has to be in the s-cis conformation to react

- 2 π-bonds disappear, and 2 new σ-bonds and 1 new π-bond is formed (the formation of the σ-bonds is the energetic driving force, making even Diels-Alder reactions forming strained ring systems possible)

- Since the reaction is exergonic, it can be concluded from the Hammond postulate that the transition states are early (i.e. substrate-like). Therefore, we can use the frontier orbitals (HOMO and LUMO) of the starting materials to describe the orbitals of the transition state of the Diels-Alder reaction (see section 3.1.1).

diene   dienophile

Diels-Alder

2 new sigma bonds
(in red)

s-*cis*   s-*trans*
('s' stands for 'sigma'-bond)

via:

Diels-Alder reactions with normal and inverse electron demand

When the frontier orbitals (HOMO and LUMO) involved in the DA are considered, we can use the HOMO of the diene and combine in with the LUMO of the dienophile to get bonding interactions leading to the products. (See Scheme on the left) However, the reverse case (LUMODiene with HOMODienophile) is also possible: This is called a DA reaction with inverse electron demand..
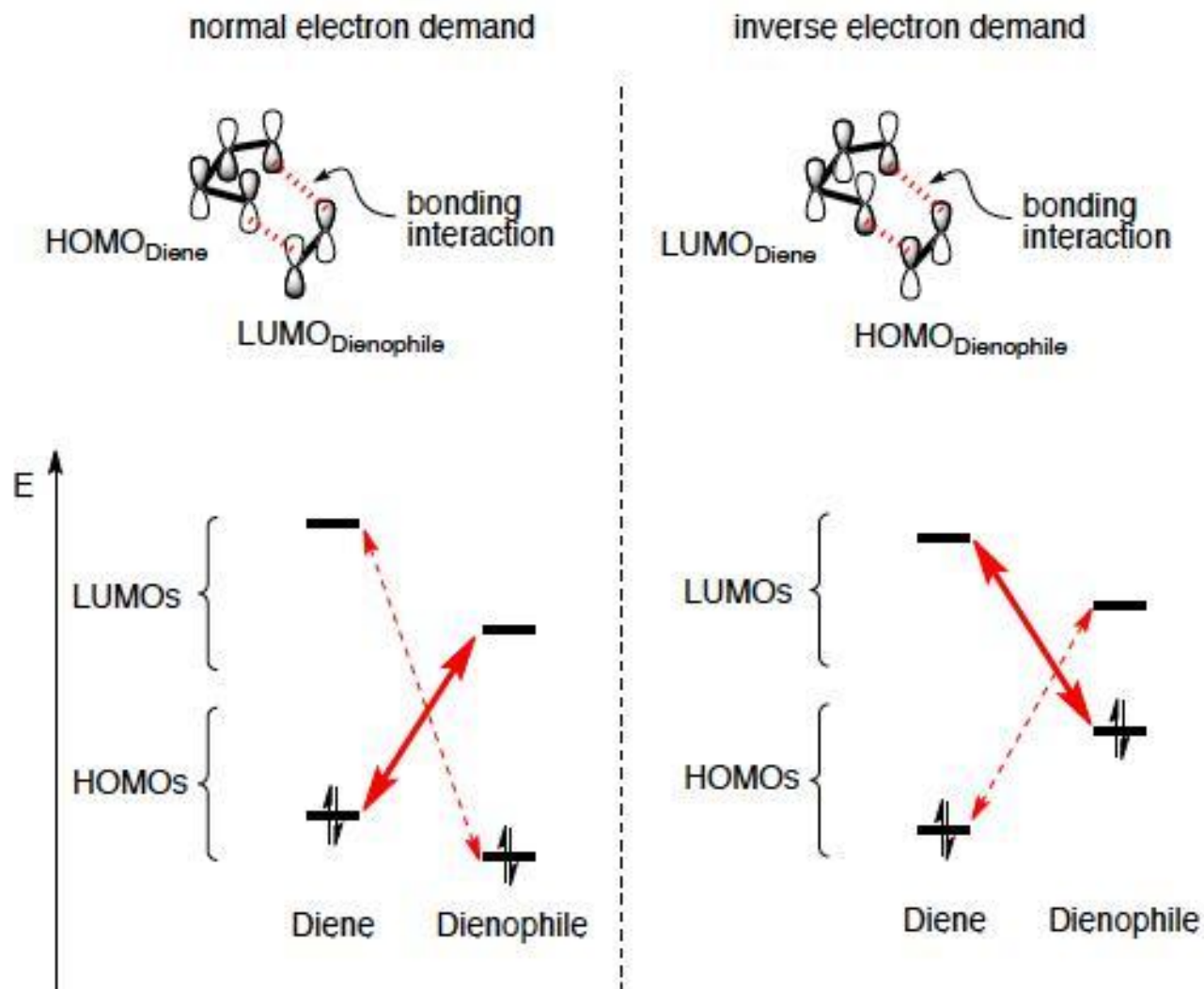
Selectivities

Consider the following case of a DA reaction between a donor-substituted diene and a acceptor-substituted dienophile. (DA reaction with normal electron demand)
Of the many (16) possible isomers, only this one (and it's enantiomer) is observed.
There are several selectivities involved in this reaction, which are typical for DA reactions…

Regioselectivity
Stereospecificity (E/Z, one-step vs two-step reactions)
Endo vs exo selectivity

Regioselectivity

We now consider the constitutional isomers of the possible products with respect to which carbon atoms of the diene and the dienophile are forming the new sigma bonds. This leads to possible "ortho, meta and para"-like products. One of the products ("para") is favored with respect to the minor product ("meta"). This effect is even more pronounced if a Lewis acid (for example AlCl3) is added to the reaction.

	para major product		meta minor product
	70	:	30
with 1 mol% AlCl₃:	95	:	5
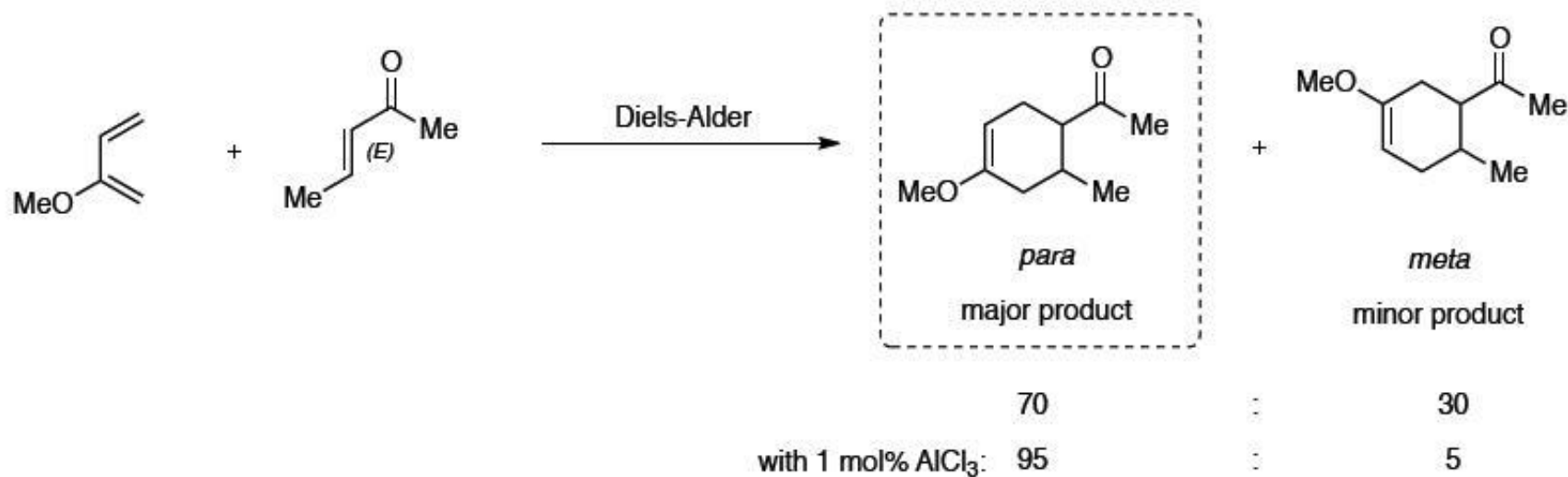
The substituents of the reaction partners not only have an effect on the energy of the frontier orbitals they also change the coefficients of the molecular orbitals at the different carbon atoms.

This is represented by an orbital with a different size (the larger the coefficient, the larger the lobes).
- in a DA reaction, the carbon atoms with the highest orbital coefficients (red numbers in scheme) will tend to react preferentially with each other (as this leads to a better orbital overlap and therefore a better stabilization).
- The larger the energy difference for the transition states leading to the different regioisomers is, the larger the regioselectivity for one of the products becomes.
- Additional activation, for example by coordination of a Lewis acid to the electron-withdrawing group of a dienophile, will result in an even larger orbital coefficient, and therefore in a higher regioselectivity of the reaction.

HOMO$_{Diene}$ LUMO$_{Dienophile}$

Diels-Alder

para

major product
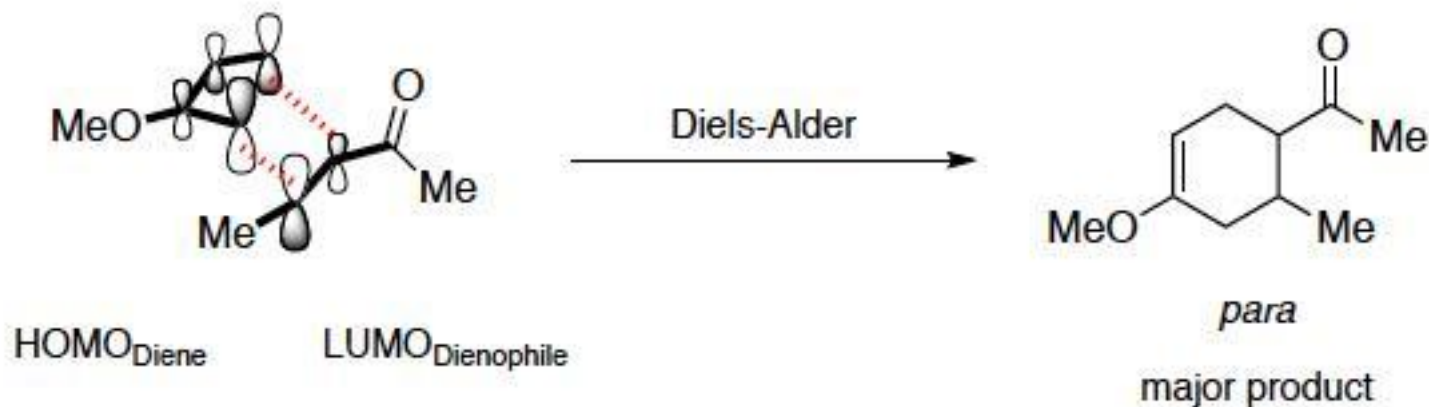
One way to predict the reactivity is to draw the reaction in a stepwise, ionic mechanism. (Keep in mind that this is not the real mechanism, but for the prediction of the regioisomers this is a helpful mnemonic).

Take the electron-rich substrate and react it with a generic electrophile and take the electron-poor reaction Partner and react it with a generic nucleophile. (Take a look at the possible resonance structures, as they clarify where to find the nucleophilic and electrophilic positions.)
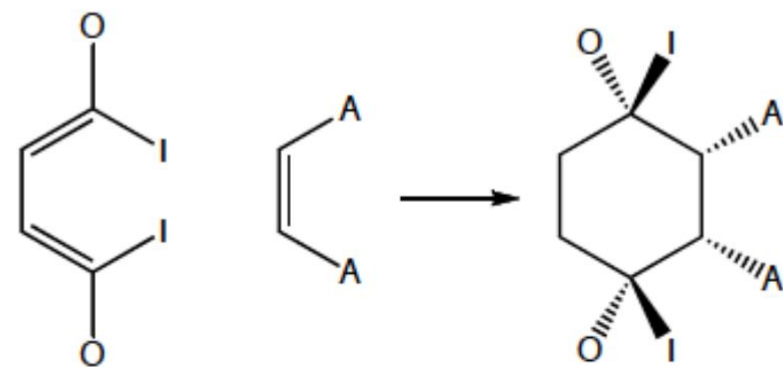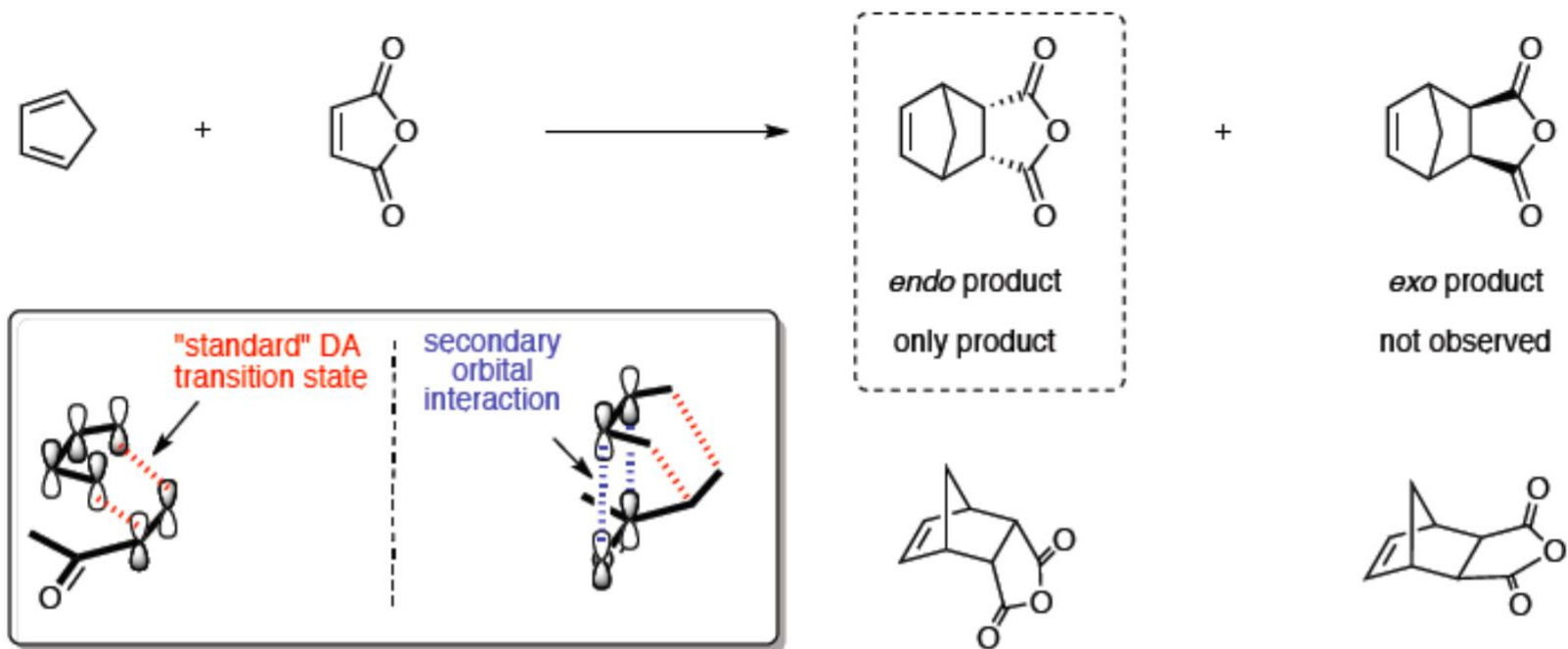
The combination of the two gives the expected DA reaction.

diene + electrophile

dienophile + nucleophile

both combined

possible resonance structures

para

major product
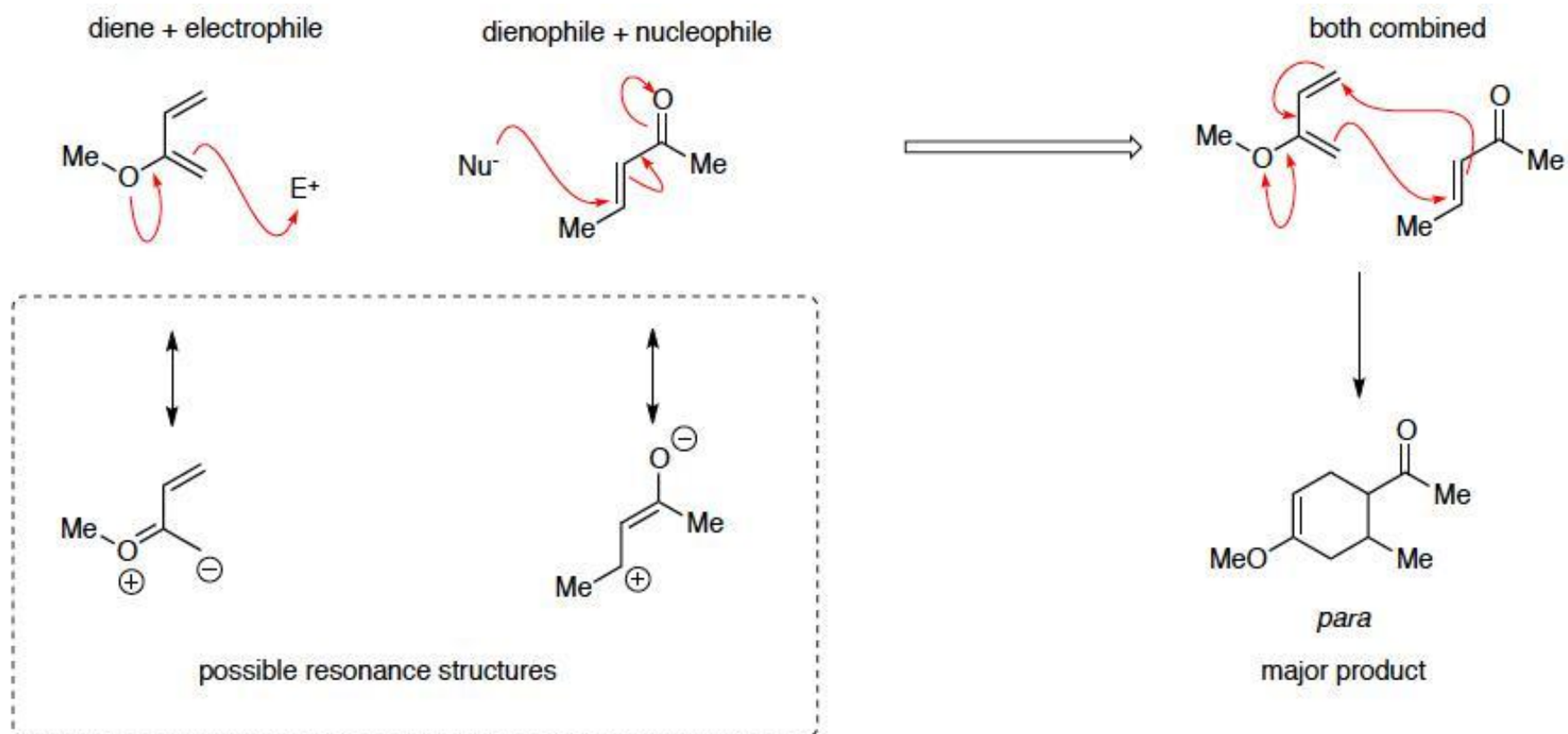
Stereospecificity (E/Z, one-step vs two-step reactions)
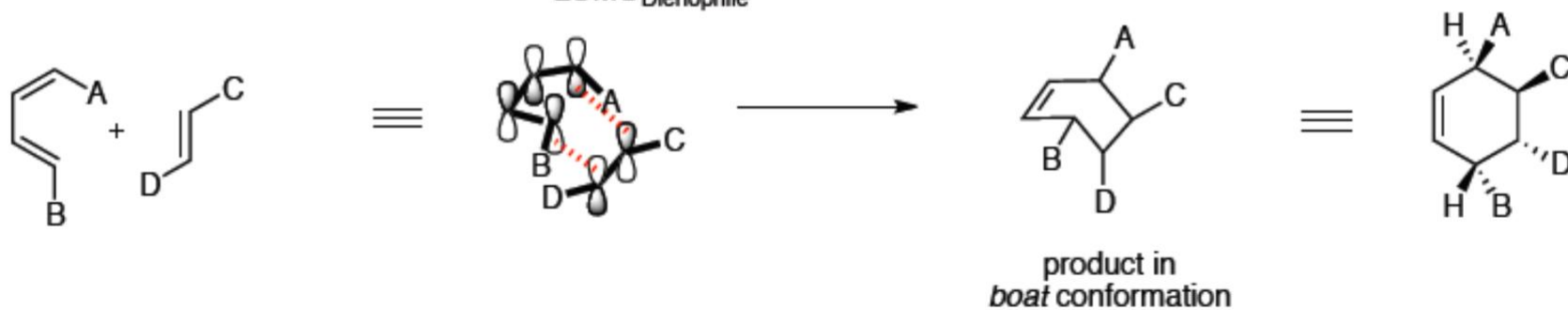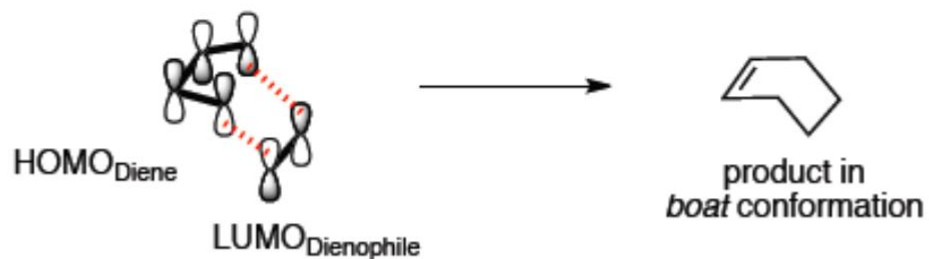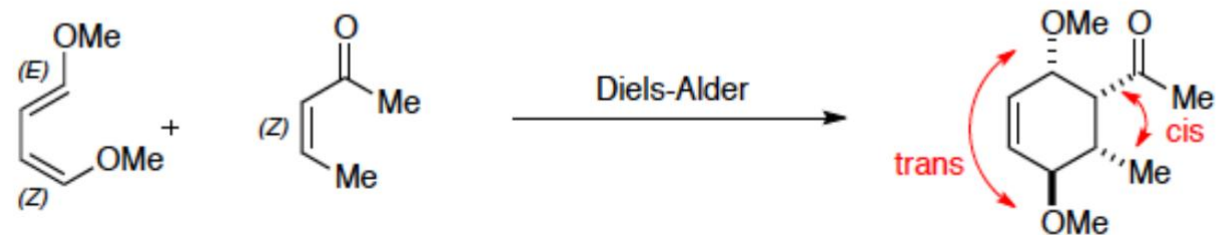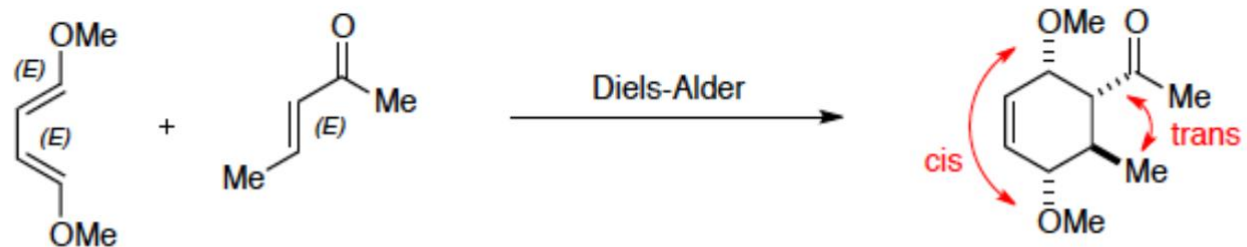
Endo vs exo selectivity- "Alder endo rule".

"standard" DA transition state | secondary orbital interaction

endo product
only product

exo product
not observed

Endo Rule

Hetero-Diels-Alder reactions

Along the same lines, both the diene and the dienophile can contain heteroatoms, furnishing heterocycles as products.
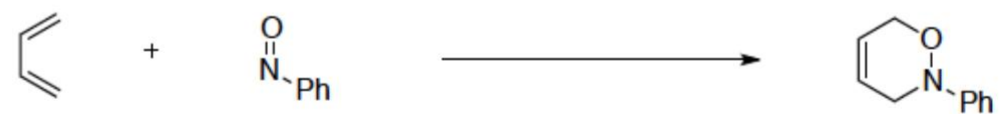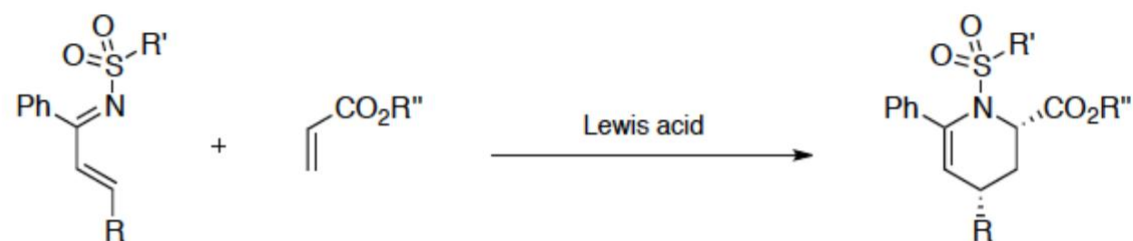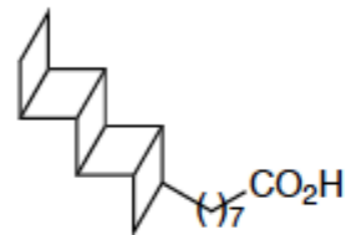

Danishefsky's diene

[2+2] Cycloadditions

photochemical [2+2]
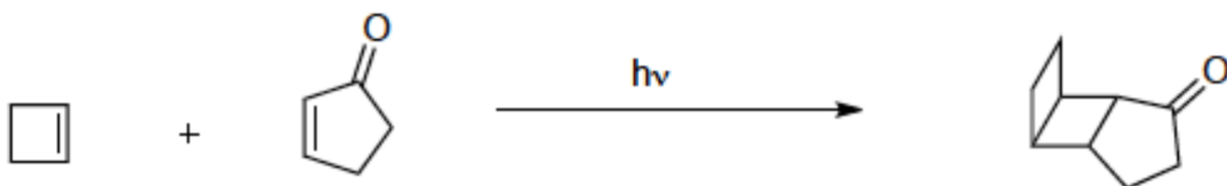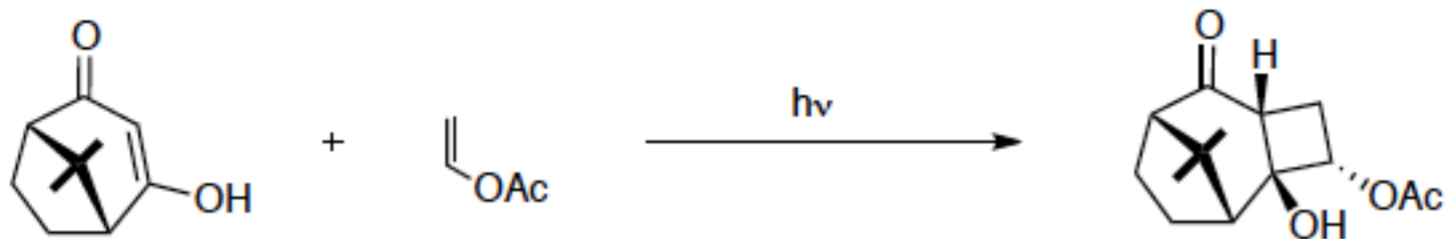
a "ladderane":
The main component of
the cell wall of an anaerobic
microbe.
Some of the cyclobutanes
are build up by [2+2] cycloaddtion

Thermal [2+2] cycloadditions

There are some examples of thermal [2+2] cycloadditions, leading to four-membered rings. (Which are in principle not allowed by the rules explained above) However, this reaction can take place under thermal conditions if the carbon taking part in the cycloaddition is also carrying a second double bond (as in an allene or an isocyanate, for example). Ketenes are a very prominent group of reagents for these transformations, however, only few are isolable, for example diphenylketene or dichloroketene. The smaller derivatives are so reactive that they spontaneously will undergo a thermal [2+2] cycloaddition with themselves.
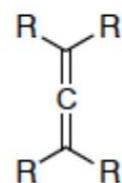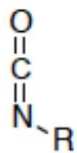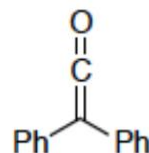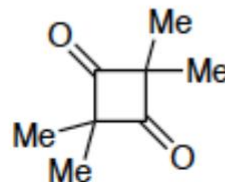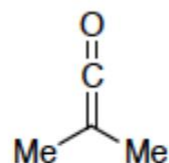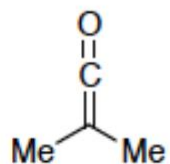

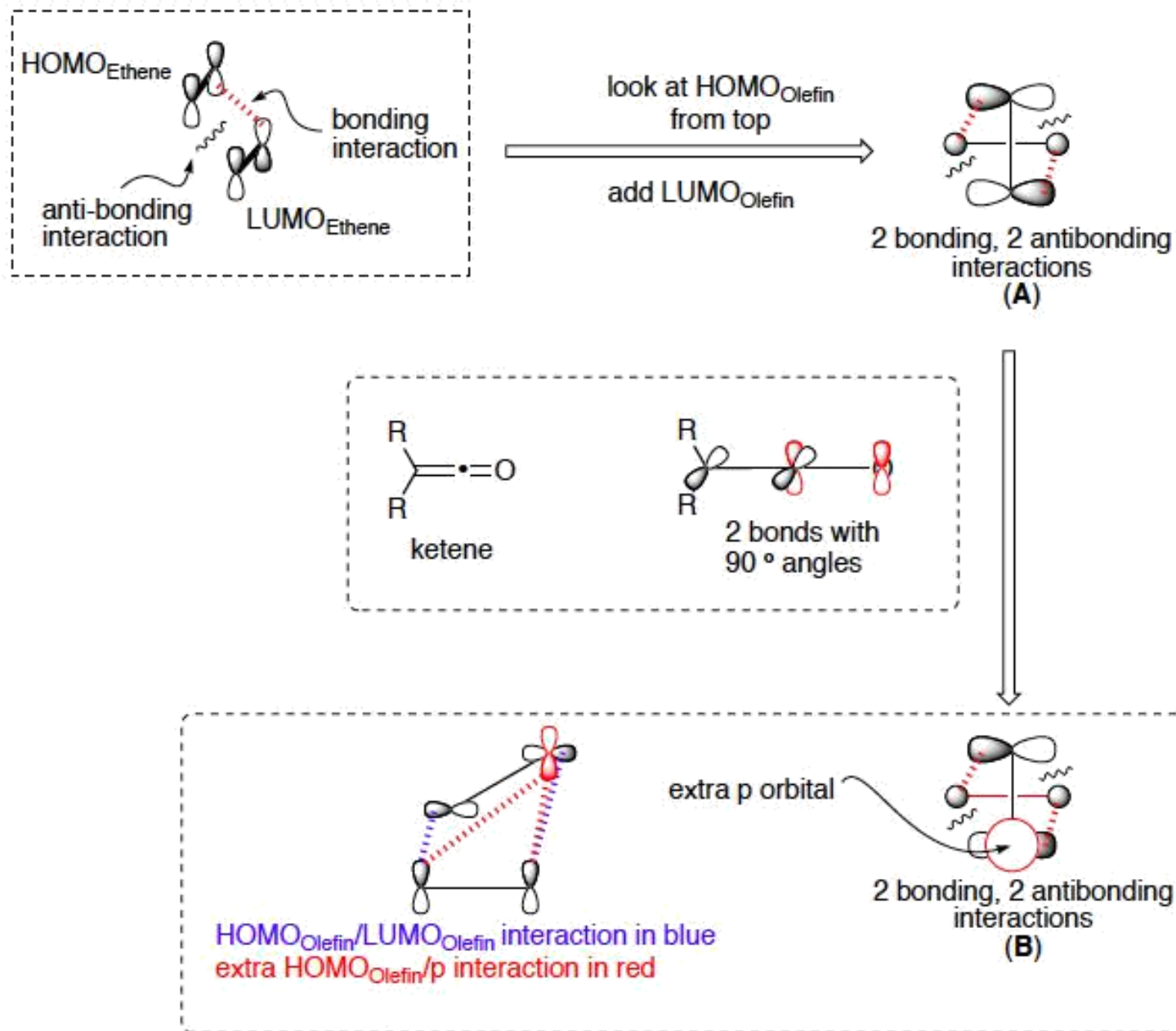allene   isocyanate   diphenylketene   dichloroketene
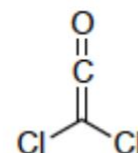
dimerization of dimethylketene

Dichloroketene can be made from dichloroacetyl chloride by elimination. If it is synthesized in the presence of cyclopentadiene, a thermal [2+2] cycloaddition takes place. It is interesting to note that in this case, no [4+2] Diels-Alder reaction with cyclopentadiene takes place. Therefore, the [2+2] cycloaddition must be much faster.
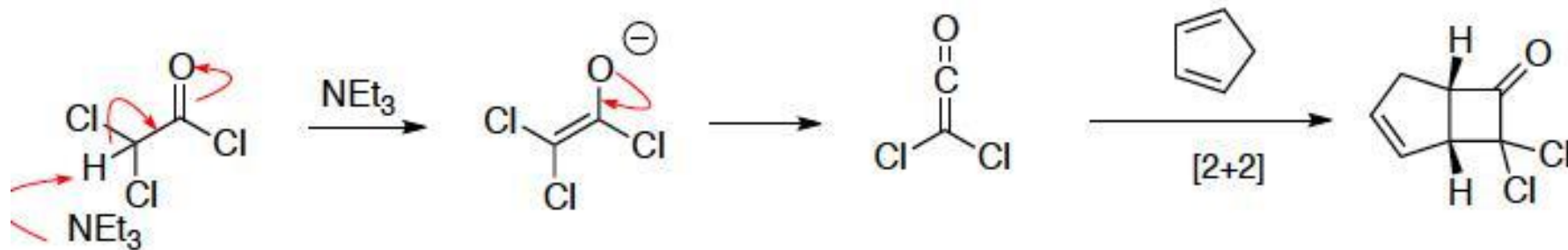

How can we explain that these special substrates do indeed undergo a thermal [2+2] cycloaddition?

HOMO$_{Ethene}$

bonding interaction

anti-bonding interaction

LUMO$_{Ethene}$

look at HOMO$_{Olefin}$ from top

add LUMO$_{Olefin}$

2 bonding, 2 antibonding interactions
(A)

ketene

2 bonds with 90 ° angles

extra p orbital

2 bonding, 2 antibonding interactions
(B)

HOMO$_{Olefin}$/LUMO$_{Olefin}$ interaction in blue
extra HOMO$_{Olefin}$/p interaction in red

additional bonding interaction has a stabilizing effect that
accounts for the thermal [2+2] cycloaddition being possible for these kind of substrates.

One practical application of this chemistry is the synthesis of β-lactams, which are prominent structural features of antibiotics.

β-lactam
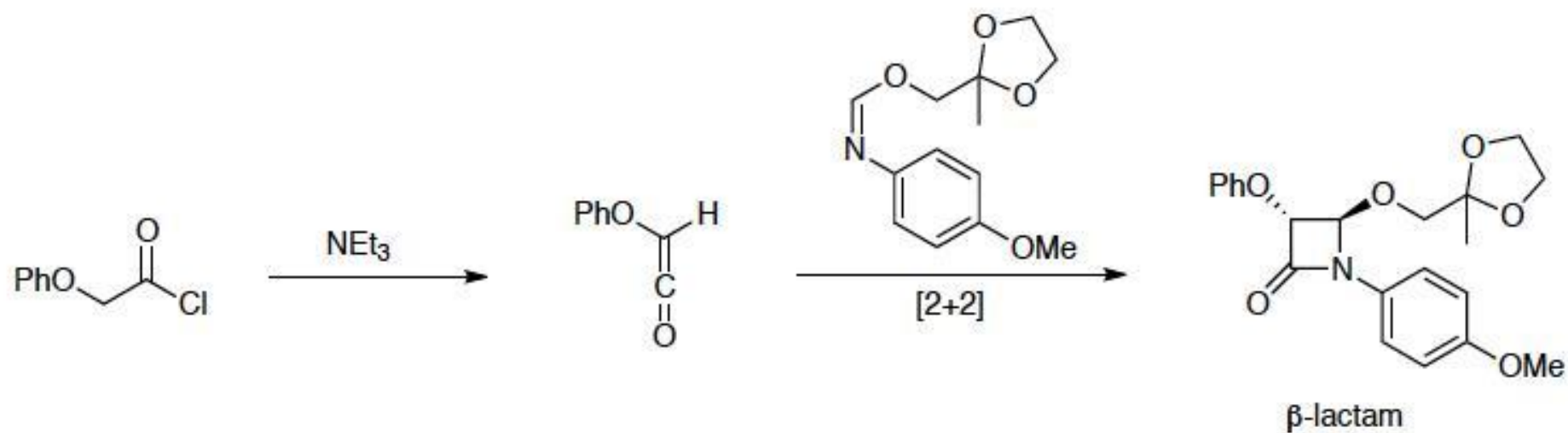
[3+2] dipolar Cycloadditions

In addition to making 6-membered rings with Diels-Alder reactions, and 4-membered ring systems by [2+2] cycloadditions, cycloadditions can also furnish 5-membered rings. This reaction is called the 1,3-dipolar cycloaddition. The reagents used for these reactions are called 1,3 dipoles, because of one of the possible resonance structures of these reagents carry a positive and a negative charge in a 1,3 relationship.
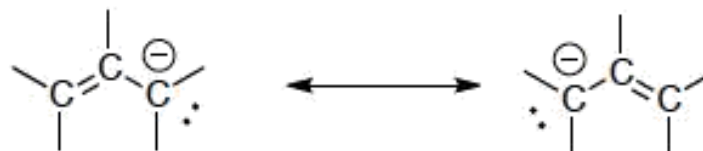
The 1,3-dipoles react with olefins to make the 5-membered rings, and in analogy to the DA reaction, the olefins are now called dipolarophiles.
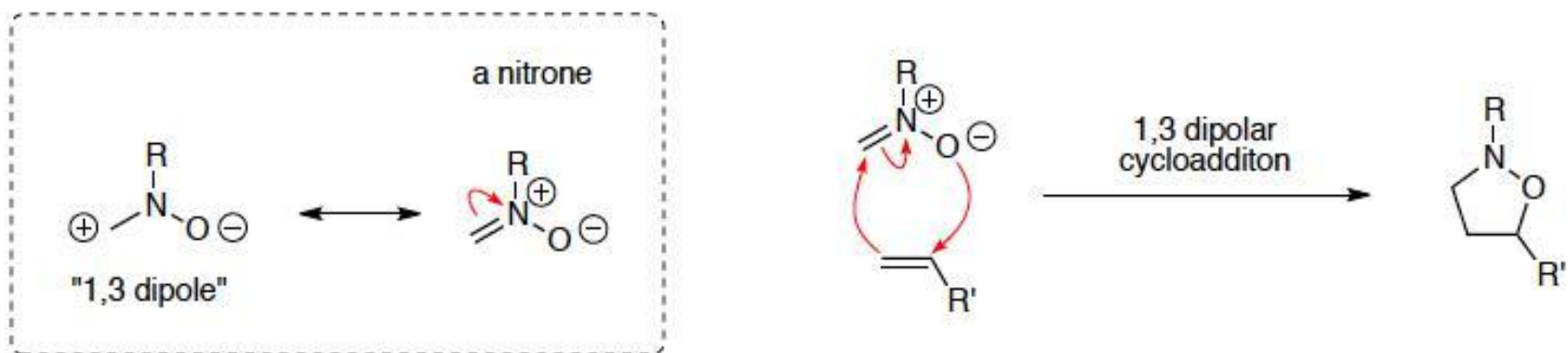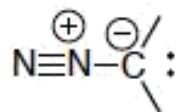

1,3-dipoles always have the general structure X-Het-Y (where X and Y are carbons or heteroatoms, Het stands for heteroatom). There are two structurally different classes, linear ones (of the "propargylic anion" type) and bent ones (of the "allyl anion type").
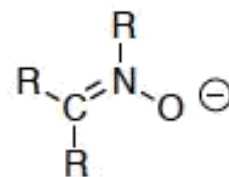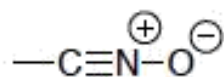
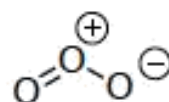propargylic anion (linear)

allyl anion (bent)

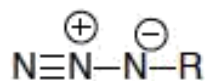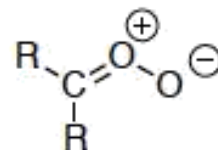N≡N–C : diazomethane

—C≡N–O nitrile oxide

N≡N–N–R azide

nitrones

ozone

carbonyl oxide

1,3 dipolar cycloadditon

HOMO_Dipole
LUMO_Olefin

LUMO_Dipole
HOMO_Olefin

E

LUMOs

HOMOs

Dipole   Olefin
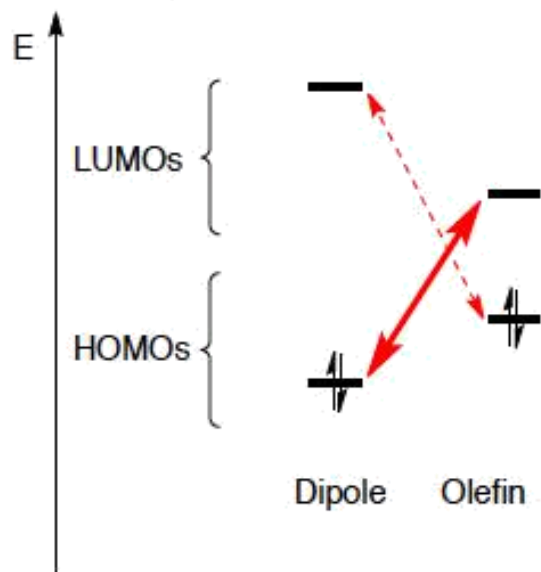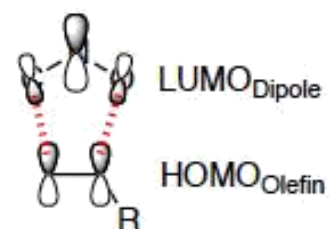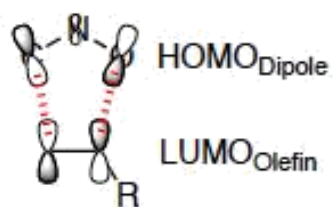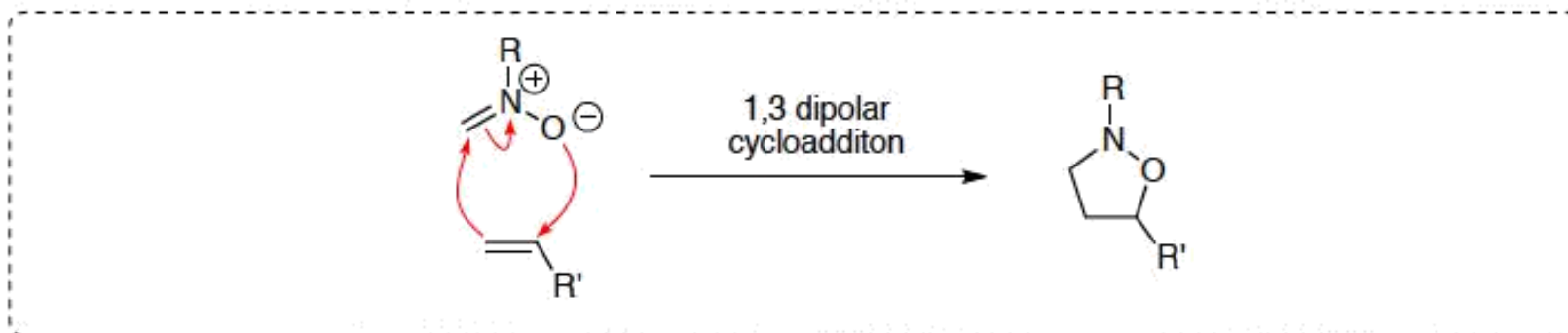
generally the case for acceptor-
substituted olefins

LUMOs

HOMOs

Dipole   Olefin
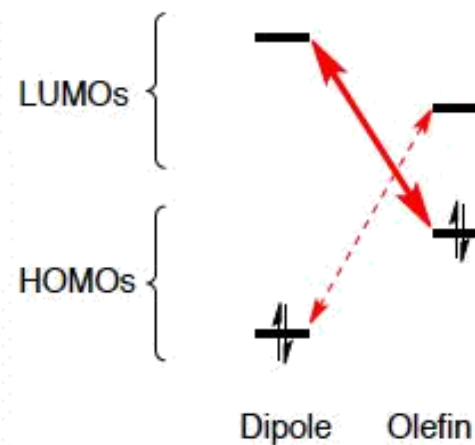
generally the case for donor-
substituted olefins

1,3-dipolar cycloaddition

primary ozonide

cycloreversion (C-C cleavage)

aldehyde

carbonyl oxide (a 1,3-dipole)

secondary ozonide

H_2O_2

SMe_2 or PPh_3

$NaBH_4$

$R\diagdown NO_2$ —NEt₃, PhNCO→ $R-\!\!\!\equiv\!\!\!\overset{\oplus}{N}-\overset{\ominus}{O}$ ←NaOH, NaOCl— $R\diagup N\diagup OH$

nitrile oxide

O_2N ... S —NEt₃, PhNCO→ (nitrile oxide intermediate) —1,3-dipolar cycloaddition→ (isoxazoline bicyclic)

LiAlH₄

biotin ← 1,3-aminoalcohol