B.Sc. Semester-VI
**GroupA / DSE-4**
Organic Synthesis

II. Pericyclic Reactions

4. Cycloaddition Reaction
(FMO Method)

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Cycloaddition Reactions

- **Two unsaturated molecules add to one another, yielding a cyclic product**
- **The Diels–Alder cycloaddition reaction is a pericyclic process that takes place between a diene (four π electrons) and a dienophile (two π electrons) to yield a cyclohexene product Stereospecific with respect to substituents**
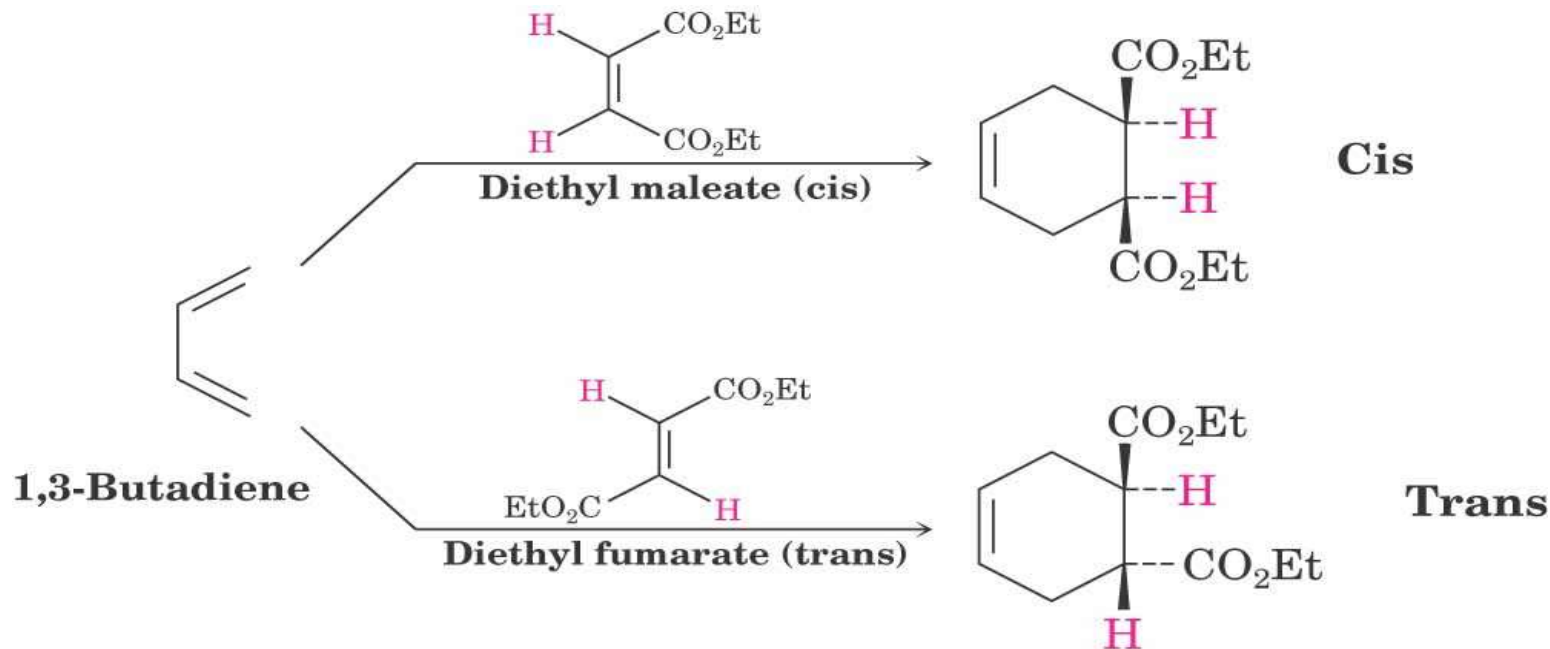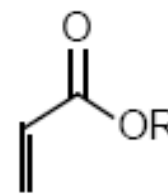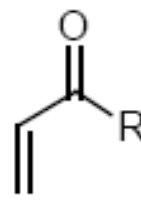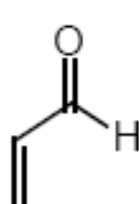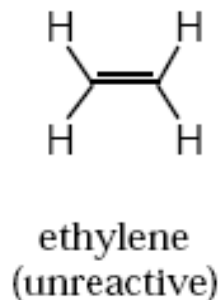
Diels-Alder Reactions

Reaction between a conjugated diene and an alkene (dienophile) to give a cyclohexene

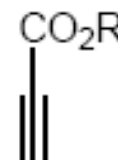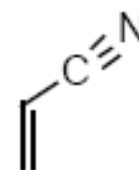Diene   Dienophile   cyclohexene
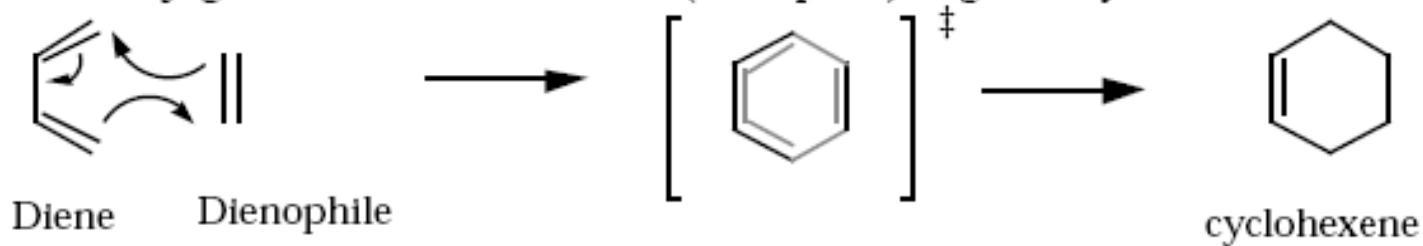
The Diels-Alder reaction is favored by electron withdrawing groups on the dienophile and electron donating groups on the diene.

Good Dienophiles:

ethylene
(unreactive)   conjugated carbonyls (aldehydes, ketones and esters)
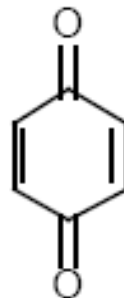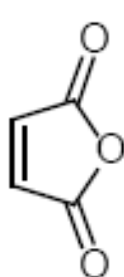
Mechanism

Mechanism: Pericyclic Reaction- proceeds in a single step via an "aromatic" transition state.

Diels-Alder
Transition State

Benzene
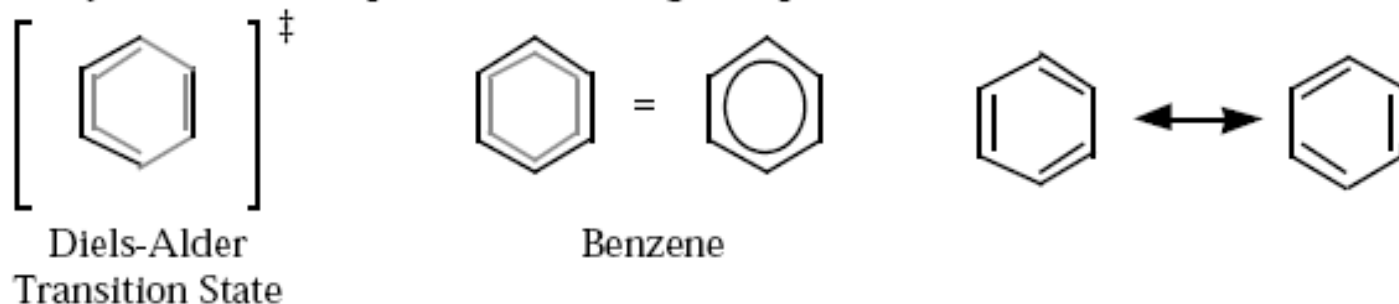
The diene must adopt an s-cis conformation to be reactive:

s-trans
(unreactive conformation)

s-cis
(reactive conformation)
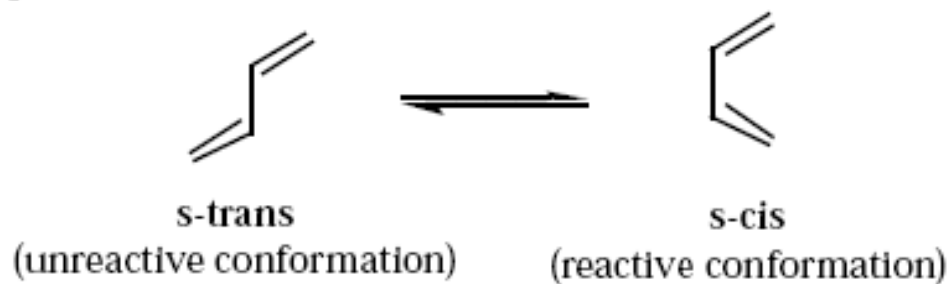
Endo vs Exo

Endo vs. Exo Transition State: Generally, the endo transition state is favored.
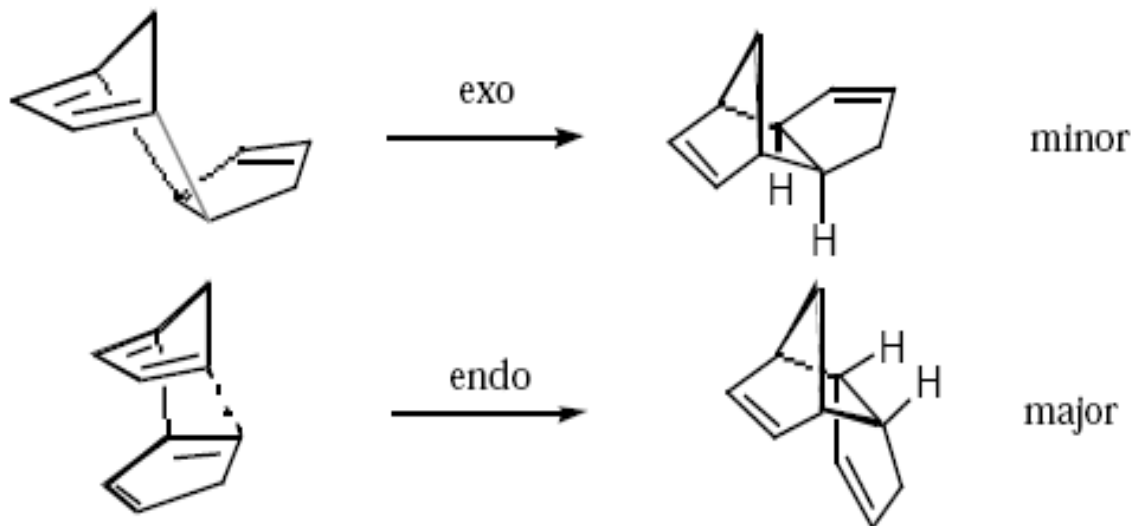
Stereochemistry: In pericyclic reactions, the stereochemistry of the reactants is preserved in the product. Recall the cylcopropanation of alkenes by carbenes which is also a pericyclic reaction.

6. Endo/Exo. Unsymmetrical dienophiles can react in two possible orientations to give two possible products, endo and exo. Endo: Unsaturated substituents on the dienophile are oriented toward the pi system of the diene. In the product, these substituents are <u>cis</u> to the "<u>out</u>" substituents of the diene. Endo is usually favored due to better van der Waals interactions between the substituents on the dienophile and the pi system of the diene. The Endo (or Alder) Rule is that this transition state is more stable, lower in energy, so this reaction proceeds faster. Exo: Substituents on dienophile are oriented away from diene pi system. In the product, these substituents are <u>trans</u> to the "<u>out</u>" substituents of the diene. The exo transition state, and therefore product, is not favored unless the endo transition state is sterically very congested or bad in intramolecular situations due to angle strain, or if the reaction is done reversibly (the exo product is usually thermodynamically more stable due to sterics).

Dienophiles

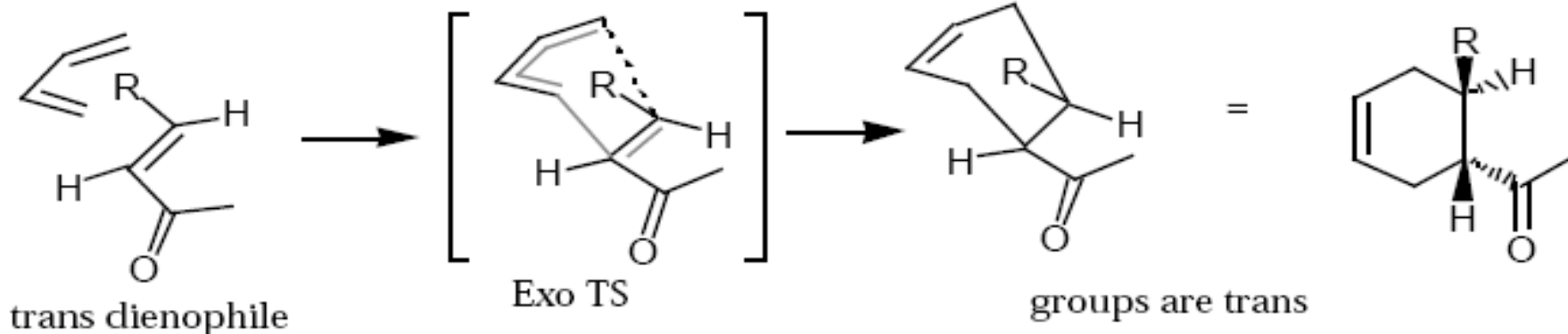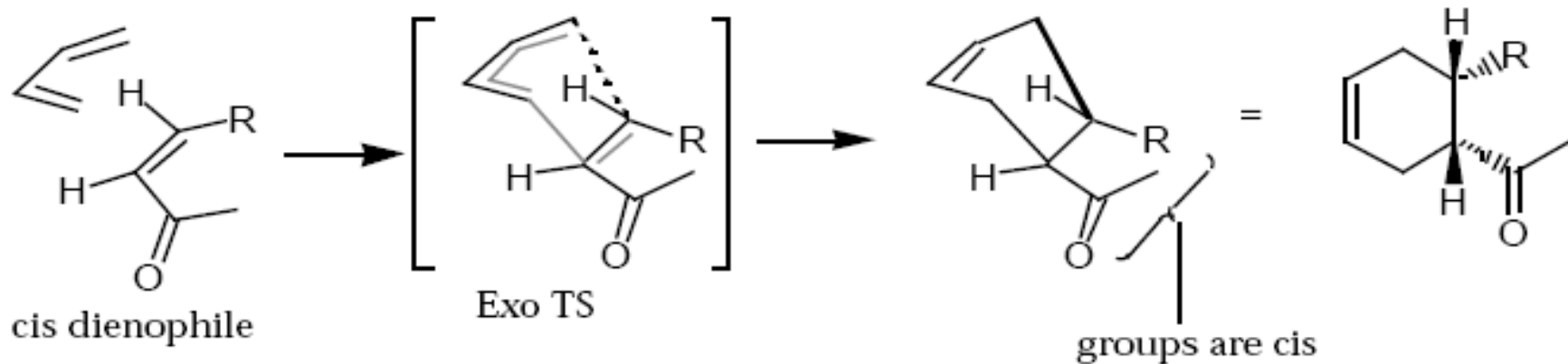Dienophile: Groups that are cis on the dienophile will be cis in the product; groups that are trans on the dienophile will be trans in the product.

Endo TS:
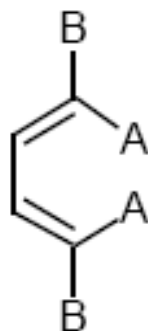

cis dienophile   Endo TS   H's are cis

trans dienophile   Endo TS   H's are trans
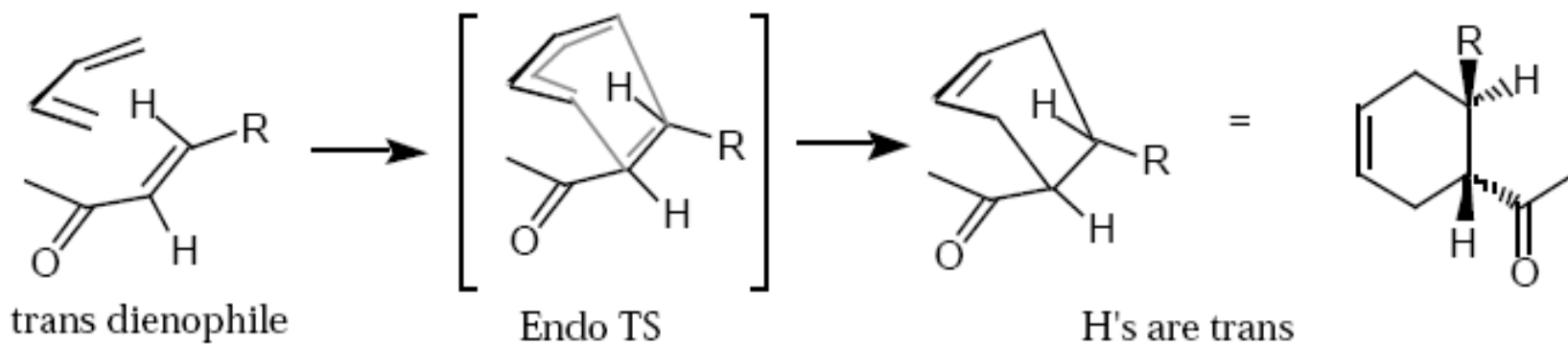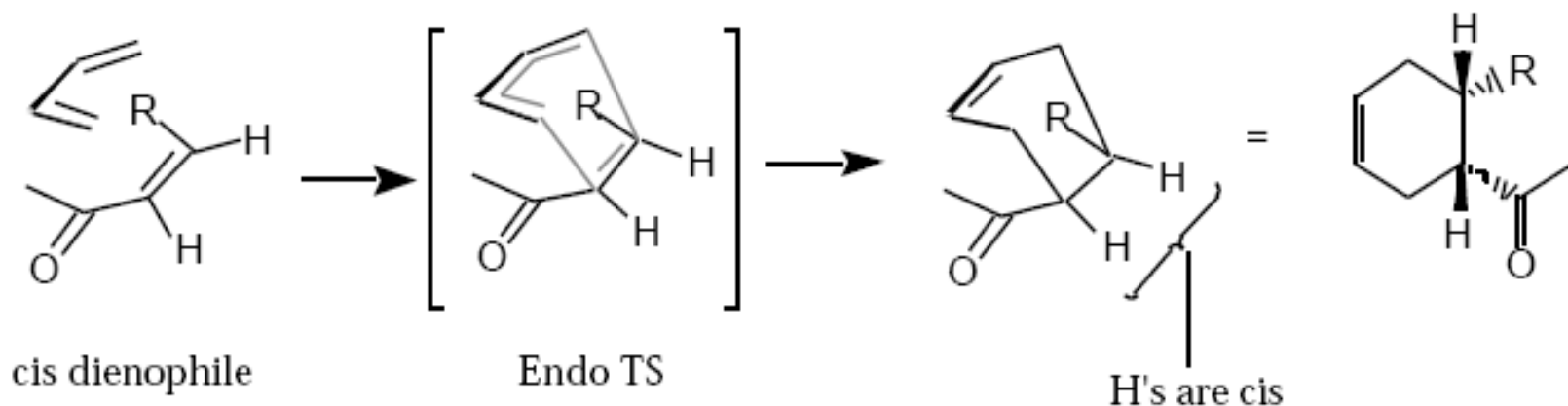
Exo and Endo Transition States

Exo TS:

cis dienophile → Exo TS → groups are cis

trans dienophile → Exo TS → groups are trans

Diene:

In the s-cis conformation:
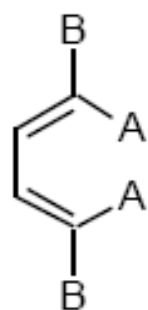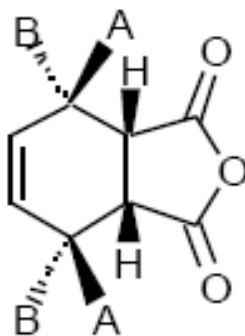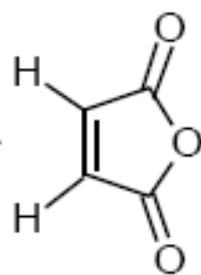
A= inner rim of diene
B= outer rim of diene

Groups on the inner rim of the diene will be cis in the product and groups on the outer rim of the diene will be cis in the product:
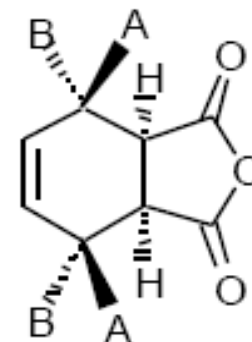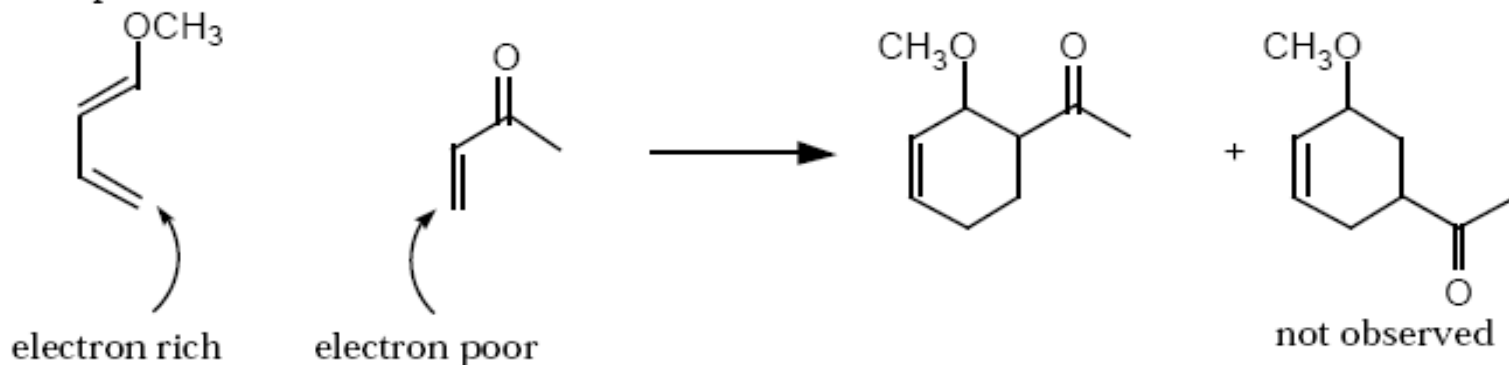

Endo TS   Exo TS

In the product, the groups of the dienophile that are endo in the transition state will be cis to the groups on the outer rim of the diene (in the s-cis conformation).

Regiochemistry of Diels-Alder Reaction

<u>Regiochemistry</u>: The regiochemistry of the Diels-Alder reaction is determined by the position of the electron donating groups of the diene, and is fully understood by molecular orbital theory. It may be easier to explain by simply looking at the resonance structures of the diene and dienophile. Typical electron donating groups on the diene are ethers, amines and sulfide; all have a non-bonding pair of electrons to donate.
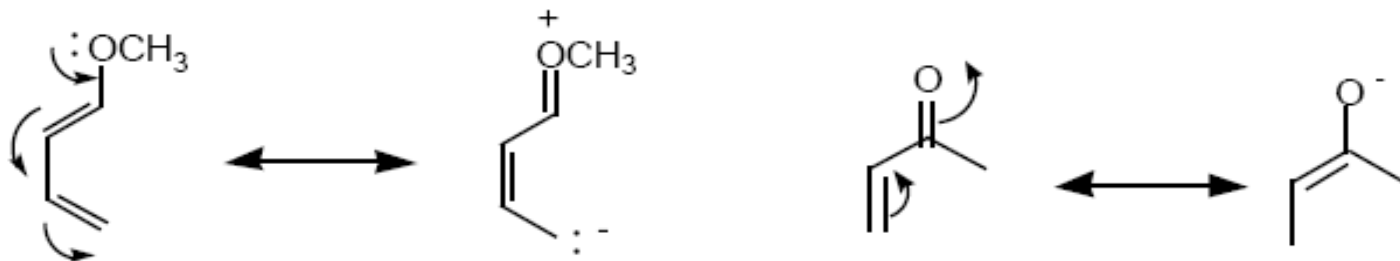
The regiochemistry of this Diels-Alder reaction is explained by looking at the dipolar resonance structures. The electron-rich carbon of the diene forms a bond with the electron-poor carbon of the dienophile.

electron rich   electron poor   not observed

When the electron donating groups is at the 2-position of the diene:

electron rich   electron poor   not observed

1.

OAc — H / H — OAc diene   + H_3CO_2C—CH=CH—CO_2CH_3 (H, H) $\xrightarrow[\text{benzene } 80°\text{ C}]{[4+2]}$ OAc / CO_2CH_3 / CO_2CH_3 / OAc product

2.

benzoquinone (O, O)   +   cyclopentadiene $\xrightarrow[40°\text{ C}]{[4+2]}$ bicyclic adduct (H, H, O, O) $\xrightarrow[\text{[2+2]}]{h\nu}$ cage product (H, H, O, O)
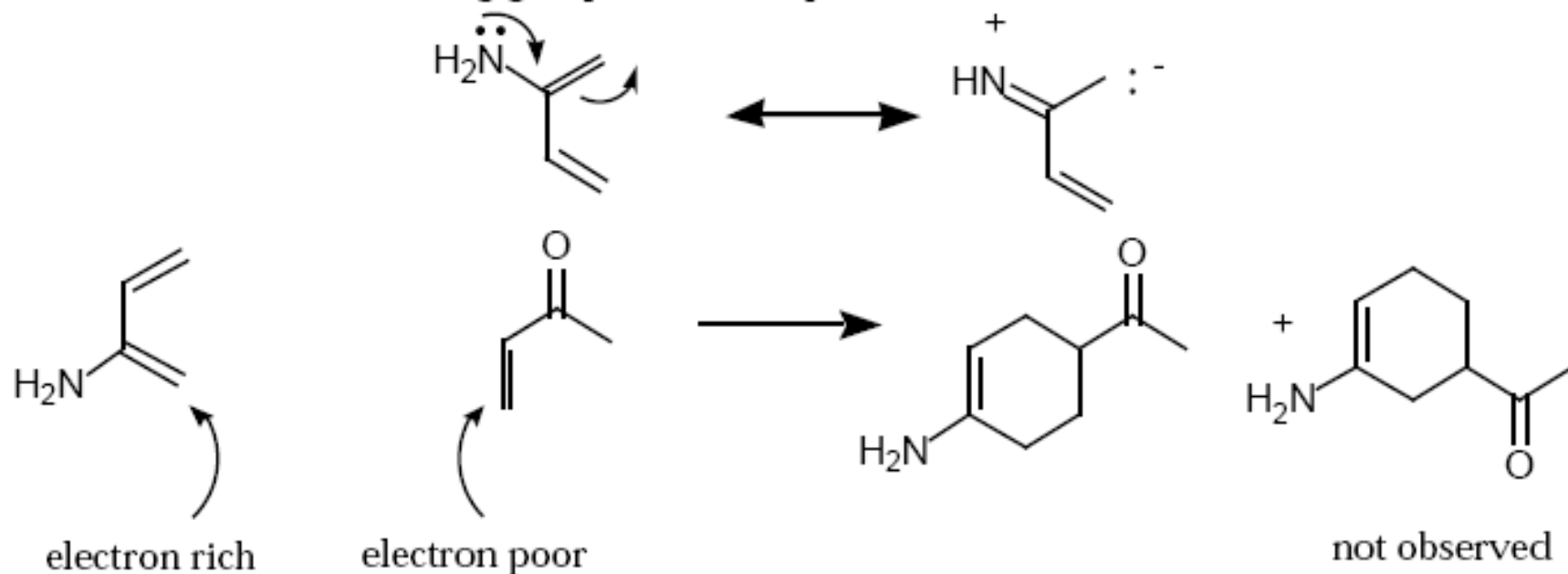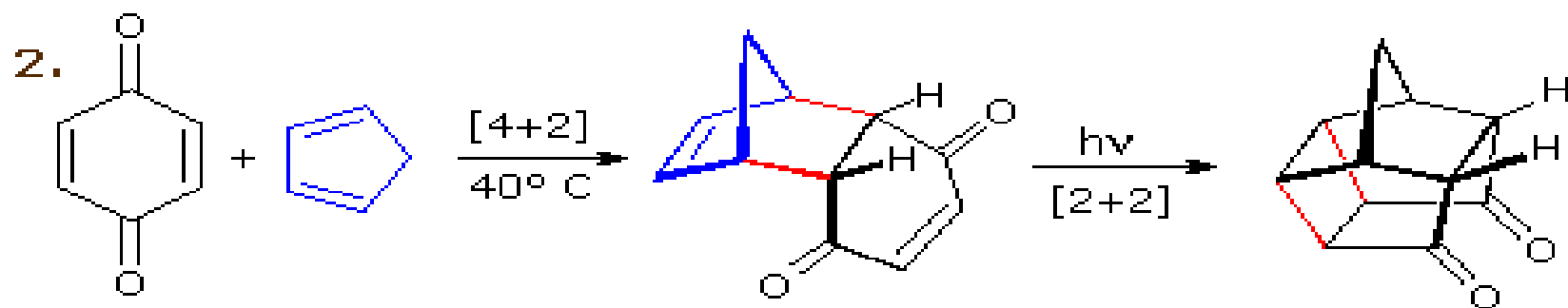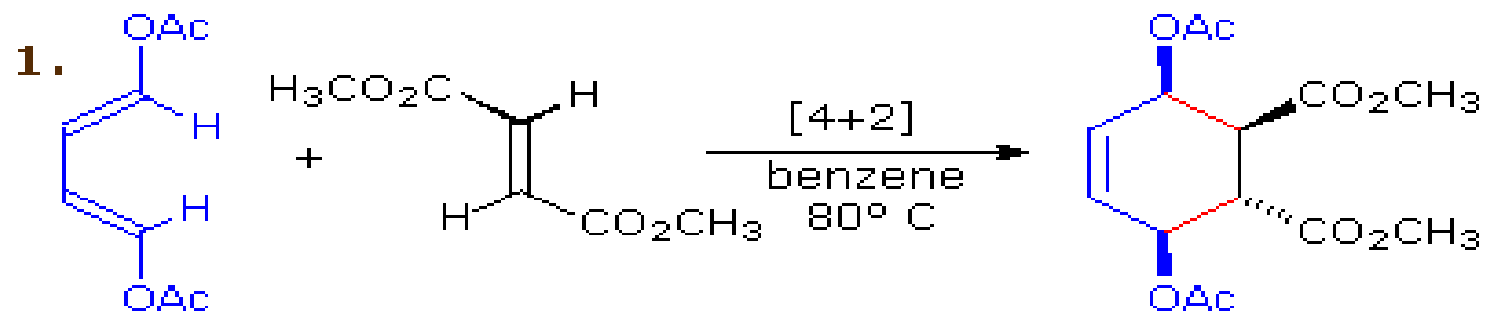
Rules for Cylcoadditions - Suprafacial Cycloadditions

- **The terminal π lobes of the two reactants must have the correct symmetry for bonding to occur**

- **Suprafacial cycloadditions take place when a bonding interaction occurs between lobes on the same face of one reactant and lobes on the same face of the other reactant**
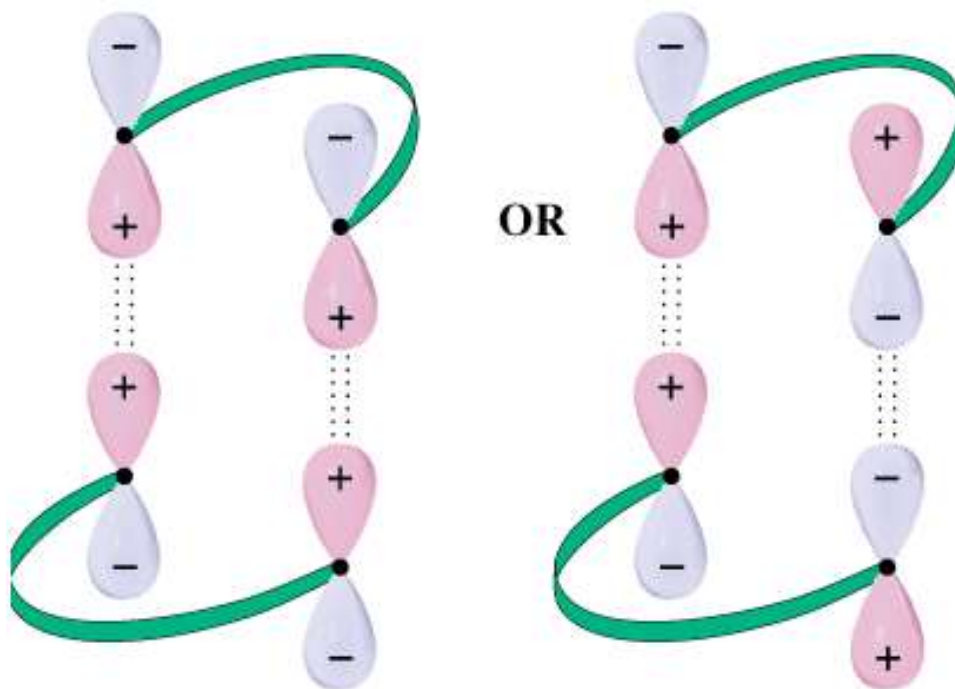
Rules for Cylcoadditions - Antarafacial Cycloadditions

- **These take place when a bonding interaction occurs between lobes on the same face of one reactant and lobes on opposite faces of the other reactant (not possible unless a large ring is formed)**
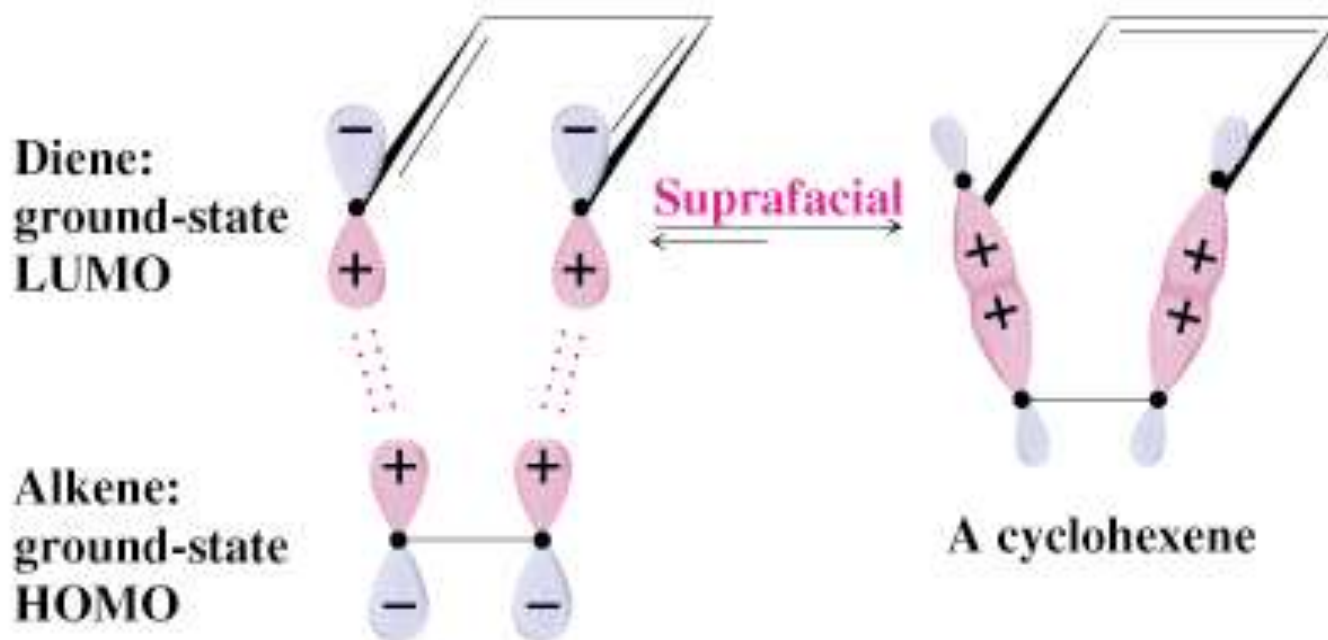

Lobes on opposite side of this π system

Lobes on same side of this π system
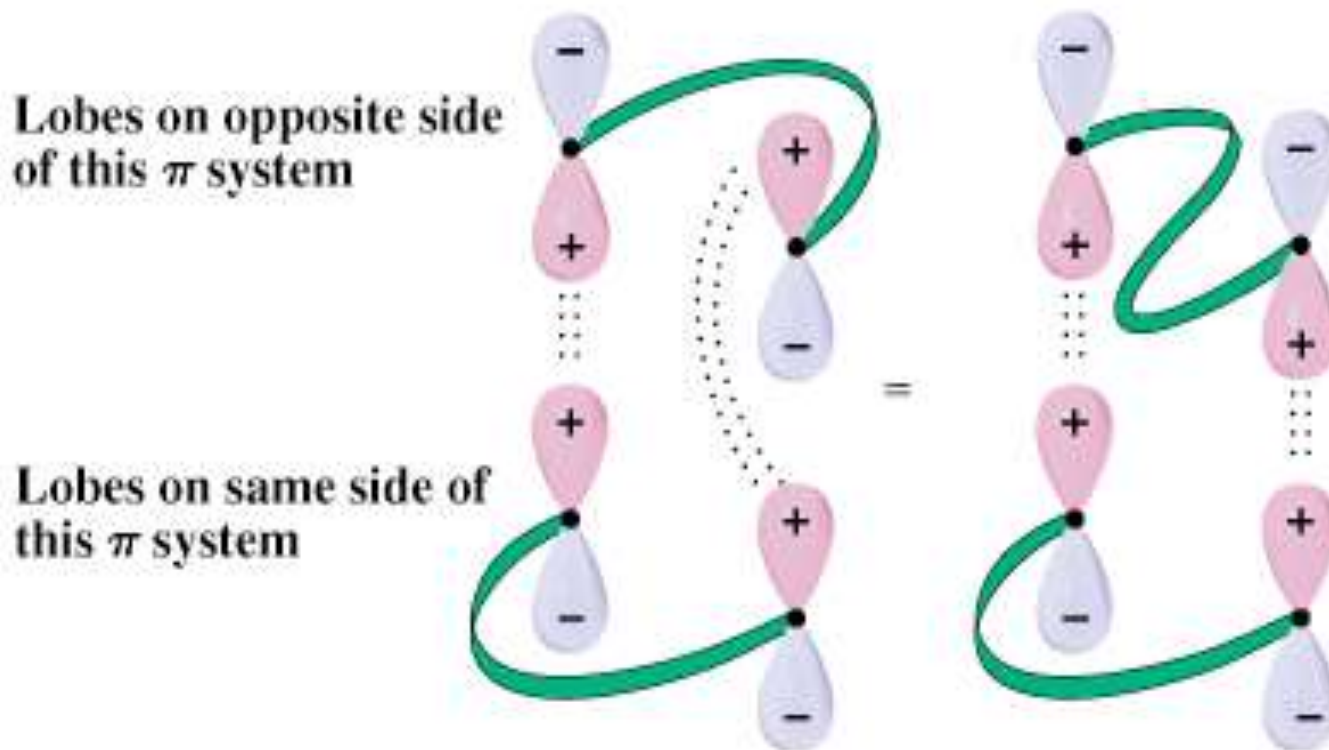
Stereochemistry of Cycloadditions

- **HOMO of one reactant combines with LUMO of other**
- **Possible in thermal [4 +2] cycloaddition**

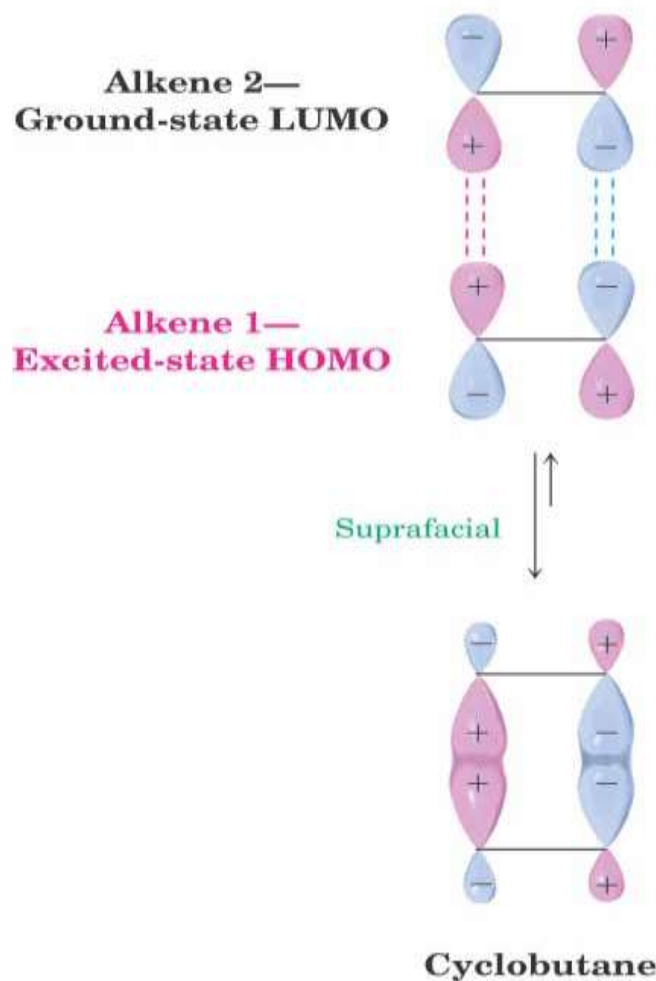# [2+2] Cylcoadditions

- **Only the excited-state HOMO of onealkene and the LUMO can combine by a suprafacial pathway in the combination of two alkenes**

(a) Thermal reaction

Alkene 2—
Ground-state LUMO

Alkene 1—
Ground-state HOMO

Antarafacial

Strained,
no reaction
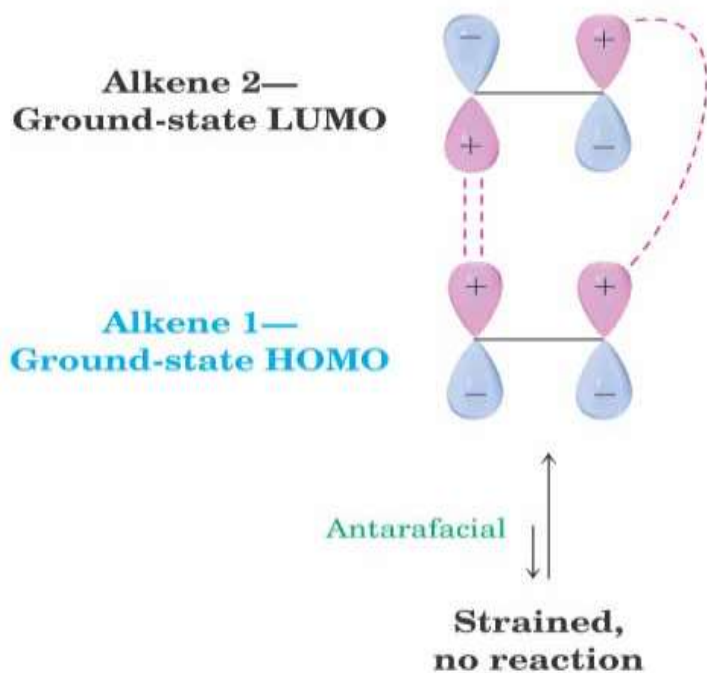
(b) Photochemical reaction

Alkene 2—
Ground-state LUMO

Alkene 1—
Excited-state HOMO

Suprafacial

Cyclobutane

Formation of Four-Membered Rings

- **Photochemical [2 + 2] cycloaddition reaction occurs smoothly**

2-Cyclohexenone   +   2-Methylpropene $\xrightarrow{h\nu}$ 40%
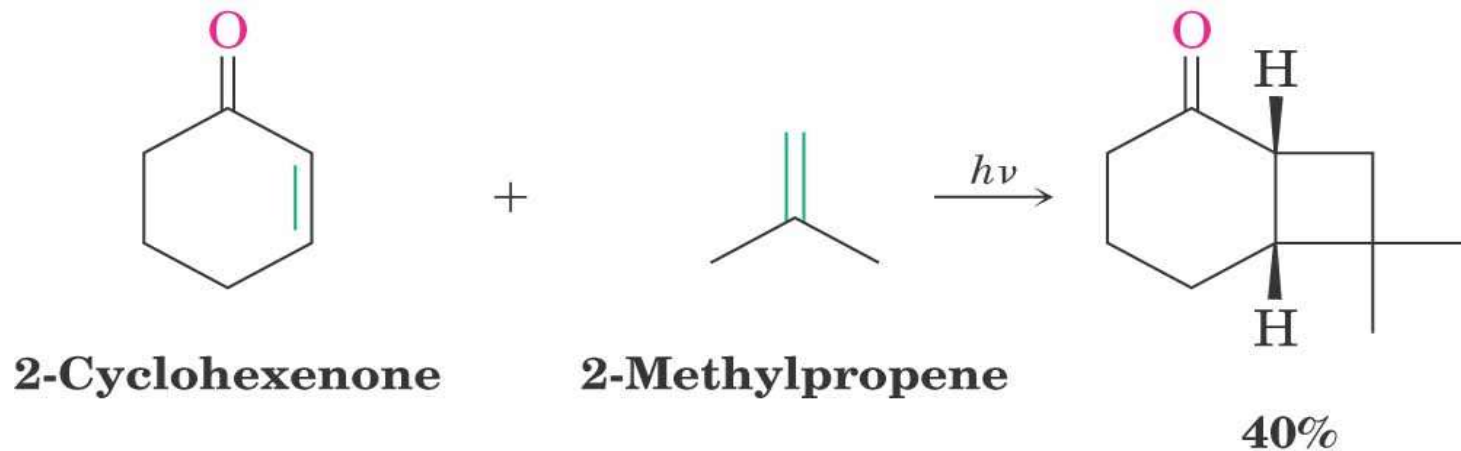
Orientation of Products
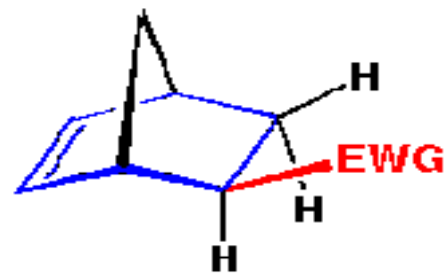

convex or **exo** face
of six membered ring

concave or **endo** face
of six membered ring

substituents placed on the six-membered ring thus occupy either an *endo* or an *exo* orientation:

endo adduct

exo adduct

Endo Rule:

HOMO-LUMO interaction also explains bond formation between ends of diene and end of double bond (same sign of oribitals, largest orbitals interact, primary orbital interaction). Also explains endo stereo-chemistry (secondary orbital interaction favors carbonyl being on the same side as the double bond in the product).

Diene

Dienophile

HOMO

LUMO

-------- primary orbital interaction

⟷ secondary orbital interaction (origin of endo stereochemistry)
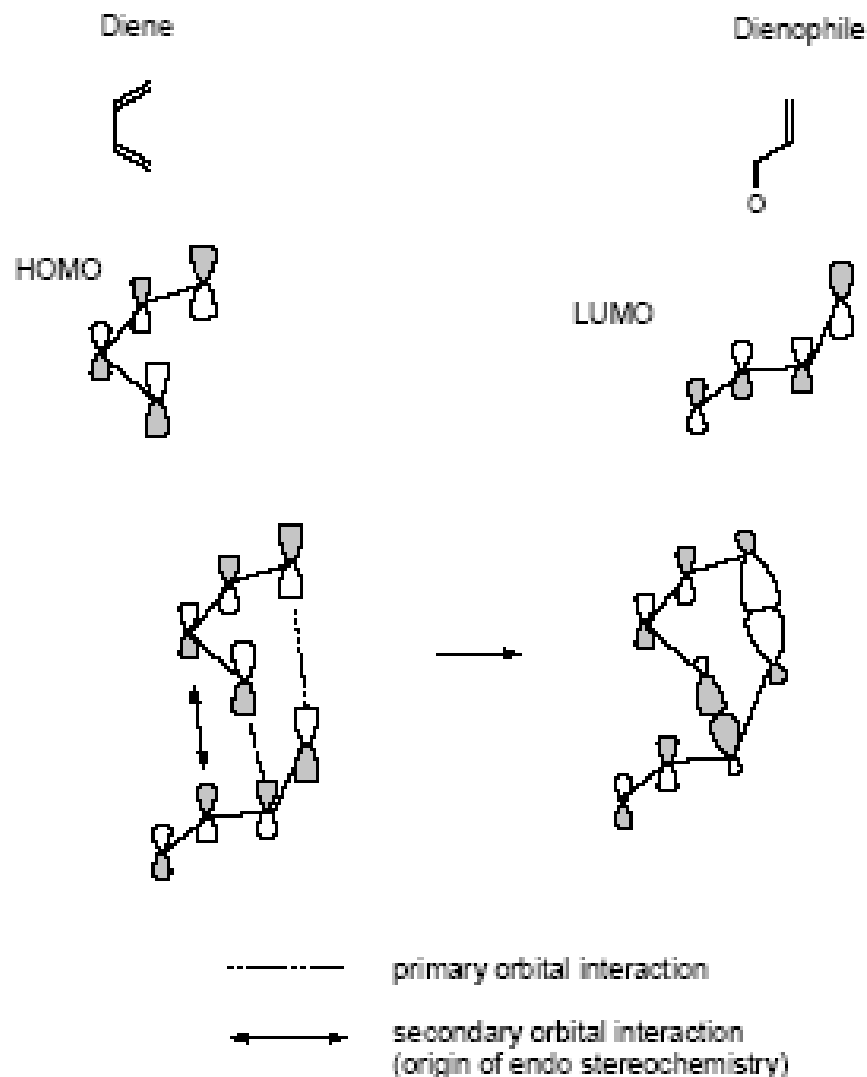
Orientation (Regiochemistry) Orientation can be understood to result from the best initial orbital overlap between the HOMO and LUMO, i.e., between the largest component p orbital of the HOMO of the diene and the largest component p orbital of the LUMO of the dieneophile. We can make a good guess at the coefficients of these orbitals by using all carbon MOs to predict the behavior of oxygen containing substrates.

Example. Predict orientation of the following reaction by FMO theory.

Diene

OCH$_3$
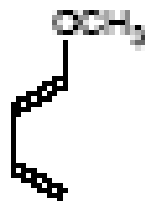
Dienophile

Simplest analogy to all carbon system is to use an anion to represent a lone pair, and a C=C to represent a C=O. Then from From the Huckel calculator:

HOMO

LUMO

Interact the largest orbital at either the 1 or 4 position of the diene (only ones shown below) with the largest orbital on the 1 or 2 position of the dienophile (only ones shown).

large-large   Major Product   large-small   minor product
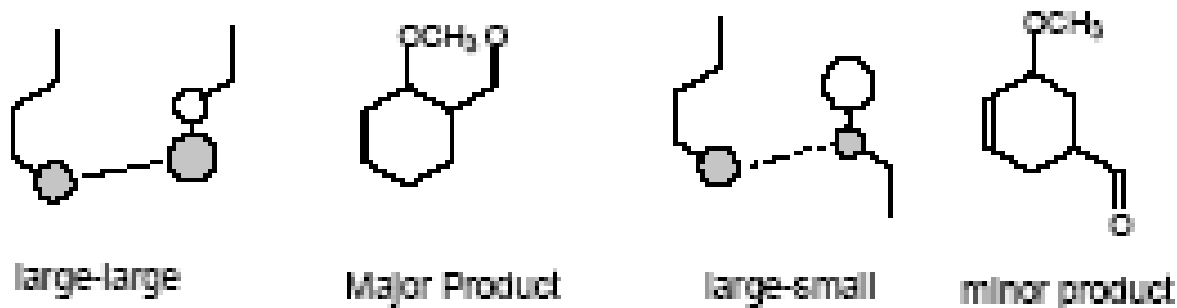
Thank You

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