Cycloaddition
and
cycloreversion reaction

For Semester V (CC12)

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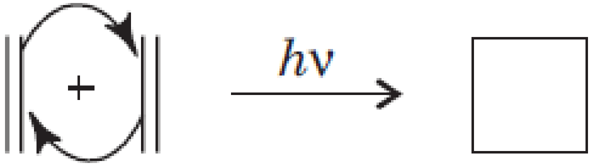
Cycloaddition reaction:

A cycloaddition is a reaction in which two unsaturated molecules undergo an addition reaction to yield a cyclic product.

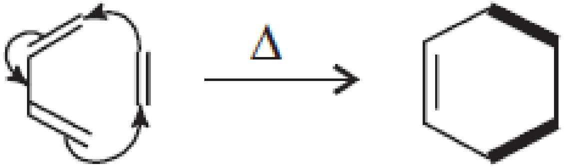
- Formation of cyclic product takes place at the expense of one π (pi) bond in each of the reacting partner and gain of two σ (sigma) bonds at the end of the both components having π (pi) bonds
- In this reaction there is loss of two π (pi) bonds of the reactants and gain of two σ (sigma) bonds in the product.



[m+ n] cycloaddition reaction

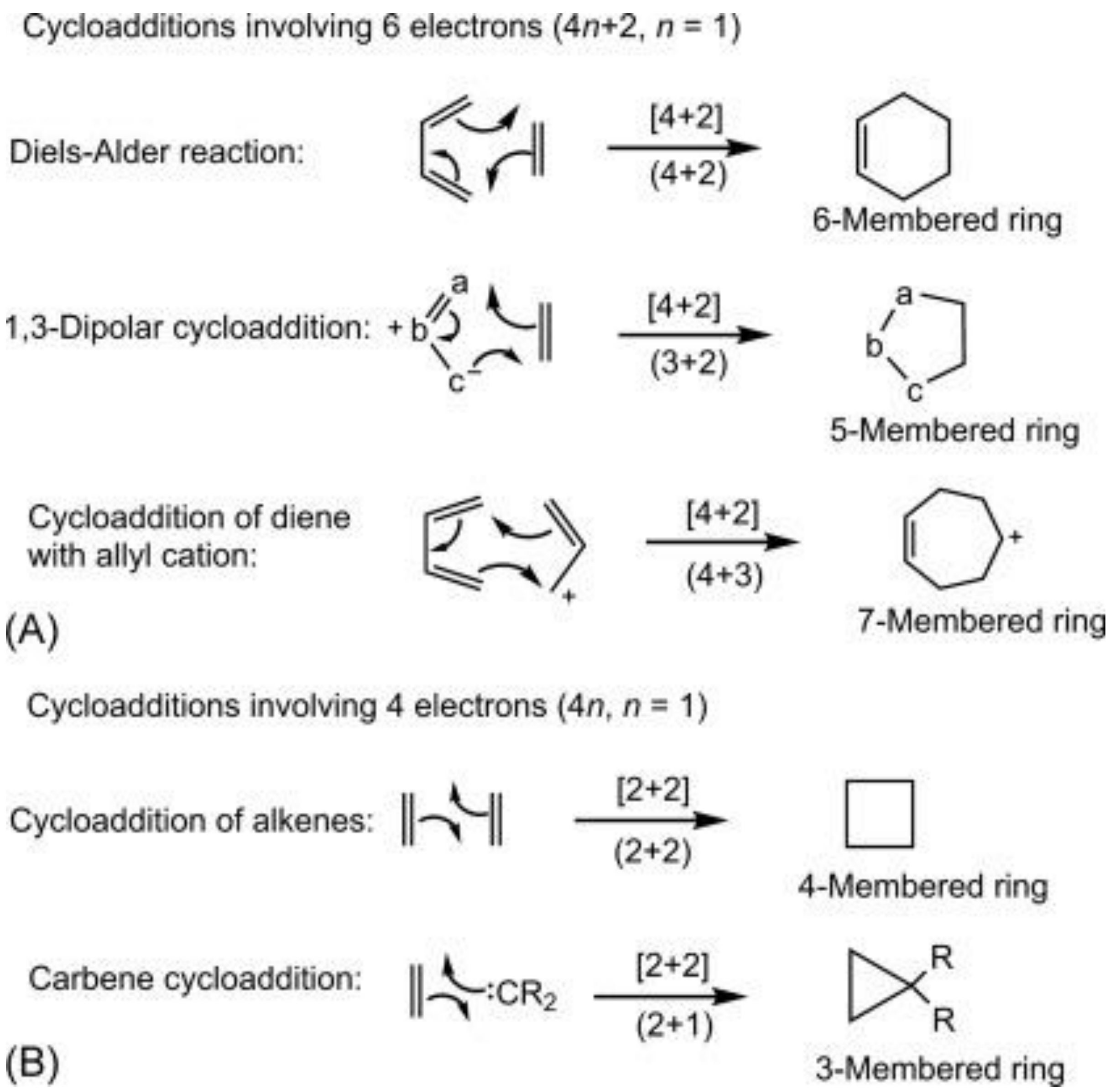
[2 + 2] cycloaddition reaction

Loss of two π bonds and
gain of two σ bonds



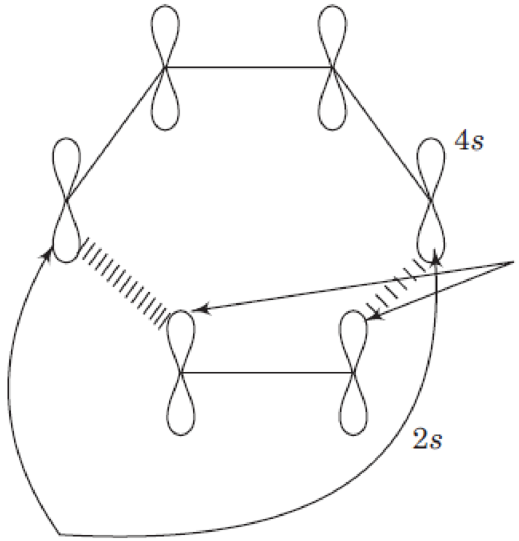
[4 + 2] cycloaddition

Classification of Cycloaddition reactions:



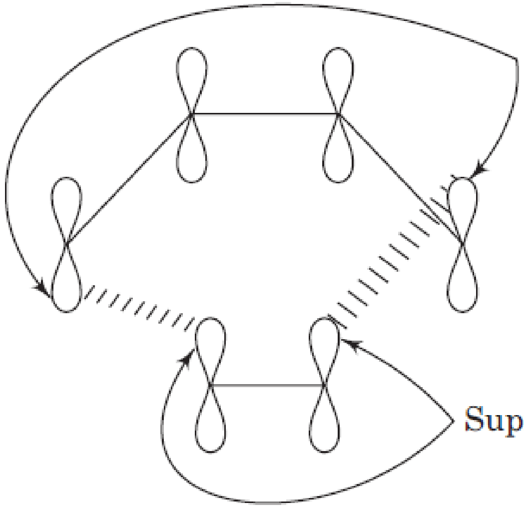
The cycloaddition reactions are classified with respect to following facts of the reaction:
(i) The number of electrons of each unit participating in cycloaddition and in presence of light or heat??
(ii) The nature of orbitals undergoing change (π or σ).
(iii) The stereochemical mode of cycloaddition (supra, syn or antara, anti).
(iv) Regioselectivity

- The stereochemical mode is given by a subscript ‘s’ or ‘a’ which indicates whether the addition occurs in a supra or antara mode on each unit.
- A cycloaddition may in principle occur either across the same face or across the opposite faces of the planes in each reacting component.
- If reaction occurs across the same face of a π system, the reaction is said to be suprafacial with respect to that π system. The suprafacial is nothing more than a syn addition. If the reaction bridges opposite faces of a π system, it is said to be antarafacial. An antarafacial is just an anti addition.



Both lobes are above the plane of the molecule or both lobes are in same plane, hence suprafacial

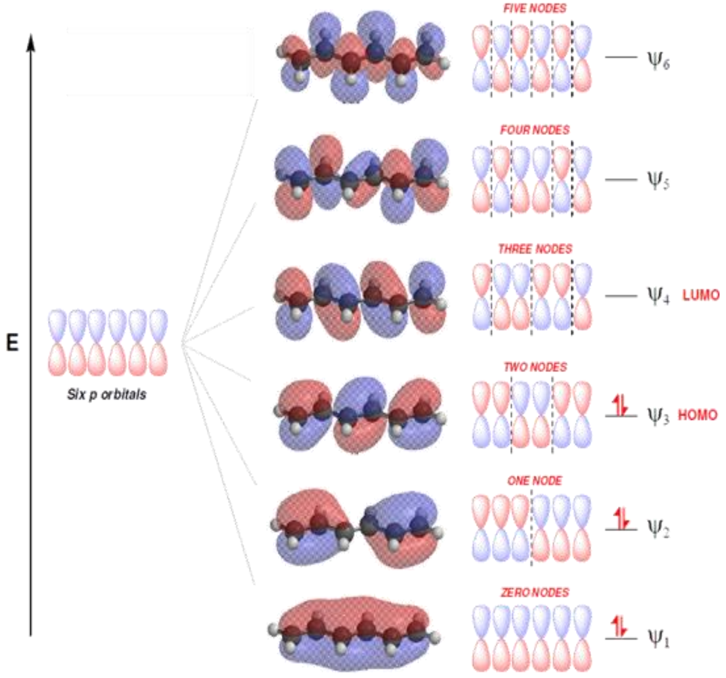
Both lobes are below the plane of the molecule or both lobes are in same plane, hence suprafacial

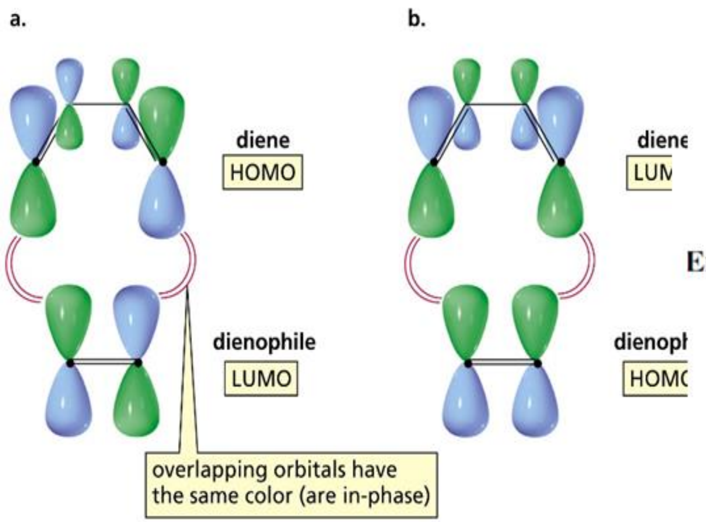


Antarafacial hence $4a$

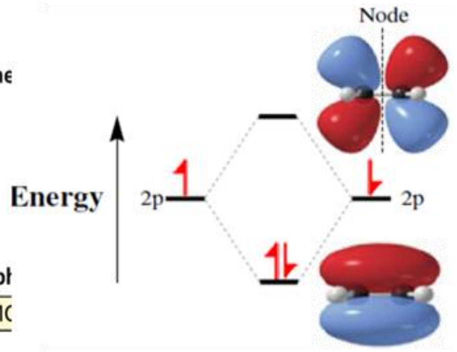
Suprafacial hence $2s$

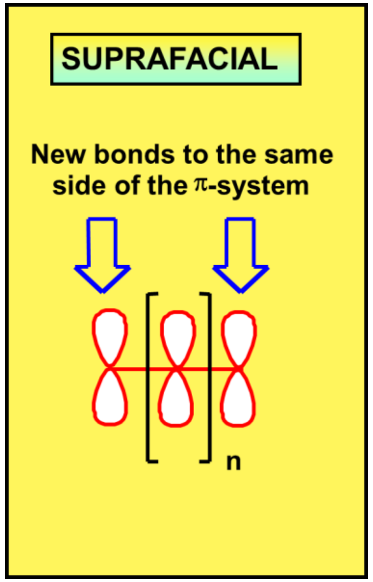
HOMO-LUMO of the reactants





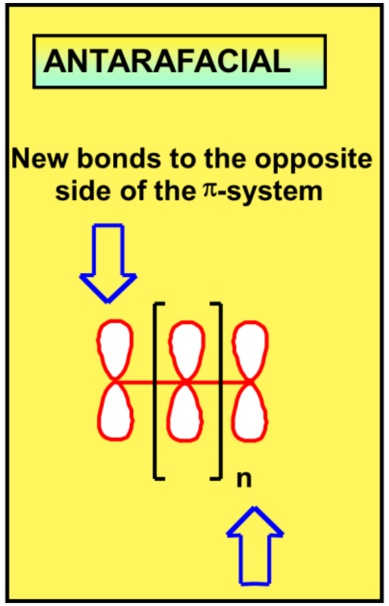
overlapping orbitals have the same color (are in-phase)





SUPRAFACIAL

New bonds to the same side of the π-system



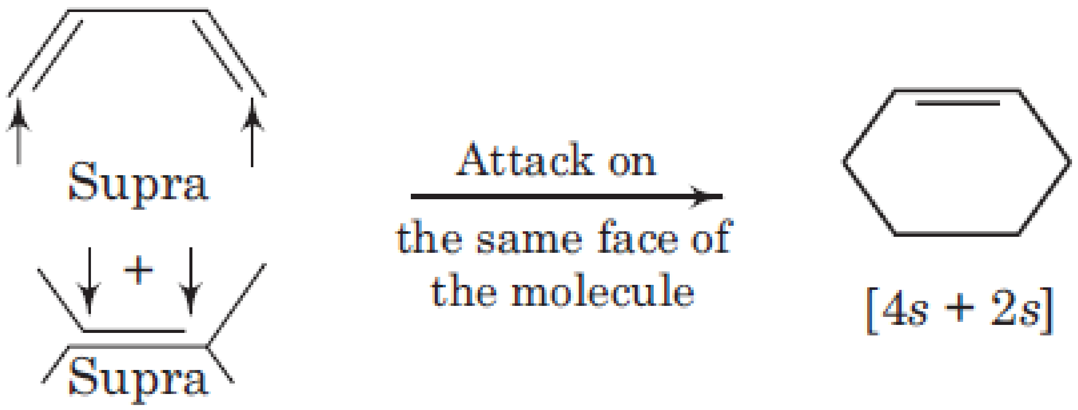
ANTARAFACIAL

New bonds to the opposite side of the π-system

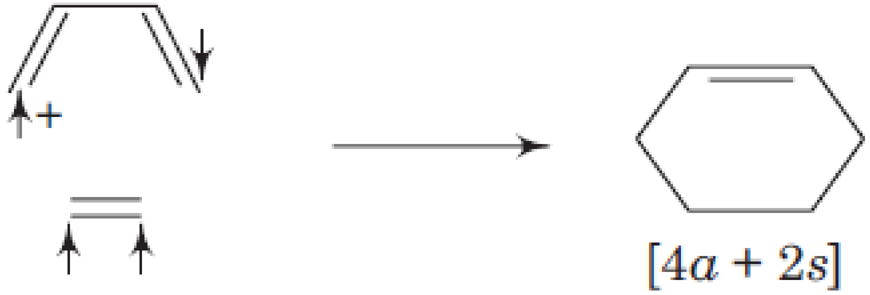
Stereochemistry of addition

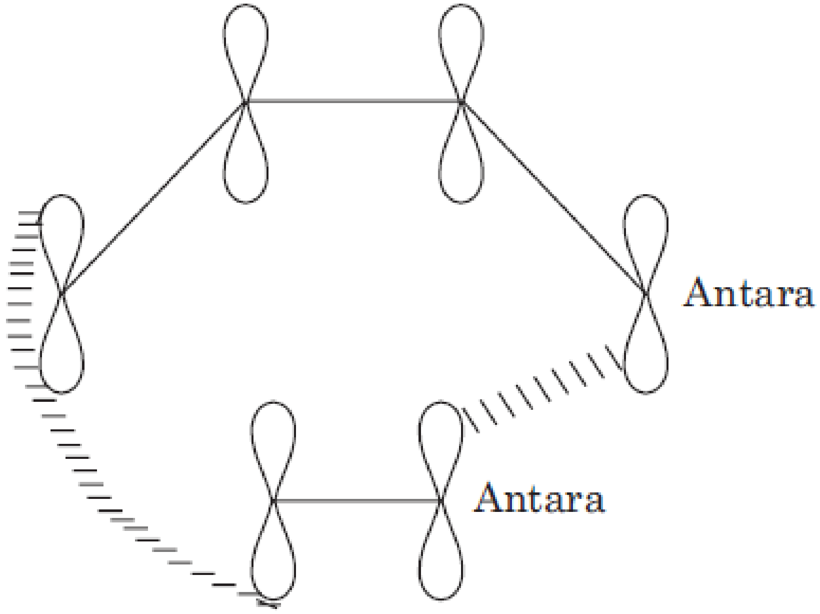
Examples:

$[4s + 2s]$ cycloaddition reaction.



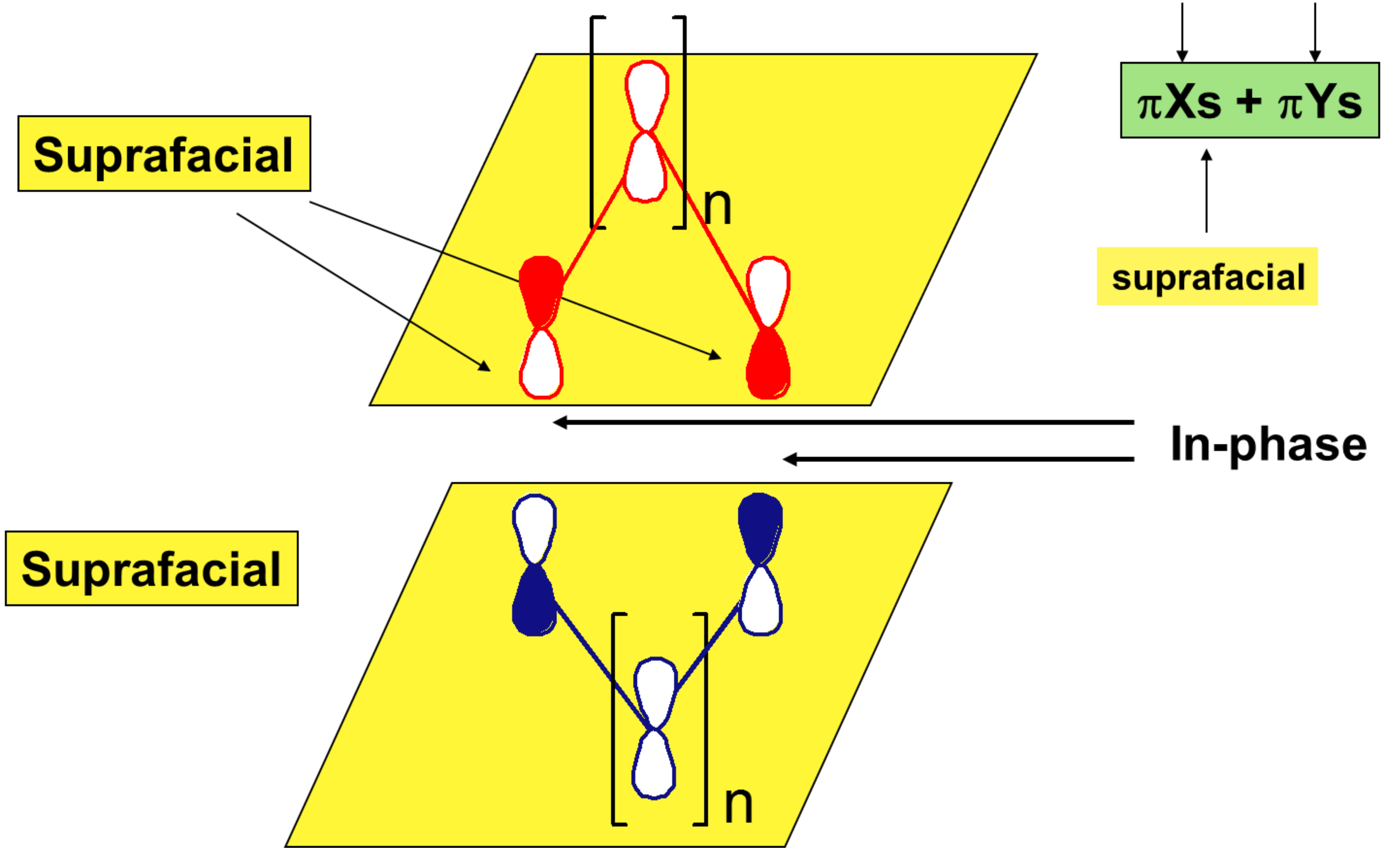
$[4a + 2s]$ cycloaddition reaction





$[4a + 2a]$ Cycloaddition reaction

Suprafacial-Suprafacial Interaction: 4n+2 π Electron Transition States



Suprafacial

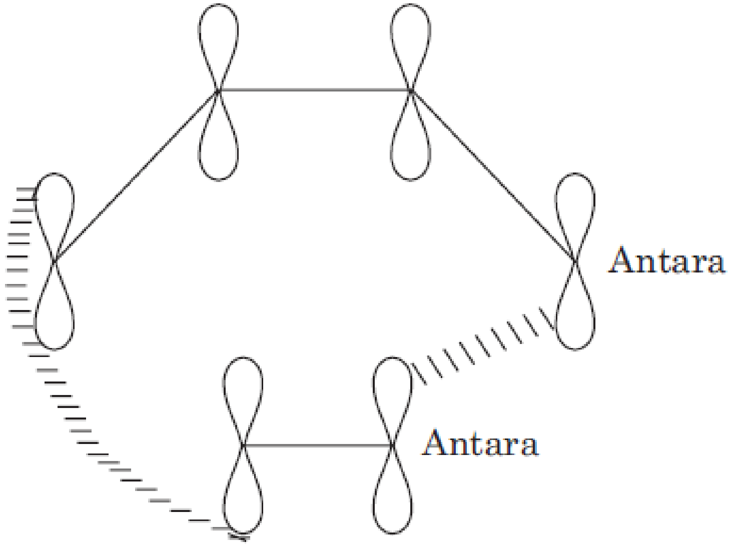
Suprafacial

Number of π-electrons in each component

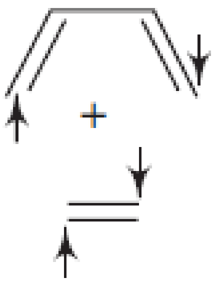
πXs + πYs

suprafacial

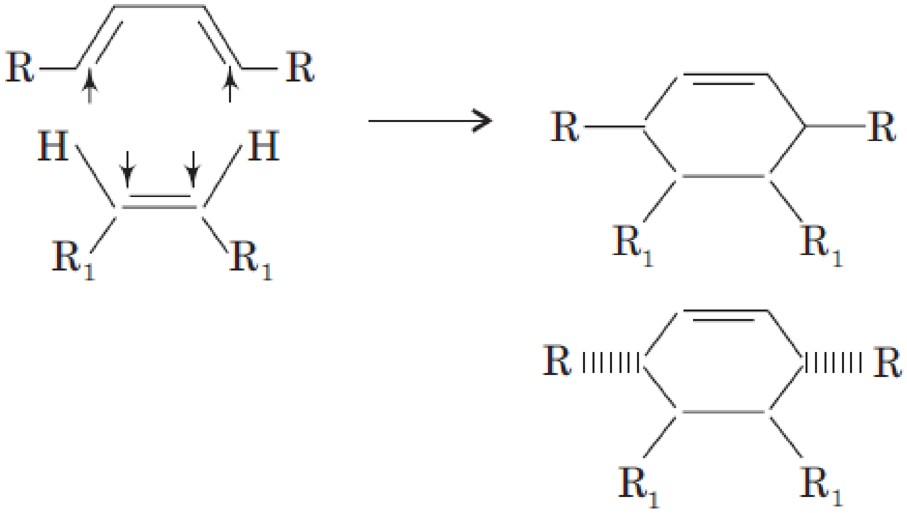
In-phase



[$4a + 2a$] Cycloaddition reaction



- In antarafacial, attack takes place with one bond forming to one surface but other bond forming to other surface.
- It is rare, it does not occur in any reaction.
- Almost all cycloaddition reactions are suprafacial on both components.



In order, for a cycloaddition to occur, there must be bonding overlap between p-orbitals at the terminal carbons of each π-electron system

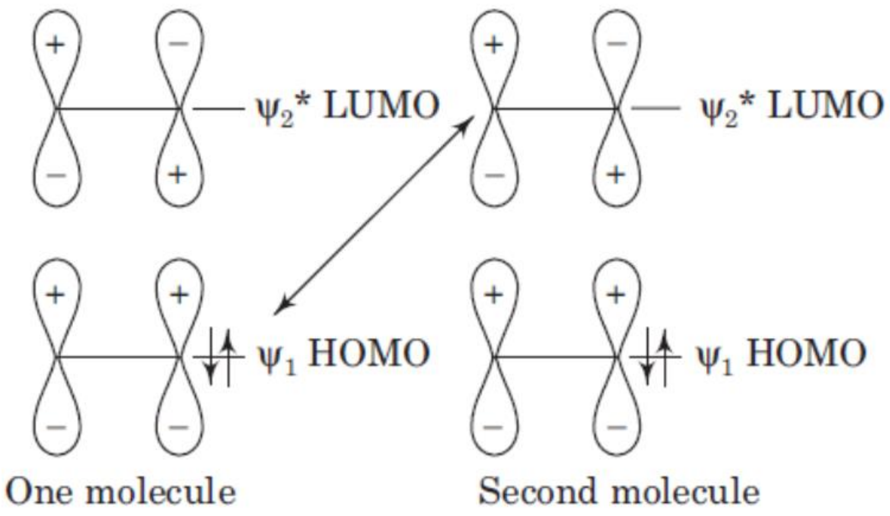
[2 + 2] cycloaddition:

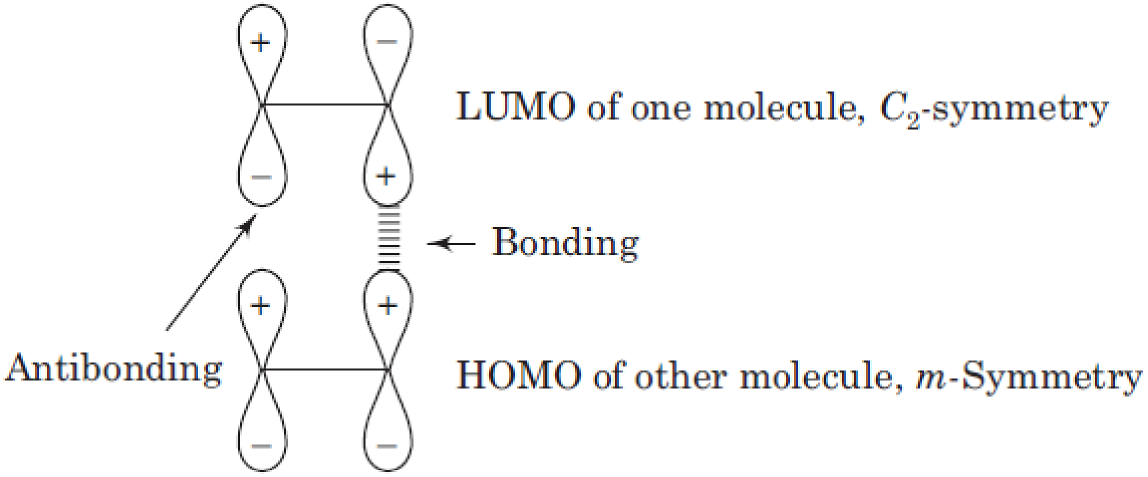
Thermal induced Cycloaddition reaction

Thermal induced [2 + 2] cycloaddition reactions are symmetry forbidden reactions

When ethylene is heated, its π electrons are not promoted, but remain in the ground state ψ1. If we examine the phase of the ground state HOMO of one ethylene molecule and the LUMO of another ethylene molecule we can see why cyclisation does not occur by the thermal induction.

Why HOMO-LUMO???



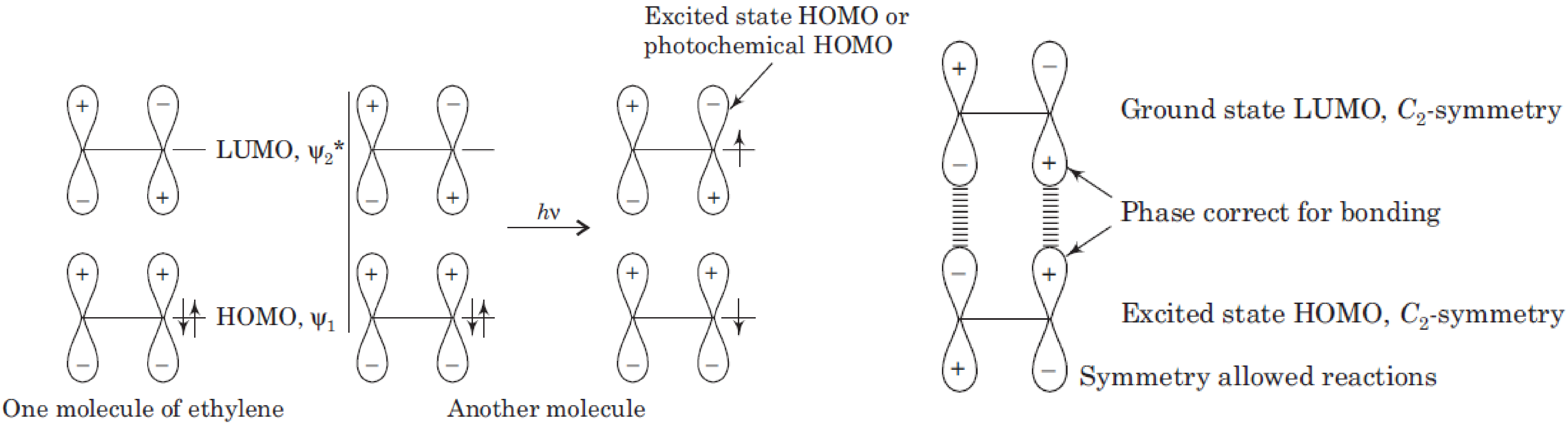


Phase wrong for overlap, symmetry forbidden.

- For bonding to occur, the phase of the overlapping orbitals must be same.
- This is not the case for the ground state HOMO and LUMO of two ethylene molecule or any other [2 + 2] system. Because the phase of the orbitals are incorrect for bonding,

  a thermally induced [2 + 2] cycloaddition is said to a symmetry forbidden reaction

Photo-Induced [2 + 2] Cycloaddition Reactions

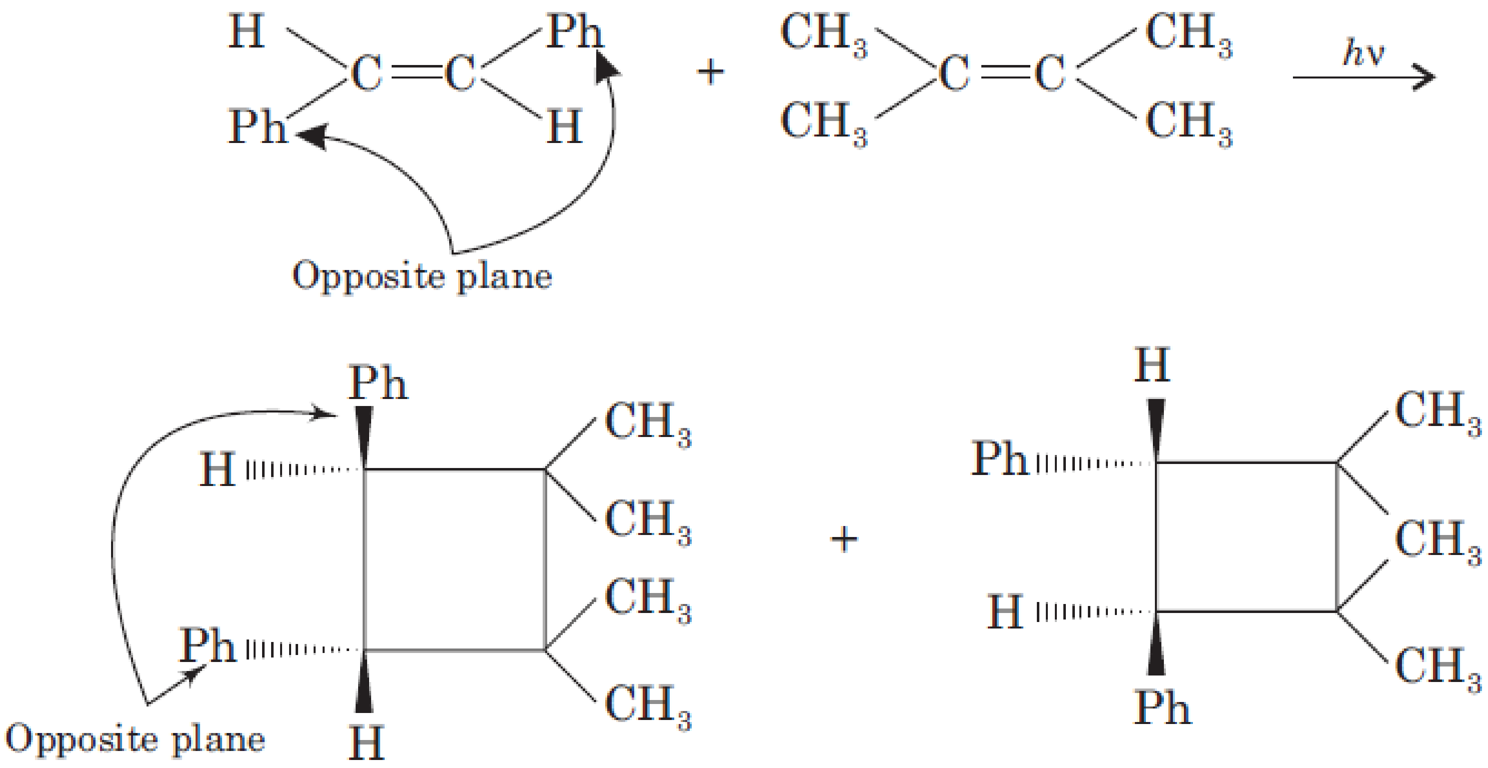


- For cycloaddition reaction both HOMO and LUMO should have same symmetry otherwise reaction will be symmetry forbidden.
- For symmetry allowed reaction if HOMO has m-symmetry then LUMO should also have m-symmetry.

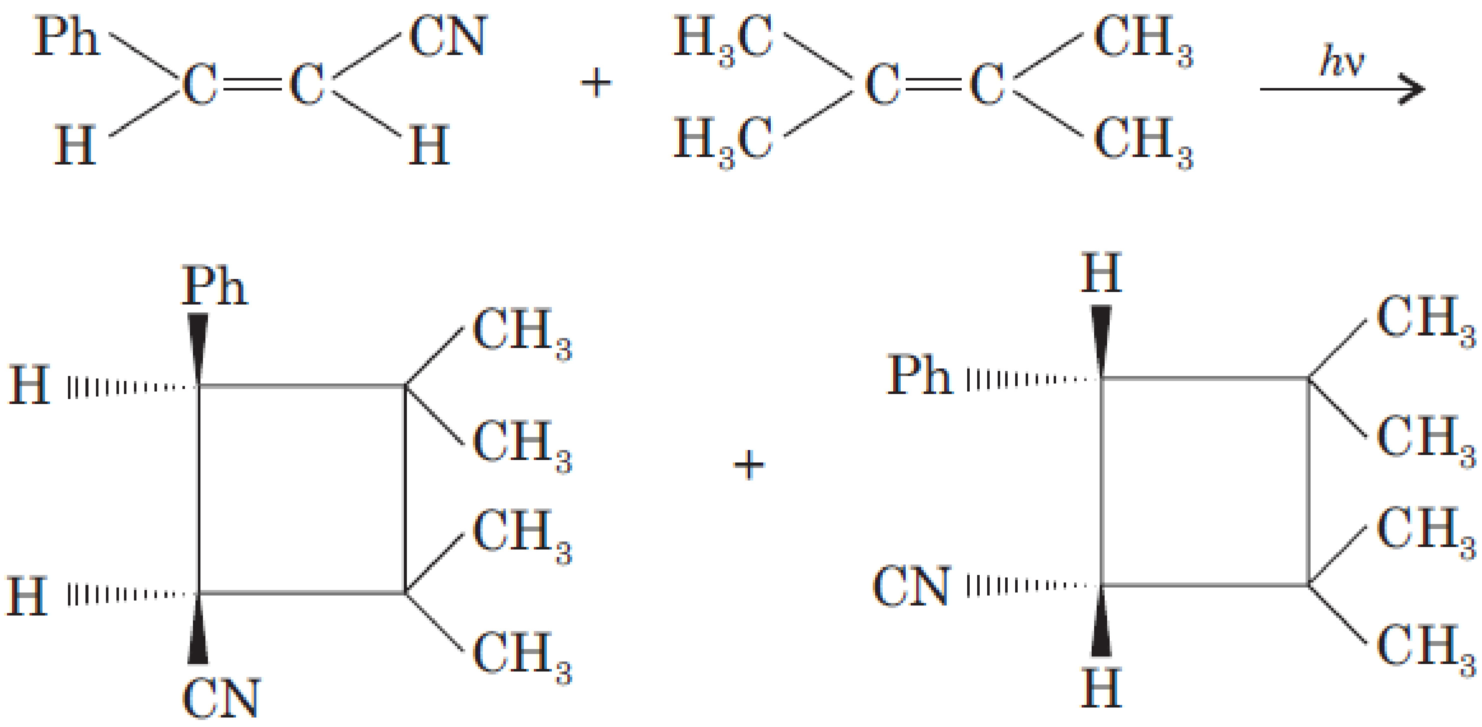
Similarly if HOMO has C2-symmetry then LUMO should also have C2-symmetry

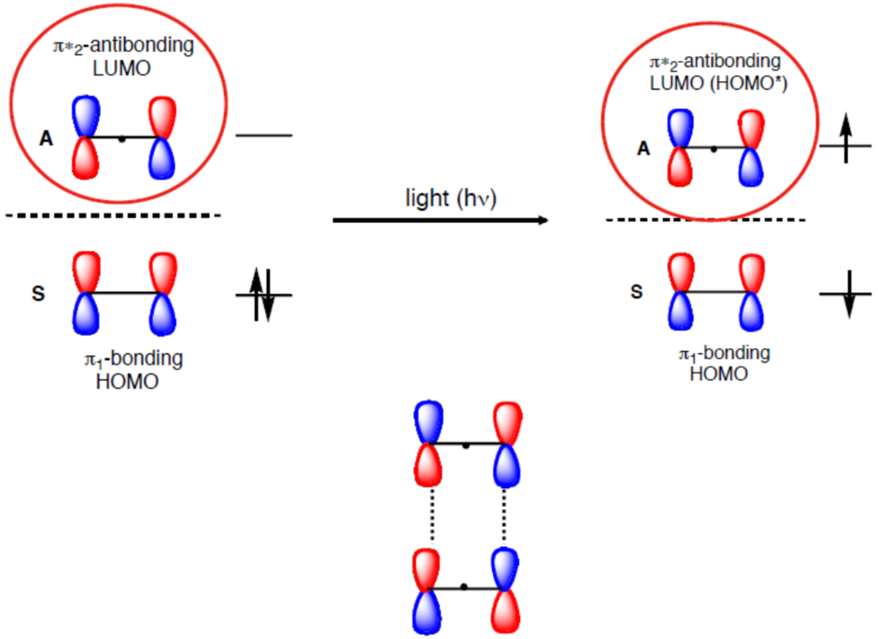
Stereochemistry:

Stereochemical integrity is maintained in cycloaddition reaction because reaction is concerted reaction

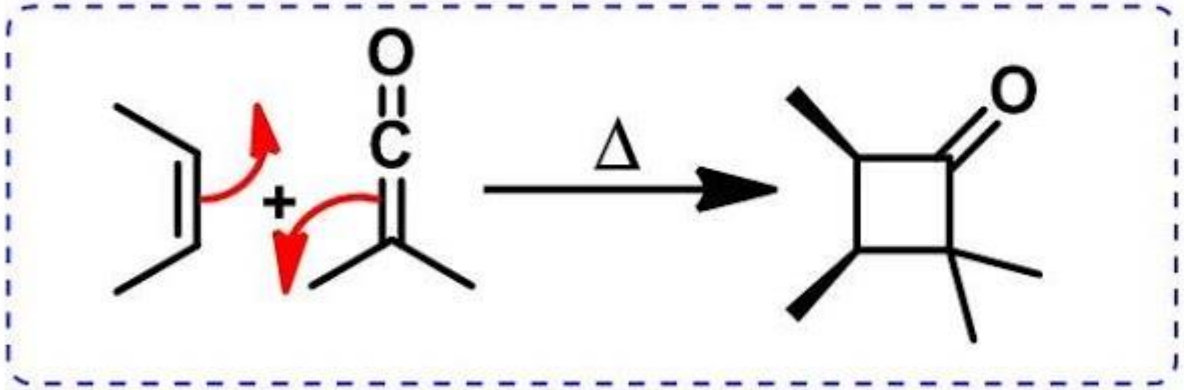


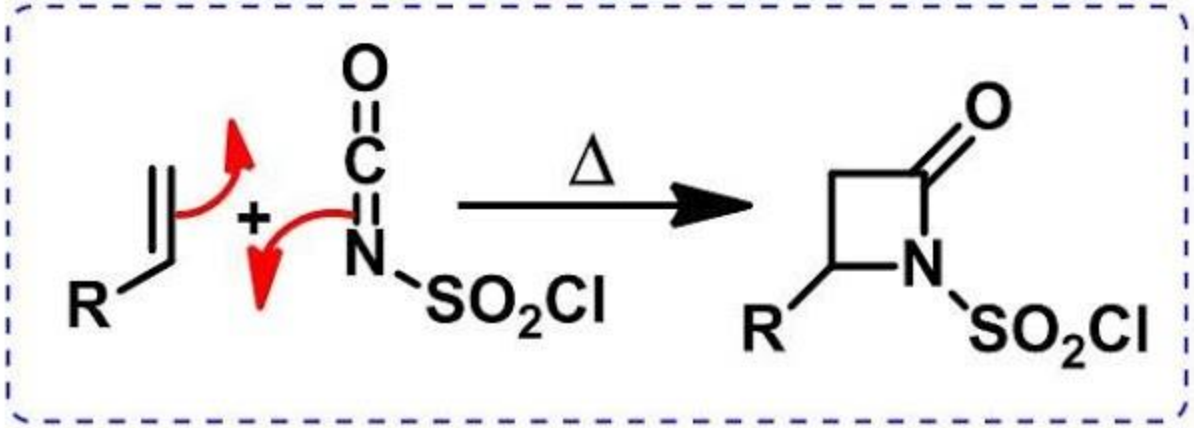
What About a [2+2] Cycloaddition?

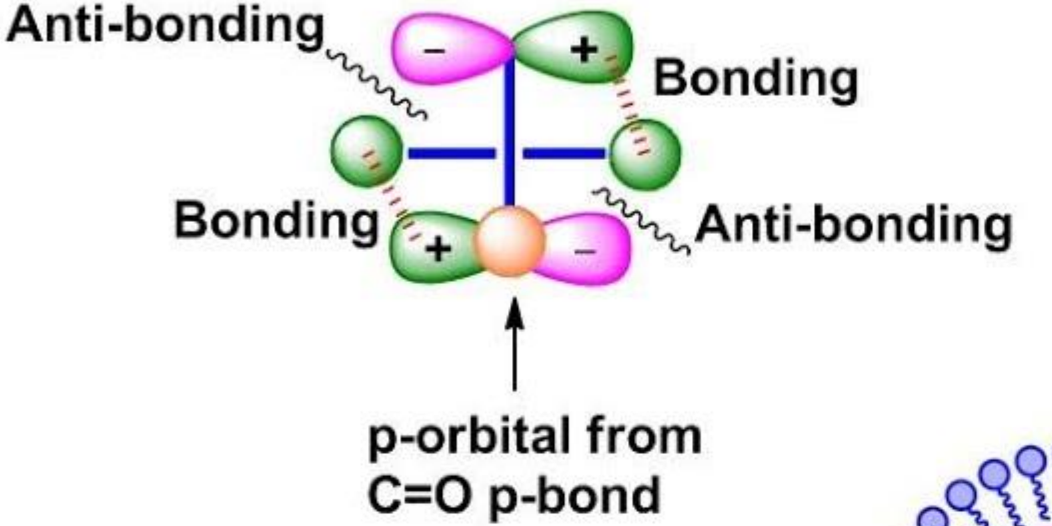




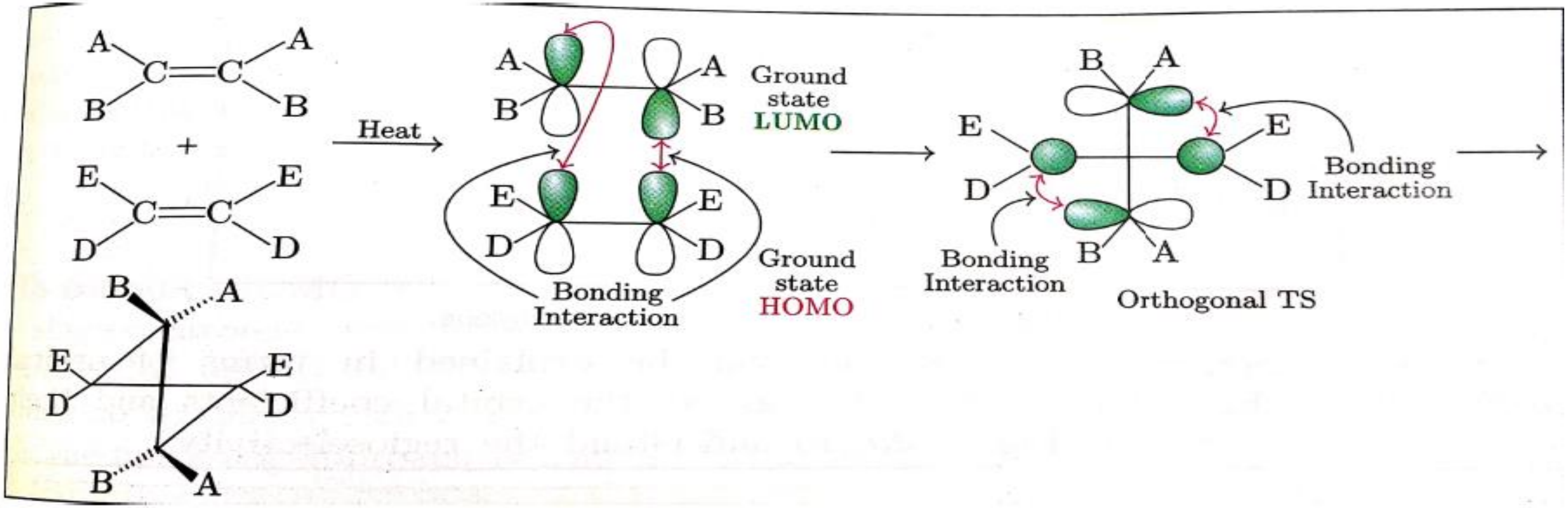
Thermal[2+2]cycloaddition reactions







FMO of [2+2] thermal cycloaddition reaction: [2+2] thermal cyclization proceeds through orthogonal transition state as depicted in following figure..



- This is π^{2s}+ π^{2a} combination, which is rare
- Here orbital overlap is minimal and non-bonding steric interaction between A,B and D,E makes it unfavorable
- The molecules where a pair of interacting substituents absent atleast at the one end of the reacting terminal , undergo thermal cyclisation eg, allenes, isocyanates, ketenes etc.

[4 + 2] cycloaddition

Let us suppose that diene (4π component) behaves as electron donor and the dienophile (2π component) as the electron acceptor (or vice-versa).
What electrons will the 4π component donate?

- Obviously there will be its valence electrons—the electrons in its HOMO (ψ2).
- The 2π component will accept these electrons to form the new bonds.

The molecular orbital used to accept these electrons must be empty since molecular orbital cannot contain more than two electrons. Therefore, the molecular orbital which accepts electron should be LUMO of the 2π component.

Thus, one component used its HOMO and the other component used its LUMO for overlapping.

Simultaneously with the merging of the π orbitals, these orbitals also undergo hybridisation to yield the new sp3 σ bonds.

Example:

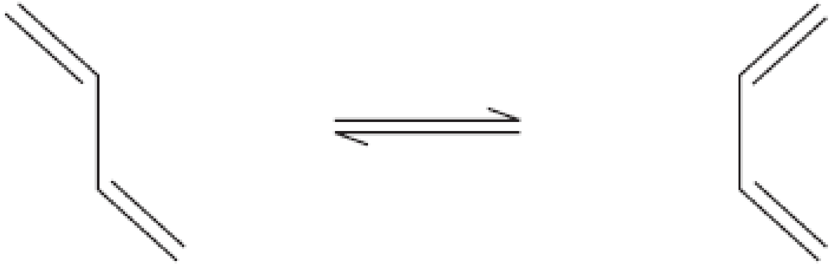
Diels-Alder reaction is the best known [4 + 2] cycloaddition reaction. This reaction is thermally allowed reaction. Diels-Alder reaction is photochemically forbidden.

Diels-Alder Reaction:

Diels-Alder reactions occur between a conjugated diene and an alkene (or alkyne),
usually called the dienophile.

The Dienes

- The diene of the Diels-Alder reaction is electron rich, while the dienophile is electron poor.
- Simple dienes such as 1, 3-butadiene are sufficiently electron-rich to be effective dienes for Diels-Alder reaction. The presence of electron releasing groups such as alkyl groups, phenyl groups or alkoxy groups may further enhance the reactivity of dienes.
- The diene component of the Diels-Alder reaction can be open-chain or cyclic but it must have s-cis conformation
- Butadiene normally prefers the s-trans conformation with the two double bonds as far away from each other as possible for steric reasons.
- The barrier to rotation about the central σ bond is small (about 30 kJ/mole at 25°C) and rotation to the less favourable but reactive s-cis conformation is rapid.

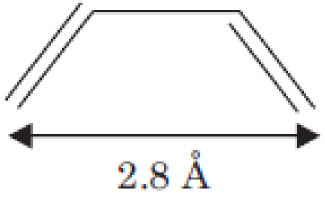


Favoured but cannot
give Diels-Alder reaction

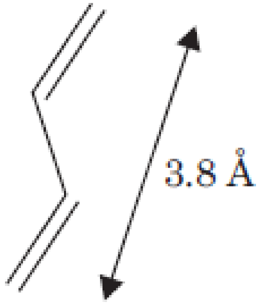
Disfavoured but can
give Diels-Alder reaction

- Cyclic dienes that are permanently in the s-cis conformation are exceptionally good for Diels-Alder reaction.
- Cyclic dienes that are permanently in the s-trans conformation and cannot adopt the s-cis conformation will not give the Diels-Alder reaction

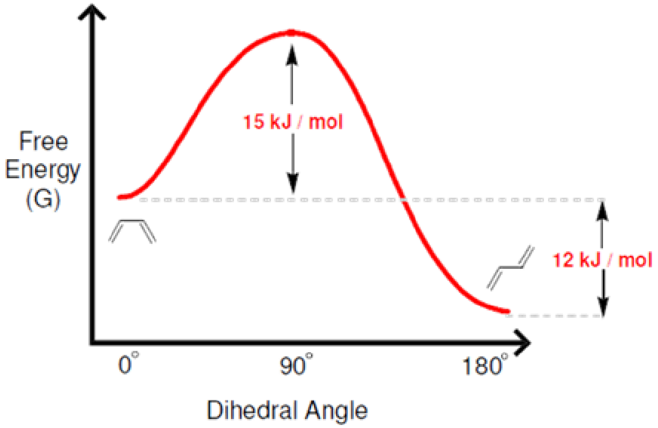
(Reason: If the diene is in the s-trans conformation, the dienophile could not ‘reach’ both ends of the diene at the same time)

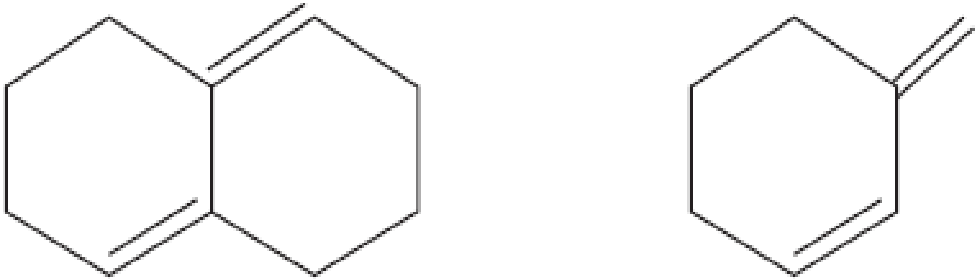


s-cis Conformation,
a requirement for the
Diels-Alder reaction



s-trans Conformation



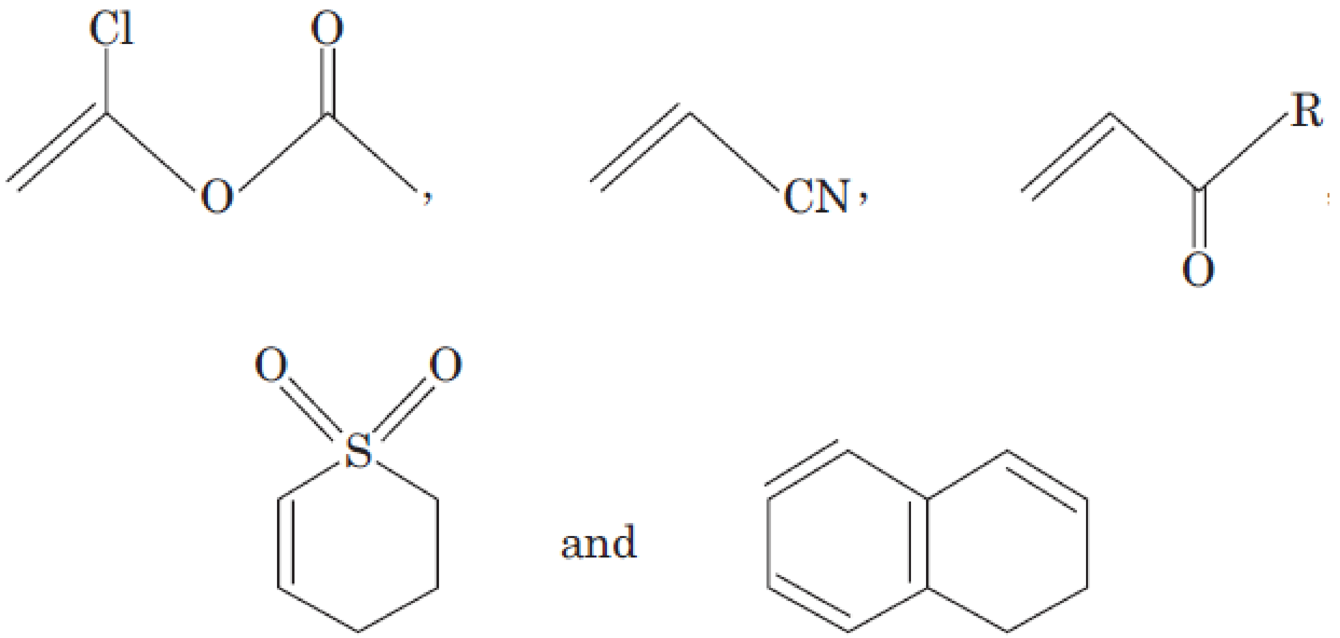


They do not serve as Diene.

The Dienophile:

- The most common dienophiles are the electron-poor alkenes and alkynes.
  (Since electron-poor alkenes and alkynes are prone to react with a diene, these are called dienophiles (lover of dienes).
- A good dienophile generally has one or more electron-withdrawing groups pulling electron density away from the π bond

Dienophiles that do undergo the Diels-Alder reaction include conjugated carbonyl compounds, nitro compounds, nitriles, sulphones, arylalkenes, arylalkynes, vinyl ethers, vinyl esters, haloalkenes and dienes etc.

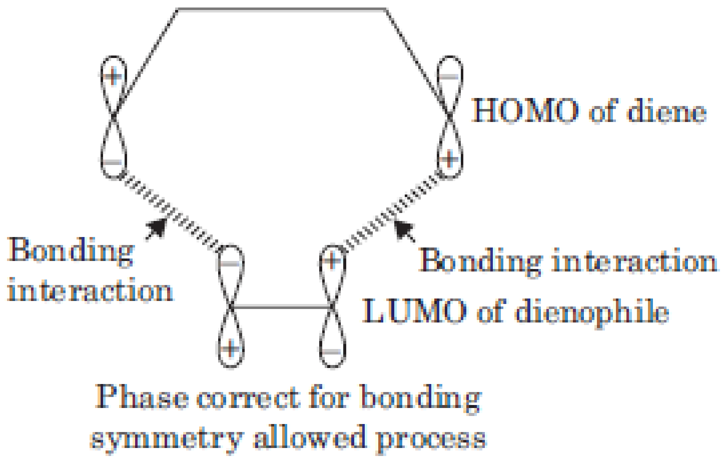


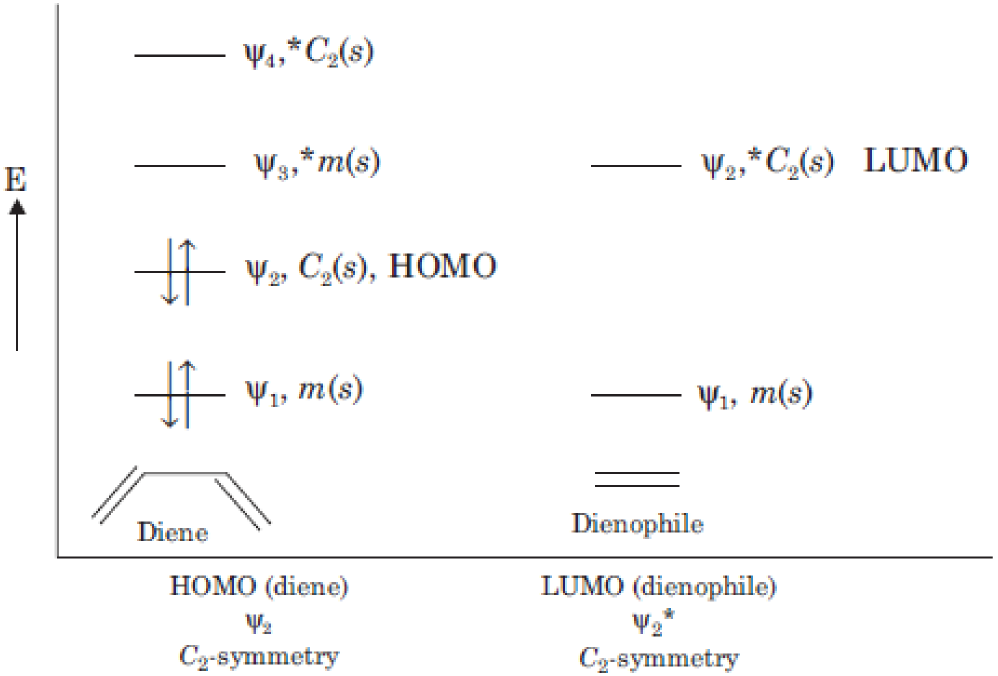
The Frontier Orbital Description of [4 + 2] Cycloadditions

- [4 + 2] cycloaddition reaction is thermally allowed whereas [2 + 2] cycloaddition reaction is photochemically allowed
- Let us examine the HOMO-LUMO interactions of only the p-orbital components that will form the new σ (sigma) bonds.
- Comparison of the HOMO-LUMO interactions will have to be made for the ground state (for a thermal induced reaction) and those for the excited state (for photo induced reaction).

Thermal induced reaction: There are two possible interactions, HOMO (diene)- LUMO (dienophile) and HOMO (dienophile)-LUMO (diene).

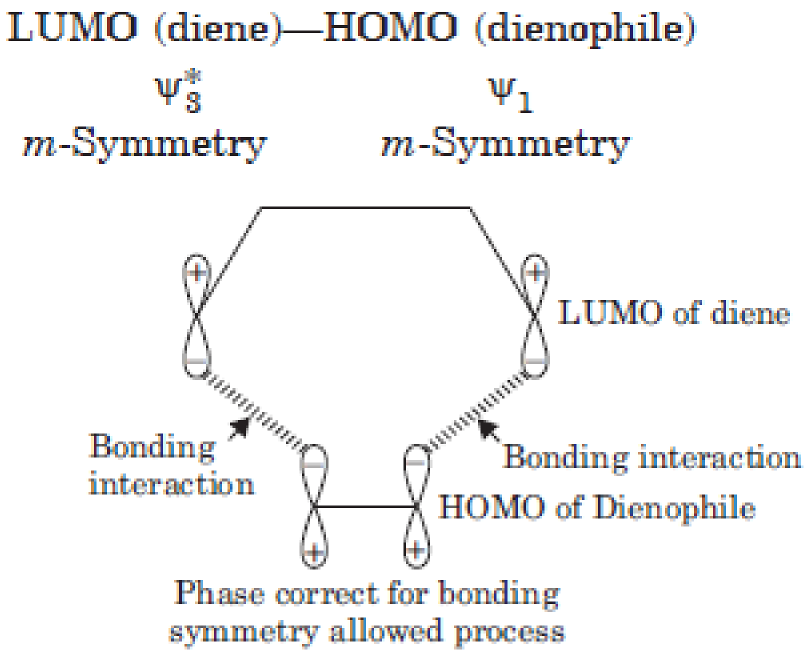
Case I: HOMO of diene and LUMO of dienophile





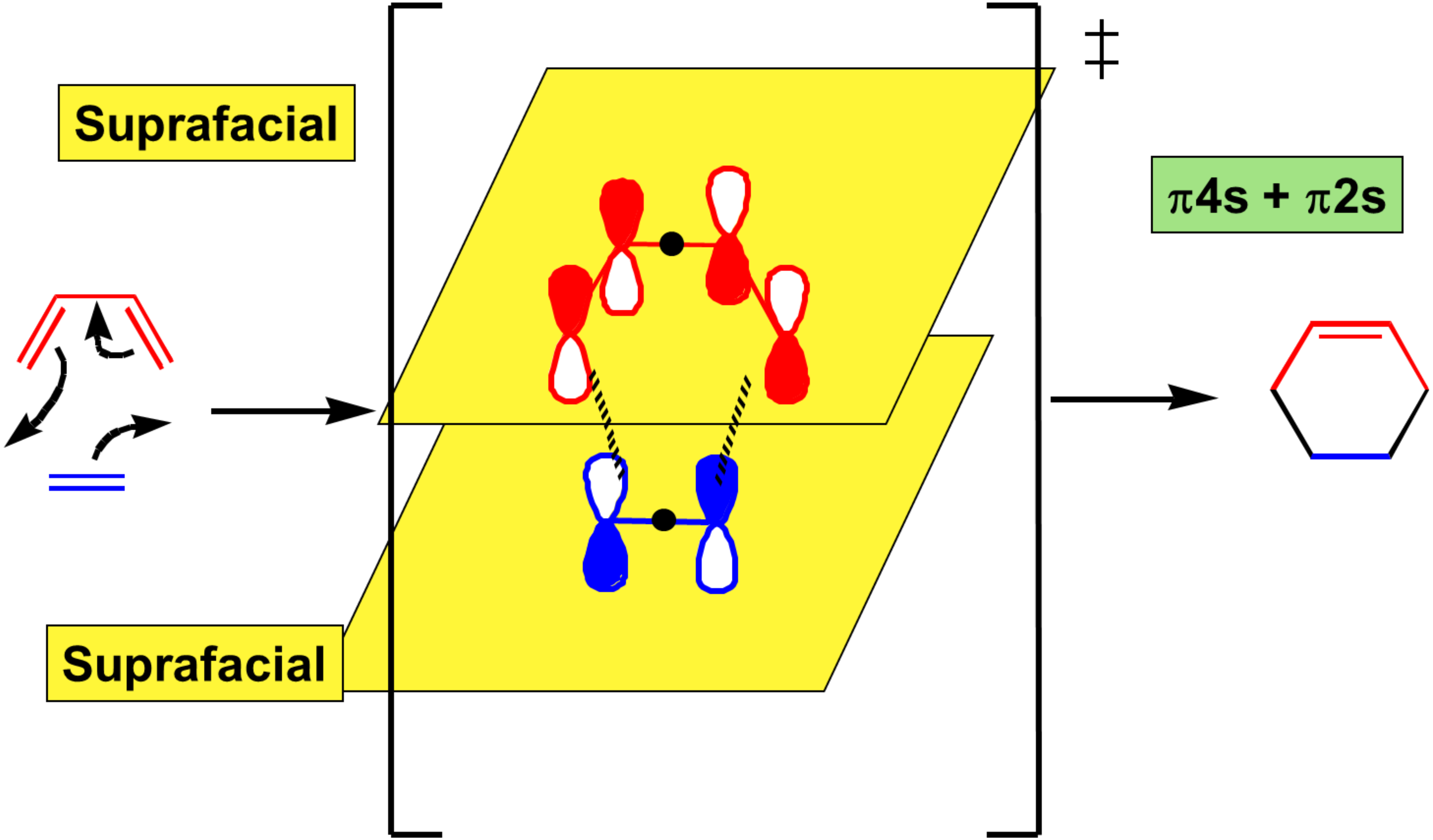
Case II: LUMO of diene and HOMO of dienophile

- In this case, the stronger interaction is between the HOMO and LUMO pair closer in energy
- The closer the two are in energy, the stronger the interaction.



- In the Diels-Alder reaction of ethylene and butadiene, the two HOMO-LUMO interactions are of equal energy and orbital symmetry is same in both reactions.
- Both interactions involve bonding overlap at the point of formation of the two new σ (sigma) bonds

Diels-Alder Cycloaddition Reaction:
6 π-Electron Transition State



Suprafacial

Suprafacial

‡

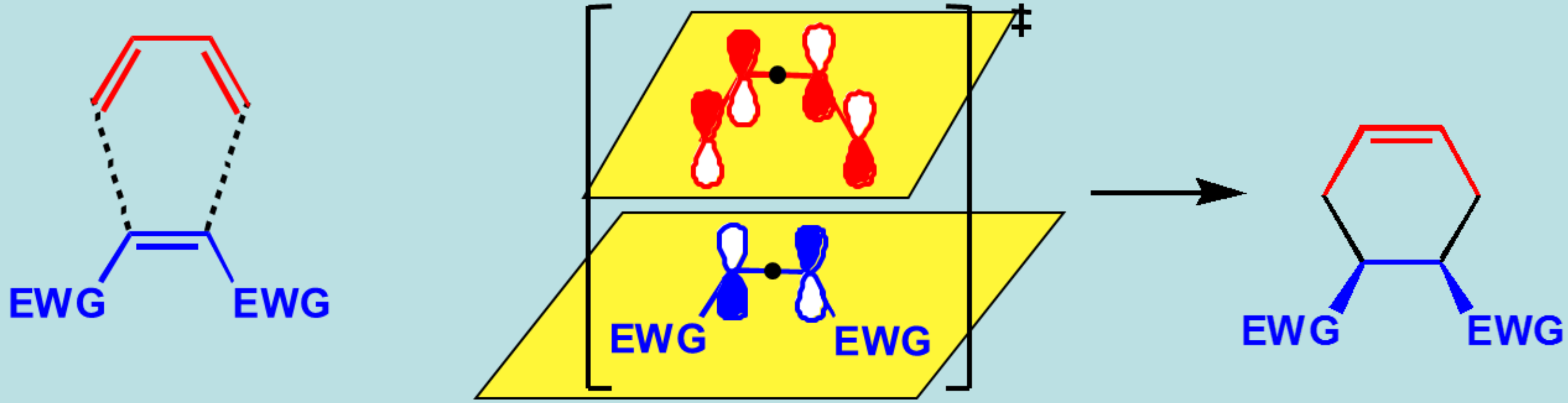
π4s + π2s

Diels-Alder Reaction Transition State Geometry

Suprafacial

Diene

HOMO – $\psi 2$



Dieneophile

LUMO – $\psi 2$

Suprafacial

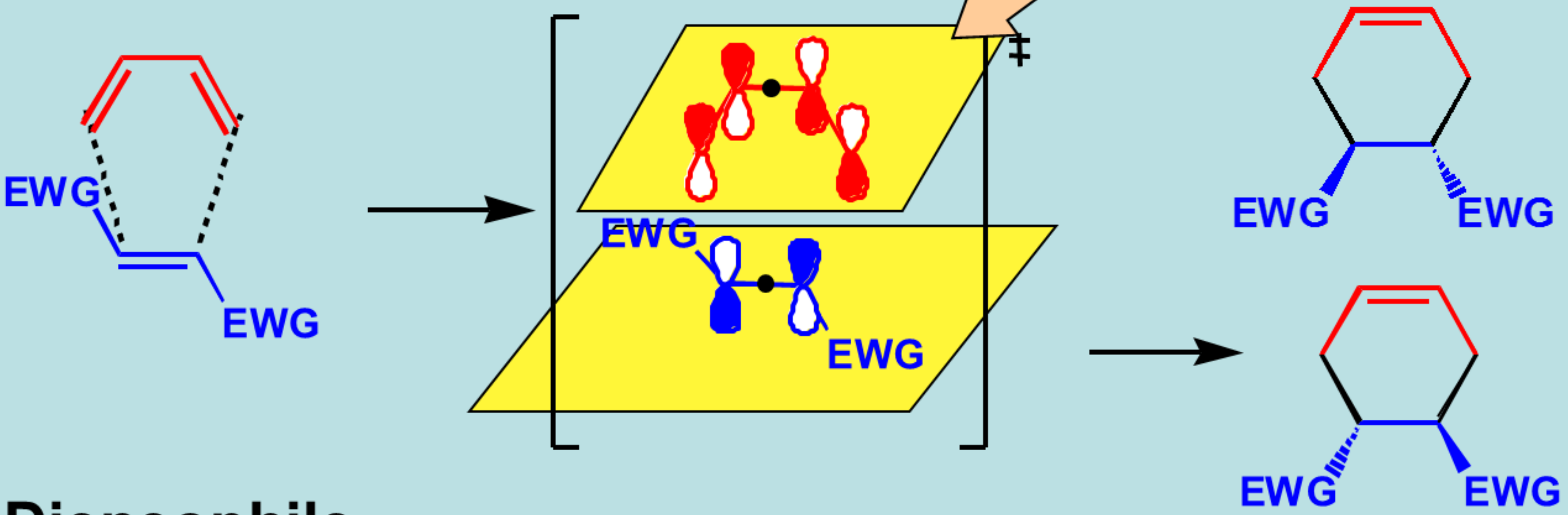
$\pi 4s + \pi 2s$

Suprafacial

Diene

HOMO – $\psi 2$

One of two equally likely transition states See Next 2 Slides…



Dieneophile

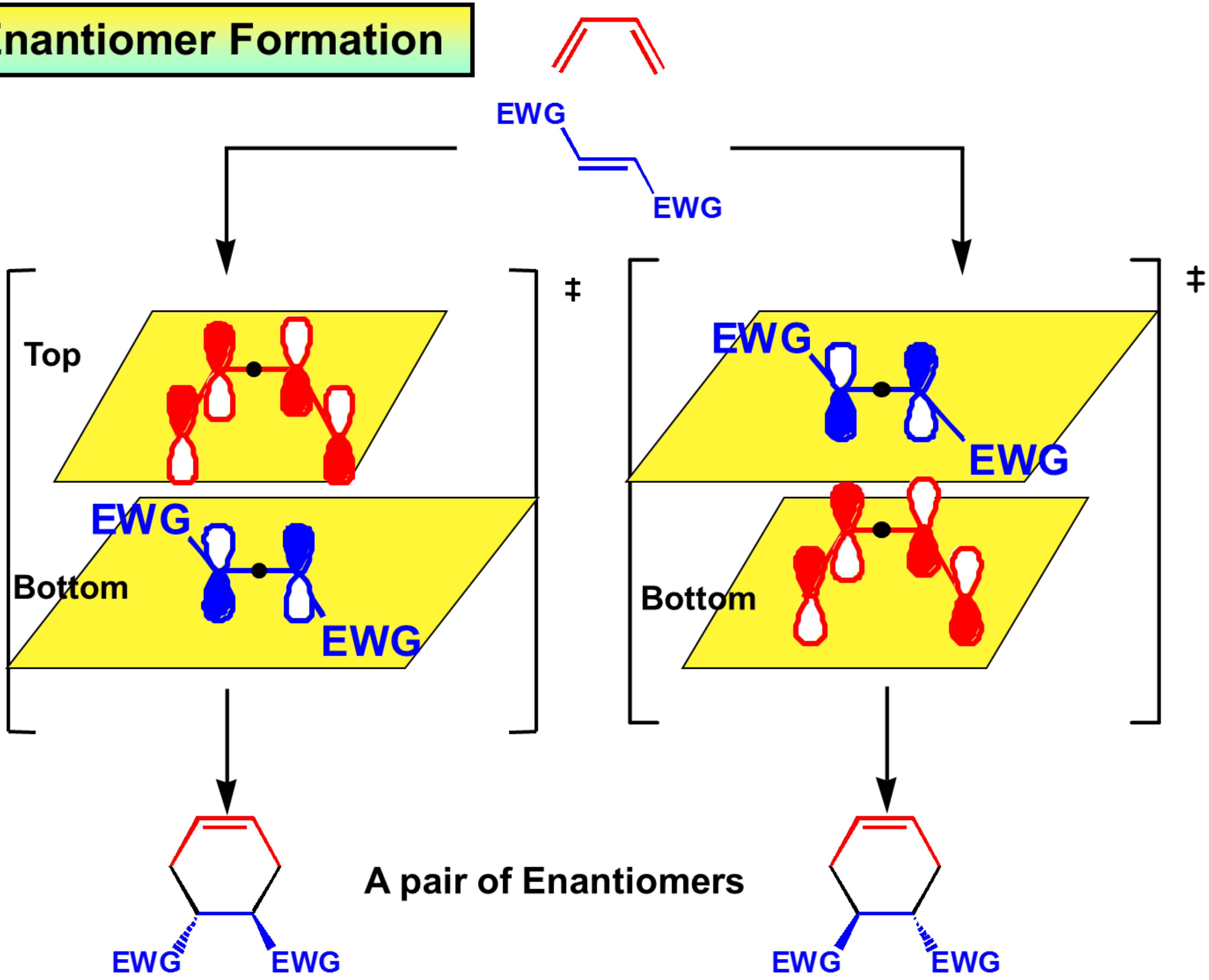
LUMO – $\psi 2$

Suprafacial

i.e. **enantiomers**

$\pi 4s + \pi 2s$

Enantiomer Formation



A pair of Enantiomers

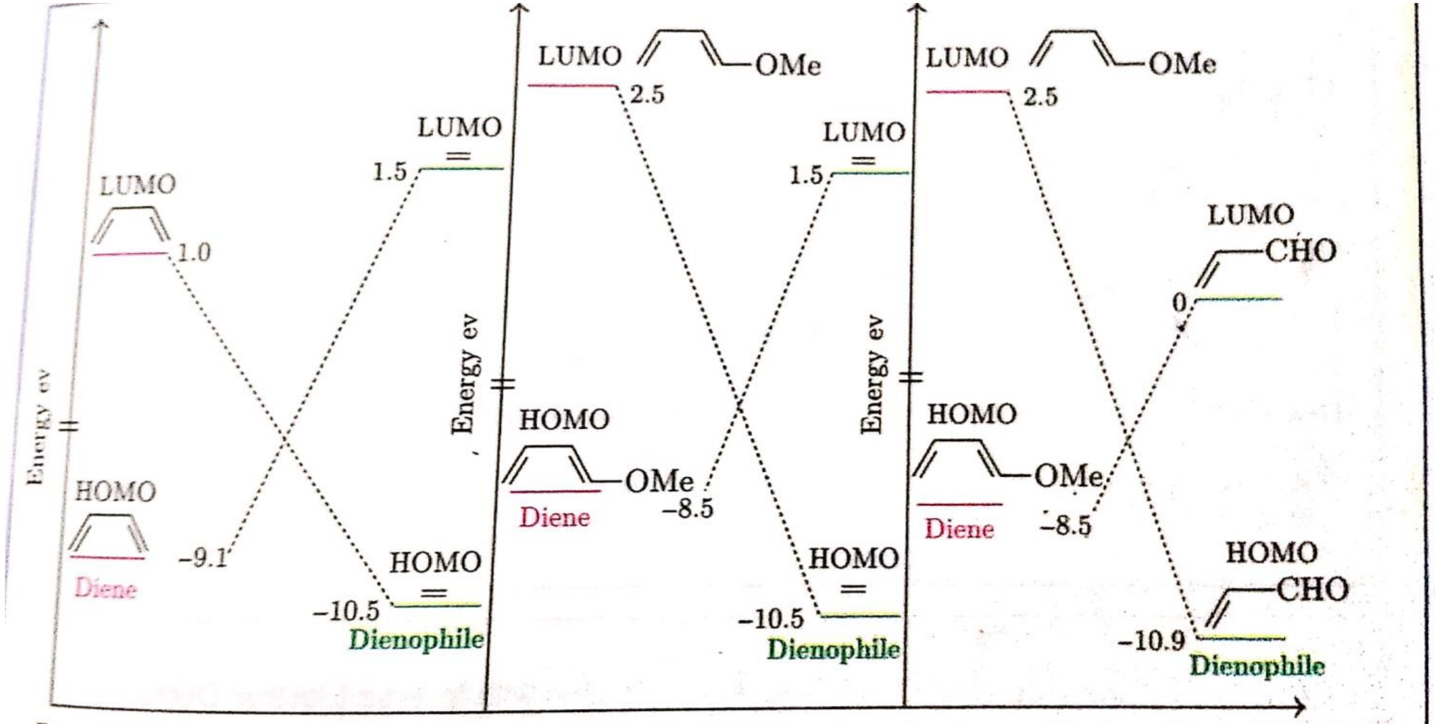
What will be the rate of the reaction for the substituted diene or dienophile??

Reactivity: E_{HOMO} and E_{LUMO} values depend upon the nature of substituents attached-

(i) ERG raises the energy of HOMO and LUMO of diene and dienophile

(ii) EWG reduces the energy of HOMO and LUMO of diene and dienophoile

(iii) A group which extends the conjugation raises the energy of the HOMO and decreases the energy of the LUMO



(a)	(b)	(c)
Diene HOMO – Dienophile LUMO	Diene HOMO – Dienophile LUMO	Diene HOMO – Dienophile LUMO
ΔE = 10.6 ev	ΔE = 10 ev	ΔE = 8.5 ev
Diene LUMO – Dienophile HOMO	Diene LUMO – Dienophile HOMO	Diene LUMO – Dienophile HOMO
ΔE = 11.5 ev	ΔE = 13 ev	ΔE = 13.4 ev

From above energy gap comparison, it can be concluded that the best Diels Alder reaction is HOMO of a diene with ERG with the LUMO of a dienophile having EWG.

Mechanism of Diels-Alder Reaction

Diels-Alder reaction is a simultaneous cyclic movement of six electrons:
four in the diene and two in the dienophile

For these three pairs of electrons to move simultaneously, however, the transition state must have a geometry that allows overlap of the two end p-orbitals of the diene with those of the dienophile

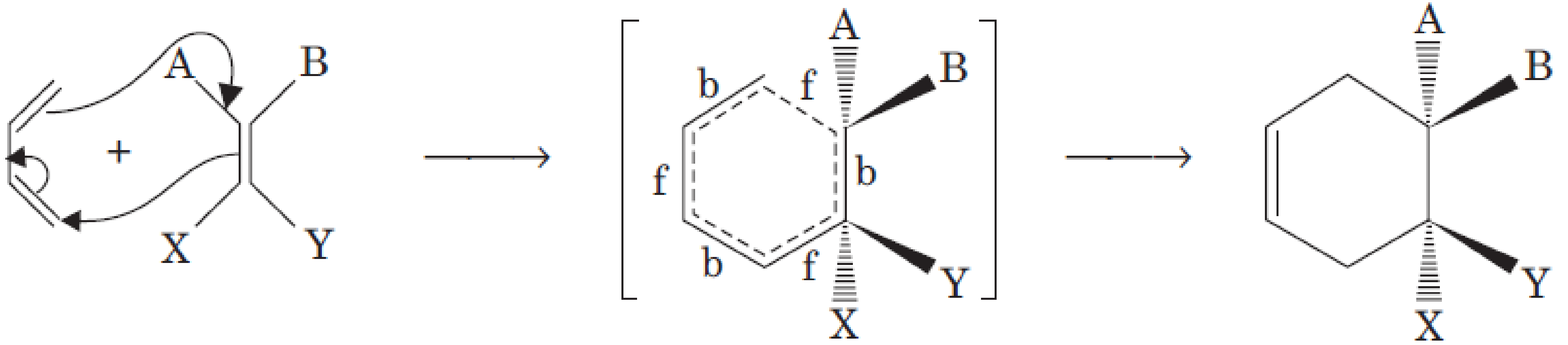


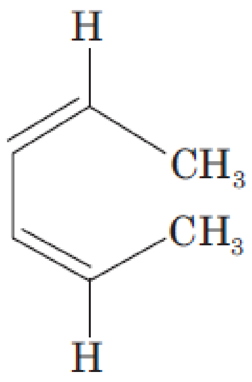
Fig. 3.1 Transition state

There are three major stereochemical features of the Diels-Alder reaction that are controlled by the requirements of the T.S.

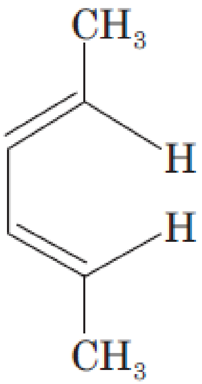
(i) s-cis conformation of the diene
(ii) syn stereochemistry
(iii) Endo and Exo stereochemistry

- When the diene is in the s-trans conformation, the end p-orbitals are too far apart to overlap with the p-orbitals of the dienophile.
- Structural feature that aid or hinder the diene in achieving the s-cis conformation affect its ability to participate in the Diels-Alder reaction

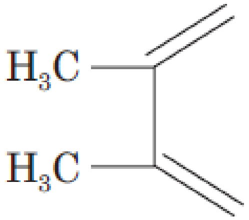
- The diene with functional groups that hinder the s-cis conformation react slower than butadiene.
- Dienes with functional groups that hinder the s-trans conformation react faster than butadiene.



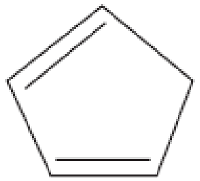
Much slower than butadiene



Similar to butadiene



Faster than butadiene

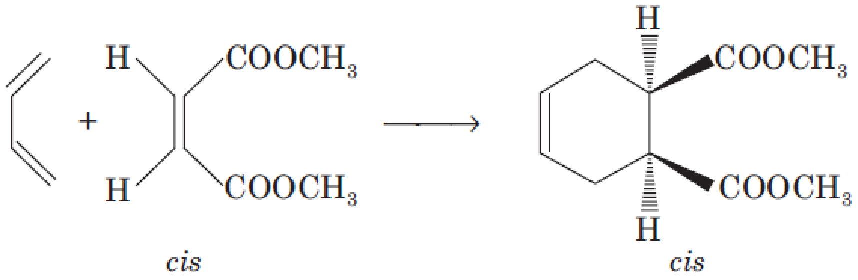


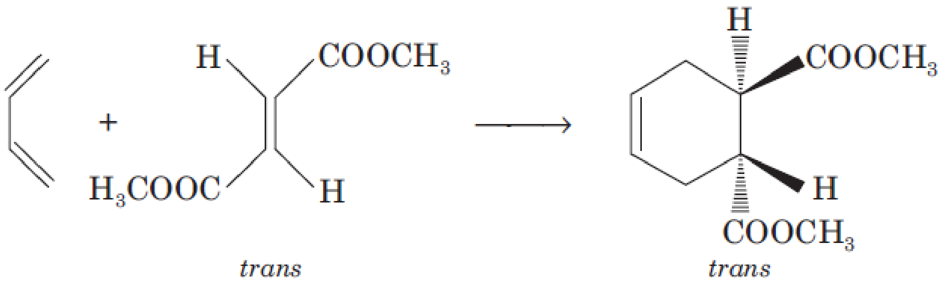
Much faster than butadiene

Syn stereochemistry

- The Diels-Alder reaction is a syn addition with respect to both the diene and dienophile
- There is no opportunity for any of the substituents that are on the same side of the diene or dienophile will be cis on the newly formed ring.

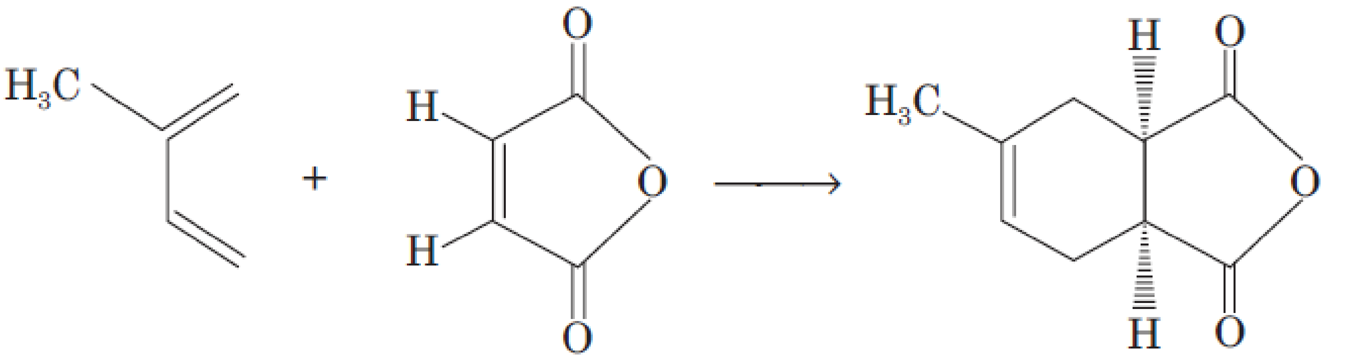
Thus, the stereochemistry of the diene and dienophile are preserved during the adduct formation





The Diels-Alder reaction is stereospecific

Substituents that are cis in the dienophile remain cis in the product; substituents that are trans in the dienophile remain trans in the product



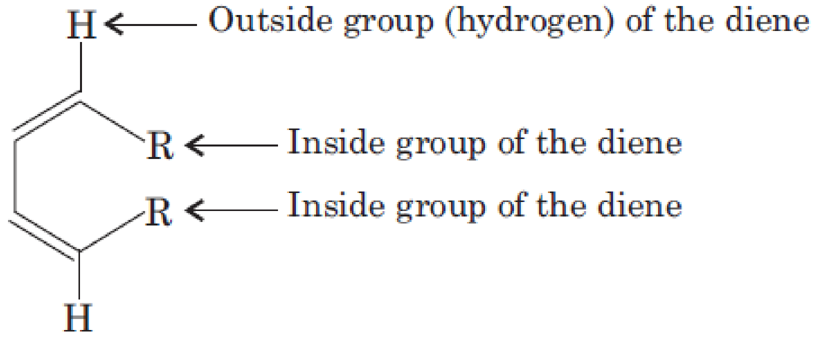
Stereochemistry of the product due to the stereochemistry in the diene: (The product stereochemistry is controlled by the geometry of the diene)

This is slightly more complicated as the diene can be cis, cis; trans, trans or cis, trans.

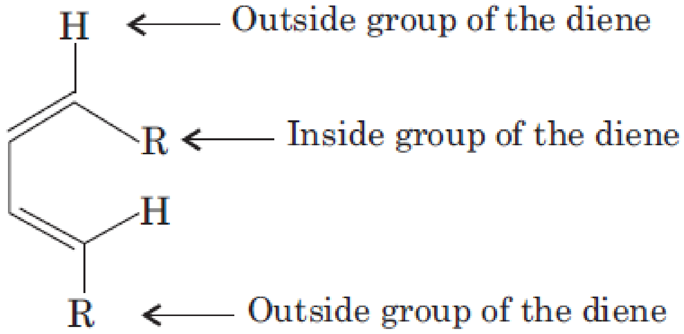
Terminal vinylic carbons (1 and 4 in butadiene) of the s-cis diene contain two substituents.
One is designated as outside group and other is designated as inside group of the diene

Outside groups at C-1 and C-4 are always trans to each other.
Similarly, two inside groups at C-1 and C-4 are cis to each other

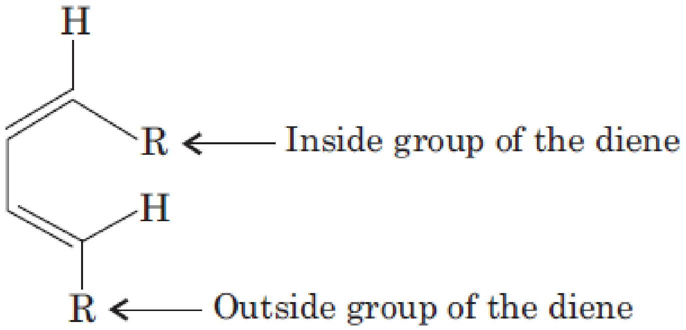
According to the structure of the transition state of the Diels-Alder reaction the outside substituents of the diene are always below the plane of the new six-membered ring of the adduct and inside substituents of the diene should always be above the plane of the new six-membered ring of the adduct..



cis-cis Diene

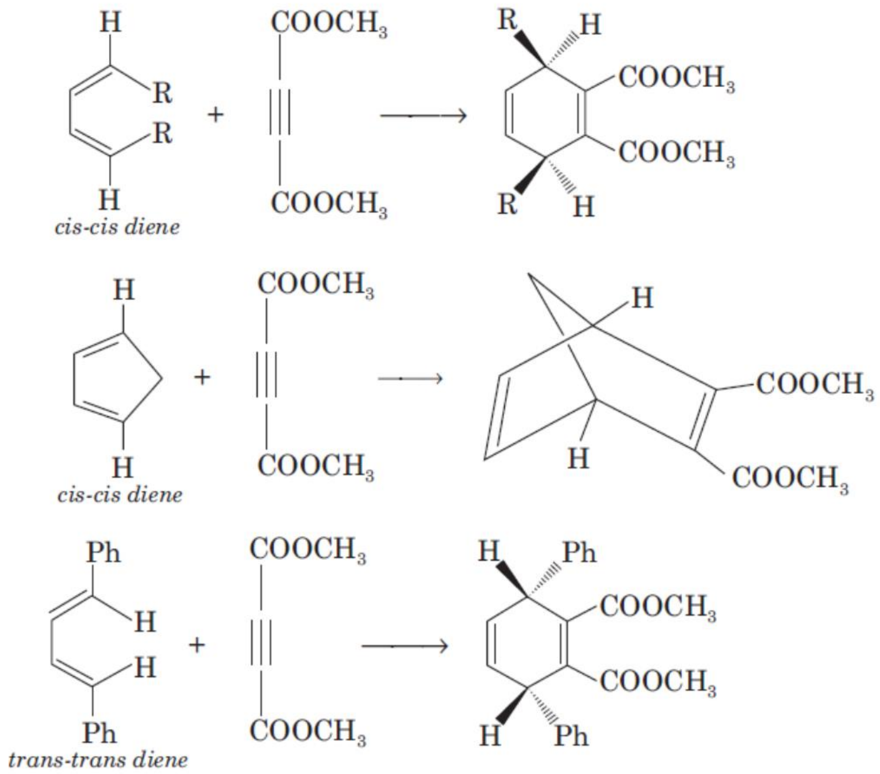


cis-trans Diene

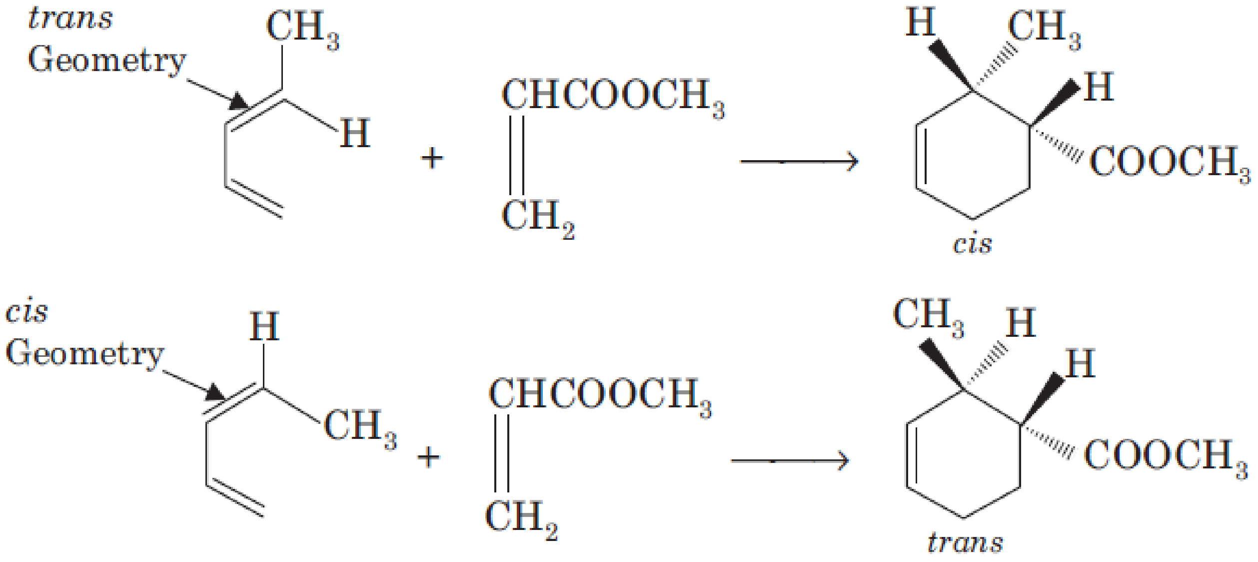


cis-trans Diene

Examples:



If trans 1, 3-pentadiene reacts with methyl propenoate,
in the product the methyl and ester groups
could be either cis or trans.
ie. the cis product is formed from trans diene and the trans product is formed from cis diene.

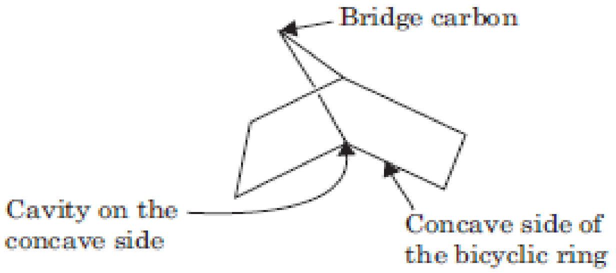


Endo and Exo stereochemistry: The Diels-Alder reaction will produce a bicyclic ring system if the diene is monocyclic.

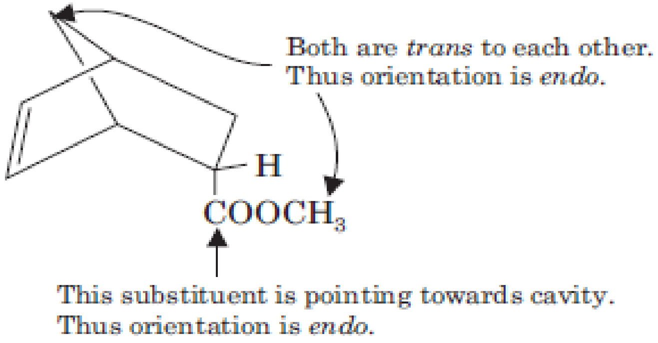
An orientation is said to be **endo** meaning that the substituent is trans to the bridge carbon or substituent projects into the cavity on the concave side of the bicyclic ring.

An orientation is said to be **exo** meaning that the substituent is cis to the bridge carbon or substituent projects out of the cavity on the concave side of the bicyclic ring.

The exo product is expected to be more stable than the endo product for steric reasons. In exo product the exo substituent points away from the more congested part, i.e., bicyclic ring but in endo product the endo substituent points towards the more congested part. Thus steric repulsion in endo is more than the exo.

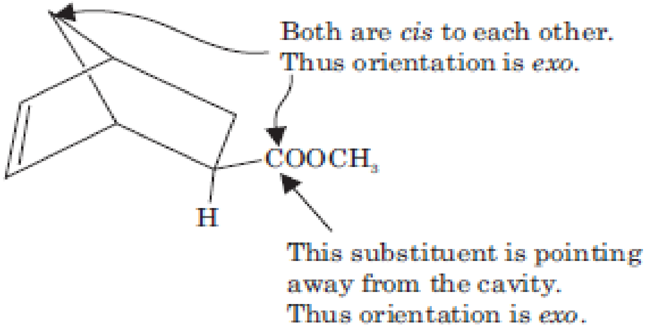


***If the dienophile has a π bond in its electron-withdrawing group then the endo product is more stable than the expected exo product (endo rule)

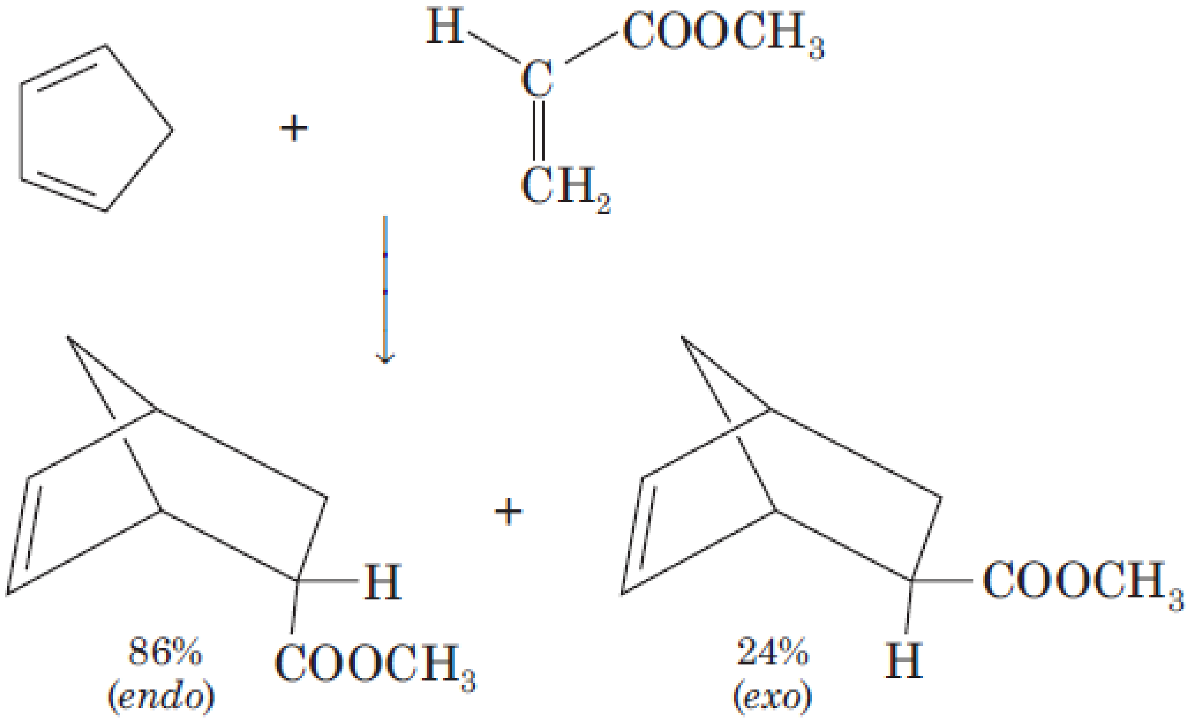


The reaction of 1, 3-butadiene with methyl propenoate produces three times as much as endo as exo product.

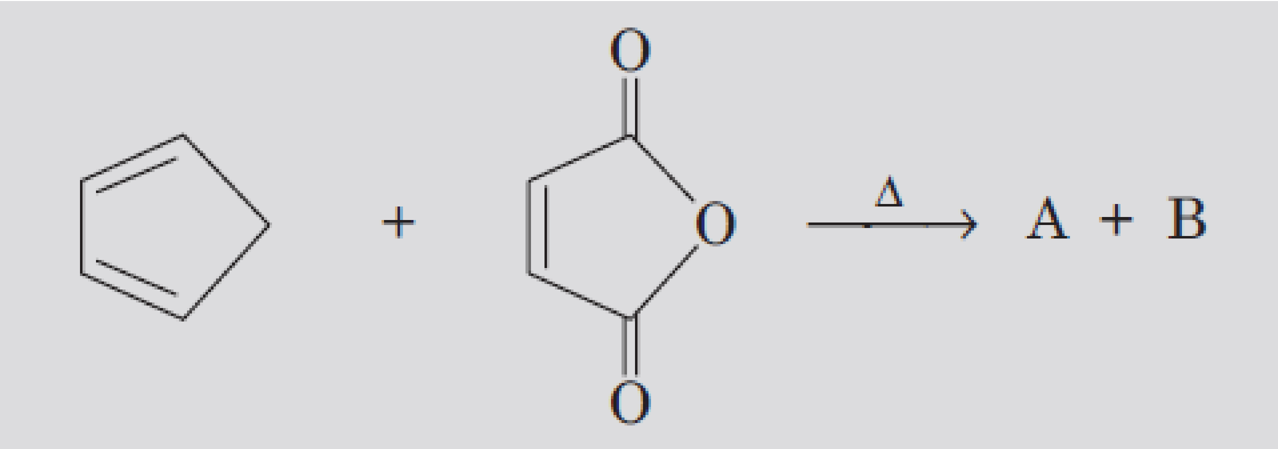
Endo product is major product due to the secondary interactions



Example:



Solve the Problem:
Explain which will be the major product and why?



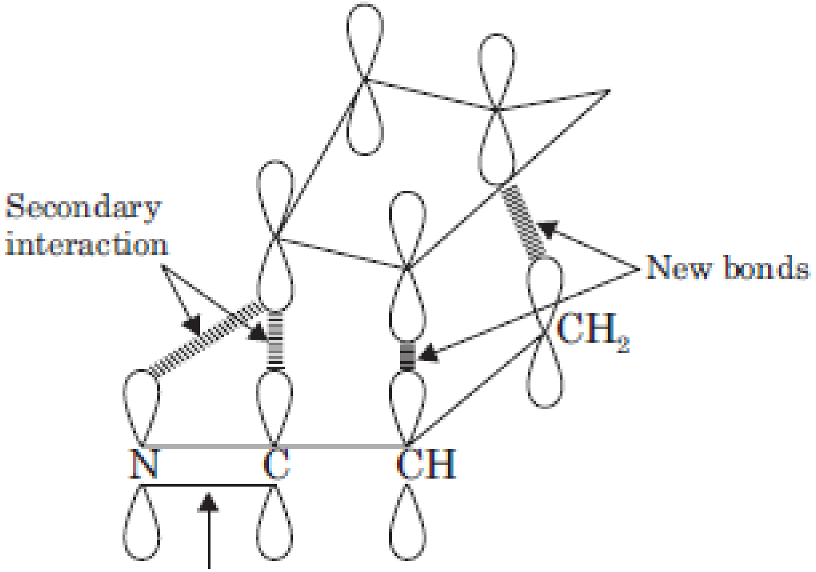
Endo orientation in bicyclic compounds

The exo product is more stable (i.e., it is thermodynamic product) than the endo product (i.e., it is kinetically controlled product) in Diels-Alder reaction

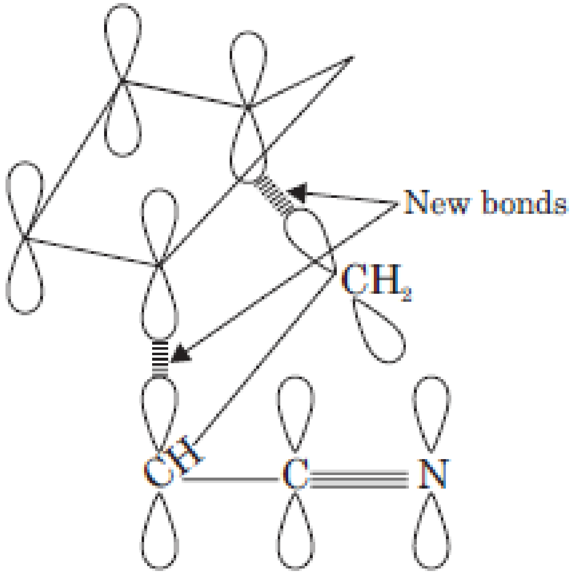
In endo orientation the electron-withdrawing group having a π bond of a dienophile is directed to the inside of the cyclic ring, i.e., electron-withdrawing group is nearer to the conjugated system of diene in the formation of transition state

In this orientation the p-orbital of the electron-withdrawing group approach the central carbon atoms (C-2 and C-3) of the diene. This proximity results in a weak secondary overlap: An overlap of the p-orbitals of the electron-withdrawing group with the p-orbitals of C-2 and C-3 of the diene.

In exo orientation the electron-withdrawing group of the dienophile is directed away from the cyclic diene conjugated system



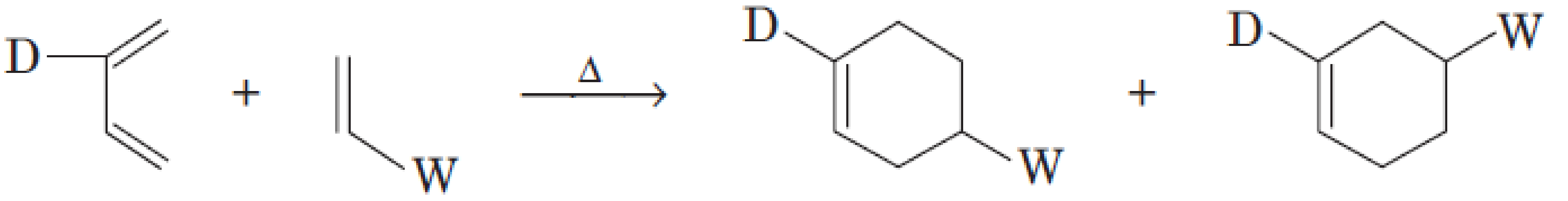
Group is near to the conjugated system of diene *endo* transition state



Exo transition state has no possible secondary interactions

Regioselectivity:

Case I: *When electron-donating group (D) is present on the middle carbon of the diene.*

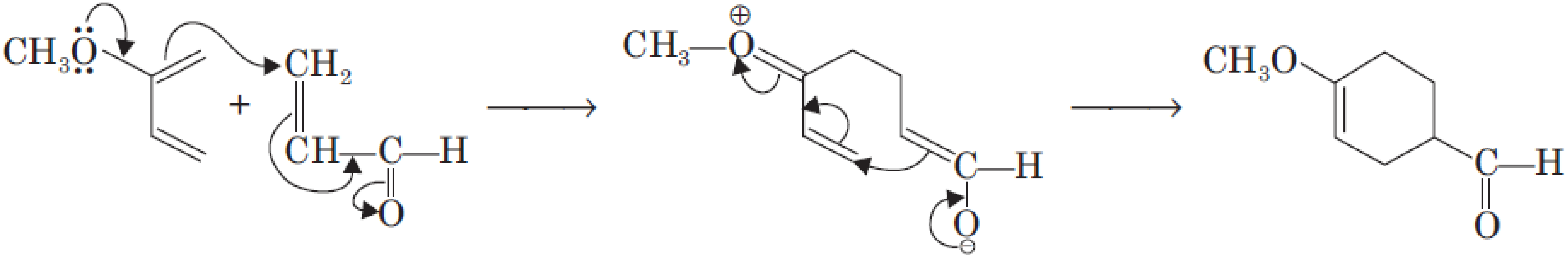


W = electron with-drawing group

1, 4-Product (formed)

1, 3-Product (not formed)

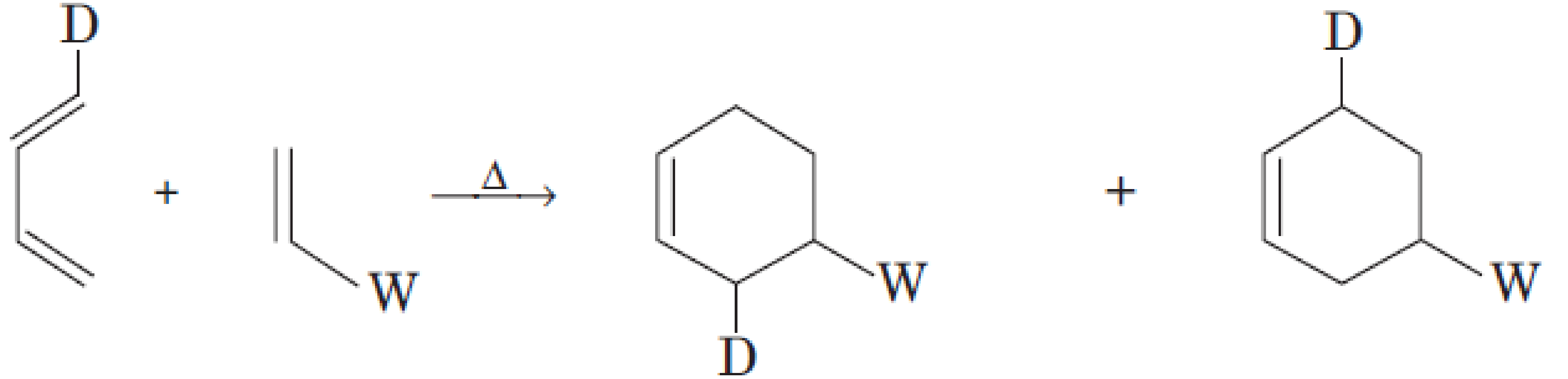
Imaginary flow of electrons in the above case is as follows:



Hypothetical intermediate

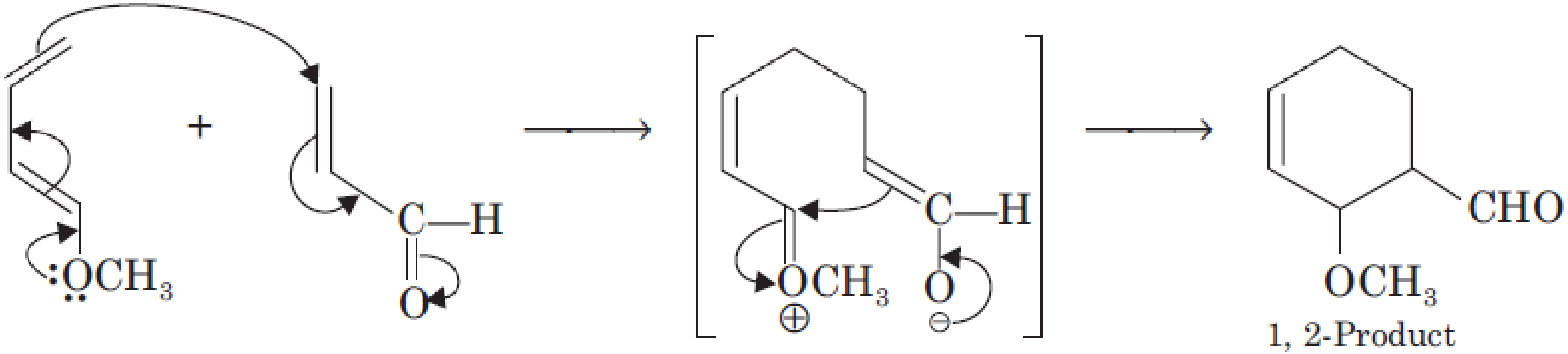
1, 4-Product

Case II: *When an electron-donating group is present at terminal carbon of the diene.*



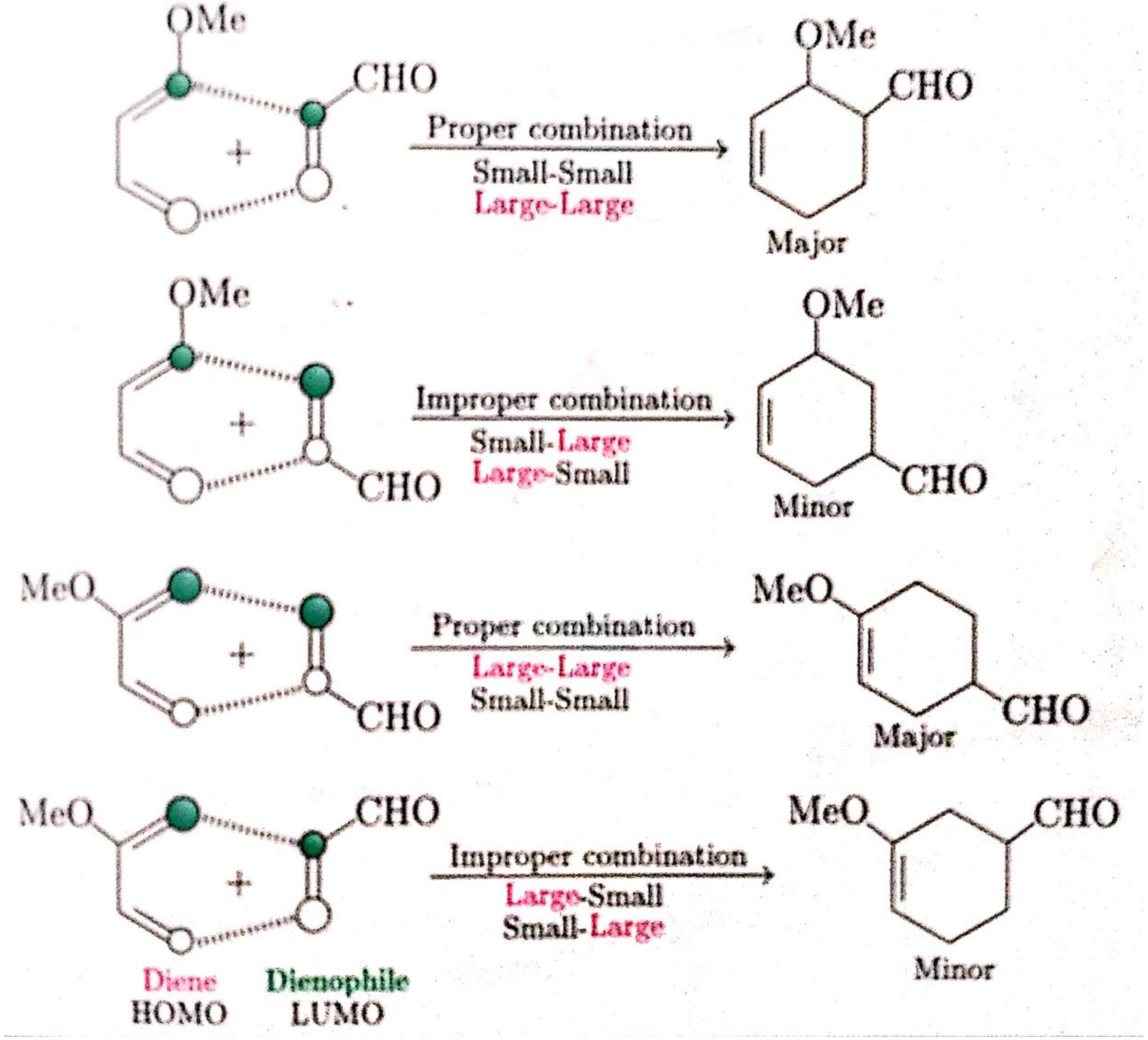
1, 2-Product (formed) 1, 3-Product (not formed)

Imaginary flow of electrons in this case is as follows:

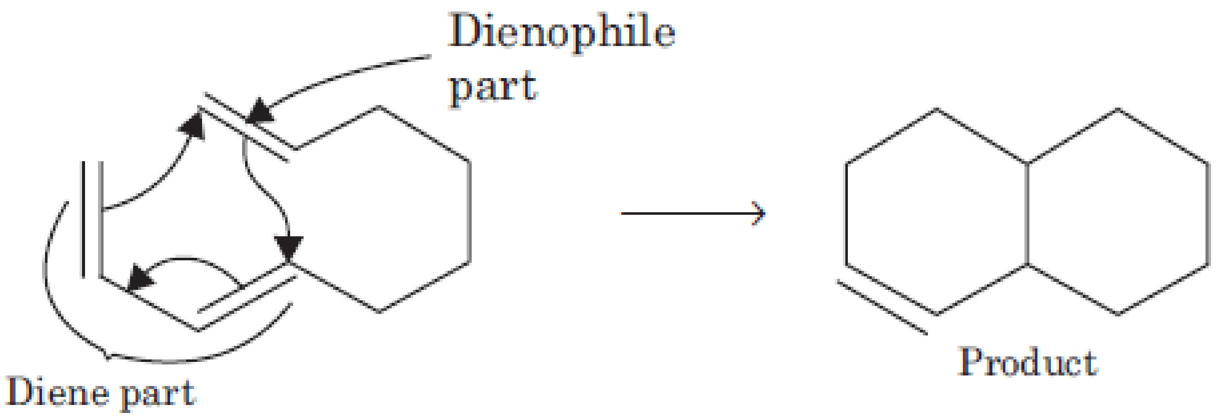


1, 2-Product

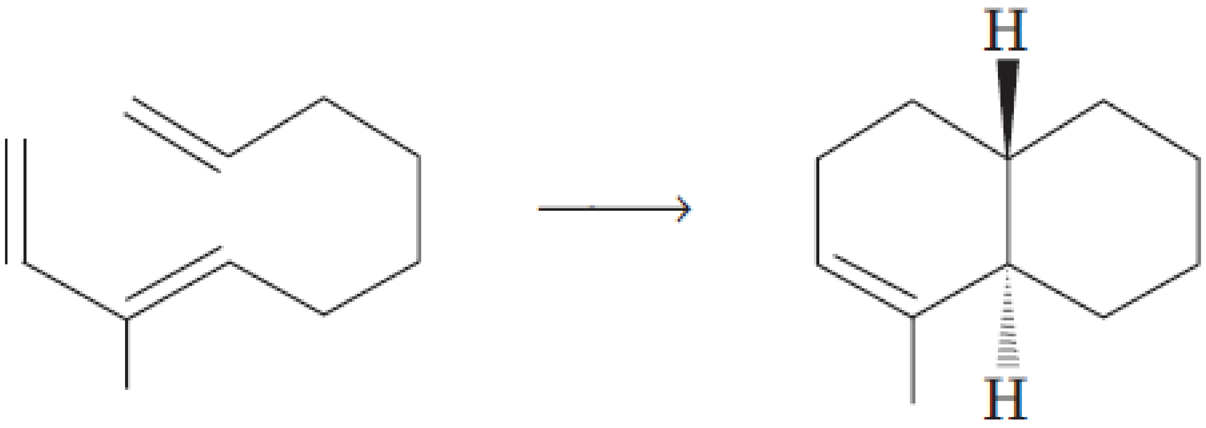
Regioselectivity can be expolained by proper matching of the Frontier orbital Coefficients of diene and dienophile during their in-phase overlap



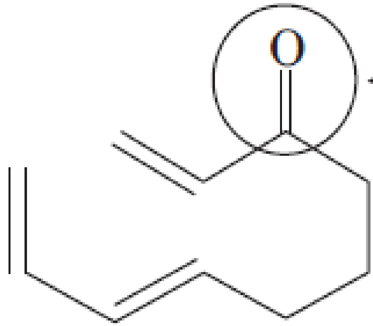
Intramolecular Diels-Alder Reactions



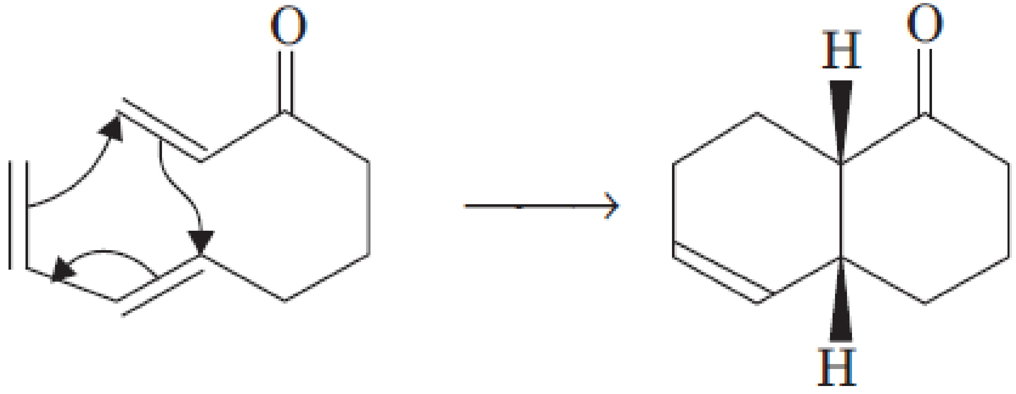
Case I: *When electron-withdrawing group is not present on dienophile*



Case II: *When dienophilic part has electron-withdrawing group which is present on inner carbon of the dienophile*



Electron-withdrawing group is present on the inner carbon of the dienophile



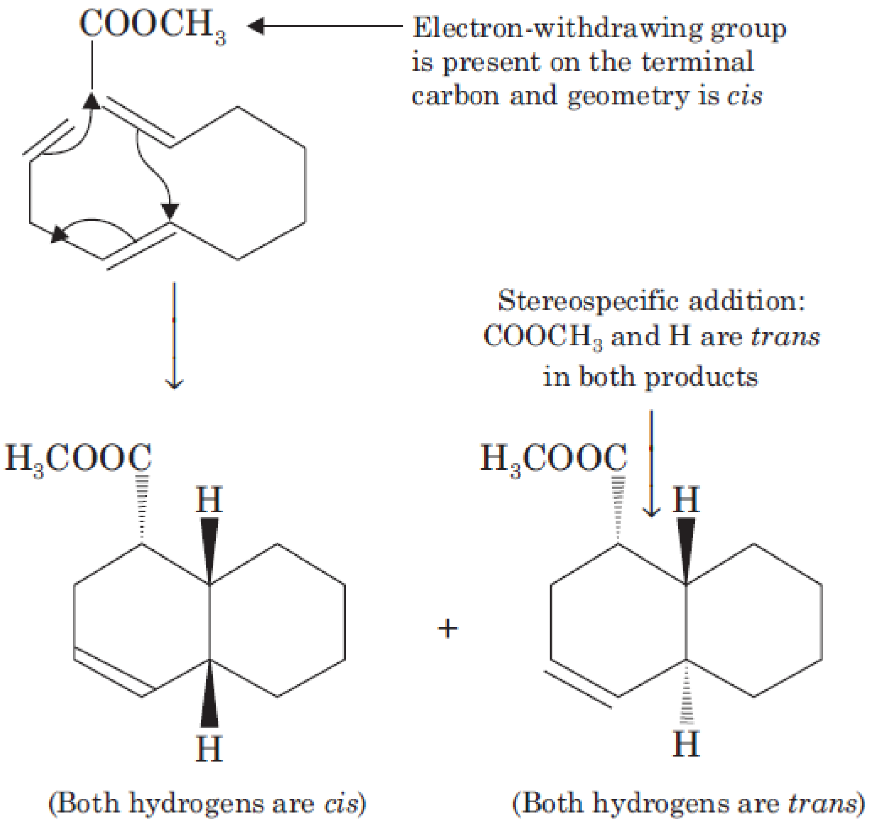
In this case both bridge hydrogens are *cis* to each other and perpendicular to the plane of the ring.

Case III: *When electron-withdrawing group is present on terminal carbon of the diene and geometry is cis*

- In this case a mixture of two products are formed. In one product both hydrogens of the fused ring carbons are cis.
- In other product both hydrogens are trans.

Electron-withdrawing group is always below the plane of the ring and trans to the bridge hydrogen.

Electron-withdrawing group is always below the plane of the ring and cis to adjacent hydrogen of the bridge carbon.



Electron-withdrawing group is present on the terminal carbon and geometry is *cis*

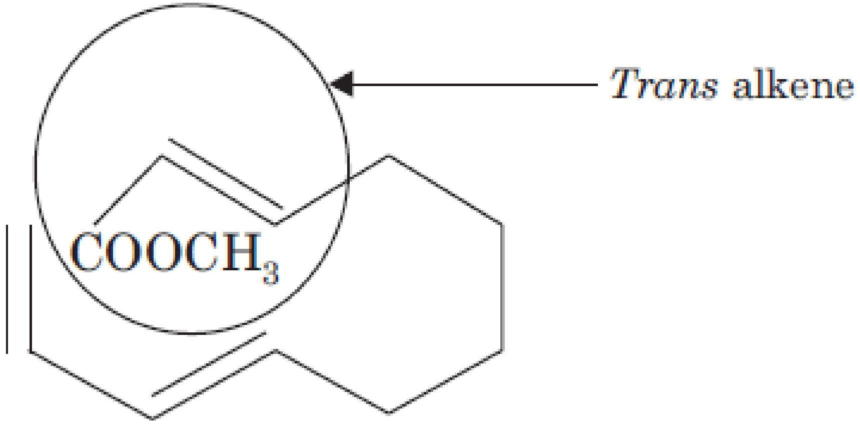
Stereospecific addition: COOCH$_3$ and H are *trans* in both products

(Both hydrogens are *cis*)

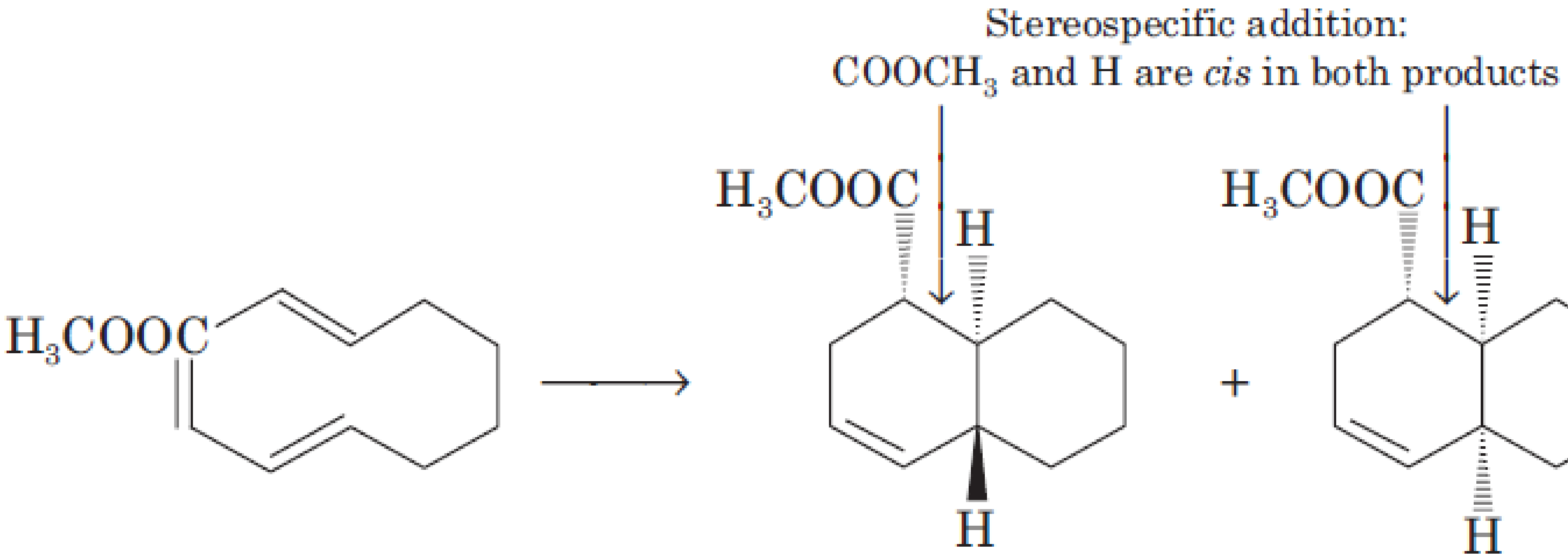
(Both hydrogens are *trans*)

Case IV: When electron-withdrawing group is present on terminal carbon of the dienophile and geometry is trans

In this case also mixture of two products are formed.
In one product both hydrogens of the bridge carbons are cis and in other product both are trans



Trans alkene



Stereospecific addition:
$COOCH_3$ and H are *cis* in both products

Electron-withdrawing group is always below the plane of the ring and cis to adjacent hydrogen of the bridge carbon.

Inverse Electron Demand: In such case a diene having EWG acts as electron acceptor and accordingly its LUMO combines with the HOMO of dienophile having ERG

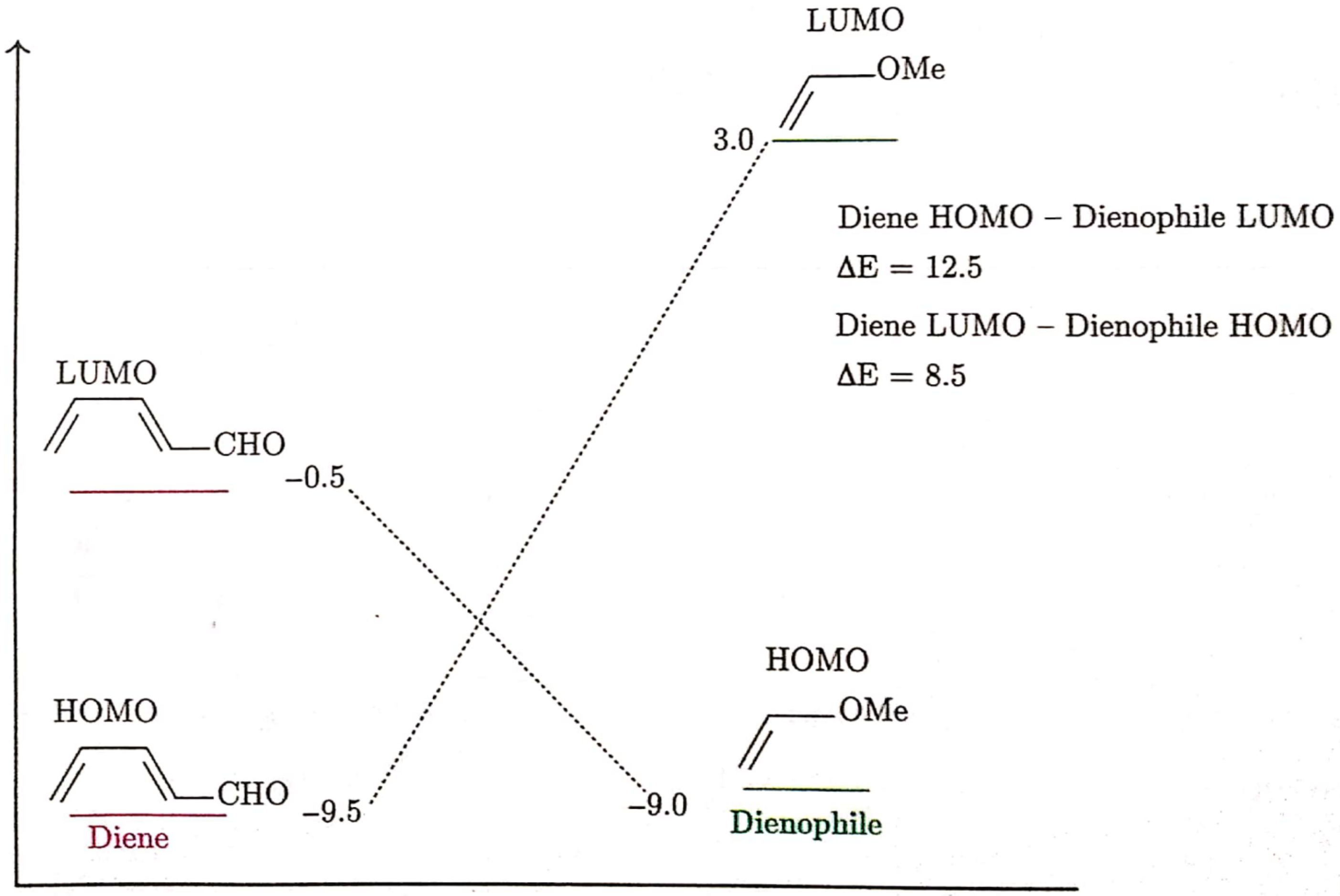
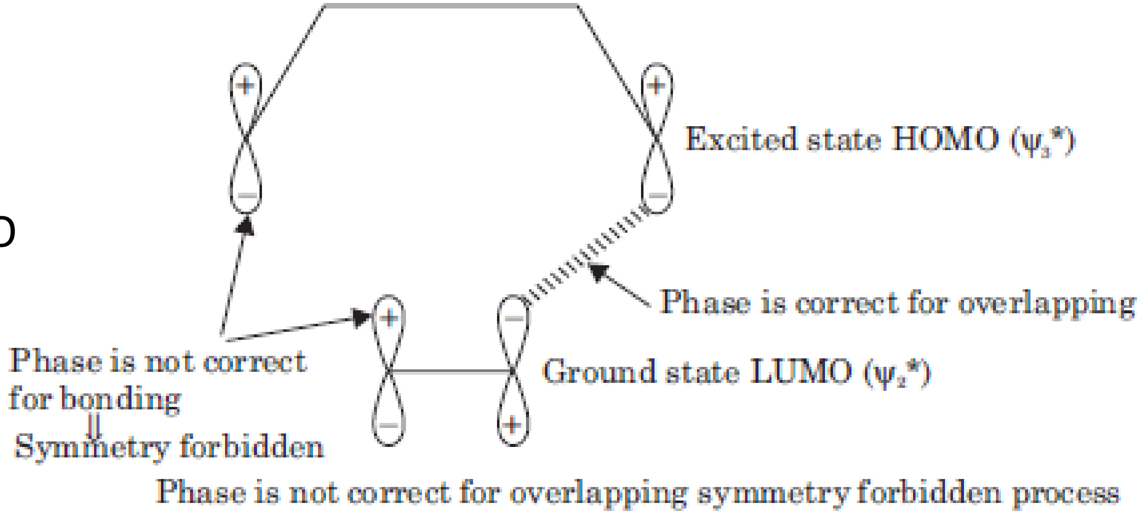


Photo induced reaction: In photo-induced cycloaddition reaction, interaction always takes place between excited state HOMO(HOMO*) of diene and ground state LUMO of dienophile and vice-versa.
Thus, there are two possible interactions.

(i) Excited state HOMO (diene) and ground state LUMO (dienophile), and
(ii) Excited state HOMO (dienophile) and ground state LUMO (diene).

When butadiene is excited by light its HOMO becomes ψ3* which has m-symmetry.
This MO cannot overlap with ground state LUMO of the ethylene which has C2-symmetry

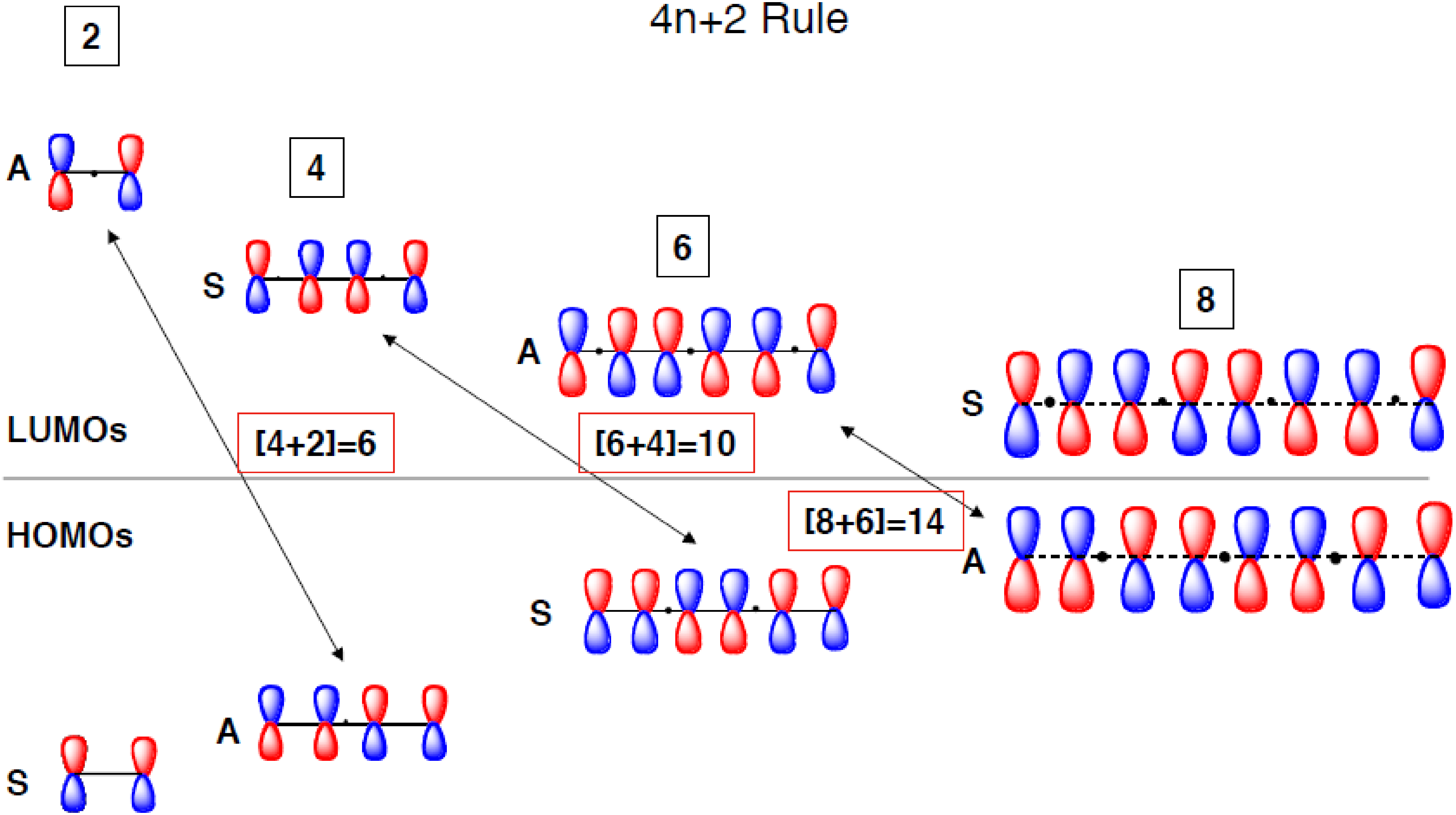


Thus, photochemical cycloaddition of [4 + 2] system is symmetry forbidden reaction.

Selection rule:

Number of electrons	*Mode of activation*	*Allowed stereochemistry*
$(4n)\pi$	Photochemical	Supra-Supra
$(4n + 2)\pi$	Thermal	Supra-Supra

Thermally Allowed Cycloadditions
4n+2 Rule



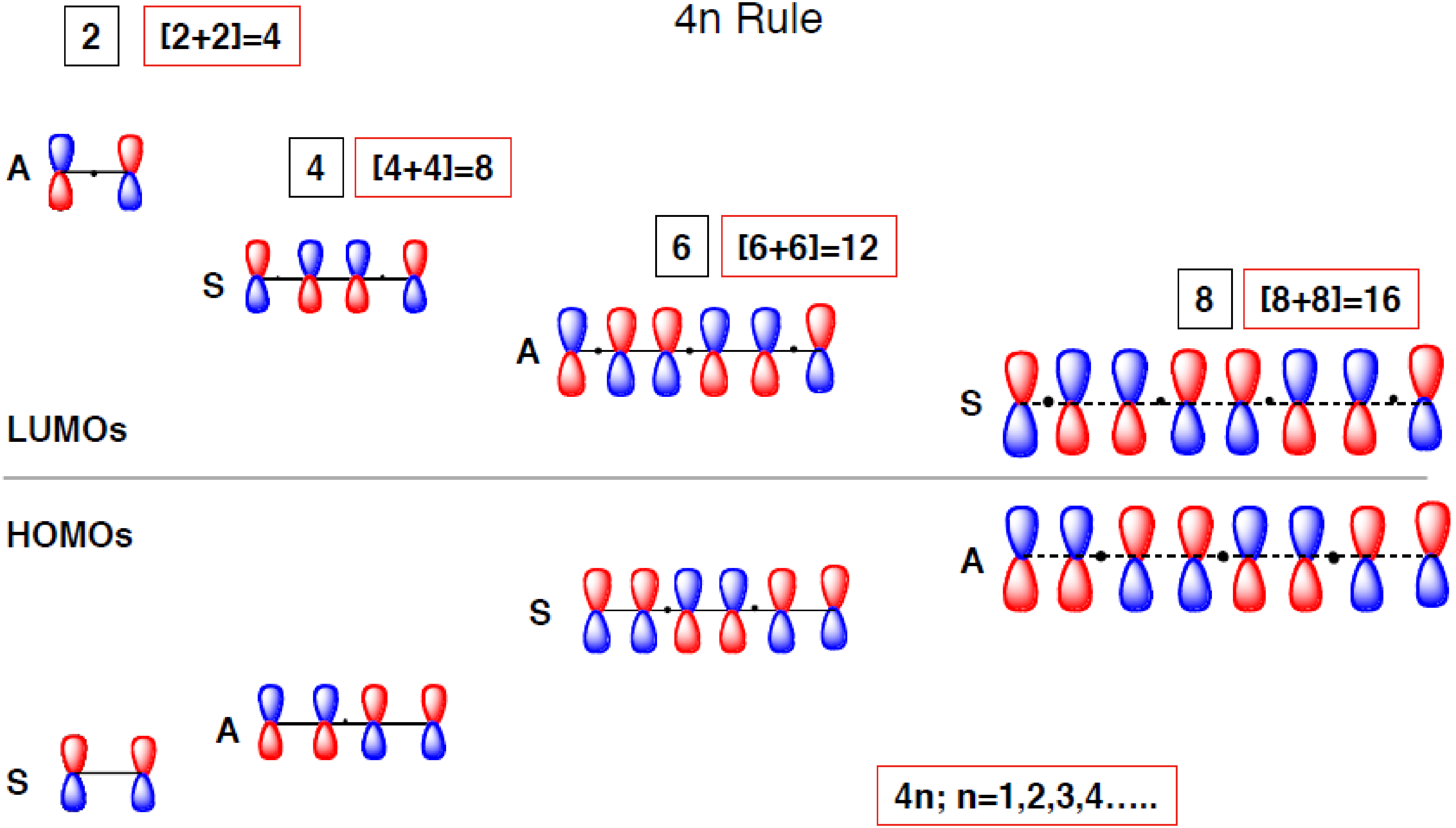
[4+2]=6

[6+4]=10

[8+6]=14

4n+2; n=1,2,3,4…..

Photochemically Allowed Cycloadditions
4n Rule



2 [2+2]=4

4 [4+4]=8

6 [6+6]=12

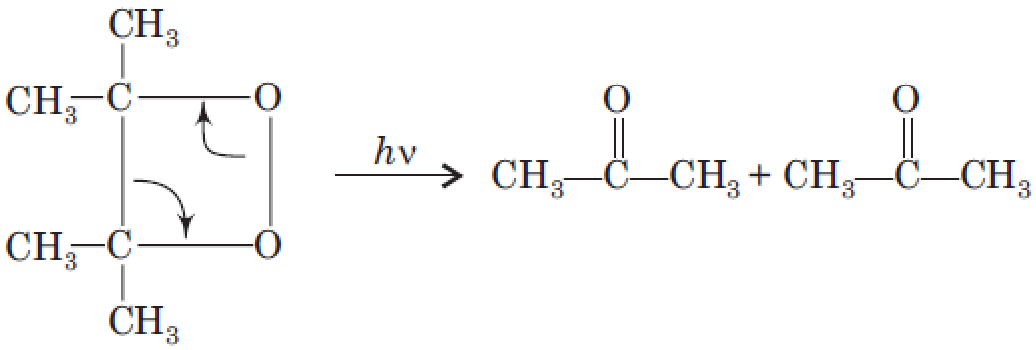
8 [8+8]=16

4n; n=1,2,3,4…..

and [2+6]=8; [8+4]=12

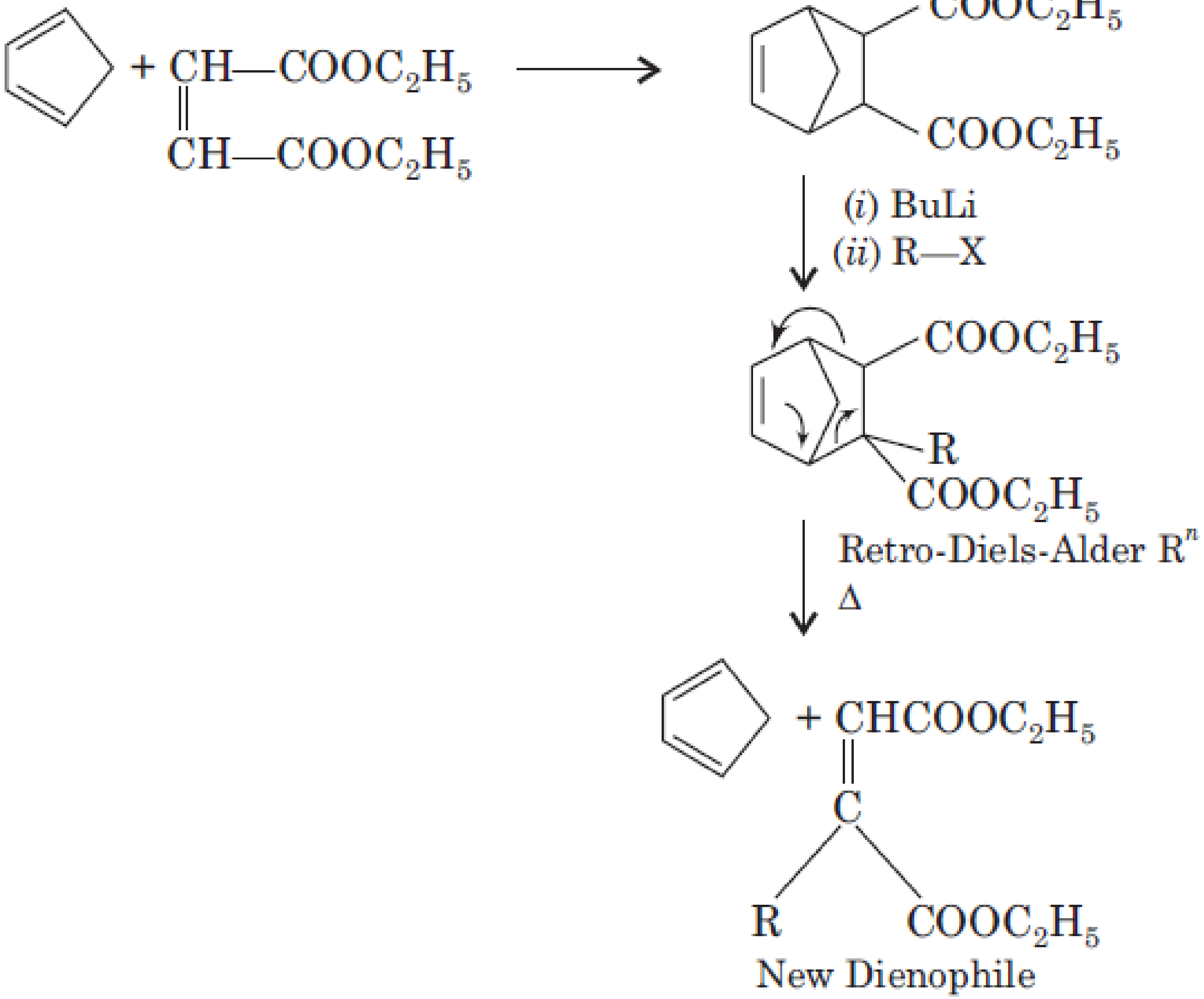
cycloreversions

The reverse of cycloaddition reactions are known as **cycloreversions** or retrograde cycloadditions. Such reactions follow same symmetry selection rules as does the cycloaddition itself.

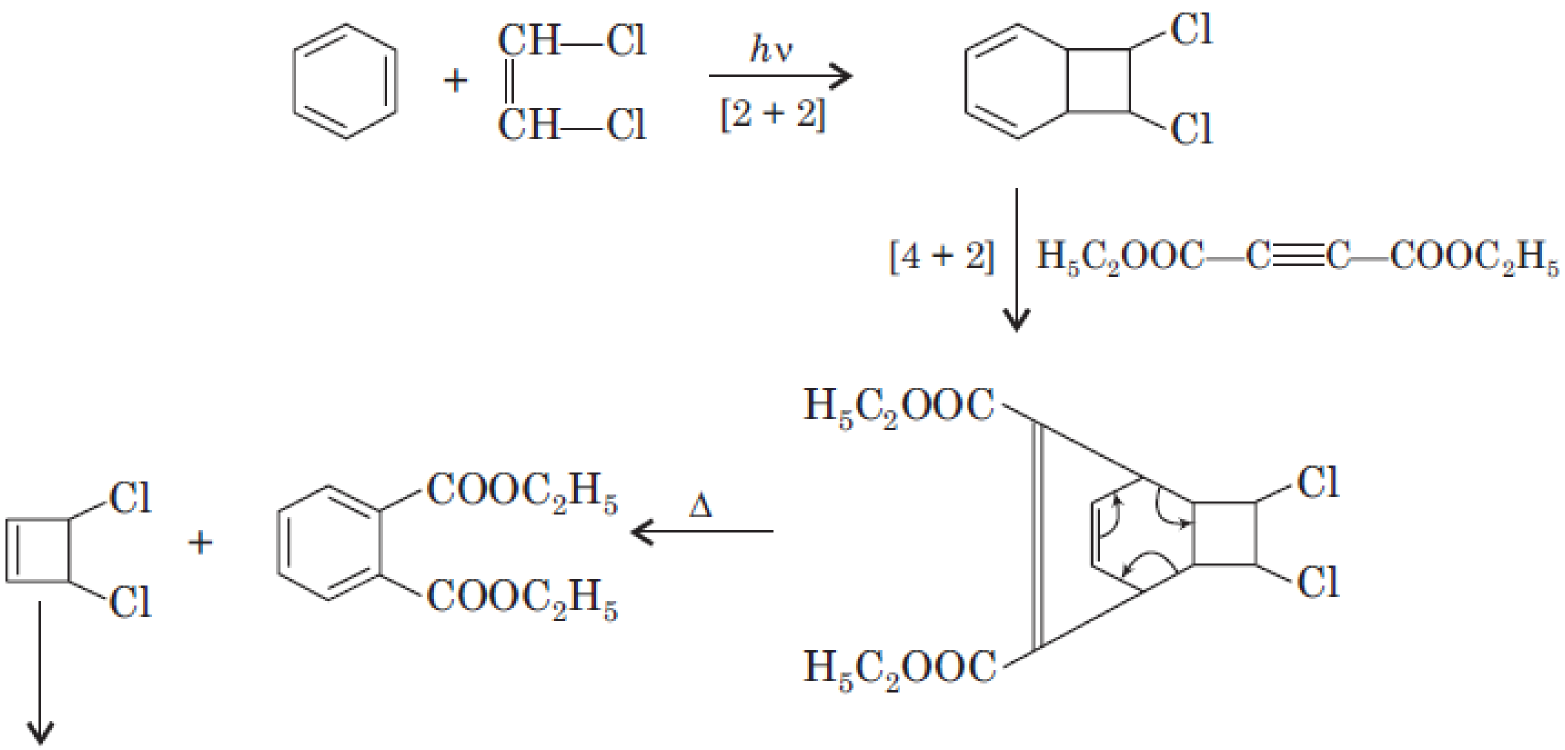


- This reaction is represented as –[2 + 2] cycloreversion. A minus sign before the designation indicates a cycloreversion reaction.
- The most common cycloreversion reaction is – [4 + 2] cyclo reversion. This reaction is commonly known as **retro-Diels-Alder reaction.**

Diels-Alder reaction is reversible, and on heating many adducts dissociate into their components. In most of the cases retro-Diels-Alder reactions take place under quite mild conditions. Retro-Diels-Alder reaction is very important in those cases where adduct obtained in Diels-Alder reaction is chemically modified and than give new diene or dienophile by retro-Diels-Alder reaction.



Retro-Diels-Alder reaction can also be used for the preparation of some reactive compounds in vapour phase (in the absence of solvent and catalyst) that are difficult to prepare by other methods.



This compound is highly reactive and used as synthetic reagent for the preparation of various compounds