

INTRODUCTION TO CHEMISTRY

CML-101



Dr. Chinmoy K. Hazra
Department of Chemistry
IIT Delhi

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Syllabus

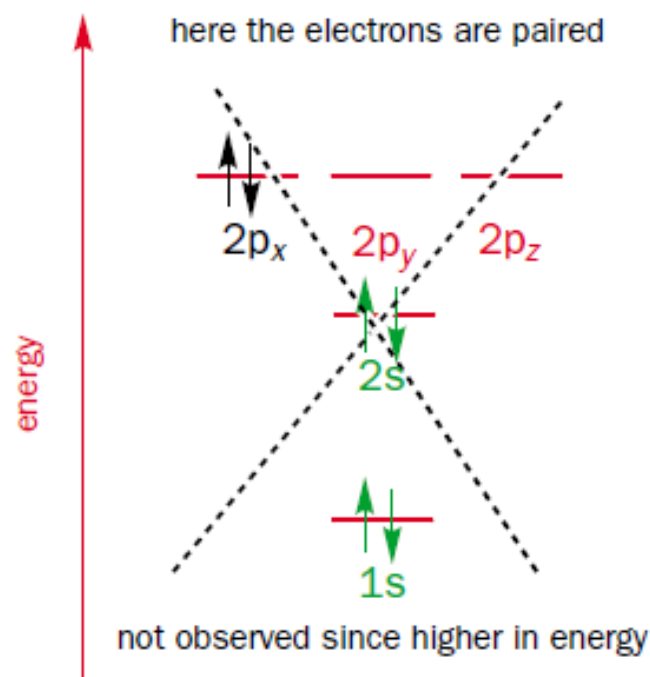
Importance of stereochemistry in drug action (warfarin, thalidomide, naproxen); R/S nomenclature, Fisher, Sawhorse, and Newmann projections

Kinetic versus thermodynamic control: selected examples using MO theory (DAR, 1,3-butadiene addition, enolate alkylation, naphthalene sulfonation)

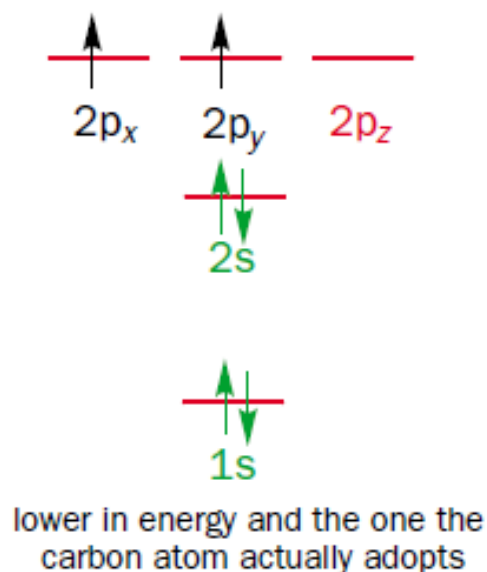
Determination of reaction mechanism: kinetic methods, isotope effects, intermediate trapping, the stereochemical outcome in reactions (NGP and elimination reaction)

Spectroscopic methods of structure determination

Putting electrons in orbitals



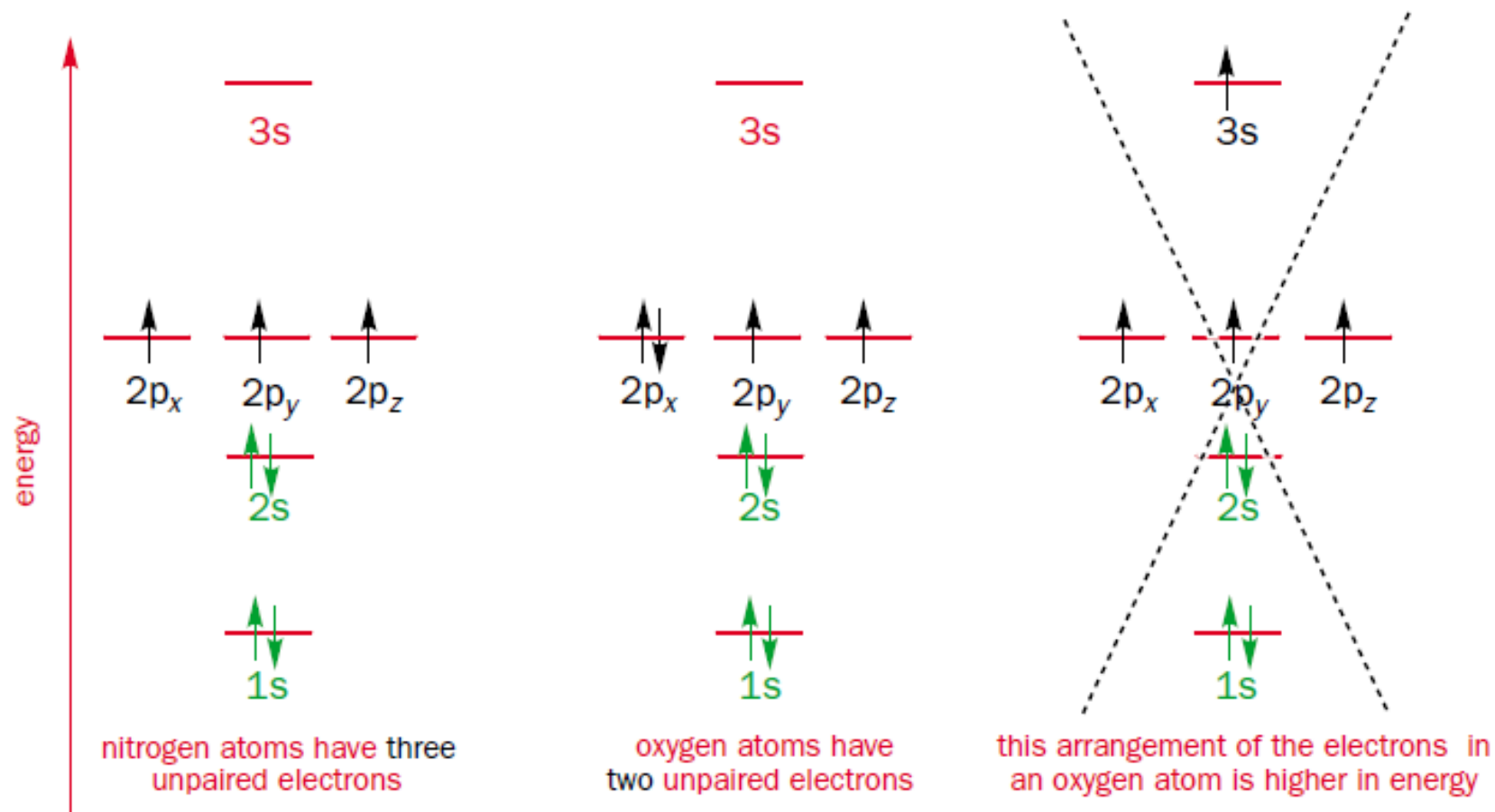
here the electrons are in different degenerate 2p orbitals with their spins parallel



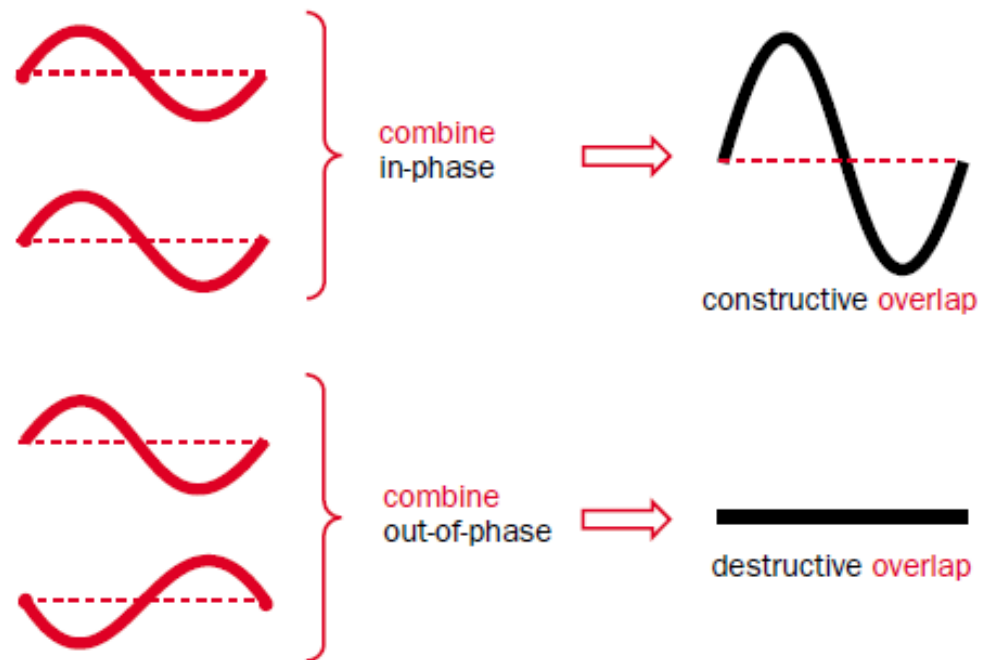
the two possible arrangements for the electrons in a carbon atom

This is known as **Hund's rule**. An atom adopts the electronic configuration that has the greatest number of unpaired electrons in degenerate orbitals. Whilst this is all a bit theoretical in that isolated atoms are not found very often, the same rule applies for electrons in degenerate orbitals in molecules.

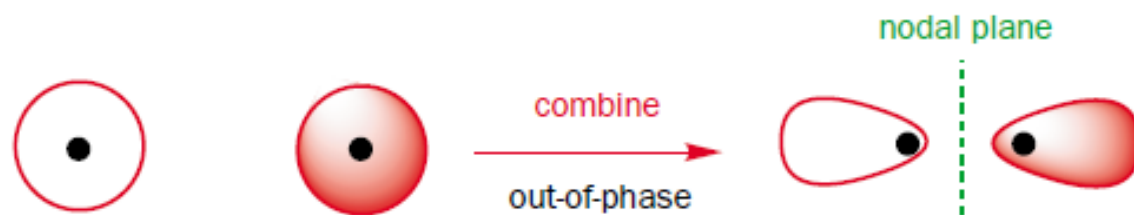
Molecular Orbital-homonuclear Diatomics



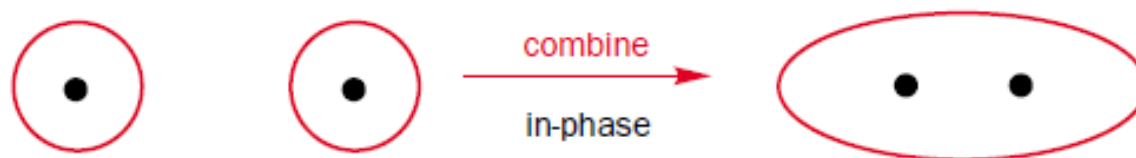
Molecular Orbital-homonuclear Diatomics



the two ways of combining a simple wave – in-phase and out-of-phase

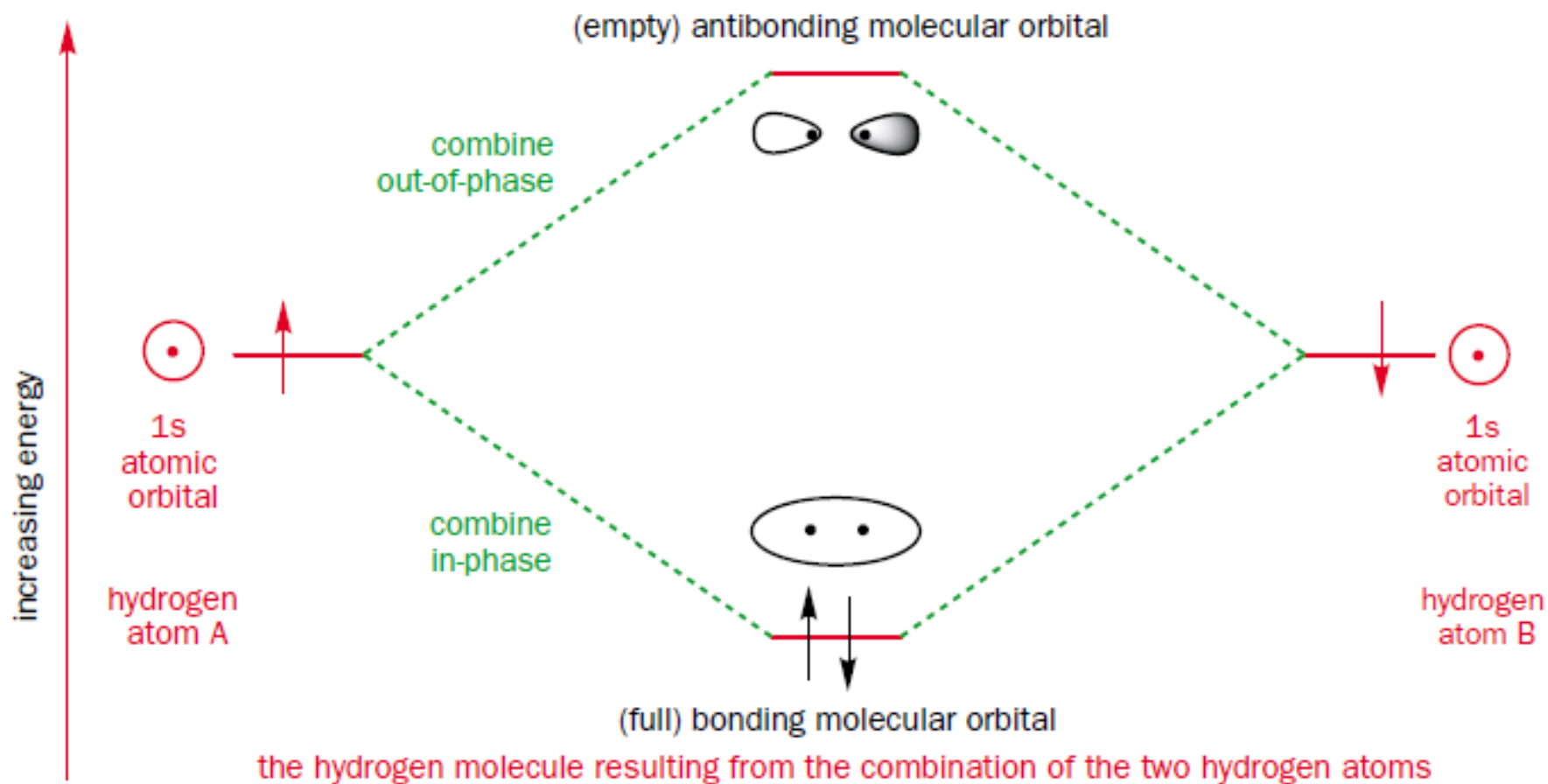


the two 1s orbitals combining out-of-phase to give an **antibonding orbital**

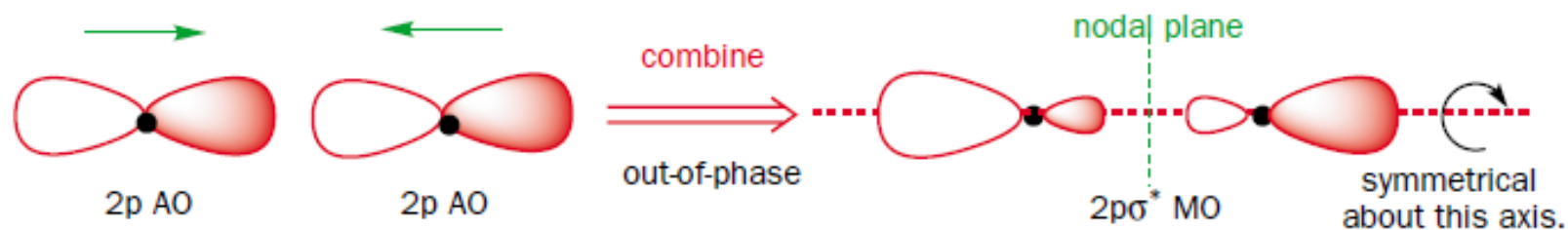


the two 1s orbitals combining in-phase to give a **bonding orbital**

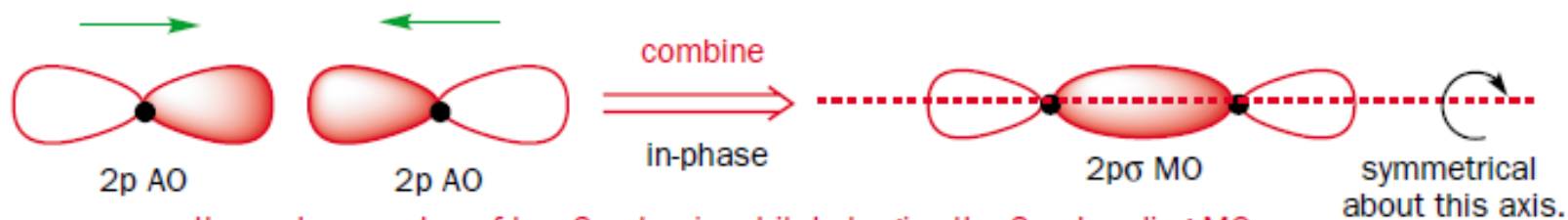
Molecular Orbital-homonuclear Diatomics



Molecular Orbital-homonuclear Diatomics

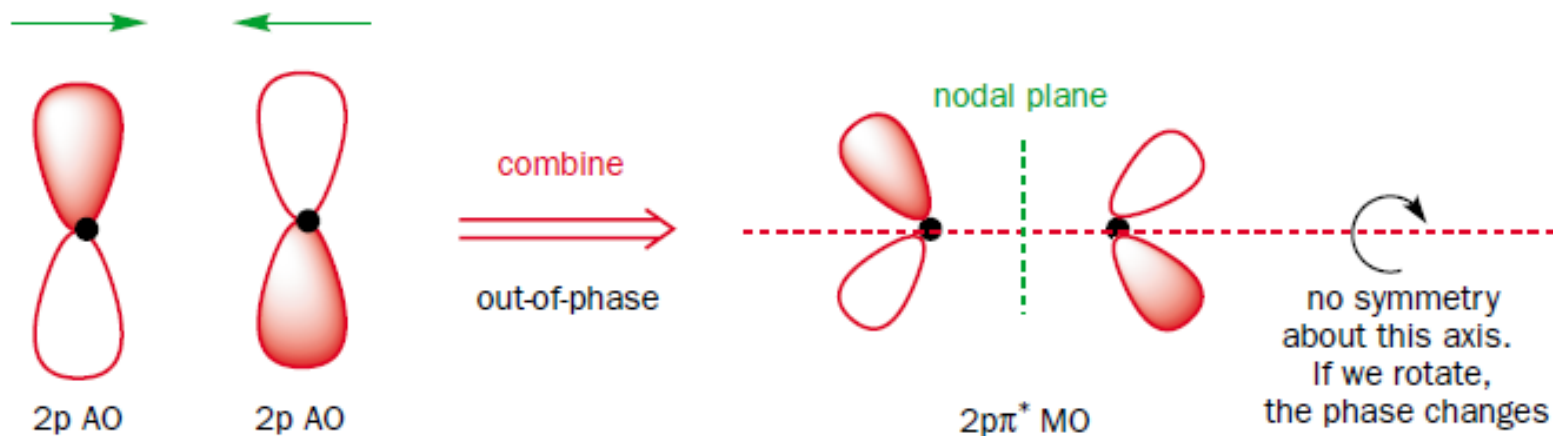


the end-on overlap of two $2p$ atomic orbitals to give the $2p\sigma^*$ antibonding MO

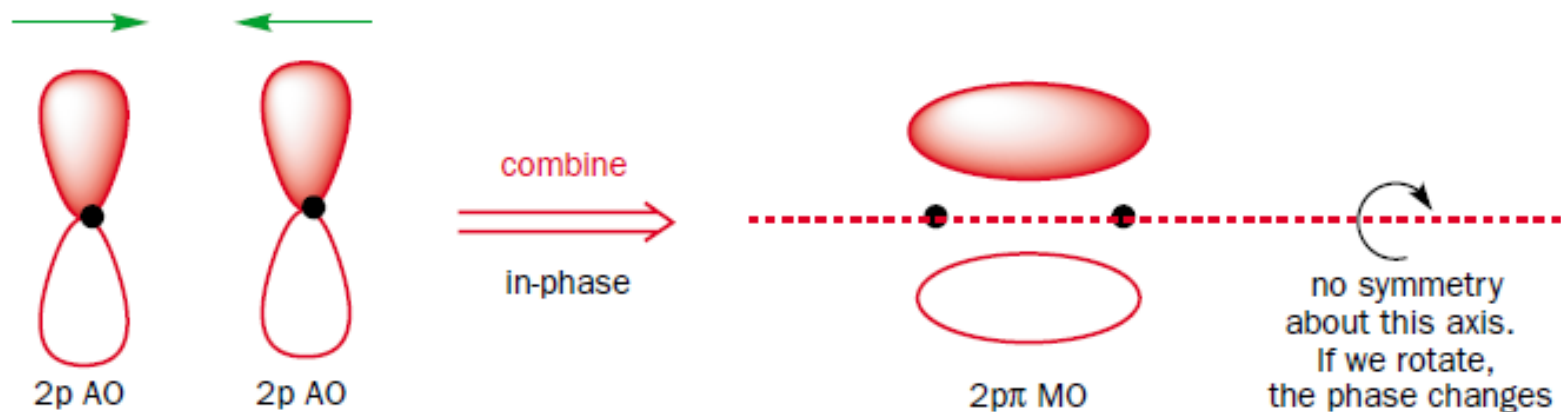


the end-on overlap of two $2p$ atomic orbitals to give the $2p\sigma$ bonding MO

Molecular Orbital-homonuclear Diatomics



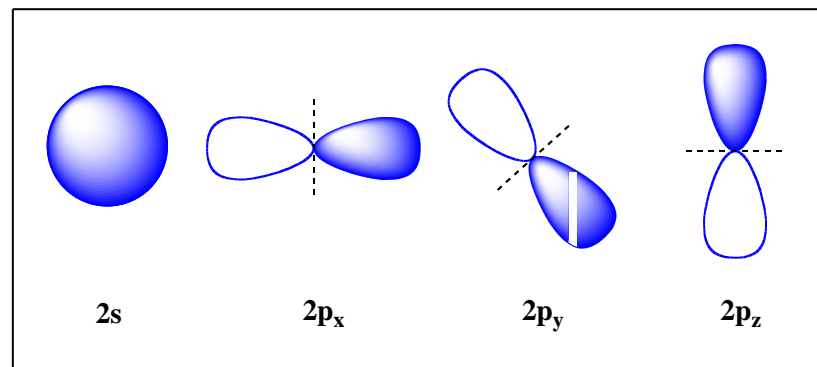
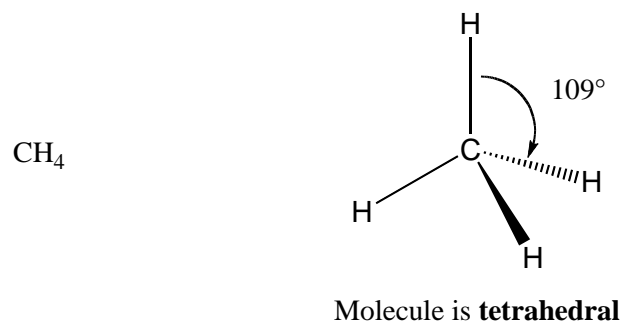
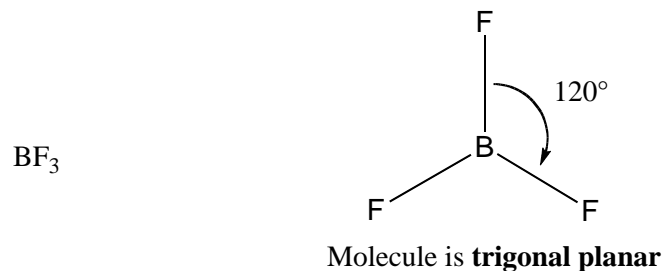
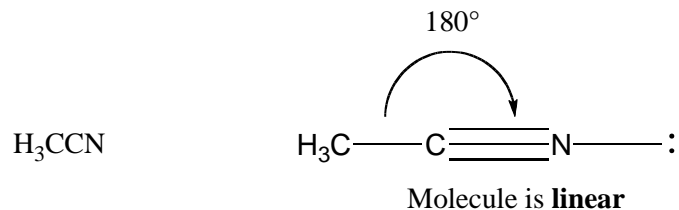
the side-on overlap of two $2p$ atomic orbitals to give the $2p\pi^*$ antibonding MO



the side-on overlap of two $2p$ atomic orbitals to give the $2p\pi$ bonding MO

3-Dimensional Structure

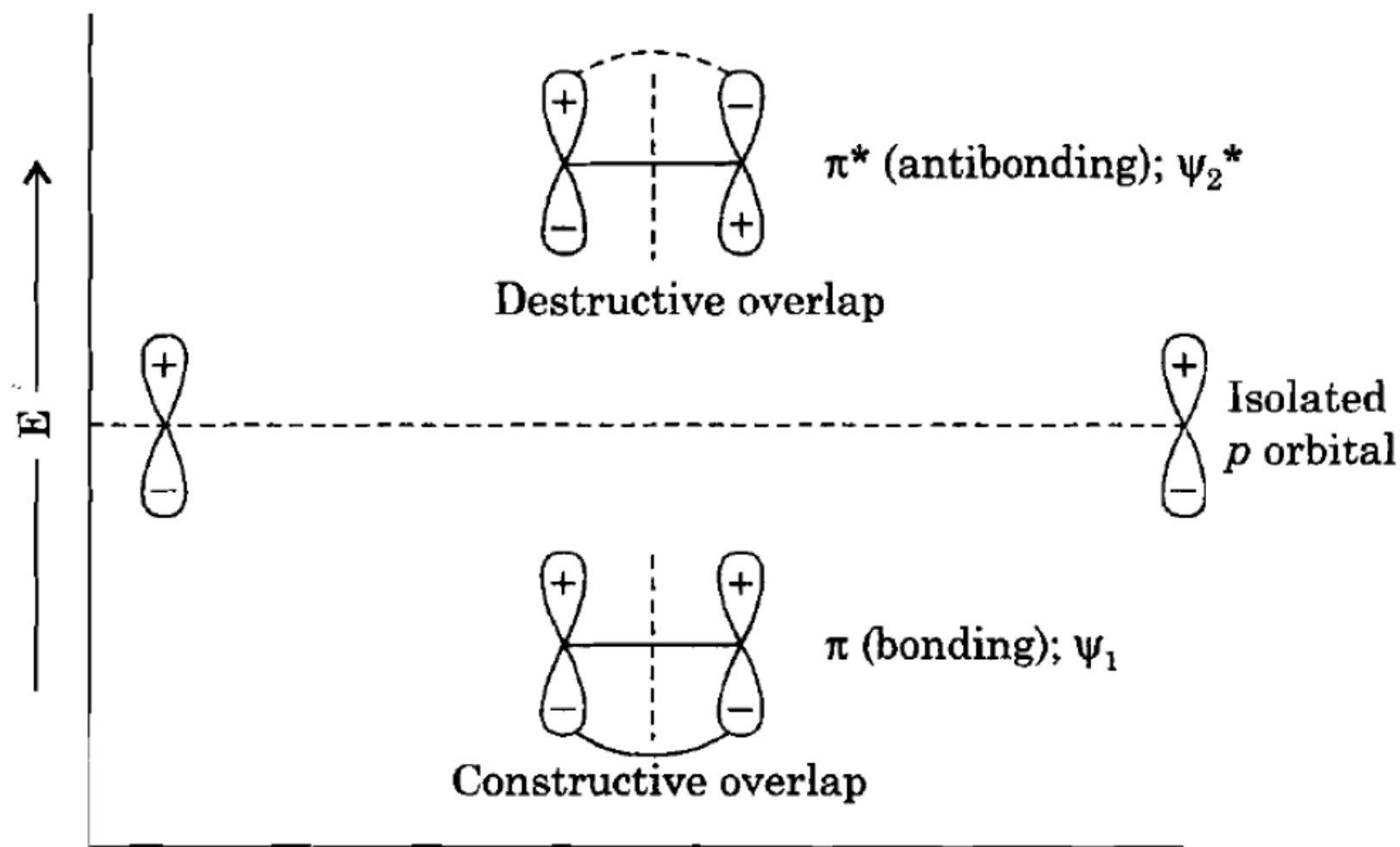
Place substituents as far apart as possible:



2nd row valence orbitals

How can these molecular shapes arise from bonding between the available orbitals?

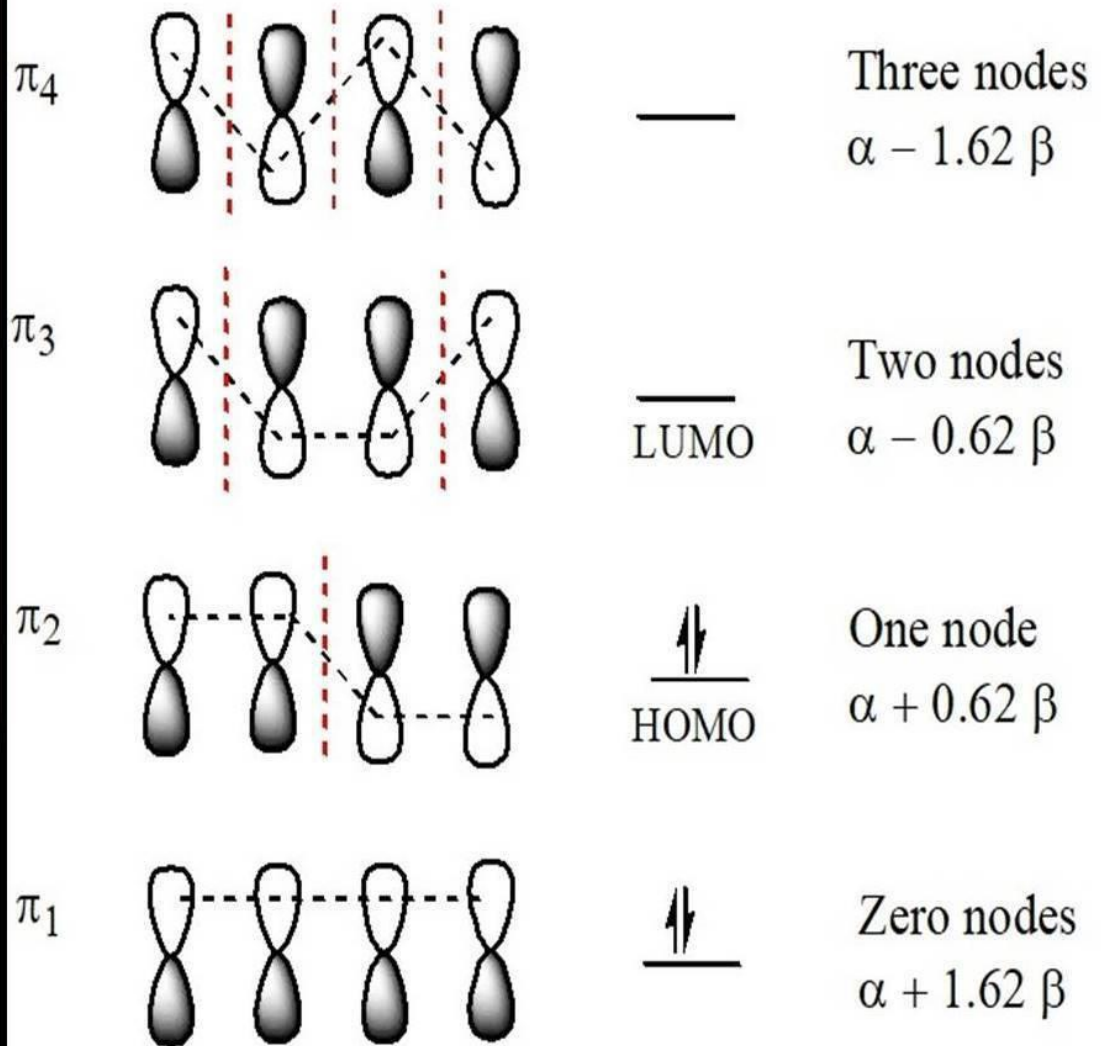
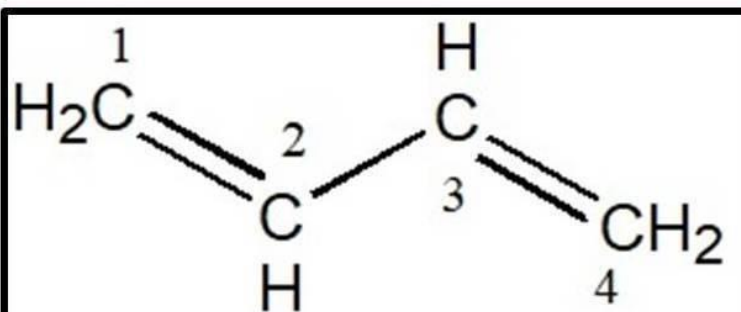
A Molecular Orbital Description



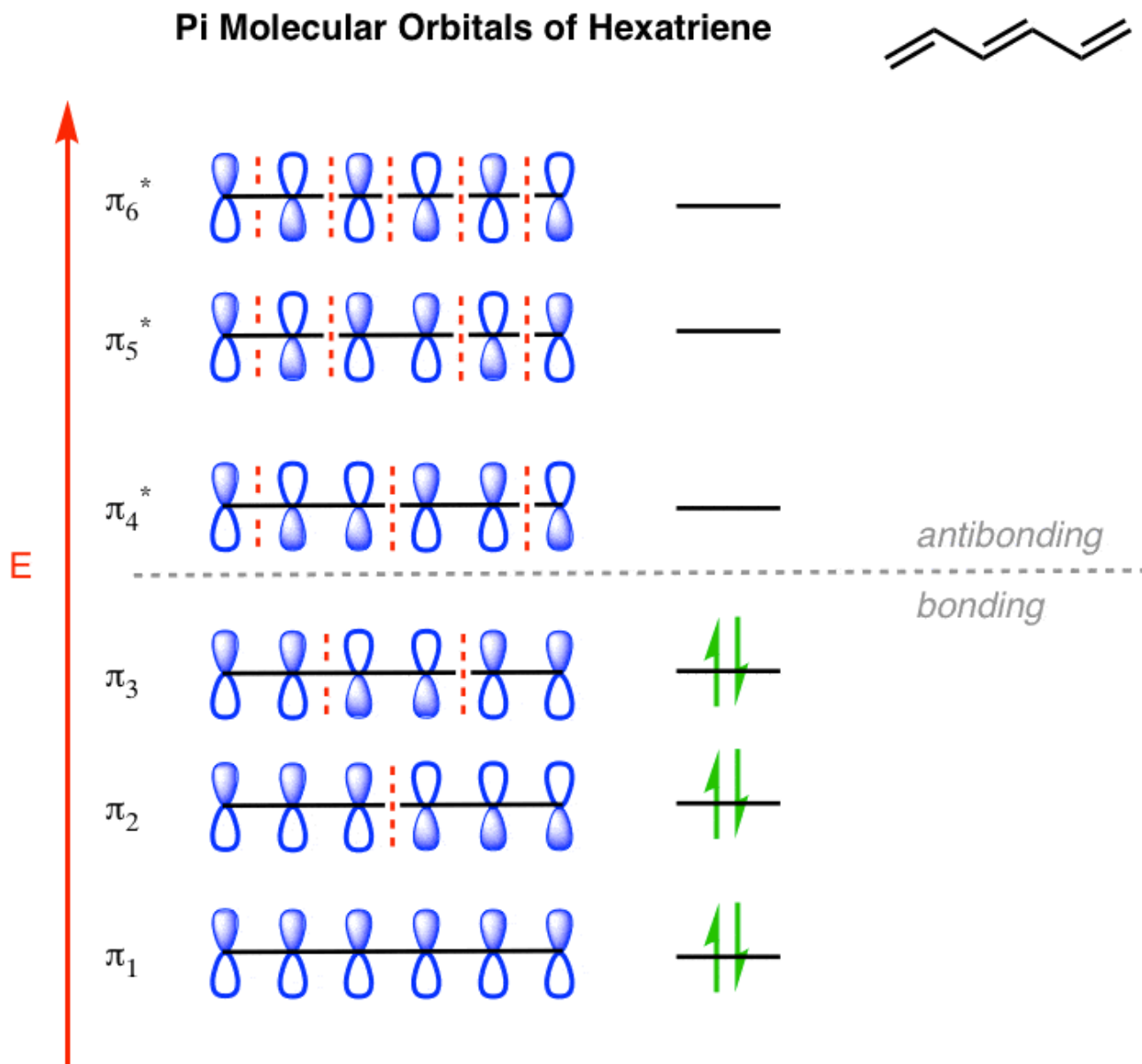
The combination of two p orbitals results in the formation of two molecular orbitals

A Molecular Orbital Description of 1,3-Butadiene

π molecular orbitals of 1,3-butadiene and the delocalization of π bonds



A Molecular Orbital Description of 1,3,5-hexa-triene



Pericyclic reaction

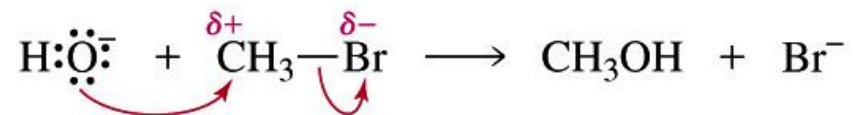
Pericyclic reactions and Woodward-Hoffmann rules for concerted cycloadditions, electrocyclizations and sigmatropic rearrangements. FMO theory.

Concerted cyclic transition state of breaking and forming bonds no electrophiles, nucleophiles, or radicals very stereospecific energy supplied by heat, Δ , thermolysis or pyrolysis or light, $h\nu$, photolysis.

Name	Bond changes	
	<u>Sigma</u>	<u>Pi</u>
<u>Electrocyclic reaction</u>	+ 1	- 1
<u>Cycloaddition (and cycloreversion)</u>	+ 2	- 2
<u>Sigmatropic reaction</u>	0	0
<u>Group transfer reaction</u>	0	0
<u>Ene reaction</u>	+ 1	- 1
<u>Cheletropic reaction</u>	+ 2	- 1
<u>Dyotropic reaction</u>	0	0

Reactions of Organic Compounds

a polar reaction



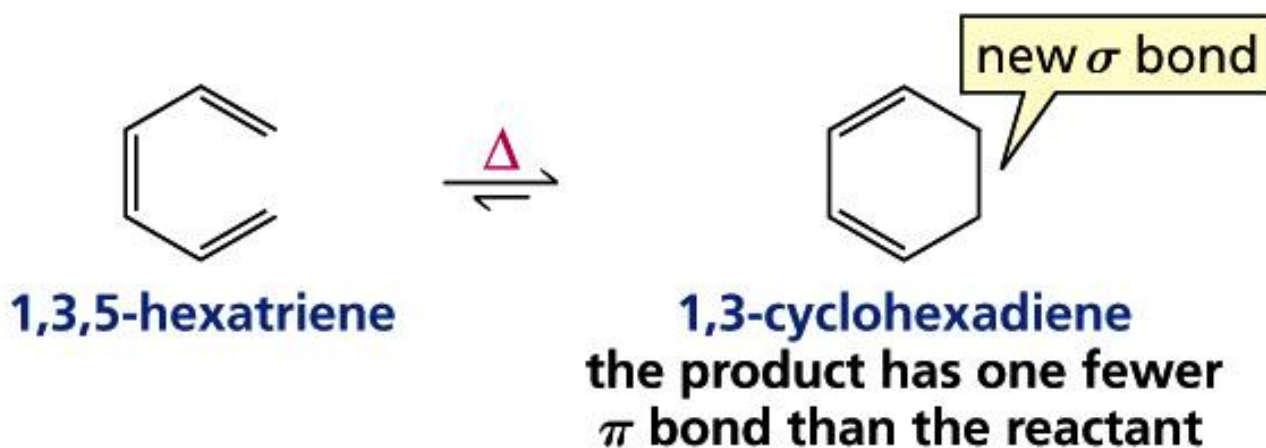
a radical reaction



A pericyclic reaction, a reaction that occurs as a result of reorganizing the electrons in the reactant (s)

Pericyclic Reaction I

an electrocyclic reaction



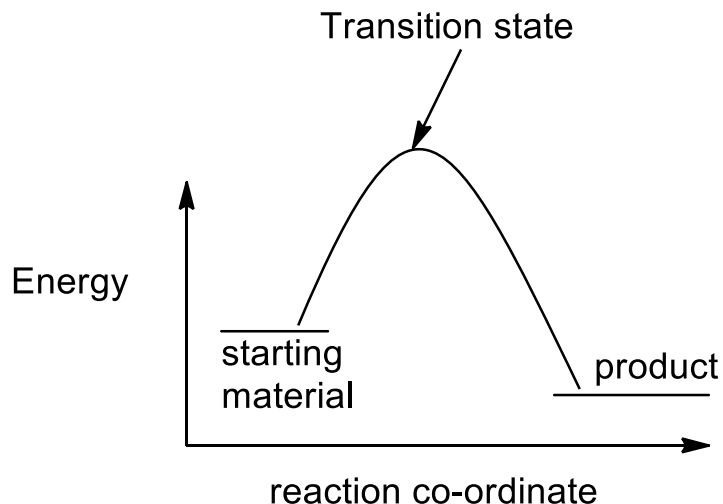
An intramolecular reaction in which a new σ bond is formed between the ends of a conjugated p system

Unexpected results of cyclization reactions

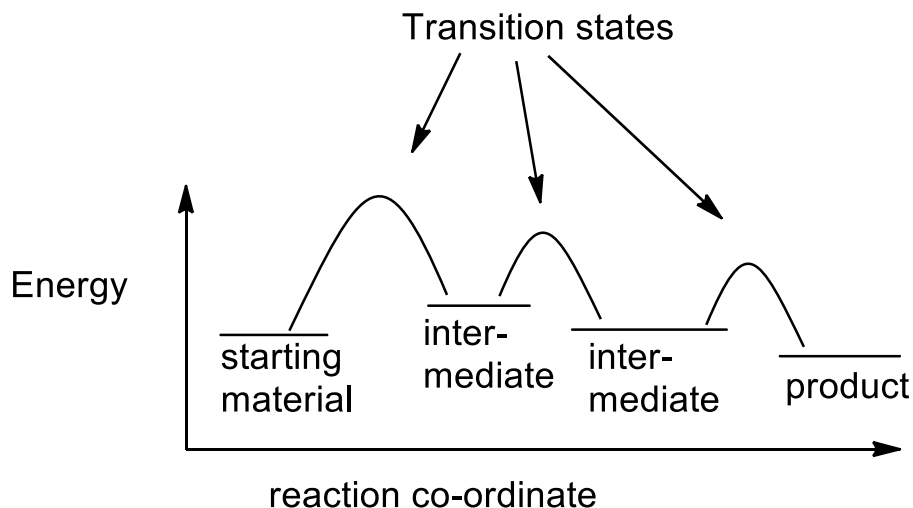
Pericyclic reactions are; “Any concerted reaction in which bonds are formed or broken in a cyclic transitions state”. (electrons move around in a circle).

i.e. there is a single transition state from start to finish, in contrast to a stepwise reaction.

Concerted reaction



Multistep reaction

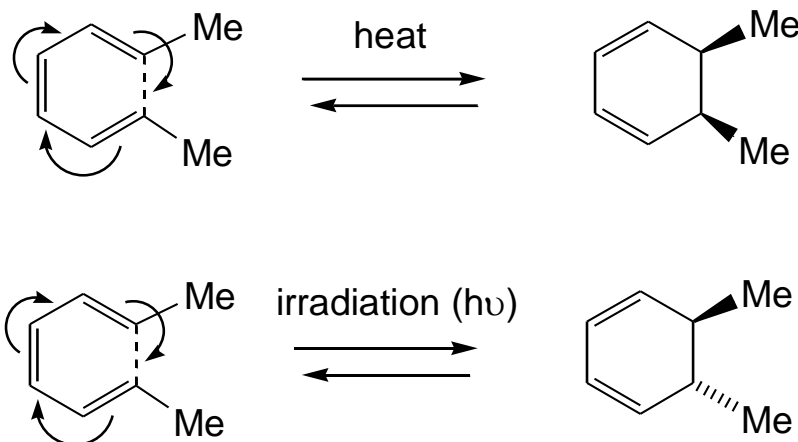


Properties of pericyclic reactions:

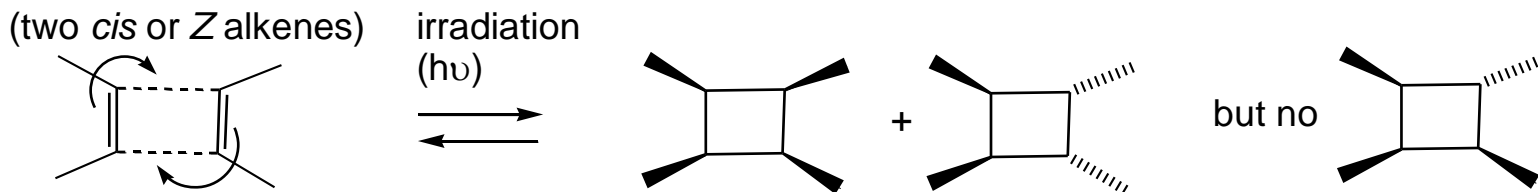
- (a) Little, if any, solvent effect
- (b) No nucleophiles or electrophiles involved.
- (c) Not generally catalysed by Lewis acids.
- (d) Highly stereospecific.
- (e) Often photochemically promoted.

Examples of pericyclic reactions

1) **Electrocyclisation reactions** – Linear conjugated polyene converted into a cyclic product in one step. The mechanism is not particularly surprising, but the stereochemistry changes depending on whether heat or irradiation (typically UV-light) is used to promote the reaction. e.g.

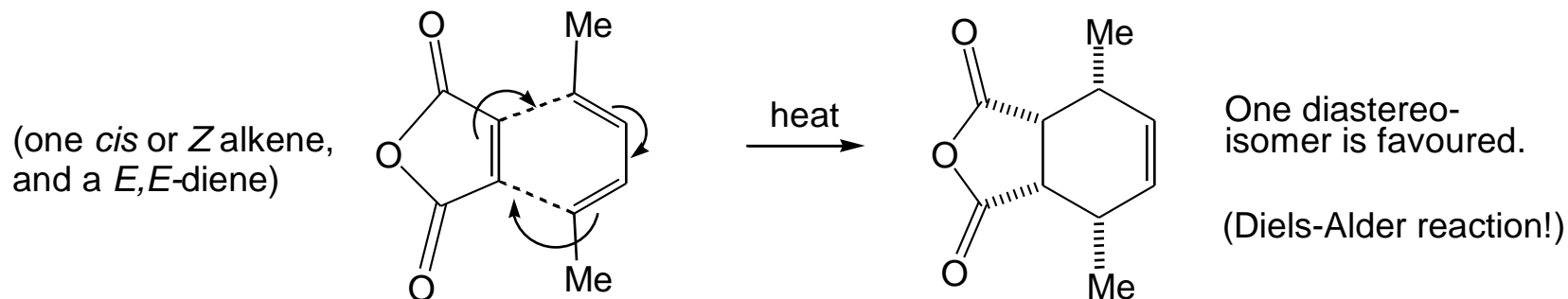


2) **Cycloaddition reactions** – Two linear conjugated polyenes converted onto a cyclic product in one step. Again, the stereochemistry of the reaction is remarkably reproducible. e.g.

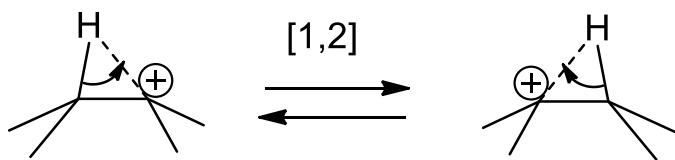


Examples of pericyclic reactions, continued:

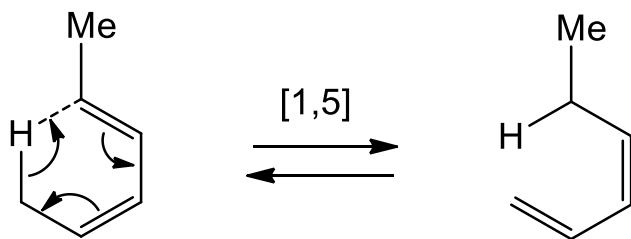
Example of a **cycloaddition** to give a **6-membered ring**:



3) **Sigmatropic rearrangement reactions**: These involve a concerted migration of atoms or of groups of atoms. E.g. migration of a σ -bond. The numbering refers to the number of atoms in the transition state on either side of where bonds are made or broken.



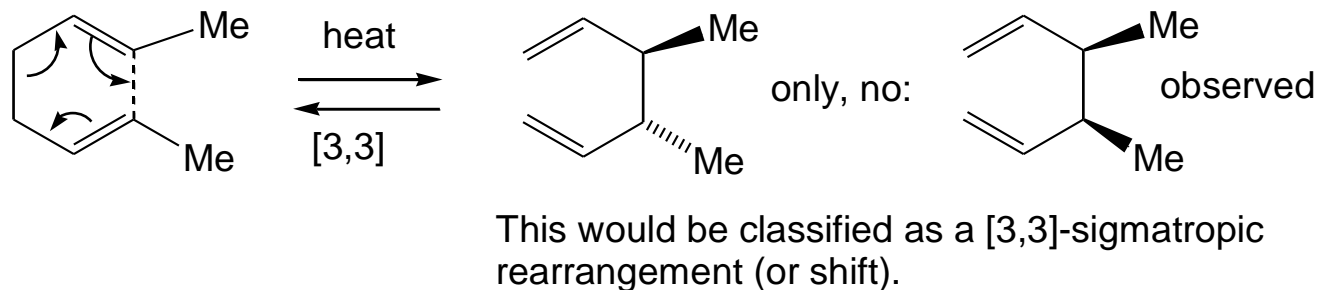
This would be classified as a [1,2]-sigmatropic rearrangement (or shift).



This would be classified as a [1,5]-sigmatropic rearrangement (or shift).

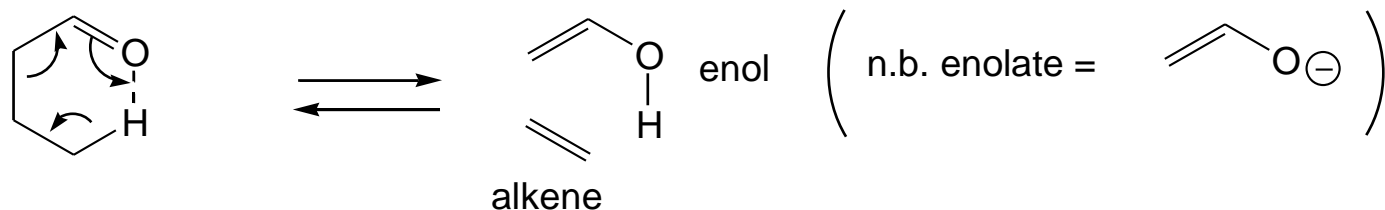
Examples of pericyclic reactions, continued:

3) **Sigmatropic rearrangement reactions:** A high level of stereochemical control is often observed.

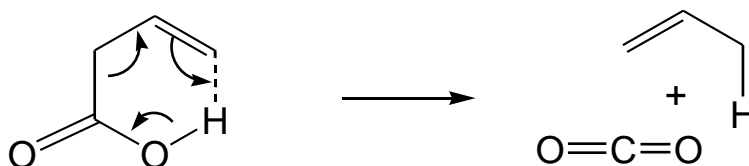


Other concerted reactions:

a) **Ene reaction** (synthetic chemists), or **Norrish rearrangement** (photochemists) or McLafferty rearrangement (for mass spectrometrists).



b) **Decarboxylation reaction:**

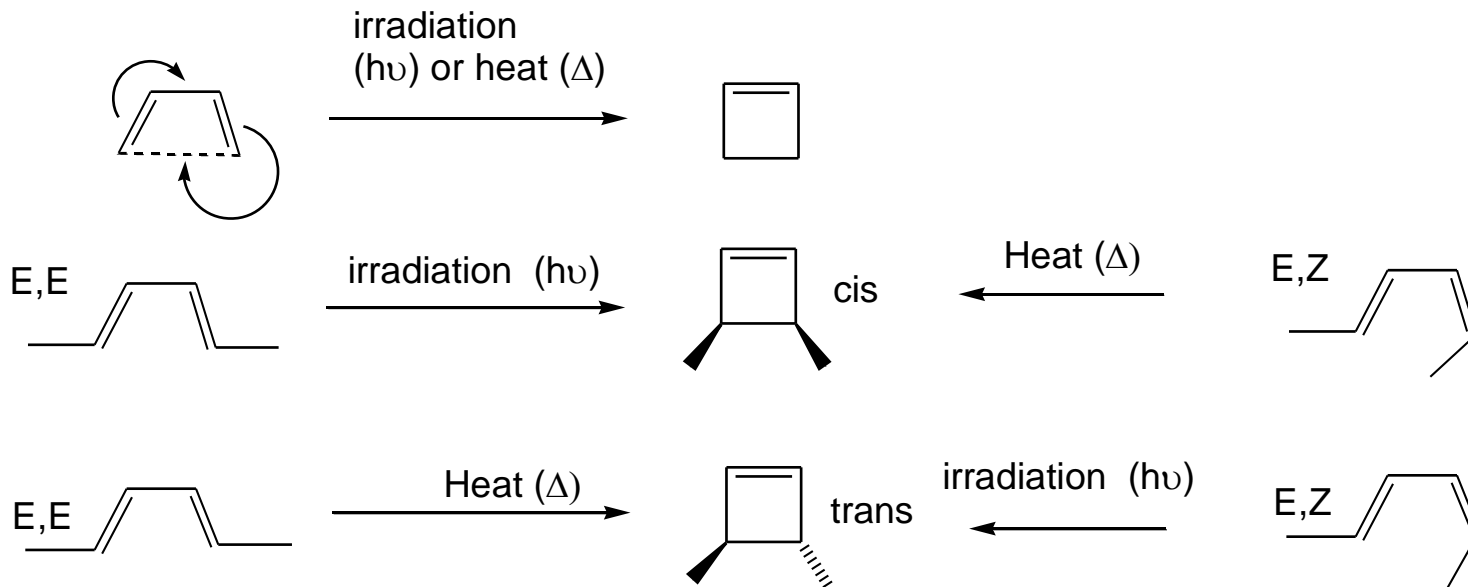


Woodward-Hoffmann theory for prediction of the stereochemistry of pericyclic reactions: Electrocyclizations.

The 'Woodward-Hoffmann' theory explains the stereochemical outcome of pericyclic reactions by considering the symmetry of the 'frontier orbitals' which are involved in the reaction. These are the orbitals which actually contribute to the bond making and breaking process. They are also the 'outermost' orbitals (of highest energy) in a structure, hence the term 'frontier'.

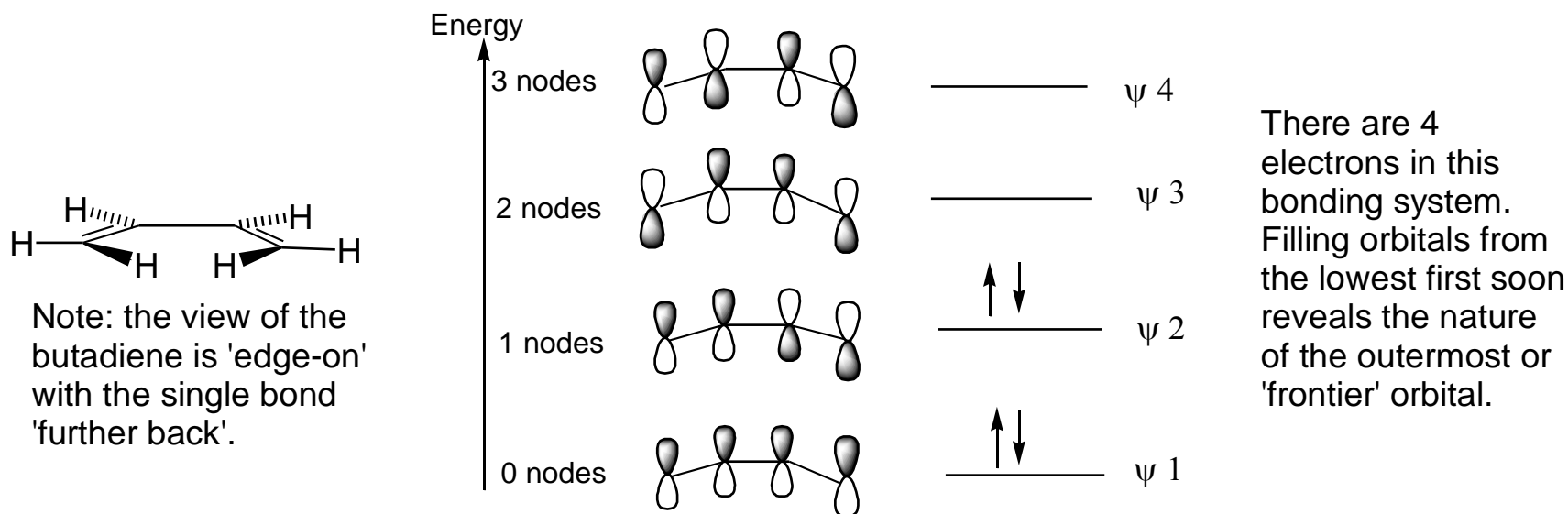
Electrocyclizations.

Consider the conversion of butadiene into cyclobutene: The mechanism is quite simple, but the stereochemistry of the product is directly related to (i) the stereochemistry of the starting material and (ii) whether heat or irradiation is employed to promote the reaction.



Woodward-Hoffmann theory applied to cyclobutene formation

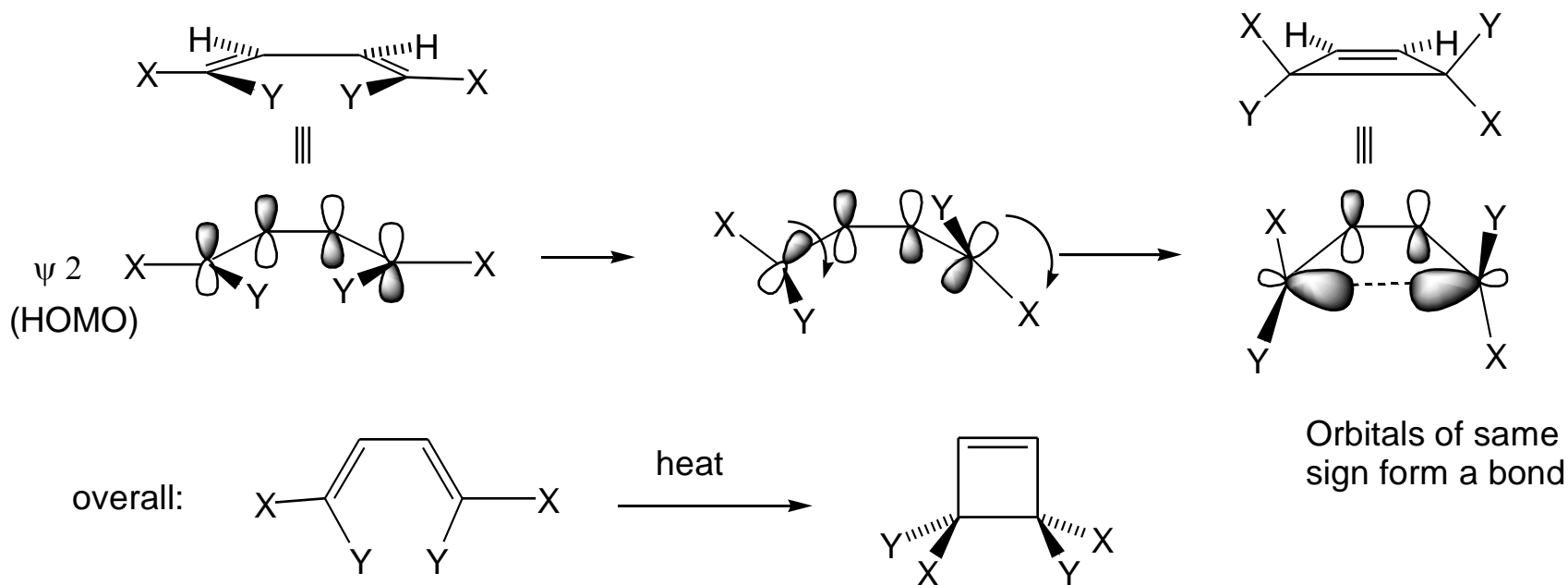
What is happening in the cyclization is that p-orbitals (which form the π -bonds) are combining in order for a new σ bond to be formed between the 'ends' of the conjugated system. However, in order for this process to happen efficiently, it is necessary for the orbitals with the same wave-function sign (phase) to 'join up'. In order to work out where these are, a quick analysis of the four molecular orbitals (formed from the 4 atomic – p – orbitals) is required.



Note: 'n' atomic orbitals, when combined, result in the formation of 'n' molecular orbitals. Low-energy orbitals are generally bonding and high energy ones are antibonding. Because the lower orbitals are filled in the butadiene system, the molecule is stable.

Woodward-Hoffmann theory applied to cyclobutene formation.

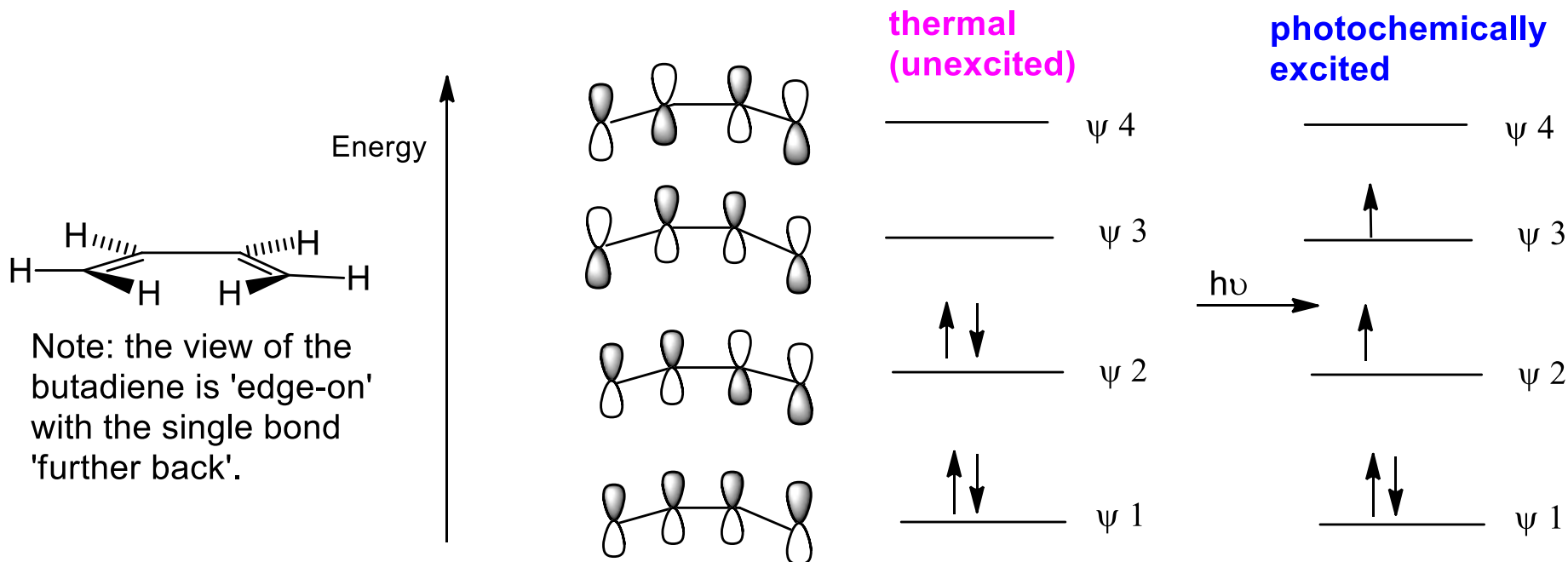
So it is now possible to see what happens when butadiene is converted to cyclobutene. In order for the new sigma bond to be formed between the newly-connected carbon atoms, the ends of the molecule have to 'rotate' in a very specific way for this to happen. We only need to consider the **highest-energy molecular orbital** (highest occupied molecular orbital, or HOMO):



The result is that the 'X' groups end up *trans* to each other, as do the 'Y' groups. Because this involves a concerted rotation of each end of the diene in the same direction (clockwise is illustrated, although anticlockwise would give same result) this is referred to as a '**conrotatory**' process. It is also referred to as '**antarafacial**' because the orbitals which link up have identical signs on *opposite* faces of the diene.

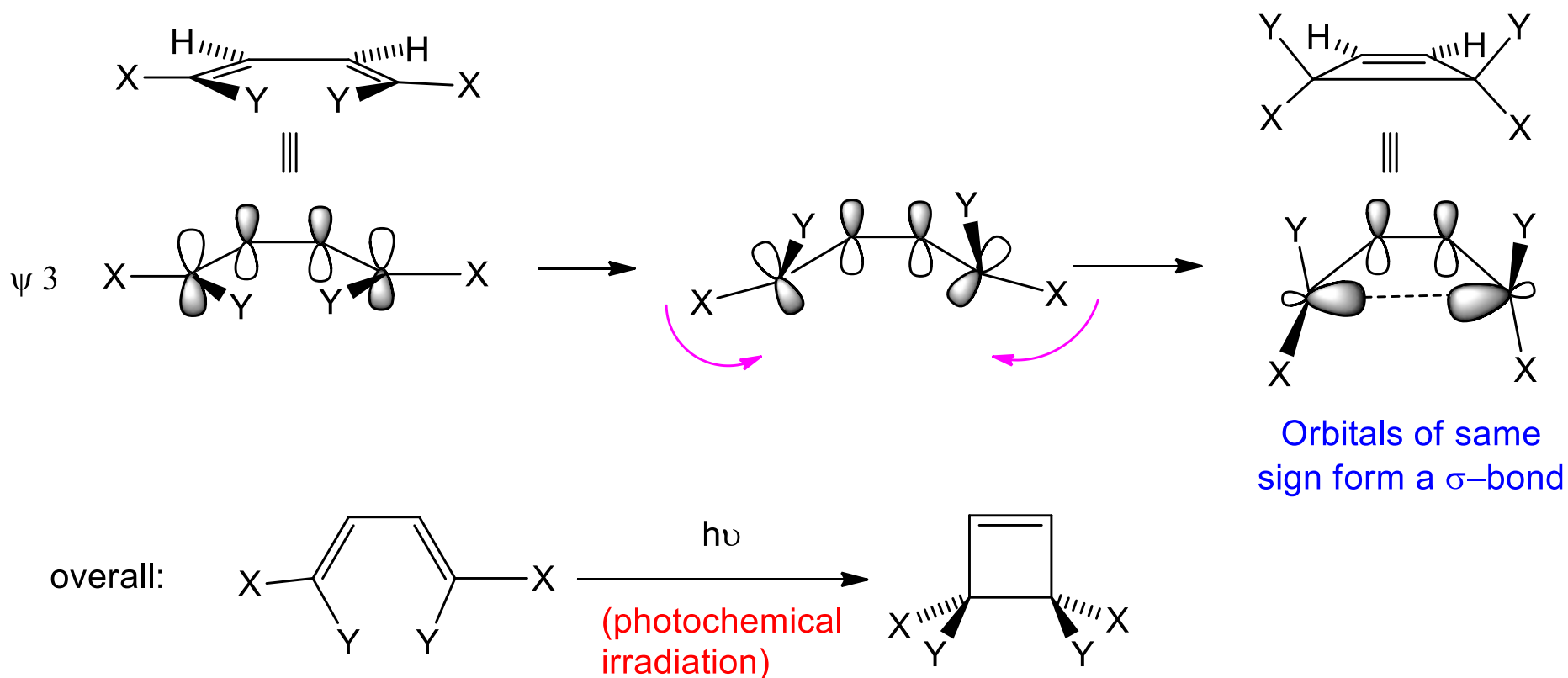
Woodward-Hoffmann theory applied to cyclobutene formation under photochemical conditions.

Under photochemical conditions, the orbitals are not changed in structure, but an electron is excited by one level. As a result, a new 'highest occupied molecular orbital' or HOMO, is defined. The photochemically-excited molecules, whilst not as numerous, are of much higher energy than the unexcited molecules, and dominate the resulting chemistry.



Now (see the next page), the manner in which the molecule changes shape upon cyclisation is very different.

Cyclisation under photochemical conditions: In the new HOMO, the 'ends' of the orbitals with the same sign are on the same face of the diene, or '**suprafacial**'. In order for these to 'join up' to form a bond, the ends of the alkene have to rotate in *opposite* directions. This process is described as '**disrotation**'.

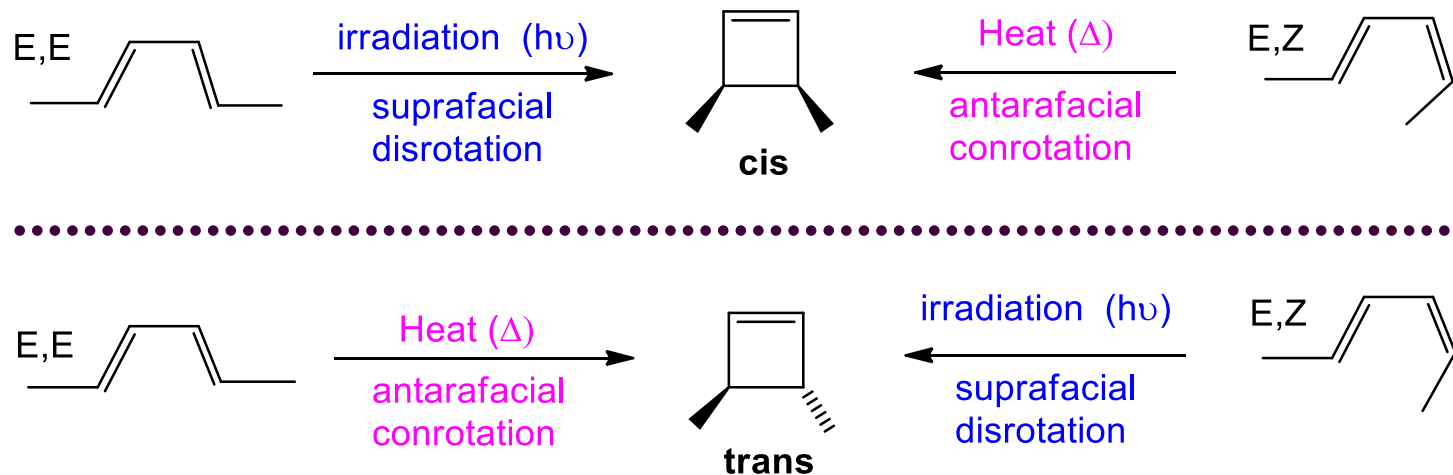


i.e., A **suprafacial**, **disrotatory** process.

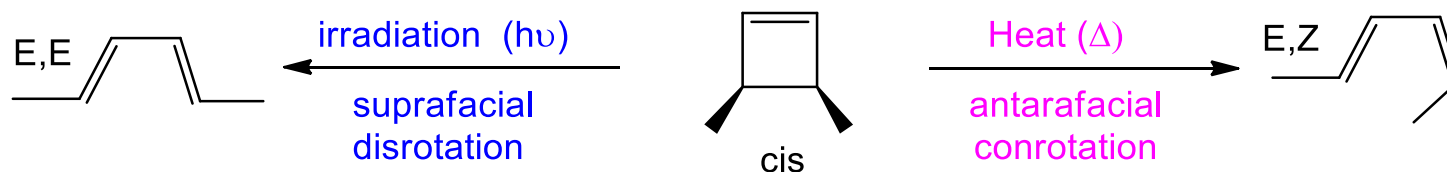
n.b. Note that the hybridisation of the carbon atoms at the ends of the diene changes from sp^2 to sp^3 in the process.

Woodward-Hoffmann theory applied to cyclobutene formation – conclusion:

It is now possible to understand all the stereochemical observations for the butadiene cyclisations which were described at the start of the section:



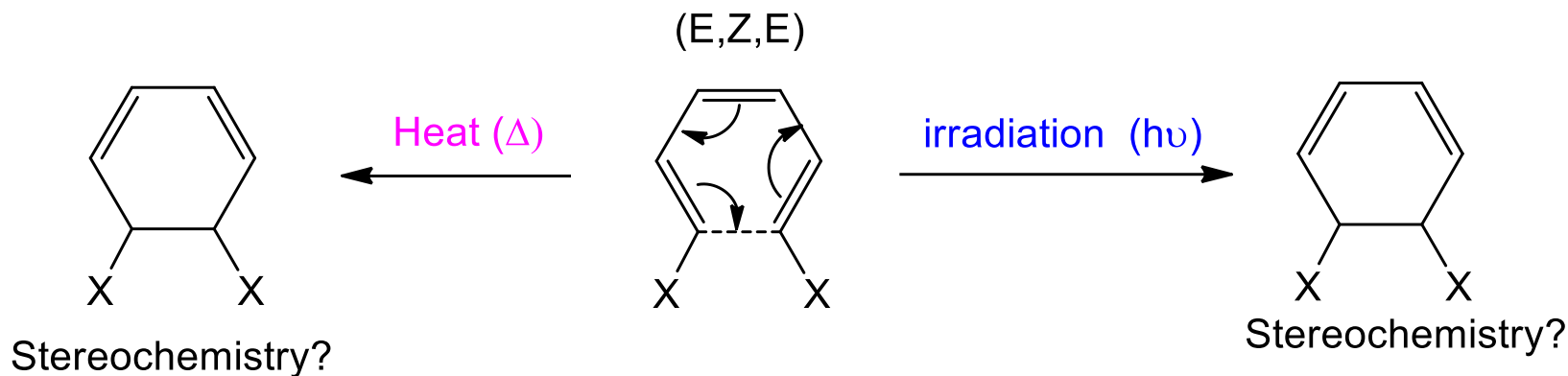
Note how **antara/conrotation** go together, as do **supra/disrotation**. Logical really. Note, also, that the rules also work in the reverse direction, e.g.



Although it should be noted that sometimes stereocontrol is lost due to competing radical reactions.

Woodward-Hoffmann theory applied to cyclohexene formation

Now that you can see how the theory applies to butadiene, try working out the stereochemical outcome of a triene electrocyclicisation, the mechanism of which is given below:



The mechanism, of course, will be the same whether heat or photochemically-induced. The **difference will be in the observed stereochemistry of the products.**

Hopefully you will appreciate that the central alkene needs to be 'Z' configuration in order for the process to work. Why not revise E and Z notation to be on the safe side?

In order to solve the problem, **you need to be able to write down the possible molecular orbitals available to the π -system of the molecule, put them in order and fill them with electrons.**
Hint; as the energy of the orbital increases, so does the number of nodes.

We shall work through the solution to this in a lecture. Then you should try the same for a tetraene and pentene. Can you see a pattern?

No of paired electron Δ $h\nu$

Odd

dis $\boxed{\uparrow\downarrow}$
 $\boxed{\uparrow\uparrow}$

Con $\boxed{\uparrow\uparrow}$ $\boxed{\downarrow\downarrow}$

Even

Con

dis

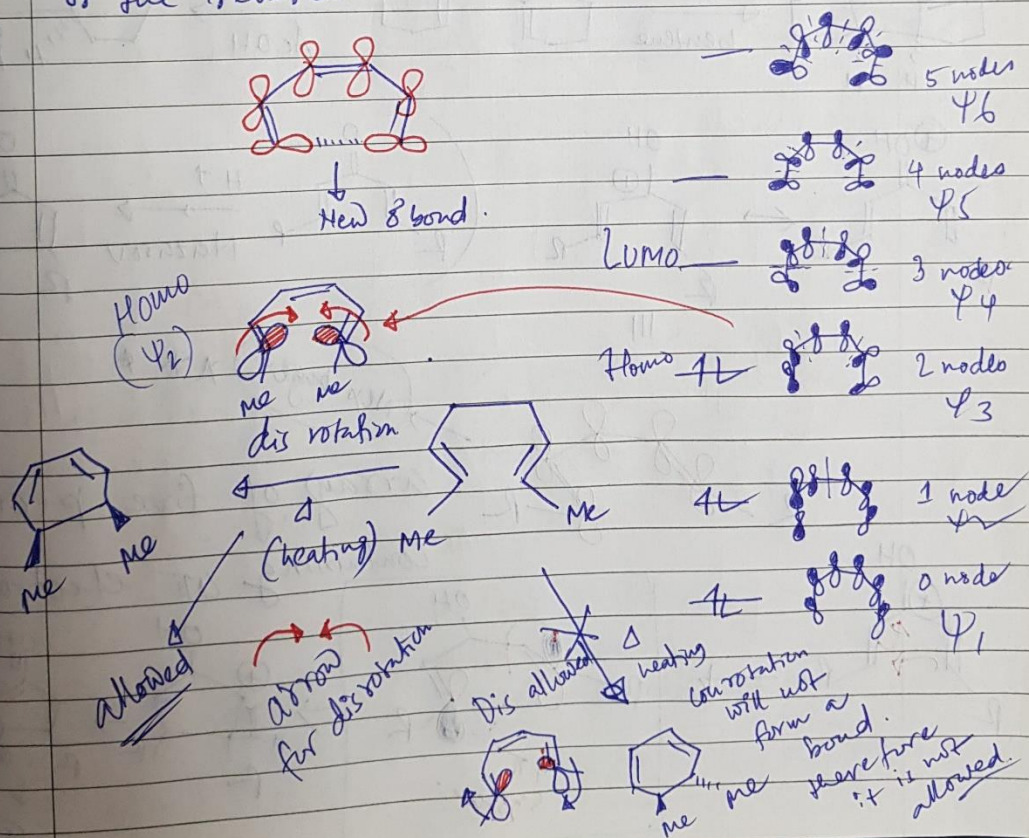
dis = dis rotation

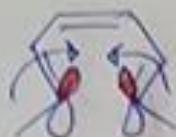
Δ = heating condition

Con = Con rotation

$h\nu$ = photo irradiation

An electrocyclic reaction is the formation of a new σ -bond across the end of a conjugated polyene or the reverse.





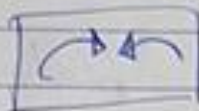
Ψ_3 - HOMO you must take



heating (Δ)



Dis rotation
is thermally allowed



Different
direction



Ψ_4 - LUMO you must take

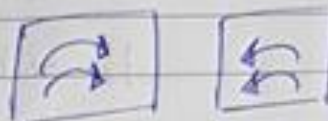
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$h\nu$



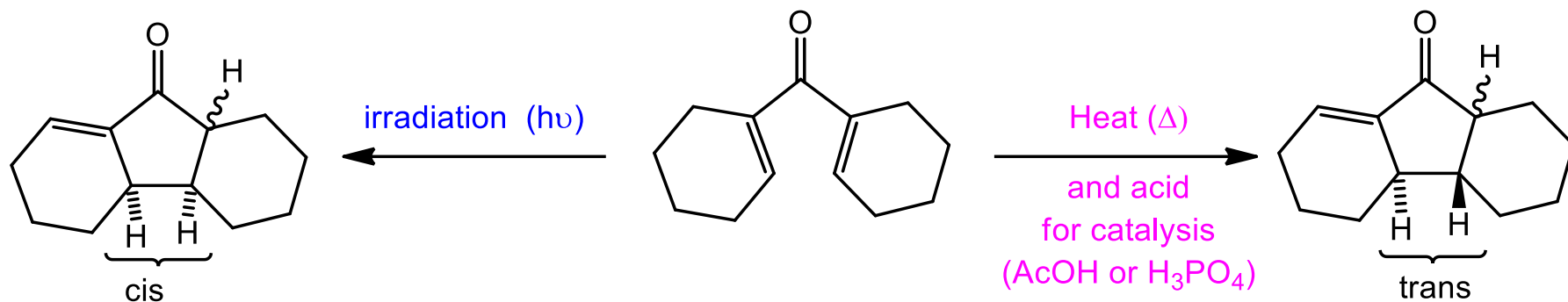
Con rotation
is photochemically
allowed



Same Same direction

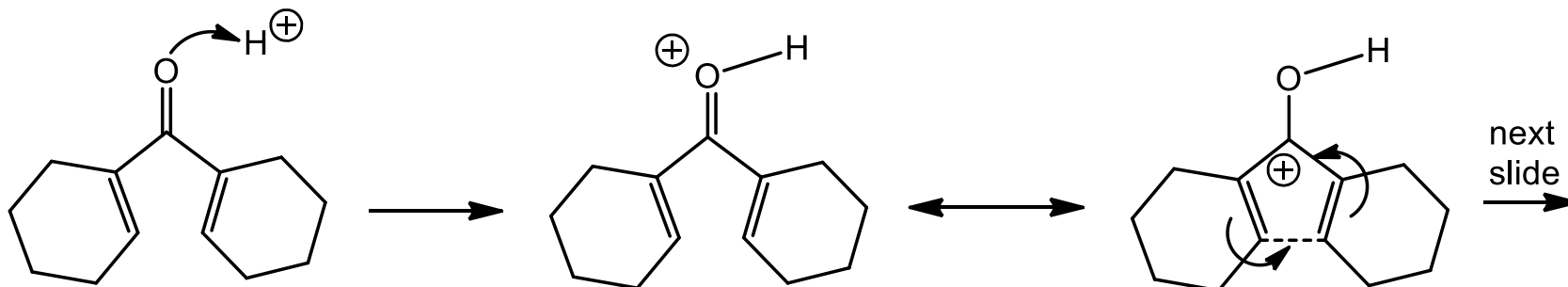
Electrocyclization reactions of cations and anions also follow the Woodward-Hoffmann rules

All you need to know is the number of electrons involved (i.e. $4n$ or $4n+2$) and whether the reaction is **photochemical** or **thermal**:



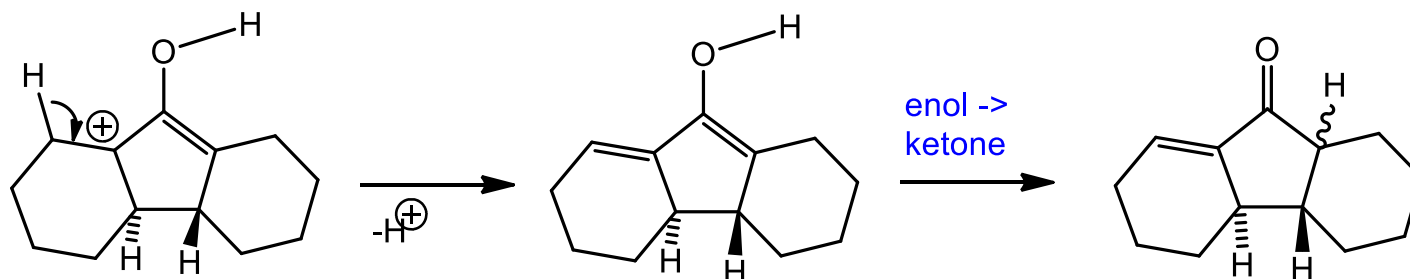
The reaction above is the Nazarov cyclisation (usually carried out under acidic/thermal conditions). Note that the position adjacent to the ketone is a mixture of isomers in each case. Only the relative stereochemistry between the lower hydrogens is controlled.

Mechanism:

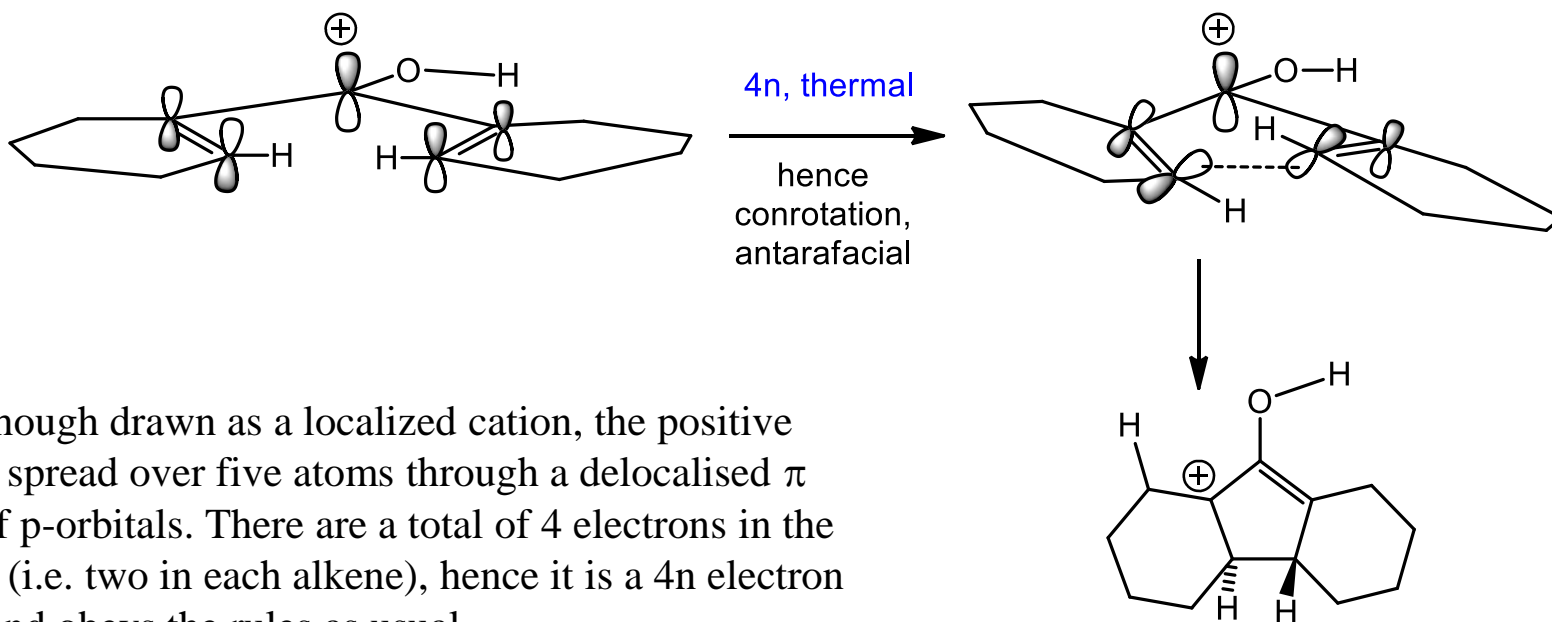


Nazarov cyclization, cont....

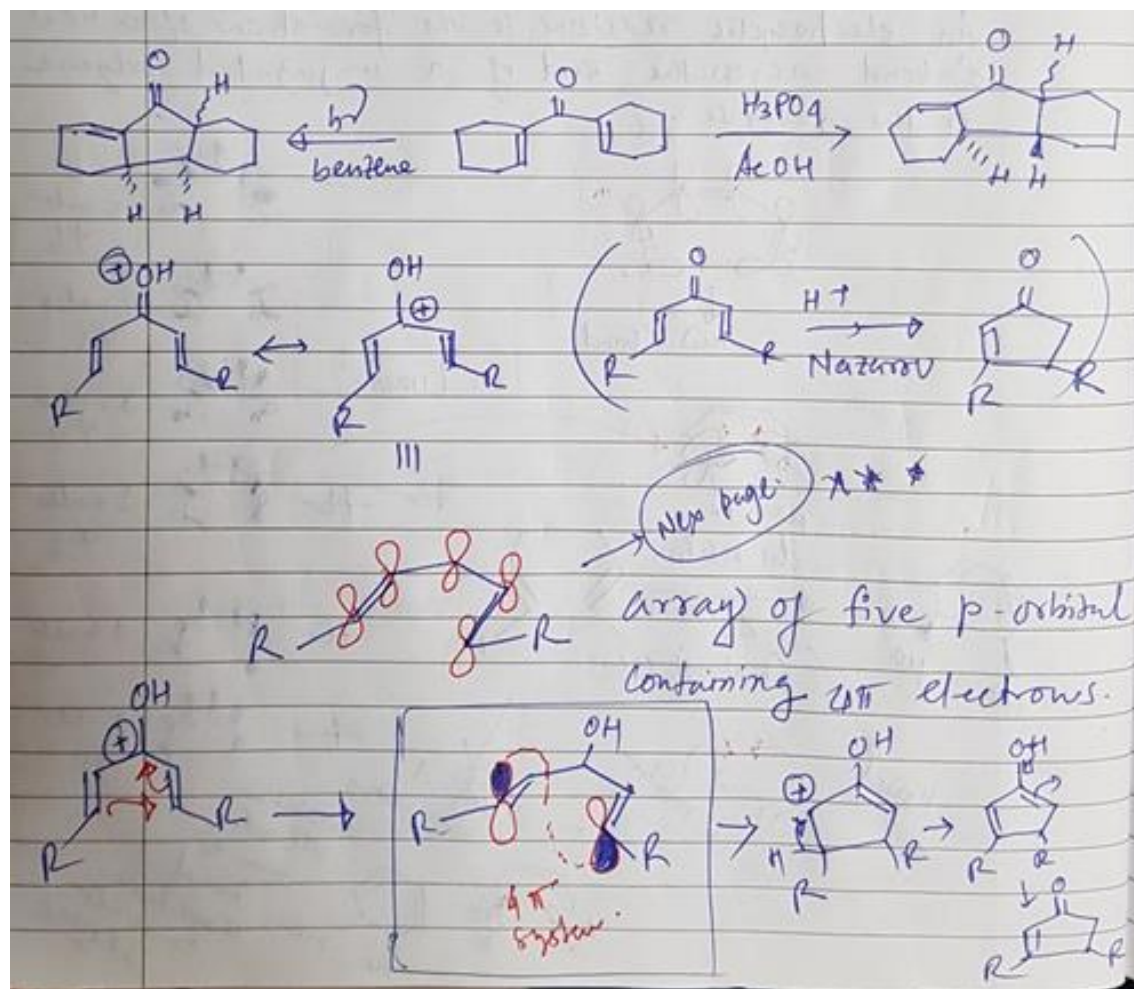
no of electron pair	Heating	Photochemical
odd	disrotation	conrotation
even	conrotation	disrotation

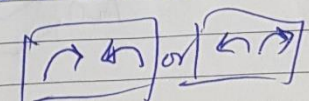
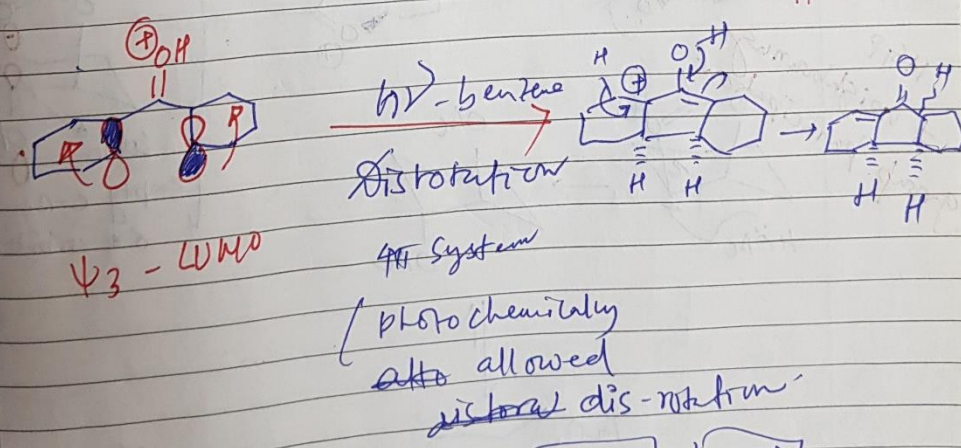
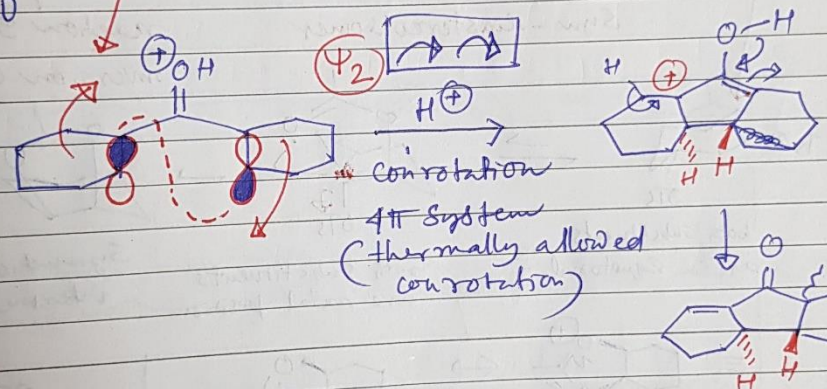
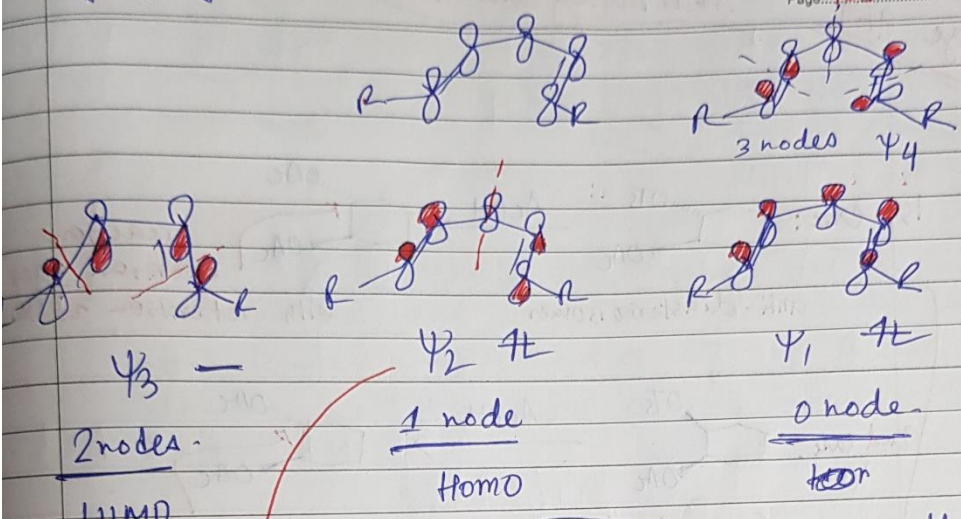


Stereochemistry in the key cyclisation step:



Note: although drawn as a localized cation, the positive charge is spread over five atoms through a delocalised π system of p-orbitals. There are a total of 4 electrons in the π system (i.e. two in each alkene), hence it is a $4n$ electron system, and obeys the rules as usual.

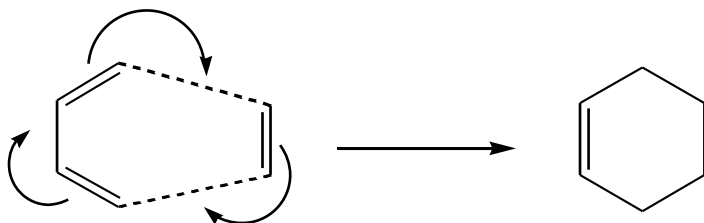




Woodward-Hoffmann theory for prediction of the stereochemistry of pericyclic reactions: Cycloaddition reactions

In cycloaddition reactions, the situation is slightly different because a) two molecules are used and b) electron flow takes place from the highest occupied molecular orbital (HOMO) of one molecule to the lowest unoccupied molecular orbital (LUMO) of the other. The stereochemistry therefore follows from the wavefunction signs of the orbitals on each molecule.

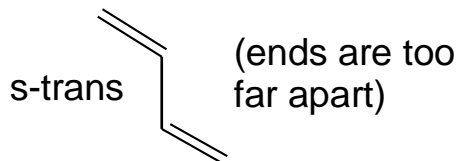
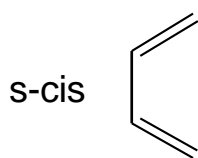
Consider the reaction of a butadiene with an alkene (**the Diels-Alder reaction**):



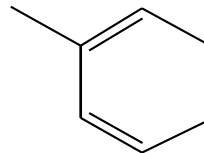
The reaction is *usually* heat-promoted, but sometimes it is carried out photochemically.

More details of the Diels-Alder reaction.

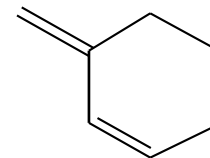
1) Diene must be in the s-cis conformation:



This will react:



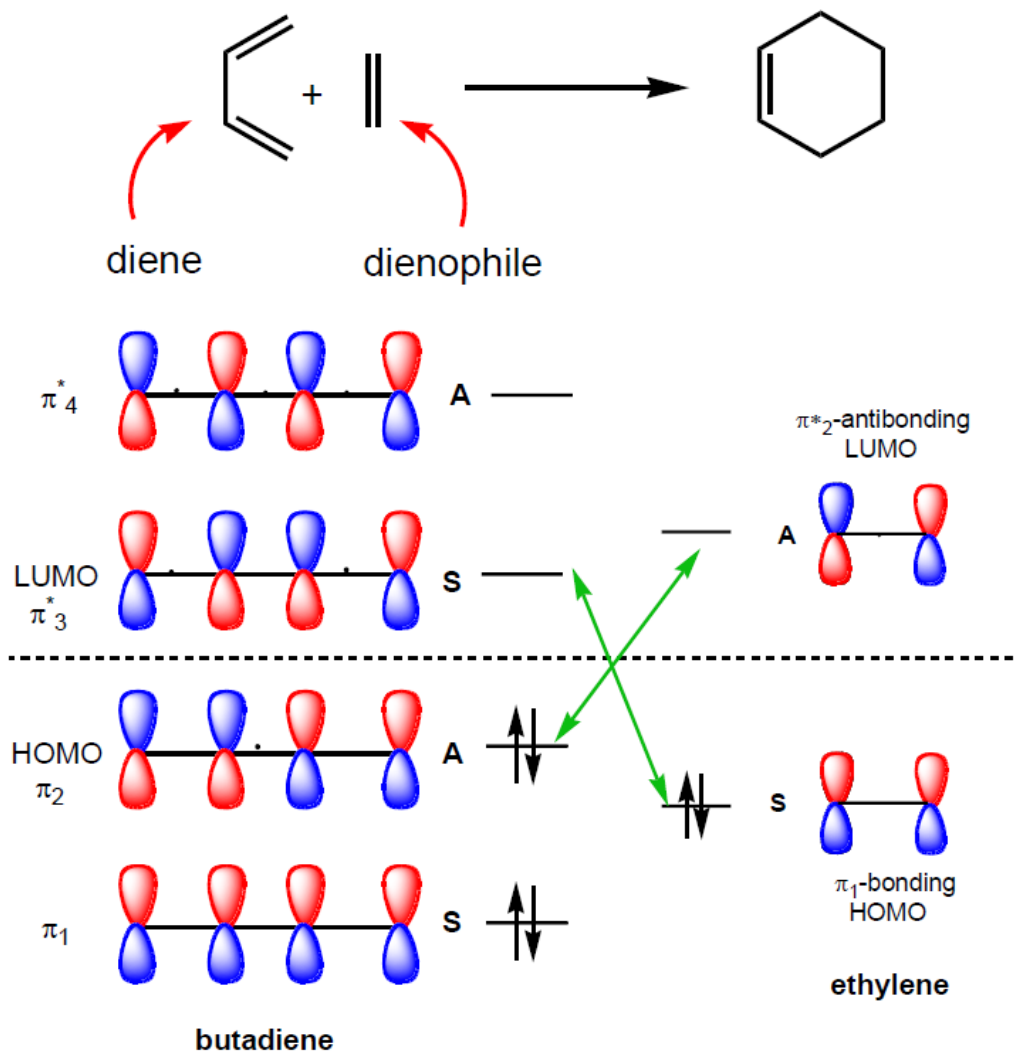
But not this:



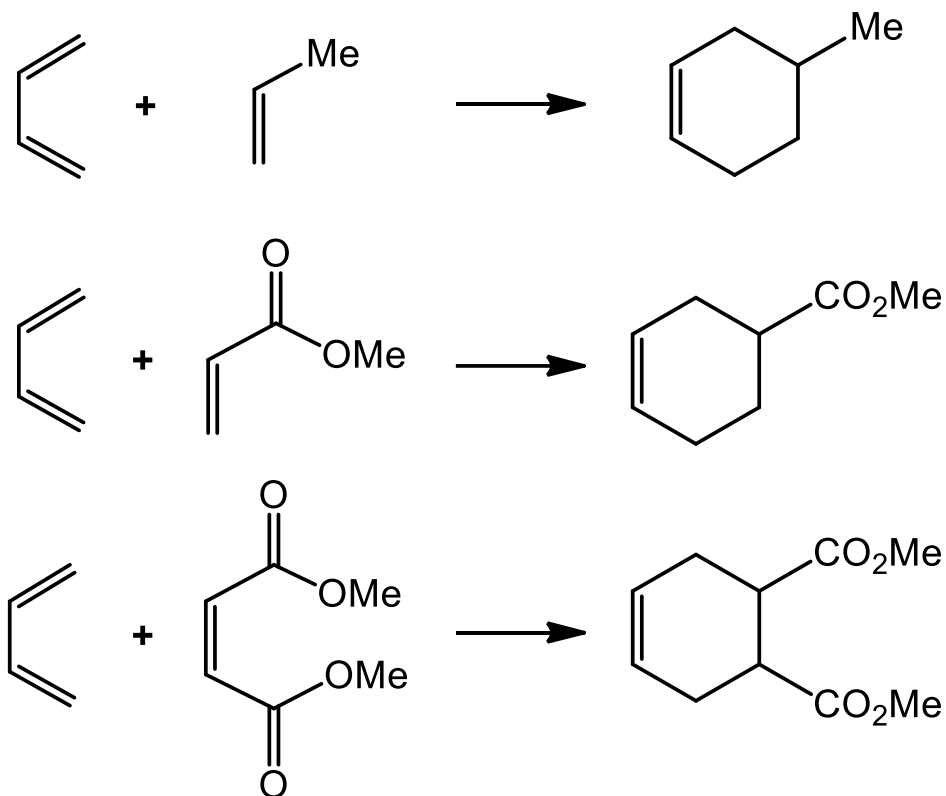
Diels-Alder reaction

Cycloaddition:

Diels-Alder Reaction An Allowed [4+2] Cycloaddition



2) Dienophiles with electron-withdrawing groups (EWG) react faster:

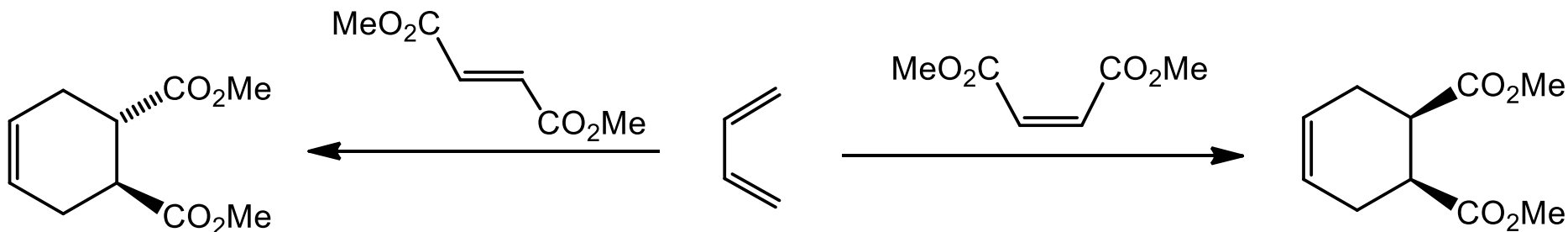


slow

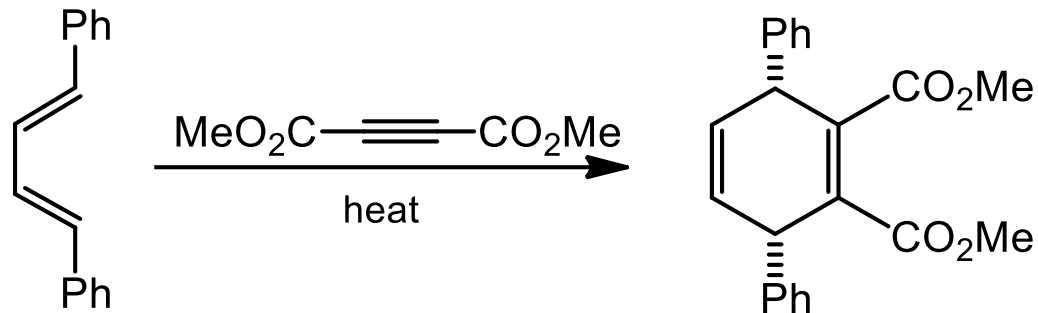
This is because the electron-withdrawing group reduces the LUMO energy and improves the overlap with the orbitals in the diene – more information later in course.

fast

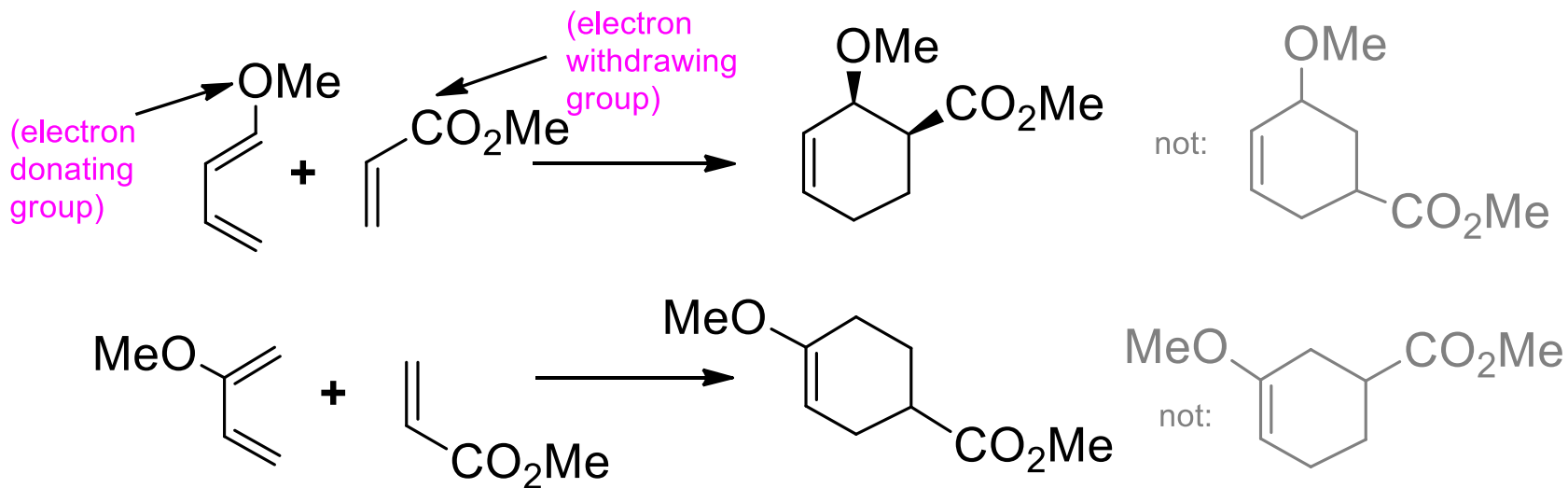
3) The reaction is stereospecific:



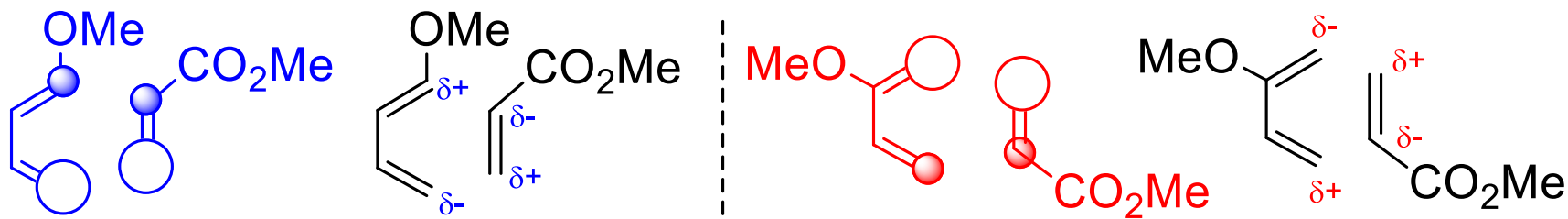
3) The reaction is stereospecific cont...



4) With unsymmetrical dienes, the reactions are regioselective:

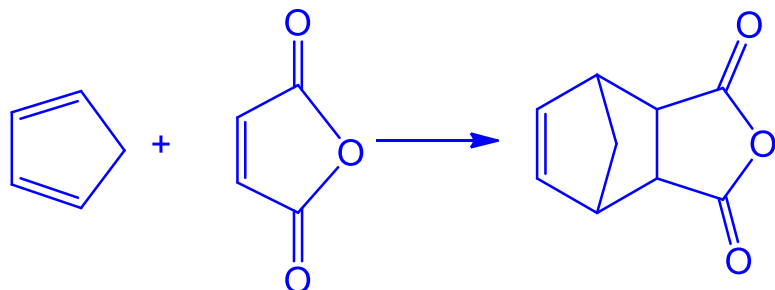


Due to size of MOs, and distribution of partial charges:

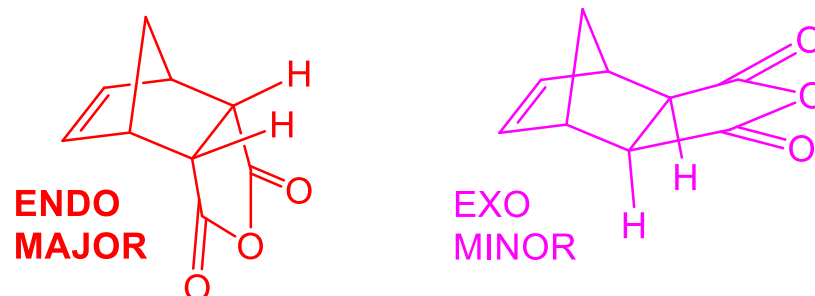


MOs closely matched in size react with each other more efficiently (stepwise analogy).

5) Endo-product often favoured:



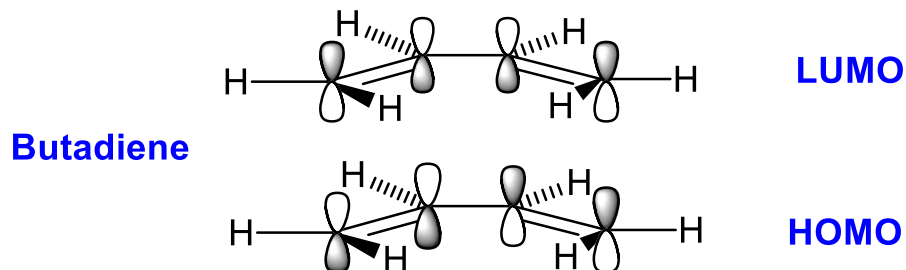
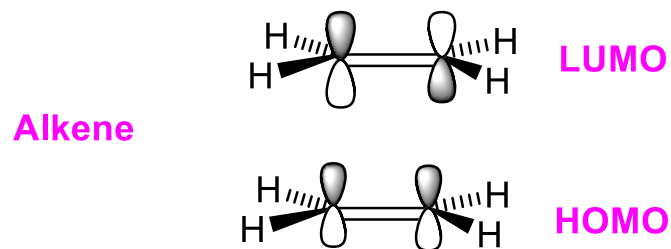
Two isomers can be formed:



In a kinetically controlled (product is fastest to form, irreversible) the ENDO is favoured but for reversible reactions (thermodynamic control) the EXO may dominate e.g. with furan.

All these observations can be explained by considering the orbitals involved in the reactions:

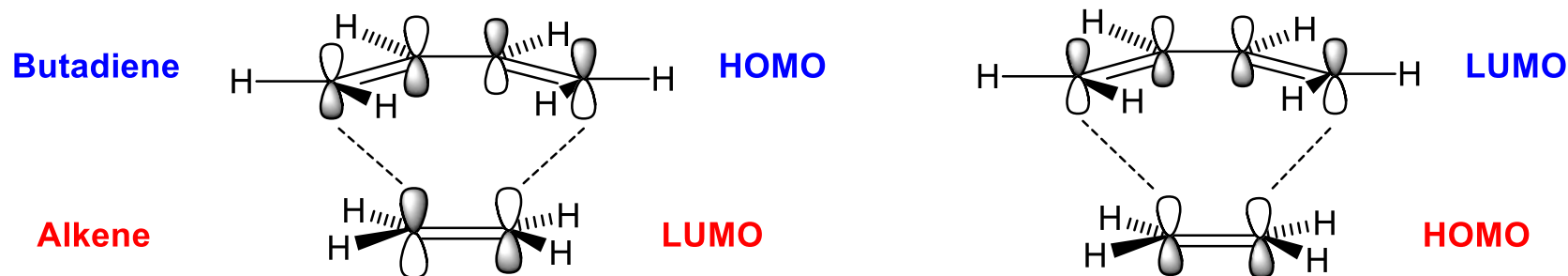
In this Diels-Alder reaction the reagents approach each other in a ‘face to face’ manner, i.e. so that the p- orbitals of the π -system can combine with each other. The relevant orbitals are shown below:



Woodward-Hoffmann theory for prediction of the stereochemistry of pericyclic reactions:

Cycloaddition reactions

So the following combinations can be employed in the *suprafacial cycloaddition reaction*:

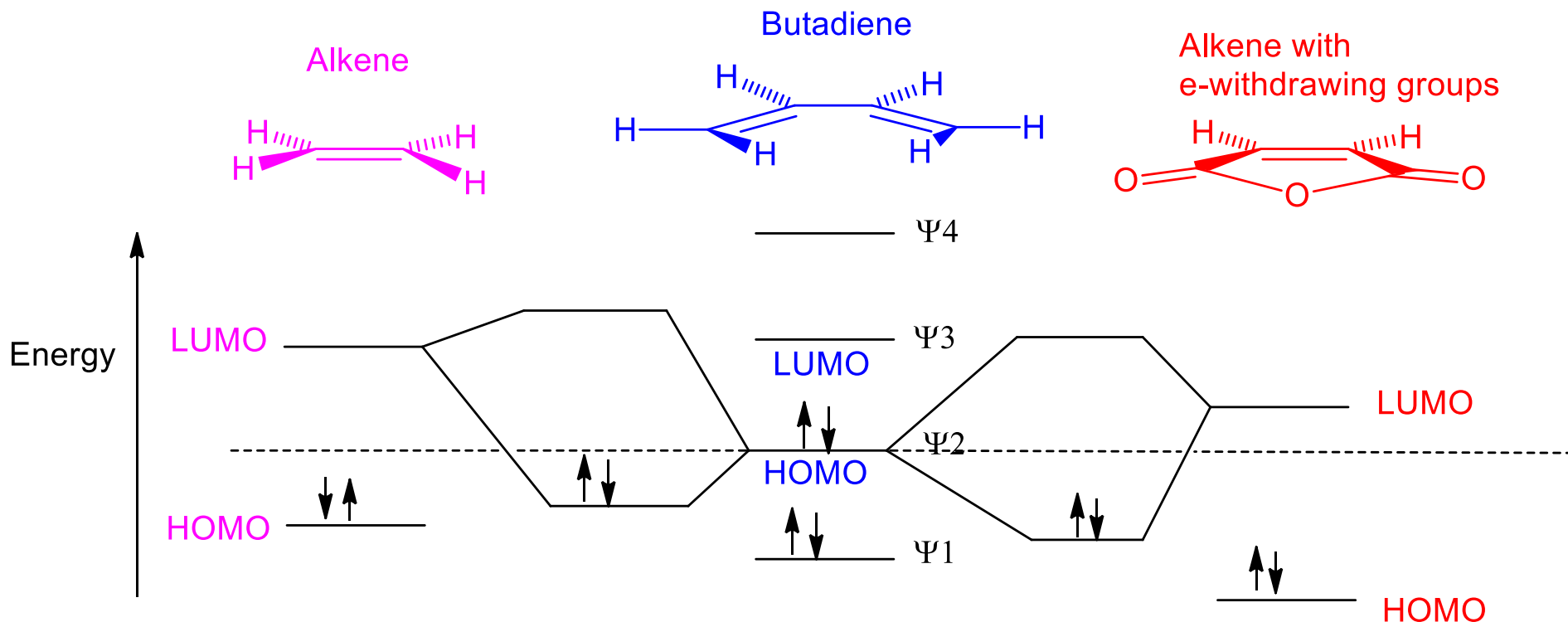


In both cases, phases of the wavefunctions on the orbitals are matched so that the reagents can approach each other in a face to face manner and also form bonds easily.

In practice, it is usually the combination of diene HOMO with alkene LUMO which leads to the product, rather than the diene LUMO and alkene HOMO. Electron-withdrawing groups on the alkene lower its LUMO energy and improve the matching to the diene HOMO. In turn this increases the reaction rate. Hence, electron-withdrawing groups on an alkene generally increase the reaction rate, often very significantly. As might be predicted, electron-donating groups on the diene also improve the rate – by pushing its HOMO energy closer to that of the alkene LUMO (see next slide).

Diels-Alder reaction: energetics

More closely-matched orbitals give a greater energetic benefit when combined. Hence the closely related butadiene HOMO and alkene LUMO represent the favoured combination. When electron-withdrawing groups are present on the alkene, the benefit is even greater because the HOMO/LUMO levels are even closer. Lewis acids speed it even further.

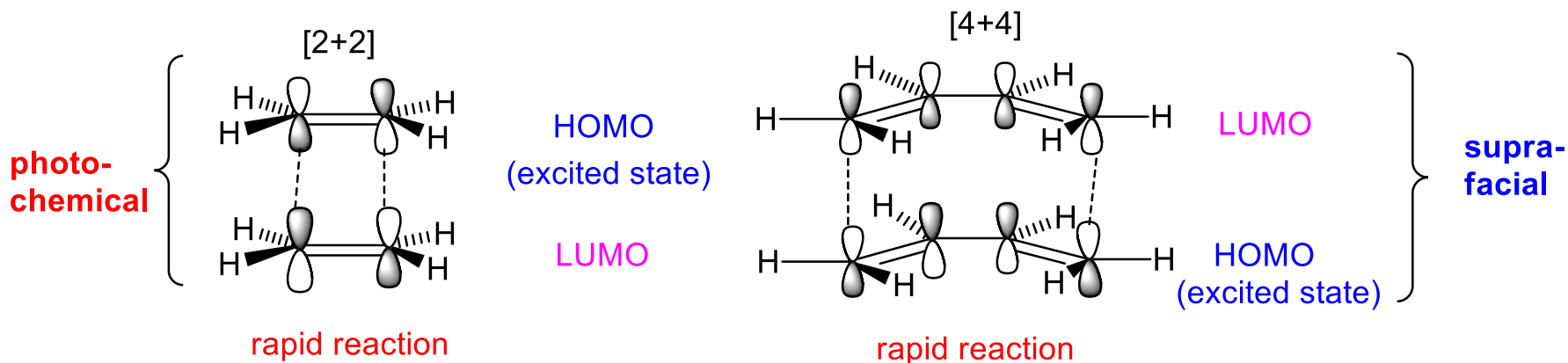
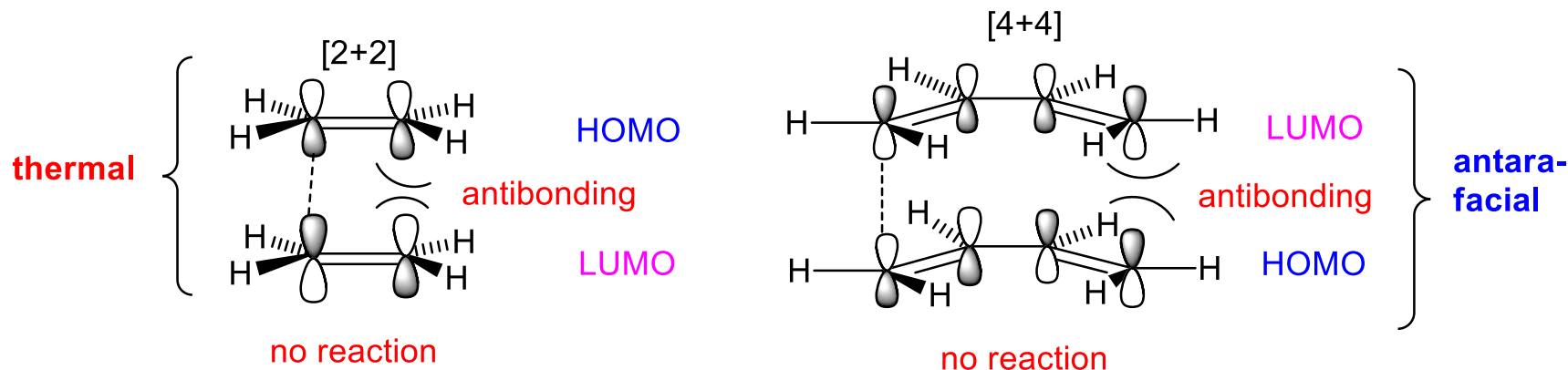


The **Diels-Alder reaction** proceeds in a *suprafacial manner*, i.e. the reagents add together in a perfectly-matched face-to-face fashion.

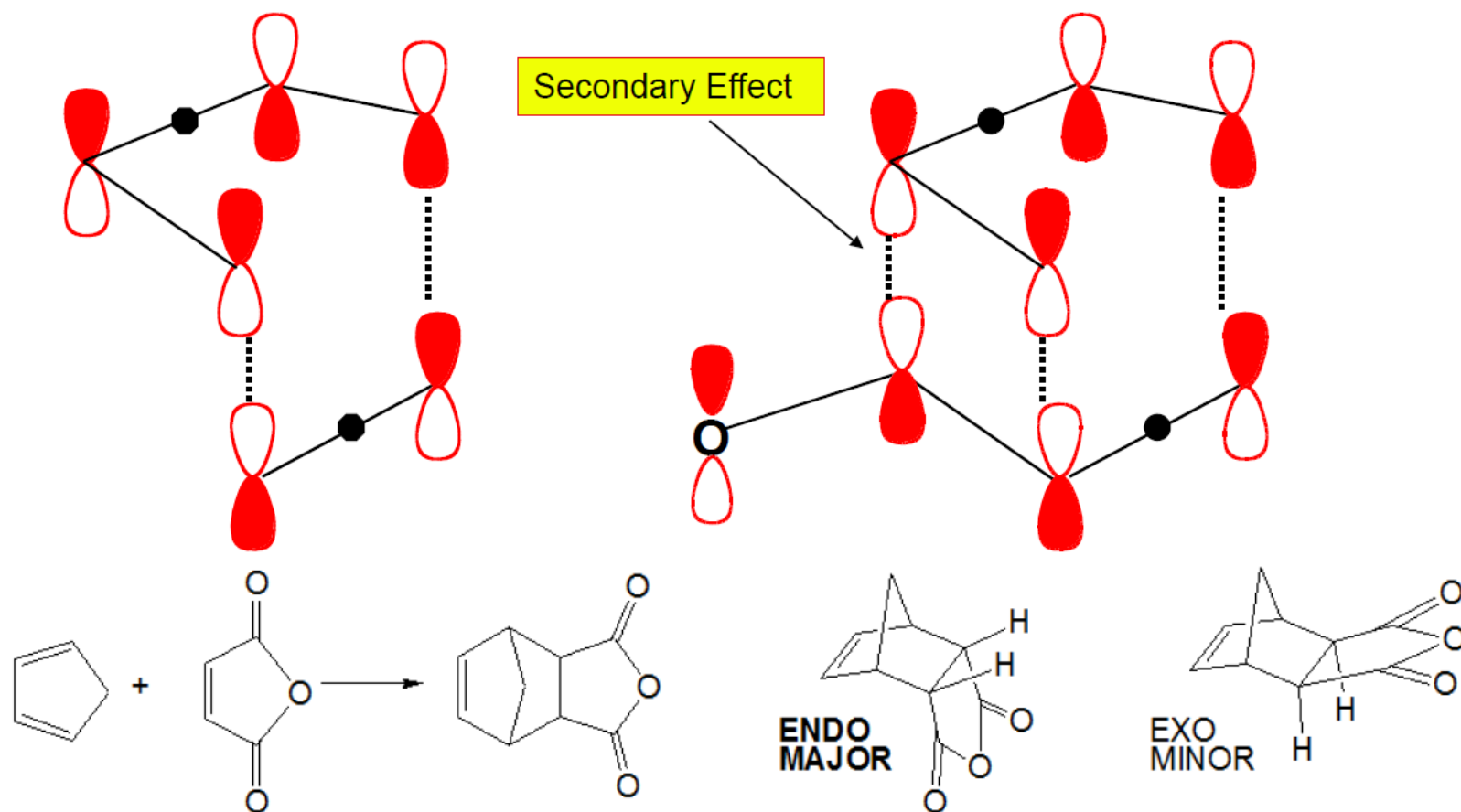
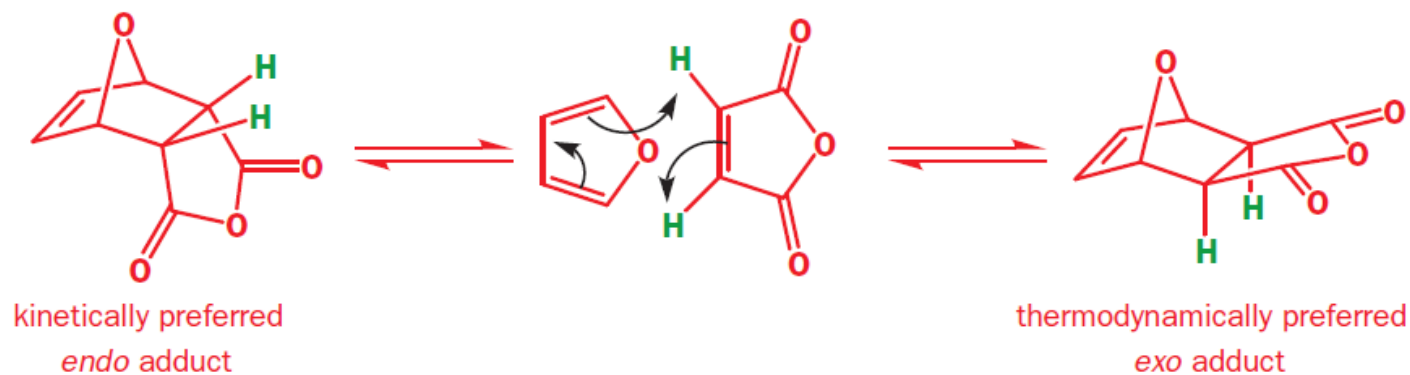
Please note: the terms 'dis'- and 'con'- rotation do not apply to cycloadditions.

Woodward-Hoffmann theory for prediction of the stereochemistry of cycloaddition reactions

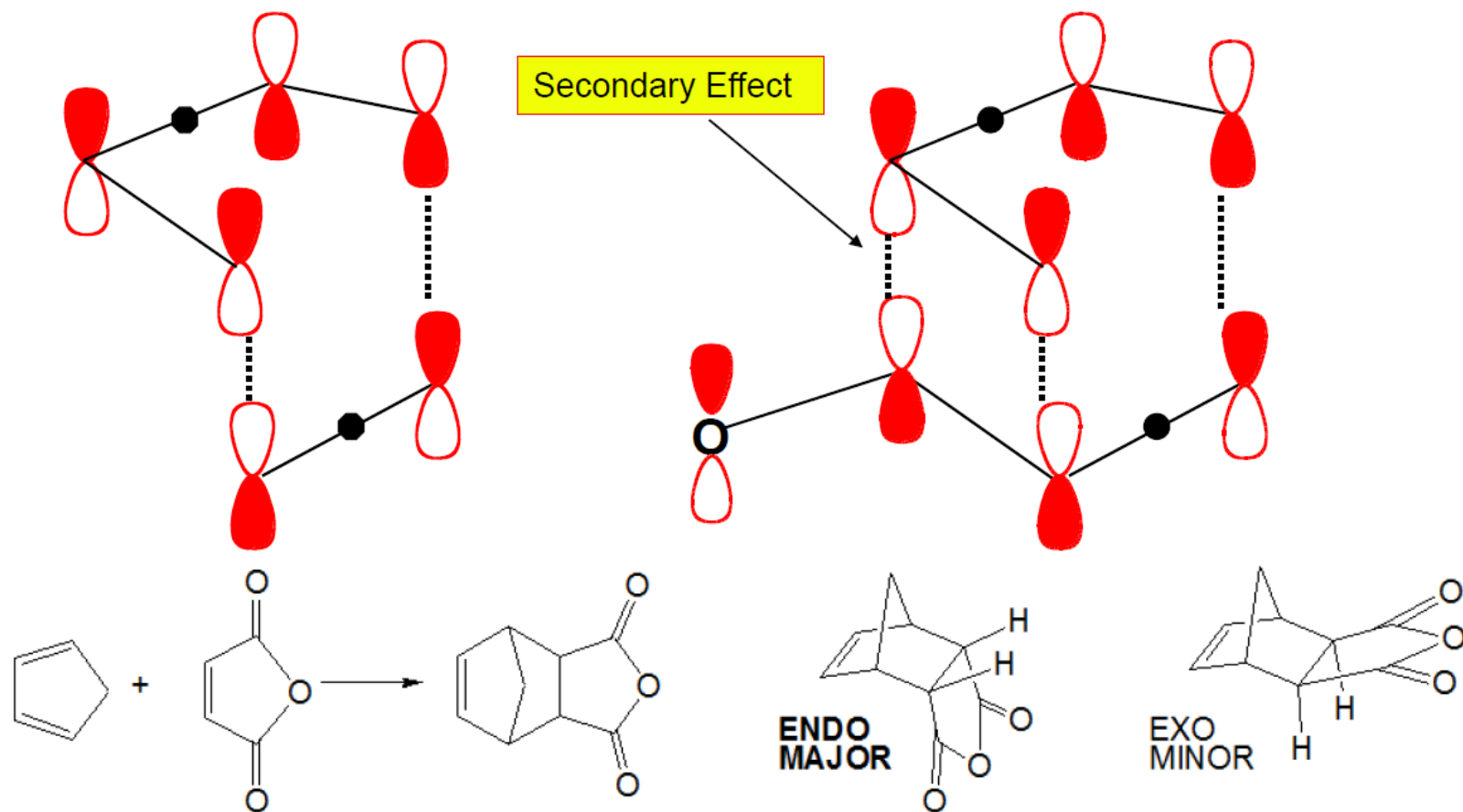
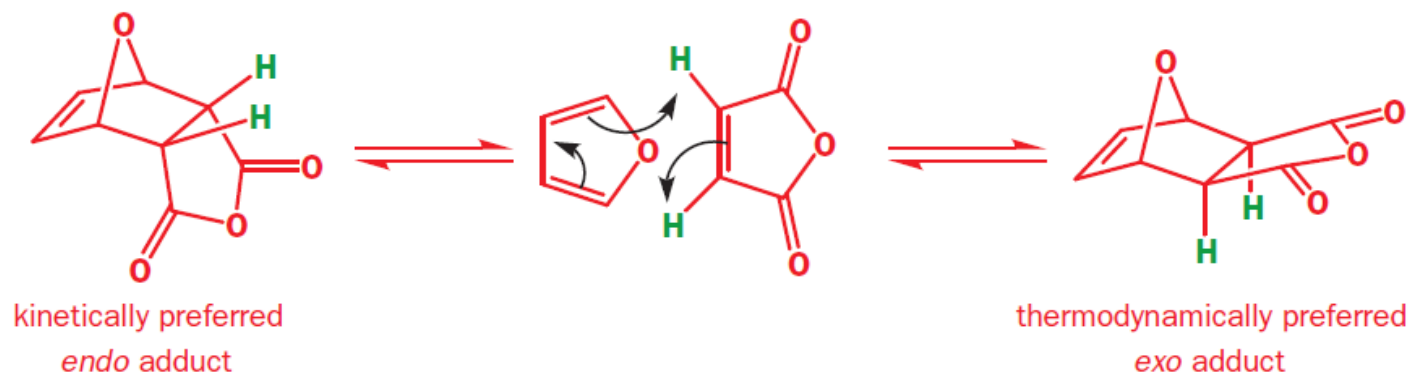
If you examine [2+2] and [4+4] cycloadditions, you will find that the combination of a HOMO and a LUMO results in an antarafacial component. Often, as a result, the reactions simply fail under thermal conditions, although they might well succeed using photochemical methods.



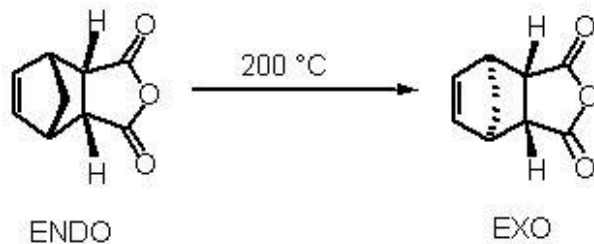
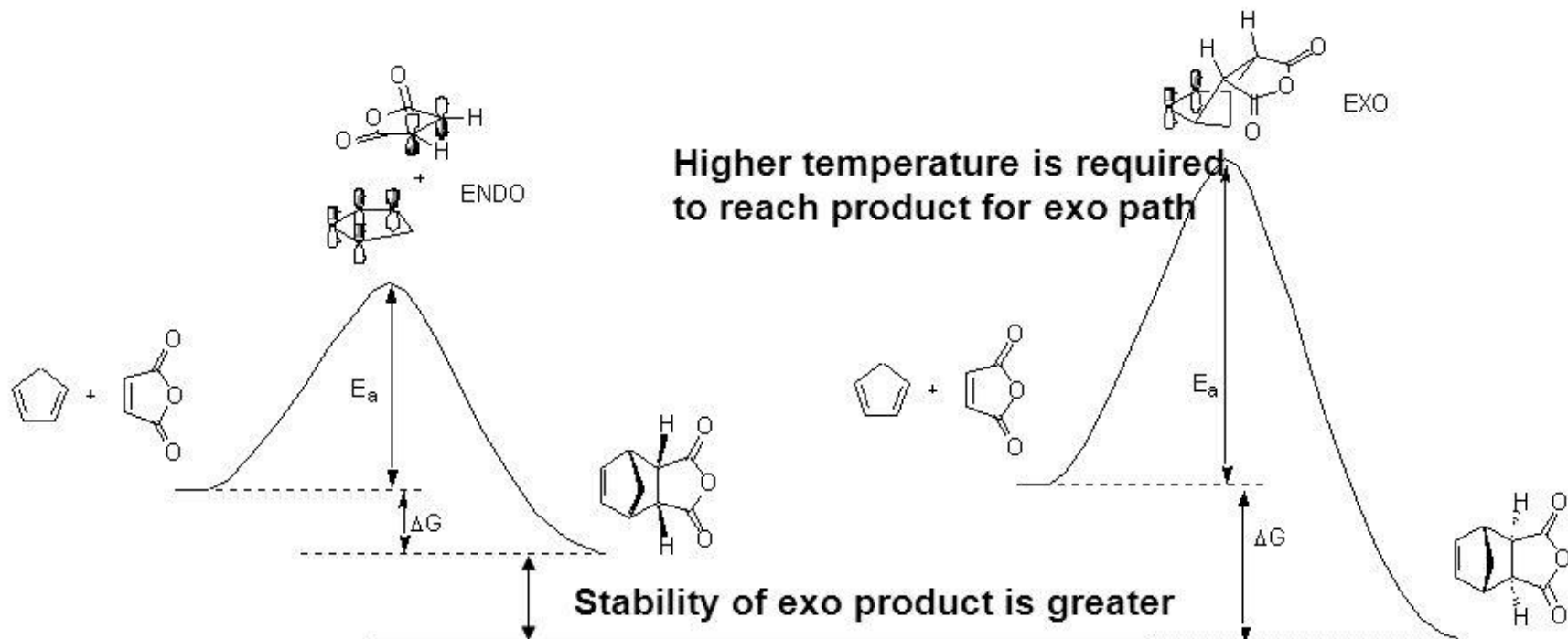
Diels Alder Reaction



Diels Alder Reaction



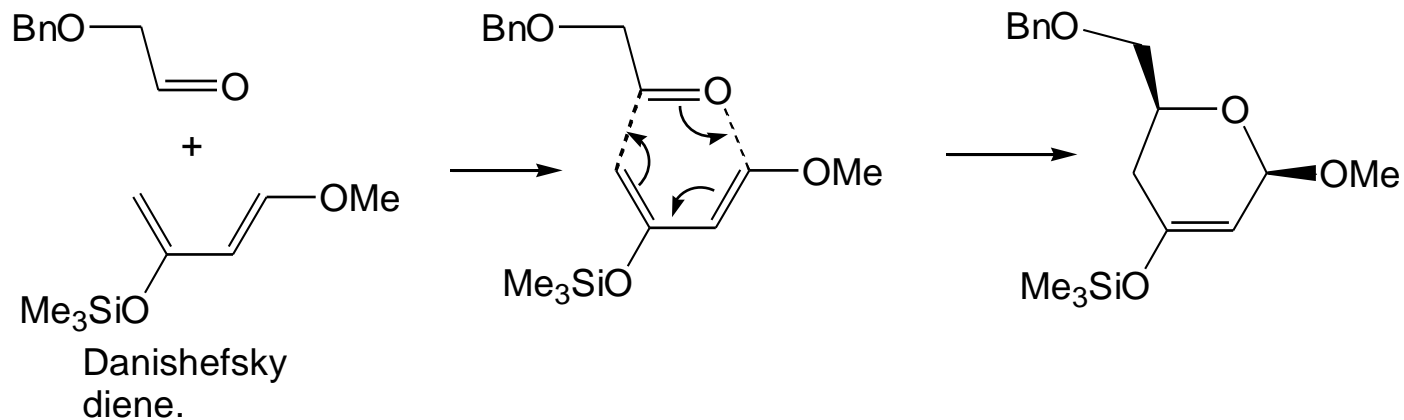
Diels-Alder Reaction



Running reaction at room temp gives kinetic product (endo)

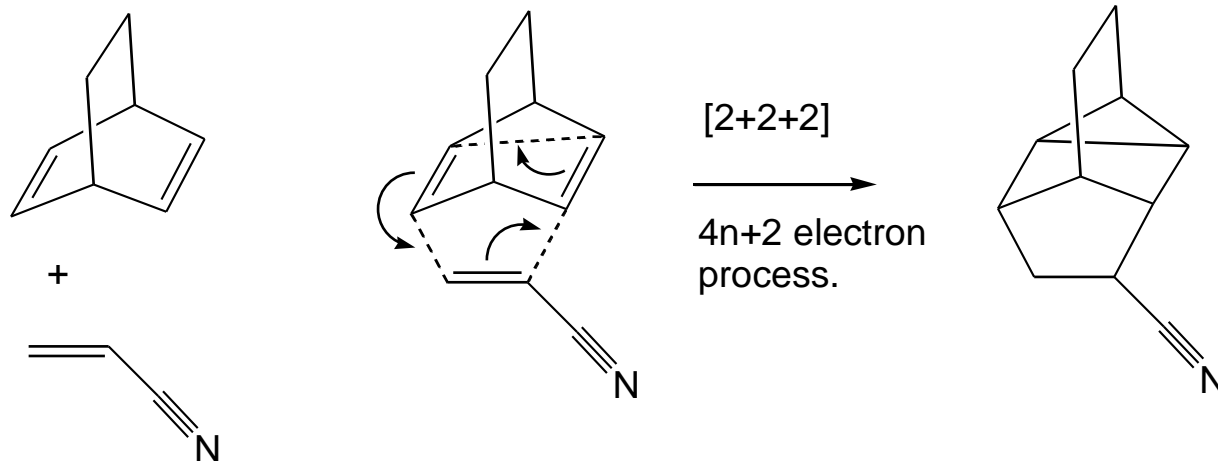
Running reaction at higher temp gives thermodynamic product (exo)

Hetero Diels-Alder reactions can be useful too



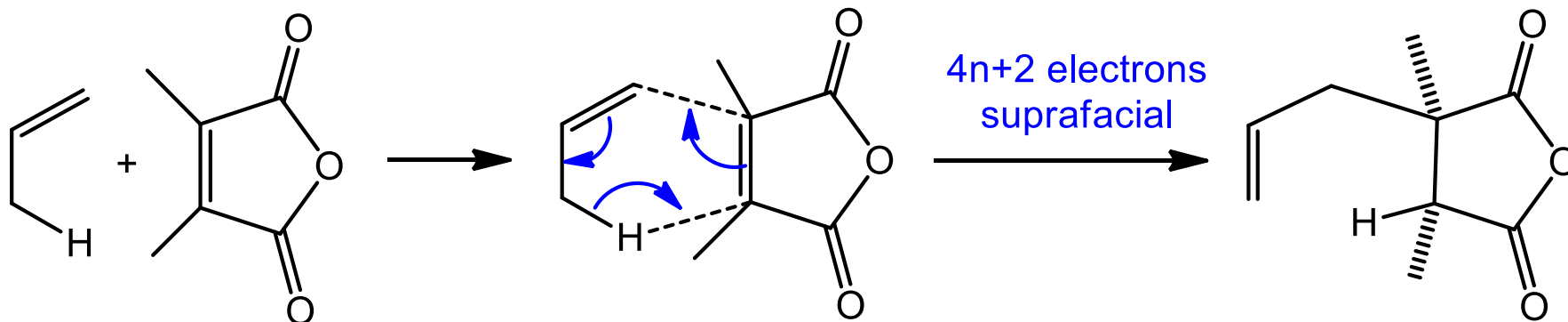
Three component Cycloadditions:

3-body collision
Is unlikely.

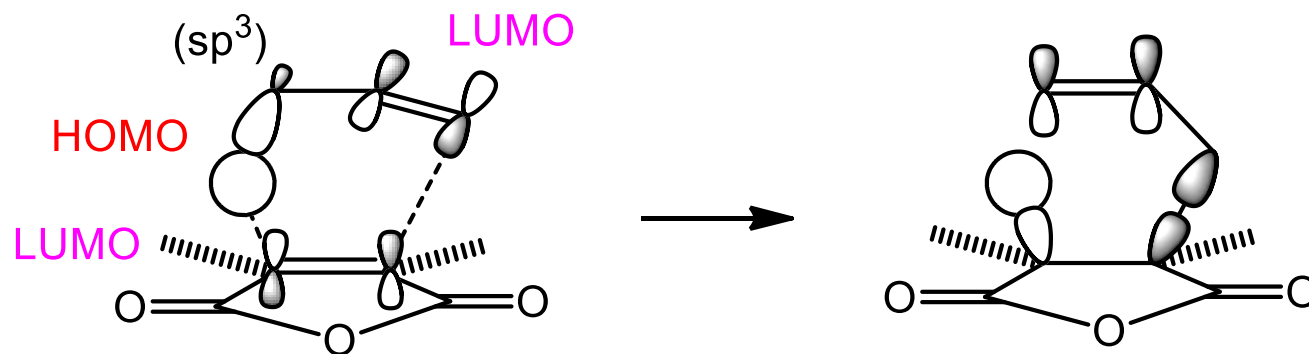


The Ene reaction; a type of cycloaddition

The ene reaction involves a cycloaddition between two alkenes, but with the formation of only a single C-C bond. A C-H bond is also formed in the process:



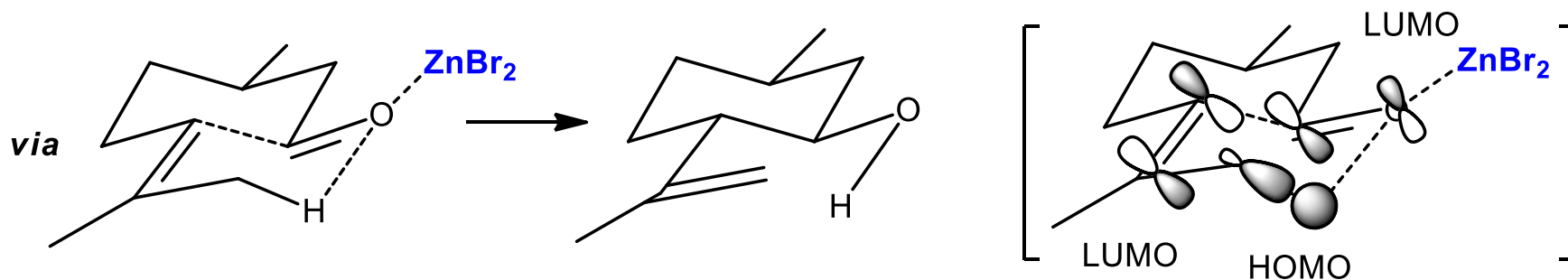
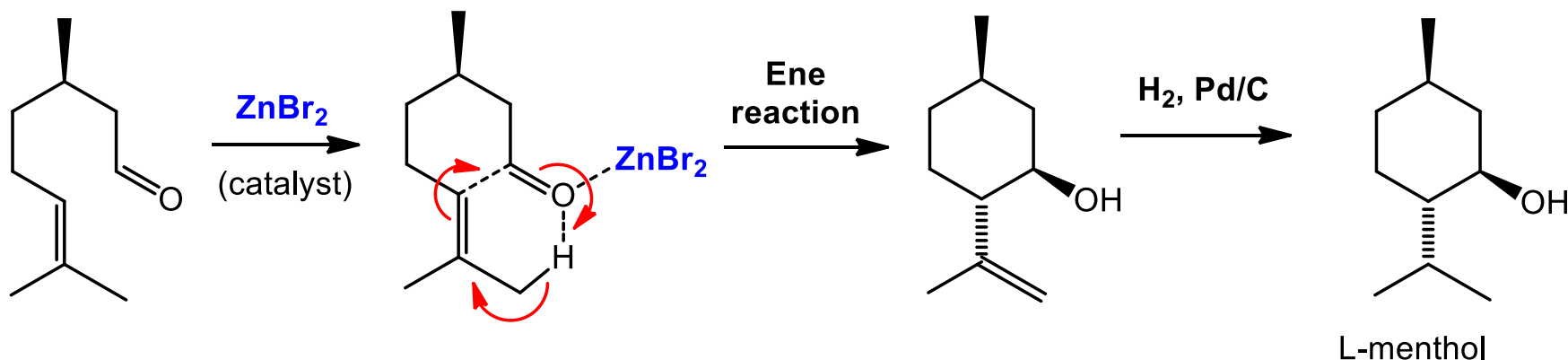
More complex as it involves 3 molecular orbital systems.



Orbital picture:

Menthol is prepared through an ene reaction:

The reaction below uses a mild Lewis acid. The chirality of the product comes entirely from the single chiral centre of the starting material. Note that the lone pair on the carbonyl oxygen is available for participation in this cyclisation.

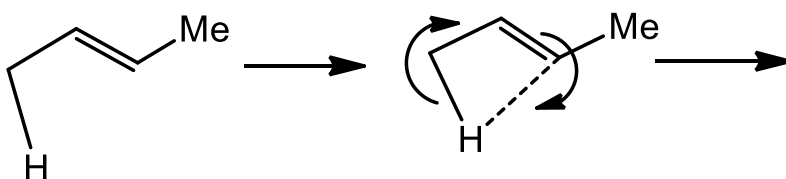


This process allows menthol to be made more efficiently than through extraction from natural sources. How would you make the starting material?

Woodward-Hoffmann theory for prediction of the stereochemistry of pericyclic reactions: Sigmatropic reactions

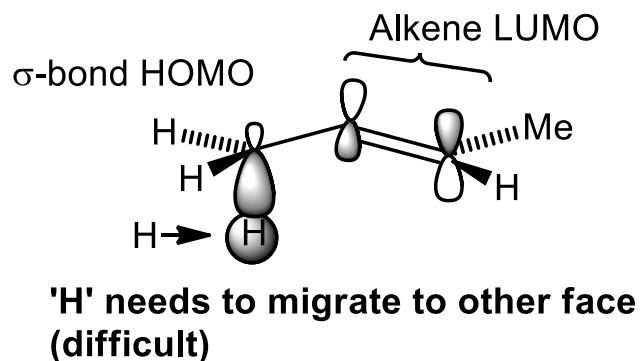
This time the rules will be given first, then the examples:

Ring size	No. electrons	Thermal	Photochemical
4,8,12...	$4n$	Antarafacial	Suprafacial
6,10,14...	$4n+2$	Suprafacial	Antarafacial



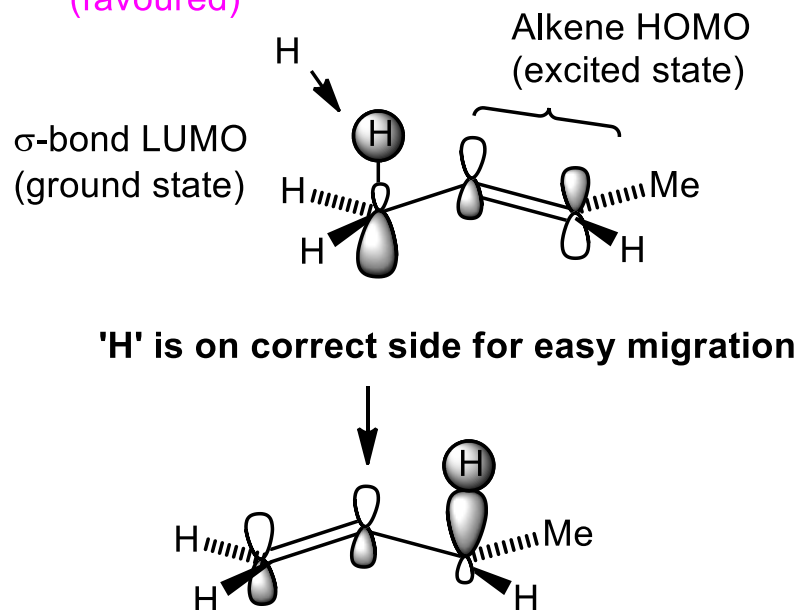
a [1,3] sigmatropic shift
(or rearrangement)

Thermal conditions:antarafacial
(disfavoured)



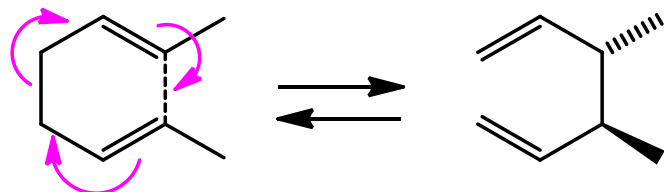
This is not often observed.

Photochemical conditions:suprafacial
(favoured)

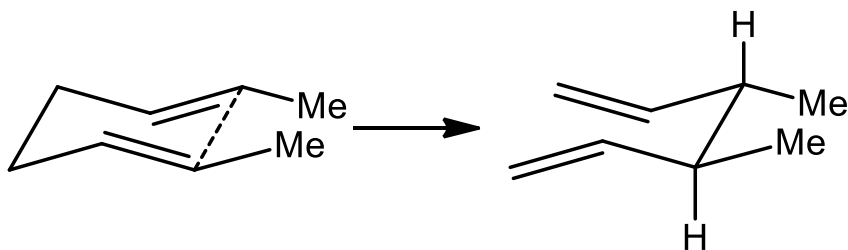


Sigmatropic [3,3]-reactions proceed suprafacially and are of great synthetic utility:

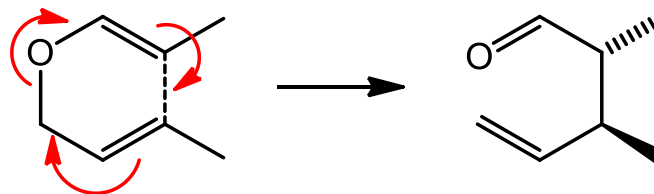
COPE rearrangement



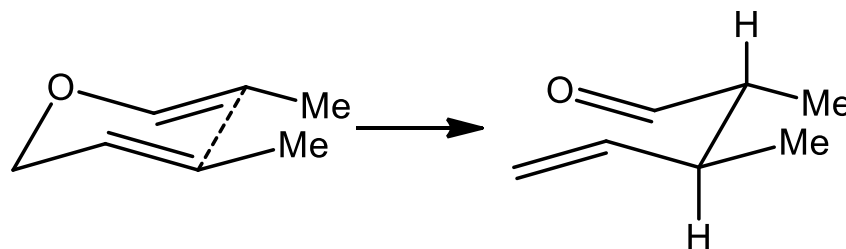
often reversible



CLAISEN rearrangement

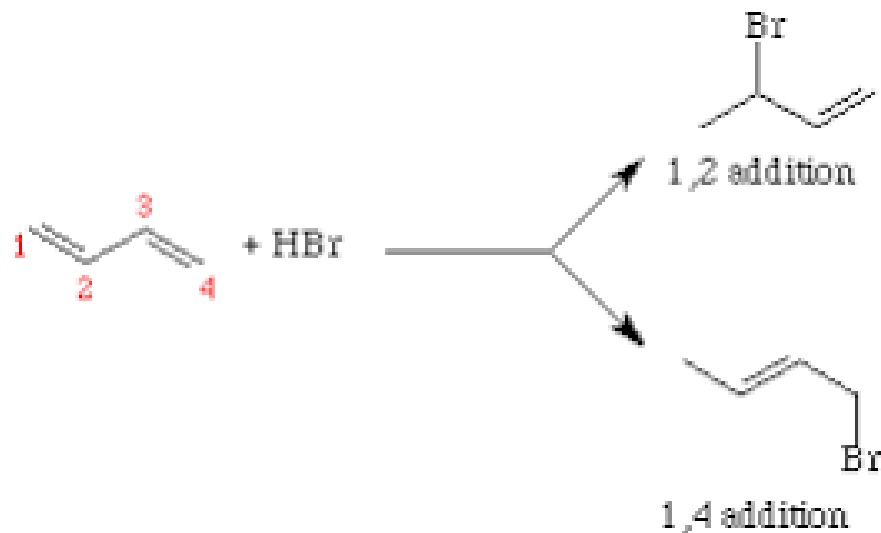


usually irreversible

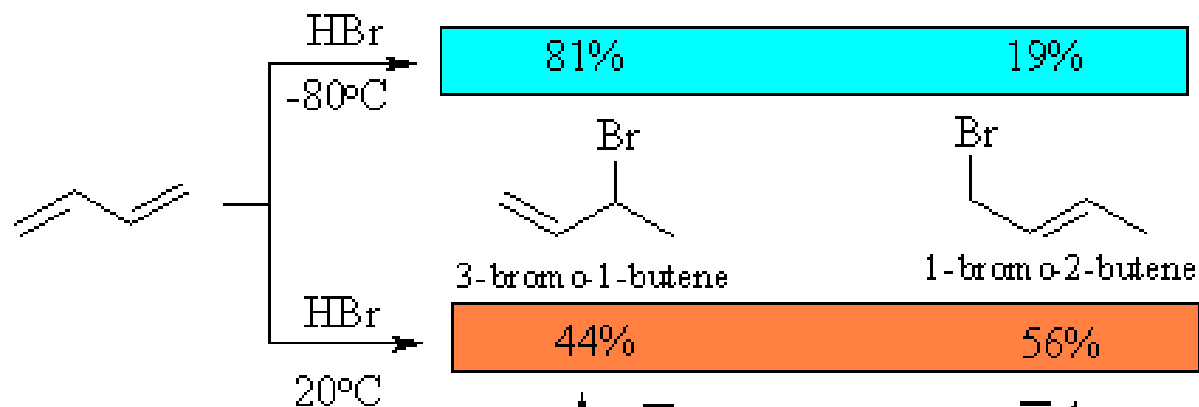
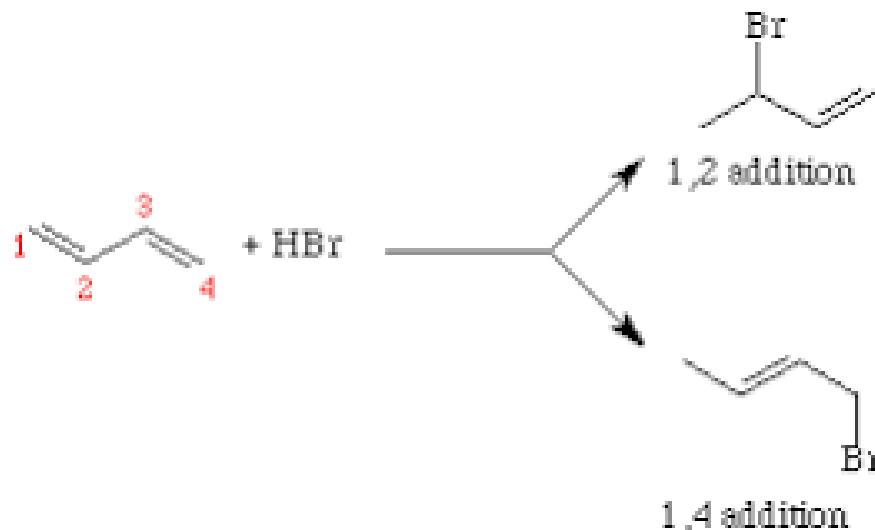


Both reactions proceed via a chair-like transition state.

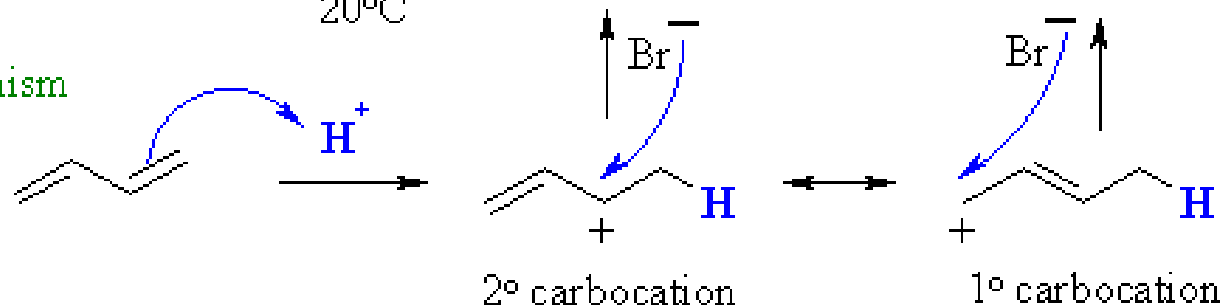
HBr addition to 1,3-butadiene: Thermodynamic and Kinetic Products



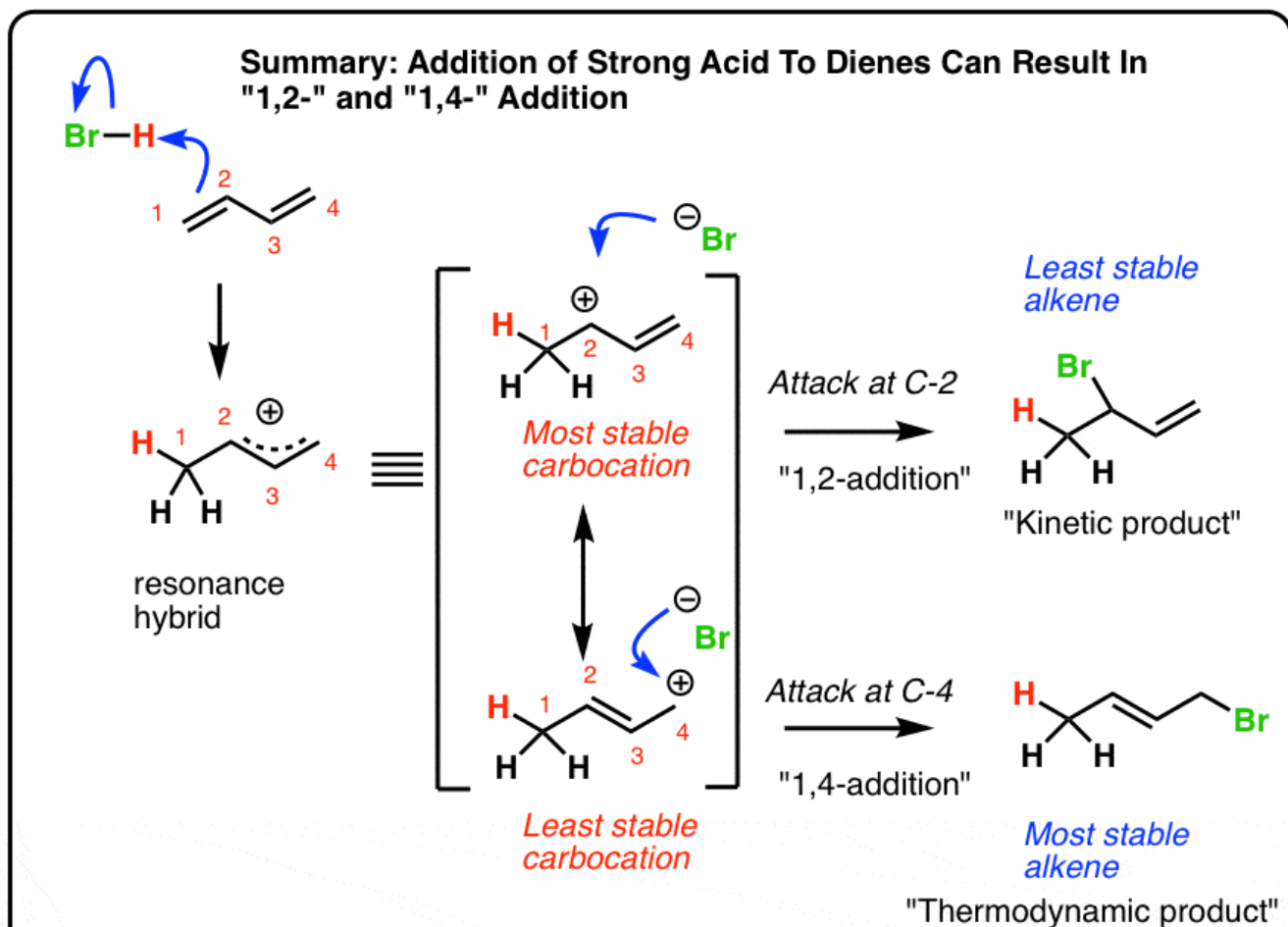
HBr addition to 1,3-butadiene: Thermodynamic and Kinetic Products



mechanism



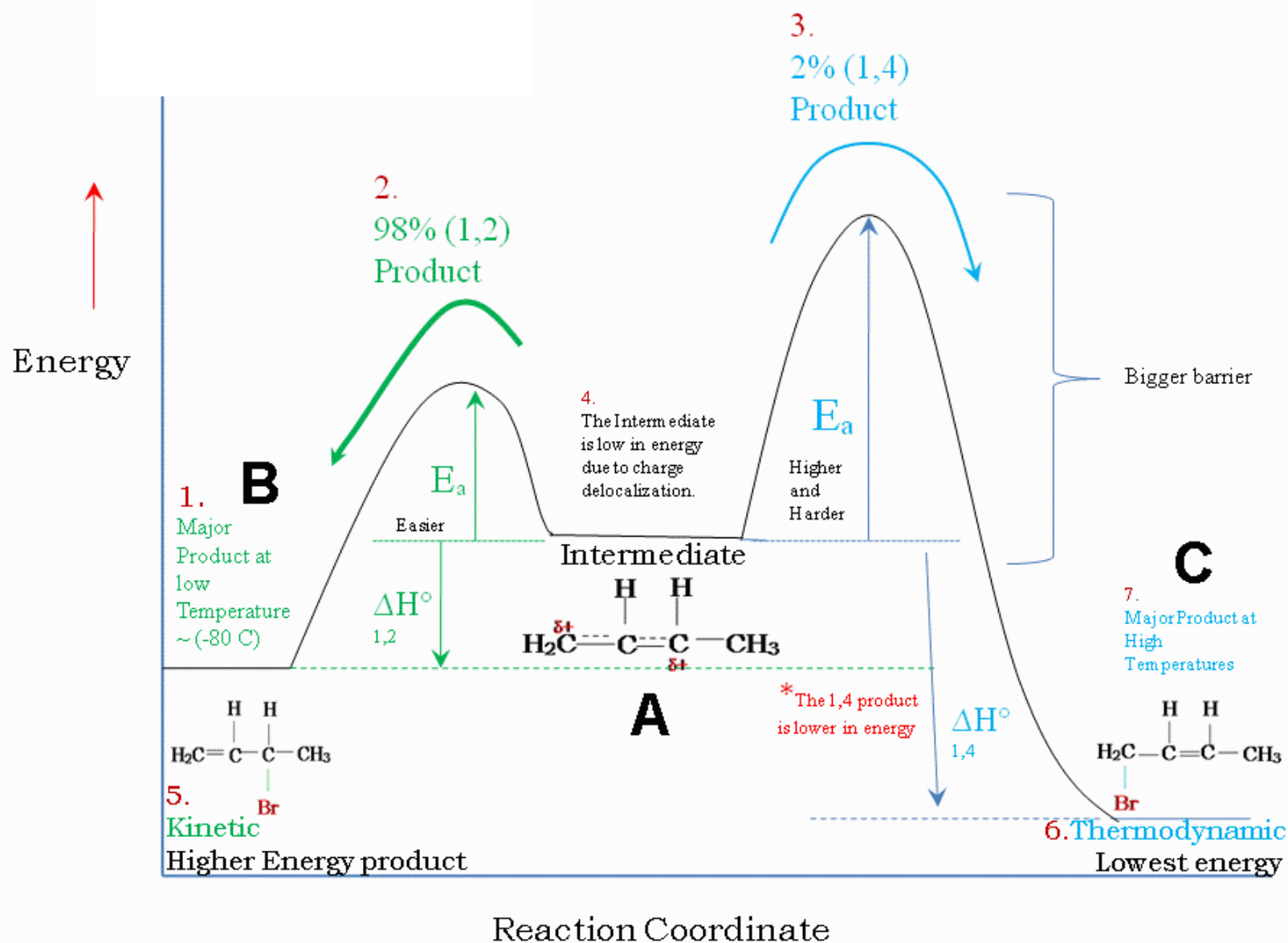
HBr addition to 1,3-butadiene: Thermodynamic and Kinetic Products



In this case, the major product can be controlled with temperature:

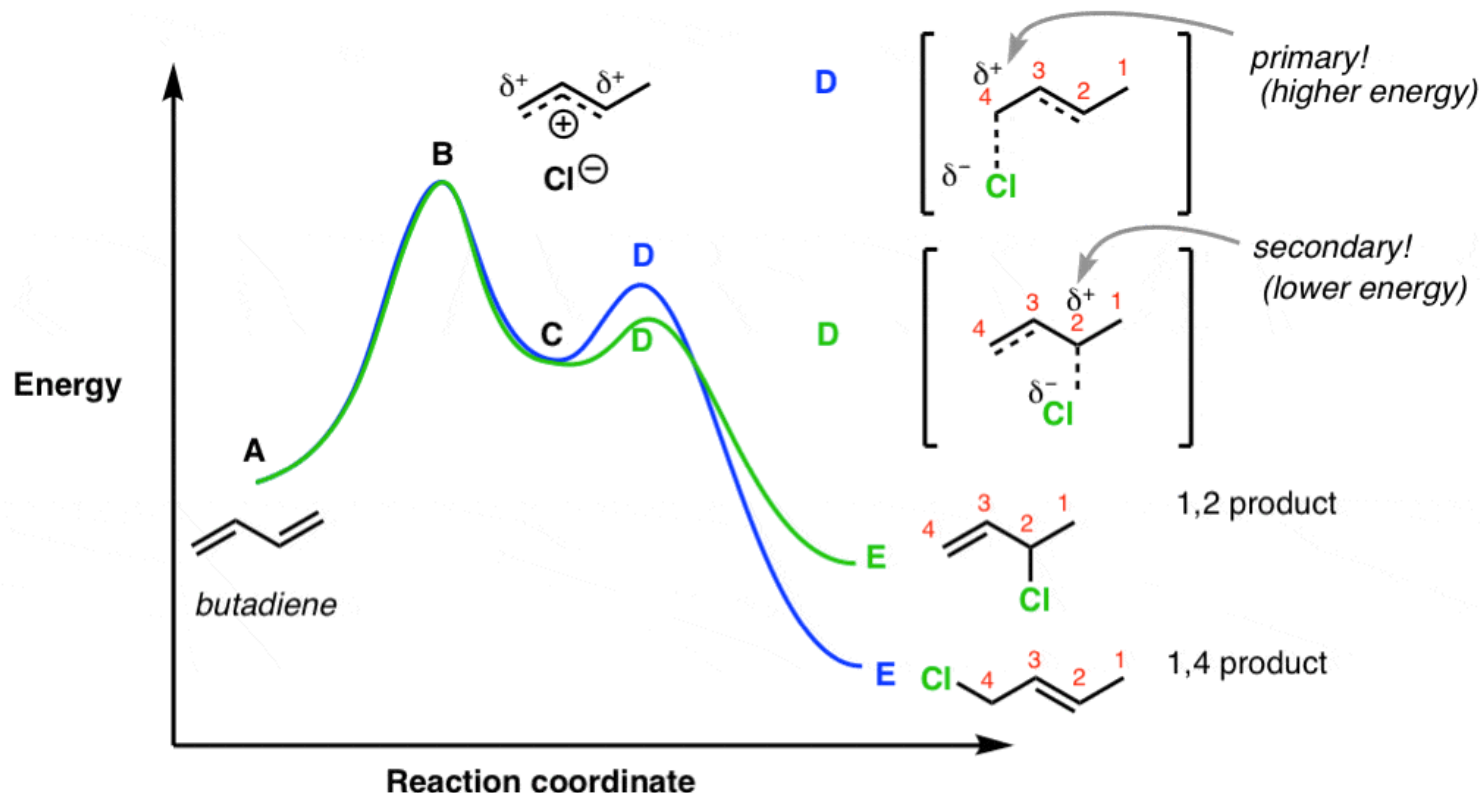
- At low temperatures, the reaction is irreversible and the lowest-energy transition state will determine the major product (i.e. addition to the carbon best able to stabilize positive charge). This is **kinetic control**.
- At higher temperatures, the reaction is reversible and the product distribution will favor the more stable product (the more substituted alkene, in this case). This is called **thermodynamic control**.

HBr addition to 1,3-butadiene: Thermodynamic and Kinetic Products



HCl addition to 1,3-butadiene: Thermodynamic and Kinetic Products

Energy coordinate for 1,2- versus 1,4- additions to butadiene

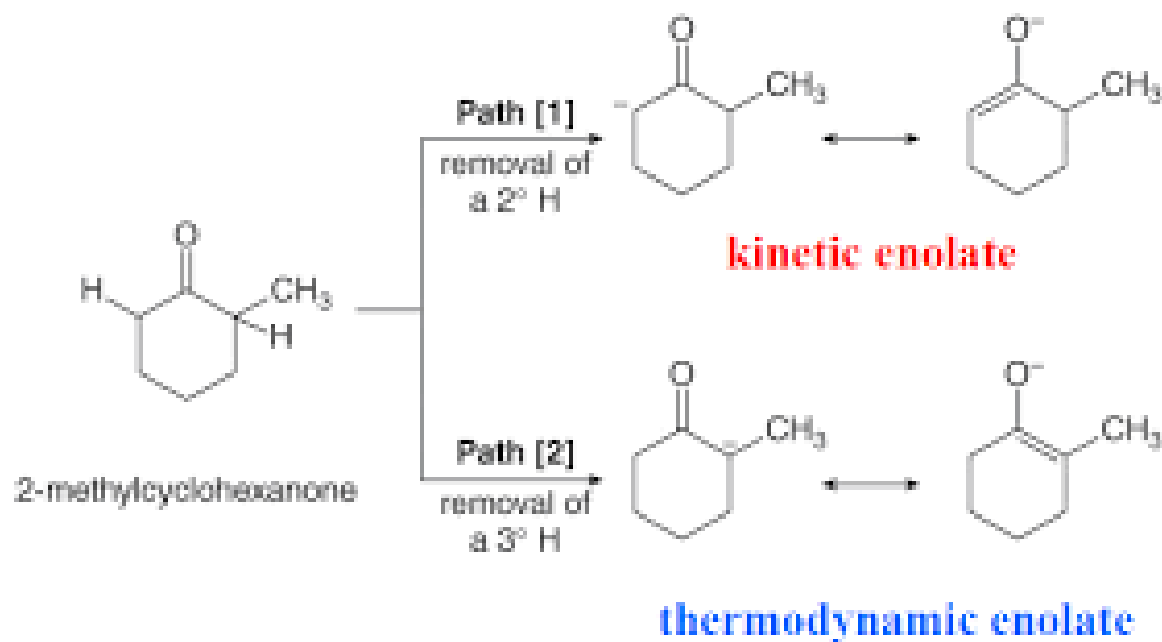


The height of transition states **D** and **D** (and therefore their reaction rate from carbocation C) is related to the stability of the positive charge in **D** and **D**.

The lower the energy, the faster the reaction. So **E** is formed faster from C here since the energy of transition state **D** is less than **D**

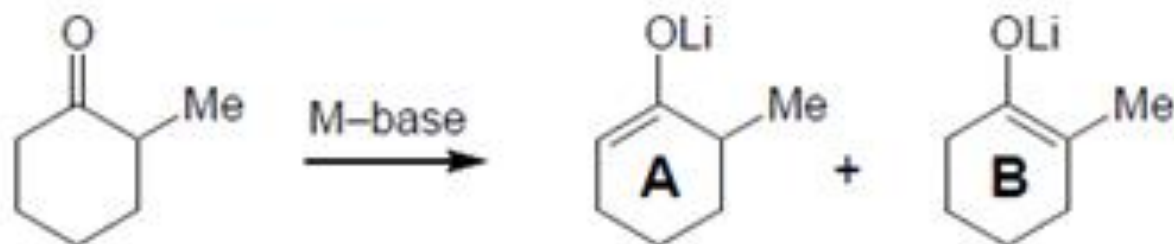
The energy of **E** and **E** is related to the greater stability of the 1,4 alkene in this case (disubstituted versus monosubstituted). **E** has a more substituted double bond than **E**, so it is more stable.

Thermodynamic and Kinetic Products of Enolates



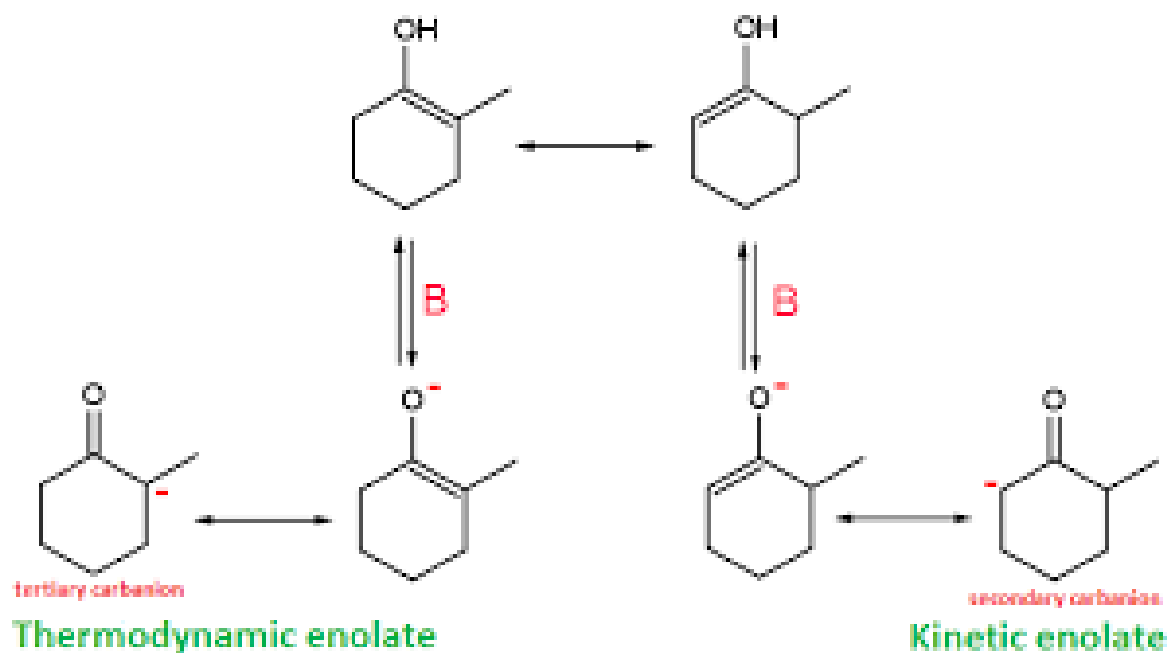
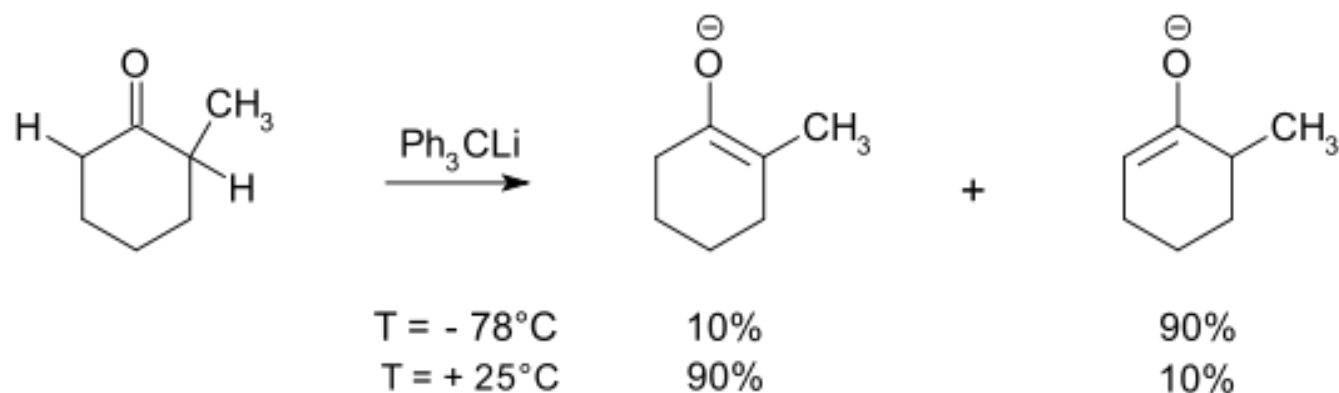
Thermodynamic and Kinetic Products of Enolates

Regioselective Enolization

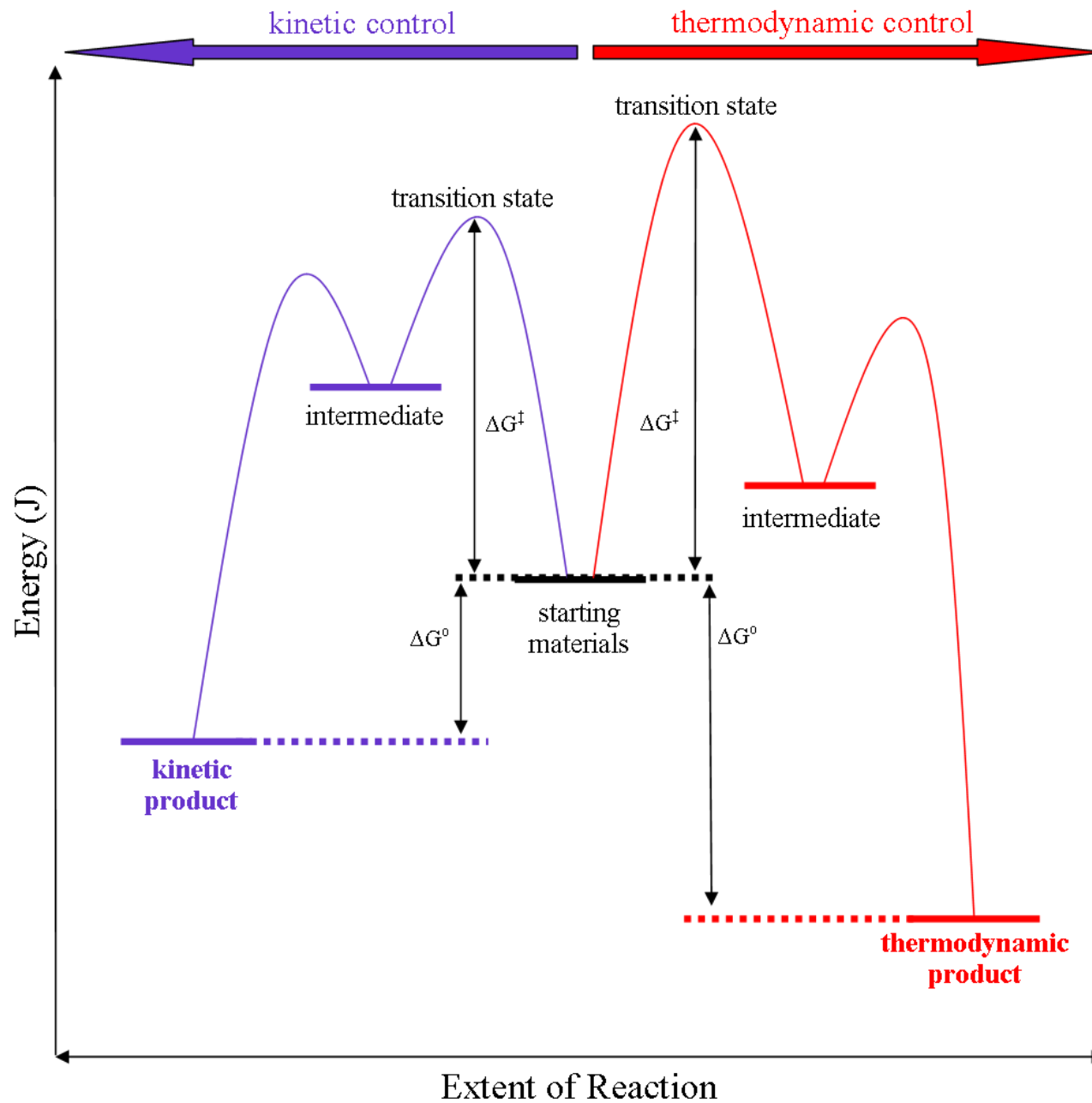


Base	temp	control	Ratio (A:B)
LiN(i-Pr) ₂	-78 °	kinetic	99:1
LiN(SiMe ₃) ₂	-78 °	kinetic	95:5
Ph ₃ C-Li	-78 °	kinetic	90:10
Ph ₃ C-Li	heat	thermo	10:90
Na-H	heat	thermo	26:74
K-H	heat	thermo	38:62

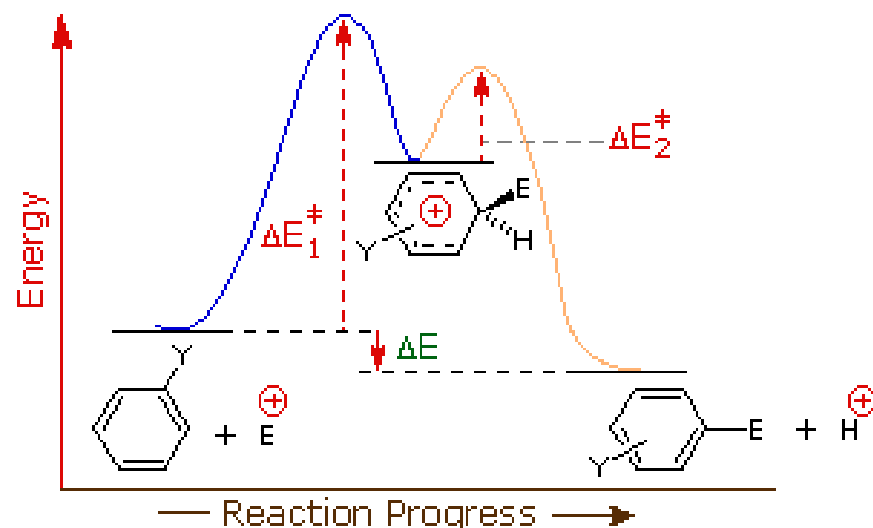
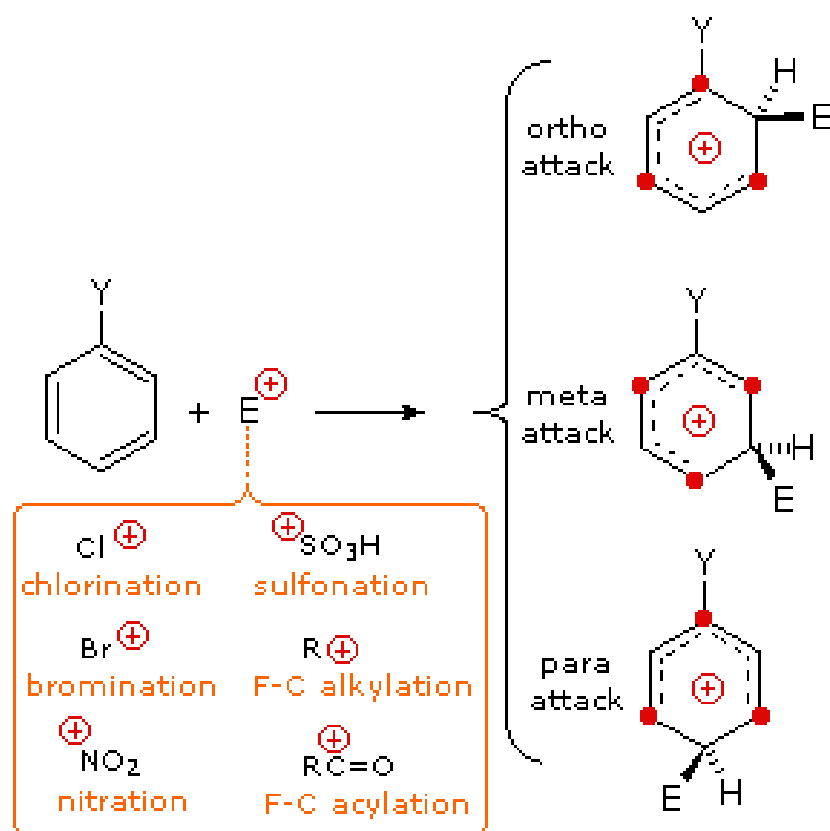
Thermodynamic and Kinetic Products of Enolates



Thermodynamic and Kinetic Products of Enolates



Aromatic Electrophilic Substitution

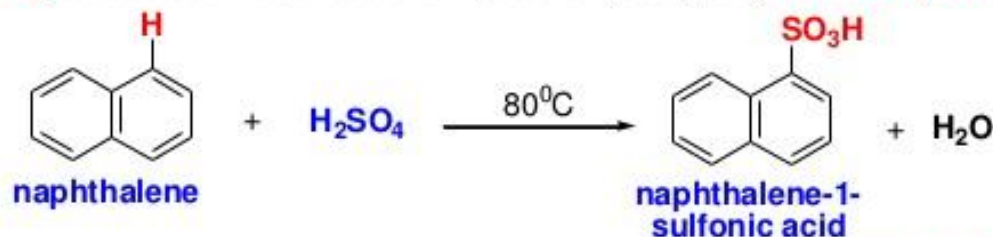


The first step in electrophilic aromatic substitution ([shown here](#)) is both rate-determining and product determining. To see the effect various substituents ($-Y$) have on the orientation of such substitutions press one of the buttons provided below.

Thermodynamic and Kinetic Products

Sulfonation of naphthalene

Sulfonation of naphthalene does not always lead to substitution at the 1-position; may occur at 2-position. If the reaction is carried out under conditions which cause it to be **irreversible (80°C)**, substitution occurs at the 1-position (90% yield; **kinetically control**).

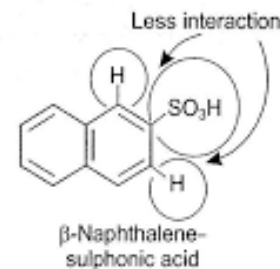
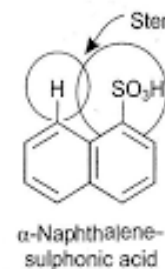


the reaction is carried out under conditions which cause it to be readily **reversible (160°C)**, substitution occurs predominantly at the 2-position (90% yield, thermodynamically control).

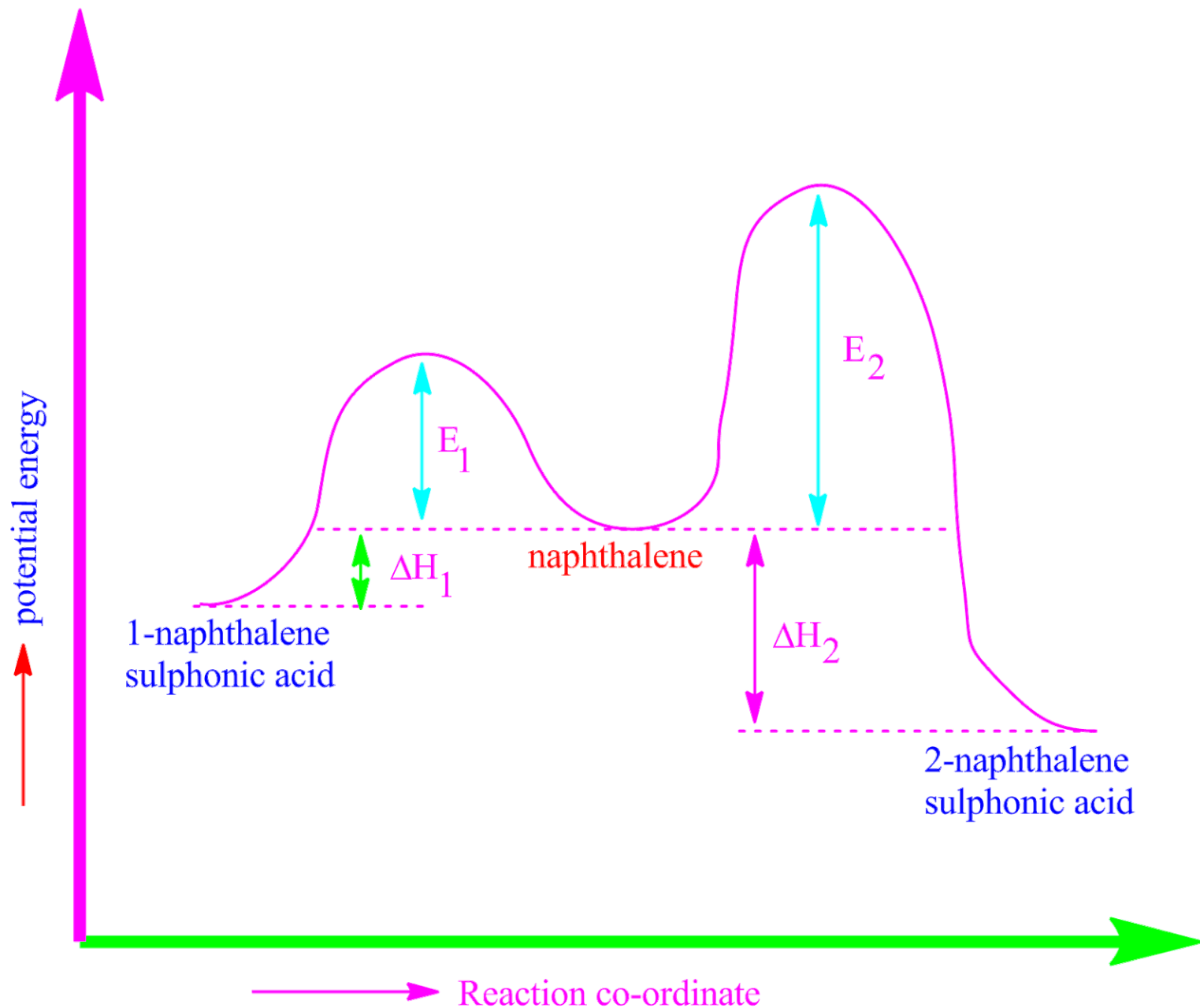


(v) Sulfonation

The lower stability of 1-8 is attributed to the steric interaction between the sulfonic group and the hydrogen atom in the 8-position.



Thermodynamic and Kinetic Products



Thermodynamic and Kinetic Products

