DAMIETTA UNIVERSITY

CHEM-405:

PERICYCLIC REACTIONS
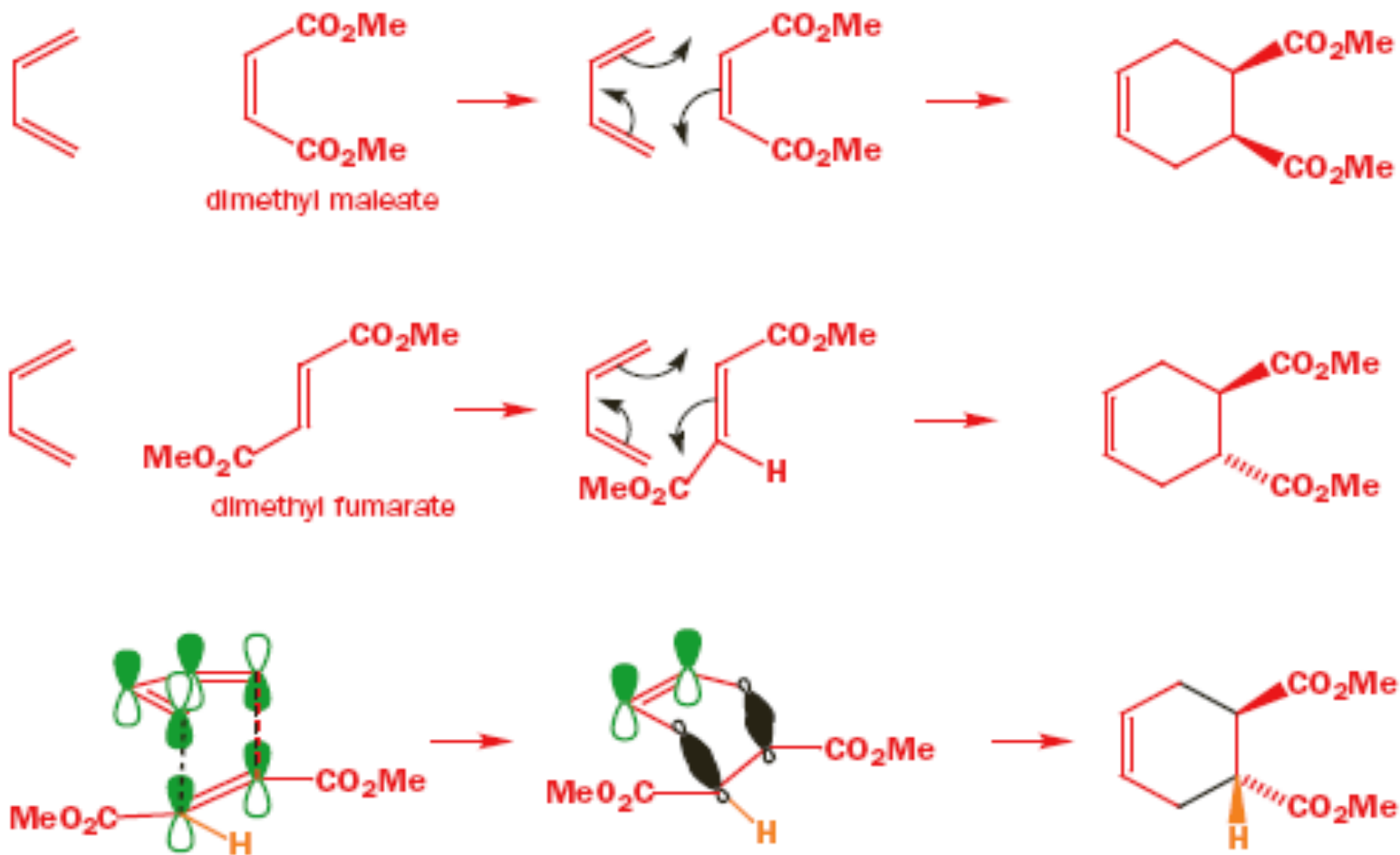
LECTURE 5

Dr Ali El-Agamey

Stereospecificity

➤ The stereochemical relationships among substituents in a suprafacial component of a cycloaddition are **preserved** in the cycloadduct.[1]

➤ Groups that are *cis* (or *trans*) to one another in the dienophile become *cis* (or *trans*) to one another in the product. The **two *out* groups in the diene become *cis* to one another in the product, as do the two *in* groups.**[1]

➤ Because one diastereomeric starting material gives one diastereomeric product, cycloadditions are said to be ***stereospecific*.**[1]
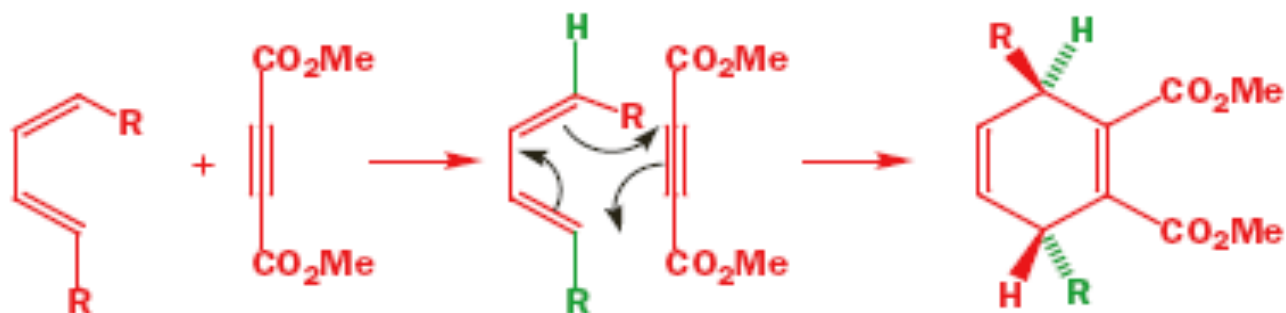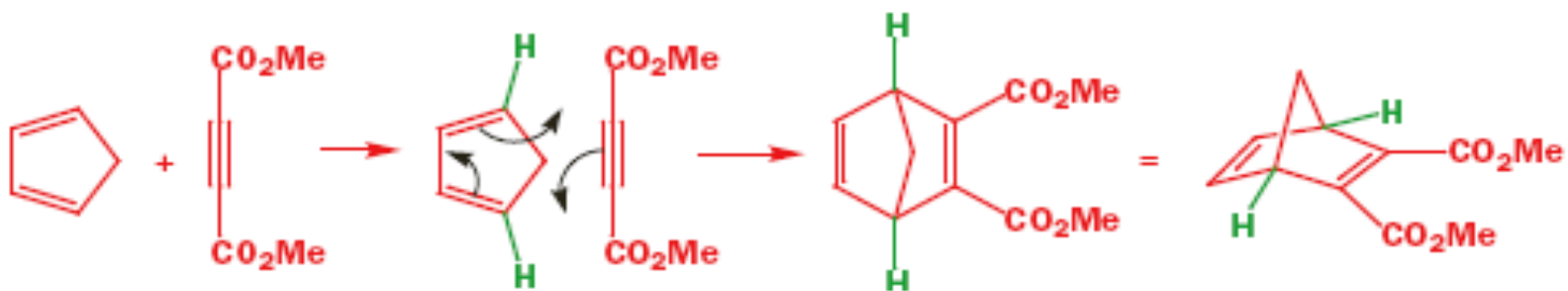
Stereospecificity

➢ Groups that are *cis* (or *trans*) to one another in the dienophile become *cis* (or *trans*) to one another in the product.

dimethyl maleate

dimethyl fumarate

Stereospecificity

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Stereospecificity

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➢ Because one diastereomeric starting material gives one diastereomeric product, cycloadditions are said to be *stereospecific*.[1]
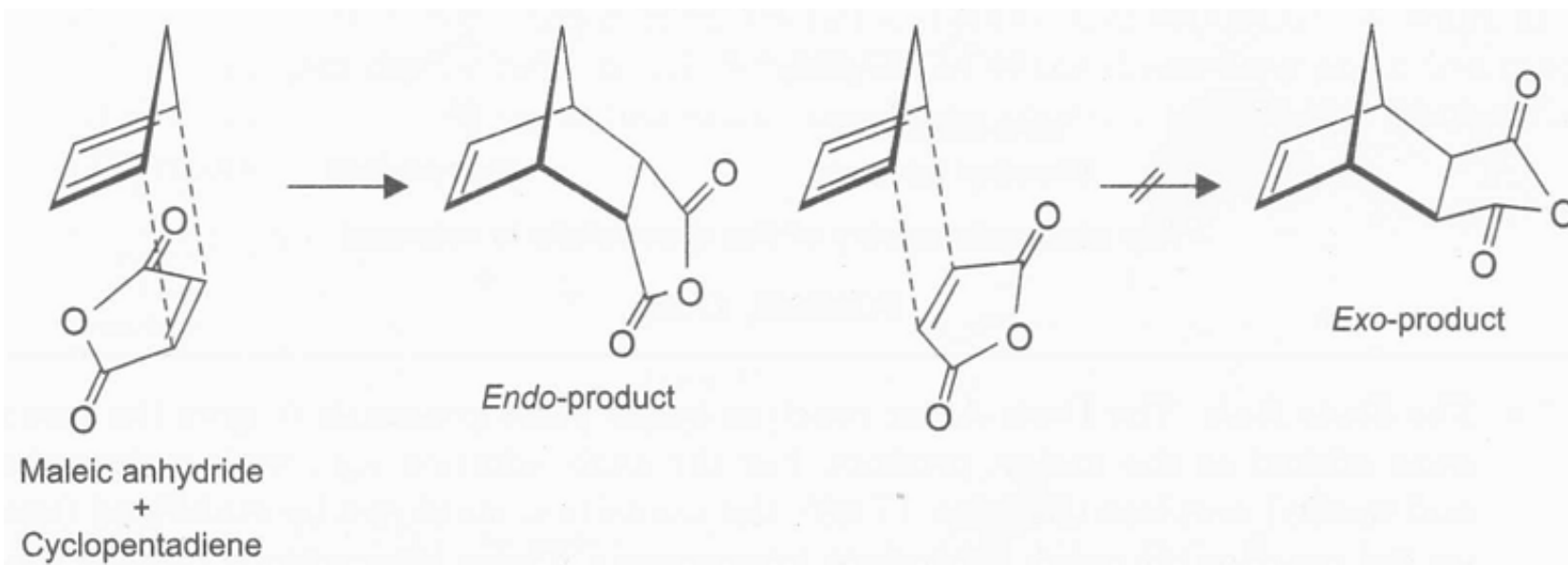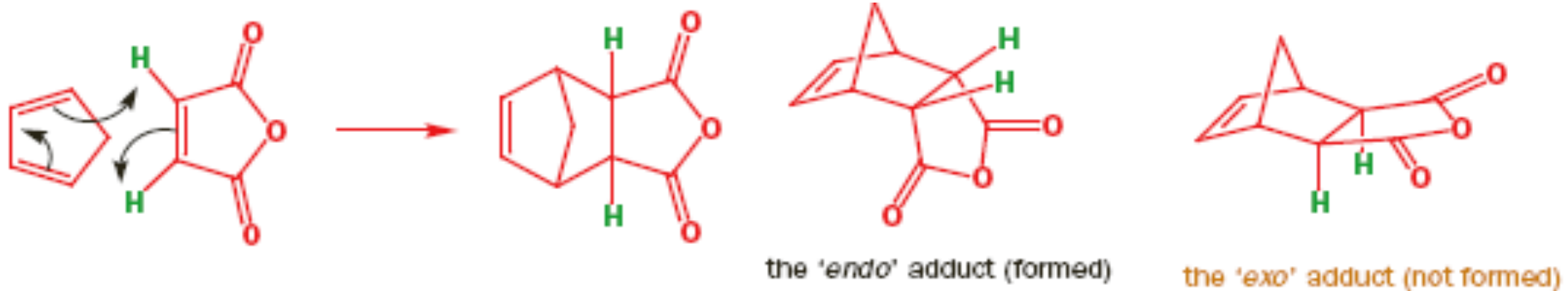
Stereoselectivity: *endo vs exo*

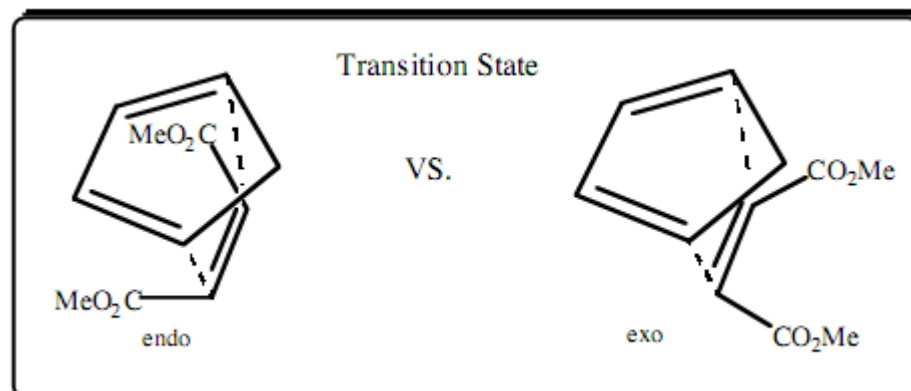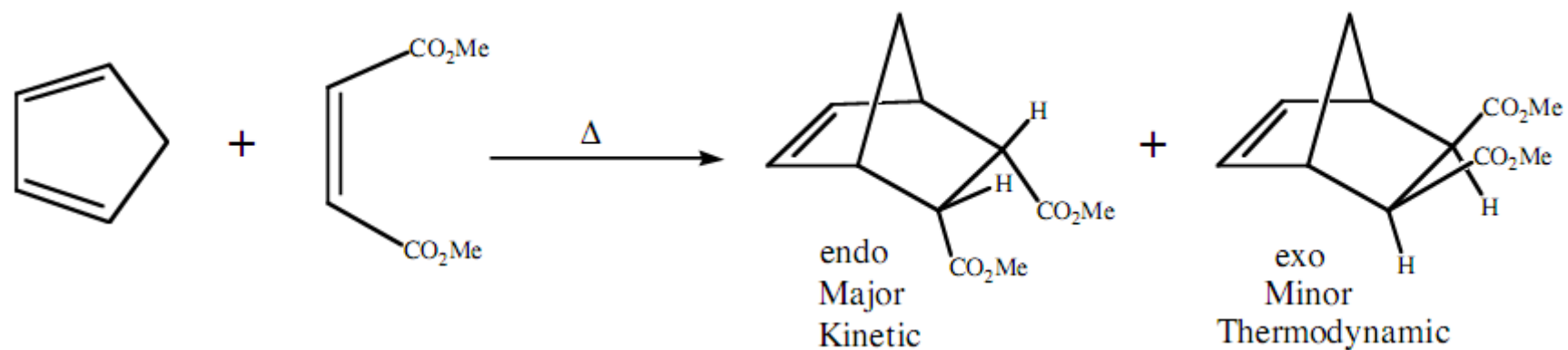the '*endo*' adduct (formed)　　the '*exo*' adduct (not formed)
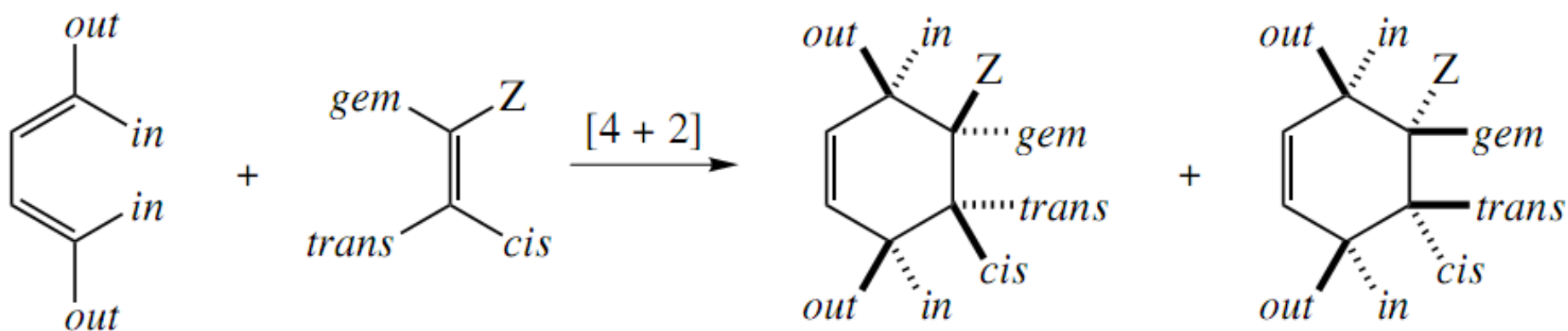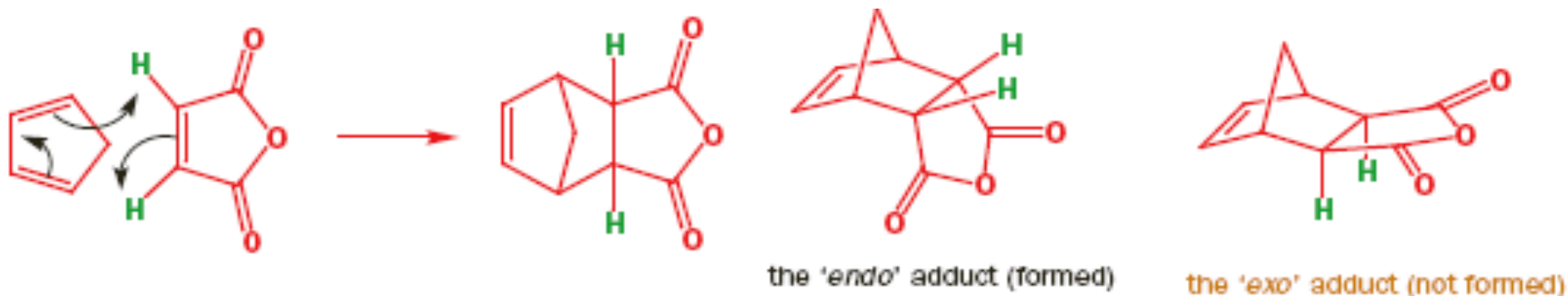
➢ There are **two possible** stereoisomeric products that are consistent with the Woodward–Hoffmann rules. The **two green hydrogen must be *cis*** in the product **but there are two possible products in which these Hs are *cis***. They are called *exo* and *endo*.[1,2]

➢ The Woodward–Hoffmann rules allow you to predict the stereochemical relationship between substituents derived from the *same* component. They do not allow you to predict the relationship between substituents derived from *different* components. Guidelines for predicting the latter kind of relationship will be discussed shortly.[1,2]

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Stereoselectivity: *endo vs exo*

the '*endo*' adduct (formed)   the '*exo*' adduct (not formed)

Maleic anhydride
+
Cyclopentadiene

Endo-product

Exo-product

Stereoselectivity: *endo vs exo*
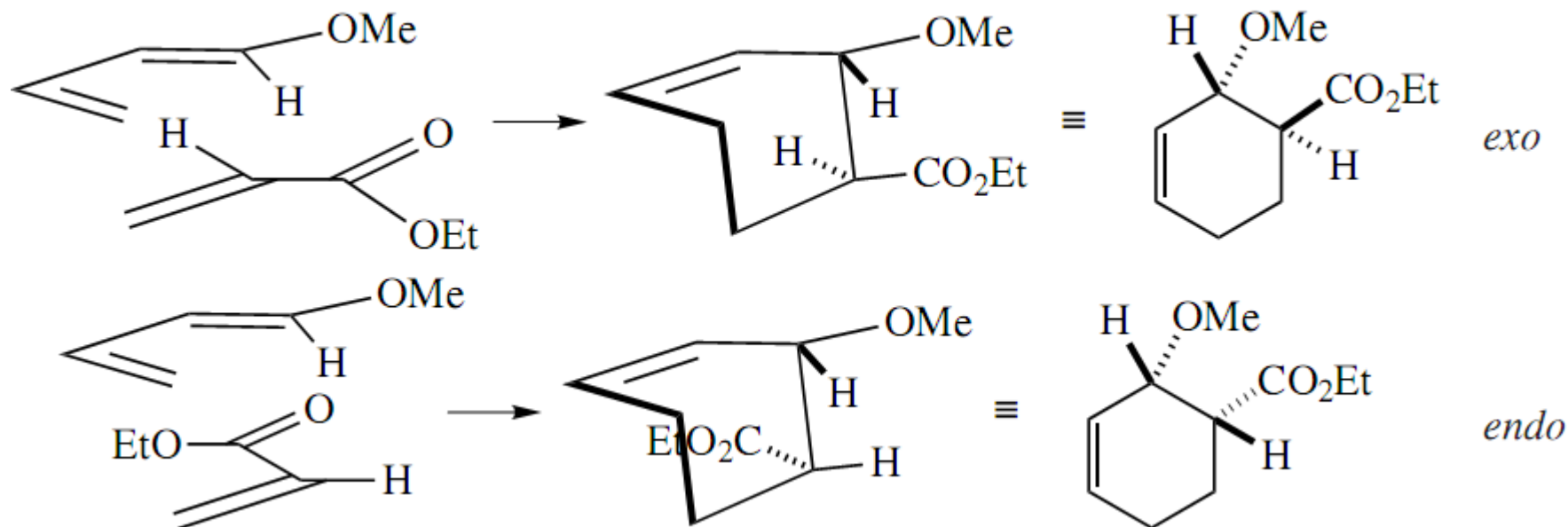
Stereoselectivity: *endo vs exo*

How can we draw the product of Diels-Alder reaction?

(The *out-endo-cis rule*): The *out-endo-cis rule* is a device for drawing the products of Diels–Alder reactions with stereochemistry consistent with the *endo* rule.

major product with endo electron-withdrawing Z group
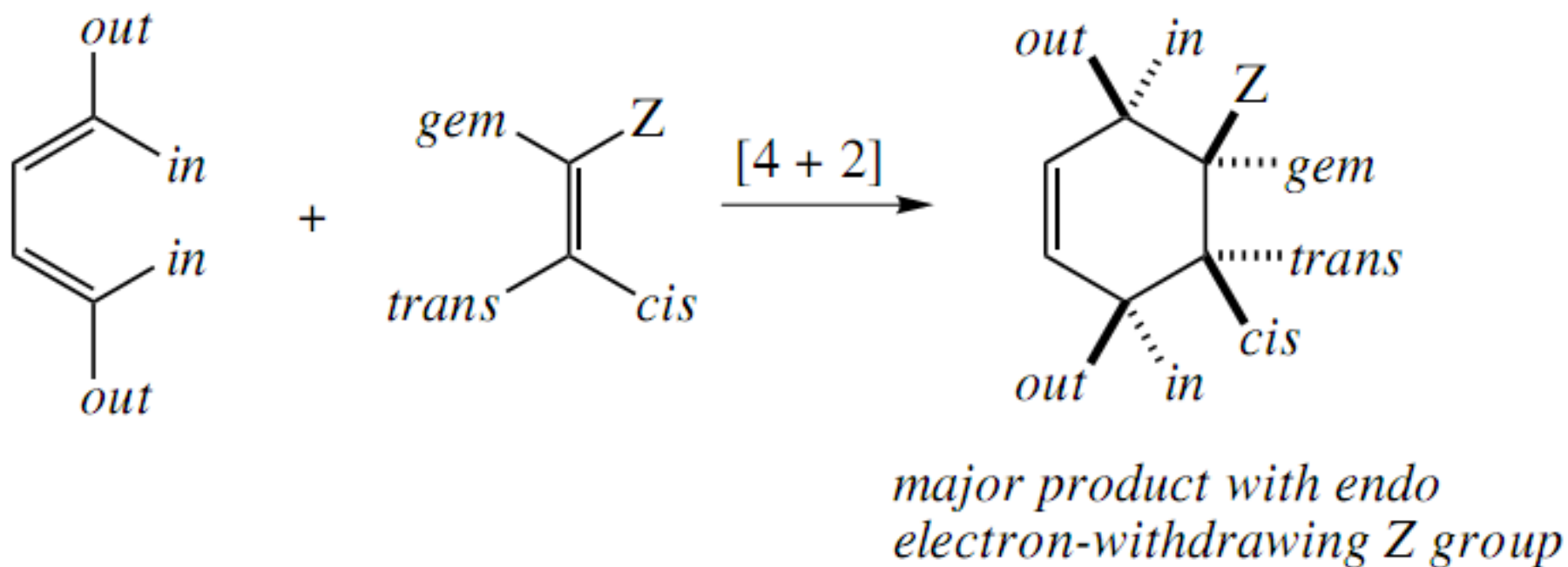
Stereoselectivity: *endo vs exo*

➢ Consider the Diels–Alder reaction between 1-methoxybutadiene and ethyl acrylate.[1]


➢ The **major product** has the MeO and CO_2Et groups on adjacent C atoms (**"ortho product"**).[1]

➢ A reaction that is **stereospecific** with respect to each component could give **either the *cis* or the *trans*** product.[1]
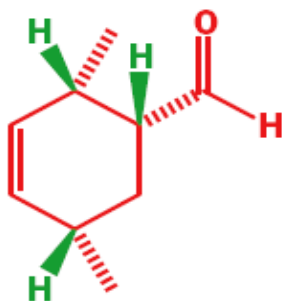
Stereoselectivity: *endo vs exo*

➤ The TS leading to the product in which the substituents are *trans* is clearly **less sterically** hindered than the other TS, and so **one would predict** that the *trans* product is predominantly obtained. However, the **major product** is the one in which the groups are *cis*.[1]
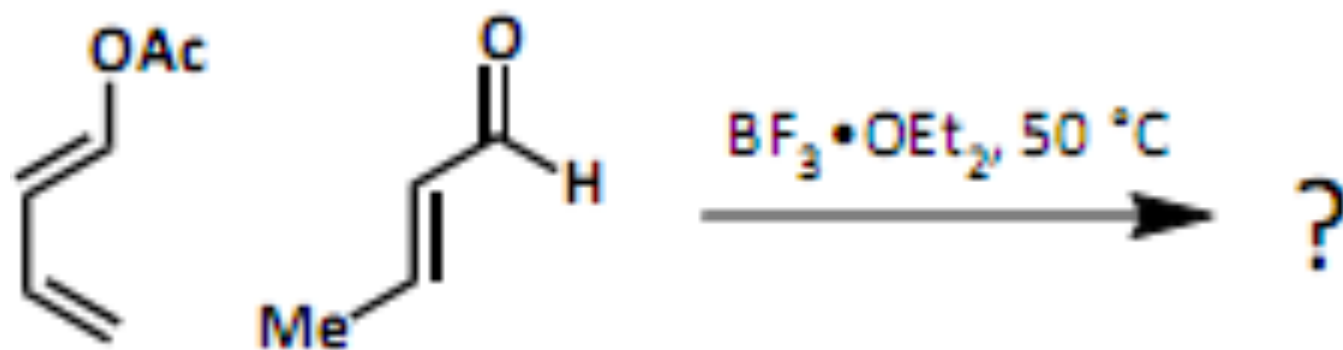
Stereoselectivity: *endo vs exo*

How can we draw the product of Diels-Alder reaction?
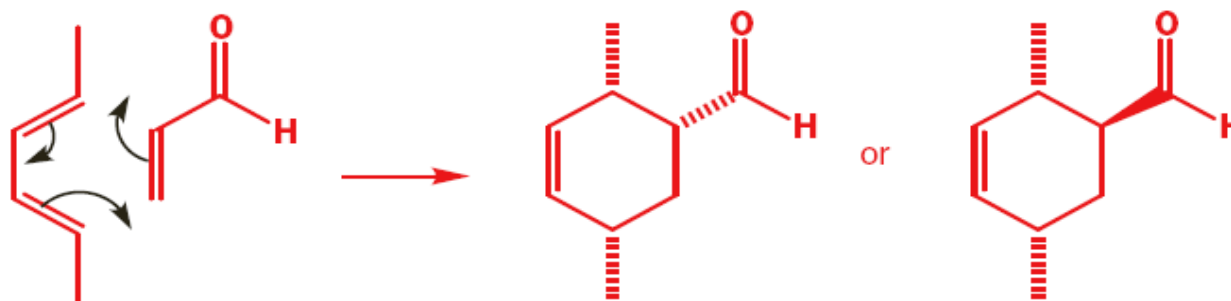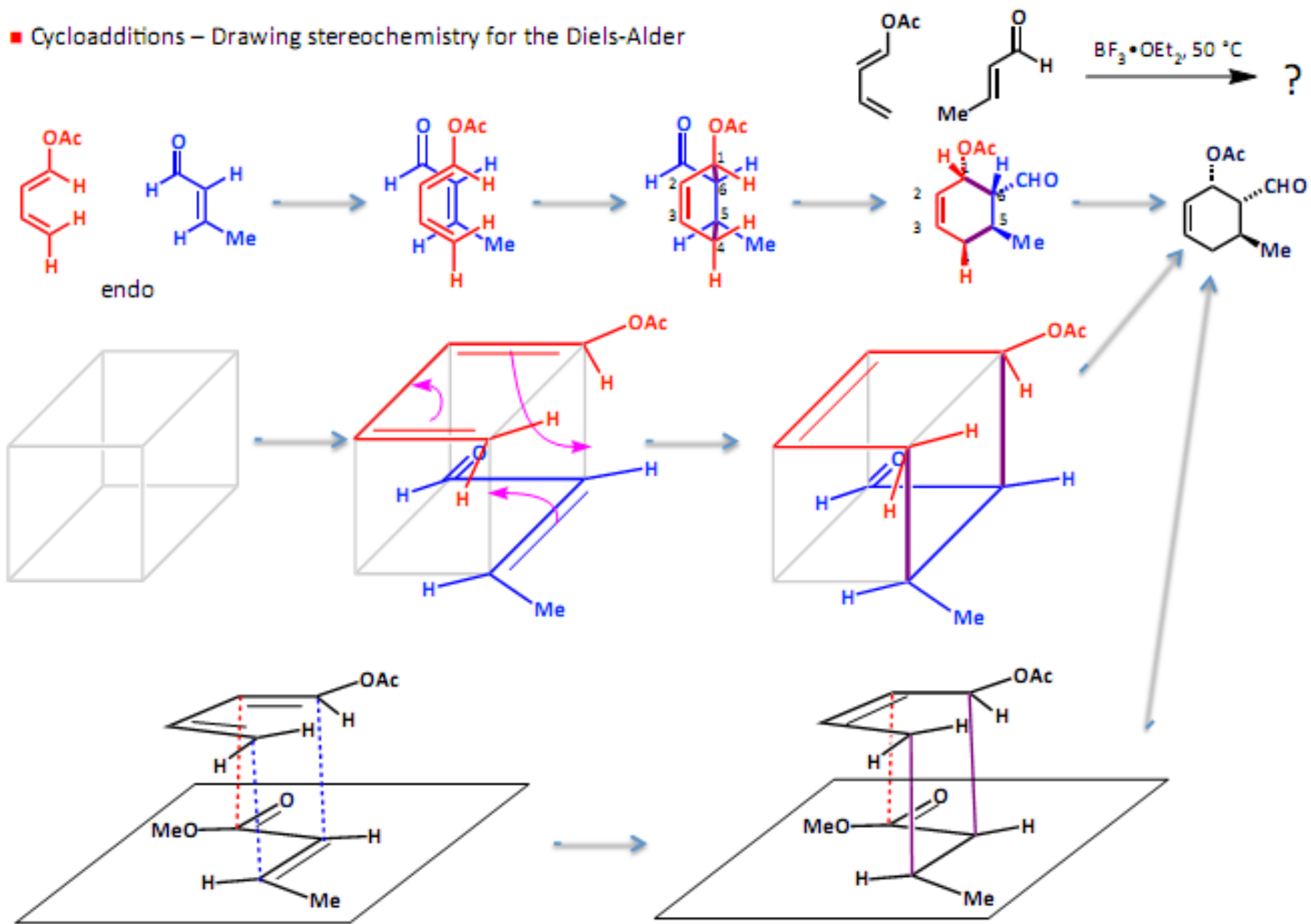

The aldehyde will be *endo*- but which compound is that?
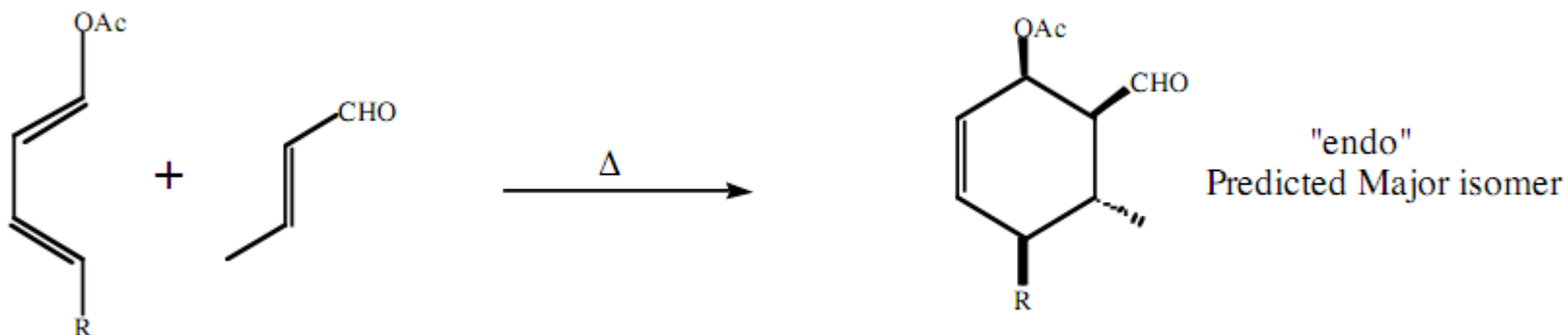Here is another way to do this.

OAc

O

H

Me

BF₃•OEt₂, 50 °C

?

■ Cycloadditions – Drawing stereochemistry for the Diels-Alder

BF$_3$•OEt$_2$, 50 °C
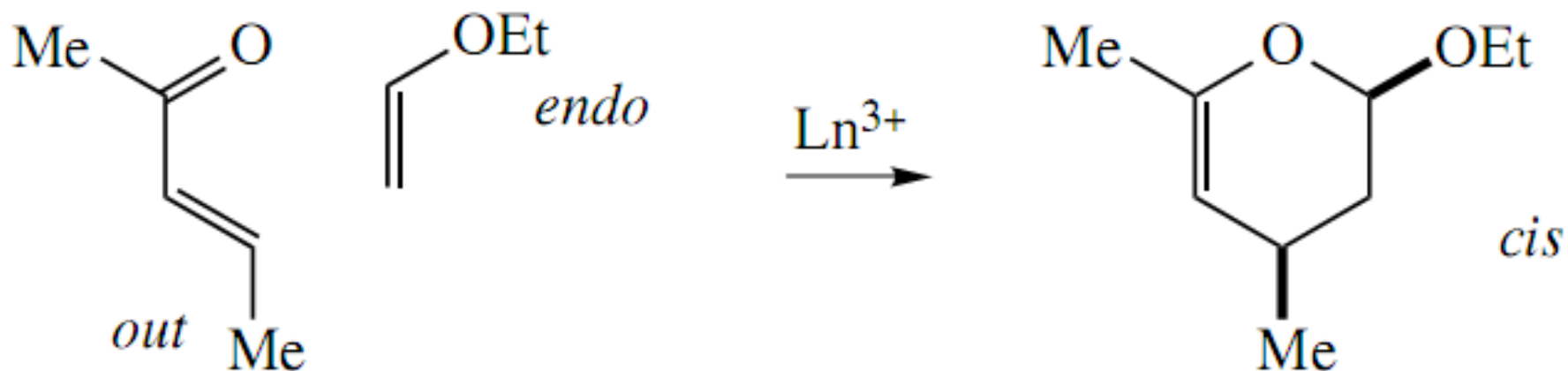
?

endo

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Stereoselectivity: *endo vs exo*

➢ Predict the stereochemistry of the major product of the following Diels–Alder reaction?

➢ Orient the two starting materials so that the strongest EDG on the diene is in a 1,2- or 1,4-relationship with the strongest EWG on the dienophile.

➢ The *out-endo-cis* rule tells you that the OAc and CHO groups are *cis* in the product.

➢ In the diene, OAc and R groups (*out*) are *cis* in the product.

➢ In the dienophile, the CHO and Me groups are *trans* in the product.

➢ Draw the **OAc up** (**or down, it doesn't matter**), and the rest of the stereochemistry follows.

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Stereoselectivity: *endo vs exo*

➢ The *endo* rule applies equally to **inverse electron-demand** Diels–Alder reactions. In these reactions, the **most electron-donating group on the dienophile** is preferentially *endo*. The *out-endo-cis* rule applies, too.
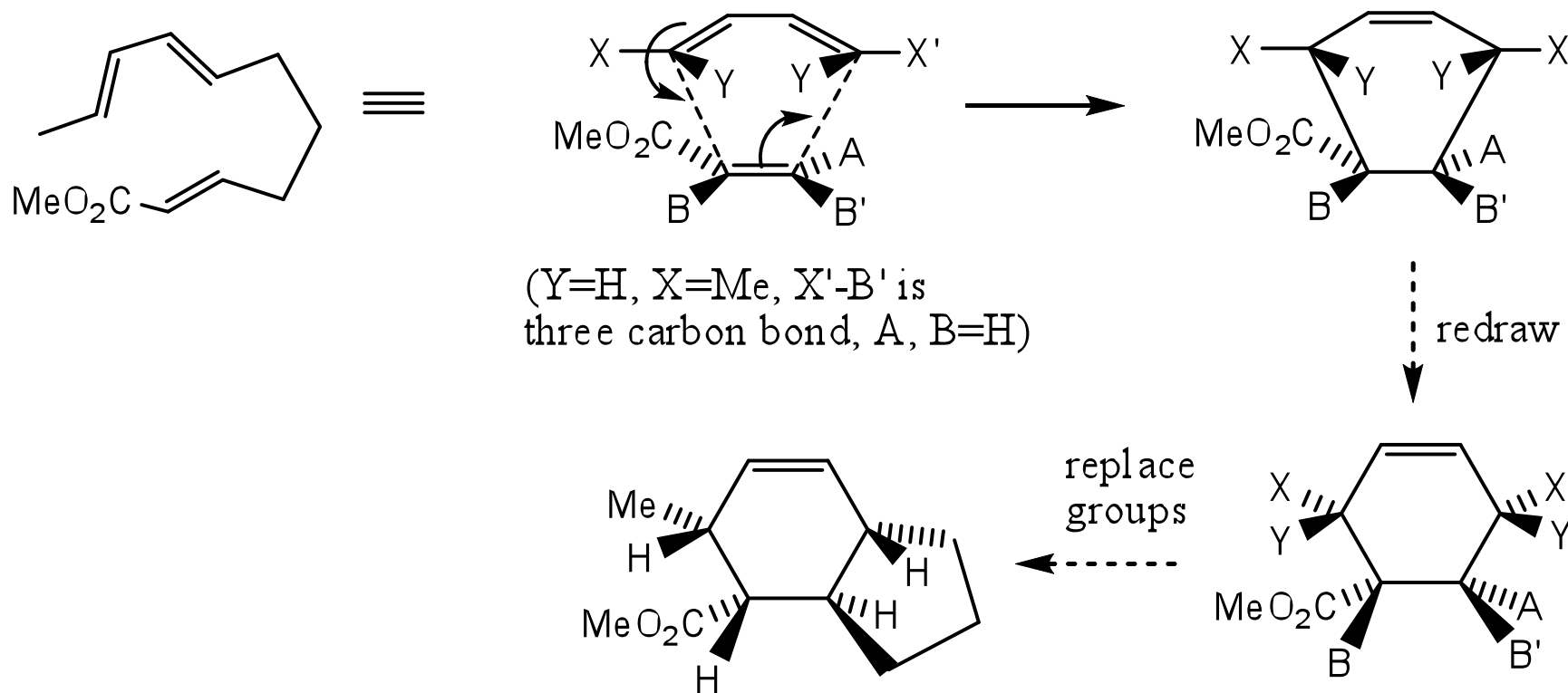
Stereoselectivity: *endo vs exo*

➤ 1,3-Dipolar cycloadditions give predominantly *endo*-products, too. Again, the *out-endo-cis* rule applies.
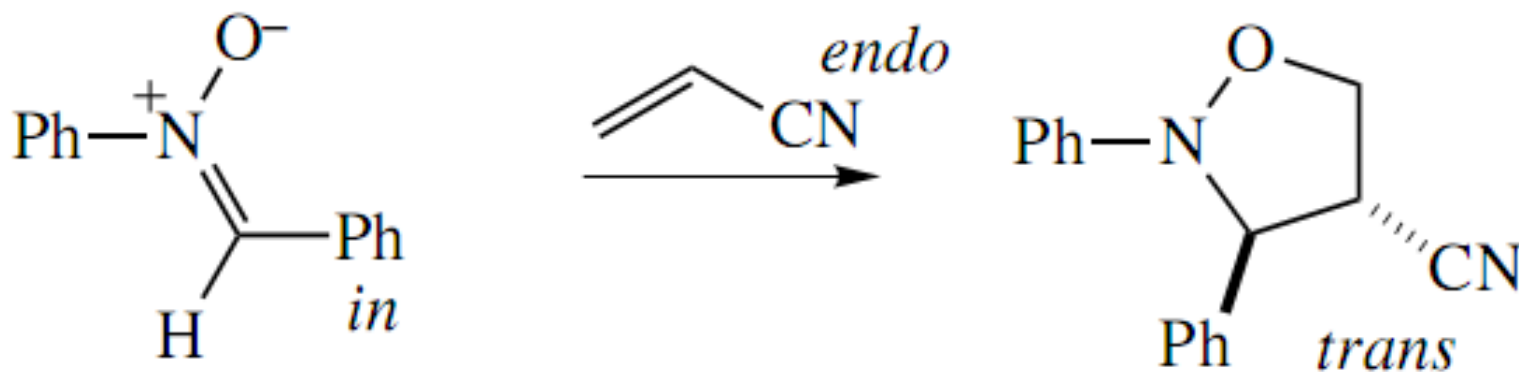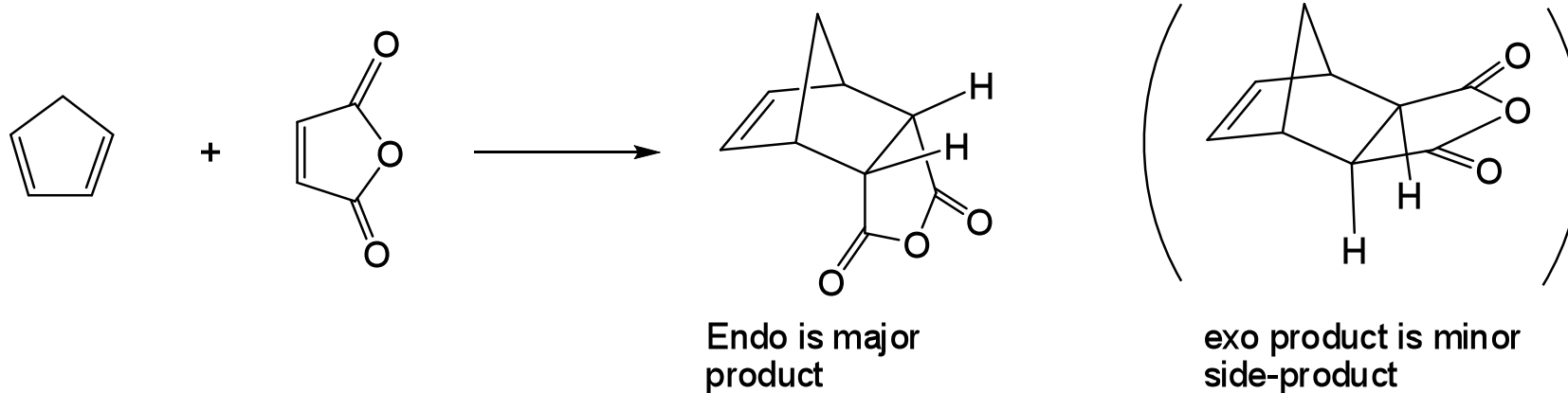
Stereoselectivity: *endo vs exo*

Example: Intramolecular version

(Y=H, X=Me, X'-B' is
three carbon bond, A, B=H)

redraw

replace
groups

Problems

Draw the transition state for the following process?

Endo is major product

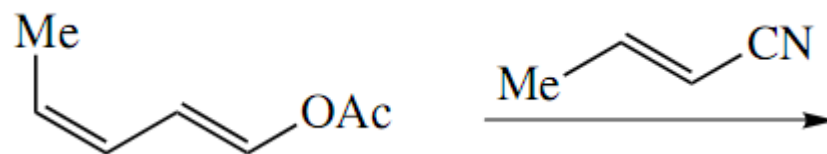exo product is minor side-product

Intramolecular Diels-Alder reactions are very powerful methods for constructing target molecules. Draw **the product** of the following intramolecular Diels-Alder reactions and **show its stereochemistry**?
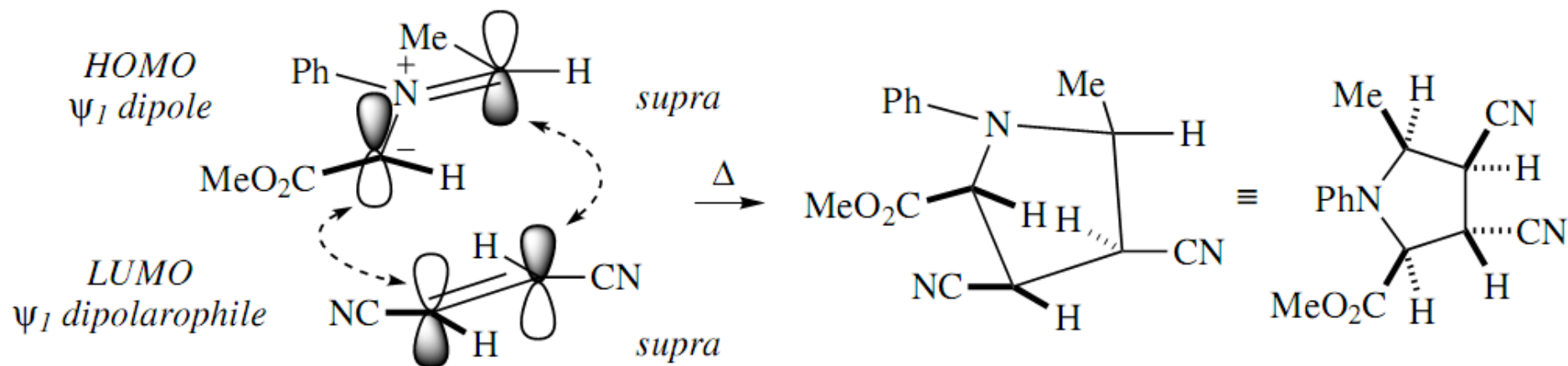

heat
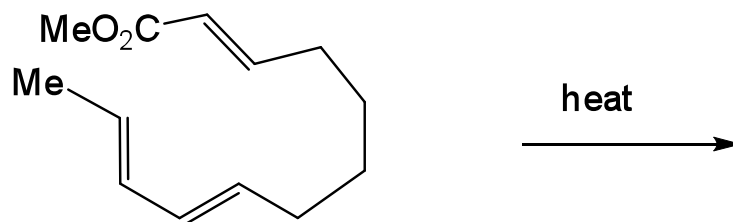
Problem

➤ Predict the stereochemistry of the major product of the following Diels–Alder reaction?

Stereospecificity

1,3-dipolar cycloadditions
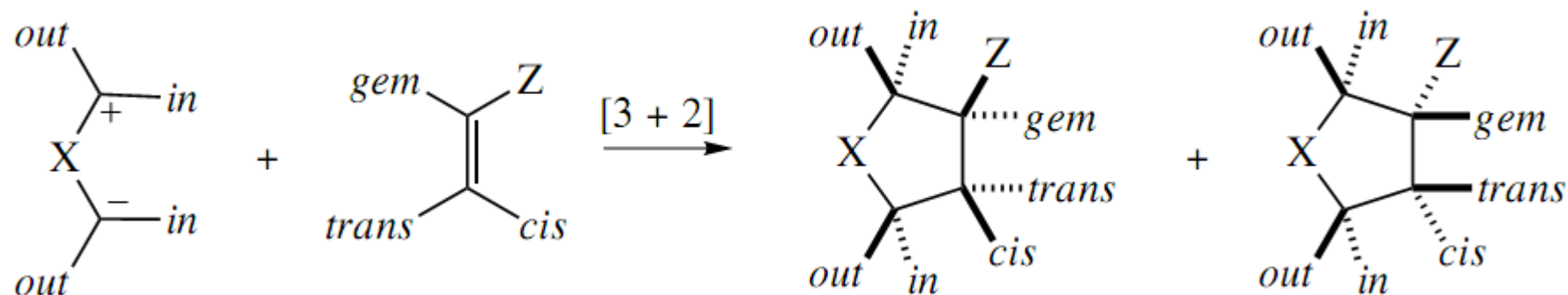
Electrocyclic reactions of cations and anions

Three-atom electrocyclizations (4 electrons)

❑ Since cycloaddition is **stereospecific** (suprafacial on both components), the stereochemistry of the products can tell us the **stereochemistry of the intermediate ylid** (4 pi electron system), and confirms that the ring opening is **conrotatory**.[4]

Electrocyclic reactions of cations and anions

Three-atom electrocyclizations (4 electrons)
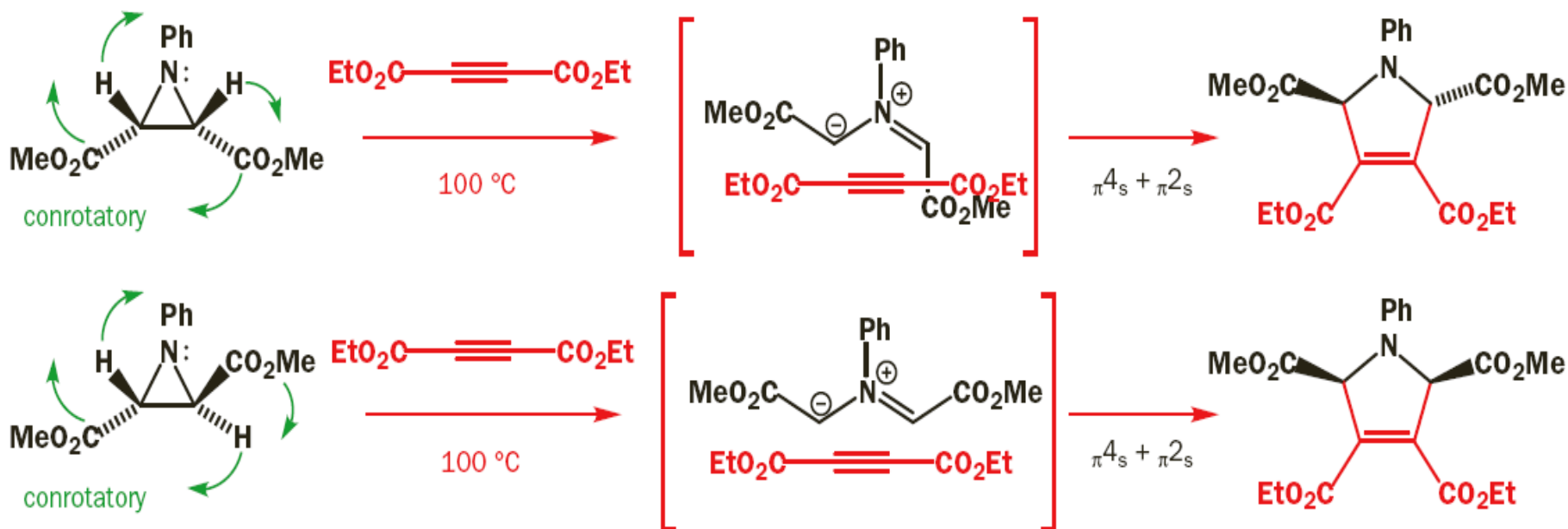
❖ Heating of oxiranes (epoxides) give the corresponding carbonyl ylids, which can be **trapped** by cycloaddition reactions.[1,2]
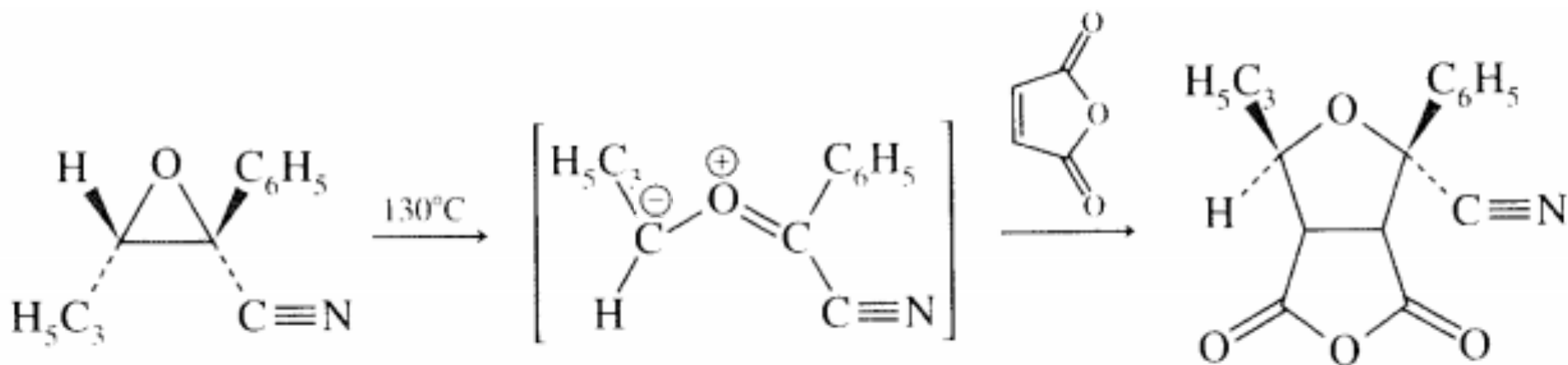
❖ These ring openings proceed stereospecifically by **conrotatory** paths.[1,2]

Questions

➢ Write the **structure of the product** of the following reaction and **predict** its **stereochemistry**.

$$H_2C \overset{\oplus}{=\!\!=} N \overset{\ominus}{=\!\!=} N \quad + \quad \text{MeO}_2\text{C} \diagdown \diagup \text{CO}_2\text{Me} \qquad \xrightarrow{\text{Heat}}$$
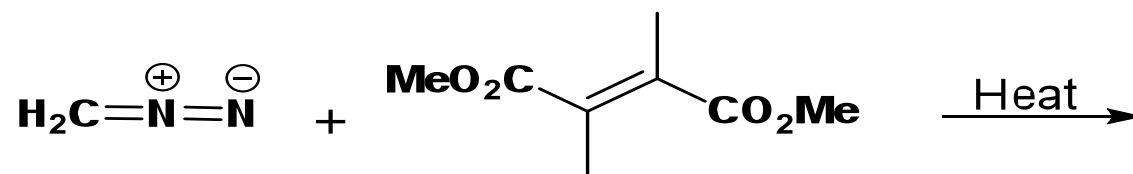
Questions

➢ Predict the **stereochemistry** of the product of the following reaction.
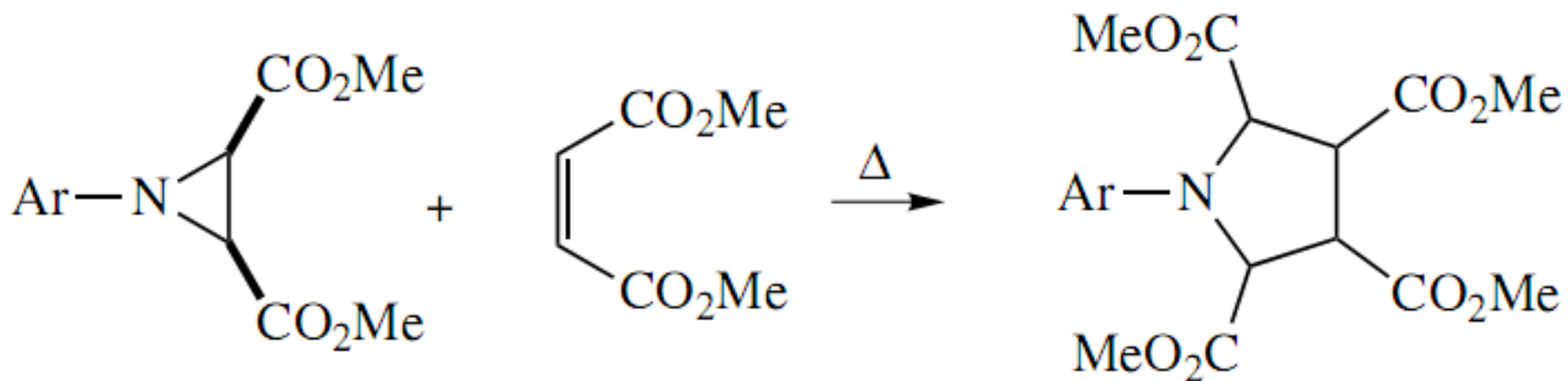
Stereoselectivity: why *endo!!!!!*

Frontier MO explanation for the *endo* rule

➤ Why is the more sterically hindered TS lower in energy?[1]

Diene HOMO-π_2

LUMO-π_3

Dienophile

LUMO-π_3 **Diene**

HOMO-π_2

Dienophile

Primary orbital overlap leads directly to the formation of new chemical bonds[2]

Stereoselectivity: why *endo!!!!!*

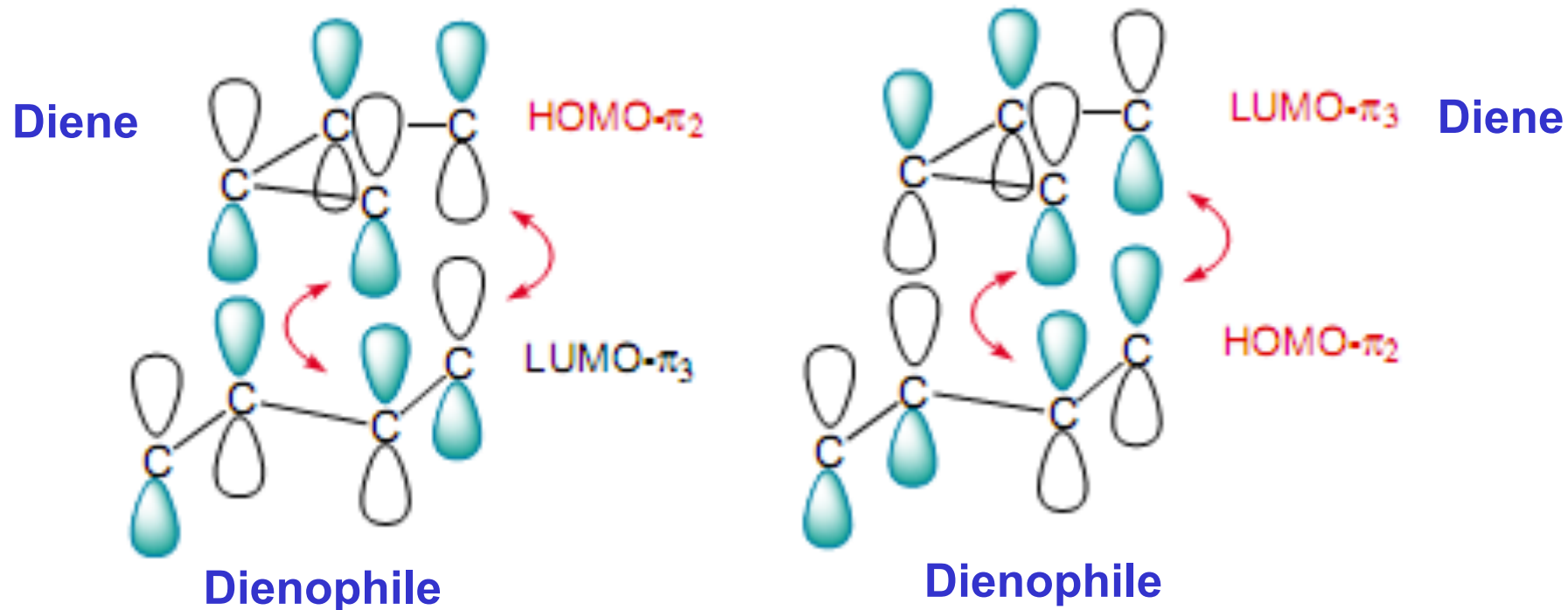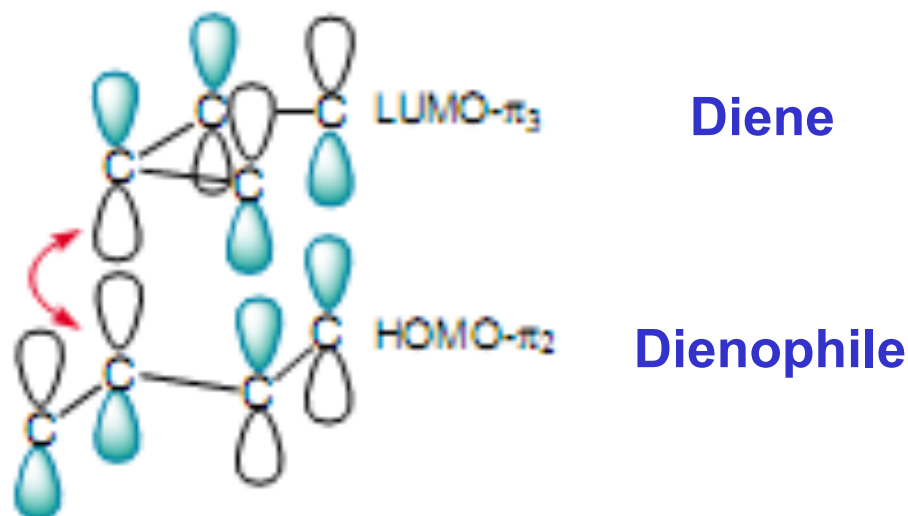➤ The most widely accepted explanation cites *secondary orbital interactions*.[1]

➤ In the more crowded approach, the orbitals of the carbonyl group of the dienophile can interact with the orbital on C2 of the diene.[1]

➤ These secondary orbital interactions **lower the energy of the TS** for *endo* cycloaddition compared to the TS for *exo* addition. So the kinetic product is the more crowded, less thermodynamically stable *endo* product.[1,2]
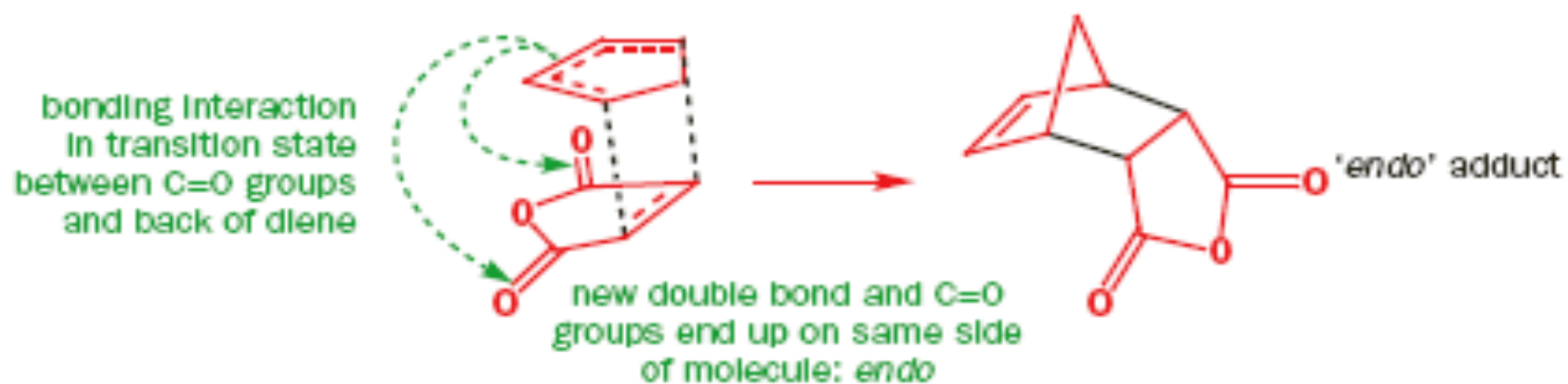
LUMO-π_3 **Diene**

HOMO-π_2 **Dienophile**

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Stereoselectivity: why *endo!!!!!*

bonding interaction
in transition state
between C=O groups
and back of diene

new double bond and C=O
groups end up on same side
of molecule: *endo*

'*endo*' adduct

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■ Cycloadditions – Drawing stereochemistry for the Diels-Alder

endo

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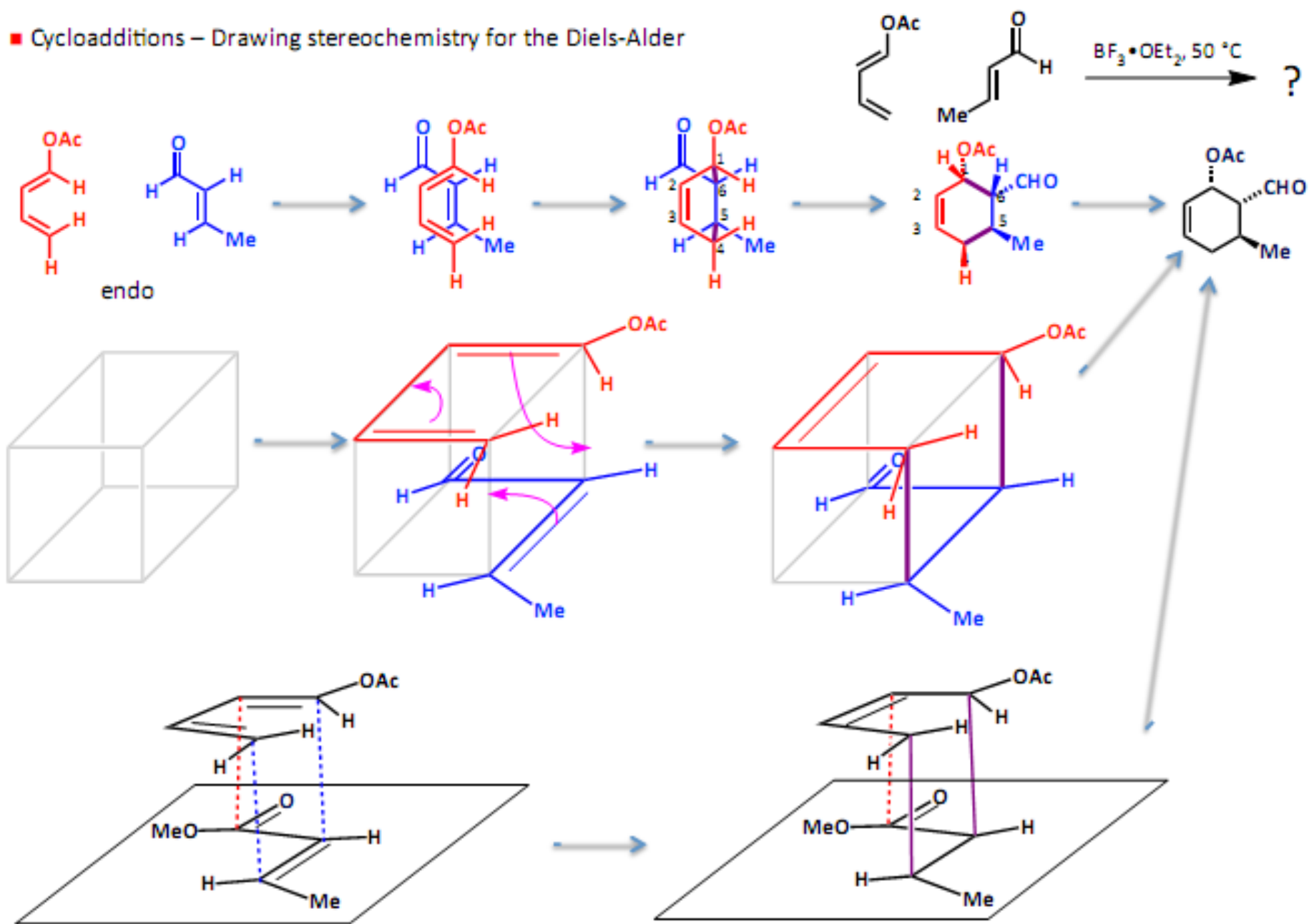
Stereoselectivity: why *endo!!!!!*
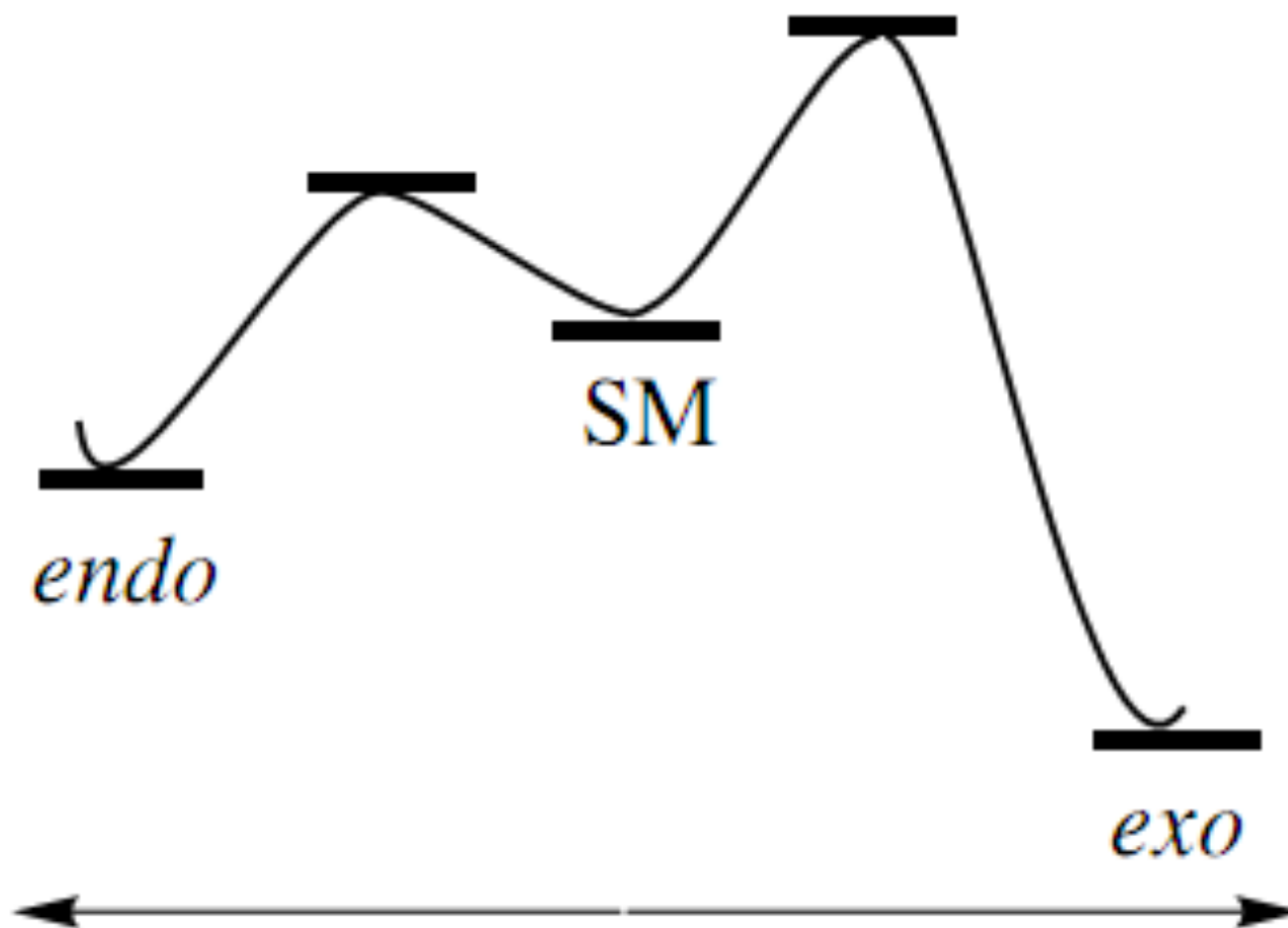
Stereoselectivity: why *endo!!!!!*

Other explanation for the *endo* rule

➤ In the following figure, the dipoles associated with the *in* C–H bond of the diene and the electron-withdrawing group of the dienophile **interact most favorably** when the electron-withdrawing group is *endo*.[1]
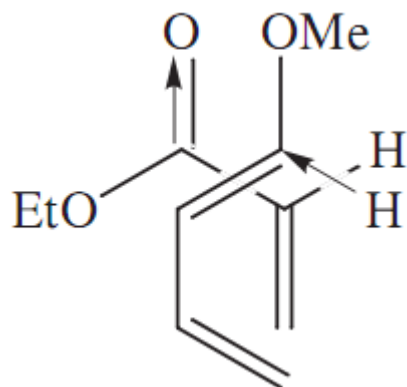
endo TS: dipoles aligned favorably
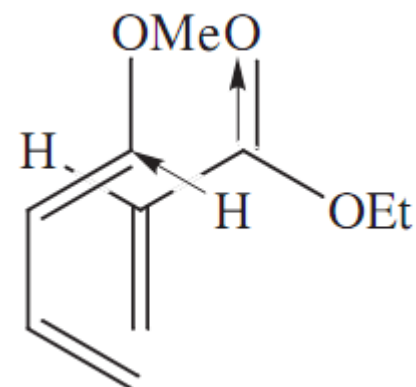
exo TS: dipoles aligned unfavorably

➤ Lewis acids increase the *endo* selectivity by polarizing the electron-withdrawing group and thus increasing the magnitude of the dipole.[1]

Factors affecting *endo/exo* product ratio

(1) **Steric factors:** Steric effects can favour the *exo*-product.

exo

endo (disfavoured)   exo (favoured)

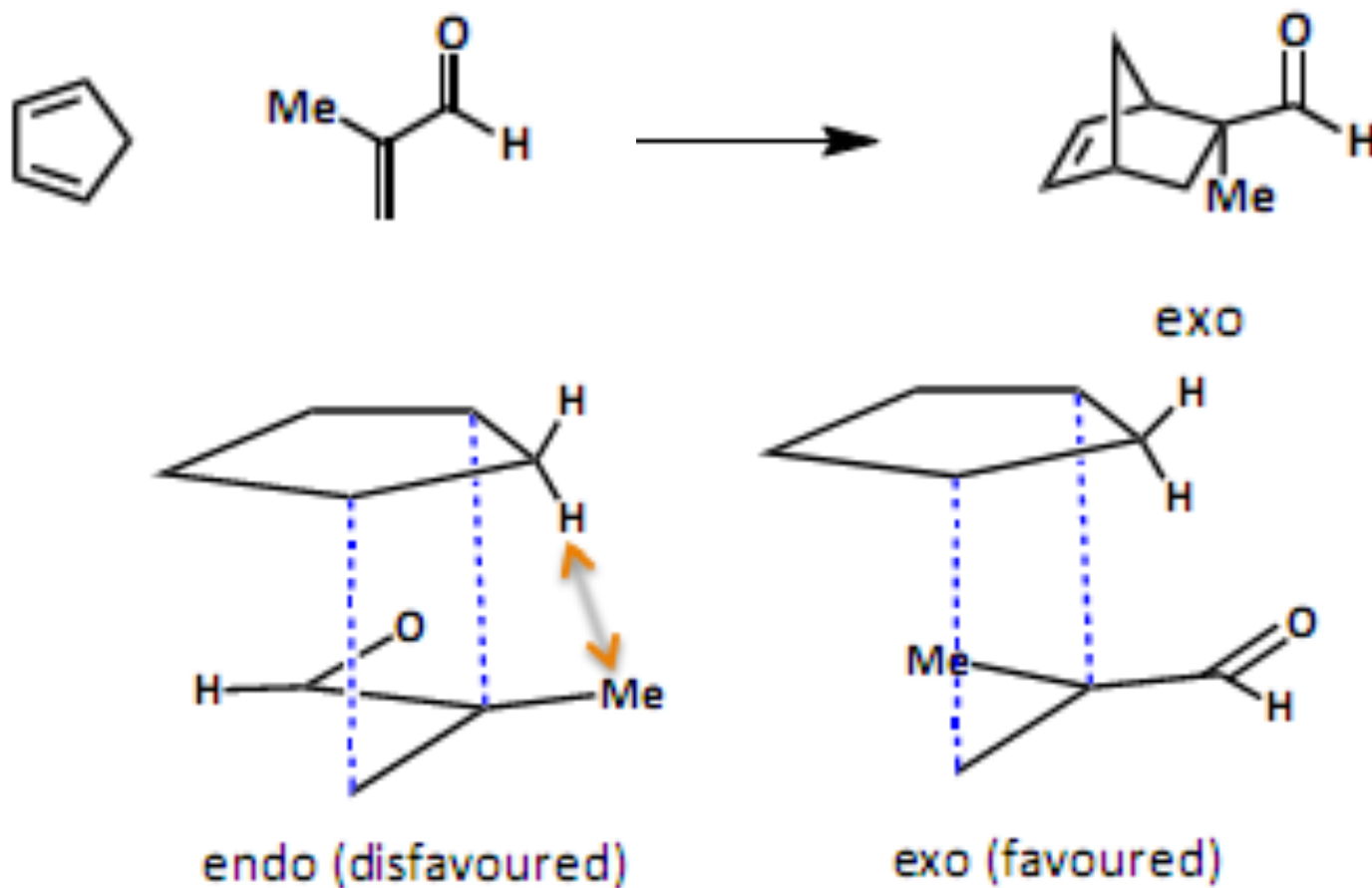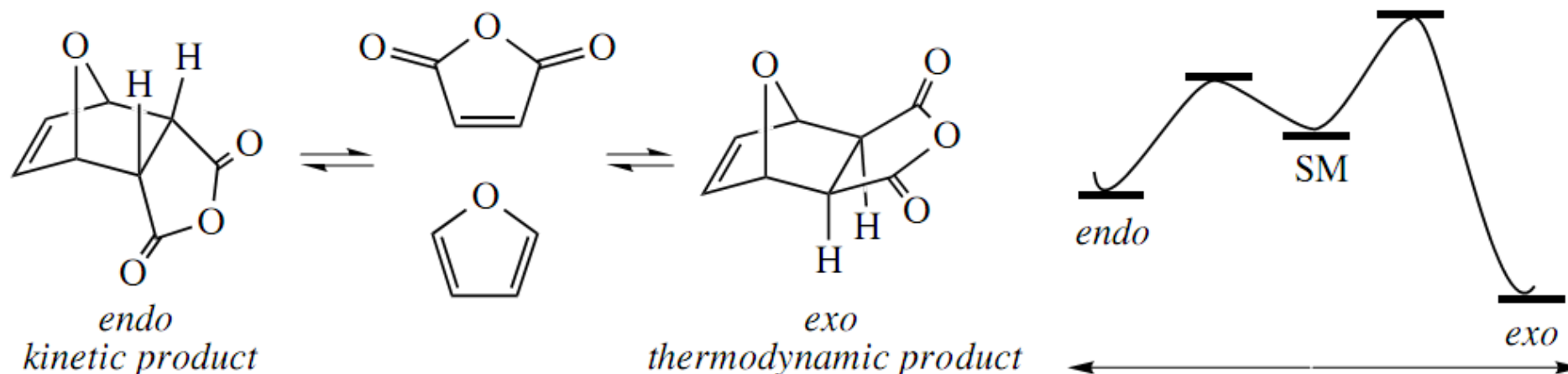# Factors affecting *endo/exo* product ratio

(2) Reversibility: In cases where the reaction readily reverses (e.g. reactions with furan), the thermodynamically preferred *exo*-adducts are usually obtained.[1]

endo
kinetic product

exo
thermodynamic product

➤   The unusually low energy of furan (an aromatic compound) allows the *retro*-Diels–Alder reaction of the *endo*-product to proceed at a reasonable rate.[2]

➤   Even though the rate of formation of the *endo*-product is faster than the rate of formation of the *exo*-product, establishment of an equilibrium between starting materials and products leads to a thermodynamic ratio that favors the *exo*-product.[2]

Factors affecting *endo/exo* product ratio

(3) Temperature: since Diels-Alder reactions is reversible at elevated temperatures, the *exo/endo* ratio depends on the reaction temperature.[2]
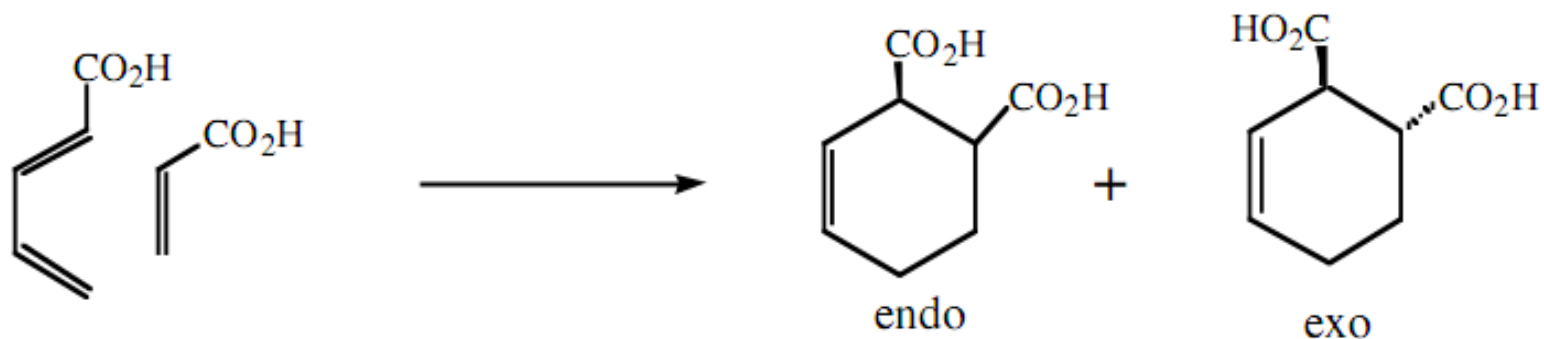
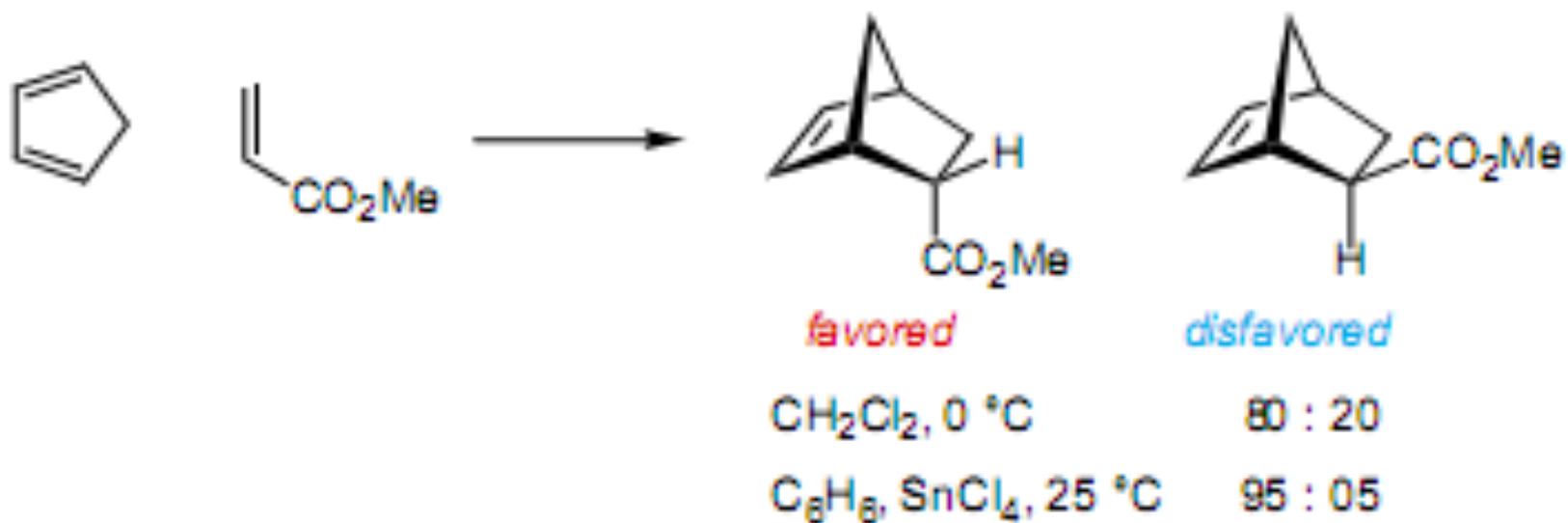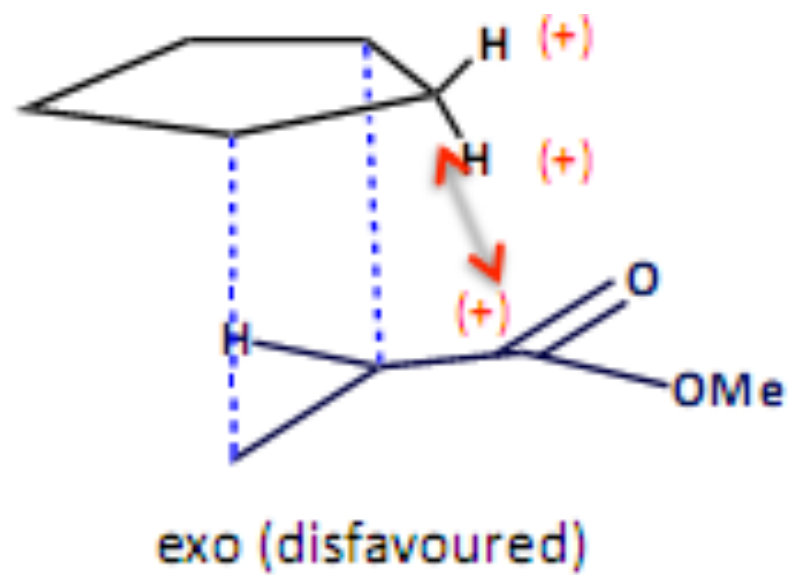| Temperature (°C)	Endo	Exo
75°	exclusively	
90°	7	1
100°	4.5	1
110°	2	1
130°	1	1

Factors affecting *endo/exo* product ratio

➢ Therefore, the use of high temperature and extended periods of time can result in the formation of the thermodynamically more favorable *exo*-product.[1]

Factors affecting *endo/exo* product ratio

(4) Lewis-acid catalysis: Lewis acid catalysis improves *endo* diastereoselection.[2]

➤ Lewis acids increase the *endo* selectivity by polarizing the electron-withdrawing group and thus increasing the magnitude of the dipole.[1]

	favored	disfavored
CH_2Cl_2, 0 °C	80 : 20	
C_6H_6, $SnCl_4$, 25 °C	95 : 05	

endo

endo (favoured)

exo (disfavoured)
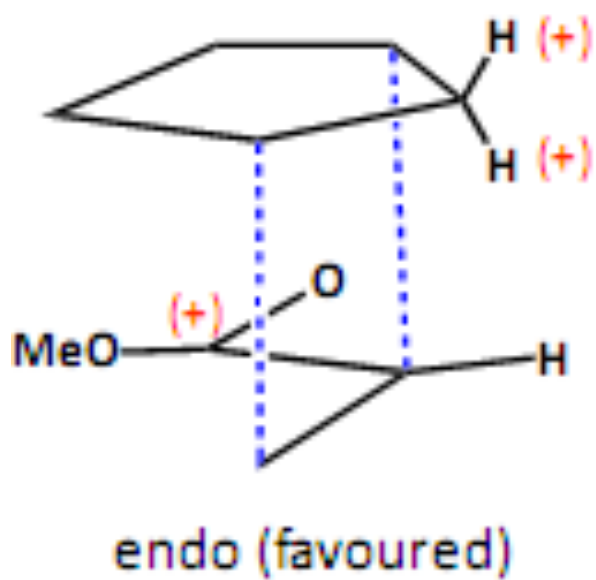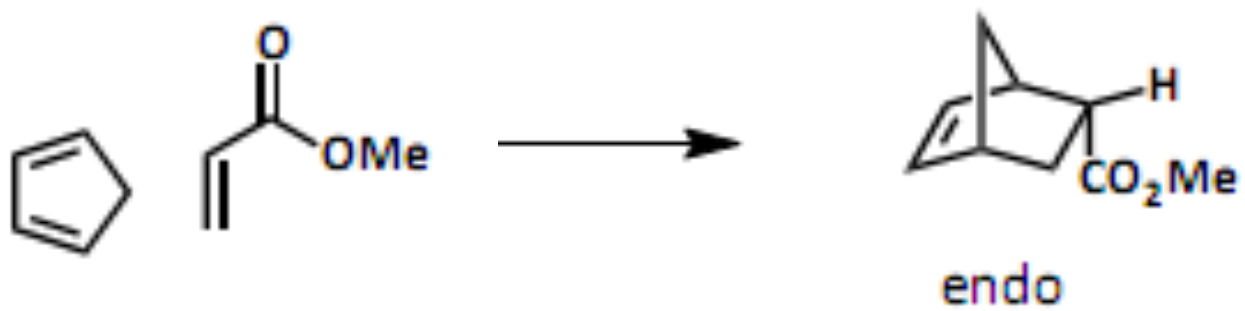
Factors affecting *endo/exo* product ratio

(5) Pressure:
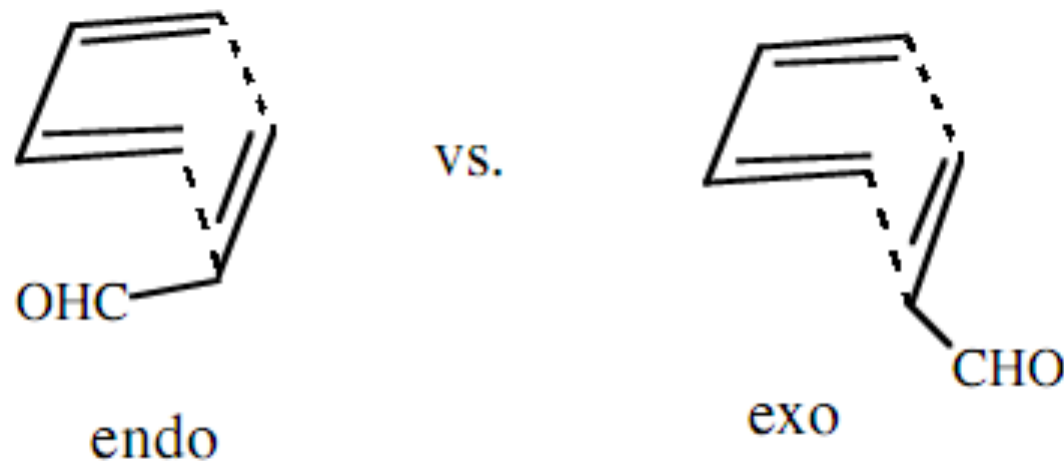
$$\Delta V^{\ddagger} = -25 \text{ to } -38 \text{cm}^3 \cdot \text{mol}^{-1}$$

TS is smaller than starting materials

$\Delta\Delta V^{\ddagger}$ Favors endo $\Longrightarrow$ ↑ pressure $\Longrightarrow$ ↑ endo:exo

Factors affecting *endo/exo* product ratio

(6) Solvent used:

➤ Since Diels–Alder reaction has no ionic intermediates, it is expected that the influence of solvent is weak.

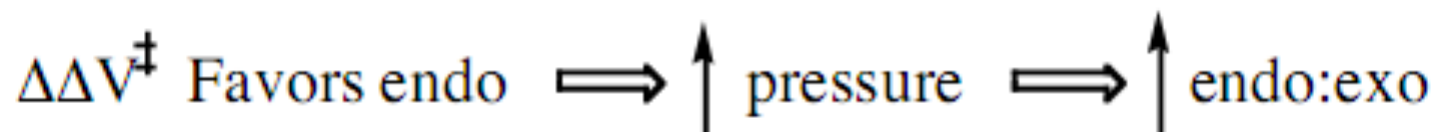➤ However, in the 1980s an extraordinary discovery was made. Water has a **large accelerating** effect on the Diels–Alder reaction!!!!!

➤ And that is not all. The *endo* selectivity of these reactions is often superior to those in no solvent or in a hydrocarbon solvent. Here is a simple example.

endo product   *exo* product
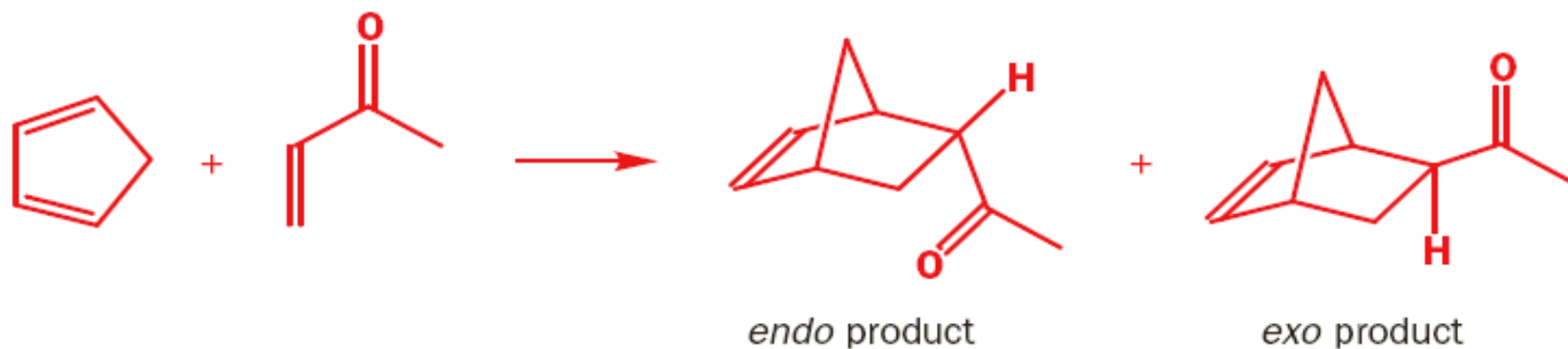
Factors affecting *endo/exo* product ratio

(6) Solvent used:

Solvent	Relative rate	*endo:exo* ratio
hydrocarbon (isooctane)	1	80:20
water	700	96:4

➢ The suggestion is that the reagents, which are not soluble in water, are **clumped together in oily drops** by the water and **forced into close proximity** *i.e.* water is not exactly a solvent.

Hydrophobic effects[1-3]

➢ It has been shown that some intermolecular Diels–Alder reactions are accelerated under hydrophobic effects in aqueous media.[1]

➢ β-Cyclodextrin has a hydrophobic cavity and if the system of a particular Diels–Alder combination can fit within the cavity a significant rate enhancement is observed.[1]

➢ For example, in aqueous medium with β-cyclodextrin as an additive, the **rate** of Diels–Alder of methyl vinyl ketone and cyclopentadiene is significantly enhanced (**1800 times** as compared to the same reaction in hydrocarbon solvent, see previous table).[1-3]

Hydrophobic effects[1-3]
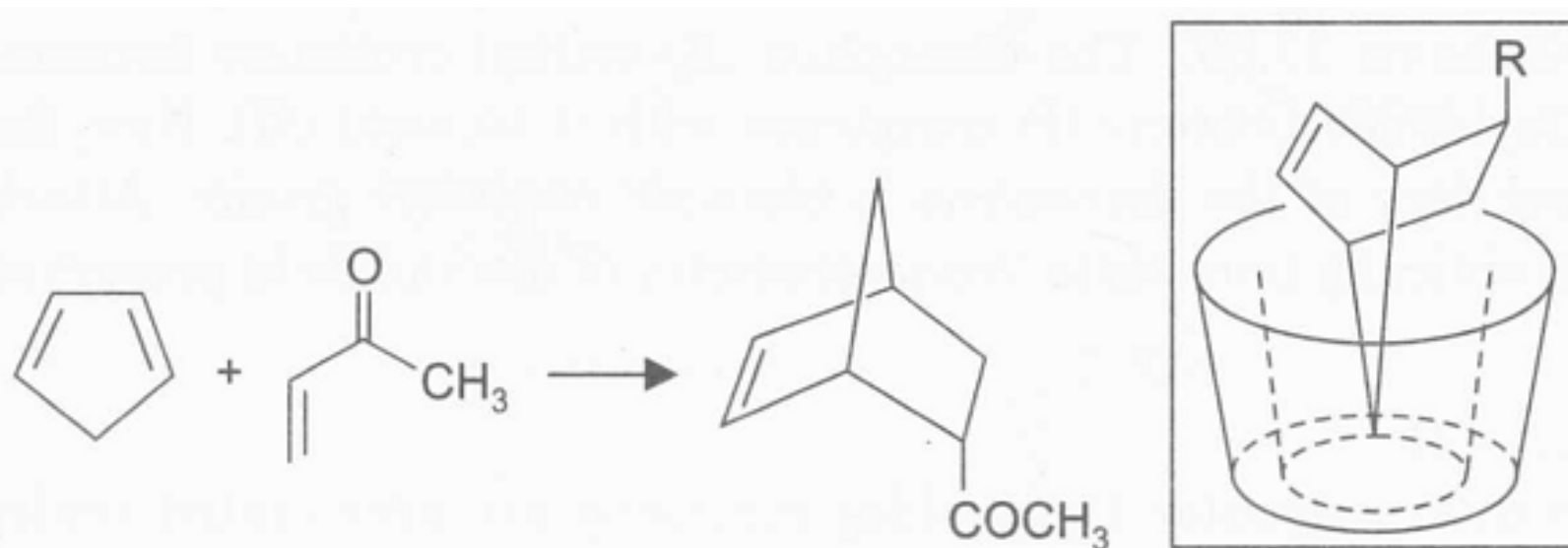
SCHEME 17.54

The hydrophobic effects of the cavity in β-cyclodextrin in aqueous medium enhance significantly this reaction rate. The cavity in β-cyclodextrin can accommodate well these reactive species.

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cycloreversions.

➤ The reverse of cycloadditions are retrocycloadditions, or **cycloreversions**.[1]

➤ Diels-Alder reactions are reversible.[2]

➤ The direction in which any pericyclic reaction takes place is determined by thermodynamics.[2]

➤ Diels-Alder reaction takes place to form a ring because two sigma-bonds are produced at the expense of two pi-bonds *i.e.* exothermic reaction.[2,3]

cycloreversions.

➢ Retro-Diels-Alder reaction is facile when one of the products is N_2, CO_2, or an aromatic ring.[1-3]

2.17   2.18   2.19   2.20

(13)