CYI101
Common CHEMISTRY(Organic)

Pericyclic reactions: Cycloaddition Reactions

Cycloaddition Reaction:

A concerted combination of two π-electron systems to form a ring of atoms having two new σ bonds and two fewer π bonds is called a cycloaddition reaction.

Two important classifications of cycloaddition reactions

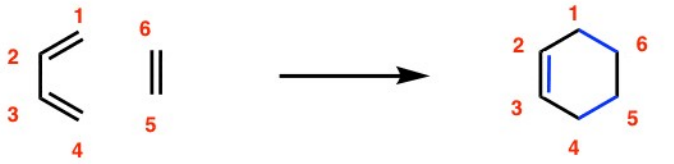
(i) [4 + 2] Cycloaddition (ii) [2+2] Cycloaddition

The most common cycloaddition reaction is the [4π+2π] cyclization known as the **Diels-Alder reaction.** Discovered by Professor Otto Diels and his student Kurt Alder in 1928 and received Nobel prize in 1950.

- *Reaction between a conjugated diene and dienophile*
- *Highly effective method for the formation of cyclohexene ring*

Diels-Alder Reaction: $\Delta\sigma = \pm 2$

The Diels-Alder Reaction:



Diene "Dienophile"

New 6-membered ring

Bonds Formed	Bonds Broken
C_1–C_6	C_1–C_2 (π)
C_2–C_3 (π)	C_3–C_4 (π)
C_4–C_5	C_5–C_6 (π)

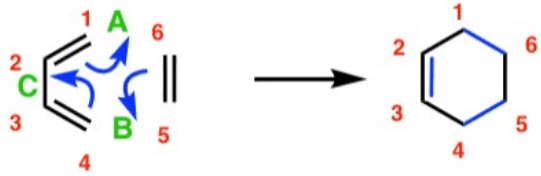
ALWAYS this pattern

- break 3 C-C pi bonds
- form 2 C–C single bonds and 1 C–C pi bond

Diels-Alder Mechanism

Can draw the direction of electron flow two ways (both give same result)

"clockwise" flow:

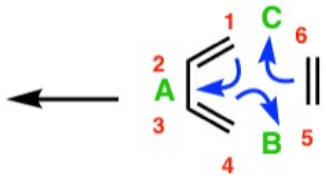


A Break C_1-C_2 (π), form C_1-C_6

B Break C_5-C_6 (π), form C_4-C_5

C Break C_3-C_4 (π), form C_2-C_3 (π)

"counter-clockwise" flow:



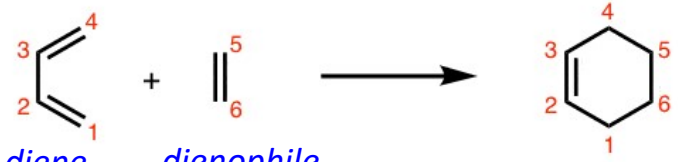
A Break C_1-C_2 (π), form C_2-C_3 (π)

B Break C_3-C_4 (π), form C_4-C_5

C Break C_5-C_6 (π), form C_1–C_6

Diels-Alder Reaction: *Diversity*

The Diels-Alder Reaction

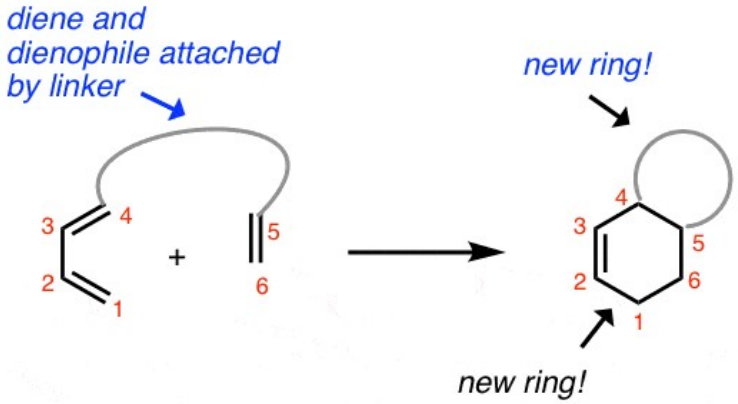


diene *dienophile*

Bonds Formed	Bonds Broken
C_1–C_6	C_1–C_2 (π)
C_4–C_5	C_3–C_4 (π)
C_2–C_3 (π)	C_5–C_6 (π)

Intermolecular

The Intramolecular Diels Alder Reaction Results In Two New Rings



Bonds Formed	Bonds Broken
C_1–C_6	C_1–C_2 (π)
C_4–C_5	C_3–C_4 (π)
C_2–C_3 (π)	C_5–C_6 (π)

Intramolecular

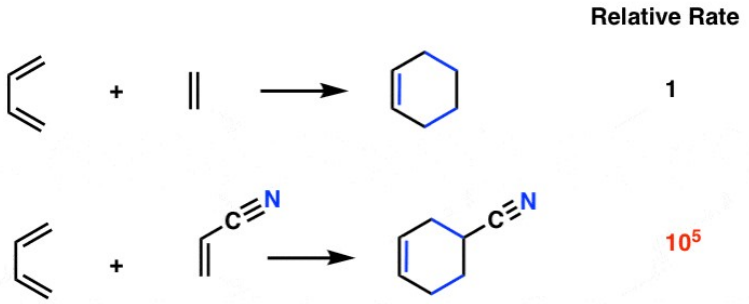
Diels-Alder Reaction: *"Diene" & "Dienophile"*

In general: **Diene** should be **e'-rich** & **Dienophile** should be **e'-deficient** (or ***Vive-versa***) for better reaction.

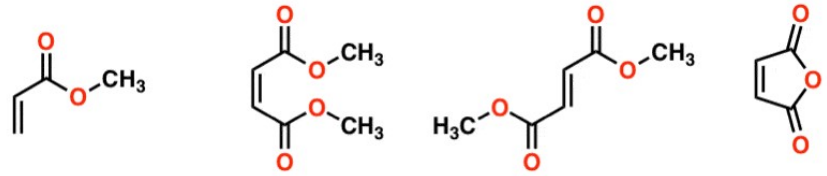
The diene must be conjugated in order for the Diels-Alder to occur:

1,4 pentadiene
(a non-conjugated diene)

Electron withdrawing groups on the dienophile increase the reaction rate

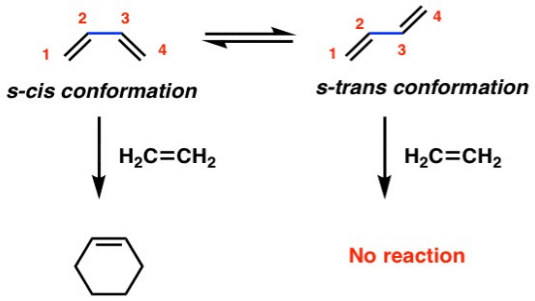


Examples of common dienophiles



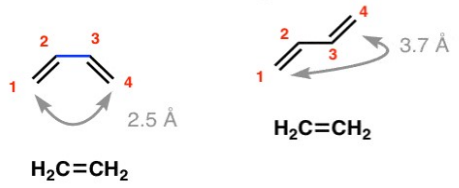
Methyl acrylate *Dimethyl maleate* *Dimethyl fumarate* *Maleic anhydride*

The diene must be in the s-*cis* conformation to participate in the Diels-Alder reaction



Why?

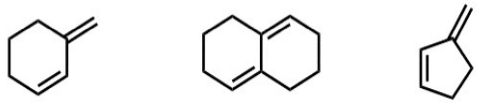
Geometry. In the *s*-trans conformation, C_1 and C_4 are too far apart to be able to react with the dienophile



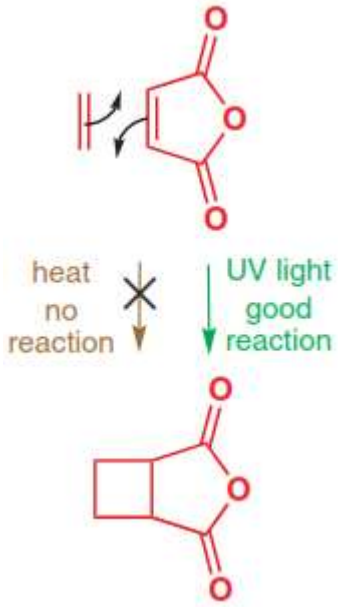
(C–C bond length: 1.33 Å)

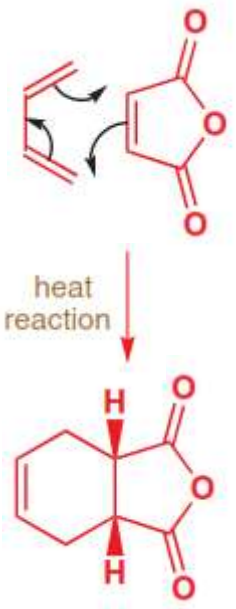
Reactive Diene:

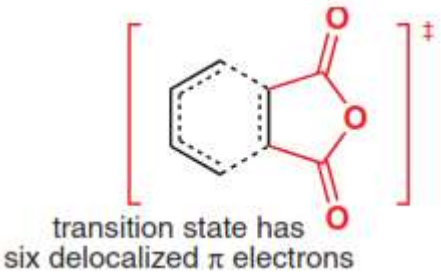
Dienes locked in the *s-trans* conformation cannot undergo the Diels Alder

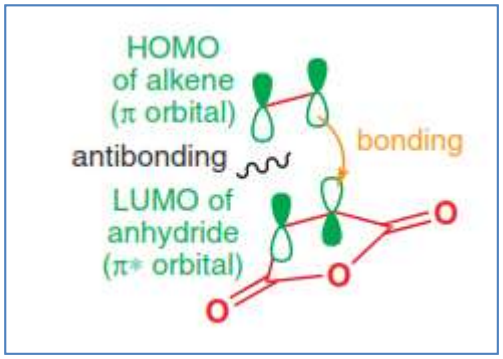


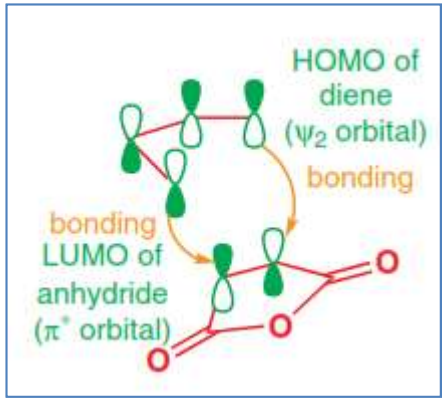
Cycloaddition Reaction: *The FMO description*

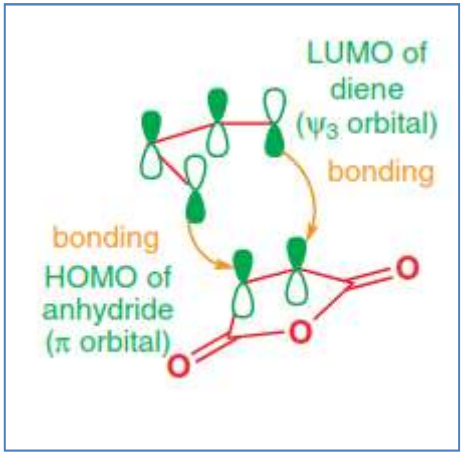




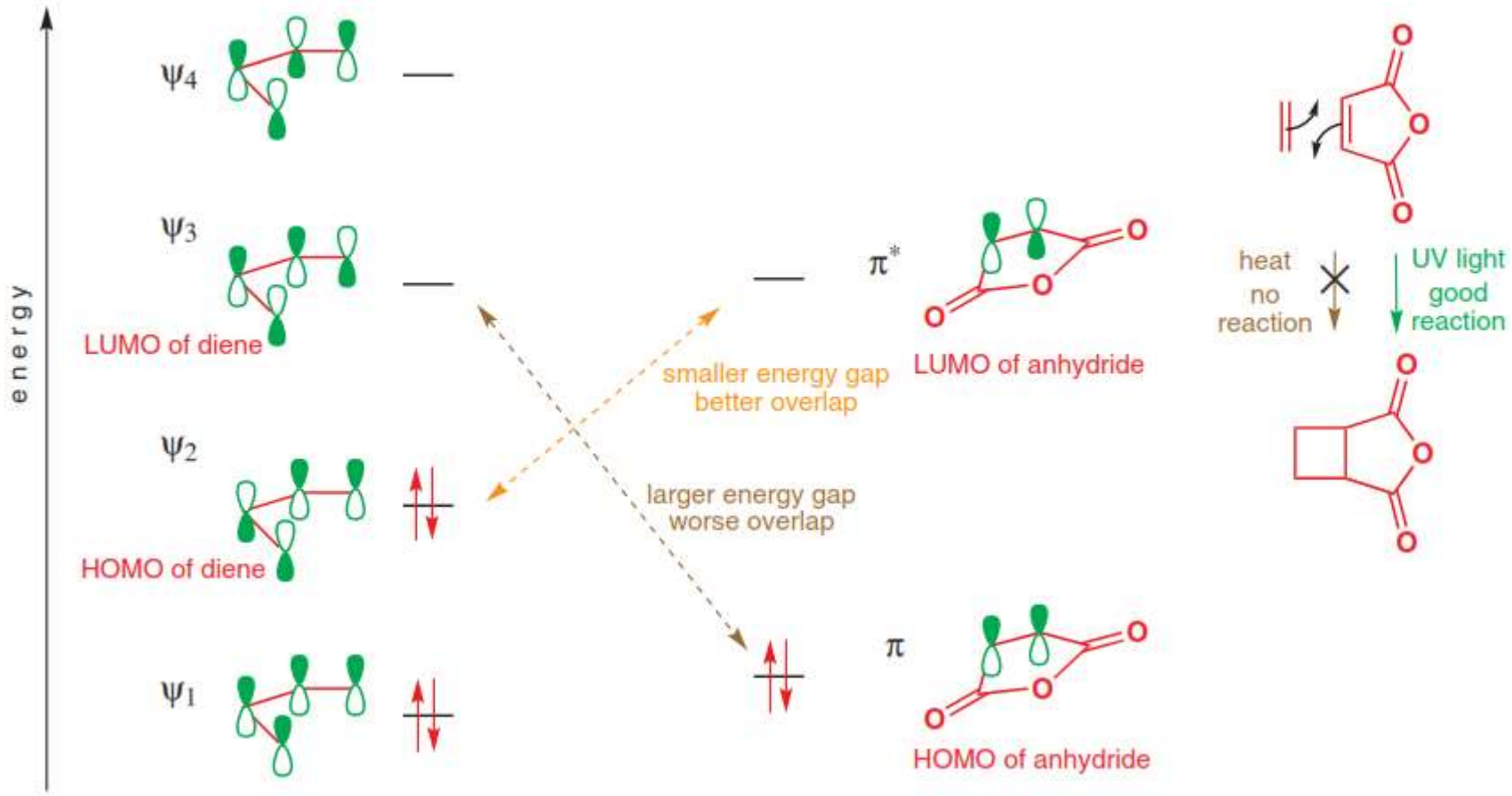








Cycloaddition Reaction: *The FMO description*

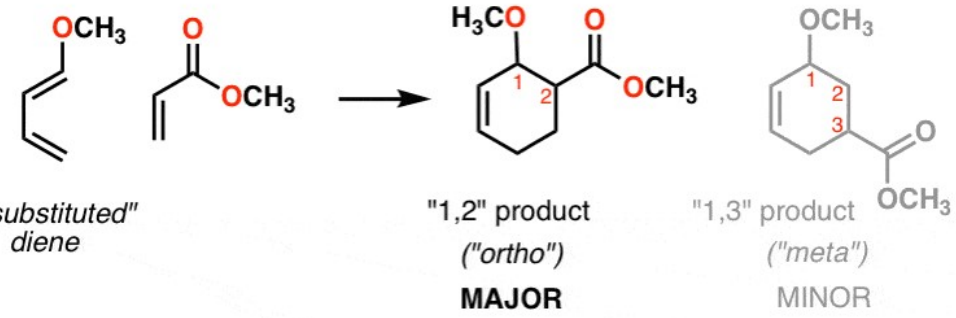


Diels-Alder Reaction: *Regioselectivity*

Regioselectivity In The Diels Alder

When non-symmetrical dienes react with non-symmetrical dienophiles, two "regioisomers" are possible

Case 1: "1-substituted" dienes: give the *"ortho"* product, not the *"meta"*

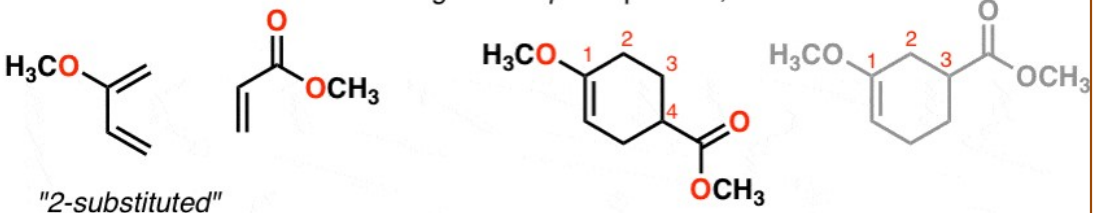


"1-substituted" diene

"1,2" product *("ortho")* **MAJOR**

"1,3" product *("meta")* MINOR

Case 2: "2-substituted" dienes: give the *"para"* product, not the *"meta"*



"2-substituted" diene

"1,4" product *("para")* **MAJOR**

"1,3" product *("meta")* MINOR

The "1,3" ("*meta*-") product is disfavored in both cases

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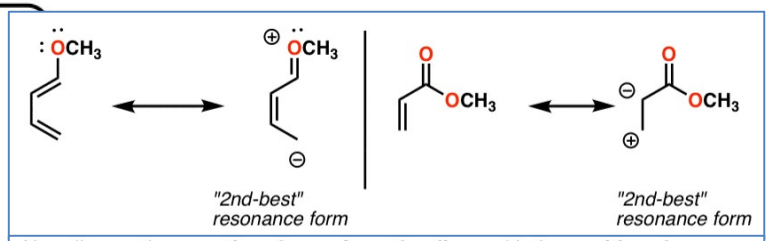
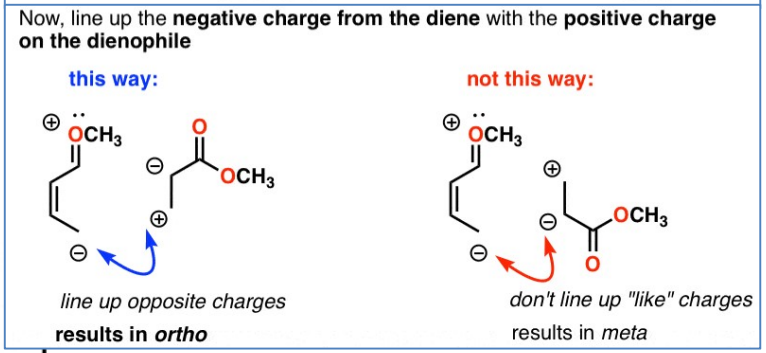
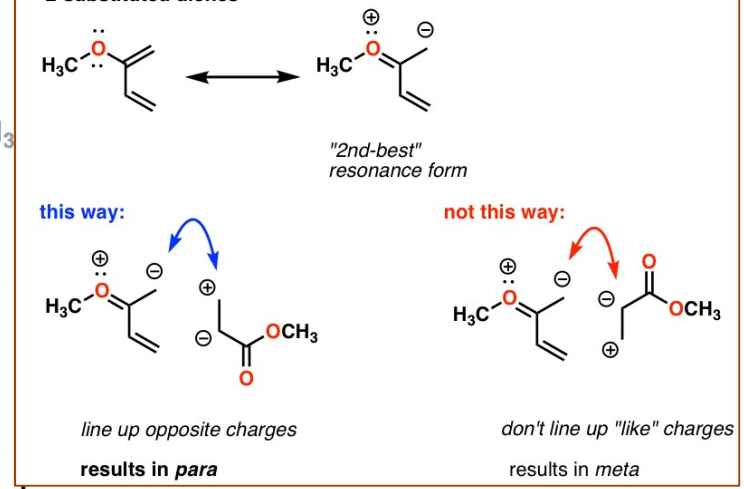


Now, line up the **negative charge from the diene** with the **positive charge on the dienophile**



results in *ortho* results in *meta*

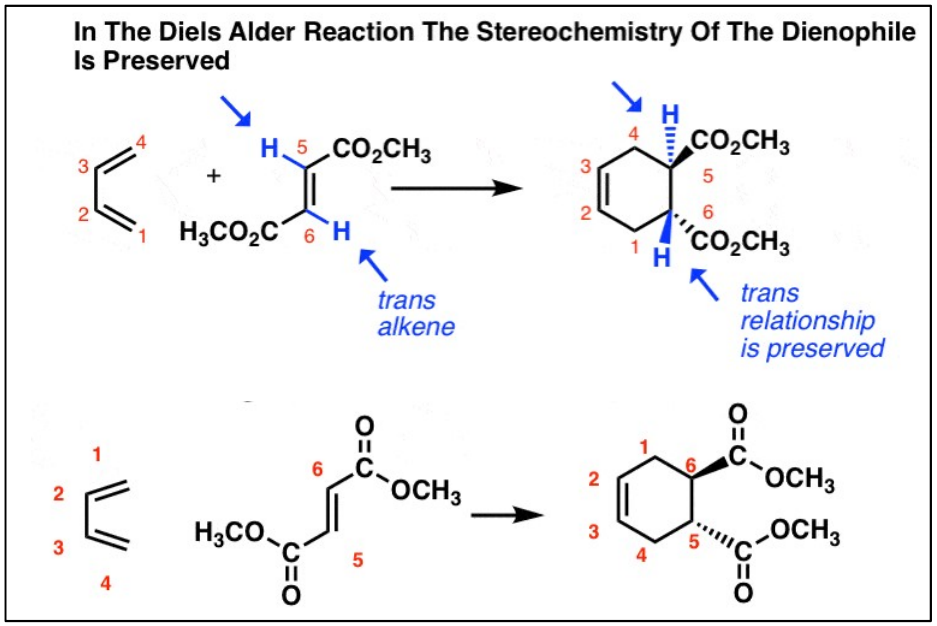
2-substituted dienes

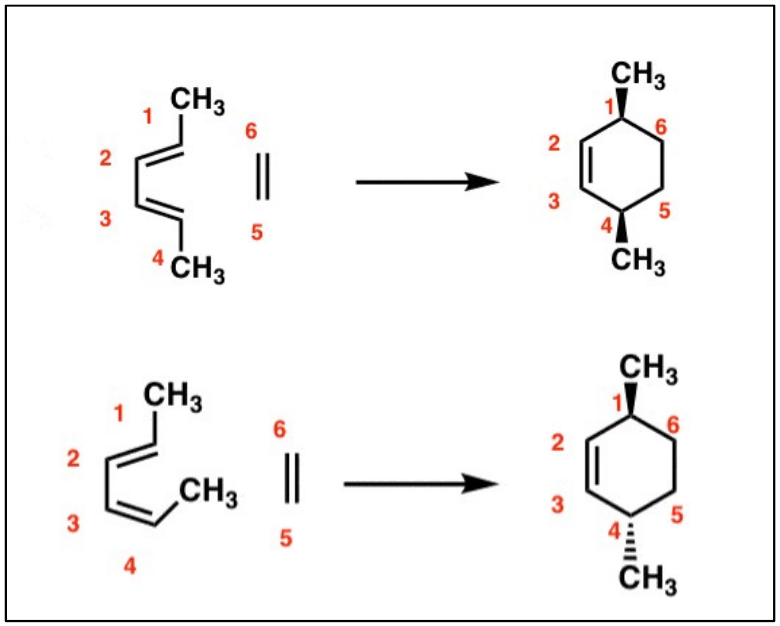


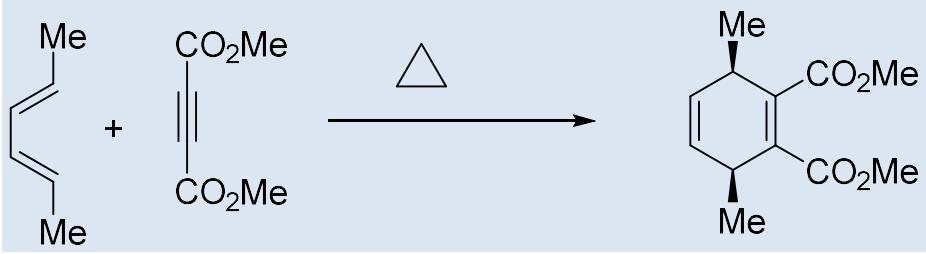
results in *para* results in *meta*

Diels-Alder Reaction: *Stereochemistry*

- Stereochemistry of both *diene* and *dienophile* retained in the product

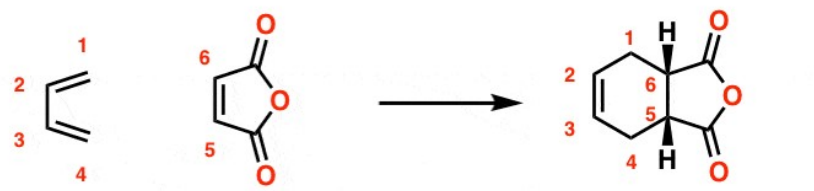






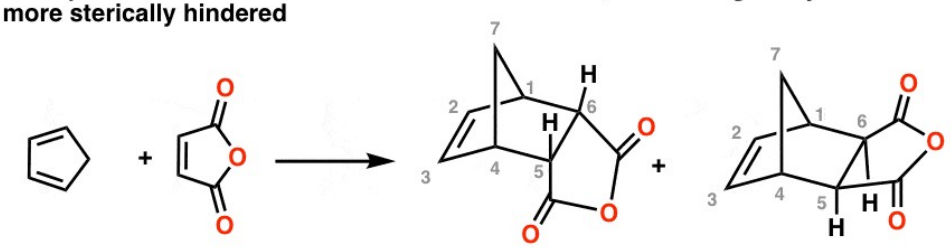
Diels-Alder Reaction of Cyclic Diene: *Regioselectivity*

Diels-Alder reaction of a cyclic dienophile



Diene | Dienophile (Maleic anhydride) | Diels-Alder Product

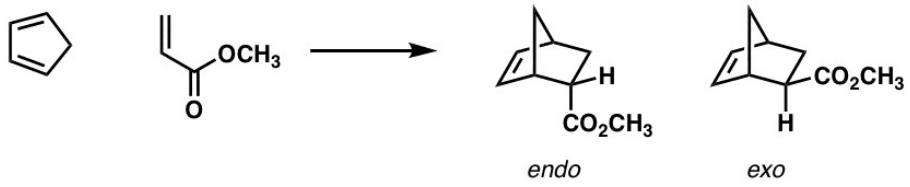
***endo* products tend to be favored in the Diels-Alder, even though they are more sterically hindered**



***endo* product** | ***exo* product**

endo: exo = 4: 1

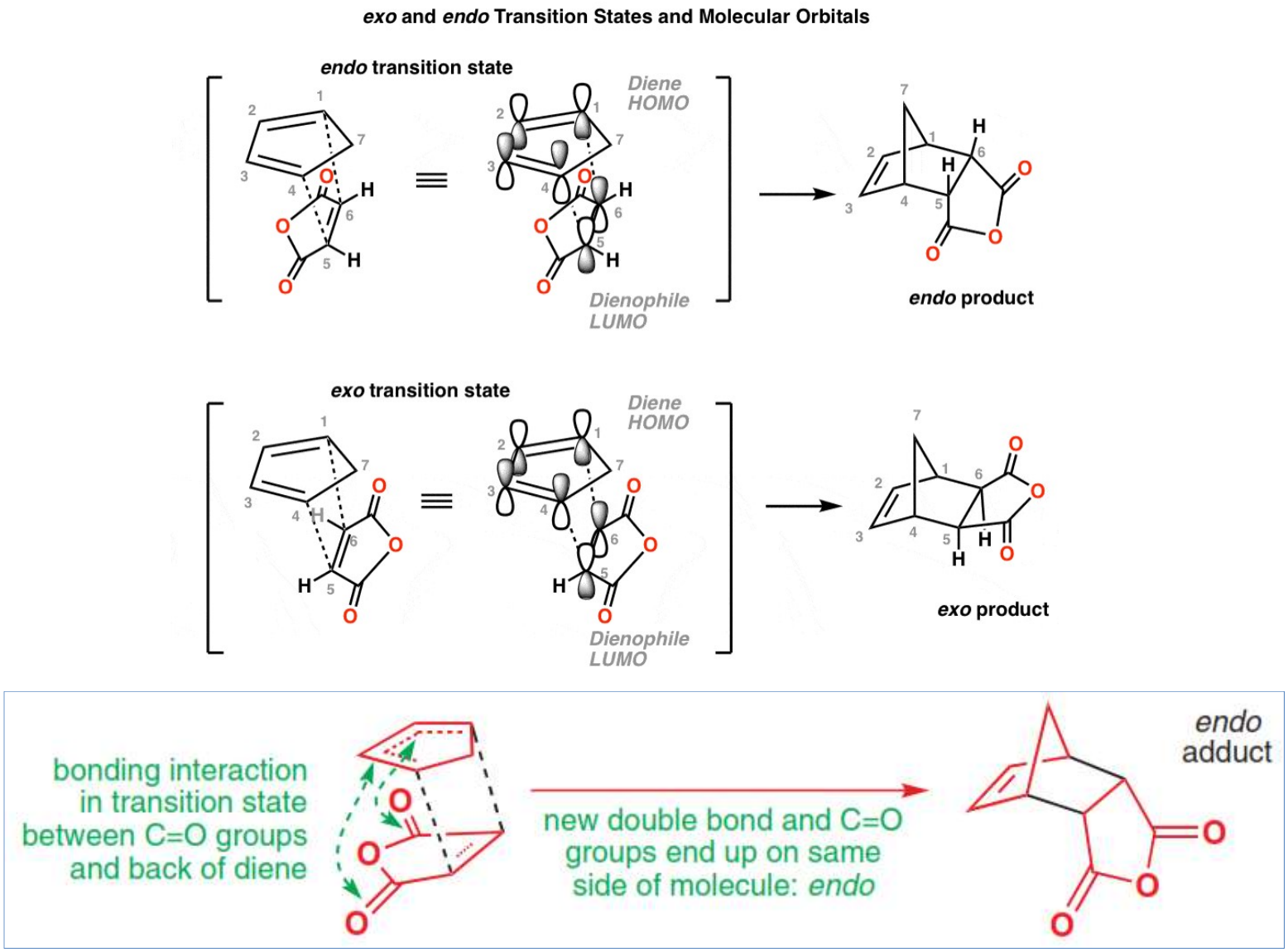
Lewis acid catalysis improves selectivity for endo:



endo | *exo*

CH_2Cl_2, 0°C	80: 20
benzene, $SnCl_4$, 25°C	95:5

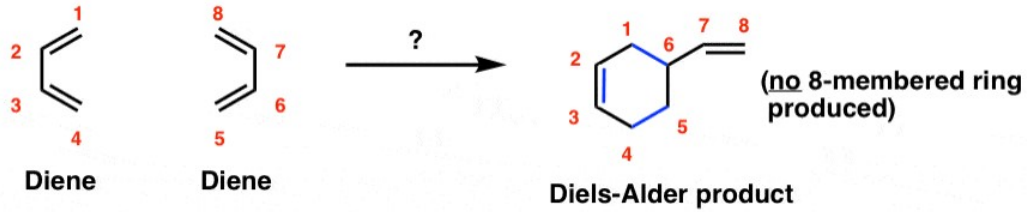
Diels-Alder Reaction: *Endo vs Exo Products*



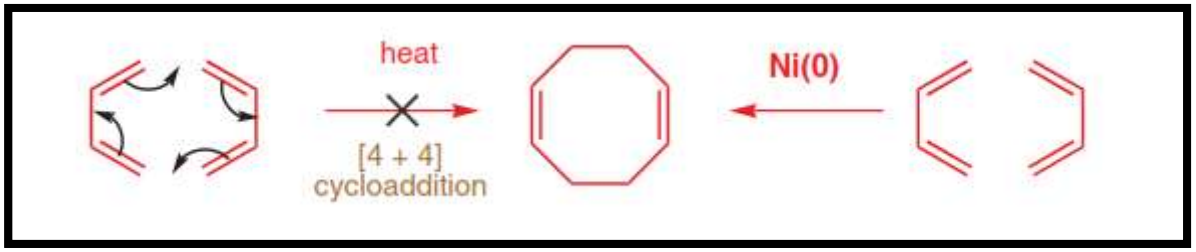
Because the C_2-C_3 orbitals of the diene HOMO are positioned close to the C=O orbitals of the dienophile LUMO, they can interact: *"secondary orbital interaction"*

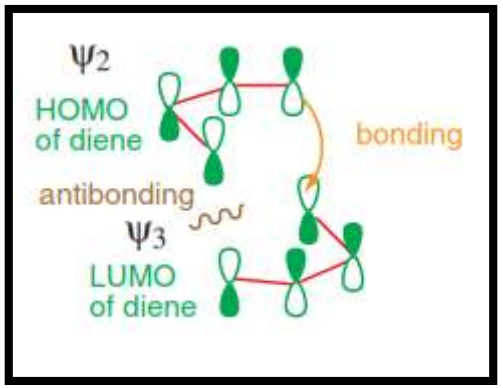
[4+2] *vs* [4+4]Cycloaddition: *Dimerization of Dienes*

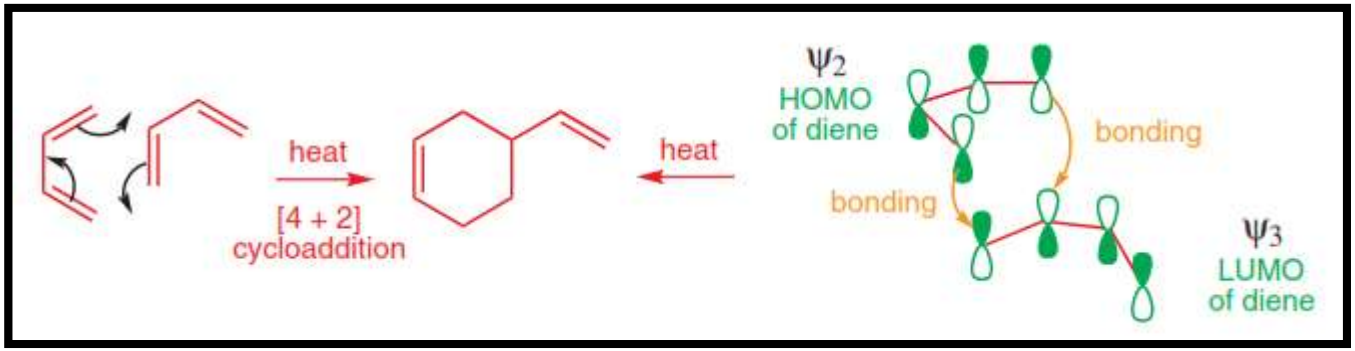
Q. What about dienes? Can we combine two dienes to make an 8-membered ring?



A. Doesn't work. We get a Diels-Alder product instead!

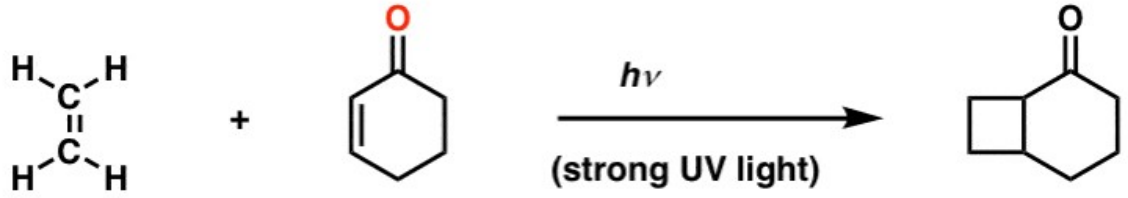






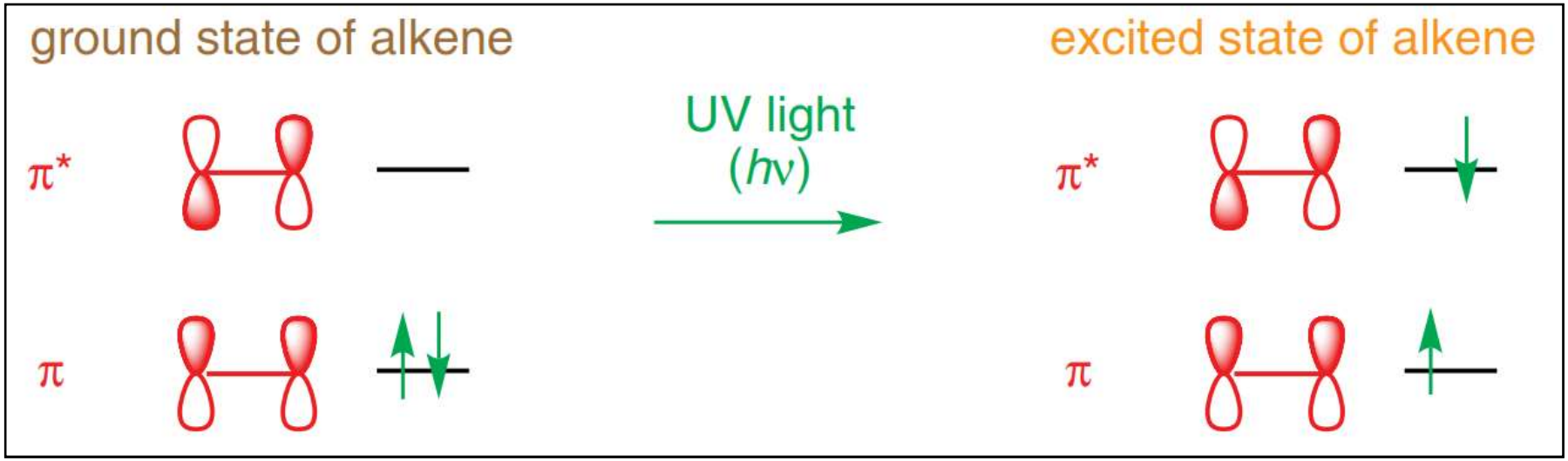
[2+2] Cycloaddition: *Under Photo-irradiation*

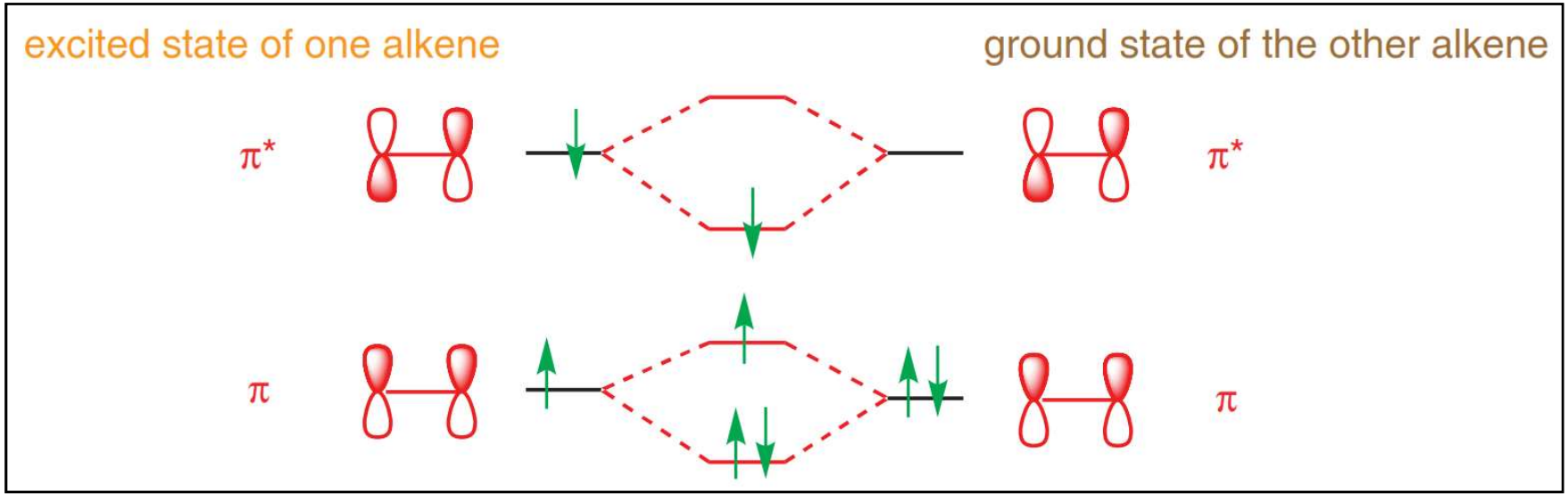
Example of a [2+2] Cycloaddition



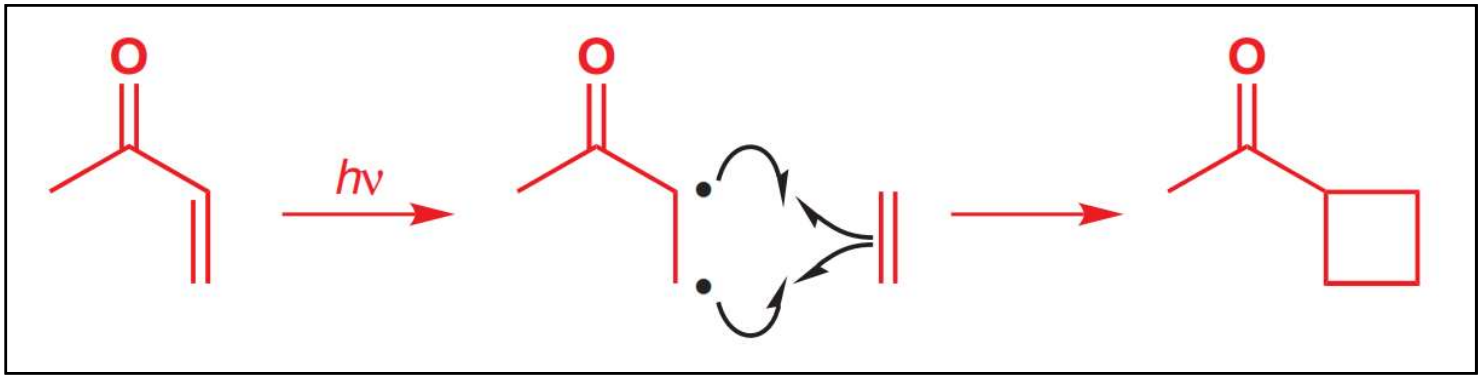
no reaction in the absence of UV light

Photochemical [2+2] Cycloaddition: *The FMO*

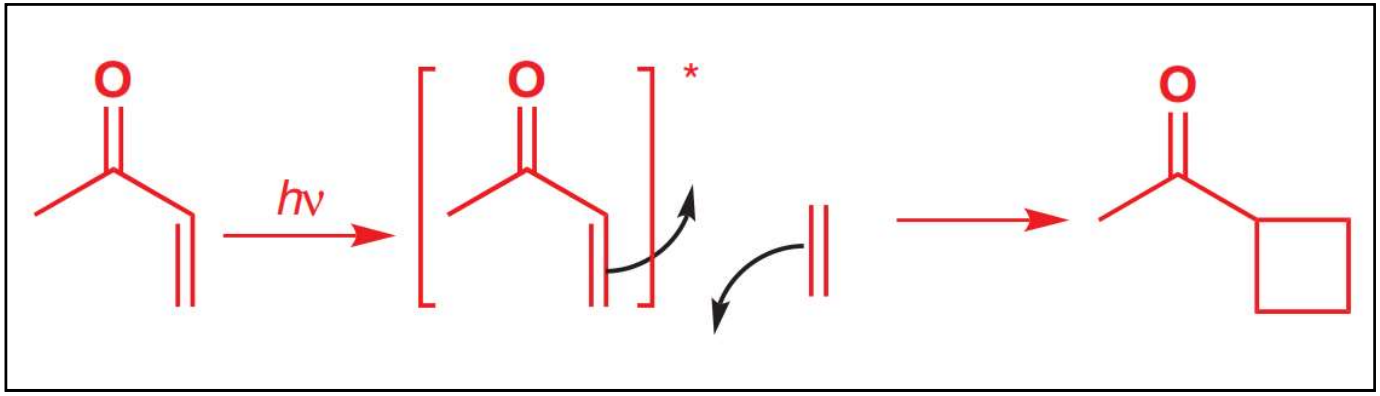


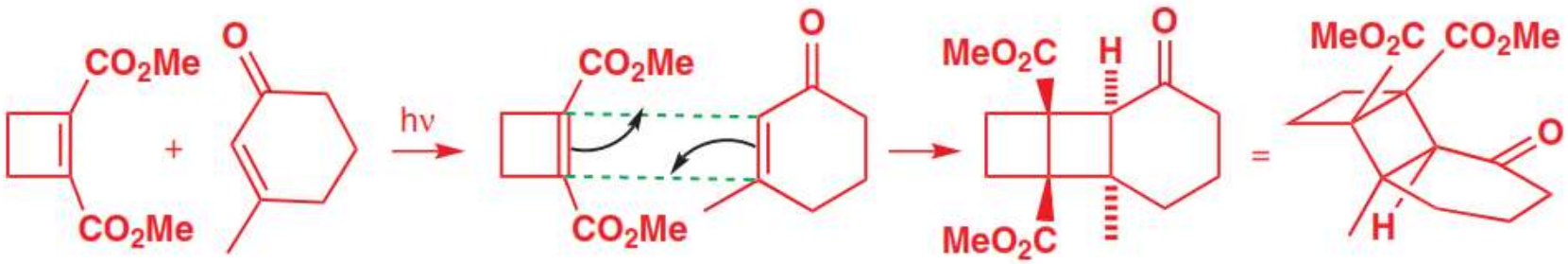


Photochemical [2+2] Cycloaddition: *The FMO*



or





Diels-Alder Reaction: *[4+2] Cycloaddition*