QFL-0341 Estrutura e reatividade de compostos orgânicos

2019 (18 de outubro)

Reações pericíclicas (cicloadições)

Literatura

Bruice (4a ed, 2006)
p. 298: espectroscopia na região do UV-VIS, Diels-Alder;

McMurry (5a ed, 2000)
p. 1235: Orbitals and organic chemistry – Pericyclic reactions (somente cicloadições)

Solomons (8a ed, 2005)
p. 549: Sistemas insaturados conjugados (UV e Diels-Alder)

Vollhardt (6a ed, 2011)
p. 28: Orbitais moleculares e ligações covalentes;
p. 609: Sistemas p deslocalizados (exceto benzeno e reações eletrocíclicas);

Clayden (2001)
p. 95: Molecular orbitals;
p. 151: Delocalization and conjugation;
p. 905: Pericyclic reaction 1 - cycloaddition

Tipos de reações orgânicas?

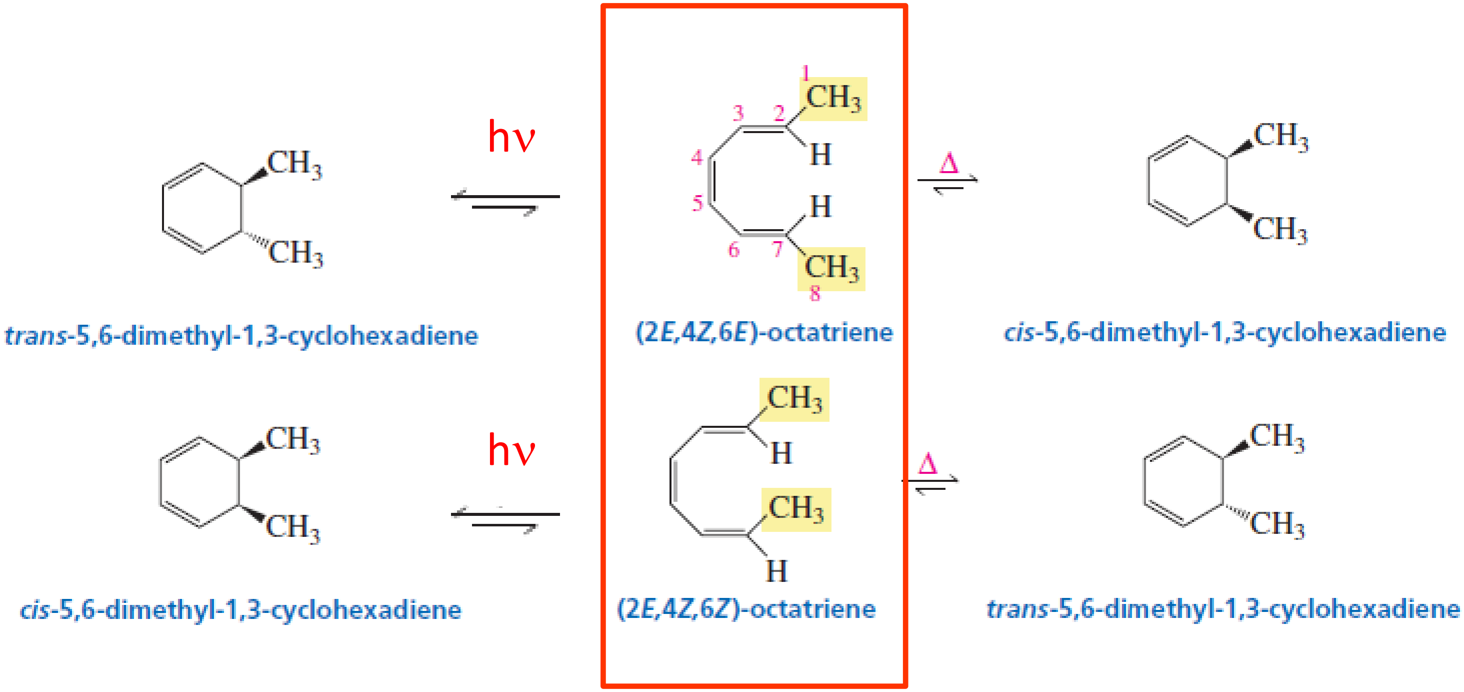
RADICALARES (Homolíticas)

POLARES (Heterolíticas)

PERICÍCLICAS (“concertadas”)

Reações pericíclicas:

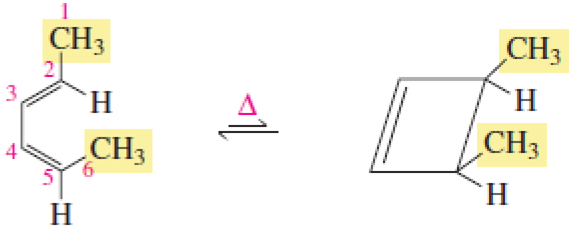
Eletrocíclicas
Rearranjos sigmatrópicos
Cicloadições



trans-5,6-dimethyl-1,3-cyclohexadiene
(2*E*,4*Z*,6*E*)-octatriene
cis-5,6-dimethyl-1,3-cyclohexadiene

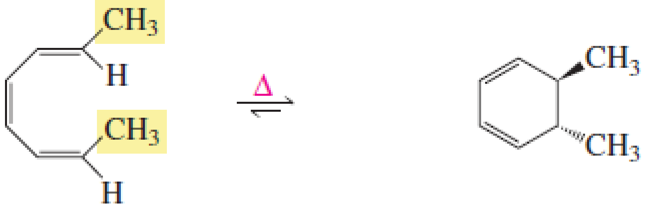
cis-5,6-dimethyl-1,3-cyclohexadiene
(2*E*,4*Z*,6*Z*)-octatriene
trans-5,6-dimethyl-1,3-cyclohexadiene

Reações eletrocíclicas



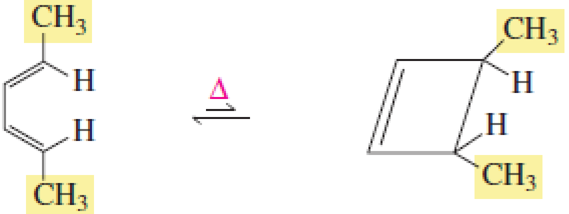
(2*E*,4*Z*)-hexadiene

cis-3,4-dimethylcyclobutene



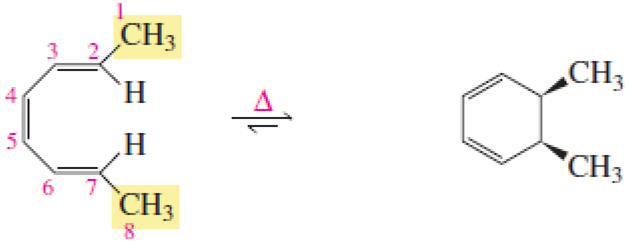
(2*E*,4*Z*,6*Z*)-octatriene

trans-5,6-dimethyl-1,3-cyclohexadiene



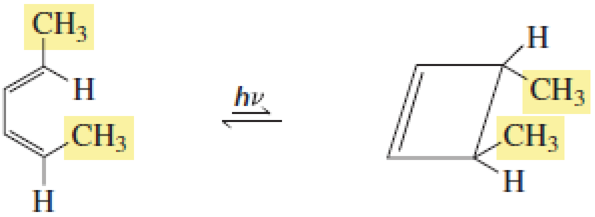
(2*E*,4*E*)-hexadiene

trans-3,4-dimethylcyclobutene



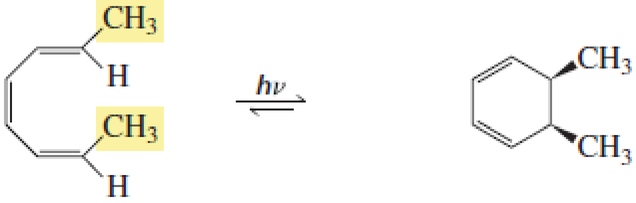
(2*E*,4*Z*,6*E*)-octatriene

cis-5,6-dimethyl-1,3-cyclohexadiene



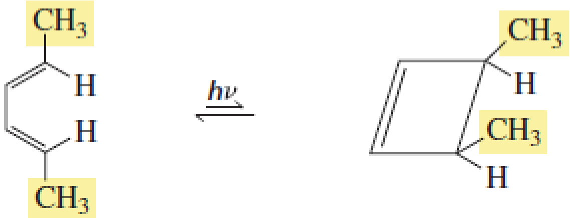
(2*E*,4*Z*)-hexadiene

trans-3,4-dimethylcyclobutene



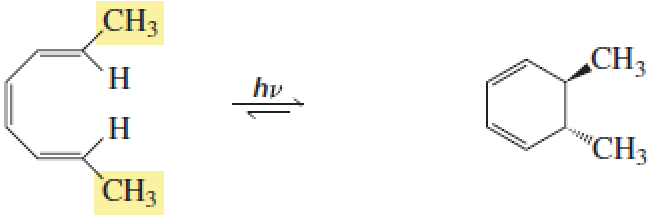
(2*E*,4*Z*,6*Z*)-octatriene

cis-5,6-dimethyl-1,3-cyclohexadiene



(2*E*,4*E*)-hexadiene

cis-3,4-dimethylcyclobutene

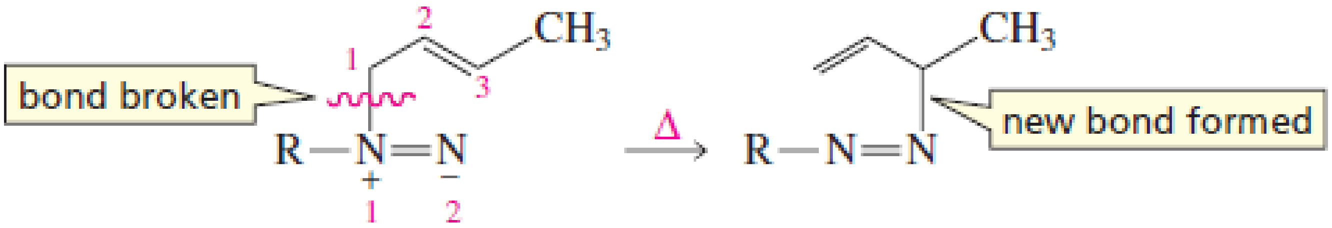


(2*E*,4*Z*,6*E*)-octatriene

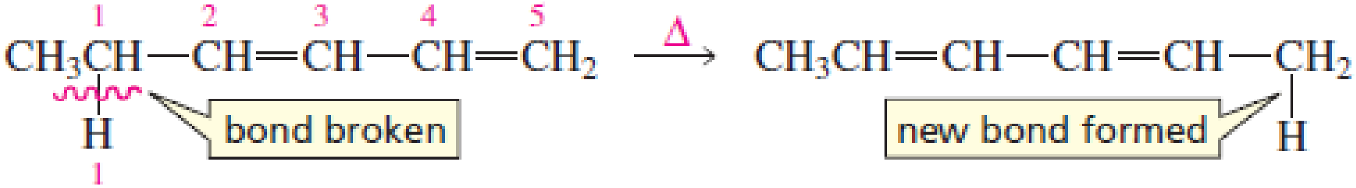
trans-5,6-dimethyl-1,3-cyclohexadiene

Rearranjos sigmatrópicos

a [2,3] sigmatropic rearrangement



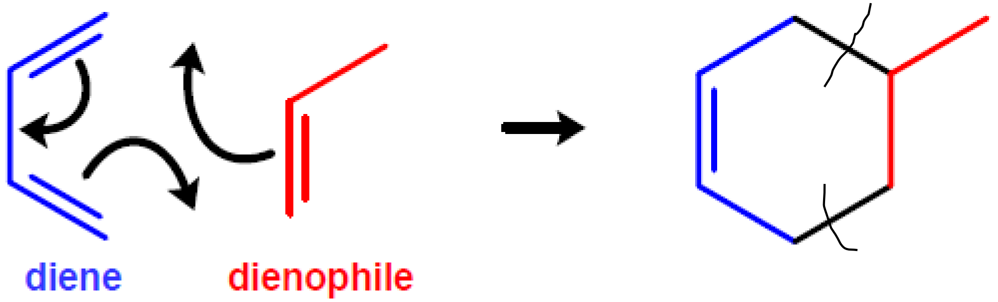
a [1,5] sigmatropic rearrangement

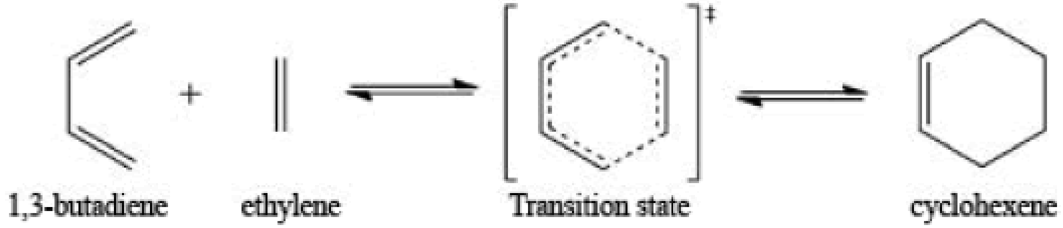


Diels-Alder reaction (a cycloaddition reaction)

1928 (Otto Paul Hermann Diels and Kurt Alder)
1950 Nobel Prize in Chemistry

- Our first “name” reaction
  - Named after chemist(s) instead of the chemistry!

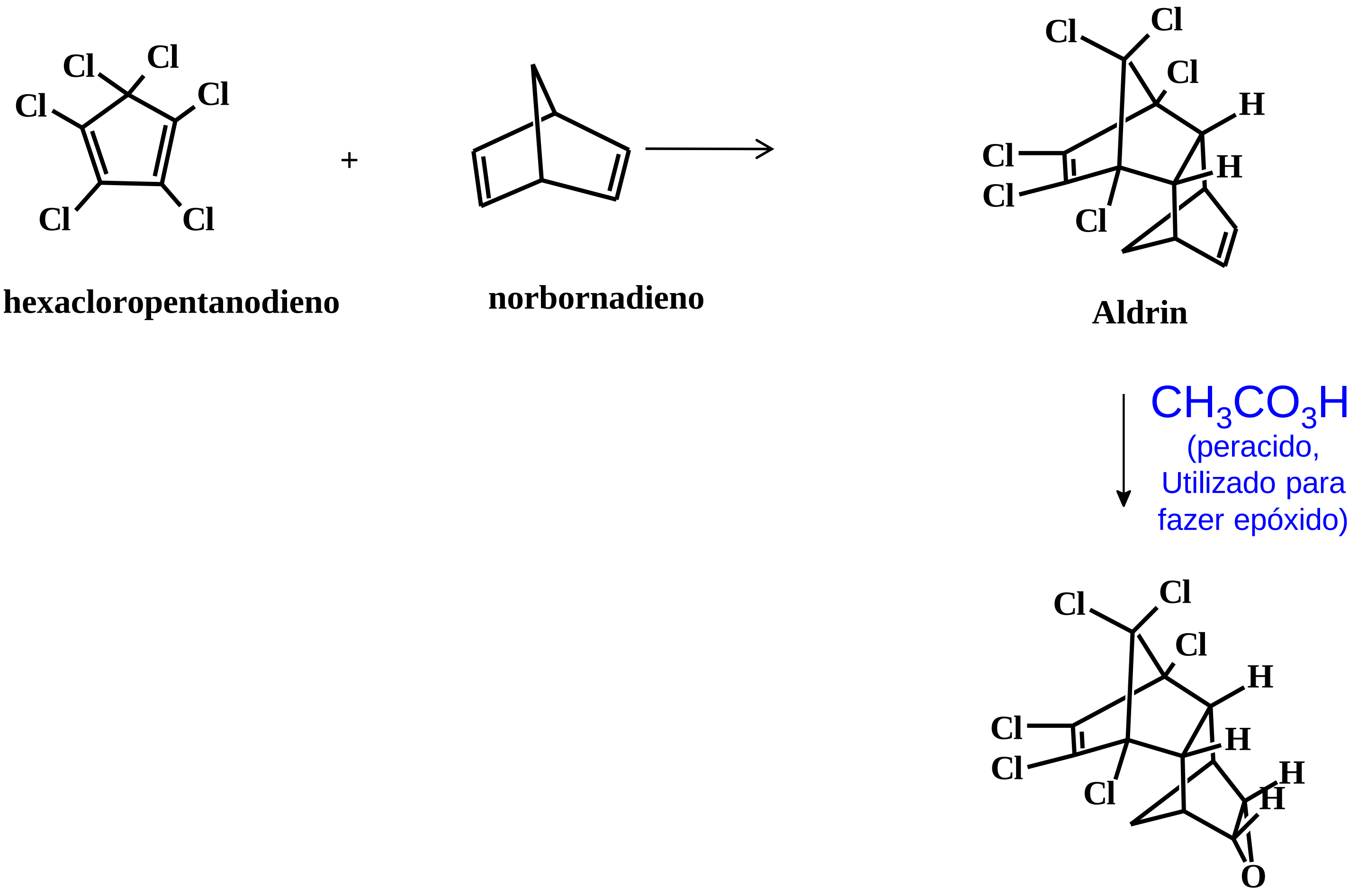




Scheme 1: The Diels-Alder reaction of 1,3-butadiene and ethylene.

Método de obtenção de aneis de 6 membros com grande aplicação em síntese

Uso da reação de Diels-Alder na síntese de Aldrin e Dieldrin (inseticidas)



hexacloropentanodieno

norbornadieno

Aldrin

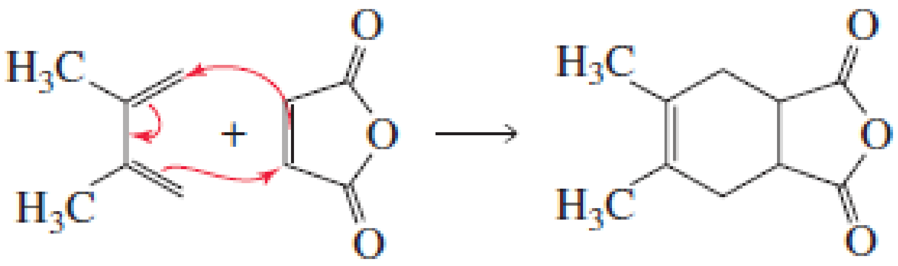
CH_3CO_3H
(peracido,
Utilizado para
fazer epóxido)

Dieldrin

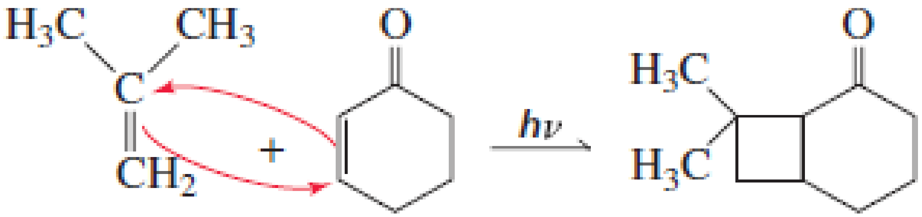
https://en.wikipedia.org/wiki/Dieldrin

Cycloaddition reactions

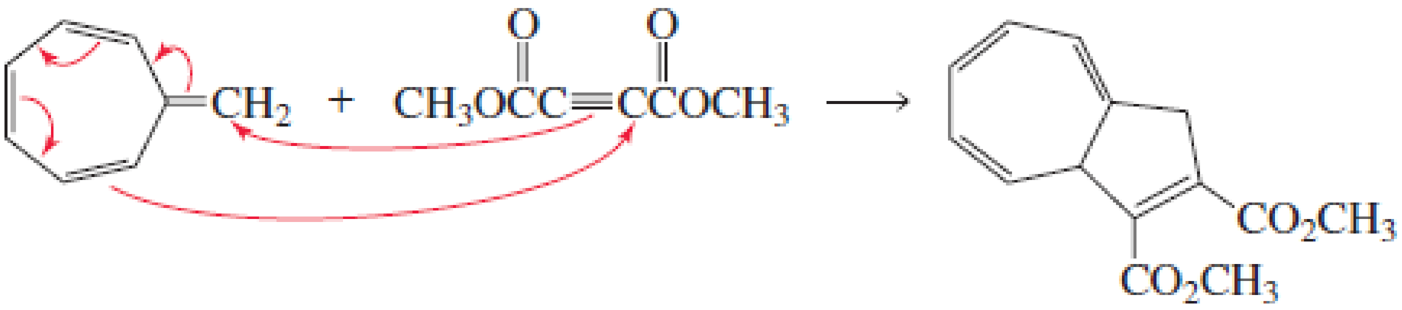
[4 + 2] cycloaddition (a Diels–Alder reaction)



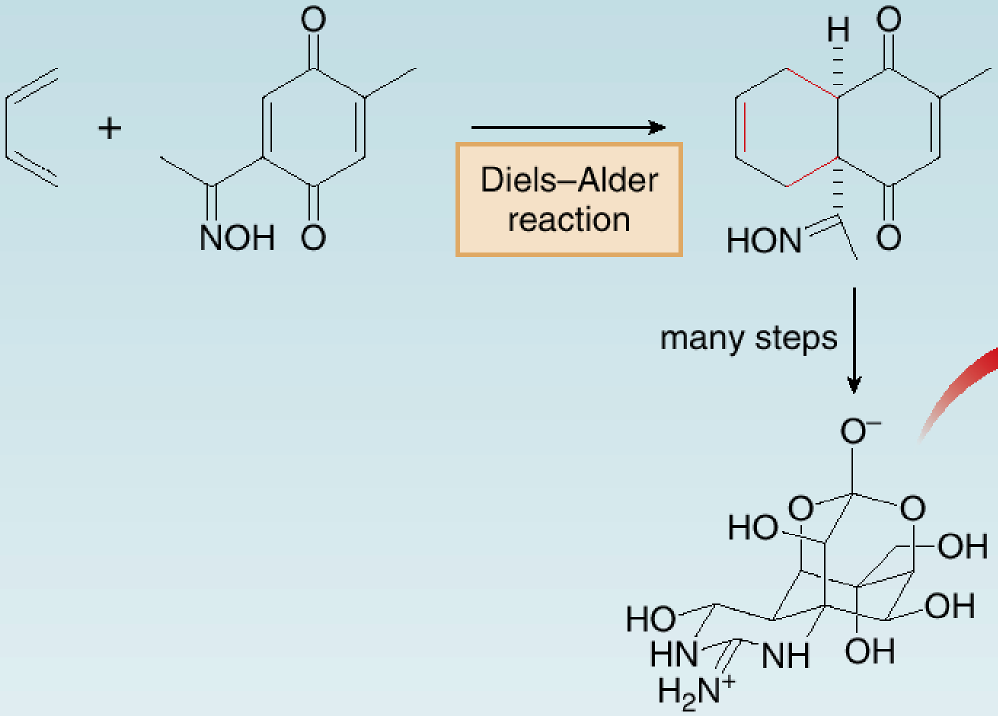
[2 + 2] cycloaddition



[8 + 2] cycloaddition

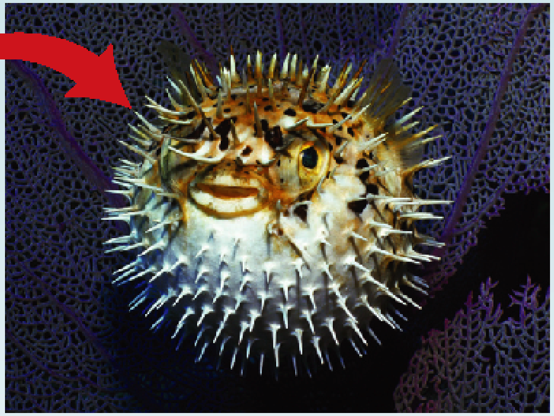


Biosynthesis of a natural product using the Diels-Alder reaction



tetrodotoxin

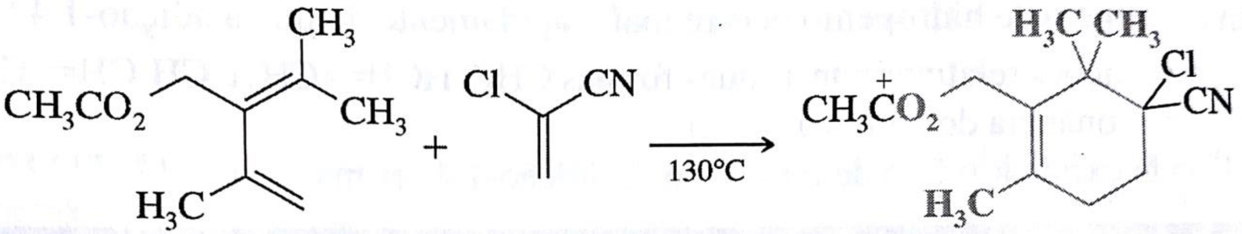
[Bonds formed from the Diels–Alder reaction are shown in red.]



Japanese puffer fish

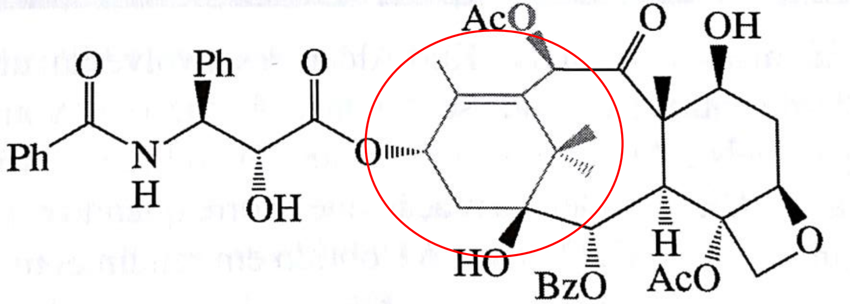
- Tetrodotoxin, a complex natural product containing several six-membered rings joined together, is a poison isolated from the ovaries and liver of the puffer fish, so named because the fish inflates itself into a ball when alarmed. Eating fish tainted with trace amounts of this potent toxin results in weakness, paralysis, and eventually death. One step in the synthesis of tetrodotoxin involves forming a six-membered ring by a Diels–Alder reaction.

Exemplo de aplicação da reação de Diels-Alder: síntese de um intermediário Na síntese do antitumoral Taxol (Paclitaxel)



85%

(Utilizado em uma síntese do Taxol®)

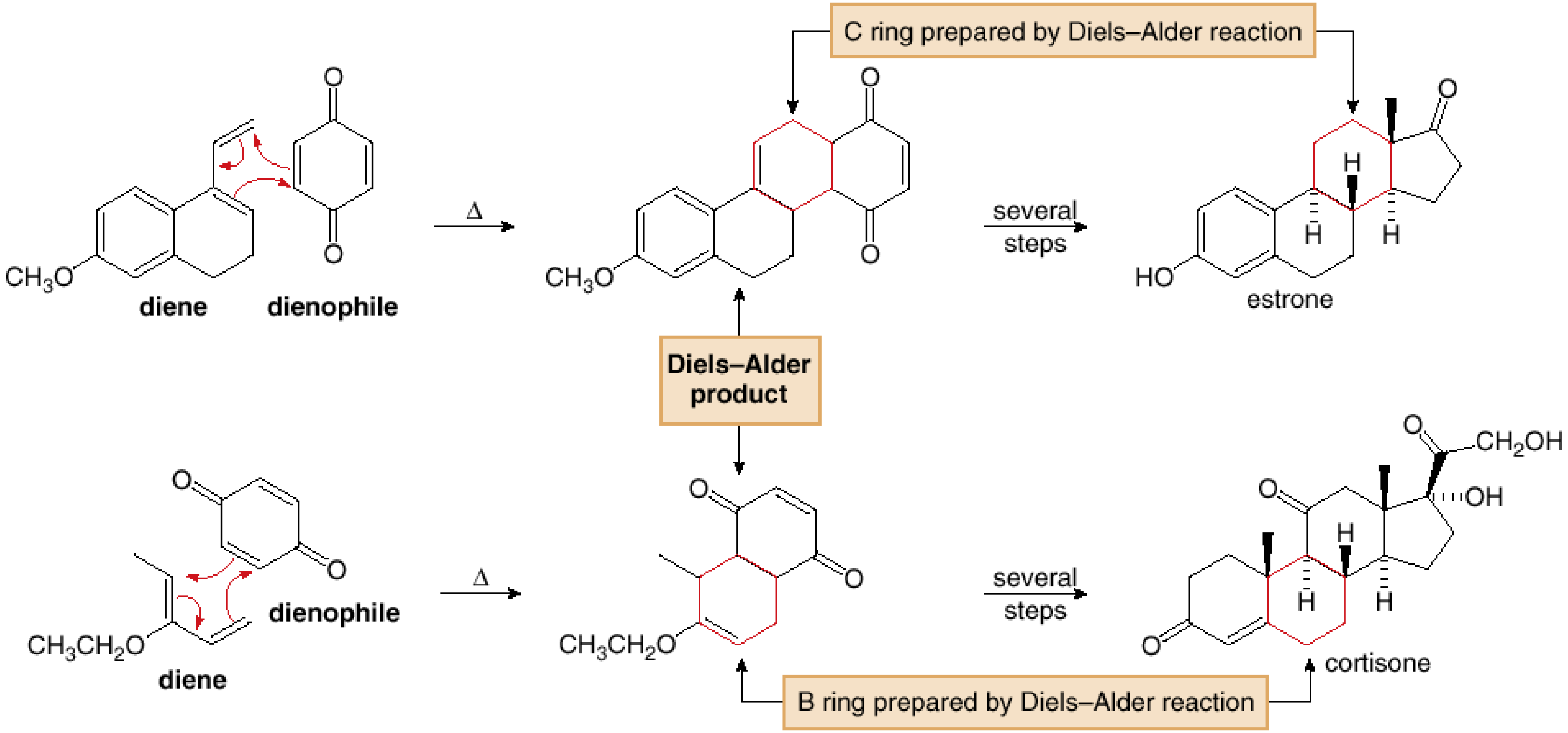


Taxol®

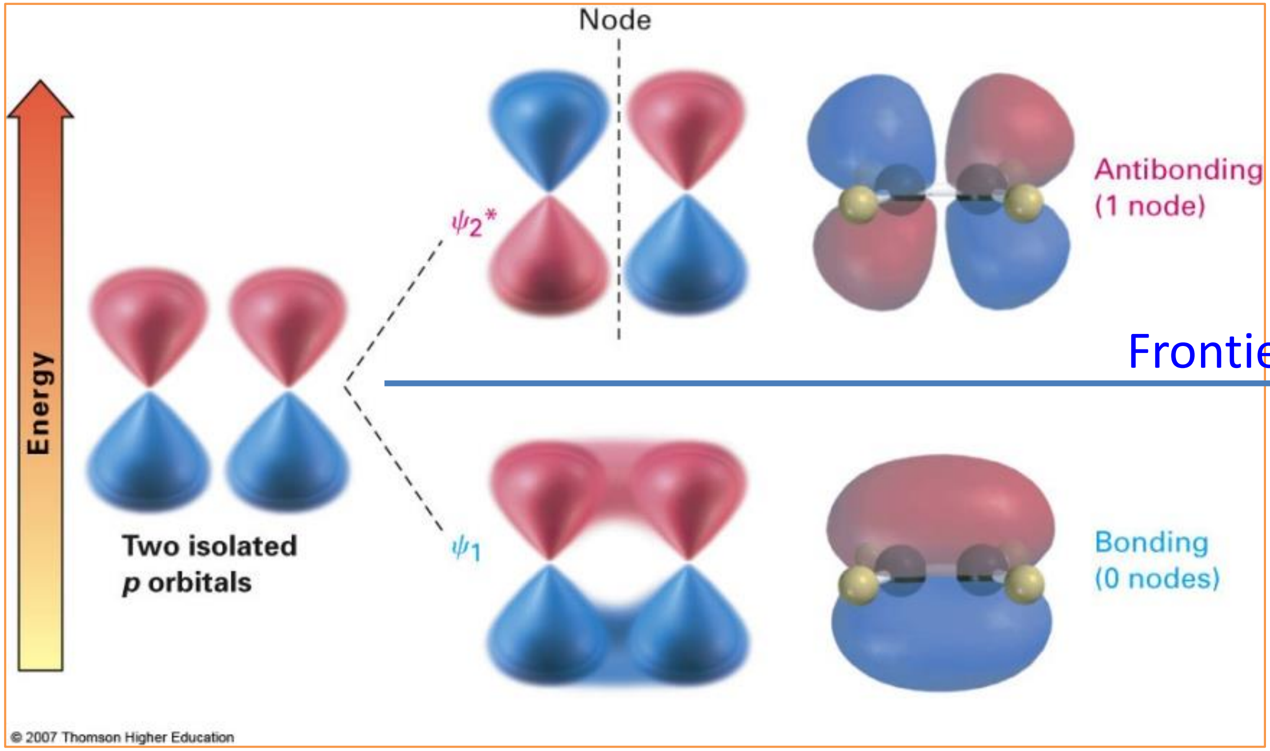
Nicolaou KC (Scripps Research Institute e Universidade da California)

Application of the Diels-Alder Reaction: Steroid Synthesis

- The key Diels-Alder reactions used to prepare the C ring of estrone and the B ring of cortisone are as follows:



Molecular Orbital Description for ethylene



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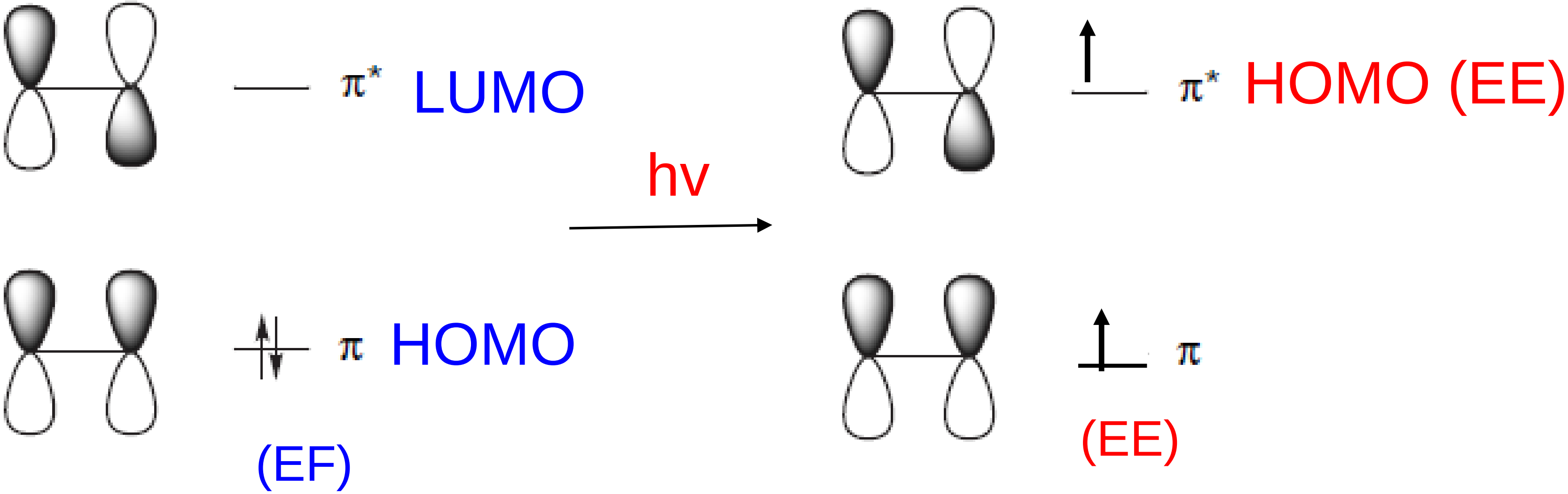
LUMO
(lowest unoccupied
Molecular orbital)

Frontiers orbitals

HOMO
(highest occupied
Molecular orbital)

No estado excitado, esse orbital que era LUMO passou a ser ocupado, tornando-se HOMO.



π^* LUMO

π HOMO

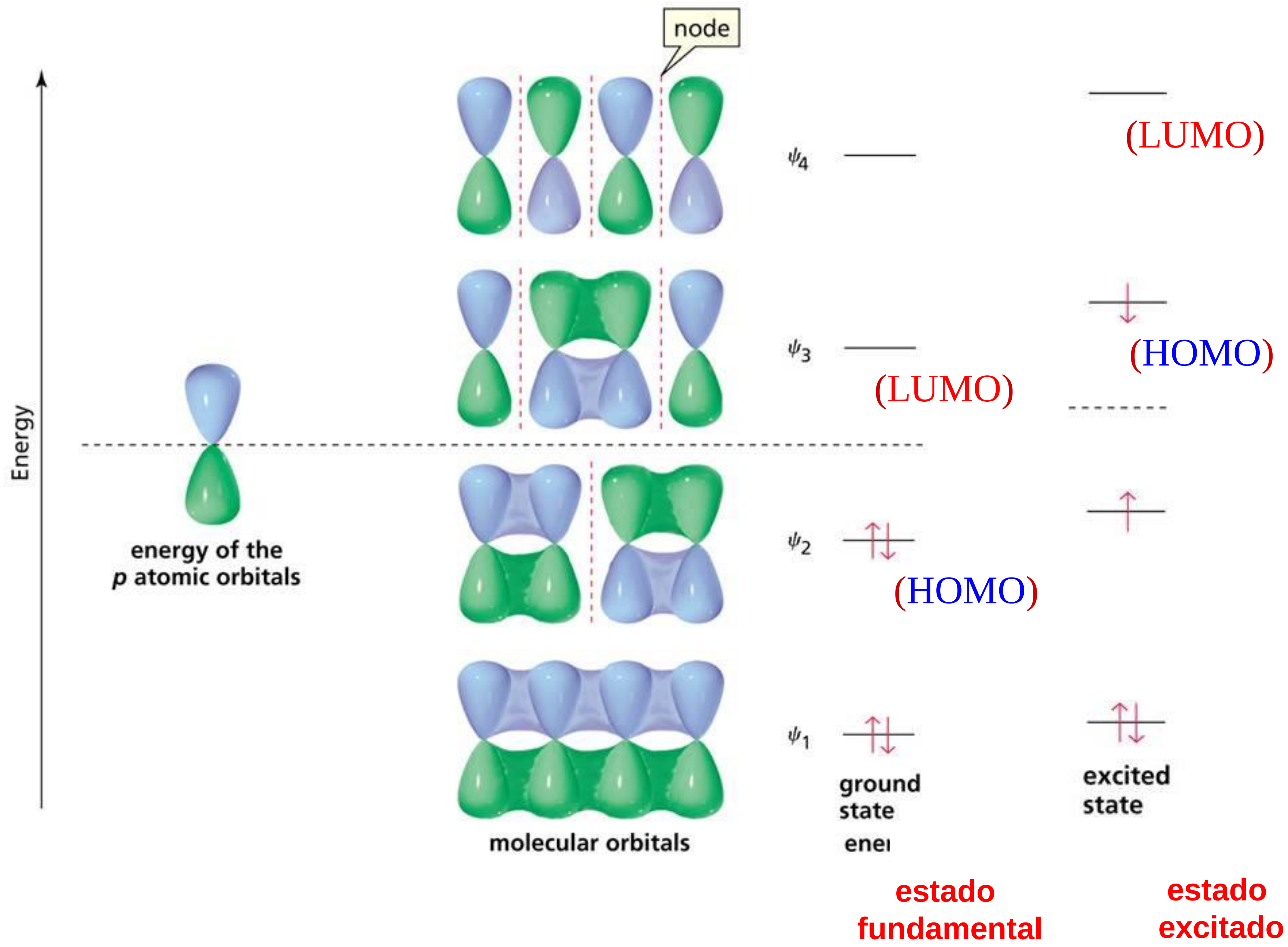
(EF)

hv

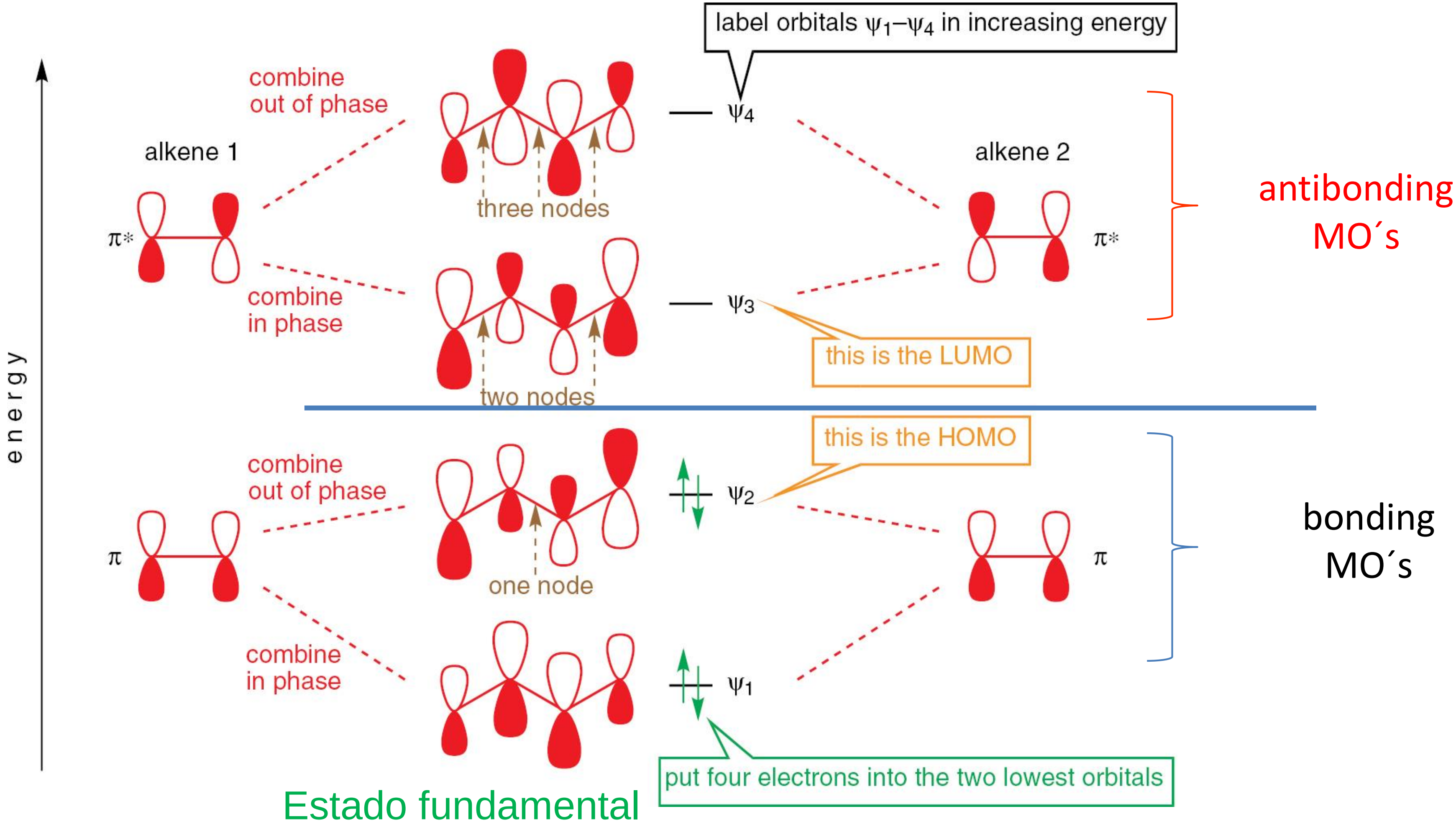
π^* HOMO (EE)

π

(EE)


node
Energy
ψ_4
ψ_3
ψ_2
ψ_1
(LUMO)
(HOMO)
(LUMO)
(HOMO)
energy of the
p atomic orbitals
molecular orbitals
ground
state
ene
excited
state
estado
fundamental
estado
excitado

Molecular Orbital Description for 1,3-butadiene and alkene



label orbitals ψ_1–ψ_4 in increasing energy

energy

alkene 1

alkene 2

π^*

π^*

π

π

combine out of phase

combine in phase

combine out of phase

combine in phase

three nodes

two nodes

one node

ψ_4

ψ_3

ψ_2

ψ_1

this is the LUMO

this is the HOMO

put four electrons into the two lowest orbitals

antibonding MO´s

bonding MO´s

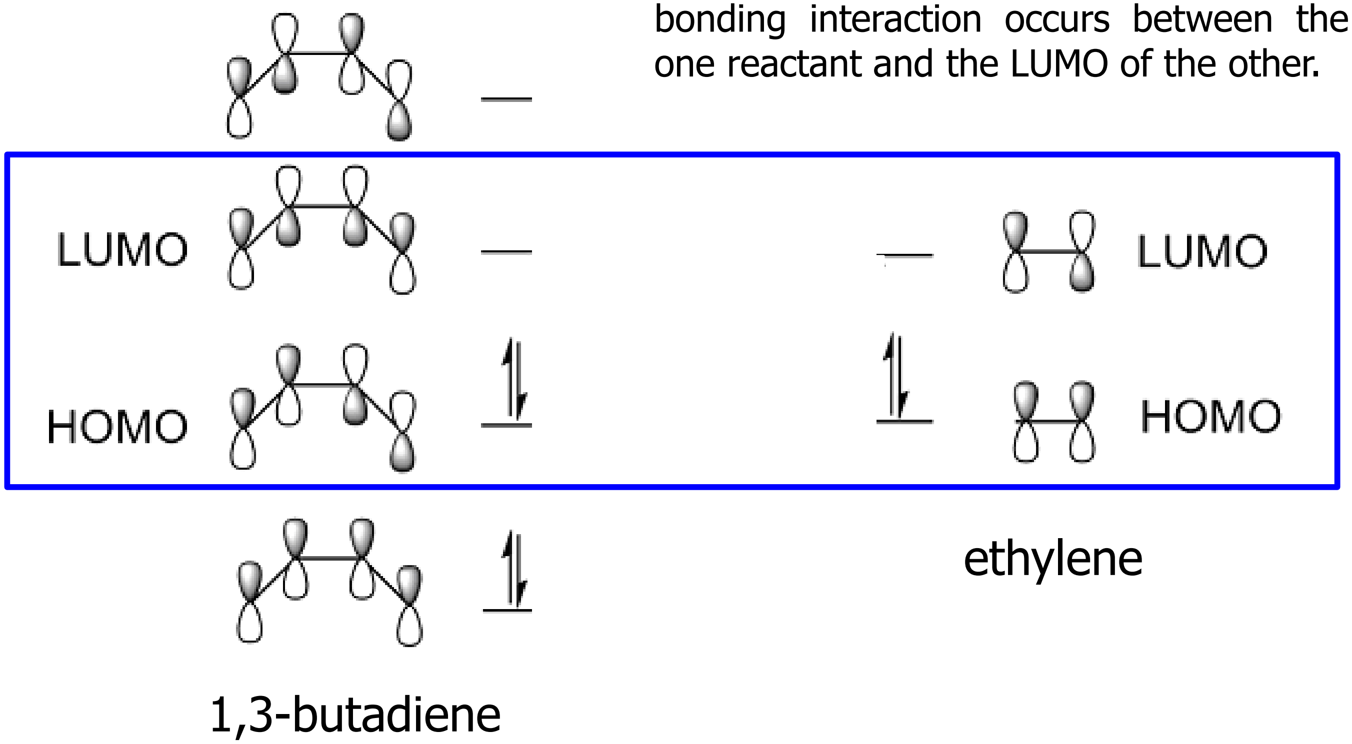
Estado fundamental

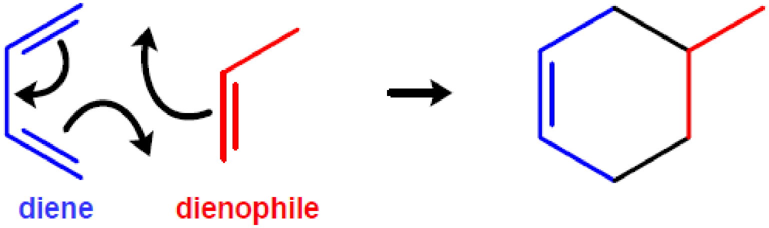
MO is bonding when the number of bonding interactions > number of nodes

MO is antibonding when the number of bonding interactions < number of nodes

Diels-Alder reaction (a cycloaddition reaction)

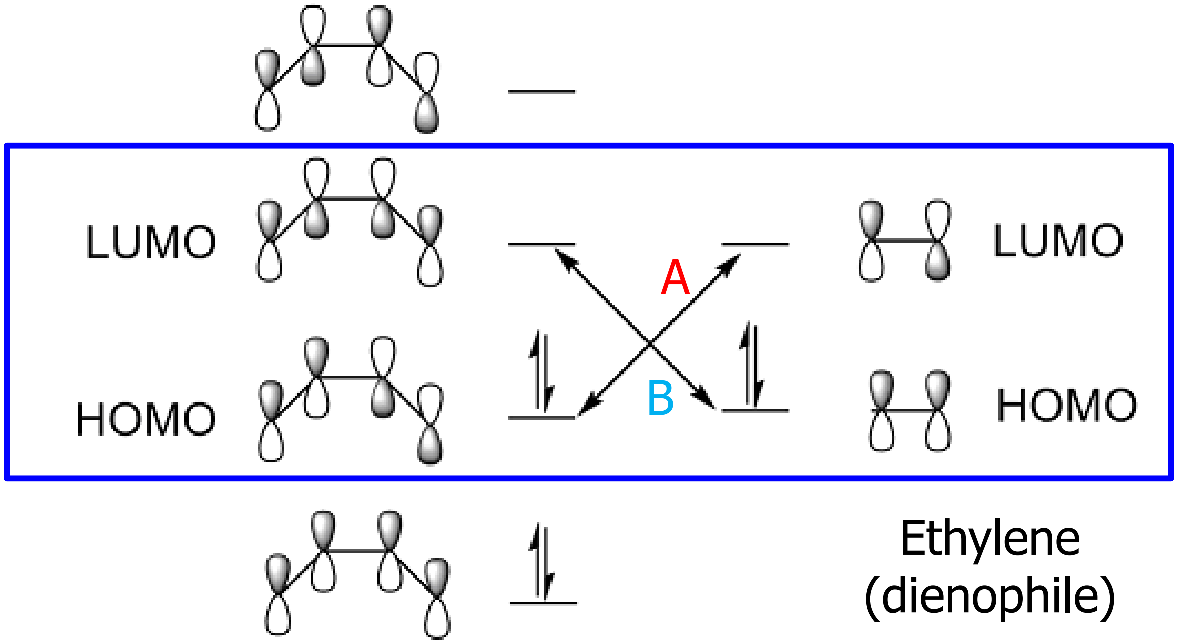
A cycloaddition reactions takes place when a bonding interaction occurs between the HOMO of one reactant and the LUMO of the other.





Frontier molecular orbital analysis of a cycloaddition reaction

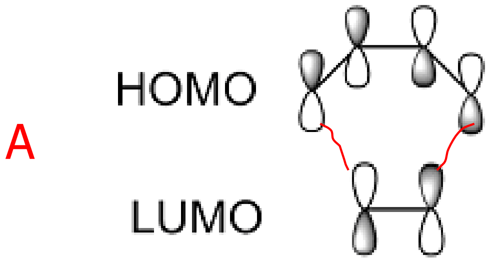
The HOMO of either of the reactants can be used with the LUMO of the other.



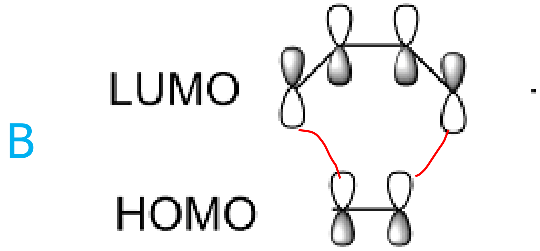
1,3-butadiene
(diene)

Ethylene
(dienophile)

Frontier
orbitals



suprafacial



suprafacial

Both situations require **suprafacial** (same face of p-orbital) overlap for bond formation.

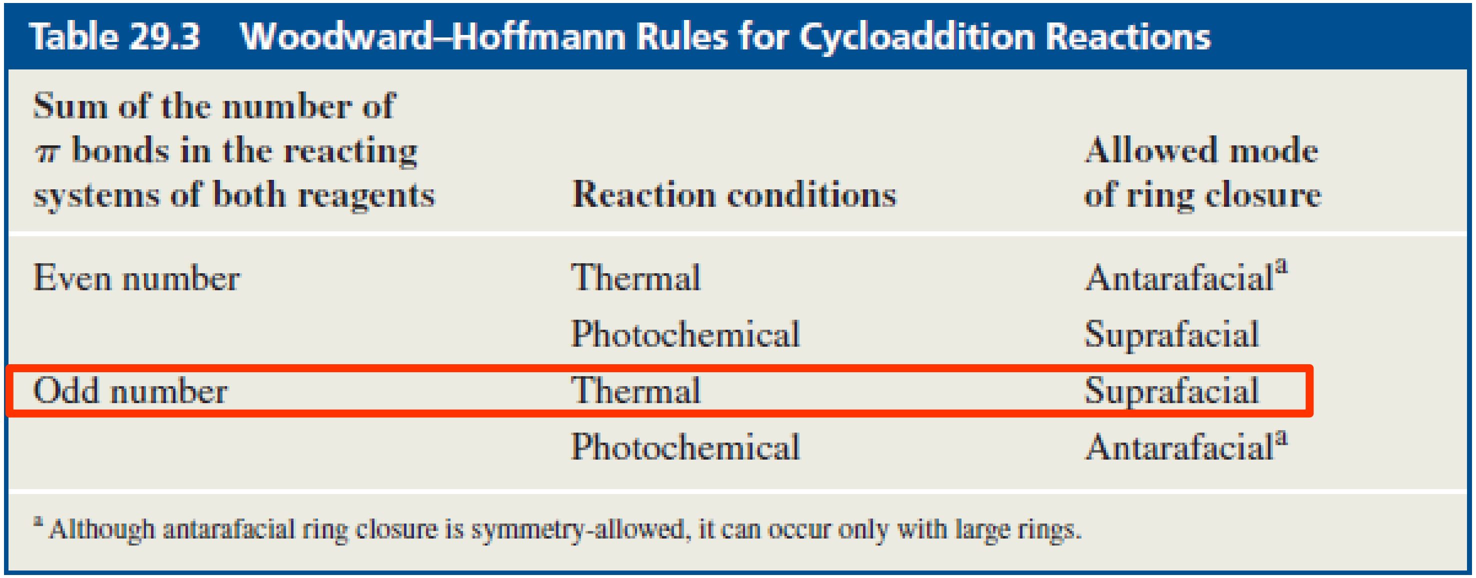


Table 29.3 Woodward–Hoffmann Rules for Cycloaddition Reactions

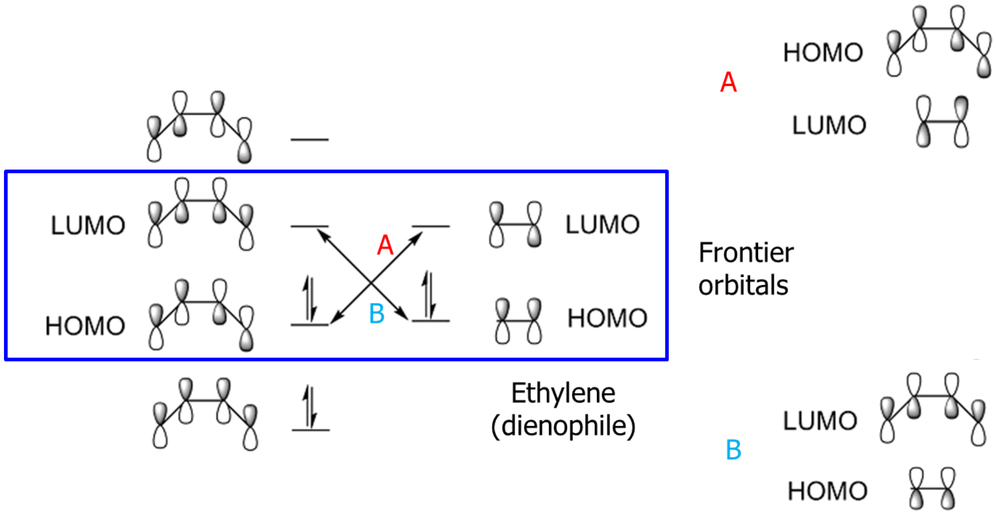
Sum of the number of π bonds in the reacting systems of both reagents	Reaction conditions	Allowed mode of ring closure
Even number	Thermal	Antarafacial[a]
	Photochemical	Suprafacial
Odd number	Thermal	Suprafacial
	Photochemical	Antarafacial[a]

[a] Although antarafacial ring closure is symmetry-allowed, it can occur only with large rings.

Diels-Alder [4+2]

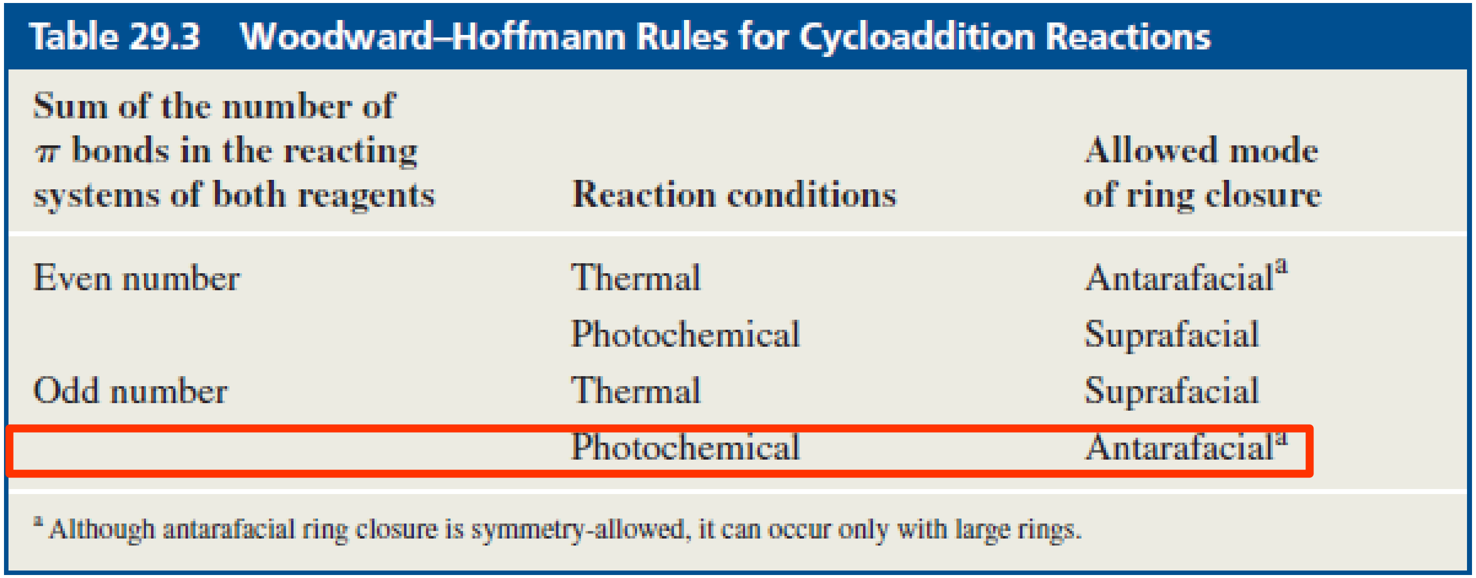
3 ligações π

Condições **térmicas** (HOMO e LUMO no **EF**)



suprafacial

suprafacial



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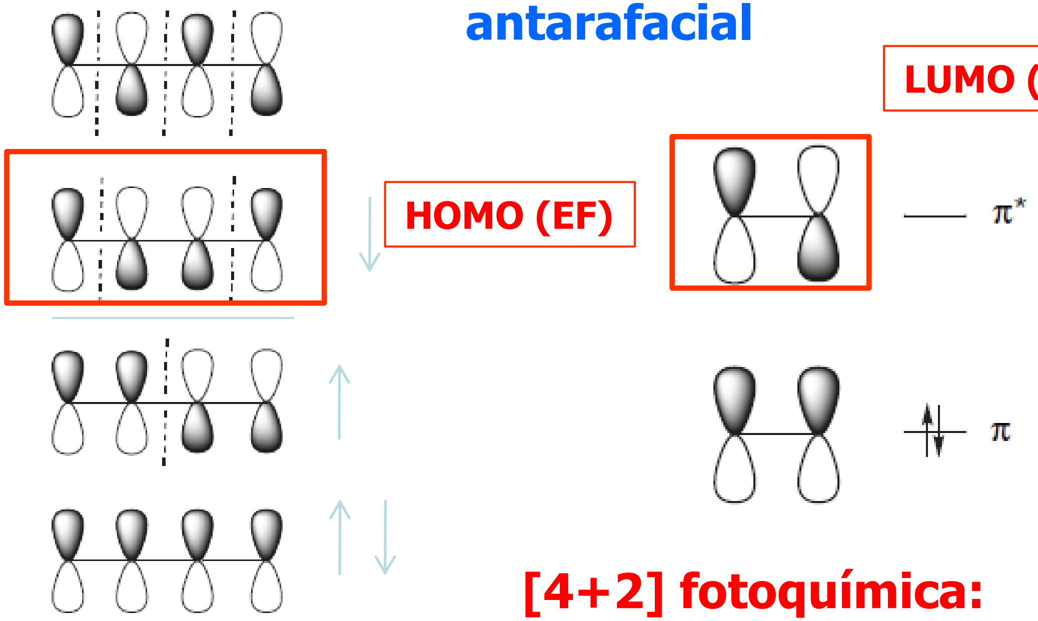
Even number	Thermal	Antarafacial[a]
	Photochemical	Suprafacial
Odd number	Thermal	Suprafacial
	Photochemical	Antarafacial[a]

[a] Although antarafacial ring closure is symmetry-allowed, it can occur only with large rings.

Diels-Alder [4+2]

3 ligações π

Condições fotoquímicas
(HOMO (EF) e LUMO (**EE**)
ou vice-e-versa



antarafacial

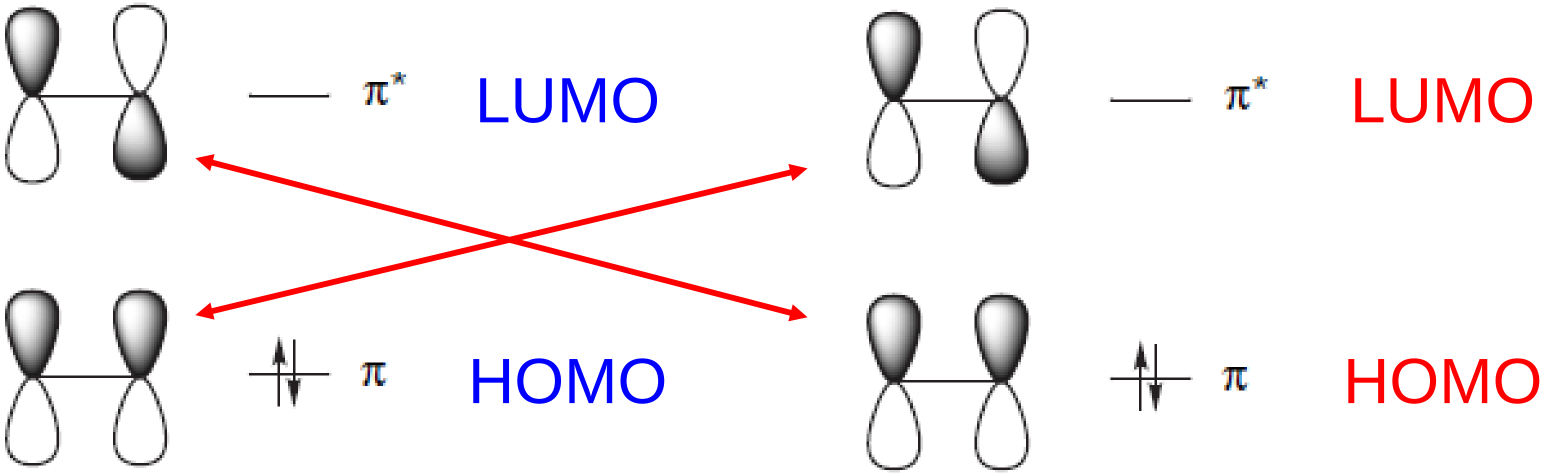
LUMO (EE)

HOMO (EF)

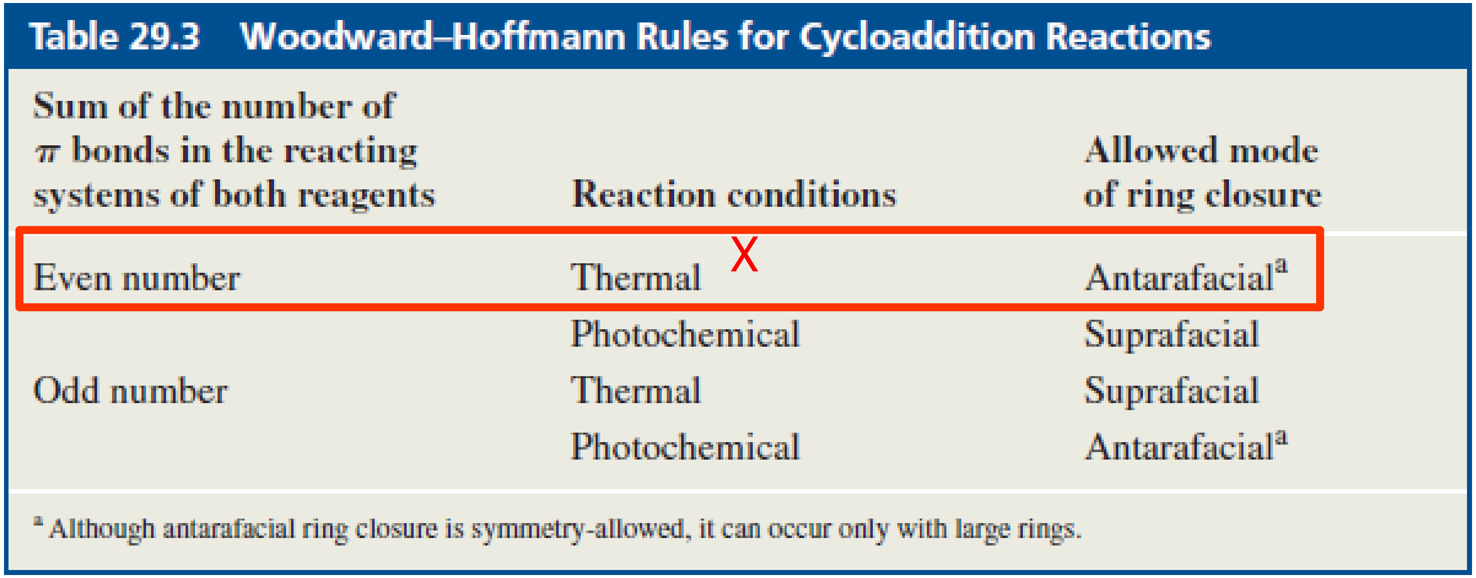
[4+2] fotoquímica:
Não ocorre!!!

According to Frontiers Orbital theory:

A cycloaddition reactions takes place when a bonding interaction occurs between the HOMO of one reactant and the LUMO of the other.



not possible for termal [2+2] reactions



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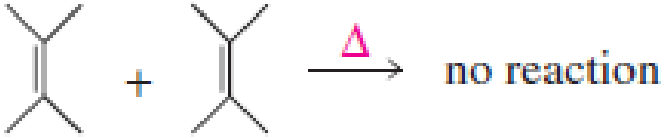
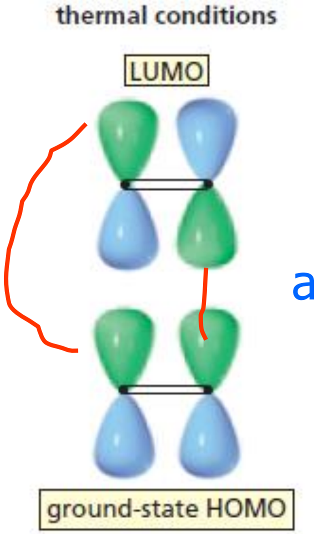
Sum of the number of π bonds in the reacting systems of both reagents	Reaction conditions	Allowed mode of ring closure
Even number	Thermal X	Antarafacial[a]
	Photochemical	Suprafacial
Odd number	Thermal	Suprafacial
	Photochemical	Antarafacial[a]

[a] Although antarafacial ring closure is symmetry-allowed, it can occur only with large rings.

Para [2+2]

2 ligações π



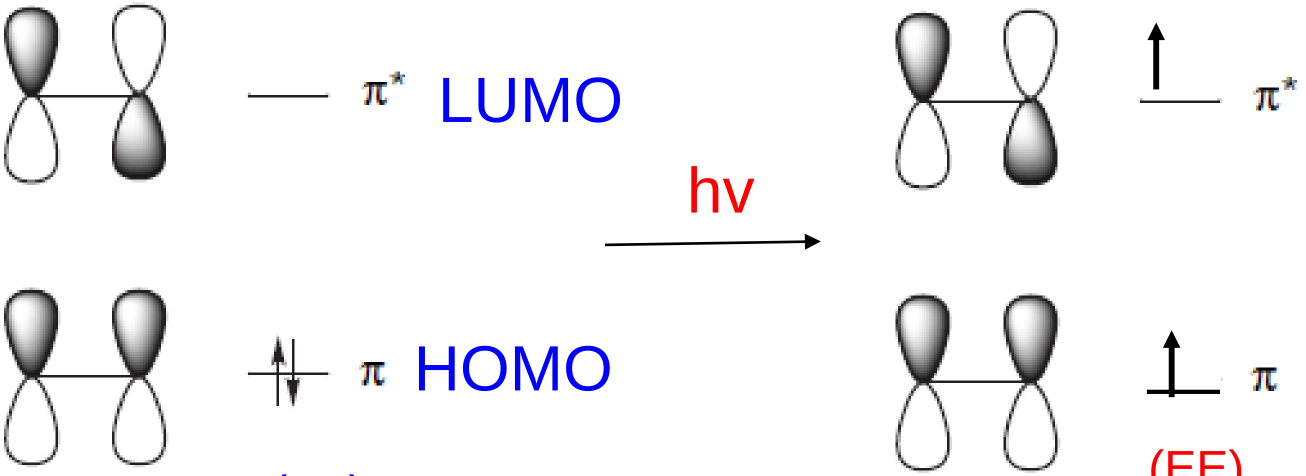


antarafacial

X

[2+2] Photochemical reactions

No estado excitado, esse orbital que era LUMO passou a ser ocupado, tornando-se HOMO.



LUMO

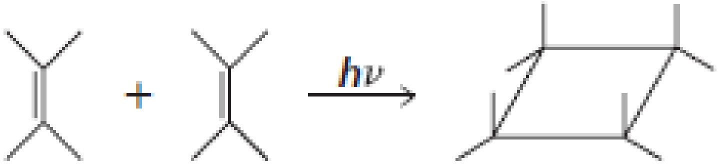
HOMO

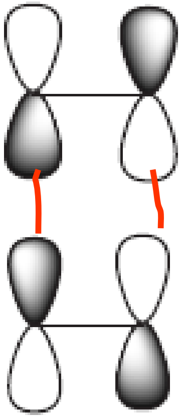
(EF)

hv

HOMO (EE)

(EE)





HOMO (EE)

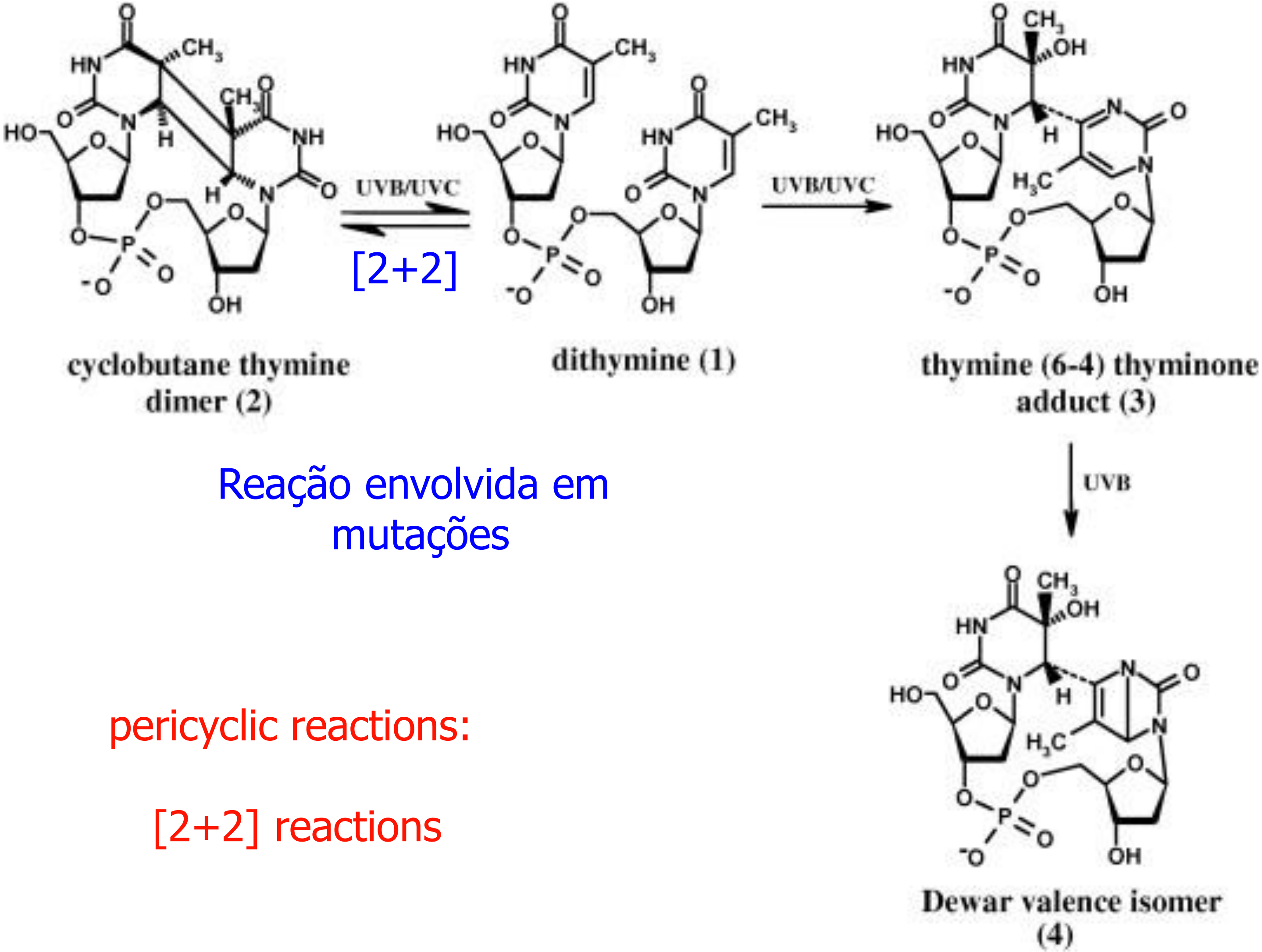
suprafacial

LUMO (EF)

In photochemical reaction: only one of the reactants is in an excited states!

UV-radiation induced thymine dimeric photoproducts

(causing ultimately mutations)



cyclobutane thymine dimer (2)

dithymine (1)

thymine (6-4) thyminone adduct (3)

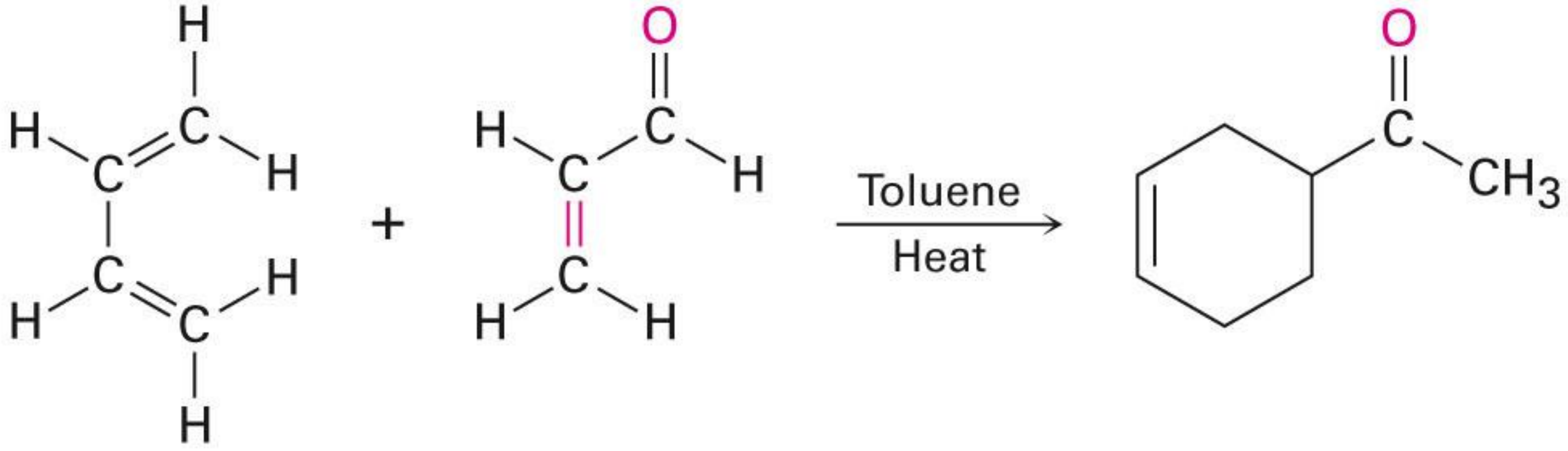
Dewar valence isomer (4)

Reação envolvida em mutações

pericyclic reactions:

[2+2] reactions

The Diels-Alder Cycloaddition Reaction



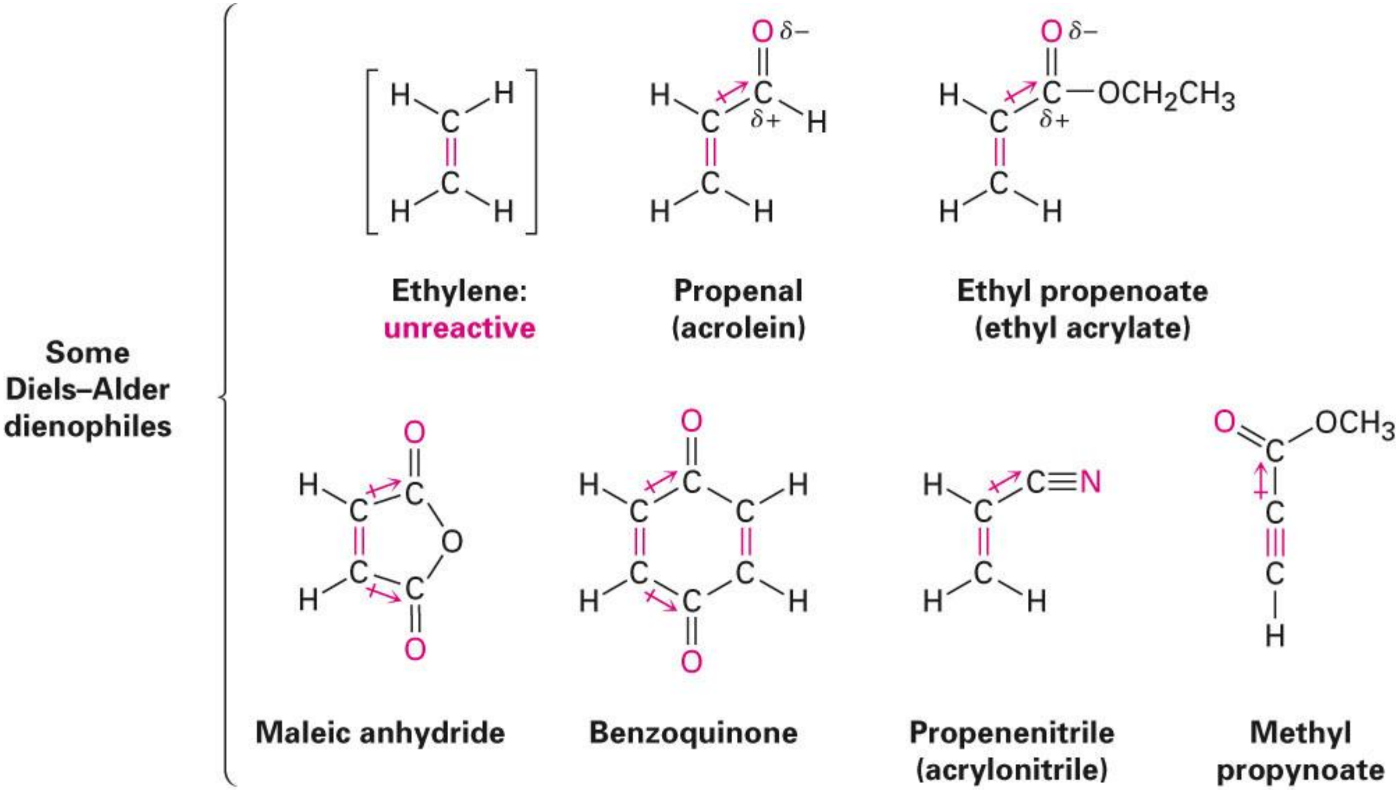
1,3-Butadiene **3-Buten-2-one** **3-Cyclohexenyl methyl ketone (96%)**

diene dienophile

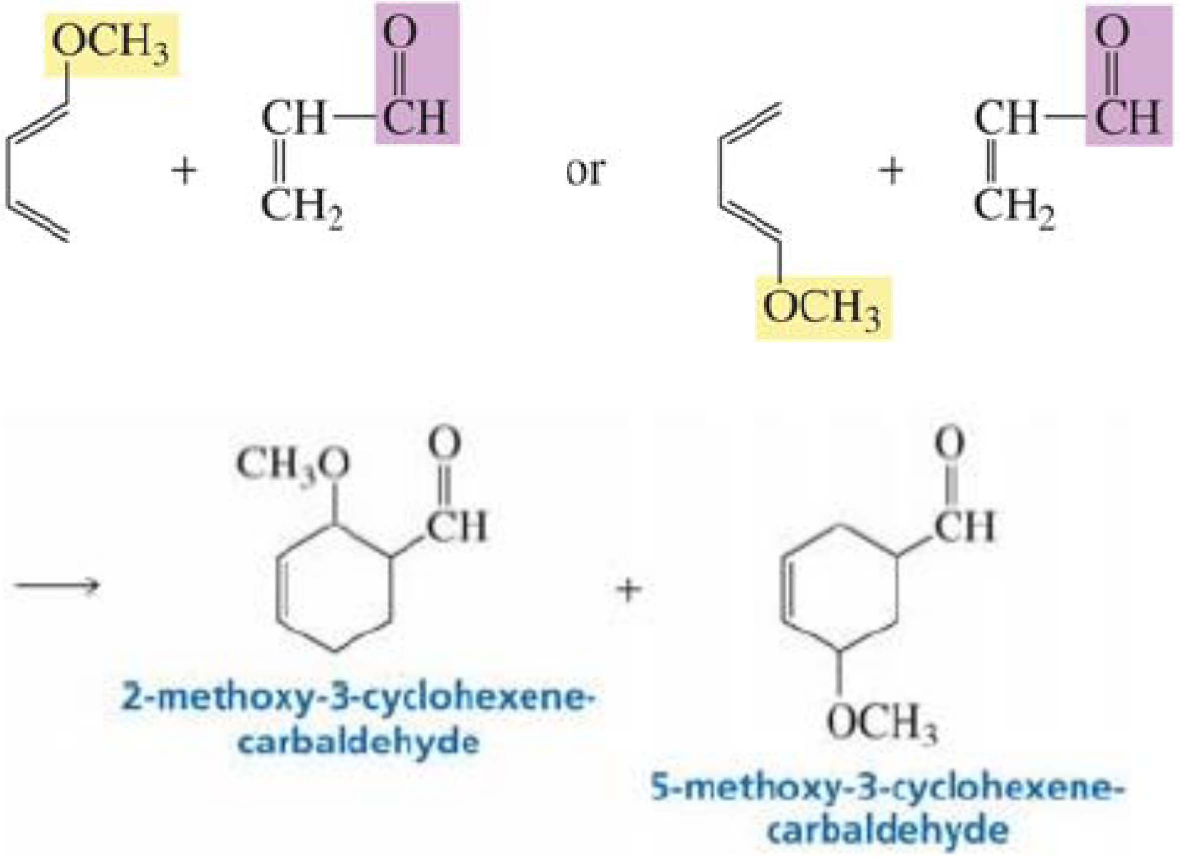
Characteristics of Diels-Alder Reaction

The alkene component is called a **dienophile**

The reaction will give better yield if the dienophile C=C is conjugated to an electron withdrawing (*retirador de eletrons*) groups, such as C=O or C≡N



- With asymmetric diene and dienophile, there are two possible regiochemical orientations

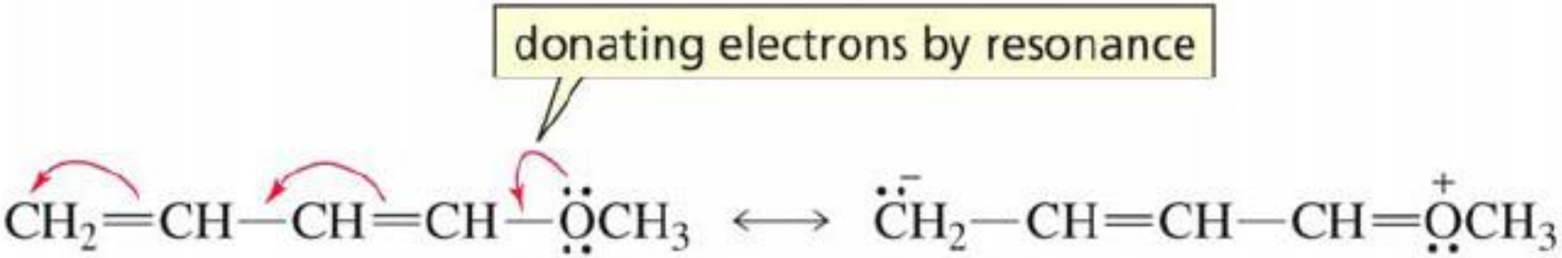


2-methoxy-3-cyclohexene-carbaldehyde

5-methoxy-3-cyclohexene-carbaldehyde

Qual seria o produto preferido?

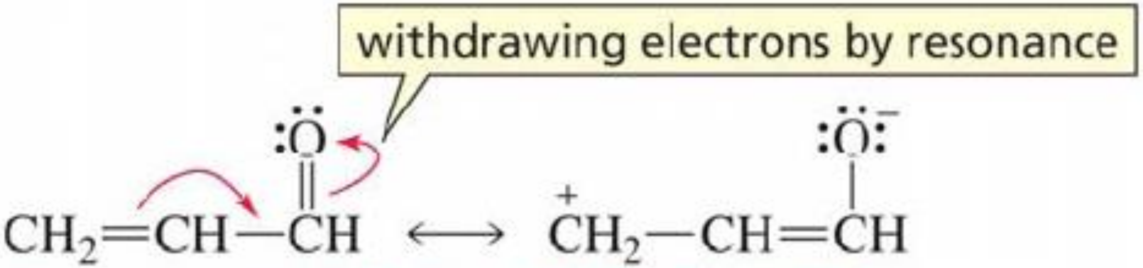
Examine the resonance contributors of the diene and dienophile



donating electrons by resonance

$$CH_2{=}CH{-}CH{=}CH{-}\ddot{\underset{\cdot\cdot}{O}}CH_3 \longleftrightarrow \overset{-}{\ddot{C}}H_2{-}CH{=}CH{-}CH{=}\overset{+}{\underset{\cdot\cdot}{O}}CH_3$$

resonance contributors of the diene

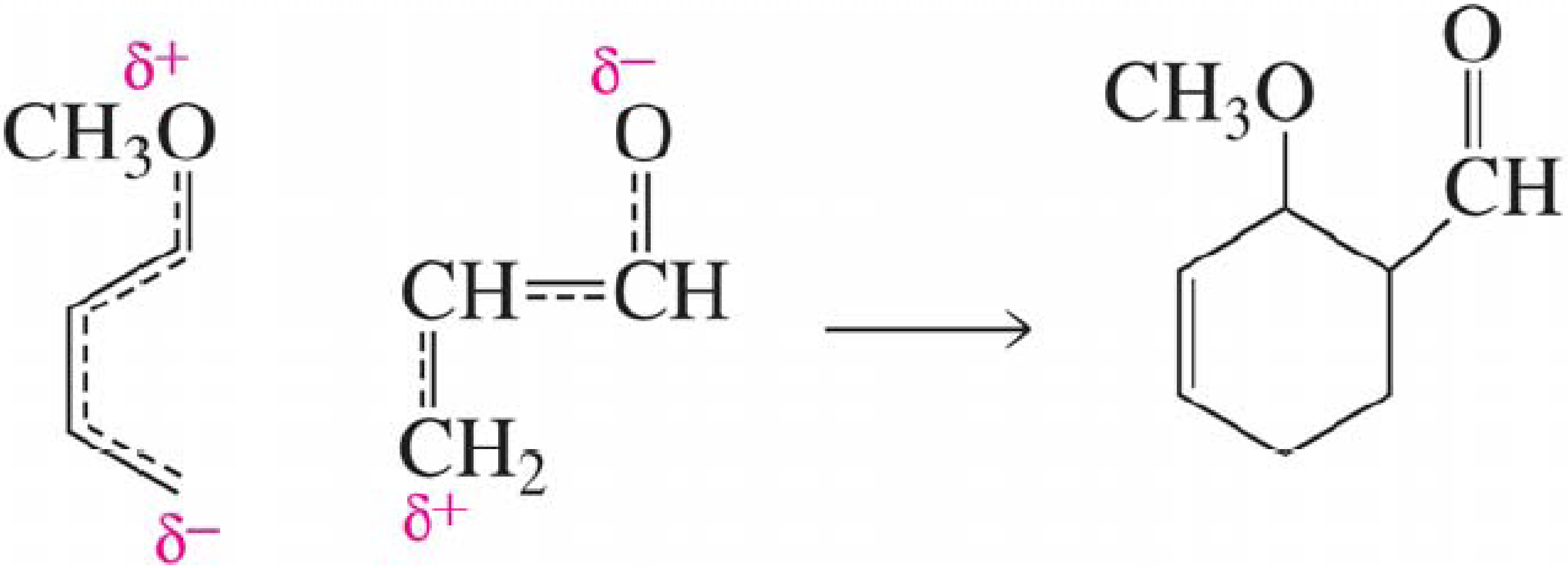


withdrawing electrons by resonance

$$CH_2{=}CH{-}\overset{\overset{:\ddot{O}}{\|}}{C}H \longleftrightarrow \overset{+}{C}H_2{-}CH{=}\overset{\overset{:\ddot{O}:^-}{|}}{C}H$$

resonance contributors of the dienophile

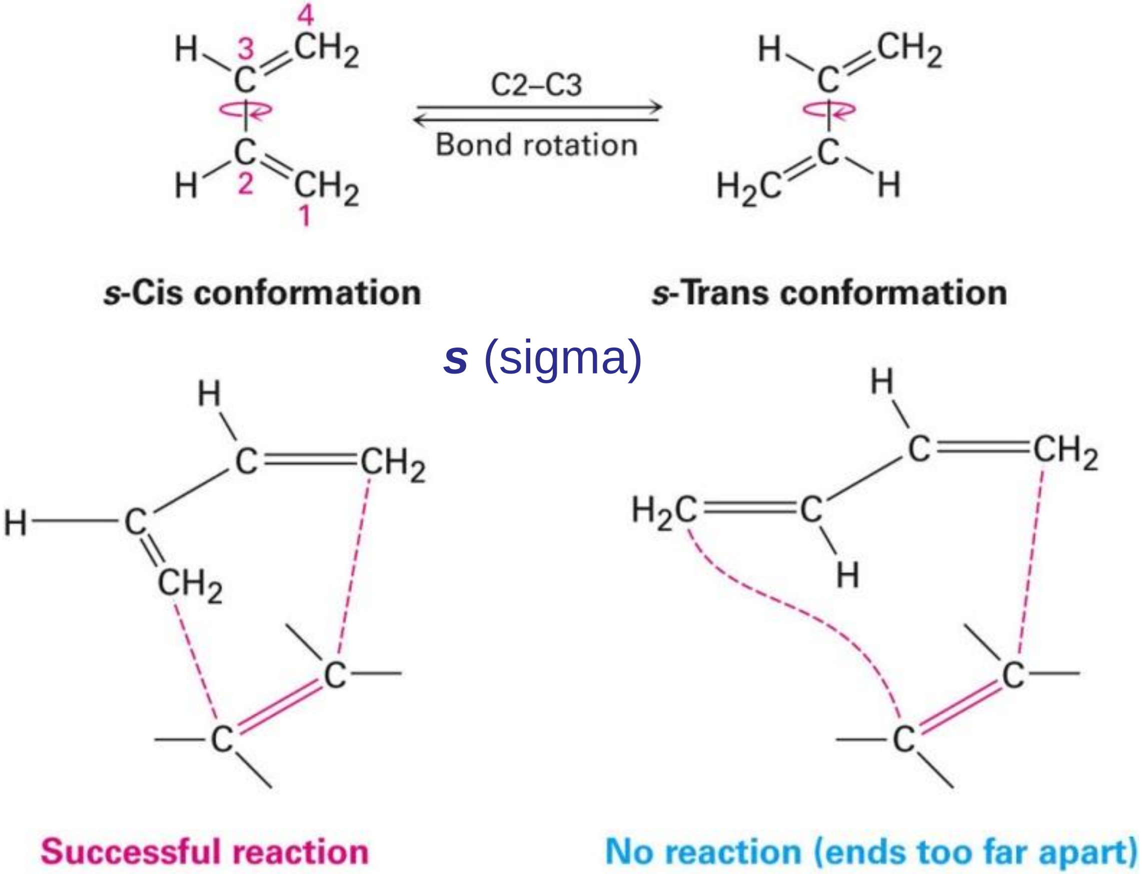
The preferred regiochemistry matches positively and negatively charged ends



Problema 1g (Lista 5a complementar)

Conformations of Dienes in the Diels-Alder Reaction

- The two double bonds in the diene are "cis" or "trans" to each other about the single bond (being in a plane maximizes overlap)
- These conformations are called *s-cis* and *s-trans* ("*s*" stands for "single bond")
- **Dienes react in the *s-cis* *conformation*** in the Diels-Alder reaction



s (sigma)

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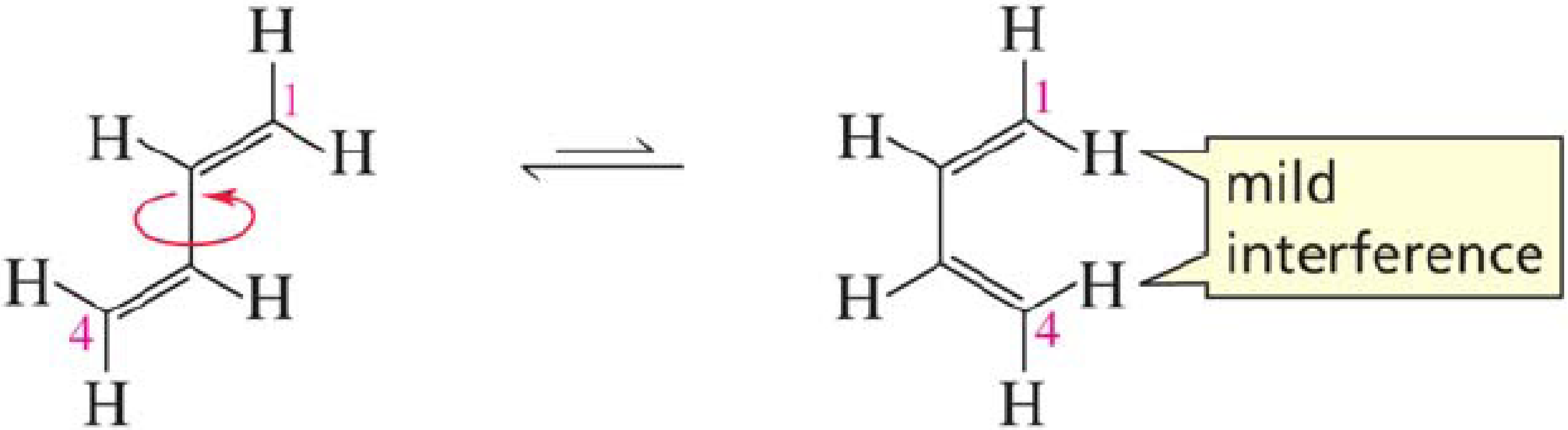
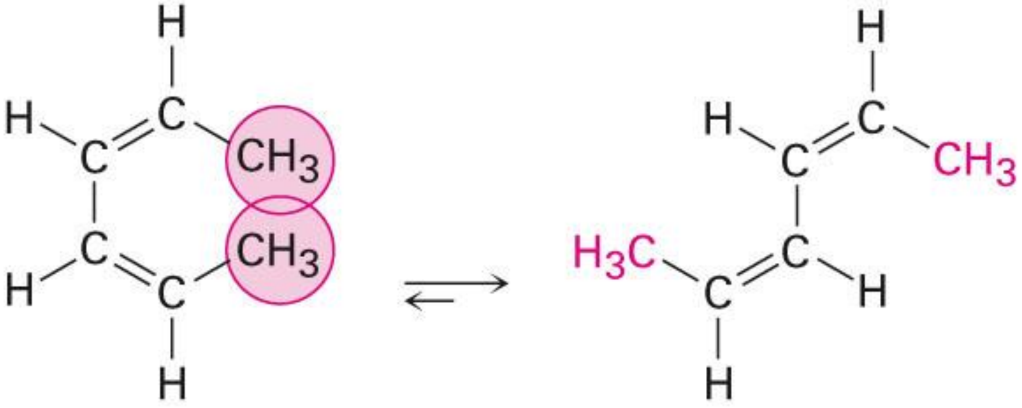
- This conformation is called “s-cis” because the sigma bond must be rotated into a pseudo-cis conformation



s-trans conformation

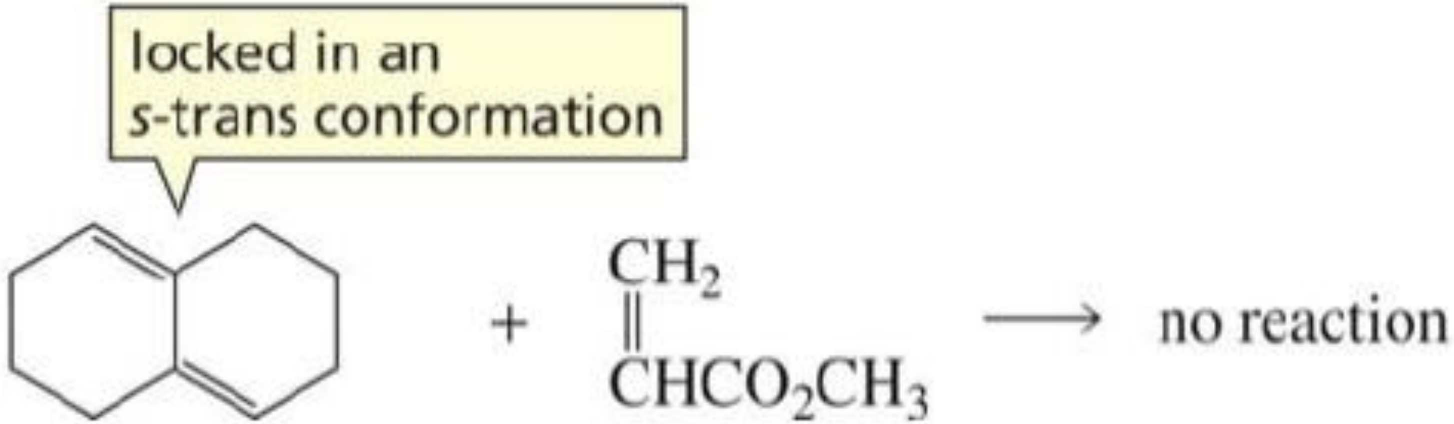
s-cis conformation

- Not all dienes can rotate to be s-cis



Severe steric strain in *s*-cis form

(2*Z*,4*Z*)-Hexadiene (*s*-trans, more stable)

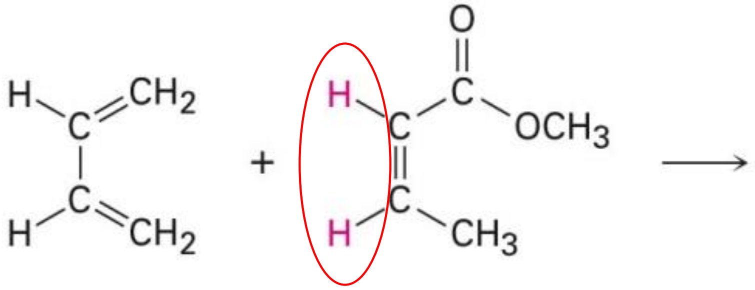


locked in an *s*-trans conformation

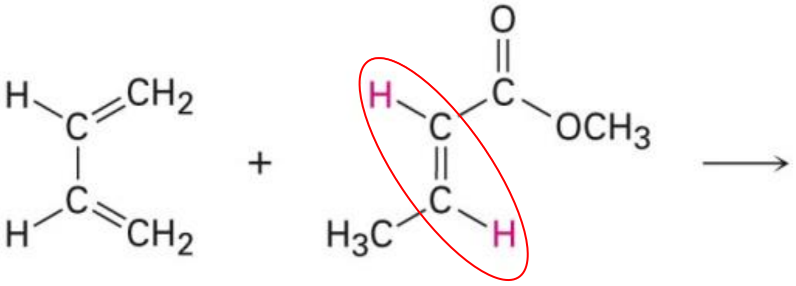
$$+\ \overset{CH_2}{\underset{CHCO_2CH_3}{\|}} \longrightarrow \text{no reaction}$$

Stereospecificity of the Diels-Alder Reaction

- The reaction is **stereospecific**: one-to-one relationship between stereoisomeric reactants and products



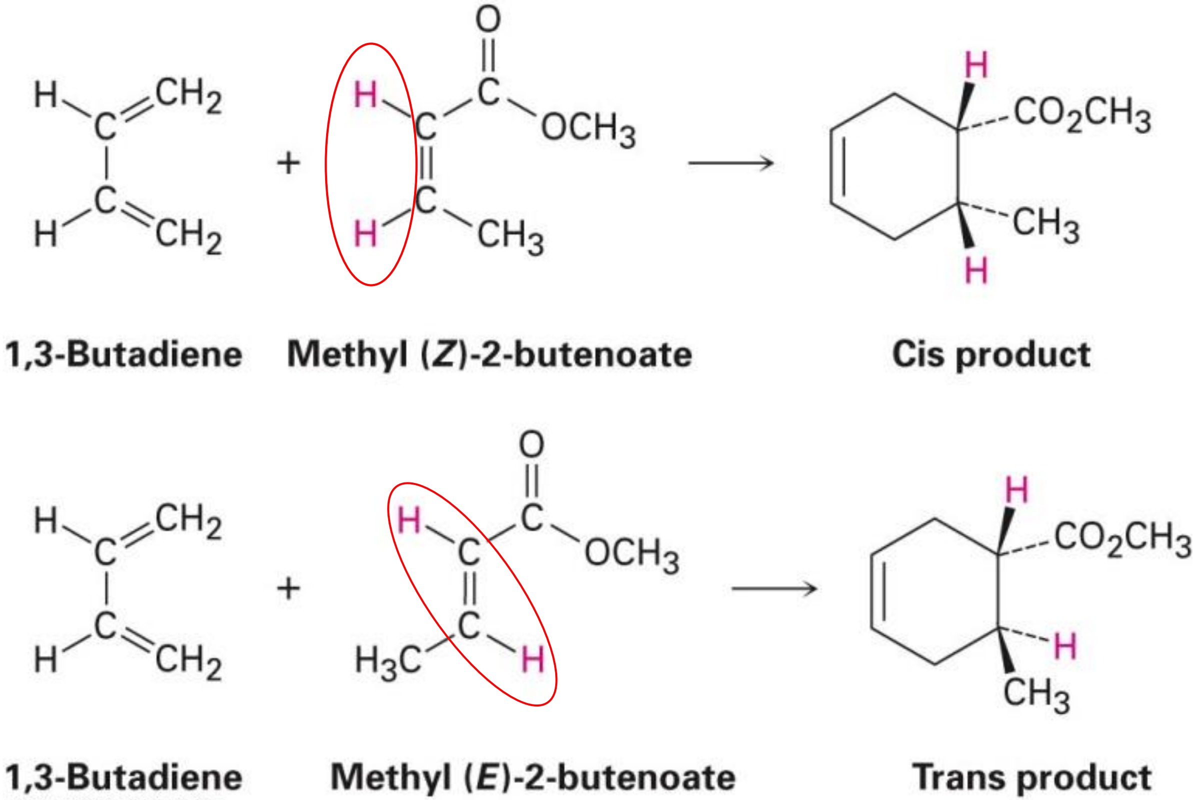
1,3-Butadiene **Methyl (*Z*)-2-butenoate**



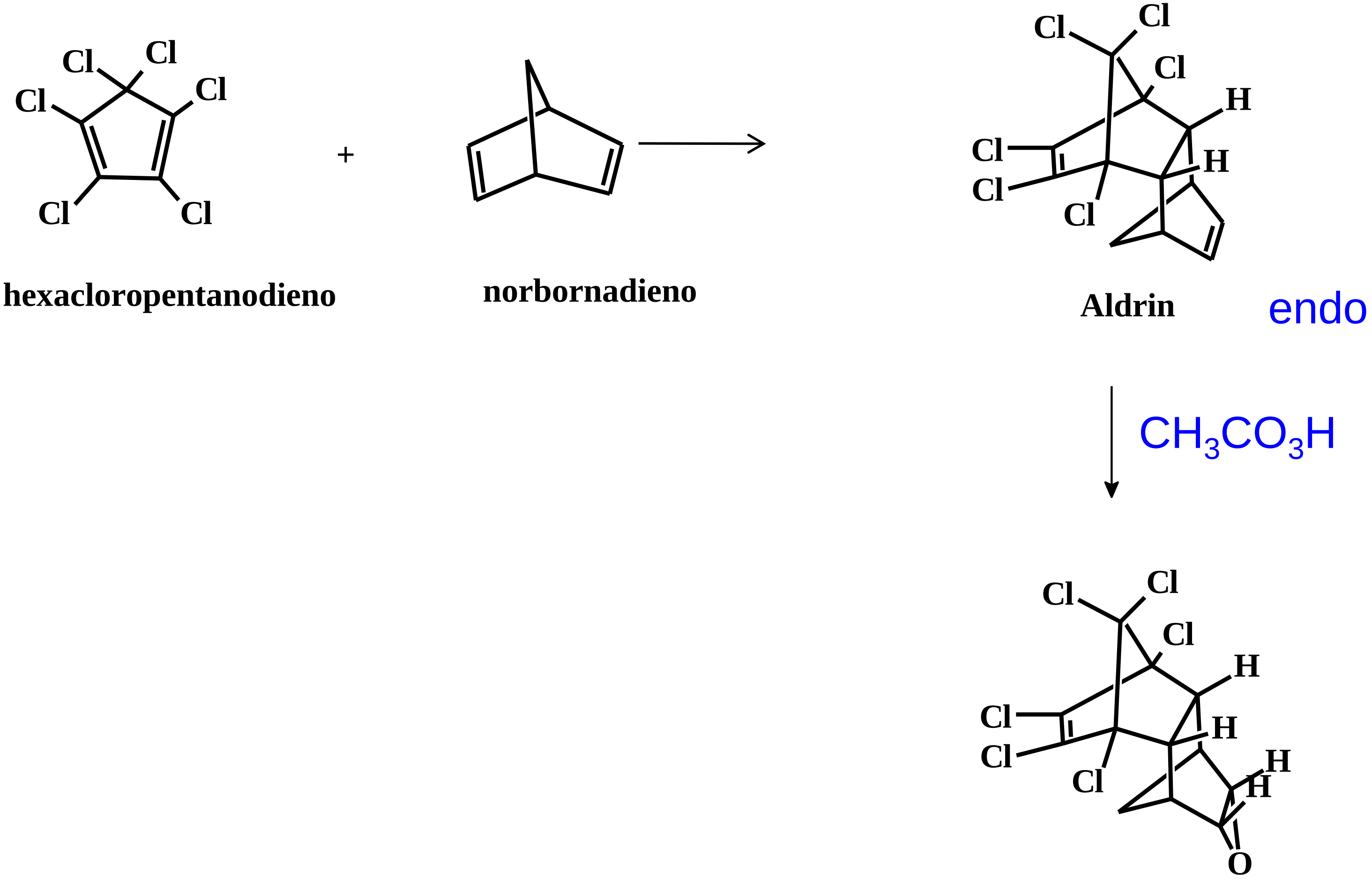
1,3-Butadiene **Methyl (*E*)-2-butenoate**

Stereospecificity of the Diels-Alder Reaction

- The reaction is **stereospecific**: one-to-one relationship between stereoisomeric reactants and products



Síntese de Aldrin e Dieldrin: estereoespecíficas



hexacloropentanodieno

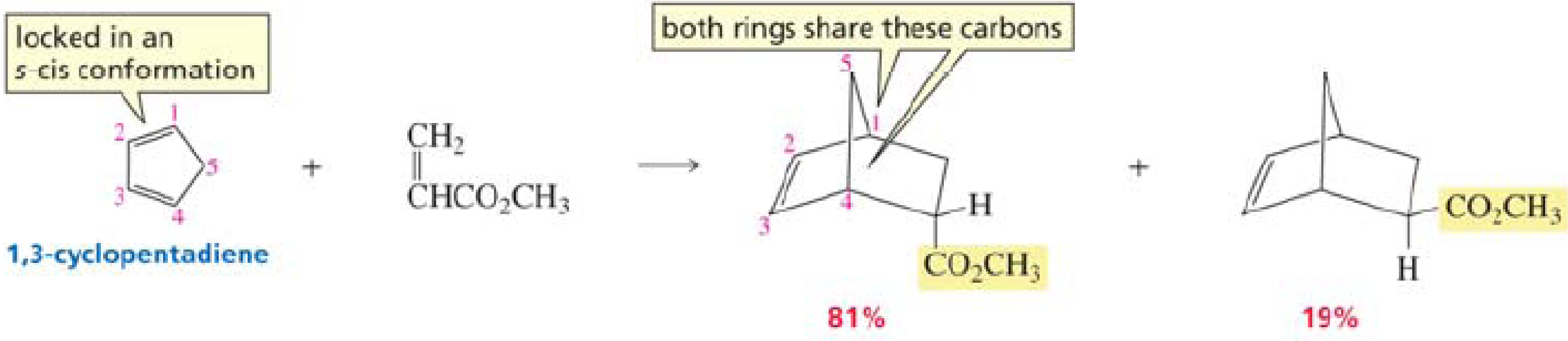
norbornadieno

Aldrin

endo

CH_3CO_3H

Dieldrin



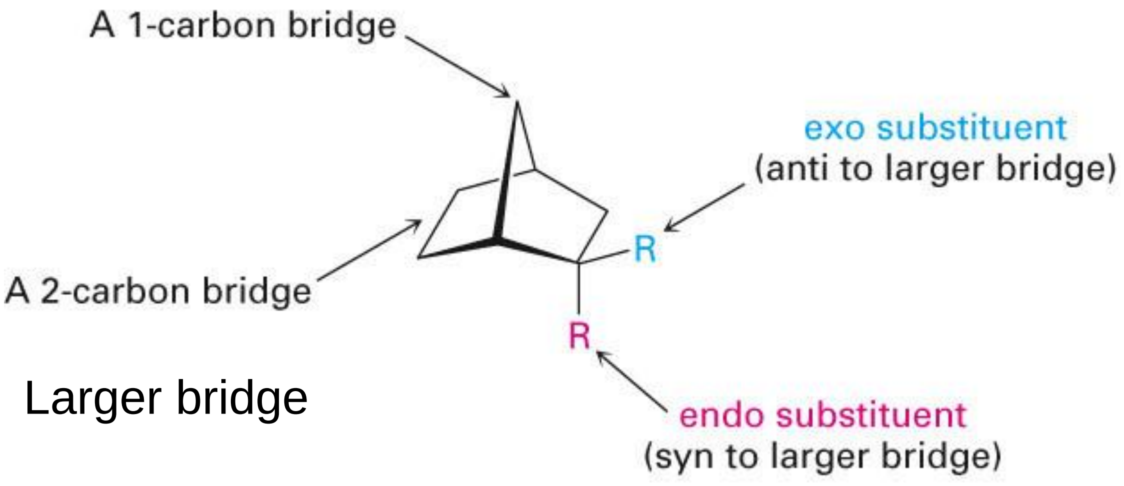
locked in an *s*-cis conformation

both rings share these carbons

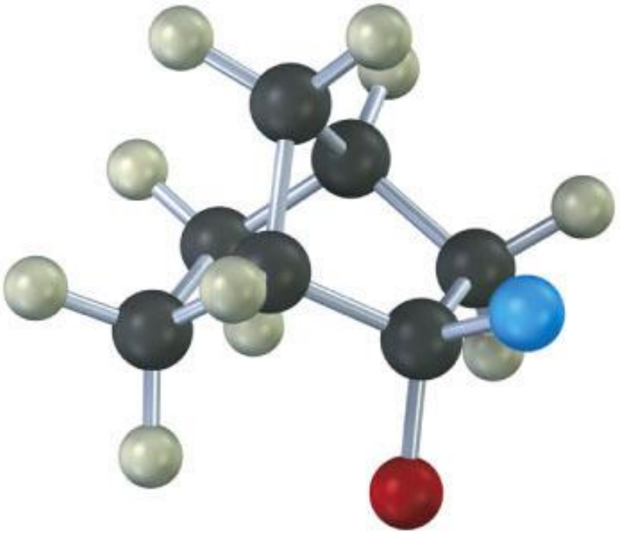
bridged bicyclic compounds

Endo vs Exo positions

Endo and **Exo** denote relative sterechemistry of groups in **bicyclic** systems



Larger bridge

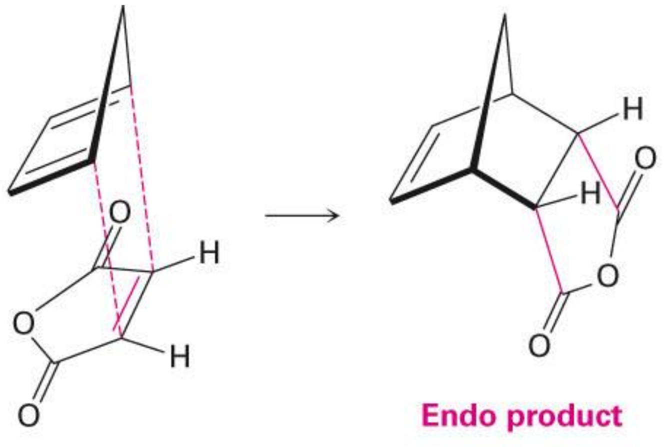


Substituent on one bridge is *exo* if it is anti (trans) to the larger of the other two bridges and *endo* if it is syn (cis) to the larger of the other two bridges

Regiochemistry of the Diels-Alder Reaction

Reactants align to produce ***endo*** (rather than *exo*) product

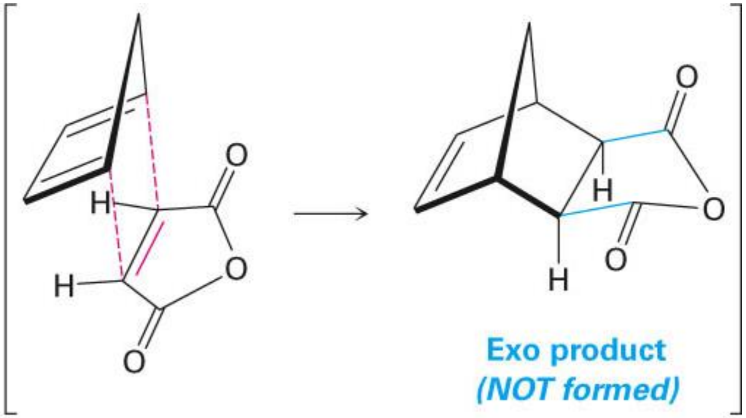
cyclopenta-1,3-diene



Endo product

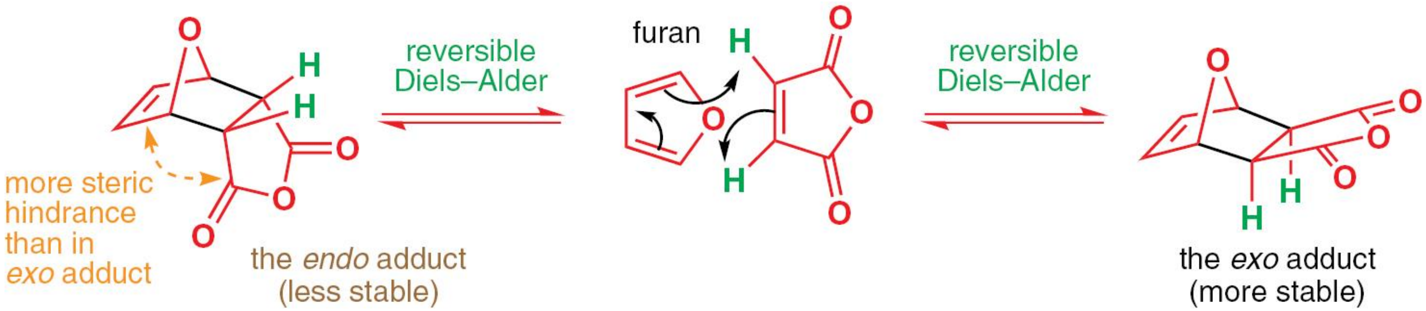
Maleic anhydride

preferential

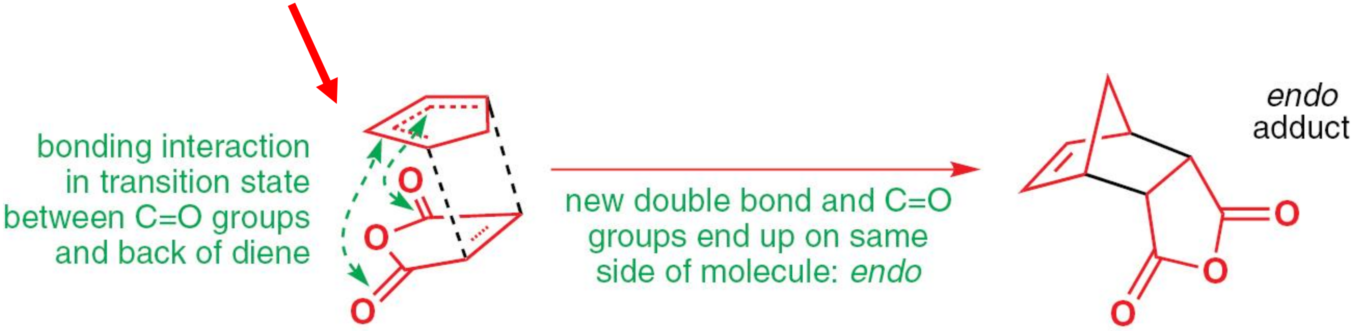


Exo product
(NOT formed)

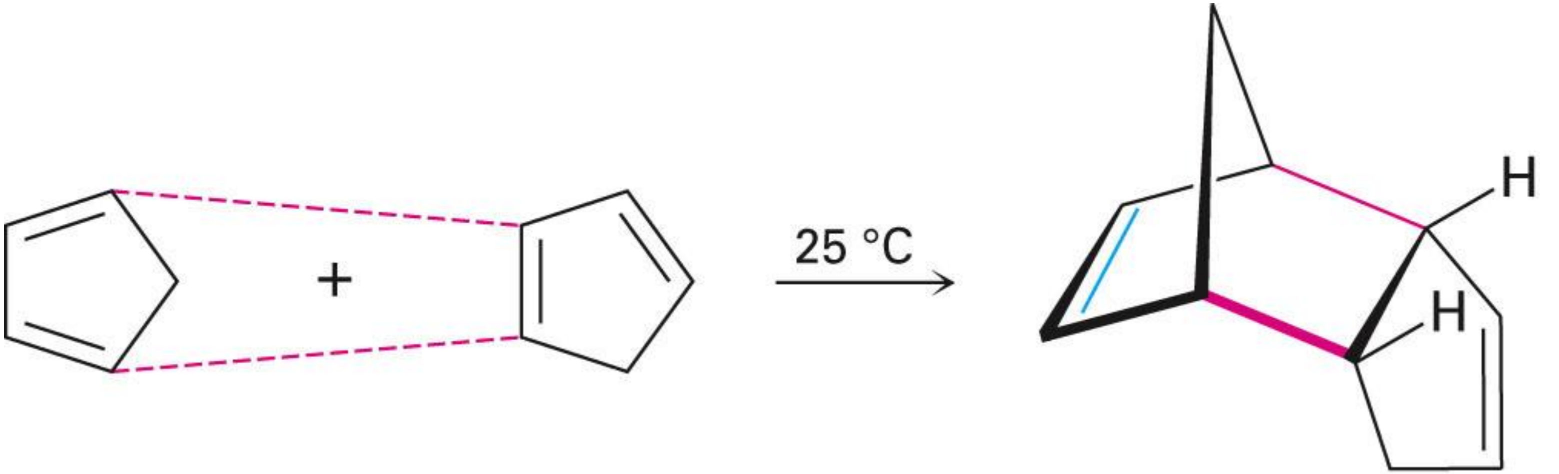
Regiochemistry of the Diels-Alder Reaction



Maior impedimento estérico,
mas há interações atrativas
No estado de transição:



Example:

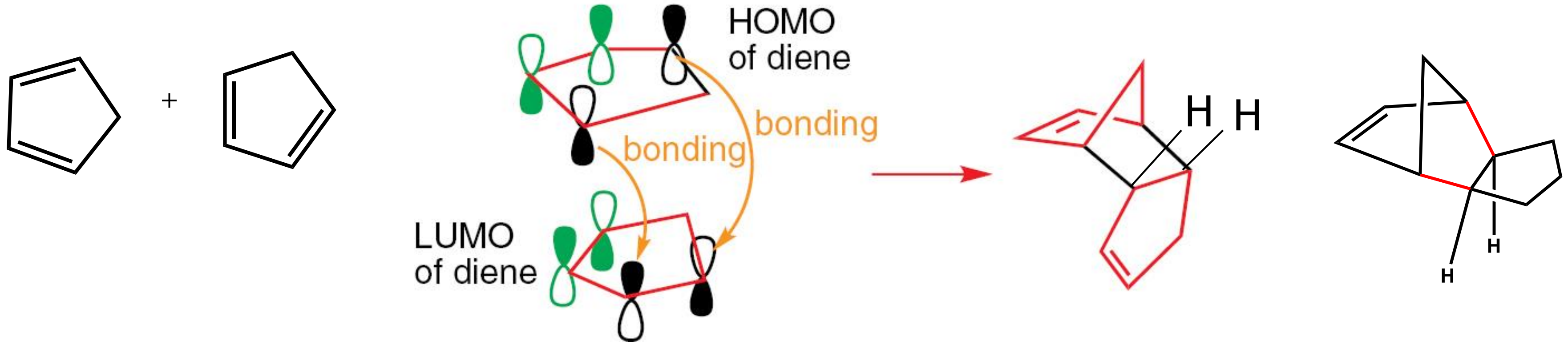


1,3-Cyclopentadiene
(*s*-cis)

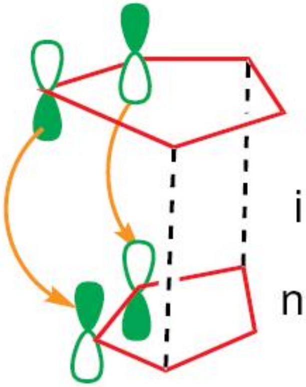
Bicyclopentadiene

Endo product formed

orbital interactions leading to new bonds



orbital interactions favouring endo product



bonding
interactions
leading to
endo product

bonding
interactions
leading to
new σ bonds