Organic Chemistry III

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27. Pericyclic Reactions

A chemical reaction in which concerted reorganization of bonding takes place throughout a cyclic array of continuously bonded atoms.

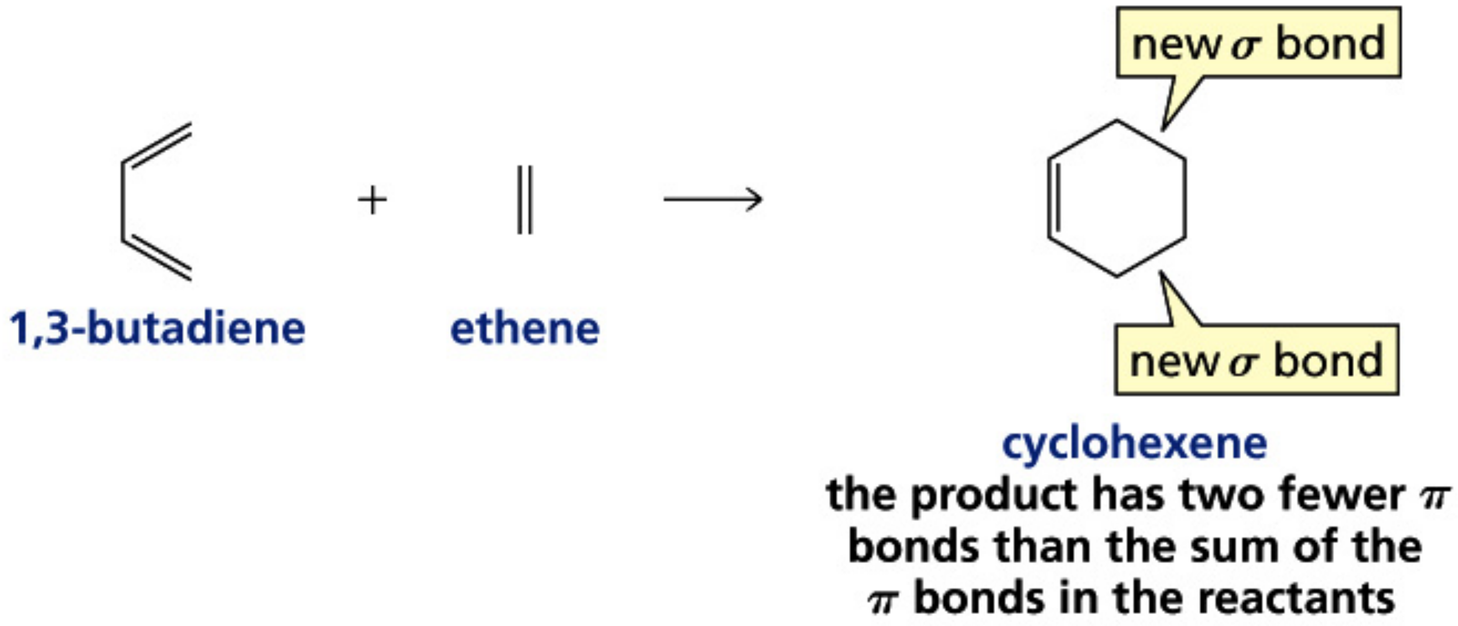
It may be viewed as a reaction proceeding through a fully conjugated cyclic transition state.

The number of atoms in the cyclic array is usually six, but other numbers are also possible.

- **Cycloaddition**
- **Electrocyclic reaction**
- **Sigmatropic rearrangement**

Pericyclic Reaction I: Cycloaddition Reaction

Two different **π** bond-containing molecules react to form a cyclic compound.



the product has two fewer π bonds than the sum of the π bonds in the reactants

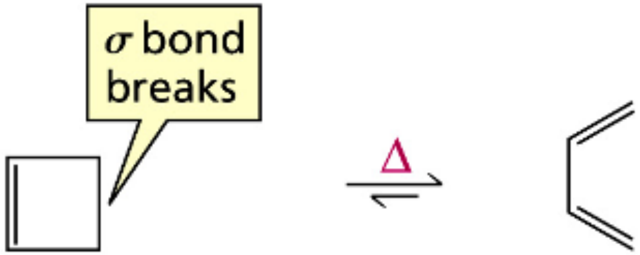
Pericyclic Reaction II: Electrocyclic Reaction

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

Electrocyclic reactions are reversible.

1,3,5-hexatriene **1,3-cyclohexadiene**

the product has one fewer π bond than the reactant

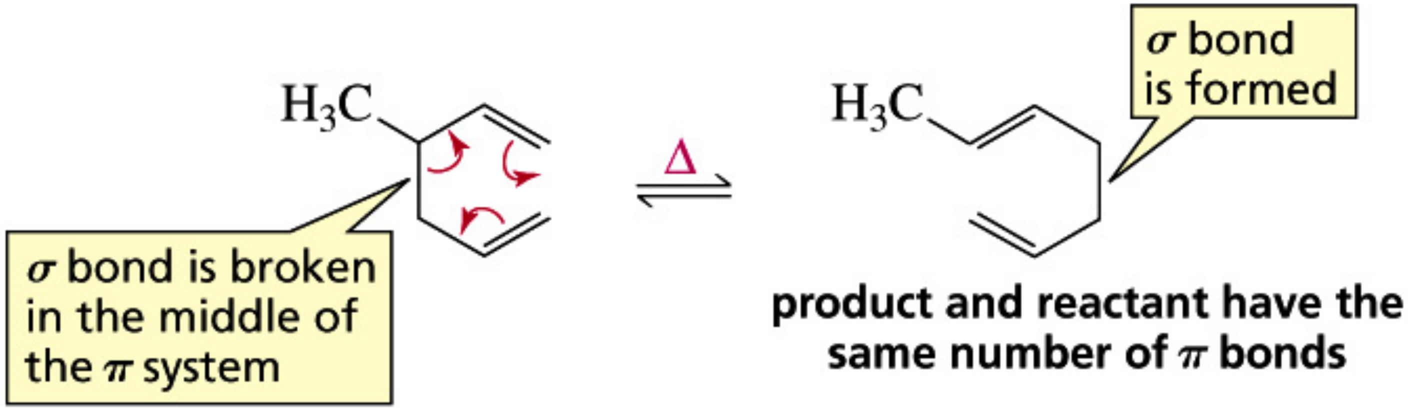


cyclobutene **1,3-butadiene**

the product has one more π bond than the reactant

Pericyclic Reaction III: Sigmatropic Rearrangements

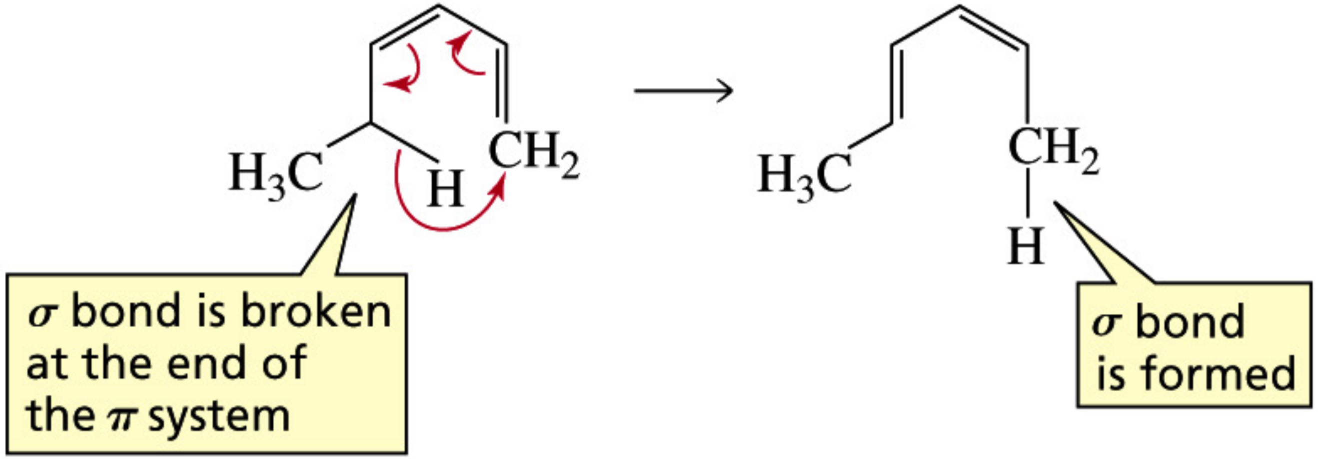
A **σ** bond is broken in the reactant, a new **σ** bond is formed in the product, and the **π** bonds rearrange.



σ bond is broken in the middle of the π system

σ bond is formed

product and reactant have the same number of π bonds



σ bond is broken at the end of the π system

σ bond is formed

Note

The electrocyclic reactions and sigmatropic rearrangements are ***intramolecular*** reactions

The cycloaddition reactions are usually ***intermolecular*** reactions

Common features among the three pericyclic reactions:

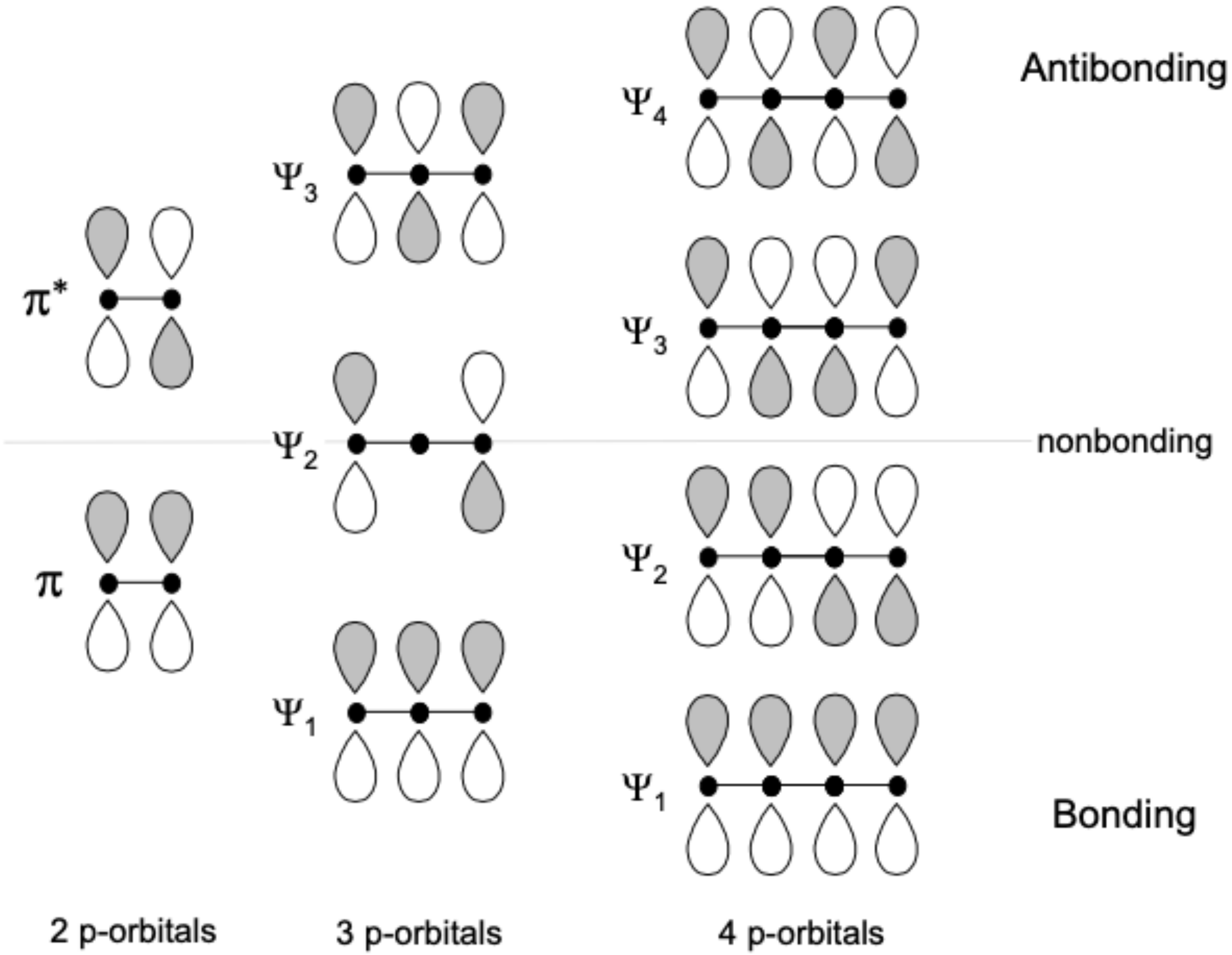
- are concerted reactions (single step)
- are highly stereoselective
- are not affected by catalysts

Conservation of Orbital Symmetry Theory

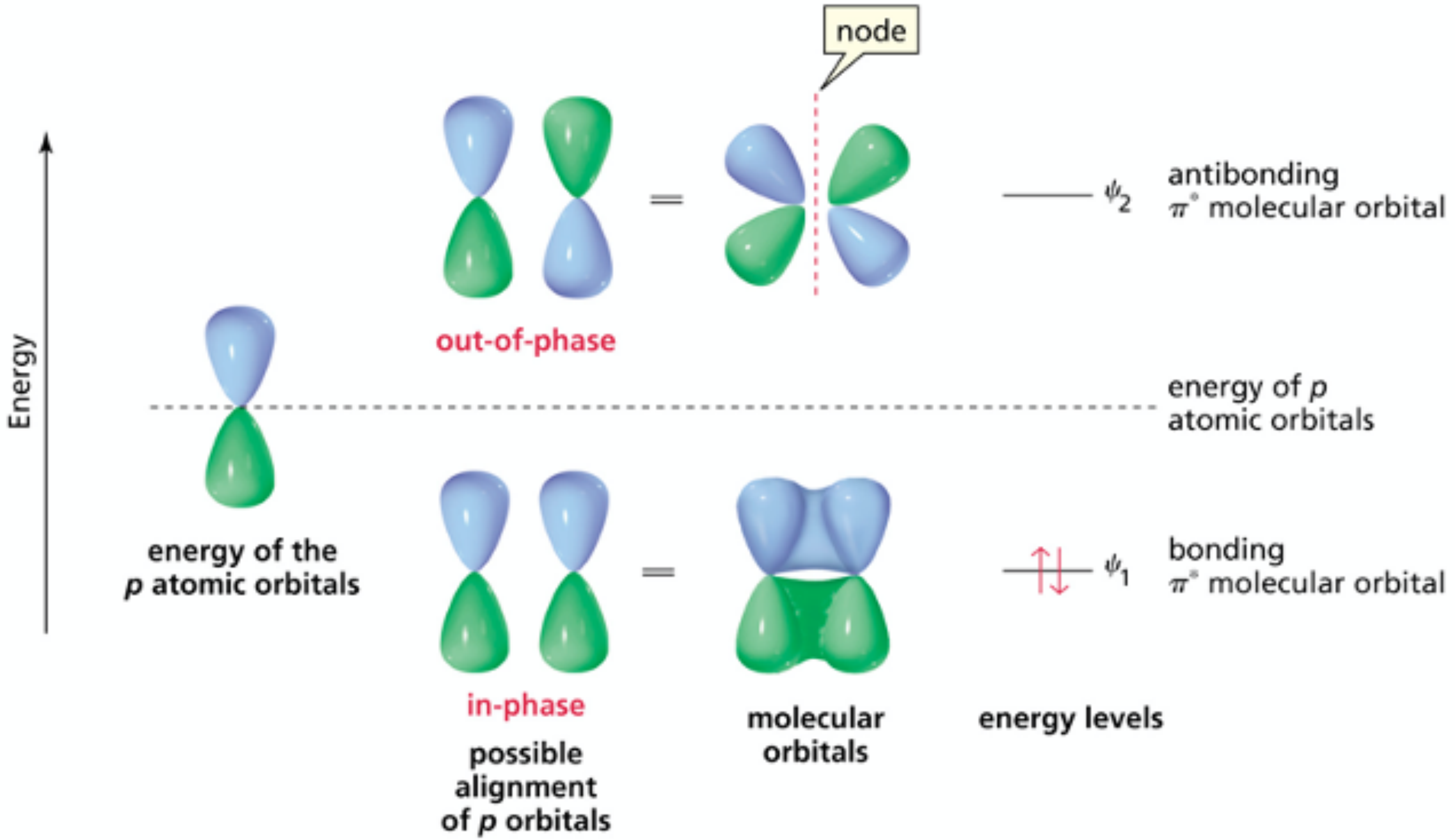
Explains the relationship among the structure and configuration of the reactant, the conditions (thermal or photochemical) under which the reaction takes place, and the configuration of the products.

States that in-phase orbitals overlap in course of a pericyclic reaction.

Conjugated π Systems



Molecular Orbital Description of Ethane



Four p atomic orbitals interact to give the four π MOs of 1,3-butadiene

ψ_1 and ψ_3 are symmetric MOs

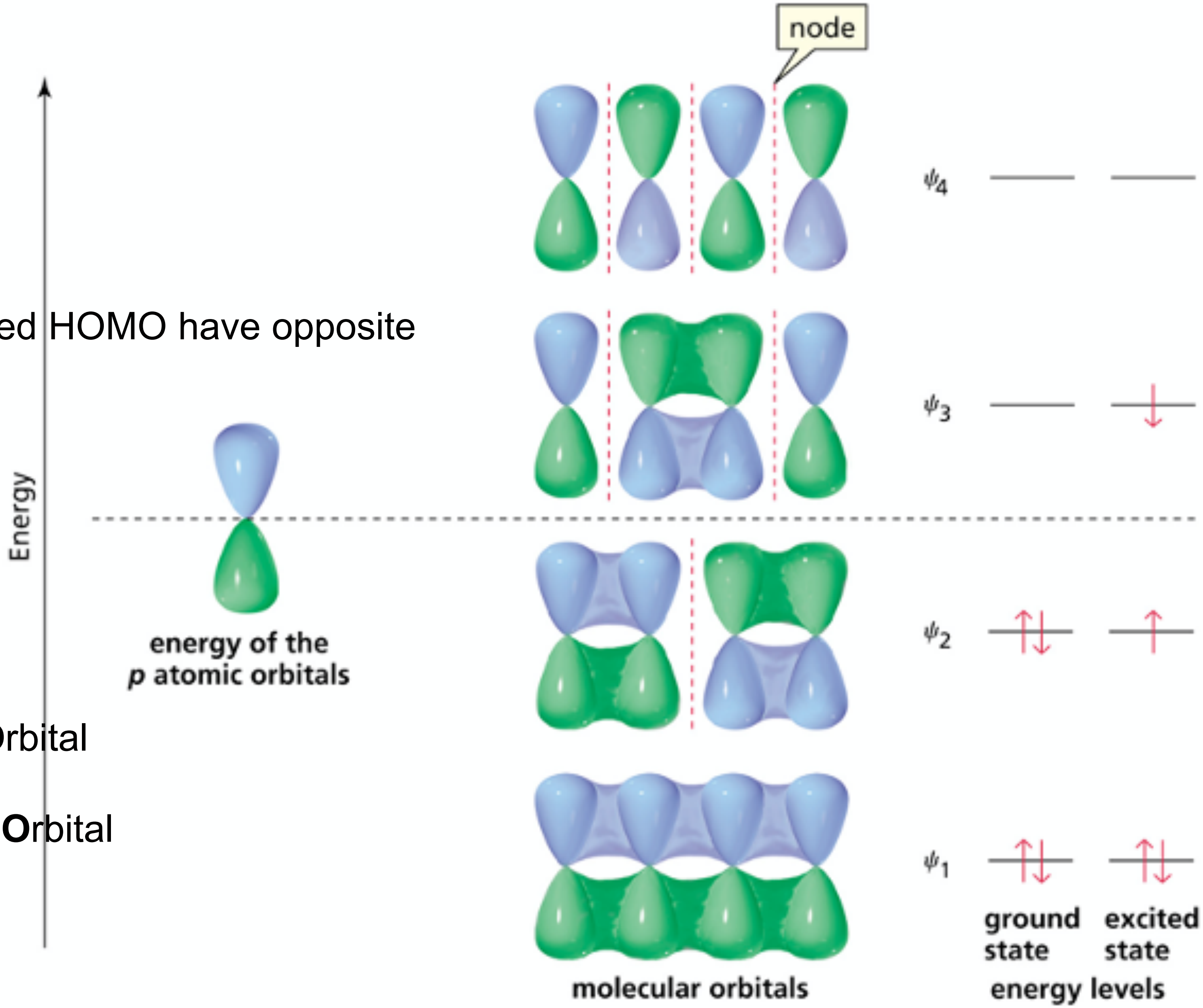
ψ_2 and ψ_4 are asymmetric MOs

The ground state HOMO and the excited HOMO have opposite symmetry.

HOMO: **H**ighest **O**ccupied **M**olecular **O**rbital

LUMO: **L**owest **U**noccupied **M**olecular **O**rbital

There are frontier orbitals.



Note

A MO is bonding if the number of bonding interactions is greater than the number of nodes

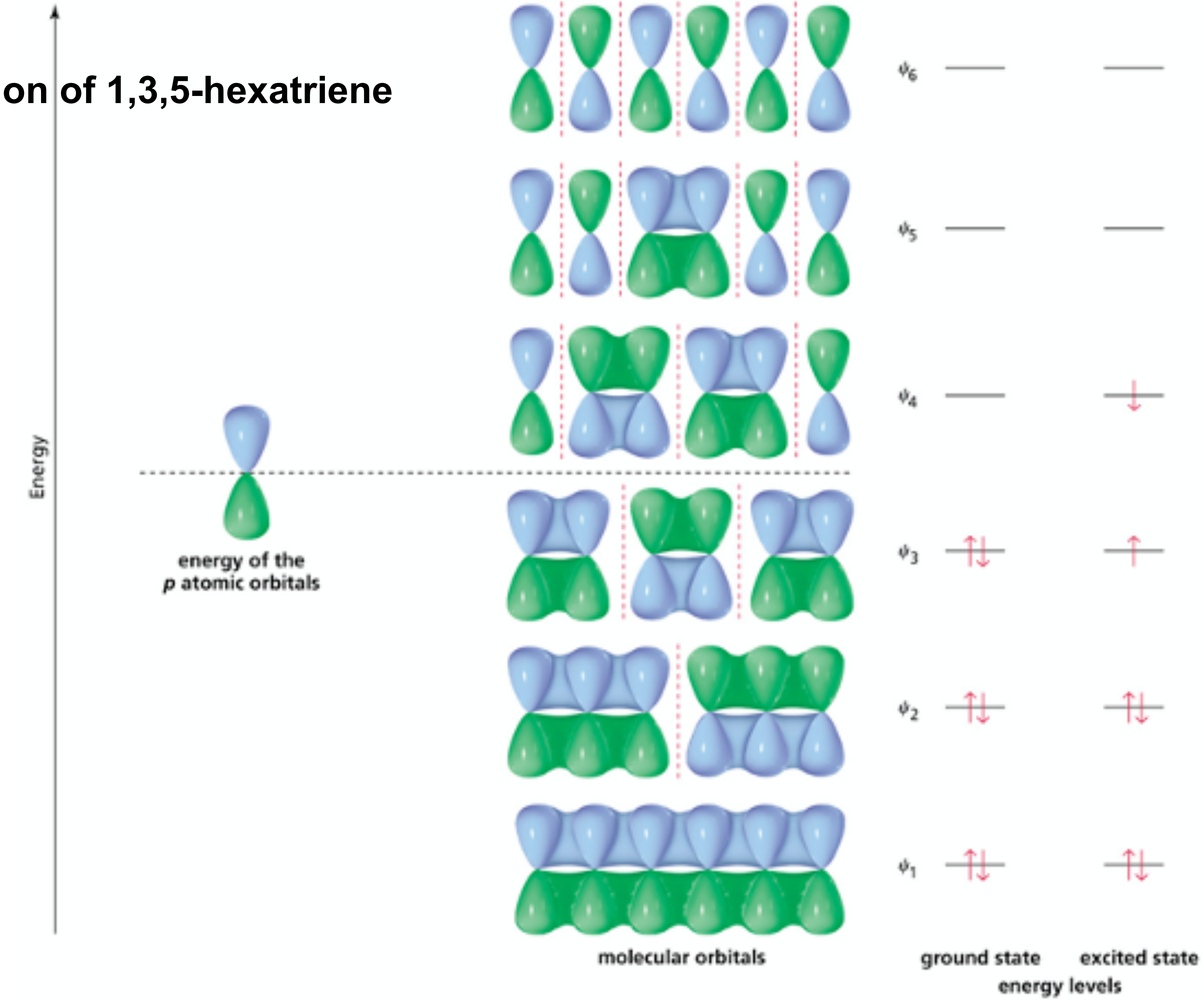
A MO is antibonding if the number of bonding interactions is fewer than the number of nodes

The normal electronic state of a molecule is known as its ground state

The ground state electron can be promoted from its HOMO to its LUMO by absorption of light (excited state)

In a thermal reaction the reactant is in its ground state; in a photochemical reaction, the reactant is in its excited state

Molecular Orbital Description of 1,3,5-hexatriene

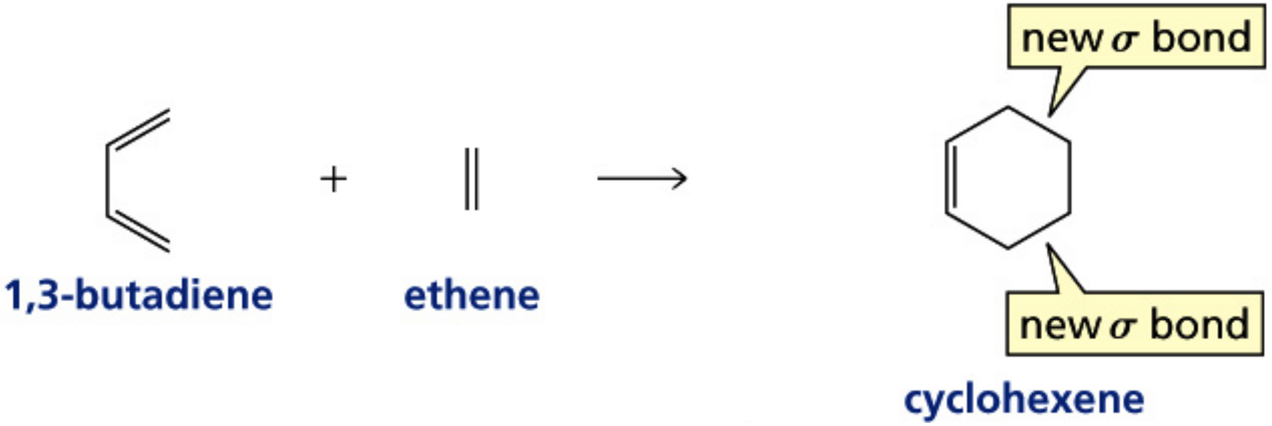


I. Cycloaddition: Diels-Alder reaction

Conjugated dienes and alkenes combine to give substituted cyclohexenes. In this transformation, known as **Diels-Alder cycloaddition**, the atoms at the ends of the diene add to the alkene double bond, thereby closing a ring.

The Diels-Alder reaction is named for **Otto Diels** and **Kurt Alder** who received the Nobel Prize in 1950 for their experiments.

When a mixture of 1,3-butadiene and ethene is heated in the gas phase, a remarkable reaction takes place in which cyclohexene is formed by the simultaneous generation of two new carbon–carbon bonds.

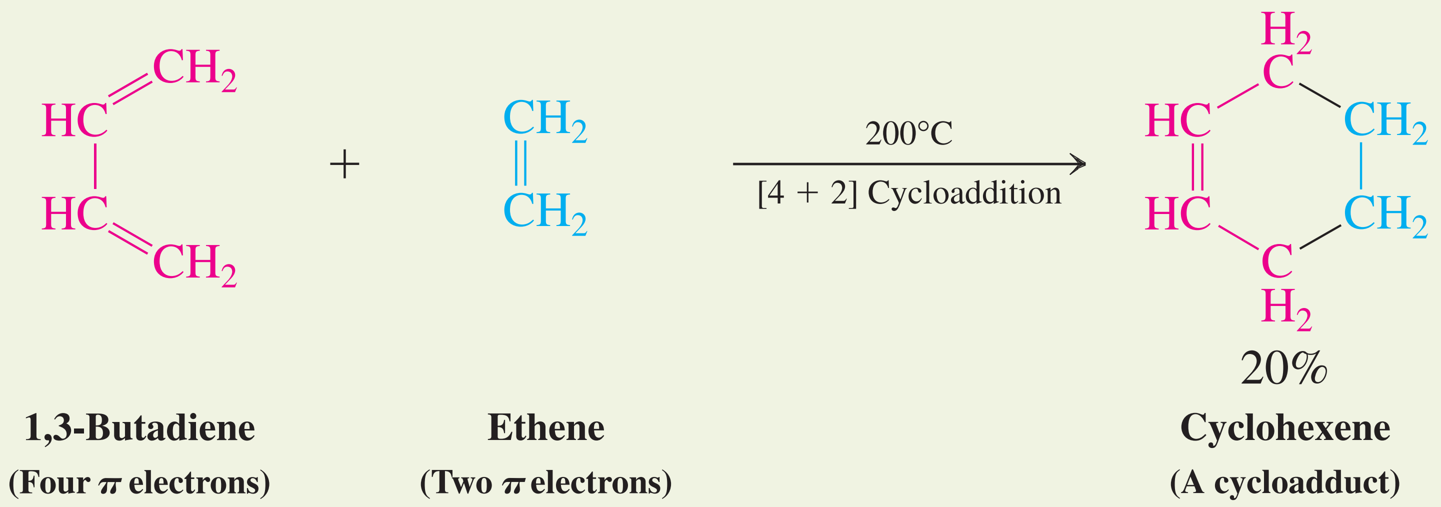


The Diels-Alder reaction is a special case of **cycloaddition reactions** between **π** systems, the products of which are called **cycloadducts.**

In the reaction, an assembly of four conjugated atoms containing four **π** electrons reacts with a double bond containing two **π** electrons. Therefore, it is also referred to as a *[4 + 2] cycloaddition.*

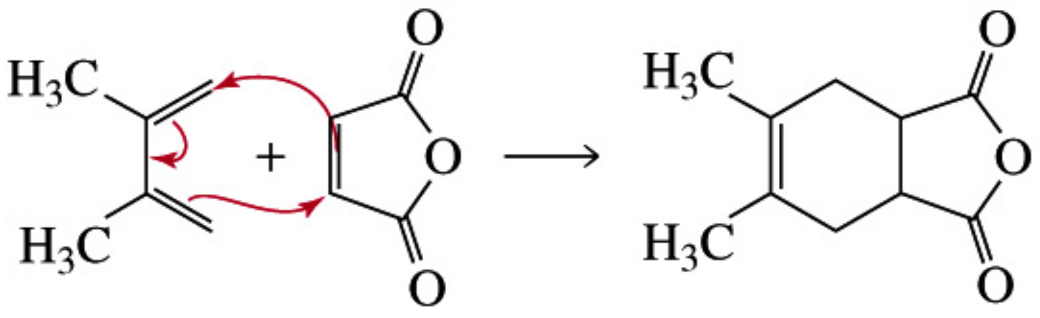
The four-carbon component is simply called ***diene**,* the alkene is labeled **dienophile (**literally, diene loving molecule).

Diels-Alder Cycloaddition of Ethene and 1,3-Butadiene

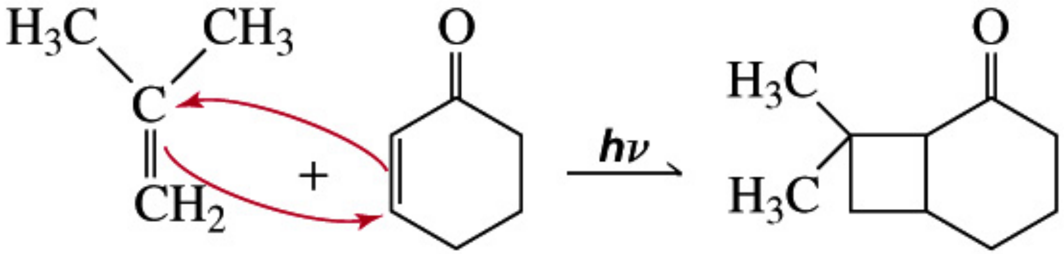


Cycloadditions are classified according to the number of **π** electrons that interact in the reaction

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



[2 + 2] cycloaddition



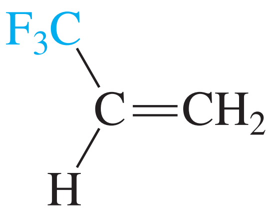
What makes a good Diels-Alder reaction? Reactivity of the diene and dienophile

The prototype reaction of butadiene and ethene actually does not work very well and gives only low yields of cyclohexene.

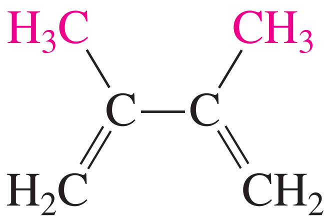
Substitution of the alkene with electron-attracting groups and of the diene with electron-donating groups therefore creates excellent reaction partners.

The trifluoromethyl group is inductively electron attracting owing to its highly electronegative fluorine atoms. The presence of such a substituent enhances the Diels-Alder reactivity of an alkene.

Conversely, alkyl groups are electron donating by induction and hyperconjugation; their presence increases electron density and is beneficial to dienes in the Diels-Alder reaction.



3,3,3-Trifluoro-1-propene
(An electron-poor alkene)

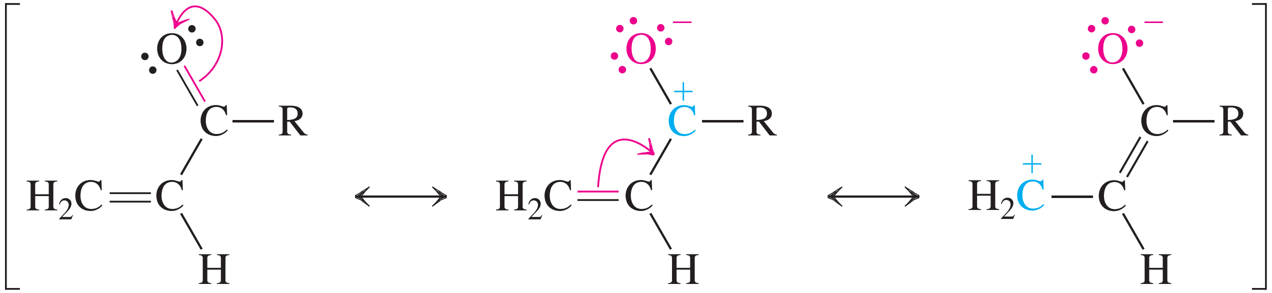


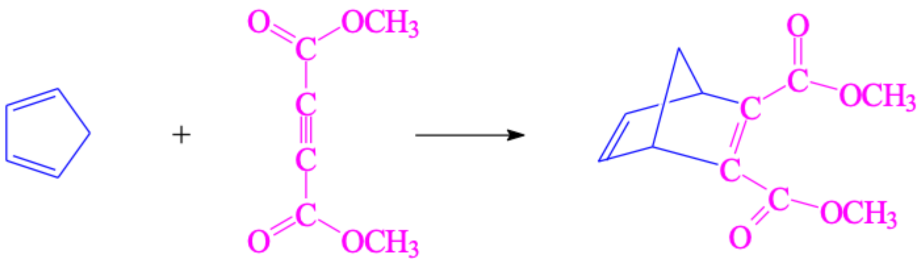
2,3-Dimethyl-1,3-butadiene
(An electron-rich diene)

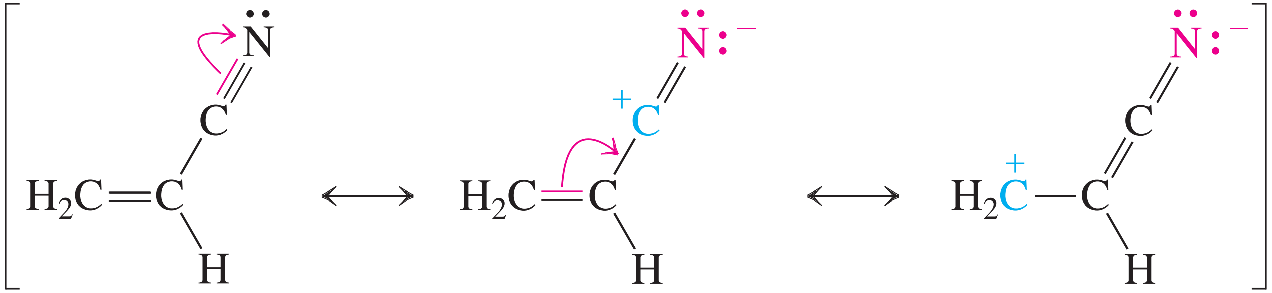
Other alkenes have substituents that interact with double bonds by resonance. Carbonyl-containing groups and nitriles are good electron acceptors by this effect.

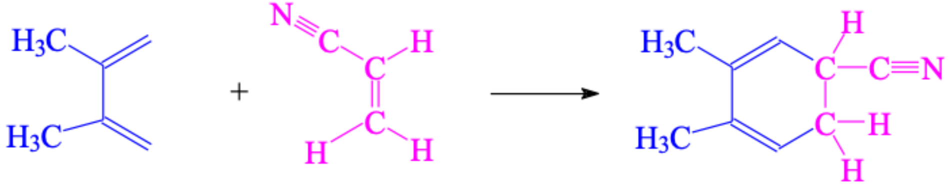
Double bonds bearing such substituents are electron poor because of the contribution of resonance forms that place a positive charge on an alkene carbon atom.

Groups That Are Electron Withdrawing by Resonance



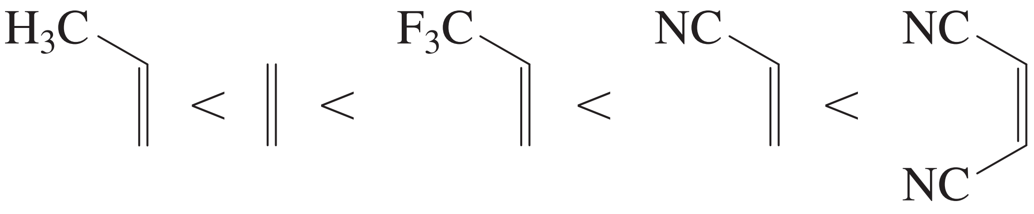




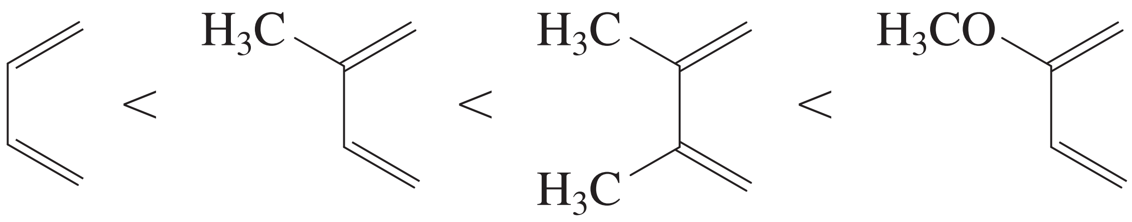


It is much better to use an **electron-poor** alkene with an **electron-rich** diene.

Some examples of the trend in reactivity of dienophiles and dienes are:



Dienophile



Diene

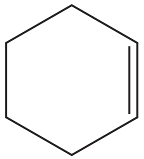
Increasing reactivity

Exercise 14-16

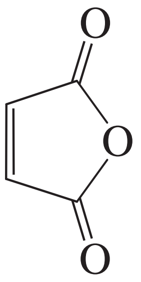
Classify each of the following alkenes as electron poor or electron rich, relative to ethene. Explain your assignments.

(a) $H_2C{=}CHCH_2CH_3$

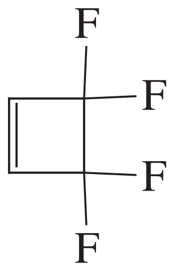
(b)



(c)

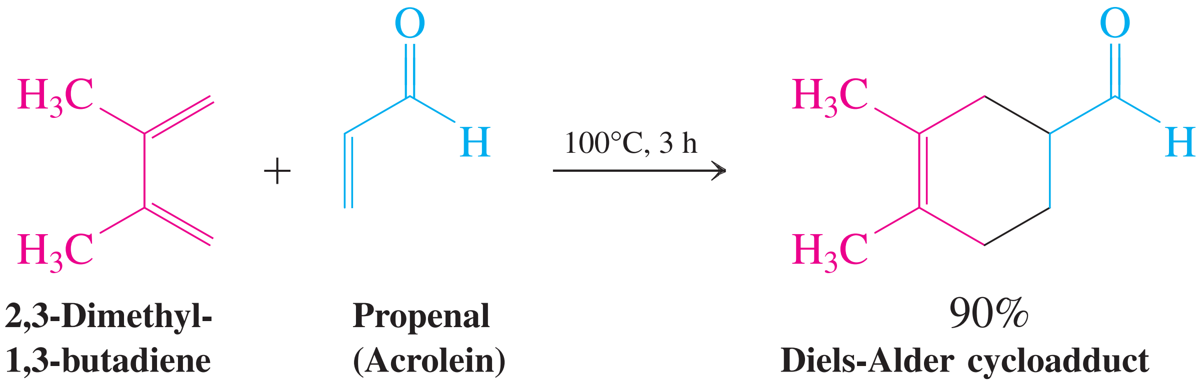


(d)



Examples of reaction partners that undergo efficient Diels-Alder cycloaddition are 2,3-dimethyl-1,3-butadiene and propenal (acrolein).

The carbon–carbon double bond in the cycloadduct is electron rich and sterically hindered. Thus, it does not react further with additional diene.



The parent 1,3-butadiene, without additional substituents, is electron rich enough to undergo cycloadditions with electron-poor alkenes.

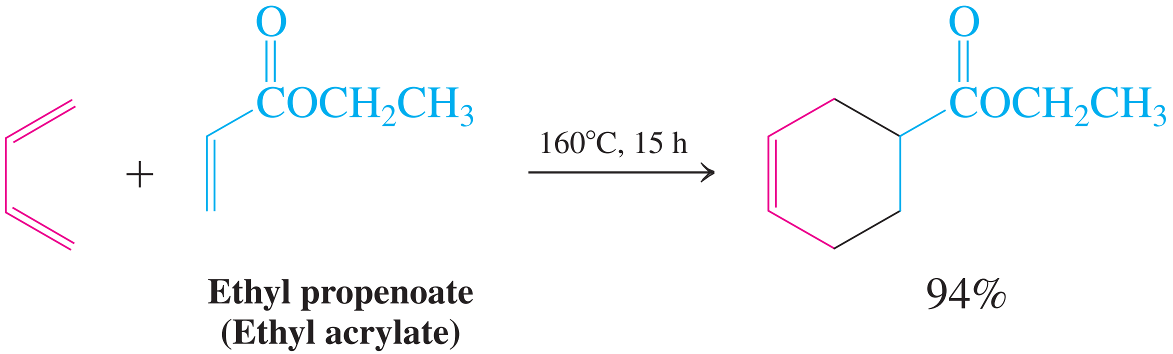
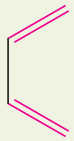
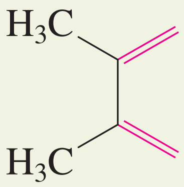


Table 14-1 Typical Dienes and Dienophiles in the Diels-Alder Reaction

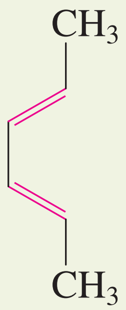
Dienes



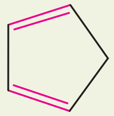
1,3-Butadiene



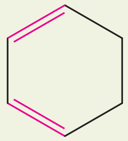
2,3-Dimethyl-
1,3-butadiene



***trans*,*trans*-**
2,4-Hexadiene

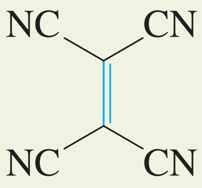


1,3-Cyclopentadiene

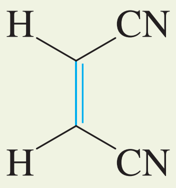


1,3-Cyclohexadiene

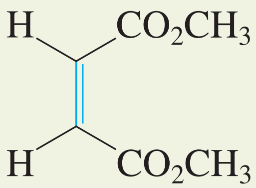
Dienophiles



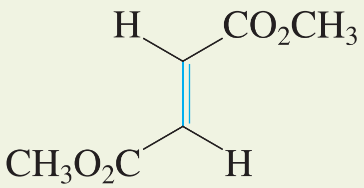
Tetracyanoethene



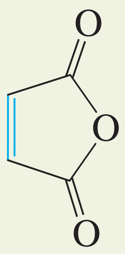
***cis*-1,2-Dicyanoethene**



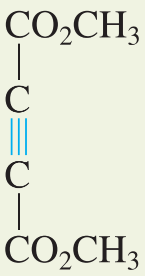
Dimethyl *cis*-2-butenedioate
(Dimethyl maleate)



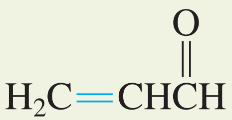
Dimethyl *trans*-2-butenedioate
(Dimethyl fumarate)



2-Butenedioic anhydride
(Maleic anhydride)

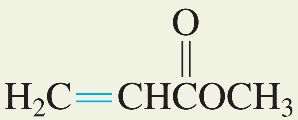


Dimethyl butynedioate
(Dimethyl acetylene-
dicarboxylate)



$$H_2C{=}CH\overset{\overset{\displaystyle O}{\|}}{C}H$$

Propenal
(Acrolein)

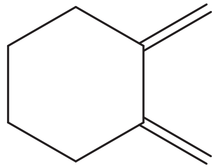


$$H_2C{=}CH\overset{\overset{\displaystyle O}{\|}}{C}OCH_3$$

Methyl propenoate
(Methyl acrylate)

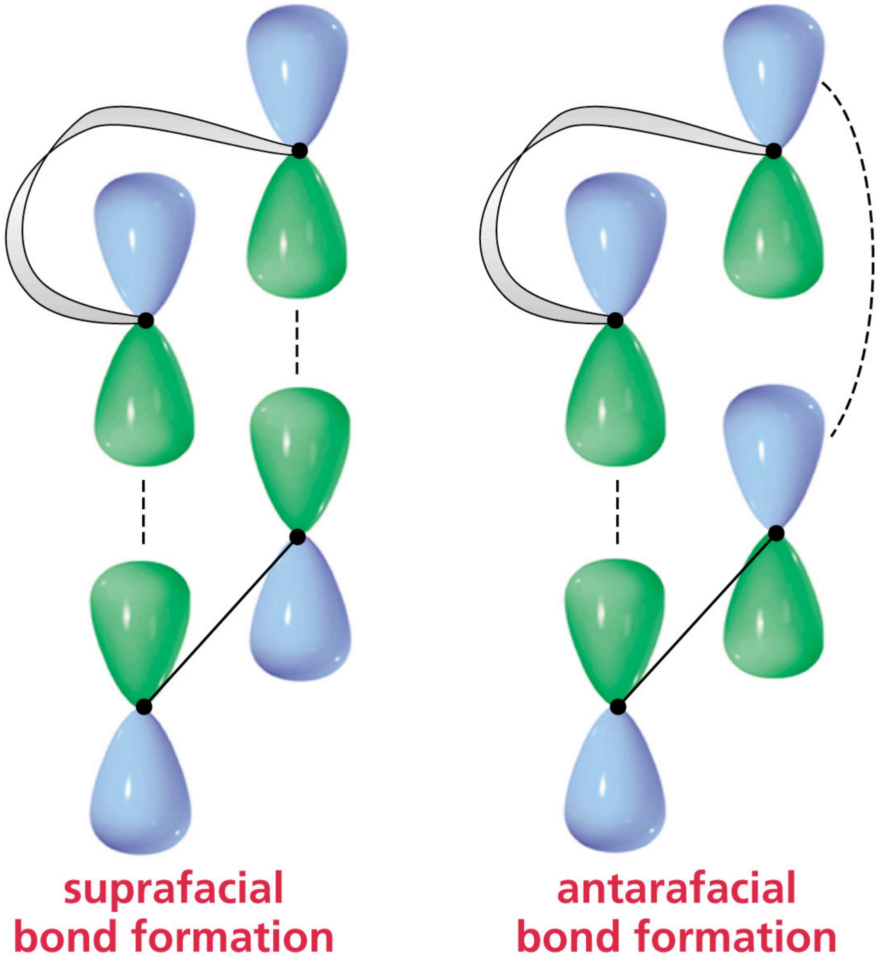
Exercise 14-18

Formulate the products of [4 + 2]cycloaddition of tetracyanoethene with (a) 1,3-butadiene; (b) cyclopentadiene; (c) 1,2-dimethylenecyclohexane.

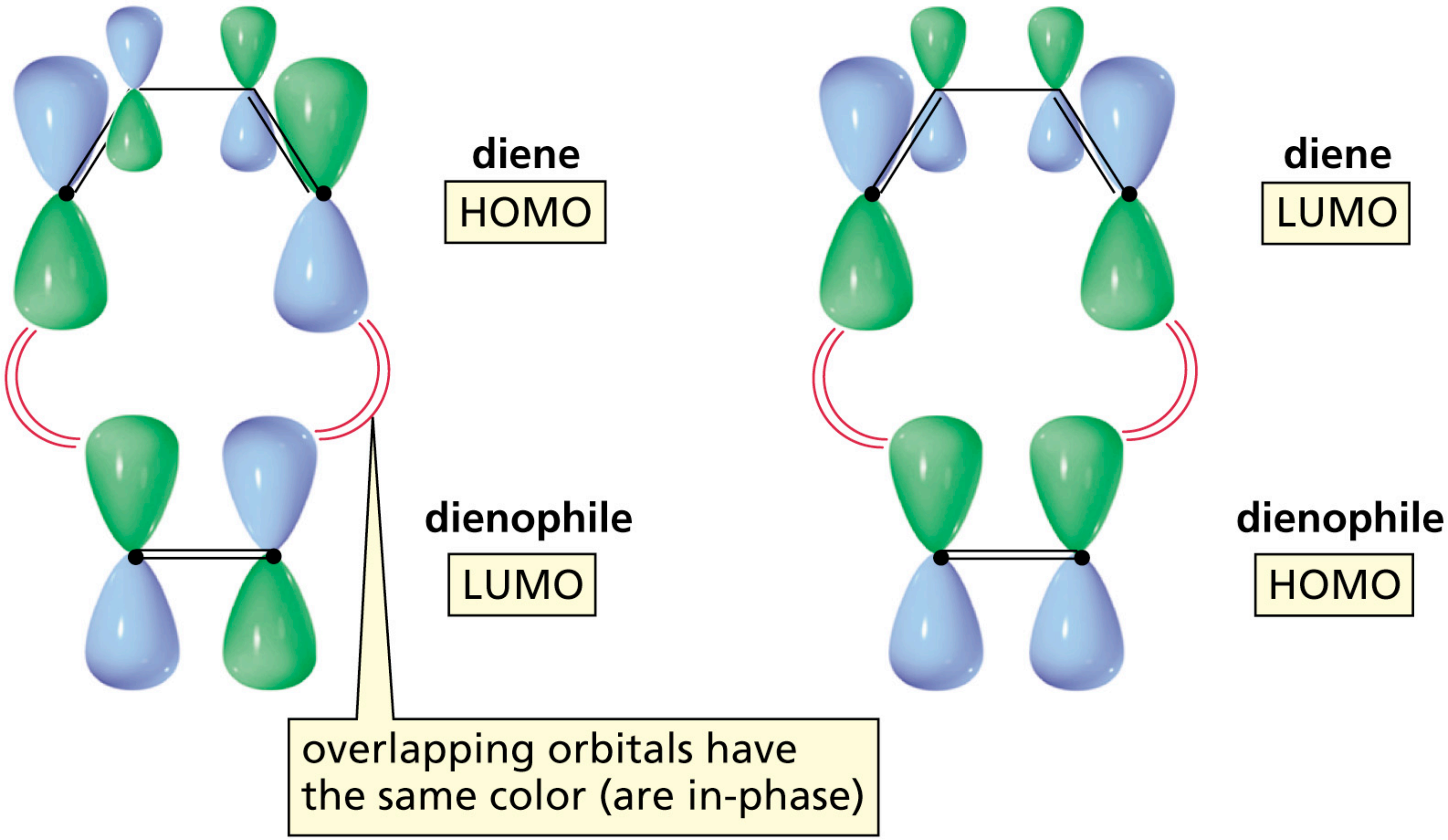


1,2-Dimethylenecyclohexane

The frontier molecular orbitals of both reactants must be considered: the HOMO and LUMO

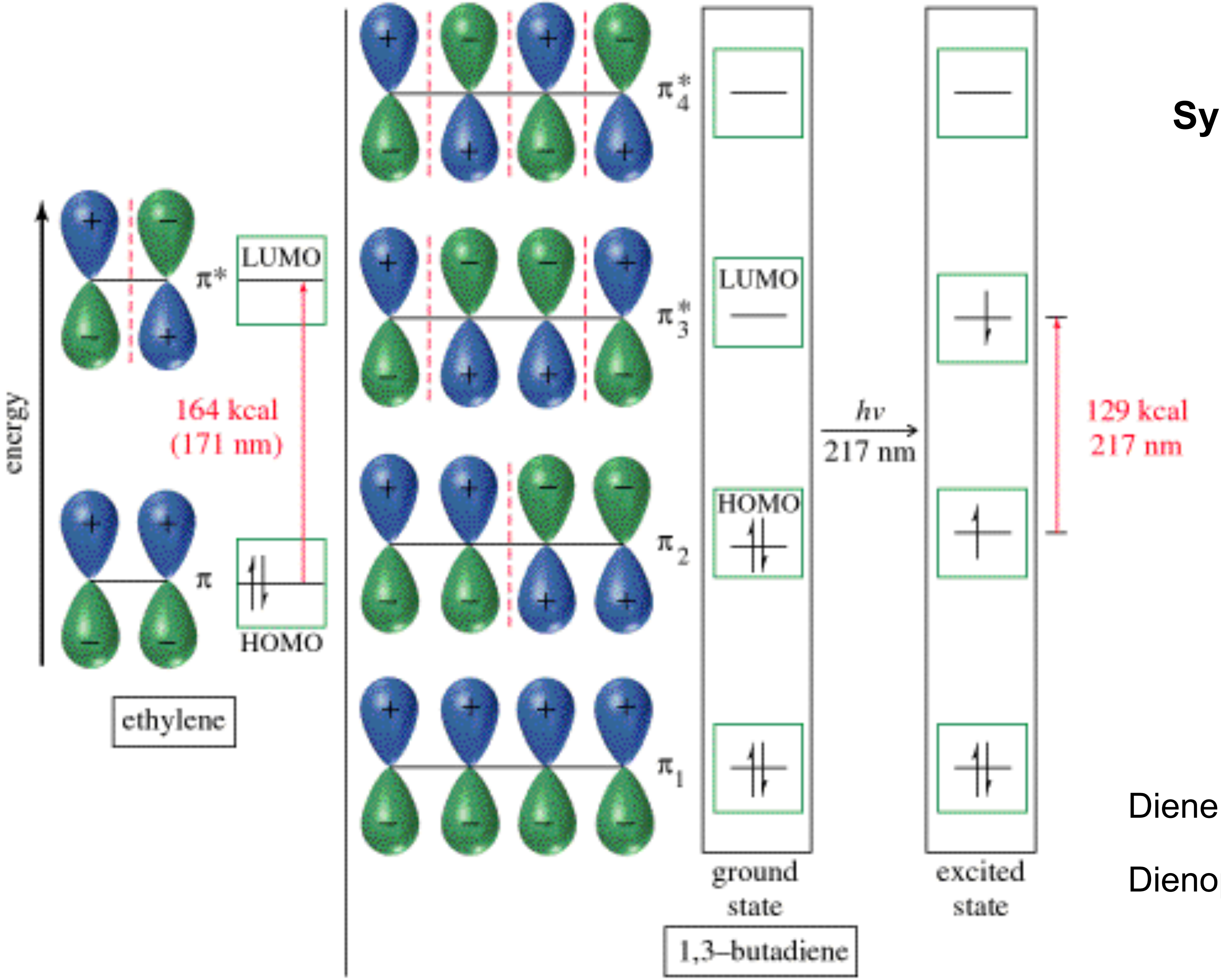


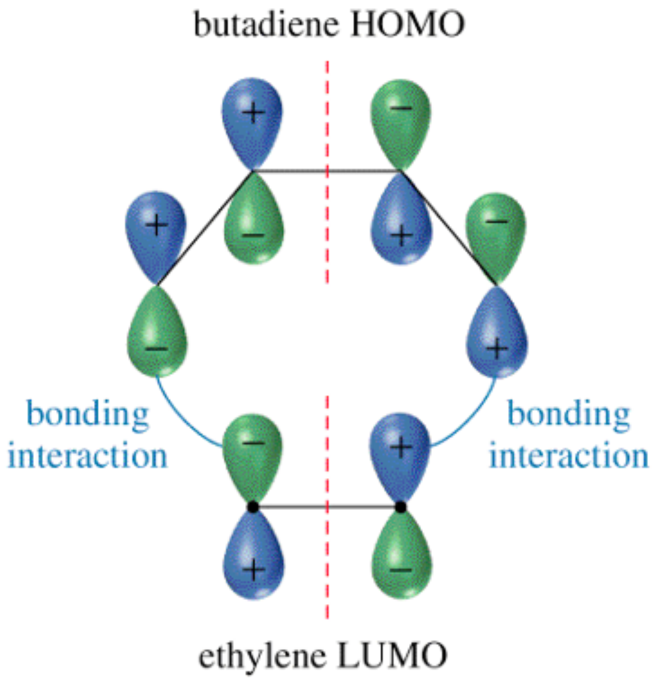
Frontier Orbital Analysis of a [4 + 2] Cycloaddition Reaction



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

Symmetry-Allowed Reaction

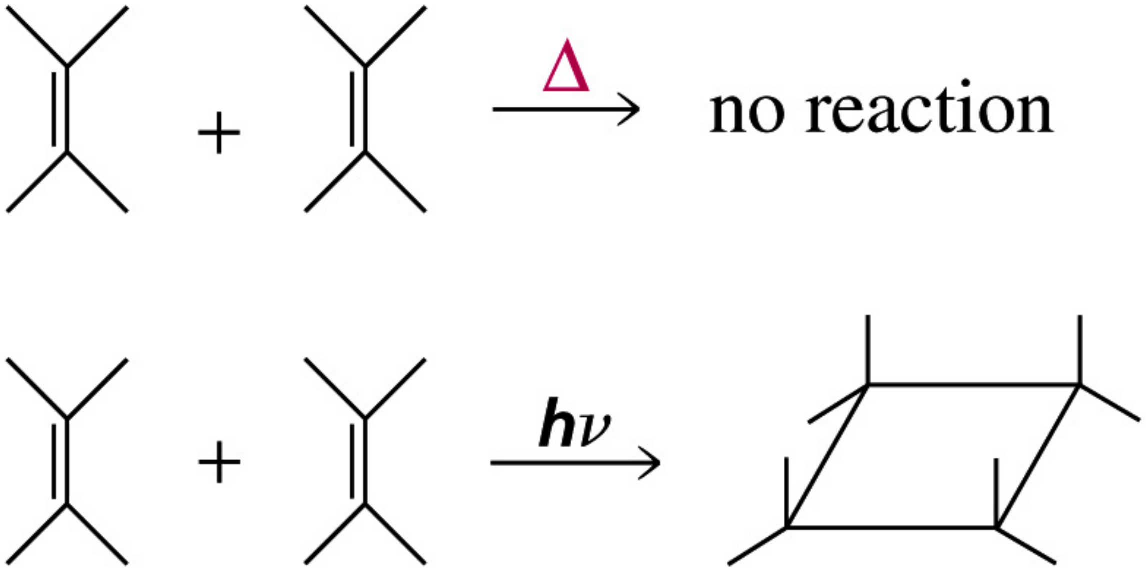




Diene contributes electrons from its HOMO

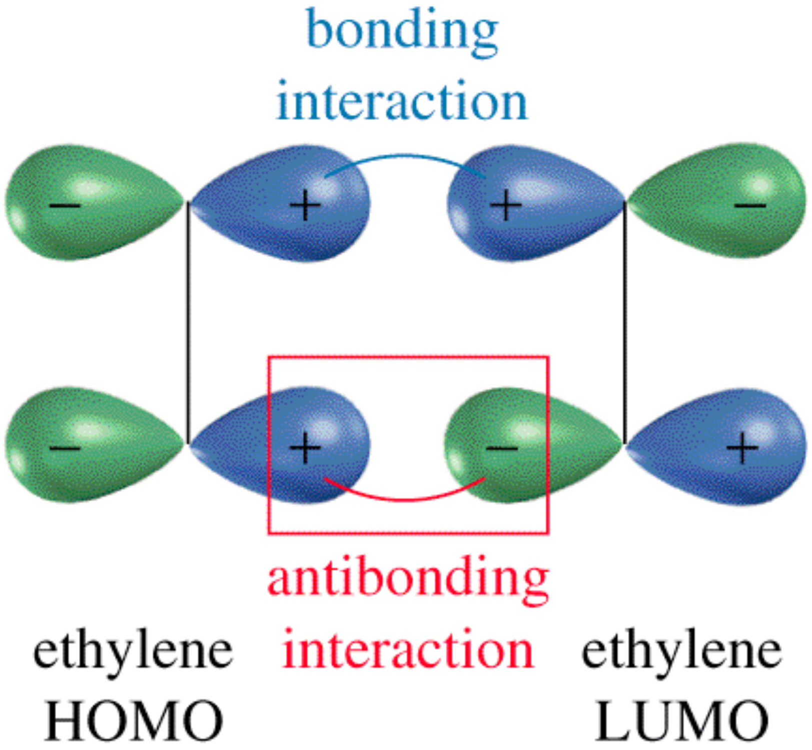
Dienophile receives electrons in its LUMO

[2 + 2] Cycloaddition Reaction



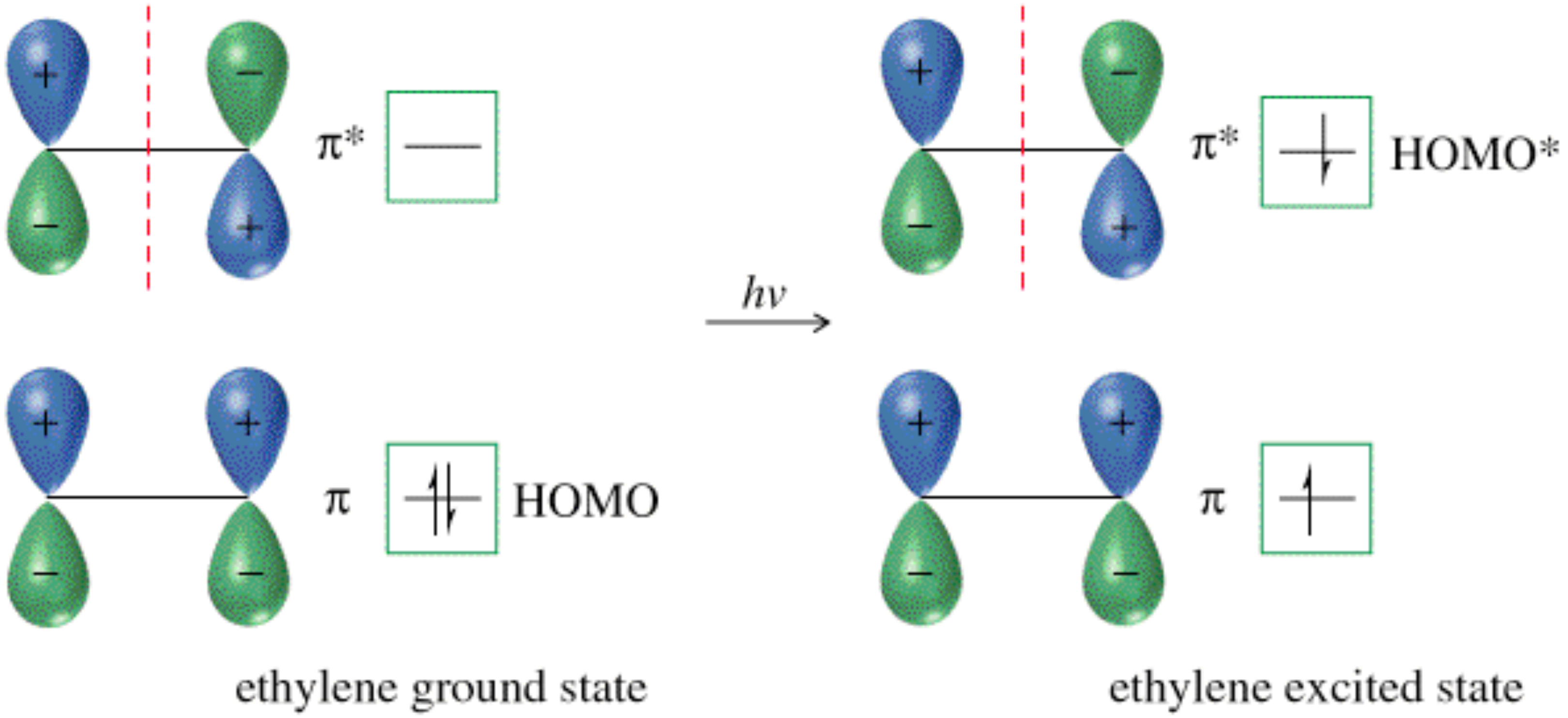
“Forbidden” Cycloaddition

[2 + 2] cycloaddition of two ethylene molecules to form cyclobutene has anti-bonding overlap of HOMO and LUMO



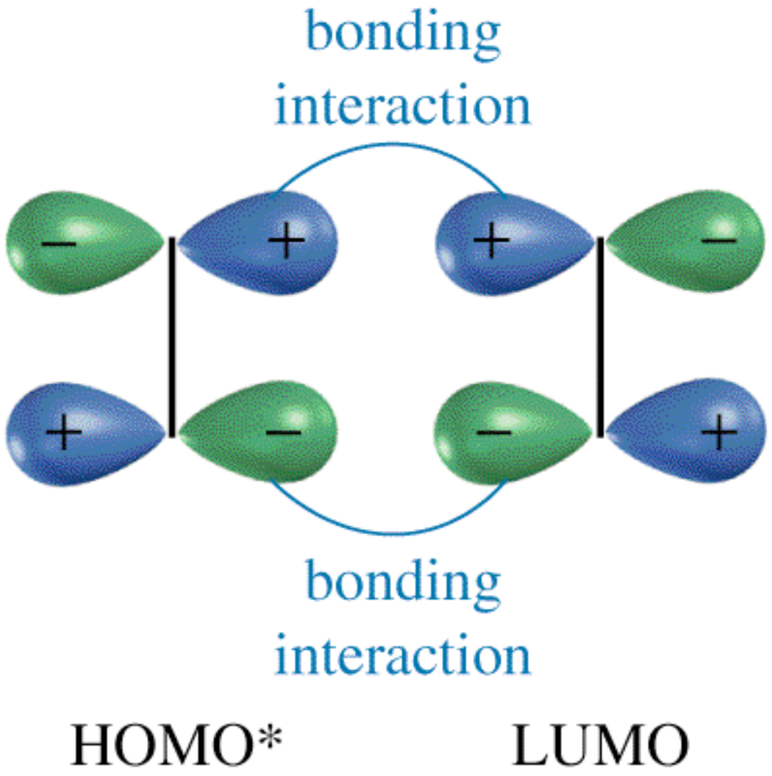
Photochemical Induction

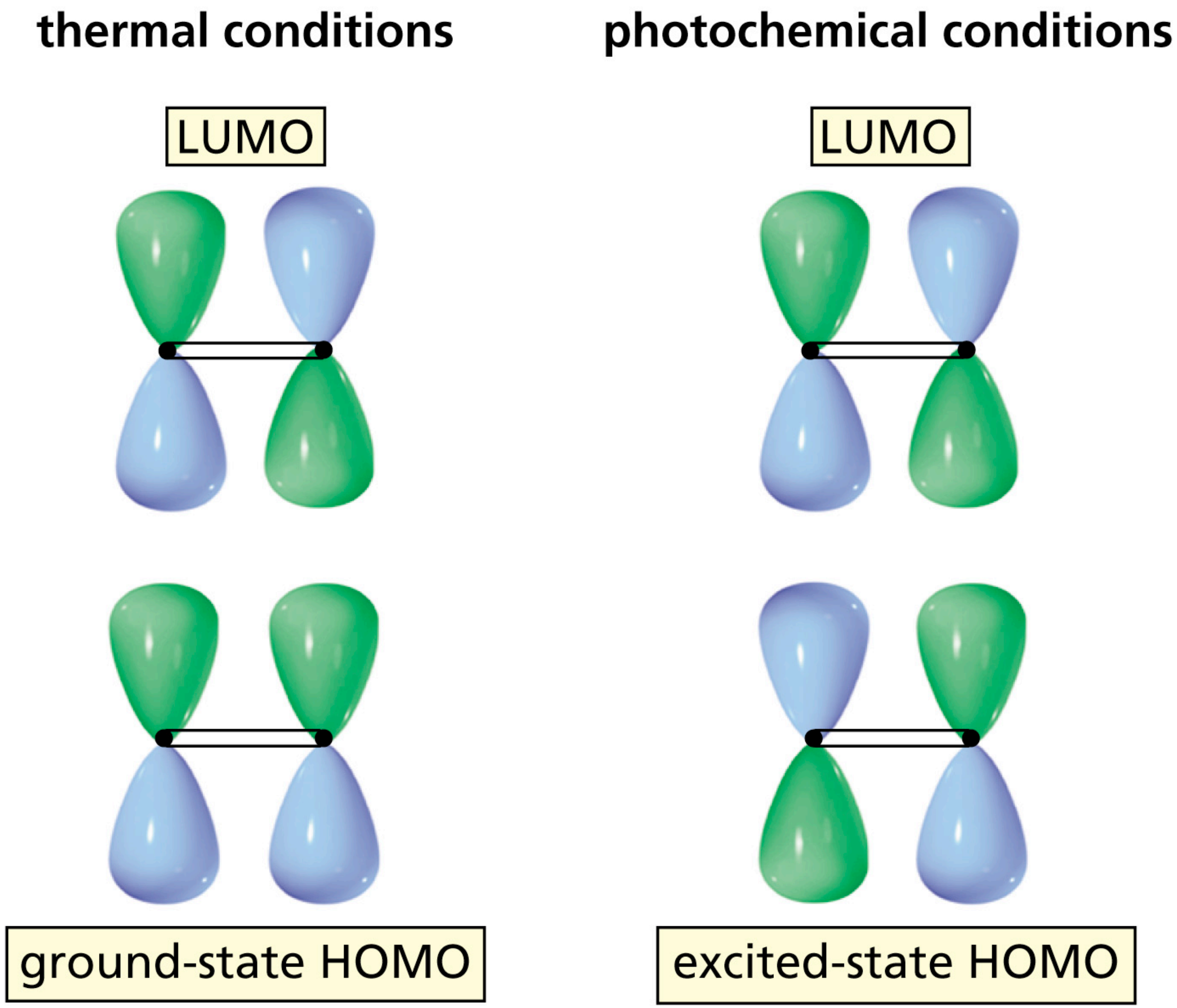
Absorption of correct energy photon will promote an electron to an energy level that was previously unoccupied.



[2 + 2] Cycloaddition

Photochemically allowed, but thermally forbidden.





Woodward-Hoffmann Rules

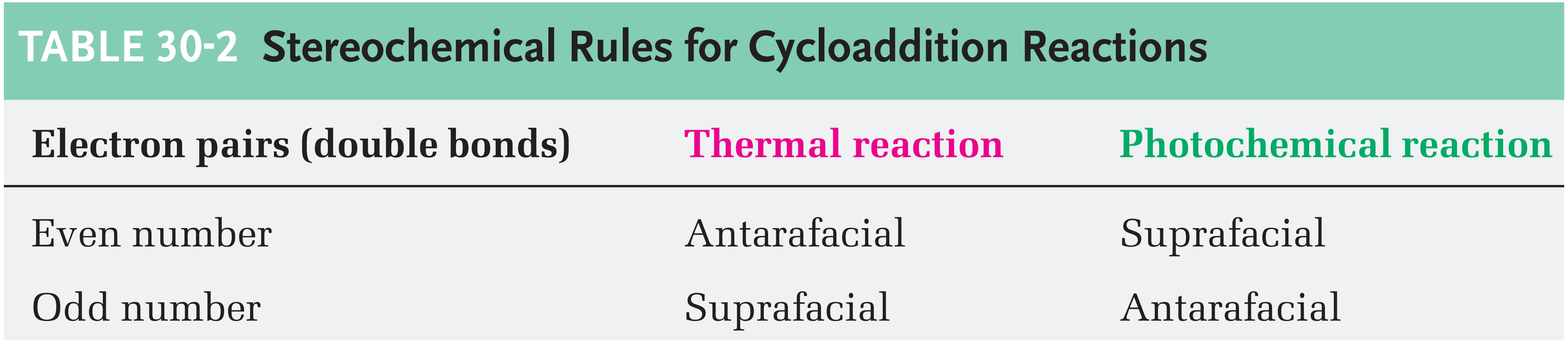


TABLE 30-2 Stereochemical Rules for Cycloaddition Reactions

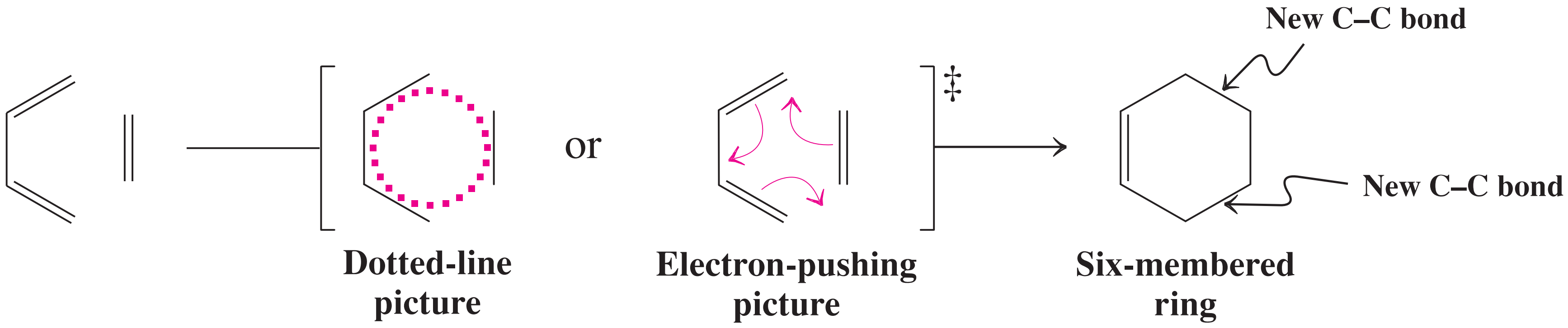
Electron pairs (double bonds)	Thermal reaction	Photochemical reaction
Even number	Antarafacial	Suprafacial
Odd number	Suprafacial	Antarafacial

The Diels-Alder reaction is concerted with a cyclic flow of electrons.

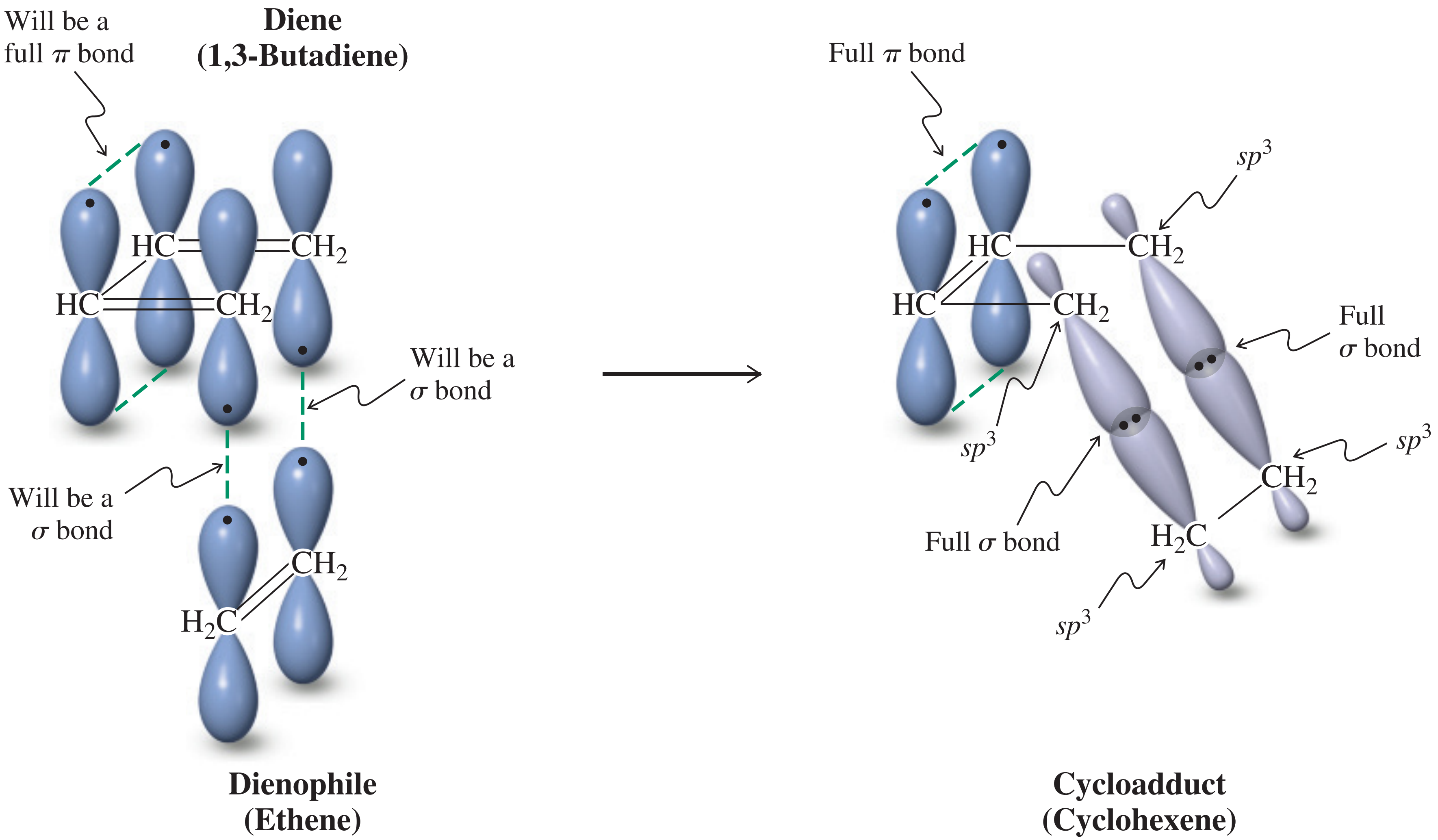
The Diels-Alder reaction takes place in **one step**. Both new carbon–carbon single bonds and the new **π** bond form simultaneously, just as the three **π** bonds in the starting materials break.

One-step reactions, in which bond breaking happens at the same time as bond making, are *concerted*. The concerted nature of this transformation can be depicted in either of two ways: by a dotted circle, representing the six delocalized **π** electrons, or by electron-pushing arrows.

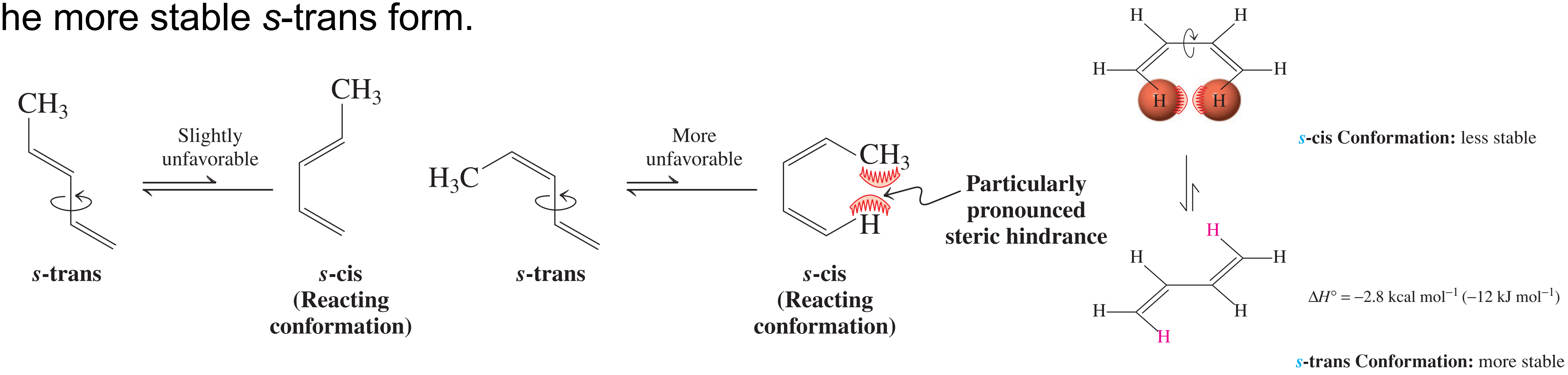
Just as six-electron cyclic overlap stabilizes benzene, the Diels-Alder process benefits from the presence of such an array in its transition state.



An orbital representation clearly shows bond formation by overlap of the *p* orbitals of the dienophile with the terminal *p* orbitals of the diene. While these four carbons rehybridize to sp^3, the remaining two internal diene *p* orbitals give rise to the new **π** bond.



The mechanism of the Diels-Alder reaction requires that both ends of the diene point in the same direction to be able to reach the dienophile carbons simultaneously. This means that the diene has to adopt the energetically slightly less favorable *s*-cis conformation, relative to the more stable *s*-trans form.



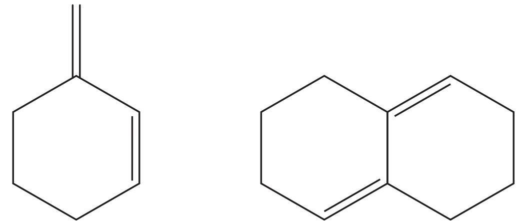
s-cis Conformation: less stable

$\Delta H° = -2.8\ \text{kcal mol}^{-1}\ (-12\ \text{kJ mol}^{-1})$

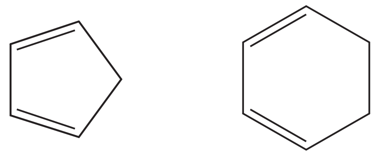
s-trans Conformation: more stable

This necessity affects the rates of the cycloaddition: When the *s*-cis form is particularly hindered or impossible, the reaction slows down or does not occur. Conversely, when the diene is constrained to *s*-cis, the transformation is accelerated.

Unreactive Dienes

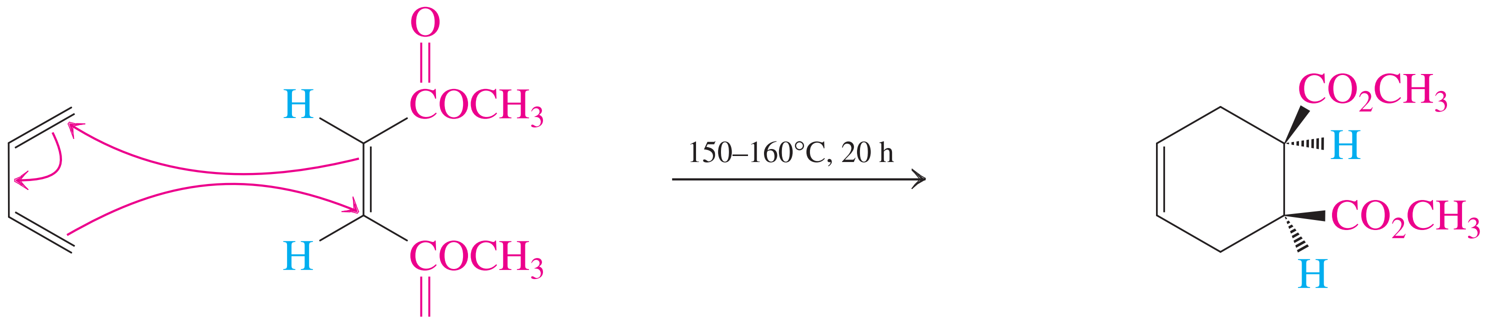


Particularly Reactive Dienes



The Diels-Alder reaction is stereospecific.

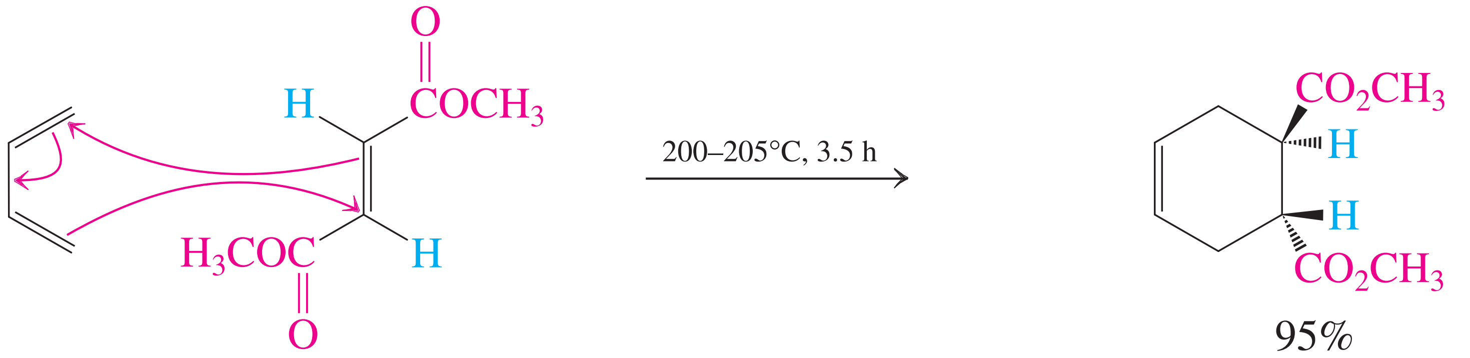
As a consequence of the concerted mechanism, the **stereochemistry** at the original double bond of the **dienophile** is **retained** in the product. The reaction is a ***syn*** addition.



68%

Dimethyl *cis*-2-butenedioate
(Dimethyl maleate)
(Cis starting material)

Dimethyl *cis*-4-cyclohexene-1,2-dicarboxylate
(Cis product)



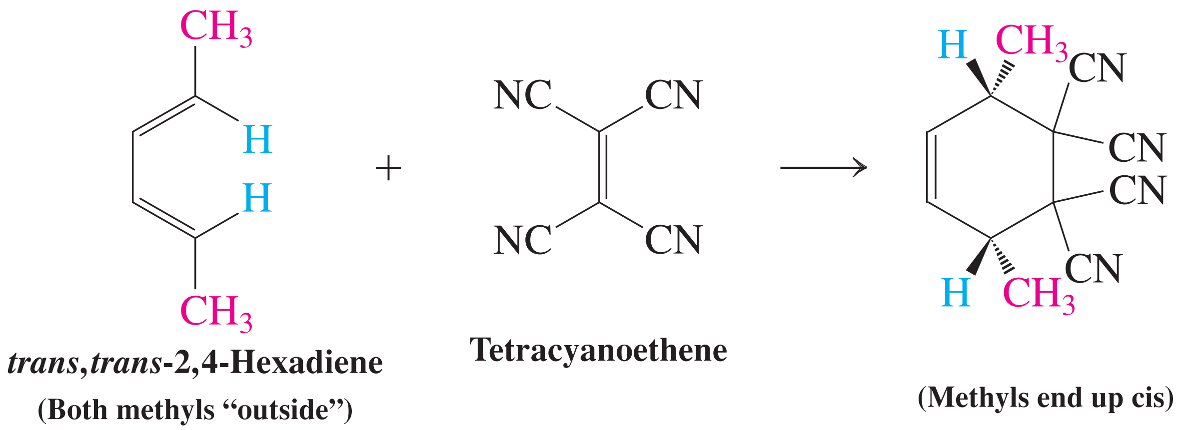
95%

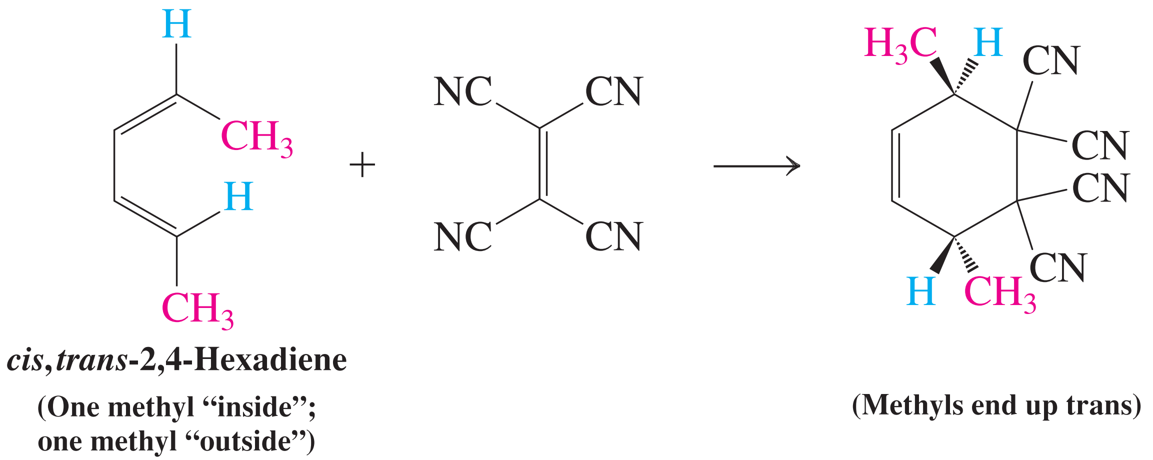
Dimethyl *trans*-2-butenedioate
(Dimethyl fumarate)
(Trans starting material)

Dimethyl *trans*-4-cyclohexene-1,2-dicarboxylate
(Trans product)

Similarly, the **stereochemistry** of the **diene** also is **retained**. Note that the cycloadducts depicted here contain stereocenters and may be either meso or chiral.

Since we begin with achiral starting materials, the products are formed as racemates (via two equal-energy transition states). As always, we are depicting only one enantiomer of a chiral (but racemic) product.

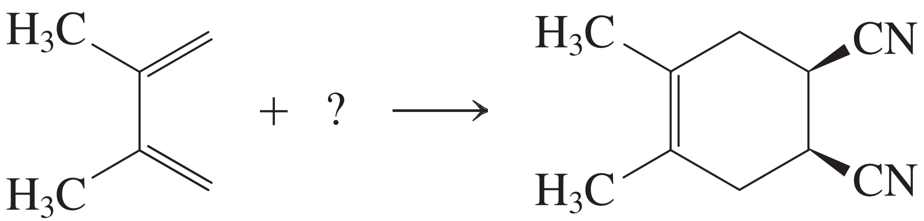




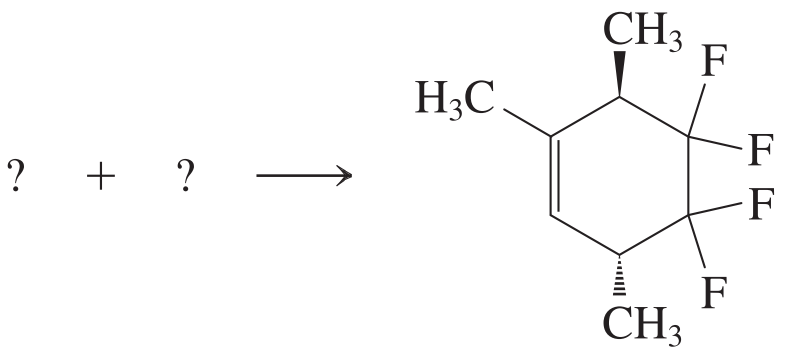
Exercise 14-20

Add structures of the missing starting materials to the following Diels-Alder reaction schemes.

(a)



(b)



Diels-Alder cycloadditions follow the endo rule.

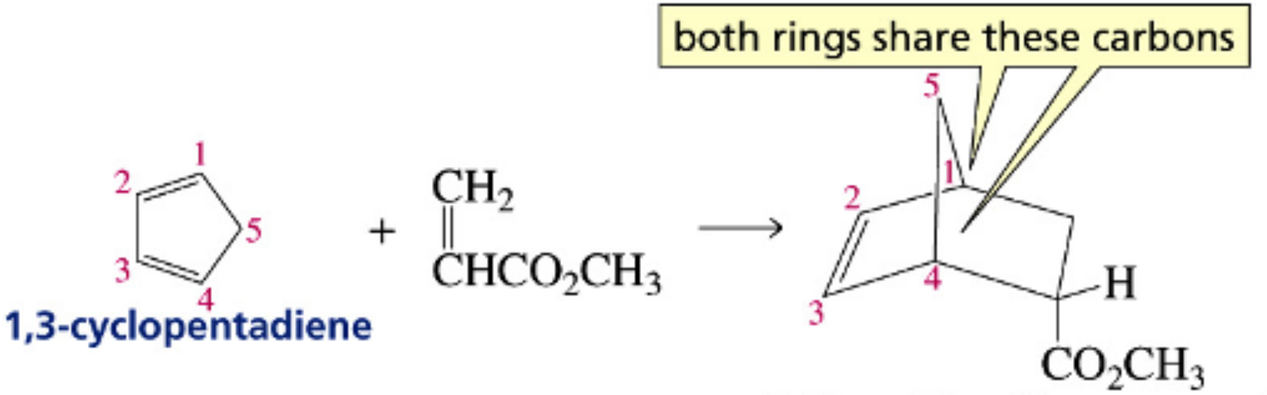
The Diels-Alder reaction is highly **stereocontrolled**, not only with respect to the substitution of the double bonds, but also the orientation of the starting materials relative to each other.

Consider the reaction of 1,3-cyclopentadiene with dimethyl *cis*-2-butenedioate. Two products are conceivable: (i) the two ester substituents on the bicyclic frame are on the same side (*cis*) as the methylene bridge, (ii) they are on the side opposite (*trans*).

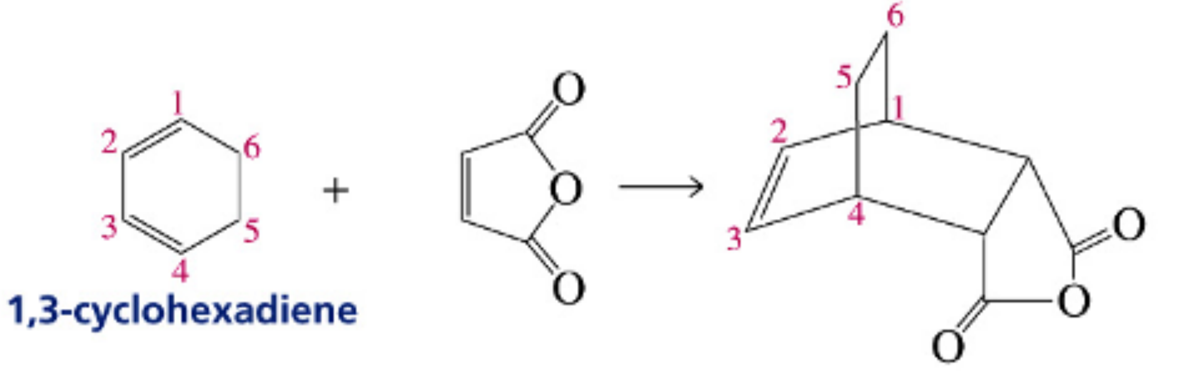
The first is called the ***exo*** adduct, the second the ***endo*** adduct (exo, Greek, outside; endo, Greek, within). The terms refer to the **position of groups in bridged systems**.

Exo substituents are placed *cis* with respect to the shorter bridge; *endo* substituents are positioned *trans* to this bridge.

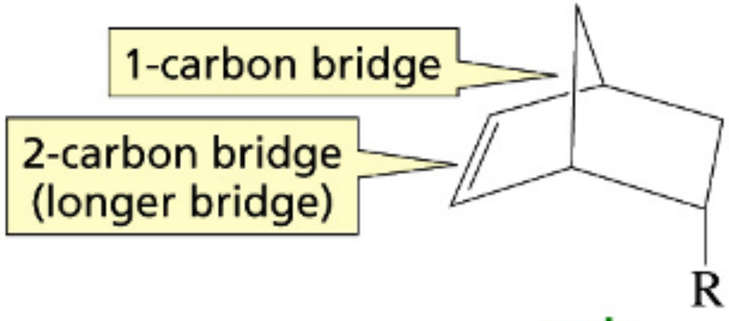
In general, in an *exo* addition, the substituents on the dienophile point away from the diene. Conversely, in an *endo* addition they point toward the diene.



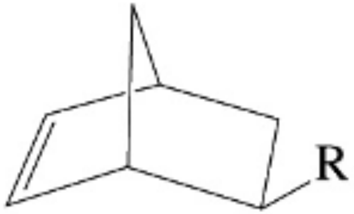
bridged bicyclic compound



bridged bicyclic compound

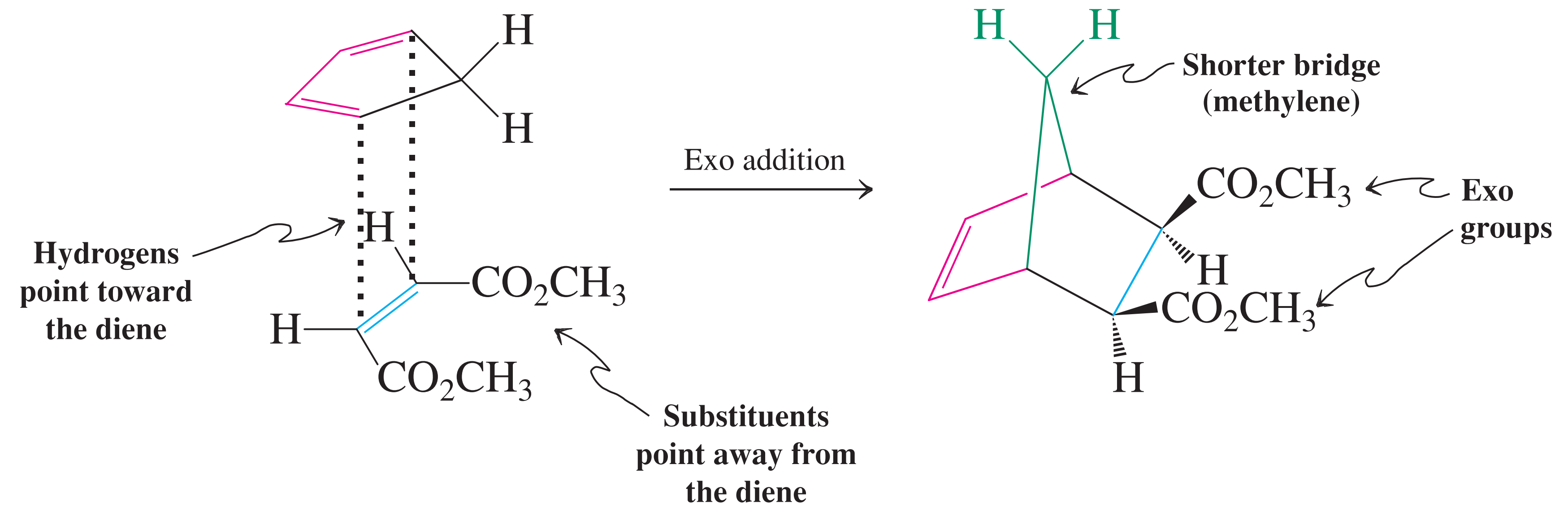


endo



exo

Exo and Endo Cycloadditions to Cyclopentadiene

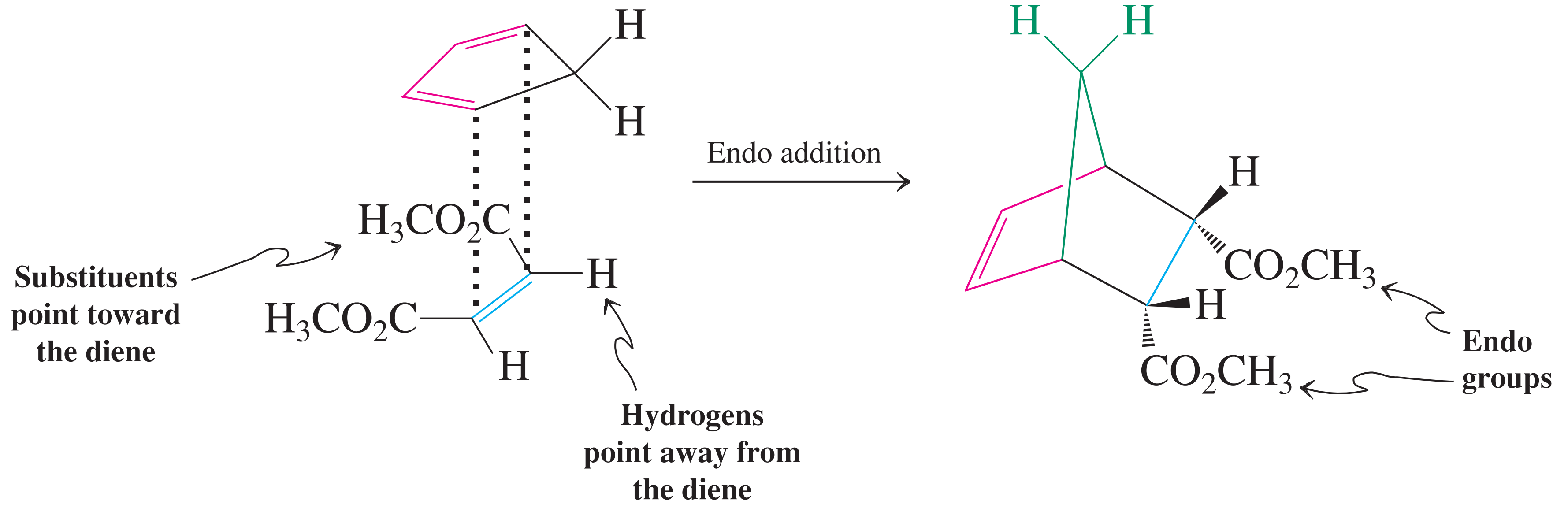


Hydrogens point toward the diene

Substituents point away from the diene

Shorter bridge (methylene)

Exo groups



Substituents point toward the diene

Hydrogens point away from the diene

Endo groups

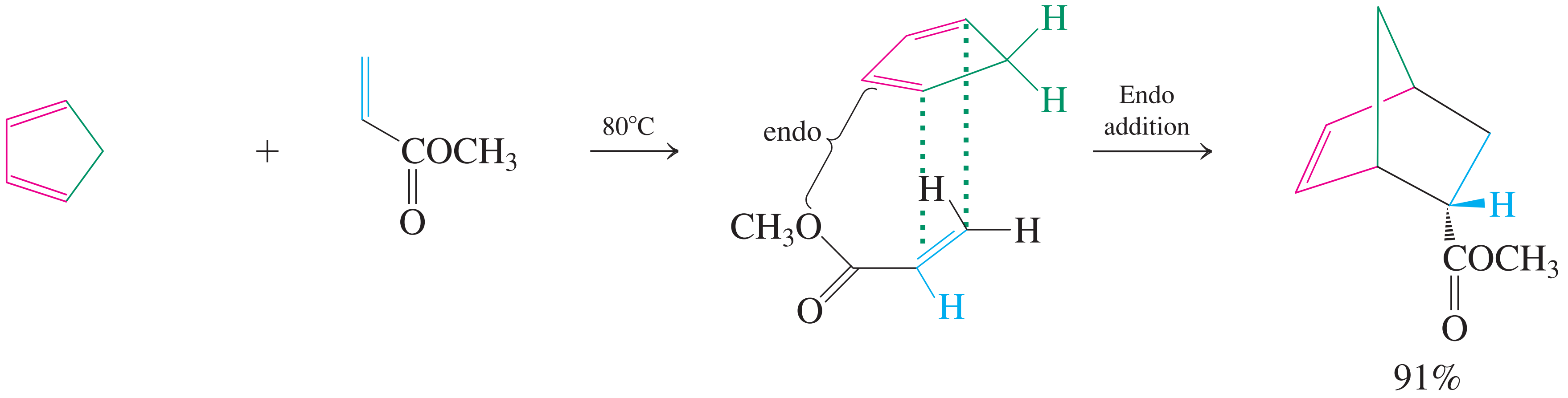
The Diels-Alder reaction usually proceeds with *endo* selectivity, that is, the product in which the activating electron-withdrawing group of the dienophile is located in the *endo* position is formed faster than the alternative *exo* isomer.

This occurs even though the *exo* product is often more stable than its *endo* counterpart.

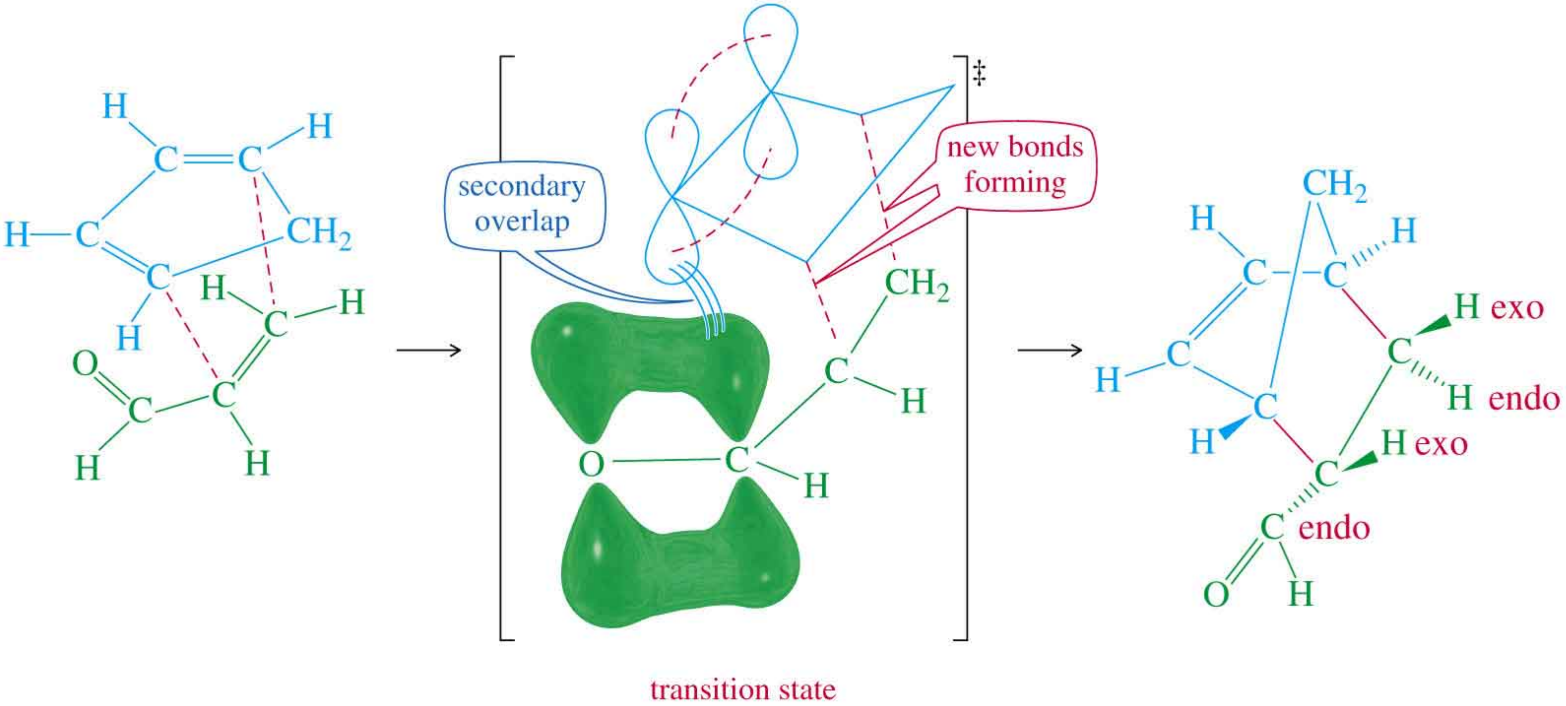
This observation is referred to as the ***endo* rule**. The **preference** for *endo* cycloaddition has its origin in a variety of **steric** and **electronic** influences on the **transition state** of the reaction.

Although the *endo* transition state is only slightly lower in energy, this is sufficient to control the outcome of most Diels-Alder reactions.

Mixtures may ensue in the case of highly substituted systems or when several different activating substituents are present.



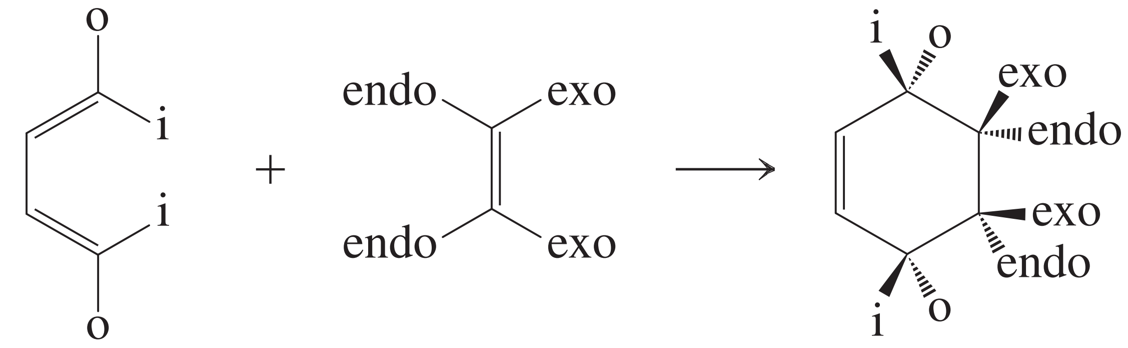
The *p* orbitals of the electron-withdrawing groups on the dienophile have a secondary overlap with the *p* orbitals of C2 and C3 in the diene.



As an aid to keeping track of the substituents and where they are going, we can use the general labels “o” (for outside) and “i” (for inside) for the two possible stereochemical orientations of groups attached to the end of the diene.

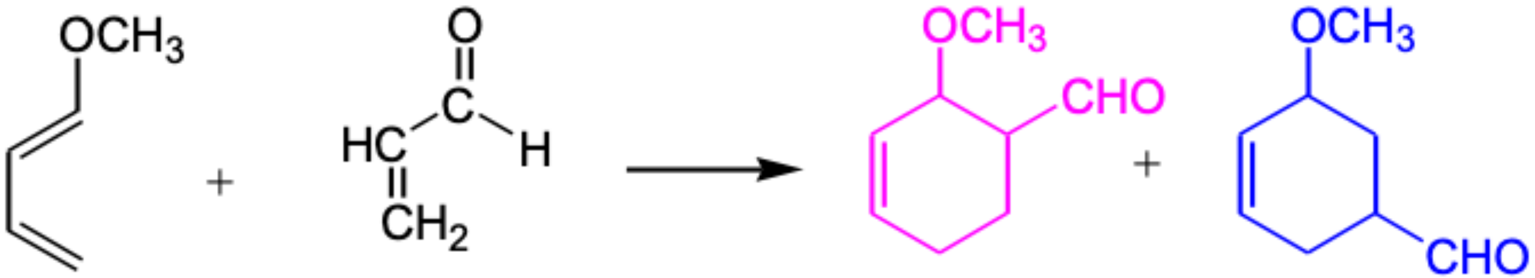
We then label the substituents on the dienophile with respect to their orientation in the transition state of the reaction as either *endo* or *exo*.

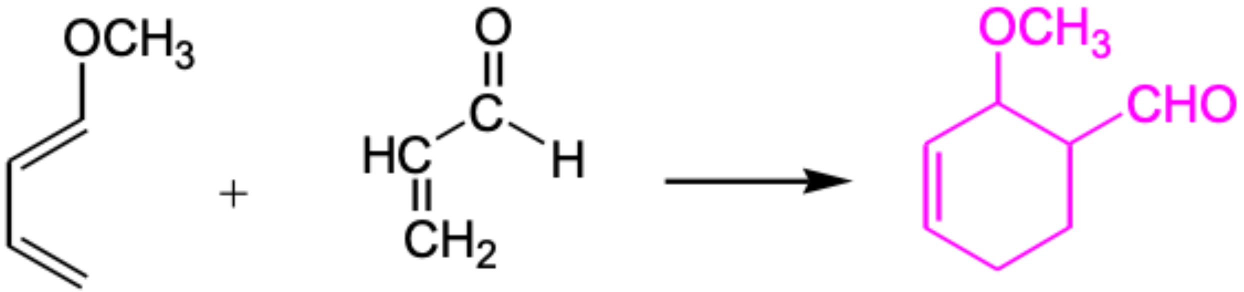
The structure of the expected product with all substituents in place shows that “o” is always *cis* to “*endo*.”

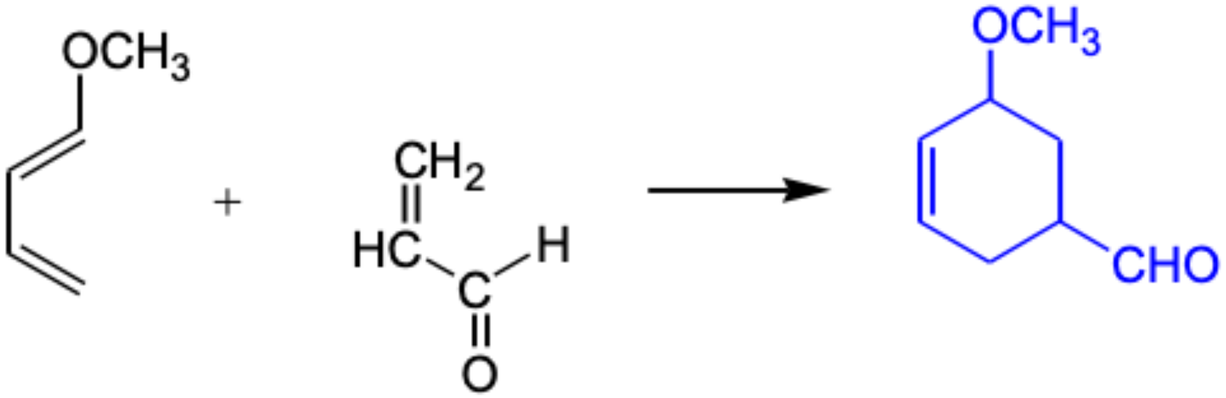


o = “outside”
i = “inside”

Predicting the Product When Both Reagents are Unsymmetrically Substituted





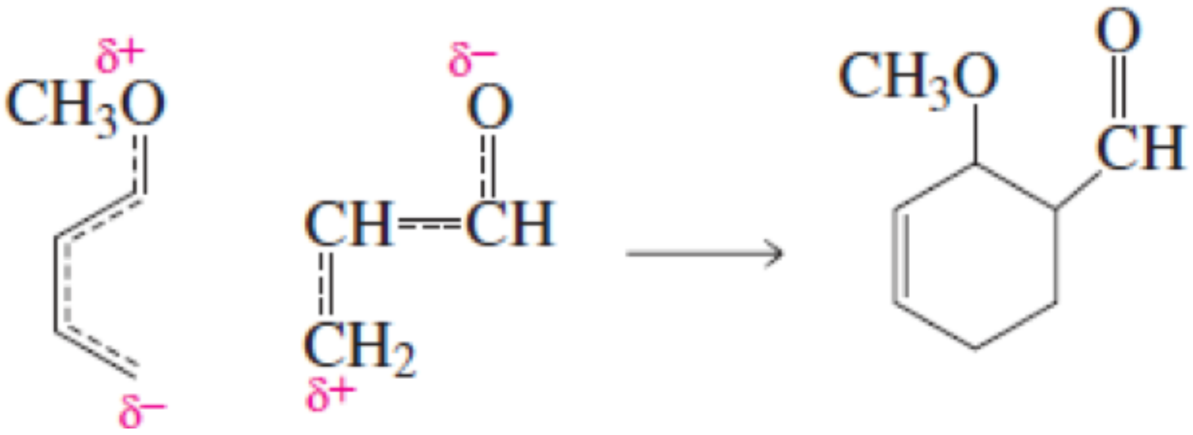


$$CH_2{=}CH{-}CH{=}CH{-}\ddot{\underset{..}{O}}CH_3 \longleftrightarrow \overset{..-}{C}H_2{-}CH{=}CH{-}CH{=}\overset{+}{\underset{..}{O}}CH_3$$

resonance contributors of the diene

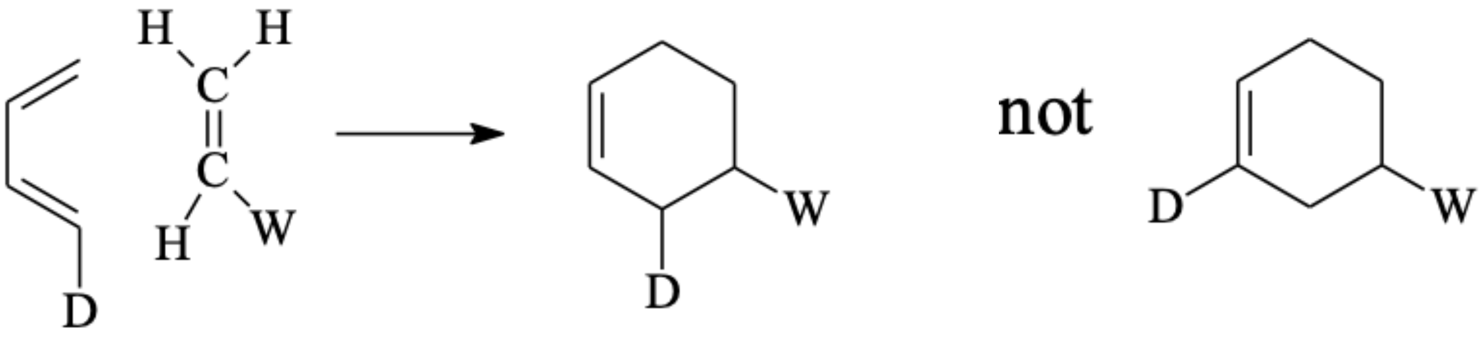
$$CH_2{=}CH{-}\overset{\overset{:\ddot{O}}{\|}}{C}H \longleftrightarrow \overset{+}{C}H_2{-}CH{=}\overset{\overset{:\ddot{O}:^-}{|}}{C}H$$

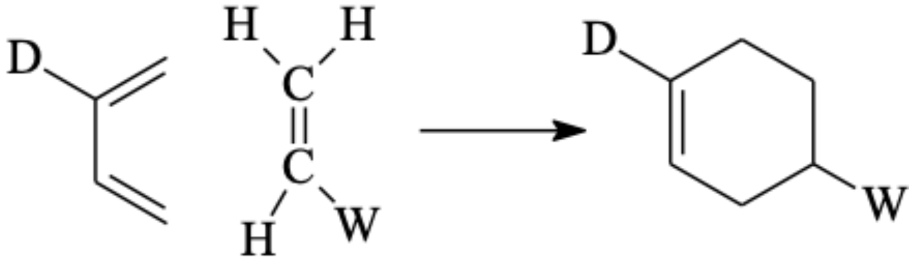
resonance contributors of the dienophile



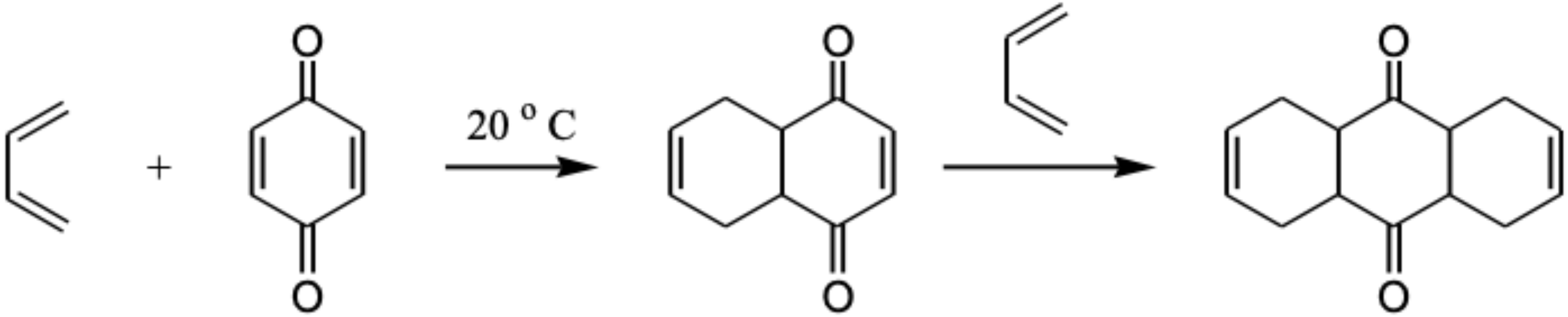
Regiospecificity/Regioselectivity

The 6-membered ring product of the Diels-Alder reaction will have electron-donating (D) and electron-withdrawing (W) groups in the position of 1,2- or 1,4- but not 1,3-.





Chemoselectivity



Exercise 14-24

The Diels-Alder reaction can also occur in an intramolecular fashion. Draw the two transition states leading to products in the following reaction.