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Chapter 1

Pericyclic Reactions

1.1. Introduction:

Definition:

Pericyclic reactions are concerted processes that occur by way of a cyclic transition state in which more than one bond is formed or broken within the cycle.

The classic example of such a process is the Diels–Alder cycloaddition reaction, one of the most common and useful synthetic reactions in organic chemistry.

Cycloaddition reactions, sigma tropic rearrangements and electrocyclic reactions all fall into the category of pericyclic processes.

1. Concerted reaction that proceed via a cyclic transition state
2. No distinct intermediates in the reaction
3. Bond forming and bond breaking steps are simultaneous but not necessarily Synchronous

Classification:

i. Electrocyclic ring closing and ring opening reaction
ii. Cycloaddition and Cyclo-reversion reaction
iii. Sigmatropic Rearrangements
iv. Chelotropic Reaction
v. Group transfer Reaction

Sub Classification:

Based on the number of π electrons involved in each component

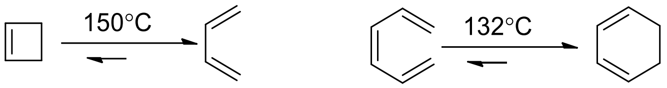
i. The numbers are written within a square bracket e.g. [2π + 2π], [2π + 4π] etc
ii. Electrocyclic ring closing and ring opening reaction (6pi), (4pi),
iii. Cycloaddition and Cyclo-reversion reaction (6pi), (4pi),
iv. Sigmatropic Rearrangements (3,3), (1,5), (1,3), (1,7),(2,3),Chelotropic Reaction
v. Group transfer Reaction (related to sigmatropic)

1.2. Electrocyclic Reactions:

Electrocyclizations, a class of pericyclic reactions, are characterized by the formation of a ring from an open-chain conjugated system, with a α-bond forming across the ends of a conjugated system (or vice-versa). Electrocyclization reactions can occur thermally or photochemically, via two possible modes known as conrotatory and disrotatory. The simplest examples of thermal electrocyclization are illustrated in below figure.

OR

An electrocyclic reaction is defined as the thermal or photochemical conversion of an acyclic conjugated system into a ring system by formation of a σ bond between the ends of the conjugated system in a concerted process, or the reverse of this reaction. These reactions are reversible in nature.



Woodward–Hoffmann rules for electrocyclic reactions are summarized in below Table:

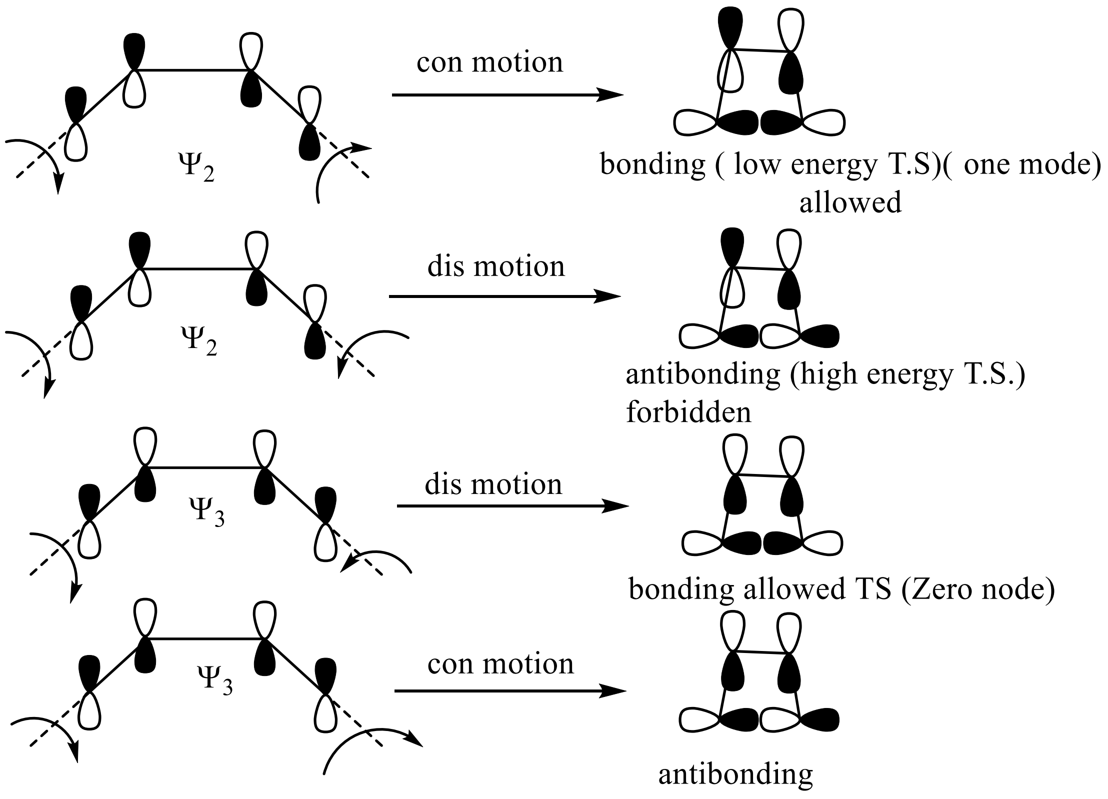


Fig: (**a**)= Thermal electrocyclization of 4npe conjugated system;
(**b**)= Photochemical electrocyclization of 4npe conjugated

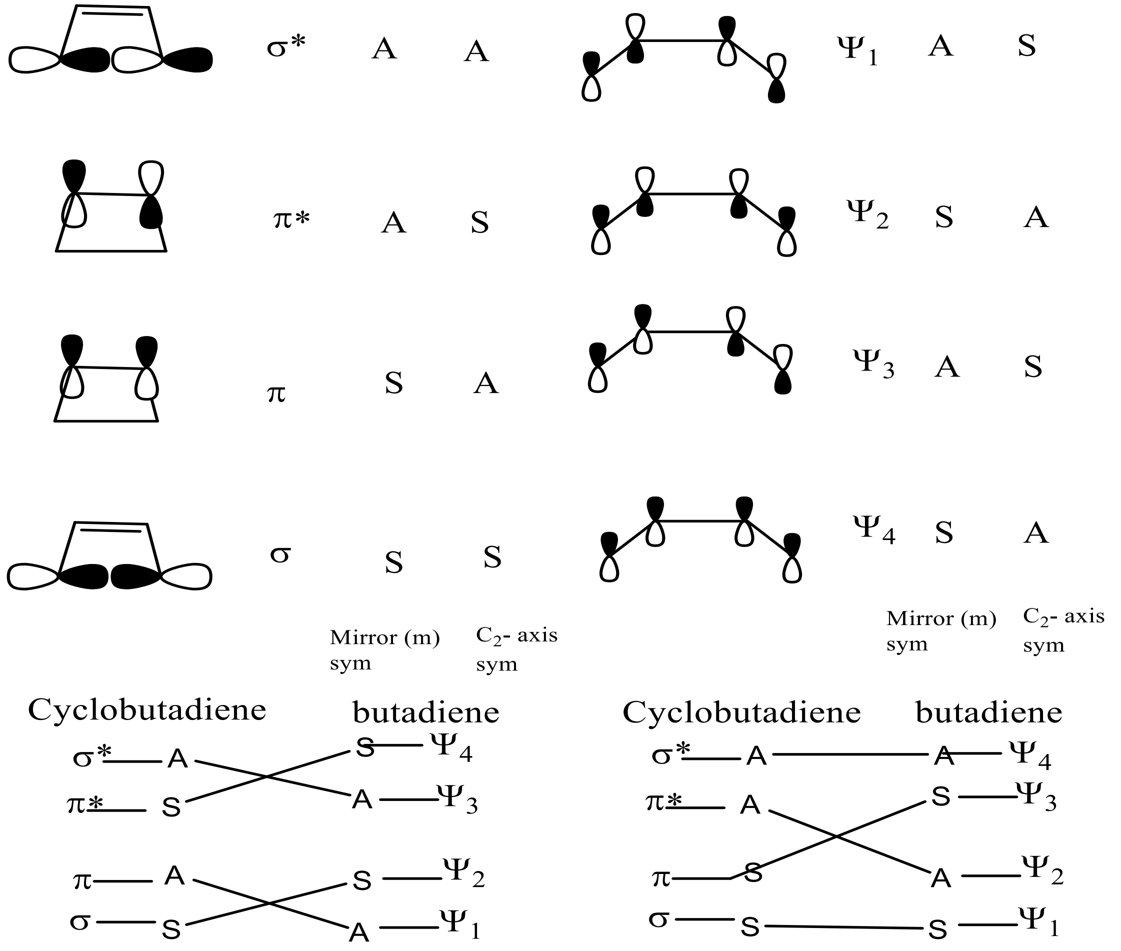
1.2.1. The Orbital Correlation Diagrams of Reactants and Products:

Longuet-Higgins and Abrahamson suggested that in any concerted process, the orbitals of the starting material and product have the same symmetry. This is also supported by Woodward and Hoffmann.

The cyclobutene–butadiene interconversion may be considered as an example to verify the fact by construction of a correlation diagram.

For cyclobutene, the bonding orbitals are σ and π, while the antibonding orbitals are σ* and π*.

For butadiene, the bonding orbitals are ψ1 and ψ2, and antibonding orbitals are ψ3 and ψ4. In thermal reaction, conrotatory ring opening of cyclobutene to butadiene, C_2 (twofold) axis of symmetry is maintained throughout the reaction, while for photochemical reaction, disrotatory ring opening, a mirror plane (m) symmetry is maintained throughout the reaction.



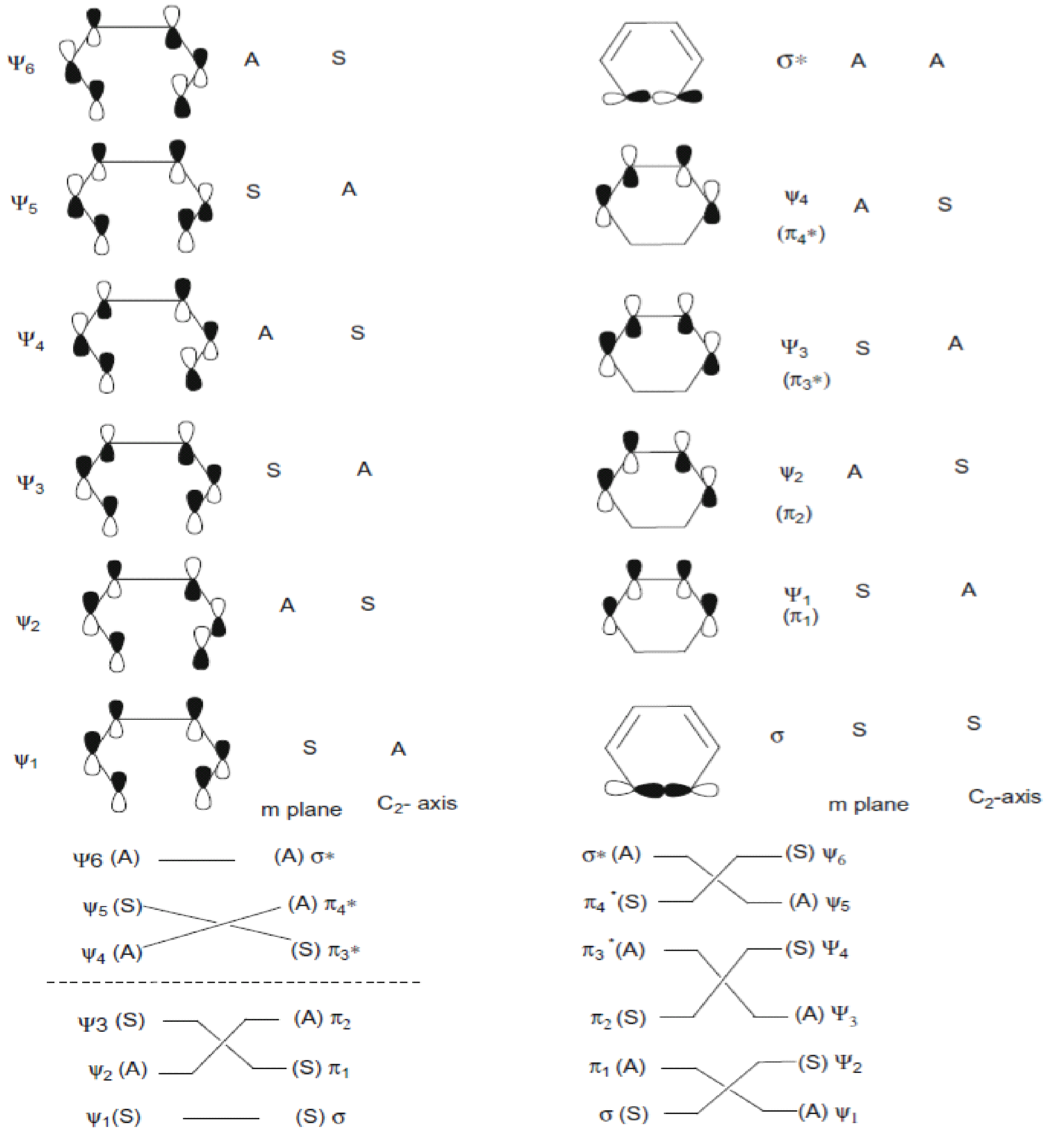
(a) C_2- axis of symmetry for conrotatory motion

(b) Mirror plane symmetry for disrotatory motion

(a)=C2-axis of symmetry is maintained in thermal conversion of cyclobutene to butadiene; **(b)**= mirror plane symmetry is maintained in photochemical conversion of cyclobutene to

Next, consider the thermal conversion of a 1,3,5-hexatriene to a 1,3-cyclohexadiene by the disrotatory motion where mirror (m)-symmetry is maintained in the orbitals of the reactant and product.

In photochemical conversion of 1,3-cyclohexadiene into 1,3,5-hexatriene or vice versa, the C2-axis of symmetry is maintained in conrotatory motion of the terminal groups.



(a) m plane classification

(b) C_2 axis classification

(a)= Mirror plane (m) symmetry is maintained inthermal conversion of 1,3,5-hexatriene into 1,3-cyclohexadiene;
(b)= C2-axis of symmetry is maintained in photochemical conversion of 1,3-cyclohexadiene into 1,3,5-hexatriene or vice versa

1.2.2. Shortcut to Determine the Product in Electrocyclic Ring Openingand Ring Closing Reaction:

ring closing eletrocyclic reaction →

Site of substituents	Con or Dis rotation	Geometry of substitution
O	D	C
O	C	T
S	C	C
S	D	T

← ring opening eletrocyclic reaction

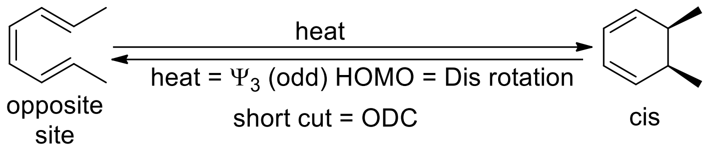
O = opposite site, S = same site, D = Dis rotation, C = Con rotation, T = trans, C = cis

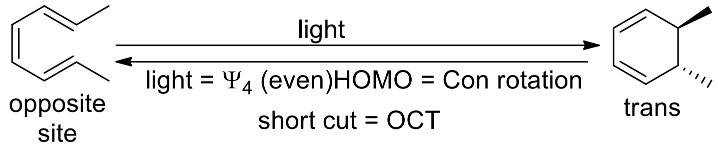
Even HOMO = Con rotatory Odd HOMO = Dis rotatory

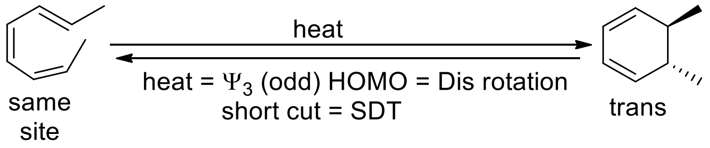
ZZ/EE= opposite site ZE/EZ= same site

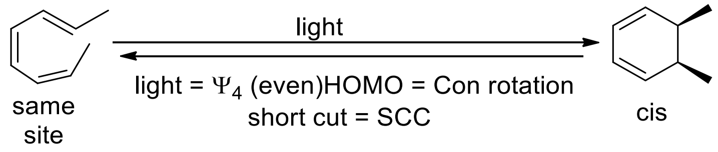
Example:

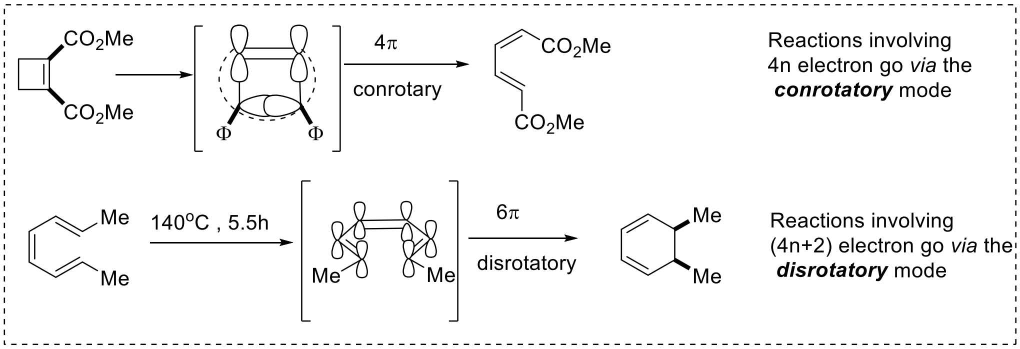
Ring opening and closing reaction:









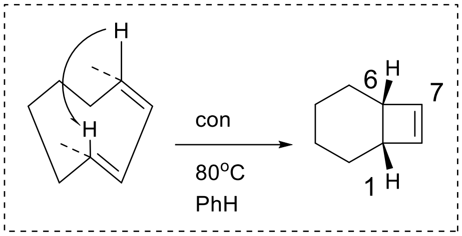


Reactions involving 4n electron go *via* the ***conrotatory*** mode

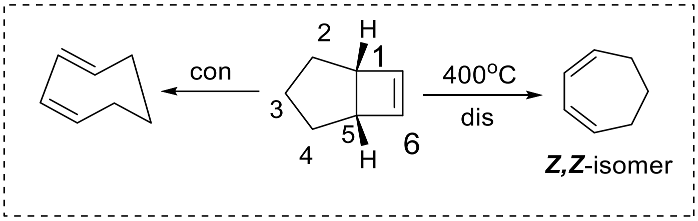
Reactions involving (4n+2) electron go *via* the ***disrotatory*** mode

1.2.3. Applications of Neutral Conjugated Systems in Electrocyclic Reactions:

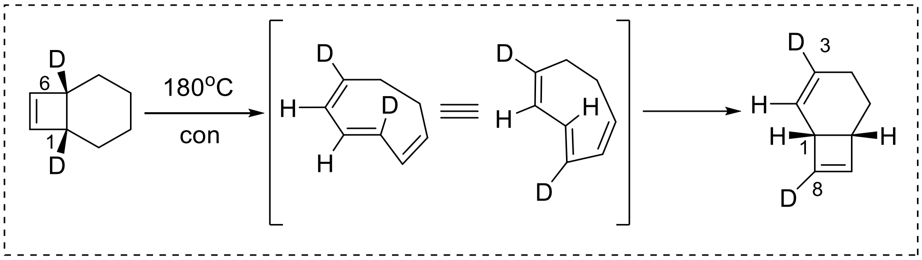
Electrocyclic reaction of E, Z-1, 3-cyclooctadiene leads to cis-bicyclo[4.2.0]- oct-7-ene because of strain associated with trans double bond.



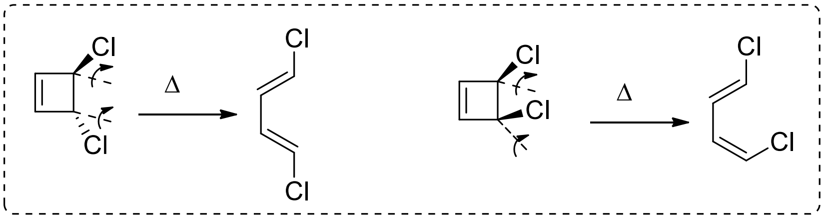
Although cyclobutenes are converted into butadienes on heating to get relief of ring strain, cis-bicyclo[3.2.0]-hept-6-ene on heating gave Z,Z-1,3-cycloheptadiene by forbidden disrotatory motion. This anomaly of the Woodward–Hoffmann rules can be accounted for by the stability of the product formed. In this case, allowed conrotatory motion gives the strained E,Z-1,3-cycloheptadiene, which is less stable due to ring strain and hence rapidly isomerizes to Z,Z-isomer at the reaction temperature in low yield.



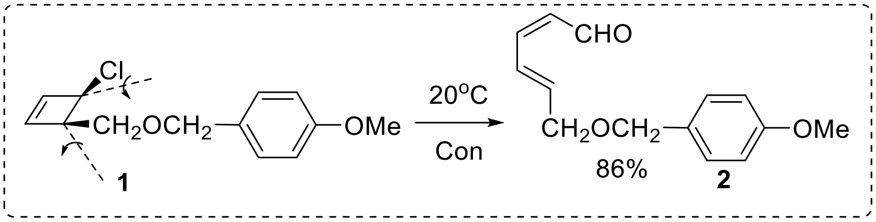
The thermal conversion of cis-1,6-dideuterio-bicyclo [4.2.0]- oct-2,7-diene to cis-3,8-dideuterio-isomer via trans-isomer.



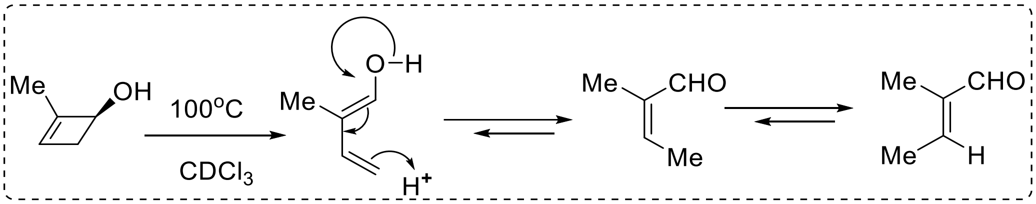
Study of the electrocyclic ring opening of cis- and trans-3,4-dichlorocyclobutenes indicated that trans-isomer reacts at lower temperature. This is due to ring opening by outward conrotatory motion of donor chlorine substituents while in case of cis-isomer, activation energy is higher as one of the chlorines rotates inward.



When a cyclobutene ring contains both electron-donating and electron-accepting substituents, conrotatory outward or inward motion of the substituents depends on the size of the substituents.

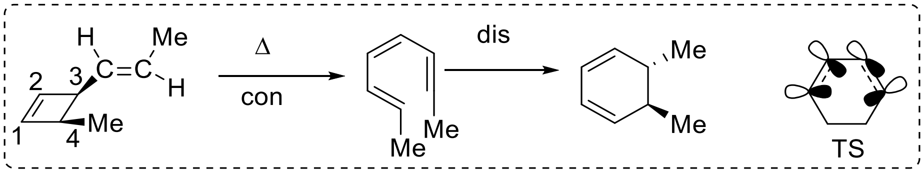


3-Hydroxy-2-methylcyclobutene on electrocyclic ring opening undergoes keto-enol tautomerization to afford the product.



Cyclobutene 9 having olefinic function at C-3 or C-4 position undergoes inward ring opening from the olefinic substituent site followed by ring closure to give the product.

This inward motion of the olefinic substituent stabilizes the HOMO of the TS by π-orbital interaction of the substituent with the donor lobes of p-orbitals of the breaking σ bond of the ring carbons.



1.2.4. Examples:

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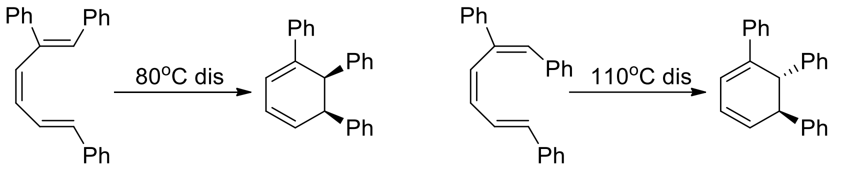

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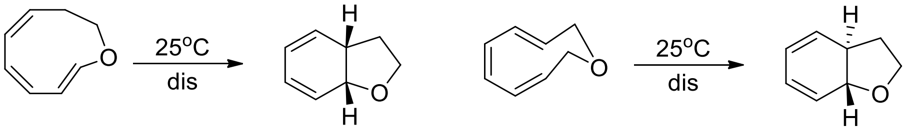

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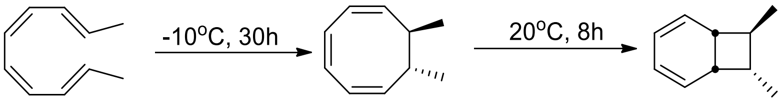
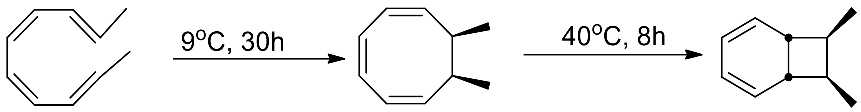
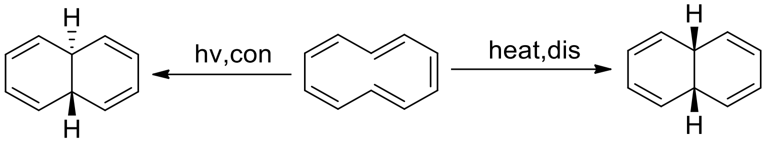
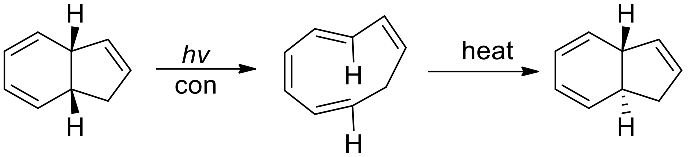
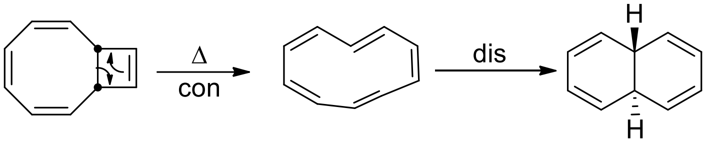
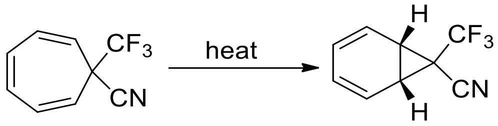


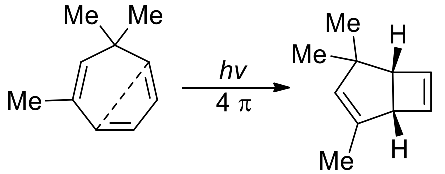
4. 

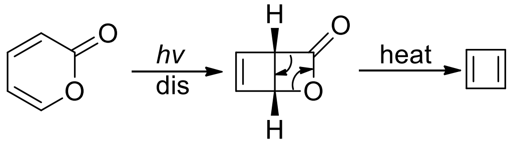
5. 

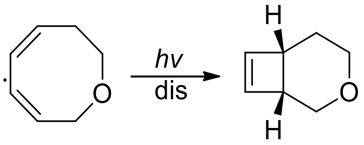
6. 

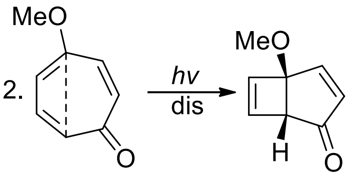
7. 

8. 

9. 

10. 

11. 

12. 

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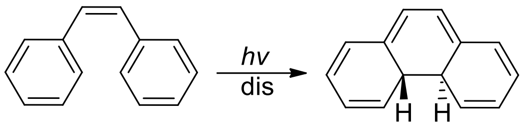

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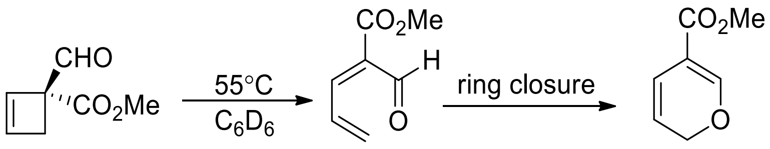

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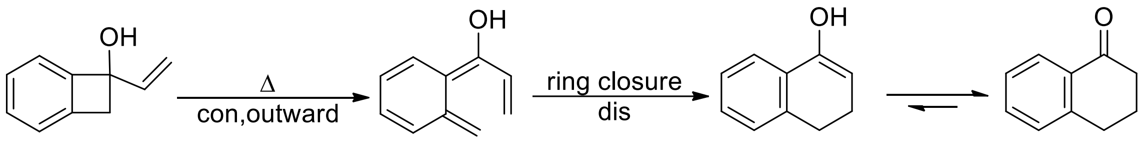

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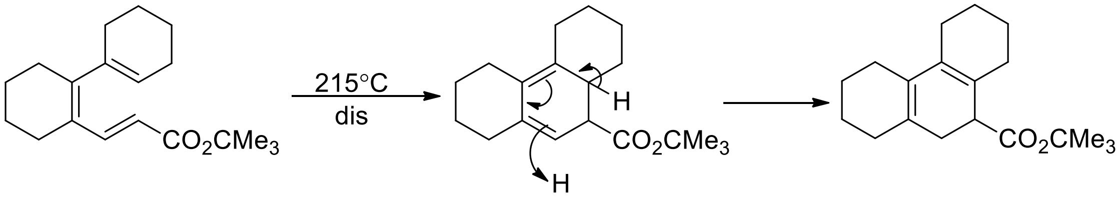
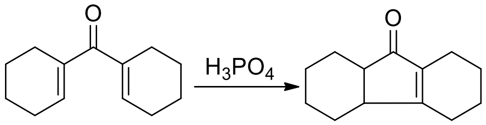
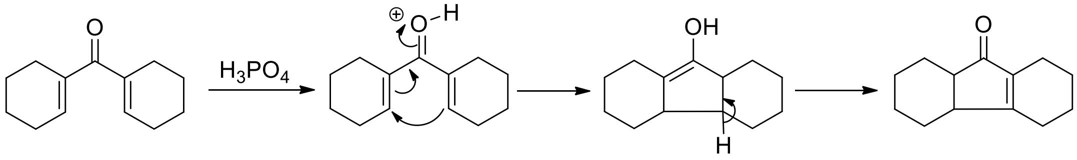


1.2.5. Nazarov Cyclization Reaction:

Acid-catalyzed cyclization of divinyl ketone occurs by conrotatory cyclization of 3-hydroxy pentadienyl cation. This type of cyclization reaction is known as Nazarov cyclization reaction.



Mechanism:



Examples:

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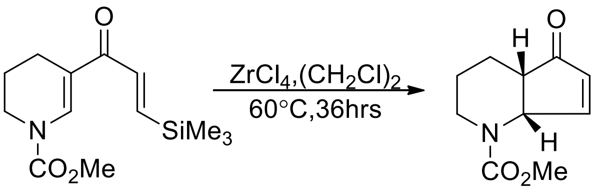

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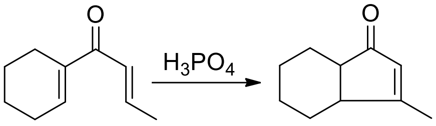

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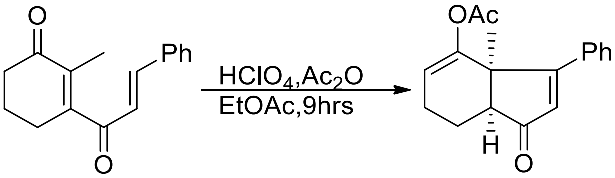

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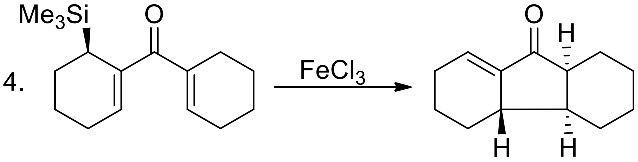

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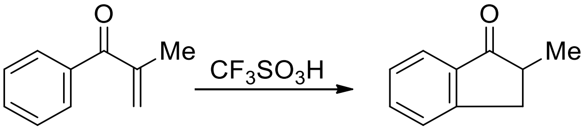


Key Points:

a. Cyclization of an acyclic conjugated polyene system

b. The terminal carbons interact to form a sigma bond

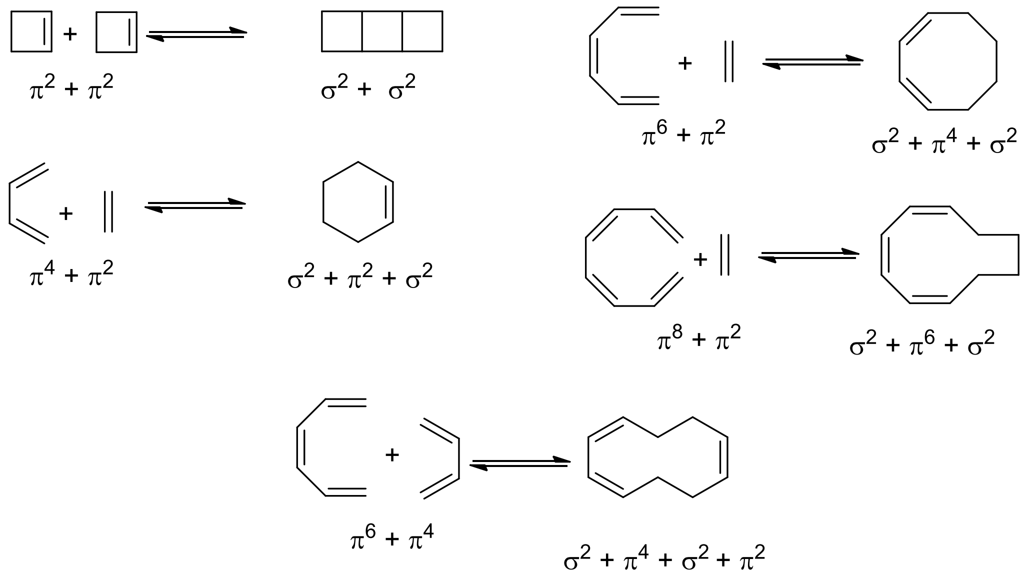
c. Cyclic transition state involving either 4n electrons or 4n+2 electrons.

d. Electrocyclization of butadiene (4n) and hexatriene (4n+2)

1.3. Cycloaddition Reactions:

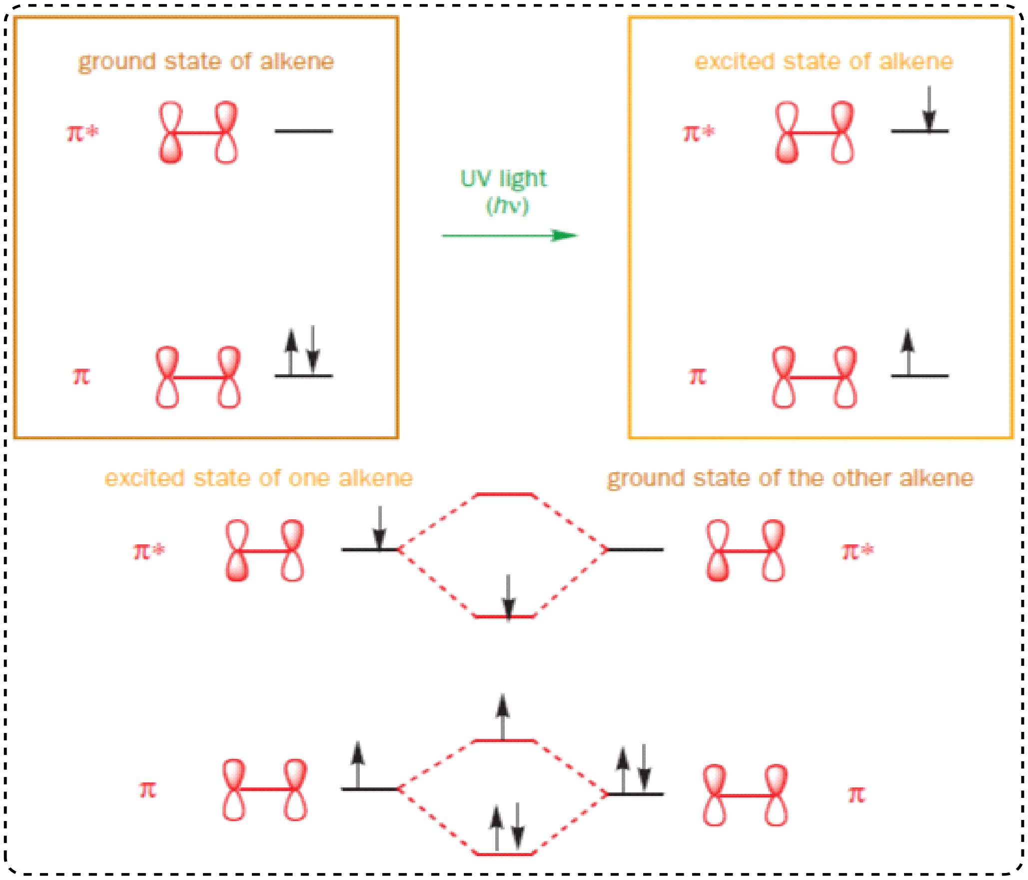
1.3.1.Introduction:

Cycloaddition reactions are the most useful pericyclic reactions in organic synthesis. These are the reactions of two π systems to form ring compounds by the breaking of two π bonds and making of two σ bonds in a concerted process. The reverse of cycloaddition reactions is known as retro-cycloaddition reactions. Both cycloadditions and cyclo-reversions proceed through cyclic transition states in which continuous flow of electrons occur among the reacting molecules. These reactions are classified according to the number of π electrons involved in each reacting molecule. The major classes are $[\pi^2+\pi^2]$, $[\pi^4+\pi^2]$, $[\pi^6+\pi^2]$, $[\pi^8+\pi^2]$, and $[\pi^6+\pi^4]$. These are simply known as [2+2]-, [4+2]-, [6+2]-, [8+2]-, and [6+4]-cycloaddition reactions and are illustrated below.



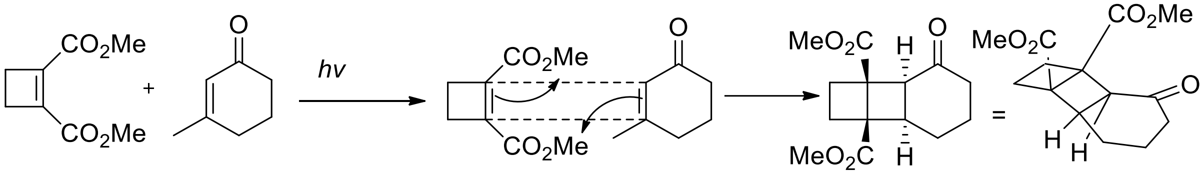
1.3.2. [2+2]-Cycloaddition Reactions:

Thermal [2+2]-cycloaddition reactions are less common, but photochemical [2+2] cycloaddition reactions are very common.



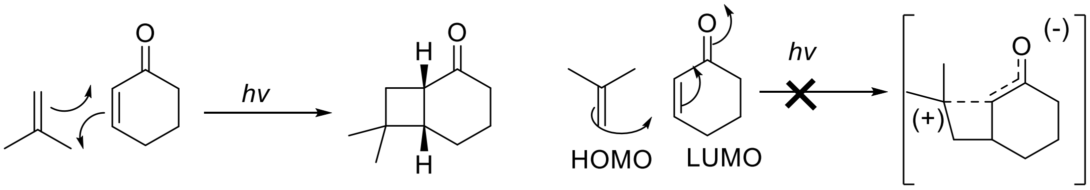
Stereochemistry of the Reaction:

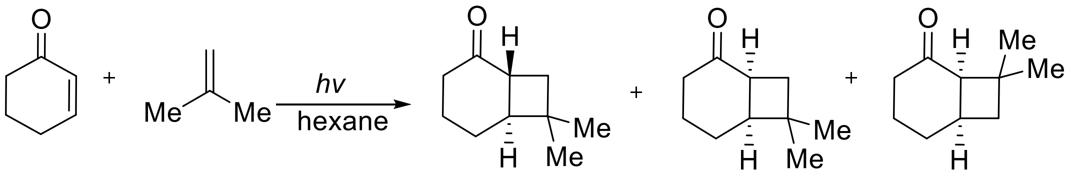
The reaction is stereospecific within each component but there is no endo rule-there is a conjugating group but no 'back of the diene'. The least hindered transition state usually results.

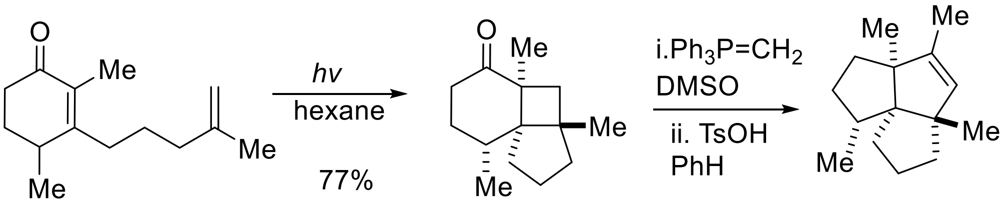


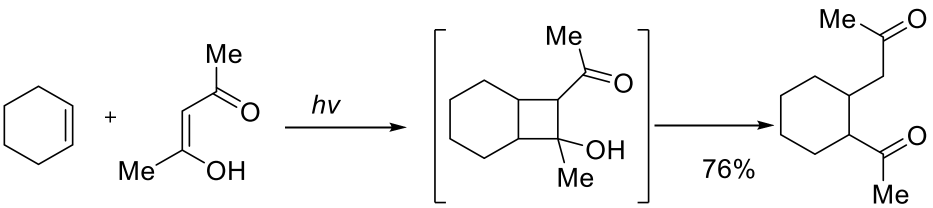
Regioselectivity/Regio-chemistry of the Reaction:

HOMO/HOMO and LUMO/LUMO interactions that no matter in the reactions of the excited state. The sizes of the coefficients in the LUMO of the alkene are the other way around to those in the HOMO. There is one electron in this pair of orbitals-in the LUMO of the enone in fact, as the enone has been excited by the light-so overlap between the two LUMOs.



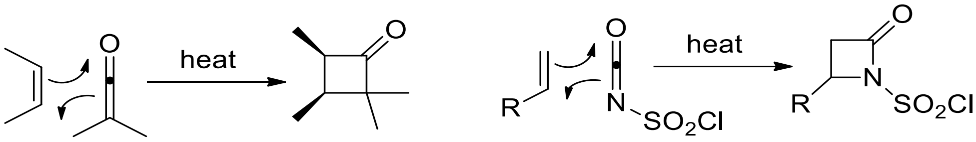






1.3.3.Thermal [2 + 2] Cycloadditions:

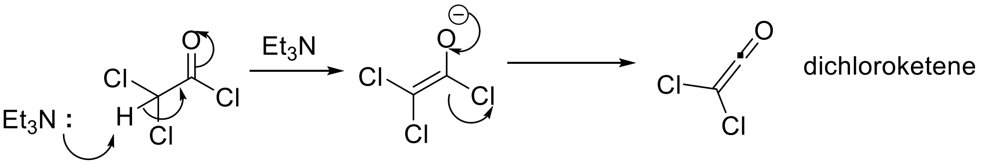
There are some thermal [2 + 2] cycloadditions giving four-membered rings. These feature a simple alkene reacting with an electrophilic alkene of a perticular type. It must have two double bonds to the *same* carbon atom. The most important examples are ketenes and isocyanates. The structures have two p bonds at right angles.

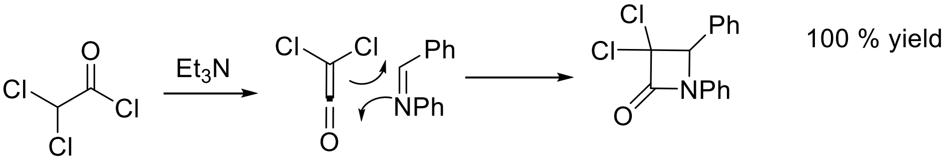


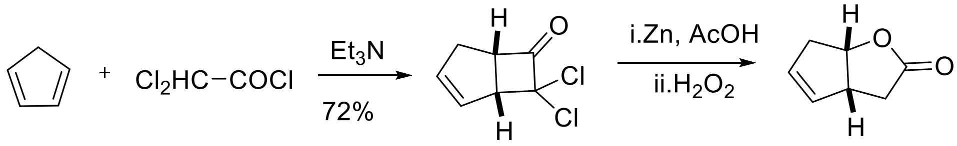
Preparation and Reactions of Ketene:

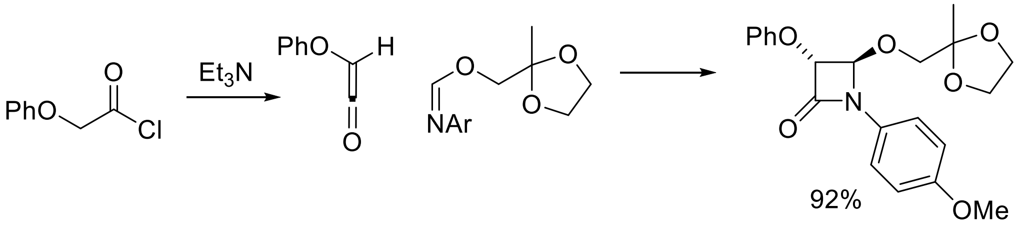
Ketene itself is usually made by high-temperature pyrolysis of acetone but some ketenes are easily made in solution.

The very acidic proton on dichloroacetyl chloride can be removed even with a tertiary amine and loss of chloride ion then gives dichloroketene in an E1cB elimination reaction.





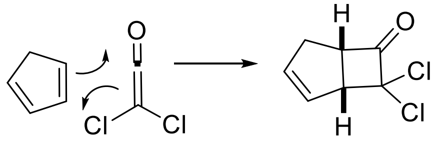




If the elimination is carried out in the presence of cyclopentadiene a very efficient Regio-and stereospecific [2 + 2] cycloaddition occurs.

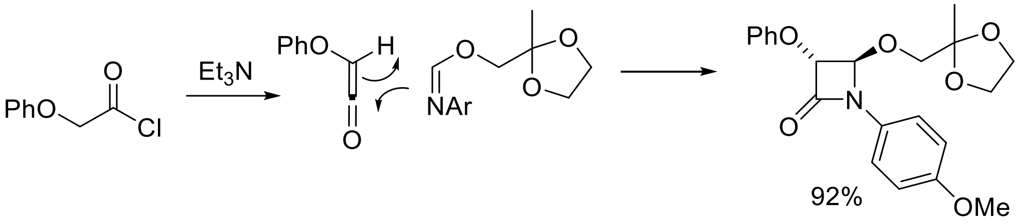
The most nucleophilic atom on the diene adds to the most electrophilic atom on the ketene and the cis geometry at the ring junction comes from the cis double bond of cyclopentadiene.

It is impressive that even this excellent diene undergoes no Diels–Alder reaction with ketene as dienophile. The [2 + 2] cycloaddition must be much faster.



If both components have one substituent, these will end up trans on the four-membered ring just to keep out of each other's way.

This example has more functionality and the product could be used to make b-lactams with antibiotic activity, such as analogues of the b-lactamase inhibitor, clavulanic acid.



Examples:

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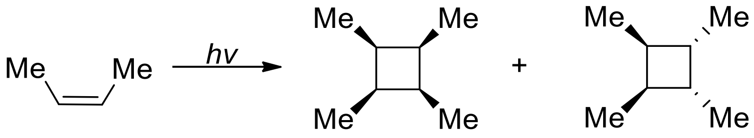

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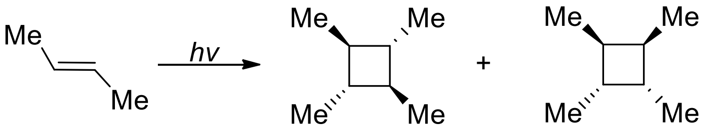

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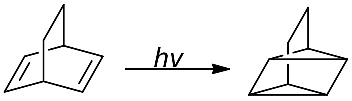

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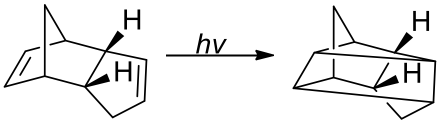

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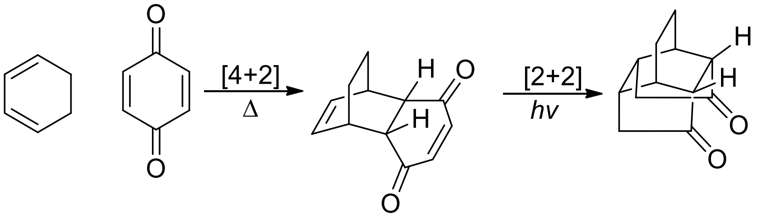

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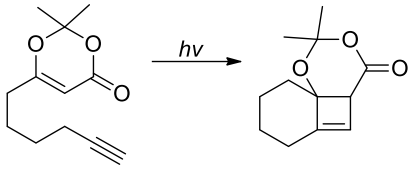

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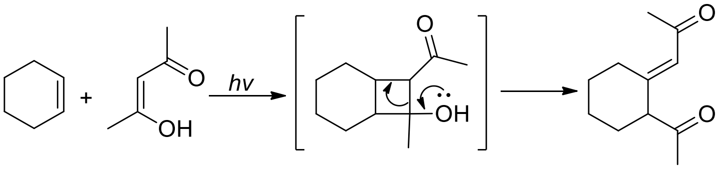

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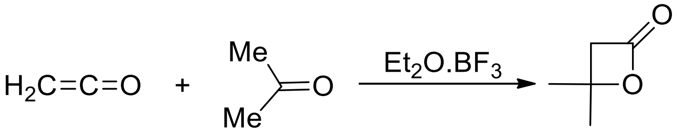

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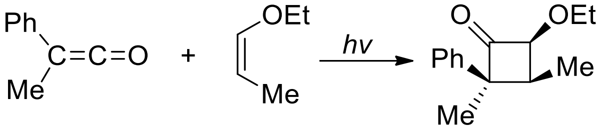
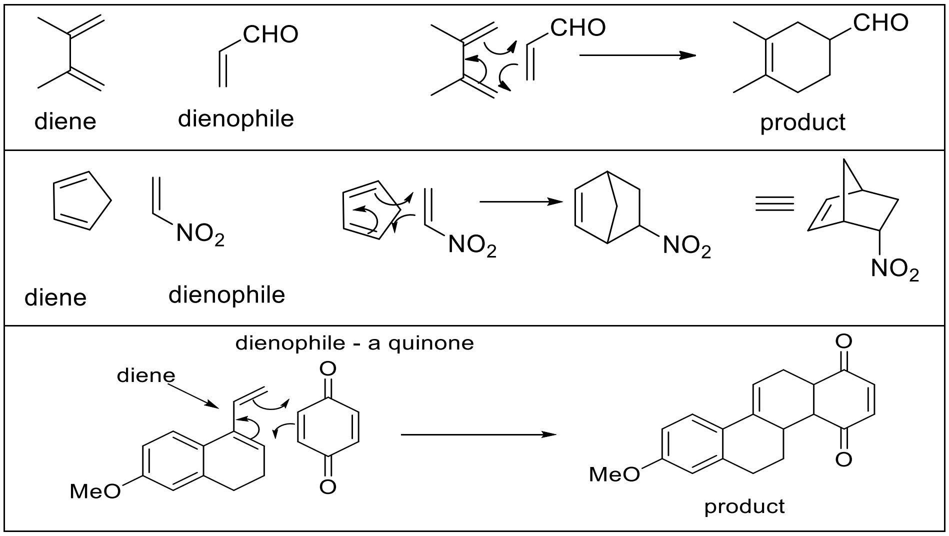


1.3.4.Diels–Alder Reaction or [4+2] Cycloaddition Reaction:

The most important type of thermal [4+2]-cycloaddition reactions is known as the Diels–Alder reaction, as this reaction was discovered by Otto Paul Herman Diels and Kurt Alder in 1928. It may be noted that both of them awarded the Nobel Prize in Chemistry in 1950 for their contributions on the development of the Diels– Alder reaction.

These reactions are defined as the concerted [4+2]-cycloaddition reactions of conjugated dienes with an alkene or alkyne. The alkene or alkyne is known as dienophile. Hence, these reactions are described as [π^4+π^2]-cycloaddition reactions.

These reactions are carried out by heating the compounds alone or in an inert solvent or in the presence of a Lewis acid. An alkene or alkyne having electron-withdrawing substituent acts as an effective dienophile. These reactions proceed stereospecifically to syn-addition with respect to both diene and dienophile.



I. Regioselectivity of Dies-Alder Reaction:

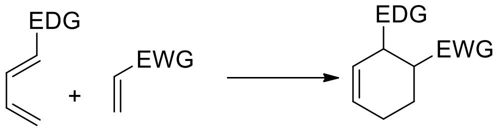
Regioselectivity of Diels–Alder reaction depends on the position of substituents in both diene and dienophile. Usually four types of D–A reactions are observed. This regioselectivity of Diels–Alder reactions can be interpreted on the basis of electron density at C-4 of the diene and C-2 of the dienophile.

For dienes with electron-releasing groups at C-1, HOMO has its largest electron density (largest HOMO orbital coefficient) at C-4. For dienophiles with electron-accepting substituents, C-2 has minimum electron density (largest LUMO orbital coefficient) in their LUMO.

Hence, the strongest frontier orbital interaction occurs between C-4 of the diene and C-2 of the dienophile in a normal electron demand D–A reaction to give 'ortho'-like product.

Similarly, in other type of normal Diels–Alder reactions, dienes with electron-releasing groups at C-2 have the largest electron density at C-1 in their HOMO. Therefore, the strongest frontier orbital interaction occurs between C-1 of the diene and C-2 of the dienophile to give 'para'-like product as major product.

Type A:



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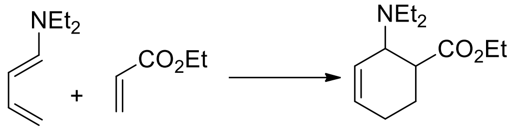

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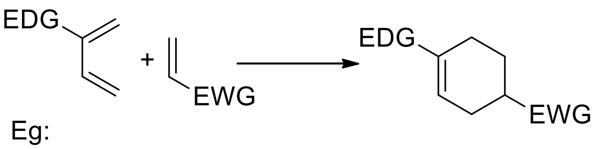

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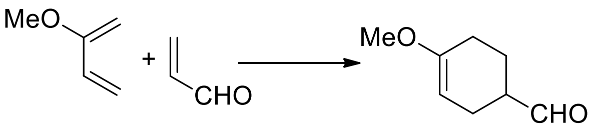
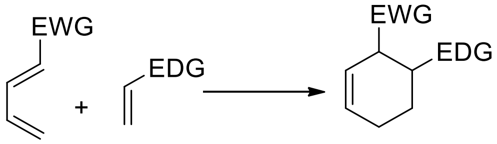


Type C:



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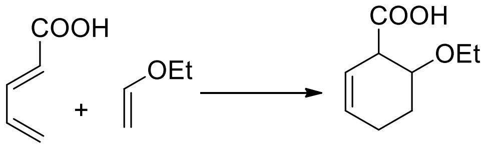
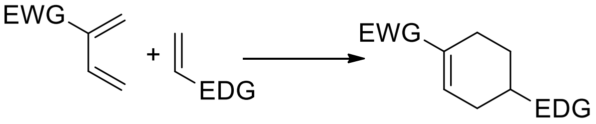
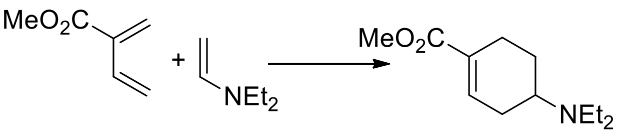


Type D:



Eg:



EDG=Electron- donating group , EWG=Electron- withdrawing group

EDG= alkyl , aryl,RO , Me_3SiO,R_2N

EWG=CHO,COR, CO_2H,CO_2R,CN,NO_2,halogen,alkenyl,aryl

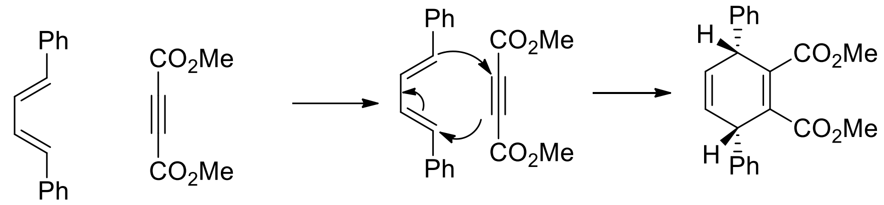
II. Stereochemistry in Dies-Alder Reaction:

- The Diels–Alder reaction is stereospecific.
- If there is stereochemistry in the dienophile, then it is retained in the product.
- Thus, *cis* and *trans*dienophiles give different diastereoisomers of the product.
- Esters of maleic and fumaric acids provide a simple example.

Stereochemistry of Diene:

With a *trans*, *trans*-diene we simply exchange the two sets of substituents, in this example putting Ph where H was and putting H where the bridging -CH2 group was.

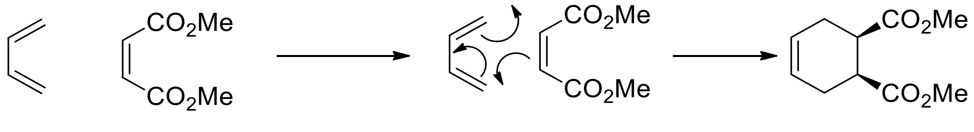
This is the reaction.



The remaining case—the *cis*, *trans*-diene—is rather than the first two, but is met sometimes.

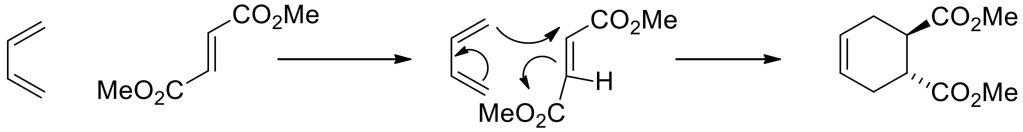
This is the unsymmetrical case and the two substituents clearly end up on opposite sides of the new six membered ring.

1.



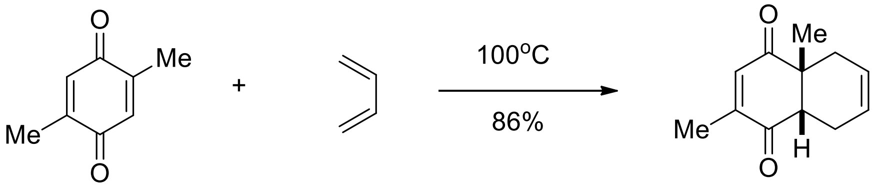
dimethyl maleate

2.



dimethyl fumarate

3.



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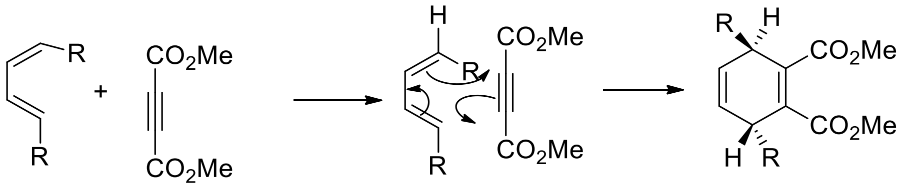
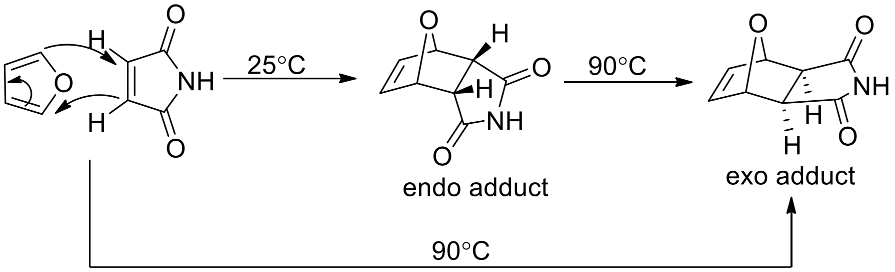


III. The *Endo* Rule for the Diels–Alder Reaction:

The D–A reaction of a cyclic diene with a cyclic dienophile may give two stereoisomeric products, endo- and exo-products depending on the conformation of the transition states.

The product in which the unsaturated substituents of the dienophile are cis to the double bond of the newly formed cyclohexene ring is called the endo-product, whereas in the product, where these substituents are trans to the double bond is called the exo-product. For example, furan on reaction with succinimide gives endo- and exo-products respectively, at different reaction conditions.

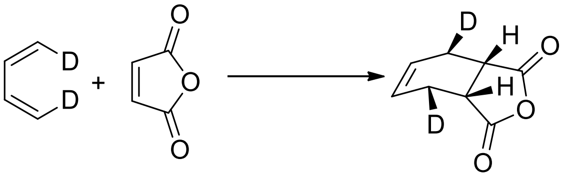


Therelativeorientationsofthedieneanddienophileina favorable TSforaDiels– Alder reaction is predicted by Alder's endo-rule.

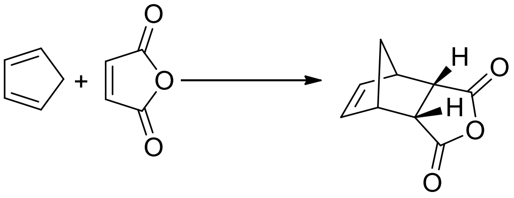
The Alder's endo-rule states that for Diels–Alder reactions of substituted butadiene derivatives with dienophiles having an electron withdrawing substituent, kinetically controlled endo-TS will be preferred over exo-TS because of secondary orbital interactions of the electron-withdrawing substituent with the butadiene π-system. The endo-TS has lower activation energy than that of exo-TS.

The product derived from endo-TS is called kinetically controlled product and the product derived from exo-TS is called thermodynamically controlled product. Frequently a mixture of both stereoisomers is formed and sometimes the thermodynamically controlled exo-product predominates.

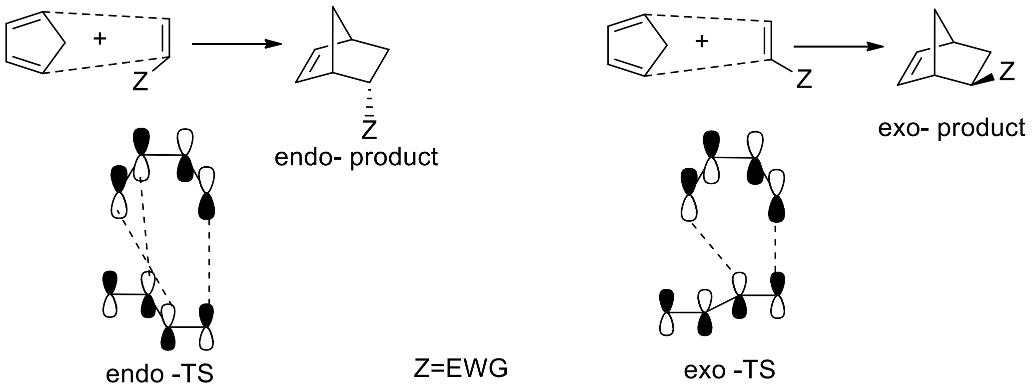
It has been observed that reaction of butadiene with maleic anhydride using deuterium-labeled but a diene gives 85 % of the endo-product.

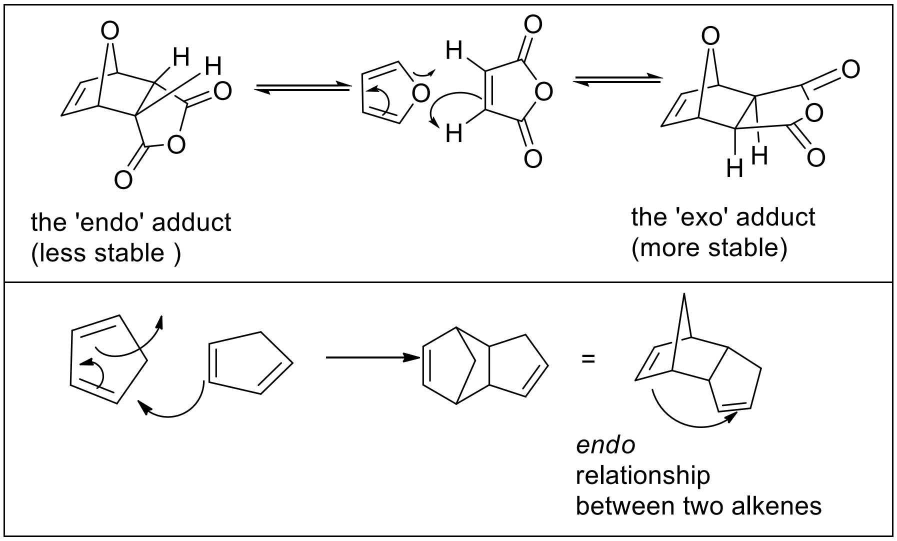


The reaction of cyclopentadiene with maleic anhydride also gives 97.5 % endo-product.



The secondary orbital interactions in preferred endo-TS are shown in below figure:



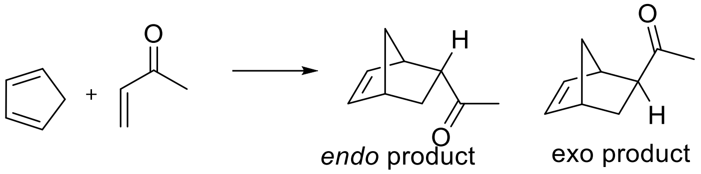


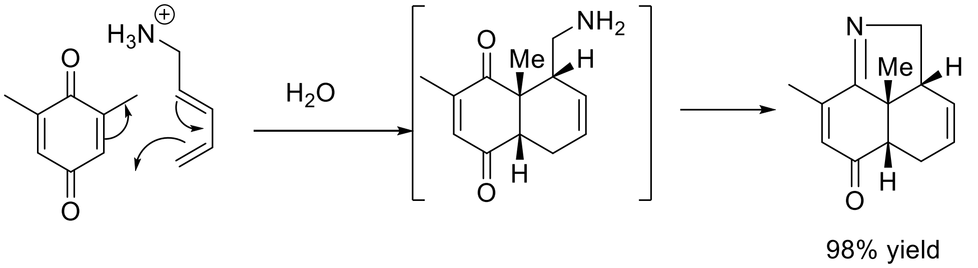
IV. Solvent in the Diels–Alder Reaction:

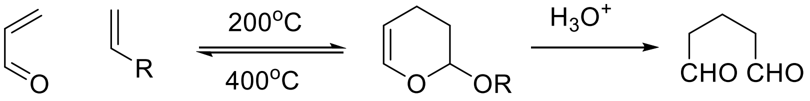
Water, a most unlikely solvent for most organic reactions, has a large accelerating effect on the Diels–Alder reaction. Even some water added to an organic solvent accelerates the reaction.

The *endo* selectivity of these reactions is often superior to those in no solvent or in a hydrocarbon solvent.

Solvent	**Relative rate**	***Endo: exo* ratio**
Hydrocarbon (isooctane)	1	80:20
Water	700	96:4







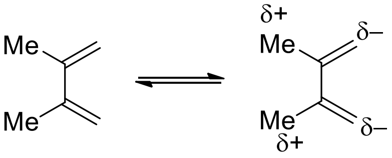
V. Substituent Effects on the Reaction Rates:

i. Steric Effects of Substituents:

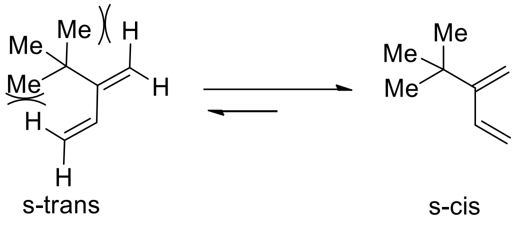
Diels–Alder reactions are sensitive to steric effects. The presence of bulky substituents on the dienophile or on the diene hinders the approach of the components to each other and decreases the rate of reaction.

2,3-Dimethylbutadiene reacts with maleic anhydride about ten times faster than butadiene due to electron-releasing effect of the methyl group.

2-tert-Butyl-1,3-butadiene is 27 times more reactive than butadiene toward maleic anhydride because the tert-butyl group favors the s-cis conformation due to high 1,3-steric interaction in the s-trans conformation.



The presence of two bulky substituents at C-1 position of a diene prevents the adoption of s-cis conformation of the diene and decreases the reaction rate. For example, 4-methyl-1,3-pentadiene is about 1000 times less reactive than trans1,3-pentadiene toward tetracyanoethene.

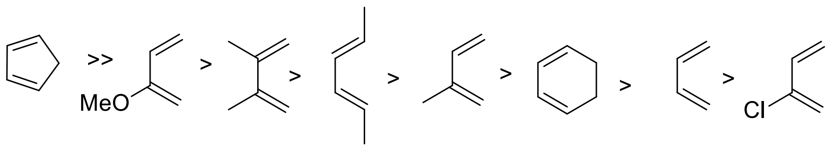


Usually cyclic dienes such as cyclopentadiene and ortho-quinodimethane are more reactive than open-chain dienes because of their **s-cis** conformations.

ii. Electronic Effects of Substituents:

In electron-demand Diels-Alder reactions, dienes are activated by electron-donating substituents, such as alkyl, $-NR_2$ and -OR.

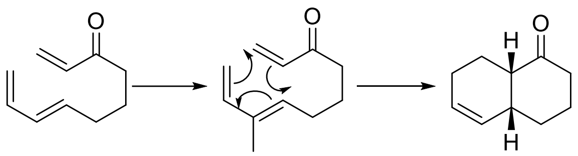
Electron-rich dienes accelerate the reaction with electron-deficient dienophiles, as illustrated by the relative reactivity trend.



VI. Intramolecular Diels–Alder Reactions:

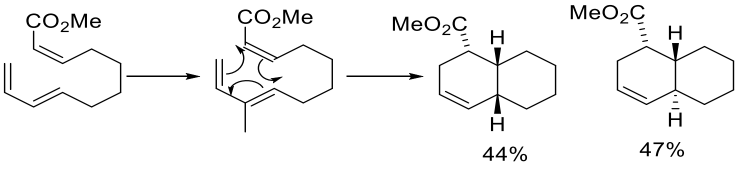
When the diene and the dienophile are already part of the same molecule it is not so important or them to be held together by bonding interactions across space and the *exo*-product is often preferred.

If carbonyl group conjugated with the dienophile. The less stable *cis* ring junction is formed because the molecule can fold so that the carbonyl group can enjoy a bonding overlap with the back of the diene. This time the linking chain has to adopt a boat-like conformation.

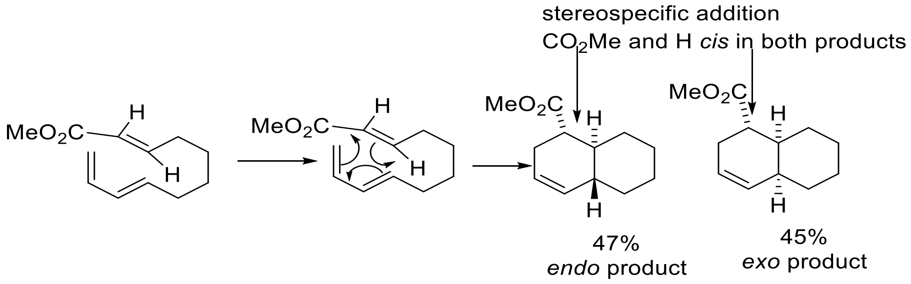


On the other hand, we give the dienophile a conjugating group at the other end of the double bond, stereoselectivity is lost.

stereospecific addition
CO_2Me and H trans in both
products



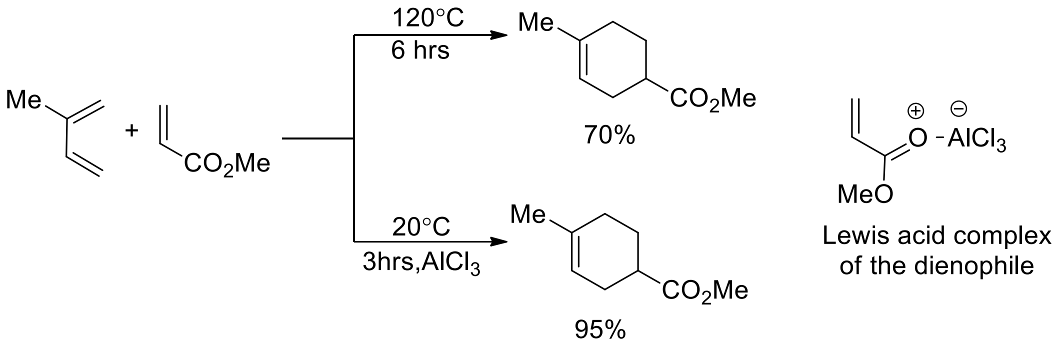
The *trans*-alkene, two products are formed and both retain the *tran-s*geometry of the dienophile. But once again a nearly 50:50 mixture of *endo* and *exo*products is formed.



VII. Lewis Acid-Catalyzed Diels–Alder Reactions:

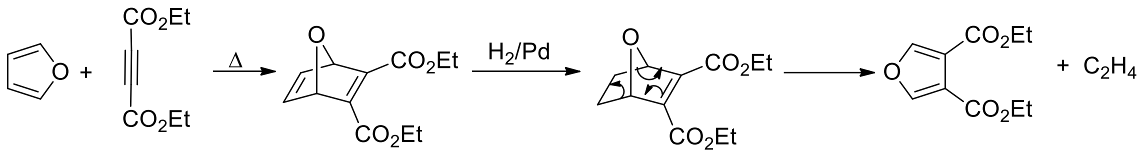
Lewis acids such as $ZnCl_2$, $SnCl_4$, $AlCl_3$, derivatives of $AlCl_3$, Me_2AlCl, and Et_2AlCl act as effective catalysts to accelerate the rates of Diels–Alder reactions by increasing the electron-withdrawing capacity of the dienophiles via the formation of Lewis acid complex.

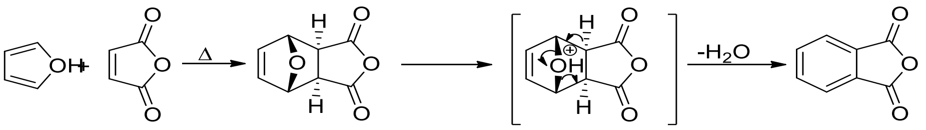
For example, the reaction of 2-methyl-1,3-butadiene with methyl acrylate takes place at room temperature and in the shorter time (3hrs) in the presence of $AlCl_3$ compared to uncatalyzed reaction, which occurs on heating at 120 °C for 6 h.



VIII. The Retro Diels–Alder Reaction:

Diels–Alder reactions are reversible, and many adducts dissociate into their components on heating.More interesting arereactions in which the original adduct is modified chemically and subsequently dissociated to yield a new diene or dienophile.





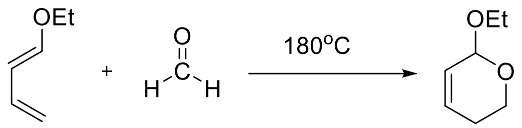
IX. Heterodienophiles:

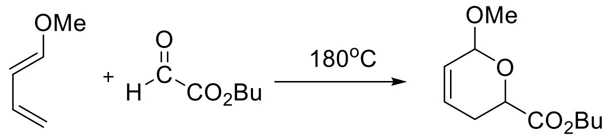
Dienes and dienophiles with a heteroatom such as N, O, or S in their π systems are known as heterodienes and heterodienophiles, and their cycloaddition reactions are called the hetero-Diels–Alder reactions.

The Diels–Alder reaction is by no means restricted to the all-carbon variant. No significant loss of reactivity is encountered when one or both of the atoms of the dienophile multiple bond with a heteroatom.

Carbonyl groups in aldehydes and ketones add to 1,3-dienes and the reaction has been used to prepare derivatives of 5,6-dihydropyrans.

Formaldehyde reacts only slowly but reactivity increases with reactive carbonyl compounds bearing electron-withdrawing groups, such as glyoxylate derivatives.

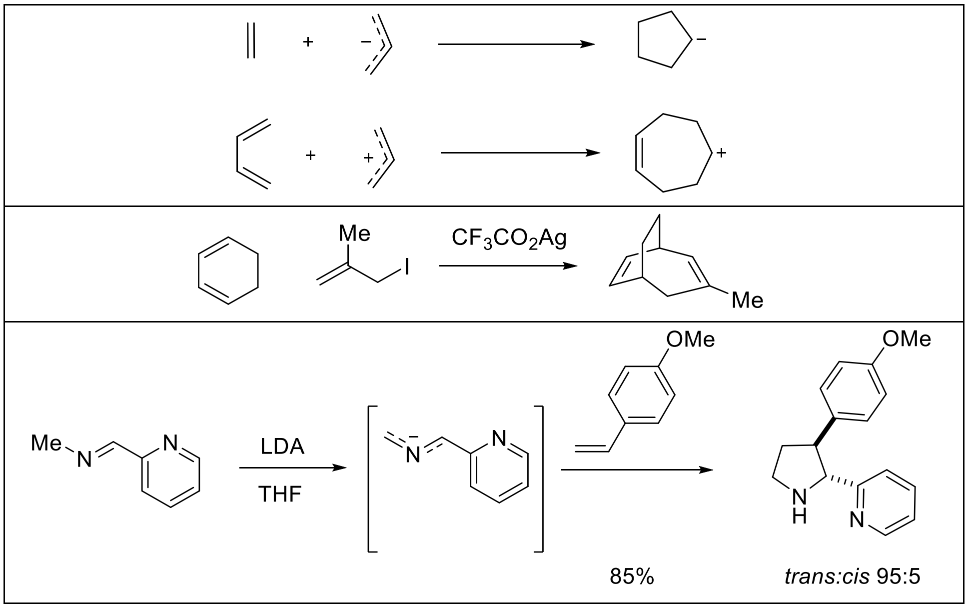




X. Cycloaddition Reactions with Allyl Anions and Allyl Cations:

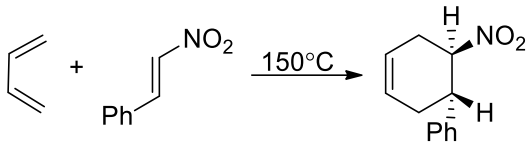
Several allyl cations can serve as dienophiles and allyl anions and pentadienyl cations as dienes in Diels–Alder cycloadditions.

The possibility of analogous six π-electron cycloadditions involving allyl anions and allyl cations to give five- and seven-membered rings respectively is predicted by the Woodward– Hoffmann rules.



XI. Examples:

1.



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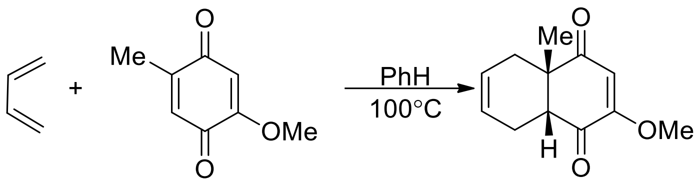

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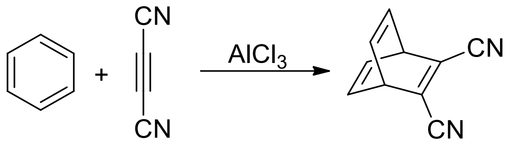

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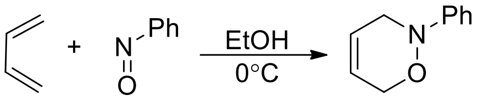

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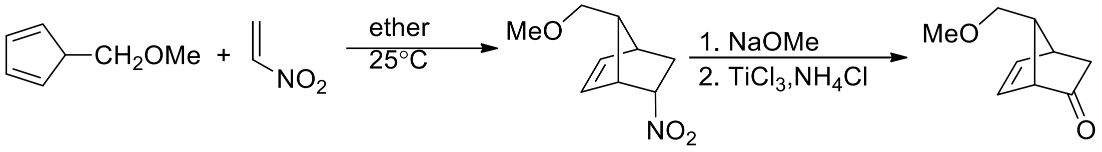

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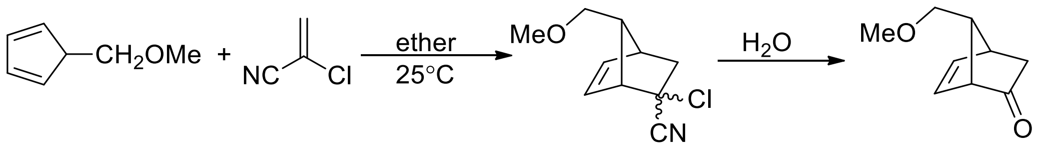

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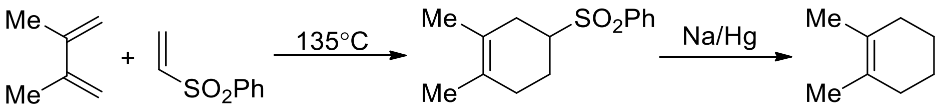

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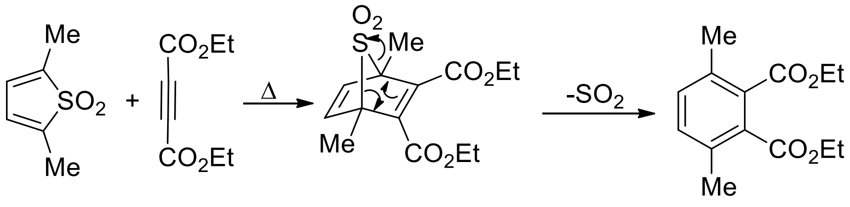

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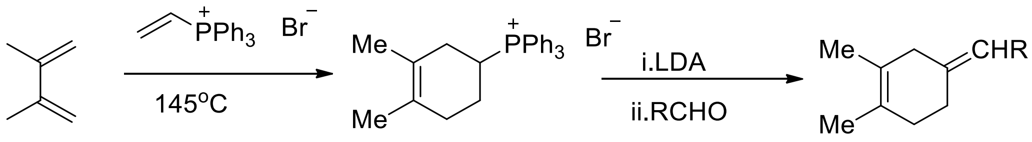

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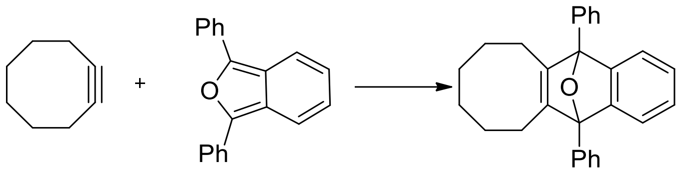

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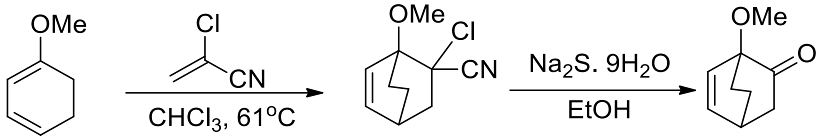

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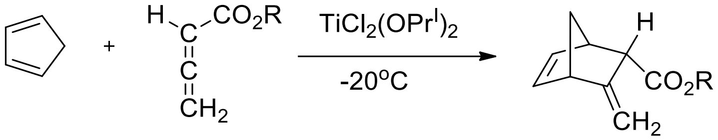

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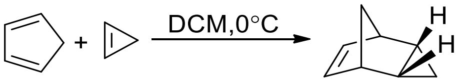

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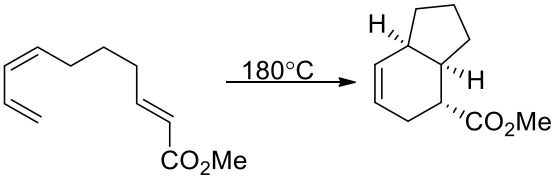

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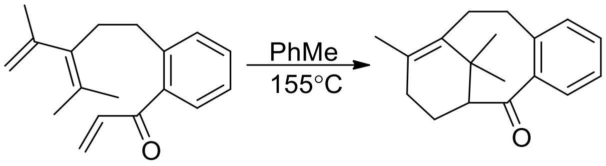

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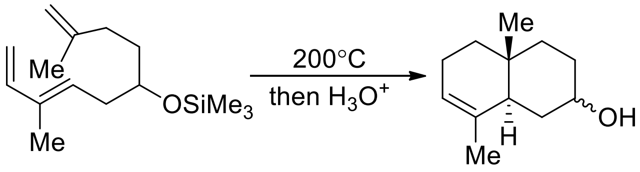

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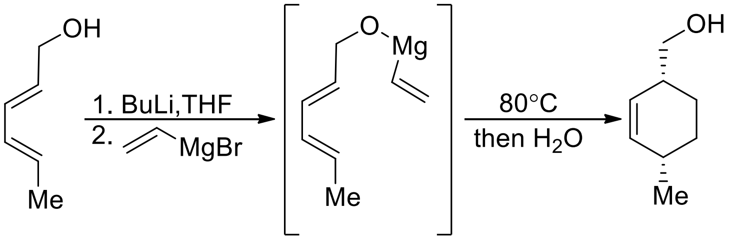
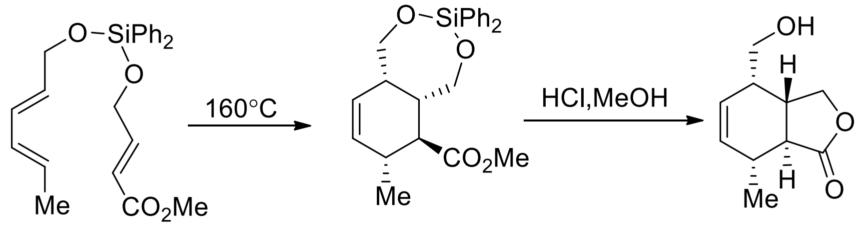
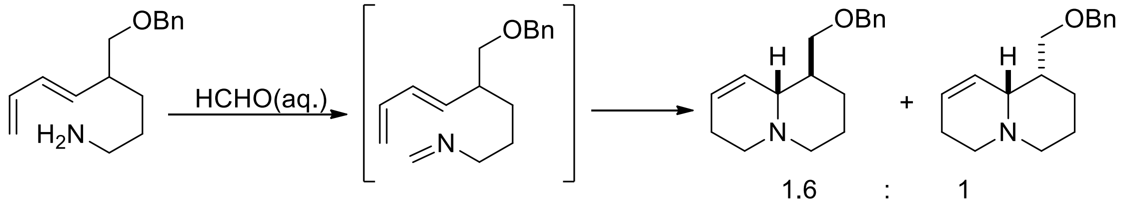
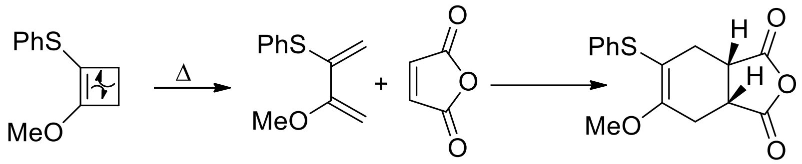
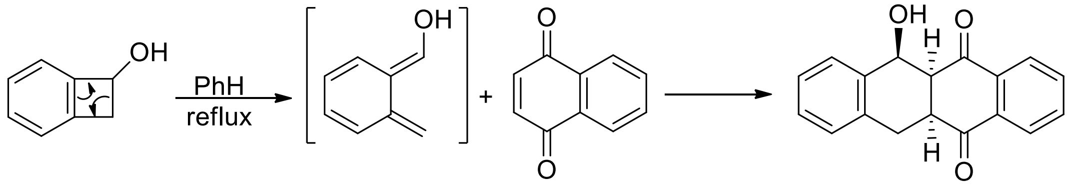
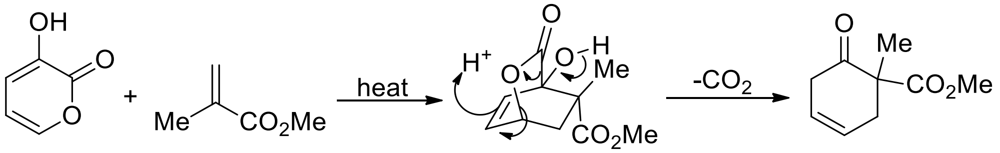


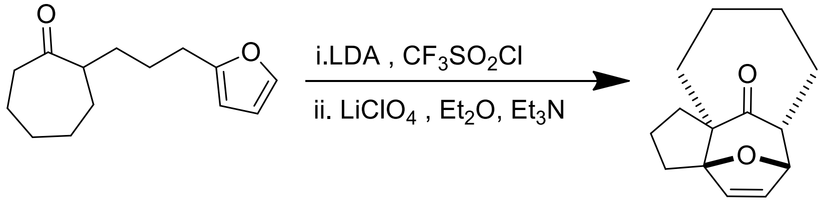
18. 

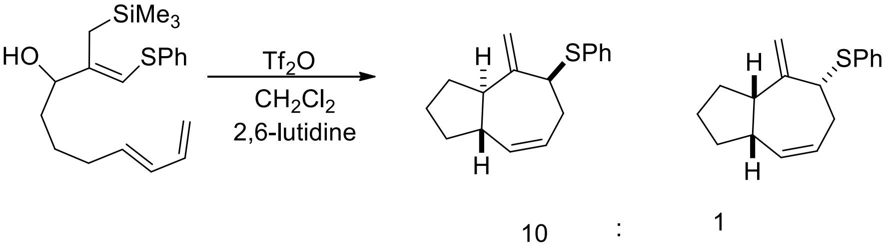
19. 

20. 

21. 

22. 

23. 

24. 

25.