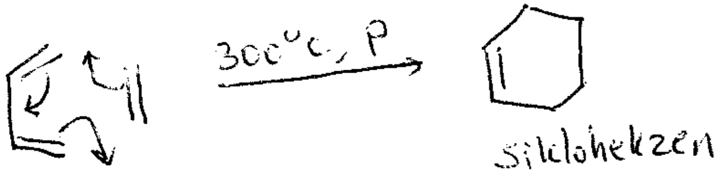
BÖLÜM 6: PERİSİKLİK REAKSİYONLAR

Bütün Sentetik yöntemler içerisinde sentezlerde perisiklik reaksiyonlar çok önemlidir. Perisiklik reaksiyonların en önemlisi, daha önce bir çok kez karşılaştığımız Diels-Alder Reaksiyonlarıdır. Şimdi bu reaksiyonu biraz daha ayrıntılı inceleyelim.

Diels-Alder reaksiyonu; etilen (alken) ve bütadienin (konjuge dien) ısıtılarak siklohekzene (veya türevine) dönüşmesi reaksiyonudur. (1928'de Alman bilim adamları, Otto Diels ve Kurt Alder tarafından bulunmuştur).



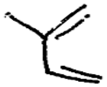
[4 +2] katılması

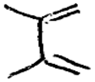
Bu reaksiyonda, alken'e "dienofil", konjuge diene ise, "dien" denir.

Bazı dien ve dienofiller :

Dienler :
(4n e⁻)


Bütadien

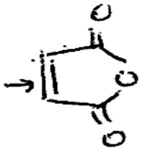

izopren

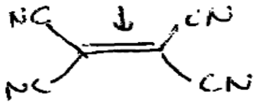

2,3-dimetil bütadien

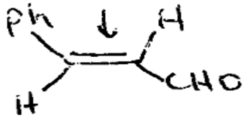

siklopentadien

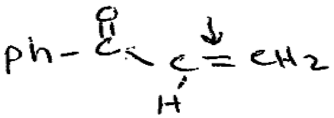

siklohekzadien

Dienofiller :
(2n e⁻)

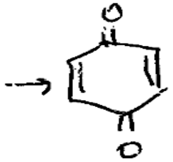

Maleik anhidrit


tetrasiyano etilen


Sinnam aldehit


$Ph-\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{\downarrow}{C}}=CH_2$

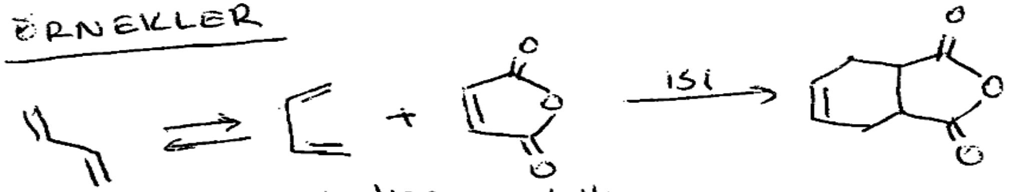
Benzoiletilen


Kinon

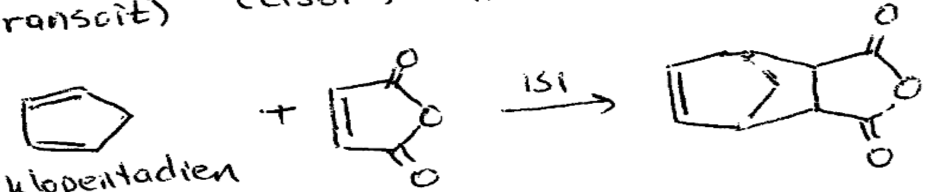
$ROOC-\overset{\downarrow}{C}\equiv C-COOR$

Dikarboalkoksi-asetilen

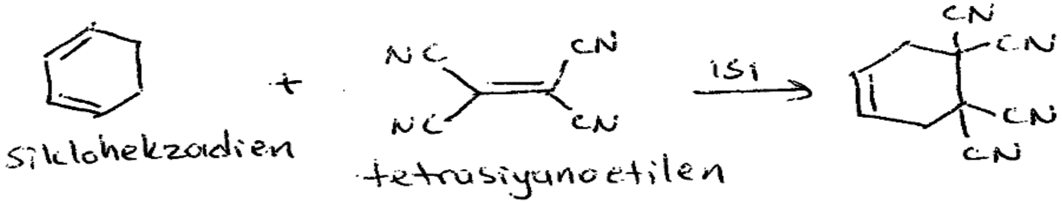
ÖRNEKLER

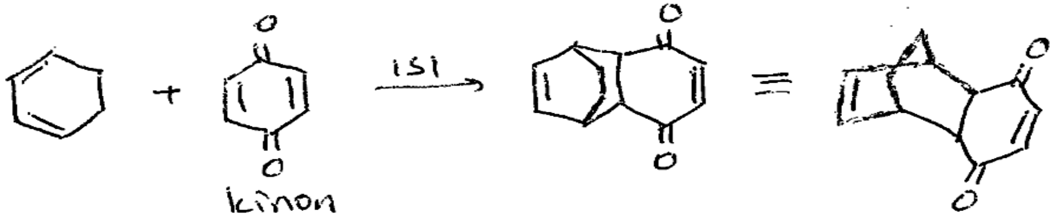


Bütadien (transoit) — Bütadien (cisoit) — maleik anhidrit

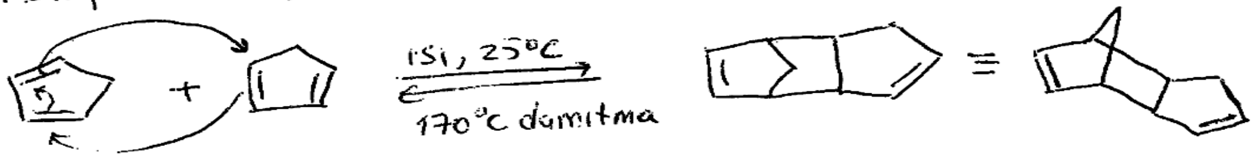


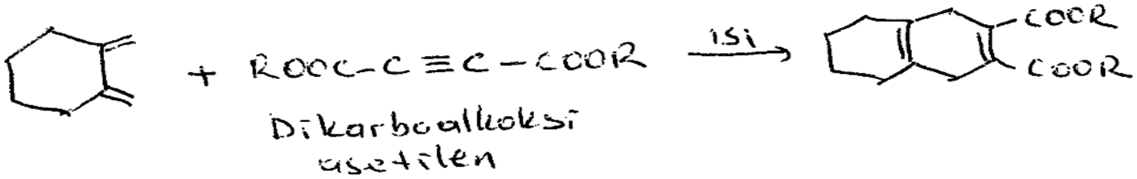
siklopentadien

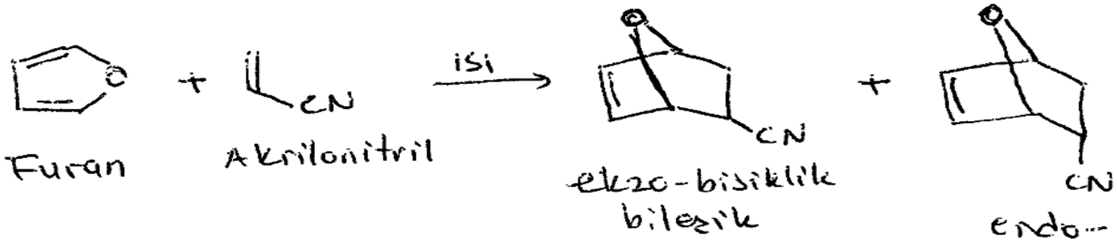


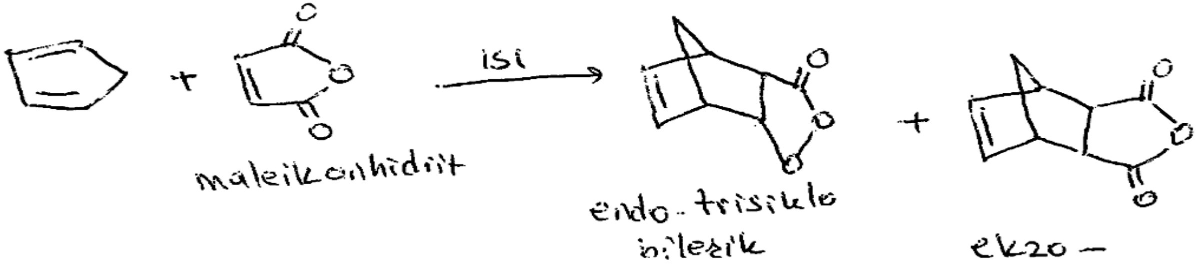


Siklopentadien, hem dien hem de dienofil olarak etkindir:







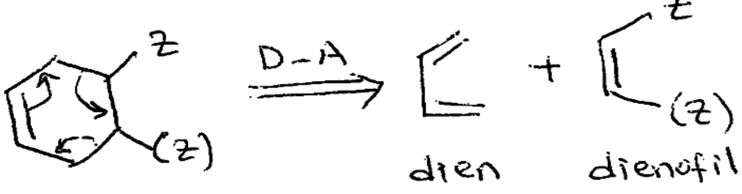


Diels-Alder reaksiyonunda katolizör gerekmez, ısı enerjisi yeterlidir. Ara ürün oluşmaz, bu tür reaksiyonlara "uyumlu reaksiyon (concerted reaction)" denir.

Dienofil (dien seven), dienin elektronlarını aldığı için elektrofil olarak düşünülebilir. Elektron çekici (-CN, -COOR, -NO_2 gibi) gruplar bağlandığında etkinleşir.

Dien, elektron(lar) saldığı için nükleofil gibi düşünülebilir. Elektron salıcı gruplar bağlandığında etkinliği artar.

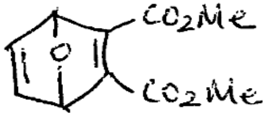
Şimdi Diels-Alder reaksiyon ürünlerindeki parçalanmayı ve sentez tasarımını örnekler üzerinde analiz edelim:



Z = COR, CO_2Et
CN, NO_2 gibi
elektron çekici
gruplar

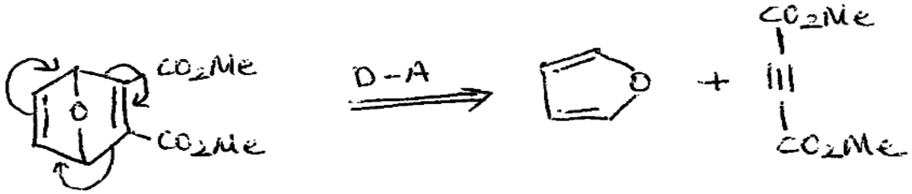
Örnekler

1. Aşağıdaki Diels-Alder ürününü (TM 1) nasıl yaparsınız?



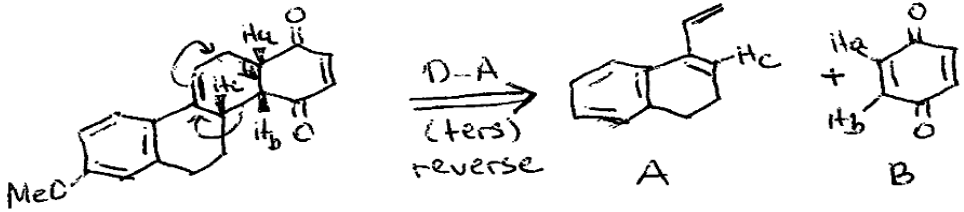
(TM 1)

Analizi : Çözüm oldukça basittir. Diels-Alder reaksiyonunun tersi yapılır.



Sentezi : Her iki çıkış maddesi de kolaylıkla hazırlanarak reaksiyona sokulur.

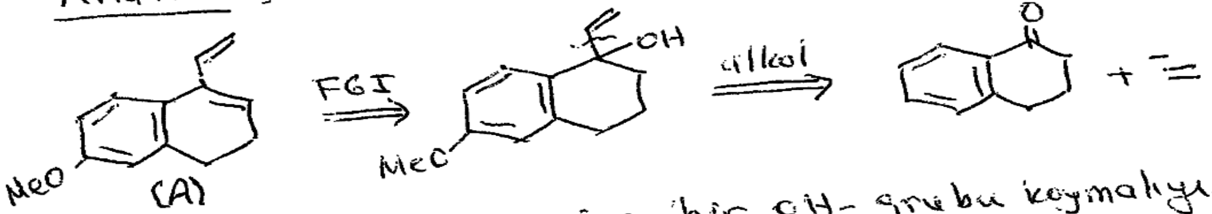
Örnek 2 : (TM2) bileşiğini nasıl yaparsınız?



Burada, stereokimyasal analizlerden de reaksiyonun doğru yazıldığı anlaşılabilir. Başlangıç maddesindeki (kinon) Ha ve Hb hidrojen atomları, cis- pozisyonundadır. B yapısındaki Ha ve Hb ile A daki Hc protonları da başlangıç maddesiyle aynıdır yani cis-'dir. Bu bakımdan, Diels-Alder reaksiyonu stereospesifik ve stereoselektifdir. [cis- ve trans- ürünler yerine sadece cis- ürün olduğunun stereoözgü (Stereospesifik) ve stereseçici (stereoselektif)].

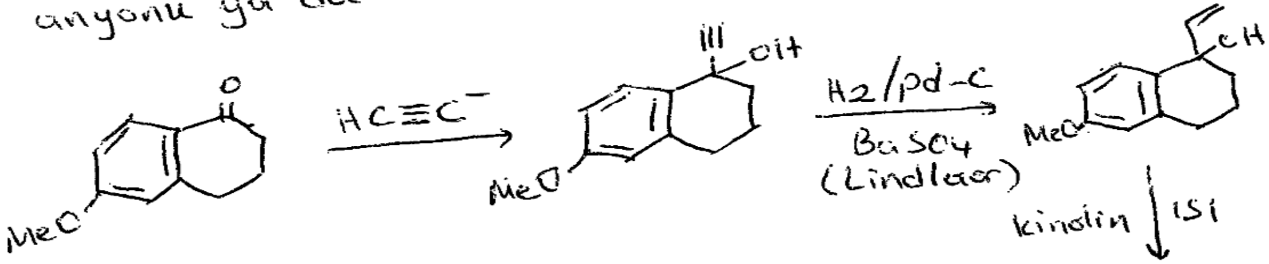
Örnek 3: Bir önceki sorudaki A dienini nasıl sentezlersiniz.

Analiz:



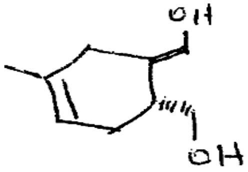
Öncelikle, çift bağ yerine bir OH- grubu koymalıyız. Bunun için en uygun yer, dallanmanın başladığı noktadır.

Sentezi: Vinil anyon synthonu (⁻=) asetilenür anyonu ya da vinil Grignard reaktifi olabilir.



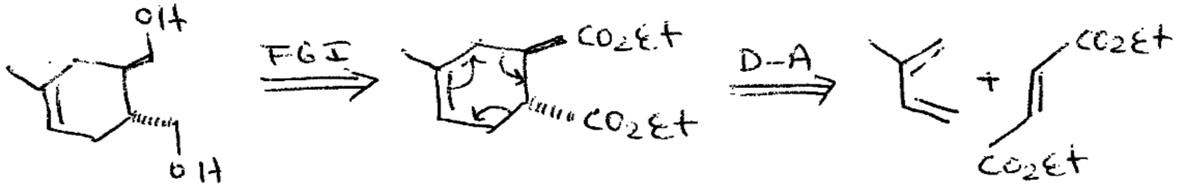
(TM2A)

Örnek 4: TM(4) bileşiğini, farklı bir fonksiyonlu grup kullanarak (FGI) sentezleyiniz. Stereokimyasal özelliğe dikkat ediniz!



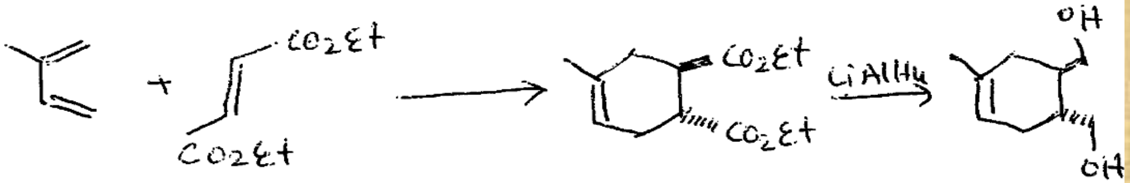
(TM4)

Örnek 5:



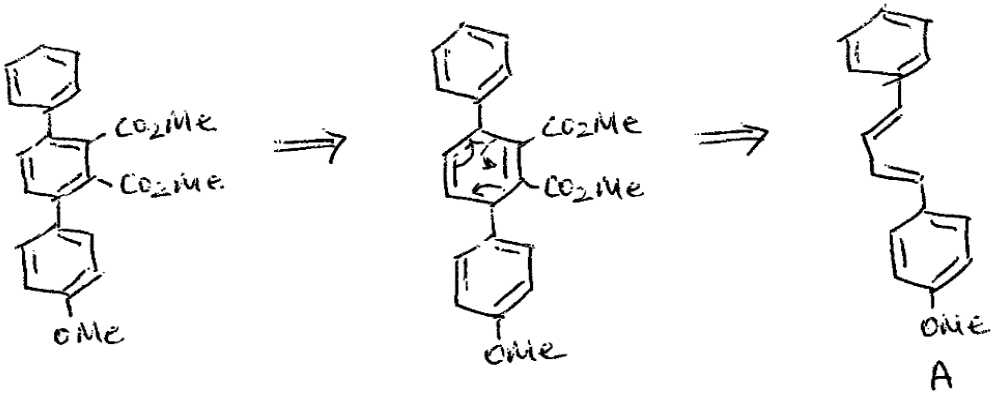
Öncelikle, uygun bir karbonil grubu bulunur.

Sentezi: Stereokimya açıdan uygun ester fumarat olmalıdır ki, katılma doğru olsun.



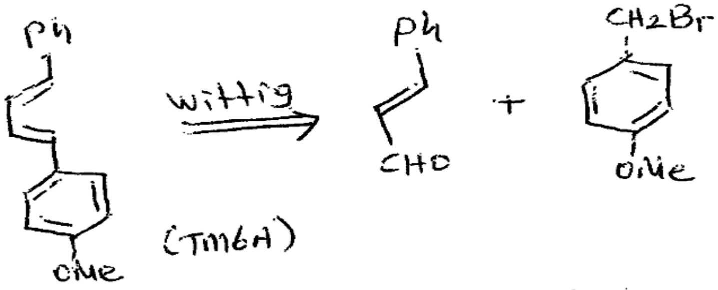
Örnek 6: TM (6), asimetrik terfenil bileşiğini nasıl yaparsınız?

Analiz: Merkez halkada elektron çekici gruplar olduğundan, D-A reaksiyonu buradan başlar:



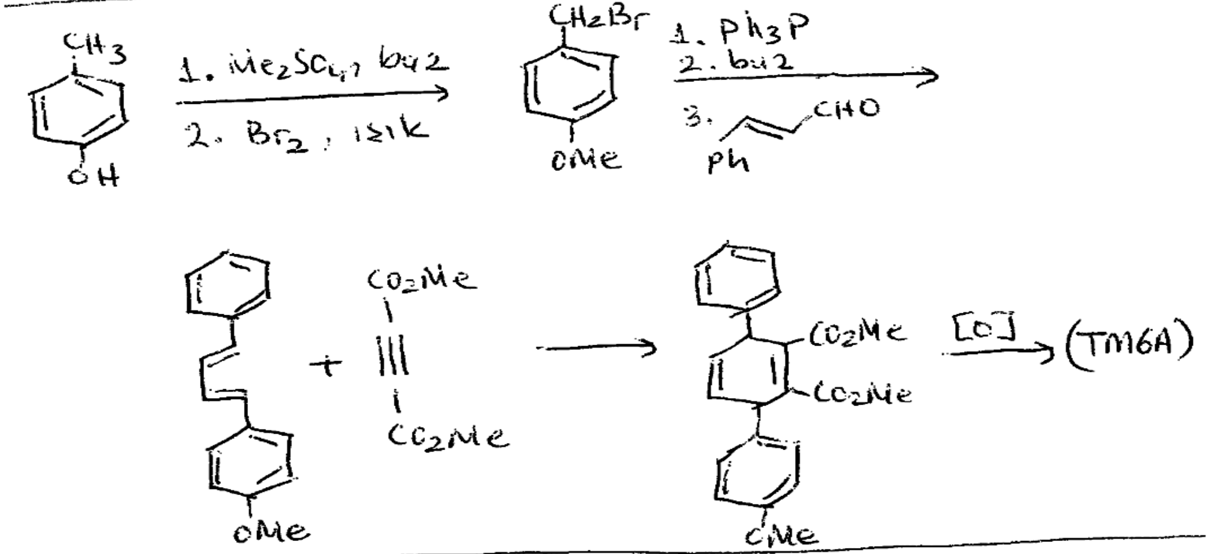
Örnek 7: Örnek 6'daki (TM6A) bileşiğinin Sentez tasarımını yapınız.

Analiz: wittig parçalanması, kolay hazırlanabilecek iki reaktif verecektir.

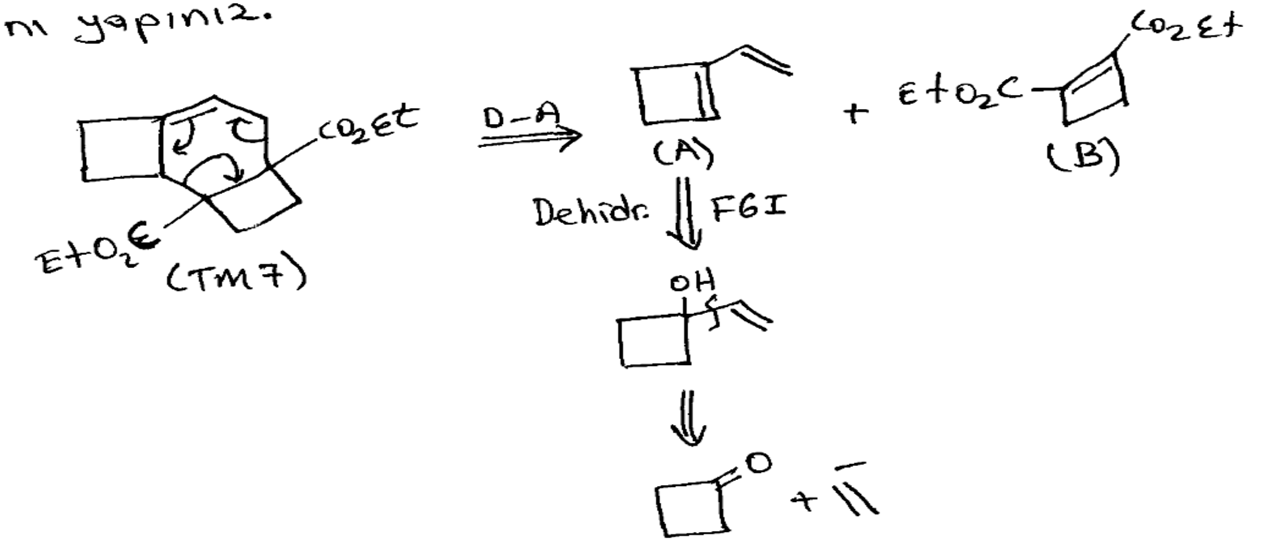


Aldehit, Sinnamaldehitten kolayca hazırlanabilir, 4-metoksi benzil bromür bileşiği de p-krezolden hazırlanabilir:

Sentezi:



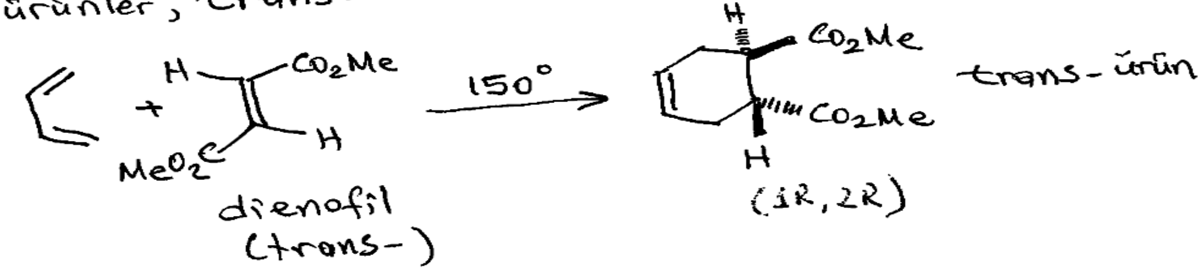
örnek 8 : Aşağıdaki bileşiğin TM(7) sentez tasarımını yapınız.

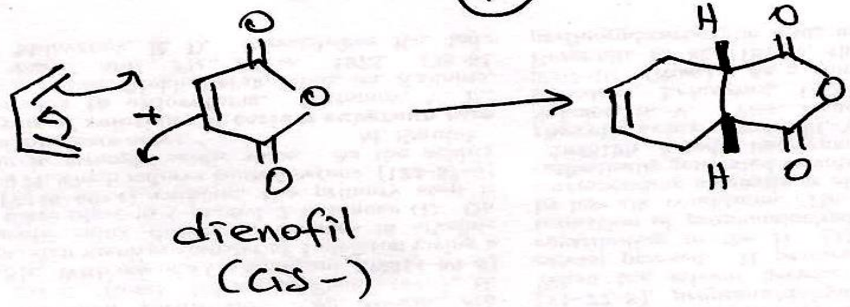


Sentezi : (A) + (B) $\xrightarrow{\text{ısı}}$ TM(7)

- stereospesiflik (stereoözgü) ve stereoselectivity (stereoseçicilik) :

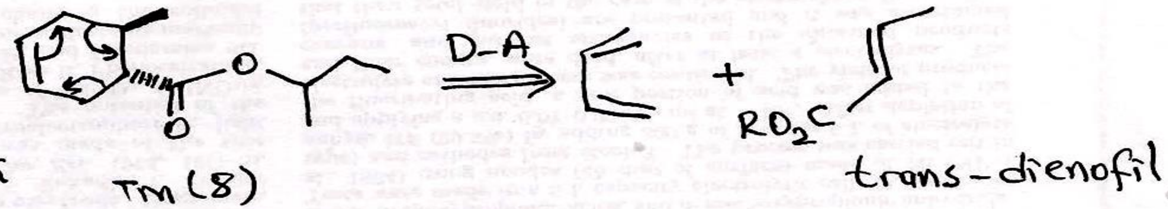
Reaksiyon bir basamakta olur böylece ne dien ne de dienofil dönmeye zaman bulamaz. cis-dienofiller cis-ürünler, trans-dienofiller trans ürünler verir.





Örnek 9: Aşağıda sentetik bir çekici olan ve Akdeniz meyve sinekleri için yem olarak kullanılan "Siglure" TM(8) bileşiğinin sentezini yapınız.

Analizi:



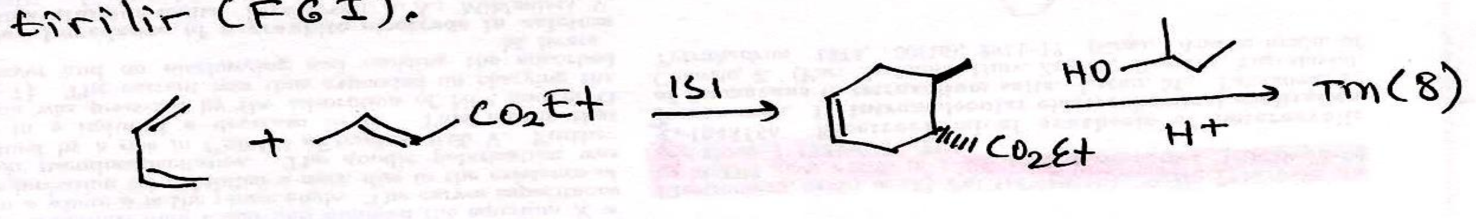
Yapıda trans-ilişki var.

TM(8)

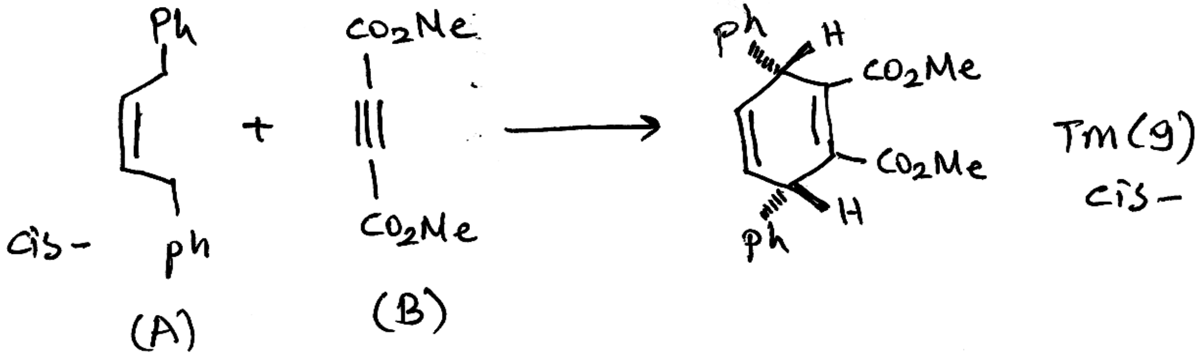
trans-dienofil

Sentezi: N. Green, M. Beroza and S. A. Hall, Adv. Pest. Control Res., 1960, 3, 129; pesticides, p. 196.

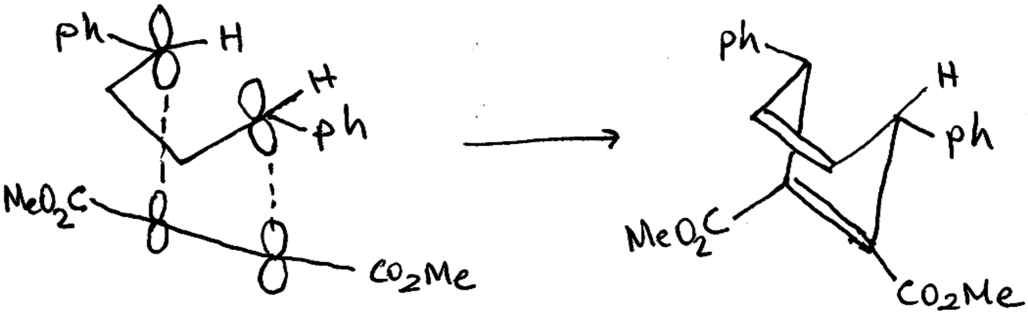
Üretimi çok kolaydır. Ucuz olan etil esterden çıkılır, D. A reaksiyondan sonra daha karmaşık olan alkolle değiştirilir (FGI).



Dienin stereokimyası tamamen ürüne de aktarılabili
örneğin, Tm(g), dien (A) ve asetilenik dienofilden
elde edilirken cis-ürün verir.

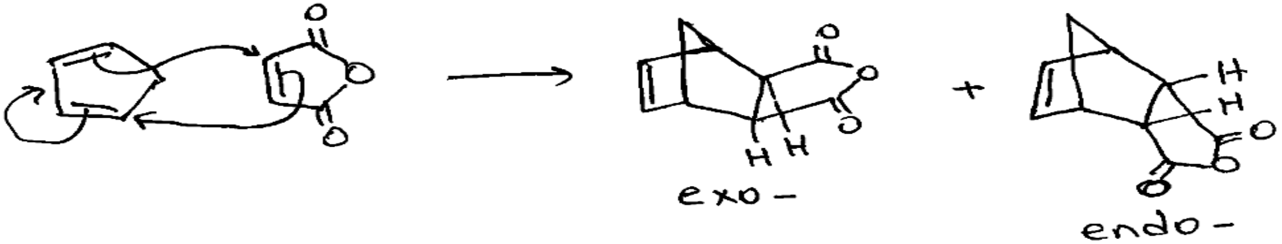


Bunun sebebi, iki reaktif (A ve B) reaksiyon vermek üzere, birbirine göre paralel olacak şekilde (paralel düzlem) bir araya gelmesidir.



Paralel düzlemde, p-orbitalleri yeni bir σ bağları vermek üzere (aynı düzlemde) etkileşir.

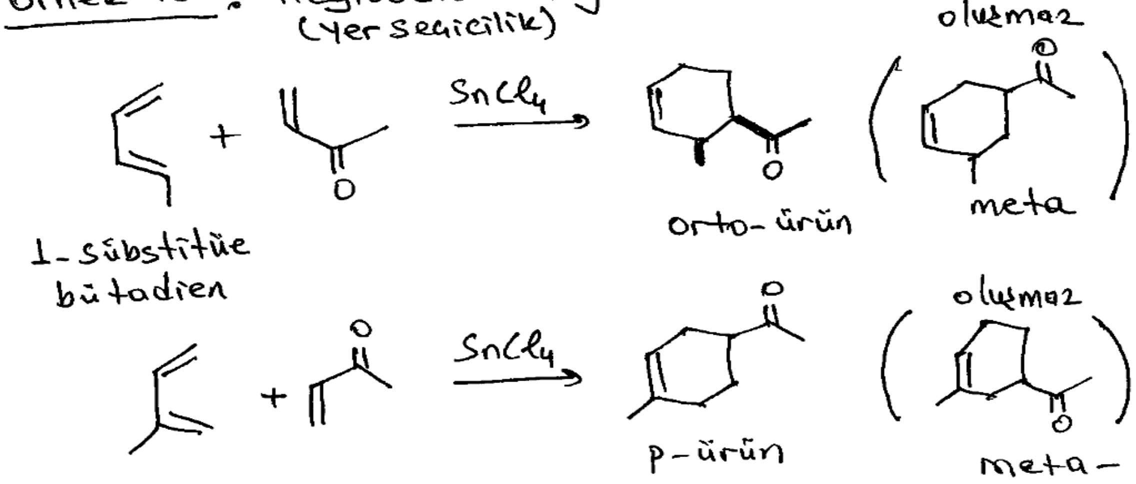
Endo seçicilik (stereoseçicilik bakımından)



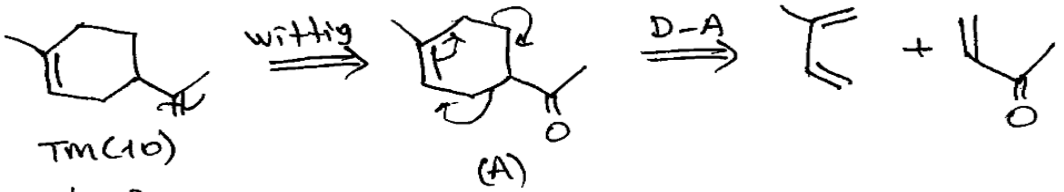
oluşan ürünler, exo- ve endo- olarak adlandırılır. Bu terimler, dienofildeki Z grupları (burada CO) ile oluşan yeni siklohekzen halkasında çift bağ arasındaki ilişkiyi gösterir. Genellikle, endo ürün (kinetik) daha kararlı olan exo ürüne tercih edilir. Burada, elektron çekici Z grubu, dieni endo geçiş basamağına çeker. Bu, etkileşme "ikincil orbital etkileşmesidir" ve bağ oluşumuna gitmez ancak geçiş basamağına yardımcı olur.

• • • → ikincil orbital etkileşmeleri
- - - → Bağ oluşumuna giden etkileşmeler

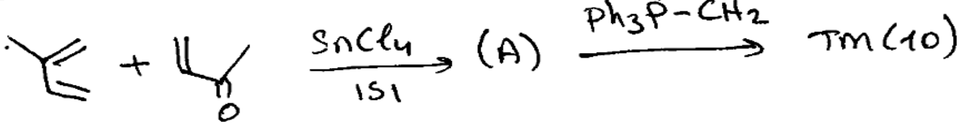
Örnek 10 : Regioselectivity (Yer seçicilik)



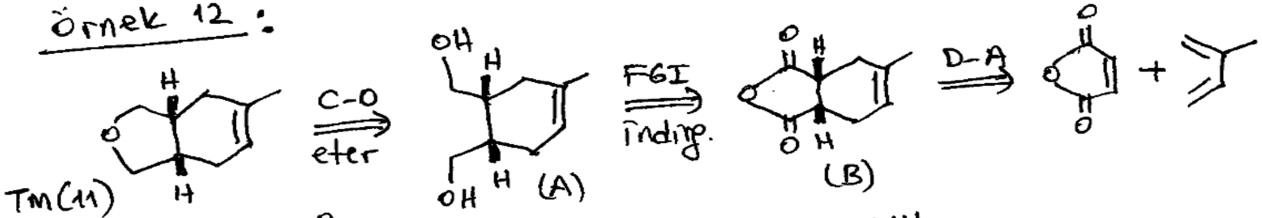
Örnek 11 : Limonen analizi



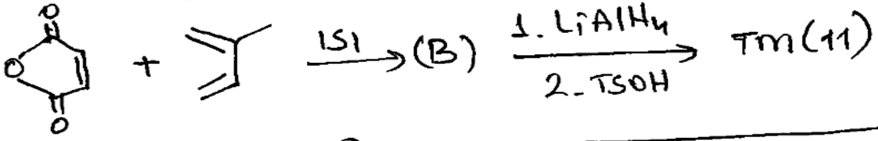
Sentezi



Örnek 12 :



Sentezi :



Pericyclic Reactions

An important body of chemical reactions, differing from ionic or free radical reactions in a number of respects, has been recognized and extensively studied. Among the characteristics shared by these reactions, three in particular set them apart.:

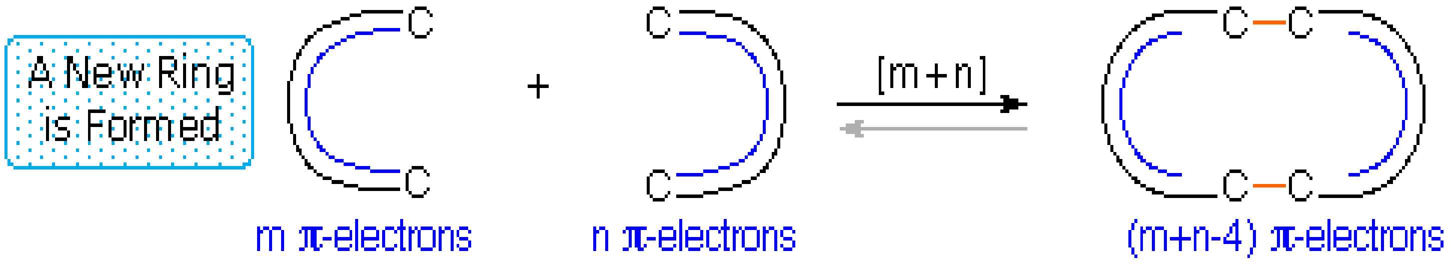
1. They are relatively unaffected by solvent changes, the presence of radical initiators or scavenging reagents, or (with some exceptions) by electrophilic or nucleophilic catalysts.

2. They proceed by a simultaneous or concerted collection of bond breaking and bond making events, often with high stereospecificity.

3. In agreement with **1** & **2**, no discernible ionic or free radical intermediates lie on the reaction path.

Since reactions of this kind often proceed by the simultaneous reorganization of bonding electron pairs by way of cyclic transition states, they have been termed **pericyclic reactions**. The four principle classes of pericyclic reactions are termed: **Cycloaddition**, **Electrocyclic**, **Sigmatropic**, and **Ene Reactions**. A general illustration of each class will be displayed by clicking on the following diagram. Corresponding intramolecular reactions, which create an additional ring, are well known.

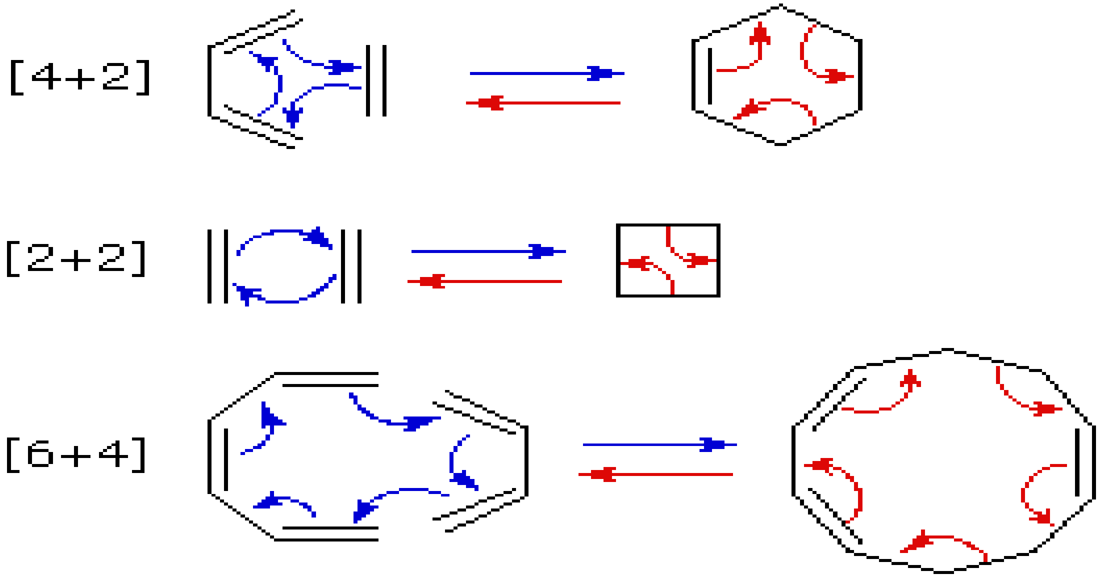
Cycloaddition Reactions



Note that two π-bonds are converted to two σ-bonds

All these reactions are potentially reversible (note the gray arrows). The reverse of a cycloaddition is called **cycloreversion** and proceeds by a ring cleavage and conversion of two sigma-bonds to two pi-bonds. The electrocyclic reaction shown above is a ring forming process. The reverse electerocyclic ring opening reaction proceeds by converting a sigma-bond to a pi-bond. As shown, the retro ene reaction cleaves an unsaturated compound into two unsaturated fragments. Finally, sigmatropic bond shifts may involve a simple migrating group, as shown in the example above, or may take place between two pi-electron systems (e.g. the Cope rearrangement).

Cycloaddition Reactions

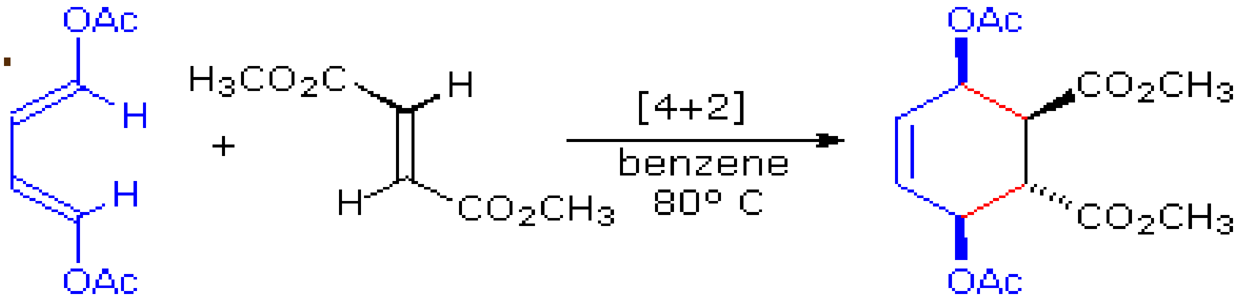


A concerted combination of two π-electron systems to form a ring of atoms having two new σ bonds and two fewer π bonds is called a cycloaddition reaction. The number of participating π-electrons in each component is given in brackets preceding the name, and the reorganization of electrons may be depicted by a cycle of curved arrows - each representing the movement of a pair of electrons.

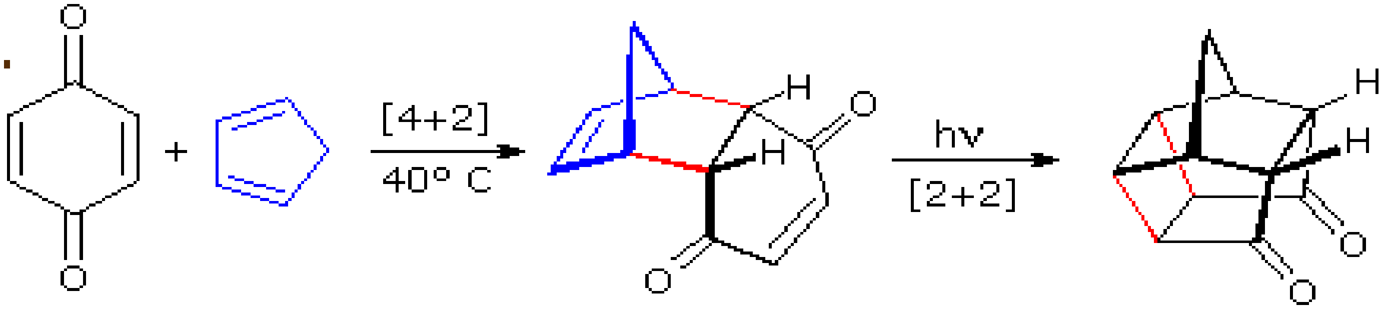
The ring-forming cycloaddition reaction is described by **blue arrows**, whereas the ring-opening **cycloreversion** process is designated by red arrows.

The most common cycloaddition reaction is the [4π+2π] cyclization known as the Diels-Alder reaction. In Diels-Alder terminology the two reactants are referred to as the **diene** and the **dienophile**. The following diagram shows two examples of [4π+2π] cycloaddition, and in the second equation a subsequent light induced [2π+2π] cycloaddition. In each case the diene reactant is colored blue, and the new σ-bonds in the adduct are colored red.

1.

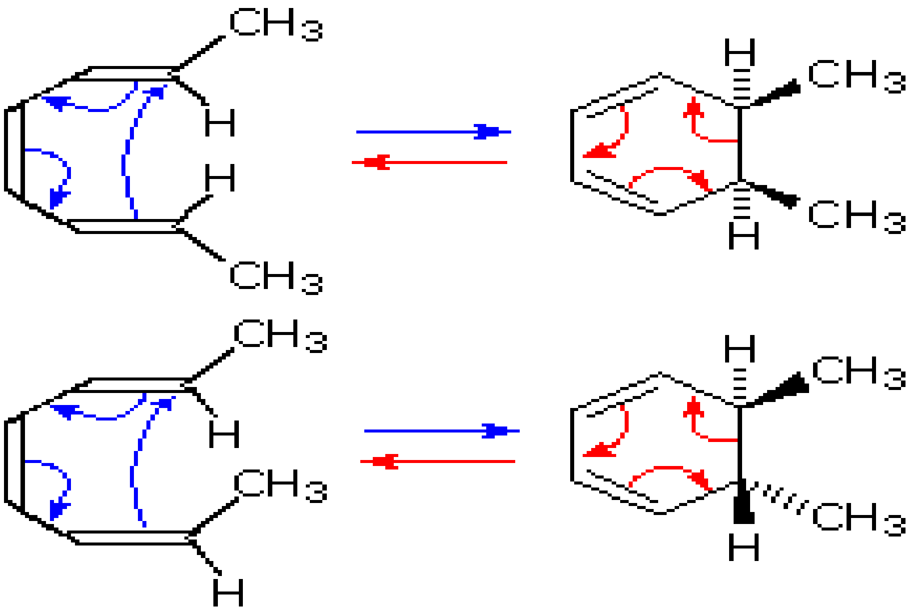


2.



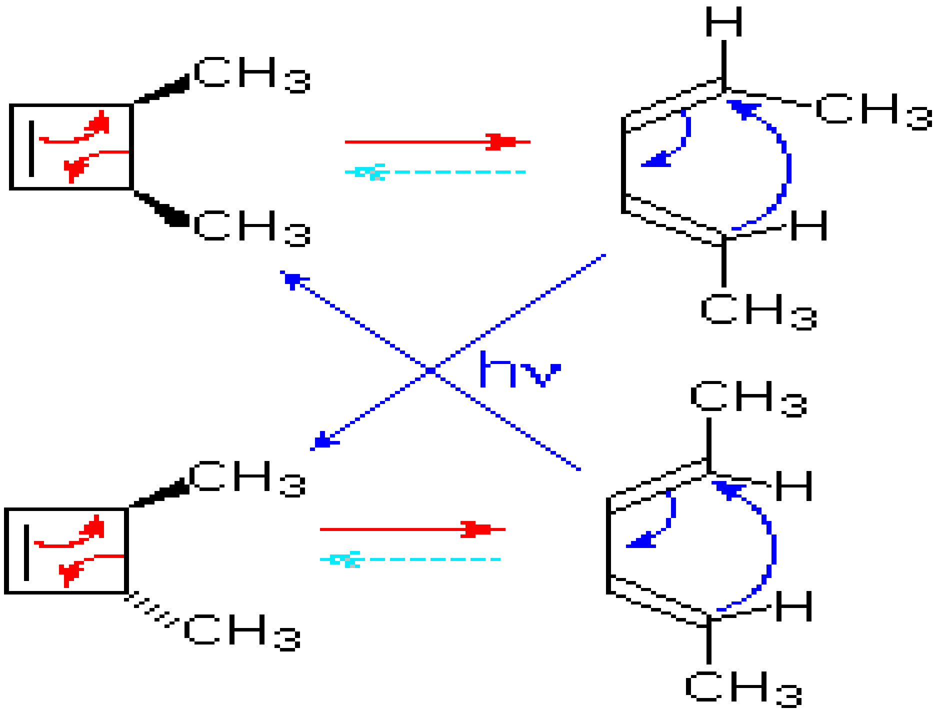
The stereospecificity of these reactions should be evident. In the first example, the acetoxy substituents on the diene have identical *E*-configurations, and they remain cis to each other in the cyclic adduct. Likewise, the ester substituents on the dienophile have a trans-configuration which is maintained in the adduct. The reactants in the second equation are both monocyclic, so the cycloaddition adduct has three rings. The orientation of the quinone six-membered ring with respect to the bicycloheptane system (colored blue) is endo, which means it is oriented cis to the longest or more unsaturated bridge. The alternative configuration is called exo.

2. Electrocyclic Reactions

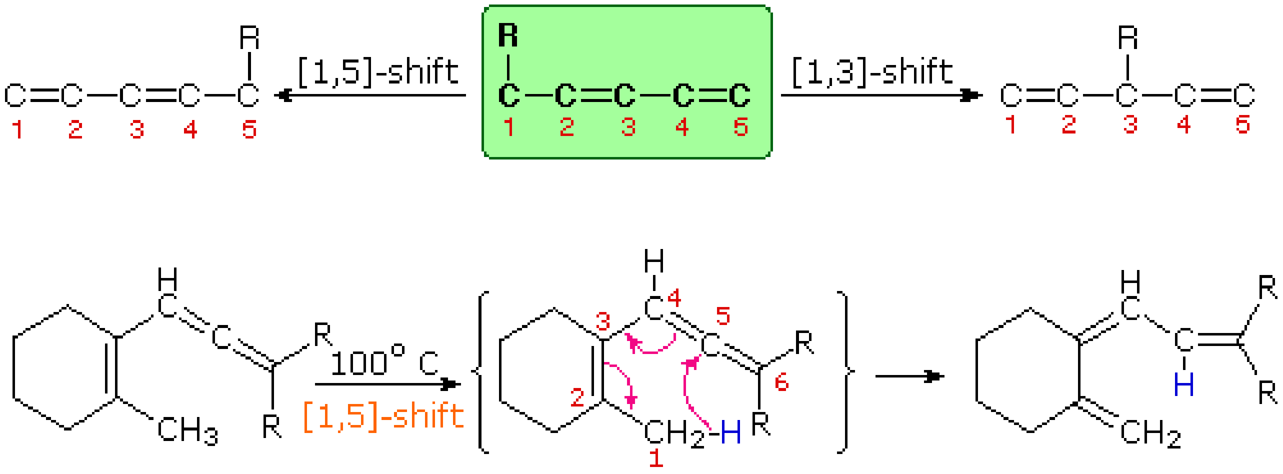


An electrocyclic reaction is the concerted cyclization of a conjugated π-electron system by converting one π-bond to a ring forming σ-bond. The reverse reaction may be called electrocyclic ring opening. Two examples are shown on the right. The electrocyclic ring closure is is designated by **blue arrows**, and the ring opening by **red arrows**. Once again, the number of curved arrows that describe the bond reorganization is half the total number of electrons involved in the process.

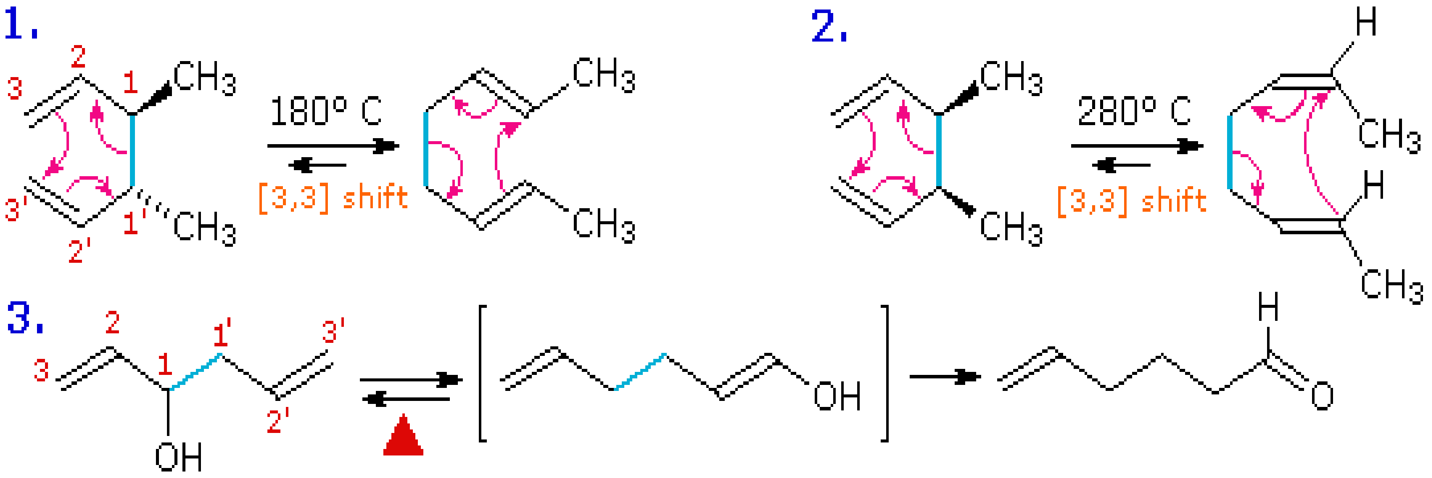
In the first case, *trans,cis,trans*-2,4,6-octatriene undergoes thermal ring closure to *cis*-5,6-dimethyl-1,3-cyclohexadiene. The sterospecificity of this reaction is demonstrated by closure of the isomeric *trans,cis,cis*-triene to *trans*-5,6-dimethyl-1,3-cyclohexadiene, as noted in the second example.



3.Sigmatropic Rearrangements

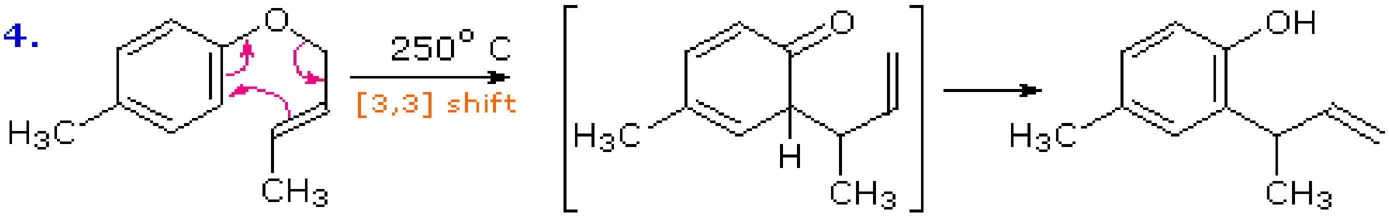


Molecular rearrangements in which a σ-bonded atom or group, flanked by one or more π-electron systems, shifts to a new location with a corresponding reorganization of the π-bonds are called sigmatropic reactions. The total number of σ-bonds and π-bonds remain unchanged. These rearrangements are described by two numbers set in brackets, which refer to the relative distance (in atoms) each end of the σ-bond has moved, as illustrated by the first equation in the diagram below. The most common atom to undergo sigmatropic shifts is hydrogen or one of its isotopes. The second equation in the diagram shows a facile [1,5] hydrogen shift which converts a relatively unstable allene system into a conjugated triene. Note that this rearrangement, which involves the relocation of three pairs of bonding electrons, may be described by three curved arrows.

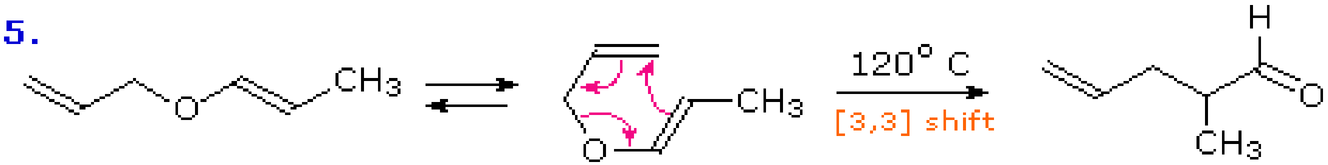


The [3,3] sigmatropic rearrangement of 1,5-dienes or allyl vinyl ethers, known respectively as the **Cope and Claisen rearrangements**, are among the most commonly used sigmatropic reactions. Three examples of the Cope rearrangement are shown in the following diagram. Reactions **1** and **2** (top row) demonstrate the stereospecificity of this reaction. The light blue σ-bond joins two allyl groups, oriented so their ends are near each other. Since each allyl segment is the locus of a [1,3] shift, the overall reaction is classified as a **[3,3] rearrangement**. The three pink colored curved arrows describe the redistribution of three bonding electron pairs in the course of this reversible rearrangement.

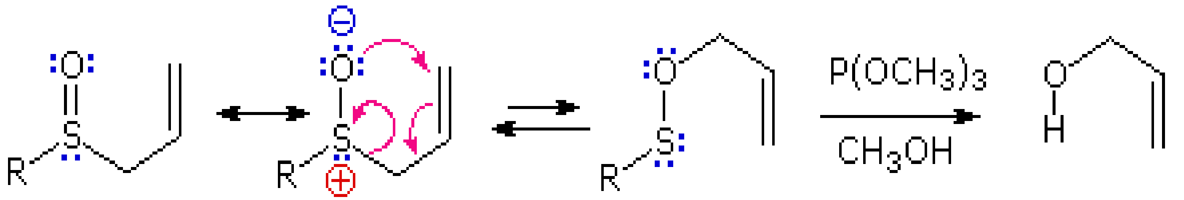
4.


H$_3$C
O
CH$_3$
250° C
[3,3] shift
O
H$_3$C
H
CH$_3$
OH
H$_3$C
CH$_3$

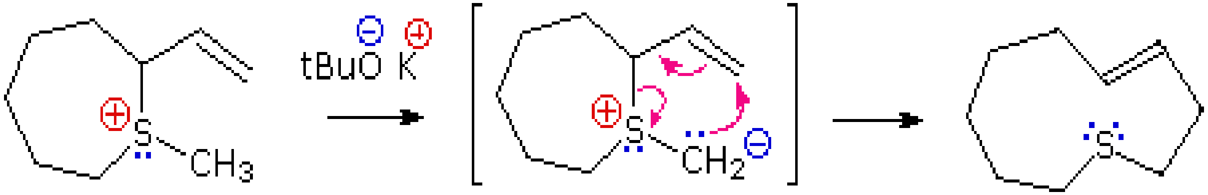
5.


O
CH$_3$
CH$_3$
O
120° C
[3,3] shift
H
O
CH$_3$

6.


:O:
S
R
O
S
R
O
S
R
P(OCH$_3$)$_3$
CH$_3$OH
O
H

7.

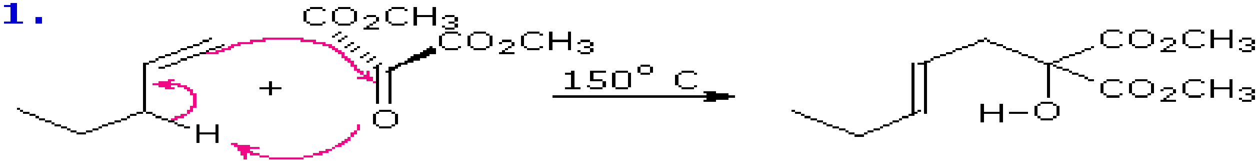

S
CH$_3$
tBuO K
S
CH$_2$
S

4. Ene Reactions

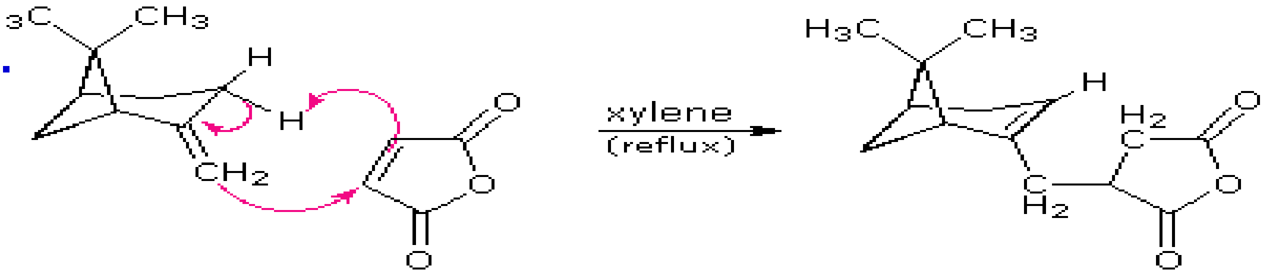
The joining of a double or triple bond to an alkene reactant having a transferable allylic hydrogen is called an **ene reaction**. The reverse process is called a **retro ene reaction**

In the bonding direction the ene reaction is characterized by the redistribution of three pairs of bonding electrons. and may be described by a cycle of three curved arrows. As noted earlier, this bond reorganization involves the overall conversion of a π-bond to a σ-bond (or the opposite in the case of retro ene fragmentation). This is the same bond bookkeeping change exhibited by electrocyclic reactions, but no rings are formed or broken in an ene reaction unless it is intramolecular. The following examples illustrate some typical ene reactions, with equation 3 being an intramolecular ene reaction. Ene reactions are favored when the hydrogen accepting reagent, the "enophile", is electrophilic. This is the case for reactions 1 and 2, which proceed under milder conditions than 3, despite the latter's intramolecular nature.

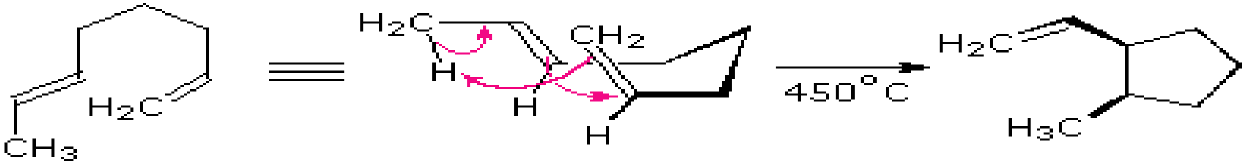
1.


CO2CH3
CO2CH3
+
O
H
150° C
CO2CH3
CO2CH3
H–O

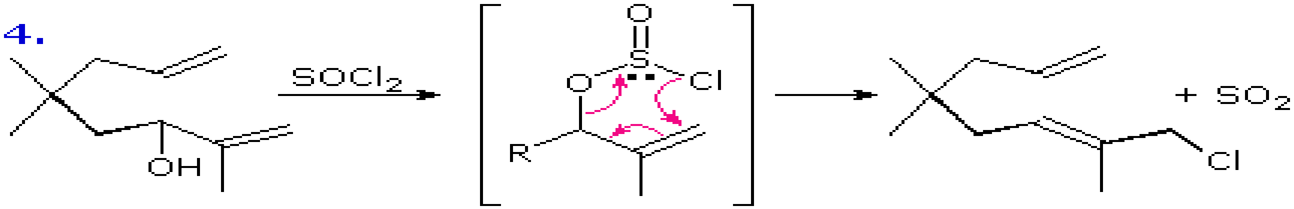
2.


H3C
CH3
H
H
CH2
O
O
O
xylene
(reflux)
H3C
CH3
H
H2
C
C
H2
O
O
O

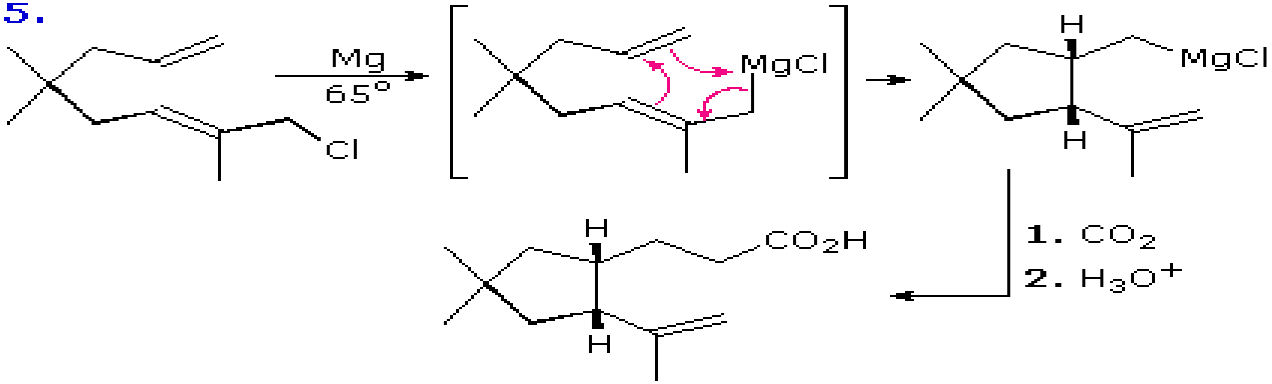
3.


H2C
CH3
H2C
CH2
H
H
H
450° C
H2C
H3C

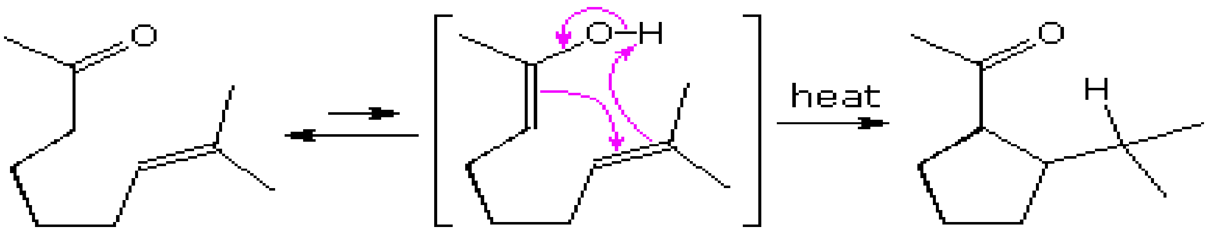
4.


OH
SOCl2
O
S
O
Cl
R
+ SO2
Cl

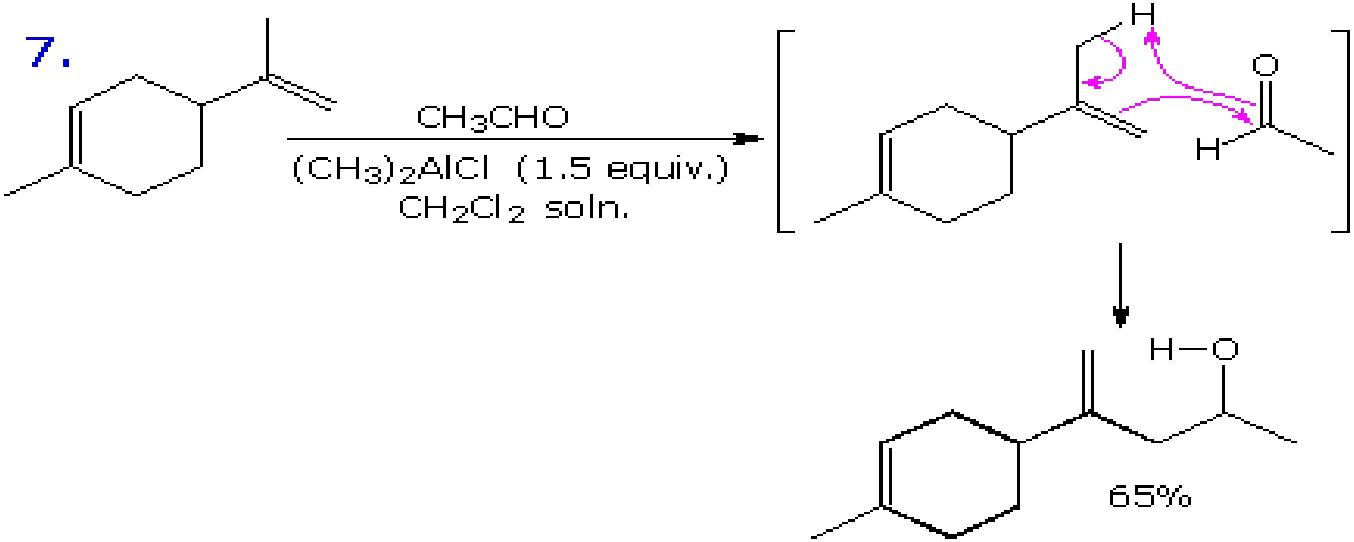
5.


Cl
Mg
65°
MgCl
H
MgCl
H
1. CO2
2. H3O+
H
CO2H
H

6.



7.

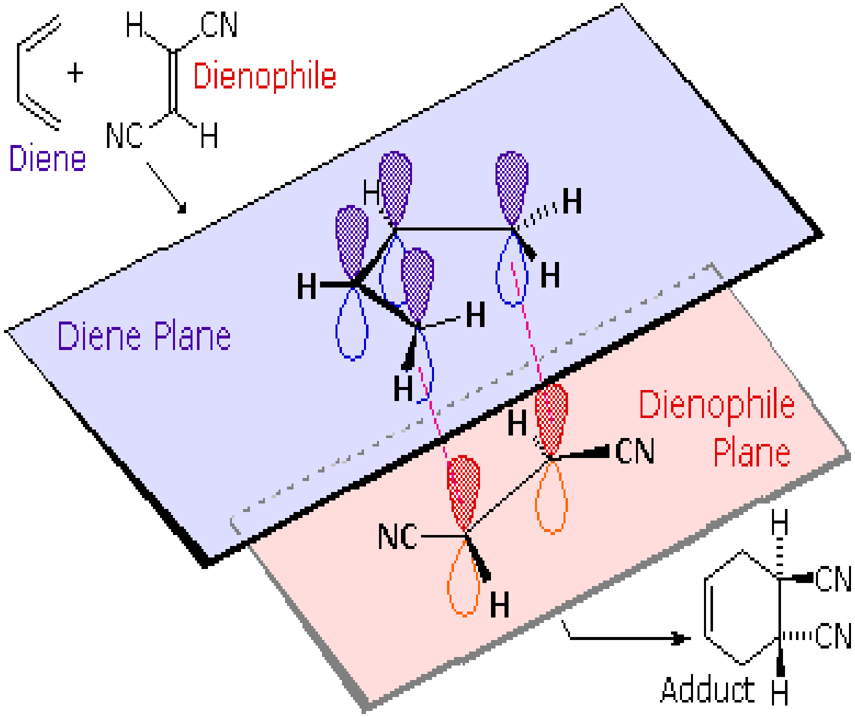


5. Stereochemical Notations

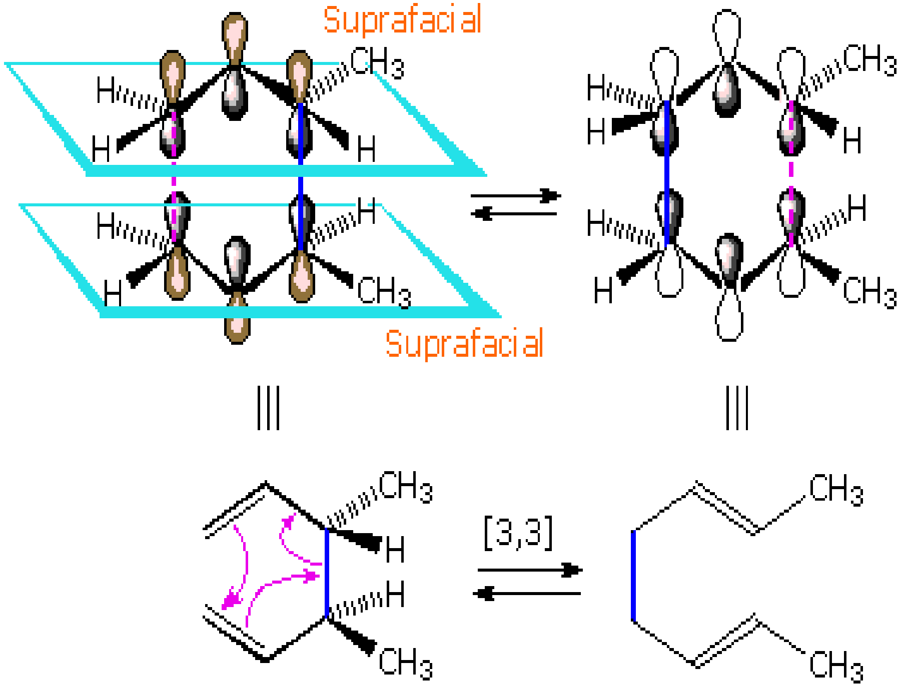
One characteristic shared by most pericyclic reactions, and noted in many cases described above, is their stereospecificity. This is not the first class of reactions for which a characteristic stereospecificity has been noted. Substitution reactions may proceed randomly or by "inversion" or "retention" of configuration. Elimination reactions may occur in an "anti" or "syn" fashion, or may be configurationally random. The terms "syn" and "anti" have also been applied to 1,2-addition reactions

Since these configurational change notations are not appropriate for pericyclic reactions, new designations are needed. Cycloaddition reactions and sigmatropic rearrangements both involve pairs of σ-bond-making events (or a coupled bond-making & bond-breaking) associated with a π-electron system. If all the bonding events take place on the same face of the π-system the configuration of the reaction is termed suprafacial. If the bonding events occur on opposite sides or faces of the π-system the reaction is termed antarafacial. Suprafacial examples of these pericyclic transformations are shown below. The bracketed numbers that designate reactions of this kind sometimes carry subscripts (s or a) that specify their configuration. Thus the cycloaddition on the left may be termed a [4s + 2s] process.

Although cycloaddition reactions are concerted (no intermediate species are formed), the two new bonds are not necessarily formed in a synchronous fashion. Depending on partial charge distribution in the diene and dienophile reactants, the formation of one bond may lead the development of the other. Such unsymmetrical transition state bonding is termed asynchronous

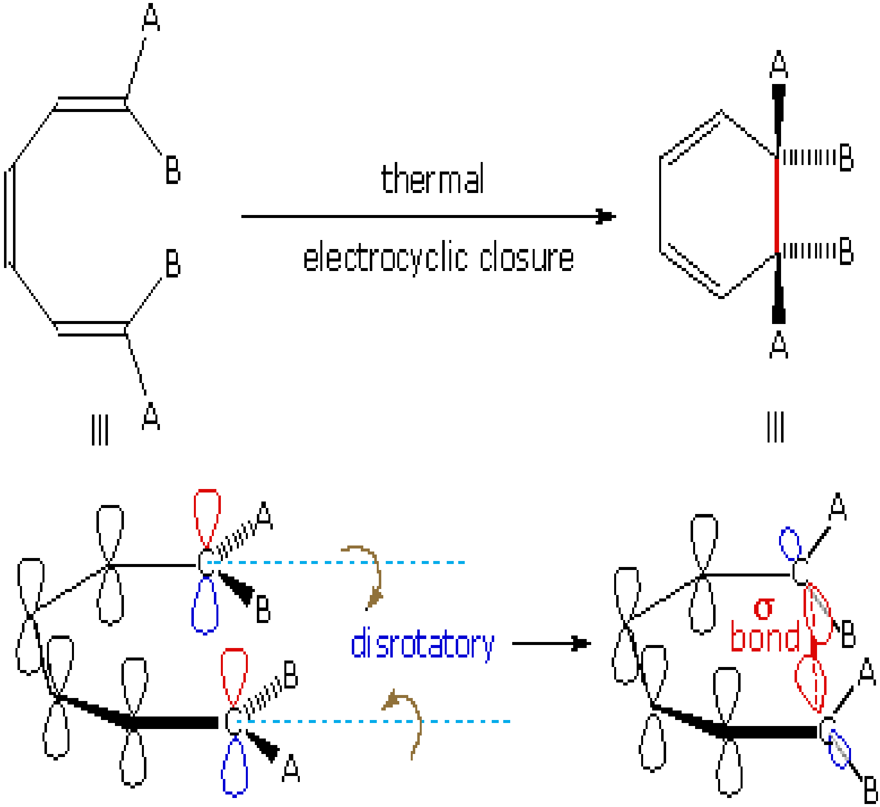


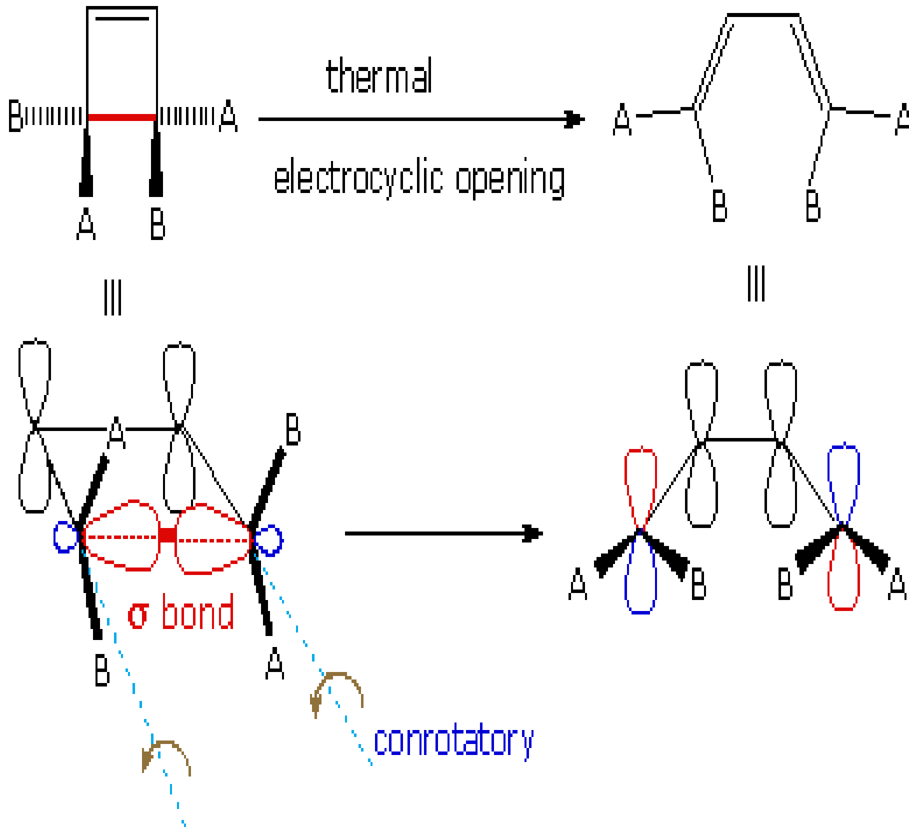
A Suprafacial [4+2] Cycloaddition



A Suprafacial [3,3] Sigmatropic Rearrangement

A different notation for configurational change is required for **electrocyclic** reactions. In these cases a σ-bond between the ends of a conjugated π-electron system is either made or broken with a corresponding loss or gain of a π-bond. For this to happen, the terminal carbon atoms of the conjugated π-electron system must be rehybridized with an accompanying rotatation or twisting of roughly 90º. When viewed along the axis of rotation, the two end groups may turn in the same direction, termed **conrotatory**, or in oppposite directions, termed **disrotatory**. The prefixes **con** and **dis** may be remembered by association with their presence in the words *concur & disagree*. These two modes of electrocyclic reaction are shown in the following diagram in the general form in which they are most commonly observed. Specific examples of these electrocyclic reactions were

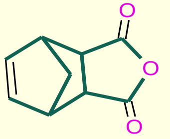




A Disrotatory Electrocyclic Closure

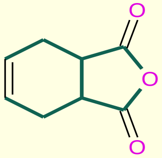
A Conrotatory Electrocyclic Opening

syf. 2



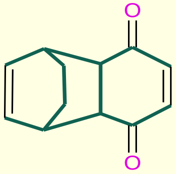
4-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione

syf. 2

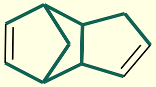


3a,4,7,7a-tetrahydro-2-benzofuran-1,3-dione

syf.3

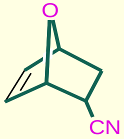


tricyclo[6.2.2.$0^{2,7}$]dodeca-4,9-diene-3,6-dione



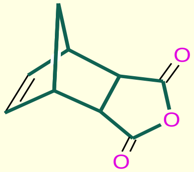
syf.3

tricyclo[5.2.1.$0^{2,6}$]deca-3,8-diene



syf.3

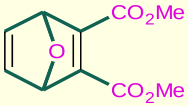
7-oxabicyclo[2.2.1]hept-5-ene-2-carbonitrile



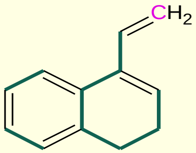
syf.3

4-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione

TM1

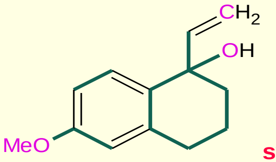


dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate



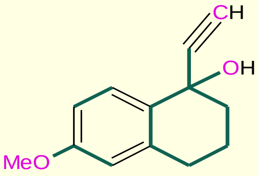
syf.5

4-vinyl-1,2-dihydro naphthalene



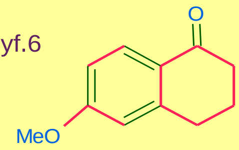
syf.6

6-methoxy-1-vinyl-1,2,3,4-tetrahydronaphthalen-1-ol

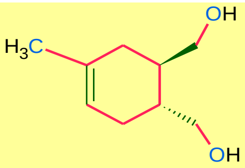


syf.6

1-ethynyl-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol syf.6



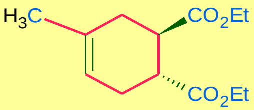
6-methoxy-3,4-dihydronaphthalen-1(2H)-one



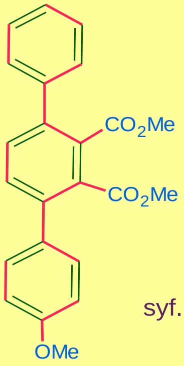
TM4

[(1R,2R)-4-methylcyclohex-4-ene-1,2-diyl] dimethanol

syf.7



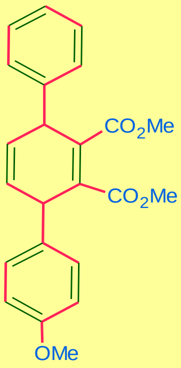
diethyl (1R,2R)-4-methylcyclohex-4-ene-1,2-dicarboxylate



syf.7

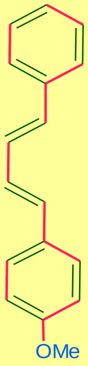
dimethyl 4-methoxy-1,1':4',1''-terphenyl-2',3'-dicarboxylate

syf.7

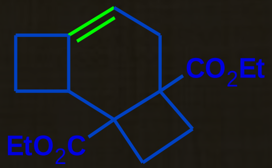


dimethyl 3-(4-methoxyphenyl)-6-phenylcyclohexa-1,4-diene-1,2-dicarboxylate

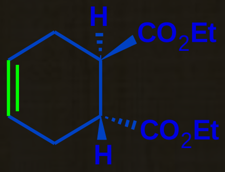
syf.7



1-methoxy-4-[(1E,3E)-4-phenylbuta-1,3-dien-1-yl] benzene *syf.9*



diethyl tricyclo[6.2.0.02,5]dec-5-ene-1,8-dicarboxylate

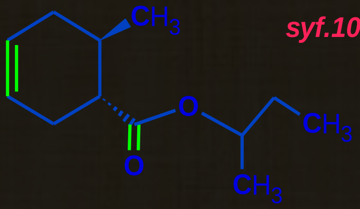


syf.9

diethyl (1R,2R)-cyclohex-4-ene-1,2-dicarboxylate

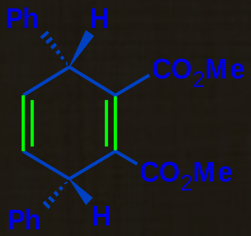
syf.10

(3aR,7aS)-3a,4,7,7a-tetrahydro-2-benzofuran-1,3-dione

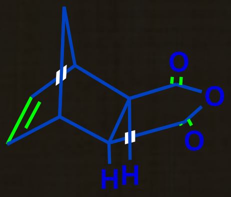


syf.10

sec-butyl (1R,6R)-6-methylcyclohex-3-ene-1-carboxylate



dimethyl (3R,6S)-3,6-diphenylcyclohexa-1,4-diene-1,2-dicarboxylate



4-oxatricyclo[5.2.1.02,6]dec-8-ene-3,5-dione