Pericyclic Reactions

4

4.1 Introduction

A pericyclic reaction is a reaction in which bonds form or break at the termini of one or more conjugated π systems. The electrons move around in a circle, all bonds are made and broken *simultaneously,* and no intermediates intervene. The requirement of concertedness distinguishes pericyclic reactions from most polar or free-radical reactions, although for many pericyclic reactions, one can also draw reasonable alternative stepwise mechanisms.

For each class of pericyclic reactions two or more of the following characteristics will be discussed: the *typical reactions, regioselectivity, stereoselectivity,* and *stereospecificity*. The discussions of typical reactions and stereospecificity will help you recognize when pericyclic reactions are occurring in a particular chemical reaction. The discussions of regioselectivity, stereoselectivity, and stereospecificity will allow you to *predict* the structures and stereochemistry of the products obtained from pericyclic reactions.

4.1.1 Classes of Pericyclic Reactions

Before discussing specific ones, it is important to learn how to describe pericyclic reactions. There are four major classes of pericyclic reactions: *electrocyclic reactions* (ring openings or ring closings), *cycloadditions*, *sigmatropic rearrangements*, and *ene reactions.*

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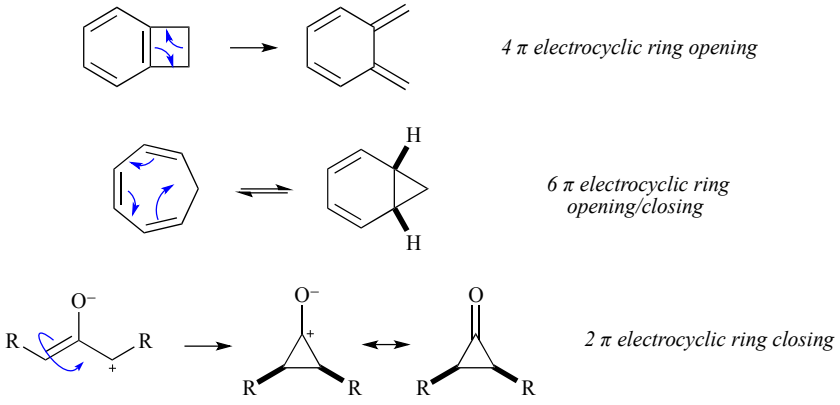
In an *electrocyclic ring closing*, a σ bond forms between the termini of a conjugated π system. An *electrocyclic ring opening* is the reverse reaction, in which a C–C σ bond breaks to give a conjugated π system in which the termini used to be σ-bonded. Empty or filled p orbitals can participate in the π system. Electrocyclic reactions are further subclassified as 2π electrocyclic, 4π electrocyclic, etc., according to how many electrons are involved in the reaction. As in all pericyclic reactions, the electrons move around in a circle. Note how the π bonds shift upon formation or cleavage of the key σ bond.

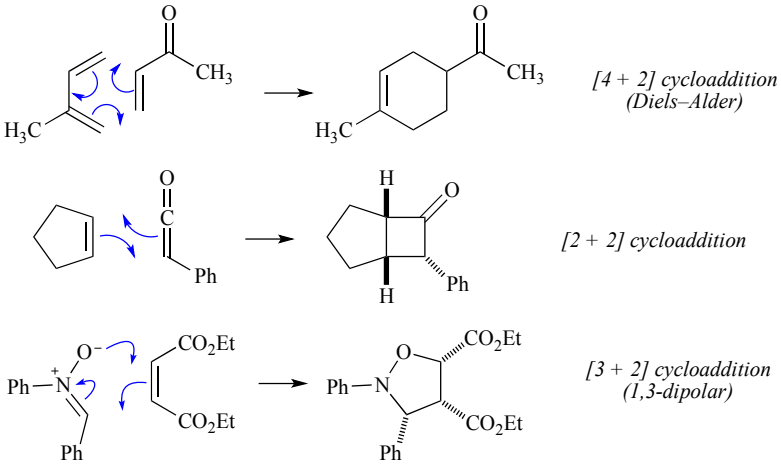


You may have trouble seeing that the last example of an electrocyclic reaction is a two-electron and not a four-electron reaction. The new σ bond is formed between the termini of a three-atom π system. That three-atom system contains two electrons. The lone pairs of O are not part of the three-atom π system, so they are not included in the electron count of the electrocyclic reaction.

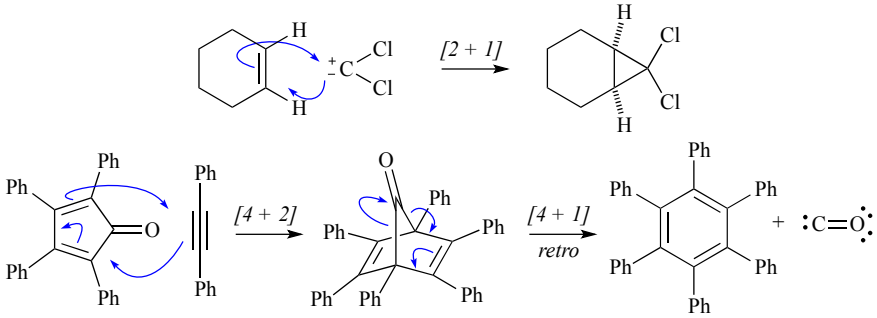
When σ bonds are formed between the ends of two π systems to give a cyclic product, the reaction is called a *cycloaddition*. The reverse reaction is called a *retrocycloaddition.* Cycloadditions are further classified as [m + n] according to the number of *atoms* in each component.[1] Again, it is important to note not only the number of atoms but also the number of electrons involved in the process. You are already familiar with the six-electron [4 + 2] cycloaddition, the *Diels–Alder reaction*. Four-electron [2 + 2] cycloadditions are less common, for reasons that will be discussed, but ketenes undergo them readily. The [3 + 2] cycloadditions (or 1,3-dipolar cycloadditions) are a very important class of six-electron cycloadditions that are used

[1]Two conventions for naming cycloadditions are used in the literature. The older convention, and the one used in this textbook, is that m and n denote the number of *atoms* in each component. Woodward and Hoffmann altered the convention to make m and n denote the number of *electrons* in each component. The number of electrons and the number of atoms are the same for reactions involving neutral species such as the Diels–Alder reaction, but they are *not* the same for reactions involving charged or dipolar species. For example, the 1,3-dipolar cycloaddition is a [3 + 2] cycloaddition according to the older convention and a [4 + 2] cycloaddition according to the newer one. Always be careful to note which convention is being used.

to make a wide variety of five-membered heterocycles. Other cycloadditions, including [8 + 2], [4 + 3], and [6 + 4] cycloadditions, are also known.

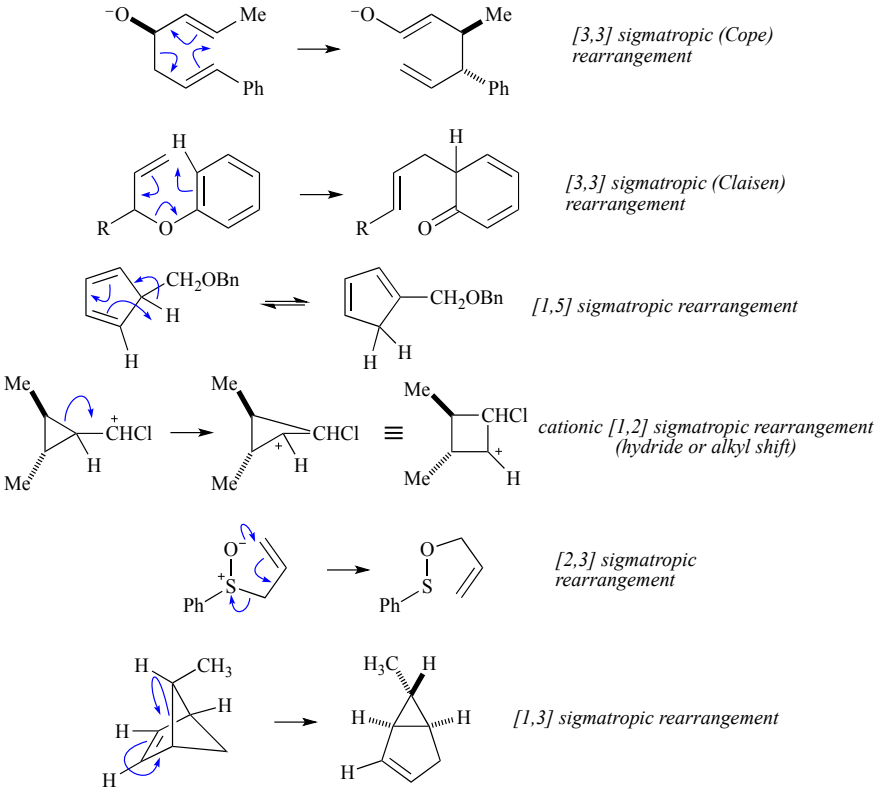


Cheletropic reactions (e.g., [2 + 1] cycloadditions and [4 + 1] retrocycloadditions) are a special class of cycloadditions in which one of the components is a single atom. The one-atom component must have one full and one empty orbital; it may be a carbene ($\pm CR_2$), SO_2 ($O{=}\ddot{S}^{+}{-}O^{-} \leftrightarrow {}^{-}O{-}\ddot{S}^{2+}{-}O^{-}$), or $C{\equiv}O$ (${}^{-}C{\equiv}O^{+} \leftrightarrow \pm C{=}O$). The [4 + 1] cycloadditions usually proceed in the retro direction with the expulsion of a stable small molecule such as CO or SO_2.

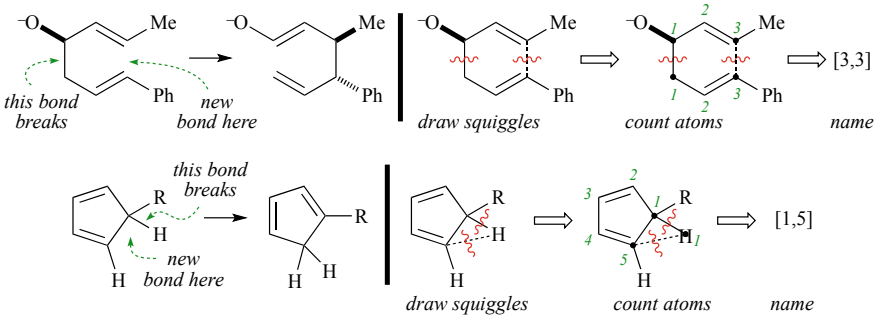


Sigmatropic rearrangements involve the cleavage of a σ bond connecting the end of one fragment with the end of another, and concerted formation of another σ bond at the other ends of the fragments. The σ bond seems to migrate, hence the name of the reaction. Sigmatropic rearrangements are subclassified as [*n*,*m*] sigmatropic rearrangements, where *n* and *m* are the number of *atoms* (not electrons) in each of the fragments. The very common [3,3] sigmatropic rearrangement is called

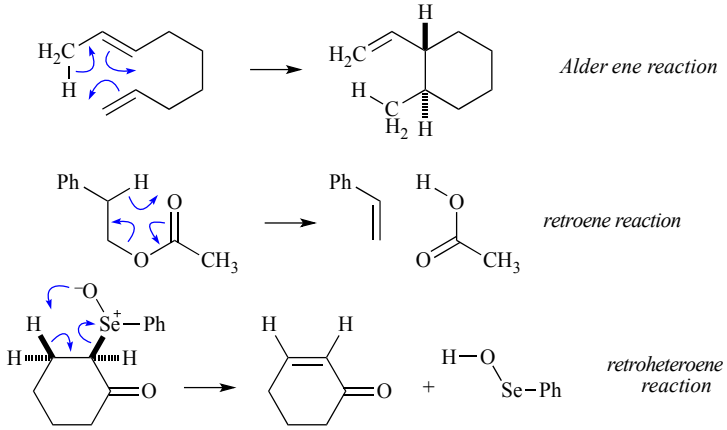
the *Cope rearrangement*. When one of the atoms in the π system is O, the [3,3] sigmatropic rearrangement is called the *Claisen rearrangement* (not to be confused with the Claisen condensation). (The initial product, a cyclohexadienone, isomerizes to a phenol, thus driving the reaction to the right.) The cationic [1,2] sigmatropic rearrangement (i.e., the 1,2-alkyl or hydride shift) has already been encountered. It is important to note the number of electrons involved in sigmatropic rearrangements, too. The [3,3] and [1,5] rearrangements are six-electron reactions, the cationic [1,2] rearrangement is a two-electron reaction, and the [1,3] rearrangement is a four-electron reaction.



Students seem to have more trouble recognizing and naming sigmatropic rearrangements than any other reaction. There is no net change in the number of σ or π bonds in a sigmatropic rearrangement. To name a sigmatropic rearrangement, draw a dotted line between the atoms where a bond forms, and draw short squiggles through the center of the bond that breaks and the dotted line. Put a heavy dot at each atom involved in σ bond formation or cleavage. Then count the number of atoms around the π system from one dot to another inclusive, being careful not to cross a squiggle.



The *ene reaction* is always a six-electron reaction. It shares some characteristics with the [4 + 2] cycloaddition and the [1,5] sigmatropic rearrangement. Like the [4 + 2] cycloaddition, a four-atom component reacts with a two-atom component, but in the ene reaction, the four-atom component consists of a π bond and an allylic σ bond (usually to a H atom), not two π bonds. Like a [1,5] sigmatropic rearrangement, a σ bond migrates, but the ene reaction also produces one σ bond at the expense of one π bond. When the reaction occurs between a C=C π bond and a C=C π bond with an allylic hydrogen, it is called the *Alder ene reaction*. The reaction may or may not be intramolecular. Retroene reactions are commonly seen, too, as in the thermal elimination of acetic acid from alkyl acetates. The *heteroene reaction* looks like a cross between a [3 + 2] cycloaddition and a [1,4] sigmatropic rearrangement. Retroheteroene reactions are used in some elimination procedures that are very important synthetically.



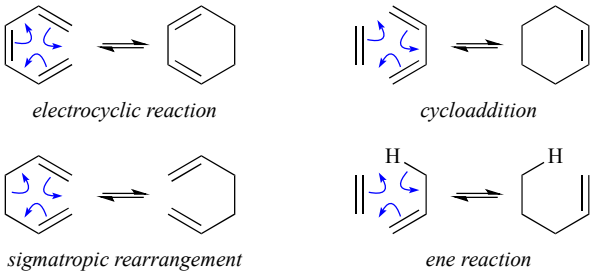
The key characteristics of the four major types of pericyclic reactions are summarized in Table 4.1.

Common error alert: *The pericyclic reactions are superficially similar to one another, and students sometimes have trouble distinguishing the different types from one another.* Archetypical, six-electron examples of each type of pericyclic

Table 4.1 Bond changes in pericyclic reactions

Reaction class	Changes in bond types
Electrocyclic reactions	One π bond $\rightleftarrows$ one σ bond
Cycloadditions	Two π bonds $\rightleftarrows$ two σ bonds
Cheletropic reactions	One π bond and X$\pm$ $\rightleftarrows$ two σ bonds
Sigmatropic rearrangements	One σ bond $\rightarrow$ new σ bond
Ene reactions	One π bond $\rightleftarrows$ one σ bond *and* one σ bond migrates

reaction are shown in the figure. (Note the *degeneracy* of the archetypical sigmatropic rearrangement.) Each archetypical reaction has three arrows moving in a circle, but each results in a different change in the patterns of bonding.

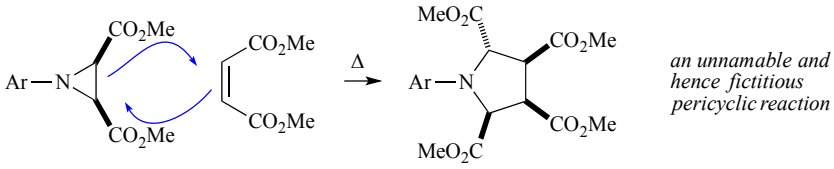


electrocyclic reaction *cycloaddition*

sigmatropic rearrangement *ene reaction*

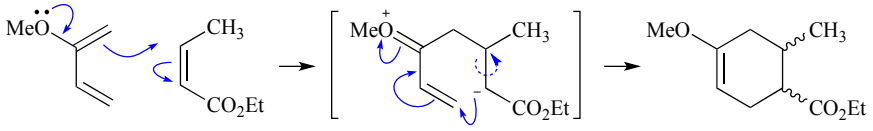
When drawing the change in bonding patterns in pericyclic reactions, it doesn't matter whether you draw the electrons moving clockwise or counterclockwise, because pericyclic reactions are *not* characterized by the movement of electron density from electron-rich to electron-poor or high-energy to low-energy sites. The electron-flow arrows are merely meant to show the change in bonding patterns as the reaction proceeds from starting material to product. However, when one component in the reaction has an atom with a formal negative charge, as in the [3 + 2] cycloaddition, the [2,3] sigmatropic rearrangement, or the retroheteroene reaction, it is important to begin your electron-pushing there.

Common error alert: *Students often draw fictional one-step pericyclic mechanisms for reactions that require more than one step.* A good guard against this sort of error is to be sure that you can name any pericyclic step in your mechanism. For example, for the following reaction, you may be tempted to draw a four-electron, one-step mechanism involving the C–C σ bond of the first starting material and the π bond of the second. Such a mechanism, however, cannot be classified in the scheme that has just been discussed, and therefore it is likely to be incorrect.



an unnamable and hence fictitious pericyclic reaction

Stereospecificity, the property that the stereochemistry of the starting materials determines the stereochemistry of the product, is one of the hallmarks of pericyclic reactions. It is possible to draw two-step, nonconcerted, polar or free-radical mechanisms for many pericyclic reactions, but these two-step mechanisms fail to account for the stereospecificity of the reactions. For example, a two-step polar mechanism can be drawn for the Diels–Alder reaction between 2-methoxybutadiene (a nucleophile) and ethyl *cis*-crotonate (an electrophile). This mechanism proceeds through a dipolar intermediate in which one new σ bond has formed. In this intermediate, there is free rotation about the two C atoms of the dienophile, so the cis stereochemical relationship between the Me and CO_2Et groups is expected to be lost in the product. In fact, though, the product is exclusively cis. This finding does not completely rule out a polar mechanism—it is possible that the intermediate exists, but that ring closure occurs more quickly than rotation about the σ bond—but it does limit the lifetime of the dipolar intermediate to such an extent that one can say *practically* that it does not exist.



loss of stereochemical integrity likely

Many stereochemical results like these, and the consistent observation of non-thermodynamic products that would not be expected from two-step mechanisms, have accumulated to support the operation of the pericyclic mechanism in *most* cases. Recent advances in experimental and theoretical techniques have allowed chemists to probe the mechanisms of pericyclic reactions at time scales far shorter than the time required to rotate about a C–C σ bond, and these experiments have supported concerted mechanisms for some pericyclic reactions and nonconcerted mechanisms for others. In practical terms, though, if no experimental or theoretical evidence rules it out, Occam's razor compels you to propose a concerted mechanism in favor of a nonconcerted one.

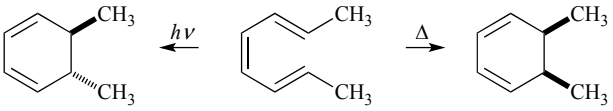
Pericyclic reactions can proceed under acidic or basic conditions. For example, the oxy-Cope rearrangement is greatly accelerated under basic conditions, while the Diels–Alder reaction is greatly accelerated by Lewis acids. Often a series of polar reactions is used to synthesize an unstable intermediate, which then undergoes a pericyclic reaction to reveal the product. In other words, a good command of polar mechanisms (Chaps. 2 and 3) is essential to understanding how to draw pericyclic mechanisms.

Like all reactions, pericyclic reactions are reversible in principle (even though they may be irreversible in practice). The forward and reverse reactions *always go through the same transition state.* As an analogy, if you wanted to travel from

Lexington, Kentucky, to Richmond, Virginia, you would choose the path that went through the lowest gap in the Appalachian mountains. If you wanted to go from Richmond back to Lexington, you would choose the same route, only in reverse. The path you chose would not depend on which direction you were traveling. Reactions obey the same principle.

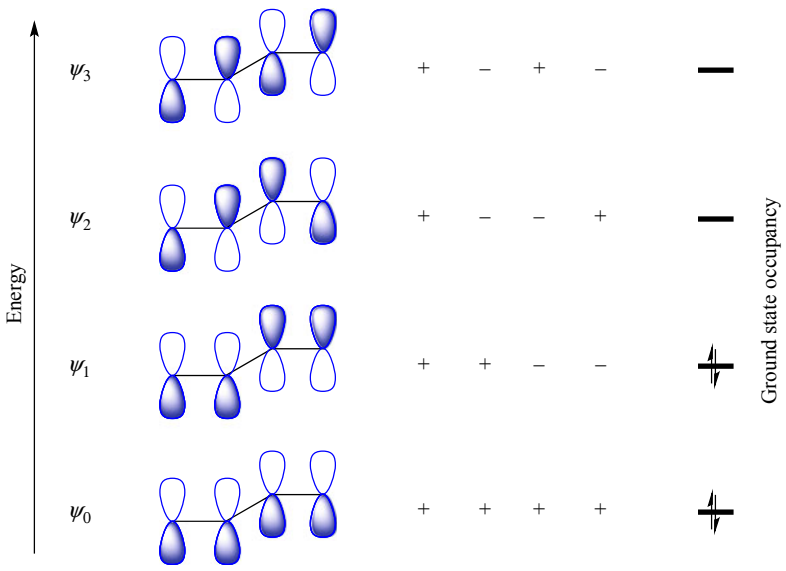
4.1.2 Polyene MOs

You may think that there's not much to say about the "no-mechanism" pericyclic reactions, but there is. First, how they proceed stereochemically and even whether they proceed at all depends on whether the reaction is conducted *thermally* or *photochemically*. For example, many [2 + 2] cycloadditions proceed *only* photochemically, whereas all [4 + 2] cycloadditions proceed thermally. Second, all pericyclic reactions proceed stereospecifically, but the stereochemistry of the products sometimes depends on the reaction conditions. For example, 2,4,6-octatriene gives *cis*-5,6-dimethylcyclohexadiene upon heating and *trans*-5,6-dimethylcyclohexadiene upon photolysis. *These phenomena can be explained by examining the MOs of the reactants.* The rules governing whether pericyclic reactions proceed and the stereochemical courses when they do proceed are known as the *Woodward–Hoffmann rules*.



The Woodward–Hoffmann rules can be rationalized by examining the properties of the *frontier MOs* of the reactants, i.e., their HOMOs (highest occupied molecular orbitals) and LUMOs (lowest unoccupied molecular orbitals). In order to understand pericyclic reactions, then, you need to be able to construct the MOs of a polyene system from the constituent *p* orbitals.

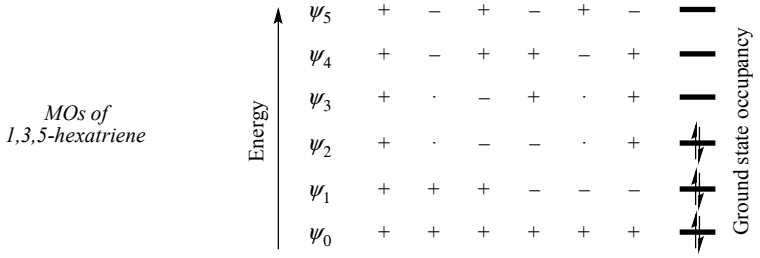
Consider 1,3-butadiene. Four *p* orbitals interact, each with its neighbors, to produce four MOs. These four MOs are called ψ_0, ψ_1, ψ_2, and ψ_3. In the lowest energy MO, ψ_0, every *p* orbital overlaps constructively with its neighbor to give an MO in which there are no *nodes*, or changes in sign between orbitals. In the highest energy MO, ψ_3, every *p* orbital overlaps destructively with its neighbor to give an MO in which there are three nodes. In the intermediate-energy MOs, ψ_1 and ψ_2, there are one and two nodes, respectively, and the MOs are constructed accordingly. Under thermal conditions, the four electrons derived from the four AOs occupy ψ_0 and ψ_1; ψ_1 is the HOMO and ψ_2 is the LUMO.



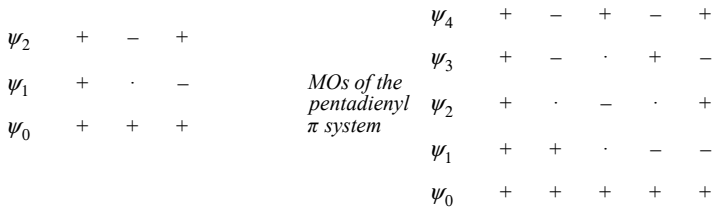
The signs of the AOs do not tell the whole story. In each MO, each AO has a coefficient associated with it that reflects the magnitude of its contribution to the MO. The coefficient can range from 0 to 1. The squares of the coefficients of one atom's AO in each MO add up to 1. The coefficients of the MOs can provide important information about reactivity.

Note that the signs of the terminal orbitals alternate from like, to opposite, to like, to opposite. A physical chemist would say that the symmetries of the MOs alternate between *symmetric* and *antisymmetric*. This property is universal among the MOs of polyenes. *You do not need to construct the complete MOs of any polyene* to determine the signs of the termini of the HOMO and LUMO, on which the properties of pericyclic reactions largely depend.

In 1,3,5-hexatriene, six AOs produce six MOs, the signs of whose termini alternate from like, to opposite, to like, etc. The number of nodes increases with each MO. In the ground state of 1,3,5-hexatriene, ψ_2 is the HOMO and ψ_3 is the LUMO. Note that in ψ_3 and ψ_4, the *p* orbitals of the second and fifth C atoms of the chain have a coefficient of zero, indicating that the *p* orbitals from those C atoms do not contribute at all to ψ_3 and ψ_4. Two of the nodes in both ψ_3 and ψ_4 pass through the centers of these two C atoms.



The symmetries of the MOs of conjugated π systems with odd numbers of atoms also alternate. The allyl system has three MOs: ψ_0 (symmetric), ψ_1 (antisymmetric), and ψ_2 (symmetric). In the allyl cation, ψ_0 is the HOMO and ψ_1 is the LUMO, whereas in the allyl anion, ψ_1 is the HOMO and ψ_2 is the LUMO. The pentadienyl system has five MOs. In the pentadienyl cation, ψ_1 (antisymmetric) is the HOMO and ψ_2 (symmetric) is the LUMO, whereas in the pentadienyl anion, ψ_2 (symmetric) is the HOMO and ψ_3 (antisymmetric) is the LUMO.



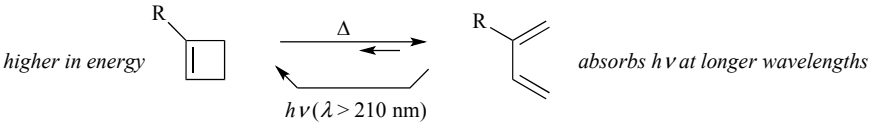
4.2 Electrocyclic Reactions

4.2.1 Typical Reactions

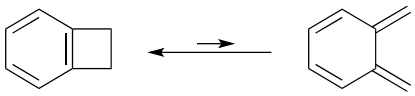
In an electrocyclic ring closing, a new σ bond forms between the termini of an acyclic conjugated π system to give a cyclic compound with one fewer π bond. In the reverse reaction, an electrocyclic ring opening, a ring σ bond that is allylic to both termini of a conjugated π system breaks to give an acyclic compound with one more π bond. Like all pericyclic reactions, electrocyclic reactions are reversible in principle. The ring-closed compound is *usually* lower in energy, because it has a σ bond in place of a π bond, but not always.

Cyclobutenes are in electrocyclic equilibrium with 1,3-butadienes. 1,3-Butadienes are lower in energy, because cyclobutenes are very strained, and it is therefore possible to convert a cyclobutene to a butadiene *thermally*. The reverse reaction, the conversion of a 1,3-butadiene to a cyclobutene, does not usually proceed under thermal conditions, as it involves an uphill climb in energy.

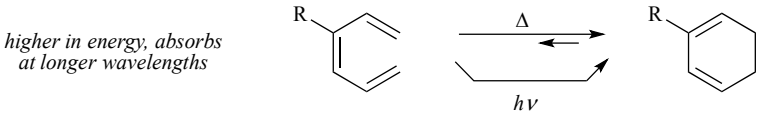
However, because they are more conjugated, 1,3-butadienes absorb light at longer wavelengths than cyclobutenes, so it is possible to convert a 1,3-butadiene to a cyclobutene *photochemically* by choosing a wavelength at which the butadiene absorbs and the cyclobutene does not.



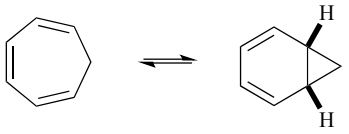
The equilibrium between the cyclobutene and the 1,3-butadiene is shifted in favor of the cyclobutene in benzocyclobutenes. The electrocyclic ring opening of a benzocyclobutene, an aromatic compound, leads to an *o-xylylene*, a nonaromatic and reactive compound. *o*-Xylylenes are useful intermediates in Diels–Alder reactions.



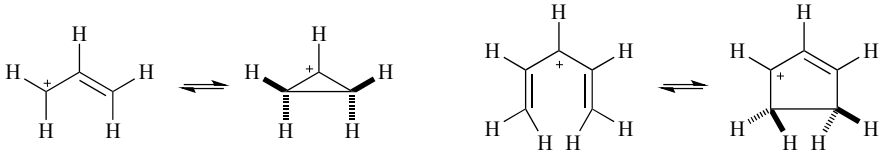
1,3-Cyclohexadienes are in electrocyclic equilibrium with 1,3,5-hexatrienes. Neither compound is strained, and the cyclohexadiene has one more σ bond than the hexatriene, so the cyclohexadiene is lower in energy. The hexatriene is more conjugated than the cyclohexadiene, so it is more reactive photochemically. Under *both* thermal and photochemical conditions, then, the cyclohexadiene is favored over the hexatriene.



The equilibrium between the 1,3-cyclohexadiene and the 1,3,5-hexatriene is less lopsided when ring closure creates a strained ring. For example, the equilibrium constant for the interconversion of 1,3,5-cycloheptatriene and norcaradiene (bicyclo[4.1.0]hepta-2,4-diene) is close to 1, and the interconversion occurs rapidly at room temperature. The ring *opening* is facile because the strain of the three-membered ring is relieved, and the ring *closing* is facile because the ends of the π system are held close together and because a C–C σ bond is gained at the expense of a π bond.

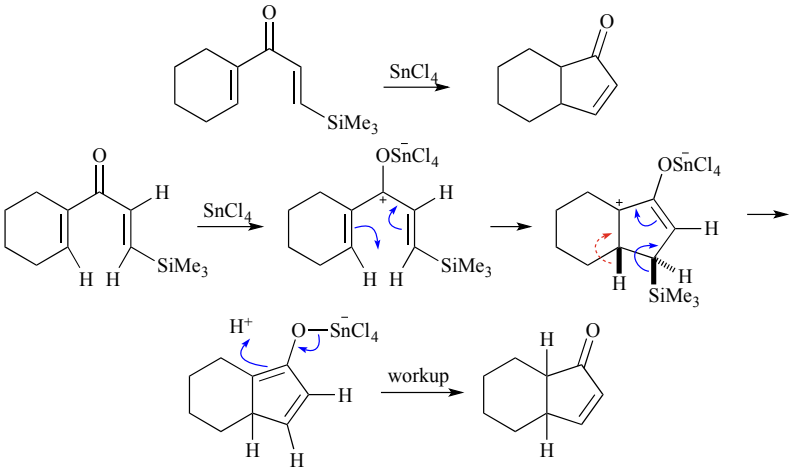


Allyl and pentadienyl cations participate in electrocyclic ring openings and closings, too. (The corresponding anions undergo similar reactions, but they are less important synthetically.) Less highly conjugated cations are produced upon ring closure of these species, but the decrease in cation stabilization is compensated by the gain of a C–C σ bond. In the case of the allyl system, the increase in strain upon ring closing makes ring opening more favored.

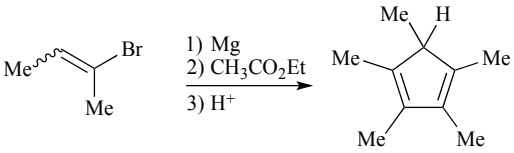


In the *Nazarov cyclization*, a divinyl ketone undergoes electrocyclic ring closing upon treatment with a Lewis acid such as $SnCl_4$ to give a cyclopentenone. The allylic cation obtained upon electrocyclic ring closure can undergo fragmentation of either of two different σ bonds to give the product. The lower energy product is usually obtained, but the tendency of the C–$SiMe_3$ bond to fragment preferentially to the C–H bond can be used to put the double bond in the thermodynamically less favorable position.

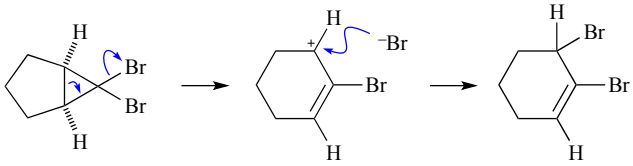
Example



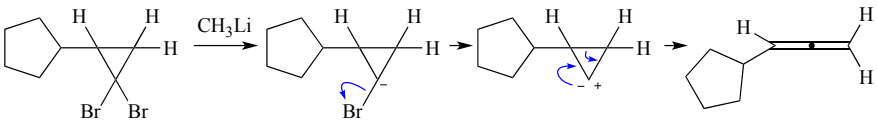
Problem 4.1 Draw a reasonable mechanism for the following preparation of pentamethylcyclopentadiene, a useful ligand for transition metals.



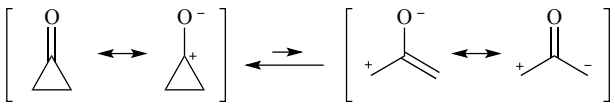
The electrocyclic equilibrium between cyclopropyl cations and allyl cations normally favors the allyl cation, because the cyclopropyl cation is both more strained and less conjugated than the starting allylic cation. For example, the cyclopropyl halide shown undergoes concerted loss of Br^- and electrocyclic ring opening to the allyl cation upon distillation. (In principle, a ring opening that is not concerted with loss of the leaving group could be drawn, but the cyclopropyl cation is very high in energy.) Addition of Br^- to the allylic cation then gives the product.



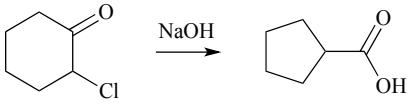
The carbene derived from halogen–metal exchange between RLi and a dibromocyclopropane can also undergo a four-electron electrocyclic ring opening to give an allene.



Cyclopropanones are in electrocyclic equilibrium with *oxyallyl cations*. The cyclopropanone is generally lower in energy, but the oxyallyl cation is not so much higher in energy that it is kinetically inaccessible. Oxyallyl cations can undergo cycloadditions, as will be discussed later.

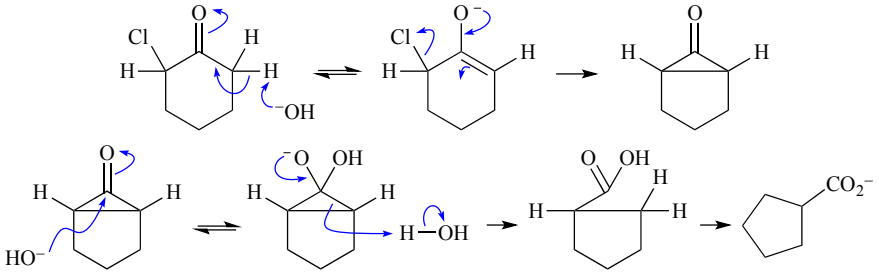


α-Haloketones rearrange to carboxylic acids in the *Favorskii rearrangement*. When the ketone is cyclic, ring contraction results.



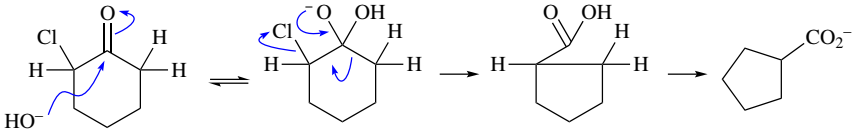
Two reasonable mechanisms can be drawn for the Favorskii rearrangement. In the first mechanism, the ketone acts as an *acid*. Deprotonation of the α-carbon that lacks the Cl atom gives an enolate. The enolate undergoes two-electron electrocyclic ring closing with expulsion of Cl^- to give a cyclopropane intermediate. Addition of HO^- to the carbonyl group of this very strained ketone is followed by strain-relieving elimination of an alkyl group to give a carbanion, which is probably quenched by solvent even as it forms.

Mechanism 1:

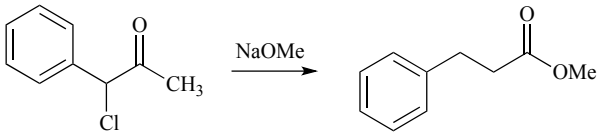


In the second mechanism, which was discussed in Chap. 2, the ketone acts as an *electrophile*. Addition of HO^- to the carbonyl group, then migration of C to its electrophilic neighbor with expulsion of Cl^-, provides the product.

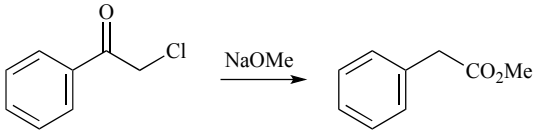
Mechanism 2:



Mechanism 2 (the semibenzilic acid mechanism) looks better, but labeling studies show that the two C atoms α to the ketone become equivalent in the course of the reaction, which is consistent only with mechanism 1 (the electrocyclic mechanism). The rearrangement of α-chloro-α-phenylacetone to methyl hydrocinnamate is also consistent only with the electrocyclic mechanism; if the semibenzilic mechanism were operative, then methyl 2-phenylpropionate would be the product.

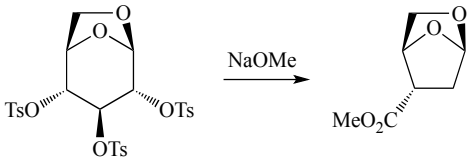


However, the rearrangement of α-chloroacetophenone to diphenylacetic acid *must* proceed by a semibenzilic acid mechanism, because a cyclopropane can't form.

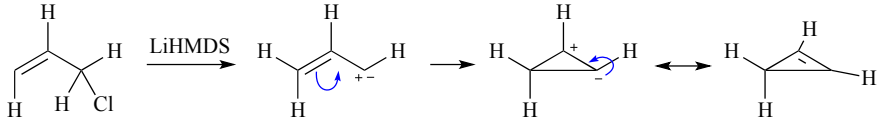


To summarize, when H atoms are present on the α-carbon opposite the leaving group, the electrocyclic mechanism usually operates; when they are not, the semibenzilic mechanism operates. Why does the electrocyclic mechanism proceed more quickly than the "more reasonable" semibenzilic mechanism for enolizable α-haloketones? Deprotonation and electrocyclic ring closing are both very rapid reactions—the latter even when a strained ring is formed—and they must simply be faster than HO^- addition and migration, despite what our "chemical intuition" tells us.

Problem 4.2 Draw a reasonable mechanism for the following reaction. A Favorskii rearrangement is involved.



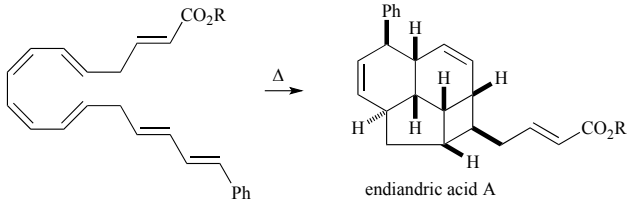
The electrocyclic ring closing of the allyl "cation" in the Favorskii rearrangement proceeds only because the cation in the product is quenched by O^-. Charge neutralization also provides the driving force for the electrocyclic ring closing of vinylcarbene to give cyclopropene. The ring closing can be drawn as either a two-electron- or a four-electron process, depending on whether the empty orbital or the filled orbital of the carbene is conjugated to the π bond.



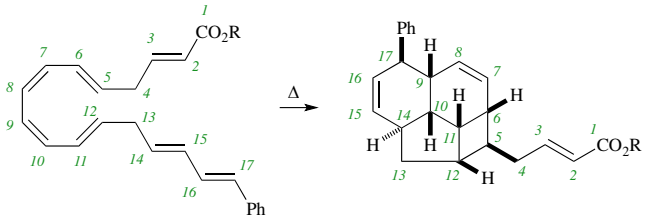
The key to identifying an electrocyclic ring *closing* is to look for the formation of a new bond at the ends of a conjugated π system. The key to identifying an electrocyclic ring *opening* is to look for the cleavage of a σ bond joining the allylic positions of a conjugated π system. Three-membered rings are closed from or opened to allylic systems by electrocyclic reactions.

Example

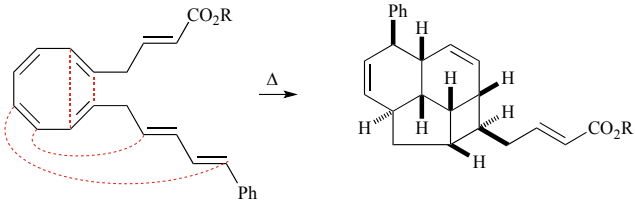
The following rearrangement reaction was proposed to be the biosynthetic pathway to the natural product endiandric acid A.



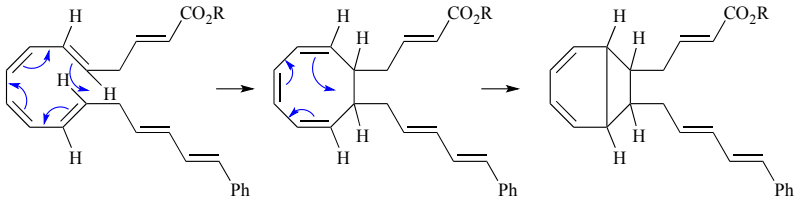
If you number the atoms, you will see that you need to make bonds at C5–C12, C6–C11, C9–C17, and C10–C14.



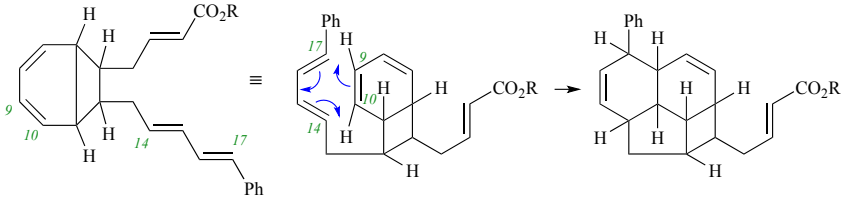
Sometimes it helps to draw dashed lines where you need to make bonds.



The starting material contains a 1,3,5,7-tetraene group (C5 to C12), and one of the bonds you need to make, C5–C12, is between the termini of that system. An eight-electron electrocyclic ring closing forms that bond. The electrocyclic reaction also creates a new 1,3,5-triene group (C6–C11), and another bond you need to make, C6–C11, is at the termini of that system. A six-electron electrocyclic ring closing forms that bond.

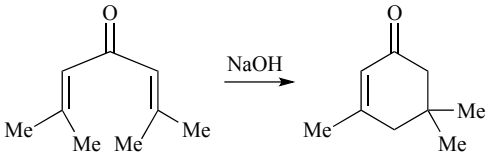


The last two bonds are formed by a Diels–Alder reaction ([4 + 2] cycloaddition) between the C9=C10 π bond and the diene from C14 to C17.

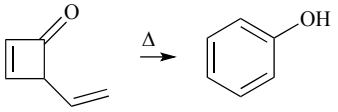


You may have been tempted to form the C5–C12 and C6–C11 bonds *simultaneously* by a [2 + 2] cycloaddition. You will soon see, though, that [2 + 2] cycloadditions of simple C=C π bonds are forbidden to occur under thermal conditions by the Woodward–Hoffmann rules.

Problem 4.3 When phorone is treated with base, isophorone is obtained by an electrocyclic ring closing. Draw a reasonable mechanism.

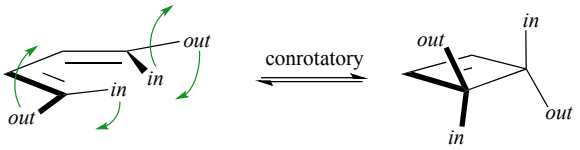


Problem 4.4 4-Vinylcyclobutenones are very unstable compounds, isomerizing rapidly to phenols. Draw a reasonable mechanism involving electrocyclic reactions.

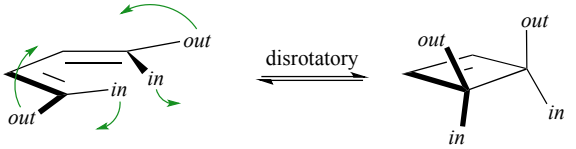


4.2.2 Stereospecificity

Of all the pericyclic reactions, the stereochemical course of electrocyclic reactions is easiest to understand, because electrocyclic reactions are unimolecular and involve only one array of orbitals. First, consider the electrocyclic ring closing of a butadiene, a four-electron reaction. The butadiene has four substituents at the termini. When the butadiene is in its reactive s-cis conformation, two of the groups can be described as *in* groups (because they are on the concave face of the arc defined by the four atoms of the butadiene group), and two as *out* groups (because they are on the convex face of the same arc). In the electrocyclic reaction, the termini of the butadiene must rotate in order for the *p* orbitals at the termini to overlap and form a bond. Two stereochemical results are possible. *The stereochemical result of the reaction depends on how the two termini rotate.* If the termini rotate in the same direction (conrotatory), then the two out groups become trans to each other, the two in groups become trans to each other, and any out group becomes cis to any in group.



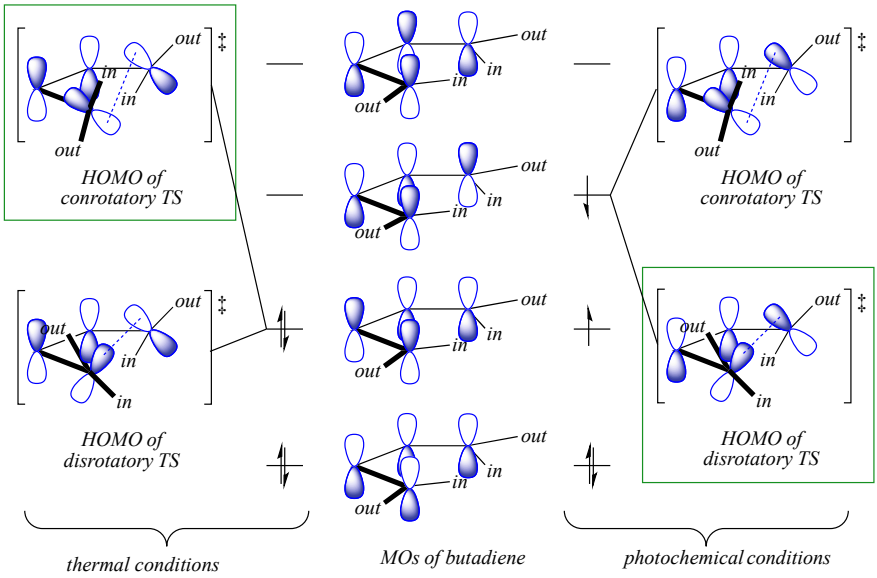
On the other hand, if they rotate in opposite directions (*disrotatory*), then the two out groups become cis to each other, the two in groups become cis to each other, and any out group becomes trans to an in group.



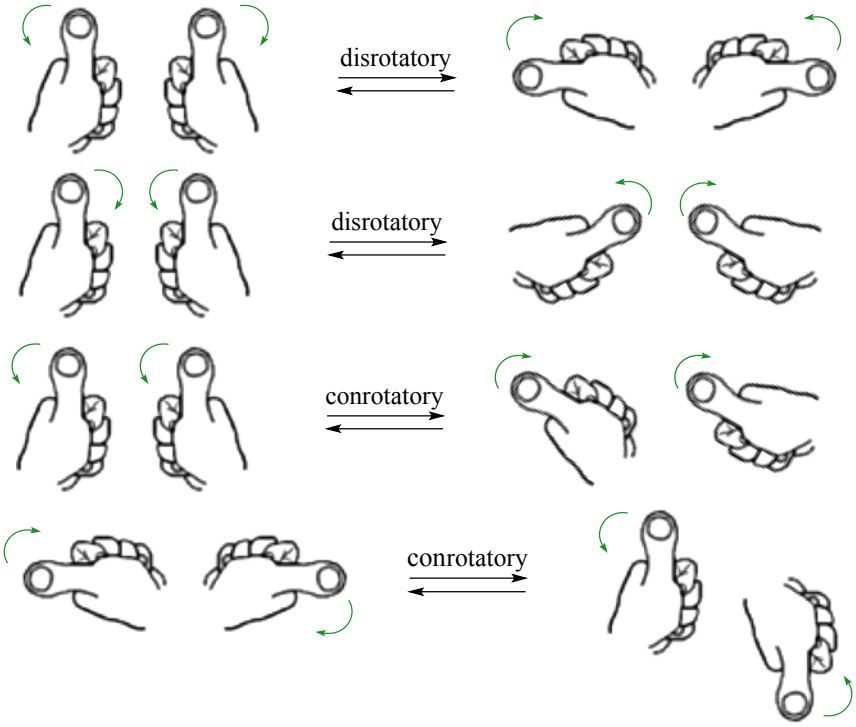
It happens that under thermal conditions the electrocyclic ring closing of butadienes always proceeds by the conrotatory pathway. There are several ways to rationalize this observation; we use the frontier MO method here. Under thermal conditions, the HOMO of 1,3-butadiene is ψ_1, and the LUMO is ψ_2. The electrocyclic ring closing proceeds so that there is a constructive interaction where bond-making takes place as the HOMO goes through the TS. Because the HOMO ψ_1 has a bonding interaction between the termini of the π system in the conrotatory TS and an antibonding interaction between the termini of the π system in the disrotatory TS, the reaction proceeds in conrotatory fashion.

Under photochemical conditions, the electrocyclic ring closing of butadienes always proceeds by the disrotatory pathway, which is the opposite of the result under thermal conditions. The FMOs make the stereochemical result easy to understand. Under photochemical conditions, an electron is promoted from the HOMO ψ_1 to the LUMO ψ_2, so ψ_2 becomes the HOMO. Molecular orbital ψ_2 has an antibonding interaction between the termini of the π system in the conrotatory TS but a bonding interaction between the termini of the π system in the disrotatory TS, so the reaction proceeds in disrotatory fashion.

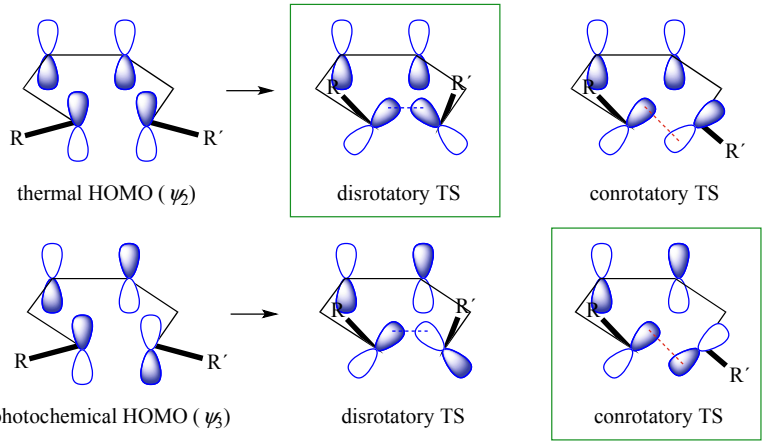
It is easier to see the FMO interactions in electrocyclic ring closing reactions than in ring opening reactions. However, the TSs for ring closing and ring opening are the same, so the stereochemistry of cyclobutene ring opening is conrotatory under thermal conditions and disrotatory under photochemical conditions—the same as the stereochemistry of butadiene ring closing.



In summary, for butadienes and cyclobutenes: Four-electron, thermal, conrotatory; four-electron, photochemical, disrotatory. The easiest way to visualize the stereochemical result is to make a fist, use your thumbs to designate substituents at the termini of the π system, and rotate your fists to determine the stereochemical result upon dis- or conrotatory ring closure or opening.



The stereochemistry of electrocyclic ring closings of 1,3,5-hexatrienes is opposite to that observed in 1,3-butadienes: under thermal conditions, they proceed by the disrotatory pathway, whereas under photochemical conditions, they proceed by the conrotatory pathway. The disrotatory TS derived from the thermal HOMO (ψ_2, symmetric) of 1,3,5-hexatriene and the conrotatory TS derived from the photochemical HOMO of 1,3,5-hexatriene (ψ_3, antisymmetric) have bonding interactions at the termini. Again, the TS for six-electron ring opening is the same as the TS for six-electron ring closing, so ring openings of 1,3-cyclohexadienes are also disrotatory under thermal conditions and conrotatory under photochemical conditions.



You may begin to discern a pattern. The Woodward–Hoffmann rules for electrocyclic reactions are as follows (Table 4.2): Electrocyclic reactions involving an odd number of electron pairs proceed through a disrotatory TS under thermal conditions and a conrotatory TS under photochemical conditions. Electrocyclic reactions involving an even number of electron pairs proceed through a conrotatory TS under thermal conditions and a disrotatory TS under photochemical conditions. In practice, you need only remember "even-thermal-con" (or any other combination) to generate the entire table.

Problem 4.5 Cycloheptatriene undergoes rapid electrocyclic ring closure under thermal conditions. Determine the structure and stereochemistry of the product.

Problem 4.6 Confirm that the proposed mechanism of formation of endriandic acid A is consistent with the observed stereochemistry of the product.

Problem 4.7 Draw the HOMO for the pentadienyl cation $H_2C{=}CH{-}CH{=}CH{-}CH_2^+$, and determine whether it should undergo disrotatory or conrotatory ring closing under thermal conditions. Then do the same for the pentadienyl anion $H_2C{=}CH{-}CH{=}CH{-}CH_2^-$. Are the stereochemical courses of these reactions consistent with the Woodward–Hoffmann rules?

The Woodward–Hoffmann rules for electrocyclic reactions can also be formulated in terms of being *suprafacial* and *antarafacial* (Table 4.3). A π system is said to react *suprafacially* in a pericyclic reaction when the bonds being made to the two

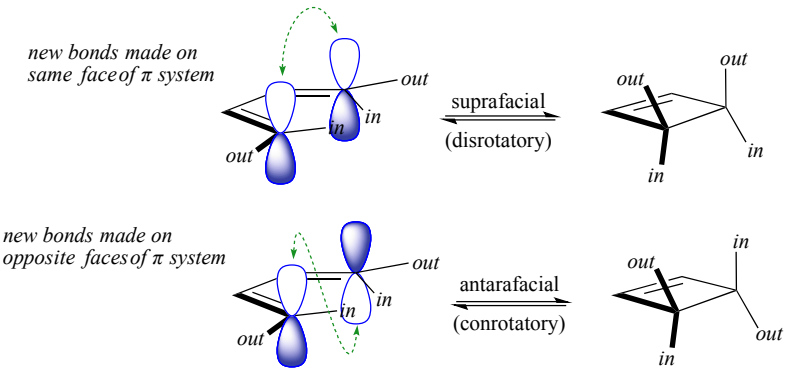
Table 4.2 Woodward–Hoffmann rules for electrocyclic reactions

Number of electron pairs	Δ	$h\nu$
Odd	Disrotatory	Conrotatory
Even	Conrotatory	Disrotatory

Table 4.3 Woodward–Hoffmann rules for electrocyclic reactions

Number of electron pairs	Δ	$h\nu$
Odd	Suprafacial	Antarafacial
Even	Antarafacial	Suprafacial

termini of the π system are made to the same face of the π system. It reacts *antarafacially* when the bonds are made to opposite faces of the π system. In electrocyclic reactions, disrotatory reactions are suprafacial, and conrotatory reactions are antarafacial.

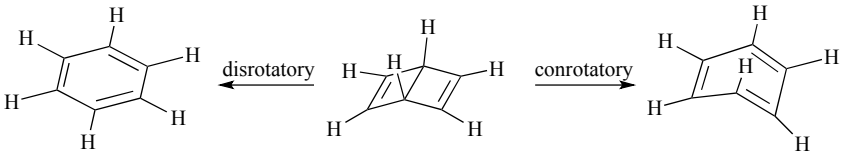


The value of the terms "suprafacial" and "antarafacial" is that, unlike "disrotatory" and "conrotatory", they can also be used to describe the way that π systems react in cycloadditions and sigmatropic rearrangements. Most importantly, when a π system reacts suprafacially, its out groups become cis in the product; when it reacts antarafacially, they become trans. Note that in disrotatory electrocyclic reactions, the out groups become cis, and in conrotatory electrocyclic reactions, the out groups become trans.

The property that the stereochemical result of an electrocyclic reaction is absolutely predictable is called *stereospecificity*. A stereospecific reaction will give you one stereochemical result when a cis starting material is used, and the opposite result when a trans starting material is used. Other examples of stereospecific reactions include S_N2 substitutions, catalytic hydrogenation of alkynes or alkenes, and dihydroxylation and bromination of alkenes.

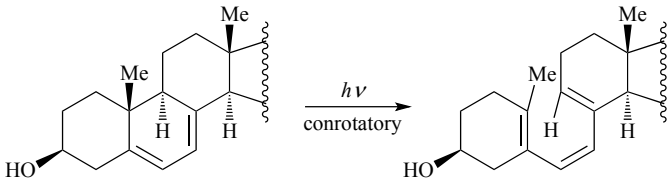
The Woodward–Hoffmann rules can be used to predict the stereochemical result of any electrocyclic ring opening or closing. There are a few conditions to the Woodward–Hoffmann rules of which you must be aware. First, the Woodward–Hoffmann rules apply only to concerted, pericyclic reactions. If an apparent electrocyclic reaction actually proceeds by a nonconcerted mechanism, the rules do not apply. Second, a reaction can be forced to proceed through the higher energy TS if the lower energy one is raised prohibitively high in energy by geometric

constraints. In these cases, the starting material is usually more stable than one would expect. For example, Dewar benzene is surprisingly stable, because for it to decompose to benzene, it must go through the "disallowed" disrotatory TS; the "allowed" conrotatory ring opening gives a trans double bond in the six-membered ring, which is prohibitively high in energy.



benzene *Dewar benzene* *argh*

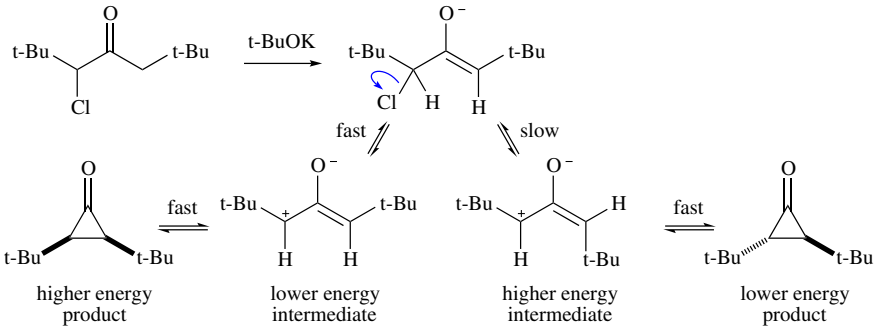
The biosynthesis of vitamin D_2 also illustrates the Woodward–Hoffmann rules. Mammals prepare precalciferol from ergosterol by a six-electron electrocyclic ring opening. The ring opening must proceed in conrotatory fashion (otherwise a trans double bond in a six-membered ring would be obtained), so it requires light. When sunlight never shines on one's skin, vitamin D_2 synthesis is inhibited, and one may develop rickets.



ergosterol *Z*-tachysterol (precalciferol)

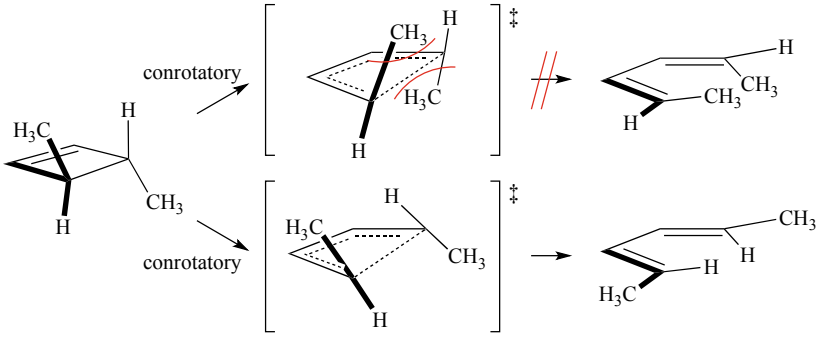
Of course, too much sunlight is bad for you, too, due to another photochemical pericyclic reaction that will be discussed later.

Two-electron electrocyclic ring openings are also stereospecific. 1-Chloro-1,3-di-*t*-butylacetone, upon treatment with base, can undergo electrocyclic ring closing to give di-*t*-butylcyclopropanone. The intermediate dipole can exist in three different diastereomeric forms. The lowest energy one has the *t*-Bu groups pointing outward. This out,out diastereomer undergoes disrotatory electrocyclic ring closing under the thermal conditions to give only the higher energy cis product, which is in fact the product that is observed first. In time, more trans product is observed, as the cis product undergoes stereospecific electrocyclic ring opening to the lower energy out,out dipole, which can undergo unfavorable equilibration to the higher energy out,in dipole, which can close to the lower energy, trans product!



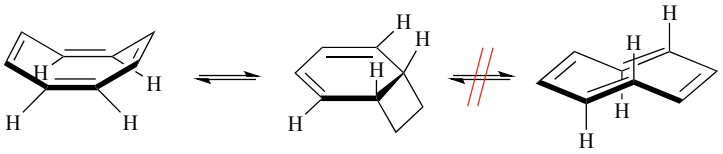
4.2.3 Stereoselectivity

Consider the electrocyclic ring opening of *trans*-3,4-dimethylcyclobutene. This compound opens in a conrotatory fashion under thermal conditions. Two products might be obtained from conrotatory ring openings allowed by the Woodward–Hoffman rules, but in fact only the trans,trans product is obtained, because there are severe steric interactions in the TS leading to the cis,cis product.

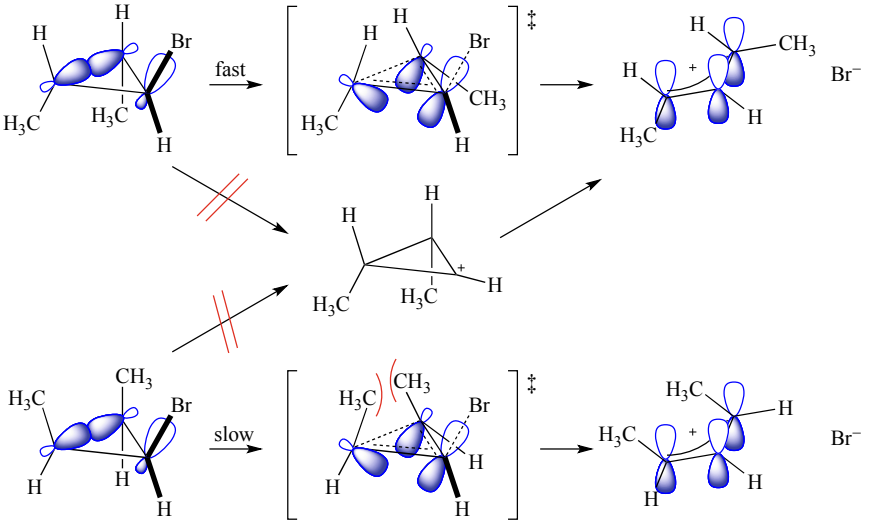


The phenomenon that one "allowed" TS is preferred over the other is called *torquoselectivity*, a special kind of stereoselectivity. The ring opening of *trans*-3,4-dimethylcyclobutene is *stereospecific* because the cis,trans isomer is never obtained, but it is *stereoselective* because the trans,trans isomer is selectively obtained over the cis,cis isomer.

Torquoselectivity is observed in a few other contexts. The ring opening of *cis*-bicyclo[4.2.0]octa-2,4-diene can occur in two disrotatory modes in principle. One of those modes, however, gives a product that has two trans double bonds in an eight-membered ring. This mode is disfavored with respect to the other disrotatory mode, which gives an all-cis product.

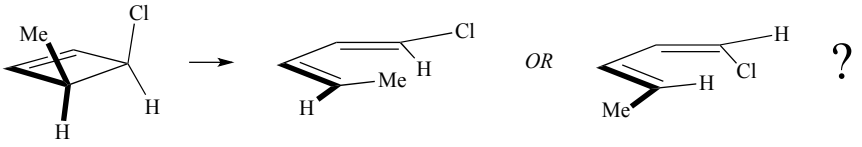


Halocyclopropanes undergo electrocyclic ring openings. Consider the two diastereomers of 1-bromo-*cis*-2,3-dimethylcyclopropane. If the Br^- left first to give a cyclopropyl cation, and then the ring opening occurred, then the trans- and cis-bromo compounds would give the same intermediate cyclopropyl cation; therefore, the allyl cation in which the two Me groups were "out" would be obtained from *either* diastereomer. Moreover, the cis-bromo compound would be expected to give the product more quickly because of steric encouragement of departure of the leaving group. In fact, though, the two isomers give isomeric allyl cations, and the trans-bromo compound reacts much more rapidly than the cis one. This result suggests that the two compounds do not proceed through a common intermediate produced by loss of Br^-, and therefore the loss of the leaving group and the ring opening must be concerted. Why does the trans-bromo compound react more quickly? The orbitals that constitute the breaking σ bond prefer to turn in the direction so that their large lobes overlap with the back lobe of the C–Br bond in the transition state (i.e., backside displacement of Br^-). In the cis-bromo compound, when the orbitals of the breaking σ bond turn in this way, the two Me groups bump into each other in the TS, so the reaction is much slower.



There are many cases where the torquoselectivity is not nearly so easy to explain or predict. For example, which diastereomer is predominantly obtained from the

electrocyclic ring opening of *cis*-3-chloro-4-methylcyclobutene? The answer is not obvious. Steric effects could easily be offset by electronic effects. Calculations of TS energies can sometimes give reasonably good predictions.

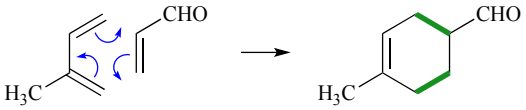


4.3 Cycloadditions

4.3.1 Typical Reactions

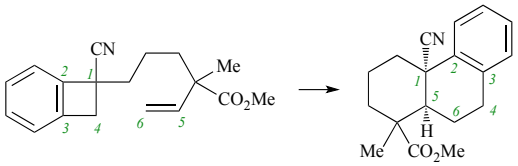
4.3.1.1 The Diels–Alder Reaction

The best-known cycloaddition is the *Diels–Alder reaction*, a six-electron, [4 + 2] cycloaddition. A 1,3-diene reacts with the π bond of a *dienophile* to give a six-membered ring with one π bond. Two new σ bonds are formed at the expense of two π bonds. The classic Diels–Alder reaction gives a carbocyclic ring, but hetero-Diels–Alder reactions, in which the new ring is heterocyclic, are widely used also.



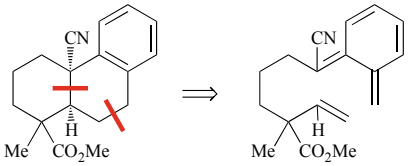
The product of the Diels–Alder reaction is a cyclohexene that has two new bonds in a 1,3-relationship. Look for the presence of such a ring in the product to determine that a Diels–Alder reaction has occurred.

Example

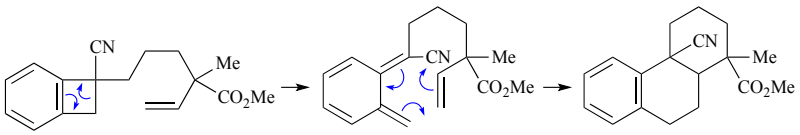


Make: C1–C5, C4–C6. Break: C1–C4. The two new σ bonds have a 1,3-relationship in a new six-membered ring, suggesting that a Diels–Alder

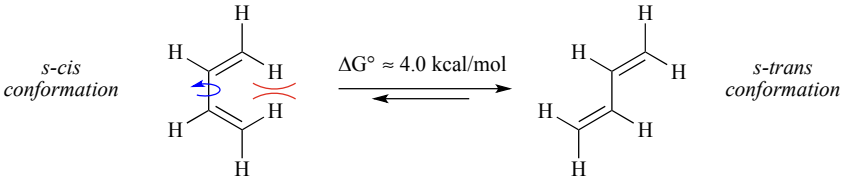
reaction has taken place. Disconnect the C1–C5 and C4–C6 bonds of the product to see the immediate precursor to the product, an *o*-xylylene. The double-bodied arrow (⇒), a *retrosynthetic arrow*, indicates that you are working backward from the product.



To get from the starting material to the *o*-xylylene, the C1–C4 bond needs to break. It can be broken by an electrocyclic ring opening of the cyclobutene. The entire mechanism in the forward direction, then, is as follows:

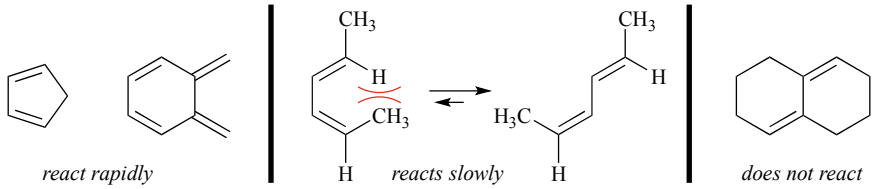


The Diels–Alder reaction requires that the diene be in the s-cis conformation, with the two double bonds of the diene coplanar and pointing in the same direction. Rotation about the σ bond between the internal C atoms of the diene interconverts the s-cis and s-trans conformations. In the s-trans conformation, there are fewer steric interactions between the *in* groups at the termini of the diene, so dienes normally reside predominantly in this lower energy (by about 4.0 kcal/mol) conformation. **Common error alert**: *Do not confuse the cis or trans configurations of the double bonds of a 1,3-diene substituted at the terminal C atoms with the s-cis and s-trans conformations of the diene.*

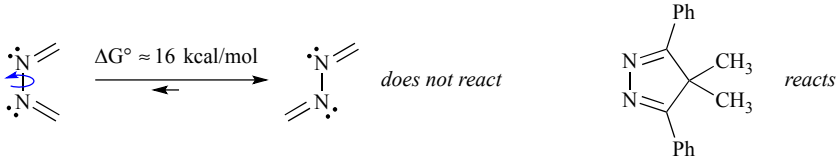


The barrier to converting the s-trans conformation to the s-cis conformation contributes to the overall activation barrier for Diels–Alder reactions. Structural factors that increase the proportion of diene in its s-cis conformation increase the rate of the Diels–Alder reaction, and factors that increase the proportion of diene in

its s-trans conformation decrease the rate of the reaction. Cyclopentadiene is one of the best dienes for the Diels–Alder reaction partly because it cannot rotate out of its s-cis conformation. In fact, cyclopentadiene undergoes [4 + 2] cycloaddition to itself so readily that it lasts only a few hours at 0 °C. *o*-Xylylenes are especially good dienes both because of their enforced s-cis geometry and because a nonaromatic starting material is transformed into an aromatic product. By contrast, dienes in which one of the double bonds is cis are poor substrates for Diels–Alder reactions because steric interactions between the *in* substituents in the s-cis conformation are particularly severe, and dienes whose s-trans conformation is enforced do not ever undergo the Diels–Alder reaction.

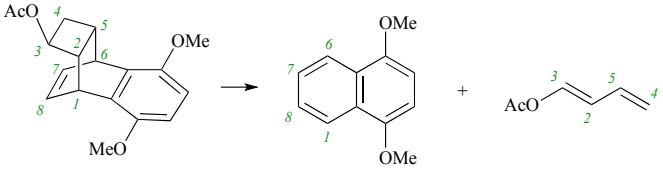


Similarly, acyclic 2,3-diazadienes (azines) have never been observed to undergo Diels–Alder reactions because the lone pairs on N repel one another, making the s-cis conformation about 16 kcal/mol higher in energy than the s-trans conformation. *Cyclic* azines, though, easily undergo Diels–Alder reactions.



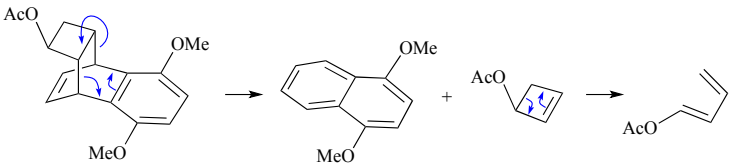
Because two σ bonds are produced at the expense of two π bonds, the Diels–Alder reaction is normally exothermic in the forward direction, but the *retro*-Diels–Alder reaction is facile when one of the products is N_2, CO_2, or an aromatic ring.

Example



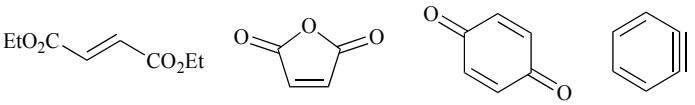
Make: none. Break: C1–C2, C3–C4, C5–C6. The C1–C2 and C5–C6 bonds are in a 1,3-relationship in a six-membered ring, and there is a C7=C8 π bond in

a 1,3-relationship to each of them in that ring. Therefore, the C1–C2 and C5–C6 bonds can be broken by a retro-Diels–Alder reaction to give the naphthalene and a cyclobutene. Cleavage of the C3–C4 bond then occurs by an electrocyclic reaction.



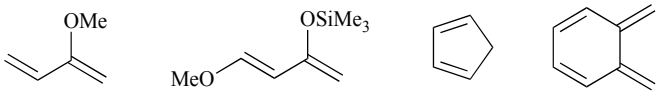
Most Diels–Alder reactions occur with what is called *normal electron demand*, in which an *electron-rich* (nucleophilic) *diene* reacts with an *electron-poor* (electrophilic) *dienophile*. The dienophile may be substituted with carbonyl, CN, sulfonyl, NO_2, or any other electron-withdrawing group. Dienophiles substituted with two electron-withdrawing groups (diethyl fumarate, maleic anhydride, benzoquinone) are particularly good substrates for the Diels–Alder reaction. Dienophiles that are not electron-poor undergo Diels–Alder reactions with electron-rich dienophiles under rather drastic conditions, if at all, although the rate of such a reaction can be increased by making it intramolecular. However, compounds with very strained double bonds (benzyne, norbornadiene) make good dienophiles even when they are not substituted with electron-withdrawing groups. Alkenes make better dienophiles than alkynes, all other things being equal.

Good Diels–Alder dienophiles

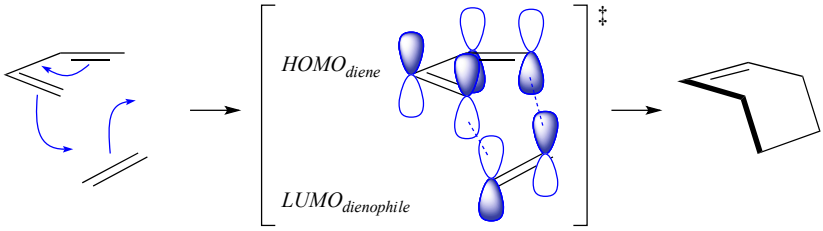


Dienes substituted with RO and R_2N groups (e.g., Danishefsky's diene, 1-methoxy-3-trimethylsilyloxy-1,3-butadiene) are particularly good substrates for Diels–Alder reactions, but alkyl-substituted dienes and even butadiene itself are common substrates. Benzene rings are very poor dienes in Diels–Alder reactions, because they lose aromaticity upon cycloaddition, but less aromatic compounds such as anthracene undergo Diels–Alder reactions more readily. Again, both cyclopentadiene and *o*-xylylenes are especially good dienes in Diels–Alder reactions.

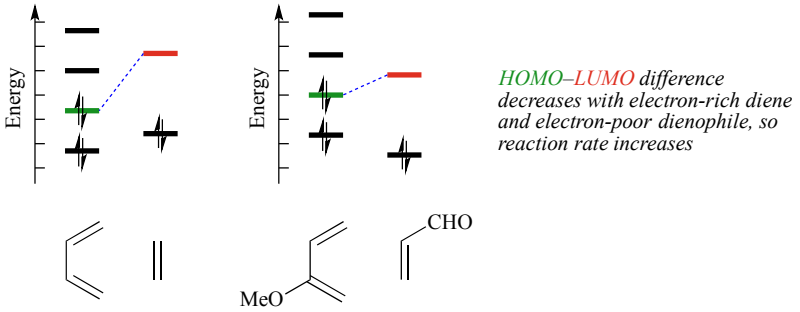
Good Diels–Alder dienes



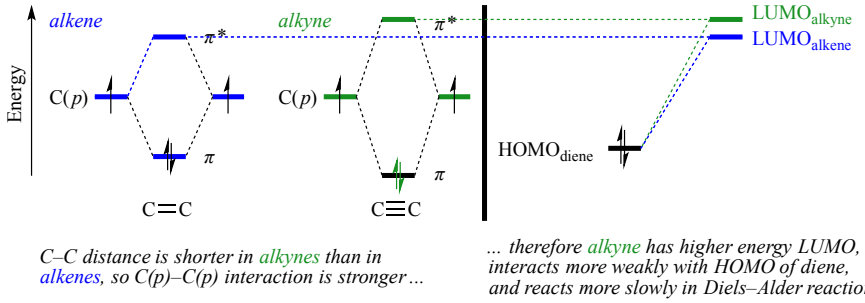
Frontier MO theory can be used to understand the dependence of the rate of the Diels–Alder reaction on the electronic nature of the substrates. Like any reaction, the rate of the Diels–Alder reaction is determined by the energy of its TS. In the TS of most Diels–Alder reactions, the *HOMO of the diene* interacts with the *LUMO of the dienophile*.



The energy of the Diels–Alder TS is directly related to the strength of the interaction between the MOs, which is in turn related to the difference in energy between the two MOs. The smaller the difference in energy between the two MOs, the stronger their interaction, the lower the energy of the TS, and the faster the reaction. The $HOMO_{diene}$, being a bonding orbital, is lower in energy than the $LUMO_{dienophile}$. Substitution of the diene with electron-donating groups raises the energy of the $HOMO_{diene}$, bringing it closer to the energy of the $LUMO_{dienophile}$, and substitution of the dienophile with electron-withdrawing groups lowers the energy of the $LUMO_{dienophile}$, bringing it closer to the energy of the $HOMO_{diene}$. Either of these substitutions brings the two orbitals closer in energy, increasing the rate of the reaction.



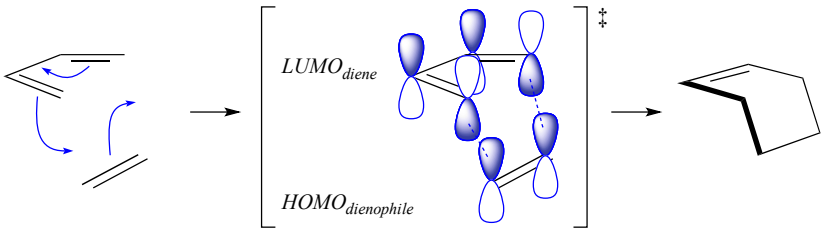
I mentioned earlier that alkynes are poorer dienophiles than the correspondingly substituted alkenes. The C≡C bond in an alkyne is shorter than the C=C bond in the corresponding alkene, so the C(*p*)–C(*p*) overlap is better, and thus the alkyne's HOMO is lower in energy and its LUMO higher in energy than the alkene's. The LUMO of the alkyne interacts more poorly with the $HOMO_{diene}$ than the lower energy LUMO of the alkene, so the Diels–Alder reaction of the alkyne is slower.



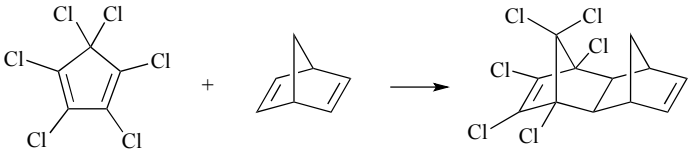
The energy of the $LUMO_{dienophile}$ can also be lowered by the use of a Lewis acid catalyst. The Lewis acid coordinates to the O of a carbonyl group substituent on the dienophile, lowering the energy of the $LUMO_{dienophile}$ and leading to an increased reaction rate. The Lewis acid also increases the regioselectivity and the stereoselectivity of the reaction. Use of a chiral Lewis acid can lead to an enantioselective Diels–Alder reaction. The development of catalytic asymmetric Diels–Alder reactions is an active area of research. **Common error alert**: *It is easy to assume that a reaction mechanism is polar acidic when a Lewis acid is present, but Lewis acids are often used to promote cycloadditions, too.*

Note that the dependence of the rate of a Diels–Alder reaction on the electronic match between $HOMO_{diene}$ and $LUMO_{dienophile}$ is a kinetic effect, not a thermodynamic one. The reaction of an electron-rich diene with an electron-rich dienophile is just as thermodynamically favorable as its reaction with an electron-poor dienophile, but it does not proceed at a perceptible rate.

Very electron-poor dienes can undergo Diels–Alder reactions with electron-rich dienophiles in the *inverse electron-demand* Diels–Alder reaction. The dominant interaction in the TS of inverse electron-demand Diels–Alder reactions is between the $LUMO_{diene}$ and the $HOMO_{dienophile}$.

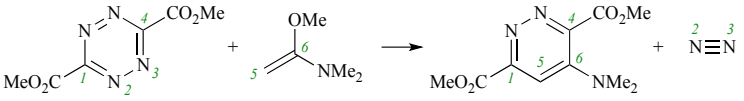


For example, the reaction of hexachlorocyclopentadiene with norbornadiene proceeds readily by an inverse electron-demand process to give Aldrin, an insecticide that has been banned because of its environmental persistence.

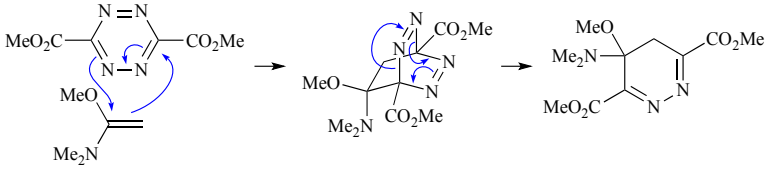


Dienes containing heteroatoms such as N and O undergo inverse electron-demand Diels–Alder reactions with electron-rich dienophiles such as enol ethers and enamines. The relatively low energy of the heteroatom *p* orbitals dramatically lowers the energy of both the $HOMO_{diene}$ and $LUMO_{diene}$.

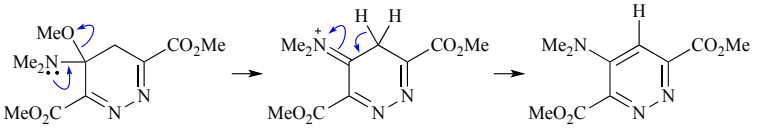
Example



Make: C1–C5, C4–C6. Break: C1–N2, C4–N3, C6–OMe. The two new σ bonds have a 1,3-relationship in the six-membered ring, suggesting a Diels–Alder reaction as the first step. The Diels–Alder adduct can undergo a retro-Diels–Alder reaction to cleave the C–N bonds and give N_2 as a coproduct.

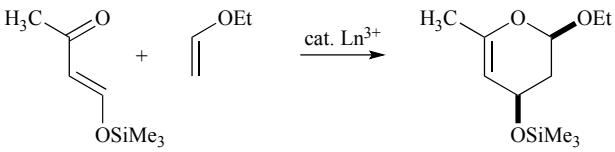


An elimination reaction (probably E1) then gives the observed product.

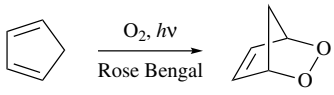


Lewis acid catalysis can lower the energy of $LUMO_{diene}$ in heterodienes even further, as in the cycloaddition of enol ethers to α,β-unsaturated carbonyl compounds. This reaction provides an important method for the synthesis of glucals,

dehydrated carbohydrates that are important building blocks in the synthesis of polysaccharides.

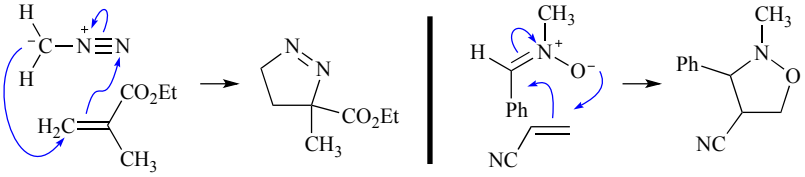


Heteroatomic dienophiles such as aldehydes and imines also participate in Diels–Alder reactions. Heteroatomic dienophiles have low-energy MOs, so they undergo normal electron-demand Diels–Alder reactions with electron-rich dienes. Singlet O_2 ($^1O_2$, O=O) also undergoes normal electron-demand Diels–Alder reactions. Atmospheric O_2 is a triplet, best described as a 1,2-diradical (·O–O·), whereas $^1O_2$ has a normal O=O π bond and no unpaired electrons. Triplet O_2 is converted to the higher energy singlet form by *hv* in the presence of a sensitizer such as Rose Bengal.

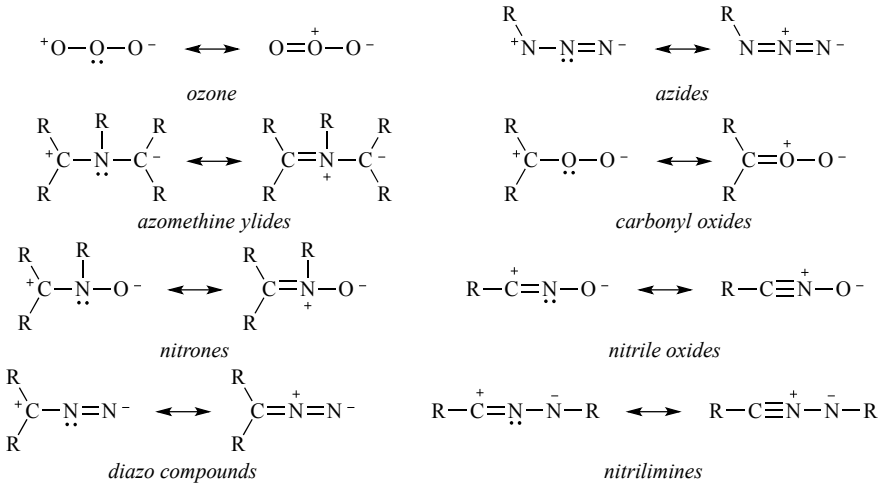


4.3.1.2 Other Cycloadditions

1,3-Dipoles react with alkenes and alkynes (*dipolarophiles*) in 1,3-dipolar cycloadditions (a.k.a., [3 + 2] cycloadditions) to give five-membered heterocycles. Many agrochemicals and pharmaceuticals contain five-membered heterocycles, and the dipolar cycloaddition is an important synthetic route to these compounds.

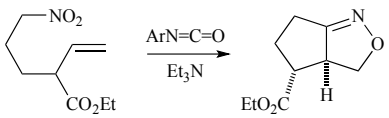


The three-atom component of the cycloaddition, the 1,3-dipole, is a compound for which a relatively low energy resonance structure can be drawn in which one terminus has a formal positive charge (and is electron-deficient) and the other terminus has a formal negative charge. All the common 1,3-dipoles have a heteroatom (N or O) in the central position in order to stabilize the electron-deficient terminus.

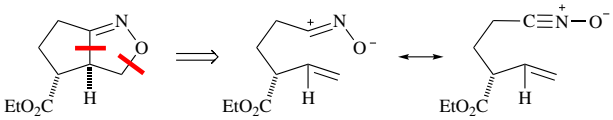


The five-membered heterocyclic product is the key to identifying a 1,3-dipolar cycloaddition. Many 1,3-dipoles are not stable, so they are generated by a series of polar reactions and then react in situ without being isolated.

Example

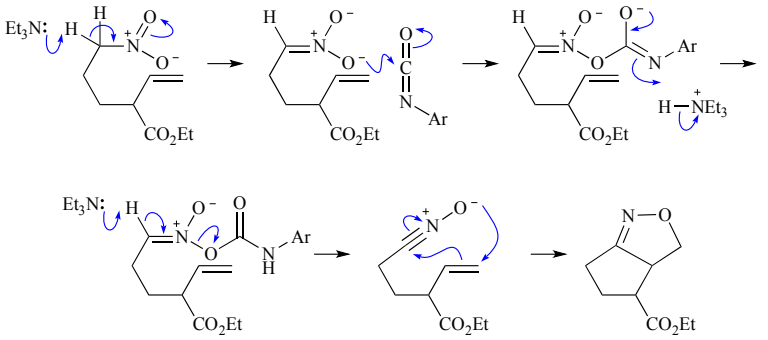


The reaction produces a five-membered heterocycle, suggesting a 1,3-dipolar cycloaddition. What penultimate intermediate would undergo a 1,3-dipolar cycloaddition to give the observed product? The two-atom component of the dipolar cycloaddition is the C=C π bond, so the three-atom component must be C–N–O. The C is likely to be the (+) terminus and the O the (–) terminus of the dipole. The 1,3-dipole in this reaction is a *nitrile oxide*, an unstable functional group that must be generated in situ.



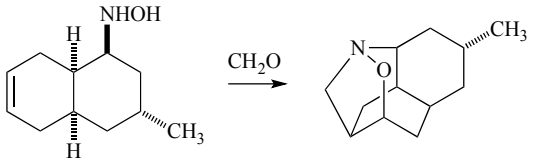
How is the nitrile oxide formed? The elements of water must be eliminated from the nitro compound, and an N–O bond must be cleaved. The O of the NO_2

group is not a leaving group, so the role of ArNCO must be to convert it into one. Nitro compounds are quite acidic ($pK_a = 9$), so deprotonation by Et_3N is the first step. Attack of O^- on the electrophilic C of the isocyanate, protonation of N, and then E2 elimination gives the nitrile oxide, which undergoes the [3 + 2] cycloaddition to give the product.



Note how this problem is most easily solved by working backwards one step from the product. This technique is very useful for solving pericyclic mechanism problems.

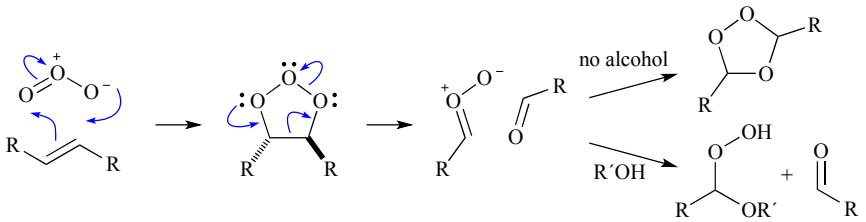
Problem 4.8 Draw a reasonable mechanism for the following reaction that involves a 1,3-dipolar cycloaddition. Hint: Work backwards one step from the product before working forward.



The selectivity of 1,3-dipoles for electron-rich or electron-poor dipolarophiles is complex. Very electron-poor dipoles such as ozone react most quickly with electron-rich and slowly with electron-poor dipolarophiles. Other dipoles, such as azides, react quickly with very electron-poor dipolarophiles, slowly with dipolarophiles of intermediate electronic character, and quickly with very electron-rich dipolarophiles. This "U-shaped reactivity" is due to a crossover in the nature of the reaction from $LUMO_{dipole}/HOMO_{dipolarophile}$-controlled to $HOMO_{dipole}/LUMO_{dipolarophile}$-controlled as the dipolarophile becomes more electron-poor. At intermediate electronic character, neither the $HOMO_{dipole}/LUMO_{dipolarophile}$ nor the $LUMO_{dipole}/HOMO_{dipolarophile}$ interaction is particularly strong, and the reaction proceeds slowly.

The reaction of ozone with alkenes is one of the most useful 1,3-dipolar cycloadditions. Ozone undergoes [3 + 2] cycloaddition to the alkene to give a

1,2,3-trioxolane, which immediately decomposes by a [3 + 2] retrocycloaddition to give a carbonyl oxide and an aldehyde. When the ozonolysis is carried out in the presence of an alcohol, the alcohol adds to the carbonyl oxide to give a hydroperoxide acetal. In the absence of alcohol, though, the carbonyl oxide undergoes another [3 + 2] cycloaddition with the aldehyde to give a 1,2,4-trioxolane.

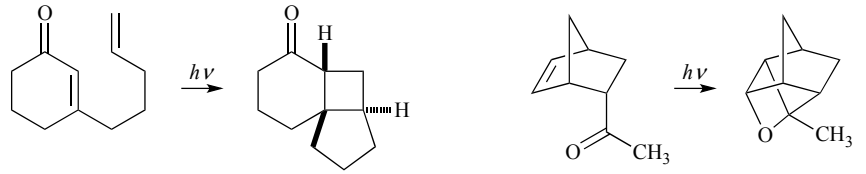


1,2,4-Trioxolanes are isolable, but they can explode when heated gently. Neither 1,2,4-trioxolanes and hydroperoxide acetals are usually isolated, though. They are decomposed in situ in one of three ways: by gentle reduction (Me_2S, Ph_3P, H_2 over Pd, or Zn/HCl) to give two aldehydes, by a stronger reduction ($NaBH_4$ or $LiAlH_4$) to give two alcohols, or oxidatively (H_2O_2 and acid) to give two carboxylic acids. (Obviously, if the alkene is tri- or tetrasubstituted, ketones and not aldehydes are obtained.) Today the Me_2S reduction is the most widely used method, as it gives the most valuable products (aldehydes) in high yields, and the coproduct (DMSO) is easily removed.

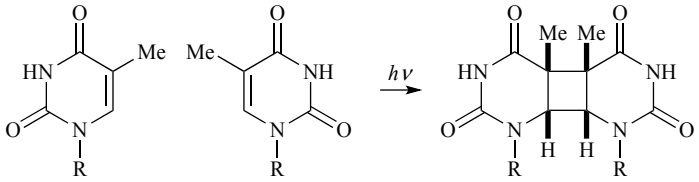
Problem 4.9 Draw a mechanism for the reaction of Me_2S with a 1,2,4-trioxolane to give two aldehydes.

The [2 + 2] cycloadditions are widely used reactions. There are basically three situations in which [2 + 2] cycloadditions are seen: when the reaction is promoted by light, when one of the components is a ketene ($R_2C{=}C{=}O$) or another *cumulene* (e.g., $RN{=}C{=}O$), or when one of the components has a π bond between C and a second-row or heavier element (e.g., $Ph_3P{=}CH_2$ or $Cp_2Ti{=}CH_2$).

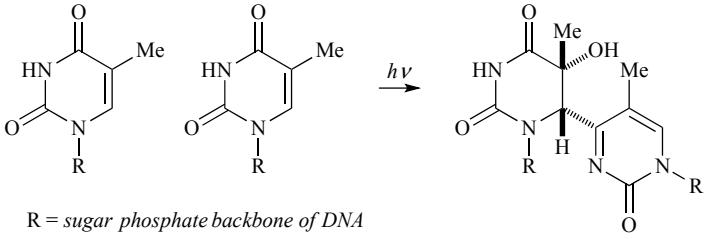
• The [2 + 2] photocycloaddition of two alkenes is widely used to form cyclobutanes. The reaction proceeds in the forward direction because the product cannot absorb light of the wavelengths that the starting material can absorb. In the Paterno-Büchi reaction, one of the two-atom components is a ketone or an aldehyde instead of an alkene. Why these [2 + 2] cycloadditions require light to proceed will be discussed later.



The light-induced [2 + 2] cycloaddition can occur in vivo. Two adjacent thymidine residues in DNA can undergo a [2 + 2] cycloaddition to give a *thymine dimer*. DNA repair enzymes excise the dimer and usually repair it correctly, but occasionally they make a mistake, and a mutation occurs. The mutation can lead to skin cancer. Sunlight is essential for your health (for the ergosterol to precalciferol electrocyclic ring opening), but not too much sunlight!

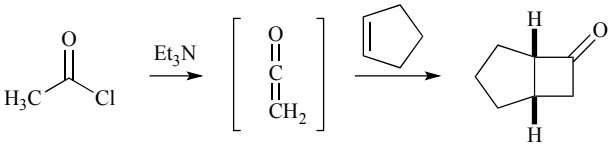


Problem 4.10 The thymine dimer shown in the preceding example is produced by a [2 + 2] cycloaddition of two C=C bonds. A different, perhaps more mutagenic thymine dimer is produced by a different [2 + 2] cycloaddition. Draw a detailed mechanism for the formation of the second type of thymine dimer.



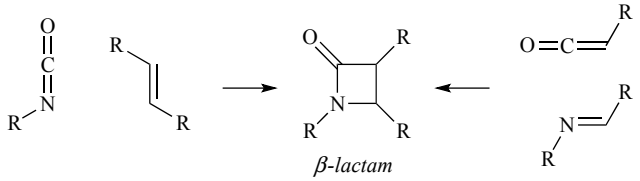
R = *sugar phosphate backbone of DNA*

• The ketene–alkene cycloaddition gives cyclobutanones in a *thermal* reaction. Most ketenes are not kinetically stable, so they are usually generated in situ, either by E2 elimination of HCl from an acyl chloride or by a Wolff rearrangement of an α-diazoketone (see Chap. 2).

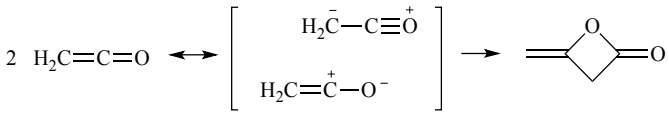


Other cumulenes such as isocyanates RN=C=O can also undergo thermal [2 + 2] cycloadditions. The [2 + 2] cycloaddition of an isocyanate and an alkene is a useful

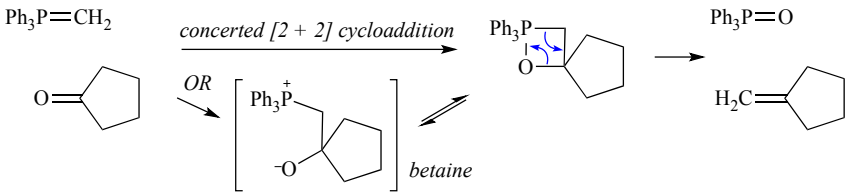
route to β-lactams, the key functional group in the penicillin and cephalosporin antibiotics, as is the [2 + 2] cycloaddition of a ketene and an imine.



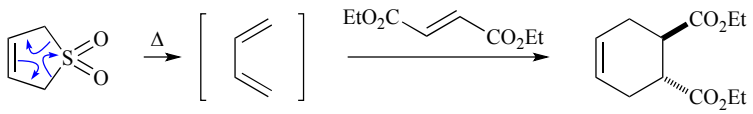
Ketenes dimerize by a [2 + 2] cycloaddition in the absence of another substrate. The electron-rich C=C π bond combines with the electron-poor C=O π bond to give a β-lactone.



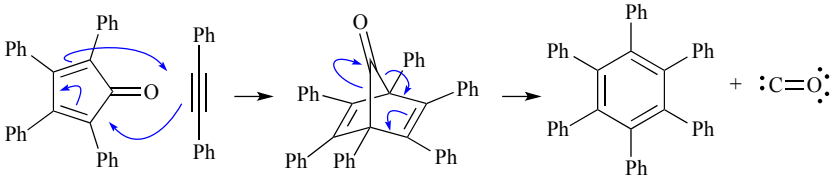
• The most important example of the third type of [2 + 2] cycloaddition is the Wittig reaction ($Ph_3P{=}CH_2 + R_2C{=}O \rightarrow Ph_3P{=}O + R_2C{=}CH_2$). The phosphorane adds to the ketone to give a phosphaoxetane, either by a concerted, [2 + 2] cycloaddition or by a two-step, polar process involving a *betaine* (pronounced BAY-tah-een) intermediate. The phosphaoxetane then undergoes [2 + 2] retrocycloaddition to give $Ph_3P{=}O$ and $R_2C{=}CH_2$.



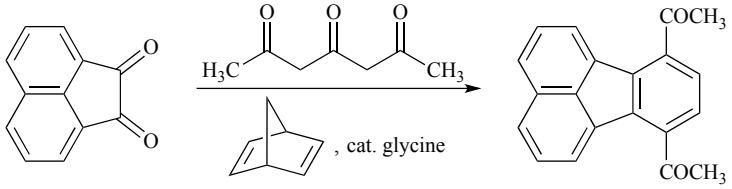
There are other kinds of cycloadditions, too. The [4 + 1] cycloaddition, a cheletropic reaction, usually goes in the retro direction for entropic reasons. 3-Sulfolene (butadiene sulfone, 2,5-dihydrothiophene 1,1-dioxide) undergoes a [4 + 1] retrocycloaddition to generate SO_2 and 1,3-butadiene, which can undergo a Diels–Alder reaction with a dienophile. It is much more convenient to use 3-sulfolene instead of 1,3-butadiene itself, as the latter compound is a gas that is prone to polymerization.



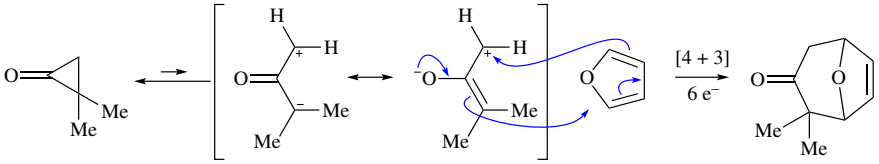
Cyclopentadienones are very prone to do Diels–Alder reactions because of their enforced s-cis conformation and their antiaromaticity. The Diels–Alder reaction of a substituted cyclopentadienone and an alkyne is followed immediately by a [4 + 1] retrocycloaddition to generate CO and an aromatic compound.



Problem 4.11 A cyclopentadienone is the starting point for a cascade of cycloadditions and retrocycloadditions in the following reaction. Draw a reasonable mechanism. Hint: Number the atoms and draw the coproducts!



The [2 + 1] cycloaddition of carbenes and alkenes to give cyclopropanes was discussed in Chap. 2. Other cycloadditions are less common, although [4 + 3], [4 + 4], [6 + 4], [8 + 2] and many other cycloadditions are certainly known. The [4 + 3] cycloaddition in particular involves an allyl cation as the three-atom component and an electron-rich diene as the four-atom component.

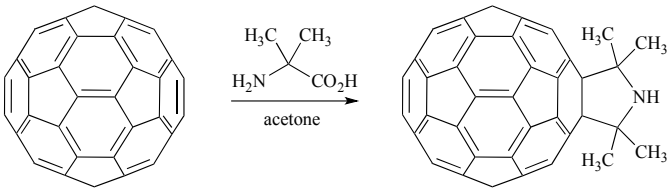


The following are some key ways of identifying cycloaddition reactions:

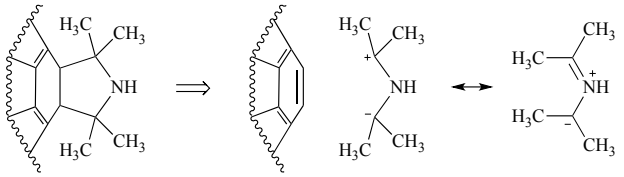
- All cycloadditions (except cheletropic reactions) form two new σ bonds between the termini of two π systems.
- If you see a new six-membered ring containing two new bonds with a 1,3-relationship and a π bond, think Diels–Alder! A six-membered ring fused to a benzene ring is often made by the [4 + 2] cycloaddition of an *o*-xylylene and a dienophile or by a [4 + 2] cycloaddition of benzyne and a 1,3-diene.

- If you see a five-membered *heterocycle,* especially one containing N, think 1,3-dipolar cycloaddition! One of the ring heteroatoms is the central atom of the 1,3-dipole.
- If you see a four-membered ring, think [2 + 2] cycloaddition, especially if the ring is a cyclobutanone (ketene) or light is required (photochemically allowed). Ketenes and other cumulenes undergo [2 + 2] cycloadditions with special facility. An oxetane (four-membered ring with one O) is often obtained from the [2 + 2] photocycloaddition of a carbonyl compound and an alkene.

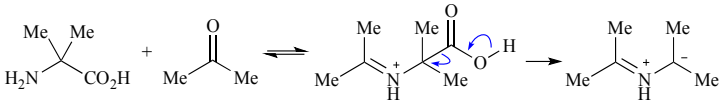
Example



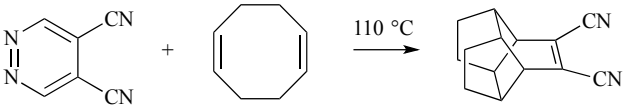
A five-membered heterocycle is formed, suggesting a 1,3-dipolar cycloaddition. A 1,3-dipole almost always has a heteroatom in the 2 position, and the heterocycle here has only one heteroatom, so the 1,3-dipole must be the azomethine ylide.



The azomethine ylide must form from the amino acid and acetone. Briefly, the amine condenses with acetone to give an iminium ion, and decarboxylation produces the 1,3-dipole, which can undergo [3 + 2] cycloaddition to C_{60} to give the observed product. By now you should be able to draw a mechanism for formation of the iminium ion.

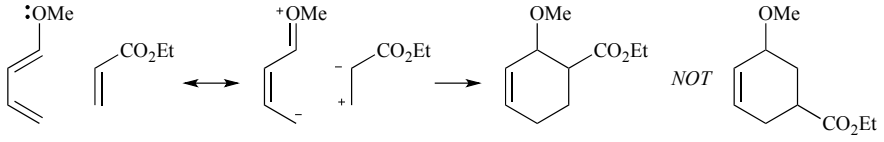


Problem 4.12 The following reaction proceeds by a series of cycloadditions and retrocycloadditions. Draw a reasonable mechanism.

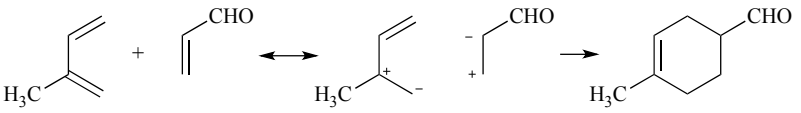


4.3.2 Regioselectivity

In the Diels–Alder reaction of *trans*-1-methoxybutadiene with ethyl acrylate, either the 1,2- or the 1,3-disubstituted product can be obtained in principle. The 1,3-disubstituted product is lower in energy (less steric hindrance), but the kinetic product is the 1,2-disubstituted compound. The easiest way to explain this phenomenon is to note that C4 of the diene is nucleophilic, and C2 of the dienophile (i.e., the β-carbon) is electrophilic. Combination of $C4_{diene}$ with $C2_{dienophile}$ gives the observed product.



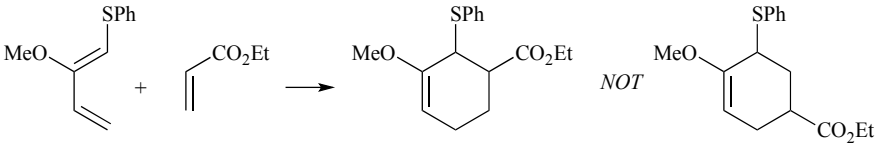
The same explanation can be used to rationalize the outcome of the reaction of isoprene (2-methyl-1,3-butadiene) with acrolein (2-propenal). In this case, though, since the diene is 2-substituted, $C1_{diene}$ is nucleophilic and combines with $C2_{dienophile}$ to give the observed product.



In fact, since most Diels–Alder reactions proceed by the reaction of nucleophilic dienes with electrophilic dienophiles, the following rule can be formulated: Diels–Alder reactions proceed to put the most electron-donating substituent on the diene and the most electron-withdrawing substituent on the dienophile either "ortho" or "para" to one another. This "ortho–para rule" misuses the terms ortho and para, which really apply only to benzene rings, but it allows one to remember the regioselectivity of these reactions fairly easily.

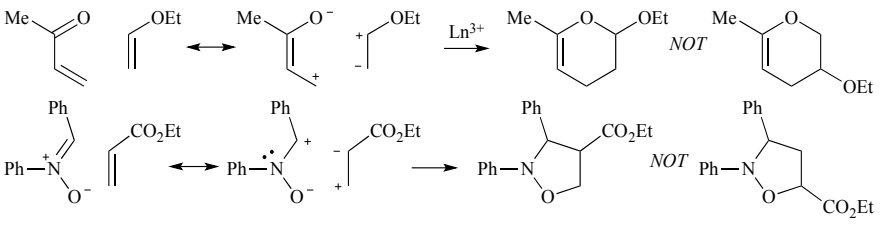
The regioselectivity of an *intramolecular* cycloaddition depends more on geometric constraints within the substrate than electronic preferences.

Sometimes the ortho–para rule doesn't work well, especially when two substituents on the diene have competing directing abilities. For example, a PhS substituent at $C1_{diene}$ is more strongly directing than a MeO substituent at $C2_{diene}$. By resonance arguments, the opposite should be the case, as MeO is a better resonance donor than PhS.



The only way the result can be explained is by looking at the coefficients of the orbitals of the HOMO of the diene and the LUMO of the dienophile. When the *p* orbitals of the diene combine in a bonding and antibonding way to make the HOMO and the LUMO, they do not contribute an equal weight to both MOs (unless the dienophile is symmetrical). (The situation is analogous to the one where C(sp^3) and O(sp^3) combine to form a σ bond: the O(sp^3) orbital contributes more to the σ orbital, and the C(sp^3) orbital contributes more to the σ^*.) *The Diels–Alder reaction proceeds so that the diene terminus with the largest coefficient in the diene HOMO interacts with the dienophile terminus with the largest coefficient in the dienophile LUMO*. It happens that the influence of substituents on C1 and C4 of the diene on the orbital coefficients is greater than that of substituents on C2 or C3. With simple dienes, the prediction from orbital coefficient arguments is usually the same as from the ortho–para rule—that the most electron-donating substituent on the diene and the most electron-withdrawing substituent on the dienophile are "ortho" or "para" in the product—but the orbital coefficient rule explains many cases that can't be explained simply by looking at resonance structures.

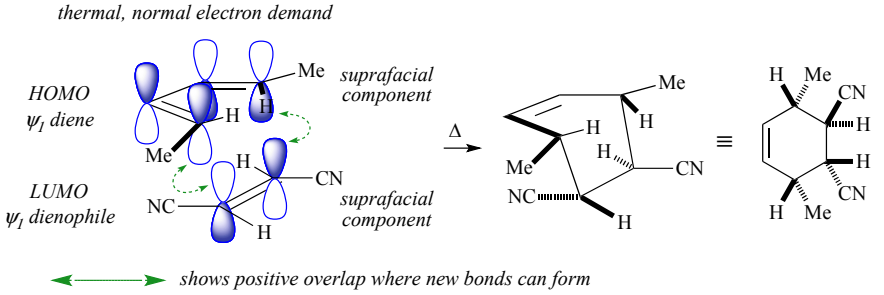
The regioselectivity of inverse electron-demand Diels–Alder reactions, 1,3-dipolar cycloadditions, and other cycloadditions can similarly be explained by resonance and orbital coefficient arguments. Determining which end of a 1,3-dipole is "nucleophilic" and which end is "electrophilic" can be dicey, though. In nitrones ($R_2C{=}\overset{+}{N}R{-}O^-$), the O is the nucleophilic end, so it reacts with the electrophilic end of a dipolarophile.



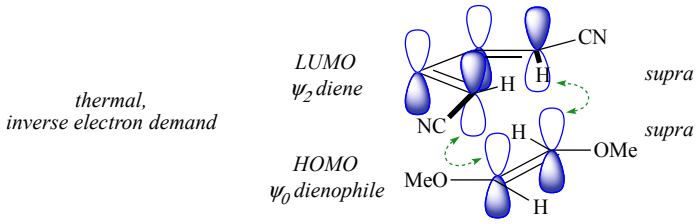
The problem with orbital coefficient arguments is that they require a calculation, whereas resonance arguments can be made using pen and paper. On the other hand, computers have made it possible for almost anyone to do a simple orbital coefficient calculation.

4.3.3 Stereospecificity

Some cycloadditions proceed thermally, whereas others require *hv*. The dependence of certain cycloadditions on the presence of light can be explained by examining interactions between the MOs of the two reacting components. Frontier MO theory suggests that the rate of cycloadditions is determined by the strength of the interaction of the HOMO of one component with the LUMO of the other. In normal electron-demand Diels–Alder reactions, $HOMO_{diene}$ (ψ_1) interacts with $LUMO_{dienophile}$ (ψ_1). Both of these orbitals are antisymmetric, so there is positive overlap between the orbitals where the two σ bonds form when both components of the reaction react from the same face of the π system (*suprafacially*).

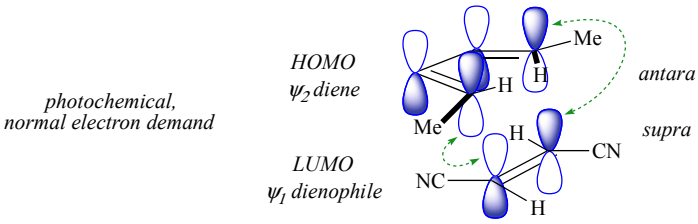


Under inverse electron demand, the symmetric $LUMO_{diene}$ (ψ_2) interacts with the symmetric $HOMO_{dienophile}$ (ψ_0). Again, there is positive overlap between the orbitals at both termini of the two π systems when both components of the reaction react suprafacially.

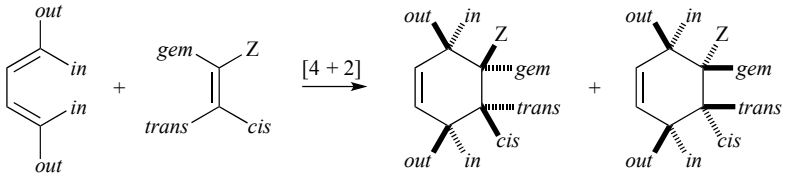


By contrast, under photochemical conditions and normal electron demand, $HOMO_{diene}$ changes from the antisymmetric ψ_1 to the symmetric ψ_2. In this case, positive overlap at both termini of the π systems can occur only if one of the π

components reacts *antarafacially*. This situation is very difficult to achieve geometrically, and hence six-electron cycloadditions do not proceed photochemically.

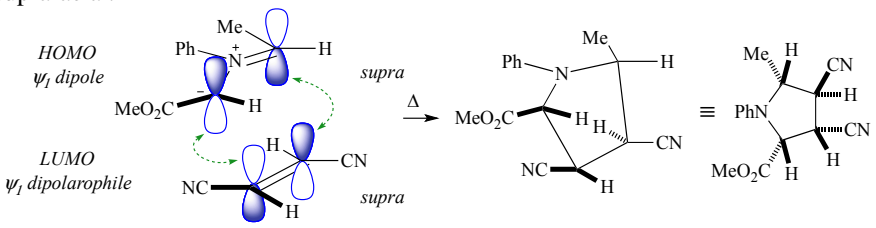


The stereochemical relationships among substituents in a suprafacial component of a cycloaddition are preserved in the cycloadduct. Groups that are cis (or trans) to one another in the dienophile become cis (or trans) to one another in the product. The two out groups in the diene become cis to one another in the product, as do the two in groups. Because one diastereomeric starting material gives one diastereomeric product, cycloadditions are said to be *stereospecific*.



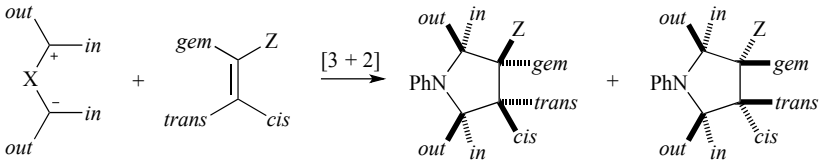
Note that two stereoisomeric products that are consistent with the Woodward–Hoffmann rules can be obtained. The Woodward–Hoffmann rules allow you to predict the stereochemical relationship between substituents derived from the *same* component. They do not allow you to predict the relationship between substituents derived from *different* components. Guidelines for predicting the latter kind of relationship will be discussed shortly.

An analogous picture can be drawn for [3 + 2] cycloadditions. These six-electron reactions can be either $HOMO_{dipole}/LUMO_{dipolarophile}$-controlled or $HOMO_{dipolarophile}/LUMO_{dipole}$-controlled. In either case, the maximum number of bonding interactions between the termini occurs when both components are suprafacial.



As in the Diels–Alder reaction, the stereochemistry of both starting materials is preserved in the products. The two out groups on the dipole become cis in the

product, as do the two in groups. The stereochemical relationships among the substituents of the dipolarophile are also preserved in the product.

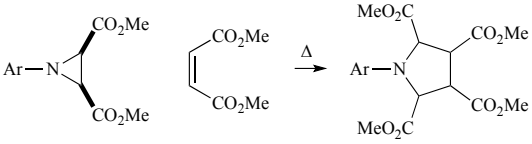


Which groups on the termini are in or out is less clear for 1,3-dipoles than it is for 1,3-dienes. The three atoms of the dipole form a curve. The terminal substituents pointing to the concave side of the curve are the in groups, and the substituents pointing to the convex side are the out groups.

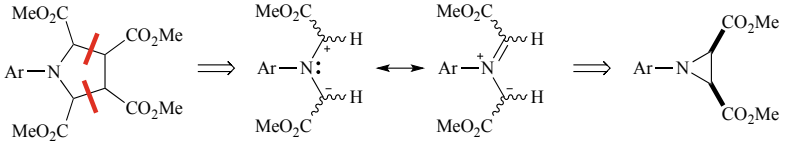
The suprafaciality of the 1,3-dipole component is important only when both ends of the dipole are C(sp^2) atoms (i.e., in azomethine ylides and carbonyl ylides). If either end of the dipole is N, O, or C(*sp*), the termini have no stereochemical relationship in either the dipole or the cycloadduct.

Example

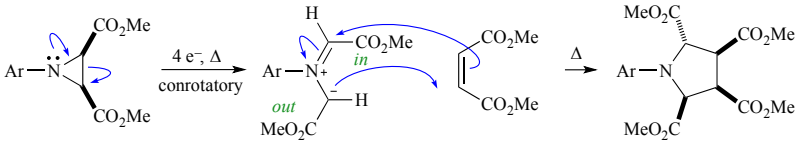
Predict the stereochemistry of the product of the following reaction



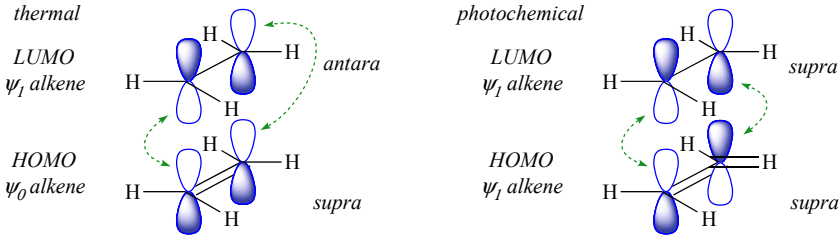
The product is clearly derived from a [3 + 2] cycloaddition. Disconnection of the appropriate bonds leads back to an azomethine ylide intermediate, which can be formed from the aziridine by electrocyclic ring opening.



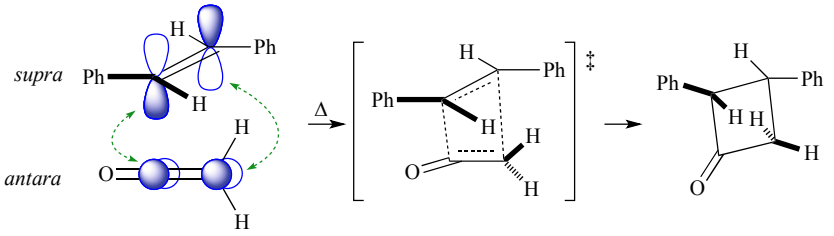
As for the stereochemistry, the electrocyclic ring opening of the aziridine is a four-electron process and is therefore conrotatory under thermal conditions. One CO_2Me group becomes an in group, and one an out group. The suprafacial nature of the [3 + 2] cycloaddition means that these two groups become trans in the product. The two ester groups on the dipolarophile, of course, retain their stereochemistry. The orientation of the esters in the product is "up, down, down, down" (or vice versa).



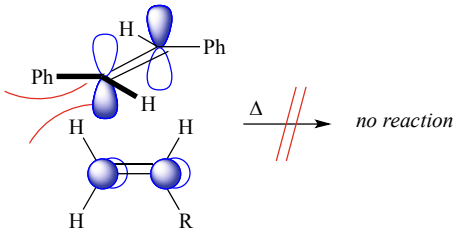
Under thermal conditions, the TS of the [2 + 2] cycloaddition is made up of the antisymmetric ψ_1 (the LUMO) of one component and the symmetric ψ_0 (the HOMO) of the other. Positive overlap between the orbitals at both termini of the π systems can be obtained only if one of the components reacts antarafacially. This orientation is very difficult to achieve geometrically, and hence [2 + 2] cycloadditions do not normally proceed under thermal conditions. However, under photochemical conditions, one of the components has an electron promoted from ψ_0 to ψ_1. Now the HOMO–LUMO interaction is between ψ_1 of the photoexcited component and ψ_1 of the unexcited component, and thus *both* components can be suprafacial in the TS. The [2 + 2] cycloaddition of most alkenes and carbonyl compounds do in fact proceed only upon irradiation with light.



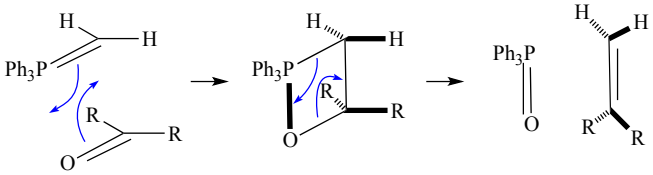
Three classes of [2 + 2] cycloadditions do proceed under thermal conditions. Ketenes ($R_2C{=}C{=}O$) undergo concerted cycloadditions to alkenes under thermal conditions because the ketene can react *antarafacially* with an alkene that reacts *suprafacially*. The two termini of the C=C π bond of the ketene react from *opposite* faces of the π bond, creating positive overlap between the orbitals at both termini of the two π systems. The antarafacial nature of the ketene does not have any stereochemical consequences, as there is no cis–trans relationship in the ketene to preserve in the product. The alkene component of the [2 + 2] cycloaddition with ketenes, however, reacts suprafacially, and its stereochemistry is *preserved* in the product.



Why is it that ketenes are able to react antarafacially, and alkenes are not? After all, the π orbital of the ketene that reacts antarafacially is also present in an alkene. In ketenes, one of the C atoms has only the sterically undemanding O atom attached to it. Common alkenes have sterically demanding substituents on *both* ends of the antarafacial component. The substituents at one end of the antarafacial alkene jut directly into the path of the other alkene in the TS, sterically inhibiting the reaction.



The second kind of thermally allowed [2 + 2] cycloaddition occurs when one of the atoms involved is a second-row or heavier element, as in the Wittig reaction. Whether the first step of the Wittig reaction actually proceeds in a concerted fashion is a matter of debate, but the point here is that a concerted mechanism is a reasonable possibility. Moreover, there is no controversy over whether the second step of the mechanism is a concerted [2 + 2] retrocycloaddition.

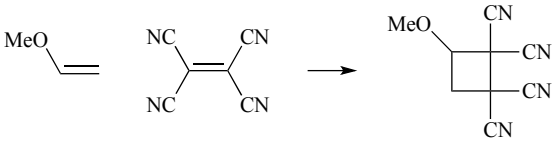


Why aren't the [2 + 2] cycloaddition and retrocycloaddition of the Wittig reaction disallowed? The Woodward–Hoffmann rules state that when the symmetries of the MOs of the reactants are mismatched in ways that we have discussed, the TS for the reaction is raised very high in energy, and the reaction is therefore "disallowed". In principle, even a disallowed reaction can proceed at sufficiently high temperatures; the reason this approach usually doesn't work is that other reactions usually take place at temperatures far below those required for the disallowed process. (However, even a symmetry-disallowed reaction involving only C=C π bonds can proceed at reasonable temperatures if it is particularly favorable, as in the electrocyclic ring opening of Dewar benzene to benzene.) Now, the Wittig reaction proceeds at ordinary temperatures because when π bonds to elements heavier than C, N, or O are involved in pericyclic reactions, factors other than mismatches in MO symmetries become much more important to the energy of the TS. In other words, the concerted mechanism for the Wittig reaction *is* disallowed by the Woodward–Hoffmann symmetry rules, but it is not *as* disallowed as the [2 + 2] cycloadditions of C=C or C=O π bonds. Other factors, including the poor

overlap of the orbitals comprising the C=P π bond, the very high energy of that bond, and the very low energy of the P–O σ bond, lower the energy of the TS of the Wittig reaction enough that it proceeds at ordinary temperatures.

Metal alkylidenes ($M{=}CR_2$) undergo thermally allowed [2 + 2] cycloadditions with alkenes during *olefin metathesis* (see Chap. 6) and other reactions for similar reasons.

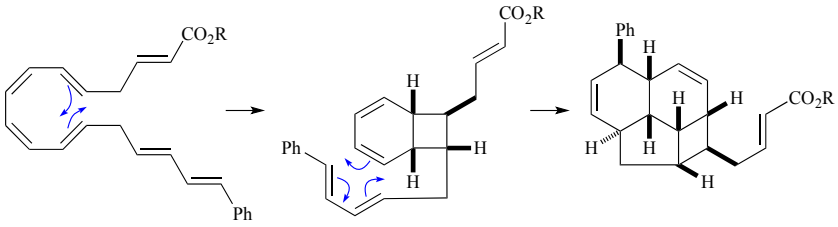
In the third class of thermally allowed [2 + 2] cycloadditions, a very electron-rich alkene is allowed to react with a very electron-poor alkene. These reactions almost certainly proceed stepwise through a zwitterionic or diradical intermediate, so they are not pericyclic reactions, and no violation of the Woodward–Hoffmann rules occurs. [2 + 2] Cycloadditions that proceed by a stepwise mechanism are nonstereospecific.



To summarize, most [2 + 2] cycloadditions are light-promoted. The only concerted thermal [2 + 2] cycloadditions involve a ketene or other cumulene or a compound in which a heavy atom such as P or a metal is doubly bound to another element. **Common error alert**: *If neither component of a thermal [2 + 2] cycloaddition is a member of these classes, the cycloaddition must proceed by a stepwise mechanism.*

Example

Provide *two* reasons why the following mechanism for the formation of endiandric acid A is unreasonable.



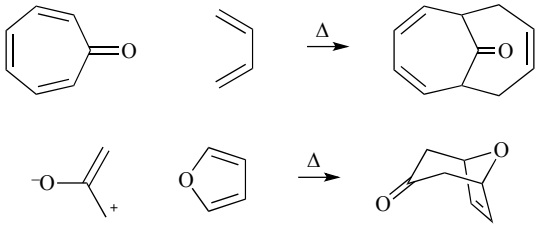
Reason 1: [2 + 2] Cycloadditions do not occur under thermal conditions unless one of the components is a ketene or has a heavy atom. No light is specified in this reaction, and ambient light is not sufficient to promote a [2 + 2] cycloaddition. Reason 2: Both π bonds that participate in the purported [2 + 2] cycloaddition have trans H substituents. In the bicyclic product, though, the two

bottom H atoms of the cyclobutane are cis. Therefore, one of the π bonds would have to be reacting antarafacially, which is geometrically impossible.

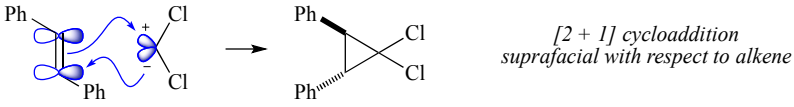
The Woodward–Hoffmann rules for cycloadditions (Table 4.4) are as follows. Both components of a cycloaddition involving an odd number of electron pairs are suprafacial under thermal conditions; under photochemical conditions, one component must be antarafacial. Both components of a cycloaddition involving an even number of electron pairs are suprafacial under photochemical conditions; under thermal conditions, one component must be antarafacial.

Photochemical suprafacial–antarafacial reactions are very rare because the geometrically simpler thermal reaction is likely to occur instead.

Problem 4.13 What do the Woodward–Hoffmann rules suggest about the facial reactivity of the components of the following thermal [6 + 4] cycloaddition and thermal [4 + 3] cationic cycloaddition?



The application of the Woodward–Hoffmann rules to cheletropic reactions is not straightforward. In the [2 + 1] cycloaddition of singlet carbenes to alkenes, the stereochemistry of the alkene is preserved in the product, so the alkene must react suprafacially. The Woodward–Hoffmann rules suggest that the carbene component of this thermal, four-electron reaction must react *antarafacially*. However, what this means for a species lacking a π system is difficult to interpret.

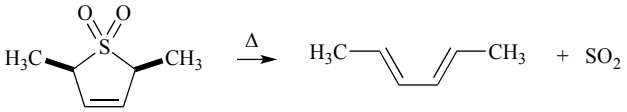


The [4 + 1] retrocycloaddition proceeds suprafacially with respect to the four-atom unit, with cis substituents on the terminal carbons of the four-atom unit

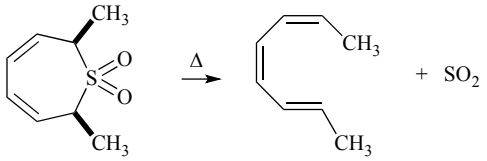
Table 4.4 Woodward–Hoffmann rules for cycloadditions

Number of electron pairs	*Δ*	*hv*
Odd	Suprafacial–suprafacial	Suprafacial–antarafacial
Even	Suprafacial–antarafacial	Suprafacial–suprafacial

becoming *out* in the product. The one-atom component must react suprafacially, but again, what this means for a species lacking a π system is difficult to interpret.

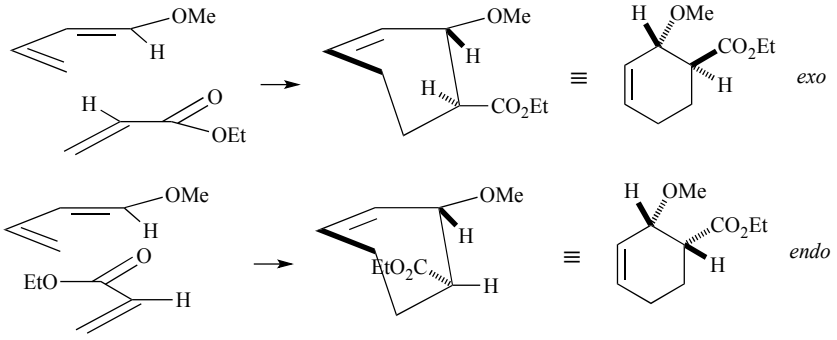


Not all cheletropic reactions proceed suprafacially with respect to the larger component. In the following [6 + 1] retrocycloaddition, the Me groups are cis in the starting material, but one becomes out in the product, and the other becomes in. Results such as these are difficult to rationalize or predict a priori.



4.3.4 Stereoselectivity

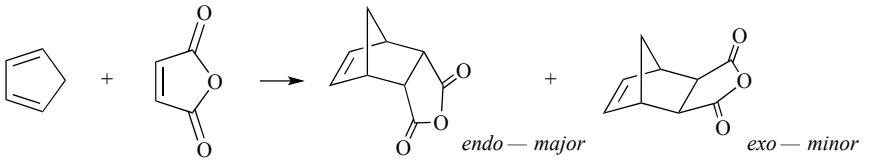
Consider the Diels–Alder reaction between 1-methoxybutadiene and ethyl acrylate. The major product has the MeO and CO_2Et groups on adjacent C atoms. A reaction that is stereospecific with respect to each component could give either the cis or the trans product. The TS leading to the product in which the substituents are trans is clearly less sterically encumbered than the other TS, and so one would predict that the trans product is predominantly obtained. However, the major product is the one in which the groups are cis.



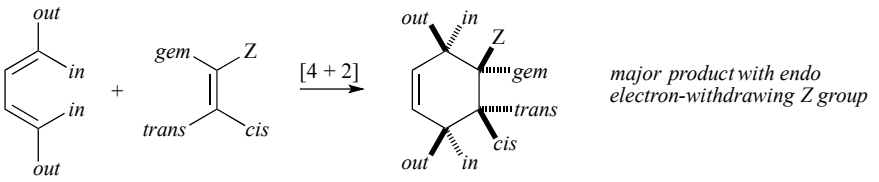
Diels–Alder reactions generally proceed selectively via the TS in which the most powerful electron-withdrawing group on the dienophile is endo, i.e., sitting

underneath the diene, as opposed to pointing away from it. This phenomenon is known as the endo rule.

The Diels–Alder reactions of dienophiles with cyclopentadiene to give norbornenes were among the earliest studied. The fact that the endo norbornene (the one in which the electron-withdrawing group derived from the dienophile was cis to the two-carbon bridge) was always obtained was called the endo rule. The rule was later extended to Diels–Alder reactions not involving cyclopentadiene, and the terms exo and endo then changed their meaning.

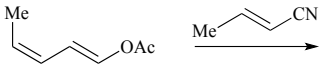


The *out–endo→cis* mnemonic device allows you to draw the products of Diels–Alder reactions with stereochemistry consistent with the endo rule. The first word of the mnemonic refers to the orientation of a group on a terminus of the diene. The second word refers to a substituent on the dienophile (usually the most electron-withdrawing one). The third word gives the stereochemical relationship of these two groups in the product. Thus, the out group on the diene and the endo group on the dienophile are cis in the product. Either of the first two words can be toggled to its opposite, as long as the third word is toggled, too: out–exo→trans, in–endo→trans, and in–exo→cis. To apply the out–endo→cis mnemonic, you must determine which group on the dienophile is the endo group. Application of the out–endo→cis mnemonic then gives the stereochemistry of the major product.



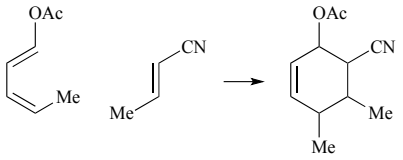
Example

Predict the stereochemistry of the major product of the following Diels–Alder reaction.

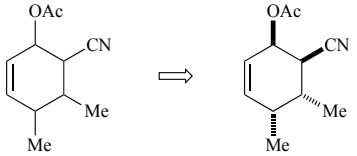


First redraw the starting material and product so that they are in the proper conformation (s-cis for the diene) and mutual orientation. Orient the two so that

the strongest electron-donating group on the diene is in a 1,2- or 1,4-relationship with the strongest electron-withdrawing group on the dienophile. Then draw the product with no stereochemistry indicated.

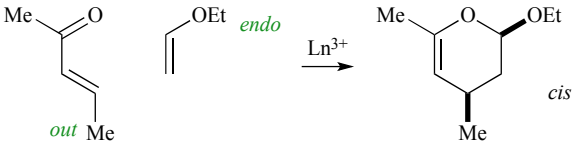


Stereochemistry: The most electron-withdrawing group on the dienophile is endo, and the out–endo→cis mnemonic tells you that the OAc and CN groups are cis in the product. The suprafacial–suprafacial nature of the Diels–Alder reaction tells you that the two out groups on the diene become cis, and that the stereochemistry of the dienophile is preserved in the product, so the OAc group (out) and the Me group opposite it (in) are trans in the product, and the CN group and the Me group next to it are also trans in the product. Draw the OAc up (or down, it doesn't matter), and the rest of the stereochemistry follows.



Common error alert: *Be certain to preserve the stereochemistry about all three π bonds.* When a diene is drawn in its s-trans conformation, as in the preceding example, students often inadvertently isomerize the π bonds when they try to redraw it in its s-cis conformation. A correct application of the out–endo→cis mnemonic then leads to an incorrect answer. Following Grossman's rule can help prevent this common error.

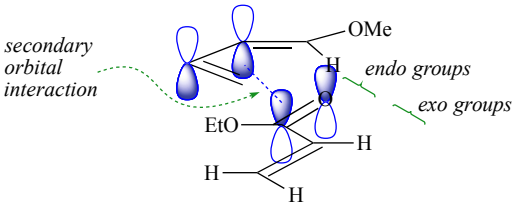
The endo rule applies equally to inverse electron-demand Diels–Alder reactions. In these reactions, the most electron-donating group on the dienophile is preferentially endo. The out–endo→cis rule applies, too.



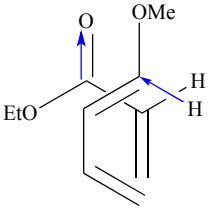
The endo/exo ratio in any particular reaction can vary a lot depending on reaction conditions and the substrates. The ratio increases in favor of the endo product when Lewis acids are used to accelerate the Diels–Alder reaction. Increased

steric interactions can turn the tide in favor of the exo product. In intramolecular Diels–Alder reactions, the ratio depends more on conformational preferences than anything else, and either exo or endo products may be obtained predominantly, depending on the reaction conditions and the particular substrate.

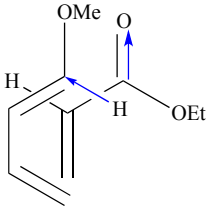
Why is the endo TS lower in energy than the exo TS? The most widely accepted explanation cites *secondary orbital interactions*. In the more crowded approach, the orbitals of the carbonyl group of the dienophile can interact with the orbital on C2 of the diene. The secondary orbital interactions in the endo TS are energetically favorable, so the kinetic product is the more crowded, less thermodynamically stable endo product.



The preference for the endo TS can also be rationalized by invoking effects other than secondary orbital interactions. For example, the dipoles associated with the in C–H bond of the diene and the electron-withdrawing group of the dienophile interact most favorably when the electron-withdrawing group is endo. Lewis acids increase the endo selectivity by polarizing the electron-withdrawing group and thus increasing the magnitude of the dipole. The endo selectivities of Diels–Alder reactions of certain substrates can also be explained by steric and solvent effects.

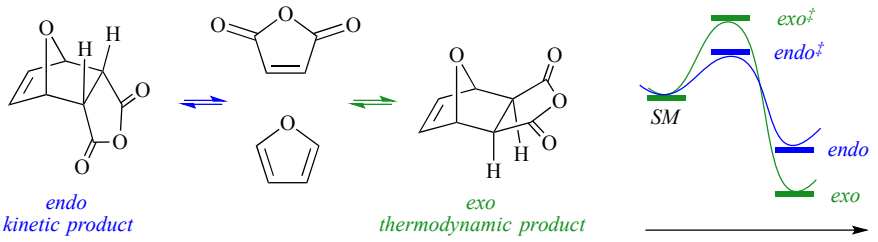


endo TS: dipoles aligned favorably

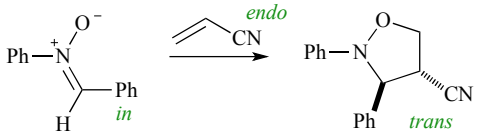


exo TS: dipoles aligned unfavorably

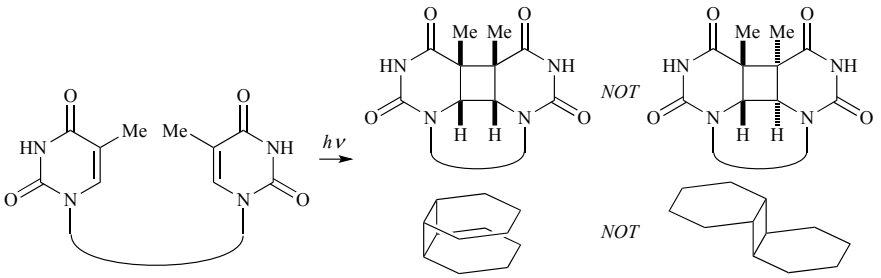
Endo selectivity is a kinetic phenomenon. If an equilibrium is established between the higher energy endo and lower energy exo products, then predominantly exo products will be seen. The cycloaddition of maleic anhydride and furan proceeds very rapidly, even at very low temperatures, to give only the exo product. The unusually low energy of furan (an aromatic compound) allows the retro-Diels–Alder reaction of the endo product to proceed at a reasonable rate. Even though the rate of formation of the endo product is faster than the rate of formation of the exo product, establishment of an equilibrium between starting materials and products leads to a thermodynamic ratio that favors the exo product.



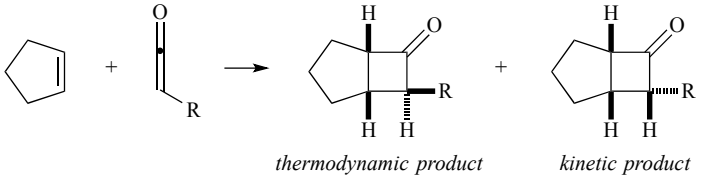
1,3-Dipolar cycloadditions give predominantly endo products, too. The out–endo→cis mnemonic applies.



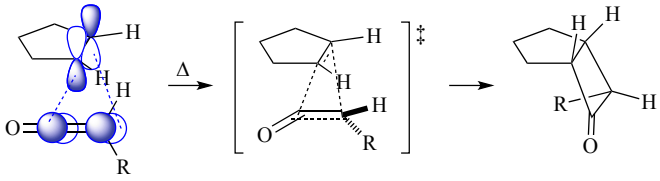
[2 + 2] Photocycloadditions also proceed to give predominantly endo products. For example, the light-induced dimerization of thymidine occurs with endo selectivity. The carbonyl group of one ring positions itself over the other ring, and the more sterically crowded stereoisomer is obtained.



In the [2 + 2] cycloaddition of monosubstituted ketenes to cycloalkenes, two products can also be obtained. The thermodynamic product, where the R group is on the convex face of the bicyclic system, is *not* obtained predominantly. In fact, the reaction is "masochistic": the larger the R group, the greater the proportion of the higher energy product.



Because the ketene must react antarafacially, the alkene approaches the ketene with the two π bonds nearly perpendicular to each other. The smaller portion of the ketene, the C=O group, sits under the ring of the alkene, while the larger portion, the CHR group, resides farther away. The H and R groups may be oriented with respect to the alkene in two ways. In the lower energy orientation, the H substituent on the ketene points up toward the alkene, while the larger R group points down. The antarafacial reactivity of the ketene causes this lower energy orientation to lead to the higher energy product, in which the R group is on the *concave* face of the bicyclic system. The larger the R group, the lower the relative energy of the TS that has the R group pointing away from the cycloalkene, and the greater the proportion of higher energy product.

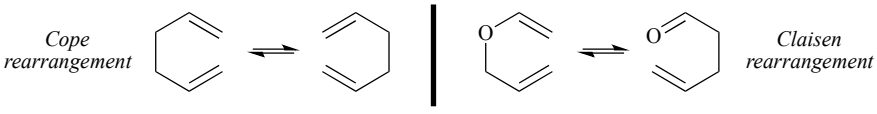


4.4 Sigmatropic Rearrangements

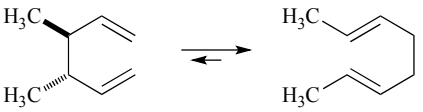
4.4.1 Typical Reactions

A sigmatropic rearrangement produces a new σ bond at the expense of a σ bond, so this reaction is the most inherently reversible of all pericyclic reactions. The position of the equilibrium depends on the relative thermodynamic and kinetic stabilities of the starting material and products. Most synthetically useful sigmatropic rearrangements are two- or six-electron processes.

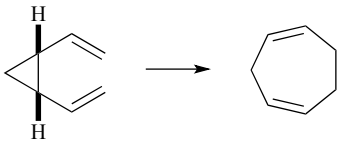
The [3,3] sigmatropic rearrangements (Cope and Claisen rearrangements) are the most widely used sigmatropic rearrangements and are probably the most widely used pericyclic reactions after the Diels–Alder and 1,3-dipolar cycloadditions. In the Cope rearrangement, a 1,5-diene isomerizes to another 1,5-diene. In the Claisen rearrangement, an allyl vinyl ether (a 1,5-diene in which the third or fourth C atom is replaced with O) isomerizes to a γ,δ-unsaturated carbonyl compound (another 1,5-diene in which the first or sixth C atom is replaced with O). Both the Cope and Claisen rearrangements normally require temperatures of 150 °C or greater to proceed, although certain types of substitution can lower the activation barrier.



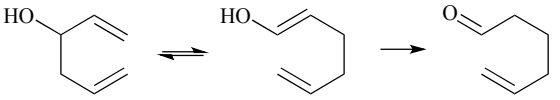
The Cope rearrangement of the simplest 1,5-diene, 1,5-hexadiene, is degenerate: the starting material is identical with the product, and the equilibrium constant for the rearrangement is 1. Substituents may shift the equilibrium to one side or the other. For example, the equilibrium between 3,4-dimethyl-1,5-hexadiene and 2,6-octadiene lies on the side of the more substituted π bonds.



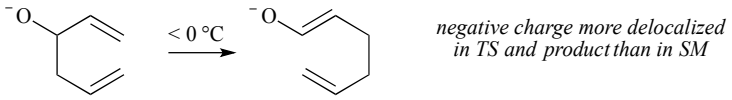
The position of the equilibrium of the Cope rearrangement is pushed even further toward one side when cleavage of the σ bond relieves ring strain. The relief of ring strain also lowers the activation barrier for the rearrangement. Thus, *cis*-1,2-divinylcyclopropane is stable only at very low temperatures.



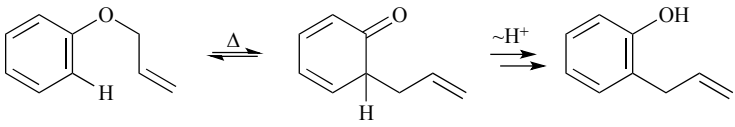
The position of the Cope equilibrium can also be altered by removing the product 1,5-diene from the reaction mixture. In the *oxy-Cope rearrangement*, a 3-hydroxy-1,5-diene undergoes the Cope rearrangement to give an enol, which isomerizes quickly to a δ,ε-unsaturated carbonyl compound. The latter compound is a 1,6-diene, not a 1,5-diene, so it is incapable of undergoing the Cope rearrangement in the retro direction. The reverse isomerization of the δ,ε-unsaturated carbonyl compound to the enol does not occur quickly enough for the retro-Cope rearrangement to proceed.



Oxy-Cope rearrangements proceed at especially low temperatures when the alcohol is deprotonated. The *anionic oxy-Cope rearrangement* is accelerated compared with the neutral reaction because the negative charge is more delocalized in the TS than in the starting material. The driving force for the anionic oxy-Cope rearrangement is no longer removal of the product diene from the equilibrium but simply delocalization of the negative charge. The starting alcohol is usually deprotonated by KH because the O–K bond is much weaker than the O–Na or O–Li bond; the crown ether 18-crown-6 is often added to isolate the K^+ counterion from the alkoxide even further.



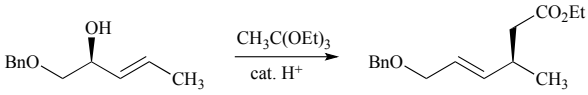
In general, Claisen rearrangements are driven in the forward direction by the formation of a C=O π bond at the expense of a C=C π bond, but there are exceptions to this general rule. For example, the first Claisen rearrangement to be discovered was the isomerization of an *O*-allylphenol to a 2-allylphenol. One might expect that in this particular case, the equilibrium would lie on the side of the aromatic compound, not the 2,4-cyclohexadienone. However, the cyclohexadienone quickly tautomerizes (by a nonconcerted mechanism!) to the aromatic 2-allylphenol, which cannot undergo the reaction in the reverse direction.



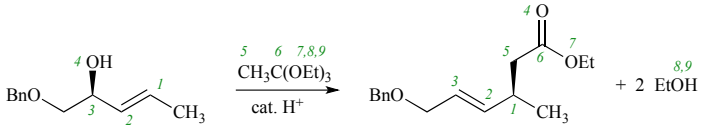
The key to identifying Cope and Claisen rearrangements is the 1,5-diene in the starting material *or* in the product. A γ,δ-unsaturated carbonyl compound (a 1,5-heterodiene) can be made by a Claisen rearrangement, and a δ,ε-unsaturated carbonyl compound can be made by an oxy-Cope rearrangement.

Example

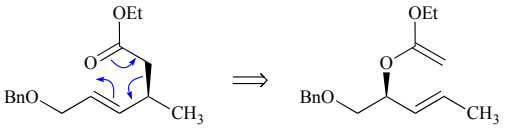
The orthoester Claisen rearrangement.



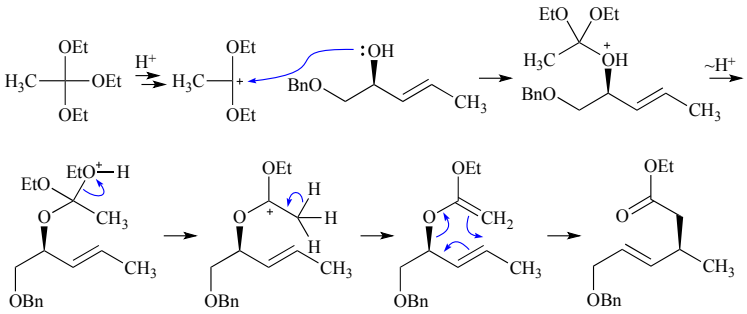
Label the atoms and draw the coproducts.



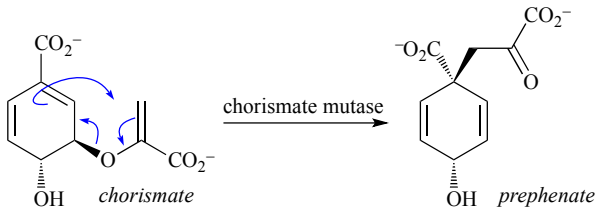
Make: C1–C5, O4–C6. Break: C3–O4, C6–O8, C6–O9. The product has a 1,5-disposition of two π bonds, C2=C3 and O4=C6. Working retrosynthetically, the C1–C5 bond can be made and the C3–O4 bond broken by a [3,3] sigmatropic (Claisen) rearrangement of a 1,5-diene precursor.



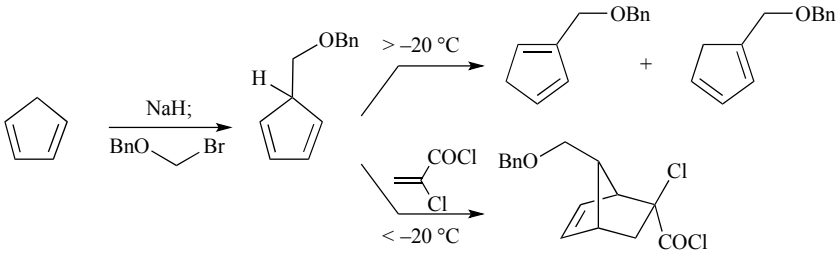
The immediate precursor to the product can be made from the alcohol and the orthoester by S_N1 substitution followed by E1 elimination.



[3,3] Sigmatropic rearrangements are rather rare in biology, but one notable example is the Claisen rearrangement of chorismate to prephenate, a key step in the biosynthesis of aromatic amino acids such as tyrosine. The enzyme chorismate mutase catalyzes this reaction by inducing chorismate to assume the conformation that is most favorable for the rearrangement to occur.

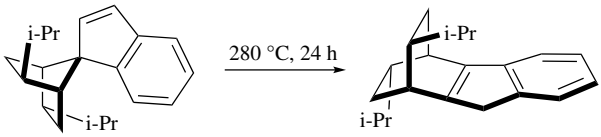


The [1,5] sigmatropic rearrangement of H atoms around a cyclopentadienyl group is an extremely facile process because the ends of the pentadienyl system are held closely to one another. The different isomers of a substituted cyclopentadiene are in rapid equilibrium (on the laboratory time scale) above 0 °C. A synthesis of prostaglandins was developed in the late 1960s in which the first two steps were (1) alkylation of cyclopentadiene with benzyloxymethyl bromide to give a 5-substituted cyclopentadiene, and (2) a Diels–Alder reaction. A dienophile that would react with the cyclopentadiene below −20 °C was sought, because at higher temperature the cyclopentadiene isomerized into its more stable 1- and 2-substituted isomers.

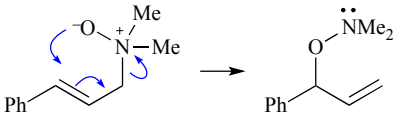


The [1,5] *alkyl* shift is also seen in cyclopentadienes, but much higher temperatures (usually >200 °C) are required. The C(sp^3) orbital is much more directional than the H(*s*) orbital, so the simultaneous overlap with two orbitals that is required in the TS is not as facile as it is with H.

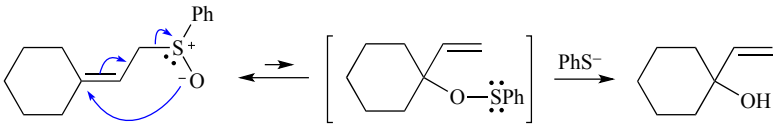
Problem 4.14 The following reaction involves [1,5] sigmatropic rearrangements. Draw a reasonable mechanism. Remember to obey Grossman's rule!



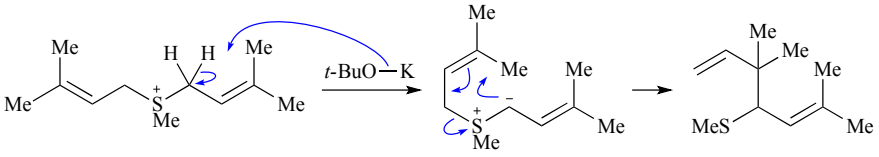
The [2,3] sigmatropic rearrangement involves the rearrangement of a 1,2-dipole to a neutral compound. An allyl group migrates from the positive end to the negative end of the dipole to neutralize the charges.



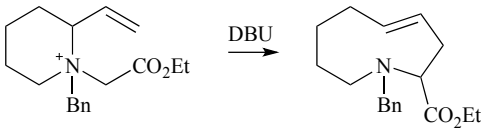
Amine oxides, sulfoxides, and selenoxides all undergo the [2,3] sigmatropic rearrangement. The equilibrium between allyl sulfoxides and allyl sulfenates lies on the side of the sulfoxide, but the equilibrium can be pushed toward the sulfenate by reduction of its O–S bond.



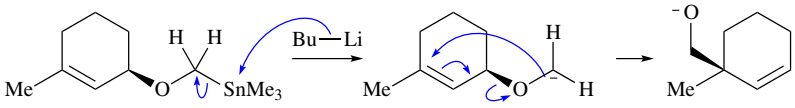
Allylsulfonium ylides (allyl $\overset{+}{S}R-\overset{-}{C}R_2$) and allylammonium ylides (allyl $\overset{+}{N}R_2-\overset{-}{C}R_2$) are also substrates for the [2,3] sigmatropic rearrangement. Both ylides are usually generated in situ by deprotonation of the sulfonium or ammonium salt.



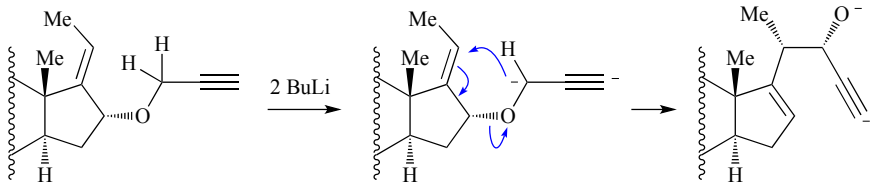
Problem 4.15 Draw a mechanism for the following [2,3] sigmatropic rearrangement. Why does this particular reaction proceed under such mildly basic conditions?



The [2,3] sigmatropic rearrangement of allyloxycarbanions is known as the *Wittig rearrangement* (not to be confused with the Wittig reaction). The requisite carbanions can be prepared by transmetallation of a stannane (tin compound). Stannanes, unlike organolithium compounds, are stable, isolable, chromatographable compounds, but they are easily converted to the organolithium compound with BuLi.

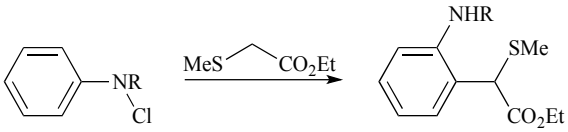


Allyl propargyl ethers also are good substrates for the Wittig rearrangement. Deprotonation of the propargyl position is relatively facile.



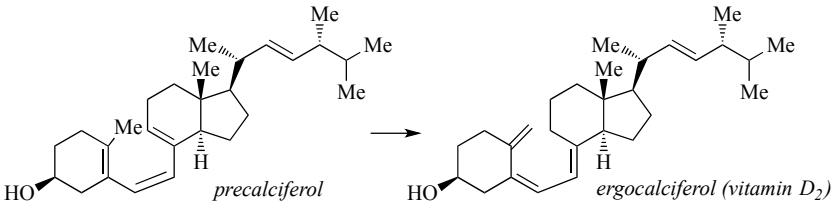
The key to identifying a [2,3] sigmatropic rearrangement is that an allylic group migrates from a heteroatom to an adjacent atom (which may be C or another heteroatom).

Problem 4.16 Upon mixing an *N*-chloroaniline and an α-mercaptoester, a nucleophilic substitution occurs, followed by a [2,3] sigmatropic rearrangement. An ortho-alkylated aniline is ultimately obtained. Draw the mechanism for this reaction.



Four-electron, [1,3] sigmatropic rearrangements are very rare. Occasionally an alkyl group can undergo a concerted 1,3-shift, but H atoms *never* undergo concerted [1,3] sigmatropic rearrangements. **Common error alert**: *The tautomerization of an enol to a carbonyl compound appears to be a [1,3] sigmatropic rearrangement at first glance, but the reaction is catalyzed by base or acid and never proceeds by a concerted pericyclic mechanism.* These observations will be rationalized in the next section.

The [1,7] sigmatropic rearrangement, an eight-electron process, is also quite rare. A 1,3,5-hexatriene can undergo a six-electron electrocyclic ring closure more rapidly and with greater release of energy than it can a [1,7] sigmatropic rearrangement. However, a very important [1,7] sigmatropic rearrangement occurs in the human body. Precalciferol (provitamin D_2) (which you may remember is made by a conrotatory electrocyclic ring opening of ergosterol) is converted to ergocalciferol (vitamin D_2) by a [1,7] sigmatropic H shift.

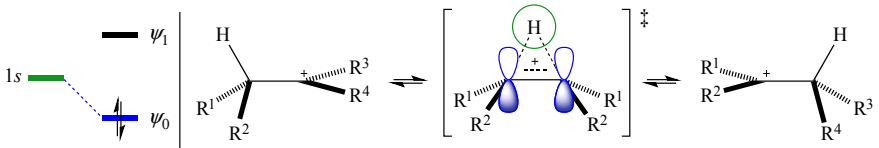


All the sigmatropic rearrangements discussed so far occur under thermal conditions. Photochemical sigmatropic rearrangements are extremely rare.

4.4.2 Stereospecificity

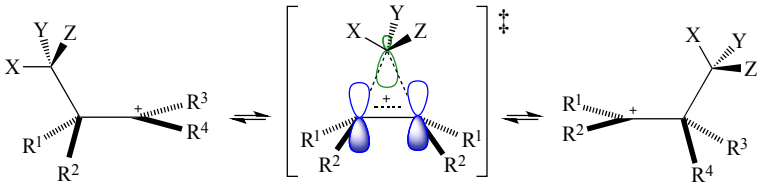
In a sigmatropic rearrangement, bonds are made and broken at the ends of two conjugated systems. The Woodward–Hoffmann rules for sigmatropic rearrangements must take both components into account.

The most common sigmatropic rearrangements are [1,2] cationic, [1,5], and [3,3] rearrangements. These rearrangements proceed readily under thermal conditions. In the cationic [1,2] hydride shift, a thermal reaction, the MOs of two components must be examined. The one-atom component, the H atom, has one orbital, the 1*s* orbital. The two-atom component has two orbitals, ψ_0 and ψ_1. Two electrons must be distributed among these three orbitals. It is clear that the H(1*s*) orbital is lower in energy than the antibonding orbital ψ_1, but it is not clear whether H(1*s*) or ψ_1 is lower in energy. If H(1*s*) is lower in energy, the two electrons will both go in H(1*s*); if ψ_0 is lower in energy, they will both go in ψ_0; and if the two MOs are equal in energy, one electron may go in each. Nevertheless, no matter how the two electrons are distributed among the two components, *the dominant HOMO-LUMO interaction in the TS is between the symmetric 1s orbital of the one-atom component and the symmetric ψ_0 of the two-atom component*. The H atom is always classified as a suprafacial component, as the 1*s* orbital is monophasic, so positive overlap in the TS between orbitals where bond-making and bond-breaking take place is produced when the two-atom component is suprafacial as well.



[1,2] cationic supra–supra

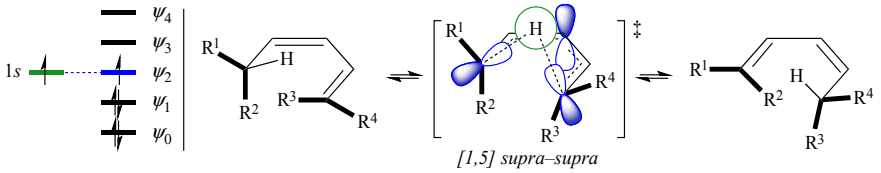
Likewise, in the cationic [1,2] alkyl shift, both components must be suprafacial for there to be positive overlap in the TS between orbitals where bond-making and bond-breaking take place. The migrating group retains its configuration because of the requirement for suprafaciality.



[1,2] cationic supra–supra

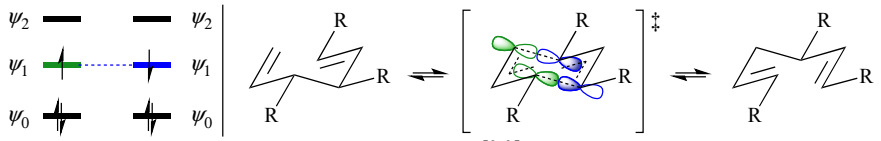
The dominant FMO interaction in the TS of the [1,5] sigmatropic rearrangement, a six-electron reaction, is between the H(1*s*) orbital and the symmetric ψ_2 of the five-atom component, no matter how the six electrons are divided among the two

components. (An interaction between two half-filled orbitals is shown.) Again, positive overlap in the TS between orbitals where bond-making and bond-breaking take place is obtained when the five-atom component reacts suprafacially.



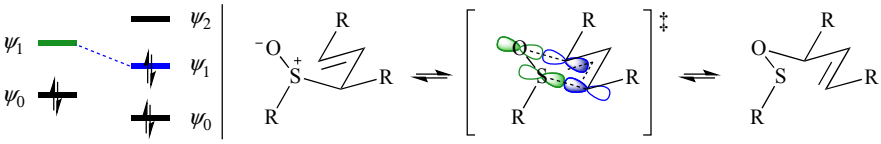
[1,5] supra–supra

The [3,3] sigmatropic rearrangement is a six-electron reaction. No matter how the six electrons are distributed among the two three-atom components, the dominant FMO interaction in the TS is between the antisymmetric ψ_1 of one component and the antisymmetric ψ_1 of the other component. The reaction proceeds suprafacially with respect to both components.



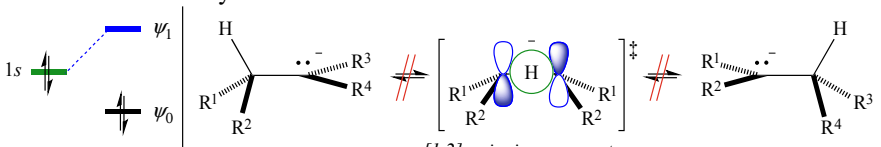
[3,3] supra–supra

Likewise, the dominant FMO interaction in the TS of the [2,3] sigmatropic rearrangement is between the antisymmetric ψ_1 orbitals of both components. The reaction proceeds suprafacially with respect to both components.



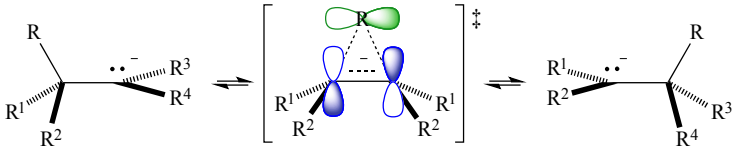
[2,3] supra–supra

By contrast, in the [1,2] anionic H shift, the dominant FMO interaction is between the symmetric 1*s* orbital of the one-atom component and the antisymmetric ψ_1 of the two-atom component. For there to be a positive overlap between orbitals where bond-making and bond-breaking take place, the two-atom component must react antarafacially. Thus, for this shift to be a thermally allowed process, the H atom must have partial bonds to the top and bottom faces of the C_2 unit simultaneously. Because this arrangement is geometrically impossible, [1,2] anionic H shifts are thermally disallowed reactions.



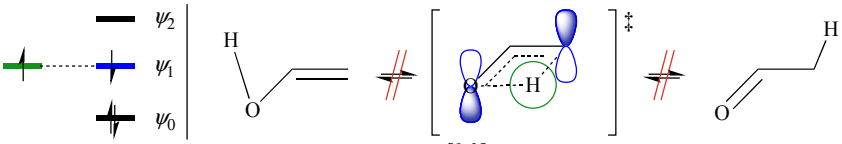
[1,2] anionic supra–antara

A thermally allowed anionic [1,2] shift can occur if the one-atom component reacts antarafacially. In the case of the alkyl shift, the C(*p*) orbital of the migrating R group can react antarafacially, with the configuration inverting upon migration. In practice, the geometric requirements for anionic [1,2] alkyl shifts are so stringent that the reactions are extremely rare.



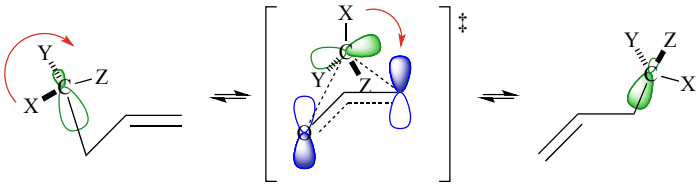
[1,2] anionic supra–antara

Thermal [1,3] H shifts such as the *concerted* rearrangement of enols to carbonyl compounds are disallowed. The allylic C–C–O unit itself can only react suprafacially, as it is geometrically impossible for the H(1*s*) orbital to bond simultaneously to a top lobe on one terminus and a bottom lobe at the other terminus, and the H atom itself must also react suprafacially, as the H(1*s*) orbital has only one lobe. The Woodward–Hoffmann rules, though, say that one of the two components of this four-electron rearrangement must react antarafacially for it to be allowed. Therefore, this rearrangement reaction always proceeds through a nonconcerted mechanism and requires acidic or basic catalysis. **Common error alert**: *A mechanism involving a concerted [1,3] sigmatropic rearrangement of H is almost always incorrect.*



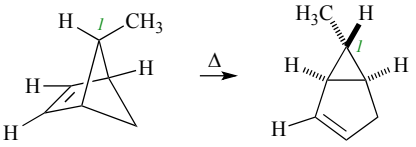
[1,3] antara–supra

On the other hand, a thermal [1,3] alkyl shift is allowed because the alkyl group can adopt an antarafacial orientation in the TS. The two lobes of the C(*p*) orbital of the migrating atom bond to opposite ends of the allylic system in the TS, and the configuration of the migrating group inverts.

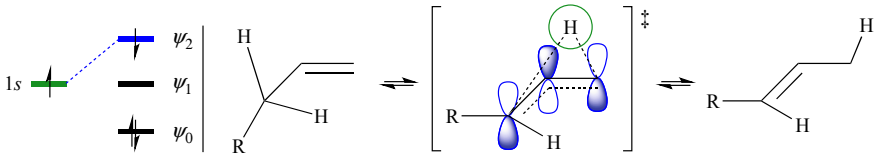


[1,3] antara–supra

Because the [1,3] sigmatropic rearrangement of alkyl groups has such stringent geometric requirements, it is quite rare. Only a handful of examples of [1,3] sigmatropic rearrangements are known. In one such example, the configuration of the migrating C inverts, demonstrating its antarafacial reactivity in the rearrangement. **Common error alert**: *A mechanism involving a [1,3] sigmatropic rearrangement of an alkyl group, though not impossible, should be viewed with suspicion.*

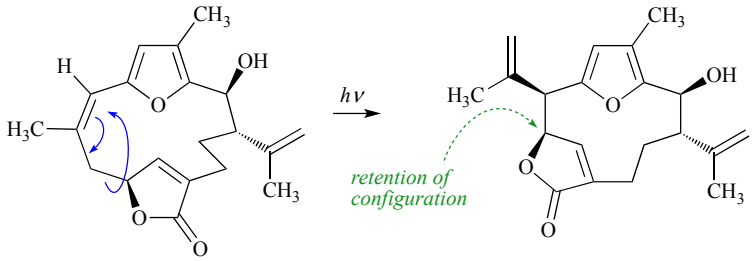


A thermal [1,3] sigmatropic rearrangement is allowed only if one component is antarafacial, but a photochemical [1,3] sigmatropic rearrangement is expected to be allowed when it proceeds suprafacially with respect to both components. The stereochemical requirement changes because under photochemical conditions, the HOMO of the three-atom component is ψ_2 (symmetric), not ψ_1 (antisymmetric).



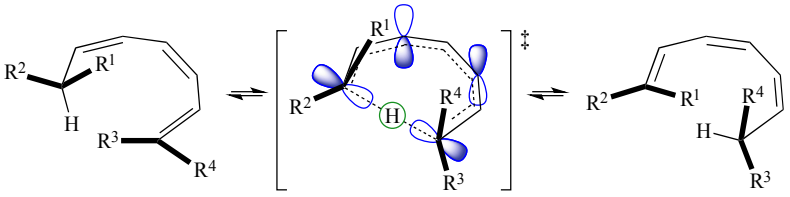
photochemical [1,3] supra–supra

Photochemical sigmatropic rearrangements are rare, but in one example, a photochemical [1,3] sigmatropic rearrangement proceeds suprafacially with respect to both components, resulting in retention of configuration about the migrating one-atom component, a stereogenic alkyl group. The reaction fails to proceed at all under thermal conditions.



A thermal, concerted [1,7] H shift is sometimes observed in acyclic systems, because the 1,3,5-triene system is floppy enough to allow the H to migrate from the top face to the bottom face (making the triene the antarafacial component). The

precalciferol–calciferol rearrangement is thermally allowed for this reason. (However, because precalciferol is formed in its excited state, it is quite possible that it undergoes a *photochemical* [1,7] sigmatropic rearrangement that is suprafacial with respect to both components.) In cyclic compounds like cycloheptatriene, though, geometric constraints prevent the H from migrating from the top to the bottom face of the C_7 π system, and the shift does not occur.



[1,7] supra–antara

In summary, the Woodward–Hoffmann rules for sigmatropic rearrangements (Table 4.5) are as follows. Both components of a sigmatropic rearrangement involving an odd number of electron pairs are suprafacial under thermal conditions; under photochemical conditions, one component must be antarafacial. Both components of a sigmatropic rearrangement involving an even number of electron pairs are suprafacial under photochemical conditions; under thermal conditions, one component must be antarafacial.

The stereochemical consequences of facial selectivity are manifested most clearly in [3,3] sigmatropic rearrangements. Consider the orthoester Claisen rearrangement, in which an allylic alcohol is converted into a γ,δ-unsaturated ester. The intermediate ketene acetal undergoes a [3,3] sigmatropic rearrangement that is suprafacial with respect to both three-atom components, so the new bond between C1 and C6 and the old bond between C3 and C4 must both be to the same face of the C4–C5–C6 component. In practice, this means that because the C3–C4 bond in the starting material comes out of the plane of the paper or screen, the C1–C6 bond in the product also comes out of the plane of the paper or screen. The same argument holds for [2,3] sigmatropic rearrangements.

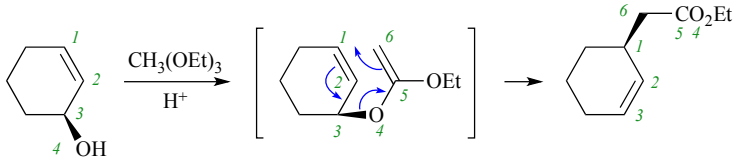
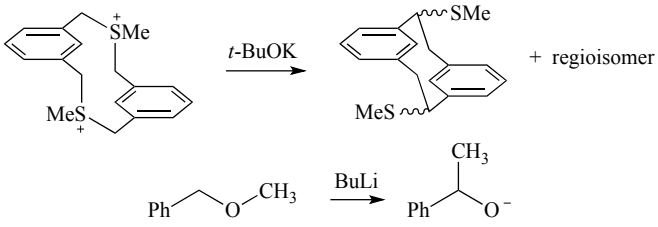


Table 4.5 Woodward–Hoffmann rules for sigmatropic rearrangements

Number of electron pairs	Δ	$h\nu$
Odd	Suprafacial–suprafacial	Suprafacial–antarafacial
Even	Suprafacial–antarafacial	Suprafacial–suprafacial

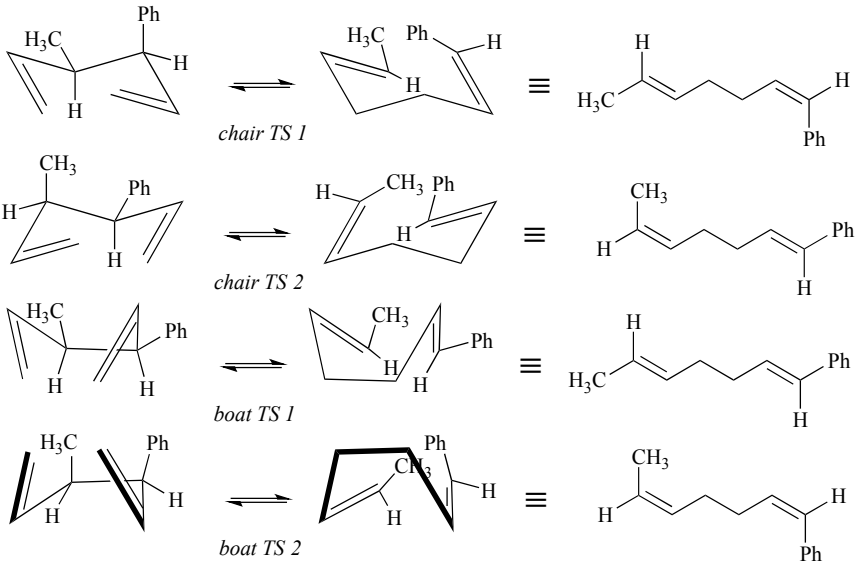
Problem 4.17 A small amount of 4-allylphenol is often obtained from the Claisen rearrangement of allyl phenyl ether. Draw a concerted mechanism for this reaction, name the mechanism, and determine whether the suprafacial–suprafacial rearrangement is thermally allowed or disallowed by the Woodward–Hoffmann rules. If it is not allowed, draw a multistep mechanism for the reaction.

Problem 4.18 Examples of the Stevens rearrangement and the nonallylic Wittig rearrangement are shown. What do the Woodward–Hoffmann rules say about the nature of these reactions? Offer two *explanations* (not necessarily mechanisms) of why these reactions proceed. (*Hint*: Think of the conditions on the applicability of the Woodward–Hoffmann rules.)



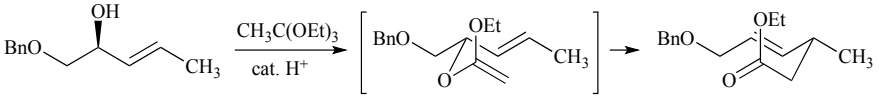
4.4.3 Stereoselectivity

Cope rearrangements must be suprafacial with respect to both components, but multiple stereochemical results are still possible. Cope rearrangements have a six-membered ring in the TS. The ring can be in any of four conformations (two chair and two boat). These different conformers can lead to different stereoisomeric products. Consider the following possible conformations of the disubstituted compound. Cope rearrangement via one chair conformation leads to a product in which the Ph-substituted π bond is cis and the CH_3-substituted π bond is trans. Rearrangement via the other chair conformation leads to a product in which the CH_3-substituted π bond is cis and the Ph-substituted π bond is trans. Rearrangement of the *same* compound via one boat conformation leads to a product in which both π bonds are trans. Rearrangement via the other boat conformation leads to a product in which both π bonds are cis. In other words, all four stereochemistries about the C=C bonds can be obtained from a single diastereomeric starting material. I must emphasize that all four possible stereochemistries are consistent with a suprafacial arrangement of both components in the TS.



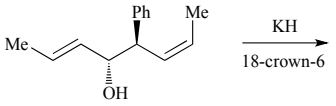
Of course, one of the four possible TSs is usually quite a bit lower in energy than the others, and this leads to *stereoselectivity* in the Cope rearrangement. The chair TSs are preferred to the boat TSs, just as they are in cyclohexanes, and chair TS 2, in which the large Ph group is pseudoequatorial and the smaller Me is pseudoaxial, is lower in energy than chair TS 1, in which Ph is pseudoaxial and Me is pseudoequatorial. However, certain substitution patterns can cause one of the boat TSs to be lower in energy. For example, if the Me and Ph groups were replaced with *t*-Bu groups, which are much too large ever to be pseudoaxial, then boat TS 1 would be preferred.

Most Cope rearrangements, especially those of simple 1,5-dienes, proceed through a chair TS, and the stereochemical consequences are easily analyzed. For example, the following *(S,E)* allylic alcohol undergoes an orthoester Claisen rearrangement to give mostly the *(R,E)* product; the alternative chair TS, which leads to the *(R,Z)* product, has a pseudoaxial $BnOCH_2$ group and so is higher in energy.

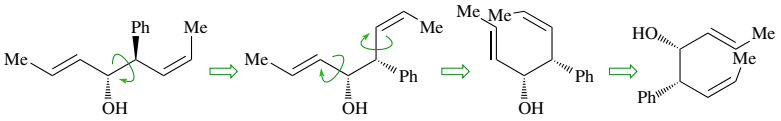


Example

Draw the product of the following oxy-Cope rearrangement (an aldehyde) with the correct stereochemistry.



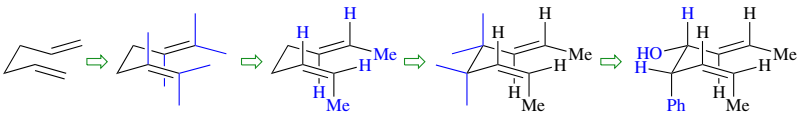
The first step is to draw the starting material in the proper conformation for the rearrangement, *without altering its stereochemistry.* The starting material is drawn in the figure such that the C2–C3 and C4–C5 bonds are in the s-trans conformation (antiperiplanar). Redraw the compound so that these two bonds are s-cis (eclipsed). After the rotation, the Ph group, formerly up, will now be down. Then rotate about the C2–C3 and C4–C5 bonds so that C1 and C6 are near one another, being careful to preserve the double bond geometries. Finally, rotate the entire structure so that the C3–C4 bond is vertical. You now have a *top view* of your starting material.



Now you need to draw the compound in its chair conformation. Draw a chair with only five sides, and then draw the two double bonds at the ends of the chain.

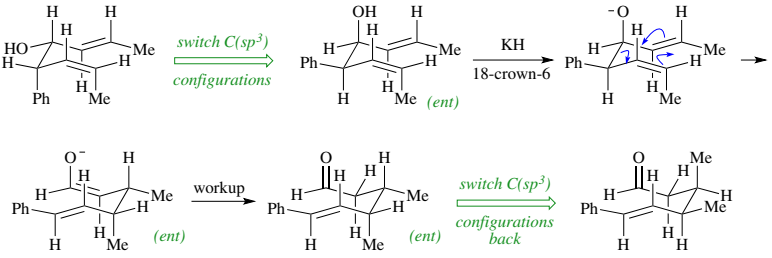
The easiest way to draw a five-sided chair is as follows. Draw a shallow V, draw an upside-down V of the same size below and to the left of the first V, and connect the ends of the two Vs on one side.

Although the termini of the 1,5-diene are sp^2-hybridized, their two substituents occupy pseudoaxial and pseudoequatorial positions. Draw the substituents of the double bonds in your chair, again being careful to preserve the double bond geometry. Note that the upper double bond in your *top view* drawing is now in the back of the chair, and the lower double bond is now in the front. Finally, draw the four bonds (two axial and two equatorial) to the C(sp^3)

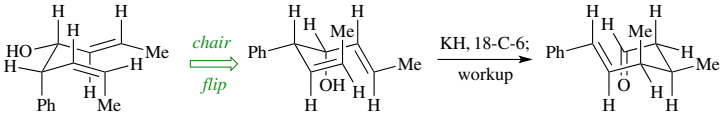


centers of your chair, and then fill in the substituents, being careful that the "down" substituents point down and the "up" substituents point up. You have now drawn your compound in a correct chair conformation.

OOPS! The chair conformation you have drawn has the largest C(sp^3) substituent, the Ph group, in an axial orientation! This means that you have not drawn the lowest energy chair conformation. The easiest solution to this problem is to switch the configurations of both C(sp^3) centers so that you have the wrong enantiomer (but still the right diastereomer), draw the rearrangement reaction, and then switch the configurations of both C(sp^3) centers in the product back to the correct enantiomeric series to give you the product.

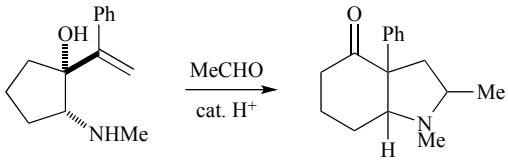


A more rigorous way of dealing with the problem is to flip the chair. When you flip the chair, all the axial substituents at C(sp^3) centers become equatorial, and vice versa. Be careful to preserve the stereochemistry about the double bonds: the pseudoaxial and pseudoequatorial substituents of the double bonds retain their orientation in the flipped chair!

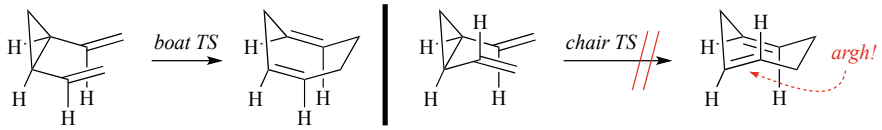


Of course, if your original chair has the largest C(sp^3) substituent in the correct, equatorial position, you don't need to worry about switching configurations or flipping the chair.

Problem 4.19 A mechanism involving a [3,3] sigmatropic rearrangement (an aza-Cope rearrangement) followed by a Mannich reaction can be drawn for the following reaction. Draw the mechanism. Then predict the stereochemistry of the product obtained when the aza-Cope rearrangement proceeds through a chair conformation.

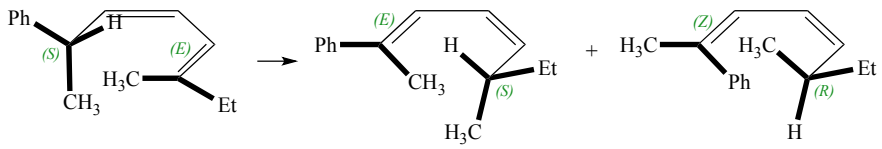


Not every Cope or Claisen rearrangement can proceed through a chair TS. Sometimes the chair TS is raised prohibitively high in energy compared with the boat TS. For example, *cis*-1,2-divinylcyclopropane undergoes a Cope rearrangement to give 1,4-cycloheptadiene. If the starting material underwent rearrangement through the chair TS, one of the π bonds in the seven-membered ring in the product would be trans, so the reaction proceeds through the boat TS.



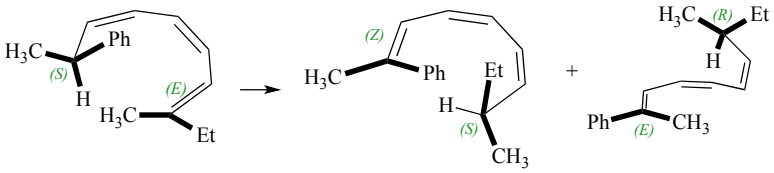
For any 1,5-diene other than a simple, acyclic one, molecular models are usually necessary to determine whether the Cope or Claisen rearrangement will proceed through a chair or a boat TS.

Cope and Claisen rearrangements are not the only sigmatropic rearrangements that show stereoselectivity. For example, consider the [1,5] sigmatropic rearrangement of the following diene. It has the S configuration about the stereocenter and the E configuration about the double bond distal to the stereocenter. Because the reaction is suprafacial with respect to the five-atom component, the H can move from the top face at one terminus to the top face at the other, or it can move from the bottom face at one terminus to the bottom face at the other. In the first case, the *(E, S)* product is obtained; in the second case, the *(Z,R)* product is obtained. The *(E,S)* product would probably be obtained selectively, as it has the large Ph group in the thermodynamically preferred position. Neither the *(E,R)* product nor the *(Z,S)* product is obtained because of the stereospecific nature of the rearrangement.



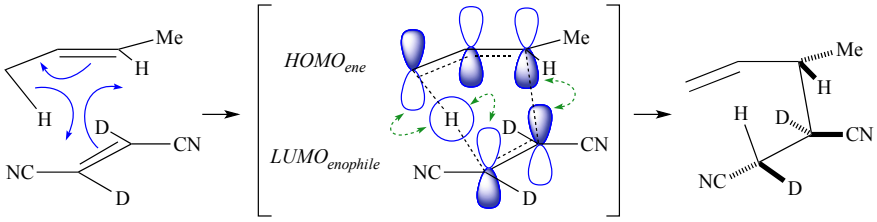
A similar argument can be made for the [1,7] sigmatropic rearrangement. The *(S, E)* starting material rearranges antarafacially with respect to the seven-atom component. The H can move from the bottom face at one terminus to the top face at the other, or it can move from the top face at one terminus to the bottom face at the

other. Either the *(E,R)* or the *(Z,S)* product, but neither the *(E,S)* nor the *(Z,R)* product, is obtained.

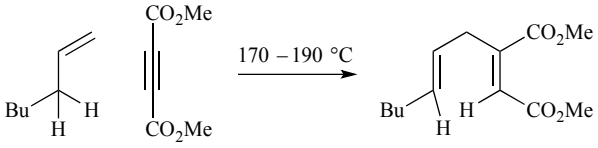


4.5 Ene Reactions

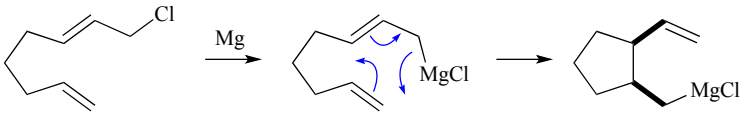
The ene reaction shares some characteristics with both the Diels–Alder reaction and the [1,5] sigmatropic rearrangement. The ene reaction is always a six-electron reaction. Like the Diels–Alder reaction, it has one four-electron component, the *ene,* and one two-electron component, the *enophile*. The two-electron component is a π bond. The four-electron component consists of a π bond and an allylic σ bond. The atom at the terminus of the σ bond is usually H; the other five atoms involved in the ene reaction may be C or heteroatoms. Because the ene reaction involves six electrons, it is suprafacial with respect to all components.



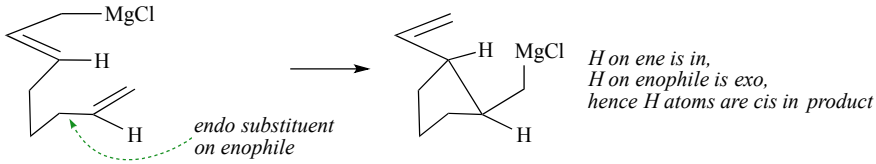
The suprafacial reactivity of the enophile means that the two new bonds to the enophile form to the same face. When the enophile is an alkyne, the two new σ bonds in the product are cis to one another.



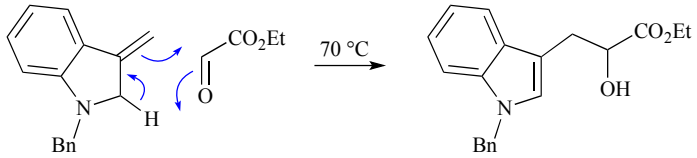
Ene reactions involving five C atoms and one H usually require very high temperatures (>200 °C) to proceed. The reaction occurs at much lower temperature if the H atom is replaced with a metal atom in the *metallaene* reaction. The metal may be Mg, Pd, or another metal.



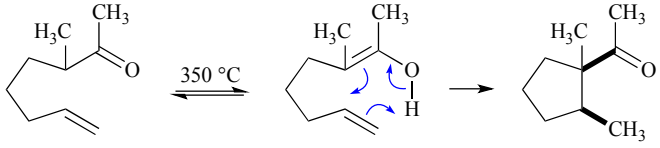
Note how the cis product is obtained in the metallaene reaction. This stereochemical result reflects the preference of this particular substrate for an endo transition state, just as in cycloadditions. In cycloadditions, though, the endo substituent of the dienophile is usually an electron-withdrawing substituent, whereas in this ene reaction the endo substituent of the enophile is simply the alkyl chain joining it to the ene.



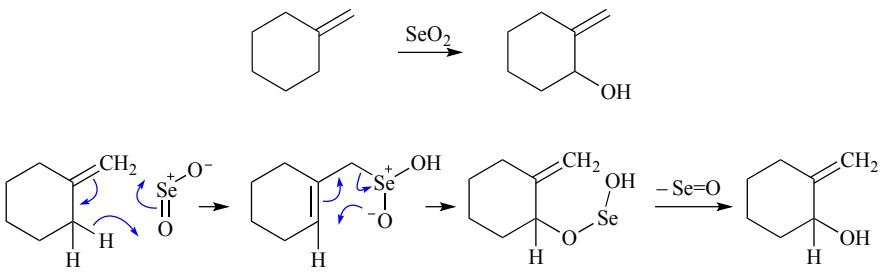
The ene reaction also occurs when heteroatoms replace C in either the ene or the enophile. The following heteroene reaction requires a much lower activation energy than normal because of the driving force of formation of the aromatic indole ring and because of the instability of ethyl glyoxylate, which has adjacent carbonyl groups.



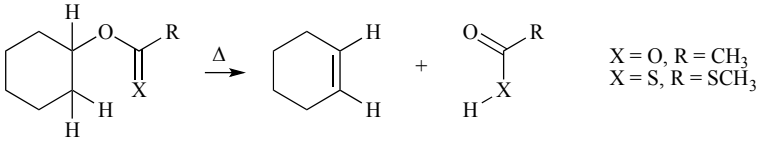
Ene reactions with enols as the ene component are driven in the forward direction by the favorable energy derived from the regeneration of the carbonyl group, just like in the oxy-Cope rearrangement. Very high temperatures may be required to generate a sufficiently high concentration of enol to make the reaction proceed.



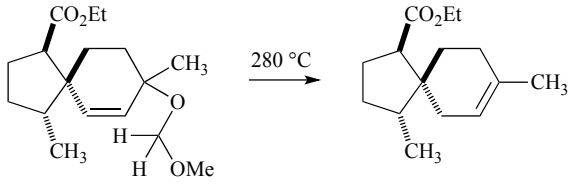
Selenium dioxide (SeO_2) is often used to hydroxylate alkenes in the allylic position. The mechanism of this transformation involves two sequential pericyclic reactions. The first reaction, an ene reaction, gives a selenenic acid. Then a [2,3] sigmatropic rearrangement occurs, and the intermediate loses SeO to give the observed product. Note how two allylic transpositions result in no allylic transposition at all!



A number of synthetically useful elimination reactions proceed thermally, with no base or acid required. These elimination reactions proceed through a concerted *retroene* mechanism. (The mechanism is sometimes called E_i.) The thermal elimination of acetic acid from alkyl acetates and the elimination of RSCOSH from alkyl xanthates (the *Chugaev reaction*) are retroene reactions.

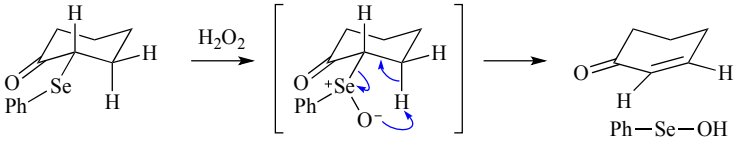


Retroene reactions are partly driven by the gain in entropy. (Entropic contributions to $\Delta G°$ are much more important at the high temperatures required for ene reactions.) The formation of the C=O π bond at the expense of the C=S π bond provides an additional driving force for the Chugaev reaction. Acetic acid elimination is enthalpically unfavorable, and it requires much higher temperatures so that the entropic contribution becomes dominant. The formation of the C=O π bond and entropic gains also provide the driving force for the elimination of methyl formate from the following allylic MOM (methoxymethyl) ether.

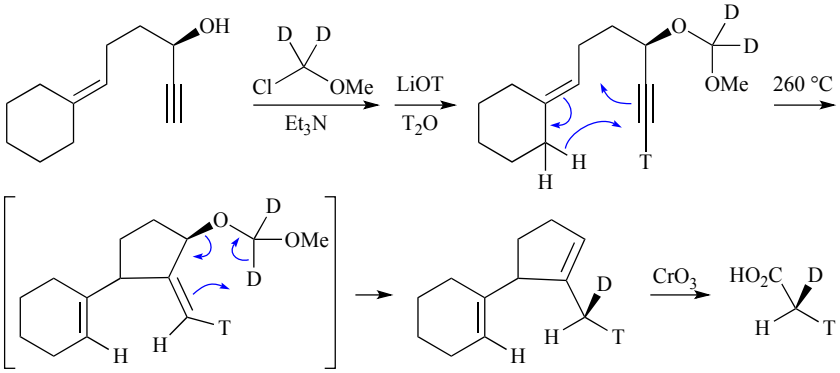


Selenoxide elimination, a *retroheteroene* reaction, is widely used for the oxidation of carbonyl compounds to the α,β-unsaturated analogs. An α-selenocarbonyl compound is oxidized to the selenoxide with one of a variety of oxidizing agents (H_2O_2, mCPBA, $NaIO_4$, O_3, etc.). The retroheteroene reaction of the selenoxide is so facile that it occurs at room temperature within minutes. Amine oxides (*Cope elimination*, not to be confused with the Cope rearrangement) and sulfoxides also undergo the retroheteroene reaction, but they require higher temperatures. Retroheteroene

reactions are driven by entropy, by charge neutralization, and sometimes by cleavage of a weak σ bond (e.g., C–Se) in favor of a C=C π bond. All retroheteroene reactions involve a 1,2-dipole, usually $\overset{+}{E}-\overset{-}{O}$, where E is a heteroatom.

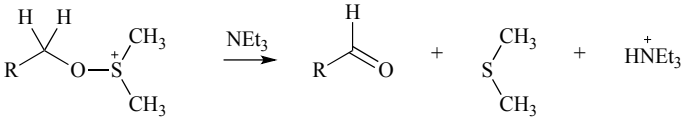


The factors that make ene and retroene reactions proceed are nicely illustrated by a synthesis of enantiopure, isotopically labeled acetic acid $CH(D)(T)CO_2H$, a very useful compound for studying the mechanisms of enzyme-catalyzed reactions. One ene and one retroene reaction occur in this synthesis. The ene reaction is driven by formation of a new σ bond at the expense of a C≡C π bond; the retroene reaction is driven by the formation of a C=O π bond in an ester. Note that both pericyclic reactions proceed stereospecifically, even at the very high temperatures required for them to proceed!



Ene reactions make one new σ bond at the expense of one π bond, like electrocyclic reactions, but they are fairly easy to distinguish from electrocyclic reactions otherwise. Look for allylic transposition of a double bond and transfer of an allylic H atom. In a retroene reaction, a nonallylic H is transferred to an allylic position.

Problem 4.20 The final step of the Swern oxidation involves elimination of Me_2S and H^+ from a sulfonio ether. An E2 mechanism for this elimination is reasonable, but a retroheteroene mechanism is actually operative. Draw the retroheteroene mechanism.



4.6 Summary

The Woodward–Hoffmann rules for all pericyclic reactions (Table 4.6) are as follows. A pericyclic reaction involving an odd number of electron pairs must have an even number of antarafacial components under thermal conditions and an odd number of antarafacial components under photochemical conditions. A pericyclic reaction involving an even number of electron pairs must have an odd number of antarafacial components under thermal conditions and an even number of antarafacial components under photochemical conditions. In practice, of course, "even number of antarafacial components" means "none", and "odd number of antarafacial components" means "one".

Pericyclic mechanisms are undoubtedly the hardest for students to draw. The superficial similarity of the mechanistic types, the way in which seemingly reasonable steps are disallowed by theoretical considerations, the simultaneous formation of many bonds, the lack of a clearly reactive center—all these features of pericyclic reactions combine to make them anathema to many students. You can learn some useful techniques to help you work through pericyclic mechanism problems. Some of these techniques have already been mentioned in the course of the discussion, but they are reiterated here for emphasis.

General considerations when drawing pericyclic mechanisms:

- Draw dashed lines between the atoms where you are forming new bonds, and draw squiggles across bonds that break. Sometimes this procedure will help you identify the pericyclic reaction you need to draw.
- In many problems, a series of polar reactions proceeds to give a reactive intermediate that then undergoes a pericyclic reaction to give the product. Look at the product, and determine what pericyclic reaction could generate it. Then draw the immediate precursor to the final product. Don't be shy about drawing electron-flow arrows on the product to help you draw the precursor with all its bonds in the correct positions. This procedure often simplifies the problem considerably.
- **Common error alert**: *Students often draw fictional pericyclic steps such as A–B + C=D → A–C–D–B.* A good preventive is to be sure that you can name any reactions that occur. If you cannot name it, it ain't a reaction!
- As always, draw your coproducts, label your atoms, make a list of bonds to make and break, and obey Grossman's rule!

Table 4.6 Woodward–Hoffmann rules for all pericyclic reactions

Number of electron pairs	Number of antarafacial components	
	Δ	$h\nu$
Odd	Even	Odd
Even	Odd	Even

Whether working forward or backward, look for some key substructures.

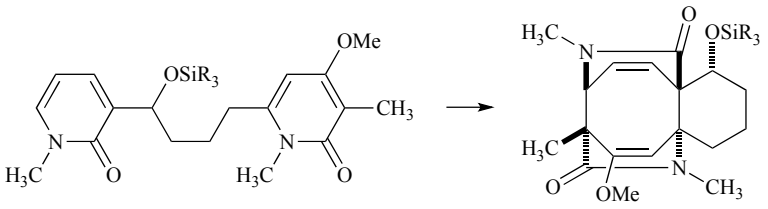
- The presence of a 1,3-butadiene or a cyclobutene in the starting material or the product may indicate a four-electron electrocyclic reaction.
- The presence of a 1,3-cyclohexadiene or a 1,3,5-hexatriene in the starting material or the product may indicate a six-electron electrocyclic reaction.
- Cyclopropyl cations and allylic cations can open and close, respectively, by two-electron electrocyclic reactions, as can the corresponding halides.
- A six-membered ring with two new σ bonds in a 1,3-relationship may indicate a [4 + 2] cycloaddition (Diels–Alder or hetero-Diels–Alder reaction). When the new ring is fused to an aromatic one, benzyne or an *o*-xylylene may have been a reactive intermediate.
- The formation of a five-membered heterocycle with two new σ bonds almost always indicates a [3 + 2] cycloaddition.
- The formation of a cyclobutanone almost always indicates a ketene–alkene [2 + 2] cycloaddition.
- Light and a cyclobutane often indicate a [2 + 2] cycloaddition. **Common error alert**: *A cyclobutane that lacks a ketone and that is produced in the absence of light is likely not formed by a [2 + 2] cycloaddition.*
- Loss of CO_2, N_2, CO, or SO_2 by cleavage of two σ bonds often indicates a retro [4 + 2] or [4 + 1] cycloaddition.
- A 1,5-diene, including a γ,δ-unsaturated carbonyl compound, often indicates a [3,3] sigmatropic rearrangement, i.e., a Cope or Claisen rearrangement.
- A δ,ε-unsaturated carbonyl compound is often the product of an oxy-Cope rearrangement. Oxy-Cope rearrangements are accelerated under strongly basic conditions (KH with or without 18-crown-6).
- The H atoms of cyclopentadienes undergo [1,5] sigmatropic rearrangements with great facility.
- Migration of an allylic group from a heteroatom to its next-door neighbor often indicates a [2,3] sigmatropic rearrangement.
- The formation of a new σ bond at the ends of two π bonds and the simultaneous migration of a H atom may indicate an ene reaction.
- The elimination of an acid such as AcOH or PhSeOH may indicate a retroene or retroheteroene reaction.
- A requirement of light (*hν*) suggests that either an electrocyclic reaction (usually a ring closing), an even-electron-pair cycloaddition (e.g., a [2 + 2] cycloaddition), or a free-radical reaction has occurred.

Good luck!

4.7 Problems

1. Determine the number of electrons involved in each of the following reactions, name the reaction's mechanism as specifically as possible, and predict whether the reaction proceeds thermally or photochemically.

(a)



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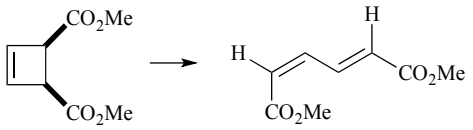

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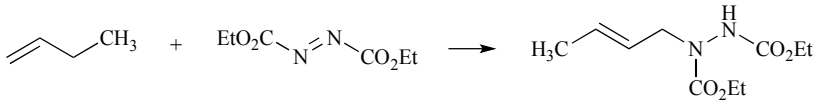

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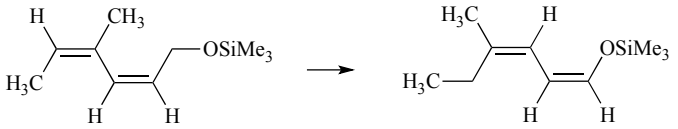

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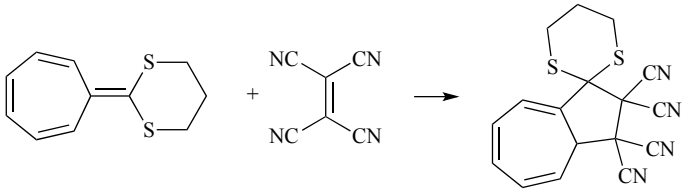
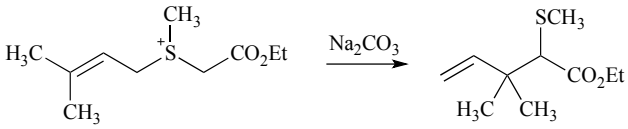


(f)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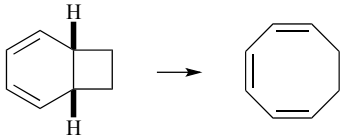
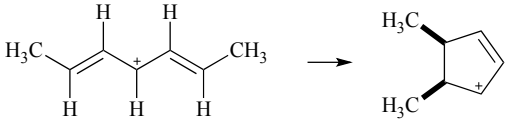
H3C
S
CO2Et
CH3
Na2CO3
SCH3
CO2Et
H3C
CH3

(g)


H
H

(h)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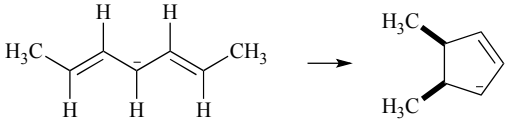
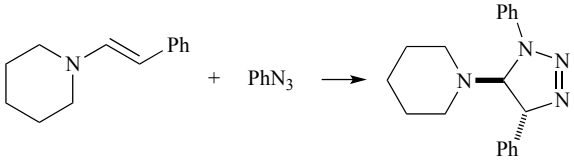
H
H3C
CH3
H
H
H
H3C
H3C

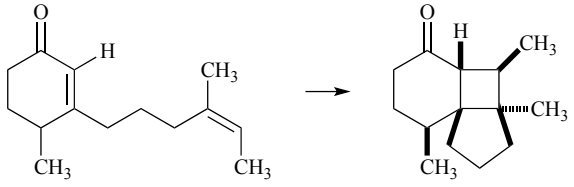
(i)


H
H
H3C
CH3
H
H
H
H3C
H3C

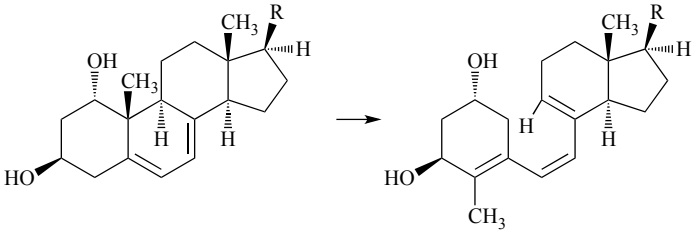
(j)


N
Ph
+
PhN3
Ph
N
N
N
N
Ph

(k)

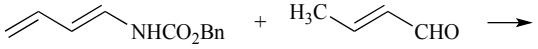

O
H
CH3
CH3
CH3
O
H
CH3
CH3
CH3

(l)

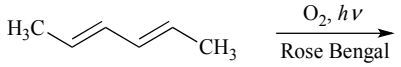


2. Predict the major product (regio- and stereoisomer) of each of the following cycloadditions. All reactions but (h) are [4 + 2] or [3 + 2] cycloadditions.

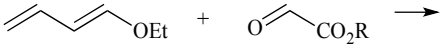
(a)



(b)



(c)



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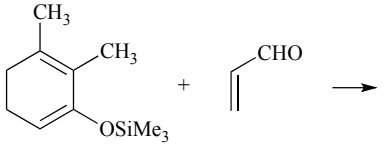
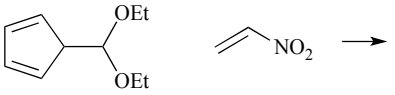


(e)



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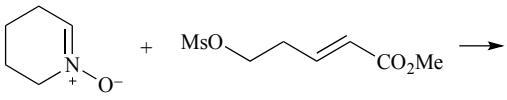
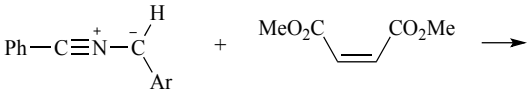
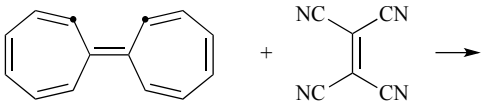


(g)

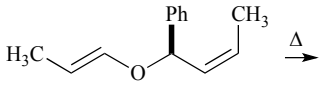


(h) The dots mark the locations where the polyene reacts.



3. 1,3,5,7-Cyclononatetraene can theoretically undergo four different electrocyclic ring closures. Draw the product of each of these reactions, determine the stereochemistry of each when it is obtained under thermal conditions, and order the products by thermodynamic stability.
4. Draw the product of each of the following [3,3] sigmatropic rearrangements, including its stereochemistry. In some cases, you may find it necessary to build molecular models in order to see the stereochemical result.

(a)



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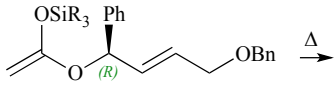

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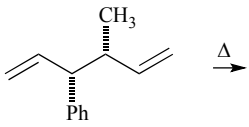

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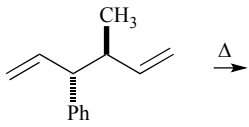

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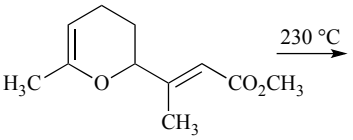

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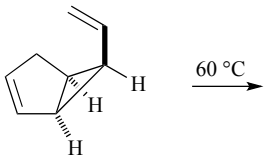

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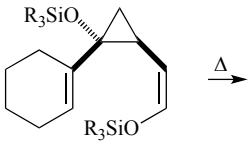
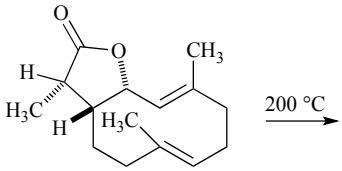
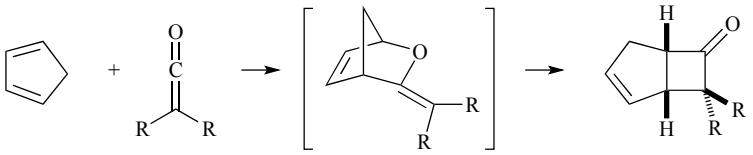


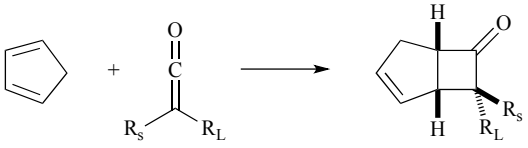
(h)





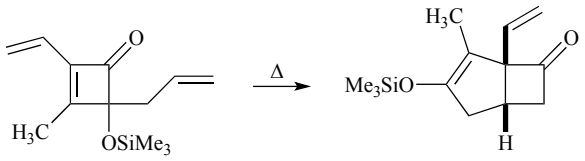
5. When ketenes react with 1,3-dienes, bicyclic cyclobutanones are obtained. The mechanism of this reaction is usually described as a one-step [2 + 2] cycloaddition reaction, but the following two-step mechanism has been proposed.

   (a) Name the two steps of the proposed mechanism.
   (b) Explain why the C=O and not the C=C bond of the ketene reacts with the 1,3-diene in the first step of the proposed mechanism.
   (c) When an unsymmetrically substituted ketene [$(R_L)(R_S)C{=}C{=}O$] is used in this reaction, the larger group (R_L) is found in the more sterically hindered endo position in the *ultimate* product ("chemical masochism"), as shown here. Use the proposed mechanism to explain (in words *and* pictures) this phenomenon. You will need to look at the stereochemical result of *both* steps of the mechanism.



6. Draw mechanisms for the following reactions.

(a)



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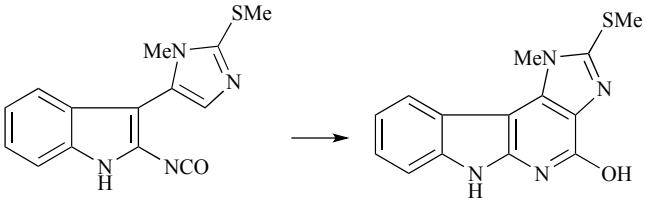

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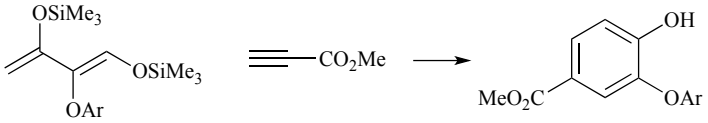

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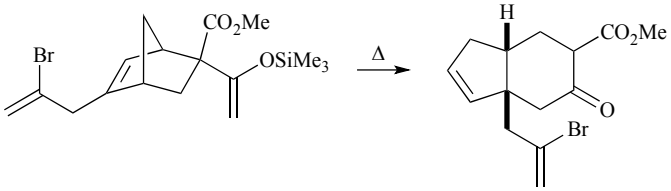

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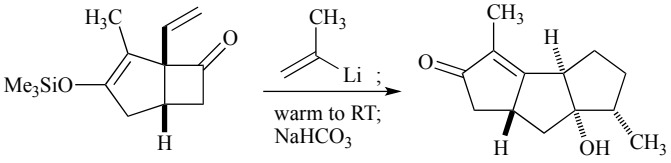

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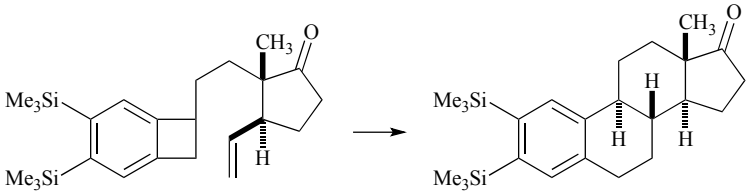
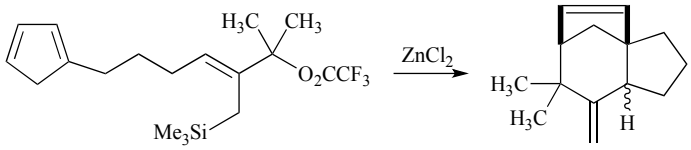
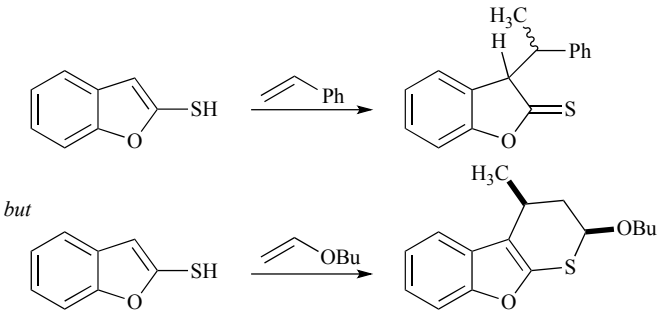


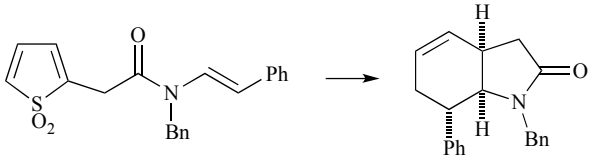
(g)



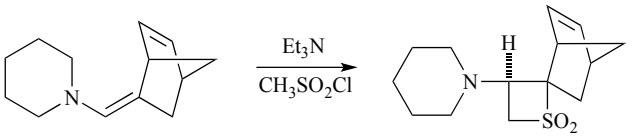
(h)



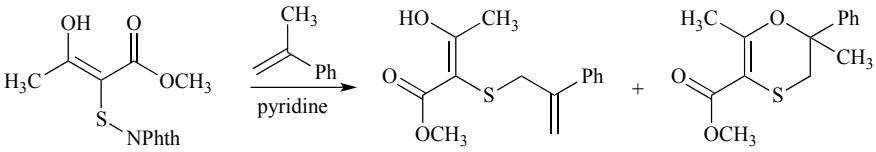
(i)



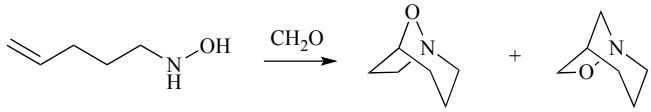
(j) Make an analogy between acyl chlorides and sulfonyl chlorides to solve this problem.



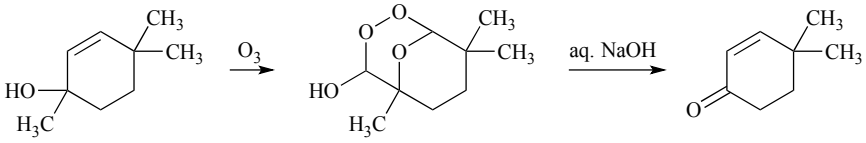
(k) NPhth = phthalimidoyl, an analog of succinimidoyl (as in NBS).



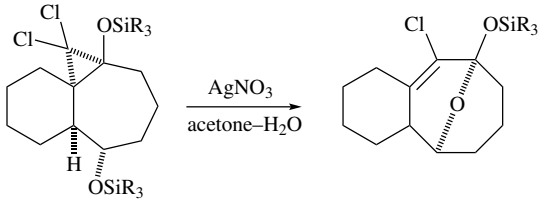
(l)



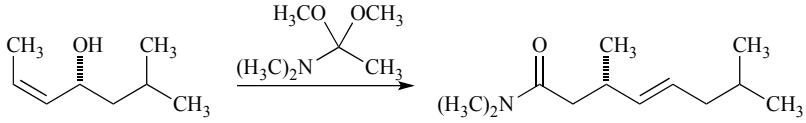
(m) Draw separate mechanisms for both reactions. The mechanism of the first reaction will be simpler to draw if you number the atoms in the very first intermediate, rather than the starting material. *Hint*: The carbon-containing coproduct of the second reaction is HCO_2^-.



(n)

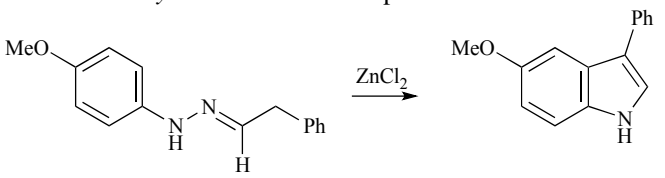


(o)

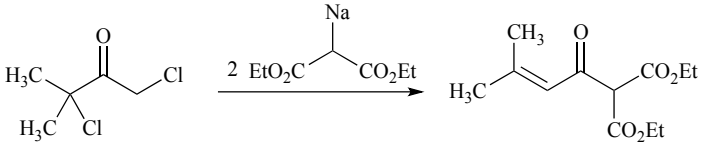


(p) What reaction could the second equivalent of the very strong, nonnucleophilic base LDA induce?

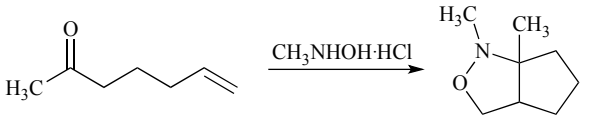
(q) The *Fischer indole synthesis*. Note the coproduct!



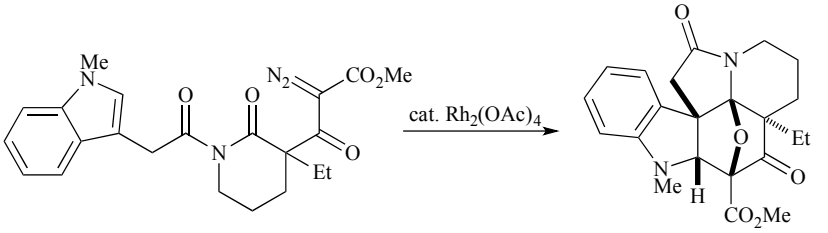
(r) *Two* equivalents of sodiomalonate are required for the following reaction to occur. *Hint*: What is the role of the second equivalent of malonate?



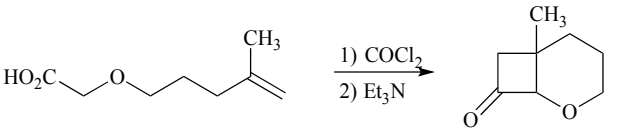
(s)



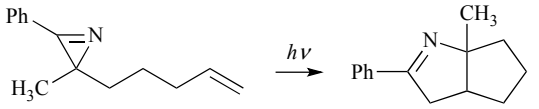
(t) The following problem is tough but doable. Number all your atoms and draw in the H atoms. Then ask, what is the role of the Rh?



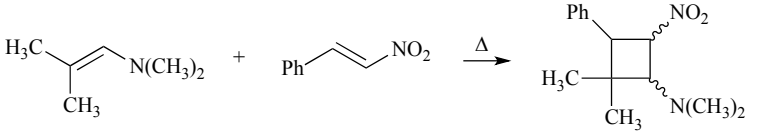
(u)



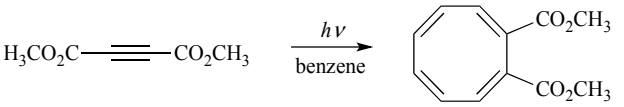
(v) The reaction is thermally allowed, but light is required to supply enough activation energy.



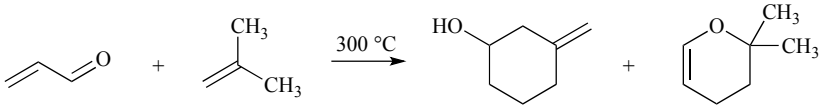
(w)



(x)



(y)



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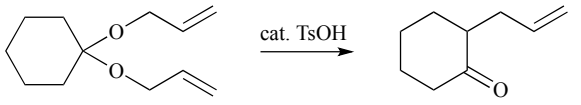
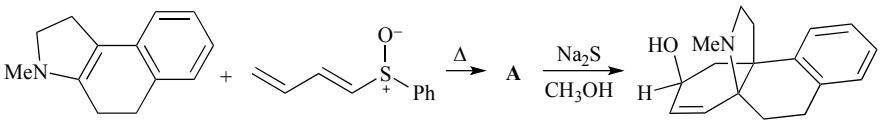


(aa) Be sure to account for the observed regio- and stereochemistry. *Hints*: (1) The C–O bond is already present in **A**. (2) Na_2S is an excellent nucleophile.



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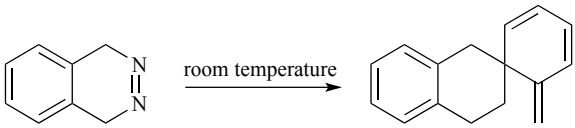
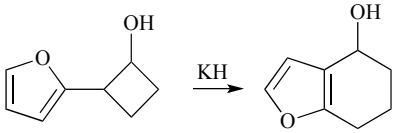
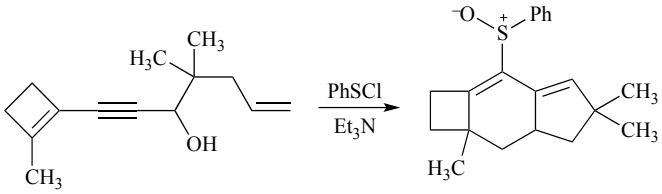


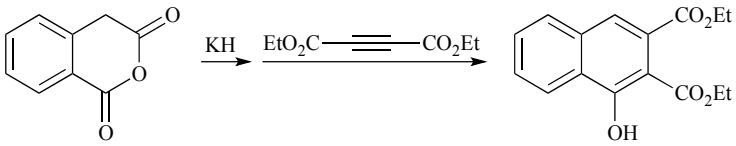
(cc)



(dd)



(ee)



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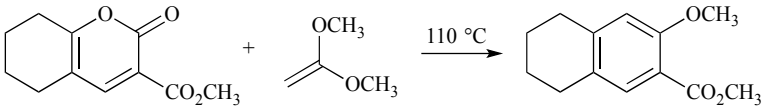
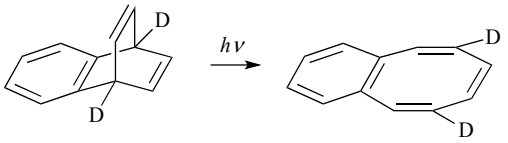
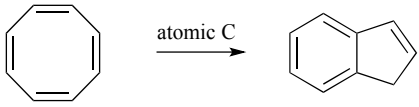


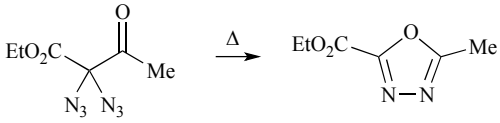
(gg) Here's a clue to rule out one of the possible mechanisms: Irradiation of benzene under the same conditions does *not* give benzocyclooctatetraene, the product of the following reaction.



(hh) Atomic C has the reactivity of ±C±, a double carbene.



(ii) The key to this very difficult problem is to number the N atoms in the product correctly. Draw the azido groups in their $RN^{-}-N^{+}_{2}$ resonance structure, draw the coproducts, and *then* number the atoms. Then, for the first step, think of a thermal rearrangement of organic azides that we have already learned.



(jj) No reaction occurs (starting material is recovered) in the absence of KO-*t*-Bu. What does that tell you about the mechanism of this reaction?