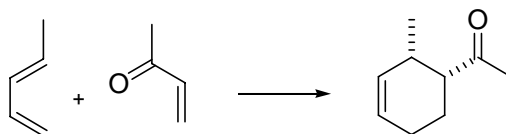


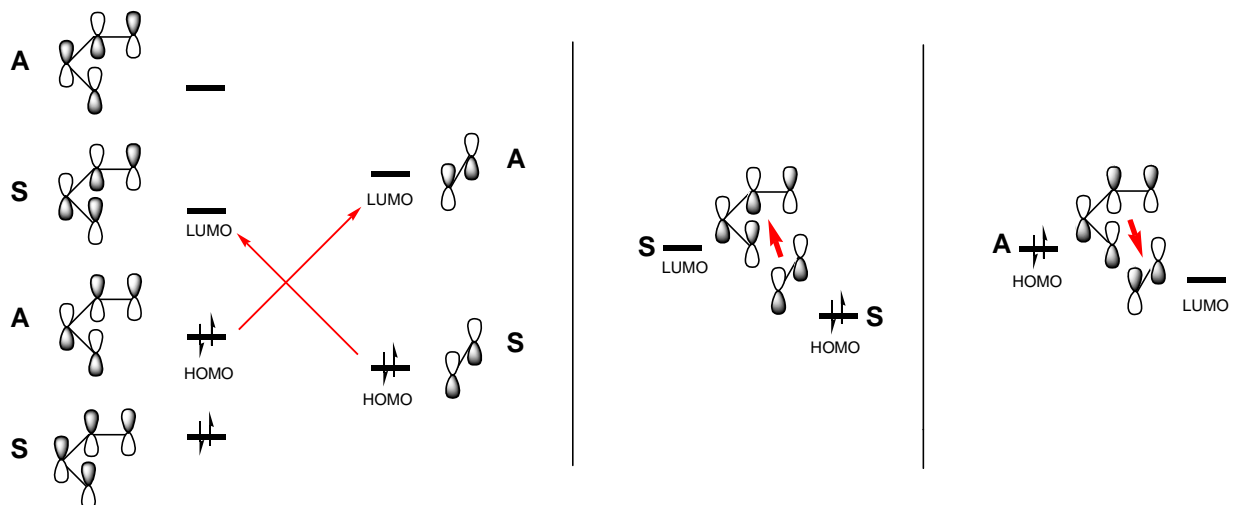
The Diels Alder reaction is a $[2\pi + 4\pi]$ cycloaddition reaction. In this reaction, a conjugated diene, the 4π component, reacts with an alkene, the 2π component. The alkene is usually called the dienophile. The reaction was discovered by German chemists, Otto Diels and Kurt Alder. They received the Nobel Prize for this achievement in 1950.



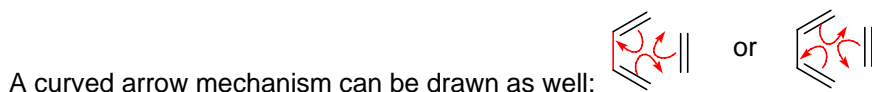
An example of a Diels - Alder reaction

Molecular Orbital Analysis.

The reaction occurs because there is a perfect symmetry match between the HOMO of the diene and the LUMO of the alkene and between the HOMO of the alkene and the LUMO of the diene. This perfect symmetry match allows two pairs of electrons to flow to form the two new bonds between the two molecules. Here is a diagram, showing these two most important MO interactions.

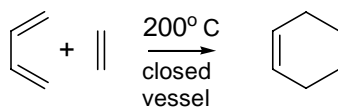


The full interaction diagram is shown on the left. The two individual important HOMO – LUMO interactions are shown on the right.



It does not matter which way the arrows are drawn. The simplest Diels-Alder reaction is the one shown here, 1-3-butadiene plus ethene. Note that the diene has to be in a *s-cis* conformation.

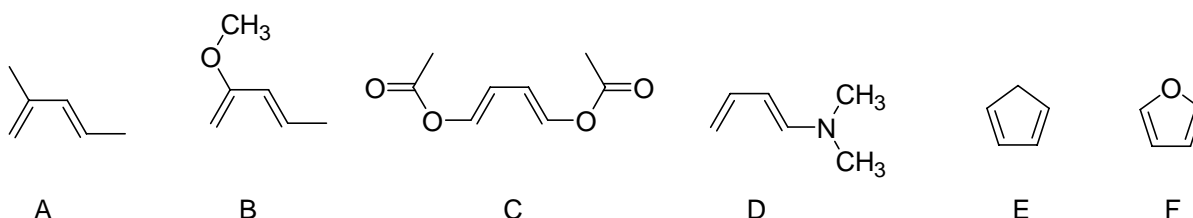
Substituents.



The simplest Diels Alder reaction between butadiene and ethene is not very favorable. It has a very large energy of activation. How can we make it more favorable? We can add substituents that enhance the flow of electrons.

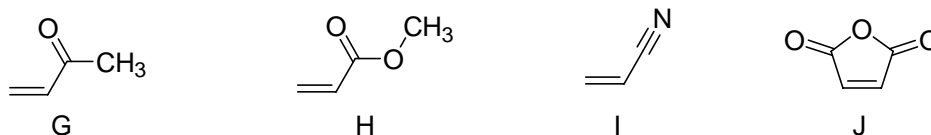
The highest energy electrons in the reaction are in the diene HOMO. If we add one or more Electron Donating Groups (**EDG**) to the diene we can make it more electron rich and an even better electron donor. We can also speed up the reaction by making ethene a better electron acceptor by adding Electron Withdrawing Groups, (**EWG**.)

Here are some examples of dienes that have been made more reactive by the addition of one or more Electron Donating Groups.



The addition of simple alkyl groups will activate the diene as in compound **A**. Substituents with oxygen or nitrogen atoms that have lone pairs are even better. Cyclopentadiene, **E**, and furan, **F**, are especially good dienes because they have a forced *s-cis* conformation.

Here are some examples of dienophiles that have been made more reactive by the addition of one or more Electron Withdrawing Groups.



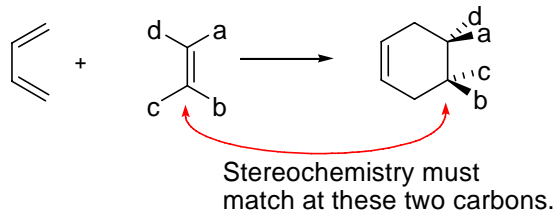
The most common electron acceptor groups are carbonyls. Most any carbonyl substituent will work, aldehydes, ketones, esters, amides or acids. A cyano group as shown in **I** is also a very good EWG. Compound **J** is maleic anhydride. It has two carbonyls pulling electrons out of the double bond making it a very powerful dienophile.

Note that an ester group attached via its O atom is a EDG as in compound **C**, but an ester group attached via the carbonyl C atom as in **H** is an EWG. Don't get these two confused.

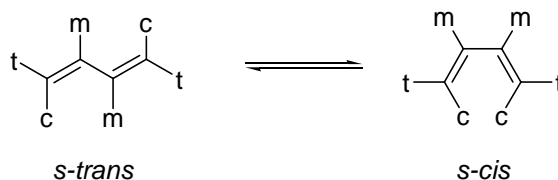
Stereochemistry.

The stereochemistry of the Diels Alder reaction is complicated, but the reaction is very powerful because the stereochemistry is well understood and predictable.

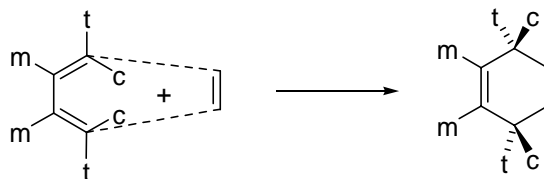
Stereochemistry of the Dienophile. The stereochemistry at the two carbons of the dienophile is conserved in the Diels Alder reaction. If two groups are *trans* in the alkene, then they will still be *trans* in the cyclohexene ring. If two groups are *cis* in the alkene, then they will still be *cis* in the cyclohexene ring. This is an absolute rule and never violated.



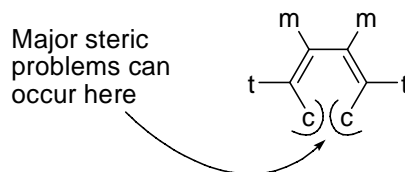
Stereochemistry of the Diene. The stereochemistry of the diene is confusing, because in its more stable form a diene will exist in the *s-trans* form. To react the diene has to rotate into the *s-cis* form. One has to be very careful to keep track of the positions of the substituents.



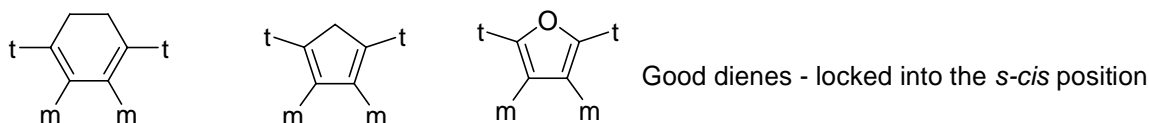
The six substitution sites have been labeled as follows. The *t* substituents are on the 1 and 4 carbon atoms and are *trans* to the other double bond. The *c* substituents are on the 1 and 4 carbon atoms are *cis* to the other double bond. The *m* substituents are on the middle carbons 2 and 3.



When the reaction occurs the *m* substituents end up on the double of the cyclohexene. The *t* sites will be *cis* to each other on one side of the ring, while the *c* sites will be *cis* to each other on the other side of the ring. In many cases the *c* sites will simply be hydrogen atoms. This is because of the fact that you can not form the *s-cis* conformation if the *c* substituents are large. The reaction will work with one small *c* group, like a methyl. But with two methyl groups it will be very slow.

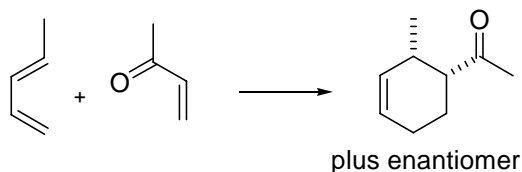


The reaction also works very well if you bridge the two *c* positions to form ring.

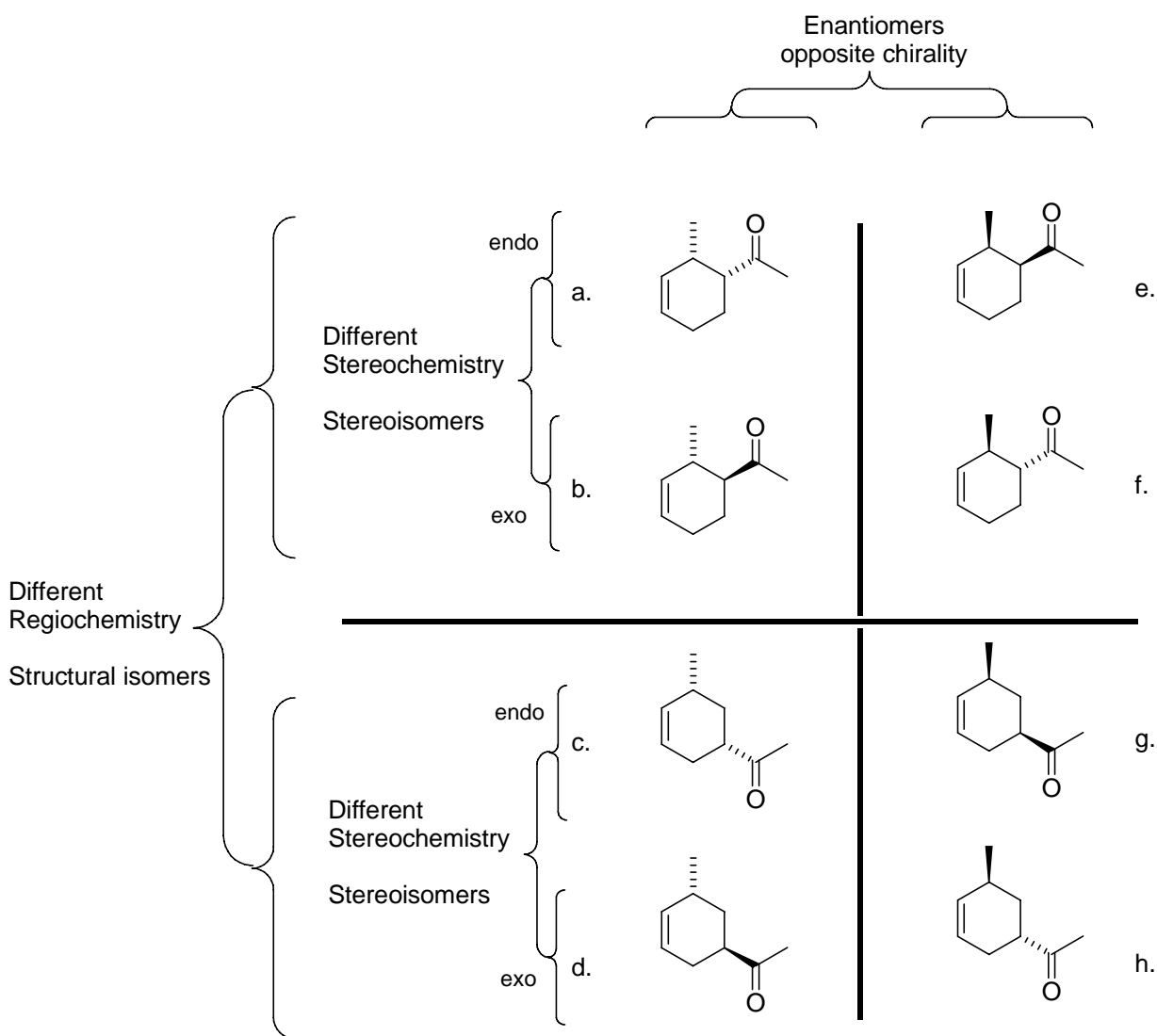


Putting the Two Parts Together.

Consider the reaction given as our first example at the beginning of this Study Guide. It is a typical example. The dienophile is electron poor because of the carbonyl group Electron Withdrawing Group. It reacts with a simple diene with one Electron Donating Group (the methyl).



The product of the reaction is correct as shown. We get a pair of enantiomers. But how would we be able to predict that this product? In reality there are eight possible products as shown in the chart below. How do we know which enantiomeric pair to predict?



Compounds (a) and (e) are enantiomers, from achiral reactants they will be produced in equal amounts

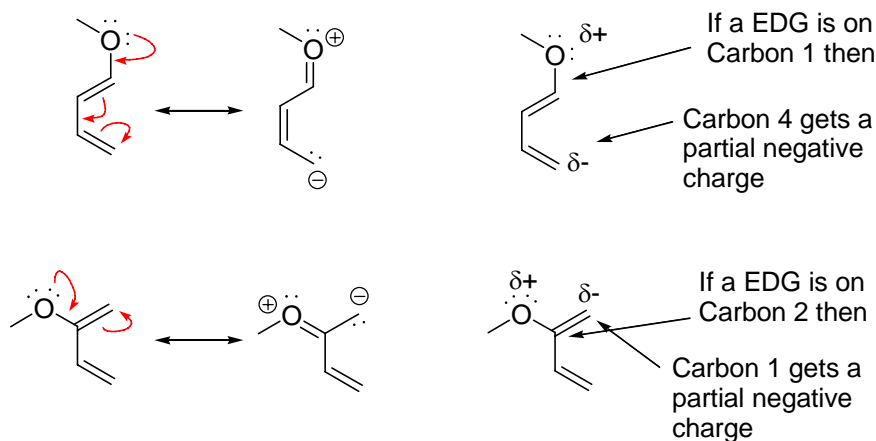
Compounds (a) and (b) are stereoisomers. The products with *cis* substituents are called **endo**, those with *trans* substituents are called **exo**.

Compounds (a) and (c) are structural isomers differing by the regiochemistry of the reaction.

So how do we distinguish between the four enantiomeric pairs? We have to make two decisions, one for the regiochemistry and one for the stereochemistry. At the end of this study guide we will see how we can target a single enantiomer. We will start by a look at the regiochemistry of the reaction.

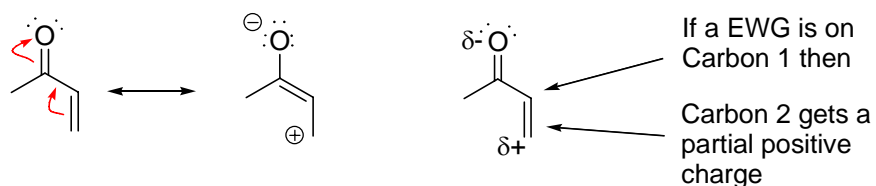
Regiochemistry of the Diels Alder Reaction

The regiochemistry of the Diels Alder reaction is determined by the patterns of electron density on the diene and the dienophile. For the diene the important thing is the partial charges found on the end C1 and C4 carbons. The most reactive dienes have Electron Donating Groups. An Electron Donating Group will dump electron density into the diene system. Where it shows up will depend upon where the EDG is located.



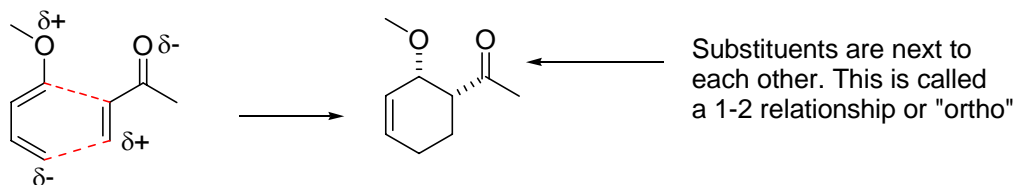
If the EDG is on carbon 1 then a partial negative charge will show up across the diene on carbon 4. If the EDG is on carbon 2 then a partial negative charge will show up on the neighboring carbon 1.

Reactive dieneophiles have Electron Withdrawing Groups, EWG. An EWG on carbon 1 will deplete the electron density on carbon 2.

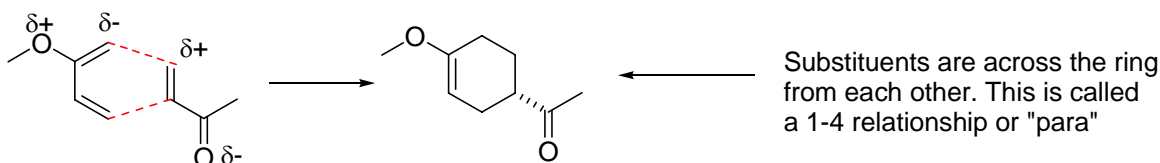


The regiochemistry of the Diels Alder reaction can then easily be determined by simply matching up the charges.

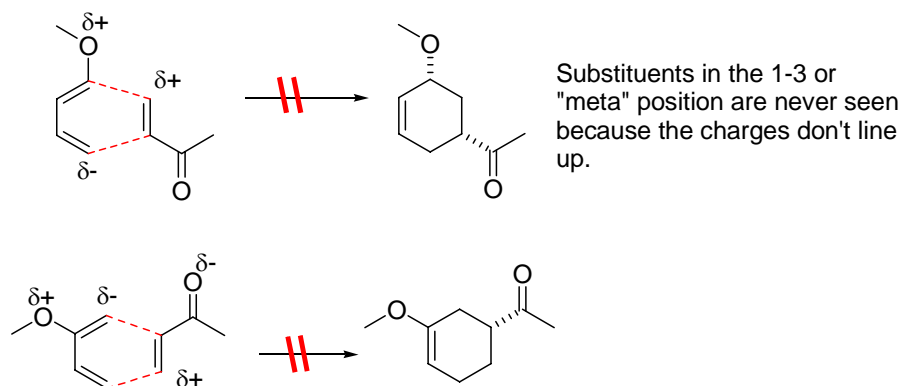
First consider a diene with a EDG at the carbon 1 position. The dienophile will approach with the EWG group next to the EDG group. This is a 1-2 or "ortho" arrangement of substituents.



If the EDG group is at the two position the dienophile will flip over and we will get a 1-4 or "para" arrangement of the substituents.

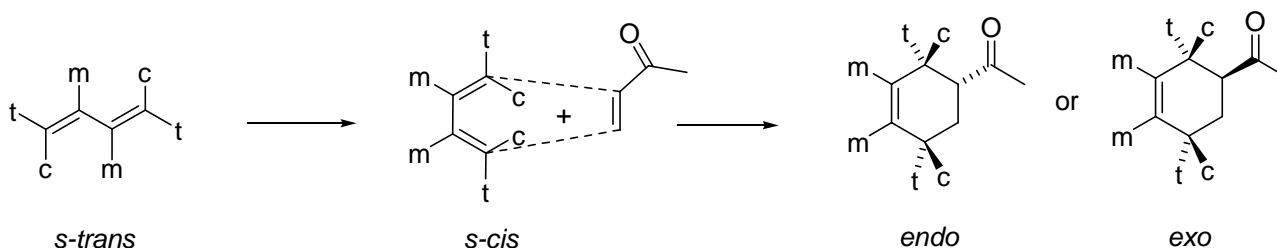


In neither case do we see a 1-3 or "meta" arrangement.

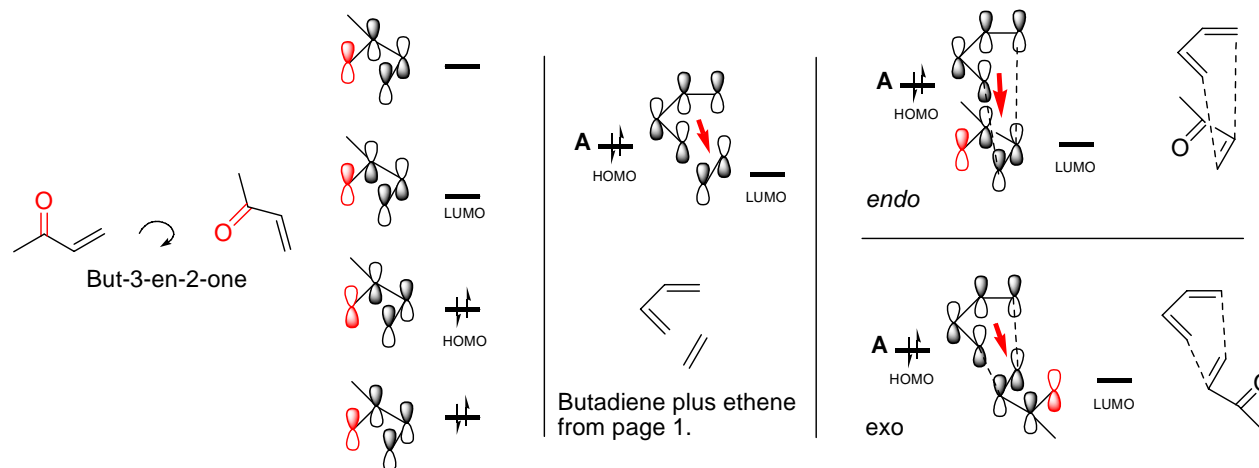


Stereochemistry of the Diels Alder Reaction.

The stereochemistry of the Diels Alder reaction determines the position of an Electron Withdrawing Group on the dienophile relative to the substituents on the diene. There are two possibilities. The EWG can be *cis* or *trans* to the "t" positions of the diene. If it is *cis* the geometry is called *endo*, if it is *trans* the geometry is called *exo*.



To understand these phenomena we need to examine the molecular orbitals of the dienophile. The dienophile in our example is actually a diene where one carbon atom has become an oxygen atom. The MO structure is thus a close analogue of butadiene.



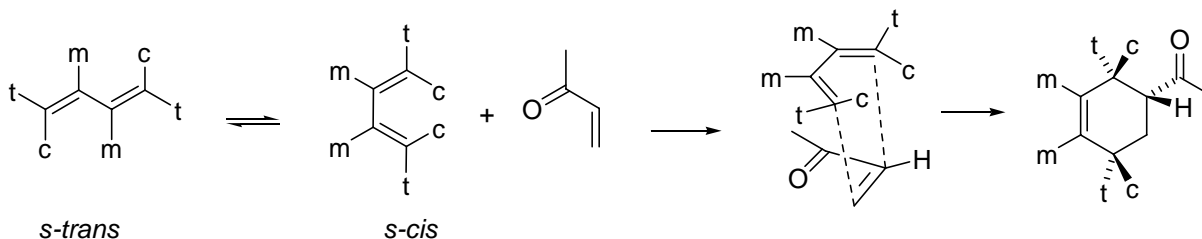
The above drawing is pretty complicated, but let us walk through it. On the left we see the dienophile. With the carbonyl added to the double bond, the dienophile is itself actually a diene. The four MOs of the dienophile are shown with the red orbital representing the oxygen contribution.

The center of the diagram shows the electron flow from the butadiene HOMO into the LUMO of ethane. This is taken from the complete diagram shown on page 1. On the right side we see the HOMO of butadiene donating electrons into the LUMO of the dienophile. There are two possible orientations.

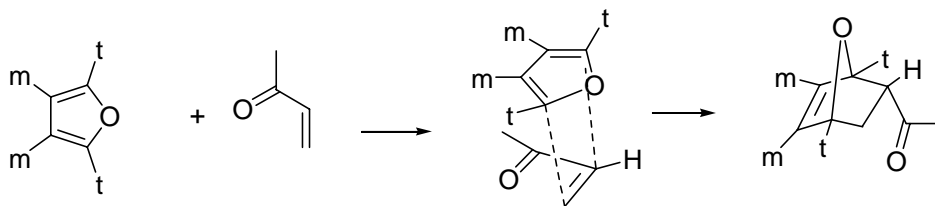
In the top right we have the *endo* geometry with the EWG group of the dienophile turned inward under the diene. Looking at the diagram we can see that all four atomic orbitals of the dienophile can overlap with the four atomic orbitals of the diene.

In the bottom right we have the *exo* geometry with the EWG group of the dienophile turned outward away from the diene. This is called the *exo* geometry. In this orientation there is no interaction with the atomic orbitals of the CO group. Overall there is less possible orbital overlap. This approach is less favorable than that of the *endo* geometry.

Endo wins!



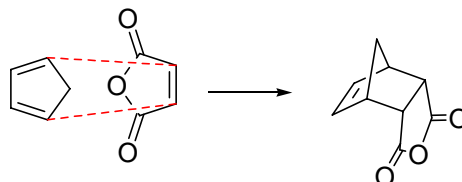
Here is another example showing the *endo* geometry with furan acting as the diene.



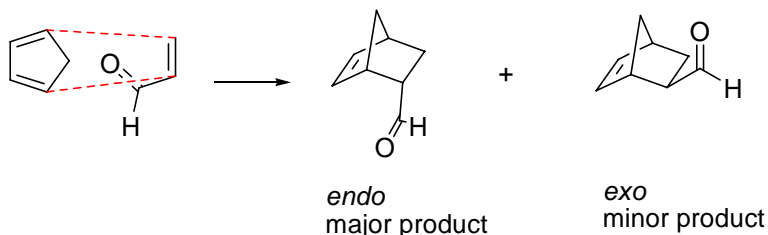
Time for some examples.

We now know how to determine both the regiochemistry and the stereochemistry of the Diels-Alder reaction. So let's look at some examples.

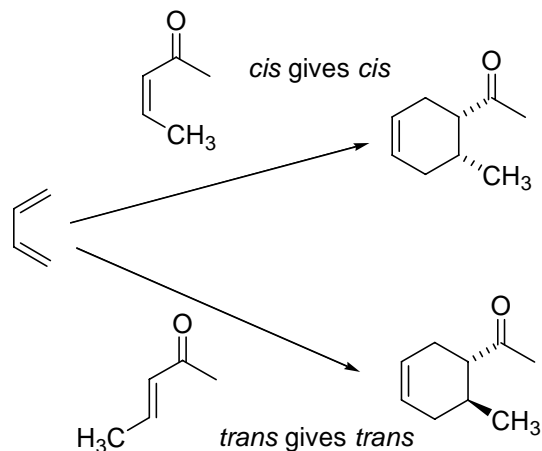
A. In this reaction the diene is cyclopentadiene and the dienophile is maleic anhydride. Both compounds are symmetrical so there is no regiochemistry issue. The addition will be *endo* so the sterically least favored product is formed.



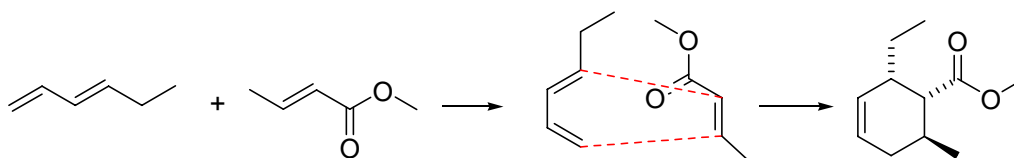
B. In this reaction the diene is cyclopentadiene and the dienophile is an aldehyde. The diene is symmetrical so there is no regiochemistry issue. The addition will favor *endo*, not *exo*.



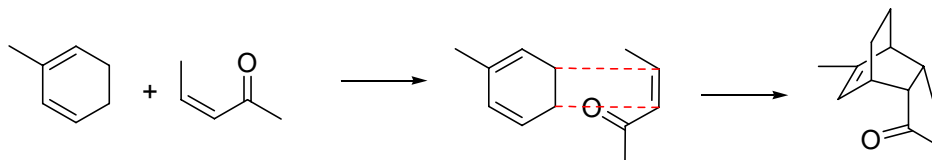
C. In these reactions we explore the stereochemistry of the dienophile. The key thing is that the stereochemistry of the dienophile is conserved. A *cis* alkene gives a *cis* substituted cyclohexene. A *trans* alkene gives a *trans* substituted cyclohexene.



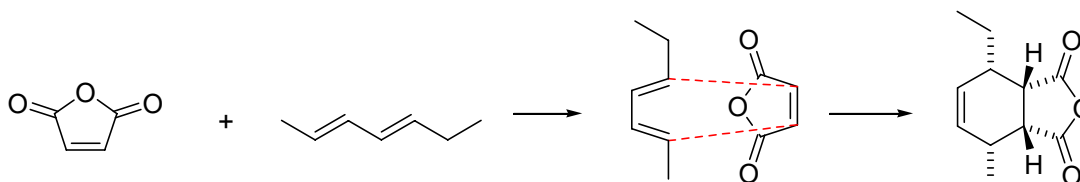
D. In this reaction the diene has a EDG (an ethyl group) on carbon 1. The dienophile has an EWG (an ester) group. The regiochemistry will be 1-2 or "ortho". The stereochemistry will be endo meaning the ethyl group and the ester will be *cis*. The methyl will be *trans* to the ester since it was *trans* in the reactant. Remember 1-2 is favored over 1-3.



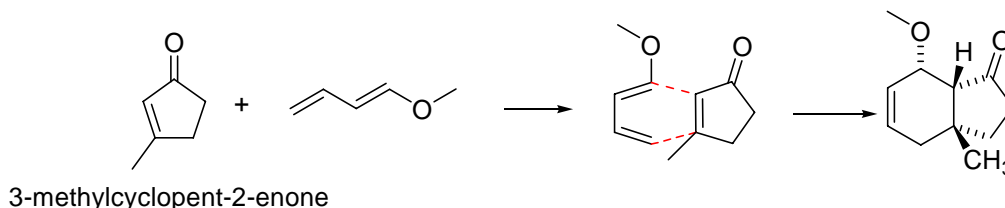
E. In this reaction the diene is a cyclohexadiene with an added methyl group. The dienophile will add endo with the ketone located across the ring 1-4 from the methyl group. Remember 1-4 is favored over 1-3.



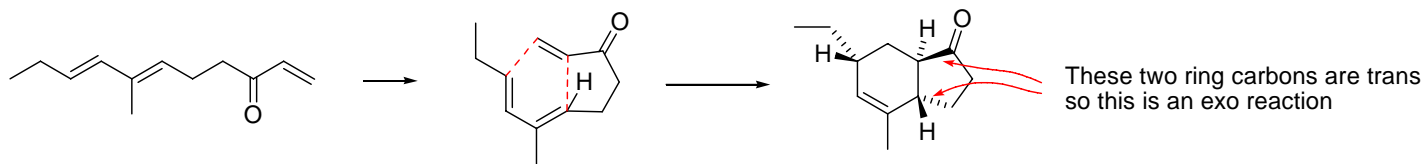
F. In this reaction the diene has electron donating alkyl groups on both carbons 1 and 4. The maleic anhydride dienophile is symmetric so there is no regiochemistry issue. The addition will be *endo*.



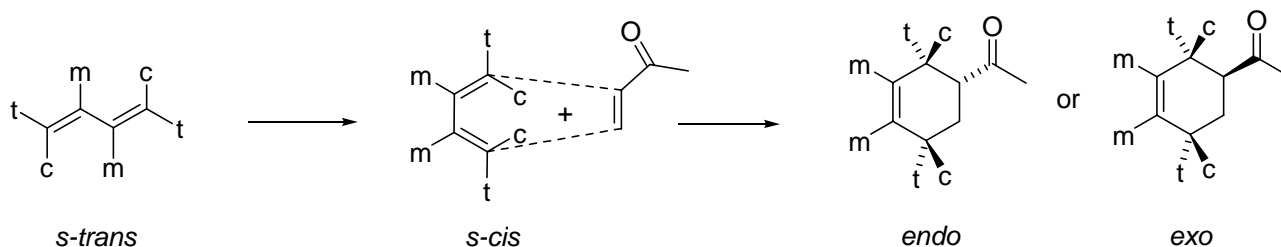
G. In this reaction the diene has a EDG (a methoxy) at carbon 1. The dienophile has a EWG carbonyl attached to one carbon and a methyl attached to the other end with a *trans* geometry. The product will form with the carbonyl next to the methoxy group (1,2). They will be mutually *cis* because the carbonyl directs the product endo. The methyl will be *trans* to the carbonyl because it was *trans* in the original reactant.



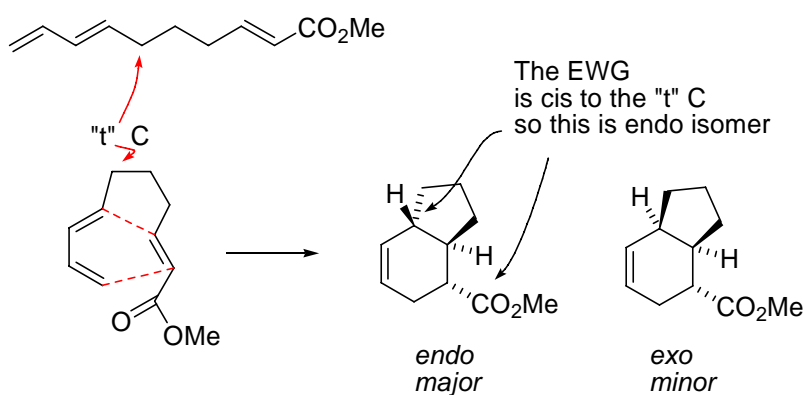
H. Here is an intramolecular example. When the reaction is intramolecular it is not always possible to follow the normal rules for regiochemistry and stereochemistry. The reaction shown below is a good example. The reaction gives the *exo* product instead of the normally expected *endo* isomer



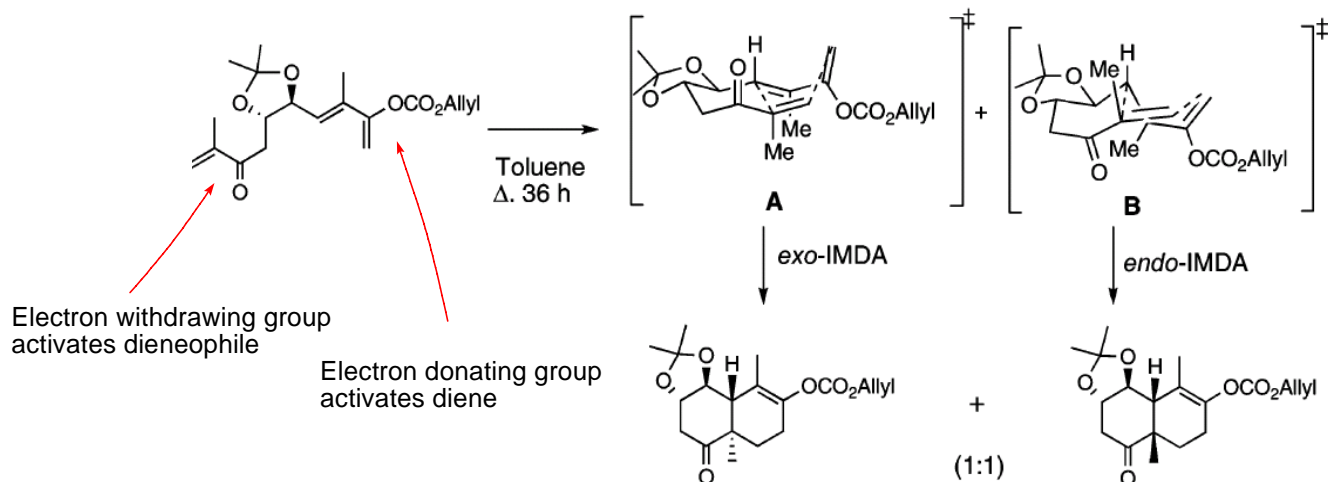
You can verify the *exo* geometry by looking at our example from before. The carbonyl below is cis to the "t" groups in the *endo* isomer, trans to the "t" group in the *exo* isomer.



I. Here is another example. This time *endo* wins.

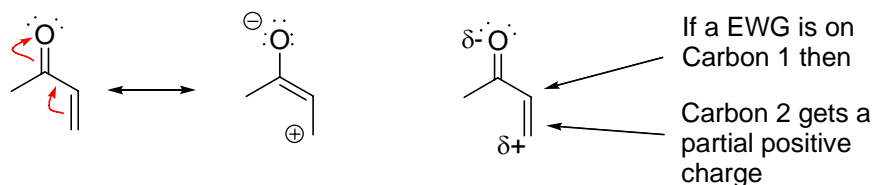


J. Here is one more example from the recent chemical literature. This time the reaction give equal amounts of the *exo* and *endo* isomers. IMDA stands for IntraMolecular Diels Alder. The two transition states are drawn. These are impossible to predict unless you are an expert. Don't worry, no one is going to ask you to predict one as complicated as this.

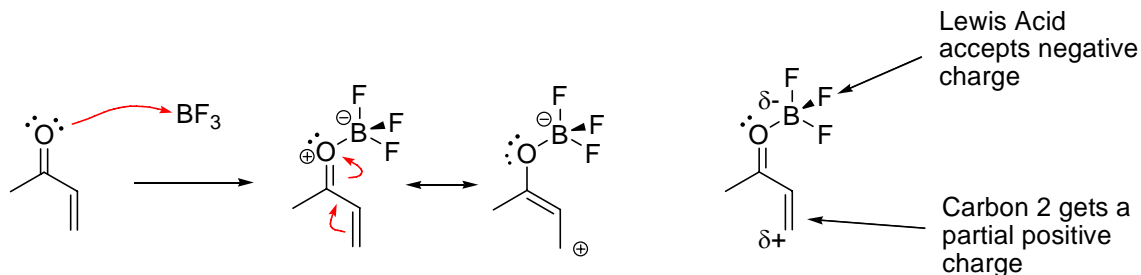


Lewis Acid Catalysis

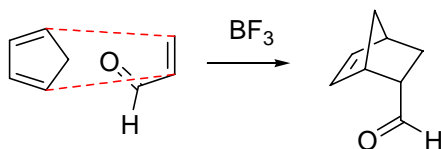
We discussed earlier the fact that an Electron Withdrawing Group on the dienophile will enhance the compounds reactivity.



This effect can be made even stronger if a Lewis acid catalyst is added to the reaction. Common catalysts are derivatives of boron, like BF_3 , or Al, like AlCl_3 .

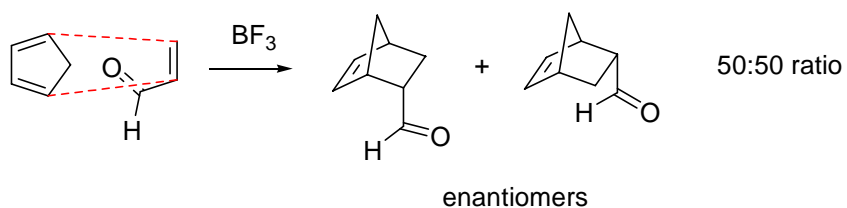


The following reaction occurs without a catalyst, but the presence of the catalyst will speed up the reaction and makes the *endo* selectivity even more favored.

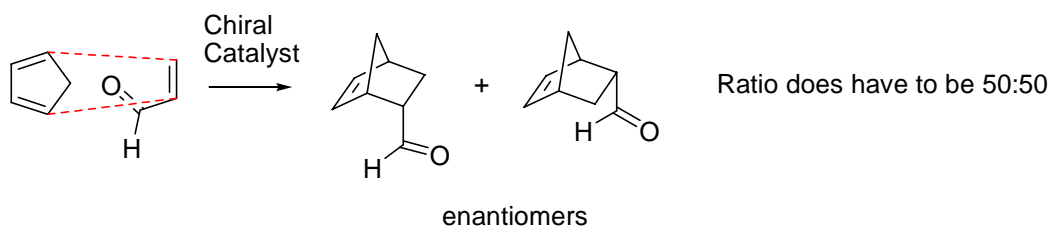


Enantiomeric Selection

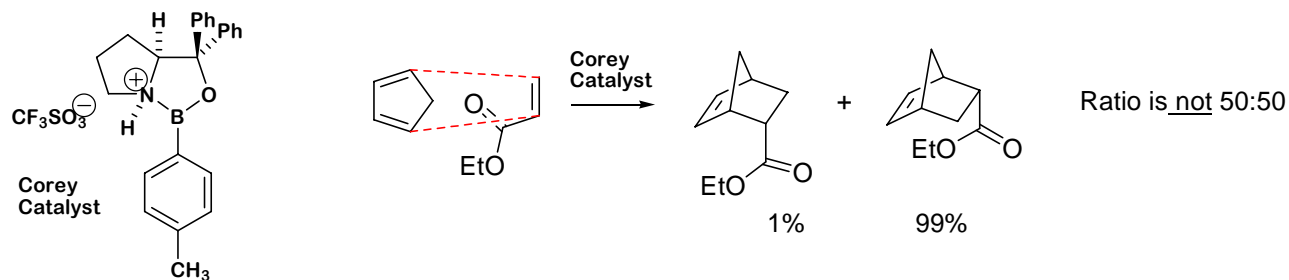
One important feature of Lewis acid catalyzed Diels Alder reaction is the fact that it gives us a route to a single enantiomer. The previous reaction actually gives two products, a pair of enantiomers.



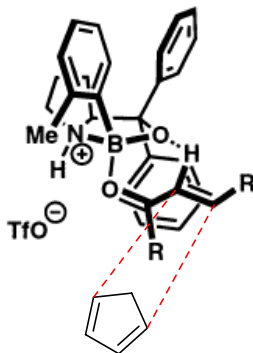
If a chiral boron catalyst is used instead of BF_3 then one of the enantiomers may be favored. This is very similar to the action of an enzyme in a living system.



Here is a real example from Professor E.J. Corey at Harvard University.



To explain the selectivity one has to look at the transition state of the reaction. The following picture can be drawn. The catalyst has formed a Lewis acid – Lewis base complex with the dienophile. Only one face to the dienophile is open so there is one favored reaction to give the predominant enantiomer.



Web References.

Follow the following links to read more about the Diels Alder reaction.

For Corey's Paper <http://pubs.acs.org/cgi-bin/article.cgi/jacsat/2002/124/i34/pdf/ja027468h.pdf>

This link will only work from a Stony Brook IP address.



J. AM. CHEM. SOC. 2002, 124, 9992–9993

Broad-Spectrum Enantioselective Diels–Alder Catalysis by Chiral, Cationic Oxazaborolidines

Do Hyun Ryu, Thomas W. Lee, and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Received June 26, 2002

The Wikipedia has a nice general article, easy to understand

http://en.wikipedia.org/wiki/Diels-Alder_reaction

The Virtual Textbook of Organic Chemistry site at Michigan State University has a nice general article on the Diels Alder reaction with sample problems.

<http://www.cem.msu.edu/~reusch/VirtualText/addene2.htm#dien3>