CYCLOADDITIONS IN ORGANIC SYNTHESIS

CYCLOADDITIONS IN ORGANIC SYNTHESIS

Introduction

Cycloaddition describes the union of two independent π-systems through a concerted process involving a cyclic movement of electrons and resulting in the formation of a new ring.

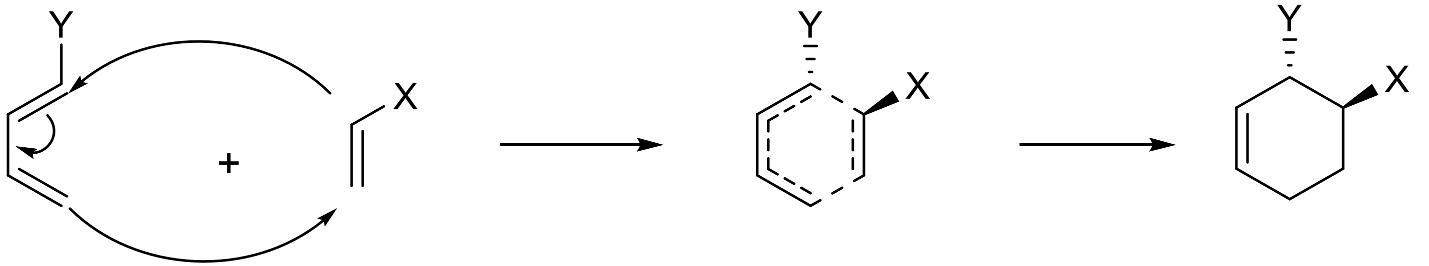
Cycloaddition reactions are considered among the most powerful bond-forming reactions in organic synthesis because of their ability to form many bonds in one step and also for their potential in generating several stereogenic centres at the same time with predictable stereochemical outcomes.

A cycloaddition reaction is categorized as a [m + n]-cycloaddition when a system of m conjugated atoms combines with a system of n conjugated atoms.

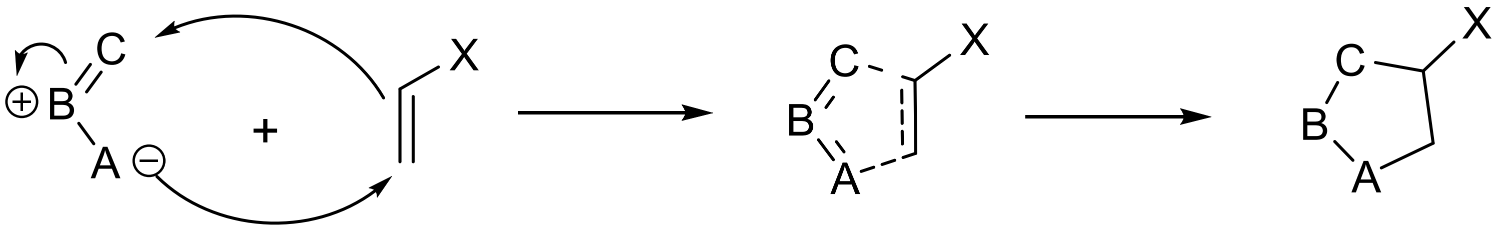
CATEGORIES OF CYCLOADDITIONS

The three most important types of cycloaddition reactions that occur by concerted reaction mechanisms are:

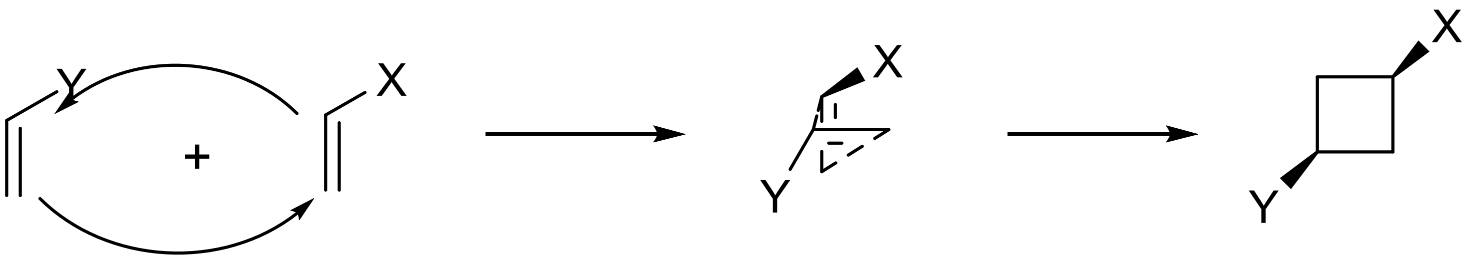
(a) The Diels-Alder Reaction: [4+2]-Cycloaddition: 6-member carbocyclic rings formed



(b) 1,3-Dipolar-Cycloaddition: [3+2]-Cycloaddition: 5-member heterocyclic rings formed

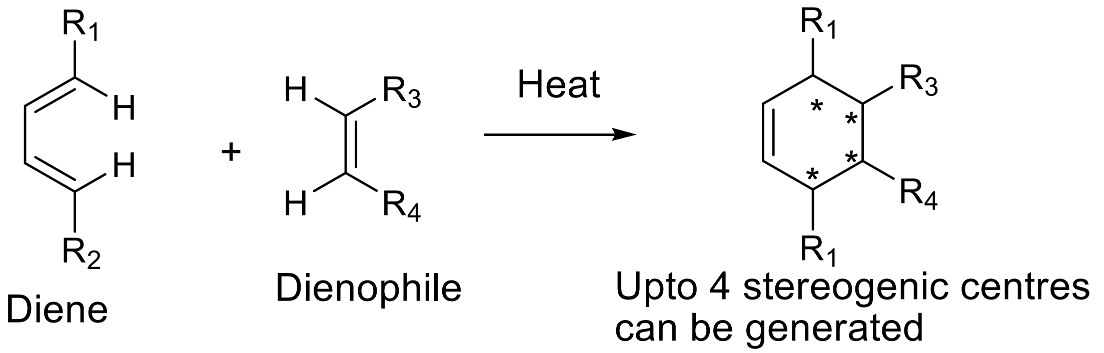


(c) [2+2]-Cycloaddition: 4-member carbocylic rings formed



The Diels-Alder Reaction

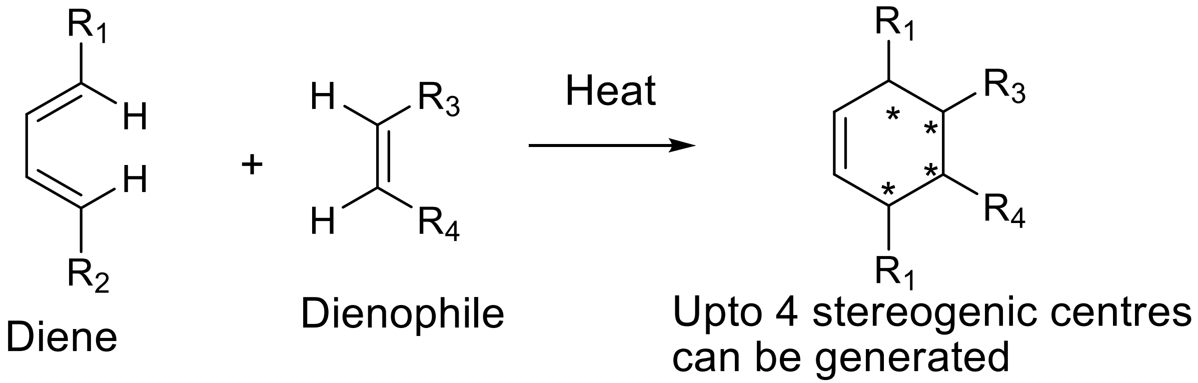
The Diels-Alder reaction is the best known of the cycloaddition reactions. It is formally a [4+2]-cycloaddition and can be represented as follows:



It represents a six-electron [4 + 2]-cycloaddition between a conjugated diene (1,3-diene) and the π-bond of a substituted alkene (dienophile) to provide a substituted cyclohexene.

The Diels Alder reaction is thermally allowed. Although there is a large activation energy (heating is required) for the Diels-Alder reaction, it is usually exothermic in the forward direction driven by the formation of two new σ-bonds at the expense of the loss of two π-bonds. Note that σ-bonds are stronger than π-bonds.

The Power of the Diels-Alder Reaction



The Diels-Alder reaction is often referred to as the most powerful reaction in all of organic chemistry because:

(a) A six-membered cyclohexene ring is generated from acyclic precursors

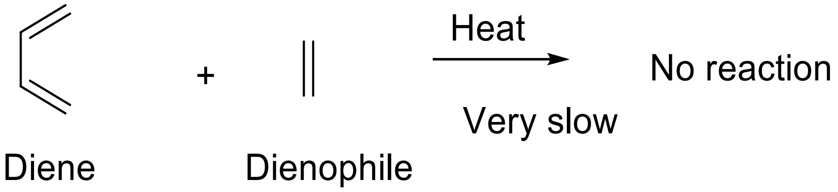
(b) The double bond in the generated cyclohexene can be further functionalized

(c) Up to a maximmum of four contiguous chiral (stereogenic) centres can be generated in a controlled and predictable manner. The stereospecificity of the reaction is firmly established.

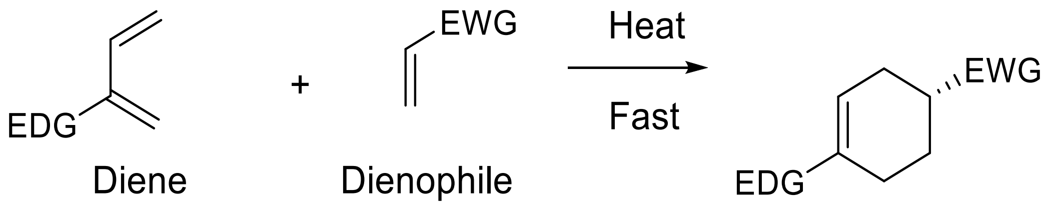
(d) All these being accomplished in a single reaction step.

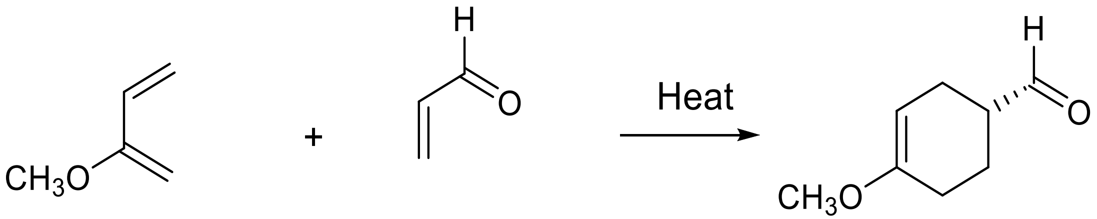
The Diels-Alder Reaction

Although the Diels Alder reaction combines a diene and a dienophile to generate a cyclohexene, the reaction between simple 1,3-butadiene and ethene is very slow that in practice, it does not readily occur.



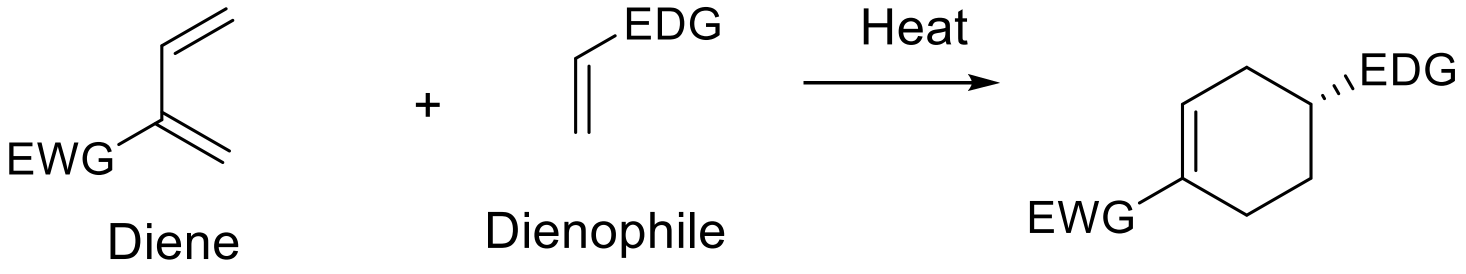
The Diels-Alder reaction can however be made more facile by employing dienes with electron-donating substituents and dienophiles with electron-withdrawing substituents. This combination corresponds to the normal electron demand and occurs readily.

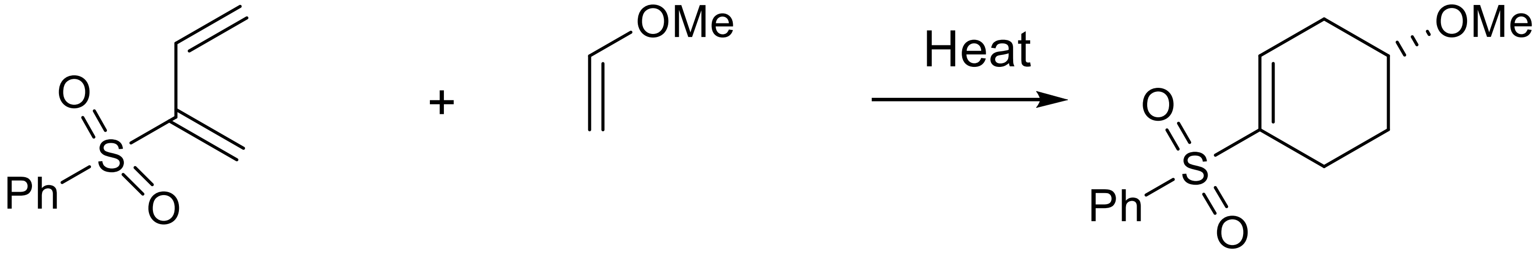




The Diels-Alder Reaction

It is significant to note that when an electron-poor diene is utilized in the Diels-Alder reaction, the preference for the dienophile is reversed with electron-rich dienophiles, such as vinyl ethers, being the best dienophiles. This combination constitutes what is called the inverse electron demand Diels-Alder reaction.

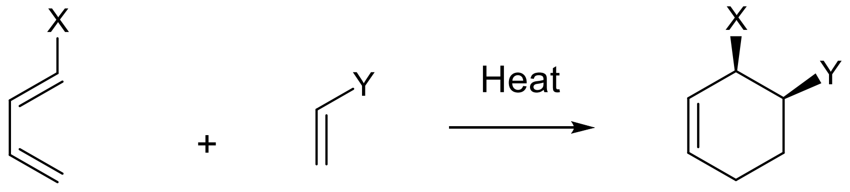




Note that the normal electron demand Diels Alder reactions are the more common

The Diels-Alder Reaction

(Dienophiles)

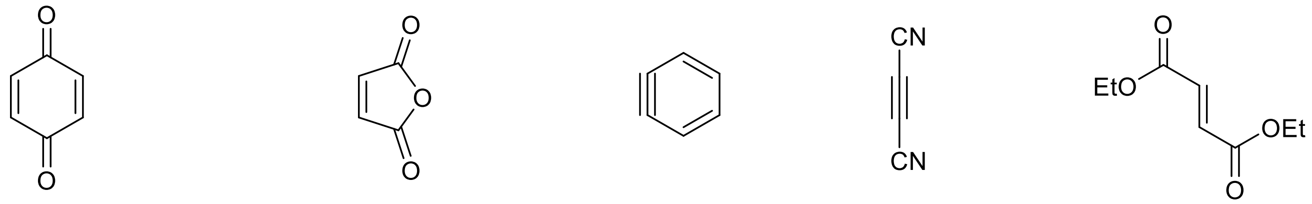


Diene Dienophile

There is a strong electronic substituent effect on the Diels-Alder reaction. Most Diels-Alder reactions occur with normal electron demand in which an electron-rich (nucleophilic) diene reacts with an electron-poor (electrophilic) dienophile.

In a typical Diels-Alder reaction the dienophiles that are most reactive towards simple dienes are those with electron-withdrawing groups conjugated to the double bond of the alkene. Thus among the most reactive dienophiles are benzoquinones, maleic anhydride, benzyne and fumarate esters.

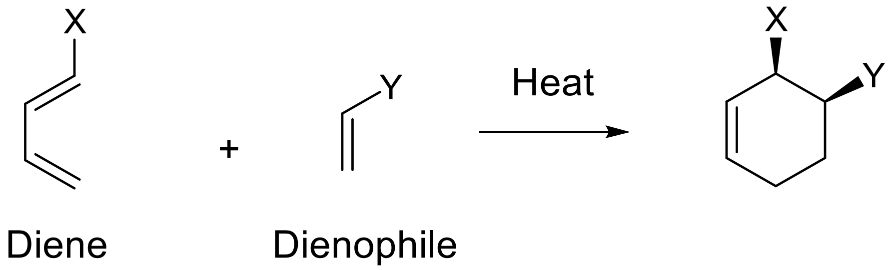
Good Diels Alder Dienophiles



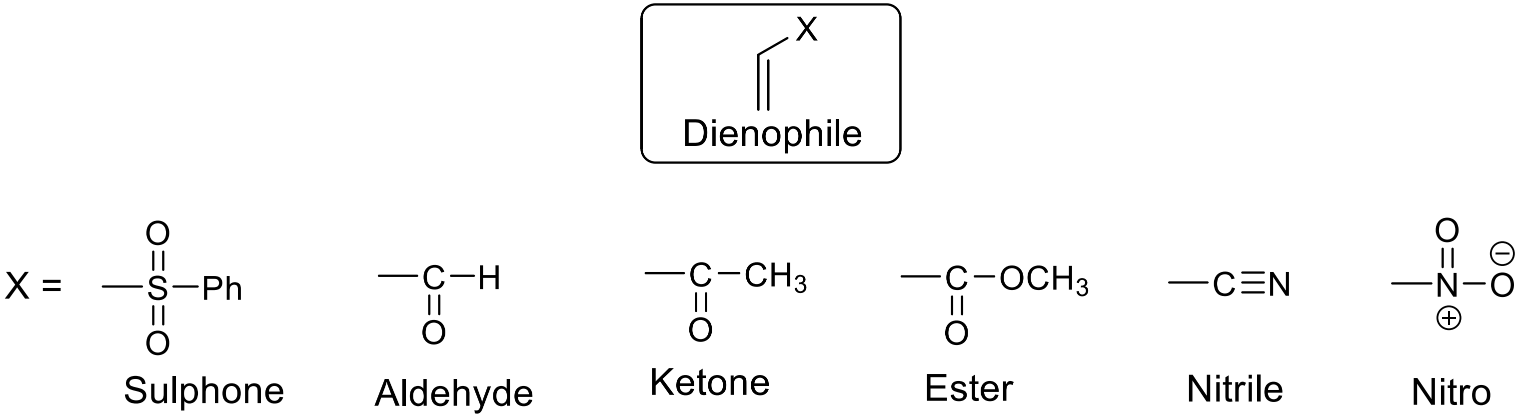
1,4-Benzoquinone Maleic anhydride Benzyne Dicyanoacetylene Diethyl fumarate

The Diels-Alder Reaction

(Dienophiles)



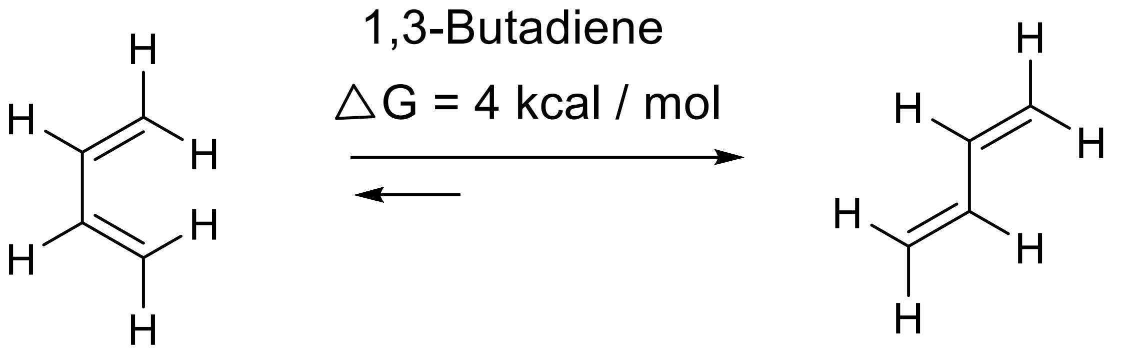
Alkenes conjugated to the following functional groups also serve as effective dienophiles: α,β-unsaturated aldehydes, ketones, esters, nitroalkenes and nitriles.



The Diels-Alder Reaction

(Dienes)

The Diels-Alder reaction requires that the two double bonds of the diene be coplanar and pointing in the same direction (i.e. be in the s-cisoid conformation). Rotation about the σ-bond between the internal carbon atoms of the diene interconverts the s-cisoid and s-transoid conformations)



1,3-Butadiene

$\Delta G = 4$ kcal / mol

s-cisoid conformation

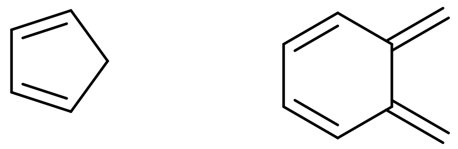
s-transoid conformation
(More stable)

In the s-transoid conformation, there are fewer steric interactions between the in groups at the termini of the diene, so dienes normally reside in this lower energy (by about 4 kcal/mol) conformation.

The Conformational Requirements of the Dienes

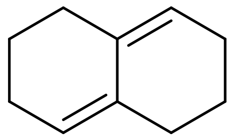
The barrier to converting the s-transoid conformation to s-cisoid conformation contributes to the overall activation barrier in the Diels-Alder reaction.

Structural factors that restrict the diene in the s-cisoid conformation enhance the rate of the Diels-Alder reaction. It is precisely for this reason that cyclopentadiene is one of the best dienes for Diels Alder reaction mainly because it can not rotate out of its s-cisoid conformation.



Locked in s-cisoid conformations

React rapidly with dienophiles



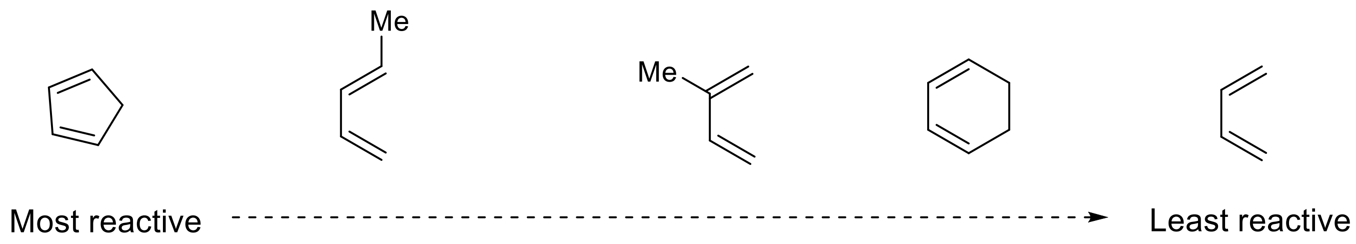
Locked in s-transoid conformation

Do not react with dienophiles

The Diels-Alder Reaction

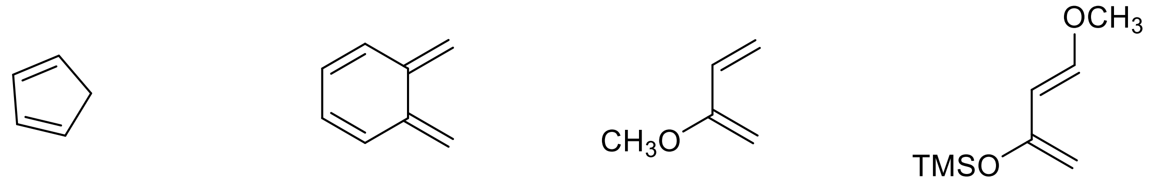
(Dienes)

Reactivity series of dienes in Diels Alder reaction



Due to the strong electronic substituent effect on the Diels-Alder reaction, the dienes that are most reactive towards simple alkenes are those with electron-donating groups. Below are some of the most reactive dienes in Diels-Alder cycloaddition reactions.

Good Dienes for Diels Alder Reaction



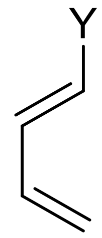
Cyclopentadiene

Danishefskys diene
1-Methoxy-3-trimethylsilyoxy-1,3-butadiene

The Diels-Alder Reaction

(Dienes)

Dienes substituted with the following electron-donating functional groups directly attached to the diene nucleus, also serve as effective dienes in Diels-Alder reactions: Alkyl, ethers (OR), amines (NR_2), sulphides (SR) and trimethyl silylethers (OTMS)

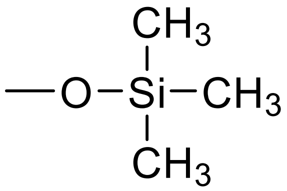


Diene

Y = Alkyl

$—OCH_3$

Methoxy



$$—O—\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{Si}}—CH_3$$

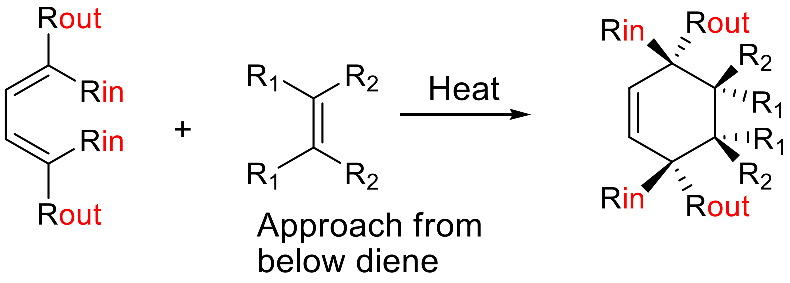
Trimethylsilyl ether

$—SCH_3$

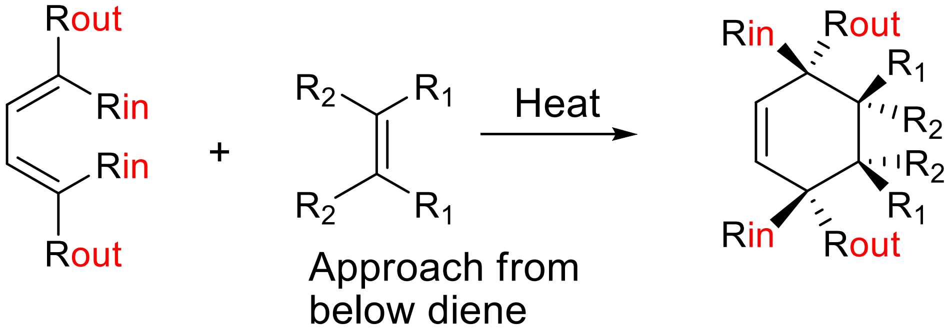
Thiomethyl

Stereochemistry of the Diels-Alder Reaction

In the transition state of the cycloaddition reaction, the planes of the diene and the dienophile must be coplanar to ensure maximum orbital overlap. Envisage the stereochemical ramifications of the reaction of a symmetrical dienophile with a diene.



This stereochemical outcome gives rise to the *cis* rule: If two substituents are *cis* in the dienophile, they will be on the same side of the resulting cyclohexene i.e the orientation of the groups on the dienophile is preserved in the product.

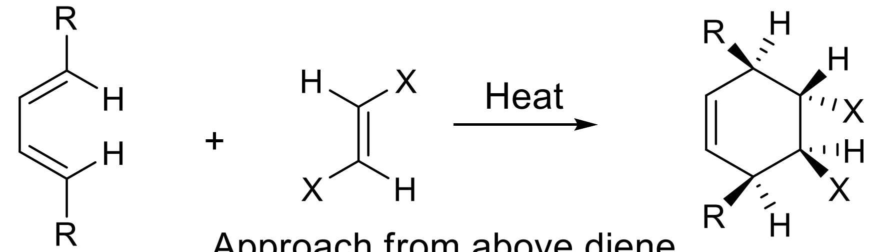


Stereochemistry of the Diels-Alder Reaction

(The Cis Principle)

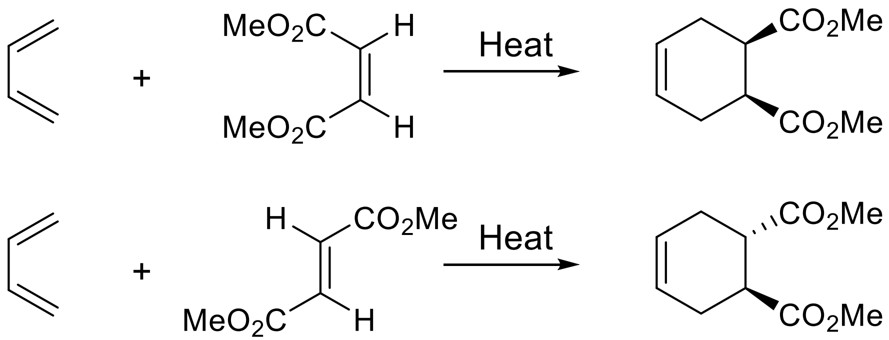
The cis principle: The geometry of the dienophile and diene are preserved in the [4 + 2]-cycloaddition.

This is an affirmation of the stereospecificity of the Diels-Alder reaction.



Approach from above diene

Unsubstituted dienes

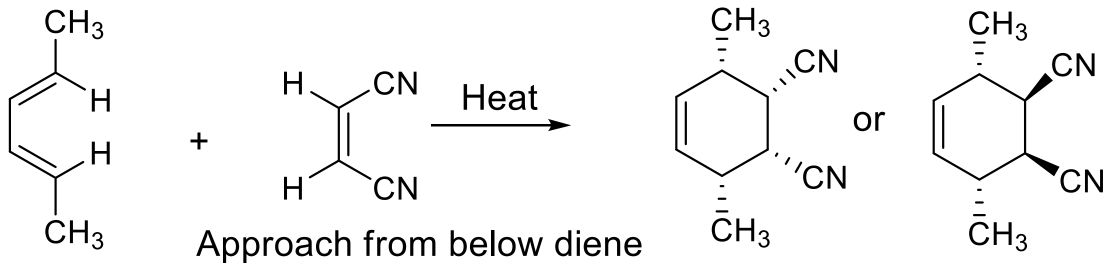


The possibility of two different diastereomers arising in a Diels-Alder reaction can be envisaged based on how the dienophile approaches the diene i.e depending on which is the leading edge of the dienophile as it approaches the diene in the TS.

Stereochemistry of the Diels-Alder Reaction

(The Alder Endo Rule)

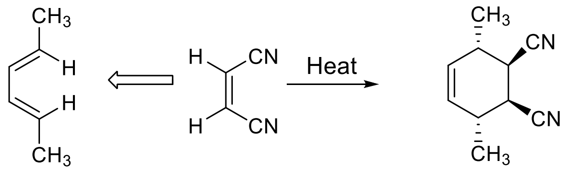
Hypothetically, two diastereomeric adducts can be anticipated from a Diels Alder reaction. Consider the Diels-Alder reaction below, for example:



Approach from below diene

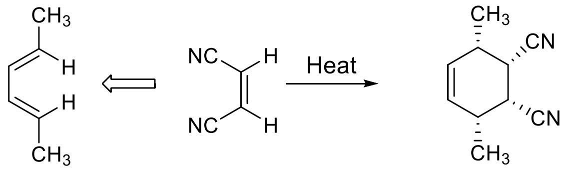
The two diastereomeric adducts are presumed to arise from two competing diene-dienophile orientations. The two orientations are described with the terms Exo and Endo.

Exo approach



Approach diene with H edge of dienophile

Endo approach



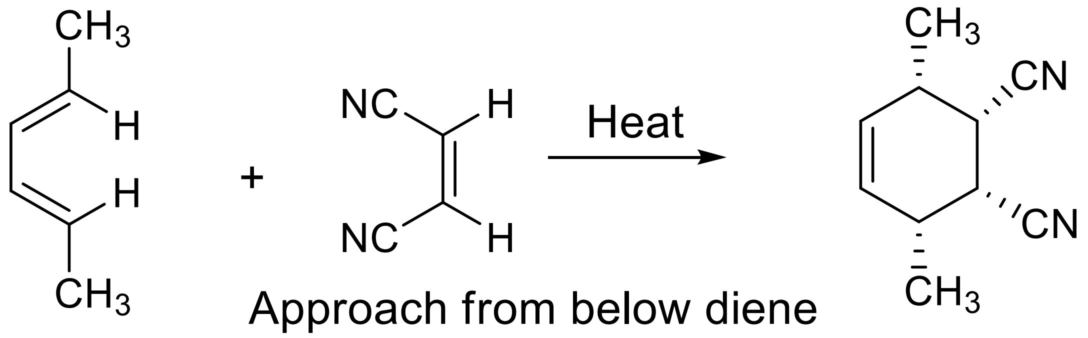
Approach diene with CN edge of dienophile

In the Endo approach, the π-substituents on the dienophile point towards the diene, while in the Exo approach, they point away from the diene.

Stereochemistry of the Diels-Alder Reaction

(The Alder Endo Rule)

In practice only one diastereomer predominates in the reaction.



Dienophiles with π-bonded substituents stabilize the TS of the Diels Alder reaction through secondary orbital interactions thus have a tendency to approach the diene with their π-bonded substituents on the leading edge (Endo approach) oriented towards the diene.

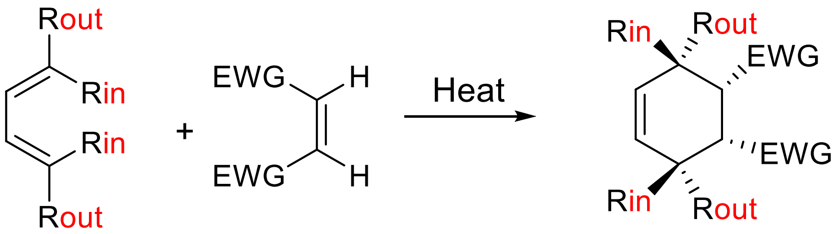
The Alder Endo Rule for predicting the stereochemistry of Diels-Alder reactions applies to reactions involving a dienophile with one or more unsaturated substituents: The rule states that the kinetic product is obtained from a transition state in which the dienophile π-substituent is “endo” with respect to the diene.

Stereochemistry of the Diels-Alder Reaction

(The Alder Endo Rule)

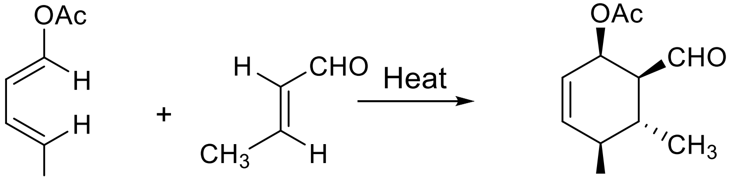
The Alder Endo rule can be restated: Of two possible diastereomeric transition states in a Diels-Alder reaction, the one providing the greatest accumulation of interacting double bonds will be preferred.

The following mnemonic (predictive model) could help to identify the Endo product of the Diels-Alder reaction.

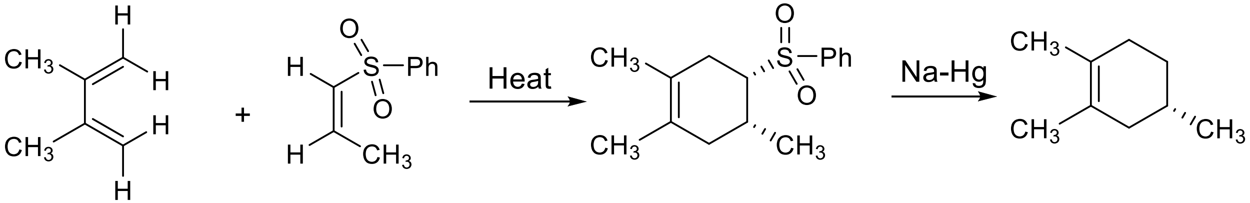


This is based on the realization that the electron-withdrawing groups commonly used to activate dienophiles have π-bonded groups that can engage in secondary orbital interactions with the diene orbitals.

Example



Approach from above diene

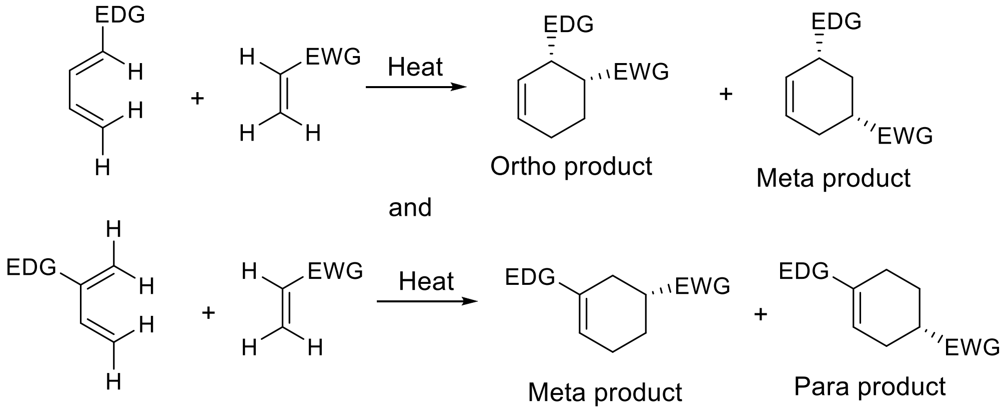


Approach from below diene

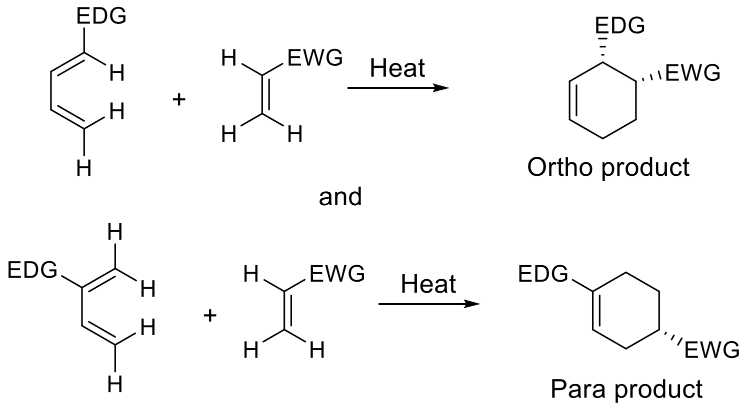
The Regiochemistry of the Diels-Alder Reaction

Bearing in mind that the most facile Diels-Alder reactions have a diene that bears an electron-donating group (EDG) and a dienophile that bears an electron-withdrawing group (EWG), for an unsymmetrically monosubstituted diene reacting with another unsymmetrical dienophile, two regio-isomeric products are ideally possible.

Ideally



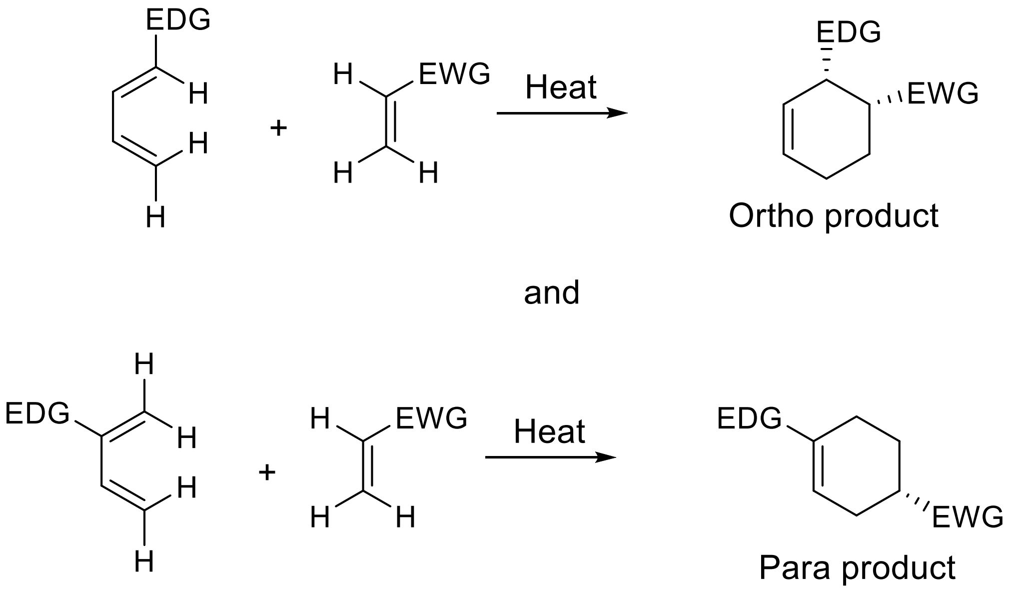
In practice



The Regiochemistry of the Diels-Alder Reaction

When unsymmetrically substituted dienes and dienophiles react in Diels-Alder reactions, ortho and para orientations in products are usually favoured over the meta orientation.

This preference can be explained in terms of the frontier orbital theory by which it is expected that the carbons with the highest coefficients in the frontier orbitals of the diene and dienophile will initiate the bonding interaction; thereby directing the orientation of substituents and thus the identity of the major regioisomer in the Diels-Alder reaction.



The Regiochemistry of the Diels-Alder Reaction

Resonance Considerations

The same regio-isomeric preference can also be predicted by analysing the partial positive and negative charges that exist in the diene and dienophile.

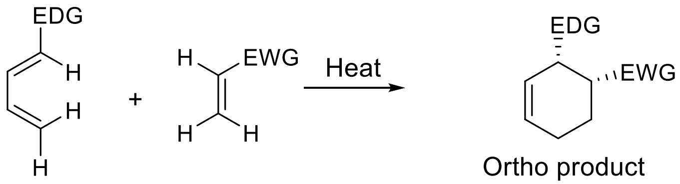
It would be expected that the terminal carbon (frontier carbon) with a partial negative charge in the diene will interact most readily with the terminal carbon bearing a partial positive charge in the dienophile.

The two carbons will initiate the bonding interaction between the diene and dienophile, thus dictating the relative orientation of substituents in the product.

The existence of partial positive/negative charge can always be determined by drawing resonance contributors for the diene and dienophile, taking their EDG and EWG character into consideration.

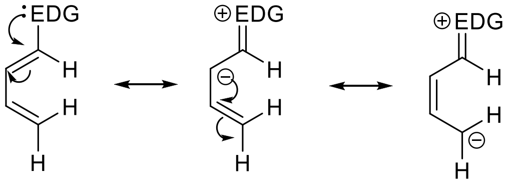
How to Predict the Regiochemical Outcome

Consider the monosubstituted diene-dienophile Diels Alder reaction featuring a diene substituted at the termini of its nucleus.



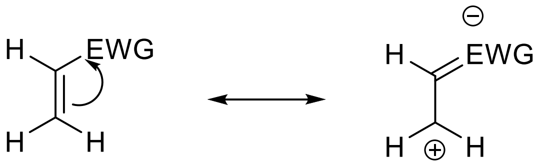
Ortho product

Resonance considerations for the electron-rich diene:



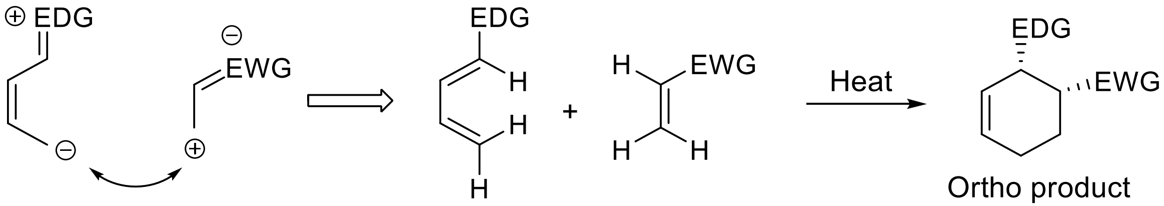
Nucleophilic terminal carbon

Resonance considerations for the electron-deficient dienophile:



Electrophilic terminal carbon

Consolidation: Matching the nucleophilic end of the diene with electrophilic end of dienophile.

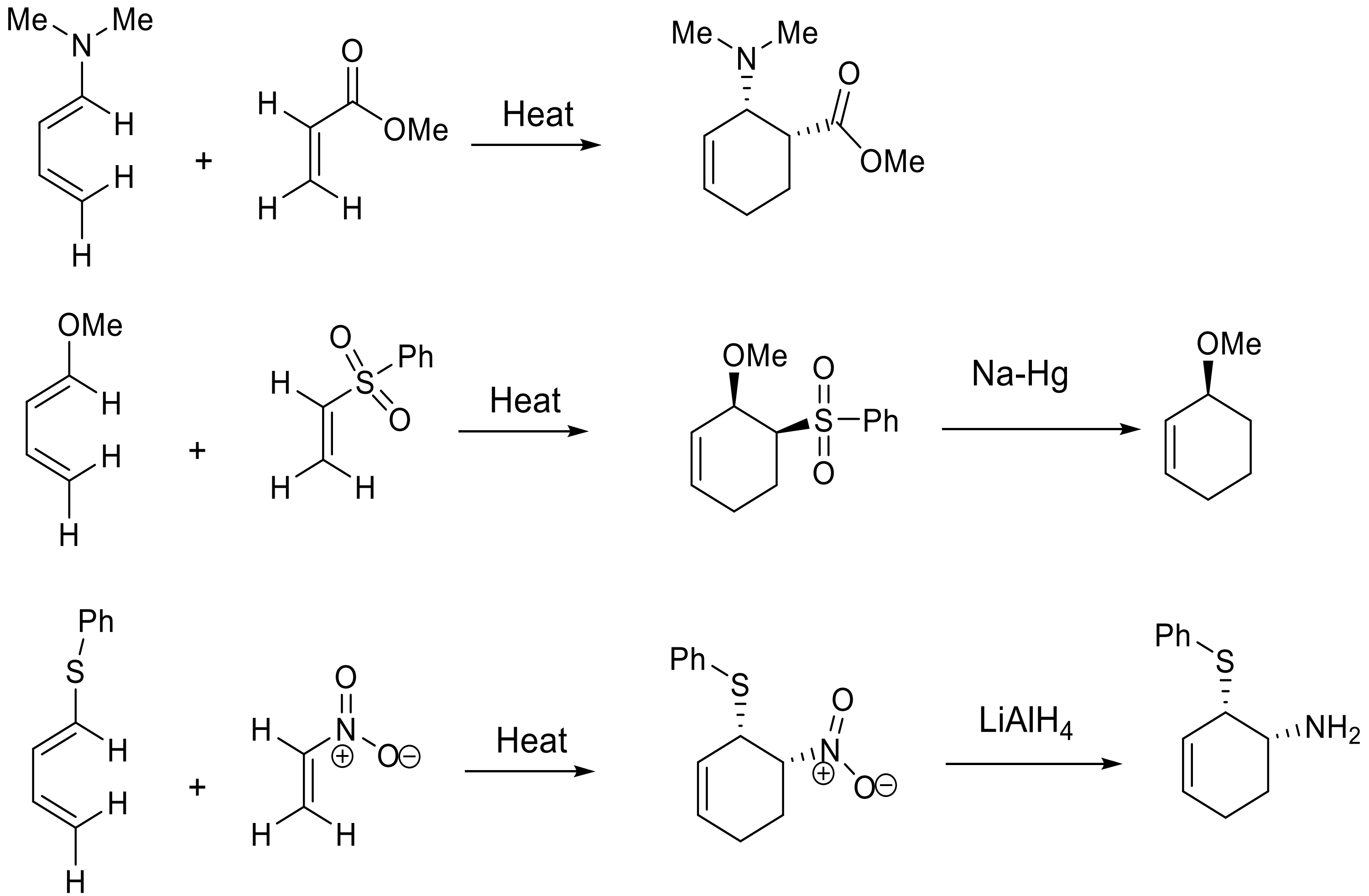


Ortho product

Predicting the Regiochemical Outcome

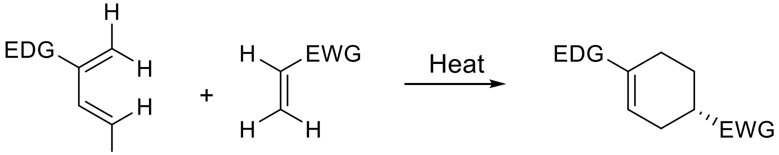
Generally,
Terminally monosubstituted dienes give 3,4-disubstituted cyclohexenes (ortho products)

Examples

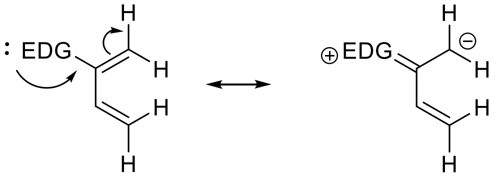


How to Predict the Regiochemical Outcome

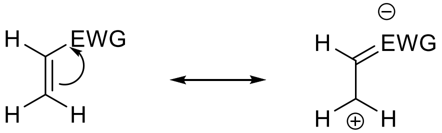
Consider the monosubstituted diene-dienophile with the diene substituted internally on its nucleus:



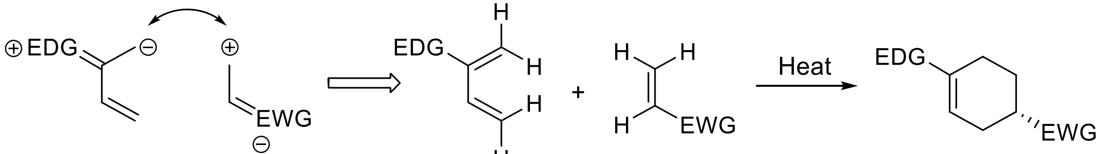
Resonance considerations for the electron-rich internally substituted diene:



Resonance considerations for the electron-deficient dienophile:



Consolidation: Matching the nucleophilic termini of the diene with electrophilic termini of dienophile.

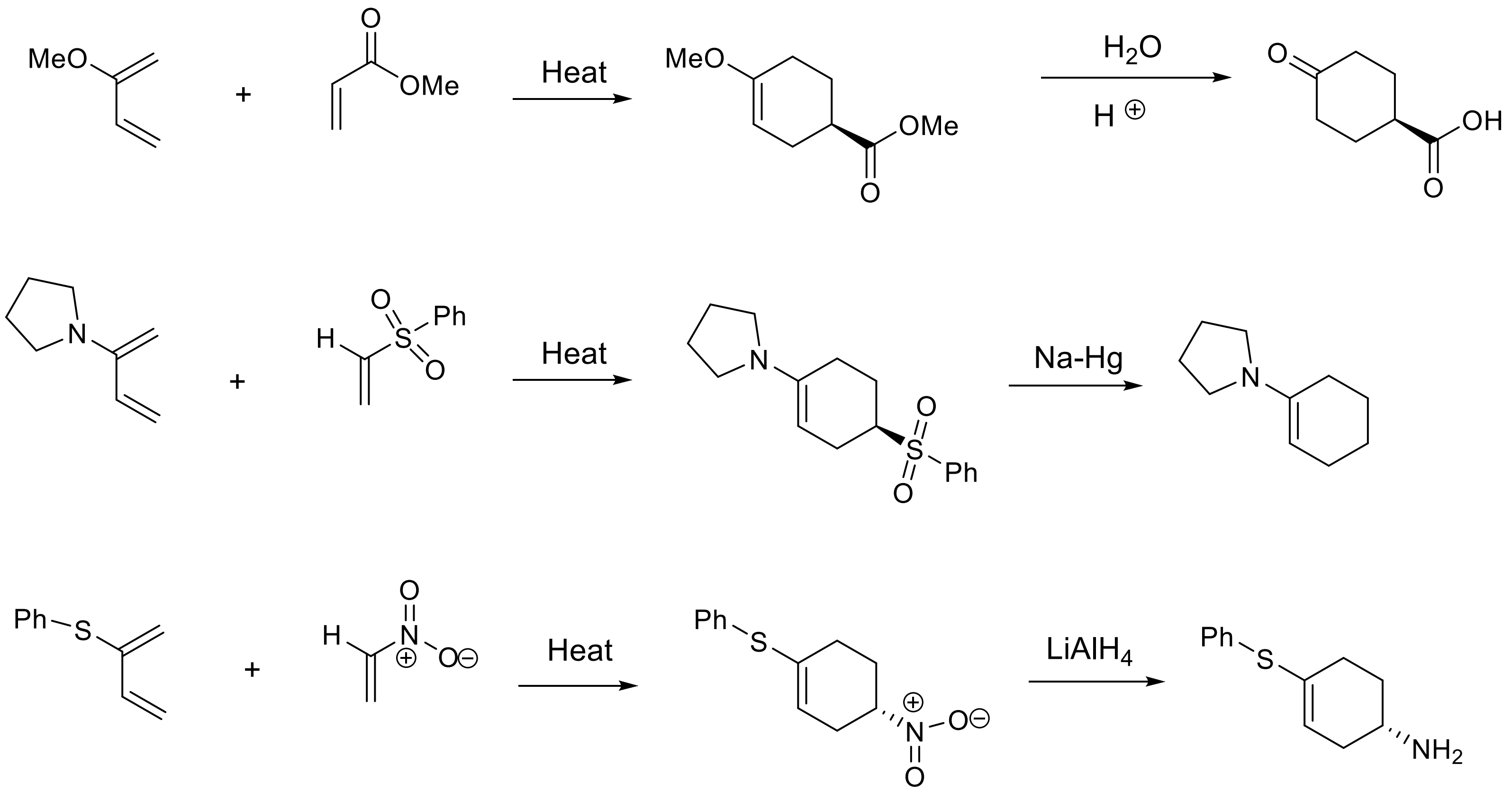


Predicting the Regiochemical Outcome

Generally,

Internally monosubstituted dienes give 1,4-disubstituted products (Para products)

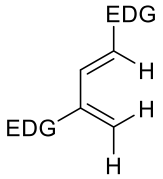
Examples



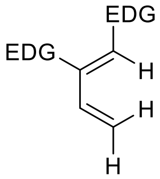
Predicting the Regiochemical Outcome

(Complimentary Dienes)

Disubstituted dienes may present chalenges in Diels-Alder reactions depending on whether the two substituents are reinforcing (complimentary) or antagonistic (non-complimentary).

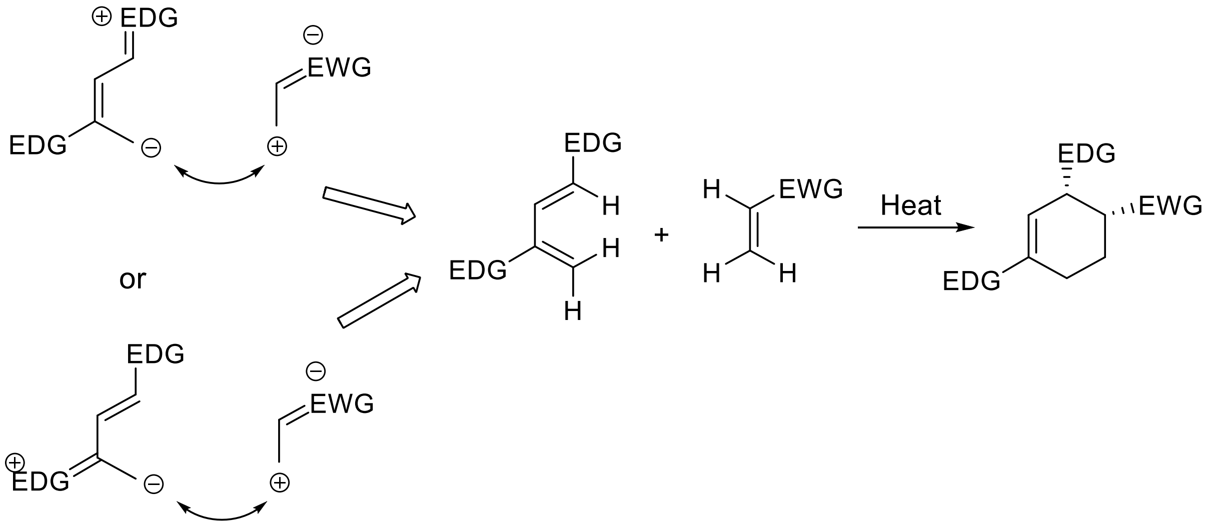


Complimentary



Non-complimentary

Consider the complimentary case of a disubstituted diene-dienophile with the diene 1,3-disubstituted to its nucleus. Matching the nucleophilic end of the diene with electrophilic end of dienophile predicts the regiochemistry shown below.



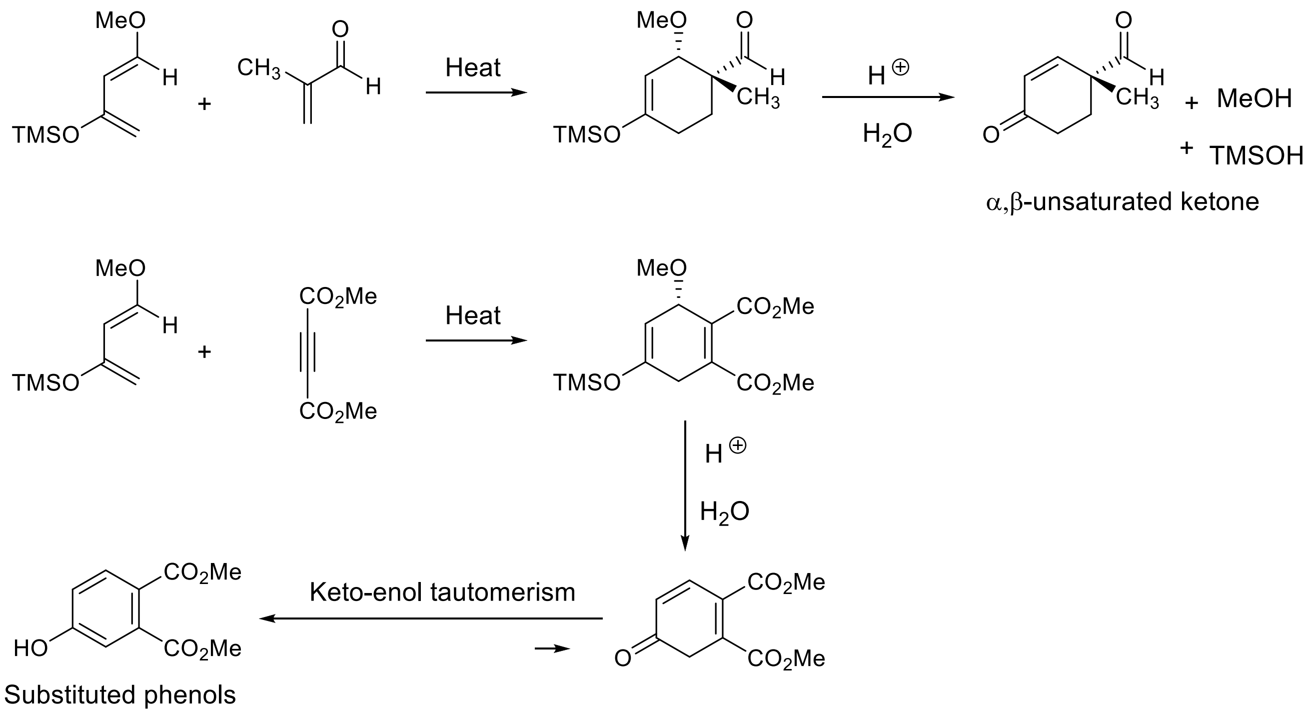
Predicting the Regiochemical Outcome

(Complimentary Dienes)

Generally,
1,3-Disubstituted dienes give 1,3,4-trisubstituted cyclohexenes

Examples: Phenols from Diels Alder Reaction

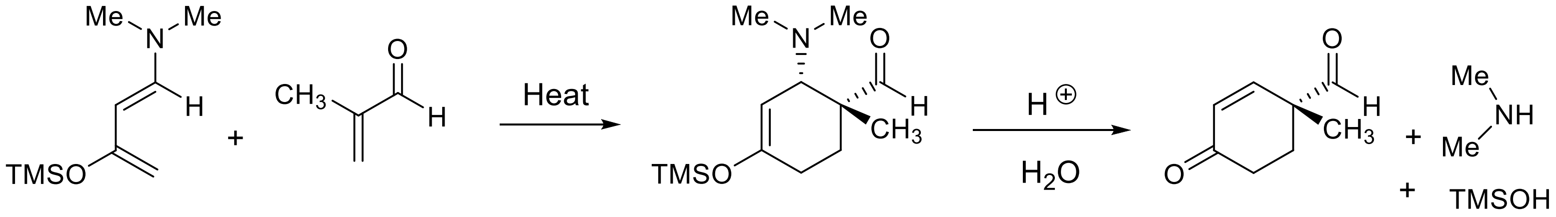
The Diels-Alder reactions of Danishefsky's diene (1-methoxy-3-trimethylsiloxy-1,3-butadiene) provides trimethylsilyloxyenol ethers, which can be hydrolysed to ketones. The methoxy group is often eliminated during the hydrolysis.



Controlling the Regiochemical Outcome

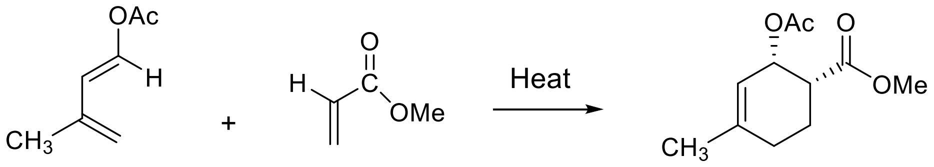
(Complimentary Dienes)

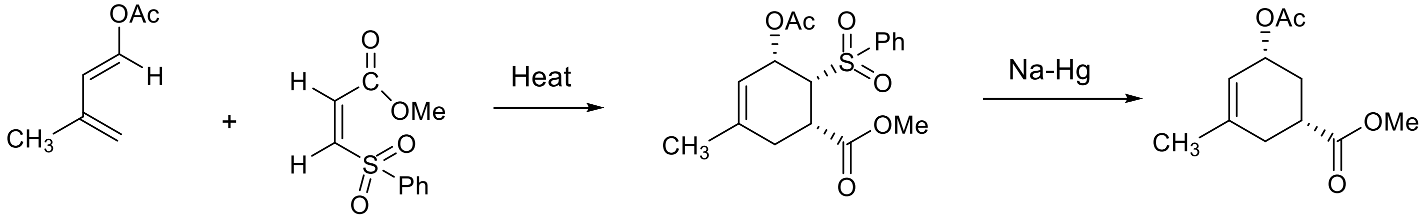
The corresponding enamine derivative shows similar reactivity



α,β-unsaturated ketone

Apparent regioselectivity can be altered by adding a controlling group that is subsequently removed.



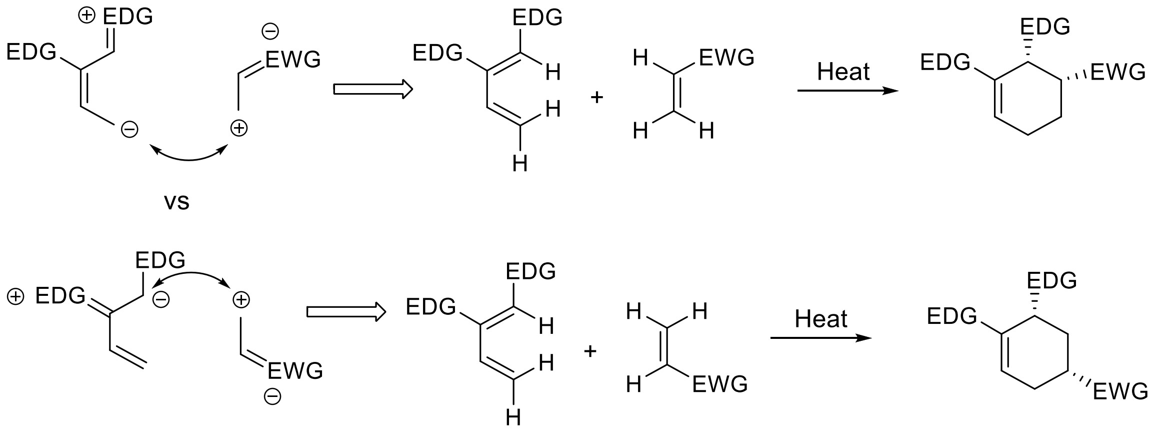


Note that SO_2Ph is more electron-withdrawing than CO_2Me and thus controls regioselectivity

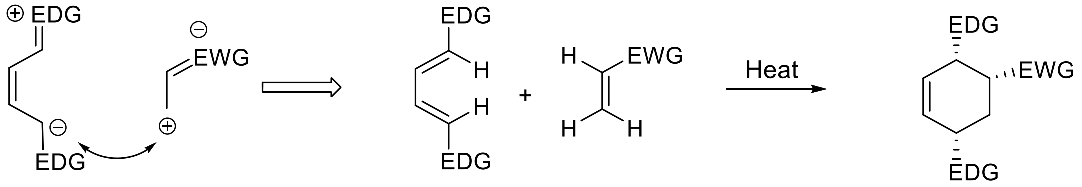
Predicting the Regiochemical Outcome

(Non-complimentary Dienes)

For the non-complimentary disubstituted diene-dienophile Diels-Alder reaction that has the diene 1,2-disubstituted to its nucleus, the situation is more complicated since there are two sets of competing arrangements leading to regio-isomeric products.



Noncomplimentary disubstituted dienes may also arise when the diene nucleus is 1,4-disubstituted.



An appropriate resonance arising for the other substituent would predict a different regiosomer for the Diels Alder adduct.

Predicting the Regiochemical Outcome

(Non-complimentary Dienes)

The predominant regio-isomer may, however, be predicted based on the electron-donating strength of the various substituents on the diene. In most cases the stronger electron donating group provides the sole product.

Electron donating strength $NHCO_2R$ > SR > OR > Alkyl > H

Decreasing strength

Examples