



Cycloaddition





Cycloaddition



Krishna P. Kaliappan
Department of Chemistry
Indian Institute of Technology-Bombay
Mumbai 400 076 INDIA
<http://www.chem.iitb.ac.in/~kpk>
kpk@chem.iitb.ac.in



Cycloaddition

- **Pericyclic reaction** involves a cyclic redistribution of bonding electrons through a **concerted process** (*i.e*, **without intermediates**)
- Concerted implies that bond-breaking and bond-forming events are simultaneous but **not necessarily synchronous (to the same extent)**

Cycloaddition

Pericyclic reactions

Electrocyclic

Sigmatropic

Group
Transfer

Cheletropic

- Cycloaddition reactions results in the formation of a new ring

- Designated as **[A+B]**

A and B refers to **number of atoms** containing **π -electrons**

- Three important classifications of cycloaddition reactions are

(i) Diels-Alder reaction or
[4 + 2] Cycloaddition

(ii) [1,3]-Dipolar or
[3+2] cycloaddition

(iii) **[2+2] Cycloaddition**



Diels-Alder Reaction

Discovered by Professor **Otto Diels** and his student **Kurt Alder** in **1928** and received Nobel prize in **1950**



Otto Diels (1876-1952)

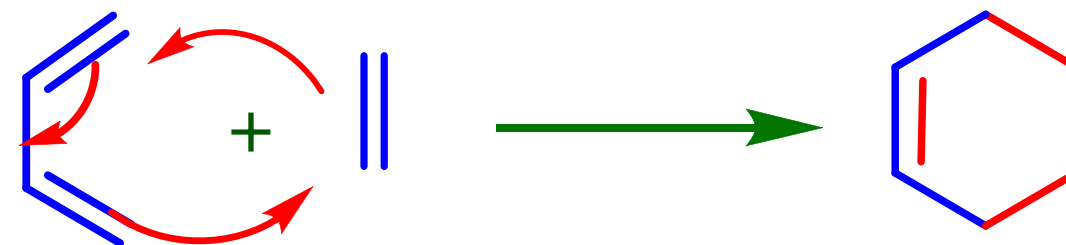


Kurt Alder (1902-1958)

“ We explicitly reserve for ourselves the application of the reaction developed by us to the solution of such problems”

➤ Reaction between a **conjugated diene** and **dienophile**

➤ Highly effective method for the formation of **cyclohexene ring**



diene

dienophile

$$\Delta\sigma = 2$$
$$\Delta\pi = -2$$

➤ Intermolecular [4+2]

➤ Intramolecular [4+2]



Diels-Alder Reaction

Intermolecular Diels-Alder Reaction

➤ Normal [4+2]

Diene is **electron-rich**

Dienophile is **electron-poor**

➤ Inverse electron-demand [4+2]

Diene is **electron-poor**

Dienophile is **electron-rich**

➤ Hetero [4+2]

Hetero atom can be a part of **Diene**

OR

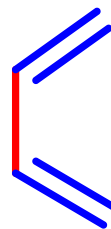
Dienophile or **both**

Requirements of Diene

➤ Diene can be **open chain** or **cyclic**

➤ For a normal Diels-Alder reaction, diene should be **electron rich** and reactivity should be enhanced by **electron donating group substituents**

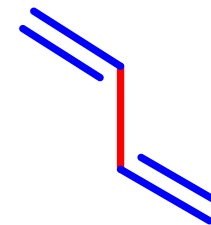
Open chain diene can acquire **two conformations**



s-cis

(reactive conformation)

Two double bonds
are **cis** to each other



s-trans

(unreactive conformation)

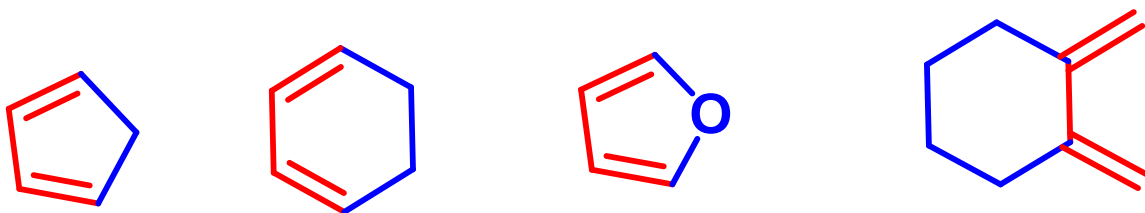
Two double bonds
are **trans** to each other



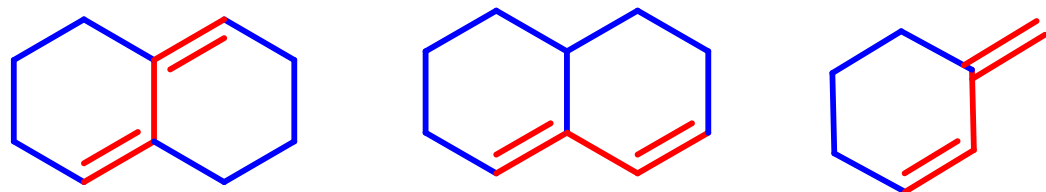
Diels-Alder Reaction

Requirements of Diene

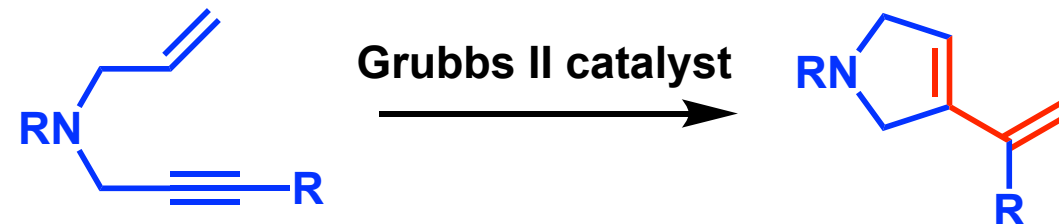
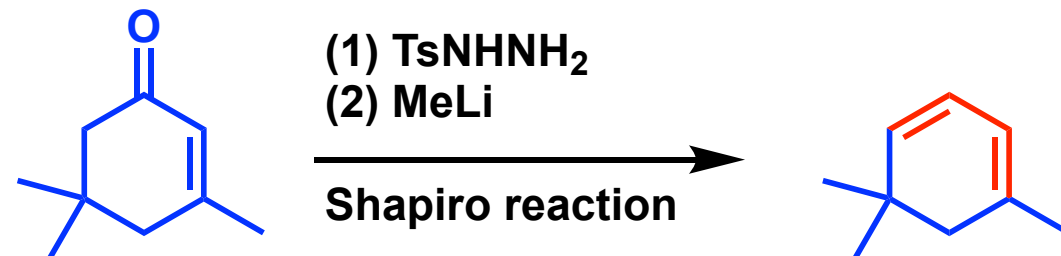
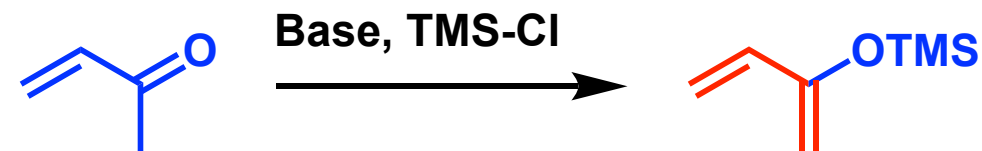
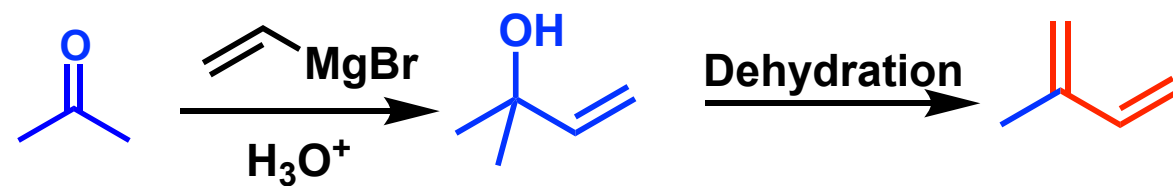
- The diene must adopt *s-cis* conformation to be **reactive**
- Cyclic dienes which adopt *s-cis* conformation are **reactive**



- Cyclic dienes which are permanently in *s-trans* conformation are **unreactive** in Diels-Alder reaction



Selected Examples of Preparation of Dienes

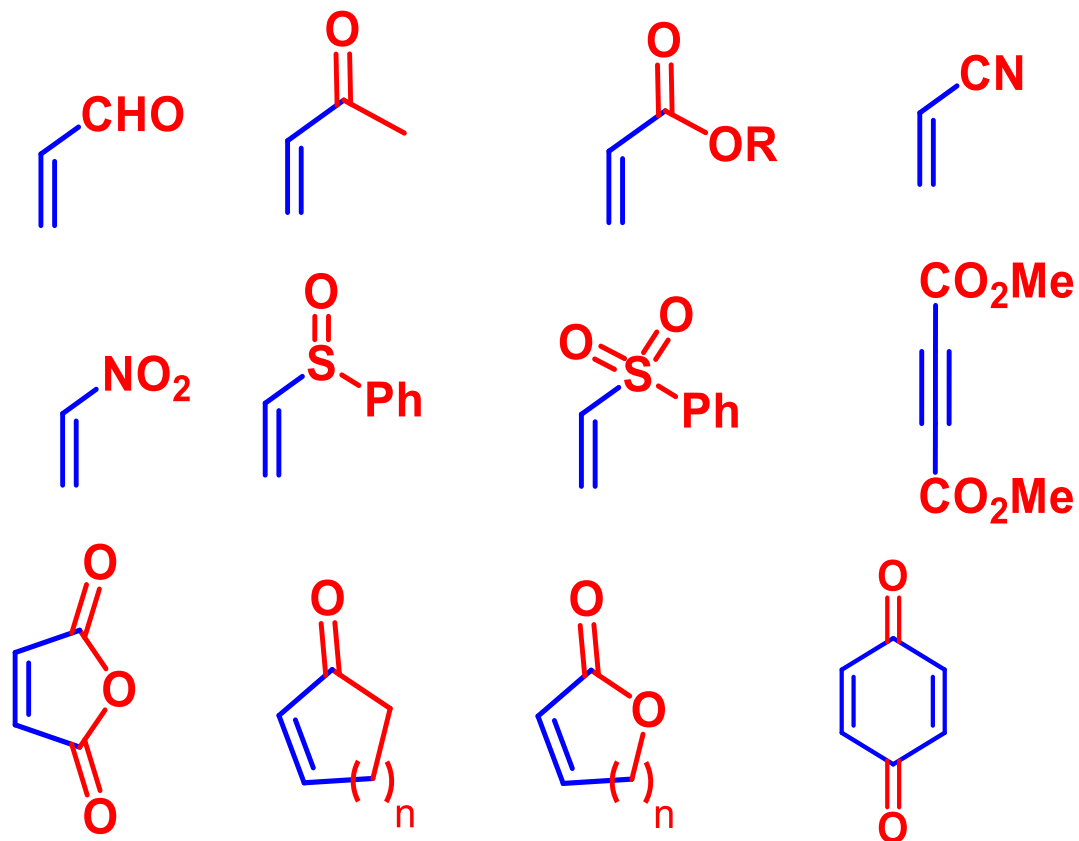




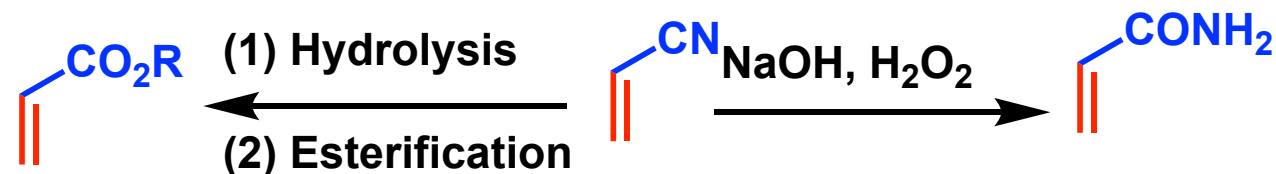
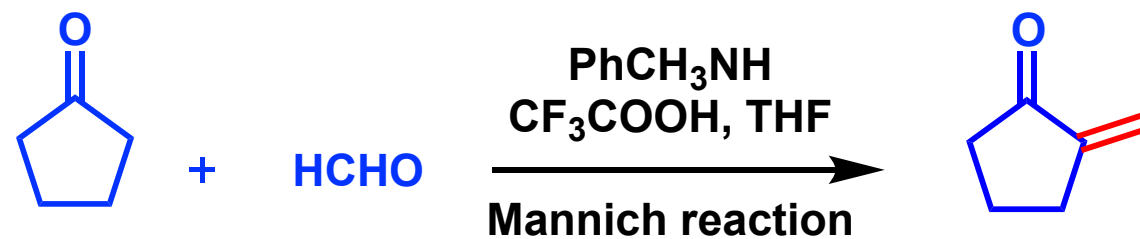
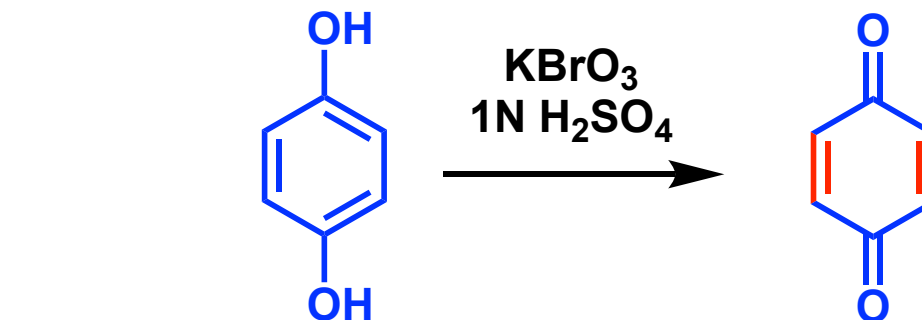
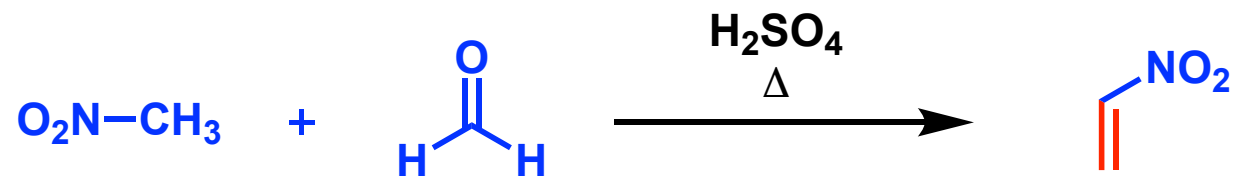
Diels-Alder Reaction

Requirements of Dienophile

- Dienophile can be **open chain** or **cyclic**
- Should be electron deficient and reactivity enhanced by **electron withdrawing** substituents



Preparation of Dienes-Selected Examples



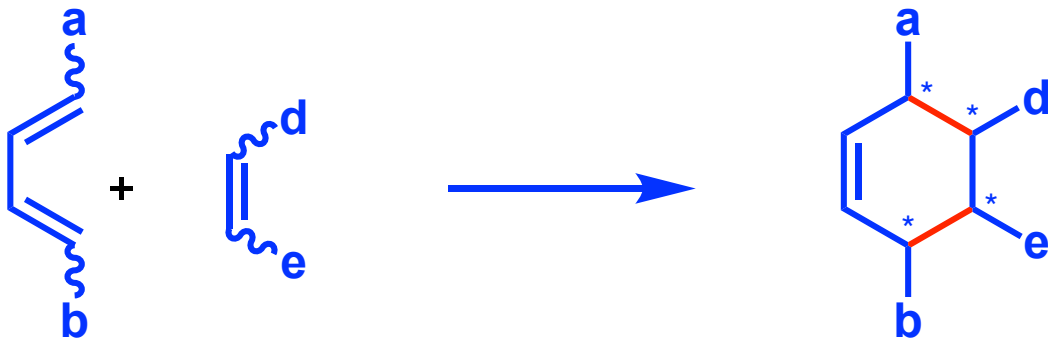


Stereochemistry



Stereochemistry of Diels-Alder Reaction

- Reaction between a diene and a dienophile can create a **maximum of four new stereo centres**



- Diels-Alder reaction is **stereospecific**
- Relative **stereochemical relationship** of diene and dienophile is **reproduced** in the product

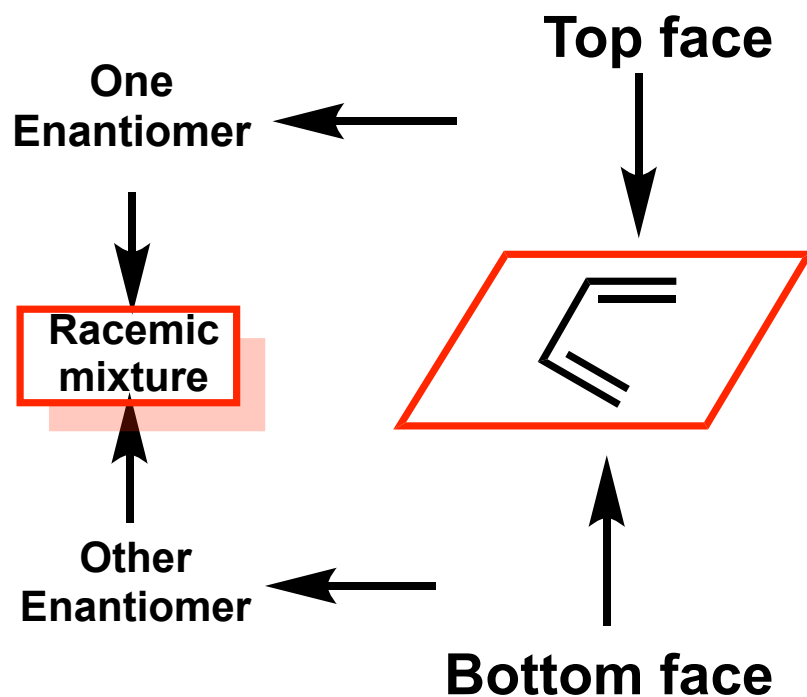
- Diels-Alder reaction occurs due to the overlapping of **p-orbitals** of diene and dienophile lying perpendicular to the plane of carbon atoms

- A given **diene** possess two faces namely **top face** and **bottom face**
- **Dienophile** can approach either of the faces and lead to **racemic mixture**
- Like wise **diene** can approach the dienophile either from the **top face** and **bottom face** leading to **racemic mixture**

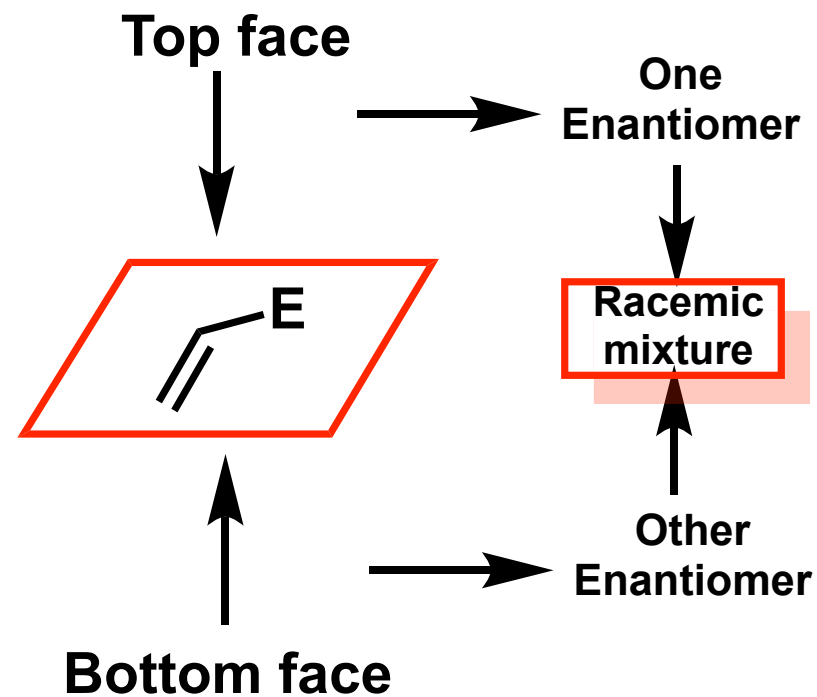


Stereochemical Possibilities

Approach of Dienophile

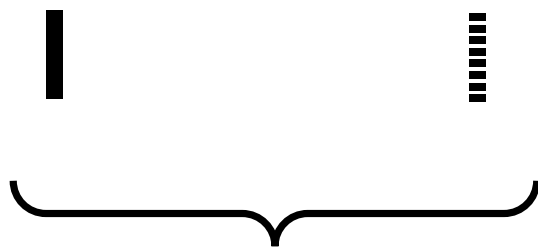


Approach of Diene

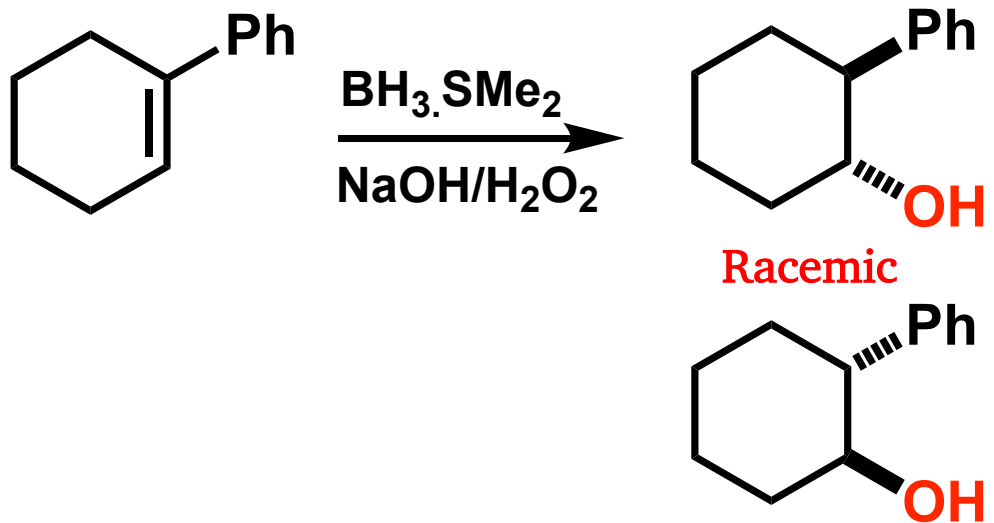




Wedge and Straight Bonds



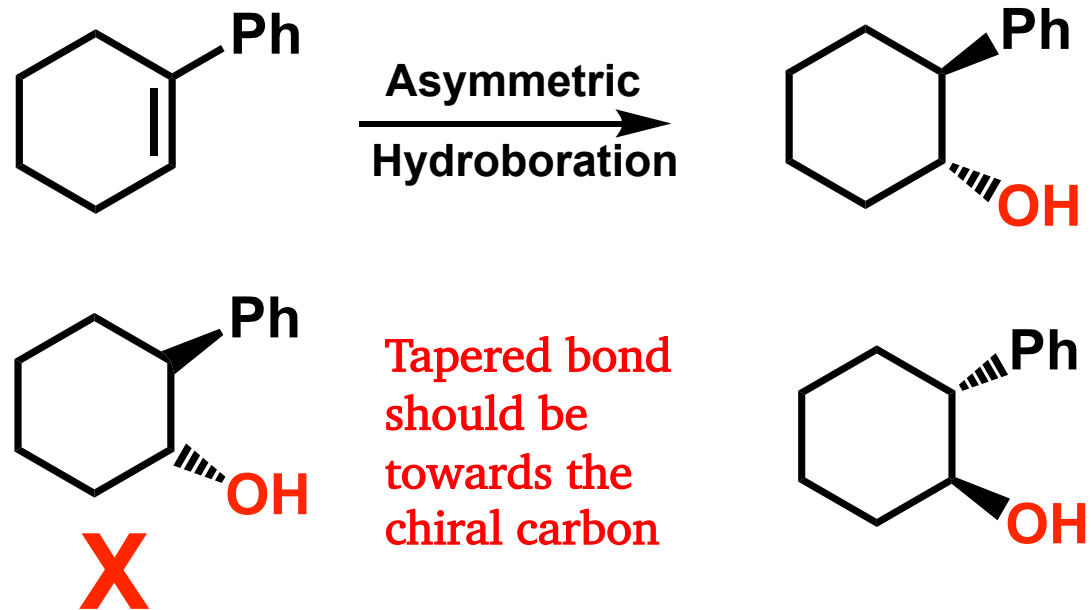
Relative Configuration



H. Maehr, *J. Chem. Educ.* **1985**, *62*, 114–120.



Absolute Configuration



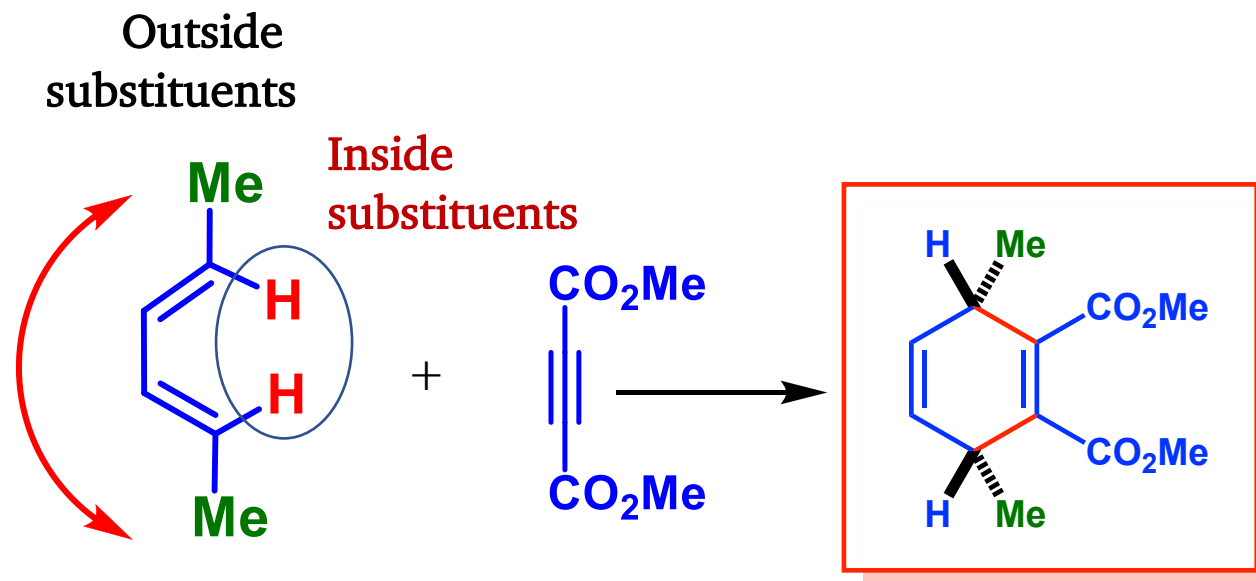


Top and Bottom Face Approach of Dienophile

Given the bottom face approach of dienophile:

Inside substituents of diene will become β -configuration in the product

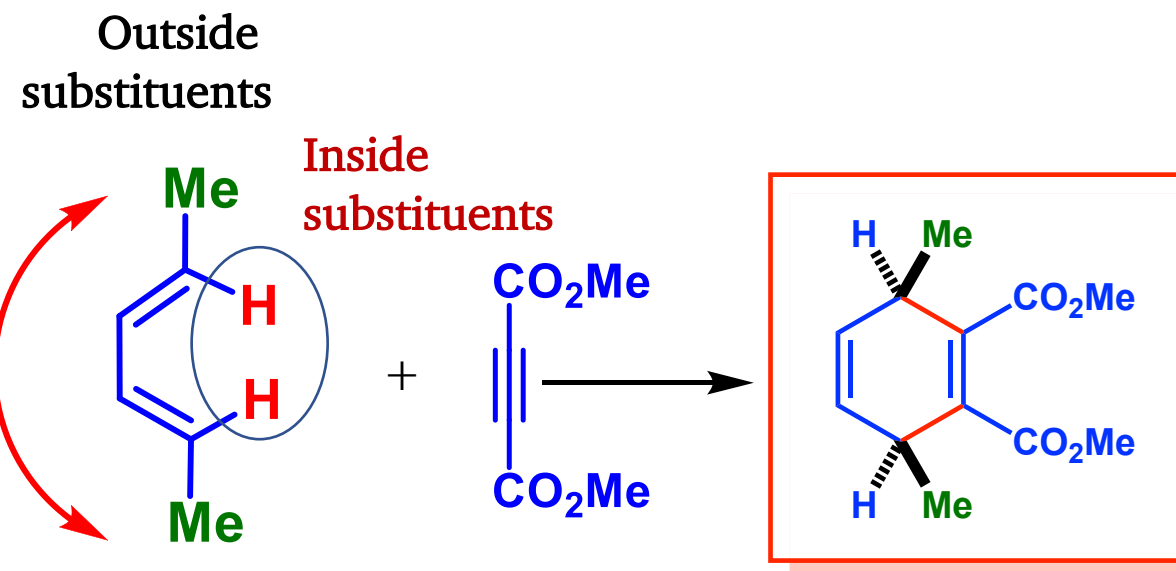
Outside substituents of diene will become α -configuration in the product



Given the top face approach of the dienophile:

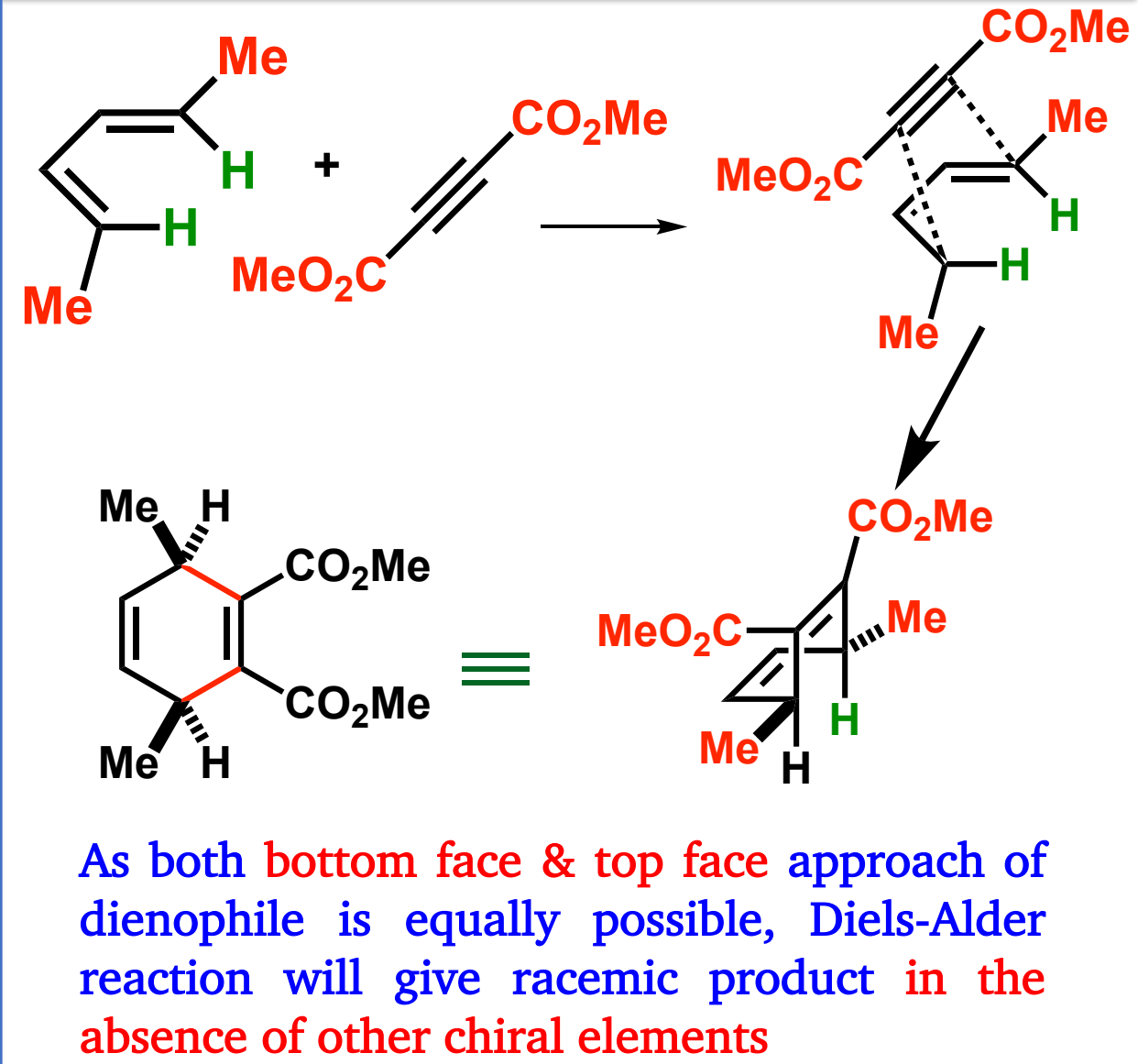
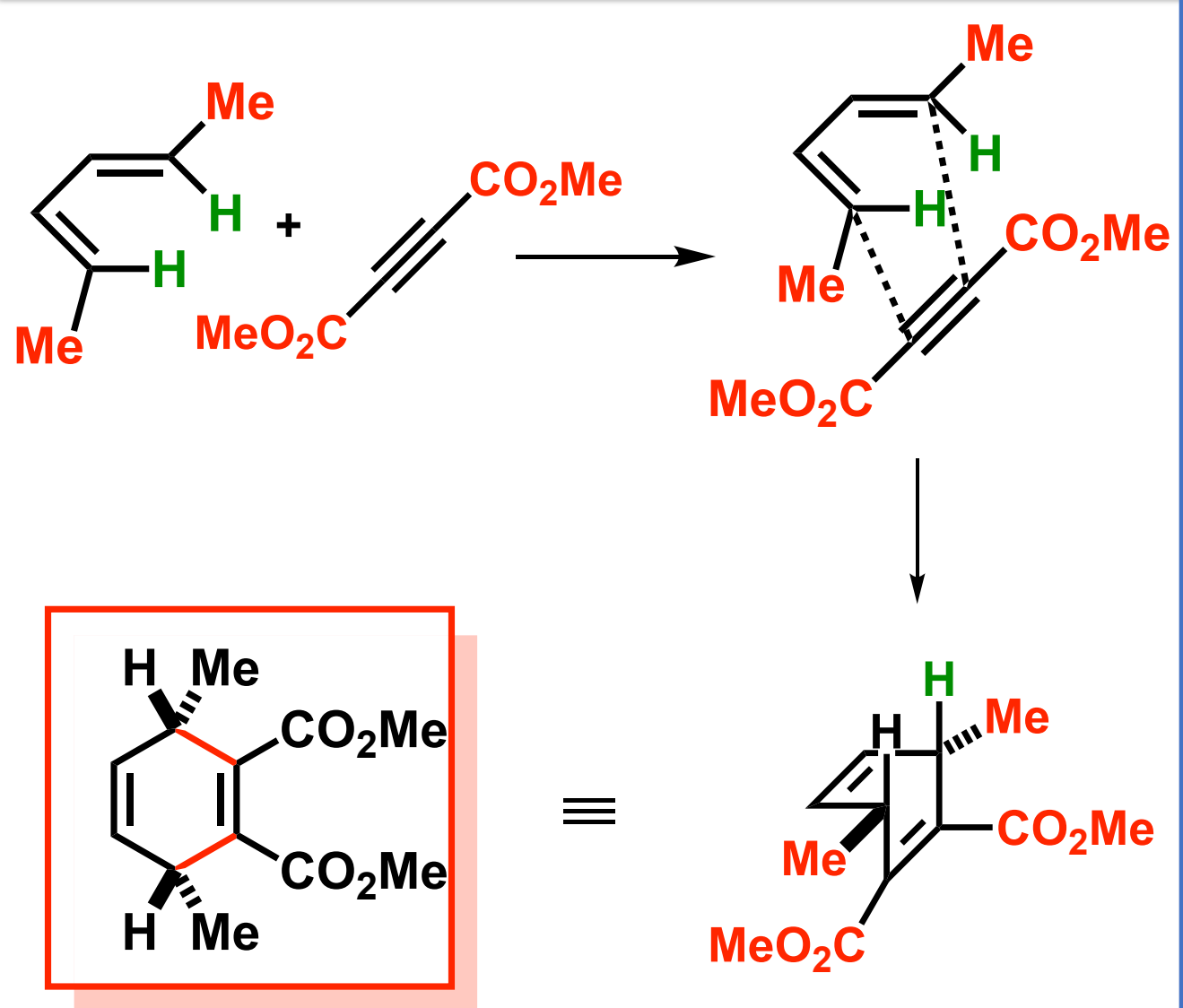
- Inside become α -configuration in the product
substituents of diene will

- Outside substituents of diene will become β -configuration in the product





Top and Bottom Face Approach of Dienophile

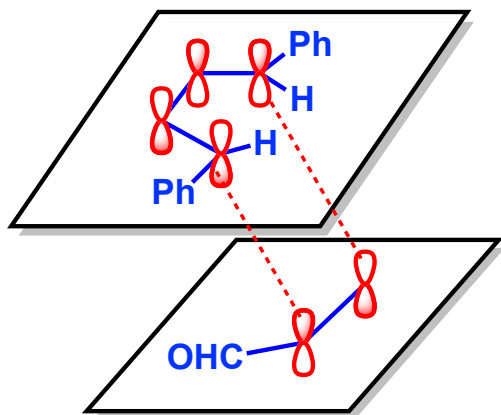
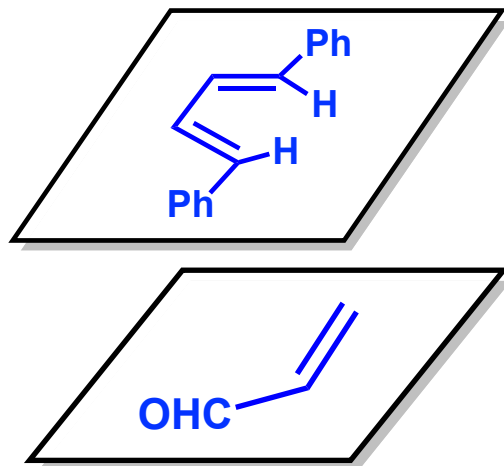




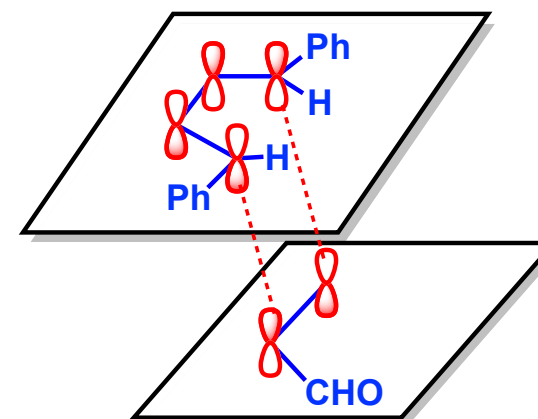
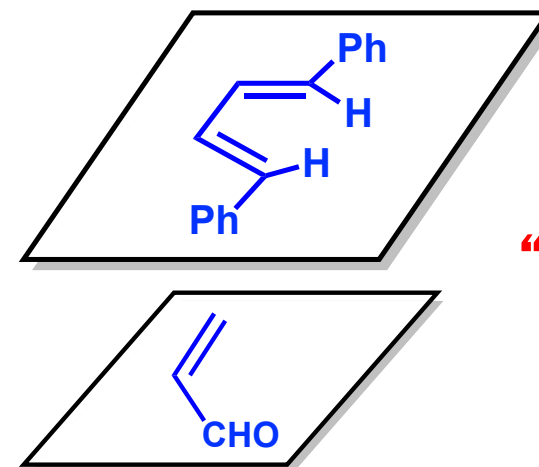
Endo & Exo

Given the **bottom face** approach of dienophile, **substituents on dienophile** can take two different orientations with respect to the plane of the diene called **endo** (inside) or **exo** (outside)

“endo”

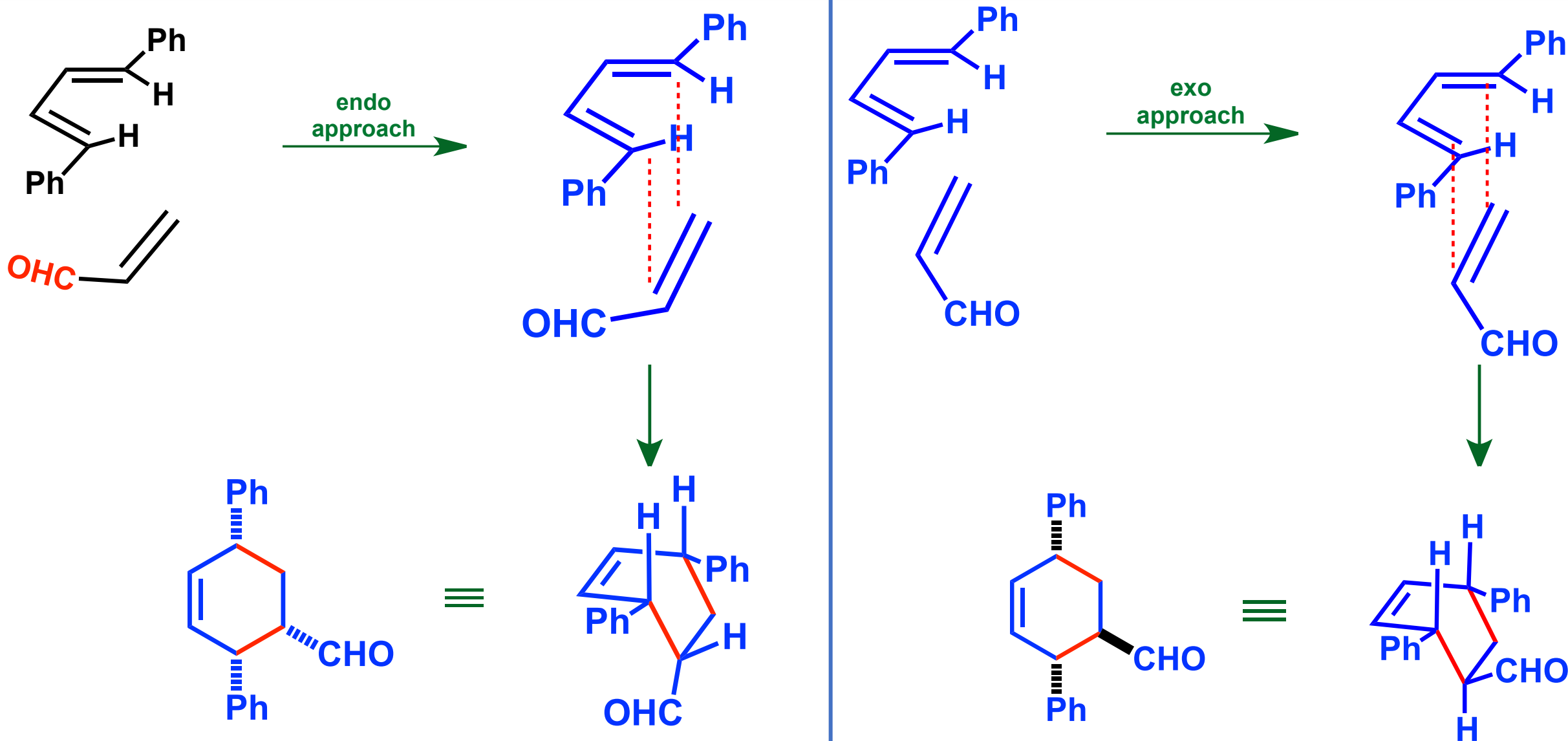


“exo”





Endo & Exo

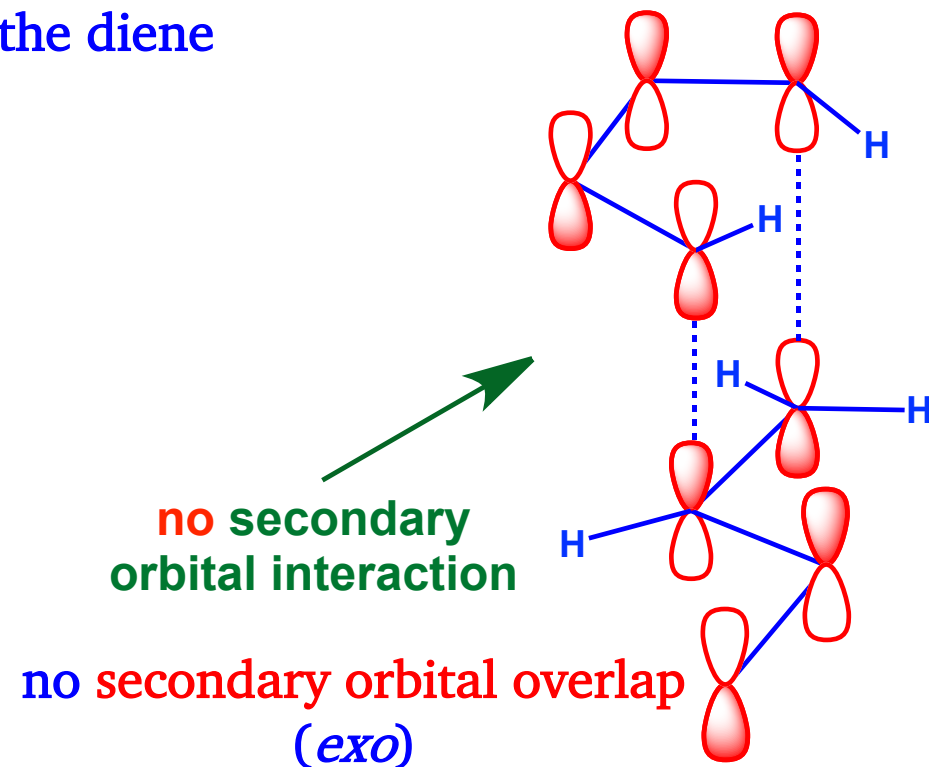
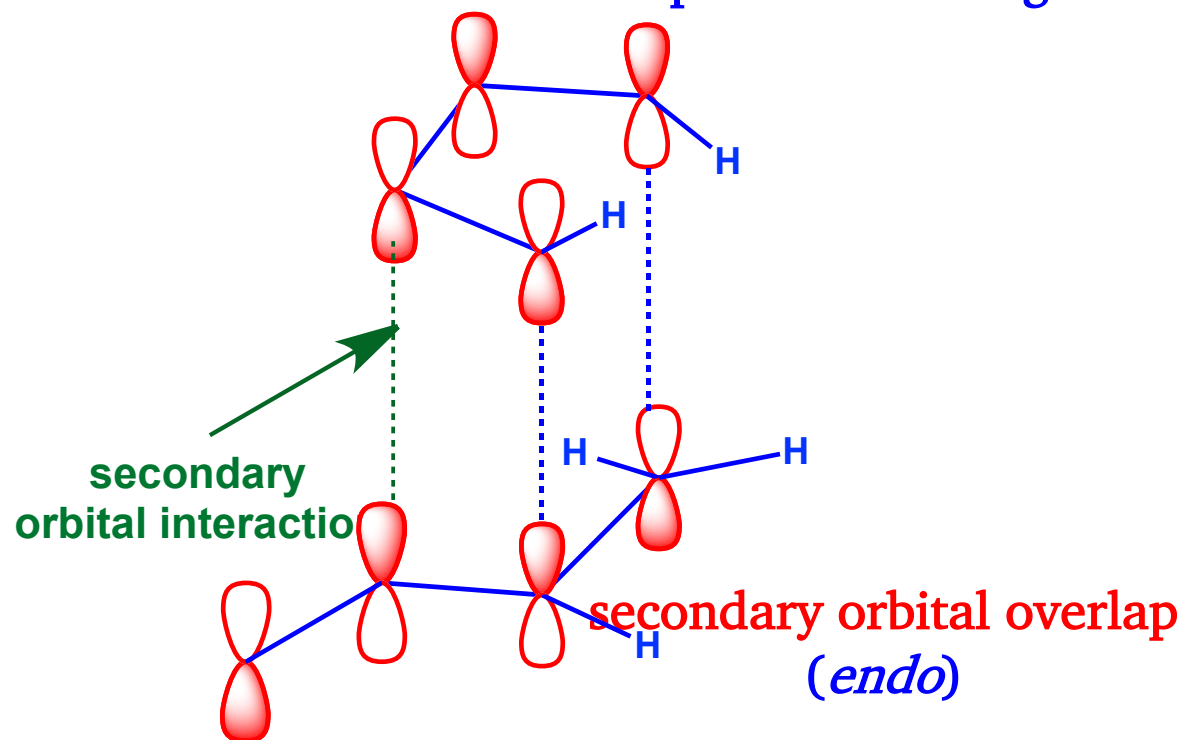




Alder's Endo Rule

Diene and Dienophile Each Providing New Stereocentre

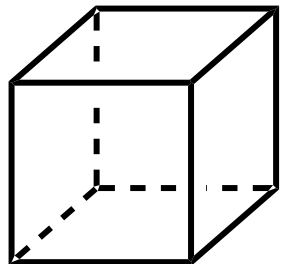
- Both diene and dienophile are **prochiral**
- $[\pi_4s + \pi_2s]$ mechanism can now lead to two **diastereomeric** products known as **endo** and **exo**
- **Endo** mode of addition is usually preferred to **exo** addition due to **secondary orbital overlap** between the dienophiles activating substituent and the diene



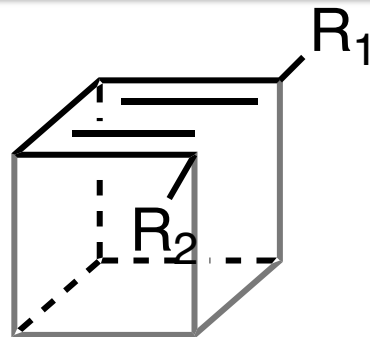


Cube Model

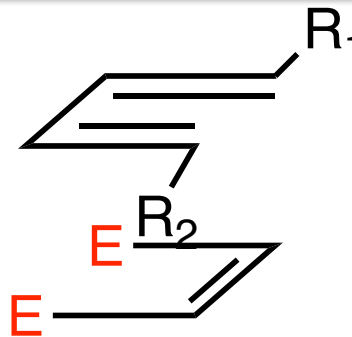
Top face



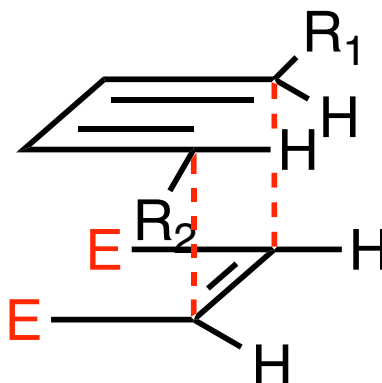
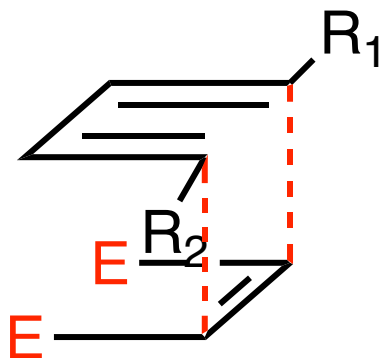
Bottom face



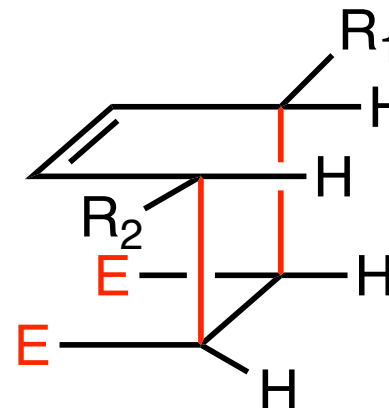
Draw the diene on the top face



Draw the dienophile on the bottom face



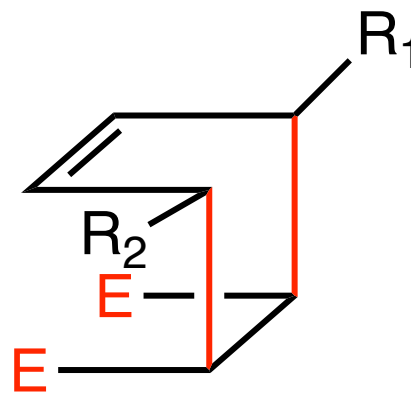
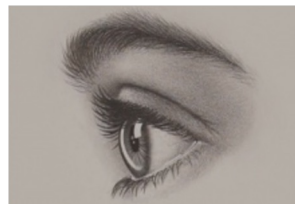
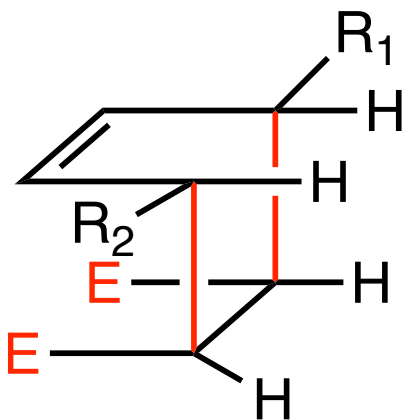
Draw other substituents



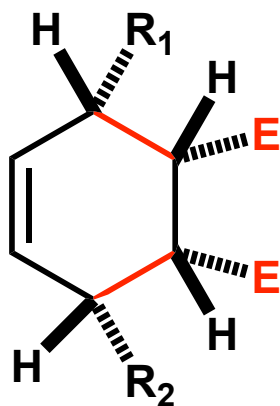
Do the reaction & draw the cyclohexene



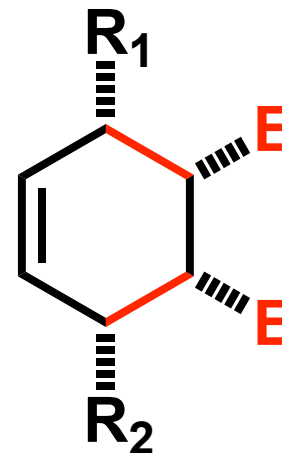
Cube Model



|||



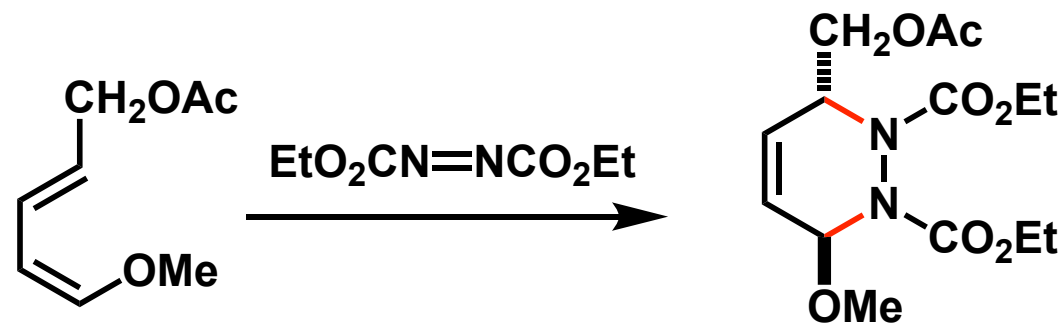
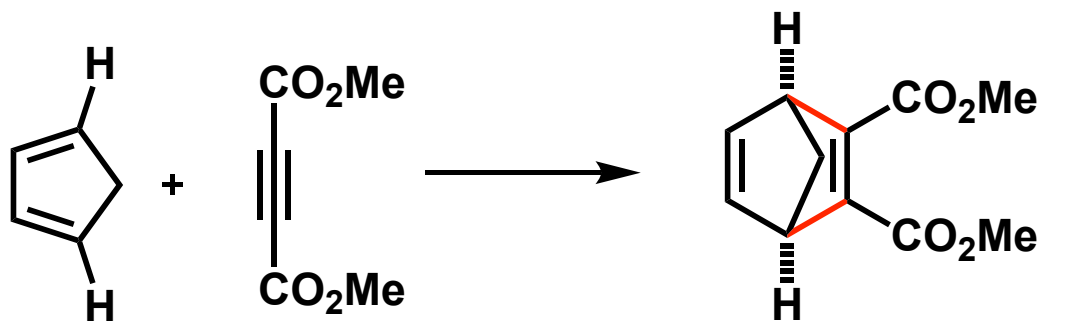
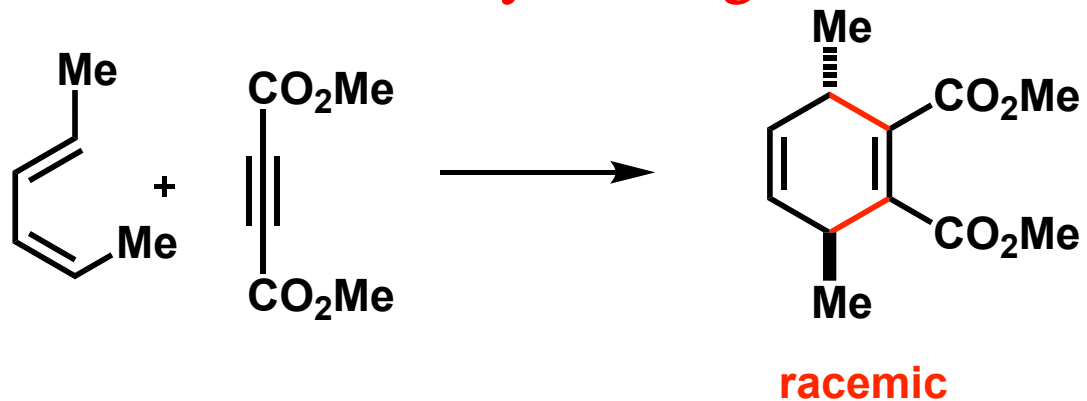
|||



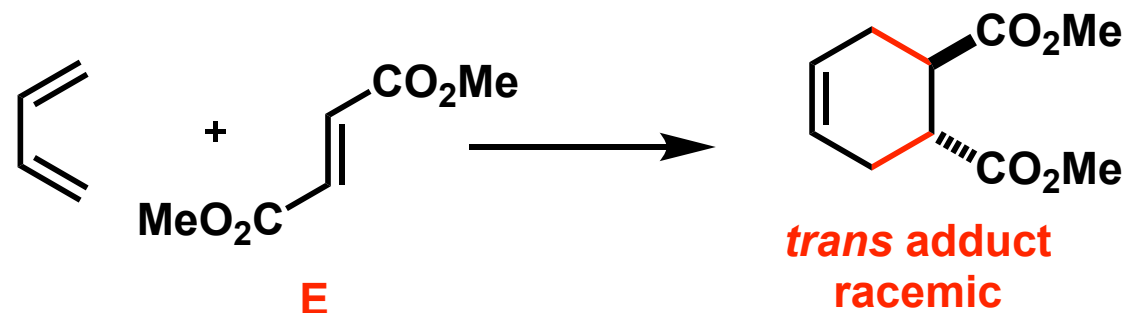
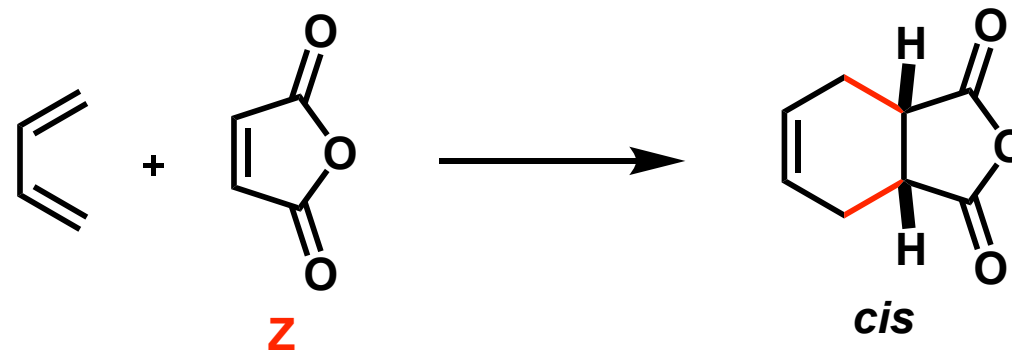


Examples

Stereochemistry coming from diene



Stereochemistry coming from dienophile

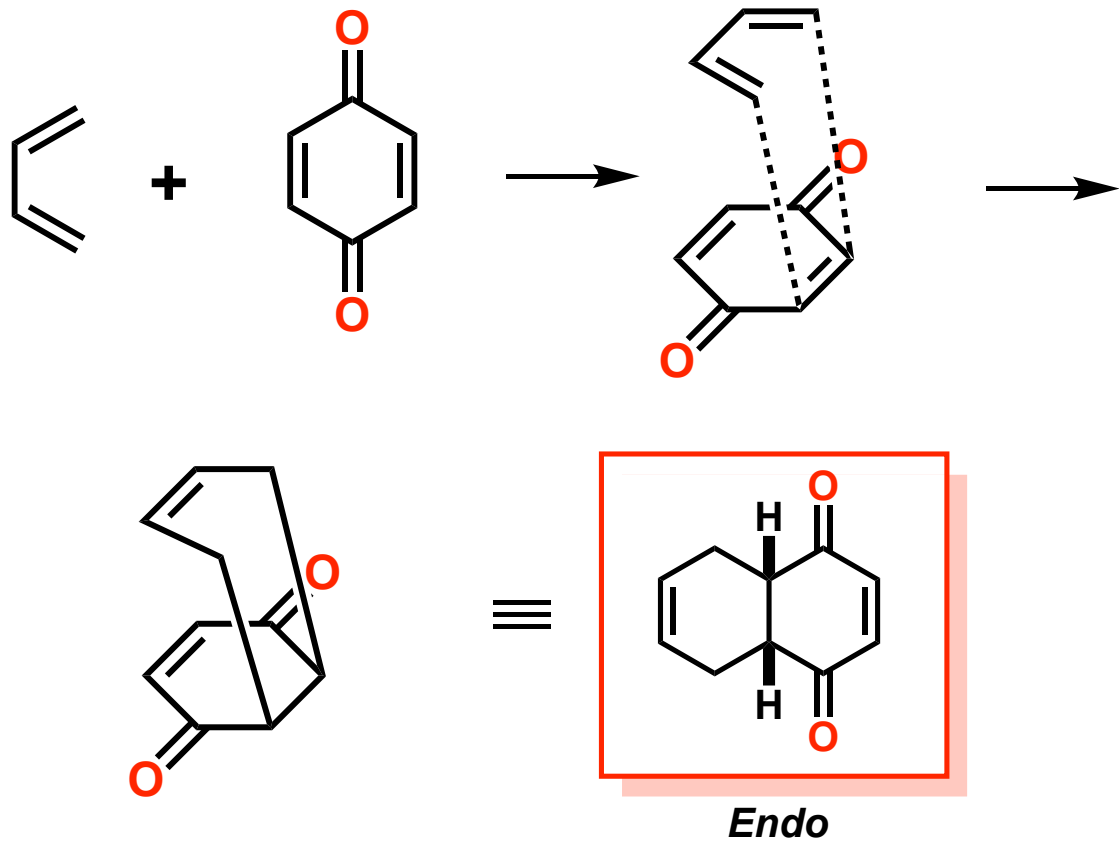


Bottom face approach of dienophile

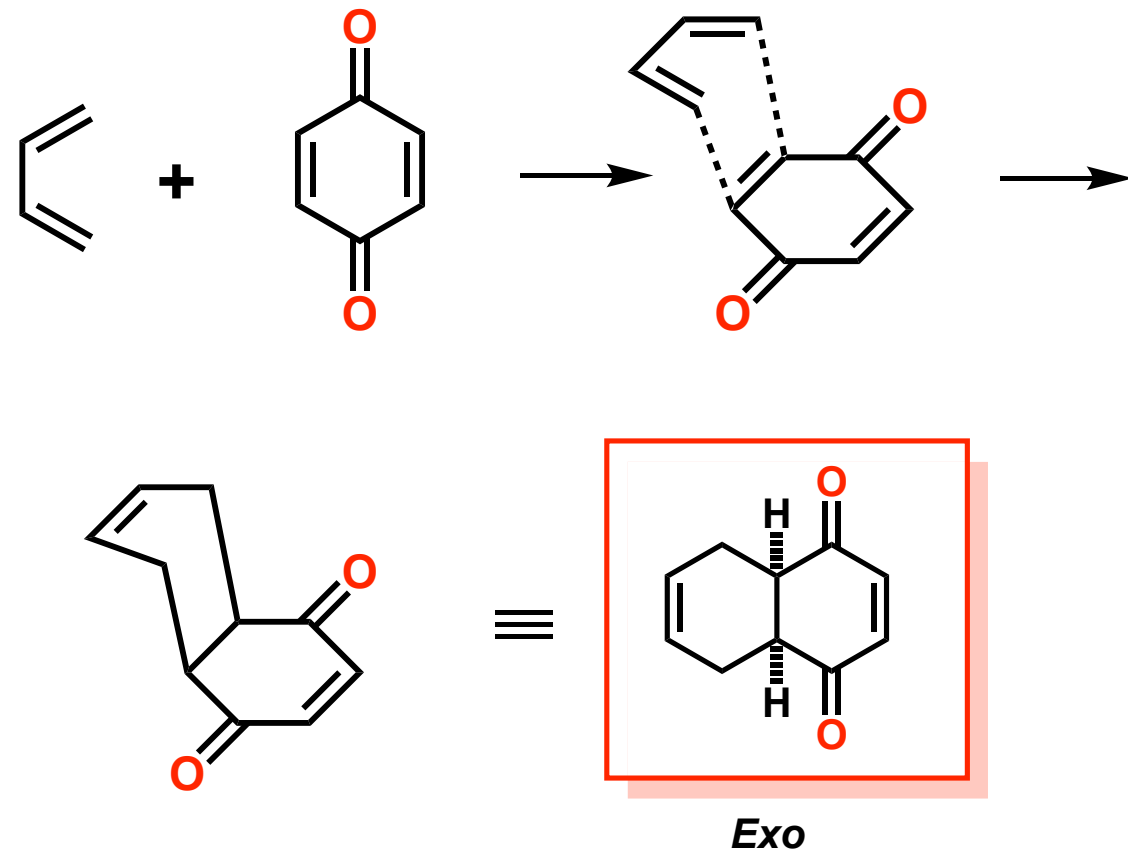


Examples

Bottom face approach of dienophile



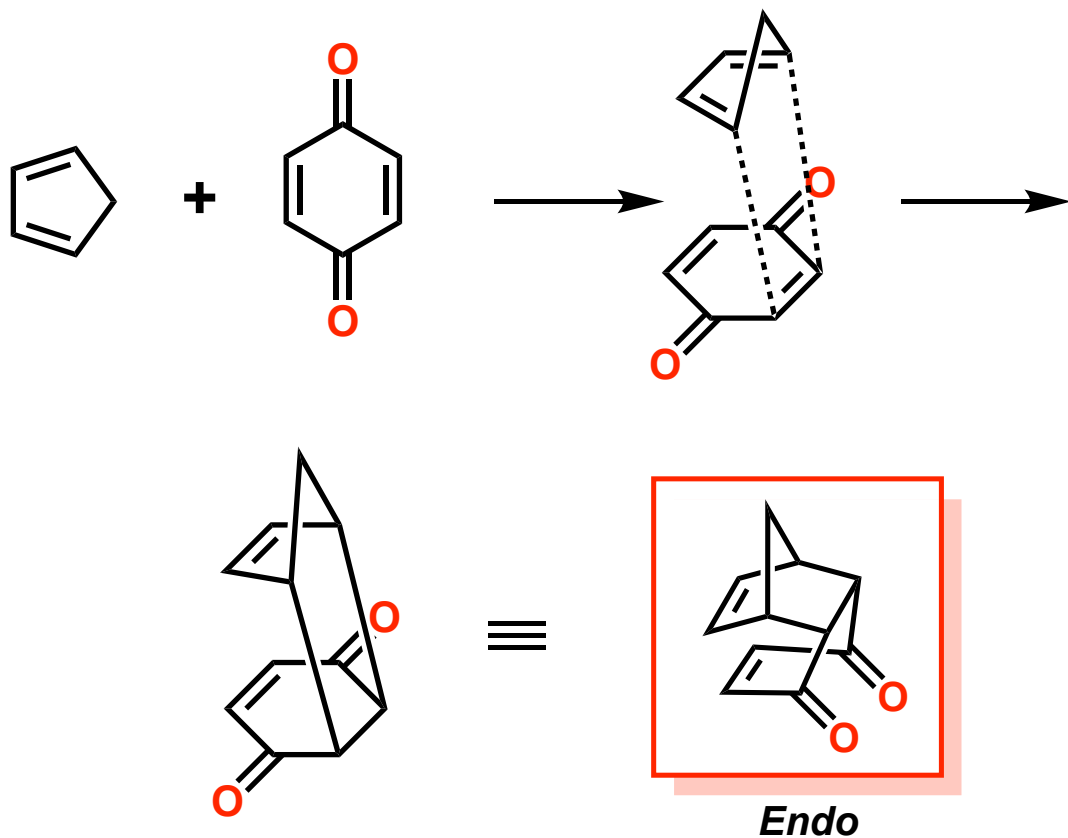
Bottom face approach of dienophile



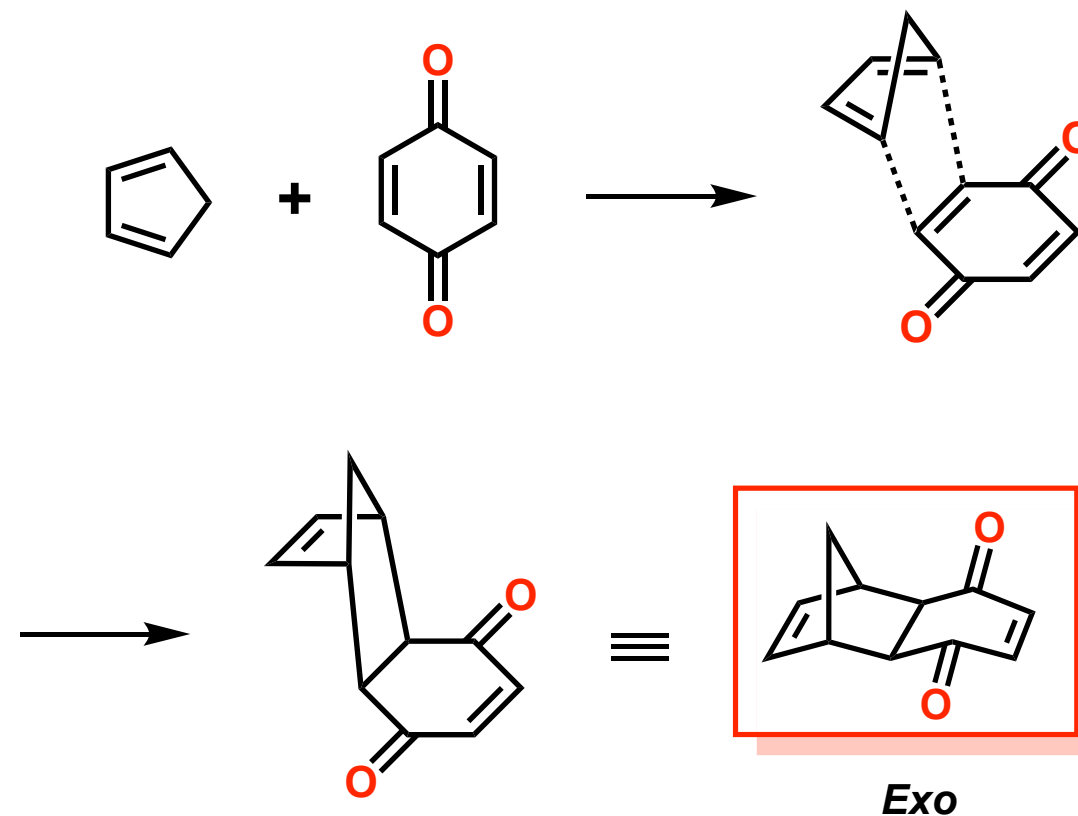


Examples

Bottom face approach of dienophile



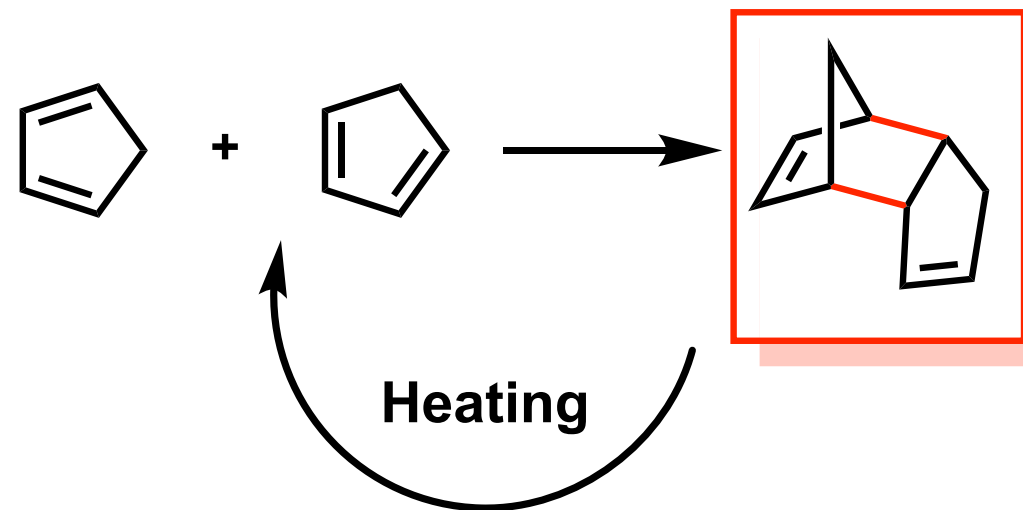
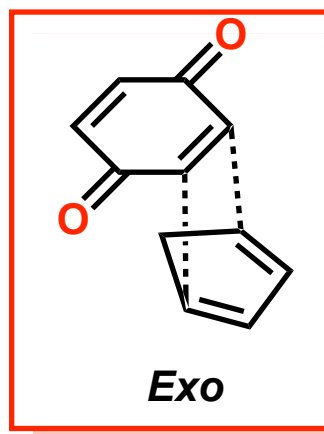
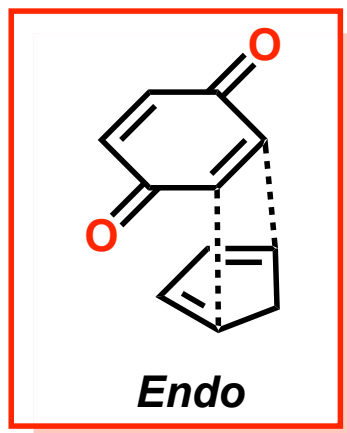
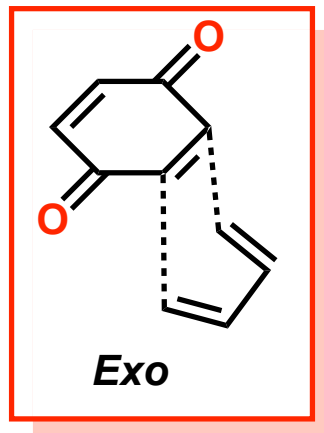
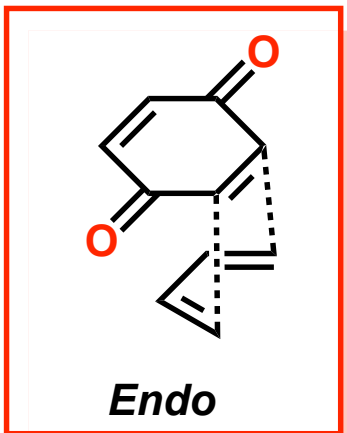
Bottom face approach of dienophile





Examples

Top face approach of dienophile

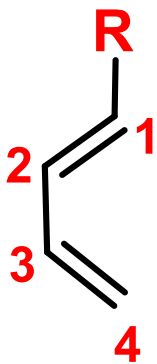




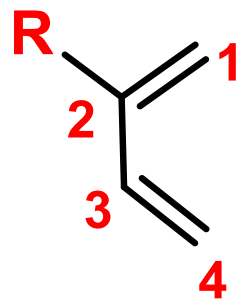
Regioselectivity in Diels-Alder Reaction

For a mono-substituted diene, outcome of the product depends on the carbon atom **where it is substituted**

Consider two classical cases, where the electron donating substituent could be present at **carbon 1** or **carbon 2**



1-substituted diene



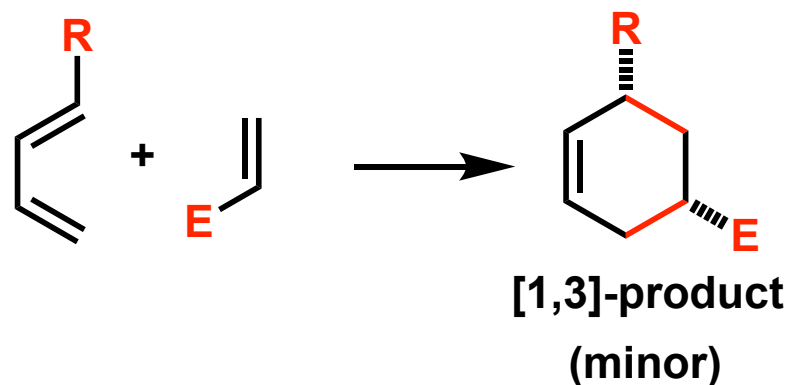
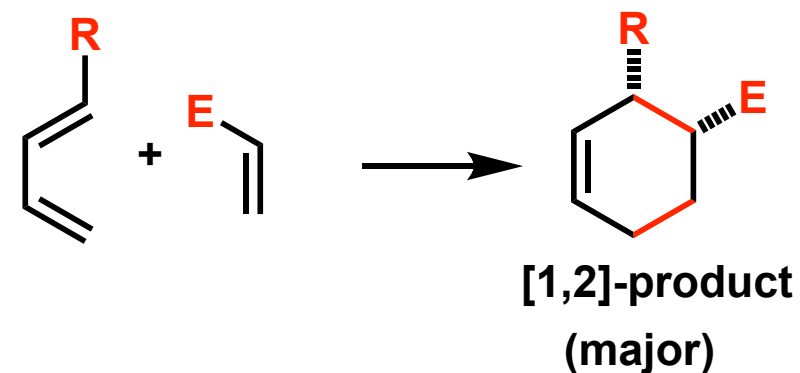
2-substituted diene

- Diels-Alder reaction is **regiospecific**, i.e. degree of regio selectivity is **high**
- The **same HOMO/LUMO pair** is involved but interacting **sites are different**
- The substituents having more **powerful EWG and EDG**, the **more regioselective** is the reaction
- The **origin of selectivity** comes from the **size of lobes (orbital coefficient)** of reactant's orbitals

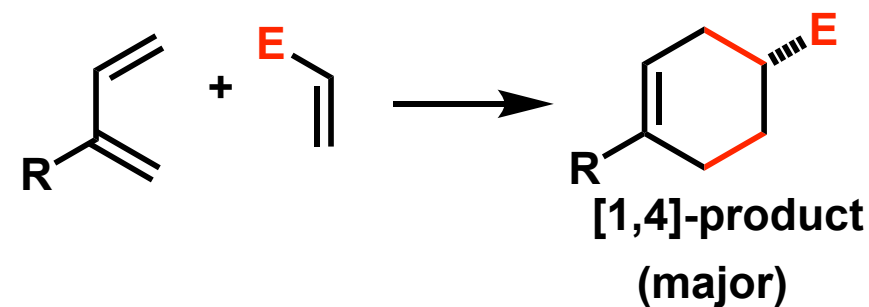
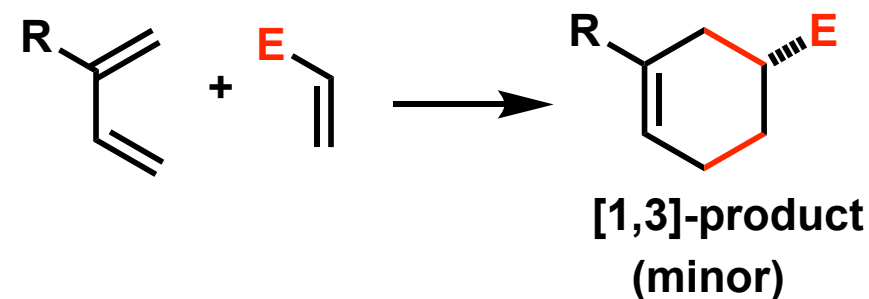


Regioselectivity in Diels-Alder Reaction

1-substituted diene reacts to give mainly [1,2]-product



2-substituted diene reacts to give mainly [1,4]-product



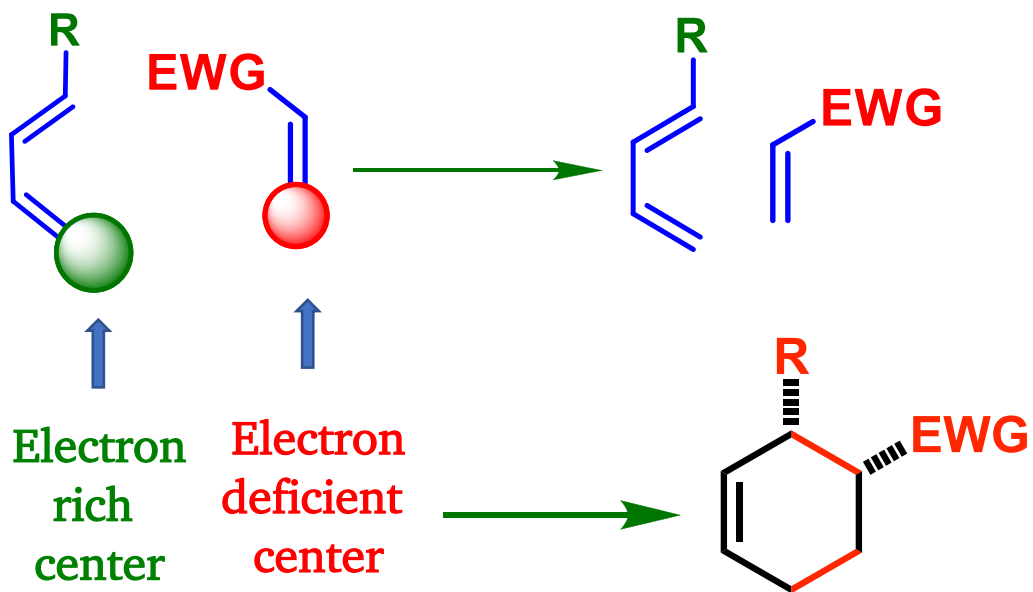
Don't write ortho, meta or para here



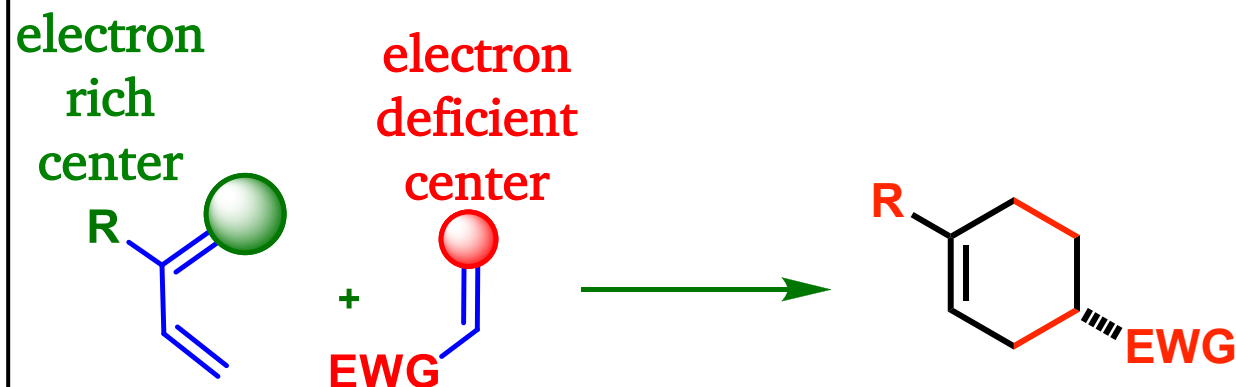
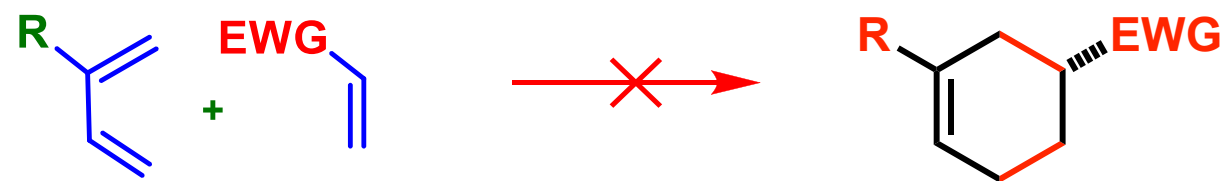
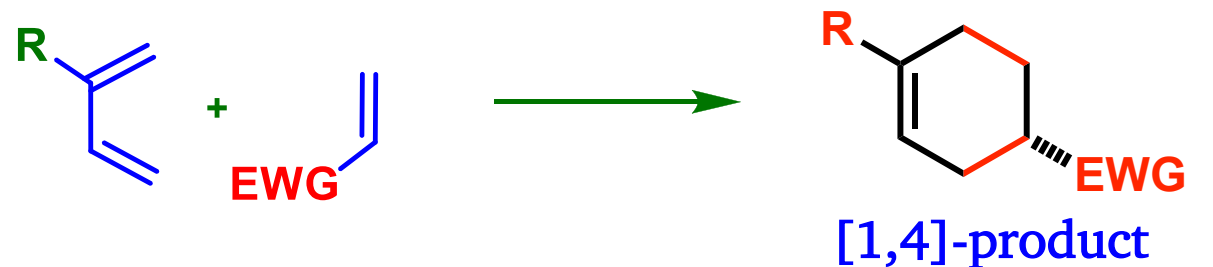
Regiochemistry of Diels-Alder Reaction

Regioselectivity for the preference of [1,2]-product can be explained by considering the **polarization** of diene and dienophile

Connect the *electron rich* center of diene to *electron deficient* center of dienophile

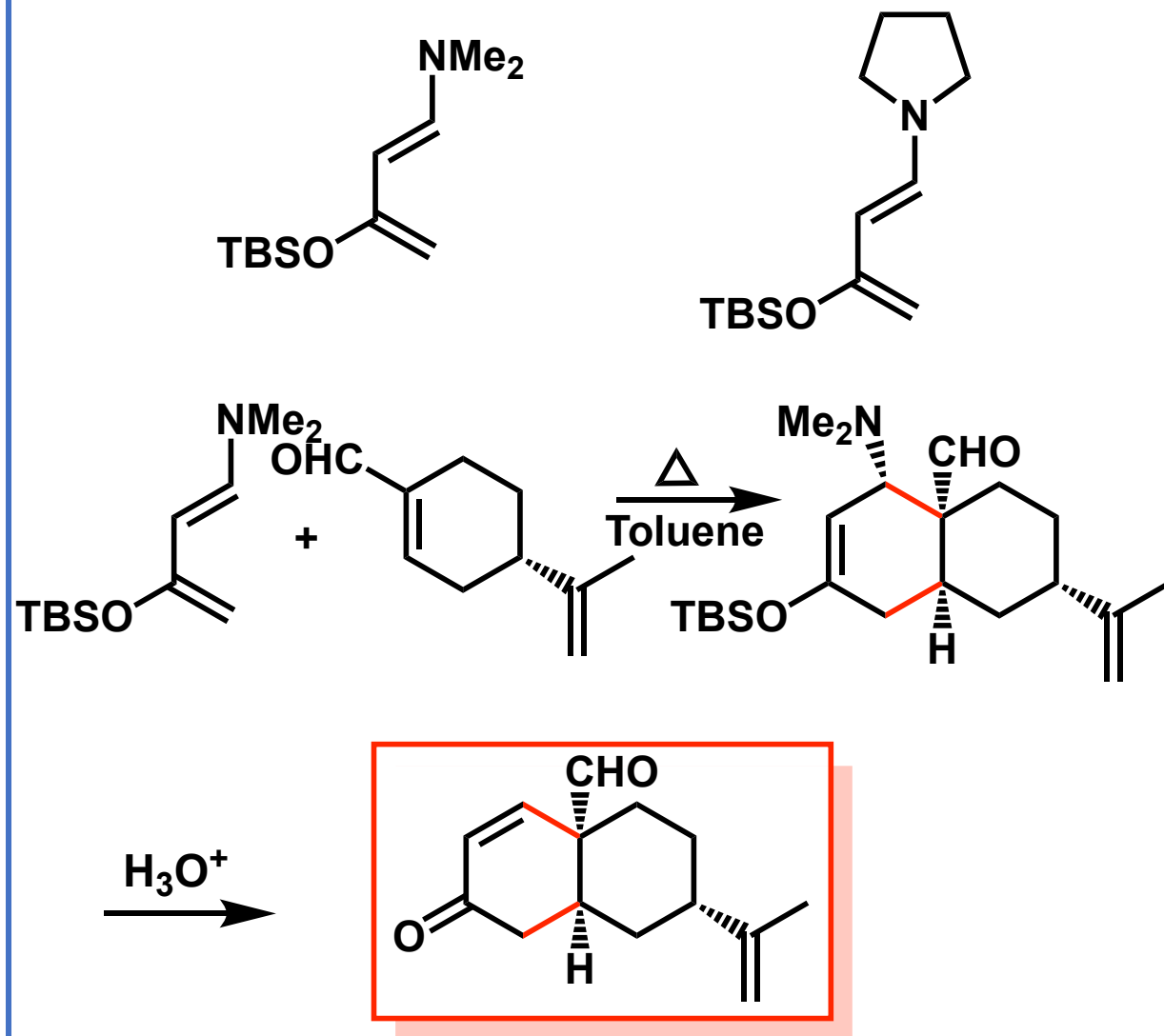
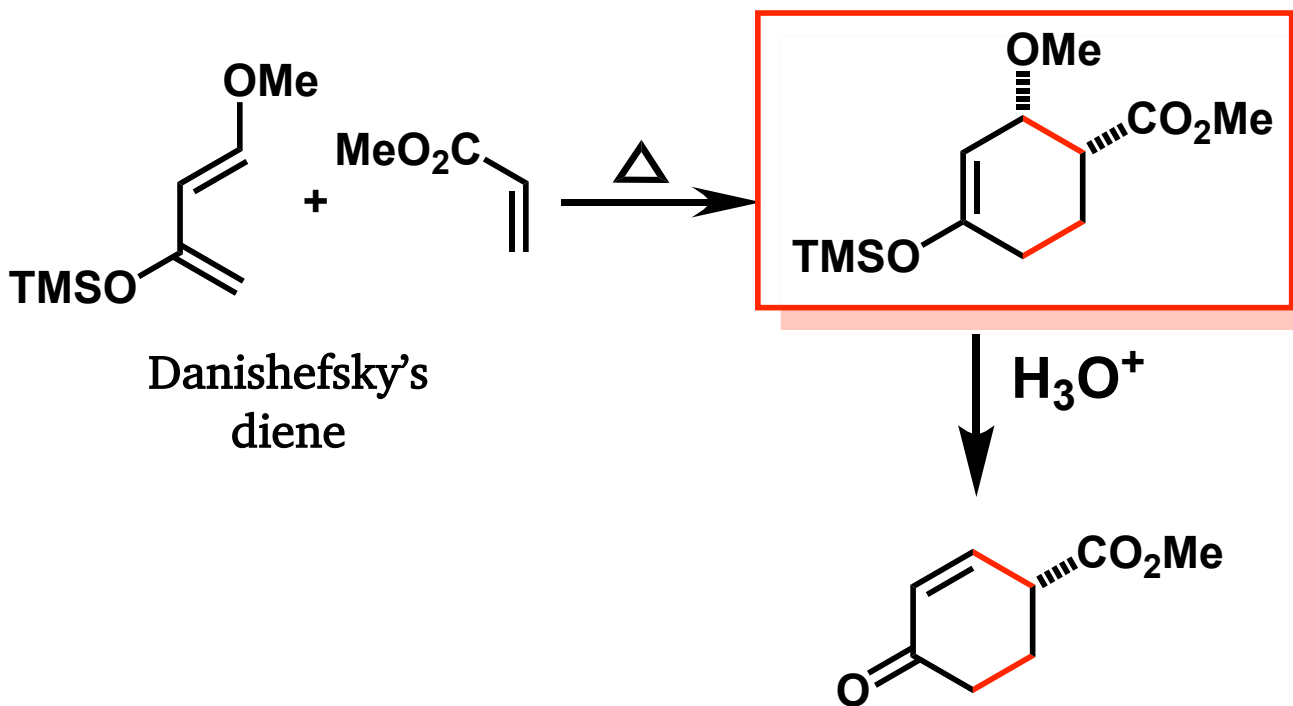
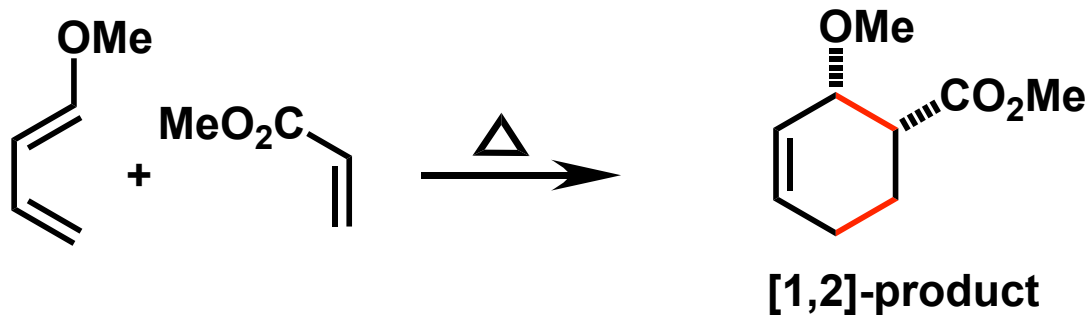


2-substituted diene reacts to give mainly [1,4]-substituted product



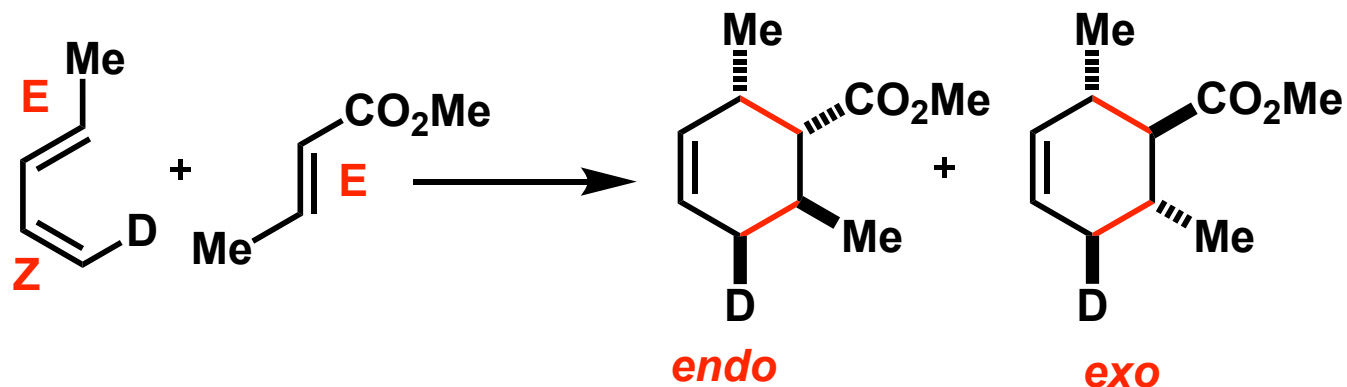


Danishefsky's Diene & Rawal's Dienes

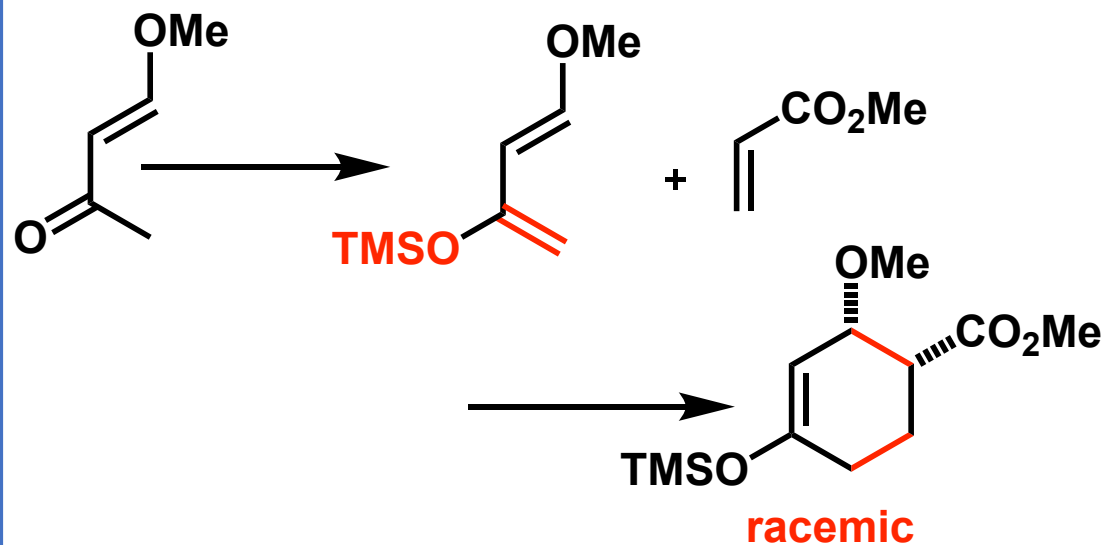
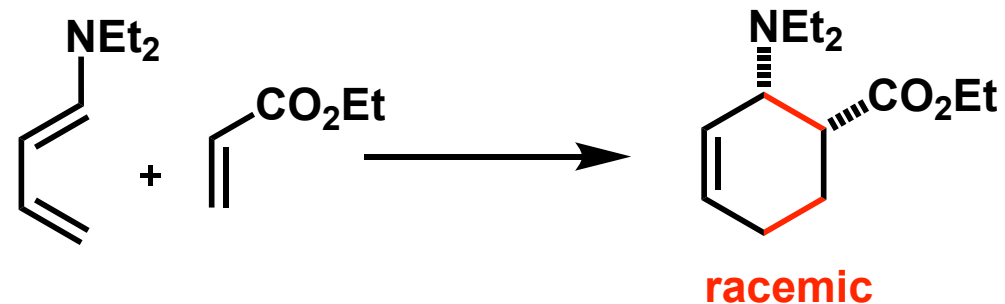
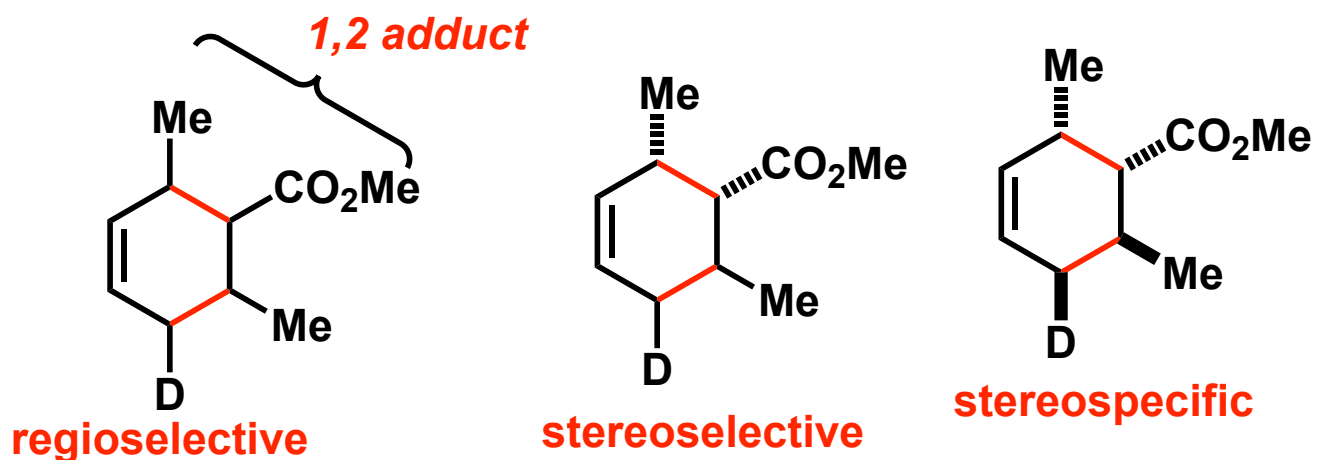




Examples

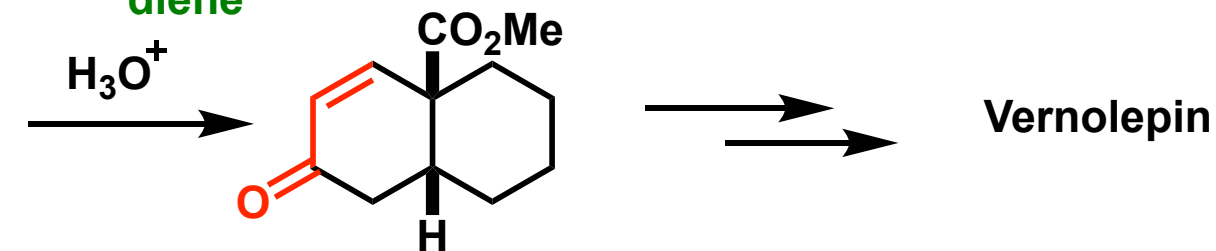
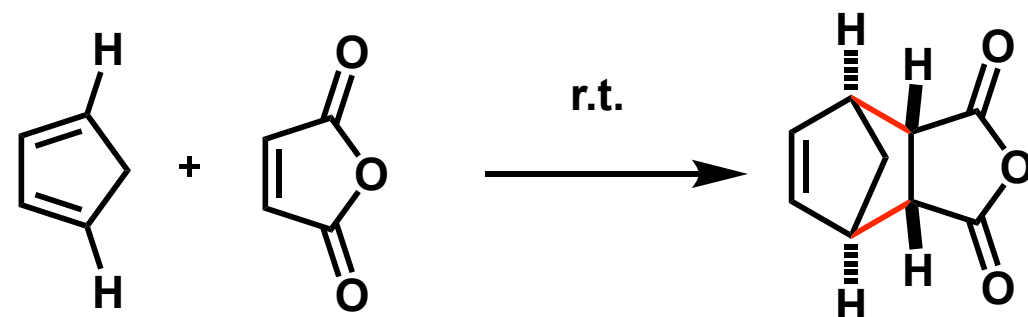
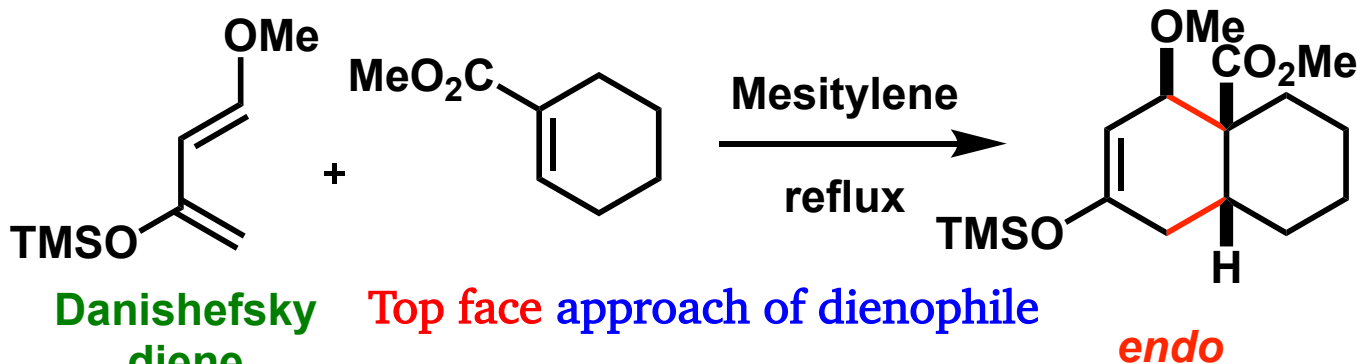


Regioselective, Stereoselective, Stereospecific



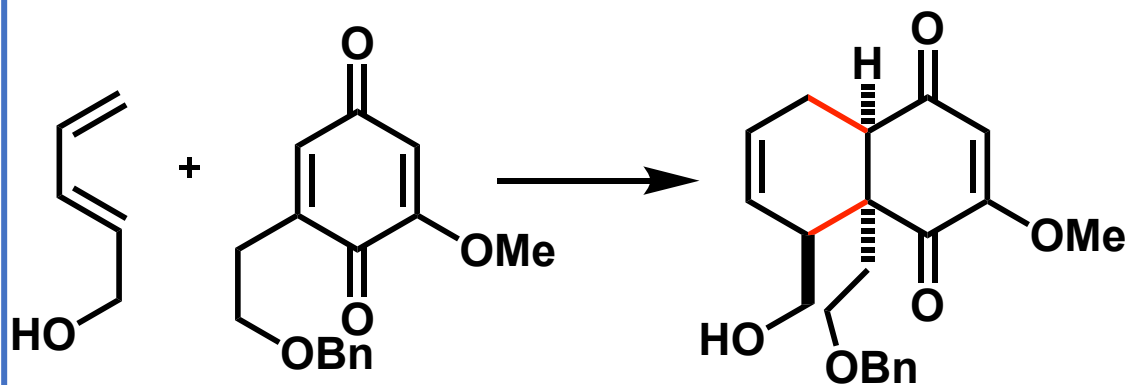
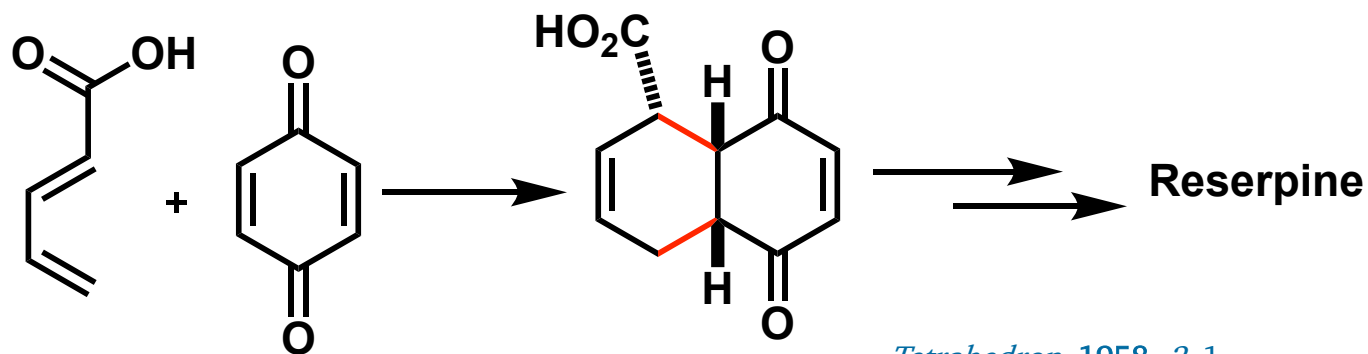


Examples



Bottom face approach of dienophile → **endo**

Woodward's approach to reserpine



Bottom face approach of dienophile

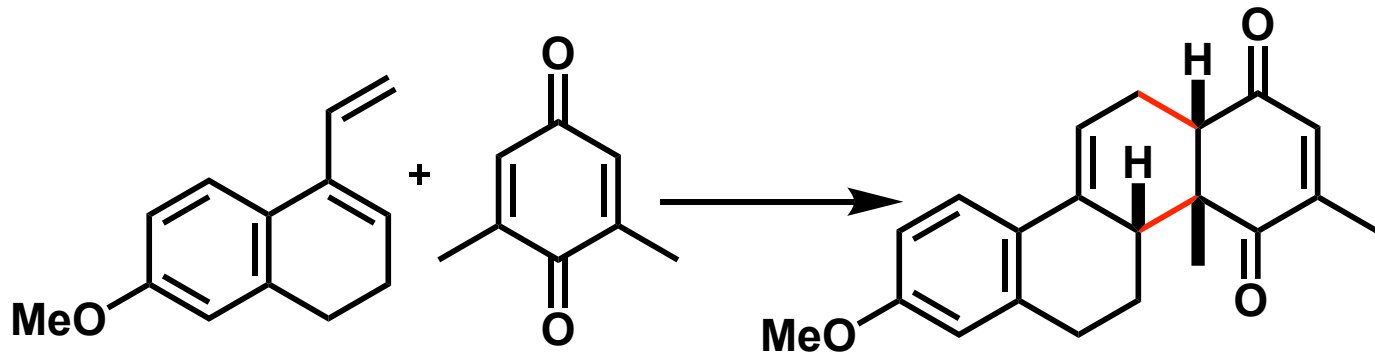
Tetrahedron, 1958, 2, 1

Top face approach of dienophile

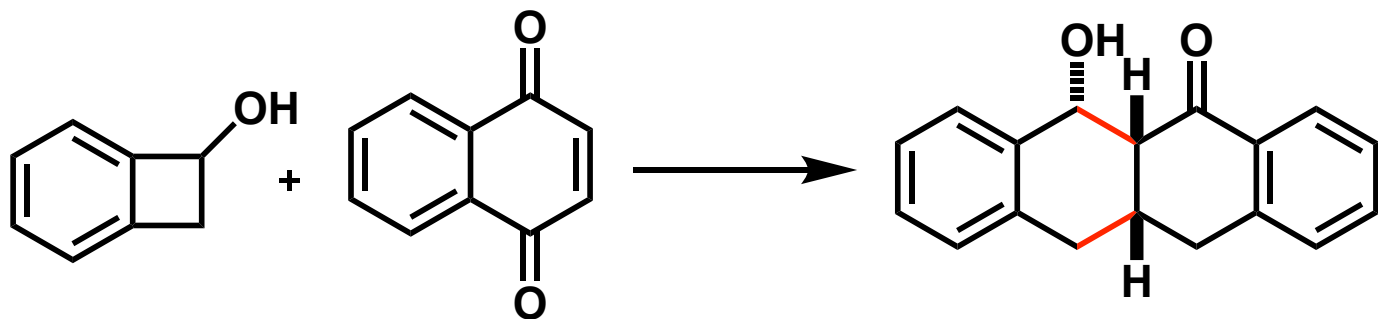
J. Am. Chem. Soc. 1978, 100, 8031



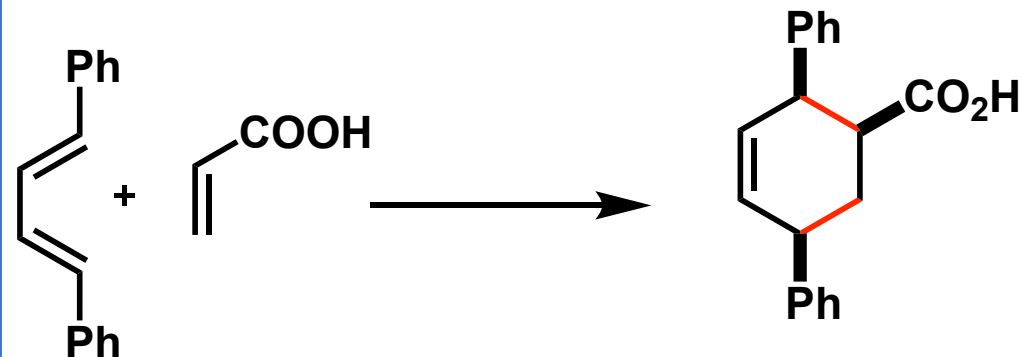
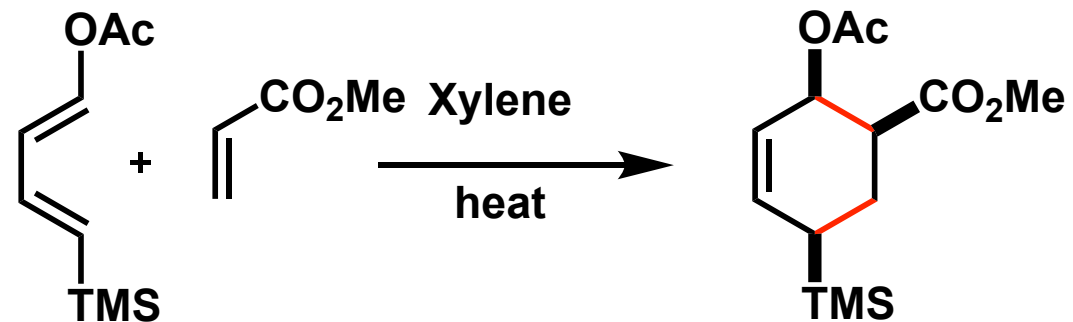
Examples



Bottom face approach of dienophile



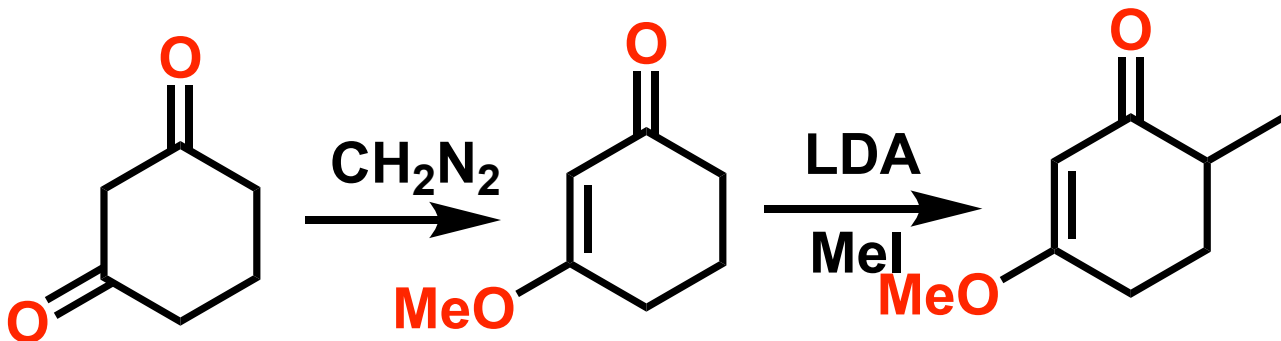
Top face approach of dienophile



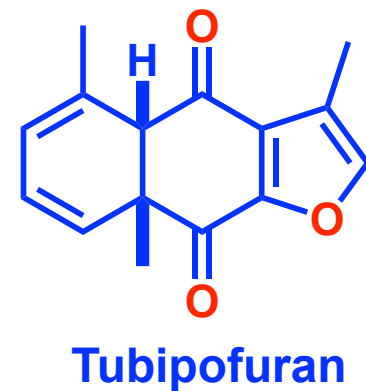
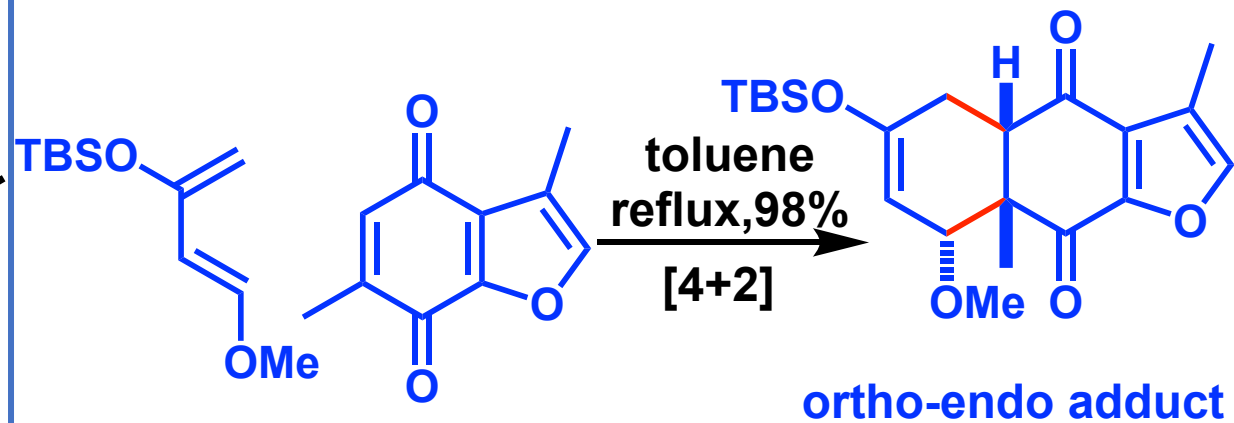
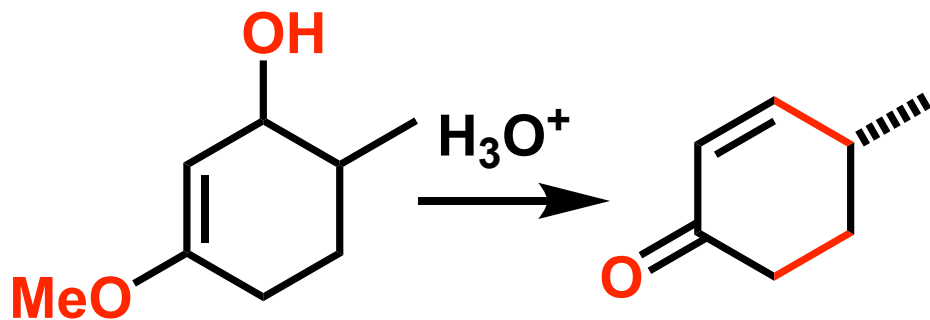
endo : *exo* = 9 : 1



Problems



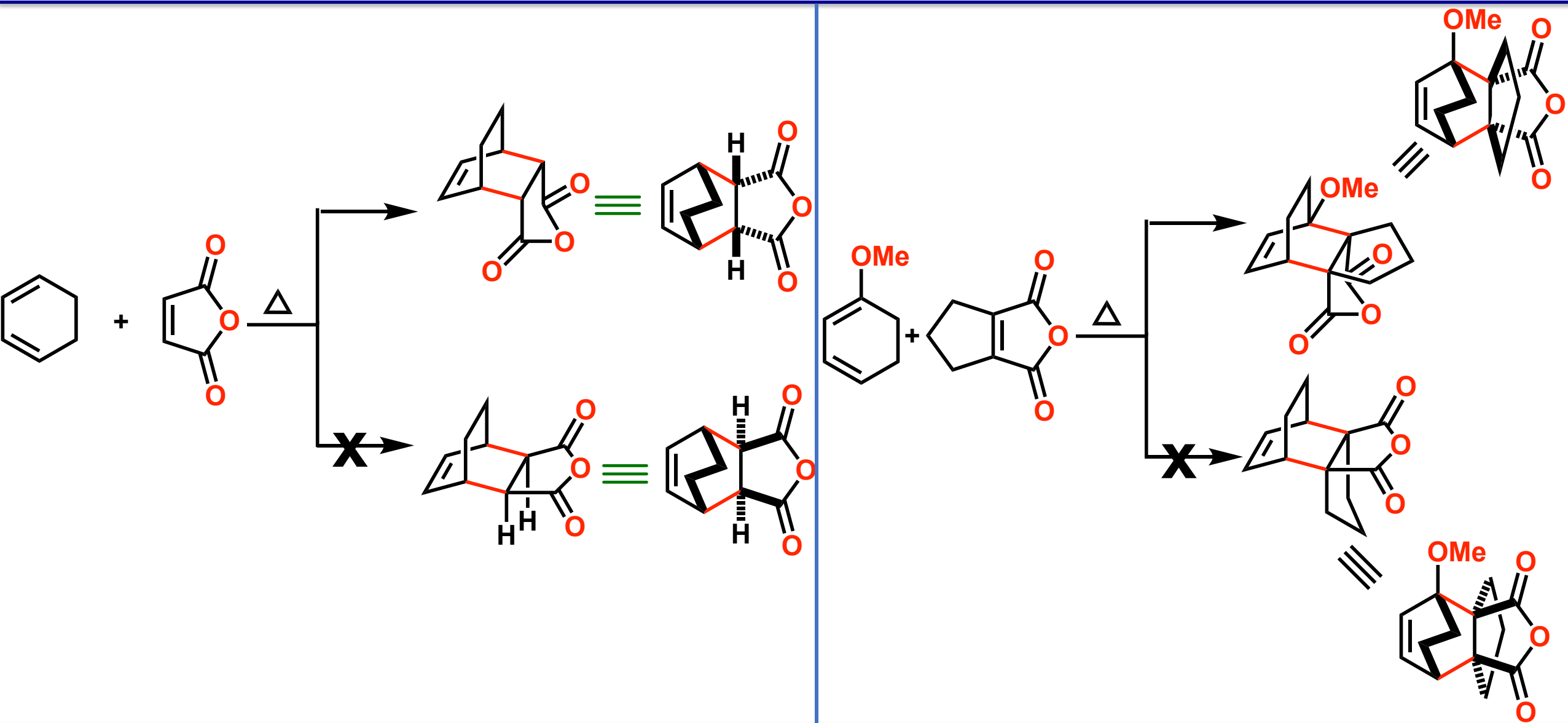
Luche
Reduction



Kanematsu, K., et al. *J. Org. Chem.* 1994, 59, 5970-5976.

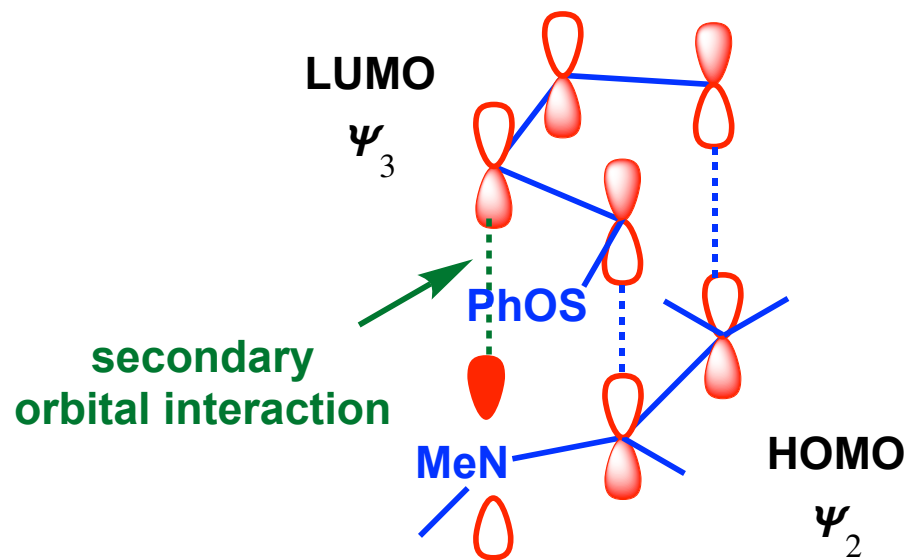
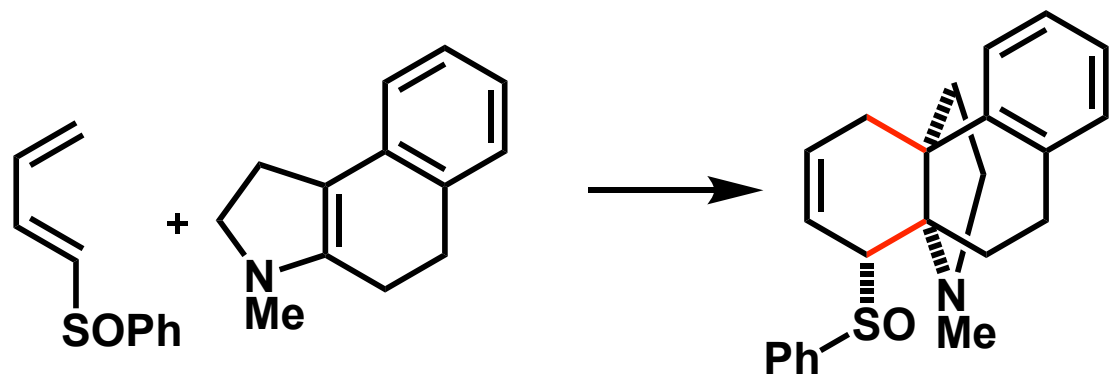


Problems

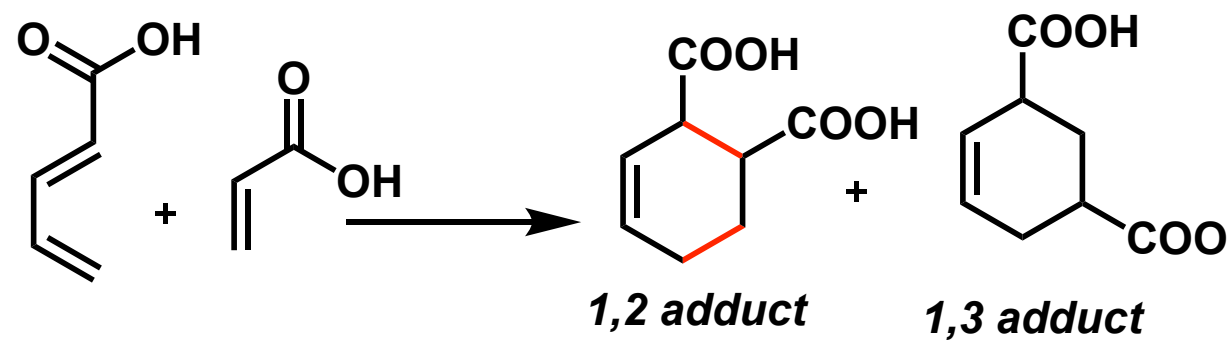




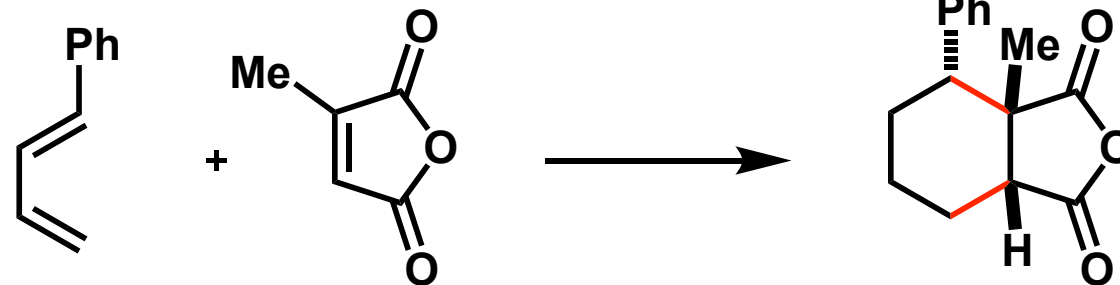
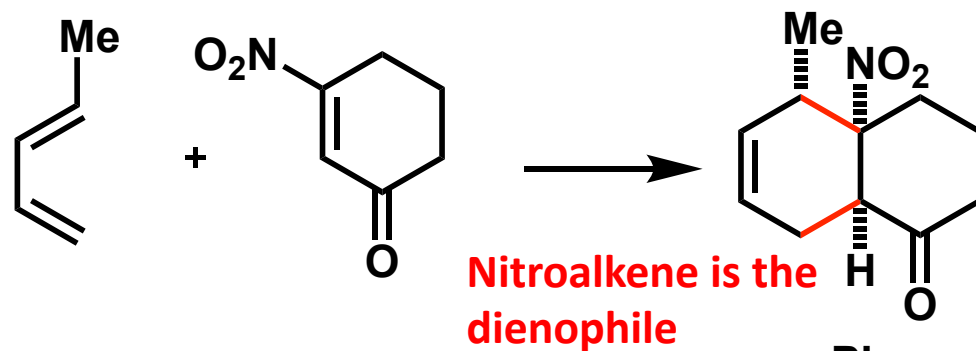
Regiochemistry of Diels-Alder Reaction



J. Am. Chem. Soc. 1972, 94, 2891



9 : 1



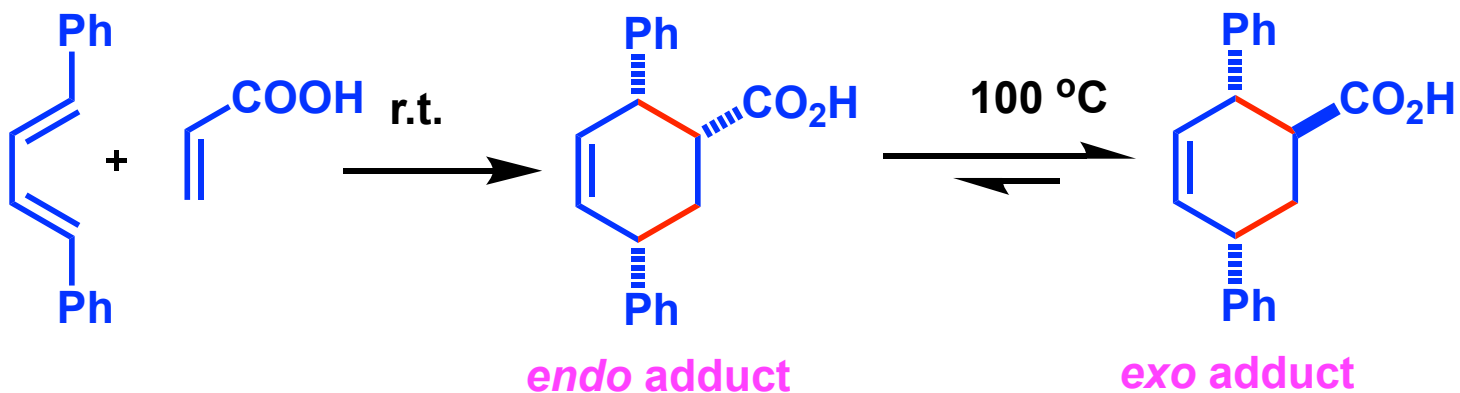


Thermodynamic Control (Reversibility)

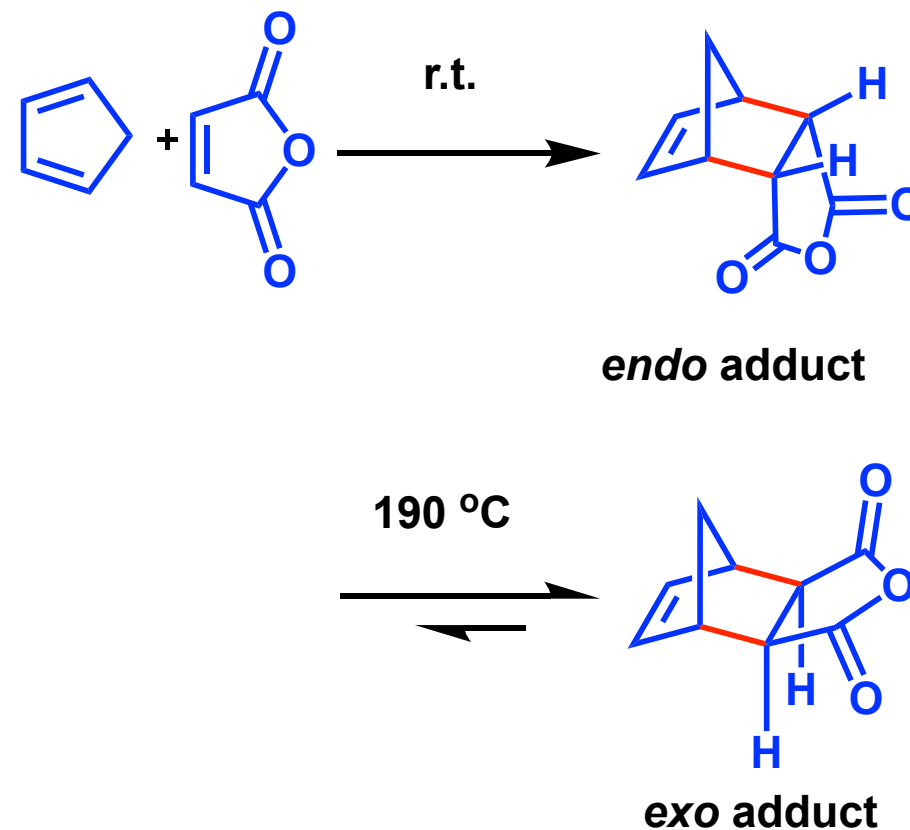
The Diels–Alder reaction is **reversible**

Under **kinetic control**, the formation of less stable but quickly formed **endo adduct** is observed as the major product

At **higher temperature**, the **energy barrier** for the reverse process is **overcome** and leads to equilibration between **endo** and **exo** adducts in favour of the **more stable exo isomer**



Initial **endo adduct dissociates** by retro-cycloaddition followed by the **re-addition**



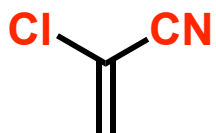


Synthetic Equivalents in Diels-Alder Reaction

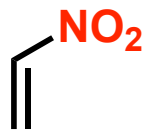
Synthetic utility of **DAR** can be enhanced by the use of masked functionality

As ketenes can not be used as such in DAR, **ketene** equivalents with masked functionality provide an alternative choice

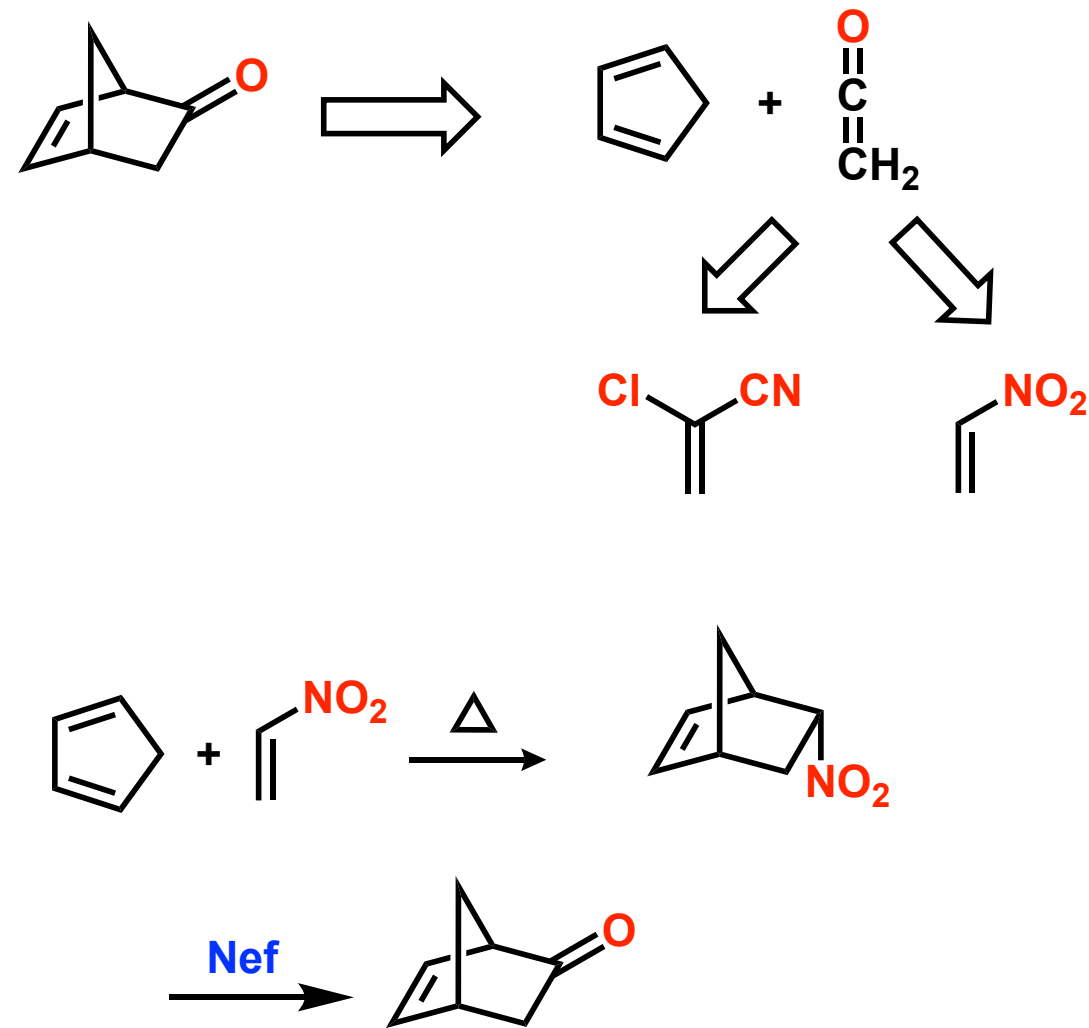
Commonly employed ketene equivalents are, **α -chloro acrylonitrile** and **nitroethylene**



α -Chloro acrylonitrile

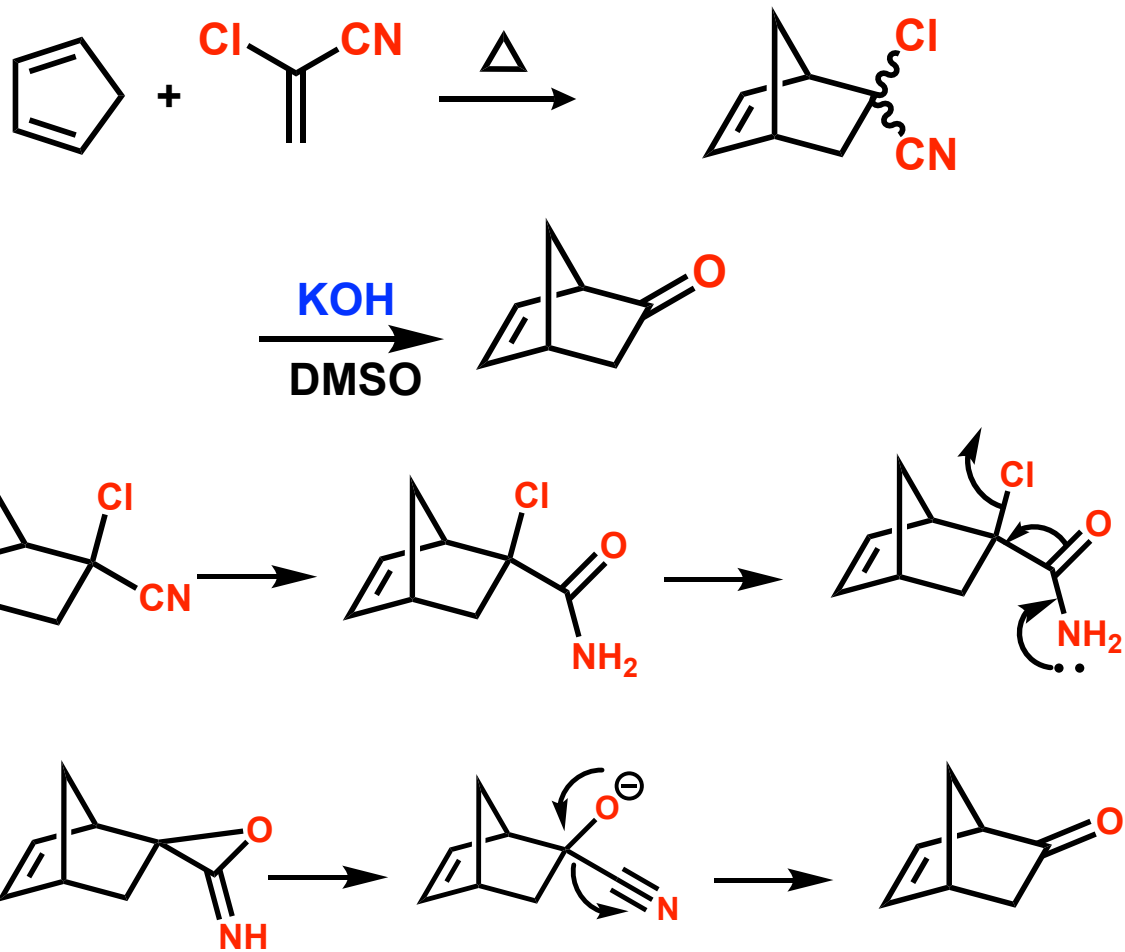


Nitro ethylene

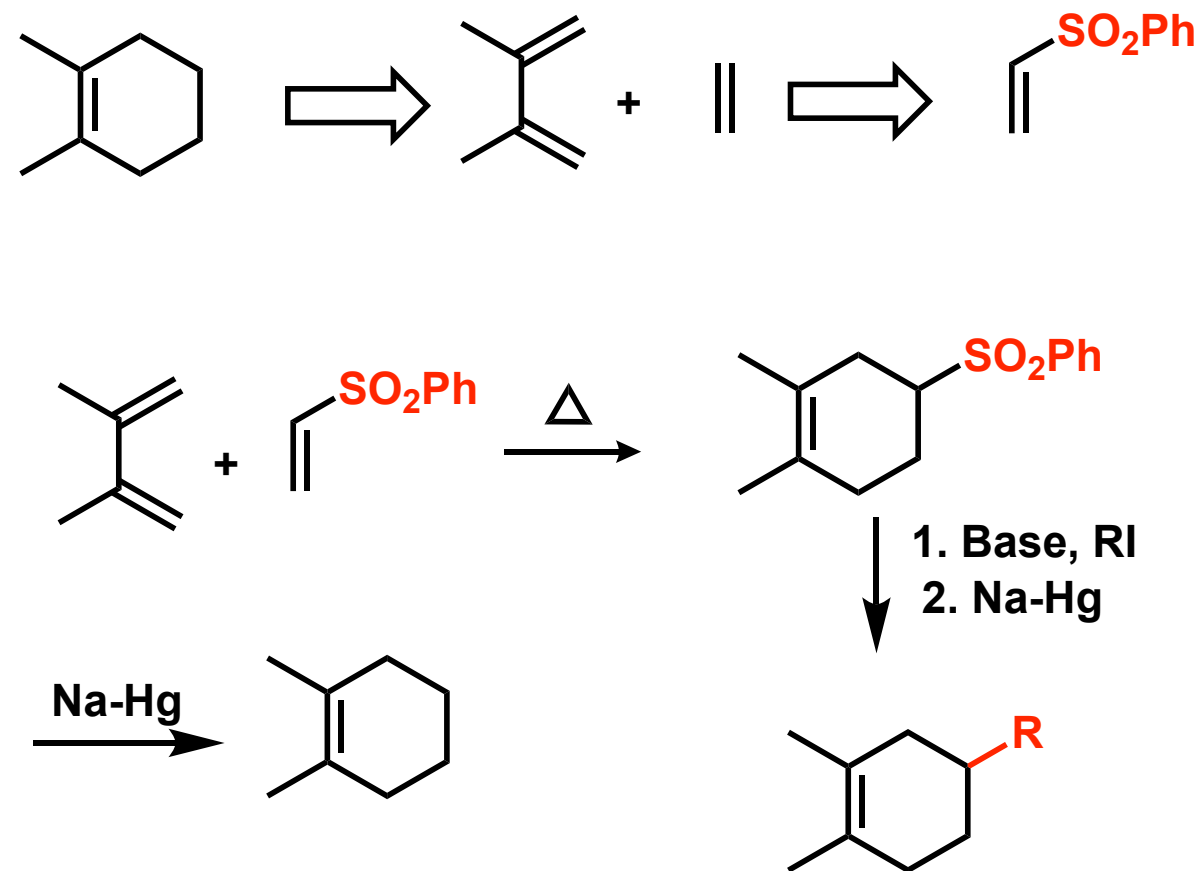




Synthetic Equivalents in Diels-Alder Reaction



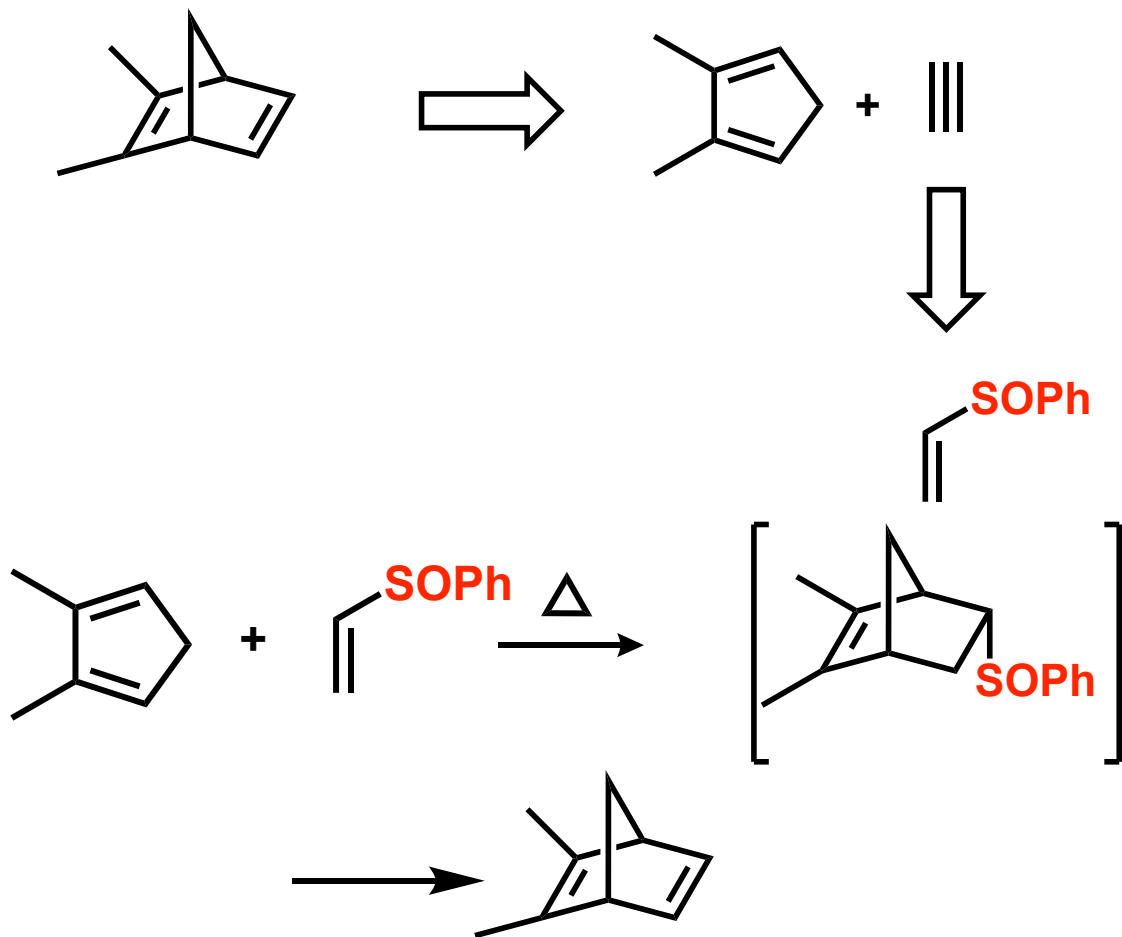
Commonly employed ethylene equivalent,
Vinyl sulfone



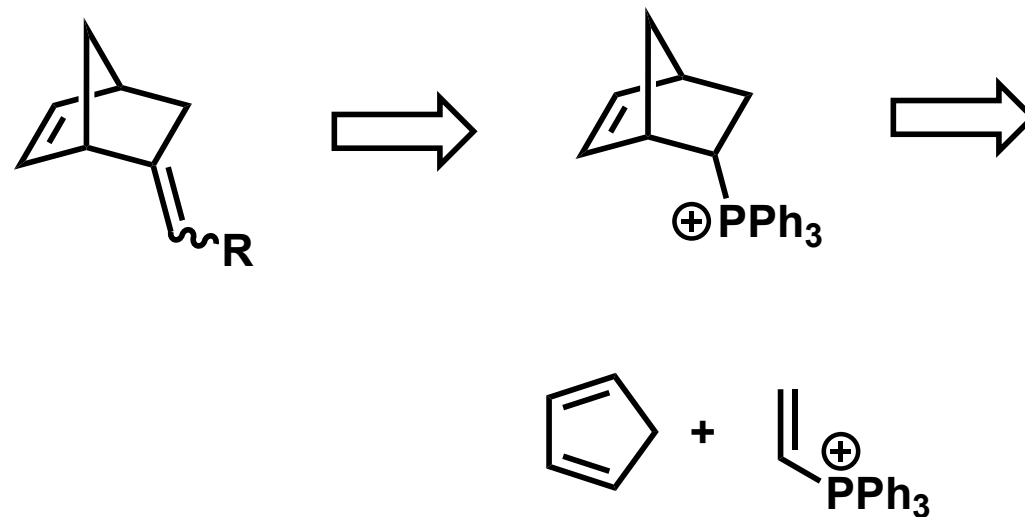


Synthetic Equivalents in Diels-Alder Reaction

Commonly employed **acetylene** equivalent,
Vinyl sulfoxide



Allene equivalent, **phosphonium salt**





Intramolecular Diels-Alder Reaction

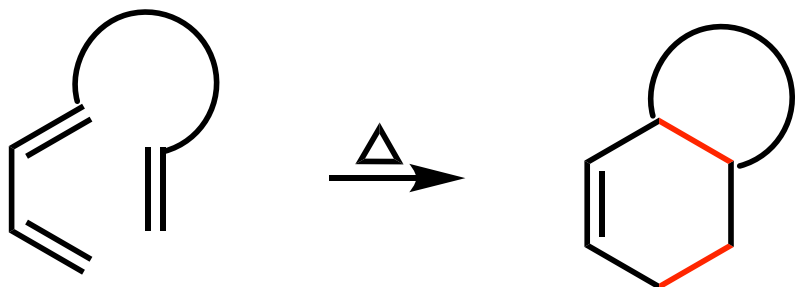
IMDA (Type I and Type II)

Intramolecular cycloaddition can provide easy access to polycyclic compounds

Type I IMDA :

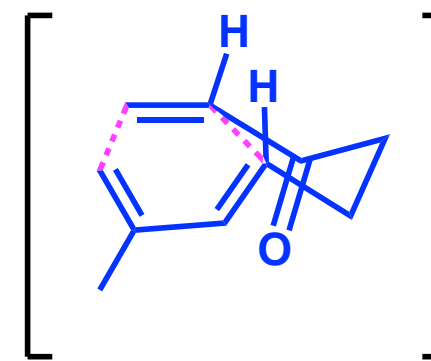
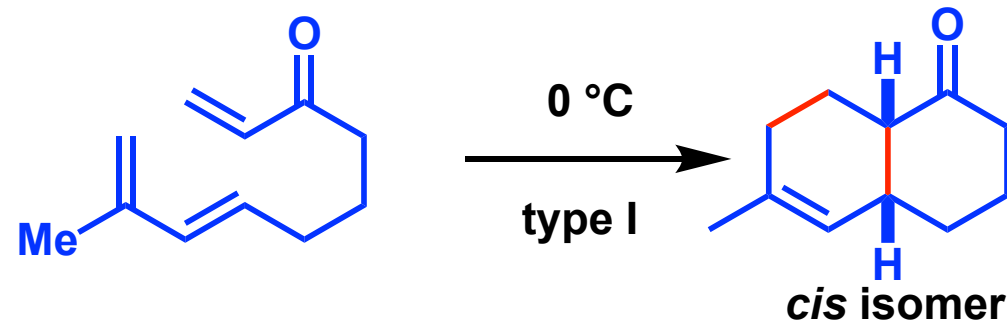
Dienophile is attached to C-1 atom of diene

Results in the formation of fused bicyclic system



Fused bicyclic system

Type I IMDA :



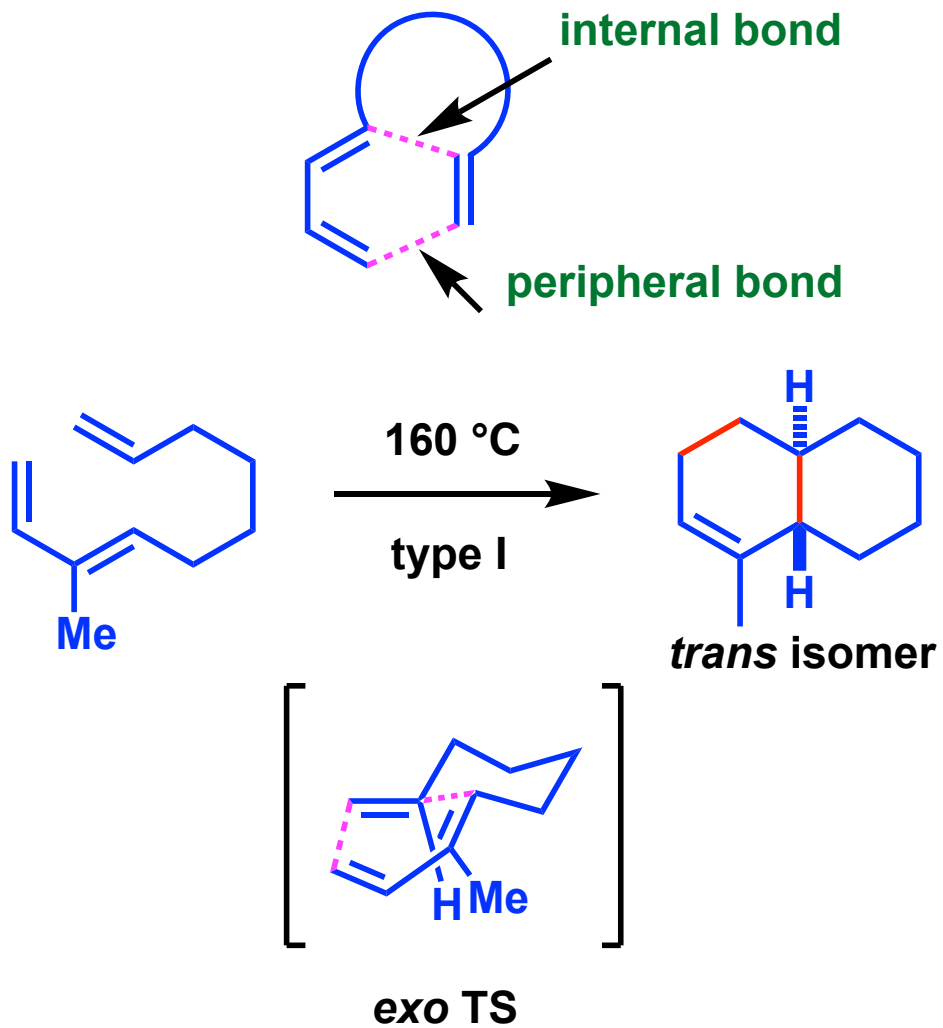
endo TS

Considering dienophile approaching from the bottom phase

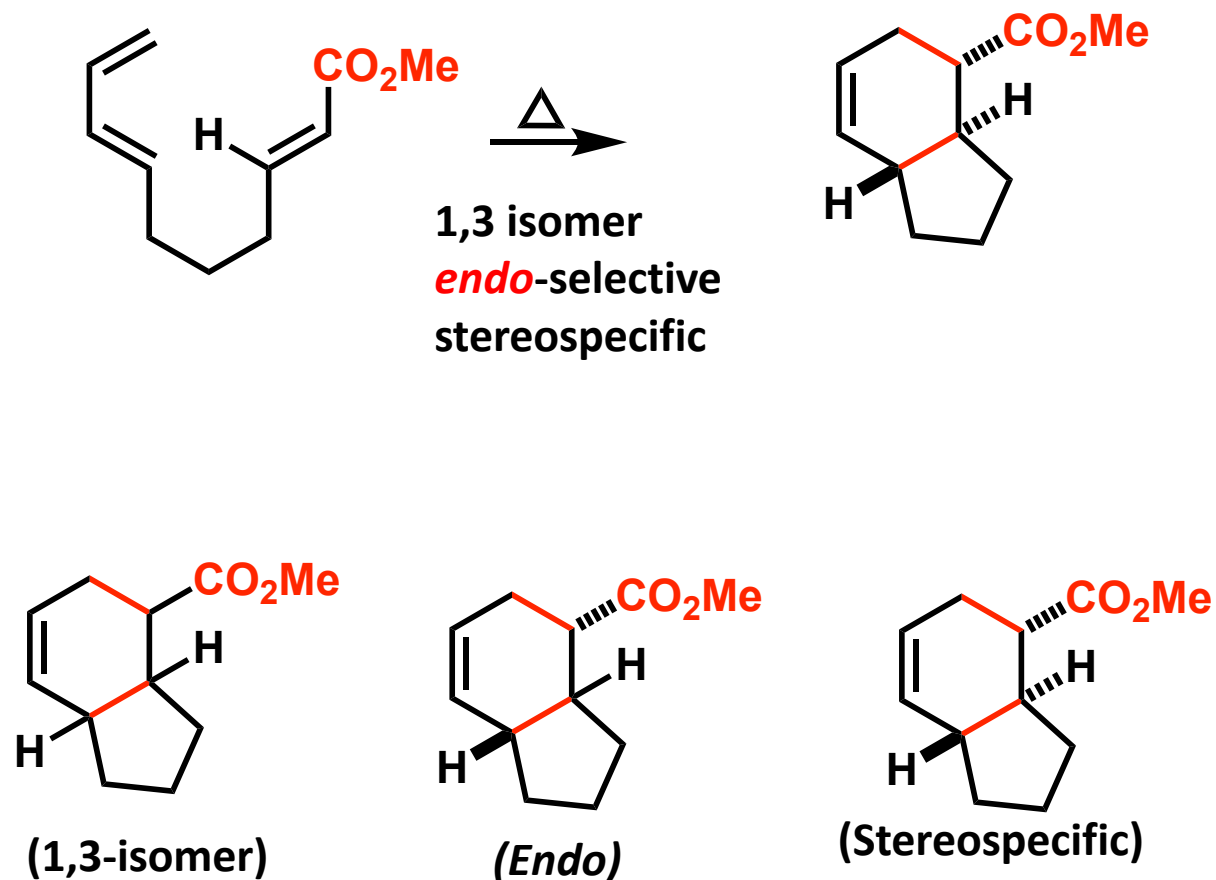
Activating carbonyl group favors the *endo* TS



Type I IMDA

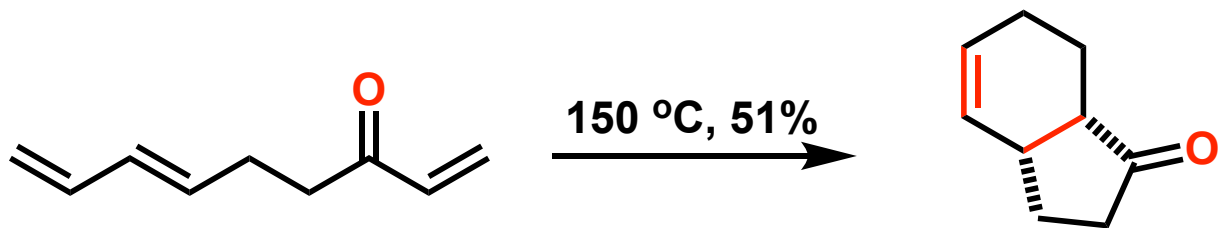
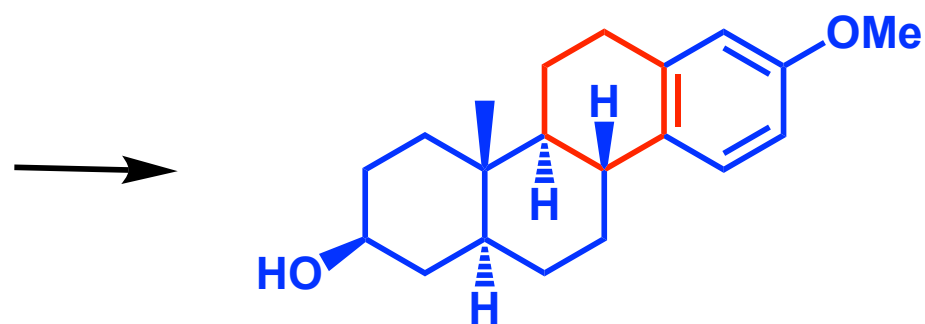
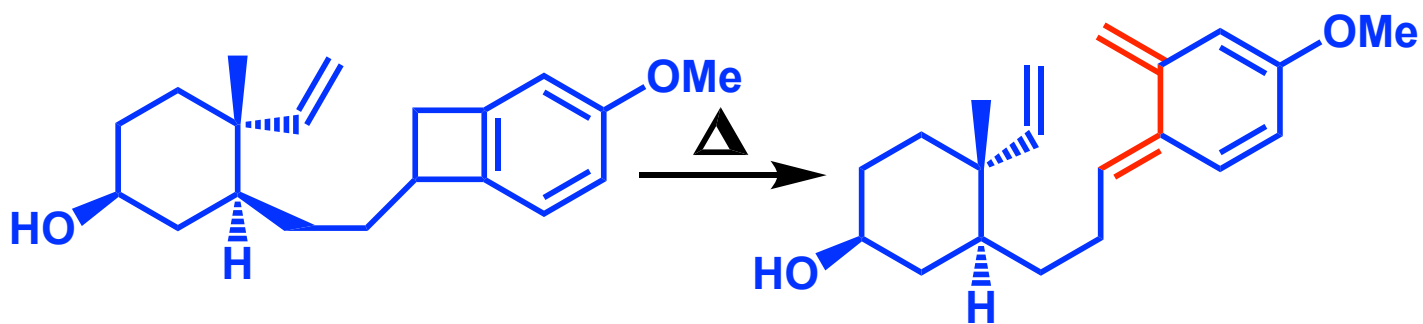


Absence of activating group favors the *exo* TS

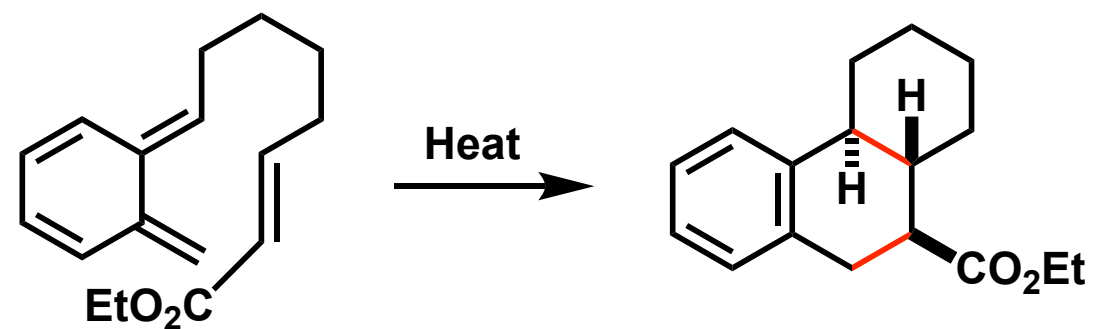
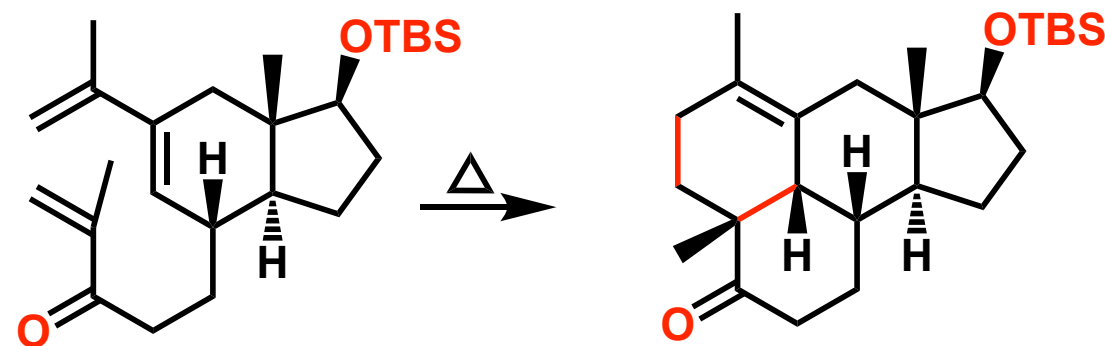
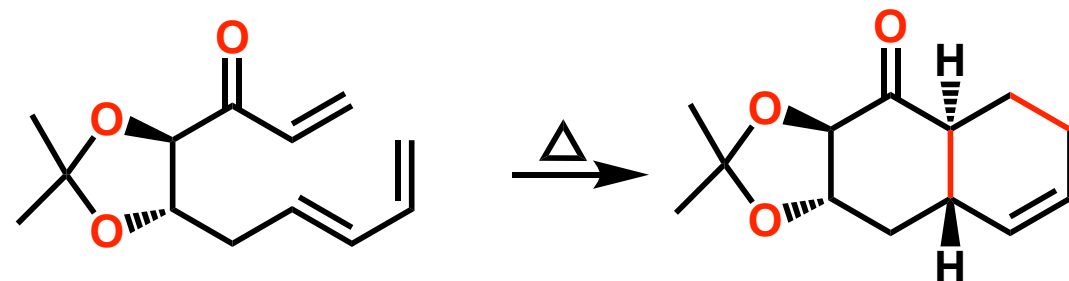




IMDA - Type I Reaction



Unless other steric factors intervene, internally activated trienes give *cis*-fused product



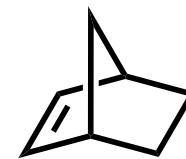
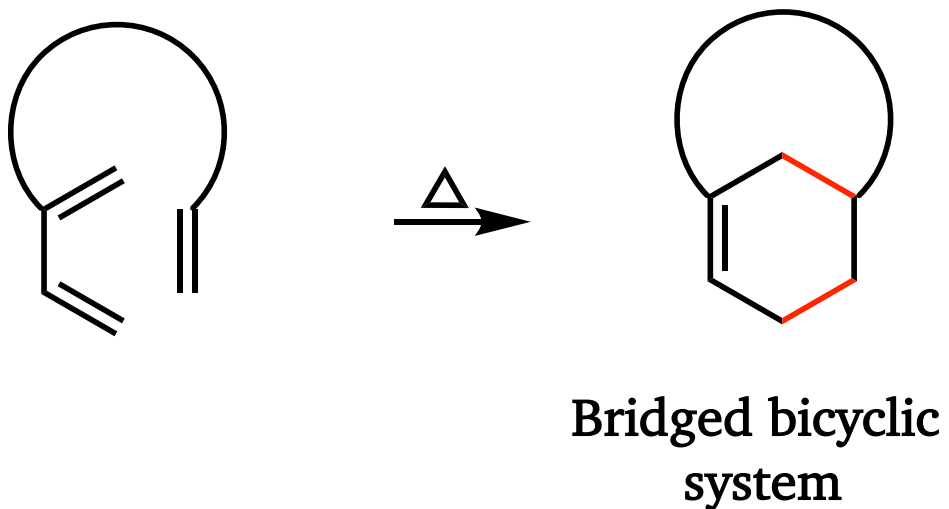


IMDA–Type II

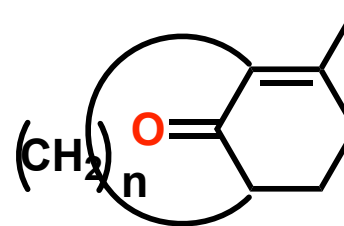
Type II IMDA:

Dienophile is attached to C-2 atom of **diene**

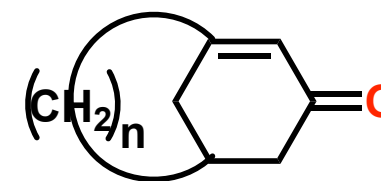
Type II IMDA generally results in the formation of **bridged bicyclic system**, provided the ring formed should be larger than six membered (should be minimum **seven** membered ring)



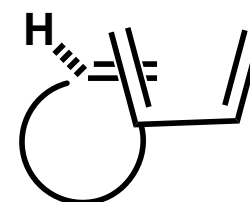
Against Bredt's rule



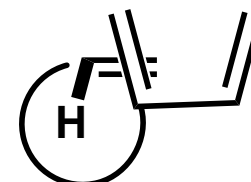
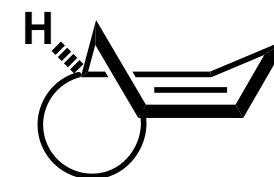
$n = 6, 7, \dots$



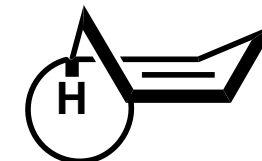
$n = 4, 5, 6$



Tether Endo

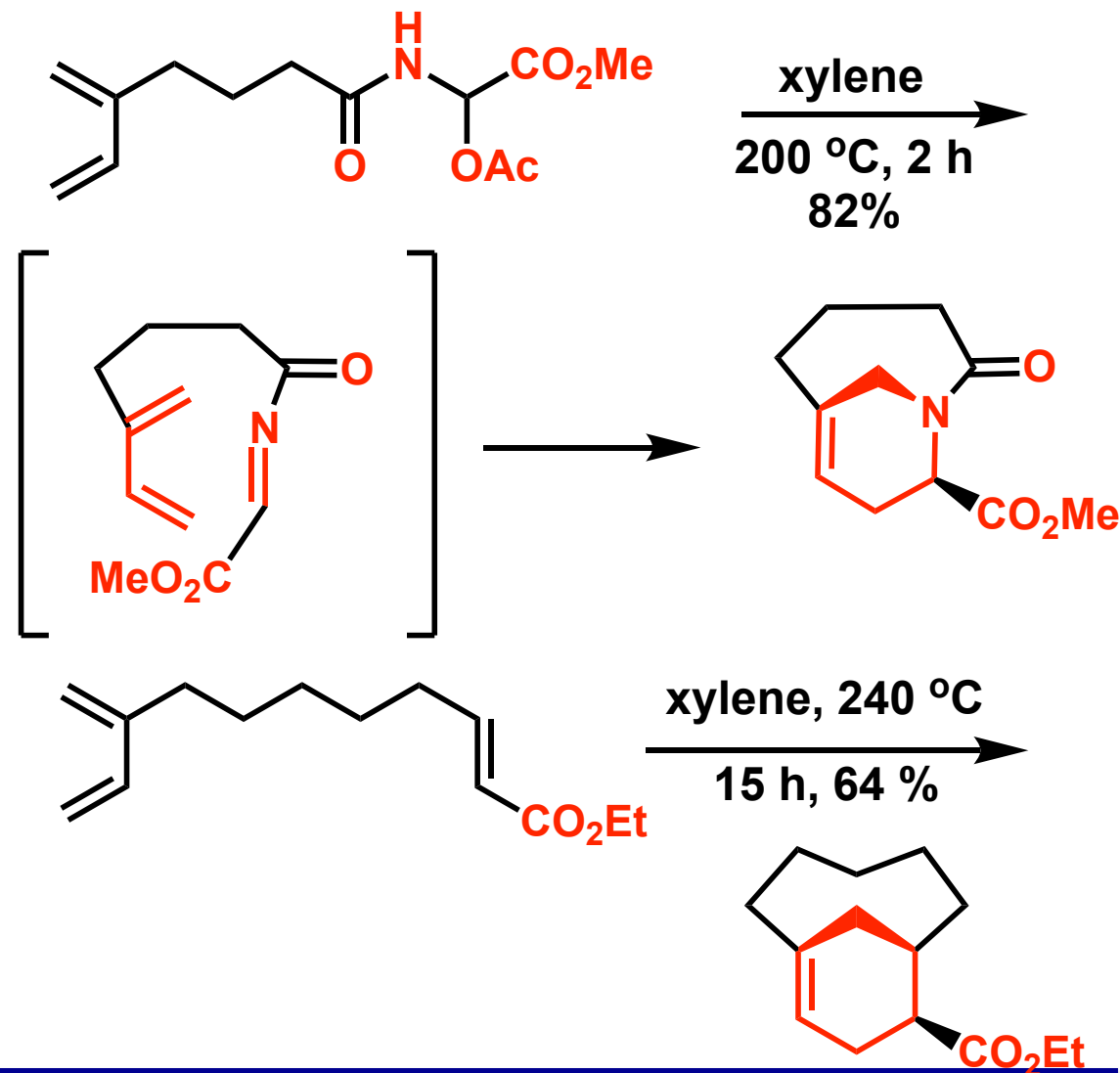
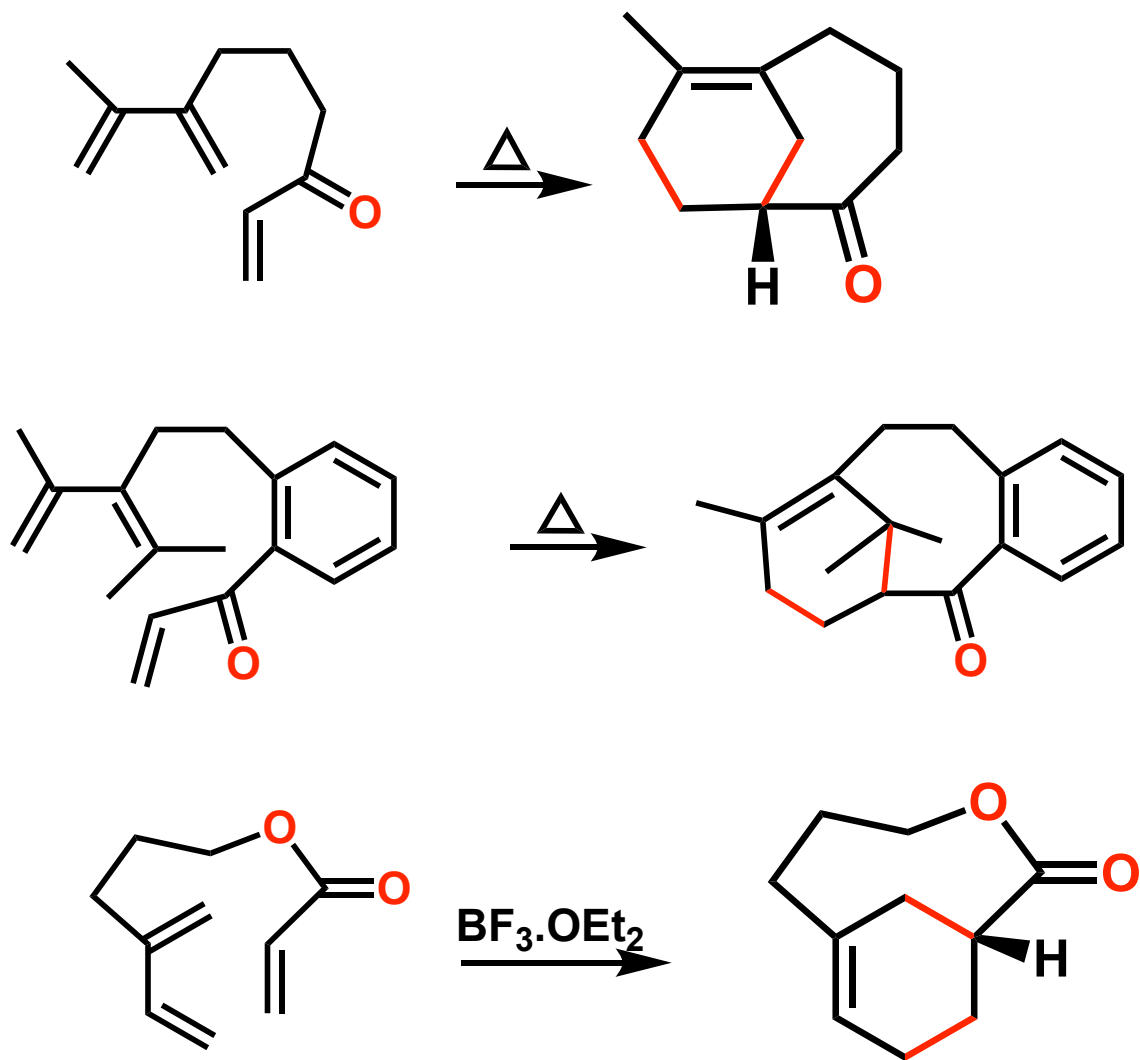


Tether Exo



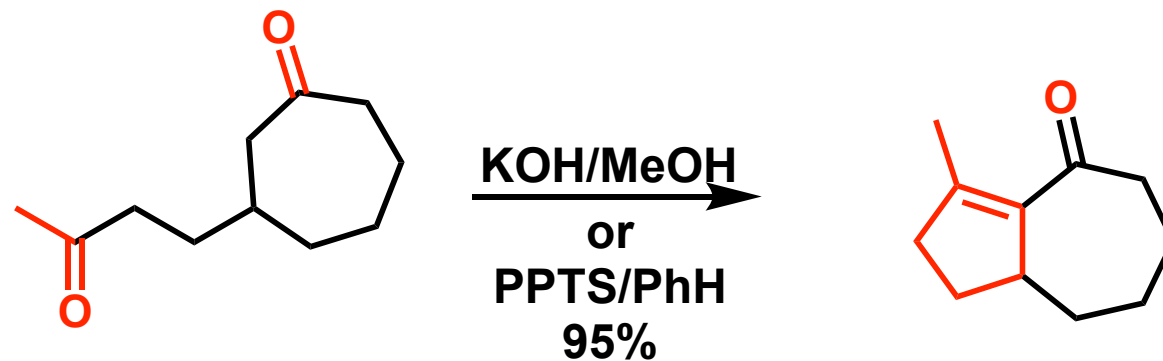
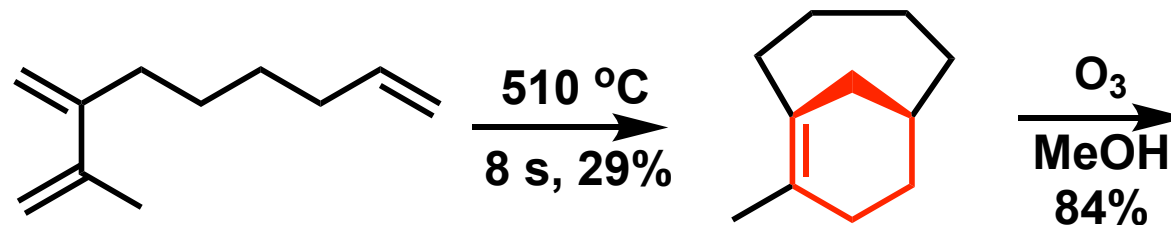
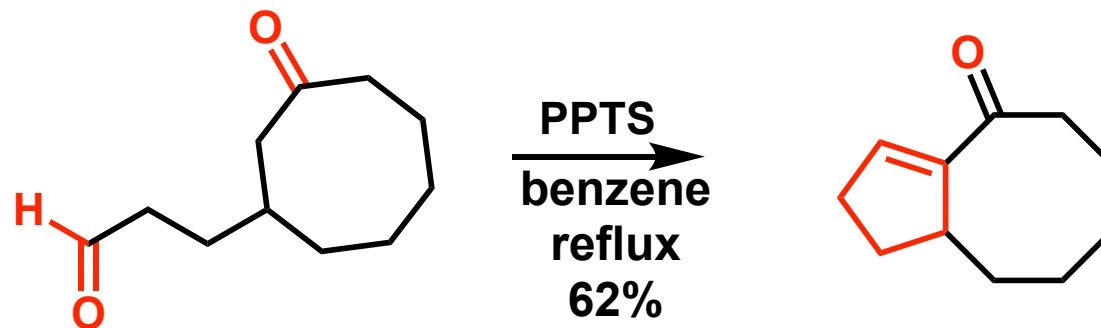
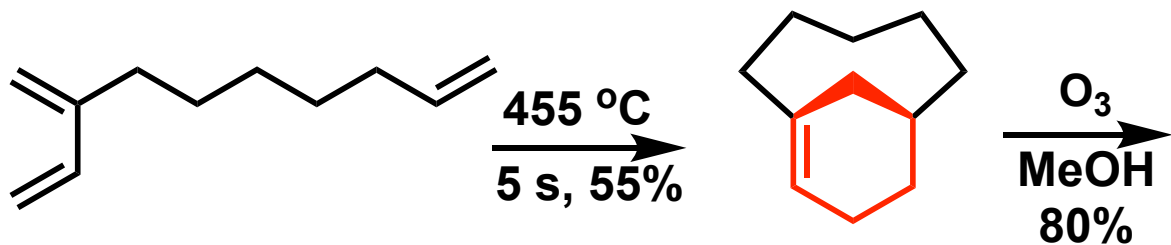
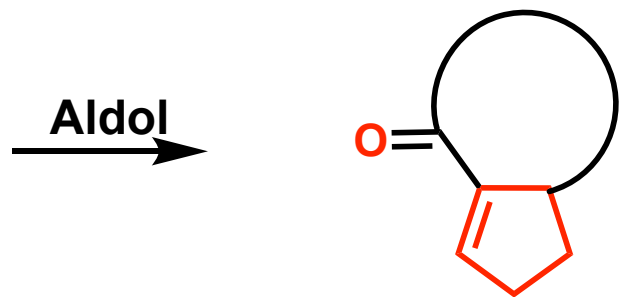
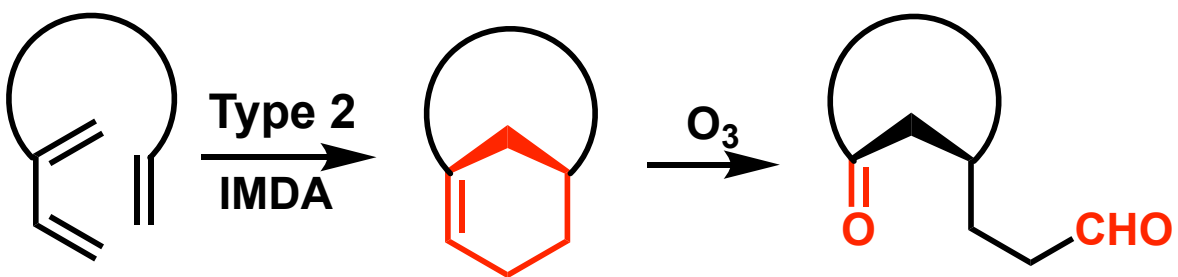


IMDA - Type II Examples





Bridged to Fused Ring Exchange

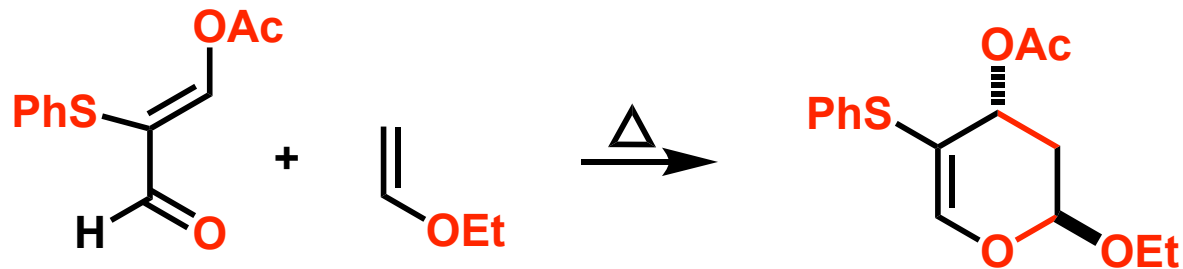
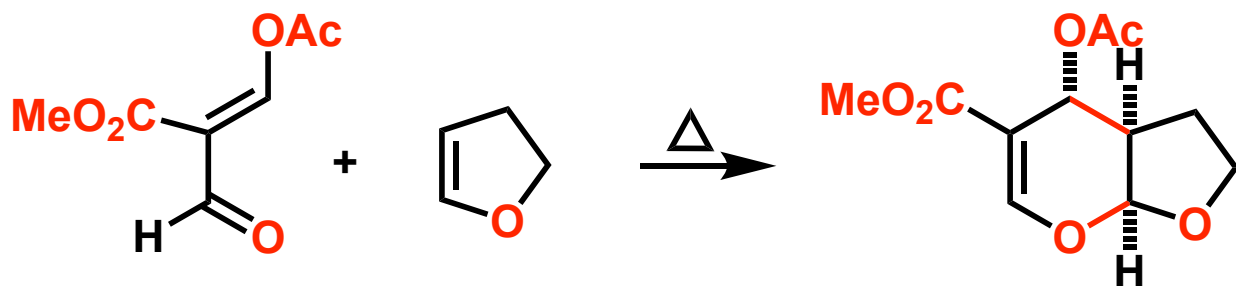




Hetero Diels-Alder Reaction

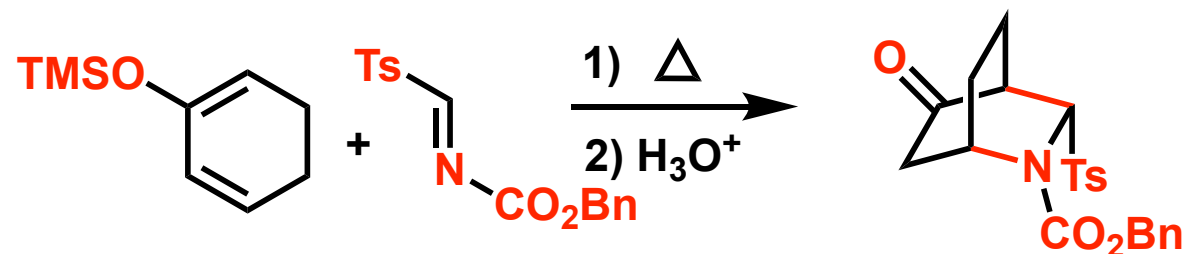
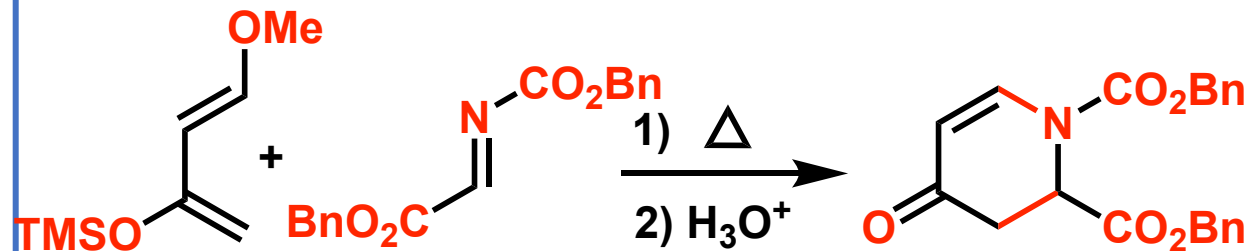
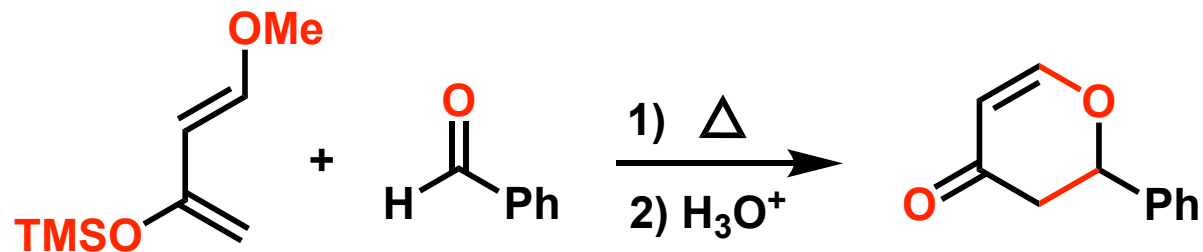
Hetero Diene:

Hetero atom is part of the diene



Hetero Dienophile:

Hetero atom is part of the dienophile



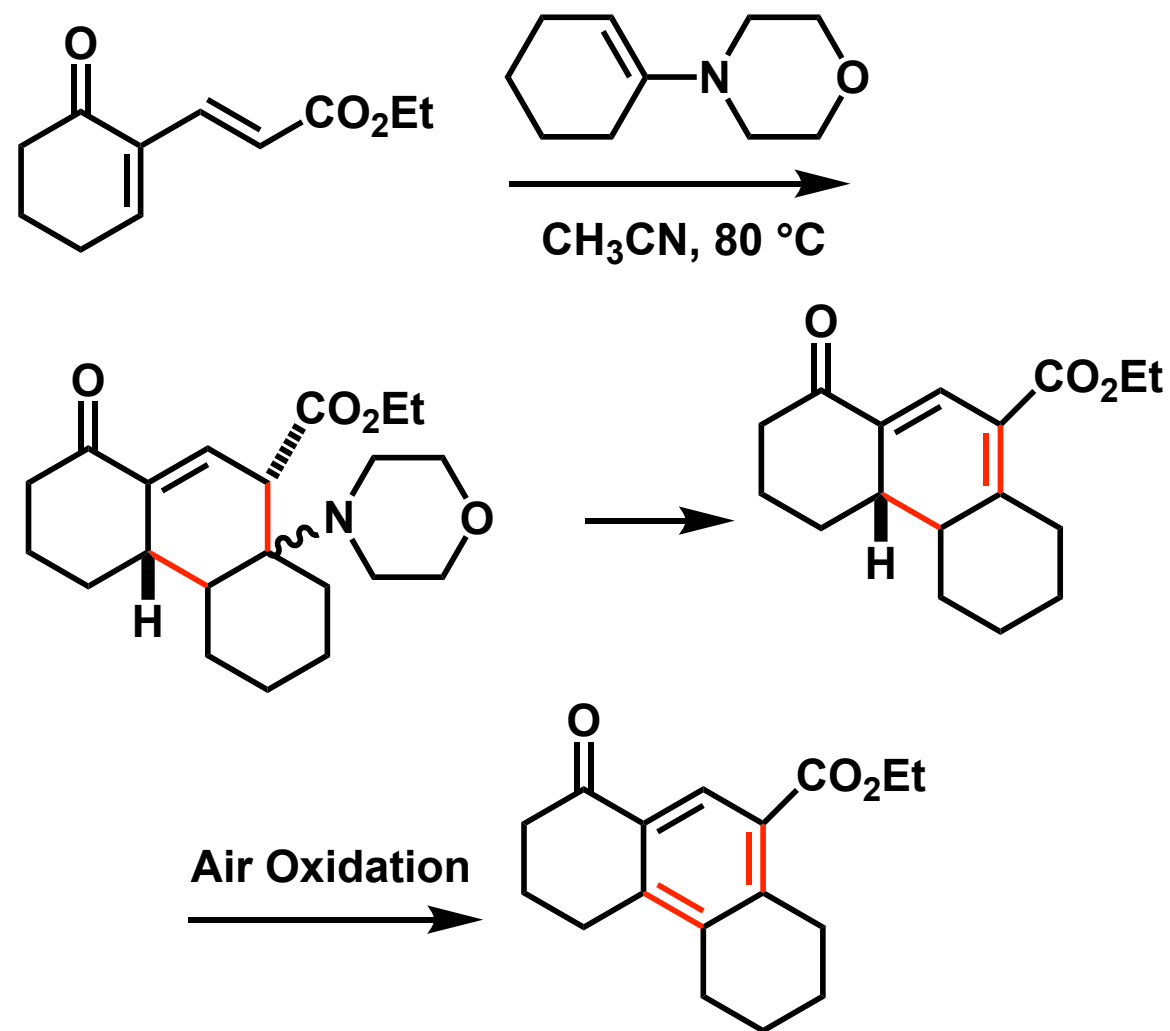
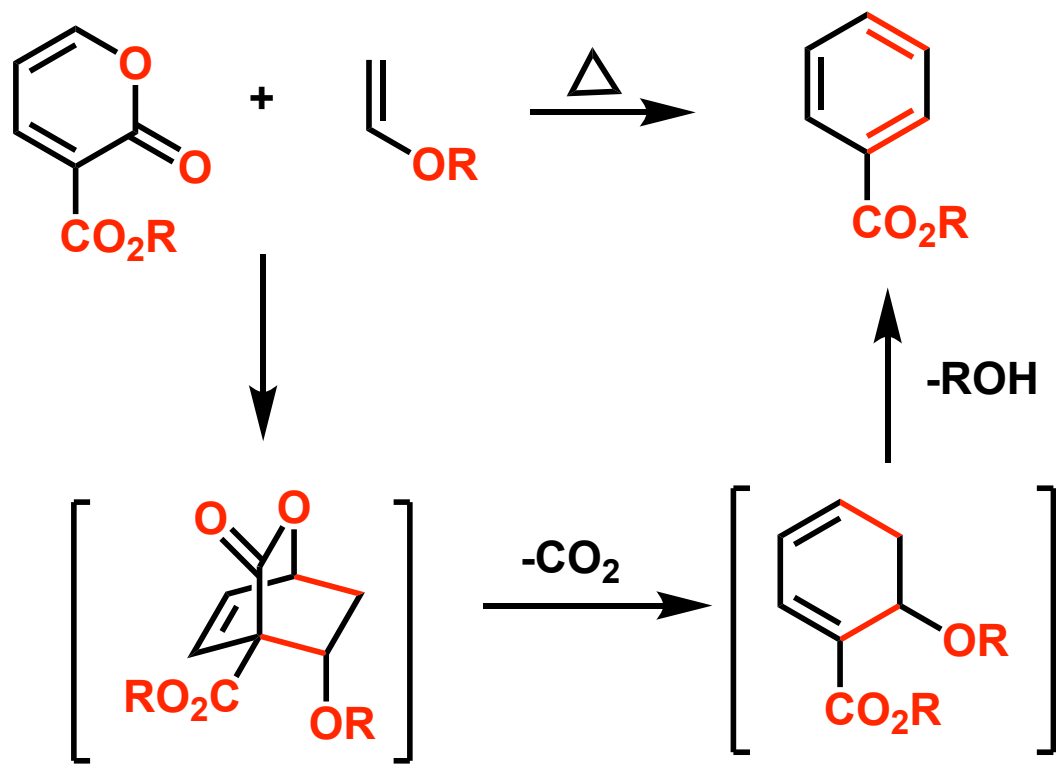


Inverse Electron Demand Diels-Alder Reaction

Inverse electron-demand [4+2]:

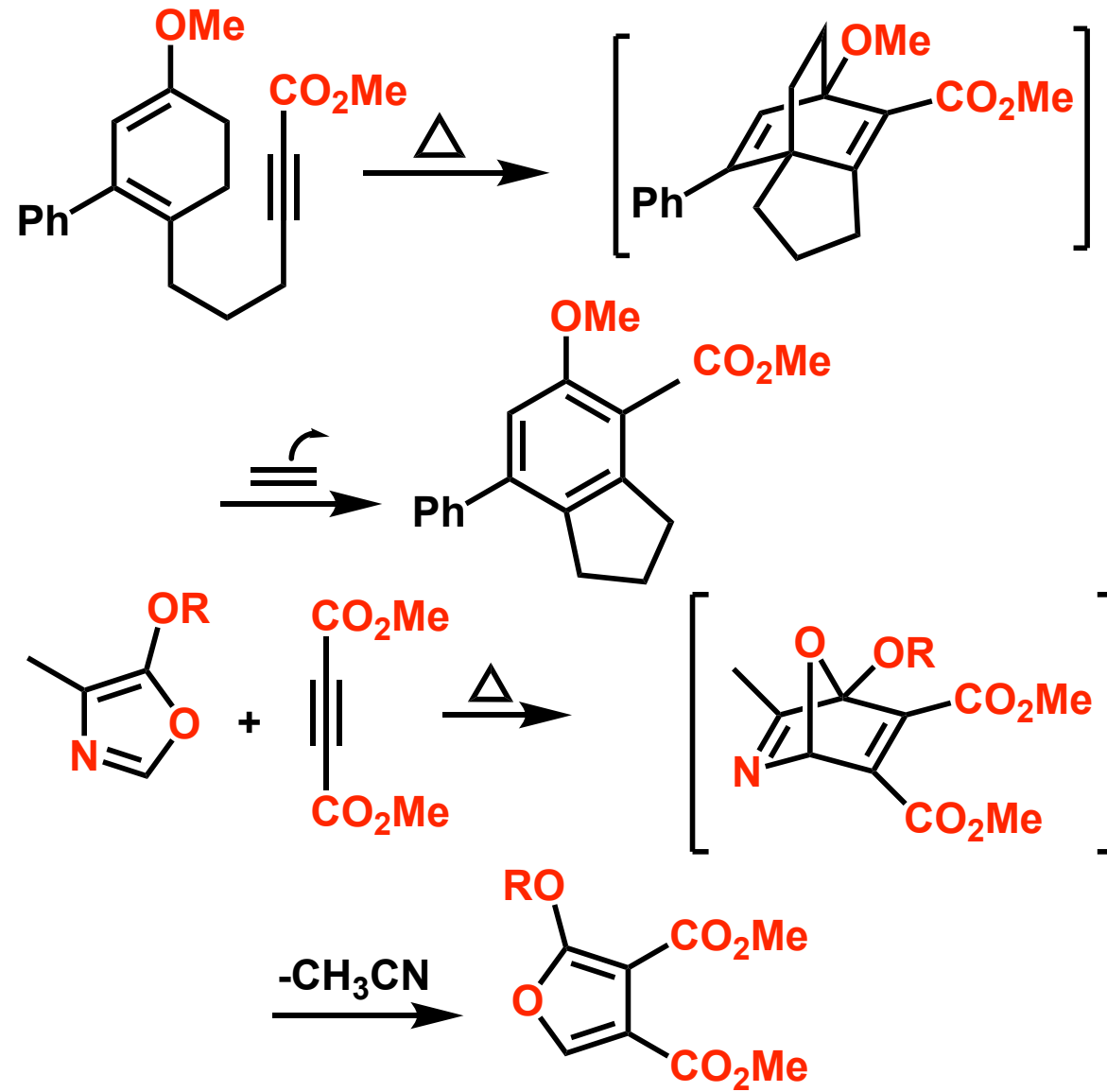
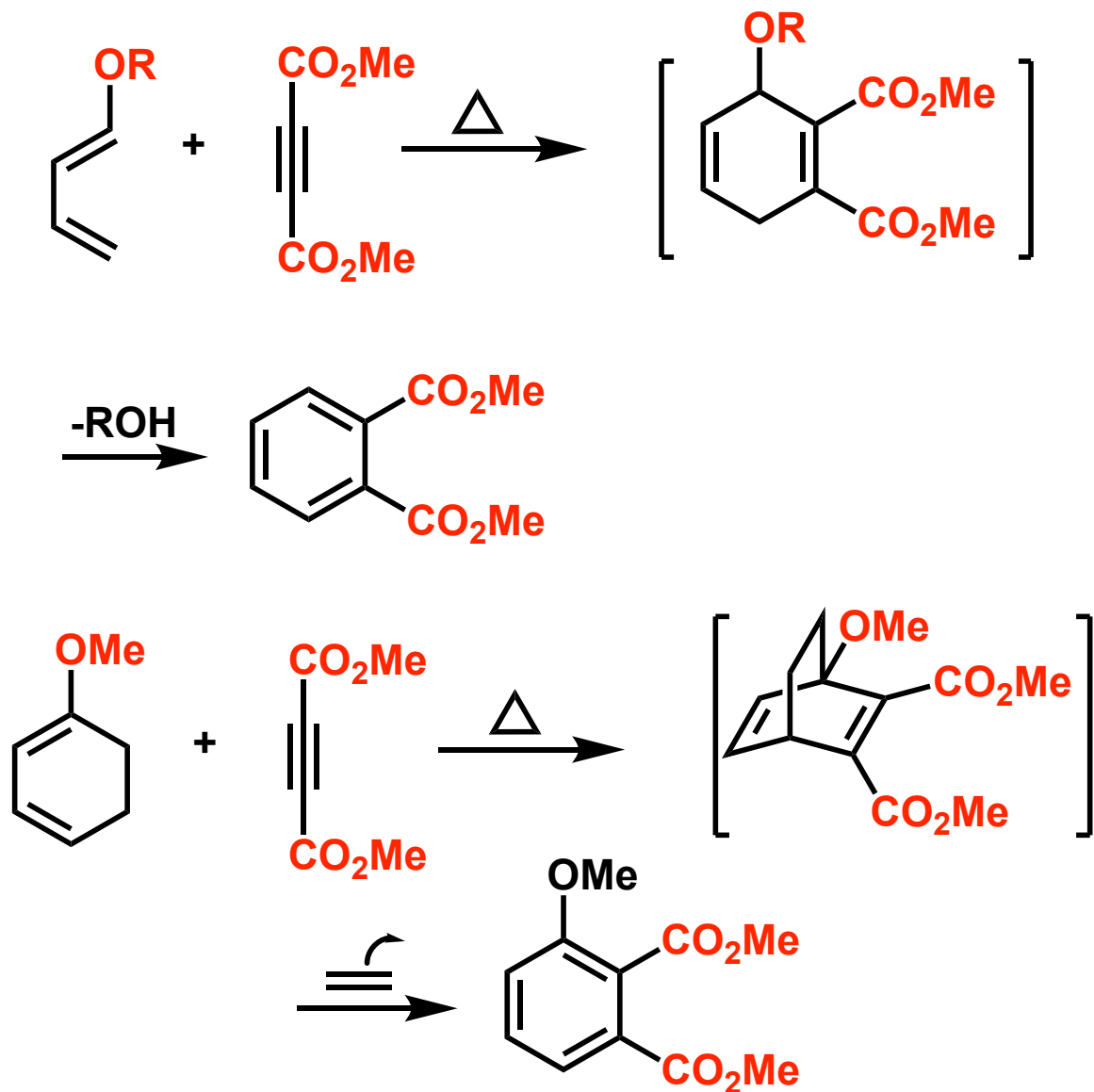
Diene is electron-deficient

Dienophile is electron-rich



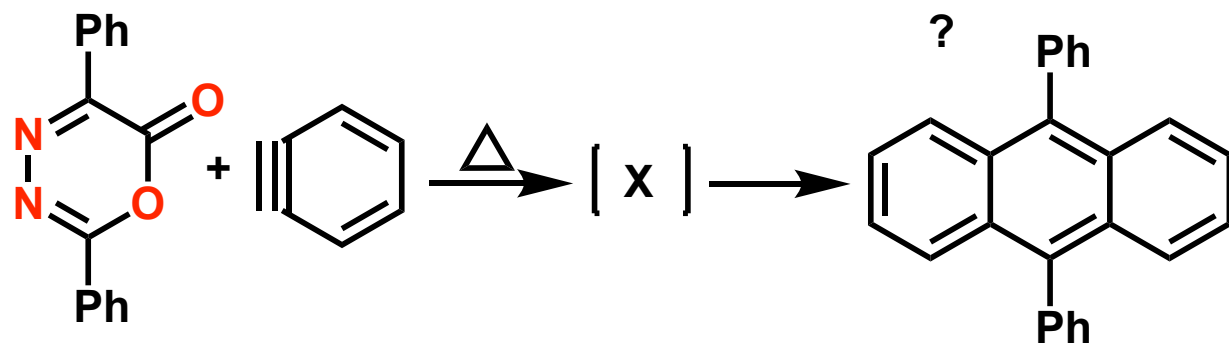
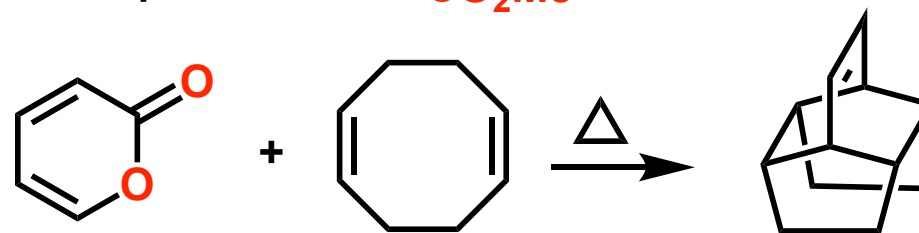
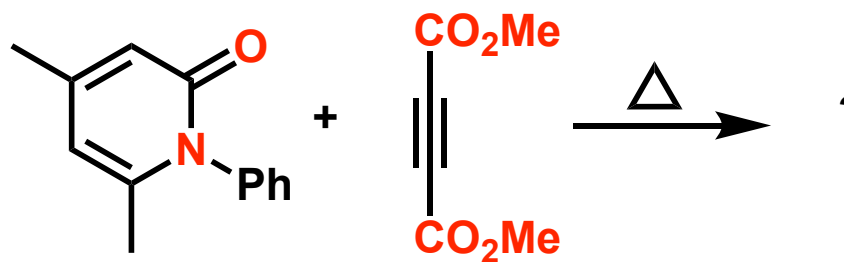
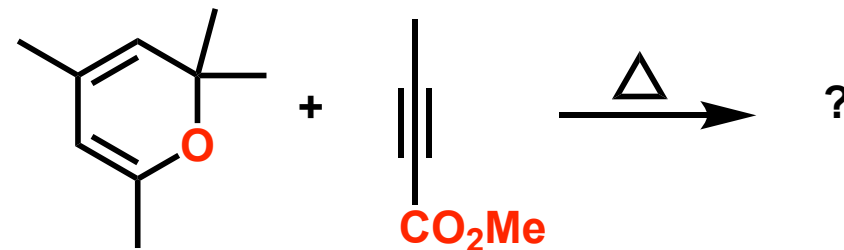
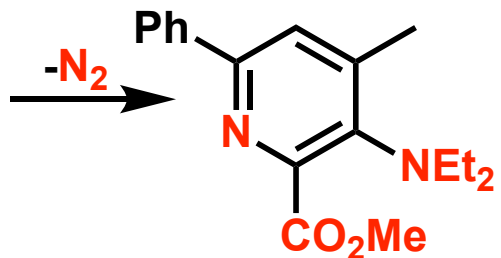
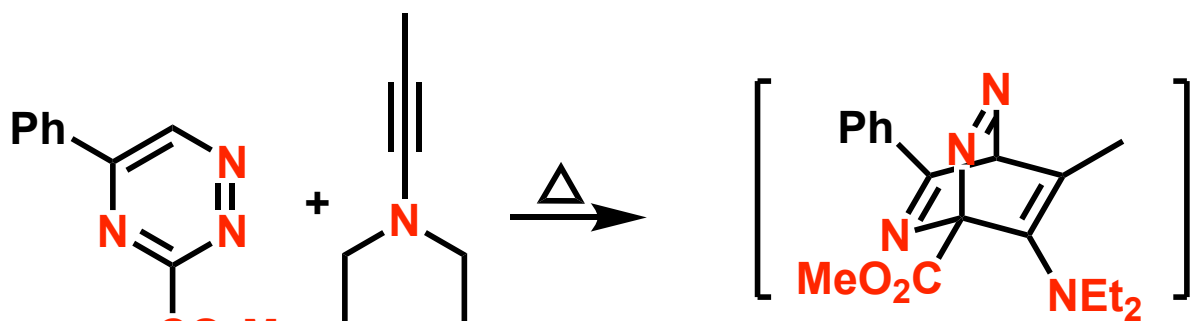
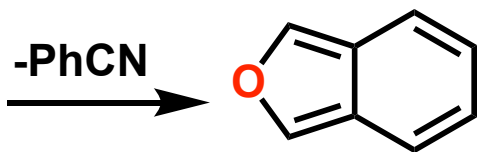
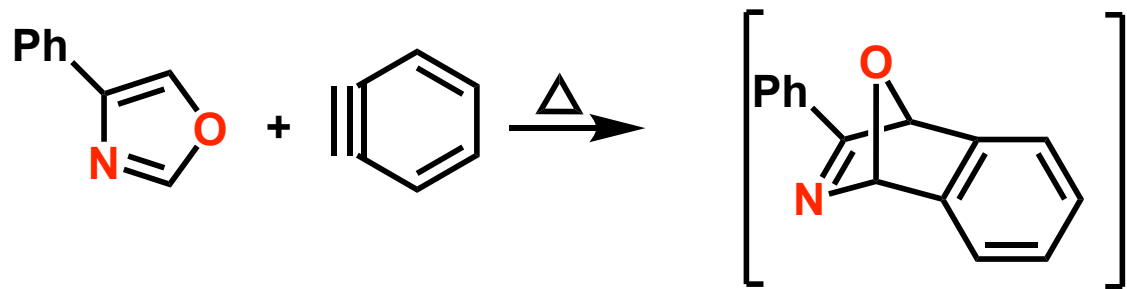


Alder-Rickert & Retro Diels-Alder Reactions





Alder-Rickert & Retro Diels-Alder Reactions

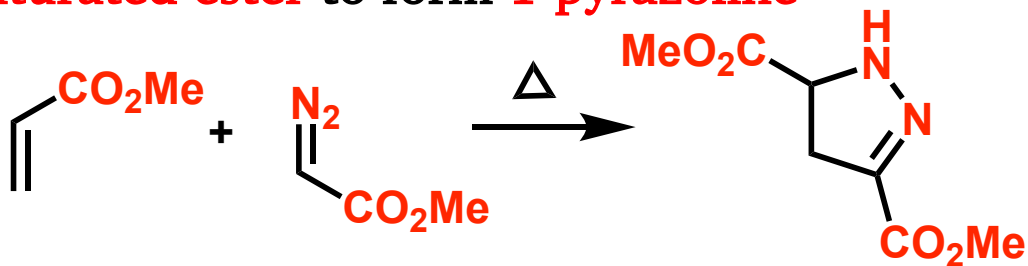




1,3-Dipolar Cycloaddition Reactions

➤ The addition of a **1,3-dipole** to an **alkene (dipolarophile)** is called **1,3-dipolar cycloaddition** reaction and it forms a new **5-membered ring**

➤ In 1888, **Buchner** reported the **first 1,3-dipolar cycloaddition** between **diazoacetic ester** and α,β -unsaturated ester to form **1-pyrazoline**



➤ In 1898, **Beckmann** discovered “**Nitrones**”

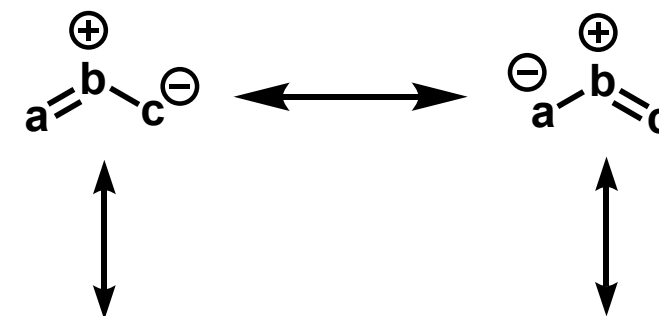
➤ In 1903, **Werner and Buss** discovered “**Nitrile Oxides**”

➤ In 1928, **Diels and Alder** discovered “[**4+2**]-cycloaddition”

➤ 1,3-Dipoles can be divided into **two types** of dipoles:

➤ **1. Allyl anion type**, characterized by “**four electrons in parallel *p* orbitals**” perpendicular to the plane of the dipole and the dipole is ‘**bent**’

Octet Structure



Sextet Structure



➤ **2. Propargyl or allenyl anions type** characterized by an “**extra π orbital**” orthogonal to the allenyl anion MO. The dipole is ‘**linear**’

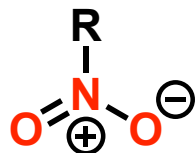




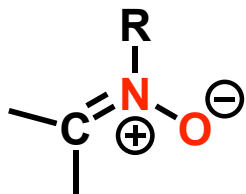
Allyl Anion Dipoles

➤ **Nitrogen** in the middle

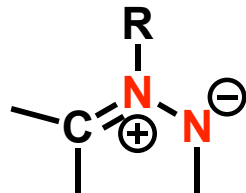
Nitro



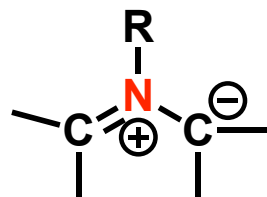
Nitrones



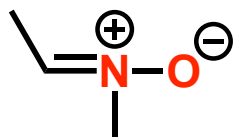
Azomethine Imines



Azomethine Ylides

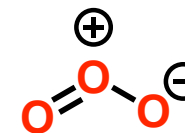


Azoxy compounds

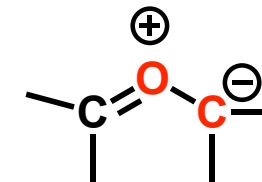


➤ **Oxygen** in the middle

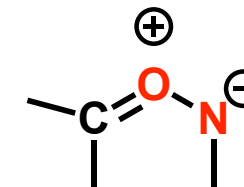
Ozone



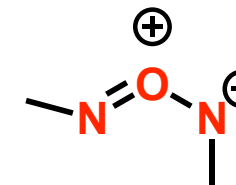
Carbonyl Ylides



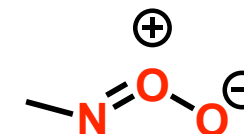
Carbonyl Imines



Nitrosimines



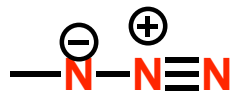
Nitrosoxides





Propargyl/Allyl Anion Dipoles

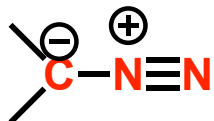
Azides



Nitrous Oxide



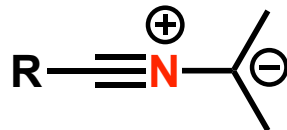
Diazoalkanes



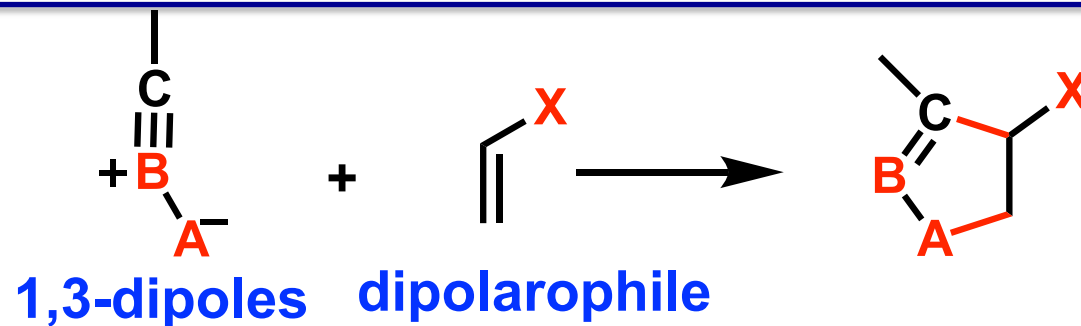
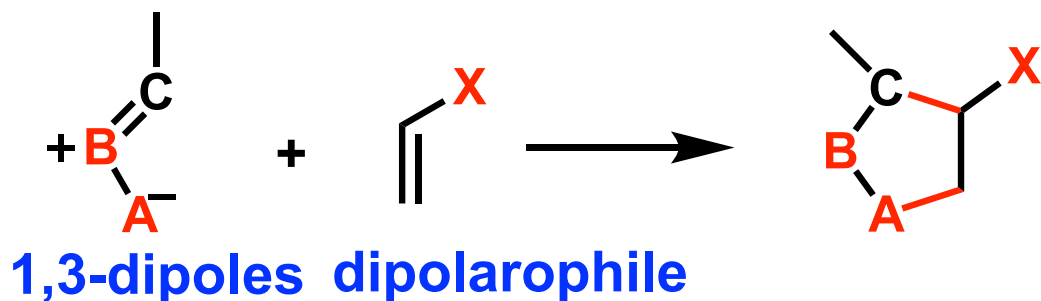
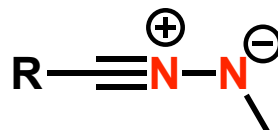
Nitrile Oxide



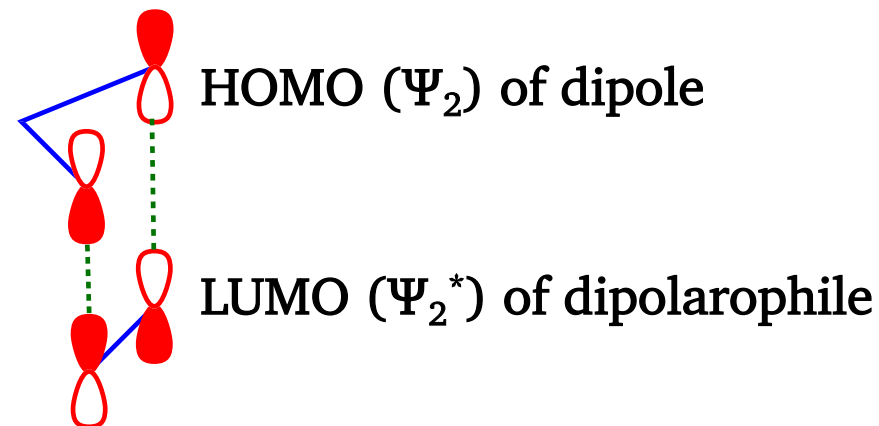
Nitrile Ylides



Nitrile Imines



4- π electrons from 1,3-dipole and two electrons from dipolarophile



Reactants approach each another in parallel planes to permit interaction between the **HOMO** and **LUMO** orbitals



Classification of 1,3-Dipolar Cycloaddition

Type I 1,3-Dipolar Cycloaddition

-HOMO of the **dipole** interacts with **LUMO** of the dipolarophile

Type II 1,3-Dipolar Cycloaddition

-FMO energies of the **dipole** and **dipolarophile** are of same level and so, **HOMO** and **LUMO** of both dipole and dipolarophile interacts

Type III 1,3-Dipolar Cycloaddition

-**LUMO** of the **dipole** interacts with **HOMO** of the dipolarophile

Type I 1,3-Dipolar Cycloaddition

-**Azomethine ylides** and **azomethineimines** are known to follow type I

Type II 1,3-Dipolar Cycloaddition

-**Nitrones** and Nitrile oxides follow type II

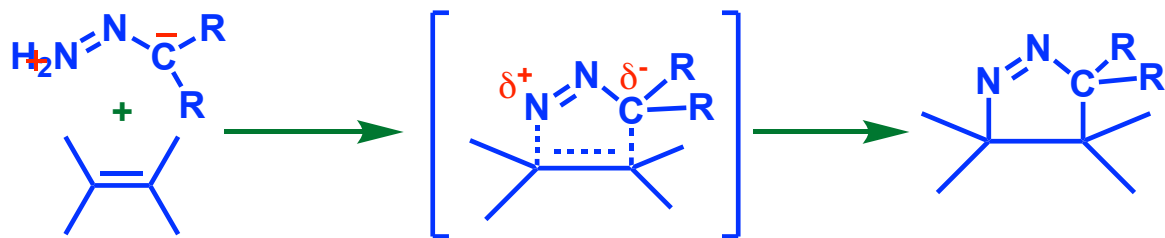
Type III 1,3-Dipolar Cycloaddition

-**Ozone** and **Nitrous oxide** follow type III

-Presence of Lewis acid can significantly alter the energy of orbitals of both the **dipole** and **dipolarophile**



Regioselectivity and Stereoselectivity

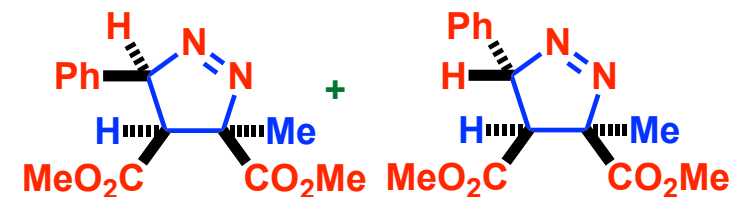
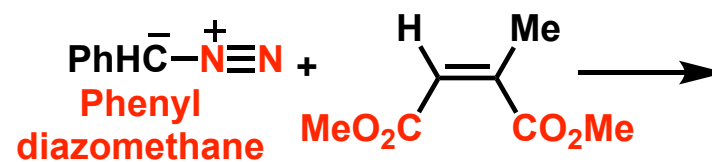
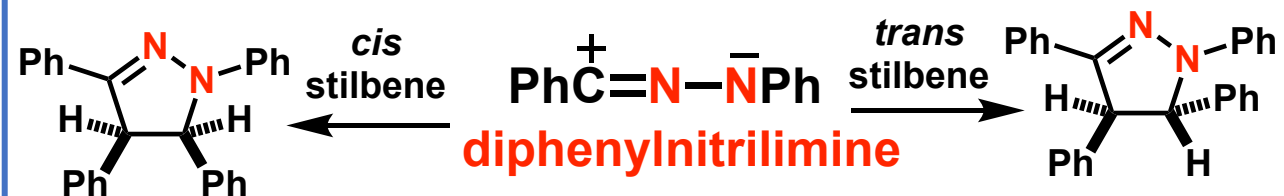


Transition state is not very polar

Not strongly affected by solvent polarity

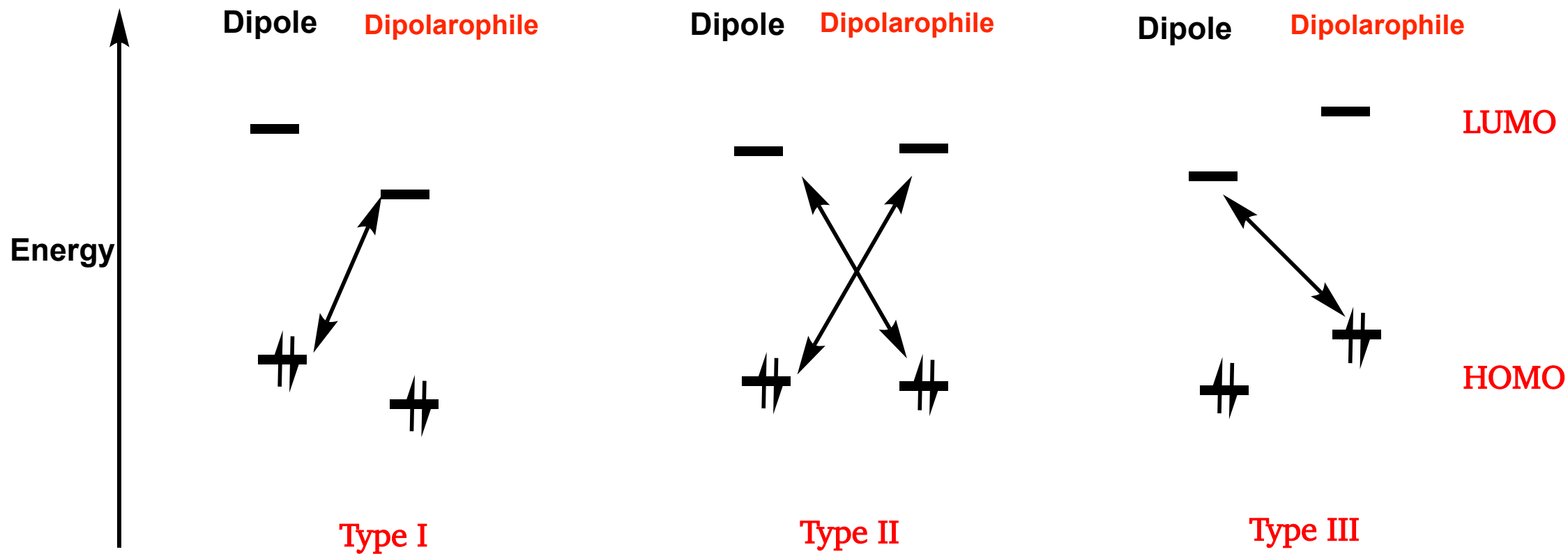
In most cases, reaction is a concerted $[4\pi_s + 2\pi_s]$ cycloaddition

Syn addition with respect to dipolorophile



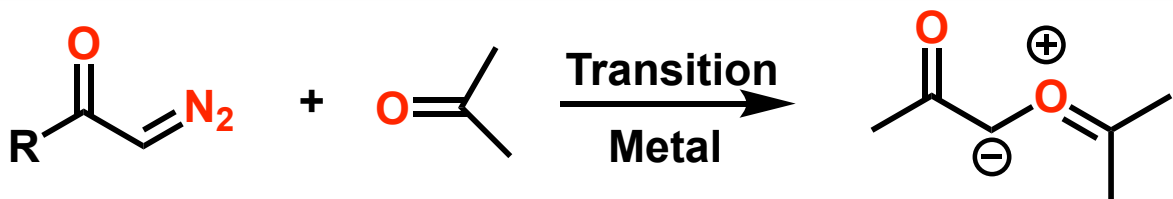


Classification of 1,3-Dipolar Cycloaddition

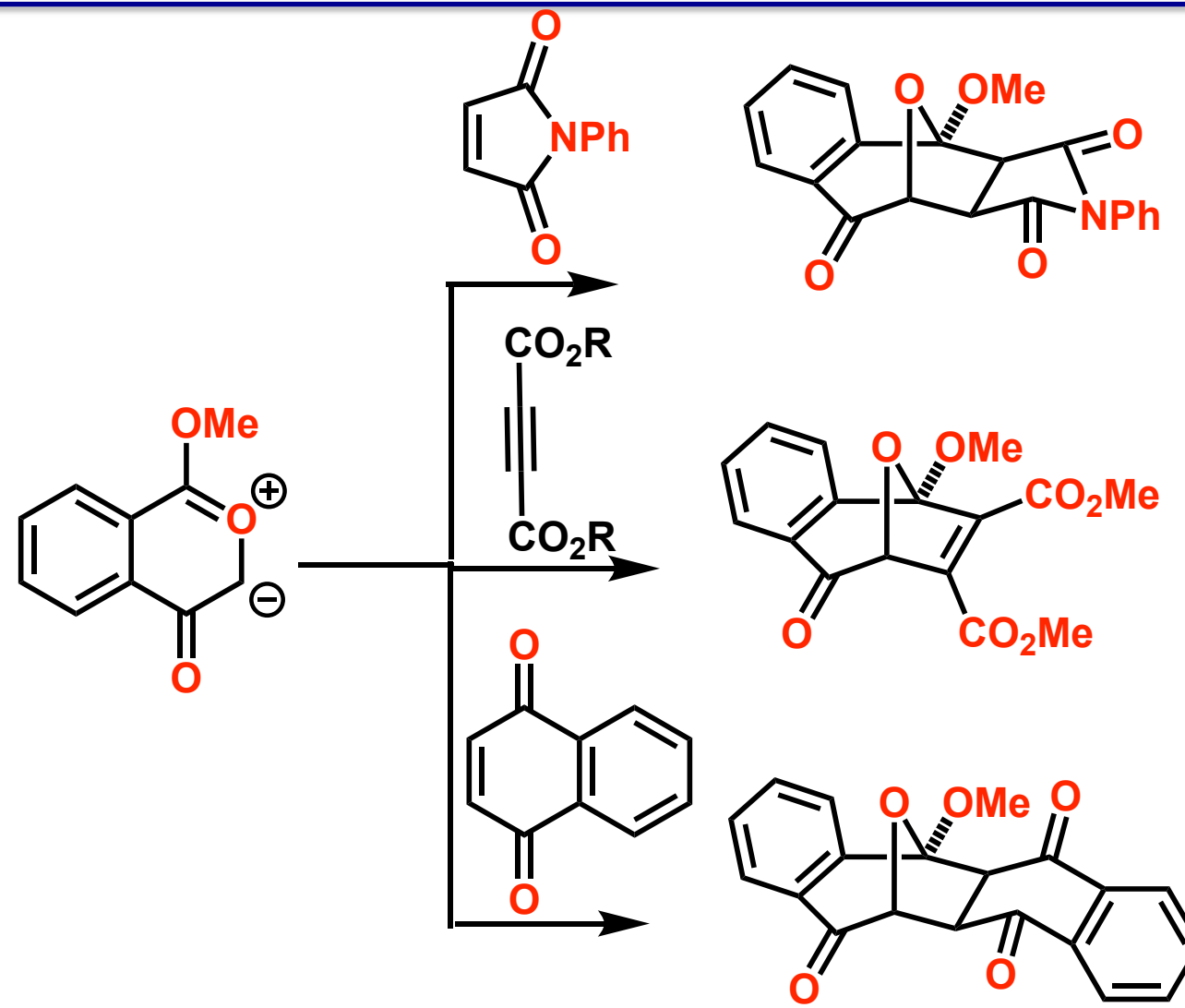
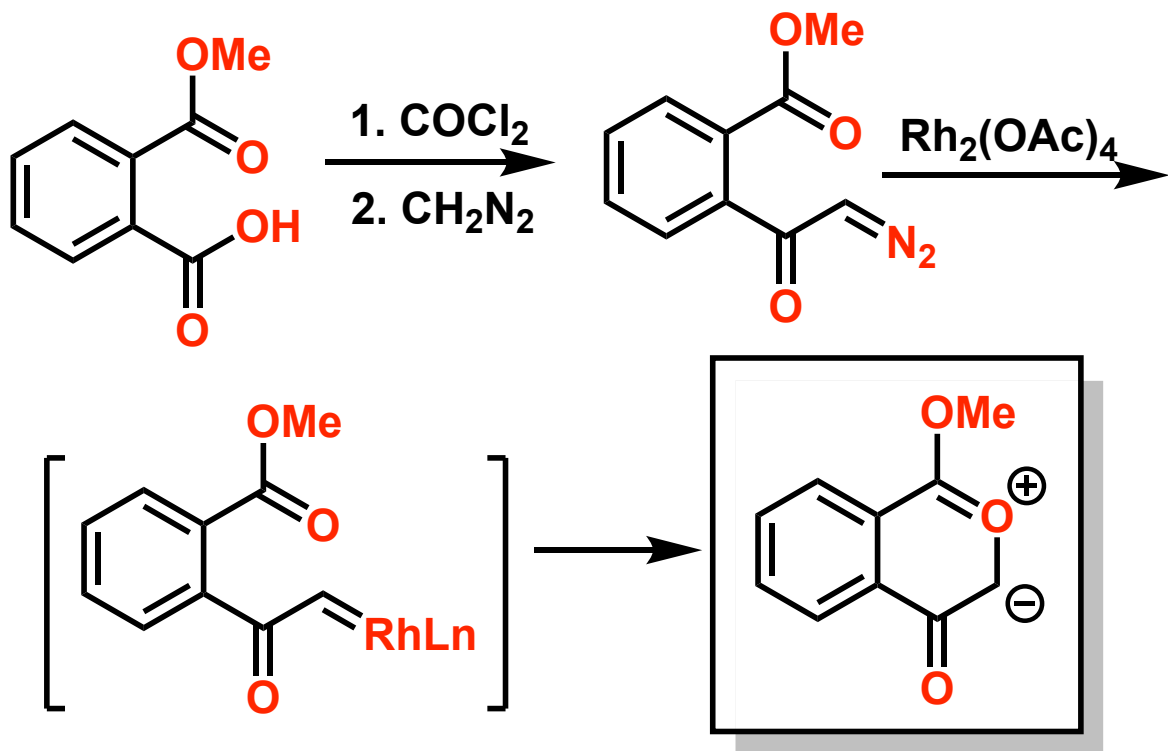




Carbonyl Ylides in 1,3-Dipolar Cycloaddition



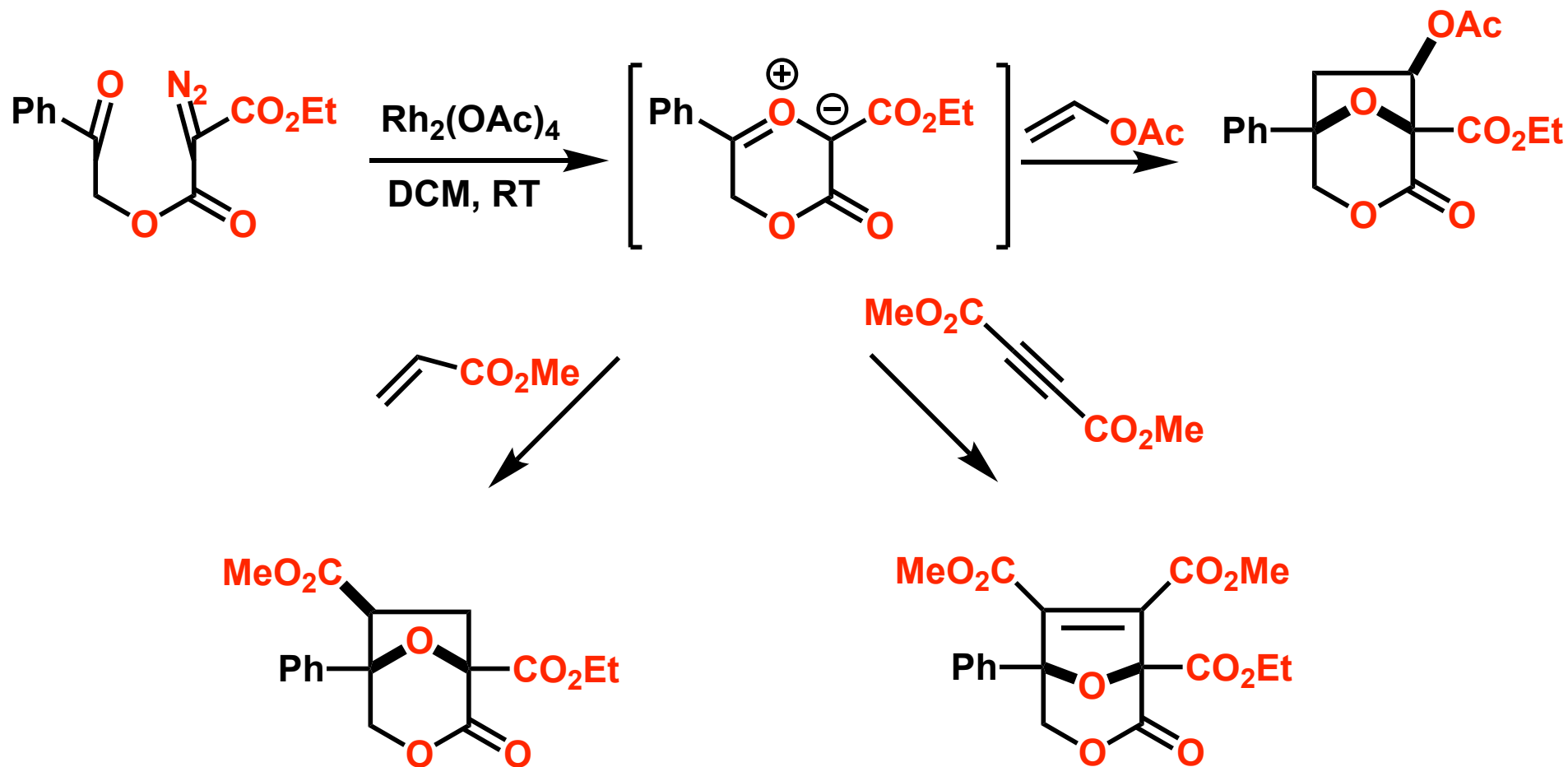
Commonly used metals are: **Rhodium** and **Copper**



Exo products

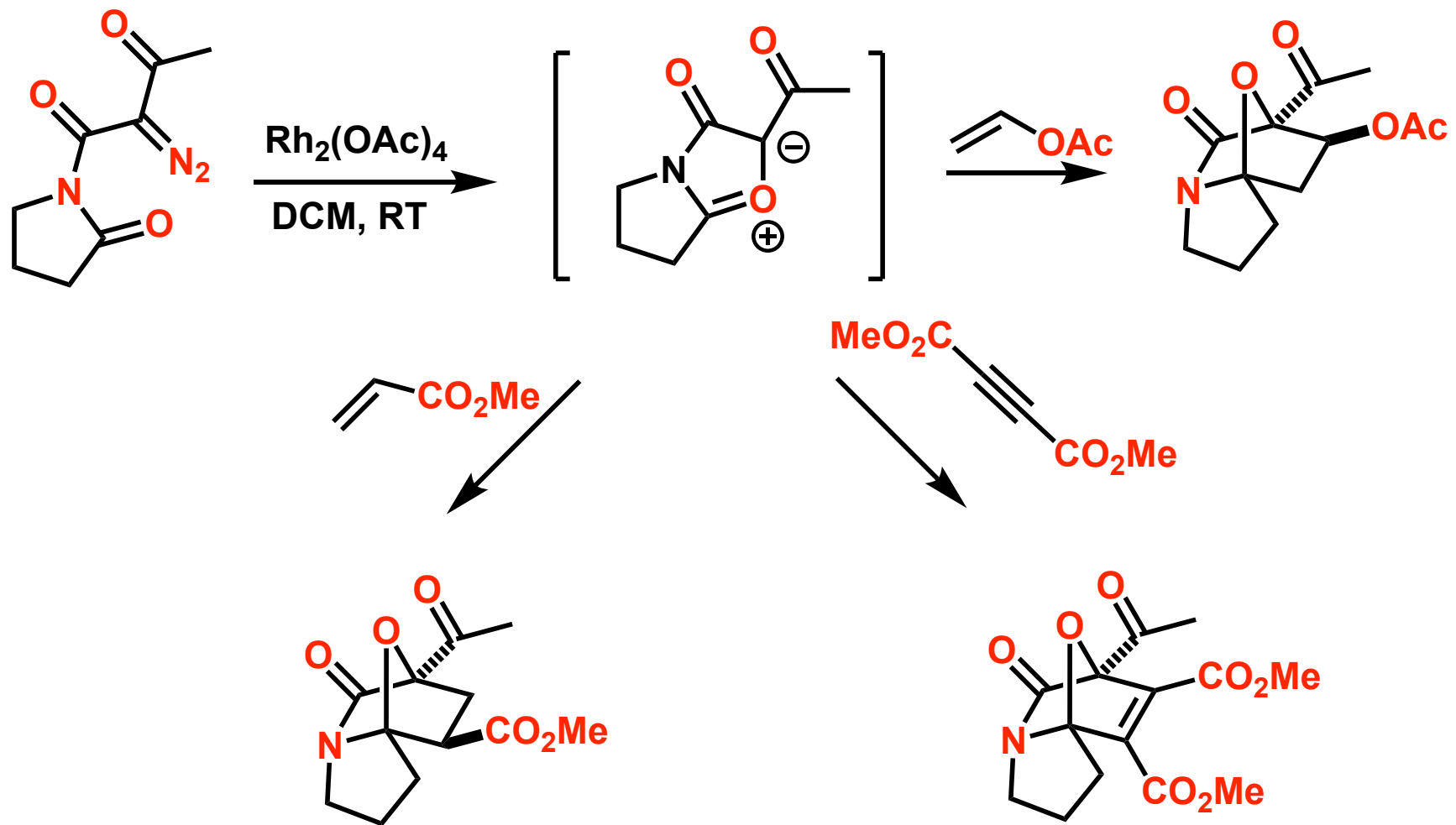


Carbonyl Ylides in 1,3-Dipolar Cycloaddition



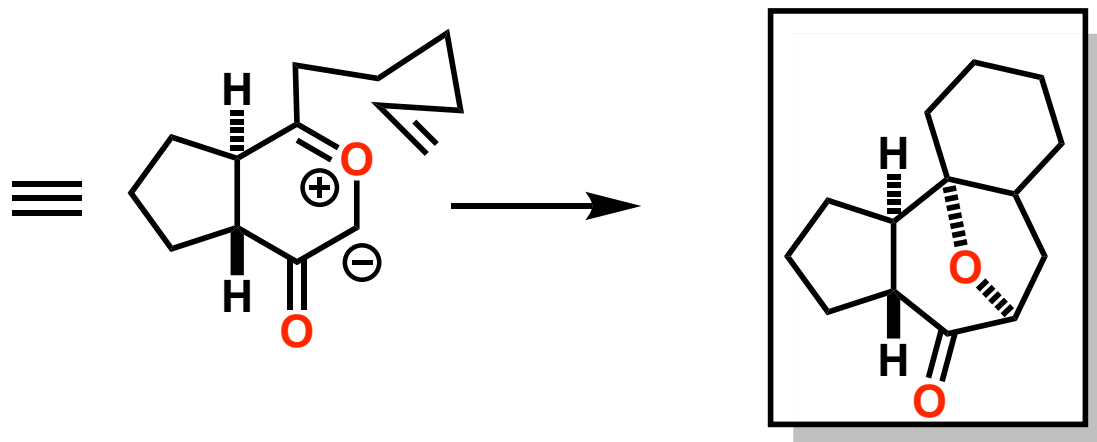
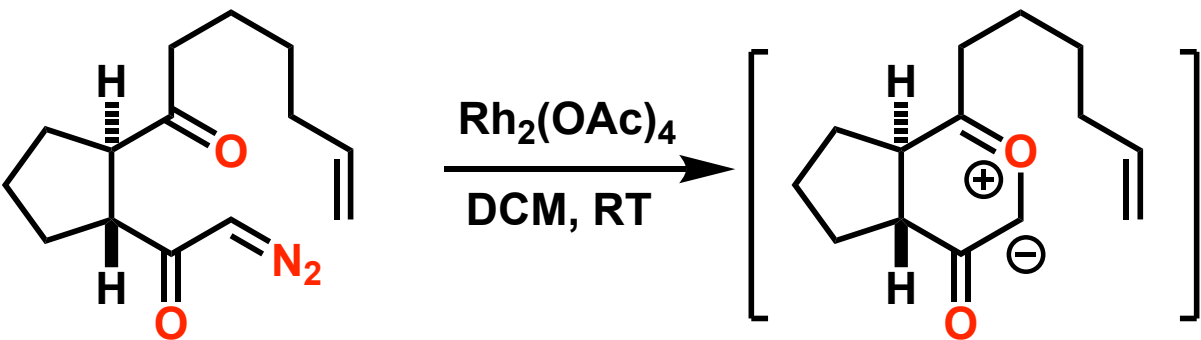


Carbonyl Ylides in 1,3-Dipolar Cycloaddition

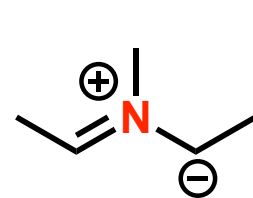




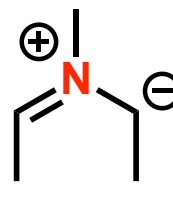
Carbonyl Ylides & Azomethine Ylides



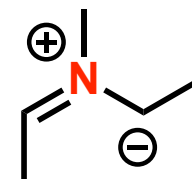
Azomethine Ylides



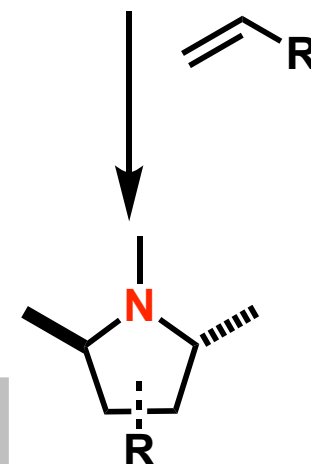
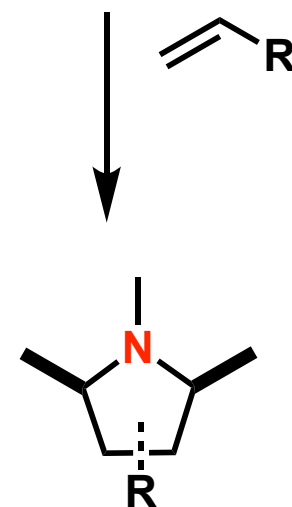
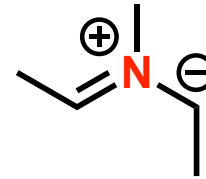
W-Shaped Ylide



U-Shaped Ylide



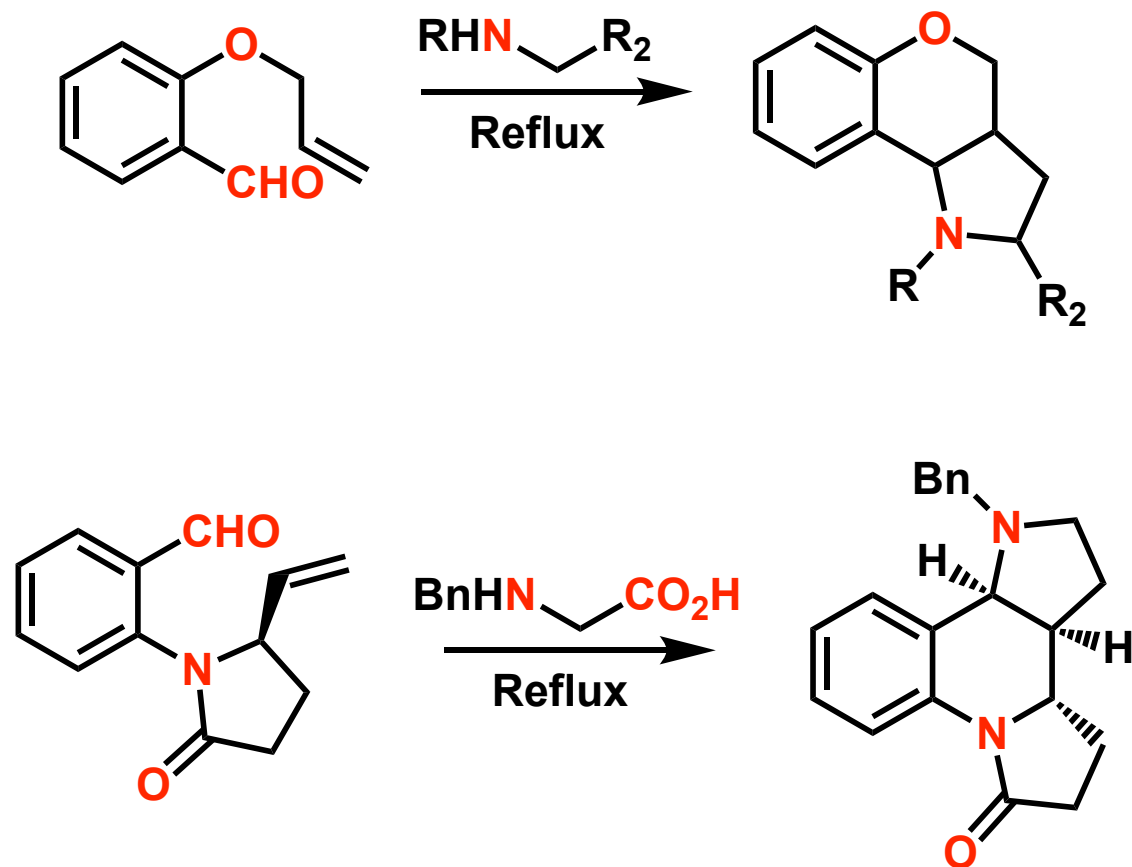
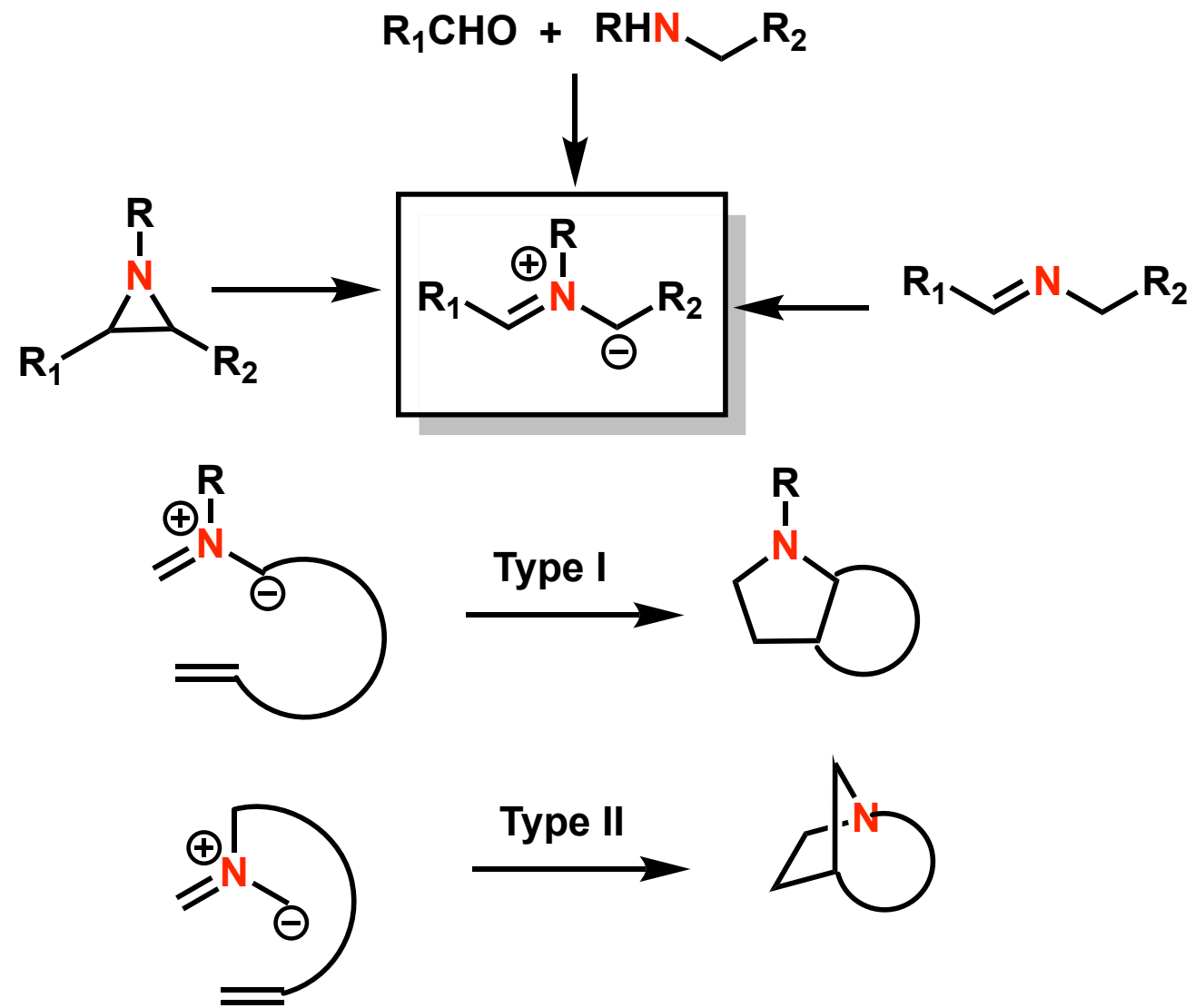
S-Shaped Ylides



Preference for S-Shaped Ylides



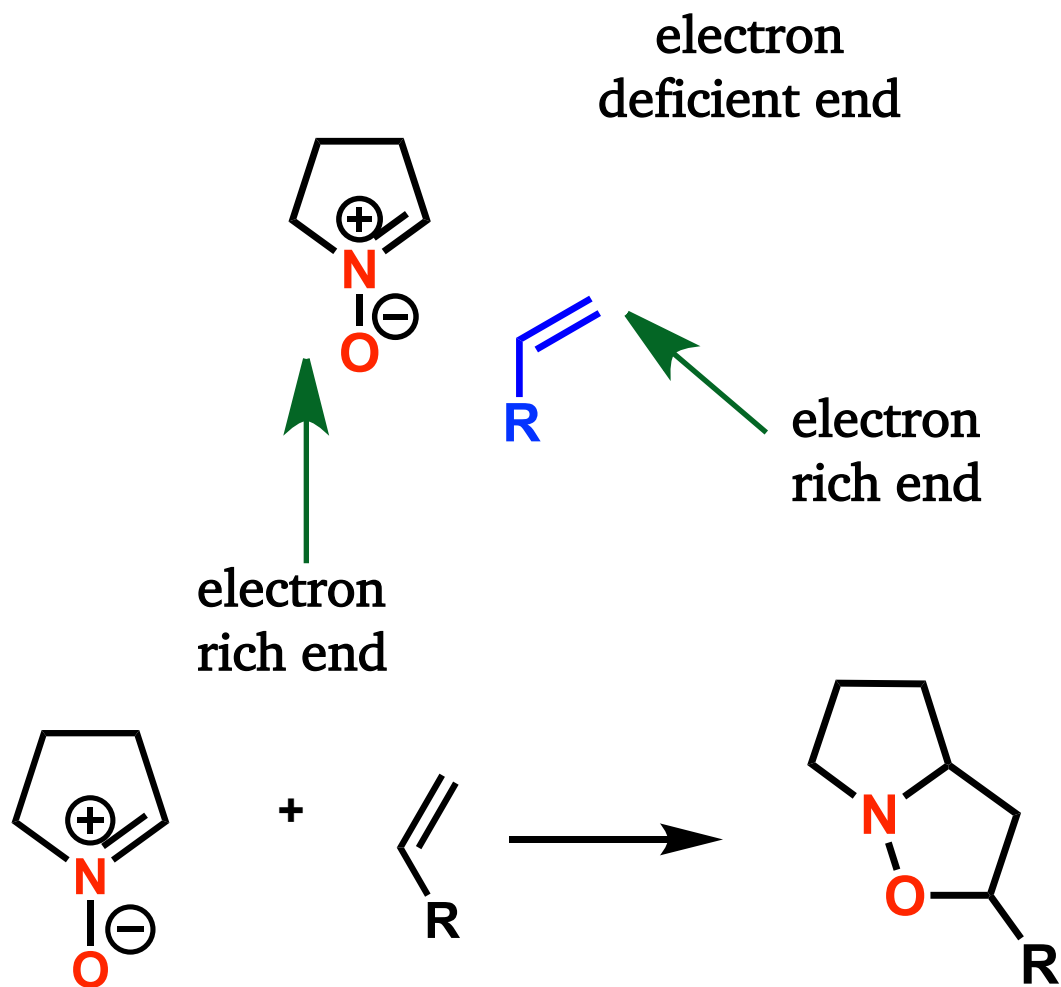
Azomethine Ylides



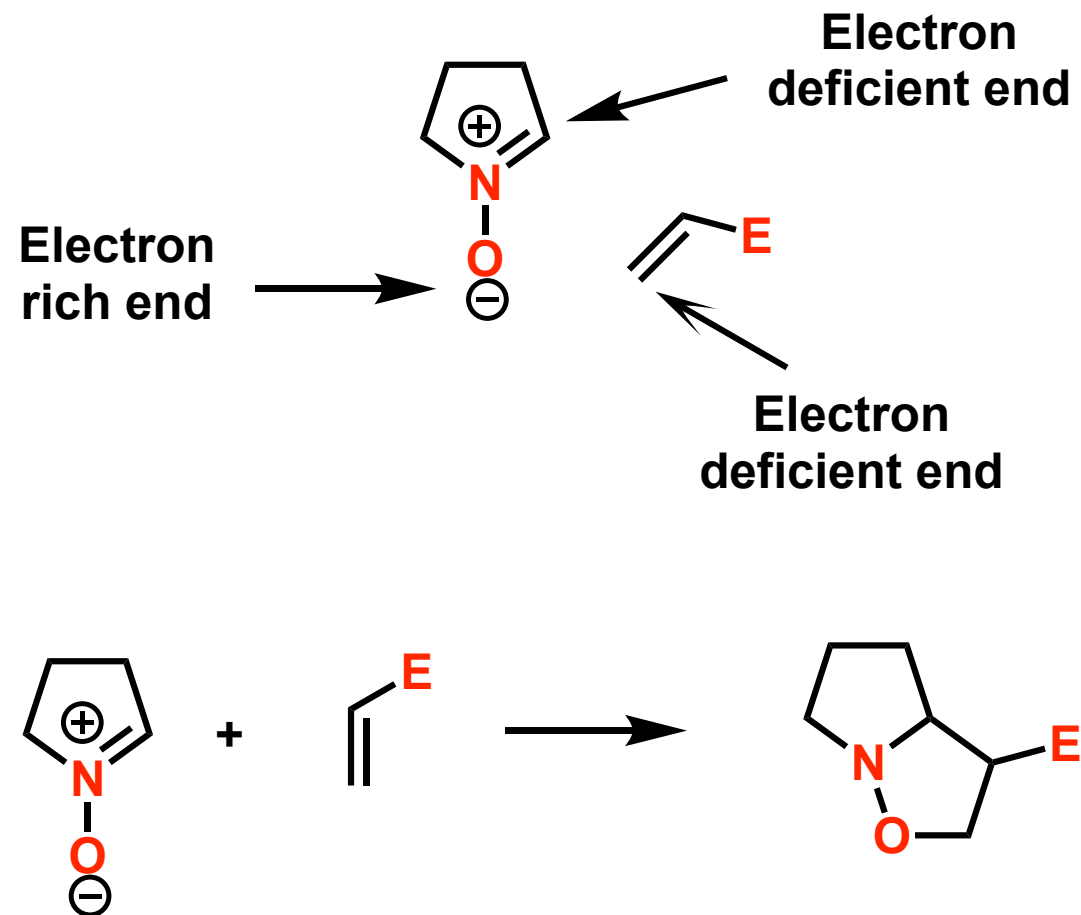


Nitrones

Regiochemistry of 1,3 dipolar cycloaddition with electron rich dipolorophiles



Regiochemistry of 1,3 dipolar cycloaddition with electron deficient dipolorophiles





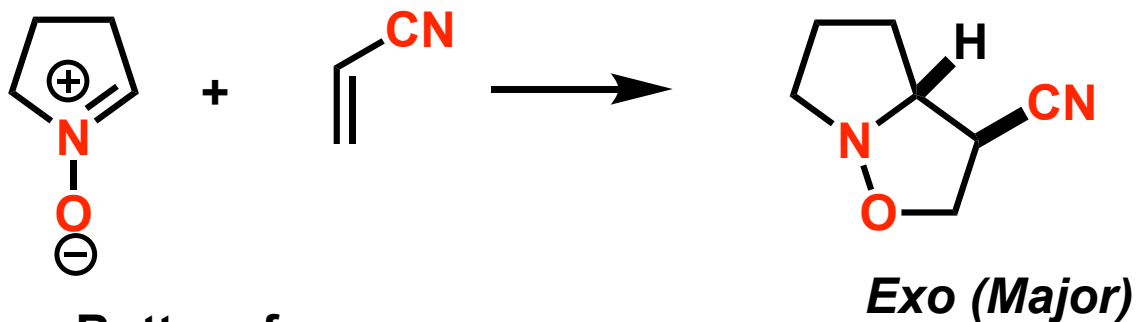
Exo/Endo

Secondary orbital interaction is very small

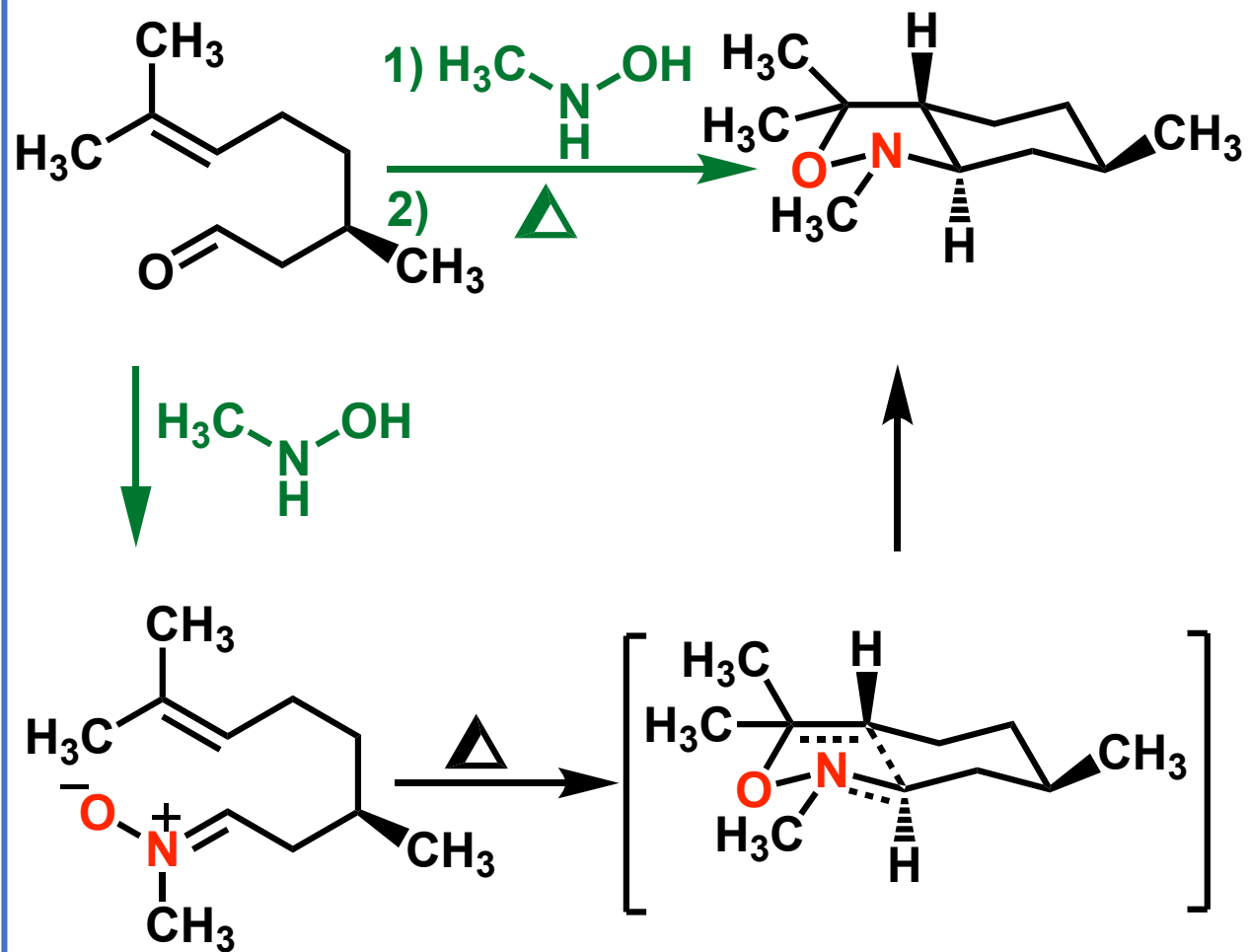
Stabilization due to secondary orbital interaction is minimal

So, mostly *endo/exo* ratio is controlled by structure of the **substrate** or **catalyst**.

Sterically less hindered substrates give mostly **exo** products.

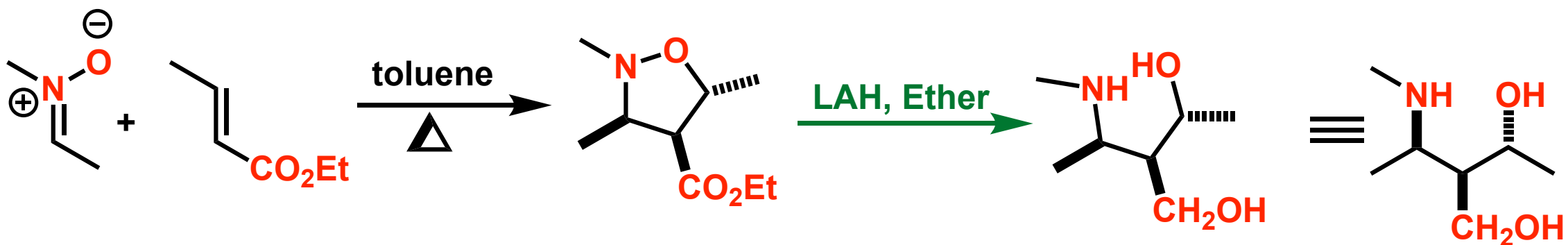
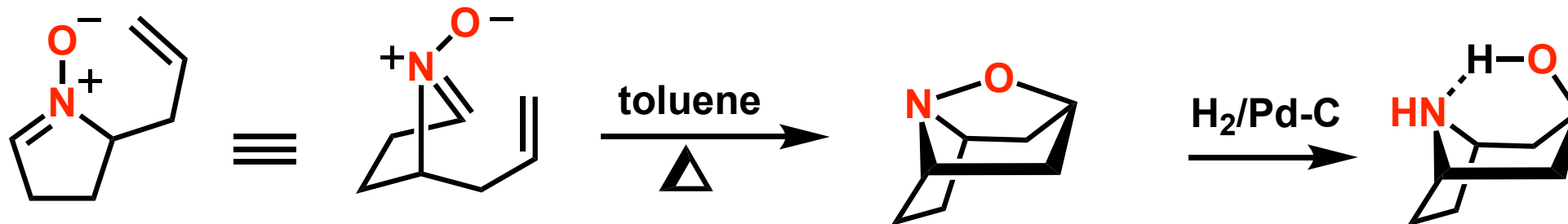


Bottom face approach of the dipolarophile



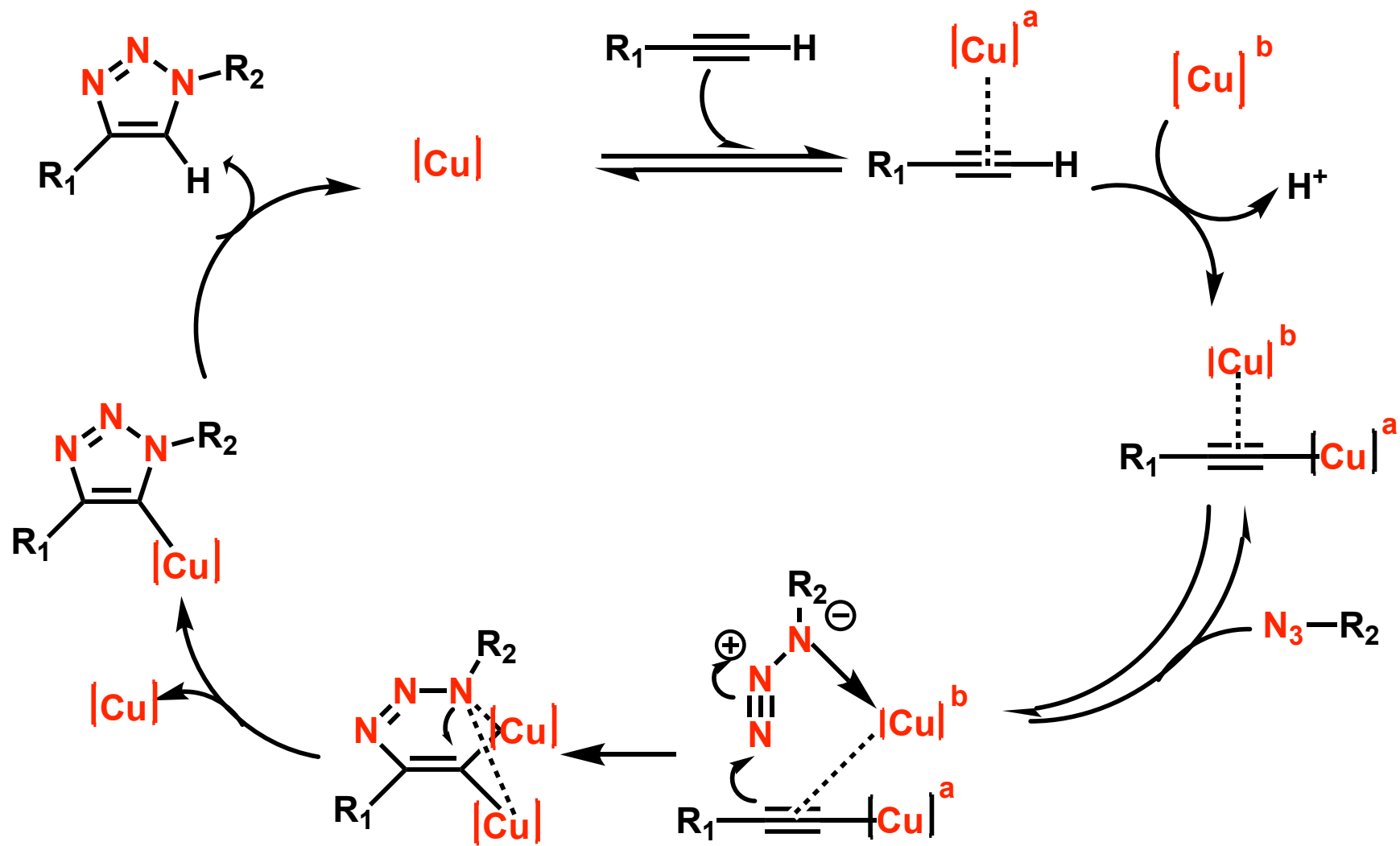


Examples



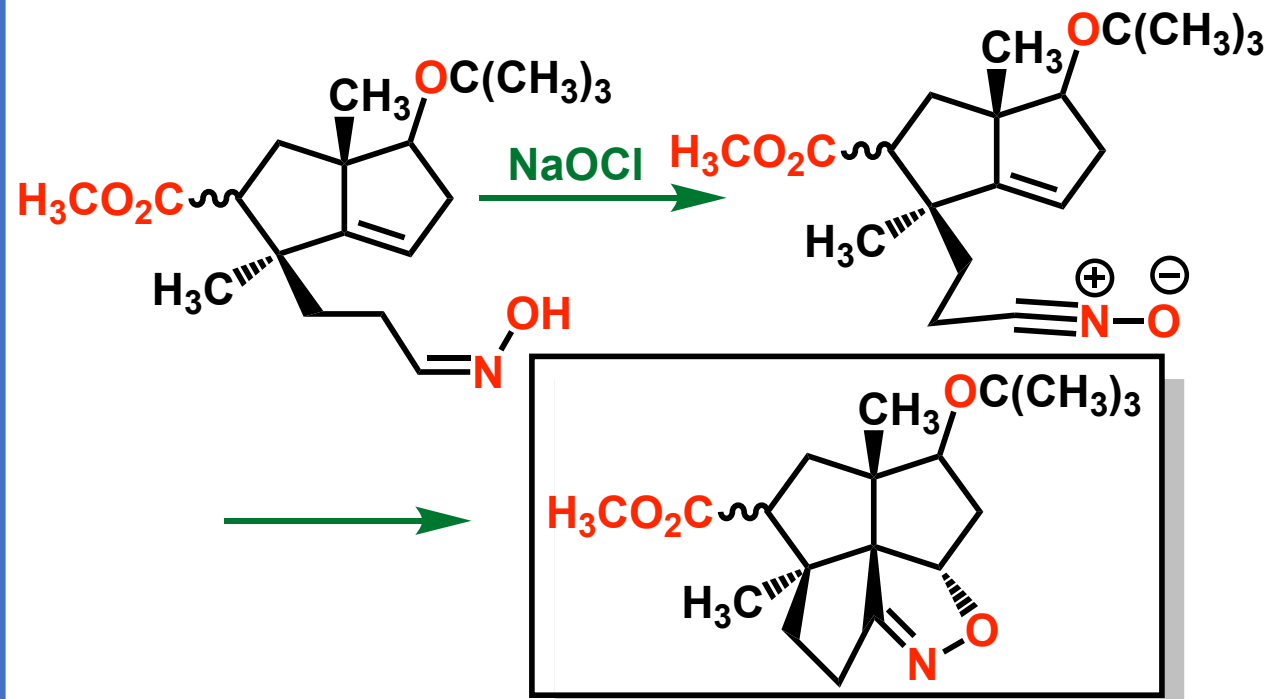
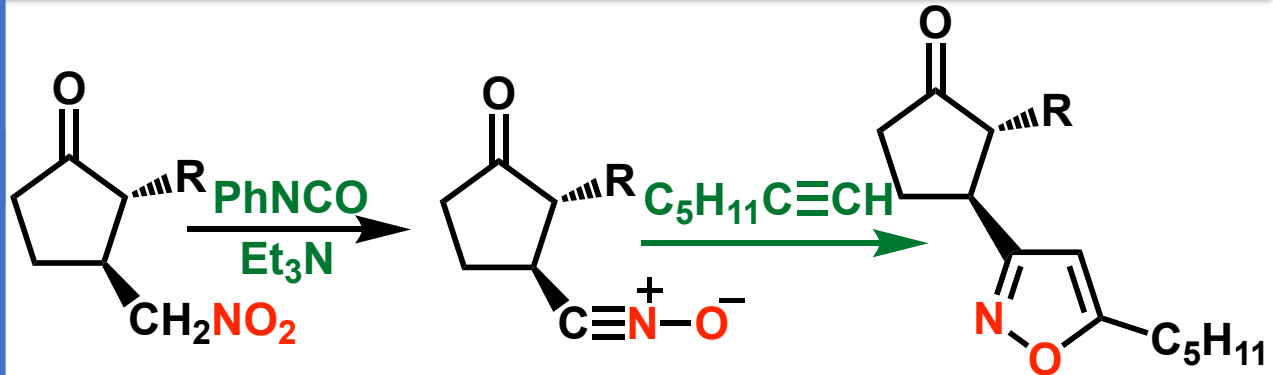
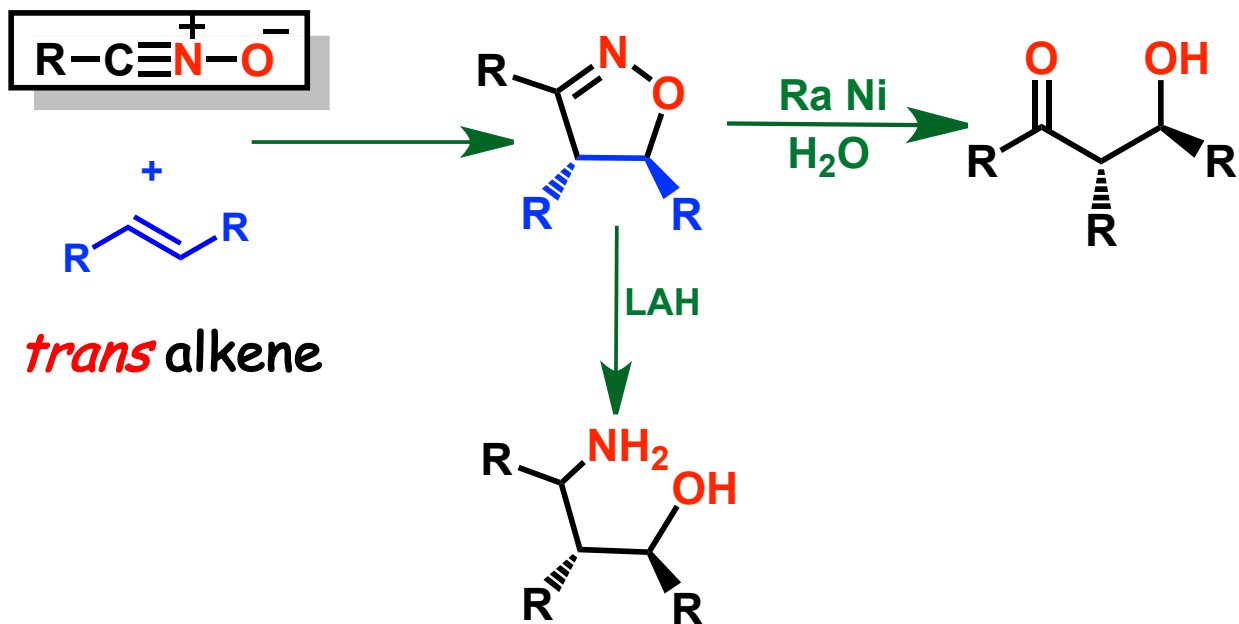
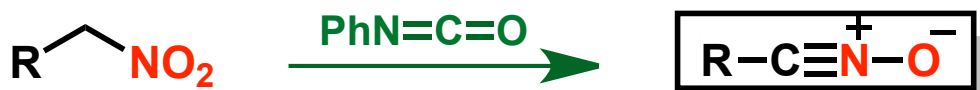
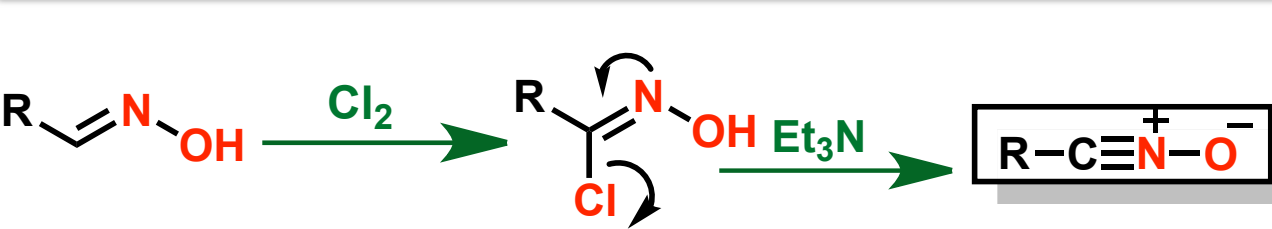


Mechanism for Click Reaction





Nitrile Oxides





Brief History of Photochemistry

Historical Perspective

Light induced reactions are older than life itself

Sunlight induced photochemistry would have started long ago

Billions of years ago, early earth was without oxygen like other planets

Plant life produced oxygen with the help of sunlight

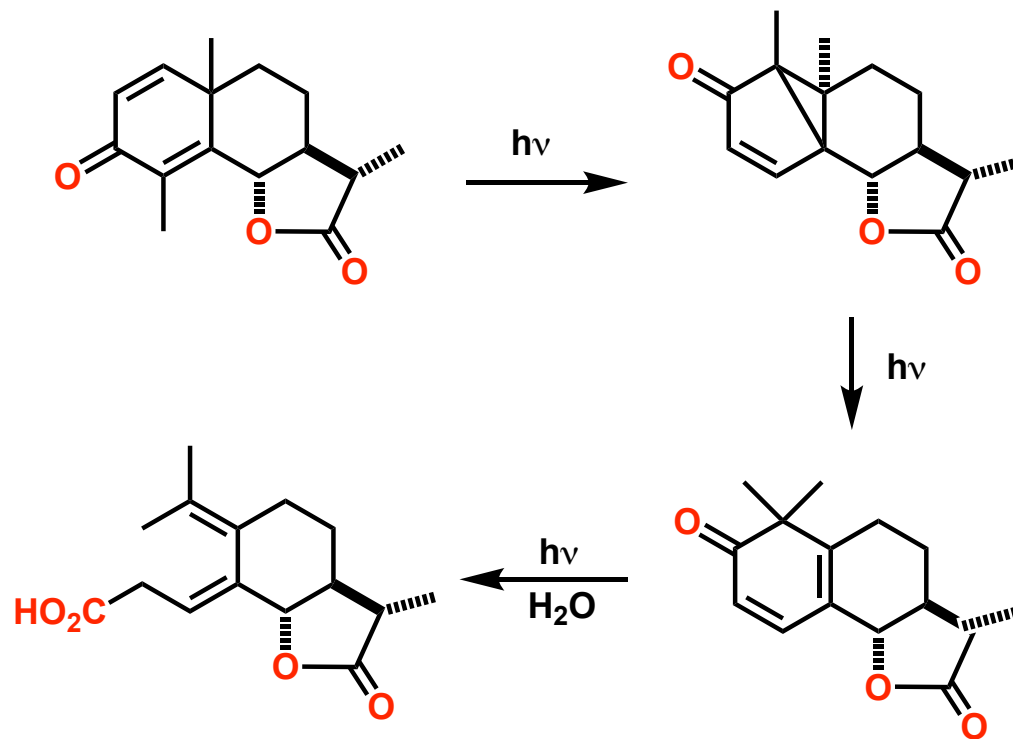
Photolysis of oxygen produced the protecting ozone layer

Alexander the Great used photochromic dyes in his army

Archimides' mirrors used sunlight to burn even ships

Priestley used sunlight to oxidize mercury to mercuric oxide (oxidation)

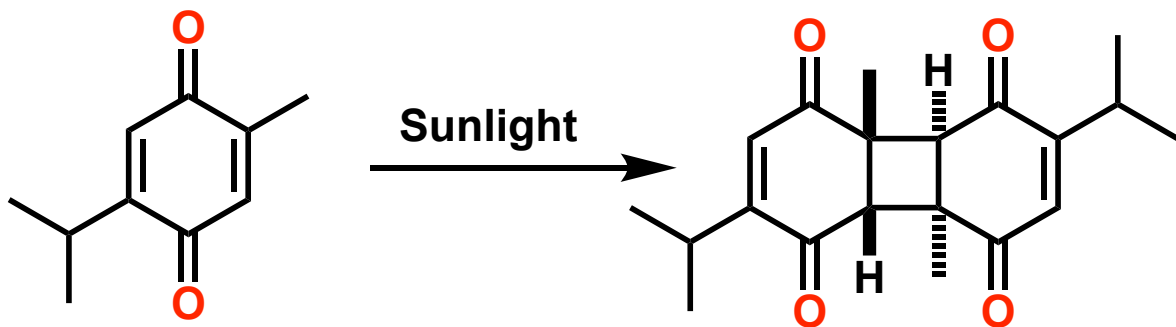
Trommstorf in 1834 observed curious conversion of **Santonin** to some other organic compound upon exposure to sunlight





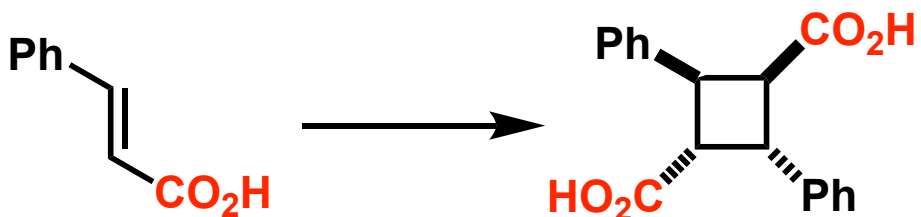
[2+2] Photocycloaddition

Historical Perspective



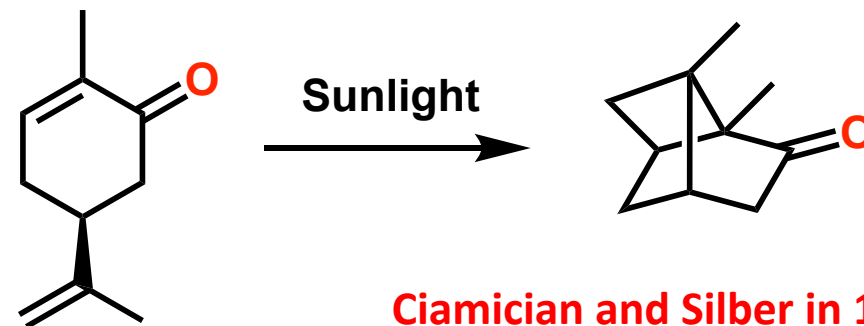
Thymoquinone

Liebermann in 1877

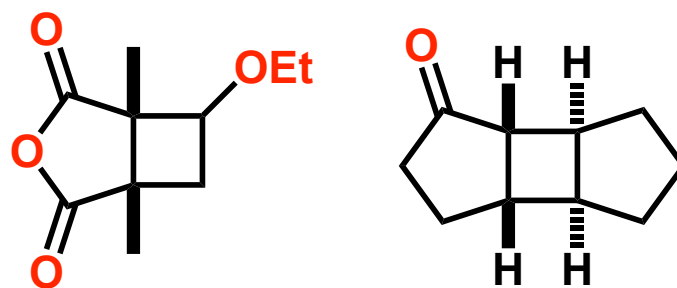


Truxillic Acid

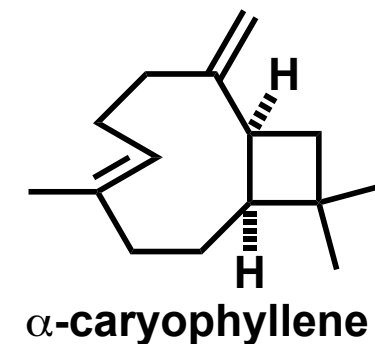
First Intramolecular [2+2] photocycloaddition



Ciamician and Silber in 1904



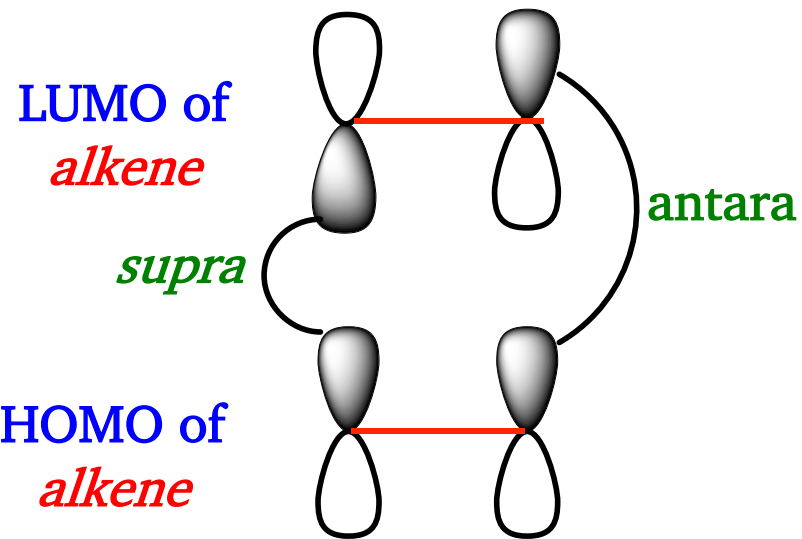
Use of one alkene excess



Use of enones

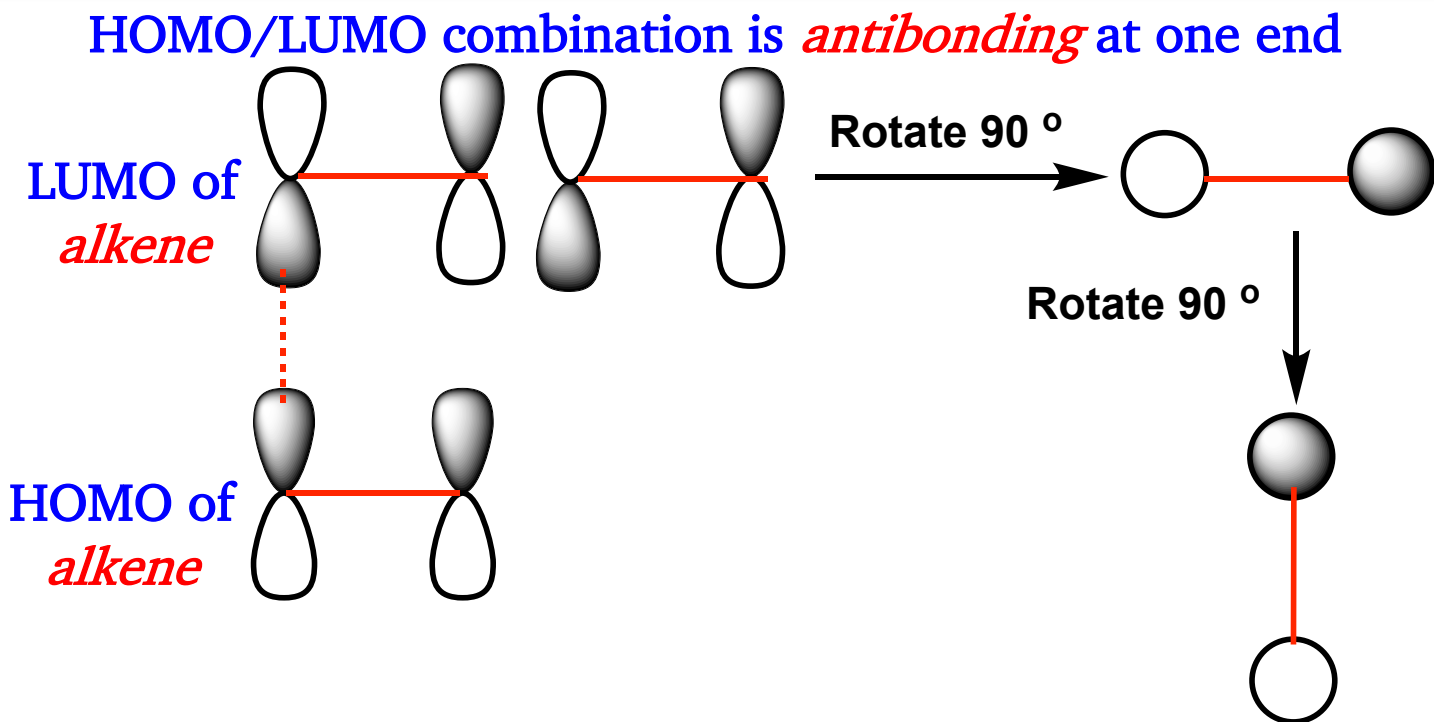


Thermal [2+2] Cycloaddition

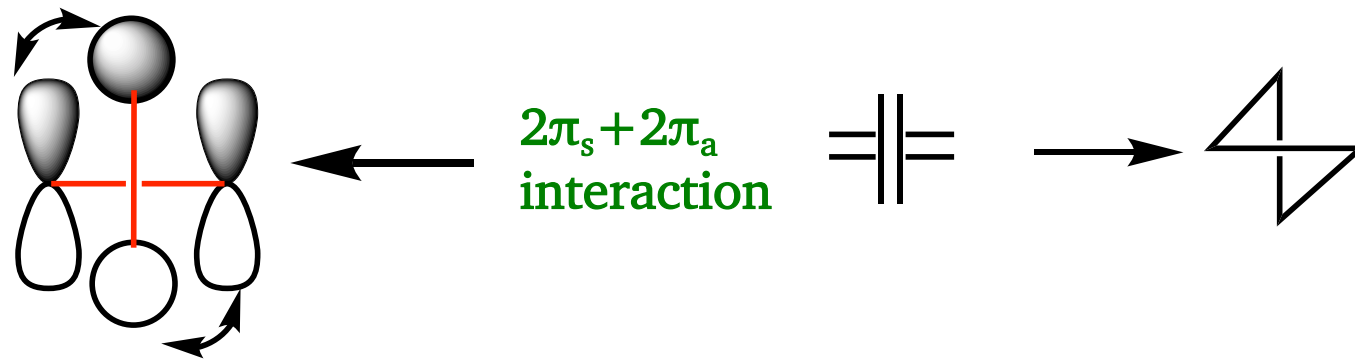


$2\pi_s + 2\pi_a$
interaction

HOMO/LUMO combination is *bonding*
at one end and *antibonding* at the other end



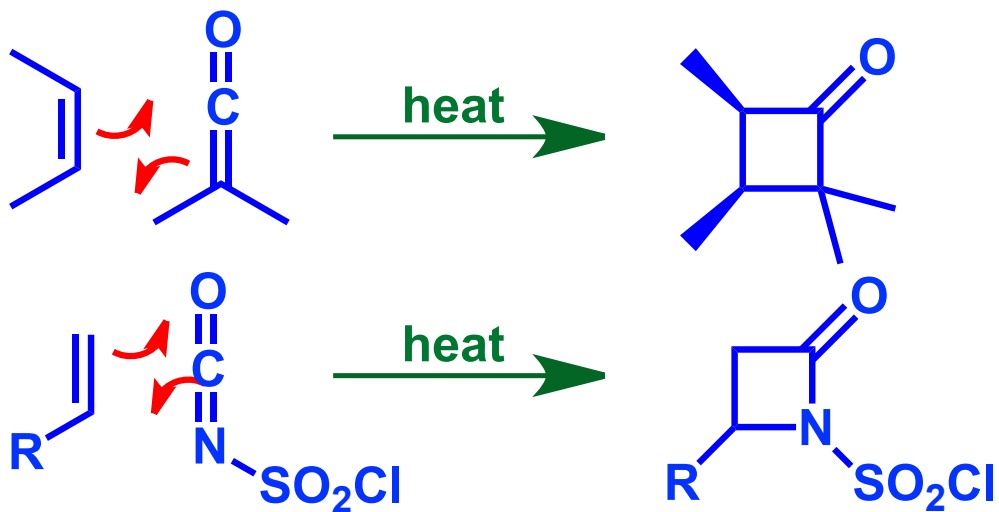
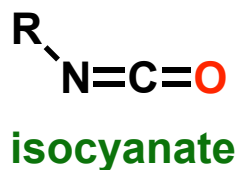
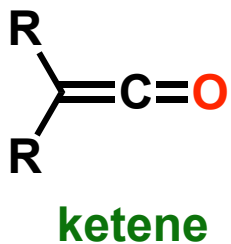
If HOMO & LUMO approaches perpendicular to each other





Thermal [2+2] Cycloaddition

It must have two double bonds at same carbon atom

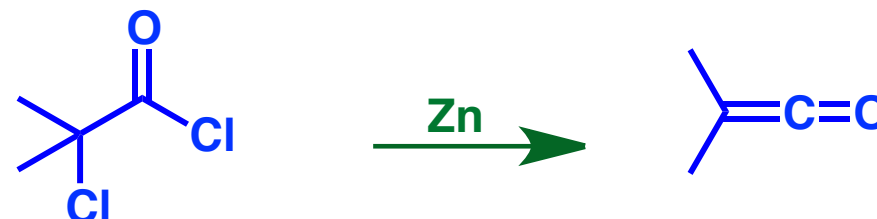
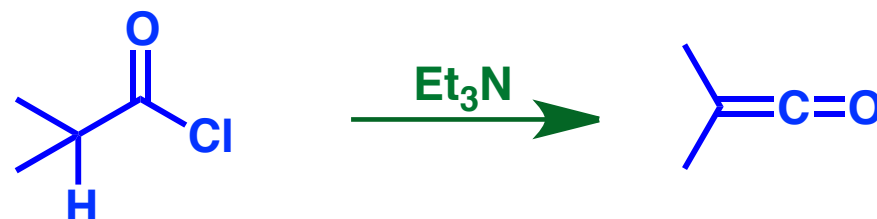
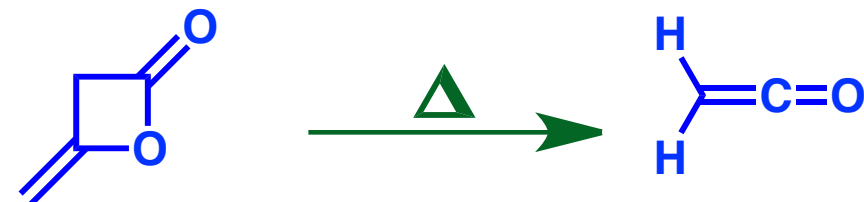


Ketenes

Central atom is **sp carbon** atom with **extra π bond**

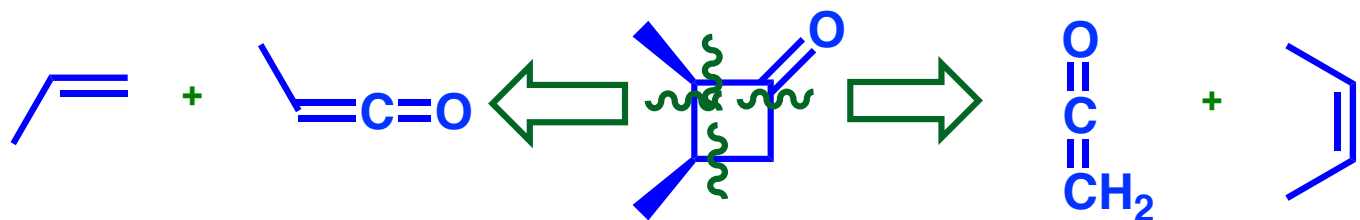
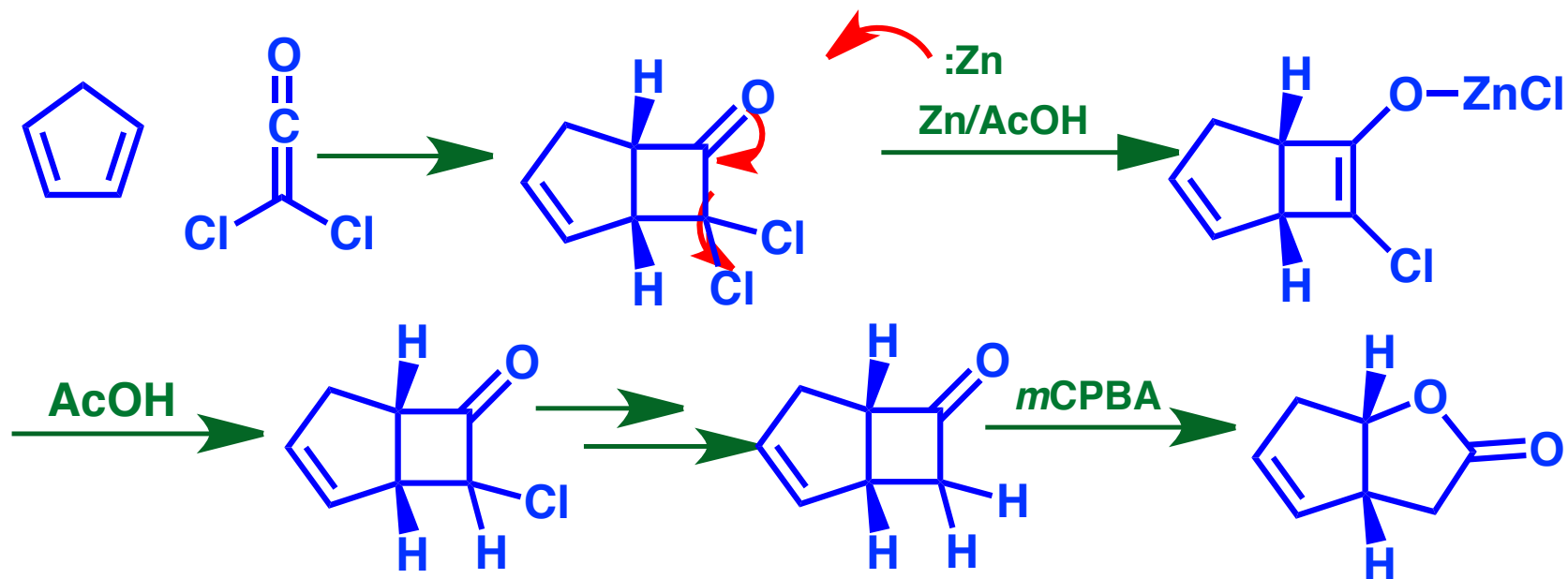
Electrophilic, low-energy LUMO

Preparation of Ketenes:





Thermal [2+2] Cycloaddition of Ketenes



Stereochemistry
can be controlled



[2+2] Photocycloaddition

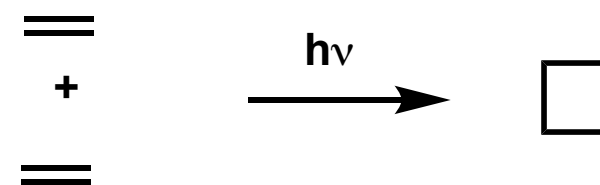
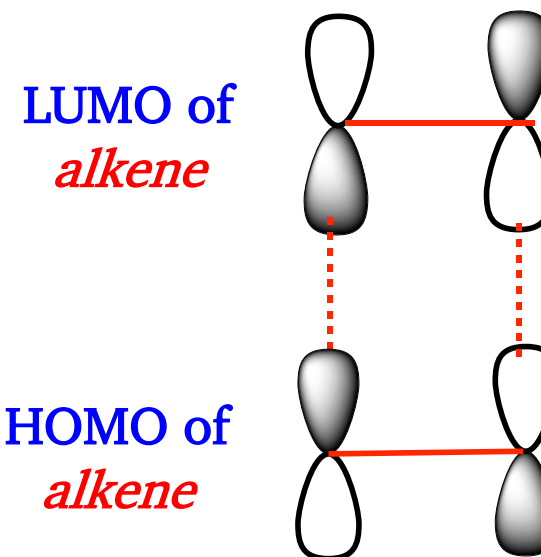
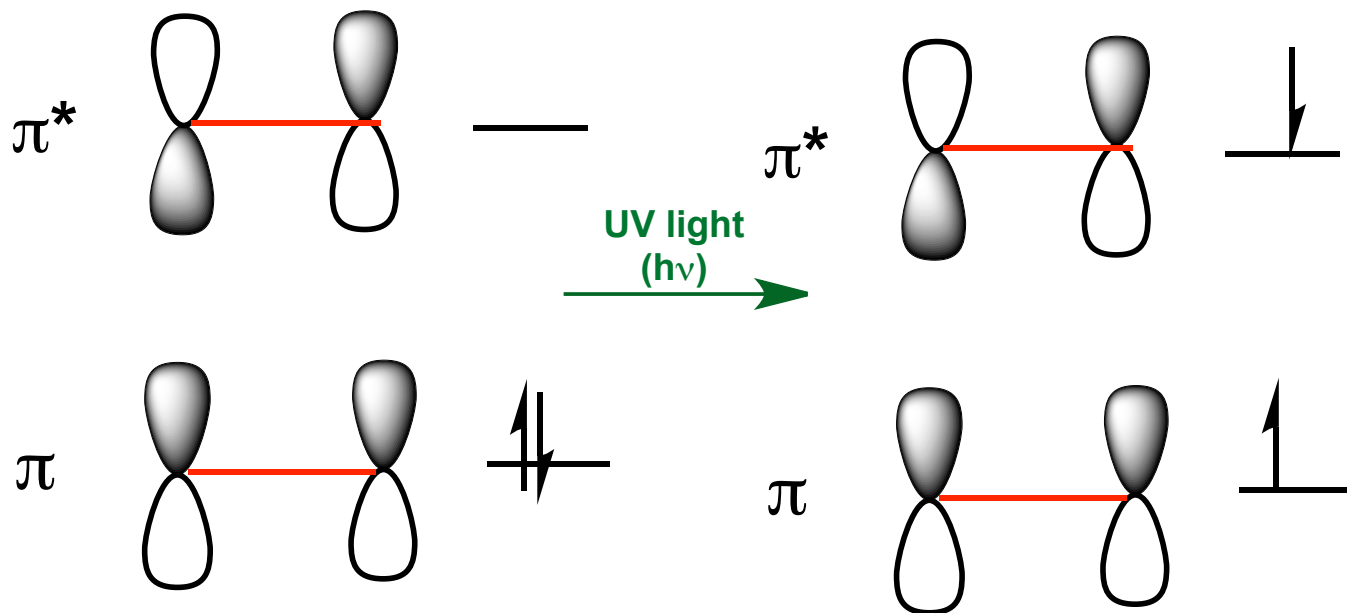
$[2_s+2_s]$ addition $\xrightarrow{\Delta}$ Not allowed

$[2_s+2_s]$ addition $\xrightarrow{h\nu}$ Allowed

Problem of incompatible symmetry is avoided by converting one of them into **excited state photochemically**

Ground state of alkene

Excited state of alkene

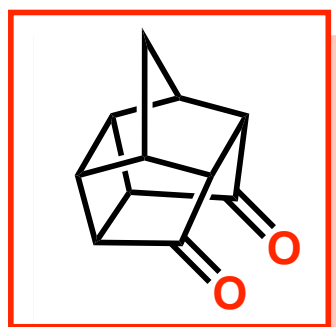
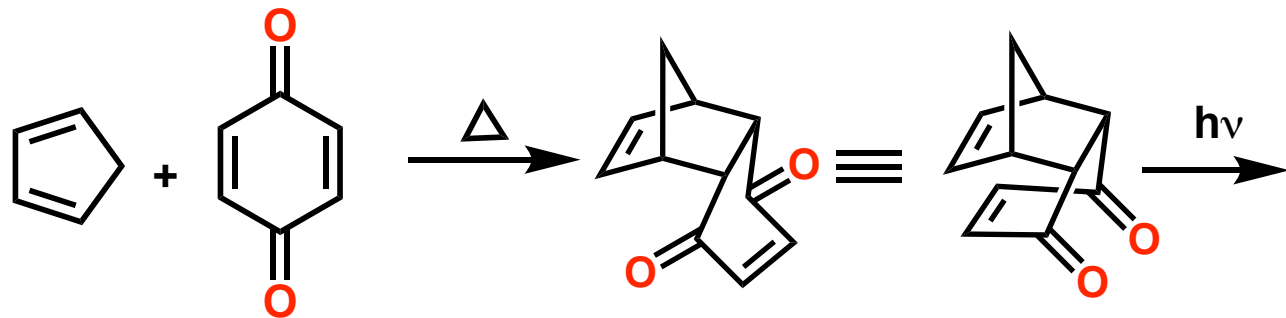


Photochemically Allowed

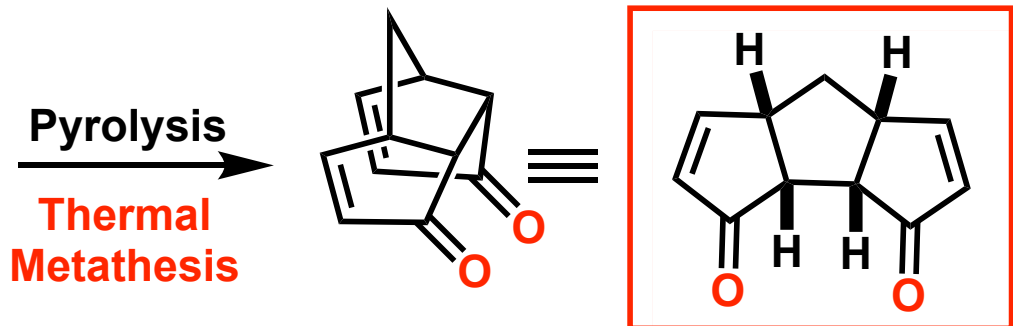
$2\pi_s + 2\pi_s$
interaction



Cookson's Dione & Mehta's Metathesis

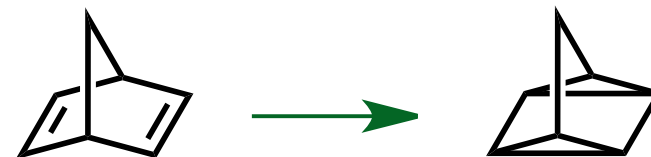
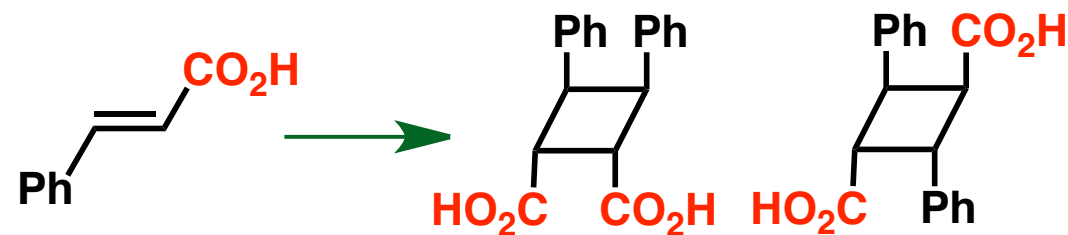
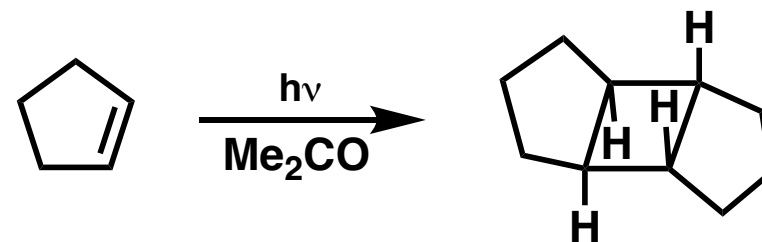


Cookson's Dione



Reported by
G. Mehta

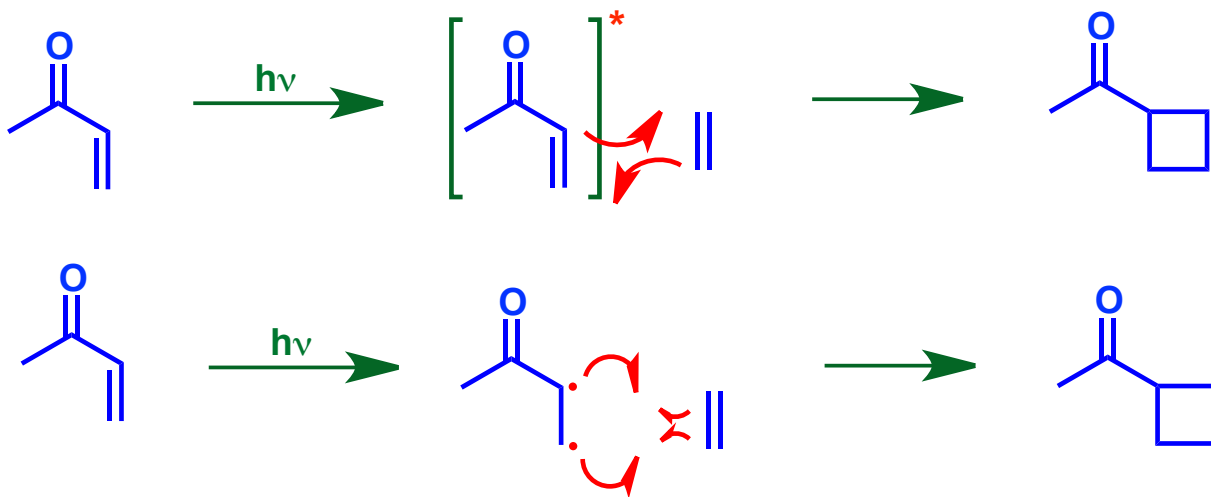
Other Examples



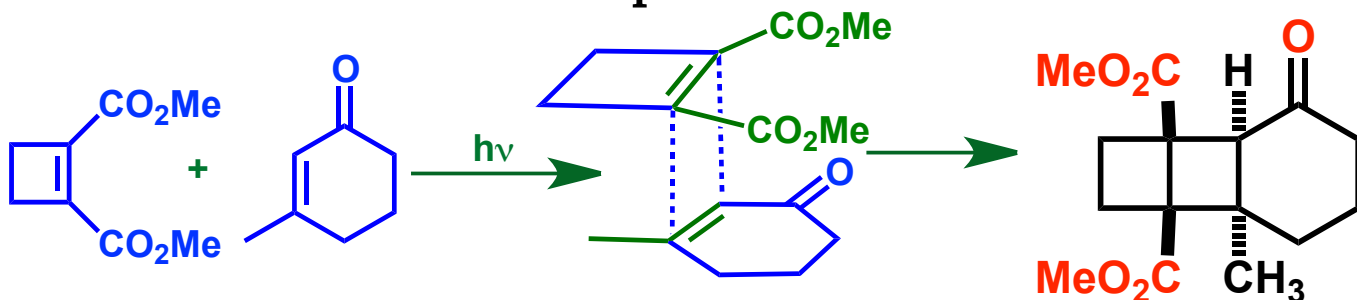


Photochemical [2+2] Cycloaddition

- Conjugated alkene absorbs UV light

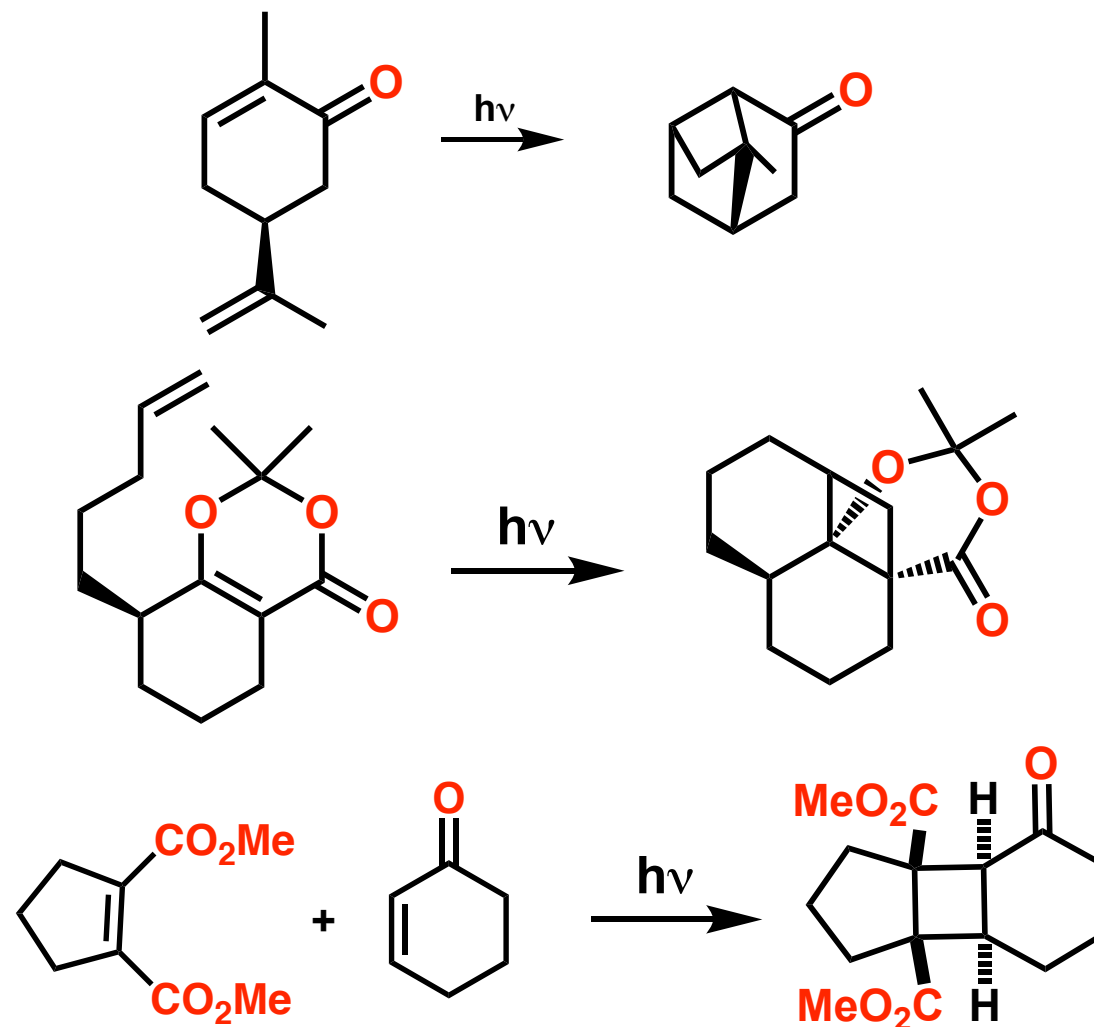


- Reaction is stereospecific



- Least hindered transition state is observed

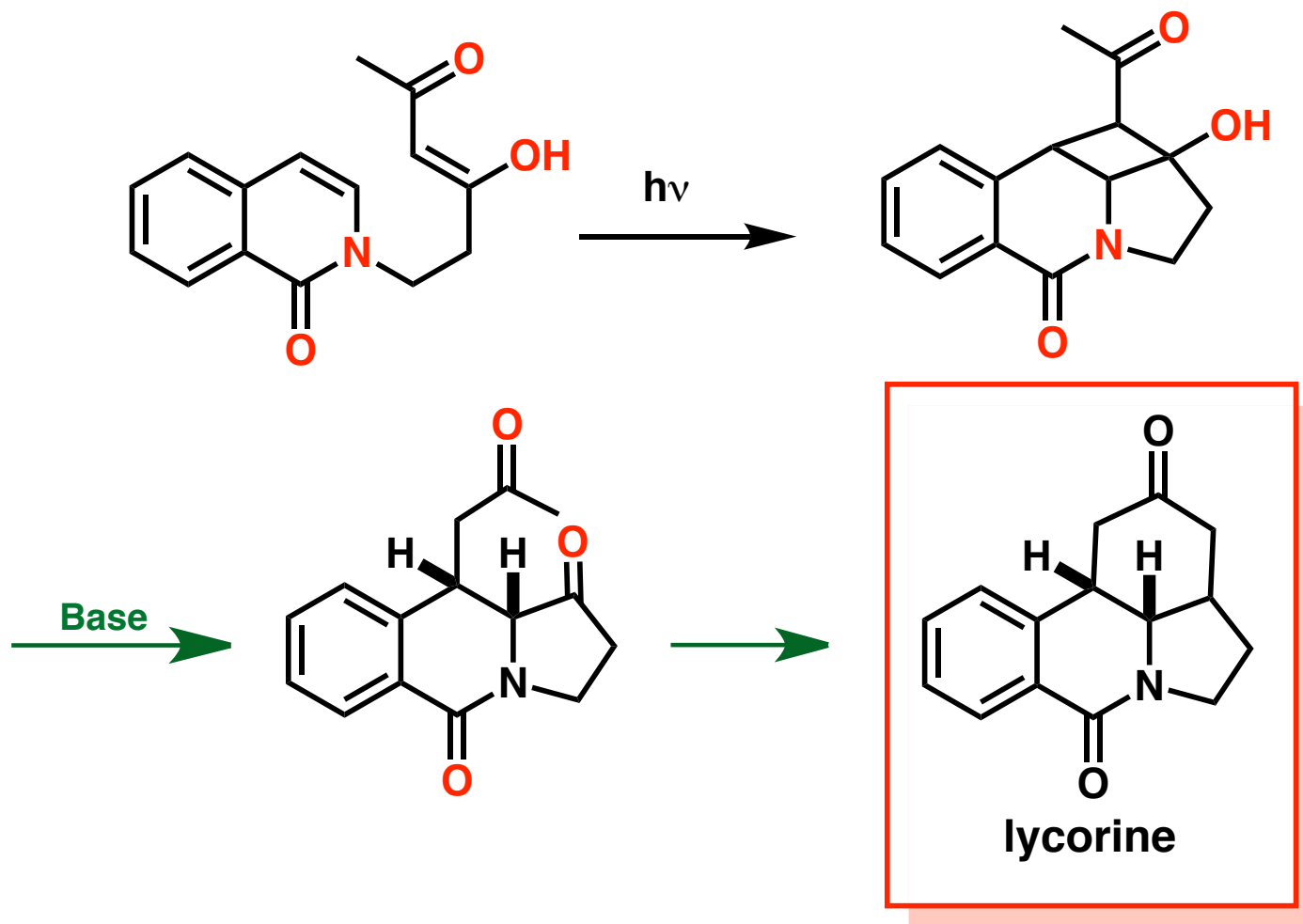
Enones with Olefins





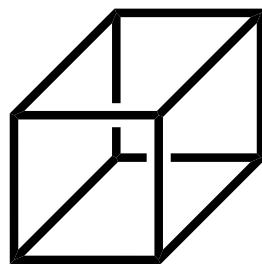
Photochemical [2+2] Cycloaddition

DeMayo Reaction (Enol with Alkene)





Synthesis of Cubane

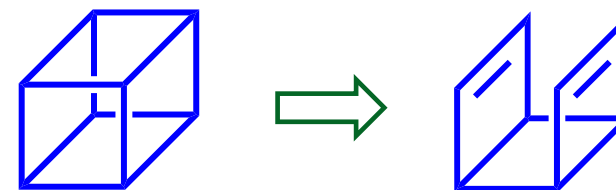


Cubane

Challenges

1. **Six** - 4 membered rings fused together
2. **No** functional groups
3. Highly **strained**
4. Low molecular weight $C_8H_8=104$

1. **4-membered rings** could be formed by photochemical reaction
2. **How many** 4-membered rings could be formed by photochemical reaction?



How about this?

Many Problems:

1. Reversibility
2. Stability of the starting material
3. Intermolecular reaction



Cubane synthesis

Solutions

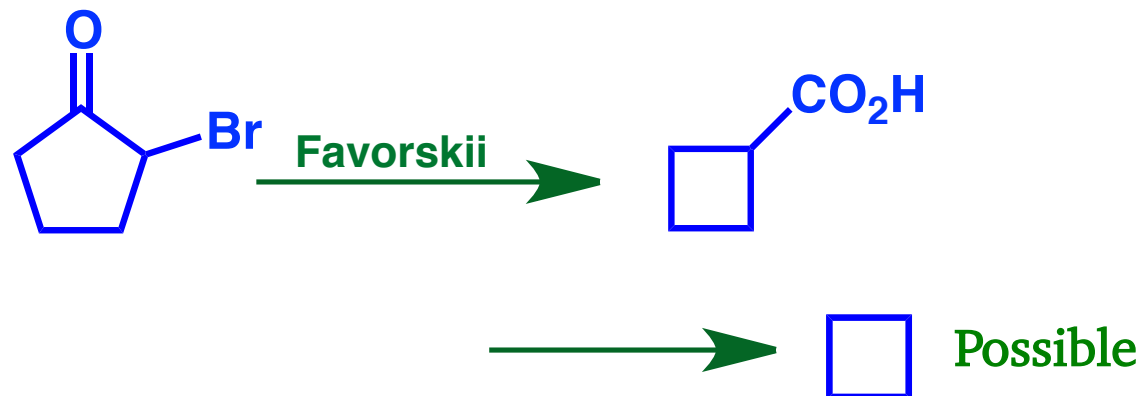
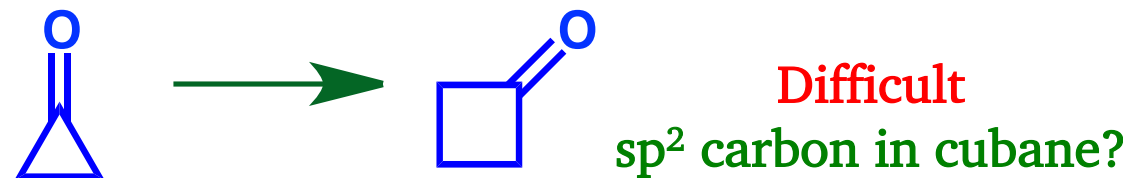
1. **Introduce** a functional group
2. **Which** functional group?
 - a. The functional group should be **removed** easily
 - b. It also should be formed **easily from another precursor**
 - c. This should be introduced along with either **ring contraction** or **ring expansion**

Ring Expansion or Ring Contraction?



Which functional group could be formed along with this reaction?

Ring Expansion or Ring Contraction?

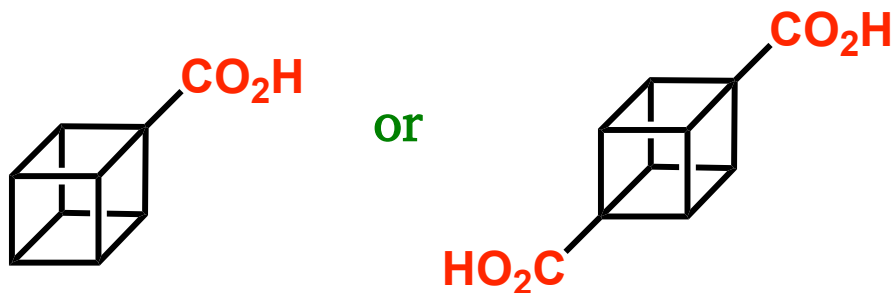


Therefore, need to go for ring contraction
- **Favorskii reaction** will be better



Cubane synthesis

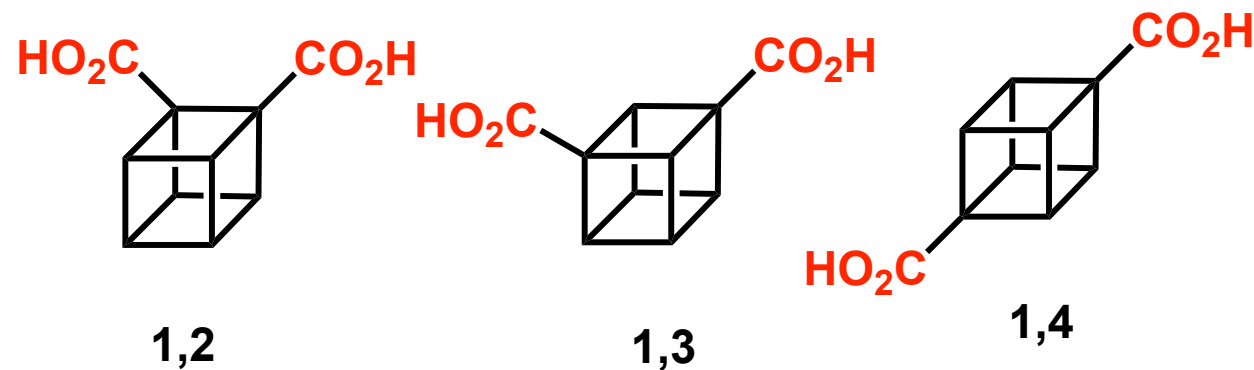
One Carboxylic Acid or Two Carboxylic Acids?



1. One carboxylic acid- precursor will have only one 5-membered ring and remaining will be 4-membered
2. Two carboxylic acid- precursor will have only two 5-membered rings and remaining will be 4-membered

Two Carboxylic Acids

Where and what is the relationship?

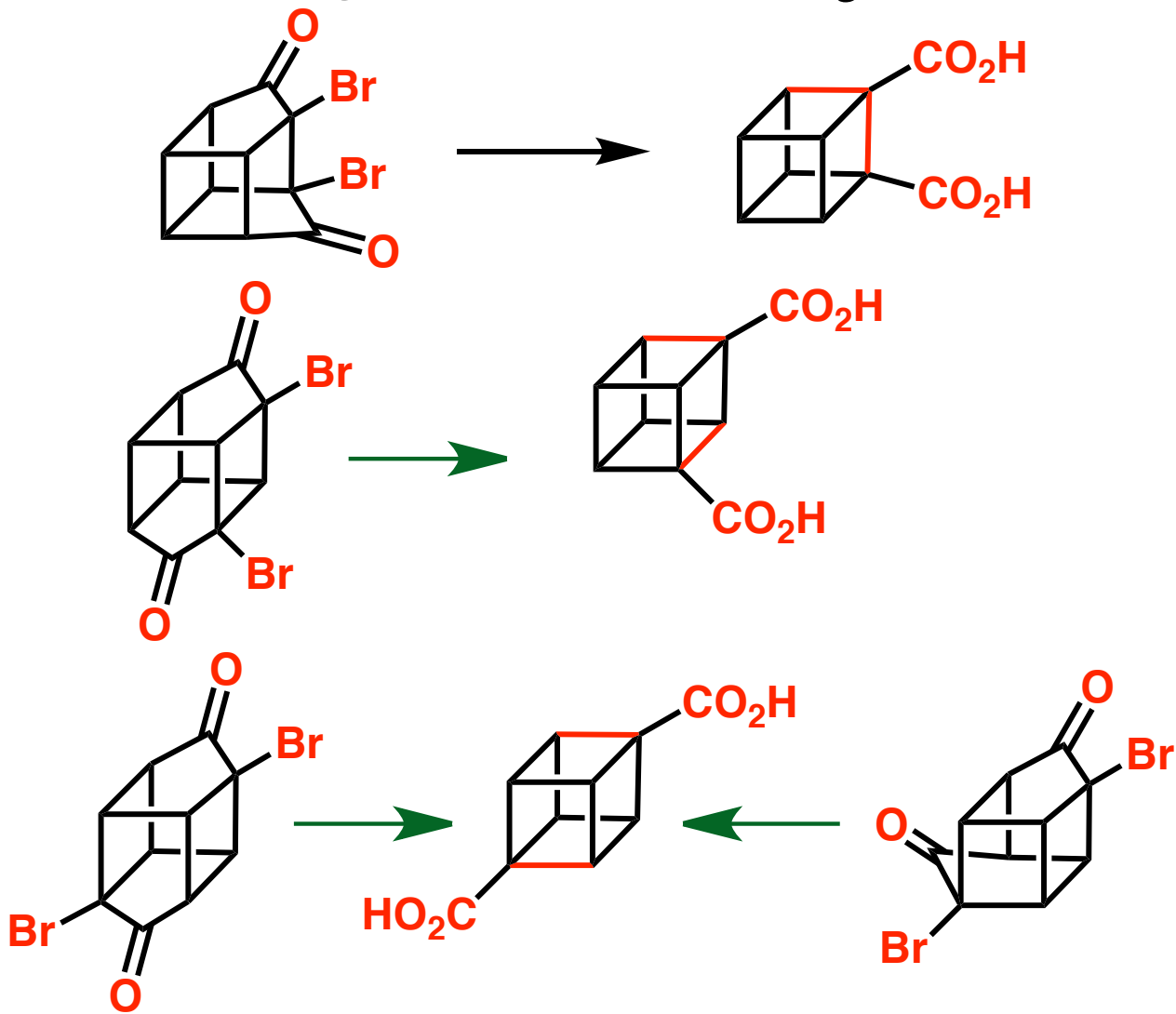


Which will be easier from synthetic point of view?

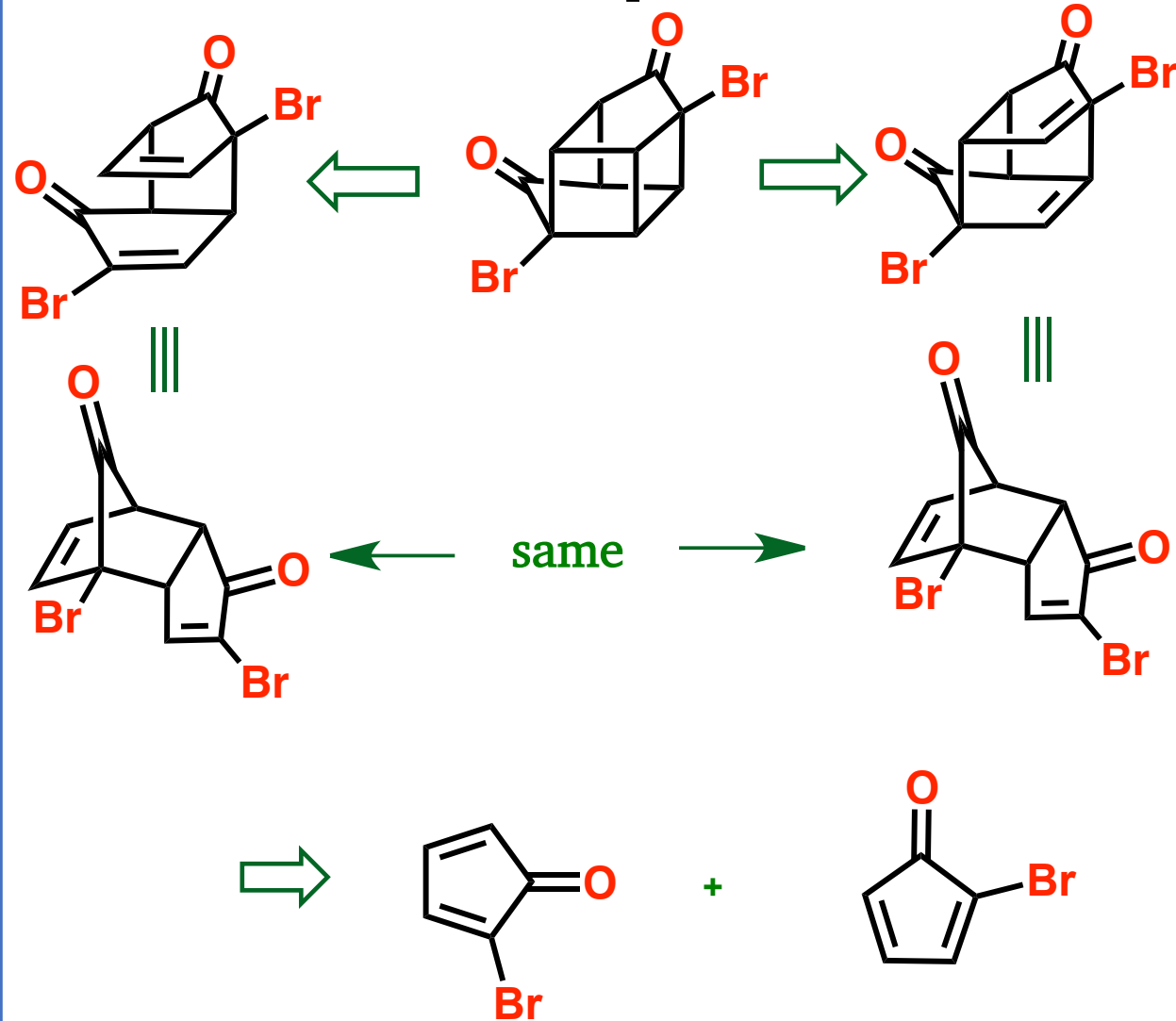


Cubane synthesis

Quasi-Favorskii Rearrangement



Two disconnections for photochemical reaction



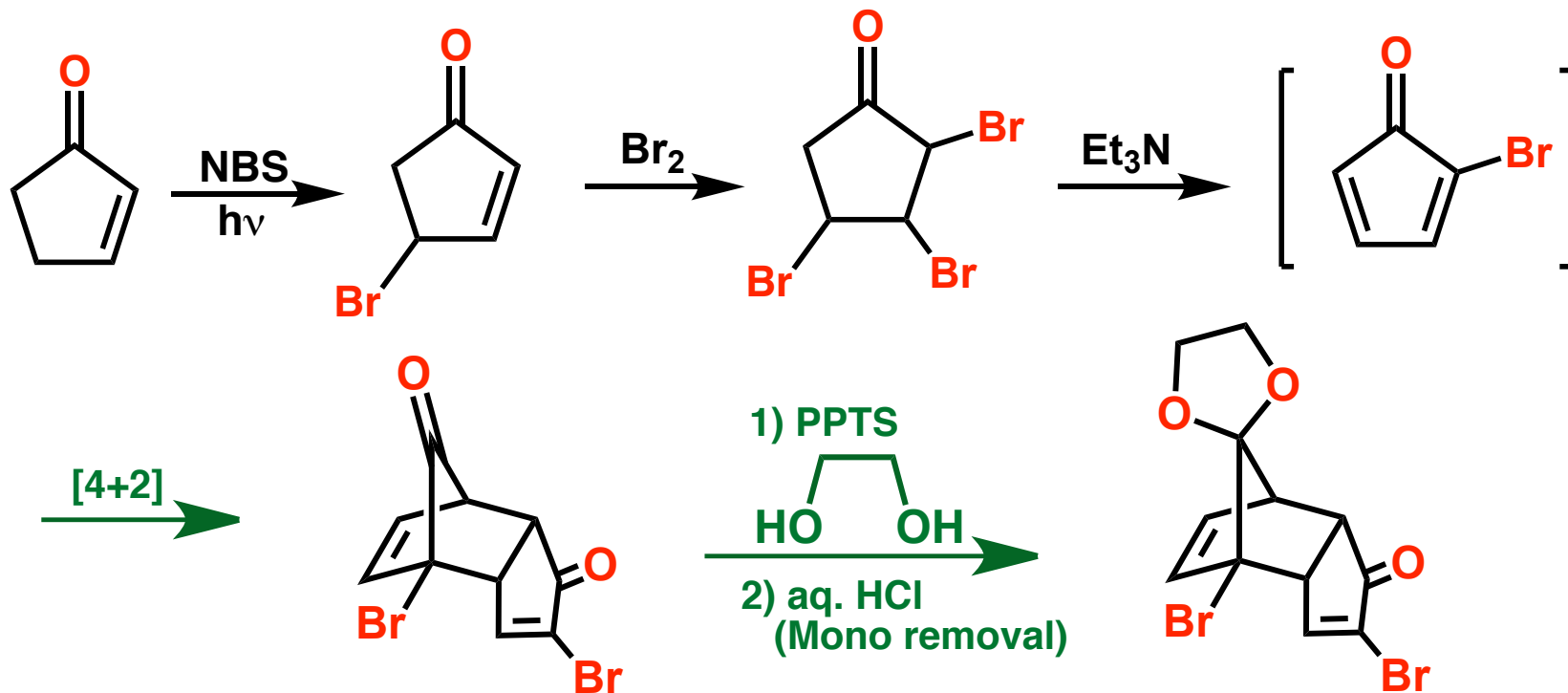


Cubane synthesis

Problems in Starting Material

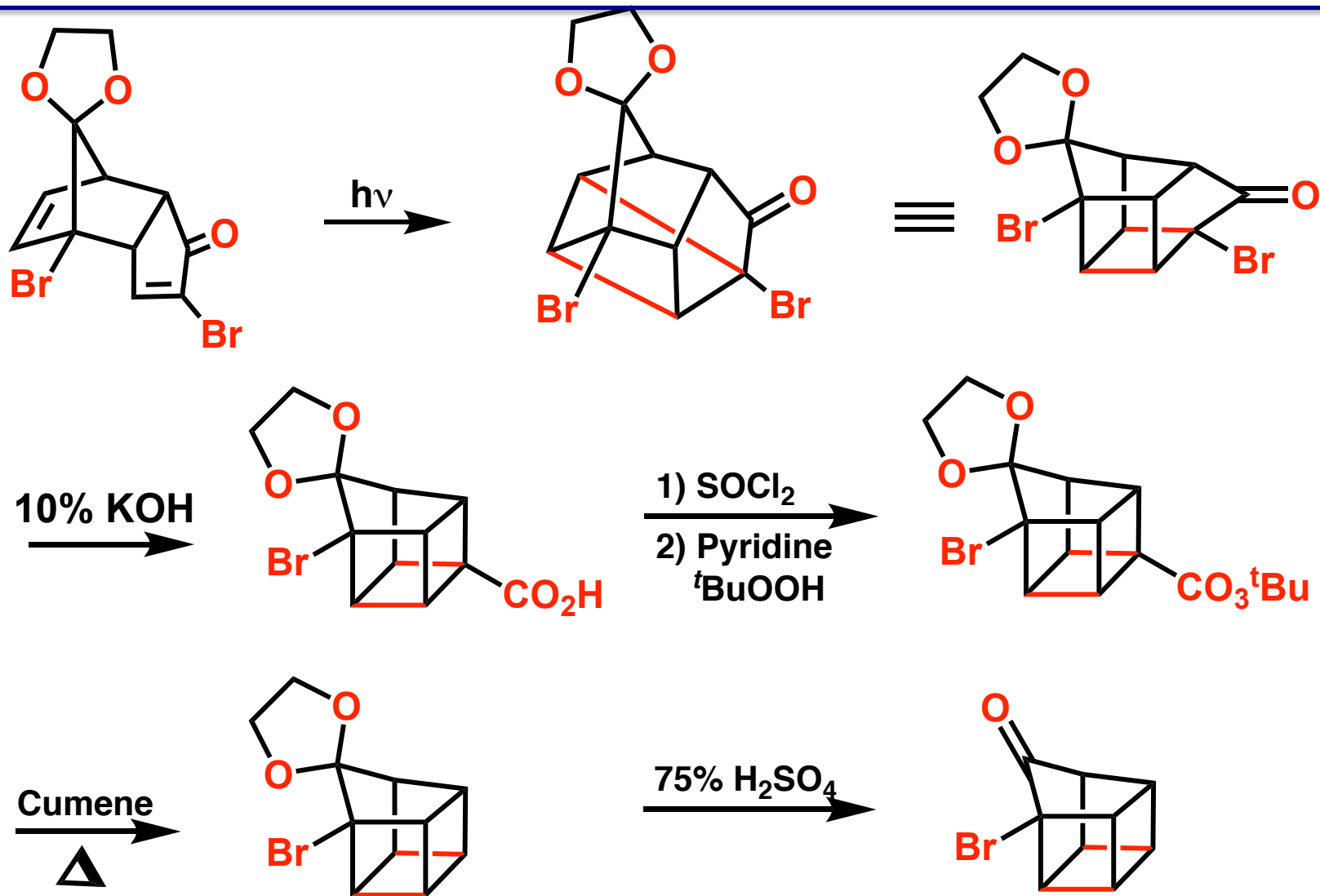
1. Cyclopentadienone is highly unstable
2. Difficult to prepare

Synthesis



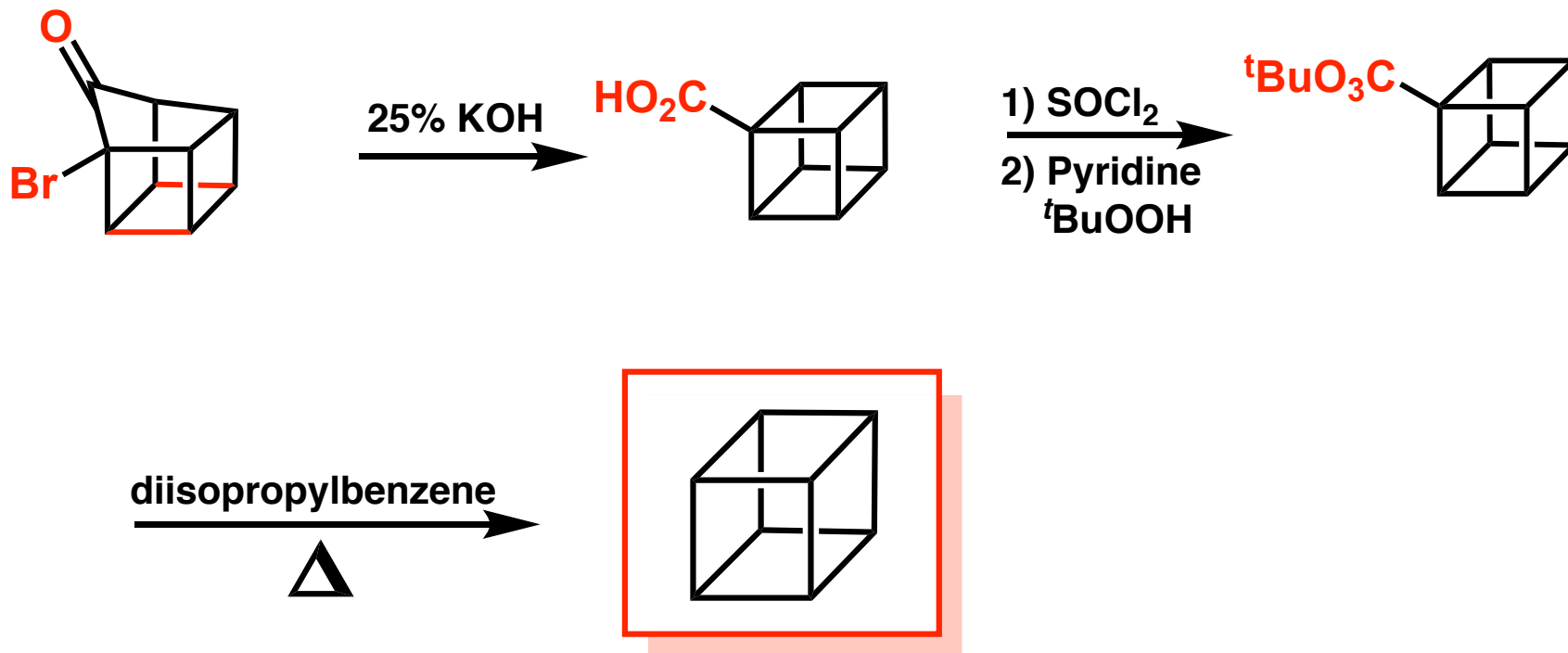


Cubane synthesis





Cubane synthesis



Philip Eaton
University of Chicago



Cubane synthesis

Modified Synthesis

