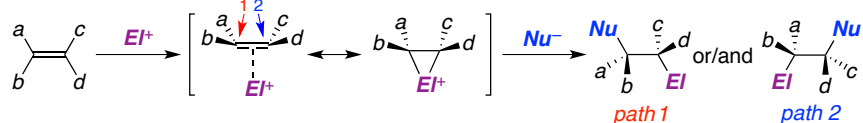


(6) Stereochemistry in the addition to alkenes

1) Stereochemistry of common electrophilic addition

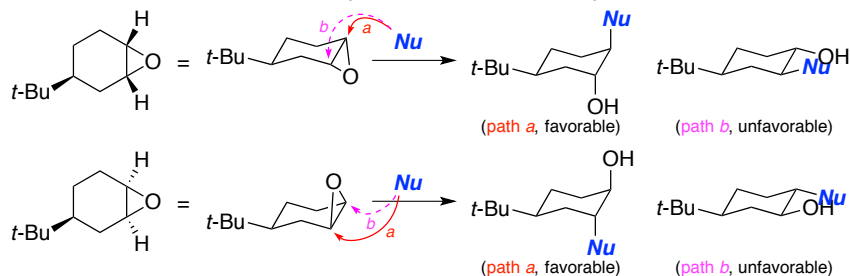
Overview

- Electrophilic addition to alkenes starts from the interaction between the C=C double bond and an electrophilic (cationic) species (E^+).
- E^+ enhances the electrophilicity of the alkene to facilitate the attack of the nucleophilic (anionic) species (Nu^-) through an S_N2 -like pathway.
- Therefore, the reaction proceeds with *anti*-selectivity.

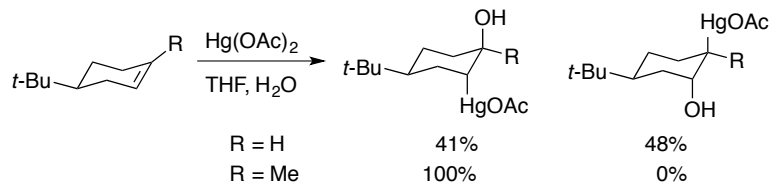


Electrophilic addition to cyclohexenes (Fürst-Plattner rule)

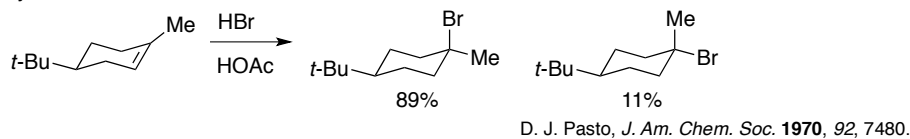
- In the epoxide opening, the nucleophilic species site-selectively attacks the carbon to form the diaxial conformer (Fürst-Plattner rule), because the ring opening is similar to the reversed reaction of the intramolecular nucleophilic substitution of halohydrins.



- Fürst-Plattner rule is adaptable for the nucleophilic attack to the 3-membered ring intermediate in the electrophilic addition to alkenes.
- Oxy-mercuration

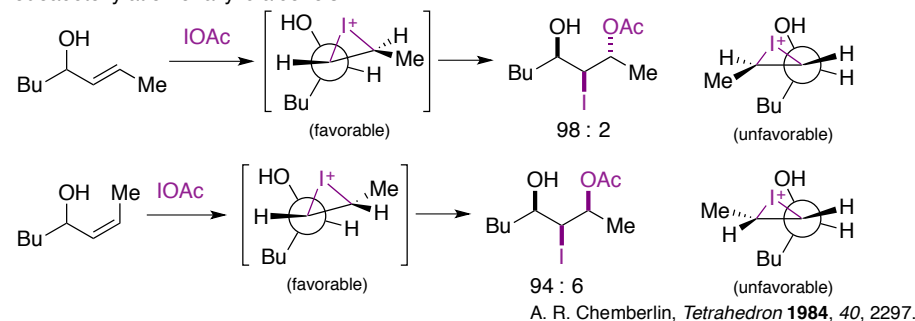


- Hydrobromination

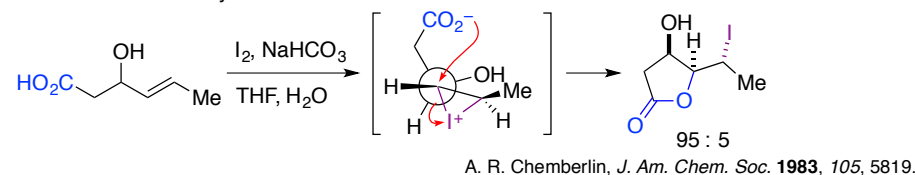


Stereoselective iodocarboxylation to acyclic alkenes

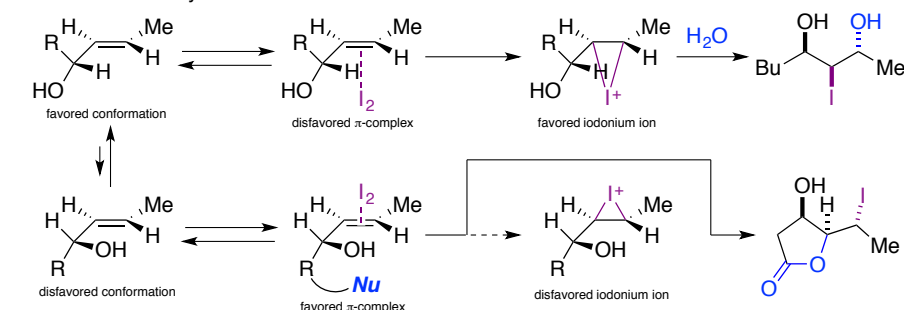
- Iodoacetoxylation of allylic alcohols



- Iodolactonization of allylic alcohols



A mechanistic analysis with MO

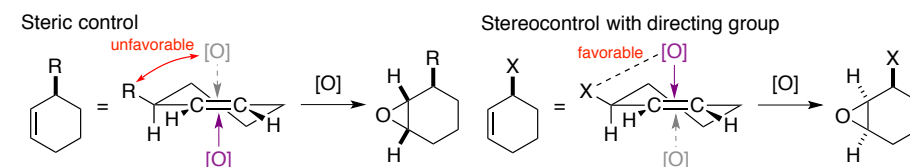


- The iodoacetoxylation or iodolactonization proceed through the iodonium ion intermediate.
- In the iodolactonization, the nucleophile can attack to the iodine-alkene π -complex intermediate because of neighboring effect.

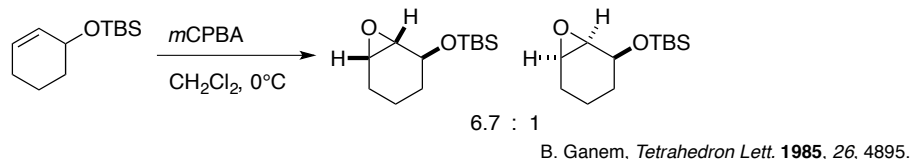
A. R. Chamberlin and W. J. Hehre, *J. Am. Chem. Soc.* **1987**, *109*, 672.

2) Epoxidation of alkenes

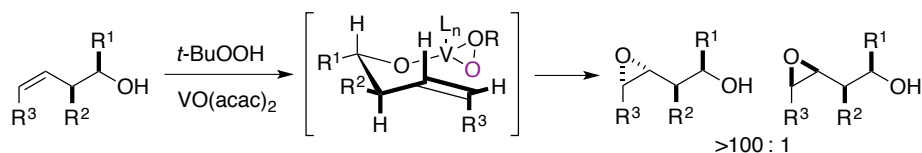
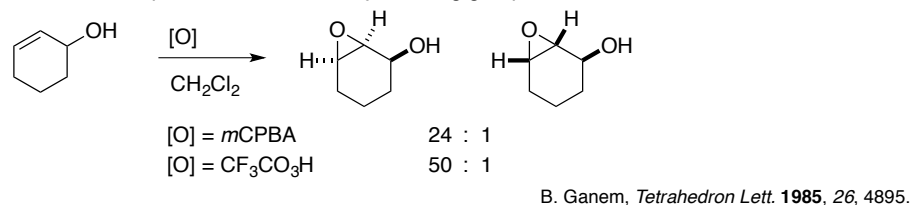
Steric repulsion vs directing group



Stereoselective epoxidation controlled by steric effect of substituent

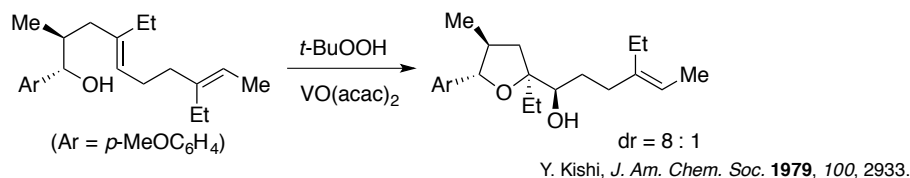


Stereoselective epoxidation controlled by directing group



The stereochemistry of the epoxidation of homoallylic alcohols is mainly controlled by the chiral center at the allylic position.

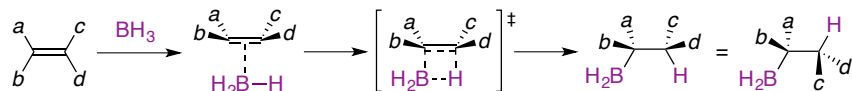
E. D. Mihelich, *J. Am. Chem. Soc.* **1981**, 103, 7690.



3) Hydroboration

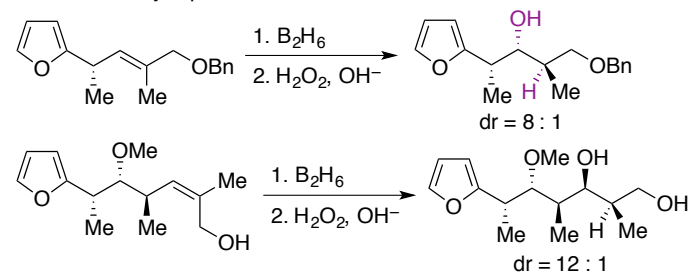
Overview

- Hydroboration proceeds through a 4-center transition state. Therefore, the reaction proceeds with *syn*-selectivity.



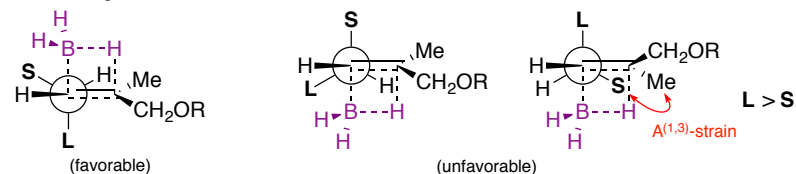
Acyclic hydroboration controlled by A^(1,3)-strain

- Stereochemistry of the hydroboration of alkenes bearing A^(1,3)-strain is controlled by the chiral center at the allylic position.



Y. Kishi, *J. Am. Chem. Soc.* **1979**, 101, 259.

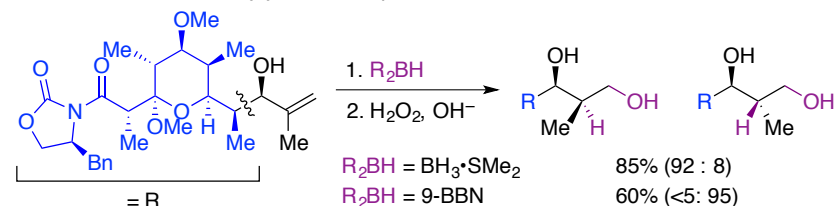
- In the transition state of the hydroboration, the hydrogen of the chiral center is oriented to the synperiplanar position of the C=C bond to avoid the A^(1,3)-strain.
- In the favorable transition state, the largest substituent is oriented to the antiperiplanar position of the forming B-C bond.



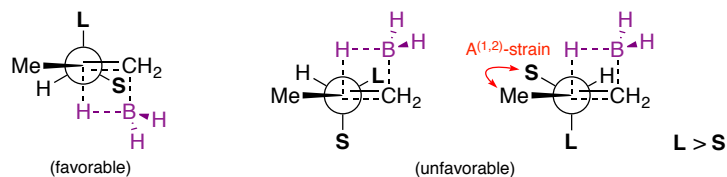
K. N. Houk, *Tetrahedron* **1984**, 40, 2257.

Acyclic hydroboration controlled by A^(1,2)-strain

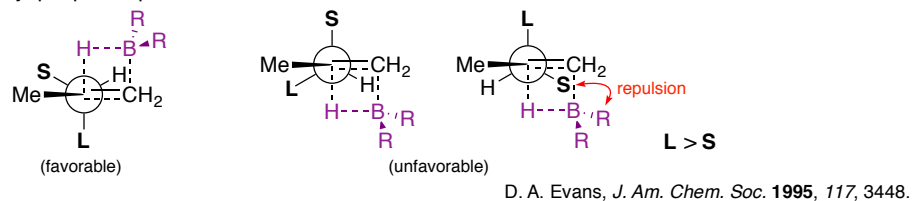
- Alkenes bearing A^(1,2)-strain also can undergo the stereoselective hydroboration controlled by the allylic chiral center.
- The stereoselective hydroboration of 2-propenyl group was used for the synthesis of Lymomycin A. The *syn*-product was selectively obtained from the reaction with BH₃, while dialkylborane, such as 9-BBN, selectively yielded *anti*-product.



- In the case of BH₃, A^(1,2)-strain controls the conformation of the transition state. Therefore, the hydrogen on the chiral center is oriented to the synperiplanar position of the methyl in the favorable transition state, because the allylic strain overcomes A^(1,3)-strain. The borane reagent attacks the C-C double bond to avoid the steric hindrance of the substituent L.



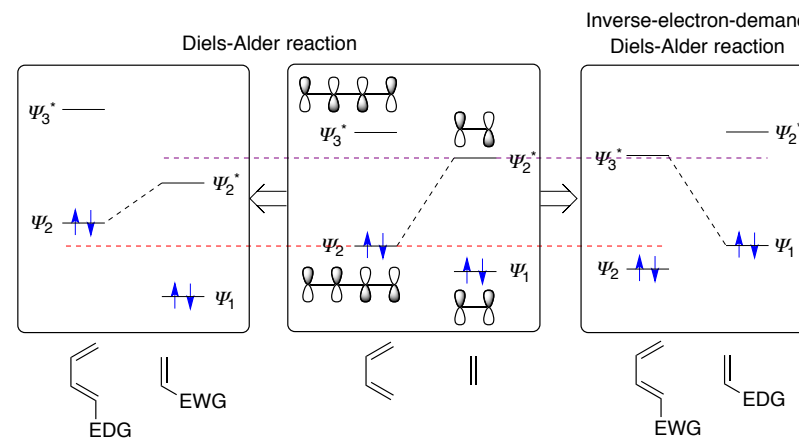
- In the case of 9-BBN, the steric repulsion between the borane reagent and the substituent **S** overcomes the $A(1,2)$ -strain. Therefore, the hydrogen on the chiral center is oriented to the synperiplanar position of the C–C double bond in the favorable transition state.



(7) Pericyclic reactions

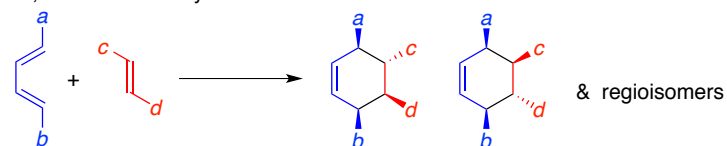
(a) Diels–Alder Reaction

- Diels–Alder reaction is the [4+2] cycloaddition of 1,3-dienes and alkenes (dienophile). Commonly, the cycloaddition proceeds through the interaction between the HOMO of diene and the LUMO of dienophile.
- In common Diels–Alder reaction, its rate is enhanced by installing an electron-withdrawing group to the alkene. Also, electron-donating group in the diene substrate accelerates the formation of [4+2] cycloadduct.
- The cycloaddition is possible to proceed with substrate combination of electron-deficient 1,3-diene and electron-rich alkene. The cycloaddition is called inverse-electron-demand Diels–Alder reaction.

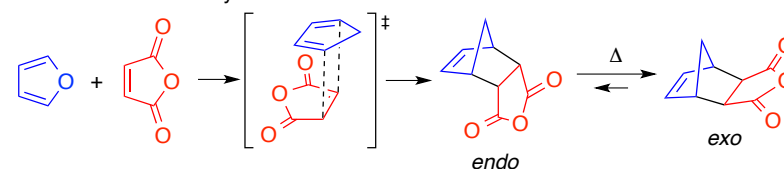


Stereochemistry in Diels–Alder reaction

- Diels–Alder reaction is stereospecific. For example, the [4+2] cycloaddition of *trans*-alkene specifically produces *trans*-4,5-disubstituted cyclohexene. Meanwhile, *cis*-alkene provides *cis*-4,5-disubstituted cyclohexene.



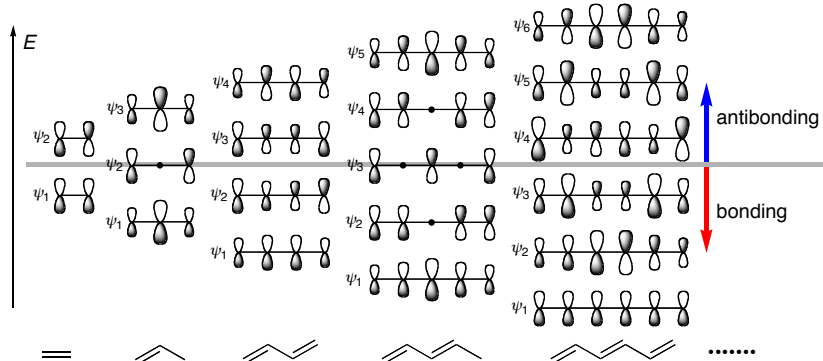
- Endo-rule: Increasing the interaction between the HOMO and LUMO is preferable for the Diels–Alder reaction. Commonly, the cycloaddition of cyclic 1,3-diene with dienophile selectively gives the *endo*-product. However, the *exo* isomer is obtained as a major product when the reaction proceeds under thermodynamic control.



(b) Frontier Molecular Orbital (FMO) Theory

1) π -Molecular orbital in conjugate system

- Pictures and phases of π -orbitals in various π -conjugation system



- Electrons was put into the orbitals on Hund's rule.
- The highest energy orbital, which is occupied with two electrons, is called HOMO (highest occupied molecular orbital).
- The lowest energy orbital, which has no electron, is called LUMO (lowest unoccupied molecular orbital).
- The orbital having an unpaired electron is called SOMO (singly occupied molecular orbital).

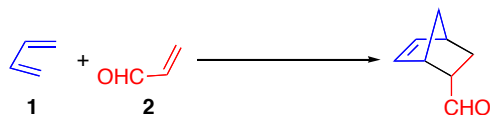
2) Frontier molecular orbital (FMO) theory

- In the reaction between two molecules, the HOMO of one (nucleophilic or electron-rich) substrate interacts with LUMO of the other (electrophilic or electron-deficient) substrate.
- A bond forms between the atoms having the largest coefficient in the HOMO and LUMO.
- A pair of molecular orbitals having the same phase leads to the bond formation. The orbital pair generates a new bonding molecular orbital.
- A pair of molecular orbitals, whose phases are different from each other, leads to the generation of an antibonding molecular orbital.

K. Fukui, *J. Chem. Phys.* **1952**, *20*, 722.

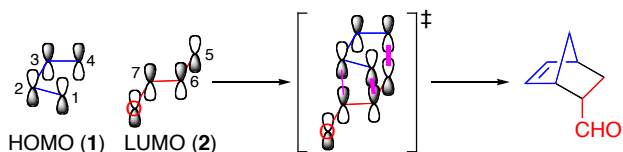
3) Applications of FMO theory

(i) Thermal [4+2] cycloaddition



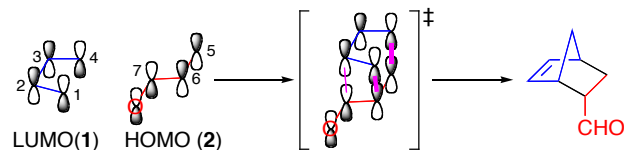
Possible HOMO–LUMO interactions

- The interaction between HOMO of **1** and LUMO of **2** in TS.



The orbitals on C1 and C4 overlap those on C6 and C5 with the same phase in TS, respectively. Therefore, the thermal cycloaddition is 'allowed'.

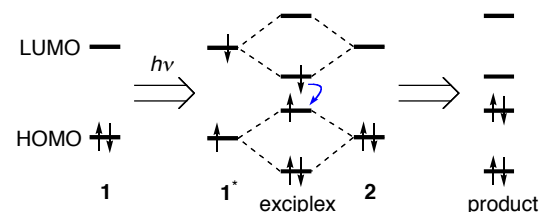
- The interaction between LUMO of **2** and HOMO of **1** in TS.



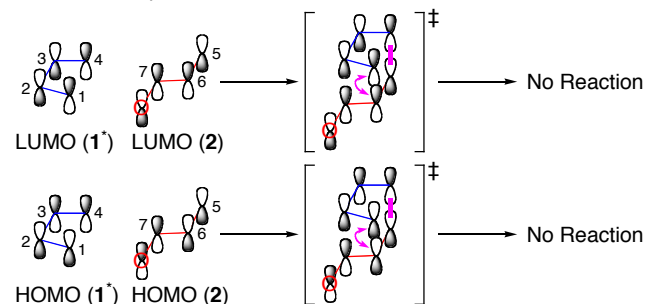
As with the interaction between HOMO of **1** and LUMO of **2**, the orbitals on C1 and C4 overlap those on C6 and C5 with the same phase, respectively. However, this orbital interaction scarcely affects common Diels–Alder reaction. The inverse-electron-demand Diels–Alder reaction was governed by this interaction.

(ii) [4+2] Photocycloaddition

- In photo-induced pericyclic reaction, one of the substrates (diene or dienophile in Diels–Alder reaction) is excited by the photo-irradiation. In the excited molecule, an electron in HOMO transfers to LUMO, giving two SOMOs.
- The higher and lower SOMOs interact with the LUMO and HOMO of the other substrate, respectively.



- In frontier molecular orbital theory, the interaction between HOMOs or LUMOs must be considered for photo reactions.



In both HOMO–HOMO and LUMO–LUMO interactions, the orbital on C4 overlaps that on C5 with the same phase. Meanwhile, the orbital on C1 overlaps that on C6 with the opposite phase. Therefore, the photocycloaddition is 'forbidden'.

(c) Woodward–Hoffmann Rule

A ground-state pericyclic change is symmetry-allowed when the total number of $(4q+2)_s$ and $(4r)_a$ components is odd ($q, r = \text{integral number}$).

R. B. Woodward, R. Hoffmann, *Angew. Chem. Int. Ed.* **1969**, 8, 781.

• Here, 'components' means a bond or orbital taking part in a pericyclic reaction as a single unit.

e.g. $\sigma 2_a \pi 4_s \omega 0_s$ etc. (molecular orbital) (Number of electrons) (reaction manner)

1) Procedure for using Woodward–Hoffmann rule

- 1) Draw the equation of the pericyclic reaction including its TS.
- 2) Choose all components (bonds or orbitals) involved with the pericyclic reaction.
- 3) Assign each component to π , σ , or ω . (non-essential)
 - π : π bond
 - σ : σ bond
 - ω : single orbital (e.g. lone pair or carbocation)
- 4) Count the number electrons in each component.
- 5) Assign each component to s or a.
 - π component

π : π bond

σ : σ bond

ω : single orbital (e.g. lone pair or carbocation)

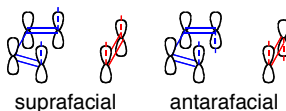
- 4) Count the number electrons in each component.

- 5) Assign each component to s or a.

• π component

s (suprafacial): The component forms new two bonds on the **same face** at both ends.

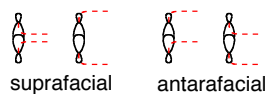
a (antarafacial): The component forms new two bonds on **opposite faces** at both ends.



• σ component

s (suprafacial): The component forms new two bonds with the large lobe of sp^3 orbital on each atom.

a (antarafacial): The component forms a bond with the large lobe of sp^3 orbital on an atom. On the other atom, the small lobe of sp^3 orbital is used for the formation of another bond.



• ω component

This component can participate in either a suprafacial or antarafacial manner.

- 6) Count the number N of $(4q+2)_s$ and $(4r)_a$ components.

• Thermal reaction

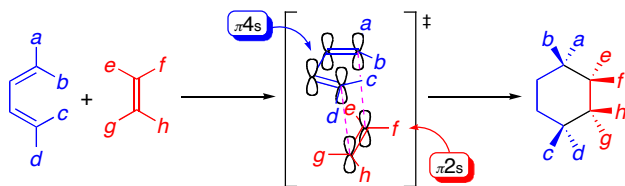
If $N = \text{odd}$, the pericyclic reaction is allowed. If $N = \text{even}$, the pericyclic reaction is forbidden.

• Photoreaction

If $N = \text{even}$, the pericyclic reaction is allowed. If $N = \text{odd}$, the pericyclic reaction is forbidden.

2) Applications of Woodward–Hoffmann rule

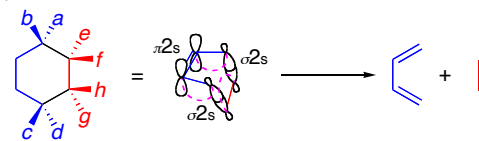
(i) Diels–Alder reaction



This reaction is classified into $[\pi 4_s + \pi 2_s]$ cycloaddition.

$N = 1 (\pi 2_s) \rightarrow \text{allowed (thermal)}$

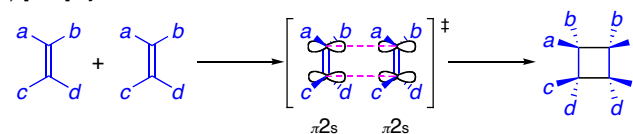
(ii) retro Diels–Alder reaction



This reaction is classified into retro $[\pi 2_s + \sigma 2_s + \sigma 2_s]$ cycloaddition.

$N = 3 (\pi 2_s, 2 \times \sigma 2_s) \rightarrow \text{allowed (thermal)}$

(iii) [2+2] cycloaddition

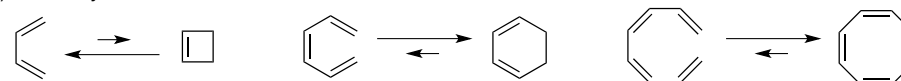


This reaction is classified into $[\pi 2_s + \pi 2_s]$ cycloaddition.

$N = 2 (2 \times \pi 2_s) \rightarrow \text{forbidden (thermal)}$

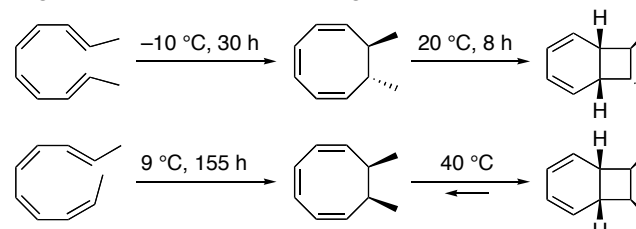
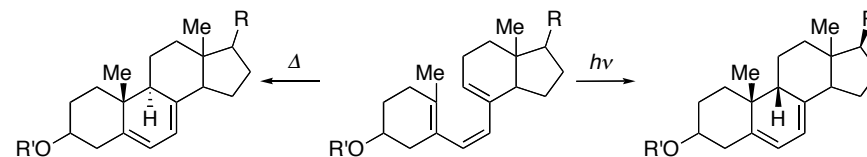
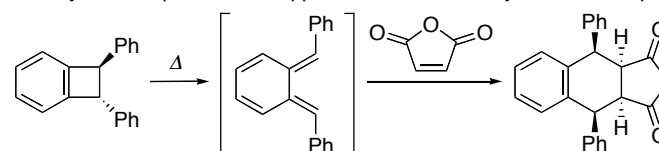
(d) Electrocyclic Reaction

1) Electrocyclic reaction of neutral molecules



• All electrocyclic reactions are allowed thermally as well as photochemically.

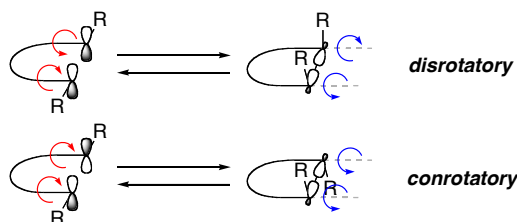
• Photocyclization proceeds in opposite stereochemistry to the corresponding thermal cyclization.



• An electrocyclic reaction is classified into disrotatory or conrotatory reaction from the viewpoint of stereochemistry.

• In disrotatory reactions, one group rotates clockwise and the other group rotates anti-clockwise.

- In conrotatory reactions, the two groups taking part in the bond formation or cleavage rotate in the same direction: both clockwise or both anticlockwise.



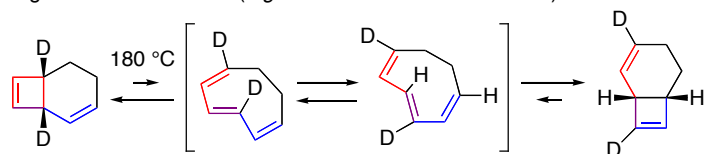
2) Woodward–Hoffmann rule in electrocyclic reaction

- Disrotatory reaction is suprafacial. Conrotatory reaction is antarafacial.

	equation	thermal reaction	photochemical reaction
4e system		con close: $[\pi 4a]$ open: $[\pi 2s + \sigma 2a]$	dis close: $[\pi 4s]$ open: $[\pi 2s + \sigma 2s]$
6e system		dis close: $[\pi 6s]$ open: $[\pi 4s + \sigma 2s]$	con close: $[\pi 6a]$ open: $[\pi 4s + \sigma 2a]$
8e system		con close: $[\pi 8a]$ open: $[\pi 6s + \sigma 2a]$	dis close: $[\pi 8s]$ open: $[\pi 6s + \sigma 2s]$

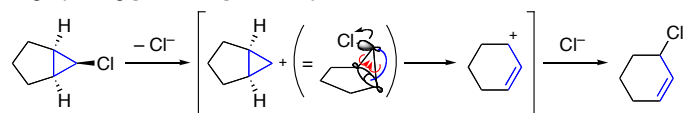
con: conrotatory, dis: disrotatory

- Any electrocyclic reactions are symmetry-allowed. However, the reaction is restricted by steric or geometrical reason. (e.g. formation of *trans*-olefin etc.)

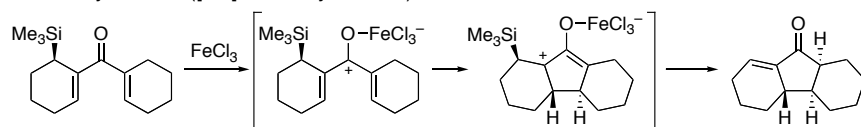


3) Electrocyclic reaction of ionic molecules

- Ring-opening $[\sigma 0a + \sigma 2s]$ electrocyclic reaction

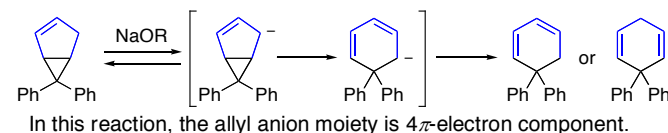


- Nazarov cyclization ($[\pi 4a]$ electrocyclization)



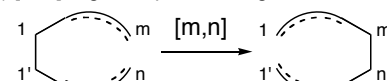
This reaction can be regarded as the electrocyclic reaction of pentadienyl cation.

- Ring-opening $[\pi 4s + \sigma 2s]$ electrocyclic reaction

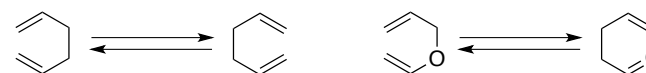


(e) Sigmatropic Rearrangement

1) $[m,n]$ -Sigmatropic rearrangements



[3,3]-Sigmatropic (Cope, Claisen) rearrangement

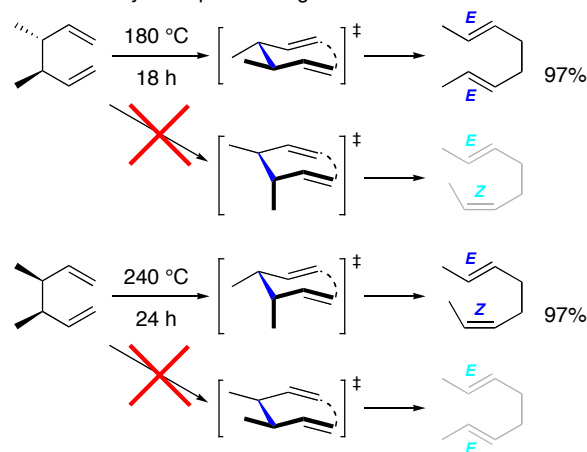


Structure of TS

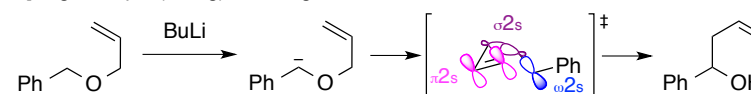


- Chair-form is commonly preferable to boat-form.
- When the dissociating bond in TS is treated as $\sigma 2s$, this rearrangement is $[\sigma 2s + \pi 2s + \pi 2s]$, in which $N = 3$. The thermal sigmatropic reaction is symmetry-allowed.
- When the dissociating bond in TS is treated as $\sigma 2a$, this rearrangement is $[\sigma 2a + \pi 2a + \pi 2s]$, in which $N = 1$. The thermal sigmatropic reaction is symmetry-allowed.

Stereochemistry of Cope rearrangement



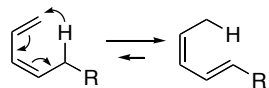
[2,3]-Sigmatropic (Wittig) rearrangement



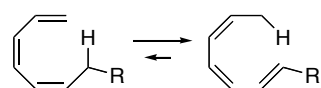
- This rearrangement is $[\sigma 2s + \pi 2s + \omega 2s]$, in which $N = 3$.
- If the [2,3]-rearrangement proceed through the corresponding benzyl cation intermediate, it will be $[\sigma 2s + \pi 2s + \omega 0s]$, in which $N = 2$. The reaction will be symmetry-forbidden.

2) [1, η]-Sigmatropic hydrogen shifts

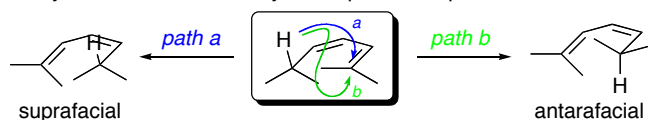
[1,5]-hydrogen shift



[1,7]-hydrogen shift

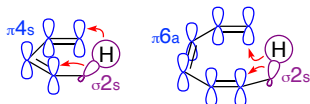


- The [1, η]-hydrogen shift is possible to proceed through either suprafacial or antarafacial pathway. The stereochemistry of the product depends on the reaction pathway.



Stereochemistry of [1, η]-hydrogen shift in Woodward–Hoffmann rule

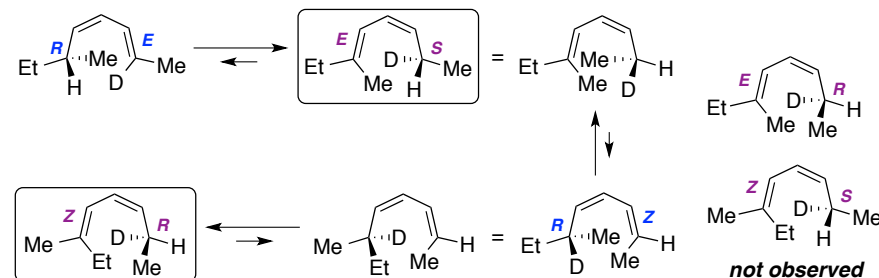
- The [1, η]-sigmatropic hydrogen shift is $[\sigma 2s + \pi(n-1)s]$ or $[\sigma 2s + \pi(n-1)a]$.
- The C–H bond participating in the reaction is always $\sigma 2s$.
- If $n = 4p + 1$, the reaction proceeds through suprafacial pathway.
- If $n = 4p - 1$, the reaction proceeds through antarafacial pathway.
- Symmetry-allowed [1, η]-hydrogen shifts may be restricted by steric or geometrical reason.



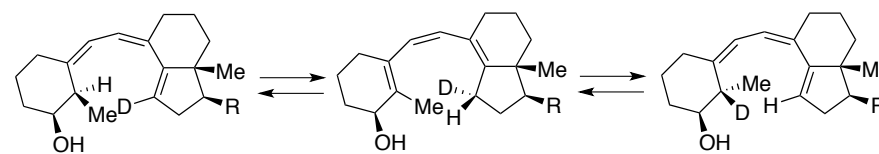
equation	thermal reaction	photoreaction
[1,3]-H shift 	a $[\sigma 2s + \pi 2a]$	s $[\sigma 2s + \pi 2s]$
[1,5]-H shift 	s $[\sigma 2s + \pi 4s]$	a $[\sigma 2s + \pi 4a]$
[1,7]-H shift 	a $[\sigma 2s + \pi 6a]$	s $[\sigma 2s + \pi 6s]$
[1,9]-H shift 	s $[\sigma 2s + \pi 8s]$	a $[\sigma 2s + \pi 8a]$

a: antarafacial, s: suprafacial

Examples



- Suprafacial pathway in [1,5]-sigmatropic hydrogen shifts was proved by the observed stereochemistry of the rearrangement product.

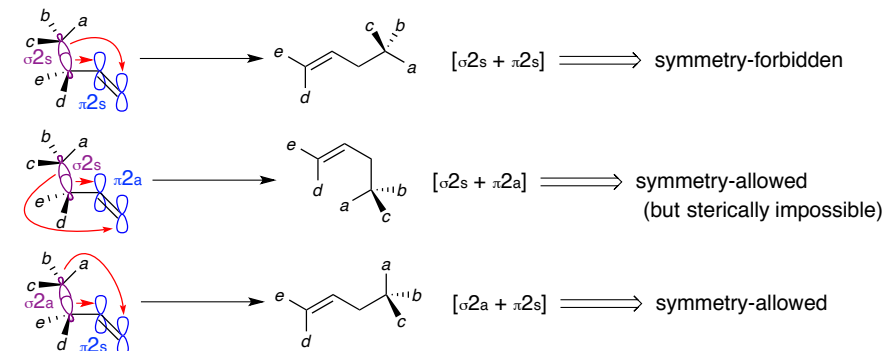


- Antarafacial pathway in [1,7]-sigmatropic hydrogen shifts was proved by the observed stereochemistry and deuterium distribution of the recovered substrate.

3) [1, η]-Sigmatropic alkyl shifts

- Antarafacial pathway is allowed for the σ component in [1, η]-alkyl shifts, while [1, η]-hydrogen shift limits the σ component to suprafacial.

[1,3]-Sigmatropic alkyl shift



- [1,3]-Sigmatropic alkyl-shift is possible to proceed, but the stereogenic center on the alkyl group inverts.

Stereochemistry of [1, η]-alkyl shift in Woodward–Hoffmann rule

- In thermal reaction with $4p+2$ electron system, the configuration of the stereogenic center in R is **retained** when R **suprafacially** migrates to the reaction terminus (si, ar).
- In thermal reaction with $4p$ electron system, the configuration **inverts** when R **suprafacially** migrates to the reaction terminus.

- In thermal reaction with $4p$ electron system, the configuration **is retained** when R **antarafacially** migrates to the reaction terminus.

	equation	thermal reaction	photoreaction
2e system		sr $[\sigma 2s + \omega 0s]$ ai $[\sigma 2a + \omega 0a]$	sr $[\sigma 2s + \omega 0a]$ ai $[\sigma 2a + \omega 0s]$
4e system		si $[\sigma 2a + \pi 2s]$ or $[\sigma 2a + \omega 2s]$ ar $[\sigma 2s + \pi 2a]$ or $[\sigma 2s + \omega 2a]$	sr $[\sigma 2s + \pi 2s]$ or $[\sigma 2s + \omega 2s]$ ai $[\sigma 2a + \pi 2a]$ or $[\sigma 2a + \omega 2a]$
6e system		sr $[\sigma 2s + \pi 4s]$ ai $[\sigma 2a + \pi 4a]$	si $[\sigma 2a + \pi 4s]$ ar $[\sigma 2s + \pi 4a]$
8e system		si $[\sigma 2a + \pi 6s]$ ar $[\sigma 2s + \pi 6a]$	sr $[\sigma 2s + \pi 6s]$ ai $[\sigma 2a + \pi 6a]$

π component: a ... antarafacial, s ... suprafacial
 σ component: r ... retention, l ... inversion

Examples

