



# **ADDITION REACTIONS**

- **KEY WORDS: ADDITION TO ALKENES AND ALKYNES, MARKOVNIKOV'S RULE, ELECTROPHILIC AND NUCLEOPHILIC ADDITIONS**

# INTRODUCTION

Conversion of multiple bonds, such as a double or a triple bond, into other functional groups are usually achieved using addition reactions. The reaction of multiple bonds will convert an unsaturated compound to more saturated and functionalized species. In this module, a number of examples of electrophilic addition to electron rich double bonds are presented. When a double bond is activated by attaching it with electron withdrawing groups, conjugated addition is observed. Regioselectivity as well as stereochemical considerations are presented in this chapter.

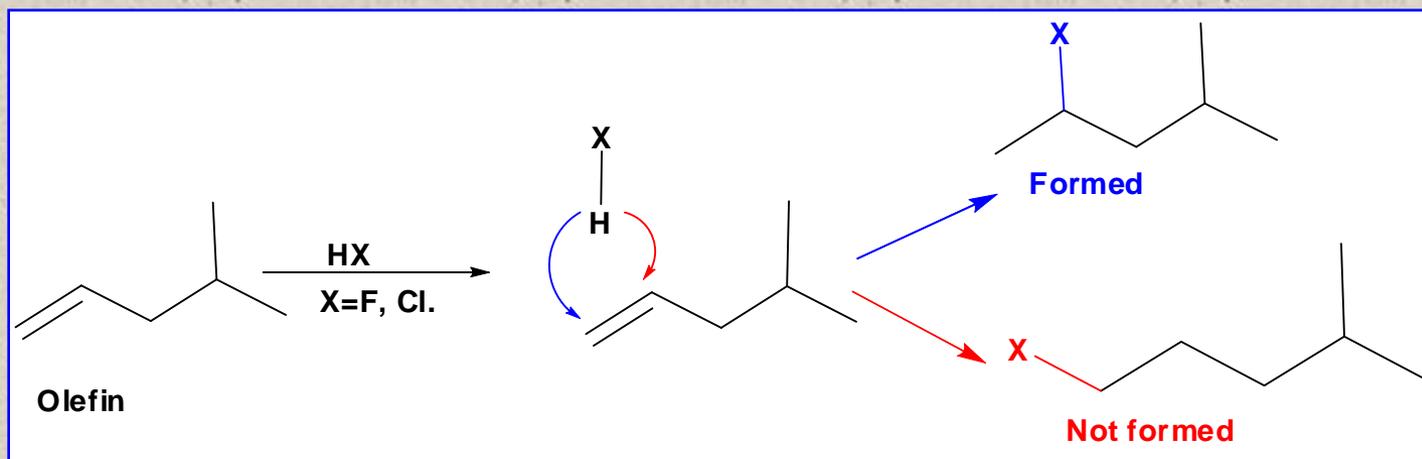


**ELECTROPHILIC  
ADDITION REACTIONS**

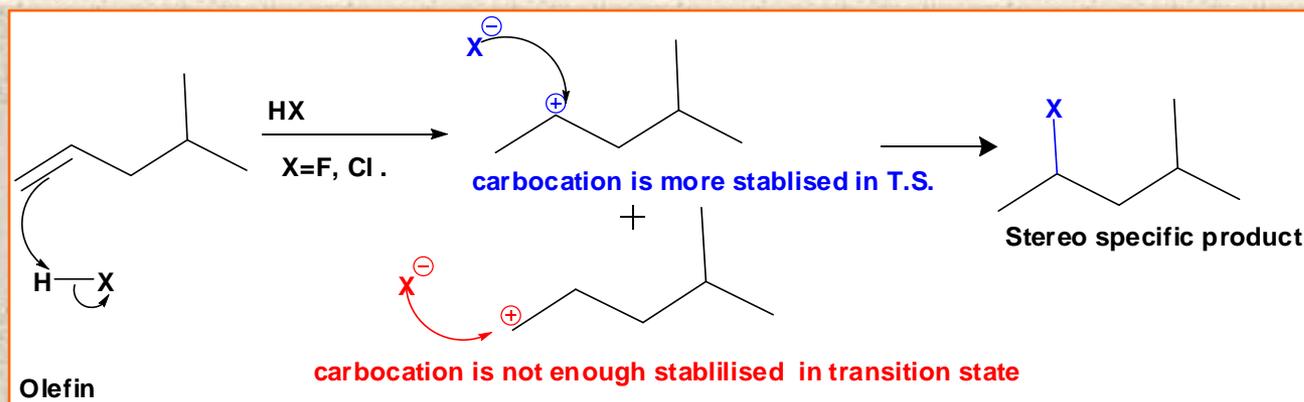
**MARKOVNIKOV' ADDITIONS**

# MARKOVNIKOV'S RULE

- Addition of hydrogen to an unsymmetrical olefin occurs at those carbon atoms with **maximum number of hydrogen atoms**. (i.e., the carbon with least substitution).
- **Electronegative group** goes to more substituted carbon atom.
- Such an addition leads to a **stabler carbocation**.
- Such a reaction may lead to constitutional isomers but actually one of the products is formed as major product.



# ORIGIN ...

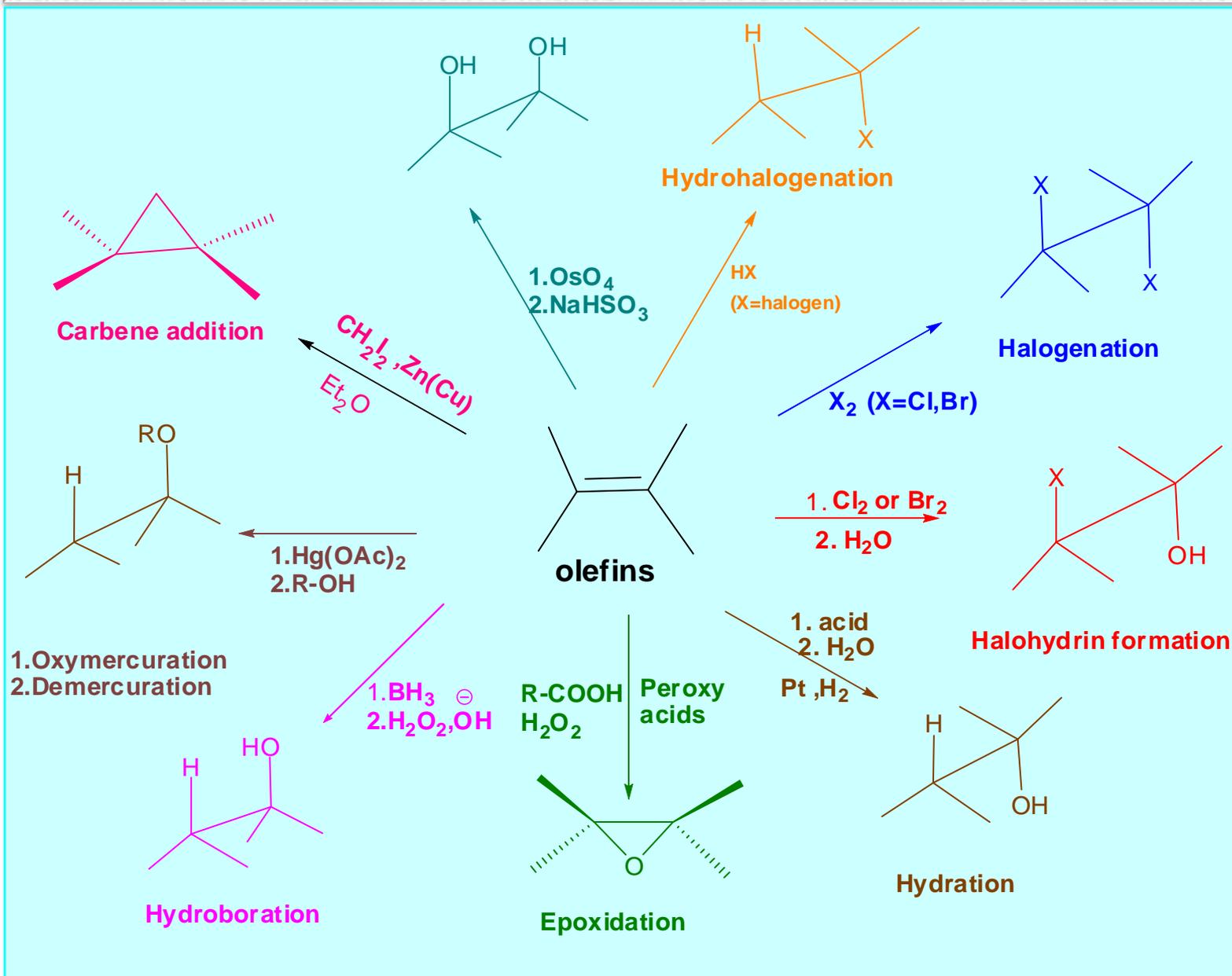


- Consider two possible sites for hydrogen addition (i) terminal or (ii) internal (substituted carbon).
- The addition of hydrogen at the terminal carbon leads to better **stabilization of carbocation**, the chances of **stabilization increases with increase in conjugation** with olefin.
- The **terminal carbocation** require higher **activation energy** which is not a favorable condition, leading to slower reaction rate. However, the generation of **non terminal carbocation** is assisted by hyperconjugative stabilization leading to a lower activation energy.

## ALKENES-SOME FACTS

- Due to trigonal planar geometry of olefin carbon atoms the addition can occur on the same side (*syn periplanar*) or on opposite sides (*anti periplanar*).
- Alkenes are generally nucleophilic. The C=C double bond provides a higher energy HOMO (highest occupied molecular orbitals).
- Electron donating groups increase the rate for electrophilic attack as they assist in carbocation and positive charge stabilization in the TS.

# REACTIONS OF ALKENES

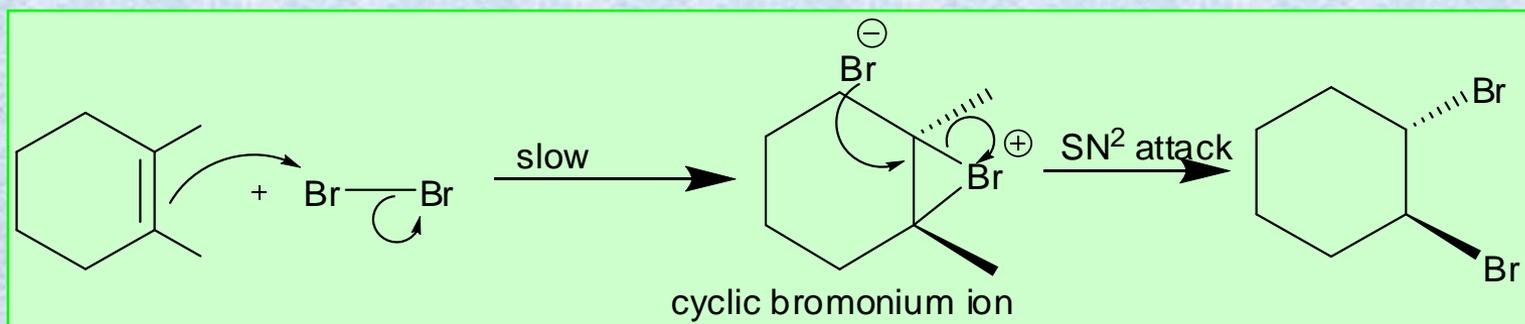


# 1. HALOGENATION REACTION

- In this reaction the pi bond of alkene and  $\sigma$  bond of halo acid is broken to form two new  $\sigma$  bonds.
- The reaction generally follows Markovnikov's addition.
- In the first step, the alkene pi bond acts as a Lewis base to add to an electrophile.
- In the second step, the halogen act as a Lewis base to attack the Lewis acid, i.e. the carbocation.
- Reaction is exothermic as reactant possesses higher energy bonds than the products .

## EXAMPLE OF BROMINATION REACTION

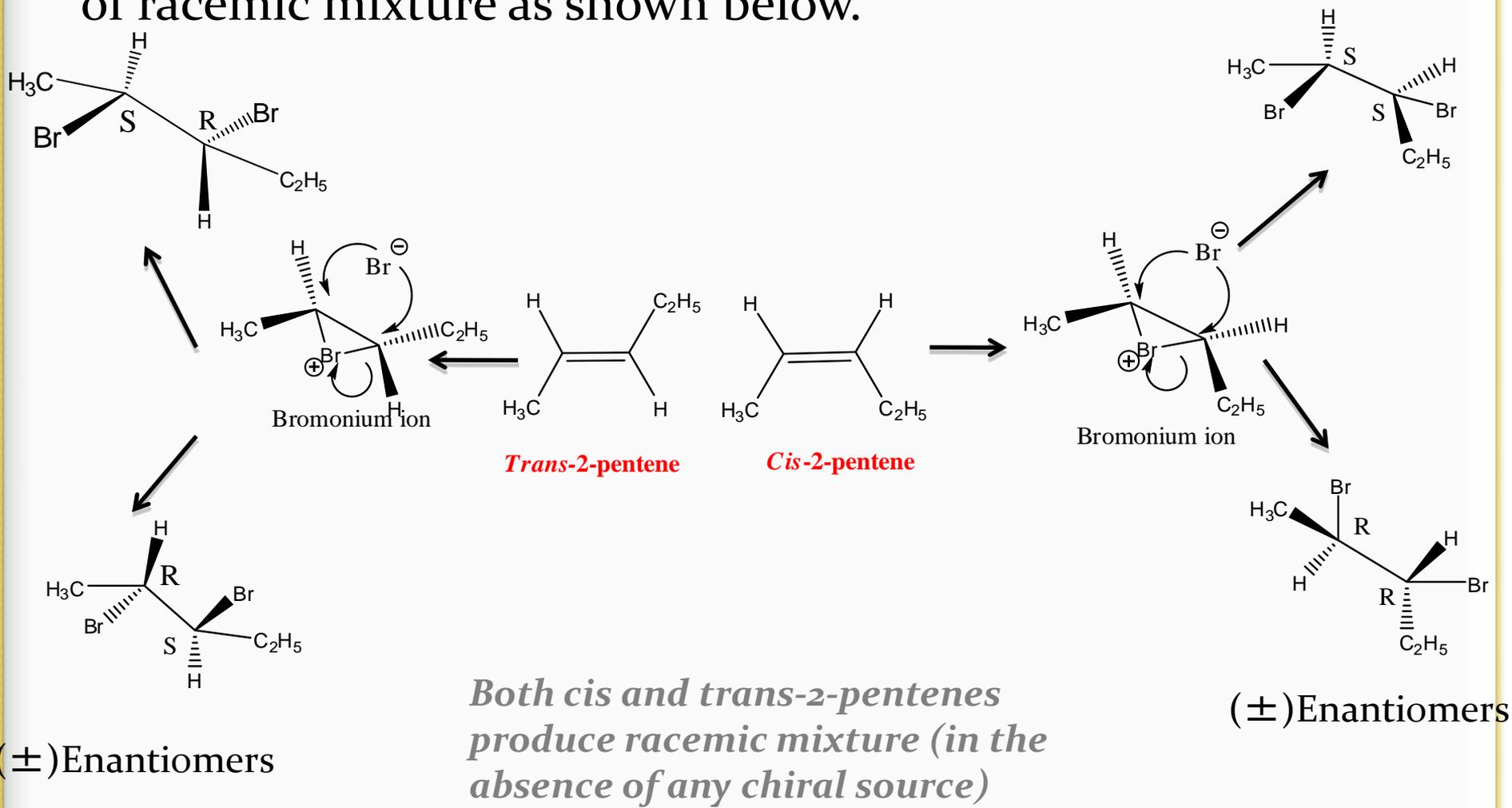
- In this reaction **alkene** interacts with **LUMO** of **bromine** (i.e. **empty  $\sigma^*$  orbital**) to form a three membered cyclic bromonium ion intermediate.
- The **bromide anion** attacks the **cyclic bromonium ion** resulting in generation of product 1,2-dibromide



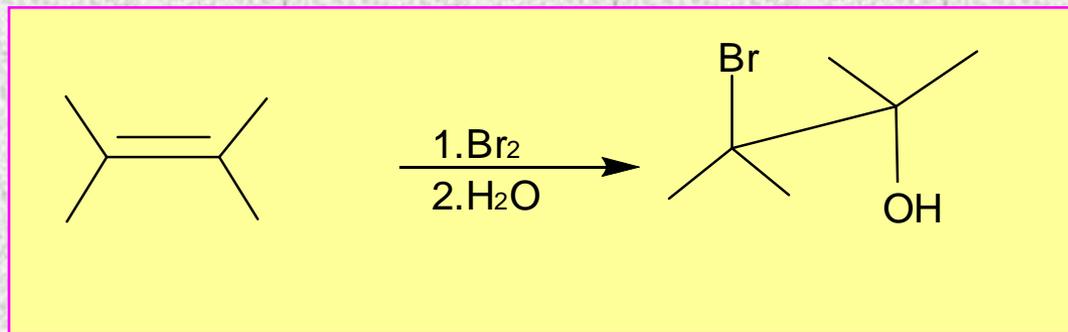
# STEREOCHEMISTRY

## STEREOSELECTIVITY

- Achiral olefin in halogenation reaction results in the formation of racemic mixture as shown below.

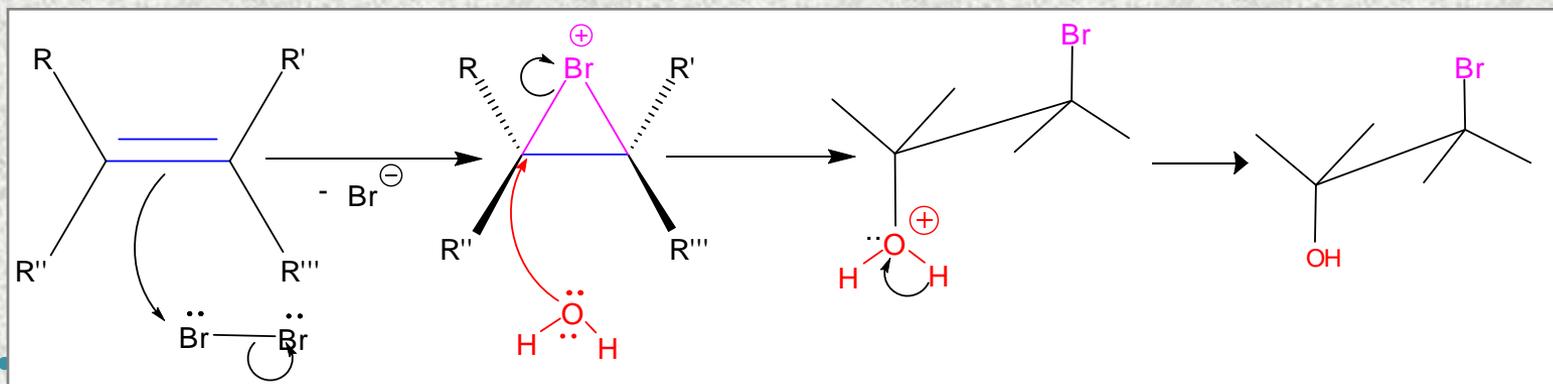


- The reaction of olefins with halo acids in the presence of aqueous solvents is termed as halohydrin reaction.
- Reaction generally follows **Markovnikov's rule**.
- The reaction takes place with **anti addition**.
- Bromine water & N-Bromo succinimide are commonly used reagents in bromohydrin formation.
- Chlorine water can be used for chlorohydrin formation.



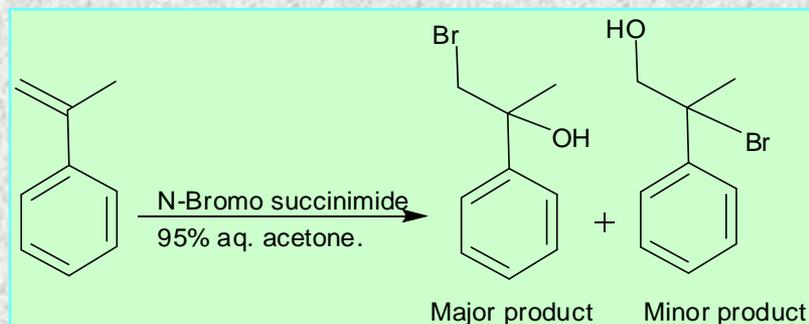
## MECHANISM (HALOHYDRIN FORMATION)

- The reaction starts with attack of  $\pi$  bond of alkene on  $\sigma^*$  bond of  $\text{Br}_2$  to form a three membered cyclic bromonium ion.
- Water can attack the bromonium ion as shown through a  $\text{S}_{\text{N}}2$  transition state. Markovnikov's rule is generally obeyed. Anti addition take place.

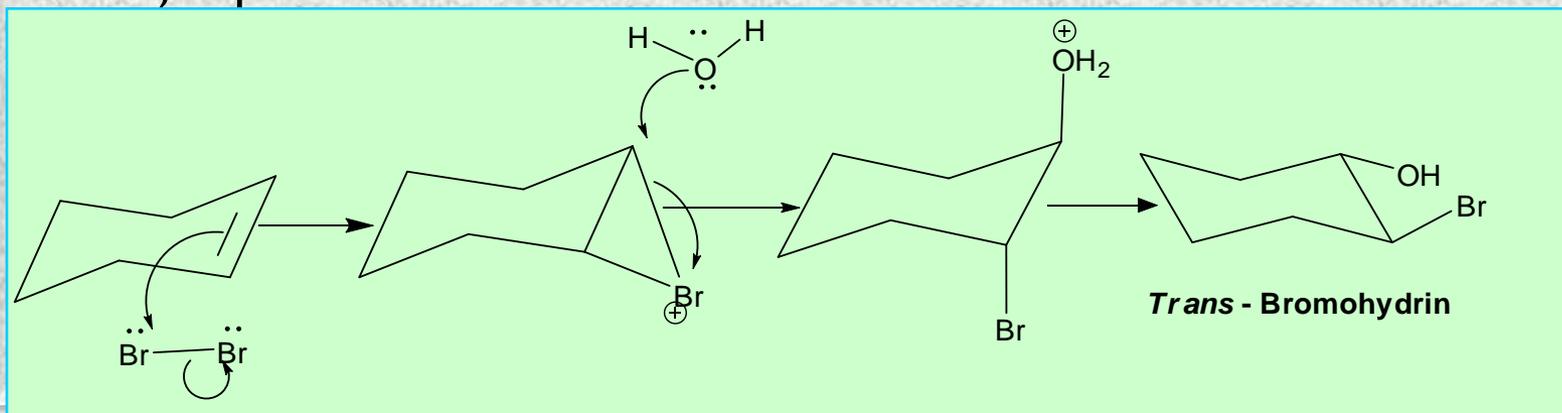


# STEREOCHEMISTRY

- Regioselectivity** :- In case of alpha methyl styrene the addition of hydroxyl occur at the more substituted carbon to give the major product.



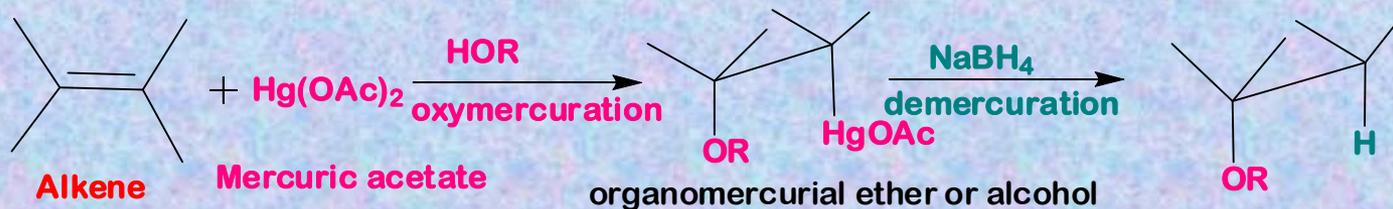
- Stereoselectivity** :- the addition of hydroxyl group occur anti to the halonium ion giving major product. In the bromohydrin formation reaction of cyclohexene we get *trans* bromohydrin as major product.



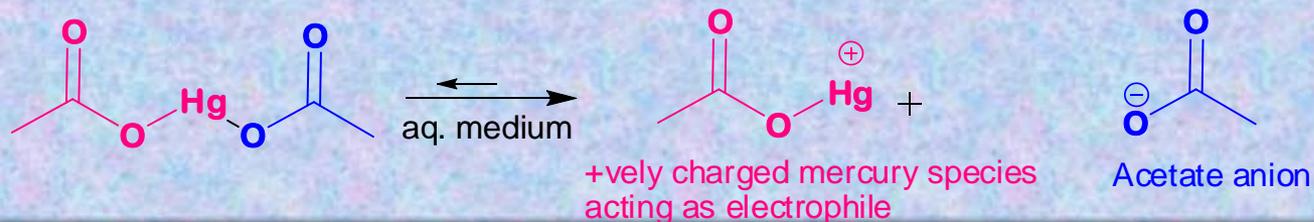
# ADDITION OF WATER OR SOLVENT TO ALKENE

( OXYMERCURATION , DEMERCURATION , SOLVOMERCURATION )

- Most of the alkenes do not favor hydration when subjected to aqueous acid.  
Here is a better approach to overcome this situation.
- **Oxomercuration** :- Convert alkene to organomercurial alcohol in aqueous solvent.
- **Demercuration** :- Transforms organomercurial alcohol to corresponding alcohol.
- **Solvomercuration** :- Transfer organomercurial ether to product ether as per the solvent used.
- General reaction :-



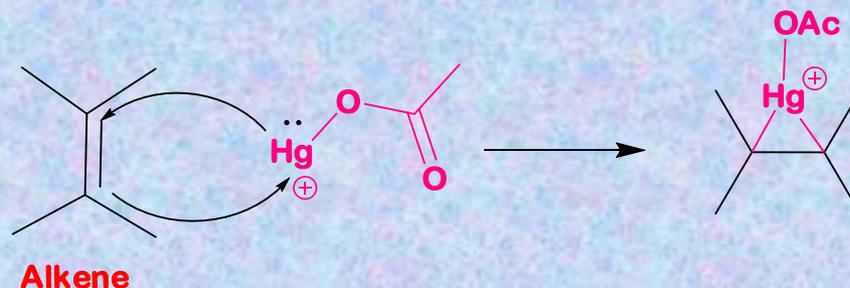
- Generation of reagent :-



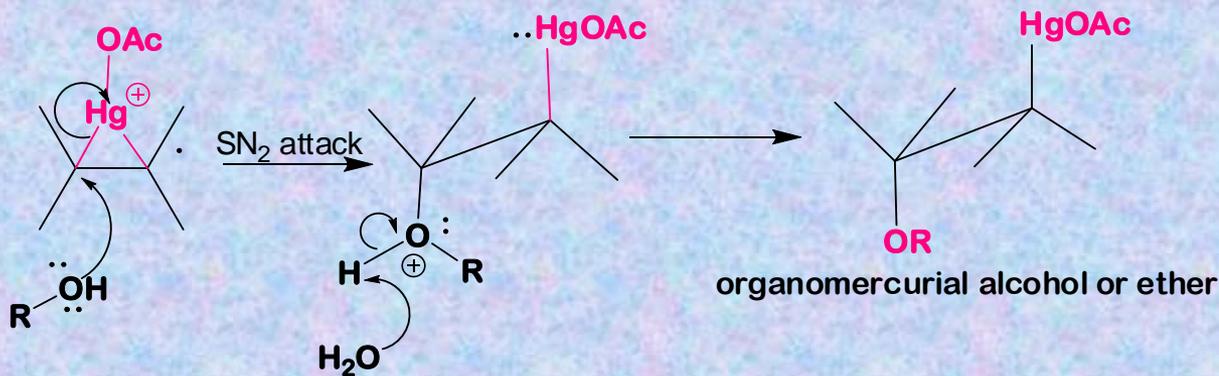
# MECHANISM ....

Mercuration /solvomercuration :-

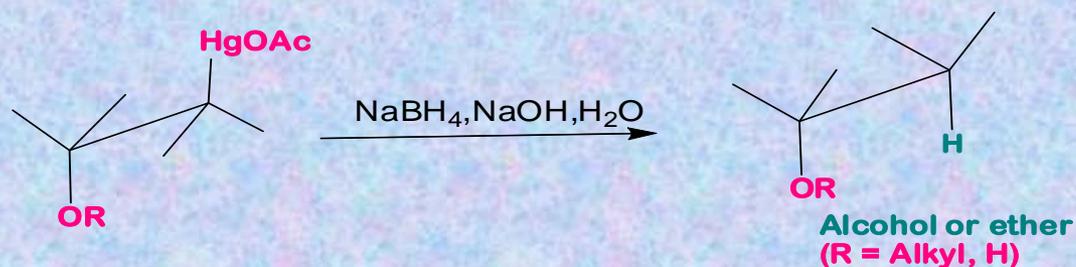
- The reaction starts with nucleophilic attack by double bond on +vely charged mercuric acetate species resulting in the formation of three membered cyclic mercurinium ion.



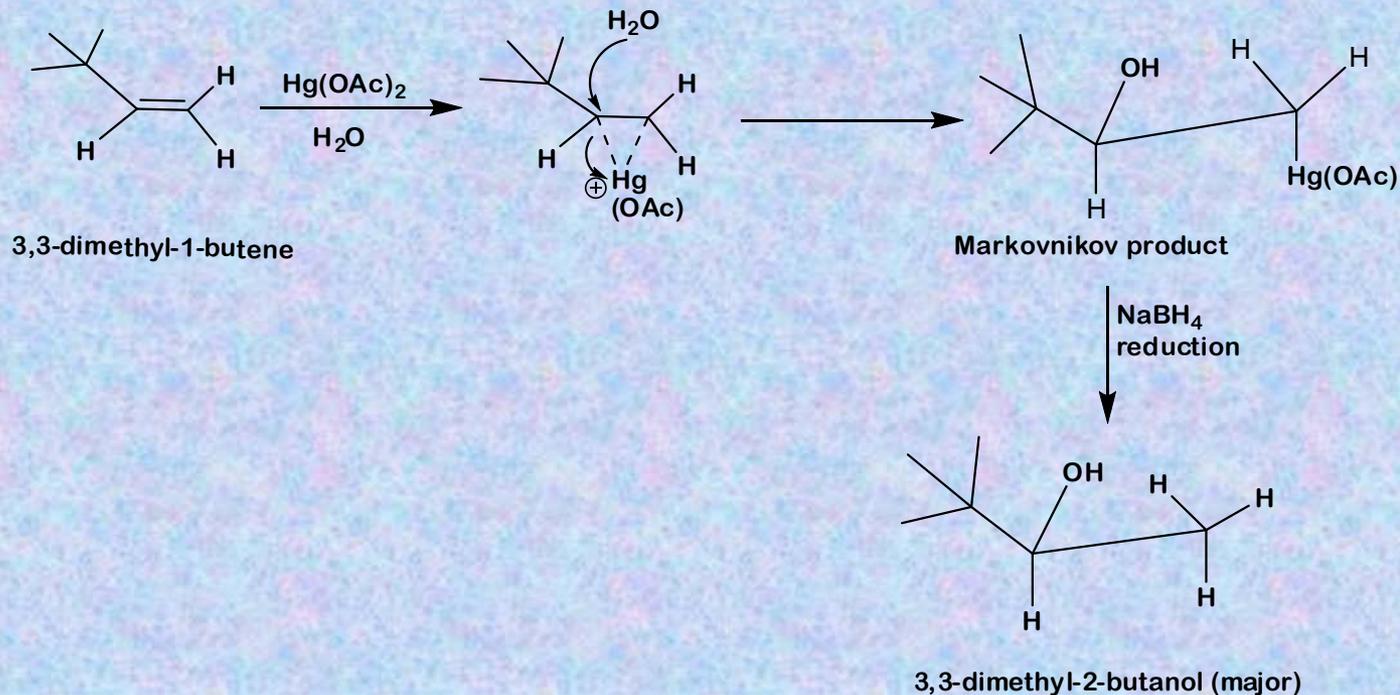
- In this step  $\text{S}_{\text{N}}2$  attack by the solvent leads to the formation of organomercurial species.



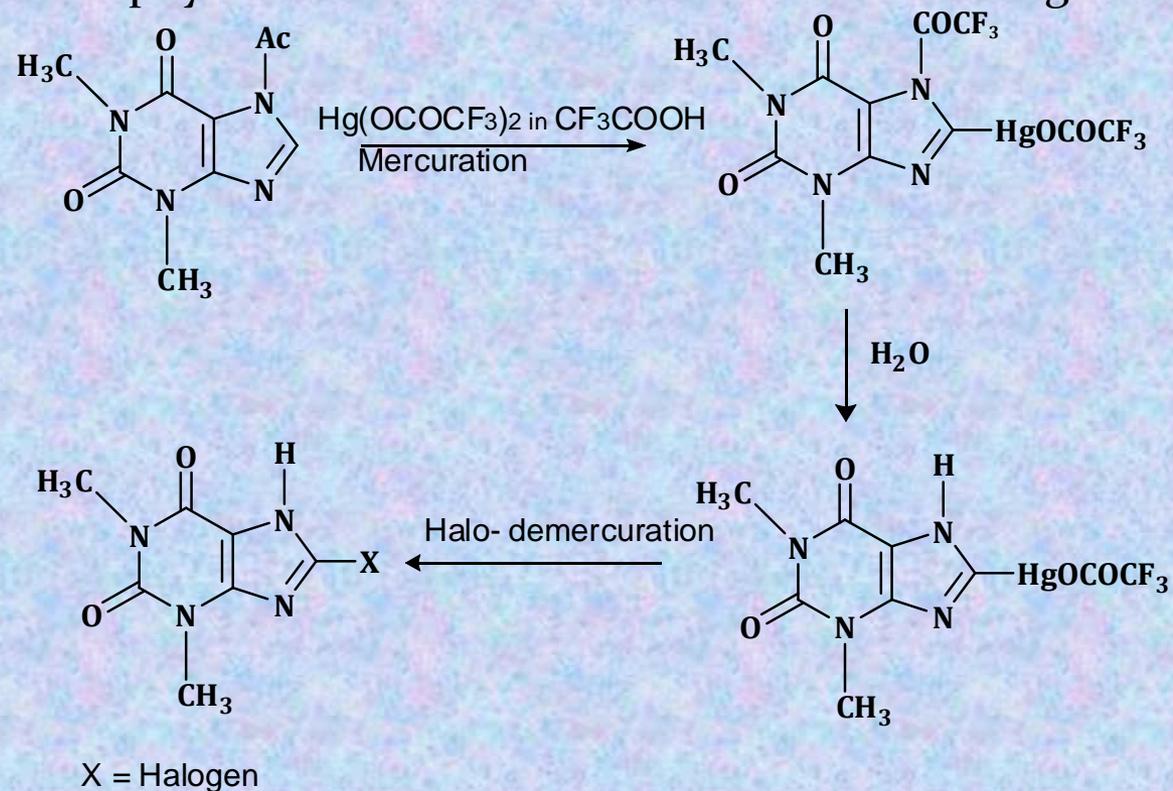
- Demercuration :- In this step there is substitution of hydrogen in place of mercuric group to give the final alcohol or ether.



- The reaction take place following Markovnikov's rule i.e. addition of hydrogen occurs at the least substituted end.



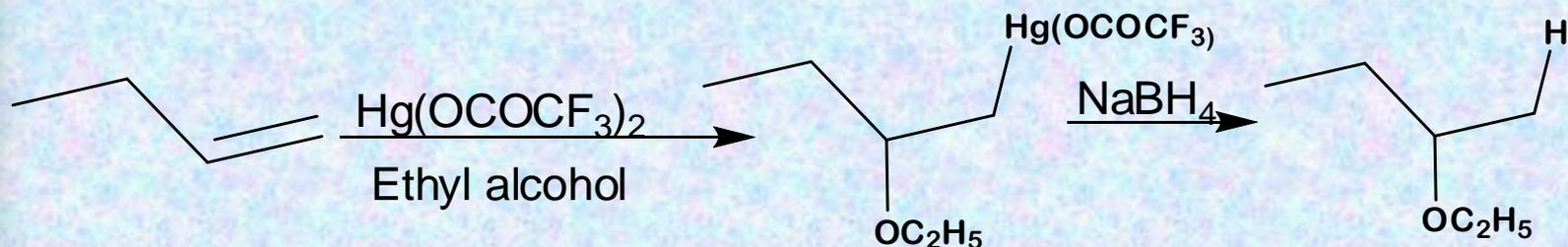
- Substituted Theophylline Mercurials and Their Demercuration Reactions.



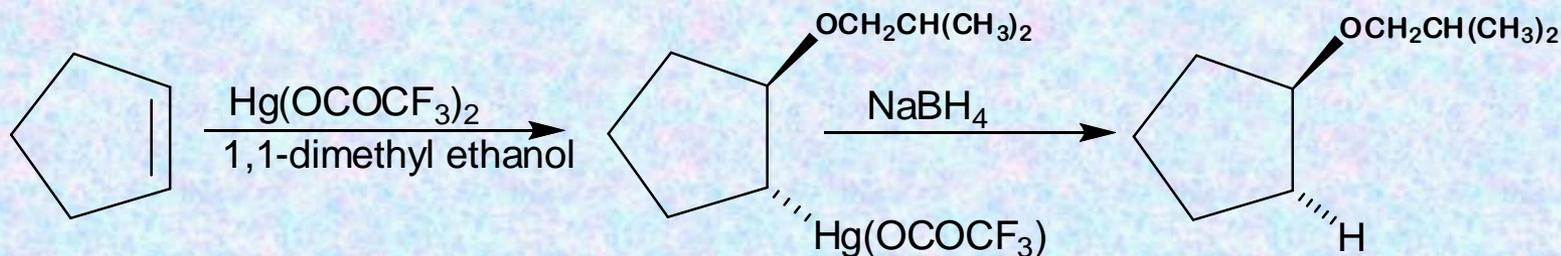
- Bergstrom, D. E.; Ruth, J. L. *J. Am. Chem. Soc.* 1976, 98, 1587.
- Korn, A. P.; Ottensmeyer, F. P.; Jack, T. R. *Inorg. Biochem.* 1979, 10, 235.

## SOLVOMERCURATION EXAMPLES...

- Solvomercuration in the presence of trifluoroacetate mercury (II) salt  $\{\text{Hg}(\text{OCOCF}_3)_2\}$ . The reason for using trifluoro acetate salt instead of acetate salt is to enhance electrophilicity .
- Examples :-1. conversion of 1-ethyl ethene to corresponding ether.



- Ether synthesis from cyclopentene.



# DIOL FORMATION REACTIONS

- Diol formation in alkenes can be achieved from various reactions :-

*Hydroxylation with Potassium permanganate.*

*Osmium tetroxide catalysed dihydroxylation.*

*Upjohn dihydroxylation.*

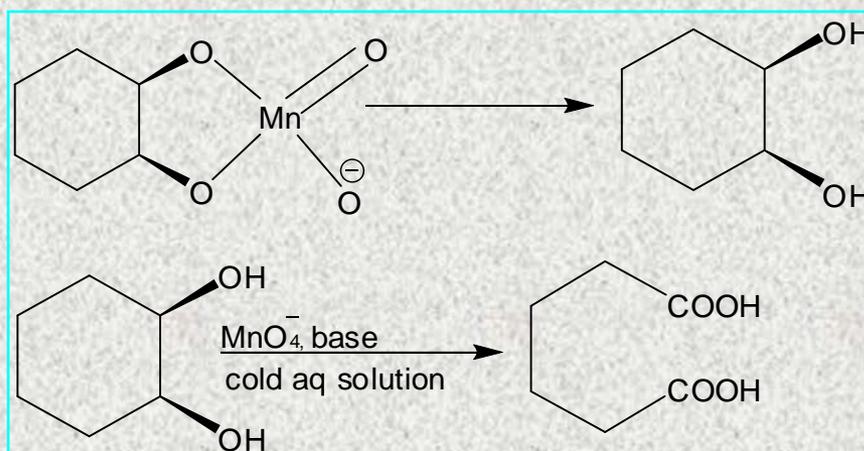
*Woodward reaction.*

*Prevost reaction.*

*Epoxide ring opening reaction.*

# HYDROXYLATION WITH POTASSIUM PERMANGNATE.

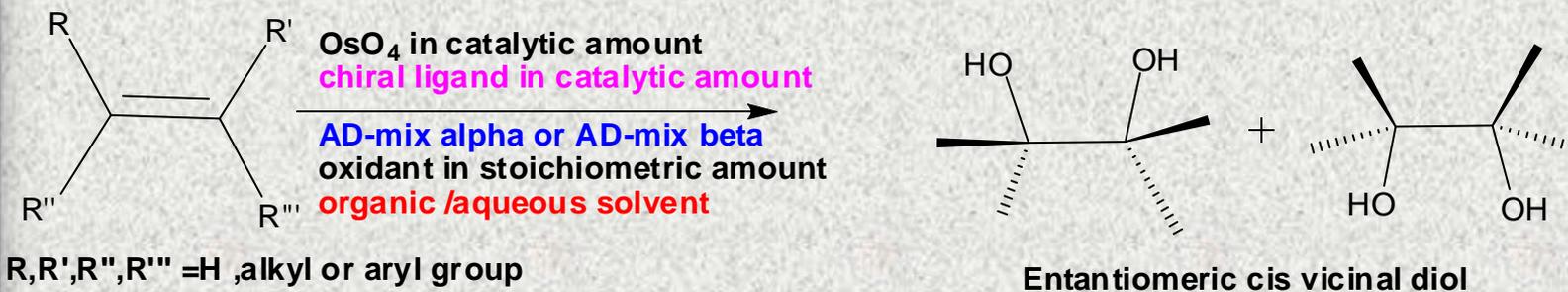
- Hydroxylation is carried out in cold media preferably in basic conditions.
- Hot conditions may lead to oxidation forming carboxylic acid
- The hydroxylation occur with *syn* addition & formation of cyclic intermediate.



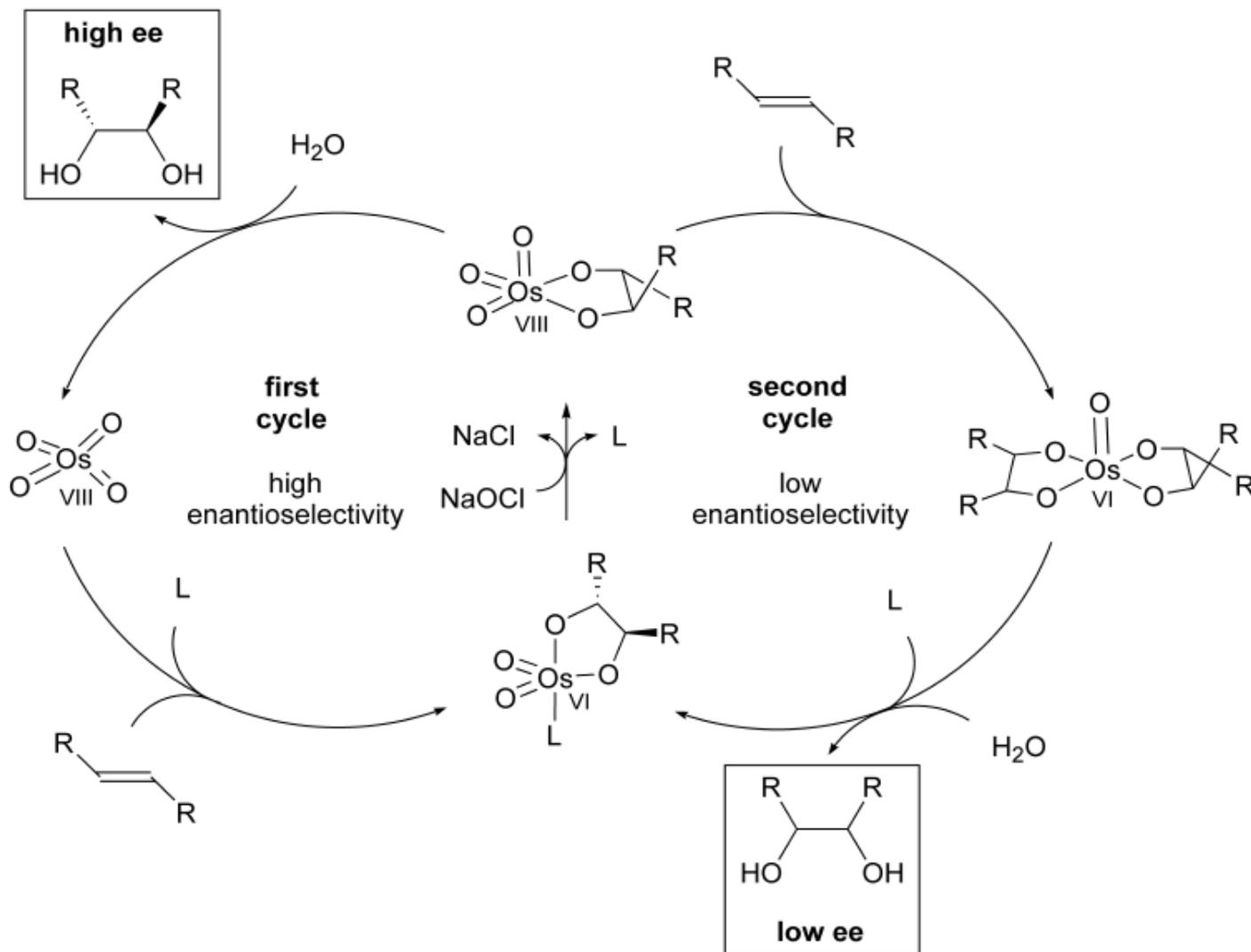
- Disadvantages :-
- The product yield obtained is very low.
- The product can be a mixture of diol & carboxylic acid.
- A better stereoselective epoxidation can be achieved with Osmium tetroxide.

# OSMIUM TETROXIDE CATALYZED ASYMMETRIC DIHYDROXYLATION (SHARPLESS DIHYDROXYLATION)

- In 1980, Sharpless reported the first asymmetric dihydroxylation of olefins by replacing pyridine with a chiral tertiary amine ligand derivatives dihydroquinine acetate with improved yield.
- The addition of diol takes place without affecting the other functional groups in the molecule.
- Reagents are commercially available as preformulated mixtures: (**Asymmetric Dihydroxylation**) AD-mix  $\alpha$  and AD-mix  $\beta$  containing the necessary bidentate chiral ligand, stoichiometric oxidant, and the osmium tetroxide in the form of dipotassium osmate dihydrate ( $K_2OsO_4(OH)_4$ ).



# Recent Developments in the Osmium-catalyzed Dihydroxylation of Olefins :



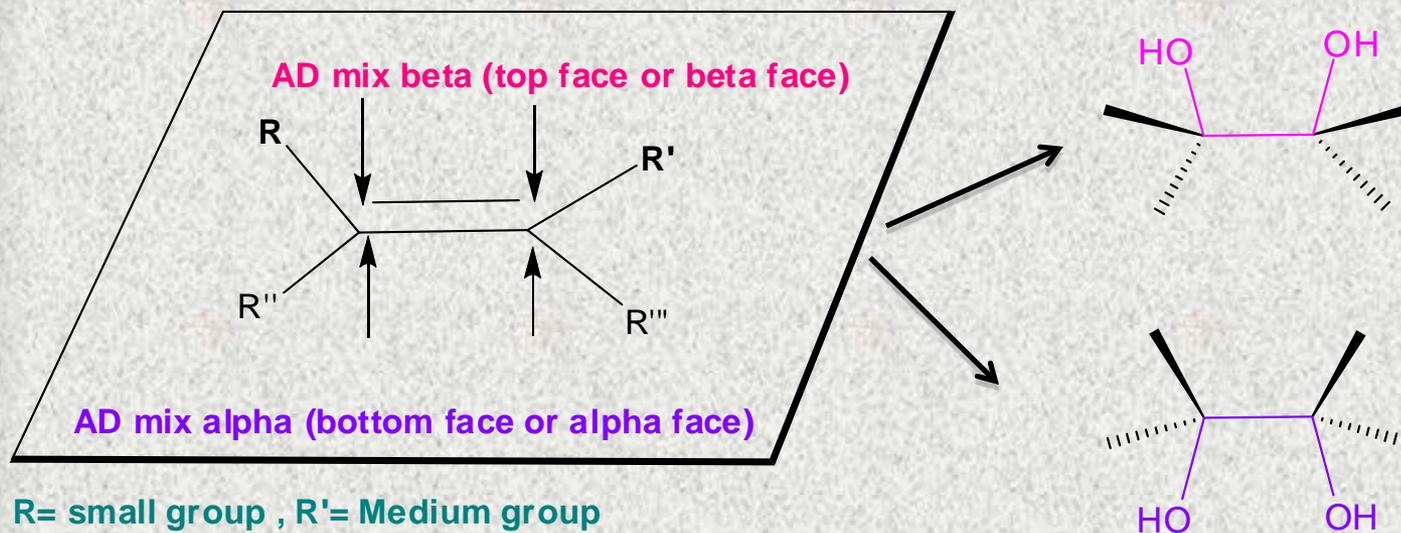
The two catalytic cycles in the asymmetric dihydroxylation

# SELECTIVITY OF ADDITION

- The addition of both hydroxyl groups occur on the syn face.
- The selectivity of the face is decided as per the reagent used.

AD-mix  $\alpha$  :- (DHQ)<sub>2</sub>PHAL + K<sub>2</sub>O<sub>8</sub>O<sub>2</sub>(OH)<sub>4</sub> + K<sub>3</sub>Fe(CN)<sub>6</sub>

AD-mix  $\beta$  :- (DHQD)<sub>2</sub>PHAL + K<sub>2</sub>O<sub>8</sub>O<sub>2</sub>(OH)<sub>4</sub> + K<sub>3</sub>Fe(CN)<sub>6</sub>

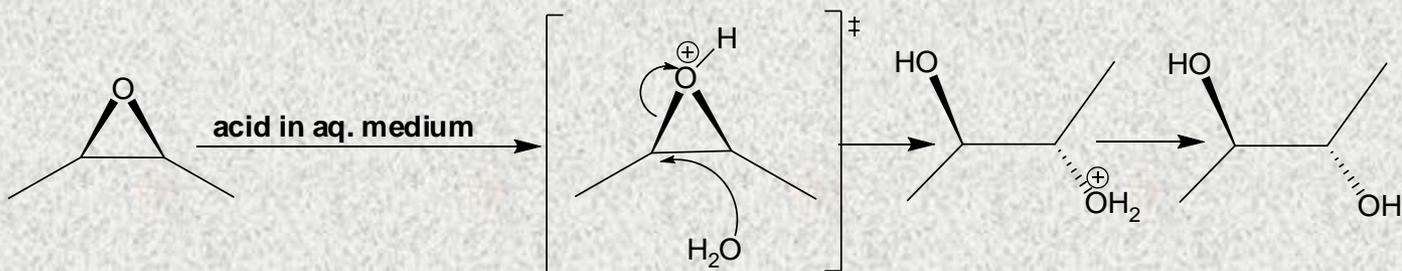


Enantiomeric *cis* or  
*vicinal diol*

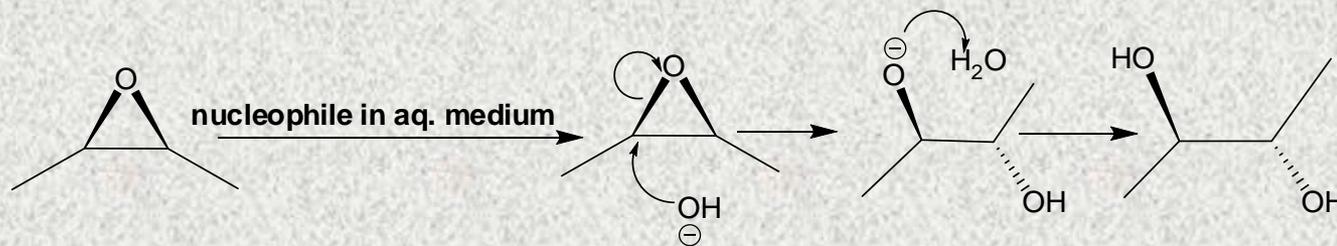
## EPOXIDE RING OPENING REACTION.

- Epoxide ring opening results in the formation of *trans* diol.
- Epoxide ring opening can be achieved by using an electrophilic or a nucleophilic reagent.
- The ring opening occurs by  $S_N2$  mechanism, hence the diol formed will exhibit a *trans* geometry.

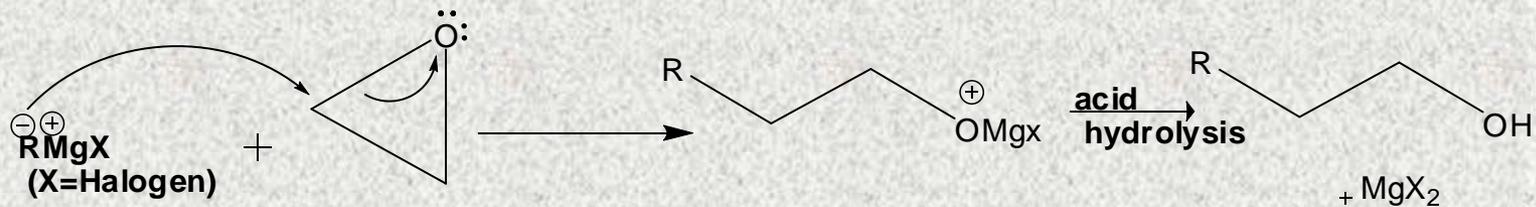
### Electrophilic ring opening



### Nucleophilic ring opening



- **Ring opening in the presence of organometallic reagents (RMgX, RLi, RC<sup>≡</sup>CM, LiAlH<sub>4</sub>, NaBH<sub>4</sub>, transition metal catalyst ):-**
- Organometallic reagents can act as nucleophile in epoxide ring cleavage reaction
- The reaction takes place by SN<sub>2</sub> attack resulting in the formation of *trans* product.
- Organometallic reagent react with epoxide in basic media as they are strong nucleophiles.
- When these nucleophilic reagent attack, it results in breaking of the epoxide ring with formation of alcohol after acidic workup.
- In the case of Grignard reaction the C-C bond formation occur at the β position from the newly formed hydroxyl group.



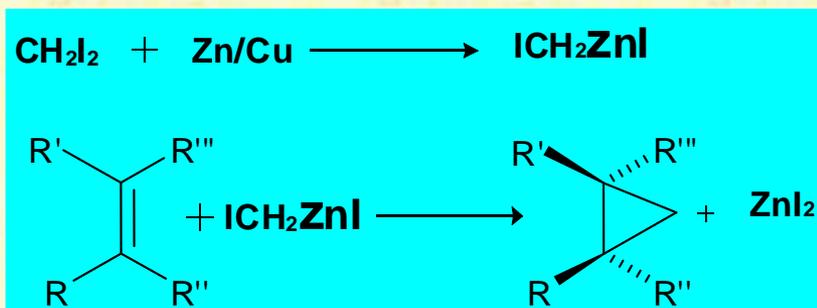


# CYCLOPROPANE RING FORMATION REACTIONS

# SIMMON-SMITH REACTION.

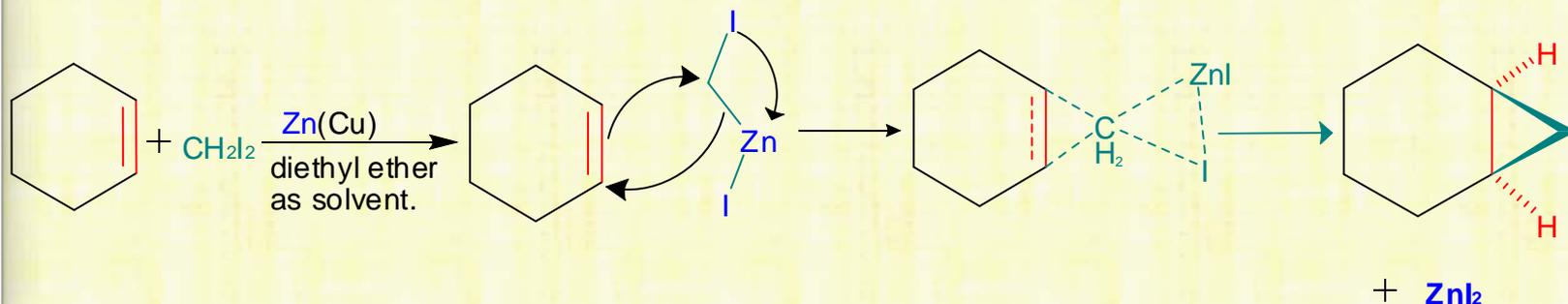
HOWARD ENSIGN SIMMONS, JR. AND R. D. SMITH

- A **Organo chelotropic**, **stereospecific** reaction of **alkene** with **di-iodo methane** (used for synthesis of non halogenated cyclopropane) in the presence of **copper-zinc couple** is called **Simmon-Smith reaction**.
- The **methylene group** is added to a **less sterically hindered face** of alkene making the reaction **stereo specific**.
- General reaction :-

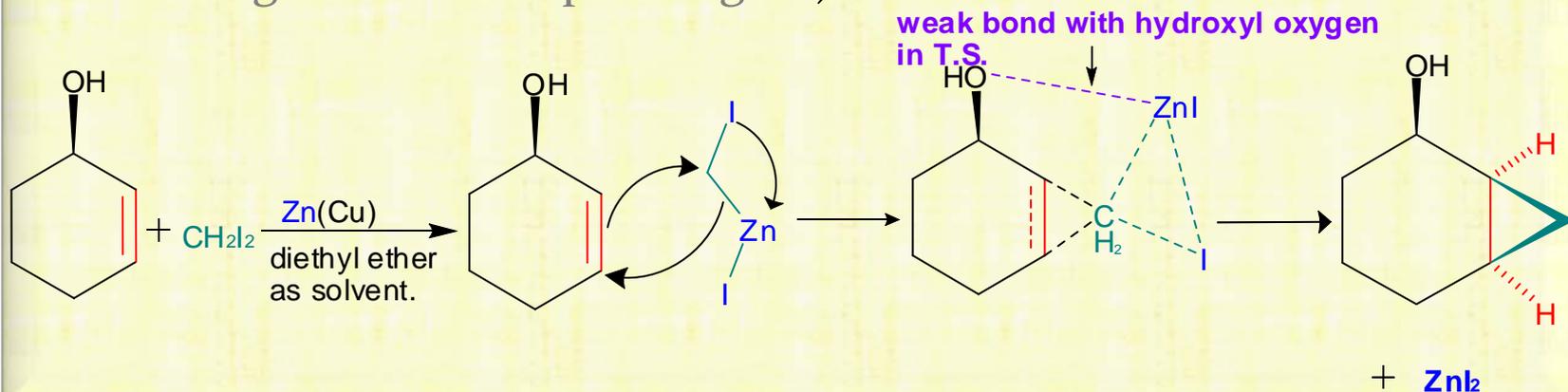


# MECHANISM

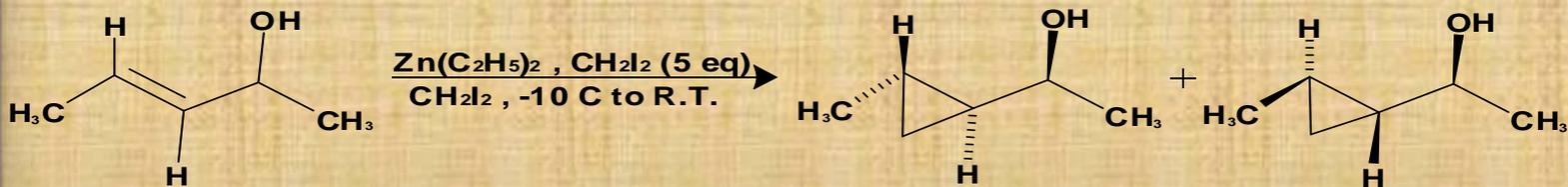
- The mechanism is concerted which involves **carbene transfer** assisted by Zinc catalyst. The stereoselectivity depends on the face on which the addition takes place & presence of different groups on the substrate.



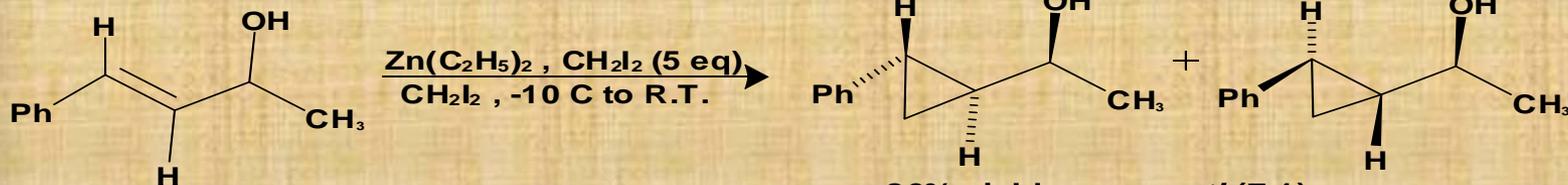
- In substrates like allylic alcohols, the cyclopropane ring formation occurs on the same side of the  $-\text{OH}$  group. (this is due to a weak bonding in the corresponding TS).



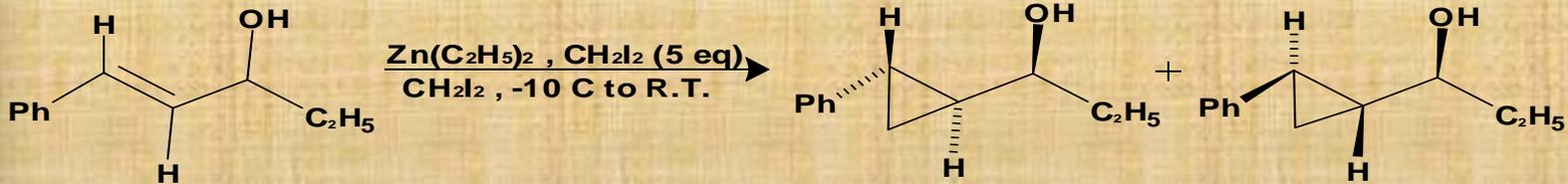
# More examples on cyclopropanation



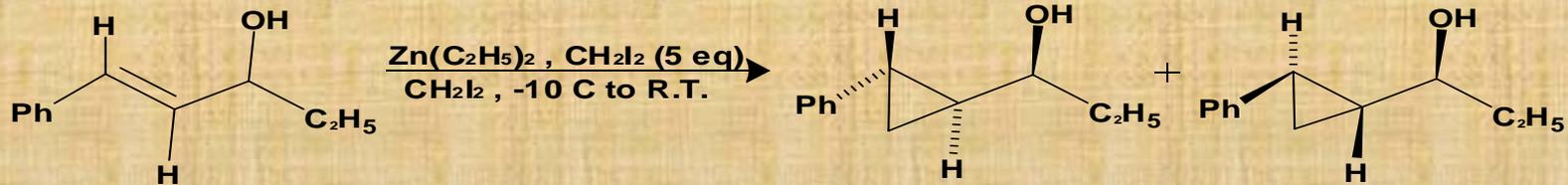
75% yield *syn* : *anti* (6:1)



86% yield *syn* : *anti* (7:1)



97% yield *syn* : *anti* (130:1)

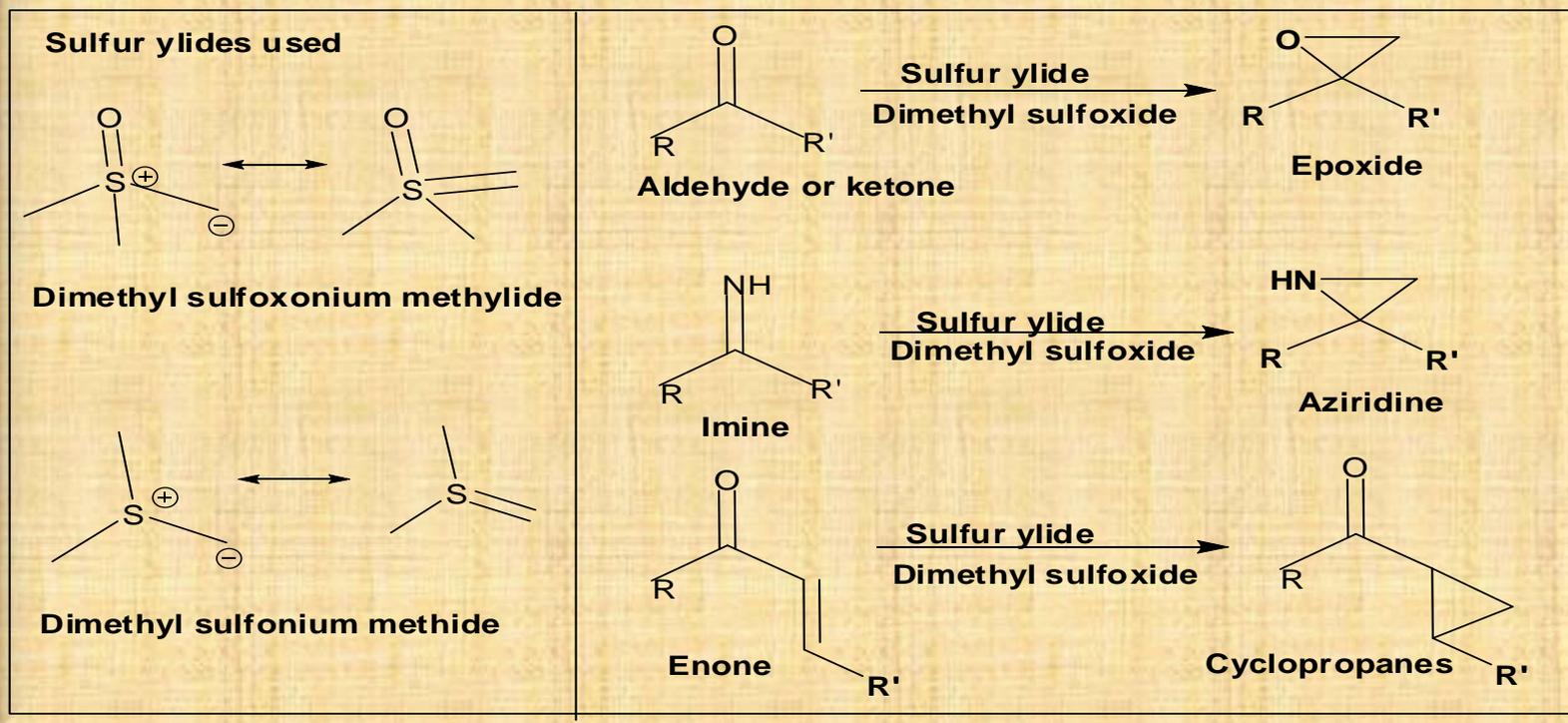


87% yield *syn* : *anti* (110:1)

# JOHNSON-COREY-CHAYKOVSKY REACTION

[A. WILLIAM JOHNSON , E.J. COREY , MICHAEL CHAYKOVSKY ]

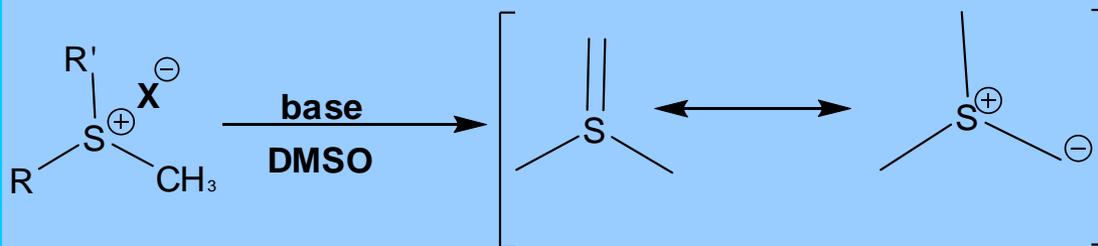
- The reaction involves the synthesis of **epoxide from aldehyde & ketone**, **aziridines from imines**, **cyclopropanes from enones**.
- The reaction is **diastereoselective** favoring *trans* substitution in the product regardless of the initial stereochemistry.
- The **ylides** are generated *in situ* by the **deprotonation of sulfonium halides with strong bases**.
- General reaction :-



# MECHANISM

- In the reaction the nucleophilic sulfur ylide attacks the carbonyl or imide substrate.
- The negative charge is transferred from anionic carbon of ylide to electronegative group of substrate as a result sulfonium cation is expelled & formation of cyclopropane or epoxide ring take place.

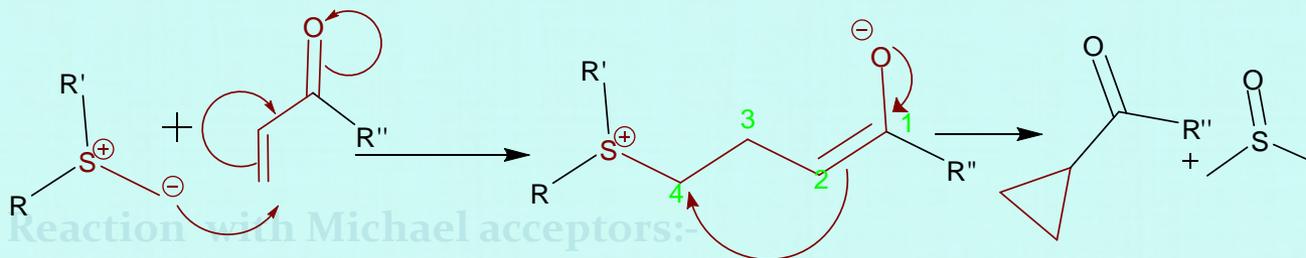
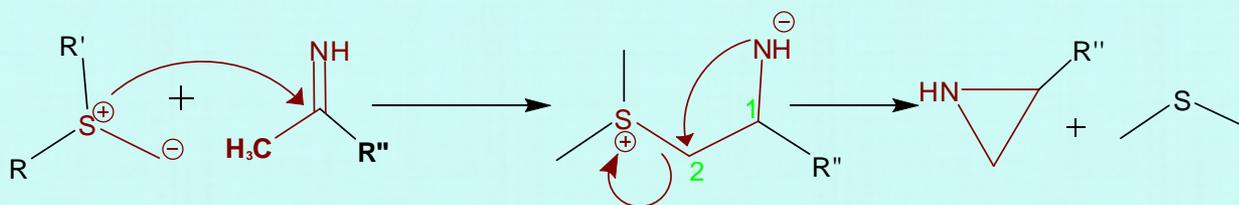
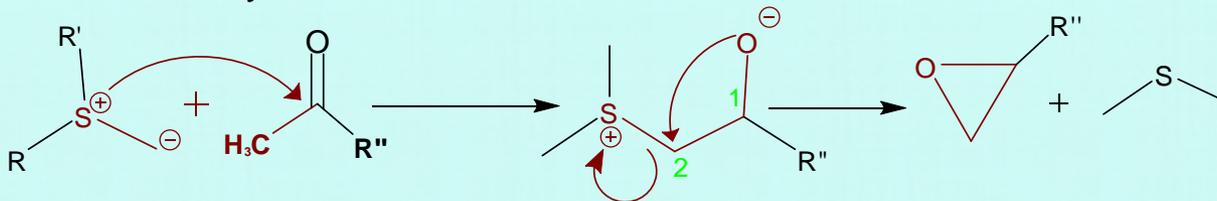
Generation of sulfonium halide (In situ ,presence of strong bases)



When R , R' are one or both **electron withdrawing group** the **ylide** formed is **stable**.

# CONTD.....

Reaction with aldehyde or ketone.



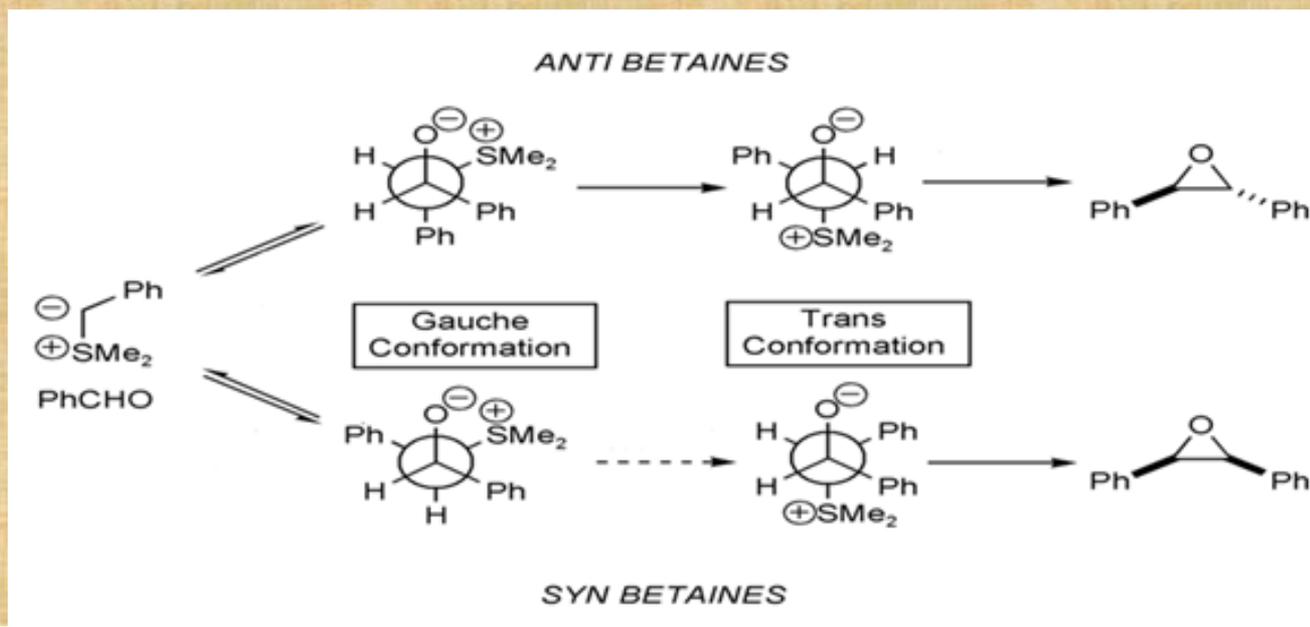
Unstabilised ylides(kinetically controlled product):-the epoxide formed is irreversible ,unstable undergoes ring closure to form 1,2 addition product i.e. epoxide.

Stabilised ylides (thermodynamic product):- ylides stabilized with electron withdrawing group give 1,4 addition product. Although 1,2 addition product is formed but it is reversible kinetic product. 1,4 addition product formation result due to strong sigma bond formation at the expense of pi bond forming stable product.

# STEREOCHEMISTRY

In cyclopropanation, the reaction occurs with *anti* betaine formation resulting in *trans* product formation.

- This is due to rotation around the central bond in a molecule to attain a more stable conformation, a back side attack result in *trans* product formation.
- In the case of the *synbetaine* the barrier to bond-rotation was higher than reversal to starting materials whereas for the *anti-betaine*, the barrier to returning to starting materials was higher than bond rotation to the *transoid* conformation.



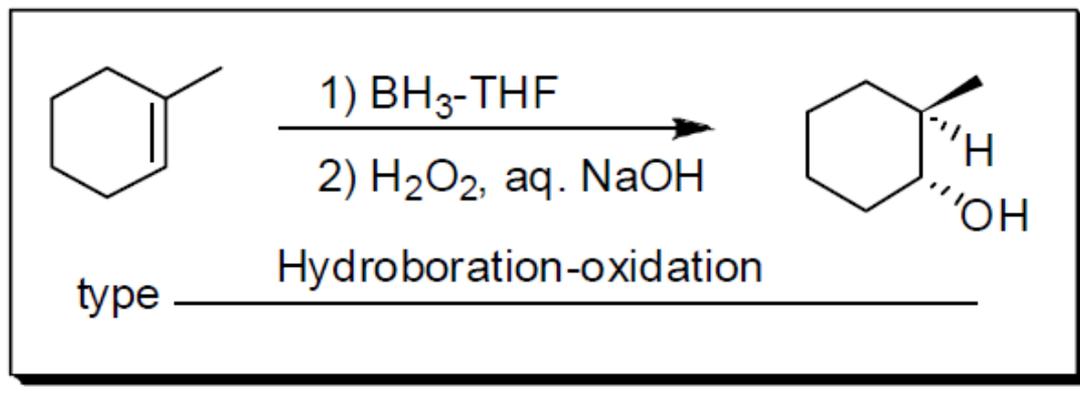
# HYDRO BORATION REACTION

HERBERT C. BROWN

- The addition of water to alkene in the presence of boron reagent are known as **hydroboration-oxidation** reaction.
- The addition follows **syn addition** with **cis stereoselectivity**.
- Unlike other addition reactions, here the **hydroxyl group** get added to the **least substituted carbon**.
- In this reaction **peroxide** also play a equal role in deciding the **site of addition**.
- In such reaction the reagent  $BH_3$  is used which consist of **electrophilic boron** and **electron donation is done by hydrogen atom**.
- **No carbocation intermediate is involved** in this reactions suggesting that a **concerted addition** take place.
- If  $BH_3$  is used as reagent it can hydroborate three alkene units. The **number of alkenes** undergoing **hydroboration are equal to no. of hydrogens attached directly to boron** in the borane reagent.
- The product obtained in such reactions are a **racemic mixture**, the **stereoselectivity** can be improved by using chiral borane reagents.

## REACTION :-

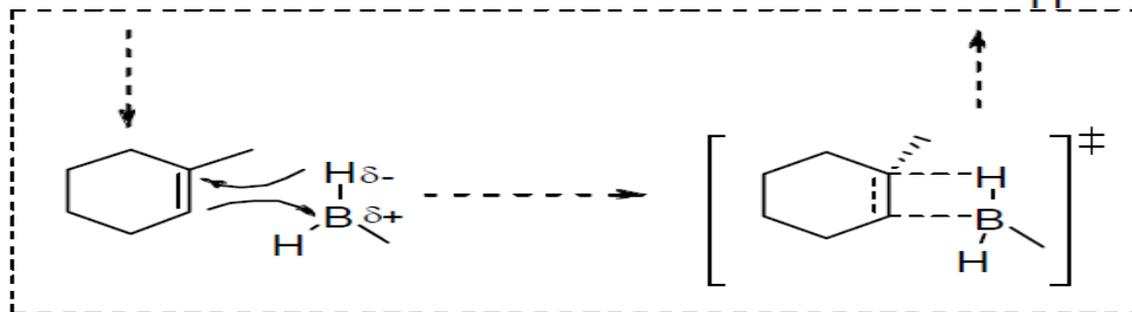
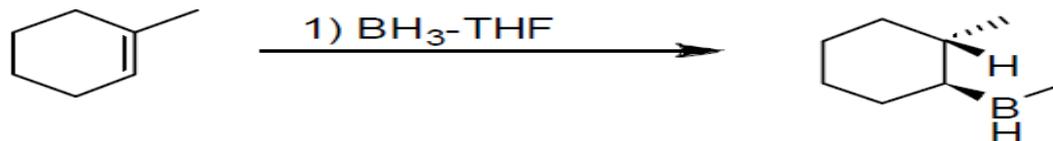
- Concerted addition of boron to sterically least hindered carbon.
- The oxidation occur in the presence of peroxide to give the *syn* addition product.



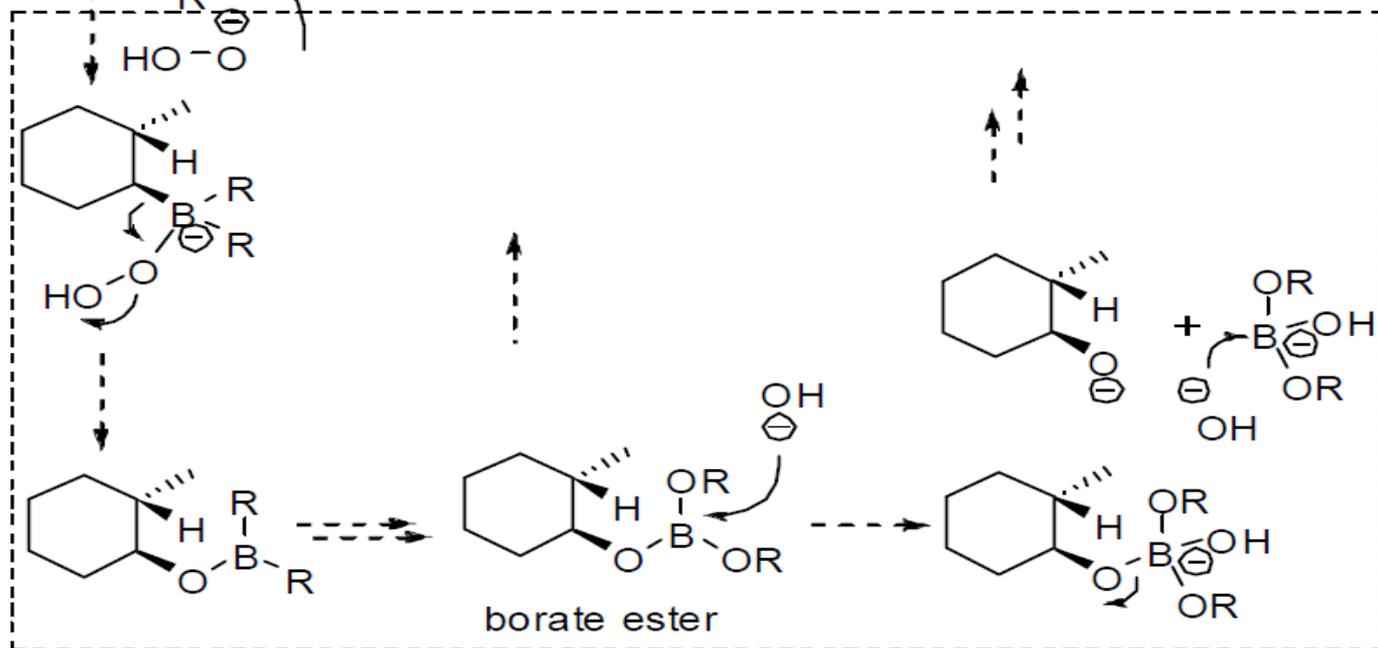
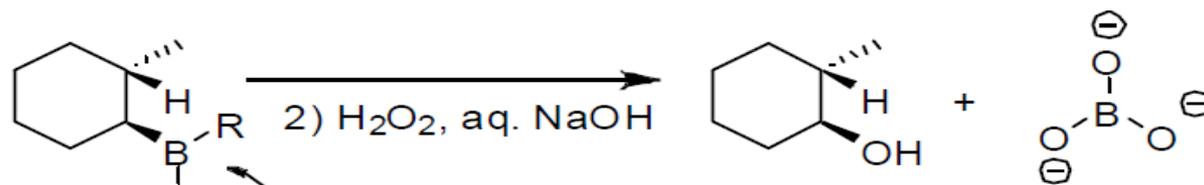
## MECHANISM OF HYDROBORATION:-

- In the first step alkene acts as a nucleophile and attack on electrophilic Boron.
- In the Second step ,Peroxide act as nucleophile & attack the electrophilic boron followed by migration of C-B bond to form C-O bond. Hydrolysis result in formation of alcohol.

First Step:



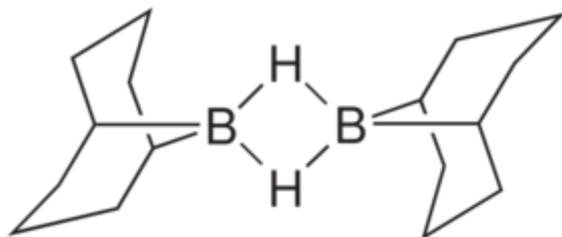
Second Step:



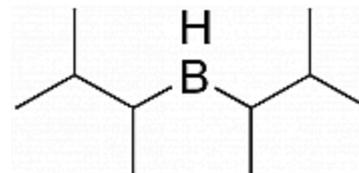
# STERESELECTIVITY

- Some of the commonly used boron reagents for regioselective hydroboration reactions.

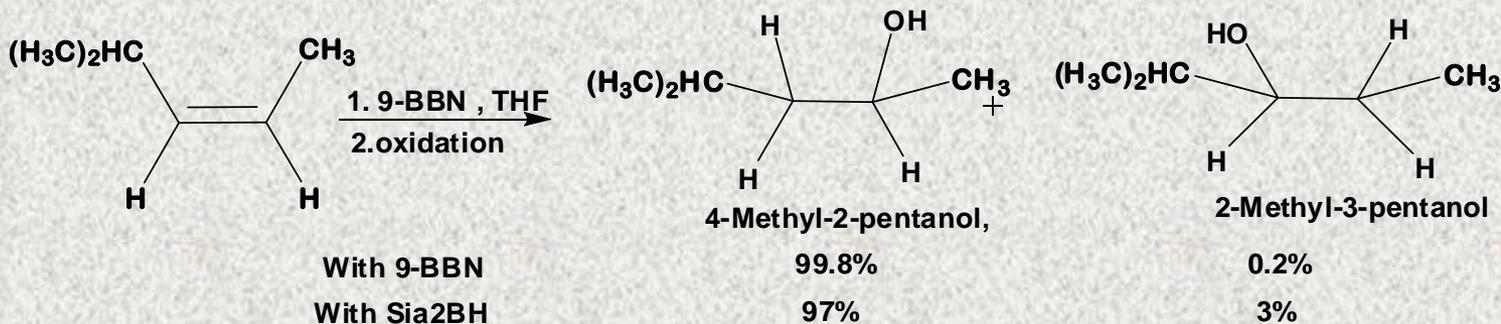
## 9-Borabicyclo(3.3.1)nonane (9-BBN)



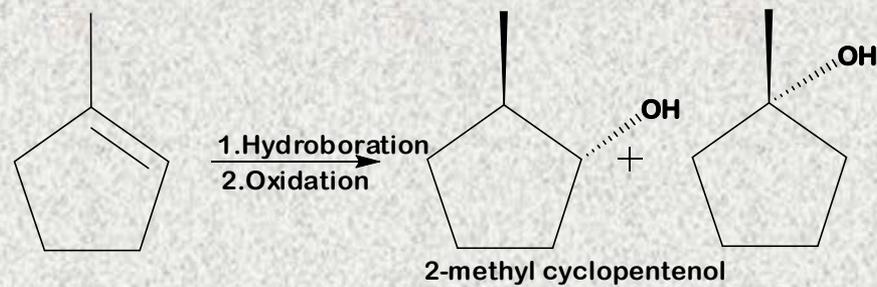
## Disiamylborane. (Sia<sub>2</sub>BH)



- EXAMPLES:-
- Hydroboration of *cis*-4-methyl-2-pentene



- Hydroboration of 1-methyl cyclopentene.



With 9-BBN

99.9%

BH<sub>3</sub>

98.5%

HBCl<sub>2</sub>

99.8%

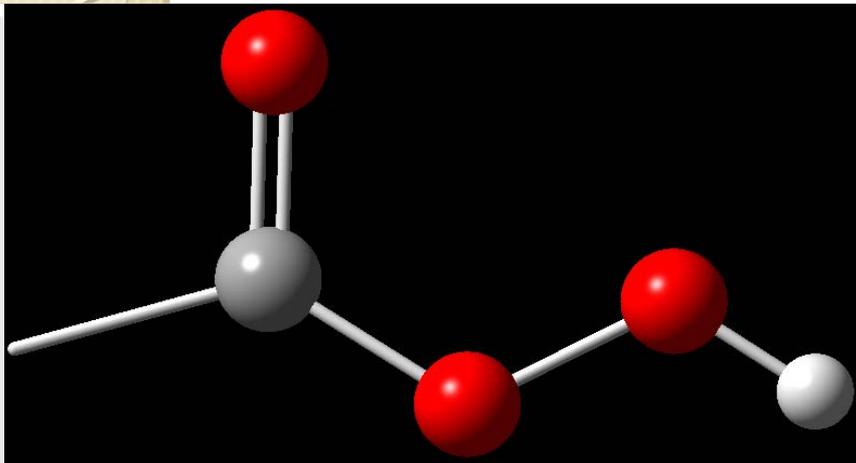


# EPOXIDATION REACTIONS

# EPOXIDE FORMATION REACTION

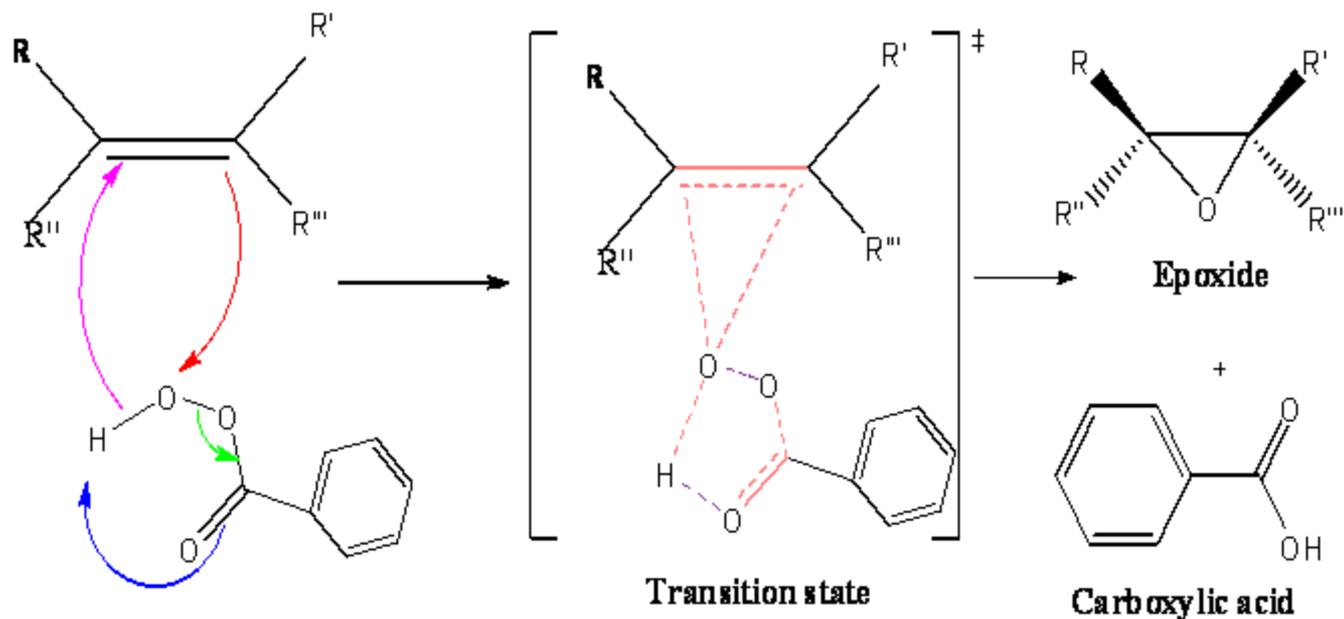
## Some General Feature of Electrophilic Epoxidation

- Epoxidation using peroxy acids is described here
- Epoxidation is favored by electron donating substituent.
- More the electron donating ability of the substituent on the double bond, higher is the energy of alkene HOMO resulting in increase in nucleophilicity.
- More nucleophilic the pi bond is, greater is interaction with the  $\sigma^*$  orbital of the electrophilic O-O bond increasing the rate of oxirane formation.



- A peroxy acid or peracid is an acid in which an acidic  $\text{-OH}$  group has been replaced by an  $\text{-OOH}$  group. They are less acidic compared to carboxylic acids.
- All peroxy acids are very powerful oxidizing agents with electrophilic properties.
- Peracids that are not commercially available are prepared by the reaction of the acid chloride or anhydride with high strength hydrogen peroxide or urea and hydrogen peroxide.
- The major attribute of peroxy acids is the presence of electrophilic oxygen between the carbonyl carbon and the  $\text{-OH}$  group, which is attacked by  $\pi$  ( $\pi$ ) bond containing compound with high electron density.
- Peroxy carboxylic acid have electron deficient low energy LUMO which is the  $\sigma^*$  O-O bond.

## MECHANISM OF EPOXIDATION



**MECHANISM** :-(the colour correspond to the steps in mechanism)

Step I :- Attack of nucleophilic alkene on electrophilic oxygen of peroxy acid.

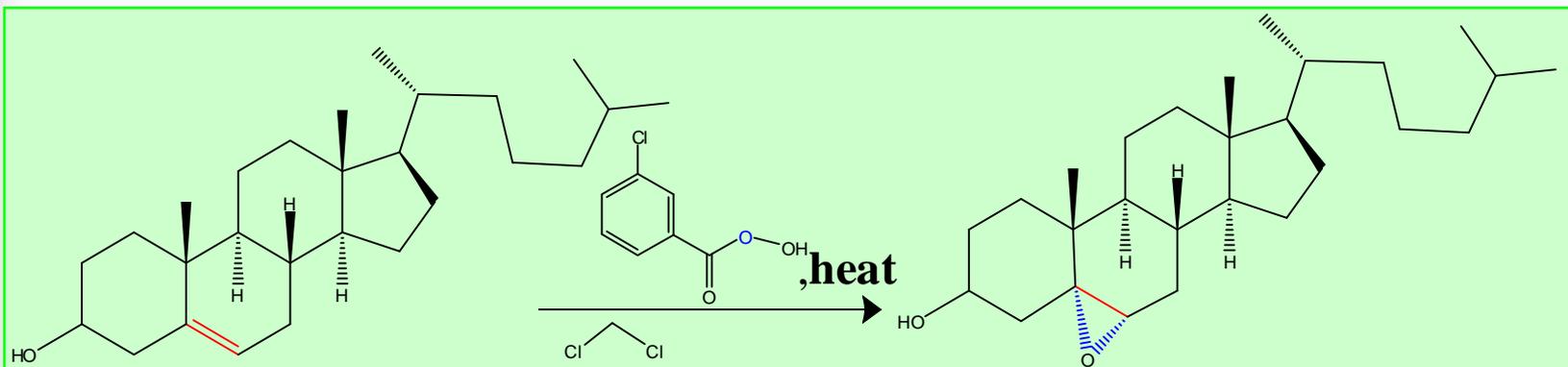
Step II :- Transfer of electron density from O-O bond to electrophilic carbonyl Oxygen.

Step III :- Attack of carbonyl oxygen on -OH Hydrogen leading to it's abstraction.

Step IV :- Release of Carboxylic acid.

# STEREOCHEMISTRY OF EPOXIDATION

- Formation of epoxide occurs on the same face of  $\pi$  ( $\pi$ ) bond being attacked, hence geometry of alkene is preserved in the product.
- e.g., epoxidation of cholesterol to  $5\alpha,6\alpha$ - epoxy cholestan- $3\beta$ -ol using m-chloro perbenzoic acid.



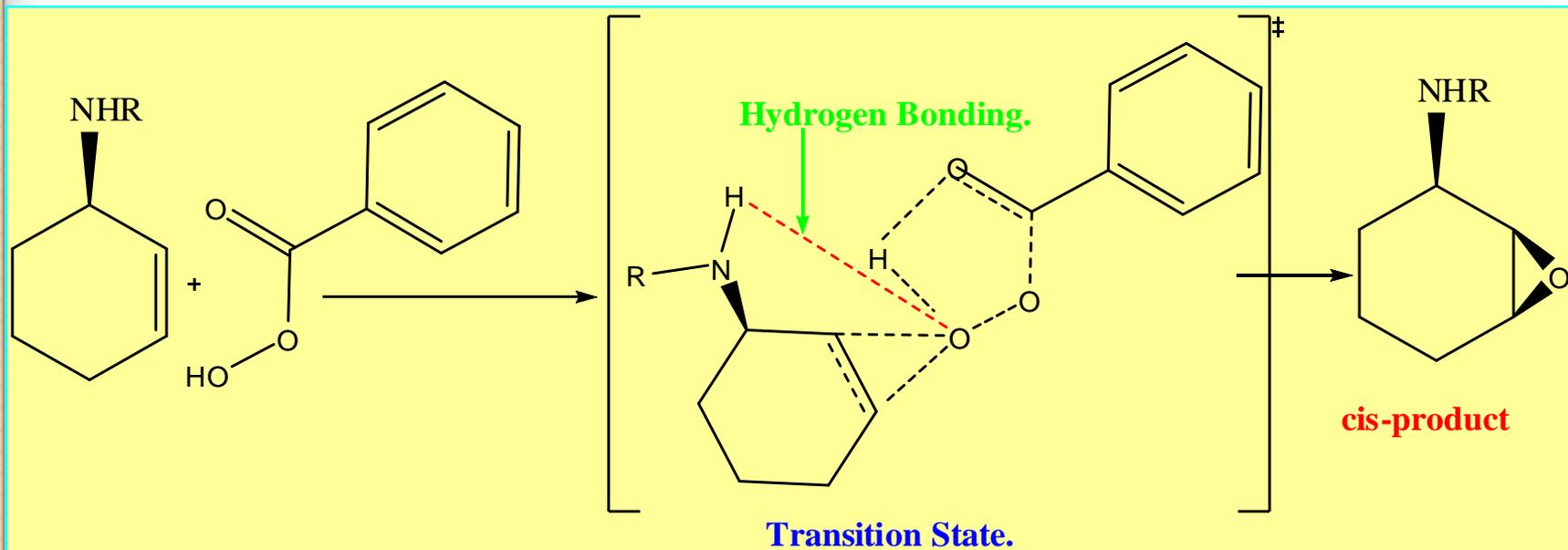
Cholesterol

$5\alpha,6\alpha$ - epoxy cholestan- $3\beta$ -ol

- Epoxidation occurs from (alpha attack) lower side of cholesterol molecule selectively .

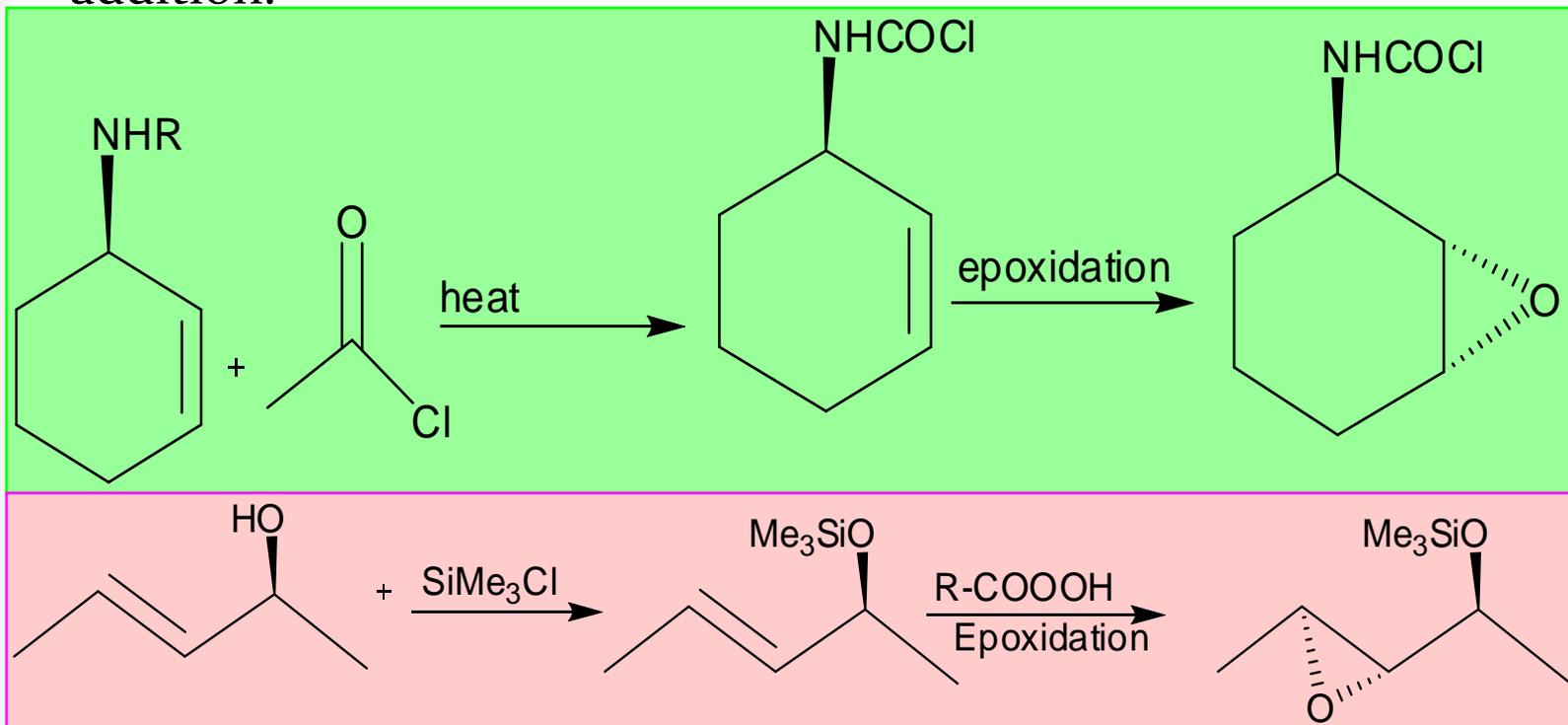
## INFLUENCE OF -OH AND -NH GROUP ON EPOXIDATION.(THE CONCEPT OF HYDROGEN BONDING).

- When an allylic alcohol or allylic amine is epoxidized the peroxy acid prefer to attack from the same side of -OH or -NH .
- The TS stabilization through hydrogen bonding leads to a *syn* product in excess.



# EPOXIDATION IN THE ABSENCE OF HYDROGEN BONDING

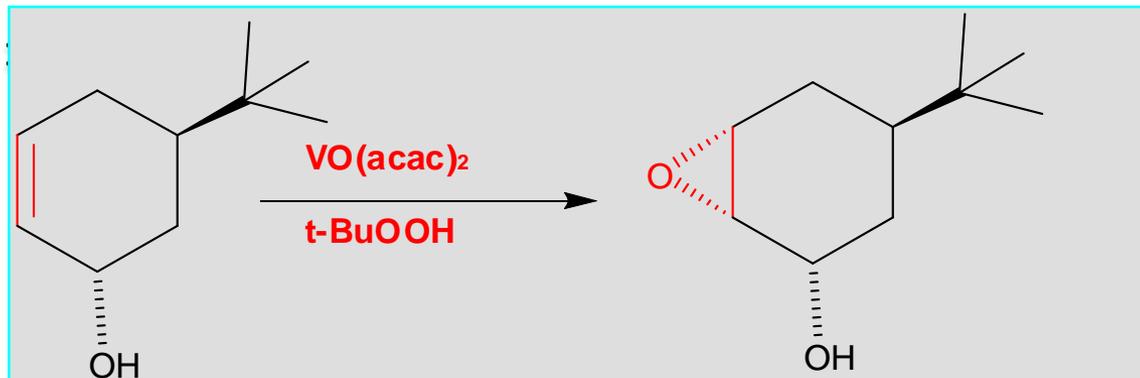
- In the example below when the amino group was masked, major product was obtained with epoxide below the plane i.e., *anti* addition.



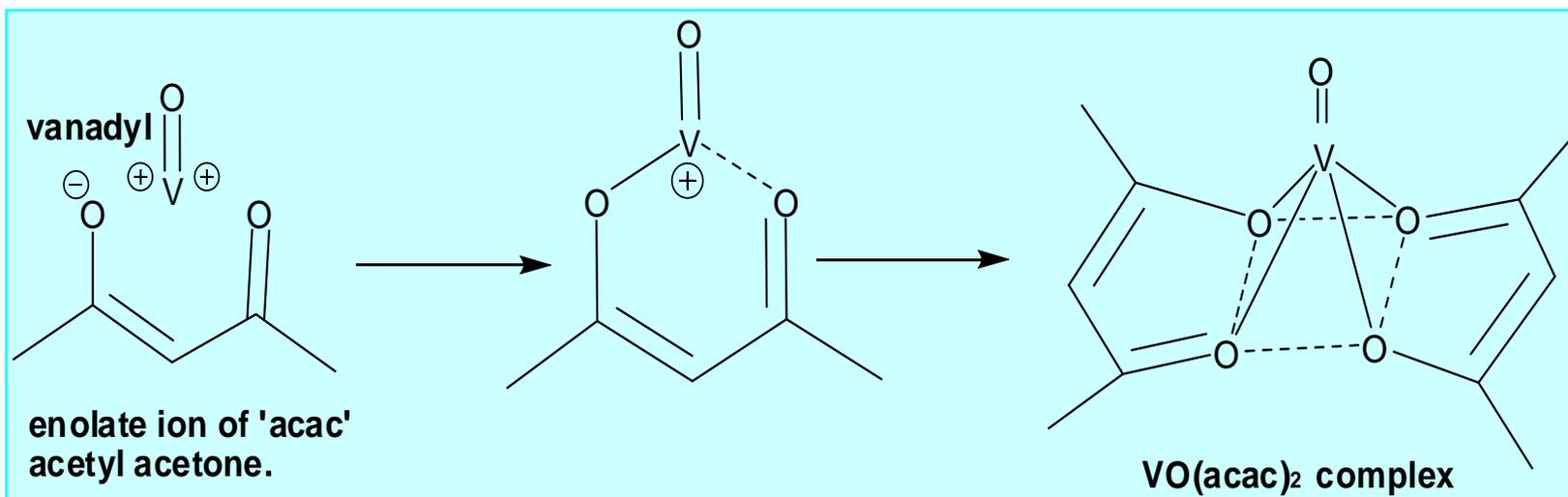
- Hence, distereotopic addition to double bond in compound with hydrogen bond donors can be controlled.

# VANADIUM CATALYZED EPOXIDATION

- **Syn epoxidation** of allylic alcohol in presence of  $\text{VO}(\text{acac})_2$  & tert-butyl hydro peroxide .
- General reaction :

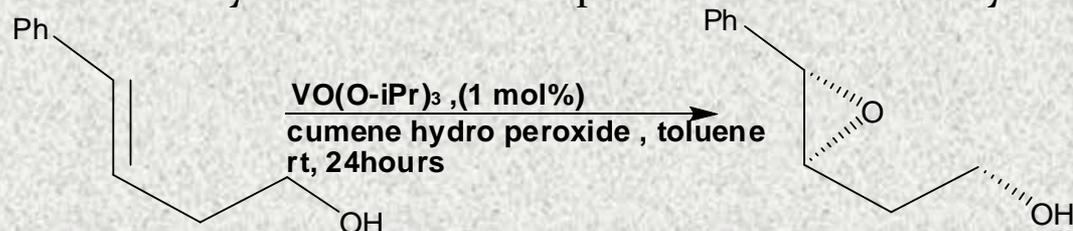


Formation of vanadyl complex :-



# REACTIONS

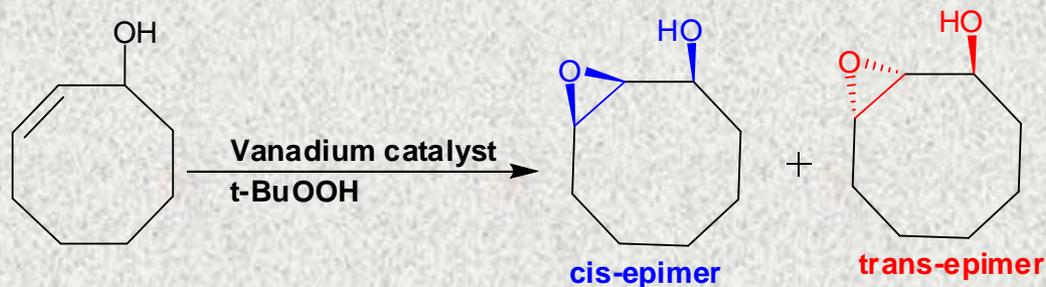
- Vanadium catalyst works best for epoxidation of homoallylic alcohol



J. AM. CHEM. SOC. 2007, 129, 286-287

90%yield,96% ee

- Homogenous catalysis showed higher yield but relatively same enantiomeric excess as in case of heterogeneous catalyst. [ACS 0002-7863/79/15OI]

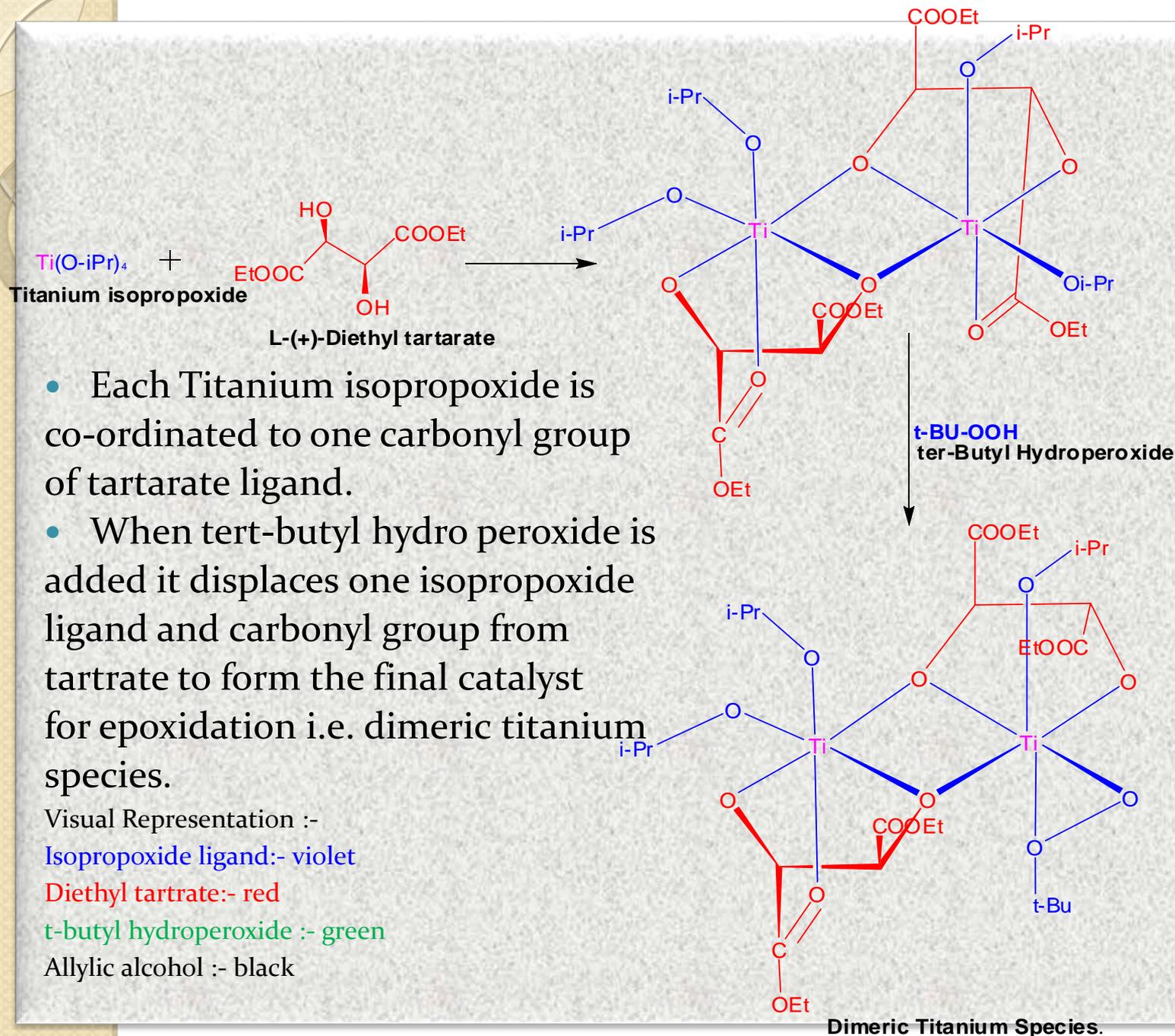


Ligand%	valency	% yield	Cis epimer	Trans epimer	system
VO(acac) <sub>2</sub>	+4	83	97	3	Homogenous
VCl <sub>4</sub>	+4	86	96	4	Homogenous
VO(SO <sub>4</sub> )	+4	65	97	3	Homogenous
V(acac) <sub>3</sub>	+3	79	97	3	Homogenous
V <sub>2</sub> O <sub>5</sub>	+5	29	95	5	Heterogenous
CsH <sub>5</sub> V(CO) <sub>4</sub>	+1	75	94	6	Homogenous

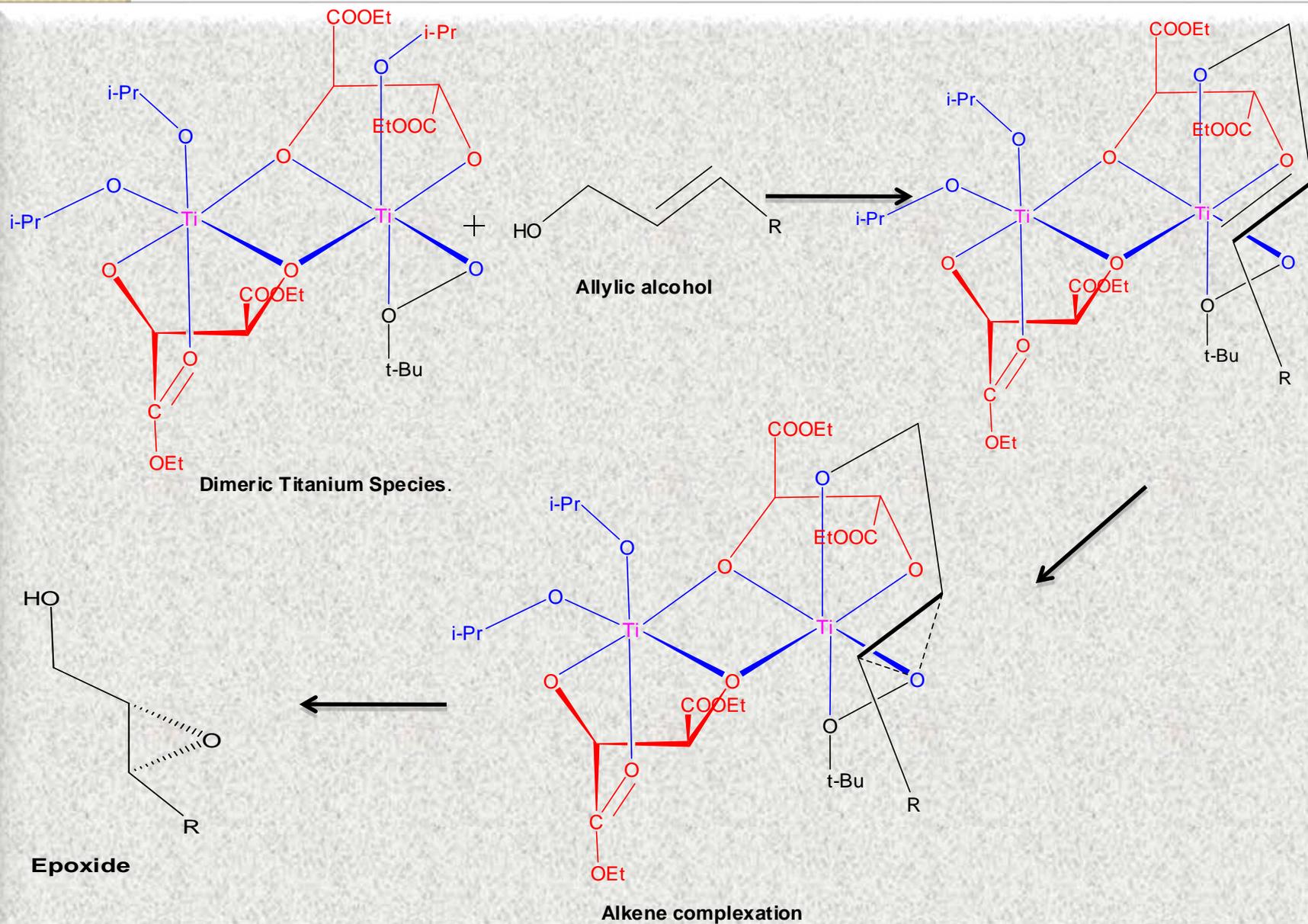
# SHARPLESS EPOXIDATION

BARRY K. SHARPLESS

- The Sharpless Epoxidation is used for enantioselective epoxidation of prochiral allylic alcohols (primary and secondary allylic alcohols)
- The asymmetric induction is achieved by adding an enantiomerically enriched tartrate derivative.
- oxidant :- hydroperoxide(*tert*-butylhydroperoxide in a stoichiometric amount).
- The catalyst is cheap, easily available, and the requirement is only 5-10% mol of the substrate when used in molecular sieves.
- Yield of Sharpless epoxidation reaction are good with more than 90% of enantiomeric excess and is determined by the isomer of diethyl tartrate or di-isopropyl tartrate used.
- 3Å Molecular sieves are used to remove water from reaction as water destroy epoxide ring and catalyst. Catalyst consumption can be reduced to 5% to 10% by use of molecular sieves.

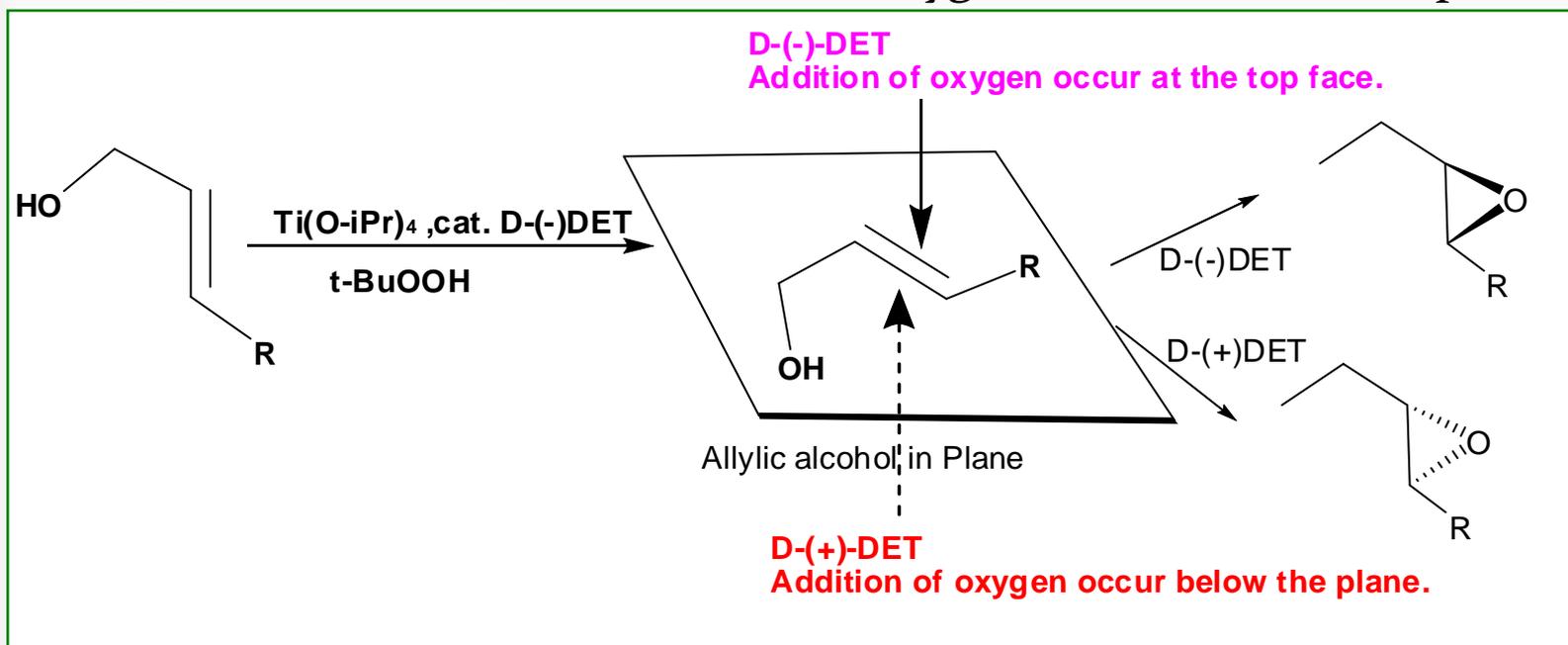


# MECHANISM OF EPOXIDATION :-

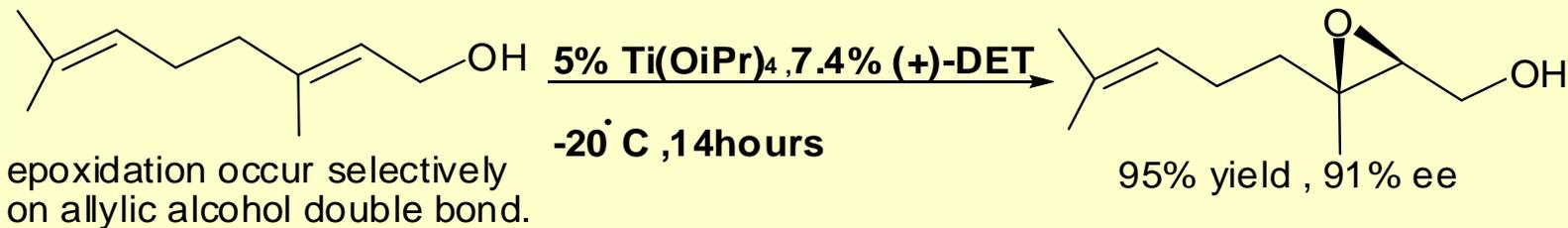


# SELECTIVITY OFFERED BY DIETHYL TARTRATE.

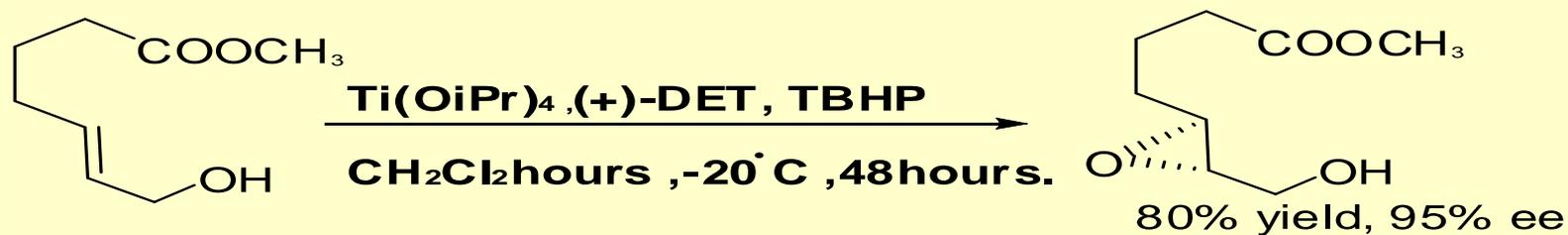
- The enantioselectivity of oxygen addition to the face of allylic alkene is dependent on which stereoisomer of diethyl tartrate (**DET**) used in the reaction.
- If (-)-**DET** is used, the addition of oxygen occurs above the plane as shown.
- If (+)-**DET** is used, the addition of oxygen occurs below the plane.



# APPLICATION OF SHARPLESS EPOXIDATION



## Intermediate for synthesis of leukotriene C1

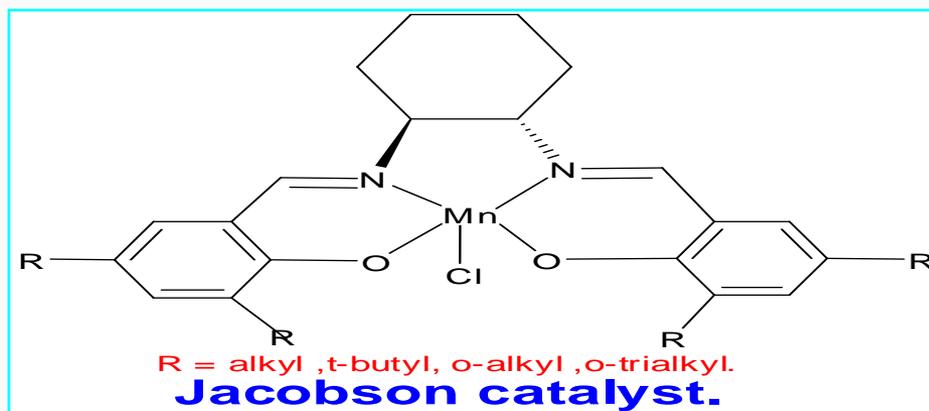


## RECENT MODIFICATIONS IN SHARPLESS EPOXIDATION (ADDITIONAL INFORMATION)

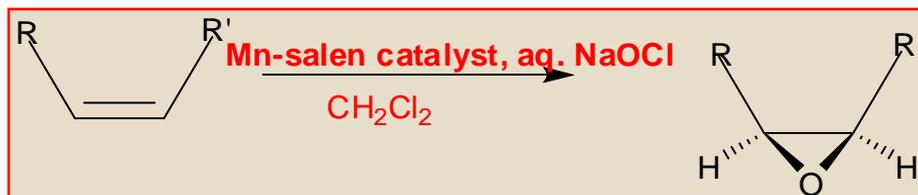
Problem	Solution	Results
<p>Presence of water lead to failure of epoxidation.</p> <ul style="list-style-type: none"><li>•epoxide ring breaking,</li><li>•Destruction of catalyst</li></ul>	<p>Use of molecular sieves which can absorb water .</p>	<ul style="list-style-type: none"><li>•Increase in yield</li><li>•Catalyst consumption reduced (10-15% of original value.)</li><li>•Ease of isolation of product</li></ul>
<p>Solubility</p> <ul style="list-style-type: none"><li>•Some reactant may not be completely soluble.</li></ul>	<p>Use of chiral polymeric support with active functional group. (e.g. polystyrene support)</p>	<ul style="list-style-type: none"><li>•Improved enantioselectivity.</li><li>•Improved yield.</li></ul>
<p>Heterogeneous catalysis</p> <ul style="list-style-type: none"><li>•Catalyst and reactant should be in different phases to perform proper isolation of product.</li></ul>	<ul style="list-style-type: none"><li>•Use of porous silica support</li><li>•Ageing of catalyst</li><li>•Change of solvent (less polar to medium polar)</li><li>•Use of polymeric support.</li></ul>	<ul style="list-style-type: none"><li>•Improved yield.</li><li>•Lesser consumption of catalyst</li><li>•Continuous reaction &amp; product Isolation is possible.</li></ul>
<p>Enantioselectivity</p>	<p>Can be improved by higher derivative of tartrate ligand (diethyl replaced by iso propyl).</p>	<ul style="list-style-type: none"><li>•Improved enantioselectivity.</li></ul>
<p>Temperature</p> <ul style="list-style-type: none"><li>•Some reaction require high temperature</li></ul>	<p>Use of catalyst like titanocene tartrate which can work at high temp. &amp; provide better steric hinderance .</p>	<ul style="list-style-type: none"><li>•Enhanced enantioselectivity and higher yield for reaction requiring high temperature.</li></ul>

## JACOBSON EPOXIDATION (EPOXIDATION OF *CIS* ALKENES).

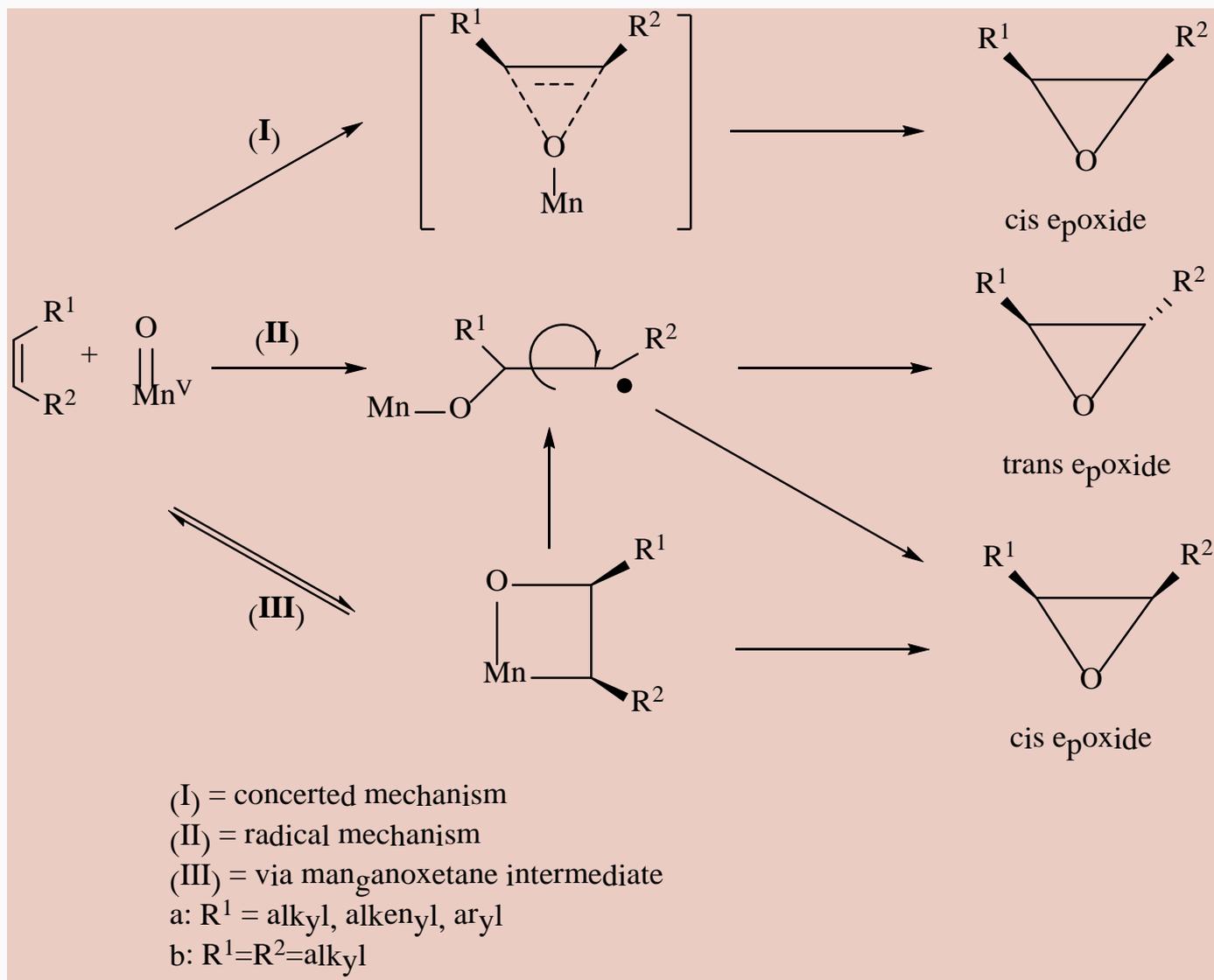
- The Sharpless asymmetric epoxidation works better with *trans* alkenes and allylic alcohols, but produces low yields with *cis*-alkenes.
- Jacobson Epoxidation can be used to overcome this problem.
- Jacobson epoxidation allows **enantioselective** epoxidation of **unfunctionalized** alkyl- and aryl- substituted olefins.
- The Jacobsen catalyst is a **C<sub>2</sub> symmetric manganese(III) salen-like complex**, in **catalytic** amounts to achieve better stereoselectivity.



- Reaction ,

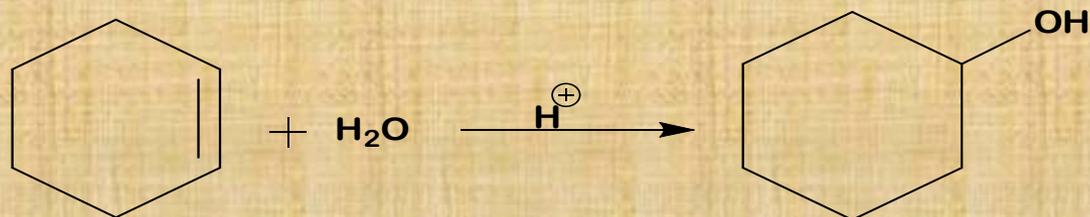


- The addition of Mn(V) species take place from the side with lower steric interaction.

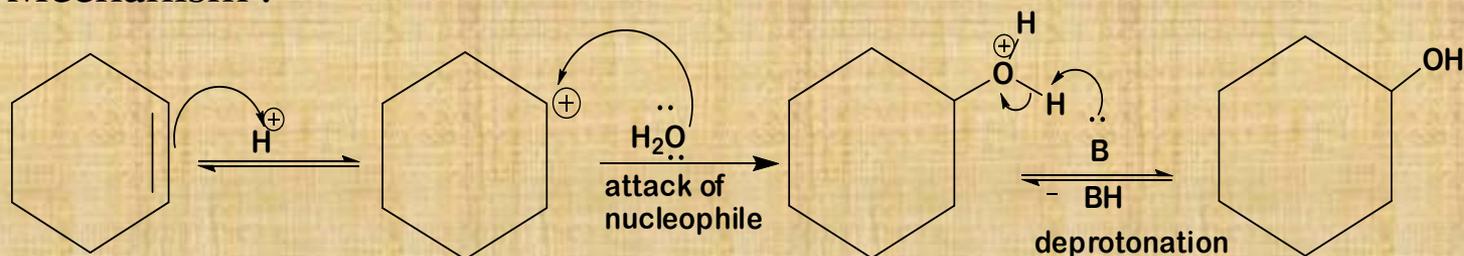


# HYDRATION REACTIONS (ADDITION OF WATER)

- General reaction :-



- Mechanism :-



Protonation to generate more stable carbocation.

- The reaction is **regiospecific** & follow **Markovnikov** rule of addition i.e. formation of carbocation at highly substituted end.
- More the substitution with electron donating group more stable is the carbocation formed.



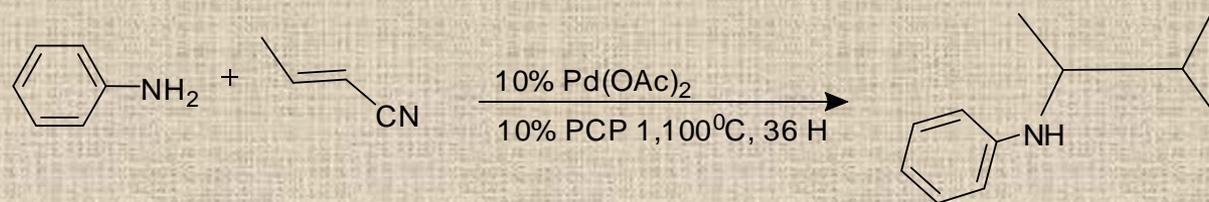
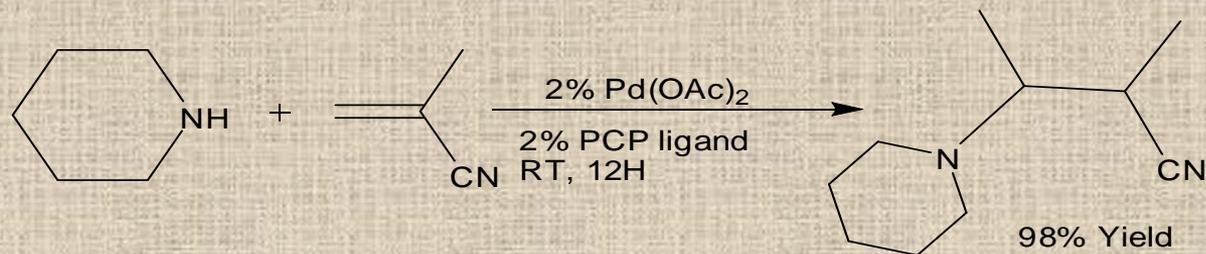
## NUCLEOPHILIC ADDITION REACTIONS OF OLEFINS

## CONDITION FOR NUCLEOPHILIC ADDITION REACTIONS

- Normally olefins have electron rich HOMO which favor its reaction with electrophiles.
- For nucleophilic addition to take place the alkene should be attached with an electron withdrawing group, which can withdraw electron density from the pi-bonds of alkenes.
- When electron withdrawing groups are attached to alkenes, the LUMO gets more stabilized. This will help to improve the interaction with the incoming nucleophile
- Some examples of this class of reactions are,
  - Conjugate addition reactions.
  - Hydroamination reaction.

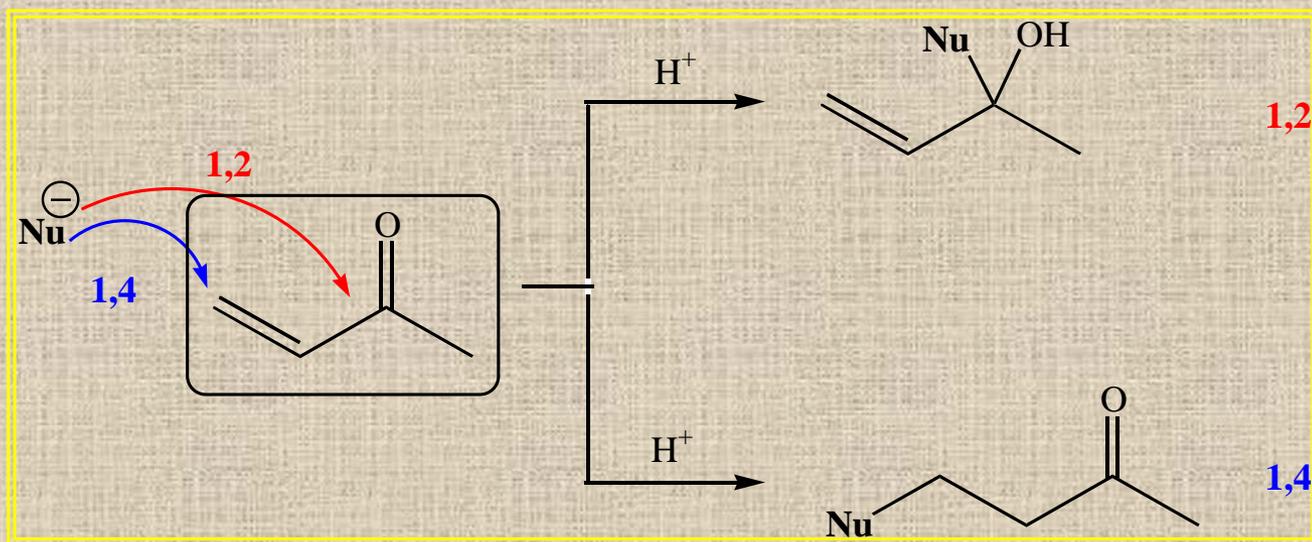
# AMINATION REACTIONS

- The addition of nucleophilic amino group across double bond are called hydroamination reactions.



## NUCLEOPHILIC CONJUGATE ADDITION

- The addition reaction of  $\alpha, \beta$ -unsaturated carbonyl compounds and  $\alpha, \beta$ -unsaturated nitriles with nucleophiles at 1,4- position is called nucleophilic conjugate addition.
- alkene having carbonyl or nitrile group in conjugation increases reactivity toward nucleophiles by resonance stabilization.

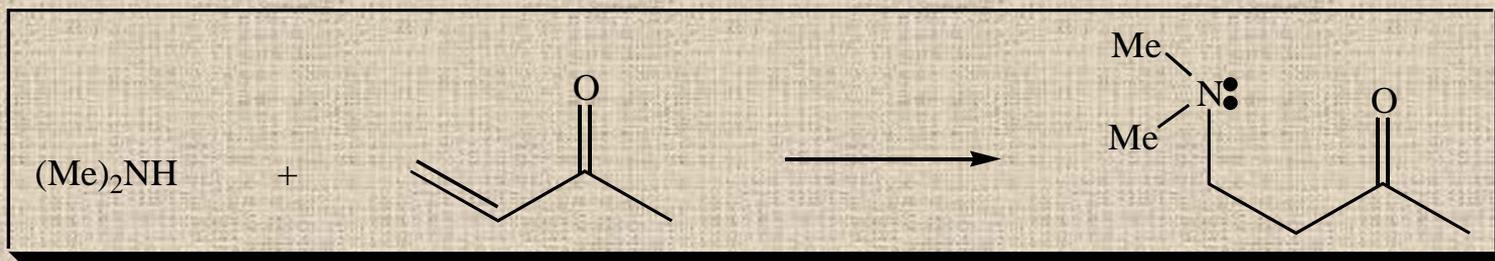
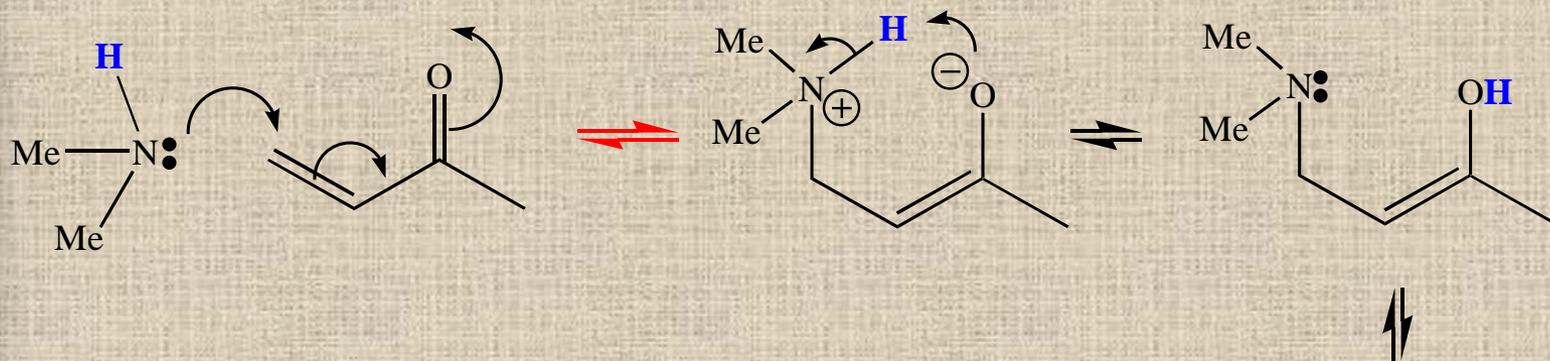


1,2-additions\* are also known as **direct addition**

1,4-additions are known as **conjugate addition**

## EXAMPLE AND KEY STEPS

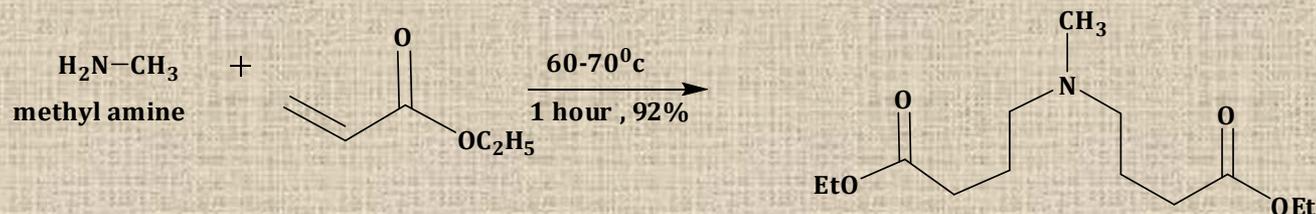
• a



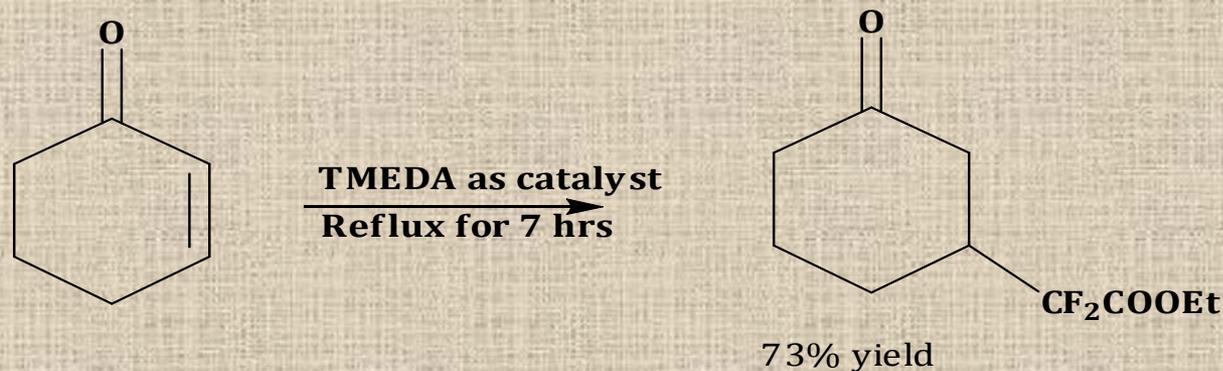
Key factors that control conjugate addition are,

- Reaction conditions
- Nature of the  $\alpha,\beta$ -unsaturated carbonyl compound
- Type of nucleophile

- **PREFERENCE FOR ADDITION AT 1,2 OR 1,4 POSITION.**
- 1,2 addition occur with stronger nucleophiles such as Grignard reagents, organolithium, lithium aluminum hydrides, sodium borohydrides.
- 1,4 addition occur with weaker nucleophiles like thiols, enolates, cyanides, organocopper reagents etc.
- More Examples for 1,4-additions



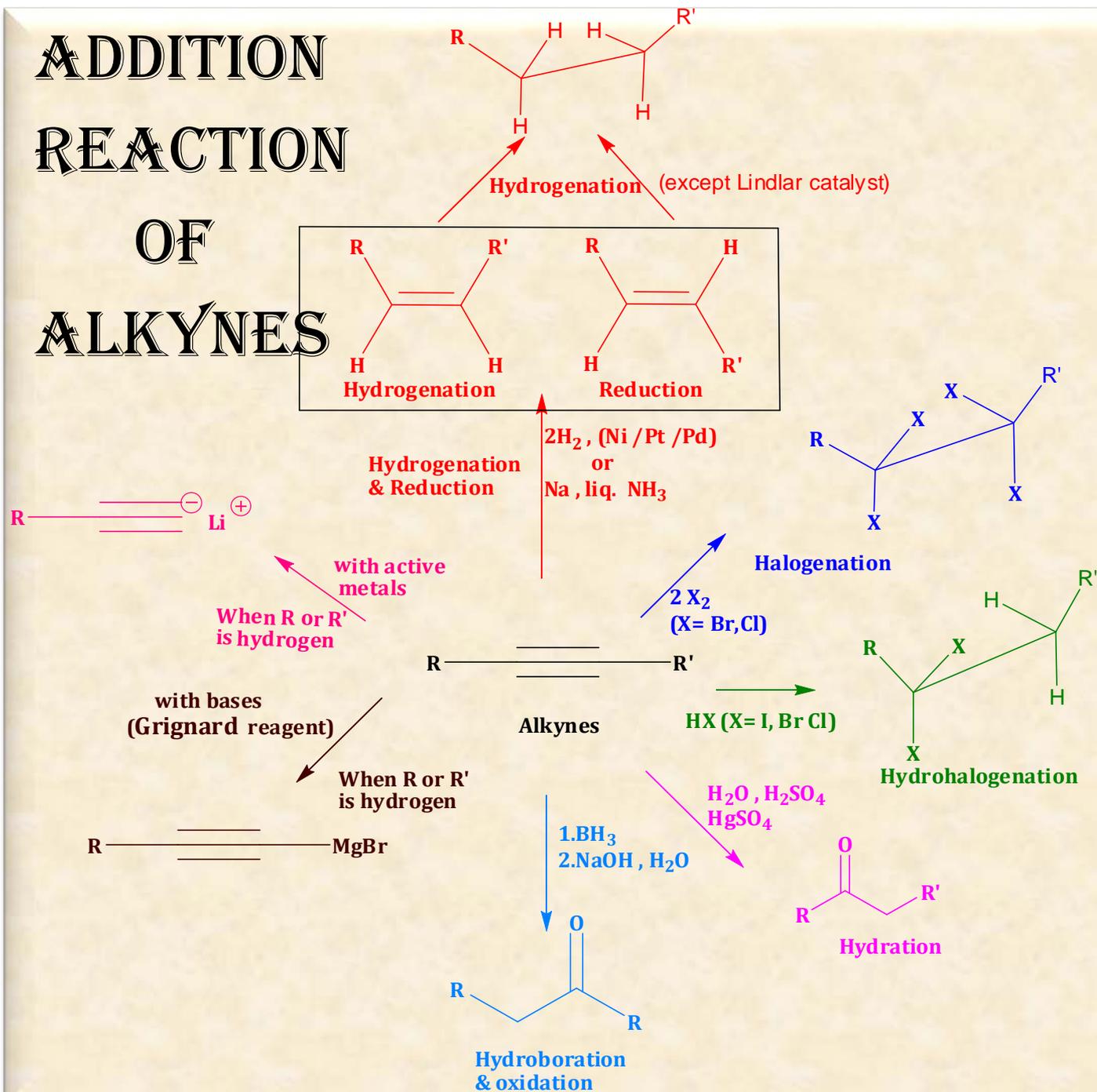
- 1,4-Addition reaction of ethyl bromodifluoroacetate to Michael acceptors .





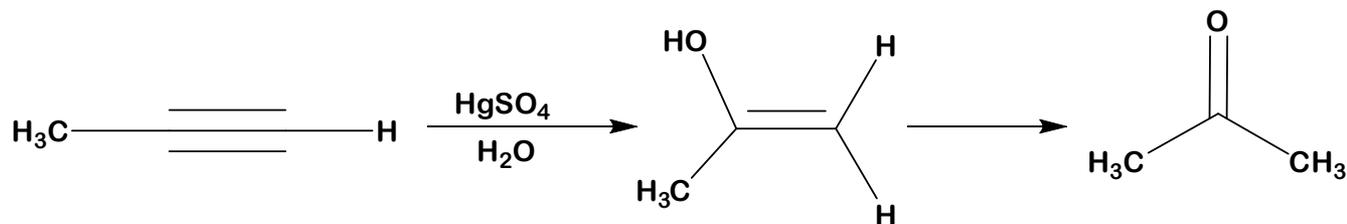
# ALKYENES

# ADDITION REACTION OF ALKYNES

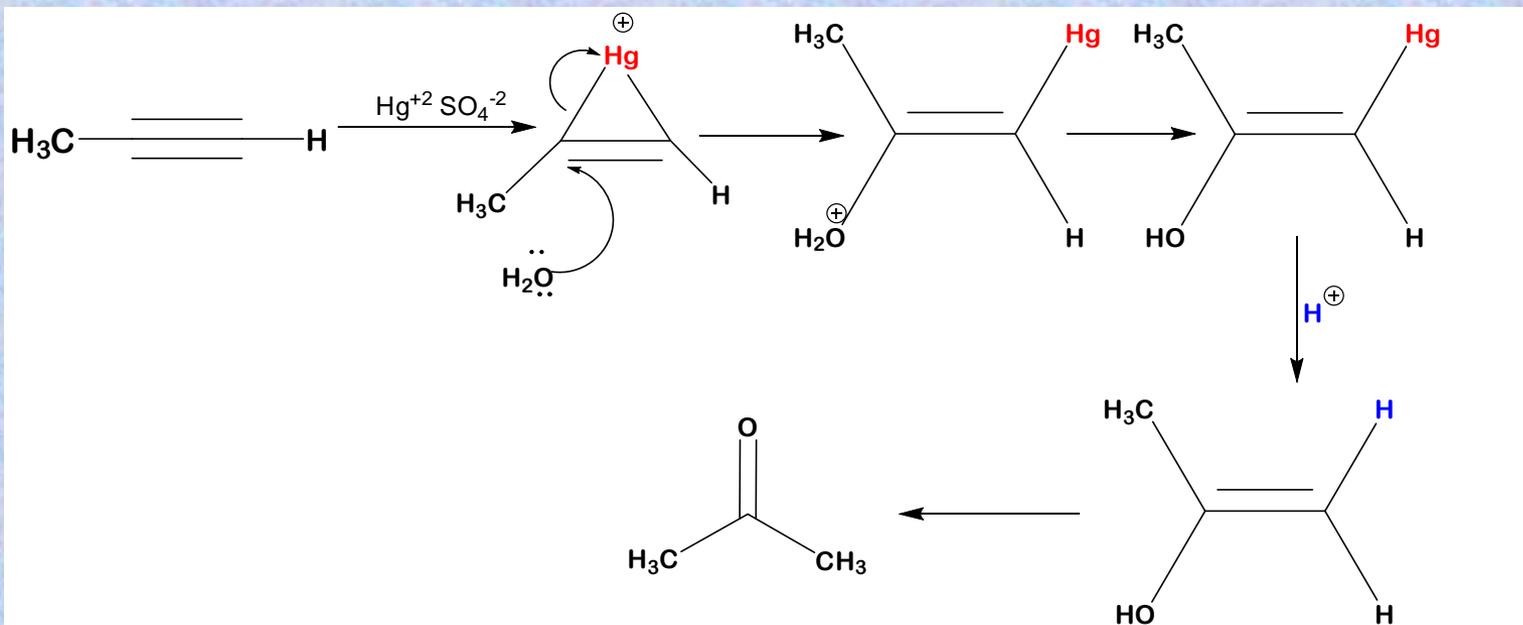


# HYDRATION REACTIONS

- Hydration in alkynes is carried out using mercuric salts as catalyst.
- The addition gives more stable carbocation as per the Markovnikov's rule.
- General reactions:-

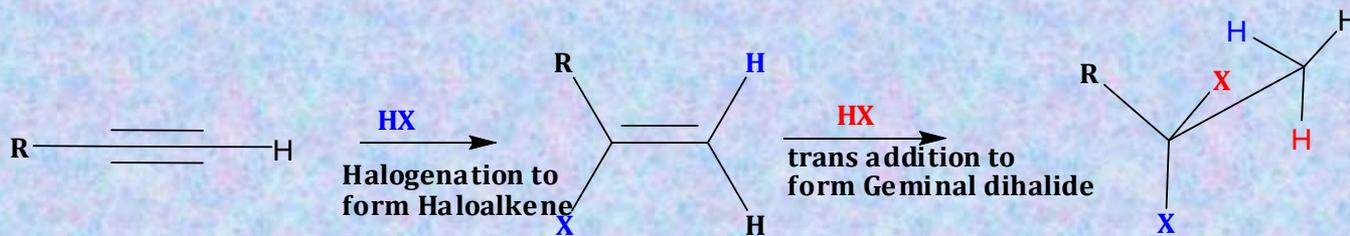


- Mechanism :-



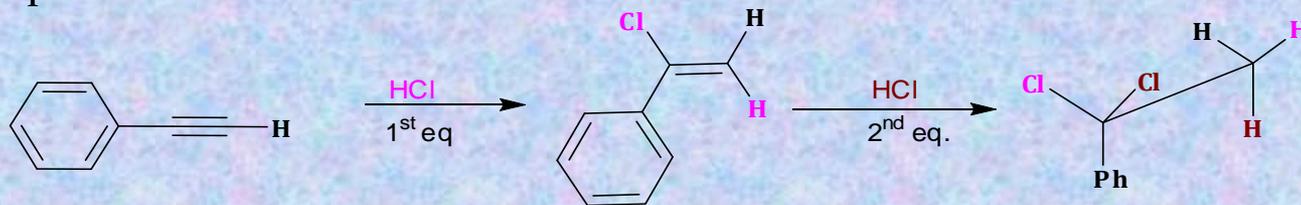
# HYDROHALOGENATIONS

- Addition reaction of haloacids occur in *anti* fashion following Markovnikov's rule i.e. the more substituted carbon result in carbocation to which halogen get attached.
- Initial attack result in haloalkene which further react to give the geminal dihalide.

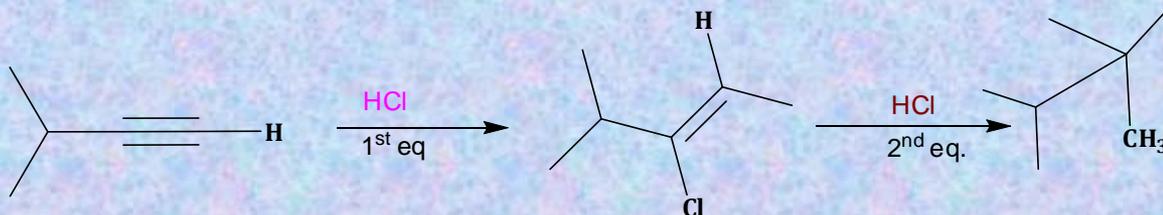


- Examples :-

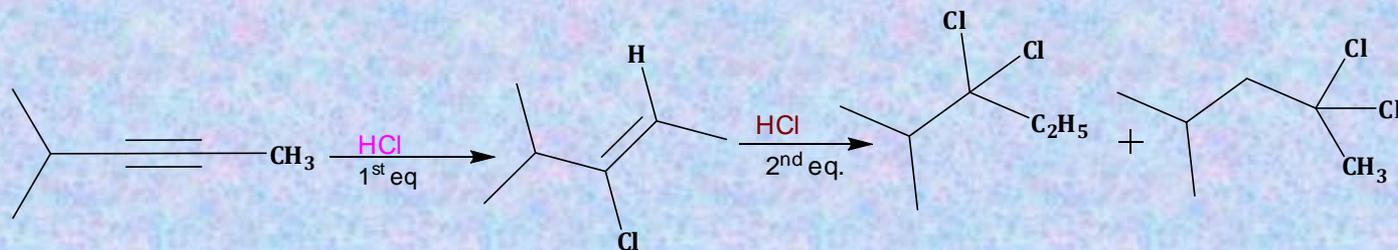
1.



2.



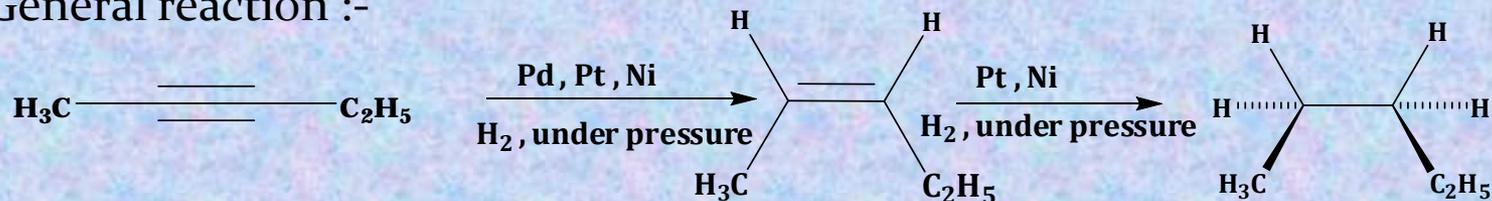
3.



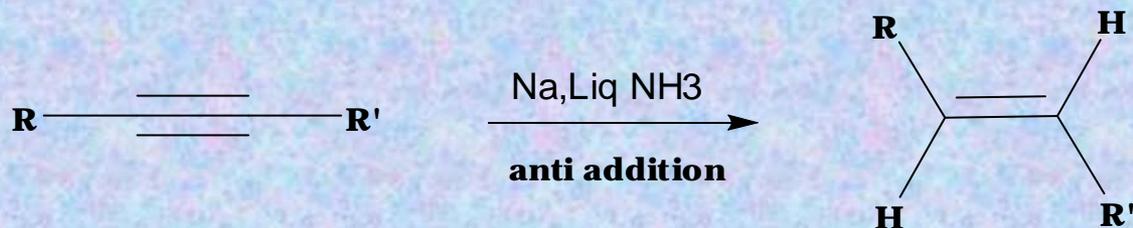
## HYDROGENATION AND REDUCTION

- **HYDROGENATION** of alkyne is carried out using gaseous hydrogen at high pressure using transition metal catalyst (Pt, Pd, Ni).
- Hydrogenation with **Lindlar's catalyst**, (prepared by deactivating palladium catalyst by treating it with lead acetate and quinoline) give alkene with no further reaction, however direct use of **Pt or Ni** will result in hydrogenation to alkane.
- Reaction in the presence of above catalyst give *cis* alkene with *syn* stereo selectivity.

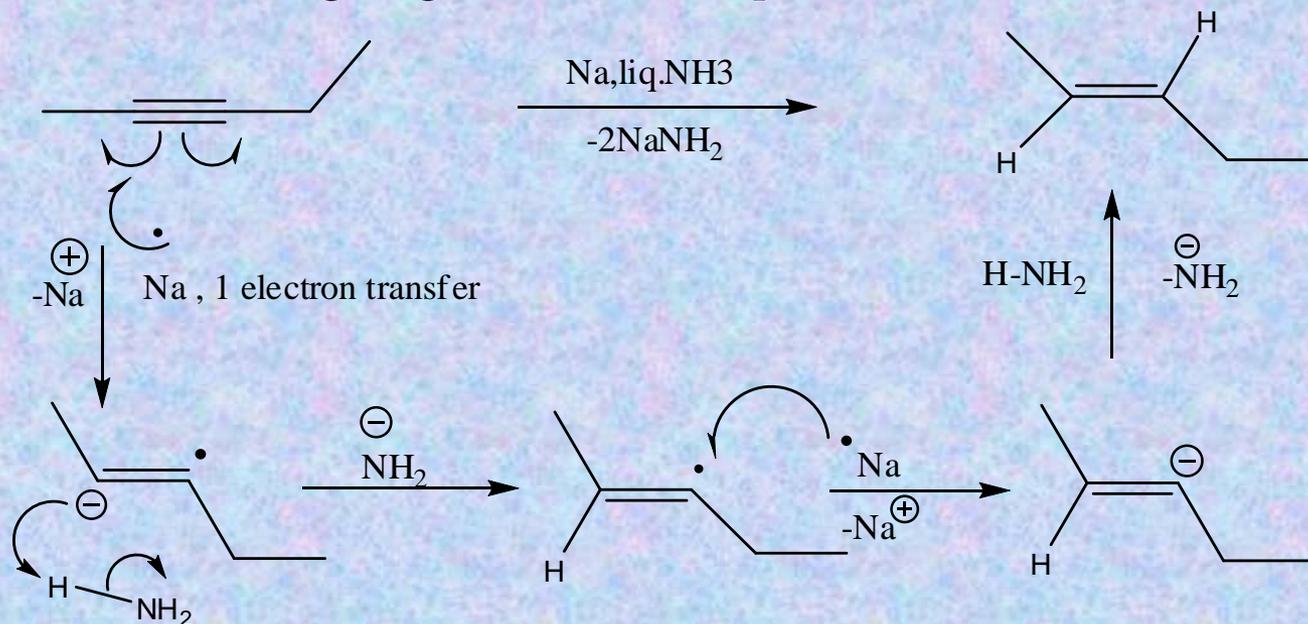
- General reaction :-



- **REDUCTION** of alkyne in presence of sodium in Liquid  $\text{NH}_3$  result in *anti* addition to give *trans* alkene.



- The mechanism proceed by generation of electronic centre at a cost of a pi bond followed by transfer of electron by metal in solvent cage (ammonia), this result in formation of anionic centre on the substrate .
- The ammonia molecule now donate proton forming the ionic soda amide again , this process repeat twice but this time from opposite centre on the second carbon , giving *trans* alkene as product.



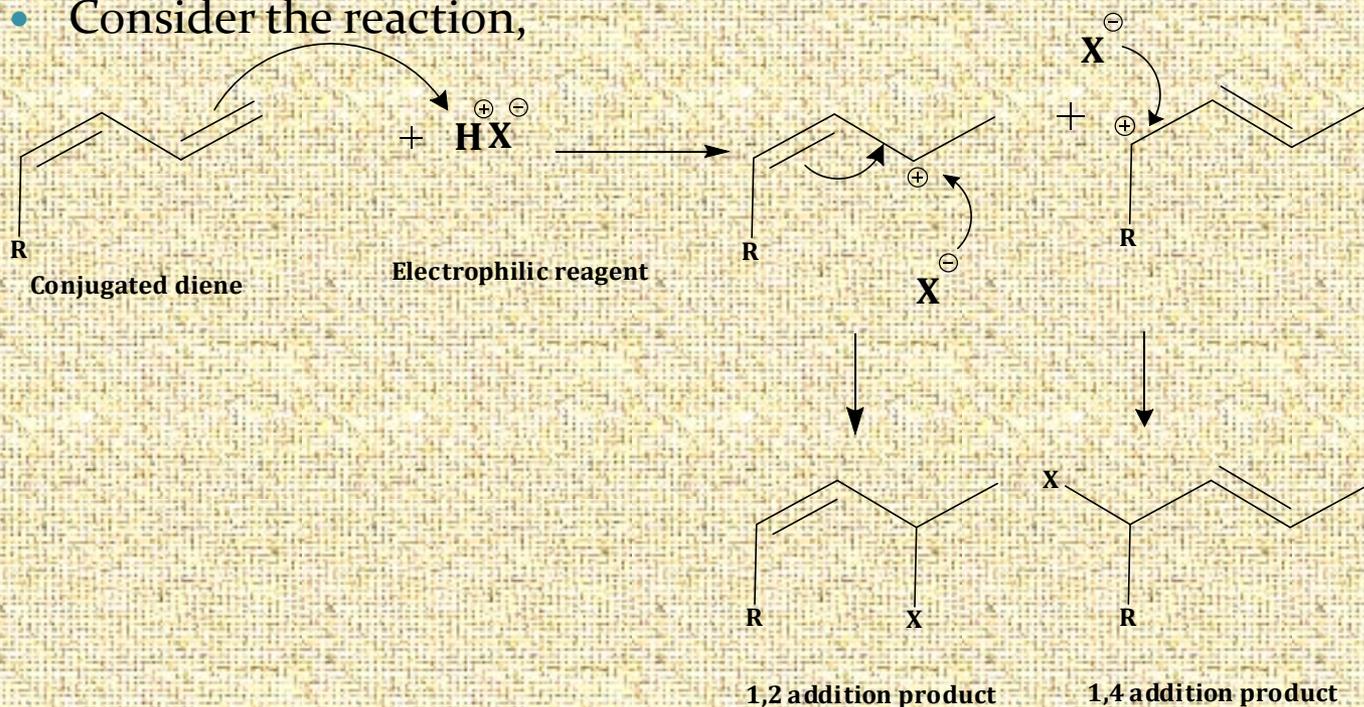
- Similar type of reaction occur in case of reduction of aromatic compounds especially benzene where the reagent posses the capacity to break the aromaticity called Birch reduction.



DIENES

# ELECTROPHILIC ADDITION

- Dienes with electrophilic reagents like halo acids give electrophilic addition reaction.
- Consider the reaction,

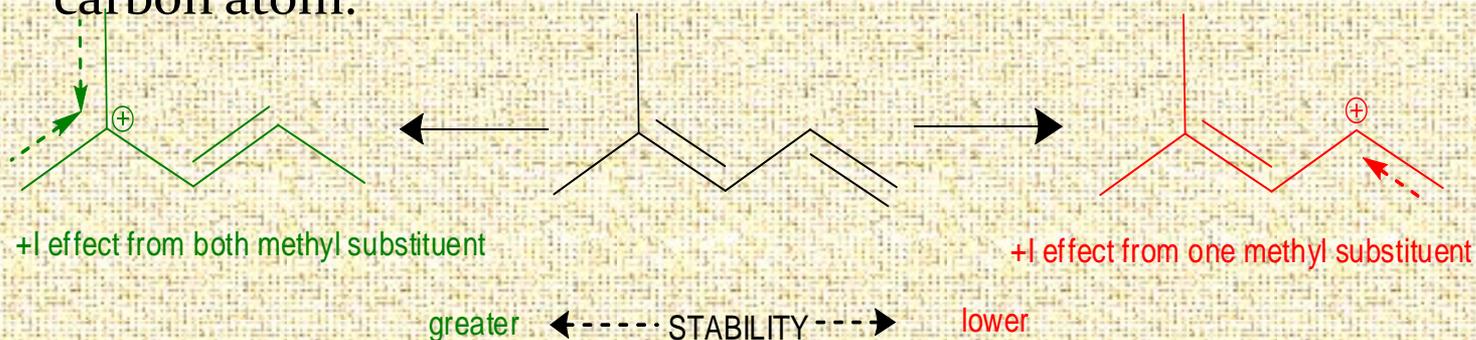


- Which is the major product formed predominantly?

- The formation of product will depend on ,

➤ **Stability of carbocation :-**

- The addition of proton occurs as per the **Markovnikov rule**, the stable carbocation will be formed at the more substituted carbon atom.



➤ **Rate of reaction :-**

- The **energy of activation** for the formation of 1,2 product is **lower** and hence formed faster. However, **equilibrium is less favored**.
- 1,4 product require higher activation energy but favors equilibrium.

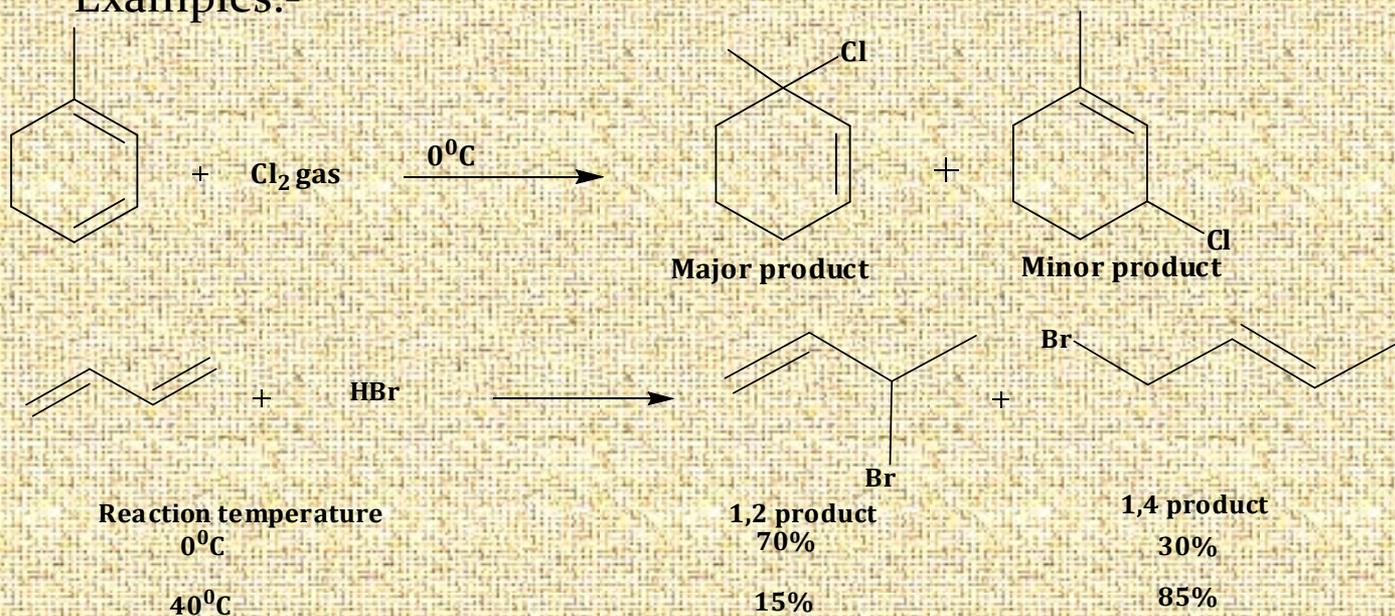
➤ **Reaction temperature:-**

- Kinetic product is product which appear first in reaction but the stable product is the thermodynamic product.
- 1,2 product is formed first at lower temperature but rearranges to 1,4 product at high temperature or on standing for some time even at low temperature.

➤ **Reagent :-**

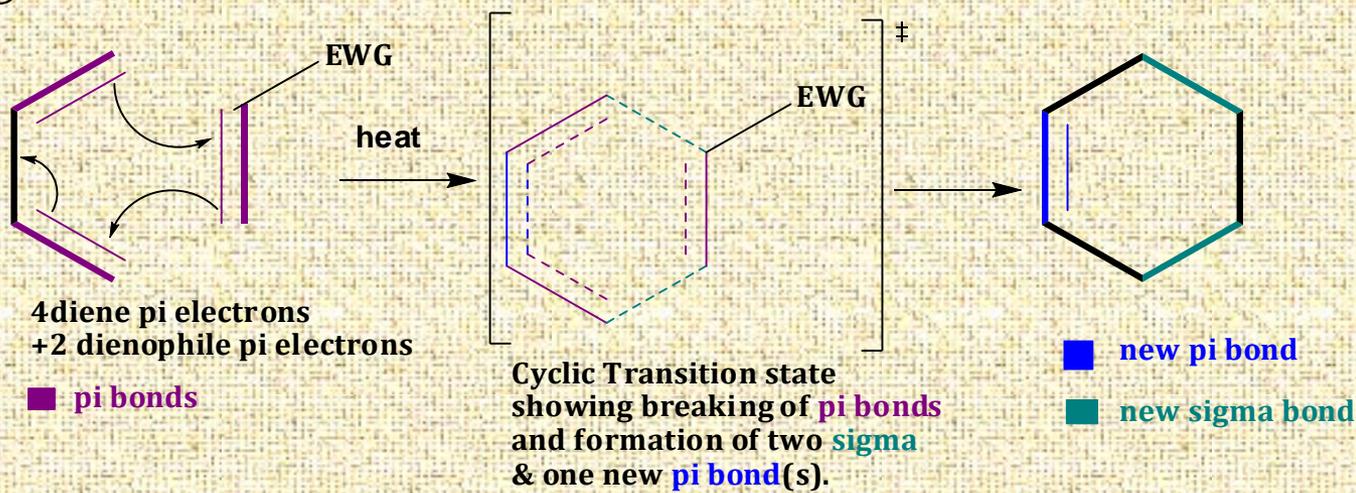
- Use of milder condition gives mixture of products , use of excess of reagent result in 1,4 product .

• **Examples:-**



## DIELS ALDER REACTION (CYCLOADDITIONS)

- A class of concerted 4+2 addition cycloaddition are known as Diels -Alder reactions.
- In this reactions two  $\pi$  bond of a conjugated diene interact with one  $\pi$  bond of dienophile (an electron deficient alkene) forming two carbon bonds in single step.
- Reaction occur with breaking of three  $\pi$  bonds (2 from diene + 1 from dienophile ) without formation of any ionic intermediate to give two new  $\sigma$  bonds one  $\pi$  bond .



## ESSENTIAL CHARACTERISTICS....

- For a Diels- Alder reaction to take place the diene should have electron rich HOMO and the dienophile with electron deficient LUMO.
- The reaction is thermally favored and not photo chemically, hence reactants should be heated at high temperature .
- This can be briefly illustrated,

- **ENERGY :-**

- **DIENE**

- Diene should be in *cis* conformation, dienes in *trans* conformation should change to *cis* conformation which require energy, hence lower the rate.
- Presence of electron donating group [EDG] on the diene increases the reactivity. EDG raises the energy of diene HOMO, this will cause more favorable energy interaction with the LUMO of the dienophile.
- Any group present on the diene will have effect on the rate and stereochemistry of reaction.

## • DIENOPHILE :-

- Dienophiles are alkenes having comparatively lower electron density than diene.
- It should possess electron withdrawing group [EWG] which can withdraw the electron density making them more electrophilic.
- This will decrease the energy of alkene LUMO favoring better orbital interaction. The presence of EDG retard the rate of reaction.

### DIENES

EWG



Reactivity :- **Least**



**Normal**

EDG



**Good**

EDG



**Excellent**

### DIENOPHILES

EWG



Reactivity :- **Excellent**

EWG



**Good**



**Normal**

EDG



**Least**

EWG :-

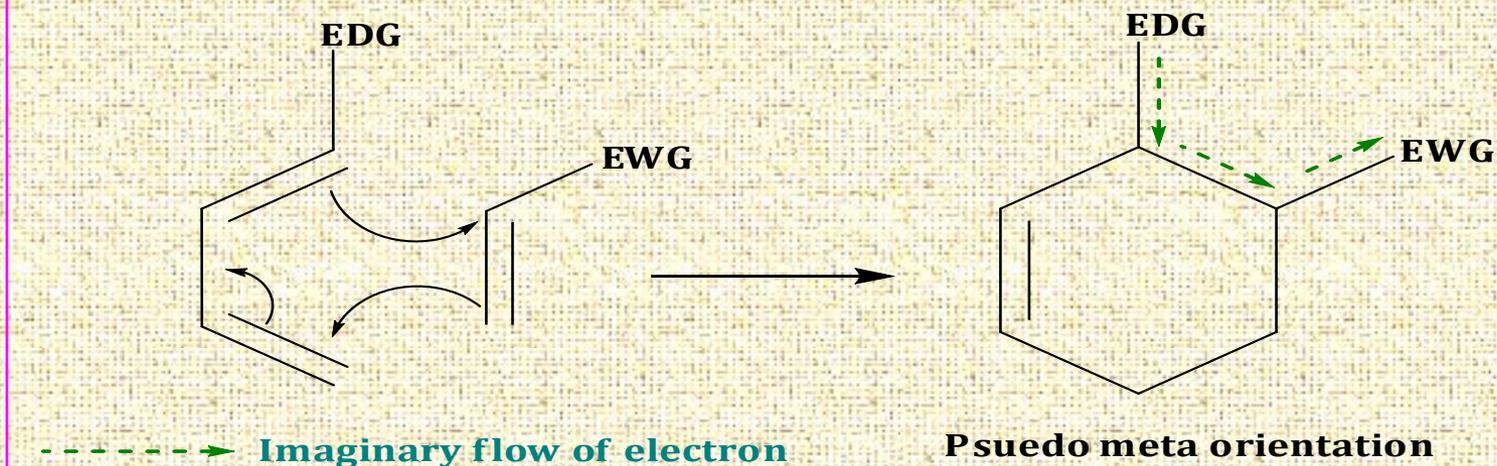
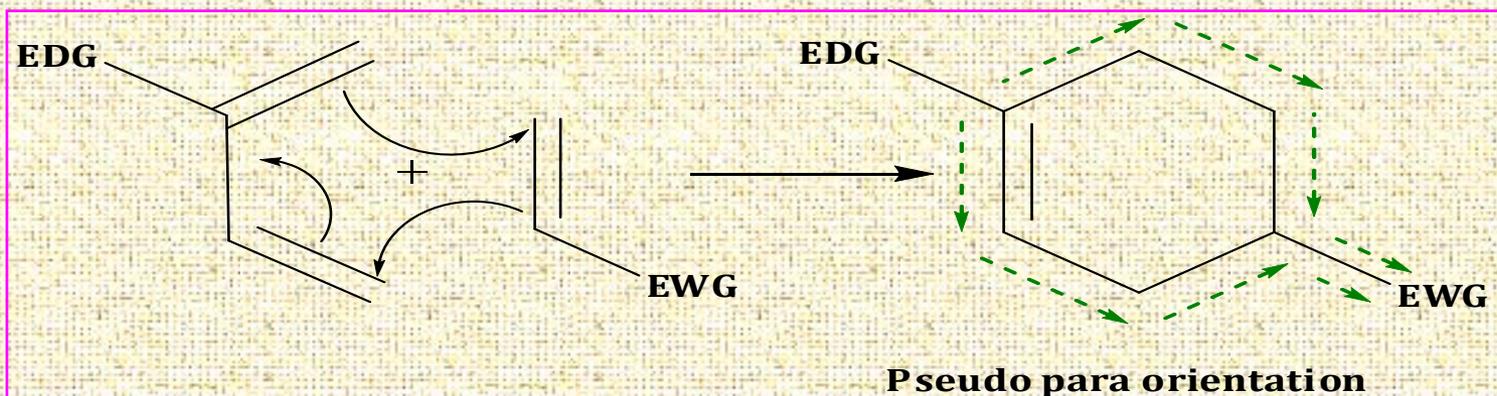
Carbonyl, ester, nitriles, quaternary amines, Halides anhydrides, nitro, ester, quaternary amines, acids etc.

EDG:-

Amines, -OR, -NHCOR, alkyl, phenyls etc.

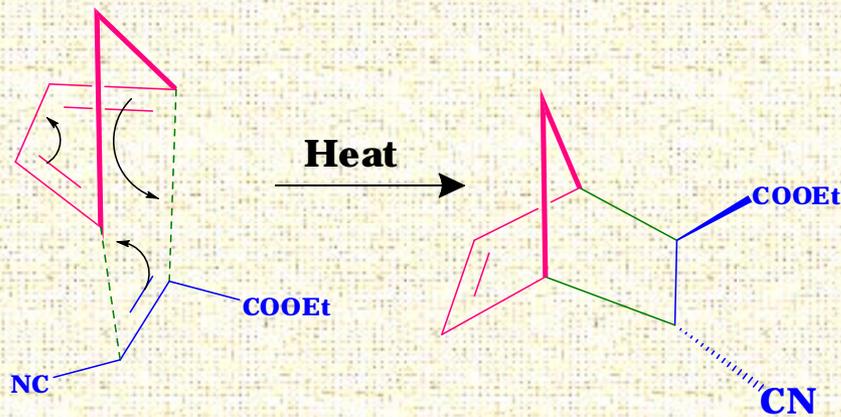
# • ORIENTATION OR REGIOSELECTIVITY :-

- As per the frontier molecular theory approach pseudo para or ortho orientation is favored in products, meta orientation is least favored.
- When diene contains an electron donating substituent and dienophile an withdrawing substituent, the orientation is such that there is maximum electron flow toward the electrophilic substituent as shown below

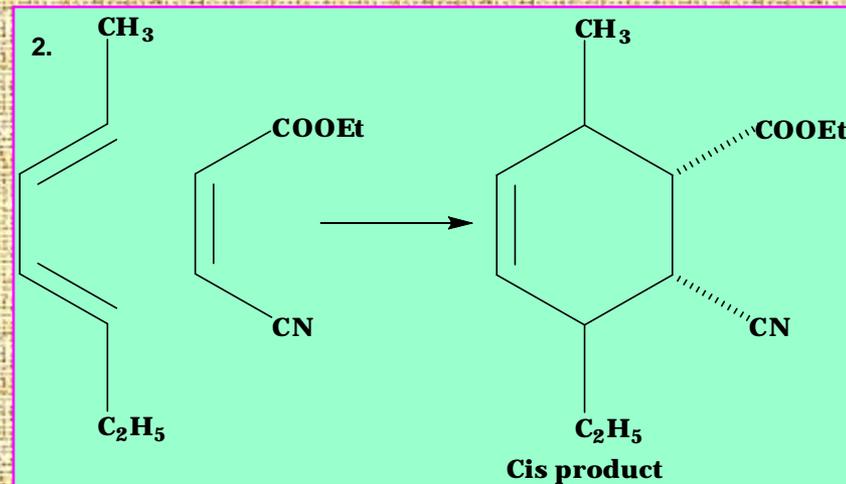
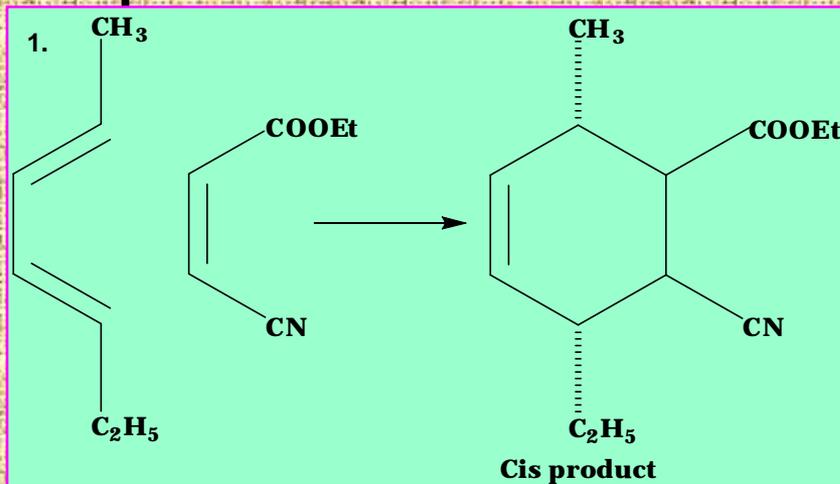


# • STEREOSELECTIVITY

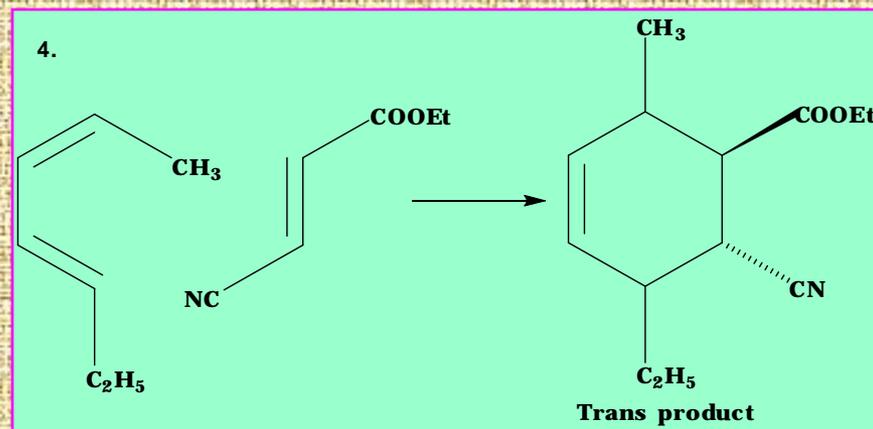
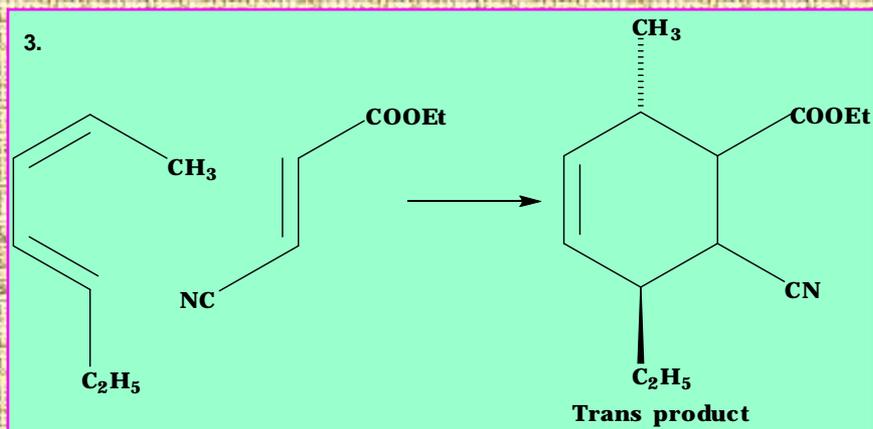
- Diels -Alder reaction exhibits excellent stereoselectivity.
- The stereoselectivity of reactant is maintained in the products both in case of diene and dienophile. The addition is *syn* addition as shown below



# Cis product:-

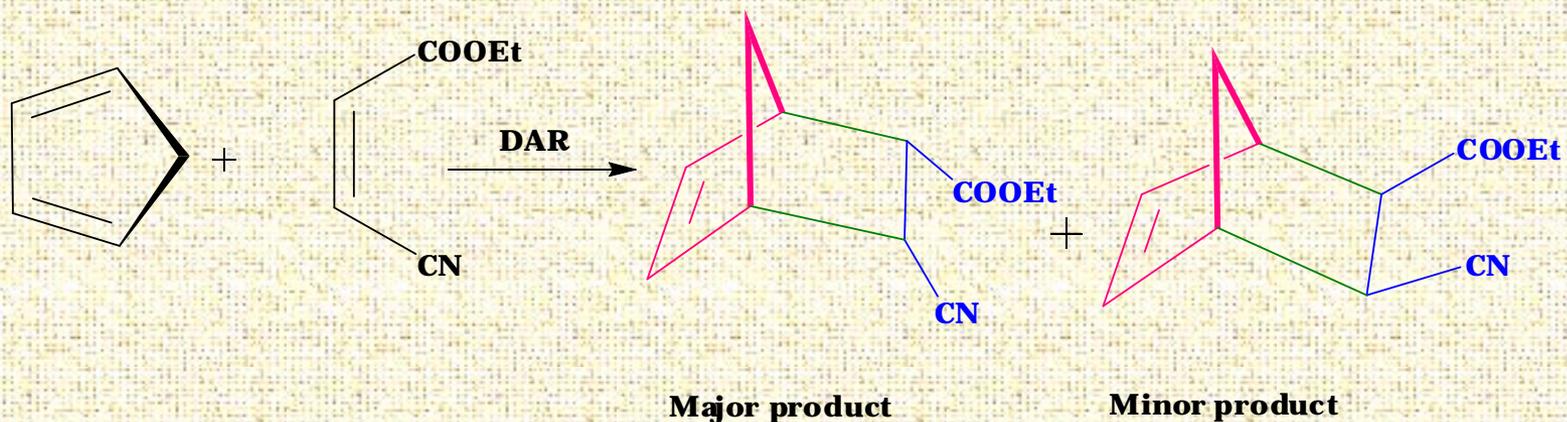


# Trans product:-



## ORIENTATION OF DIENOPHILE AND END/EXO PRODUCT

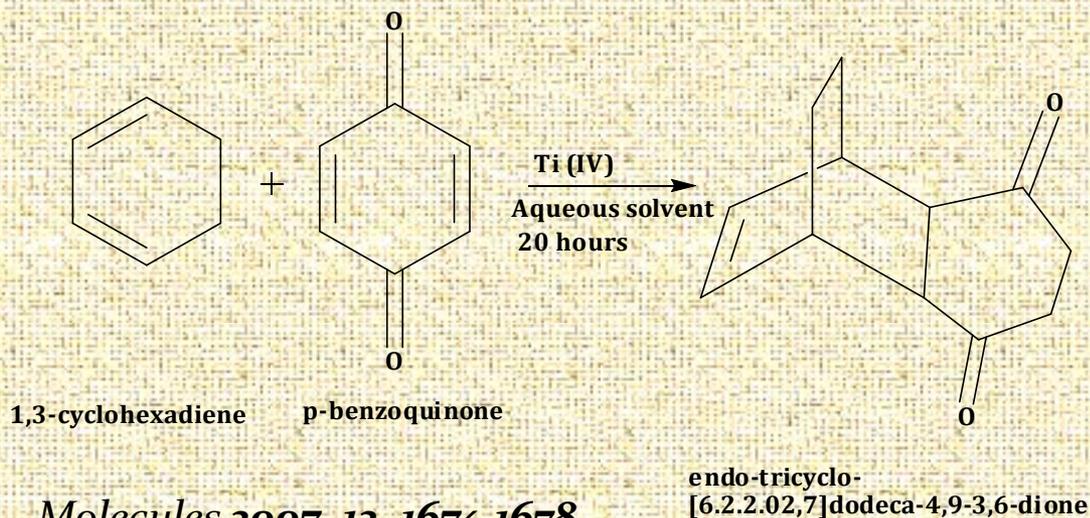
- Dienophile are electron deficient. They would try to approach the diene in such a manner that the electron withdrawing group will remain toward the newly developing  $\pi$  bond, giving *endo* as the major product.



- In general, Diels Alder reaction are thermodynamically controlled. *Exo* product is the kinetic product that appear as a minor product in the reaction.

# CATALYSIS

- Catalyst increases electron withdrawal capacity of dienophile making it lower in energy thereby decrease the HOMO-LUMO gap between diene and dienophile.
- This can be achieved by using Lewis acid catalysts ( $\text{AlCl}_3$ ,  $\text{SnCl}_4$ ,  $\text{BF}_3$ ,  $\text{TiCl}_4$  etc. ). Lewis acid coordinates with Lewis base of the dienophile making it more electrophilic by withdrawing the electron density.
- Examples:-

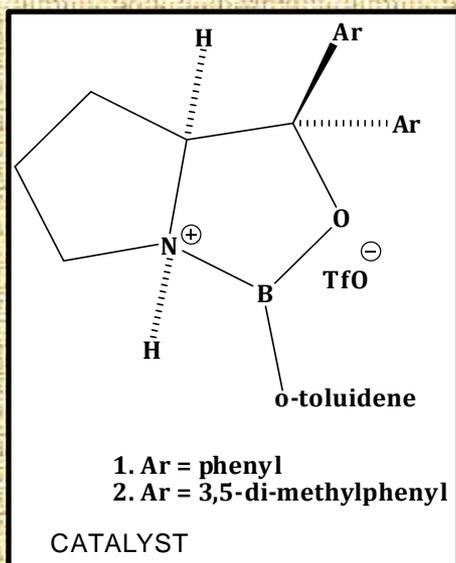


- *Molecules* 2007, 12, 1674-1678

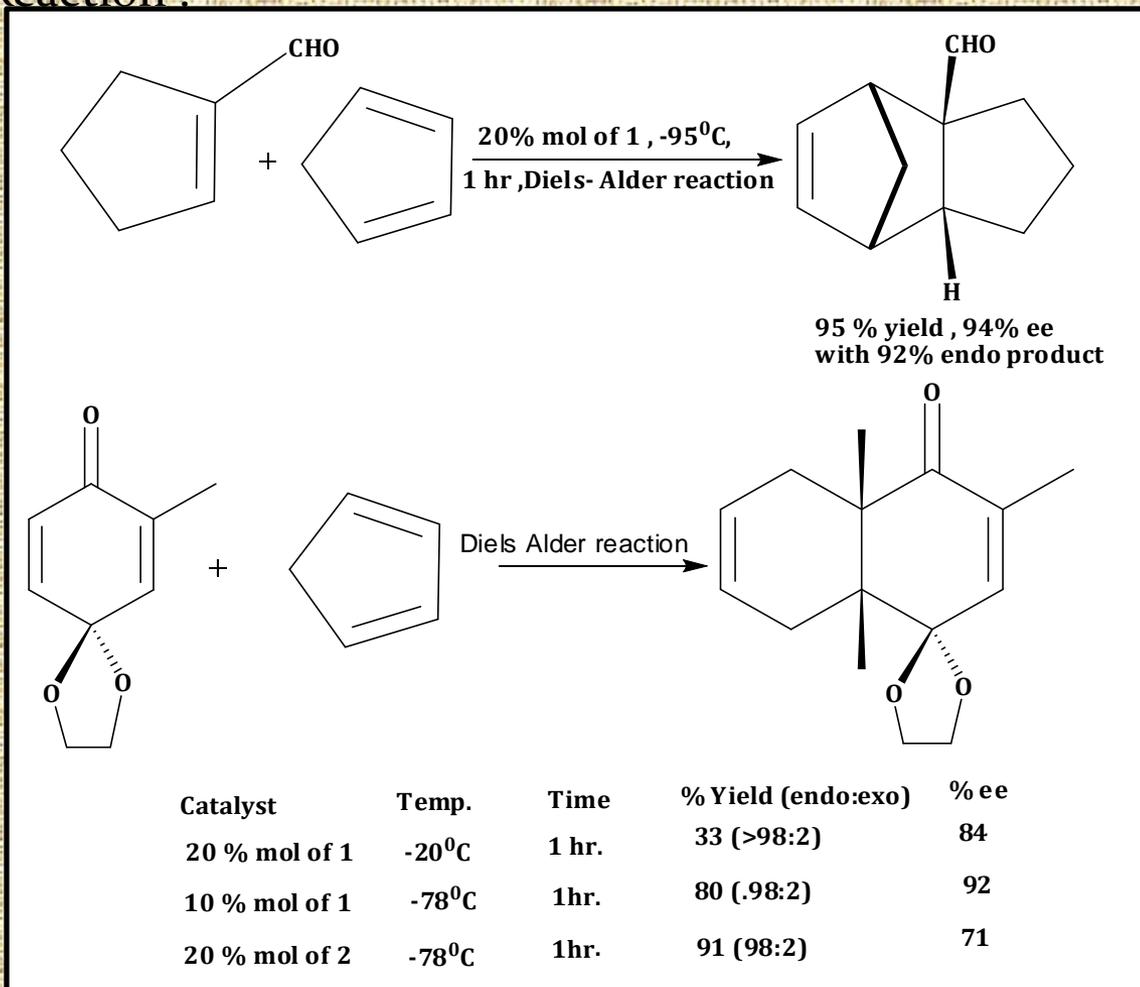
Conc.	Yield
0 % mol	61 %
5 % mol	83 %

- **Enantioselective Diels-Alder Catalysis by Chiral, Cationic Oxazaborolidines .**
- Oxazaborolidines when protonated with trifluoromethanesulfonic (triflic) acid gave an enantioselective catalyst for reaction of 2-substituted acroleins.

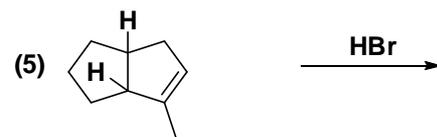
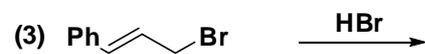
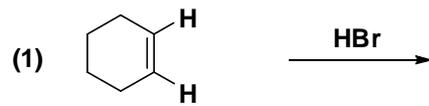
Reaction :-



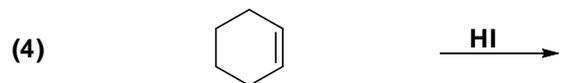
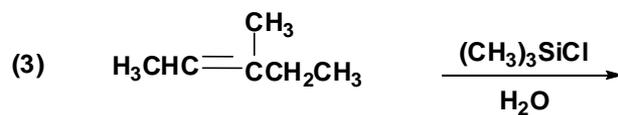
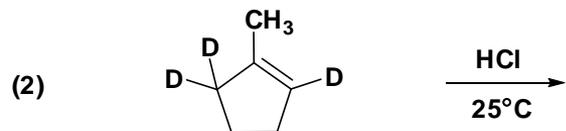
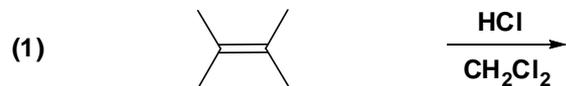
J. AM. CHEM. SOC.  
2002, 124, 9992-9993



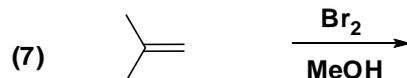
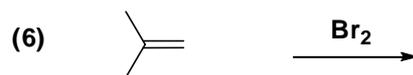
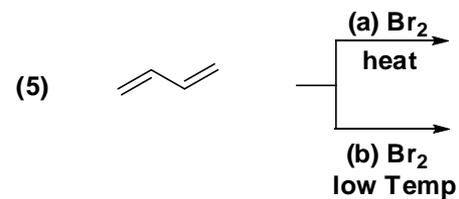
## (I. A) Addition of HBr across carbon-carbon double bond



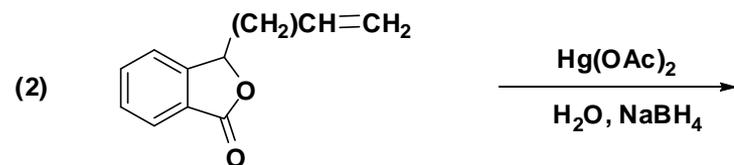
**(I. B)** Addition of HCl and HI across carbon-carbon double bond



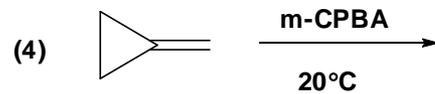
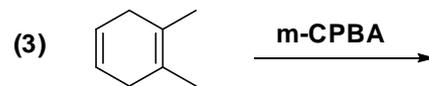
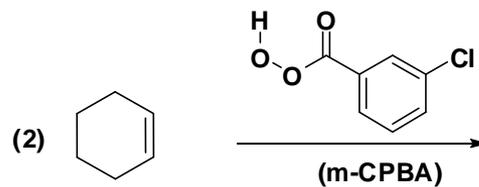
**(I. C)** Addition of  $\text{Br}_2$  across carbon-carbon double bond



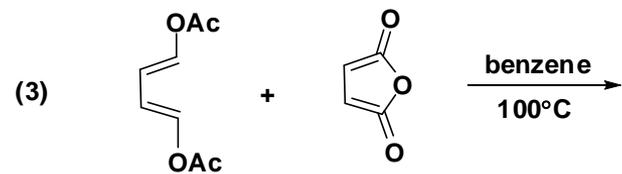
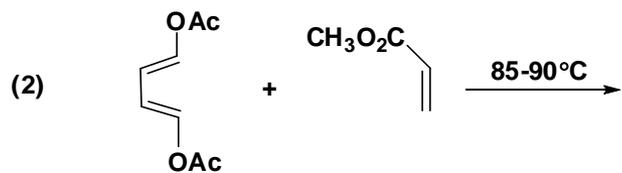
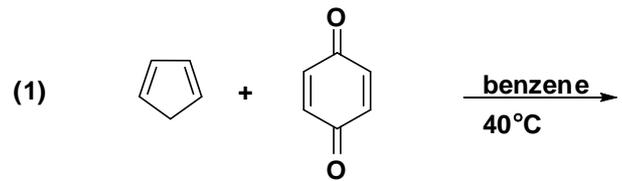
## (I. D) Oxymercuration-Reduction



## (I. D) Epoxide formation

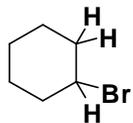


## (I. E) Cycloaddition reactions



## Solutions of Addition of HBr across carbon-carbon double bond

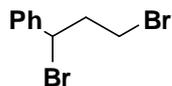
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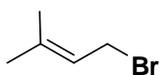
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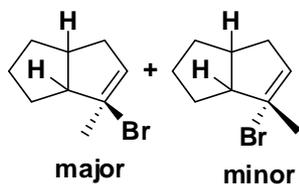
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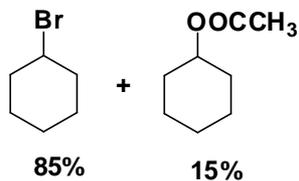
(4)



(5)

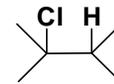


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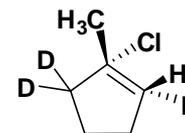


## Solutions of Addition of HCl and HI across carbon-carbon double bond

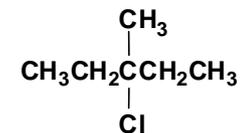
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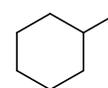
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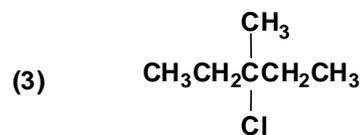
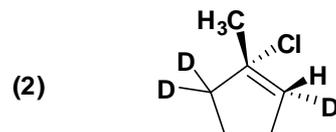
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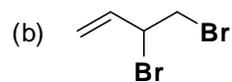
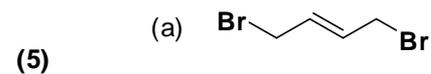
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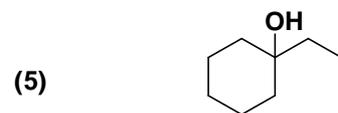
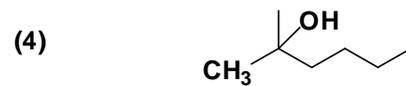
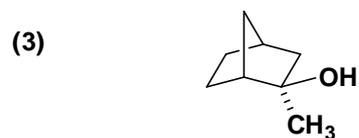
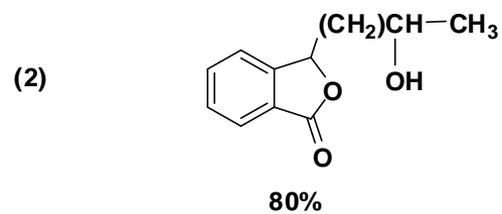
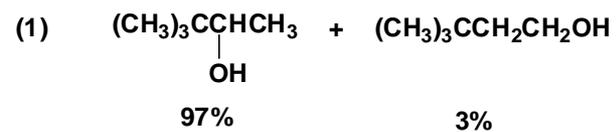
## Solutions of Addition of HCl and HI across carbon-carbon double bond



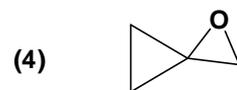
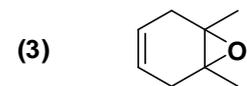
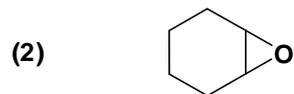
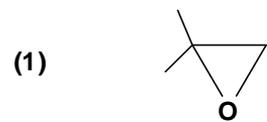
## Solutions of Addition of Br<sub>2</sub> across carbon-carbon double bond



## Solutions of Oxymercuration-Reduction

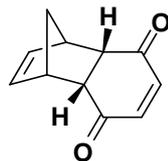


## Solutions of Epoxide formation

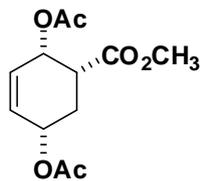


## Solutions of Cycloaddition reactions

(1)



(2)



(3)

