

## **MCH-204:ORGANIC CHEMISTRY**

**UNIT-III: Mechanistic and stereochemical aspects of addition reaction  
Involving electrophiles & nucleophiles**

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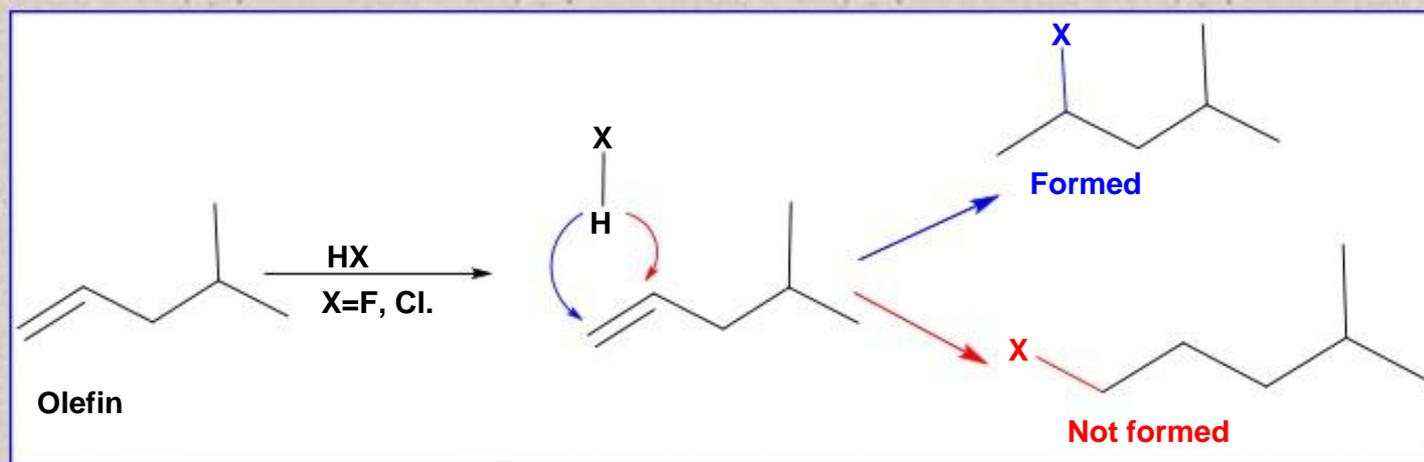


# ELECTROPHILIC ADDITION REACTIONS

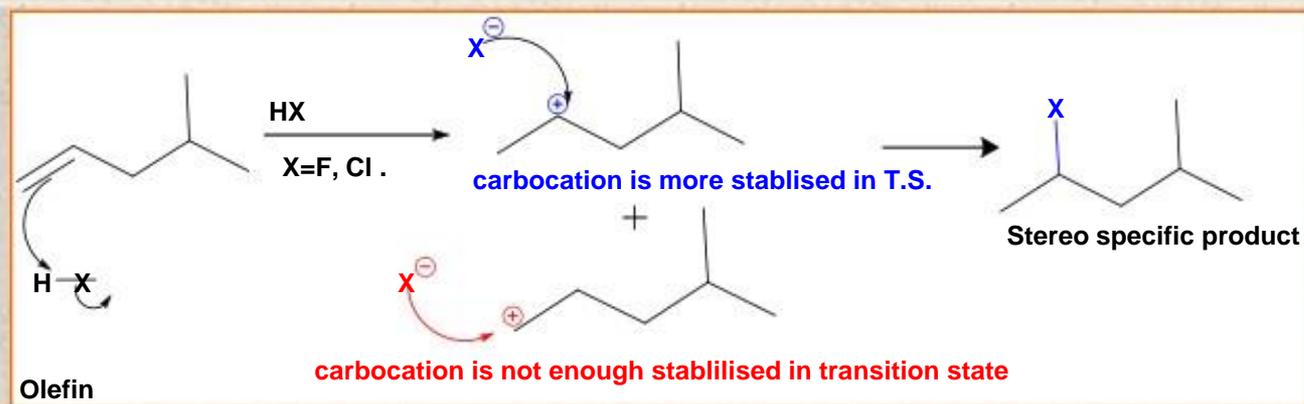
## MARKOVNIKOV' ADDITIONS

# 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 ...

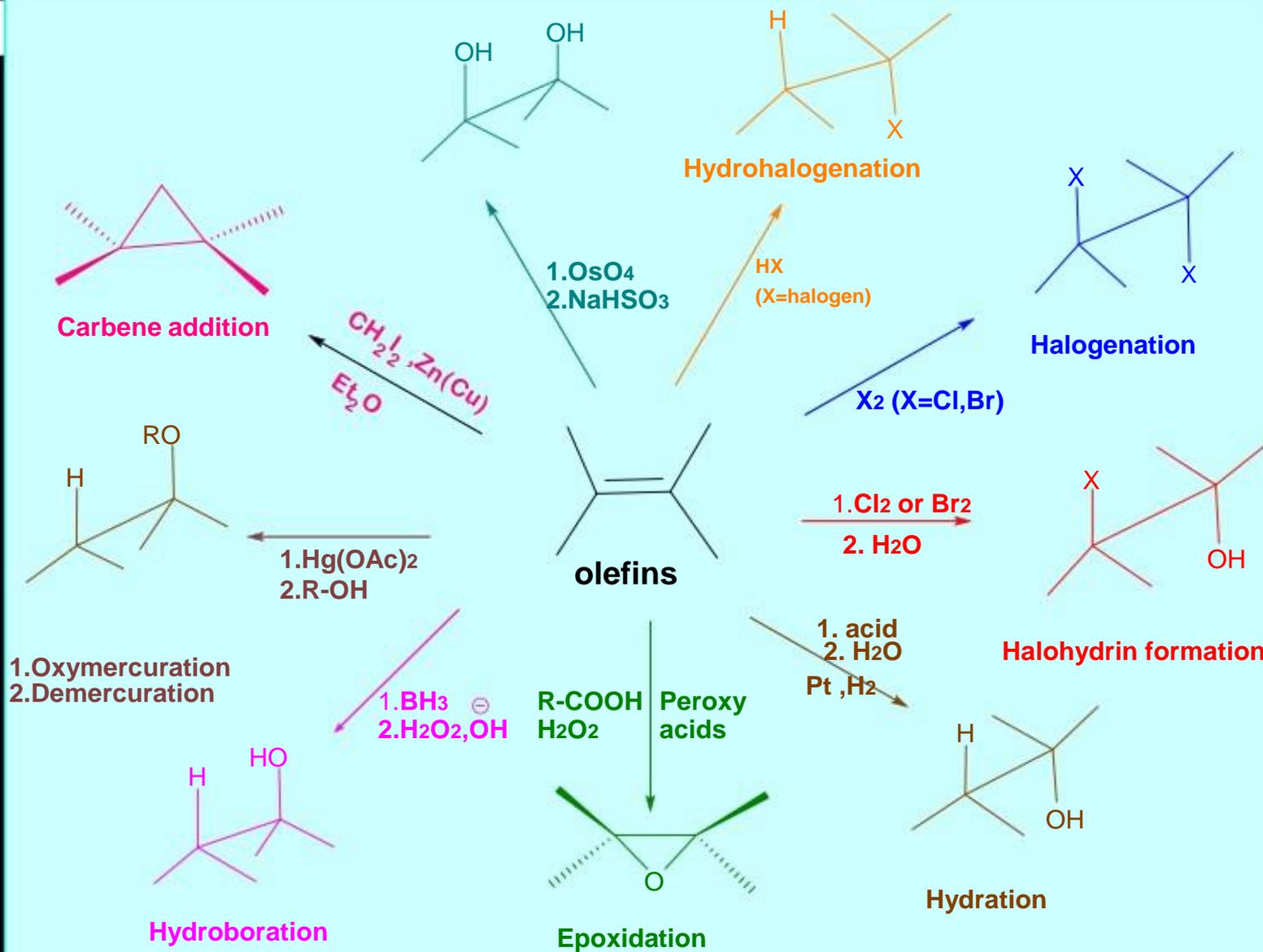


- Consider two possible sites for hydrogen addition (i) terminal or (ii) internal (substituted carbon).
- The addition of hydrogen at the terminal carbon leads to better **stabilization of carbocation**, the chances of **stabilization increases with increase in conjugation** with olefin.
- The **terminal 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

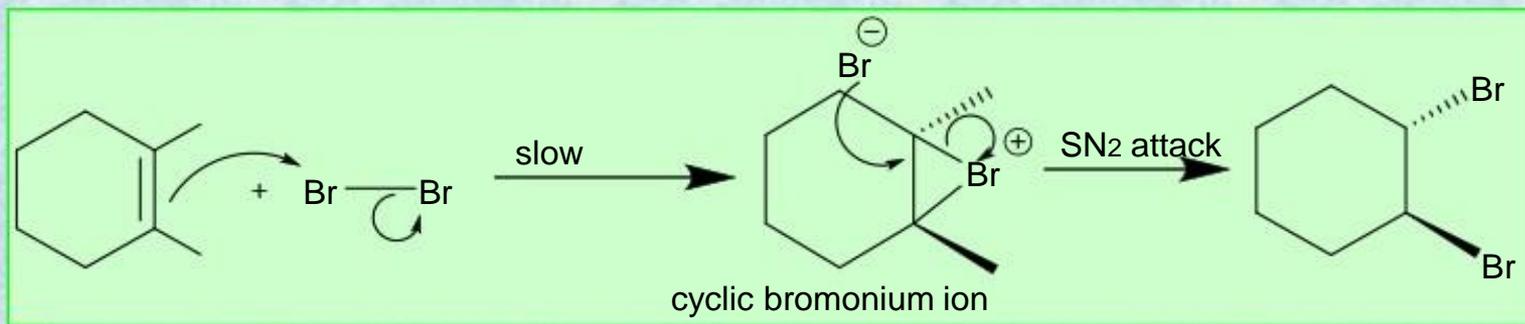


# 1. HALOGENATION REACTION

- 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

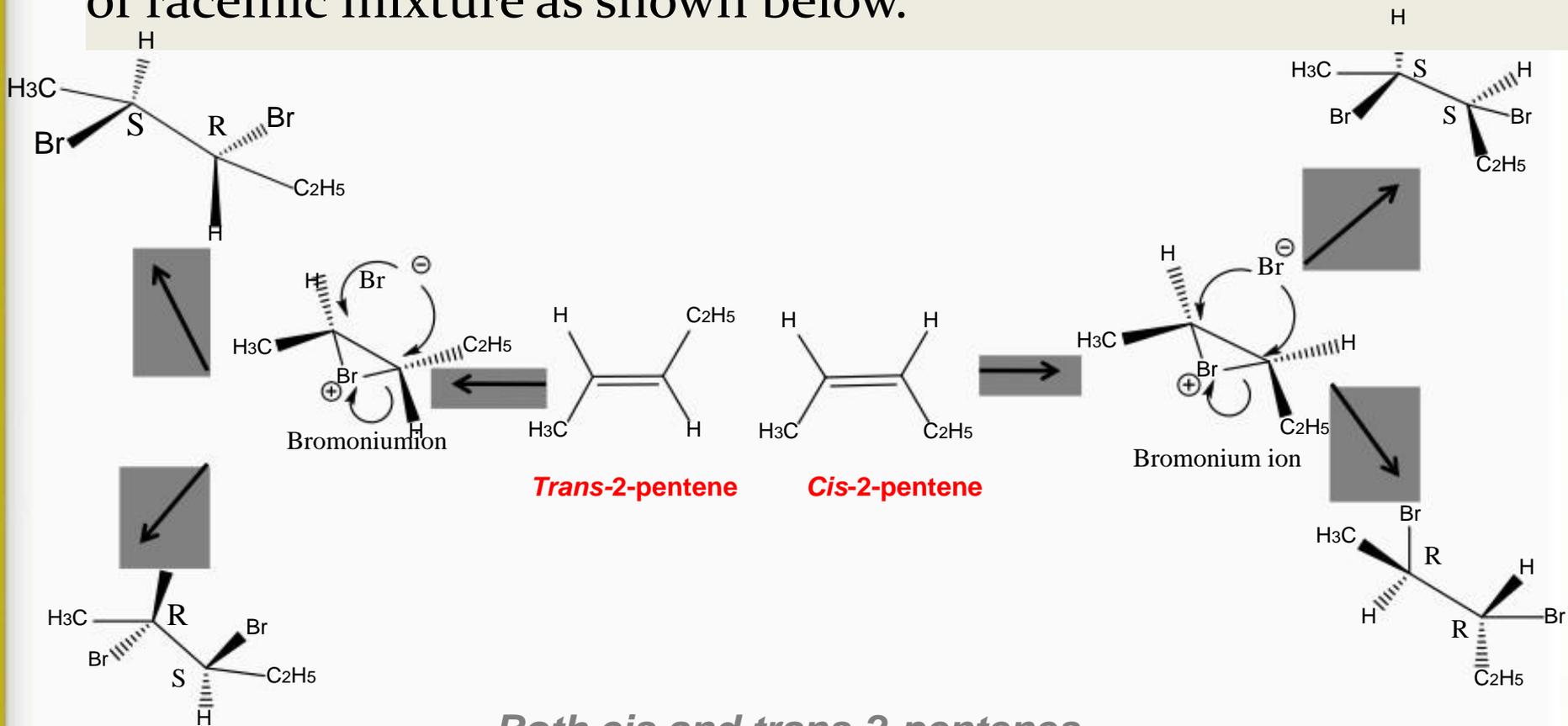
- In this reaction **alkene** interacts with **LUMO** of **bromine** (i.e. **empty  $\sigma^*$  orbital**) to form a three membered cyclic bromonium ion intermediate.
- The **bromide anion** attacks the **cyclic bromonium ion** resulting in generation of product 1,2-dibromide



# STEREOCHEMISTRY

## STEREOSELECTIVITY

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

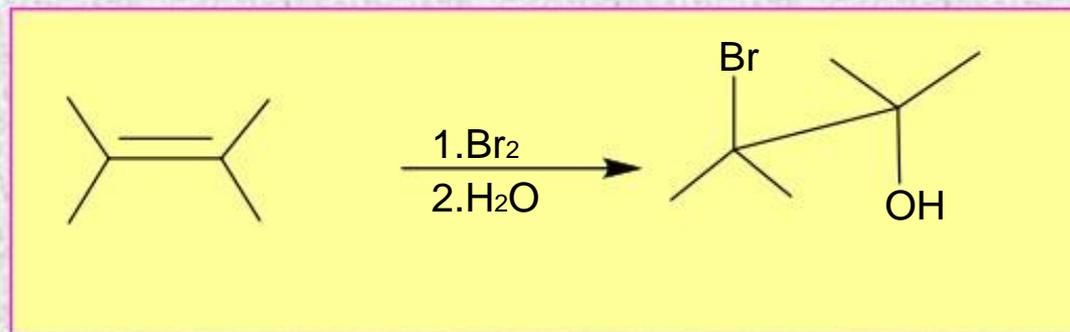


*Both cis and trans-2-pentenes produce racemic mixture (in the absence of any chiral source)*

**(±) Enantiomers**

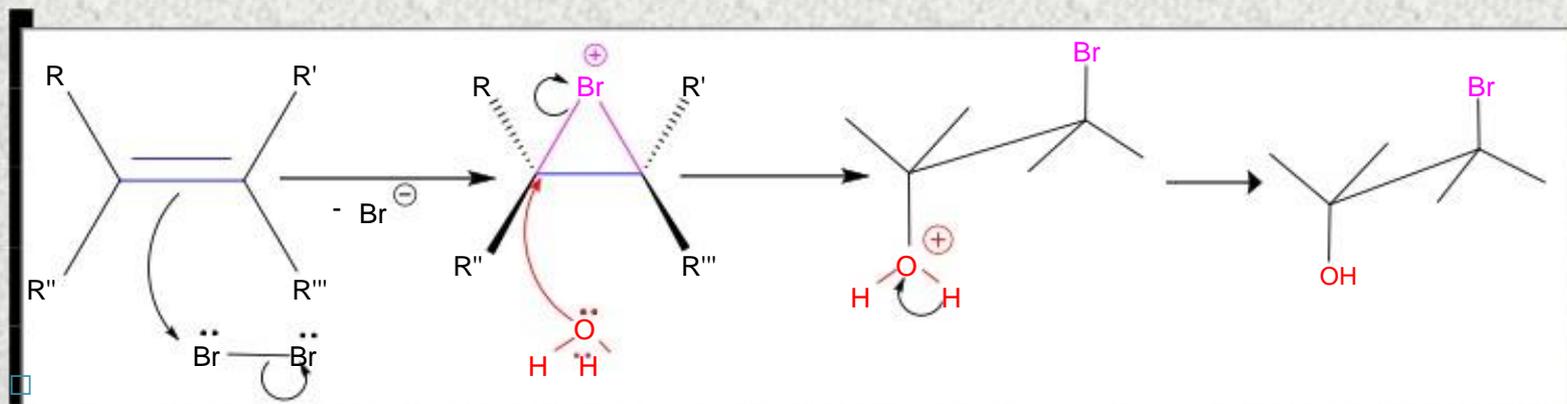
**(±) Enantiomers**

- 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.



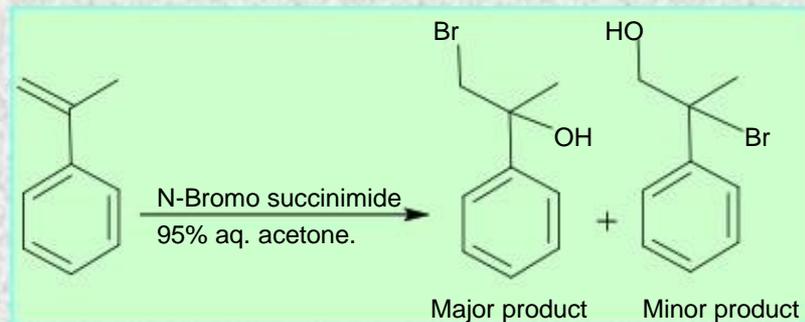
## MECHANISM (HALOXYDRIN FORMATION)

- 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.

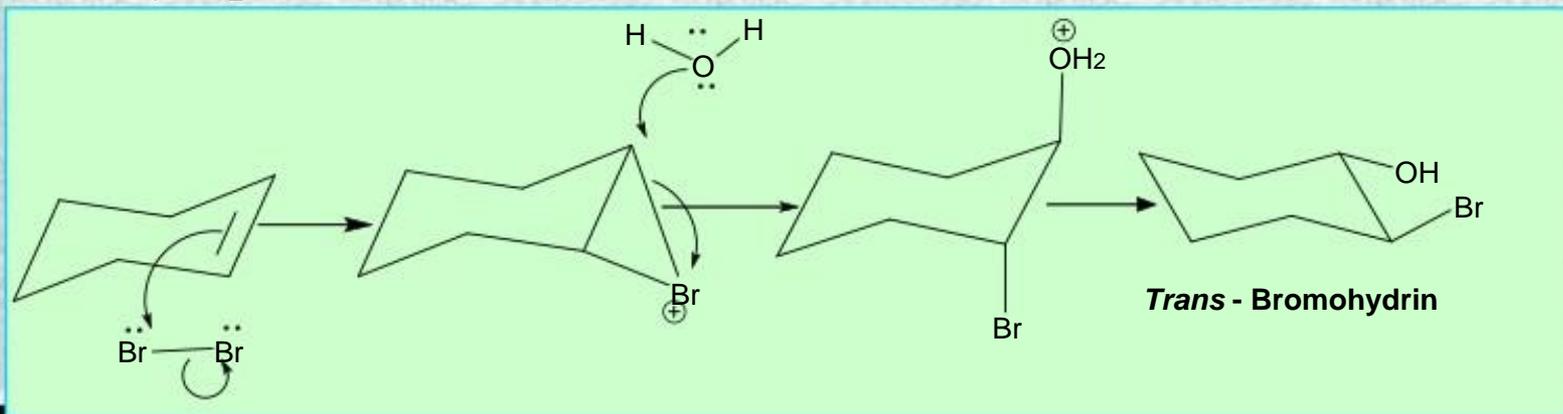


# STEREOCHEMISTRY

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



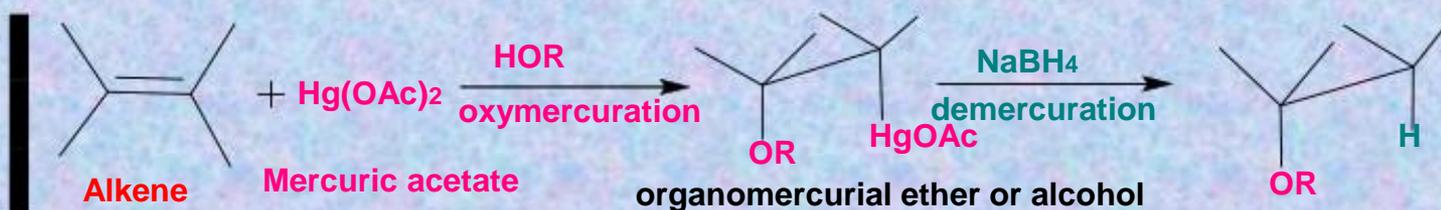
- **Stereoselectivity** :- the addition of hydroxyl group occur anti to the halonium ion giving major product. In the bromohydrin formation reaction of cyclohexene we get *trans* bromohydrin as major product.



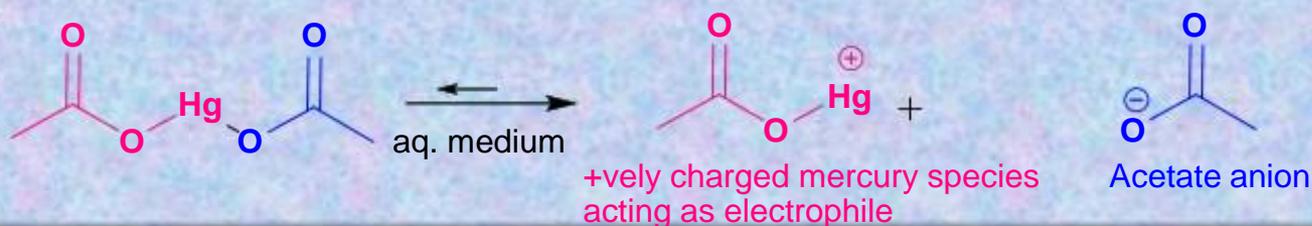
# ADDITION OF WATER OR SOLVENT TO ALKENE

( 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 :-



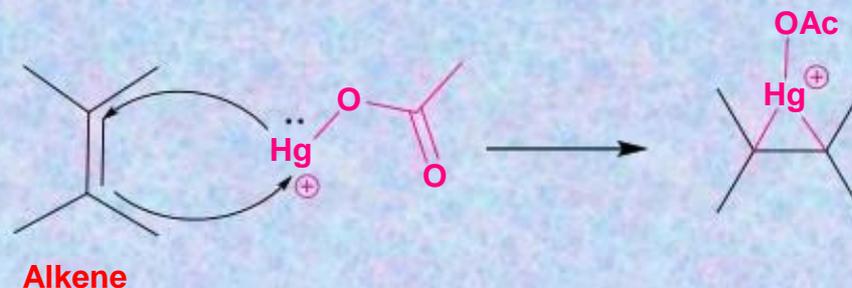
- Generation of reagent :-



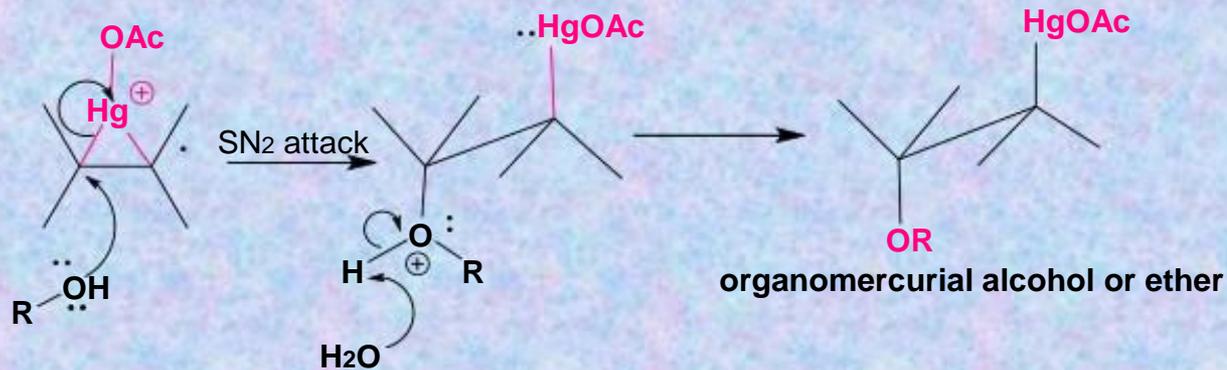
# MECHANISM ....

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.

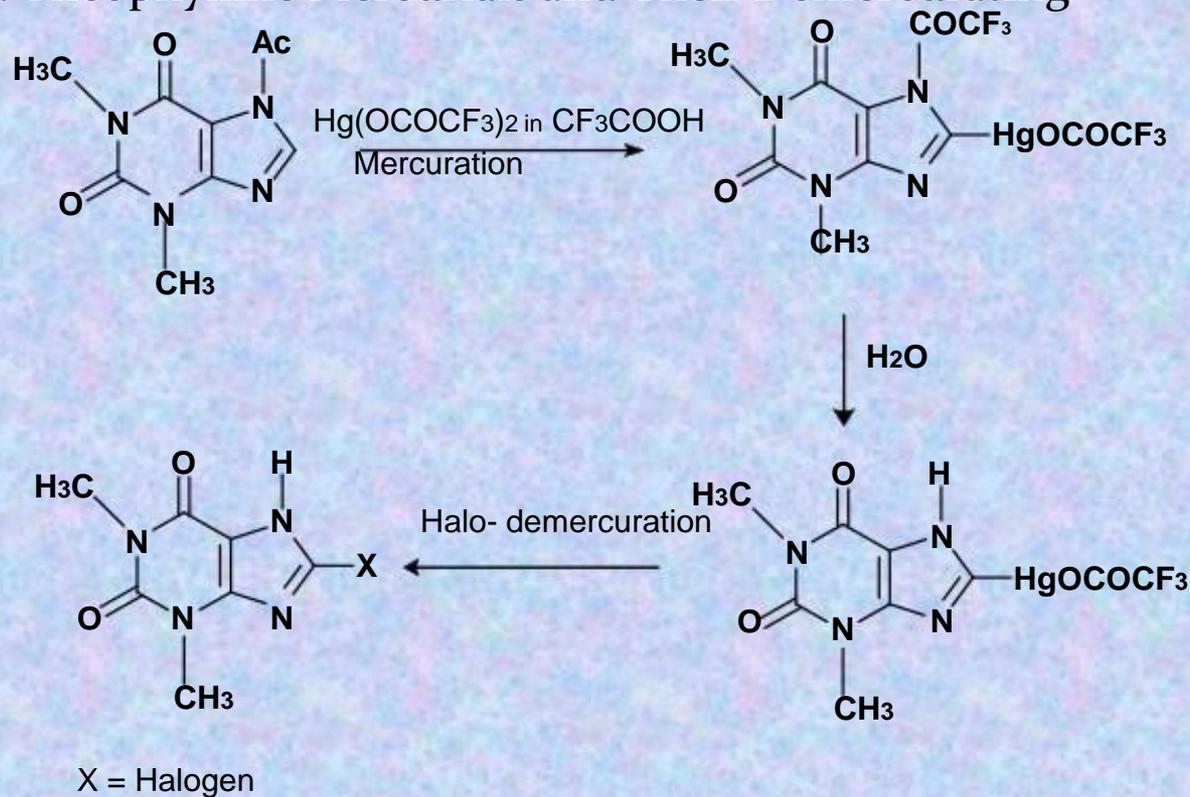


- In this step  $\text{S}_{\text{N}}2$  attack by the solvent leads to the formation of organomercurial species.





□ Substituted Theophylline Mercurials and Their Demercuring 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.

# DIOL FORMATION REACTIONS

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

*Hydroxylation with Potassium permanganate.*

*Osmium tetroxide catalysed dihydroxylation.*

*Upjohn dihydroxylation.*

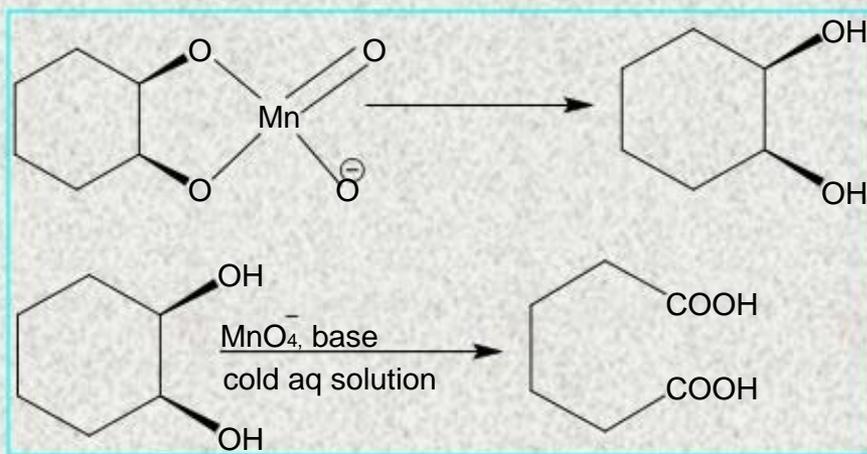
*Woodward reaction.*

*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.

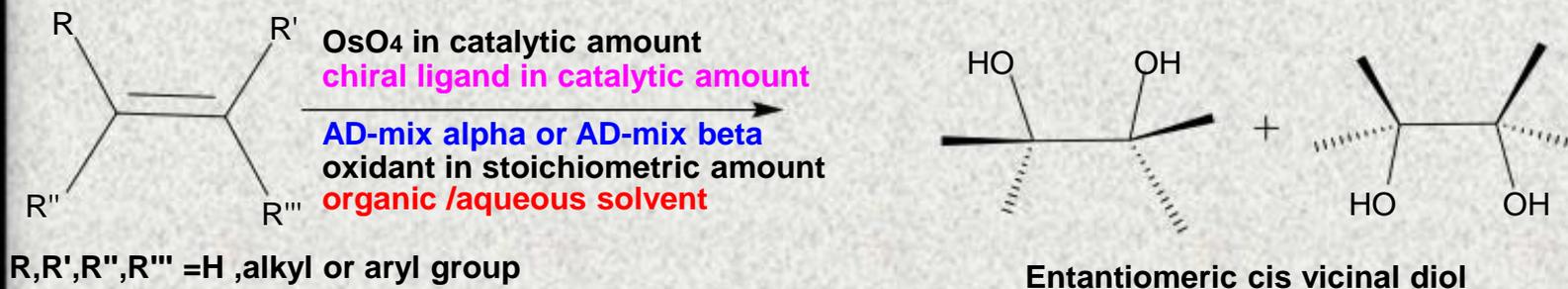


- Disadvantages :-
- The product yield obtained is very low.
- The product can be a mixture of diol & carboxylic acid.
- A better stereoselective epoxidation can be achieved with Osmium tetroxide.

# 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 Dehydroxylation) 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 ( $K_2OsO_4(OH)_4$ ).

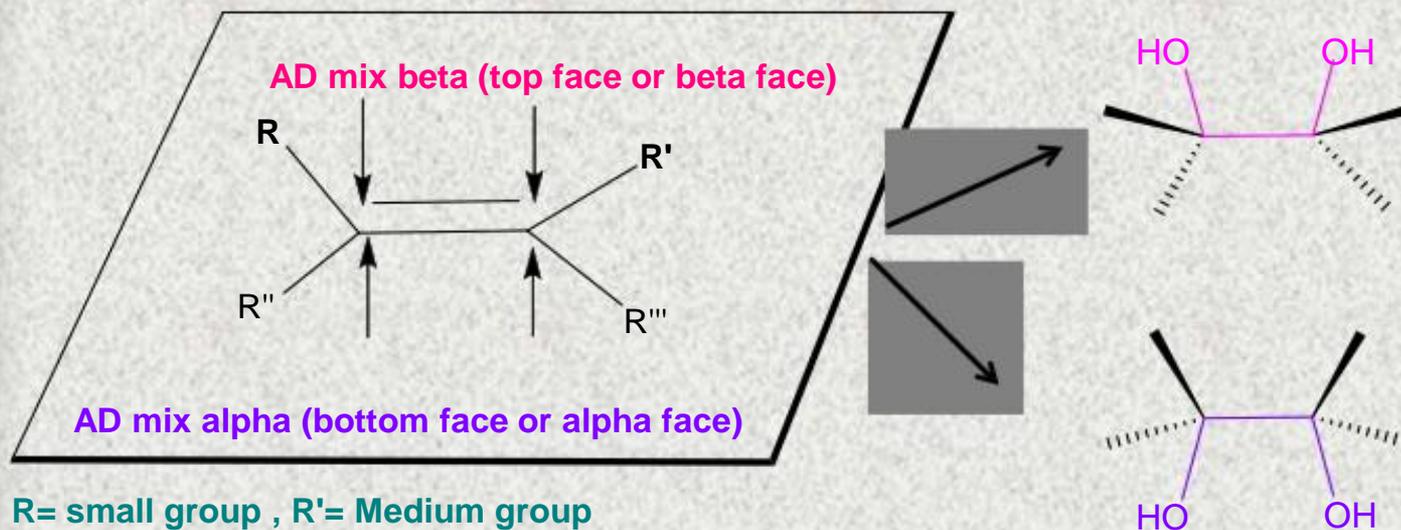


# SELECTIVITY OF ADDITION

- 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>



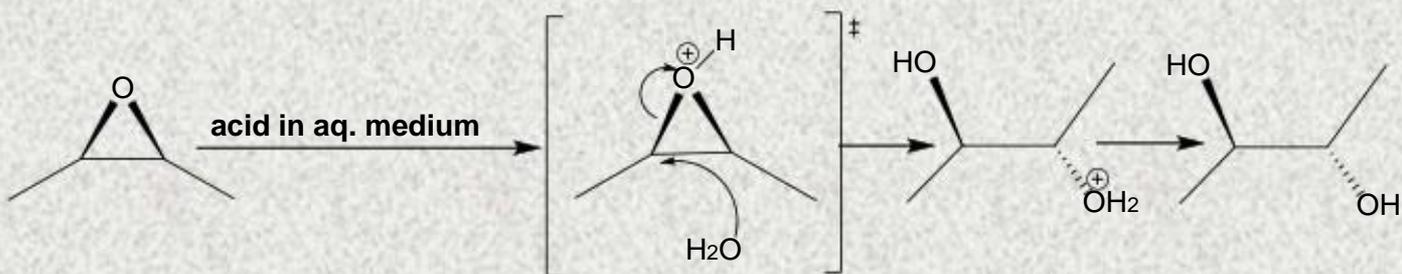
R= small group , R'= Medium group  
R''= Large group , R'''= Smallest group or H

Enantiomeric *cis* or  
*vicinal diol*

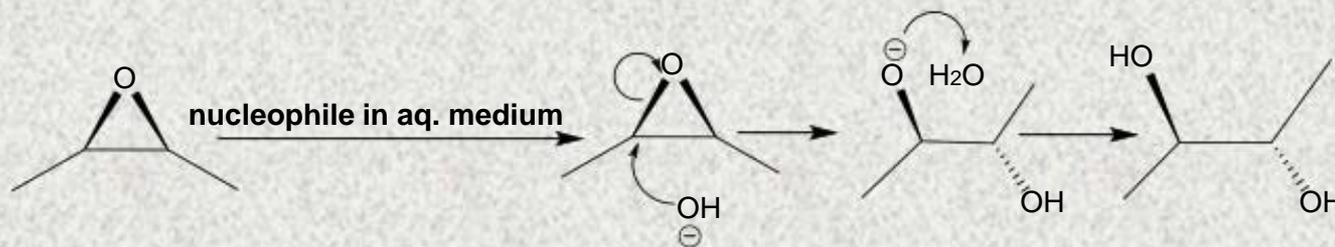
# EPOXIDE RING OPENING REACTION.

- 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.

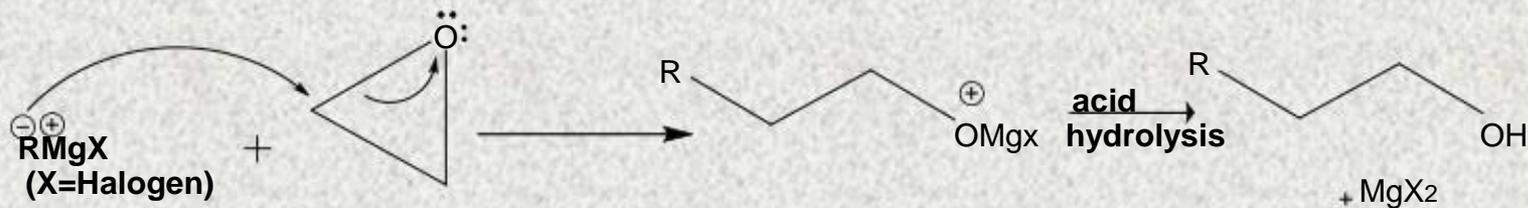
## Electrophilic ring opening



## Nucleophilic ring opening



- **Ring opening in the presence of organometallic reagents (RMgX, RLi, RC<sup>o</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 S<sub>N</sub>2 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.



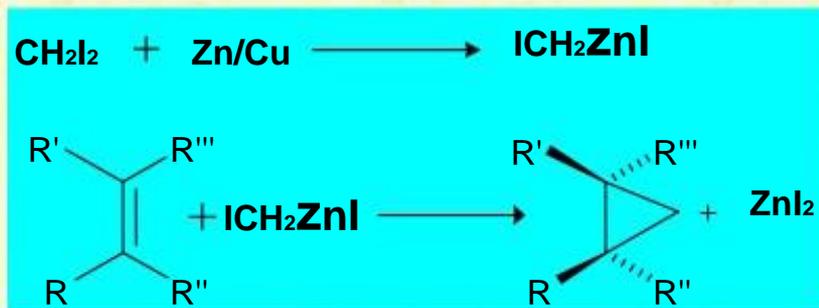


# CYCLOPROPANE RING FORMATION REACTIONS

# SIMMON-SMITH REACTION.

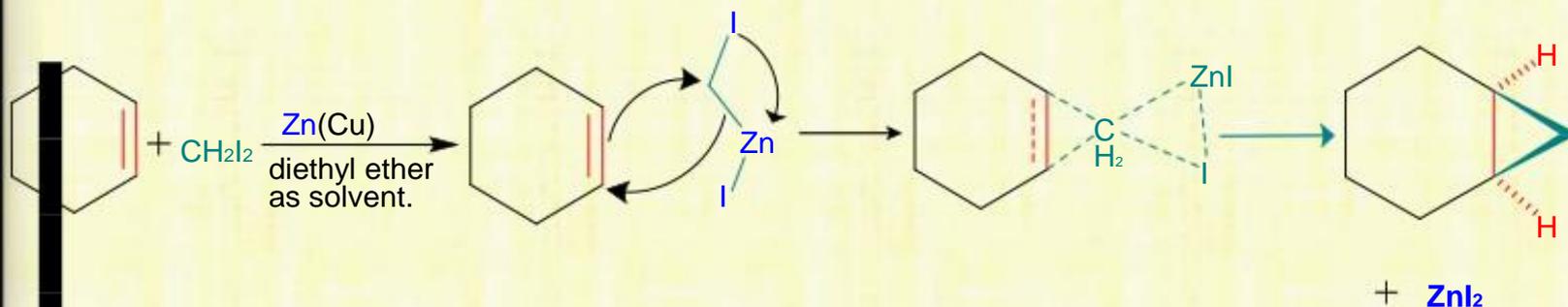
HOWARD ENSIGN SIMMONS, JR. AND R. D. SMITH

- 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 :-

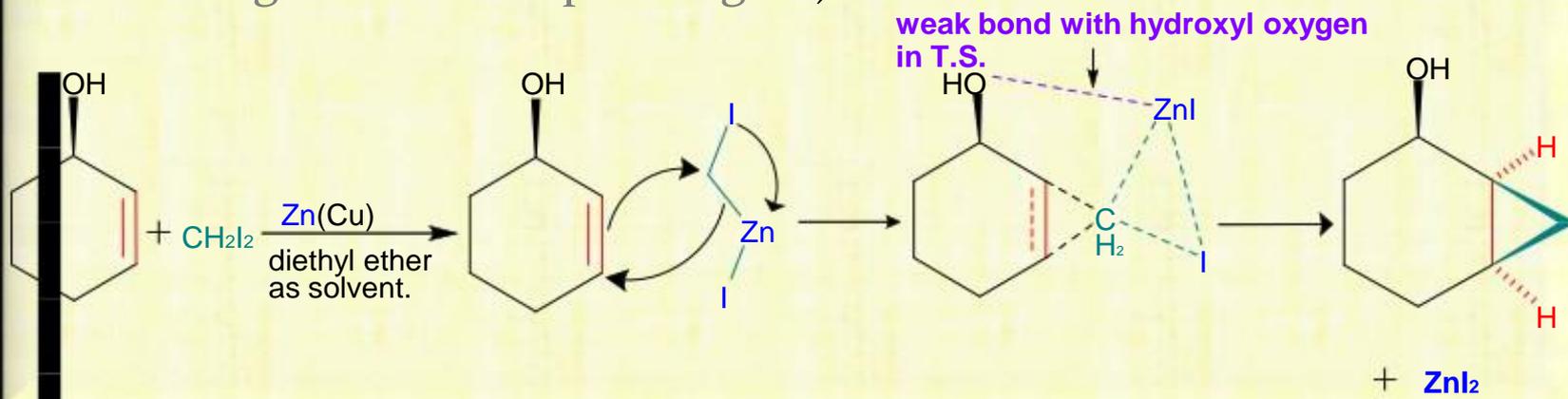


# MECHANISM

- 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).



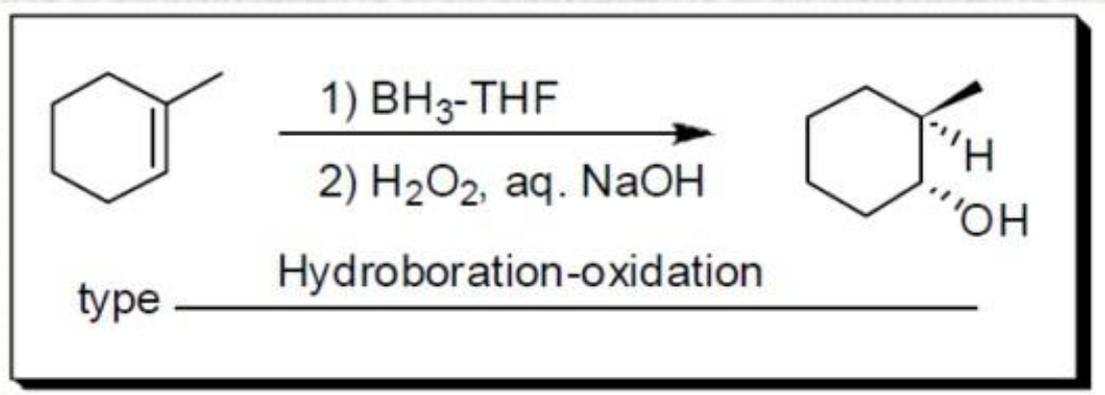
# HYDROBORATION REACTION

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  $\text{BH}_3$  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  $\text{BH}_3$  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 :-

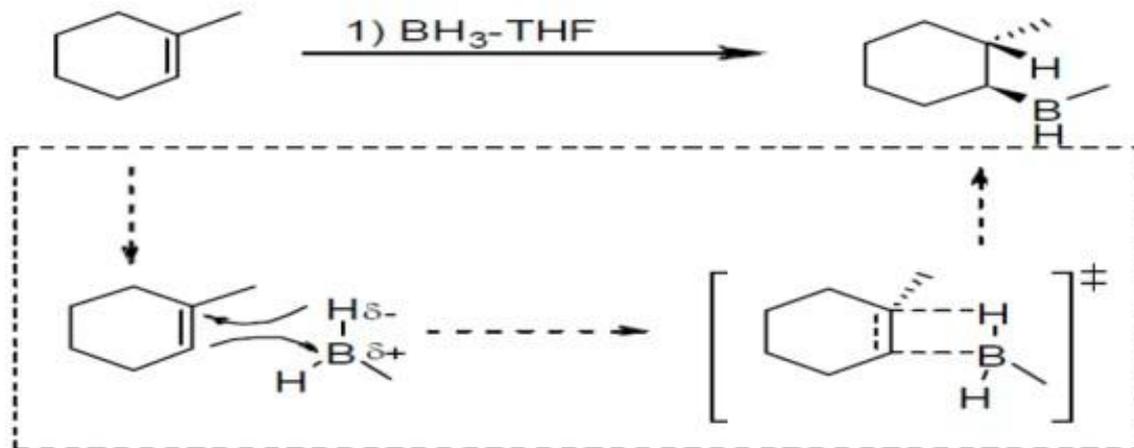
- Concerted addition of boron to sterically least hindered carbon.
- The oxidation occur in the presence of peroxide to give the *syn* addition product.



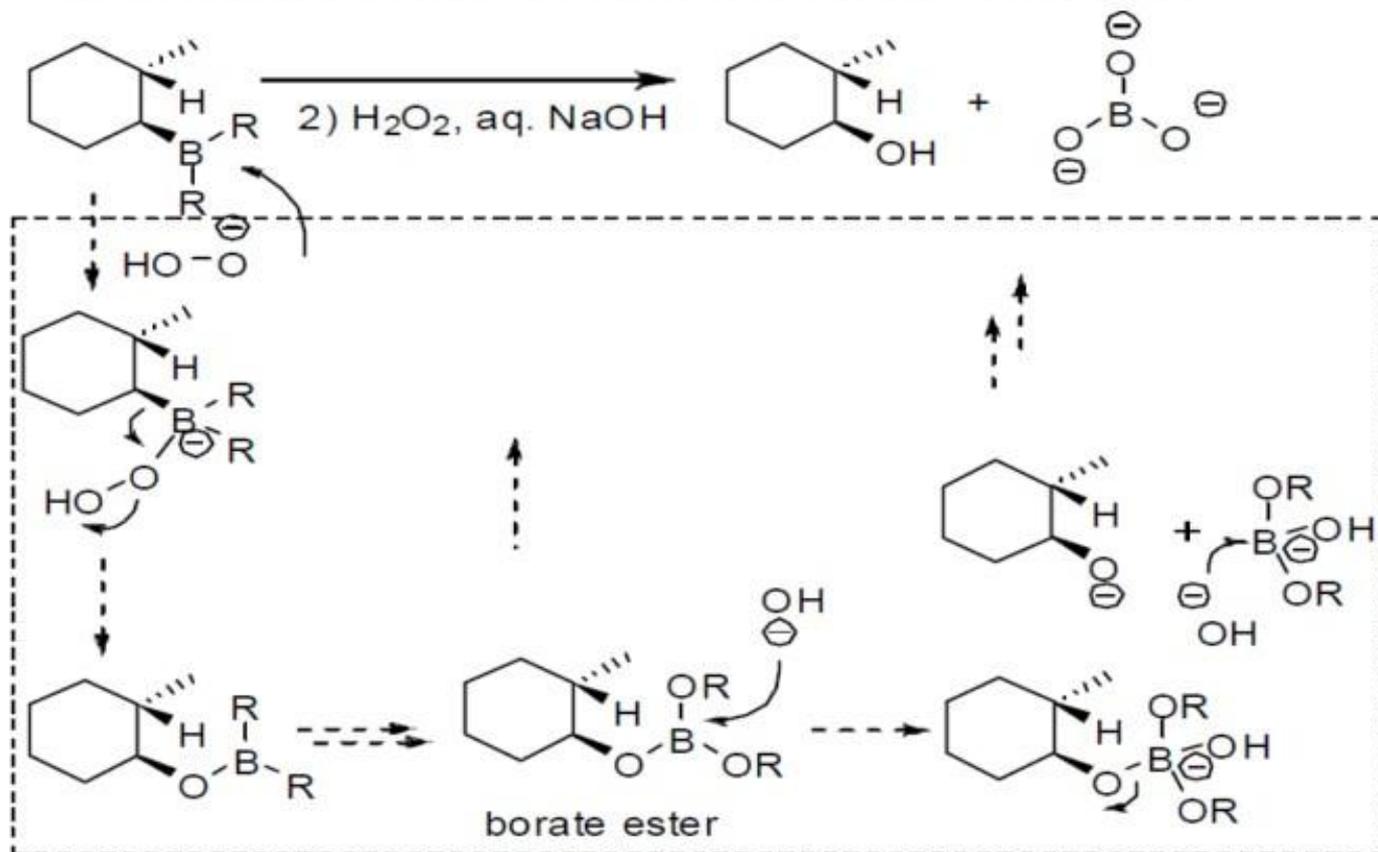
## MECHANISM OF HYDROBORATION:-

- 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.

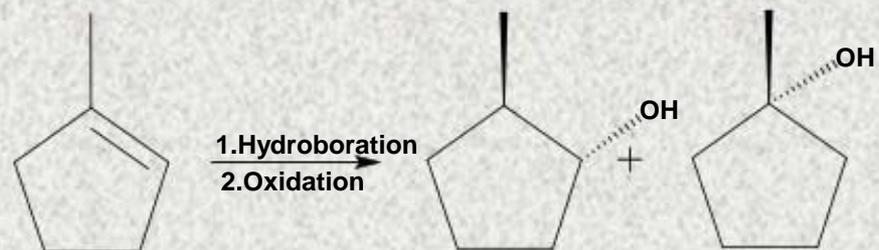
First Step:



Second Step:



□ Hydroboration of 1-methyl cyclopentene.



2-methyl cyclopentanol

With 9-BBN

99.9%

BH<sub>3</sub>

98.5%

HBCl<sub>2</sub>

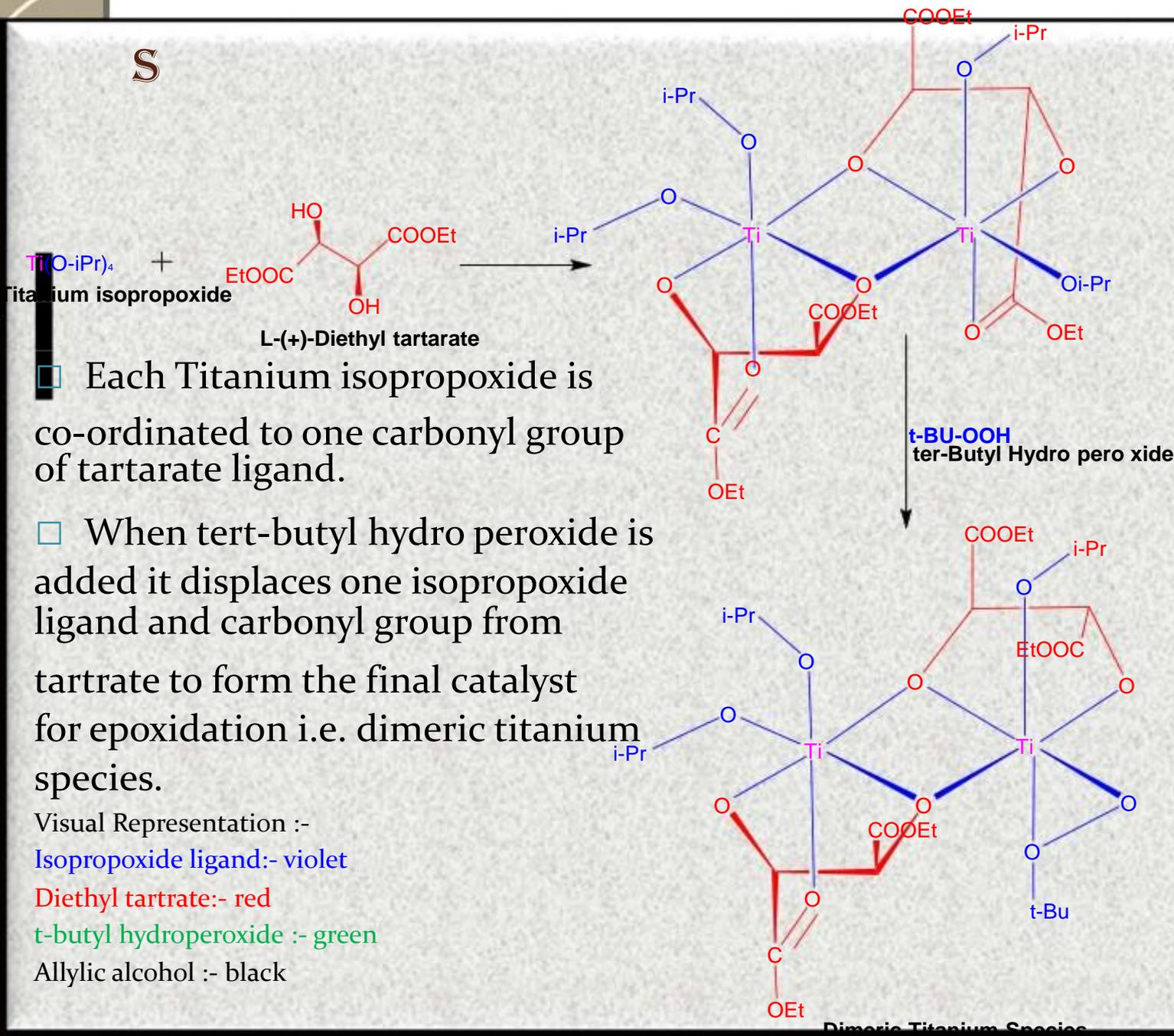
99.8%

# 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.

S



□ Each Titanium isopropoxide is co-ordinated to one carbonyl group of tartarate ligand.

□ When tert-butyl hydro peroxide is added it displaces one isopropoxide ligand and carbonyl group from tartrate to form the final catalyst for epoxidation i.e. dimeric titanium species.

Visual Representation :-

Isopropoxide ligand:- violet

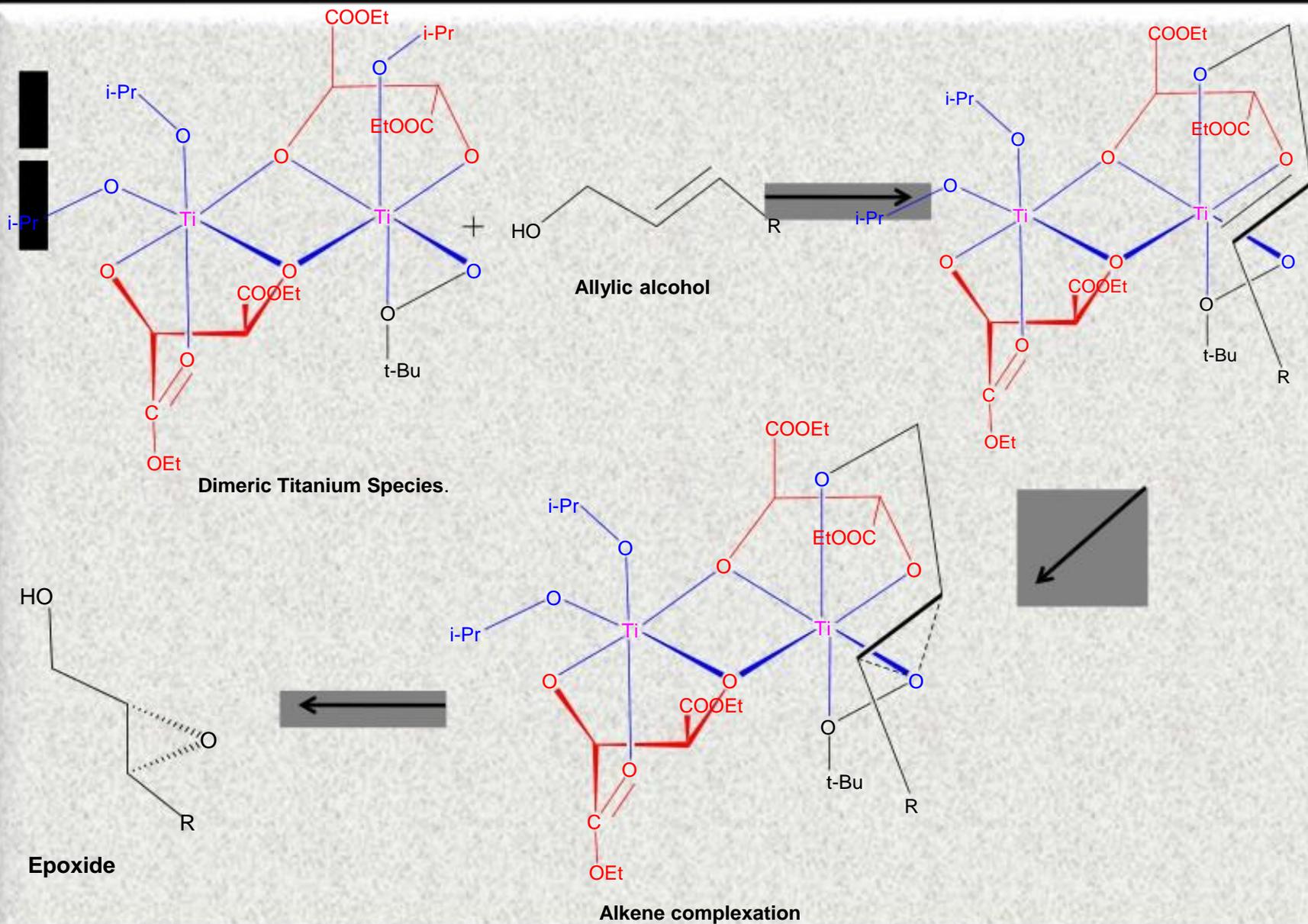
Diethyl tartrate:- red

t-butyl hydroperoxide :- green

Allylic alcohol :- black

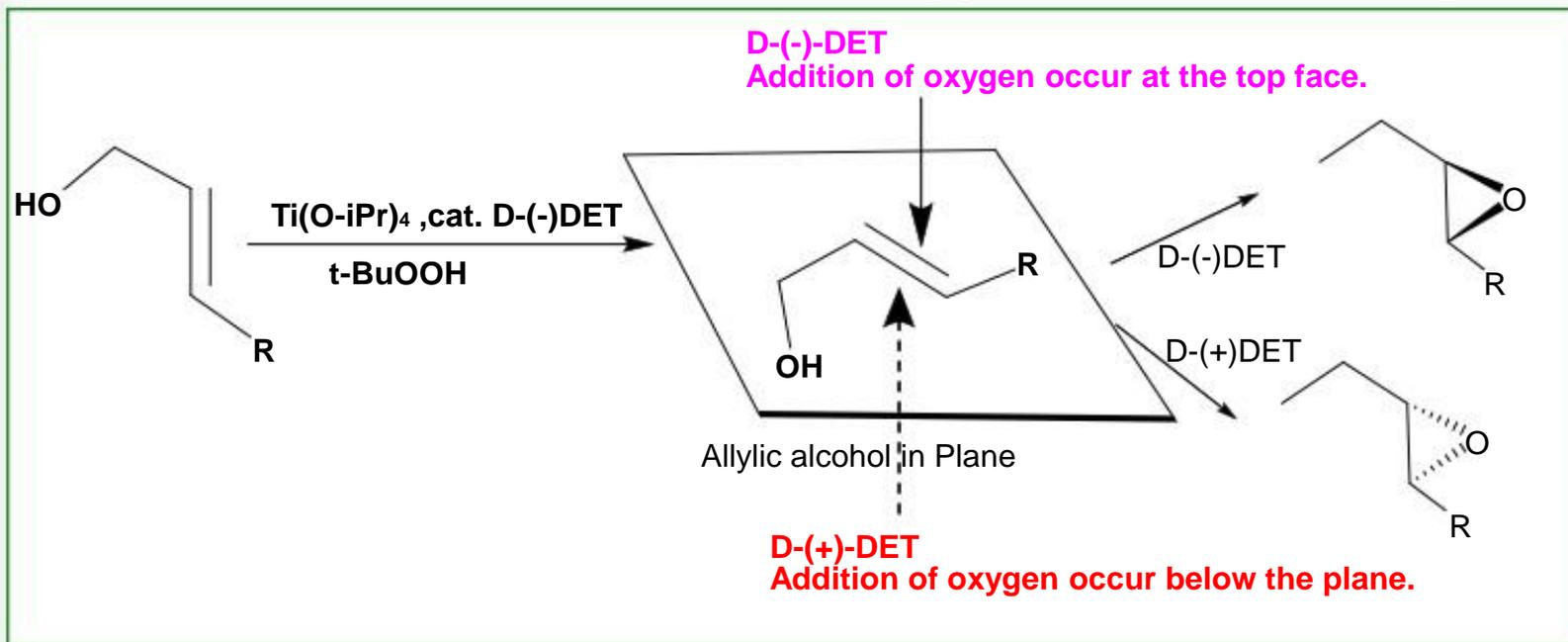
Dimeric Titanium Species

# MECHANISM OF EPOXIDATION :-

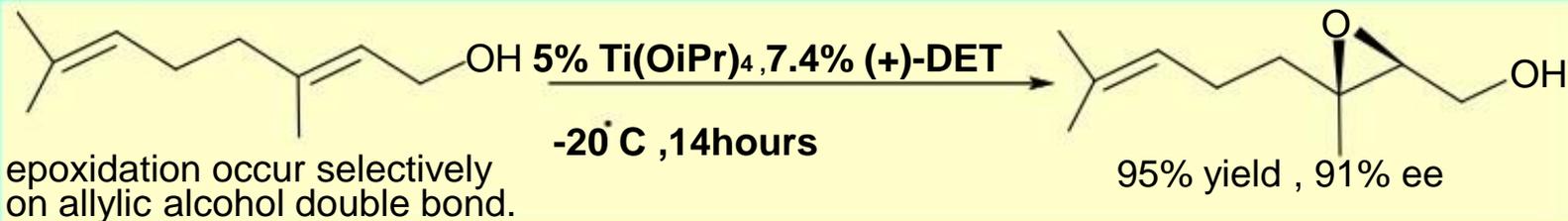


# SELECTIVITY OFFERED BY DIETHYL TARTRATE.

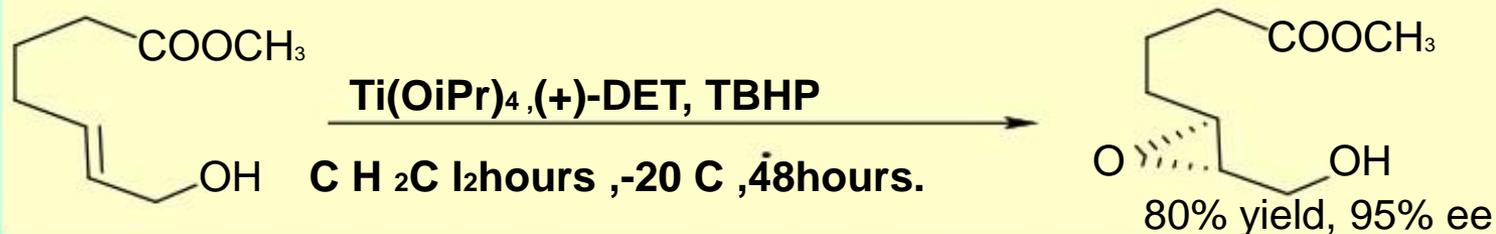
- The enantioselectivity of oxygen addition to the face of allylic alkene is dependent on which stereoisomer of diethyl tartrate (**DET**) used in the reaction.
- If **(-)-DET** is used, the addition of oxygen occurs above the plane as shown.
- If **(+)-DET** is used, the addition of oxygen occurs below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

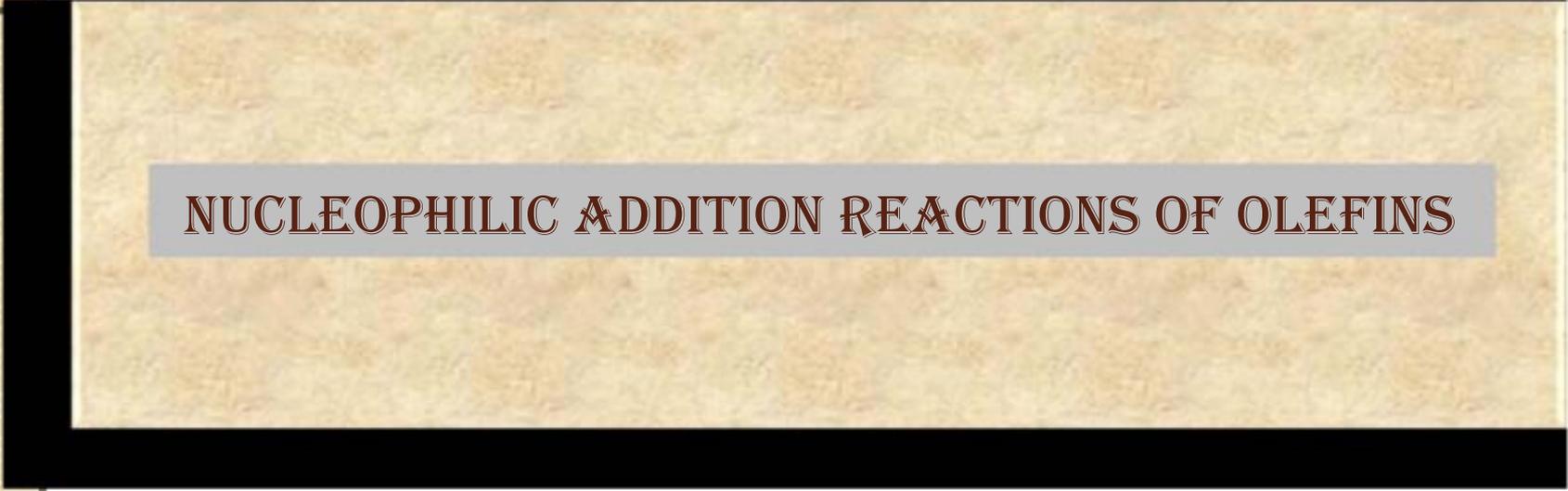


# APPLICATION OF SHARPLESS EPOXIDATION



## Intermediate for synthesis of leukotriene C1





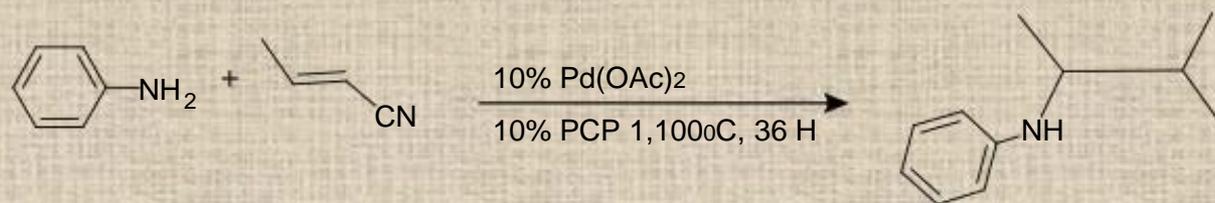
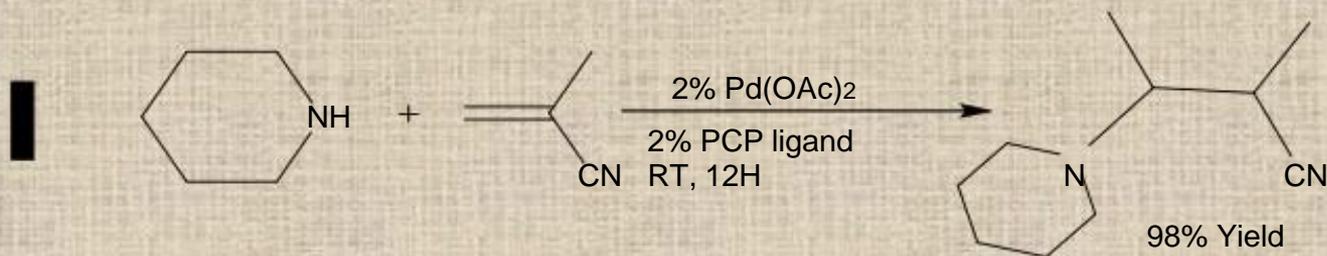
# NUCLEOPHILIC ADDITION REACTIONS OF OLEFINS

## 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.

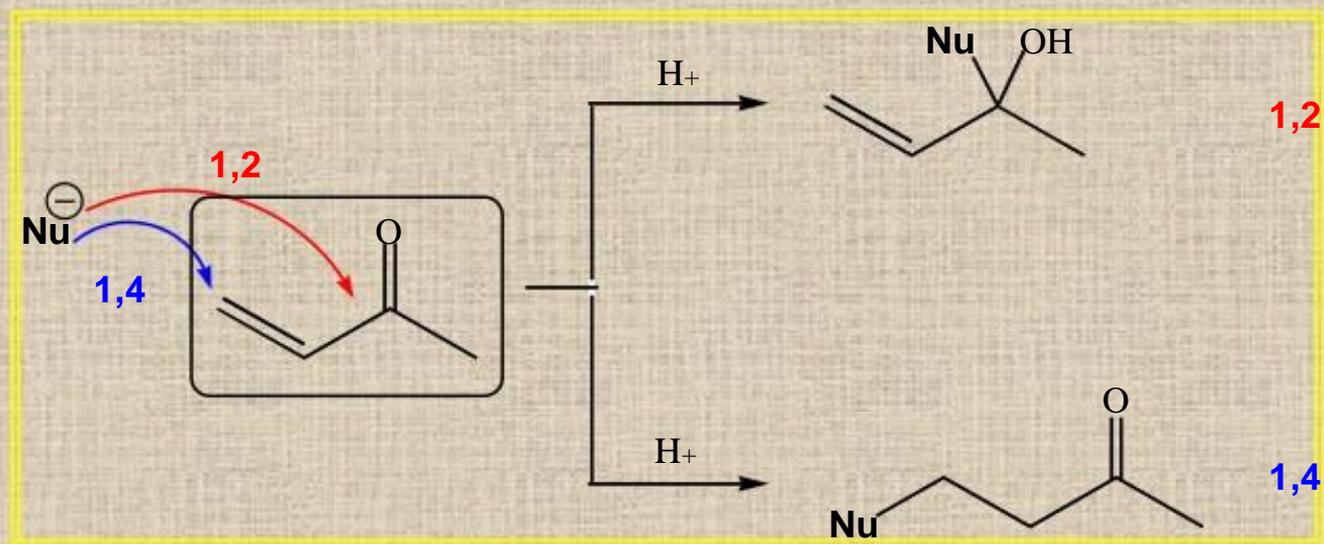
# AMINATION REACTIONS

- 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.

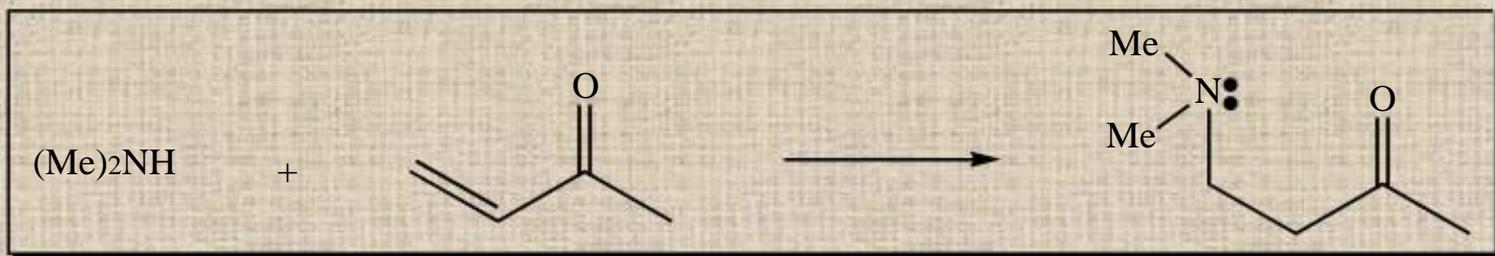
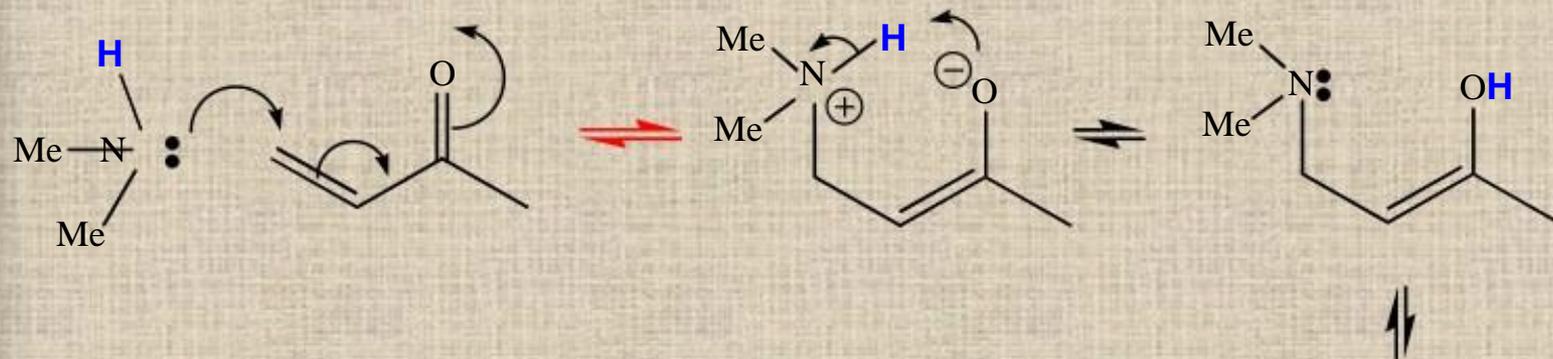


1,2-additions\* are also known as **direct addition**

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

## EXAMPLE AND KEY STEPS

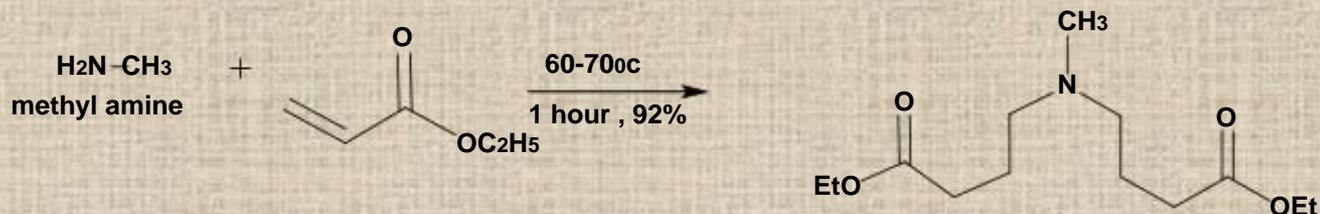
□ a



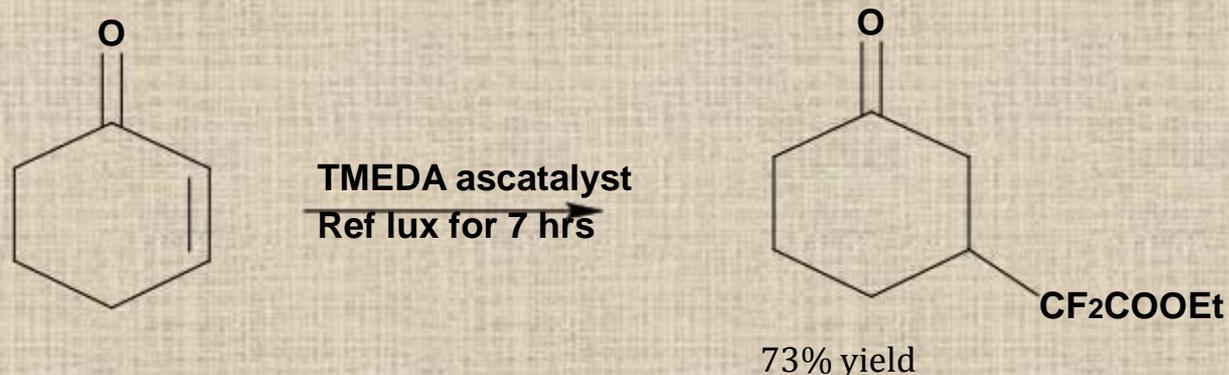
Key factors that control conjugate addition are,

- (i) Reaction conditions
- (ii) Nature of the  $\alpha,\beta$ -unsaturated carbonyl compound
- (iii) 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

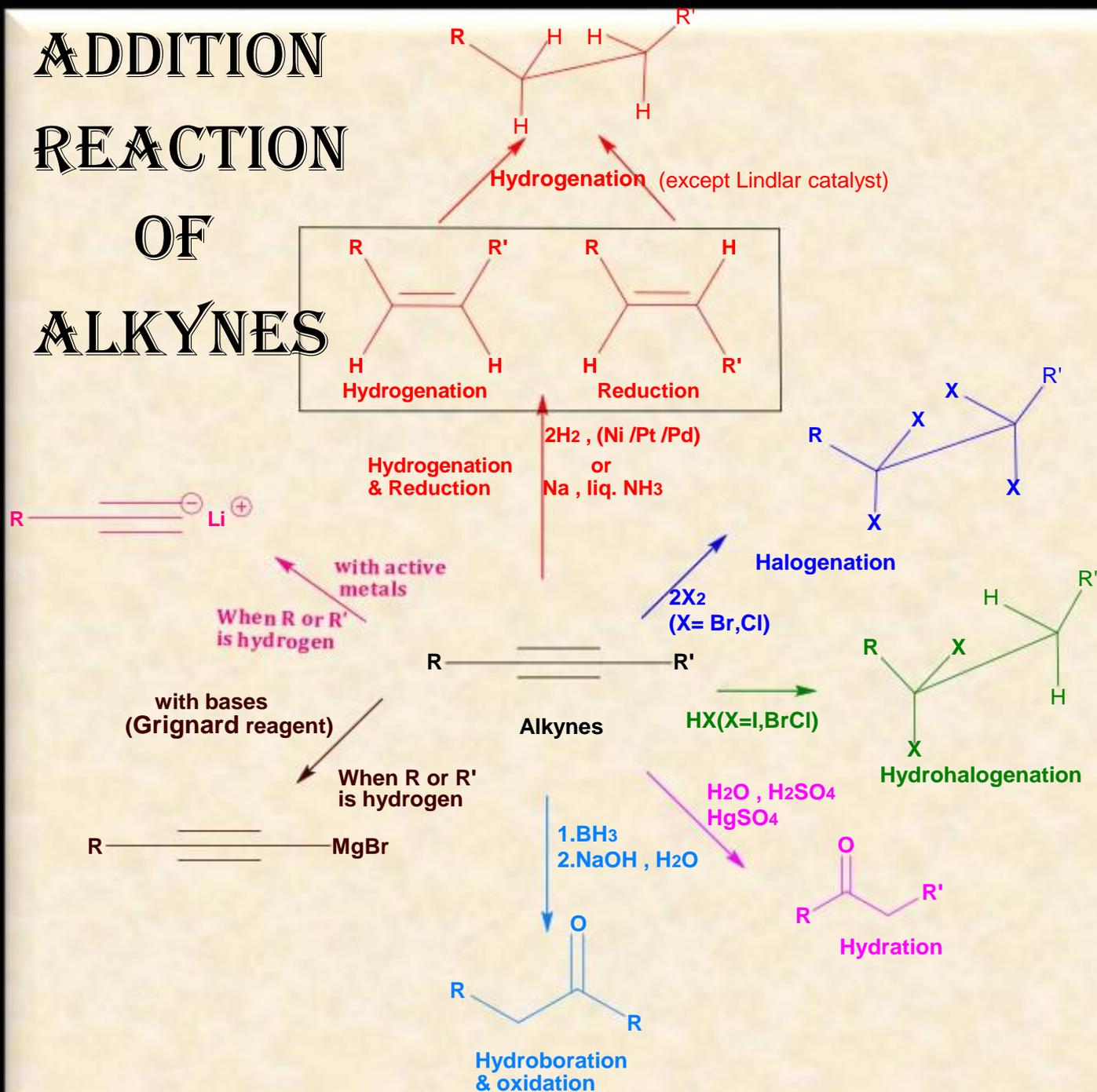


- 1,4-Addition reaction of ethyl bromodifluoroacetate to Michael acceptors.



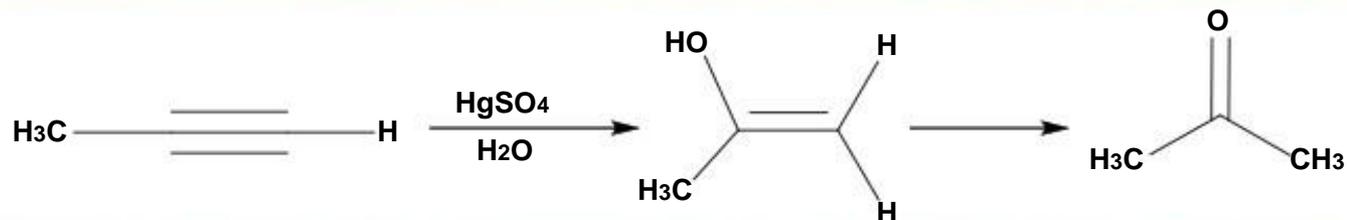
# ALKYENES

# ADDITION REACTION OF ALKYNES

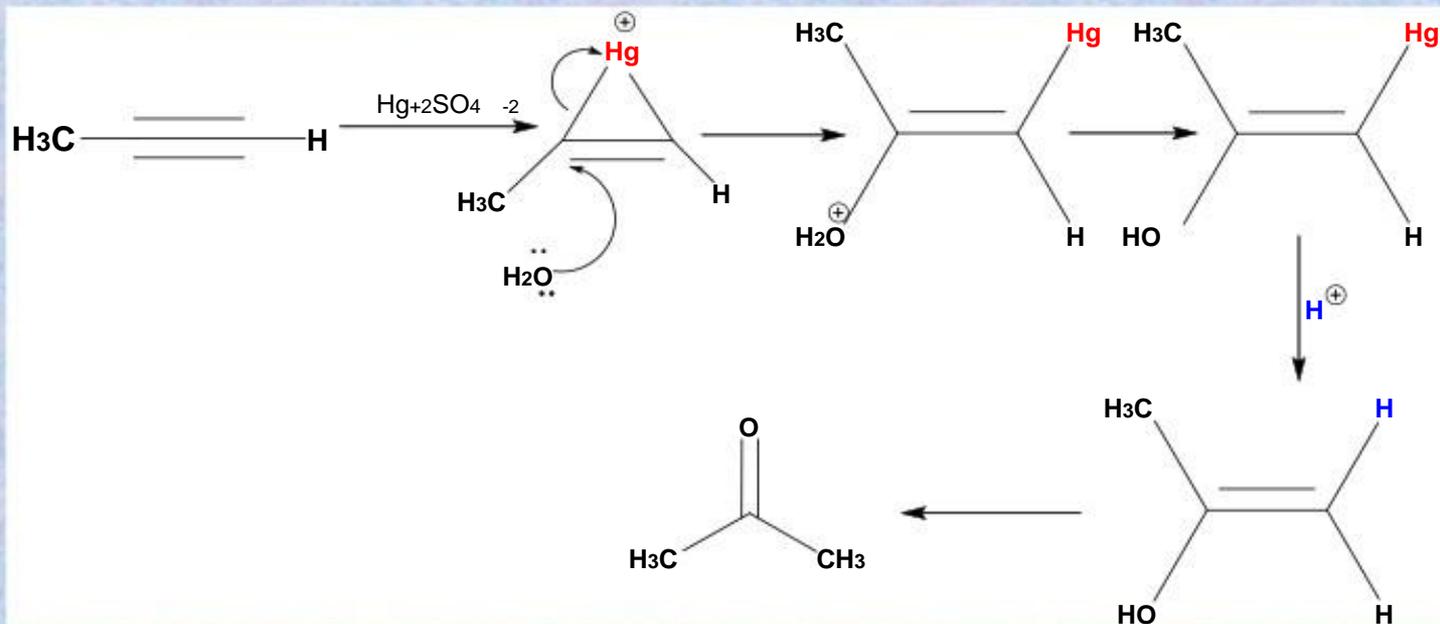


# HYDRATION REACTIONS

- 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:-

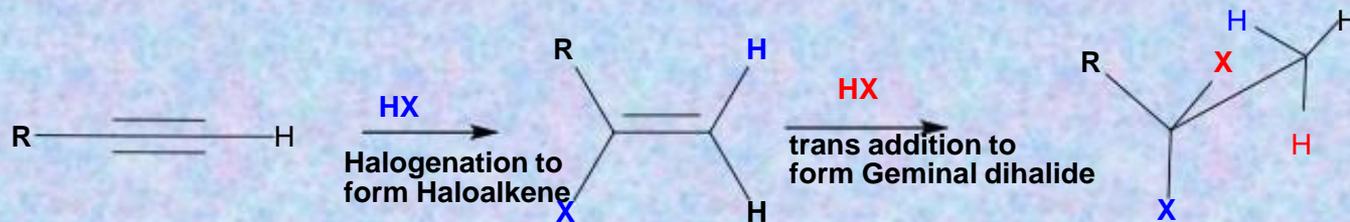


- Mechanism :-



# 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.

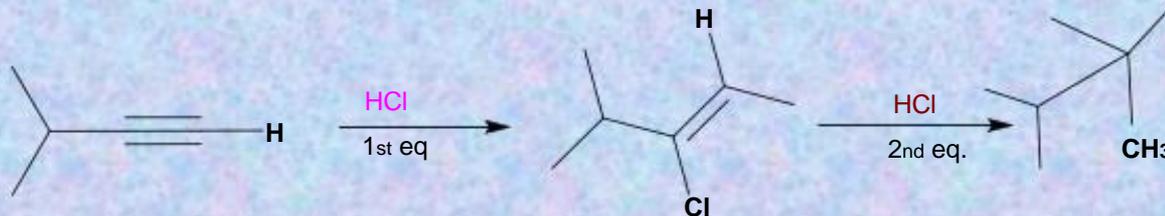


□ Examples :-

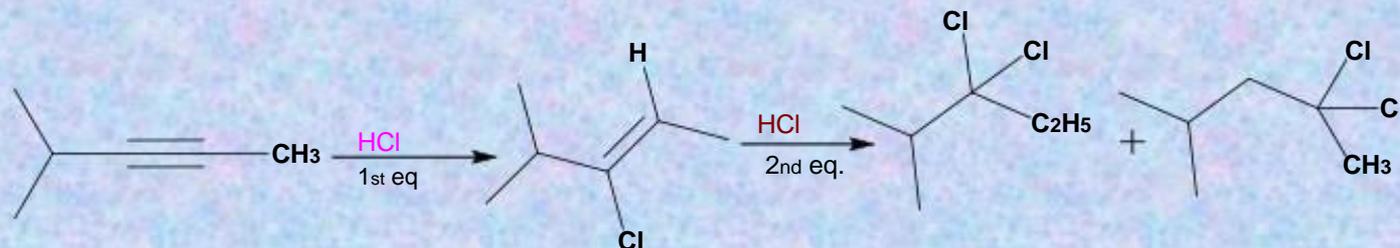
□ 1.



□ 2.



□ 3.

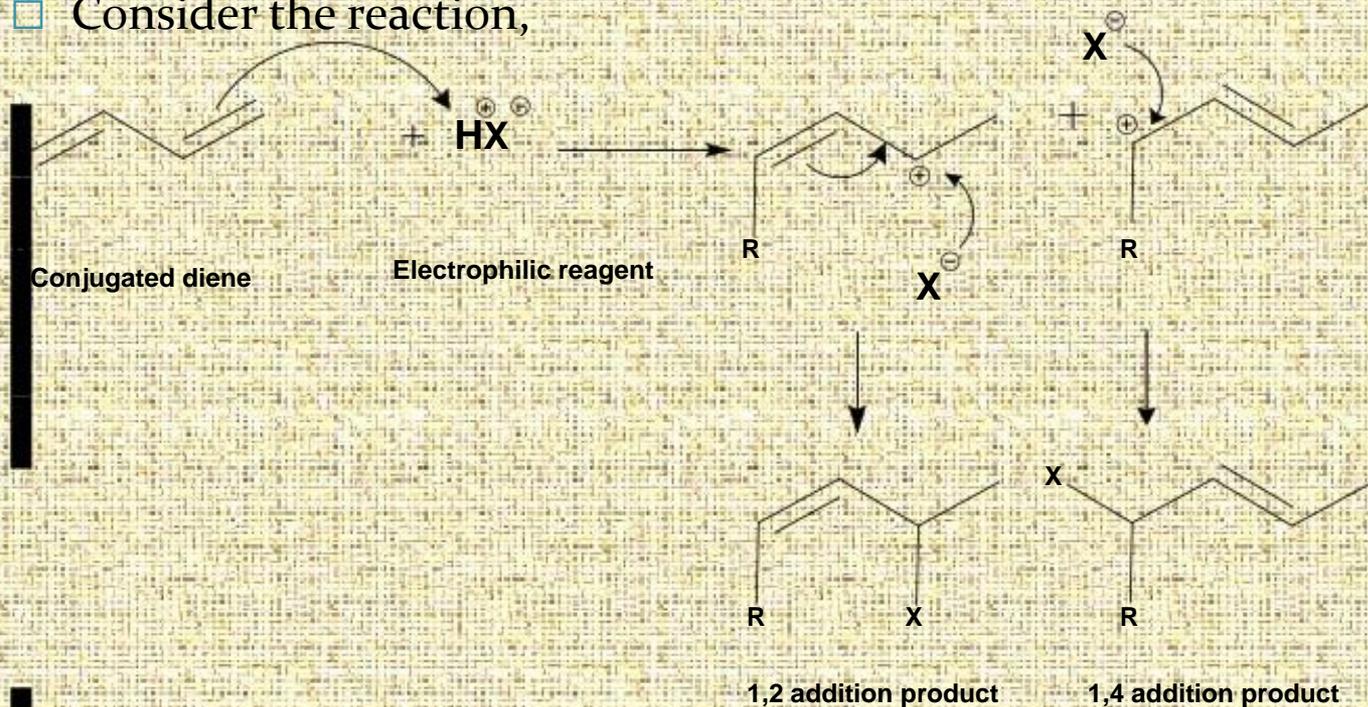




DIENES

# ELECTROPHILIC ADDITION

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

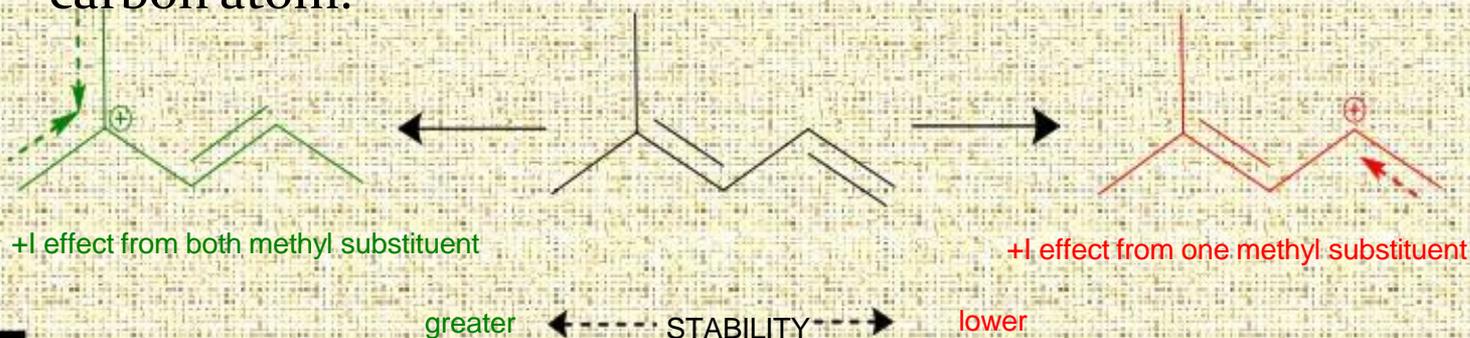


- Which is the major product formed predominantly?

□ 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.

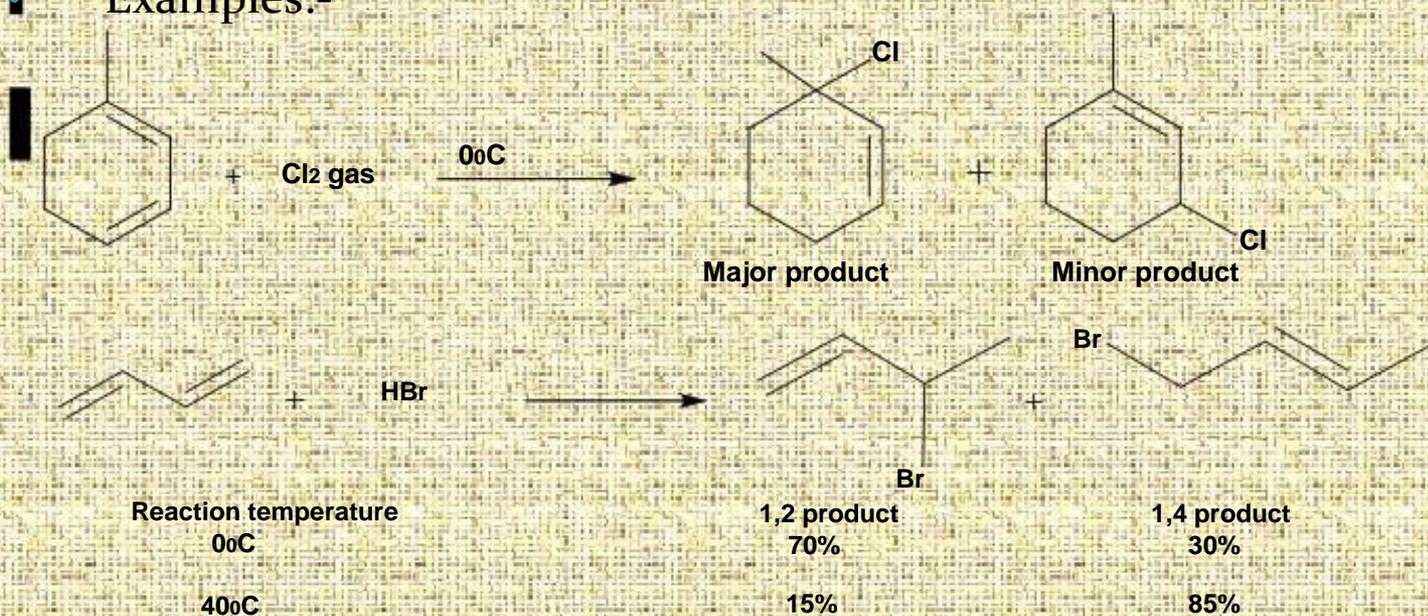
## □ Reaction temperature:-

- 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.

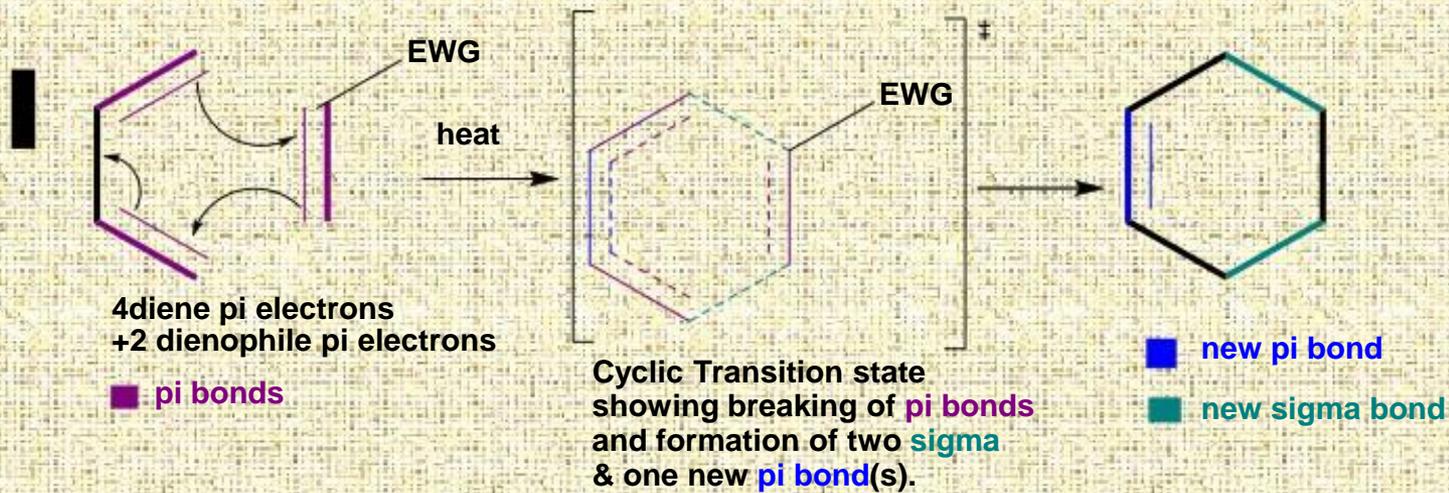
## □ Reagent :-

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

## • Examples:-



# DIELS ALDER REACTION (CYCYLOADDITIONS)



## 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



Reactivity :- **Least**      **Normal**      **Good**      **Excellent**

### DIENOPHILES



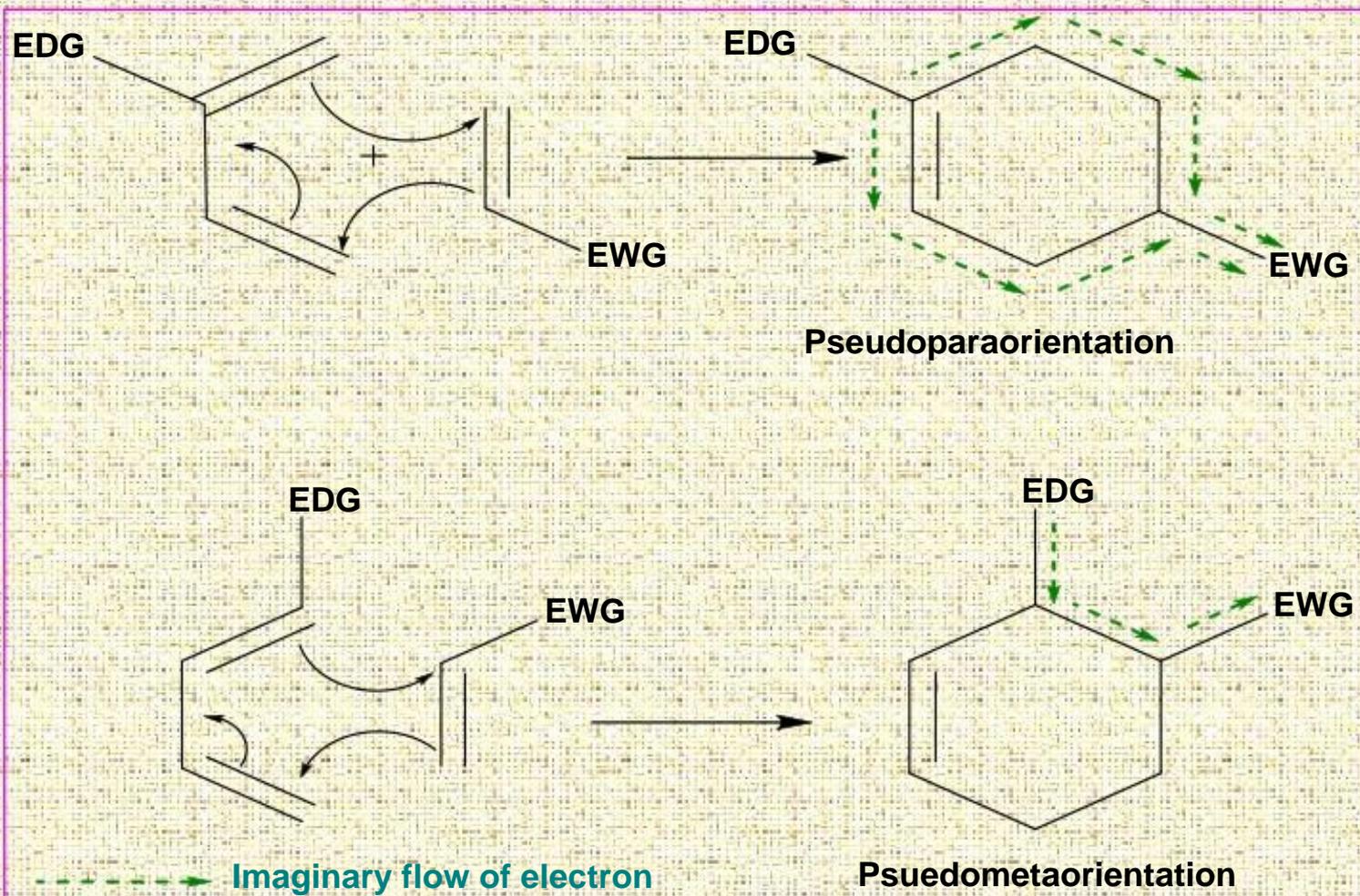
Reactivity :- **Excellent**      **Good**      **Normal**      **Least**

**EWG :-**  
Carbonyl , ester,  
nitriles , quaternary  
amines, Halides  
anhydrides, nitro ,  
ester, quaternary  
amines, acids etc.

**EDG:-**  
Amines , -OR,  
-NHCOR , alkyl,  
phenyls etc.

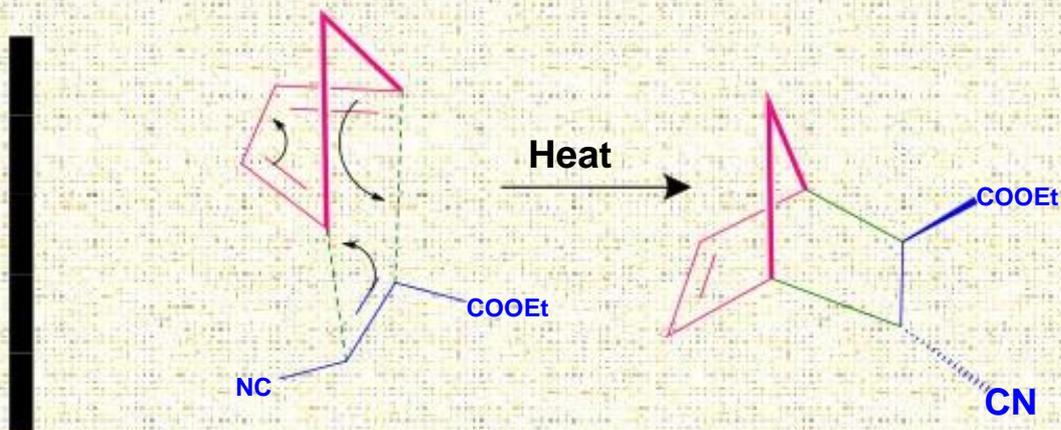
# □ ORIENTATION OR REGIOSELECTIVITY :-

- 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

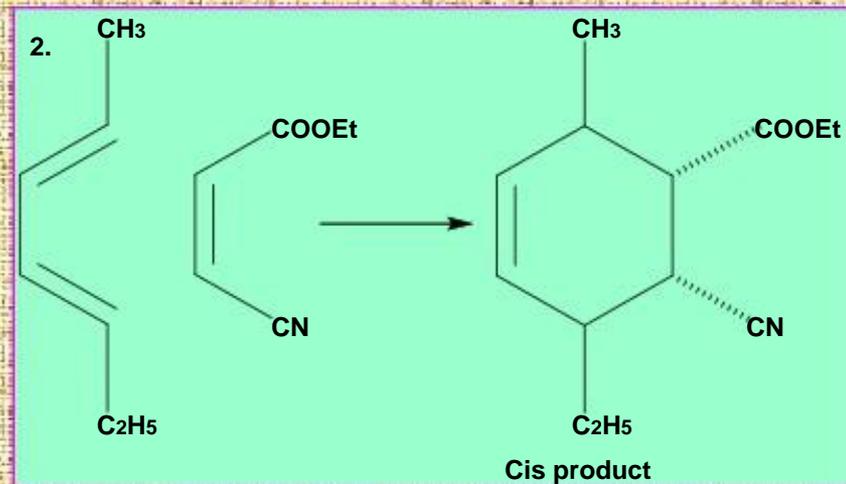
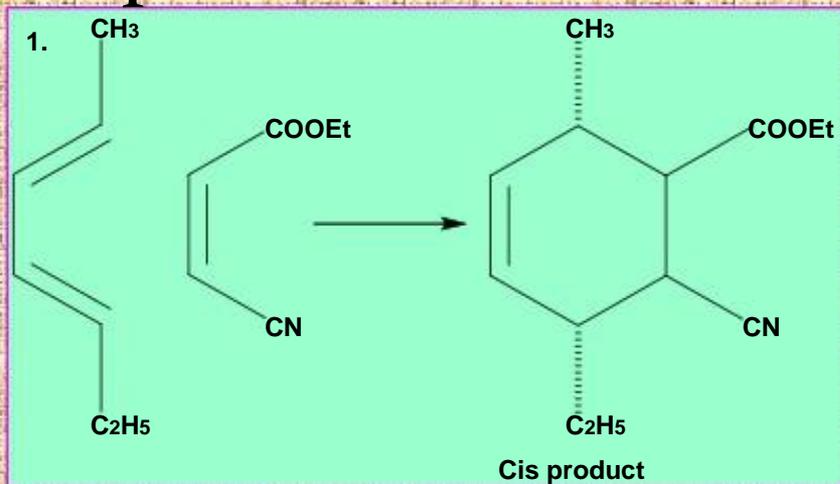


# □ STEREOSELECTIVITY

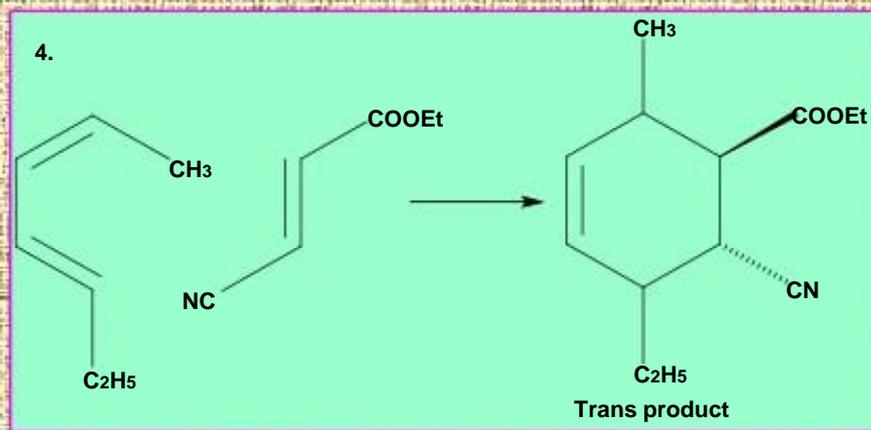
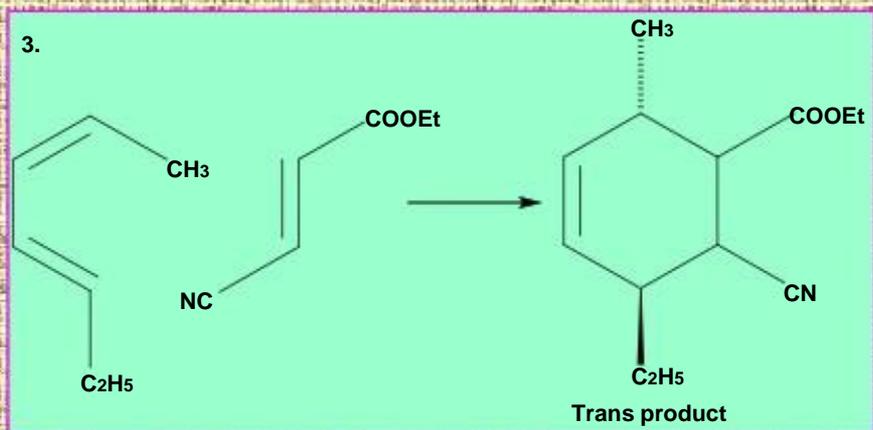
- Diels -Alder reaction exhibits excellent stereoselectivity.
- The stereoselectivity of reactant is maintained in the products both in case of diene and dienophile. The addition is *syn* addition as shown below



# Cis product:-

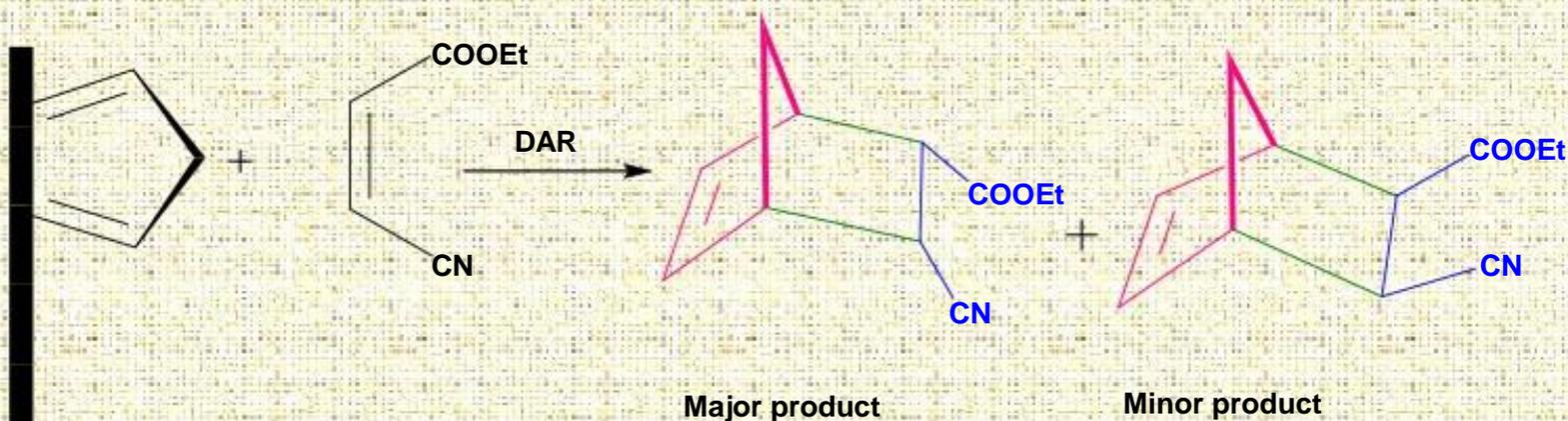


# Trans product:-



## ORIENTATION OF DIENOPHILE AND END/EXO PRODUCT

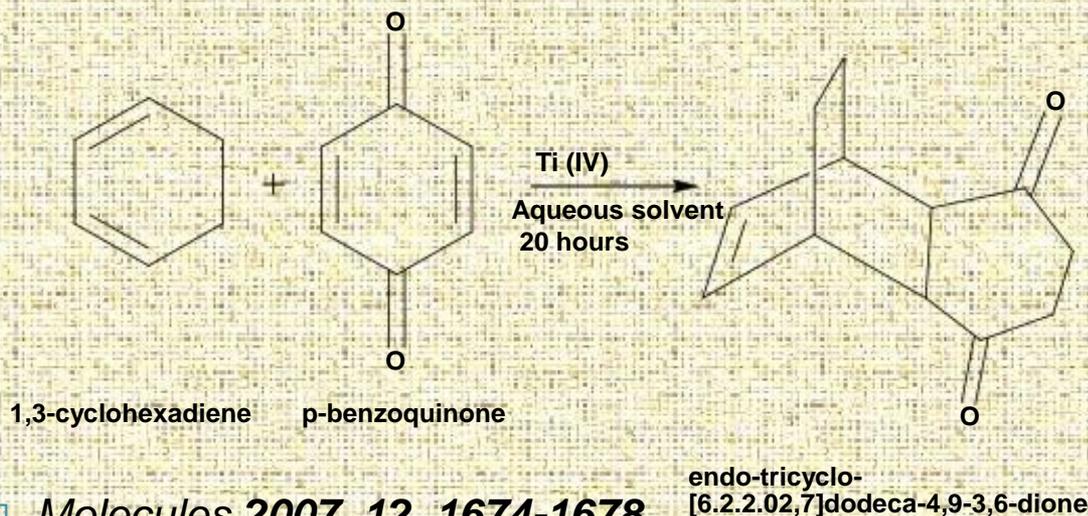
- Dienophile are electron deficient. They would try to approach the diene in such a manner that the electron withdrawing group will remain toward the newly developing  $\pi$  bond, giving *endo* as the major product.



- 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 %