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SCHOOL OF SCIENCE & HUMANITIES

DEPARTMENT OF CHEMISTRY

UNIT – I -Mechanisms and Determination Methods– SCYA7302

UNIT 1

MECHANISMS AND DETERMINATION METHODS

1.0. Introduction

Organic reactions involves the conversion of one functional group into another by the attack of the reagent.

Substrate + Reagent $\longrightarrow$ Intermediates + Products

1.1Types of organic Reactions:

- Substitution Reaction
- Addition Reaction
- Elimination Reaction
- Rearrangements

a) Substitution Reaction

Reactions in which atom or group linked to carbon atom is replaced by another atom or group.

$$CH_3Cl + OH^- \longrightarrow CH_3OH + Cl^-$$

Category:

- Substitution at saturated carbon atom
- Substitution at unsaturated carbon atom

Mediated by nucleophile, electrophile and Free radicals.

b)Addition Reaction

Compounds with unsaturation in the molecule have a tendency to add with a reagent without eliminating a group or atom.

$$CH{\equiv}CH + H_2 \xrightarrow{Ni} CH_2{=}CH_2 \longrightarrow CH_3\text{-}CH_3$$

The reactions are Mediated by nucleophile and electrophile.

c)Elimination Reaction

The number of groups or atoms attached to the carbon decrease and the degree of unsaturation increases.

$$CH_3\text{-}CH_2\text{-}Br + RO^- \longrightarrow CH_2{=}CH_2 + Br^- + ROH$$

These reactions are categorized based on the molecularity of the equation

D)REARRANGEMENTS

The reactions in which the carbon skeleton is changed to give structural isomer of the original molecule. Atoms or groups shift from one position to another within the molecule resulting in a new molecular structure.

1.2 MECHANISMS FOR SUBSTITUTION REACTIONS

1.2.a. Nucleophilic Substitution Reactions: (S_N): Nucleophiles reacts at electron deficient centers.

Eg: Conversion of alkyl halide to alcohols is of two types

1) **S_N1- Substitution Nucleophilic Unimolecular.**

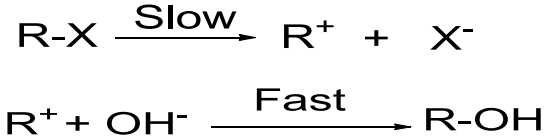
In this reaction, the rate is dependent on the concentration of alkyl halide only.

2) S_N2- Substitution Nucleophilic Bimolecular.

The rate is dependent on concentration of alkyl halide and OH^- ions.

i) S_N1- Substitution Nucleophilic Unimolecular.

Step wise Mechanism:



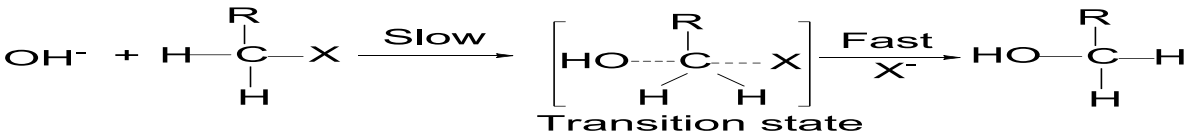
Rate α [R-X] independent of OH^-

The reaction follows First order Kinetics.

Stereochemistry: Racemic compounds.

ii) S_N2- Substitution Nucleophilic Bimolecular.

Concerted Mechanism



Rate α [alkyl halide] [OH^-]

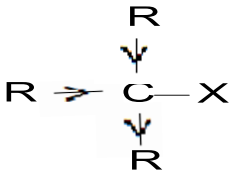
The reaction follows Second order Kinetics.

Stereochemistry: Complete inversion of configuration.

Factors Governing S_N1 and S_N2

1) Structure of the Substrate:

Primary alkyl halide undergoes S_N2 while tertiary alkyl halide undergoes S_N1 mechanism. Secondary alkyl halide undergoes both S_N1 and S_N2 .Tertiary alkyl halides the 3 alkyl groups increases the electron density around the central carbon atom for the formation of carbocation



2) Steric effect:

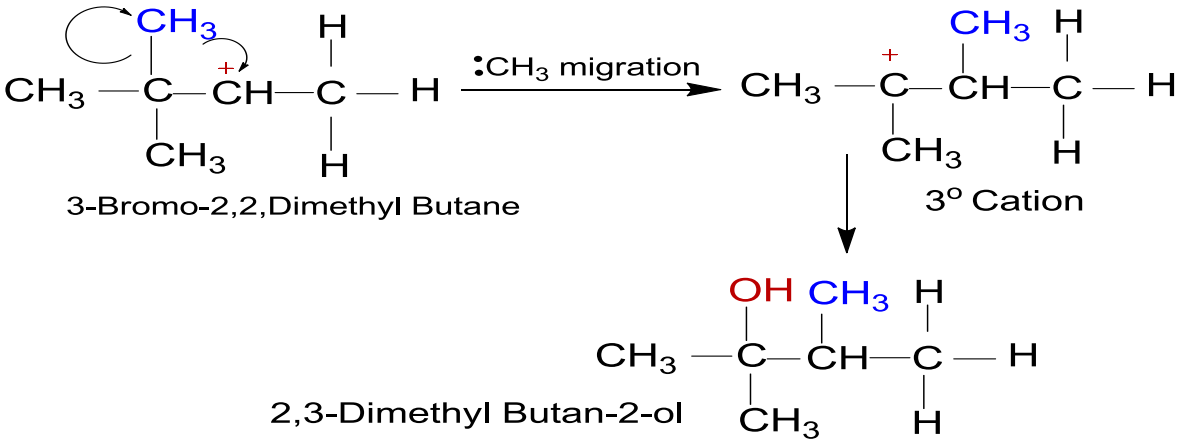
S_N2 mechanism involves attack of nucleophile from the opposite side of the leaving group. Hence, in tertiary alkyl halide the 3 alkyl groups prevents the attack of nucleophile thereby it follows S_N1 mechanism.S_N2 mechanism operates in primary alkyl halide and the rate of the reaction decreases with the increase in the alkyl group.

$$CH_3X > CH_3CH_2X > n\text{-}C_4H_9X$$

3) Rearrangement of carbocations

S_N1 mechanism favours- stable carbocation hence it may undergo either 1,2 alkyl shift or hydride shift.

1,2 alkyl shift:

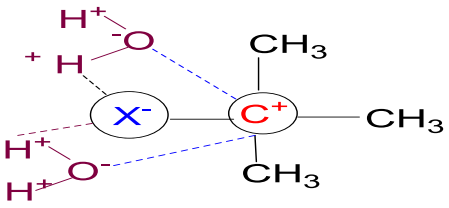


4) Solvent Effect

Protic solvents like water, alcohol favours S_N1 mechanism but slows down S_N2 mechanism. Aprotic solvents like DMSO, DMF favours S_N2 mechanism. Solvent molecules orient with

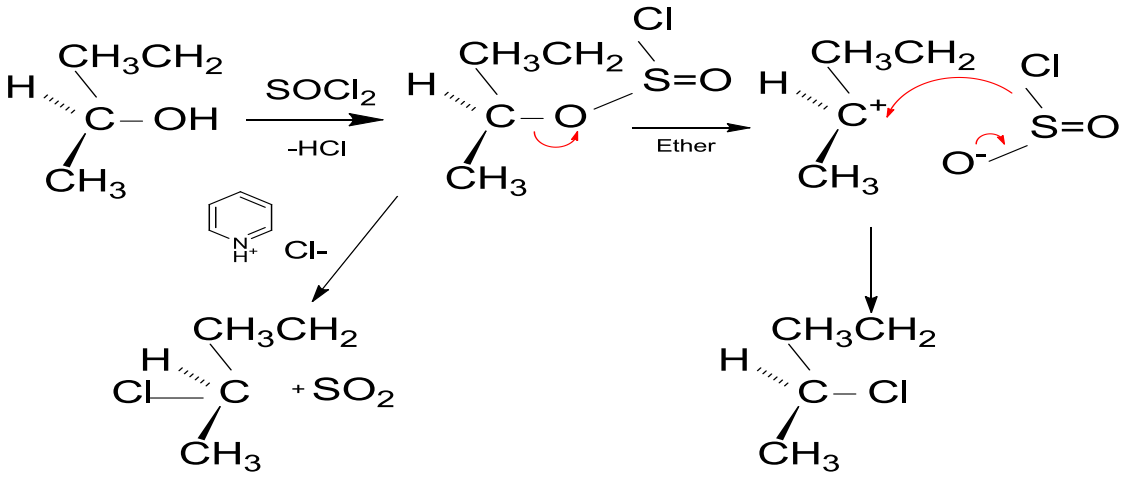
their negative end towards the carbocation and positive end towards the anion favouring carbocation formation with lowering in activation energy which compensates for bond breaking.

❖



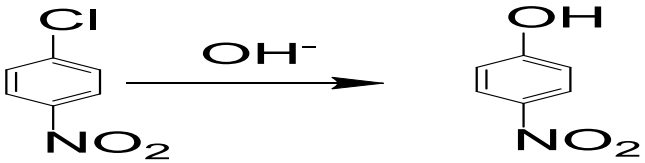
iii) Substitution Nucleophilic Internal (Sni)

Substitution reaction takes place by intra molecular process.

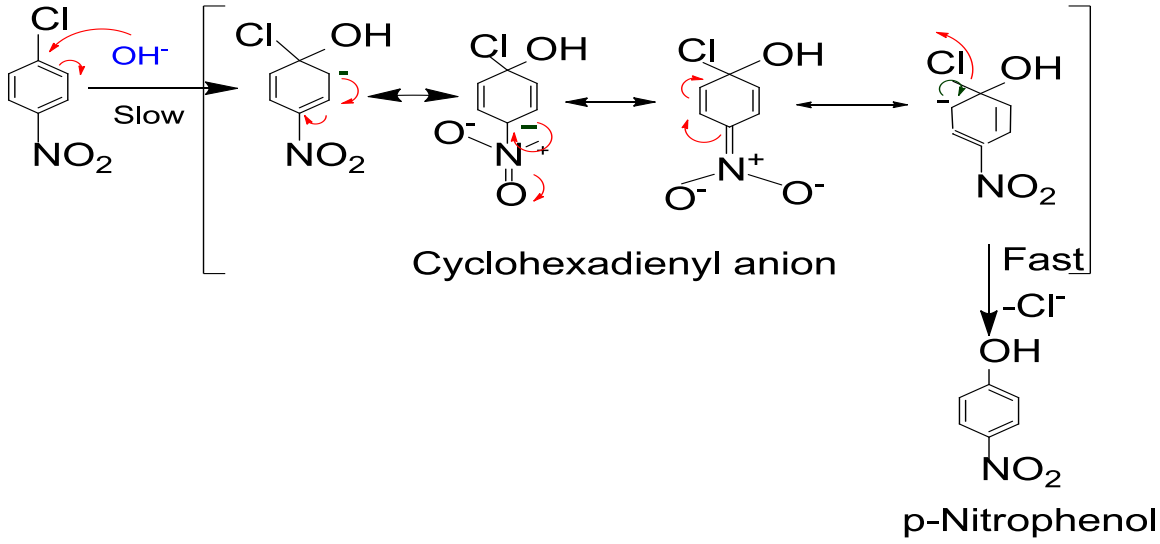


iv) Aromatic Nucleophilic substitution (S_NAr)

It occurs in the substrate with sufficient π-electron deficient systems due to the presence of electron withdrawing groups (nitro) at ortho or para positions.It is a two step process-addition and elimination sequence with the first step being the rate determining step.



It differs from S_N1 and S_N2, the Ar-X bond is not broken until after the rate determining step. The nature of the leaving group affects the rate at which nucleophile attacks.



1.2.b Electrophilic Substitution

Electrophiles attack the substrate rich in electrons.

Types:

Electrophilic substitution at saturated carbon atom or unsaturated carbon atom or at aromatic systems.

Designated:

S_E1: Electrophilic substitution Unimolecular.

S_E2: Electrophilic substitution Bimolecular

i) S_E1- Substitution Electrophilic Unimolecular

It occurs in Two steps:

1. Slow ionization to form Carbanion

$$R\text{-}X \xrightarrow{\text{Slow}} R^- + X^+$$

2. Fast combination of the anion with the electrophile to form Products.

$$R^- + E^+ \longrightarrow R\text{-}E$$

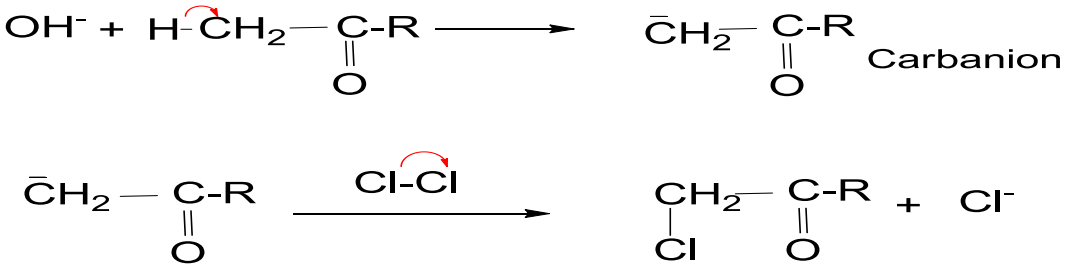
Rate α [substrate] independent of electrophile.

kinetics-First order

Stereochemistry: Racemic Mixture

Chlorination of acetone to α-chloroacetone.

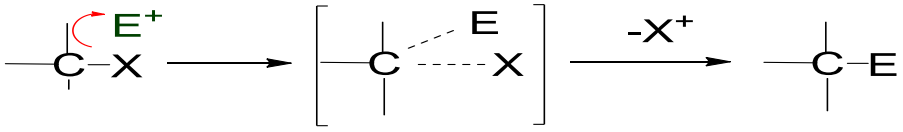
$$CH_3COCH_3 + Cl_2 \longrightarrow ClCH_2COCH_3 + Cl^-$$



ii) S_E2- Substitution Electrophilic Bimolecular

It takes place by concerted Mechanism.

Incoming group approaches the reactive site from the front side as the leaving group.



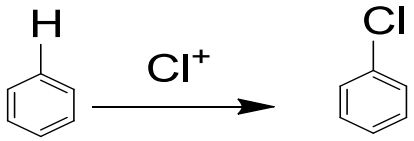
Rate α [Substrate] [Electrophile]

Kinetics: Bimolecular

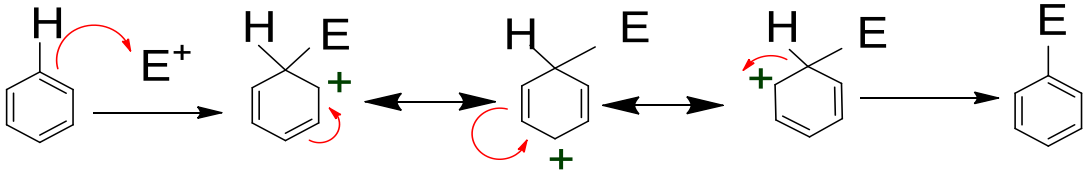
Stereochemistry: Retention of configuration.

iii) Electrophilic substitution at aromatic system.

Chlorination of Benzene

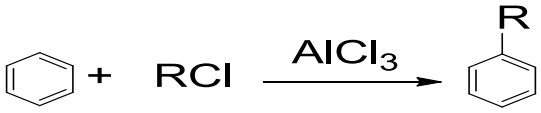


Carbocation is stabilised by resonance.

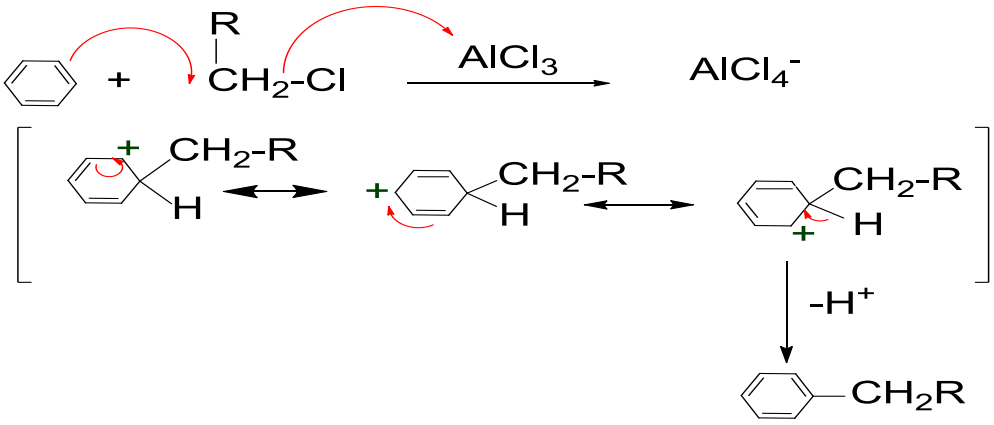


Eg: Friedel-Crafts Reaction

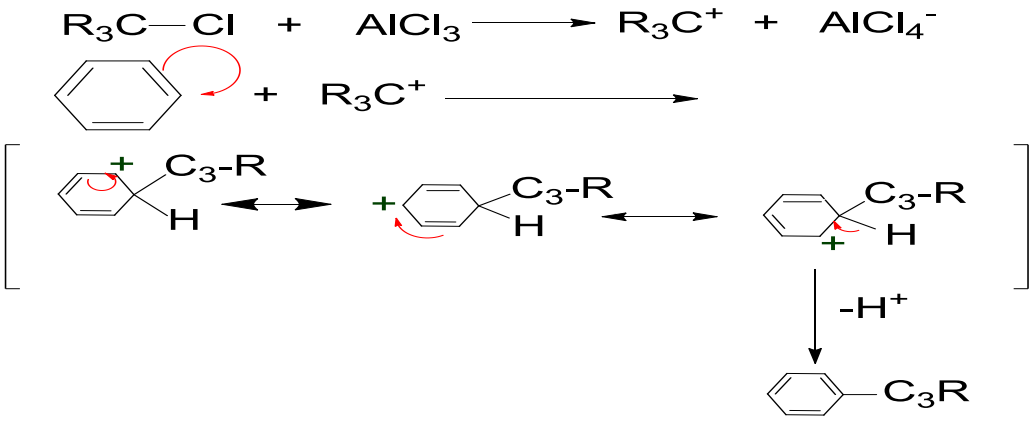
Alkylation: Electrophilic substitution Reaction.Primary and secondary alkyl halide follows S_E2 mechanism while tertiary alkyl halide follows S_E1 mechanism



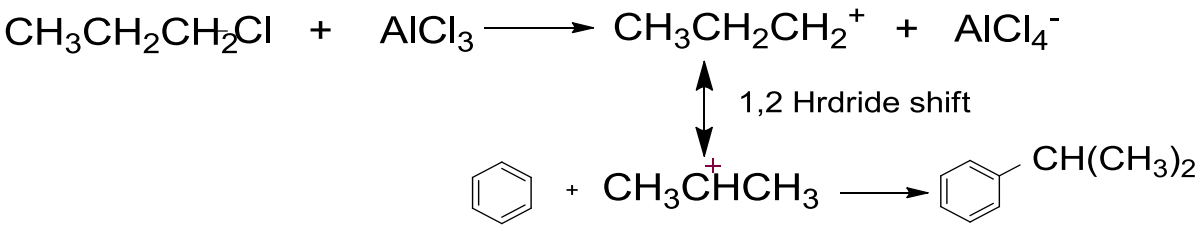
Primary alkyl halide- S_E2 Mechanism



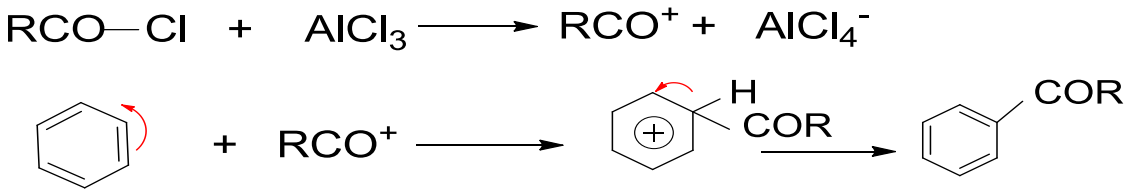
Tertiary alkyl halides –S_E1 Mechanism.



Benzene on reaction with n-propyl chloride undergoes 1,2 hydride shift to form isopropyl cation.



Friedel-Crafts acylation:



1.3 Elimination Reaction

Two substituent from a pair of adjacent atoms in a molecule are removed resulting in an unsaturation. The two groups removed from the substrate are

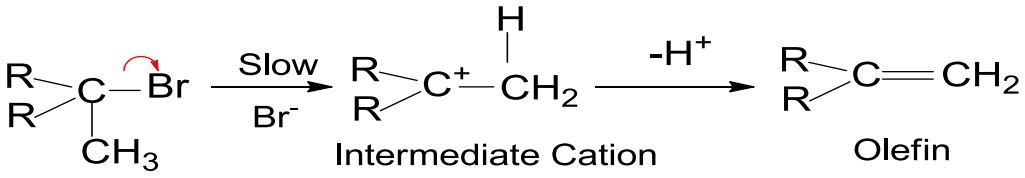
1. Electrophile usually a proton, and
2. Nucleophile may be X^-, OH^-, $RCOO^-$.

Elimination can be

α- Elimination: Two groups are removed from the same carbon atom

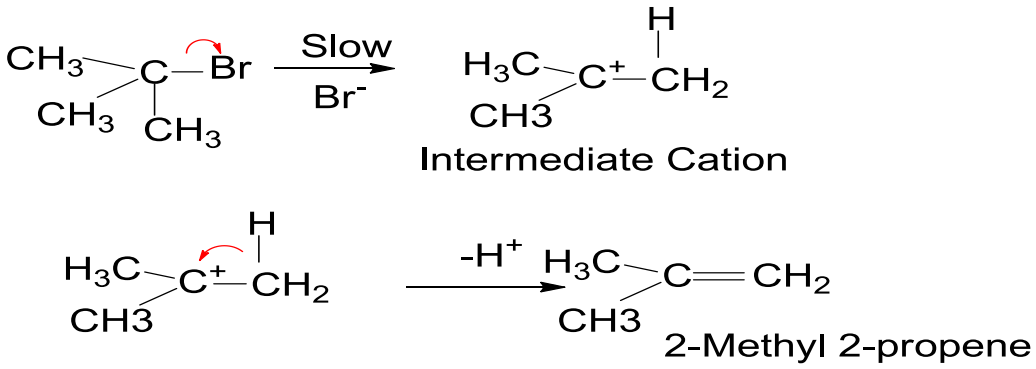
β-Elimination: Two groups are removed from adjacent carbon atom.

1.3.1E_1 Mechanism:

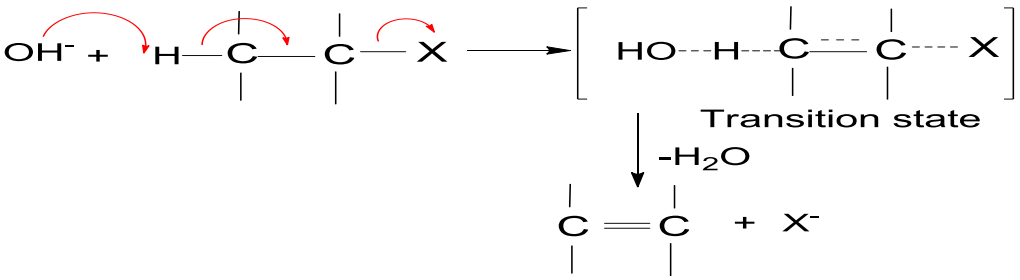


Dehydrohalogenation of alkyl halide.

E_1 Mechanism:

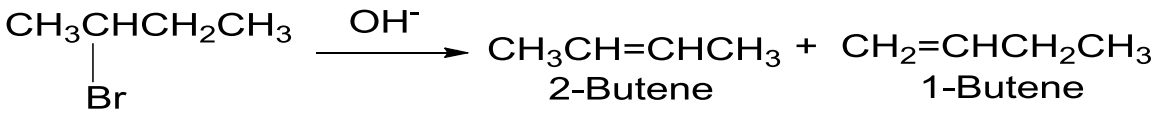


1.3.2E_2 Mechanism:(Trans elimination):

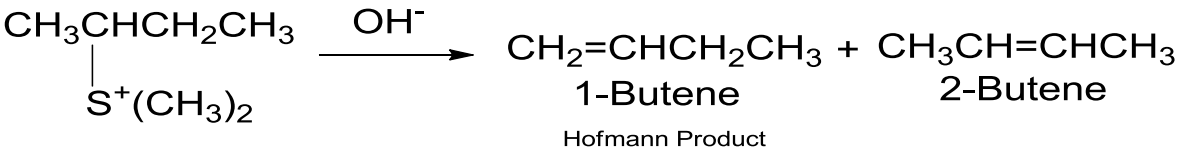


1.3.3 Rules For Elimination Reaction:

Saytzeff Rule: Olefin with large number of alkyl groups around C=C bond (More substituted alkene).



Hofmann Rule: Olefins with least number of alkyl groups around C=C bond (least substituted Olefin)



1.4 Addition Reactions

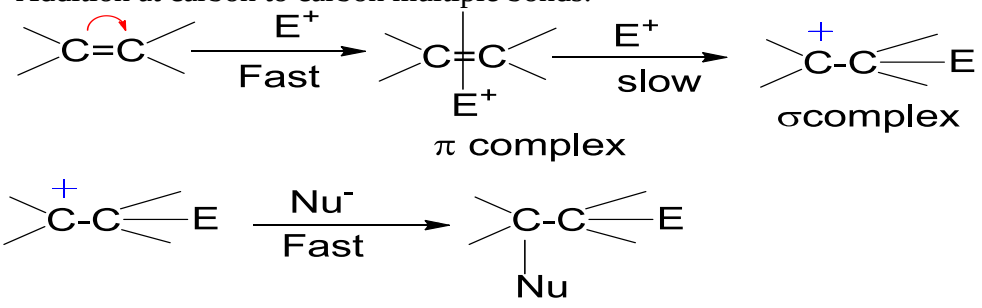
Reactions of double or triple bonds.

In alkenes and alkynes, the molecules are attacked by electrophiles.

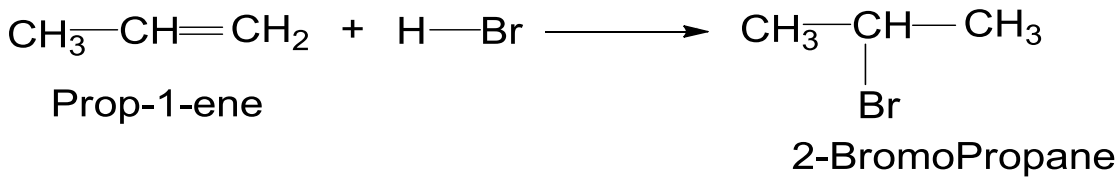
In carbonyl group, the molecules are attacked by nucleophiles..

Two Types

1. Addition at carbon to carbon multiple bonds.

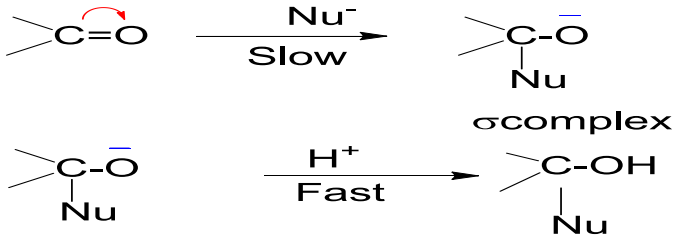


Addition of halogen acids to olefins.



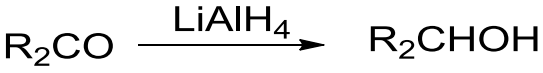
Markownikoff's Rule: the negative part of the reagent adds to the carbon constituting the double bond poor in hydrogen.

Addition at carbon to oxygen multiple bonds

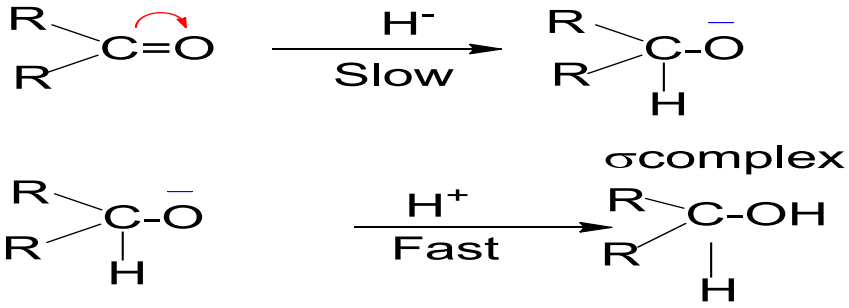


Hydride Transfer Reaction

Reduction of ketone to secondary alcohol

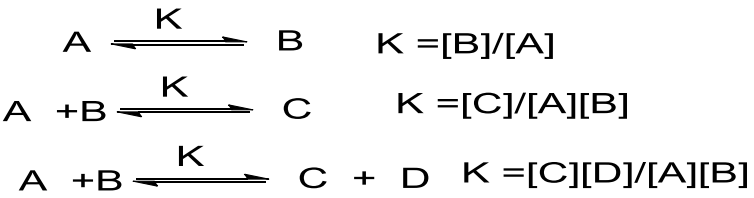


Mechanism:



1.5 EQUILIBRIA AND FREE ENERGY

Equilibria: concentration of reactants and products don't change.



The free energy change of the reaction is related to equilibrium constant by,

$\Delta G^o = -RT\ln K$

$= -2.303\ RT \log K$ (Kcal/mol, R=1.986cal/deg-mol)

$\Delta G^o = -1.36 \log K$ (Kcal/mol) at 298K

ΔG^o = (Free energy of products)-(Free energy of reactants)

$\Delta G^o = -1.36 \log K$ (Kcal/mol) at 298K.

K=10, ΔG^o= -1.36 Kcal/mol.

K=0.1, ΔG^o= +1.36 Kcal/mol.

K=1, ΔG^o= 0 Kcal/mol.

The Gibbs standard Free energy is related to enthalpy and entropy

$$\Delta G^o = \Delta H^o - T\Delta S^o$$

ΔH^o = (enthalpy of products) –(enthalpy of reactants)

ΔS^o = (entropy of products) –(entropy of reactants)

ΔH^o = ΔH^o for bonds being broken- ΔH^o for bonds being formed

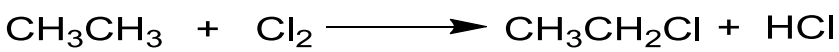
Eg 1: Chlorination of Methane:

Combustion of Methane

Exothermic nature –change in the order or freedom of motion of a system.

Greater the entropy of the system, favourable negative value of ΔG^o

Eg 2 : Chlorination of ethane to give chloroethane and HCl



ΔH^o =-28kCal/mol

ΔS^o = +0.5e.u

At room temp, T ΔS^o = -0.15Kcal/mol

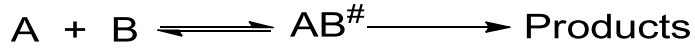
ΔG^o= ΔH^o –for chemical reactions involving bond breaking and bond formation.

1.6 Exergonic and Endergonic Reactions

Exergonic Reactions-Products are more stable;Reaction release more energy.

Endergonic Reactions-reactants are more stable and reaction consume more energy.

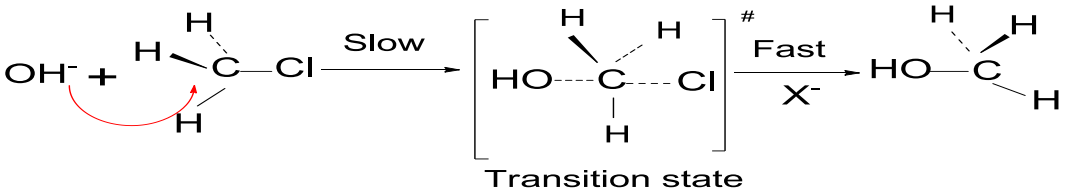
Transition state Theory



E_a= $\Delta H^{\#}$ + RT; $\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#}$; $k=Ae^{-Ea/RT}$

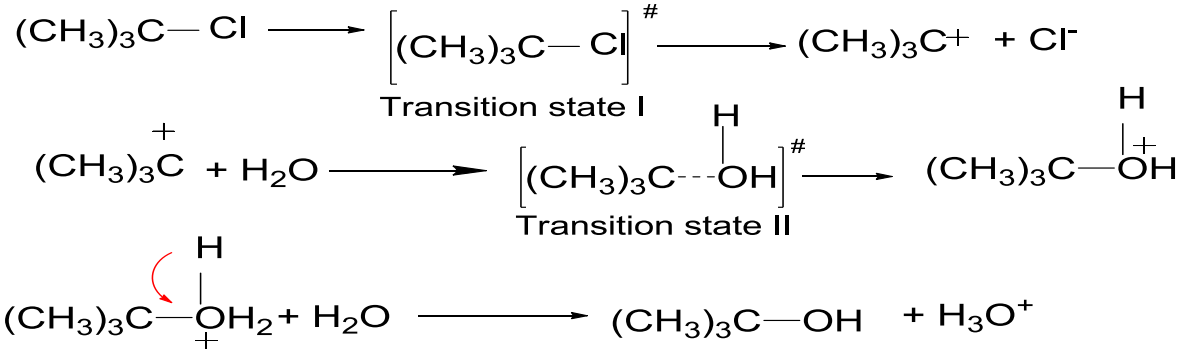
Reaction Profile -S_N2

Transition state has definite geometry, charge distribution and no finite existence



Reaction Profile -S_N1

Intermediates have fully formed bonds; species which is a product and reactant.

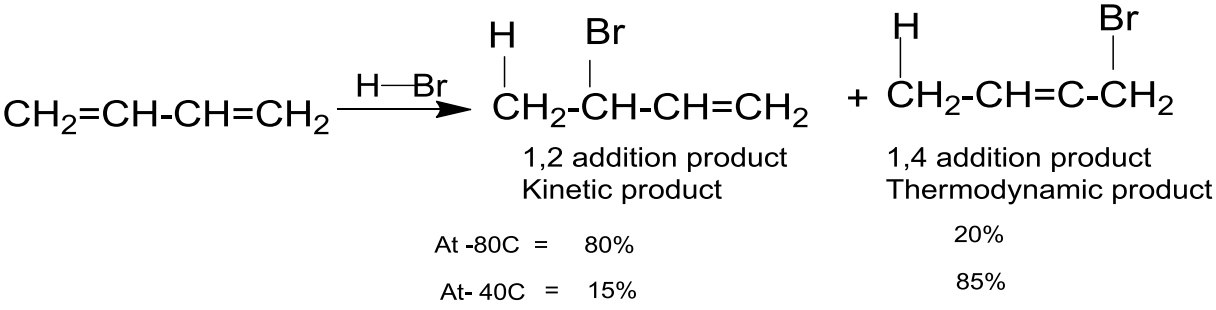


1.7 Thermodynamic and kinetic controlled Reactions:

Consider the addition of HBr to 1,3 butadiene where the products are

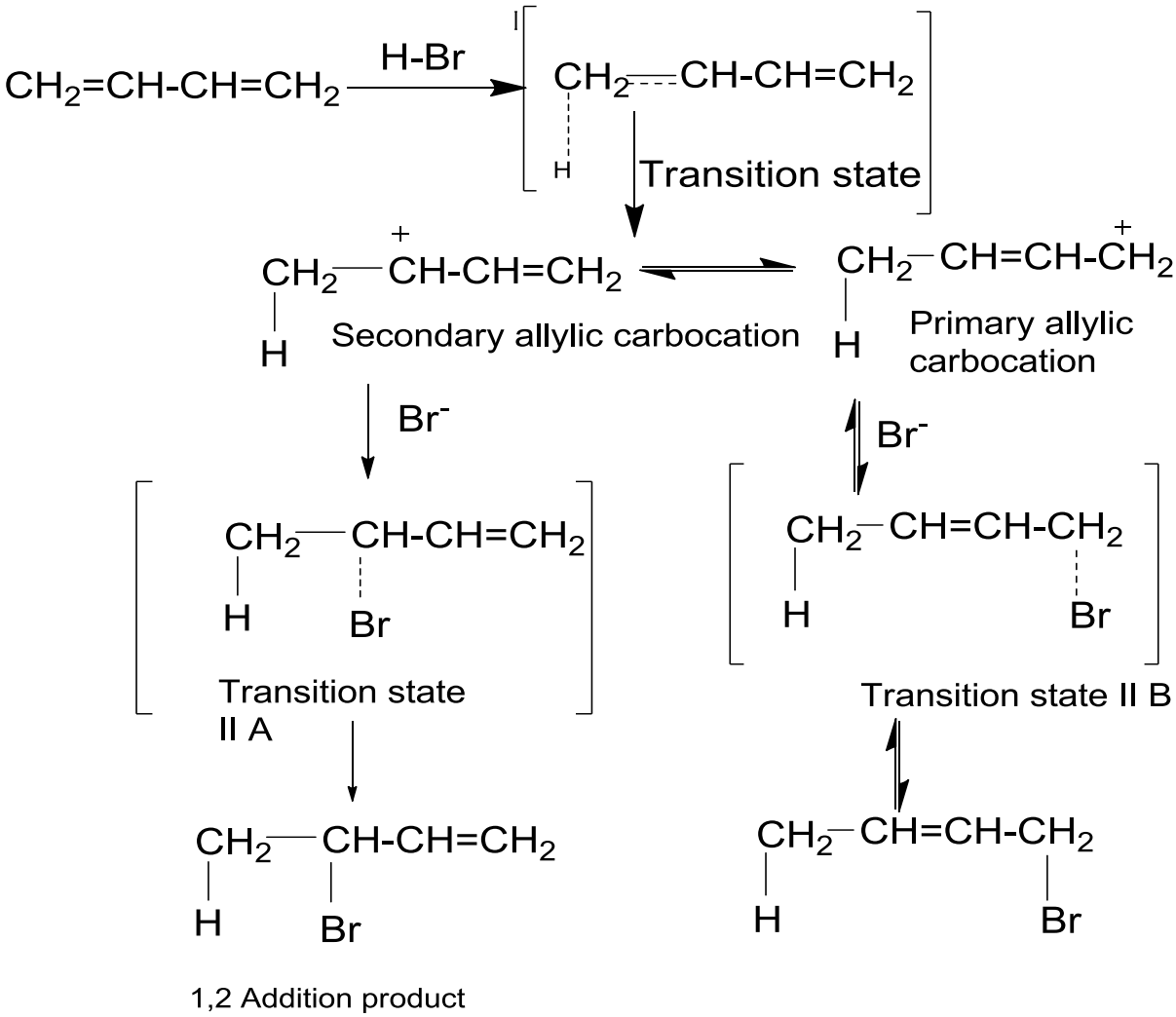
Rapidly formed -Kinetic product.

Stable product- Thermodynamic product.

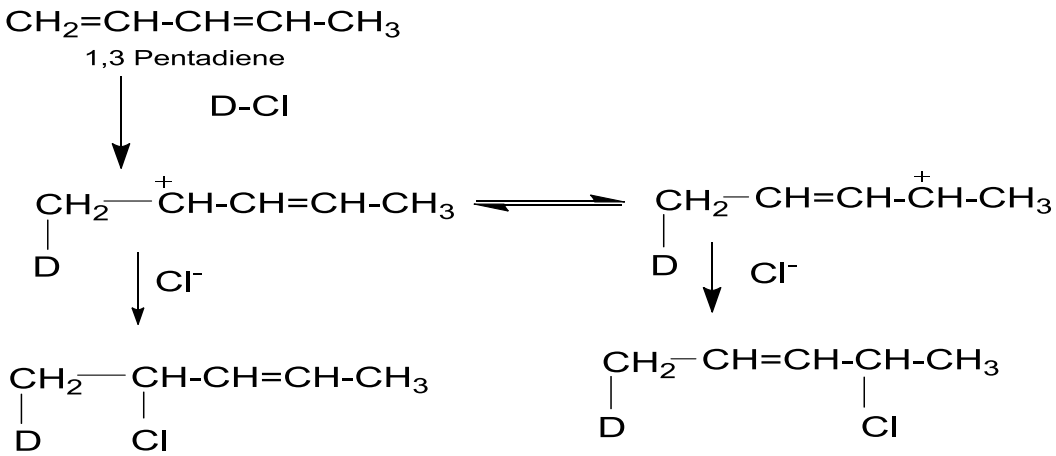


The addition of HBr to 1,3-buta diene can lead to either 1,2 addition or 1,4 addition product. The formation of 1,4 addition product requires higher energy transition state which is a thermodynamic product, while 1,2 addition product has a less energy transition state and is formed rapidly even at low temperatures.

Mechanism:

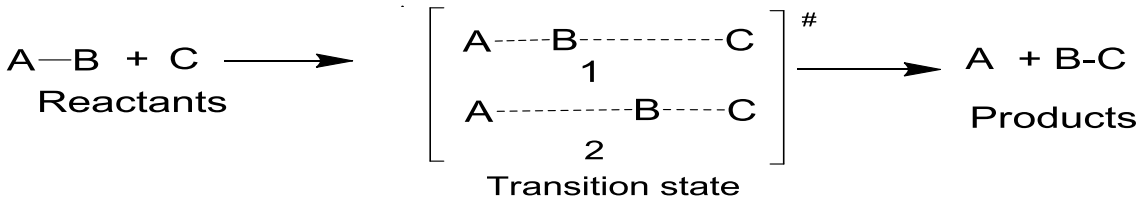


Addition of DCl to 1,3 –Pentadiene



1.8 Hammond Postulate

1. Structure of Transition state is used to predict the products.
2. Structure of Transition state lies between the structure of reactants and products.



Transition state 1-Exergonic reaction- Resembles the reactants than the products.

A-----B----------C

Transition state 2-Endergonic reactions- Resembles the products than the reactants

A----------B-----C

- The structure of transition state is more similar to the structure close in its energy

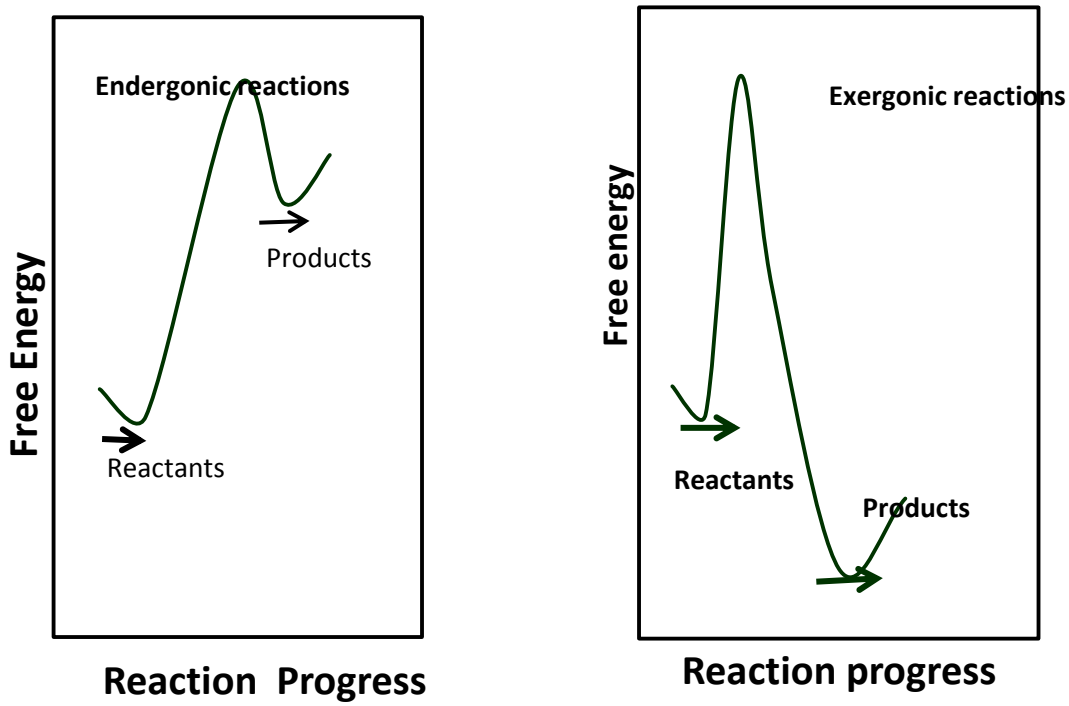
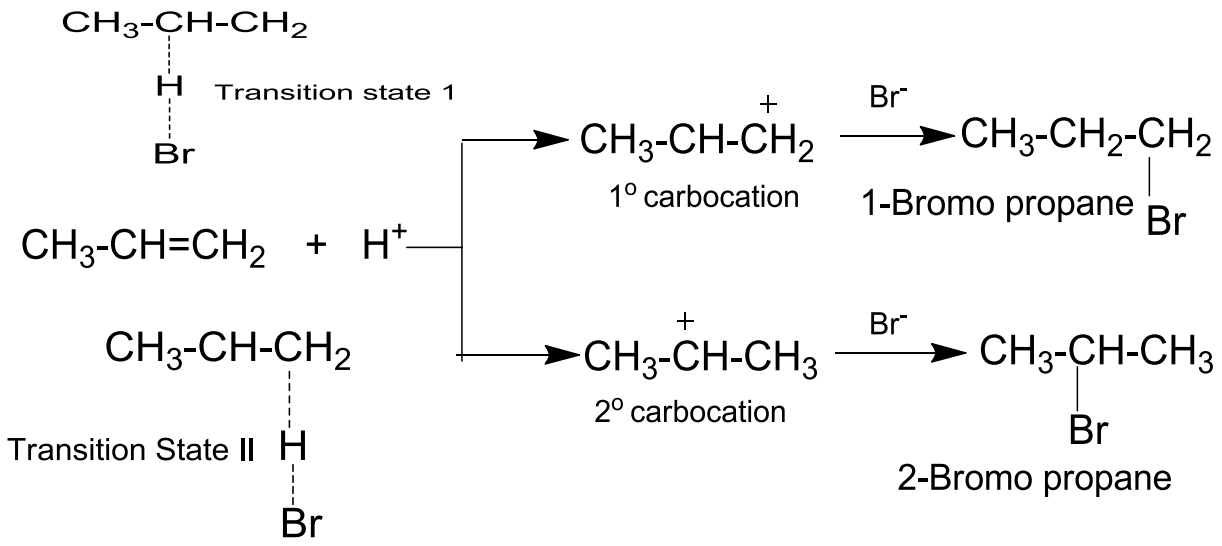


Fig 1.1 Free energy profile for endergonic and exergonic reactions.

In endergonic reactions, the free energy of the products is larger than the free energy of the reactants while in the exergonic reactions, the free energy of the products is less than the free energy of the reactants.

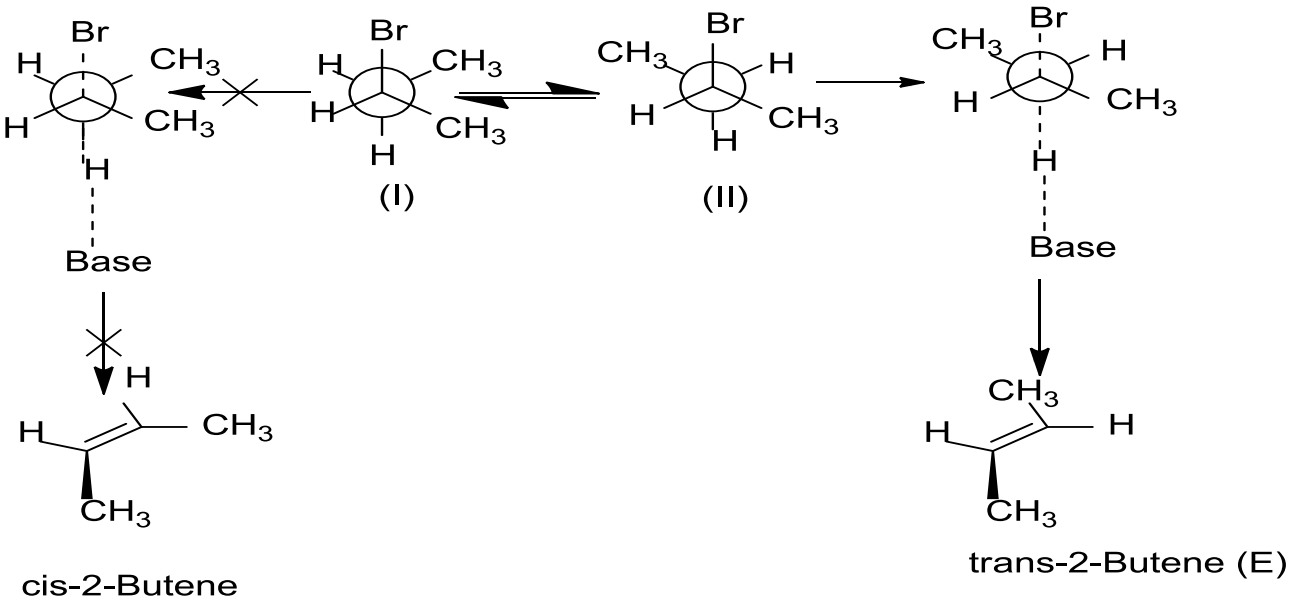
Consider a Regioselective Reaction:of 1-propene



1.9 Curtin –Hammett Principle

Chemical reactions involving conformers in which the two conformers are rapidly interconverting with each other relative to the rate of product formation. The product formation depends only on the relative energies of the representative transition state involved and not on the relative populations of the ground state conformers.

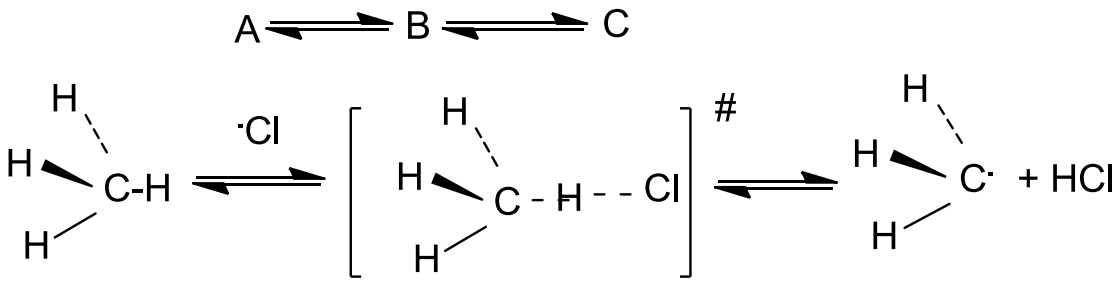
Consider a stereoselective elimination of 2-bromo butane



1.10 Macroscopic Reversibility.

At equilibrium, the individual molecular processes and the exact reverse processes must have an equal probability of occurring.

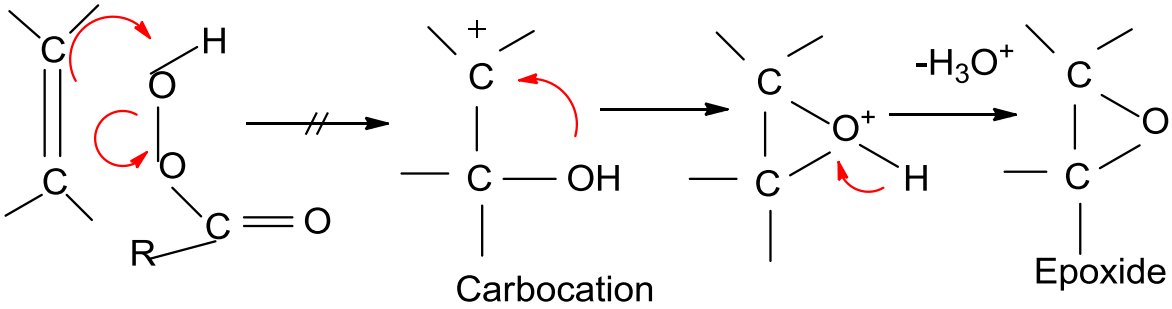
Consider a free radical reaction of chlorination of methane



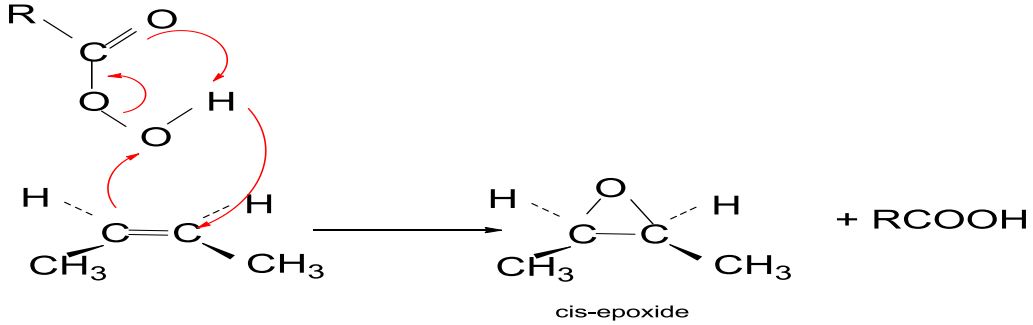
1.11Methods of Determining Mechanisms

i) Identification of products.

Epoxidation of alkene: Formation of carbocation suggests a possibility of a mixture of cis-trans epoxide.

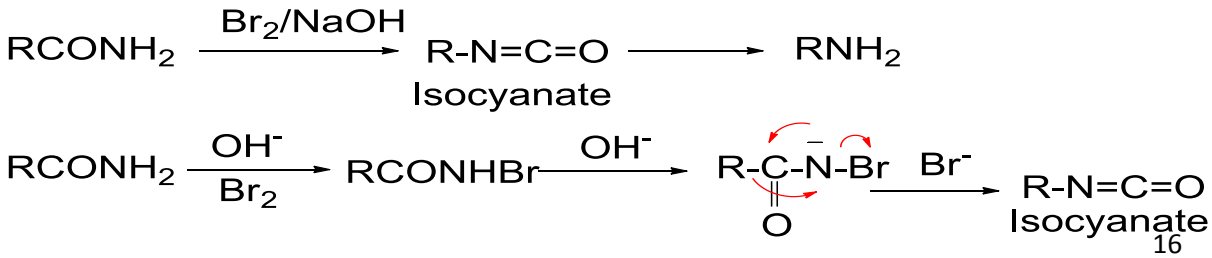


Reaction in which two new bonds are formed at the same time doesn't change the stereochemistry of the olefin



ii) Detection of intermediates

a) Direct isolation: Hoffmann rearrangement:



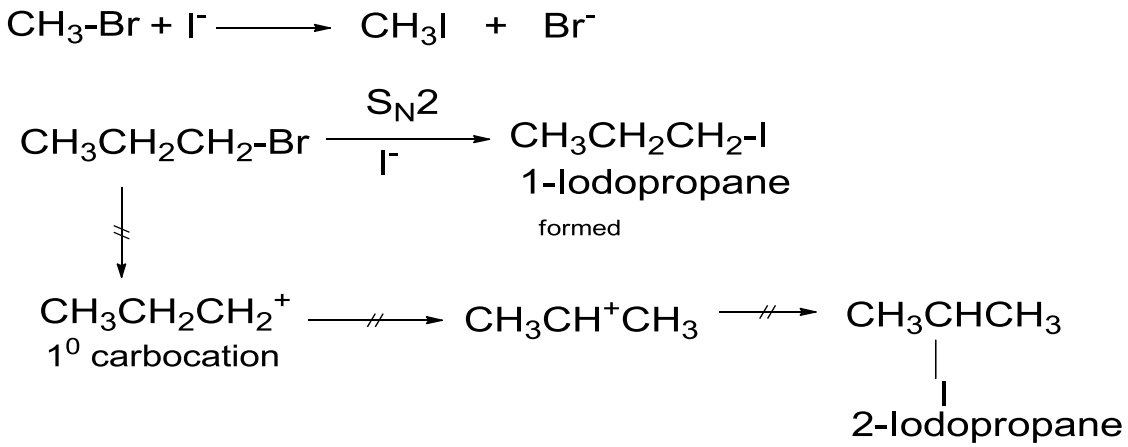
b) Spectroscopic Determination

Reactions involving benzyne as an intermediate is detected by IR spectroscopy –stretching frequency of 1846 cm^{-1} which is intermediate between double and triple bond.

^{13}C NMR- δ=182.7 ppm are also not of pure triple bonds.

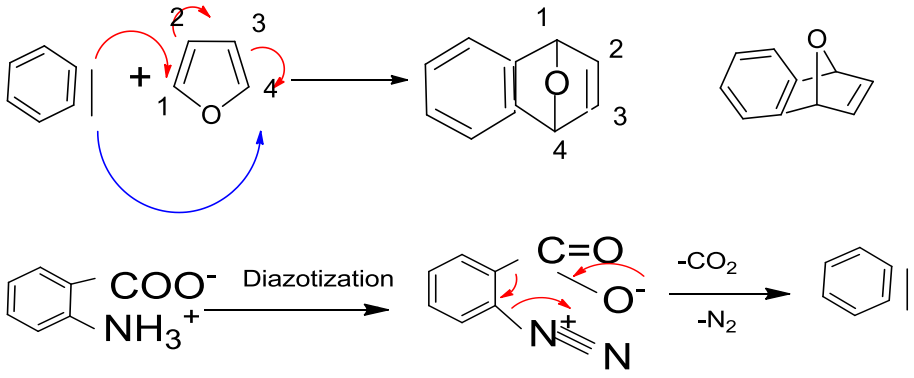
c) Indirect Evidence:

Formation of one alkyl halide from another. Reaction follows S_N2-Concerted mechanism



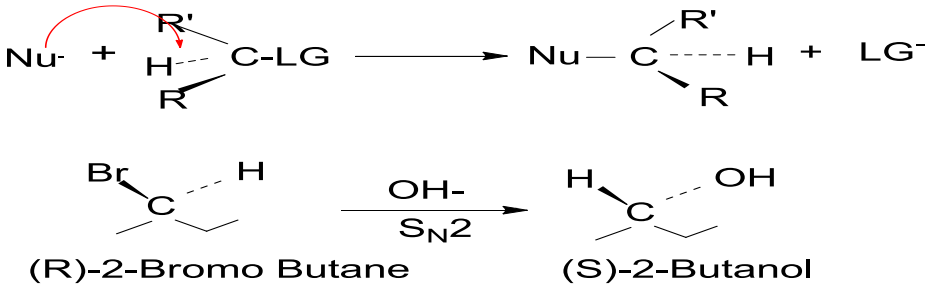
d) Trapping:

Benzynes are identified by reacting with dienes to form Diels-Alder adduct.

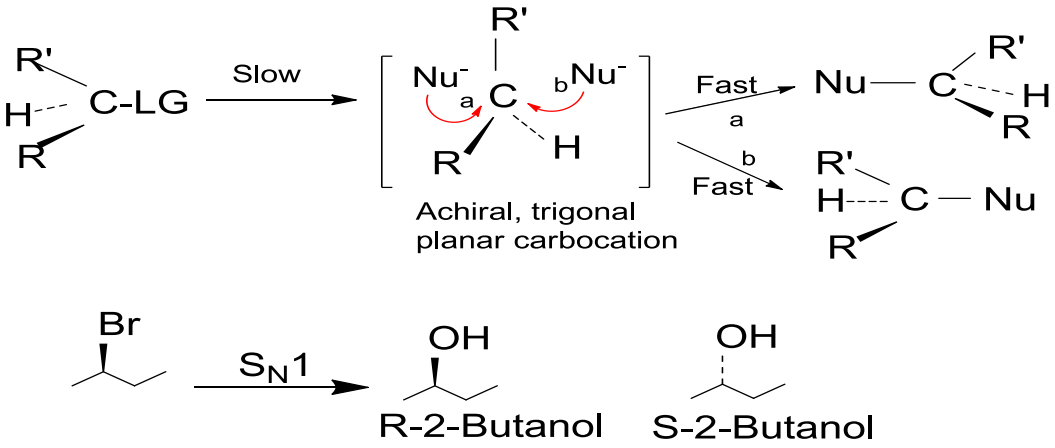


iii) Stereochemical Evidence

Chiral alkyl halide is used as the starting material, for an S_N2 the inversion can be detected due to change in the configuration while for an S_N1 reaction, racemization occurs.



S_N1 Reaction: Racemic Mixture

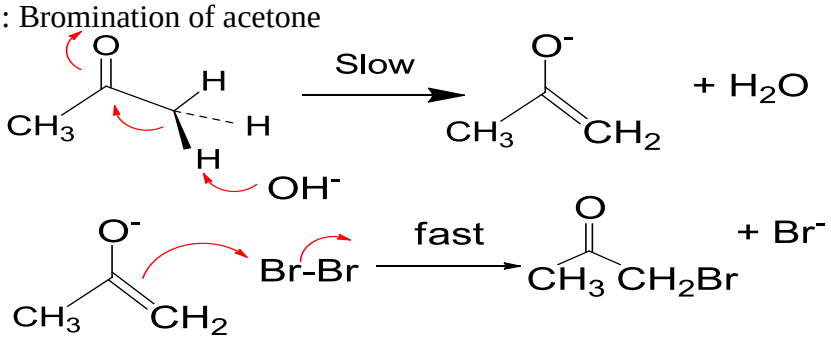


iv) Kinetic Isotope Effects

$$\text{Deuterium Kinetic Isotope effect} = k_H/K_D = \frac{\text{Rateconstant of H-reactant}}{\text{Rate constant of D-reactant}}$$

C-D bond is 1.2 kcal/mol more stronger than C-H bond. k_H/k_D values are greater than 1.5 –Primary kinetic isotope effect, C-H(D) bond breaks in the rate determining step. k_H/k_D is 1-1.5, Secondary kinetic isotope effect- C-H(D) bond cleavage is not involved in the rate determining step.

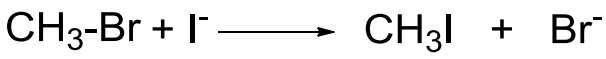
Eg 1: Bromination of acetone



k_H/k_D = 7 primary kinetic isotope effect indicates that the proton removal is involved in the rate determining step.

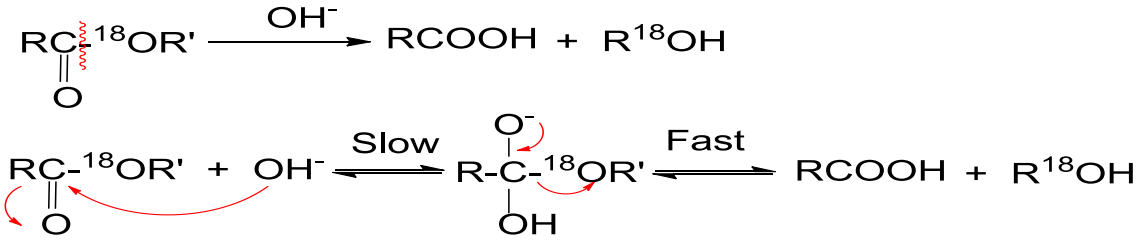
v) Kinetic Evidence

Rate is dependent on the concentration of both reactants in the rate determining step and hence it is bimolecular in nature.

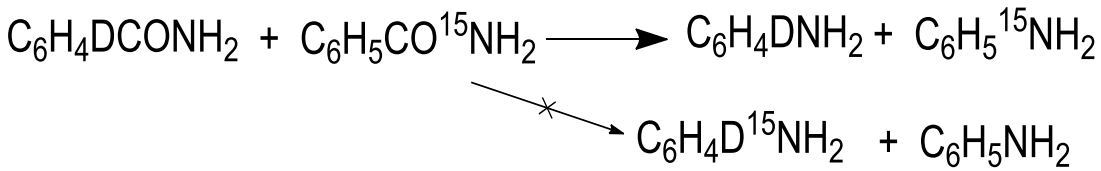


Rate= $k[CH_3Br][I^-]$

vi) Isotopic Labelling: ^{18}O, isotropic tracer has been used in base promoted ester hydrolysis reaction, proceeds by acyl oxygen cleavage and the reaction is independent on the structure of R and R'. The alcohol is enriched with ^{18}O.



vii) Crossover Experiments: Hoffmann Reaction: Reaction proceeds by intra molecular rearrangement. Migrating group doesn't separate from the substrate. Mixture of 3-deuteriobenzamide and ^{15}N benzamide gives deuteriobenzamine and benzamine. Not mixed anilines are not formed.



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SCHOOL OF SCIENCE & HUMANITIES

DEPARTMENT OF CHEMISTRY

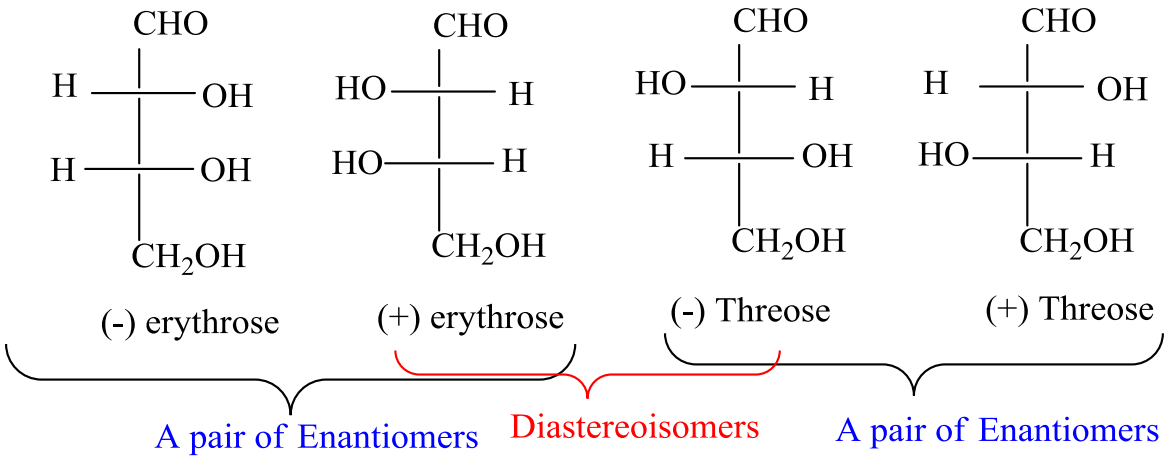
UNIT – II STEREO, ENANTIO, REGIO, CHEMO SELECTIVE REACTIONS – SCYA7302

UNIT 2

STEREO, ENANTIO, REGIO, CHEMO SELECTIVE REACTIONS

2.0. Introduction

Enantiomers- Chiral molecules with one or more stereocenters which are non superimposable mirror images. Diastereoisomers- Stereoisomers which are non-superimposable and non-mirror images.



2.1 Optical Rotation

Optically active compound rotates the plane polarized light either to Right- dextrorotatory ,d (+) or Left- levorotatory, l(-).Optical rotation is measured using a polarimeter and it is a function of Concentration, Sample thickness, Temperature and wavelength.

Optical rotation or specific rotation or denoted by $[\alpha]_{\lambda}^{t}$

$$[\alpha]_{\lambda}^{t} = \alpha \times 100/(l \times C)$$

$$[\alpha]_{\lambda}^{t} = \alpha /(l \times d_{t})$$

t= temperature in °C

λ= wavelength of polarized light D= 5893 Å

c= concentration of sample in g/100mL.

l= sample thickness in dm.; α= observed angle of rotation in degrees

d= density of pure liquid in g/mL.

Molecular rotation of the optical compound is denoted by [M]

$[M] = [\alpha]_{\lambda}^{t}$ Mol. weight/(100).

Optical yield or Enantiomeric excess (ee) or diastereomeric excess (de) in %

ee or de (%) = $[\alpha]_{\lambda}^{t}$ product x100/ $[\alpha]_{\lambda}^{t}$ of E

For a racemic mixture, the optical purity is zero.

2.2 Optical Isomers

The possible optical isomers for a molecule with a chiral centre is given in the Table.2.1

Table 2.1 Optical isomers with a compound with chiral centre

Compound	Optical active forms	Optical inactive forms
Chiral carbons, molecule can't be divided into two equal and similar halves	2^{n}	0
Even number of chiral carbons, molecule can be divided into two equal and similar halves	$2^{(n-1)}$	$2^{(n-2/2)}$
Odd number of chiral carbons, molecule can be divided into two equal and similar halves	$2^{(n-1)}$-$2^{(n-1)/2}$	$2^{(n-1/2)}$

Ex:1 Calculate the specific rotation of an optically pure compound (A) in ° with a conc. of 5g/10mL and sample thickness of 100mm measured at a wavelength of 589 nm and at 25°c, gives a rotation of +40°.

$$[\alpha]_{\lambda}^{t} = \alpha \times 100/(l \times C)$$

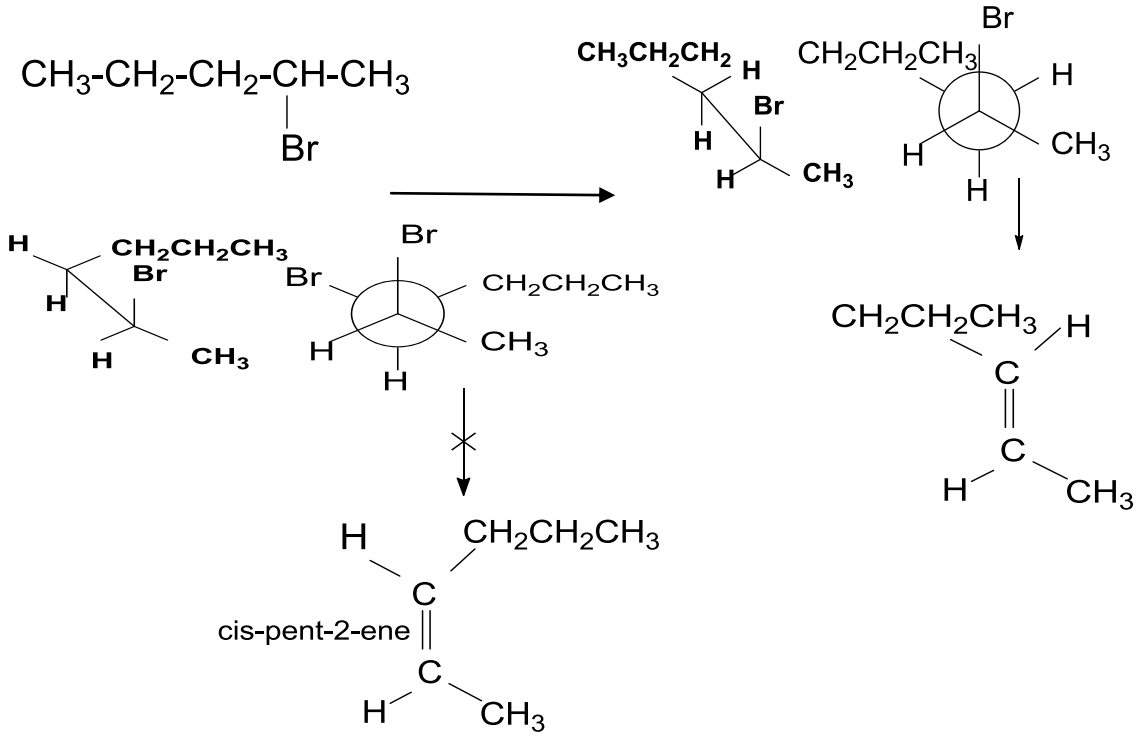
$$= +40 / 1x \ 5/10 = +80°$$

2.3 Stereoselective Reactions

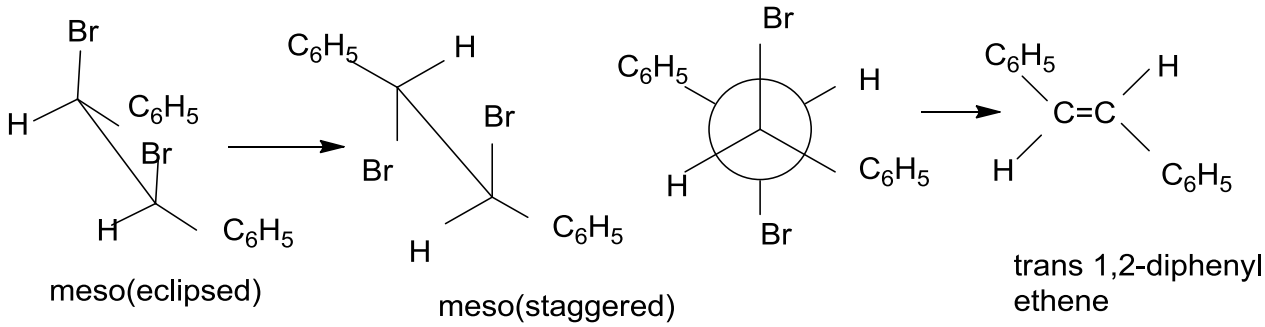
Predominantly one stereoisomer. One stereoisomer is formed more rapidly. Two equally pathway are available for the same mechanism. Due to difference in free energy of the transition state only one isomer is formed in preference over the other. Both addition and elimination reaction exhibit stereoselctive reactions.

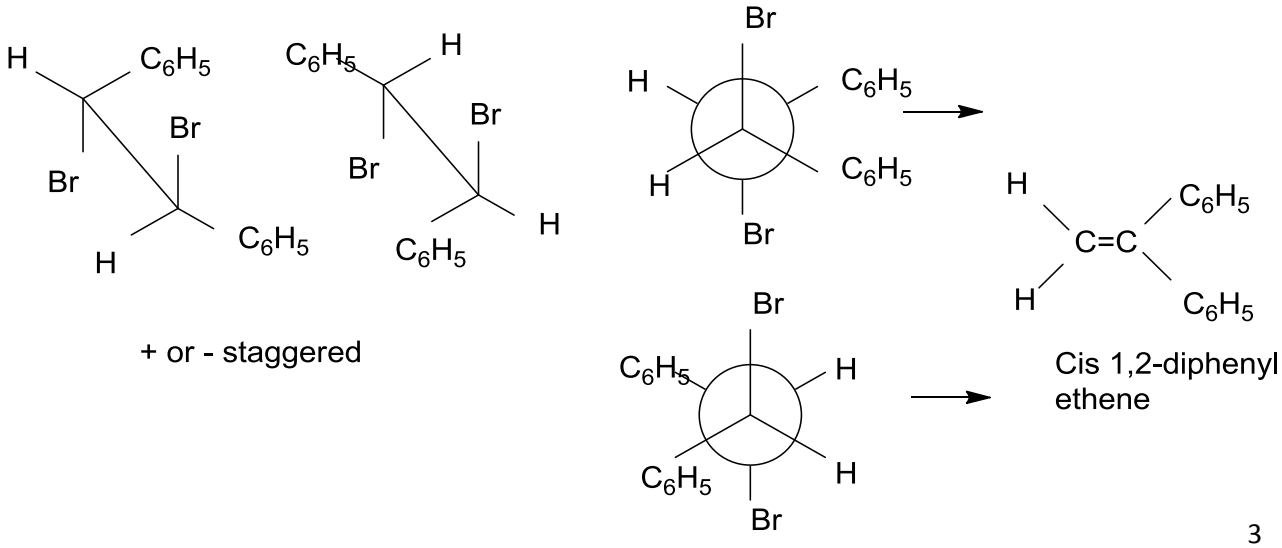
a) Stereoselective dehydrohalogenation of 2-bromo pentane

- Saytzeff ‘s rule, 2-pentene will predominate in the reaction .
- To know whether the product exists in E or Z isomer-Curtin-Hammett principle.

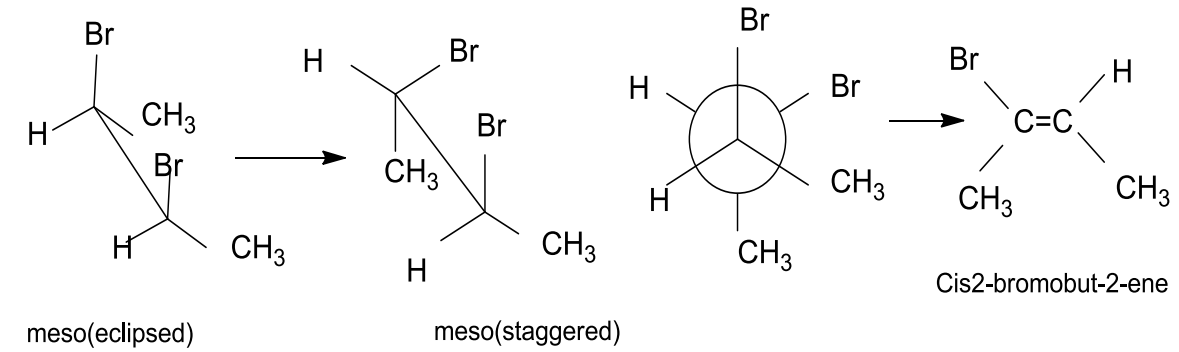


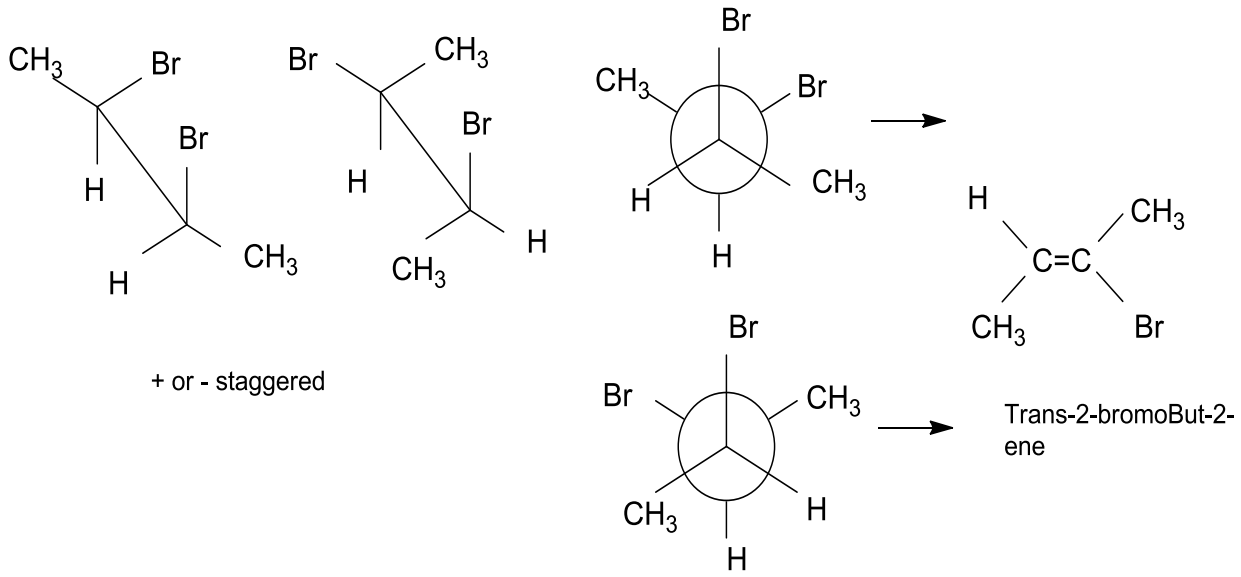
b) Consider a elimination of HBr from 1,2 dibromo 1,2 diphenyl ethane to form alkene





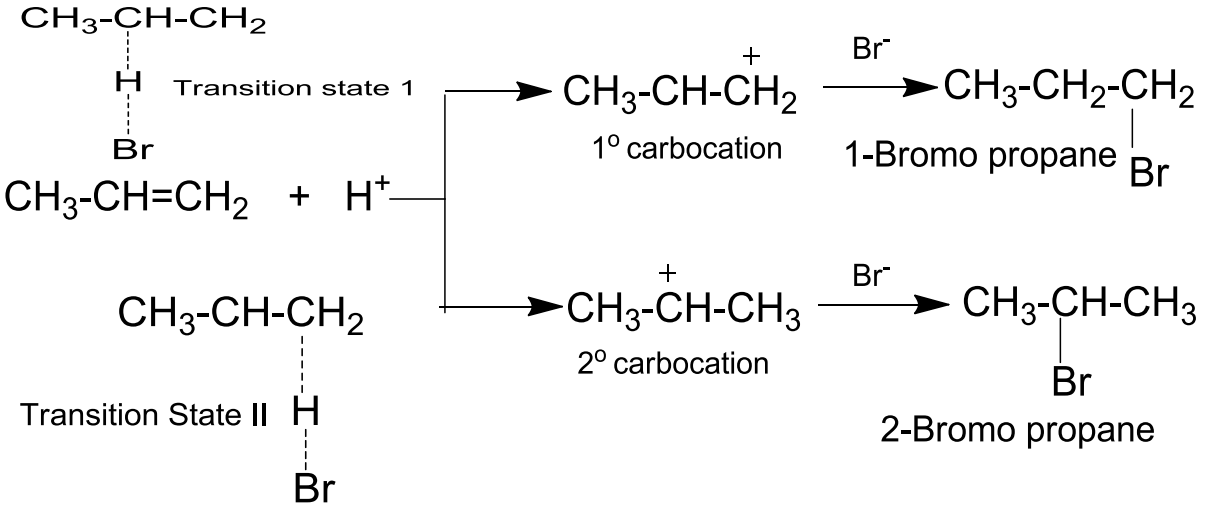
c) Consider a elimination of HBr from 1,2 dibromo butane



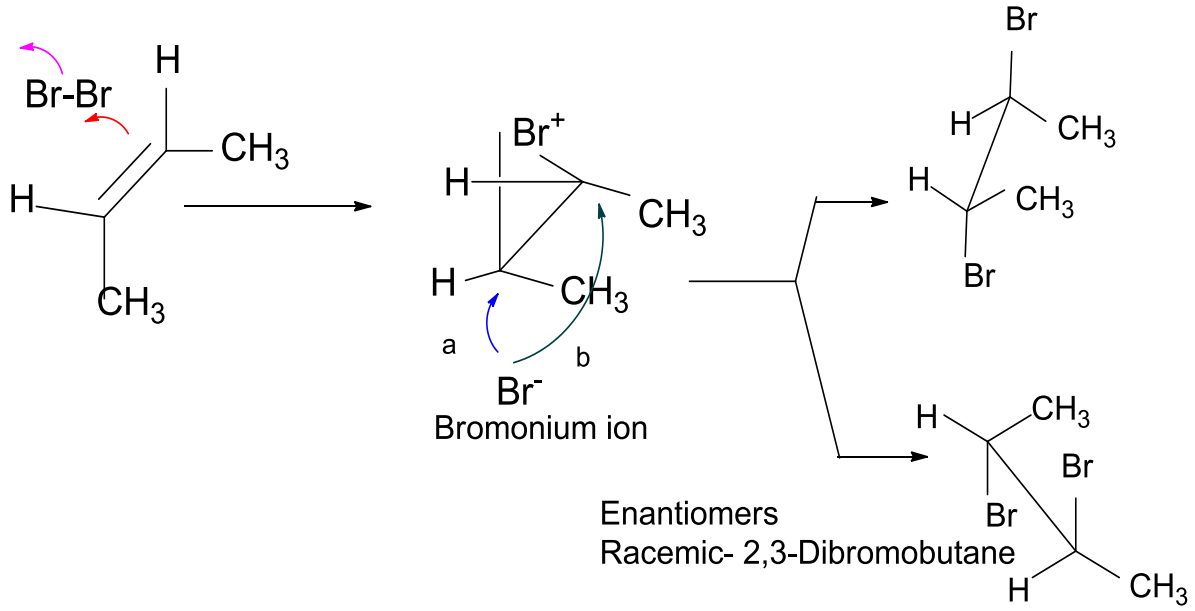


2.4 Regioselective Reactions

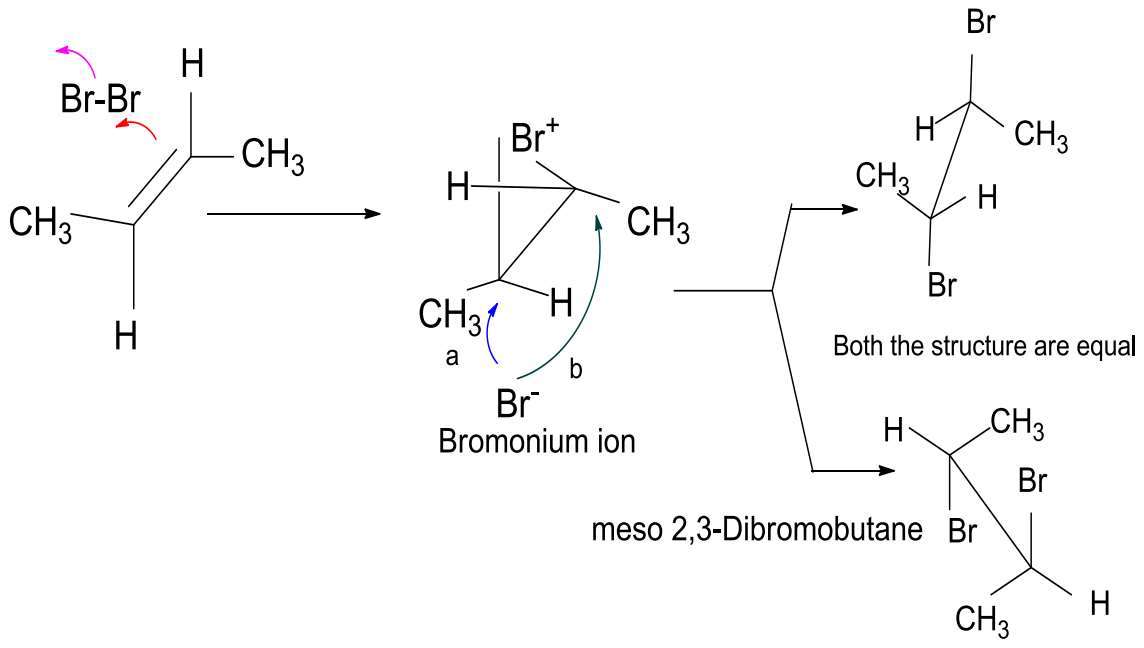
A chiral molecule can predominantly forms only one stereoisomer is known as Regioselective reactions. Consider a reaction of 1-propene which forms 2-bromopropane as the major product.



a) Addition of halogens to Cis-2-Butene: Cis alkenes on bromination gives a racemic 2,3 dibromo alkane. Bromine ion attacks the bromonium ion equally from a and b from opposite face by S_N2 reactivity



b) Addition of halogens to trans-2-Butene: Trans alkenes on bromination gives a meso 2,3 dibromo alkane. Bromine ion attacks the bromonium ion equally from a and b from opposite face by S_N2 reactivity

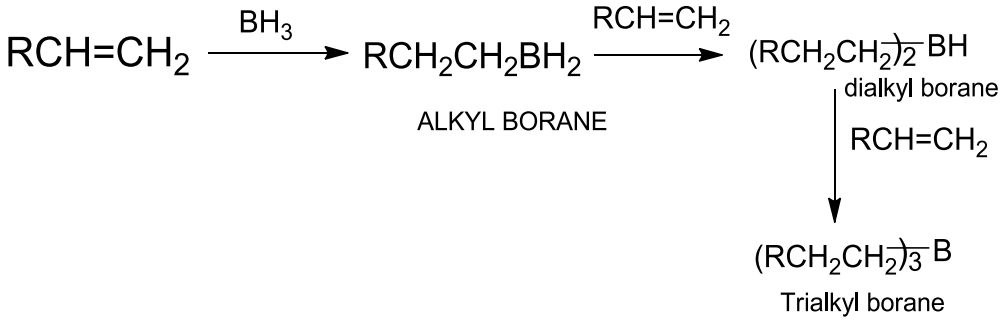


2.5 Hydroboration Reactions

Addition of B-H bond to carbon containing multiple bonds.

Alkylborane can be oxidised in which boron is replaced by –OH.

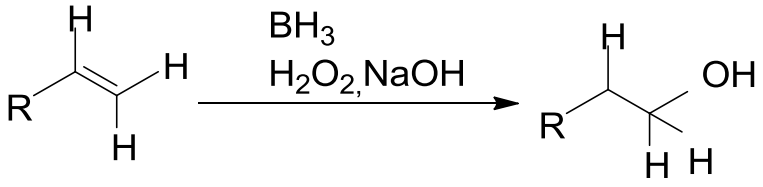
Stereochemistry is the syn-addition.



Mechanism:

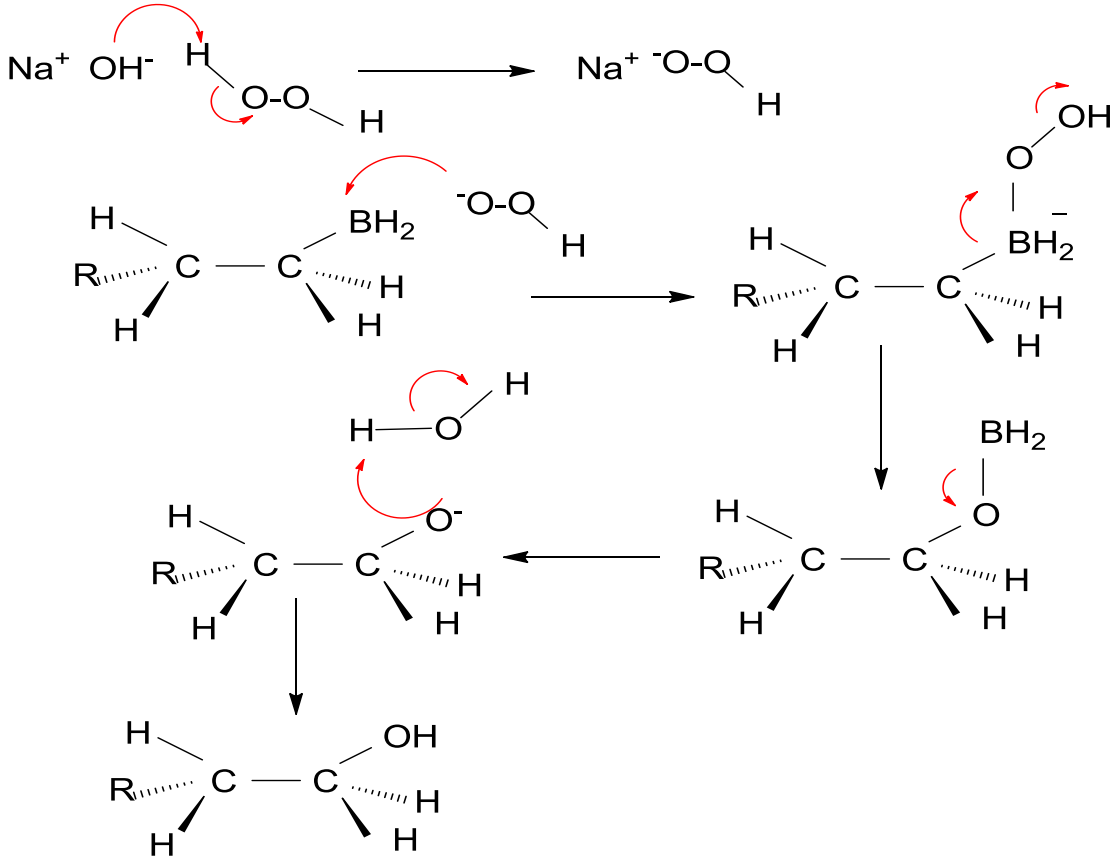
The π-bond in alkene is electron rich while the boron is electron poor. The reaction is initated via the co-ordination of BH3 with the π electrons of the double bond followed by the formation of carbon-hydrogen bond via four centre transition state. The addition is dominated by steric considerations. It is a regioselective reactions with the boron becomes attached to the less substituted and less sterically congested carbon. The hydrogen being bonded to the more crowded carbon. The alkylborane producta sre not primarily isolated but are converted by subsequent reactions directly to desired products. The most important reactionof the alkylborane is the oxidation with alkaline hydrogen peroxide to give an primary alcohol.

Alkene gets converted to primary alcohol in alkaline hydroboration reation. The addition of water to the intermediate follows Anti-Markownikov rule.



The oxidation of trialkyl borane with alkaline hydrogen peroxide replaces the boron atom with a hydroxyl group in the same stereochemical position. The net result of hydroboration and the oxidation-hydrolysis is the addition of water across a double bond with a Anti-Markownikov orientation.

Mechanism;



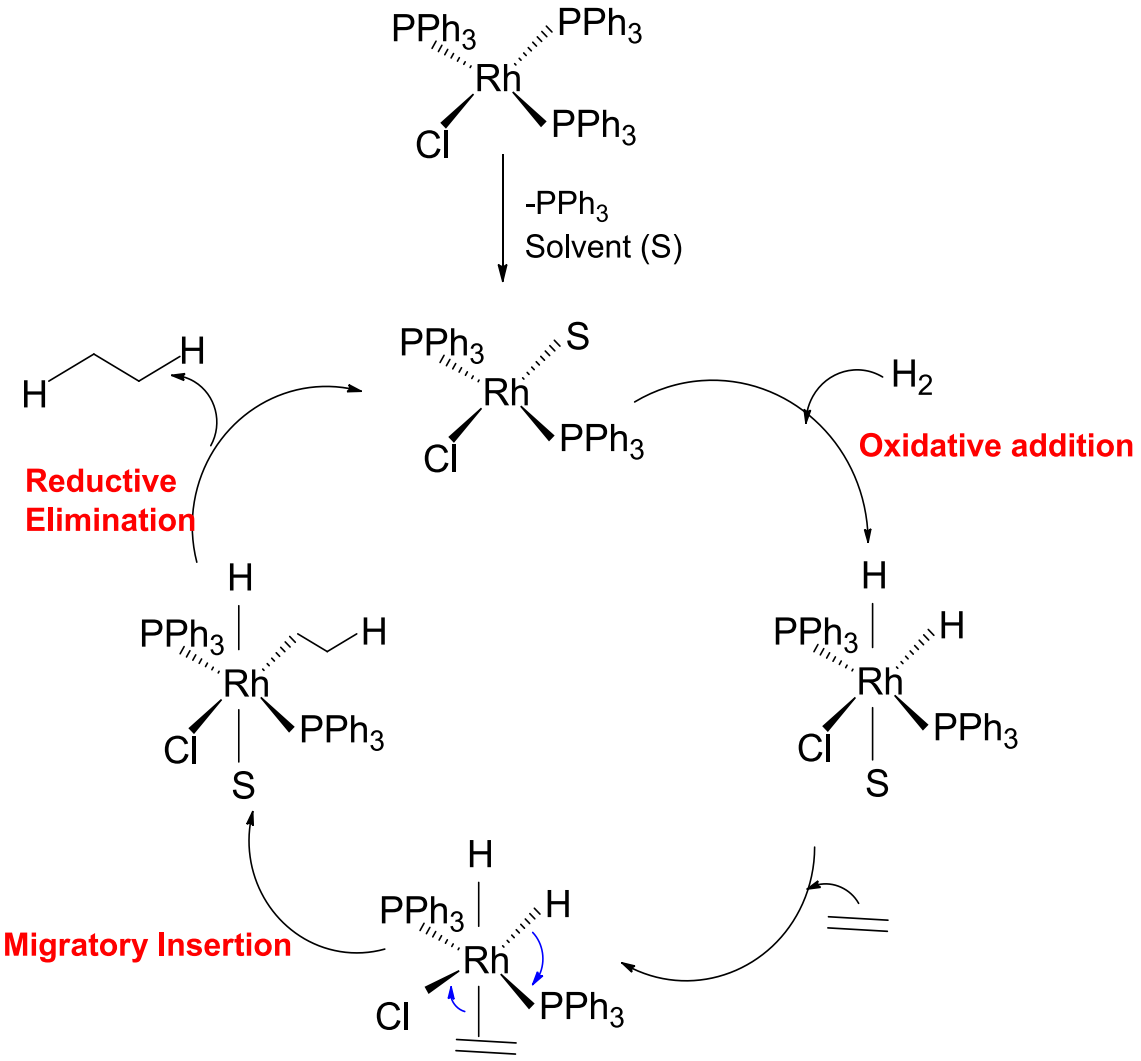
2.6 Enantioselective Reactions

One Enantiomer is formed in preference over the other.Optically active compound is formed from achiral starting material.Chiral catalyst or a reagent.

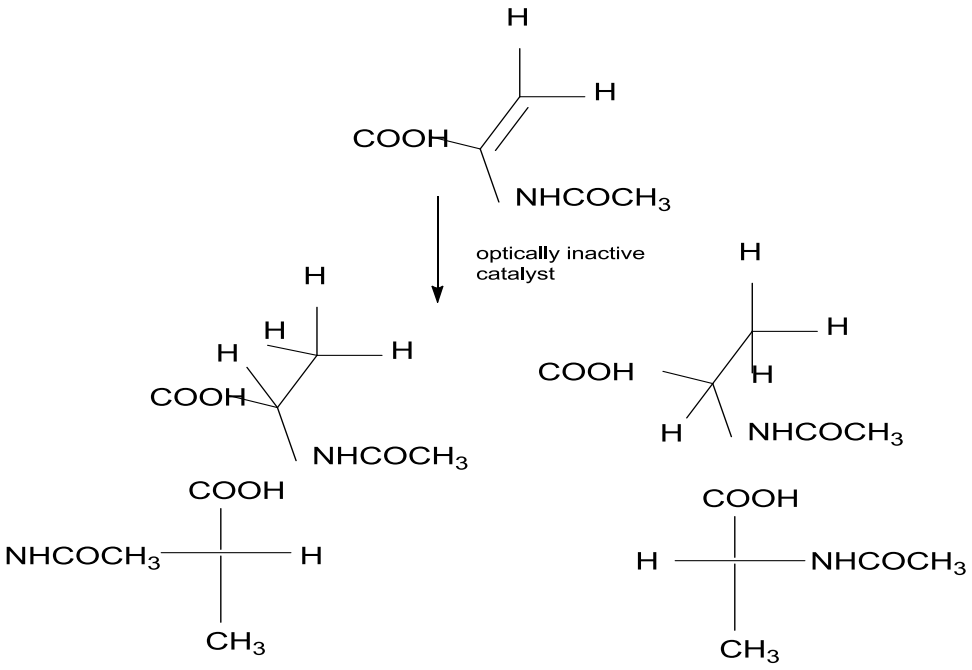
Eg: Epoxidation of allylic alcohol; Hydrogenation of alkene; Dihydroxylation of alkenes; Reduction of ketones

a) Hydrogenation of alkene:

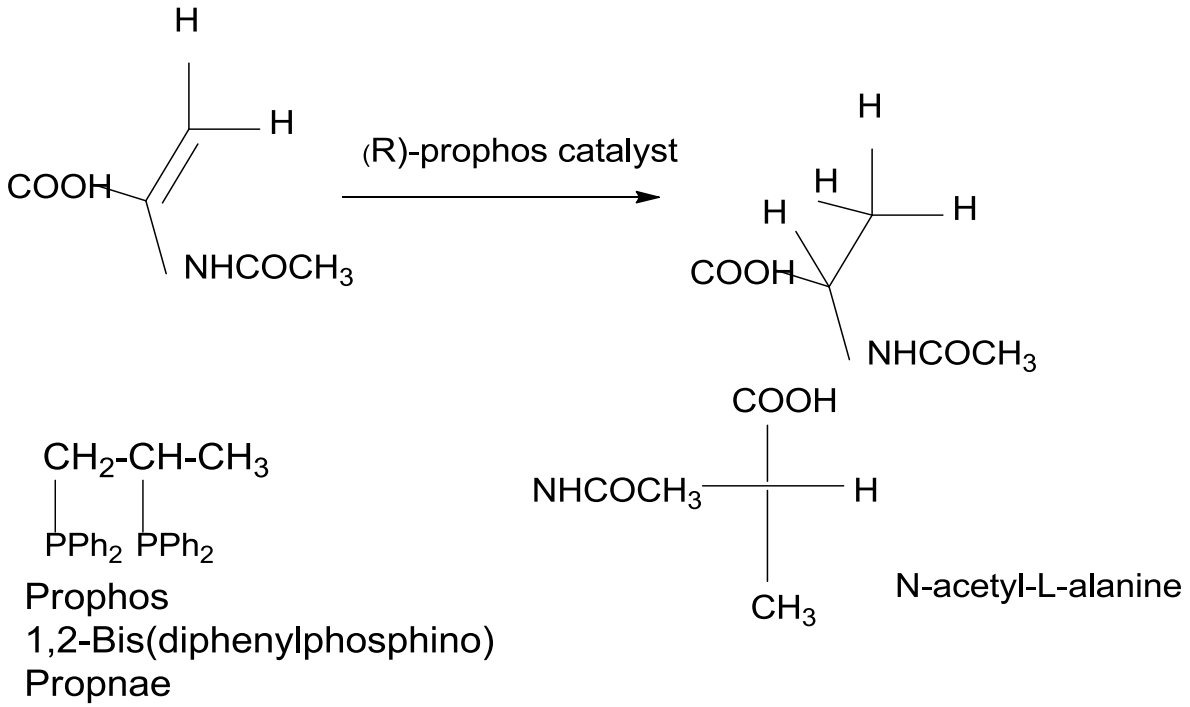
Alkene undergoes hydrogenation using Wilkinson's catalyst to form alkane. The reaction proceeds by exchanging one phosphine ligand for a solvent molecule to afford a complex which then bind to two hydrogen atom of the metal. displacement of the solvent molecule by the alkene follows a stepwise syn-transfer and the saturated molecule leaves the metal centre.



1-acetamidopropenoic acid is treated with Wilkinson's catalyst – Racemic Mixture



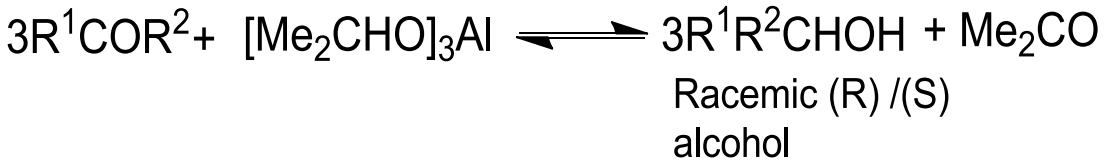
In the presence of optically active catalyst, a stereoisomer is obtained.



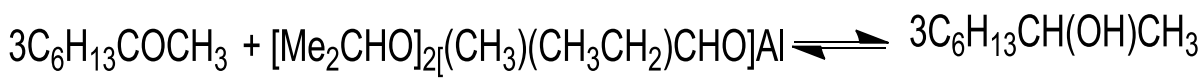
b) Reduction of aldehydes and ketones

Meerwein-Poondorf-Verley reaction [MPV] :

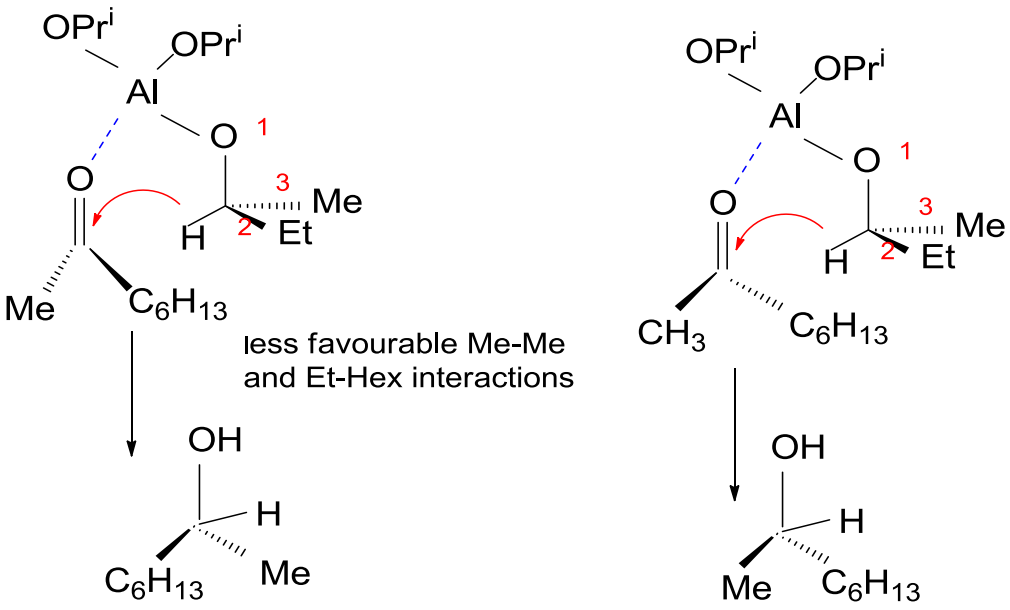
Reduction of carbonyl to alcohols in aluminium isopropoxide in isopropanol medium. Transfer of hydride ion from the isopropoxide to the carbonyl compound takes place by a six-membered cyclic transition state.



Aluminium alkoxide is derived from optically active (S)-butane-2-ol reacts with 6-methyl heptan2-one results in enantiomeric S-6 methylheptan2-ol.



Two diastereomeric transition state differing in energy

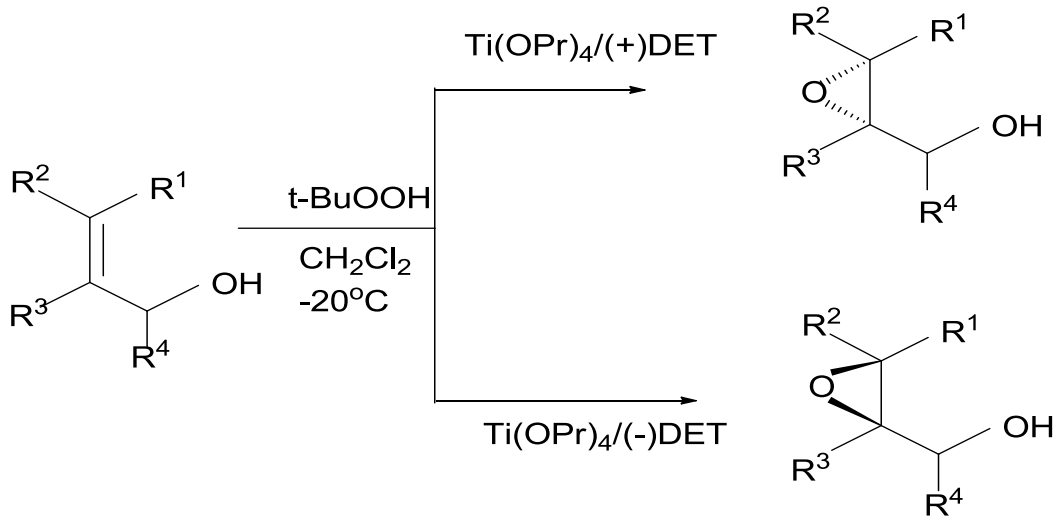


c) Sharpless asymmetric Epoxidation:

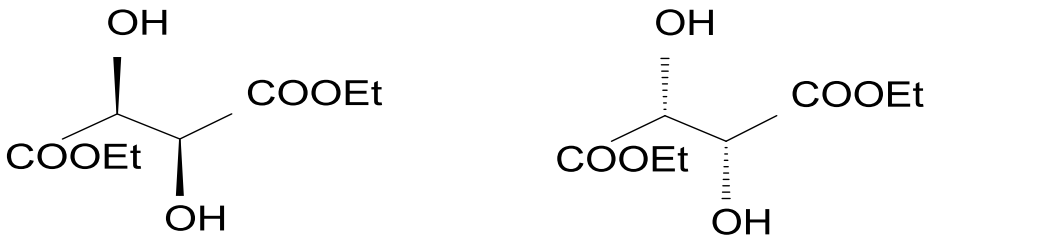
Oxidation of allylic alcohol to epoxides. The epoxidation is carried out with t-Butylhydroperoxide and the catalyst Titanium tetraisopropoxde/Diethyl tartrate. The procedure is highly enantioselective with enantiomeric pure tartrate esters are included

Table 2.2 The reaction conditions for Sharpless epoxidation reaction.

Substrate	Allyl alcohol
Oxidant	t-Butylhydroperoxide
Catalyst	Titanium tetraisopropoxde/Diethyl tartrate
Solvent	Dichloromethane at 20^{o}C.
Stereochemistry:	Right [Alcohol] (+)DET Wedge; (-)DET) Dash Left [Alcohol] (+)DET Dash; (-)DET) Wedge



The structure of the oxidant , DET which determines the stereochemistry of the product is given below



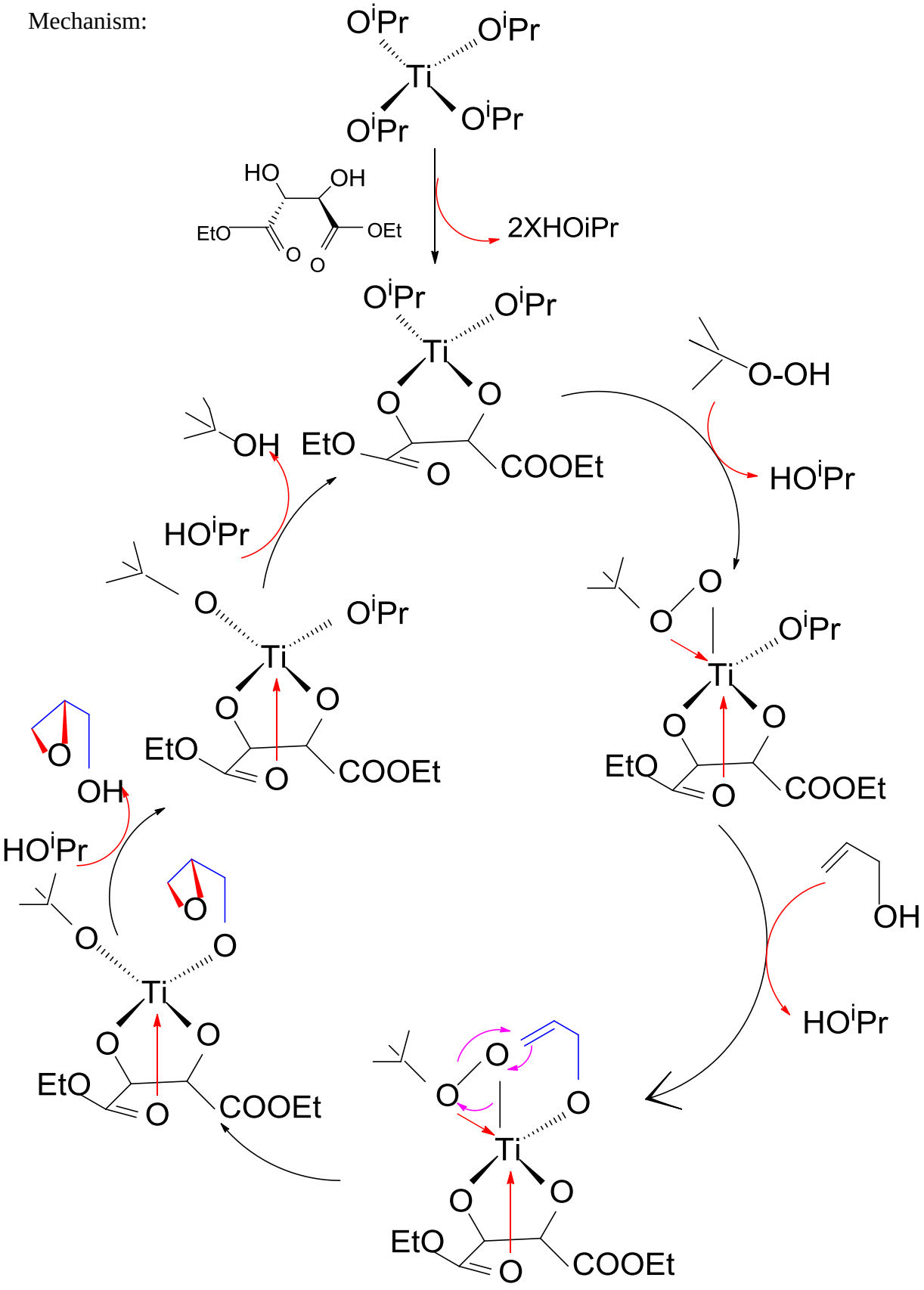
2S,3S (-) Diethyltartrate

2R,3R (+) Diethyltartrate

Mechanism:

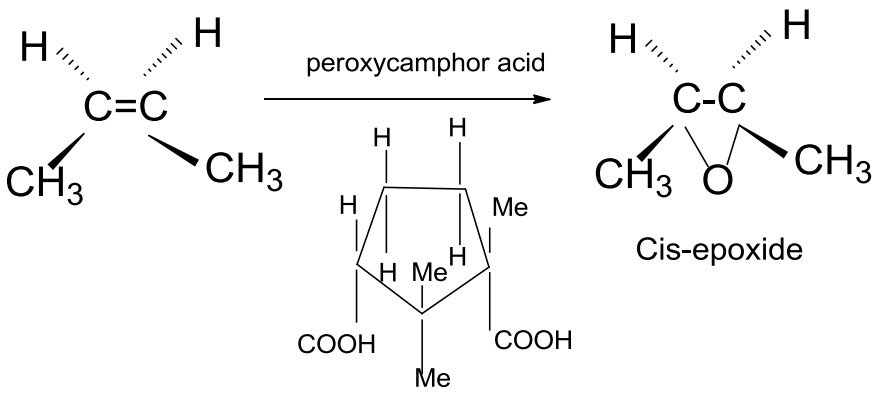
The reaction proceeds with an alkoxy -exchange between the two alkoxide residues in the titanium complex and the two hydroxyl groups in the tartrate ester to give an complex. The remaining isopropoxide residue undergoes further exchange with the hydroxyl group of the allylic alcohol and the hydroxyl group of the peroxide. The co-ordination activates the peroxide and the topography of the complex determines the favourable enantioselective transfer of oxygen to the olefinic centre to form the product either a cis or trans epoxide.

Mechanism:



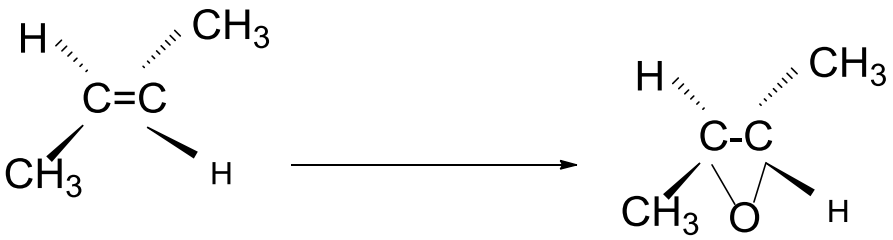
d) Oxidation of alkenes to epoxides:

It is an Enantioselective oxidation using peracids. Syn addition of oxygen atom to the double bond. Ring formation occurs in a single step.

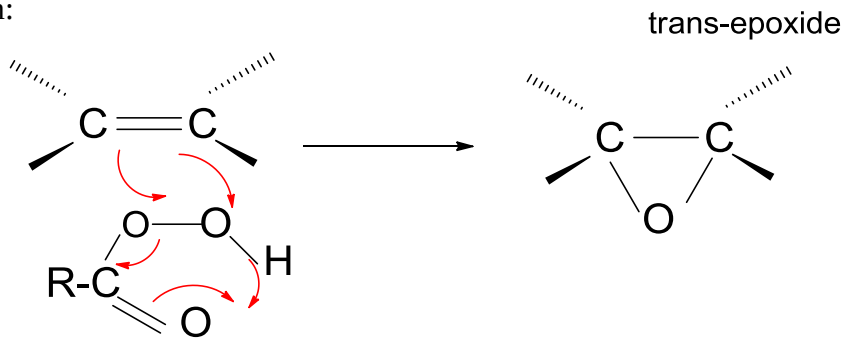


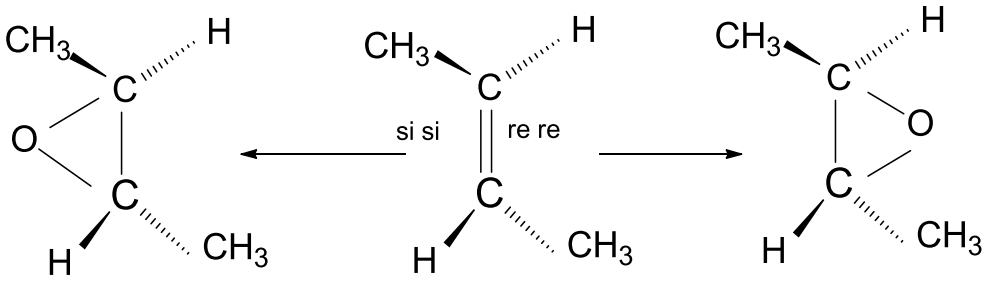
Trans alkene gives trans-epoxide.Usually, the syn addition occurs from the less hindered side.

Substituted epoxides exhibits optical and geometrical isomerism. Trans alkene results in chiral molecule. Cis alkene results in achiral molecule.



Mechanism:



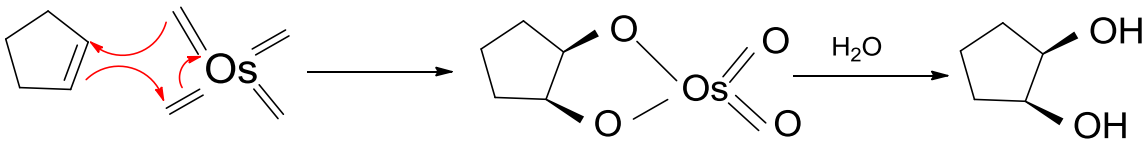


S-isomer trans R-isomer

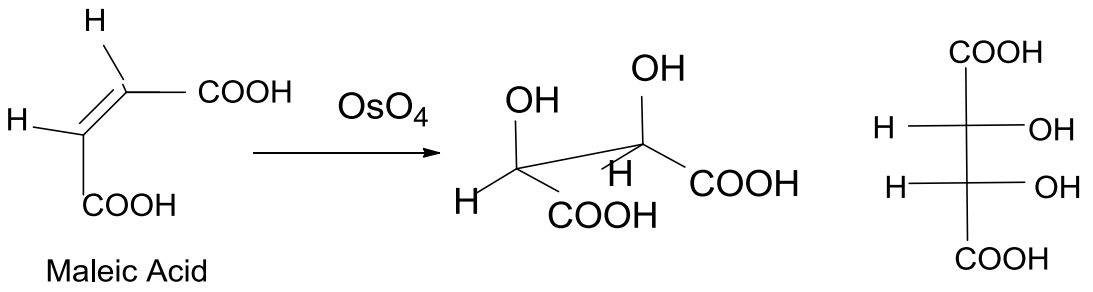
e) Dihydroxylation Reactions

With OsO_4: Reactions proceed with a cyclic intermediate to form cis-diols.

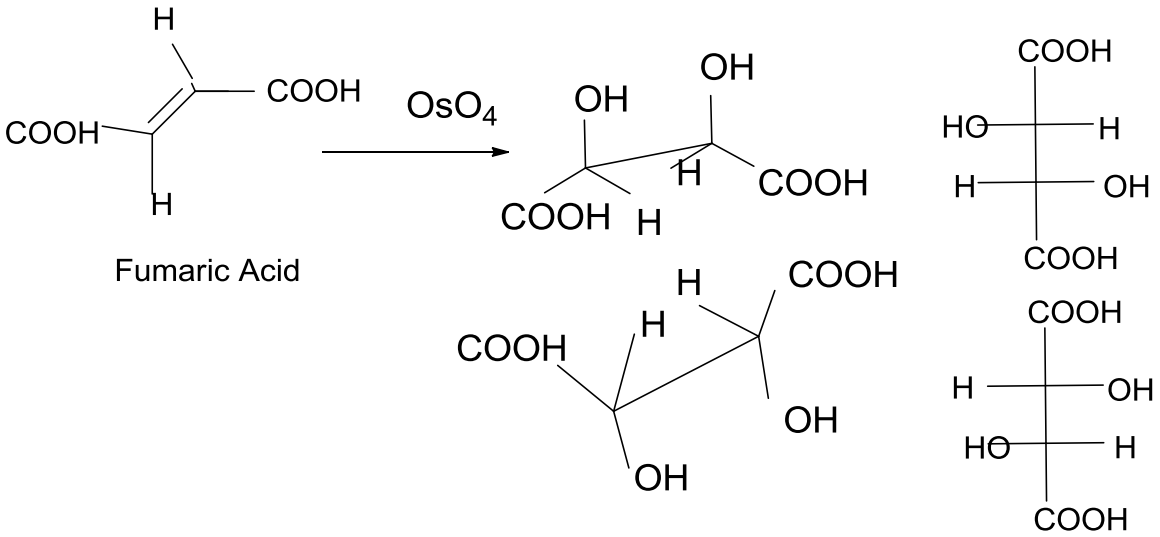
Reaction is stereospecific with syn addition of oxygen to π bond of the alkene to form cis diols



Syn-addition is preferred as the bonds formed in the cyclic intermediate is decomposed by the fission of the bonds between oxygen atom and the metal.

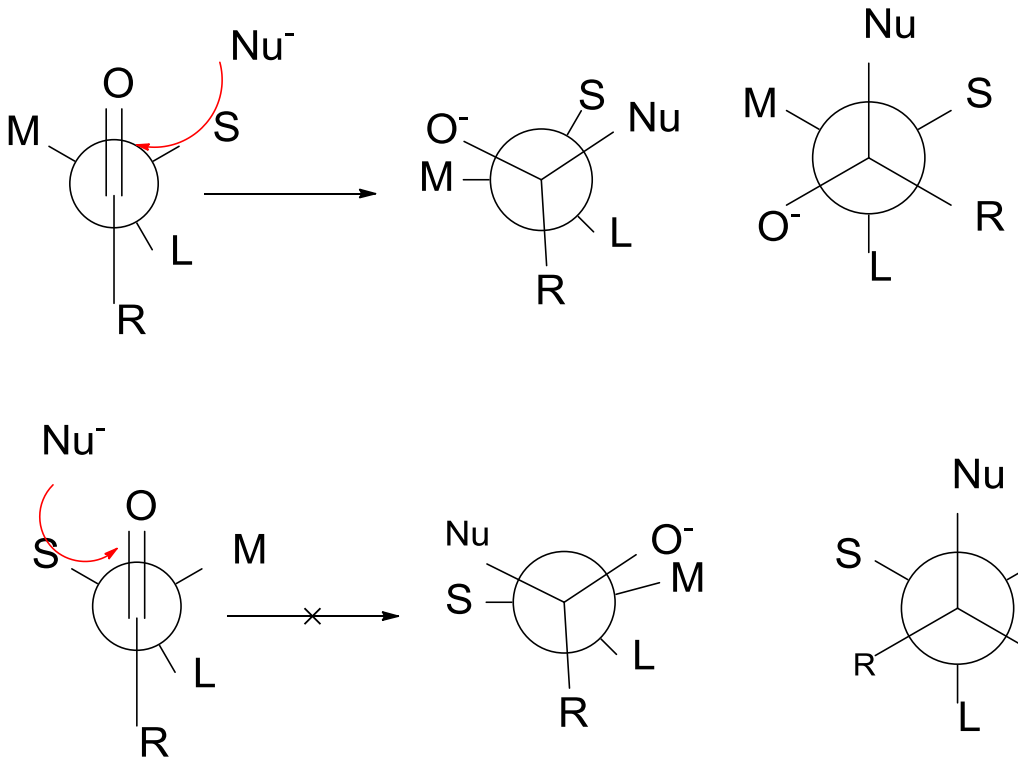


Fumaric acid gives Racemic mixture

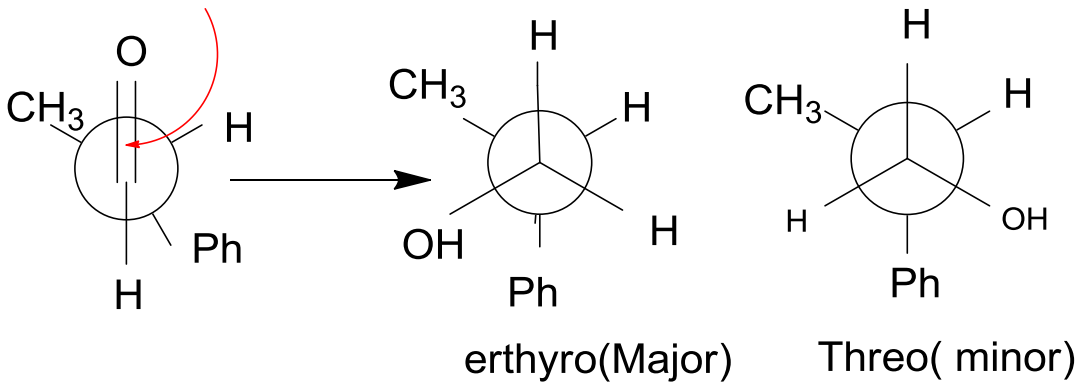


2.7 Cram's Rule:

In a Kinetically controlled addition to a carbonyl carbon atom which has a chiral centre in the α position, anion attacks from the side containing the small group and the chiral is so oriented that the medium group is in eclipsing to the carbonyl group.

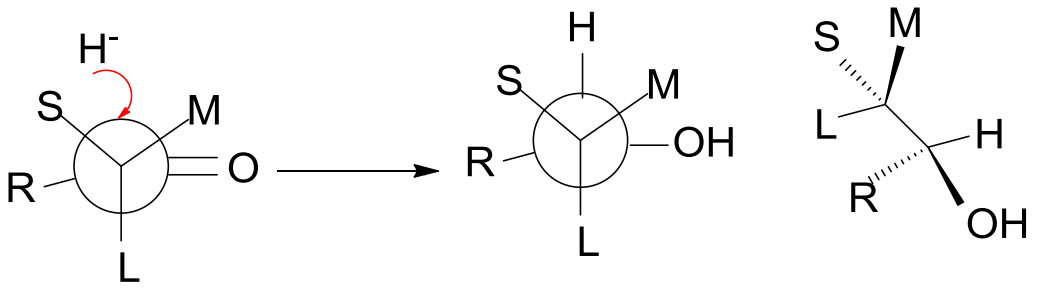


2-Phenyl propanaldehyde on reduction form alcohols with erthyo as the major product.

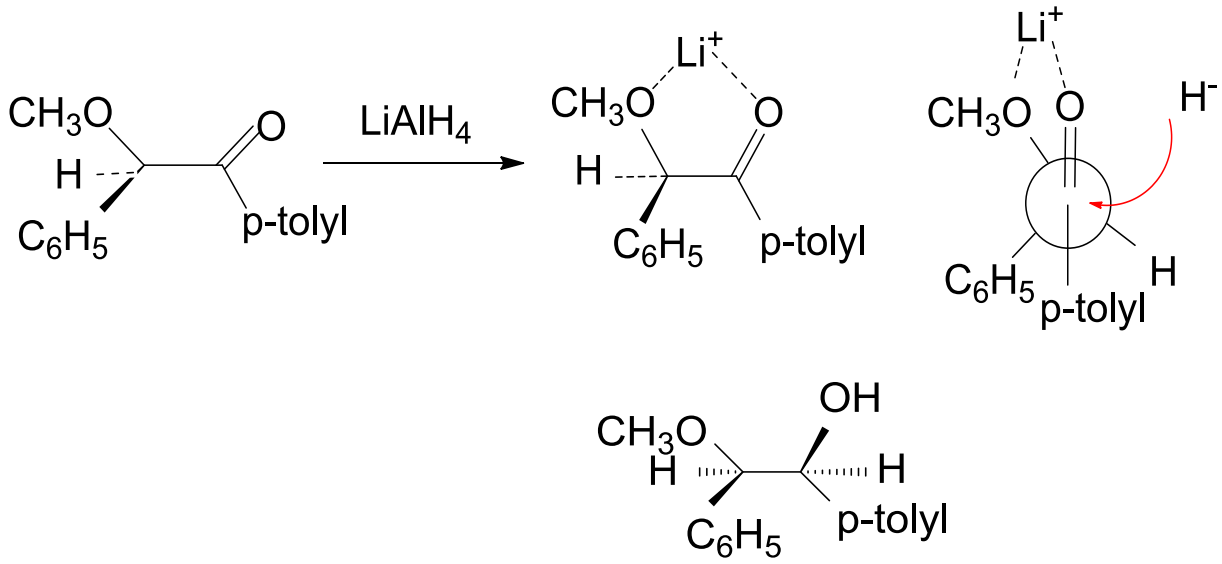


2.8 Felkin-Anh Model

The C-L bond is perpendicular to the carbonyl group with L, M and S substituents are arranged in clockwise direction. The nucleophile attack from the less hindered side with an obtuse angle to the carbonyl group.



Felkin-Anh Model is applied to compound with alkoxy, hydroxyl or other complexing group as substituents.



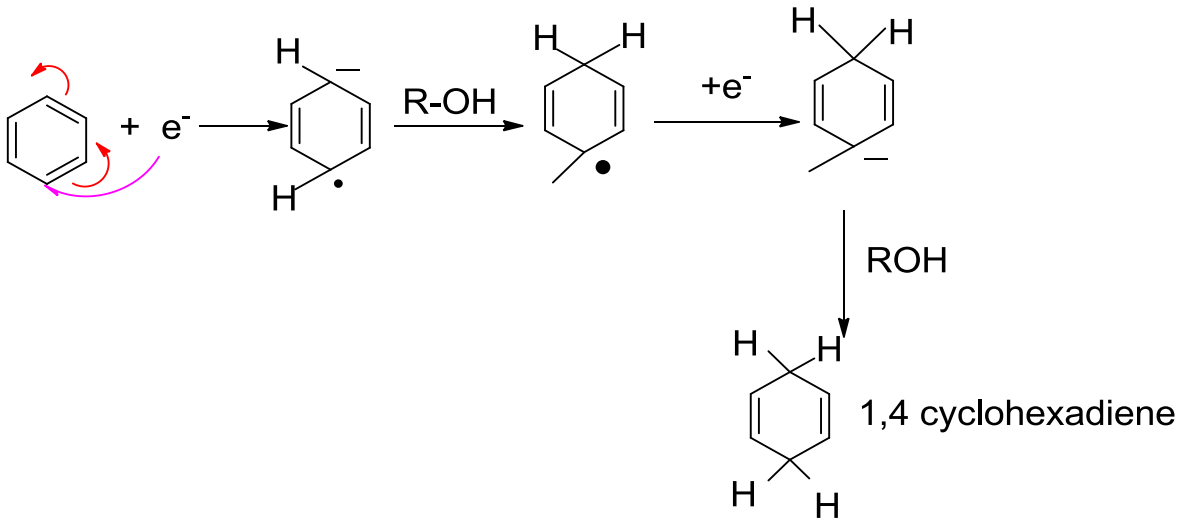
2.9 Chemoselective Reactions

Preferential reaction of one functionalgroup by a reagent is known as chemoselective reactions. several oxidation and reducing agents acts as chemoselective reagent to bringabout organic synthesis.

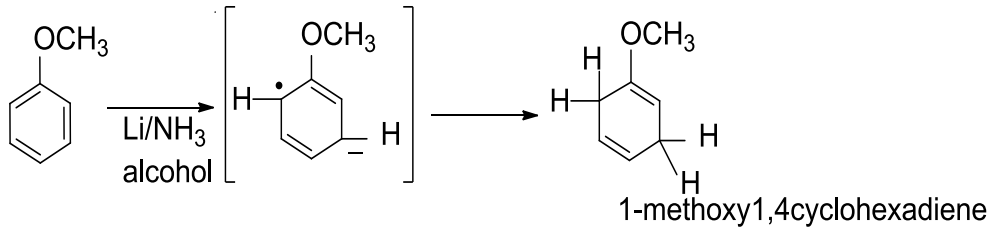
Eg: Metal in liquid ammonia, acetylides, Wilkinson's catalyst, OsO_4, $KMnO_4$ bring selectivereduction or oxidation of the functional group to form the product.

a) Metal in liquid ammonia: Birch Reduction

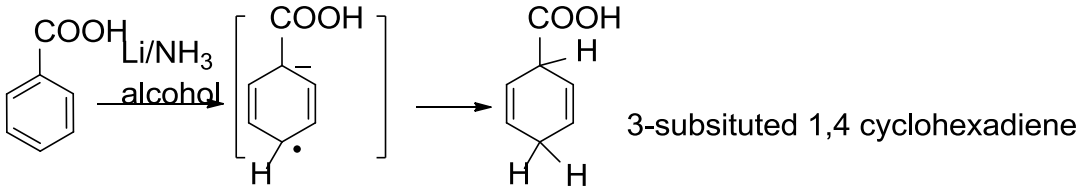
Reaction in which aromatic system can be reduced to form dienes.



- Presence of electron releasing groups:

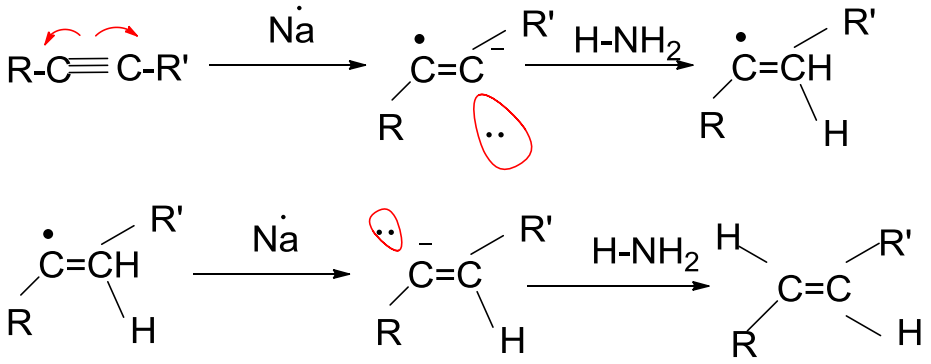


- Presence of electron withdrawing groups:

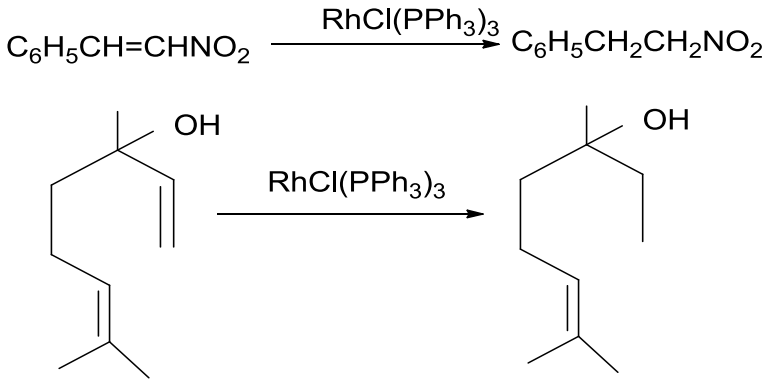


b) Acetylenes:

It form trans-alkenes. Series of electron and proton-transfer steps.Radical anion formed is a strong base and therefore removes a proton from NH_3 Vinylic anion favours the more stable trans configuration with bulky groups as far apart as possible. Alkynes gives trans-alkenes

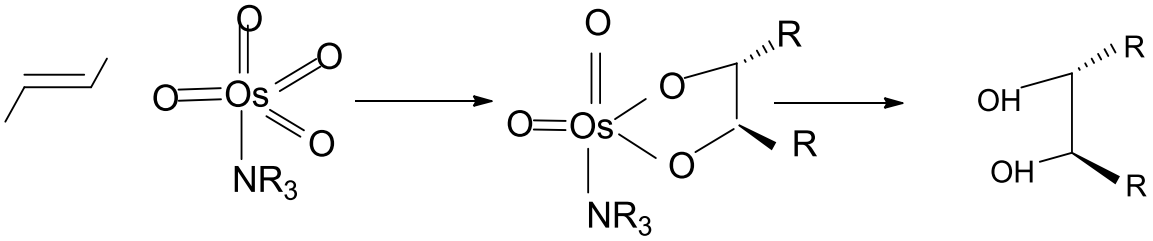


c) Chemoselective nature of Wilkinson's catalyst: -CO, CN, -NO_2 are not attacked and selective reductions are carried.



d) Chemo-Enantioselective reaction

OsO_4 with chiral ligand results in optical active reagent to form an enantiomeric product.



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DEPARTMENT OF CHEMISTRY

UNIT – III - ASYMMETRIC SYNTHESIS – I – SCYA7302

UNIT 3

ASYMMETRIC SYNTHESIS – I

3.0. Introduction

- Conversion of achiral starting material iinto chiral product in a chiral environment.
- Substrate and reagent combine to form diastereomeric transition states One of the two reactants must have a chiral element to induce asymmetry at the reaction site.
- Asymmetry is created by conversion of trigonal carbons to tetrahedral ones at the site of the functionality.
- Enantiomeric Transition state yields a racemic product.

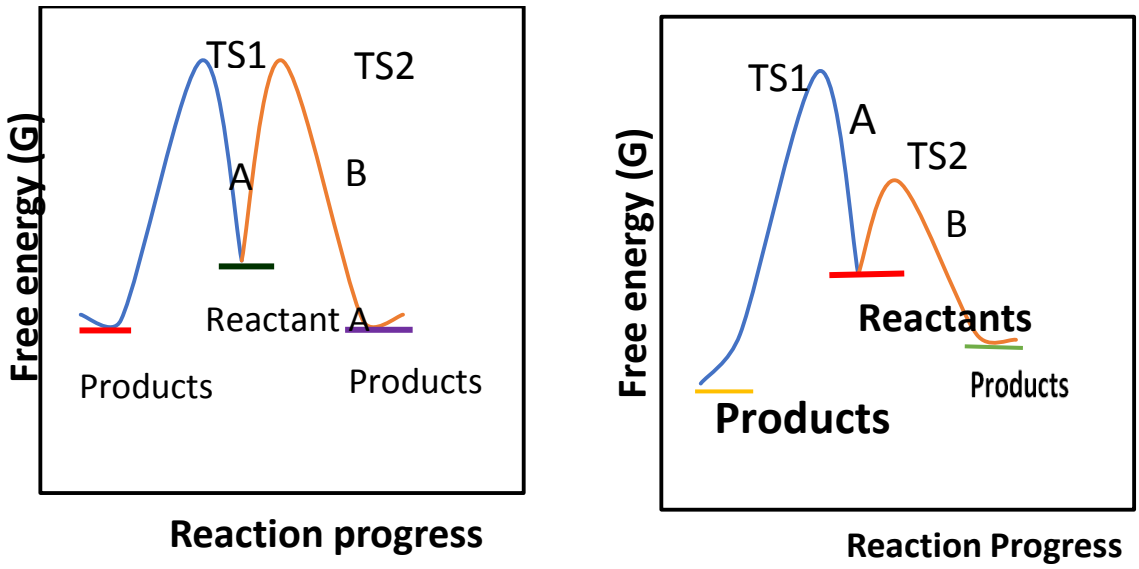


Fig.3.1 Enantiomeric and Diastereomeric Transition state

- Diastereomeric Transition state yields a enantiomeric excess compound. The asymmetric synthesis takes place by following methods;

i. Chiron approaches
ii. Acyclic Diastereoselective approaches
iii. Double asymmetric synthesis

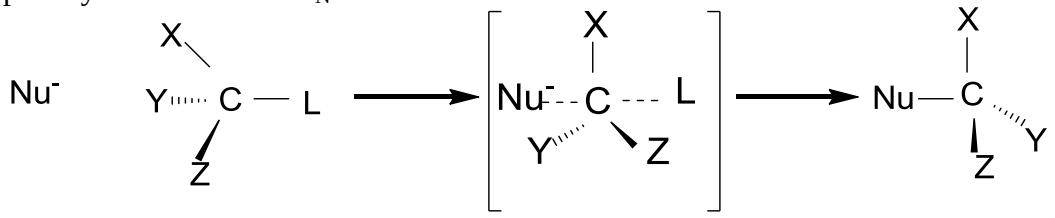
3.1 Chiron approaches

Naturally occurring chiral compounds provide an enormous range and diversity of possible starting materials, enantiomeric purity

Table 3.1 Examples of Chiral pool

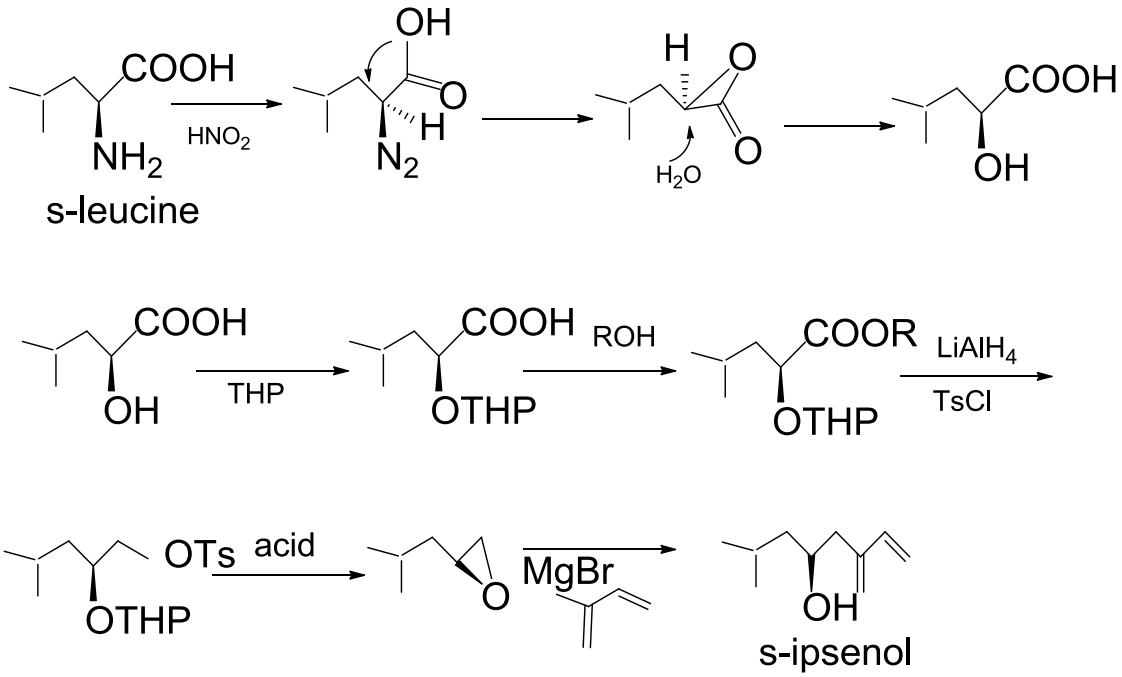
Amino Acids	Hydroxy Acids	Carbohydrates
l-alanine	l-lactic acid	d-arabinose
l-arginine	d-lactic acid	l-arabinose
d-asparagine	(S)-malic acid	l-ascorbic acid
l-asparagine	(Poly)-3(R)-hydroxybutyrate	

Chiral pool synthesis follows S_N2 mechanism

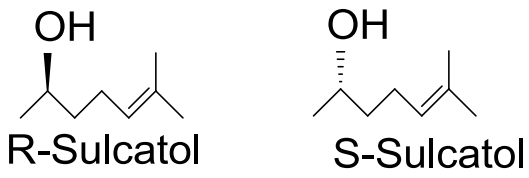


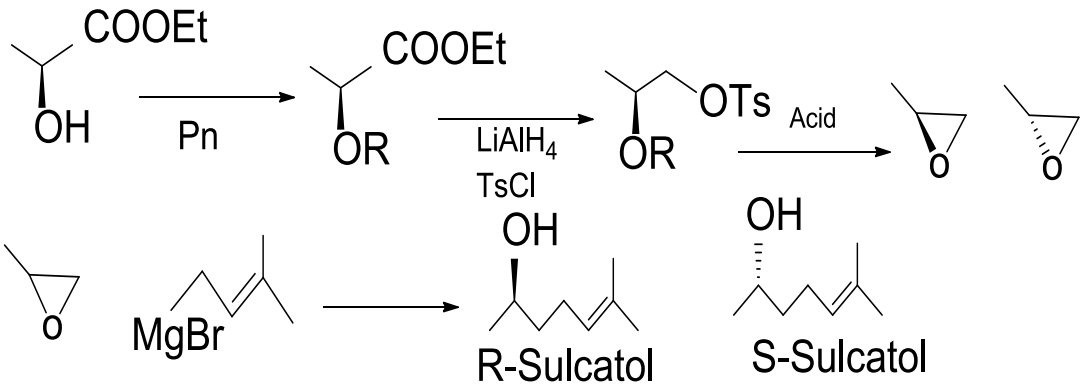
Eg; 1

Male bark beetles producesa pheromone which is a diene alchol, (s)-ipsenol, produced from (s)-leucine.



Eg 2: Another insect pheromone is called sulcatol, secondary alcohol. It is a mixture of 65:35 enantiomers.





3.2 Acyclic Diastereoselective Approaches

Asymmetric synthesis involves the formation of a new stereogenic unit in the substrate by a chiral group derived from a naturally occurring chiral compound.

It can be divided into four major classes,

(1) substrate controlled methods;

(2) auxiliary-controlled methods;

(3) reagent-controlled methods, and

(4) catalyst-controlled methods.

1) Substrate-controlled reaction

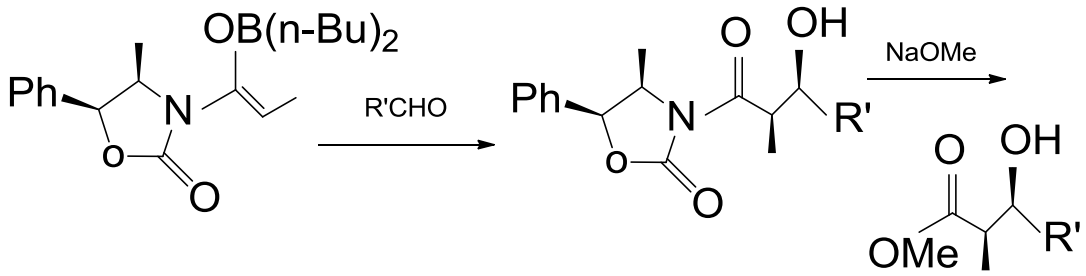
First generation of asymmetric synthesis

It is based on intramolecular contact with a stereogenic unit that already exists in the chiral substrate. Formation of the new stereogenic unit most often occurs by reaction of the

substrate with an achiral reagent at a diastereotopic site controlled by a nearby stereogenic unit.

S* + R ⟶ P*

Chiral boron enolates reacts with aldehydes with high stereoselective syn-aldol.



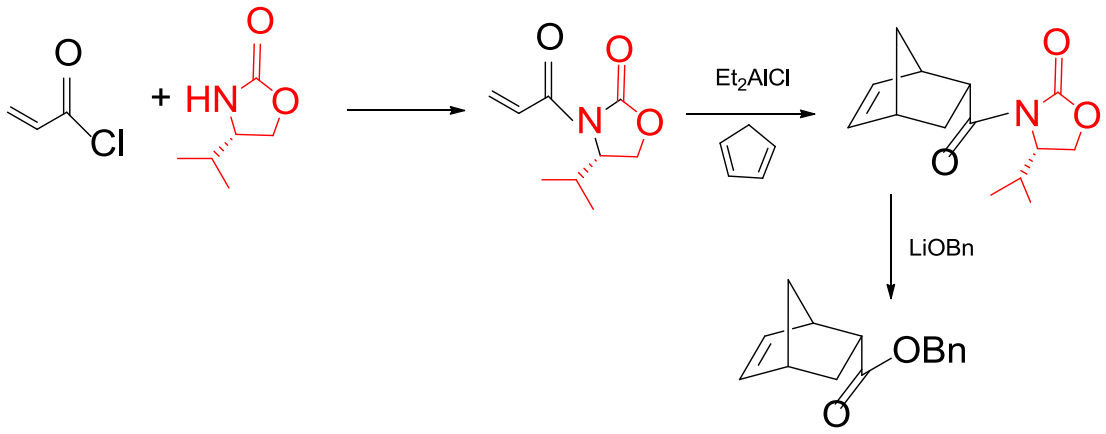
2) Auxiliary-controlled reaction

Second generation of asymmetric synthesis.

Asymmetric control is achieved intramolecularly by a chiral group in the substrate. The directing group, the ``chiral auxiliary'', is deliberately attached to the original achiral substrate in order to direct the enantioselective reaction. The chiral auxiliary will be removed once the enantioselective transformation is completed.

S + A* —R→ P-A* ⟶ P*

Diel-Alder's reaction: Reaction of achiral dienophile with auxillary reagent is reacted with diene to form stereoselective product.



3) Reagent-controlled methods

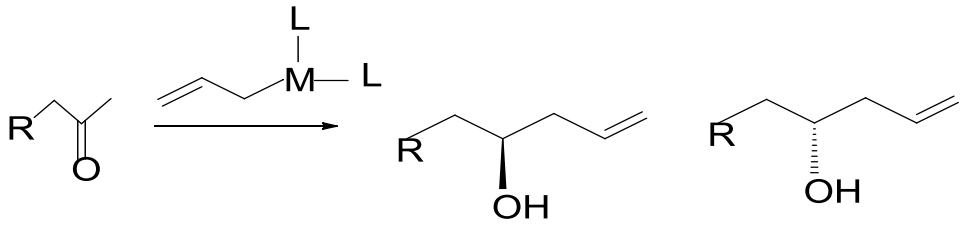
Achiral substrate is directly converted to the chiral product using a chiral reagent. The stereocontrol is now achieved intermolecularly.

$$S + R^* \longrightarrow P^*$$

The reaction of a chiral substrate with a chiral reagent in which two new stereogenic units are formed stereoselectively in one step.

$$S^* + R^* \longrightarrow P^*$$

Eg: Addition of chiral metal allyls to achiral aldehydes where the metal is B,Ti, Sn and Si. The chirality is induced by the ligands attached to the metal.



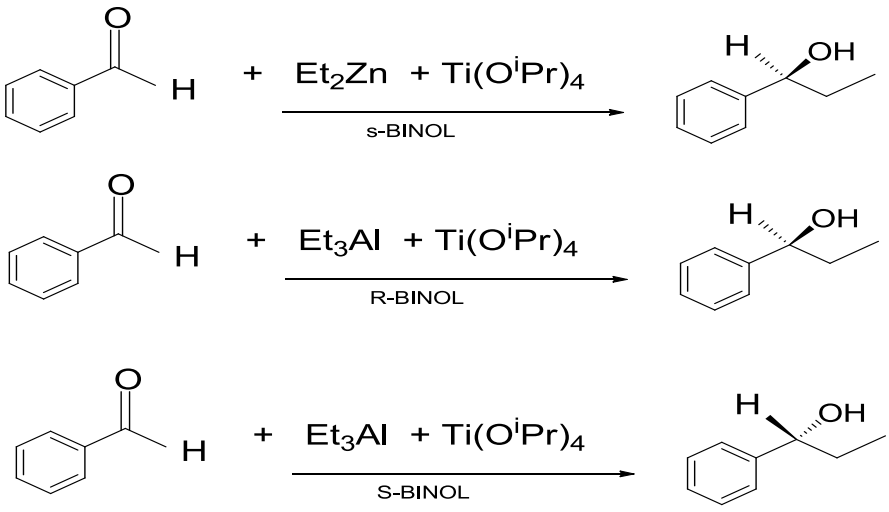
4) Catalyst-controlled methods

Application of chiral catalysts to induce the conversion of achiral substrates to chiral product

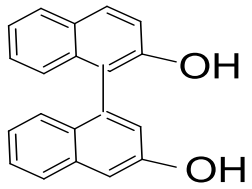
$$S \xrightarrow{\text{cat*/L*}} P^*$$

The addition of a ligand increases the reaction rate of an existing catalytic transformation

Eg: Alkylation of aldehydes

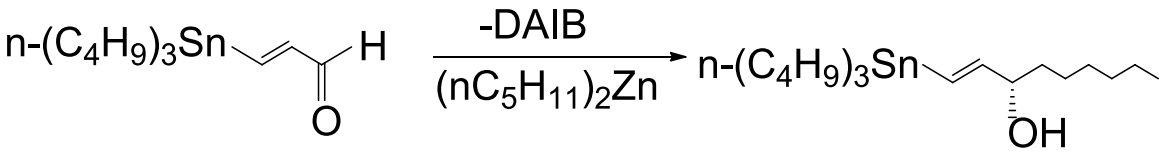


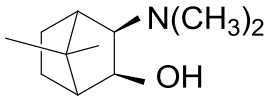
The catalyst used is Binaphthol, which is a atropisomers arises from restricted rotation about single bonds.



BINOL

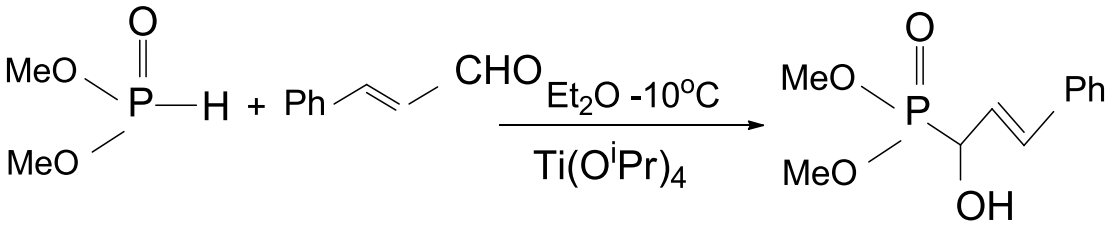
Eg: Alkylation of aliphatic aldehyde





3-exo (dimethylamino) isoborenol

DAIB



3.3 Double Asymmetric Synthesis:

Reaction of an enantiomerically pure substrate and an enantiomerically pure reagent.

Chiral substrate *A-C(x) is converted to A*-(*Cn)-C(z) by process I, where both C(x) and C(z) denote appropriate functional groups for the chemical operation. a chiral reagent *B-C(y) is allowed to react with *A-C(x) to provide a mixture of stereoisomers Đ*A-*C-*C-*B (process II).

The reagent *B-C(y) is chosen in such a manner that high stereoselectivity at *C is achieved in the reaction

1. When the desired *A-*C-*C-*B is the major product in the matched pair reaction, the resultant stereoselectivity should be higher than the diastereo facialselectivity of *A-C(x).

2. If the product *A-*C-*C-*B occurs as the minor product, this presents a mismatched pair reaction, The diastereofacial selectivity of the reagent must be large enough to outweigh that of *A-C(x) in order to create the desired *C-*C stereochemistry with high selectivity.

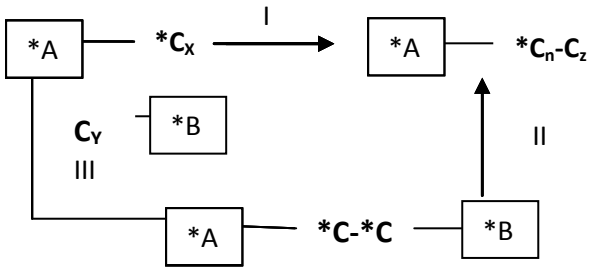
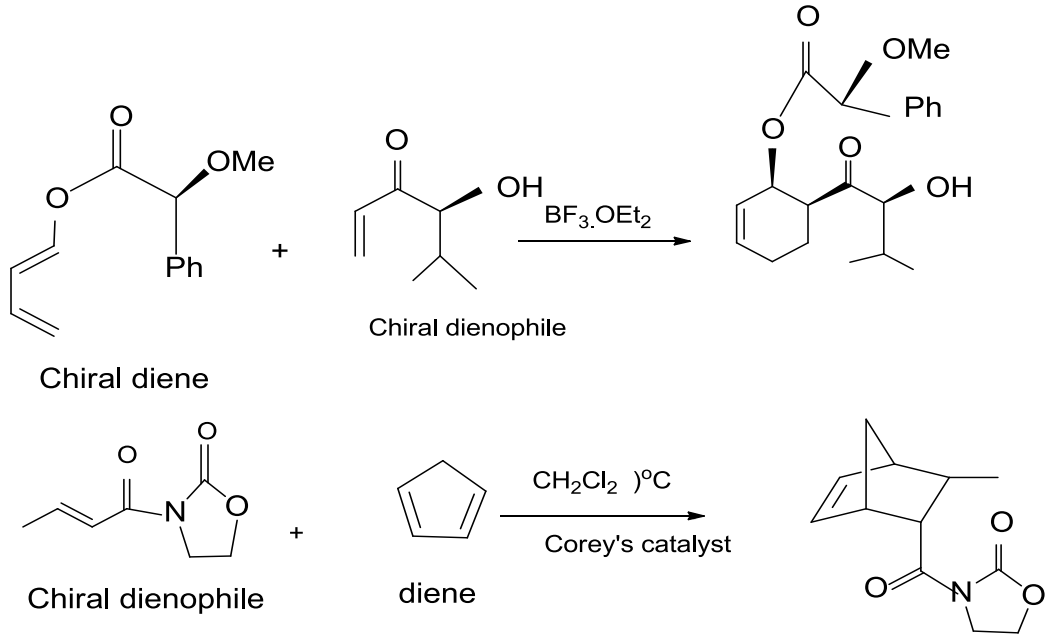


Fig. 3.2 Chiral centres in Double asymmetric Reactions



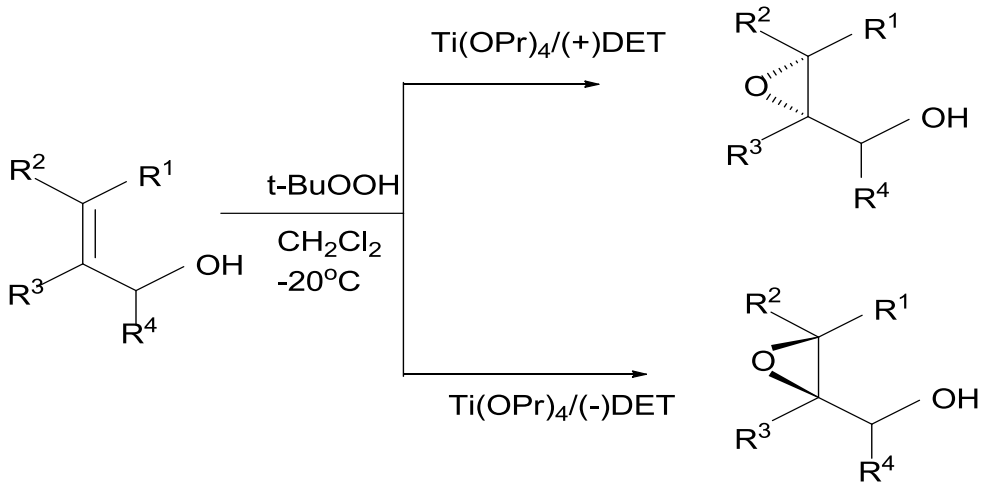
3.4 Asymmetric Oxidations:

a) Sharpless asymmetric epoxidation:

Oxidation of allylic alcohol to epoxides. The epoxidation is carried out with t-Butylhydroperoxide and the catalyst Titanium tetraisopropoxde/Diethyl tartrate.

Mechanism:

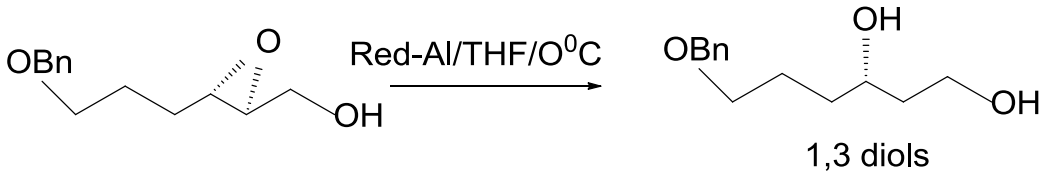
The reaction proceeds with an alkoxy -exchange between the two alkoxide residues in the titanium complex and the two hydroxyl groups in the tartrate ester to give an complex. The remaining isopropoxide residue undergoes further exchange with the hydroxyl group of the allylic alcohol and the hydroxyl group of the peroxide. The co-ordination activates the peroxide and the topography of the complex determines the favourable enantioselective transfer of oxygen to the olefinic centre to form the product either a cis or trans epoxide.

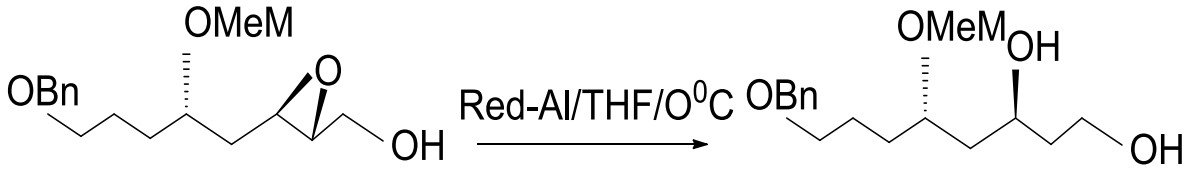


b) Selective opening of 2,3 epoxide alcohols

i) Red-Al: sodium bis(2-methoxyethoxy)aluminum hydride:

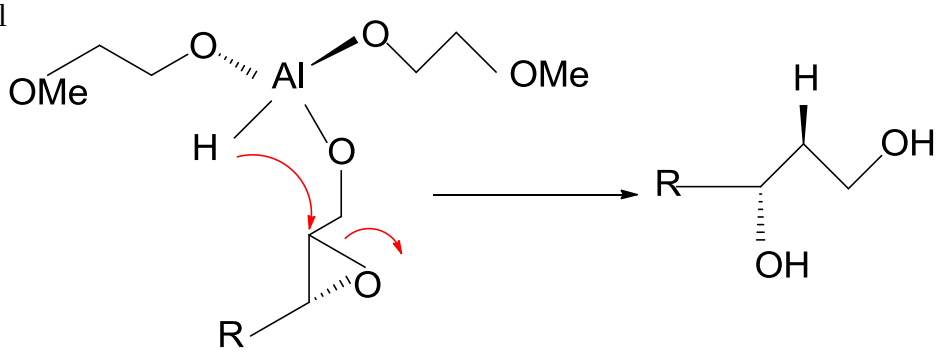
Ring opening results in the formation of 1,3 diols with the transfer of hydride occurs at the least substituted side.





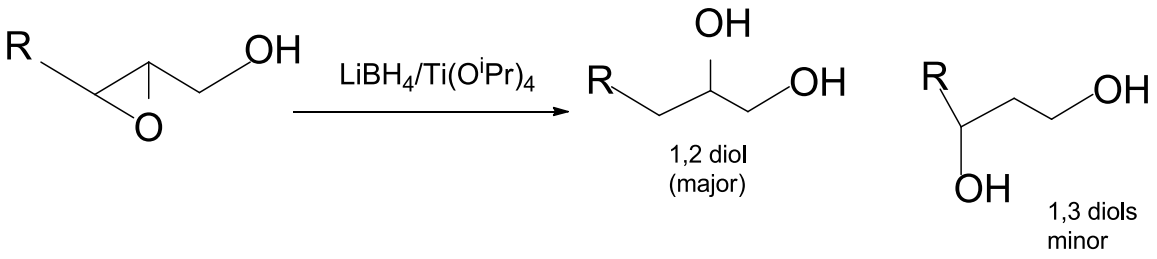
Mechanism:

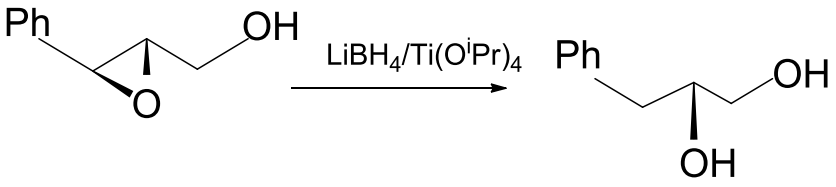
Red-Al

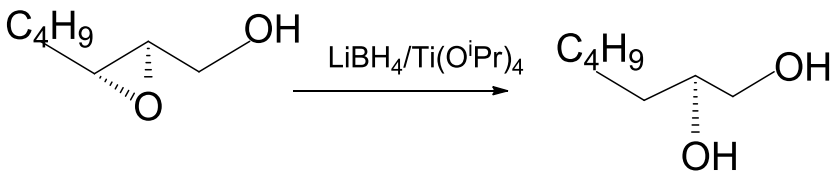


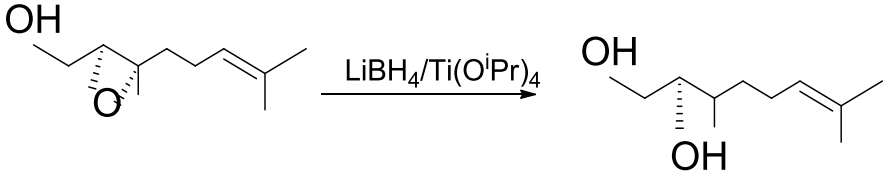
ii) $LiBH_4/Ti(O^iPr)_4$

Ring opening results in the formation of 1,3 diols with the transfer of hydride occurs at the least substituted side.

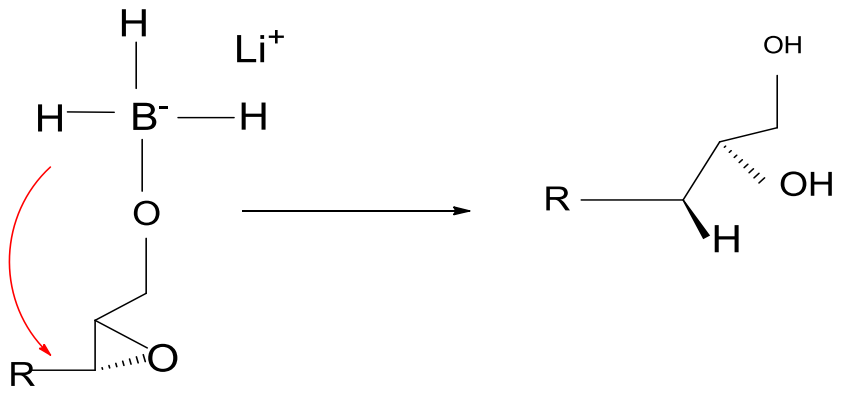




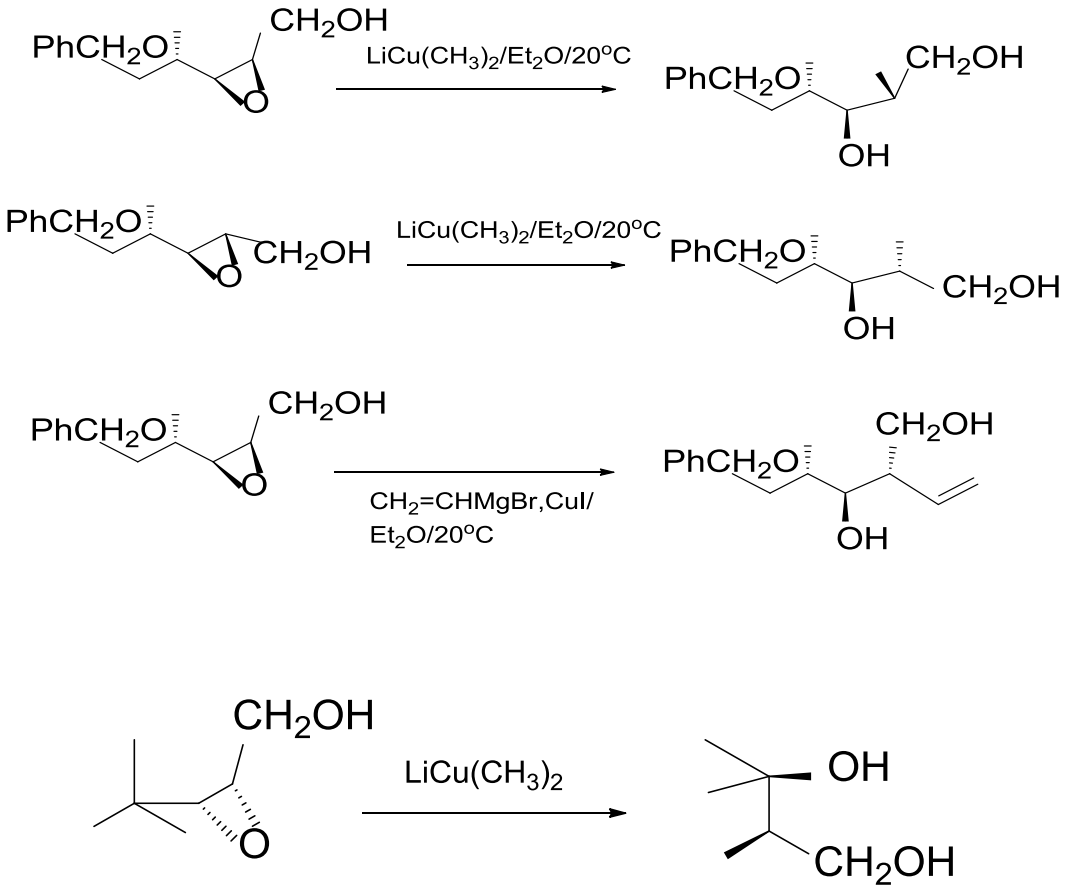




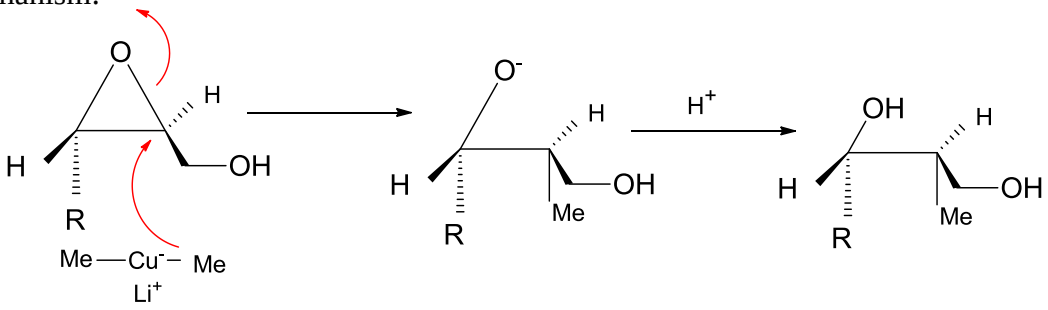
Mechanism:



iii) Organometallic reagents-Gilman Reagents: Ring opening takes place at the least substituted side with the alkyl group act as nucleophile.

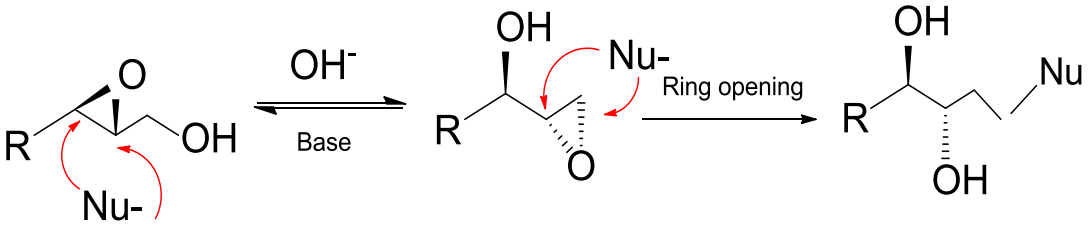


Mechanism:

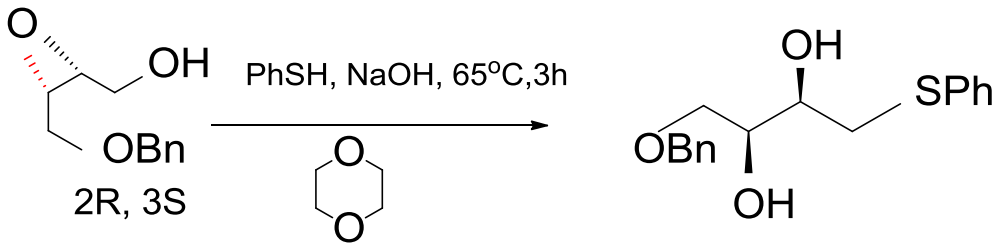


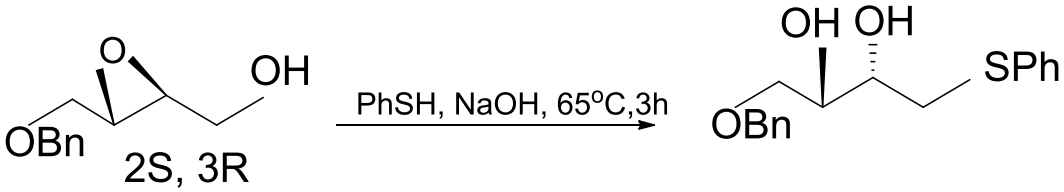
iv) Payne Rearrangement:

Nucleophilic ring opening takes place at c1 in the presence of a base to form 2,3 diols.



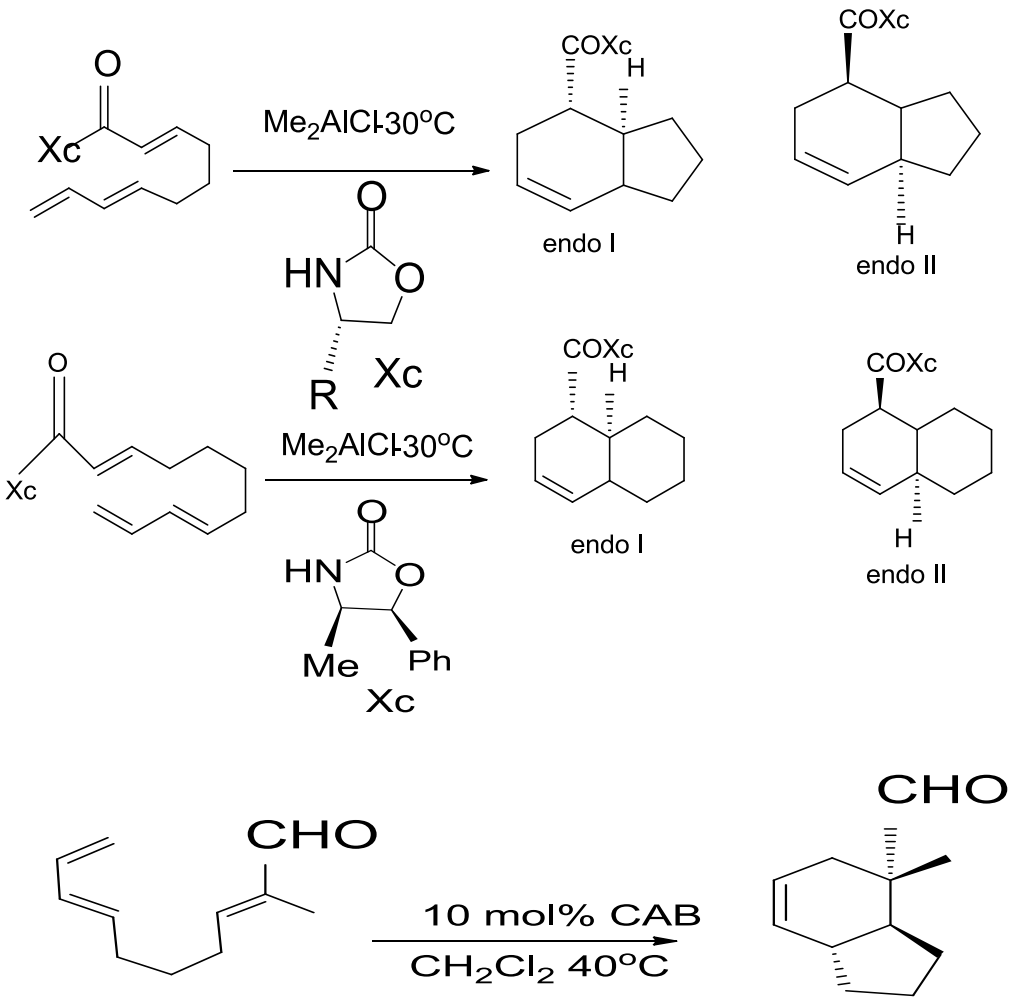
Nu: PhS^-, BH_4^-, CN^-, $TsNH^-$





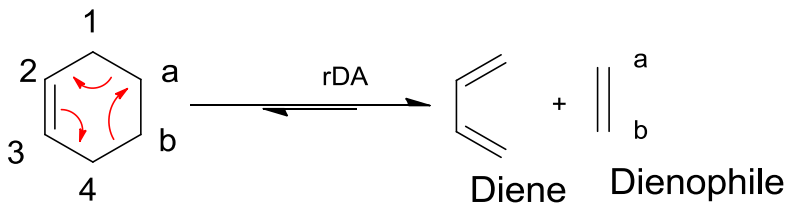
3.5 Intra molecular Diels-Alder Reaction

Dienophile bearing chiral auxillary can be used in this reaction to produce natural products.



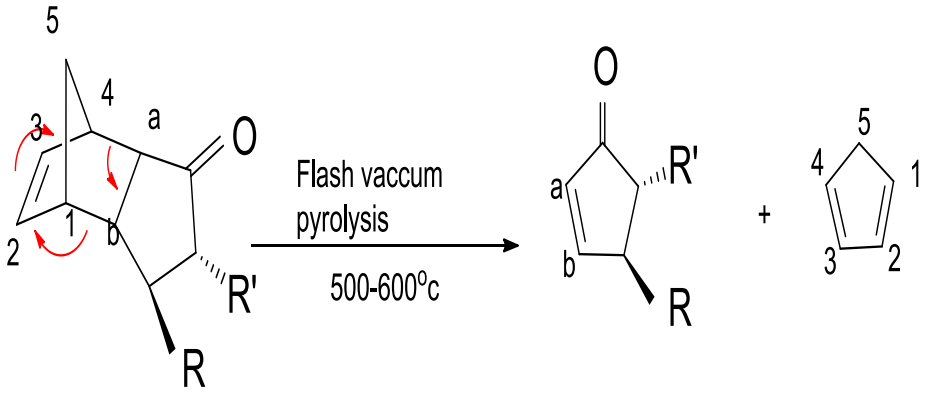
3.6 Retro Diels Alder reaction

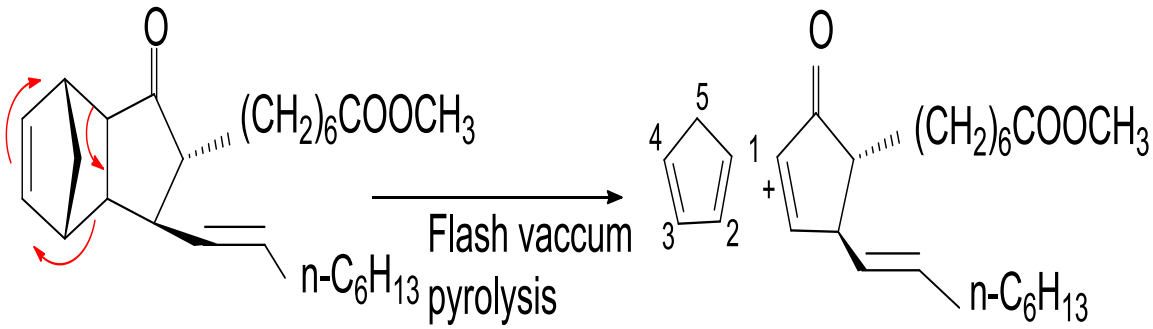
On heating, adduct produces a diene and a olefin containing double bond. During this reaction two single bond breaks to form two pi bonds with a total 3 pi bonds in both diene and dienophile.

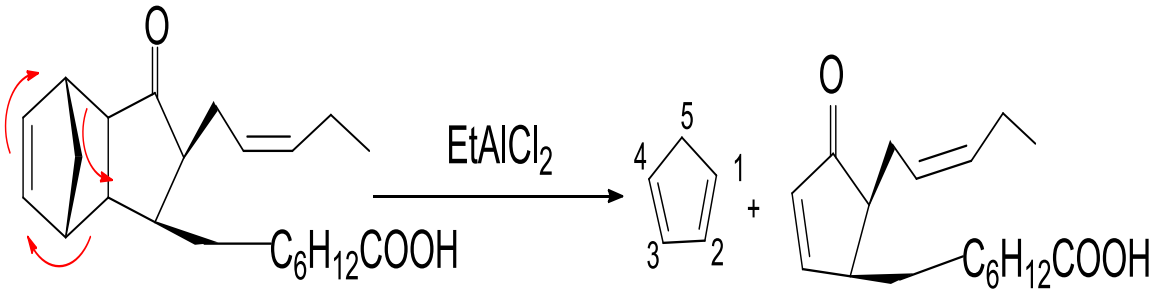


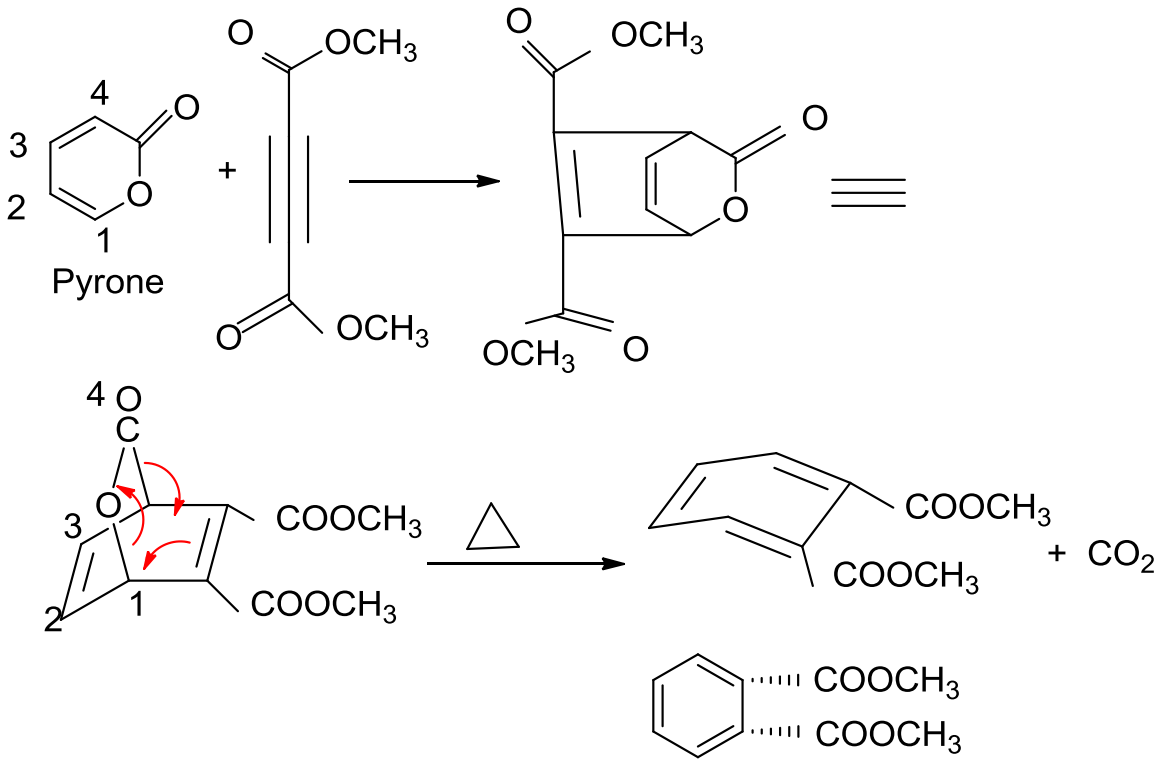
The diene and dienophile is used for various organic synthesis. Usually, the retro-diels alder reaction takes place in flash vaccum pyrolysis at 500- 600^0 c to form diene, with the dienophile in this cases mostly is a cyclopentadiene. this reaction is highly useful in the preparation of 4,5-dialkyl cyclopentenone product which are usually thermodynamically less stable. The alkene , cyclopentadiene is protected by this cyclopenteneone group and can be prepared by flash vacuum pyrolysis. The alkenes which are difficult to synthesize by conventional methods can be obtained by retro diels-alder reaction.

The following examples where the alkene,cyclopentadiene can be obtained by this method.

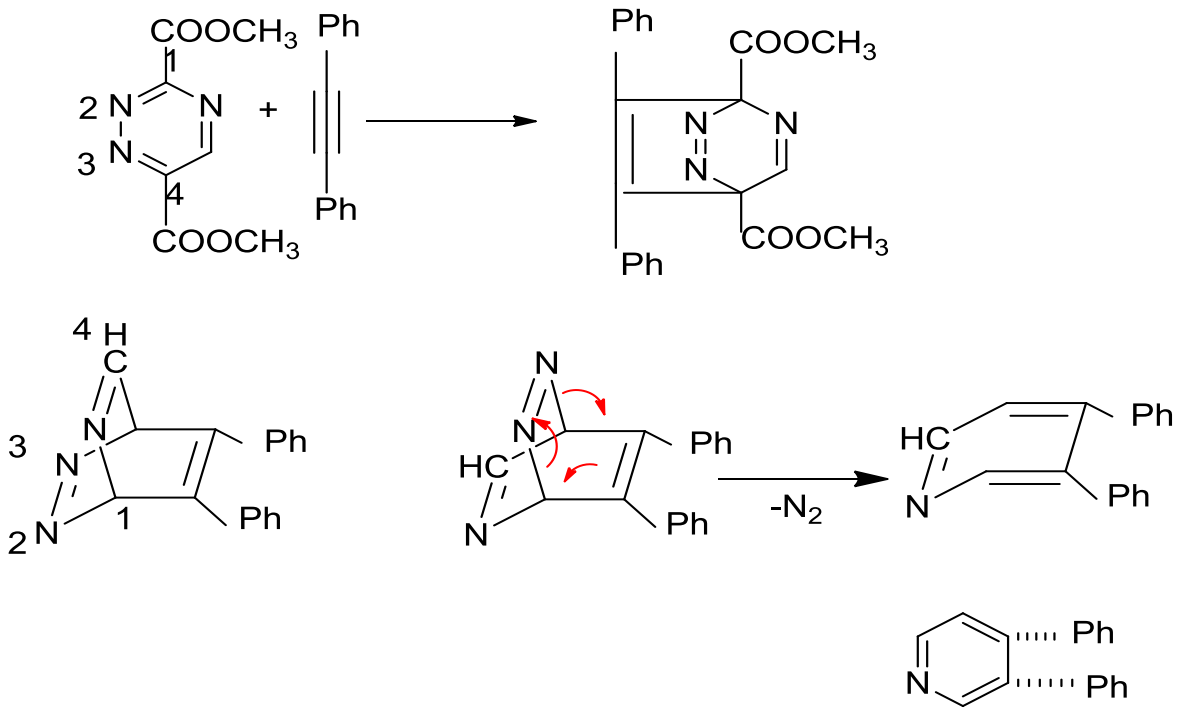




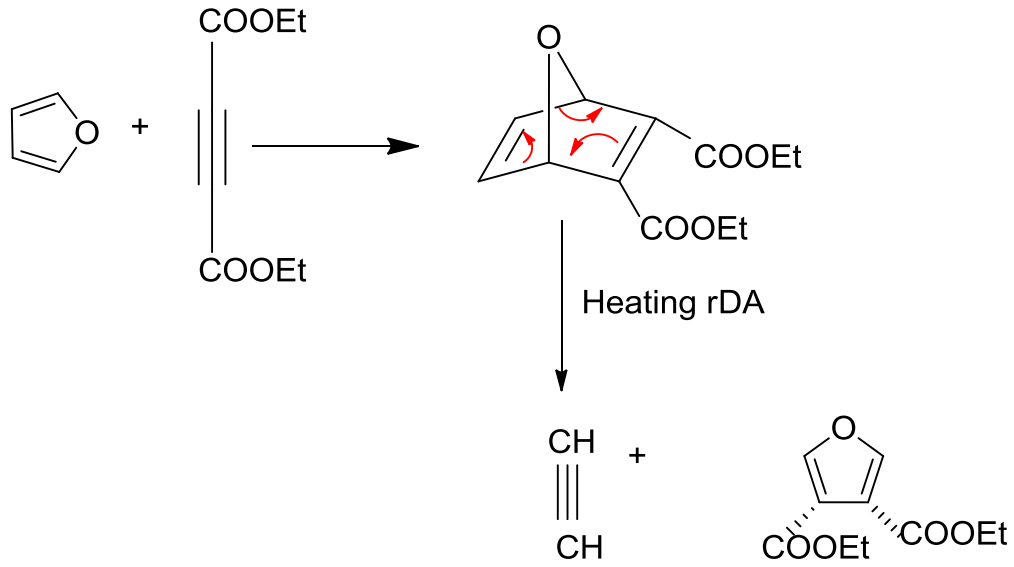




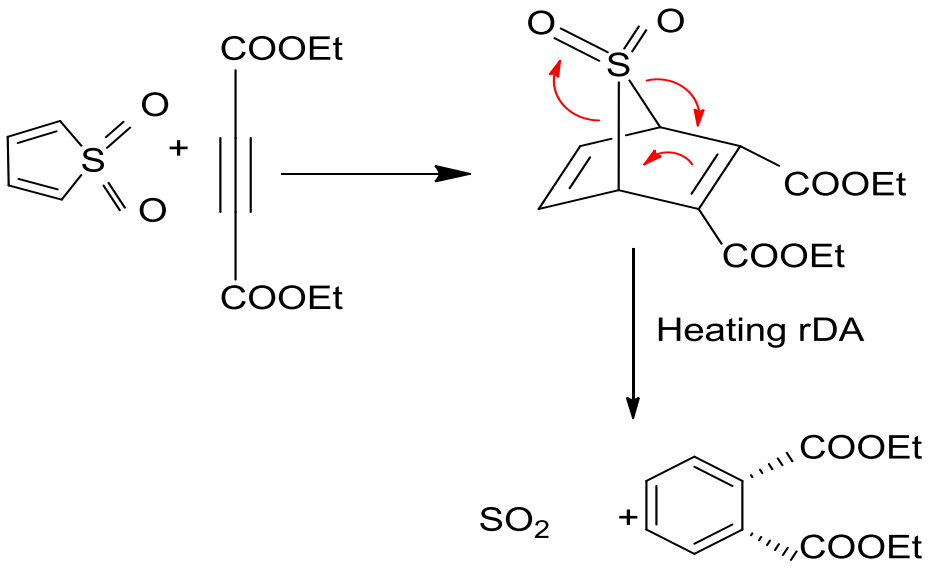
Case 1: CO_2 is eliminated



Case 2 : Acetylene is eliminated.



Case 3 : SO_2 is eliminated



References:

1. Clayden, Greeves, Warren and Wothers., Organic chemistry, 2nd Edition, Oxford University, 2012.

2. J. March's Advanced Organic Chemistry Reaction, Mechanisms and Structure, Wiley 2007.

3. Guo-Qiang Lin, Yue-Ming Li, Albert S.C. Chan., Principles and applications of Asymmetric synthesis,John Wiley 2001.

4. Finar I. L., Organic Chemistry, 6th Edition, Pearson Education Asia, 2004.

5. Carey F. A., and Sundberg R. J., Advanced Organic Chemistry Part-A and B, 5th edn, Springer Publishers 2007.

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SCHOOL OF SCIENCE & HUMANITIES

DEPARTMENT OF CHEMISTRY

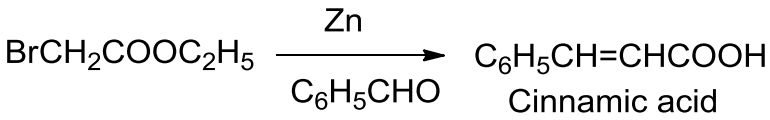
UNIT – IV - ASYMMETRIC SYNTHESIS –II – SCYA7302

UNIT 4

ASYMMETRIC SYNTHESIS –II

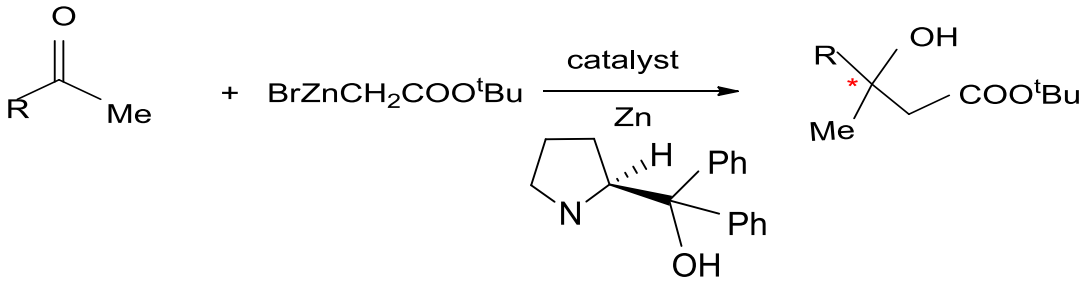
4.1 Asymmetric Reformatsky Reaction

It is a crossed condensation reaction leads to aldol type products. It involves the addition of organozinc reagent to the carbonyl group of an aldehyde or ketone. The raection extends the carbon skeleton of an aldehyde or ketone with a reaction of α-bromoester with carbonyl compound to form β-hydroxy ester. The organozinc reagent is less reactive, hence nucleophilic adddition to the ester goup does not occur.



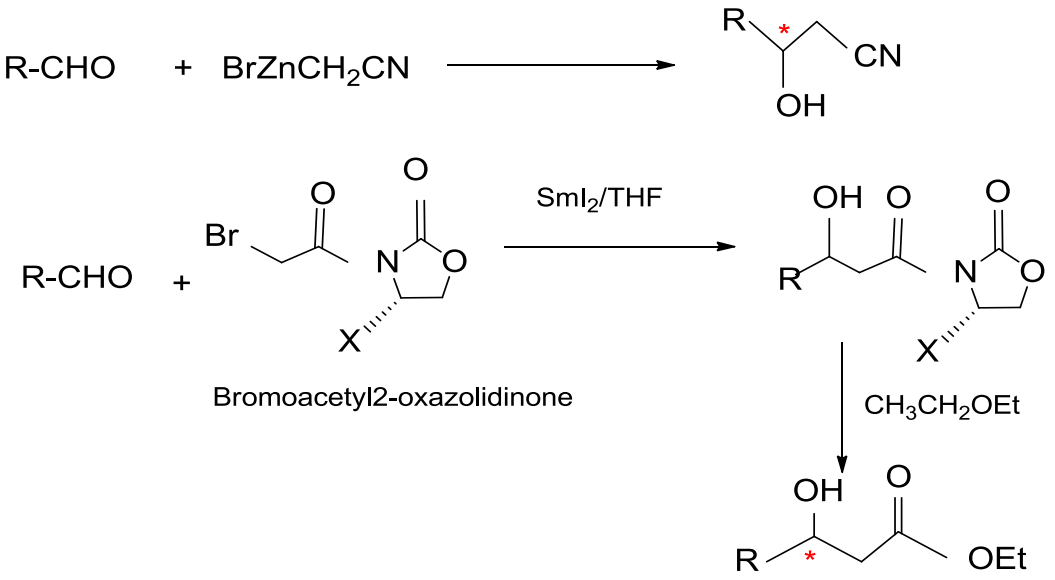
Mechanism:

The ester enolate anion is first formed which act as a nucleophile to attack a ketone or an aldehyde. The reaction is not pH dependent since the enolate attacks the ketone more rapidly compared to its ester precursor.



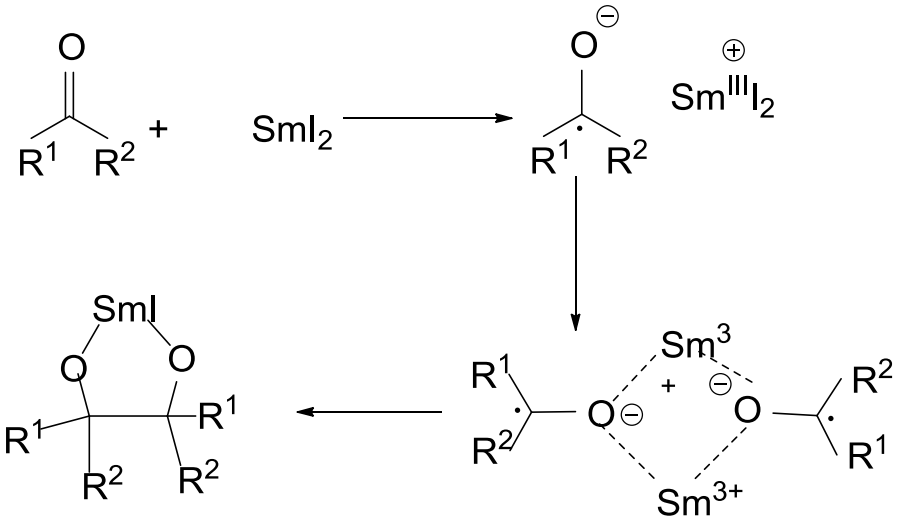
Eg:1 Asymmetric synthesis of Chiral aldol using SmI_2

Samarium Iodide (SmI_2) exerts a good chelation with an oxygen moiety in the enolate and this results in highly stereoselective intra or intermolecular 1,2 or 1,3 asymmetric induction. SmI_2 mediates intermolecular Reformatsky reaction using α-bromoacetyl-2-oxazolidinone as the chiral auxillary. The reaction is highly diastereomeric excess (de) for straight high aldehydes. The following reaction gives a stereomeic hydroxy esters with de of >99%.



Mechanism:

The catalyst SmI2 forms chelate moiety with the ketone or the enolate of the ester to form 5-membered intermediate compound which then attacks the aldehyde to from the hydroxy ester.



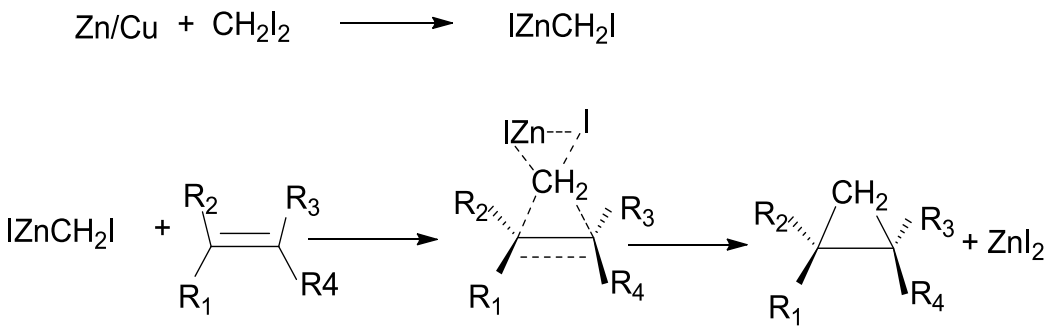
4.2 Double Asymmetric Cycloaddition (Cyclopropanation)

Simmons-Smith Reaction

Conversion olefin to a cyclopropane ring structure using Zn/Cu couple and CH_2I_2 in ether. The reaction involves reaction of a double bond compound with diiodo methane and

Zn-Cu couple, the attacking species is an organozinc intermediate (ICH_2ZnI), a carbene like species called carbenoid. It behaves like a singlet methylene and reacts with alkene stereospecifically in a sinle step (concerted step) to form cyclopropane derivatives.

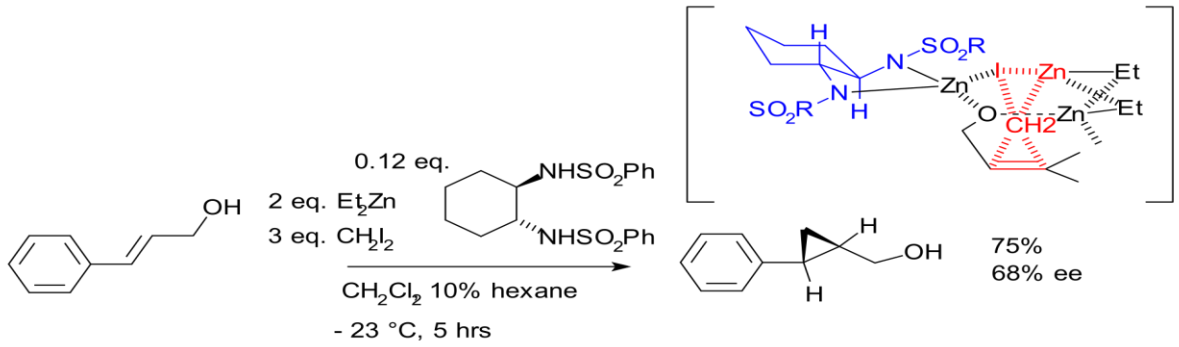
Instead of Zn/Cu couple, diethyl zinc is used the reaction is known as Furukawa modification.



Reactions:

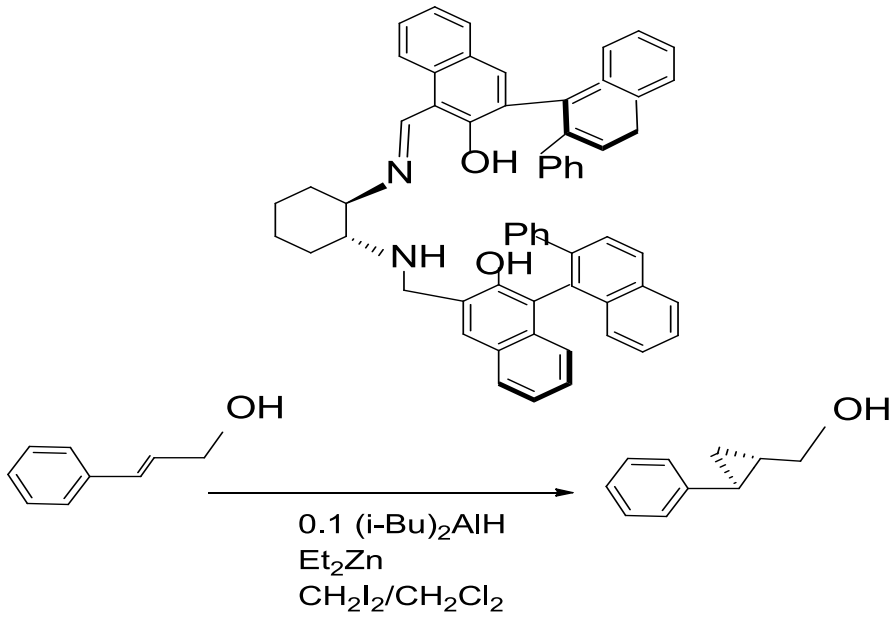
Eg:1 Cinnamyl alcohol with chiral Bis sulphanoamide in dichloromethane.

The chiral bis sulphanoamide catalyzed cyclopropanation of allylic alcohol. The free hydroxyl group of allylic alcohol is necessary for producing a chiral environment with the carbenoid promoting the complexation as alkoxide to form cyclopropane ring structure.



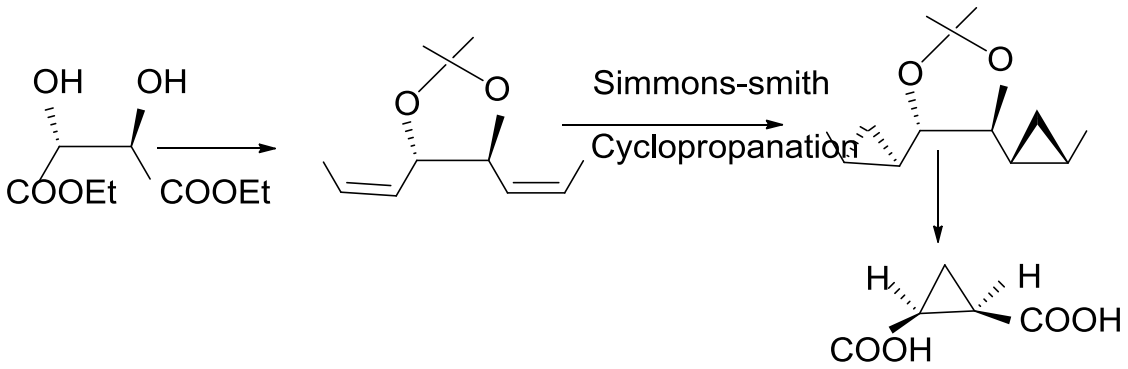
Eg:2 Cinnamyl alcohol with DIBAL and salen ligand

The free hydroxyl group of allylic alcohol complexes with the carbenoid structure and at the same time with Al from DIBAL and Nitrogen from Salen promoting the formation of enantiomeric excess cyclopropane ring structure.



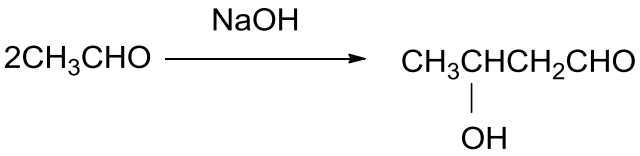
C) Double asymmetric cyclo propanation:

The curacin, antimitotic drug consists of thiazoline bearing a chiral cyclopropane ring containing a carboxylic ring is obtained diester tartrate by asymmetric induction processs.

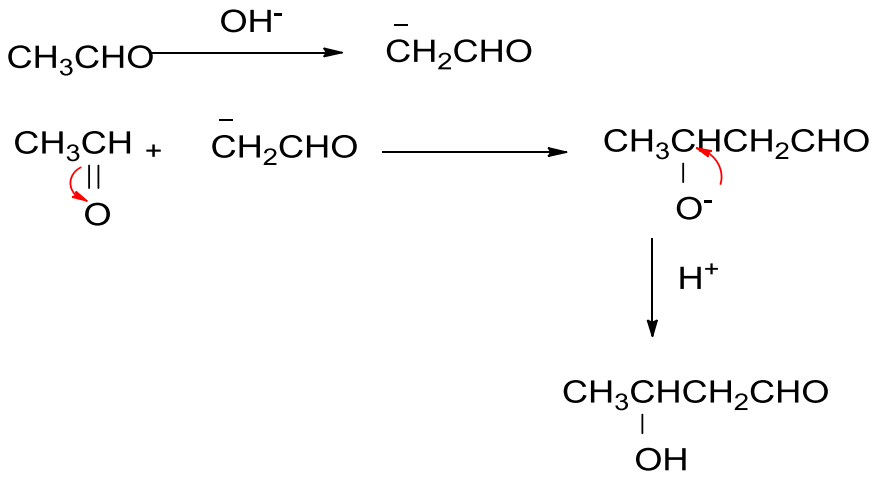


4.3 Aldol Condensation

4.3.1Base Catalyzed: The enolate adds to carbonyl compound to form β-hydroxycarbonyl compound.



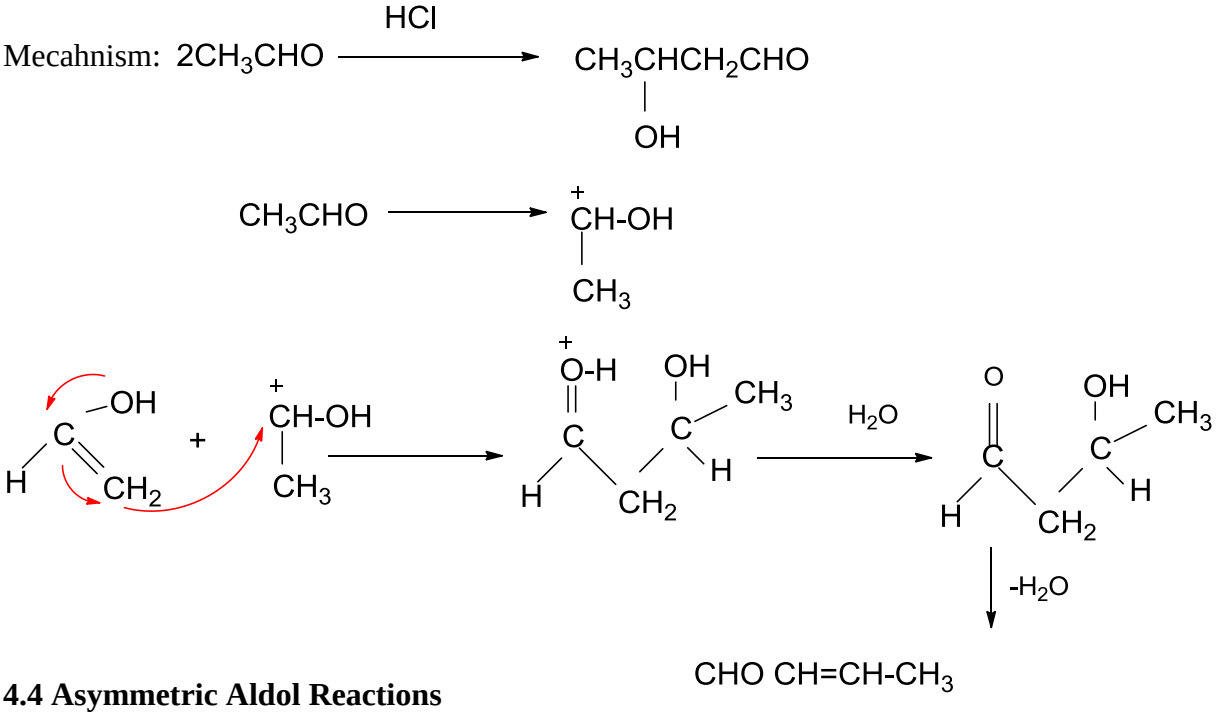
Mechanism:



4.3.2 Acid Catalyzed Reactions:

Aldehyde is pronated and adds to the enolate to form β-hydroxycarbonyl compound which undergoes de hydration to form α,β-unsaturated carbonyl compound

Mecahnism:



4.4 Asymmetric Aldol Reactions

It refers to the condensation of a nucleophile enolate species with an electrophilic carbon moiety to form C-C bond. The relative syn/anti as well as R/S configuration is achieved by metal counter ions, ligands binding through these metals.

Types:

Substrate controlled; Reagent controlled; Double asymmetric

a) Substrate Controlled reactions:

Addition of chiral enolate (or allyl metal reagent) to a chiral aldehyde (chiral centre at α position). Diastereoselectivity is determined in the transition state by Cram-Felkh-Ahn model. Chiral enolates are formed by chiral auxillaries in the form of esters, acyl amides, imides or boron enolates.

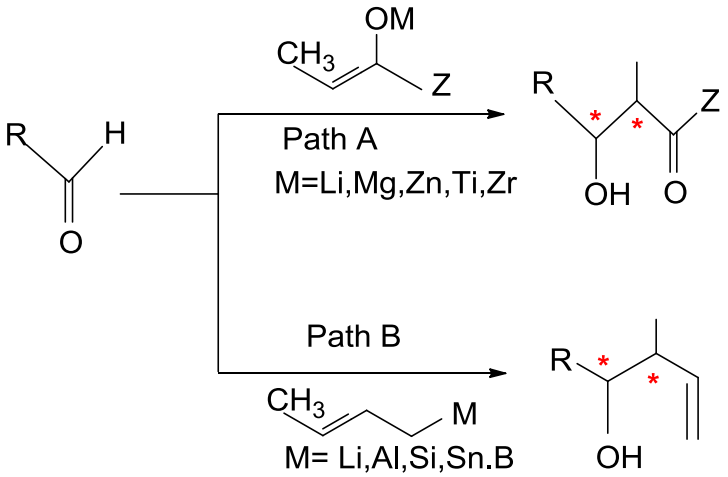
b)Reagent Controlled Reactions:

Addition of chiral or allyl reagent to an achiral aldehyde.

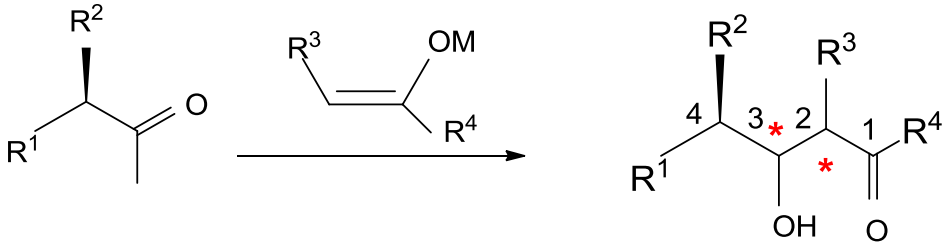
c) Double asymmetric Reactions:

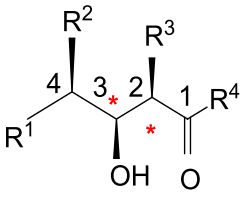
Addition of a chiral enolate or allyl metal reagent to a chiral aldehyde. Enhanced stereoselectivity can be obtained when both the aldehyde and the reagent exhibit complementary facile addition.

General Mechanism:

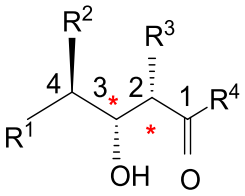


Aldol reaction of an aldehyde with metal enolates creates two new chiral centres in the product to form 4 possible stereoisomers.

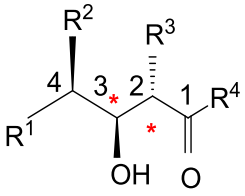




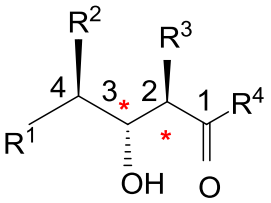
2,3-syn-3,4-syn



2,3-syn-3,4-anti

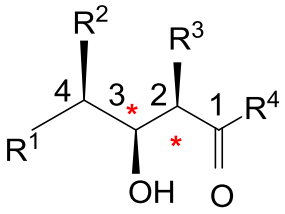


2,3-anti-3,4-syn

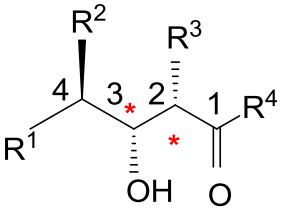


2,3-anti-3,4-anti

Z enolates results in syn aldol

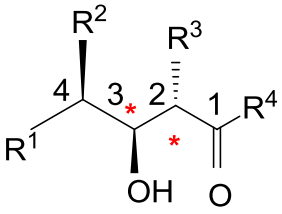


2,3-syn-3,4-syn

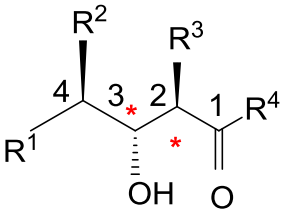


2,3-syn-3,4-anti

E enolates leads to anti aldol



2,3-anti-3,4-syn



2,3-anti-3,4-anti

When the enolate attacks the aldehyde in a re attack it forms 2,3-syn 3,4 syn and 2,3 anti 3,4 syn while with si attack it forms 2,3 syn 3,4 anti and 2,3 anti 3,4 anti.

Stereochemistry is achieved by

- Proper size of the substrate moiety in the enolate
- Proper choice of the reagent
- Conditions for enolization

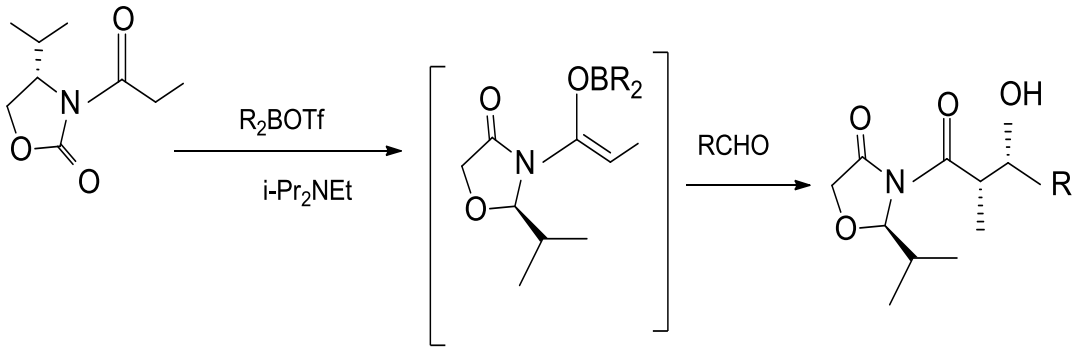
4.5 Substrate Controlled Aldol Reactions:

Addition of chiral enolate (or allyl metal reagent) to a chiral aldehyde (chiral centre at α position). Diastereoselectivity is determined in the transition state by Cram-Felkh-Ahn

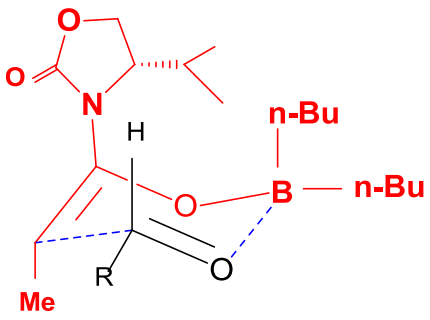
model. Chiral enolates are formed by chiral auxillaries in the form of esters, acyl amides, imides or boron enolates.

Eg.1:N-acyl oxazolidones:

Z-boron enolates are prepared from N-acyl oxazolidones on reaction with din-butyl boron trifilate and triethyl amine in CH_2Cl_2 at -78°c . N-acyl oxazolidones known as Evans auxiliaries undergoes aldol reaction to form syn aldol.



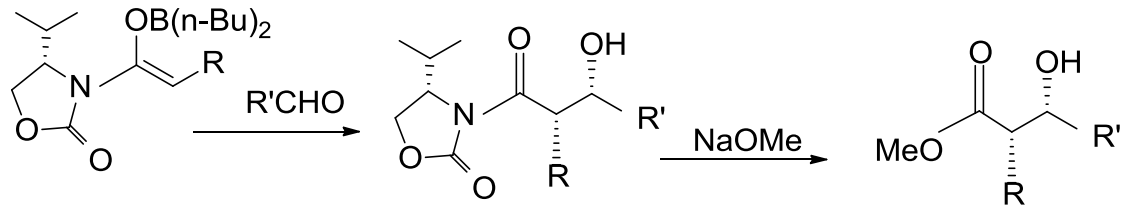
The structure of the transition state is the bidendate chealtion of the boron with the oxazolidine carbonyl and the enolate oxygen via chair type transition state.



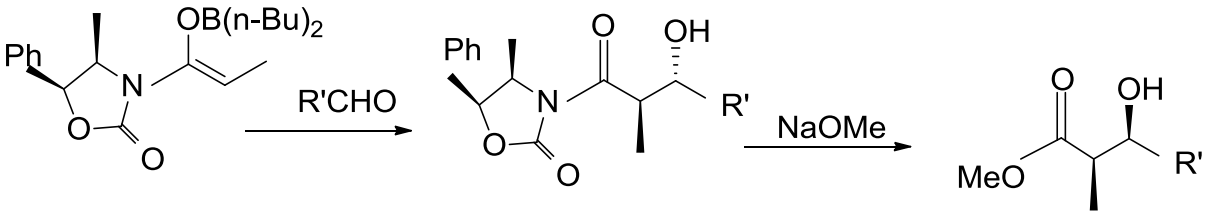
Reactions:

N-acyl oxazolidines and phenyl substituted acyl oxazolidines on reaction with aldehyde forms only a syn-aldol. The stereochemistry of the product is dependent on the enolate structure and boron and steric effect on N-acyl oxazolidines doesn't have any effect.

a)

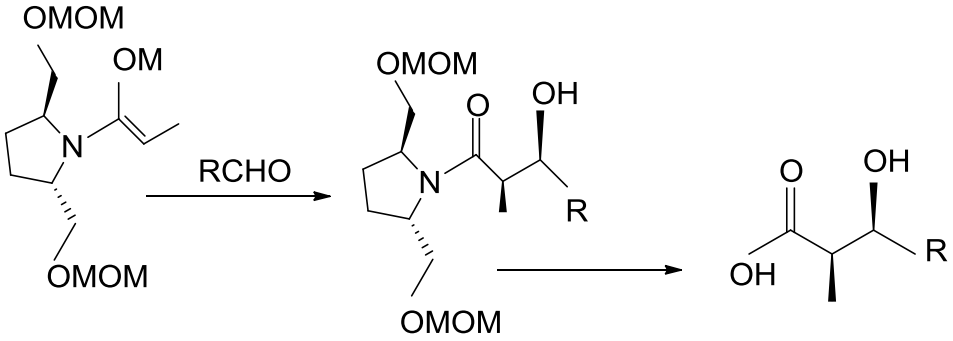


b)

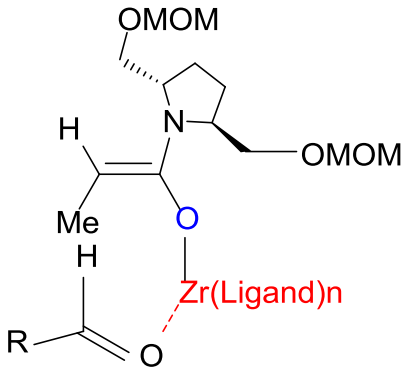


Eg.2: Pyrrolidines Reactions:

Trans-2,5 disubstituted pyrrolidine with zirconium enolate exhibits high stereoselectivity and it is obtained by reaction of lithium enolate with Zirconium salts by ion-exchange reactions.

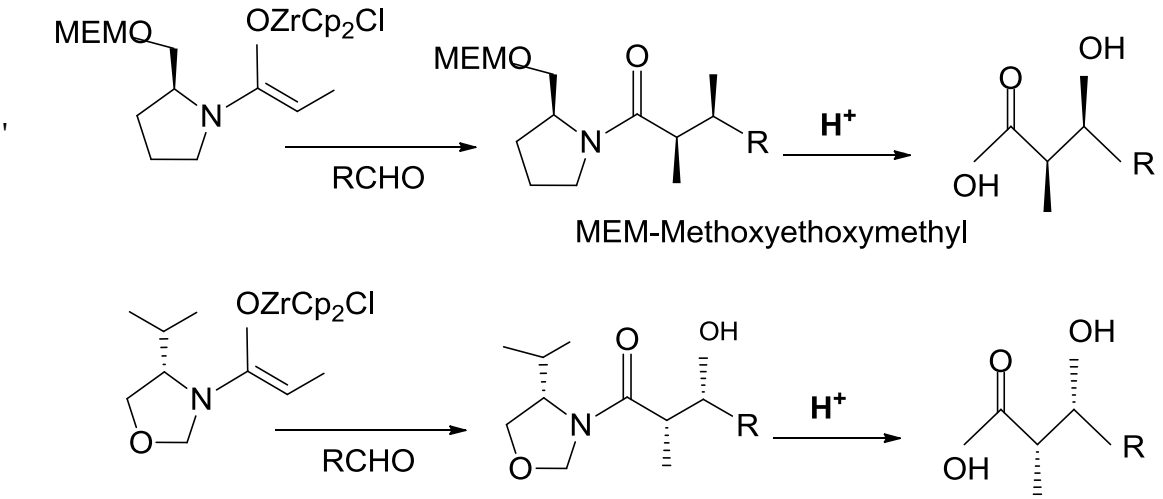


The structure of the transition state is, with MOM is methoxymethyl ether in which the Zr-bearing bulky ligand is located at the bottom hemisphere with respect to the plane of Z-enolate. The aldehyde co-ordinates with Zr atom and approaches at the same side adopting a chair like transition leading to the formation of erythro/syn aldol.



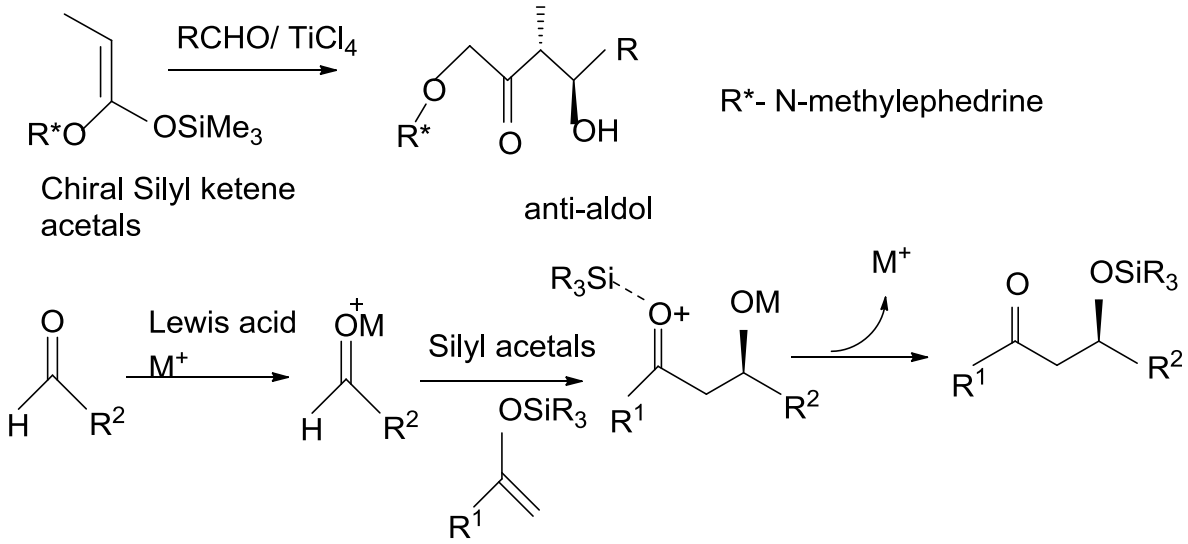
Eg.3 Proline Reactions:

Effective chiral reagents of proline amides with zirconium enolate is obtained from the corresponding lithium enolate with metal exchane reactions of Cp_2ZrCl_2. Diastereoselectivity is achieved by zirconium complex to form syn aldol.

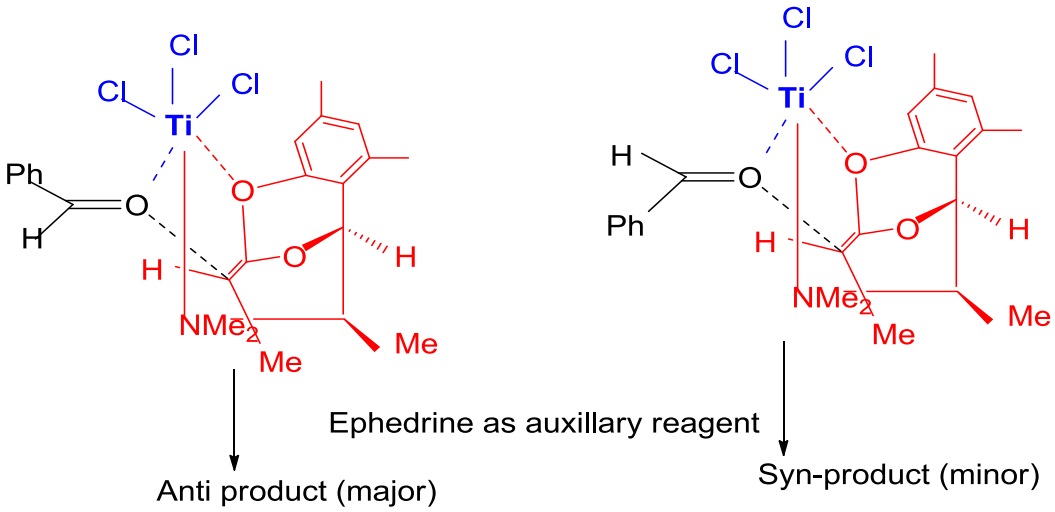


Eg.4 Silyl Ketene acetals: Mukaiyama aldol reaction

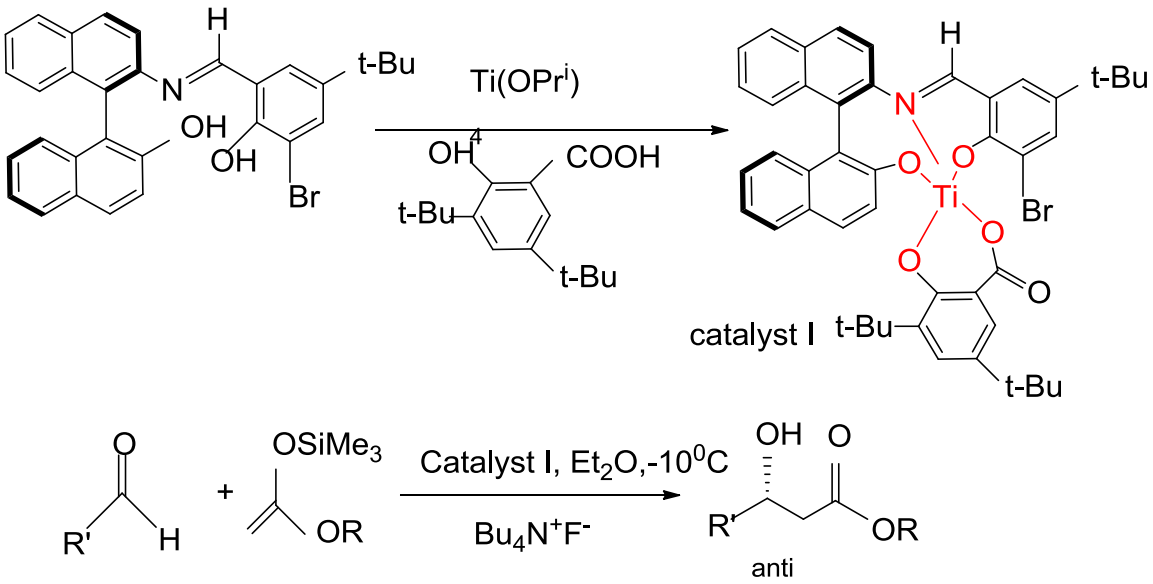
The reaction of silyl enol ether with an aldehyde in the presence of $TiCl_4$ gives a condensation product, aldol via atransition state with aloss of chlorotrimethyl silane. The aldehyde approaches the enol silyl ether in the metal centered transition state resulting in the formation of anti-aldol.



The transition state for Mukaiyama aldol reaction is where the ciral enol of silyl ketene acetals, aldehyde and ephedrine group binds to TiCl4 by two-electron donating to form cis-ocathedral six-co ordinated complexes. The formation of C-Cbond on the six-co-ordinated metal is highly stereoselctive in nature. The titanium is co-ordinated with oxygen from both the aldehyde and the alkene enol ether resulting in the formation of anti- aldol as the major product.



The asymmetric aldol reaction id performed with the addition of aldehyde to ketene acetals with high selectivity in the presence of 3,5-di-t-butyl salicyclic acid as the ligand for $TiCl_4$.

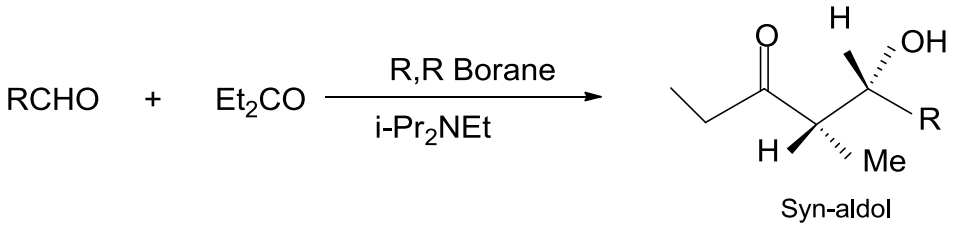


4.6 Reagent Controlled Aldol Reactions:

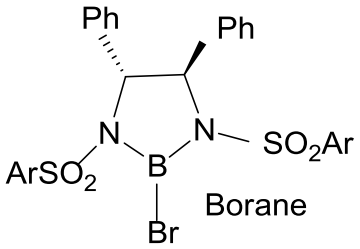
Addition of chiral or allyl reagent to an achiral aldehyde.

Eg.1 Chiral aryl borane –Corey's reagent

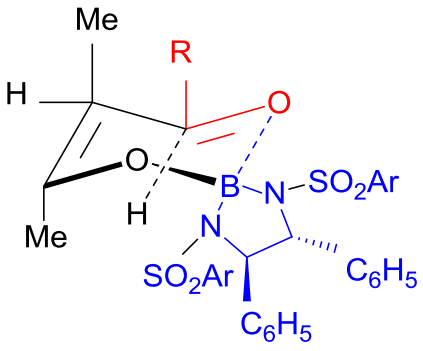
A solution of allyl tributyl tin with borane auxiliaries results in a chiral allyl borane which reacts with aldehydes to form allyl alcohols with high stereoselectivity. Chiral borane reacts with aldehyde and ketone to form syn aldol.



The structure of the catalyst borane which act as a chiral auxiliaries.

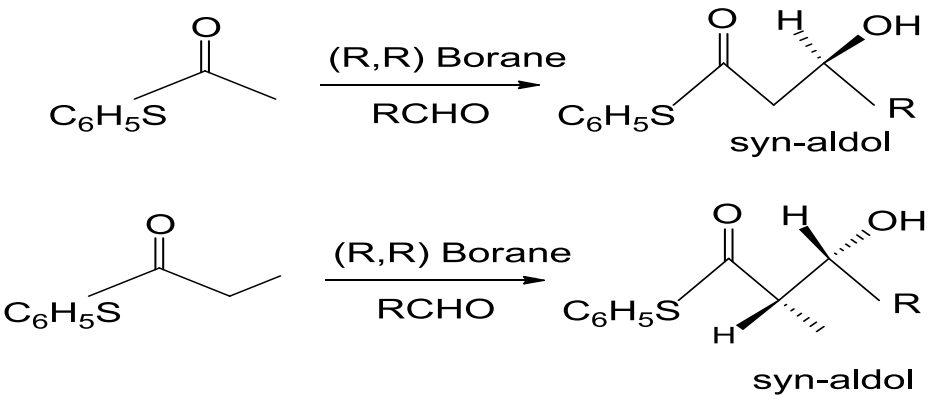


The structure of the transition state is the phenyl group of the borane forces the vicinal N-sulfonyl substituent to occupy the face of the five-membered ring opposite to the position where it is linked. The spatial position of the chair-like transition state favours for the syn-aldol formation.

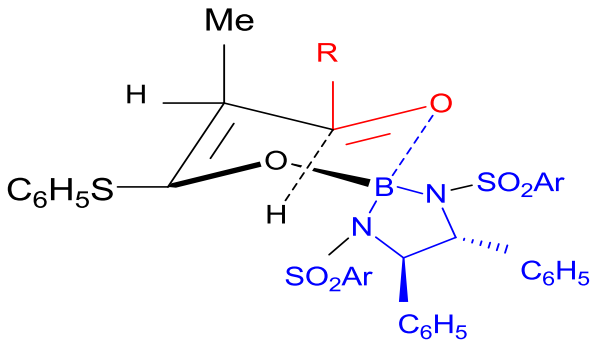


a) Reaction with phenyl thioacetate :

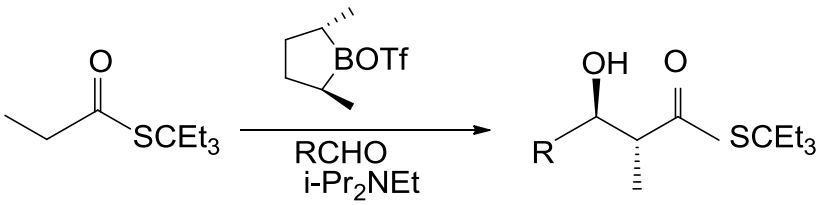
The reaction proceeds with the formation of syn aldol with either phenyl thioacetate or higher substituted thioacetate.



The structure of transition state is similar to that for ketone here the presence of phenyl thio in the chair -like transition state doesn't alter the stereochemistry of the borane resulting in the formation of syn-aldol.



b) Miscellaneous Reactions:



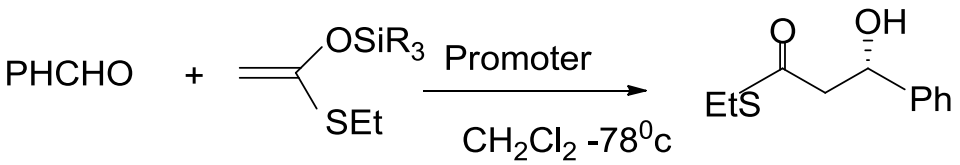
4.7 Catalyst Controlled Aldol Reactions:

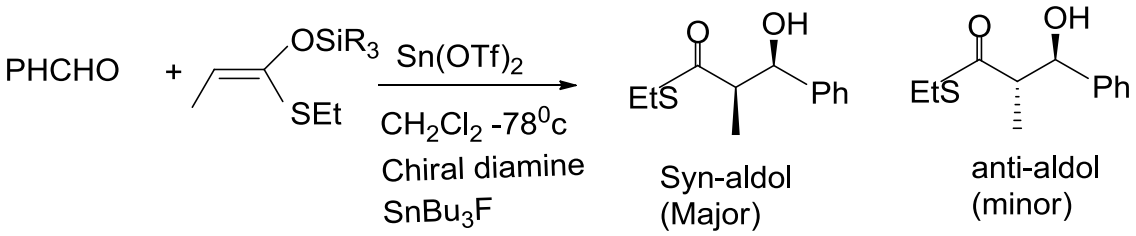
The reaction of achiral aldehyde and enolate takes place in the presence of an chiral environment, catalyst.

Eg.1 Mukaiyama reactions:

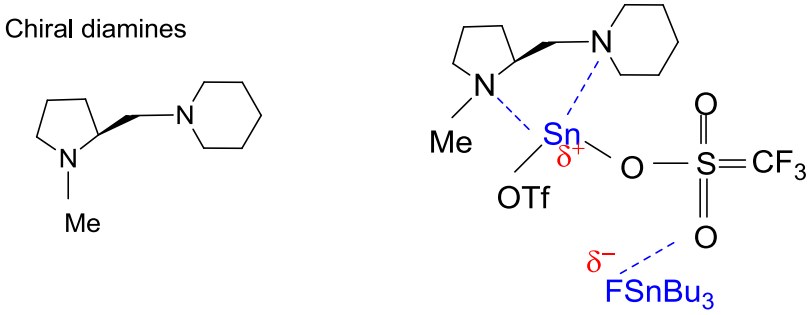
Tributyl tin fluoride, stannous difilate are more effective catalyst for asymmetric aldol reactions. Tin diflate is treated with chiral diamines as catalyst promoter followed by the

reaction of aldehyde and silyl enol ether in the presence of tributyl tin fluoride to form syn aldol



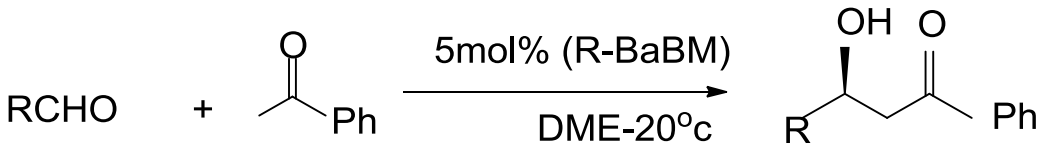


The promoters are chiral diamines and the structure of transition state is formed with rspect to tin. The divalent tin has vacant 'd' orbitals which form complexes with two nitrogen atoms of the chiral amines leaving one vacant d orbital to be co-ordinated with an aldehyde. The cationic centre of Sn(II) activates the aldehyde at the sametime the electronegative fluoride interacts with the silicon atom of the enol ether (not shown) to make it highly reactive. The dual process results in the formation of entropically favoured intermediate, ultimately leads to syn-aldol.

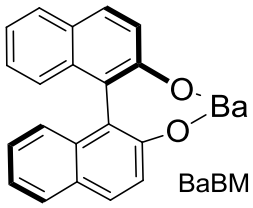


Eg.2 Shibasaki's system –

Bimetallic system (BM) is formed from binaphthol and barium salts to form Shibasaki system (BaBM) which is a far superior catalyst for direct aldol reaction.



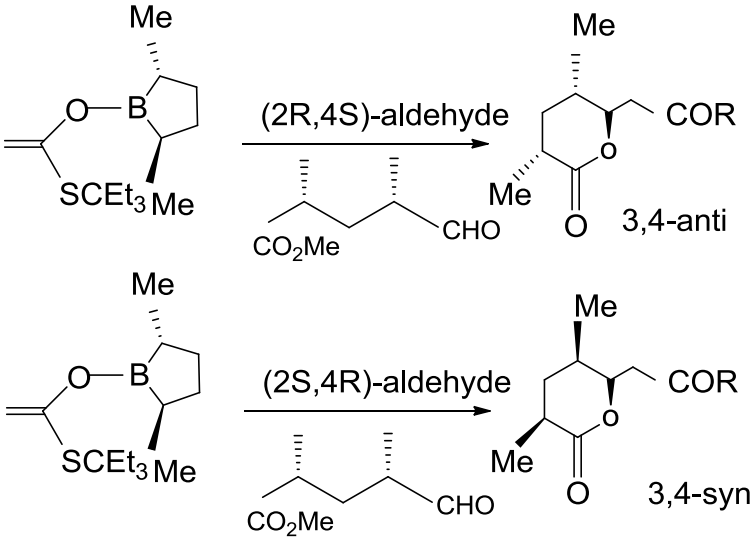
The catalyst is BaBM, contains a lewis acid centre to activate and control the orientation of the aldehyde and lewis base centres favourinf for the addition of ketone to form aldol.



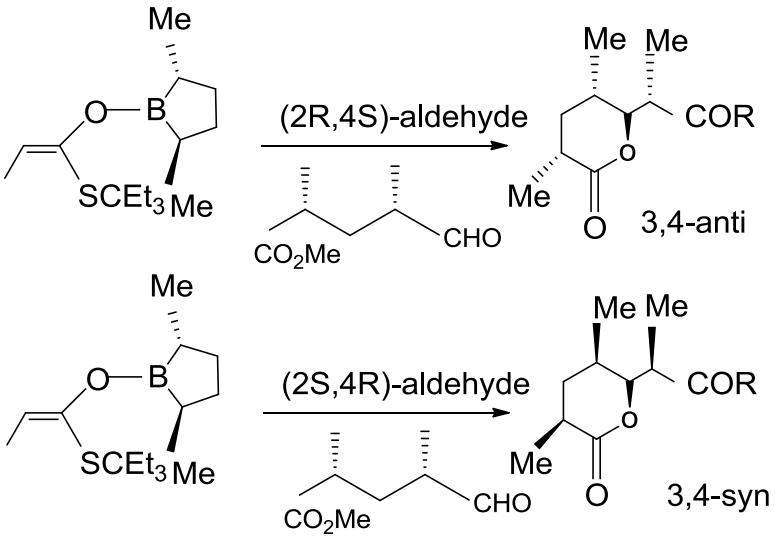
4.8 Double Asymmetric Aldol Reactions

Addition of a chiral enolate or allyl metal reagent to a chiral aldehyde. Enhanced stereoselectivity can be obtained when both the aldehyde and the reagent exhibit complementary facile addition. Reaction of a chiral compound with achiral enolate to form a diastereomeric product.

The interaction of chiral aldehyde with ciral enoalte forms a stereoselective aldol. The reaction of chiral enolate with 2R and 4S aldehyde results in anti- aldol. On changing the chirality of the aldehyde to 2S and 4R reverse the results to form syn aldol. High stereoselectivity is achieved in double asymmetric aldol reactions.

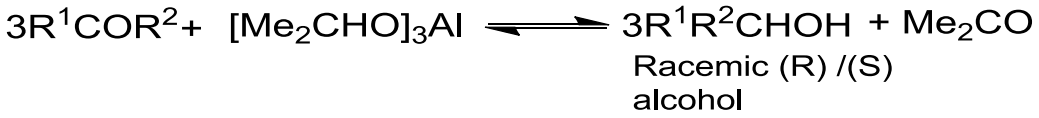


The reaction is further investigated with methyl substituted chiral enolates. the reaction of the enolates with 2S and 4R forms anti-aldol with the change in the chiralityof the aldehyde in case of methyl enolates the reuslts are reversed with the formation of syn-aldol.

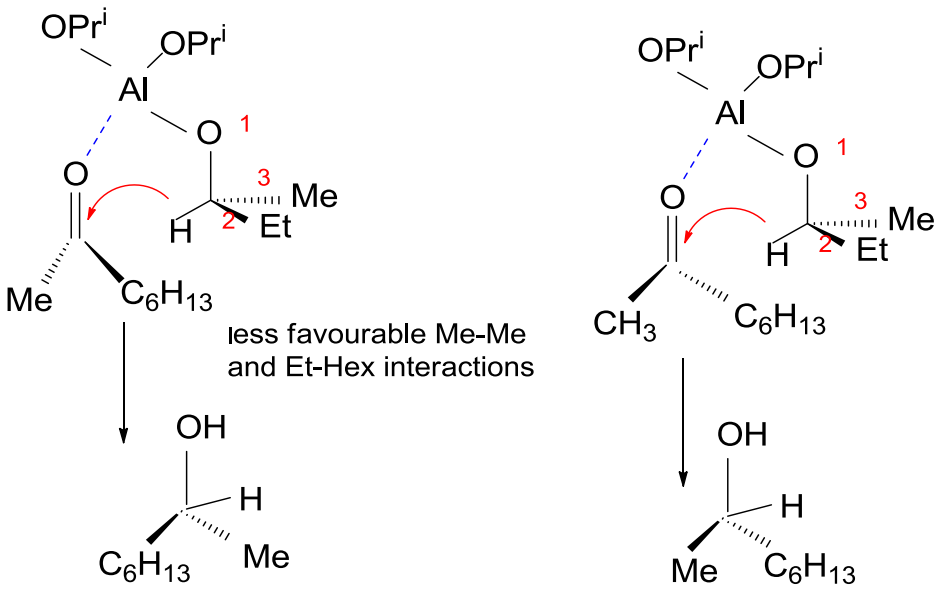


4.9 Asymmetric Transfer Hydrogenation: (Meerwein-Poondorf-Verley Reaction)

Meerwein-Poondorf-Verley reaction-reduction of carbonyl to alcohols in aluminium isopropoxide in isopropanol medium. Transfer of hydride ion from the isopropoxide to the carbonyl compound takes place by a six-membered cyclic transition state. Inthis reduction, the hydride ion is donated by carbon unlike a metal hydride.

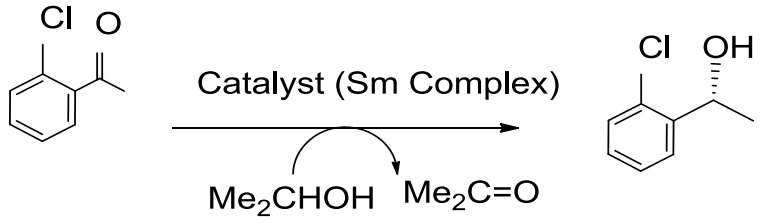


The Diastereomeric transition state

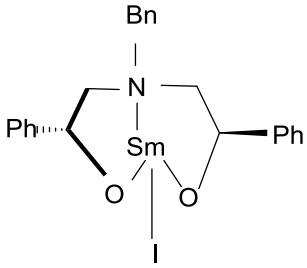


Eg:1 Using Sm(III) complex:

The asymmetric transfer hydrogenation of ketones using Sm (III) complexe at ambient temperature in 2-propanol is given with the Sm co-ordinated between Nitrogen and Oxygen

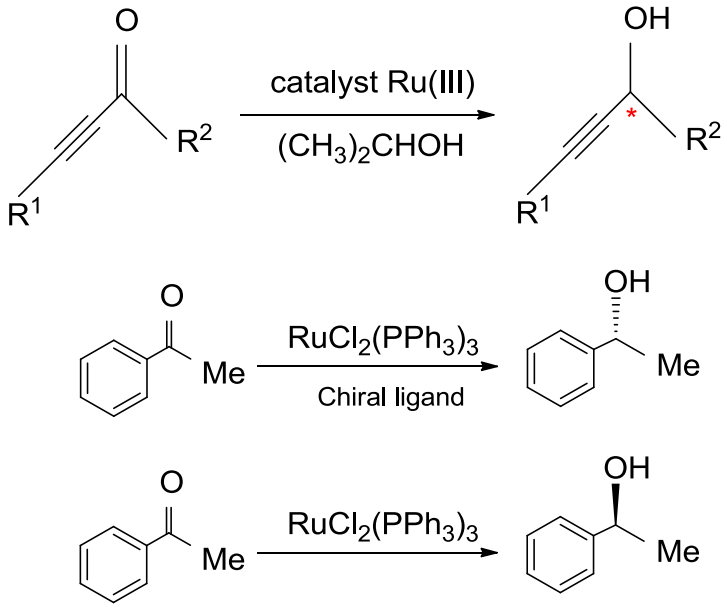


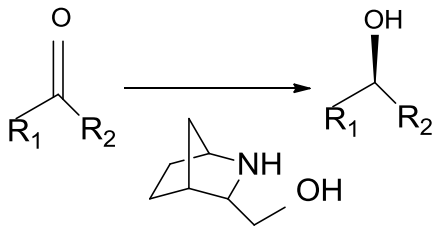
The Sm(III) complex with oxygen and nitrogen functional groups containing molecules



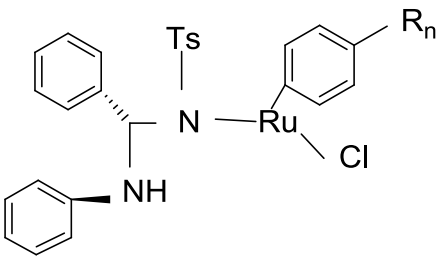
Eg:2 Using Ruthenium catalyst:

Asymmetric transfer hydrogenation is highly efficient for the preparation of secondary alcohols in the presence of Ru-based catalyst at room conditions. the reaction can be completed within 5 minutes. The conversion is achieved using chiral Ru(II) complex as the catalyst and 2-propanol as the hydrogen donor. Some of the examples of the reaction is given below.



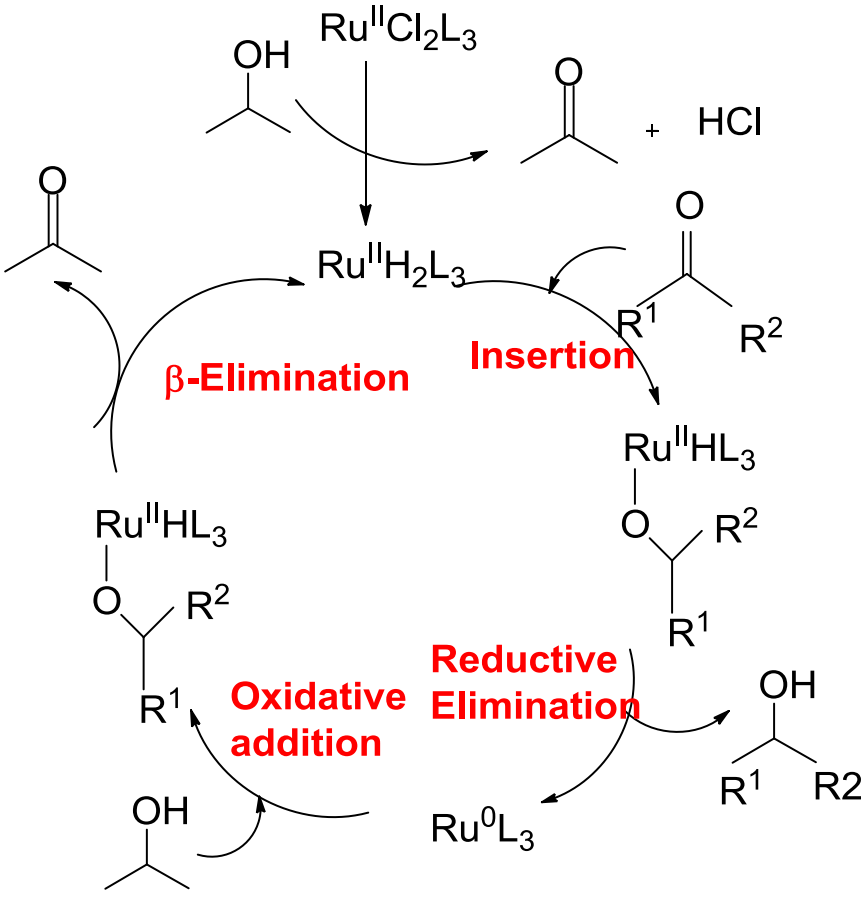


The structure of the catalyst is



Mechanism:

The mechanism takes place in four steps:



1) Insertion: The catalyst is Ruthenium(II) complex with the replacement of the chloro ligand by hydrogen of 2-propanol followed by the addition of ketone in which one of the hydrogen is realced by the ketone to form a 5-membered co-ordinated complex.

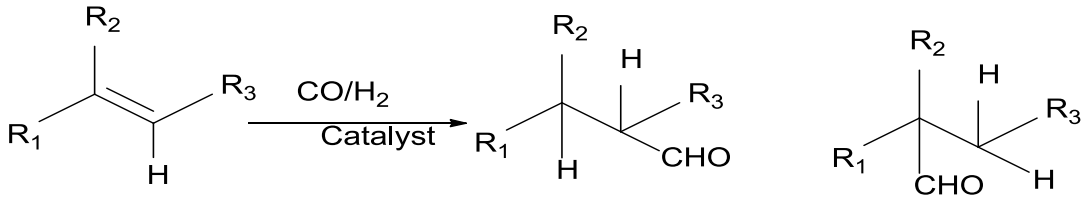
2) Reductive Elimination: In the complex, the hydride ion is transferred to the ketonic group tofrom secondary alcohol with the reduction of Ru from +2 oxidation state to zero.

3) Oxidative Addition: To recover the catalyst, the Ru is allowed to react with the solvent to form Hydrogen co ordinated complex where the oxidation state increased to +2.

4) β-Elimination: The alcoholic group is oxidized to ketone with the formation of catalyst with Ru (II) complex.

4.10 Asymmetric Hydroformylation

Optically active aldehyde play an important precursors for biologically active compounds and is achieved through hydroformylation reaction. It is a potential route to prepare enantiomeric pure aldehydes using inexpensive olefins and synthesis gas with Rh and Co catalyst.

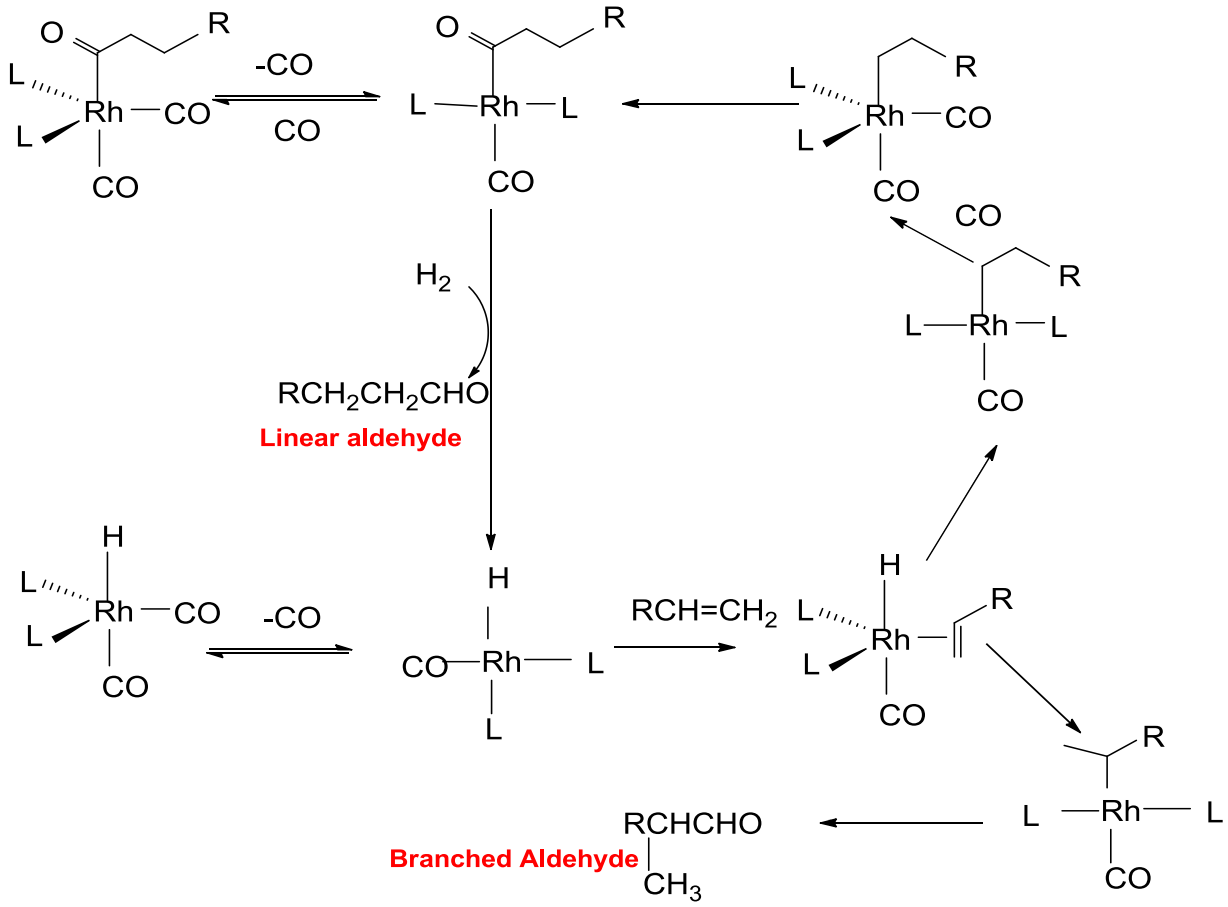


The limitations of Co catalyst is it involves high temperature and pressure which may not be desirable for industrial purposes. Rh complexes ensures regioselectivity and stereoselectivity of the reaction Regioselectivity involves the addition of hydride which converts the five co-ordinated alkene to four co-ordinated primary or secondary alkane. Chiral aldehydes are unsatble undergoes racemization which is prevented by using triethyl formate as trapping agent to produce diacetals.

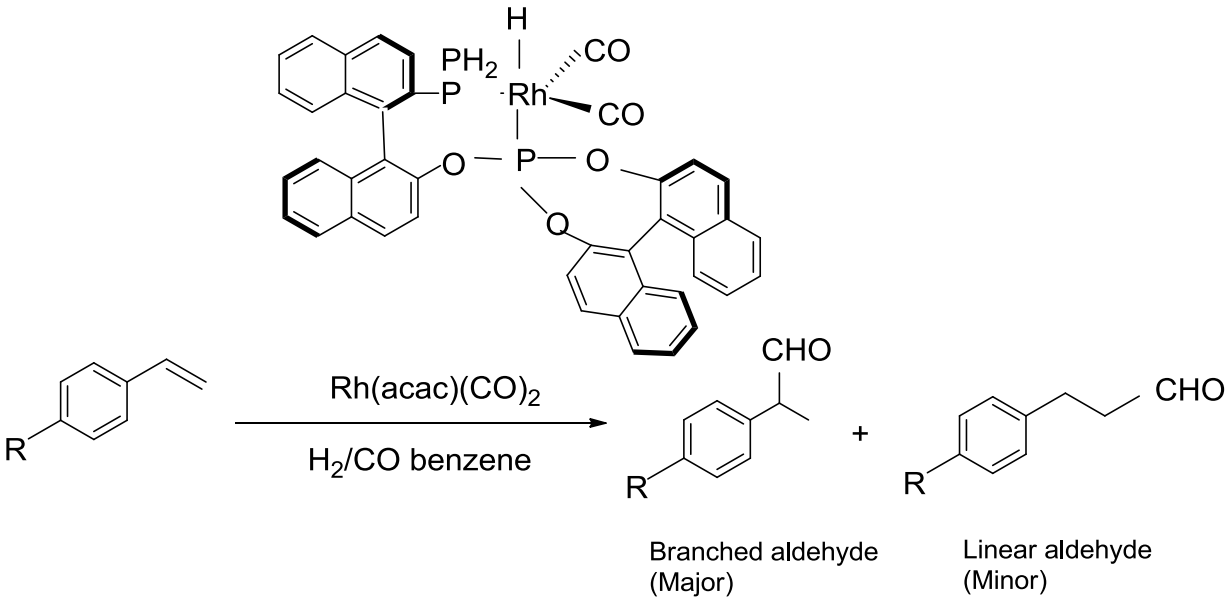
Mechanism:

The mechanism of rhodium-phosphine catalysed hydroformylation reaction is presented below. The aldehyde regioselectivity is determined in the hydride step which converts the 5-co ordinated H(alkene)-Rh-$(CO)L_2$ into either a primary or secondary 4-co-ordinated (alkyl)Rh$(CO)L_2$. The 5-co-ordinated trigonal bipyramidal bisphosphine Rh species is the most important intermediate with the two phosphine ligands occupy the twoequatorial or one equatorial and one axial position. Using a chiral diphosphine complex as the catalyst, branched aldehydes are obatined in ee. Biphosphite ligands with bulky substituents are used to produce linear aldehydes from 1-alkenes while 1, substituted alkenes forms branched

aldehydes in good yield. The presence of electron withdrawing groups affects the formation of the product with the presence of electron withdrawing groups in the two equatorial position results in the linear aldehyde while its presence in the axial positions favours the formation of branched aldehyde.



Eg.1: Styrene to form branched aldehydes in good yield than linear aldehydes.



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SCHOOL OF SCIENCE & HUMANITIES

DEPARTMENT OF CHEMISTRY

UNIT – V -Reagents in Organic synthesis– SCYA7302

UNIT 5

REAGENTS IN ORGANIC SYNTHESIS

5.0. Introduction

Organic compounds with a carbon-metal bond. CH_3Li, C_2H_5MgBr. Excludes compound where the metal atom is bonded through heteroatom.CH_3ONa. Electro negativity of carbon is 2.5 which is much higher than most of the metals which lie between 0.9-1.8.

5.1 Preparation:

(1) Electronegativity difference **($\Delta x \geq 1$)**, it can be prepared by direct reduction of alkyl halide with the metal.

$$RX + 2Li \longrightarrow RLi + LiX$$

$$RX + Mg \longrightarrow RMgX$$

(2)Electronegativity difference ($\Delta x < 1$), it can be prepared by transmetallation method – covalent nature. Electronegativity of copper is 1.8, Cd is 1.5, Zn is 1.7 and Hg is 1.5.

$$\text{Step 1} \quad RX + 2Li \longrightarrow RLi + LiX$$

$$\text{Step 2} \quad 2RLi + CdCl_2 \longrightarrow R_2Cd + 2LiCl$$

Step 1- organometallic compound of non-transition metal is prepared by direct reduction of alkyl halide with metal.

Step 2: The organometallic compound of non transition metal is allowed to react with salt of higher electronegativity.

a)Preparation of dialkyl mercury

$$RX + Mg \longrightarrow RMgX$$

$$RMgX + HgCl_2 \longrightarrow R_2Hg + MgXCl$$

b) Preparation of lithium dialkyl cupurate

$$RX + 2Li \longrightarrow RLi + LiX$$

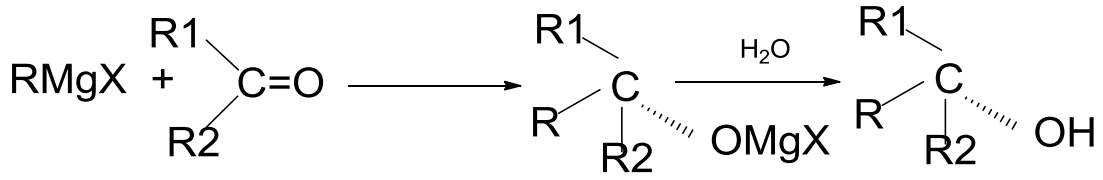
$$RLi + CuI \longrightarrow R_2CuLi + LiI$$

5.2 Chemical Reactions:

Rich source of carbanions or nucleophile: Carbon-metal bonds are highly polar due to electronegativity difference. Magnitude of electronegativity determines the polarity or ionicity of C-M bond. In Grignard reagent, R-Mg is 1.3, 52% ionic. R-Li is 1.5, 60% ionic.Highly sensitive to protic solvents, prepared in ether or aprotic solvents.

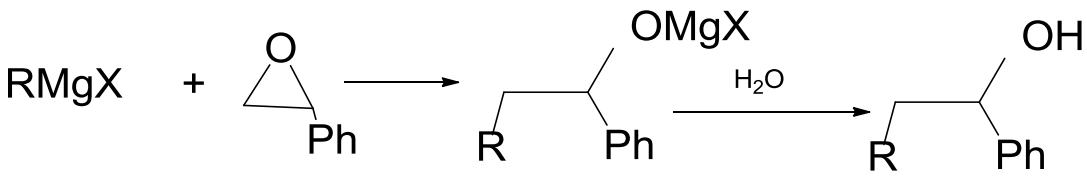
a) Nucleophilic addition:

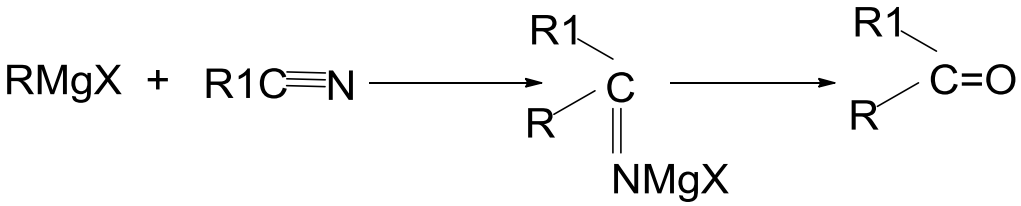
RMgX and RLi are excellent nucleophile R^- and attack the electron deficient carbon atom of many heteropolar multiple bonds to form FGI.



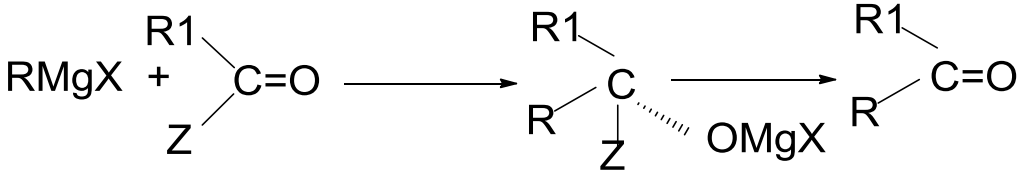
Nucleophilic addition to form tetrahedral intermediate. Adduct reacts with water to form final product.

b) Reaction of epoxide and nitrile



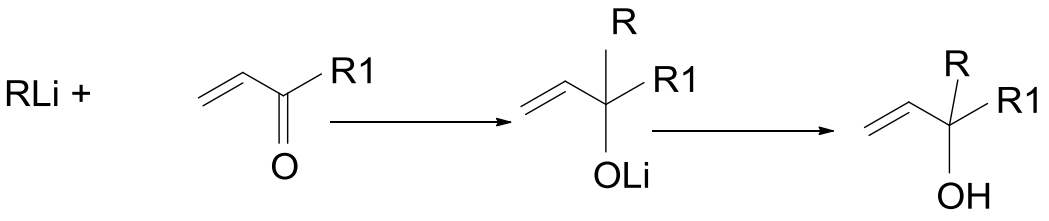


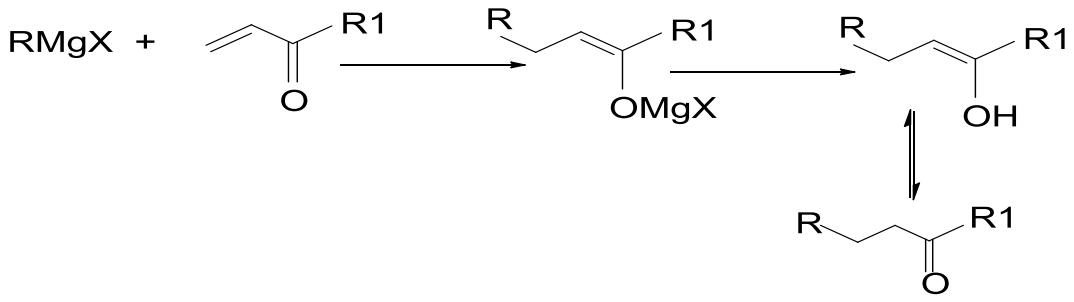
c) Reaction of acid derivatives:



d) Regioselectivity to α,β unsaturated carbonyls

Grignard reagent is covalent in nature, act as softer nucleophile attack the electron deficient β-carbon atom. RLi attacks the hard electron deficient carbonyl carbon atom,





5.3 ORGANO COPPER COMPOUNDS

5.3.1 Preparation of Gilman's Reagent:

a) Transmetallating the Grignard's reagent or organolithium.

$$MeMgBr \xrightarrow{CuCl} MeCu + MgBrCl$$

$$CuBr \xrightarrow{RLi/Et_2O\ (-78^0C)} R_2CuLi + LiBr$$

The organocopper reagents with the general formula R_2CuLi-Lithium organo cuprates or lithium dialkyl cuprates or Gilman's reagent.

b) Prepared from alkyl halide:

$$CH_3X + Li \longrightarrow CH_3Li$$

$$2CH_3Li + CuI \longrightarrow (CH_3)_2CuLi$$

5.3.2 Chemical Reactions:

a) Reactions with alkyl or aryl halides:

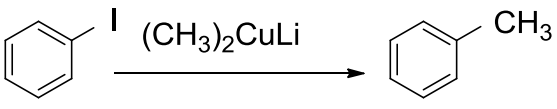
Alkyl halides: Organocuprates are able to displace halide ion from primary and secondary alkyl halides to form hydrocarbon

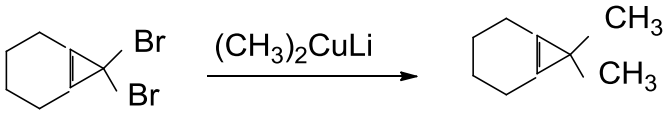
$$(CH_3)_2CuLi + CH_3(CH_2)_6CH_2I \longrightarrow CH_3(CH_2)_6CH_2CH_3$$

$$(CH_3CH_2CH(CH_3))_2CuLi + CH_3(CH_2)_3CH_2I \longrightarrow (CH_3CH_2CH(CH_3)(CH_2)_4CH_3$$

3-methyl octane

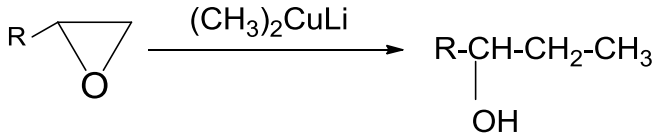
Aryl halides:



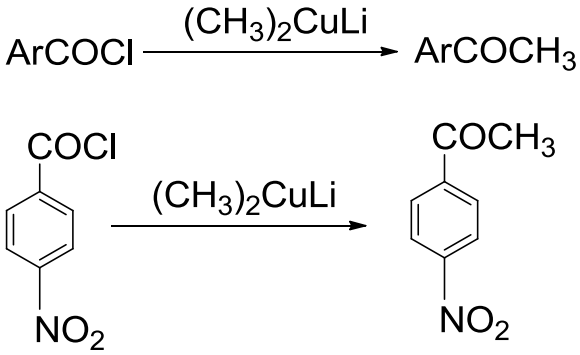


b) Reaction with epoxide:

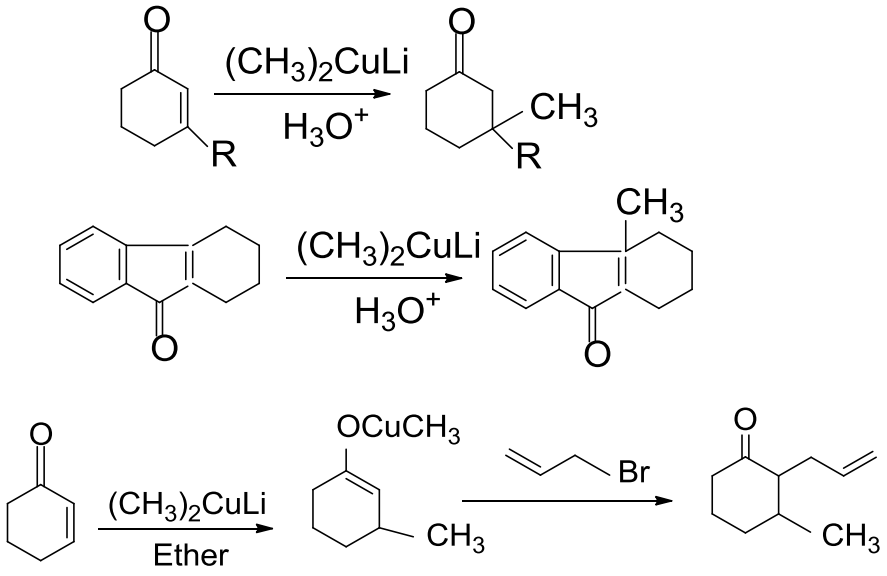
Epoxide is attacked at the least substituted carbon atom to give corresponding alcohol.



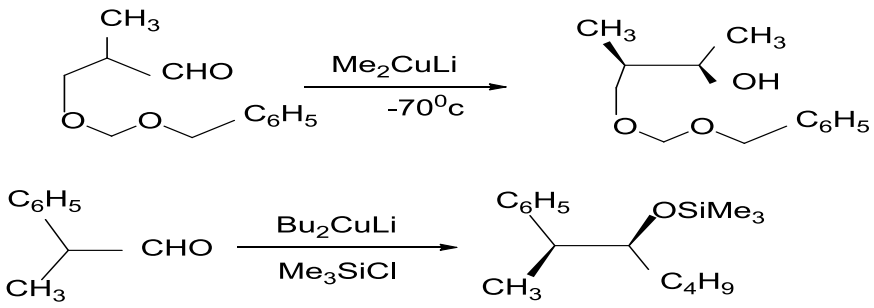
c) Reactions with Acid chloride: Forms Ketones.



d) Reactions with α,β unsaturated carbonyl compound: Conjugated addition compound - 1,4 addition product.



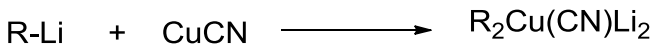
e) Reaction with aldehydes and ketones: It forms anti and syn aldol (30:1).



5.3.2 High order cuprates $R_2Cu(CN)Li_2$

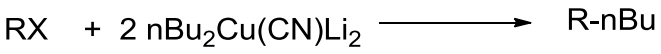
1) Preparation:

i) Reaction of organolithium with cuprous cyanide.

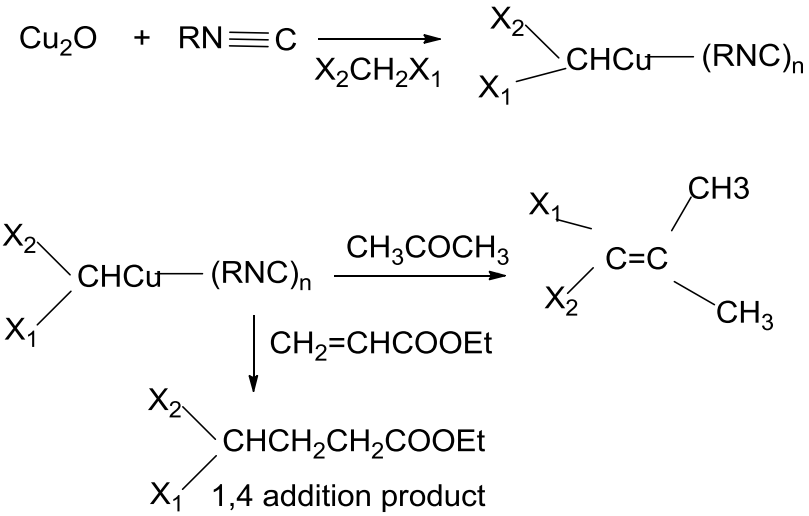


2) Chemical Reactions:

a) Alkyl halide: Reagents react faster with alkyl halides



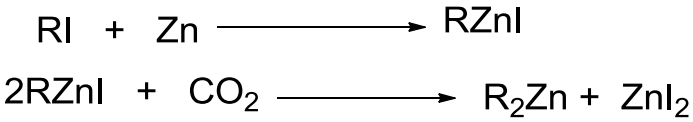
b) Active Methylene group: Copper-isonitrile complex is prepared by mixing Cu_2O with alkyl isonitrile and reacting with active methylene group



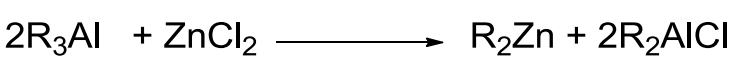
5.4 ORGANOZINC COMPOUNDS

5.4.1 Preparation

Alkyl iodide on treatment with Zn fillings followed by CO_2 distillation gives dialkyl zinc derivative.



Trialkyl aluminum on reaction with $ZnCl_2$ gives dialkyl zinc derivatives.

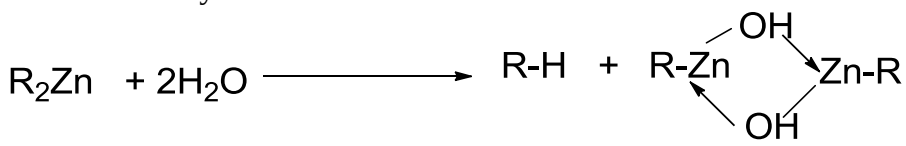


Physical Properties: Non-polar, soluble inorganic solvents, inflammable in air, less reactive than Grignard's reagent.

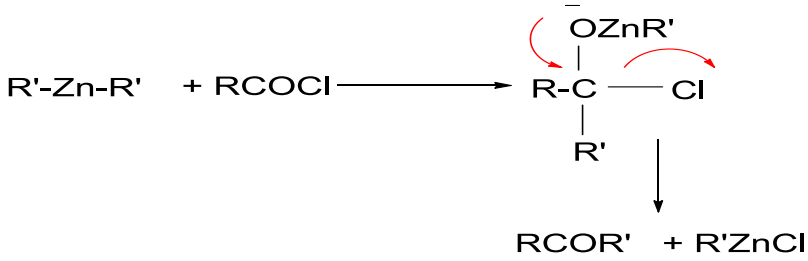
5.4.2 Chemical Properties:

a)Reactions with water:

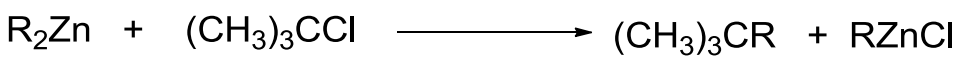
Reacts with water forms Hydrocarbon.



b) Reactions with acid chloride: It forms ketones.

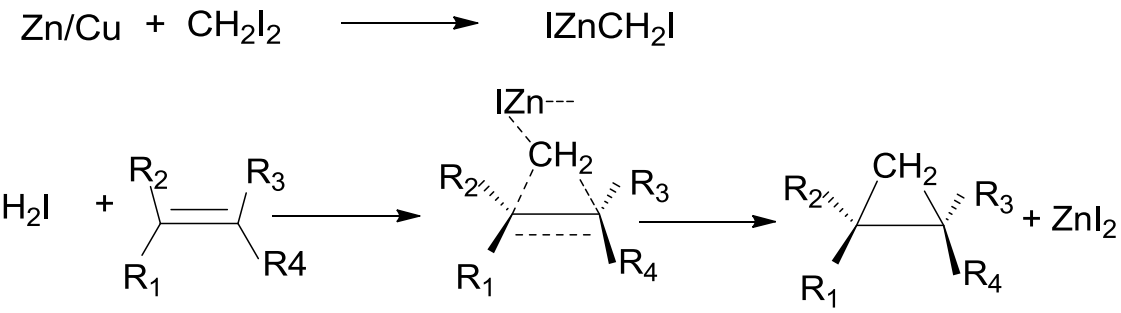


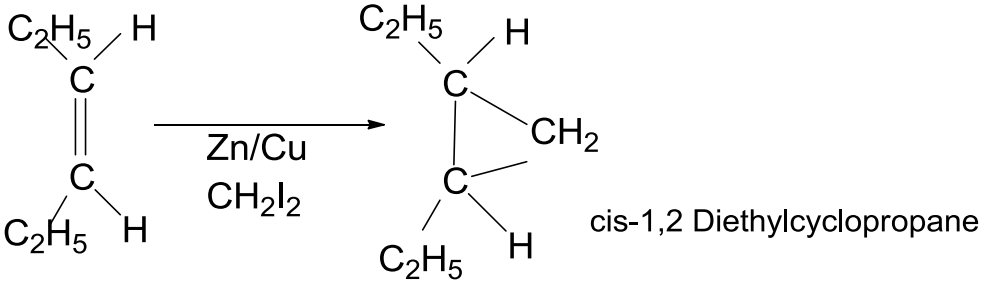
c) Reaction with alkyl halides: Reacts with tertiary halide to from hydrocarbon.

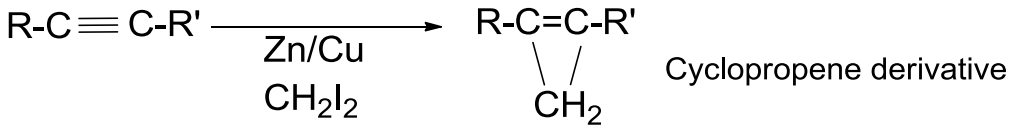


d) Simmons-smith reaction:

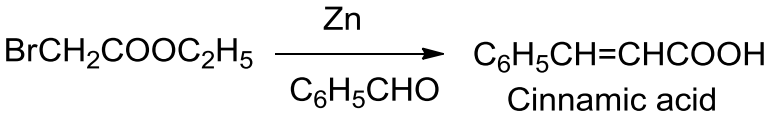
Reaction of olefinic compound with Zn/Cu couple in di iodomethane-cyclopropane derivatives. Forms organozinc intermediate [ICH_2ZnI]-carbene like species.Stereospecific reaction with the cis- addition of CH_2 group to less hindered side of double bond.

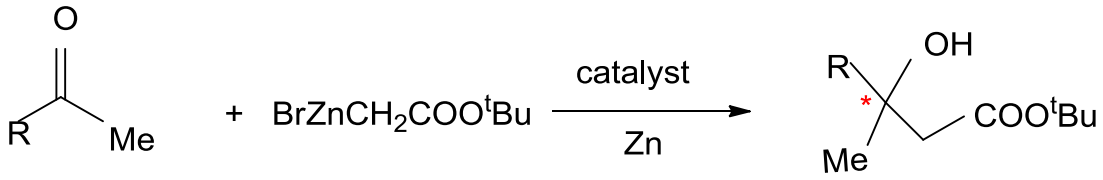






e) Reformatsky reaction: Reaction of α-bromoester with carbonyl compound to form β-hydroxy ester.

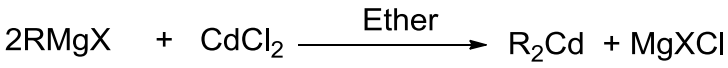


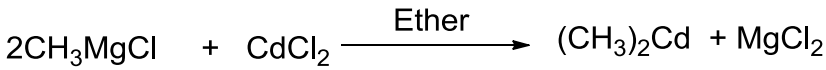


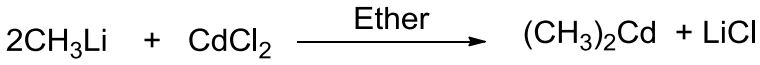
5.5 ORGANO CADMIUM COMPOUNDS

5.5.1 Preparation:

a) Action of $CdCl_2$ on Grignard's reagent or alkyl lithium



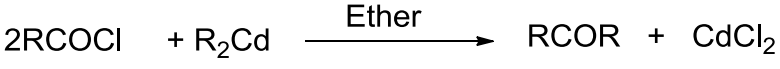


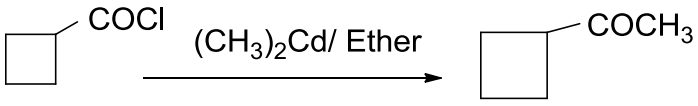


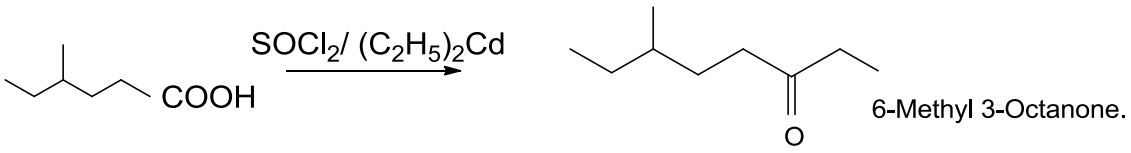
Physical Properties: Volatile liquids, Doesn't react with esters or ketones.

5.5.2 Chemical Properties:

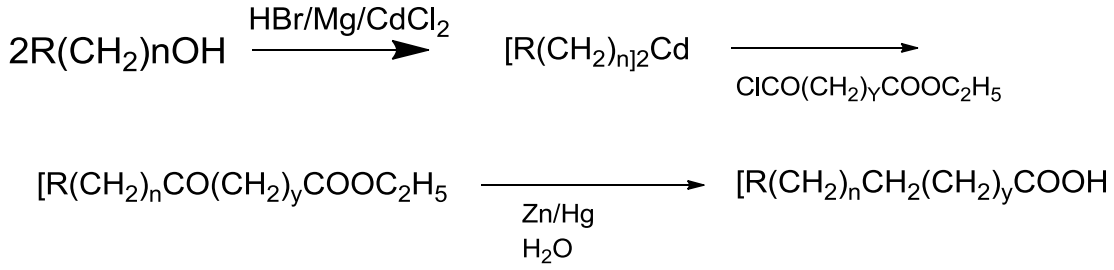
a) Reacts with acid chlorides: Organo cadmium compounds reacts with acid chlorides to form ketones.







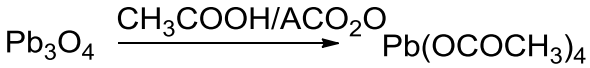
b) Synthesis of long chain esters or acids.



5.6 ORGANO LEAD COMPOUNDS- LEAD TETRA ACETATE-LTA [$Pb(OCOCH_3)_4$]

5.6.1 Preparation:

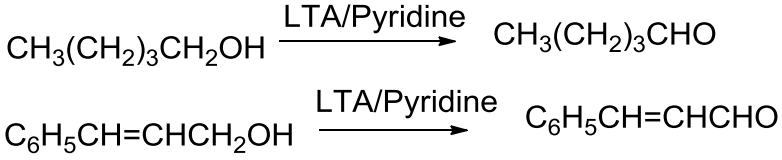
Adding red lead oxide (Pb_3O_4) to a mixture of acetic acid and anhydride at 60-80^oC and its is cooled and separated as LTA.



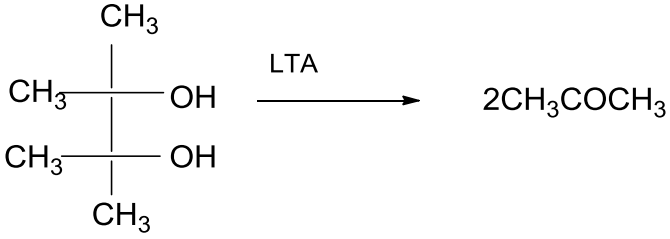
Physical Properties: Drying agent for solvents, oxidising agent

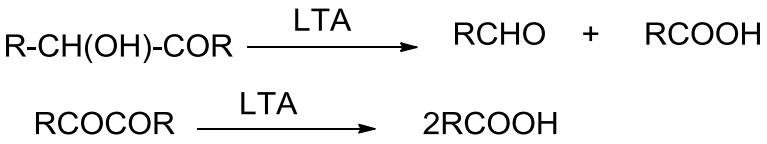
5.6.2 Chemical Properties:

a) Reactions with monohydric alcohols: Oxidises alcohol to aldehyde without affecting the double bond.

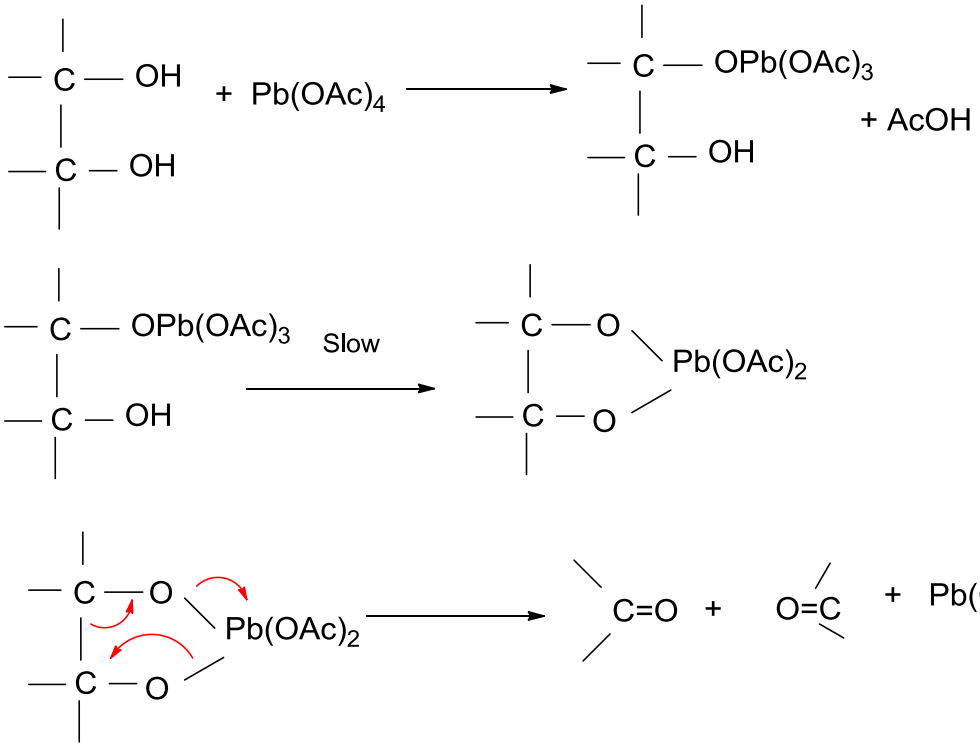


b)Reactions with 1,2 diols:

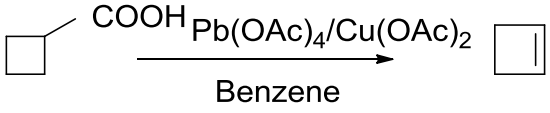




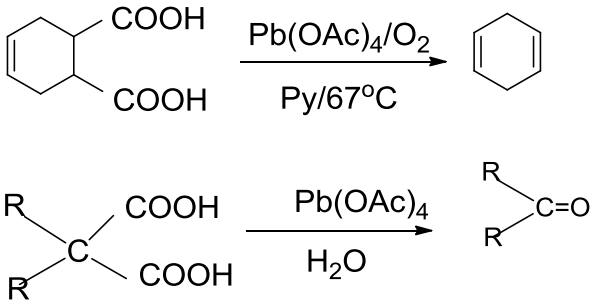
Mechanism:



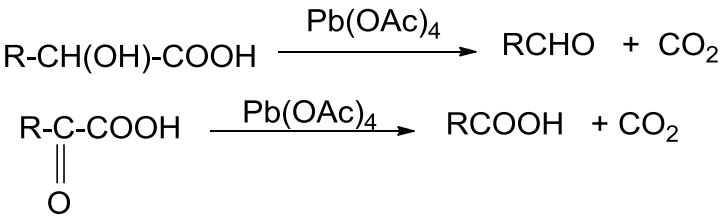
c) Reactions with monocarboxylic acids: (Oxidative decarboxylation): On oxidation with LTA in the presence of Cu(II) salts, the acids gives alkenes.



d) Dicarboxylic acids: LTA promotes decarboxylation to form unsaturated compound



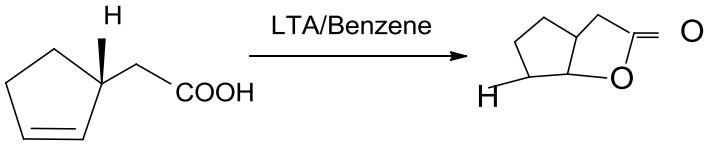
e) With α-substituted acids: They are cleaved to carbonyl compound and CO_2.



f) Dehydrogenation and cyclization:

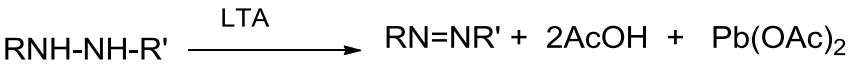
Cyclization of saturated alcohols:Alcohols with δ hydrogen undergoes dehydrogenation with LTA to form tetrahydro furans as major product.

Cyclization of carboxylic acids:

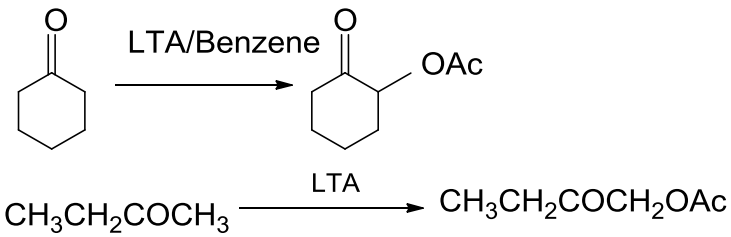


Dehydrogenation: LTA oxidises primary amine to nitriles

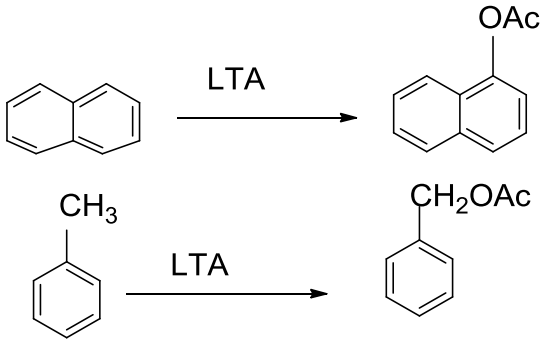
N,N'-disubstituted hydrazines are readily dehydrogenated to azo compound.



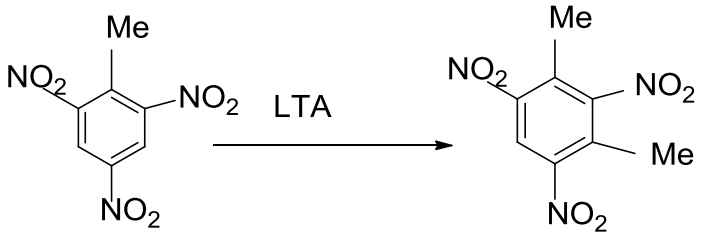
g) Acetoxylation: Ketones in enol form can be acetoxylated at α position



Acetoxylation in aromatic compounds:



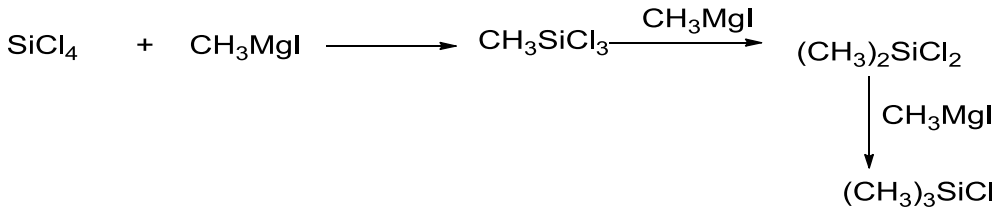
h) Nuclear methylation:



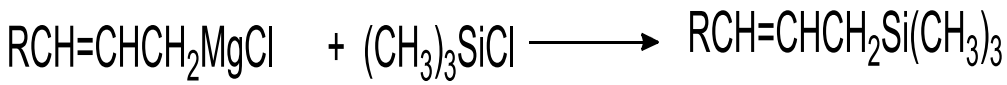
5.7 ORGANOSILICON COMPOUNDS

5.7.1 Preparation- Chlorotrimethyl silanes

Reaction of Grignard's reagent with silicon chloride.

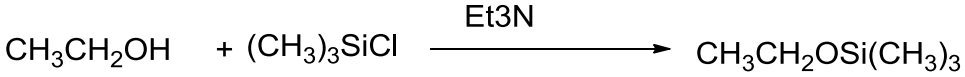


Allyl trimethyl silane is prepared by reaction of chlorotrialkyl silanes and allyl magnesium bromide.

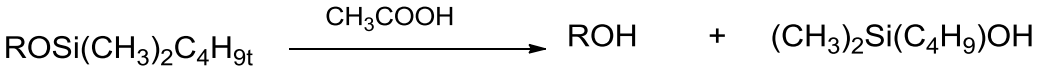


5.7.2 Chemical Reactions:

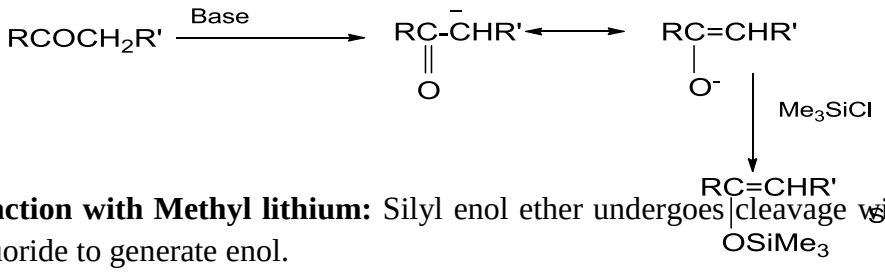
a) Protecting Group: Chlorotrialkylsilanes is used as a protecting group for alcohols, thioalcohols, amines and terminal alkynes with deprotecting group as HF,KF and aq.NaOH. As a protecting agent it forms silyl ethers.



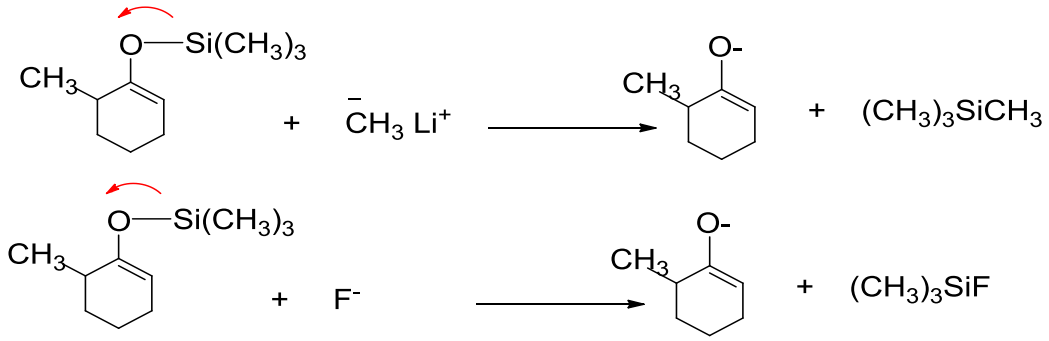
b) Action of NaOH: silyl ethers can be cleaved by aq.NaOH or acids.



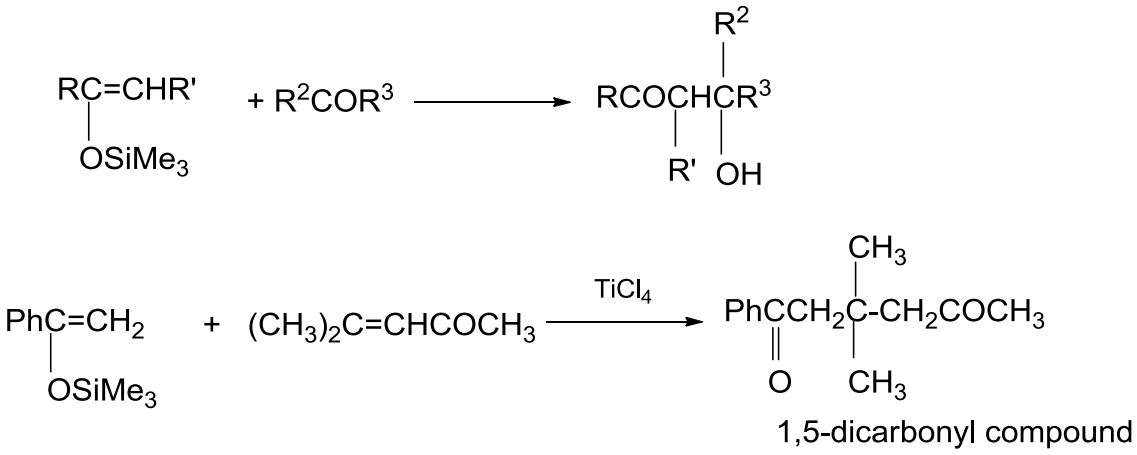
c) Conversion of enolates to silyl enol ethers. Trialkyl chlorosilanes can trap the enolate to give silyl enol ether.



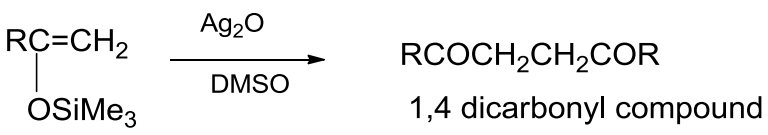
d) Reaction with Methyl lithium: Silyl enol ether undergoes cleavage with methyl lithium and fluoride to generate enol.



e) Reaction with aldehydes and Ketone: Silyl enol undergoes aldol condensation and unsaturated ketones.

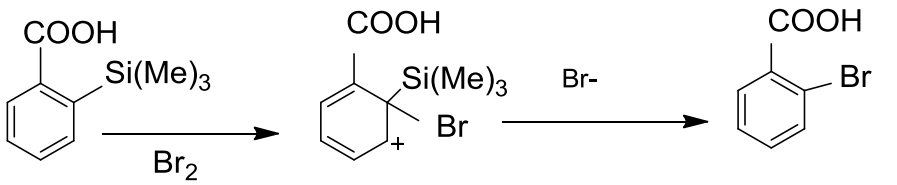


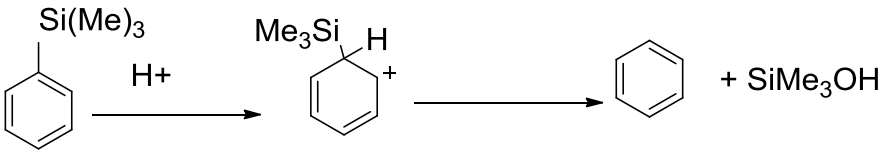
f) Dimerization: Silyl ethers dimerizes to from 1,4 diketone.



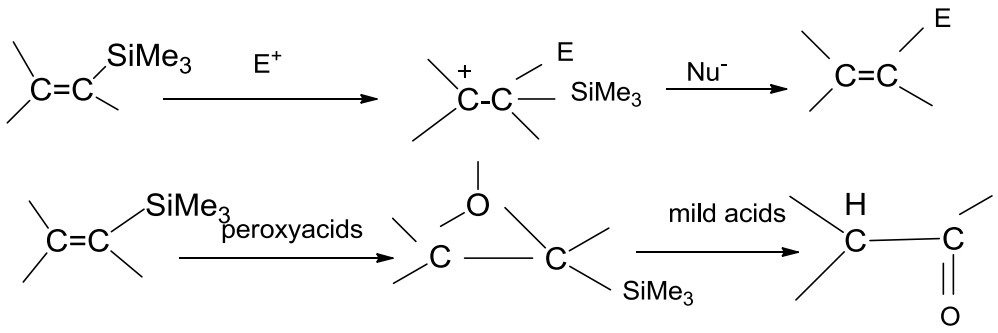
5.7.2 ARYLSILANES AND ALLYLSILANES

Chemical Reaction: Electrophilic substitution at the site of trimethyl silyl group. The incoming electrophile is directed by silyl group to the carbon atom carrying silyl group.

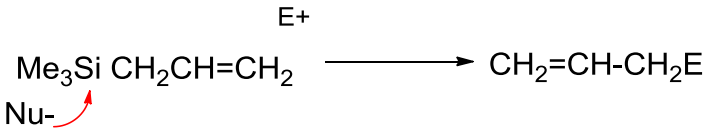




Alkenyl silanes undergoes electrophilic substitution directed by silyl group.

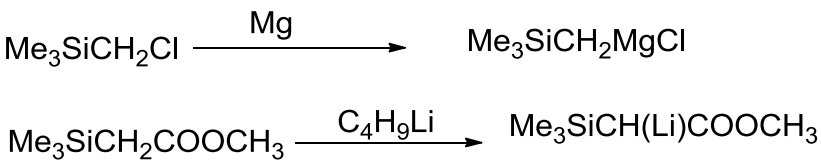


Allylsilanes undergoes electrophilic attack at the γ-carbon and the double bond is shifted to α,β position.



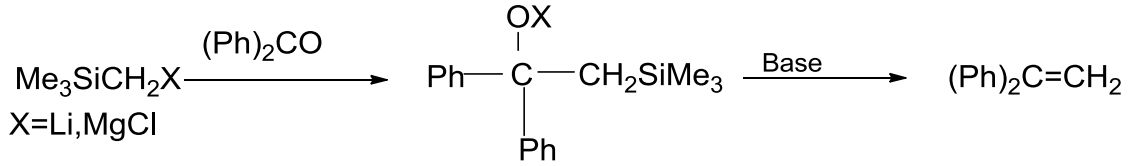
5.7.3 SILYL CARBANIONS

Preparation: α-Trimethyl silyl substituted carbanions are readily formed by reaction with Li or Mg or by reacting with weakly acidic silanes (silanes containing CH group adjacent to electron withdrawing group) with butyl lithium.



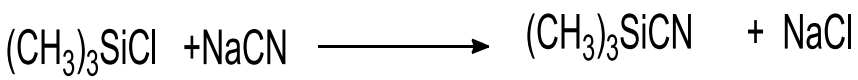
Chemical Reaction:

a)Peterson Olefination: Silyl carbanion on reaction with aldehyde or ketone gives β-silyl alcohol derivative which on treatment with a base forms alkene.



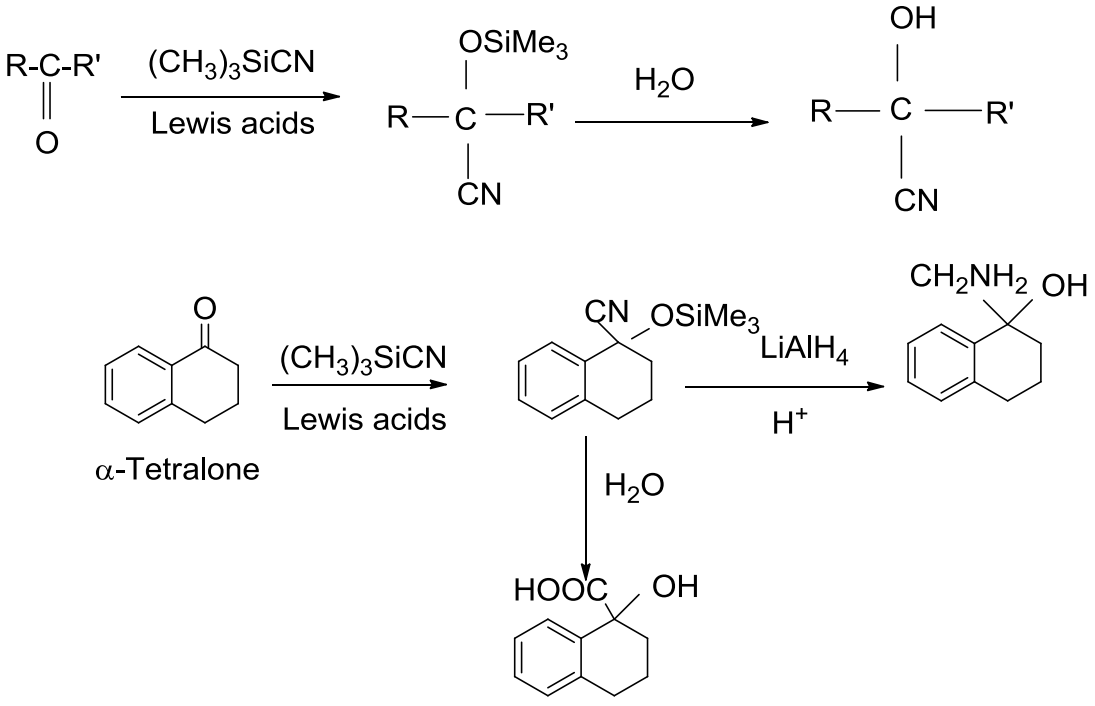
5.7.4 TRIMETHYL SILYLCYANIDES

Preparation: Treating Trimethylsilanes with metallic cyanides

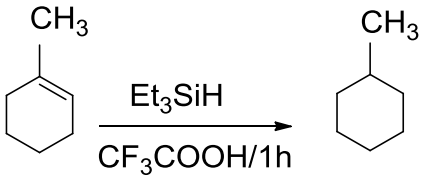


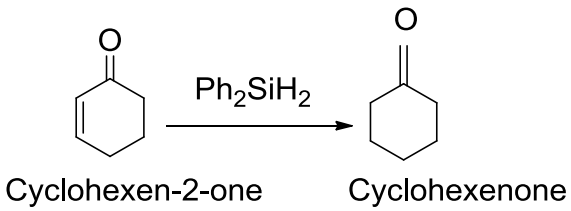
Chemical properties:

a) Reaction with ketones: Trimethyl silylcyanides reacts with ketones in the presence of lewis acids to from o-trimethylsilyl cyanohydrin which on hydrolysis gives hydroxyacids.

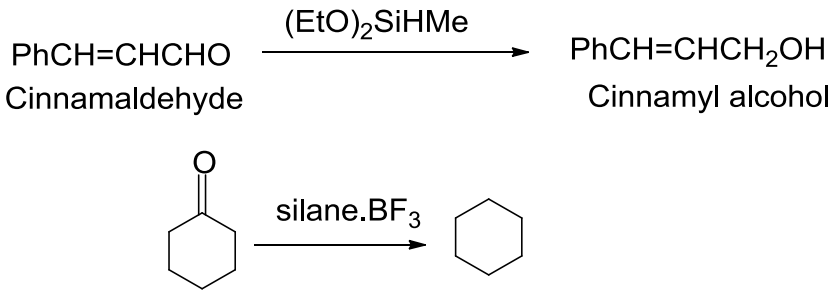


b) Reduction of double bond: Methyl cyclo hexene on reduction with triethylsilane forms methylcyclohexane





c) Reduction of conjugated aldehyde: In the presence of EDG to silanes the carbonyl is selectively reduced to alcohol.



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