Sarika.V ASYMETRIC SYNTHESIS Amrutha.G Claydon

Unit-6

(14 copy) All living Systems are chiral environments. Each Nature (God) has chosen to make all its living structures from chiral molecules (amino acids and sugars) and nature has selected a single enantiomeric form of each. All amino acid in our body has S configurations not R. There is no clear relationship btwn molecular chirality and the chirality of life forms. Right and left handed people are made from amino acids and sugars of same handedness. Thus majority of natural substances exist in one enantiomeric form, and the other enantiomeric form has extremely different properties from this one. Thus there is an urgent need to make compounds as single enantiomers. This is what we are dealing in assymetric synthesis

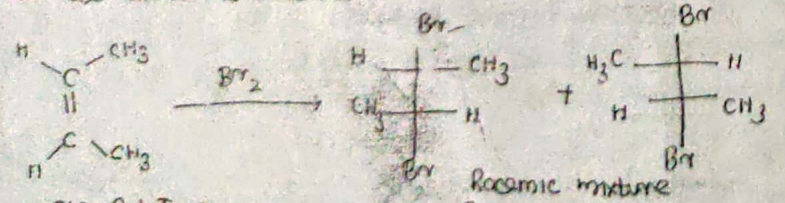
Stereoselectivity and Stereospecificity

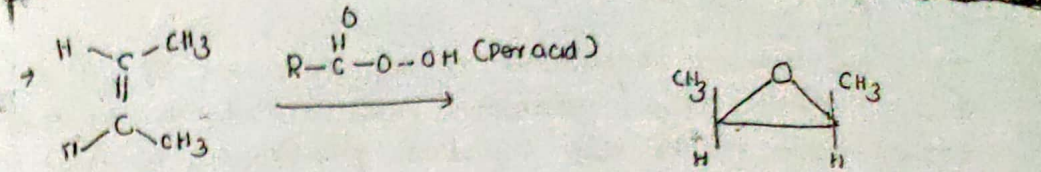
Jagadamba Singh

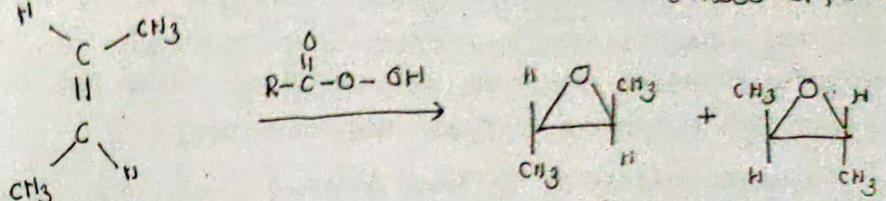
① Stereospecific Synthesis :-

A reaction or synthesis in which a particular stereoisomer reacts to give one specific stereoisomer of the product is called stereospecific reaction (synthesis). Such reaction is said to display stereospecificity. A stereospecific reaction gives a different stereoisomer of the product from each stereoisomer of the starting material.

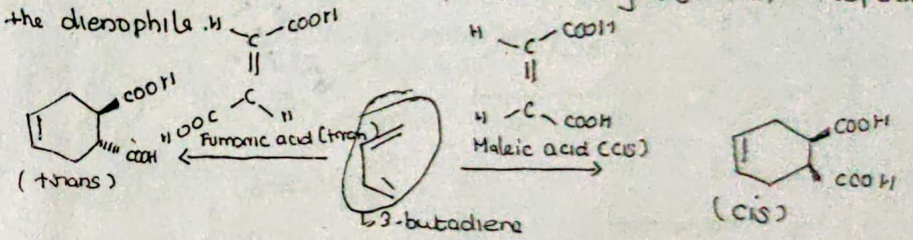
eg: Addition of bromine (anti addition) to cis-2-butene gives racemic-2,3-dibromobutane, while trans isomer gives meso-2,3-dibromo butane



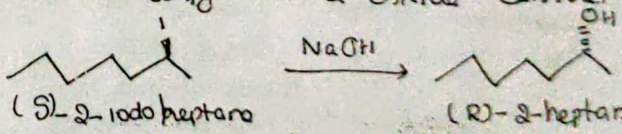




→ Diels alder reaction is stereospecifically cis with respect to the dienophile.



→ An SN2 reaction is stereospecific and proceeds with inversion of config at a chiral centre.



(2) Stereoselective reaction - Asymmetric Synthesis

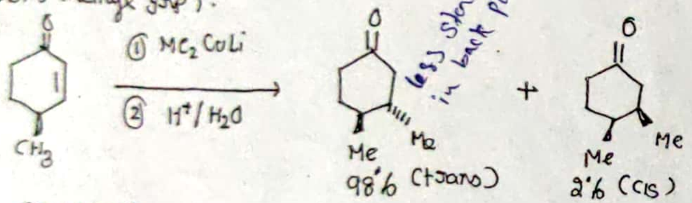
A reaction (or synthesis) in which one stereoisomer (or one pair of enantiomers) is formed predominantly or exclusively out of several stereoisomeric possibilities is called stereoselective rxn (synthesis). Such a reaction is said to display stereoselectivity. In a stereoselective reaction one stereoisomer is formed (or destroyed) more rapidly than other, thus resulting in predominance of the favoured stereoisomer in the mixture of products

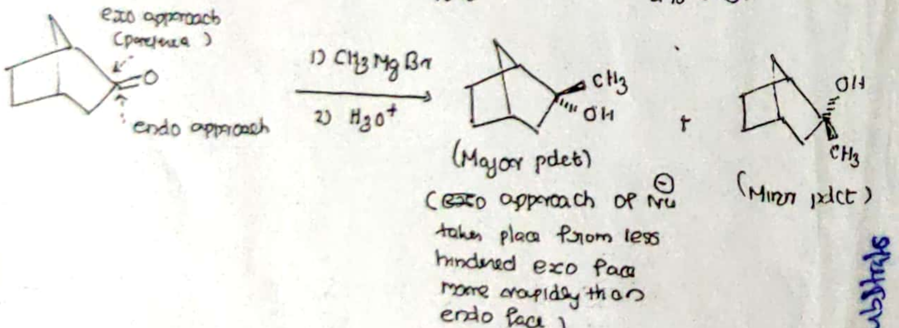
→

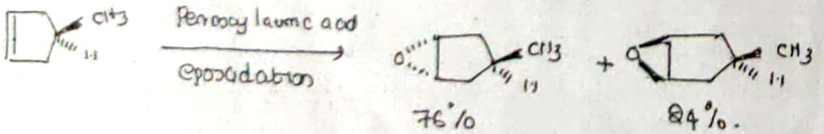
Lidialkyl cuprate - Gillman's reagent

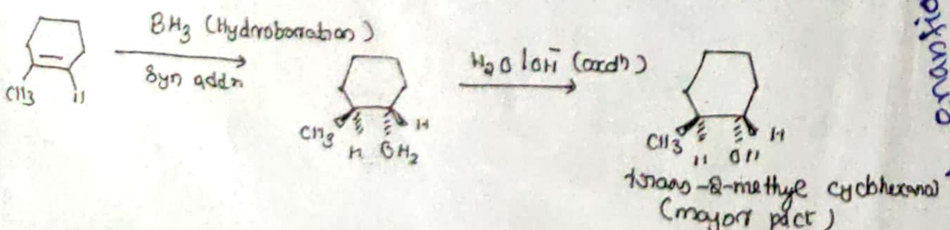
The stereoelectronic requirement of the mechanism of a stereoselective reaction offers alternative paths so that the rexn may proceed either via the most favourable path (kinetic control) or via the path which gives the most stable stereomer as the major product (thermodynamic control). In other words due to differences either in the free energies of activation of the alternative reaction or in the thermodynamic stabilities in the products, one isomer is formed assymetrically.

eg: Conjugate addition of lithium dimethyl cuprate to 4-methyl cyclohexenone is highly stereoselective and trans pdct as the major pdct bec^n the approach of the bulky cuprate reagent occurs predominantly on the less sterically hindered face of the enone. (away from methyl grp).



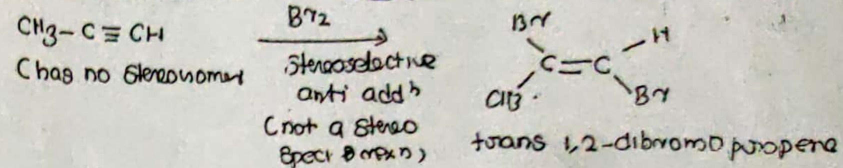


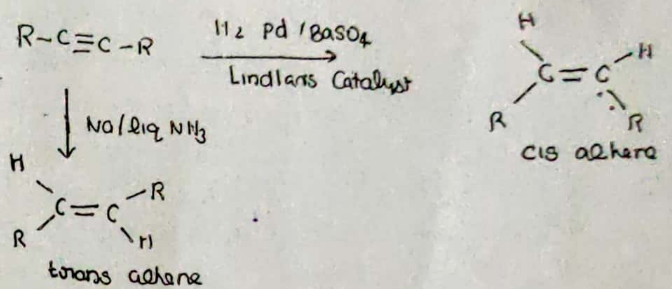


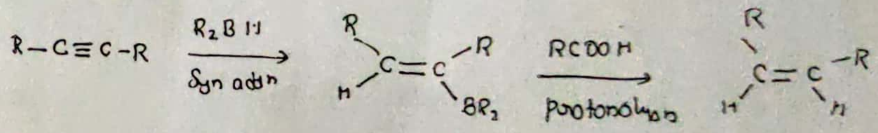


All stereospecific rexns are stereoselective but reverse is not true.

If a rexn is carried out on a compound, having no stereoisomers the rexn cannot be stereospecific but at most it could be stereoselective.







All these reactions are stereoselective rexn not stereospecific.

1st generatn method
chiral substrate based synthesis

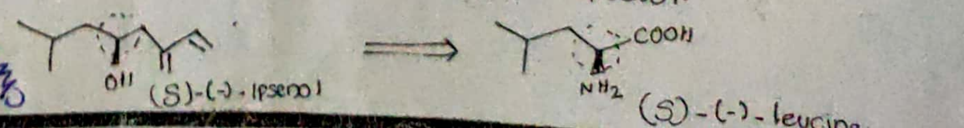
IMP

chiral pool - enantio. pure substrate
chiral environment

Chiral pool synthesis of beetle pheromone component (S)(-)-Ipsenol from S(-)-leucine — clayden

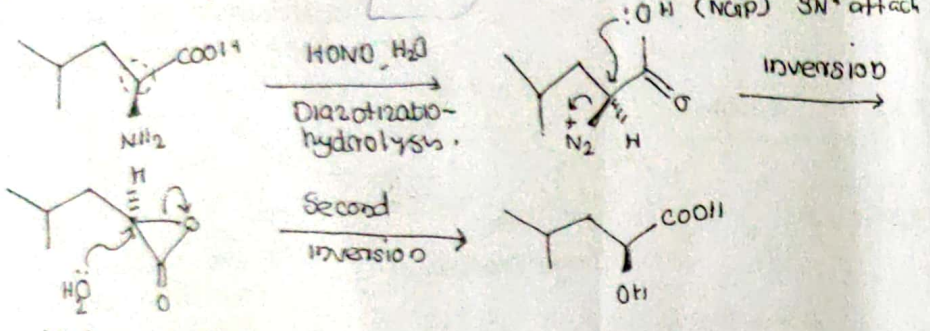
A more economical way of making compounds as a single enantiomers is to manufacture them using an enantiomerically pure natural product as a starting material. This method is known as chiral pool strategy. The chiral pool is that collection of cheap, readily available pure natural products, usually amino acids or sugars, from which pieces containing required chiral centres can be taken and incorporated into the product.

→ Male bark beetles of the genus 'Ips' produce a pheromone that is a mixture of several enantiomerically pure compounds. One is a simple diene alcohol (S)-(-)-ipsenol.

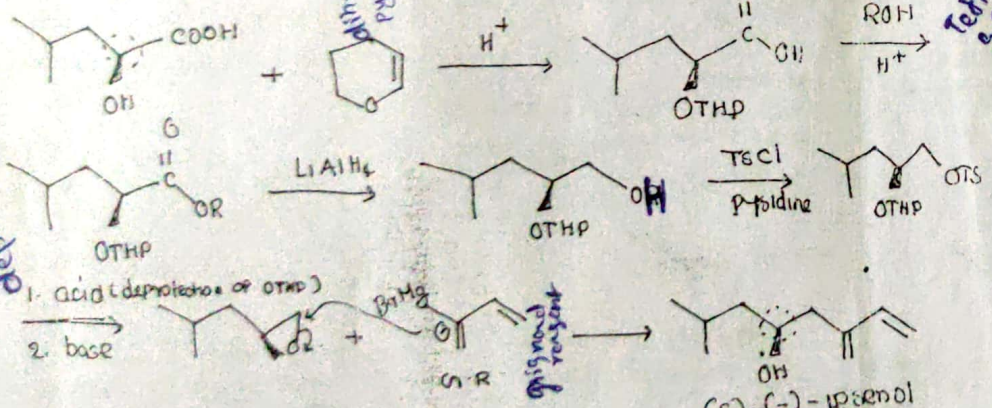


~~One is a Simple~~

Japanese chemists in the 1970's noted the similarity of part the structure of Ipsenol (chiral part) to the widely available amino acid (S)-leucine and decided to exploit this in a chiral pool synthesis, using the stereogenic centre of leucine to provide stereogenic centre of Ipsenol.



The amino group needs to be converted to a hydroxy group with retension of config^{n}. Diazotization followed by hydrolysis do this through neighbouring group participation forms Carboxylic acid.

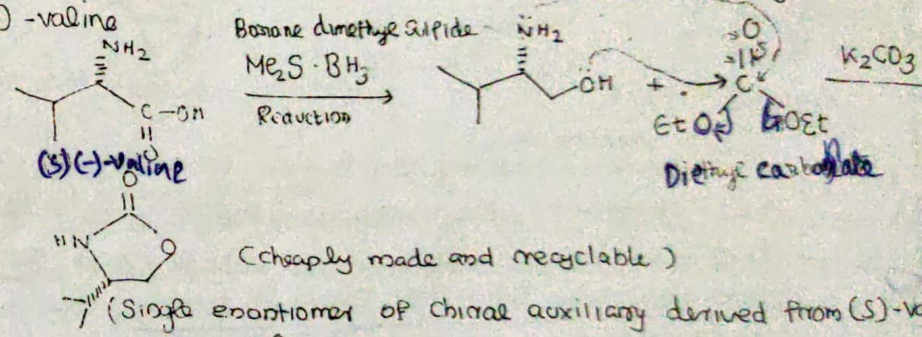


The alcohol was protected as the THP derivative, Reduction of the acid, via the ester, then allowed introduction of the tosyl leaving group, which was displaced to make an epoxide. The epoxide reacted with a Grignard reagent carrying the diene portion of the target molecule.

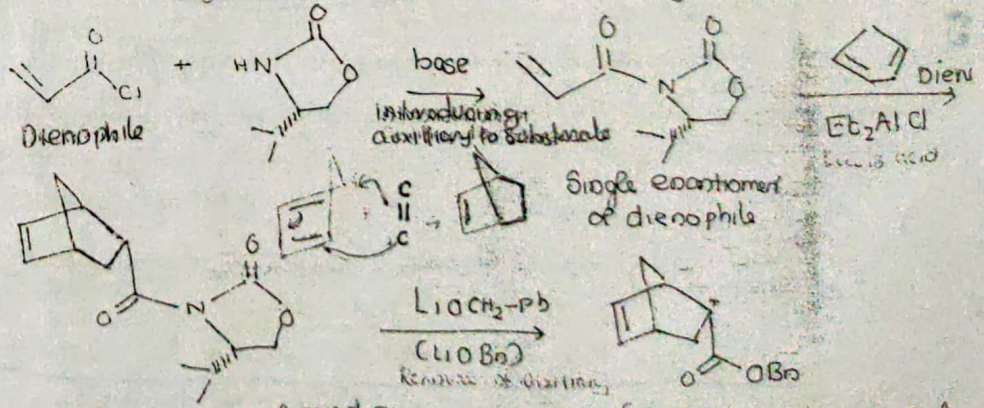
Chiral auxiliaries - Clayton

A chiral auxiliary is an enantiomerically pu compound (usually derived from simple natural product l an amino acid), which is attached to the starting mater and a diastereoselective rexn is carried, which because o the enantiomeric purity of the chiral auxiliary, gives o one enantiomer of the product. Then the chiral auxilia is removed by, for example hydrolysis, leaving the produc of the reaction as a single enantiomer. The best chi auxiliaries can be recycled, so although stochio ~~chem~~ metri quantities are needed, there is no wastage.

(1) Synthesis of Evans Oxazolidinone chiral auxiliary from (S)-valine



(Single enantiomer of chiral auxiliary derived from (S)-va



this adduct is formed as a single diastereoisomer

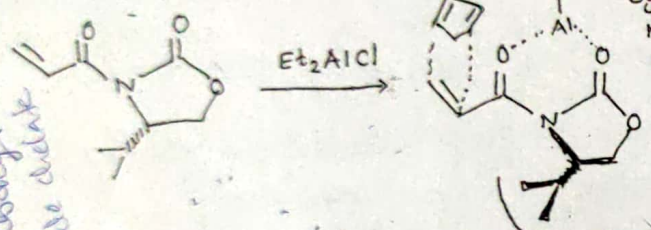
(Single enantiomer only

removal of the chiral auxiliary reveals this compo as a single enantiomer

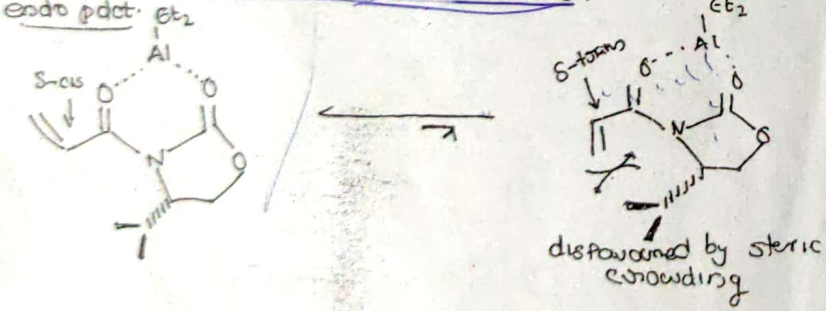
(Chiral auxiliary controlled Diels-Alder rexn gives single the prod

In Diels-Alder rexn the addition of diene across dienophile is diastereoselective and generally mainly endo product. When all the starting materials in the rexn are achiral, the product formed is necessarily racemic. (50:50 mixture of two enantiomers)

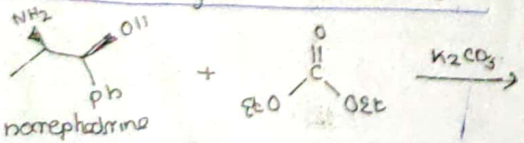
But when a chiral auxiliary having a stereogenic centre (which is enantiomerically pure) when attached with one of the starting material, diastereomerically and enantiomerically pure single product will be the enantiomer



In the structure of auxiliary bearing dienophile co-ordinated with Lewis acid ~~Structure~~, the bulky isopropyl group shields the back face of the alkene from attack, and cyclopentadiene can approach from the front face only, thus will give the endo pdct.

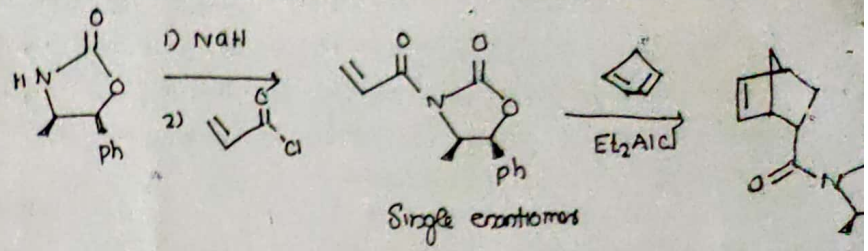


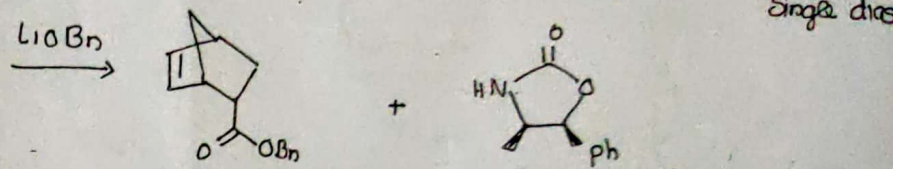
auxiliary also has the effect of fixing the conformation of the ~~bond~~ single bond as S-cis (not S-trans).



Naturally occurring and cheap

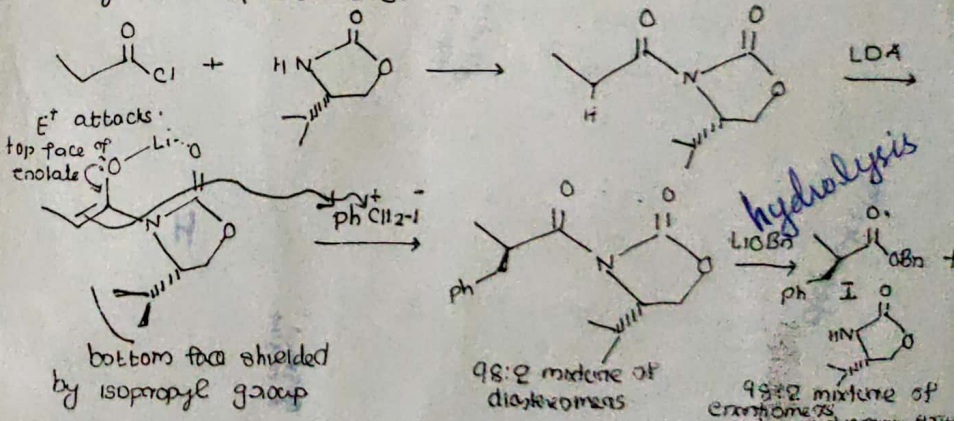
~~...~~ ...amb (appetite suppressant)





Alkylation of chiral enolates – ~~Chir~~ Chydon

Evans oxazolidinone chiral auxiliaries can be used for alkylation of enolates.



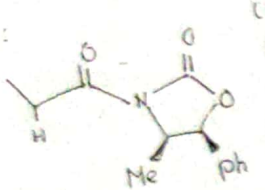
Treatment with a base (LDA) at low temperature produces an enolate, and the auxiliary has been designed to favour attack by the electrophile on only one face of that enolate. Coordination of the lithium ion to the carbonyl oxygen makes the whole structure rigid, fixing the isopropyl group, which give maximum hindrance to the bottom face attack of electrophile.

Enantiomeric excess: Enantiomeric excess (ee) is defined as the excess of enantiomer over the other, expressed

Catalysts – 3rd generation method
enzymes – 4th
Al-acidic mildly 6membered T.S
2-carbonyl O-cyclic
Ylide chelate
mode

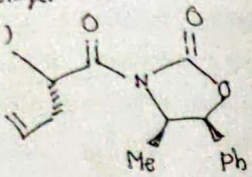
is a percentage of the whole. So 98:2 mixture of enantiomer contains 4% racemates and 96% of one enantiomer ie 96% ee. So in our chiral auxiliary controlled reaction we still have 1 or 2% minor diastereomer. But if we recrystallize our 98:2 mixture of diastereoisomer, and then the removal of chiral auxiliary has been done, then the ee can be increased to 100%.

eg:

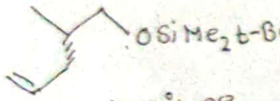


(Sodium bis (trimethyle silyle) amide

1. $NaN(SiMe_3)_2$ (base)
2. allyle iodide $CH_2=CH-CH_2-I$



1. $LiAlH_4$
2. t Bu Me_2SiCl



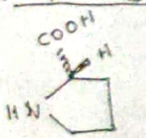
>99% ee

98:2 diastereomers

↓ recrystallization

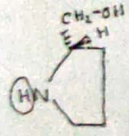
>99:1 diastereomers

Asymmetric α-Substitution of a carboxylic acid and ~~Synthesis~~ of ~~optically active β-hydroxy acids~~ – Kalsi



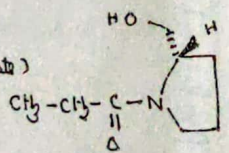
(S)-(-) proline

$LiAlH_4$



(S)-prolinol (chiral pyrolidine unit)

$CH_3-CH_2-C(=O)-X$ (Carboxylic acid substrate)



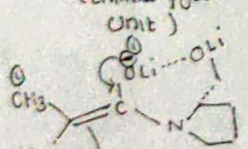
Amide

Base

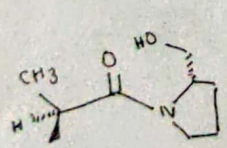
$(CH_3-CH)_2-\bar{N}\,Li^+$

(LDA)

Deprotonation

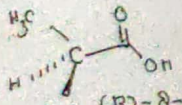


Chiral (Z)-enolate



hydrolysis

chiral auxiliary opp. part

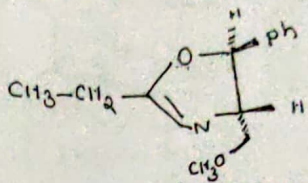


(R)-2-Butylpropanoic acid (88% ee)

+ (S)-prolinol

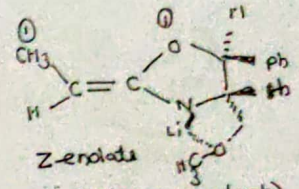
The chiral enolate is alkylated with butyle iodide which mainly occurs from the top face of the molecule, which is the less-hindered direction of approach. Thus the electrophilic attack occurs on the Si face of the double bond, the Re-face being hindered by the chiral auxiliary.

chiral aza-enolates asymmetric synthesis of α-alkyle carboxylic acids- Kalsi



(1) Chiral Oxazolines

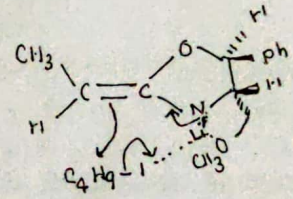
LDA



Z-enolate

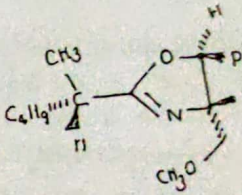
(Major product) chelated compd (Li is below the plane of the ring)

C_4H_9-I

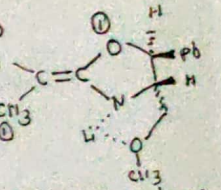


(alkylation takes place on the opposite side of bulky phenyle group)

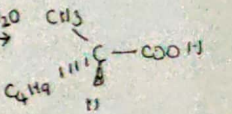
-LiI



H_3O^+/H_2O

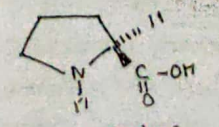


(Minor product) E-enolate



Chiral Oxazolines on treatment with LDA gives the Z-enolate. The major product on lithiation gives chelated compd in which Lithium is held below the plane of the ring by the methoxyl group. Alkylation takes place from underside of the molecule ie on the side opposite the bulky phenyl substituent (this direction is provided by the lithium and further shows that both the methoxy group and phenyl group are essential for the observed optical yield).

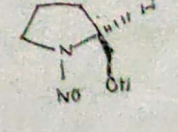
Enantioselective alkylation of aldehydes and ketones via chiral hydrazones – Kalsi



S-(-)-Proline

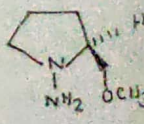
(1) $LiAlH_4$

(2) C_2H_5ONO

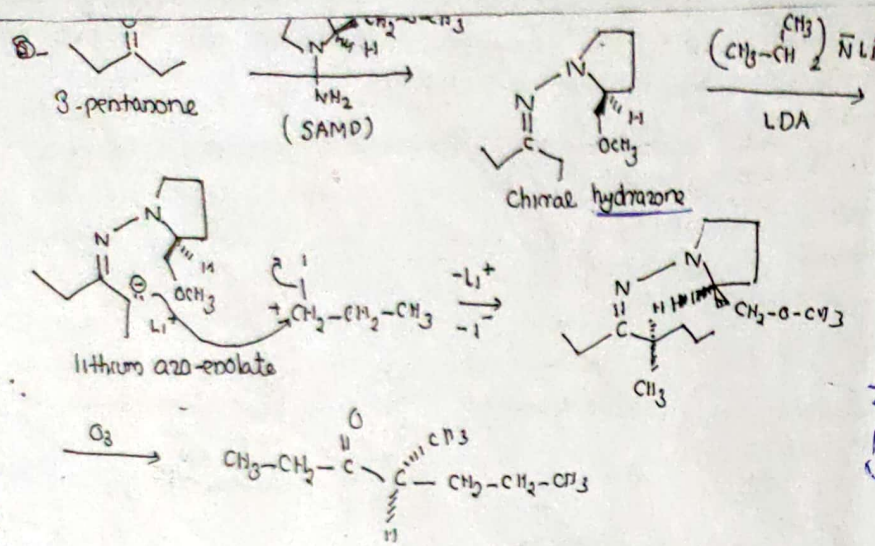


(1) NaH, CH_3I

(2) $LiAlH_4$



S-1-amino-2-(methoxy methyle)-pyrrolidine (SAMP)



S(+)-4-methyl-3-heptanone
(ee 97%)

S-1-Amino-2-methoxy-methylpyrrolidine is called SAMP and its enantiomer as RAMP are employed as chiral auxiliaries in enantioselective alkylation of aldehydes and ketones. An easy way to bring about an asymmetric alkylation α to a carbonyl group is to just convert a ketone to a chiral imine or hydrazone followed by deprotonation with a strong base. Thus the hydrazone of 3-pentanone on treatment with LDA affords a complex (the α-hydrogens of hydrazones are acidic). The resulting lithium aza-enolate adopts an orientation and is stabilized by forming a complex involving the lithium cation the α-carbanion and the chiral auxiliary (at the methoxy group). This chiral chelated carbanion is a nucleophile which will react with alkyl halides via nucleophilic substn to form exclusively only one of the two diastereomers (S,S) and not (R,S). On ozonolysis the S,S-diastereomer afforded the S-enantiomer of 4-methyl-3-heptanone and the chiral auxiliary is recovered as the N-nitroso compound which may be reduced back to SAMP

Prefered fdct. is determined by starting alcohol

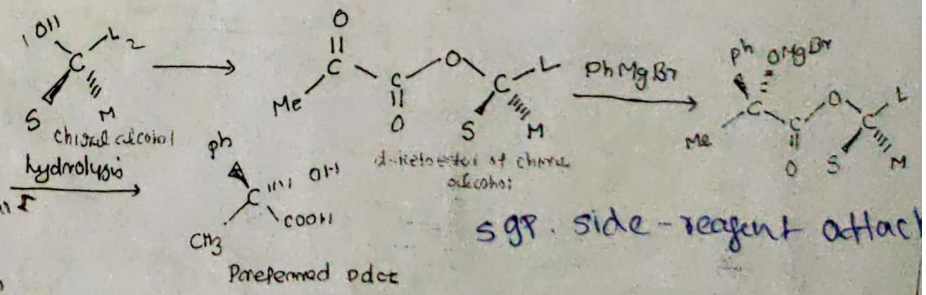
C=N— : -hydrazones

Asymmetric inductors — Nasipuri

Asymmetric induction defines the extent of asymmetry induced at a prochiral centre of the substr either by the chirality of the reagent or by one or mo chiral centres present in the substrate molecule itself. In enantioselective rex? asymmetric induction is equal to enantiomeric excess (ee) and in diastereoselective react (giving rise to a new centre) it is equal to the diastereome excess (de)

Prelog's rule — Jagadamba Singh + Nasipuri

This rule relates to the course of asymmetric Synthesis when a Grignard reagent is added to a ketoni group C=O of an α-ketoester of a chiral alcohol SMLC-OH (S, M and L stand for small, medium and large groups respectively If the reactive conformation of the ketoester is I, the GR wi attack the ketonic carbon from the less hindered side ie from the side of the group S as shown below.

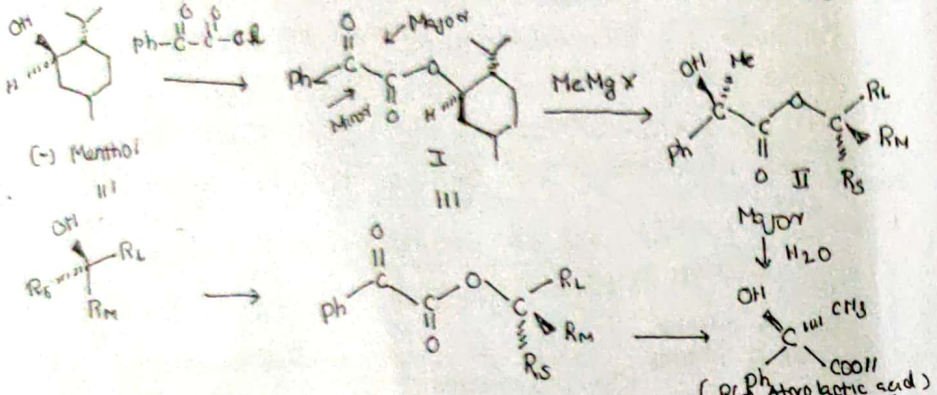


sgp. side - reagent attack

Prelog's rule correlates the configuration of the α-hydroxy acid obtained with that of the starting alcohol (SMLC-OH) incorporated in to the α-ketoester. The config of the predominantly formed α-hydroxy acid is related to the config of the chiral alcohol (SMLC-OH) used.

Prelog's rule has been used to assign the config of numerous alcohols. In most cases the alcohol is esterified with Pyruvic acid and the ester is reacted with PhMgBr. The atrolactic

Acid obtained after hydrolysis is identified polarimetrically as (S)-(+) or R(-) and the config^n of the alcohol is deduced from this. If the acid is S then the alcohol is R and vice versa.



Methyl magnesium bromide approaches the electrophilic carbon (of the ketonic C=O) from the side of R_S more easily than from the side of R_M. The preferred diastereomer is thus (II) which on complete hydrolysis affords atrolactic acid enriched in R(-) enantiomer.

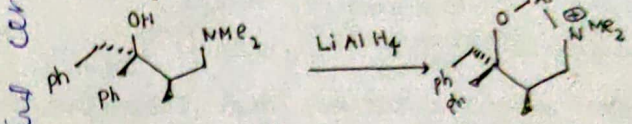
R – X , $R^{\oplus}$

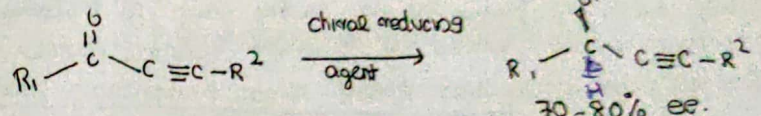
R – Mg – X , $R^{\ominus}$

Chiral reagent / chiral catalyst Controlled asymmetric Synthesis

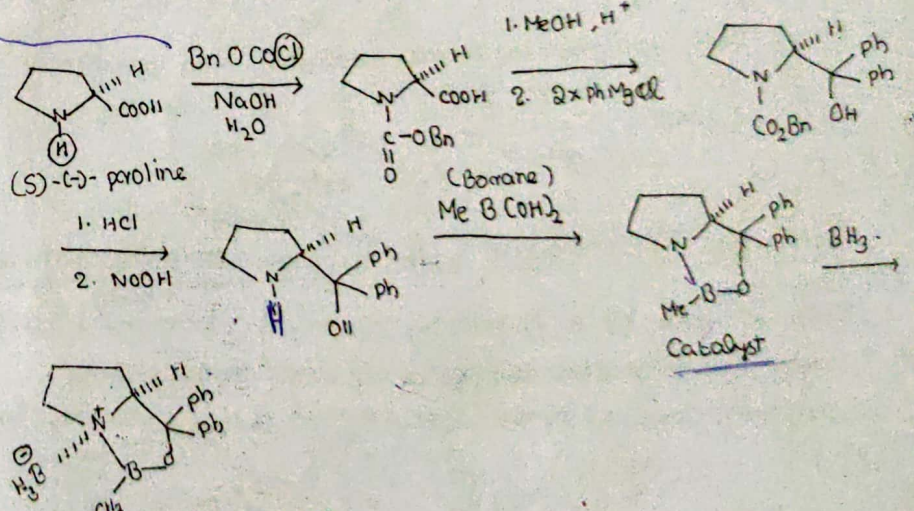
Claydon.

If we want to create a new chiral centre in a molecule, our starting material must have prochirality - the ability to become chiral in one simple transformation. This can be done by using chiral reducing agent:

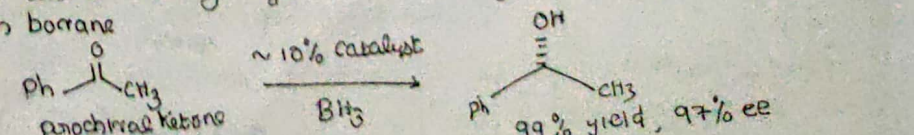


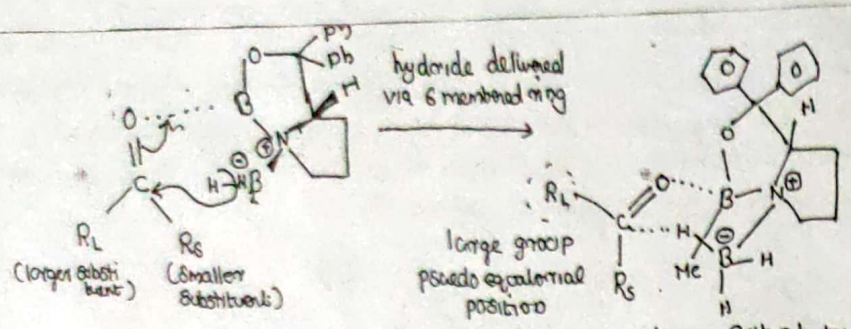


More effective reagent is the chiral borohydride analogue developed by Corey, Bakshi and Shibita. It is based upon a stable boron heterocycle made from an amino alcohol derived from proline, and is known as the CBS reagent.

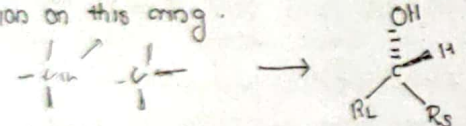


The active reducing agent is made by complexing the heterocycle with borane

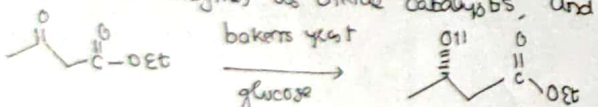




CBS reduction are best when the ketone's two substituents are well differentiated sterically. only when the ketone is complexed with the boron atom in the ring it becomes electrophilic enough to be reduced by the weak hydride source. The $H^{\ominus}$ is delivered via a six membered cyclic transition state with the enantioselectivity arising from preference of the larger of the ketones two substituents (R_L) for the psedoequatorial position on this ring.

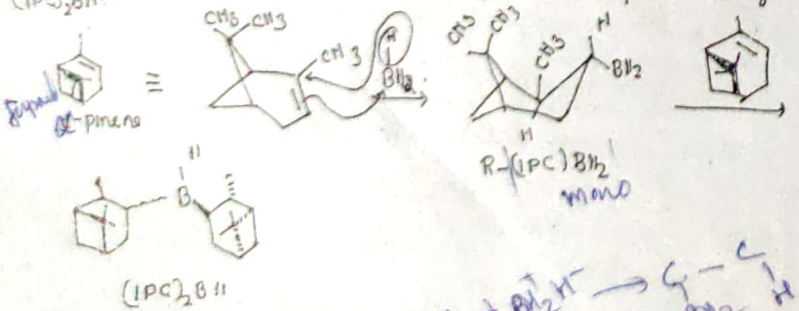


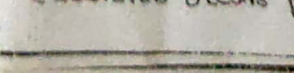
→ Nature uses enzymes as chiral catalysts, and get almost 100% ee.



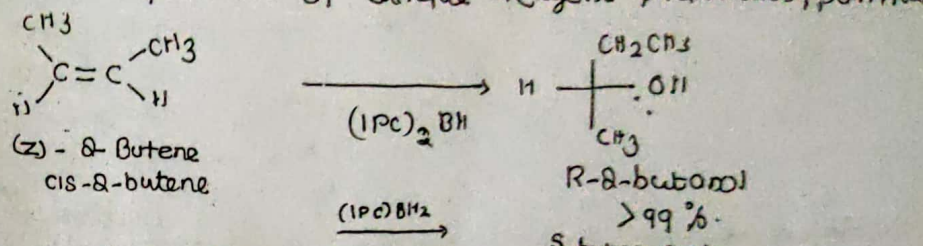
Asymmetric hydroboration with diisopino campheyl boranes - Kagi

Hydroboration of a naturally occurring terpenoid hydrocarbon d-pinene (which is chiral) gives chiral alkyl boranes - monoisopino campheyl borane $(IPC)BH_2$ or diisopino campheyl borane $(IPC)_2BH$.

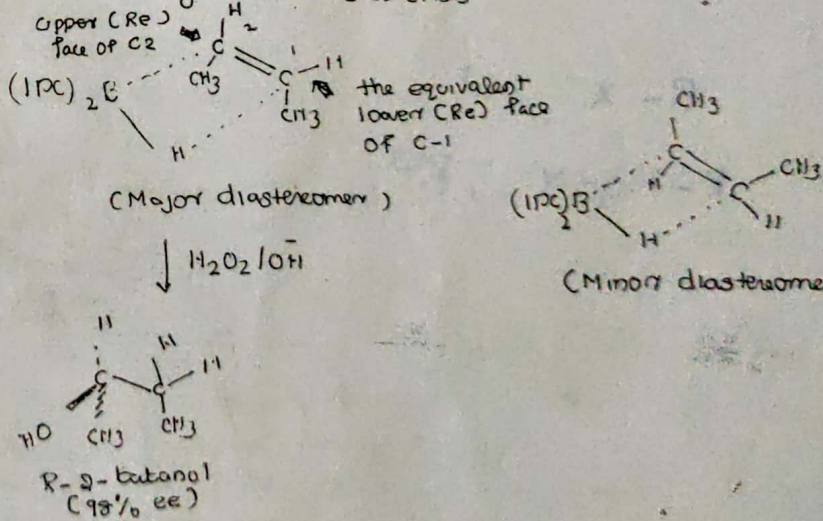


$C{=}C + BH_2H \rightarrow$  $\xrightarrow[OH^-]{H_2O_2}$ 

The use of chiral borane $(IPC)_2BH$ in its optically pure form in the hydroboration of the prochiral (Z)-but-2 followed by oxidation gives (R)-butan-2-ol with high optical purity. Monoisopino campheye borane $(IPC)BH_2$ reac with (Z)-but-2-ene to give (S)-butan-2-ol, and this reflec on the importance of correct reagent preparation/purifica



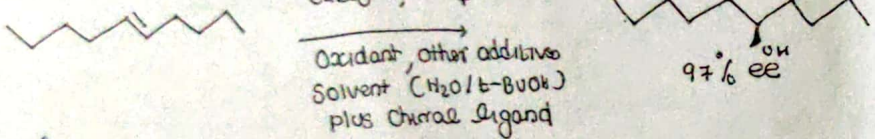
It has been shown that $(IPC)BH_2$ is a very good enant selective reagent for hydroboration of trans-alkene trisubstituted alkenes and 1-substituted cycloalkenes. $(IPC)_2BH$ on the other hand, works very well with Cl olefins with high enantioselection



The mechanism of the reaction b/wn (Z)-but-2-ene (cis-2-butene) with $(IPC)_2BH$ involves a different interaction of the two faces of the alkene with the chiral borane to give diastereomeric (triorgano) boranes (addition occurs preferentially to one face). A chiral alcohol

is then produced after oxidative hydrolysis with H_2O_2 and base. The transition state leading to (R) alcohol is much lower in energy. One may consider the orientation of the alkyl groups on olefin with respect to $(IPC)_2BH$ portion in the T.S leading to major diastereomer. $(IPC)_2BH$ is a very bulky dialkyl chiral borane, when compared to cis-2-butene in which the comparison to attack resistance by attack of $(IPC)_2BH$ is H versus methyl. The alcohol is formed by the attack of bulky borane to the upper (Re) face of C2 on the equivalent lower face (Re) of C-1.

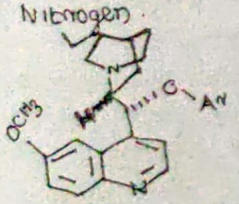
Asymmetric dihydroxylation — Sharpless



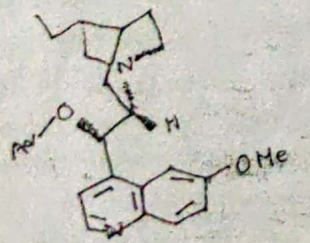
conditions

The active reagent is based on osmium (VIII) and is used in dust catalytic amounts. $K_3Fe(CN)_6$ is used as another oxidant to reoxidize the osmium after each catalytic cycle. Bec^2 OsO_4 is volatile and toxic, the osmium is usually added as $K_2OsO_2(OH)_4$ which forms OsO_4 in the reaction mixture. The other additives include K_2CO_3 and methanesolfonamide ($MeSO_2NH_2$) which increases the rate of the reaction. The chiral ligands are based on the alkaloids dihydroquinidine and dihydroquinine, which coordinate to the osmium through

Nitrogen.

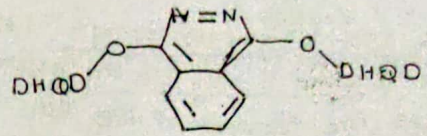


dihydroquinidine
(when Ar = H)
= DHQD.
Sp. rotation = +282° (in EtOH)
(Cinchona alkaloids)

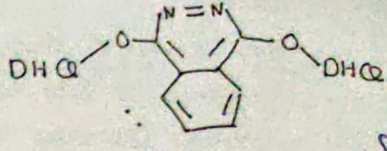


dihydroquinine
when Ar = H
= DHQ
Sp. rotation = −148° (in ethanol)

The alkaloids DHQD and DHQ must be attached to an aromatic group Ar. The most generally applicable ligands are these two phthalazines in which each aromatic group Ar carries two alkaloid ligand:



$(DHQD)_2PHAL$

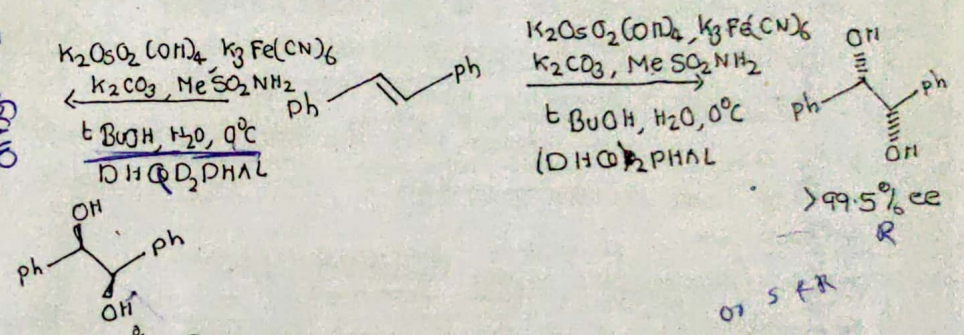


$(DHQ)_2PHAL$

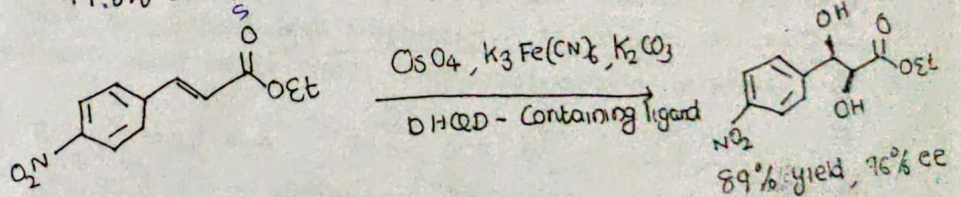
(phthalazine-based ligands)

dihydroquinine phthalazine

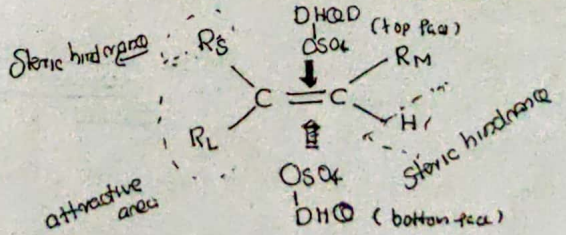
specific rotation (+ & (−) for each



or S-R



Enantioselectivity in Sharpless asymmetric dihydroxylation



When the substrate is arranged as shown above, with the largest (R_L) and next largest groups (R_M) bottom left and

targeted opposite upper the plane dihydroquinidine (OsO_4 preferred quinine below plane

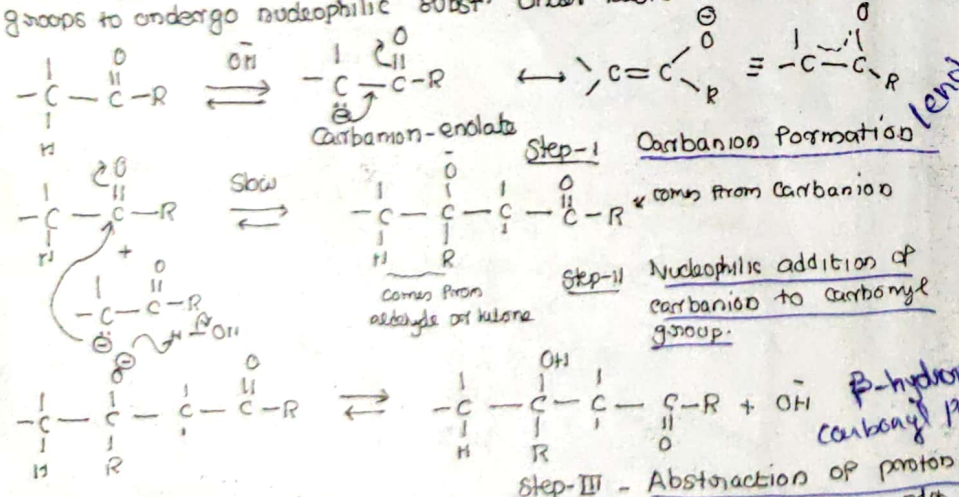
top right respectively, DHQD-based ligands will direct asym to dihydroxylate from the top face of the double bond and DHQ-based ligands will direct it to dihydroxylate the bottom.

Here the ligand forms some sort of 'chiral pocket' like an enzyme active site, with the osmium sitting at the bottom of it. Alkenes can only approach the osmium if they are correctly aligned in the chiral pocket, and steric hindrance forces the alignment shown in the scheme above. The analogy with an enzyme active site goes even further, since it appears that part of the pocket is attractive to aromatic or strongly hydrophobic groups. This part appears to accomodate R_L, that is the reason why the selectivity in the dihydroxylation of trans stilbene is so high

(Asymmetric aldol reaction Essay)

INTRODUCTION -

Two important aspects of aldol addition of carbonyl compounds are the acidity of α-hydrogens and tendency of their carbonyl groups to undergo nucleophilic substn under basic conditions

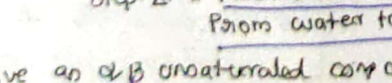


Step-I Carbanion formation

Step-II Nucleophilic addition of carbanion to carbonyl group.

Step-III - Abstraction of proton from water to form pdct

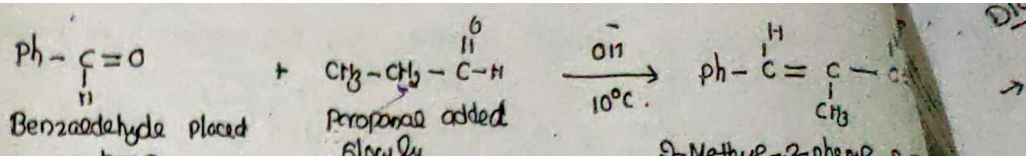
The aldol pdct on heating can give an α,β unsaturated comp'd (condensatn)



Enolate formation - must have α-H (carbonyl gp.) is alkyl gp. Don't

β-hydroxy carbonyl pdct.

Enolate formation



example for crossed aldol condensation

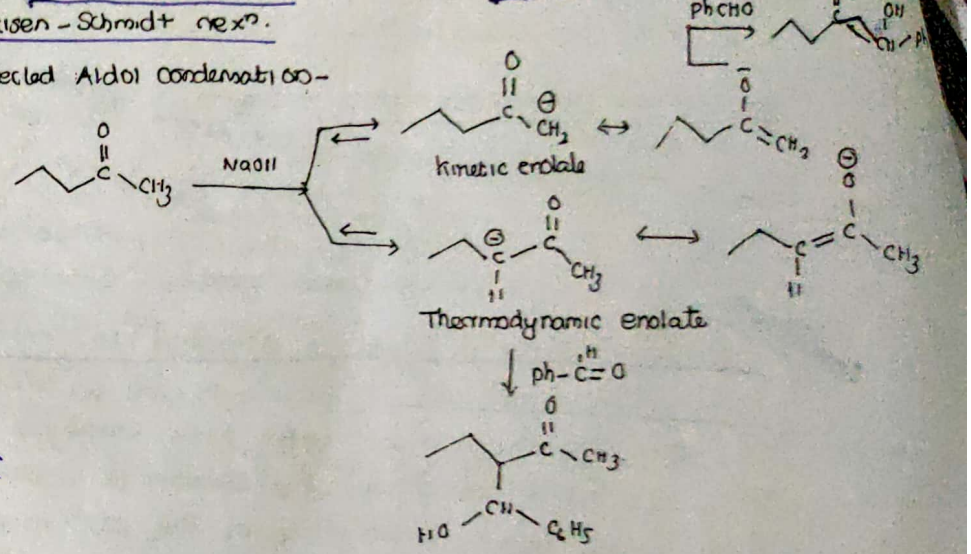
→ Aldol reαn which starts from two diff carbonyl compds is called Crossed aldol condensation

→ A crossed aldol reαn in which one component is a heteroαn is called Claisen-Schmidt reαn.

condensatn

atleast 1

Directed Aldol condensation -



→ Thermodynamic enolate is more stable (it has more substituted double bond formed with a weaker base like $\bar{O}H/H_2O$, this enolate will predominate at eqbm

→ kinetic enolate is less stable. It is formed easily and faster when a strong and very bulky bases like LDA is employed. (LDA has difficulty to abstract proton from more hindered parts)

→ Aldol condensation of two different carbonyl comps can give a molecule with two stereocenters. (two stereogenic carbons). Two diast ereomers and their enantiomers are possible to give in all 4 stereoisomers. This reαn can be made both diastereoselective as well as enantioselective.

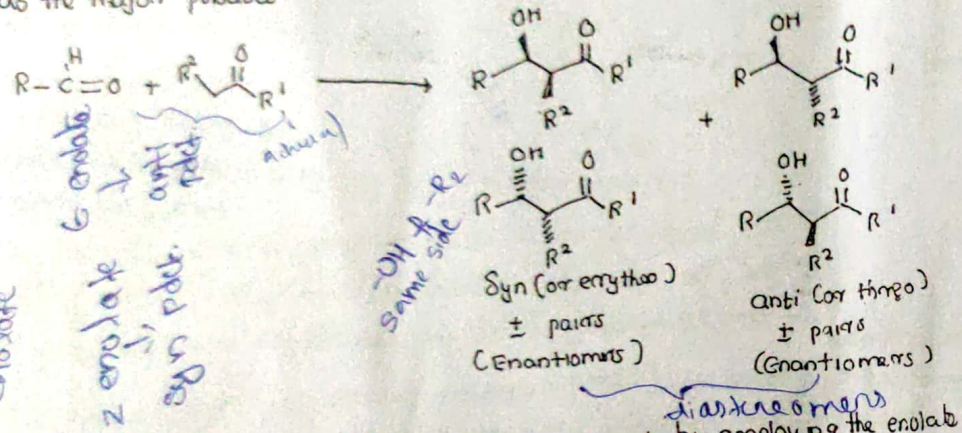
Aldol addition → β-OH-C=O

Aldol condensatn → α, β unsaturated compound

Diastereoselectivity in Aldol reactions (Directed aldol rexn)

→ The aldol reaction creates two stereocentres from achiral starting material, mostly 4 stereoisomers of the aldol product arises. Thus syn or anti diastereomers are produced, each as a pair of enantiomers.

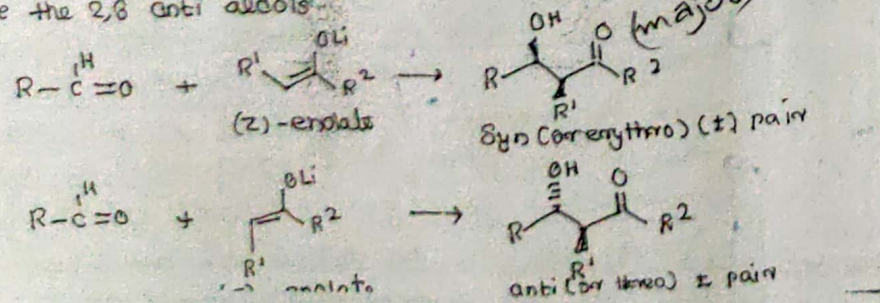
→ Diastereoselection involves (racemic) syn or (racemic) anti product as the major product.

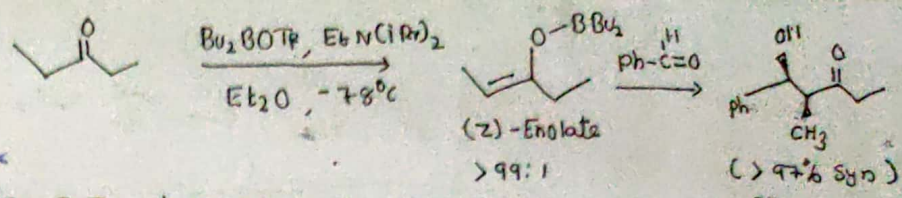


→ Diastereoselectivity in the aldol rexn is achieved by employing the enolate of desired stereochemistry (E or Z).

→ Enolates are generated from a ketone and a base in the presence of chlorotrimethyl silane when the enolates are trapped as silyl enol ethers. These are separated and purified by chromatography and then converted in to pure (Z)- or (E)- enolate with fluoride ion (Nu subst^n of $\bar{F}$ at Si atom, rexn is fast bec^2 Si–F bonds are very strong)

→ Z enolates give mainly 2,3-syn aldols while the E-enolates give the 2,3 anti aldols.





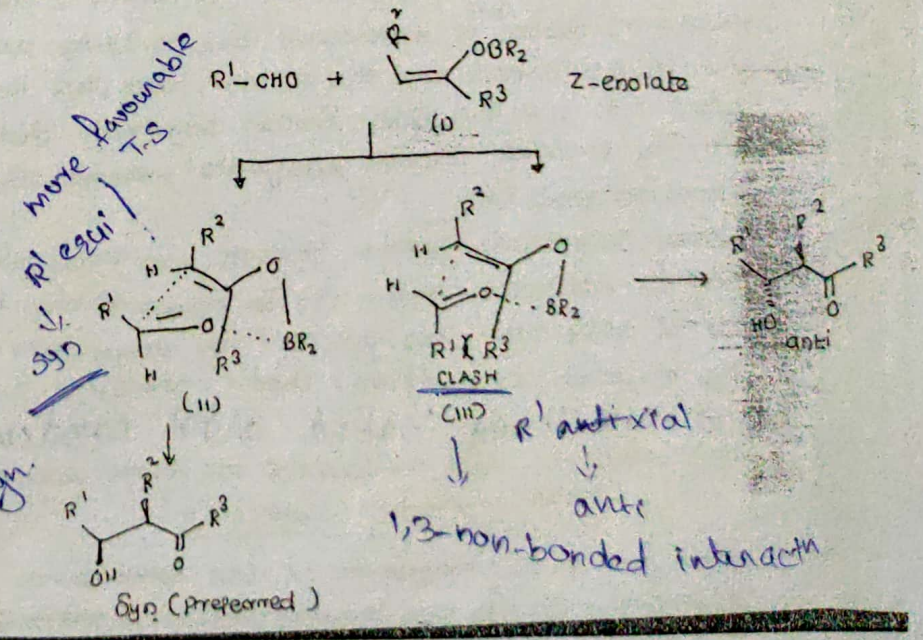
Bu_2BOTf – dialkyl boron triflouro methane Sulphonate (triflate)

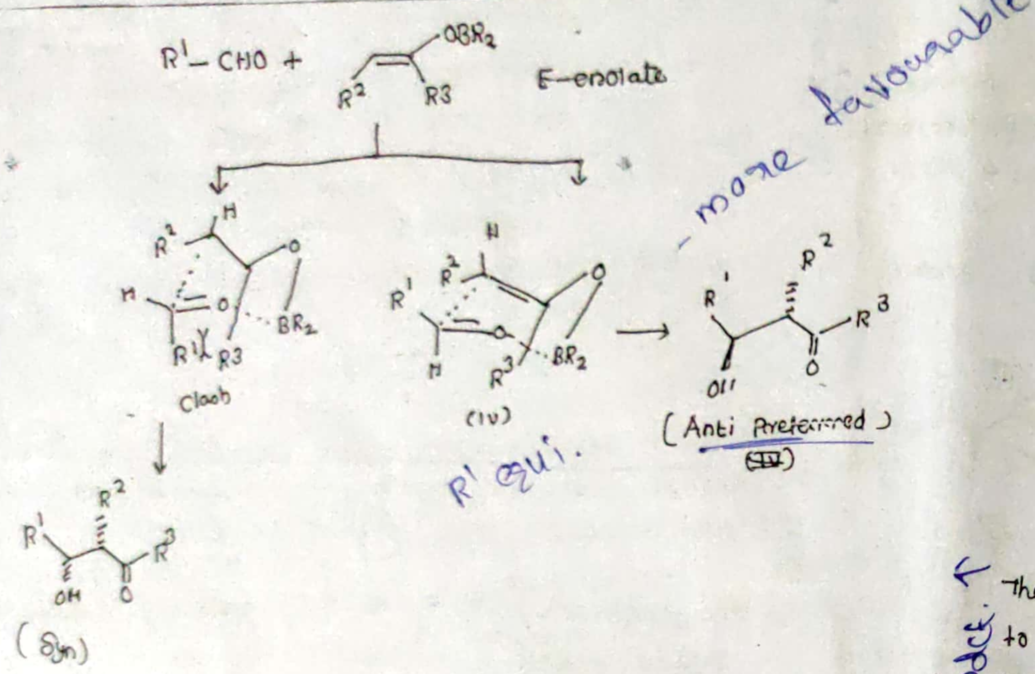
$Et\,N(iPr)_2$ – diisopropyl ethyl amine

→ Boron enolates give better stereoselectivity than lithium enolate. The B–O bonds are shorter (thus magnification of steric interact in the transition state) than Li–O bonds.

The diastereoselectivity of the aldol reaction – A chair like transition state – Zimmerman–Traxler transition state

The diastereoselectivity is achieved by the reaction proceed via a chair like six membered transition state in which the ligated metal atom is bonded to the oxygen atom of the aldehyde as well as to that of enolate.





If the geometry of the enolate is fixed, the only variable is the orientation of the aldehyde, and one deals with transition states of different stabilities. This is so since the electron rich enol double bond and the electrophilic carbonyl carbon atom can be brought in to close proximity via two transition states. eg: in the z enolate, one of the transition states (iii) is disfavoured due to 1,3-non bonded interaction b/w the substituents and thus the rexn takes place largely via transition state (ii) to give syn aldol. Similar arguments show that the rexn with the E-enolate proceeds ~~through the~~ preferentially through the transition state (iv).

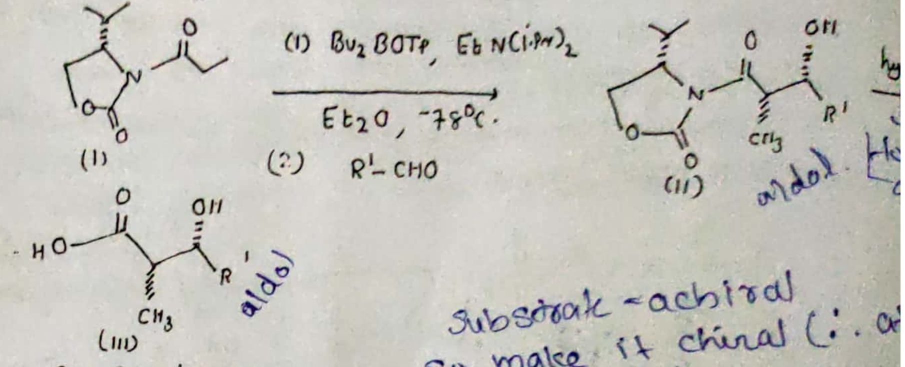
Overall the reaction proceeds through most favourable six membered ring ~~the~~ transition state. This six membered ring transition state for the aldol rexn was proposed by Zimmerman and Traxler. This is called Zimmerman - Traxler transition state)

Application

chiral auxilliary based aldol condensation

Enantioselective aldol condensation via chiral enolates (Double asymmetric synthesis)

when one of the components in aldol condensation is optically active, the reaction may becomes highly enantioselective in which case only one of the four stereoisomers predominates. enolates with chiral auxiliary group (chiral boron enolates) used with success. Thus chirality ~~chirality~~ is introduced in to partner and after the rexn it is removed.



One enantiomer

Substrate - achiral so make it chiral (∴ oxazolidonone).

The propionamide 1 as it z-boron enolate reacts with achiral al.. to give syn aldols almost exclusively. On hydrolysis enantiomeric.. pure 3-hydroxy-2-methyl carboxylic acids (iii) are formed.

Pdct.

This type of a reaction where an optically active substrate (ch.. enol derivative) reacts to generate both new stereocentres enantios..tively is called double asymmetric synthesis.

enantioselectivity

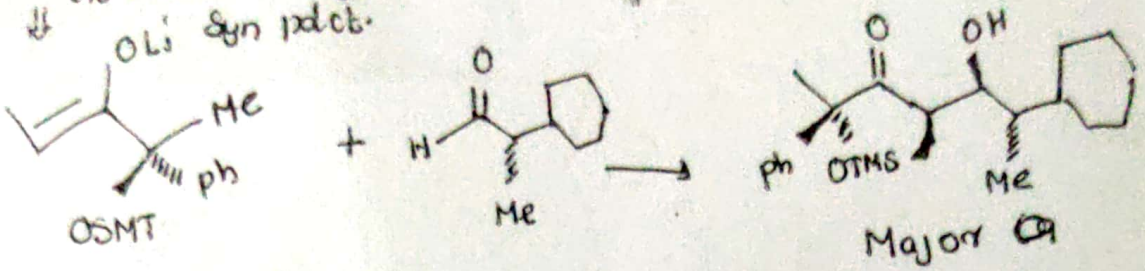
Matched and mismatched aldol reactions - Google Search

The aldol condensation problem is complicated when b.. aldehyde and enolate substrate are chiral an possess controlling stereogenic centres (usually α) This is a comm.. problem in complex natural product synthesis. In this cas.. each substrate has an inherent facial bias when both substrates have the same bias, they reinforce the facial selectivity leading to improved stereoselectivity (reinforced stereoselection). This is the matched case.

when the inherent facial bias in one substrate opposes that in the other, stereoselectivity is reduced. This is mismatched case. One substrate usually exerts a stronger facial bias than the other and on occasion can completely override the inherent facial preference of its partner.

In this case one substrates control the stereochemical outcome entirely. This can be desirable.

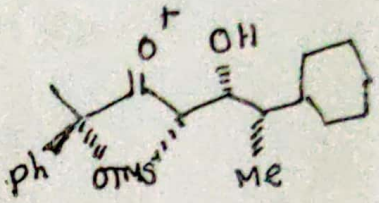
Cis enolate will give syn prdct.



Major Pdt

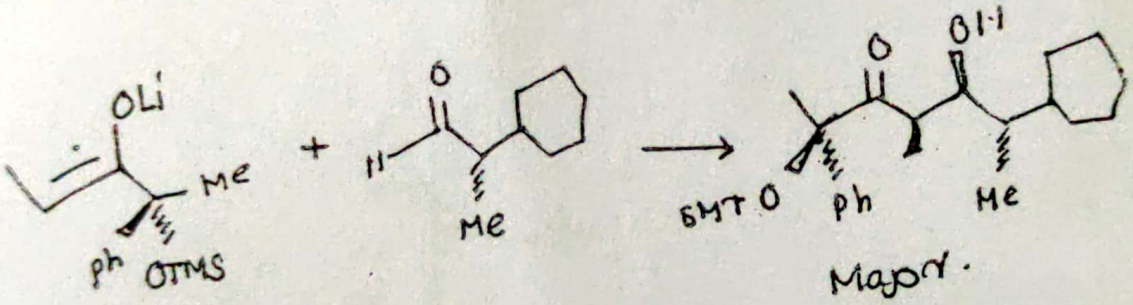
MATCHED CASE

(both stereogenic centres have the same facial bias)



Minor

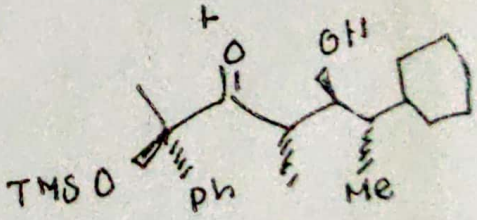
(9:1)



Major.

MISMATCHED CASE

(-Ph)



Minor

1.3:1

Same facial bias - Matched case

" " - Mismatched "

Opp. "

12 copy

Dr. Mohammed Musthafa. TN
D/o chemistry
Asst. Prof.

13 copy

4

2 5 8

VNN

3 copy

Sarika. V

Amrutha.

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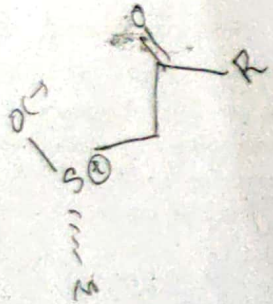
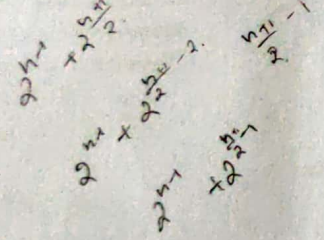




Asymmetric Synthesis

Unit-6

ISOMERISM - II

kalsi

In general chemical reactions give products in the racemic form, bec^2 the reactants, reagents or solvents used are achiral and are themselves racemic. In the absence of a chiral influence, a rexn producing enantiomers gives them in equal amounts (racemic mixture) via the transition states of identical energies. These reactions, therefore, take place at identical rates to give equal amounts of the enantiomers. So stereoselective synthesis are designed for the synthesis of one enantiomer from an stereoisomeric possibilities.

Principle of asymmetric synthesis

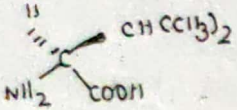
For the preferential formation of one stereoisomer (either enantiomer or diastereomer) over the other, either the reactant, or the reagent, or the solvent must be the pure enantiomeric form. The chiral agent must play an active part in the reaction and has to be integral to the transition state, so that two diastereoisomeric transition states are formed. Consequently one stereoisomer is produced more rapidly than the other.

Clayden + Kalsi

The chiral pool - Natures 'ready made' chiral centres

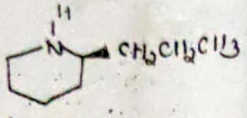
The chiral pool is the collection of cheap readily available pure natural products usually amino acids or sugars, from which pieces containing the required chiral centres can be taken and incorporated in to the product.

Some examples of molecules in the chiral pool

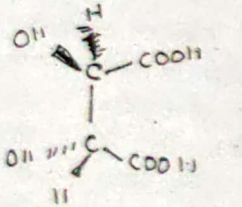


S(+) valine.
(an α-amino acid)

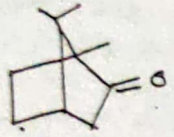
R-(+)-α-pinene
(a terpene)



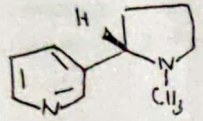
(+) conine
(an alkaloid)



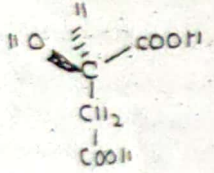
(+)-Tartaric acid
(an α-hydroxy acid)



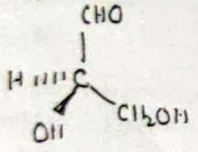
Camphor
(a terpene)



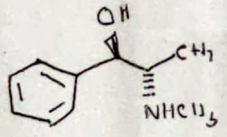
(-) Nicotene
(an alkaloid)



(+)-Malic acid
(an α-hydroxy acid)



D-Glyceraldehyde
(a carbohydrate)

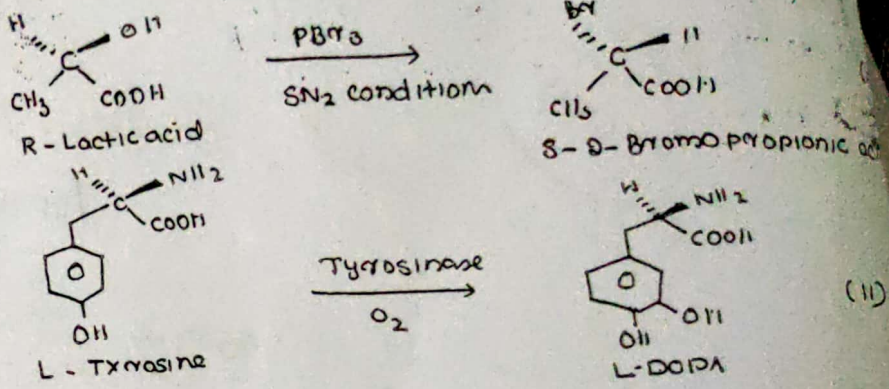


(-) Ephedrine
(an amino acid)

Principle categories of asymmetric synthesis - Kalsi

(A) The use of chiral substrates (First generation methods)

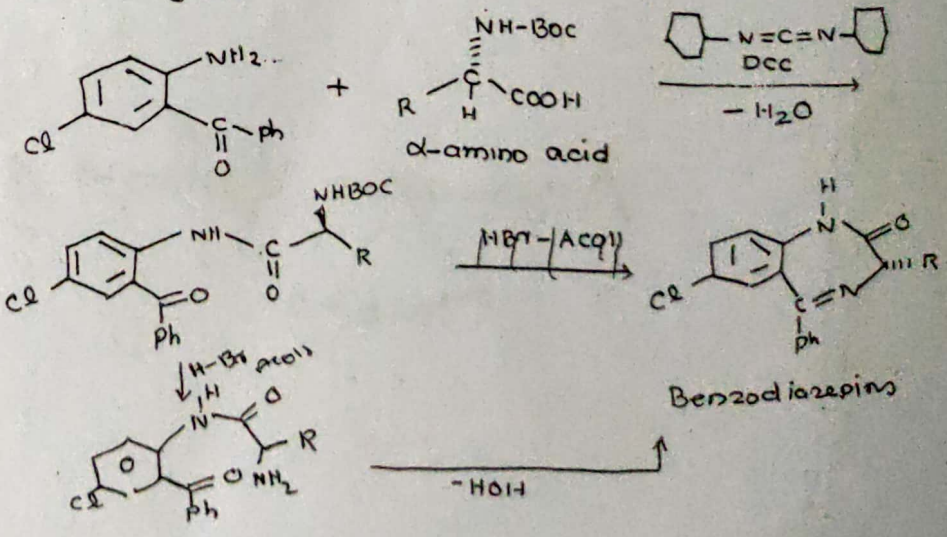
First generation method require the use of enantiomerically pure natural products eg: steroids terpenoids, alkaloids, amino acids etc (chiral pool). So here we will use the stereochemistry of readily available natural materials. Most commonly used material are amino acids and carbohydrates. A chiral material from the chiral pool may lead to a straightforward method to make an enantiomerically pure product (asymmetric synthesis). It may react in a stereospecific pathway[1] or without effecting any existing stereocentre (11).



α-amino acids in the synthesis of benzodiazepins

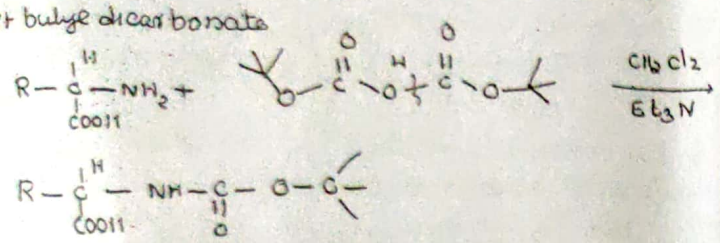
- www.sussex.ac.uk (google search)

All protein amino acids belong to L-Series. Most of these have S configuration. These α-amino acids are used in the synthesis of pharmaceutically important benzodiazepines. Stereocentre can be incorporated starting from alanine onwards. These amino acids are also used for the preparation of chiral auxilaries and chiral ligands.

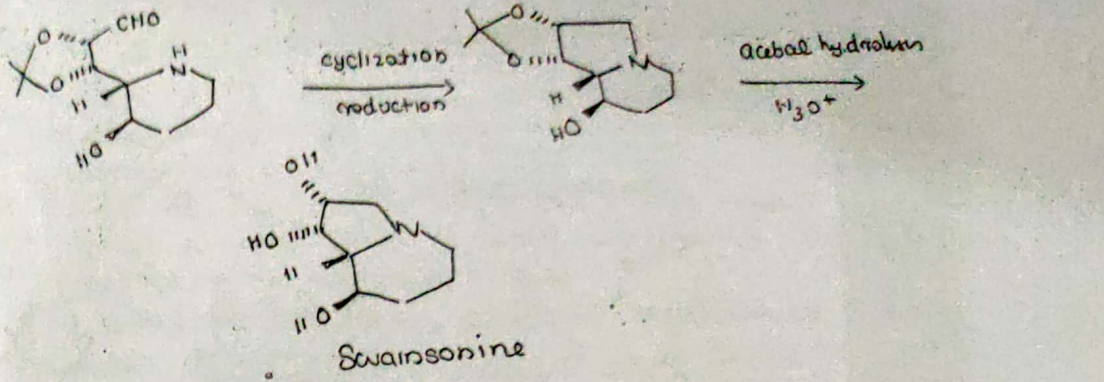


→ Dcc is a dehydrating agents for the preparation of amide bond from acid and amines.

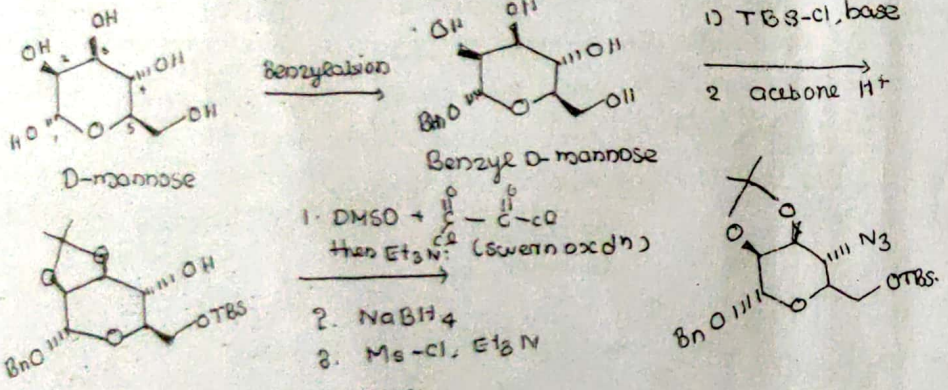
→ amino groups in amino acids are protected as t-butoxy carbonyl with (Boc) ditert butyle dicarbonate



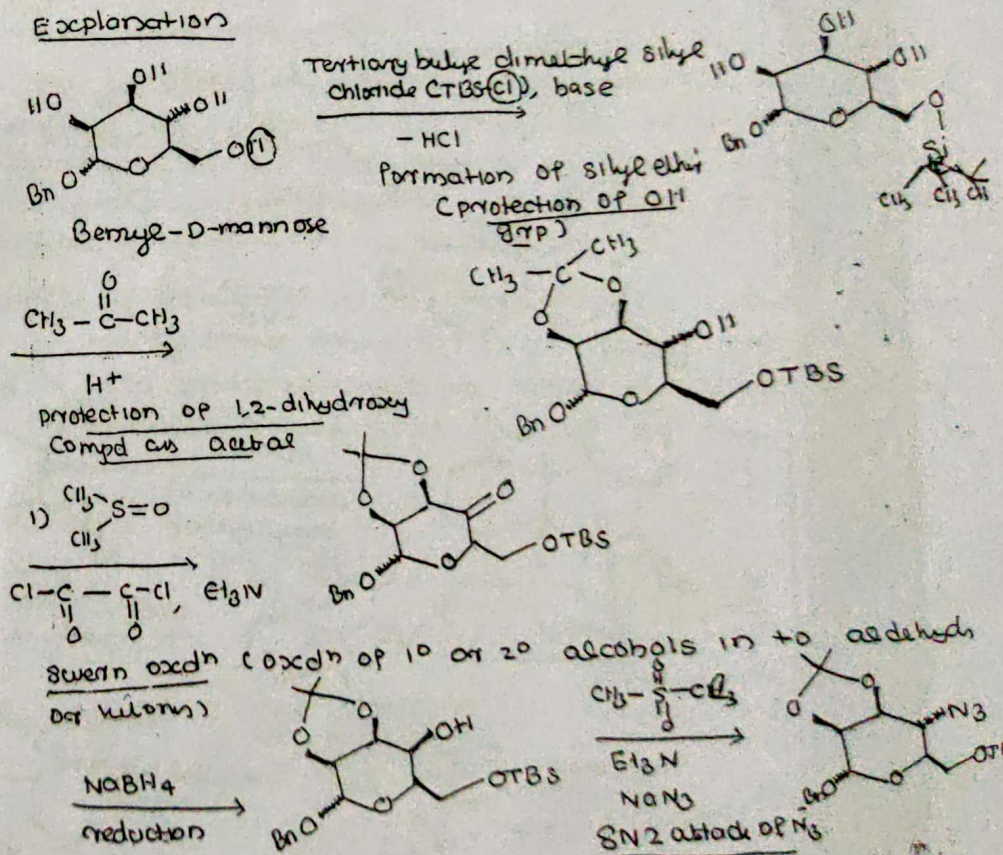
→ Boc-deprotection can be done under acidic conditions

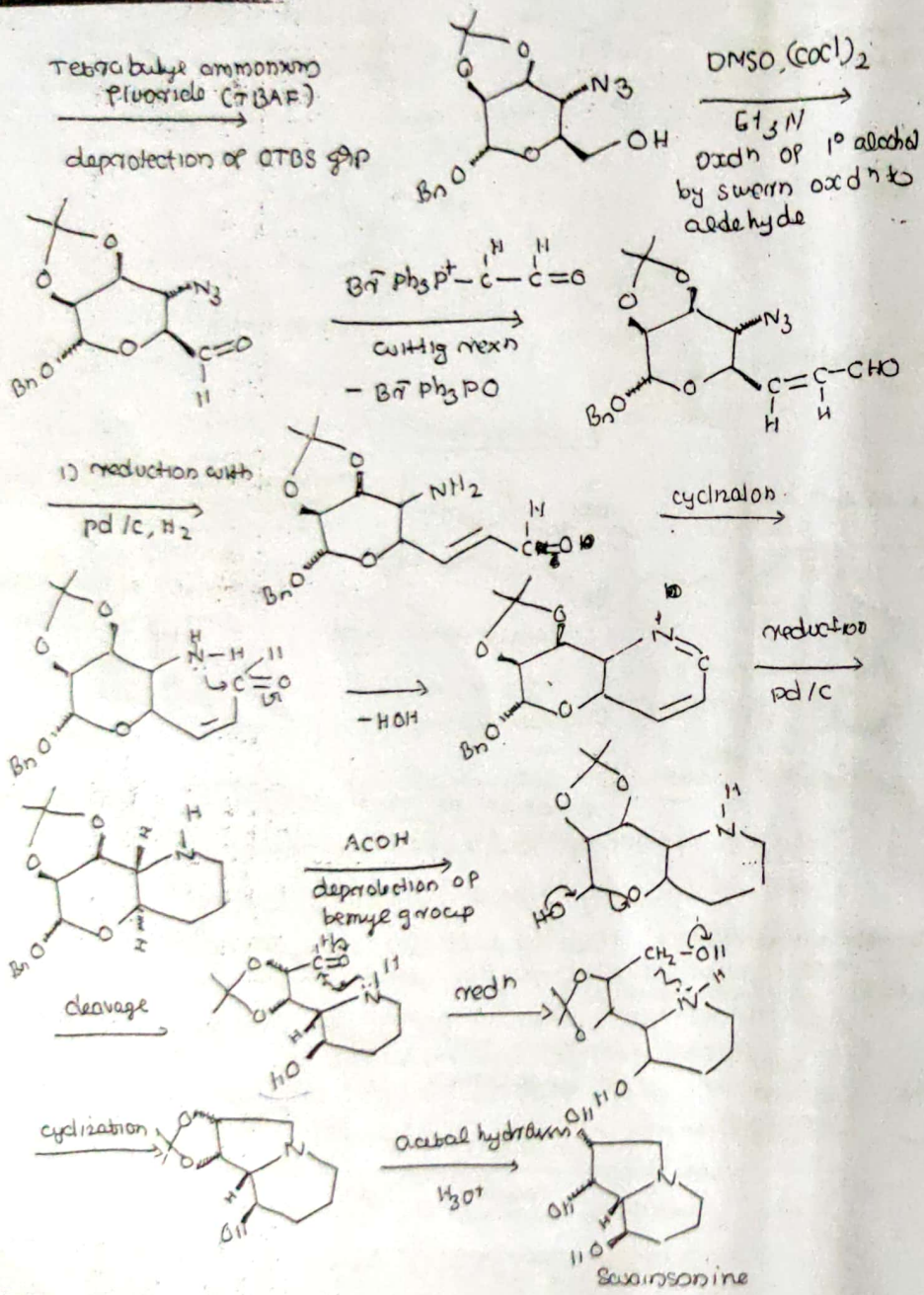


Benzyle D-mannose to Swainsonine

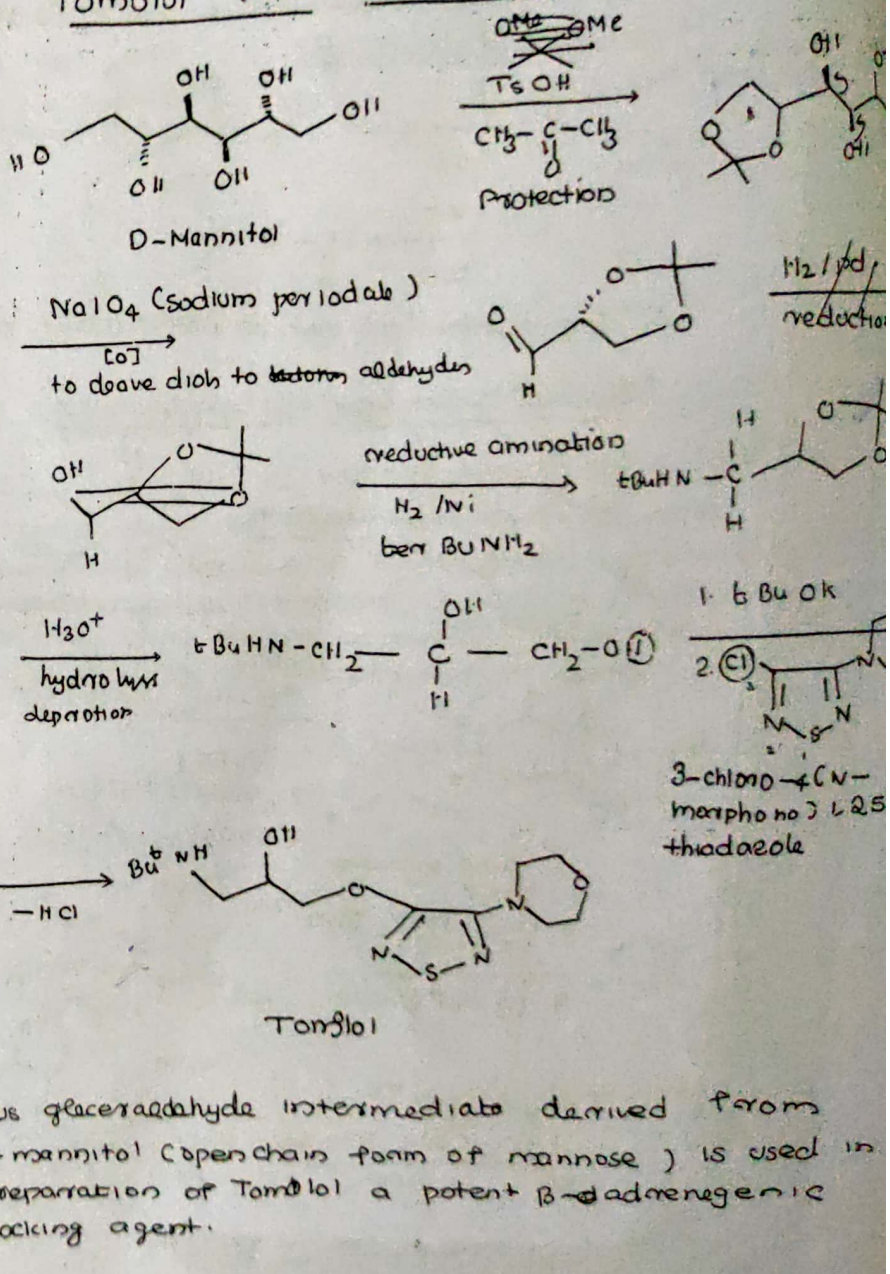


Explanation





Tomolol from D-mannitol



Thus glyceraldehyde intermediate derived from D-mannitol (open chain form of mannose) is used in preparation of Tomolol a potent β-adrenergic blocking agent.

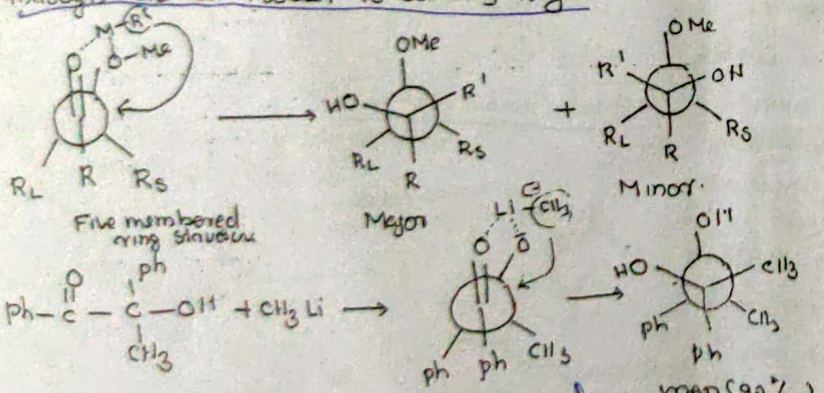
Asymmetry induction compared to Cram's rule

Cram's chelation control — Nasipuri

* Refer Cram's rule from conformational analysis-II

→ If there is a chelating group (Lewis base) then Cram chelation control can be used to predict the outcome.

→ If the chiral centre in the ketone contains an α-group such as OH, NH_2 and OCH_3 which is capable of coordinating with the reagents, the stereochemistry of the product is predicted by Cram's rule based on a rigid (chelate) cyclic model in which the metallic part of the reagent is doubly coordinated to form a five membered ring. The nucleophile preferentially approaches the electrophilic carbon from the side of R_S. If the chelating group is R_M, the cyclic model predicts the same stereochemistry as the open chain model, but if it is R_S or R_L opposite stereochemistry follows. Assymmetric induction through chelate model is usually high.



5 membered chelate bcoz of Li (electrophile)

lone pair gp. - med, small

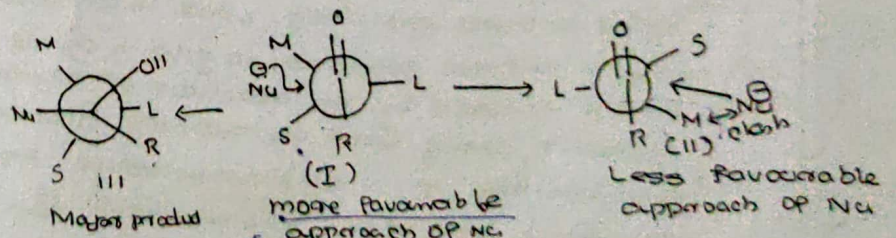
Felkin - Ahn model — Kalsi

The Felkin-Ahn developed a variation based on theoretical calculations in terms of steric intersections and predicts more fully, the results of chiral induction and is preferred. The Felkin Ahn (FA) model differs from Cram's rule in the conformation adopted by the carbonyl compd.

→ In the FA model the C-L bond is positioned perpendicular to the carbonyl group. This is unlike Cram's rule where L is assumed to be antiperiplanar to the C=O gp. This arrangement removes unfavorable eclipsing interactions b/wn L and R.

→ The nucleophile approaches the carbonyl carbon in a plane tr to that of CO fragment from the side opposite to the C-L bond and at an obtuse angle with C=O which corresponds nearly to the tetrahedral angle of Nu-C-O in the product.

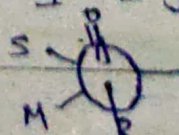
→ The consideration of the reactive conformation (I and II) shows that (I) is of lower energy due to less steric interaction b/wn the nucleophile and the smallest group S to give (III) as the major product.

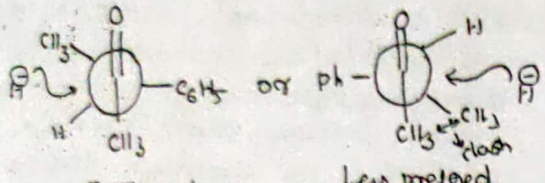


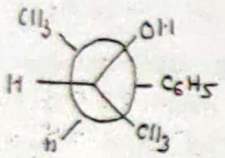
same as Cram's rule small gp. side.

L & R gp. eclipsed → steric interact,

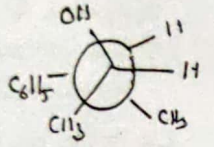
L gp. - Felkin Ahn model - more stable.







(2R,3S)-3-phenyle butan-2-ol
(Major)



(2S,3S)-3-phenyle butan-2-ol (Minor)

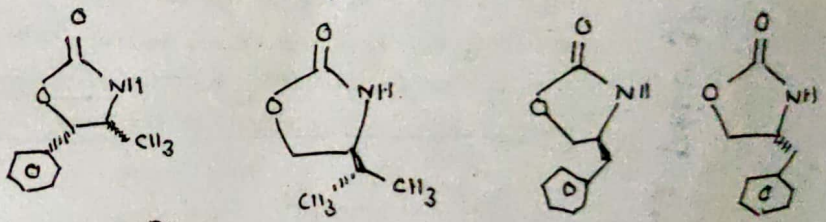
The use of chiral auxiliaries (second generation methods - Kalsi + Claydon.

An enantiomerically pure compd (usually derived from simple natural product like amino acid) called a chiral auxiliary, which is attached chemically to the achiral substrate to give a chiral intermediate. This is followed by the reactions of asymmetric synthesis, during which the auxiliary dictates the preferred stereochemistry. ie a diastereoselective rexn is carried out, which bec² of the enantiomeric purity of the chiral auxiliary, gives only one enantiomer of the product. At the end of the synthesis the chiral auxiliary is removed for example by hydrolysis, leaving the product of the reaction as single enantiomer. the best chiral auxiliaries can be recycled, thus there is no wastage.

Evans Oxazolidinones

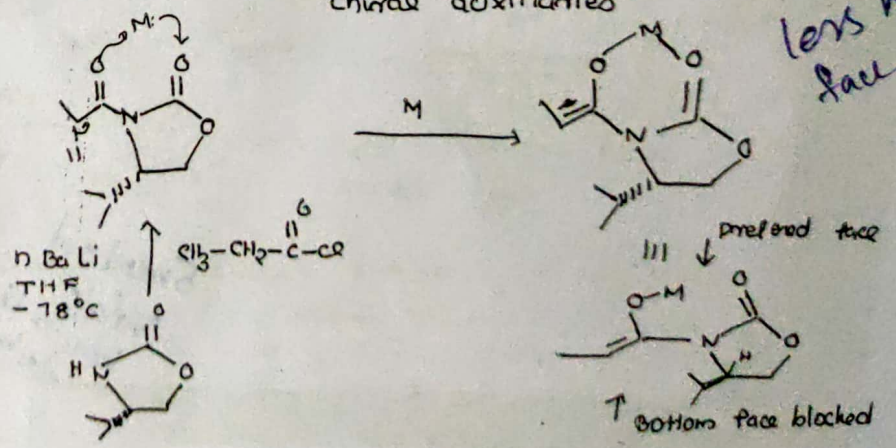
Oxazolidinone auxilaries popularized by David Evans have been applied to many stereoselective transformations including aldol rexns, alkylation rexns and Diels alder reactions. The oxazolidinones are substituted at the 4 and 5 positions. Through steric hindrance, the substituents direct the direction of substitution of various groups. The auxiliary is subsequently removed through hydrolysis

Oxazolidinones can be prepared from amino acids or readily available amino alcohols.

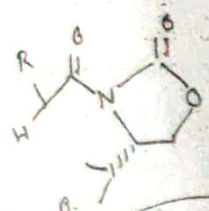


① alkylation rexns

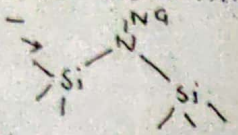
Commercially available oxazolidinone chiral auxiliaries



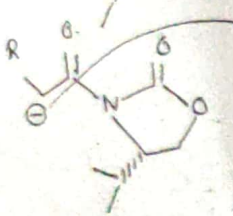
less hinde
face thro



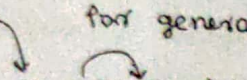
1) NaHMDS (Sodium bis (trimethyle silyle) amide –

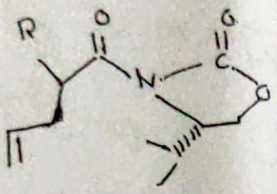


for generation of enolate



enolate

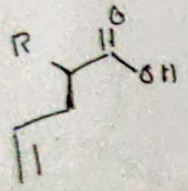




diastereomer

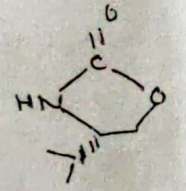
removal of auxiliary

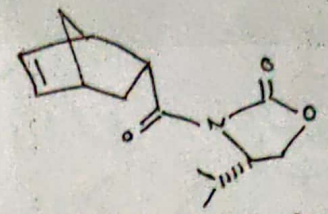
KOH (hydrolysis)



enantiomer

+



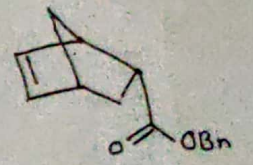


this adduct is formed as a single diastereomer

Lithium benzyle ether

?

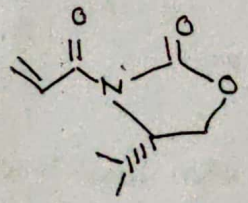
$LiOBn$



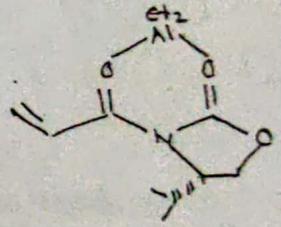
removal of the chiral auxilary reveals this compound as a single enantiomer

+

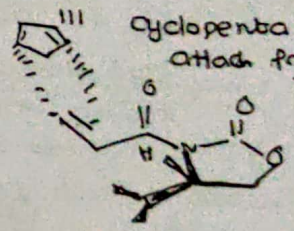
chiral auxilary recovered can be recycled



Et_2AlCl



cyclopentadiene must attack from top face



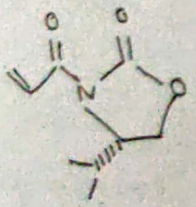
bottom face is shielded (this controls stereochemistry)

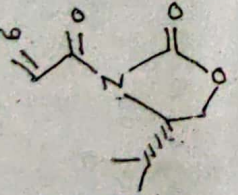
② ~~aldol reactions~~ Diels–Alder rexns

base

$-HCl$

Single enantiomer derived from (S)-valine





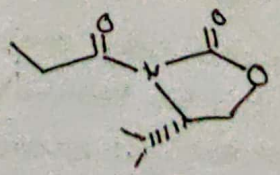
achiral diene

Et_2AlCl

Dienophile

Single enantiomer of dienophile

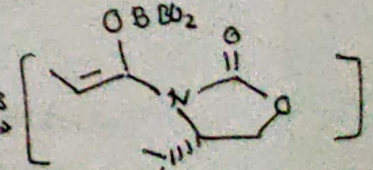
opp. to bulky (isopropyl) grp. dienes attack



③ aldol reaction

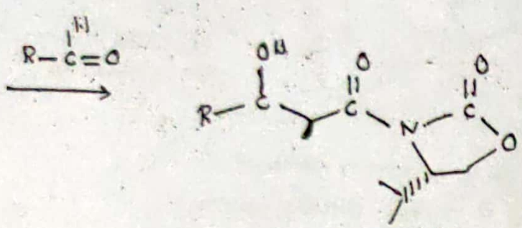
$Bu_2BOSO_2CF_3$

iPr_2NEt

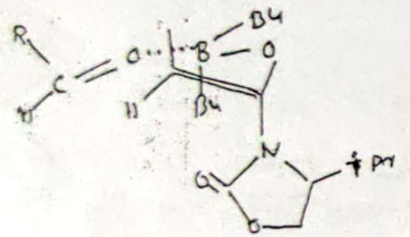


geometry of the enolate determines syn or anti aldol.

Syn/anti aldol - auxilliary depend
↓
cetric ↓ 1.

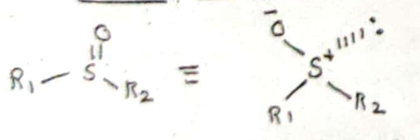


auxiliary determines absolute stereochemistry



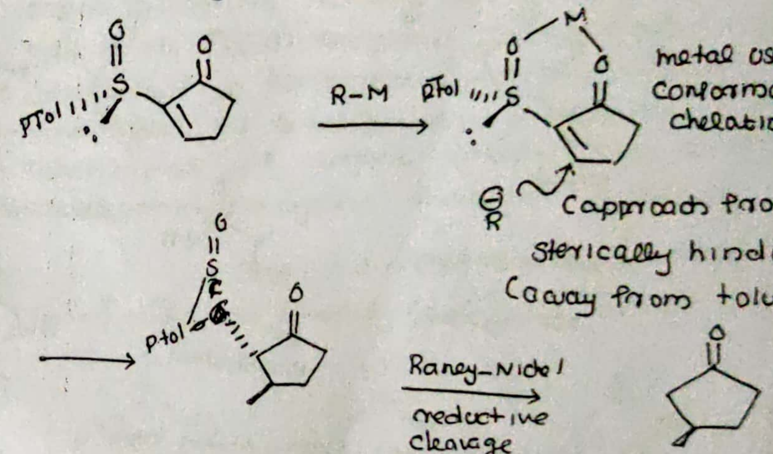
aldehyde approaches from the least hindred face due to auxilariary which controls stereochemistry. The Lewis acidic boron activates carbonyl oxygen by co-ordination and arranges 6-membered transition state.

Chiral Sulfoxides

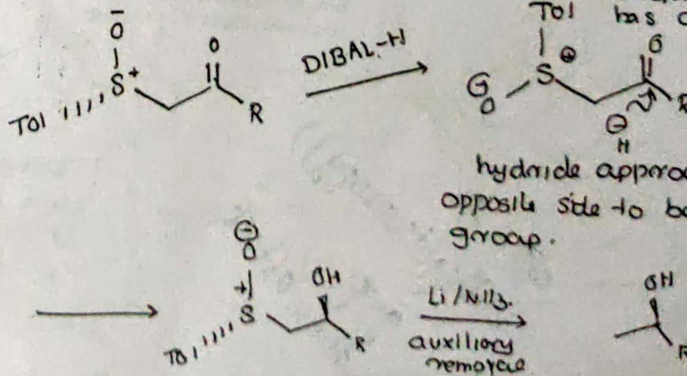


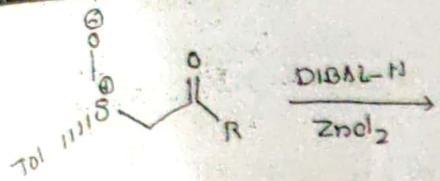
stereogenic centre (chiral)

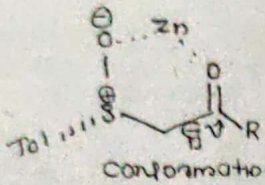
Sulfoxides are conformationally stable at room temperature and hence can be separated into pure enantiomers. The barrier to inversion via a bipyramidal intermediate for most sulfoxide compds is in the range of 38-41 kcal/mol[2]. Sulfoxides will only racemize under harsh conditions temp excess of 200°c. Thus sulfoxides are used as chiral auxili[ary] in a range of rexn. chiral sulfoxides have been [used] to induce good diastereoselectivities



→ Sulfoxides can be used to control reduction of ketones. Depending on reaction conditions either diastereoisomer can be produced with complete control.

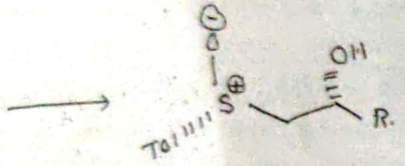




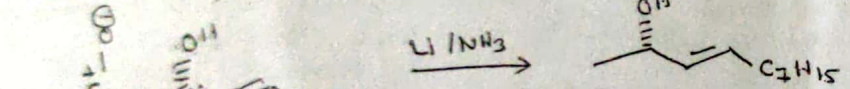


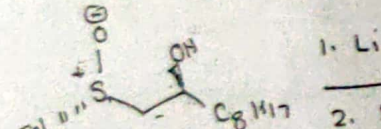
Conformation controlled by chelation

(H^- approaches from the opposite side of bulky group

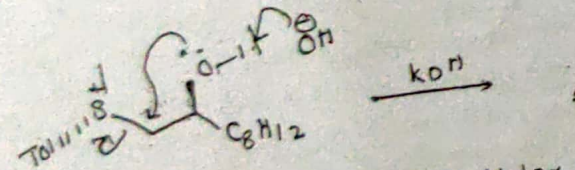


Auxiliary removal



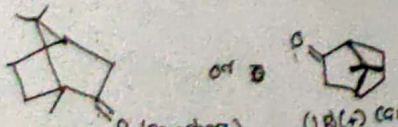


1. $LiAlH_4$ (for redⁿ of sulfoxide)
2. Me_3OBF_4 (for cation formation)



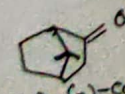
Camphor derivative in Diels-Alder reaction

Camphor is a readily available chiral material and its derivative is used widely in assymetric Diels-Alder reactions.

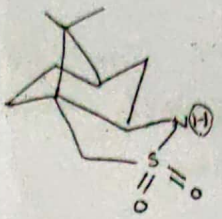


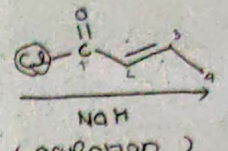
or

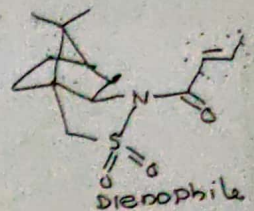
(1R)(+) camphor

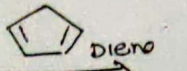


(1S)-(-)-camphor

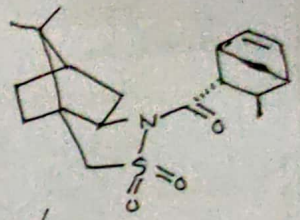




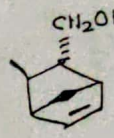




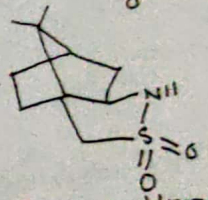
Et_2AlCl_2 (lewis acid activates enone)
-78^oC, 1hr



auxilary removal
$LiAlH_4$



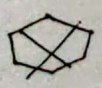
+

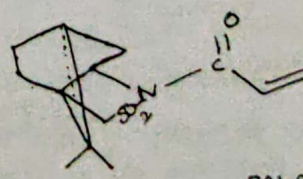


chiral auxiliary can be recovered and used again

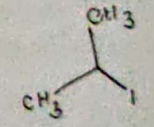
Camphor derivative in Radical reactions

the radical reactions utilising Camphor derivative are found to occur with excellent diastereoselectivity

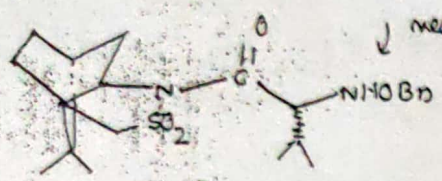




+

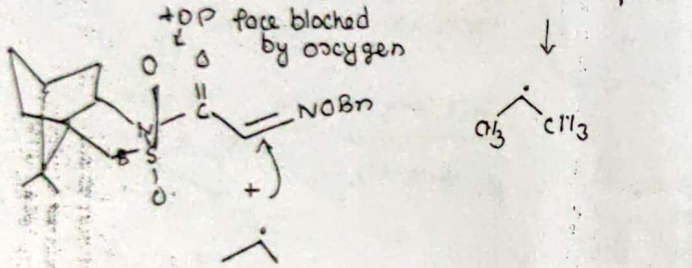


BCy_3SnH, Et_3B

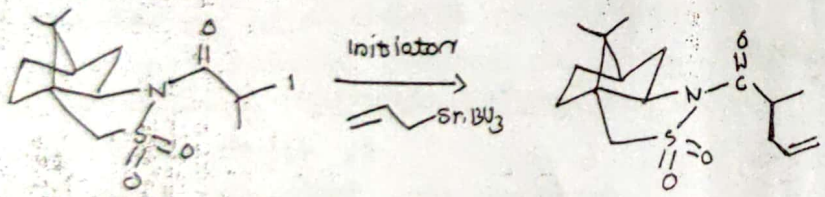


Mechanism

$Et_3B + O_2 \longrightarrow Et^{\cdot} + H-SnBu_3 \longrightarrow Bu_3Sn^{\cdot} +$



The donor/acceptor properties can be readily reversed to give chiral radicals.



Chiral reagents and chiral catalyst (Third generation method)

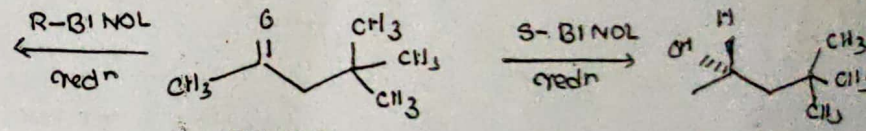
A prochiral unit can be converted into a chiral one by attaching the chiral influence to the substrate as that we did in chiral auxiliaries or by introducing the chiral influence on the reagent. Thus chiral reagents gained much importance in asymmetric synthesis.

Substrate —Chiral reagent—R→ Substrate

R

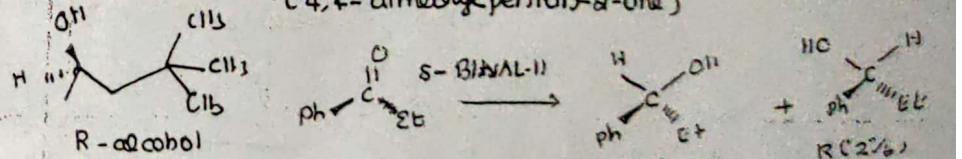
BINOL (1,1'-bi 2-naphthol)

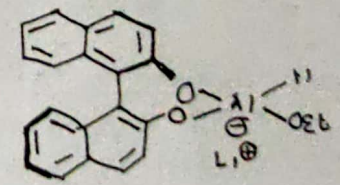
BINOL is commonly used as an asymmetric reducing agent and is derived from optically active binaphthol, ethanol and $LiAlH_4$. The tetrahedral array of atoms around Al locks effectively the aromatic ring in to one configuration and does not allow racemisation unless the C–C–C–C–Al–O ring is disrupted. Reduction of ketones, preferentially unhindered acyclic and conjugated enones / proceeds with high selectivity with this reagent.

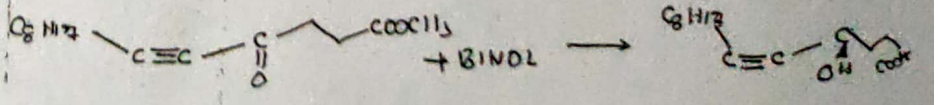


DIMPO
(4,4-dimethylpentan-2-one)

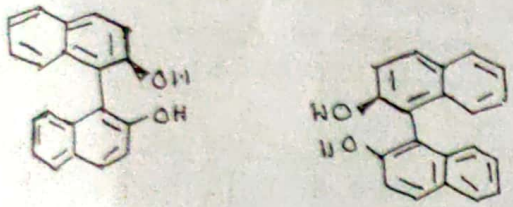
S-alcohol



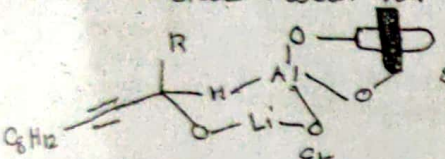


I 

Due to restricted rotation around the central bond binaphthol has axial chirality, and the two forms are not superimposable.



proposed transition state model for rexn I



Orientation of BINOL system controls carbonyl approach.

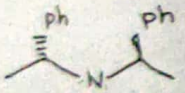
unsaturated group is equatorial

ethoxide forms bridge to allow 6 membered transition state

?

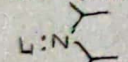
Lithium di(1-phenyle ethyle amide) – LDPA

kassim sir's note + advanced synthesis (google search)



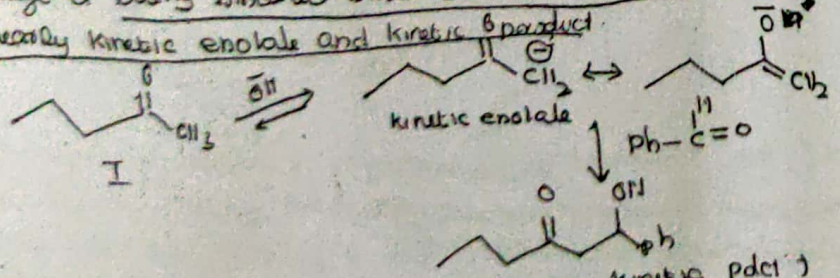
Li (Base)

[LDA – Lithium diisopropyle amide



]

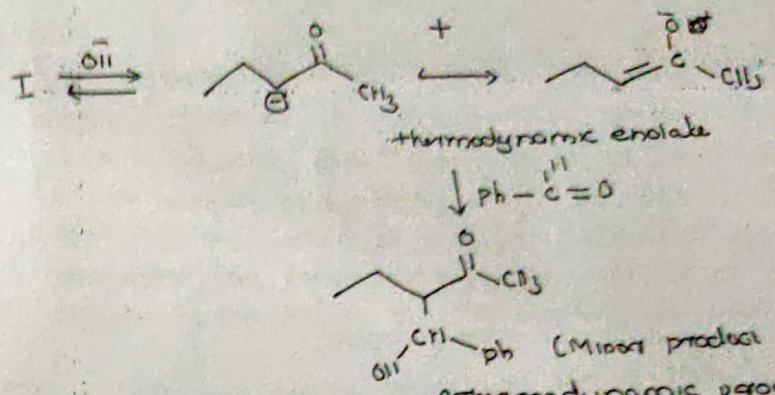
An aldol reaction carried out by using $\bar{O}H/H_2O$ will give kinetic (abstraction of proton from less hindered carbon) as well as thermodynamic (abstraction of proton from more hindered carbon) products, whereas on the usage of bulky hindered base LDPA to give partly and clearly kinetic enolate and kinetic β product



I

kinetic enolate

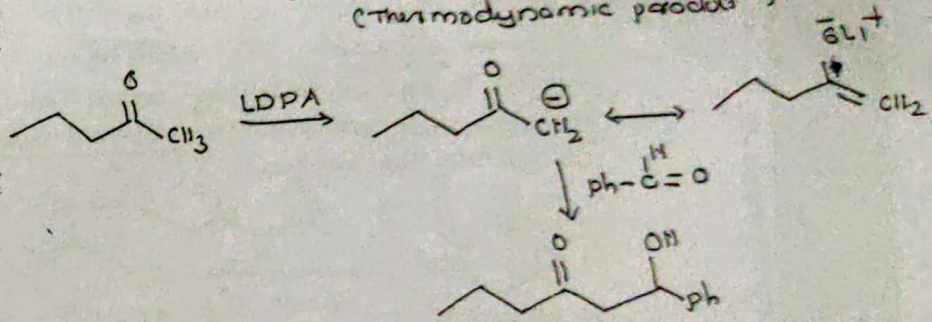
(Major – kinetic pdct)



thermodynamic enolate

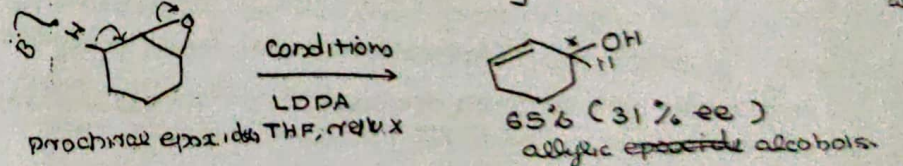
(Minor product)

(Thermodynamic product)



kinetic product (Major)

(II) prochiral epoxides can undergo asymmetric deprotonation into enantiomerically enriched allylic ~~epoxides~~ alcohols



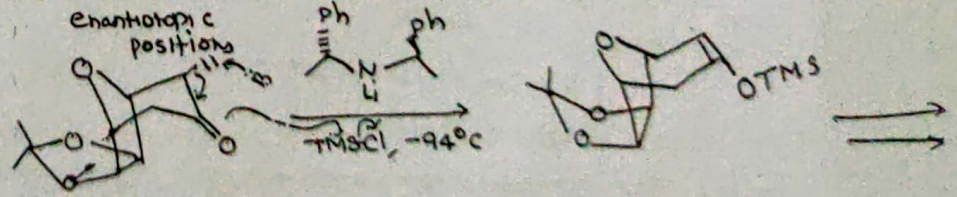
prochiral epoxides

conditions: LDPA, THF, reflux

65% (31% ee)

allylic ~~epoxide~~ alcohols

(III) These chiral bases (lithium di(1-phenyle ethyle amide) can also be used to desymmetrise prochiral ketones.

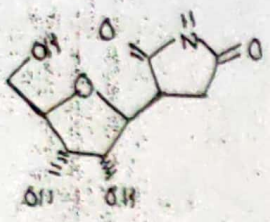


enantiotopic positions

plane of symmetry makes it prochiral

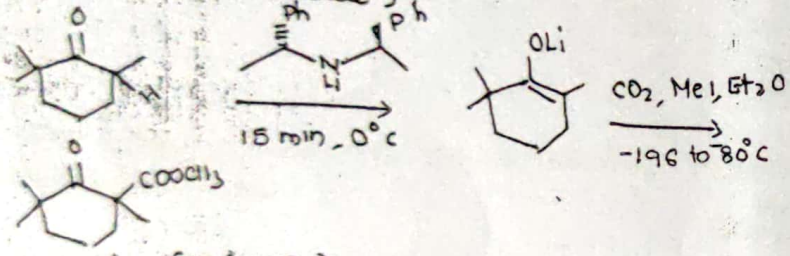
TMSCl, –94°C

OTMS



Showdomycin

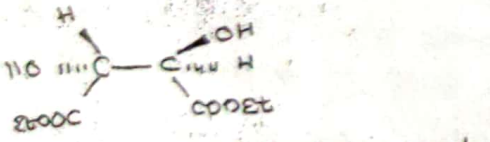
(iv) chiral base used in the asymmetric reactions of achiral enolates. The enantiomerically pure lithium amide is non-covalently associated with achiral enolate and behaves like chiral auxiliary (without being bound to the molecule)



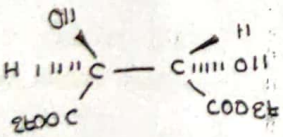
90% (97% ee)

Thus overal chiral lithium amides are versatile bases for desymmetrisation and in resolution reactions

Tartarates — Kalsi + Claydon.

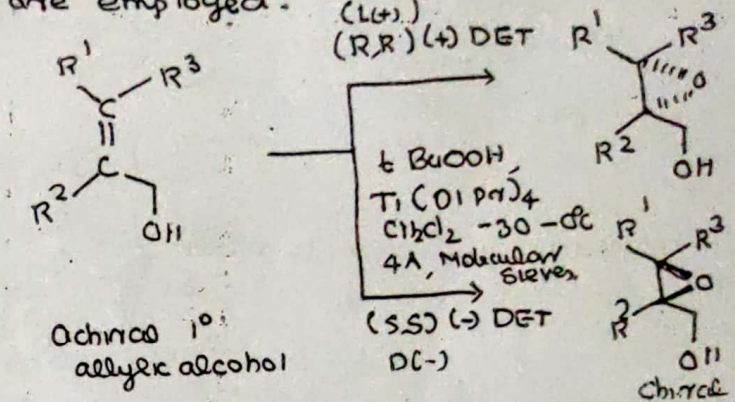


(R,R)-(+)-Diethyltartarate
(R,R)-(+)-DET



(S,S) (-)-DET

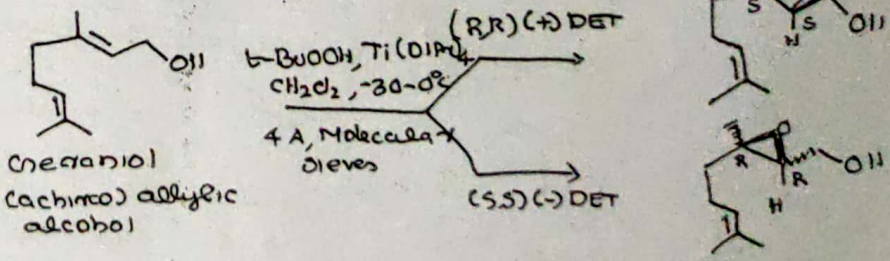
(1) The major application of tartarates comes in Sharpless asymmetric epoxidations, where the oxidation of an allylic alcohol is carried out with t-butyl hydroperoxide and titanium tetraisopropoxide. The procedure results highly enantioselective produc when enantiomerically pure tartarate este are employed.



→ the technique is one of the best methods for t conversion of an achiral allylic alcohol in to chiral epoxide.

→ the epoxidation is brought about by ter-butyl hydroperoxide, catalyzed by titanium (IV) tetra is propoxide in the presence of (+) or (-) DET.

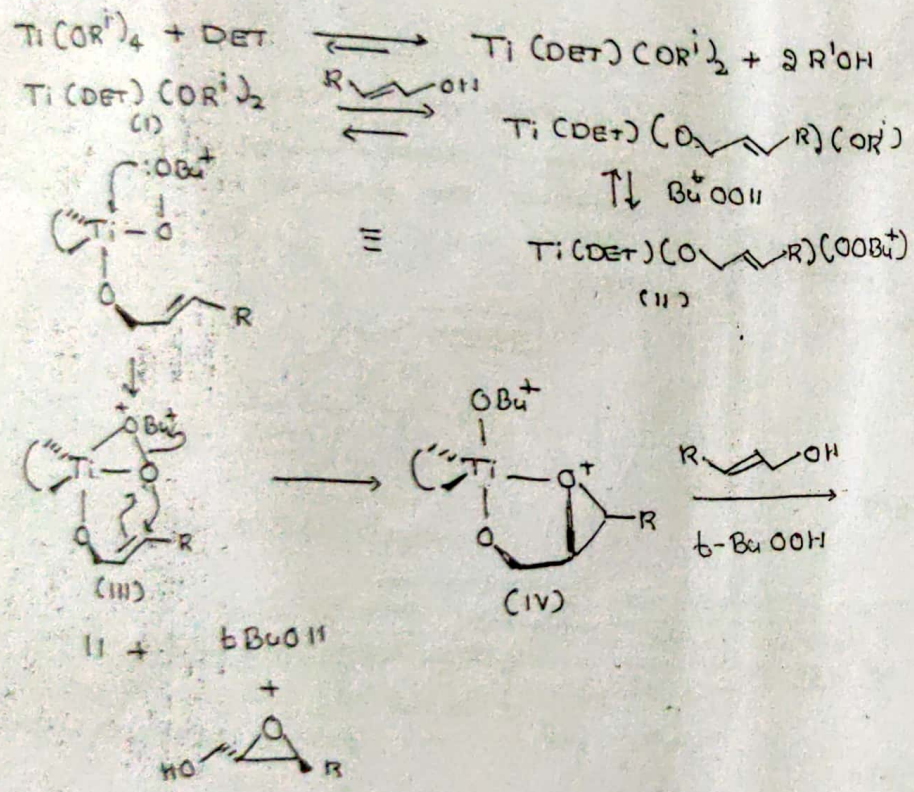
→ The reaction creates two stereocentres with pre dictable stereochemistry depending on which enantio mer of DET is used. With the use of (R,R) isom of DET one isomer of the epoxide is obtained predominantly. By replacing with the other isome of DET (S,S), the other enantiomeric epoxide is obtained.



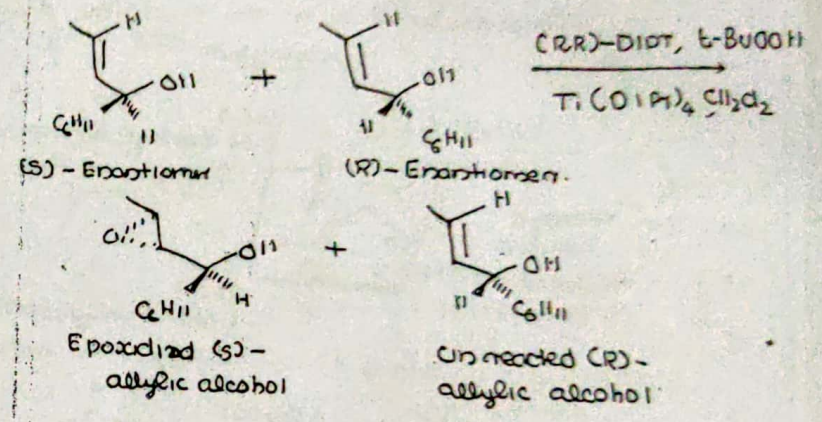
→ The reaction is highly sensitive to the presence of water (hydrolysis of the complex), it is therefore carried out in the presence of molecular sieves (inorganic silicates which have small channels, where only water can enter).

→ The major catalytic species in this enantioselective epoxidation reaction is a binuclear titanium complex.

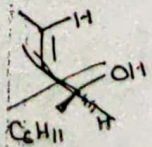
Mechanism



The reaction starts by the displacement of two isopropoxy groups in one titaniumtetra isopropoxide with two hydroxyl groups in the tartarate ester (DET) to give I. Further the remaining isopropoxy groups are replaced with the hydroxyl group of allylic alcohol followed by the hydroxyl group of the peroxide. These successive displacement setup preferred disposition of the alkene and the oxidant as in (II). The coordination activates the peroxide and it is this topography which determine, the favourable enantioselective transfer of oxygen to the chiral centre via the complex IV.

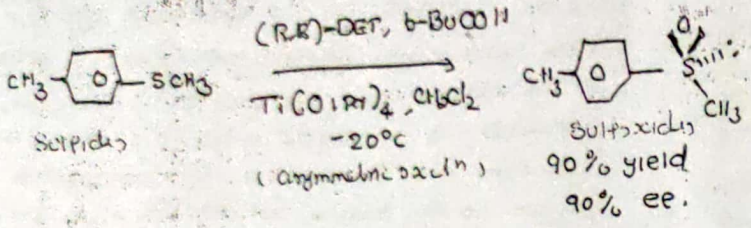
→ 

The titanium catalyst is sensitive to pre-existing chirality in the substrate. As a result, the epoxidation of racemic secondary allylic alcohols with a given tartarate-titanium-isopropoxide combination occurs rapidly only with one of the enantiomers. The other slower reacting enantiomer is left behind.



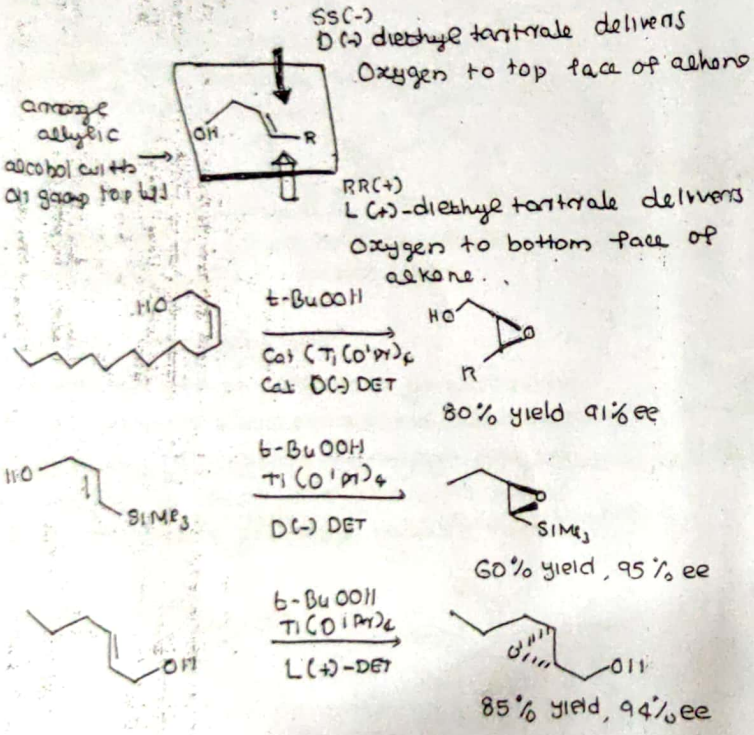
(RR)-DIPT = Diisopropyltartarate ester.

② The tartarate ester as are also used for the asymmetric oxidation of sulfides to sulfoxides. In this reaction water is actually needed inorder to achieve good selectivity



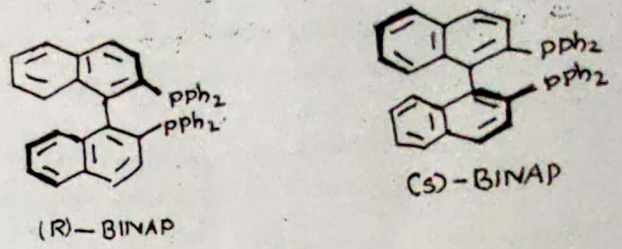
Sulphide

enantioselectivity in the sharpless asymetric epoxidation

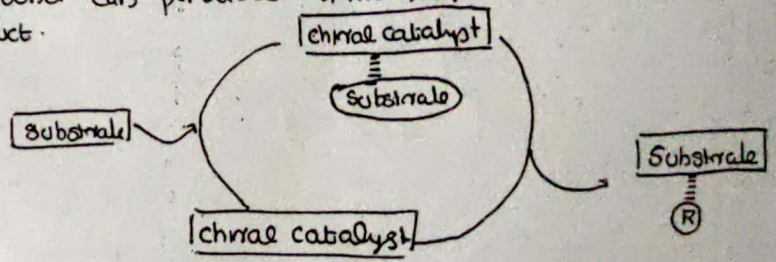


(R)-BINAP (1,1'-binaphthyle diphosphine ligand)

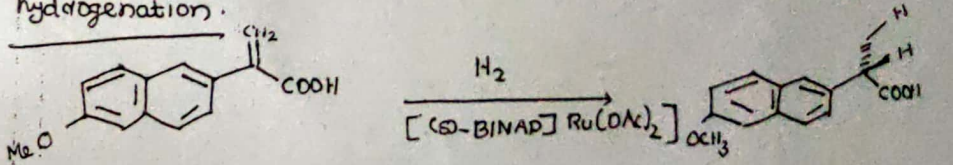
– Google search + claydon



Chiral (stoichiometric) reagents are a very important class of compounds for assymetric synthesis. The beauty of chiral catalysis is that one molecule of chiral compound can produce millions of molecules of enantioenrich product.



BINAP is commonly employed for asymmetric hydrogenation.



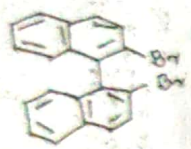
(S)-naproxen
analgesic drug

The catalyst select a single enantiotopic face of the double bond and adds hydrogen across it.

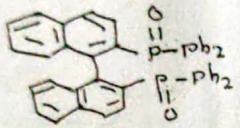
BINAP is a chelating diphosphine, the metal sits btwn the two phosphorous atoms firmly anchored

in a chiral environment. BINAP has no chiral centres but has axial chirality by virtue of restricted rotation about the bond joining the two naphthalene ring systems. For the interconversion of two enantiomers of BINAP, the PPh_2 group would have to force its way either either past the other PPh_2 group or round the bladk hydrogen. Both pathways are too strained for racemization to occur.

Resolution of BINAP -

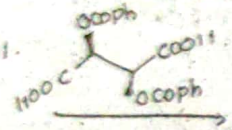


1. Mg
2. Ph_2POCl

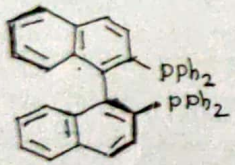


racemic dibromide

racemic bis phosphine oxide



1.
2. Crystallize
3. base
4. Reduce ($HSiCl_3$) (Stereoretentive)



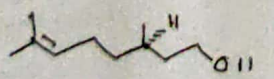
(S)-BINAP

BINAP-ruthenium (II) is particularly good at catalysing the hydrogenation of allylic alcohols and of α,β unsaturated carboxylic acids to give acids bearing α-stereogenic centres.

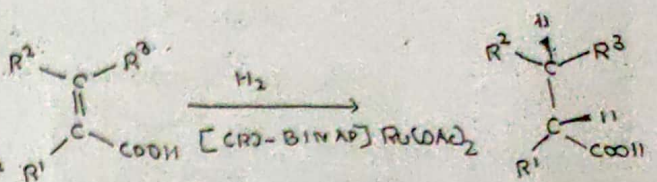
geraniol
allylic alcoholic system

H_2

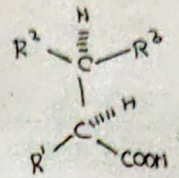
$[(S)\text{-BINAP}]Ru(OAc)_2$

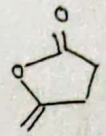


R-citronellol



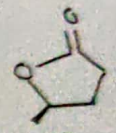
α,β-unsaturated carboxylic system



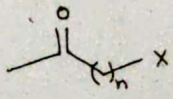


H_2, BINAP-Ru(II)

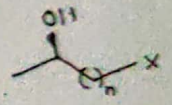
CH_2Cl_2



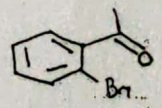
94% ee



H_2, (R)-BINAP-Ru(II)

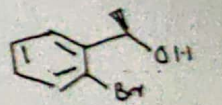


X = $-NR_2$, -OH, -COOR, COOH, Br, etc

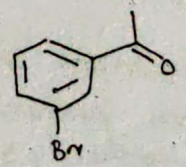


Ru(R)-BINAP Br_2

H_2 (100 atm)

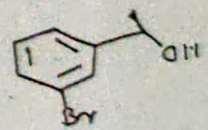


92% ee

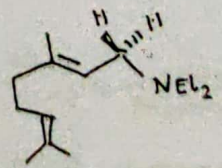


Ru(R)-BINAP Br_2

H_2 (100 atm)

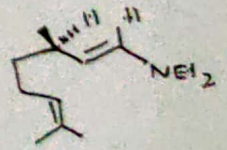


< 1% product



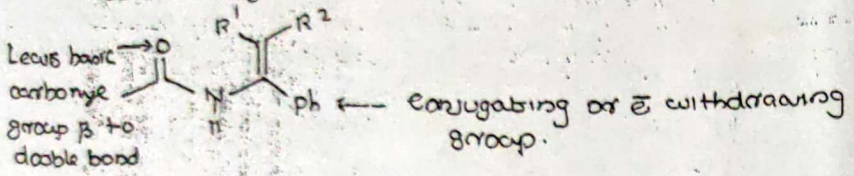
allylic amine

$Rh[(S)\text{-BINAP}]_2^+$



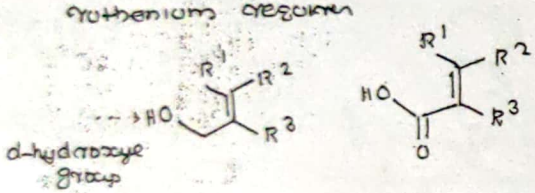
98% ee.
enamine

Rhodium requires-

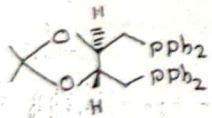


Ru will hydrogenate both e⁻-rich and e⁻ poor double bonds. Ru[BINAP][OAc]$_2$ works best if the double bond carries an α-hydroxeye group.

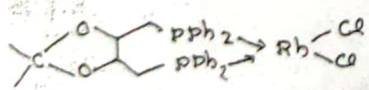
ruthenium requires



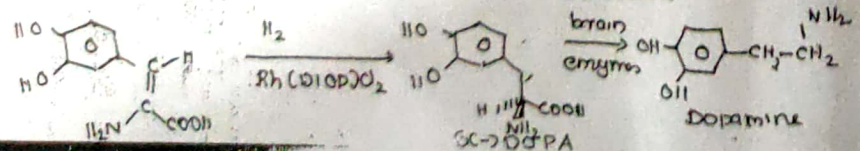
(R,R) DIOP — Kasim Sir's note



We- asymmetric reaction
(R,R)-DIOP is another important chiral diphosphine ligand. Its ruthenium or rhodium complex have the same action (asymmetric reduction) as described in BINAP - section. Structure of Rh(DIOP)Cl$_2$ is given below



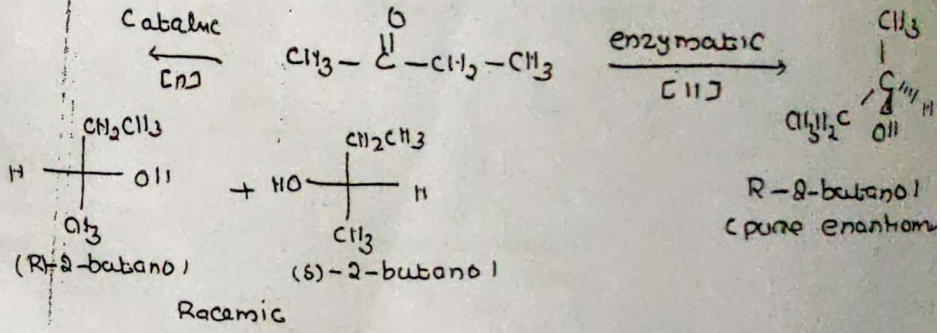
This is used to synthesize (-) form of DOPA



— Kasi

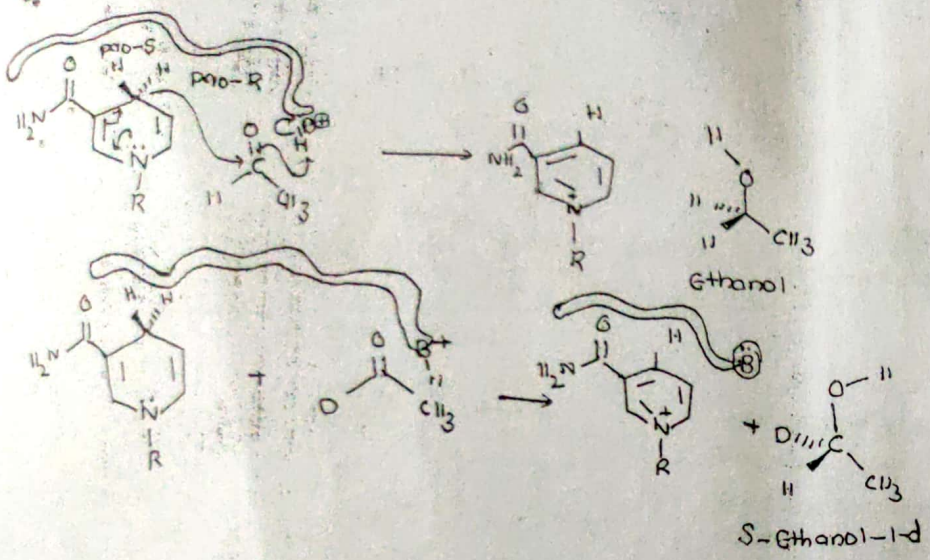
Enzymatic methods (Fourth generation methods)

Enzymes (catalytic proteins) are chi
and they act as chiral catalyst for the reduct
reactions. The hydrogen atom required for reduc
is not provided by enzyme but by the relevant
coenzyme like NADH.

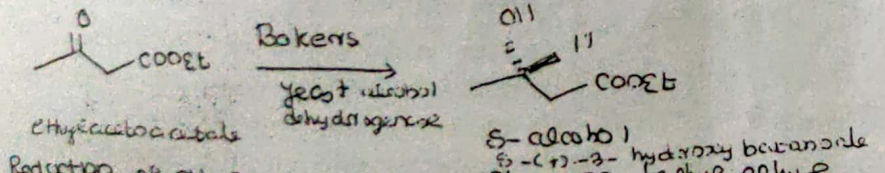


catalytic hydrogenation gives chiral but racemic 2-butanol. Addn of H$_2$ to one face of carbonyl gp gives the (R) product while addn to the other face gives the (S) product. Chiral enzymes can differentiate b/wn these two faces and gives only single pure enantiomer only.

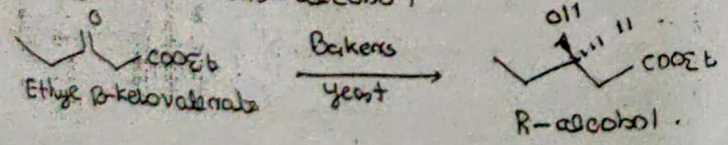
Acetaldehyde is reduced to ethanol with yeast alcohol dehydrogenase (YAD) Baker yeast in the presence of the hydride donating Coenzyme NADH. Acetaldehyde has two enantiotopic faces (Re and Si) and NADH has two diastereotopic hydrogen (pro R and pro S). It is established that during the reduction of acetaldehyde, the pro R 'H' from NADH is transferred only to the Re face of acetaldehyde.



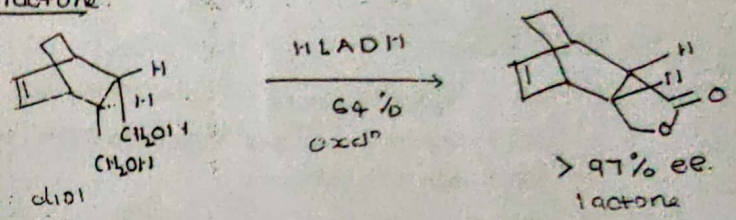
One may carry out the reductions using whole cells like bakers yeast where both the enzyme and the coenzyme are provided by the organisms Thus ethylacetoacetate is reduced selectively to ethyle (S)-(+)-3-hydroxy butanoate using one of the reducing enzymes found in Bakers yeast alcohol dehydrogenase.



Reduction of ethyle β-ketovalerate (having methyle ethyle groups) gave the (R)-alcohol



Meso compounds undergo enantioselective reaction in the presence of enzymes. horse liver alcohol dehydrogenase (HLADH) selectively oxidises the diol to the lactone.

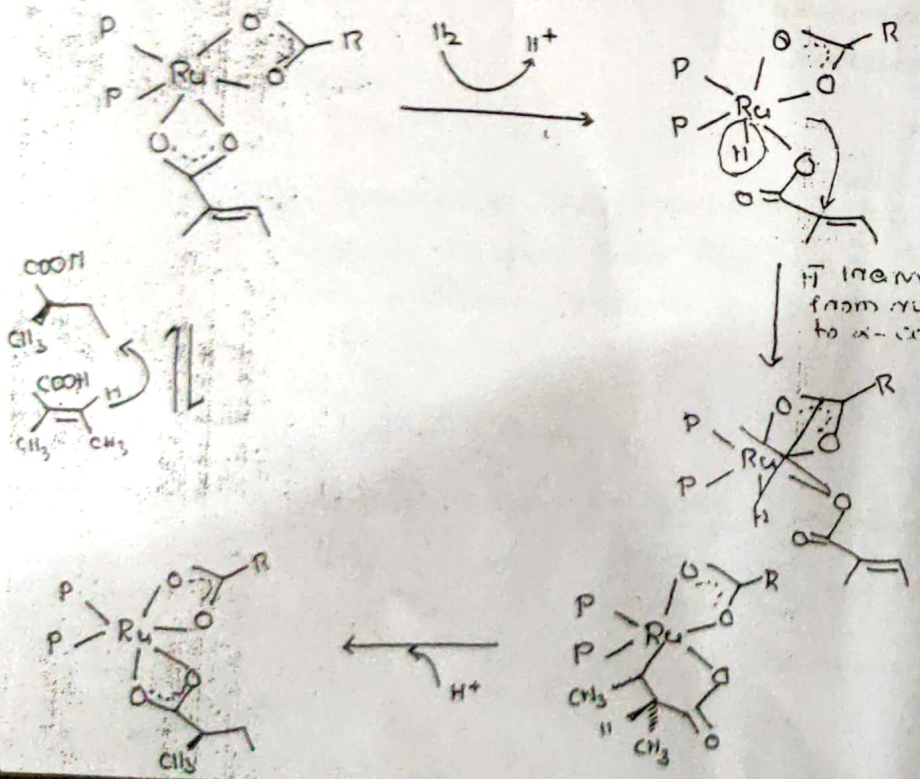


* Refer more from Corey and Sundberg.

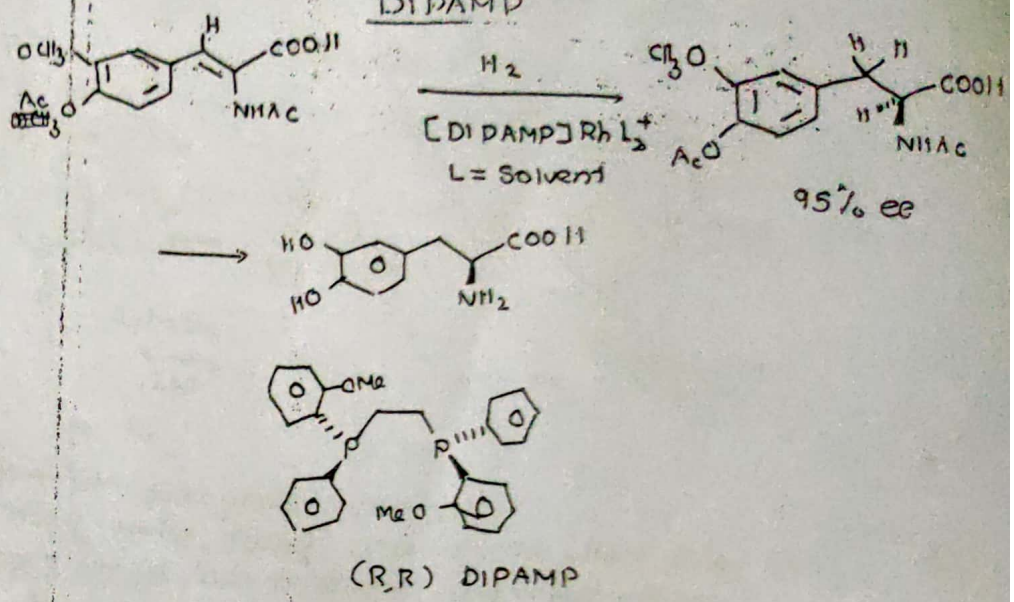
here the hydrogenation H comes from the same molecule by [1,3]-sigmatropic shift made possible by participation of the metal orbitals.

Mechanism — Carey

α,β-unsaturated acids can be reduced enantioselectively with ruthenium and rhodium catalysts having chiral phosphine ligands. The mechanism of such reactions using Ru(BINAP)$(O_2CCH_3)_2$ is consistent with the idea that coordination of the carboxy group establishes the geometry at the metal ion. The configuration of the product is established by the hydride transfer from ruthenium to the α-carbon that occurs on formation of the alkyl-metal intermediate. The second hydrogen is introduced by protonolysis.



DIPAMP

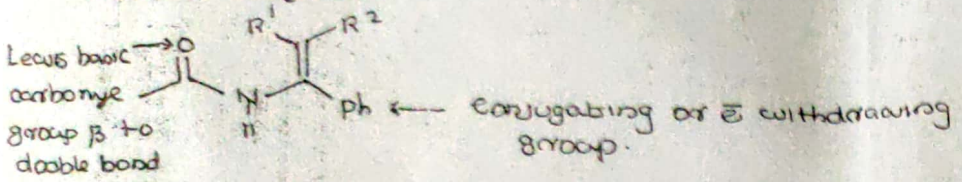


DIPAMP's chirality resides in the two stereogenic phosphorous atoms. the catalyst imposes chirality on the hydrogenation by coordinating to both amide group and the double bond of the substrate. Two diastereoisomeric complexes result, since the chiral catalyst can coordinate to either of the enantiotopic faces of the double bond. The enantioselectivity in the reaction arises because one of the diastereoisomeric complexes reacts much more rapidly with hydrogen than the other, ultimately transferring both hydrogen atoms to the same face of the double bond.

Choice of ligands — Calaydon

The range of diphosphine ligands used in catalytic enantioselective hydrogenation is enormous and many of them can be used with Rh or Ru. Rh will not give good ees only when hydrogenating electron poor or conjugated double bonds that carry a β-carbonyl group (necessary for chelation)

Rhodium requires-



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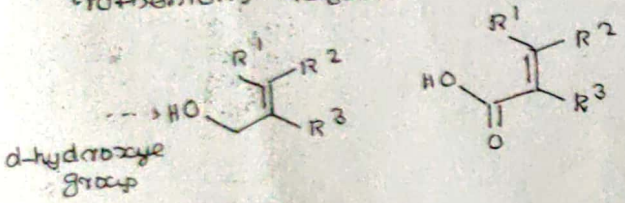
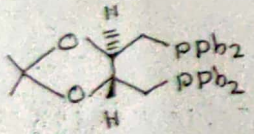


(R,R) DIOP — Kasim Siri's note



Asymmetric reduction

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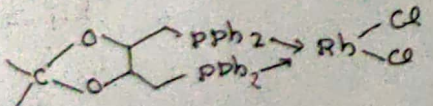

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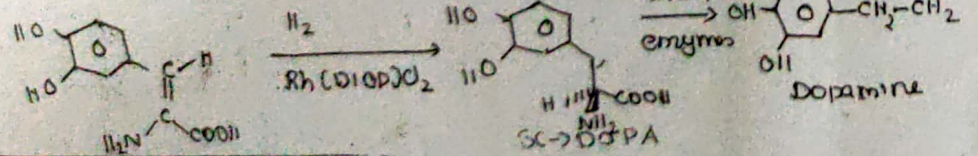

— Kasi

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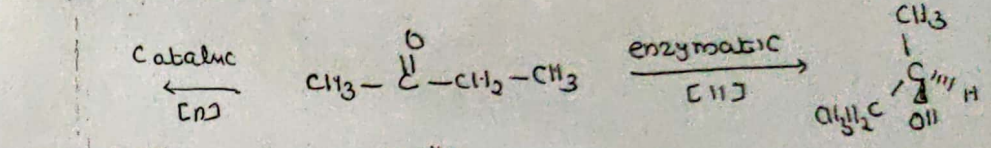
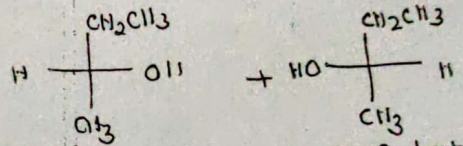
Enzymes (catalytic proteins) are chiral and they act as chiral catalyst for the reduction reactions. The hydrogen atom required for reduction is not provided by enzyme but by the relevant coenzyme like NADH.





Racemic

R-2-butanol (pure enantiomer)

Catalytic hydrogenation gives chiral but racemic 2-butanol. Addn of H$_2$ to one face of carbonyl gp gives the (R) product while addn to the other face gives the (S) product. Chiral enzymes can differentiate b/wn these two faces and gives pure single pure enantiomer only.

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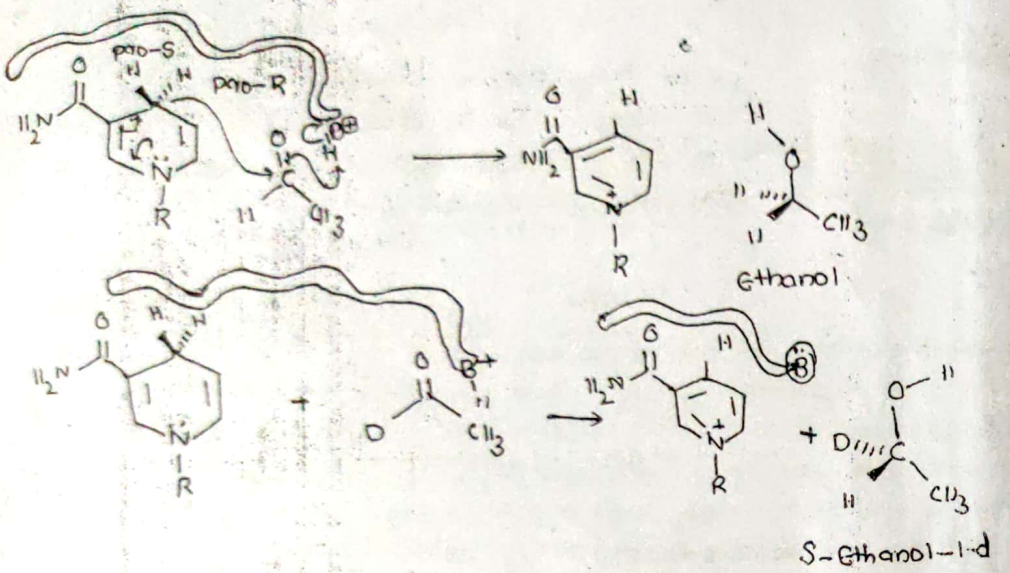

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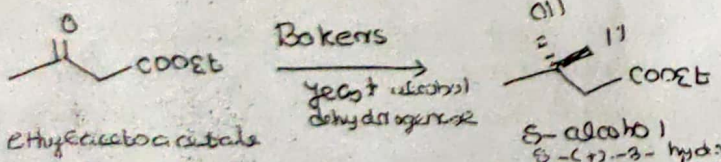

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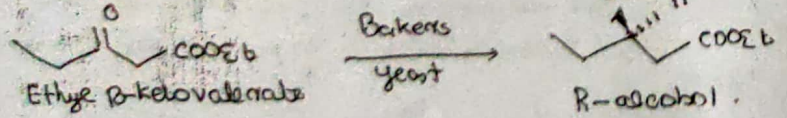

Meso compounds undergo enantioselective reaction

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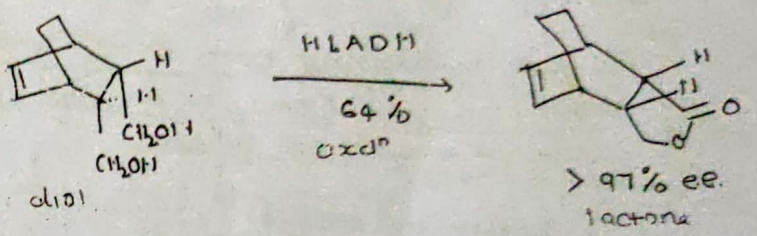

* Refer more from Corey and Sundberg