DYNAMIC STEREOCHEMISTRY (DCE)
SEM VI: BCHEM 0606

TOPIC:ASYMMETRIC SYNTHESIS, ASYMMETRIC INDUCTION

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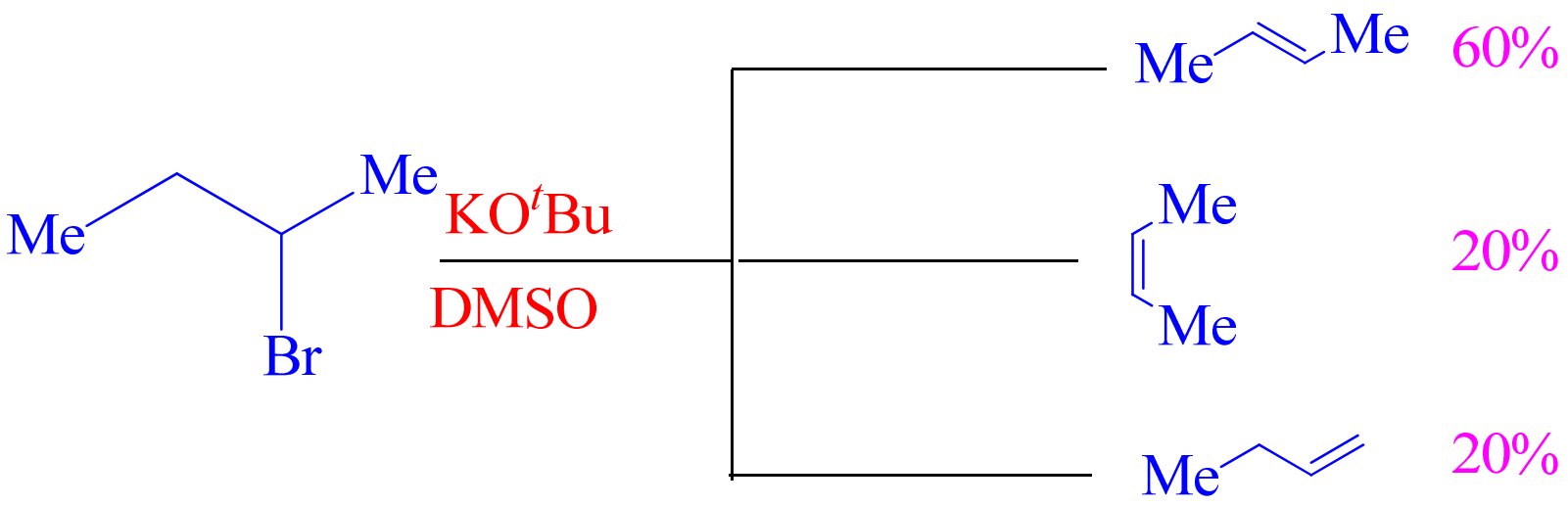
Some Terminology:

Stereoselective reaction:

A Stereoselective reaction is one in which the reactant generates one specific stereoisomeric product in greater extent than the other stereoisomeric product.

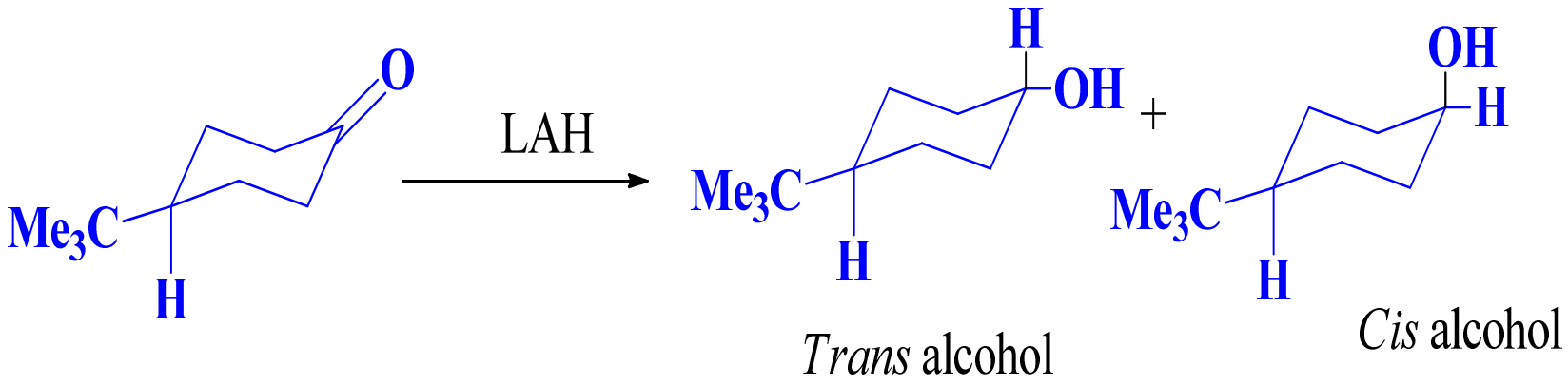
Stereoselectivity is the property of a chemical reaction that yields an unequal mixture of stereoisomers from a single reactant.

Stereoselectivity may be partial, where the formation of one stereoisomer is favored over the other, or it may be total where only one stereoisomer is formed



Stereoselective Reaction

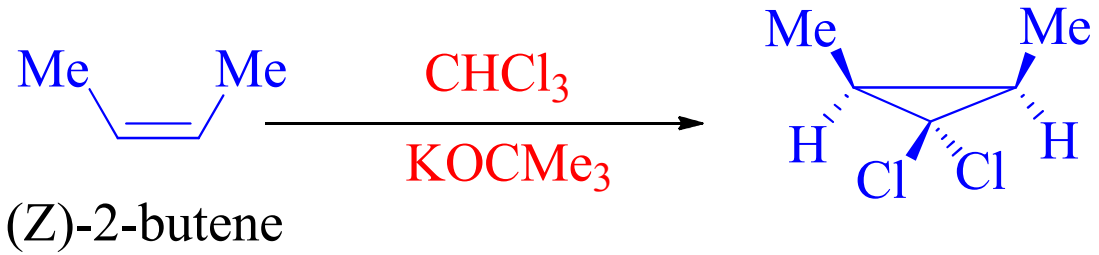
Reduction of 4-t-butylcyclohexanone with lithium alluminium hydride stereoselectively produce equtorial trans alcohol with small amount of cis isomer.



Stereospecific reaction : A stereospecific reaction is one when a stereochemical reaction produces only one stereoisomeric product. or

A reaction in which only a specific isomer reacts, in such a way that its configuration influences the configuration of the product

Different stereoisomeric product generates from different stereoisomeric reactants,That is, a given isomer leads to one product while another stereoisomer leads to the opposite product.



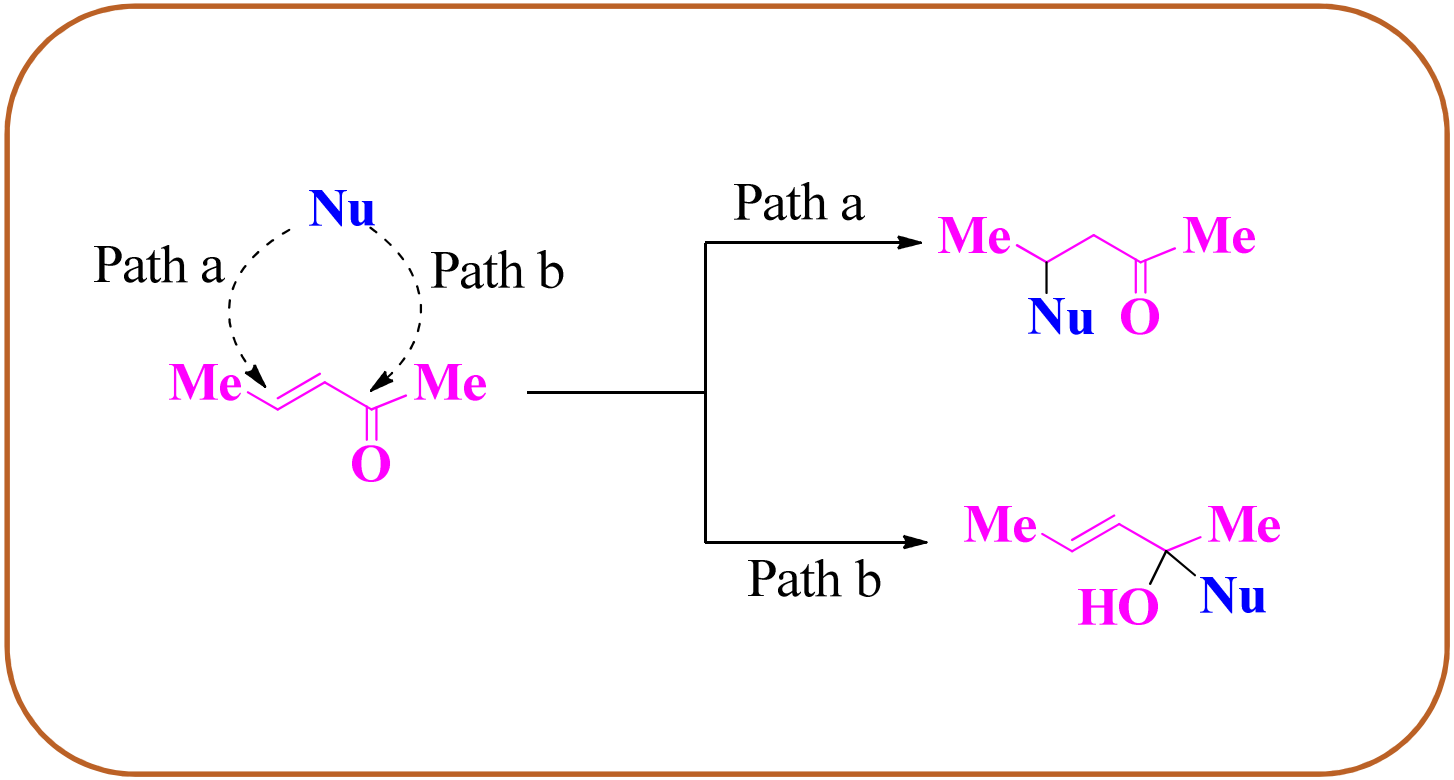
Stereospecific Reaction

Regioselectivity:

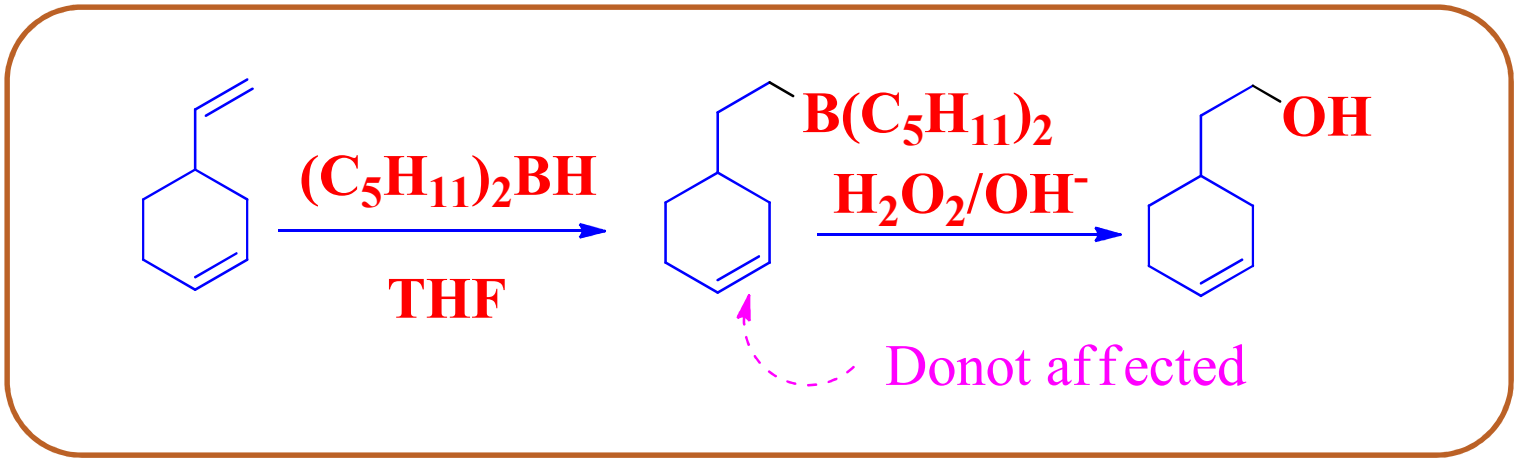
Where it will react? or preferential position of reaction.

Regioselective or site selective Reaction: When a reaction takes place in a particular site of a molecules in spite of presence of other site and predominately produce one positional isomer in greater extent in a mixture of product is reffered as regioselective reaction.

Nucleophilic addition to unsaturated ketone is an example of regioselective reaction, addition can takes place either 1,2 or 1,4 fashion.



Hydroboration reaction of the given substrate regiospecifically attacks terminal double bond inspite of the presence of other double bond to afford the alcohol.



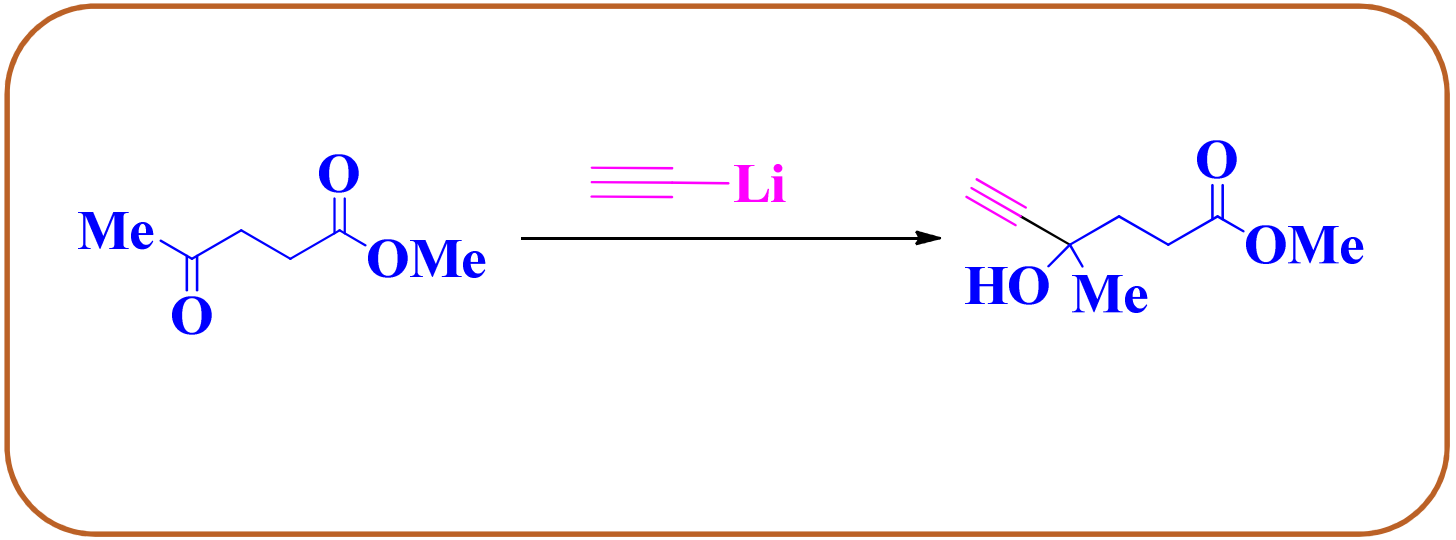
Chemoselectivity?

Which functional group will react.

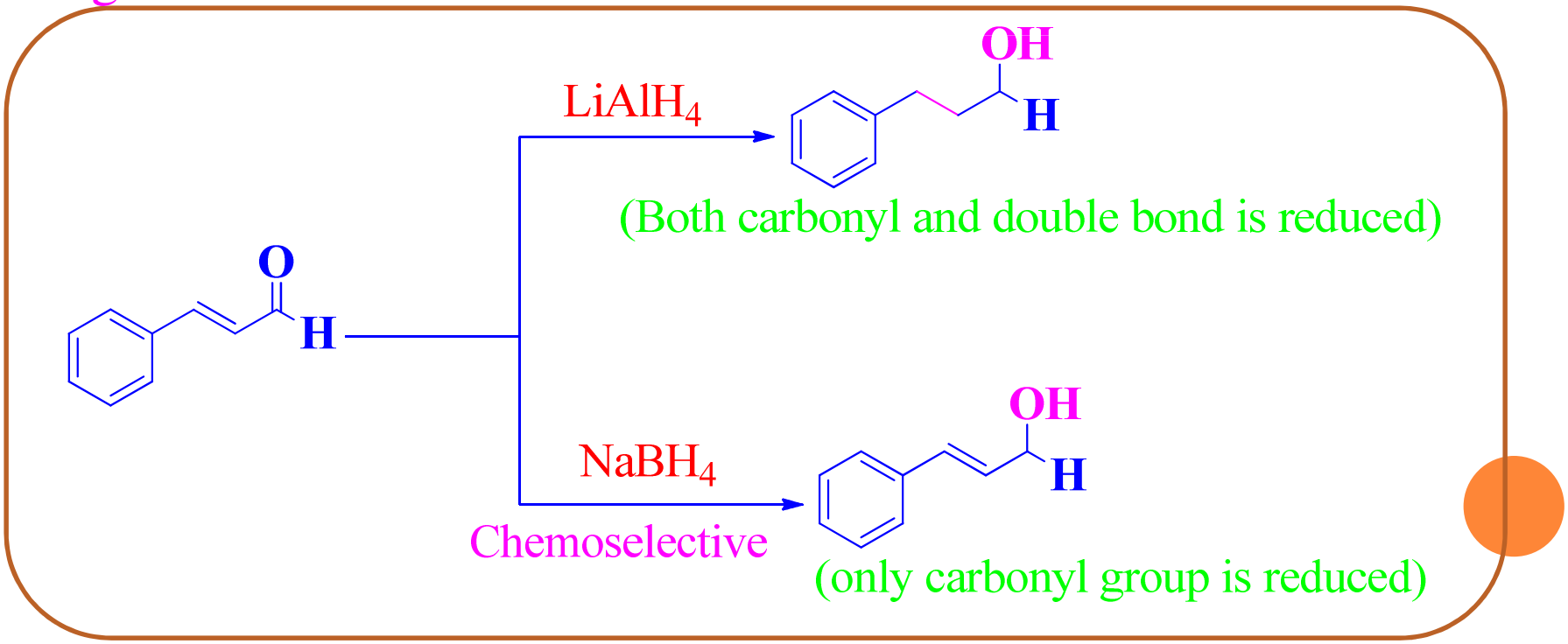
A chemoselective reaction is one when a reagent brings the change in a particular functional group in spite of presence of the other functional group present.

Chemoselective Reaction:

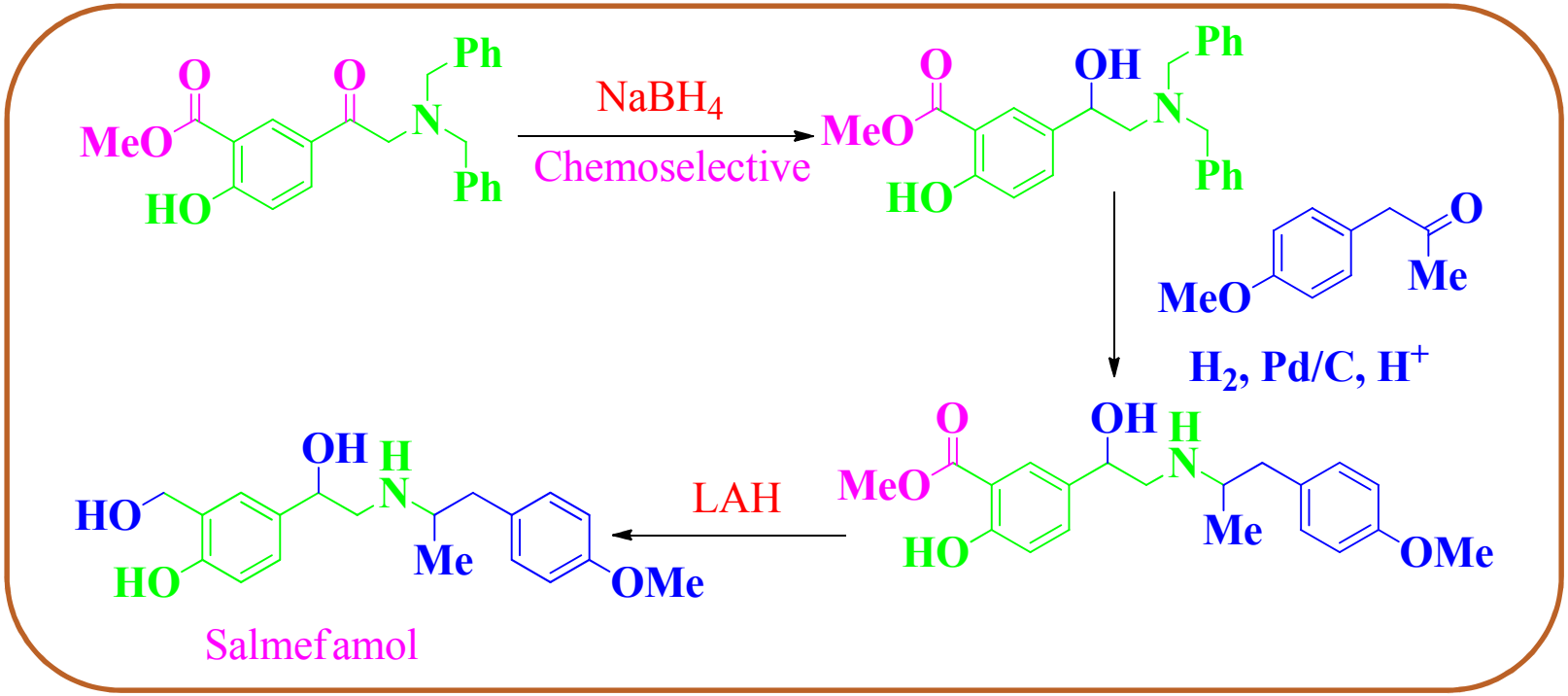
Grignard reagent and organolithium reagent is more reactive towards the keto group than ester and when applied that reagent to the compound contain both the functionality, chemoselectively a tertiary alcohol is generated without affecting the ester group.



Lithium aluminum hydride and sodium borohydride are used as reducing agent, are powerful hydrogen donor. But LAH is less reactive than sodium borohydride due lower electropositivity of boron atom compare to aluminium atom and hence more selective towards reduction and prefered as a chemoselective reagent.

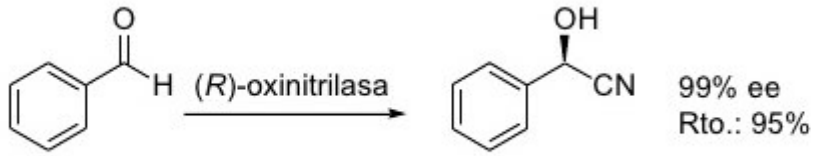


Chemoselectivity of sodium borohydride is best used in the synthesis of anti-asthama drug salmefamol. sodium borohydride in the first step of the reaction sequence, reduce keto group chemoselectively without affecting the ester group and in the last step less selective LAH is used to reduce the ester group to lead the product.



Enantioselective Reaction:

Anenantioselective reaction is one in which oneenantiomer is formed in preference to the other, in a reaction that creates an optically active product from an achiral starting material, using either a chiral catalyst, anenzymeor a chiral reagent.



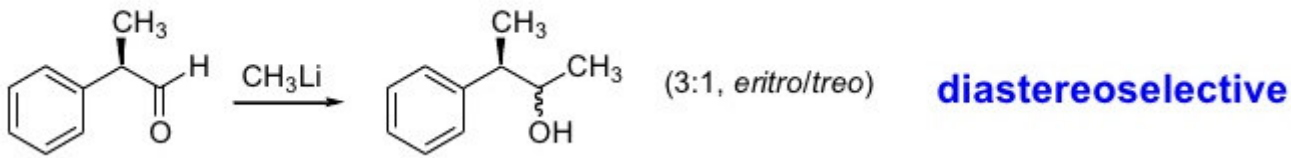
99% ee
Rto.: 95%

enantioselective

Diastereoselective Reaction:

A diastereoselective reaction is one in which one diastereomer is formed in preference to another, establishing a preferred relative stereochemistry.

In this case, either two or more chiral centers are formed at once such that one relative stereochemistry is favored



Optical Purity or Enantiomeric excess (ee)

The enantiomeric excess(ee) is defined as the excess of one enantiomer over the other generated in an enantioselective reaction and is usually expressed as a percentage of the whole. It usually gives a measure of the efficiency of the enantioselective reaction.

The **optical purity or the enantiomeric excess (% ee) of a sample can be determined as follows:**

Optical purity = % enantiomeric excess = % enantiomer1-% enantiomer2

= 100 [α]mixture/ [α]pure sample

% ee=100 ([R]-[S]) / ([R]+[S])

where [R] = concentration of the R-isomer

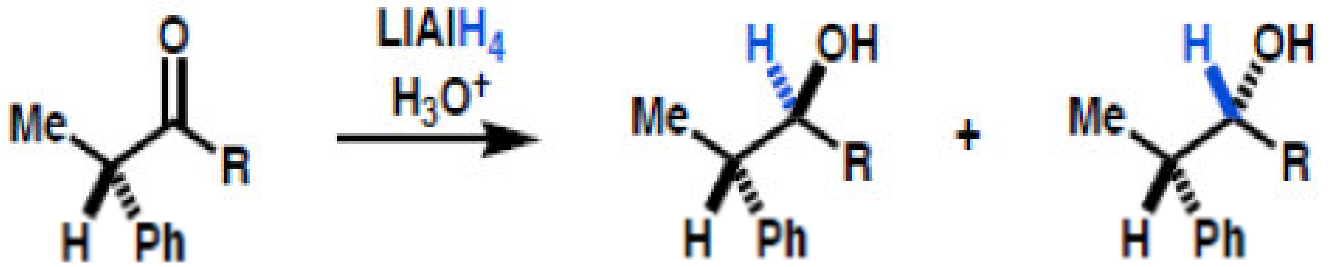
[S] = concentration of the S isomer

Enantiomeric excess(ee)is a measurement of purity used for chiral substances:

Ratio of Product	% of ee
50:50	0%
60:40	20%
75:25	50%
90:10	80%
99:1	98%
99.5: 0.5	99%

Diastereomericexcess (d.e.)

= (major diastereomer(%) –minor diastereomer(%))



R = Me	25%	:	75% (50% de)
R = *t*-Bu	2%	:	98% (96% de)

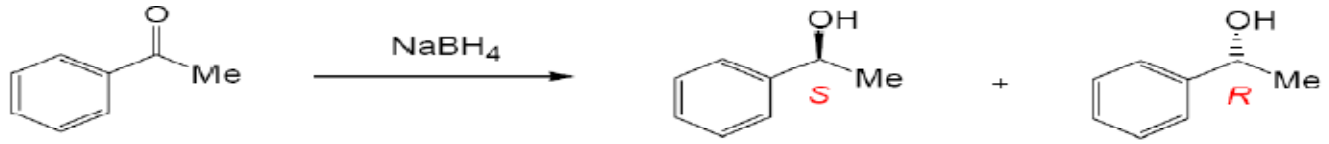
$$\%\ \text{de} = \text{diastereisomeric excess} = \frac{[major] - [minor]}{[major] + [minor]} = \%major - \%minor$$

Asymetric Synthesis

Asymmetric synthesis as defined a reaction in which an achiral unit in an ensemble of substrate molecules is converted into a chiral unit in such a manner that unequal amounts of stereoisomers are produced

or **more simply we can say that the synthesis of a compound by a method that favours the formation of chiral molecules in unequal amounts. It is also known as Enantioselective synthesis, or chiral synthesis.**

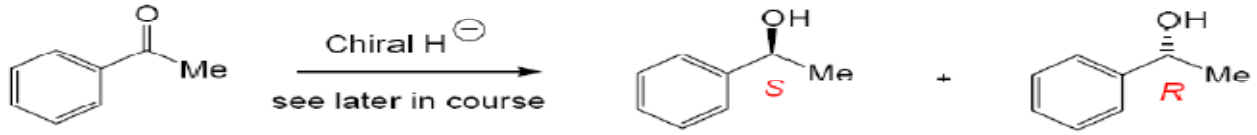
Racemic Reaction



50 : 50

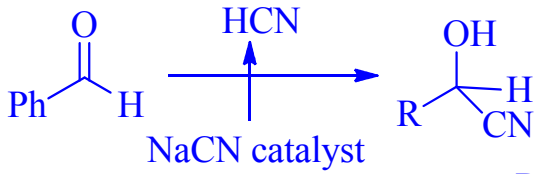
(Not chiral synthesis)

Asymmetric Reaction



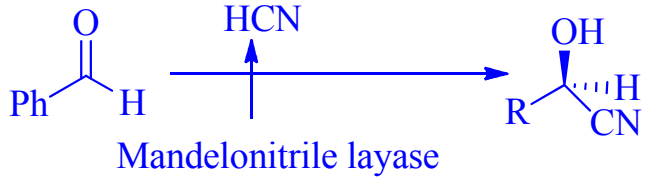
97.5 : 2.5

Racemic Reaction:



Racemic mandelonitrile

Assymetric reaction:



R(+) Mandelonitrile

Importance of asymetric synthesis:

❖ Many of the building blocks of biological systems, such as sugars and amino acids, nucleocides are produced exclusively as one enantiomer.

❖ Living systems possess a high degree of chemical chirality and will often react differently with the various enantiomers of a given compound in our living system. The other enantiomer or diastereomer may not have any physiological activity and may have harmful physiological effect.

- Near 60% of the drugs are chiral and the drugs are sold as a single enantiomer.
- Drug industry is growing at the rate rapidly. Therefore the ability to synthesize single enantiomers of chiral molecules is important but it can also be difficult to achieve.

Strategies of Asymmetric Synthesis:

To access enantiomerically pure molecules for biological applications as drugs, sweeteners and moisturizers, there is need for adoption of efficient strategies for asymmetric synthesis.

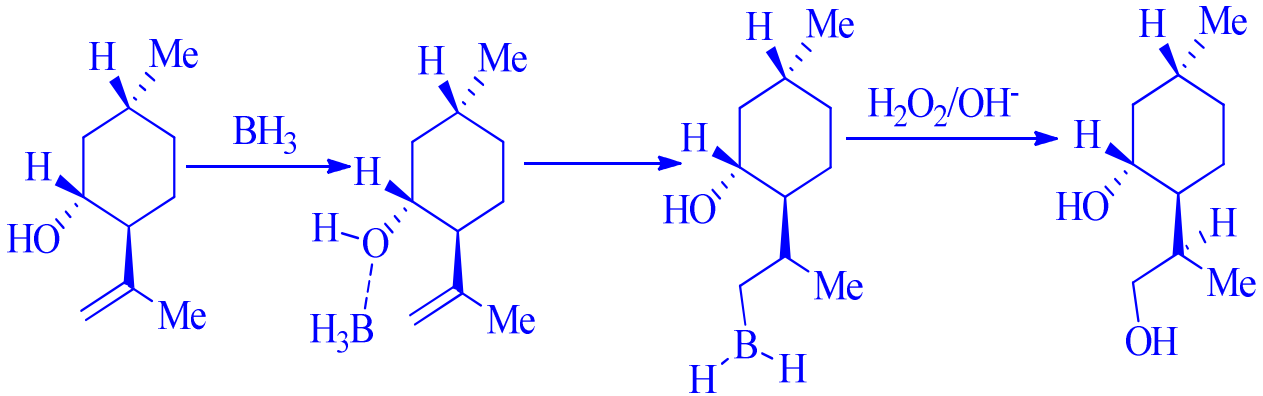
The main strategies of asymmetric synthesis are

1) ***Using Chiral Substrates***
2) ***Chiral pool synthesis or chiron approach***
3) ***Chiral auxiliary approach***
4) ***Using Chiral Reagent and Asymmetric catalysis.***

Asymetric synthesis using chiral substrates:

Under this category of asymmetric synthesis the new stereocenter is generated under the influence of chiral centre already present in the molecule.

a) Consider the hydroboration oxidation of the following compound, interaction of the hydroxyl group with the electro-deficient borane directs the hydroboration from the rear face.

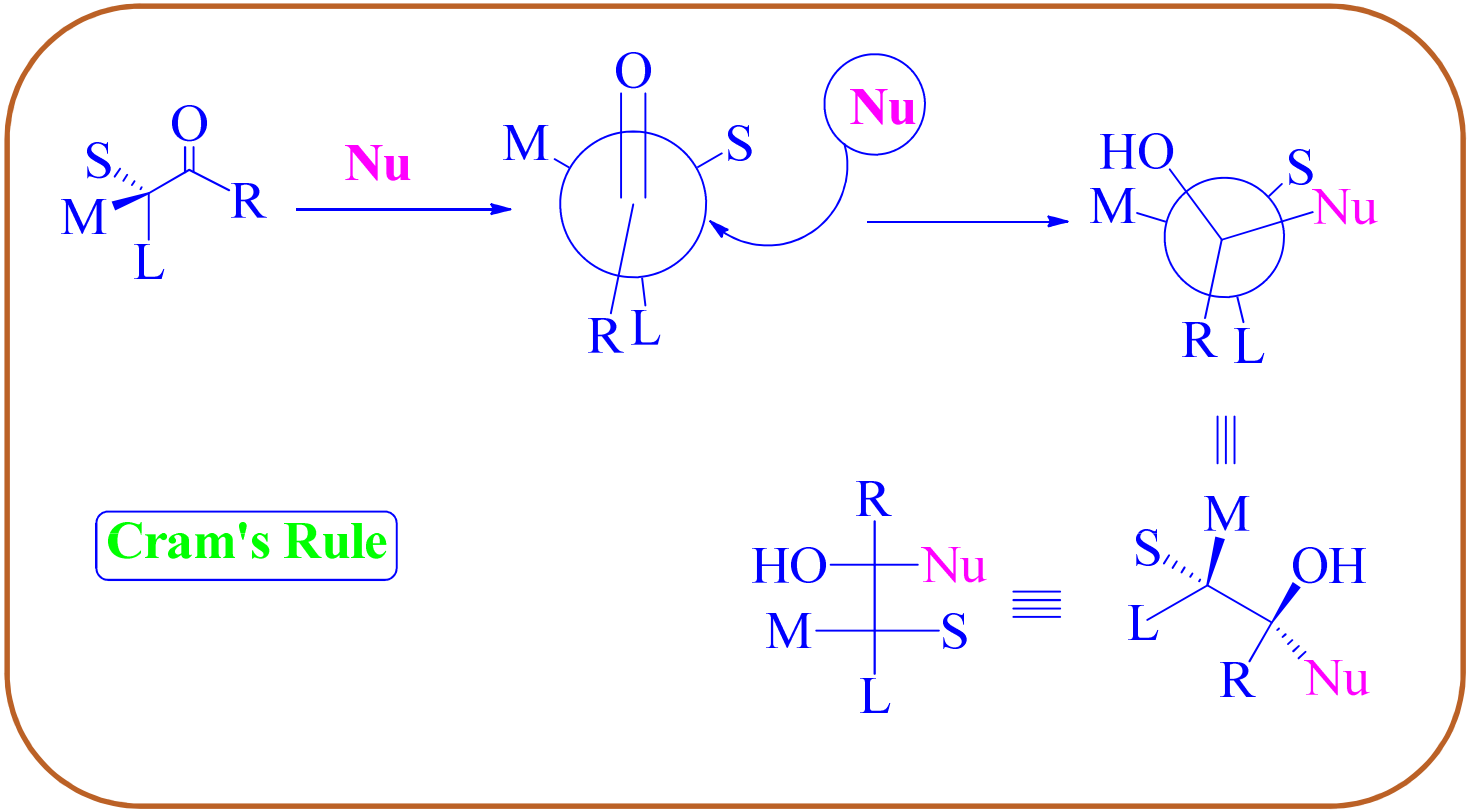


b)Diastereoselective Synthesis:

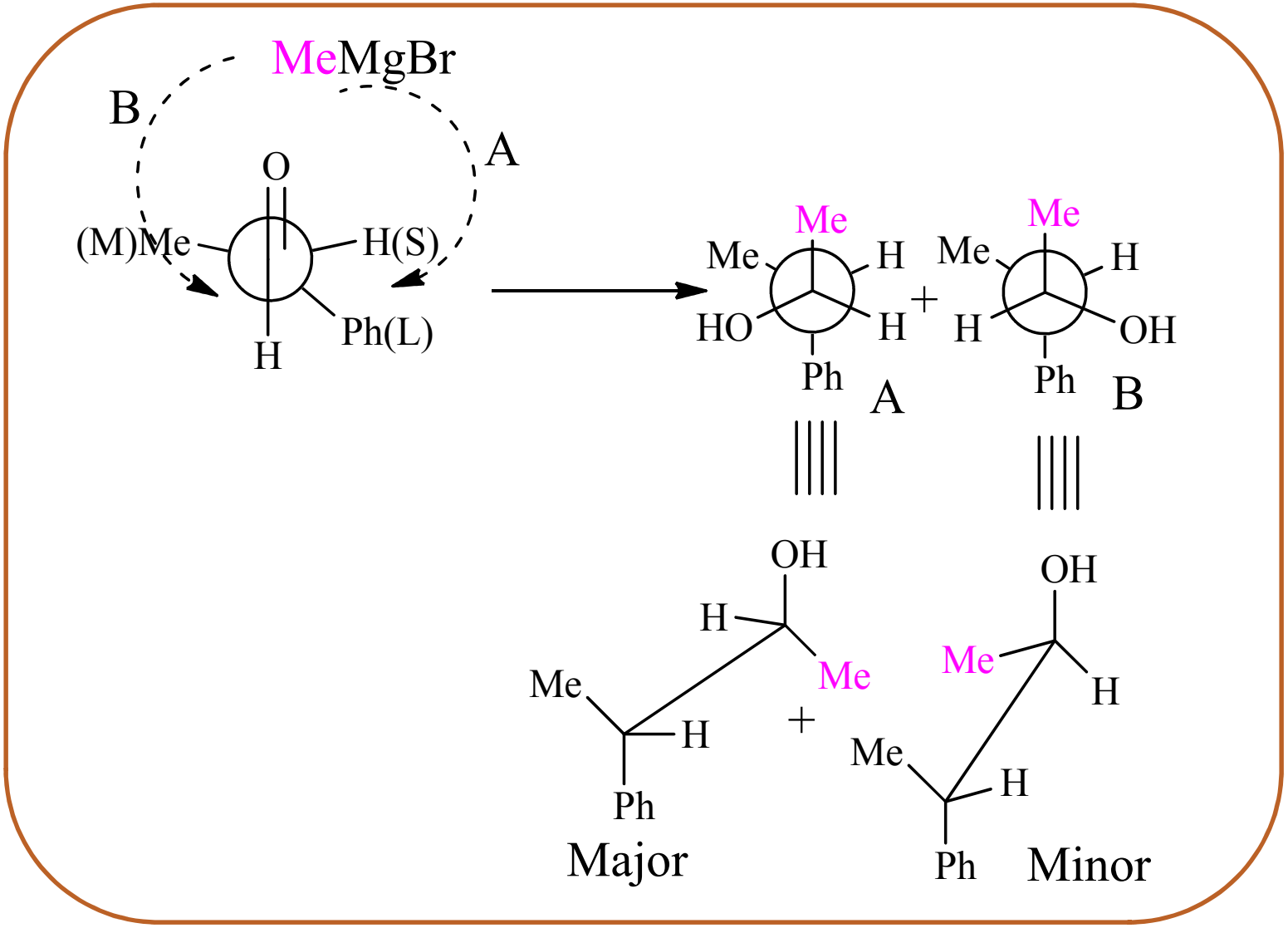
Carbonyl 1,2-asymmetric induction→Cram's rule

- In this case reaction generates diastereoisomers in unequal amounts.
- Nucleophilic addition to the carbonyl carbon atom with adjacent chiral center is an example of asymmetric synthesis and the stereochemistry of the product is explained by the Cram's rule.
- According to the Cram's rule L group orients *trans* to the carbonyl oxygen atom and nucleophile preferentially enter from the less hindered side.

Mechanistic interpretation:



Example: Stereochemistry of the major product formed on Grignard reaction of α- phenylpropionaldehyde is explained based on the Cram's model.



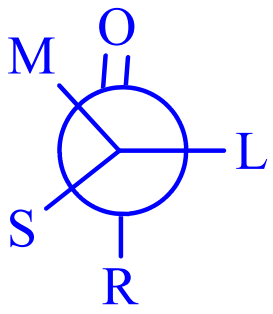
Limitation of cram's model:

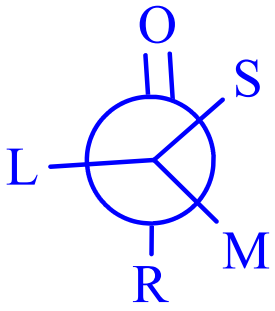
i) If a strong electronegative element present in the chiral center then Cram's model cannot explain the stereochemistry of the product. To explain the facts placed the electronegative atom in the *trans* position of the carbonyl oxygen atom and draw the mechanism. This is due to the stability factor.

ii) If chiral carbon atom contains any group (OH, NH_2, OR) that have coordinating capability with the reagent then Cram's model failed to explain the product stereochemistry.

Felkin-Anh Model

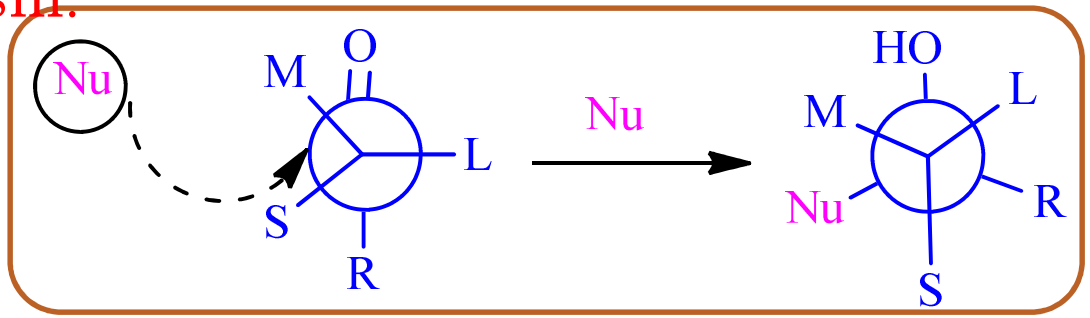
- ✓ An alternative of Cram's model to explain carbonyl 1,2-asymmetric induction.
- ✓ According to this model L substituent orients perpendicular to the carbonyl group.
- ✓ Between two possible models, the preferred stable model is one in which the R group is flanked in between L and S groups.



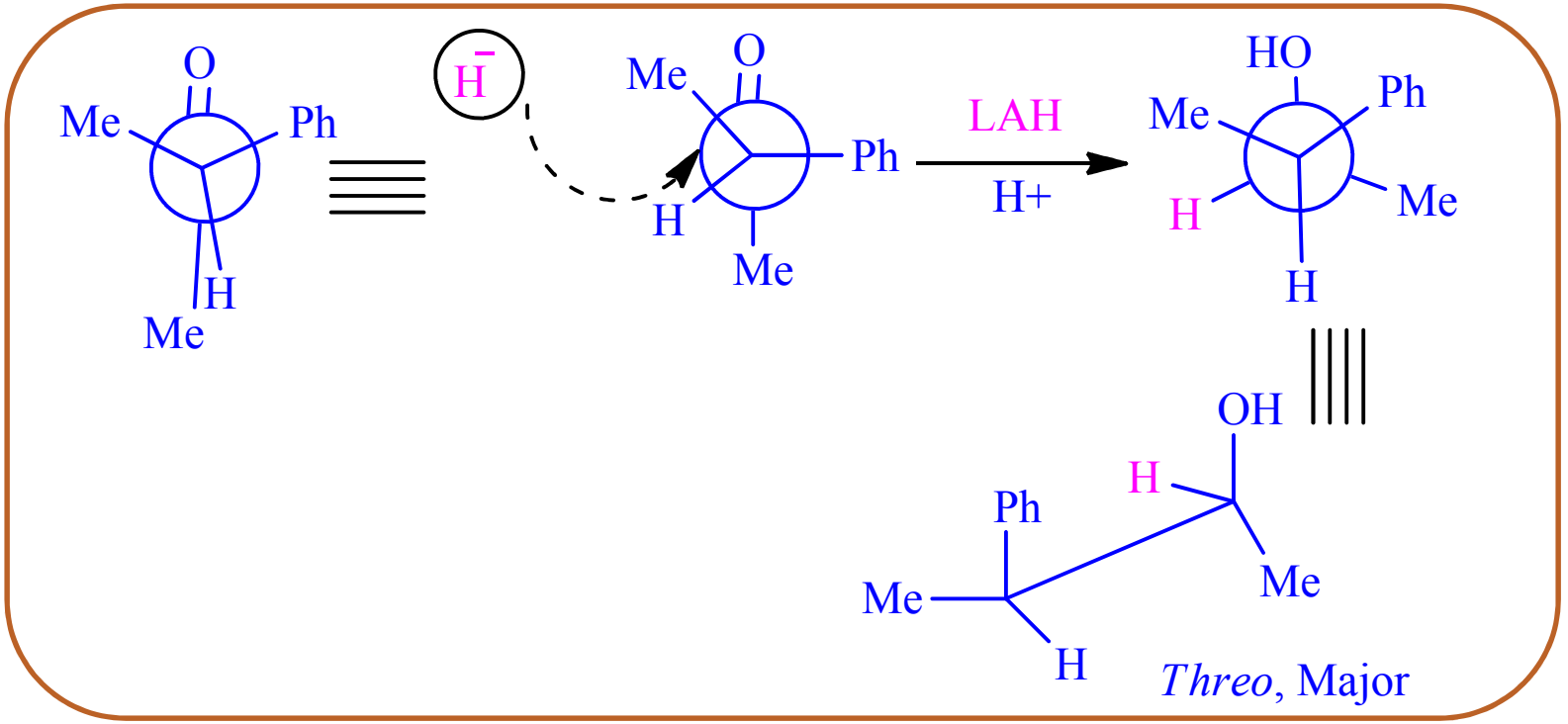


Preffered Model

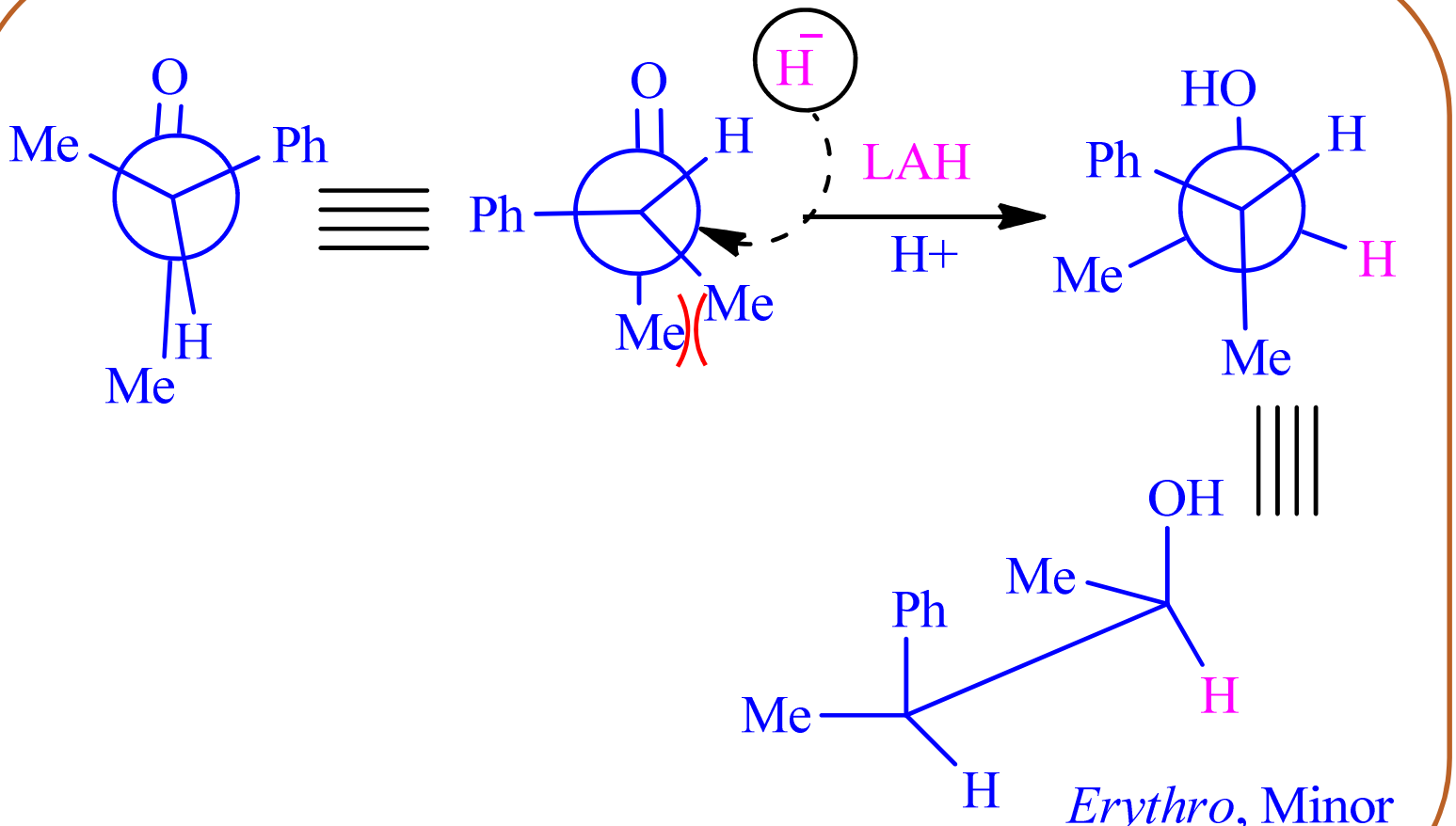
General Mechanism:



The reduction of (S)-3-phenylbtanone using LAH give *threo* diastereomer as major product. The formation of *erythro* product as minor quantity is due to the steric reason as shown below-

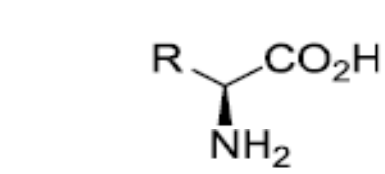


Formation of minor product:

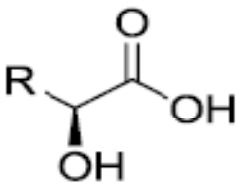


Chiron Approach to Asymmetric Synthesis /Chiral pool synthesis:

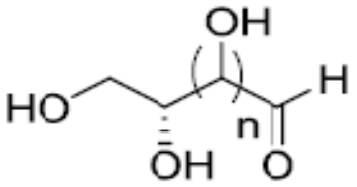
Chiral pool: This refers to a collection of enantiomerically pure molecules available from nature. Common chiral starting materials derived from nature include amino acids, chiral carboxylic acids and monosaccharides.



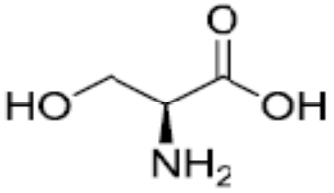
Natural L-Amino acids



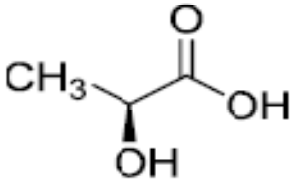
α-Hydroxy acids



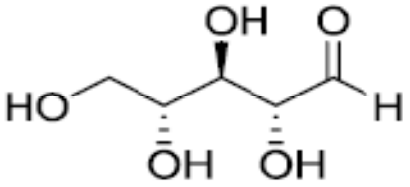
Natural D-Sugars



L-Serine



(S)-Lactic acid
(Milk)



D-Ribose

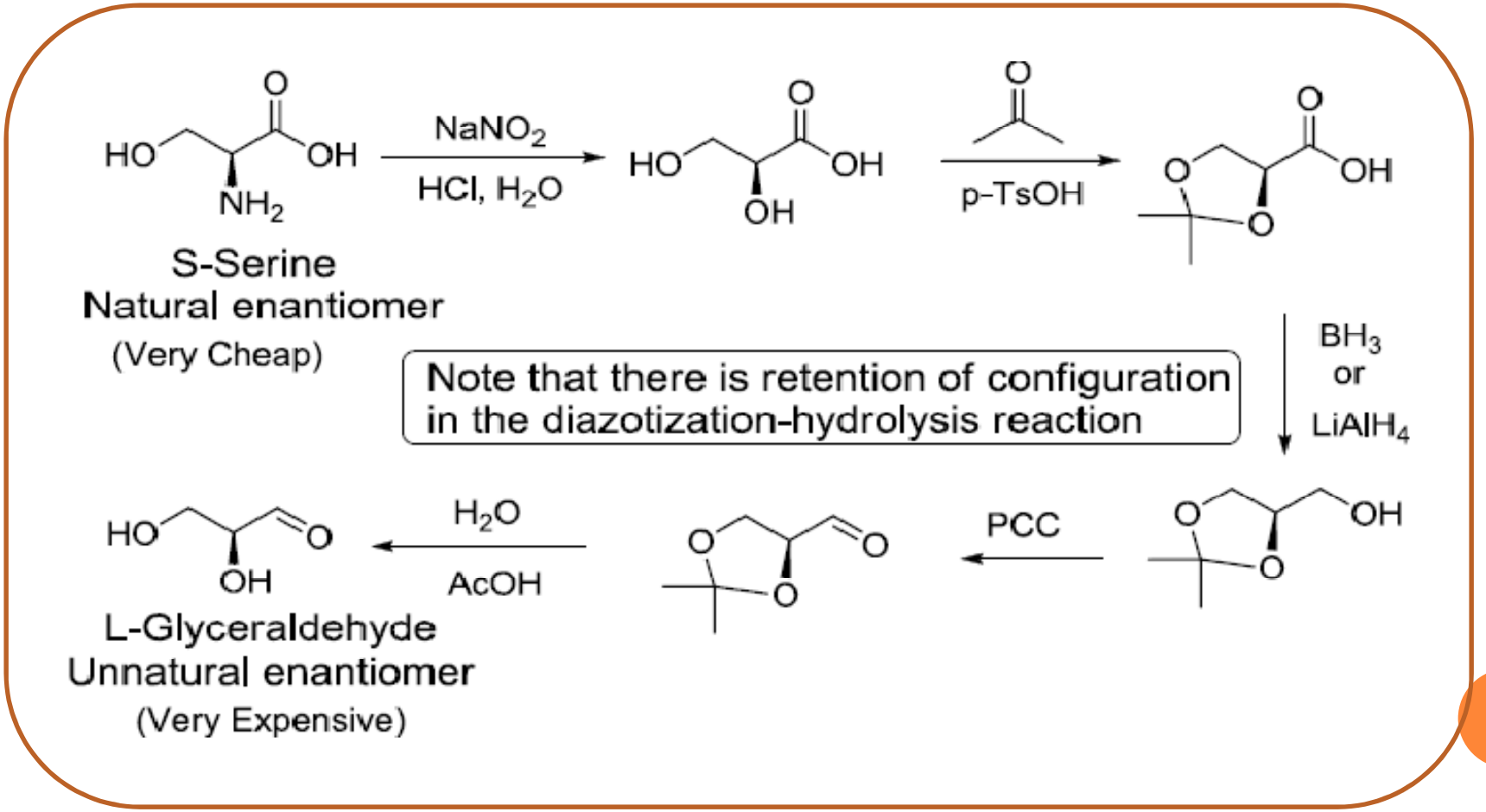
Chiral pool asymetric synthesis:

A chiron approach or chiral pool synthesis refers to a synthetic process that employs a member of the chiral pool as a starting material (SM) in the synthesis of a target molecule (TM).

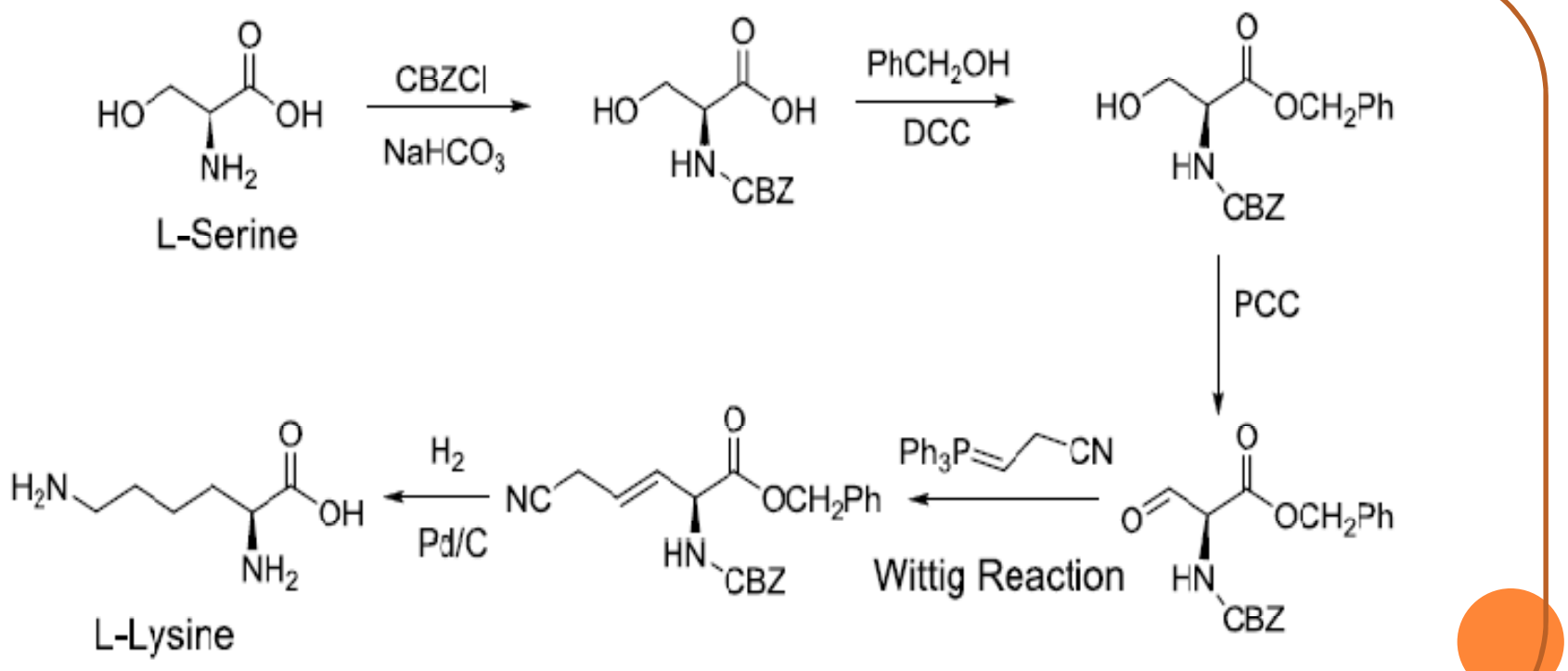
The chiral centre(s) in the starting material are (but not all are always) preserved in the target molecule (TM). It may use pre-existing chiral centres from the chiral pool substrate to influence formation of new chiral centres. The new chiral centres can be generated through substitution or addition reactions.

Functional Group Inter-conversion:

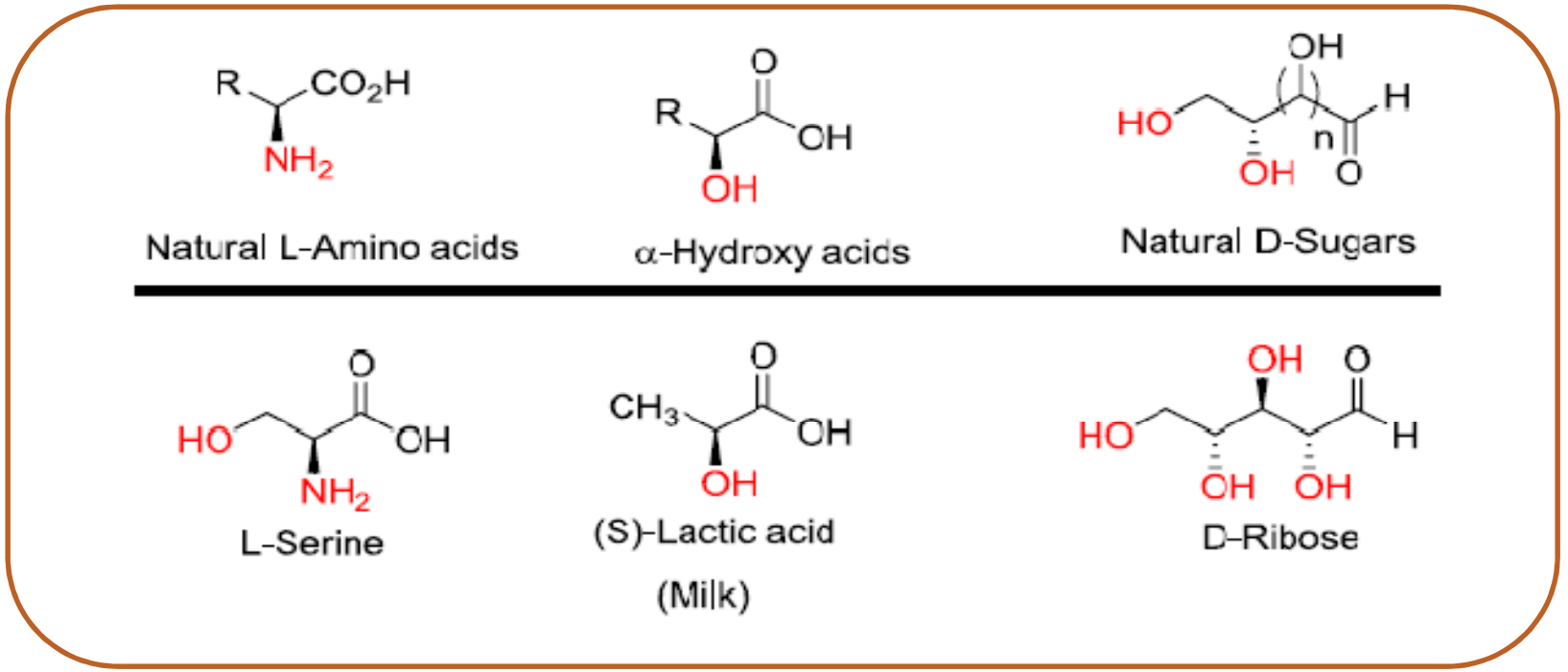
i) Consider the Chiral pool synthesis of L-glyceraldehyde, the unnatural sugar, from the natural amino acid L-Serine.



ii) Another example of functional group inter-conversion in Chiral pool synthesis of the essential amino acid, L-lysine from the natural non-essential amino acid L-serine can also be achieved.



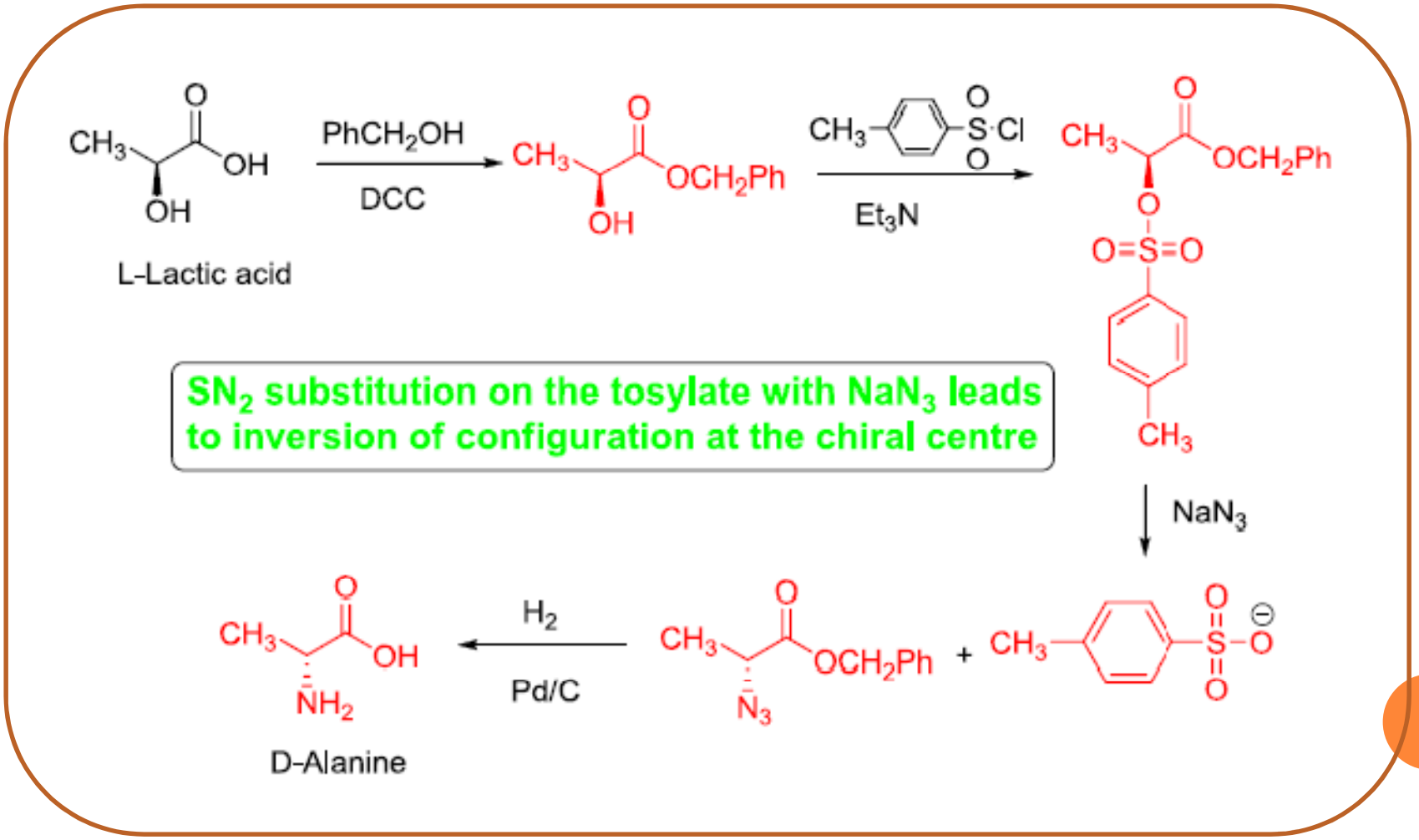
Introduction of New Chiral Centres through Substitution Reactions: Chiral pool substrates that are commonly used in organic synthesis contain functional groups that are poor leaving groups.



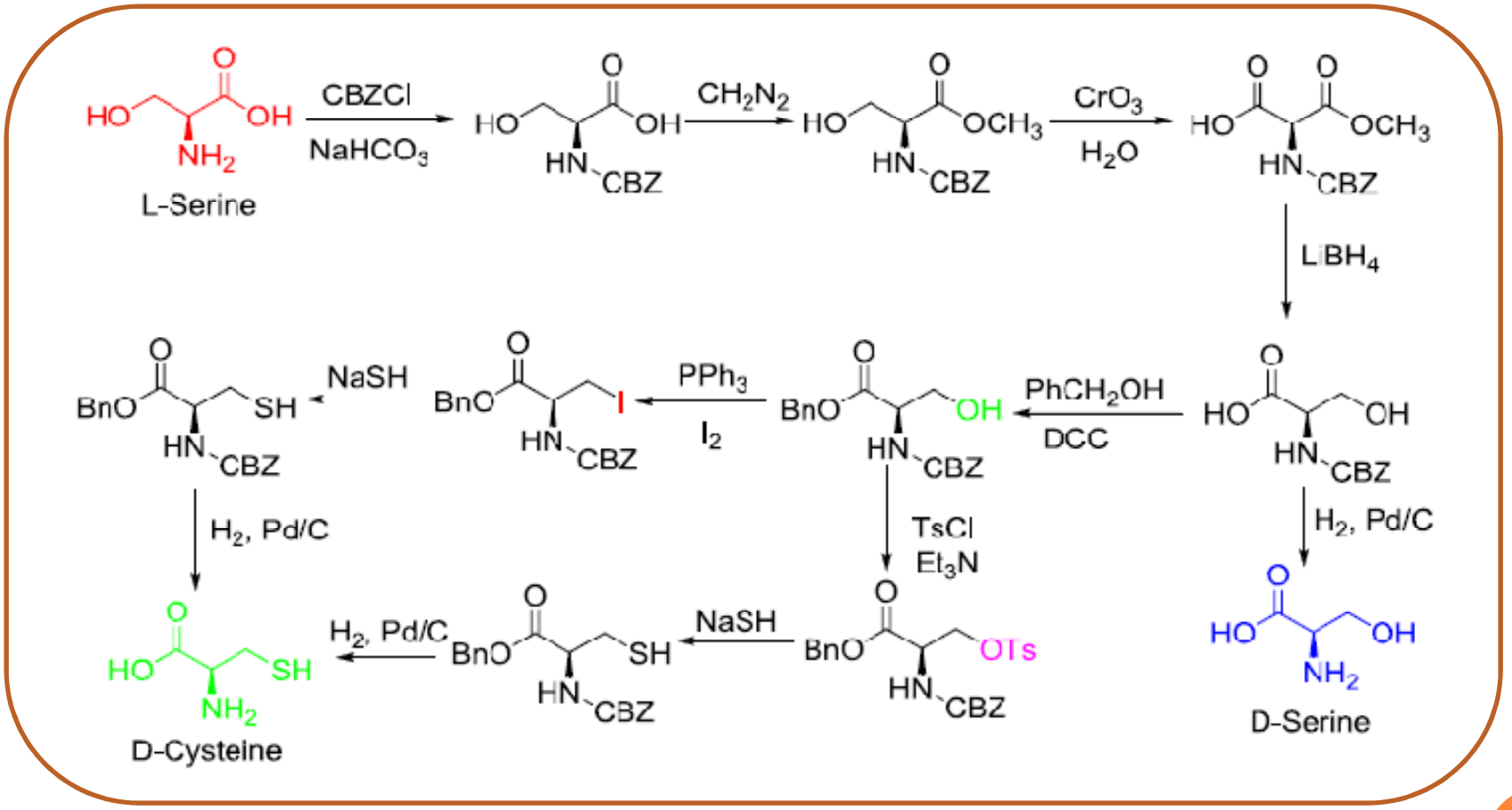
These functional groups have to be converted into good leaving groups that can be used in substitution reactions.

a) Synthesis of Unnatural Amino Acids:

i) The chiral pool synthesis of D-alanine from L-lactic acid can be achieved via conversion to *p*-toluenesulphonate.

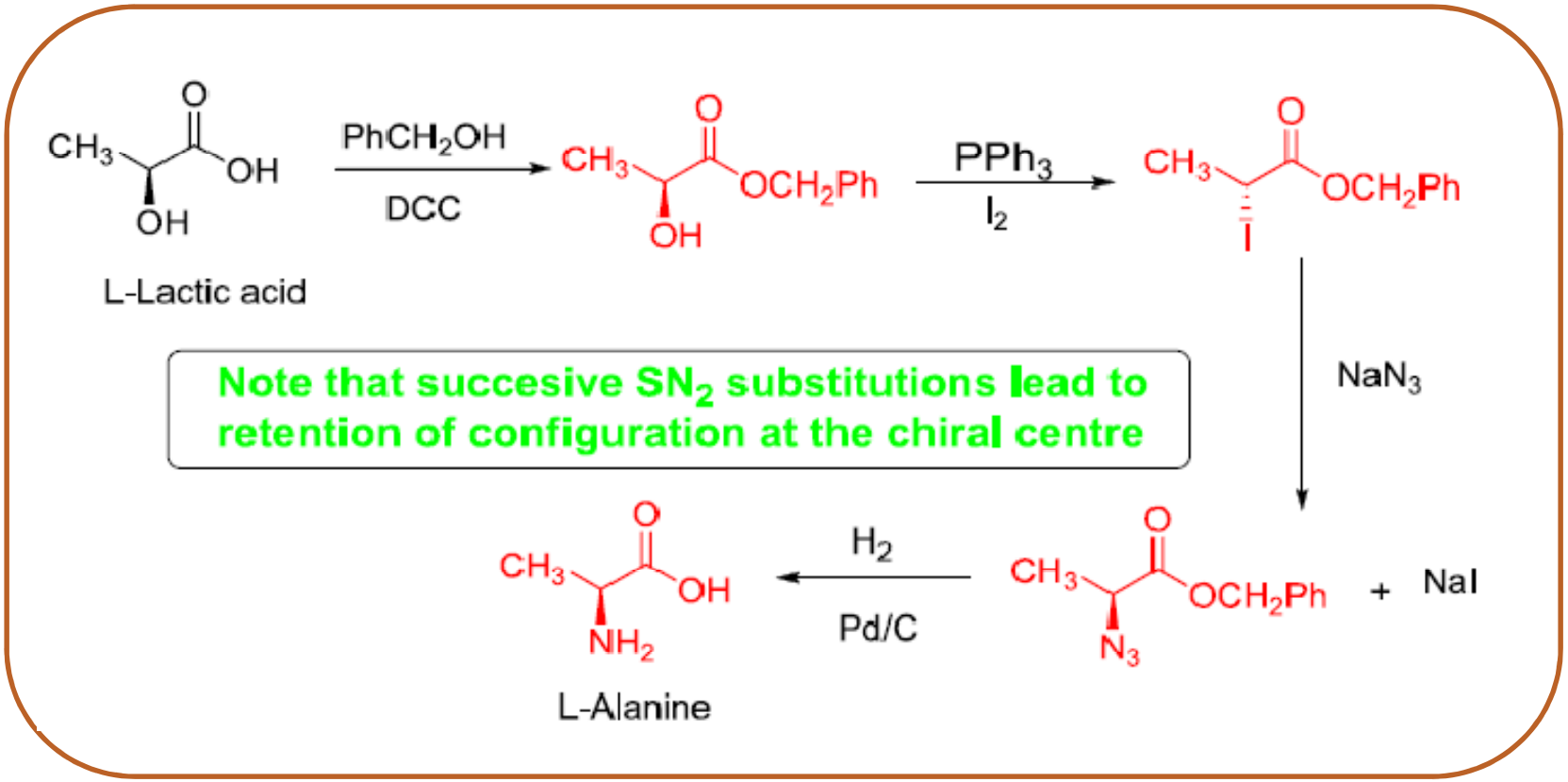


ii) Chiral pool synthesis of the unnatural amino acid, D-cysteine, from the natural L-serine is feasible.



b) Synthesis of Natural Amino Acids:

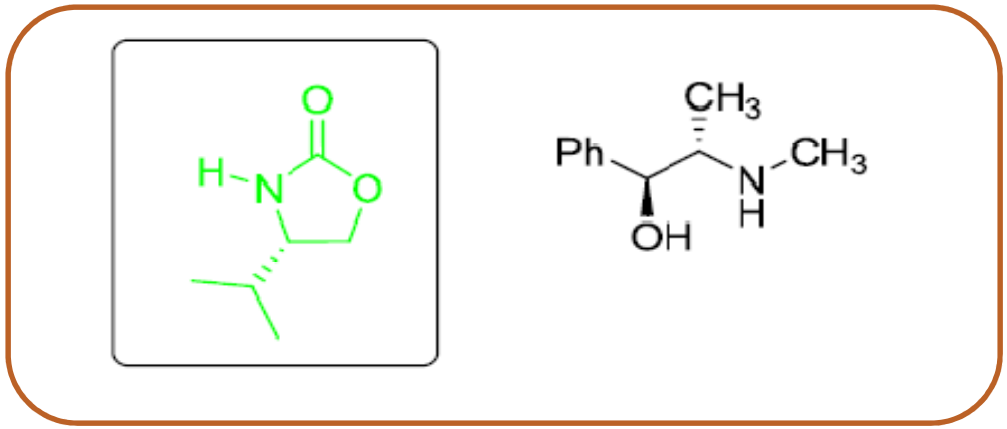
The chiral pool synthesis of L-alanine from L-lactic acid can be achieved via double inversion through an iodide.



Chiral Auxiliary Approach to Asymmetric Synthesis:

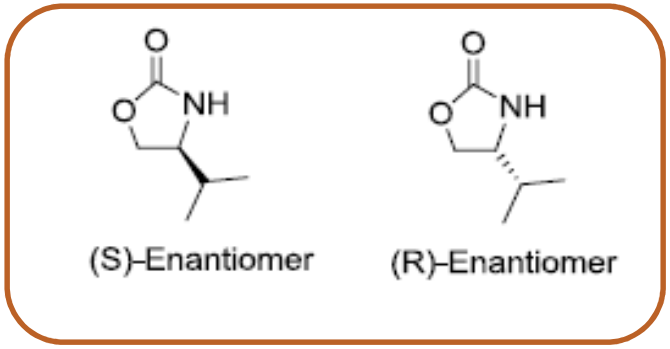
A chiral auxiliary is a chiral molecular unit that can be temporarily incorporated in an achiral substrate to guide selective formation of one of a possible pair of enantiomers. Chiral auxiliaries are optically active compounds and introduce chirality in otherwise achiral starting materials.

Examples of chiral auxiliaries used in the alkylation of enolates.

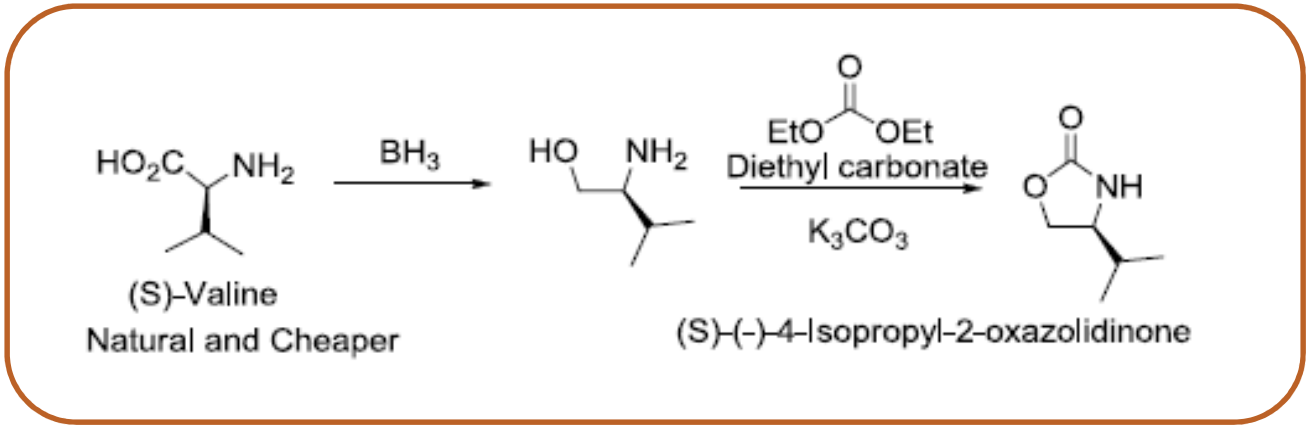


Qualities of good Chiral Auxiliaries:

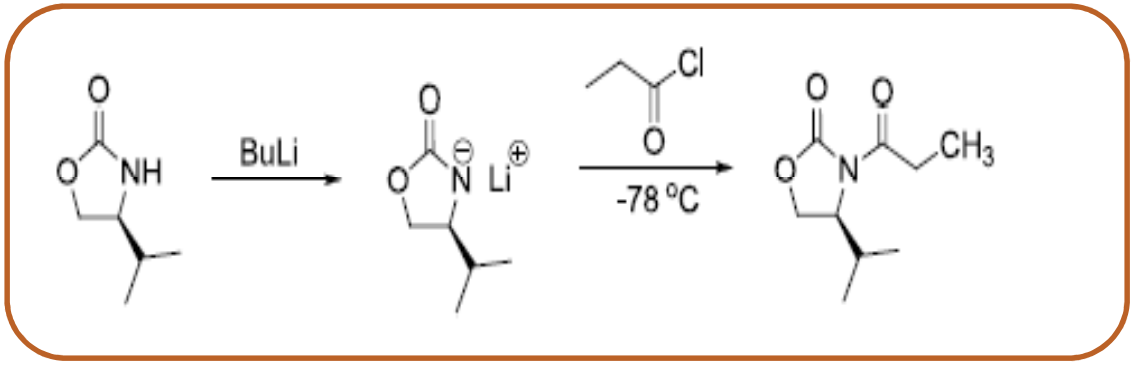
(a) Enantiomerically pure: Must be available in both enantiomeric forms.



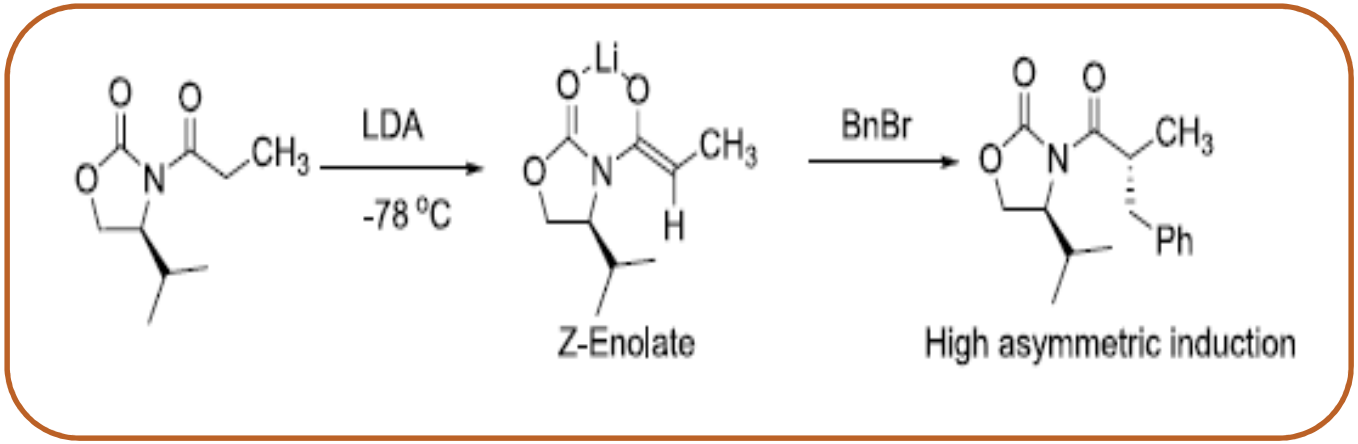
(b) *Cheap and easy to obtain in quantity.*



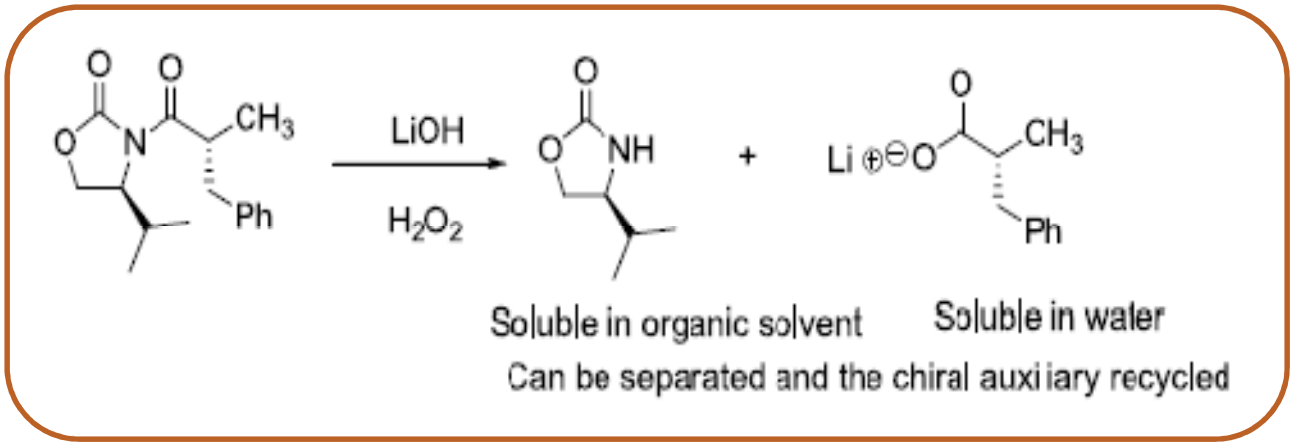
(c) *Must be readily incorporated onto the achiral substrate*.



(d) *It should provide good levels of asymmetric induction leading to high enantiomeric excess (ee). Steric bias plays a major role in facial differentiation.*



(e) *Needs to be selectively cleaved from the substrate under mild conditions.*

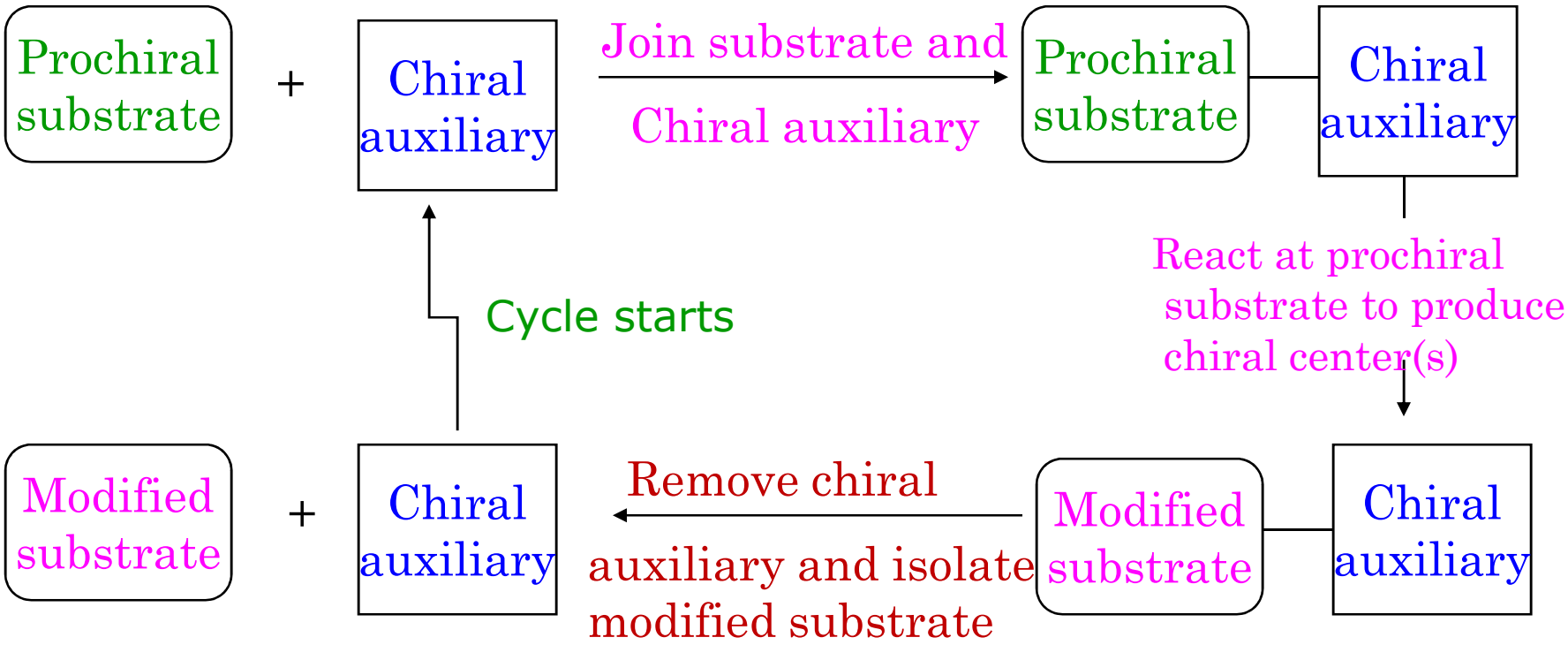


(f) *Easy purification of diastereomers.*

(g) *Must be recoverable and re-useable.*

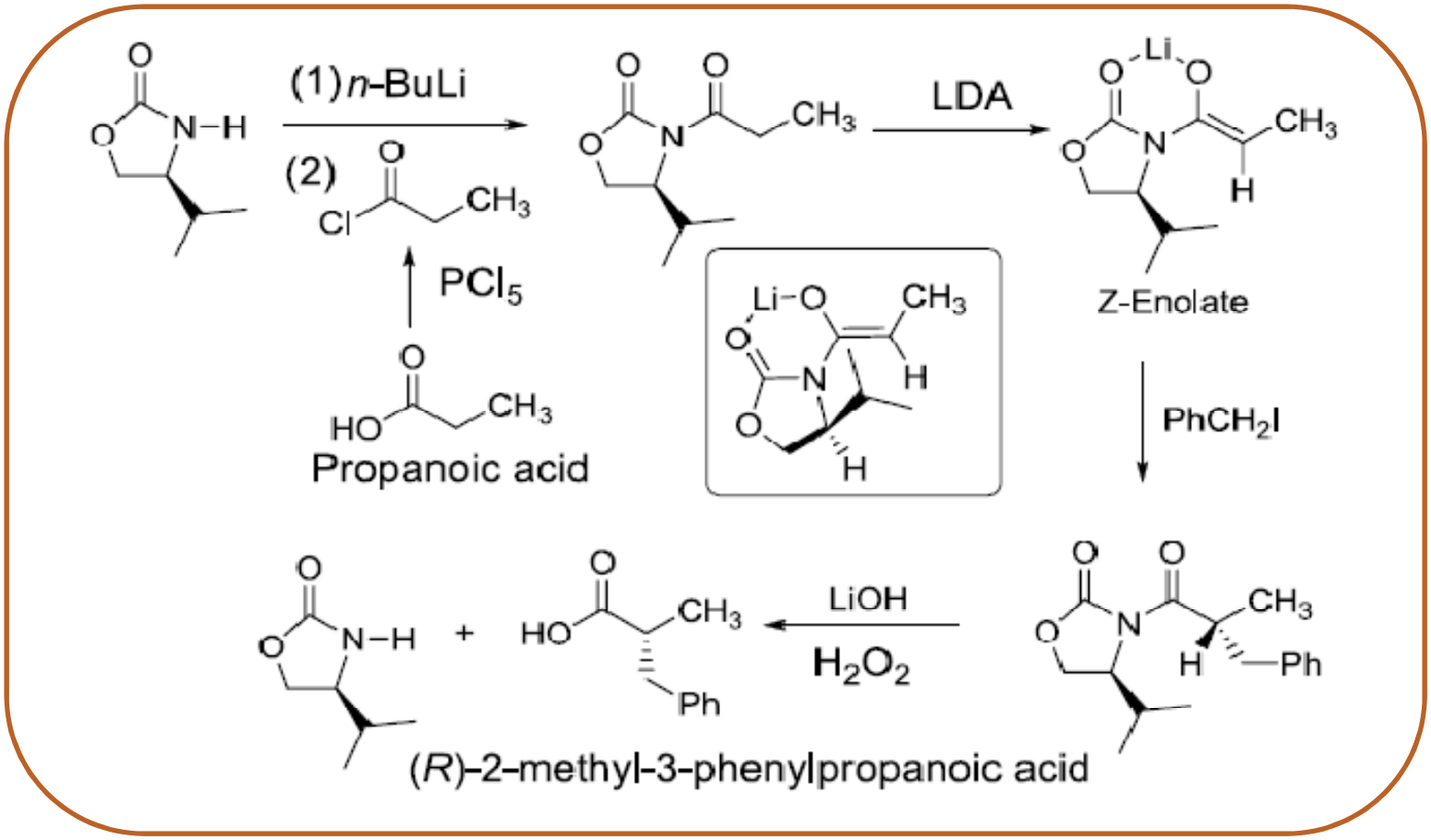
How Does a Chiral Auxiliary Work?

Schematic Representation of activity of Chiral Auxiliary :

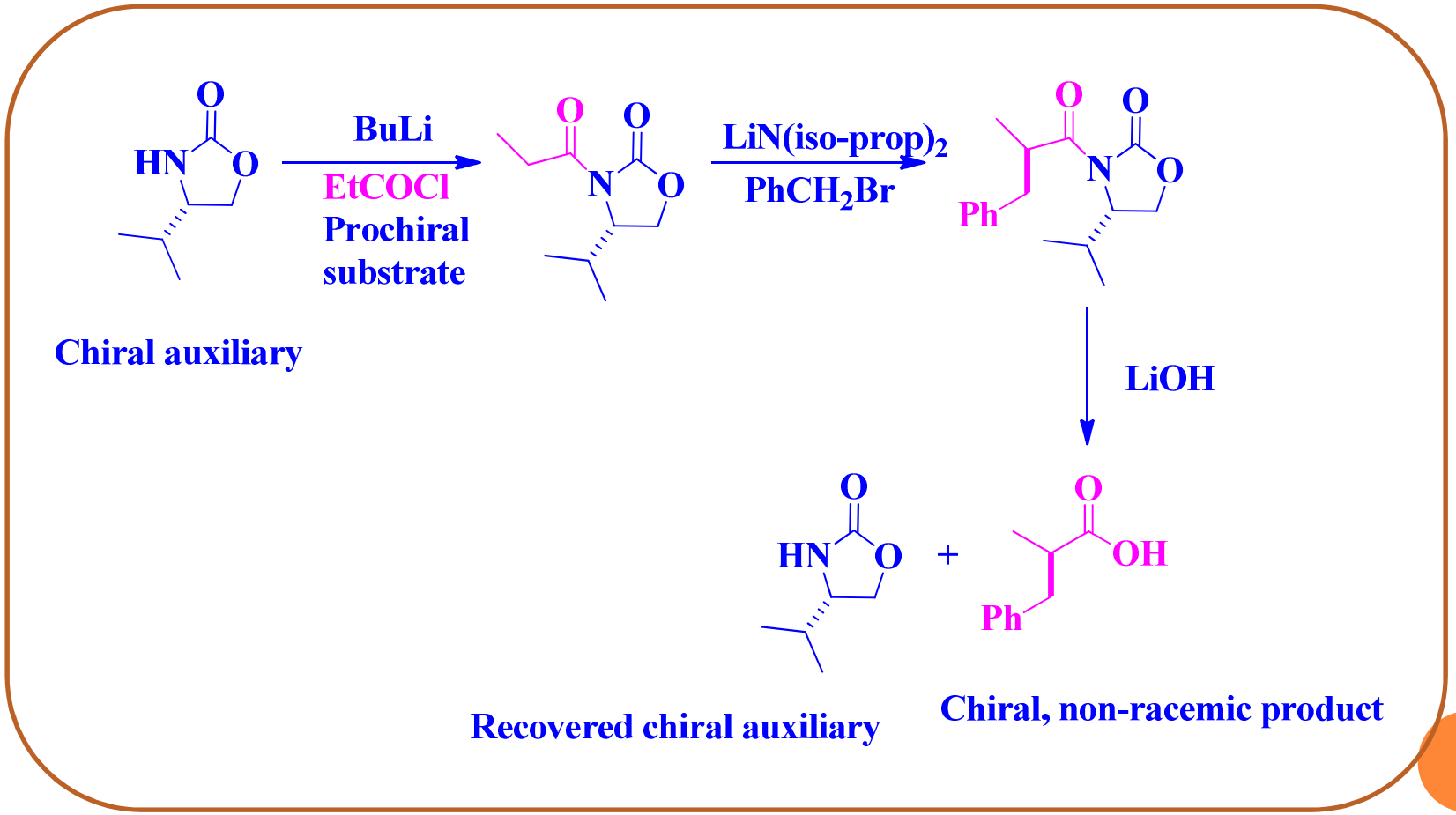


a) Asymmetric Enolate Alkylation through chiral auxiliary

Optically active carboxylic acids can be prepared with high enantiomeric excess based on the chiral auxiliary approach to asymmetric synthesis.

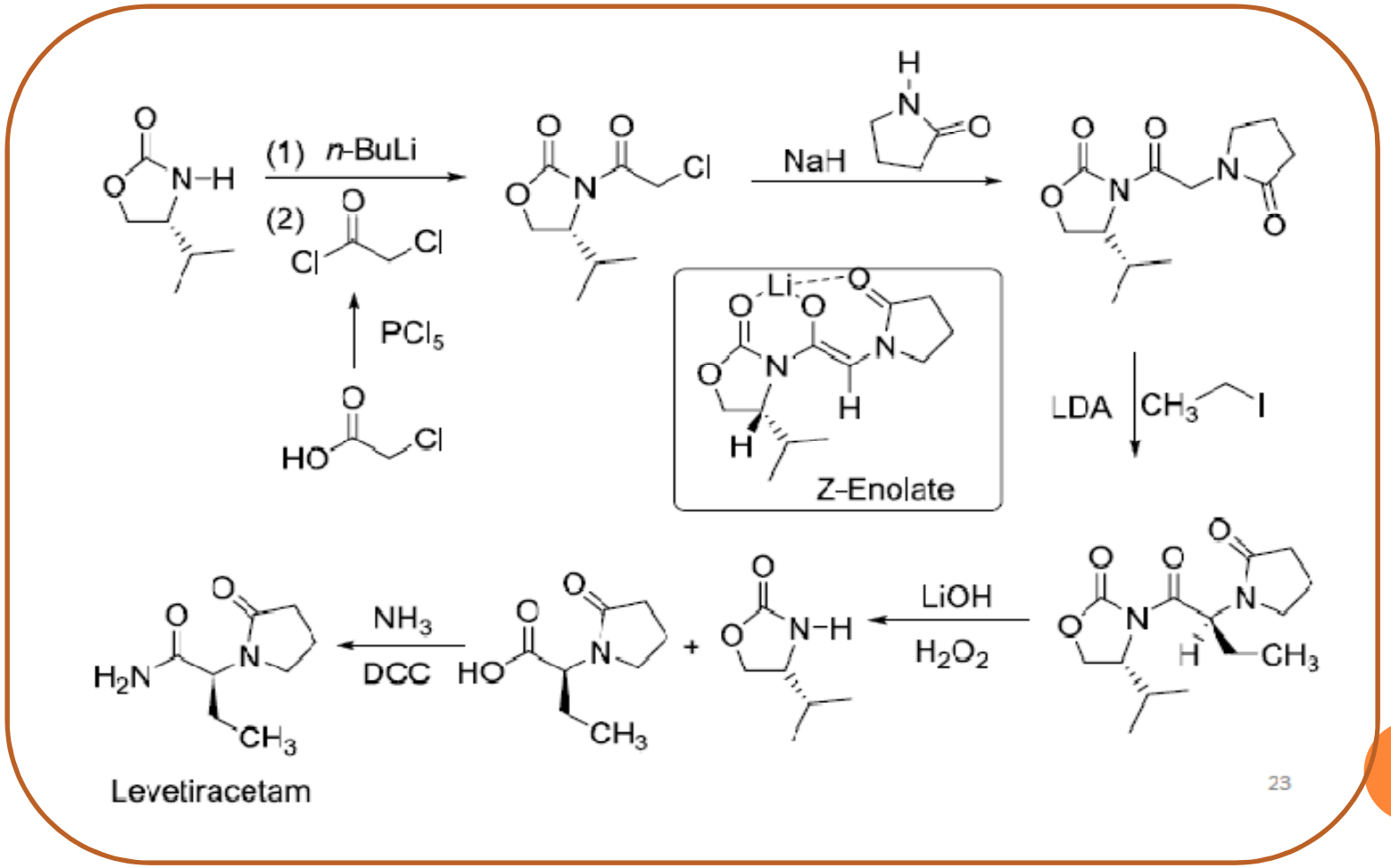


b) Assymetric synthesis of other enantiomer of chiral 2-methyl-3-phenylpropanoic acid through chiral auxiliary method.

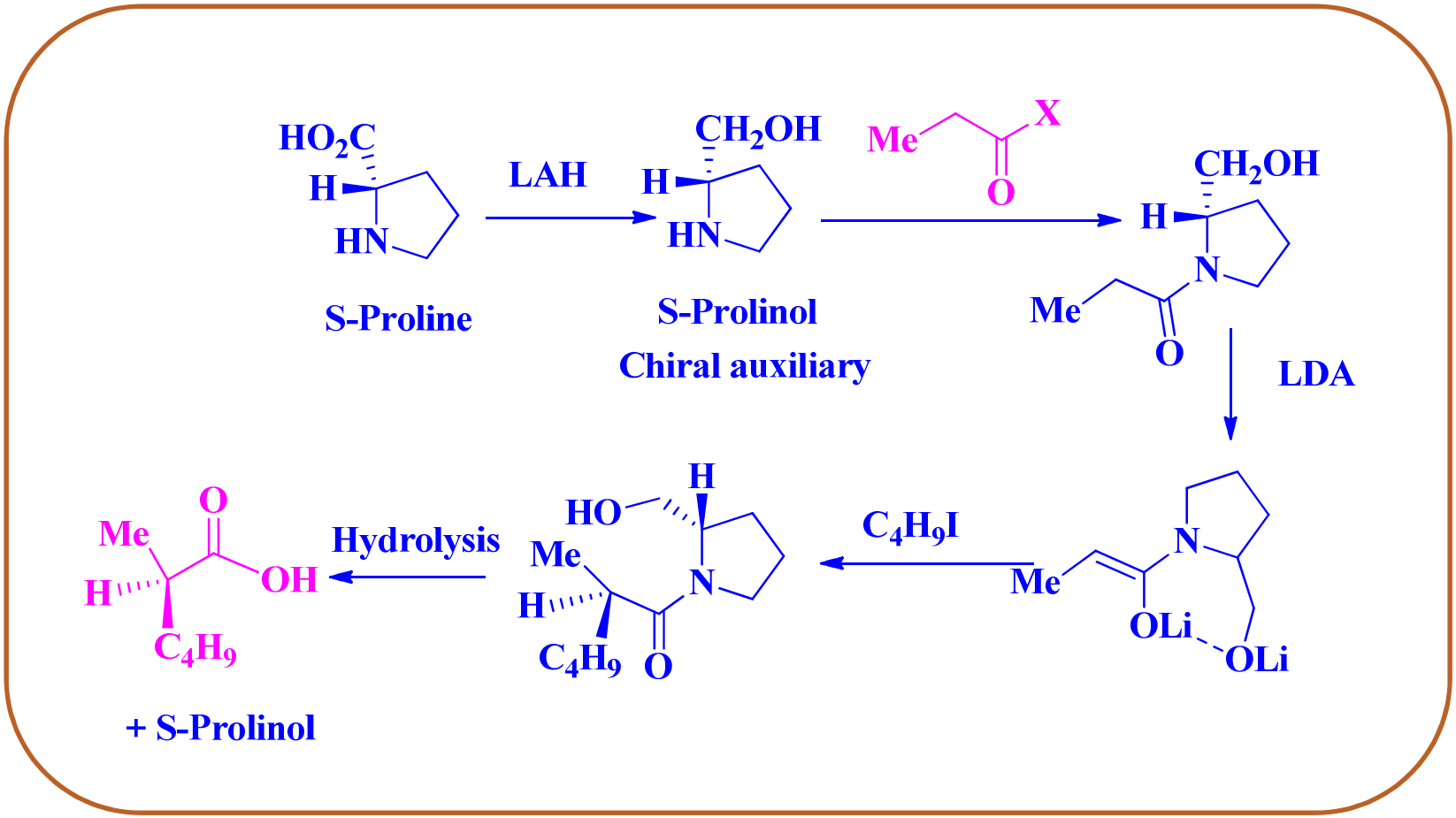


c) Asymmetric Synthesis of an Antiepileptic Drug:

The antiepileptic drug, levetiracetam, can be synthesized based on the chiral auxiliary approach as outlined below.



d) Chiral approach towards the synthesis of chiral acid compound.

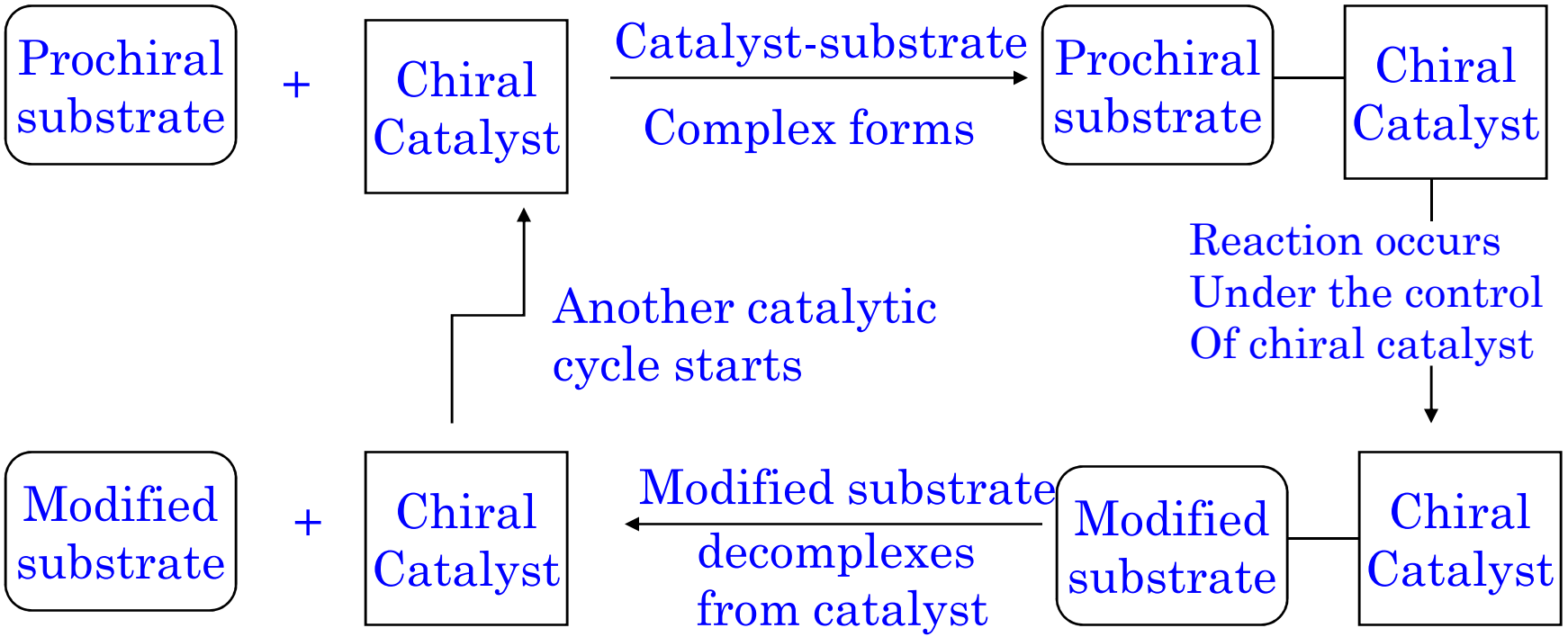


Assymetric Synthesis using of Chiral Reagent and Asymmetric catalysis:

Small amounts of chiral, enantiomerically pure (or enriched) catalysts promote reactions and lead to the formation of large amounts of enantiomerically pure or enriched products. Mostly, three different kinds of chiral catalysts are employed:

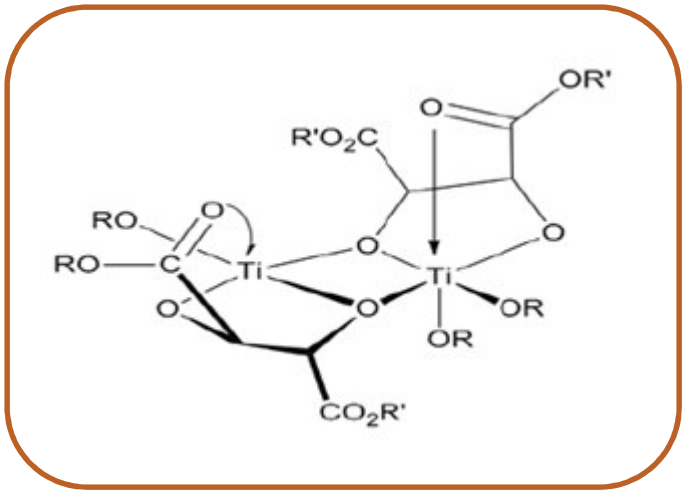
- Metal complexes derived from chiral ligands
- Chiral organocatalysts
- Biocatalysts

Schematic Representation of Asymmetric Catalysis

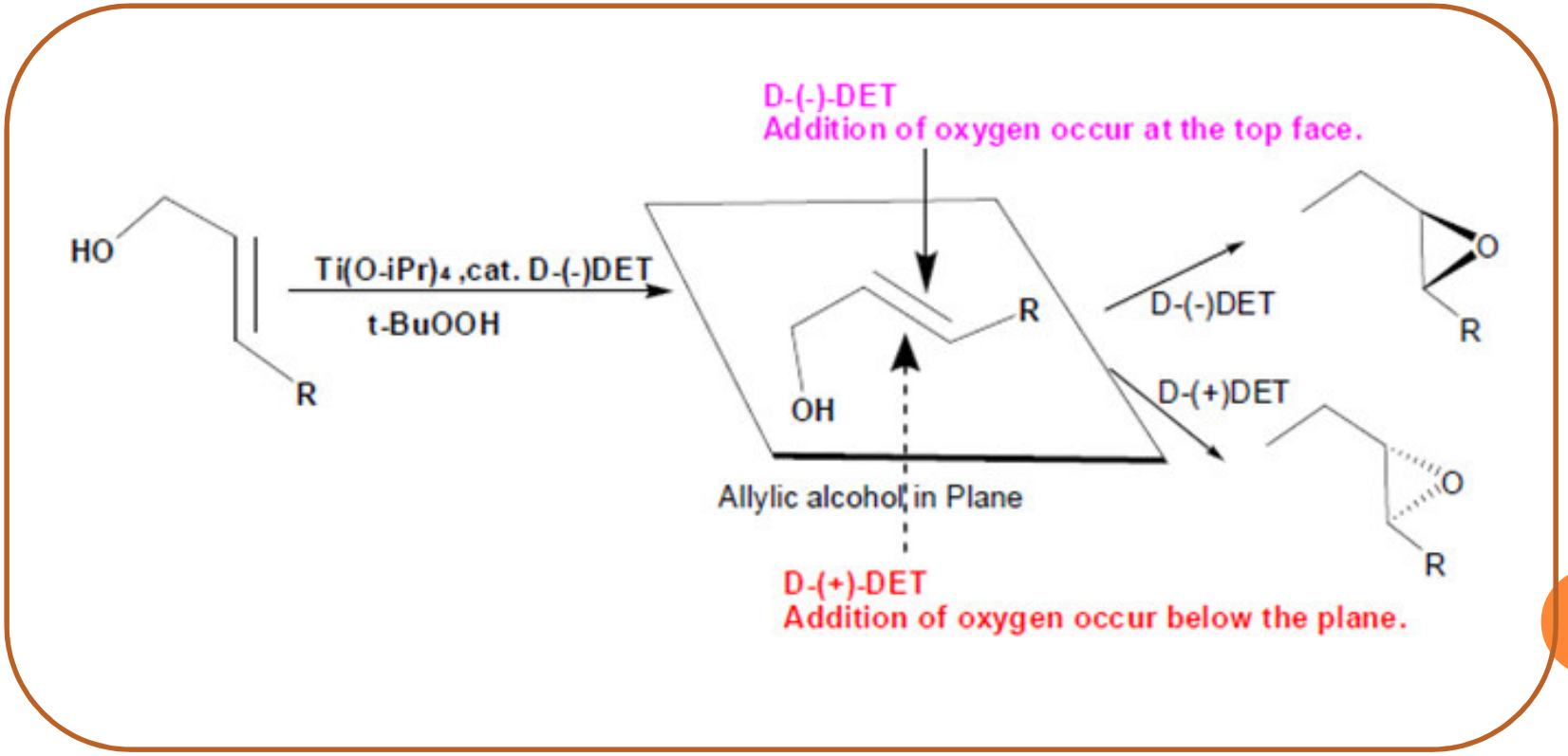


a) **Sharpless epoxidation reaction:**

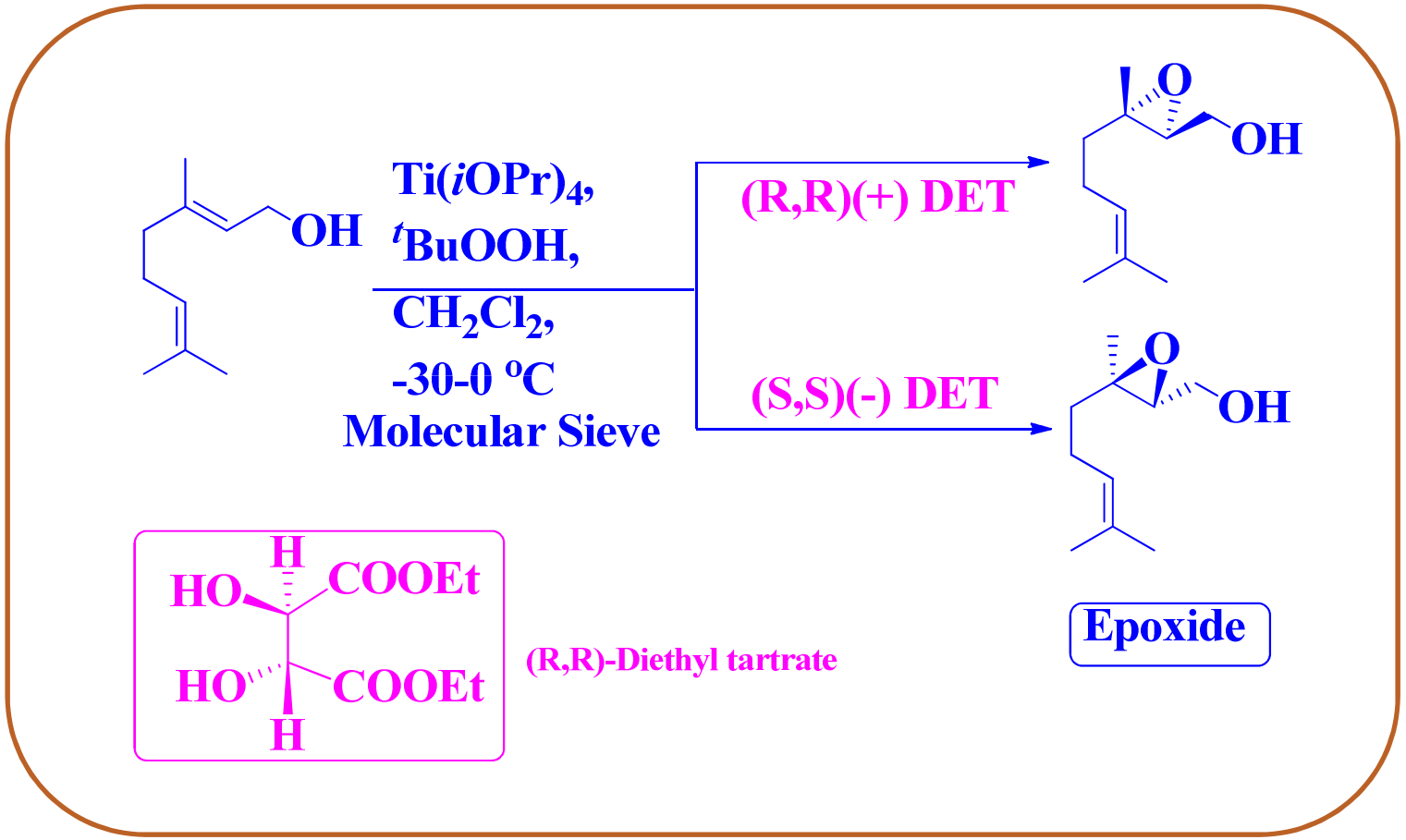
The Sharpless Epoxidation is an enantioselective epoxidation of allylic alcohols. Converts primary and secondary allylic alcohols into 2,3 epoxyalcohols. The oxidizing agent is *tert-buty hydroperoxide.* Enantioselectivity is achieved by a catalyst formed from titanium tetra(isopropoxide) and diethyl tartrate.

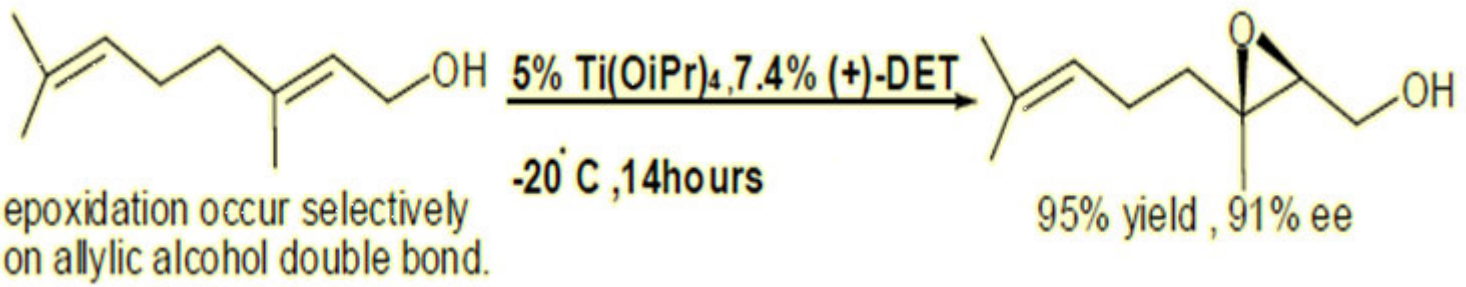


Orientation of Oxygen atom: The reaction is enantioselective (only one enantiomer produced). Formation of Enantiomer depends on the stereochemistry of catalyst. If the allylic alcohol is drawn so that the hydroxyl methyl group is at the lower right then the oxygen atom is deliverd at the **bottom face in presence of D(+) diethyl tartarate** and the oxygen atom is deliverd from the **top face in presence of the D(-) diethyl tartarate**.

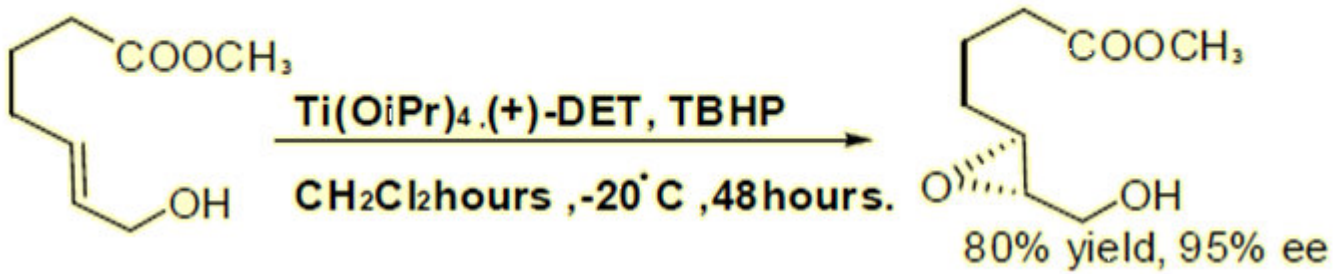


Example


OH
Ti(iOPr)4,
tBuOOH,
CH2Cl2,
-30-0 °C
Molecular Sieve
(R,R)(+) DET
(S,S)(-) DET
O
OH
O
OH
H
HO
COOEt
HO
COOEt
H
(R,R)-Diethyl tartrate
Epoxide



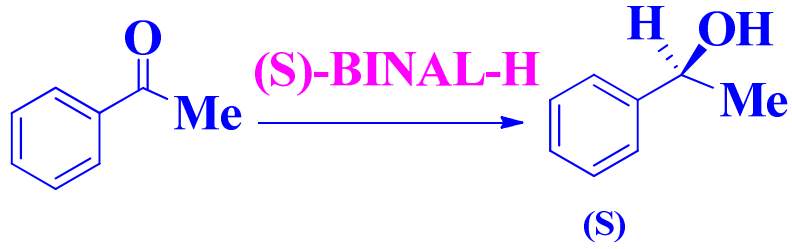
Intermediate for synthesis of leukotriene C1



b) Assymetric reduction via chiral metal hydride complex:

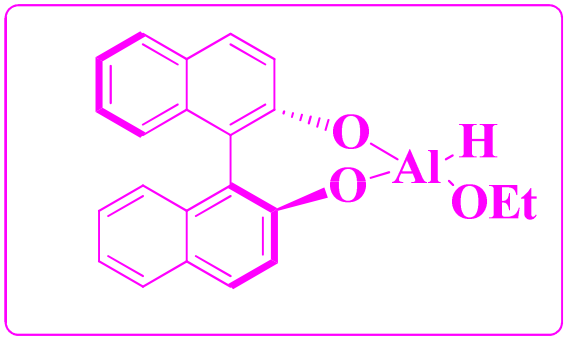
Commonly used asymmetric reducing agent is (BINAL-H). Sodium borohydride or lithium borohydride modified with chiral auxiliary i.e (S or R)-BINAL-H are highly enantioselective reagent. Generally RR-reducing agent gives R-alcohol while the SS-reagent gives S- enantiomer.

Ex: Acetophenone or 4,4-dimethylpentan-2-one when treated with (S)-BINAL-H it gives S-alcohol with high enantioselectivity.



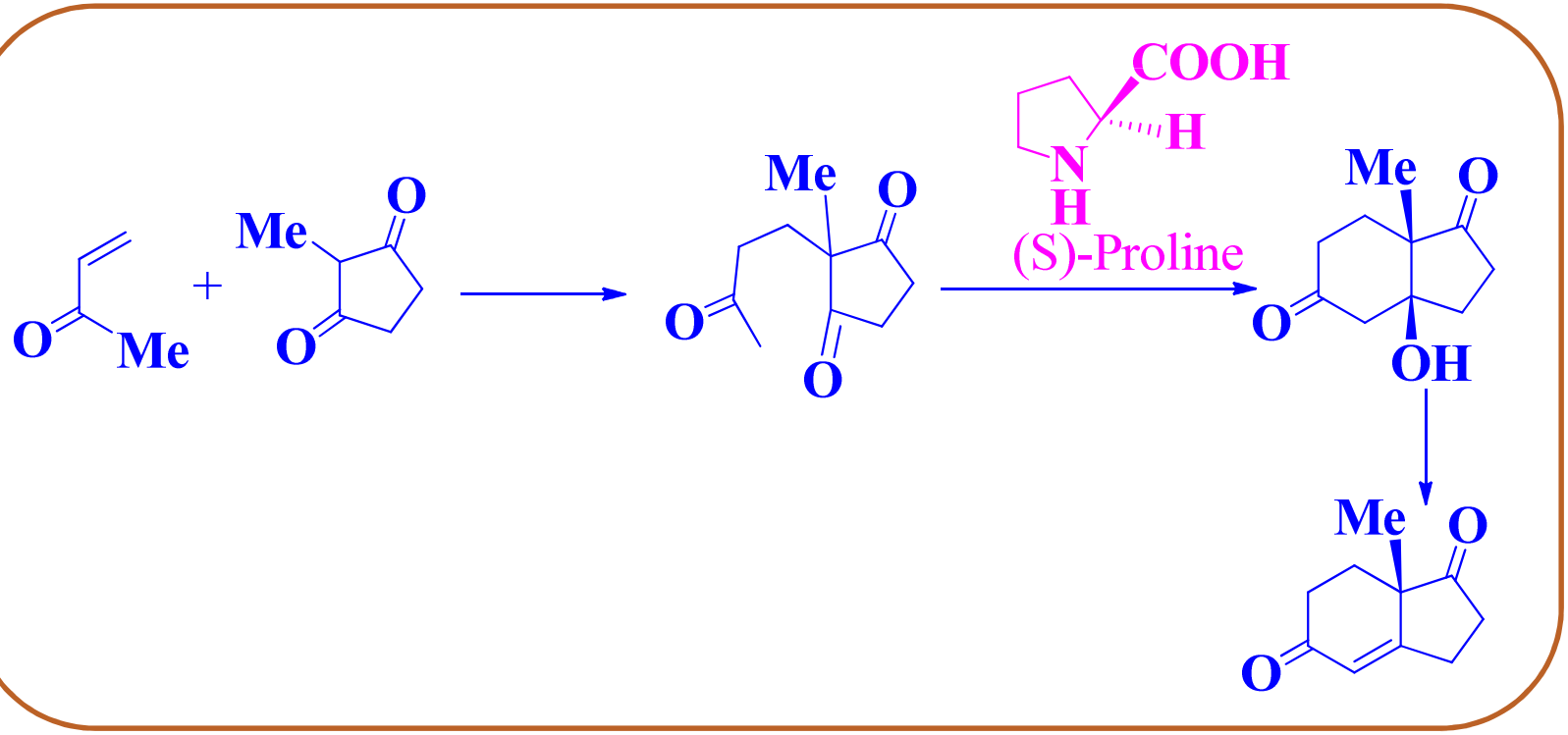
(S)

(S)

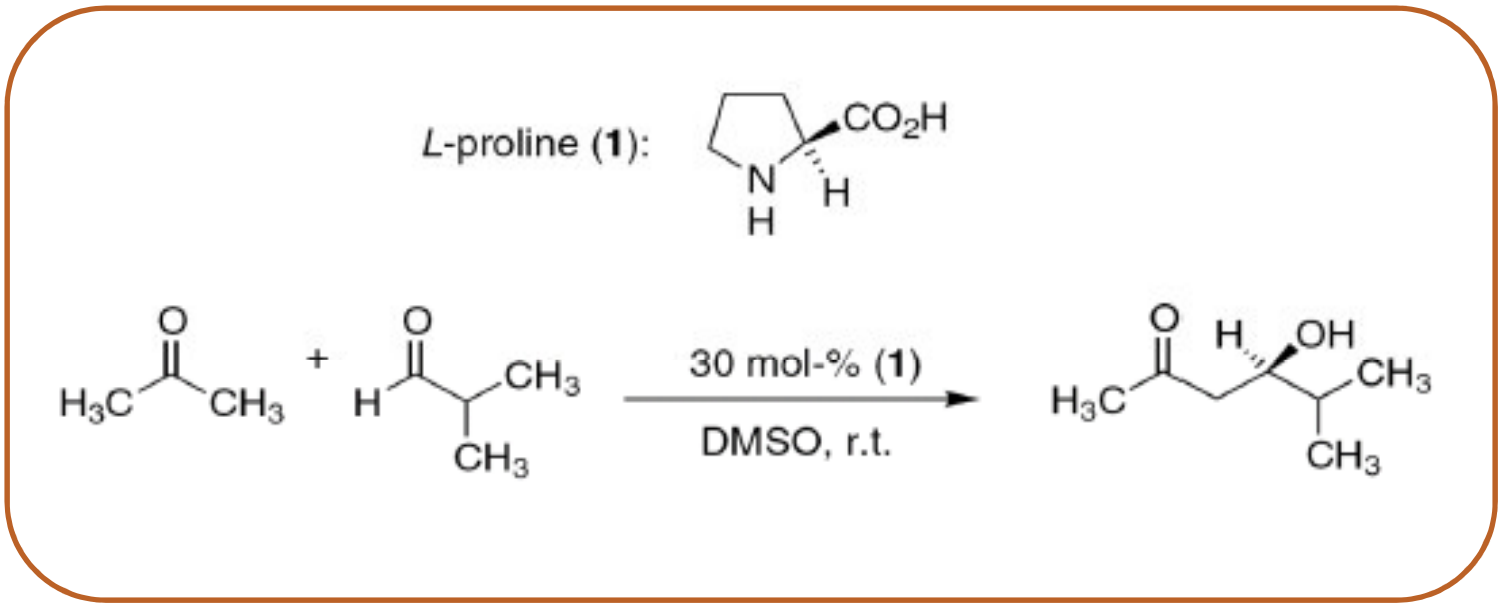


(S)-BINAL-H

Asymmetric Organocatalysis: When Rabinson annulations is carried out with chiral base (S-proline) the overall process of addition and cyclization step gives the bicyclic hydroxyl diketone and the product is obtained in 94% optical purity.



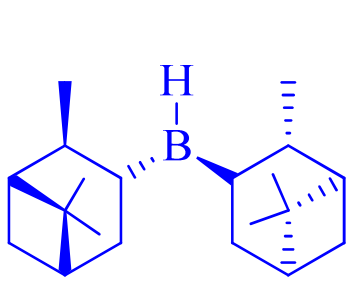
Proline catalysed aldol condensation:



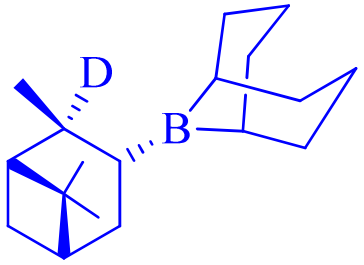
Asymetric hydroboration oxidation:

Use of Chiral borane

Asymmetric hydroboration oxidation is carried out using chiral alkyl borane such as monoisopinocampheylborane $(Ipc)BH_2$ or diisopinocampheylborane $(Ipc)_2BH$, Alpine borane.

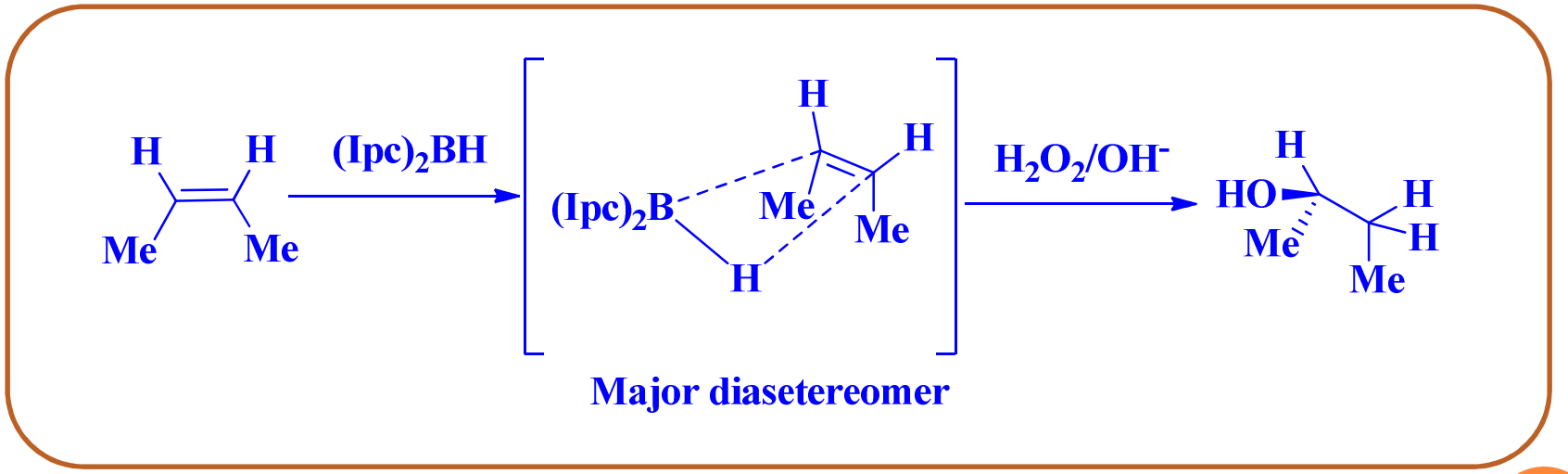


$(Ipc)_2BH$



Alpine Borane

a) The hydroboration of (Z)-but-2-ene followed by oxidation using optically pure form of Chiral diisopinocampheylborane $(Ipc)_2BH$ gives (R)-butane-2-ol with high optical purity. Whereas same reaction with monoisopinocampheylborane $(Ipc)BH_2$ results in the formation of (S) butane-2-ol.



b) Deuteriated analogue of Alpine borane on reaction with benzaldehyde produces monodeuteriated primary alcohol high optical purity.