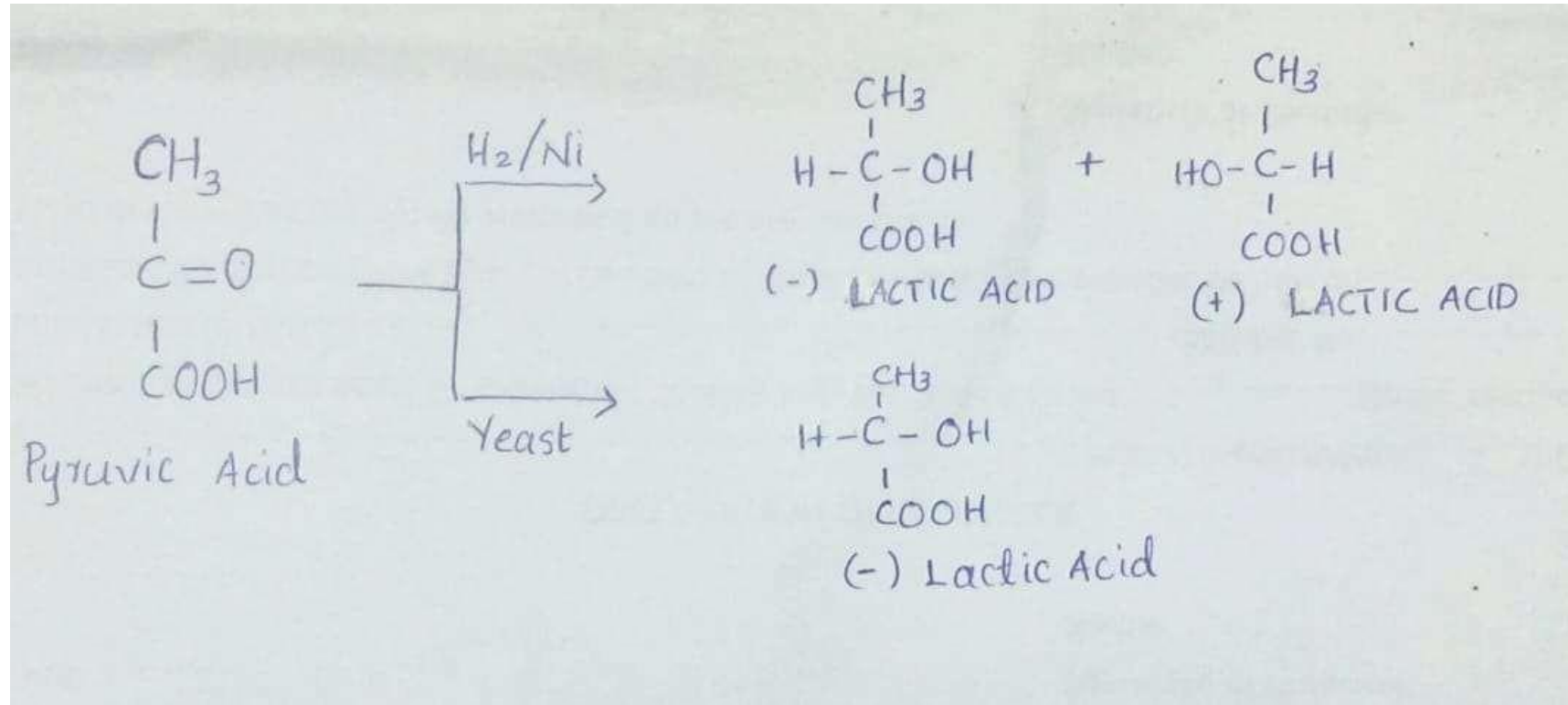


Asymmetric synthesis

Asymmetric synthesis

- ❖ Asymmetric synthesis is a reaction in which an achiral unit in a substrate molecule is converted into a chiral unit in such a manner that unequal amounts of stereoisomers (enantiomers or diastereomers) are produced
- ❖ When a compound containing an asymmetric carbon (CHIRAL) is synthesized by conventional laboratory methods from an achiral compound the product is a racemic mixture.
- ❖ If such a synthesis carried out under chiral influence, only one of optically active isomer will form preferentially over the other.

EXAMPLE :reduction of pyruvic acid.



Chiral environment is the necessary condition for asymmetric synthesis.

DEPENDING ON THE RELATIONSHIP BETWEEN PRODUCTS FORMED DURING ASYMMETRIC SYNTHESIS ,REACTION MAY BE **ENANTIOSELECTIVE** OR **DIASTEREOSELECTIVE** .

A+B

C + D

—————> STEREISOMERS

C and D formed in unequal amounts

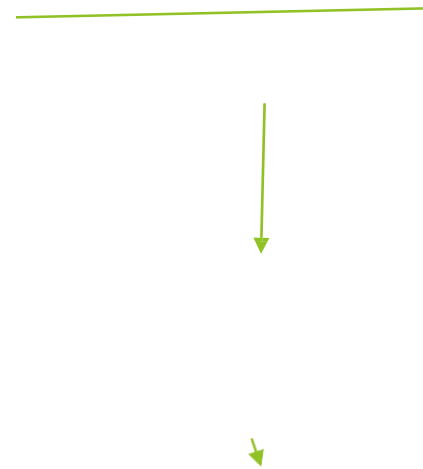
STERESELECTIVE

C and D are diastereomers

C and D are enantiomers

DIASTEREOSELECTIVE

ENANTIOSELECTIVE



STEREOSPECIFIC REACTIONS

VERSUS

STEREOSELECTIVE REACTIONS

A stereospecific reaction is a reaction in which the stereochemistry of the reactant completely determines the stereochemistry of the product without any other option

Gives a specific product from a certain reactant

Final product depends on the stereochemistry of the reactant

A stereoselective reaction is a reaction in which there is a choice of pathway, but the product stereoisomer is formed due to its reaction pathway being more favorable than the others available

Can result in multiple products

Selectivity of the reaction pathway depends on differences in steric effects and electronic effects

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FUNDAMENTALS

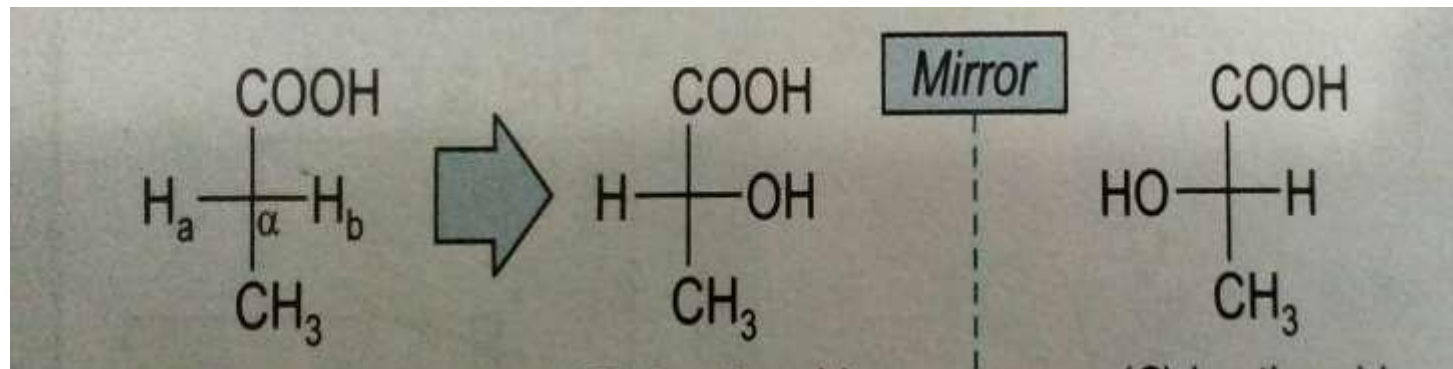
One of the two conditions need to be met for successful asymmetric synthesis.

A) PROCHIRALITY

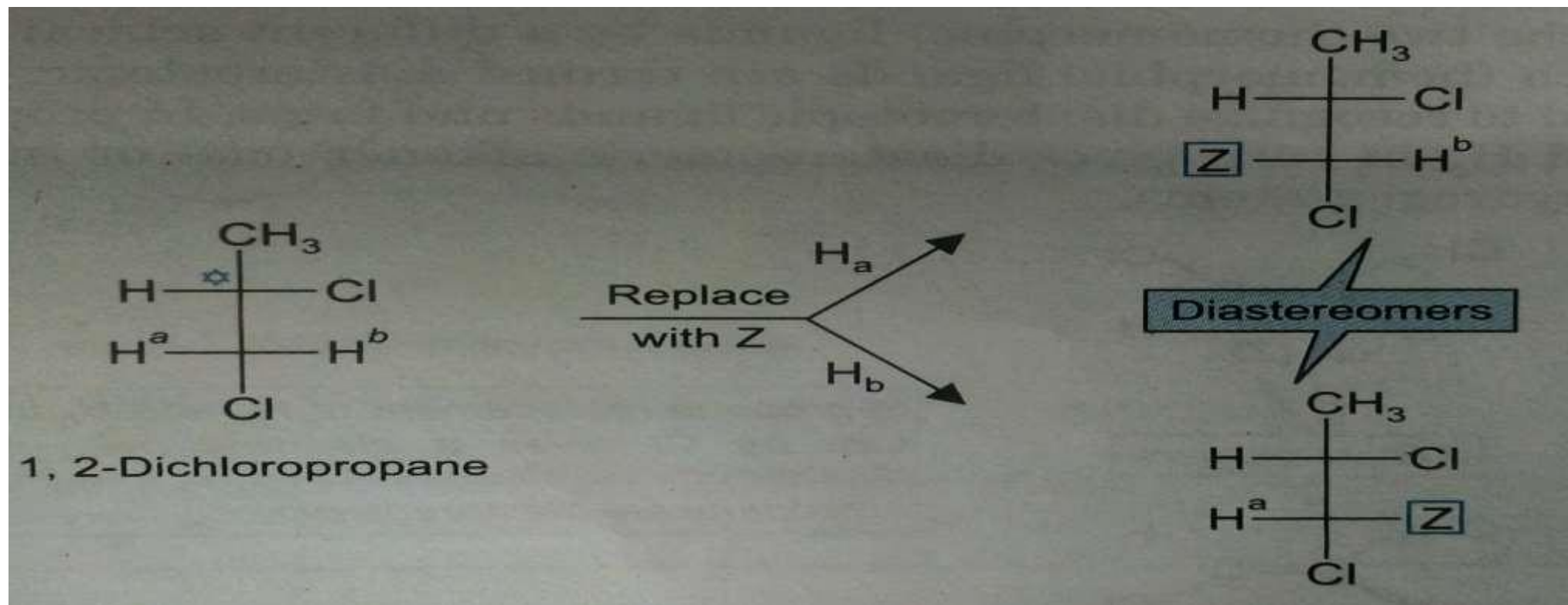
A tetrahedrally bonded achiral atom have general formula $Cabc_2$ will become a chiral center $Cabcd$ on replacement of one of the identical ligand c with a different ligand d is called a prochiral centre and the molecule is said to be prochiral.

DEPENDING ON THE PRODUCT FORMED FROM A PROCHIRAL CENTRE, THE MOLECULE WILL BE ENANTIOTOPIC OR DIASTEREOTOPIC .

Eg:Enantiotopic



Eg:Diastereotopic



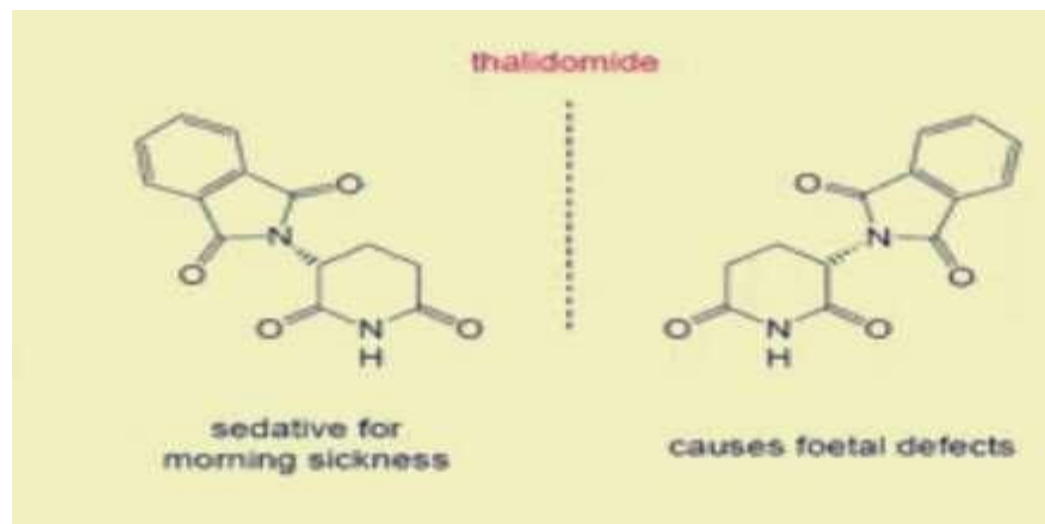
B) ASYMMETRIC INDUCTION

The second condition of asymmetric synthesis is brought about in the reaction pathway by the presence of an element of chirality, which plays an active role in the reaction.

Property of chirality is induced by chiral reagent, solvent, catalyst or circularly polarized light

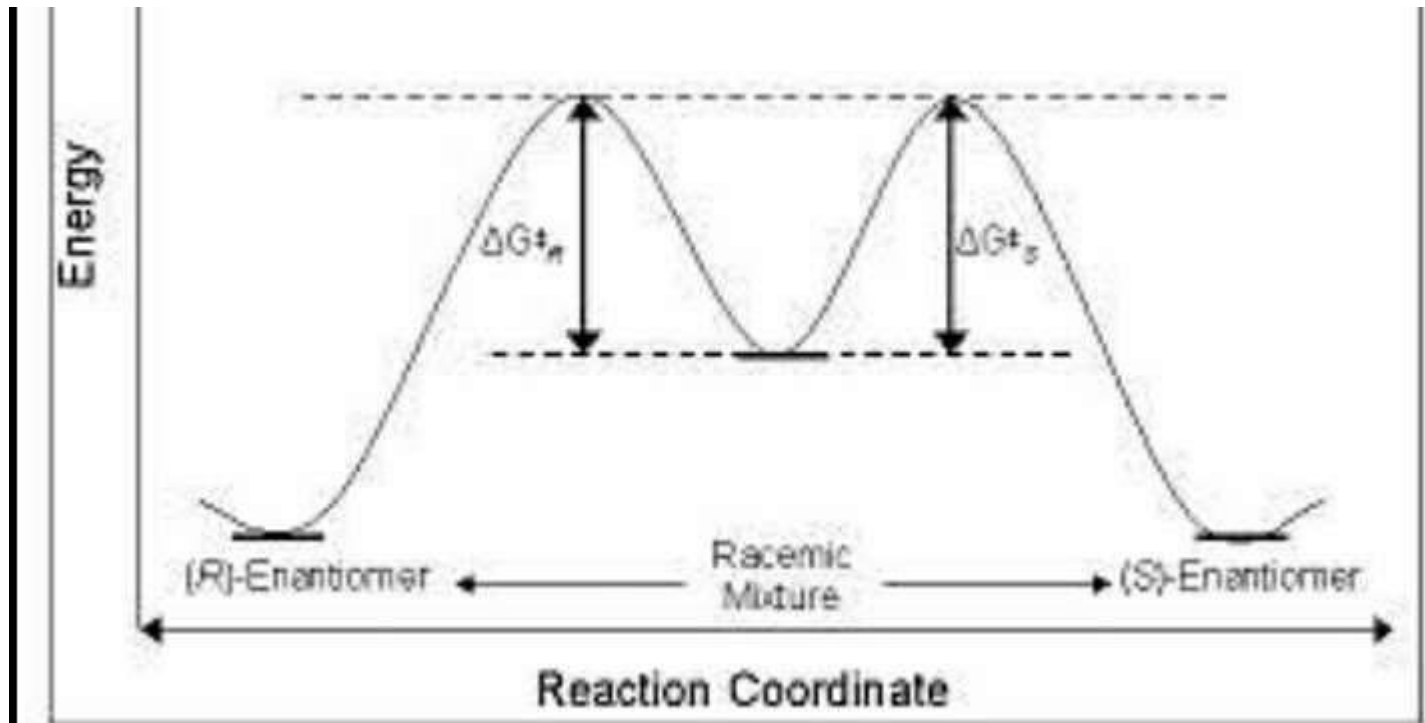
WHY ASYMMETRIC SYNTHESIS IMPORTANT

- Before 1940 optically pure compound is obtained by isolation from natural products, resolution of racemic mixture and by laboratory controlled enzymatic reactions, but the yield of optically pure compound was very less.
- All natural or biologically occurring molecules are chiral . Because nature uses enzymes ,these are biological catalysts.
- Synthesis of optically pure substance are important because different enantiomers or diastereomers of a compound have **different biological activity**. Eg:+ and - thalidomide have different action with biological receptors.

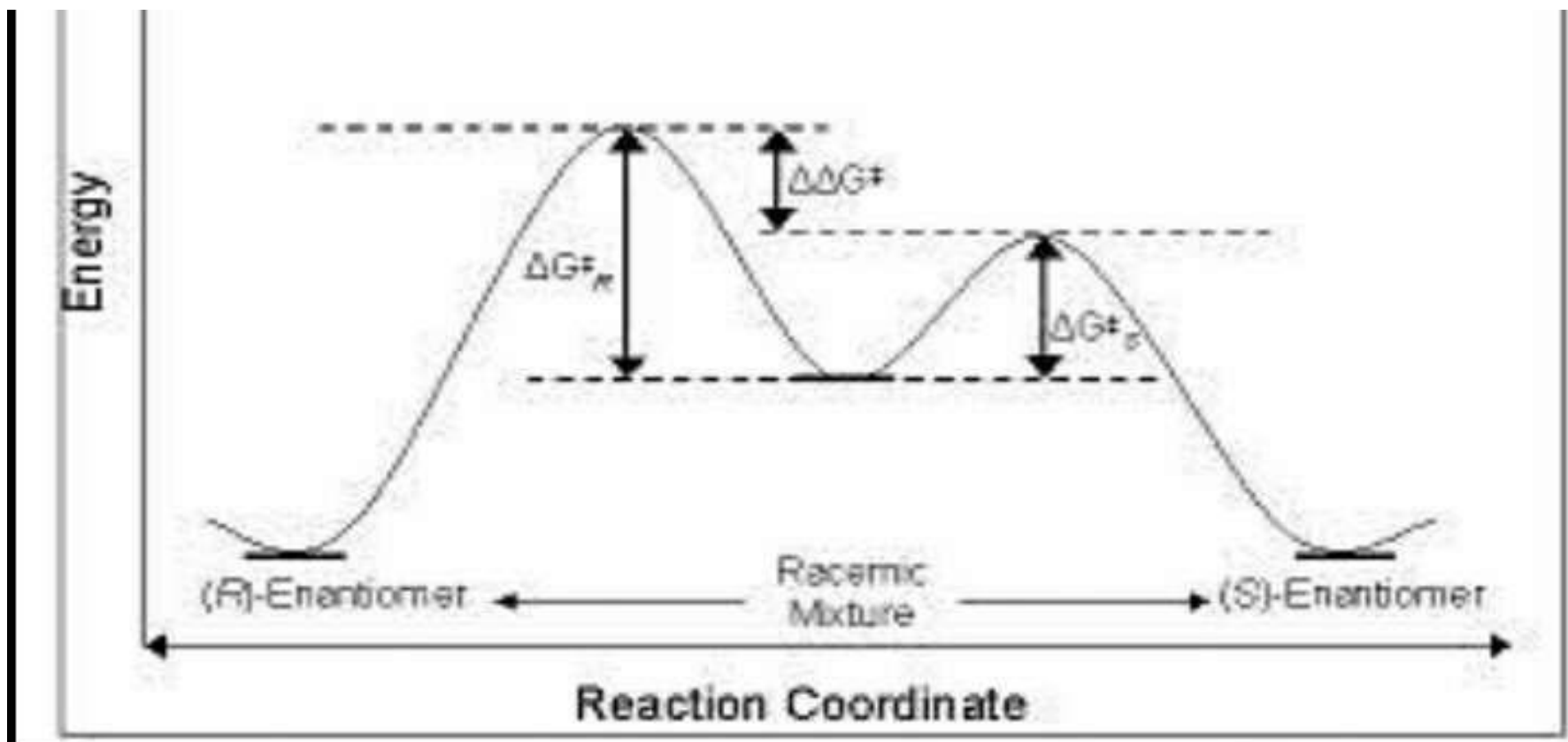


MECHANISM OF ASYMMETRIC SYNTHESIS

- The aim is to make enantiomers into diastereomers . To make this possible ,we need to incorporate reagents or catalysts having chirality.
- The reaction will now proceed differently for different enantiomers because of the difference in energy of transition state.
- In the absence of chiral influence, reaction producing enantiomers in equal amounts via transition states of identical energies (**enantiomeric transition state**) . These reactions therefore takes place at identical rates to give equal amounts of enantiomers



- If we are using chiral components , then we could make the possible enantiomeric transition state , **diastereomeric transition state** with different activation energy which results in unequal amounts of isomers.
- We have to go through a diastereomeric transition state to achieve asymmetric synthesis.



MAJOR APPROACHES IN ASYMMETRIC SYNTHESIS

□ Asymmetric synthesis are of two types

A) PARTIAL ASYMMETRIC SYNTHESIS

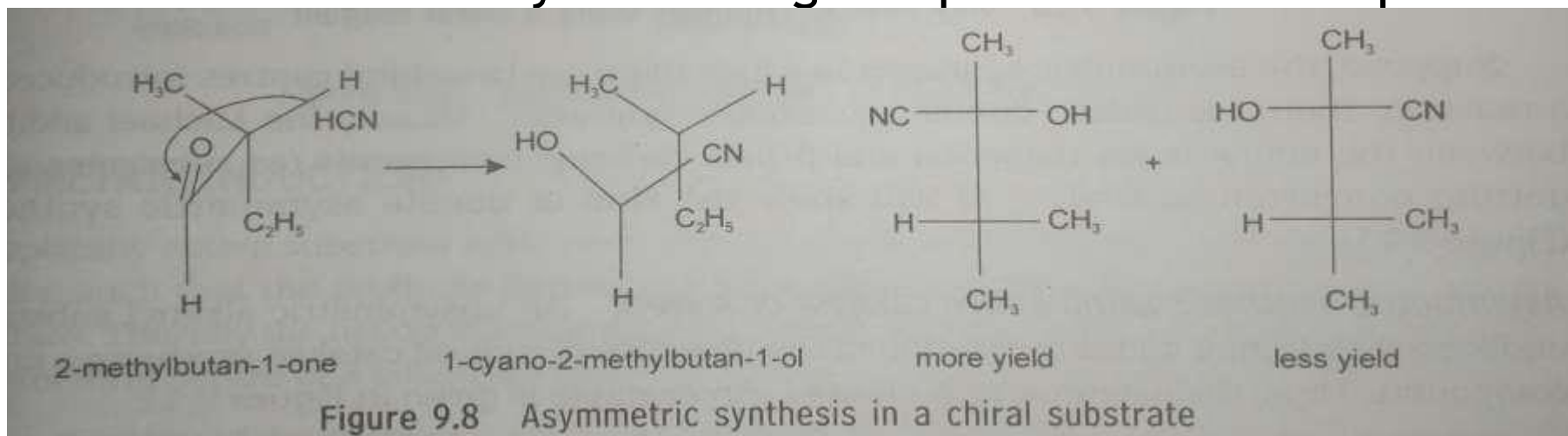
synthesis of a new chiral center from an achiral center by **using optically active reagents** .

□ Different methods of partial asymmetric synthesis are:

1) Use of chiral substrate (first generation method)

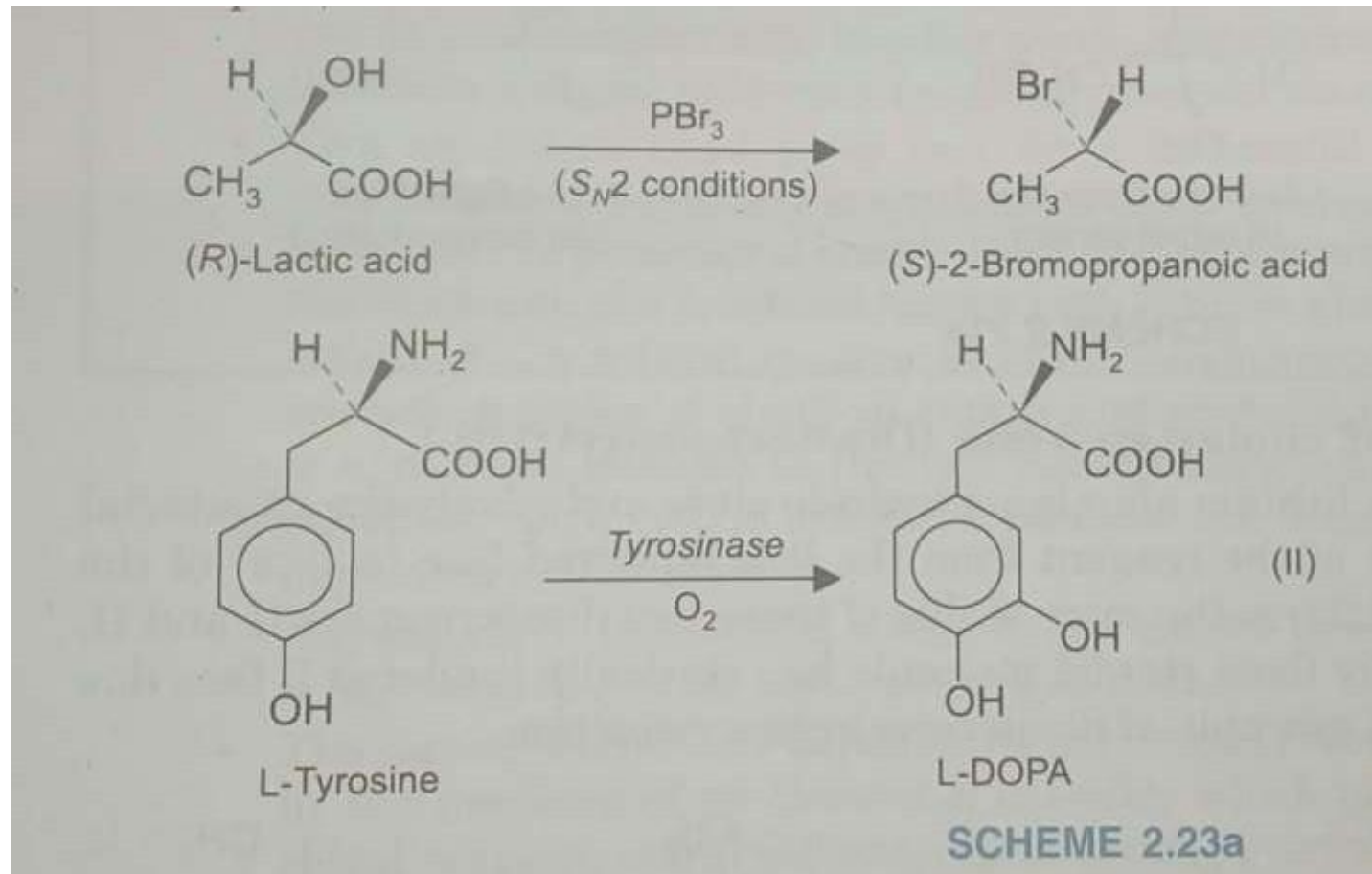
□ It uses nature's ready-made chiral centers as starting materials .

□ More economical way of making compounds in enantiopure form.

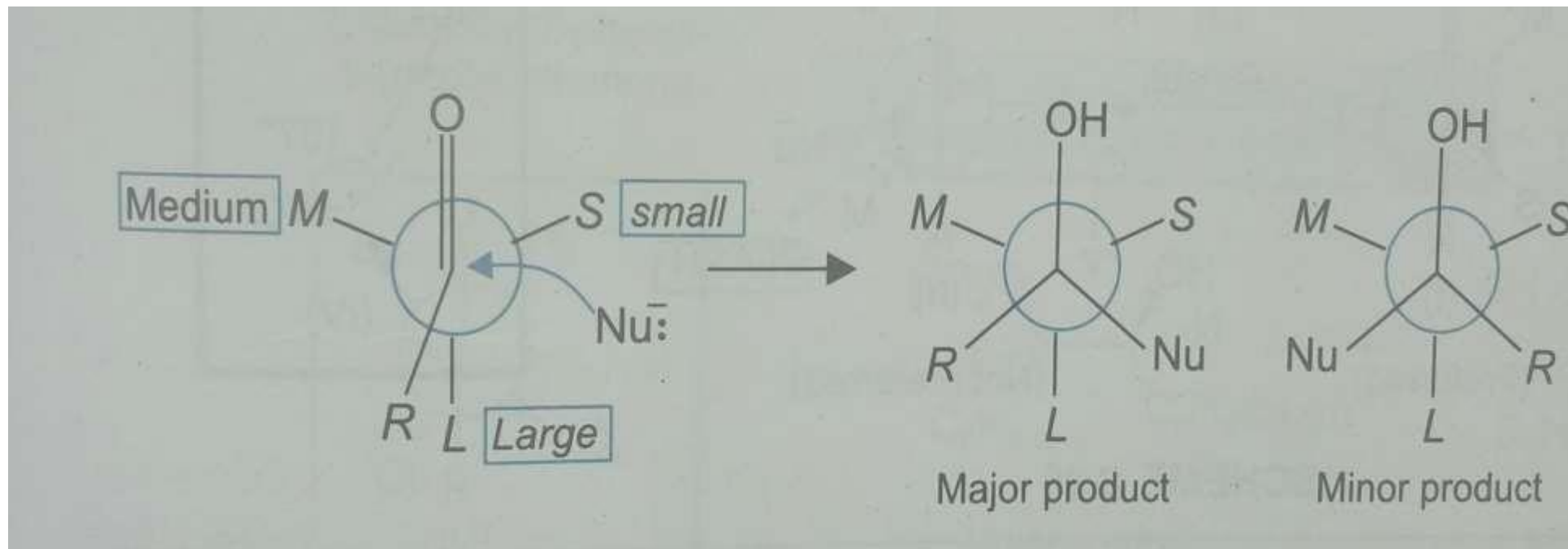


Eg: Conversion of L-tyrosine into L-DOPA

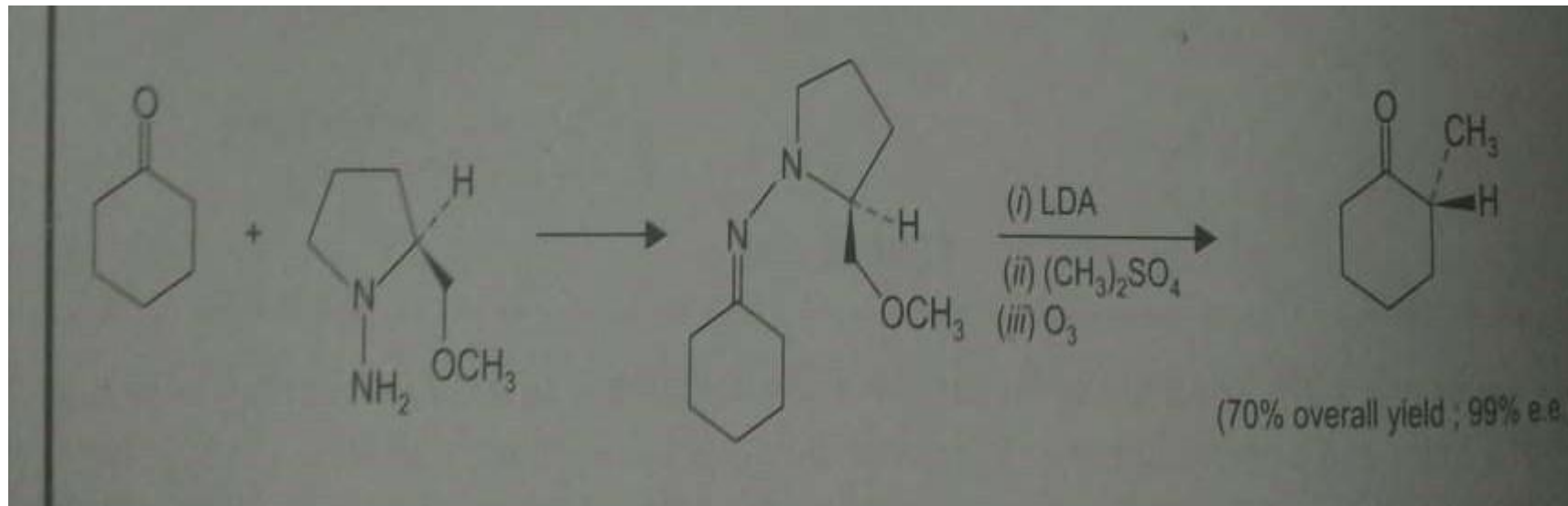
- In this conversion starting material L-tyrosine is a naturally occurring chiral molecule .
- This conversion doesn't affect the existing stereocenter .



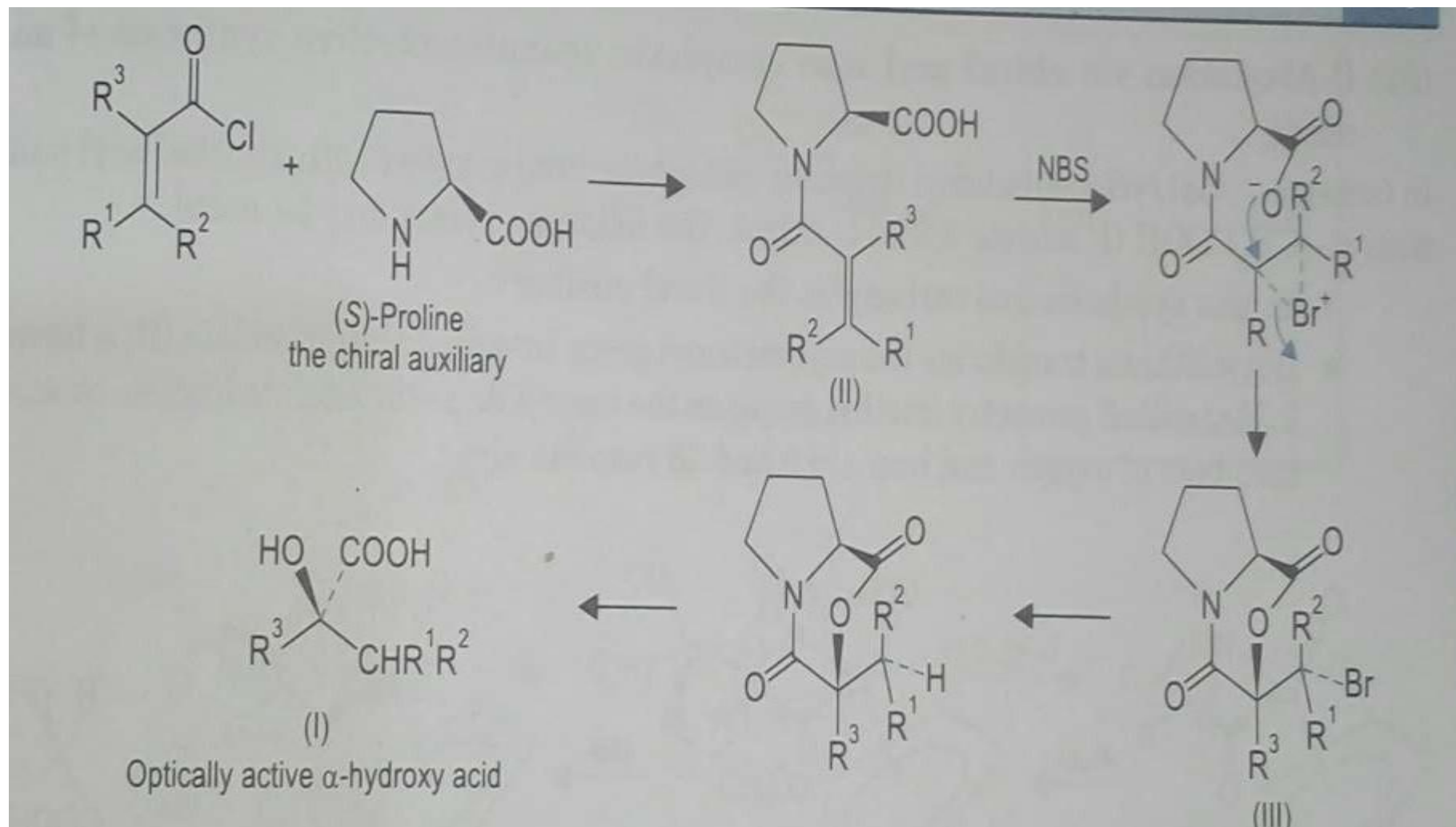
- This method is also known as “ CHIRAL POOL ” STRATEGY.
- Chiral pool is the collection of cheap , readily available natural products .
Eg:(+)*nicotine*, (+)*tartaric acid*, *D-glyceraldehyde* etc .
- Nucleophilic attack on acyclic carbonyl compounds :
- For certain additions to $C=O$ groups of chiral aldehyde or ketones **CRAM'S RULE** is useful to predict which diastereomer will predominate .



- 2) Use of chiral auxiliary (second generation method)
- In this approach a prochiral substrate attach with a chiral auxiliary to give a chiral intermediate.
- During which auxiliary dictates the preferred stereochemistry.
- Finally we can remove the auxiliary from product to use it again .
- Eg: asymmetric alkylation of cyclohexanone using SAMP .



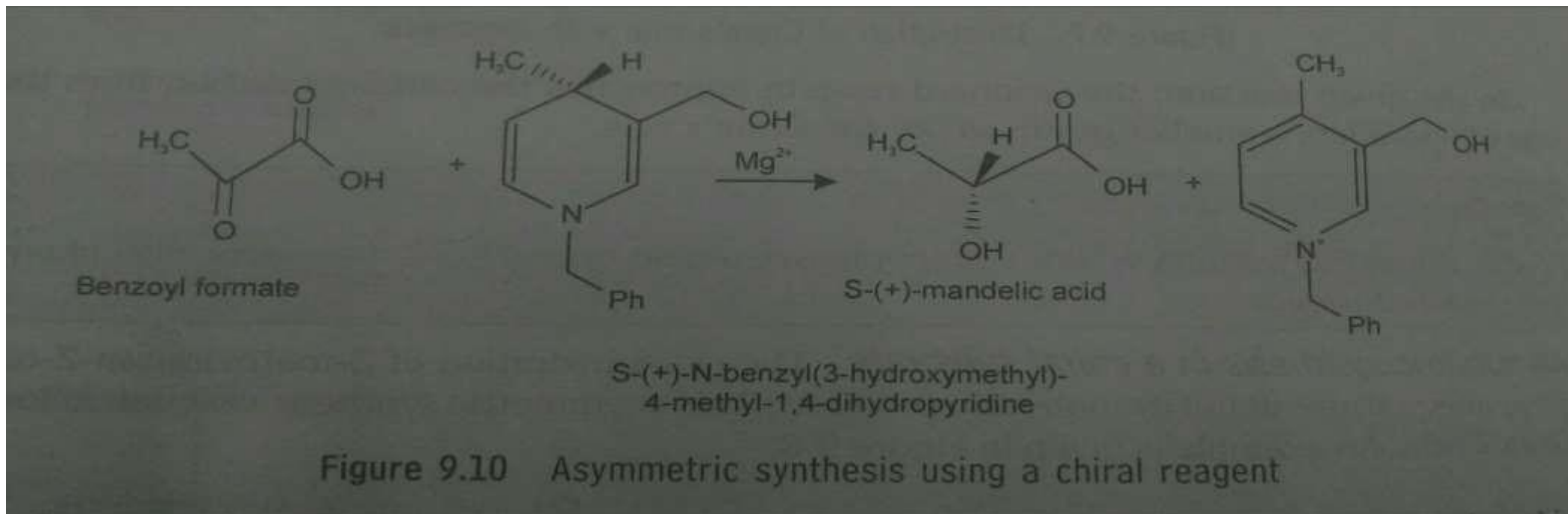
Eg: Asymmetric halolactonization - Synthesis of α -hydroxyl acid



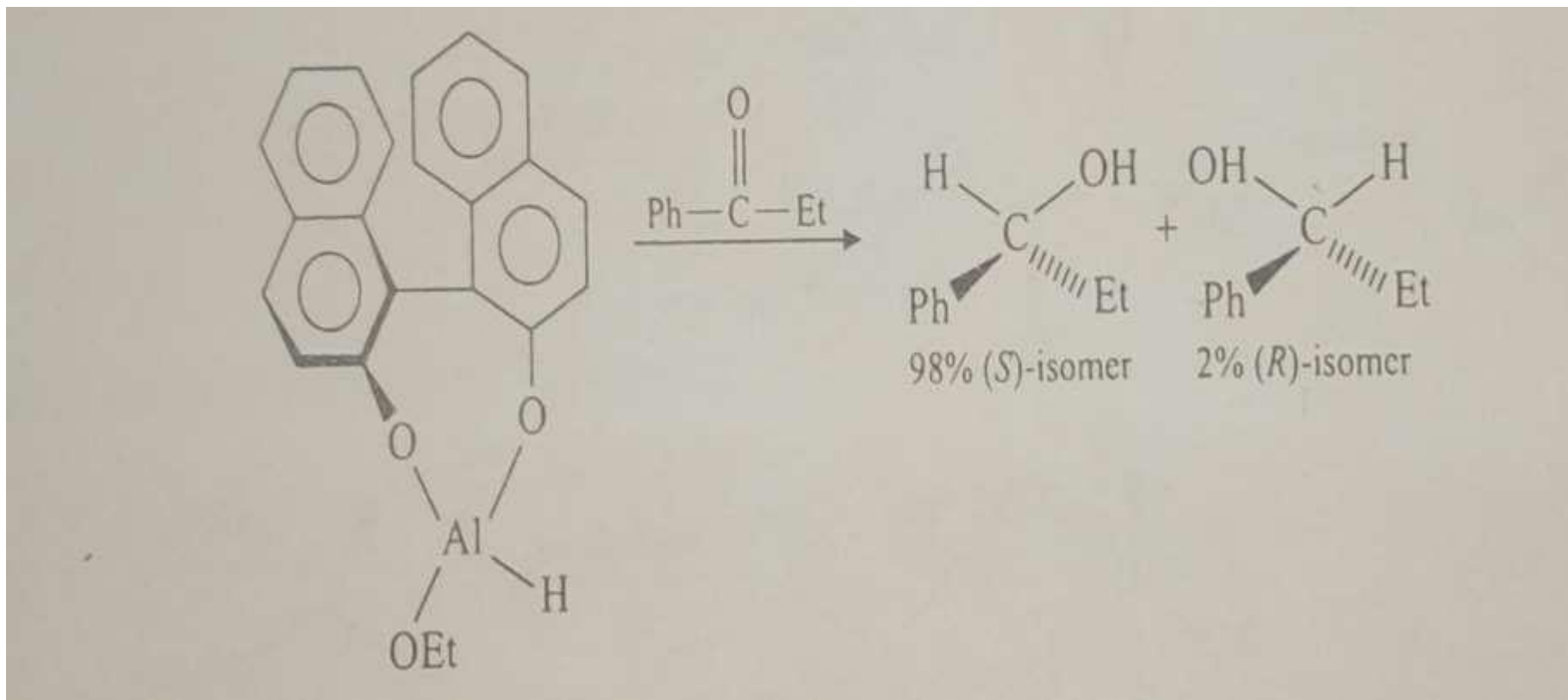
3) Use of chiral reagents (third generation methods)

- In this method an inactive substrate is converted selectively into one of the enantiomers (enantiospecific).
- In this type of synthesis a chiral reagent turns achiral by transforming an achiral substrate to chiral. Thus the reagent is “self-immolative”

eg:

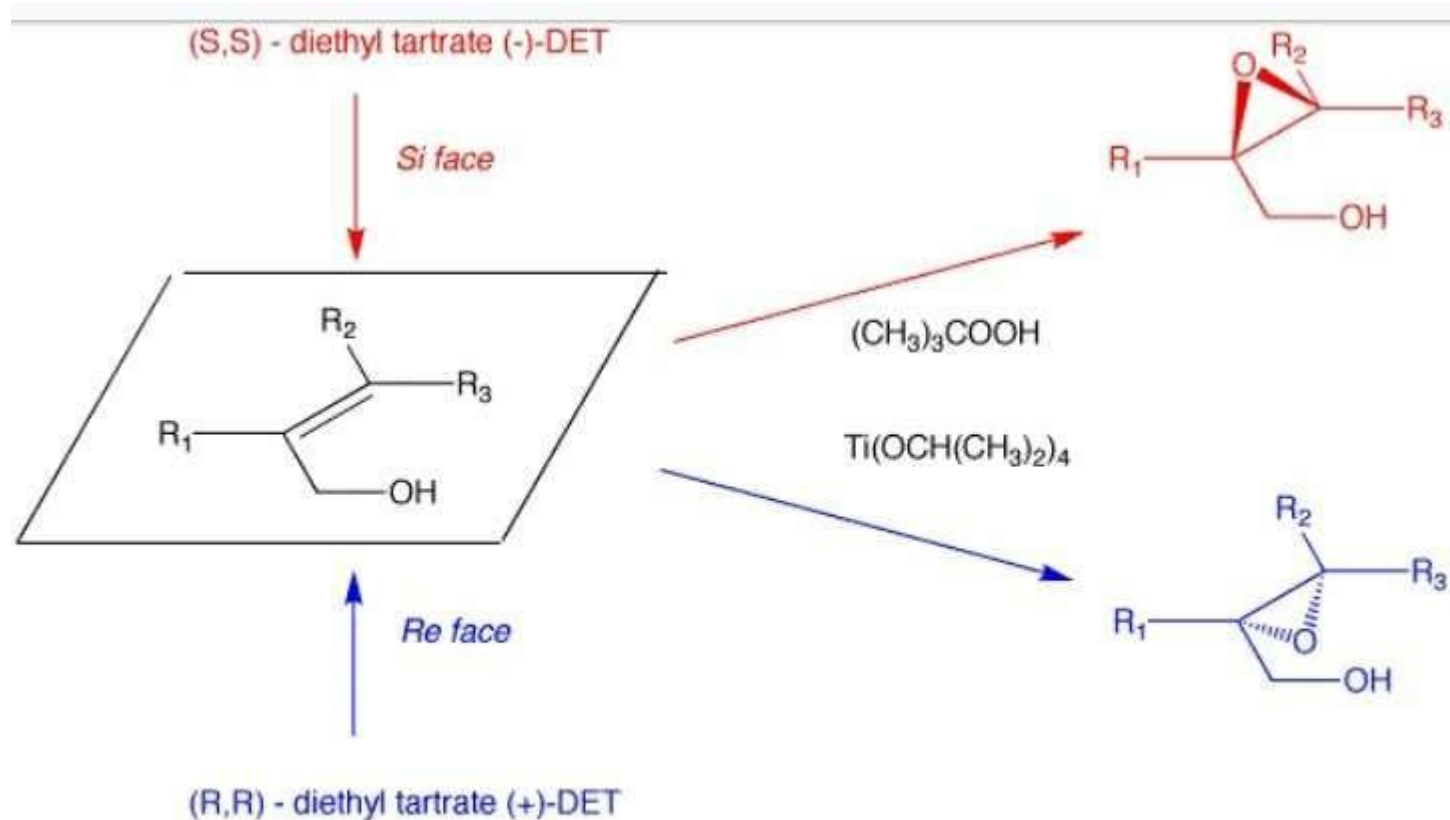


Eg: Reduction of a prochiral carbonyl group enantioselectively by a chiral reducing agent

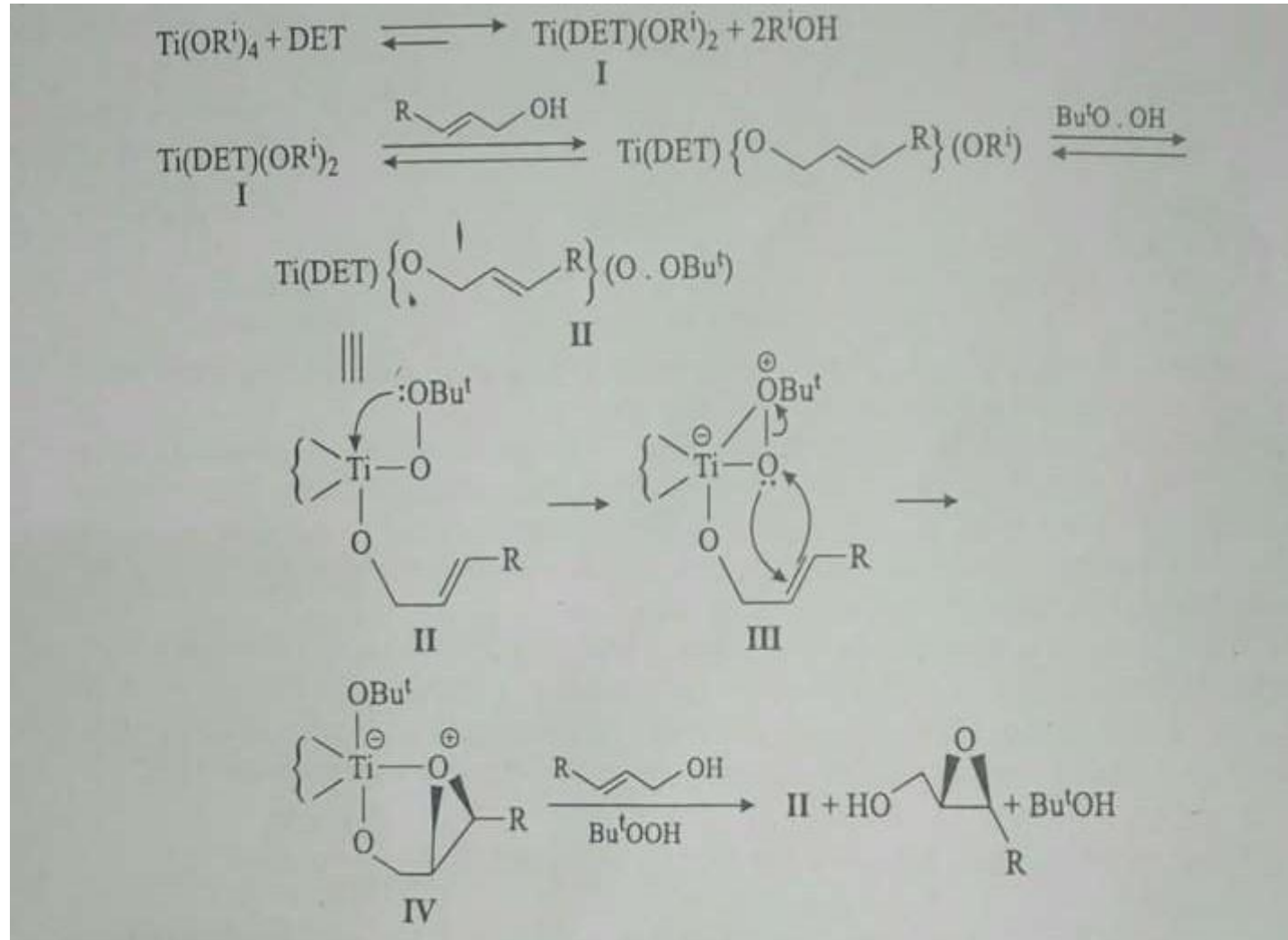


4) Use of chiral catalyst

- Effective optically pure catalysts are much more promising, because reagents are required in stoichiometric amounts, while catalysts are required only in very small amounts.
- **Eg: Sharpless asymmetric epoxidation**- It is an enantioselective reaction that oxidises alkenes to epoxides.

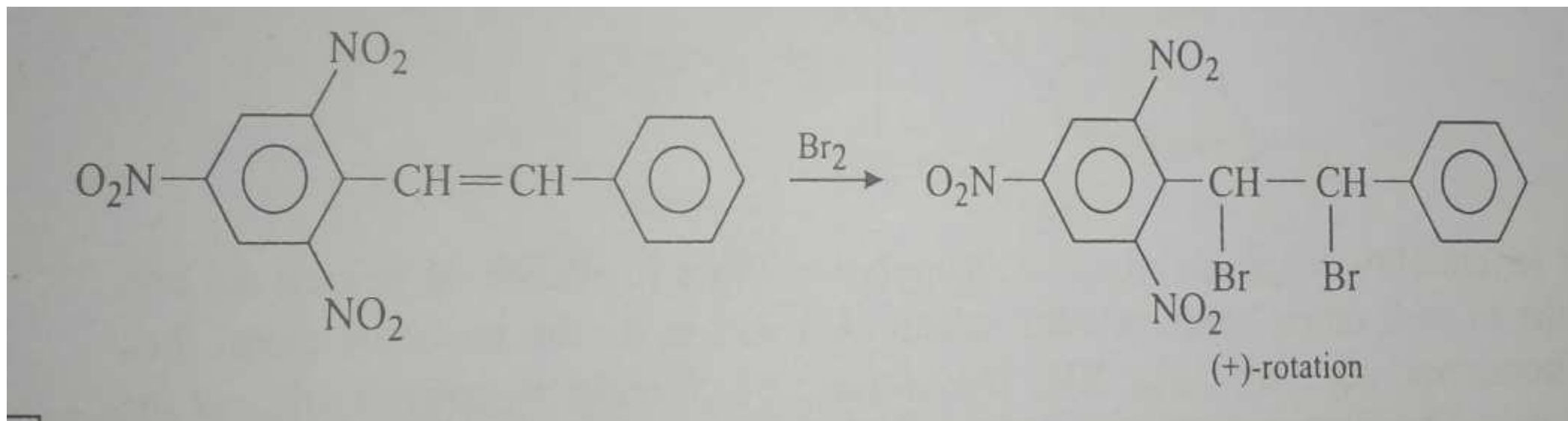


The mechanism of Sharpless asymmetric epoxidation involves following steps .

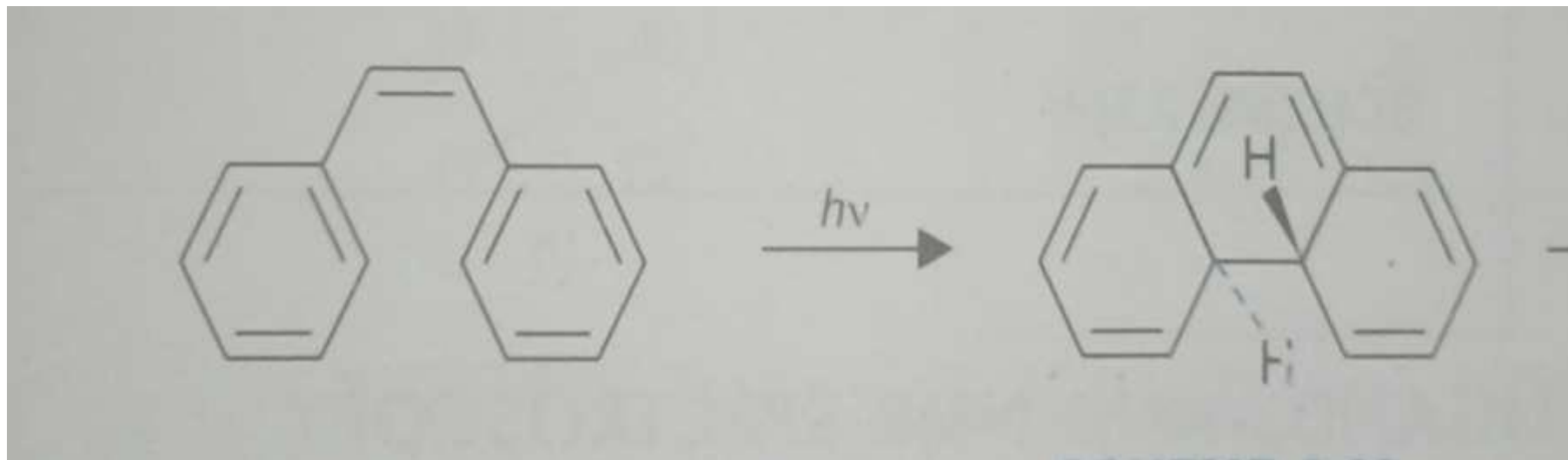


B) ABSOLUTE ASYMMETRIC SYNTHESIS

- It is the synthesis of optically active products from achiral substrate **without the use of optically active reagents** .
- In this type of synthesis a physical presence of chirality is necessary .
- Eg: addition of bromine to 2,4,6-trinitrostilbene give a dextrorotatory product.
- Here we are **using circularly polarized light** for the induction of chirality.



Eg: Light induced cyclisation of 1,2 -diarylethylenes to dihydrophenanthrene derivatives



- The role of circularly polarized light is reminiscent of an optically active compound in conventional resolution.
- It combines with individual enantiomers of diarylethylene, forming a pair of excited states which are diastereomerically related and thus formed and decomposed at different rates.

Advantages and disadvantages of different methods

METHODS	ADVANTAGES	DISADVANTAGES
RESOLUTION	Both enantiomers are available	Maximum 50% yield
CHIRAL POOL	100 % ee is guaranteed	Often only 1 enantiomer available
CHIRAL AUXILIARY	Often excellent ee & can recrystallize to purify to high ee	Extra steps to introduce and remove auxiliary
CHIRAL REAGENT	Often excellent ee & can recrystallize to purify to high ee	Only few reagents are successful and often for few substrates
CHIRAL CATALYST	Economical, only small amounts of recyclable material used	Only few reactions are really successful.

□ REFERENCES

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2. BASIC ORGANIC CHEMISTRY : Ernest L Eliel