Asymmetric Induction (Methods of asymmetric synthesis):

Asymmetric induction (also called enantio-induction) refers to the control of stereoselectivity exerted by an existing chiral centre on the formation of a new chiral centre. It describes the preferential formation in a chemical reaction of one enantiomer or diastereoisomer over the other. Asymmetric induction is a key element in asymmetric synthesis. For example: conversion of enantiomers into diastereomers, since diastereomers have different reactivity, but enantiomers do not. Since diastereomers have different reactivities, there will be preferential formation of one diastereomer. A chiral auxiliary with a high asymmetric induction provides high enantiomeric excesses. The effect of asymmetric induction is to lower the transition state energy for the formation of one enantiomer over the other.

Asymmetric induction was introduced by Hermann Emil Fischer based on his work on carbohydrates. Several types of induction exist:

(i) Internal asymmetric induction makes use of a chiral center bound to the reactive center through a covalent bond and remains so during the reaction. The starting material is often derived from chiral pool synthesis.

(ii) In related asymmetric induction the chiral information is introduced in a separate step and removed again in a separate chemical reaction. Special synths are called chiral auxiliaries.

(iii) In external asymmetric induction chiral information is introduced in the transition state through a catalyst of chiral ligand. This method of asymmetric synthesis is economically most desirable.

Strategies for asymmetric induction can be controlled by: substrate, auxiliary, reagent, catalyst or environment.

(i) Substrate Control Asymmetric Synthesis (1st Generation Asymmetric Synthesis):

A diastereoselective reaction where the formation of a chiral centre is controlled by another chiral centre already present in the substrate is called as 1st generation or substrate controlled asymmetric synthesis. If the substrate is chiral, the reagent does not necessarily have to be chiral for an asymmetric synthesis, too. In this case, the stereoselectivity is controlled by the stereochemistry of the substrate. The substrate is obviously applied in stoichiometric amounts. Therefore, the asymmetric synthesis is a stoichiometric, substrate-controlled method. The chiral substrate of such asymmetric syntheses frequently derives from the large pool of chiral natural products. These starting products are often easily available in an enantiomerically (or diastereomERICally) pure form and are, therefore, cheaper than chemically synthesized enantiomerically (or diastereomerically) pure starting products. Examples of such chiral natural products are carbohydrates, optically active carbon acids, terpenes, and sesquiterpenes. However, for many asymmetric syntheses, no suitable chiral substrate can be found in the chiral pool of natural products. In such a case, the advantages of reagent- or catalyst-controlled asymmetric syntheses are obvious: they are broadly applicable and contain a high flexibility with respect to the range of starting products and products.

(ii) Auxiliary Control Asymmetric Synthesis (2nd Generation Asymmetric Synthesis):

2nd generation or auxiliary-controlled asymmetric synthesis methods is that where a chiral auxiliary is covalently attached to the substrate and, through that, controls the asymmetric induction. This strategy, with intermolecular controlled induction, is basically the same in first and second generation methods. The difference is the attachment and removal of the auxiliary in the latter.
Example: Alkylation reaction with valine derived chiral auxiliary

(i) Attachment of chiral auxiliary

\[
\text{ClCH}_2\text{CO}_2\text{H} + \text{HN-Val} \rightarrow \text{ClCH}_2\text{CO}_2\text{Val}
\]

(ii) Diastereoselective reaction

\[
\text{LiClCO}_2\text{H} + \text{LiClCO}_2\text{Val} \rightarrow \text{ClCH}_2\text{CO}_2\text{Val} + \text{ClCH}_2\text{CO}_2\text{Val}
\]

(iii) Removal of auxiliary

\[
\text{OH} + \text{HN-Val}
\]

or

\[
\text{OH} + \text{HN-Val}
\]

(iii) Reagent Control Asymmetric Synthesis (3rd Generation Asymmetric Synthesis):

In organic synthesis, reagent control is an approach to selectively forming one stereoisomer out of many. The stereoselectivity is determined by the structure and chirality of the reagent used. When chiral allyl metals are used for nucleophilic addition reaction to achiral aldehydes, the chirality of the newly generated alcohol carbon is determined by the chirality of the allymetal reagents. The chirality of the allymetal reagents usually comes from the asymmetric ligands used. The metals in the allymetal reagents include boron, tin, titanium, silicon, etc.
(iv) Catalyst Control Asymmetric Synthesis (4\textsuperscript{th} Generation Asymmetric Synthesis):

An asymmetric synthesis can also be achieved by applying a chiral catalyst. The catalyst can be an enzyme or a synthetic catalyst, usually one such as a chiral transition-metal catalyst. Catalytic modifications of the first, second and third generation methods tend to be considered together with this new fourth generation. One general procedure involves a reaction of a chiral substrate with a chiral reagent and is especially useful in reactions where two new stereogenic units are formed stereo selectively in one step. Examples:

(a) 

(b) 

Enantiomeric and Diastereomeric Excess:

Enantiomeric excess (ee) is a measurement of purity used for chiral substances. It is 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. Mathematically, it is defined as the absolute difference between the mole fraction of each enantiomer:

\[ ee = F_R + F_S \]

Where, \( F_R \) is mole fraction of the major enantiomer and \( F_S \) is mole fraction of the major enantiomer. Summation of mole fractions of the both enantiomers is always equal to one. i.e. \( F_R + F_S = 1 \). The value of \( F_R \) and \( F_S \) can be calculated, as:

\[ F_R = \frac{R}{R+S} \quad \text{and} \quad F_S = \frac{S}{R+S} \]

Where, \( R \) and \( S \) are each enantiomer in the mixture. Therefore,

\[ ee = \frac{R}{R+S} - \frac{S}{R+S} \]

or

\[ ee = \frac{R-S}{R+S} \]

In practice, it is most often expressed as a percent enantiomeric excess. Therefore,

\[ ee = \frac{R-S}{R+S} \times 100 \]

or \[ \% ee = (F_R - F_S) \times 100 \]

Enantiomeric excess reflects the degree to which a sample contains one enantiomer in greater amounts than the other. A racemic mixture has an ee of 0%, while a single completely pure enantiomer has an ee of 100%. A sample with 70% of \( R \) isomer and 30% of \( S \) isomer will have an ee of 40%. This can also be thought of as a mixture of 40% pure \( R \) with 60% of a racemic mixture (which contributes 30% \( R \) and 30% \( S \) to the overall composition).

For mixtures of diastereomers, there are analogous definitions and uses for diastereomeric excess and percent diastereomeric excess.

Practice Problem:

Q 1. A sample of 2-bromobutane has an enantiomeric excess (e.e.) of 75% favouring the \( d \)-enantiomer. What is the percentage of each enantiomer?

Ans: \% \( d \) = ? and \% \( l \) = ?

We have equation:
\[
\% \text{ee} = \% d - \% l \\
\% d - \% l = 75\% \quad \text{-------------(1)} \\
\% d + \% l = 100\% \\
\text{or} \quad \% d = 100\% - \% l \quad \text{-------------(2)}
\]

From equation (1) and (2) we get,

\[(100\% - \% l) - \% l = 75\%\]

Therefore,

\[\% l = 12.5\%\]

To find the value of \% \text{d} put the value of \% \text{l} in equation (2), as:

\[\% d = 100\% - 12.5\% = 87.5\%\]

We can check the answer by plugging the values of \% \text{d} and \% \text{l} in the following equation, as:

\[\% \text{ee} = \% d - \% l = 87.5\% - 12.5\% = 75\%\]

So a mixture with 75\% \text{ee} is actually composed of 87.5\% of the major enantiomer and 12.5\% of the minor enantiomer. As we said above, another way of looking at it is that it’s 75\% composed of the major enantiomer, and 25\% of a racemic mixture.

Q2. What does enantiomeric excess tell?

Ans:

Enantiomeric excess (ee) is a measurement of purity used for chiral substances. It reflects the degree to which a sample contains one enantiomer in greater amounts than the other.

Q3. How do you calculate enantiomeric excess?

Ans:

To calculate the enantiomeric excess, you divide the observed specific rotation by the maximum specific rotation of the excess enantiomer. We can calculate the percent of each enantiomer as described in this Socratic question. So, the mixture contains 67 \% (\text{-})-X and 33 \% (\text{+})-X.

Discrimination of Enantiomers or Enantio Discrimination:

Discrimination between enantiomers is an important subject in chemistry, medicinal chemistry and biological chemistry because they exhibit markedly different activity, bioactivity and toxicity. Chiral molecules may create a totally different effect on many processes such as biological processes in nature and life. In general, just one out of a pair of enantiomers produces the characteristic effect and the other either has no effect or has a totally different (and sometimes toxic) effect due to the pair interaction energy of the two. Therefore the different effect of enantiomers on human beings, enantio discrimination (chiral recognition) is becoming a very active area in food, environment, clinic, medical, and pharmaceutical industry.

Chiral recognition is a chemical interaction, frequently occurring in living systems, by which a given chiral molecule (receptor/host) recognizes a particular stereoisomer (substrate/guest).

Enantio discrimination is the ability to discriminate between enantiomers by which a given chiral molecule (receptor/host) recognizes a particular stereoisomer (substrate/guest). Various techniques such as: polarimeter, enzymes (found in living systems), NMR, cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS), chromatography, liquid chromatography, capillary electrophoresis, etc., have been applied to discriminate and separate the racemic compounds.

Examples:

1. (1R, 2R)-2-amino-1, 2-diphenyl ethanol had been developed to discriminate tryptophan enantiomers.
2. Enzymes are chiral capable of distinguishing between enantiomers. Only one enantiomer of a pair fits properly into the chiral active site of an enzyme.

For example: epinephrine hormone secreted by the adrenal medulla. Synthetic epinephrine is given to a patient. The (-) form has the same stimulating effect as the natural hormone. The (+) form lacks this effect and is mildly toxic.

Resolution or Chiral or Optical Resolution of Racemic Mixture:

Structural isomers and diastereomers have different physical properties such as boiling point, melting point, density, refractive index, solubility, etc. Therefore, they can be separated by common separation techniques like distillation, re-crystallization, chromatography, etc.
Since enantiomers have identical physical properties, they cannot be separated by conventional methods. They can be separated by resolution. **Resolution** is the separation process of enantiomers from an equimolar mixture (called racemate or racemic mixture or racemic modification) by physical or chemical methods. This method of the resolution of racemates can also be applied to non-equimolar mixtures of enantiomers that are usually obtained by asymmetric synthesis, since asymmetric synthesis can never have a stereoselectivity of 100%.

**Resolution** has been done if the crystalline forms of two enantiomers are visibly different from each other. It is an important tool in the production of optically active drugs. Louis Pasteur was the first to conduct optical resolution when he discovered the concept of optical activity by the manual separation of left-handed and right-handed sodium ammonium tartrate crystals in 1849.

**Resolution** is necessary to prepare optically pure compounds because different enantiomers in any racemic mixture have different activity. For example: in the racemic mixture of cetirizine, the levocetirizine has been found to be less sedating than dextrocetirizine.

![Cetirizine Molecules](image)

Similarly, levodopa (l-dopa), an enantiomer of dopa, is used in the treatment of Parkinson’s disease. Its d-form causes serious side effects, such as granulocytopenia.

![Levodopa Molecule](image)

In another example, Mefloquine (Antimalarial) marketed in the form of its racemic mixture where the erythro form is more active than threo form.

**Methods of Resolution of Racemates:**

**Following methods can be used for resolution of racemic mixtures:**

- Mechanical separation or or spontaneous resolution
- Preferential crystallization
- Biochemical separation
- By diastereomerism (Pasteur-1858)
- Precipitation
- Chromatographic separation
- Kinetic method

**Kinetic Resolution of Racemates:**

**Kinetic resolution** (also known as kinetically controlled asymmetric transformation) is based on the fact that one of the enantiomer of racemic mixture reacts faster than other with optically active compound. If the difference in kinetics of reaction between enantiomers is large enough, then enantiomers can be separated by stereoselectively converting only one of the enantiomers. Since this is based on different reaction rates, the separation technique is called kinetic resolution.
Examples:

(i) Kinetic resolution of mandelic acid using menthol. Menthol reacts faster with (+) mandelic acid than with (-) mandelic acid.

(ii) Kinetic resolution of racemates by stereoselective enzymic conversion of one enantiomer.

(iii) Kinetic resolution of allylic alcohols with one enantiomer of a chiral epoxidation agent.

(i) Kinetic resolution of epoxides with primary amine.