ASYMMETRIC SYNTHESIS

Abstarct

The goal of asymmetric synthesis is the chemical conversion of a molecule into a specific stereoisomer (enantiomer). In spite of the fact that asymmetric chemistry can be conducted stoichiometrically, it is most commonly carried out in a catalytic mode, mainly by applying organometallic catalysts or an enzyme (biocatalysis).

Keywords: asymmetric synthesis, asymmetric catalysis, chiral pools, chirality, importance of, enantiomeric excess.

Author

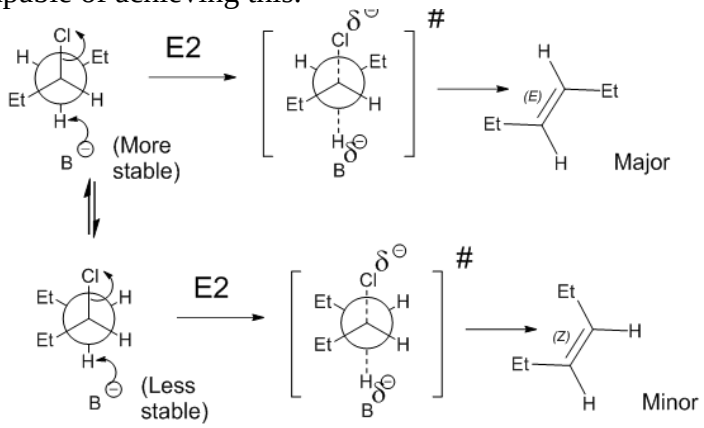
Subhabrata Mabhai
Assistant Professor
Department of Chemistry
Mahishadal Raj College, East Midnapore
Mahishadal, West Bengal, India

I. INTRODUCTION

During asymmetric synthesis, an achiral unit in a substrate is converted into a chiral unit in such a way that different amounts of stereoisomers (enantiomers or diastereomers) are produced.

When an achiral compound is converted into a compound with an asymmetric carbon (CHIRAL) using traditional laboratory techniques, the result is a racemic mixture. One optically active isomer will arise preferentially over the other if such a synthesis is carried out under chiral influence.

1. **Stereoselective reaction:** A reaction that produces one stereoisomer of a product preferentially over another. Several stereoisomers can form, but only one predominates in this type of reaction. A mechanism that allows for multiple TS conformations or geometries is capable of achieving this.



2. **Stereospecific reaction** Reactions in which stereochemically different starting compounds produce stereochemically different products. These happen only when the mechanistic path requires efficient symmetry to allow orbital overlap. e.g., S_N2 reactions.

If two stereoisomeric reactants S_1 and S_2, react with reagent R separately to yield products P_1 and P_2, respectively, such that P_1 and P_2 are stereoisomeric to each other, then the reactions are termed stereospecific.

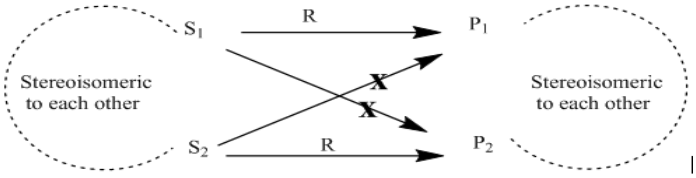
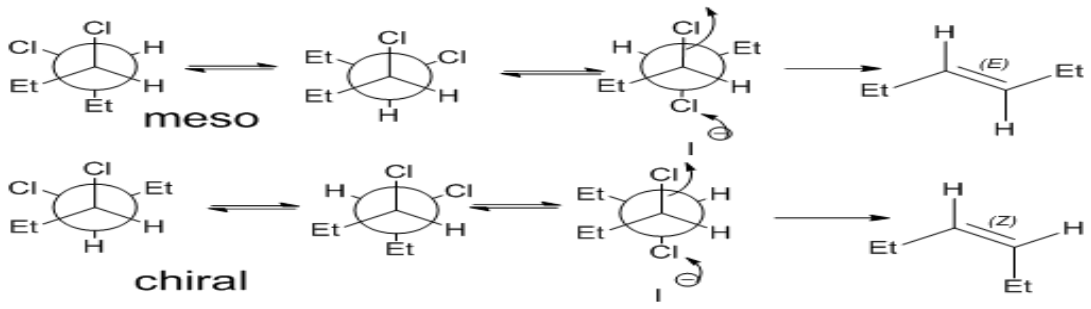


Illustration of the stereospecific reaction



The E2 elimination shown above occurs through the antiperiplanar arrangement, which leads to a specific diastereomeric product. (E)-alkene is formed from the meso diastereomer, whereas (Z) alkene is formed from the chiral diastereomer

3. **Asymmetric synthesis:** Asymmetric induction or absolute asymmetric synthesis involves converting achiral or racemic precursors into optically active products without optically active catalysts or auxiliary materials. Asymmetric synthesis involves highly enantioselective reactions (high ee) or enantiospecific (100% ee).

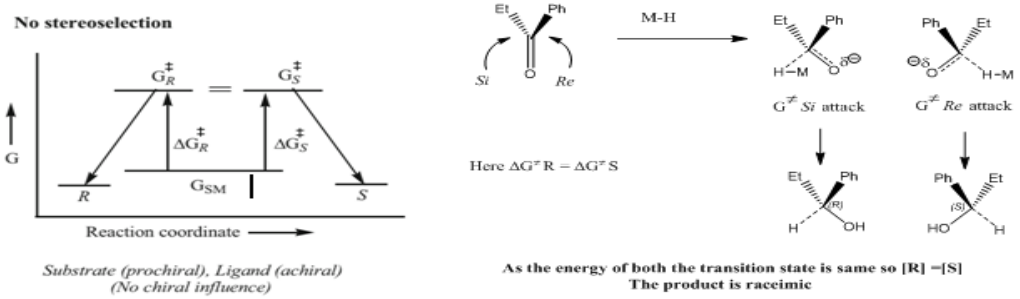
   Enantiopure molecules were previously accessed by resolution before efficient asymmetric synthesis methods were developed.

4. **Facial selectivity:** The two prochiral faces are non-equivalent based on the steric ground. The root cause of selectivity in a chemical reaction is, beyond any doubt, the difference in steric hindrance felt by the reagent.

   But for cyclic alkenone role of other factors like stereo electronic, electrostatic, and directing effect of some other groups is also essential.

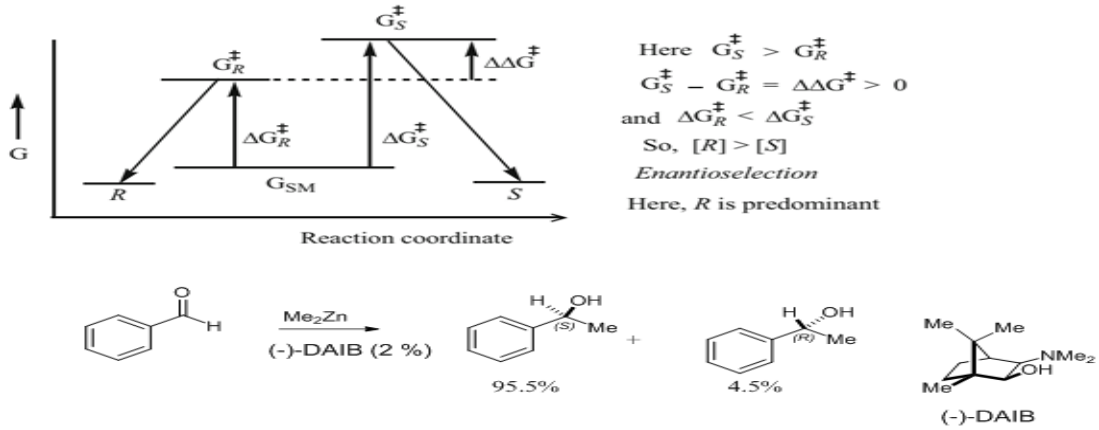
II. ABSENCE OF STEREO SELECTION.

A prochiral center, when it undergoes a reaction devoid of any chiral influence, produces a racemic product since the transition state for this type of reaction is equal energy and enantiomeric in nature.



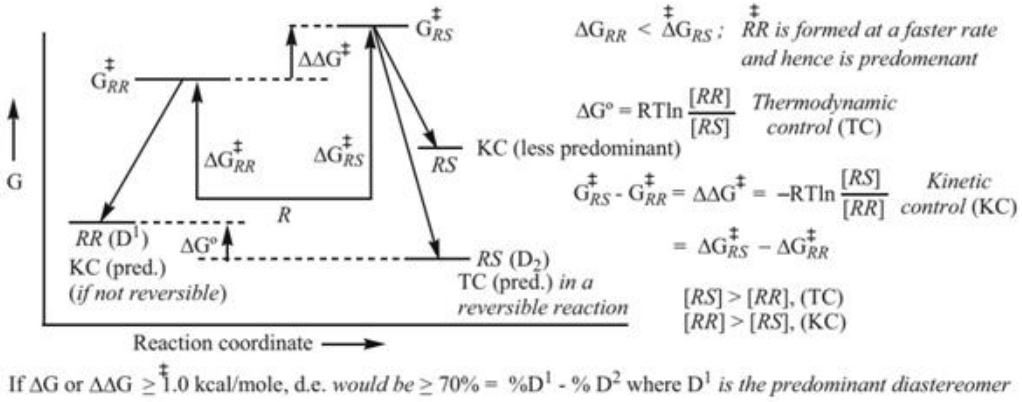
1. Presence of stereo selection

- **Enantioselection:** The enantioselective reaction produces enantiomeric pair of a chiral product in unequal amounts. In an auxiliary-based reaction, if one step is diastereoselective and after removal of the auxiliary, if one enantiomer is produced in excess over the other, then the reaction is termed an enantioselective synthesis.

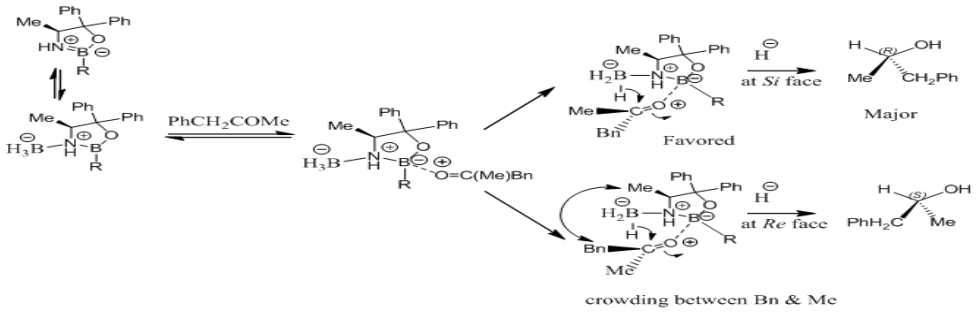


Here the ligand is chiral (responsible or showing chiral influence) and the molecule posses a prochiral centre.

- **Diasterteoselection:** Diastereoselection results from the participation of diastereomeric transition states (with different free energies); causing irreversible diastereomer formation through less activation energy and thus more quickly in a kinetically controlled way.



In the presence of a chiral centre in a diastereoselective reaction,among the two possible diastereomeric TS's of different energy , one isomer with the new stereogenic centre is produced in a larger amount.



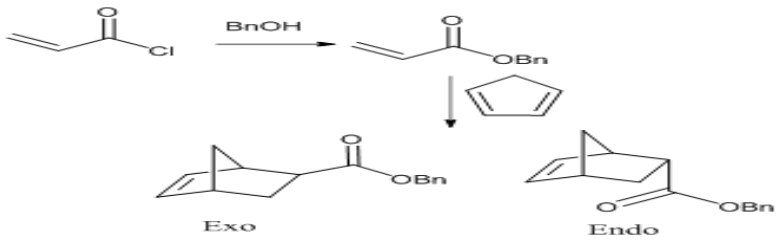
A fine example is the synthesis of glucononitrile and mannononitrile from (+)-arabinose. Since the two products are diastereoisomeric, thus the transition states leading to them would also be expected to be diastereoisomeric. This makes them different in their respective free energies. Since the starting state [(+)-arabinose] is the same for the two

reactions, the activation energies are expected to differ, and the rate at which the two products are formed will also be different. In fact, before the actual findings, it was believed that the mannonic acid nitrile predominated to such an extent that it was believed to be the product of this reaction.

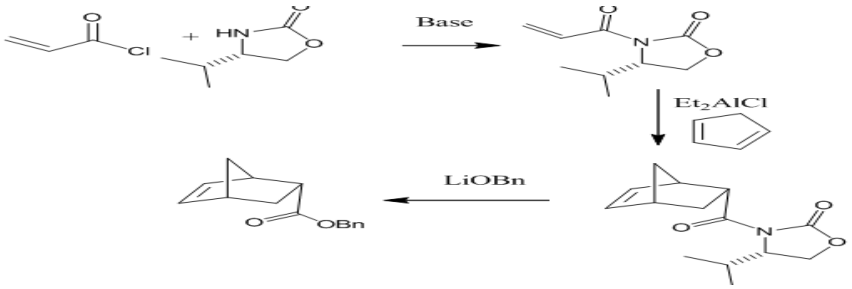
- **Chiral auxiliary** It refers to a stereogenic group or unit that is temporarily incorporated into an achiral organic compound to influence its stereochemical outcome. The chirality present in the substrate allows enantioselective synthesis via diastereoselective reaction. In the absence of a stereogenic center in a molecule, a chiral auxiliary can be used that can be eliminated in the later case.

For a successful chiral auxiliary-based synthesis, the following criteria should be fulfilled:

- The auxiliary should be readily available (from nature or by synthesis) in optically pure form
- preferably at a low cost.
- The auxiliary must have a functional group for easy linking with the substrate
- The auxiliary should induce a high degree of stereo selection
- It should be easily removable from the diastereomeric product without causing racemization of the newly created stereocenter
- It is better if the auxiliary is recoverable and reusable, especially when costly.



Chiral auxiliary controlled Diels aider reaction gives a single product Endo.



- **Chiral reagent:** Stereochemistry initially resides on the reagent.

- **Advantages**

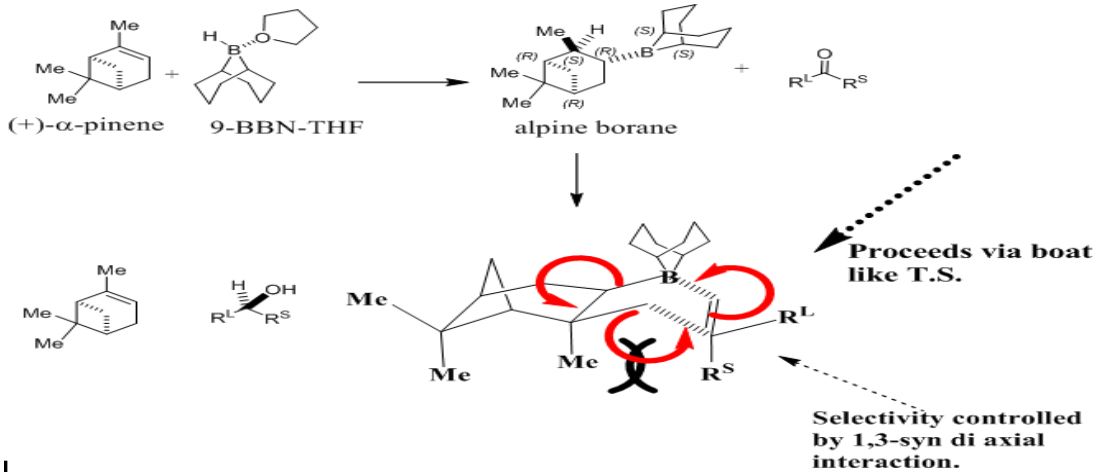
No coupling/cleavage steps are required.
Often override substrate control.
It can be far milder than chiral auxiliaries.

- **Disadvantages**

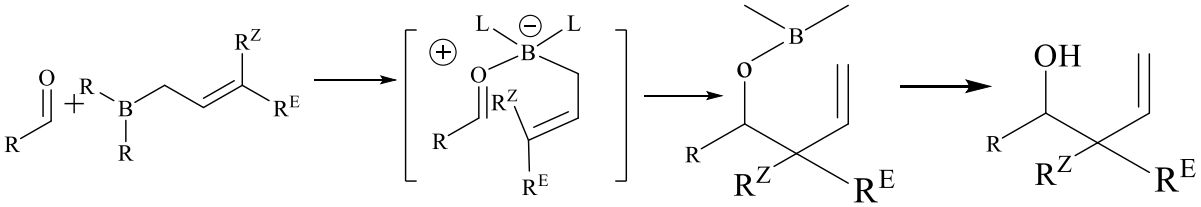
Need a stoichiometric quantity (not atom economic)
Frequently expensive

Problematic work-ups.

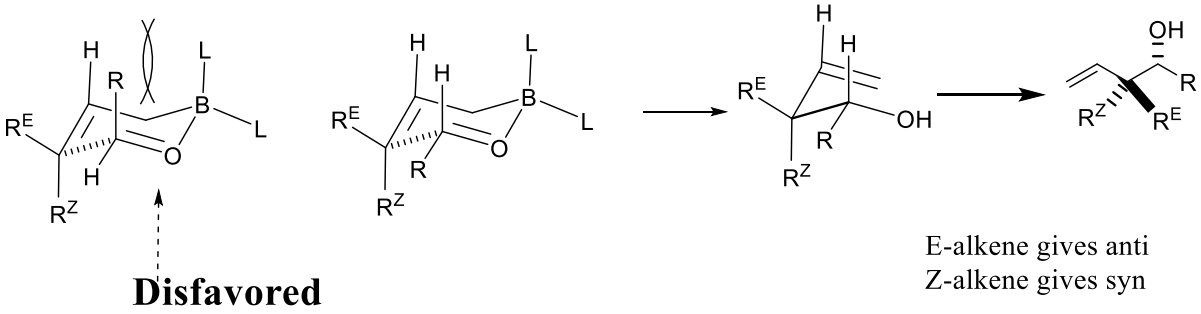
Since they work on the prochiral substrate or without regard to the chirality of the substrate, chiral reagents are unquestionably better than chiral auxiliaries. To reduce carbonyl, a large no.of chiral reagents have been developed. We usually add a chiral element to a standard reagent to make them chiral.

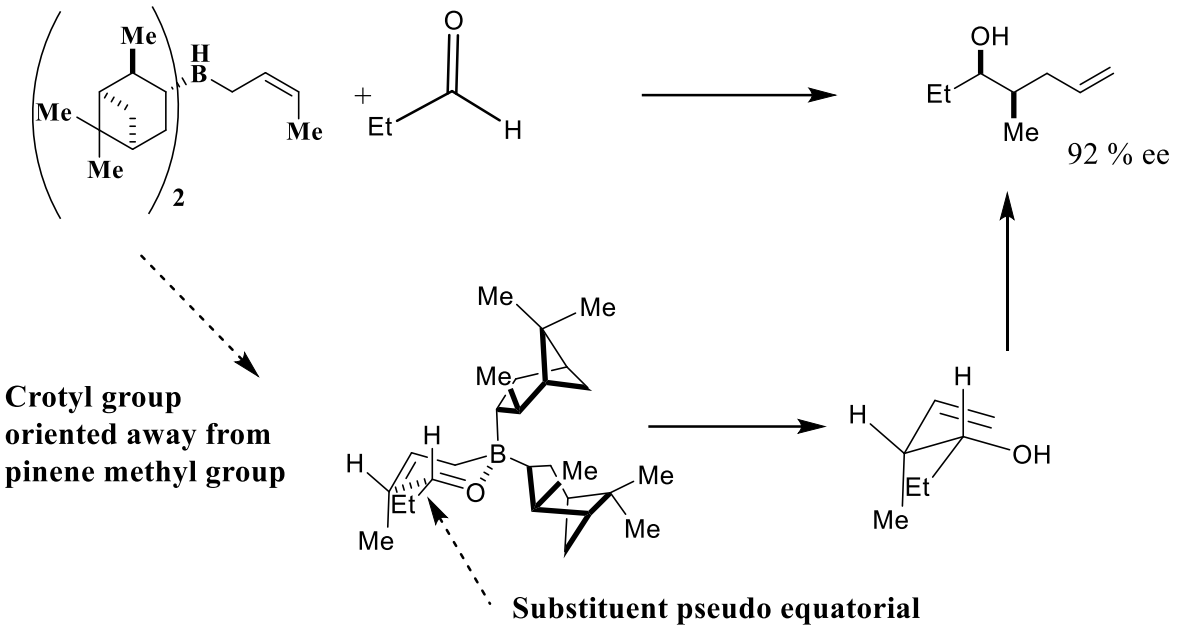


- **Chiral allyl boron reagent**

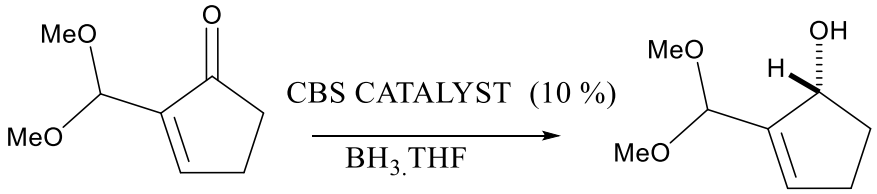


The reaction proceeds via a 6-membered cyclic transition step. Alkene geometry controls the relative stereochemistry.

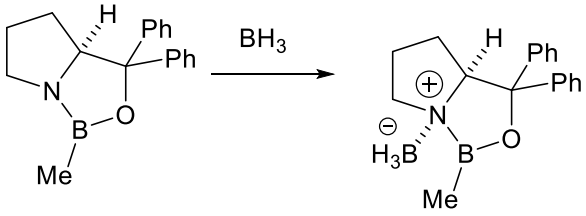




- **Chiral catalysis :** In a chiral environment, if a reagent speeds up the rate of a reaction (without being destroyed), thus generating millions of new chiral molecules, then it is called chiral auxiliaries. in the following example a chiral reagent derived from a proline derivative brings the ketone and borane close together in a chiral environment

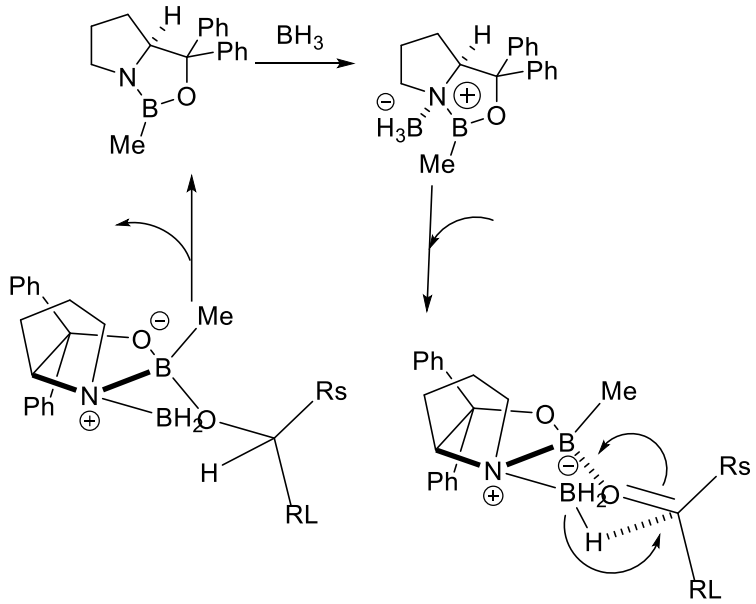


.

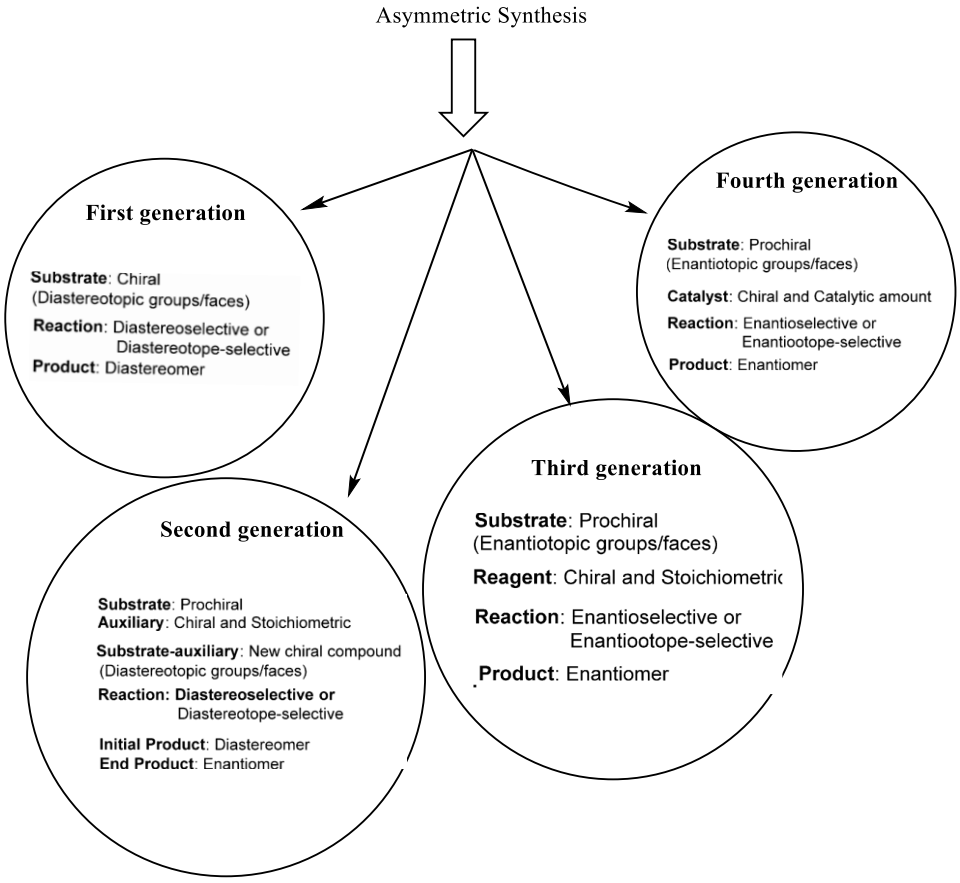


CBS catalyst
Proline derivative

Active Catalyst



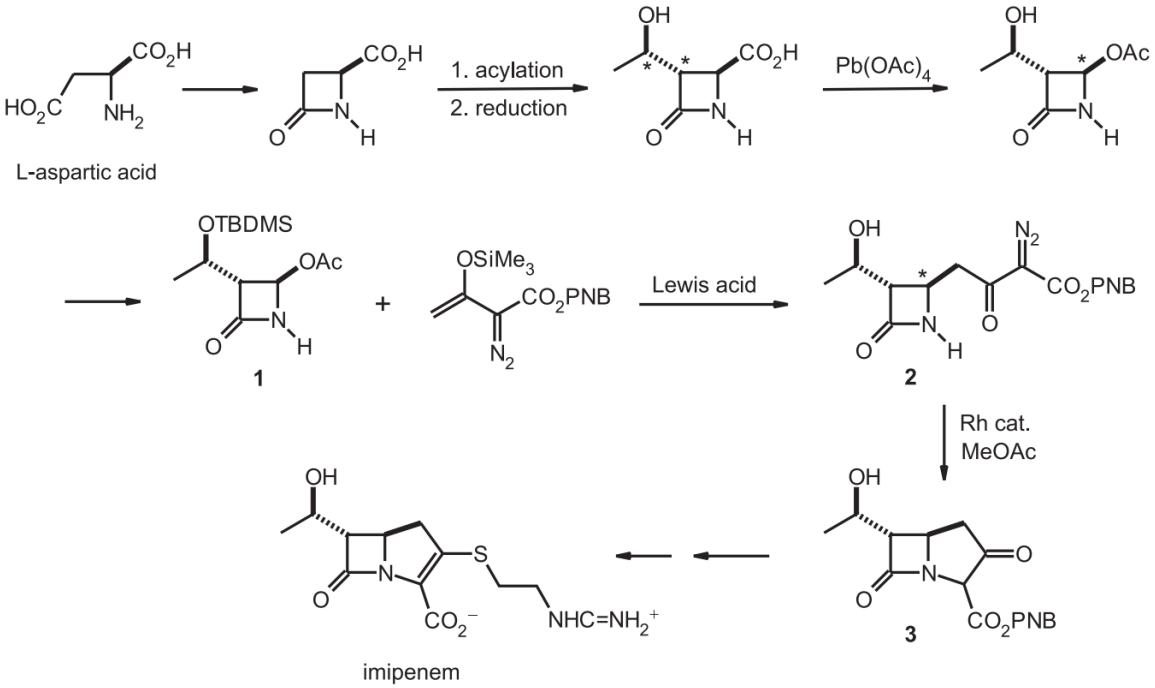
2. **Designing asymmetric synthesis :** There are four approaches by which we can design asymmetric synthesis.



Strategies to adopt for asymmetric synthesis

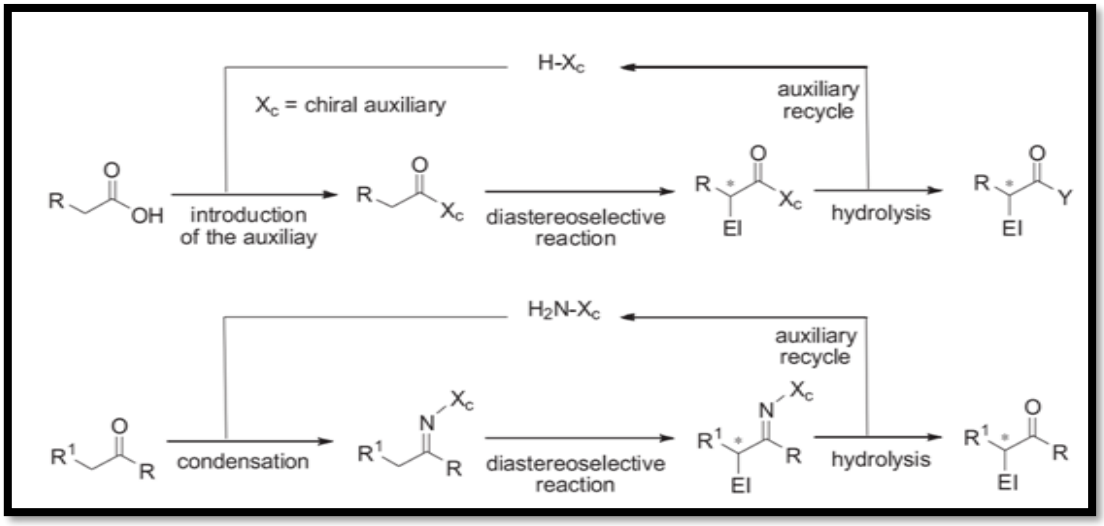
- Chiral pool or Chiron approach
- Chiral auxiliary approach.

1. **Use of chiral substrate (first generation method):** Asymmetrical synthesis of the first generation occurs by controlling the chiral center formation by another chiral center present in the substrate**.** Asymmetric synthesis does not necessarily require chiral reagents if the substrate is chiral. The stereochemistry of the substrate controls stereoselectivity in this case. Substrates are used in stoichiometric amounts. Therefore, the asymmetric synthesis is a stoichiometric, substrate-controlled method. In such asymmetric synthesis, chiral natural products are frequently used as chiral substrates. Because they are readily available in enantiomerically (or diastereomerically) pure form, these starting products are often cheaper than those synthesized chemically.Such chiral natural products include carbohydrates, optically active carbon acids, terpenes, and sesquiterpenes. This method is also known as the "CHIRAL POOL" STRATEGY.

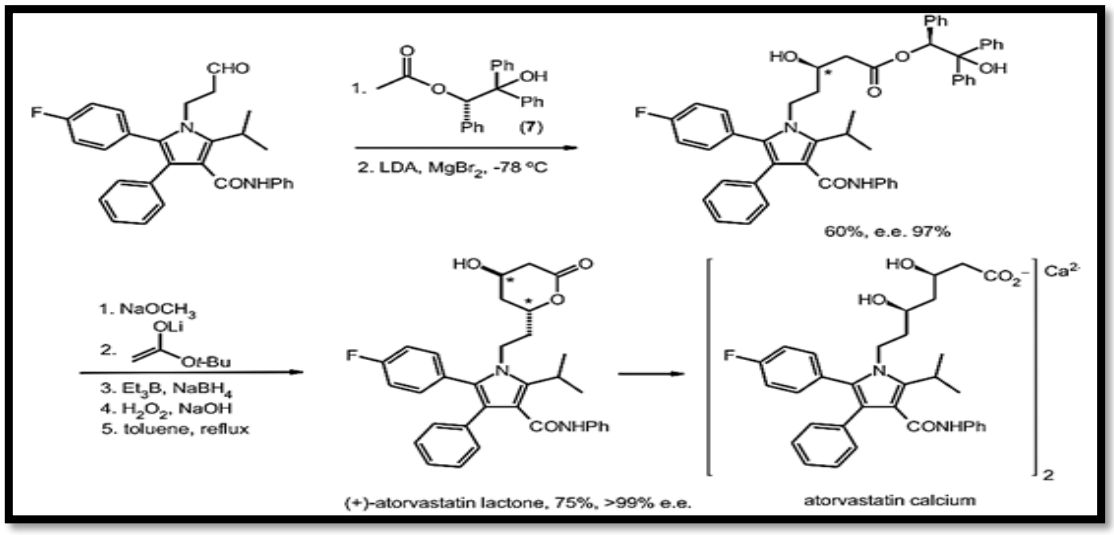


Chiral pool synthesis of imipenem

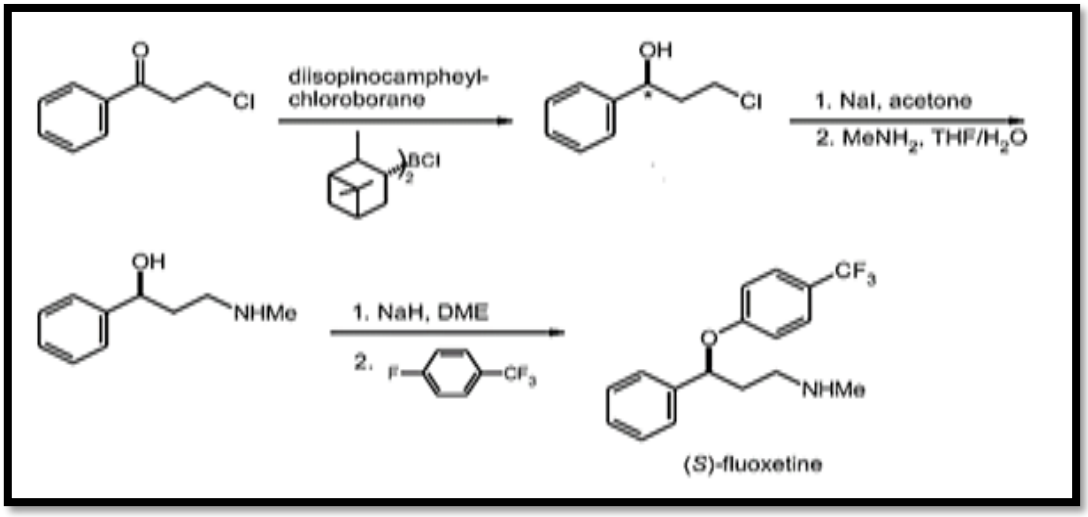
2. **Auxiliary Control Asymmetric Synthesis (2nd Generation Asymmetric Synthesis):** Here. a covalently attached chiral auxiliary regulates the asymmetric induction. This intermolecular controlled induction strategy is used in first and second-generation methods. The difference is the attachment and removal of the auxiliary in the latter Chiral auxiliary mediated diastereoselective aldol reaction: synthesis of (+)-atorvastatin lactone



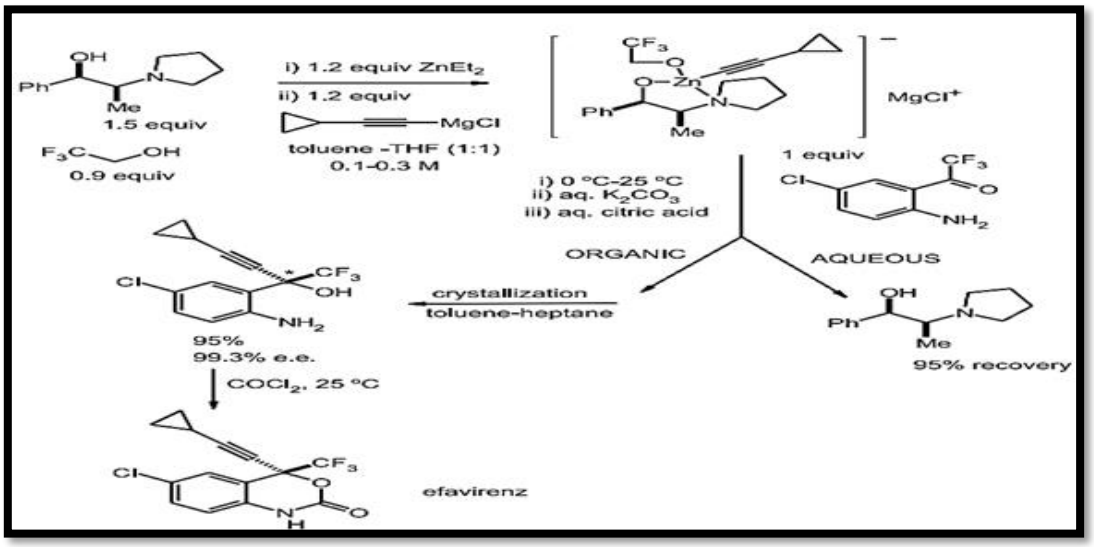
Diastereoselective synthesis with chiral auxiliaries



3. **Asymmetric Synthesis Regulated by Reagent (3rd Generation Asymmetric Synthesis):** The method of synthesizing molecules employing an enantiomerically pure chiral reagent is known as the third-generation asymmetric synthesis. The substrate, in this case, is prochiral. Here, the asymmetric induction is regulated by the reagent's chirality.



Asymmetric reduction with chiral reagent: synthesis of (*S*)-fluoxetine



Chiral organozinc reagent: efavirenz synthesis.

4. **Catalyst Regulated Asymmetric Synthesis (Asymmetric Synthesis of 4th Generation):** 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.