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A REVIEW ON RECENT ADVANCES IN ASYMMETRIC SYNTHESIS AND ITS APPLICATIONS.

[1]Archana Chaskar*, [2]Prof. Ramdas Darade,

1. Department of pharmaceutical chemistryLoknete Shri Dada Patil pharate College of pharmacy,MandavganPharata Tal. Shirur, Dist. Pune (412211).

2. Department.of pharmaceutical chemistryS.N.D College of pharmacy Yeola Dist. Nashik

***Guide Name:**

1. Prof.S.A.Waghmare.CEO,Loknete Shri Dada Patil pharate College of pharmacy,MandavganPharata Tal. Shirur, Dist. Pune (412211).

2.Dr.H.V. Kambale.Principal,Loknete Shri Dada Patil pharate College of pharmacy, MandavganPharata Tal. Shirur, Dist. Pune (412211).

ABSTRACT:

The constantly growing demand for enantiopure substances from different disciplines, especially from the pharmaceutical industry, requests development of new and highly efficient and also environmentally friendly methods for the production of single enantiomers of the compounds required.Asymmetric reactions have experienced a remarkable progress over the past decades. Modern organic synthesis focused on the synthesis of enantiomerically pure molecules by the use of chiral substrates/auxiliaries and enantioselective organocatalysis and reagents. Asymmetric synthesis provides a major synthetic challenge in biological and medicinal chemistry, due to the importance of chiral containing compounds tremendous progress has been made for the formation of new bonds in a stereo and enantio controlled manner. This review details the need, methods of asymmetric synthesis.This review summarizes application of reaction in synthesis of natural product and also focuses on recent advances in asymmetric synthesis.

KEY WORDS:

Asymmetric Synthesis,Advances in Asymmetric Synthesis and Its Applications,Recent Advances.

INTRODUCTION:

The role of chirality in drug development is on the rise in the past forty years, ever since the thalidomide case has triggered interest in the interactions of individualstereoisomers with bioreceptors. The demand forready access to stereoisomers (both diastereoisomersand enantiomers) of drug molecules has stimulated in turn basic research in the field of stereoselective synthesis (either diastereoselective or enantioselective). As a result of developments in the synthesis of pure enantiomers, as well as the recognition of differences in diastereoselective interactions of enantiomers with chiral receptors and due to strict procedures for drug registration, a large and increasing proportion of new drugs are now made of enantiopure ingredients. Indeed, currently more than 50% of commercial drugs have at least one stereogeniccenter and among the top ten best selling drugs nine are composed of chiral molecules, among them five are single enantiomers and only one is achiral.[1]

ASYMMETRIC SYNTHESIS:

The basic principle of asymmetric synthesis is using enantiopure reactant or reagent or catalyst or chiral auxiliary, in such a manner that unequal amounts of stereoisomers are produced. Asymmetric synthesis creates a new chiral centre. If this synthesis is done at the expense of old chiral centre, then it is called "*Self-immolative asymmetricsynthesis*".

NEED FOR ASYMMETRIC SYNTHESIS:

In all living organisms the chemical reactions are catalyzed by the bio-catalysts. All cellular reactions are mediated and catalyzed by enzymes. Enzyme catalysed reactions without exception produces only one of the 2n stereoisomer. Every enzyme has an active site into which the substrate has to enter, bind and get transformed. The active site of an enzyme is a cavity having amino acid functional groups oriented into it. The active site has ability to discriminate the two faces of a prochiral centre. Thus an enzyme can discriminate the two enantiomers of a compound.[2]

METHODS OF ASYMMETRIC SYNTHESIS:

Asymmetric Synthesis broadly covers methods to prepare enantiopureproducts. There are four approaches for synthesisof enantiomer of the target molecule.

(a) Chiral pool synthesis
(b) Using chiral auxilliaries
(c) Asymmetric catalysis
(d) Resolution of racemic mixture.

(a)Chiral Pool Synthesis–

It is the easiest approach of all where an enantiopure starting material is manipulated through a synthetic scheme designed to convert it into an enantiopure product. An example is the synthesis of HIV protease inhibitor Ritonavir developed by the Abbott group where scientists used readily available (S)-phenylalanine as starting material. [3] The chiral pool approach to synthesis ofoptically active targets can be extremely attractive if nature happens to provide an abundant supply of a starting material appropriate for the synthetic target. Accordingly, considerable effort and creativity has been directed toward using inexpensive chiral pool elements in target-oriented synthesis. In the best cases, some of the most practical and brilliant syntheses ever devised have used this approach. The Stork syntheses of prostaglandin A2 and F2 are classic examples [4]

(b)Chiral Auxilliaries–

This is an approach which involves use of a chiral auxiliary, which forms an adduct to the starting material and physically blocks one of the possible trajectories favouring the synthesis of one of the isomer. The chiral auxiliary is then removed in later steps. Oxazolidinones were usedas chiral auxiliaries in chiral allylation. The approach has been applied in diastereoselective alkylations, aldol additions, α-aminations, Michael additions, and Diels–Alder cycloadditions, among others to generate a number of synthetically useful enantiopure intermediates of industrial importance where chiral oxazolidinones were used as chiral auxiliaries.

(c)Enantioselective catalysts and reagents-

The third approach is using enantioselective catalysts and reagents to induce chirality in achiral starting materials. An example is thesynthesis of Cetrizine hydrochloride where the Corey-Bakshi-Shibatareduction conditions were employed. And the reaction has since been exploited by organic chemists in anumber of natural product syntheses lactones, terpenoids, alkaloids,steroids, and biotins, and has been utilized on large scale in industry.The methodology used by Knowles while working for the MonsantoCompany in an enantioselective hydrogenation step in the industrialproduction of L-DOPA also works on the principle of enantioselectivecatalysis.

(d) Chiral Resolution –

Itis the simplest method among all other approaches of asymmetric synthesis, without requiring any advanced catalyst or reagent systems and involves separation of enantiomers from the racemic mixture. However this method has the disadvantage that the maximum yield of the desired enantiomer is only 50%.The various methods include: Resolution by crystallization, using chiral resolving agent like tartaric acid and brucine to form diastereomers where one of those is favored thus allowing separation. Another method is by using chiral stationary phases to separate enantiomers by chromatography. This strategy is very commonly employed in small scale synthesis but others are important for large scale production of medicinal. [3]

APPLICATIONS OF ASYMMETRIC REACTIONS IN THE SYNTHESIS OF NATURAL PRODUCTS:

1. The Synthesis of Erythronolide A

Facing the challenge of synthesizing the antibiotic erythromycin A, Woodward's group took advantage of a cyclic system to achieve diastereofacial selectivity, the so-called cyclic approach. This approach was taken to deal with the common problem of low diastereoselectivity associated with acyclic substances.

2. The Synthesis of 6-Deoxyerythronolide

Considering the entire synthesis of 6-Deoxyerythronolide, clearly the construction of such a complicated molecule with all the desired stereogenic centers is highly tedious and demanding work. Therefore, an entirely different conceptual method based on double asymmetric induction was finally developed as a less complex synthetic strategy. A good example is the synthesis of 6-deoxyerythronolide B, which bears the same chiral centers as erythronolideA.

3.The Synthesis of Rifamycin S

Among the syntheses of complicated natural products, the total synthesis of rifamycin S is another example that shows how a complicated structure can be constructed by applying the concept of double asymmetric synthesis. Rifamycin S is one of the ansamycin antibiotics, characterized by a distinct structural feature: a macro-lactam with a long aliphatic ansachain joined to an aromatic nucleusat two nonadjacent positions. The intermediate and its precursorconstitute another example of forming a subunit of the final product via typical aldol reaction.

4.The Synthesis of Prostaglandins

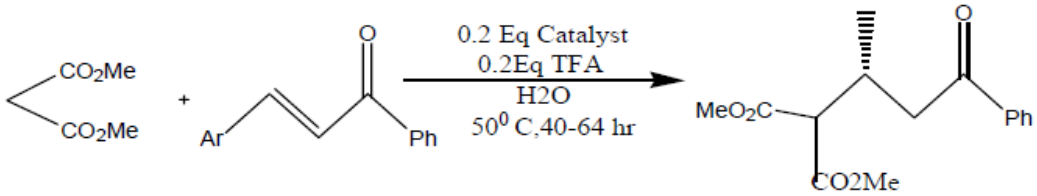
The synthesis of prostaglandins (PGs) is another good example of a preparationin which asymmetric organic reactions play an important role.

5. The Total Synthesis of Taxol

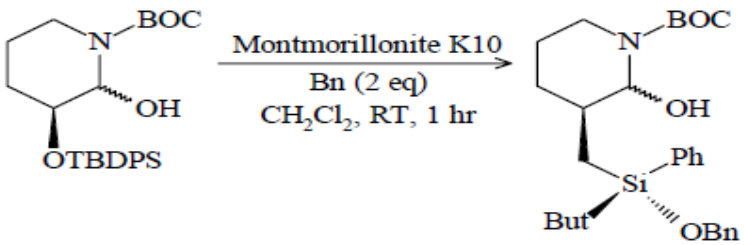
Since the discovery of the high anticancer activity of taxol, much attention has been drawn to its asymmetric synthesis. The total synthesis stood for more than 20 years as a challenge for organic chemists. The compound taxoids are diterpenoids isolated from Taxus species and have a highly oxidized tricyclic carbon framework consisting of a central eight-membered and two peripheral six-membered rings. Over the past few years, several groups have accomplished the total synthesis of taxol by way of independent and original pathways. The successful synthesis of taxol can be considered one of the landmarks of organic synthesis. The total synthesis generally involves two stages: the synthesis of the side chain and the synthesis of the polycyclic ring system. [5]

Environmentally Friendly Approach of Asymmetric Synthesis:

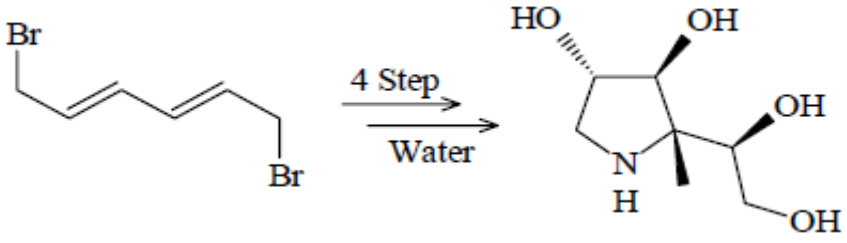
Mao et al. developed an enantioselective Michael addition of malonates to α,β-unsaturated ketones catalyzed by a primary-secondary diamine catalyst containing a long alkyl chain by using water as green solvent. [6]



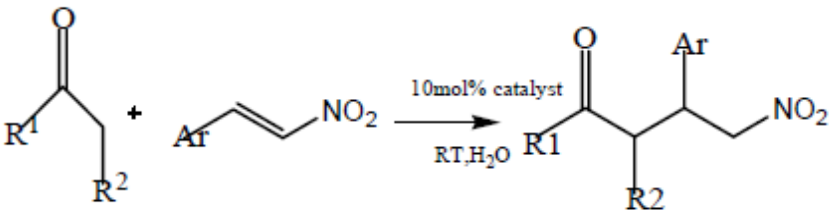
Tomooka et al. developed asymmetric synthesis of arylhydroxycyclic amines and silanols by a novel aryl migration from silicon to carbon by utilizing Montmorillonite K 10.[7]



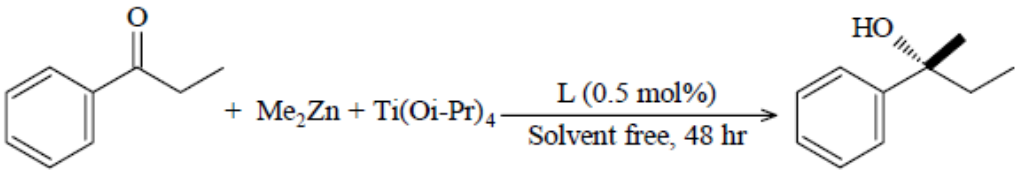
Ulf M. Lindstrom et al. worked on asymmetric synthesis of a pyrrolidine azasugar from achiral biselectrophile without the use of protecting groups. The reaction was completed in only four steps in water.[8]



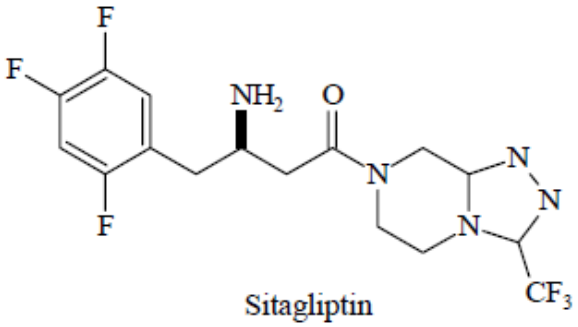
Wei Wang and coworkers developed addition reaction between ketones and aldehydes and nitro olefins by using flourous (s) pyrrolidine sulfomide as recyclable organocatalyst. Water was taken as green media. The protocol gives efficiency with high to excellent levels of 68-95% enantioselecticvity and ≥16:1 dr, disteroslectivity. [9]



Jeon et al. have developed the enantioselective addition of alkyl groups to ketones by the the reaction of propiophenone with dimethyl zinc gives the addition product with 92% ee in solvent free conditions with 84% ligand recovery.[10]

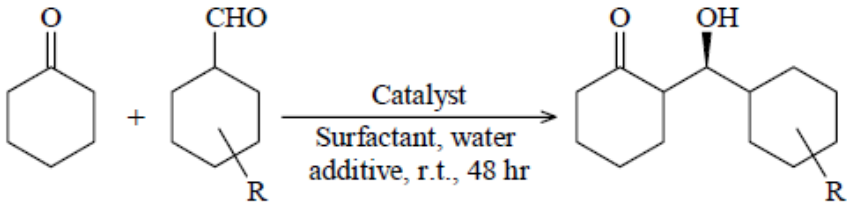


Hansen et al. have developed a highly efficient synthesis of sitagliptin, a potent and selective DPP- 4 inhibitor for the treatment of type 2 diabetes mellitus. The yield was reported 82% with 99.6 wt % purity. This eco-friendly synthesis reduces the total waste generated per kilogram. [11]



Sitagliptin

Pinaka et al. worked on the direct asymmetric aldol reaction in aqueous micellar media catalysed by chiral β-amino alcohols. The green asymmetric synthesis furnished the corresponding β-hydroxy ketones with up to 93% isolated yield and 89% ee. [12]



RECENT ADVANCES IN ASYMMETRIC SYNTHESIS:

1. Asymmetric C–O bond formation with CO_2-

(i)Asymmetric synthesis of chiral cyclic carbonates and polycarbonates from epoxides with CO_2 -

The synthesis of chiral cyclic carbonates and polycarbonates by transition metal catalysed enantioselective incorporation of CO2 into epoxides is one of the most significant processes in the utilization of CO_2.

(ii) Nucleophilic attack to CO_2 in tandem with asymmetric C–O bond formation-

Although much progress has been made in the development of enantioselective CO_2 incorporation into epoxides *via* kinetic resolution to afford the corresponding chiral cyclic carbonates, a drawback with these kinetic resolutions is themaximum theoretical yield of 50% leading to waste of half ofthe materials. An alternative approach to chiral carbonates is the nucleophilic attack of alkoxide to CO2 and following attack to carbon-based electrophiles with asymmetric C–O bond formation. When other nucleophiles, such as amines and thiolates, are used, chiral carbamates and carbonothioatescan be generated.

2. Asymmetric C–C bond formation with CO_2 -

(i) Asymmetric α-amino acids synthesis with CO_2through chiral reagent control–

As crucial yet basic units of proteins, α-amino acids play an important role in biological processes. Although many methods have been developed to generate chiral α-amino acids, direct carboxylation of amines and their derivatives with CO_2 offers an efficient and attractive approach.

(ii) Transitional-metal-catalyzed asymmetric carboxylation of unsaturated substrates -
The transition-metal-catalyzed incorporation of $CO_2$to unsaturated hydrocarbons, such as alkynes, alkenes, allenes, and 1,3-dienes, has proved to be a powerful and versatile protocol for chemical fixation of CO_2. Tremendousprogress has been achieved in the hydrogenative, alkylative and arylative carboxylation, heterocarboxylation, and carboxylativecyclization with $CO_2$to generate functionalized carboxylic acids and derivatives.

(iii) Asymmetric electrocarboxylation with CO_2 -
With electrons as clean reductant, electrochemical synthesis complies well with the criteria of green and sustainable chemistry and has attracted prominent recognition in de-veloping novel and useful transformations, includingcarboxylation of unsaturated substrates and organohalides with CO2 to form carboxylic acids and derivatives. However, asymmetric electrochemical carboxylation with CO2 has been challenging since enantioselective electron transfer is not possible in principle and the electron cannot possess chirality. Thus, the development of catalytic enantioselective variants is still in their infancy. Most of the reported studies relied on the electrocarboxylation of chiralsubstrates to prepare chiral carboxylic acid derivatives. [5]

3. Asymmetric synthesis using chiral-encoded metal -
ThittayaYutthalekha et al reported the use of mesoporous metal structures with encoded geometric chiral information for inducing asymmetry in the electrochemical synthesis of mandelic acid as a model molecule. The chiral-encoded mesoporous metal, obtained by the electrochemical reduction of platinum salts in the presence of a liquid crystal phase and the chiral template molecule, perfectly retains the chiral information after removal of the template. Starting from a prochiral compound we demonstrate enantiomeric excess of the (R)-enantiomer when using (R)-imprinted electrodes and vice versa for the (S)-imprinted ones. [6]

4. Use of Cyclodextrin in Asymmetric Reaction -
(a) Asymmetric Oxidation Reaction:
Cyclodextrins have been used as chiral reaction containers for the asymmetric oxidation of aryl alkyl sulfides in moderate to poor enantiometric excesses by Drabowicz, Mikolajczyk, and Czarnik.

(b) Asymmetric Reduction Reaction :
In the aspect of asymmetric reduction, Park et al. studied the asymmetric reduction of various prochiral ketones with sodium borohydride using β-cyclodextrin and its derivatives as a chiral template and found that the enantioselectivity in the asymmetric reduction of ketones to secondary alcohols was dependent on the structures of hosts and ketones, as well as the reaction temperature. In addition, the results indicated that the absolute configuration of the products depended on the conformational structure of the guest-host complexes, and the decrease of the degrees of freedom of the guest in the complexes was a major factor for the improvement of enantioselectivity.

(c) Asymmetric Addition Reaction:
Cyclodextrin was also used in the asymmetric addition reaction.Pitchumani et al. studied the asymmetric Michael addition of nitromethane and aliphatic thiols in aqueous media using per-6-amino-β-cyclodextrin as a chiral base catalyst. A better enantiomeric excess (60.6%) was observed in water at room temperature with good yield. The catalyst could be recovered and reused with little loss in its activity. The mechanism of the asymmetric addition of nitromethane and aliphatic thiols through the inclusion complex with per-6-amino-β-cyclodextrin was proposed. Using the same catalyst, Pitchumani et al. reported the asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones with high yield (up to 99%) and enantiomeric excess (up to 99%). [15]

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