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Different Strategies of Asymmetric Synthesis

Ritu Sapra [1*], Sanjay Jain [1], Khushboo Arora [1], Sumeet Prachand [1], Hemant Khambete [1]

[1] *Faculty of Pharmacy, Medi-Caps University, Indore-453331, Madhya Pradesh*

***Corresponding Author:** Ritu Sapra*
**Assistant Professor, Faculty of Pharmacy, Medi-Caps University, Indore, Madhya Pradesh*
Email ID: ritu.mehndi@gmail.com

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Abstract:
Asymmetric synthesis is one of the significant subjects of research in recent times. It incorporates regulating stereochemistry of compounds to produce enantiomerically pure chemical substances. Chiral auxiliaries/substrates and enantioselective reagents and organocatalysis are used for the synthesis of enantiomerically pure molecules in organic synthesis. Significance of chiral compounds results in the generation of new bonds in a stereo and enantio-controlled method. Separation of enantiomers from enantiomerically impure sources is a difficult process. Asymmetric synthesis finds its challenging applications in medicinal chemistry, pharmacology, life sciences, chromatography, and extraterrestrial chemistry. This article features the eco- friendly approach and cost-effectiveness of different strategies of asymmetric synthesis.

Keywords: *Asymmetric Synthesis, Chiral substrates/auxiliaries, Enantioselective organocatalysis, Eco-friendly.*

Introduction:

Asymmetric synthesis results in the formation of one or more chirality elements in a molecular substrate and in this reaction unequal quantity of stereoisomeric products are formed. General strategies of asymmetric synthesis are chiral auxiliary technique, chiral pool synthesis, and double asymmetric synthesis. This article encapsulates different strategies used for the asymmetric synthesis of specific chemical compounds. Asymmetric synthesis of different aromatic and aliphatic aldehydes produces highly enantioselective and relatively diastereoselective products. An environment-friendly asymmetry synthesis strategy involves water as a green media and green solvent. This procedure produces chemical compounds with good levels of enantioselectivity and diastereoselectivity. The catalytic asymmetric reaction is approvingly eco-friendly and enantioselective. [1,2]

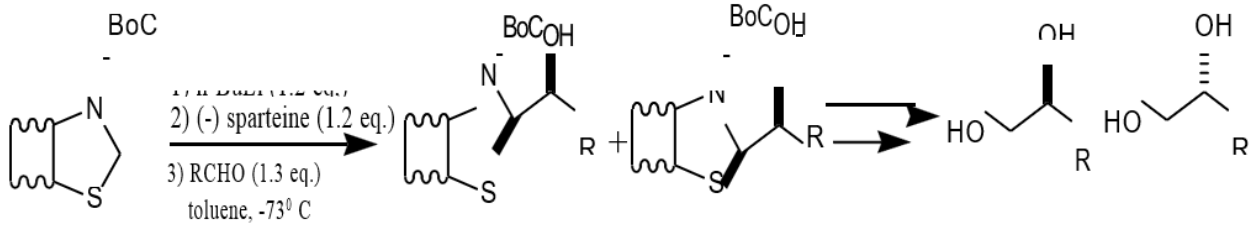
The Chiral pool represents a group of naturally available enantiomerically pure molecules like chiral carboxylic acids, amino acids, and monosaccharides. A chiral pool synthesis or Chiron approach is an asymmetric synthesis strategy in which synthesis of the target molecule is done with the element of the chiral pool as the starting material. Substitution or addition reactions help in the formation of new chiral centers and the target molecule preserves the starting material's chiral center. [3,4]

A Chiral auxiliary is a molecular unit which is fused temporarily in a chiral substrate to direct and facilitate the development of a pair of the enantiomer. In a chiral auxiliary strategy, only the preferred channel is available for reaction and another channel of reaction on the chiral molecular substrate is blocked. As the chiral auxiliaries are optically active and enantiopure substances, the reaction paths are diastereomeric and are not

equal. The stereocenterformed temporarily by the chiral auxiliary strategy guides the formation of the second stereocenter whose stereochemistry can be streamlined. [5,6]
Double asymmetric synthesis incorporates reaction between the enantiomerically pure reagent and substrate and this method is important in the synthesis of acyclic compounds. A chiral substrate with a precise functional group is converted into the preferred functional group for the chemical reaction. A mixture of stereoisomers is formed by the reaction of the chiral reagent and the chiral substrate and the chiral reagent is selected to attain desired stereochemistry and high stereoselectivity. [7,8]

Results and Discussion:

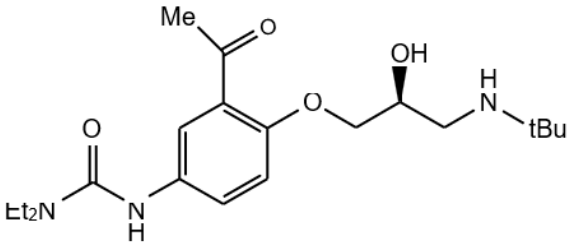
(i) Products with high enantioselectivity and mild diastereoselectivity are formed by the reaction of different aromatic and aliphatic aldehydes. The reaction between N-Boc-benzothiazolidine and lithiated N-Boc-thiazolidine with benzophenone, and (+)-sparteine in toluene as catalyst followed by addition of various aldehydes results inproducts with 97% ee and 93% ee, respectively[9,10]. And the reactants function as chiral formyl anion equivalents. Every diastereomer is transformed into optically active diols.



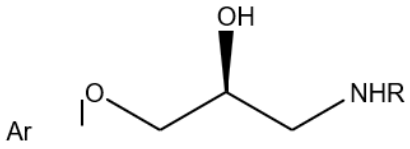
upto 93 % ee

***Scheme 1*: The enantioselective reaction of lithiated N-Boc-thiazolidine Li with variousaldehydes.**

(ii) Enantioselective synthesis of aryl oxy propanolamines via OsO_4 catalyzed dihydroxylation is an applicable approach for the asymmetric synthesis of different β-adrenergic blocking agents and celiprolol. [11,12].

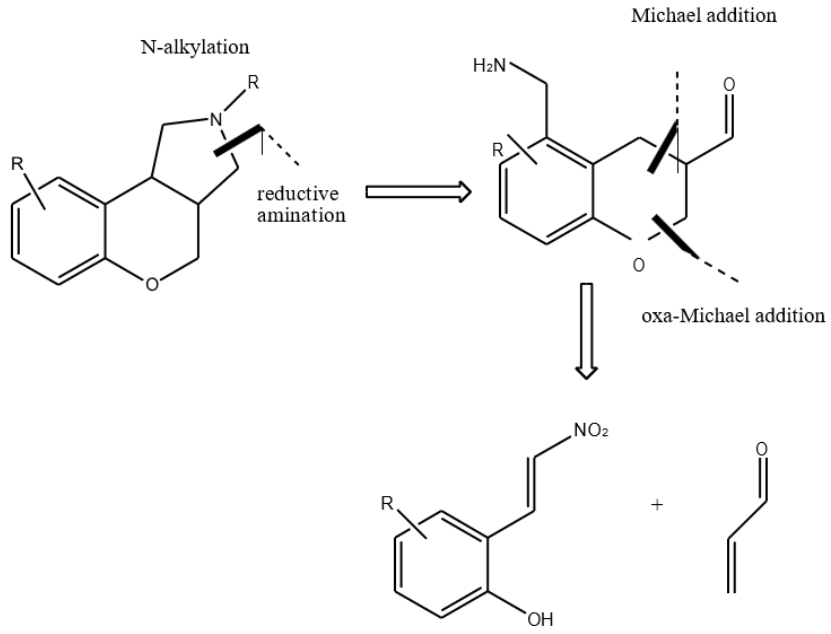


Celiprolol



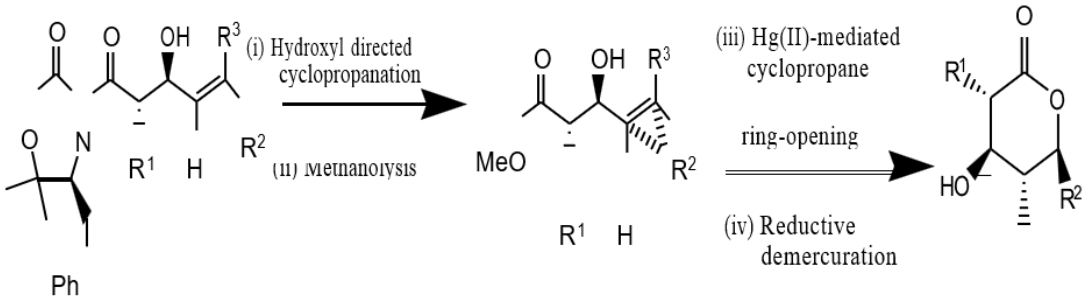
Aryloxypropanolamines

(iii) Michael reaction makes use of an organocatalyst like diphenylprolinol TMS ether to provide remarkable yields and stereoselectivities (dr: 94:6-97:3, 93-98%ee). This is accomplished by the enantioselective synthesis of benzopyrano [3, 4-c] pyrrolidine core by Domino Oxa-Michael **[13,14]**.



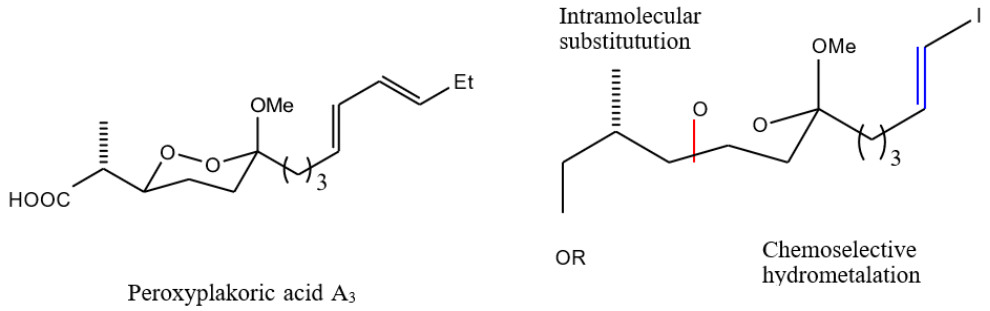
Scheme 2: Asymmetric synthesis of N-alkylated benzo [3,4-c]pyrrolidines D via an organocatalytic domino oxa- Michael/Michael reaction – retrosynthetic analysis.

(iv) A practical asymmetric synthesis approach of chiral delta-lactones which includes numerous contiguous stereocenters has been established. This reaction depends upon Hg (II) mediated cyclopropane ring, methanolysis, and series of Evans' aldol, hydroxyl-directed cyclopropanation which are initial reactions for stereo control.[15,16]



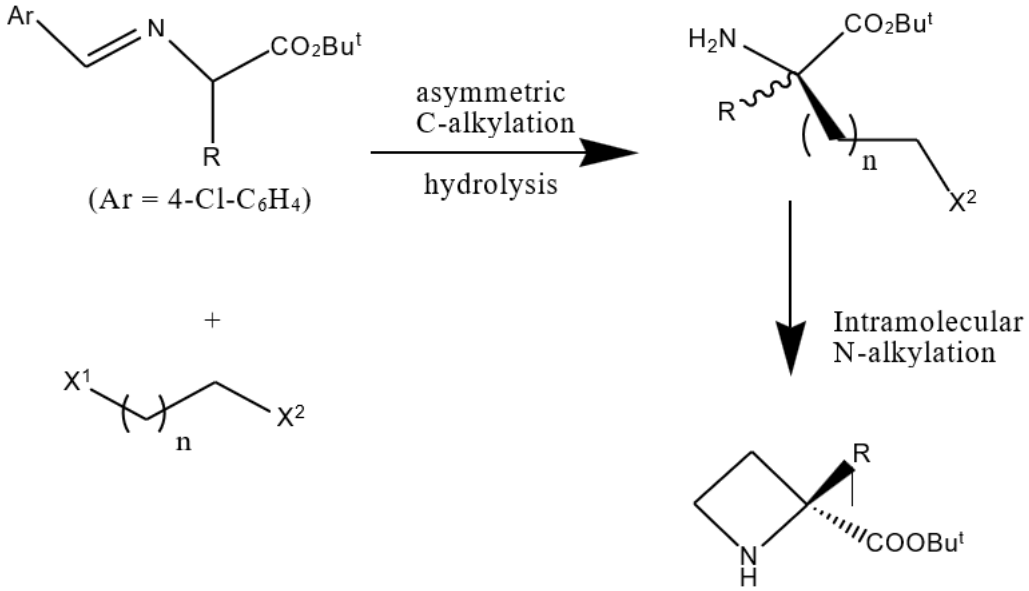
Scheme 3: **Asymmetric synthesis of chiral δ-lactones containing multiple contiguous stereocenter**

(iv) Enantiomeric synthesis of dioxane propionate core of the peroxyplakorates is done by accurate intramolecular alkylation of a hydroperoxy acetal. A synthon or destructural unit within a molecule for the polyunsaturated side chains of the peroxyplakorates is established with the help of chemoselective hydrometallation of an alkyne in presence of peroxide.[17,18]



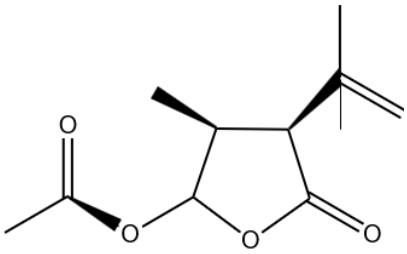
***Scheme 4*: Assymetric synthesis of 1,2-Dioxanes.**

(v) Catalytic enantioselective synthesis of different cyclic α-alkyl-amino acid derivatives with a tetrasubstituted α- carbon like α-alkyl prolines is achieved. This is realized by enantioselective phase-transfer C-alkylation of α-alkyl- amino acid derivatives, followed by intramolecular N-alkylation.[19,20]



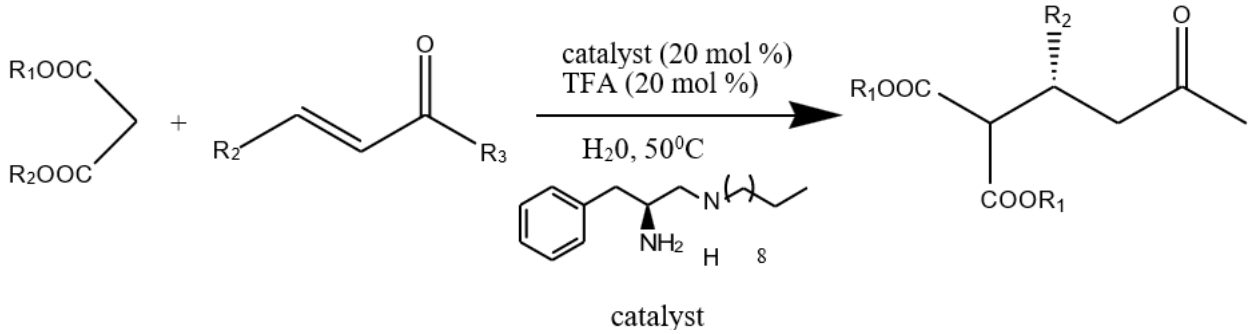
***Scheme 5*:** Asymmetric synthesis of cyclic α-alkyl-α-amino acid derivatives by C,N-double alkylation

(vi) A high performing γ-lactone, (−)-acetomycin with antitumor activity was synthesized using an asymmetric approach in five stages to get nearly perfect enantioselectivity. This important phase is achieved by the esterificationof 5-hydroxy-4- methyl-2(5H)-furanone with large scale lipase catalyzation to give the product (−)-(5R)-5-acetoxy- 4-methyl-2(5H)-furanone with an ee of 99% .[21,22]



***Scheme 6*: (-)-Acetomycin, a highly functionalized γ-lactone with antitumor activity**

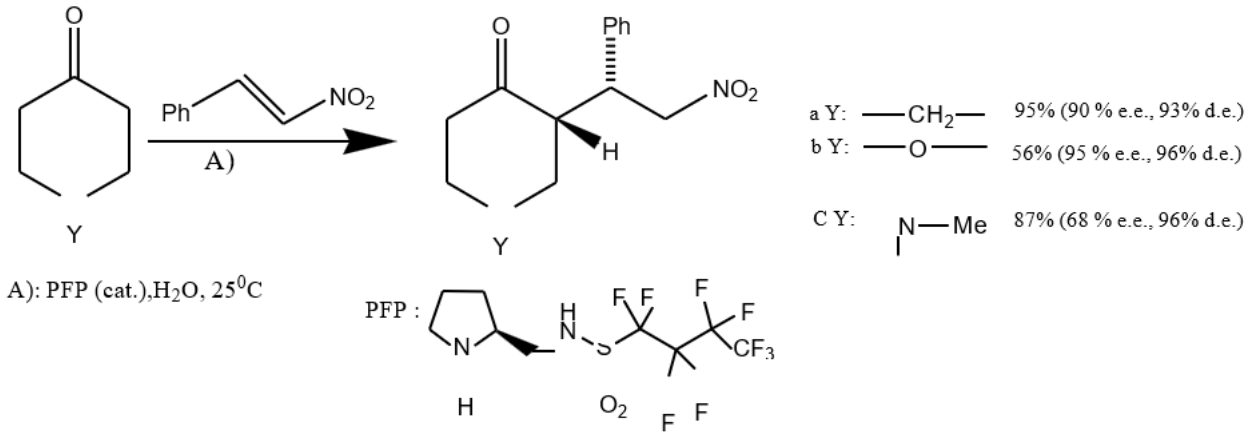
(vii) An eco-friendly approach employs primary-secondary diamine containing a long alkyl chain as a catalyst and with water as a green solvent for the asymmetric synthesis of Michael addition of malonates to α, β-unsaturated ketones.[23,24,25]



catalyst

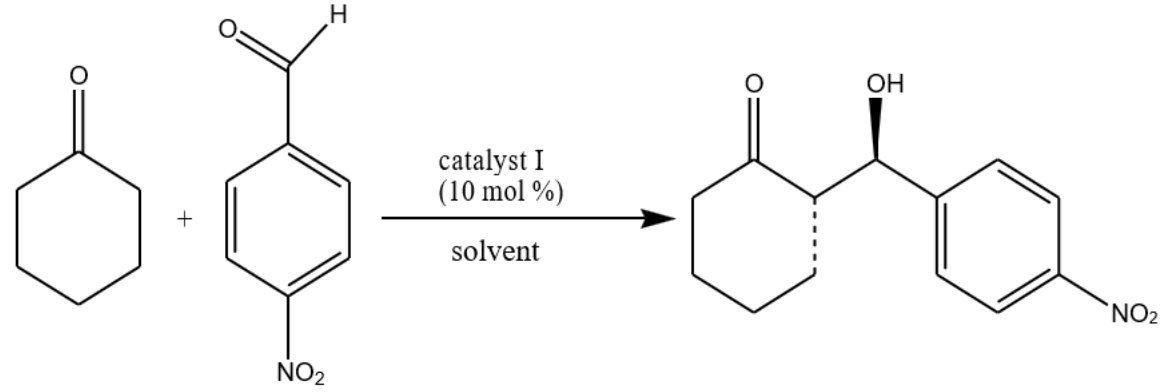
***Scheme 7*: Michael addition of malonates to R,β-unsaturated ketones in water to be catalyzed by a primary-secondary diamine catalyst containing a long alkyl chain.**

(viii) Another eco-friendly approach uses fluorous (s) pyrrolidine sulfonamide as a recyclable organocatalyst for the asymmetric synthesis approach of addition reaction of ketones and aldehydes and nitroolefins with water as green media. This procedure gives products with greater diastereoselectivity in the range of ≥16:1 dr, and efficient enantioselectivity in the levels of 68-95%.[26,27]



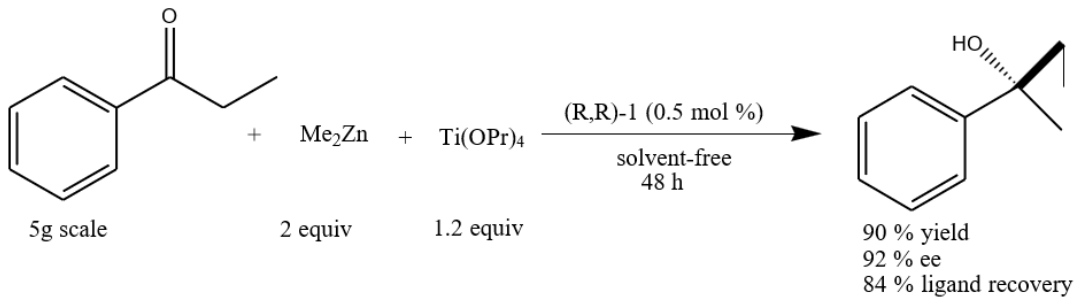
***Scheme 8*: Highly enantioselective Michael addition reaction of ketones and aldehydes with nitroolefins using Fluorous (S) pyrrolidine sulfonamide as organocatalyst**.

(ix) In addition, the fluorous (S) pyrrolidine sulfonamide organocatalyst is used for the high enantioselective aldol reaction in water with a higher yield of enantioselectivity 98% ee and with >20:1 dr as diastereoselectivity. The organocatalyst can be reused as it can be regained from the reaction mixtures.[28]



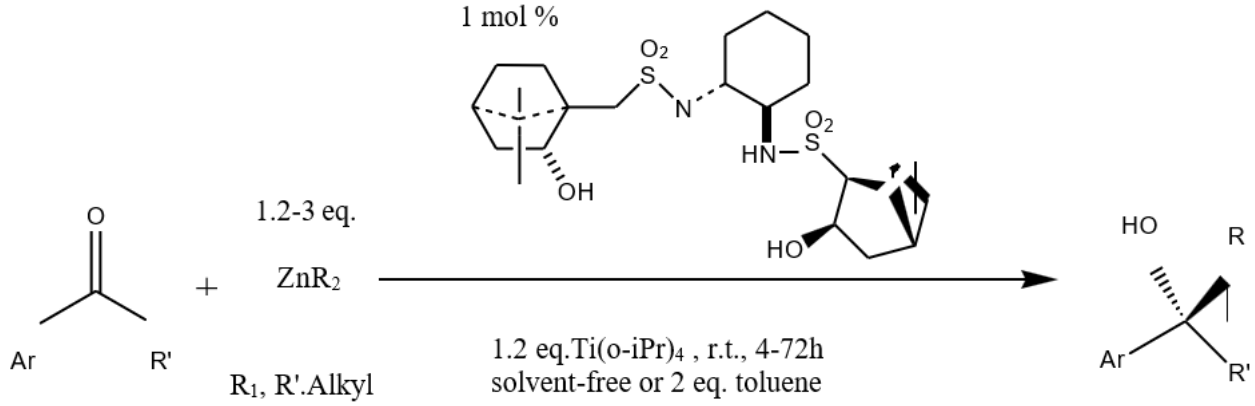
***Scheme 9*: Fluorous (S) Pyrrolidine Sulfonamide Promoted Aldol Reaction of Cyclohexanone 1 with 4-Nitrobenzaldehyde on Water.**

(x) Asymmetric synthesis in solvent-free environment and 84% recovery of the ligand is realized by the enantioselective addition of alkyl groups to ketones, by the reaction of propiophenone with dimethylzinc to give a product with 92% ee.[29]



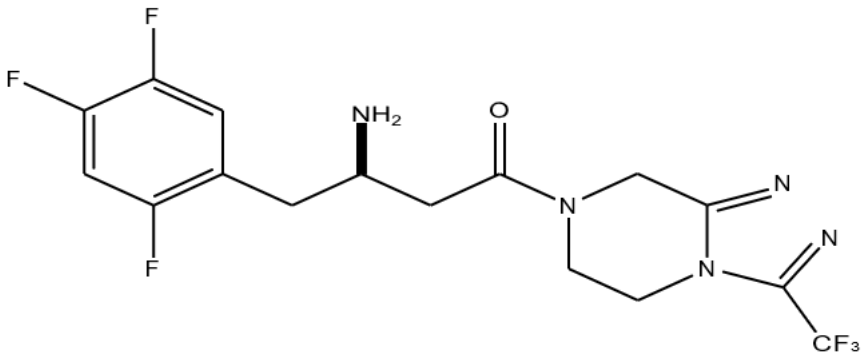
***Scheme 10*: enantioselective addition of alkyl groups (dimethylzinc) to ketones(propiophenone)**

(xi) An eco-friendly and extremely enantioselective reaction is developed by adding alkyl and functionalized alkylgroups to ketones in an asymmetric catalytic reaction without solvents and with high concentration. The catalytic asymmetric addition of alkyl groups to ketones under highly concentrated and solvent-free conditions permits reduction in catalyst loading by a factor of 2- to 40-fold compared with standard reaction conditions employing toluene and hexanes[30-32]

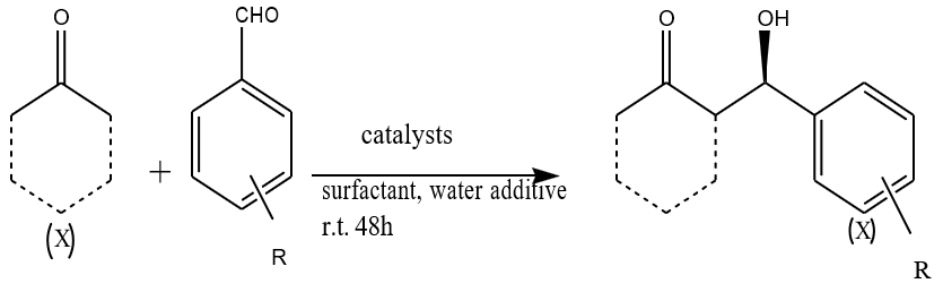


Scheme 11: Catalytic asymmetric addition of alkyl groups to ketones under highly concentrated and solvent-freeconditions

(xii) An eco-friendly asymmetric synthesis to reduce the total waste generated is realized by the effective synthesis of Sitagliptin, a powerful and selective DPP-4 inhibitor and used in type 2 diabetes mellitus (T2DM) therapy. This synthesis gives a yield of the order of 82% with 99.6 wt. % purity.[33]



(xiii) Green asymmetric synthesis is realized by direct asymmetric aldol reaction in aqueous micellar media for which the catalyst is β-amino alcohols. The product obtained is β-hydroxy ketones with 89% ee and 93% isolated$_{yield.}$[34,35].



Scheme 12: Direct asymmetric aldol reaction between ketones and aromatic aldehydes catalyzed by β-amino alcohols in aqueous micellar media.

Conclusion:

The significance of chiral compounds and asymmetric synthesis has instigated this article, in the hope that this will inspire further research into asymmetric synthesis. Scientists should develop high yielding, cost-effective and specific asymmetric synthesis methods with the main challenge being its eco-friendly approach. It is undeniable and evident that numerous applications of such procedures will be realized in the near future. This paper made an attempt to summarize the synthetic capability of auxiliaries/substrates, enantioselective organocatalysis, and eco- friendly procedures in the area of asymmetric synthesis.

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