

RECENT PROGRESS IN ASYMMETRIC SYNTHESIS AND ITS FACILE ACCESS TO ENVIRONMENTALLY BENIGN APPROACH

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ABSTRACT

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 most practical of the methods available in asymmetric synthesis and its facile access to eco-friendly techniques including cost effectiveness and facile scale-up.

Key words: Asymmetric synthesis, Chiral substrates/auxiliaries, Organocatalysis, Eco-friendly, Scale up techniques.

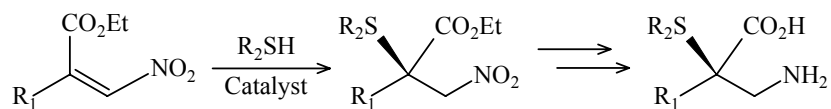
INTRODUCTION

Asymmetric synthesis deals with making of enantiomerically pure compounds by controlling the absolute stereochemistry. Laboratory synthesis will always give a mixture of enantiomers from enantiomerically impure starting material and afterwards separation of enantiomers has always been regarded as one of the most challenging problems for chemists, scientists working in the fields of chromatography, asymmetric synthesis, mechanistic studies, studies of structure-function relationship of proteins, pharmacology, medicine, extraterrestrial chemistry, life sciences etc. This review summarizes different strategies for enantioselective synthesis of targeted frameworks. The potential advantages of asymmetric synthesis have inspired this review. In turn, it is hoped that a comprehensive compilation of different works in this area will stimulate further investigations into asymmetric reactions. A challenge facing organic chemists, to develop advance processes in asymmetric reactions that are not only selective, efficient, and high yielding, but that are also environmentally friendly. Therefore, we also reviewed eco-friendly works in this area. Eco-friendly asymmetric synthesis, however, is a relatively new area and we are not very much aware of reviews devoted to this topic.

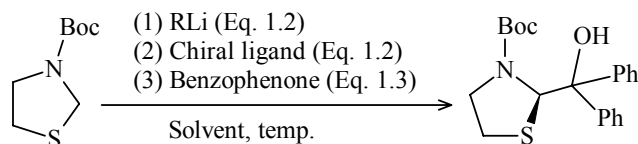
RESULTS AND DISCUSSION

Lu and co-workers¹ developed a method for the addition of thiols to nitroalkenes by using thiourea

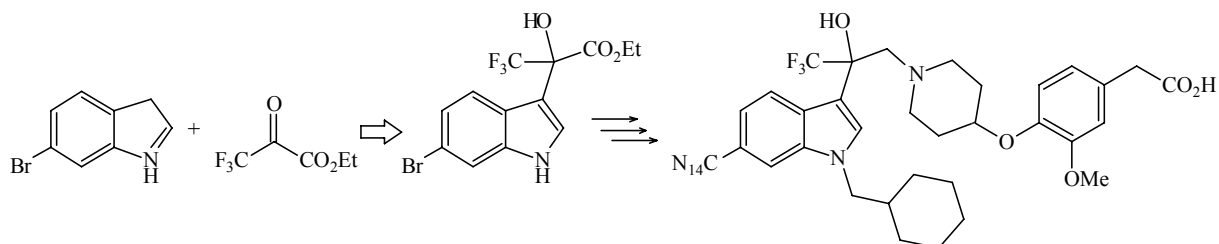
as organocatalyst. This conjugate addition gives good yield and good enantio selectivity.



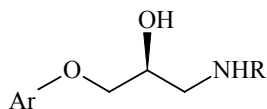
Wang et al.² developed the reaction of lithiated N-Boc-thiazolidine and N-Boc-benzothiazolidine with benzophenone in the presence of (+)-sparteine afforded the products with up to 97% ee and 93% ee, respectively. The reaction with various aromatic and aliphatic aldehydes also gives the products with moderate diastereoselectivity and high enantioselectivity. Each diastereomer could be converted to optically active diols. Consequently, lithiated N-Boc-thiazolidine and N-Boc-benzothiazolidine serve as chiral formyl anion equivalents.



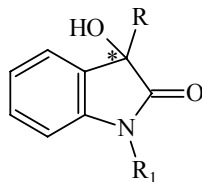
Sumiyoshi et al.³ synthesized carbon-14-labeled selective glucocorticoid receptor modulator by addition of 6-bromoindole to ethyl trifluoro pyruvate catalyzed by cinchona alkaloid. The product formed in >99.5% pure with >99% ee.



Sayyed et al.⁴ developed asymmetric synthesis of aryl oxy propanolamines via OsO_4 catalyzed dihydroxylation. They give a simple and effective procedure for the enantioselective synthesis of several β -adrenergic blocking agents incorporating the first asymmetric synthesis of celiprolol.

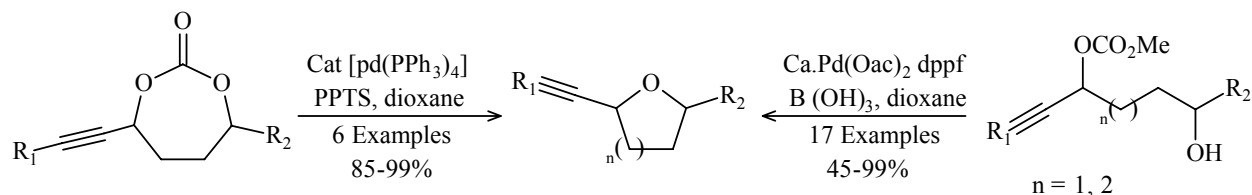


Kumar and Chimni⁵ worked on catalytic asymmetric synthesis of 3-hydroxyoxindole, a potentially bioactive molecule.

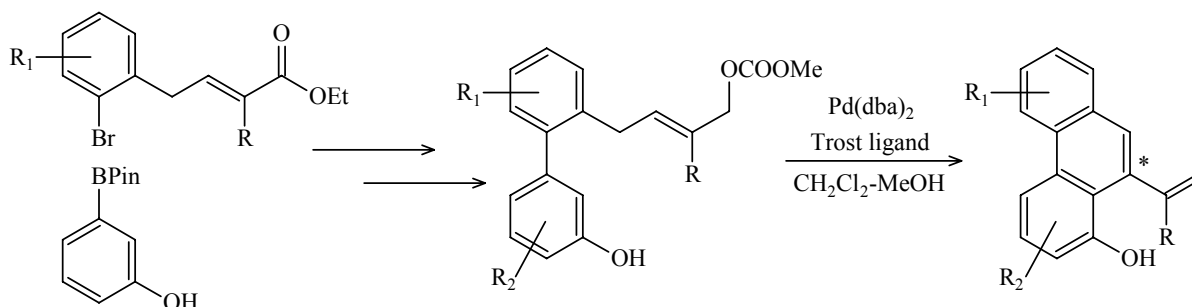


Wang et al.⁶ developed a short asymmetric synthesis of the benzopyrano[3,4-c]pyrrolidine core by domino Oxa-Michael/Michael reaction by using an organocatalyst. This cascade was efficiently catalyzed by diphenylprolinol TMS ether furnishing the products in good to excellent yields (62-91%) and excellent stereoselectivities (dr: 94:6-97:3, 93-98%ee).

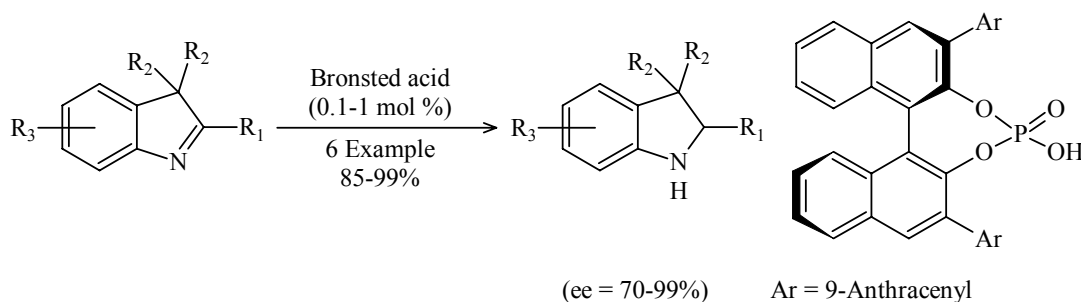
Daniels et al.⁷ worked on cyclizations of cyclic and acyclic propargylic carbonates catalyzed by palladium give 2-alkynyl oxacycles. The reactions proceed with very high stereoselectivity for both *syn*- and *anti*-disubstituted furans and pyrans.



Suzuki et al.⁸ worked on Pd-catalyzed asymmetric synthesis of chiral 9,10-dihydrophenanthrenes via intramolecular Friedel-Crafts allylic alkylation of phenols, which produces 10-vinyl or 10-isopropenyl chiral 9,10-dihydrophenanthrene derivatives in high yield with up to 94% ee.

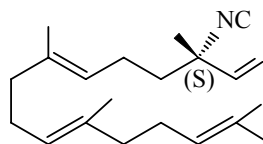


Rueping et al.⁹ developed asymmetric synthesis of indolines by catalytic enantioselective reduction of 3*H*-Indoles. This brønsted acid catalyzed transfer hydrogenation of indole derivatives with Hantzsch dihydropyridine as the hydrogen source constitutes an efficient method for the synthesis of various optically active indolines with high enantioselectivities.



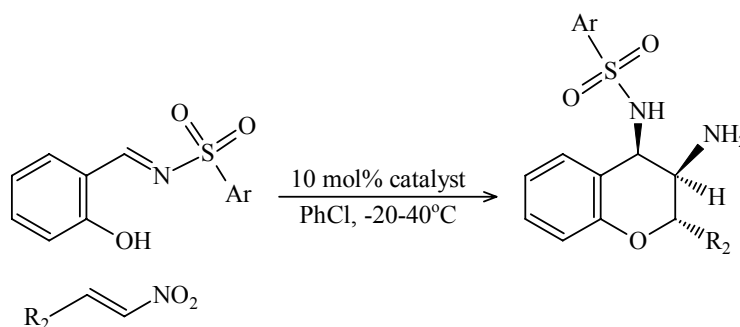
Asymmetric synthesis of chiral delta-lactones developed by Peed et al.¹⁰ containing multiple contiguous stereocenters. A versatile methodology for the asymmetric synthesis of chiral delta-lactones containing multiple contiguous stereocenters has been developed that relies on a series of Evans' aldol, hydroxyl-directed cyclopropanation, methanolysis, and Hg(II) mediated cyclopropane ring-opening reactions for stereocontrol.

Ichikawa et al.¹¹ worked on [3.3] sigmatropic rearrangement of allyl cyanate to give (+)-Geranyllinaloisocyanide, starting with (-)-lactic acid methyl ester. The synthesis enables assignment of the *S* configuration of the C(3) isocyano substituted, quaternary stereogenic center in natural geranyllinalo isocyanide.



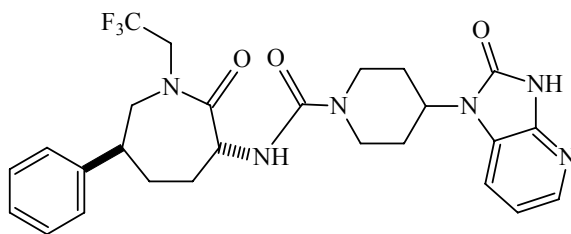
(+) - Geranylinaloisocyanide

Hou et al.¹² developed chiral multifunctional organocatalysed asymmetric synthesis of polysubstituted 4-amino- and 3,4-diaminochromanes. A series of multifunctional catalysts with two chiral diaminocyclohexane units were developed and used in the asymmetric oxa-Michael-aza-Henry cascade reaction of salicyl aldimines with nitro olefins. The method gives high yield (upto 97%) with excellent stereo selectivity upto 98% enantiomeric excess and >99:1 diastereomeric excess.

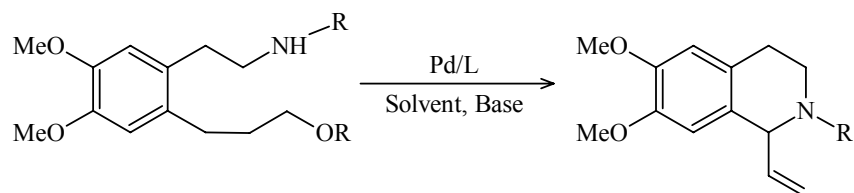


Xu et al.¹³ developed the stereo specific intramolecular alkylation of a hydroperoxyacetal provides the basis for the first asymmetric synthesis of the dioxanopropionate core of the peroxyplakorates. Chemoselective hydrometallation of an alkyne in the presence of a peroxide is used to introduce a synthon for the polyunsaturated side chains of the peroxyplakorates. The route suggests a general solution for the 1,2-dioxane unit in many peroxide natural products.

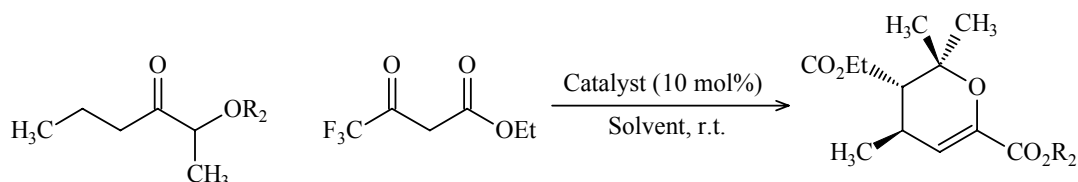
Xu et al.¹⁴ developed asymmetric synthesis of telcagepant, a CGRP receptor antagonist for the treatment of migraine. This synthesis features the first application of iminium organocatalysis on an industrial scale. The key to the success of this organocatalytic transformation was the identification of a dual acid co-catalyst system, which allowed striking a balance of the reaction efficiency and product stability effectively. As such, via an iminium species, the necessary C-6 stereogenicity was practically established in one operation in >95% ee.



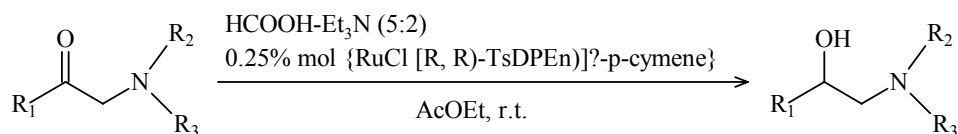
Shi and Ojima et al.¹⁵ developed Pd-catalyzed synthesis of 1-vinyltetrahydro isoquinoline through intramolecular allylic amination. The remarkable feature of this protocol is its excellent enantiopurity (up to 96% ee) and 100% product selectivity. 1-Vinyl tetrahydro quinoline thus obtained is a highly versatile intermediate for the synthesis of various biologically active alkaloids of medicinal properties.



Wang et al.¹⁶ developed asymmetric conjugate addition of ethyl 4,4,4-trifluoroacetate and other trifluoromethyl substituted nucleophiles to α,β -unsaturated α -keto esters. A number of trifluoromethyl substituted dihydro pyrans with three consecutive chiral centers were obtained in excellent yields.

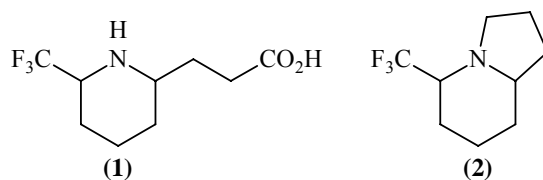


Kosmalski et al.¹⁷ developed asymmetric synthesis of β -dialkylamino alcohols by transfer hydrogenation of α -dialkylamino ketones with formic acid-triethylamine, catalyzed by $\text{RuCl}[(\text{R},\text{R})\text{-TsDPEN}](\text{g-p-cymene})$, produces the corresponding β -di alkylamino alcohols, 97-99% ee.

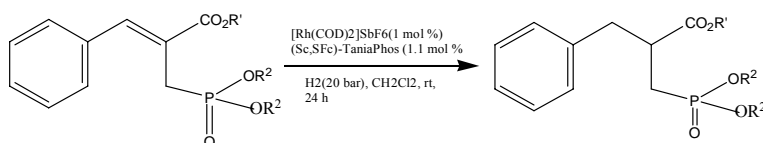


Kano et al.¹⁸ developed catalytic asymmetric synthesis of various cyclic α -alkyl-amino acid derivatives having a tetra substituted α -carbon, such as α -alkyl prolines has been accomplished by asymmetric phase-transfer C-alkylation of α -alkyl-amino acid derivatives and subsequent intramolecular N-alkylation.

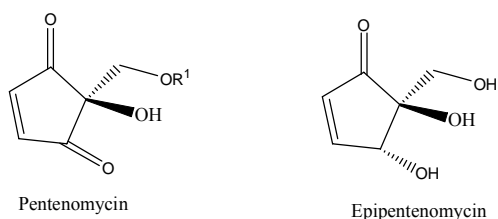
Jatoi et al.¹⁹ developed asymmetric synthesis of trifluoromethyl-piperidine-based α -amino acids **1** and of indolizidines bearing a trifluoromethyl group **2**. The intramolecular Mannich type process gives desired compounds in a highly enantiomeric form.



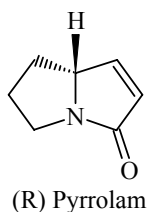
Luo et al.²⁰ developed Rh-catalyzed Asymmetric synthesis of 2-alkyl-3 phosphono propanoic acid derivatives. The methodology gives excellent enantioselectivity (90-98% ee) with high catalytic activity.



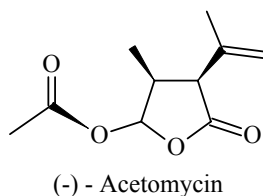
Pohmakotr et al.²¹ have asymmetrically synthesized pentenomycin, epipentenomycin and their derivatives by intramolecular acylation of α -sulfinyl carbanions.



Huang et al.²² described asymmetric synthesis of natural (-)-pyrrolam. The stereogenic center was developed via a highly trans diastereoselective reductive alkylation method. The intramolecular amide N-substitution and tosic acid elimination led to the desired compound.

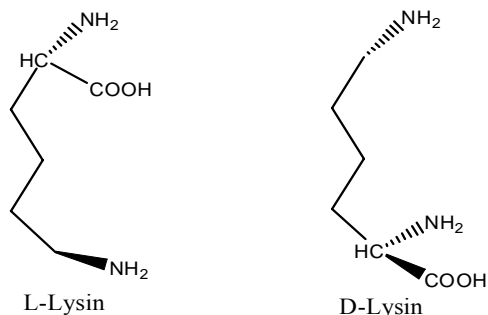


Kinderman and Feringa²³ synthesized (-)-acetomycin a highly functionalized γ -lactone with antitumor activity, the molecule was prepared in five steps with nearly complete enantioselectivity. The key step was realized by a large scale lipase catalyzed esterification of 5-hydroxy-4-methyl-2(5H)-furanone providing (-)-(5R)-5-acetoxy-4-methyl-2(5H)-furanone 3 with an ee of 99%.



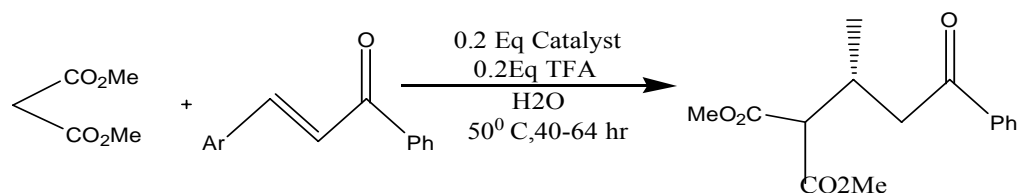
Simpson and Zhao²⁴ described asymmetric syntheses of (1R, 3R, 4S)- and (1S, 3R, 4S)-(3,4-difluorocyclopentyl)-alanine derivatives by using a sequence of epoxide opening, asymmetric alkylation, and fluorination, polyfluorinated cyclopentylamino acids with defined stereo chemistry.

Stalker et al.²⁵ described asymmetric synthesis of two new conformationally constrained lysine derivatives.

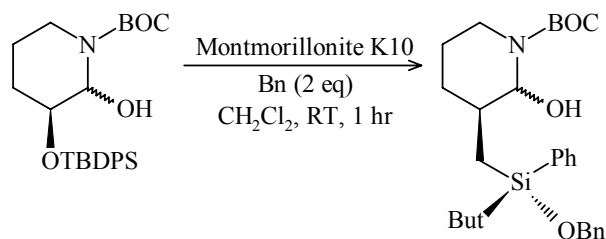


Environmentally friendly approach

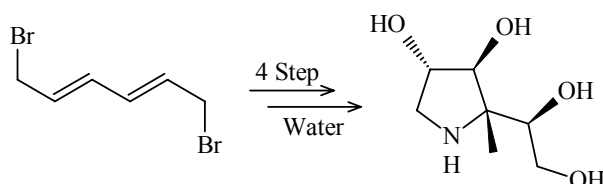
Mao et al.²⁶ developed an enantioselective Michael addition of malonates to α,β -unsaturated ketones catalyzed by a primary-secondary diamine catalyst containing a long alkyl chain by using water as green solvent.



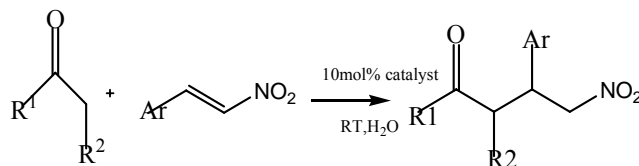
Tomooka et al.²⁷ developed asymmetric synthesis of arylhydroxycyclic amines and silanols by a novel aryl migration from silicon to carbon by utilizing Montmorillonite K 10.



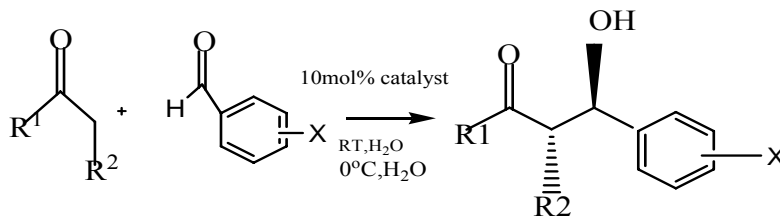
Ulf M. Lindström et al.²⁸ worked on asymmetric synthesis of a pyrrolidine azasugar from achiral bis-electrophile without the use of protecting groups. The reaction was completed in only four steps in water.



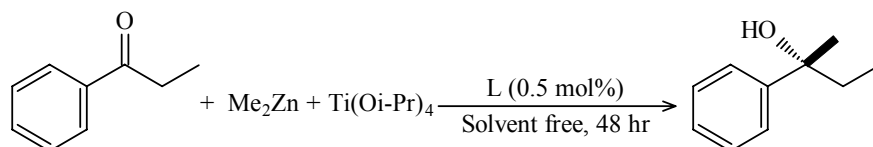
Wei Wang^{29(a)} and coworkers developed addition reaction between ketones and aldehydes and nitro olefins by using fluoros (*S*) pyrrolidine sulfonamide as recyclable organocatalyst. Water was taken as green media. The protocol gives efficiency with high to excellent levels of 68-95% enantio selectivity and $\geq 16:1$ dr, diastereoselectivity.



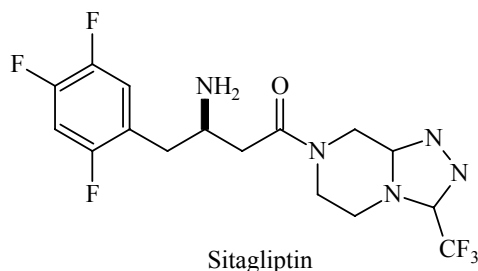
Wei Wang^{29(b)} has developed highly enantioselective aldol reaction in water by using fluoros (*S*) pyrrolidine sulfonamide organocatalyst. The catalyst can be recovered from the reaction mixtures and reused. The yield is up to 98% ee with $>20:1$ dr.



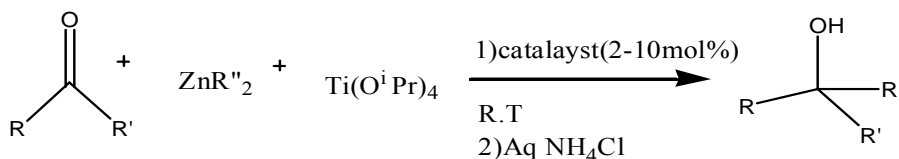
Jeon et al.³⁰ have developed the enantioselective addition of alkyl groups to ketones by the reaction of propiophenone with dimethyl zinc gives the addition product with 92% ee in solvent free conditions with 84% ligand recovery.



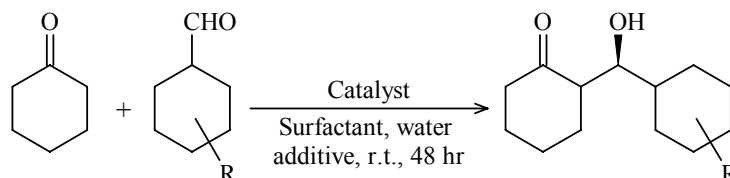
Hansen et al.³¹ have developed a highly efficient synthesis of sitagliptin, a potent and selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus (T2DM). The yield was reported 82% with 99.6 wt % purity. This eco-friendly synthesis reduces the total waste generated per kilogram.



Jeon et al.³² developed the catalytic asymmetric addition of alkyl and functionalized alkyl groups to ketones under highly concentrated and solvent-free conditions. The catalytic asymmetric reaction is highly enantioselective and more environmental friendly.



Pinaka et al.³³ 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.



CONCLUSION

Many notable examples of asymmetric synthesis have been reported. It is certain that many more applications will be developed in the near future. This survey attempted to summarize the synthetic potential of substrates/auxiliaries, enantioselective organocatalysis and eco-compatible protocols in the area of asymmetric synthesis.

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