Futuristic Trends and Opportunities in Organic Synthesis-Asymmetric organocatalysis

Monica Dinodia

Department of Chemistry, Hansraj College

University of Delhi

Delhi, India

[**monicadinodia@yahoo.co.in**](mailto:monicadinodia@yahoo.co.in)

ABSTRACT

Organic synthesis is the **art and science of constructing organic molecules and**has an enormous impact on human life and their well-being. It has benefitted the society by providing nutritional supplements, medicines, vitamins, cosmetics, high energy fuels, polymers and plastics to name a few. This discipline has also **facilitated the emergence and development of other disciplines and technologies** namely biology and biotechnology, chemical biology, medicinal chemistry, physics, materials science and nanotechnology. After survey on the recent publications, asymmetric organocatalysis is identified to be the most recent methodologies in the synthesis of organic compounds.

Keywords— Organic synthesis; asymmetric organocatalysis; chemical biology; nanotechnology; medicinal chemistry

# INTRODUCTION

Organic chemistry[[1]](#footnote-1) is the study of organic compounds, their structure, including their synthesis, and application. Over the years, there is a tremendous growth in the synthesis of organic molecules, to meet the ever increasing needs of society since the successful synthesis of urea[[2]](#footnote-2) in 1828 by Friedrich Wöhler. Since then many efforts have been put in by the scientific community for the development of new bio-active molecules, novel materials with properties, like bio-compatibility, new catalysts for selective transformations, and so on. This discipline has also **facilitated the emergence and development of other disciplines and technologies** namely biology and biotechnology, chemical biology, medicinal chemistry, physics, materials science and nanotechnology.

The use of organic compounds as catalysts is known from a very long time, but their usage as asymmetric catalysts has become important in the past few decades, due to their selectivity in lots of reactions[[3]](#footnote-3). Asymmetric organocatalysis has evolved a lot since the early work on the use of cinchona alkaloids for the reaction between HCN (hydrogen cyanide) and aldehydes, reported in 1912 by Breding and Fiske[[4]](#footnote-4). This was followed by various enantioselective important publications of MacMillan and List, which finally resulted in the 2021 Nobel Prize in Chemistry[[5]](#footnote-5). Being easily available, either from natural or synthetic starting materials, organocatalysts are therefore, easy to obtain, saving cost, time, and energy[[6]](#footnote-6). A variety of efficient, small-molecule organocatalysts have widened the field of organic synthesis, namely chiral proline derivatives, thioureas, brønsted acids, *N*-heterocyclic carbenes, the quaternary ammonium salts derived from cinchona alkaloids[[7]](#footnote-7) etc.

Milder conditions involved in the organocatalysis in comparison to most metal catalysts, and their low toxicity finds them suitable in medicinal chemistry[[8]](#footnote-8). In addition to the reduction of the activation energy of the reaction, organocatalysis is also important in terms of green chemistry. Since the use of catalysts is involved, which is one of the green chemistry principles, organocatalysis is greener[[9]](#footnote-9) than traditional catalysis. It uses, mainly oxygen-stable reagents, reducing the cost of the synthesis and saves energy. Organocatalysis is compatible with various functional groups which are sensitive to other processes—this leads to escape of the protection step, this in turn lowers the total number of reaction steps. Non formation of metallic waste and avoidance of metals in the products, finds them applications in medicinal chemistry.

Asymmetric organocatalyis is useful for the synthesis of natural products, chiral drugs, and bioactive molecules. Šebesta et al. designed four new *N*-sulfinyl-*N*’-(pyrrolidinylmethyl)urea and *N*-sulfinyl-*N*’-(pyrrolidinylmethyl)thiourea bifunctional organocatalysts[[10]](#footnote-10) (**Scheme 1**) and used them in Michael additions of aldehydes to nitroalkenes using both solvent-free conditions and in solution. The *N*-sulfinylurea catalyst was more effective than the thiourea catalyst. Enantioselectivities reached upto 98% ee. The additional stereogenic center on the sulfur plays only a minor role on the stereoselectivity of the reaction, which is mainly due to the proline configuration. Using Ball-milling conditions[[11]](#footnote-11), good yields of the Michael products were obtained but enantiomeric purities was less than in solution. DFT calculations proved a dual activation mode, namely enamine activation of aldehydes and hydrogen-bond activation of nitroalkenes.



**Scheme 1: Michael addition reaction of aldehydes with nitroalkenesusing *N*-sulfinyl-*N*’-(pyrrolidinylmethyl)urea/thiourea bifunctional organocatalysts.**

Zhang[[12]](#footnote-12) et al. published the organocatalytic asymmetric synthesis of spiro-*δ*-lactam oxindoles (**Scheme 2)** with several stereogenic centers through a [3 + 3] annulation reaction. Their method is a metal free, novel, simple and efficient for the synthesis of bioactive spiro-*δ*-lactam oxindoles involving a range of substrates, with good diastereoselectivities and enantioselectivities.



**Scheme 2: Synthesis of bioactive spiro-*δ*-lactam oxindoles.**

The (3 + 2)-cycloaddition reaction between 4-(alk-1-en-1-yl)-3-cyanocoumarins with imines derived from salicylaldehyde (**Scheme 3)** is reported by Albrecht group[[13]](#footnote-13) using quinine-derived organocatalyst. Compounds with two biologically relevant units, were obtained with good chemical and stereochemical selectivity. Further, some selected transformations of the cycloadducts were also reported.



### **Scheme 3: Cycloaddition reaction between 4-(alk-1-en-1-yl)-3-cyanocoumarins and imines.**

Introduction of chiral spiro *N*,*N*-acetal carbon stereocenters and axially chiral 3-arylindoles[[14]](#footnote-14) (**Scheme 4)** through the (3 + 2) annulation of α-(3-isoindolinonyl) propargylic alcohols with 1-(3-indolyl)naphthalen-2-ols using a chiral phosphoric acid (CPA) was reported by Xia et al., the reaction resulted in pyrrolo[1,2-*a*]indoles having both spiro isoindolinone-indoline and atropisomeric naphthalenol skeleton in yields upto 77-95% and 73-96% ee.



**Scheme 4:** **Building of pyrrolo[1,2-*a*]indoles.**

Bania[[15]](#footnote-15) group came up with a report on the asymmetric Diels–Alder reaction between alkylidene pyrazolones with allyl ketones (**Scheme 5)**. The reaction was activated by a bifunctional thiourea catalyst. The product, trisubstituted tetrahydropyrano[2,3-*c*]pyrazoles were obtained in moderate to good yields, with diastereo- and enantioselectivities. They have also reported a decarbonylation reaction as an application.



**Scheme 5:** **Diels–Alder reaction involving alkylidene pyrazolones with allyl ketones.**

Through the aza-Friedel–Crafts reaction, an efficient coupling of electron-rich aromatic systems with imines can be easily and efficiently done for the facile introduction of aminoalkyl groups into the aromatic system. This reaction introduces aza-stereocenters which can then be tuned by organocatalysts. Biswas[[16]](#footnote-16) in his review reported recent advances in asymmetric aza-Friedel–Crafts reactions catalyzed by organocatalysts. Sharma coworkers[[17]](#footnote-17) in their article compiled the literature published in the last 10 years on the asymmetric aza-Michael reaction of amines and amides catalysed by organocatalysts. The authors reported both types of the organocatalysts, i.e., those acting through non-covalent interactions and those working through covalent bond formation. The review reported cinchona alkaloids, squaramides, chiral amines, phase-transfer catalysts and chiral bifunctional thioureas, which activate the substrates through hydrogen bond formation. High yields and high enantiomeric excesses were obtained in most of these reactions. N-heterocyclic carbenes and chiral pyrrolidine derivatives on the other hand, acting through covalent bond formation such as the iminium ions with the substrates were also included.

Substituted chiral pyrrolidines are the heterocyclic structural frameworks which are commonly present in bioactive natural and synthetic products[[18]](#footnote-18). Since the discovery and implementation of organocatalysis, chiral pyrrolidines have taken a leading role as organocatalysts, as they are able to efficiently carry out different transformations in an enantioselective and eco friendly way, without using the metals.

The organocatalyst, chiral spiro (S)-1-benzylspiro[indoline-3,2′-pyrrolidin]-2-one was used to carry out the enantioselective aldol condensation between isatins and acetone, and was reported by Zou coworkers[[19]](#footnote-19) , an array of chiral 3-hydroxy-3-(2-oxopropyl)-indolin-2-ones (Scheme 6) in excellent yields were synthesized in upto 97% yield and good enantioselectivities (upto 82% ee). Compared to the chiral prolinamide organocatalyst, the [enantioselectivities](https://www.sciencedirect.com/topics/chemistry/enantioselectivity" \o "Learn more about enantioselectivities from ScienceDirect's AI-generated Topic Pages) of their catalysts were due to steric control rather than amide NH [hydrogen bonding](https://www.sciencedirect.com/topics/chemistry/hydrogen-bonding)  (for [enamine](https://www.sciencedirect.com/topics/chemistry/enamine) organocatalysis). An enantioselective organo-catalyzed reaction for an efficient access under mild conditions to chiral bicyclic γ-butyrolactones in good yields[[20]](#footnote-20), good [enantioselectivities](https://www.sciencedirect.com/topics/chemistry/enantioselectivity)/[diastereoselectivities](https://www.sciencedirect.com/topics/chemistry/diastereoselectivity" \o "Learn more about diastereoselectivities from ScienceDirect's AI-generated Topic Pages) has been established by Bai et al. by the reaction of furanones with α,β-unsaturated ketones.



**Scheme 6: Synthesis of 3-hydroxy-3-(2-oxopropyl)-indolin-2-ones 18.**

The use of proline-based organocatalysts has gained significant importance in organic synthesis, mainly in enantioselective synthesis. Proline and its derivatives are quite effective chiral organocatalysts in aldol reaction, which is one of the most important C-C bond forming reactions in organic synthesis. Numerous, highly efficient, proline-based organocatalysts, including polymer based chiral species, have been reported for aldol reaction. These polymer-supported organocatalysts demonstrated high stability under the reaction conditions and showed the best results, mainly in terms of its recyclability and reusability. These potential and their economic advantages including being greener, have led to the development of many more polymer-supported proline catalysts. Shajahan[[21]](#footnote-21) in their review, published recent findings for asymmetric aldol reactions using various polymer immobilized proline- based chiral organocatalysts. Chemists from Hoffmann-La Roche and Schering AG in 1971, independently carried out intramolecular aldol reaction catalyzed by proline, this transformation is now known as the Hajos–Parrish–Eder–Sauer–Wiechert reaction. List and Barbas came up with a report in 2000 that L-proline was also able to catalyze intermolecular aldol reactions with non-negligible enantioselectivities. In that same year, MacMillan reported efficient catalysis by imidazolidinones derived from natural amino acids on asymmetric Diels–Alder cycloadditions. These two reports sparked the origin of modern asymmetric organocatalysis. An important breakthrough in this upcoming field happened in 2005, when Jørgensen and Hayashi independently came up with the use of diarylprolinol silyl ethers for the asymmetric functionalization of aldehydes. During the last 20 years, there has been a tremendous development in asymmetric organocatalysis and it has emerged as a very powerful technique for the facile construction of complex molecules. Quintavalla[[22]](#footnote-22) et al. in their review, starting from 2008, highlights the most recent developments in the asymmetric synthesis of organocatalysts derived from or are related to proline.

Organocatalysts, namely thiourea-based iminophosphorane (BIMP) with SPhos- or BIDIME phosphine units were developed and used in the asymmetric addition of nitromethane with *N*-Boc-protected trifluoromethyl aryl ketimines (**Scheme 7)** by Sanz coworkers[[23]](#footnote-23) under mild conditions with no need of additional base. The product, α-Trifluoromethyl β-nitroamines were obtained in 40–82% yields and 80–95% enantioselectivities. The catalysts which was obtained from the reaction of a chiral 1,2-amino alcohol-derived thiourea-organoazide with electron-rich phosphines, promote the aza-Henry reaction on fluorinated ketimines with the highest enantioselectivity (95% ee). The reaction could be done on a gram scale, without any loss of enantioselectivity. BIMP acted as superbase as well as H-bond donor.



**Scheme 7:** **Reaction between nitromethane and *N*-Boc-protected trifluoromethyl aryl ketimines using Thiourea-based iminophosphorane (BIMP) organocatalysts.**

Quinine-based aminoindanol-thiourea catalyzed the Michael addition/alkylation reaction between 3-chlorooxindoles and α-cyano chalcones (**Scheme 8)** and was investigated by Wang coworkers[[24]](#footnote-24). A series of spirooxindoles substituted with cyclopropane motif were efficiently synthesized in moderate to excellent diastereo- and enantioselectivity and these in turn were further transformed to various structural diverse products. Density functional theory (DFT) calculations conveyed that the intramolecular hydrogen bonds in the chiral catalyst were important for the stereocontrol of the reaction.



**Scheme 8: Asymmetric Michael addition reaction between 3-chlorooxindoles and α-cyano chalcones catalyzed by quinine-derived aminoindanol-thiourea.**

Lattanzi[[25]](#footnote-25) in her report discussed their achievements, on the asymmetric synthesis of new three, five, and six membered heterocyclic compounds, also spiro compounds with quaternary chiral centres. Combinations of Michael and aldol reactions enabled them to expand the number of compounds from tetrahydrothiophenes and lactones to hybrid scaffolds with heterocyclic units at the spirocenter. On combining visible light photocatalysis with organocatalysis, lots of progress is reported in organic synthesis. In these double catalytic reactions, photocatalysts/photosensitizers absorb visible light and induce their photo-excited states which in turn activate unreactive substrates through electron or energy transfer mechanisms, and organocatalysts are involved in controlling the reactivities of the other substrates. Shen et al. in their review[[26]](#footnote-26) discussed the recent findings of reactions involving the combination of organocatalysis and photocatalysis in the synthesis of organic compounds. Review by Hughes[[27]](#footnote-27) coworkers reported work in asymmetric organocatalysis from patent literature since 2018. Reactions catalyzed by Cinchona alkaloids as free base as well as quaternary salts, phosphonium salts, proline-based catalysts, and chiral phosphoric acids were discussed. The group also highlighted asymmetric organocatalysis for the preparation of pharmaceutical intermediates in industries. By taking pregabalin, as an example, Giorgianni et al. in their perspective[[28]](#footnote-28) discussed the importance and role of organocatalysts. Chiral primary α-amino amides, with adjacent enamine bonding site (Bronsted base site), a hydrogen bonding site (Bronsted acid site), and flexible bulky substituent groups, are important bifunctional organocatalysts for numerous asymmetric organic conversions. Primary α-amino amides are better suited organocatalysts than other primary amino organocatalysts, such as chiral diamines and cinchona-alkaloid-derived primary amines. Also primary α-amino amides are less expensive alternatives, easy to synthesize, air-stable, and allow for the introduction of a variety of functional groups. In recent years, Reddy group[[29]](#footnote-29) have published work on the organocatalysis by simple primary α-amino amides and their derivatives on various reactions namely, aldol reaction, allylation of aldehydes, Strecker reaction, reduction of N-Aryl imines, Michael tandem reaction, opening of epoxides, asymmetric hydrogen transfer, hydrosilylation and reaction of aldehydes with N-specific nitrosobenzene.

In their review, Reyes et al.[[30]](#footnote-30) highlighted the use of organocatalysts for the synthesis of enantio-pure compounds which are of relevance to the medicinal chemists[[31]](#footnote-31) and pharmaceutical companies.

**CONCLUSION**

There had been an enormous development opportunities in the synthesis of organic moieties in the 21st century. Organic synthesis is the **art and science of constructing organic moleculesand**has an enormous impact on human life and their well-being. It has benefitted the society by providing nutritional supplements, medicines, vitamins, cosmetics, high energy fuels, polymers and plastics to name a few. Organic chemistry is a highly innovative discipline. This discipline has also **facilitated the emergence and development of other disciplines and technologies** namely biology and biotechnology, chemical biology, medicinal chemistry, physics, materials science and nanotechnology. Based on the publication trends, asymmetric organocatalysis in organic synthesis is featured as the most recent trend in organic synthesis. This Chapter aims at discussing some recent, novel and advanced examples showing the multifaceted potential of this upcoming and important field.

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