Futuristic Trends and Opportunities in Organic Synthesis-Asymmetric organocatalysis

Monica Dinodia

Department of Chemistry, Hansraj College

University of Delhi

Delhi, India line

[**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. Based on the publication trend analysis, asymmetric organocatalysis in organic synthesis is identified and featured as the most recent trends in organic synthesis.

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

# INTRODUCTION

Organic chemistry[[1]](#footnote-1) is a subject of studying organic compounds, synthesis, structure, performance, and application. Over the years, there is a rapid growth in the synthesis of both simple and complex molecules, aimed to meet the needs of society in all aspects of life since 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 biologically active compounds, new materials with innovative properties, like bio-compatibility, new catalysts allowing highly selective transformations, and so on. Organic chemistry forms the basis of a series of related disciplines such as materials science, life science, medicinal chemistry, environmental science, etc.

Organic compounds have been used for decades as catalysts, but their application in asymmetric catalysis has become even more important in recent years due to their effective selectivity in a wide range of reactions[[3]](#footnote-3). Asymmetric organocatalysis has evolved a lot since the early reports involving the use of cinchona alkaloids for the HCN (hydrogen cyanide) addition to aldehydes, published in 1912 by Breding and Fiske[[4]](#footnote-4). This was followed by first highly enantioselective reports in the second half of the last century, until the hype initiated in 2000 by the important publications of MacMillan and List, which finally culminated in the 2021 Nobel Prize in Chemistry[[5]](#footnote-5). In general, the organocatalysts are easily available, either from natural or synthetic starting materials, therefore, saving cost, time, and energy[[6]](#footnote-6). A plethora of highly effective small-molecule organocatalysts have enriched the field of organic synthesis, including chiral proline derivatives, *N*-heterocyclic carbenes, thioureas, brønsted acids, and phase-transfer catalysts (PTC), such as the quaternary ammonium salts derived from cinchona alkaloids[[7]](#footnote-7).

Furthermore, the experimental application requires milder conditions when compared with most metal catalysts, and the low toxicity of the organocatalysts brings great utility to medicinal chemistry[[8]](#footnote-8). In addition to the primary advantage of the use of catalysts, which is the reduction of the activation energy of the reaction, organocatalysis is also important in the context of green chemistry, since the execution of reactions using catalysis is considered as one of the main points of this expanding area of chemistry. Organocatalysis can be greener[[9]](#footnote-9) than traditional catalysis because the use of catalysts is itself, a green chemistry principle. It employs mild conditions, consequently saving energy. It uses, in general, oxygen-stable reagents and does not require anhydrous conditions, reducing the cost of the synthesis; it is compatible with several functional groups that could be sensitive to other processes—this reduces the need for protection groups, lowering the total number of reaction steps. It prevents the formation of metallic waste and avoids traces of metals in the products, which is an essential feature for applications in medicinal chemistry.

Asymmetric organocatalytic methods have extended beyond the academia and undergone scale-up for the production of chiral drugs, natural products, and enantiomerically enriched 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 they were further evaluated in Michael additions of aldehydes to nitroalkenes both under solvent-free conditions and in solution. The *N*-sulfinylurea catalyst was more efficient than the corresponding thiourea. For some substrates, enantioselectivities reached 98% ee. The additional stereogenic center on the sulfur plays only a minor role on the stereoselectivity of the reaction, which is governed mainly by the configuration of the proline moiety. Under ball-milling conditions[[11]](#footnote-11), the Michael adducts were obtained in good yields but with slightly lower enantiomeric purities than in solution. DFT calculations confirmed a dual activation mode, which combines enamine activation of aldehydes and hydrogen-bond activation of nitroalkenes.



**Scheme 1: Michael additions of aldehydes to nitroalkenesusing *N*-sulfinyl-*N*’-(pyrrolidinylmethyl)urea and *N*-sulfinyl-*N*’-(pyrrolidinylmethyl)thiourea bifunctional organocatalysts**

Zhang[[12]](#footnote-12) et al. published the first organocatalytic asymmetric synthesis of densely functionalized spiro-*δ*-lactam oxindoles (**Scheme 2)** with multiple stereogenic centers through a [3 + 3] annulation reaction. This protocol provides a metal free, novel, simple and efficient strategy for the synthesis of biologically important spiro-*δ*-lactam oxindoles using a range of substrates, with excellent diastereoselectivities and enantioselectivities (up to >95 : 5 dr and 99% ee).



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

The application of organocatalytic bifunctional activation in the remote (3 + 2)-cycloaddition between 4-(alk-1-en-1-yl)-3-cyanocoumarins and imines derived from salicylaldehyde (**Scheme 3)** is reported by Albrecht group[[13]](#footnote-13). Compounds with two biologically relevant units, have been obtained with good chemical and stereochemical efficiency. The stereochemical outcome of the process results from the application of a quinine-derived catalyst. Selected transformations of the cycloadducts leading to further chemical diversity have been demonstrated.



### **Scheme 3: (3 + 2)-cycloaddition between 4-(alk-1-en-1-yl)-3-cyanocoumarins and imines**

Organocatalytic enantioselective construction of chiral spiro *N*,*N*-acetal carbon stereocenters and axially chiral 3-arylindoles[[14]](#footnote-14) (**Scheme 4)**  has been achieved *via* a chiral phosphoric acid (CPA)-catalyzed (3 + 2) annulation of α-(3-isoindolinonyl) propargylic alcohols with 1-(3-indolyl)naphthalen-2-ols by Xia et al., affording a broad scope of pyrrolo[1,2-*a*]indoles bearing both enantioenriched spiro isoindolinone-indoline and atropisomeric naphthalenol frameworks in 77-95% yields and 73-96% ee.



**Scheme 4:** **Construction of chiral spiro *N*,*N*-acetal carbon stereocenters and axially chiral 3-arylindoles**

Bania[[15]](#footnote-15) group came up with a report on the first catalytic asymmetric inverse-electron-demand Diels–Alder reaction between alkylidene pyrazolones and allyl ketones (**Scheme 5)**. Allyl ketone gets activated by a bifunctional thiourea catalyst and acts as a dienolate in this reaction. The trisubstituted tetrahydropyrano[2,3-*c*]pyrazoles were obtained in moderate to good yields with high diastereo- and enantioselectivities. Few applications, including a decarbonylation reaction, have been demonstrated.



**Scheme 5:** **Diels–Alder reaction between alkylidene pyrazolones and allyl ketones.**

The aza-Friedel–Crafts reaction allows an efficient coupling of electron-rich aromatic systems with imines for the facile incorporation of aminoalkyl groups into the aromatic ring. This reaction has a great scope of forming aza-stereocenters which can be tuned by different asymmetric catalysts. Biswas[[16]](#footnote-16) in his review assembles recent advances in asymmetric aza-Friedel–Crafts reactions mediated by organocatalysts. The mechanistic interpretation with the origin of stereoselectivity is also explained. Sharma coworkers[[17]](#footnote-17) in their article overviews the literature published during the last 10 years concerning the asymmetric aza-Michael reaction of amines and amides catalysed by organocatalysts. Both types of the organocatalysts, i.e., those acting through non-covalent interactions and those working through covalent bond formation have been applied for the asymmetric aza-MR. The review includes the examples wherein cinchona alkaloids, squaramides, chiral amines, phase-transfer catalysts and chiral bifunctional thioureas have been used, which activate the substrates through hydrogen bond formation. Most of these reactions resulted in high yields and high enantiomeric excesses. On the other hand, N-heterocyclic carbenes and chiral pyrrolidine derivatives acting through covalent bond formation such as the iminium ions with the substrates have also been included.

Substituted chiral pyrrolidines represent one of the most common heterocyclic structural motifs that are present in biologically active natural and synthetic compounds[[18]](#footnote-18). Since the advent of organocatalysis, chiral pyrrolidines have assumed a leading position as organocatalysts, as they are able to efficiently promote several different transformations in an enantioselective and environmentally friendly way, avoiding the use of metals.

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



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

The use of proline-based organocatalysts has acquired significant attention in organic synthesis, especially in enantioselective synthesis. Proline and its derivatives are proven to be quite effective chiral organocatalysts for a variety of transformations, including the aldol reaction, which is considered as one of the important C-C bond forming reactions in organic synthesis. A large number of highly efficient proline-based organocatalysts, including polymer-supported chiral analogues, have been identified for aldol reaction. The use of polymer-supported organocatalysts exhibited remarkable stability under the reaction conditions and offered the best results, particularly in terms of its recyclability and reusability. These potential benefits along with their economic and green chemistry advantages have led to the search for many polymer-supported proline catalysts. Shajahan[[21]](#footnote-21) in their review, published recent developments in exploring various polymer immobilized proline- based chiral organocatalysts for asymmetric aldol reactions. In 1971, chemists from Hoffmann-La Roche and Schering AG independently discovered a new asymmetric intramolecular aldol reaction catalyzed by the natural amino acid proline, a transformation now known as the Hajos–Parrish–Eder–Sauer–Wiechert reaction. These remarkable results remained forgotten until List and Barbas reported in 2000 that L-proline was also able to catalyze intermolecular aldol reactions with non-negligible enantioselectivities. In the same year, MacMillan reported on asymmetric Diels–Alder cycloadditions which were efficiently catalyzed by imidazolidinones deriving from natural amino acids. These two seminal reports marked the birth of modern asymmetric organocatalysis. A further important breakthrough in this field happened in 2005, when Jørgensen and Hayashi independently proposed the use of diarylprolinol silyl ethers for the asymmetric functionalization of aldehydes. During the last 20 years, asymmetric organocatalysis has emerged as a very powerful tool for the facile construction of complex molecular architectures. Quintavalla[[22]](#footnote-22) et al. in their review highlights the most recent advances in the asymmetric synthesis of organocatalysts deriving from or related to proline, starting from 2008.

Thiourea-based iminophosphorane (BIMP) organocatalysts featuring SPhos- or BIDIME phosphine units have been developed and successfully applied in the asymmetric addition of nitromethane to *N*-Boc-protected trifluoromethyl aryl ketimines (**Scheme 7)** by Sanz coworkers[[23]](#footnote-23) under mild conditions with no need of additional base. α-Trifluoromethyl β-nitroamines were obtained in 40–82% isolated yields and 80–95% enantioselectivities. A careful evaluation of the catalytic activity of BIMPs indicates that the catalysts derived from the combination via Staudinger 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, leading to the amine featuring a tetrasubstituted stereocenter in up to 95% ee. The reaction was performed also on gram scale, without loss of enantioselectivity. BIMP acted as superbase as well as H-bond donor.



**Scheme 7:** **Asymmetric addition of nitromethane to *N*-Boc-protected trifluoromethyl aryl ketimines using Thiourea-based iminophosphorane (BIMP) organocatalysts.**

Michael addition/alkylation reaction between 3-chlorooxindoles and α-cyano chalcones catalyzed by quinine-derived aminoindanol-thiourea (**Scheme 8)** was investigated by Wang coworkers[[24]](#footnote-24). A series of spirooxindoles incorporating a densely substituted cyclopropane motif were efficiently obtained with moderate to excellent diastereo- and enantioselectivity and further transformed to products with versatile structural diversity. Density functional theory (DFT) calculations indicated that the tentative intramolecular hydrogen bonds in the chiral catalyst were crucial for the stereocontrol.



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

Lattanzi[[25]](#footnote-25) in her report discussed on their achievements, on asymmetric methodologies to access novel three, five, six membered heterocycles, including spiro compounds bearing quaternary stereocenters. The cascade combinations of Michael and aldol reactions allowed them to expand the panel of compounds from tetrahydrothiophenes and lactones to hybrid scaffolds embedding key heterocyclic units at the spirocenter. Taking advantage of synergistic visible light photocatalysis with organocatalysis, remarkable progress has recently been achieved in modern chemical synthesis. In these dual catalytic systems, photocatalysts or photosensitizers absorb visible light to induce their photo-excited states which can activate unreactive substrates via electron or energy transfer mechanisms, and organocatalysts are usually employed to control the chemical reactivities of the other substrates. Shen et al. in their review[[26]](#footnote-26) mainly focuses on the recent development of cooperative catalysis by the combination of organocatalysis and photocatalysis in recent organic synthesis. Review by Hughes[[27]](#footnote-27) coworkers explores contributions in asymmetric organocatalysis from the patent literature since 2018, including reactions catalyzed by *Cinchona* alkaloids as free base and quaternary salts, phosphonium salts, proline-derived catalysts, and chiral phosphoric acids. Examples of processes employing asymmetric organocatalysis for the industrial preparation of pharmaceutical intermediates are highlighted. By focusing on pregabalin, as a case study, Giorgianni et al. in their perspective[[28]](#footnote-28) aims to show how a process amenable to industry of a simple chiral molecule can be tackled in several different ways using organocatalysis. Chiral primary α-amino amides, consisting of an adjacent enamine bonding site (Bronsted base site), a hydrogen bonding site (Bronsted acid site), and flexible bulky substituent groups to modify the steric factor, are proving to be extremely valuable bifunctional organocatalysts for a wide range of asymmetric organic transformations. Primary α-amino amides are less expensive alternatives to other primary amino organocatalysts, such as chiral diamines and cinchona-alkaloid-derived primary amines, as they are easy to synthesize, air-stable, and allow for the incorporation of a variety of functional groups. In recent years, Reddy group[[29]](#footnote-29) have demonstrated the catalytic use of simple primary α-amino amides and their derivatives as organocatalysts for the aldol reaction, Strecker reaction, Michael tandem reaction, allylation of aldehydes, reduction of N-Aryl mines, opening of epoxides, hydrosilylation, asymmetric hydrogen transfer, and N-specific nitrosobenzene reaction with aldehydes.

In their review, Reyes et al.[[30]](#footnote-30) highlighted the application of organocatalysis in the synthesis of enantio-enriched molecules that may be of interest to the pharmaceutical industry and the medicinal chemists[[31]](#footnote-31).

**CONCLUSION**

In the 21st century, organic chemistry faces new development opportunities. 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 selected advanced recent examples underscoring the diversity and potential of this still growing and vibrant field.

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