Review Article

Status of Asymmetric Catalysis in India during the Last Ten Years

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Asymmetric catalysis is one of the emerging techniques where a catalytic amount of molecule containing chiral information can catalyse the transformation of a pro-chiral substrate into the major enantiomer. These catalytic asymmetric processes decreased drastically cost and time associated with the preparation of chiral intermediates. Based on these applications, asymmetric catalysis emerged as the most promising area in the synthesis of optically active compounds, as those are important intermediates in medicinal to material chemistry.

The design of asymmetric catalysts, and practices in both academia and industry have considerably increased in recent years in India. The interest shown by our asymmetric catalysis practitioners and researchers is largely reflecting the global trend towards the both metal- and metal-free approaches comprising variety of enantioselective bond formations, which can help in accomplishing the economical and ideal synthesis of natural products, drugs and agrochemicals.

Herein, we have compiled the recent developments in asymmetric catalysis in India during the last one decade.

Keywords: Asymmetric Catalysis; Organocatalysis; C-C Bond Formation; Weak Interactions; Supramolecular Assembly; Singh's Catalyst; L-Proline

Introduction

Evolution of organic chemistry comprises of commencement from the isolation of natural products and growing further up to development of many organic materials. In this process of evolution, organic chemistry has witnessed numerous protocols for various organic reagents, a variety of organic synthetic transformations, a range of natural product synthesis

and catalytic asymmetric synthesis of various complex scaffolds. In all these, the terrain of catalytic asymmetric synthesis is vast and continuously thriving and has seen enormous growth in different directions like enzyme-catalysis, metal/chiral ligand-catalysis, iminium- and enamine-catalysis, *NHC*-catalysis, etc. Even though the initial growth of catalytic asymmetric synthesis (for example incidences of discovery of

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Noyori asymmetric hydrogenation and Sharpless asymmetric epoxidation) was slow, it took off exponentially in the last one decade. As an evidence of this, we might have observed mushrooming of large number of pharmaceutical companies that are catering to many societal needs by using many of these catalytic asymmetric reactions. The contribution made by the Indian researches to this field of catalytic asymmetric synthesis is substantial. Herein, we are attempting to present the contribution made by the Indian scientists to the development of catalytic asymmetric synthesis during the last one decade.

Results and Discussion

From last 23 years, Singh's group (Bisai *et al.*, 2012) developed many useful catalytic asymmetric reactions by using both metal and metal-free approaches. Especially, in the last one decade he has developed excellent catalytic asymmetric protocols for the synthesis of aldol and Michael adducts by using his own lab-made prolinamide organocatalysts and later on the prolinamide organocatalyst was widely used by many other groups also and became famous as Singh's catalyst.

Singh's group demonstrated that small organic molecules such as **3a** and **3b**, which are the Singh's catalyst, could function as highly efficient organocatalysts for asymmetric List-Lerner-Barbas (LLB) aldol reaction of both acyclic and cyclic ketones **1** with different aldehydes **2** in an aqueous medium (Maya *et al.*, 2007). In most of the cases, >99% *ee* was achieved by using 0.5 mol % of the Singh's catalyst in brine. Stereochemical outcome of the reaction was explained by the transition state **TS-1** as shown in Scheme 1, which is based on a previous model supported by DFT calculations. Through hydrogen bonding with NH and OH of the catalyst, the aldehyde **2** gets activated, in a manner such that C-C bond formation takes place from its *Re*-face. The reaction was discussed to take place under biphasic basic conditions with hydrophobic effect, where the organocatalyst and substrates assembled in water and sequestered the transition state **TS-1** from water. The organic molecules aggregated by excluding water from the organic phase, thereby driving the equilibrium toward the enamine formation. Added advantage of the catalyst was that it did not require any acid additive to achieve high

Scheme 1: Singh's small organic molecule catalysed LLB-aldol reaction of acyclic and cyclic ketones with different aldehydes in brine

enantioselectivity (Maya *et al.*, 2007). After this work, this catalyst became popular as Singh's catalyst in the area of catalytic asymmetric organocatalysis.

In 2014, Singh's group (Bisai *et al.*, 2014) reported a CuI-pybox-diPh (**Cu^I-8**)-catalysed highly enantioselective alkynylation/lactamization cascade for the synthesis of diversely substituted isoindolinones **9**, which are having immense biological importance (Scheme 2, Bisai *et al.*, 2014). The cascade effected one C-C and two C-N bond-forming events in one reaction vessel in good to excellent yields and *ee*'s. Furthermore, the methodology was extended to the synthesis of optically pure tetrahydroisoquinoline scaffolds in a two-step sequence (Bisai *et al.*, 2014).

Scheme 2: Singh's approach of CuI-pybox-diPh (**Cu^I-8**)-catalysed highly enantioselective alkynylation/lactamization cascade for the synthesis of diversely substituted isoindolinones

For the last 15 years, Ramachary's group (Ramachary *et al.*, 2011) developed many catalytic sequential one-pot reactions to construct achiral and

Scheme 3: Ramachary's approach of *D*-proline 11-quinine thiourea **12** as supramolecular-organocatalyst for asymmetric Michael addition of ketone **1** to *ortho*-hydroxy nitrostyrenes **10**

chiral molecules, which are useful in natural products synthesis, pharmaceuticals and agrochemicals. During the evolution of these sequential one-pot reactions, they have discovered few original organocatalytic asymmetric reactions which are used as key reactions in the development of the sequential one-pot reaction cascades.

In 2012, Ramachary *et al.* designed a new and efficient supramolecular catalytic system for the asymmetric Michael reaction of cyclohexanone with functionally rich 2-(2-nitrovinyl)phenols **10** to give the desired hexahydroxanthenols **13** with high yield, *ee* and *de* values (Scheme 3, Ramachary *et al.*, 2012). The authors provided strong evidence for the existence of the proposed 19-membered cyclic *pre*-TS supramolecular assembly, through on-line monitoring by using ESI-HRMS technique. They explained that the reaction most likely proceeded through the transition state **TS-2** (Scheme 3), with four important interactions among the substrates and the catalysts namely, carboxylic group of *D*-proline **11** undergoing proton exchange with quinoline moiety of quinine thiourea **12**, two NH groups of quinine thiourea **12** hydrogen bonding with NO_2 group of 2-(2-nitrovinyl)phenol **10**, secondary amine group of *D*-proline **11** forming *syn*-enamine with cyclohexanone and lastly phenolic OH group of 2-(2-nitrovinyl)phenol **10** protonating carbonyl group of *D*-proline **11**, consequently forming the rigid 19-membered

Scheme 4: Ramachary's *reflexive*-Michael (*r*-M) reaction for accessing drug-like six-membered spirooxindoles employing aminoenyne-catalysis

supramolecular cyclic *pre*-TS to control the facial selectivity. This work initiated the study of *pre*-TS of catalytic asymmetric reactions through supramolecular organocatalysis, and will become fourth dimension of asymmetric catalysis (Ramachary *et al.*, 2012).

Subsequently in 2013, Ramachary's group discovered an organocatalytic asymmetric *reflexive*-Michael (*r*-M) reaction between unmodified ynones **16** and 2-(2-oxindolin-3-ylidene)malononitriles **17** to access functionalized chiral six-membered spirooxindoles **19** in good yields and excellent enantio selectivities by using aminoenyne-catalysis (Scheme 4, Ramachary *et al.*, 2013). *epi*-Quinine- NH_2 **18** as catalyst and 2- $\text{FC}_6\text{H}_4\text{CO}_2\text{H}$ as co-catalyst were used for the reaction in toluene at room temperature. Ynones **16** were selectively transformed *in situ*, into 2-aminobuta-1,3-enynes, which participated as mild nucleophiles in the *r*-M reaction to furnish the products. The reaction proceeded by a stepwise manner between the *in situ* generated 2-aminobuta-1,3-enynes and the olefins **17**. Rationalization for the high stereoselectivity of the products formed was provided with the help of the transition state **TS-3** where the *Si*-face of **17** approached the *Si*-face of 2-aminobuta-1,3-enynes (aminoenynes) due to the strong hydrogen-bonding/electrostatic attraction/ $\text{CH}\cdots\pi$ and halogen (F)- π interactions and less steric hindrance/electrostatic repulsion as shown in Scheme 4 (Ramachary *et al.*, 2013). *In situ* generation and study of 2-aminobuta-1,3-enynes as key intermediates in asymmetric catalysis will become one of the branches in asymmetric organocatalysis soon.

Scheme 5: Chandrasekhar's method of synthesis of enantiopure cyclohexane fused tetrahydropyrans using domino Michael-ketalization under organocatalysis

In 2009, Chandrasekhar *et al.* reported a synthesis of enantiopure tetrasubstituted cyclohexane fused tetrahydropyrans **22** using domino Michael-ketalization of cyclohexanone **1a** with various hydroxymethyl nitro-olefins **20** under organocatalysis (Scheme 5, Chandrasekhar *et al.*, 2009). Excellent diastereocontrol and enantioselectivity were observed in the presence of 20 mol% of chiral pyrrolidine-triazole **21** as catalyst, and 10 mol% of TFA as co-catalyst under the solvent free conditions. Based on the literature precedence, the authors have provided a plausible transition state **TS-4**, to explain the stereocontrol and specificity of the reaction (Scheme 5, Chandrasekhar *et al.*, 2009).

Scheme 6: Kantham's protocol for asymmetric hydrosilylation of ketones using nano-CuO in the presence of chiral ligand

In 2007, Kantham's group described an asymmetric hydrosilylation of aryl alkylketones **1** to afford chiral secondary alcohols **24** with good yields and excellent enantioselectivity by using nanocrystalline copper(II) oxide and (*S*)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP, 5 mol %) in the presence of organosilanes as stoichiometric reducing agent (Scheme 6, Kantam *et al.*, 2007). PhSiH₃ was the most active reducing agent with this

catalytic system and toluene was the best solvent both in terms of product yield and *ee*. The higher enantioselectivity of the products was correlated to the smaller crystallite size which effectively complexes with the chiral auxiliary. The authors have performed catalyst recycle experiments to prove that the nano-CuO catalyst can be reused for several cycles without loss of activity and selectivity (Kantam *et al.*, 2007).

Scheme 7: Chimni's technique for synthesis of chiral 3-aminooxindoles through chiral squaramide-catalysed enantioselective decarboxylative addition of β -keto acids to isatin imines

For the last one decade, Chimni and co-workers were continuously working to develop sustainable asymmetric reactions by using organocatalysts. Recently in 2017, Chimni *et al.*, divulged an efficient chiral squaramide-catalysed enantioselective decarboxylative addition of various β -keto acids **26** to isatin iminederivatives **25** to afford the chiral 3-aminooxindole derivatives **28** in high yield and excellent enantioselectivities (Scheme 7, Kaur *et al.*, 2017). A wide range of substituted isatinimines **25** and β -keto acids **26** reacted well under optimized reaction conditions. The authors have proposed a transition state model to rationalize the stereochemistry of the product. The NH of the squaramide catalyst **27** seems to activate and orient isatinimine **25** through double H-bonding, while the β -ketoacid **26** gets activated by the tertiary amine of the catalyst **27** through decarboxylation. Finally, *Re*-face addition of the decarboxylated β -keto acid enolate to the activated isatinimine **25** via the transition state **TS-5** results in the formation of the (*S*)-configured 3-aminooxindole products (Kaur *et al.*, 2017).

Scheme 8: Moorthy's process of organocatalysed Biginelli cyclocondensation of aromatic and aliphatic aldehydes with ethyl acetoacetate and urea

Moorthy and co-workers developed interesting organocatalysts based on sterics and hydrogen-bonding, as best catalysts for high asymmetric induction in LLB-aldol and Michael reactions (Saha and Moorthy, 2011). In 2011, Moorthy and co-workers carried out an extensive systematic investigation involving the synthesis of a series of catalysts, screening studies and emerged with the sterically hindered organocatalyst **30** as the best catalyst. Organocatalyst **30** contains a strong hydrogen-bonding site, which is reinforced with chirality and is shown to promote the Biginelli cyclocondensation of aromatic as well as aliphatic aldehydes with ethyl acetoacetate and urea so as to furnish dihydropyrimidinones **31** (DHPMs) in remarkably high enantioselectivity (Scheme 8, Saha and Moorthy, 2011). As presented in the transition state **TS-6**, the essential step responsible for the stereo induction constitutes the attack of the (*E*)-enamine-ester derived from the catalyst **30** and the β -ketoester **29** on to the *Re*-face of the iminoamide formed in situ between the carbonyl compound **2** and urea.

Scheme 9: Pradeep Kumar's method for asymmetric synthesis of both *anti*-/syn-1,3-amino alcohols **33a**/**33b** using proline-catalysed sequential α -aminooxylation/ α -amination and Horner-Wadsworth-Emmons (HWE) olefination of aldehydes as the key step

For nearly a decade now, Pradeep Kumar's team has been working on asymmetric synthesis, accomplishing total synthesis of many natural products, through organocatalytic asymmetric approaches. In 2010, Pradeep Kumar and his group published a novel and general method for asymmetric synthesis of both *anti*-/syn-1,3-amino alcohols **33a**/**33b** from commercially available and inexpensive starting materials (Scheme 9, Jha *et al.*, 2010). They have utilised sequential proline-catalysed α -aminooxylation/HWE-olefination/olefin reduction/alcohol protection/ester reduction/proline-catalysed α -amination/Horner-Wadsworth-Emmons (HWE) olefination of aldehydes **2** as the key steps. By using this sequential method the authors accomplished, a short synthesis of the bioactive molecule, (*R*)-1-((*S*)-1-methylpyrrolidin-2-yl)-5-phenylpentan-2-ol (Jha *et al.*, 2010).

In 2014, Namboothiri *et al.* disclosed cascade reactions of 1,3-dicarbonyls **34** including 2-hydroxy-1,4-naphthoquinone (lawsone), with Morita-Baylis-Hillman acetates of nitroalkenes **35** using a quinine derived chiral squaramide organocatalyst **27** for the formation of pyrans and dihydropyranonaphthoquinones (lapachones) **36** in good to excellent yields and high diastereo and enantioselectivities (Scheme 10, Nair *et al.*, 2014). The authors claim that the transformation involves an S_N2'-intramolecular *oxa*-Michael addition sequence and is amenable for scale-up even with a very low catalyst

Scheme 10: Namboothiri's way of chiral squaramide-catalysed asymmetric synthesis of pyranones and pyranonaphthoquinones via cascade reactions of 1,3-dicarbonyls with Morita-Baylis-Hillman acetates of nitroalkenes

loading (1 mol%) without an appreciable loss in yield or selectivity. In the plausible mechanism furnished by the authors, using lawsone and MBH acetate was outlined in **TS-7**. The first step was initiated by deprotonation of lawsone by the tertiaryamine of the quinuclidine moiety resulting in an enolate, which then adds to the MBH acetate from the *Si*-face in a Michael fashion. Stereoselective Michael reaction is induced by activation of the nitrogroup by double H-bonding with the squaramide moiety of the chiral catalyst **27**, which then leading to elimination of the acetate in the overall S_N2' reaction (Nair *et al.*, 2014). In the second step (not shown here), the enolate generated from the carbonyl group adds to the *in situ* generated nitroalkene activated by the squaramide moiety from the *Re*-face in a 6-*endo*-trig intramolecular *oxa*-Michael fashion, giving rise to the desired dihydropyrans.

Kesavan's group has been working consistently on asymmetric catalysis, since last few years, through both metal and organocatalytic approaches resulting in construction of fascinating and complex structures. In 2016, Kesavan's group published an efficient, organocatalytic, inverse-electron demand hetero-Diels-Alder reaction of isatylidene β,γ -unsaturated α -ketoesters **37** with cyclic β -oxoaldehydes **38** for the synthesis of diverse bispiro-3,4-dihydropyrans **40** consisting of oxindole moieties with three contiguous chiral centers and vicinal quaternary stereocenters in very good yields of up to 92% and excellent enantioselectivity of up to 99% *ee* by using a proline-derived thiourea organocatalyst **39** (Scheme 11, Vishwanath *et al.*, 2016). The dihydropyran-oxindole

Scheme 11: Kesavan's process of asymmetric synthesis of bispiro-3,4-dihydropyrans consisting of oxindole moieties with three contiguous chiral centers and vicinal quaternary stereocenters using a proline-derived thiourea organocatalyst

architecture **40** containing two adjacent spiro rings has been efficiently constructed.

For the last one decade, Mukherjee's group developed a few excellent asymmetric reactions using metal-free organocatalysts. In 2013, Mukherjee *et al.* accomplished the first catalytic asymmetric iodoetherification of oximes with the help of the bifunctional thiourea catalyst **42a** (Scheme 12, Equation 1, Tripathi and Mukherjee, 2013). A variety of β,γ -unsaturated ketoximes **41** were cyclized using commercially available *N*-iodosuccinimide (NIS) to furnish Δ^2 -isoxazolines **43** containing a quaternary stereogenic center in high yield with good to excellent enantioselectivity. An oxime having aliphatic substitution on the olefin was an active substrate for the reaction and aromatic substitution on the oxime carbon atom appears to be essential for achieving a good level of enantioselectivity (Tripathi and Mukherjee, 2013).

Scheme 12: Mukherjee's method of catalytic asymmetric iodoetherification of oximes using bifunctional thiourea catalyst

Very recently, the same group reported the first catalytic enantioselective synthesis of 5,6-dihydro-4*H*-1,2-oxazines **45** bearing an oxygen-containing quaternary stereogenic center through iodoetherification of γ,δ -unsaturated oximes **44** (Scheme 12, Equation 2, Suresh *et al.*, 2018). The reaction was catalysed by the cinchona alkaloids-based bifunctional tertiary aminothiurea **42b** and furnished the products in good to excellent yields with

moderate to high enantioselectivities (Suresh *et al.*, 2018).

In 2015, Mukherjee and co-workers disclosed an excellent organocatalytic enantioselective formal C(sp²)-H alkylation *via* desymmetrization on prochiral 2,2-disubstituted cyclopentene-1,3-diones **46** (Scheme 13, Equation 1, Manna and Mukherjee, 2015). The reaction was catalysed by the bifunctional tertiary amino-urea derivative **48a**, utilizing air-stable and inexpensive nitroalkanes **47** as the alkylating agents to deliver the five-membered carbocycles **49** containing an all-carbon quaternary stereogenic center remote from the reaction site in excellent enantioselectivity (Manna and Mukherjee, 2015).

In 2016, based on the very same C(sp²)-H alkylative desymmetrization approach, Mukherjee *et al.* discovered a new way for the enantioselective synthesis of monosubstituted quinone-DA adducts **51** from *meso*-DA adducts **50** (Scheme 13, Equation 2, Sarkar and Mukherjee, 2016). In this case, the reaction

Scheme 13: Mukherjee's method of organocatalytic enantioselective formal C(sp²)-H alkylation *via* desymmetrization of prochiral 2,2-disubstituted cyclopentene-1,3-diones and norbornenoquinones catalysed by bifunctional tertiary amino-urea derivatives

was catalysed by the tertiary amino-thiourea derivative **48b**, to generate densely functionalized products **51** bearing at least four contiguous stereogenic centers in moderate to good yields with excellent enantioselectivities (Sarkar and Mukherjee, 2016).

In 2016, Biju *et al.* demonstrated an enantioselective synthesis of pyrazolone-fusedspirocyclohexadienones **56** by the reaction of α,β -unsaturated aldehydes **52** with α -arylidene pyrazolinones **53** under oxidative *N*-heterocyclic carbene (NHC)-catalysis (Scheme 14, Yetra *et al.*, 2016). This formal [3+3] annulation reaction proceeded through a vinylogous Michael addition/spiroannulation/dehydrogenation cascade to afford the spirocyclic compounds **56** with an all-carbon quaternary stereocenter in moderate to good yields and excellent *ee* values. A plausible mechanism for this NHC-catalysed spiroannulation reaction, explained by the authors is presented in Scheme 14. First, the

Scheme 14: Biju's technique of enantioselective synthesis of spirocyclohexadienones by NHC-catalysed formal [3+3] annulation reaction of enals

carbene generated from the chiral triazolium salt **54** undergoes 1,2-addition to enal **52** followed by proton transfer to generate the nucleophilic Breslow intermediate **57**. The enaminol **57** in the presence of oxidant **55** generated the key chiral α,β -unsaturated acyl azolium intermediate **58**. Vinylogous Michael addition of the dienolate intermediate

(generated from the α -arylidene pyrazolinone **53**) to the α,β -unsaturated acyl azolium **58** generated the *NHC*-bound enolate intermediate **59**, which upon intramolecular proton transfer generated the acyl azolium **60**. Further, intramolecular enolate C-acylation resulted in the formation of spiropyrazolone with regeneration of the free carbene. In the presence of excess oxidant **55**, spiropyrazolone afforded the spirocyclohexadienone product **56** (Yetra *et al.*, 2016).

In 2015, Patil *et al.* reported catalytic enantioselective hydroamination-hydroarylation of alkynes under the catalysis of $(R_3P)AuMe$ **63**/(*S*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate **64** ((*S*)-TRIP) as represented in Scheme 15 (Shinde *et al.*, 2015). The alkyne **62**

Scheme 15: Patil's way of gold(I)/chiral Brønsted acid catalysed enantioselective hydroamination-hydroarylation of alkynes

was reacted with a range of pyrrole-based aromatic amines **61** to give pyrrole-embedded *aza*-heterocyclic scaffolds **65** bearing a quaternary carbon center. The presence of a hydroxyl group in the alkyne tether was found to be very crucial for obtaining products in high yields and enantioselectivities (Shinde *et al.*, 2015).

In 2016, Ghorai and co-workers revealed an excellent sequential dearomatization/enantioselective intramolecular *oxa*-Michael reaction of *in situ* generated 4-hydroxyl cyclohexadienones **67** using cinchona-alkaloid-based chiral bifunctional squaramide catalyst **68** (Scheme 16, Reddy *et al.*, 2016). The reaction sequence provided a broad array of chiral sterically hindered tetrahydrofurans and tetrahydropyrans attached to a cyclohexadienone

Scheme 16: Ghorai's approach of organocatalysed enantioselective synthesis of cyclohexadienone containing spirocyclic ethers through oxidative dearomatization/*oxa*-Michael addition sequence

moiety **69** inspiro-fashion in good yields and excellent enantioselectivities (Reddy *et al.*, 2016).

Recently, Reddy *et al.* developed an organocatalysed asymmetric conjugate addition of 2-substituted 3-indolinones **70** to maleimides **71** using chiral bifunctional squaramide catalyst **72** derived from quinidine (Scheme 17, Yarlagadda *et al.*, 2018).

Scheme 17: Reddy's protocol for accessing 3-indolinone-2-carboxylate-succinimide adducts through organocatalytic enantioselective Michael addition of 2-substituted 3-indolinones to maleimides by using a chiral bifunctional squaramide derived from quinidine

The reaction generated 3-indolinone-2-carboxylate-succinimide adducts **73** in high yields with excellent diastereo and enantioselectivities. The authors elucidated the observed selectivity by the 3-indolinone-2-carboxylate attacking the *Re* face of the maleimide **71** as shown in the *pre*-transition state of **TS-8** (Yarlagadda *et al.*, 2018).

In 2015, Indresh Kumar *et al.* described a one-pot formal [4+2]-cycloaddition approach for enantioselective synthesis of *N*-PMP-1,2-dihydropyridines (DHPs) **76** from the readily available aldimines **75** and aqueous glutaraldehyde **74** (Scheme 18, Ramaraju *et al.*, 2015). The reaction proceeded

Scheme 18: Indresh Kumar's process for enantioselective synthesis of *N*-PMP-1,2-dihydropyridines (DHPs) using amino-catalytic direct List-Barbas-Mannich reaction/cyclization followed by IBX mediated chemo- and regioselective oxidation sequence

through proline-catalysed direct List-Barbas-Mannich reaction/cyclization followed by an IBX-mediated chemo- and regioselective oxidation sequence. A series of *N*-PMP-1,2-DHPs were prepared in high yields and excellent enantioselectivities. Both the enantiomers of 1,2-DHPs were accessible by shifting the catalyst configuration (Ramaraju *et al.*, 2015).

In 2016, Ramasastry and co-workers reported the first enantioselective organocatalytic intramolecular Morita-Baylis-Hillman (IMBH) reaction of sterically highly demanding β,β -disubstituted enones (Satpathi and Ramasastry, 2016). The IMBH reaction of β,β -disubstituted- α,β -unsaturated electronwithdrawing systems, generated a variety of cyclopenta[*b*]annulated arenes and heteroarenes **79** in excellent enantiopurities and near-quantitative yields in short reaction times (Scheme 19, Equation 1). The bifunctional organocatalyst **78a** only in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) delivered the desired products in excellent enantiomeric excesses and yields. It is noteworthy to mention that the enantioinduction was observed only in HFIP solvent. The authors attributed the success of the reaction to extraordinary level of synergism between the *ortho* functionalities, bifunctional catalyst, and the fluorinated solvent as shown in **TS-9** (Satpathi and Ramasastry, 2016).

Consequently, in 2017, the same group extended the enantioselective organocatalytic IMBH reaction to the dienones **80** and realized the formation of highly

functionalized cyclopenta-fused arenes and heteroarenes **81** in excellent yields and enantioselectivities (Scheme 19, Equation 2, Satpathi *et al.*, 2017).

Scheme 19: Ramasastry's way of synthesis of highly functionalized cyclopenta-fused arenes and heteroarenes utilizing enantioselective organocatalytic intramolecular Morita-Baylis-Hillman (IMBH) reaction of enones and dienones

Very recently, Pan *et al.* developed an organocatalytic asymmetric domino Michael/acyl transfer reaction between γ/δ -hydroxyenones **83/85** and α -nitroketones **82** using the cinchona alkaloid derived bifunctional amino-squaramide catalyst **27** to furnish products having nitro, keto, and ester functionalities (Scheme 20, Mondal and Pan, 2018).

Scheme 20: Chandra Pan's method of organocatalytic asymmetric domino Michael/acyl transfer reaction between γ/δ -hydroxyenones and α -nitroketones in the presence of cinchona alkaloid derived bifunctional amino-squaramide catalyst

The reaction proceeded through conjugate addition and consequent acyl transfer to deliver a range of 2-(nitromethyl)-4-oxo-4-arylbutyl benzoates **84** and 3-(nitromethyl)-5-oxo-5-arylpentylbenzoates **86** in high yields and with excellent enantioselectivities (Mondal and Pan, 2018).

Bisai's group has done an extensive work in the area of total synthesis of alkaloids, synthesizing diverse intermediates and many natural products utilizing various organocatalytic asymmetric reactions. In 2015, Bisai and co-workers achieved the total syntheses of spiro-(pyrrolidinyl-oxindole) alkaloids, (+)-coerulescine (**90**) and (+)-horsfiline (**91**), and hexahydropyrrolo[2,3-b]indole alkaloids, (-)-deoxyeseroline (**92**) and (-)-esermethole (**93**) sharing an all-carbon quaternary stereocenter, utilizing an organocatalytic asymmetric aldol reaction in the presence of the thiourea catalyst **88** (Scheme 21, Equation 1, De *et al.*, 2015). The same strategy was also employed for the first total syntheses of architecturally interesting prenylated pyrroloindole alkaloids, (-)-pseudophrynamines 272A and 270 (De *et al.*, 2015).

Scheme 21: Bisai's route to synthesis of spiro (pyrrolidinyl-oxindole) alkaloids **90** and **91** and hexahydropyrrolo[2,3-b]indole alkaloids **92** and **93** and the enantioenriched tetracyclic core **96** of ergot alkaloids *via* organocatalytic asymmetric aldol reaction

Similarly in 2018, the same group developed a route for the enantioselective synthesis of the tetracyclic skeleton **96** of ergot alkaloids *via* the key organocatalytic enantioselective aldol reaction followed by a key Pd-catalysed directed coupling accelerated by the DavePhos ligand (Scheme 21,

Equation 2, Bhunia *et al.*, 2018). With this strategy they were able to synthesize the key tetracyclic intermediate in up to 95% *ee* with high yield (Bhunia *et al.*, 2018).

In 2010, Sudalai *et al.* reported the hydrolytic kinetic resolution (HKR) of racemic *syn*- or *anti*-alkoxy- and azido-epoxides ($\pm$)-**97** catalysed by Co(salen) complex **98** to afford a series of enantioenriched *syn*- or *anti*-alkoxy- and azido-epoxides **97** and the corresponding 1,2-diols **99** (Scheme 22, Reddy *et al.*, 2010). The authors successfully employed the strategy in a concise, enantioselective synthesis of bioactive molecules such as (*S,S*)-reboxetine and (+)-*epi*-cytoxazone. The reaction was conveniently carried out under mild conditions and displayed a wide range of substrate scope (Scheme 22, Reddy *et al.*, 2010).

Scheme 22: Sudalai's method of Co(III)(salen)-catalysed hydrolytic kinetic resolution (HKR) of two stereocentered alkoxy- and azido-epoxides

In 2009, Sekar and co-workers developed an efficient, economic and environmentally friendly enantioselective oxidation of racemic benzoin (α -hydroxy ketones) **100** catalysed by a chiral iron complex using molecular oxygen as a terminal oxidant in the presence of 5 mol% of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), with good selectivity and excellent enantiomeric excess, resulting in kinetic resolution of secondary alcohols under mild reaction conditions (Scheme 23, Muthupandi *et al.*, 2009).

In 2014, Ramanathan and co-workers designed and synthesized the conformationally rigid chiral bicyclic (CRCB) skeleton-tethered bipyridine *N,N'*-dioxide **104** and utilized it as an organocatalyst in the enantioselective ring opening of *meso*-epoxides using

Scheme 23: Sekar's method of chiral iron complex catalysed enantioselective oxidation of racemic benzoin **100**, thereby achieving oxidative kinetic resolution

tetrachlorosilane (SiCl_4) in chloroform at 30°C (Scheme 24, Gnanamani *et al.*, 2014). The catalyst was found to exhibit good enantioselectivity for substituted *cis*-stilbene epoxides and the saturated cyclic *meso*-epoxides displayed moderate enantioselectivity. With 0.5 mol% loading of the catalyst, the chlorohydrins **105** were generated in up to 97% yield and up to 93% *ee*. The possible creation of transient axial chiral environment around hypervalent silicon species due to the presence of conformationally rigid chiral bicyclic skeleton-tethered bipyridine *N,N'*-dioxide was anticipated to be responsible for the enantioselectivity observed in the desymmetrization of *meso*-epoxides (Scheme 24, Gnanamani *et al.*, 2014).

Scheme 24: Ramanathan's conformationally rigid chiral bicyclic skeleton-tethered bipyridine *N,N'*-dioxide **104** as organocatalyst for asymmetric ring opening of *meso*-epoxides

In 2009, Ghosh *et al.* accomplished an organocatalytic asymmetric Michael addition of alkyl

methyl ketones to a silylalkylidene malonate **106**, in the presence of a combination Barbas catalyst (*S*)-*N*-(2-pyrrolidinylmethyl)pyrrolidine **107**/trifluoroacetic acid, with high regio- and enantioselectivity (Scheme 25, Chowdhury *et al.*, 2009). The silyl group seemed to have played crucial roles in regioselection and substrate reactivity.

Scheme 25: Ghosh's approach for highly regio- and enantioselective organocatalytic conjugate addition of alkyl methyl ketones to β -silylmethylene malonate **106**

In 2012, Peddinti and co-workers reported synthesis of some prolinamide organocatalysts in high yields and demonstrated the catalytic activity of these sugar-based prolinamide organocatalysts in asymmetric List-Lerner-Barbas-aldol (LLB-aldol) reactions in various solvents and at different temperatures (Scheme 26, Agarwal *et al.*, 2012). The organocatalyst **109** was found to be an efficient and powerful organocatalyst for the enantioselective LLB-aldol reaction of various cyclic or acyclic ketones with aromatic aldehydes and the corresponding LLB-aldol adducts **4** were obtained with high levels of diastereoselectivity (up to 99:1) and enantioselectivity (up to 99%) in very good yields.

Scheme 26: Peddinti's method of application of sugar-based prolinamides as organocatalyst in asymmetric List-Lerner-Barbas-aldol (LLB-aldol) reaction

In 2017, Hajra and his group developed a quinine-derived trifunctional sulphonamide catalyst **111** for the effective asymmetric organocatalytic tandem *aza*-

Henry reaction-cyclization of isatin-derived ketimines **25** and nitroalkane-mesylates **110** for the asymmetric synthesis of spiro-pyrrolidine/piperidine-oxindoles **112** in very good yields and selectivity (Scheme 27, Hajra *et al.*, 2017). The increase in yield and enantioselectivity achieved was attributed to the additional hydrogen bonding C6'-OH group installed in the catalyst.

Scheme 27: Hajra's quinone-based trifunctional organocatalyst for tandem α -Henry reaction-cyclization toward asymmetric synthesis of spiroindole-pyrrolidine/piperidines

In 2013, Kumaraswamy *et al.* developed a method for preparing stereodefined δ -/ γ -alkoxy- β -hydroxy- α -alkyl-substituted Weinreb amides **115** containing two successive hydroxyl-alkyl stereocenters, through a catalytic dynamic kinetic resolution-asymmetric transfer hydrogenation (DKR-ATH) reaction (Scheme 28, Kumaraswamy *et al.*,

Scheme 28: Kumaraswamy's approach of enantioselective synthesis of δ -/ γ -alkoxy- β -hydroxy- α -alkyl-substituted Weinreb amides via dynamic kinetic resolution-asymmetric transfer hydrogenation (DKR-ATH)

2013). The striking feature that was revealed in the investigation was the necessity of δ - or γ -benzyloxy or alkoxy substitution in the substrates ($\pm$)-**113** for the reaction to proceed. Further, the authors coupled this strategy with organocatalysed asymmetric

epoxidation thereby culminating the synthesis of a critical intermediate of (-)-brevisamide and its diastereomers.

In 2015, Ravi P. Singh *et al.* reported an asymmetric vinylogous Michael reaction of 2-silyloxyfuran **117** to cyclohexenone, medium and large cyclic enones **116** catalysed by the chiral primary diamine **118** to provide *syn*-Michael adducts (cycloalkane connected γ -butenolide) with contiguous tertiary followed by quaternary stereocenters with good yields, diastereo and enantioselectivities (Scheme 29, Jadhav *et al.*, 2015).

Scheme 29: Ravi P. Singh's technique of asymmetric vinylogous Michael reaction of cyclic enones **116** with silyloxy furans **117** catalysed by the chiral primary diamine **118**

In 2017, Appayee *et al.* achieved highly regioselective γ -alkylation of linear α,β -unsaturated aldehydes **52** with alcohols **120** by using organocatalyst **121**, benzoic acid, trifluoroethanol (TFE) as a co-solvent in toluene and further

Scheme 30: Appayee's route of highly regio- and enantioselective γ -alkylation of linear α,β -unsaturated aldehydes **52**

demonstrated in situ kinetic resolution for enantioenrichment of the γ -alkylated products (Scheme 30, Kutwal *et al.*, 2017). This method has brought together the activation of an electrophile facilitated by TFE and in situ kinetic resolution to achieve excellent selectivity under dienamine catalysis as shown in the *pre*-transition state of the reaction (TS-10, Scheme 30).

In 2017, Siva and co-workers designed and synthesized novel proline based efficient chiral organocatalysts for highly enantioselective asymmetric Darzens reaction of α -chloroketones **123** and substituted α -chloroketones with various aromatic and aliphatic aldehydes **2**, to directly produce optically active di- and tri-substituted chiral epoxides **125** with higher yields (up to 97%) and excellent *ee*'s (up to 99%) under mild reaction conditions (Scheme 31, Ashokkumar *et al.*, 2017).

Scheme 31: Siva's method of highly enantioselective asymmetric Darzens reaction catalysed by proline based organocatalyst **124** for the synthesis of di- and tri-substituted epoxides

Very recently, Chandra and his group reported an organocatalytic enantioselective Michael addition of α -cyanoacetates **127** to *p*-quinone diimide **126** using the chiral bifunctional thiourea **12** in excellent yields and enantioselectivities. The initially formed Michael adducts underwent cyclization to yield functionally rich, fused cyclic imidines **128** bearing a quaternary benzylic chiral center (Scheme 32, Reddy *et al.*, 2018). The authors carried out density functional theory calculations of the competing transition states to explain the observed stereochemical outcome.

Scheme 32: Chandra's approach of organocatalysed asymmetric Michael addition of α -cyanoacetates **127** to *p*-quinone diimide **126**

Very recently, Kinage *et al.* reported synthesis of some chiral ionic liquids (CILs) of amino acid amide and their application as novel organocatalyst for asymmetric transfer hydrogenation (ATH) of acetophenone at room temperature. These CILs **129** (6 mol%) of amino acid amide along with base showed very high yields and excellent enantioselectivities in transfer hydrogenation of acetophenones **1** with isopropyl alcohol (Scheme 33, Javle *et al.*, 2018). The

Scheme 33: Kinage's utilization of chiral amino-acid-amide based ionic liquids (CILs) **129** as stereo selective organocatalyst in asymmetric transfer hydrogenation of acetophenone

authors also evaluated the reusability of CILs in ATH of acetophenone and found that the CILs could be reused three times without any significant change in yield and enantiomeric excess.

In 2014, Koley's group described an asymmetric, organocatalytic, one-pot Mannich cyclization between a hydroxylactam and acetal by

employing MacMillan's catalyst **132**, to provide fused, bicyclic alkaloids **133** bearing a bridgehead N atom (Scheme 34, Koley *et al.*, 2014). Both aliphatic and aromatic substrates were used in this transformation to furnish chiral pyrrolizidinone, indolizidinone, and quinolizidinone derivatives in up to 89% yield and 97% *ee*. The authors also achieved the total syntheses of (-)-epilupinine, (-)-tashiromine, and (-)-trachelanthamidine, thus demonstrating the generality of the catalytic asymmetric process.

Scheme 34: Koley's route for organocatalytic asymmetric Mannich cyclization of hydroxylactams with acetals toward total syntheses of (-)-epilupinine, (-)-tashiromine, and (-)-trachelanthamidine

In 2010, Kureshy *et al.* prepared a series of new recyclable chiral dicationic chromium(III)salen complexes bearing different substituents, at the 3,3'- and 5,5'-positions of the salen unit and used as catalysts for the highly enantioselective aminolytic kinetic resolution of racemic *trans*-epoxides **134** with different anilines **6** (0.5 equiv.) as nucleophiles at room temperature (Scheme 35, Kureshy *et al.*, 2010). When the catalyst **135** was used in 2 mol%, the *anti*-β-amino alcohols **136** were obtained in excellent yields (>99% with respect to the nucleophile) and enantioselectivities (*ee*>99%) with the concomitant recovery of corresponding epoxides in high optical purity (*ee* up to >99%) and quantitative yields in 12 h. The catalyst **135** was recyclable in the aminolytic kinetic resolution.

Scheme 35: Kureshy's process of reusable chiral dicationic chromium(III)salen **135** catalysed aminolytic kinetic resolution of *trans*-epoxides

It is impossible to close the discussion without touching the pioneering work done by Periasamy's group since 2012, on the enantioselective synthesis of chiral allenes using readily accessible chiral secondary amines as chiral auxiliaries (Periasamy *et al.*, 2018). Though this does not qualify for this terrain of catalytic asymmetric reactions, it has everything to do with chiral synthesis of structurally important allenes. Very recently, their group developed a method for highly enantioselective synthesis of chiral β-allenoates **139** from 1-alkynes **7**, propiolates **138**, and chiral secondary amines **137** via the corresponding transient oxazolidine intermediates and propargylamine derivatives (Scheme 36). The intermediate propargylamine was isolated in 50% yield and converted to give the β-allenoate in 68% yield with 96% *ee* upon reaction with ZnI₂. The authors discussed the mechanism to involve oxazolidine and iminium ions formed in situ followed by addition of alkynyl zinc complex to produce the propargylamine that gives the corresponding allenoate via a 1,5-hydrogen shift in the presence of ZnI₂ (Periasamy *et al.*, 2018).

Scheme 36: Periasamy's process of asymmetric synthesis of chiral β-allenoates **139** via phosphine-catalysed and ZnI₂-promoted preparation of oxazolidines and propargylamines using chiral amines **137**, 1-alkynes **7**, and propiolates **138**

For the last one decade, Sunoj and his group have continually given extraordinary support to the experimental outcome of many metal and metal-free catalytic reactions in terms of enantio- and diastereoselectivity through theoretical calculations and thereby paving the way forward for better understanding and designing of novel and complex asymmetric reactions (Sunoj, 2016). In 2015, Sunoj *et al.* have addressed a fundamental problem of chiral induction in asymmetric catalysis when two chiral catalysts act synergistically in a reaction and established the origin of high precision enantio- and diastereoselectivity in the cooperative dual-catalytic α -allylation of 2-phenylpropionaldehyde through transition state modeling by using density functional theory (Bhaskararao and Sunoj, 2015). Later on in 2016, Sunoj *et al.* have divulged the mechanistic insights through density functional theory computations on a three-component cooperative asymmetric catalytic reaction between a diazo ester, a carbamate, and an imine, catalysed by dirhodium acetate and chiral phosphoric acid (Brønsted acid), suggesting a cooperative participation of both the catalysts in the stereocontrolling step of the reaction (Kisan and Sunoj, 2016).

Conclusion

We have highlighted here the various investigations carried out by the Indian research groups to display the potential of asymmetric catalysis. Even though

the progress seems slow, it is steady and impressive. It encompasses the development of certain interesting organocatalysts and their applications in different asymmetric reactions, asymmetric organic synthesis and also in natural product synthesis. It also showcases various reaction categories such as asymmetric hydrogenation, asymmetric oxidation and asymmetric catalysis via chiral metal complexes, heterogeneous asymmetric catalysis and a variety of kinetic resolution reactions. Besides, we notice a range of different types of catalytic systems such as chiral metal complexes, simple organocatalysts, bifunctional thiourea catalysts, chiral squaramide catalysts, NHC catalysts, phosphine catalysts, supramolecular-organocatalysts etc., in use. In future, we believe asymmetric catalysis will continue to flourish further to develop more new concepts, new catalytic systems, new chemical reactivity and above all more environmental friendly sustainable processes for asymmetric synthesis. Especially, asymmetric organocatalysis and supramolecular-organocatalysis will become ideal technique for academic to industrial practitioners and also become alternative tool for enzyme-catalysis in all aspects in the near future.

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