



Available Online at [www.hithaldia.in/locate/ECCN](http://www.hithaldia.in/locate/ECCN)  
All Rights Reserved

---

#### ORIGINAL CONTRIBUTION

## Development in Organocatalysis – The Green Chemistry Aspect; A Review Update

Nibadita Purkait \* and Gourisankar Roymahapatra \*

Haldia Institute of Technology, ICARE Complex, Haldia, India

(Received Date: 10<sup>th</sup> November, 2016; Revised Date: 20<sup>th</sup> January, 2017; Acceptance Date: 10<sup>th</sup> February, 2017)

---

#### ABSTRACT

The organocatalysis is the catalysis with small organic molecules, where an inorganic element is not part of the active reaction transition and having facile reaction course, selectivity, environment friendliness. The beginning of green chemistry is commonly considered as a reply to the need of reducing the damage of the environment by synthetic materials and the processes involved producing them. This review update articulate on recent development in organocatalysis in ‘green’ aspect, and its key trends, challenges and scope in coming days. In this article we have tried to discuss recent update in the field on a green chemistry perspective.

**KEYWORDS** — Green chemistry, Organocatalysis

---

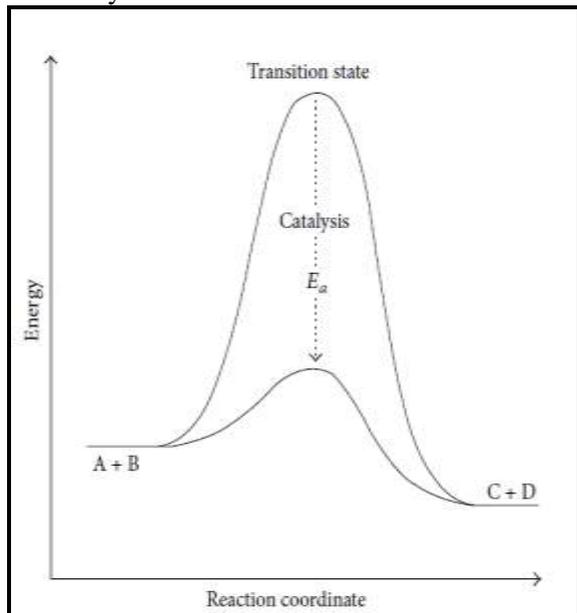
### 1. INTRODUCTION

Organocatalysis - the catalysis with small organic molecules, where an inorganic element is not part of the active reaction transition and having facile reaction course, selectivity, environment friendliness, has achieved considerable attention over the past years. In contrast to many transition metal catalysts which are toxic for human health and environment, and the removal of metal impurities from reaction mixture is quite expensive, organocatalysis being another main field in modern organic synthesis along with biocatalysis (mainly enzyme catalysis) and metal catalysis, leading to *green* or *sustainable chemistry* because of its stability to air and water, easily handled experimentally, relatively nontoxic and readily separated from the crude reaction mixture and also the preparation of the catalysts is much easier as it relies on the well-developed synthetic resource for tailor-making organic structures. The main four types of organocatalysts: Lewis bases [1], Lewis acids [2-3], Brønsted bases [1], and Brønsted acids [4] initiate their catalytic cycles by either providing or removing electrons or protons from a substrate or a transition state. According to Ostwald [5], “a catalyst

*accelerates the chemical reaction without affecting the position of the equilibrium*”. A catalyst usually interacts with reactants to give products through the formation of intermediates. It affects the rate of approach to equilibrium of a reaction but not the position of the equilibrium (Figure 1). Again, it also provide suitable control of chemical conversions i.e., the selectivity of a chemical process; increasing the rate of a desired reaction pathway but not the rates of undesired side reactions.

During the last decade, diverse experimental protocols have made organocatalysis even *greener* alternative by using friendlier reaction conditions, by the application of solvent-free methodologies [6-10], through the design and synthesis of more selective catalysts [11-12], developing multicomponent one-pot organocatalytic reactions [13-14], by recycling and reusing organocatalysts [15-16], by means of the application of more energy-efficient activation techniques [17], among other approaches. Lindstrom *et. al.* [18] reported an extensive review especially on stereo selective organic reactions in water and very recently Roymahapatra *et.al.*, [19] reported a short review to get a brief status on approach of

organocatalysis techniques towards green chemistry'



**Figure-1:** Schematic illustration of the effect of a catalyst on the transformation of a chemical reaction (A+B to C+D). [3]

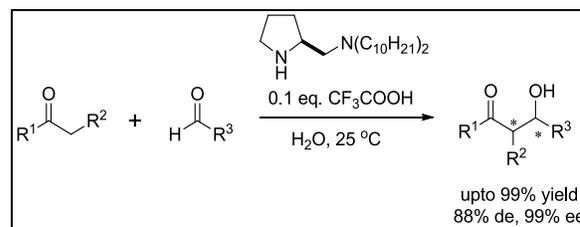
Keeping in mind the tremendous importance of organocatalysis, in this article we have tried to report an update on some of the remarkable advancements that have made it possible to develop even more sustainable (greener) organocatalyzed methodologies.

## 2. WATER IN ORGANOCATALYSIS

The green aspect of organocatalysis is further fulfilled if the other constituents involved in the reaction are also user friendly.

The most important constituent in a reaction is the solvent because it is always present in excess. Water is one such solvent which satisfies this criterion of green chemistry being it low cost and environmentally safe [20-22] also it is a suitable solvent in various biosynthetic reactions [23]. Initially water was not treated as suitable solvent because most of the non-polar organic compounds are insoluble in water. When reaction is carried out in water, there is a significance chance of getting water contamination. This discharged unwanted water will result more pollution than a reaction carried out in traditional organic solvents with the

proper after-treatment work-up. Water possesses some unique physical properties such as high surface tension, hydrogen bonding capability, polarity and the ability to induce the hydrophobic effect, which make it an important solvent for organic reaction [20-24]. Water as solvent in organic reactions was first highlighted in the 1980s by Breslow and co-workers in the Diels–Alder reactions where strong rate acceleration was observed in water relative to organic solvents [25-26]. Later S. Narayan *et al.* showed that several uni- and bimolecular reactions were greatly accelerated when carried out in vigorously stirred aqueous suspensions [27]. Sakthivel *et.al.* [28] reported the use of water in an organocatalyzed aldol reaction (Scheme-1). It was found that the reaction between acetone and 4-nitrobenzaldehyde proceeds well in the presence of a small amount (less than 4 vol %) of water. Later in an illustrative example [29], they found that hydrophobic diamine (10 mol %) constitutes an efficient bi-functional catalyst in the aldol

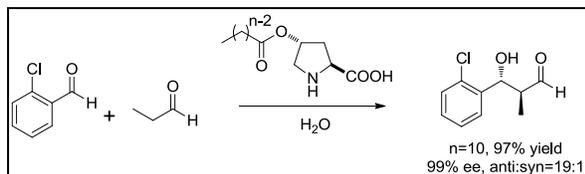


**Scheme-1.** Organocatalyzed aldol reaction in water medium by Barbas *et al.*

reaction of cyclic ketones with aromatic aldehydes in water and in the presence of one equivalent of TFA, affording the aldol products with high diastereo- and enantioselectivity.

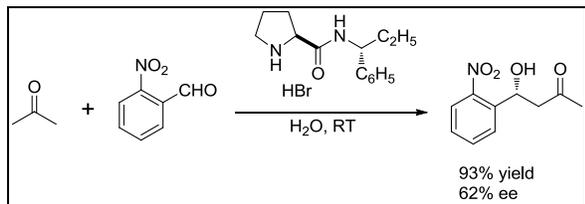
Janda and co-workers [30-33] utilized nornicotine to catalyze the aldol reaction of acetone and p-chlorobenzaldehyde in water getting enantioselectivity of 20%. Nyberg *et al.* [34-35] observed significantly higher yields on addition of water to an intermolecular aldol reaction catalyzed by L-proline. Hayashi and co-workers [36-38] reported the aldol reaction (Scheme-2) using tertiary butyl diphenyl silicon-protected hydroxyproline (10 mol %) as organocatalyst for the reaction of cyclic ketones with aliphatic and aromatic aldehydes in water,

obtaining the antialdol adducts with up to 99% ee.



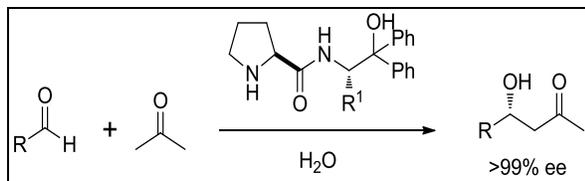
**Scheme-2.** Organocatalyzed aldol reaction in water medium by Hyashi *et al.*

Later a number of works has been published on the organocatalysis in water medium. In 2006, Chimni and Mahajan reported protonated chiral prolinamide catalyzed enantioselective direct aldol reaction (Scheme-3). Which only happen to occur in water with 50% ee. [39].



**Scheme-3.** Organocatalyzed aldol reaction in water medium by Chimni and Mahajan.

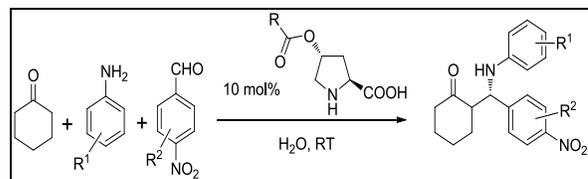
Raja *et al.* developed prolinamide catalysts and contributed significantly to organocatalyzed aldol reaction in water medium (Scheme-4) [40] The yield and enantioselectivity of the reaction was high in brine compare to water because of the salting out effect which increases the hydrophobic effect [41-43].



**Scheme-4.** Organocatalyzed aldol reaction in water medium by Singh *et al.*

Mase *et al.* also showed a highly enantioselective (97% ee) direct Michael addition of aldehydes and ketones to nitro-olefins catalyzed by a diamine/TFA bifunctional organocatalyst [44]. Heterogeneous organocatalysis are also been reported using

water as solvent. Alza *et al.* [45] reported a polymer supported triazole linked organocatalyst for Michael addition of ketones to nitro-olefins in water with a maximum of 99% enantioselectivity. For same type of reaction Zu *et al.* used a recyclable fluoros (S)-pyrrolidinesulfonamide organocatalyst to get up to 93% enantioselectivity [46] and Luo *et al.* synthesized surfactant type asymmetric organocatalysts (SATO) and obtained high enantioselectivities up to 98% and diastereoselectivities up to 99:2 [47]. Later other scientists were also synthesized various types of catalysts for example bifunctional pyrrolidine-thiourea catalyst by Cao *et al.* [48] binaphthyl based chiral diamine organocatalysts by Singh and Maya [42]; OTMS-substituted diphenyl prolinol by D. Ma and group [49-51] TMS-protected diaryl-prolinol by Carlone *et al.* [52] prolinol based Organocatalysts by Palamo *et al.* [53] prolinol catalyst by Loh's group [54]. Organocatalysed Mannich reaction are also been reported in water [55-59]. Hayashi *et al.* [55] synthesized silyloxytetrazole hybrid catalyst and silyloxy proline to carry out asymmetric Mannich reactions in water. Other Organocatalysed Mannich reactions were also done by Tao and co-workers [60] by several amphipathic organocatalysts derived from isosteviol and proline (Scheme 5).



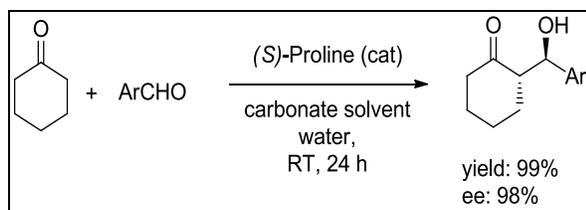
**Scheme-5.** Organocatalyzed Mannich reaction in water medium by Tao *et al.*

In the presence of water the reactions proceeded efficiently affording the expected products in good to excellent yields and high stereoselectivity. The formation of a hydrophobic chiral pocket induced by the presence of the lipophilic isosteviol unit was proposed to be the transition state of the addition reaction. Additionally due to the formation of hydrogen bonding by the free hydroxyl groups of water in the interfacial surface leads to the observed improvement of the activity and

stereoselectivity as a consequence of the more rigid transition state. In conclusion, from the “green” chemistry perspective, the use of water as a reaction medium offers a number of benefits: it obviously avoids the use of toxic, volatile and/or corrosive solvents, it usually minimizes the amount of catalyst that is required for the reaction, it frequently induces a significant acceleration of the reaction rate, it facilitates the isolation and purification of the products. Nevertheless, a frequent criticism directed to the treatment of the aqueous phase at the end of the reaction consist the lack of a general or practical procedure to prevent the contamination of clean water sources.

### 3. ORGANIC CARBONATE SOLVENT IN ORGANOCATALYSIS

During recent years, linear and cyclic organic carbonates have been extensively used as alternative solvents in organocatalyzed reactions [61]. Organic carbonates belong to a class of aprotic highly dipolar solvents (AHD) like DMSO or DMF. Because of their apparent easy availability, low cost, low toxicity and biodegradability, organic carbonates have also been considered as “green” solvents in organocatalytic reactions. Also they are widely

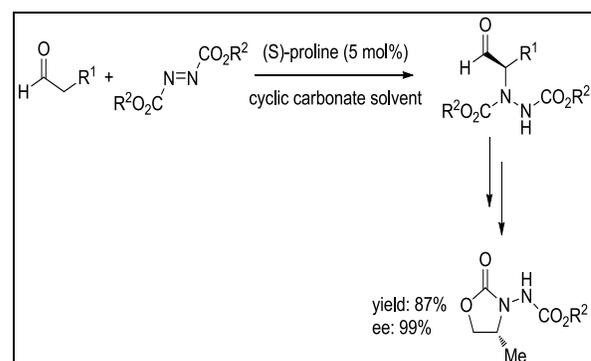


**Scheme 6.** Organocatalyzed aldol reaction in organic carbonate medium by North et al.

used in organic synthesis because of their high dipole moment and high dielectric constant, higher selectivities, rates, yields, limited miscibility with water, high polarity, hydrogen-bond acceptor properties. The lower aliphatic carbonates form azeotropic mixtures with several organic solvents [62]. Ethylene carbonate finds extensive use as a solvent. Five-membered cyclic carbonates are polar, for this reason they are excellent solvents, e.g., for poly-(acrylonitrile) [63]. In 2009 North et al. [64]

evaluated ethylene and propylene carbonate (Scheme 6) as sustainable solvents in the asymmetric aldol reaction catalyzed by (S)-proline (10 mol %).

The reaction of cyclic and acyclic ketones with aromatic aldehydes led to the formation of the desired aldol products in good chemical yields and good to excellent stereoselectivities. In related work North et al. [65] studied the effect of chiral solvent of propylene carbonate in organocatalyzed aldol reactions. They found that using the appropriate combination of carbonate solvent and the “matching” proline enantiomer, the stereoselectivity of aldol adducts can be improved considerably. North and group also showed that propylene carbonate is an environmentally friendly and sustainable replacement for dichloromethane and acetonitrile in proline-catalysed  $\alpha$ -hydrazinations of aldehydes and ketones (Scheme-7) [66]. The reaction of aldehyde with diethyl azodicarboxylate in presence of 5 mol% of (S)-proline in cyclic carbonate medium gives 87% yield and over 99% ee. In this case, no significant difference was observed for yield and enantioselectivity when the reactions were carried out in racemic and enantiomerically pure solvent, nor was there a difference between reactions carried out using the two enantiomers of proline in (R)-propylene carbonate.



**Scheme-7.** Organocatalyzed  $\alpha$ -hydrazination of aldehydes in cyclic carbonate solvent.

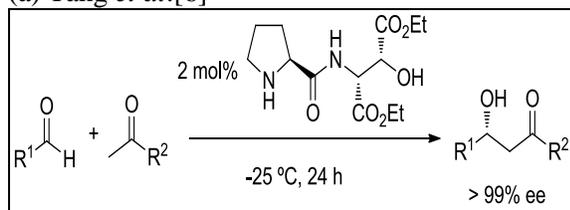
Regarding the actual “greenness” of organic carbonate solvents, the principal drawback is related to their preparation. Traditionally, the

synthetic routes followed in the industrial scale preparation of linear carbonates include the use of hazardous phosgene. On the other hand, the preparation of cyclic carbonates, despite involving 100% atom economical reactions, requires as starting material propylene oxide, which is highly toxic. Again in organic synthesis and catalysis it is more important to solve the question of product separation. As cyclic organic carbonates having high boiling point, distillative removal of the solvent is nearly impossible. In some polymer applications it is possible as the polymer precipitates out of the solvent. Nevertheless, new approaches directed to the preparation of organic carbonates using “greener” methodologies have been reported recently [67-68]. Ethylene carbonate can be utilized as a solvent in the separation of different aromatic amines.

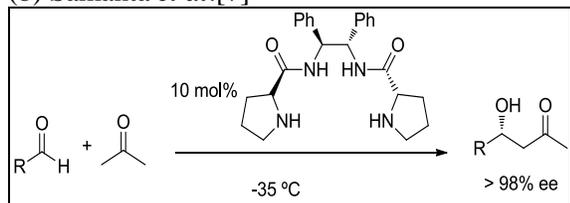
#### 4. SOLVENT-FREE ORGANOCATALYSIS

In some organocatalyzed processes, a new strategy has been developed to avoid the use of auxiliary solvents. In this method, large excess of a reagent is used which acts as

(a) Tang *et al.*[6]



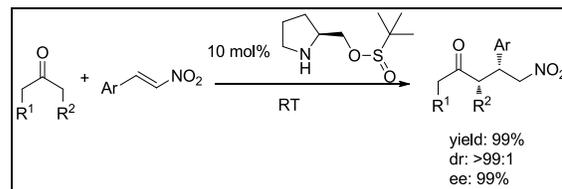
(b) Samanta *et al.*[7]



**Scheme-8(a, b).** Solvent free organocatalytic aldol reaction.

reaction medium. For example, in aldol and Michael reactions it is possible to employ an excess of the nucleophilic component to perform the reactions under solvent-free

conditions. In this regard, Tang *et al.* [6], Samanta *et al.*[7] and Chen *et al.*[8] evaluated the aldol reaction of aromatic aldehydes using an excess of acetone (27–45 equiv.) under “solvent-free” conditions (Scheme-8). For example, (S)-proline derivatives catalyzed the desired reaction affording the aldol adducts in high yields and with excellent enantioselectivities. But, the use of a large excess of one of the reagents is not a true “green” solution. Rather, the use of approximately equimolar amounts of reactants (1: 1–1: 10 equiv.), is more real in solvent-free green methodologies. In this context, the work of Zeng and Zhong [9] have reported that using only 3 equivalents of cyclohexanone as substrate, the Michael addition to nitro-olefins catalyzed by prolinolsulfinyl ester (10 mol %) proceeded in excellent yields and with high enantio- and diastereo-selectivities, under solvent free conditions at room temperature (Scheme-9).



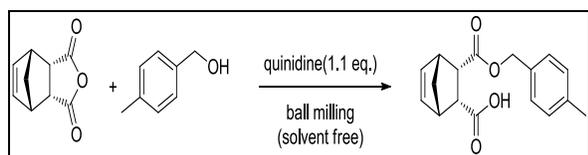
**Scheme-9.** Solvent free organocatalytic Michael addition reaction.

Recently, many works under solvent free conditions have been done in good to very good yields, and with very high diastereo- and enantioselectivities [67-68]. The implementation of the solvent-free concept in organocatalyzed reactions represents a genuine advancement towards the goal to make the organocatalytic process “greener”. Indeed, reactions performed under highly concentrated conditions or in the total absence of solvent gives relevant advantages such as environmental safety, cost savings, and decrease in reaction times. Thus, the attributes associated with solvent-free strategies help to make the overall organocatalyzed process more sustainable. But, it is important to understand that although the reactions may take place efficiently under solvent free condition, large

amounts of volatile solvents are required for the work-up and the separation of the organocatalyst from the product mixture.

## 5. ALTERNATIVE REACTION TECHNIQUES: HIGH-SPEED BALL MILLING

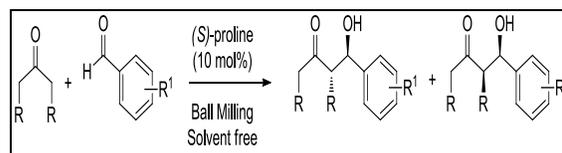
Besides the above methodologies, it is important to mention that High-Speed Ball Milling (HSBM) is a sustainable mechano-chemical technique is being increasingly used in synthetic organic chemistry to promote several synthetically useful reactions, under solvent free conditionstechniques canhelp to reduce the amount of undesired hazardous chemicals(including solvents), and increase the selectivity towards thegiven product/s [69]. However, it is important to clarify that mechano-chemical activation does not necessarily imply a solvent-free process, because mechano-chemistry can occasionally be performed in the presence of solvents which facilitate the stirring, grinding or milling process. The advantages of the HSBM technique have also been applied in the area of organocatalysis. The alkaloid-mediated asymmetric opening of a cyclicmeso anhydride (Scheme 10) was studied as the



**Scheme 10.** Solvent-Free Asymmetric Organocatalysis in a Ball Mill.

initial organocatalytic testreaction in the ball mill [70-73]. The reaction was performed at low temperatures (e.g., -60 °C) in an organicsolvent, e.g. toluene or toluene/carbon tetrachloridemixtures, products with high enantiomeric excess (up to 99% ee) areformed after 24–48 hours in almost quantitative yields. In this field, Bolm et al., reported that the asymmetric aldol reaction under solvent-free conditionsand catalyzed by (S)-proline (10 mol%) in a ball mill, employing a 1.1 : 1 ketone/aldehyde ratio, proceeded efficiently to give selectively the anti-aldol diastereomeric

products in high yields and with up to 99% enantiomeric excess [74] (Scheme 11).



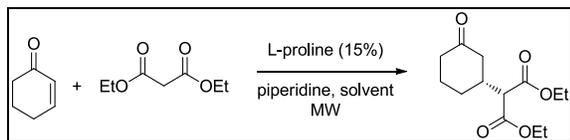
**Scheme 11.** Solvent-Free Asymmetric Organocatalyzed aldol reaction in a Ball Mill.

In this study, Bolm and co-workers [70-72] demonstrated that the efficiency of the process using High-Speed Ball Milling (HSBM) was superior relative to traditional magnetic stirring: reaction times were shorter, and chemical yields and stereoselectivities were higher.

## 6. MICROWAVES, ULTRASOUND AND HIGH PRESSURE

Besides HSBM, other special techniques which have been classified as “green” alternatives in organic synthesis have also been applied to organocatalytic reactions. In particular, microwave irradiation, ultrasound or the use of high pressure have proved to be most promising. But, it is worth commenting that in connection with one of the principles of “green” chemistry (‘the design for energy efficiency’), “green” synthetic methods should be preferably conducted at ambient temperature and atmospheric pressure, with the purpose to minimize the amount of energy required to increase the temperature or the pressure in the reactor. However, in the case of MW irradiation one has to recall that the observed enhancement of the reaction rate is in part associated with the rapid heating caused by MW irradiation relative to the same reaction using conventional heating methods [75]. It must be said that in addition to energy efficiency considerations, organocatalytic reactions employing MW, ultrasound or high pressure are generally performed in organic solvents such as DMF, DMSO, THF, CH<sub>3</sub>Cl or CH<sub>2</sub>Cl<sub>2</sub>, which are considered undesired reaction media in the “green” chemistry field. A real improvement in the “greenness” of organocatalysis using these special techniques could be obtained by performing the MW,

ultrasound or high pressure reactions in the absence of solvent.



**Scheme 12.** Microwave-Assisted Organocatalytic Solvent-Free Synthesis.

In this context, in 2010 Procopio and co-workers reported the microwave-assisted organocatalytic conjugate addition of diethyl malonate to several enones, under various conditions. Surprisingly, the reaction catalyzed by 15 mol% of (S)-proline proved to work well under solvent-free conditions, using only a slight excess of diethyl malonate (1.2 equiv.) [76]. The Michael adducts were obtained in short reaction times with good yields and moderate to excellent enantioselectivities (40–99% ee) (Scheme 12).

## 7. CONCLUSION

There is no doubt that “green” chemistry and organocatalysis represent remarkable developments in the chemistry of the XXI century. All “green” contributions in the field of organocatalysis are very valuable because in addition to the preparation of the desired products, chemists implicitly have the social compromise to be more creative in the design of friendlier methodologies that prevent or at least reduce deleterious environmental impact. During the last ten years, the progress of organocatalysis has been accompanied, in a synergetic combination, by “green” approaches that have made organocatalytic processes even “greener”. The above considerations inspired us to make a review and highlight here some recent relevant approaches that from our viewpoint show clearly how the expansion of a new area can be made in a sustainable way.

---

*Dr. N. Purkait earned her M.Sc. (2009) degree from Indian Institute of Technology Guwahati, India. Then she moved to Germany to persue her Ph.D. (2012) from Technical University of Berlin, Germany. She then moved to Spain to work as postdoctoral research fellow (2012-2014) at Institut Català d'Investigació Química with Prof. Kilian Muñoz. In 2015 she joined the faculty of Dept. of Applied Sciences, Haldia Institute of Technology (HIT), Haldia, India, as Assistant Professor of Chemistry. Her main areas of research are Synthetic organic chemistry, Catalysis and Green chemistry. \*Email: nibaditaa@gmail.com*

---

*Dr. G. Roymahapatra is now working as an Associate Professor of Chemsitry at Dept. of Applied Sciences, Haldia Institute of Technology (HIT), Haldia, India. Previously he worked at GIST Haldia as a Lecturer of Chemistry (2011-2015), and MCPI Haldia as a Senior Chemist (2003-2011). He did his graduation from Medinipur College (Vidyasagar University), M.Sc. from CSJM University, and PhD from Jadavpur University, India. His areas of research are NHC Chemistry, DFT and Catalysis. Dr. Roymahapatra got ‘Distinguished Young Scientist – 2014’ (chemical science) award from World Science Congress, Kolkata, India in 2014 and selected as Editorial Board member of ‘Education in Chemical Science & Technology’ published by Indian Chemical Society, Kolkata, India in 2017. \*Email: gourisankar1978@gmail.com*

## REFERENCES

- [1] K. Matsui, S. Takizawa, H. Sasai, ‘A Brønsted Acid and Lewis Base Organocatalyst for the Aza-Morita-Baylis-Hillman Reaction’, *Synlett*, **2006**, 761-765.
- [2] L. Li, T. J. Marks, ‘New Organo-Lewis Acids. Tris(β-perfluoronaphthyl)borane (PNB) as a Highly Active Cocatalyst for Metallocene-Mediated Ziegler–Natta α-Olefin Polymerization’, *Organometallics*, **1998**, 17 (18), 3996–4003.

- [3] Y.-X. Chen , C. L. Stern , S. Yang , T. J. Marks, 'Organo-Lewis Acids As Cocatalysts in Cationic Metallocene Polymerization Catalysis. Unusual Characteristics of Sterically Encumbered Tris(perfluorobiphenyl)borane', *J. Am. Chem. Soc.*, **1996**, *118* (49), 12451–12452.
- [4] I. R. Shaikh, 'Organocatalysis: Key Trends in Green Synthetic Chemistry, Challenges, Scope towards Heterogenization, and Importance from Research and Industrial Point of View', *Journal of Catalysts*, **2014**, doi.org/10.1155/2014/402860.
- [5] W. Ostwald, *Verhandlungen der Gesellschaft Deutscher Naturforscher und Ärzte*, **1895**, 155–168.
- [6] Z.Tang, Z-H. Yang, X.-H.Chen, L.-F.Cun, A. -Q. Mi, Y.-Z.Jiang, L.-Z.Gong, 'A Highly Efficient Organocatalyst for Direct Aldol Reactions of Ketones with Aldehydes', *J. Am. Chem. Soc.***2005**, *127*, 9285-9289.
- [7] S. Samanta, J. Liu, R. Dodda, C.-G. Zhao, 'C<sub>2</sub>-Symmetric Bisprolinamide as a Highly Efficient Catalyst for Direct Aldol Reaction', *Org. Lett.***2005**, *7*(23), 5321-5323.
- [8] J.-R.Chen, X.-L.An, X.-Y.Zhu, X.-F.Wang, W.-J. Xiao, 'Rational Combination of Two Privileged Chiral Backbones: Highly Efficient Organocatalysts for Asymmetric Direct Aldol Reactions between Aromatic Aldehydes and Acyclic Ketones', *J. Org. Chem.***2008**, *73*, 6006-6009.
- [9] X. Zeng, G. Zhong, 'Prolinol Sulfinyl Ester Derivatives: Organocatalytic Michael Addition of Ketones to Nitroolefins under Neat Conditions', *Synthesis*, **2009**, *9*, 1545-1550.
- [10] J-R. Chen, X-Y. Li, X-N. Xing, W-J. Xiao, 'Sterically and Electronically Tunable and Bifunctional Organocatalysts: Design and Application in Asymmetric Aldol Reaction of Cyclic Ketones with Aldehydes', *J. Org. Chem.*, **2006**, *71* (21), 8198–8202.
- [11] J. G. Hernández, E. Juaristi, 'Recent efforts directed to the development of more sustainable asymmetric organocatalysis', *Chem. Commun.*, **2012**, *48*(44), 5396-5409.
- [12] C. Shen, H. Liao, F. Shen, P. Zhang, 'Novel synthesis of carbohydrate-derived organocatalysts and their application in asymmetric aldol reactions', *Catalysis Communications*, **2013**, *41*, 106–109.
- [13] C. M. Marson, 'Multicomponent and sequential organocatalytic reactions: diversity with atom-economy and enantiocontrol', *Chem. Soc. Rev.*, **2012**, *41*, 7712-7722.
- [14] J. Duan, J. Cheng, P. Li, 'DBU-Catalyzed One-Pot Multicomponent Reaction for the Synthesis of Spirocyclic Tetrahydrothiophene Derivatives', *Current Organocatalysis*, **2016**, *3*(2), 216 – 220.
- [15] R. Mrówczyński, A. Nan, J. Liebscher, 'Magnetic nanoparticle-supported organocatalysts – an efficient way of recycling and reuse', *RSC Adv.*, **2014**, *4*, 5927-5952.
- [16] J. Großeheilmann, H. Büttner, C. Kohrt, U. Kragl, T. Werner, 'Recycling of Phosphorus-Based Organocatalysts by Organic Solvent Nanofiltration', *ACS Sustainable Chem. Eng.*, **2015**, *3* (11), 2817–2822.
- [17] Y. Su, M. J. Bouma, L. Alcaraz, M. Stocks, M. Furber, G. Masson, J. Zhu, 'Organocatalytic Enantioselective One-Pot Four-Component Ugi-Type Multicomponent Reaction for the Synthesis of Epoxy-tetrahydropyrrolo[3,4-*b*]pyridin-5-ones', *Chemistry*, **2012**, *18*(40), 12624-12627.
- [18] U.M. Lindstrom, 'Stereoselective Organic Reactions in Water', *Chem. Rev.*, **2002**, *102*, 2751-2772.
- [19] G. Roymahapatra, A. K. Adak, T. Samanta, P. K. Khatua, R. N. Jana, 'Approach of Organocatalysis Techniques towards "Green Chemistry"', *International Journal of Innovative Practice and Applied Research (IJIPAR)*, **2016**, *5*(5), 131-142.
- [20] R. Breslow, 'Artificial enzymes', *Science*, **1982**, *218*(4572), 532-537.
- [21] A. J. Kirby, 'Enzyme Mechanisms, Models, and Mimics', *Angew. Chem., Int. Ed.*, **1996**, *35*, 706-724.

- [22] A. Heine, G. Desantis, J. G. Luz, M. Mitchell, C.-H. Wong, I. A. Wilson, 'Observation of covalent intermediates in an enzyme mechanism at atomic resolution', *Science*, **2001**, 294(5541), 369 -374 and references therein.
- [23] D. G. Blackmond, A. Armstrong, V. Coombe, A. Wells, 'Water in Organocatalytic Processes: Debunking the Myths', *Angew. Chem., Int. Ed.* **2007**, 46, 3798-3800.
- [24] Y. Jung, R. A. Marcus, 'On the Theory of Organic Catalysis "on Water"', *J. Am. Chem. Soc.* **2007**, 129, 5492-5502.
- [25] R. Breslow, 'Hydrophobic effects on simple organic reactions in water', *Acc. Chem. Res.*, **1991**, 24, 159-164.
- [26] R. Breslow, 'Determining the Geometries of Transition States by Use of Antihydrophobic Additives in Water', *Acc. Chem. Res.*, **2004**, 37(4), 471-478.
- [27] S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, "'On Water": Unique Reactivity of Organic Compounds in Aqueous Suspension', *Angew. Chem., Int. Ed.*, **2005**, 44, 3275 - 3279.
- [28] K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, 'Amino Acid Catalyzed Direct Asymmetric Aldol Reactions: A Bioorganic Approach to Catalytic Asymmetric Carbon-Carbon Bond-Forming Reactions', *J. Am. Chem. Soc.* **2001**, 123, 5260-5267.
- [29] Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, 'Organocatalytic Direct Asymmetric Aldol Reactions in Water', *J. Am. Chem. Soc.*, **2006**, 128, 734-735.
- [30] T. J. Dickerson, K. D. Janda, 'Aqueous Aldol Catalysis by a Nicotine Metabolite', *J. Am. Chem. Soc.*, **2002**, 124, 3220-3221.
- [31] T. J. Dickerson, T. Lovell, M. M. Meijler, L. Noodleman, K. D. Janda, 'Nornicotine Aqueous Aldol Reactions: Synthetic and Theoretical Investigations into the Origins of Catalysis', *J. Org. Chem.*, **2004**, 69, 6603-6609.
- [32] C. J. Rogers, T. J. Dickerson, K. D. Janda, 'Kinetic isotope and thermodynamic analysis of the nornicotine-catalyzed aqueous aldol reaction', *Tetrahedron*, **2006**, 62, 352 -356.
- [33] A. P. Brogan, T. J. Dickerson, K. D. Janda, 'Enamine-Based Aldol Organocatalysis in Water: Are They Really "All Wet"?'', *Angew. Chem. Int. Ed.* **2006**, 45(48), 8100-8102
- [34] A. I. Nyberg, A. Usano, P. M. Pihko, 'Proline-Catalyzed Ketone-Aldehyde Aldol Reactions are Accelerated by Water', *Synlett*, **2004**, 11, 1891-1896.
- [35] P. M. Pihko, K. M. Laurikainen, A. Usano, A. I. Nyberg, J. A. Kaavi, 'Effect of additives on the proline-catalyzed ketone-aldehyde aldol reactions', *Tetrahedron*, **2006**, 62, 317-328.
- [36] Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, 'Highly Diastereo- and Enantioselective Direct Aldol Reactions in Water', *Angew. Chem., Int. Ed.*, **2006**, 45, 958-961.
- [37] Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji, 'Combined Proline-Surfactant Organocatalyst for the Highly Diastereo- and Enantioselective Aqueous Direct Cross-Aldol Reaction of Aldehydes', *Angew. Chem., Int. Ed.*, **2006**, 45, 5527-5529.
- [38] Y. Hayashi, 'In Water or in the Presence of Water?', *Angew. Chem., Int. Ed.*, **2006**, 45(48), 8103-8104.
- [39] S. S. Chimni, D. Mahajan, 'Small organic molecule catalyzed enantioselective direct aldol reaction in water', *Tetrahedron: Asymmetry*, **2006**, 17, 2108-2119.
- [40] M. Raj, V. K. Singh, 'Organocatalytic reactions in water', *Chem. Commun.*, **2009**, 6687-6703.

- [41] M. Raj, V. Maya, S. K. Ginotra, V. K. Singh, 'Highly Enantioselective Direct Aldol Reaction Catalyzed by Organic Molecules', *Org. Lett.*, **2006**, 8, 4097-4099.
- [42] V. Maya, M. Raj, V. K. Singh, 'Highly Enantioselective Organocatalytic Direct Aldol Reaction in an Aqueous Medium', *Org. Lett.*, **2007**, 9, 2593-2595.
- [43] M. R. Vishnumaya, V. K. Singh, 'Highly Efficient Small Organic Molecules for Enantioselective Direct Aldol Reaction in Organic and Aqueous Media', *J. Org. Chem.*, **2009**, 74, 4289-4297.
- [44] N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, 'Organocatalytic Direct Michael Reaction of Ketones and Aldehydes with  $\beta$ -Nitrostyrene in Brine', *J. Am. Chem. Soc.*, **2006**, 128(15), 4966-4967.
- [45] E. Alza, X. C. Cambeiro, C. Jimeno, M. A. Perica's, 'Highly Enantioselective Michael Additions in Water Catalyzed by a PS-Supported Pyrrolidine', *Org. Lett.*, **2007**, 9, 3717-3720.
- [46] L. Zu, J. Wang, H. Li, W. Wang, 'A Recyclable Fluorous (S)-Pyrrolidine Sulfonamide Promoted Direct, Highly Enantioselective Michael Addition of Ketones and Aldehydes to Nitroolefins in Water', *Org. Lett.*, **2006**, 8, 3077-3079.
- [47] S. Luo, X. Mi, S. Liu, H. Xu, J.-P. Cheng, 'Surfactant-type asymmetric organocatalyst: organocatalytic asymmetric Michael addition to nitrostyrenes in water', *Chem. Commun.*, **2006**, 3687-3689.
- [48] Y.-J. Cao, Y.-Y. Lai, X. Wang, Y.-J. Li, W.-J. Xiao, 'Michael additions in water of ketones to nitroolefins catalyzed by readily tunable and bifunctional pyrrolidine-thiourea organocatalysts', *Tetrahedron Lett.*, **2007**, 48(1), 21-24.
- [49] S. Zhu, S. Yu, D. Ma, 'Highly Efficient Catalytic System for Enantioselective Michael Addition of Aldehydes to Nitroalkenes in Water', *Angew. Chem., Int. Ed.*, **2008**, 47(3), 545-548.
- [50] A. Ma, S. Zhu, D. Ma, 'Enantioselective organocatalytic Michael addition of malonates to  $\alpha,\beta$ -unsaturated aldehydes in water', *Tetrahedron Lett.*, **2008**, 49, 3075-3077.
- [51] J. Wang, F. Yu, X. Zhang, D. Ma, 'Enantioselective Assembly of Substituted Dihydropyrones via Organocatalytic Reaction in Water Media', *Org. Lett.*, **2008**, 10(12), 2561-2564.
- [52] A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jorgensen, 'A simple asymmetric organocatalytic approach to optically active cyclohexenones', *Chem. Commun.*, **2006**, 4928-4930.
- [53] C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, 'Water-compatible iminium activation: organocatalytic Michael reactions of carbon-centered nucleophiles with enals', *Angew. Chem. Int. Ed.*, **2007**, 46, 8431-8435.
- [54] J. Lu, F. Liu, T.-P. Loh, 'Enantioselective Michael Addition of Dicyanoolefins to  $\alpha,\beta$ -Unsaturated Aldehydes in Aqueous Medium', *Adv. Synth. Catal.*, **2008**, 350, 1781-1784.
- [55] Y. Hayashi, T. Urushima, S. Aratake, T. Okano, K. Obi, 'Organic Solvent-Free, Enantio- and Diastereoselective, Direct Mannich Reaction in the Presence of Water', *Org. Lett.*, **2008**, 10(1), 21-24.
- [56] Y.-C. Teo, J.-J. Lau, M.-C. Wu, 'Direct asymmetric three-component Mannich reactions catalyzed by a siloxy serine organocatalyst in water', *Tetrahedron: Asymmetry*, **2008**, 19(2), 186-190.
- [57] L. Cheng, X. Wu, Y. Lu, 'Direct asymmetric three-component organocatalytic anti-selective Mannich reactions in a purely aqueous system', *Org. Biomol. Chem.*, **2007**, 5, 1018-1020.
- [58] M. Amedjkouh, M. Brandberg, 'Asymmetric autocatalytic Mannich reaction in the presence of water and its implication in prebiotic chemistry', *Chem. Commun.*, **2008**, 3043-3045.

- [59] N. Srinivas, K. Bhandari, 'Proline-catalyzed facile access to Mannich adducts using unsubstituted azoles', *Tetrahedron Lett.*, **2008**, 49(49), 7070-7073.
- [60] Y.-J. An, C.-C. Wang, Z.-P. Liu, J.-C. Tao, 'Isosteviol-Proline Conjugates as Highly Efficient Amphiphilic Organocatalysts for Asymmetric Three-Component *Mannich* Reactions in the Presence of Water', *Helv. Chim. Acta*, **2012**, 95, 43-51.
- [61] B. Schaffner, F. Schaffner, S. P. Verevkin, A. Borner, 'Organic Carbonates as Solvents in Synthesis and Catalysis', *Chem. Rev.* **2010**, 110, 4554-4581.
- [62] Beilstein Handbuch der Organischen Chemie; Springer Verlag: Berlin, **1921**; Vol. III, p 4.
- [63] Jefferson Chemical Corp. Techn. Bull. **1960**.
- [64] M. North, F. Pizzato, P. Villuendas, 'Organocatalytic, Asymmetric Aldol Reactions with a Sustainable Catalyst in a Green Solvent', *Chem. Sus. Chem.*, **2009**, 2, 862-865.
- [65] M. North, P. Villuendas, 'A Chiral Solvent Effect in Asymmetric Organocatalysis', *Org. Lett.* **2010**, 12, 2378-2381.
- [66] C. Beattie, M. North, P. Villuendas, 'Proline-Catalysed Amination Reactions in Cyclic Carbonate Solvents', *Molecules*, **2011**, 16, 3420-3432.
- [67] T. Sakakura, J.-C. Choi, H. Yasuda, 'Transformation of Carbon Dioxide', *Chem. Rev.* **2007**, 107, 2365-2387.
- [68] D. R. Magar, C. Chang, Y.-F. Ting, K. Chen, 'Highly Enantioselective Conjugate Addition of Ketones to Alkylidene Malonates Catalyzed by a Pyrrolidiny-Camphor-Derived Organocatalyst', *Eur. J. Org. Chem.*, **2010**, 11, 2062-2066.
- [69] A. Bruckmann, A. Krebs, C. Bolm, 'Organocatalytic reactions: effects of ball milling, microwave and ultrasound irradiation', *Green Chem.*, **2008**, 10, 1131-1141.
- [70] C. Bolm, A. Gerlach, C. L. Dinter, 'Simple and Highly Enantioselective Nonenzymatic Ring Opening of Cyclic Prochiral Anhydrides', *Synlett*, **1999**, 195-196.
- [71] C. Bolm, I. Schiffrers, C. L. Dinter, A. Gerlach, 'Practical and Highly Enantioselective Ring Opening of Cyclic Meso-Anhydrides Mediated by Cinchona Alkaloids', *J. Org. Chem.*, **2000**, 65, 6984 - 6991.
- [72] C. Bolm, I. Atodiresei, I. Schiffrers, 'Asymmetric alcoholysis of meso-anhydrides mediated by alkaloids', *Org. Synth.*, **2005**, 82, 120-125.
- [73] Y. Chen, P. McDaid, L. Deng, 'Asymmetric Alcoholysis of Cyclic Anhydrides', *Chem. Rev.* **2003**, 103, 2965 - 2984.
- [74] B. Rodríguez, T. Rantanen, C. Bolm, 'Solvent-Free Asymmetric Organocatalysis in a Ball Mill', *Angew. Chem. Int. Ed.*, **2006**, 45, 6924-6926.
- [75] J. D. Moseley, C. O. Kappe, 'A critical assessment of the greenness and energy efficiency of microwave-assisted organic synthesis', *Green. Chem.*, **2011**, 13, 794-806.
- [76] A. Procopio, A. De Nino, M. Nardi, M. Oliverio, R. Paonessa, R. Pasceri, 'A New Microwave-Assisted Organocatalytic Solvent-Free Synthesis of Optically Enriched Michael Adducts', *Synlett*, **2010**, 12, 1849-1855.