Organocatalytic reactions in water

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Organocatalysts have emerged as a third major way of catalyzing a wide variety of reactions, besides metal catalysts and biocatalysts. They have gained tremendous importance because of their green chemistry perspective. The criteria for green chemistry would be largely fulfilled if the major component of the reaction mixture, *i.e.* the solvent, is water which is a suitable solvent in various biosynthetic reactions. In this *feature article* we have described reactions promoted by organocatalysts in a large excess of water, without any organic solvent or excess of any reactant. We have also explained the structural features required for organocatalysts to work well in aqueous media.

Introduction

Organocatalysis is a reaction carried out by sub-stoichiometric amounts of organic compounds which do not contain even a small amount of enzyme or inorganic element.[1–3] Although metal catalyzed reactions[4] have wider substrate scope, they are associated with a few drawbacks such as high cost involved in the preparation of catalysts and toxicity of metals which can be carried over to products.[1–3] Organic compounds, as compared to metals, are more stable, less expensive, non-toxic, readily available, and environmentally friendly. Besides, organocatalytic reactions are less sensitive to the presence of water or air in comparison to metal catalyzed reactions. Thus, the reproducibility and operational simplicity of these reactions are enhanced. Organocatalysts provide better alternatives not only to metal catalysts but also to biocatalysts. They provide broad substrate scope in contrast to enzymes which are highly substrate specific and cannot tolerate even a minor change in the structure of the reactants.[1–3] In addition, organocatalysts display another advantage over both metal catalysts and enzymes in that they are easily amenable to solid support, leading to easy recovery of the catalyst and simplification of the reaction work up.

Since enzymes are known for high catalytic activity and stereospecificity, similar characteristics displayed by small organic molecules have always been considered as one of the reasons for intense activity.[5] These organic molecules work by activating substrates either through strong interactions such as covalent bonding or weak interactions such as van der Waals forces or hydrogen bonding.[1–3] These interactions result in considerable acceleration of the reaction rate.[6]

Although organic molecules have been used as catalysts for a long time,[7] their application in enantioselective synthesis has arisen as a major concept only in the past few years. Most of the reactions catalyzed by these approaches are enantioselective in nature and thus the use of organic molecules enables the chemist to understand the origin of chirality in the prebiotic environment.

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Vinod K. Singh

Vinod K. Singh received his MSc in Chemistry from B.H.U. in 1980 and PhD in 1986 from MS University Baroda. After two years in Canada (University of Calgary and U.B.C. Vancouver) and three years in the USA (Harvard University, E.J. Corey) as a post-doctoral fellow, he joined I.I.T. Kanpur in 1990 as an Assistant Professor and rose to the position of Professor. He is currently Umang Gupta Chair Professor at the same institute and Founder Director of the Indian Institute of Science Education and Research Bhopal. He works in the area of synthetic organic chemistry with emphasis on asymmetric synthesis.

A pioneering organocatalyzed asymmetric reaction was reported independently by two groups: Hajos and Parrish at Hoffmann–La Roche Inc.[8] and Eder, Sauer and Wiechert while working at Schering AG[9] over three decades ago. They carried out one of the important C–C bond formation reactions *i.e.* the intramolecular aldol reaction of triketones by using L-proline. Although these reactions were discovered long back, their potential was realized only recently after the discovery by List and Barbas *et al.* in 2000 that L-proline can also catalyze the intermolecular aldol reaction,[10] parallelled by a report by MacMillan *et al.* on the enantioselective organocatalytic Diels–Alder reaction[11] in the same year. After these discoveries, organocatalysis has become the focal point of research.

Organocatalysis has gained tremendous importance because of its green chemistry perspective. This objective would be completely fulfilled only if the other constituents involved in the reaction also possess similar properties. The most important constituent in a reaction is the solvent because it is always present in excess. One such solvent which satisfies this criterion of green chemistry is 'water' which is a suitable solvent in various biosynthetic reactions responsible for sustaining life. This has made chemists look at the possibility of using water as a reaction medium in synthetic organic chemistry.[5] Besides, water possesses some unique physical properties such as high surface tension, hydrogen bonding capability and polarity. All these properties have an important role to play in the ultimate influence that water exerts on organic reactions.

Initially, water was not considered to be a suitable solvent for organic reactions. This was mainly because the functional groups present in the reactants may themselves react with water molecules and secondly, most of the organic reactants are non-polar and thus insoluble in water. In addition to this, water may interfere with the transition state formed between organocatalyst and substrate molecules. This disrupts the hydrogen bonds and other polar interactions, thus deteriorating the catalytic activity and stereocontrol. Therefore, it was presumed that reaction in water leads to slow reaction rates and lower yields of desired products.[12]

The major breakthrough occurred after the studies done by Breslow in the 1980s on the Diels–Alder reaction in water.[13] These studies concluded that organic reactions can proceed well in aqueous media, which offer several advantages over those occurring in organic media. Further studies by Sharpless *et al.*[14] showed that several uni- and bimolecular reactions were greatly accelerated when carried out in vigorously stirred aqueous suspensions.

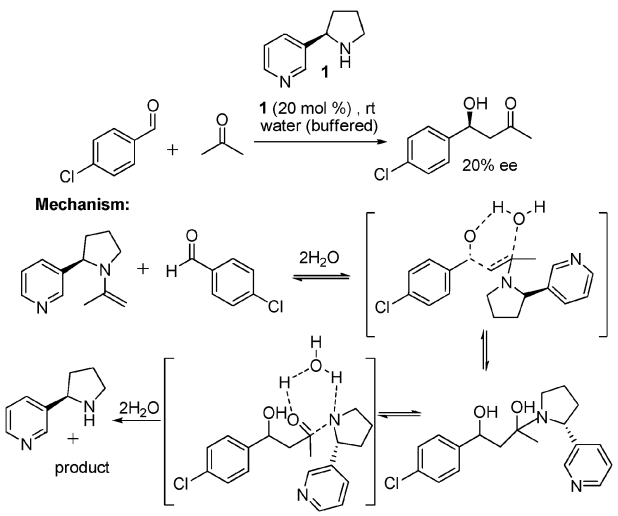
Although water does not dissolve organic reagents, it still accelerates the rate of many reactions.[15] The simple principle behind this is that water avoids mixing with the organic reagents because that will lead to its structural organization, which decreases the entropy of the reaction mixture leading to a thermodynamically unfavourable process. To avoid this situation, water molecules bring the organic reagents close to each other, resulting in 'hydrophobic hydration'. Now, the reaction can take place in a concentrated organic phase away from water molecules, resulting in rate enhancement.[5]

As mentioned earlier, organocatalysts are stable and can tolerate the presence of moisture and air. Thus, considerable efforts have been made in developing water-compatible small organic molecules. Recently, there was some debate to clarify the terminology on whether reactions carried out in water should be called 'in water', 'on water' or 'in the presence of water'.[16] It is a matter of semantics about using these terminologies. In our opinion the reaction that occurs in an excess of water, without any organic solvent or excess of any reactant, can be termed as a reaction 'in water' regardless of whether the reaction takes place in the homogeneous or heterogeneous phase. With this viewpoint, this feature article aims to critically describe most of the reactions catalyzed by 'organocatalysts in water' during the past few years. A variety of C–C and C–heteroatom bond forming reactions (such as aldol, Mannich, Michael, azidolysis, Diels–Alder, Hantzsch, cycloadditions, *etc.*) catalyzed by organocatalysts in water are known. The examples reported herein are a selection of the recent significant contributions, which in our opinion have had major impact in this area. Further, this review demonstrates the ideas and challenges that are essential for the progress of this field.

Aldol reaction

The aldol reaction is one of the important carbon–carbon bond formation reactions in organic chemistry. A wide range of small organic molecules including L-proline are known to catalyze the asymmetric aldol reaction. Most of these reactions occur either in organic media or utilize water as a cosolvent or additive.[17] Extensive research is going on to design small organic molecules which can carry out the aldol reaction in water.

The pioneering work by Janda *et al.*[18] utilized nornicotine **1** to catalyze the aldol reaction of acetone and *p*-chlorobenzaldehyde in water (Scheme 1). Although they could achieve only a moderate enantioselectivity of 20%, it was the first experiment to show the role of water in an 'organocatalytic aldol reaction.' They proposed that water plays a dual role in catalyzing this reaction. Initially, hydrogen-bonded water activates the aldehyde for nucleophilic attack, by transferring the proton. Then, another molecule



Scheme 1

of water hastens the hydrolysis of the imine, resulting in the product with concomitant regeneration of the catalyst. The combined effect of these factors increases the rate of the reaction. This explanation was supported by a computational study.[18c] The absence of any product in organic solvents further proved the importance of water in the reaction. Pihko *et al*. observed significantly higher yields on addition of water to an intermolecular aldol reaction catalyzed by L-proline.[19] Pihko proposed that water assists in the hydrolysis of oxazolidinone, which acts as a parasite and deactivates proline, and thus, increases the rate and yield of the reaction.

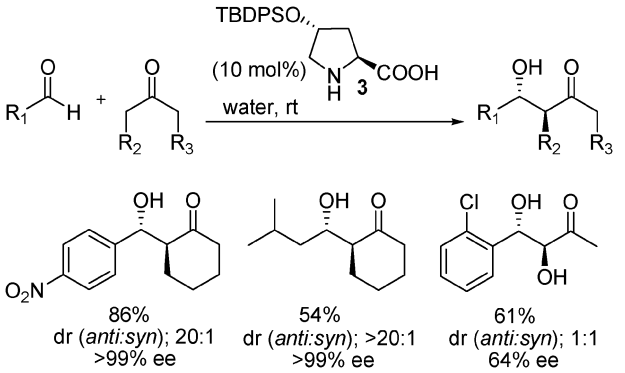
After the work by Janda *et al*., a number of contributions have been made in the literature using water as a solvent in various organocatalytic aldol reactions. Some of the highly efficient water compatible organocatalysts successfully used in aldol reactions are discussed below. The aldol reaction in water either occurs in the homogeneous or heterogeneous phase. Based on this, we have divided it into two sections.

Aldol reactions in heterogeneous media

The reaction in the heterogeneous phase occurs either in a biphasic medium or in a form of emulsion. For a catalyst to work well in heterogeneous media, it should contain sufficient hydrophobic groups incorporated in its basic skeleton for hydrophobic interactions to occur. Thus, the reaction takes place in a hydrophobic cavity away from water molecules resulting in high reactivity and selectivity. Some of the catalysts which fulfil this criteria and efficiently catalyze the aldol reaction are described in this section.

Barbas *et al*.[20] carried out a highly enantioselective direct aldol reaction catalyzed by a protonated diamine **2** as a bifunctional organocatalyst. This enantioselective methodology was good only for cyclic ketones to get a maximum of 99% ee. Acyclic ketones gave only moderate enantioselectivities (Scheme 2). They hypothesized that a small organic catalyst with appropriate hydrophobic groups assembled with the hydrophobic reactants in water and sequestered the transition state from water. As a result, the outcome of the reaction should be similar to that performed in organic solvents.

Further, Hayashi and coworkers,[17d,21] reported that a silyloxy proline **3**[17d] catalyzed highly enantioselective and diastereoselective direct aldol reaction in water. They found that just 1 mol% of catalyst was sufficient enough to catalyze the reaction with >99% ee (Scheme 3).

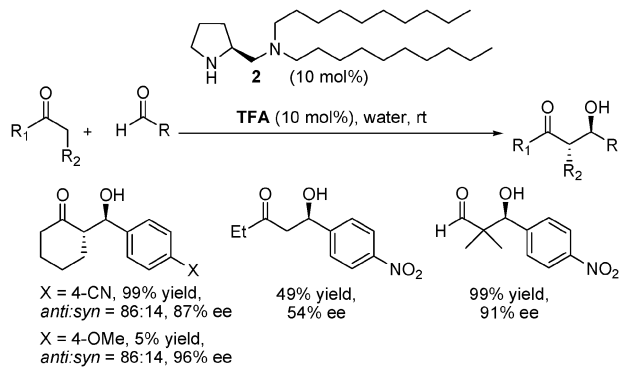


Scheme 3

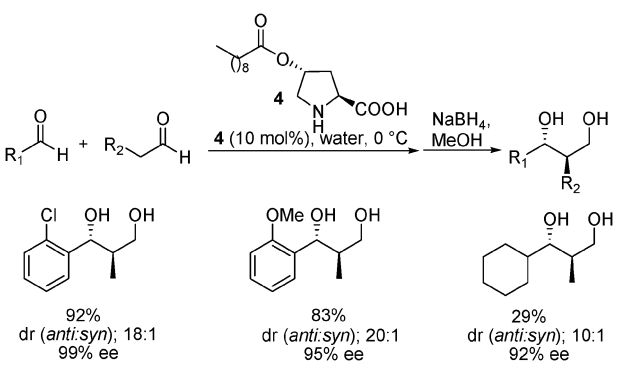
They proposed that this catalyst works in a biphasic medium. The catalyst failed to provide any product if one of the partners was water miscible. No product formed between two aldehydes such as propanal and 2-chlorobenzaldehyde.[46a] This is because of insufficient mixing of these substrates, as propanal is water soluble and 2-chlorobenzaldehyde is not. This limitation led to the discovery of surfactant-proline-derived organocatalysts **4**[21] for highly stereoselective crossed aldol reaction in water between two different aldehydes (Scheme 4). The reaction occurs in the emulsion, which allows mixing of the two substrates, thus resulting in high yield, enantiomeric excess, and diastereomeric ratio.

Chimni and Mahajan[22] in 2006, reported that a protonated chiral prolinamide **5** catalyzed enantioselective direct aldol reaction in water. They found that there was no reaction in the absence of water. For the reaction of acetone with *p*-nitrobenzaldehyde, they could obtain a maximum of 50% ee (Scheme 5).

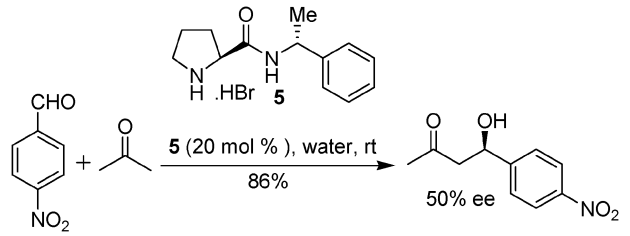
The above-mentioned catalysts have the limitation of giving moderate enantioselectivity with water miscible ketones such as acetone. Therefore, there was a great need for a chiral organocatalyst that could overcome these drawbacks. Singh *et al*. developed such a catalyst and contributed significantly to this field. They designed prolinamide catalysts bearing a non-polar *gem*-diphenyl group **6**, **7** and **8** that worked very efficiently for acetone in water. The advantage of the reaction is that the catalyst works equally well under neat conditions (Scheme 6).[23a] Very high yields and enantioselectivities were observed in water for a broad range of aldehydes and ketones.[23b,c] The advantage of catalyst **8** is that it gives high



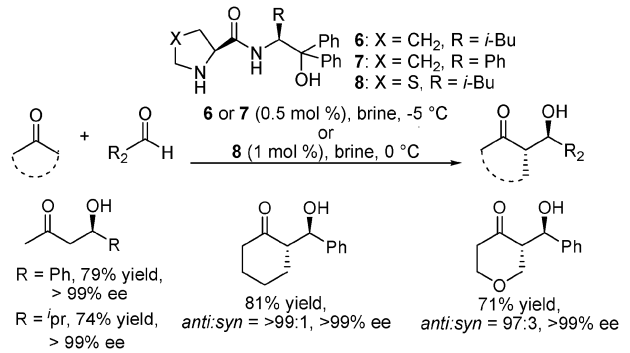
Scheme 2



Scheme 4



Scheme 5



Scheme 6

enantioselectivity with highly reactive aldehydes such as 4-nitrobenzaldehyde and naphthylaldehyde as compared to catalysts **6** and **7**.[23c] It was observed that yields and ees were superior in brine to those in water as a 'salting out effect' increases the 'hydrophobic effect'.[23b,c]

To investigate the role of water or brine in the direct asymmetric aldol reaction, control experiments were performed on the reaction of acetone and benzaldehyde using catalyst **8** and results are compiled in the form of a graph as shown in Fig. 1.[23c] It is evident from the graph that as the ratio of water was gradually increased, the time required for the completion of the reaction decreased to 6–8 h and the enantioselectivity of the product increased to 97%. This shows that water not only acts as a medium but also influences the rate and enantioselectivity. The rate enhancement can be explained on the basis of the hydrophobic effect which results in a concentrated organic phase above the aqueous phase and thus segregates the transition state away from the water molecules resulting in

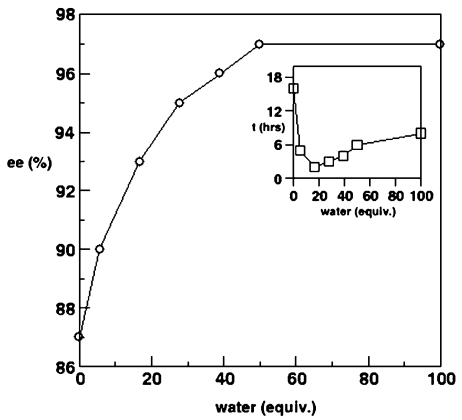


Fig. 1

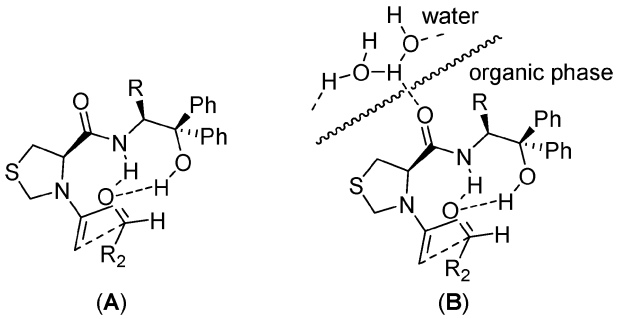


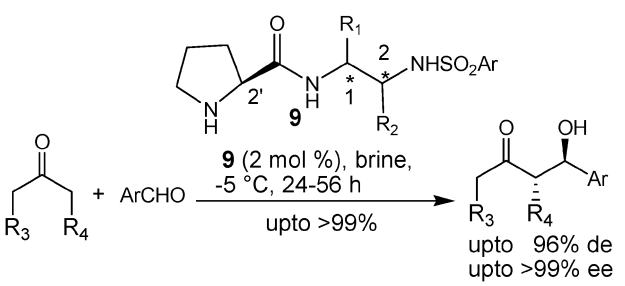
Fig. 2

high reactivity. Further, studies of these hydrophobic surfaces[23d–f] showed that hydroxy groups of the surface water molecules suspended at the hydrophobic interface might form hydrogen bonds with the amide oxygens but not with the NH and OH groups of the catalyst as they are surrounded by hydrophobic groups, leading to transition state **B** as shown in Fig. 2.[23c] As compared to transition state **A**, the reaction proceeds *via* transition state **B** by forming an additional hydrogen bond, thus making amidic NH more acidic leading to a compact transition state. Such compact networks ensure high enantioselectivity. This explains the increase in enantioselectivity of the aldol products in water.[23c]

Singh and Gandhi further synthesized another series of prolinamide catalysts **9** in which the β-amino alcohol moiety as shown in the above catalyst was replaced by a β-amino sulfonamide (Scheme 7).[24] These prolinamides **9** were synthesized *via* regioselective and stereoselective ring opening of chiral aziridines with azide anion.[24] These catalysts proved to be highly efficient for carrying out direct asymmetric aldol reactions, both with cyclic as well as acyclic ketones in brine with 2 mol% of catalyst loading, and afforded the products in excellent yields (up to 99%) and enantioselectivities (up to >99%).[24]

Further, study of the aldol reaction of acetone with aldehydes showed that there was no effect of changing the stereochemistry at C-1 and C-2 on the ee of the reaction if the reaction was carried out in an aqueous medium. However, a change in stereochemistry at C-2 had a significant effect on the ee of the reaction when the same reaction was carried out in neat acetone. The results can be explained by transition state models TS1 and TS2 (Fig. 3).[24]

When the stereochemistry at C-2 is inversed from *R* to *S*, there is a possibility of C–H–π interaction between the phenyl group at C-2 and a hydrogen of the aromatic ring of benzaldehyde if the attack takes place from the *Si*-face of



Scheme 7

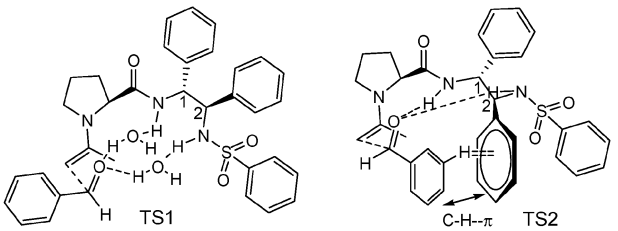


Fig. 3

aldehyde (TS2) rather than the *Re*-face. This interaction stabilizes TS2 to a certain extent and hence leads to a drop in ee of the product. This C–H–π interaction is disturbed when the reaction is carried out in an aqueous medium because water molecules enter into the spaces between the catalyst and participate in H-bonding with the substrates and the catalyst TS1. Hence, the effect of changing the stereochemistry at C-1 and C-2 on the reaction in brine was not observed.[24]

From the above reports, it is evident that if a hydrophobic group is attached to proline or prolinamide, the catalyst would efficiently catalyze the aldol reaction in water.[25] This goal can be achieved by functionalization of the hydroxy group in 4-hydroxy L-proline.

Various functionalized 4-hydroxy prolines **10**, **11** and **12**[26] have been reported for carrying out asymmetric aldol reactions in water (Fig. 4). These catalysts catalyzed the asymmetric aldol reaction of cyclic ketones and aldehydes in water with high yields, diastereo- and enantioselectivities. 4-(*tert*-Butyldiphenylsilyloxy)pyrrolidine-2-carboxylic acid **10**[26a] synthesized by Zhao *et al.*, efficiently catalyzed the cross aldol reactions of ketones and β,γ-unsaturated keto esters, leading to chiral tetrasubstituted centers with high diastereoselectivities and enantioselectivities (Scheme 8). The reaction catalyzed by these organocatalysts occurs in the hydrophobic organic phase away from the water molecules *i.e.* a biphasic medium, which is responsible for the high reactivity and stereoselectivity.

On similar lines, other prolinamide based organocatalysts have been synthesized to carry out asymmetric aldol reactions in water. The L-proline based dipeptide **13**[27] was discovered by Li *et al.* and successfully applied to the asymmetric aldol reaction of unmodified ketones with various aldehydes such as aromatic, aliphatic, heteroaromatic and unsaturated aldehydes in water at 0 °C (Scheme 9). The products were obtained in high yields, diastereo- and enantioselectivities.

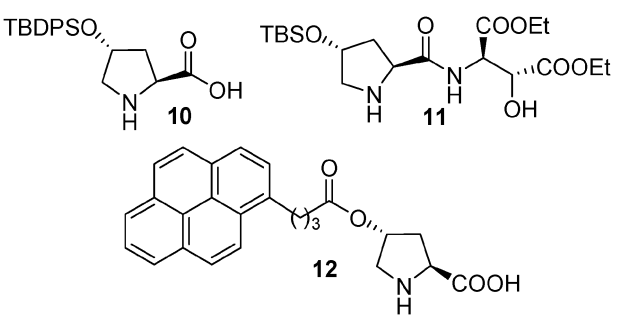
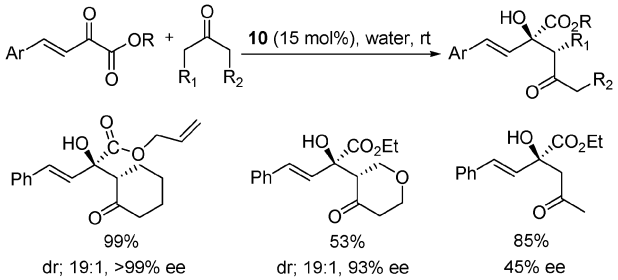
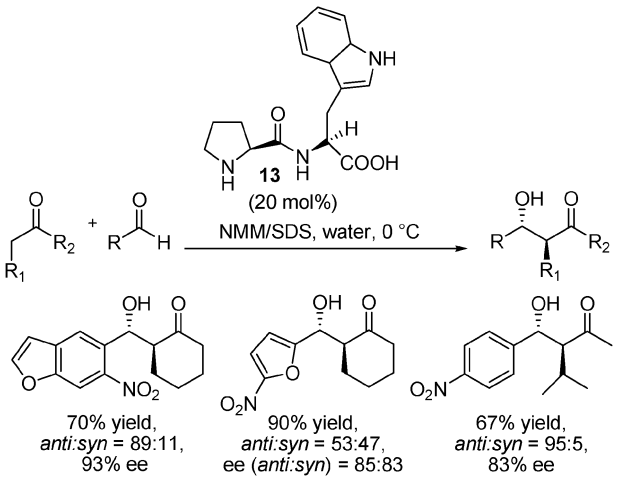


Fig. 4



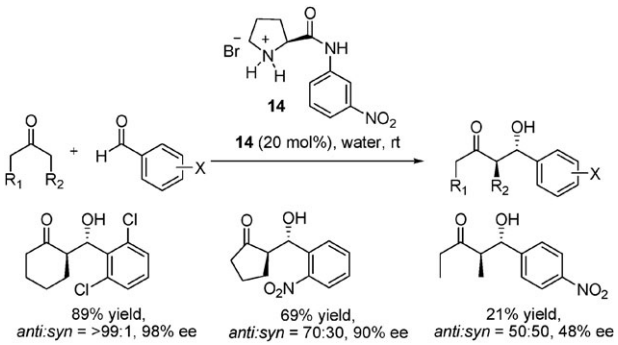
Scheme 8



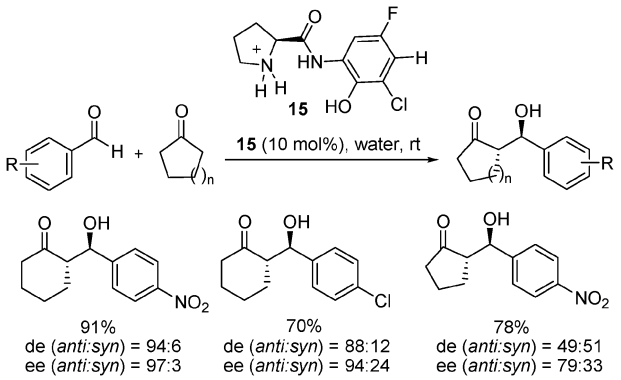
Scheme 9

Chimni *et al.* synthesized protonated chiral (*S*)-prolinamide derivatives **14** bearing aromatic rings[28] as water compatible organocatalysts for direct asymmetric aldol reactions, with the view that aryl groups provide suitable hydrophobic interactions and the amidic NH group provides appropriate hydrogen bonding on suitable orientation of the substrate (Scheme 10). The reaction afforded high yields, diastereo- and enantioselectivities for cyclic ketones and aryl aldehydes. On reaction with acyclic ketones, moderate yields and enantioselectivities were obtained with prolonged reaction time.

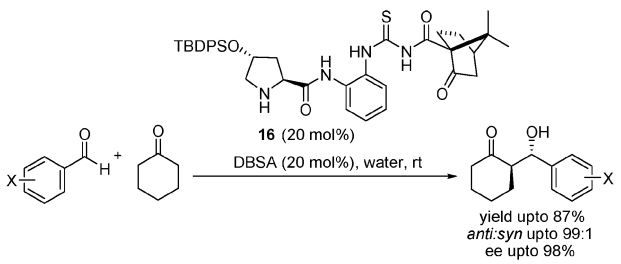
Another series of prolinamides **15** was derived by Vilaivan and Sathapornvajana[29] from 2-aminophenols with the aim of introducing an extra hydrogen bonding site in the prolinamide structure (Scheme 11). Very good yields, diastereoselectivities and enantioselectivities were achieved for the asymmetric aldol reactions of cyclohexanone and aromatic aldehydes.



Scheme 10



Scheme 11

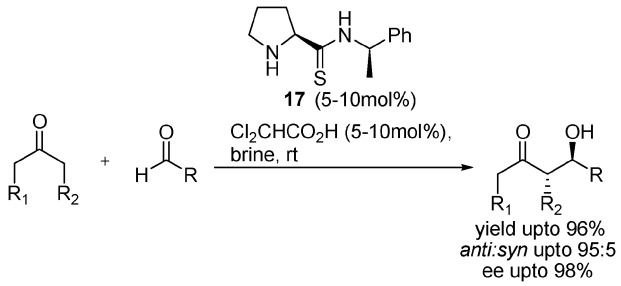


Scheme 12

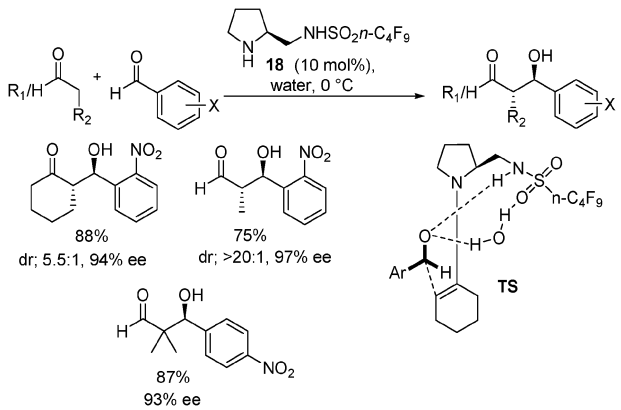
After a prolinamide had been synthesized and successfully employed as a catalyst for asymmetric aldol reactions in water, a related, insoluble bifunctional organocatalyst bearing a camphor scaffold with a thio-urea motif and amine functionality **16** was reported by Chen *et al.* (Scheme 12).[30] The rigid camphor scaffold serves a dual function: it acts as an efficient stereo-controlling element and secondly it increases the hydrophobic characteristics of the catalyst so it assembles with hydrophobic reactants in water. High yields, diastereo- and enantioselectivities of the *anti*-aldol products were obtained for the reaction of cyclohexanone with aryl aldehydes in water.

Coming in tandem with the above concept, Gryko and Saletra[31] synthesized L-prolinethioamide catalyst **17** for the direct asymmetric aldol reaction of cyclic ketones with aryl aldehydes in water (Scheme 13). Water is a suitable medium for this reaction as high yields and stereoselectivities were obtained. The reaction occurs in a hydrophobic organic phase *i.e.* in biphasic medium, which is evident from conducting the experiments with 'salting in' and 'salting out' salts. The rate and stereochemical outcome of the reaction were affected by hydrophobic aggregation, which proved that reactions were run at hydrophobic control.

Wang *et al.* synthesized a new series of fluorous (*S*)-pyrrolidine sulfonamide catalysts **18** (Scheme 14).[32] The reactions showed a broad substrate scope with ketones and reactive aromatic aldehydes. One of the advantages of this fluorous tag is its strong electron withdrawing nature that increases the acidity of the NH proton of the sulfonamide which thus provides a strong hydrogen bonding interaction with the substrate. Besides, this fluorous tag provides a handle for catalyst recycling by using a fluorous solid-phase extraction technique.



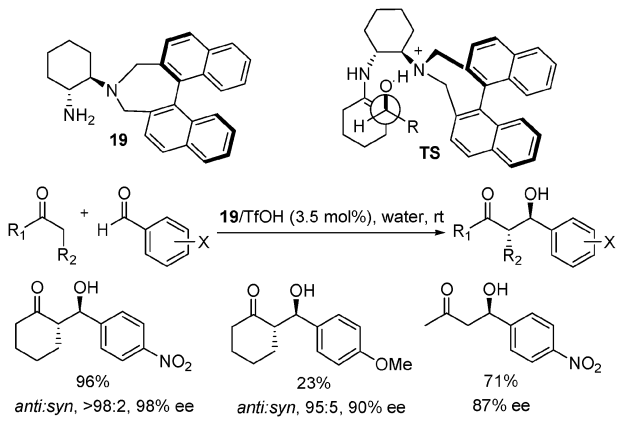
Scheme 13



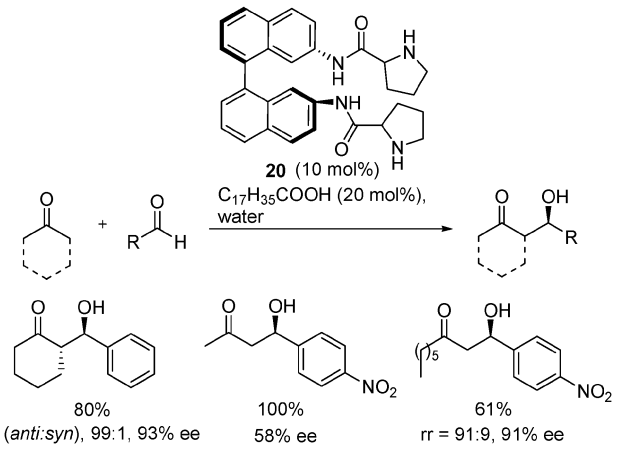
Scheme 14

The unique features associated with a chiral binaphthyl group have led to the synthesis of binaphthyl based catalysts. A chiral binaphthyl group in a catalyst plays a dual role as it acts as a second source of chirality, thus it increases the tunability of the catalyst. Secondly, the binaphthyl group provides hydrophobicity to the catalyst, thus it facilitates the formation of a hydrophobic phase with reactants in water, resulting in high rate and stereoinduction.

Shao *et al.* synthesized bifunctional primary amine binaphthyl catalyst **19**,[33] which efficiently catalyzed the asymmetric aldol reaction of aryl aldehydes with cyclic ketones in water with high diastereoselectivities and enantioselectivities (Scheme 15). On reaction with acyclic ketones such as acetone, moderate des and ees were observed. This may be due to the hydrophilic nature of acetone.



Scheme 15

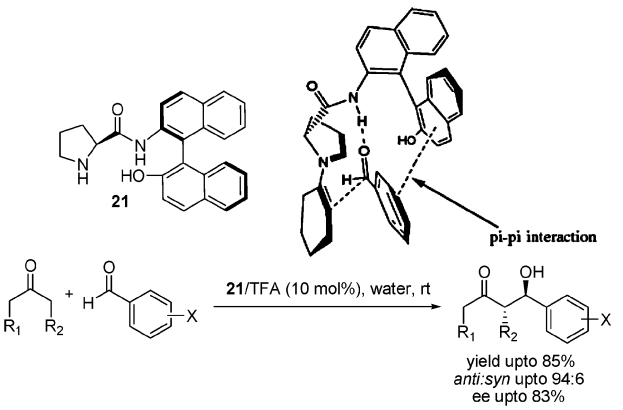


Scheme 16

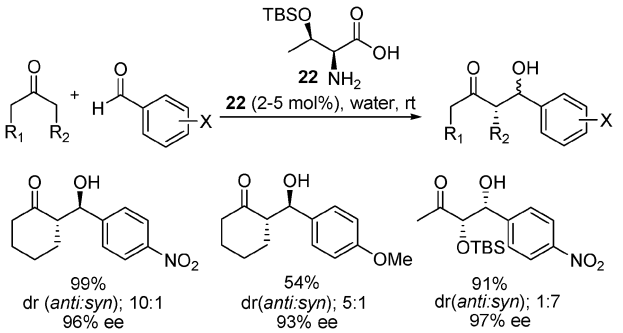
Similarly, another series of 1,1′-binaphthyl-2,2′-diamine-based (*S*)-prolinamides **20**[34] were reported. Benaglia *et al.* synthesized these catalysts for carrying out asymmetric aldol reactions in water using stearic acid as an additive (Scheme 16).[34a] High diastereoselectivities and enantioselectivities were observed for a broad range of substrates including cyclohexanone and acyclic ketones such as 2-octanone and 2-butanone with aromatic aldehydes. It was argued that a carboxylic acid having a long alkyl chain such as stearic acid facilitated the formation of the hydrophobic environment where the reaction takes place, resulting in high reactivity and stereoselectivity. Another advantage associated with this catalyst was its easy recyclability.

Zhang *et al.* synthesized another series of NOBIN-based pyrrolidine organocatalysts **21**[35] for asymmetric aldol reactions of cyclohexanone and aldehydes in water (Scheme 17). While determining the scope and limitations, it was found that reaction afforded high yields and stereoselectivities for a broad range of cyclic ketones and aldehydes, but the catalytic system could not be extended to acyclic ketones and aliphatic aldehydes.

It has already been reported that primary amino acids efficiently catalyze the asymmetric aldol reactions of hydroxyacetone in organic media to give *syn*-aldol products with high yields and stereoselectivities. The explanation related to this reaction has already been reported in previous



Scheme 17

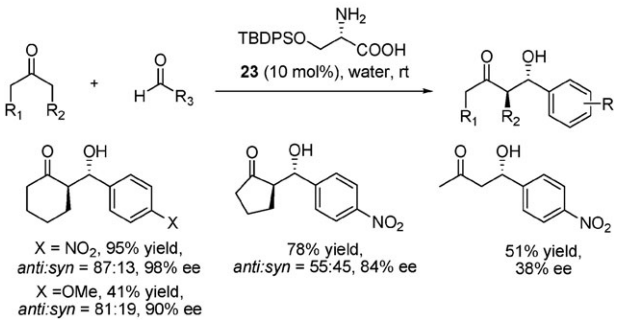


Scheme 18

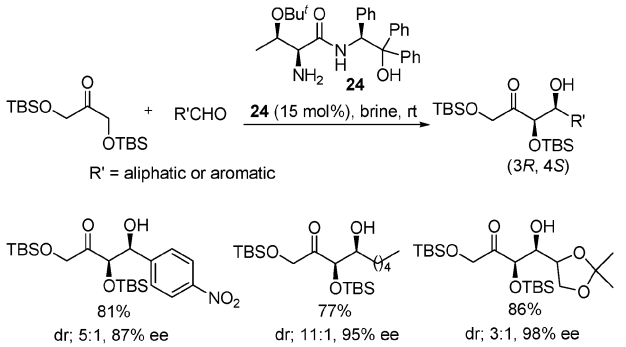
reviews.[1–3] Parallel to this idea, Lu *et al.* synthesized a primary amino based hydrophobic catalyst having a silyloxy group at the hydroxy function of L-threonine **22** (Scheme 18).[36] This catalyst gave *anti*-aldol products with cyclic ketones and *syn*-aldol products with acyclic ketones (such as protected hydroxyacetone) on reaction with aromatic aldehydes, with high ee and de. The limitation associated with this catalyst **22** is that it does not work well with aliphatic aldehydes. It was argued that silyloxy groups were expected to coordinate with aromatic groups of the substrates by hydrophobic interactions which was not the case with aliphatic aldehydes.

Likewise, Teo synthesized the silyloxy-L-serine organocatalyst **23** to catalyze direct asymmetric aldol reactions of cyclic ketones and aromatic aldehydes in water, *via* a two-phase system (Scheme 19).[37] High enantioselectivities and diastereoselectivities were observed for a broad range of substrates. A similar reaction was also performed with L-serine in water but no product was observed even after 2 days. This clearly indicated that the hydrophobic effect of the serine-derived organocatalyst was essential for the formation of a hydrophobic cavity, thus conducting the aldol reaction in an enantio-controlled fashion in water.

Analogous to the previous concept, Barbas *et al.*[38] very recently reported primary O-tBu-L-Thr based amide catalysts **24** bearing a *gem*-diphenyl group (as reported by Singh *et al.*[23a–c] (Scheme 6)) for carrying out asymmetric *syn*-aldol reactions with hydroxyacetone in water (Scheme 20). These catalysts gave high yields and stereoselectivities with protected hydroxyacetone in water, whereas with unprotected hydroxyacetone reaction did not proceed. This may be due to the



Scheme 19

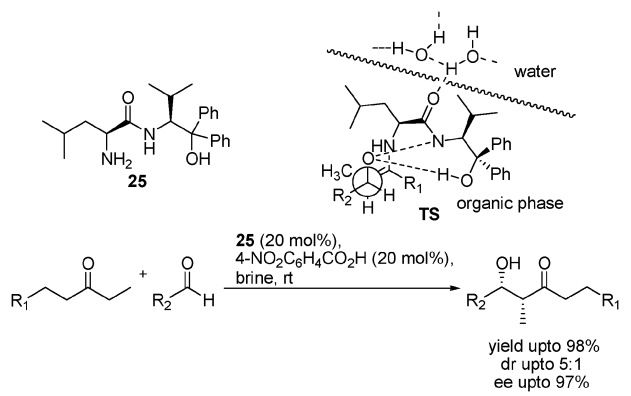


Scheme 20

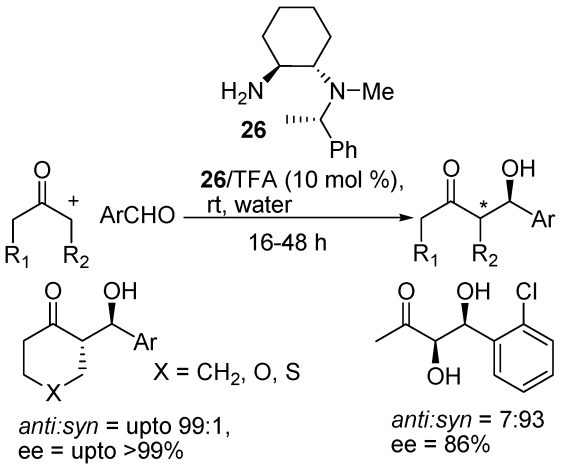
hydrophilic nature of hydroxyacetone. This was the first report where non-aromatic aldehydes, especially aliphatic aldehydes, gave good results with high yields and enantioselectivities.

At the same time, Gong *et al.*[39] independently reported primary amino acid based amide catalyst **25** bearing a *gem*-diphenyl group for carrying out asymmetric aldol reactions of aliphatic ketones with aromatic aldehydes in water (Scheme 21). High ees and des were observed for a broad range of substrates by using *p*-nitrobenzoic acid as an additive in brine. The enantioselectivity of the reaction decreases with increase in the length of the aliphatic ketone. Further, the reaction of aldehydes with 1,3-dihydroxyacetone did not proceed in water.

On similar lines, Singh *et al.* synthesized a series of primary tertiary diamines **26** containing aromatic groups for asymmetric aldol reactions of cyclic and acyclic ketones with aromatic aldehydes in water (Scheme 22).[40b] The idea behind this design was that the aromatic groups would form a hydrophobic cavity with reactants and the reaction would successfully take place in this cavity, resulting in high enantioselectivity and diastereoselectivity. It was found that the presence of a strong Brønsted acid such as TFA is essential to obtain high enantioselectivity and diastereoselectivity. Under the optimized set of reaction conditions catalyst **26**/TFA was explored on different sets of aldehydes and cyclic ketones to determine the general synthetic utility of the catalyst. In all the cases, the reaction afforded *anti*-aldol products with high diastereo- and enantioselectivities. When hydroxyacetone was used as a donor, the *syn*-aldol product was obtained with 86% ee in water. The enantioselectivity increased to >99% in



Scheme 21



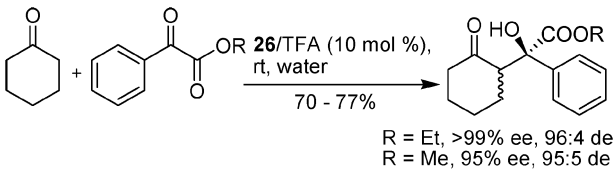
Scheme 22

the presence of a mixed solvent system *i.e.* DMF/water (10 vol%). This may be because a mixed solvent system provides an ideal environment for the maximum solubility of both hydrophilic hydroxyacetone and hydrophobic aldehydes (Scheme 22).

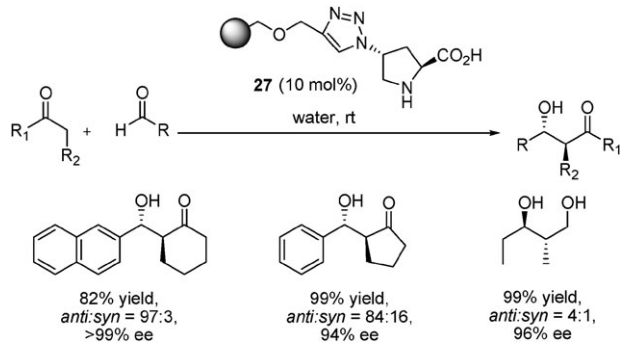
Next, a rare example of an aldol reaction of two ketones, where ketones act as both donor and acceptor was attempted.[40] The reaction of cyclohexanone and phenyl glyoxylates was carried out to generate the crucial tetrasubstituted carbon centre in an aqueous medium (Scheme 23).[40b] Gratifyingly, it was found that reaction with a catalytic amount of **26**/TFA (10 mol%) in water at room temperature gave the desired aldol products with good yields, excellent diastereoselectivities and enantioselectivities (Scheme 23).

It is known that amino acids are responsible for stereo-induction and they can be easily immobilized on a solid surface. This led to the development of several immobilized versions of catalysts.[41] The immobilization of amino acids on solid supports allows easy isolation of products from the reaction mixture and catalyst recyclability. Such catalysts provide an oversimplified version of enzymes in which the amino acid plays the role of the enzyme active site and the polymer represents the polypeptide backbone which is not directly involved in the catalytic cycle.

More recent efforts by Pericàs *et al.* involved the synthesis of 4-hydroxy proline **27** anchored on polystyrene resin obtained by click chemistry.[42] The reaction of cyclic ketones with aromatic aldehydes in water gave products with high diastereoselectivities of up to 97 : 3 and enantioselectivities of up to >99% (Scheme 24). Studies showed that both resin and the triazole moiety are beneficial for obtaining high stereoselectivity and reactivity. The reaction occurs in a single gel like phase rather than a multiphase system as observed with



Scheme 23



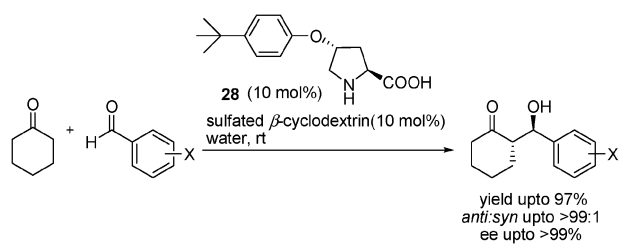
Scheme 24

other polymer based organocatalysts. The successful self condensation of propanal showed that the reaction does not occur in a concentrated organic phase as these reactants are hydrophilic in nature. The reaction with acyclic ketones such as acetone and hydroxyacetone gave products with low yields and moderate enantioselectivities. The advantages associated with this catalyst were its easy recyclability and reusability with no loss in activity.

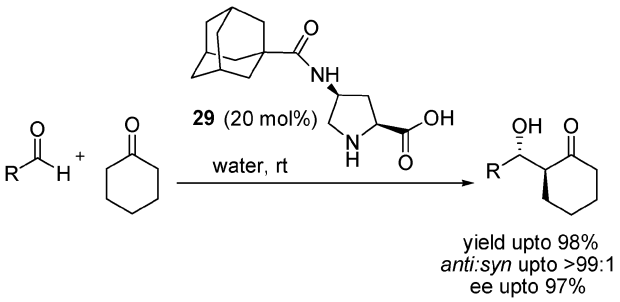
An interesting non-covalent immobilization technique was exploited by Armstrong *et al.*[43] in the synthesis of *tert*-butylphenoxyproline/cyclodextrin system **28** (Scheme 25). High stereoselectivities were observed for reaction of cyclohexanone with a broad range of aromatic aldehydes regardless of the substituent present on the aromatic ring but low yields were observed with aromatic aldehydes having an electron releasing group. This reaction occurs in the hydrophobic cavity formed by cyclodextrin in water. The role of water is to bring this hydrophobic catalyst and reactant close together in the form of tiny oil droplets. This resulted in separation of bulk water from the reaction transition state leading to high reactivity and stereoselectivity.

Another example utilizing the non-covalent immobilization technique deals with the inclusion complex of a proline derivative and β-cyclodextrin **29**.[44] In this case, an apolar adamantyl ring serves as the handle for including the amino acid into the β-cyclodextrin cavity (Scheme 26). High yields, diastereo- and enantioselectivities were observed for the aldol reaction of cyclohexanone with aromatic aldehydes in water. The advantage of the system is that after extraction of the product, the catalyst remains in the aqueous layer and can be reused in subsequent reactions.

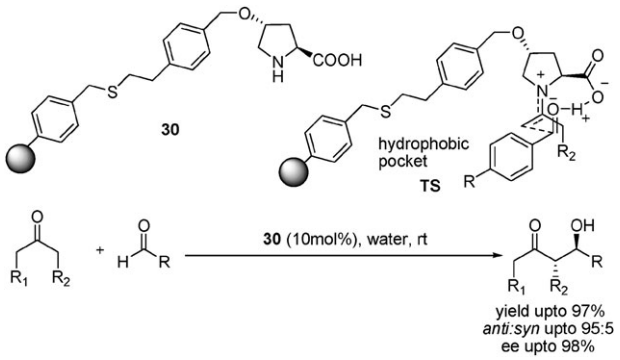
A simple synthetic methodology for the preparation of polystyrene supported L-proline **30** was reported by Noto *et al.* (Scheme 27).[45] This system was applied in the direct aldol reaction of several ketones with aromatic aldehydes in



Scheme 25



Scheme 26

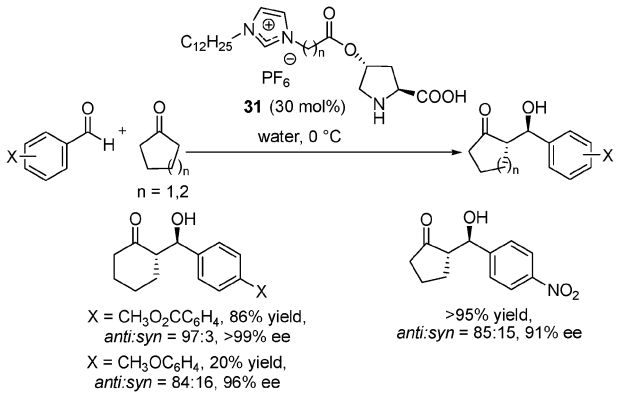


Scheme 27

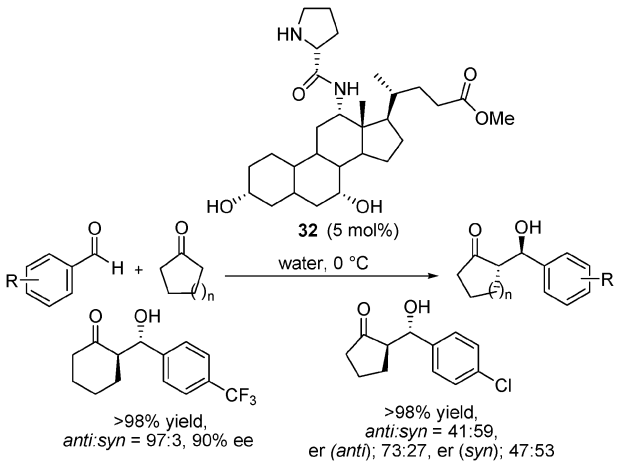
water. The reaction furnished aldol products with high yields and excellent diastereoselectivities and enantioselectivities. The observed high stereoselectivity was explained in terms of the hydrophobic microenvironment generated by the polystyrene chain of the catalyst whereas the hydrophilic pyrrolidine part resides at the interface of the organic and aqueous media. The reactants accumulate in this cavity by the hydrophobic interactions with polystyrene chain, thus reaction occurs in this concentrated organic phase. The crucial role played by the polystyrene chain in water was evident by carrying out the reactions in the homogeneous phase with hydrophilic reactants such as furfuraldehyde, pyran-4-one and acetone, leading to products with lower stereoselectivities.

Zlotin *et al.*[46a] synthesized new amphiphilic (*S*)-proline-modified task-specific chiral ionic liquid **31**, bearing hydrophobic (PF_6^-) anions for asymmetric aldol reactions in water (Scheme 28). This hexafluorophosphate salt gave a suspension in water and in this water suspension system high yields, diastereo- and enantioselectivities were observed for the reaction of cyclohexanone with aryl aldehydes. This catalyst can be recycled easily and retained its activity and selectivity over at least 5 reaction cycles. A similar type of catalyst was reported by Trombini *et al.*[46b] for carrying out highly enantioselective aldol reactions in water. High enantioselectivities and diastereoselectivities were observed for the reaction of cyclohexanone with different aldehydes.

The quest to obtain high reactivities and stereo-induction for asymmetric aldol reactions in water led Iuliano and Puleo[47] to synthesize bile acid derived organocatalysts **32** in which D-prolinamide is linked at the 12th position of cholic acid methyl ester (Scheme 29). In addition, the free hydroxyl groups at the 7th and 3rd positions guaranteed the good level



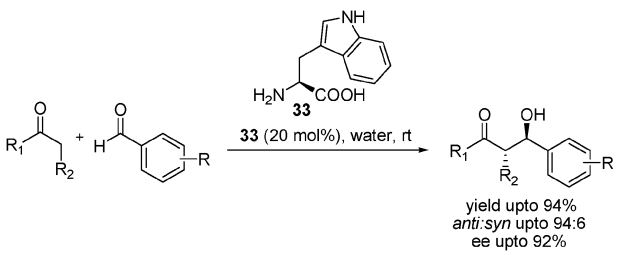
Scheme 28



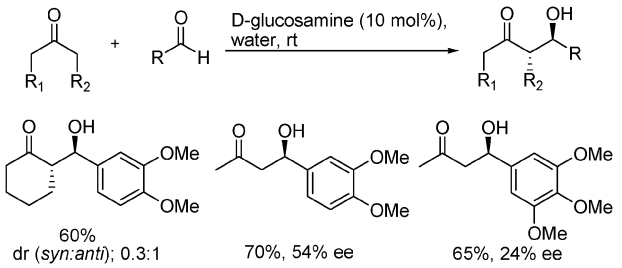
Scheme 29

of asymmetric induction. As expected, these organocatalysts gave high yields, diastereo- and enantioselectivities for aldol reactions between cyclic ketones and aromatic aldehydes in water.

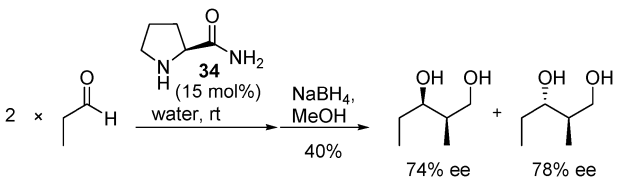
An idea of using simple organic molecule[48] led Lu *et al.*[48b] and Amedjkouh[49] to use naturally available simple amino acids (without any modifications) to conduct asymmetric aldol reactions in water (Scheme 30). As was hypothesized earlier, hydrophobic amino acid **33** as a catalyst would balance both the influence of hydrophobic interactions and hydrogen bonding in the transition state, required for conducting asymmetric aldol reactions in water. Based on the above assumption, various amino acids were explored. The best results in terms of yields, diastereo- and enantioselectivities were observed with L-tryptophan and L-phenylalanine. The



Scheme 30



Scheme 31



Scheme 32

high activity of aromatic amino acids as compared to proline in water is mainly because of the hydrophobicity, which explains the reason for the poor miscibility of these acids in water, resulting in heterogeneous mixtures.

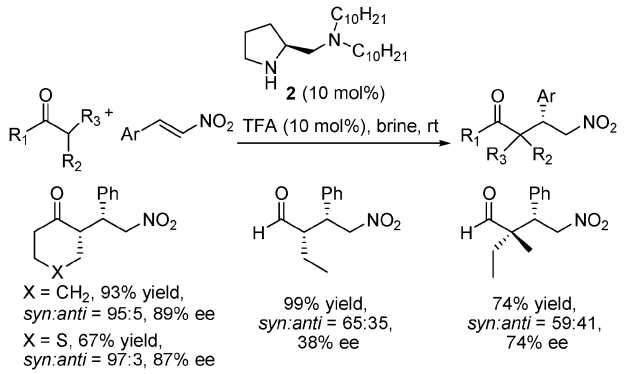
Tripathi *et al.*[50] used D-glucosamine, a natural amino sugar, as an organocatalyst for direct aldol reactions in water (Scheme 31). The reactions afforded aldol products in high yields for various aromatic aldehydes and ketones. In most of these cases enantioselectivity was less than 10%. The best enantioselectivity was observed in the reaction of 3,4-dimethoxybenzaldehyde with acetone.

Homogeneous catalysis

Homogeneous catalysis is the term given to those reaction mixtures in which all the components of the reaction are homogeneously dissolved in the water. All the catalysts reported so far carried out the reaction in heterogeneous media (either in a biphasic medium or as emulsion). Hayashi *et al.*[51] reported the first example of an organocatalytic asymmetric aldol reaction which occurs in the homogeneous phase in water (Scheme 32). They used proline amide catalyst **34** to carry out the self aldol reaction of propanal because of its hydrophilic nature. High de and ee were observed with the proline amide catalyst in water. The rate of the reaction decreased with dilution, which indicated that the reaction occurred in homogeneous medium. This was further evidenced from the observation that there was no reaction under neat conditions.

Michael reaction

Among the various C–C bond formation reactions, 1,4-conjugate additions play a significant role in organic synthesis.[52] Their strategic importance is evident by considering that a Michael addition reaction represents the initiating step in various complex inter- and intramolecular tandem processes.[53] Therefore, chemists have developed various catalytic asymmetric approaches for this important reaction.[54]



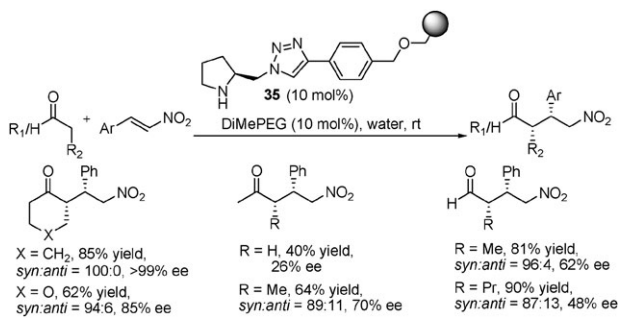
Scheme 33

Among the Michael acceptors, nitroalkenes are very attractive, as the nitro group can be further transformed into a nitrile oxide, ketone, amine or carboxylic acid, *etc*., providing a wide range of synthetically interesting compounds.[55] In particular, the Michael reaction of ketones and aldehydes with nitroolefins results in the formation of γ-nitro carbonyls which are valuable building blocks in organic synthesis.[56]

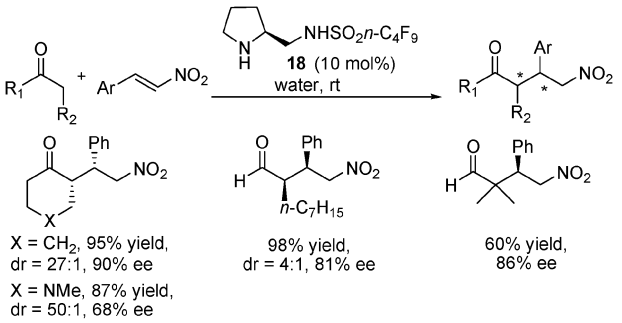
Few examples of organocatalytic Michael reactions in water have been reported in the literature. For instance, Barbas *et al*.[57] showed a highly enantioselective (97% ee) direct Michael addition of aldehydes and ketones to nitroolefins catalyzed by a diamine/TFA bifunctional organocatalyst **2** (Scheme 33). Brine was preferred over water as the reaction medium because amine catalysts initiate the polymerization in water. The best results were obtained in brine because in these electrolyte-rich solutions the anion intermediate undergoes complexation with metal cations which decreases the polymer propagation responsible for the side products. High yields and stereoselectivities were observed for broad range of ketones and aldehydes, as donors and nitroolefins, as acceptors.

Similarly, Pericàs *et al*.[58] reported a polymer supported organocatalyst **35** for Michael addition of ketones to nitroolefins in water with a maximum of >99% enantioselectivity (Scheme 34). Optimal operation in water and full recyclability make the triazole linker attractive for the immobilization of the organocatalyst. Michael additions of aldehydes to nitroolefins were also carried out using the same catalyst. High conversions and diastereoselectivities were obtained for linear aliphatic aldehydes but with moderate enantioselectivities.

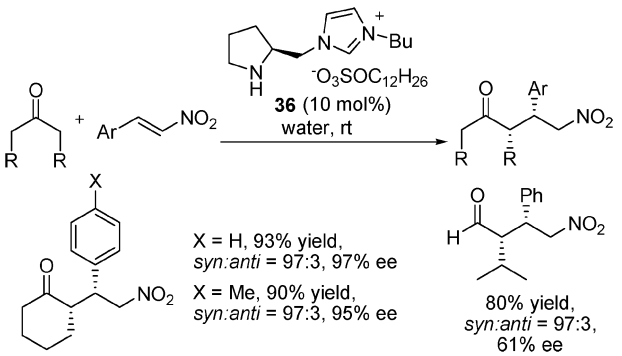
Wang *et al*.[59] used a recyclable (reused up to six cycles) fluorous (*S*)-pyrrolidine sulfonamide organocatalyst **18** for



Scheme 34



Scheme 35



Scheme 36

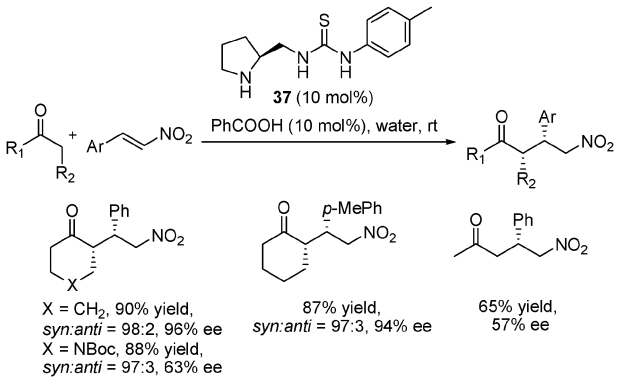
direct Michael reactions of ketones and aldehydes with nitroolefins in water with up to 93% enantioselectivity (Scheme 35).

Cheng *et al*.[60] synthesized surfactant-type asymmetric organocatalysts (SATO) **36** for the Michael addition of ketones and aldehydes to nitroolefins in water (Scheme 36). High enantioselectivities up to 98% and diastereoselectivities up to 99 : 2 were observed in water without using any organic solvent or additional additive. These SATO **36** work in a dual manner; that is, they function as asymmetric catalysts to accelerate the reactions and simultaneously act as surfactants, thus helping solubilize the organic substrates.

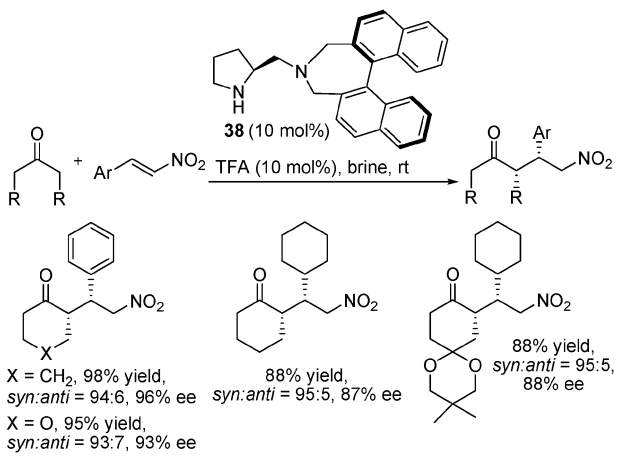
Almost all the examples of organocatalytic Michael reactions in water mentioned above suffer from some or other limitations such as limited substrate scope, high catalyst loadings, long reaction times and use of additives. One of the major challenges facing organic chemists was to devise a protocol that allows the successful use of two solid reactants. Therefore, there still remained a great need for a highly efficient catalytic strategy with respect to reactivity, selectivity and substrate scope.

Xiao *et al*.[61] reported easily tunable and bifunctional pyrrolidine-thiourea catalyst **37** for asymmetric Michael additions of ketones to nitroolefins in water (Scheme 37). The reaction of cyclic ketones with nitroolefins gave high yields, enantioselectivities and diastereoselectivities irrespective of the nature of the substituents on the aryl ring of the nitroolefin.

Singh and Maya synthesized novel binaphthyl based chiral diamine organocatalysts **38** for Michael additions of ketones to nitroolefins in brine (Scheme 38).[62] High diastereoselectivities of up to >95% and enantioselectivities of up to



Scheme 37



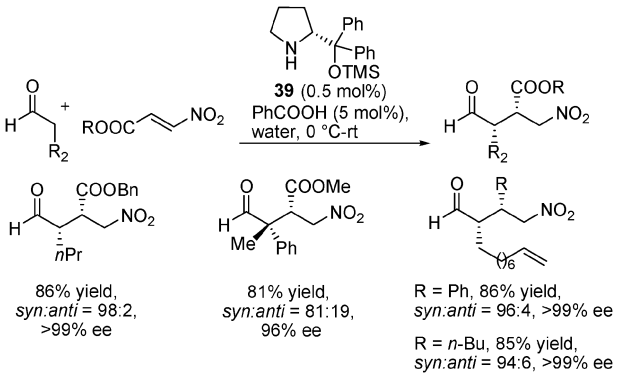
Scheme 38

99% ee were observed for a broad range of β-nitroolefins (both aromatic and aliphatic) and cyclic ketones. The high yields and enantioselectivities in aqueous/brine medium were explained by the hydrophobic environment created by the binaphthyl group in the reaction.[28] This helps in solubilizing the organic donor and acceptor molecules in a small volume, thus increasing the reactivity and stereoselectivity.

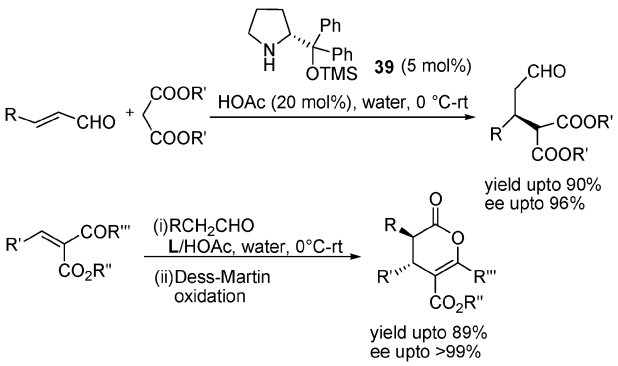
Recently, Ma *et al.*[63] synthesized OTMS-substituted diphenyl prolinol **39** for carrying out asymmetric Michael addition reactions of aldehydes and β-nitro acrylates (Scheme 39). These catalysts catalyzed the reactions very efficiently in water, leading to products with excellent diastereoselectivities (98 : 2) and enantioselectivities (>99%). They exhibited large substrate scope with regard to both aldehyde and β-nitro acrylate.

Later on, these catalysts were applied in the reactions of aldehydes with simple aryl or alkyl nitroolefins. For aryl-nitroolefins, excellent results were obtained with just 0.5 mol% catalyst loading which is the lowest loading reported to date for Michael reactions. Further, the reaction of malonates and α,β-unsaturated aldehydes gave excellent results in terms of yields and stereoselectivities (Scheme 40).[63] A similar catalyst was utilized to carry out the cascade Michael addition and cyclization of aldehydes and α-keto-α,β-unsaturated esters (Scheme 40).[63c]

Likewise, Jørgenson *et al.*[64] used TMS-protected diaryl-prolinol **40** to carry out Michael reactions of esters with



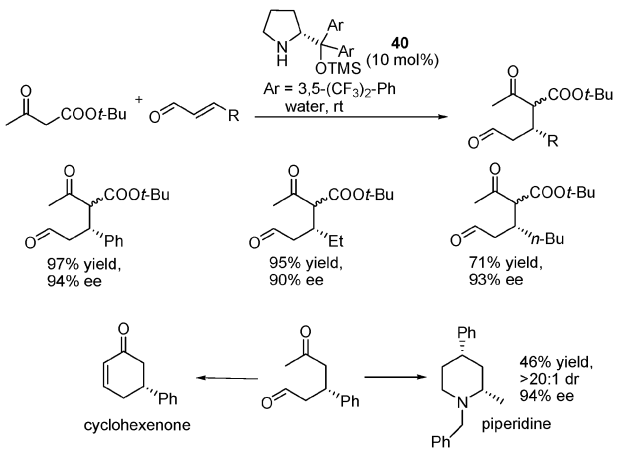
Scheme 39



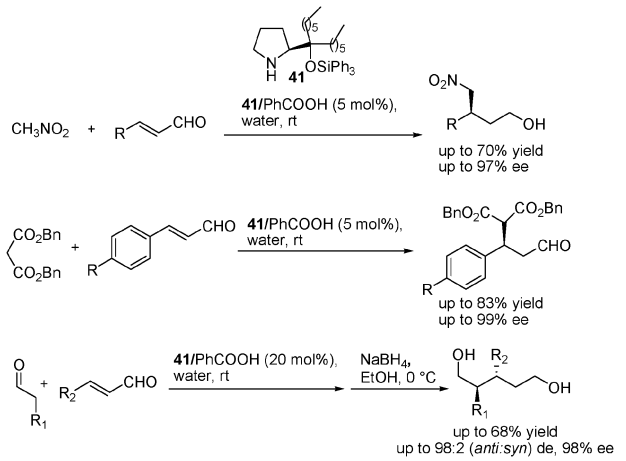
Scheme 40

α,β-unsaturated aldehydes in water (Scheme 41). High yields and enantioselectivities were observed with a broad range of esters and α,β-unsaturated aldehydes. The Michael product thus obtained was used for the synthesis of an optically active cyclohexenone and acted as an excellent starting material for the synthesis of biologically active compounds such as optically active piperidines.

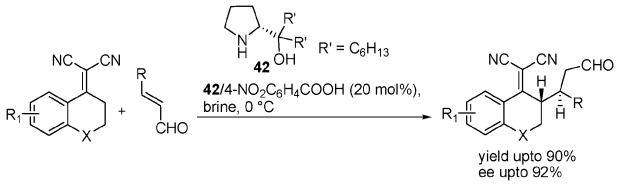
Palamo *et al.*[65] synthesized a new series of prolinol based organocatalysts **41** that enable imminium type catalysis of enals in water (Scheme 42). The catalyst was studied by carrying out Michael addition of nitromethane to enals. High yields and enantioselectivities were observed for a broad range



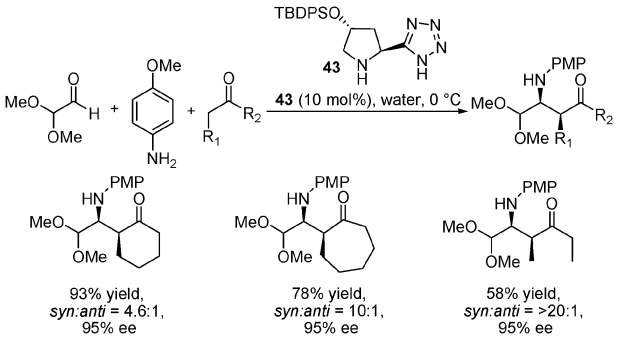
Scheme 41



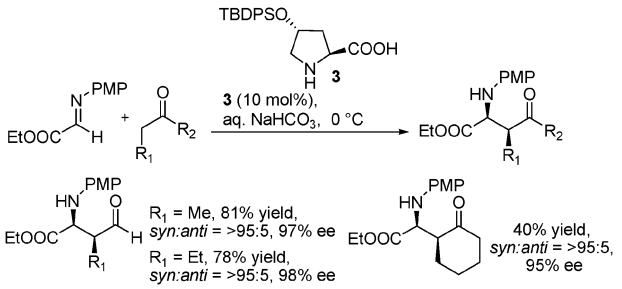
Scheme 42



Scheme 43



Scheme 44



Scheme 45

of substrates. Further, this catalytic system efficiently catalyzes the conjugate addition of malonates leading to products with high yields and enantioselectivities. The potential of these catalysts was evaluated by carrying out intermolecular Michael additions of aldehydes to enals. In all cases very high diastereoselectivities in favor of the *anti*-adduct and high enantioselectivities were obtained.

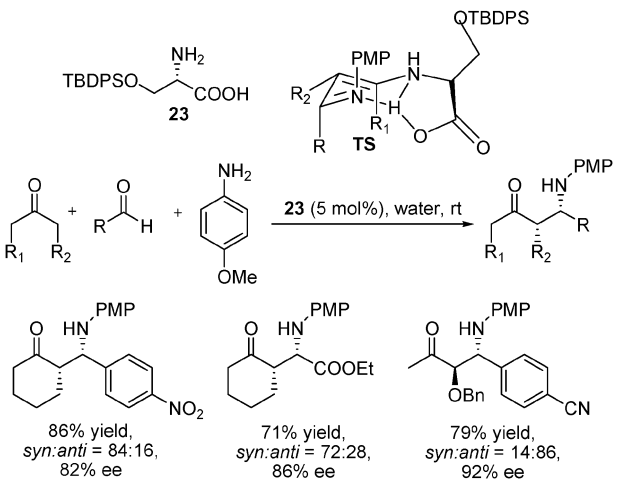
Loh *et al*. reported the use of prolinol catalyst **42** in carrying out Michael additions of vinylmalononitriles to α,β-unsaturated aldehydes in water.[66] High yields and enantioselectivities were observed when brine was used as a reaction medium with 4-nitrobenzoic acid as an additive (Scheme 43).

Mannich reaction

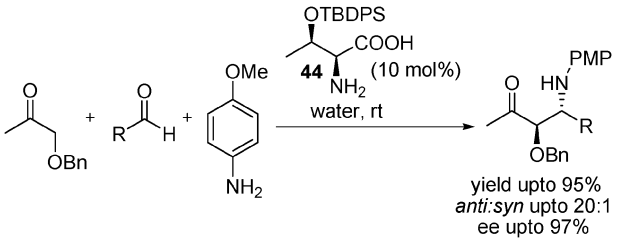
The direct asymmetric Mannich reaction catalyzed by small organic molecules provides a convenient route for the synthesis of optically active α- or β-amino acid derivatives and γ-amino alcohols.[67] The generated Mannich adducts can be further transformed to a variety of bioactive molecules.[68] Similar reaction in water offers an eco-friendly route to biologically active molecules. In this section recent contributions to the organocatalyzed asymmetric Mannich reaction in water are demonstrated.

Hayashi *et al*.[69] synthesized silyloxytetrazole hybrid catalyst **43** and silyloxy proline to carry out asymmetric Mannich reactions in water (Scheme 44). One pot reaction of dimethoxy acetaldehyde with *p*-anisidine and ketones catalyzed by the silyloxytetrazole hybrid catalyst, gave *syn*-products with high yields and enantioselectivities even in the presence of a large excess of water. The sodium salt of silyloxy proline **3** was effective for catalyzing the reaction with α-iminoethyl glyoxylate leading to products with high yields and enantioselectivities (Scheme 45). The high efficiency of this catalyst showed that the sodium ion plays the same role as shown by the carboxylic group. These reactions occur in the organic phase above the aqueous phase *i.e*. in biphasic medium.

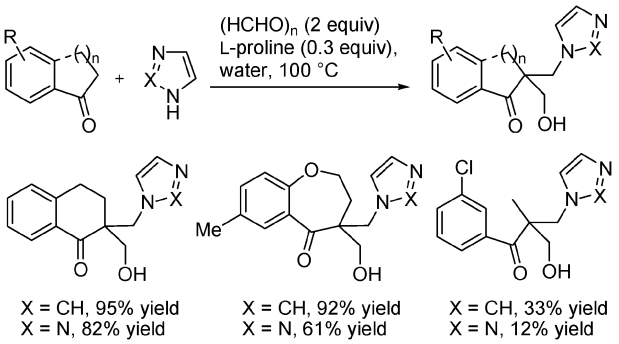
Teo *et al*.[70] synthesized highly efficient silyloxy serine organocatalysts **23** for carrying out three component asymmetric Mannich reactions in water *via* biphasic media (Scheme 46). High enantioselectivities and yields were observed for a large variety of cyclic and acyclic ketones as donors and aromatic aldehydes and ethyl glyoxylate as acceptors. The preference for *syn*-selectivity and the stereochemical outcome of the products was explained by a six-membered chair-like transition state model TS (Scheme 46).



Scheme 46



Scheme 47



Scheme 48

All the organocatalysts reported above gave *syn*-selective Mannich products, whereas *anti*-selective Mannich reactions are considerably more challenging. In order to obtain *anti*-selective Mannich products in water, Lu *et al.*[71] synthesized organocatalysts **44** derived from L-threonine (Scheme 47). The reaction of *o*-benzyl hydroxyacetone with *p*-anisidine and aromatic or aliphatic aldehydes resulted in *anti*-1,2-amino alcohols in good to excellent yields and enantioselectivities. Mannich reactions with aliphatic aldehydes having both linear and branched alkyl chains afforded products with high yields and enantioselectivities.

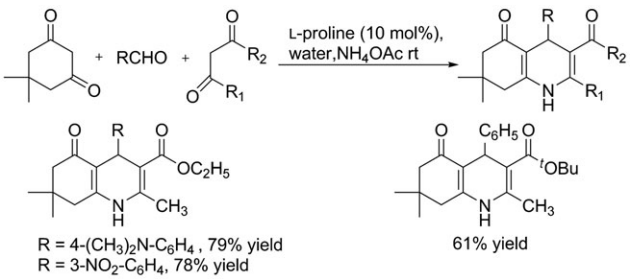
Amedjkouh and Brandberg reported an autocatalytic asymmetric Mannich reaction in water.[72] The Mannich adduct, which acts as a bifunctional catalyst, showed excellent reactivity and stereoselectivity. Better results were obtained in the presence of a buffer solution having pH 7.

Bhandari and Srinivas[73] reported a novel and facile method for the formation of a C–C–N bond with unsubstituted azoles catalyzed by proline in water under Mannich conditions (Scheme 48). The reaction was applicable to a large variety of ketones, resulting in Mannich–aldol type products in good to excellent yields. The double addition product obtained in water was deformylated readily to the desired Mannich product under basic conditions.

Miscellaneous reactions

Hantzsch reaction

1,4-Dihydropyridyl compounds are one of the most important classes of drug molecules that possess some unique medicinal properties such as neuroprotectant, platelet *anti*-aggregatory and cerebral antischemic activity[74] and are used for the treatment of cardiovascular disease.[75] From the green chemistry perspective, an ideal approach to synthesize these molecules is the organocatalytic Hantzsch reaction in water.



Scheme 49

Kumar and Maurya[76] reported a novel approach for the efficient synthesis of polyhydroquinoline derivatives *via* an unsymmetrical Hantzsch reaction using L-proline in water (Scheme 49). The reaction of substituted aldehydes, dimedone and acetylacetones or acetoacetate esters, catalyzed by L-proline in water afforded polyhydroquinoline derivatives in moderate to high yields. The reaction showed broad applicability with regard to substrate molecules.

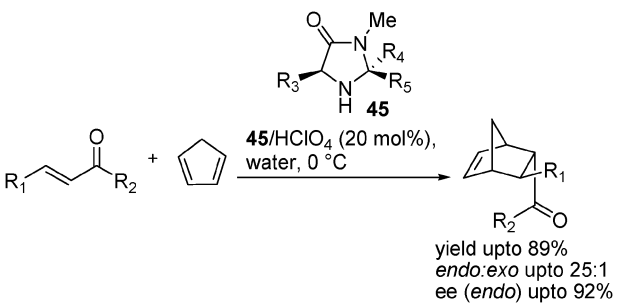
Cycloadditions

Since, organocatalysis in water emerged as a green complement to metal catalysis with remarkable achievements in aldol, Michael, Mannich and Hantzsch reactions as shown above, there is a great need for not only increasing the number but the type of organic reactions catalyzed by small organic molecules in water.

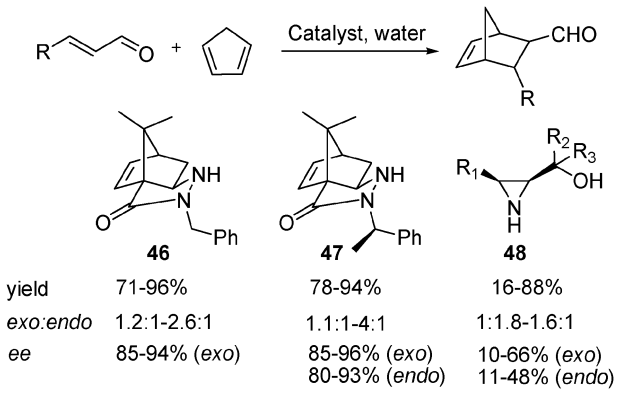
MacMillan and Northrup reported the organocatalyzed stereoselective Diels–Alder reaction (4 + 2 cycloaddition) of dienes with α,β-unsaturated ketones in water by using organocatalyst **45** and $HClO_4$ as an additive (Scheme 50).[77]

Further, Ogilvie *et al.* reported the use of cyclic hydrazide catalysts **46**·$HClO_4$, **46**·TfOH[78] and **47**·TfOH[79] in carrying out Diels–Alder reactions of cyclopentadiene and α,β-unsaturated aldehydes. These catalysts gave cycloaddition products with high yield, diastereoselectivity and enantioselectivity (Scheme 51). Also, Bonini *et al.* synthesized aziridin-2-ylmethanols **48**·$HClO_4$ to catalyze the same 4 + 2 cycloaddition reaction of cyclopentadiene and α,β-unsaturated aldehydes.[80] The products were obtained with low to moderate enantioselectivities (Scheme 51).

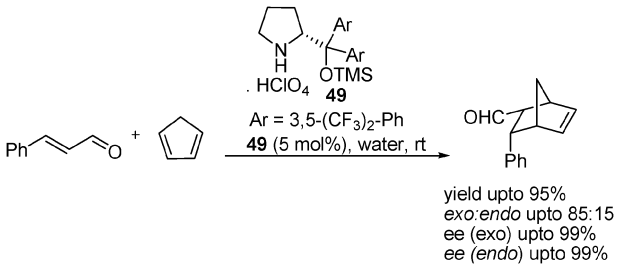
Hayashi *et al.* reported that diarylprolinol silyl ether salt **49** catalyzed the Diels–Alder reaction in the presence of water.[81] The products were obtained with high *exo*-selectivities and



Scheme 50

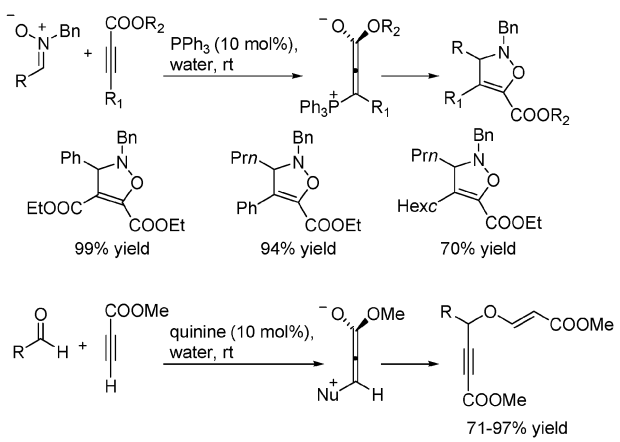


Scheme 51

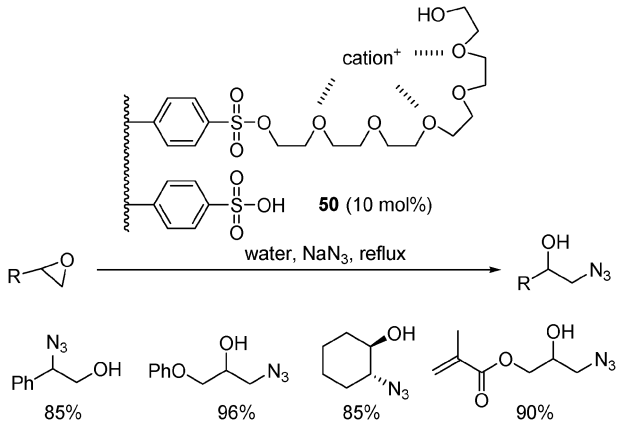


Scheme 52

excellent enantioselectivities. The role of water is to accelerate the reaction and increase the enantioselectivity (Scheme 52). Garciá-Tellado *et al.*[82] reported the first regioselective organocatalyzed 1,3-dipolar cycloaddition of conjugated alkynolates and nitrones in water (Scheme 53). This reaction was catalyzed either by tertiary phosphines or tertiary amines, and resulted in activated zwitterionic allenolates which underwent reaction with nitrones to give products in high yields and regioselectivities. This reaction exhibited large substrate scope with regard to both nitrones and alkynolates. Also, these activated zwitterionic allenolates reacted with terminal alkynes and aliphatic aldehydes to generate propargylic enol ethers in water with very high yields (71–97%). Water is the essential medium for conducting these reactions as in organic solvents reaction did not proceed. The remarkable feature of this



Scheme 53



Scheme 54

reaction is that since a lot of charged intermediates are involved even the reactivity displayed by these species in organic solvent is fully maintained in water.

Azidolysis

Likewise, Kiasat *et al.*[83] synthesized poly(ethylene glycol) grafted onto Dowex resin **50** to carry out regioselective organocatalyzed azidolysis of epoxides in water (Scheme 54).

It was found that this solid–liquid PTC catalyzed the reaction efficiently to afford azidohydrin in excellent yield under mild reaction conditions. Both steric and electronic factors are responsible for the observed high regioselectivity. In the case of aliphatic epoxides reaction occurred at the less substituted side due to steric reasons. Whereas, in the case of aromatic epoxides electronic factors predominate over steric factors and attack occurred at the benzylic position because of the charge delocalisation on the benzylic carbon.

Conclusions

Organocatalysis has evolved as the third major way of catalyzing the wide variety of organic reactions, besides enzymes and metal catalysis. From a green chemistry perspective, the development of highly stereoselective organocatalytic methodology in an aqueous medium has become the most desirable area of organic chemistry. Considerable progress in this field has been made in the past few years. Notably, highly efficient organocatalytic reactions in water such as aldol, Michael, Mannich and Hantzsch reactions, cycloadditions and azidolysis have been developed. Despite the advantages associated with organocatalysis, it cannot outweigh the significance of bio- and metal catalysis. For example, some of the very important transition metal catalyzed reactions such as cross-coupling and metathesis reactions are still unlikely for organocatalysis. Therefore, aqueous organocatalysis still needs to be explored so as to develop a highly efficient organocatalyst that does multiple reactions extremely well with even wider practical applications.

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