DOI: 10.1002/adsc.200800731

Water in Stereoselective Organocatalytic Reactions

Michelangelo Gruttadauria,[a,*] Francesco Giacalone,[a] and Renato Noto[a]

[a] Dipartimento di Chimica Organica "E. Paternò", Università di Palermo,Viale delle Scienze, Pad. 17, 90128, Palermo, Italy
Fax: (+39)-091-596-825; e-mail: mgrutt@unipa.it

Received: November 26, 2008; Published online: January 12, 2009

Abstract: In this review, recent advances in asymmetric organocatalytic reactions carried out with variable amounts of water, from substoichiometric to a large excess (reaction medium), are discussed. We also summarize several proposed mechanisms for the different possibilities of the action of water both in the increased activity of the catalyst and in the asymmetric induction. Finally, the application of this catalytic methodology to the enantioselective synthesis of valuable compounds through enamine or iminium catalysis is presented.

Keywords: aldol reaction; Diels–Alder reaction; Mannich reaction; Michael addition; organic catalysis; water

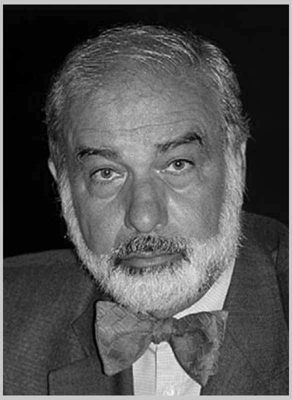
1 Introduction

Asymmetric organocatalysis is receiving great interest in the last years. Books,[1] special journal issues[2] and many reviews[3] have been published on this topic. More recently, efforts have also been devoted to asymmetric organocatalytic reactions performed using water as reaction medium. The use of water as reaction medium experienced a great development after Breslow's reports on acceleration of the Diels–Alder reaction performed in water.[4] An interesting discussion appeared in the literature about how to consider these reactions when water is used as reaction medium. Sharpless has defined as "on water" reactions a group of organic reactions that take place as an emulsion and that exhibit a reaction rate acceleration compared to the same reaction in an organic solvent.[5] Hayashi has discussed the use of "in water" or "in the presence of water" terminology.[6] He proposed to use "in water" when the reactants participating in the reaction are homogeneously dissolved whereas "in the presence of water" should be used for a reaction that proceeds in a concentrated organic phase with water being present as a second phase that influences the reaction in the organic phase. While the observed effect for "on water" reactions is rate acceleration, the observed effect for "in the presence of water" reaction is an increased enantioselectivity. The enhanced activity of organic catalysis "on water" has been recently theoretically investigated.[7] Free OH groups of interfacial water molecules play a key role in catalyzing reactions *via* the formation of hydrogen bonds. Indeed, calculations showed that approximately one in every four interfacial water molecule has a dangling OH group that protrudes into the organic phase, then, catalysis is expected when these OH's form stronger hydrogen bonds with the transition state than with the reactants. However, the use of water in organocatalytic processes has been questioned by Blackmond.[8] Two questions have been exposed: about the greenness and about the efficiency of an organocatalytic reaction carried out under aqueous conditions. We agree about the idea that combining the words "aqueous" and "organocatalytic" does not necessarily provide an environmental and economical process, however, we believe that an organocatalytic reaction carried out in an aqueous medium can be a very efficient process.

Since the re-discovery of proline as a useful organocatalyst[9] a huge number of papers have appeared in the literature. Even in the first full paper on organocatalytic reactions catalyzed by proline the role of water was investigated.[10] It was reported that the reaction of acetone and 4-nitrobenzaldehyde tolerated a

Michelangelo Gruttadauria (1964) studied chemistry at the University of Palermo where, in 1992, he became a researcher in the group of Prof. R. Noto. In 1994–1995 he joined the research group of Prof. E. J. Thomas at the University of Manchester (U.K.) working on stereoselective synthesis with chiral allylstannanes. Since 2006 he is full professor of organic chemistry at the University of Palermo. His fields of interest have been heterocycle synthesis, physical organic chemistry and stereoselective synthesis using organoselenium chemistry. His current interests include organocatalysis, supported ionic liquids, new recyclable materials for organocatalytic reactions and sailing with his 40.7 Beneteau. He is co-author of about 80 papers.

Francesco Giacalone (1975) since June 2005 is a postdoctoral scientist at the University of Palermo under the supervision of Prof. R. Noto. He obtained his Ph.D. degree in organic chemistry from the University Complutense of Madrid in 2004 after completing his thesis work on the synthesis of electroactive materials for organic solar cells under the supervision of Professors J. L. Segura and N. Martín. With the latter he worked as a postdoctoral ESF Fellow scientist (2004–2005) in molecular electronics. His current research interests focus on the synthesis of novel active and recyclable organocatalysts.



Renato Noto (1946) obtained his chemistry degree at the University of Palermo in 1970. He is, since 1990, full professor of organic chemistry. He began his research activity in the field of physical organic chemistry with Professor Domenico Spinelli. Successively, his interest was concentrated to stereocontrolled synthesis of functionalized heterocyclic rings and to studies on inclusion equilibria of aromatic molecules in cyclodextrins. Recently he started a study on the effect of ionic liquids on several organic reactions. He is Director of the Organic Chemistry Department and Professor of the 1st organic chemistry course for the degree course in chemistry, and he also holds supramolecular chemistry courses for the specialized degree courses in chemistry. He is author of about 140 publications and 4 reviews.

small amount of water (<4 vol%) without affecting the enantiomeric excess of the aldol product. However, increasing the amount of water severely compromised the enantioselectivity and decreased the rate of formation of the aldol product.

Later, Ward reported that the presence of 1 equiv. of water improved the yields while maintaining excellent stereoselectivity in the reaction between thiopyranone and aldehydes in DMF.[11] Pihko reported that water allowed the use of a smaller excess of the donor ketone and increased the yield of the aldol products when cyclic ketones were employed.[12] Water suppresses the formation of proline-oxazolidinone that has been considered as a parasitic species.[13] Then, it has been suggested that the role of water is to prevent deactivation rather than to promote activity. Further studies were also presented about the role of water.[14] Such studies, carried out on the proline-catalyzed reaction between acetone and 2-chlorobenzaldehyde, allowed one to hypothesize a conflicting role of water. Water increases the total catalyst concentration due to suppression of unproductive species and decreases the relative concentration of productive intermediates by shifting the iminium ion back to proline.[14] Seebach and Eschenmoser have raised doubts about the fact that oxazolidinones are unproductive and parasitic species in proline-catalyzed aldol reactions.[15] Moreover, it has been reported that Seebach's proline-derived oxazolidinone overhauls L-proline and is at least as efficient as (*S*)-5-(pyrrolidin-2-yl)tetrazole in several organocatalytic aldol reactions.[16] In the case of the proline/

HCO_3^--catalyzed Baylis–Hillman reaction in DMF:water (9:1), it has been proposed that the cyclic enamine, formed by intramolecular attack of proline's carboxylate moiety on the α,β-unsaturated iminium ion, is the reactive intermediate.[17]

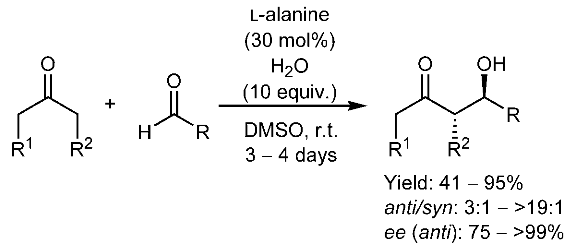
Rate acceleration in the proline-catalyzed aldol reaction without negative, or even with a positive effect on stereoselectivity was observed when water was used at up to 500 mol% in DMF solution.[12b] On the other hand, the proline-catalyzed aldol reaction carried out only in water does not take place or takes place with low enantioselectivity.[10,18] Proline and its derivatives operate by bifunctional catalysis and play the role of a simplified version of the type I aldolase enzymes, promoting the formation of an enamine and its enantioselective condensation with an aldol acceptor. In nature, type I aldolases enantioselectively catalyze this reaction in an aqueous environment. Even if proline acts as a simplified version of the type I aldolase enzymes it does not work in water. This has prompted researchers to devote their efforts to perform such reactions in water. Indeed, small molecules-organocatalyzed reactions in water with useful asymmetric induction would have immense synthetic utility. Moreover, amino acids organocatalysis in water could explain the development of homochirality in the early Earth.[19]

Recently, two reviews have described selected examples of organocatalytic reaction in aqueous media.[20] This review will deal principally with asymmetric enamine[21] and iminium[22] organocatalysis, in which water plays a crucial role, then reporting more detailed examples. As discussed before, we will report examples in which water both increases activity and stereoselectivity of the organocatalyst, when used from a substoichiometric amount to a very large excess (reaction medium).

2 Aldol Reactions

2.1 Primary Amino Acids as Catalysts

In the past few years a great deal of attention has been devoted to the naturally occurring amino acids as organocatalysts due both to its low cost and high enantiopure availability.[23] Even the simplest chiral amino acid, L-alanine, was able to catalyze the aldol reaction in excellent stereoselectivity, but with long reaction times, when employed in aqueous (10 equiv.) DMSO (Scheme 1). In such a reaction medium good results were also obtained with other amino acids, namely L-valine and L-isoleucine, as well as by using L-alanine-tetrazole.[24] The addition of water was crucial for the success of the reaction, indeed, in List's initial report some primary amino acids failed to catalyze aldol reactions.



Scheme 1. Aldol reaction catalyzed by L-alanine.

Proline was found to be not active as catalyst in water, whilst the more hydrophobic L-tryptophan gave good results when was used in such a media (Figure 1). To explain the stereochemical outcome, the authors proposed a model for the transition state in which the enamine attacks the aldehyde from the *Re* face and the aromatic side chain of tryptophan facilitates the formation of a hydrophobic core with other hydrophobic substrates in water (Figure 1).[25] Under the same conditions, fair results were shown also by L-leucine and L-phenylalanine.

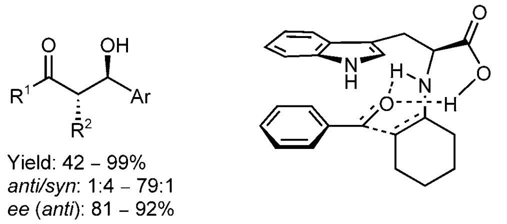


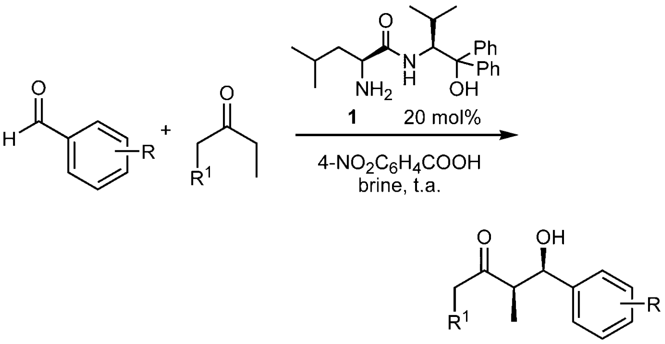
Figure 1. Proposed transition-state for L-tryptophan catalyzed aldol reaction.

Amedjkouh employed L-tryptophan (20 mol%) in water for the same reaction obtaining aldol products with lower stereoselectivity. The use of L-histidine led to a reversed enantioselectivity with the formation of equal amounts of *anti* and *syn* isomers, although in a rather slow reaction. The use of an organic base increased the yield and *syn* isomer, but the enantioselectivity decreased.[26]

Very recently, L-arginine-catalyzed aldol reactions in water as reaction medium have been reported.[27] No reaction took place in common organic solvents. However, only aromatic aldehydes with electron-withdrawing groups reacted giving aldol products with no enantioselectivity and very poor diastereoselectivity.

2.1.1 Modified Primary Amino Acids

Substituted amides derived from primary amino acids, for istance compound **1**, were synthesized and tested in the aldol reaction with 3-pentanone and aromatic aldehydes (Scheme 2).[28]



Yield: 78 – 98%
anti/syn: 1:4 – 1:7
ee (*syn*): 73 – 95%

Scheme 2. Aldol reactions catalyzed by compound **1**.

The presence of water (or brine) increased both the reaction rate and the stereoselectivity when compared to the reaction carried out under neat conditions. Brine as reaction medium was employed in the reaction between 4-nitrobenzaldehyde and several aliphatic ketones in the presence of 4-nitrobenzoic acid as additive. High yields and stereoselectivities were observed. However, no reaction was observed under aqueous conditions when dihydroxyacetone was used.

Probably, dihydroxyacetone was dissolved in the aqueous phase and then was isolated from the organocatalyst. The positive effect of water, when aliphatic ketones were used, was ascribed to the hydrogen bond formed between a free hydroxy group of surface water molecules at the hydrophobic interface with the amide oxygen atom of the organocatalyst (Figure 2).

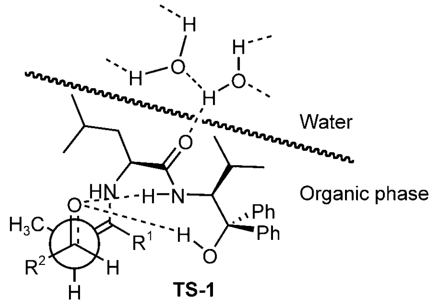
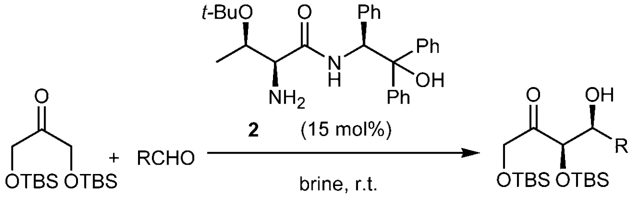


Figure 2. Proposed transition state for aldol reaction catalyzed by **1**.

Such a bond increases the acidity of the amide NH and then strengthens the related hydrogen bond with the aldehyde.

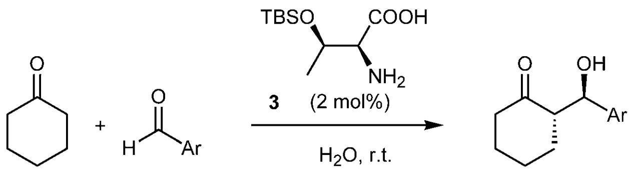
Catalyst **2** was used in the aldol reaction between dihydroxyacetone and aldehydes under non-aqueous condition (Scheme 3).[29] Such a reaction failed when carried out in aqueous media. Then, the more hydrophobic TBS-protected dihydroxyacetone was employed. Moreover, protecting groups can have considerable value in multistep synthesis. For this ketone donor, brine was found to be a suitable reaction medium, giving aldol products in good yields and high enantioselectivities.



Yields: 55 – >99%
syn/anti: 3:1 – 11:1
ee (*syn*): 87 – 98%

Scheme 3. Aldol reactions catalyzed by compound **2**.

Since several simple hydrophobic amino acids, such as tryptophan, were found to be active in aqueous media, and following Hayashi's idea of derivatizing the OH group of hydroxyproline with hydrophobic silyl groups (*vide infra*), further studies were carried out by using silyloxy derivatives of L-serine and L-threonine. In particular, TBS-protected L-threonine **3** was found to be an active and selective catalyst (Scheme 4).[30]



Yields: 54 – 99%
anti/syn: 4:1 – 19:1
ee (*anti*): 91– 99%

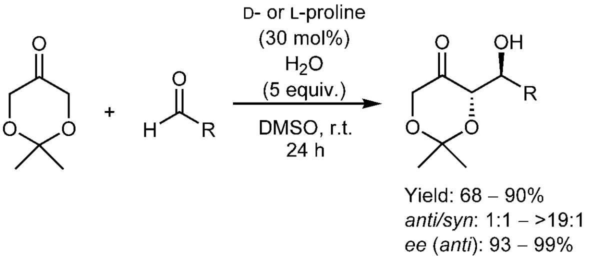
Scheme 4. Aldol reactions catalyzed by compound **3**.

2.2 Proline

No enantioselectivity was observed in the proline-catalyzed aldol reactions in phosphate buffer[31] and aqueous micelles.[32] When proline was used with camphorsulfonic acid as co-catalyst good yields and stereoselectivities were obtained using a 4:1 (v/v) ketone:water ratio.[33]

The use of proline (30 mol%) as catalyst in the reaction between dimethyl-1,3-dioxan-5-one and 4-nitrobenzaldehyde in DMSO led to low yields and stereoselectivities. Improved performances were displayed when 5 equivalents of water were used, furnishing aldol products in high yields and stereoselectivities with a set of aldehydes (Scheme 5).[35]

Two examples of cross-aldol reactions with aqueous formaldehyde to give α-hydroxymethylated ketones in high *ee* values were reported using L-proline (10 mol%) in DMSO.[35]



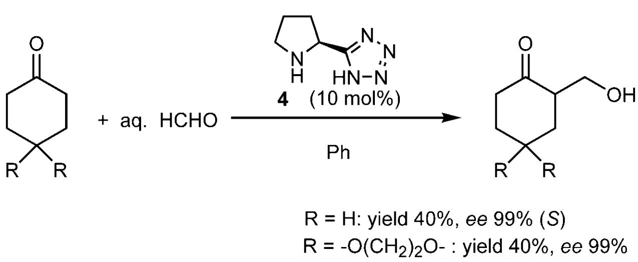
Scheme 5. D- and L-proline catalyzed aldol reactions between dimethyl-1,3-dioxan-5-one and aldehydes.

In 2007 it was reported that simple proline is able to catalyze aldehyde-aldehyde and aldehyde-ketone aldol reactions enantioselectively under dry and wet conditions. Although this procedure presented some advantages such as no modification required for proline and a completely organic solvent-free procedure, reaction times were long and up to 30 mol% of proline was employed. Interestingly, the authors concluded that since proline may have been present in the prebiotic era, these results may be an evidence that proline could have promoted enantioselective aldol reactions in the presence of water and so created enantiomerically-enriched organic compounds on the early Earth.[36]

A simple proline derivative showing similar acidity was proline-tetrazole **4**. Interestingly, it displayed different behaviour when used in water, indeed, while the use of a high amount of water caused decreased *ee* value in the reaction between acetone and 4-nitrobenzaldehyde,[10] addition of up to 10% water to DMF led to a small increase in enantioselectivity in the same reaction when the proline-tetrazole catalyst was employed.[37]

A similar behaviour was observed in the aldol reaction between cyclopentanone and chloral monohydrate. The reaction with L-proline was sluggish while the reaction with proline-tetrazole **4** and chloral monohydrate or anhydrous chloral and water (100 mol%) gave high yield and stereoselectivity (Scheme 6). Addition of a higher amount of water increased the enantioselectivity of the reaction and decreased the diastereoselectivity. On the other hand, the use of a catalytic amount of water (20 or 50 mol%) disabled the catalytic cycle (*ca.* 5% conversion). The authors hypothesized that water could prevent the formation of the iminium ion from catalyst and chloral.[38] This reaction was carried out with a set of ketones giving aldol products in high stereoselectivity.

The same catalyst was also used in the α-hydroxymethylation of two ketones under aqueous conditions (Scheme 7). Although the turnover number was modest, products were obtained in excellent enantioselectivity.

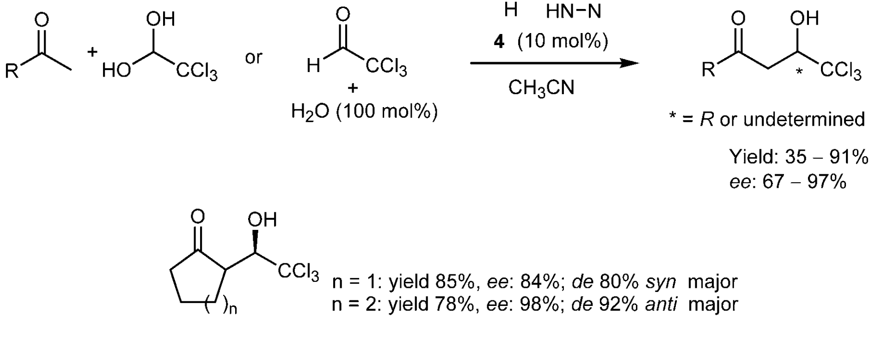


Scheme 7. Proline-tetrazole catalyzed aldol reactions.

2.3 Prolines Substituted in the 4-Position

As discussed before, proline was found to be not effective as catalyst when employed in neat water, so this finding has led several authors to start with the development of a number of proline derivatives of general formulae **I**, **II** and **III** (Figure 3) to use for the asymmetric direct aldol reaction in water.

In 2006, Hayashi and co-workers reported highly enantioselective aldol reactions in water employing a TBDPS-protected hydroxyproline (**5** in Scheme 8).[39] They investigated several catalysts in the aldol reaction in the presence of water showing that the most effective were proline derivatives with a hydrophobic



Scheme 6. Proline-tetrazole catalyzed aldol reactions.

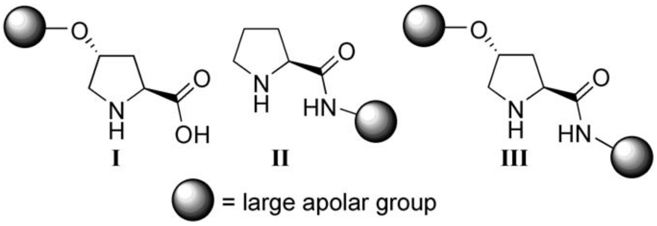
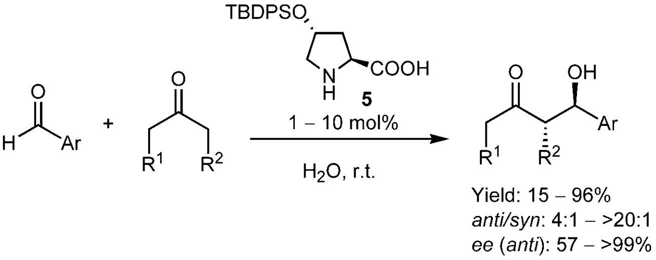


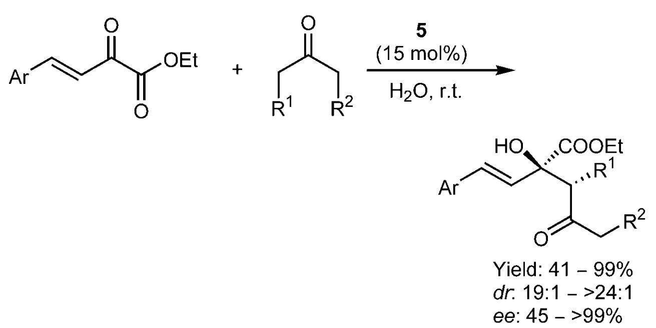
Figure 3. General formula for substituted prolines.



Scheme 8. TBDPSO-Pro catalyzed aldol reactions.

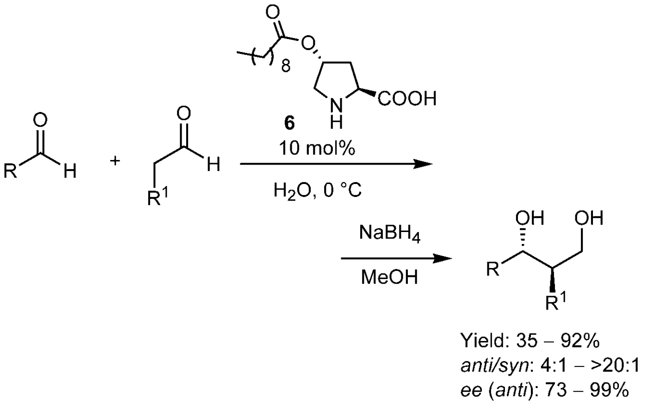
moiety such as *trans*-siloxy-L-proline or *cis*-siloxy-D-proline. Water was crucial in affecting the stereoselectivity of the reaction. Indeed, poor results were obtained when neat reaction conditions or dry organic solvents were employed. The authors carried out also a detailed study on the effect of the amount of water, on the amount of catalyst and applied the best conditions to a variety of substrates. Excellent results were obtained, since they performed several reactions with only 1 mol% of catalyst. Finally, it was reported that a large-scale preparation was successful with only 2 equivalents of ketone and 3 equivalents of water, without any organic solvent.[18]

The same catalyst has been very recently employed by Zhao in the construction of quaternary carbon centers through cross-aldol reactions between ketones and β,γ-unsaturated keto esters in water (Scheme 9). Screening of solvents (DMF, $CHCl_3$, toluene, *i*-PrOH, EtOH, MeOH) evidenced that in toluene the reaction occurred with high stereoselectivity while protic solvents gave a faster reaction. The use of water gave also a faster reaction and higher yields and stereoselectivitity were obtained.[40]



Scheme 9. Cross-aldol reactions between ketones and β,γ-unsaturated keto esters.

Hayashi also reported the use of 4-substituted acyloxyproline derivatives, such as compound **6**, for the enantioselective aldehyde cross-aldol reaction with excellent results without the need of additional co-solvent or additives (Scheme 10).[41] Probably, emulsions offer an ideal reaction environment in which organic molecules can be assembled through hydrophobic interactions thus enabling the aldol reaction to proceed efficiently.

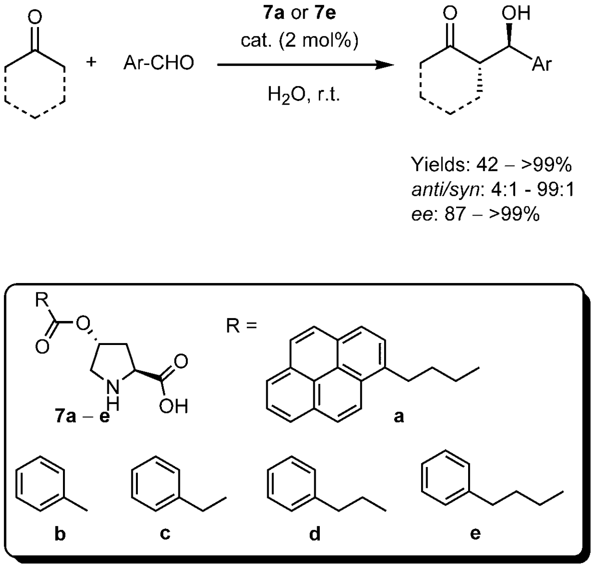


Scheme 10. 4-Acyloxyproline-catalyzed aldol reactions.

An amphiphilic L-proline derivative bearing a long alkyl chain on the 4-position *via* an ether bond was tested as catalyst in the aldol reaction both in organic solvents and in water. Reactions with cyclohexanone carried out using water, as reaction medium, gave better yields and stereoselectivities than those in organic solvents or neat conditions. Also in this case, proline derivatization gave a more active catalyst compared to native proline in water. Interestingly, the configuration and the *ee* value of the aldol product obtained in the reaction between acetone and 4-nitrobenzaldehyde showed to be dependent on the amount of water.[42]

Another group reported the use of three 4-substituted acyloxyproline derivatives, previously reported by Hayashi for the cross-aldol reaction. It was also found that organic solvents or neat conditions gave very poor results while the use of water furnished a water/oil emulsion giving the aldol product in high enantioselectivity. The higher yields and stereoselectivities were ascribed to the large interfacial area and uniformly distributed catalyst molecules in the emulsion system.[43]

Water gave a higher stereoselectivity compared to neat conditions or organic solvents, such as toluene, $CHCl_3$ and DMSO, when catalyst **7a** was used (Scheme 11).[44] This catalyst gave excellent results at room temperature in only 2 mol% loading without the need of an additive. The hydrophobic catalyst **7e**



Scheme 11. 4-Acyloxyproline-catalyzed aldol reactions.

was also employed with very good results, while less hydrophobic catalysts **7b–7d** gave poorer results. Interestingly, catalyst **7a** gave also excellent stereoselectivity even at 50 °C. These results further demonstrated that, in order to achieve high activity and stereoselectivity, it may be sufficient to have the proper acyloxy substituent in the 4-position of proline without the need of additional chiral backbones in the molecule.

Again, as in the work of Tao,[42] the configuration and the *ee* value of the aldol product obtained in the reaction between acetone and 4-nitrobenzaldehyde showed to be dependent on the amount of water. Moreover, a model for the explanation of the observed stereoselectivities, when water was employed as reaction medium, was provided (Figure 4). Such a model could be operative for proline derivatives of type **I**.

Hydrophobically modified ionic liquid-based organocatalysts were also prepared and used in water. Proline catalyst **8** (Figure 5), which was not soluble in water, was used in a few aldol reactions with good results.[45] However, because of the hydrolysis of the PF_6 anion,[46] the use in water could affect the results.

On the other hand, a water-soluble organocatalyst was designed in order to work in the asymmetric aldol reaction under aqueous biphasic conditions by a modulation of its partition coefficients in different aqueous biphasic environments.[47] The cationic moiety of catalyst **9** (Figure 5) contained three hydrophilic portions that rendered it very soluble in water. The highly hydrophobic anion allowed the catalyst to be transported to the organic phase of the biphasic ketone-water system where the aldol reaction took place with high yields and stereoselectivities. The hydrophilicity of catalyst **9** allowed also its separation from products by partitioning them between water and ether.

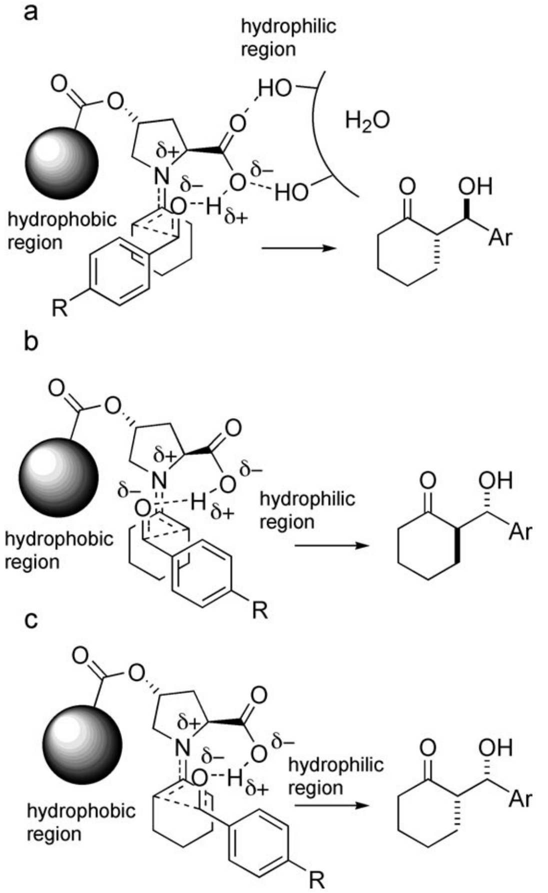


Figure 4. Proposed transition states for the aldol reaction catalyzed by proline derivative of type I: **a**) favoured; **b**) and **c**) disfavoured.

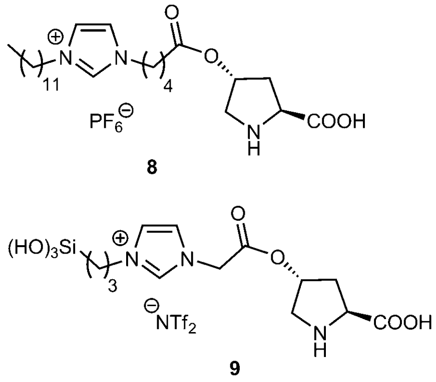


Figure 5. Chemical structures of compounds **8** and **9**.

2.3.1 Polymer-Supported Prolines

Since highly hydrophobic substituents in the 4-position of proline can enhance both activity and stereoselectivity of catalysts when employed in water, several researchers developed the use of highly hydrophobic supports, such as polystyrene, for proline immobilization. This approach enables the recovery of the catalyst and, because polystyrene may be regarded as a large apolar substituent, could favour stereocontrol of the aldol reaction in water. Pericás prepared a hydroxyproline anchored to a polystyrene support using a 1,2,3-triazole as linker (**10**, Figure 6).[48] Water gave better stereoselectivities compared to DMSO, DMF or neat conditions. In order to increase the yields DiMePEG was used as additive. Aldol products were obtained in good yields and stereoselectivities (Scheme 12).

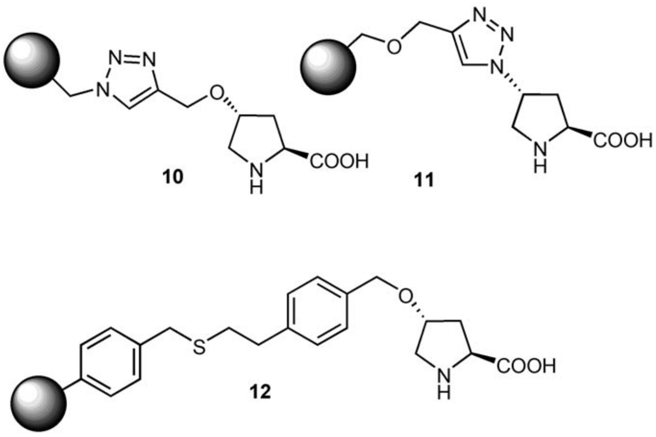
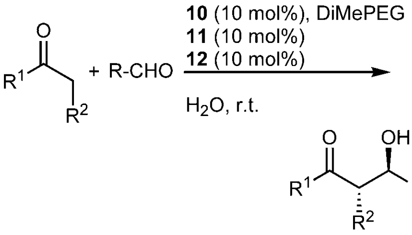


Figure 6. Structures of polymer-supported proline.



10: yield: 42 – 97%; *anti/syn*: 58:42 – 98:2; *ee* (*anti*): 45 – 97%
11: yield: 16 – 99%; *anti/syn*: 84:16 – 97:3; *ee* (*anti*): 94 – >99%
12: yield: 33 – 99%; *anti/syn*: 68:32 – >99:1; *ee*(*anti*): 66 – 98%

Scheme 12. Polymer-supported proline-catalyzed aldol reactions.

More recently, the same authors reported a new polystyrene-supported proline that was claimed to behave as an artificial aldolase because it was able to swell in water in spite of the hydrophobicity of the polymer backbone (**11**, Figure 6). The swollen resin showed a water content of up to 24% in weight, building in such a way an aqueous microenvironment. This material parallels the effect of essential water on some natural enzymes used in organic media. Indeed, it was demonstrated that only the water molecules that had swollen the resin gave the catalytic properties to this material. This property arose from the formation of a hydrogen-bond network connecting the proline and the 1,2,3-triazole linker. Catalyst **11** was used in a 10 mol% loading without any additive to give aldol products in high stereoselectivity (Scheme 12).[49]

A different polystyrene-based supported proline (**12**, Figure 6) for the aldol reaction between several ketones and aryl aldehydes with high stereoselectivities was also reported (Scheme 12). Screening of solvents showed that these reactions take place only when water was used. This solvent effect, coupled with the high stereoselectivities observed, was explained with the formation of a hydrophobic core in the inner surface of the resin whereas the hydrophilic proline moiety lies in the interface resin/water (Figure 7). Such a microenvironment both promoted the aldol reaction and increased the stereoselectivity. The authors hypothesized that solvents, such as DMSO or DMF, do not promote the reaction simply because they are good solvents. Ketones and aldehydes are well dissolved while the catalytic centre is supported on a material having a very low surface area. This strongly favours the repartition of the reactants in the liquid phase. When water is used as reaction medium, the reactants are forced in the hydrophobic pocket of the resin. In other words, the reaction proceeds in a concentrated organic phase. In this case the catalyst both promoted "on water" and "in the presence of water" aldol reactions.[50]

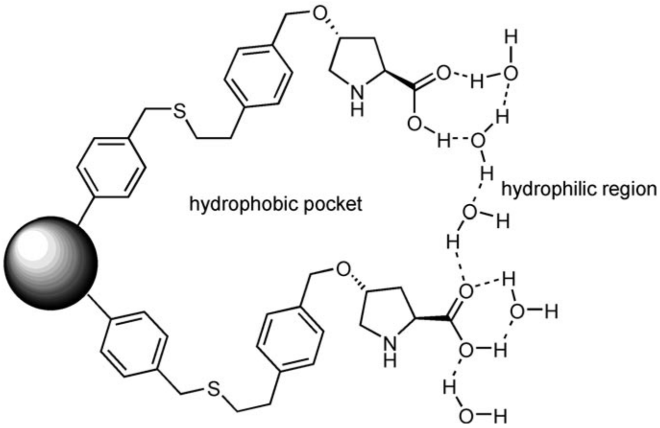


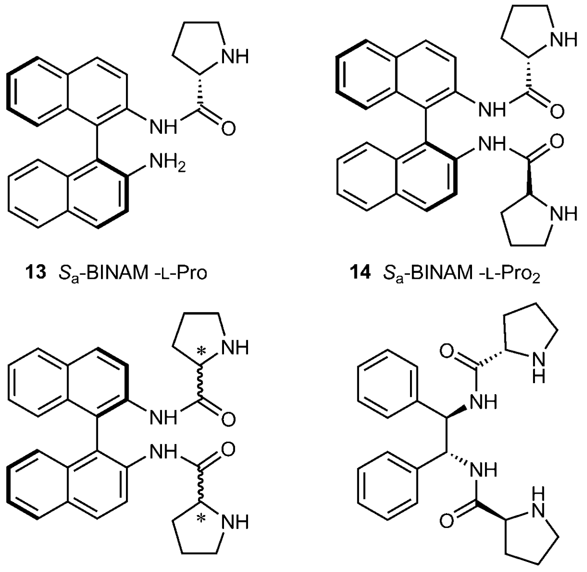
Figure 7. Proposed structure of the polystyrene-supported proline in the presence of water.

Water both increased yields and stereoselectivities when used as co-solvent with DMF or in ketone/water mixtures in the aldol reaction catalyzed by other polystyrene-supported proline catalysts.[51]

2.4 Prolinamides

Molecules of the types **I–III** are insoluble in water then, according to Hayashi, they will give reactions "in the presence of water". In order to have a reaction "in water" Hayashi and co-workers investigated the self-aldol reaction of propanal in water using several amino acids, amino amides or dipeptides. They found that simple prolinamide catalyzed the reaction "in water" with good enantioselectivity.[52]

Four BINAM-prolinamides (**13–15**) were tested as catalysts in the aldol reaction between acetone, 2-butanone and cyclohexanone and several aldehydes (Figure 8).[53] The best reaction conditions were found when water was used as a 1:1 mixture with DMF. However, reaction times were rather long. Later, the BINAM-prolinamide **14** was found to be an effective catalyst for the reaction between 4-nitrobenzaldehyde and several ketones in DMF:water or in neat water. In addition, the presence of benzoic acid as additive decreased sensitively the reaction time.[54] The same additive and catalyst were used in the aldol reaction with four α-substituted ketones.[55] Reactions were carried out in DMSO or DMF. The presence of water as co-solvent or as the sole reaction medium gave decreased stereoselectivities except in the reaction with an SMe-substituted ketone.



13 S_a-BINAM -L-Pro

14 S_a-BINAM -L-Pro$_2$

15a R_a-BINAM -L-Pro$_2$; * = L
15b R_a-BINAM -D-Pro$_2$ * = D

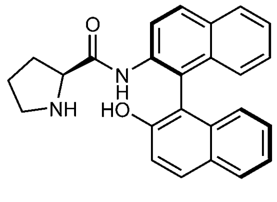
16

Figure 8. Prolinamides **13–16**.

Catalyst **14** was also employed by another research group. In this case only water was used as reaction medium in the presence of 20 mol% of benzoic or stearic acid as additive, with good results.[56]

Prolinamide **16** was used in water in the presence of TFA, as additive, in the aldol reaction between cyclohexanone or acetone and four aryl aldehydes with excellent stereoselectivity.[57]

In 2007 Jiang demonstred that NOBIN-prolinamide **17** (Figure 9) in the presence of TFA as additive give rise to aldol products in good yields and stereoselectivities.[58] Nevertheless, protection of the hydroxy group of catalyst **17** with a CH_3 gave similar results indicating that the OH group had little influence in the transition state. Probably, the NH hydrogen bonding and π-π interaction may play a role for the observed selectivity.



17 NOBIN

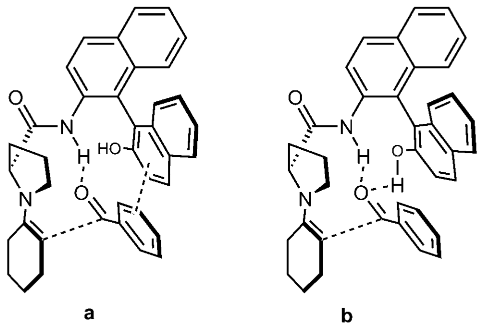


Figure 9. **a**) Proposed TS for the aldol reaction in water. **b**) Proposed TS for the reaction in dioxane.

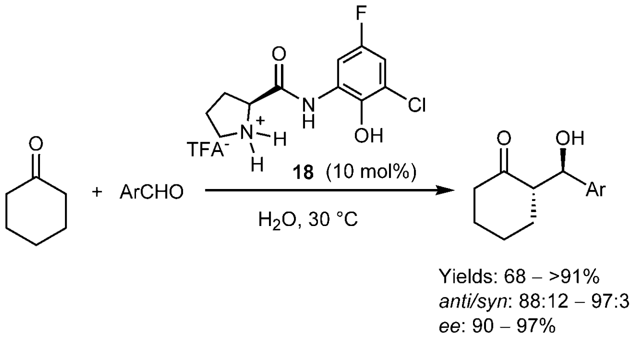
Also Lattanzi and co-workers employed **17** finding high stereoselectivities with dioxane as solvent at 4 °C and using only 1.1 equiv. of water.[59] Interestingly they reported that the methoxy derivative showed a lower *ee*, then they pointed out the important role played by the OH group. The different stereochemical outcome with respect to the previous work could be due to the different medium employed (water *vs.* dioxane:water).

Simple prolinamide derivatives were found to be active as catalysts in the aldol reaction between acetone and several aromatic aldehydes in water. However, although in some case the reaction was completed in 30 min, enantioselectivities were low.[60]

Good results were obtained without the need of an additional chiral backbone in the amide moiety by using *N*-(2-hydroxyphenyl)-prolinamides. Several derivatives were prepared and the best results were observed with **18** (Scheme 13). Such a catalyst was employed both in $CHCl_3$ and water. Improved enantioselectivities, with the expense of yield, were observed when the reaction medium was changed from $CHCl_3$ to water.[61]

L-Prolinamide-based catalysts were tested by Gong in the aldol reactions of aldehydes with hydroxyacetone or fluoroacetone (Scheme 14).[62] Using 20–30 mol% of catalyst **19**, excellent enantioselectivities and high regioselectivities, in favour of the usually disfavoured 1,4-diol, were observed for hydroxyacetone. Also fluoroacetone gave good regioselectivities and high enantioselectivities. Theoretical studies on the transition states by using a microsolvatation model revealed that the role of water in controlling the regioselectivity arises from the hydrogen bonds formed between water and the amide oxygen of the proline amide and the hydroxy group of hydroxyacetone.

On the other hand, when R was a TBSO group (**20** in Scheme 14), the reaction between acyclic and cyclic ketones and several aromatic aldehydes in water at 25 °C, gave high stereoselectivities with only 1 mol% of catalyst.[63] Coupling the use of water with the highly hydrophobic catalyst **20** gave increased stereoselectivity compared the use of the less hydrophobic catalyst **19** in $CHCl_3$ at –25 °C. For istance, the aldol product formed in the reaction of cyclohexanone and 4-nitrobenzaldehyde was obtained in 94% *ee* and >99:1 *dr* using **20** in water compared to 79% *ee* and 95:5 *dr* using **19** in $CHCl_3$.[64]



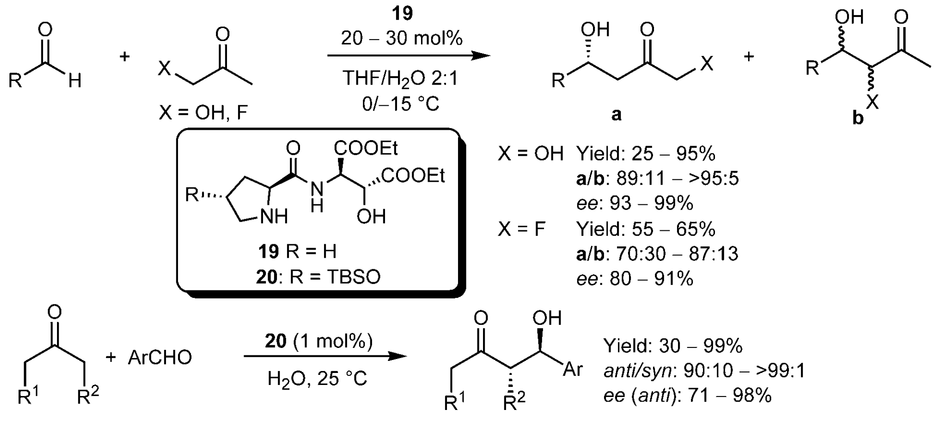
Scheme 13. Aldol reactions catalyzed by prolinamide **18**.

Prolinamides **21** and **22** gave high enantioselectivities in the reaction between acetone and several aromatic aldehydes when used under neat conditions at –40 °C in 5 or 10 mol% loadings.[65] Interestingly, the same catalysts were found to be very active when used in brine as reaction medium. High to excellent stereoselectivities were observed when they were employed at –5 or –10 °C in 0.5 mol% loading without any acid additive (Scheme 15).[66]

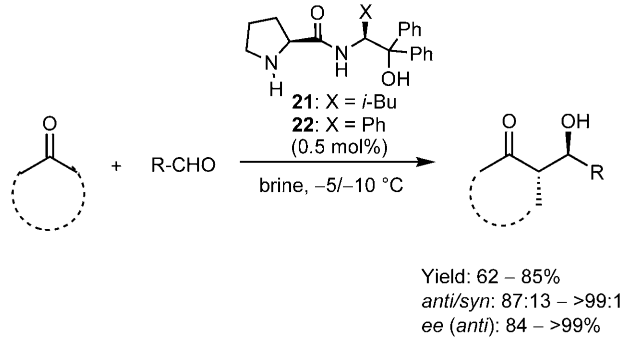
The excellent results obtained with prolinamides **21** and **22** prompted us to investigate if these organocatalysts were active when immobilized. With this in mind, two polystyrene-based supported prolinamides **23** and **24** were prepared and successfully tested in the asymmetric direct aldol reaction using both cyclic and acyclic ketones and various aryl aldehydes (Scheme 16).[67]

The use of organic solvents such as $CHCl_3$, CH_2Cl_2, tetrahydrofuran, toluene and diethyl ether gave very low yields while the reaction took place, with high *ee* values, when the above solvents were used as a 1:2 (v/v) water/solvent mixture. The optimal reaction conditions were found with a 1:2 (v/v) water/chloroform mixture. This mixture was the best compromise between the good swelling properties of chloroform and the formation of a concentrated organic phase due to the presence of water (Figure 10). The enantioselectivities obtained when employing acetone as the ketone were, to the best of the authors knowledge, the highest achieved with a supported proline derivative.

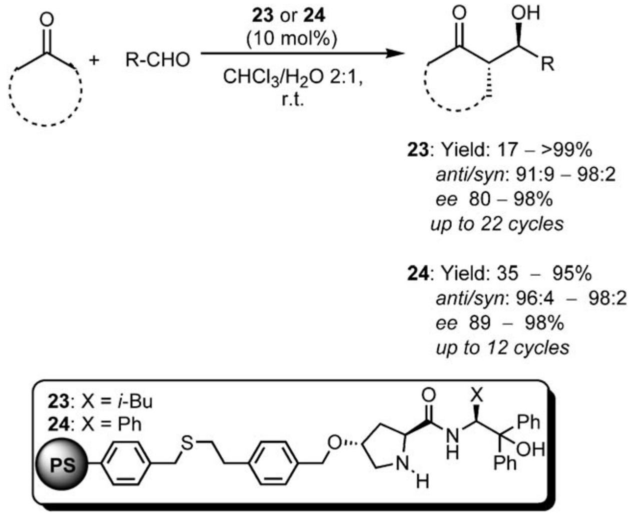
Brine was used as reaction medium for several prolinamide derivatives **25a–e** (Figure 11).[68] Prolinamide **25e** was chosen as the most promising catalyst. It was used in 20 mol% with AcOH (40 mol%) as additive



Scheme 14. Aldol reactions catalyzed by prolinamides **19** and **20**.



Scheme 15. Aldol reactions catalyzed by prolinamides **21** and **22**.



Scheme 16. Aldol reactions catalyzed by polymer supported-prolinamides **23** and **24**.

at 0 °C. The same catalyst gave similar results when used in $CHCl_3$ at −25 °C.[69]

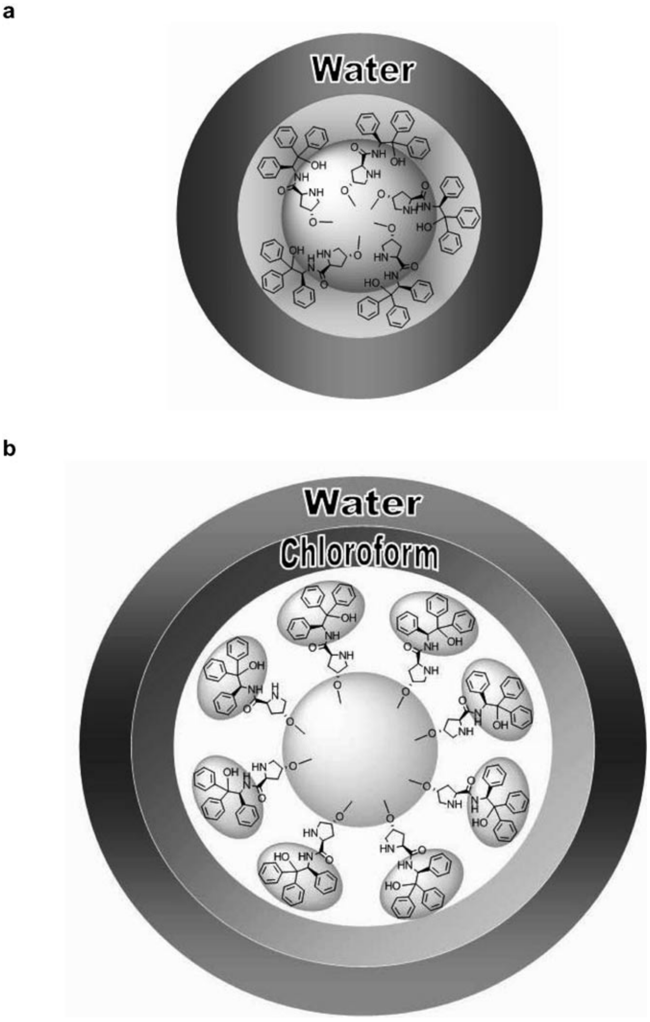


Figure 10. a) Proposed unswelled catalyst structure in the presence of water. **b**) Proposed swelled catalyst structure in the presence of chloroform/water mixture.

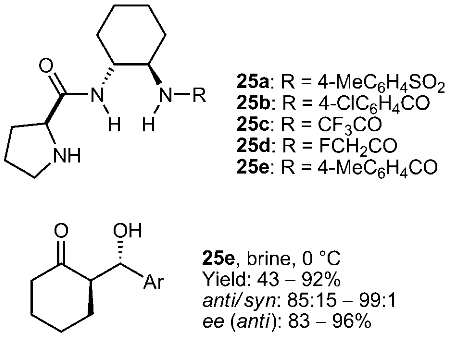
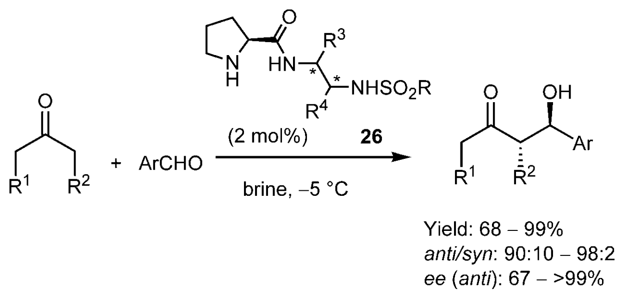


Figure 11. Structures of catalysts **25a–e**.

More recently, several substituted prolinamides derived from chiral enantiopure aziridines, of general formula **26**, were used in aldol reactions. Optimization of the reaction conditions with cyclic ketones showed that no product was formed when the reaction was carried out in organic solvents such as $CHCl_3$ and DMF. Optimal conditions were found when brine was employed as reaction medium at −5 °C (Scheme 17).[70] Aldol products were obtained from good to high enantioselectivities. These conditions were also used in the reaction with acetone giving good enantioselectivities. Screening of organic solvents showed that, differently from cyclohexanone, the reaction took place but with lower enantioselectivity. The reaction between acetone and benzaldehyde showed that *ee* value was high whatever the configuration of the R^3 and R^4 carbon atoms when the reaction was carried out in brine, while when it was carried out in neat acetone the *ee* value was lower when the R^4 carbon atom had an *S* configuration. A model, explaining the role of water, for this outcome was given. In particular, when the reaction was carried out in an aqueous medium, the water molecules form H-bonding with the amide groups and the aldehyde as



Scheme 17. Aldol reactions catalyzed by prolinamides **26**.

shown in TS-1. When the reaction was carried out without water the *ee* value decreased because of the favourable C–H-π interaction between the phenyl group and hydrogen of the aromatic ring of the benzaldehyde (TS-2) (Figure 12).

Also *N*-prolylsulfonamides have been checked as organocatalysts for the aldol reaction. In 2006 Wang tested six different catalysts in water (**27a–f**, Figure 13).[71] The dendritic catalysts bearing more hydrophobic groups **27d–f** gave higher reactivity and stereoselectivity than catalysts with less hydrophobic groups. In particular, the second generation catalyst **27e** provided the best results.

Very recently, Carter described that the addition of one equivalent of water increased the diastereoselectivity of the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde catalyzed by sulfonamide **28** (20 mol%) in $ClCH_2CH_2Cl$.[72] These conditions were applied to other substrates giving aldol products in high stereoselectivity (yield: 16–91%; *dr*: 29/1–99/1; *ee*: 59–>99%). Moreover, the reaction can be carried out with a catalyst loading as low as 2 mol% under neat conditions. However, a single equivalent of water was still added to improve the reaction rate and selectivity.

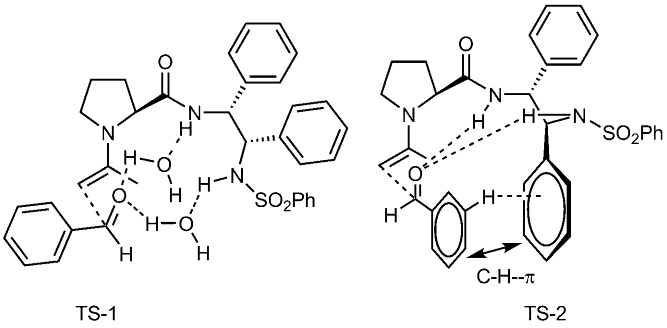


Figure 12. Proposed transition states (ref.[70]).

Water, as the sole reaction medium, was employed in the aldol reaction catalyzed by camphor-containing thiourea-amine catalysts **29–33** with dodecylbenzenesulfonic acid as additive (Figure 14).[73] Stereoselectivities were high but the reaction times were long.

Water was found to be a suitable reaction medium also for the aldol reaction of several cyclic ketones with aromatic aldehydes using L-prolinethioamide **34** as catalyst (Figure 14). Such a catalyst was effective for electron-deficient aldehydes and in the presence of $Cl_2CHCOOH$ as additive.[74]

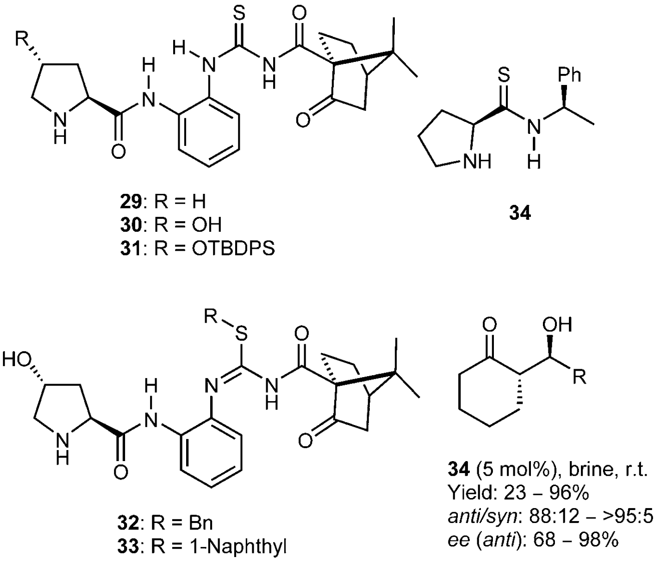


Figure 14. Structures of catalysts **29–34**.

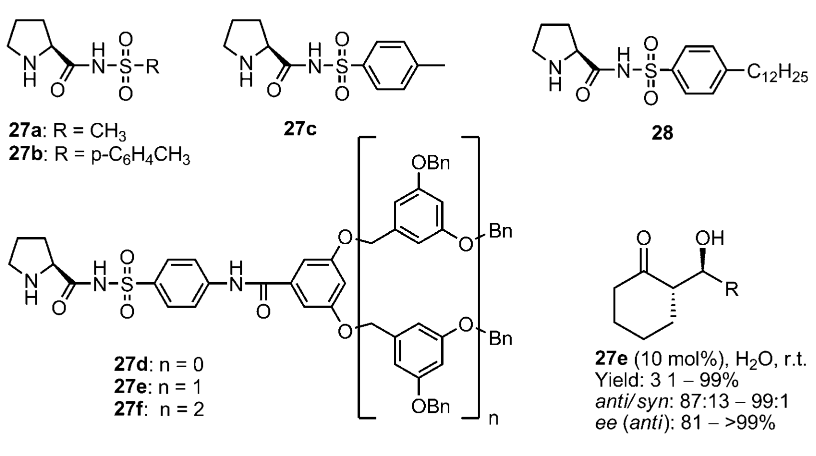


Figure 13. Structures of catalysts **27a–f** and **28**.

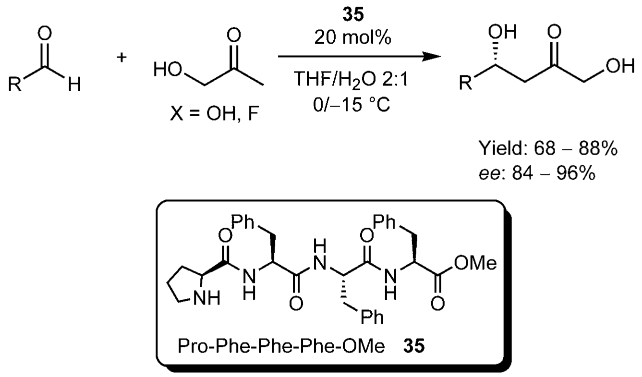
2.5 Dipeptides and Small Peptides as Catalyst

In addition to simple amino acids also simple dipeptides were found to be useful in the direct asymmetric aldol reaction. In 2005, Córdova reported that L-Ala-L-Ala (30 mol%) enantioselectively catalyzed the aldol reaction in DMSO:water (10 equiv.).[75] The same authors reported that also other simple dipeptides, such as L-Val-L-Phe and L-Val-L-Val, catalyzed successfully the aldol reaction in DMSO:water 1:1 or MeOH:water 1:1.[76] More detailed examples were subsequently reported both using simple amino acids or dipetides.[77] In every case, the solvent of choice was DMSO:water (10 equiv.). Interestingly, for the L-Ala-L-Ala dipeptide, when dry DMSO was used, lower enantioselectivity and reversed diastereoselectivity were obtained. In addition, L-valine-tetrazole gave an aldol product with high stereoselectivity when used in water as reaction medium.

As previously seen, prolinamides were found to be able to catalyze the aldol reaction, also several dipeptides were investigated using water as reaction medium. The dipeptide Pro-Trp was found to be the most efficient for cyclic and acyclic ketones and various aldehydes. However, in order to reach good activity and stereoselectivities, reactions were carried out in the presence of additives (NMM/SDS or DABCO/PEG400) at 0 °C.[78]

The use of water was crucial in controlling the regioselectivity of aldol reactions of aldehydes with hydroxyacetone. The reactions were catalyzed by L-proline-based small peptides such as **35** (Scheme 18).

When the reactions were carried in aqueous media, chiral 1,4-diols, which are disfavoured products in similar aldol reactions catalyzed by aldolases or L-proline, were obtained as the major products.[79]

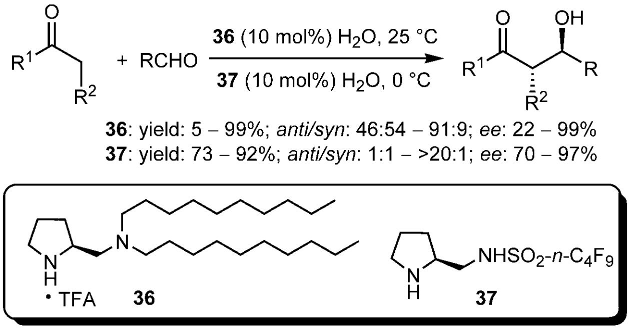


Scheme 18. Aldol reactions catalyzed by oligopeptide **35**.

2.6 Pyrrolidine-Based Derivatives

In 2005, Janda reported a Hammett correlation of nornicotine analogues in the aqueous aldol reaction showing that arylpyrrolidines bearing electron-withdrawing substituents exhibited greater activity than other pyrrolidine-based catalysts in water. These findings were interpretated as a promise for the development of improved aldol catalysts in aqueous media.[80]

In 2006 Barbas and Takabe reported highly enantioselective aldol reactions in water.[81] They used a TFA salt of a pyrrolidine derivative bearing long alkyl groups as catalyst in 10 mol% loading at room temperature obtaining good yields and diastereoselectivities (**36**, Scheme 19).



Scheme 19. Aldol reactions catalyzed by pyrrolidines **36** and **37**.

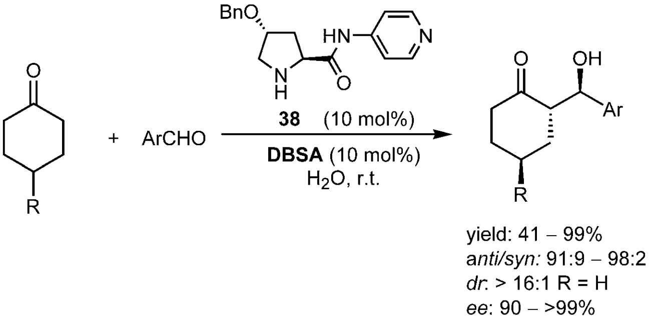
Water was also found to be a better reaction medium with respect to DMSO or neat conditions in the reaction between cyclohexanone and aromatic aldehydes catalyzed by fluorous (*S*)-pyrrolidine-sulfonamide **37** (Scheme 19). Reactions carried out with 10 mol% of catalyst at 0 °C gave aldol products with good stereoselectivities.[82]

2.7 Miscellaneous

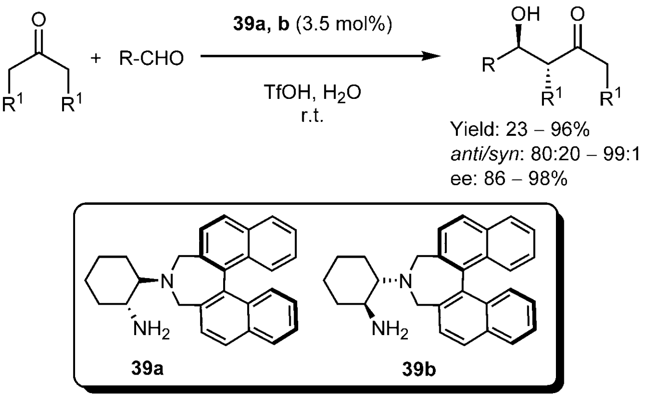
A different approach for the organocatalytic aldol reaction in water was reported by Cheng. Simple mixing of chiral amines and surfactants with Brønsted acids such as *p*-dodecylbenzenesulfonic acid (DBSA) led to highly effective and selective catalysts in water. In particular, amine **38** and DBSA gave aldol products from cyclohaxanones and aromatic aldehydes in high yields and stereoselectivities (Scheme 20).

The data obtained allowed one to hypothesize that DBSA contributed to the enhanced activity and enantioselectivity most likely by protonating the pyridinyl ring that consequentely activated the amide hydrogen-bond donor in hydrophobic micellar media.[83]

Primary amine organocatalysts **39a**, **b** bearing central and axial chiral elements were found to be very stereoselective catalysts in the aldol reaction between several ketones and aromatic aldehydes (Scheme 21).[84] Water as reaction medium and TfOH as additive were used at room temperature with low



Scheme 20. Aldol reactions catalyzed by compound **38**.



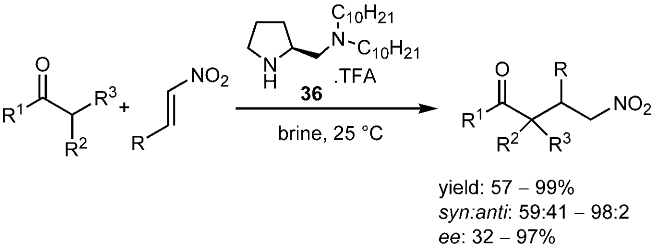
Scheme 21. Aldol reactions catalyzed by primary amines **39a**, **b**.

catalyst loading (3.5 mol%). The chiral binaphthyl group of the organocatalyst facilitates the formation of a hydrophobic core, thus promoting the reaction in water. The two chiral elements in **39a** are matched, indeed catalyst **39b** gave lower stereoselectivity (*dr* and *ee* values).

Very recently, simple chiral amine-polyoxometalate hybrids were prepared and used, with a very low loading (0.33 mol%), in the aldol reaction under either neat or aqueous conditions. Aldol products were obtained from low to high yields (21–98%) and high stereoselectivity (*anti/syn*: 47:53–99:1, *ee*: 23–98%).[85]

3 Michael Reactions

Barbas found that catalyst **36**, described for the asymmetric aldol reaction in water,[81] worked also very well in the Michael reaction of ketones and aldehydes with nitrostyrenes (Scheme 22).



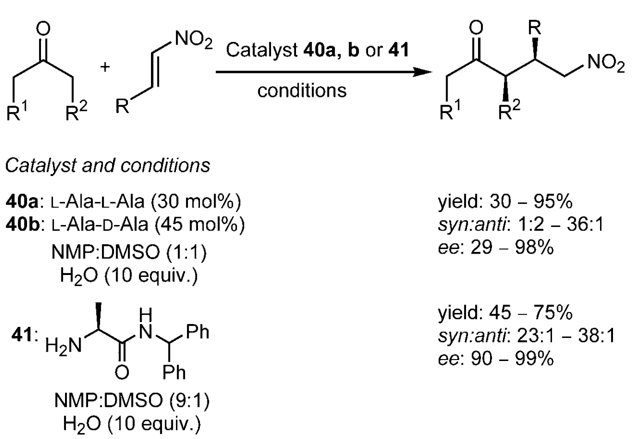
Scheme 22. Michael reaction catalyzed by **36·TFA** salt.

It was shown that brine, as reaction medium, improved yield and stereoselectivity compared to reaction in organic solvent or water. The authors claimed that, due to hydrophobic interactions, aldehyde or ketone donors assembled in brine. Catalyst **36** with its hydrophobic chains and the acceptor molecule dissolved in the liquid organic phase. This aggregation excluded water from the organic phase and drove the equilibrium towards enamine formation. This was further facilitated by a salting-out effect. Then, Michael reactions occurred quickly in this concentrated organic phase.[86]

Instead of water or brine, as the sole reaction medium, water was used as additive (10 equiv.) in order to increase the efficiency and circumvent the need of adding an acidic additive. In addition, water would facilitate hydrogen bonding and proton transfer that could improve the enantioselectivity. Then, using *N*-methylpyrrolidone:DMSO as solvent and water as additive, simple dipeptides, such as L-Ala-L-Ala (**40a**) and L-Ala-D-Ala (**40b**), catalyzed the Michael addition of ketones to nitrostyrenes with high yields and stereoselectivities (Scheme 23).[87]

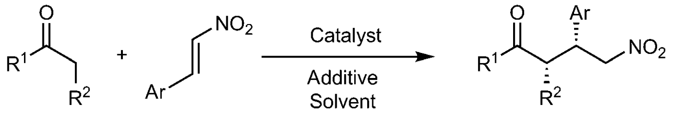
Small amounts of water (10 equiv.) were also used in order to significantly accelerate as well as improve the stereoselectivity of Michael addition of ketones to nitrostyrenes carried out in *N*-methylpyrrolidone:DMSO. These reactions were catalyzed by **41** to give products in high stereoselectivities (Scheme 23).[88]

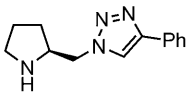
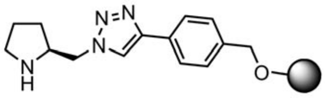
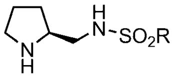
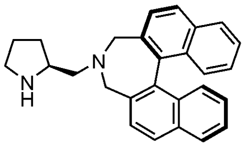
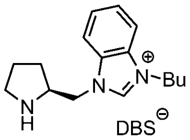
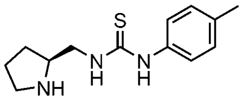
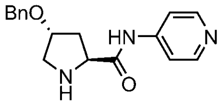
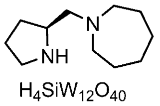
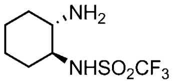
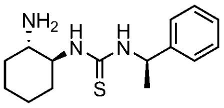
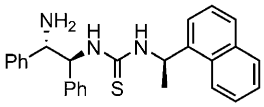
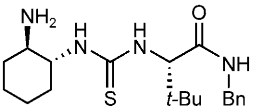
Following Barbas' findings, more papers dealt with the use of pyrrolidine-based organocatalysts using water as reaction medium. The chiral pyrrolidine-triazole catalyst **42** gave high stereoselectivities in the Michael addition of cyclohexanone or acetone to nitrostyrenes (Table 1). The reactions proceeded



Scheme 23. Michael reactions catalyzed by dipeptides **40a**, **b** or by **41**.

Table 1. Performances of compounds **37–38**, **42–52** as catalysts in the Michael reaction.



Catalyst		mol%	Solvent	Additive	Yield [%]	*dr* (*syn*:*anti*)	*ee* [%]	Ref.
42		10	water	–	89–99	9:1–>99:1	65–>99	[89]
43		10	water	DiMePEG (10 mol%)	40–85	89:11–>99:1	26–>99	[90]
44: R = CF_3 **37**: R = *n*-C_4F_9		10	water	–	68–93	16:1–50:1	68–>95	[92]
45		10	brine	TFA	70–98	94:6–99:1	82–99	[93]
46		20	water	–	64–>99	94:6–99:1	91–98	[94]
47		10	water	benzoic acid	72–98	87:13–>99:1	79–>99	[95]
38		15	water	DBSA	67–99	94:6–99:1	81–87	[83]
48		5	water	–	79–99	93:7–96:4	86–88	[85]
49		15	$CHCl_3$/H_2O (15 mol%)	–	33–94	–	57–96	[96]
50		15	toluene/H_2O (200 mol%)	AcOH (15 mol%)	85–93	–	84–92	[97]
51		15	toluene/H_2O (200 mol%)	AcOH (15 mol%)	82–99	14:86–83:17	90–>99	[98]
52		20	CH_2Cl_2/H_2O (500 mol%)	–	34–98	2.1:1–>50:1	92–99	[99]

smoothly both in $CHCl_3$ and water. However, the aqueous medium promoted the process more efficiently pushing the reactions to completion within a shorter time. Each reaction was carried out in both reaction media showing that water generally gave better reactivity and enantioselectivity.[89]

A polymer-supported version of the above catalyst, **43**, was later reported for the same reactions. Also in this case, water was the reaction medium of choice while the use of DiMePEG as additive led to a greater improvement both in conversion and in stereoselectivity.[90]

Whereas (*S*)-pyrrolidine trifluoromethanesulfonamide **44** served as an effective catalyst for the Michael addition of aldehydes to nitrostyrenes in *i*-PrOH,[91] the more hydrophobic analogue **37** displayed great activity in water as a result of the enhanced aggregation between the catalyst and the substrates in the aqueous environment. High yields and stereoselectivities were obtained.[92]

The highly hydrophobic chiral diamine **45** (Table 1) was also employed in the same reactions. Screening of solvents showed that brine, with TFA as additive, was the best reaction medium. Other solvents such as DMSO or toluene gave poor enantioselectivity, while high yields and stereoselectivities were obtained with organic solvents such as MeCN, $CHCl_3$, CH_2Cl_2, MeOH, EtOH and *i*-PrOH. Again, high yields and stereoselectivities in aqueous medium were explained by the hydrophobic environment created by the binaphthyl group.[93]

Water was used as reaction medium for the Michael addition of cyclohexanone to nitrostyrenes without any organic solvents or additional additives. As catalyst the ionic liquid-type compound **46** having the *p*-dodecylbenzenesulfate (DBS) anion was chosen. This surfactant-type organocatalyst gave high yields and stereoselectivities under these conditions. It was suggested that the reaction should occur through interfacial catalysis and results could be rationalized by considering the hydrophobic effect in an aqueous micellar system. Interestingly, the Michael products could be separated from the bulk water without using any organic solvent.[94]

Also the simple pyrrolidine-thiourea catalyst **47** (Table 1) was found to be active in the asymmetric Michael addition of cyclohexanone to nitrostyrenes when the reactions were carried out in water with benzoic acid (10 mol%) as additive at 35 °C.[95]

Using the same strategy reported for aldol reactions, Cheng investigated the Michael addition of cyclohexanone to nitrostyrenes using pyrrolidine organocatalysts in the presence of surfactant Brønsted acids in water as reaction medium. In this case high diastereoselectivities and good enantioselectivities were obtained using catalyst **38**.[83]

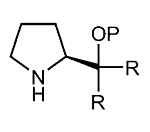
Catalyst **48** was used both under neat and aqueous conditions. Much less cyclohexanone was used under the latter conditions, showing the advantage of the aqueous system.[85]

Good results were also obtained with primary amine catalysts. In these cases, however, organic solvents were employed and water was used in low amount (from 15 to 500 mol%), but its presence allowed significant improvements. The enantioselective addition of ketones to nitrostyrenes was developed by using the novel bifunctional sulfonamide primary amine catalyst **49** (Table 1). No reaction took place when water was used as reaction medium. The best solvent was $CHCl_3$. However, addition of water increased the yield and enantioselectivity, probably because it increased the catalyst turnover due to facilitating the release of the primary amine catalyst from the imine. Moreover, the authors reported an explanation about the role of water in the enhancement of enantioselectivity.[96]

Finally, three different primary thiourea-based catalysts, **50**–**52**, were also used with very good results.[97–99]

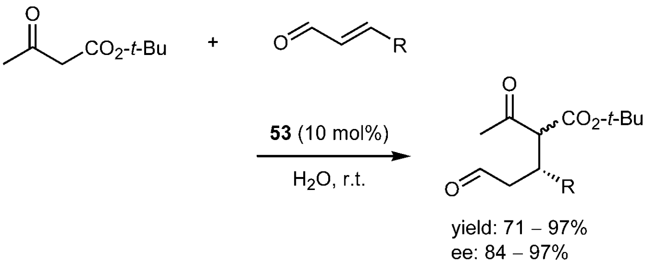
Also α,α-disubstituted prolinols **53**–**57** (Figure 15) were succesfully used in water. Catalyst **53** worked well in the Michael addition of *tert*-butyl 3-oxobutyric ester with α,β-unsaturated aldehydes under neat conditions or using water as reaction medium (Scheme 24).[100]

Even Carlsberg beer worked very well as reaction medium. Also in this case, it was proposed that reagents and the catalyst "cluster together" in H_2O and the reaction probably occurred in the organic phase



53: P = TMS, R = 3,5-$(CF_3)_2$-C_6H_3
54: P = TMS, R = Ph
55: P = $SiPh_3$, R = C_6H_{13}
56: P = TMS, R = C_6H_{13}
57: P = H, R = C_6H_{13}

Figure 15. Structure of α,α-disubstituted prolinols **53**–**57** employed in Michael reaction.

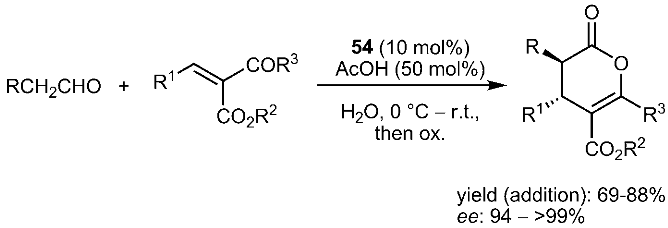


Scheme 24. Michael reaction catalyzed by α,α-disubstituted prolinol **53**.

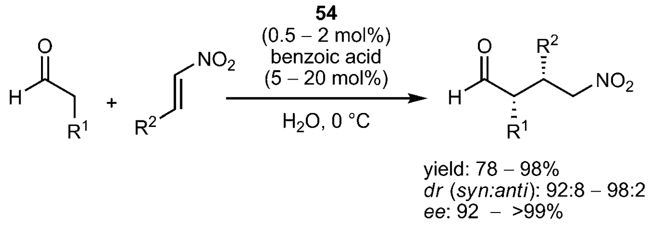
constituted by the aldehyde, the β-keto ester and the formed product.

Enantioselective syntheses of tetrasubstituted dihydropyrones were accomplished in water media by using catalyst **54** (Scheme 25).[101]

The same catalyst was, more recently, used in the addition of aldehydes to 3-nitroacrylates and aryl- and alkyl-substituted nitroalkenes (Scheme 26).[102] Water was the reaction medium of choice with benzoic acid as additive to improve the reaction rate and diastereoselectivity. Under these conditions high stereoselectivities were observed.



Scheme 25. Synthesis of tetrasubstituted dihydropyrones catalyzed by **54**.

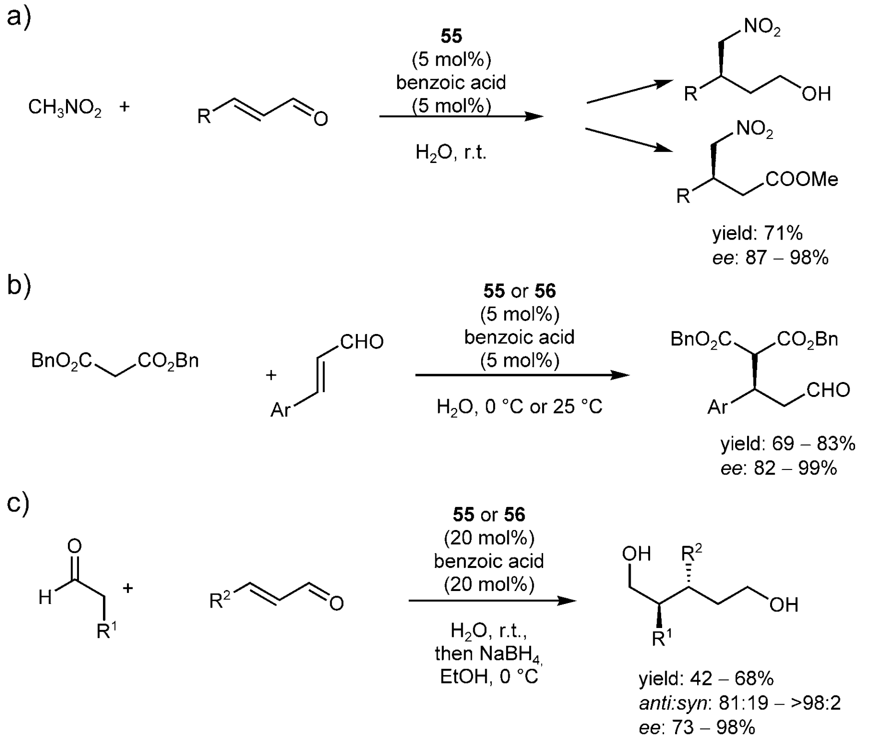


Scheme 26. Michael reaction catalyzed by α,α-disubstituted prolinol **54**.

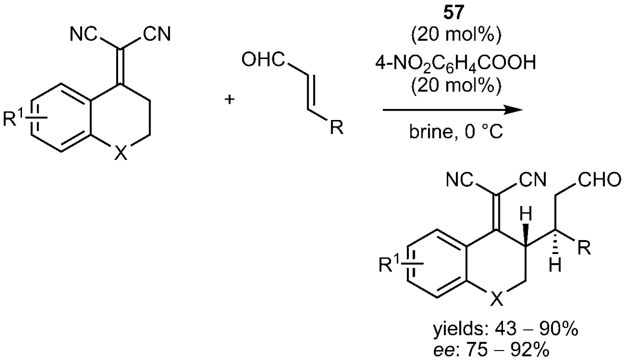
Following the idea of the favourable role played by hydrophobic alkyl chains in water-compatible enamine-mediated catalysis and the assumption that for effective control of iminium geometry and face shielding a bulky group should be located near the hydrogen atom of the catalyst, catalyst **55** was successfully employed in several reactions. High stereoselectivities were observed when **55** was used in water, with benzoic acid as additive, in the addition of nitromethane or benzyl malonate or aldehydes to α,β-unsaturated aldehydes (Scheme 27).[103]

Also the direct vinylogous Michael addition reaction of vinylmalononitriles to α,β-unsaturated aldehydes was carried in aqueous medium. Screening of five dialkyl-(*S*)-prolinols showed that catalyst **57** gave high yields and *ee* values when employed in brine at 0 °C with 4-nitrobenzoic acid as additive (Scheme 28).[104]

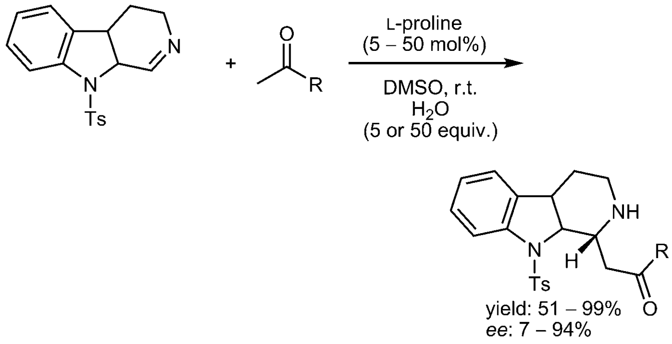
A different organocatalyst, not based on amino acid derivatives, was successfully employed in the asymmetric addition of malonate to nitrostyrenes (Scheme 29). Reactions catalyzed by sodium demethylquinine salt proceeded in either organic solvent (THF or toluene) or water giving the product in high



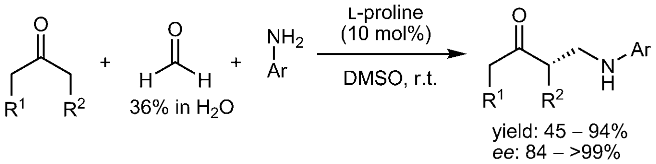
Scheme 27. Addition reactions between α,β-unsaturated aldehydes and **a**) nitromethane, **b**) benzyl malonate, **c**) aldehydes catalyzed by **55** or **56**.



Scheme 28. Addition reaction of vinylmalononitriles to α,β-unsaturated aldehydes catalyzed by **57**.



Scheme 30. L-Proline-catalyzed reaction between 9-tosyl-3,4-dihydro-β-carboline and ketones.



Scheme 31. L-Proline-catalyzed three-component Mannich reaction.

yield. However, water gave higher enantioselectivity than organic solvent. Moreover, enantioselectivity depended significantly on the concentration of the substrate in water. Catalyst **58** was used for a set of substrates in only 1 mol% loading giving the products in moderate to high *ee*.[105]

4 Mannich Reactions

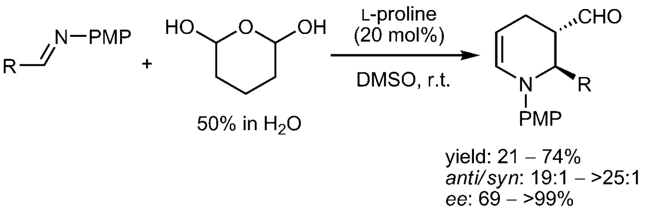
There are several examples reporting the use of variable amounts of water in the organocatalyzed enantioselective Mannich reaction.

Water was found to affect the stereoselectivity of the products between 9-tosyl-3,4-dihydro-β-carboline and ketones in the presence of L-proline as a catalyst in DMSO (Scheme 30).[106] This effect was also observed in CH_2Cl_2 and acetone.

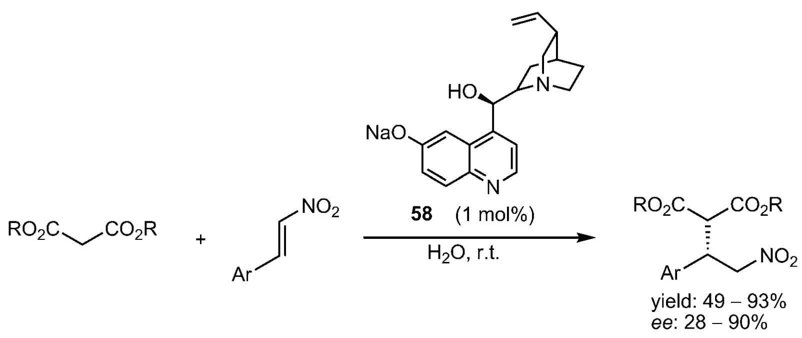
An aqueous solution (36%) of formaldehyde was successfully employed in the proline-catalyzed reaction of ketones and aromatic amines in DMSO as solvent to give the direct α-aminomethylation with high *ee* values (Scheme 31).[107]

High stereoselectivities were observed in the catalytic reaction of aqueous tetrahydro-2*H*-pyran-2,6-diol with preformed *N*-PMP aldimines in DMSO to give tetrahydropyridines through a cascade Mannich-type/intramolecular cyclization reaction (Scheme 32). Screening of catalysts showed that proline was the catalyst of choice.[108]

Wet DMSO was used in the reaction between ketones and imines catalyzed by acyclic β-amino acids, such as β-homovaline **59**. Under these conditions,



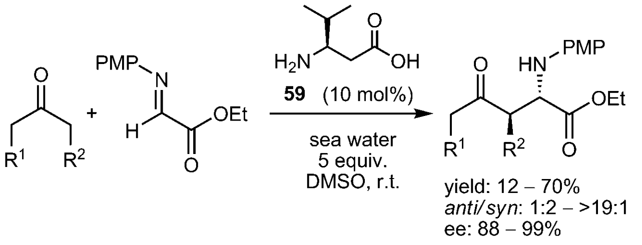
Scheme 32. Cascade Mannich-type/intramolecular cyclization reaction.



Scheme 29. Addition of malonate to nitrostyrenes catalyzed by sodium demethylquinine **58**.

Mannich products were obtained with high stereoselectivities (Scheme 33).[109]

More recently, a few reports dealt with the use of water as the sole reaction medium. An autocatalytic asymmetric Mannich reaction was observed in an aqueous environment. In contrast with organic solvents, water had a significant impact on enantioselectivity. A buffer solution at pH 7 provided better results.[110]



Scheme 33. β-Homovaline-catalyzed Mannich reaction.

A three-component Mannich reaction of *O*-benzyl hydroxyacetone with *p*-anisidine and aldehydes was carried out using the TBDPS-protected L-threonine catalyst **60a**, which gave the best results among a series of catalysts investigated (Scheme 34).[111] Such a reaction was carried out for the first time using water as the sole reaction medium with good to high stereoselectivities. In the absence of water the *ee* value was lower.

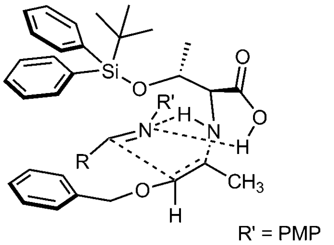


Figure 16. Proposed transition-state for Mannich reaction catalyzed by TBDPS-protected L-threonine **60a**.

The high stereoselectivities observed were rationalized by means of the transition state depicted in Figure 16. The authors stated that the geometry of the enamines resulting from the *O*-benzyl hydroxyacetone and *O*-(*tert*-butyldiphenylsilyl)threonine was *Z*, probably due to the hydrophobic interactions of hydrophobic moieties or π-π staking of the aromatic components (Figure 16). Later a TBDPS-protected L-serine catalyst **60b** was used in the same conditions for the above reactions giving good stereoselectivities.[112] It is interesting to note that reversed diastereoselectivity was displayed (*syn vs. anti*) when cyclohexanone was used as the ketone (yield: 71–86%; *dr syn:anti*: 72:28–84:16; *ee*: 74–86%).

5 Diels–Alder Reactions

The reversible formation of iminium ions with chiral imidazolidinone **61** under aqueous condition is a valuable platform for the development of enantioselective Diels–Alder reactions (Figure 17).

MacMillan showed that aqueous methanol, in the presence of HCl as additive, was a suitable reaction

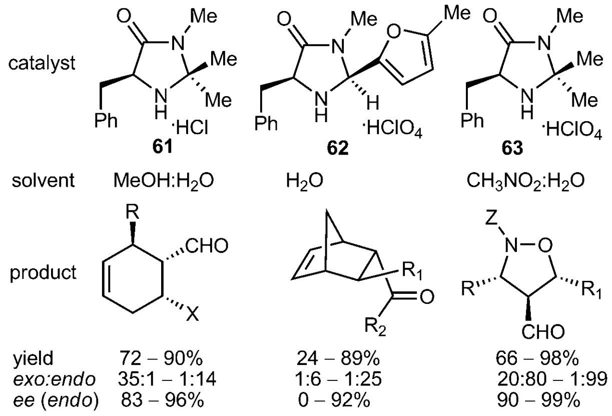
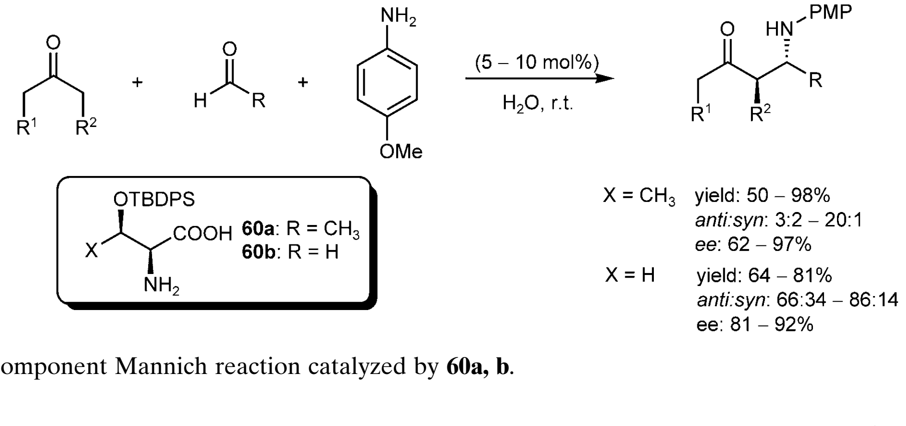


Figure 17. Structures and performances of catalysts **61**–**63** in the Diels–Alder reaction.



Scheme 34. Three component Mannich reaction catalyzed by **60a, b**.

medium for the stereoselective Diels–Alder reaction between dienes and α,β-unsaturated aldehydes. This was the first example of a highly enantioselective organocatalytic Diels–Alder reaction.[113] Only water, in the presence of $HClO_4$, was used in the same reaction catalyzed by compound **62**, where α,β-unsaturated ketones were employed.[114] Nitromethane:water was used in the first example of an enantioselective organocatalytic 1,3-dipolar cycloaddition between nitrones and α,β-unsaturated aldehydes in the presence of catalyst **63**,[115] while THF:water was used in the first enantioselective organocatalytic Friedel–Crafts alkylation.[116] In this latter case, as catalyst, compound **61** was used as its TFA salt.

Pro-chiral cyclohexanones were selectively prepared with pyrrolidine catalysis in water.[117] These results opened the way for further investigations using different organocatalysts under wet conditions.

1,2-Diamino-1,2-diphenylethane **64** was used in the reaction between crotonaldehyde and cyclopentadiene. The reaction was optimized with the use of 5 mol% of catalyst in dioxane:water (95:5) in the presence of HCl (**64a**). Using more than 10% (by volume) of water both enantio- and stereoselectivity decreased. Salt **64b**·(DBSA: *p*-dodecylbenzenesulfonic acid, which acted both as Brønsted acid and surfactant) was found to be a good catalyst for the cycloaddition in water, but the stereocontrol was less effective than that obtained with salt **64a** in wet dioxane. Similar results were obtained with catalyst **64c** (Figure 18).[118]

A catalytic amount of water promoted the Diels–Alder reaction of dienes with α-acyloxyacroleins catalyzed by a diammonium salt of chiral 1,1′-binaphthyl-2,2′-diamine and trifluoromethanesulfonimide (**65**).[119]

Cyclic hydrazide catalysts **66**·$HClO_4$, **66**·TfOH[120] and **67**·TfOH[121] gave good results when employed in water (Figure 19). Catalyst **66**·$HClO_4$ was also used in a variety of aqueous solvent mixtures and optimal catalyst performance was noted in water.

Also aziridin-2-ylmethanols **68** were tested as catalysts in the Diels–Alder reaction between cyclopentadiene and α,β-unsaturated aldehydes. The **68**·HCl salts were generally used in MeOH:water while the **68**·$HClO_4$ salts were used in water. However, only low to moderate *ee* values were obtained.[122]

The pyrrolidine-based organocatalyst **69** was used, with TFA as additive, for the stereoselective [3+2] cycloaddition of azomethine imines with α,β-unsaturated aldehydes. In this case the solvent of choice was THF and water was employed as additive. Indeed, in the absence of water the reaction rate was considerably decreased. The authors claimed that the addition of water could be helpful for hydrolysis of the iminium intermediate after the cycloaddition reaction (Figure 20).[123]

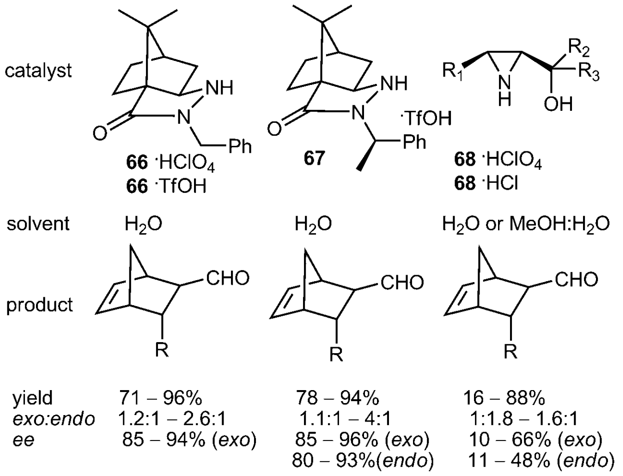


Figure 19. Structures and performances of catalysts **66–68** in the Diels–Alder reaction.

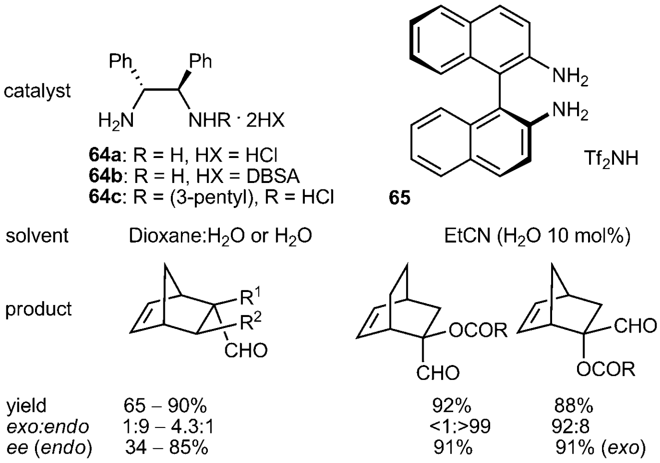


Figure 18. Structures and performances of catalysts **64a–c** and **65** in the Diels–Alder reaction.

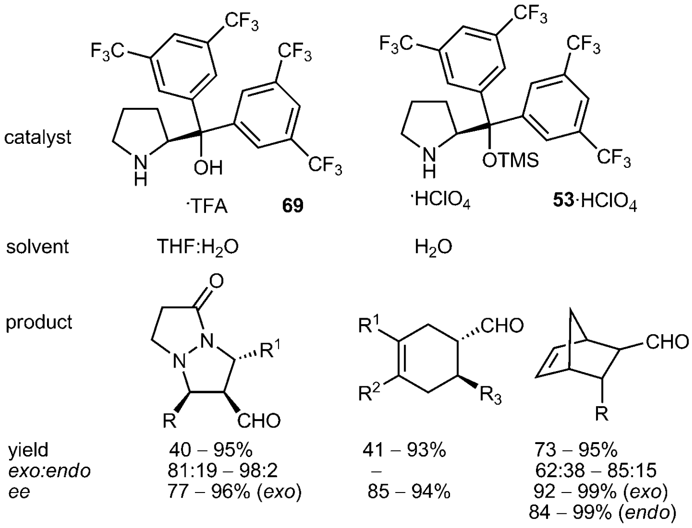


Figure 20. Structures and performances of catalysts **69** and **53**·$HClO_4$ in the Diels–Alder reaction.

Catalyst **53**·$HClO_4$ was successfully employed in the reaction between dienes and α,β-unsaturated aldehydes. In this case water was found to be the best reaction medium and its amount was important for the outcome of the reaction. Studies on water effects indicated that the reaction proceeded in the organic phase and did not proceed at the interface between the water and the organic phase and a small amount of water dissolved in the organic phase accelerated the reaction and affected the transition state.[124]

Also immobilized versions of organocatalysts for the Diels–Alder reaction were employed using variable amounts of water. Water was used in the presence of ionic liquids such as [bmim]PF_6 and [bmim]OTf. A high *ee* value was obtained with [bmim]PF_6:water 95:5 while for [bmim]OTf, in order to reach a moderate yield and *ee* value, the amount of water was increased to 20% (volume). However, it is probable that hydrolysis of the anion could play an important role.[125]

The fluorous imidazolidinone derivative **70** was successfully used in CH_3CN:water 95:5 (Figure 21).[126] Acetonitrile:water mixtures were also used for the reaction between dienes and α,β-unsaturated aldehydes with imidazolidinones supported on JandaJel (**71**), silica (**72**)[127] and poly(ethylene glycol) (**73**)[128] or entrapped into montmorillonite **74** (Figure 21).[129]

6 Conclusions

As can be seen from the data reported in this review, water plays a central role both in achieving higher activity and selectivity of catalysts. Beneficial effects of water can be observed from catalytic amounts to truly aqueous conditions. However, its function depends on the amount used.

A catalytic amount of water may be helpful in promoting the reaction because it may avoid poisoning of the catalyst, for instance, it could prevent the formation of unproductive iminium ion from catalyst and reactive aldehydes such as chloral or suppress the formation of proline-oxazolidinone that is believed to be a parasitic specie. On the other hand, water could increase the efficiency of the process because it may release the catalyst by hydrolyzing the final iminium species formed in the organocatalytic reaction, for instance, after the cycloaddition reaction between an α,β-unsaturated iminium ion and a dienophile or by releasing an amine catalyst from the corresponding imine. Then, a catalytic water and acid might accelerate the reaction by facilitating the interconversion of the different intermediates of the catalytic cycle.

The use of a higher amount of water is correlated with the use of more hydrophobic catalysts, both in the presence of acid additives or in their absence.

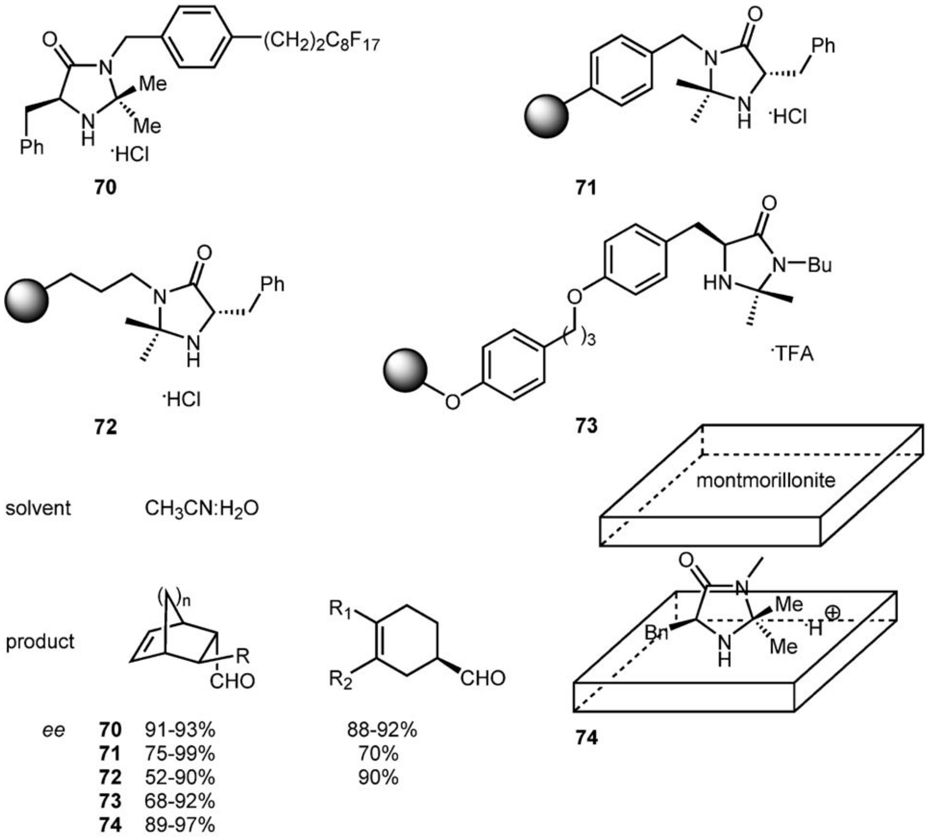


Figure 21. Structures and performances of supported catalysts **70**-**74** in the Diels–Alder reaction.

Janda argued that the need for an acid additive in the case of the aldol reaction catalyzed by pyrrolidine derivative **36** suggested the occurrence of a general base mechanism.[130] The presence of TFA in a stoichiometric amount offered a buffered system that minimized the above mechanism in favour of an enamine catalysis and, on the other hand, increased the amphiphilic character of the catalyst. The increased amphiphilic character can cause the formation of micelles, then catalysis could occur in a concentrated organic phase in which the hydrophobic catalyst may sequester the reactive intermediate from water and the corresponding transition states, leading to different stereisomers, may experience higher differences with respect to those in a truly organic environment.

In the case of several amides, it is also reasonable that a certain amount of catalyst can be disactivated by excess of ketone with formation of the corresponding unreactive imidazolidinone.[131] Therefore, the presence of an acid additive can help the hydrolysis of the imidazolidinone regenerating the catalytic active species.

Looking at the examples reported, it could be seen that acid additives were usually added when no acid protons were present in the catalyst structure, while when acid protons, such as carboxylic, tetrazolic, sulfonamidic protons, were present no acid additives were added. However, in some cases, in which no acid protons were present, (for example, prolinamide derivatives) the combination of a highly hydrophobic catalyst and the presence of water avoided the use of acid additives. In these cases, the positive effect of water could also be ascribed to the fact that it may reinforce the acidity of the amide NH bond, because of the hydrogen bond formed between a free hydroxy group of surface water molecules at the hydrophobic interface with the amide oxygen atom of the organocatalyst.

When highly hydrophobic catalysts were employed in the presence of water, reactions may be predisposed to favour transition states that optimize hydrophobic interactions.[132] In this context one can regard the transition states, reported for example, in Figure 1, Figure 4 and Figure 16, of reactions that proceeded in a concentrated organic phase. However, the absence of water could also favour hydrophobic interactions, depending on the stereochemistry of the catalyst, that can give a decreased stereoselectivity (see Figure 12). Water plays a role also in the case of immobilized catalysts. In this case its function depends on the structure and morphology of the support and/or the linker. Finally, the possibility that small organic molecules could act as enantioselective catalyst in homogeneous aqueous solution such as in the case of prolinamide-catalyzed self-condensation of propanal, should be remembered .[52] This aspect has not been so explored to date and, in our point of view, constitutes an exciting field for further interesting investigations.

Whether or not these reactions are carried out with a catalytic amount of water or in truly aqueous medium, the most important aspect was that water increased the efficiency and stereoselectivity of the catalyst, and this is, in our opinion, extremely interesting from a synthetic point of view. On the other hand a deeper understanding of the role of water, whatever the amount employed, can help in the design of more active and selective organocatalysts.

Acknowledgements

Financial support from the University of Palermo (Funds for selected topics) and the Italian MIUR within the National Project "Catalizzatori, metodologie e processi innovativi per il regio- e stereocontrollo delle sintesi organiche" are gratefully acknowledged.

References

[1] a) A. Berkessel, H. Gröger, (Eds.), *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**; b) P. I. Dalko, (Ed.), *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**.

[2] a) Special issue on organocatalysis: *Chem. Rev.* **2007**, *107*, 5413–5883; b) special issue on organocatalysis: *Acc. Chem. Res.* **2004**, *37*, 631–847; c) special issue on organocatalysis: *Adv. Synth. Catal.* **2004**, *346*, 1007–1249; d) special issue on organocatalysis: *Tetrahedron* **2006**, *62*, 243–502.

[3] a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; b) G. Guillena, D. J. Ramón, *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492; c) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; d) M. Gruttadauria, F. Giacalone, R. Noto, *Chem. Soc. Rev.* **2008**, *37*, 1666–1688; e) D. A. Longbottom, V. Franckevičius, S. Kumarn, A. J. Oelke, V. Wascholowski, S. V. Ley, *Aldrichimica Acta* **2008**, *41*, 3–11; f) J. L. Vicario, D. Badìa, L. Carrillo, *Synthesis* **2007**, 2065–2092; g) M. J. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discovery Today* **2007**, *12*, 8–27.

[4] D. C. Rideout, R. Breslow, *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.

[5] S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem.* **2005**, *117*, 3339–3343; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275–3279.

[6] Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281–8282; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104.

[7] Y. Jung, R. A. Marcus, *J. Am. Chem. Soc.* **2007**, *129*, 5492–5502.

[8] D. G. Blackmond, A. Armstrong, V. Coombe, A. Wells, *Angew. Chem.* **2007**, *119*, 3872–3874; *Angew. Chem. Int. Ed.* **2007**, *46*, 3798–3800.

[9] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

[10] K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.

[11] D. E. Ward, V. Jheengut, *Tetrahedron Lett.* **2004**, *45*, 8347–8350.

[12] a) A. I. Nyberg, A. Usano, P. M. Pihko, *Synlett* **2004**, 1891–1896; b) P. M. Pihko, K. M. Laurikainen, A. Usano, A. I. Nyberg, J. A. Kaavi, *Tetrahedron* **2006**, *62*, 317–328.

[13] B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5839–5842.

[14] N. Zotova, A. Franzke, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2007**, *129*, 15100–15101.

[15] D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikoszovich, B. Linder, *Helv. Chim. Acta* **2007**, *90*, 425–471.

[16] C. Isart, J. Burés, J. Vilarrasa, *Tetrahedron Lett.* **2008**, *49*, 5414–5418.

[17] M. Gruttadauria, F. Giacalone, P. Lo Meo, A. Mossuto Marculescu, S. Riela, R. Noto, *Eur. J. Org. Chem.* **2008**, 1589–1596.

[18] S. Aratake, T. Itoh, T. Okano, N. Nagae, T. Sumiya, M. Shoji, Y. Hayashi, *Chem. Eur. J.* **2007**, *13*, 10246–10256.

[19] S. Pizzarello, A. L. Weber, *Science* **2004**, *303*, 1151.

[20] a) C-F. Pan, Z-Y. Wang, *Coord. Chem. Rev.* **2008**, *252*, 736–750; b) J. Mlynarski, J. Paradowska, *Chem. Soc. Rev.* **2008**, *37*, 1502–1511.

[21] S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569.

[22] A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416–5470.

[23] a) L.-W. Xu, Y. Lu, *Org. Biomol. Chem.* **2008**, *6*, 2047–2053; b) F.-H. Peng, Z.-H. Shao, *J. Mol. Catal. A: Chem.* **2008**, *285*, 1–13.

[24] A. Córdova, W. Zou, I. Ibrahem, E. Reyes, M. Engqvist, W.-W. Liao, *Chem. Commun.* **2005**, 3586–3588.

[25] Z. Jiang, Z. Liang, X. Wu, Y. Lu, *Chem. Commun.* **2006**, 2801–2803.

[26] M. Amedjkouh, *Tetrahedron: Asymmetry* **2007**, *18*, 390–395.

[27] Y.-Y Peng, Q. Wang, J.-Q. He, J.-P. Cheng, *Chin. J. Chem.* **2008**, *26*, 1454–1460.

[28] M.-K. Zhu, X.-Y. Xu, L.-Z. Gong, *Adv. Synth. Catal.* **2008**, *350*, 1390–1396.

[29] S. S. V. Ramasastry, K. Albertshofer, N. Utsumi, C. F. Barbas III, *Org. Lett.* **2008**, *10*, 1621–1624.

[30] X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, *Adv. Synth. Catal.* **2007**, *349*, 812–816.

[31] A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, 3024–3025.

[32] Y.-Y. Peng, Q.-P. Ding, Z. Li, P. G. Wang, J.-P. Cheng, *Tetrahedron Lett.* **2003**, *44*, 3871–3875.

[33] Y.-S. Wu, Y. Chen, D.-S. Deng, J. Cai, *Synlett* **2005**, 1627–1629.

[34] I. Ibrahem, W. Zou, Y. Xu, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, 211–222.

[35] J. Casas, H. Sundén, A. Córdova, *Tetrahedron Lett.* **2004**, *45*, 6117–6119.

[36] Y. Hayashi, S. Aratake, T. Itoh, T. Okano, T. Sumiya, M. Shoji, *Chem. Commun.* **2007**, 957–959.

[37] A. Hartikka, P. I. Arvidsson *Tetrahedron: Asymmetry* **2004**, *15*, 1831–1834.

[38] H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017–2020; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986.

[39] Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem.* **2006**, *118*, 972–975; *Angew. Chem. Int. Ed.* **2006**, *45*, 958–961.

[40] C. Zheng, Y. Wu, X. Wang, G. Zhao, *Adv. Synth. Catal.* **2008**, *350*, 2690–2694.

[41] Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji, *Angew. Chem.* **2006**, *118*, 5353–5353; *Angew. Chem. Int. Ed.* **2006**, *45*, 5227–5229.

[42] Y.-Q. Fu, Y.-J. An, W.-M. Liu, Z.-C. Li, G. Zhang, J.-C. Tao, *Catal. Lett.* **2008**, *124*, 397–404.

[43] L. Zhong, Q. Gao, J. Gao, J. Xiao, C. Li, *J. Catal.* **2007**, *250*, 360–364.

[44] F. Giacalone, M. Gruttadauria, P. Lo Meo, S. Riela, R. Noto, *Adv. Synth. Catal.* **2008**, *350*, 2747–2760.

[45] D. E. Siyutkin, A. S. Kucherenko, M. I. Struchkova, S. G. Zlotin, *Tetrahedron Lett.* **2008**, *49*, 1212–1216.

[46] G. S. Fonseca, A. P. Umpierre, P. F. P. Fichtner, S. R. Teixeira, J. Dupont, *Chem. Eur. J.* **2003**, *9*, 3263–3269.

[47] M. Lombardo, S. Easwar, A. De Marco, F. Pasi, C. Trombini, *Org. Biomol. Chem.* **2008**, *6*, 4224–4229.

[48] D. Font, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2006**, *8*, 4653–4655.

[49] D. Font, S. Sayalero, A. Bastero, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2008**, *10*, 337–340.

[50] a) F. Giacalone, M. Gruttadauria, A. Mossuto Marculescu, R. Noto, *Tetrahedron Lett.* **2007**, *48*, 255–259; b) M. Gruttadauria, F. Giacalone, A. Mossuto Marculescu, S. Riela, R. Noto, *Eur. J. Org. Chem.* **2007**, 4688–4698.

[51] a) Y.-X. Liu, Y.-N. Sun, H.-H. Tan, W. Liu, J.-C. Tao, *Tetrahedron: Asymmetry* **2007**, *18*, 2649. 31; b) Y.-X. Liu, Y.-N. Sun, H.-H. Tan, J.-C. Tao, *Catal. Lett.* **2008**, *120*, 281.

[52] S. Aratake, T. Itoh, T. Okano, T. Usui, M. Shoji, Y. Hayashi, *Chem. Commun.* **2007**, 2524–2526.

[53] G. Guillena, M. C. Hita, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 729–733.

[54] G. Guillena, M. C. Hita, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 1493–1497.

[55] G. Guillena, M. C. Hita, C. Nájera, *ARKIVOC* **2007**, 260–269.

[56] S. Guizzetti, M. Benaglia, L. Raimondi, G. Celentano, *Org. Lett.* **2007**, *9*, 1247–1250.

[57] J. Paradowska, M. Stodulski, J. Mlynarski, *Adv. Synth. Catal.* **2007**, *349*, 1041–1046.

[58] C. Wang, Y. Jiang, X.-X. Zhang, Y. Huang, B.-G. Li, G.-L. Zhang, *Tetrahedron Lett.* **2007**, *48*, 4281–4285.

[59] A. Russo, G. Botta, A. Lattanzi, *Tetrahedron* **2007**, *63*, 11886–11892.

[60] S. S. Chimni, D. Mahajan, *Tetrahedron: Asymmetry* **2006**, *17*, 2108–2119.

[61] S. Sathapornvajana, T. Vilaivan, *Tetrahedron* **2007**, *63*, 10253–10259.

[62] X.-H. Chen, S.-W. Luo, Z. Tang, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Chem. Eur. J.* **2007**, *13*, 689–701.
[63] J.-F. Zhao, L. He, J. Jiang, Z. Tang, L.-F. Cun, L.-Z. Gong, *Tetrahedron Lett.* **2008**, *49*, 3372–3375.
[64] Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289.
[65] M. Raj, V. Maya, S. K. Ginotra, V. K. Singh, *Org. Lett.* **2006**, *8*, 4097–4099.
[66] V. Maya, M. Raj, V. K. Singh, *Org. Lett.* **2007**, *9*, 2593–2595.
[67] a) M. Gruttadauria, F. Giacalone, A. Mossuto Marculescu, R. Noto, *Adv. Synth. Catal.* **2008**, *350*, 1397–1405; b) M. Gruttadauria, F. Giacalone, A. Mossuto Marculescu, A. M. P. Salvo, R. Noto, *ARKIVOC* **2009**, *viii*, 5–15.
[68] W.-P. Huang, J.-R. Chen, X.-Y. Li, Y.-J. Cao, W.-J. Xiao, *Can. J. Chem.* **2007**, *85*, 211–216.
[69] J.-R. Chen, H.-H. Lu, X.-Y. Li, L. Cheng, J. Wan, W.-J. Xiao, *Org. Lett.* **2005**, *7*, 4543–4545.
[70] S. Gandhi, V. K. Singh, *J. Org. Chem.* **2008**, *73*, 9411–9416.
[71] Y. Wu, Y. Zhang, M. Yu, G. Zhao, S. Wang, *Org. Lett.* **2006**, *8*, 4417–4420.
[72] H. Yang, R. G. Carter, *Org. Lett.* **2008**, *10*, 4649–4652.
[73] Z.-H. Tzeng, H.-Y. Chen, C.-T. Huang, K. Chen, *Tetrahedron Lett.* **2008**, *49*, 4134–4137.
[74] D. Gryko, W. J. Saletra, *Org. Biomol. Chem.* **2007**, *5*, 2148–2153.
[75] W. Zou, I. Ibrahem, P. Dziedzic, H. Sundén, A. Córdova, *Chem. Commun.* **2005**, 4946–4948.
[76] P. Dziedzic, W. Zou, J. Háfren, A. Córdova, *Org. Biomol. Chem.* **2006**, *4*, 38–40.
[77] A. Córdova, W. Zou, P. Dziedzic, I. Ibrahem, E. Reyes, Y. Xu, *Chem. Eur. J.* **2006**, *12*, 5383–5397.
[78] M. Lei, L. Shi, G. Li, S. Chen, W. Fang, Z. Ge, T. Cheng, R. Li, *Tetrahedron* **2007**, *63*, 7892–7898.
[79] Z. Tang, Z.-H. Yang, L.-F. Cun, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, *Org. Lett.* **2004**, *6*, 2285–2287.
[80] C. J. Rogers, T. J. Dickerson, A. P. Brogan, K. D. Janda, *J. Org. Chem.* **2005**, *70*, 3705–3708.
[81] N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734–735.
[82] L. Zu, H. Xie, H. Li, J. Wang, W. Wang, *Org. Lett.* **2008**, *10*, 1211–1214.
[83] S. Luo, H. Xu, J. Li, L. Zhang, X. Mi, X. Zheng, J.-P. Cheng, *Tetrahedron* **2007**, *63*, 11307–11314.
[84] F.-Z. Peng, Z.-H. Shao, X.-W. Pu, H.-B. Zhang, *Adv. Synth. Catal.* **2008**, *350*, 2199–2204.
[85] J. Li, S. Hu, S. Luo, J.-P. Cheng, *Eur. J. Org. Chem.* **2009**, 132–140.
[86] N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967.
[87] Y. Xu, W. Zou, H. Sundén, I. Ibrahem, A. Córdova, *Adv. Synth. Catal.* **2006**, *348*, 418–424.
[88] Y. Xu, A. Córdova, *Chem. Commun.* **2006**, 460–462.
[89] Z.-Y. Yan, Y.-N. Niu, H.-L. Wei, L.-Y. Wu, Y.-B. Zhao, Y.-M. Liang, *Tetrahedron: Asymmetry* **2006**, *17*, 3288–3293.
[90] E. Alza, X. C. Cambeiro, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2007**, *9*, 3717–3720.
[91] W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393–1395; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369–1371.
[92] L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077–3079.
[93] V. Maya, V. K. Singh, *Org. Lett.* **2007**, *9*, 1117–1119.
[94] S. Luo, X. Mi, S. Liu, H. Xu, J.-P. Cheng, *Chem. Commun.* **2006**, 3687–3689.
[95] Y.-J. Cao, Y.-Y. Lai, X. Wang, Y.-J. Li, W.-J. Xiao, *Tetrahedron Lett.* **2007**, *48*, 21–24.
[96] F. Xue, S. Zhang, W. Duan, W. Wang, *Adv. Synth. Catal.* **2008**, *350*, 2194–2198.
[97] D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Adv. Synth. Catal.* **2006**, *348*, 826–832.
[98] S. Wei, D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Catal. Today* **2007**, *121*, 151–157.
[99] M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514–6518; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366–6370.
[100] A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, 4928–4930.
[101] J. Wang, F. Yu, X. Zhang, D. Ma, *Org. Lett.* **2008**, *10*, 2561–2564.
[102] S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555–558; *Angew. Chem. Int. Ed.* **2008**, *47*, 545–548.
[103] C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, Á. Puente, S. Vera, *Angew. Chem.* **2007**, *119*, 8583–8587; *Angew. Chem. Int. Ed.* **2007**, *46*, 8431–8435.
[104] J. Lu, F. Liu, T.-P. Loh, *Adv. Synth. Catal.* **2008**, *350*, 1781–1784.
[105] F.-X. Chen, C. Shao, Q. Wang, P. Gong, D.-Y. Zhang, B.-Z. Zhang, R. Wang, *Tetrahedron Lett.* **2007**, *48*, 8456–8459.
[106] T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett.* **2003**, *5*, 4301–4304.
[107] I. Ibrahem, J. Casas, A. Córdova, *Angew. Chem.* **2004**, *116*, 6690–6693; *Angew. Chem. Int. Ed.* **2004**, *43*, 6528–6531.
[108] R.-G. Han, Y. Wang, Y.-Y. Li, P.-Fei Xu, *Adv. Synth. Catal.* **2008**, *350*, 1474–1478.
[109] P. Dziedzic, A. Córdova, *Tetrahedron: Asymmetry* **2007**, *18*, 1033–1037.
[110] M. Amedjkouh, M. Brandberg, *Chem. Commun.* **2008**, 3043–3045.
[111] L. Cheng, X. Wu, Yixin Lu, *Org. Biomol. Chem.* **2007**, *5*, 1018–1020.
[112] Y.-C. Teo, J.-J. Lau, M.-C. Wu, *Tetrahedron: Asymmetry* **2008**, *19*, 186–190.
[113] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
[114] A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458–2460.
[115] W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875.
[116] N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371.
[117] D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 6743–6746.
[118] K. H. Kim, S. Lee, D.-W. Lee, D.-H. Ko, D.-C. Ha, *Tetrahedron Lett.* **2005**, *46*, 5991–5994.

[119] A. Sakakura, K. Suzuki, K. Nakano, K. Ishihara, *Org. Lett.* **2006**, *8*, 2229–2232.

[120] M. Lemay, W. W. Ogilvie, *Org. Lett.* **2005**, *7*, 4141–4144.

[121] M. Lemay, L. Aumand, W. W. Ogilvie, *Adv. Synth. Catal.* **2007**, *349*, 441–447.

[122] B. F. Bonini, E. Capitò, M. Comes-Franchini, M. Fochi, A. Ricci, B. Zwanenburg, *Tetrahedron: Asymmetry* **2006**, *17*, 3135–3143.

[123] W. Chen, X.-H. Yuan, R. Li, W. Du, Y. Wu, L.-S. Ding, Y.-C. Chen, *Adv. Synth. Catal.* **2006**, *348*, 1818–1822.

[124] Y. Hayashi, S. Samanta, H. Gotoh, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 6736–6739; *Angew. Chem. Int. Ed.* **2008**, *47*, 6634–6637.

[125] J. K. Park, P. Sreekanth, B. M. Kim, *Adv. Synth. Catal.* **2004**, *346*, 49–52.

[126] Q. Chu, W. Zhang, D. P. Curran, *Tetrahedron Lett.* **2006**, *47*, 9287–9290.

[127] S. A. Selkälä, J. Tois, P. M. Pihko, A. M. P. Koskinen, *Adv. Synth. Catal.* **2002**, *344*, 941–945.

[128] M. Benaglia, G. Celentano, M. Cinquini, A. Puglisi, F. Cozzi, *Adv. Synth. Catal.* **2002**, *344*, 149–152.

[129] T. Mitsudome, K. Nose, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Tetrahedron Lett.* **2008**, *49*, 5464–5466.

[130] A. P. Brogan, T. J. Dickerson, K. D. Janda, *Angew. Chem.* **2006**, *118*, 8278–8280; *Angew. Chem. Int. Ed.* **2006**, *45*, 8100–8102.

[131] a) D. Gryko, R. Lipiski, *Eur. J. Org. Chem.* **2006**, 3864–3876; b) A. Bak, M. Fich, B. D. Larsen, S. Frokjaer, G. J. Friis, *Eur. J. Pharm. Sci.* **1999**, *7*, 317–323.

[132] U. M. Lindström, F. Andersson, *Angew. Chem.* **2006**, *118*, 562–565; *Angew. Chem. Int. Ed.* **2006**, *45*, 548–551.