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Catalysis in Water

Catalysts Based on Amino Acids for Asymmetric Reactions in Water

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Asymmetric organometallic and organocatalytic processes in aqueous systems are currently of great interest. A few years ago, only a few practitioners studied the subject; now organic reactions in water have become one of the most exciting research areas. The quest to identify water-compatible catalysts has evoked an intense search for new possibilities. Following nature's lead, the application of amino acids as sources of chiral information seems particularly promising for aqueous systems. Herein we provide an overview of very recent advances in the area of asymmetric catalysis in water with amino acids and their derivatives as effective catalysts or essential components of catalysts.

1. Introduction

As a solvent, water has a special status because of its role as the medium for all of the chemical reactions of life. In this context, it is quite surprising that the potential of water as a medium for asymmetric synthesis has long been neglected. Indeed, water is a desirable solvent for catalysis with respect to environmental concerns, safety, and cost. The variety of interactions between water and substrates (hydrogen bonding or interactions related to polarity, acidity, hydrophobicity etc.) make water interesting from an industrial as well as laboratory perspective.[1] In this regard, processes using water as a reaction medium have recently attracted a great deal of attention.[2]

For synthetic chemists, a very important goal is to perform catalytic enantioselective reactions, especially enantioselective carbon–carbon bond-forming reactions, in water without any organic solvents.[3] Thus, the development of enantioselective reactions using water as a solvent is now intensively investigated, although enzyme-catalyzed reactions were long thought to be the only candidates. It is highly desirable to develop a chemical system that, like an enzyme, can effect organic reactions in water with excellent efficiency and stereoselectivity.

Although asymmetric synthesis has reached extraordinary levels of sophistication in the last years, the development of asymmetric catalysis in water is still in progress. Only recently catalytic asymmetric reactions promoted by water-compatible Lewis acids with chiral ligands have been developed; most Lewis acids are not stable in water.[4]

Seminal work by List, Lerner, and Barbas on the intermolecular proline-catalyzed direct asymmetric aldol reaction[5] opened a new platform for designing metal-free asymmetric catalysts, although their application was initially limited to organic solvents. Most recently, the challenge of developing efficient aqueous-phase organocatalytic processes has also been tackled. Recent progress in the area initiated constructive discussion on the role and practical merits of water as a solvent. Thus water and water-based reaction media were debated with regards to terminology (that is, whether a reaction is carried out "in water", "in the presence of water", or "in the presence of large excess of water"). More importantly the question was asked, "How 'green' is an organocatalytic reaction carried out in the presence of water?"[6] Nevertheless, the way for mimicking enzymes' mode of action in their natural aqueous environment seems to be open for organic chemists.

The development of novel chiral catalysts is the most important aspect of this area of green chemistry. For both metal-assisted and metal-free strategies new water-soluble chiral units are obviously of utmost importance. While the de novo design of water-compatible chiral ligands and catalysts is an attractive but largely unexplored field, naturally occurring chiral units seem to be interesting and "natural" sources of

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chirality. The application of amino acids is particularly exciting as they are the building blocks of enzymes, which promote asymmetric reactions in nature.

Asymmetric synthesis using both natural and unnatural α-amino acids has been tremendously important from synthetic as well as industrial viewpoints, and numerous new methodologies have been developed the last decades. Additionally, the past few years have witnessed impressive growth in the application of natural amino acids as efficient (organo)-catalysts. Enantioselective organocatalysis in water afforded unsatisfactory results until only recently.

In contrast to the broad acceptance of amino acids as water-tolerant organocatalysts, their applications as chiral ligands in metal complexes seem to be limited to organic solvents. When one considers the natural abundance of α-amino acids, it is surprising that their use as ligands in Lewis acid catalysis remains largely unexplored. This may be because of their poor solubility in the organic solvents traditionally used for metal-promoted asymmetric transformations. In water, however, solubility is not an issue; free amino acids should have great potential as asymmetric ligands.

Thus, from the standpoints of both green chemistry and chiral economy the use of amino acids seems reasonable. The application of natural and modified amino acids as chiral catalysts and ligands for asymmetric synthesis in water is the subject of this Minireview. This field is an area of intense research, because the development of aqueous versions of reactions catalyzed by small-molecule catalysts presents a challenge.

2. Metal-Assisted Asymmetric Reactions

Asymmetric induction through the use of Lewis acids bearing chiral ligands is still at the core of asymmetric synthesis. The activity of the catalyst depends on the sort of Lewis acid, while the asymmetric induction is related to the attachment of chiral organic ligands to the central metal atom. Various kinds of Lewis acids have been developed, and many have been applied in synthesis and in industry. However, asymmetric catalysis in water or aqueous solvents is difficult because many Lewis acid type catalysts are not stable in the presence of water. Advances in this field have required the development of novel, mostly transition-metal catalysts that exhibit at least kinetic stability towards water. The second challenge is designing a chiral ligand for reactions in aqueous media with appropriate binding properties to the central metal cation and as well as with satisfactory solubility in water. To address this issue some catalytic asymmetric reactions with water-compatible Lewis acids bearing chiral ligands have been developed.[3,4]

The water solubility of organometallic catalysts can be generally enhanced by modifying known ligands, typically by introducing a polar group. Another and still underestimated possibility is, however, application of natural, water-soluble, chiral units. Molecules of naturally occurring sugars and amino acids are equipped with many hydrophilic groups and thus are soluble in water.

Jacek Mlynarski was born in Poland in 1971. He studied chemistry at the Jagiellonian University in Kraków before he moved to Warsaw, where he received his PhD (2000) from the Institute of Organic Chemistry of the Polish Academy of Sciences. In 2002 he joined the Institute of Organic Chemistry in Warsaw, where he has been a group leader since 2008. His scientific interests include enantioselective synthetic methodology that relies on metal-based chiral catalysts.

Joanna Paradowska was born in Warsaw, Poland, in 1984. She studied chemistry at Rzeszow University of Technology, graduating in 2007. She then moved to the Institute of Organic Chemistry, Polish Academy of Science and joined Jacek Mlynarski's group. Her primary research interest is the development of water-compatible catalysts for direct asymmetric aldol reactions.

Maciej Stodulski studied chemistry at the University of Bialystok and graduated in 2005. He is currently carrying out PhD research at the Institute of Organic Chemistry, Polish Academy of Sciences under the supervision of J. Mlynarski. His research is directed toward the development of new asymmetric synthesis methodology relying on metal-based chiral catalysts and applications to the synthesis of biologically important compounds.

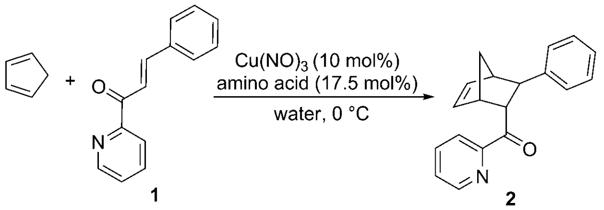
Unprotected amino acids are rarely used as chiral units in metal-catalyzed reactions. Nevertheless, application of Lewis acids bearing chiral ligands derived from natural amino acids was shown to be possible in water and will be presented in this section.

2.1. Diels–Alder Reaction

The benefits of water as a solvent for Lewis acid catalyzed reactions was observed for the very first time for the Diels–Alder reaction. In fact, the discoveries made by Breslow[7] and Grieco[8] in the early 1980s opened the door for future development in the field. The reactions conducted in water were found to be much faster than those in organic solvents; this acceleration based on the solvent effects of water was studied in detail only recently.[9]

Owing to its well-understood mechanism, the Lewis acid catalyzed Diels–Alder reaction was chosen as a model reaction for asymmetric synthesis. The asymmetric hetero-Diels–Alder reaction of Danishefsky's diene catalyzed by chiral lanthanide complexes in the presence of water was presented by Mikami et al.[10] Condensation of the diene with butyl glyoxylate in toluene in the presence of a chiral lanthanide bis(trifluoromethanesulfonyl)amide gave the corresponding cyclized product in 74% yield and 54% *ee*. The significant effect of water as an additive was increased enantioselectivity and the chemical yield. Addition of 10 equivalents of water to the mixture increased the enantiomeric excess to 66% and the yield to 88%.

The first catalytic, enantioselective Diels–Alder reaction in water was developed by Engberts and his group,[11] who studied a catalyst system incorporating a central Cu^{2+} cation and α-amino acid ligands. They screened a series of ligands for the reaction between 3-phenyl-1-(2-pyridyl)-2-propen-1-one (**1**) and cyclopentadiene (Scheme 1). The Diels–Alder adducts were obtained in yields generally exceeding 90% and in good selectivities of up to 74% *ee*. This enantioselectivity was higher than that observed in organic solvents. α-Amino acids with aromatic substituents were found to cause a significant increase in the equilibrium constant (K_a) for the binding of the dienophile to the ligand/metal ion complex (Table 1). This ligand-accelerated catalysis is likely to be a consequence of arene–arene interactions between the aromatic ring of the α-amino acid ligand and the pyridine ring of the dienophile.



Scheme 1. Asymmetric Diels–Alder reaction catalyzed by copper(II) and an amino acid.

Table 1: Influence of α-amino acid ligands on the K_a and *ee* of the Diels–Alder reaction of dienophile **1** with cyclopentadiene.

Entry	Ligand	K_a [M^{-1}]	*ee* [%][a]
1	–	1.16×10^3	–
2	L-valine	5.71×10^2	3
3	L-phenylalanine	8.66×10^2	17
4	L-tyrosine	1.40×10^3	36
5	*N*-methyl-L-tyrosine	2.45×10^3	74
6	*N,N*-dimethyl-L-tyrosine	1.66×10^3	73
7	L-tryphtophan	3.02×10^3	33
8	N^{α}-methyl-L-tryphtophan	5.05×10^3	74

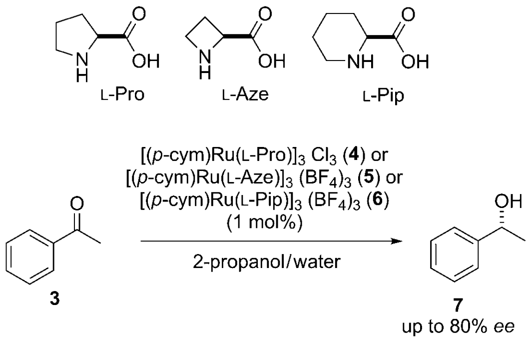
[a] Only the results for the major (> 90%) *endo* isomer of the Diels–Alder adduct are shown.

These reactions were the first catalytic enantioselective Lewis acid catalyzed cycloaddition reactions in water. Chiral induction in Diels–Alder reactions in water has also been achieved through the use of an amino acid chiral auxiliary attached to dienophile,[12] but this approach requires a stoichiometric amount of the chiral auxiliary.[13] In Section 4 we will describe an example of a metal-free organocatalyst for the enantioselective Diels–Alder reaction of ketones that acts by lowering the LUMO.

2.2. Reduction of Prochiral Substrates

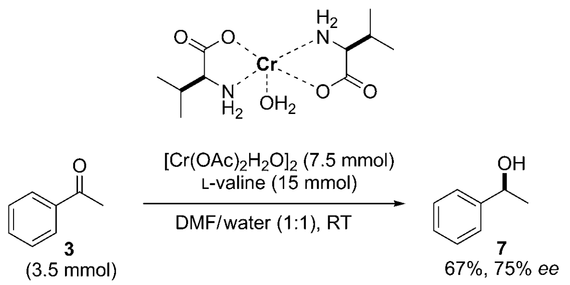
The hydrogenation of prochiral substrates in water or in a two-phase system is one of the most studied reactions.[14] This work is, to some extent, inspired by studies on the enzymatic reduction of ketones and the kinetic resolution of chiral alcohols in water. In particular, the asymmetric reduction of prochiral ketones to give enantiomerically pure secondary alcohols, which can serve as valuable chiral building blocks, is an interesting challenge. Moreover, catalytic asymmetric hydrogenation and hydride addition are among the most important reactions in the industrial production of chiral compounds from achiral substrates.

Joó and co-workers used ruthenium complexes with chiral amino acid ligands as catalysts for the enantioselective reduction of prochiral ketones by hydride transfer in wet 2-propanol.[15] The reduction of acetophenone, substituted acetophenones, and other aryl ketones was accomplished with 2-azetidinecarboxylic acid, 2-piperidinecarboxylic acid, proline, and alanine; good rates and selectivities up to 86% *ee* were reported. The same complexes showed poor hydrogenation activity for the reduction of ketones and olefinic substrates in aqueous solution (Scheme 2). Ruthenium complexes based on proline-derived amides were further designed for the asymmetric hydride-transfer reduction of substituted acetophenones, although in organic solvents.[16]



Scheme 2. Asymmetric transfer hydrogenation of aryl ketones promoted by ruthenium complexes having ligands derived from proline. *p*-cym = *p*-cymene.

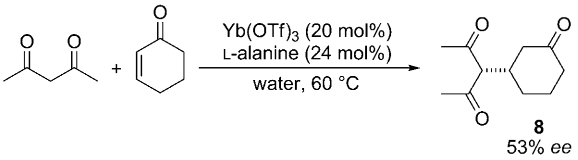
Water-soluble chiral complexes have also been developed which incorporate free amino acids for reaction under truly homogeneous conditions. The reduction of prochiral ketones by stoichiometric amounts of chromium(II)/L-amino acid complexes in DMF/water (1:1) under mild conditions proceeded in good yields and up to 74% *ee*.[17] Natural amino acids (His, Leu, Lys, Phe, Trp, Ala, Asp, Glu, Pro, Val, Asp) were tested as the source of chiral information in experiments conducted with media containing a high percentage of water. The enantioselectivities observed were highly dependent on the structure of the ligand and the composition of the metal–ligand complex. The best selectivities were achieved using CrL_2 complexes (Scheme 3).[17a]



Scheme 3. Enantioselective reduction of acetophenone (**3**) by a chromium(II)–valine complex.

2.3. Michael Reaction

The Michael addition is a well-studied reaction for the formation of carbon–carbon bonds; its enantioselective variant in water, however, remains limited to few examples.[18] In 2007 Lindström and Wennerberg reported preliminary results on the use of α-amino acids as rate-accelerating ligands in the Lewis acid catalyzed Michael addition reaction in aqueous two-phase systems.[19] High-yielding reactions were observed with various donors and a wide range of acceptors, and a ligand acceleration factor of 138 was measured for alanine in the ytterbium triflate catalyzed addition of ethyl acetoacetate to methyl vinyl ketone. More interestingly, a number of α-amino acids were screened for chiral induction in the reaction between acetylacetone and 2-cyclohexen-1-one (Scheme 4). The observed *ee* values of adducts **8** were modest; alanine gave the best results. Under similar conditions sterically more demanding amino acids such as valine and isoleucine gave results similar to those with alanine, the sterically least demanding α-amino acid. The authors claimed that the enantioselectivities of the reactions were the highest observed with native α-amino acids as ligands for Lewis acids in pure water.



Scheme 4. Asymmetric Michael addition catalyzed by ytterbium(III) and alanine.

2.4. Direct Asymmetric Aldol Reaction

The asymmetric aldol reaction is undoubtedly one of the most important reactions for the construction of C–C bonds in organic synthesis.[20] The ability to control the enantioselectivity of the newly generated stereogenic centers has established this reaction as the principal chemical transformation for the stereoselective construction of complex polyol architectures.[21] The aldol reaction is also crucial for the biosynthesis of carbohydrates, keto acids, and some amino acids. In nature, type I and II aldolases catalyze this reaction in water with excellent enantiocontrol through an enamine mechanism and by using a metal cofactor, respectively.[22] It is highly desirable to develop chemical systems that can mimic the action of enzymes and promote organic reactions in water with high efficiency and stereoselectivity.

An exciting approach to enhancing the efficiency of the aldol reaction is to design a compound that will catalyze the direct aldol addition (if possible asymmetrically) without preformation of the nucleophile.[23] Another challenge is to find a catalyst capable of activating the donor and the acceptor carbonyls simultaneously in water.[24] Two strategies have been employed to mimic the aldolases' mode of action in direct asymmetric aldol reactions in aqueous media: 1) organocatalysts, including modified amino acids and small peptides, acting as type I aldolases and 2) metal-catalyzed aldol reactions generally based on zinc complexes.

2.4.1. Direct Aldol Reaction Promoted by Zinc Complexes

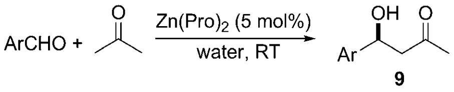
Despite the great potential of direct asymmetric aldol reactions, only a few methods have been reported for the metal-assisted activation of donor and acceptor. Chiral complexes mimicking the mode of action of type II aldolases have been developed recently; however, they are water-sensitive and thus reactions must be carried out under anhydrous conditions in organic solvents.[25]

The application of Lewis acidic metal complexes methods bearing chiral ligands as catalysts in aqueous solvents is still difficult. Among the metals that can be considered suitable for catalysis in water, zinc appears the most promising as it is used frequently in nature for this purpose. Zinc can accommodate several coordination geometries and act as an efficient Lewis acid even when surrounded by water molecules.[26] In the design of zinc-containing catalysts for the direct asymmetric aldol reaction in aqueous media, the use of amino acids or related N-donor ligands seems very attractive. Their ability to tightly bind zinc ions suggests that they might be suitable for the construction of asymmetric catalysts analogous to type II aldolases, in which the zinc ion is tightly coordinated by three histidine residues in the active site.[27]

The first application of an in situ generated zinc complex with amino acid ester ligands (TyrOEt) was presented in 1985.[28] The readily available catalyst, although reactive, was unselective and led to racemic products by direct condensation of acetone with *p*-nitrobenzaldehyde.

The first example of an asymmetric direct aldol reaction of acetone in water was described by Darbre et al.[29] Zinc complexes of a range of amino acids were tested in the aldol reaction of acetone and *p*-nitrobenzaldehyde with the best results observed for proline, lysine, and arginine.[29a] When the zinc–proline complex was the catalyst in acetone/water (2:1), **9** (Ar = 4-$NO_2C_6H_4$) was obtained in 6% yield and 21% *ee*. The complex prepared from proline and zinc acetate catalyzed the aldol reaction of acetone and a wide range of aromatic aldehydes in aqueous media, accepting even deactivated aldehydes (Table 2).[29b] Enantiomeric excesses of up to 56% could be obtained with only 5 mol% Zn(Pro)$_2$ at room temperature. This homogeneous reaction was conduct-

Table 2: Direct asymmetric aldol reaction of aromatic aldehydes and acetone catalyzed by Zn^{II}-proline complex.



Entry	Ar	Time [h]	Yield [%]	*ee* [%]
1	4-$NO_2C_6H_4$	95	18	56
2	2-$NO_2C_6H_4$	94	18	5
3	4-$MeOC_6H_4$	48	36	38
4	2-$MeOC_6H_4$	75	36	32
5	4-ClC_6H_4	95	36	5
6	4-CNC_6H_4	91	22	27
7	Ph	32	48	5
8	1-naphthyl	75	45	31

ed in homogeneous acetone/water solution (1:2), making acetone not only the reactant but also the solvent. The reaction is enantioselective only for activated aromatic aldehydes, in particular *p*-nitrobenzaldehyde. The aldol reaction catalyzed by zinc complexes is regio- and stereoselective with hydroxy- and dihydroxyacetone but leads unfortunately to racemic hydroxyaldols.

The new catalyst incorporates a metal center that can act as a Lewis acid in water and mimicks type II aldolases' mode of action. On the other hand, the complex could also form an enamine intermediate, in analogy to the type I aldolases. The fact that proline alone is not an efficient catalyst indicates that enamine formation is unfavorable under the reaction conditions. The zinc complex gave the *S* enantiomer of the aldol in excess, whereas with proline alone the *R* enantiomer was predominant. Both observations support the postulate that the zinc ion coordinates to the ketone in order to facilitate the enolate formation while the proline ligand provides the chiral environment only (Figure 1, **10**). Nevertheless, the authors propose a mechanism involving zinc-assisted enamine formation, where zinc complexation only stabilizes the enamine intermediate in water (Figure 1, **11**). Preliminary evidence has been reported,[30] but further studies are needed to clarify the role of metal cation.

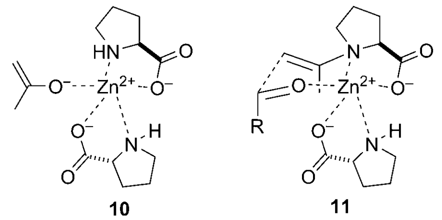
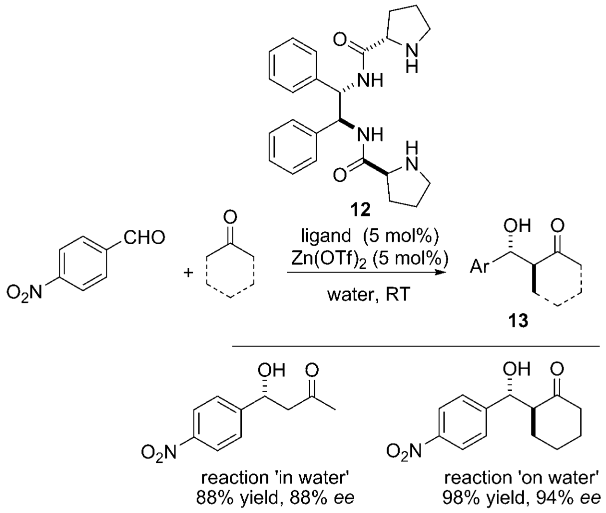


Figure 1. Proposed intermediates for the zinc-assisted formation of enolates and enamines in water.

The highly enantioselective direct aldol reaction of aliphatic ketones in the presence of water was presented recently. We demonstrated that zinc triflate and the chiral C_2-symmetrical prolinamide ligand **12** are an efficient catalyst system for asymmetric aldol reactions in a ketone/water mixture (9:1).[31] A loading of only 0.5–5 mol% of the in situ generated zinc(II) complex promoted the aldol reaction between acetone and aromatic aldehydes in homogeneous solution to give products with high enantioselectivity (up to 90% *ee*, Scheme 5). The catalyst was also selective in biphasic systems. Both excellent enantioselectivity and *anti* selectivity were documented when cyclohexanone was employed as a substrate. The essential role of water was apparent: When the reaction was carried out in anhydrous cyclohexanone, only a trace of product was isolated. The catalytic system can be used without organic solvents as well as in solvent mixtures.



Scheme 5. Direct asymmetric aldol reaction in water catalyzed by a zinc(II) complex of bis(prolinamide) **12**.

For this catalyst, formation of the enamine intermediate can be assumed. This observation was supported by the fact that the protonated ligand **12** (with trifluoroacetic acid) catalyzed direct aldol reactions as an organocatalyst with excellent diastereo- and enantiocontrol, and furnished the corresponding aldols in up to 99% *ee*.[31] Thus, this study reveals an interesting overlap in aqueous asymmetric aldol reaction between the application of metal complexes and organocatalysis.

From the perspective of green chemistry it is highly desirable that the catalysts can be recovered and reused. Kudo et al. reported a direct asymmetric aldol reaction under aqueous conditions catalyzed by N-terminal prolyl peptides; to aid in recovery of the catalyst the peptides were immobilized on a polymer support.[32] Several several amino acids were screened, and a PEG-PS resin-supported tripeptide (D-Pro-Tyr-Phe) gave the best results for the reaction of acetone with *p*-nitrobenzaldehyde (90% yield, 33% *ee*). Addition of $ZnCl_2$ resulted in further improvement. The best results were obtained when the reaction was performed in acetone/water/THF (1:1:1) using 20 mol% of the peptide and $ZnCl_2$ (66% yield, 73% *ee*). The peptide catalyst could be removed from the reaction mixture by filtration and reused at least five times without significant loss of activity and selectivity.

3. Asymmetric Organocatalysis in Water

The report by List, Lerner, and Barbas[5] of an intermolecular direct aldol reaction catalyzed by proline opened a new era in asymmetric synthesis. Asymmetric reactions using low-molecular-weight organic molecules as catalysts, referred to as organocatalysis, are a rapidly developing area of research.[33] Recent advances in organocatalysis include a wide range of reactions, which have also been employed for the asymmetric synthesis of complex molecules.[34]

3.1. Enamine-Based Organocatalysis of the Aldol Reaction in Water

The concept formulated by List describing asymmetric enamine catalysis[35] for the direct asymmetric aldol reaction is similar to the mechanism of carbon–carbon bond formation formulated for aldolases[22] and more recently for designed catalytic antibodies.[36] Nature's aldolases use a combination of acids and bases in their active sites to accomplish the direct aldolization of unmodified carbonyl compounds in the asymmetric environment created by amino acid residues. Type I aldolases rely on the Lewis base catalysis of a primary amino group.[22]

Unlike enzymatic reactions in nature, reactions catalyzed by amino acids mimicking type I aldolase's mode of action have been carried out typically in organic solvents. Proline catalyzes direct aldol reactions with high enantioselectivity in polar organic solvents such as DMSO and DMF, but in the presence of water[37] or a buffer solution, nearly racemic products were obtained.[38] The first artificial water-compatible organocatalysts with high enantioselectivities were catalytic antibodies.[39] These biomacromolecular catalysts are proposed to form an enamine intermediate in the active site similar to that found in aldolases. The stability of the enamine in water is one of the most important aspects in the development of small-molecule organocatalysts for asymmetric aldol reactions in water.[6a] Recent progress in the application of organocatalysts for direct asymmetric aldol and Mannich reactions has been summarized recently.[24,40]

Early studies conducted by the research groups led by Reymond[41] and Janda[42] demonstrated small-molecule enamine-based aldol reactions under buffered aqueous conditions. Only nornicotine catalyzed asymmetric aldol reactions, albeit with moderate enantioselectivity (20% *ee*),[42] while no asymmetric induction was obtained using proline or other amino acids.[41]

Since 2003, efforts have been made to develop efficient organocatalysts for asymmetric intermolecular aldol reactions in water. First studies of the role of water in organocatalytic processes were presented by Pihko and co-workers.[43] The presence of water was demonstrated to enhance the yield in the proline-mediated direct aldol reaction. They suggested that the role of water is to prevent deactivation of the substrate (water suppresses the formation of proline oxazolidinones) rather than promote activity. Blackmond et al. have delineated two conflicting roles for water: It not only suppresses the formation of the active enamine intermediate, but its presence also increases the total catalyst concentration within the catalytic cycle owing to the suppression of spectator species.[44]

The addition of water was observed to have a highly beneficial effect on reactions that were conducted with equimolar amounts of ketone and aldehyde. Proline (**14**),[45] various proline derivatives (**15**–**17**),[46] and some other amino acids[47] were used as catalysts in aqueous organic solvents with some success (Figure 2).

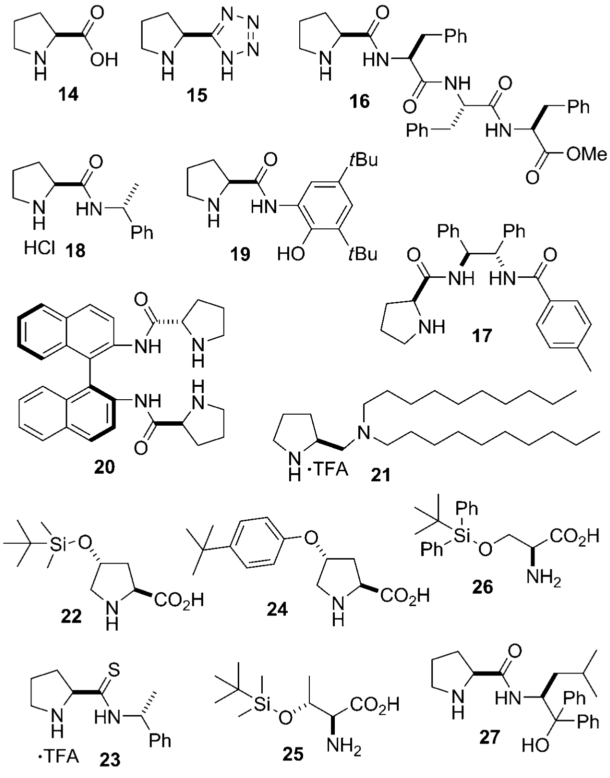


Figure 2. Catalysts derived from amino acids for asymmetric aldol reactions in aqueous organic solvents. TFA = trifluoroacetic acid.

Though asymmetric aldol reactions catalyzed by the proline-derived amides **18**[48a–c] and **19**,[48d] diamide **20**,[48e] and tryptophan[48f–g] have been developed in water without organic cosolvents, only moderate enantioselectivities were observed.

In 2006, the groups led by Barbas[49] and Hayashi[50] independently presented highly enantioselective direct aldol reactions promoted by diamine **21** and siloxyproline **22**, respectively. Although siloxyproline **22** showed better substrate scope, application of this catalyst for water-soluble ketones was limited.[50]

Further examples of highly enantioselective aldol reactions in water are known.[51] The efficient and nearly quantitative reaction of cyclohexanone in the presence of a large amount of water was described to be promoted by protonated proline amides **12**,[31] pralinethioamide **23**,[51a] and *tert*-butylphenoxyproline **24**.[51h]

Whereas in the natural enzyme the enamine is formed at the lysine residue in the active site,[22] most catalysts contain a cyclic proline motif for this purpose. Studies of enantioselective organocatalytic reactions promoted by primary amino acids and their derivatives[47] provided new and interesting results.[40] The most promising applications of siloxythreonine **25**[51c] and serine **26**[51b] must be seen, however, as reactions "in the presence of water" rather than "in water".

In one of the most recent reports in the field, Singh et al. described proline-derived organocatalysts **27** capable of mediating the direct asymmetric aldol reaction of ketones with aldehyde acceptors in high enantioselectivities and with low catalyst loading (0.5 mol %) in aqueous medium.[51d] Switching from water to brine resulted in better yields and *ee* values. The proline amide catalyst was quite general with regard to the aldehyde donors: Not only aromatic but also some α-substituted aliphatic aldehydes served as substrates. In all cases good yields along with excellent diastereo- and enantioselectivities (> 99 % *ee*) were reported.

The catalytic cycle of the aldol addition reaction catalyzed by proline amide **27** proceeds via an enamine intermediate, and the stereochemical outcome of the reaction can be explained by a transition state in which the aldehyde is activated by hydrogen bonding with the NH and OH groups of the catalyst (Figure 3).

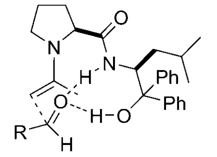
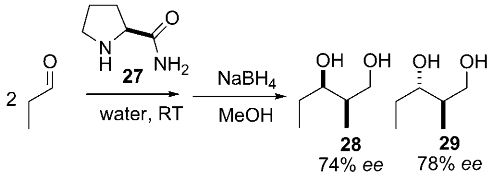


Figure 3. Favored transition-state model proposed by Singh et al.

The reactions described proceed in concentrated organic phase; water is present only as a second phase that influences the reaction in the organic phase.[6b] In the case of water-soluble ketones (like acetone) brine is required to concentrate the organic substrate in the organic phase. Recently, Hayashi's group found that proline amide **27** acts efficiently in homogeneous solution with water for the enantioselective self-aldol reaction of propanal (Scheme 6).[52] The good level of enantioselectivity (up to 78 % *ee*) was explained by the activation of the carbonyl group of the substrate by an amide proton of the catalyst in the same way that the carboxylic acid proton of proline would.

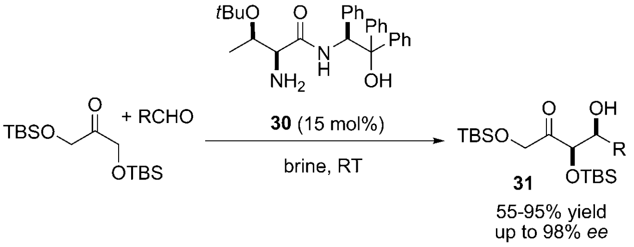


Scheme 6. Self-aldol reaction of propanal in water promoted by amino amide **27**.

Meanwhile, efforts also have been made on organocatalyst recycling using solid-phase supports and fluorous phases.[53]

Hydroxy- and dihydroxyacetone (DHA) are versatile C_3 building blocks in the chemical and enzymatic synthesis of carbohydrates. DHA-based aldol reactions are of huge importance because they provide direct access to natural and modified polyol architectures. These compounds served as substrates in asymmetric aldol reactions in aqueous organic solvents, as described by Gong et al., using the L-proline-based small peptide **16**.[46b]

The research groups led by Lu[51c] and Barbas[54] independently reported that hydrophobic threonine derivatives could catalyze direct aldol reactions between O-protected hydroxyacetone and various aromatic aldehydes in the presence of small amounts of water. Recently, a novel threonine-based organocatalyst **30** was developed that effectively catalyzes the reaction of protected DHA with a variety of aldehydes in brine to provide *syn* aldols (Scheme 7).[55]



Scheme 7. *syn*-Selective aldol reaction of dihydroxyacetone in brine. TBS = *tert*-butyl(dimethyl)silyl.

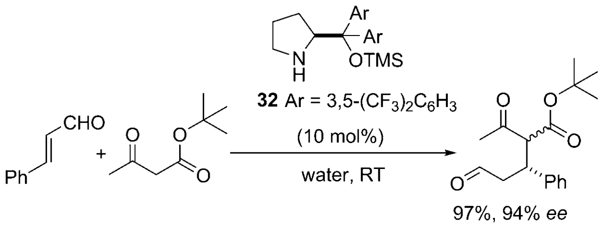
The *tert*-butyl(diphenyl)silyl-protected threonine catalyst **25** and the serine-based catalyst **26** could also be used for the direct three-component Mannich reaction of hydroxyacetone with *p*-anisidine and aromatic or aliphatic aldehydes.[56] The direct *anti*-selective Mannich reaction proceeded in the presence of water in a two-phase system. Good enantioselectivities were obtained with aromatic aldehydes for both cyclohexanone (*syn* selectivity) and *O*-benzylhydroxyacetone donors.

3.2. Michael Reaction

Over the past years significant progress in the area of asymmetric Michael additions has been made using organocatalysts. Prominent examples of water-tolerant organocatalysts have also been noted for this reaction. Barbas and coworkers developed a catalytic direct asymmetric Michael reaction that can be performed in brine without added organic solvents. The bifunctional catalyst **21** (the TFA salt of a diamine) demonstrated excellent reactivity, disatereoselectivity, and enantioselectivity for the reaction of ketones or aldehydes with β-nitrostyrene.[57]

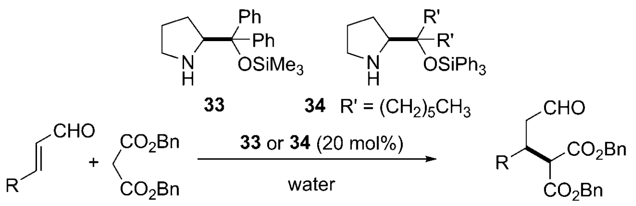
In their construction of optically active cyclohex-2-enone derivatives Jørgensen et al. started with the extension of the asymmetric Michael reaction of α,β-unsaturated aldehydes to β-ketoesters as nucleohiles under "environmentally friendly reaction conditions".[58] The *tert*-butyl oxobutyrate reacted smoothly with cinnamaldehyde in water using pyrrololidine **32** as the catalyst (Scheme 8).

Two examples of the enantioselective Michael addition of benzyl malonate to substituted acroleins in water have also



Scheme 8. Organocatalytic Michael addition of *tert*-butyl 3-oxobutyrate with α,β-unsaturated aldehydes.

been presented using siloxy prolinols **33** and **34** (Scheme 9).[59] All of the amines employed belong to a family of prolinol-based compounds that enable catalysis through an iminium derivative of the enal in aqueous systems to provide high enantioselectivities under protic conditions.



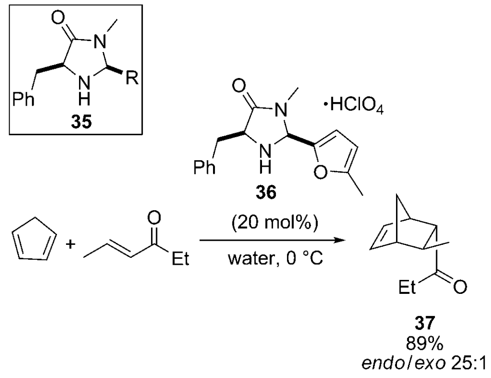
Scheme 9. Reaction of benzyl malonate and enals in water catalyzed by **33** and **34**.

4. Other Catalysts Prepared from Amino Acids

The preceding sections focused on practical applications of asymmetric catalysts bearing amino acid functions or having structures closely related to amino acids. There are, however, many nitrogen-based ligands and organocatalysts that are derived from amino acids. Some of them have been used successfully for asymmetric carbon–carbon bond formation in water.[60]

In 1999 MacMillan's group developed the concept of iminium activation, which is based on the capacity of chiral amines to function as enantioselective LUMO-lowering catalysts for a broad range of synthetic transformations. For this purpose, chiral secondary amines based on the imidazolidinone architecture **35** were developed which incorporated amino acid motifs. To date, this activation strategy based on LUMO lowering has led to the development of over 30 different enantioselective transformations for asymmetric synthesis.[61] In 2002, MacMillan and Northrup presented the first catalytic Diels–Alder reaction in water based on a metal-free imidazolidinone catalyst. They reported the activation of acyclic and cyclic enones for enantioselective catalytic [4+2] cycloaddition using catalyst **36**.[62] The chirality of the catalyst originated from an amino acid precursor; **36** was prepared from (*S*)-phenylalanine methyl amide. The reaction of 4-hexen-3-one and cyclopentadiene provided the Diels–Alder product **37** in 89% yield and with good stereoselectivity (90% *ee* for the *endo* isomer; Scheme 10).

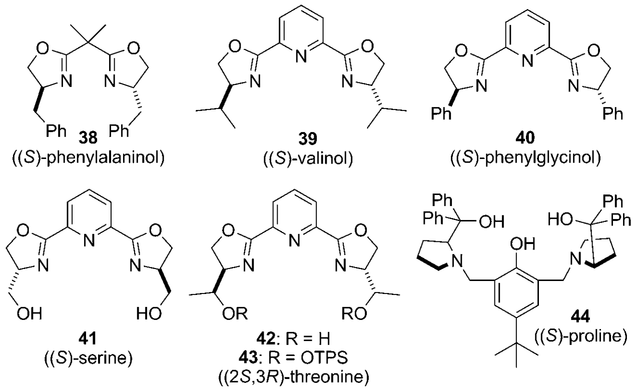
The C_2-symmetric bisoxazolines (box) derived from amino acids have received a great deal of attention as ligands



Scheme 10. Organocatalytic activation in Diels–Alder reaction between 4-hexen-3-one and cyclopentadiene in water.

in coordination chemistry and in asymmetric catalysis.[63a] When the box ligand is combined with a pyridine ring as a spacer, the pybox tridentate ligand results.[63b] The versatility of these ligands has been demonstrated in numerous catalytic asymmetric syntheses. As pybox is easy to prepare, applications of new derivatives are easily realizable.

Scheme 11 shows ligands used for the construction of water-tolerant chiral Lewis acids and the promotion of asymmetric reactions in aqueous solutions. A ruthenium-catalyzed asymmetric cyclopropanation of styrene in aqueous media was developed by Nishiyama and co-workers.[64] The water-soluble pybox derivative **41** was the ligand of choice for this transformation which was essentially assisted by water in biphasic or homogeneous alcoholic media. An analogous rhodium-catalyzed transformation was presented by Carette et al. with the pybox derivative **39** as a source of chirality.[64c]



Scheme 11. Ligands derived from amino acids and substrates for their preparation (in brackets).

The first example of the indium-mediated allylation of aldehydes was described by Loh and Zhou; the same pybox derivative **39** served as a ligand, and Ce(OTf)$_3$ hydrate was used as a Lewis acid promoter.[65] Li and Wei developed a highly enantioselective direct alkyne–imine addition in water catalyzed by Cu^{I} and **40**.[66]

Several examples of water-compatible Lewis acids for asymmetric Mukaiyama aldol reactions (using complexes Cu/

38, Zn/**39**–**43**, and Fe/**43**) have appeared in the literature.[26,67] Interesting water-stable gallium Lewis acids with the proline-derived chiral ligand **44** were described by Wang, Li, and co-workers.[67d]

During the last 20 years the use of soluble chiral organometallic catalysts has led to important advances in asymmetric synthesis. Examples of water-soluble chiral ligands derived from amino acids, in particular for asymmetric hydrogenation in aqueous media, can be found in previously published review articles.[2,3,68]

5. Conclusions

Organic reactions in water are currently of great interest, and asymmetric catalysis in aqueous media is an established new tool in organic chemistry. A tremendous amount of effort has been applied to mimick enzymes, which act with high efficiency in the aqueous environment of living cells. Aside from synthetic ligands, naturally occurring compounds have also been investigated as chiral catalysts and chirality-generating components. Amino acids, among the most important compounds in the cycle of terrestrial life, now become even more important owing to their application as catalysts in asymmetric synthesis.

Thus, asymmetric reactions promoted by amino acid based chiral metal complexes have been realized; examples include the asymmetric hydrogenation of prochiral ketones, the aldol addition, and related reactions. Organocatalysis also plays an increasingly important role in synthetic methodology. Most recently, scientists have developed efficient amino acid based aqueous organocatalytic processes.

Although the field is still in its infancy, the development of organic reactions in aqueous media should benefit academia and industry, including green chemistry. Nevertheless, this does not mean that other strategies are less important. Rather, they are complementary and facilitate the synthesis of the desired target molecules as well as learning and real understanding of life and nature.

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[60] Our intention was to demonstrate the practical utility of amino acids and related compounds for asymmetric synthesis aqueous media. In this section examples have been added on referees' request.

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