Catalytic asymmetric aldol reactions in aqueous media

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Nature has perfected the stereospecific aldol reaction by using aldolase enzymes. While virtually all the biochemical aldol reactions use unmodified donor and acceptor carbonyls and take place under catalytic control in an aqueous environment, the chemical domain of the aldol addition has mostly relied on prior transformation of carbonyl substrates, and the whole process traditionally is carried out in anhydrous solvents. The area of aqua-asymmetric aldol reactions has received much attention recently in light of the perception both of its green chemistry advantages and its analogy to eon-perfected enzyme catalysis. Both chiral metal complexes and small chiral organic molecules have been recently reported to catalyze aldol reactions with relatively high chemical and stereochemical efficiency. This *tutorial review* describes recent developments in this area.

1. Introduction

The aldol reaction, in addition to being an effective method for the formation of carbon–carbon bonds in organic synthesis, is also a critical biological reaction in the context of metabolism.[1,2] Enzymes (aldolases) have evolved to catalyze the metabolism and catabolism of highly oxygenated metabolites, and are found in many biosynthetic pathways of carbohydrates, keto acids and some amino acids.[3] In the drive towards green, sustainable methodologies in the chemical laboratory and even in manufacturing, biocatalysis has much to offer as it operates in an environmentally acceptable solvent: water. Broad synthetic utility of enzymes are limited, however, by the lack of large-scale compatibility and typically narrow substrate acceptance.

Although enzymatic processes in nature occur in an aqueous environment by necessity, water has been a solvent to be avoided for common organic reactions. However, from a green chemistry perspective, the use of water instead of organic solvent is preferred to decrease environmental contamination. Indeed, water is a safe, harmless, and environmentally benign solvent. Moreover, water has unique physical and chemical properties, such as high dielectric constant and high cohesive energy density relative to most organic solvents. In this respect some reactions are accelerated by water, while others are inhibited in this medium. The varied interactions between water and substrates (hydrogen bonding, polarity, acidity, hydrophobicity *etc*.) make water an interesting candidate as a solvent or co-solvent from an industry and laboratory perspective. In this regard, organic reactions in aqueous media are of current interest. In addition, from practical and synthetic standpoints, a benefit of using water is immediately evident as it is not necessary to dry solvents and substrates for reactions in aqueous media.

Although several interesting reactions with unique reactivity and selectivity have been developed in water or water–organic solvents,[4] development of an asymmetric aqua aldol reaction is still on going. Recently, given the synthetic utility of the asymmetric aldol reaction, there is a growing search for an organic catalysts that can effectively promote this reaction in water. The search for simple catalysts that mimic the selectivity of biochemical methods yet offer more general substrate acceptance has been the subject of intense research. Several

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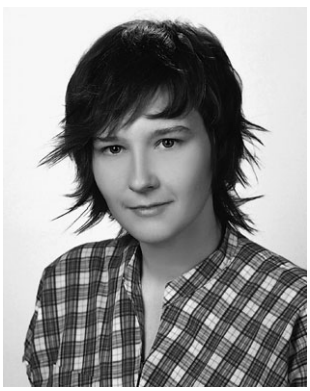
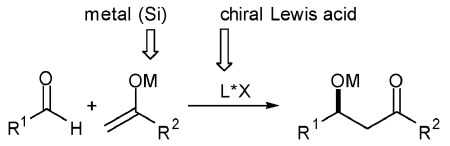


Joanna Paradowska was born in Warsaw, Poland. She studied chemistry at Rzeszow University of Technology graduating in 2007. Then she moved to the Polish Academy of Sciences and joined Jacek Mlynarski's group. She is currently working towards her PhD. Her primary research interests include water compatible catalysts for direct asymmetric aldol reactions and general aspects of asymmetric catalysis.



Scheme 1 The Mukaiyama reaction.

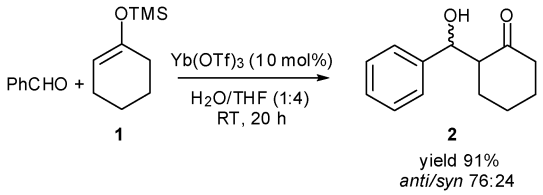
interesting attempts have been developed and for the purpose of this review, they will be grouped into two categories: (1) indirect catalytic aldol reactions which rely on prior transformation of the carbonyl pro-nucleophiles into their corresponding enolate; and (2) direct calatytic aldol reactions represented by biocatalysts (aldolases) and catalytic antibodies which perfectly meet the atom economy principle by using unmodified carbonyl donors. A successful catalytic version of direct asymmetric aldol reactions that are reliant upon transition metal complexes or purely organic molecules (organocatalyst) in water is currently a highly sought-after goal.

Although many researchers have developed synthetic mimics of active sites of enzymes to realize enzymatic activity, this review focus our attention on the medium of enzymatic reactions—water—which play a major role in the reaction.

2. Indirect catalytic aldol addition reactions

While virtually all the biochemical aldol reactions use unmodified donor and acceptor carbonyls and take place under catalytic control in nature, most chemical methods required the conversion of donor substrates into more reactive species using no less than stoichiometric amounts of metal containing reagents or extra steps.[2] The catalytic activation of the acceptor aldehyde towards the addition of a silyl enol ether, commonly referred to as the Mukaiyama reaction, has been a particularly successful means of performing asymmetric aldol reactions (Scheme 1).[5] These Lewis-acid catalyzed aldol-type reactions of silyl enol ethers with aldehydes and ketones have been found to be particularly useful due to their high regio- and stereoselectivities.[6] In the reaction cycle the chiral catalyst coordinates to the aldehyde creating an asymmetric environment, which is then attacked by an enolate derivative from the less hindered face to produce the aldol adduct in an asymmetric manner.[7]

Relatively fast decomposition of silyl enol ethers in protic solvents seemed to limit the application of the water as a reaction medium. Pioneering experiments by Lubineau demonstrated, however, that even uncatalyzed aldol addition of silyl enol ethers to aldehydes in water could proceed, though yields were poor.[8] The next problem is how to execute an asymmetric aldol reaction in aqueous media. This seems to be tricky in light of the application of Lewis acid-type catalysts of a highly water labile nature. Although various kinds of reactions have been developed in aqueous solvents recently, asymmetric catalysis promoted by chiral Lewis acids in such media is still at an initial stage mostly because of the water incompatibility of known catalysts.[9–11] Moreover, enantioselective versions of chiral Lewis acid mediated reactions in aqueous solvents are difficult to achieve because competitive ligand exchange between a chiral catalyst and water molecules easily occurs, and this affects enantioselectivity. Huge efforts toward



Scheme 2 Aqueous Mukaiyama reaction promoted by ytterbium(III) triflate.

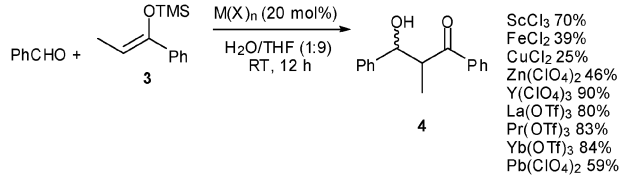
the development of Lewis acids tolerant of aqueous solvent in the past decade has allowed also for successful catalytic asymmetric Mukaiyama–aldol reactions in water.

2.1 Metal complexes as water tolerant Lewis acids for aldol reactions

The development of novel catalysts is an important aspect of modern stereoselective synthesis. In this respect, application of water tolerant catalysts has recently become an important area of research. Lewis-acid catalyzed reactions are of great interest because of their unique reactivities, selectivities, and usually mild reaction conditions used.[12] Although various kinds of Lewis acid have been developed and many have been applied in industry, these Lewis acids must be generally used under strictly anhydrous conditions. The presence of even small amount of water stops the reaction, because most Lewis acids immediately react with water rather than with the substrates. Traditional Lewis acids ($AlCl_3$, BF_3, $TiCl_4$, $SnCl_4$ *etc.*) are of a highly water-labile nature. This, in fact, is the result of their mode of action which relies on coordination with one or more Lewis-basic sites of the reactant, usually a nitrogen or oxygen atom(s). Water, being a Lewis base as well, can easily coordinate to Lewis acids especially when present in large excess as a solvent. Although it was long thought impossible, the development of Lewis acid catalyzed reactions in water is being intensively investigated and developed. Extensive studies by Kobayashi revealed that a wide range of lanthanide triflates[13] and some other metal salts[14] can be used with great success to promote selected organic reactions in water.

The synthetic application of water compatible Lewis acids was initially investigated for the stereoselective Mukaiyama aldol reaction of benzaldehyde with cyclohexanone-derived silyl enol ether (**1**). The reaction was promoted by $Yb(OTf)_3$ in water–THF (1 : 4) solution to give the corresponding aldol adduct in high yield (Scheme 2).[15]

Interestingly, when this reaction was carried out in dry THF, the yield of the aldol adduct was very low. This catalyst is not only compatible with water, but it is also activated by water. Judging from these findings, the mechanism of Lewis acid catalysis in water can be assumed to be as follows: When



Scheme 3 Effect of metal salts in the Mukaiyama aldol reaction in aqueous solvent.

metal compounds are added to water, the metals dissociate and hydration occurs immediately. If an aldehyde exists in the system, there is a chance for it to coordinate to the metal cations instead of the water molecules and the aldehyde is then activated. According to this mechanism, it was expected that many Lewis acid catalyzed reactions should be successful in water solution. Indeed, metal salts other than those derived from rare earth elements were also found to be water-compatible Lewis acids.[11]

To select other Lewis acids that can be used in aqueous solvents and to find general criteria for water compatible Lewis acids, Group 1–15 metal salts (chlorides, perchlorates and triflates) were screened in the aldol reaction of benzaldehyde with silyl enol ether **3** in water–THF (1 : 9) (Scheme 3). This screening revealed that not only Sc^{III}, Y^{III}, and Ln^{III} but also Fe^{II}, Cu^{II}, Zn^{II}, Cd^{II}, and Pb^{II} worked as catalyst in this medium to afford the desired aldol adduct in good to high yields.[16]

The reaction was suitable for testing the catalytic ability of the metal salts as Lewis acid catalysts in aqueous media, because the silyl enol ether is water sensitive and if the Lewis acid hydrolyzes in water, the enol ether decomposes rapidly and the desired reaction proceeds no further. When the salts of B^{III}, Si^{III}, P^{III}, P^{IV}, Ti^{IV}, V^{III}, Ge^{IV}, Zr^{IV}, Nb^{V}, Mo^{V}, Sn^{IV}, Sb^{V}, Hf^{IV}, Ta^{V}, W^{VI}, Re^{V} and Tl^{III} were used, decomposition of the silyl enol ether occurred rapidly and no aldol adduct was obtained. On the other hand, no product or only a trace amount of the product was detected when metal salts of Li^{I}, Na^{I}, Mg^{II}, Al^{III}, K^{I}, Ca^{II}, Cr^{III}, Mn^{II}, Co^{II}, Ni^{II}, Ga^{III}, Ru^{III}, Rh^{III}, Pd^{II}, Ag^{I}, Ba^{II}, Os^{III}, Ir^{III}, Pt^{II}, Au^{I}, Hg^{II}, and Bi^{III} were used. Some of the salts are stable in water, but have low catalytic activity. From these results, the authors noticed a correlation between the catalytic activity of the metal cations and two kinds of constant for the metal cations: hydrolysis constant (K_h) and exchange rate constant for substitution of inner-sphere water ligands (water exchange rate constants, WERC). First, the appropriate metal salt should have an intermediate hydrolysis constant. When the pK_h value is too low, cations are easily hydrolyzed and oxonium ions are generated, but when the pK_h value is too high, the Lewis acidity is generally too weak for efficient catalysis. In the Mukaiyama aldol reaction between substrates depicted in Scheme 3, the Lewis acids that were defined as active had pK_h values in the range 4.30–18.08.[16] Large WERC values are necessary to have sufficiently fast exchange between the water molecules coordinated to the metal and the aldehyde substrate, and so to act as an efficient catalyst. For the mentioned reaction catalysts, WERC values were greater than $3.2 \times 10^6\ M^{-1}\ s^{-1}$.

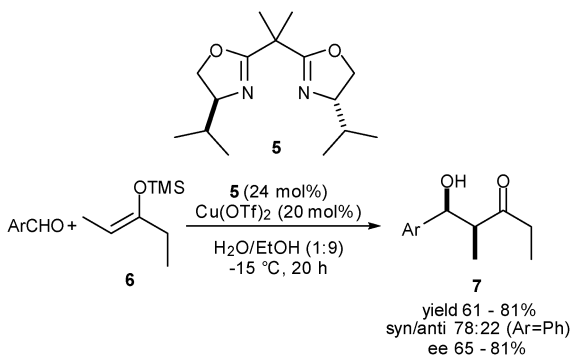
The development of Lewis acids tolerant of aqueous solvent has allowed for successful catalytic, stereoselective aldol-type reactions in water. The remaining important question was how to execute this reaction under asymmetric control. Two main difficulties need to be addressed for such reactions to work efficiently. Firstly, the vast majority of chiral catalysts applied in modern synthesis possess low water solubility, secondly, chiral ligands and coordinated metal complexes tend to be unstable in water. Thus, the most important feature in the design of chiral ligands for reactions in aqueous media is the binding property to a central metal cation. A ligand with strong coordinating ability often leads to reduction of the Lewis acidity of the metal cations and, as a result, to a low yield of the desired products. On the other hand, weaker binding ability of the ligand results in generating free metal cations coordinated immediately by solvent molecules instead of the ligand. This leads to a decrease in the enantioselectivity of the products by competition between the chiral Lewis acid and achiral free Lewis acid-catalyzed pathways.

Along with the latest development in Lewis acid-catalyzed Mukaiyama aldol reactions in aqueous media, some asymmetric attempts have been discovered very recently. Major developments associated with these methods are disclosed in the following section.

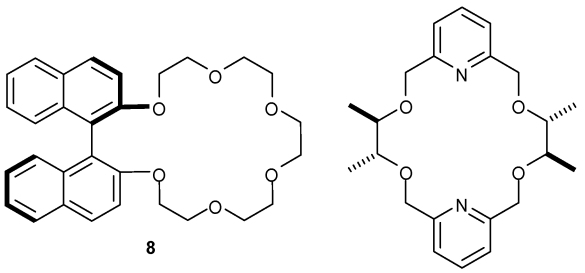
2.2 Examples of Mukaiyama-type aldol reactions in aqueous media

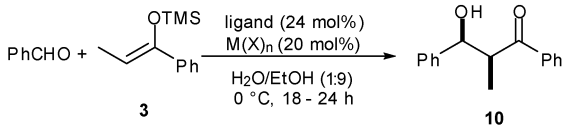
Chiral Lewis acid-mediated asymmetric aldol reactions of aldehydes with silicon enolates (asymmetric Mukaiyama aldol reaction) have been elaborated into the most convenient asymmetric aldol methodology starting from achiral substrates to create asymmetric centers at the β-position or the α- and β-positions of the aldol adducts. Enantioselective Mukaiyama aldol reactions in aqueous media, although still not fully recognized, constitute an important advance in the area. The discovery of water-compatible Lewis acids has greatly expanded its application to asymmetric aqueous Mukaiyama reactions, but the asymmetric version of the reaction is still difficult to achieve. Thus, the most important feature in designing catalysts for Mukaiyama reactions in aqueous media is to find appropriate chiral ligands with good binding properties to the central cation. An attractive solution to address this issue is based upon the well-known concept of multicoordination.

The first catalytic asymmetric reactions in aqueous media were performed with $Cu(OTf)_2$ and a chiral *box*-type ligand.[17] Combination of the copper salt and isopropyl-bis(oxazoline) ligand (**5**) was effective for aldol reactions of silyl enol ether **6** with aldehydes in aqueous ethanol (Scheme 4). Surprisingly, simple aromatic aldehydes (benzaldehyde) gave the aldol products with good enantioselectivity. The same combination of Cu–*box* in dry organic solvents was reported to be effective only for bidentate type aldehydes.[18] These results indicate that



Scheme 4 Mukaiyama aldol reactions catalyzed by chiral copper catalysts.

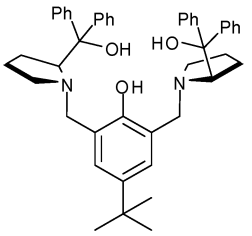




3 10

$M(X)_n$	ligand	de %	ee %
AgOTf	**8**	50	5
$Pb(OTf)_2$	**8**	80	55
$Yb(OTf)_3$	**9**	2	0
$Y(OTf)_3$	**9**	10	7
$Eu(OTf)_3$	**9**	78	51
$Sm(OTf)_3$	**9**	78	55
$Pr(OTf)_3$	**9**	80	79
$Ce(OTf)_3$	**9**	86	82
$La(OTf)_3$	**9**	78	79

Scheme 5 Mukaiyama aldol reactions catalyzed by crown ether-type chiral Lewis acids.



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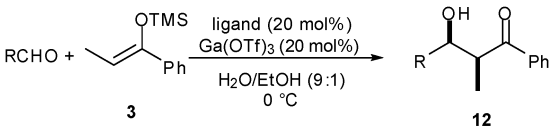


3 12

aldehyde (R)	yield %	de %	ee %
Ph	85	70	85
4-Me-Ph	89	80	88
4-MeO-Ph	80	76	84
4-Cl-Ph	77	64	78
PhCH=CH	90	80	86
1-naphthyl	87	60	82
$4\text{-}NO_2\text{-}Ph$	82	54	62
$CH_3(CH_2)_4$	78	74	30

Scheme 6 Mukaiyama aldol reaction catalyzed by gallium-based chiral Lewis acids.

water molecules not only accelerate the reaction but also play an essential role in good enantioselectivity.

More recently, both transition metals and rare earth metals upon coordination to newly designed chiral crown ether-type chiral ligands were demonstrated as effective Lewis acids for asymmetric Mukaiyama reaction in aqueous media. Nagayama and Kobayashi found that lead(II) triflate efficiently catalyzed the aqua aldol reaction of benzalehyde and **3** upon complexation to the chiral 18-crown-6 type ligand **8** (Scheme 5).[19] In this case, a good fit in size between the metal cation and the crown ligand is an important factor for good stereoselectivity.

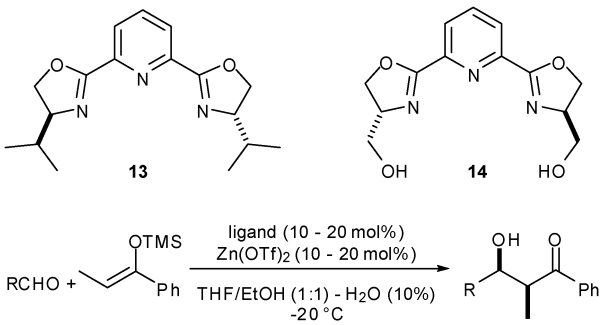
Such a tendency is even more visible for the combination of rare earth triflates and bis(pyridine-18-crown-6) ligand **9**, where the ionic diameter of the metal cation greatly influences both diastereo- and enantioselectivity (Scheme 5).[20] For the larger cations such as La, Ce, Pr, and Nd, enantioselectivities were high, while the smaller cations such as Sc and Yb showed no enantioselection.

An interesting example of ligand stabilization of a Lewis acid was recently reported for a gallium-catalyzed aldol reaction.[21] It has been noted that $Ga(OTf)_3$ is known to decompose in the presence of water, which results in the rapid acid-promoted decomposition of silicon enolates. However, in the presence of a chiral Ga complex prepared from $Ga(OTf)_3$ and chiral Trost-type semi-crown ligand **11**, silicon enolates reacted with aldehydes in water–ethanol to afford the desired aldol adducts **12** in moderate to high yields and diastereoselectivities (Scheme 6). This result indicates that multidentate chiral ligand **11** stabilized the gallium salt in the presence of water to prevent decomposition of $Ga(OTf)_3$. Moreover, this gallium-promoted Mukaiyama reaction is tolerant of higher water–organic solvent ratios when compared to previously described systems.

In general, combinations of silicon enolates derived from aromatic ketones and aromatic aldehydes gave high diastereo- and enantioselectivities, while use of either silicon enolates derived from aliphatic ketones or aliphatic aldehydes resulted in lower yields and selectivities.

This tendency is general for all catalytic system described above. The elaborate methodologies failed when applied to aliphatic aldehydes, for which a remarkable drop in the reaction enantioselevtivity was commonly observed. To address these deficiencies and develop new and simple methodologies, Mlynarski and co-workers reported chiral zinc,[22] and iron[23] catalysts with *pybox*-type ligands for asymmetric aqueous Mukaiyama reactions. Both isopropyl- (**13**) and hydroxymethyl-*pybox* (**14**) turned out to be promising sources of chirality. Under these elaborate conditions the reaction of silicon enolates with aldehydes proceeds with good to high yields and remarkably high *syn*-diastereostereoselectivities. Zinc-based catalysts allows an increase in water content in the reaction mixture up to 50%, and elaborate catalytic systems can be successfully applied for aliphatic aldehydes without significant loss of diastereo- and enantioselectivity of the aldol coupling process (Scheme 7).[22]

Application of iron-based chiral Lewis acids to asymmetric synthesis seems to be particularly exciting as iron is one of the most abundant metals on Earth and consequently one of the cheapest and most environmentally acceptable. Interest in well-defined iron complexes as catalyst for bond-forming reactions is an area of ongoing development, but enantioselective transformations promoted by iron complexes constitute precious and rare examples.[24] Previously chiral iron-complexes have never been demonstrated as catalysts for asymmetric Mukaiyama reactions, not to mention in aqueous



aldehyde (R)	yield %	de %	ee %
Ph	84	92	75
4-Me-Ph	62	88	74
4-MeO-Ph	77	84	70
2-MeO-Ph	85	100	72
4-Cl-Ph	85	90	72
2-Cl-Ph	83	96	70
PhCH=CH	79	82	72
$CH_3(CH_2)_2$	69	88	73
$CH_3(CH_2)_4$	63	88	70

Scheme 7 Mukaiyama aldol reaction catalyzed by zinc-based chiral Lewis acids.

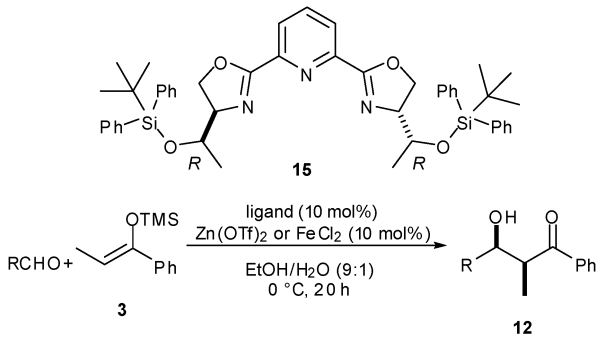
media, where the said catalytic system must meet more stringent requirements.

Application of iron complexes with convenient chiral ligands **13** and **14** was possible yet problematic because of some instability of the iron complexes in aqueous media.[23] Following up on this development the authors used a hindered hydroxyethyl-*pybox* derivative (he-*pybox*) **15** which provides rapid access into *syn*-aldols **12**.[25] This new hindered, lipophilic *pybox* ligand was designed with the aim of increasing the steric bulk and reducing the unwanted oxidation of Fe^{II} to Fe^{III}. The use of only 10 mol% of this designed chiral catalyst allowed better reactivity and enantioselectivity than with commercial ligands. This water-stable iron-based chiral Lewis acid promoted condensation of aromatic silyl enol ethers with a range of aldehydes with good yields, excellent *syn*-distareoselectivity and up to 92% ee (Scheme 8).

The combination of the same he-derived *pybox* ligand with Zn^{II} salt has been also demonstrated as a remarkably efficient and water-compatible chiral Lewis acid (Scheme 8).[25] Aqueous ethanol proved to be the optimal solvent for both catalysts and water plays an essential role in attaining good yield and enantioselectivity in the reactions.

The same geometry of the resulting complex was postulated as it was observed for other metal–*pybox* ligands. The zinc ion is thought to coordinate to three nitrogen atoms (in the planar geometry) resulting in the octahedral structure of the whole complex where octahedron positions are held by water molecules. Due to the bulky lipophilic substituents, the attack towards the coordinated carbonyl group is more effectively shielded from the one face.[22,25]

Formaldehyde, being one of the most important C1 electrophiles in organic synthesis, was beyond the reach of known water-compatible catalysts for a long time. Whereas hydroxymethylation of the enolate component with formaldehyde provides an efficient method to introduce the CH_2OH synthon at the α-position to carbonyl groups, no one of the known



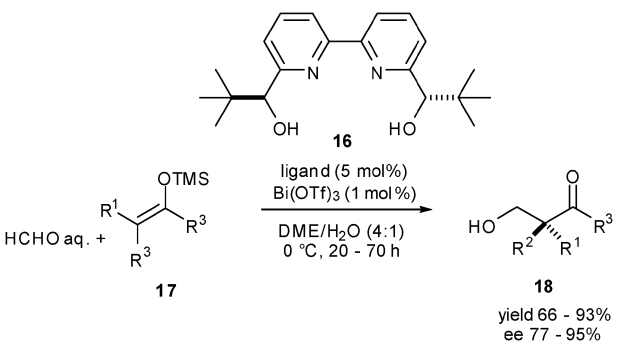
aldehyde (R)	yield %	de %	ee %
$FeCl_2$			
Ph	84	92	84
4-Me-Ph	95	90	84
4-MeO-Ph	94	92	92
2-MeO-Ph	83	92	80
4-Cl-Ph	88	82	78
2-Cl-Ph	81	74	79
PhCH=CH	98	60	64
$Zn(OTf)_2$			
Ph	92	86	90
4-Me-Ph	92	84	90
4-MeO-Ph	90	86	95
2-MeO-Ph	85	100	80
PhCH=CH	98	80	87

Scheme 8 Examples of Mukaiyama aldol reactions catalyzed by iron- and zinc-based chiral Lewis acids.

chiral Lewis acids was selective enough for such Mukaiyama-type transformations.

In 2005, highly enantioselective, catalytic hydroxymethylation reactions of silicon enolates with an aqueous formaldehyde solution were developed by using a novel bismuth complex prepared from $Bi(OTf)_3$ and chiral bypiridine **16**.[26] The reaction of various silyl enol ethers **17** with formaldehyde proceeded smoothly in the presence of only 1 mol% of the bismuth catalyst to afford the hydroxymethylated adducts **18** in high yields and with high enantioselectivities (Scheme 9). $Bi(OTf)_3$ is unstable in the presence of water but is stabilized by the basic ligand **16**.

This interesting example along with the catalyst prepared from a gallium salt (Scheme 6) introduce a new trend in asymmetric catalysis in water.[11] This concept is based on the finding that some basic ligands stabilize Lewis acids in water. The use of chiral basic ligands leading to new types of water-



Scheme 9 Mukaiyama aldol reactions catalyzed by a chiral bismuth catalyst.

compatible chiral Lewis acids may enable a wide range of asymmetric catalysis in water.

Although most organic materials have limited solubility in water, the presented examples show that water when combined with organic solvents can be an acceptable reaction medium for asymmetric aldol reactions. From the viewpoint of today's environmental consciousness, however, it is desirable to avoid the use of harmful organic solvents. This problem could be overcome by using surfactants, which solubilise organic materials or form an emulsion with them in water. Such methodology has occasionally been used for aldol reactions,[10] although never in asymmetric versions.

3. Direct catalytic aldol addition reactions

Applications of catalytic amounts of chiral promoter for control of the aldol reactions is undoubtedly a big achievement of modern organic chemistry. There has been some success in the use of asymmetric catalysts, although they normally rely on a Mukaiyama-type process, involving enol silyl ether. This reaction required the conversion of the donor substrate into more reactive species such as enol silyl ether using no less than stoichiometric amounts of silicon reagent and base. From atom economic perspectives, such stoichiometric amounts of reagents should be excluded from the procedures. An exciting challenge in enhancement of the efficiency of the aldol reaction is to find a compound that will catalyze *direct aldol addition* without pre-formation of the nucleophile and to do so asymmetrically.[27] The clue for development of purely chemical methods of the direct catalytic aldol reaction is to find small molecules capable of simultaneously activating the donor and the acceptor carbonyls in water.

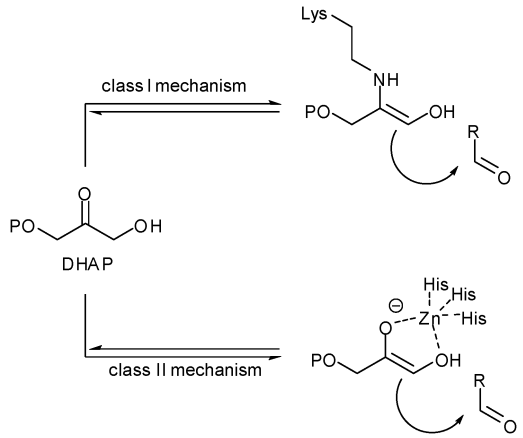
In nature, type I and II aldolases catalyze this reaction in water with excellent enantiocontrol through an enamine mechanism and by using a metal cofactor, respectively. Understanding of the mode of action of natural aldolases is essential for achieving direct catalytic asymmetric aldol reactions with artificial small molecular catalysts and thus it will be discussed briefly in the next section followed by examples of applications of metal complexes and purely organic molecules (organocatalysts).

3.1 Biochemical catalysts: aldolases

Enzymes are increasingly recognized as useful catalysts for organic synthesis. There are two types of enzymatic catalysts that effect aldol addition: the aldolases, a group of naturally occurring enzymes that catalyze aldol condensations *in vivo*, and catalytic antibodies (being a new protein-type catalyst that have been developed in recent years to mimic the aldolases).[28]

Stereoselective formation of the carbon–carbon bond in nature is assisted by enzymes named lyases, which catalyze the usually reversible addition of carbon nucleophiles to carbonyl groups. Aldolases belong to the group of lyases and have evolved to catalyze the anabolism and catabolism of highly oxygenated metabolites. They are essential for many biosynthetic pathways of carbohydrates, keto acids and some amino acids.[29]

Aldolases can be classified according to their mechanism and the whole family is divided into two classes. Class I



Scheme 10 Active sites of the aldolase-catalyzed aldol reactions. Mechanism of class I and II aldolases.

aldolases activate the donor by forming a Schiff base as an intermediate in the active site. This activated donor then adds stereoselectively to the acceptor aldehyde (Scheme 10). In the class II aldolases, a metal co-factor is bound in the enzyme active site *via* coordination to three histidine residues. These coordinated metal cations (mostly Zn^{II} but also Co^{II} or Fe^{II}) act as a Lewis acid to activate the carbonyl donor substrate as is depicted in Scheme 10. The presented mechanisms utilize dihydroxyacetone phosphate (DHAP) as the donor substrate.[3]

Enzymes bind their respective donor substrates with high specificity and generally will not accept any other donors. This is a main drawback for their broad synthetic utility; enzyme application is usually limited by their lack of substrate generality and lack of large-scale compatibility. Despite the fact that the inherent specificity of aldolases leads to a limited number of substrates and stereochemical outcomes being available, some interesting examples of their applications are recorded in the literature.[3] Nevertheless, the use of aldolases and catalytic antibodies in every-day chemical practice is highly limited and the development of artificial molecules mimicking the aldolase mode of action in their natural aqueous environment is today one of the leading hot topics in asymmetric synthesis.

It is highly desirable to develop chemical systems that can mimic the action of enzymes and perform organic reactions in water with perfect efficiency and stereoselectivity. Two strategies have been employed to mimic the aldolase mode of action in aqueous direct asymmetric aldol reactions: (1) organocatalysts, including modified amino acids and small peptides, acting as class I aldolases, and (2) metal-catalyzed aldol reactions based generally on zinc complexes.

3.2 Water compatible organocatalysts

Asymmetric aldol additions of unmodified ketones or aldehydes promoted by purely organic molecules is an important modern achievement in the area. The seminal work by List *et al.* on the intermolecular application of the proline-catalyzed direct asymmetric aldol reaction opened the way for exciting new research.[30] Now, the concept of application of small organic molecules (organocatalysts) as catalysts has received great attention.[31]

Unlike enzymatic reactions in nature, amino acid-type catalyzed reactions mimicking the class I aldolase mode of action have typically been carried out in organic solvents. Proline was demonstrated to catalyze direct aldol reactions with high enantioselectivity in polar organic solvents such as DMSO and DMF, but when the reaction was performed in the presence of water or a buffer solution, racemic products were obtained.[32] The first artificial water-compatible organocatalysts with high enantioselectivities were catalytic antibodies.[33] For this biomacromolecular catalyst an enamine-based active site similar to those found in aldolases is postulated. This mechanistic issue is one of the more important aspects of developing small-molecule-organocatalyzed asymmetric aldol reactions in water.

From a chemical point of view, water is often found to distort transition states due to its ability to form hydrogen bonds, resulting in lowered enantioselectivity or demand for higher catalyst loading. Moreover, to promote enantioselectivity by an enamine-based mechanism in water, general base catalysis must be minimized.[34] It has been demonstrated by Janda *et al*. that the enamine, which had been considered to be easily hydrolyzed in the presence of water, can be generated and react with an electrophile to afford an aldol under buffered conditions albeit in moderate ee.[34,35] A more detailed clarification of the role of water in proline-mediated aldol reactions was reported recently.[36]

All early studies with small organic molecules in aqueous media had limited success[37] until recently when the research groups of Barbas[38] and Hayashi[39] independently reported efficient small molecule amine-derived chiral catalysts which act with high enantiocontrol in the presence of a larger excess of water without assistance of organic solvents. In both cases highly hydrophobic proline-derivatives have been used as catalysts for direct aldol reactions. Asymmetric aldol reaction of cyclohexanone and aromatic aldehydes was selected as a model (Scheme 11). Both siloxyproline **19** and diamine **20** demonstrated excellent reactivity, diastereoselectivity, and enantioselectivity in water. Application of catalyst **20** was, however, shown to be limited mainly to cyclic ketones while aldol addition to acetone, 2-butanone and 2-octanone was less promising.[38]

Siloxyproline **19** showed better substrate flexibility, but application of this catalysts for water-soluble ketones was still restricted. Though the aldol reactions of acetone and hydroxyacetone proceeded in the presence of water, the enantioselectivities were only moderate.[39]

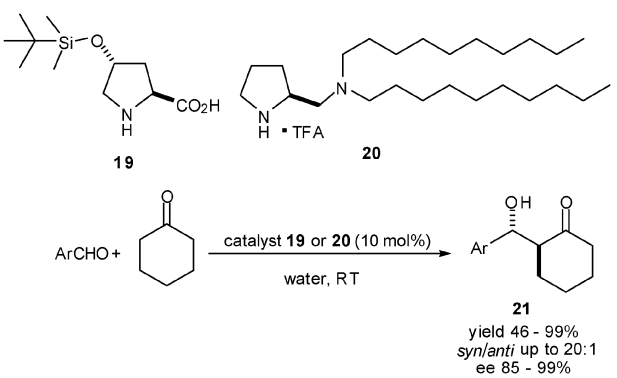
Following these papers, water and water-based reaction media were controversially discussed not only because of the difficulties in distinguishing whether the reactions are performed "in water" or "in the presence of water",[34] but whether or not water is really a green solvent.[40] The reactions catalyzed by siloxyproline **19** proceed in the presence of only three equivalents of water without any organic solvent and as a consequence there is less water than either of the reactants. In this respect cyclohexanone can be regarded as a solvent. Thus the term "in the presence of water" should be used for a reaction that proceeds in a concentrated organic phase with water being present as the second phase. In contrast the term "in water" is suggested to be used for reactions in which the participating substrates and catalyst are homogeneously dissolved in water.[34,39]

Nevertheless, even in the presence of a large amount of water, an organic phase is formed, the enamine is generated and adds to the aldehyde in this phase asymmetrically. This was observed for non-modified proline which catalyzes the enantioselective aldol reactions even in the presence of large amounts of water, though enantioselectivities were still only moderate.[41] Just recently, Hayashi's group found that proline amide acts efficiently "in water" for the enantioselective self-aldol reaction of propanal (Scheme 12).[42] The good level of enantioselectivity (up to 78% ee) was achieved when Pro-NH_2 was used as a catalyst. It was postulated that an amide proton of the catalyst likely activates the carbonyl group in the same way as does the carboxylic acid proton of proline. The last example is also interesting as it shows proline-catalyzed aldolization of enolizable aldehydes, which is still a challenging goal.

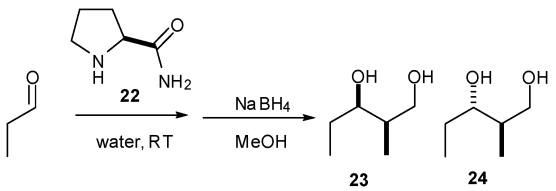
An important development in the field was presented recently, when Sing and co-workers reported two proline-derived organocatalysts capable of mediating the direct asymmetric aldol reaction of ketones with aldehyde acceptors in high enantioselectivities and with low catalyst loading (0.5 mol%) in aqueous medium.[43] Switching from water to brine resulted in better yields and ee's.

Both amide-type derivatives **25** and **26** (Scheme 13) were quite general catalysts with regard to the aldehyde donors. Not only aromatic but also some α-substituted aliphatic aldehydes have been used as substrates. In all cases good yields alongside excellent diastereo- and enantioselectivities (>99% ee) were reported.

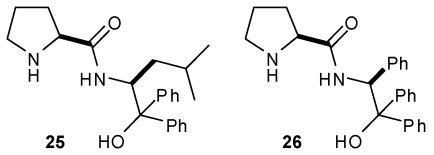
The catalytic cycle of the proline-amide-catalyzed aldol addition reaction proceeds *via* an enamine intermediate and



Scheme 11 Aldehyde–ketone aldol reactions promoted by siloxyproline **19** or aminoproline **20**.



Scheme 12 Amino amide promoted self-aldol reaction of propanal in water.



Scheme 13 Two organocatalysts designed for efficient direct aldol reactions in brine.

the stereochemical outcome of the reaction can be explained by a transition state (Fig. 1) where aldehyde is activated by hydrogen bonding with the NH and OH of the catalyst.[43] The model requires formation of the enamine, so again, the general base catalysis must be minimized to promote enantioselectivity by an enamine mechanism in water. The authors reason that the reaction takes place under biphasic conditions, with a hydrophobic assembly of catalyst and substrate at the center of reactivity. Aggregation of organic molecules excludes water from the organic phase (brine salting-out effect) and drives the equilibrium toward enamine formation.

It has been known for some time that some hydrophobic interactions can have a significant influence on organic reactions.[44] Such an effect was used for the rational design of the Lewis acid-type catalysts[25] and play an important role in the presented organocatalytic processes. In nature also, aldolase enzymes catalyze aldol reactions with water in hydrophobic pockets to diminish contact between water molecules and the reaction transition state. A rationalized concept of a hydrophobic surrounding in an aqueous aldol reaction was presented by Hayashi *et al*. who developed a catalytic asymmetric cross aldol reaction of two different aldehydes in the presence of water, catalyzed by a combined proline–surfactant organocatalyst.[45] An organic phase–water emulsion was proposed as an ideal reaction environment in which organic molecules can be assembled through hydrophobic interactions.

Recently an asymmetric catalytic system in water mediated by sulfated β-cyclodextrin which can bind an organocatalyst (*tert*-butylphenoxyproline) and an associated hydrophobic reactant was presented.[46] The system demonstrated excellent enantioselectivity for stoichiometric direct aldol reaction of only cyclohexanone and aromatic aldehydes.

3.3 Metal complexes as catalysts for direct aldol addition in water

In contrast to the growing development in direct asymmetric aldol reactions promoted by purely organic molecules, application of methods utilizing Lewis acids that rely on the catalysis of metal complexes bearing chiral ligands is still troublesome in aqueous solvents. Mimicking the mode of action of class II aldolases, the chiral homo- and heterometallic complexes developed recently have reported to be water-sensitive and thus the reactions have been carried out under anhydrous conditions in organic solvents.[2,27]

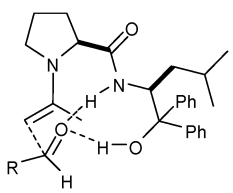


Fig. 1 Favoured transition state model proposed by Sing and coworkers.[43]

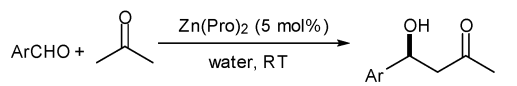
In this area, continuous exploration of metal complexes seems to be rational as some aldolases facilitate enolate formation in water using a metal cofactor in the active site (Scheme 10). Among several metals that can be considered as suitable for metal-catalysis in water, zinc looked the most appealing as it is most abundant in nature for this purpose. Zinc can accommodate several coordination geometries and act as an active Lewis acid even when surrounded by water molecules. In the development strategy for designing zinc-containing catalysts for the direct asymmetric aldol reaction in aqueous media, the use of *N*-donor ligands seemed very attractive. Their ability to tightly bind zinc ions suggested that they might serve as good templates to construct asymmetric catalysts by analogy to type II aldolases in which the zinc ion is tightly coordinated by three histidine residues in the reaction active site (Scheme 10).

The first application of a zinc complex generated *in situ* with amino acid ester ligands was presented in 1985.[47] Readily available catalysts were unselective, leading to racemic products.

An interesting example of an asymmetric direct aldol reaction of acetone in water was presented by Darbre and coworkers.[48] The zinc–proline complex, prepared from proline and zinc acetate, was shown to catalyze the aldol reaction of acetone and a wide range of aromatic aldehydes in aqueous media, accepting even deactivated aldehydes (4-methoxybenzaldehyde) which was beyond the reach of organocatalysts for a long time. Enantiomeric excess of up to 56% could be obtained with only 5 mol% of the $Zn(Pro)_2$ at room temperature (Scheme 14). This homogeneous reaction proceeds in excess acetone–water mixture (1 : 2) making acetone not only the reactant but also the reaction solvent.

The reaction is enantioselective only for activated aromatic aldehydes, mainly *para*-nitrobenzaldehyde (Scheme 14). The aldol reaction is regio- and stereoselective with hydroxyl- and dihydroxyacetone, leading unfortunately to racemic hydroxyaldols.

The new catalyst incorporates a metal that can act as a Lewis acid in water. The authors postulate a mechanism involving a zinc-assisted enamine formation, where zinc complexation only stabilizes the enamine intermediate (Fig. 2). In



27

aldehyde (Ar)	yield %	time, h	ee %
4-NO_2-Ph	95	18	56
2-NO_2-Ph	94	18	5
4-MeO-Ph	48	36	38
2-MeO-Ph	75	36	32
4-Cl-Ph	95	36	5
4-CN-Ph	91	22	27
Ph	32	48	5
1-naphthyl	75	45	31

Scheme 14 Direct aqueous aldol reactions of aromatic aldehydes and acetone catalyzed by a zinc complex.

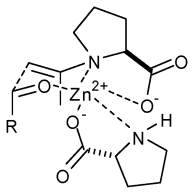


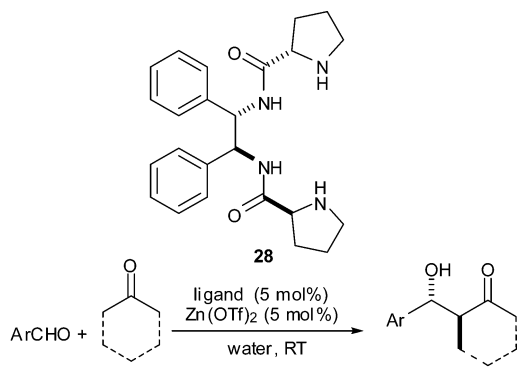
Fig. 2 Proposed intermediate for zinc-assisted enamine formation in water.

spite of some evidence, only further studies on this subject can clarify the role of the metal cation.[48,49]

The presented methodology has been further extended to the aldolisation of glycolaldehyde to give tetroses and the cross-aldolisation of glycolaldehyde and glyceraldehyde to give pentoses in water (10% ee).[50]

Recently Mlynarski and co-workers demonstrated a combination of zinc triflate and chiral C_2-symmetrical prolinamide ligand **28** as an efficient catalyst for highly enantioselective direct aldol reactions essentially assisted by water.[51] The presence of only 0.5–5 mol% of the *in situ* generated Zn^{II}-complex afforded an asymmetric intermolecular aldol reaction between unmodified ketones and aldehydes to give *anti*-products with excellent enantioselectivities ranging from 86–98% ee (Scheme 15).

High selectivity of the catalyst was maintained for non-cyclic ketones (acetone) making the elaborate methodology especially promising. The essential role of water was observed when the reaction was carried out in pure cyclohexanone. In this case only a trace of product was isolated. The elaborate catalytic system is flexible enough to work in organic-solvent free conditions as well with co-solvents.



aldehyde (R)	yield %	de %	ee %
acetone			
4-NO_2-Ph	88	-	88
4-Cl-Ph	80	-	90
4-Br-Ph	83	-	88
Ph	77	-	90
4-MeO-Ph	21	-	86
cyclohexanone			
4-NO_2-Ph	98	90	94
4-Cl-Ph	56	96	94
4-Br-Ph	56	92	96
Ph	46	96	94
4-CN-Ph	94	92	93

Scheme 15 Direct asymmetric aldol reactions in the presence of water catalyzed by a zinc complex.

The same protonated ligand **28** (with trifluoroacetic acid) is found to catalyze aqua direct aldol reactions as an organocatalyst with excellent diastereo- and enantiocontrol and furnish the corresponding aldols in up to 99% ee.[51] Thus, the presented study reveals an interesting area of aqueous asymmetric aldol reaction between the application of metal complexes and organocatalysis. To date these are the best results reported for the direct aldol reaction catalyzed by small artificial metal complexes in aqueous media.

4. Future prospects and challenges

Aqueous chemistry which predominates in biological processes is now perceived as an inspiration for designing artificial catalysts mimicking asymmetric bio-processess. Moreover, the development of synthetic aqueous chemistry may also aid our understanding of the detailed mechanisms of the chemistry of life.

Considerable interest has developed recently in asymmetric catalysis in water. Catalytic asymmetric aldol addition reactions of prochiral substrates have been one of the most studied reactions under the above conditions recently. The synthesis of enantiopure molecules in aldol reactions using water as the reaction medium is now, at least, preliminarily recognized, although it long seemed to be mainly confined to the realm of enzymes.

While aldolases and catalytic antibodies can tolerate substrates with unprotected functional groups and promote the reaction in aqueous solution, application of the chemical aldol reaction was mostly limited to various organic solvents.

An opportunity to attempt Mukaiyama-type and direct aldol reactions in aqueous media did not appear until the elaboration of Lewis acids compatible with water. Since then, great progress toward efficient, selective and predictable catalysis has been made, however newly developed methodologies still suffer from narrow substrate scope.

A main challenge for future research on the direct asymmetric aldol reactions is development of organocatalysis as well as catalysis by metal complexes in regard to more demanding substrates. Extension of those methodologies for more difficult carbonyl donors and acceptors, especially hydroxyketones would make synthesis of complex polyhydroxyl architectures possible. Furthermore it may open the way to enantioselective synthesis of molecules such as carbohydrates under control of enzyme mimicking compounds in aqueous media.

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