In water, on water, and by water: mimicking nature's aldolases with organocatalysis and water

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We review recent developments and applications of aldolase-type organocatalytic direct transformations in aqueous media without addition of organic solvent.

1. Introduction

Aldolases are essential, ubiquitous enzymes involved in glycolysis, gluconeogenesis and the Calvin cycle. They catalyze both carbon–carbon bond formation and cleavage in a stereoselective fashion in an aqueous *in vivo milieu*. For synthetic chemists, aldolases have become useful tools in modern synthetic organic chemistry, in particular in carbohydrate synthesis; for instance, fructose 1,6-diphosphate aldolase (FDP aldolase) converts D-glyceraldehyde 3-phosphate and dihydroxyacetone phosphate into D-fructose-1,6-diphosphate reversibly *in vitro*.[1] Native aldolases are classified into two groups based on the mechanism of donor substrate activation. Class I aldolases activate substrates through an iminium ion formation step followed by enamine formation, whereas class II aldolases activate substrates by forming a zinc enolate. Development of a class I aldolase-mimicking antibody catalyst has provided another useful tool in organic chemistry.[2] Aldolase antibodies such as Ab 38C2 and its antipodal antibody siblings catalyze a wide variety of crossed and self-aldol reactions, including intramolecular aldol reactions *in vitro*. Aldolase antibodies also catalyzed iminium-based Michael and decarboxylation reactions.[3] The narrow substrate specificity of natural aldolases is vital for life, but not necessarily useful for organic synthesis. Interestingly, antibody aldolases catalyze reactions involving over 100 different substrate combinations with high rate enhancements.

Near the end of the 20th century, small metal-free organic molecules attracted attention as organocatalysts.[4] Organocatalysts that mimic aldolases were widely studied due to mechanistic insight and impetus gained through study of aldolase antibodies and the versatility, maneuverability, simplicity, and safety promised by organocatalysis. In general, organocatalytic reactions are carried out in a one-pot operation by stirring a carbonyl compound, an amine and an electrophile in conventional organic solvents, such as DMSO, DMF, or $CHCl_3$, which are toxic, flammable and volatile. Removal of water is not required for the formation of enamine intermediates that proceed to react directly with an electrophile. This water-tolerance is a desirable characteristic of an organocatalyst. However, unlike native aldolases or aldolase antibodies, in the presence of bulk water aldolase-type organocatalytic reactions generally result in very poor yield and stereoselectivity.[5]

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It is instructive to note that enzyme aldolases form a hydrophobic 'reaction flask' at their active site that diminishes contacts between bulk water and the reaction transition states; small organocatalysts cannot form this protected pocket and, therefore, it has been assumed and most typically observed that organocatalytic reactions with aqueous solvents result in poor yield and stereoselectivity. It is a common misconception to consider enzymatic reactions as actually taking place 'in water'. An enzyme-catalyzed reaction might more instructively be regarded as taking place in organic solvent wherein the enzyme itself is essentially a water-soluble reaction flask that presents a stereodefined array of organic side-chains that affect catalysis. As noted by the Sharpless group, the use of water as the only supporting medium for a reaction provides for ease of product isolation, high specific heat capacity, high specific inductive capacity, unique redox stability and a non-exhaustible resource, even if the rate acceleration is negligible.[6] This review highlights developments in bond-forming reactions catalyzed by aldolase-type organocatalysts in aqueous media without addition of organic solvents (Fig. 1).[7]

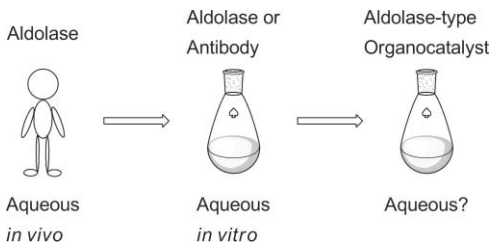
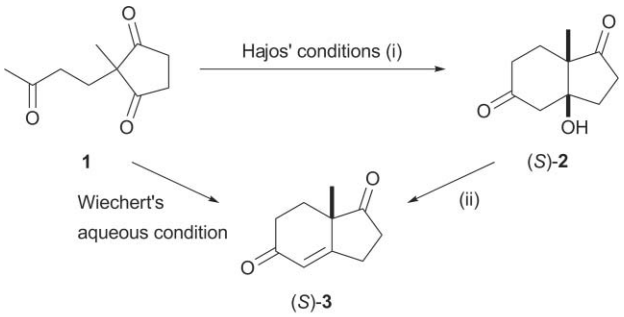


Fig. 1 From aldolases *in vivo* to organocatalysis in water.

2. Direct asymmetric aldol reactions in aqueous media

In the early 1970s, the Hajos group at Hoffmann-La Roche, Inc.[8] and the Wiechert group at Schering A.-G.[9] independently reported the intramolecular direct aldol reaction of triketone **1** catalyzed by L-proline. Hajos' anhydrous condition in DMF afforded the aldol product (*S*)-**2** in 100% yield, subsequent acid-promoted dehydration provided (*S*)-Hajos–Wiechert ketone **3** in 99% yield with 95% ee. In contrast, Wiechert's aqueous condition (in MeCN/1 M $HClO_4$ aq = 10 : 1, $H_2O \approx 15$ equiv.) directly produced the ketone **3** in 87% yield with 84% ee in



Hajos' conditions: (i) L-proline (3 mol%), DMF, 20 h, under Ar, y. 100%
(ii) 0.01 M *p*-TsOH in benzene, reflux, y. 99%, 95% ee

Wiechert's condition: L-proline (47 mol%), MeCN/1 M $HClO_4$aq = 10/1, reflux, 22 h, y. 87%, 84% ee

Scheme 1 Organocatalytic synthesis of (*S*)-Hajos–Wiechert ketone **3**.

one-pot operation (Scheme 1). A quarter-century later, the first organocatalytic intermolecular direct aldol reaction was reported by our group.[10] Under our conditions, a small amount of water (less than 4 vol%) did not affect the enantiomeric excess of aldol product, however 20 vol% water resulted in a substantial decrease in enantioselectivity.[10b] Other early studies reported water-tolerant aldolase-type organocatalysts, but it was not possible to achieve high yield and stereoselectivity in the aqueous direct aldol reaction without addition of any organic solvent.[5]

In 2006, the Hayashi group and our group independently reported two distinct strategies for aqueous organocatalytic direct cross-aldol reactions of various ketone and aldehyde donors with aldehyde acceptors. *trans*-L-Siloxyproline (Fig. 2, **4a**) was a key catalyst for high diastereo- and enantioselectivities in the aldol reaction of cyclohexanone (**19**, 5 equiv.) with *p*-nitrobenzaldehyde (**20**) in the presence of water (18 equiv.); the reaction proceeds in a two-phase system (Table 1, entry 1).[11] Without organic solvent or in an organic solvent such as DMSO there is lower diastereo- and enantioselectivity. This high efficiency is probably due to the solubility of the catalyst **4a** in organic solvent. Hydrophobic siloxyproline **4a** is not very soluble in water but is soluble in the organic phase formed by the aldehyde and ketone substrates. Although the role of water is not clear, water is essential for high stereoselectivity. Since these procedures use a small amount of water (3–18 equiv.), these reactions are generally called "direct aldol reactions in the presence of water".[12]

Table 1 The direct aldol reactions of cyclohexanone (**19**) with *p*-nitrobenzaldehyde (**20**) in aqueous media without addition of organic solvents

Entry	Catalyst (mol%)	Donor (equiv.)	H_2O (equiv.)	Yield (%)	De (%)[a]	Ee (%)[b]
1	**4a** (10)	5	18	86	90	>99
2	**5** (10)	2	111	99	78	94
3	**5** (10)	1	111	98	70	92
4	**5** (1)	2	111	91	62	91
5	**5** (0.5)	2	111	81	62	89
6	**6** (2.5)	1.2	111	97	86	93
7[c]	**7** (0.5)	4	55	NI[d]	74	91
8	**8** (2)[e]	1	22	100	92	>99
9	**9** (1)	2	55	99	>98	94
10	**10** (10)	10	111	92	67	90

[a] *Anti* product was obtained as a major isomer. [b] The ee is indicated for the *anti* product. [c] Brine was used as aqueous media. [d] Not indicated in detail. [e] Sulfated β-CD (10 mol%) was added.

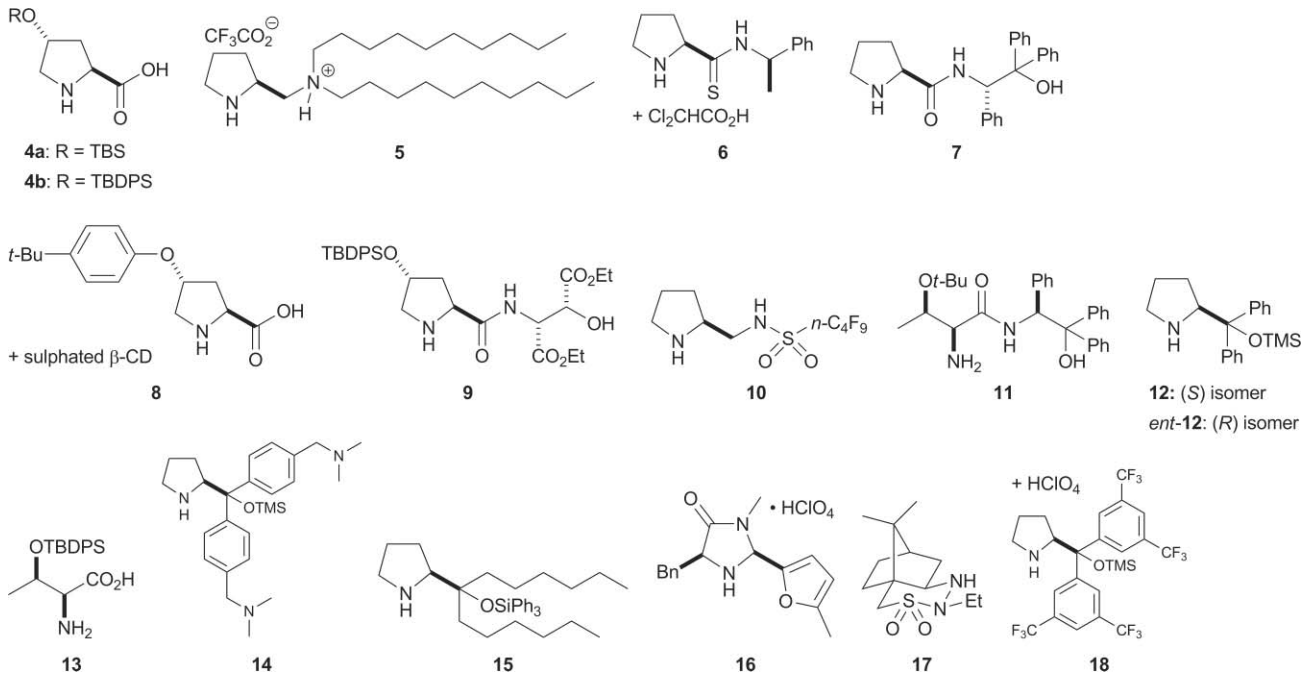
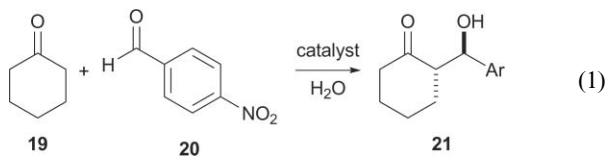
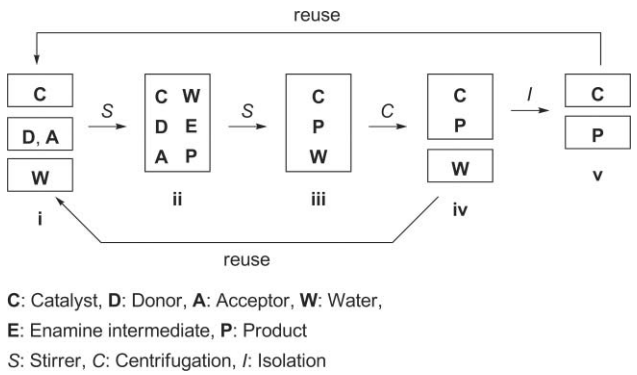


Fig. 2 Water-compatible aldolase-type organocatalysts.



(1)

Our designed small diamine catalyst (**5**, 10 mol%) smoothly catalyzes the direct cross-aldol reaction of cyclohexanone (**19**, 2 equiv.) with *p*-nitrobenzaldehyde (**20**) in bulk water (111 equiv.), giving the aldol product **21** in quantitative yield with 94% ee (Table 1, entry 2).[13] Other ketones and aldehydes were also efficient donors in this reaction. In addition, a stoichiometric amount of donor was enough to achieve the reaction, thereby increasing the economy of the reaction (entry 3). Catalyst loading could also be decreased to 1–0.5 mol% (entries 4 and 5),[14] although no reaction was observed at 1 mol% catalyst loading using DMSO only as solvent. Furthermore, crude aldol products are easily isolated by removal of water using centrifugal separation; no extraction and washing are needed. The recovered catalyst as well as water can be used again (Scheme 2).



Scheme 2 Easy phase separation and reuse of water and catalyst.

Interesting temperature-dependent changes were observed in this system (Fig. 3). When this direct aldol reaction was carried out in DMSO at 10 mol% catalyst loading, enantioselectivity sharply decreased to 52% ee as the temperature was raised to 50 °C. This observation, decreasing ee with increasing temperature, is quite general in asymmetric synthesis in organic solvents. On the other hand, with water as solvent, the enantioselectivity was only slightly decreased at elevated temperature and 10 mol% catalyst loading (94 ⇒ 90% ee). At 0.5 mol%, reactivity was improved and enantioselectivity was maintained (y. 52 ⇒ 86%, 89 ⇒ 72% ee).[14] These results suggested that hydrophobic interaction plays

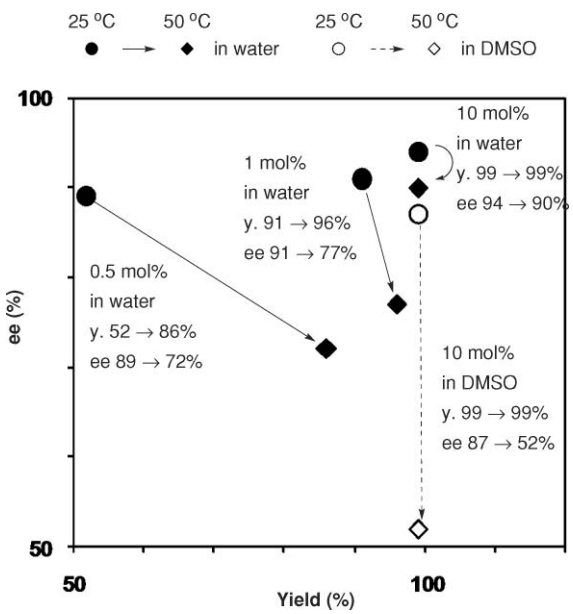


Fig. 3 Temperature-dependent properties in the direct aldol reactions.

an important role for reactivity as well as high enantioselectivity, since increased temperature (and entropy) leads to an increased hydrophobic effect.

Aldolase-type organocatalyst **5** forms an emulsion in the reaction solution of water and organic substrates. Although the origin of the rate acceleration and excellent enantioselectivity in an aqueous enamine-based aldol reaction is very complex subject, we propose that organocatalyst **5** with appropriate hydrophobic groups improves the chemical yield and stereoselectivity compared to reaction in organic solvent through the following mechanism (Fig. 4, i). A liquid organic donor assembles in water due to hydrophobic interactions and forms a metastable micelle with the catalyst **5**. Aggregation of the organic molecules excludes water from the organic phase and drives the equilibrium toward enamine formation. The enamine intermediate composed of the carbonyl donor and the catalyst **5** is more hydrophobic than that of the catalyst **5**, therefore the enamine intermediate moves into organic phase. It is believed that carbon–carbon bond formation between the enamine intermediate and the aldehyde acceptor occurs rapidly in the highly concentrated organic micellular phase through a transition state similar to that observed in organic solvents and then hydrolysis of the enamine intermediate proceeds.[13,15]

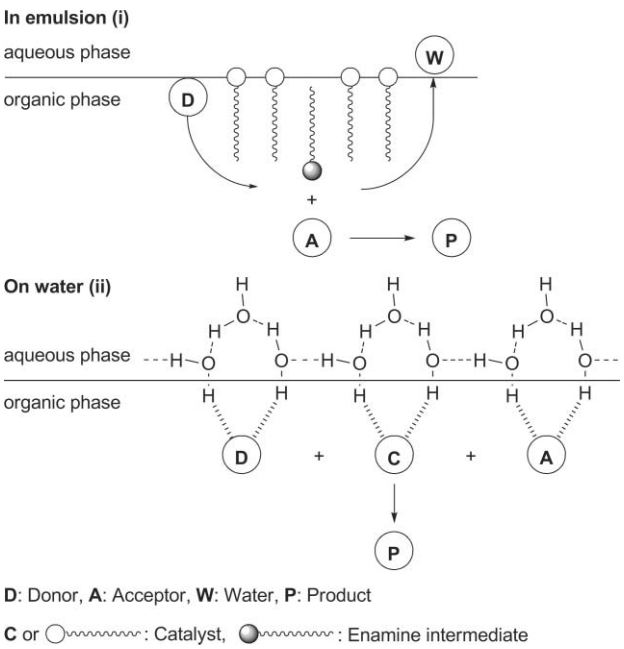


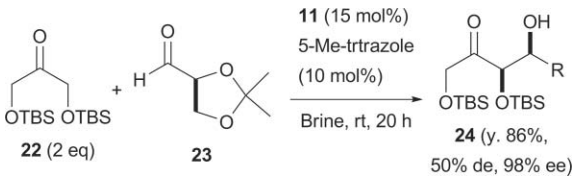
Fig. 4 Cartoons of in emulsion and/or on water catalysis.

Recently, an "On water mechanism" has been proposed.[16] This intriguing proposal suggests that a free OH group at an oil–water phase boundary protrudes into the organic phase. This dangling hydrogen can then play an important role in catalyzing reactions *via* the formation of hydrogen bonds to a donor, an acceptor and/or a catalyst (Fig. 4, ii).

A great number of studies on direct aldol reaction in aqueous media without addition of organic solvents have now been reported.[17] Here, we highlight several of these reports. The Gryko group described a highly efficient aqueous aldol reaction: treatment of 4-nitrobenzaldehyde (**20**) with as little as 1.2 equivalents of cyclohexanone (**19**) in the presence of the protonated thioamide catalyst **6** (2.5 mol%) affords the aldol product **21** in 97% yield with high diastereo- and enantioselectivity (Table 1, entry 6). Furthermore, from investigations of different salting-out and salting-in conditions, the group proved that the rate of acceleration and the stereochemical outcome of the reaction are affected by hydrophobic aggregation.[18] The Singh group demonstrated an efficient aldol reaction with very low catalyst loading (0.5 mol%). Excellent stereoselectivities were observed using the prolinamide catalyst **7** in brine (Table 1, entry 7). High reactivity and stereoselectivity are due to the salting-out effect as well as double activation of the aldehyde acceptor *via* hydrogen bonding with both NH and OH of the catalyst.[19]

Another excellent catalyst system was reported by the Armstrong group in 2007. Quantitative yields were obtained for stoichiometric direct aldol reactions by addition of sulfated β-CD (10 mol%), which binds *tert*-butylphenoxyproline (**8**, 2 mol%) and associated hydrophobic reactants (Table 1, entry 8). Simple filtration or phase separation affords the highly enantiomerically pure aldol product (**21**).[20] Recently, the highly reactive organocatalyst **9** was reported by Gong's group. The catalyst (**9**, 1 mol%) efficiently catalyzes the direct aldol reaction (entry 9).[21] The double hydrogen bonds are strengthened by two electron-withdrawing ester groups of the catalyst **9**; moreover, hydrophobicity is increased by the siloxy group. A report by the Wang group combines fluorous separations with catalysis in water.[22] Catalyst **10**, fluorous (*S*)-pyrrolidine sulfonamide, was shown to be a very effective catalyst in the direct aldol reaction of ketones with aromatic aldehydes providing the products in good yield with high diastereo- and enantioselectivity (entry 10). Fluorous extraction allowed catalyst recovery and reuse for seven cycles.

Finally, since the initial motivation of this field was aimed at replacing the well-known dihydroxyacetone aldolases with organocatalysts, it should be noted that each of the four key DHA aldolases can now be replaced with organocatalysts. One such practical organocatalytic strategy designed to mimic the L-rhamnulose, L-phosphate and D-fructose 1,6-diphosphate aldolases has utilized threonine-based catalysts such as **11**. Reaction of protected dihydroxyacetone **22** with a variety of aldehydes provided *syn*-aldol products **24** with good yields and ee's up to 98% in brine allowing for the direct synthesis of a range of carbohydrates and their derivatives (eqn (2)).[23]

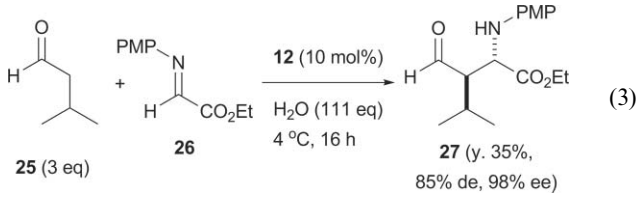


(2)

3. Direct Mannich reaction in aqueous media

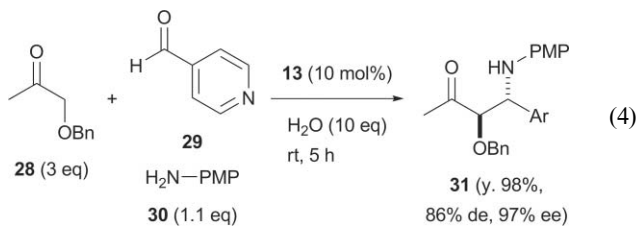
The development of organocatalytic direct Mannich reactions has received considerable attention in recent years, because these reactions are useful for the synthesis of chiral amino acids, β-lactams, amino sugars, imino sugars, and amino alcohols.[24] Although the imine substrate is generally sensitive to hydrolysis, Mannich reactions catalyzed by aldolase-type organocatalysts in aqueous media have been known for some time, with the notable coupling of the Mannich reaction in a one-pot Mannich–allylation reaction in mixed aqueous/organic media.[25] Studies without the addition of organic solvents have been reported.

The asymmetric Mannich reaction of *p*-methoxyphenyl (PMP)-protected ethyl iminoglyoxylate (**26**) with isovaleraldehyde (**25**, 3 equiv.) in water (111 equiv.) is efficiently catalyzed by (*S*)-2-[diphenyl(trimethylsiloxy)methyl]pyrrolidine (**12**, 10 mol%) (eqn (3)). The *anti*-Mannich product **27** was obtained in 35% yield with excellent stereoselectivity (85% de, 98% ee), though yield and diastereoselectivity were slightly decreased in comparison with those of the reaction performed in organic solvent ($CHCl_3$, 24 h, 4 °C, 68% yield, >90% de, 98% ee) probably due to hydrolysis of the imine **26**.[26]



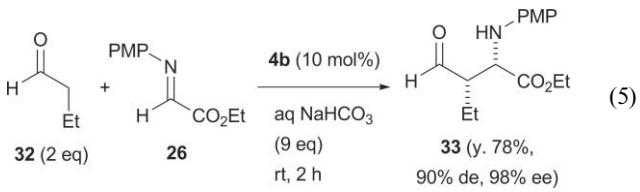
(3)

Lu's group observed excellent yield and stereoselectivity in the direct asymmetric three-component Mannich reaction of *O*-Bn-hydroxyacetone (**28**, 3 equiv.) with *in situ* prepared imine from 4-pyridinecarboxaldehyde (**29**) and *p*-anisidine (**30**, 1.1 equiv.) in the presence of water (10 equiv.). An L-threonine-derived organocatalyst (**13**, 10 mol%) gave the corresponding protected *anti*-Mannich product **31** in 98% yield with enantioselectivity of 97% (eqn (4)).[27]



(4)

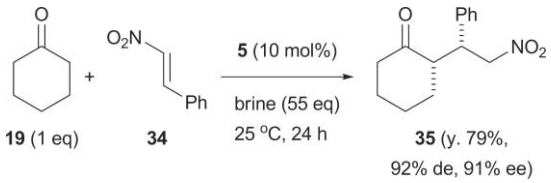
Basic aqueous conditions improved the asymmetric Mannich reaction of water-sensitive imine **26** as reported by Hayashi's group (eqn (5)). The *syn*-Mannich product was obtained in 78% yield with excellent stereoselectivity (90% de, 98% ee), in the reaction of the imine **26** with the aldehyde (**32**, 2 equiv.) by using the sodium salt of siloxyproline catalyst **4b** (10 mol%) in the presence of aqueous $NaHCO_3$ (9 equiv). Thus, the use of organic solvents can be reduced compared to the conventional direct Mannich reactions in organic solvents.[28]



(5)

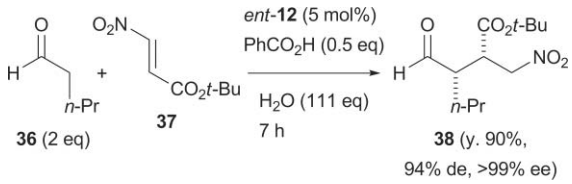
4. Direct Michael reaction in aqueous media

The scope of aldolase-type organocatalyst-based Michael reactions has been extended over the past four years.[29] A direct asymmetric Michael reaction of a stoichiometric amount of cyclohexanone (**19**, 1 equiv.) with β-nitrostyrene (**34**) that can be performed in brine (55 equiv.), seawater, or deep seawater (from a depth of 397 m in Suruga Bay in Japan) without addition of organic solvents was developed by our group (eqn (6)). A proline-derived catalyst (**5**, 10 mol%) efficiently catalyzed Michael reactions and afforded the Michael product **35** in 79% yield with excellent stereoselectivity (92% de, 91% ee), even when only an equimolar amount of the donor to acceptor was used. The crude product was obtained by removing the brine and the desired Michael product was then obtained by recrystallization from ethyl acetate (73%, *syn* isomer, >99% ee). No extraction, washing, or chromatography was needed to isolate the product **35** with excellent purity.[30]



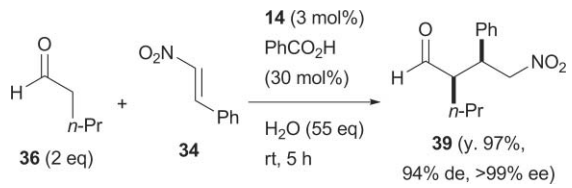
(6)

The Ma group developed an efficient asymmetric aqueous Michael addition of aldehyde donor (**36**, 2 equiv.) to the nitroalkene **37** (eqn (7)). Previous routes required a large excess of aldehyde donor source as well as high catalyst loadings in conventional organic solvent. Diarylprolinol ether (*ent*-**12**, 5 mol%) catalyzes the formation of enamine intermediate in the presence of benzoic acid (0.5 equiv.) in water (111 equiv.); the desired product **38** was obtained in 90% yield with extremely high stereoselectivity (94% de, >99% ee).[31] Using the same catalyst system, the Ma group later demonstrated an effective enantioselective assembly of substituted dihydropyrones *via* the addition of aldehydes to α-keto-α,β-unsaturated esters. The reaction proceeds in water with an acid co-catalyst to provide hemiacetals that are readily oxidized to a variety of interesting dihydropyrones with ee's typically exceeding 98%.[32]



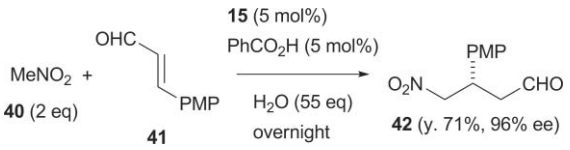
(7)

Quite recently, a new strategy for the Michael addition. of aldehydes to nitroolefins on water has been developed by Ni's group (eqn (8)).[33] The diarylprolinol ether (**14**, 3 mol%) protonated *in situ* by benzoic acid catalyzed the Michael addition in excellent diastereo- and enantioselectivities. The aqueous phase containing the catalyst **14** was readily recovered and used again for the next reaction cycle simply by addition of substrates.



(8)

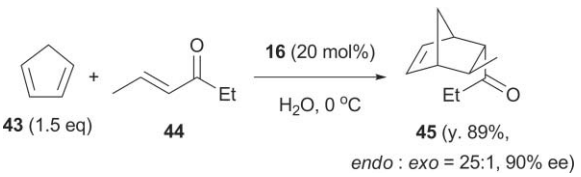
There are two complementary modes of activation in Michael reactions. One is enamine-based activation of the donor (described above); the other one is iminium-based activation of the Michael acceptor. Palomo's group demonstrated that enal **41** was activated by prolinol-based catalyst **15** (5 mol%) in the presence of benzoic acid (5 mol%) in water (55 equiv.) to give an iminium intermediate, which was directly converted with nitromethane (2 equiv.) to the Michael product **42** in 71% yield with 96% ee (eqn (9)).[34,35]



(9)

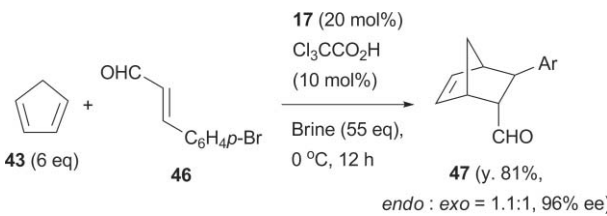
5. Direct cycloaddition reaction in aqueous media

The activation of α,β-unsaturated carbonyl compounds as dienophiles *via* LUMO-lowering iminium formation has been applied to Diels–Alder reactions.[36] Given the pioneering studies of Breslow concerning acceleration of the Diels–Alder reaction in water,[37] MacMillan also studied the enantioselective Diels–Alder reaction through [4 + 2]-cycloaddition of cyclopentadiene (**43**, 1.5 equiv.) to enone **44** in the presence of the iminium catalyst (**16**, 20 mol%) in water (eqn (10)).[38] Excellent levels of enantiofacial discrimination (90% ee) were achieved by use of the heteroaromatic-substituted catalyst **16**. Cycloaddition product **45** was purified directly by silica gel chromatography without further workup.



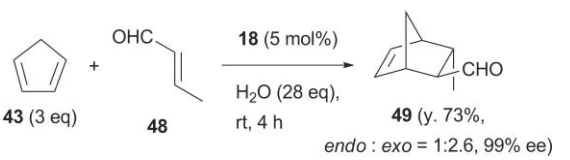
(10)

Lee's group reported that brine (55 equiv.) was an effective reaction media in the Diels–Alder reaction of cyclopentadiene (**43**, 6 equiv.) with the enone **46** (eqn (11)). Cyclic sulfonyl hydrazine (**17**, 20 mol%) with trichloroacetic acid (10 mol%) as co-catalyst efficiently yielded the product **47** in 81% yield with 96% ee.[39]



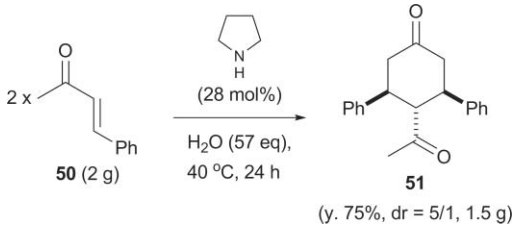
(11)

Recently, the Hayashi group demonstrated an interesting role of water in the enantioselective Diels–Alder reaction. The reaction of cyclopentadiene (**43**, 3 equiv.) with the enal **48** catalyzed by α,α-diphenylprolinol trimethylsilyl ether (**18**, 5 mol%) in water (28 equiv.) furnished the corresponding product in 73% yield with 99% ee (eqn (12)). Water accelerates the reaction and increases the enantioselectivity. Interestingly, initial stirring for one minute was sufficient to achieve the reaction. Additional stirring did not improve the reaction efficiency. Furthermore, the reaction was slow and the enantioselectivity decreased in brine; hence, salting out is detrimental to this reaction. Hayashi *et al.* noted that the role of water in their reaction is different from that of Breslow's well-known homogeneous reaction "in water" and that of Sharpless' "on water" reaction.[40]



(12)

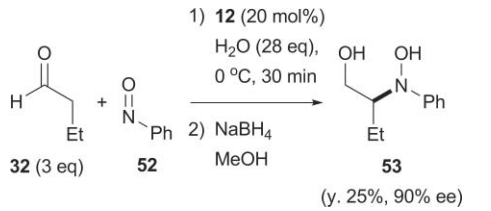
In addition to the LUMO-lowering iminium-based strategies, combinations with HOMO-raising dienamine approaches founded on the aldolase strategy have also been successfully performed in water. Prochiral cyclohexanones **51** are readily prepared on a gram scale under pyrrolidine catalysis in water (eqn (13)).[41,42]



(13)

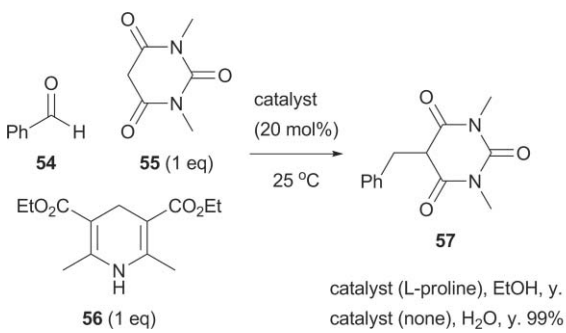
6. Multicomponent, cascade and other reactions in aqueous media

The practical application of water as a solvent continues to be explored for a wide-range of aldolase-like reactions. Palomo demonstrated that the direct and regioselective oxyamination reaction of aldehydes with nitrosobenzene (**52**) in the presence of organocatalyst (**12**, 20 mol%) in water (28 equiv.) to afford the oxyaminated products with excellent regio- and enantioselectivities (eqn (14)).[43]



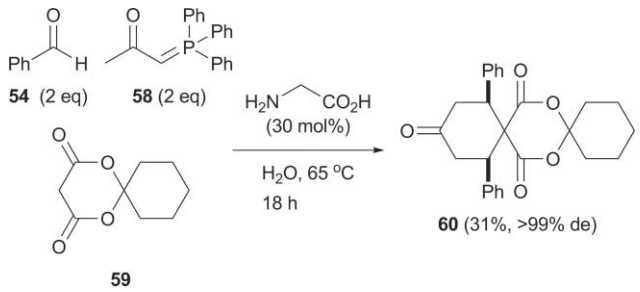
(14)

Another emerging class of reactions attempts to combine multiple elements of reaction economy, these are multicomponent and cascade-type reactions in water. Ramachary *et al.* have reported 3 and 4 component reactions. Significantly, in the cascade olefination/hydrogenation reaction (eqn (15)), water was found to catalyze the reaction in the absence of organocatalyst wherein proline catalysis was required when organic solvent was used.[44]



(15)

Water was also shown to be an effective reaction medium in glycine-catalyzed stereospecific assembly of spirotriones *via* a three-component Wittig/Knoevenagel/Diels–Alder reaction sequence in one pot (eqn (16)).[45] Structurally unique spirotrione **60** was obtained as a single diastereomer.



(16)

Conclusions

The role of water in organocatalysis is often complex and not well understood. Water may play multiple roles such as presenting 'dangling' hydroxyl groups that can participate in catalysis or act as a passive medium. Organocatalytic reactions in water have the following notable features: 1) reactions are often accelerated relative to those in organic solvent, 2) both diastereo- and enantioselectivities are often higher than for the reaction performed in an organic solvent, 3) low catalyst loading can be achieved, 4) even if the reactions are stoichiometric, the reaction product might be more readily isolated, and 5) the use of organic solvent is minimized. These features make aqueous-based organocatalytic processes advantageous from economic and ecological points of view. The catalysts themselves are typically very hydrophobic and the reactions are believed to take place in an organic phase, mimicking an enzyme's sequestration of substrates away from bulk water. Organocatalysis that uses aqueous solvent is rapidly advancing and improvements in key synthetic reactions like the aldol and Michael reactions are now continuously being reported. The combination of aqueous organocatalysis with multicomponent/one-pot/cascade-type reactions provides for a convergence of reaction and ecological economies. We believe that development of the next generation of water-compatible organocatalysts, in parallel with detailed analysis of the role of the water molecule, and continued expansion of organocatalytic reactions will move the field of organic chemistry toward the "ideal organic synthesis" making nature's reaction media the media of the synthetic chemist.

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