

# In Water or in the Presence of Water?\*

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## Stichwörter:

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Water exhibits special properties as compared to commonly employed organic solvents. For instance, Breslow and co-workers reported acceleration of the Diels–Alder reaction “in water” with the reaction performed at very high dilution to dissolve the reactants,<sup>[1]</sup> while Sharpless and co-workers described “on water” conditions under which substantial rate acceleration was observed when the organic reactants were insoluble in the aqueous phase.<sup>[2]</sup> Regardless of whether the reactants are soluble or not in water, reactions using this solvent have attracted great attention from a synthetic point of view because water is environmentally friendly and safe, and the problems of pollution that arise with organic solvents can be avoided.<sup>[3]</sup>

The aldol reaction is a synthetically important carbon–carbon bond-forming reaction.<sup>[4]</sup> Enzymes and antibodies can catalyze the asymmetric aldol reaction using water as a medium<sup>[4,5]</sup> when some reaction proceeds in a hydrophobic pocket. There are several examples of the asymmetric aldol reaction “in the presence of water”; for example, the Mukaiyama aldol reaction is catalyzed

by a combined chiral Lewis acid/surfactant catalyst “in the presence of water” (up to 69 % *ee*).<sup>[6]</sup> Zn/proline also promotes the aldol reaction in aqueous media with moderate enantioselectivity (up to 56 % *ee*).<sup>[7]</sup> In this case, a mixture of acetone and water was used, with the acetone acting not only as nucleophile but also as co-solvent.

After the seminal discovery of the proline-mediated, asymmetric aldol reaction by List, Lerner, and Barbas<sup>[8]</sup> which proceeds in a polar organic solvent, many papers concerning similar asymmetric aldol reactions have appeared. Some reactions have been performed under aqueous conditions,<sup>[9,10]</sup> with the presence of water reported to increase the reactivity and stereoselectivity.<sup>[9]</sup> At the time we started our research on the aldol reaction “in the presence of water”, to the best of our knowledge there had been no reports of a highly enantioselective, catalytic aldol reaction proceeding “in the presence of water” without using any organic solvent.

At the end of 2005, Barbas and co-workers<sup>[11]</sup> and our own group<sup>[12]</sup> both independently reported the asymmetric aldol reaction “in the presence of water”. We recently published another paper concerning this topic.<sup>[13]</sup> Our first report described an aldehyde–ketone aldol reaction catalyzed by siloxyproline (Scheme 1),<sup>[12,14]</sup> and the second report concerned an aldehyde–aldehyde reac-

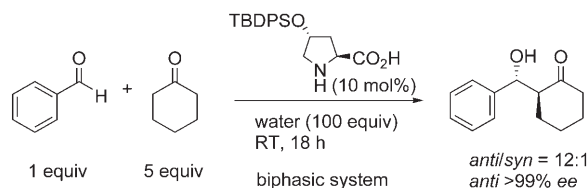
tion catalyzed by a combined proline/surfactant organocatalyst (Scheme 2).<sup>[13]</sup> Both reactions proceed in the presence of a large excess of water to afford the aldol products with excellent diastereo- and enantioselectivities. In the system using the siloxyproline catalyst, water appears to play a special role as a decrease in diastereomer ratio and enantioselectivity was observed under solvent-free conditions or in organic solvents. Thus, the reaction does not simply occur in a “concentrated organic phase” as suggested by Janda and co-workers.<sup>[15]</sup>

In the main discussion of both papers, we used the phrase “in the presence of water” and described clearly that both reactions proceed in an organic phase, as a biphasic system in the first report<sup>[12]</sup> and as an emulsion in the second.<sup>[13]</sup> One of the important and novel points observed with these reactions, in my opinion, is that highly enantioselective reactions proceed even “in the presence of a large excess amount of water”.<sup>[13,14]</sup> This is a first asymmetric aldol reaction with excellent enantioselectivity in the presence of a large amount of water.

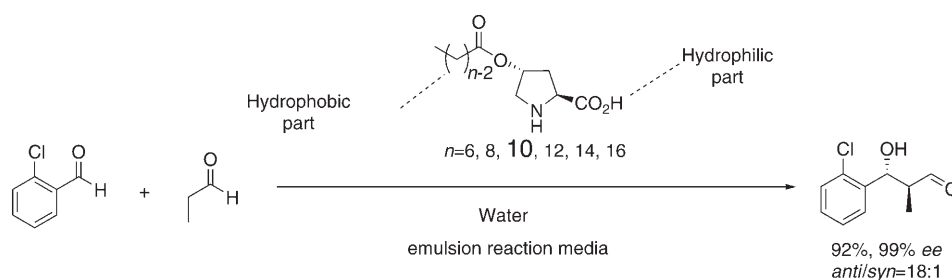
There have been several reports on the asymmetric aldol reaction using water as the only medium, one in which the reactants are not soluble. These reactions are described differently in the various papers, sometimes as “in water” and sometimes as “aqueous”.

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**Scheme 1.** Aldehyde–ketone aldol reaction (TBDPSP = *tert*-butyldiphenylsilyl).



**Scheme 2.** Aldehyde–aldehyde aldol reaction in an emulsion.

What is a suitable term to describe the present reactions? Previously it had seemed to me that “aqueous” might not be suitable because it does not necessarily mean a reaction in which water is the only medium, but also includes the combined use of water and organic solvent. Nor would “on water” be suitable because these reactions are not necessarily accelerated “in the presence of water” in the way Sharpless has described.<sup>[2]</sup> Janda and co-workers have now proposed the term “concentrated organic phases”.<sup>[15]</sup> This may often be appropriate, but I feel it does not adequately represent the effect of water or the difference seen between conditions with water present and solvent-free conditions, as we observed in the reaction reported in the earlier of our two papers.<sup>[12]</sup> What expression best conveys the effect of water in this reaction? We propose to use the terminology “in the presence of water”.

As there is confusion over the terminology “in water”, it is necessary at this point to clarify the terms “in water” and “in the presence of water”. We propose to define “a reaction in water” as one in which the reactants participating in the reaction are dissolved homogeneously in water (or buffer, for pH control), whereas “a reaction in the presence of water” should be used for a reaction that proceeds in a concentrated organic phase with water being present as a second phase that influences the reaction in the organic phase. Sharpless’ reactions “on water” are covered by the more general term “in the presence of water”.<sup>[2]</sup>

Although the development of a small organic molecule that catalyzes the enantioselective, direct aldol reaction “in water”—and not just “in the presence of water”—with suitable asymmetric induction has been a longstand-

ing challenge,<sup>[15]</sup> we have recently developed such a small-molecule catalyst. These exciting results will be reported in due course.<sup>[16]</sup>

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