

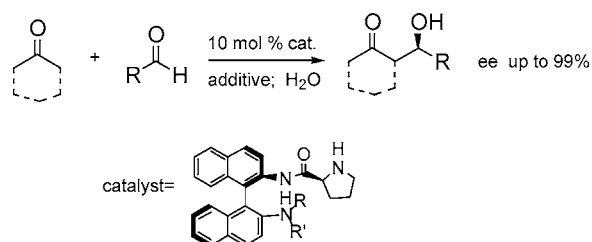
# Enantioselective Direct Aldol Reaction “on Water” Promoted by Chiral Organic Catalysts<sup>†</sup>

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Received January 2, 2007

## ABSTRACT



1,1'-Binaphthyl-2,2'-diamine-based (S)-prolinamides in the presence of stearic acid were able to promote the direct aldol condensation of cyclohexanone and other ketones with different aldehydes in the presence of a massive amount of water in very good yields, high diastereoselectivity, and up to 99% ee. The behavior of both C<sub>2</sub>- and C<sub>1</sub>-symmetric catalysts in combination with different additives was investigated, and a preliminary experiment of recovering and recycling of the catalytic system was also attempted.

The use of water as reaction solvent has many positive effects in terms of cost, safety, and environmental impact.<sup>1</sup> However, although in the past decade much effort has been put into the study of chemical synthesis in water, only a relatively limited number of enantioselective organic reactions can be effectively carried out in this solvent.<sup>2</sup> Different expedients have been adopted to circumvent the solubility problems, including the use of organic cosolvents, surfactants, and hydrophilic auxiliaries.<sup>3</sup>

So far the field of enantioselective organocatalysis in water has afforded even more unsatisfactory results. In the past few years a number of chemically robust organocatalysts have become available, their application encompassing many

fundamental reactions of organic chemistry.<sup>4</sup> However, early studies about the use of chiral organic catalysts in aqueous medium met with only limited success.<sup>5</sup> Only very recently Barbas<sup>6</sup> and Hayashi<sup>7</sup> reported very efficient proline-derived chiral catalysts for the aldol condensation “in water”. After those breakthrough contributions in the past few months, other examples of stereoselective reactions in aqueous solvent

<sup>†</sup> Dedicated to Prof. Achille Umani-Ronchi on his 70th birthday.

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were described, promoted by tryptophan,<sup>8</sup> small peptides,<sup>9</sup> pyrrolidine-based catalysts,<sup>10</sup> or proline-related systems.<sup>11</sup>

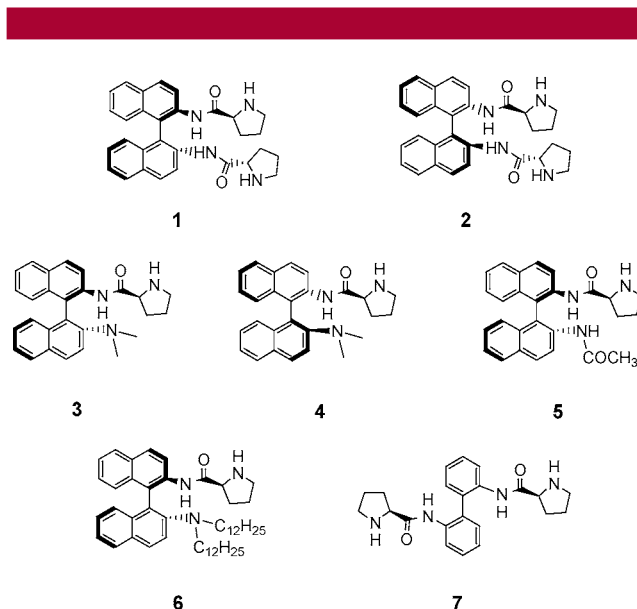
It should be noted that among all of the reported systems only two organocatalysts really seem to work in the presence of a large amount of water,<sup>6a,7b</sup> while other catalysts suffer from different drawbacks: some of them work in mixed aqueous organic solvent<sup>9,11b</sup> or require the use of surfactants,<sup>9,10</sup> and others are supported<sup>11a</sup> or dendritic<sup>11c</sup> systems whose preparation needs chemical manipulation. Often a large excess of ketone is employed,<sup>7a,8,10,11b,c</sup> and the catalysts perform in what, even if is defined as an aqueous medium, really is a wet organic system.<sup>12</sup>

The development of chiral organic molecules able to catalyze stereoselective reactions in pure water is the true challenge. We wish to report here that 1,1'-binaphthyl-2,2'-diamine-based (*S*)-prolinamides in combination with a proper additive are efficient catalysts for direct aldol condensation in the presence of a large amount of water, by employing a small excess of ketone; the system has shown good generality and is active enough to promote the reaction also of less reactive aldehydes.<sup>13</sup>

Recently we<sup>14</sup> and others<sup>15</sup> have reported the synthesis of new organocatalysts obtained by connecting the proline moiety to a 1,1'-binaphthyl-2,2'-diamine scaffold, easily prepared in a few steps from inexpensive, commercially available, enantiopure materials.<sup>16</sup>

Differently functionalized *C*<sub>2</sub>- and *C*<sub>1</sub>-symmetric binaphthyl-2,2'-diamine-based (*S*)-prolinamides were prepared and tested as catalysts (Figure 1). Enantiomerically pure compounds **1**–**5** were synthesized according to the published procedure.<sup>14</sup> Starting from the mono *N*-acetyl (*R*)-binaphthyl diamine, catalyst **6** was synthesized in only four steps and 75% overall yield.

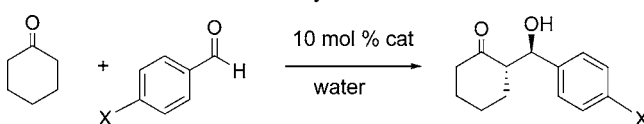
In order to compare the activity in water of binaphthyl versus biphenyl-based catalytic systems, enantiomerically pure **7** was also prepared in 51% overall yield.



**Figure 1.** Proline-based catalysts **1**–**7**.

First the prolinamide derivatives were employed in the test aldol condensation between cyclohexanone and 4-nitro benzaldehyde (Scheme 1, X = NO<sub>2</sub>). By working in a 1:1

**Scheme 1.** Aldol Reaction of Cyclohexanone with 4-Nitro Benzaldehyde in Water



water/cyclohexanone mixture, both *C*<sub>2</sub>-symmetric catalysts **1** and **2** afforded the product in quantitative yields and high, comparable stereo- and enantioselectivities (entries 1 and 3 of Table 1). However by running the reaction in the presence of a large amount of water (0.8 mL of water for 0.06 mL of cyclohexanone and 0.03 g of aldehyde) the (*S*)-binaphthyl-derived catalyst **2** proved to be superior to catalyst **1** in terms of enantioselectivity (entries 2 and 4, 95% vs 69% ee). After only 12 h at 2 °C, catalyst **2** promoted the aldol condensation in 87% yield, 95/5 *anti/syn* ratio, and 93% ee for the *anti* isomer (entry 5). Even at room temperature the product was obtained with high enantioselectivity (91%), although with lower diastereocontrol (*anti/syn* 80/20, entry 6).

The *C*<sub>1</sub>-symmetric catalysts were also tested in the same reaction conditions. Whereas all compounds **3**–**5** catalyzed the aldol condensation in comparable enantioselectivities, only slightly inferior to those obtained with catalyst **2**, they gave different results in terms of chemical activity. Mono *N,N*-dimethyl (*R*)-binaphthyl-derived catalyst **3** afforded the product in 100% yield, whereas the analogous (*S*)-binaphthyl-based catalyst **4** and the mono *N*-acetyl derivative **5** promoted the reaction in low yields (entries 7–9). Catalyst **6** seems to behave not very differently from catalyst **3** in the diastereo-

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(12) For a very interesting discussion of enantioselective organocatalysis "in water" or "in the presence of water", see: (a) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, 45, 8100. (b) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, 45, 8103.

(13) We agree with Prof. Janda's opinion<sup>12a</sup> that so far no organic catalyst may be considered really working "in water", since all of the organocatalysts developed are insoluble in water. We also agree with Prof. Hayashi<sup>12b</sup> in defining "in the presence of water" as a more appropriate expression for reactions described in refs 6 and 7. However, it must be noted once again that the catalysts of refs 6 and 7b are the only ones working in the presence of a large excess of water, while this is not true in the other systems.

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(16) For other organocatalysts prepared according to these principles, see: Pignataro, L.; Benaglia, M.; Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Org. Chem.* **2006**, 71, 1458.

**Table 1.** Aldol Reaction of Cyclohexanone with 4-Nitro Benzaldehyde in Water (Scheme 1, X = NO<sub>2</sub>)<sup>a</sup>

entry	time (h)	catalyst	yield <sup>b</sup> (%)	dr <sup>c</sup>	ee <sup>d</sup> (%)
1 <sup>e</sup>	60	<b>1</b>	100	88/12	88
2	60	<b>1</b>	94	88/12	69
3 <sup>e</sup>	60	<b>2</b>	100	95/5	92
4	60	<b>2</b>	90	92/8	95
5	12	<b>2</b>	87	95/5	93
6 <sup>f</sup>	12	<b>2</b>	100	80/20	91
7	12	<b>3</b>	100	90/10	87
8	12	<b>4</b>	47	93/7	89
9	12	<b>5</b>	21	99/1	84
10	12	<b>6</b>	44	93/7	67
11	12	<b>7</b>	85	84/16	63

<sup>a</sup> Reaction conditions: 0.8 mL of H<sub>2</sub>O, 0.6 mmol of ketone, 0.2 mmol of aldehyde, 0.02 mmol of catalyst, 2 °C. <sup>b</sup> Yields determined after chromatographic purification. <sup>c</sup> Diastereomeric excess determined by NMR. <sup>d</sup> Enantiomeric excess determined by HPLC (Chiracel OJ-H). <sup>e</sup> Reaction run in 1/1 ketone/H<sub>2</sub>O mixture. <sup>f</sup> Reaction run at 25 °C.

control of the reaction but gave the product with diminished enantioselection (entry 10).

Finally the biphenyl-based catalyst **7** promoted the reaction in good yields but lower diastereoselectivity and especially lower enantioselectivity compared to catalyst **2** (entry 11). These results seem a clear indication that the identification of the matching configurations of the stereogenic elements in the molecule is not straightforward, but the stereogenic axis of the binaphthyl diamine plays an important role in helping to stereocontrol the condensation.<sup>14,15c</sup>

When catalyst **2** was employed in the condensation in water of cyclohexanone with a nonactivated aldehyde, such as benzaldehyde, the product was obtained in very low yield (entry 1, Table 2). However, the use of an acidic additive

**Table 2.** Aldol Reaction of Cyclohexanone with Benzaldehyde in Water (Scheme 1, X = H)<sup>a</sup>

entry	time (h)	catalyst	additive	yield <sup>b</sup> (%)	dr <sup>c</sup>	ee <sup>d</sup> (%)
1	90	<b>2</b>		15	nd	nd
2	12	<b>2</b>	PhCO <sub>2</sub> H	71	86/14	73
3	12	<b>2</b>	(+)-PhCH(OH)-CO <sub>2</sub> H	68	95/5	84
4	12	<b>2</b>	(-)-PhCH(OH)-CO <sub>2</sub> H	65	96/4	87
5	12	<b>2</b>	C <sub>11</sub> H <sub>23</sub> CO <sub>2</sub> H	85	96/4	89
6	12	<b>2</b>	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	80	99/1	93
7	12	<b>3</b>	C <sub>11</sub> H <sub>23</sub> CO <sub>2</sub> H	67	99/1	83
8	12	<b>3</b>	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	77	97/3	81
9	12	<b>5</b>	PhCO <sub>2</sub> H	30	99/1	95
10	12	<b>5</b>	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	40	99/1	95
11	12	<b>6</b>	PhCO <sub>2</sub> H	100	85/15	60
12	12	<b>6</b>	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	100	90/10	76
13	12	<b>7</b>	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	28	96/4	83

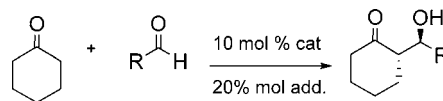
<sup>a</sup> Reaction conditions: 0.8 mL of H<sub>2</sub>O, 0.6 mmol of ketone, 0.2 mmol of aldehyde, 0.02 mmol of catalyst, 0.04 mmol of additive, 2 °C. <sup>b</sup> Yields determined after chromatographic purification. <sup>c</sup> Diastereomeric excess determined by NMR. <sup>d</sup> Enantiomeric excess determined by HPLC (Chiracel OD).

allowed the yield of the process to improve dramatically.<sup>17</sup> Organocatalyst **2** in the presence of benzoic acid promoted the reaction in 71% yield and 73% ee (entry 2). The use of both enantiomers of malic acid allowed further increase in the enantioselectivity of the process but brought to the product the same level (and the same sense) of enantiocontrol (entries 3 and 4). A further improvement came when lauric acid was used as additive (85% yield, 96/4 *anti/syn* ratio, and 89% ee, entry 5). Along this line best results were obtained with stearic acid as additive, which afforded the product in 80% yield basically as a single *anti* isomer in 95% ee (entry 6).

The C<sub>1</sub>-symmetric catalyst **5** promoted the reaction in lower yields but comparable, very high stereo- and enantioselectivity, suggesting that chemical activity would depend only on the number of catalytic sites present in the molecule, such as the number of proline residues. The catalyst **3** afforded the product in both lower yield and stereoselectivity compared with **2**. The use of long alkyl chains at the nitrogen, as in catalyst **6**, brought better yields but even worse enantioselectivities (entries 11 and 12 vs entries 7 and 8). Finally also in the additive-assisted reaction in water, **7** afforded lower stereo- and enantiocontrol and dramatically lower yield (entry 13, Table 2).

Noteworthy catalysts type **2** seem to perform better in water than in organic solvent;<sup>14</sup> our working hypothesis is that the binaphthyl moiety may build a sort of hydrophobic pocket where the reaction takes place. Water would play a decisive role in keeping the reactants and the catalyst in close contact. In this picture the presence of long-chain carboxylic acids should contribute to the construction of a lipophilic cavity surrounded by massive bulk water.

The use of catalyst **2** in the presence of an acid additive was extended to other aldehydic substrates (Scheme 2). In

**Scheme 2.** Enantioselective Aldol Reactions of Cyclohexanone in Water Promoted by Catalyst **2**

the case of reactive aldehydes the addition of an acid caused an acceleration of the reaction without any detriment to the enantioselectivity of the process (Table 3). For example, the condensation of 4-nitro benzaldehyde without any additive afforded after 6 h the product in 45% yield, but in the presence of benzoic acid after only 2 h the reaction was complete with 91% ee. Also with 2-chloro benzaldehyde in the presence of stearic acid the reaction was complete after only 12 h with 87% ee. With pentafluorobenzaldehyde the use of stearic acid improved the enantioselectivity up to 65% (entries 6 and 7). The presence of stearic acid successfully promoted the condensation even of a deactivated aldehyde, such 4-methoxy benzaldehyde (87% ee for the *syn* isomer).

(17) The use of acids as additive has been already reported; see refs 14 and 11b and citations within.

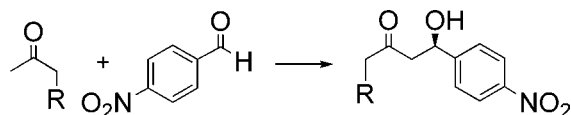
**Table 3.** Aldol Reactions in Water Promoted by Catalyst **2**<sup>a</sup>

entry	time (h)	additive	R	yield <sup>b</sup> (%)	dr <sup>c</sup>	ee <sup>d</sup> (%)
1	12		4-NO <sub>2</sub> Ph	87	95/5	93
2	6		4-NO <sub>2</sub> Ph	45	95/5	91
3	2	PhCOOH	4-NO <sub>2</sub> Ph	100	92/8	91
4	72		2-ClPh	100	90/10	87
5	12	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	2-ClPh	100	97/3	87
6	72		F <sub>5</sub> C <sub>6</sub>	35	98/2	53
7	12	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	F <sub>5</sub> C <sub>6</sub>	37	99/1	65
8	12	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	Ph	80	99/1	93
9 <sup>e</sup>	12	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	4-OMePh	57	50/50	87

<sup>a</sup> Reaction conditions: 0.8 mL of H<sub>2</sub>O, 0.6 mmol of ketone, 0.2 mmol of aldehyde, 0.02 mmol of catalyst, 0.04 mmol of additive, 12 h, 2 °C.

<sup>b</sup> Yields determined after chromatographic purification. <sup>c</sup> Diastereomeric excess determined by NMR. <sup>d</sup> Enantiomeric excess determined by chiral HPLC. <sup>e</sup> Reaction run at 25 °C; ee % determined for *syn* isomer.

The combination of compound **2** and stearic acid proved to be an efficient catalytic system also for the condensation “on water” of ketones other than cyclohexanone (Scheme 3). For example, the reaction of 4-nitrobenzaldehyde with

**Scheme 3.** Aldol Reactions Promoted by Catalyst **2**

2-octanone without additive proceeded after 72 h in the usual conditions in 61% yield and 77% ee for the *anti* isomer (entry 1, Table 4), but in the presence of stearic acid after only 2 h the product was obtained with the same yield, 91/9 *anti/syn* ratio, and 91% ee (entry 2). Also the reaction of methyl ethyl ketone afforded the aldol product in 90% yield and 91% enantioselectivity. It is worth mentioning that the reaction promoted by the same catalytic system in only 2-butanone afforded the product in high yields but lower enantioselectivities, clearly pointing at a positive effect of the aqueous environment in the condensation process (entries 3 and 4).

The reaction with acetone afforded the product after 12 h in 100% yield but lower enantioselection.

Finally, a preliminary experiment to recover and recycle the catalytic system was attempted for the condensation

**Table 4.** Aldol Reactions in Water Promoted by Catalyst **2**<sup>a</sup>

entry	time (h)	additive	R	yield <sup>b</sup> (%)	rr <sup>c</sup>	ee <sup>d</sup> (%)
1	72		C <sub>5</sub> H <sub>11</sub>	61	99/1	77
2	12	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	C <sub>5</sub> H <sub>11</sub>	61	91/9	91
3 <sup>e</sup>	12	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	CH <sub>3</sub>	90	70/30	95
4 <sup>f</sup>	12	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	CH <sub>3</sub>	100	88/12	73
5 <sup>e</sup>	12	C <sub>17</sub> H <sub>35</sub> CO <sub>2</sub> H	H	100		58

<sup>a</sup> Reaction conditions: 0.8 mL of H<sub>2</sub>O, 0.6 mmol of ketone, 0.2 mmol of aldehyde, 0.02 mmol of catalyst, 0.04 mmol of additive, 12 h, 2 °C.

<sup>b</sup> Yields determined after chromatographic purification. <sup>c</sup> Regioisomeric ratio determined by NMR. <sup>d</sup> Enantiomeric excess determined by chiral HPLC.

<sup>e</sup> Reaction run in 1:1 ketone/H<sub>2</sub>O mixture. <sup>f</sup> Reaction run in only ketone.

between cyclohexanone and benzaldehyde catalyzed by **2** and stearic acid. The “heterogeneous” nature of the reaction medium, with the organocatalyst being mostly not soluble in both water and pentane, might make the recovery of the catalytic species quite troublesome. At the end of the reaction pentane was added and the biphasic system was separated; to the recovered “suspension” in aqueous phase, new reagents were added and the reaction was run again.<sup>18</sup> The product was obtained by simple evaporation of the pentane phase. Following this procedure the recycle of the stearic acid/**2** catalytic system provided the product in 45% yield, 98/2 *anti/syn* ratio, and 93% ee (compared to 80% yield, 99/1 *anti/syn* ratio, and 93% ee of the first cycle). Although the methodology needs further work to be optimized, the recycle the catalyst is feasible.<sup>19</sup>

**Acknowledgment.** This work was supported by MIUR: “Nuovi metodi catalitici stereoselettivi e sintesi stereoselettiva di molecole funzionali”.

**Supporting Information Available:** Synthesis and characterization of catalysts **6** and **7**; general procedures for aldol reactions and HPLC analysis details for aldol products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) Our system may be described as an “emulsion” rather than a biphasic system, like Barbos’ reactions.<sup>6</sup> Please note once again in our conditions a small excess of ketone is used and the ratio water/ketone is almost double compared to both refs 6 and 7b.

(19) For a proline-based recoverable organocatalytic system for reactions in water, see ref 11c. For a general overview on recoverable chiral organic catalysts, see ref 4c and Benaglia, M. *New J. Chem.* **2006**, 30, 1525.