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Direct Catalytic Asymmetric Aldol Reactions Assisted by Zinc Complex in the Presence of Water

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Abstract: A combination of zinc triflate and chiral C_2-symmetrical prolinamide ligand leads to high enantioselectivities in direct aldol reactions essentially assisted by water. The presence of 5 mol% of the catalyst affords an asymmetric intermolecular aldol reaction between unmodified ketones and aldehydes to give *anti*-products with excellent enantioselectivities ranging from 86–98% *ee*. The same bis(prolinamide) ligand is found to catalyze the direct aldol reactions in the presence of water (or in water) with excellent stereocontrol and furnish the corresponding aldols in up to 99% *ee*. For the demonstrated catalytic systems organic solvent-free conditions are applied.

Keywords: aldol reaction; asymmetric synthesis; Lewis acids; organocatalysis; proline; water

The ability to control the enantioselectivity of the aldol condensation has established this reaction as the principal chemical transformation for the stereoselective construction of complex polyol architectures.[1] However, most known methodologies require pre-activation of the nucleophilic or donor partner.[2] An exciting challenge to enhance the efficiency of the aldol reaction is to find a compound that will catalyze the direct aldol addition without prior stoichiometric formation of the substrate[3] as it takes place in biological-type catalysts, i.e., enzymes[4] and antibodies.[5] Pioneering studies by Shibasaki,[6] Trost,[7] List,[8] Barbas[9] and MacMillan[10] have outlined the first examples of enantioselective direct aldol reactions, an important class of organic and metal-catalyzed transformations that do not require the pre-generation of enolates or enolate equivalents.

Reactions in which water is used as the solvent are another important issue and the development of enantioselective reactions in aqueous media is an extensively investigated topic.[11] In this regard, direct aldol reactions in water seem to be a challenging issue which needs to be intensively explored. In the 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.[2b] The first reports of chemical organocatalysts for this process have just appeared.[12]

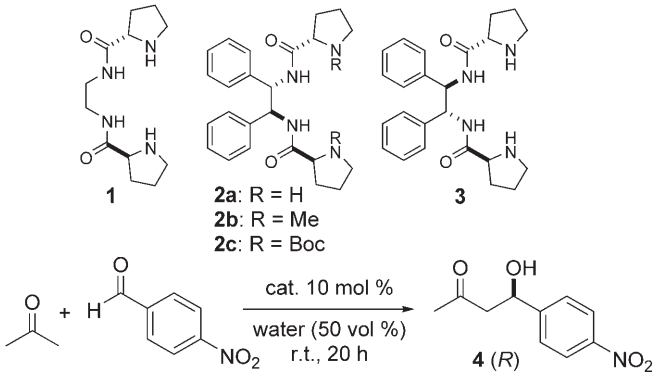
In contrast, application of methods utilizing Lewis acids that rely on the catalysis of metal complexes bearing chiral ligands is troublesome in aqueous solvents. Mimicking the mode of action of class II aldolases, the homobimetalic Zn-BINOL complexes developed by Shibasaki[6c,d] as well as Trost's Zn-semi crown ethers[7] were reported to be water-sensitive and thus the reactions have been carried out under anhydrous conditions in organic solvents. Nevertheless, continuous exploration of zinc complexes seems to be rational as most aldolases contain an active site Zn(II) cofactor facilitating the enolate formation in water.[13]

We have recently presented a chiral Zn(II) complex for Mukaiyama aldol reactions which proceed in aqueous organic solvent,[14] but this is an indirect method that requires pre-formation of a silyl enol ether as a nucleophile. Here we present our studies toward the identification of chiral metal complexes that function as efficient aldol reaction catalysts.

In the development strategy for designing a zinc-containing catalyst 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 on which to construct asymmetric catalysts. Using stronger coordinating elements such as nitrogen was envisioned by analogy to type II aldolases in which the zinc ion is tightly coordinated by three histidine residues in the reaction active site.[15]

After many trials we found that chiral bis(prolinamides) **2** and **3**, readily synthesized in two steps from protected proline and chiral diphenylethylenediamines,[16] meet these design criteria. The ligands with a two-carbon linker between both amino acid moieties were found as the most attractive candidates in the first stage of the optimization.

Table 1. Screening of efficient catalyst in the direct asymmetric aldol reaction of acetone with *p*-nitrobenzaldehyde.



Entry	Catalyst	Yield [%][a]	*ee* [%][b]
1	**1**	82	14
2	**1**/$Zn(OTf)_2$	90	24
3	**2a**	65	6
4	**2a**/$Zn(OTf)_2$	92	60
5	**2b**/$Zn(OTf)_2$	0	-
6	**2c**/$Zn(OTf)_2$	0	-
7	**3**	78	12
8	**3**/$Zn(OTf)_2$	98	27

[a] Isolated yield.
[b] Enantiomeric excess was determined by HPLC analysis on a chiral phase column (Chiralpak AS-H).

Table 2. Prolinamide **2a**/$Zn(OTf)_2$-catalyzed direct asymmetric aldol reaction of acetone with *p*-nitrobenzaldehyde in aqueous solvents.

Entry	Solvent	Catalyst loading	Yield [%]	*ee* [%][d]
1[a]	water	10 mol %	36	36
2[b]	THF-H_2O (1:1)	10 mol %	76	58
3[b]	THF-H_2O (9:1)	10 mol %	70	82
4[b]	THF-H_2O (9:1)	5 mol %	70	80
5[b]	THF-H_2O (9:1)	1 mol %	55	84
6[b]	THF-H_2O (9:1)	0.5 mol %	45	88
7[c]	acetone-H_2O (9:1)	5 mol %	87	86

[a] *Conditions:* acetone (2.5 mmol) and *p*-nitrobenzaldehyde (0.50 mmol) in water (2 mL) at room temperature for 20 h.
[b] *Conditions:* acetone (2.5 mmol) and *p*-nitrobenzaldehyde (0.50 mmol) in solvent (2 mL) at room temperature for 20 h.
[c] *Conditions:* acetone (0.9 mL) and *p*-nitrobenzaldehyde (0.50 mmol) and water (0.1 mL) at room temperature for 20 h.
[d] Enantiomeric excess was determined by HPLC analysis on a chiral phase (Chiralpak AS-H).

The reaction of acetone with *p*-nitrobenzaldehyde was explored as a test. Initial experiments were performed using a 1:1 mixture of acetone and water. To find the optimal reaction parameters we tested the ligands **2** and **3** with chiral backbones as well as their analogue **1** with an ethylenediamine moiety. Application of all tested ligands as catalysts to the aldol reaction led to promising results, namely, the condensation proceeded efficiently in aqueous medium in all cases. Disappointingly, the *ee* was poor (Table 1). However, addition of zinc trifluoromethanesulfonate increased the selectivity as reflected in higher *ee*s. The best results with respect to yield and enantioselectivity were observed with catalyst **2a** and $Zn(OTf)_2$ as additive. The addition of $Zn(OTf)_2$ increased the enantioselectivity from 6 to 60% (entry 3 *vs.* 4). We did not observe the formation of **4** in the presence of $Zn(OTf)_2$ and L-proline (1:2) under similar reaction conditions.

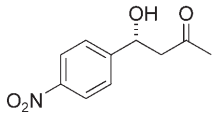
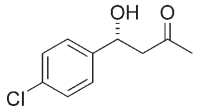
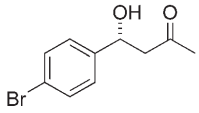
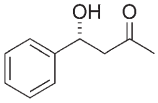
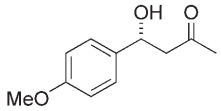
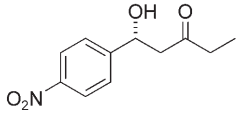
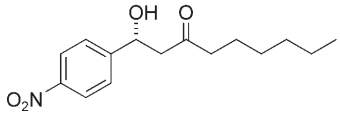
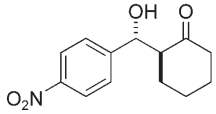
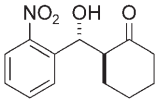
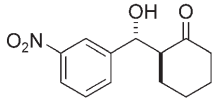
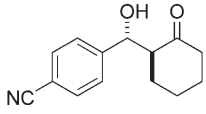
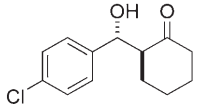
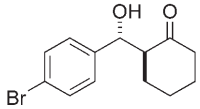
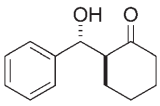
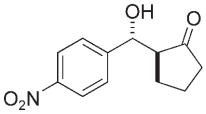
Thus, the reaction catalyst composed of **2a** and $Zn(OTf)_2$ was adopted as our standard to explore optimal reaction conditions. When the aldol reaction was carried out with different amounts of water, the *ee* decreased with a corresponding increase in the water concentration (Table 2). In water alone the zinc complex gave the (*R*) enantiomer in 36% *ee* (entry 1). The reaction carried out in organic co-solvent proceeded well, and only 3–5 equivs. of ketone are necessary to obtain good yield and *ee* (entries 2–6). Remarkably, lowering the catalyst loading to 0.5 mol% showed a significant increase in enantioselectivity with some loss in yield (entry 4 *vs.* 6). We were delighted to find that the reaction without harmful co-solvents proceeded also well when 5 mol% of the catalyst was applied.

Thus, the conditions of entry 7 were adopted for further reactions. Following on from these results, we turned our attention to broadening the range of substrates. The scope of this class of aldol reaction using diamide **2a**/$Zn(OTf)_2$ catalyst in the presence of water was examined and the results are summarized in Table 3. The reaction has broad applicability with respect to the aldehyde. Aldehydes with electron-withdrawing substituents show higher reactivity. In all cases, however, the reaction proceed smoothly at room temperature, and enantioselectivity was good to high (entries 1–6). Both excellent enantioselectivity and *anti* selectivity were obtained when cyclohexanone was employed (entries 8–14). The aldol reactions of *ortho*- and *metha*-substituted aldehydes show higher selectivity than those of *para*-substituted aldehydes.

Retention of the good level of *ee* in the reaction with non-cyclic ketones (entries 1–7) is a valuable observation as the application of previously demonstrated catalysts resulted in lower stereoselectivity with these important substrates.[12]

The new catalyst developed incorporated zinc that can act as a Lewis acid in water. In this respect the

Table 3. The direct catalytic asymmetric aldol reaction in the presence of water catalyzed by **2a**-$Zn(OTf)_2$ (5 mol%): Substrate scope.

Entry	Product	Yield (%)[a]	*anti*/*syn*[b]	*ee* (*anti*) (%)[c]
1		88	-	88[d]
2		80	-	90
3		83	-	88
4		77	-	90
5		21	-	86
6		54	-	88
7		33	-	84
8		98	95/5	94
9		56	98/2	97
10		71	98/2	97
11		94	96/4	93
12		56	98/2	94
13		56	96/4	96
14		46	98/2	94
15		82	44/66	46 (*anti*); 18 (*syn*)

[a] Yield refers to combined yield of isolated diastereomers. *Conditions:* prolinamide catalyst **2a** (0.025 mmol, 5 mol%), $Zn(OTf)_2$ (0.025 mmol), aldehyde (0.50 mmol) in ketone/water mixture (9/1, 1 mL) at room temperature for 20 h.

[b] Diastereoselectivity was determined by HPLC and ^{1}H NMR analysis of the isolated diastereomers.

[c] Enantiomeric excess was determined by HPLC analysis on a chiral phase (Chiralpak AD-H and AS-H).

[d] This system seems to be selective for the formation of the *R* configuration.[17]

catalyst can be seen as mimic of class II aldolases. Formation of an enamine in the active site can be assumed. This mechanism can be supported by the observation of inactivity of the ligands **2b** and **2c** having protected amino groups (Table 1, entries 5 and 6). Based on the observation that zinc salts do not catalyze the aldol reaction, we can assume that both zinc salt and proline motives are necessary for catalysis. On the other hand, poor reaction selectivity without metal additives (Table 1) indicates that zinc-assisted enamine formation can be essential for the asymmetric aldol reaction promoted under our reaction conditions. We assume that zinc as an aqua complex coordinates amide and carbonyl groups of aldehyde in a chiral surrounding. Moreover, coordination to zinc stabilizes the enamine in water, making the condensation with the aldehyde possible, as was proposed by Darbre and co-workers.[13]

Thus, we observed that the direct aldol reaction promoted by small organic molecules can be efficiently supported by water-compatible Lewis acid additives. To test this hypothesis, the aldol reaction of cyclohexanone and *para*-nitrobenzaldehyde was performed using prolinamide **2a** in the presence or absence of additives.

We found that a number of metal salts can improve the outcome of the aldol reaction. Among others complexes of zinc and rare earth element salts turned out to be the most promising. Application of zinc triflate resulted in high reactivity and selectivity of the catalyst (Table 3). In a reaction conducted at 0 °C the *ee* reached smoothly 98% with perfect diastereoselec-

Table 4. The direct catalytic asymmetric aldol reaction in the presence of water catalyzed by prolinamide **2a** (5 mol%) with various additives. Metal complexes (entries 1–16) *vs.* organocatalytic attempts (entries 17–30).

Entry	R-C_6H_4CHO, R =	Additive	Ketone/Water	Temp. [°C]	Yield [%][a]	*anti/syn*[b]	*ee* [%][c]
Metal salts							
1	*p*-NO_2	$Zn(OTf)_2$	cyclohexanone	r.t.	trace	-	-
2	*p*-NO_2	$Zn(OTf)_2$	cyclohexanone/water (9/1)	0	93	98/2	98
3	*p*-CN	$Zn(OTf)_2$	cyclohexanone/water (9/1)	0	64	97/3	97
4	*p*-Cl	$Zn(OTf)_2$	cyclohexanone/water (9/1)	0[d]	35	99/1	98
5	*p*-Br	$Zn(OTf)_2$	cyclohexanone/water (9/1)	0[d]	37	99/1	98
6	H	$Zn(OTf)_2$	cyclohexanone/water (9/1)	0[d]	13	99/1	98
7	*p*-NO_2	$Zn(OTf)_2$	acetone/water (9/1)	0	80	-	91
8	*p*-NO_2	$Zn(OTf)_2$	cyclohexanone/water (1/1)	r.t.	86	87/13	80[e]
9	*p*-NO_2	$Sc(OTf)_3$	cyclohexanone/water (9/1)	r.t.	55	50/50	54
10	*p*-NO_2	$Yb(OTf)_3$	cyclohexanone/water (9/1)	r.t.	81	96/4	95
11	*p*-NO_2	$Yb(OTf)_3$	cyclohexanone/water (9/1)	0	50	99/1	99
13	*p*-NO_2	$Yb(OTf)_3$	cyclohexanone (5 equivs.) in water[f]	r.t.	65	82/18	82
14	*p*-NO_2	$Yb(OTf)_3$	cyclohexanone (5 equivs,) in water	0	60	95/5	91
15	*p*-CN	$Yb(OTf)_3$	cyclohexanone (5 equivs.) in water	0	81	92/8	86
16	*p*-Cl	$Yb(OTf)_3$	cyclohexanone (5 equivs.) in water	0	28	98/2	93
Brønsted acids							
17	*p*-NO_2	-	cyclohexanone/water (9/1)	r.t.	98	85/15	75
18	*p*-NO_2	TfOH	cyclohexanone/water (9/1)	r.t.	30	97/3	97
19	*p*-NO_2	TFA	cyclohexanone/water (9/1)	rt	99	96/4	92
20	H	TFA	cyclohexanone/water (9/1)	r.t.[d]	76	98/2	94
21	*p*-NO_2	TFA	cyclohexanone/water (9/1)	0	81	98/2	98
22	*p*-NO_2	TFA	cyclohexanone/water (1/1)	r.t.	93	97/3	93
23	*p*-NO_2	TFA	cyclohexanone (5 equivs.) in water	r.t.	90	93/7	87
24	*p*-NO_2	TFA	cyclohexanone (5 equivs.) in water	0	20	99/1	95
25	*p*-NO_2	TFA	cyclohexanone (5 equivs.) in water	0[g]	89	96/4	95
26	*p*-CN	TFA	cyclohexanone (5 equivs.) in water	0[g]	94	96/4	93
27	*p*-Cl	TFA	cyclohexanone (5 equivs.) in water	0[g]	45	98/2	95
28	*p*-NO_2	-	acetone/water (9/1)	r.t.	76	-	22
29	*p*-NO_2	TFA	acetone/water (9/1)	r.t.	90	-	90
30	*p*-NO_2	TFA	acetone/water (9/1)	0	91	-	92

[a] Yield refers to combined yield of isolated diastereomers. *Conditions:* prolinamide catalyst **2a** (0.025 mmol, 5 mol%), additive (if used, metal salts: 0.025 mmol or acids, 0.050 mmol), aldehyde (0.50 mmol) in ketone/water mixture (1 mL).

[b] Diastereoselectivity was determined by HPLC and ^1H NMR analysis of the isolated diastereomers.

[c] Enantiomeric excess was determined by HPLC analysis on a chiral phase (Chiralpak AD-H and AS-H).

[d] Reaction time 44 h.

[e] When the condensation of cyclohexanone and *p*-nitrobenzaldehyde was tested in the biphasic system (cyclohexanone-water, 1:1, 1 mL) the catalyst (5 mol%) was soluble in the water phase. After the reaction, both phases were separated, and the product was easily isolated from the organic phase (96% yield, 84% *ee*). As the active species remained in the aqueous phase, the second run was carried out by addition of cyclohexanone and aldehyde to give a similar result (80% yield, 85% *ee*).

[f] Conditions: prolinamide catalyst **2a** (0.025 mmol, 5 mol%), additive (if used, metal salts: 0.025 mmol or acids, 0.050 mmol), aldehyde (0.50 mmol), cyclohexanone (260 μL, 2.50 mmol) in water (1 mL).

[g] Reaction time 70 h, catalyst loading 10 mol%.

tivity and reasonable reactivity of the catalytic system with only 5 mol% catalyst loading (Table 4, entry 2). It is important to underline that 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 (Table 4, entry 1).

Our results show also that the zinc complex is an efficient catalyst that promotes the aldol reaction in the presence of water without an organic co-solvent. The reaction selectivity was affected, however, by the increasing the amount of water in the reaction mixture (entry 8). This unwelcome tendency can be overcome by application of an ytterbium complex which seems to give a much more water-tolerant catalyst (entries 10–16). In this case the aldol reaction proceed well in water with only 5 equivalents of ketone (entries 13–16).

It is interesting that the catalyst operates both in homogeneous solution and biphasic media. This last observation is of fundamental importance for the easy recovery of the chiral catalyst and its re-usability making this methodology extremely exciting (entry 8).

To make sure that the reaction is promoted by the zinc complex and not by prolinamide **2a** supported by triflic acid (assuming hydrolysis of the zinc salt) we tested the catalytic activity of the protonated organocatalyst. Thus, the catalyst having counterion OTf^- gave a comparable enantiomeric excess (Table 3 entry 8 *vs.* Table 4 entry 18) but the effect on the rate of reaction was tremendous. The aldol reaction promoted by catalyst **2a**-TfOH gave only 30% conversion, and the reaction was stopped at 0 °C, while zinc complex showed both good reactivity and selectivity at a lower temperature (Table 4 entry 2).

On the other hand, the promising influence of the Brønsted base on the reaction enantioselectivity (entry 18 *vs.* 17) forced us to test the calatytic activity of the protonated prolinamide **2a** in the aldol reaction.[18] For this purpose organocatalyst **2a** was tested with different counterions. The best results with respect to yield, diastereoselectivity, and enantioselectivity were observed with TFA as additive (entry 19). The same selectivity was observed for unactivated aldehyde (entry 20) and acetone (entries 29 and 30) when only 5 mol% of the catalyst were used. Moreover, a preliminary study showed that a good level of *ee* and excellent diastereoselectivities were maintained in water at 0 °C (entries 23–27). In this case the catalyst loading was raised to 10 mol% and slightly longer reaction time was needed.

In summary, we have succeeded in carrying out the metal-assisted direct asymmetric direct aldol reaction in aqueous media. To date these are the best results reported for the direct aldol reaction catalyzed by a small artificial metal complex in aqueous media. The high selectivity of the catalyst was maintained for non-cyclic ketones making the elaborated methodology especially promising in the literature background. As the chiral backbone of the catalyst can be easily modified, the findings reported herein present a new and flexible approach. Moreover, we have demonstrated that the same bis(prolinamide) catalyst can promote the direct aldol reactions of aliphatic ketones with various aldehydes without an organic co-solvent in the presence of water or even in water in some cases. The amount of organocatalyst can be reduced to 5 mol%. The present study reveals an interesting area of aqueous asymmetric aldol reactions between application of metal complexes and organocatalysis. Further studies focusing on the full scope of this and related systems are in progress and will be reported in due course.

Experimental Section

Typical Procedure for the Asymmetric Aldol Reaction

Prolinamide **2a** (10 mg, 0.025 mmol, 5 mol%) and $Zn(OTf)_2$ (9 mg, 0.025 mmol, 5 mol%) were added to a mixture of cyclohexanone (or appropriate ketone) (0.9 mL) and water (0.1 mL) at room temperature and stirred for 15 min. *p*-Nitrobenzaldehyde (75 mg, 0.5 mmol) was added to the suspension and the whole reaction mixture was stirred for 20 h. The reaction mixture was poured onto a silica gel column and eluted with hexane-ethyl acetate (3:2) to afford (2*S*,1′*R*)-2-hydroxy(4-nitrophenyl)methylcyclohexanone; yield: 123 mg (98%); *anti*:*syn* = 97:3 (by ^{1}H NMR and HPLC analysis); *ee* 94% (Chiralpak AD-H, hexane-*i*-PrOH = 4:1, flow rate 0.5 mL min^{-1}, λ = 254 nm): *anti*: t_1 = 21.6 min, t_2 = 23.3 min (major); *syn*: t_1 = 25.2 min, t_2 = 32.5 min (major)).

References

[1] *Modern Aldol Reactions*, (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2004**.

[2] a) C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2004**, *33*, 65; b) T. D. Machajewski, C.-H. Wong, *Angew. Chem. Int. Ed.* **2000**, *39*, 1352.

[3] a) B. Alcaide, P. Almendros, *Eur. J. Org. Chem.* **2002**, 1595; b) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236; c) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, *37*, 570; d) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580.

[4] a) H. J. M. Gijsen, L. Qiao, W. Fitz, C.-H. Wong, *Chem. Rev.* **1996**, *96*, 443; b) W. D. Fessner, in: *Modern Aldol Reactions*, (Ed. R. Mahrwald), Wiley-VCH, Weinheim, **2004**, p 201 and references cited therein.

[5] a) J. Wagner, C. F. Barbas III, R. A. Lerner, *Science* **1995**, *270*, 1797; b) F. Tanaka, C. F. Barbas III, in: *Modern Aldol Reactions*, (Ed. R. Mahrwald), Wiley-VCH, Weinheim, **2004**, p 273.

[6] a) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871; b) N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168; c) N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466; d) S. Matsunaga, T. Ohshima, M. Shibasaki, *Adv. Synth. Catal.* **2002**, *344*, 3.

[7] a) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003; b) B. M. Trost, H. Ito, E. R. Silcoff, *J. Am. Chem. Soc.* **2001**, *123*, 3367; c) B. M. Trost, E. R. Silcoff, H. Ito, *Org. Lett.* **2001**, *3*, 2497.

[8] a) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386; b) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.

[9] S. Kandasamy, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260.

[10] A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798.

[11] a) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751; b) D. Sinou, *Adv. Synth. Catal.* **2002**, *344*, 221; c) C.-J. Li,

Chem. Rev. **2005**, *105*, 3095; d) U. M. Lindström, F. Andersson, *Angew. Chem. Int. Ed.* **2006**, *45*, 548; e) M. C. Pirrung, *Chem. Eur. J.* **2006**, *12*, 1312.

[12] For representative papers see: a) Y. Hayashi, T. Sumiya, J. Takahashi, H. Gatoh, T. Urushima, M. Shoji, *Angew. Chem. Int. Ed.* **2006**, *46*, 958; b) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734; c) Z. Jiang, Z. Liang, X. Wu, Y. Lu, *Chem. Commun.* **2006**, 2801; d) J.-R. Chen, H.-H. Lu, X.-Y. Li, L. Cheng, J. Wan, W.-J. Xiao, *Org. Lett.* **2005**, *7*, 4543; e) S. S. Chimni, D. Mahajan, *Tetrahedron: Asymmetry* **2006**, *17*, 2108.

[13] Previously, a Zn-proline-catalyzed aldol reaction was reported to occur in aqueous media with poor to moderate enantiomeric excess: R. Fernandez-Lopez, J. Kofoed, M. Machuqueiro, T. Darbre, *Eur. J. Org. Chem.* **2005**, 5268.

[14] J. Jankowska, J. Mlynarski, *J. Org. Chem.* **2006**, *71*, 1317.

[15] W. D. Fessner, A. Schneider, H. Held, G. Sinerius, C. Walter, M. Hixon, J. V. Schloss, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2219.

[16] a) M. J. Alcón, M. Iglesias, F. Sánchez, I. Viani, *J. Organomet. Chem.* **2000**, *601*, 284; b) S. Samanta, J. Liu, R. Dodda, C.-G. Zhao, *Org. Lett.* **2005**, *7*, 5321.

[17] All isolated aldol adducts were found to have the (3*R*)-(entries 1–7) and (2*S*,1′*R*)-stereochemistries (entries 8–15).

[18] Previously proline and protonated prolinamides were demonstrated as organocatalysts in aqueous media: a) S. S. Chimni, D. Mahajan, V. V. S. Babu, *Tetrahedron Lett.* **2005**, *46*, 5617; b) P. M. Pihko, K. M. Laurikainen, A. Usano, A. I. Nyberg, J. A. Kaavi, *Tetrahedron* **2006**, *62*, 317; c) S. S. Chimni, D. Mahajan, *Tetrahedron: Asymmetry* **2006**, *17*, 2108; d) G. Guillena, M. del Carmen Hita, C. Nájera, *Tetrahedron: Asymmetry* **2006**, *17*, 1493; e) Y.-Q. Fu, Z.-Ch. Li, L.-N. Ding, J.-Ch. Tao, S.-H. Zhang, M.-S. Tang, *Tetrahedron: Asymmetry* **2006**, *17*, 3351; f) J.-R. Chen, X.-Y. Li, X.-N. Xing, W.-J. Xiao, *J. Org. Chem.* **2006**, *71*, 8198, and references cited therein.

