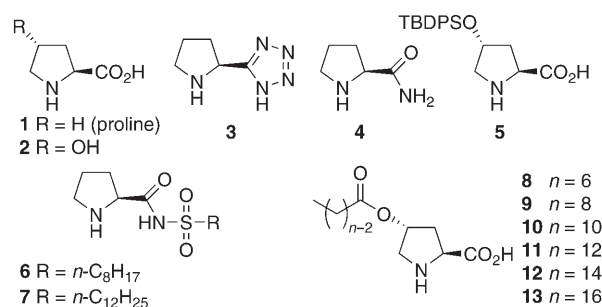


Combined Proline–Surfactant Organocatalyst for the Highly Diastereo- and Enantioselective Aqueous Direct Cross-Aldol Reaction of Aldehydes**

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As water offers several advantages over organic solvents, reactions in aqueous media have received a great deal of attention in recent years.^[1] However, the asymmetric aldol reaction in water has proved very difficult to achieve.^[2] While proline has been reported to catalyze aldol reactions efficiently in polar solvents such as dimethyl sulfoxide (DMSO) and *N,N*-dimethylformamide (DMF),^[3] and while a small amount of water is beneficial in some proline-mediated aldol reactions,^[4] only low enantioselectivities have been obtained in water even in the presence of a surfactant.^[5] There have been no successful asymmetric aldol reactions performed using organocatalysts in water in the absence of an organic cosolvent or other additives. Recently, we reported that a siloxypoline effectively catalyzes the highly diastereo- and enantioselective aldol reaction of ketones and aldehydes in the presence of water.^[6] Barbas and co-workers reported the asymmetric aldol reaction of ketones and aldehydes in water catalyzed by a combination of a diamine and an acid.^[7] Herein, we describe how combined proline–surfactant organocatalysis promotes the asymmetric direct aldol reaction of two different aldehydes in the presence of water and no other additives, with high diastereo- and enantioselectivity. The original version of this reaction reported by MacMillan and Northup was carried out in a polar organic solvent under proline catalysis, with introduction of the aldehyde donor by syringe pump.^[8]

The reaction of *o*-chlorobenzaldehyde and propanal (5 equiv) was selected as a model and performed in the presence of 18 equivalents of water and several putative organocatalysts (10 mol %, 24 h; see Scheme 1). The aldols were isolated after reduction to the corresponding diols



Scheme 1. Organocatalysts examined in this study. TBDPS = *tert*-butyl-diphenylsilyl.

(Table 1). No reaction proceeded when proline (**1**), hydroxyproline (**2**), or proline-tetrazol (**3**)^[4a,9] were employed. With

Table 1: Effect of the organocatalyst and amount of water on the aldol reaction of *o*-chlorobenzaldehyde and propanal.^[a]

Entry	Catalyst	Amount of water [equiv]	Yield [%] ^[b]	<i>anti</i> / <i>syn</i> ^[c]	<i>ee</i> [%] ^[d]
1	1	18	< 5	–	–
2	2	18	< 5	–	–
3	3	18	< 5	–	–
4	4	18	30	2:1	71
5	5	18	50	8:1	98
6	6	18	14	18:1	96
7	7	18	17	20:1	95
8	8	18	39	14:1	96
9	9	18	57	18:1	97
10	10	18	60	20:1	99
11	11	18	54	17:1	96
12	12	18	15	> 20:1	96
13	13	18	32	11:1	94
14	10	0	71	16:1	97
15	10	5	58	17:1	97
16	10	54	65	12:1	94
17	10	125	58	13:1	95
18 ^[e]	10	18	92	19:1	99
19 ^[f]	10	18	97	19:1	99

[a] The reaction was conducted with 0.4 mmol of *o*-chlorobenzaldehyde and 2.0 mmol of propanal at 0 °C for 24 h. [b] Isolated yield. [c] Determined by ¹H NMR spectroscopy. [d] *ee* value of *anti* isomer, determined by chiral HPLC after conversion into the benzoyl ester (see Supporting Information). [e] The reaction was performed for 70 h. [f] The reaction was performed with 15 mmol of *o*-chlorobenzaldehyde and 45 mmol of propanal for 96 h.

siloxypoline,^[6,10] two phases were formed as previously described^[6] and the aldols were obtained with excellent diastereo- and enantioselectivities. The moderate yield can be ascribed to insufficient mixing of the reagents, as propanal is water-soluble while *o*-chlorobenzaldehyde is not. Emulsions may be the ideal reaction medium for achieving effective mixing, as demonstrated by Kobayashi et al. for several surfactant-combined organometallic catalysts, which promote organic reactions in water or aqueous organic solvents.^[2]

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[**] This work was partially supported by the Toray Science Foundation and a Grand-in-Aid for Scientific Research on Priority Areas 16073219 from MEXT.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

First, we examined proline *N*-sulfonyl amides **6** and **7** containing long alkyl chains (Scheme 1). Though similar *N*-arylsulfonyl amides are excellent aldol catalysts in organic solvents, as reported by Berkessel et al.^[11] and Ley and co-workers,^[9] **6** and **7** were found to be poor catalysts: an emulsion did not form in the reaction mixture, and the products were obtained in low yield. Next, we developed the novel catalysts **8–13**, which contain both a proline unit and a long alkyl chain and which were easily prepared in large quantities from commercially available L-4-hydroxyproline. An emulsion was formed in the reaction mixture and excellent diastereo- and enantioselectivities were attained using catalysts **8–13**, while the chain length dramatically affected the yield. Neither very long nor very short chains were effective, whereas catalyst **10** with a decanoate moiety was found to be the most efficient.

The yield was increased to 92 % on prolonging the reaction time (70 h). Diastereo- and enantioselectivities decreased slightly as the amount of water in the reaction was increased. The reaction also proceeded efficiently under neat reaction conditions, though slight decreases in diastereo- and enantioselectivities were observed. This result provides evidence that the reaction proceeds in the organic phase, created inside the emulsion when the reaction is performed in the presence of water. Note also that the reaction can be performed on a 15-mmol scale with 3 equivalents of propanal to afford 2.9 g of aldol with 99 % *ee* and 19:1 *anti* diastereoselectivity.

The generality of the reaction was also investigated (Table 2). The reaction was highly diastereo- and enantioselective, and hardly any dehydration products were generated in every case investigated. Not only propanal but also isovaleraldehyde and 3-phenylpropanal were successfully employed as the donor. Note the excellent diastereoselectivity obtained in entries 4 and 15 (Table 2), which is in marked contrast to the low d.r. (3:1) reported for the corresponding proline-mediated aldol reactions in DMF.^[8] The low yield obtained with aliphatic aldehydes such as cyclohexylcarbaldehyde and propanal can be ascribed to inefficient mixing due to insufficient hydrophobicity of the acceptor aldehydes, as only in these cases was an emulsion not formed. Commercially available aqueous dimethoxyacetaldehyde was also a successful acceptor (Table 2, entry 14). In their procedure using benzaldehyde as the acceptor, MacMillan and Northup employed an excess amount of benzaldehyde (10 equiv) with slow addition of propanal over 16 h.^[8] In the present protocol, the nucleophilic aldehyde (5 equiv) was used without slow addition. Although the self-aldol products of propanal were formed (ca. 30 %), they could easily be removed by column

Table 2: Enantioselective direct aldehyde cross-aldol reaction in the presence of water.^[a]

Entry	R ¹	R ²	<i>t</i> [h]	Yield [%] ^[b]	<i>anti/syn</i> ^[c]	<i>ee</i> [%] ^[d]
1	<i>o</i> -chlorophenyl	Me	70	92	18:1	99
2	<i>p</i> -chlorophenyl	Me	110	90	> 20:1	99
3	<i>p</i> -fluorophenyl	Me	110	76	> 20:1	99
4	phenyl	Me	73	88	> 20:1	99
5	2-naphthyl	Me	110	54	> 20:1	99
6	1-naphthyl	Me	80	49	> 20:1	98
7 ^[e]	<i>p</i> -tolyl	Me	68	65	> 20:1	99
8	<i>o</i> -methoxyphenyl	Me	72	83	20:1	95
9	<i>p</i> -methoxyphenyl	Me	70	38	> 20:1	97
10	cyclohexyl	Me	118	29	10:1	92
11 ^[f]	2-furyl	Me	68	58	8:1	92
12 ^[e]	<i>o</i> -chlorophenyl	<i>i</i> Pr	68	61	10:1	73
13 ^[e]	<i>o</i> -chlorophenyl	Bn	93	57	14:1	92
14 ^[g]	dimethoxymethyl	Bn	62	35	4:1	93
15 ^[f,g]	ethyl	Me	96	35	10:1	89

[a] Unless otherwise shown, the reactions were conducted with 0.4 mmol of acceptor aldehyde and 2.0 mmol of donor aldehyde and water (130 μ L) in the presence of 10 mol % of **10** at 0 °C. [b] Isolated yield. [c] Determined by ¹H NMR spectroscopy. [d] *ee* value of *anti* isomer (see Supporting Information). [e] 20 mol % of **10** was employed. [f] The reaction was performed at room temperature. [g] 3.8 equiv of water was employed.

chromatography. The same predominant enantiomer was formed as with L-proline in DMF,^[8] which indicates the involvement of a similar transition state to that reported.

In summary, we have developed a catalytic, direct asymmetric cross-aldol reaction of two different aldehydes in the presence of water, catalyzed by a novel combined proline–surfactant organocatalyst **10**. Neither organic cosolvent nor additional acid is necessary. Though the precise reaction mechanism is not clear at the moment, emulsions seem to offer an ideal reaction environment in the presence of water, in which organic molecules can be assembled through hydrophobic interactions thus enabling the aldol reaction to proceed efficiently.

Experimental Section

General procedure (Table 1, entry 19): *o*-Chlorobenzaldehyde (1.69 mL, 15.0 mmol), and then propanal (3.25 mL, 45 mmol) were added to a mixture of (2*S*,4*R*)-4-decanoyloxypyrrolidine-2-carboxylic acid (**10**; 413 mg, 1.5 mmol) and water (4.9 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 96 h, then MeOH (60 mL) and NaBH₄ (5.67 g, 150 mmol) were added. The reaction mixture was stirred for a further 1 h at 0 °C and was then quenched with pH 7.0 phosphate buffer solution. The organic materials were extracted with chloroform three times, and the combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated in vacuo after filtration. Purification by column chromatography (silica gel; hexane/AcOEt 20:1 to 3:1) gave (1*R*,2*R*)-1-(*o*-chlorophenyl)-2-methylpropane-1,3-diol (2.9 g, 14.5 mmol, 97 %) as a colorless oil: *anti/syn* 19:1 (by ¹H NMR spectroscopy of the crude mixture). Enantioselectivity was determined after conversion into the corresponding monobenzoylester: 99 % *ee* (by HPLC on a Chiralpak AS-H column, λ = 254 nm,

*i*PrOH/hexane 1:100, 1.2 mL min⁻¹; *t*_R = 15.2 min (major), 17.2 min (minor)).

Received: March 23, 2006

Revised: June 7, 2006

Published online: July 20, 2006

Keywords: aldol reaction · asymmetric synthesis · green chemistry · organocatalysis · surfactants

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