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Highly Efficient and Reusable Dendritic Catalysts Derived from *N*-Prolylsulfonamide for the Asymmetric Direct Aldol Reaction in Water

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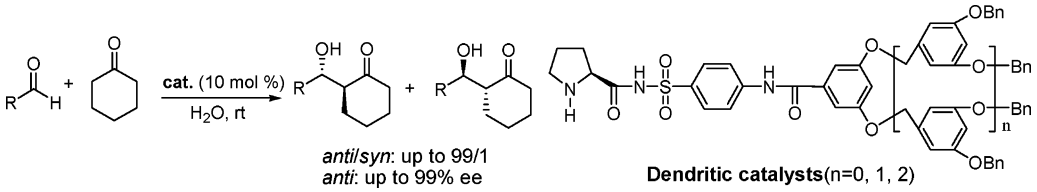
ABSTRACT



The direct aldol reactions catalyzed by chiral dendritic catalysts derived from *N*-prolylsulfonamide gave the corresponding products in high isolated yields (up to 99%) with excellent *anti* diastereoselectivities (up to >99:1) and enantioselectivities (up to >99% ee) in water. In addition, catalyst 1e may be recovered by precipitation and filtration and reused for at least five times without loss of catalytic activity.

The aldol reaction is recognized as one of the most powerful carbon−carbon bond-forming reactions in modern organic synthesis.[1] The great synthetic usefulness of the catalytic asymmetric aldol reaction has powered a rapid evolution of numerous highly enantioselective chiral catalysts, and in recent years, more attention has been paid to developing organocatalysts for the asymmetric direct aldol reactions.[2]

Because water is safe, economical, and environmentally benign, it has been employed in catalytic asymmetric reactions as a substitute for conventional organic solvents.[3] The development of catalytic asymmetric direct aldol reactions in aqueous organic solvents has been explored by using metal complexes.[4] Although organocatalysts (such as proline and several chiral diamines) showed the catalytic activity for the direct aldol additions in buffered aqueous media, the observed diastereo- and enantioselectivities are still disappointing.[2h,5] In contrast, the biochemical aldol reactions catalyzed by the aldolases and antibodies occur perfectly in aqueous media.[6] The use of aldolases and antibodies, however, has been

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seldom applied in practical synthesis, presumably because of their narrow substrate scope. To achieve highly catalytic activity and excellent enantioselectivity of organic reactions in water, much effort has been devoted to understanding the nature of the interrupting ionic interactions, hydrogen bonds, and hydrophobic interactions in aqueous media.[7] Very recently, Takabe[8] and Hayashi[9] independently reported highly diastereo- and enantioselective direct aldol reactions in water. Nonetheless, development of new organocatalysts for the direct asymmetric aldol reactions in water is still warranted to achieve high reactivity and high diastereo- and enantioselectivity, as well as catalyst recovery and reuse.

Dendrimers are well-defined macromolecules with controllable structures, which offer a unique tool for fine-tuning catalytic activity through their microenviroment. Other advantages of dendritic catalysts include the combination of both homogeneous and heterogeneous catalysis[10] and possibile catalyst recovery by using membrane, nanofiltration techniques[11] or selective precipitation.[12] Recently, we have reported the synthesis of some new polyether dendritic chiral pyrrolidinylmethanol derivatives and their applications in catalytic asymmetric reactions.[13] Herein, we wish to report that the recyclable chiral amphiphilic dendritic catalysts derived from prolyl *N*-sulfonamides catalyze highly diastereo- and enantioselective direct aldol reactions in water, resulting in the corresponding *anti* aldol products in a nearly optically pure form.

Prolyl *N*-sulfonamides (**C2**) have been used in some catalytic asymmetric reactions.[14] Structurally similar to proline (**C1**) and *N*-(2-pyrrolidinylmethyl)sulfonamides (**C3**),[15] these compounds (**C2**) are expected to have a broad range of applications in asymmetric catalysis (Figure 1). We

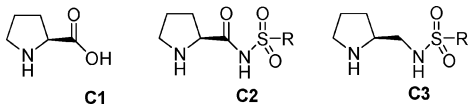
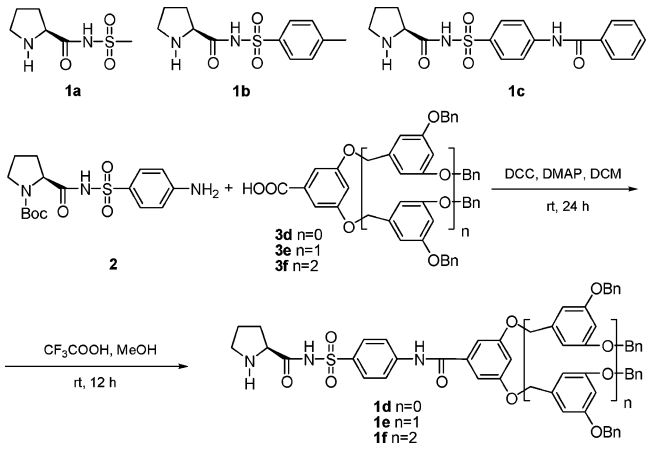


Figure 1. Structure of proline and its devative organocatalysts.

hypothesized that the prolyl *N*-sulfonamide compounds (**C2**) with polyether dendritic wedges as hydrophobic groups should assemble with hydrophobic reactants in water and sequester the transition state from water and, therefore, high asymmetric induction may be achieved in water.[8,9] Thus, we synthesized a series of chiral dendritic catalysts derived from prolyl *N*-sulfonamides and investigated their catalytic activities in the asymmetric direct aldol reaction in water.

The synthetic procedures for dendritic catalysts **1d**−**f** are shown in Scheme 1. The reaction of Boc-L-proline with

Scheme 1



4-nitrobenzsulfonamide provided **2**, which was then reacted with **3d**−**f**, followed by deprotecting the Boc group to give

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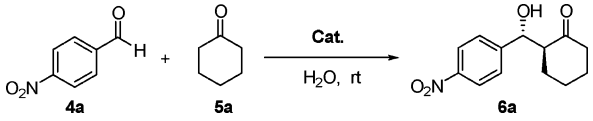
1d−**f** in moderate yields. These ligands were purified by flash column chromatography and characterized by ^{1}H NMR spectra, MALDI mass spectrometry, and elemental analyses. All results were in full agreement with the proposed structures. Catalysts **1a**,[16] **1b**,[12a,14c−d] and **1c** were also synthesized for comparison of their reactivty and efficiency with **1d**−**f** (see Supporting Information).

The catalytic activity of **1a**−**f** for the asymmetric direct aldol reaction was investigated by performing a model reaction of 4-nitrobenzaldehyde and cyclohexanone. In our initial experiment, the reaction was performed in water using a catalytic amount (10 mol %) of prolyl *N*-sulfonamide, while other conditions were the same as reported for organocatalyzed direct asymmetric aldol reaction.[8a,9] The results are summarized in Table 1.

Table 1. Effect of Catalyst on the Reaction of 4-Nitrobenzaldehyde with Cyclohexanone[a]



entry	catalyst	catalyst loading (mol %)	time (h)	yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	**1a**	10	24	58	96:4	97
2	**1b**	10	24	66	97:3	97
3	**1c**	10	24	84	94:6	94
4	**1d**	10	24	92	97:3	98
5	**1e**	10	24	99	99:1	99
6	**1f**	10	24	86	99:1	99
7	**1e**	20	20	99	98:2	>99
8	**1e**	5	48	99	97:3	98
9	**1e**	2	48	75	96:4	98
10[e]	**1e**	**10**	**24**	**99**	**>99:1**	**>99**
11[f]	**1e**	10	24	99	97:3	97

[a] The reaction was performed with **1** (0.05 mmol), **4a** (76 mg, 0.5 mmol), water (1 mL), and **5a** (0.103 mL, 1.0 mmol) at room temperature. [b] Combined yields of isolated diastereomers. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis of the *anti* product. [e] 3 equiv of **5a** was used in this reaction. [f] 5 equiv of **5a** was used in this reaction.

It is interesting to find that the aldol reaction proceeds efficiently in water, and excellent results were obtained with these catalysts. The *anti*-aldol products were obtained as the major product in good to excellent yields (58−99%) with high diastereoselectivity and enantioselectivity. As expected, the dendritic catalysts **1d**−**f** bearing more hydrophobic groups showed much better reactivity and higher selectivity than catalysts **1a**−**c** with less hydrophobic groups. Notably, the second generation catalyst **1e** provided the best results in isolated yields, diasteroselectivity and enantioselectivity

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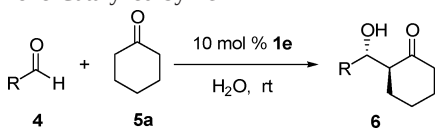
Table 2. Results of Reaction of Various Aldehydes with Cyclohexanone Catalyzed by **1e**[a]



entry	R	product	time (h)	yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	4-$O_2NC_6H_4$-	**6a**	24	99	>99:1	>99
2	3-$O_2NC_6H_4$-	**6b**	24	99	97:3	>99
3	2-$O_2NC_6H_4$-	**6c**	24	99	98:2	99
4	4-$F_3CC_6H_4$-	**6d**	24	95	99:1	99
5	4-NCC_6H_4-	**6e**	24	97	>99:1	98
6	4-FC_6H_4-	**6f**	72	85	98:2	95
7	4-ClC_6H_4-	**6g**	72	87	99:1	99
8	4-BrC_6H_4-	**6h**	72	91	98:2	99
9	2,4-$Cl_2C_6H_3$-	**6i**	48	95	99:1	97
10	C_6H_5-	**6j**	48	94	98:2	96
11	4-MeC_6H_4-	**6k**	72	57	94:6	95
12	4-$MeOC_6H_4$-	**6l**	72	31	96:4	96
13	4-$BnOC_6H_4$-	**6m**	72	36	99:1	>99
14	1-naphthyl-	**6n**	48	82	93:7	89
15	2-naphthyl-	**6o**	48	98	99:1	>99
16	2-furanyl-	**6p**	72	94	98:2	81
17	4- pyridinyl-	**6q**	24	98	87:13	94
18	cyclohexyl-	**6r**	48	62	93:7	96

[a] The reaction was performed with **1e** (0.05 mmol), **4** (0.5 mmol), water (1 mL), and **5a** (0.154 mL, 1.5 mmol) at room temperature. [b] Combined yields of isolated diastereomers. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis of the *anti* product.

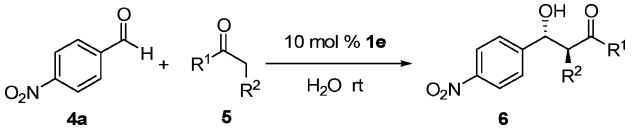
(Table 1, entry 5). The third generation catalyst **1f** showed a comparable selectivity, but a drop in reactivity was observed (Table 1, entry 6). The higher generation catalysts **1d** and **1f** are sparingly soluble in water; stable emulsions were formed upon addition of the aldehyde and cyclohexanone with vigorous stirring in water.

Thus, catalyst **1e** was selected for the subsequent studies. First, the influence of catalyst loading on the reaction was examined (Table 1, entries 5 and 7−9). It is found that a higher enantioselectivity was observed by increasing the catalyst amount to 20 mol %; the reaction was slightly faster, but the diastereoselectivity dropped slightly (Table 1, entry 7 vs 5). The reaction slowed remarkably and a significant drop in diastereoselectivity was observed by decreasing the catalyst loading to 5 mol % and further to 2 mol %. Examination of the effects of reactants ratio on the reaction indicated that 3 equiv of donor cyclohexanone to 1 equiv of acceptor aldehyde gave the best results (Table 1, entry 10). Thus, the optimum reaction conditions are achieved by performing the reaction of 3 equiv of cyclohexanone with 1 equiv of aldehyde and 10 mol % catalyst loading in water.

The major product **6a** generated from **1e** has (2*S*,1*R*)[8a] absolute stereochemistry. Therefore, the enamine intermediate catalyzed by **1e** favors a *re*-facial attack on the arylaldehyde, which is in accord with that of L-proline-catalyzed aldol reactions in DMSO.[8a,17]

To examine the scope of the aldol reactions by using the dendritic catalyst **1e** in water, a series of aldehydes were evaluated under the optimized reaction conditions, and the results are summarized in Table 2. In general, regardless of the electronic nature of the aromatic aldehydes, excellent diastereoselectivities and enantioselectivities were obtained. For the electon-deficient aromatic aldehydes (Table 2, entries 1−9 and 17), the reaction proceeded smoothly to afford the aldol adducts in 24 h. For the neutral and electon-rich aromatic aldehydes (Table 2, entries 11−13), the reactions commonly required a longer time (72 h), and lower isolated yields were obtained for electon-rich ones (Table 2, entries 11−13). It is worthy to note that reaction of the aliphatic cyclohexanecarboxaldehyde with cyclohexanone also afforded the corresponding aldol product with an excellent diastereoselectivity and enantioselectivity under the same conditions (Table 2, entry 18). Other ketones were also evaluated under the same conditions, and the aldol products were obtained in good yields with high enantioselectivities, albeit with somewhat decreased diastereoselectivities (Table 3).

Table 3. Reaction of Various Ketones with 4-Nitrobenzaldehyde Catalyzed by **1e**[a]



entry	R^1	R^2	product	time (h)	yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	$-(CH_2)_3-$		**6s**	18	96	79:21	98
2	$-(CH_2)_5-$		**6t**	72	59[f]	77:23	99
3[e]	CH_3	H	**6u**	72	71[f]		87
4[e]	CH_3	CH_3	**6v**	72	70[f]	87:13	89

[a] The reaction was performed with **1e** (0.05 mmol), **4a** (0.5 mmol), water (1 mL), and **5** (0.154 mL, 1.5 mmol) at room temperature. [b] Combined yields of isolated diastereomers. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis of the *anti* product. [e] 20 equiv of **5** was used in this reaction. [f] Aldehyde **4a** recovery was 35%, 23%, and 26%.

One major advantage of dendritic catalysts is that they may be easily separated from reaction mixtures through precipitation due to the solubility change in different solvents. Thus, different solvents were tested (Table 4) to precipitate the dendritic catalysts in an effort to recover the catalyst, and we found that a cosolvent of *n*-hexane/EtOAc (1:1) is the best one (entry 5). After the completion of the reaction, catalyst **1e** may be quantitatively recovered by simply adding 1:1 *n*-hexane/EtOAc to the reaction mixture. Furthermore, it was found that the recovered catalyst may be reused five times without loss of reactivity and enantioselectivity (Table 4, entries 5−9).

Table 4. Recovery of Catalyst **1e** in the Aldol Reaction of **4a**[a]

entry	catalyst	recovery solvent	product yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)	yield of recovered catalyst (%)
1	**1e**	MeOH	92	>99:1	>99	98
2	**1e**	Et_2O	95	>99:1	>99	96
3	**1e**	EA	99	>99:1	>99	90
4	**1e**	*n*-hexane	<50	>99:1	>99	>99
5	**1e**	*n*-hexane/EtOAc[e]	99	>99:1	>99	94
6	**1e**[f]	*n*-hexane/EtOAc[e]	99	99:1	>99	95
7	**1e**[g]	*n*-hexane/EtOAc[e]	97	99:1	>99	97
8	**1e**[h]	*n*-hexane/EtOAc[e]	99	99:1	>99	94
9	**1e**[i]	*n*-hexane/EtOAc[e]	99	>99:1	>99	96

[a] The reaction was performed with **1e** (0.05 mmol), **4a** (0.5 mmol), water (1 mL), and cyclohexanone (0.154 mL, 1.5 mmol) at room temperature. [b] Combined yields of isolated diastereomers. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis of the *anti* product. [e] Ratio of *n*-hexane and EtOAc is 1:1. [f] Recovered catalyst was used (cycle 1). [g] Recovered catalyst was used (cycle 2). [h] Recovered catalyst was used (cycle 3). [i] Recovered catalyst was used (cycle 4).

In conclusion, we have synthesized some chiral dendritic catalysts derived from prolyl *N*-sulfonamide. The catalysts may be used in the asymmetric direct aldol reactions in water, a safe, economical, and environmentally benign solvent, to generate the products in good to excellent yields (up to 99%) with excellent diastereoselectivities (up to >99:1) and enantioselectivities (up to >99%). Furthermore, these dendritic catalysts may be recovered and reused without loss of reactivity.

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Supporting Information Available: General experimental methods, analytic data and spectra of the corresponding compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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