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Highly Enantioselective Aldol Reactions Catalyzed by a Recyclable Fluorous (*S*) Pyrrolidine Sulfonamide on Water

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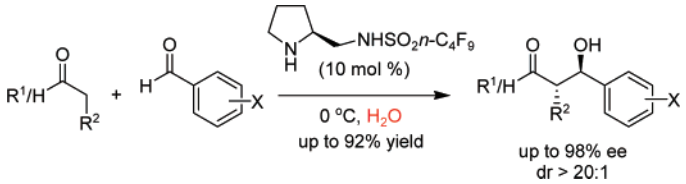
ABSTRACT



Fluorous (*S*) pyrrolidine sulfonamide serves as an efficient promoter for highly enantioselective aldol reactions of ketones and aldehydes with aromatic aldehydes on water. A notable feature of the organocatalyst is that it can be recovered from the reaction mixtures by simple fluorous solid-phase extraction and subsequently reused (up to seven cycles) without a significant loss of catalytic activity and stereoselectivity.

Interest in organocatalysis has increased spectacularly in the past few years as a result of both the novelty of the concept and unique activation modes and, more significantly, because of the fact that the operational simplicity, less toxicity, efficiency, and selectivity make many organocatalytic reactions superior to those carried out using more conventional methods.[1] However, their drawbacks also have been realized. One of the major limitations using organocatalyst catalyzed reactions is high catalyst loadings (10−30 mol %) generally required to complete the transformations in reasonable timescales. This will raise a cost concern when a large amount of chiral materials are used for a large scale of synthesis in industrial applications. In spite of significant efforts devoted to the development of highly active organocatalysts aimed at lowering catalyst loading, it has proved to be a significant challenging task, and limited success has been achieved so far. An alternative strategy is to design recyclable and subsequently reusable versions of organocatalysts.

Despite the fact that the original ideas behind organocatalysis arise from enzyme active site motifs that display their catalytic activity in natural aqueous environments,[2] organocatalytic reactions have thus far typically been carried out in organic solvents because water interferes with organocatalysts and disrupts hydrogen bonds and other polar interactions, accordingly in many cases deteriorating catalytic activity and stereocontrol. On the other hand, water is an ideal reaction medium, as it offers unparalleled and unique features: cheap, clean, easy to handle, hazardless, and environmentally benign.[3] Therefore, the development of organocatalytic asymmetric reactions using water as the reaction medium has received considerable interest.[4−6] Meanwhile, efforts also have been made on organocatalyst recycling using ionic liquids, solid-phase support, and fluorous

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(3) For reviews on organic synthesis in water, see: (a) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751. (b) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (c) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997.

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technologies.[7−10] However, to the best of our knowledge, no such organoctalyst has been reported, which possesses unique features of promoting asymmetric transformations on water and convenient recovery and reuse.

To this end, recently our group has developed the first water-compatible and readily recyclable organocatalyst, fluorous (*S*) pyrrolidine sulfonamide **I** (Figure 1), and

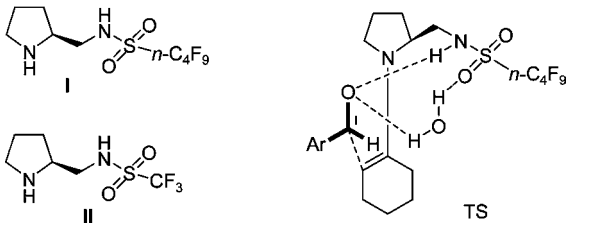

Figure 1. Chiral pyrrolidine sulfonamide organocatalysts and a proposed transition state model of aldol reaction.

successfully employed this unique organocatalyst to a highly enantioselective Michael addition reaction of ketones and aldehydes with nitroolefins.[8] In our continuing effort on expanding the scope of this useful organocatalytic system, in this communication, we wish to describe a study, which has resulted in a highly enantioselective aldol reaction—one of the most important carbon−carbon bond-forming reactions in organic synthesis.

The analogue (*S*) pyrrolidine trifluoromethane sulfonamide **II** has been demonstrated for a highly enantioselective aldol reaction in an aprotic DMSO rather than in water.[11] The question is whether the fluorous (*S*) pyrrolidine sulfonamide **I** can be applied for catalyzing the same process in water with a similar efficiency since as discussed above, generally, the use of water as the reaction medium leads to poor catalytic activity and enantioselectivity as a result of disrupting the interactions between substrates and catalyst in the transition state.

On the basis of the unique structural features of the catalyst **I**, we contemplated that **I** could catalyze an aldol reaction in water with high catalytic activity and high stereocontrol. As observed, catalyst **II** displays high catalytic activity and stereoselectivity as a result of unique activation modes of involving two H-bond interactions where the sulfonamide group, substrate, and water are involved (Figure 1).[12] This implies that water is beneficial to the process. Moreover, the strong electron-withdrawing effect of the fluorous tag in **I** enhances the acidity of the NH proton of the sulfonamide and thus provides a stronger hydrogen-bonding interaction with the substrate. Finally, the fluorous tag can also provide a handle for the catalyst recycle by using the fluorous solid-phase extraction technique.[9,10]

To test the hypothesis, we carried out a model reaction of an aqueous solution of cyclohexanone **1a** and 4-nitro benzaldehyde **2a** in the presence of 10 mol % of fluorous (*S*) pyrrolidine sulfonamide **I** (Table 1). Initially, a reaction with a ratio of 2:1 of **1a**/**2a** at rt was performed, and an emulsive mixture was observed, indicating a heterogeneous system was involved (entry 1). The process proceeded smoothly, and the desired product **3a** was obtained in 90% yield. However, moderate ee (70%) and poor dr (2:1) were observed. Lowering temperature to 0 °C resulted in enhancing the enantioselectivity and dr but prolonged the reaction

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(5) For examples of organocatalyzed aldol reactions in aqueous environment, see: (a) Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 3220. (b) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, Yamamoto, S. H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983. (c) Cordova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586. (d) Samanta, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321. (e) Dziedzic, P.; Zou, W.; Hafren, J.; Cordova, A. *Org. Biomol. Chem.* **2006**, *4*, 38. (f) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317. (g) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 734. (h) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958. (i) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5527. (j) Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653. (k) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417. (l) Chen, X.-H.; Luo, S.-W.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Chem.−Eur. J.* **2007**, *13*, 689. (m) Huang, W.-P.; Chen, J.-R.; Li, X.-Y.; Cao, Y.-J.; Xiao, W.-J. *Can. J. Chem.* **2007**, *85*, 208. (n) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593. (o) Wu, X.; Jiang, Z.; Shen, H.-M.; Lu, Y. *Adv. Synth. Catal.* **2007**, *349*, 812. (p) Aratake, S.; Itoh, T.; Okano, T.; Usui, T.; Shoji, M.; Hayashi, Y. *Chem. Commun.* **2007**, 2524. (q) Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2008**, *10*, 337.

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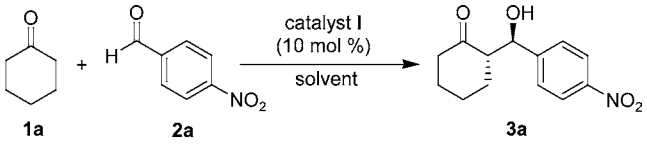
Table 1. Exploration of Fluorous (*S*) Pyrrolidine Sulfonamide Promoted Aldol Reaction of Cyclohexanone **1a** with 4-Nitrobenzaldehyde **2a** on Water[a]



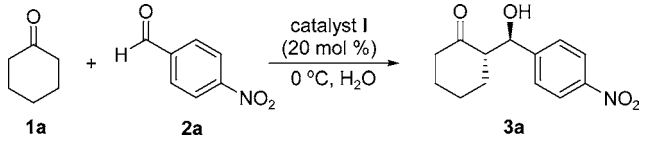
1a **2a** **3a**

entry	ratio **1a/2a**	*T* (°C)	solvent	*t* (h)	yield (%)[b]	ee (%)[c]	dr[d]
1	2:1	rt	H_2O	12	90	70	2:1
2	2:1	0	H_2O	24	60	83	4:1
3	5:1	0	H_2O	20	90	86	4.5:1
4	10:1	0	H_2O	9	92	90	5:1
5	10:1	rt	H_2O	8	95	73	2:1
6	10:1	rt	DMSO	10	90	55	4:5
7	10:1	0	neat	18	95	60	2:1

[a] Unless specified, a mixture of cyclohexanone (**1a**) with a specified amount and catalyst **I** (7.62 mg, 0.01 mmol) in a solvent (0.2 mL) or neat condition was stirred for 20 min followed by the addition of 4-nitrobenzaldehyde (**2a**) (15.1 mg, 0.1 mmol), and the mixture was stirred for a specified reaction time period. [b]Isolated yields. [c]Determined by chiral HPLC analysis (Chiralcel OD−H). [d]Determined by ^{1}H NMR.

time (entry 2). The reaction efficiency dramatically improved when the donor/acceptor ratio was increased (entries 3 and 4). When the reaction was carried out in DMSO (entry 6) or a neat condition (entry 7), poorer enantioselectivities were observed. This implies that water plays a role in governing the selectivity (Figure 1). These studies prompted us to choose the reaction conditions using **1a**/**2a** with a ratio of 10:1 at 0 °C in water for evaluation of the feasibility of the catalyst recycling by employing the fluorous silica gel based solid−liquid extraction technique.

Table 2. Recycling and Reuse of Fluorous (*S*) Pyrrolidine Sulfonamide Promoted Aldol Reaction of Cyclohexanone **1a** with 4-Nitrobenzaldehyde **2a** on Water[a]

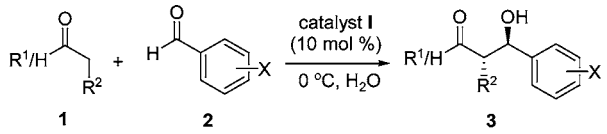


1a **2a** **3a**

cycle	*t* (h)	yield (%)[b]	ee (%)[c]	dr[d]
1	6	90	90	5:1
2	7	92	90	5:1
3	12	90	90	5:1
4	13	90	90	5:1
5	19	91	89	5:1
6	24	92	87	5:1
7	40	88	87	5:1

[a] Unless specified, a mixture of cyclohexanone (**1a**) (98 mg, 1 mmol) and catalyst **I** (7.62 mg, 0.02 mmol) in H_2O (0.2 mL) were stirred at 0 °C for 20 min followed by the addition of 4-nitrobenzaldehyde (**2a**) (15.1 mg, 0.1 mmol), and the mixture was stirred at 0 °C for a specified reaction time period. See the procedure for catalyst recovery in Supporting Information. [b]Isolated yields. [c]Determined by chiral HPLC analysis (Chiralcel OD−H). [d]Determined by ^{1}H NMR.

Table 3. Catalytic Asymmetric Aldol Reactions of Ketones and Aldehydes **1** with Aromatic Aldehydes **2**[a]



1 **2** **3**

entry	product	t (h)	yield (%)[b]	ee (%)[c]	dr[d]
1	**3a**	9	92	90	5:1
2	**3b**	72	80	90	>20:1
3	**3c**	24	92	89	11:1
4	**3d**	24	93	86	5.5:1
5	**3e**	72	86	92	7:1
6	**3f**	72	73	93	>20:1
7	**3g**	22	88	94	5.5:1
8	**3h**	24	85	70	1:1
9	**3i**	24	75	97	>20:1
10	**3j**	59	87	93	-

[a] Unless specified, see footnote *a* in Table 2. [b]Isolated yields. [c]Determined by chiral HPLC analysis (Chiralpak AS−H or Chiralcel OD−H). [d]Determined by ^{1}H NMR.

When 20 mol % of fluorous (*S*) pyrrolidine sulfonamide **I** was employed to promote the aldol reaction of cyclohexanone **1a** with 4-nitro benzaldehyde **2a** (Table 2), we found that the fluorous (*S*) pyrrolidine sulfonamide was cleanly recovered (>90%) from the reaction mixture by the simple fluorous solid-phase extraction, and the catalyst could be repeatedly reused (see Supporting Information for details). In each run, the recovered catalyst retained its high activity, high levels of enantioselectivity (>87% ee), and good

diastereoselectivity (5:1 dr) even after seven cycles despite some degree of loss of activity observed in cycles 2−7.

Having established the recoverable and reusable capacity of the fluorous (*S*) pyrrolidine sulfonamide, we next probed the generality of its use as a promoter for aldol reactions. As revealed in Table 3, the processes proceeded smoothly with 10 mol % of catalyst and gave rise to highly enantioenriched adducts in good yields. Significant structural variation of aromatic aldehydes, which possess either electron-donating (entry 6) or withdrawing (entries 1−5, 7) groups and contain a variety of substitution patterns (*para*-, *meta*- and *ortho*-, entries 1−7), could efficiently participate in the process with achieving high enantioselectivities (86−94% ee) and good to high diastereoselectivities (>5:1). The catalytic system also worked out for the challenging substrate cyclopentanone. In this instance, the aldol process proceeded smoothly in high yield (85%) and with good enantioselectivity (70% ee) (entry 8). Moreover, notably, in addition to ketones, aldehydes could also participate in this aqueous aldol reaction as donors with excellent levels of enantioselectivity (entries 9 and 10), and this greatly expands the scope of the reaction. Even more significant was the observation that *iso*-butyraldehyde underwent the fluorous (*S*) pyrrolidine sulfonamide catalyzed aldol reaction with 4-nitro benzaldehyde to furnish a product containing adjacent quaternary and tertiary carbon centers with results similar to those we obtained using catalyst **II** in DMSO (entry 10).[11,13] The limitation of the **I**-catalyzed aldol process was also realized. No reaction occurred for less reactive acceptors, such as benzaldehyde, probed.

In conclusion, the results from the investigation demonstrate that the fluorous (*S*) pyrrolidine sulfonamide is a robust and effective catalyst for highly enantioselective aldol reactions on water, and it is readily recovered and reused without significant loss of catalytic activity and stereoselectivity. Expanding the scope of the unique organocatalyst catalyzed asymmetric transformations is underway in this laboratory.

Acknowledgment. We are grateful for the generous financial support from the National Science Foundation (CHE-0704015) and for the kind gift from the American Chemical Society-PRF (G1 type).

Supporting Information Available: Experimental procedures and spectral data for compounds **3a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) To our knowledge, there are only two examples of organocatalyzed asymmetric aldol reactions involved in the formation of stereogenic quaternary carbon centers by Barbas and co-workers and us: (a) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420 and ref 11. It is noted that a much shorter reaction time (2 h) for the same reaction is observed in the study reported by Barbas.