The Organocatalytic Enantioselective Michael Addition of Aldehydes to Vinyl Sulfones in Water

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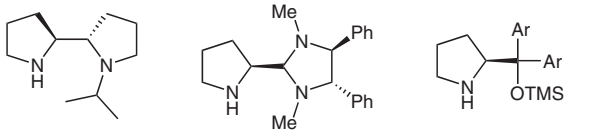
Abstract: The first organocatalytic enantioselective Michael addition of aldehydes to vinyl sulfones in water was achieved using our rationally designed organocatalyst. The rigid nature of the tricycle with an inherent chiral pocket provides a well-organized chiral environment, which together with the hydrophobic pocket, enabled this elusive reaction to proceed smoothly in water.

Key words: organocatalytic, vinyl sulfone, Michael addition, aqueous reaction

The pursuit of efficient and environmentally benign methods for the construction of C–C bonds has always been an important goal in contemporary organic synthesis. Water as a reaction medium to perform organic reactions has attracted much attention due to its cheap, safe, and environmentally benign character.[1] Furthermore, the unique physical and chemical properties as well as its important role in biological system stimulate new reactions and new reactivities, rendering the study of water-based reaction highly appealing for biomimetic chemistry. In this context, enantioselective C–C bond formation in water[2] is far more challenging, while organocatalytic reactions in water[3] provide another green approach to enantiomerically enriched compounds given that general metal catalysts are not stable in water.

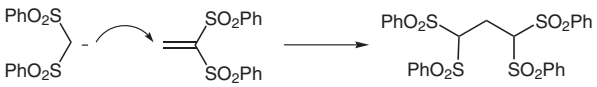
Sulfones are very useful and versatile intermediates in organic synthesis, and the asymmetric Michael addition of aldehydes to vinyl sulfones provides facile access to various optically pure sulfones, as well as a wide range of highly functionalized chiral synthons after desulfonylation.[4] Despite its importance in organic synthesis, however, only sporadic reports of asymmetric organocatalytic Michael addition of aldehydes to vinyl sulfones had surfaced to date, while the reaction of preformed enamine from ketones with vinyl sulfones is long recognized.[5] In 2005, Alexakis and co-workers reported the first organocatalytic conjugate addition of aldehydes to vinyl bis(sulfone) by use of the isopropyl-substituted bipyrrolidine (iPBP) catalyst **1** to afford the product in modest to good enantioselectivities (up to 80% ee).[6a] Later the same group reported higher enantioselectivity could be achieved using the catalyst **2** (Figure 1).[6] Soon after that, Palomo group[7] and Lu group[8] independently found that diphenylprolinol silyl ether catalyst **3** could efficiently catalyze this reaction in high enantioselectivity (Figure 1). However, in these limited reports, high catalyst loading (up to 25 mol%) and low temperature (–60 °C) were necessary to get reasonable yields and good enantioselectivities.



1 **2** **3a** Ar = Ph **3b** Ar = 3,5-$(CF_3)_2C_6H_3$

Figure 1

Moreover, it has been found that water has a detrimental effect to this reaction and leads to undesirable side products which necessitate the use of anhydrous $CHCl_3$ as solvent, regardless of the fact that organocatalysts have been recognized as the simplest 'enzyme' mimick, which can promote organic reactions in water. This is because water will accelerate the formation of dimeric side products by retroaddition of vinyl sulfone with in situ generated bis(phenylsulfonyl)methane anions (Scheme 1). The elusive character of this reaction seemingly makes it impossible carry out this reaction in water. In sharp contrast to the sizeable reports on the asymmetric conjugate addition of aldehydes to nitroolefins in water,[9] there is still no report on the asymmetric Michael addition of aldehydes to vinyl sulfones in water since it is a challenging task. From the point of view of the synthetic convenience and energy saving, the development of this reaction in water at room temperature is highly desirable.



Scheme 1

In continuation of the development of new green organic synthetic methods and new reactions in water, we recently became interested in developing new chiral ligand and water-tolerant chiral organocatalyst.[10] Towards this goal, we have rationally designed tricyclic structurally rigid organocatalyst **I** inspired by the unique conformation of the hexahydropyrrolo[2,3-*b*]indole natural product skeleton,[11] surpassing proline to accomplish the work that pro-

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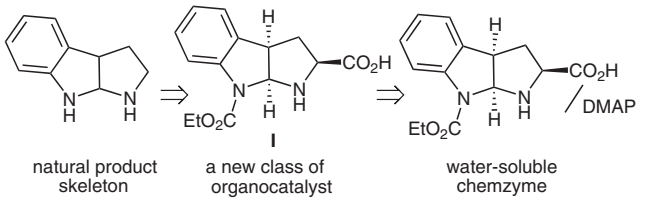
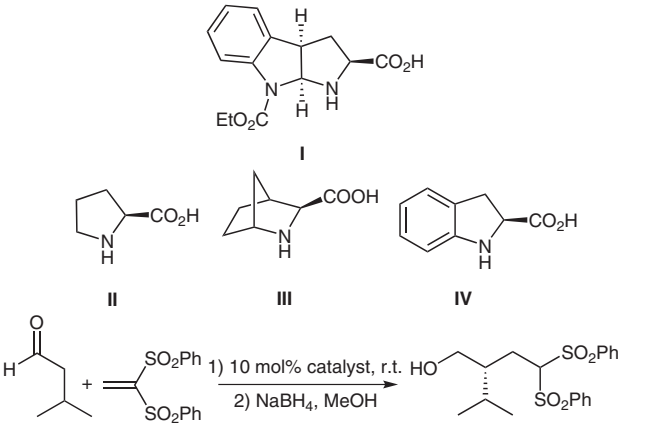
line fails. It has been found that **I**/DMAP could efficiently catalyze the asymmetric Michael addition of aldehydes to nitroalkenes both in organic solvent and in water in high yields and excellent enantioselectivities (Scheme 2).[10c]

The chiral pocket embedded in this catalyst and its chemzymatic behavior encouraged us to investigate its catalytic ability in other organocatalytic reactions in water, especially those which cannot be achieved using current methods. Herein, we report the first organocatalytic enantioselective Michael addition of aldehydes to vinyl sulfones in water at room temperature by use of our rationally designed catalyst **I**/DMAP, and the chiral adducts were obtained in modest to good enantioselectivities.



Scheme 2

Table 1 Asymmetric Michael Addition of Isovaleraldehyde to Vinyl Sulfone[a]



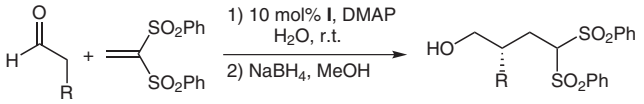
Entry	Catalyst	Solvent	Yield (%)[b]	ee (%)[c]
1	**I**	$CHCl_3$	41	56
2	**I**	MeOH	38	88
3	**II**	MeOH	33	17
4	**III**	MeOH	25	34
5	**IV**	MeOH	<10	n.d.[d]
6	**I**/DMAP	MeOH	28	64
7	**I**/DMAP	H_2O	53	73
8	**I**	H_2O	n.r.[e]	n.d.
9	**I**/NaOH	H_2O	n.r.	n.d.
10	**II**/DMAP	H_2O	n.r.	n.d.
11	**III**/DMAP	H_2O	n.r.	n.d.
12	**IV**/DMAP	H_2O	n.r.	n.d.

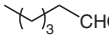
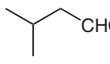
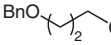
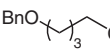
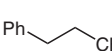
[a] The reactions were performed with isovaleraldehyde (0.4 mmol), vinyl sulfone (0.1 mmol), and catalyst (0.01 mmol) in solvent (0.5 mL) at r.t., unless otherwise specified.
[b] Purified yield after column chromatography.
[c] The ee value was determined by chiral HPLC analysis on the corresponding primary alcohol.
[d] n.d. = not determined.
[e] n.r. = no reaction.

At the outset, the Michael addition of isovaleraldehyde to vinyl sulfone was selected as the model reaction, and some similar chiral amino acid organocatalysts **II**–**IV** were also screened (Table 1). The generally used solvent chloroform is not good for our catalyst **I** (Table 1. entry 1). Although good enantioselectivity was observed in methanol, the yield was low (Table 1, entry 2). Catalyst **II**, **III**, and **IV** gave much less desirable results in methanol (Table 1, entries 3–5). The yield and enantioselectivity was not improved after addition of DMAP, but gave acceptable results in water (Table 1, entries 6 and 7). However, no reaction was observed when the reaction was carried out in pure water using either **II**/DMAP, **III**/DMAP, **IV**/DMAP, **I**/NaOH, or **I** itself (Table 1, entries 8–12). This interesting phenomenon is consistent with the observations in the Michael addition of aldehydes to nitroalkenes, and further demonstrated the superiority of catalyst **I**. The chiral pocket of **I** serves as a catalytic site by assembling hydrophobic reactants in water, thereby sequestering water from the transition state and function as a chemzyme to successfully promote this reaction in water.

Next, different substrates were screened to examine the generality of the reaction (Table 2).[12] As we can see from Table 2, different aldehydes, either linear or branched aldehydes, can be applied to this reaction. The chiral ad-

Table 2 Asymmetric Michael Addition of Aldehydes to Vinyl Sulfone[a]



Entry	Aldehydes	Yield(%)[b]	ee (%)[c]
1		41	59
2		49	58
3		54[d]	73
4		59	63
5		44	70
6		62	50

[a] The reactions were performed with aldehydes (1 mmol), vinyl sulfone (0.1 mmol), and catalyst (0.01 mmol) in H_2O (0.5 mL) at r.t., unless otherwise specified.
[b] Purified yield of aldehyde adduct after column chromatography.
[c] The ee value was determined by chiral HPLC analysis on the corresponding primary alcohol.
[d] Aldehyde used: 4 equiv.

ducts could be acquired in moderate yields and modest to good enantioselectivities in pure water using our catalyst **I**/DMAP.

In summary, we have disclosed the first organocatalytic Michael additions of aldehydes to vinyl sulfones in water. Although it is quite challenging to carry out this reaction in water, our catalyst **I**/DMAP could promote this reaction smoothly in water with moderate yields and modest to good enantioselectivities. However, for proline and other amino acid catalysts, they all failed to catalyze the reaction. This fully demonstrated the chemzymatic behavior of our rationally designed organocatalyst. We believe that the rigid nature of the tricycle with an inherent chiral pocket provides a well-organized chiral environment, which together with the hydrophobic pocket, enabled this elusive reaction to proceed smoothly in water.

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(12) **Typical Reaction Procedure**
To a mixture of 1,1-bis(phenylsulfonyl)ethylene (31 mg, 0.1 mmol), catalyst **I** (2.8 mg, 0.01 mmol), and DMAP (1.2 mg, 0.01 mmol) in H_2O (0.5 mL) was added isoveraldehyde (34.4 mg, 0.4 mmol) and stirred vigorously for 12 h at r.t. Then MeOH (1 mL) was added and the mixture was cooled to 0 °C before $NaBH_4$ (8 mg, 0.2 mmol) was added. After stirring at 0 °C for 0.5 h, the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhyd $MgSO_4$, and concentrated under reduced pressure. The desired products were purified with silica gel column chromatography (EtOAc–hexanes = 1:2). The ee was determined by HPLC with Chiralpak AS-H column at 220 nm (2-PrOH–hexane = 20:80), 0.5 mL/min, t_R(major) = 40.0 min, $t_{R(}$minor) = 47.0 min; $[\alpha]_D^{20}$ +3.1 (*c* 2.3, $CHCl_3$, 589 nm);

yellow light solid; R_f = 0.15 (EtOAc–hexane = 1:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.93 (m, 4 H), 7.72–7.67 (m, 2 H), 7.59–7.54 (m, 4 H), 5.22 (dd, *J* = 3.3, 7.2 Hz, 1 H), 3.73 (dd, *J* = 3.3, 11.0 Hz, 1 H), 3.51 (dd, *J* = 7.9, 11.0 Hz, 1 H), 2.37–2.13 (m, 2 H), 1.78–1.57 (m, 3 H), 0.85 (d, *J* = 3.4 Hz, 3 H), 0.82 (d, *J* = 3.4 Hz, 3 H). ^{13}C NMR (75 Hz, $CDCl_3$): δ = 138.0, 137.7, 134.5, 129.7, 129.5, 129.1, 129.0, 81.6, 64.7, 44.4, 29.8, 26.1, 19.4, 19.2. HRMS (ESI-TOF): *m/z* calcd for $C_{19}H_{25}SO_2$: 333.1347 $[M + H]^+$; found: 333.1342.