DOI: 10.1002/adsc.201000344

Highly Active Water-Soluble and Recyclable Organocatalyst for the Asymmetric 1,4-Conjugate Addition of Nitroalkanes to α,β-Unsaturated Aldehydes

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Received: May 3, 2010; Revised: August 19, 2010; Published online: October 7, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000344.

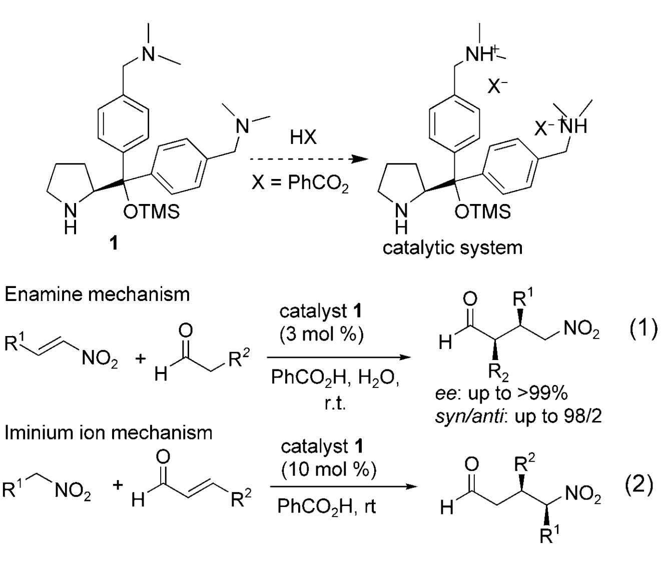
Abstract: A novel strategy for the catalytic asymmetric conjugate addition of nitroalkanes to α,β-unsaturated aldehydes in aqueous media has been developed by using diarylprolinol silyl ether in combination with benzoic acid as a water-soluble organocatalyst providing the desired adducts in good to excellent enantioselectivities (up to 95% *ee*). This catalyst can be recycled at least five times with only a slight reduction in activity and selectivity. In addition, the synthetic procedure presented is simple, practical and environmentally benign.

Keywords: aldehydes; asymmetric catalysis; catalyst recycling; C–C bond formation; Michael addition

Asymmetric organocatalysis has attracted great interest over the past decade.[1] Within this category, the organocatalyzed conjugate addition reaction is a particularly interesting and powerful synthetic method for the construction of C–C bonds in modern chemistry because it provides chiral functionalized products. These compounds can be used as versatile synthetic building blocks for the synthesis of biologically active compounds and natural products.[2] Thus, it is not surprising that many organocatalysts have been developed for this cornerstone reaction.[3] Among these organocatalysts, chiral secondary amines, which stand out as one of the most active and enantioselective catalysts with broad substrate generality, have expanded the scope of organocatalysis.[4] However, performing organocatalysis in aqueous media is still challenging due to the fact that water often inhibits the catalyst's activity and disrupts hydrogen bonds and other polar interactions.[5] On the other hand, aqueous organocatalysis has economic, environmental, and processing benefits compared to its use in typical organic solvents. Moreover, when a water-soluble organocatalyst is used, the water-insoluble products can be isolated easily by simple separation and the catalytic system can be recycled. Therefore, development of an organocatalyst that is not only active in aqueous media but also stable and completely soluble in this solvent would be highly desirable.

Recently, much effort has been devoted to the development of water-compatible organocatalysts for performing organic transformations in aqueous media. Significant progress has been made for conjugate addition of aldehydes and ketones to α,β-unsaturated carbonyl compounds by activating the carbonyl compounds through a nucleophilic enamine mechanism.[6] However, limited success has been achieved so far for the conjugate addition of carbanions to α,β-unsaturated aldehydes in aqueous systems through electrophilic iminium ion mechanism.[7,8] This is probably due to the lower stability of iminium ion intermediate in the presence of water. Furthermore, the high reactivity of α,β-unsaturated aldehydes undergoing 1,2-addition reaction in competition with the 1,4-conjugate addition could be another reason. To the best of our knowledge, there is only one report in the literature using dialkylprolinol silyl ether as an efficient organocatalyst for the 1,4-conjugate addition of nitromethane to α,β-unsaturated aldehydes in water to give excellent enantioselectivity.[6d] It should be noted that all organocatalysts reported so far for asymmetric reactions in aqueous media have a common feature that the catalysts were specifically designed to contain large hydrophobic groups, which accurately serve as a "concentrated organic phase". The hydrophobicity of catalysts causes them to assemble with hydrophobic reactants in water and sequester the formation of enamine or iminium transition state from water. As a result, the reaction is not really proceeding in water and is more likely performed in "organic solvent".[9] Thus, a special design of water-soluble organocatalyst is required for performing these reactions in aqueous media with good stereoselection.[10]

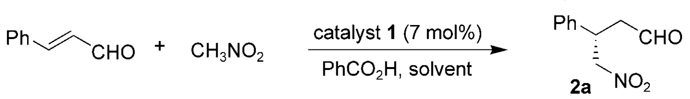
With the goal of developing a recyclable catalyst that displays high activity and enantioselectivity in aqueous media, our group has reported a water-soluble and recyclable catalyst, diarylprolinol silyl ether **1** in combination with Brønsted acid, which catalyzed the asymmetric Michael addition of aldehydes to nitroolefins in aqueous media with excellent diastereo- and enantioselectivities through activation of aldehydes by an enamine mechanism [Scheme 1, Eq. (1)].[11,12] To further develop our catalytic system, we evaluated the iminium ion-based, organocatalytic direct asymmetric 1,4-conjugate addition of nitroalkanes to α,β-unsaturated aldehydes in the presence of water with *i*-PrOH as cosolvent [Scheme 1, Eq. (2)].[13] Furthermore, we found that the catalytic system can be easily recovered and reused at least 5 times with only a slightly decreased enantioselectivity.



Scheme 1.

To examine the performance of catalyst **1**, the 1,4-conjugate addition reaction of nitromethane and cinnamaldehyde to afford γ-nitroaldehyde **2a** was performed using benzoic acid as an additive. Screening of solvents and the ratio of benzoic acid to catalyst was investigated to optimize the reaction conditions. The results are summarized in Table 1. Initially, the reaction was performed in water with 7 mol% of catalyst **1** in the absence of benzoic acid as additive. There was no product **2a** observed after 72 h (entry 1). However, the reaction proceeded to afford the product **2a** in 84% yield at room temperature after 72 h when 28 mol% of benzoic acid was added (entry 2). When the amount of benzoic acid was increased to 42 mol%, the reaction time decreased to 48 h with comparable enantioselectivity (entry 3). However, further increases of the benzoic acid loading did not improve the yield and selectivity (entry 4). When the amount of donor CH_3NO_2 was reduced to 2 equivalents, the enantioselectivity was increased from 88% to 93%; but the yield was decreased and a longer reaction period was needed (entry 5). Lowering the temperature to 4 °C further improved the enantioselectivity to 95% (entry 6). Different water/alcohol solvent systems were examined that resulted in the desired product **2a** in similarly high enantioselectivities (entries 7–10). The optimal result was obtained by using a solvent mixture of water:*i*-PrOH in a ratio of 3:1 affording product **2a** in 80% yield with 94% *ee* (entry 11). The absolute stereochemistry of

Table 1. Optimization of the reaction conditions of nitromethane with cinnamaldehyde.[a]



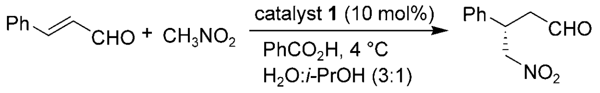
Entry	Solvent	*T* [°C]	$PhCO_2H$ [mol%]	CH_3NO_2 [equiv]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	H_2O	r.t.	0	4	72	0	–
2	H_2O	r.t.	28	4	72	84	87
3	H_2O	r.t.	42	4	48	80	87
4	H_2O	r.t.	70	4	48	80	88
5	H_2O	r.t.	42	2	60	50	93
6	H_2O	4	42	2	60	51	95
7	H_2O:MeOH 3:2	4	42	2	48	78	90
8	H_2O:EtOH 3:2	4	42	2	48	80	91
9	H_2O:*i*-PrOH 3:2	4	42	2	48	82	94
10	H_2O:*i*-PrOH 2:1	4	42	2	48	77	93
11	**H_2O:*i*-PrOH 3:1**	**4**	**42**	**2**	**48**	**80**	**94**

[a] Reactions performed on a 0.4-mmol scale using catalyst **1**, benzoic acid, and solvent (0.5 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC of the product.

product **2a** was determined to be (*S*) by comparing its optical rotation with literature values by using (*S*)-diphenylprolinol silyl ether as catalyst.[8b]

Next, the recyclability of the catalytic system (10 mol% of catalyst **1** was used) was studied in a reaction of nitromethane with cinnamaldehyde under standard reaction conditions. Upon completion of the reaction, we found that the aqueous catalytic system was easily recovered after extraction of the product **2a** by addition of a solvent mixture of hexane:Et_2O (4:1). The recovered aqueous phase was reused for the next cycle directly by addition of fresh portions of benzoic acid, nitromethane, cinnamaldehyde, and cosolvent *i*-PrOH. The performace of the recycled catalyt **1** was evaluated by prolonged and identical reaction times, respectively (Table 2). As shown in Table 2, the reactivity and enantioselectivity of the recovered catalyst **1** system dropped gradually after the first cycle with prolonged reaction time (Table 2, left column). However, the enantioselectivity was retained in high levels and only slightly decreased in cycles 3–5 with identical reaction times (Table 2, right column). These results demonstrate that catalyst **1** is the first effective recyclable organocatalyst for the asymmetric conjugate addition reactions between nitroalkanes and α,β-unsaturated aldehydes in aqueous media with excellent stereoselectivities. It is also amendable to a very simple, practical and green procedure for catalyt recovery.

Table 2. Recycling studies of water-soluble **1**-catalyzed reaction of nitromethane with cinnamaldehyde.[a]



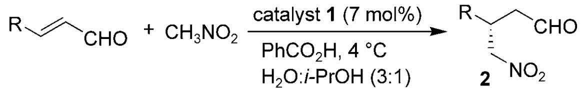
Cycle	*t* [h]	Yield [%][b]	*ee* [%][c]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	37	84	93	40	86	93
2	48	76	92	40	75	93
3	53	70	92	40	67	92
4	84	73	89	40	58	91
5	120	64	84	40	45	89

[a] Reactions performed on a 0.5-mmol scale using catalyst **1**, benzoic acid, nitromethane (2 equiv.), H_2O:*i*-PrOH (0.5 mL).

[b] Isolated yield.

[c] Determined by chiral HPLC of the product.

Table 3. Reaction of nitromethane with α,β-unsaturated aldehydes catalyzed by **1**.[a]



Entry	R	Product	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	**2a**	46	82	93
2	4-FC_6H_4	**2b**	55	68	91
3	2-ClC_6H_4	**2c**	55	66	94
4	4-BrC_6H_4	**2d**	55	65	93
5	2-$NO_2C_6H_4$	**2e**	48	48	94
6	4-$NO_2C_6H_4$	**2f**	68	74	89
7	2-$MeOC_6H_4$	**2g**	48	70	91
8	4-$MeOC_6H_4$	**2h**	64	70	94
9	2-furanyl	**2i**	53	73	87
10	Me	**2j**	20	62	84

[a] Reactions performed on a 0.4-mmol scale using catalyst **1**, benzoic acid, nitromethane (2 equiv.), H_2O:*i*-PrOH (0.5 mL).

[b] Isolated yield.

[c] Determined by chiral HPLC of the product.

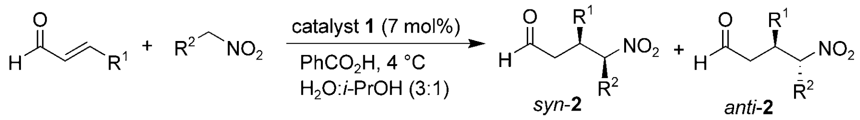
Encouraged by these results, we next probed the scope of this asymmetric conjugate reaction with nitromethane and a variety of α,β-unsaturated aldehydes in a solvent mixture of H_2O:*i*-PrOH (3:1) at 4 °C (Table 3). The results show that the reaction proceeds efficiently for all cinnamaldehyde derivates bearing both electron-deficient and electron-rich substituents on the phenyl ring affording the corresponding products **2b–h** in moderate to good yields (48–74%) with high enantioselectivities (89–94% *ee*) (entries 2–8). The heteroaromatic α,β-unsaturated aldehyde was also a suitable substrate affording the product **2i** in good enantioselectivity and yield (entry 9). Furthermore, catalyst **1** is also highly effective for conjugate addition of nitromethane to an aliphatic α,β-unsaturated aldehyde providing the desired product **2j** in good yield (62%) and enantioselectivity (84% *ee*) (entry 10).

Finally, the structural effect of nitroalkanes on the conjugate addition was also investigated, and the results are summarized in Table 4. The reactions worked well with nitroethane and nitropropane to give the desired products **2k–n** in 73–95% yields with high enantioselectivities (89–94% *ee*) for both *syn* and *anti* diastereomers. However, the *dr* selectivities were poor.

The large-scale 1,4-conjugate addition was carried out, in which 10 mmol of cinnamaldehyde reacted with nitromethane under standard reaction conditions. After the reaction was completed, the reaction mixture was separated into two phases. The aqueous phase was removed by simple separation and the organic phase was purified by flash chromatography on silica gel to give the desired product **2a** in 82% yield with high enantioselectivity (94% *ee*). Notably, the procedure is green and practical, and no organic solvent is required for the work-up step.

In conclusion, a new, highly efficient, asymmetric conjugate addition of nitroalkanes with α,β-unsaturated aldehydes catalyzed by a novel water-soluble organocatalyst, diarylprolinol silyl ether **1** in combination

Table 4. Reaction of itroalkane with α,β-unsaturated aldehydes catalyzed by **1**.[a]



Entry	R^1	R^2	Product	*t* [h]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]
1	Ph	Me	**2k**	50	83	2/3	90/93
2	2-$NO_2C_6H_4$	Me	**2l**	50	88	2/1	92/91
3	2-$MeOC_6H_4$	Me	**2m**	48	95	1/2	89/91
4	2-$NO_2C_6H_4$	Et	**2n**	60	73	3/2	94/94

[a] Reactions performed on a 0.4-mmol scale using catalyst **1**, benzoic acid, nitroalkane (2 equiv.), and H_2O:*i*-PrOH (0.5 mL).

[b] Isolated yield.

[c] Determined by ^1H NMR.

[d] Determined by chiral HPLC of the product.

with benzoic acid, in aqueous media has been developed. The main advantages of this catalyst are the low donor nitroalkane loading (2 equiv.), the use of aqueous media, and the recyclable catalytic nature of the system with high enantioselectivities (84–94% *ee*). These remarkable advantages make this approach very suitable for practical use. Further studies focusing on the scope of this unique organocatalyst to catalyze asymmetric transformations and the modification of the dimethylamine moiety by synthesis of ammonium ionic liquid-supported catalysts are currently under investigation and will be reported in due course.

Experimental Section

General Procedure for 1,4-Conjugate Addition of Nitroalkanes to α,β-Unsaturated Aldehydes (Table 3 and Table 4)

To a mixed solution of H_2O:*i*-PrOH = 3:1(v/v, 0.5 mL) was added an α,β-unsaturated aldehyde (0.4 mmol), nitroalkane (0.8 mmol), catalyst (0.028 mmol) and benzoic acid (0.168 mmol). The reaction mixture was stirred at 4 °C for the time indicated in the Table 3. The products were extracted with Et_2O:hexane = 1:3 (v/v). The combined organic phase was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel to yield the desired addition product **2**.

Acknowledgements

We are grateful to the Robert A. Welch Foundation (T-0014) and Office of Graduate Studies & Research at Texas A&M University – Commerce for financial support of this research. We are grateful to Martha Clevenger for her assistance.

References

[1] For recent reviews, see: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; b) *Acc. Chem. Res.* **2004**, *37* (No. 8), special issue on organocatalysis; c) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719; d) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065; e) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; f) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; g) *Chem. Rev.* **2007**, *107* (No. 12), special issue on organocatalysis.

[2] a) H. R. Olpe, H. Demieville, V. Baltzer, W. L. Bencze, W. P. Koella, P. Wolf, H. L. Haas, *Eur. J. Pharmacol.* **1978**, *52*, 133; b) N. G. Bowery, *Trends Pharmacol. Sci.* **1982**, *31*, 401; c) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**.

[3] For some selected examples, see: a) B. List, P. Pojarlier, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423; b) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737; c) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369; d) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; e) C. Palomo, S. Vera, A. Mielgo, E. Gomez-Bengoa, *Angew. Chem.* **2006**, *118*, 6130; *Angew. Chem. Int. Ed.* **2006**, *45*, 5984; f) S. Mosse, A. Alexakis, *Org. Lett.* **2006**, *8*, 3577; g) S. V. Pansare, K. Pandya, *J. Am. Chem. Soc.* **2006**, *128*, 9624; h) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599; i) M. T. Barros, A. M. F. Phillips, *Eur. J. Org. Chem.* **2007**, 178; j) S. Sulzer-Moss, A. Alexakis, *Chem. Commun.* **2007**, 3123; k) M. Wiesner, J. F. Revell, H. Wennemers, *Angew. Chem.* **2008**, *120*, 1897; *Angew. Chem. Int. Ed.* **2008**, *47*, 1871; l) A. Ma, S. Zhu, D. Ma, *Tetrahedron Lett.* **2008**, *49*, 3075; m) M. Wiesner, G. Upert, G. Angelici, H. Wennemers, *J. Am. Chem. Soc.* **2010**, *132*, 6.

[4] For reselected recent reviews, see: a) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; b) X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037; c) S.

Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178.

[5] For the reviews on organic reactions in aqueous media, see: a) *Organic Synthesis in Water*, (Ed.: P. A. Grieco), Blackie Academic & Profesional, London, **1998**; b) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751; c) C.-J. Li, L. Cheng, *Chem. Soc. Rev.* **2006**, *35*, 68; d) M. C. Pirrung, *Chem. Eur. J.* **2006**, *12*, 1312; e) J. Paradowska, M. Stodulski, J. Mlynarsk, *Angew. Chem.* **2009**, *121*, 4352; *Angew. Chem. Int. Ed.* **2009**, *48*, 4288.

[6] For some selective examples of conjugate addition reactions in aqueous media, see: a) N. Mase, K; Watanabe, H; Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 4966; b) L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077; c) V. Singh, V. K. Singh, *Org. Lett.* **2007**, *9*, 1117; d) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, A. Puente, S. Vera, *Angew. Chem.* **2007**, *119*, 8583; *Angew. Chem. Int. Ed.* **2007**, *46*, 8431; e) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555; *Angew. Chem. Int. Ed.* **2008**, *47*, 545.

[7] For examples of reactions in aqueous media *via* iminium ion intermediates, see: A. Ma, S. Zhu, D. Ma, *Tetrahedron Lett.* **2008**, *49*, 3075; and ref.[6d]

[8] For examples of reactions of nitroalkanes as nucleophiles in typical organic solvents *via* iminium ion intermediates, see: a) L. Hojabri, A. Hartikka, F. M. Moghaddam, P. I. Arvidsson, *Adv. Synth. Catal.* **2007**, *349*, 740; b) L. Zu, H. Xie, H. Li, J. Wang, W. Wang, *Adv. Synth. Catal.* **2007**, *349*, 2660; c) H. Gotoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2007**, *9*, 5307; d) Y. Wang, P. Li, X. Liang, T. Y. Zhang, J. Ye, *Chem. Commun.* **2008**, 1232.

[9] For recent reviews about organocatalysis in aqueous media, see: a) A. P. Brogan, T. J. Dickerson, K. D. Janda, *Angew. Chem.* **2006**, *118*, 8278; *Angew. Chem. Int. Ed.* **2006**, *45*, 8100; b) Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103; c) M. Gruttadauria, F. Giacalone, R. Noto, *Adv. Synth. Catal.* **2009**, *351*, 33; d) M. Raj, V. K. Singh, *Chem. Commun.* **2009**, 6687.

[10] The results from Prof. Barbas' group indicated that the aldol reaction could not proceed in water when catalyst did not include a hydrophobic group, see: N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 734.

[11] Z. Zheng, B. L. Perkins, B. Ni, *J. Am. Chem. Soc.* **2010**, *132*, 50.

[12] For references of water-soluble organocatalysts, see: a) M. Freund, S. Schenker, S. B. Tsogeva, *Org. Biomol. Chem.* **2009**, *7*, 4279; b) J. Wu, B. Ni, A. D. Headley, *Org. Lett.* **2009**, *11*, 3354.

[13] For the recyclable organocatalyzed conjugate addition of dialkyl malonates and nitroalkanes to α,β-unsaturated aldehydes in organic solvents, see: a) O. V. Maltsev, A. S. Kucherenko, S. G. Zlotin, *Eur. J. Org. Chem.* **2009**, 5134; b) I. Mager, K. Zeitler, *Org. Lett.* **2010**, *12*, 1480.