Highly Enantioselective Organocatalytic Michael Addition of Ketones to Nitroolefins in the Presence of Water

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Abstract: Chiral pyrrolidine-based organocatalysts, in combination with ionic-liquid-supported Brønsted acids, catalyze the enantioselective Michael addition of ketones and aldehyde to nitroolefins in high yields with high enantioselectivities (ee ≤ 96%) and diastereoselectivities (*syn*/*anti* ratio ≤ 98:2). This novel process provides synthetically useful γ-nitrocarbonyl compounds, which can be easily transformed into other invaluable precursors of biologically active compounds. In addition, the synthetic procedure presented is simple and practical.

Key words: organocatalysts, asymmetric synthesis, Michael addition, ketones, nitroolefins

The organocatalytic enantioselective Michael addition of ketones or aldehydes to electron-deficient nitroolefins is one of the most powerful tools for the stereocontrolled formation of carbon–carbon bonds in organic synthesis.[1] The resulting optically active Michael adducts, γ-nitrocarbonyl compounds, are versatile building blocks since the nitro and carbonyl groups can be further transformed into other invaluable precursors of biologically active compounds.[2] As a consequence, a great deal of effort has been devoted toward the development of more active and stereoselective organocatalysts for this cornerstone reaction, and significant progress has been achieved in recent years.[3] Especially, the pyrrolidine-based secondary amines, which stand out as one of the most efficient and enantioselective catalysts with broad substrate generality, have expanded the scope of organocatalysis.[4] However, most of organocatalytic reactions are performed in organic solvents, and only limited reactions have been reported which effectively proceed in water with high enantioselectivities.[5] From a green chemistry perspective, the use of water instead of organic solvent has many advantages in terms of economic, environmental, and processing benefits. Therefore, it would be highly desirable to develop a water-compatible organocatalyst that effectively catalyzes asymmetric Michael addition in water with high selectivity.

Recently, chiral pyrrolidine derivative organocatalysts, bearing long alkyl side chains,[6] naphthyl,[7] and bulky[8] groups, have been developed for asymmetric Michael addition of ketones or aldehydes to nitroolefins in aqueous media with high stereoselectivity (Figure 1).[9] However, all these organocatalysts developed for asymmetric Michael addition in aqueous media have a common feature that the catalysts were specifically designed to contain large hydrophobic groups (long alkyl side chains, naphthyl, and bulky groups), which accurately serve as a 'concentrated organic phase'.[10] The hydrophobicity of these catalysts forces them into close contact with hydrophobic reactants in water and excludes the reaction transition state from water. Interestingly, to the best of our knowledge, there is no report in the literature using such pyrrolidine derivative bearing hydrophilic or less hydrophobic groups (short alkyl side chain) as an efficient organocatalyst for the asymmetric Michael addition in aqueous media.[11]

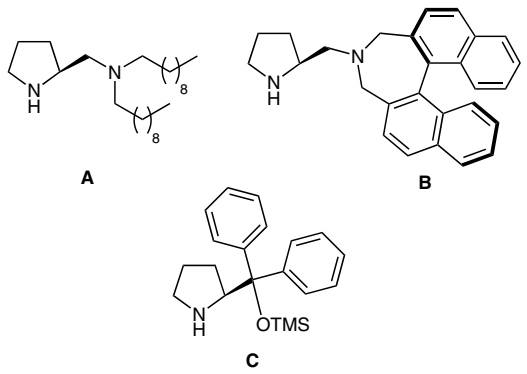

Figure 1 Examples of organocatalysts for the asymmetric Michael addition in water

To this end, our group has recently developed such organocatalysts, which possess hydrophilic groups and promote highly asymmetric transformations in aqueous media.[12] With our continuing goal of developing water-compatible catalysts that display high activity and enantioselectivity in aqueous media, we wish to report the chiral pyrrolidine–ionic-liquid-supported (ILS) Brønsted acid conjugates as effective catalysts for the asymmetric direct Michael addition of ketones to nitroolefins in high yields (≤ 99%) and stereoselectivities (ee ≤ 96%, *syn*/*anti* ≤ 98:2).

To examine the performance of catalysts **1a**–**e**,[4g,13–15] the Michael addition of cyclohexanone with nitrostyrene was selected as a model reaction for screening the catalysts and Brønsted acids as additives (Figure 2). The results are listed in Table 1. Initially, the reaction was performed in water with 20 mol% of catalyst **1a** in the presence of ILS benzoic acid **2a** as additive. The reaction proceeded

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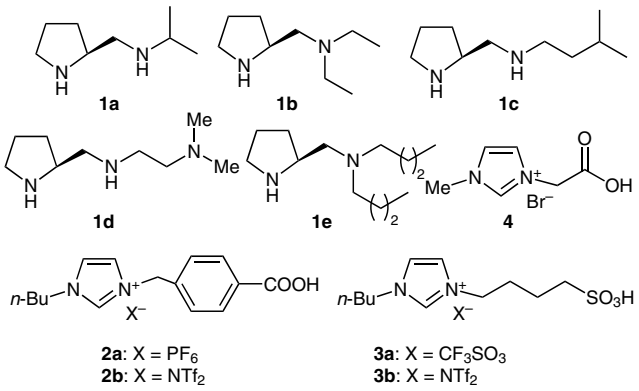
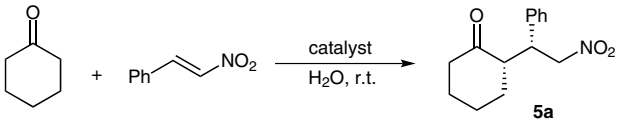


Figure 2 Pyrrolidine-based organocatalysts **1a–e** and ionic liquid supported Brønsted acid **2–4**

smoothly to afford the Michael adduct **5a** in good yield (79%) and diastereoselectivity (*syn*/*anti* = 89:11), but in low enantioselectivity (ee: 17%, Table 1, entry 1). Among this series of catalysts examined, diamine catalyst **1e** in combination with **2a** gave the best yield (91%) as well as enantio- and diastereoselectivity (ee: 88%, *syn*/*anti* = 95:5, Table 1, entries 2–5).[16] However, when general Brønsted acids (TsOH and TFA) were used as additives, only powdery and insoluble solid side products were formed (Table 1, entries 7 and 8). The same phenomenon of polymerization of nitrostyrene was observed by Barbas' research group using **A** (Figure 1) as catalyst and TFA as additive in water.[17] Interestingly, when catalyst **1e** in combination with benzoic acid was used as catalytic system, Michael adduct **5a** was obtained in moderate yield (78%) with high stereoselectivity (ee = 88%, *syn*/*anti* = 95:5, Table 1, entry 9). In light of the above results, we further optimized the reaction conditions using catalyst **1e** by screening acid additives. The influence of catalyst loading was also investigated (Table 1, entries 6 and 10–14). When the amount of catalyst **1e** and ILS acidic additive **2a** were decreased to 10 mol%, the reaction time was increased to 12 hours with comparable yield and stereoselectivity (Table 1, entry 5 vs. entry 10). Other ILS acidic additives **2b**, **3a**,**b**, and **4** were also examined (Table 1, entries 6 and 11–13), and the use of acid **3a** provided the best results in terms of both the yield (99%) and selectivity (ee = 92%, *syn*/*anti* = 97:3, Table 1, entry 12). Further decrease in both the catalyst **1e** and acid **3a** loading to 5 mol%, the reaction time was increased to 36 hours with slightly dropped selectivity (Table 1, entry 14). The absolute stereochemical outcome of product **5a** can be explained by a model based on the literature.[6a]

On the basis of the results summarized in Table 1, the reaction conditions of entry 12 (Table 1) were chosen to study the scope of the asymmetric Michael addition of a few cyclic ketones to a variety of nitroolefins with catalyst **1e** in combination with acid additive **3a**, and the results are summarized in Table 2.[18] The results showed that the reactions proceeded efficiently with cyclohexanone and nitroolefins bearing both electron-deficient and electron-rich substituents on the phenyl ring affording the corresponding products **5b–i** in high yields (84–99%) with high selectivities (ee ≤ 92%, *syn*/*anti* ≤ 98:2, Table 2, entries 1–8). Tetrahydrothiopyran-4-one was also a suitable Michael donor and afforded the corresponding Michael adduct **5j** in 98% yield with 96% ee and a *syn*/*anti* ratio of 95:5 (Table 2, entry 9). 2-(2-Nitrovinyl)furan was also a suitable Michael acceptor (Table 2, entry 10). However, when cyclopentanone was used as a substrate, only moderate yield and enantioselectivity were obtained despite of high diastereoselectivity (Table 2, entry 11). Acetone was also examined as a Michael donor; however, only a powdery and insoluble solid side product was formed. Furthermore, catalyst **1e** is also effective for the Michael addition of the aldehyde pentanal to nitrostyrene providing the desired product **5m** in good yield (80%) and enantioselectivity (75% ee, Table 2, entry 12).

Table 1 Optimization of the Reaction Conditions of Cyclohexanone to Nitrostyrene[a]

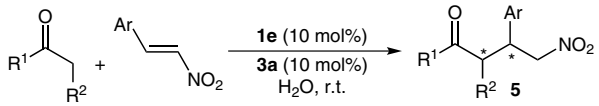


Entry	Catalyst (mol%)[b]	Time (h)	Yield (%)[c]	ee (%)[d]	*syn*/*anti*[e]
1	**1a**/**2a** (20)	2	79	17	89:11
2	**1b**/**2a** (20)	2	91	66	93:7
3	**1c**/**2a** (20)	2	85	68	94:6
4	**1d**/**2a** (20)	2	75	69	92:8
5	**1e**/**2a** (20)	2	91	88	95:5
6	**1e**/**4** (20)	2	71	88	85:15
7	**1e**/TFA (20)	2	[f]	–	–
8	**1e**/TsOH (20)	2	[f]	–	–
9	**1e**/$PhCO_2H$ (20)	2	78	88	95:5
10	**1e**/**2a** (10)	12	92	89	95:5
11	**1e**/**2b**(10)	12	85	90	95:5
12	**1e**/**3a** (10)	10	99	92	97:3
13	**1e**/**3b** (10)	10	97	87	94:6
14	**1e**/**3a** (5)	36	90	91	93:7

[a] Reactions performed on 0.4 mmol scale using catalyst **1a–e**, additives, cyclohexanone (5 equiv), and H_2O (0.8 mL).
[b] Equivalent amount of catalyst and additive were used.
[c] Isolated yield.
[d] Determined by chiral HPLC of the product.
[e] Determined by ^1H NMR spectroscopy.
[f] Polymerization.

In conclusion, a highly efficient asymmetric Michael addition of ketones and aldehyde to nitroolefins catalyzed by a water-compatible organocatalyst, diamine **1e** in combination with ILS sulfonic acid **3a**, in water has been developed. The present reactions accommodated a range of

Table 2 Michael Addition of Ketones to Nitroolefins[a]



Entry	R^1, R^2	Ar	Time (h)	Yield (%)[b]	ee (%)[c]	*syn*/*anti*[d]
1	$(CH_2)_4$	4-MeC_6H_4	10	**5b** 98	90	94:6
2	$(CH_2)_4$	4-$MeOC_6H_4$	12	**5c** 97	92	93:7
3	$(CH_2)_4$	3-$MeOC_6H_4$	12	**5d** 98	90	98:2
4	$(CH_2)_4$	2-FC_6H_4	12	**5e** 98	92	97:3
5	$(CH_2)_4$	4-ClC_6H_4	16	**5f** 84	89	94:6
6	$(CH_2)_4$	4-BrC_6H_4	10	**5g** 98	91	94:6
7	$(CH_2)_4$	2-BrC_6H_4	14	**5h** 86	91	97:3
8	$(CH_2)_4$	4-$O_2NC_6H_4$	8	**5i** 99	90	95:5
9[e]	$C_2H_4SCH_2$	Ph	9	**5j** 98	96	95:5
10	$(CH_2)_4$	2-furyl	10	**5k** 99	92	94:6
11	$(CH_2)_3$	Ph	24	**5l** 60	57	94:6
12	H, *n*-Pr	Ph	36	**5m** 80	75	71:29

[a] Reactions performed on 0.4 mmol scale using ketones (5 equiv) in H_2O (0.8 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC of the product.
[d] Determined by ^1H NMR spectroscopy.
[e] Ketone (3 equiv) was used.

Michael acceptors providing products in high yields, high enantio- and diastereoselectivities under rather mild reaction conditions. In addition, the synthetic procedure presented is simple. These remarkable advantages make this approach very suitable for practical use.

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References and Notes

(1) For recent reviews, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. For special issues on organocatalysis, see: (b) *Chem. Rev.* **2007**, *107*, 5413–5883. (c) *Synthesis* **2011**, 1815–2009.
(2) (a) Bowery, N. G. *Trends Pharm. Sci.* **1982**, *31*, 401. (b) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, **2001**.
(3) For selected recent reviews, see: (a) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138. (b) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.
(4) For some selected examples, see: (a) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F. III. *Tetrahedron Lett.* **2001**, *42*, 4441. (c) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (d) Betancort, J. M.; Barbas, C. F. III. *Org. Lett.* **2001**, *3*, 3737. (e) Wang, W.; Wang, J.; Li, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 1369. (f) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212. (g) Palomo, C.; Vera, S.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 5984. (h) Mosse, S.; Alexakis, A. *Org. Lett.* **2006**, *8*, 3577. (i) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624. (j) Sulzer-Moss, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123. (k) Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. *J. Am. Chem. Soc.* **2010**, *132*, 6.
(5) For reviews on organic reactions in aqueous media, see: (a) Li, C.-J.; Cheng, L. *Chem. Soc. Rev.* **2006**, *35*, 68. (b) Paradowska, J.; Stodulski, M.; Mlynarski, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 4288.
(6) (a) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2006**, *128*, 4966. (b) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077. (c) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 8431.
(7) (a) Singh, V.; Singh, V. K. *Org. Lett.* **2007**, *9*, 1117. (b) Syu, S.; Kao, T.-T.; Lin, W. *Tetrahedron* **2010**, *66*, 891. (c) Luo, C.; Du, D.-M. *Synthesis* **2011**, 1968.
(8) (a) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 545. (b) Ma, A.; Zhu, S.; Ma, D. *Tetrahedron Lett.* **2008**, *49*,

3075. (c) Maltsev, O. V.; Kucherenko, A. S.; Zlotin, S. G. *Eur. J. Org. Chem.* **2009**, 5134. (d) Mager, I.; Zeitler, K. *Org. Lett.* **2010**, *12*, 1480.

(9) For some selected examples of aldol reactions in aqueous media, see: (a) Hayashi, Y.; Aratake, S.; Okano, T.; Takahashi, J.; Sumiya, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5527. (b) Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653. (c) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417. (d) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2006**, *128*, 734.

(10) For recent reviews about organocatalysis in aqueous media, see: (a) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 8100. (b) Hayashi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 8103. (c) Mase, N.; Barbas, C. F. III. *Org. Biomol. Chem.* **2010**, *8*, 4043.

(11) The results from Prof. Barbas' group indicated that the Aldol reaction could not proceed in water when catalyst did not include hydrophobic group. See ref. 9d.

(12) (a) Wu, J.; Ni, B.; Headley, A. D. *Org. Lett.* **2009**, *11*, 3354. (b) Zheng, Z.; Perkins, B. L.; Ni, B. *J. Am. Chem. Soc.* **2010**, *132*, 50. (c) Ghosh, S. K.; Zheng, Z.; Ni, B. *Adv. Synth. Catal.* **2010**, *352*, 2378. (d) Sarkar, D.; Bhattarai, R.; Headley, A. D.; Ni, B. *Synthesis* **2011**, 1993.

(13) Akahane, Y.; Inomata, K.; Endo, Y. *Heterocycles* **2011**, *82*, 1727.

(14) Peschke, B.; Bak, S.; Hohlweg, R.; Pettersson, I.; Refsgaard, H. H. F.; Viuff, D.; Rimvall, K. *Bioorg. Med. Chem.* **2004**, *12*, 2603.

(15) Gao, Q.; Liu, Y.; Lu, S.-M.; Li, J.; Li, C. *Green Chem.* **2011**, *13*, 1983.

(16) Chiral pyrrolidines **1c** and **1d** were found to be effective organocatalysts for Michael addition of ketones to nitroolefins with high selectivity in organic solvent DMF. See ref. 4g.

(17) Under the same reaction conditions, Prof. Barbas' group found that Michael addition of cyclohexanone to nitrostyrene catalyzed by diamine **A** bearing long alkyl chains (Figure 1) with TFA gave 54% yield of product **5a** with 89% ee and a *syn*/*anti* ratio of 95:5. See ref. 6a.

(18) **Typical Procedure for the Asymmetric Michael Addition**
To a solution of the amine catalyst **1e**[19] (8.5 mg, 0.04 mmol) and ILS sulfonic acid **3a**[20] (16.4 mg, 0.04 mmol) in H_2O (0.8 mL) was added ketone (2.0 mmol) at r.t. The reaction mixture was stirred for 20 min, and then nitroolefin (0.4 mmol) was added. The reaction mixture was stirred until complete conversion of the nitroolefin (monitored by TLC) and then extracted with CH_2Cl_2 (2 × 2 mL). The combined organic phase was concentrated under vacuum to give the crude residue, which was purified by flash column chromatography (silica gel, hexane–EtOAc) to afford the Michael adduct **5**. The *syn*/*anti* ratio was determined by ^{1}H NMR spectroscopy of the crude mixture and the ee was determined by chiral HPLC.
Analytic Data of 5a
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.22 (m, 3 H), 7.17 (d, *J* = 7.2 Hz, 2 H), 4.95 (dd, *J* = 12.4, 4.4 Hz, 1 H), 4.64 (dd, *J* = 12.4, 10.0 Hz, 1 H), 3.77 (dt, *J* = 14.4, 4.8 Hz, 1 H), 2.74–2.64 (m, 1 H), 2.54–2.33 (m, 2 H), 2.14–2.04 (m, 1 H), 1.83–1.50 (m, 4 H), 1.30–1.18 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.9, 137.7, 128.9, 128.2, 127.8, 78.9, 52.5, 43.9, 42.7, 33.2, 28.5, 25.0. HPLC (Chiralpak AD-H, *i*-PrOH–hexane = 10:90, flow rate = 0.5 mL/min, λ = 254 nm): t_R (minor) = 19.4 min; t_R (major) = 24.7 min; ee = 92%.

(19) Gao, Q.; Liu, Y.; Lu, S.-M.; Li, J.; Li, C. *Green Chem.* **2011**, *13*, 1983.

(20) Cole, A. C.; Jensen, J. L.; Ntai, I.; Tran, K. L. T.; Weaver, K. J.; Forbes, D. C.; Davis, J. H. Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5962.

