

# Fine-Tunable Organocatalysts Bearing Multiple Hydrogen-Bonding Donors for Construction of Adjacent Quaternary and Tertiary Stereocenters via a Michael Reaction

Zhi-Hai Zhang, Xiu-Qin Dong, Dong Chen, and Chun-Jiang Wang\*<sup>[a]</sup>

The Michael addition reaction is widely recognized as one of the most general and versatile methods for formation of C–C bonds in organic synthesis.<sup>[1]</sup> Therefore, it is not surprising that the development of enantioselective catalytic protocols for this reaction has attracted much attention.<sup>[2]</sup> Efforts aimed at achieving asymmetric Michael addition by using powerful and environmentally friendly organocatalysts have been explored intensively in recent years.<sup>[3,4]</sup> Of particular interest is the reaction between trisubstituted carbon nucleophiles and electron-deficient olefins to form Michael adducts containing adjacent quaternary and tertiary stereocenters, which are key units in complex natural products and highly valuable synthetic building blocks. Despite its great synthetic potential, only limited successful protocols have been reported to achieve high levels of enantio- and/or diastereoselectivity.<sup>[5]</sup> Compared with other asymmetric catalysis, the reaction simultaneously creating adjacent quaternary and tertiary stereocenters in one step is still in its infancy and the development of novel efficient catalysts showing high reactivity, enantioselectivity and diastereoselectivity still remains a great challenge.

Recently, we reported a new class of bifunctional amine/thiourea catalysts **I** bearing multiple hydrogen-bonding donors, which showed excellent performance in catalytic asymmetric addition of acetylactone to nitroolefins and highly *anti*-selective nitro-Mannich reaction.<sup>[6,7]</sup> Extending the interest of these organocatalyst in asymmetric catalysis, herein we report that another novel family of readily available, fine-tunable multiple hydrogen-bonding donor organocatalysts **II**<sup>[8,9]</sup> results in high enantioselectivity, diastereose-

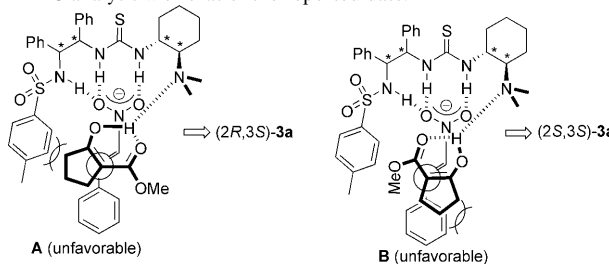
lectivity and broad scope in the asymmetric Michael addition of  $\alpha$ -substituted  $\beta$ -ketoesters to various nitroolefins.<sup>[5c,e]</sup>

Although amine/thioureas **I** were shown to be highly efficient for the addition of various of symmetric and asymmetric 1,3-diketones to nitroolefins, our initial attempts to apply **I** to promote the addition of  $\alpha$ -substituted  $\beta$ -ketoesters to nitroolefins were unsuccessful (Table 1). The reaction of methyl 2-oxo-cyclopentanecarboxylate (**1a**) to nitroolefin (**2a**) with catalysts **I** in CH<sub>2</sub>Cl<sub>2</sub> went to completion at room temperature in less than 0.5 h, which was consistent with the case of 1,3-diketone,<sup>[6]</sup> but the adduct **3a** was formed in very low diastereoselectivity with moderate to good enantioselectivity for the major diastereomer, even at lower temperature

Table 1. Representative results for Michael addition of  $\alpha$ -substituted  $\beta$ -ketoester **1** and nitroolefin **2a** catalyzed by organocatalysts **I**.<sup>[a]</sup>

Entry	Catalyst	<i>T</i> [°C]	<i>t</i> [h]	Yield <sup>[b]</sup> [%]	dr <sup>[c]</sup>	<i>ee</i> [%] <sup>[d,e]</sup>
1	<b>I-A</b>	RT	0.5	92	74:26	29
2	<b>I-B</b>	RT	0.5	96	50:50	72
3	<b>I-C</b>	RT	0.5	91	65:35	80
4	<b>I-D</b>	RT	0.5	94	59:41	80
5	<b>I-D</b>	–45	10	97	58:42	84

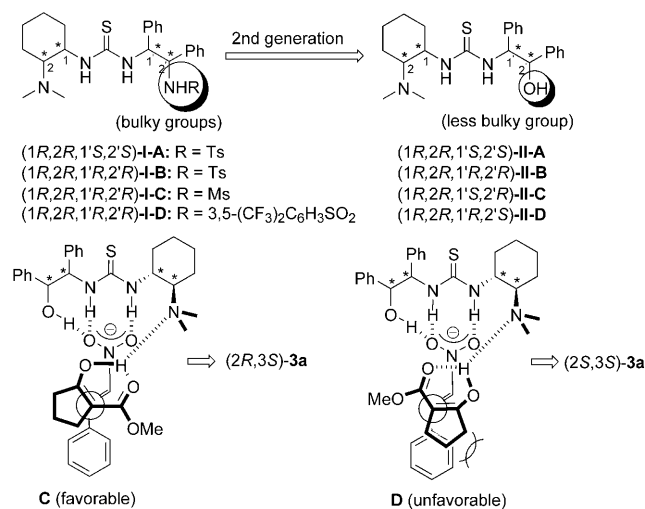
[a] Unless otherwise noted, the reaction was carried out with 0.22 mmol of **1a** and 0.2 mmol of **2a** in 0.25 mL CH<sub>2</sub>Cl<sub>2</sub>. [b] Isolated yield. [c] Determined from crude <sup>1</sup>H NMR spectra. [d] Enantiomeric excesses were determined by chiral HPLC analysis. [e] The absolute configuration of **3a** was determined to be (2*R*,3*S*) by comparing the retention time of chiral HPLC analysis with that of the reported date.



[a] Z.-H. Zhang, X.-Q. Dong, D. Chen, Prof. Dr. C.-J. Wang  
College of Chemistry and Molecular Sciences  
Wuhan University, 430072 (PR China)  
Fax: (+86) 27-68754067  
E-mail: cjwang@whu.edu.cn

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.200801420>.

(Table 1, entries 1–5). Based on those experimental data and the study of the reported transition-state models of Michael reaction of  $\beta$ -ketoesters with nitroolefins,<sup>[5c,10]</sup> we envisioned that replacing the bulky sulfonamide  $\text{NHSO}_2\text{R}$  with less bulky  $\text{OH}$  group in the corresponding organocatalysts could facilitate forming more favorable transition-state and thereby significantly enhance the diastereoselectivity and enantioselectivity (Scheme 1).



Scheme 1. Design of the 2nd generation fine-tunable and less bulky amine thiourea organocatalysts **II** bearing multiple hydrogen-bonding donors.

We then investigated the effect of the fine-tunable organocatalysts **II** on the model reaction. Gratifyingly, these reactions afford good to excellent diastereo- and enantioselectivities with the similar reaction rate at room temperature in  $\text{CH}_2\text{Cl}_2$ <sup>[11]</sup> (Table 2), and catalyst **II-D** was revealed as the best one in terms of diastereoselectivity and enantioselectivity. Interestingly, the reaction temperature remarkably affected the diastereo- and enantioselectivity, which was different from the case of 1,3-diketone.<sup>[6]</sup> Reducing reaction temperature to  $-45^\circ\text{C}$  achieved a dr of 98:2 with 99% *ee* for the major diastereomer within 10 h<sup>[12]</sup> (Table 2, entry 6). The current catalysis demonstrated significant improvements over previous results that gave lower diastereo- and enantioselectivity or required longer reaction time (2–4 d).<sup>[5c,e]</sup>

To evaluate the scope of this Michael reaction, a representative set of aryl and alkyl substituted nitroolefins were surveyed under the optimal experimental conditions. As shown in Table 3, A variety of aryl nitroolefins (**2a–j**) reacted smoothly with  $\beta$ -ketoesters (**1**) within 12–20 h to afford the corresponding adducts (**3a–j**) in high yields, excellent diastereoselectivities and enantioselectivities (Table 3, entries 1 and 2–11). It appears that the steric and electronic properties of the substituents on the aromatic rings have a very limited effect on the selectivities. Alkyl nitroolefins (**2k–n**) also worked well in these reaction to give the desired products (**3k–n**) with excellent diastereoselectivities (96:4–

Table 2. Screening studies of asymmetric Michael addition of  $\alpha$ -substituted  $\beta$ -ketoester **1** and nitroolefin **2a** catalyzed by organocatalysts **II**.<sup>[a]</sup>

Entry	Catalyst	<i>T</i> [ $^\circ\text{C}$ ]	<i>t</i> [h]	Yield [%] <sup>[b]</sup>	dr <sup>[c]</sup>	<i>ee</i> [%] <sup>[d]</sup>
1	<b>II-A</b>	RT	1	95	93:7	69
2	<b>II-B</b>	RT	1	93	82:18	78
3	<b>II-C</b>	RT	1	97	87:13	68
4	<b>II-D</b>	RT	1	95	90:10	89
5	<b>II-D</b>	$-25$	5	93	97:3	97
6	<b>II-D</b>	$-45$	10	98	98:2	99

[a] Unless otherwise noted, the reaction was carried out with 0.22 mmol of **1a** and 0.2 mmol of **2** in 0.25 mL  $\text{CH}_2\text{Cl}_2$ . [b] Isolated yield. [c] Determined from crude  $^1\text{H}$  NMR spectra. [d] Enantiomeric excess values were determined by chiral HPLC analysis.

97:3) and high enantioselectivities (90–94% *ee*) (Table 3, entries 12–15).

Table 3. Asymmetric Michael addition of  $\alpha$ -substituted  $\beta$ -ketoester **1** and nitroolefins **2** catalyzed 2nd generation organocatalysts **II**.<sup>[a]</sup>

Entry	R <sup>2</sup>	Yield [%] <sup>[b]</sup>	dr <sup>[c]</sup>	<i>ee</i> [%] <sup>[d]</sup>
1	Ph ( <b>2a</b> )	98	98:2	99
2 <sup>[e]</sup>	Ph ( <b>2a</b> )	98	98:2	97
3	<i>o</i> -Me-Ph ( <b>2b</b> )	97	98:2	99
4	<i>m</i> -Me-Ph ( <b>2c</b> )	95	97:3	99
5	<i>p</i> -Me-Ph ( <b>2d</b> )	91	99:1	99
6	<i>o</i> -Cl-Ph ( <b>2e</b> )	95	97:3	99
7	<i>p</i> -Cl-Ph ( <b>2f</b> )	90	98:2	99
8	<i>o</i> -Br-Ph ( <b>2g</b> )	94	97:3	99
9	<i>m</i> -MeO-Ph ( <b>2h</b> )	90	96:4	98
10	<i>p</i> -MeO-Ph ( <b>2i</b> )	91	94:6	97
11	<i>p</i> -F-Ph ( <b>2j</b> )	89	97:3	99
12 <sup>[f]</sup>	amyl ( <b>2k</b> )	89	96:4	94
13 <sup>[f]</sup>	<i>i</i> Pr ( <b>2l</b> )	93	97:3	90
14 <sup>[f]</sup>	<i>i</i> Bu ( <b>2m</b> )	92	97:3	94
15 <sup>[f]</sup>	Cy ( <b>2n</b> )	89	97:3	90

[a] Unless otherwise noted, the reaction was carried out with 0.22 mmol of **1** and 0.2 mmol of **2** in 0.25 mL of  $\text{CH}_2\text{Cl}_2$  at  $-45^\circ\text{C}$ . [b] Isolated yield. [c] Determined from crude  $^1\text{H}$  NMR spectra. [d] Enantiomeric excesses were determined by chiral HPLC analysis. [e] 5 mol % catalyst was used and the reaction completed in 20 h. [f] Reaction at  $0^\circ\text{C}$ .

Finally, to explore more deeply the scope and generality of this catalytic system, other trisubstituted carbon nucleophiles were also examined with a 10 mol % of catalyst **II-D**. As shown in Figure 1, various cyclic and acyclic compounds proved to be excellent substrates for this reaction, providing high diastereoselectivities and enantioselectivities.

The significant role of the multiple hydrogen-bonding donors played in this system could be demonstrated through the control experiments using less bulky methylated (1*R*,2*R*,1'*R*,2'*R*)-**II-E**, (1*R*,2*R*,*S*)-**II-F** and (1*R*,2*R*,*R*)-**II-G** as the catalyst under the optimized reaction condition (Figure 2): the reactions became a little sluggish and the diastereoselectivities of the products still remained at the similar levels, which was coincident with the proposed transition

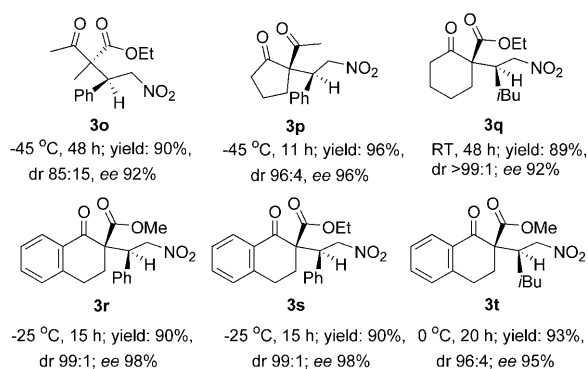


Figure 1. Results of Michael addition of nitroolefins with other cyclic and acyclic trisubstituted carbon nucleophiles catalyzed by organocatalysts **II-D**.

state mentioned above, however, the enantioselectivities decreased remarkably comparing with the results achieved by the corresponding organocatalyst **II-D**.

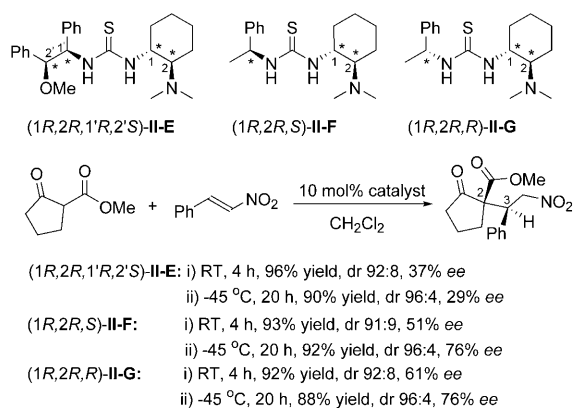


Figure 2. Control experiments to evaluate the role of the multiple hydrogen-bonding donors played in the fine-tunable organocatalysts **II-D**.

In summary, elaborately designed fine-tunable bifunctional amine/thiourea organocatalysts, relying on multiple hydrogen-bonding donors, show excellent activity, diastereoselectivity, enantioselectivity and structural scope in the asymmetric Michael addition of  $\alpha$ -substituted  $\beta$ -ketoesters to nitroolefins. This reaction provides an easy entry to access high functional compounds featuring adjacent quaternary and tertiary stereocenters in one step. Further studies aimed at diversifying the structure of the fine-tunable bifunctional organocatalyst bearing multiple hydrogen-bonding donors and their applications in other catalytic asymmetric reactions are underway in our lab.

## Experimental Section

**General procedure for the synthesis of organocatalysts II-A–D:** (1R,2R)-2-Isouthiocyanato-*N,N*-dimethylcyclohexanamine (194 mg, 1.05 mmol) was added at room temperature to a solution of corresponding 2-amino-1,2-

diphenylethanol (1 mmol) in anhydrous THF (10 mL). The solution was stirred overnight. TLC analysis indicated completion of the reaction. The reaction mixture was concentrated in vacuo. The residue was purified by flash silica gel chromatography to yield the corresponding organocatalyst.

**General procedure for asymmetric Michael addition of  $\alpha$ -substituted  $\beta$ -ketoesters and nitroolefins catalyzed organocatalysts II-D:** The catalyst **II-D** (5.0 mg, 0.0126 mmol) was added to a vial containing  $\alpha$ -substituted  $\beta$ -ketoester (0.126 mmol) and nitroolefin (0.25 mmol) in dichloromethane (0.2–0.6 mL) at -45 °C, TLC analysis indicated completion of the reaction after about 12–20 h. Then the reaction mixture was concentrated under vacuum to obtain the crude product. The crude product was purified by flash silica gel chromatography to afford the product, which was then analyzed by chiral HPLC to determine the enantiomeric excess.

## Acknowledgements

The authors thank Dr. Bo Xu for helpful discussions. This work is supported by National Natural Science Foundation of China (20642005, 20702039) and the startup fund from Wuhan University.

**Keywords:** asymmetric catalysis • hydrogen bonds • Michael addition • organocatalysis

- [1] P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**.
- [2] For recent reviews of asymmetric Michael addition reactions, see: a) K. Tomioka, Y. Nagaoka, M. Yamaguchi, in *Comprehensive Asymmetric Catalysis, Vol. III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, New York, **1999**, pp. 1105, Chapters 31.1 and 31.2; b) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171; c) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877; d) J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688.
- [3] For selected reviews of organocatalysis, see: a) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; b) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; c) *Acc. Chem. Res.* **2004**, *37*, 487–631, whole issue. Special issue on organocatalysis; d) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; e) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim **2004**; f) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719; g) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299; h) B. List, *Chem. Commun.* **2006**, 819; i) *Tetrahedron* **2006**, *62*, 243–502, whole issue; organocatalysis in organic synthesis; j) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 7658; *Angew. Chem. Int. Ed.* **2006**, *45*, 7496; k) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876; l) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; m) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418; n) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713.
- [4] For recent reviews of organocatalytic asymmetric Michael addition, see: a) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; b) D. Almasi Almasi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299.
- [5] a) F. Wu, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem.* **2006**, *118*, 4407; *Angew. Chem. Int. Ed.* **2006**, *45*, 4301; b) F. Wu, H. Li, R. Hong, L. Deng, *Angew. Chem.* **2006**, *118*, 961; *Angew. Chem. Int. Ed.* **2006**, *45*, 947; c) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107; *Angew. Chem. Int. Ed.* **2005**, *44*, 105; d) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11204; e) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119; f) N. Mase,

- R. Thayumanavan, F. Tanaka, C. F. Barbas, III, *Org. Lett.* **2004**, *6*, 2527; g) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482.
- [6] a) C.-J. Wang, Z.-H. Zhang, X.-Q. Dong, X.-J. Wu, *Chem. Commun.* **2008**, 1431–1433; b) C.-J. Wang, Z.-H. Zhang, X.-Q. Dong, Z.-Y. Xue, H.-L. Teng, *J. Am. Chem. Soc.* **2008**, *130*, 8606.
- [7] Relevant publications on nitro-Michael reactions catalyzed by bifunctional thiourea-based catalysts, see: a) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451; b) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170; c) D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Adv. Synth. Catal.* **2006**, *348*, 826; d) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366; e) S. Wei, D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Catal. Today* **2007**, *121*, 151; f) K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li, J.-A. Ma, *Org. Lett.* **2007**, *9*, 923; g) D. Xue, Y.-C. Chen, Q.-W. Wang, L.-F. Cun, J. Zhu, J.-G. Deng, *Org. Lett.* **2005**, *7*, 5293; h) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367; i) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481; j) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; k) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119; l) J. Lubkoll, H. Wennemers, *Angew. Chem.* **2007**, *119*, 6965; *Angew. Chem. Int. Ed.* **2007**, *46*, 6841.
- [8] The synthesis of the organocatalysts **II** see Supporting Information for details.
- [9] Other kinds of organocatalysts having multiple hydrogen-bonding donors have already been developed, see: a) R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem.* **2005**, *117*, 6734; *Angew. Chem. Int. Ed.* **2005**, *44*, 6576; b) Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589; c) A. Berkesel, K. Roland, J. M. Neudorfl, *Org. Lett.* **2006**, *8*, 4195; d) Y. H. Liu, L. H. Chen, M. Shi, *Adv. Synth. Catal.* **2006**, *348*, 973.
- [10] A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151.
- [11] Results of the solvent screening studies at room temperature: CH<sub>2</sub>Cl<sub>2</sub> (93% yield, dr 90:10, ee 89%); THF (90% yield, dr 76:24, ee 73%); CHCl<sub>3</sub> (92% yield, dr 75:25, ee 73%); EtOAc (88% yield, dr 74:26, ee 87%); MeCN (91% yield, dr 87:13, ee 73%); DMSO (70% yield, dr 64:36, ee 6%); MeOH (87% yield, dr 85:15, ee 0%).
- [12] The absolute configurations of the major products were assigned by HPLC and optical rotation comparisons with the published results (see Supporting Information for details).

Received: July 13, 2008  
Published online: August 26, 2008