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Organocatalytic Asymmetric Michael Addition of 2,4-Pentandione to Nitroolefins

Jian Wang,[†] Hao Li,[†] Wenhu Duan,[‡] Liansuo Zu,[†] and Wei Wang*,[†]

Department of Chemistry, University of New Mexico, Albuquerque, New Mexico 87131-0001, and Shanghai Institute of Materia Medica, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, Shanghai, 201203, People's Republic of China

wwang@unm.edu

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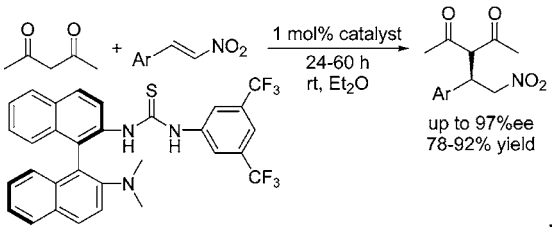
ABSTRACT



A novel binaphthyl-derived amine thiourea organocatalyst has been developed and demonstrated to efficiently catalyze Michael addition reactions (using as low as 1 mol % loading) of diketones to nitroalkenes with remarkably high enantioselectivities.

One of the important Michael addition reactions is the addition of nucleophiles to electron deficient nitroalkenes.[1,2] Because the versatile nitro functionality can be easily transformed into an amine, nitrile oxide, ketone, carboxylic acid, hydrogen, etc.,[2b] various enantioselective processes have been reported mainly by employing stoichiometric amounts of enantiopure additives.[3] Catalytic asymmetric versions of this reaction have also been achieved by using chiral metal−ligand complexes.[4] Recently, more environmentally friendly, metal-free organocatalysts have been developed to catalyze efficient asymmetric Michael addition reactions.[5−7] In these approaches, the donors employed have been restricted to aldehydes and ketones,[5] malonate esters,[6] and ketoesters.[7] Herein, we wish to report a novel class of organocatalyst, bifunctional binaphthyl-derived amine thioureas, which we have shown to be valuable for catalyzing highly enantiose-

[†] University of New Mexico.
[‡] Chinese Academy of Sciences.

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, UK, 1992.

(2) For recent reviews of asymmetric Michael addition reactions, see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (c) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (d) Sibi, M.; Manyem, S. *Tetrahedron* **2001**, *56*, 8033.

(3) (a) Ono, N.; Miyake, H.; Kamimura, A.; Hamamoto, L.; Tamura, R.; Kaji, A. *Tetrahedron* **1985**, *41*, 4013. (b) Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2002**, *124*, 11689. (c) Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305.

(4) For selected examples, see: (a) Kobayashi, N.; Iwai, K. *J. Org. Chem.* **1981**, *46*, 1823. (b) Ji, J.; Barnes, D. M.; Zhang, J. S.; King, A.; Wittemberg, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215. (c) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192. (d) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262. (e) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *5*, 79.

(5) For organocatalytic asymmetric Michael additions of aldehydes and ketones to nitroolefins, see: (a) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *43*, 1369. (b) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (c) Ender, D.; Seki, A. *Synlett* **2002**, 26. (d) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 2527. (e) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Synthesis* **2004**, 1509. (f) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559. (g) Ishii, T.; Fiujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558. (h) Cobb, A. J. A.; Longbottom, D. A. D.; Shaw, M.; Ley, S. V. *Chem. Commun.* **2004**, 1808. (i) Hayashi, Y.; Gotoh, T.; Hayasji, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (j) Kotrusz, P.; Toma, S.; Schmalz, H.-S.; Adler, A. *Eur. J. Org. Chem.* **2005**, 1577.

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lective Michael addition reactions using 1,3-dioxo compounds as donors.[6b,7,8] Furthermore, in this preliminary study, we have demonstrated that the Michael adducts can be readily converted to synthetically and biologically useful building blocks, α-substituted-β-amino acids.

In the past few years, the utilization of chiral ureas/thioureas has emerged as a viable strategy in the design of efficient organocatalysts for asymmetric organic transformations.[6,9−12] Notable examples include Jacobsen's ureas/thioureas for a variety of reactions[10] and Takemoto's amine thioureas for Michael addition and aza-Henry reactions.[6a,b,11] It is noted that both catalyst systems are built upon the *trans*-cyclohexane diamine scaffold. More recently, cinchona alkaloids-based thioureas have been employed for the Michael addition reaction as well.[12] However, thioureas derived from another important "privileged" structure, binaphthyl, have not been reported yet.[13] We envisioned that including a thiourea and an amine moiety on that scaffold could lead to a new class of bifunctional organocatalysts, which would provide high catalytic activity and high enantioselectivity toward organic reactions. The results from this investigation disclosed that the newly designed organocatalyst **VI** displayed remarkably catalytic activity (1 mol % catalyst loading) in bond-forming processes while achieving excellent levels of enantioselectivities (up to 97% ee) by its dual functional activations of substrates (Figure 1).

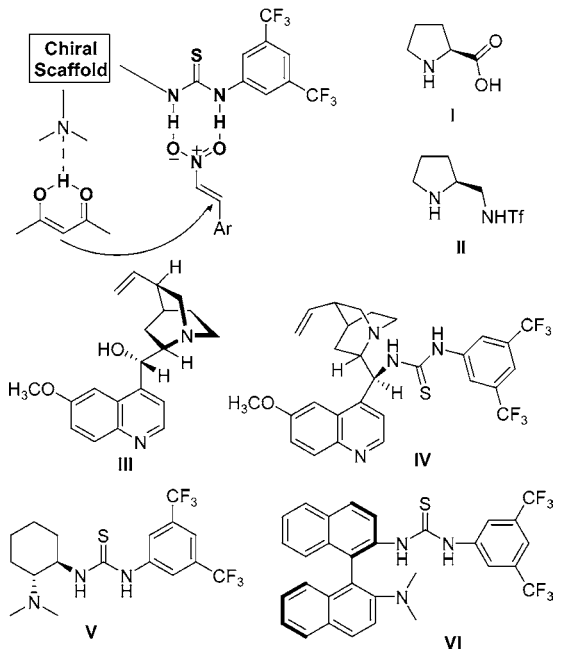
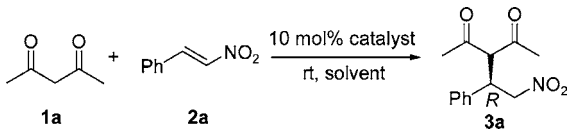


Figure 1. Screened organocatalysts.

In the initial study, six organocatalysts were screened for the process (Figure 1 and Table 1). They include compounds

Table 1. Results of Organocatalyst Screening for Asymmetric Michael Addition Reactions of 2,4-Pentanedione (**1a**) and *trans*-β-Nitrostyrene (**2a**)[a]



entry	catalyst	solvent	*t* (h)	yield (%)[b]	ee (%)[c]
1	**I**	THF	60	<10	n.d.[d]
2	**II**	THF	30	<10	n.d.[d]
3	**III**	THF	48	52 (90)[g]	17
4	**IV**	THF	48	47 (95)[g]	96
5	**V**	THF	8	92	84
6	**VI**	THF	3.5	93	95
7	**VI**	toluene	7	89	91
8	**VI**	Et_2O	5	95	97
9[e]	**VI**	Et_2O	15	92	95
10[f]	**VI**	Et_2O	28	95	95
11	**VI**	DMSO	2	96	5

[a] Unless otherwise specified, the reaction was carried out with 2 equiv of **1a** and 1 equiv of **2a** in the presence of 10 mol % of catalyst at room temperature on a scale of 0.17 mmol of **2a**. [b] Isolated yields. [c] Enantiomeric excess (ee) determined by chiral HPLC analysis (Chiralpak AS-H). [d] Not determined. [e] 2 mol % of catalyst used. [f] 1 mol % of catalyst used. [g] Yields based on recovered starting materials.

I−**V**, which have been used for catalyzing various reactions[9−12] and the newly designed **VI**.[14] A reaction between 2,4-pentandione **1a** and *trans*-β-nitrostyrene **2a** in THF at room temperature in the presence of one of the six catalysts (10 mol %) was used to evaluate their catalytic activities. The results showed that catalysts **I**−**III** exhibited poor activities (Table 1, entries 1−3). In contrast, thioureas **IV**−**VI** afforded promising results (entries 4−6). Under the same reaction conditions, catalyst **IV** gave the product **3a** in high enan-

(6) For organocatalytic asymmetric Michael addition of malonates to nitroolefins, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906.

(7) For organocatalytic asymmetric Michael addition of ketoesters to nitroolefins, see: Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105.

(8) Catalyst **V** (10 mol %) also tested for the reaction in toluene, see ref 6b: 80% yield and 89% ee and cinchona alkaloids have been employed for the process, but very low enantioselectivities (26−29% ee) were obtained: Brunner, H.; Kimel, B. *Monatsh. Chem.* **1996**, *127*, 1063.

(9) For reviews related to ureas/thioureas catalysis, see: (a) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062. (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (c) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.

(10) For Jacobsen's urea and thiourea catalysis, see: (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279. (c) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012. (d) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466. (e) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. (f) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.

(11) For Takemoto's amine thioureas for catalysis, see: (a) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (b) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032 and refs 6a and 6b. (c) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807. (d) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898.

(12) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967.

(13) For a review of "privileged" structures in catalysis, see: Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

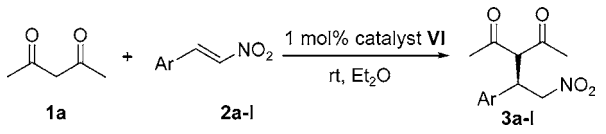
(14) For preparation of the catalyst, see the Supporting Information.

tioselectivity (96% ee), but required a long reaction time. The **V**-catalyzed process was accomplished in a much shorter time, but a lower enantioselectivity was observed. The new organocatalyst **VI** proved to be the best choice for further investigation. In this instance, not only did the reaction proceed to completion within 3.5 h, but a high reaction yield (93%) and high enantioselectivity (95% ee) were achieved as well.

A survey of nine solvents revealed that a variety of solvents were tolerated by this Michael addition reaction.[15] Generally, in polar solvents such as DMSO (Table 1, entry 11), almost no enantioselectivity for product **3a** was observed probably because of the destruction of hydrogen bonding interactions between the thiourea and the nitro group in the substrate by strongly H-bonding acceptor solvents. As expected, when reactions were conducted in less polar solvents, high enantioselectivities were obtained (entries 6−10). With Et_2O as solvent, the Michael adduct **3a** was isolated with the highest ee (97%) in 95% yield (entry 8). Further optimization of this process showed that the reaction could be performed with as low as 1 mol % of catalyst loading (entry 10), where a comparable result (95% ee, 87% yield) was achieved without an excessive increase in reaction time.

With optimized reaction conditions in hand, the scope of the reaction was explored (Table 2).[16] The Michael addition

Table 2. Catalyst **VI** Catalyzed Michael Addition Reactions of 2,4-Pentanedione (**1a**) to *trans*-β-Nitrostyrenes[a]



entry	Ar	t (h)	yield (%)[b]	ee (%)[c]
1	Ph (**3a**)	26	87	95
2	4-Me-C_6H_4 (**3b**)	36	84	93
3	4-MeO-C_6H_4 (**3c**)	36	92	97
4	4-BnO-C_6H_4 (**3d**)	26	90	94
5	4-Cl-C_6H_4 (**3e**)	24	91	97
6	4-Br-C_6H_4 (**3f**)	27	89	95
7	2-BnO-C_6H_4 (**3g**)	48	80	89
8	2-MeO-C_6H_4 (**3h**)	30	92	97
9	4-CF_3-C_6H_4 (**3i**)	24	86	83
10	2,4-$(MeO)_2$-C_6H_3 (**3j**)	36	88	91
11	3-BnO-4-MeO-C_6H_4 (**3k**)	60	78	88
12	2,3-$(MeO)_2$-C_6H_3 (**3l**)	36	87	92

[a] See footnote *a* in Table 1. [b] Isolated yield after chromatographic purification. [c] Determined by chiral HPLC analysis (Chiralpak AS-H, or AD and Chiralcel OD-H).

reaction of 2,4-pentanedione **1a** with a variety of nitroolefins **2** was probed. The results showed that, in general, the reactions took place efficiently (78−92% yield) with high to excellent levels of enantioselectivity (83−97% ee) for all of the nitroolefins tested. The processes were applicable to *trans*-β-nitrostyrenes bearing electron-withdrawing (Table 2, entries 5, 6, and 9) and electron-donating substituents (entries 2−4, 7−8, and 10−12). For one of the products, the absolute configuration **3f** was determined by X-ray crystallography to be *R* (Figure 2).[17]

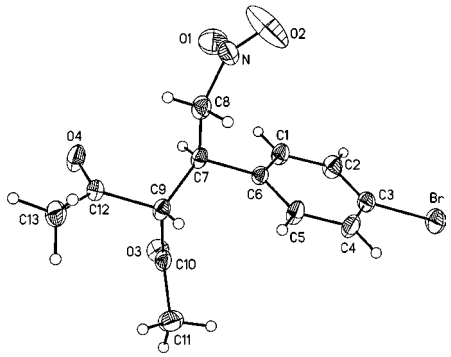
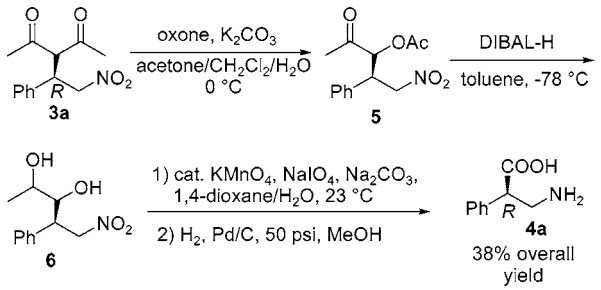


Figure 2. X-ray crystal structure of **3f**.

It was anticipated that the Michael adducts **3** could be employed for the efficient preparation of α-substituted β-amino acids (Scheme 1).[18] This transformation was

Scheme 1. Synthesis of α-phenyl-β-alanine **4a**



demonstrated as follows. Compound **3a** was converted into α-acetoxyketone **5** by Bayer−Villiger oxidation, and subsequently reduced to diol **6**. Following the cleavage of the diol by sodium periodate in the presence of $KMnO_4$, hydrogenation of the nitro group with Pd/C gave α-phenyl-β-alanine **4a** in a 38% overall yield. Its positive optical

(15) Other solvents also were tested: $CHCl_3$—4.5 h (reaction time), 98% yield, 95% ee; ethyl vinyl ether—7.0 h, 89% yield, 91% ee; anisole—7.0 h, 93% yield, 91% ee; ethylene glycol dimethyl ether—7.0 h, 90% yield, 92% ee; and DMF—4.0 h, 94% yield, 4% ee.

(16) Diethyl malonate was also evaluated for the process with *trans*-β-nitrostyrene **2a** under the same reaction conditions to give adduct in 94% yield and 86% ee (24 h).

(17) See the Supporting Information for X-ray crystallographic information; CCDC 279501 also contains the supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk.

(18) Barbas and co-workers and we have developed organocatalytic, enantioselective Mannich-type reactions for the preparation of α- and β-amino acids: (a) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III *J. Am. Chem. Soc.* **2002**, *124*, 1842. (b) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III *J. Am. Chem. Soc.* **2002**, *124*, 1866. (c) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243.

rotation ($[\alpha]^{25}_D$ +88.2, *c* 0.5, H_2O) corresponds to the *R* configuration of **4a** (lit.[19] $[\alpha]^{25}_D$ +85, *c* 0.2, H_2O). Thus, the Michael adduct **3a** with *R* configuration was further confirmed.

In summary, we have developed a new bifunctional binaphthyl-derived amine thiourea **VI**, which serves as an efficient organocatalyst for asymmetric Michael addition of a 1,3-diketone to nitroolefins. This catalyst has allowed us to demonstrate the first highly enantioselective Michael reaction of a 1,3-diketone as donor with β-nitrostyrenes. Because of its high catalytic activity, utilization of the catalyst **VI** in an amount as low as 1 mol % is sufficient for the process. Moreover, the Michael addition products can be readily converted into the valuable α-substituted-β-amino acids building blocks. Further investigation of the full scope of this Michael reaction, its mechanism, and applications of the novel organocatalyst **VI** in other reactions is underway in our laboratory and the results will be reported in due course.

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Supporting Information Available: Experimental procedures and ^1H, ^{13}C NMR and HRMS data for catalyst **VI** and products **3** and X-ray crystallographic information of **3f** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Davies, H. M. L.; Ren, P. *Tetrahedron Lett.* **2001**, *42*, 3149.