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

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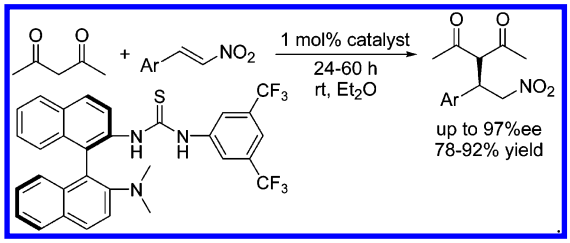
## ABSTRACT




**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-

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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).

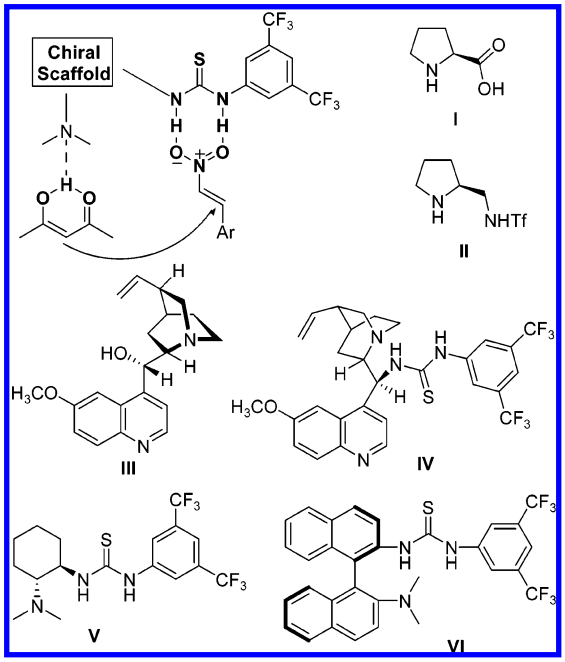
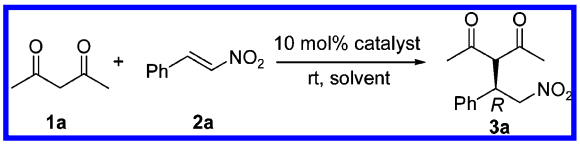



**Figure 1.** Screened organocatalysts.

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.

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(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.

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

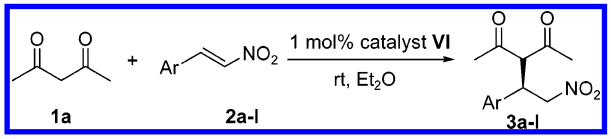
(14) For preparation of the catalyst, see the Supporting Information.

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*-$\beta$-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*-$\beta$-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]

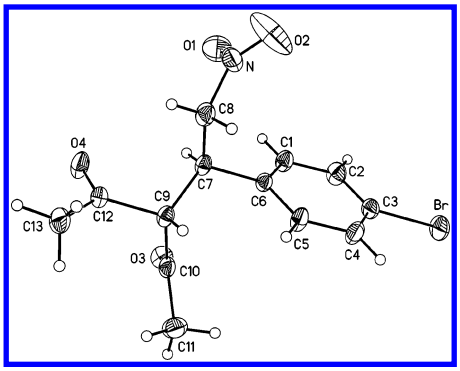
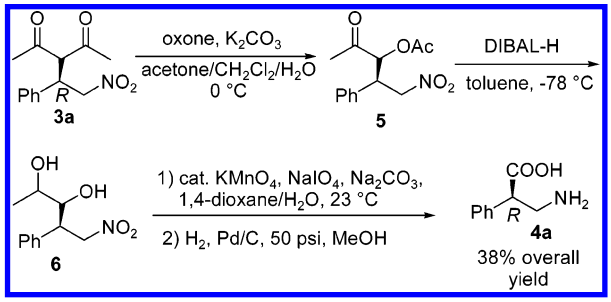



**Figure 2.** X-ray crystal structure of **3f**.

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

**Scheme 1.** Synthesis of α-phenyl-$\beta$-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-$\beta$-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*-$\beta$-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 $\beta$-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 $\beta$-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 $\alpha$-substituted-$\beta$-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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