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Organocatalytic Enantioselective Michael Addition of 2,4-Pentandione to Nitroalkenes Promoted by Bifunctional Thioureas with Central and Axial Chiral Elements

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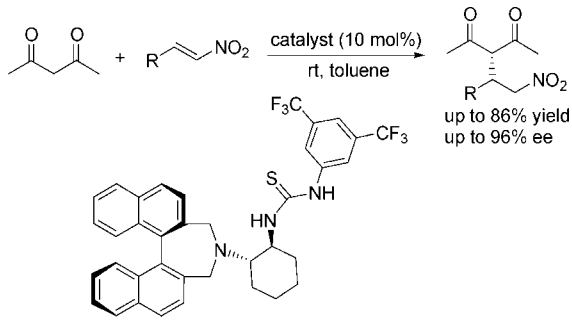

Two novel bifunctional amine-thiourea organocatalysts **1** and **2**, which both bear central and axial chiral elements, have been developed to promote enantioselective Michael reaction between 1,3-dicarbonyl compounds and nitro olefins. The catalyst **2** afforded the desired products with good levels of enantioselectivity (up to 96% ee), showing clearly that two chiral elements of **2** are matched, and enhance the stereochemical control.

The nitroalkanes are important building blocks and intermediates in organic synthesis because the nitro group can be easily transformed into other useful groups such as amines and carbonyls.[1] Michael addition of carbon-centered nucleophiles to nitro olefins represents a direct and powerful approach to chiral nitroalkanes. As a result, a considerable of effort has been devoted to the development of catalytic enantioselective versions of the process.[2]

Although the catalytic asymmetric versions of this reaction have been achieved, most required metal catalysts or strict reaction conditions.[3] Recently, the development of organocatalytic asymmetric Michael addition reactions of nitro olefins has received growing attention.[4] Impressive progress has been made in the development of metal-free bifunctional organic catalysts for the enantioselective addition of aldehydes and ketones,[5] malonate esters,[6] and ketoesters[7] to nitroalkenes. Nonetheless, few successful organocatalysts have been demonstrated for the enantioselective addition of 1,3-diketone compounds to nitro olefins. Recently, Wang and co-workers have developed the first highly enantioselective organocatalytic Michael addition of 2,4-pentandione to aryl nitroalkenes.[8] As part of our interest in asymmetric organocatalysis,[9] we want to describe a novel type of bifunctional chiral amine-thiourea organocatalyst for promoting the Michael reaction between 1,3-diketone compounds and nitro olefins with good levels of enantioselectivity (up to 96% ee). In addition, other types of 1,3-dicarbonyl compounds such as malonate ester and β-ketoester were also briefly investigated.

In the past few years, chiral urea and thiourea derivatives have emerged as new and efficient organocatalysts for various enantioselective reactions.[10] Among them, Takemoto's amine-thioureas,[11] Jacobsen's ureas/thioureas,[12] and cinchona alkaloid-

(1) For reviews, see: (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. (b) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017.

(2) For reviews, see: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (b) Almasi, D.; Alonso, D. A.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (c) Vicario, J. L.; Badia, D.; Carrillo, L. *Synthesis* **2007**, 2065.

(3) For selected examples, see: (a) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958. (b) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148. (c) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700. (d) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *5*, 79. (e) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262. (f) Luchaco-cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192. (g) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716. (h) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215.

(4) For a review, see: Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

(5) For selected examples, see: (a) Xiong, Y.; Wen, Y.; Wang, F.; Gao, B.; Liu, X.; Huang, X.; Feng, X. *Adv. Synth. Catal.* **2007**, *349*, 2156. (b) Wei, S.; Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Catal. Today* **2007**, *121*, 151. (c) Tsogoeva, S. B.; Wei, W. *Chem. Commun.* **2006**, 1451. (d) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826. (e) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (f) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. (g) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *43*, 1369. (h) Hayashi, Y.; Gotoh, T.; Hayasji, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (i) Tsogoeva, S. B.; Yalalov, D. A.; Hateley, M. J.; Weckbecker, C.; Huthmacher, K. *Eur. J. Org. Chem.* **2005**, 4995. (j) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147. (k) Cobb, A. J. A.; Longbottom, D. A. D.; Shaw, M.; Ley, S. V. *Chem. Commun.* **2004**, 1808. (l) Ishii, T.; Fiujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558. (m) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 2527. (n) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Synthesis* **2004**, 1509. (o) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559. (p) Enders, D.; Seki, A. *Synlett* **2002**, 26. (q) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.

(6) For selected examples, see: (a) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) Li, Y.; Wang, H.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (d) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

(7) 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) (a) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713. (b) Cinchona alkaloids have also been employed for the process, but very low enantioselectivities (26−29% ee) were achieved: (c) Brunner, H.; Kimel, B. *Monatsh. Chem.* **1996**, *127*, 1063.

(9) Peng, F.; Shao, Z. *J. Mol. Catal. A: Chem.* **2008**, *285*, 1.

(10) For a review, see: (a) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. For selected references, see: (b) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (c) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *8*, 407. (d) Zhang, Z.; Schreiner, P. R. *Synthesis* **2007**, 2559.

(11) For reviews, see: (a) Takemoto, Y.; Miyabe, H. *Chimia* **2007**, *61*, 269. (b) Takemoto, Y. *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 1139. (c) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299.

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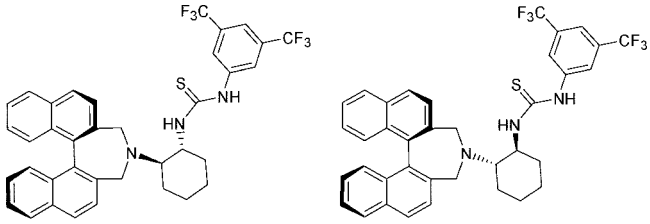
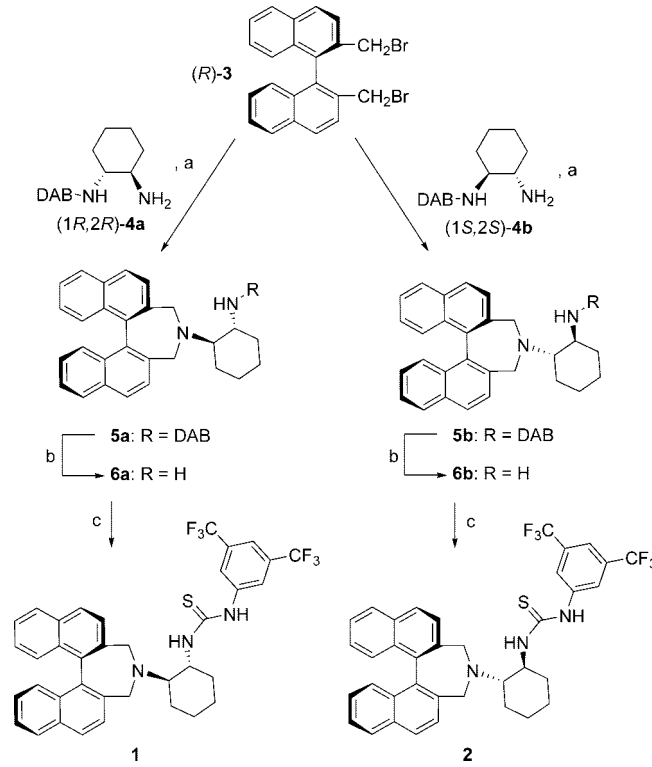


FIGURE 1. Designed bifunctional catalysts **1** and **2** with both central and axial chiral elements.

based thioureas[13] are the most popular, and have been widely used in many asymmetric reactions. In addition, other types of thiourea catalysts such as imidazole-thioureas,[5i] guanidine-thioureas,[14] pyrrolidine-thioureas,[15] and oxazoline-thioureas[16] have been found to be useful for different asymmetric transformations. It is noted, however, that most of them contain central chirality as the only asymmetric element. Chiral urea and thiourea organocatalysts bearing two different types of stereogenic structures in the same molecule are few. We envisioned that appropriately introducing a second chiral element in a chiral urea/thiourea molecule could facilitate its tunability, and would lead to finding an optimal chiral organocatalyst. To achieve catalytic enantioselective Michael reaction into nitro olefins with thioureas, we designed novel bifunctional organocatalysts **1** and **2** bearing both central and axial chiral elements (Figure 1). The influence of these elements on the enantioselectivity of Michael addition of 2,4-pentandione to nitroalkenes was also studied. To the best of our knowledge, this is the first highly enantioselective organocatalytic Michael reaction of nitro olefins promoted by amine-thioureas containing both central and axial chiral elements.

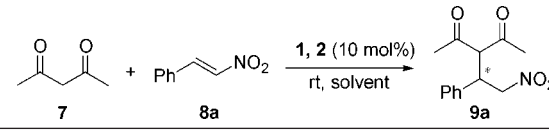
The two bifunctional chiral amine-thioureas **1** and **2**, carrying the same absolute configuration of the binaphthyl unit, but differing in the two stereogenic centers of the cyclohexyl scaffold, were synthesized by following the procedure described in Scheme 1. The reaction of (*R*)-2,2′-di(bromomethyl)-1,1′-binaphthyl **3**[17] with DAB (1,3-dimethyl-5-acetylbarbituric acid)-monoprotected (1*R*,2*R*)- and (1*S*,2*S*)-cyclohexyldiamines **4a** and **4b** in CH_2Cl_2 in the presence of Et_3N as the base gave the corresponding tertiary amines **5a** and **5b** in 76% and 74% yield,

SCHEME 1. Synthesis of Organocatalysts 1 and 2[a]



[a] Reagents and conditions: (a) Et_3N, CH_2Cl_2, 35 °C, **5a** 76%, **5b** 74%; (b) KOH, 96% EtOH, 50 °C, **6a** 89%, **6b** 90%; (c) 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene, THF, rt, **1** 91%, **2** 92%.

TABLE 1. Enantioselective Addition of 2,4-Pentandione (7) to *trans*-β-Nitrostyrene (8a) Catalyzed by Amine-Thioureas 1 and 2[a]



entry	catalyst	solvent	yield (%)	ee (%)[b]
1	**1**	toluene	84	78(*R*)
2	**2**	toluene	82	93(*S*)
3	**2**	DCM	80	89(*S*)
4	**2**	THF	78	84(*S*)
5	**2**	Et_2O	81	90(*S*)
6	**2**	DMSO	63	28(*S*)

[a] The reaction was performed with *trans*-β-nitrostyrene (**8a**) and 2,4-pentandione (**7**) (2 equiv) in the presence of catalysts (10 mol %) at room temperature for 16 h. [b] Enantiomeric excess (ee) was determined by chiral HPLC analysis (Chiralpak AS-H).

respectively.[18] Subsequent deprotection of **5a** and **5b** with KOH in 96% EtOH solution at 50 °C afforded primary amines **6a** and **6b** in 89% and 90% yield, respectively. Finally, condensation of **6a** and **6b** with 1 equiv of 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene in THF provided the chiral amine-thiourea catalysts **1** and **2** in 91% and 92% yield, respectively.

The efficacy of bifunctional amine-thioureas **1** and **2** as chiral organocatalysts was initially evaluated by using the reaction of 2,4-pentandione **7** with *trans*-β-nitrostyrene **8a** in toluene at room temperature (Table 1). Under the same conditions, catalyst **2** gave desired product **9a** in higher enantioselectivity (93% ee,

(12) For a review, see: Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.

(13) For selected examples, see: (a) Diner, P.; Nielsen, M.; Bertelsen, S.; Niess, B.; Jorgensen, K. A. *Chem. Commun.* **2007**, 3646. (b) Wang, J.; Zu, L.; Li, H.; Xie, H.; Wang, W. *Synthesis* **2007**, 2576. (c) Lubkoll, J.; Wennemers, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6841. (d) Gu, C.; Liu, L.; Sui, Y.; Zhao, J.; Wang, D.; Chen, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 455. (e) Hynes, P. S.; Stranges, D.; Stupple, P. A.; Guarna, A.; Dixon, D. J. *Org. Lett.* **2007**, *9*, 2107. (f) Amere, M.; Lasne, M. C.; Rouden, J. *Org. Lett.* **2007**, *9*, 2621. (g) Liu, T.; Cui, H.; Chai, Q.; Long, J.; Li, B.; Wu, Y.; Ding, L.; Chen, Y. *Chem. Commun.* **2007**, 2228. (h) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Mazzanti, A.; Sambri, L.; Melchiorre, P. *Chem. Commun.* **2007**, 722. (i) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599. (j) Song, J.; Shih, H. W.; Deng, L. *Org. Lett.* **2007**, *9*, 603. (k) Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (l) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (m) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929. (n) Wang, Y.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156. (o) Li, H.; Wang, Y.; Deng, L. *Org. Lett.* **2006**, *8*, 4063. (p) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967.

(14) (a) Sohtome, Y.; Takemura, N.; Takada, K.; Takagi, R.; Iguchi, T.; Nagasawa, K. *Chem. Asian J.* **2007**, *2*, 1150. (b) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643.

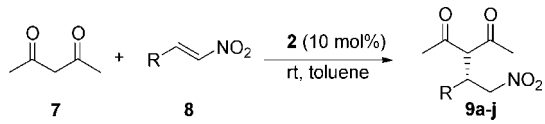
(15) (a) Cao, C.; Ye, M.; Sun, X.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901. (b) Cao, Y.; Lai, Y.; Wang, X.; Li, Y.; Xiao, W. *Tetrahedron Lett.* **2007**, *48*, 21.

(16) Chang, Y.; Yang, J.; Dang, J.; Xue, Y. *Synlett* **2007**, 2283.

(17) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679.

(18) Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5978.

TABLE 2. Organocatalytic Enantioselective Addition of 2,4-Pentandione (7) to Various Nitro Olefins 8 Promoted by Amine-Thioureas 2[a]



entry	R	yield (%)	ee (%)[b]
1	Ph (**8a**)	82	93
2	4-Cl-C_6H_4 (**8b**)	86	94
3	4-Br-C_6H_4 (**8c**)	84	94
4	2-CF_3-C_6H_4 (**8d**)	81	91
5	2-BnO-C_6H_4 (**8e**)	78	96
6	2,3-$(MeO)_2$-C_6H_3 (**8f**)	83	96
7	4-Me-C_6H_4 (**8g**)	80	93
8	4-MeO-C_6H_4 (**8h**)	85	92
9	4-BnO-C_6H_4 (**8i**)	83	90
10	*i*-Bu (**8j**)	80	76[c]

[a] The reaction was performed with 2,4-pentandione (**7**) (2 equiv) and nitro olefins **8** in the presence of catalyst **2** (10 mol %) at room temperature. [b] Enantiomeric excess (ee) was determined by chiral HPLC analysis (Chiralpak AS-H, OD-H, and AD/AD-H). [c] Absolute configuration was not determined.

entry 2), whereas catalyst **1** afforded product **9a** in lower enantioselectivity (78% ee, entry 1), as well as a reversal of the absolute configuration of product **9a**. These results demonstrate that the two chiral elements in chiral amine-thiourea catalyst **2** are matched, enhancing the stereochemical control, whereas the two chiral elements in chiral amine-thiourea catalyst **1** are mismatched. Furthermore, the central chiral element of catalysts predominates the absolute configuration of product **9a**. Next, the influence of the solvents was investigated by using the bifunctional organocatalyst **2**. In polar solvents such as DMSO (Table 1, entry 6), lower enantioselectivity for product **9a** was observed. This is probably due to the destruction of hydrogen bonding interactions between the thiourea and the nitro group in the substrate in strongly H-bonding-acceptor solvents. As expected, when reactions were conducted in less polar solvents, higher enantioselectivities were obtained (entries 2−5, Table 1). With toluene as the solvent, the Michael adduct **9a** was isolated with the highest ee (93%) in 82% yield (entry 2).

Experiments that probe the scope and limitations of the nitroalkene substrates utilizing the bifunctional catalyst **2** are summarized in Table 2. The Michael addition reactions of aromatic nitro olefins **8a**−**i** with 2,4-pentandione (**7**) proceeded smoothly with good enantioselectivities (90−96% ee). It appears that the position and the electronic property of the substituents for aromatic rings of nitroalkenes are well tolerated by the Michael addition reactions. Whether electron-withdrawing (entries 2−4, Table 2), -donating (entries 5−9, Table 2), or -neutral (entry 1, Table 2) groups on aromatic rings were used, the reactions proceeded smoothly to give the desired adducts in good yields (78−86%) with good enantioselectivities (90−96% ee). The Michael reaction of aliphatic nitro olefin **8j** reacted with 2,4-pentandione **7** to afford the desired product **9j** in 80% yield and 76% ee value (entry 10, Table 2). Although the enantioselectivity of the product with aliphatic nitro olefin is not so high as the enantioselectivity with aromatic nitroalkenes, this is the first example of enantioselective addition of 1,3-diketone to aliphatic nitro olefin. Absolute configurations of **9a**−**i** were determined by comparing the retention time of HPLC of products with those of literature data.

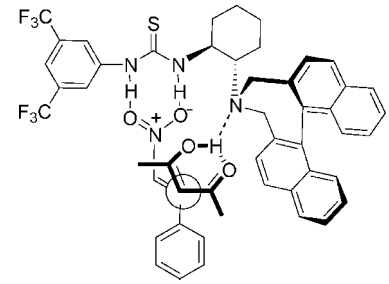
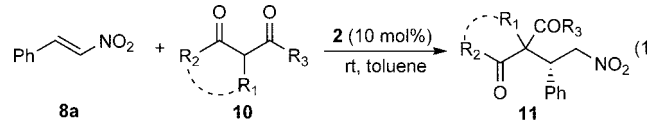


FIGURE 2. Proposed catalytic reaction mode through double activation.

Other types of 1,3-dicarbonyl compounds **10** were also applicable to the present catalytic system (eq 1). For α-monosubstituted 1,3-diketone **10a**, malonate ester **10b**, and *β*-ketoester **10c**, the corresponding adducts were obtained in good yields (75−81%) and enantioselectivities (80−84%) at the *β*-position to the nitro group.



(1)

	yield (%)	*ee* (%)
10a: R_1, R_2 = $CH_2CH_2CH_2$, R_3 = Me	76	83*1
10b: R_1= H, R_2 = R_3 = OMe	81	84
10c: R_1= H, R_2 = Me, R_3 = OEt	80	80*2

*1 *dr* = 94/6 diastereomeric mixture; *2 1:1 diastereomeric mixture

A plausible catalytic mode representing the prototypical addition of 2,4-pentandione (**7**) to *trans*-*β*-nitrostyrene (**8a**) in the presence of **2** as a catalyst is shown in Figure 2, in which a thiourea moiety of the catalyst **2** interacts through hydrogen bonding with a nitro group of the nitroalkene and enhances their electrophilicity while the tertiary amine deprotonates an acidic proton of 2,4-pentandione (**7**), generating a ternary complex. The synergistic steric hindrance from the chiral dihydroazepine moiety of bifunctional catalyst **2** might be responsible for the increased stereocontrol of the Michael addition reaction. Nevertheless, the real catalytic mechanism still needs further investigation.

In summary, we have developed two novel bifunctional amine-thiourea organocatalysts **1** and **2**, which both bear central and axial chiral elements, for promoting the enantioselective Michael reaction between 1,3-dicarbonyl compounds and nitro olefins.[19] Catalyst **2** afforded the desired products with levels of enantioselectivity of up to 96% ee, showing clearly that two chiral elements of **2** are matched, and enhance the stereochemical control. Our research might have implications for the design of novel chiral organocatalysts. Utilization of these bifunctional amine-thiourea organocatalysts in other asymmetric reactions is under way in our laboratory.

Experimental Section

Typical Procedure for Michael Addition Reaction Catalyzed by Bifunctional Catalyst 2. The catalyst **2** (6.63 mg, 0.01 mmol, 10 mol %) was added to a vial containing 2,4-pentanedione **7** (20

(19) The catalysts can be recovered and reused after further purification. For example, the Michael addition reaction of 2,4-pentandione (**7**) and *trans*-*β*-nitrostyrene (**8a**) in the presence of recovered catalyst **2** (10 mol %) afforded adduct **9a** in 73% yield and 89% ee (1st run).

mg, 0.2 mmol) and *trans*-β-nitrostyrene **8a** (14.9 mg, 0.1 mmol) in dry toluene (1 mL) at room temperature. After 16 h of stirring, the reaction mixture was quenched with 1 M aqueous HCl solution, extracted with EtOAc, and dried over Na_2SO_4. The crude product was purified by flash silica gel chromatography to give 20.4 mg (82%) of the adduct **9a** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 3H), 7.19−7.16 (m, 2H), 4.64−4.59 (m, 2H), 4.35 (d, J = 10.8 Hz, 1H), 4.26−4.22 (m, 1H), 2.26 (s, 3H), 1.92 (s, 3H); HPLC (Chiralpak AS-H, isopropyl alcohol/hexane = 15/85, flow rate 1.0 mL/min, λ = 210 nm) t_{major} = 14.1 min, t_{minor} = 20.2 min.

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Supporting Information Available: The synthesis of catalyst **2**, Michael addition procedure, spectroscopic data of compounds **5b**, **6b**, and **2** adducts **9**, **11**, and chiral HPLC data for the adducts **9**, **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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