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Chiral Binaphthyl-Derived Amine-Thiourea Organocatalyst-Promoted Asymmetric Morita–Baylis–Hillman Reaction

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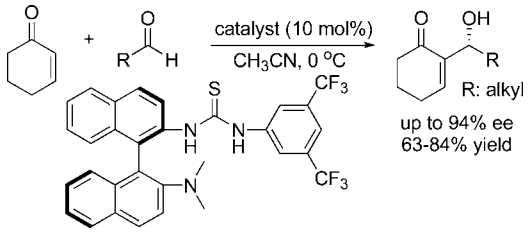
ABSTRACT



A new bifunctional binaphthyl-derived amine thiourea organocatalyst has been developed to promote enantioselective Morita–Baylis–Hillman reaction of cyclohexenone with a wide range of aldehydes. The process, catalyzed by the amine thiourea, affords synthetically valuable chiral allylic alcohol building blocks in high yields and high enantioselectivities.

In recent years, the Morita−Baylis−Hillman (MBH) reaction, which involves forming new C−C bonds and generating highly functionalized chiral allylic alcohols, has received considerable interest in organic synthesis.[1] Therefore, not surprisingly, a considerable amount of effort has been devoted to the development of catalytic, enantioselective versions of the processes. However, discovering catalytic systems for asymmetric MBH reactions has proven to be a synthetic challenge, and to date, few successful chiral catalysts have been demonstrated for this process.[2,3] Among them, notably, the research groups of Hatakeyama[2a] and Chen,[2b] respectively, have developed quinidine-based chiral amines and chiral Lewis acids as catalysts for promoting addition of acrylates to aldehydes. Schaus et al.[2c] reported an elegant BINOL-derived Brønsted acid, and Shi[2d] and Miller[2e] independently used an amino acid as organocatalyst for the asymmetric MBH reactions of α,β-unsaturated ketones with aldehydes. However, both cases require adding a Lewis base for facilitating the reactions. From an operational and atom-economic standpoint, the utilization of bifunctional catalysts is highly desirable, but such catalysts have not been developed yet. Moreover, generally, a bifunctional catalyst can activate two functional groups in

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(1) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049.

(2) For selected examples of the MBH reactions, see: (a) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219. (b) Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. *J. Org. Chem.* **2003**, *68*, 915. (c) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094. (d) Shi, M.; Jiang, J.-K.; Li, C.-Q. *Tetrahedron Lett.* **2001**, *42*, 127. (e) Imbriglio, J. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2003**, *5*, 3741. (f) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241. (g) Marko, I. E.; Giles, P. R.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015. (h) Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533. (i) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589. (j) Karur, S.; Hardin, J.; Headley, A.; Li, G. *Tetrahedron Lett.* **2003**, *44*, 2991. (k) Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* **2002**, 2412. (l) Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* **2002**, 1856.

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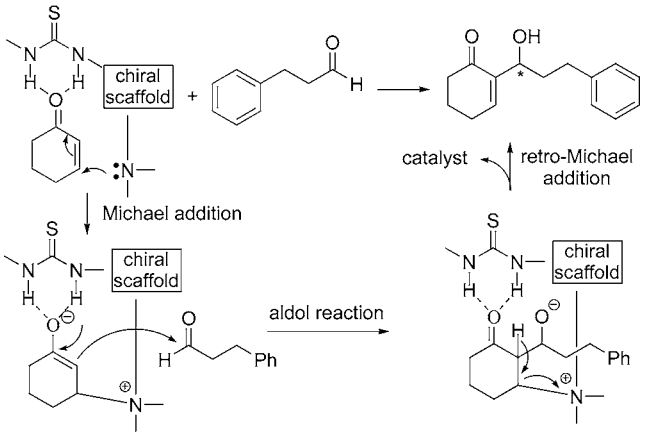
their substrates via synergistic interactions and, thus, specifically control transition state structure, leading to higher catalytic activity and better enantioselectivity.[4] In this communication, we wish to first report a novel type of bifunctional organocatalyst, the chiral amine-thiourea for catalyzing highly enantioselective MBH reactions.

Recently, thiourea-based organocatalysts have been widely used for effective activation of carbonyls, imines, and nitro groups through efficient double hydrogen-bonding interactions.[5,6] We envisioned that appropriately positioning a thiourea and a tertiary amine in a chiral scaffold could result in a new type of bifunctional organocatalyst. The thiourea group would serve as an acid to activate a carbonyl group in α,β-unsaturated systems and, subsequently, facilitate the Michael addition of the tertiary amine to the β-position of the substrate (Scheme 1). Two well-studied chiral scaffolds,

Scheme 1. Proposed Catalytic Cycle for Amine-Thiourea-Promoted MBH Reaction



trans-cyclohexane diamine and binaphthyl diamine, were selected for harboring the thiourea and amine moieties (Figure 1).[7] Compound **I** has been used previously for Michael addition[6h,i,k] and aza-Henry[6j] reactions, whereas binaphthyl-derived amine thioureas **II**−**IV** are first proposed here as organocatalysts for promoting asymmetric transformations. They were readily synthesized from commercially available (*R*)-binaphthyl diamine (see Supporting Information).

(3) aza-MBH reactions also have been studied; for selected examples, see: (a) Shi, M.; Chen, L.-H.; Li, C.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790. (b) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (c) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507. (d) Perlmutter, P.; Teo, C. C. *Tetrahedron Lett.* **1984**, *25*, 5951. (e) Balan, D.; Adolfsson, H. *J. Org. Chem.* **2001**, *66*, 6498. (f) Bertenshaw, S.; Kahn, M. *Tetrahedron Lett.* **1989**, *30*, 2731. (g) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183. (h) Azizi, N.; Saidi, M. R. *Tetrahedron Lett.* **2002**, *43*, 4305. (i) Richter, H.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 2729. (j) Takagi, M.; Yamamoto, K. *Tetrahedron* **1991**, *47*, 8869. (k) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680.

(4) (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236. (b) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *43*, 1369. (c) Breinbauer, R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 3604.

(5) For recent reviews related to use of ureas/thioureas as organocatalysts for organic reactions, see: (a) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (b) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062.

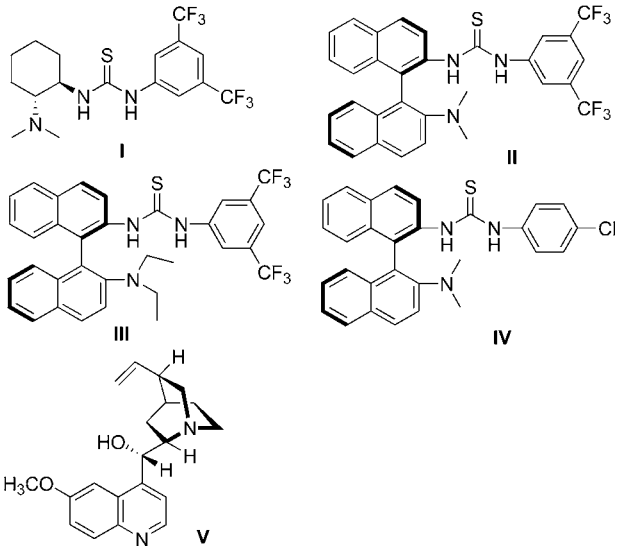
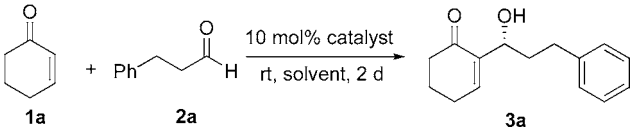


Figure 1. Screened organocatalysts.

An exploratory study using a model reaction of 2-cyclohexen-1-one **1a** with 3-phenylpropionaldehyde **2a** in the presence of 10 mol % catalyst in CH_2Cl_2 at room temperature was conducted to determine the catalytic ability of bifunctional organocatalysts **I**−**V** (Figure 1 and Table 1). Examination of the results revealed that their catalytic activities varied significantly. Cyclohexanediamine-derived amine thiourea **I**, which provided high enantioselectivities for the Michael

Table 1. Optimization Reaction Conditions of Catalytic Asymmetric MBH Reactions of 2-Cyclohexen-1-one (**1a**) with 3-Phenylpropionaldehyde (**2a**)[a]



entry	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	**I**	CH_2Cl_2	21	39
2	**II**	CH_2Cl_2	83	71
3	**III**	CH_2Cl_2	56	73
4	**IV**	CH_2Cl_2	18	*e*
5	**V**	CH_2Cl_2	<10	*e*
6	**II**	toluene	80	77
7[d]	**II**	toluene	63	80
8	**II**	CH_3CN	83	80
9[d]	**II**	CH_3CN	80	83
10	**II**	Et_2O	82	77
11[d]	**II**	Et_2O	72	73
12	**II**	DMSO	47	70

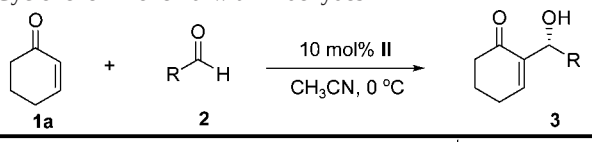
[a] Unless otherwise specified, the reaction was carried out with 5 equiv of **1** and 1 equiv of **2** in the presence of 10 mol % catalyst in CH_2Cl_2 for 2 d. [b] Isolated yields. [c] Enantiomeric excess (ee) determined by chiral HPLC analysis (Chiralcel OD-H). [d] At 0 °C. [e] Not determined.

addition[6h,i,k] and aza-Henry reactions,[6j] showed poor activity toward the MBH reaction. Low reaction yield (21%) and low enantioselectivity (39% ee) were observed (Table 1, entry 1). The newly designed binaphthylamine thiourea **II** afforded the most promising catalytic capacity in terms of reaction yield (83%) and enantioselectivity (71% ee) (Table 1, entry 2). The more bulky analogue **III** displayed similar enantioselectivity (73% ee) but gave a lower yield (56%) (entry 3) in this exploring screening. Catalyst **IV** showed only low catalytic activity in the MBH reaction (18% yield, entry 4). The significant difference in catalyst activities among **II**−**IV** is presumably due to the stronger H-bonding interaction with the carbonyl group of cyclohexenone **1a**, imposed by 3,5-bis(trifluoromethyl) phenyl in **II** and **III** over the *p*-Cl phenyl group in **IV**.[8] The catalytic activity of bifunctional cinchona alkaloid **V** was also evaluated and turned out to be poor (<10% yield) after 48 h (entry 5).

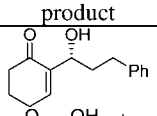
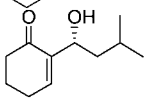
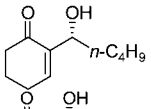
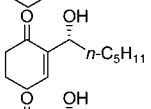
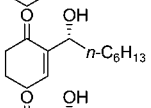
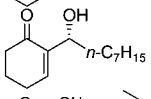
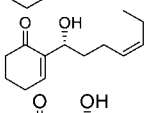
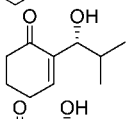
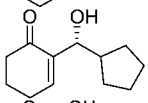
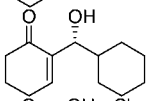
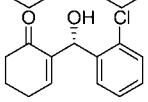
Solvent effects on this process using **II** as the organocatalyst were probed next (Table 1, entries 6−12).[9] The results showed that a variety of solvents can be employed for the **II**-catalyzed MBH reaction. The better results were provided when the reactions were performed in toluene (80% yield, 77% ee, entry 6), CH_3CN (83% yield, 80% ee, entry 8), and Et_2O (82% yield, 77% ee, entry 10) in the presence of 10 mol % **II** at room temperature. Encouraged by these results, we studied the effects of temperature on the reaction in these three solvents. Lowering the temperature to 0 °C resulted in improving enantioselectivities without significantly sacrificing reaction yields (Table 1, entries 7, 9, and 11). In more polar media, such as DMSO, the reaction proceeded slowly (47% yield, entry 12). These studies prompted us to select the reaction conditions using CH_3CN as solvent at 0 °C in the presence of 10 mol % **II** to probe the scope of the MBH reactions.

Reactions of 2-cyclohexen-1-one **1a** with various aldehydes **2** were carried out under the optimized reaction conditions**.** As the results summarized in Table 2 show, the reactions proceeded smoothly to generate chiral allylic alcohols **3** in good yields (63−84%, entries 1−10) and high

Table 2. Catalyst **II**-Catalyzed MBH Reactions of 2-Cyclohexen-1-one **1a** with Aldehydes **2**[a]



1a **2** **3**

entry	product	t (h)	yield (%)[b]	ee (%)[c]
1		48	80	83
2		72	72	80
3		48	84	81
4		60	75	81
5		72	71	80
6		72	74	82
7		72	82	81
8		72	63	94
9		96	71	90
10		120	67	92
11		108	55	60

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

to excellent enantioselectivies (80−94% ee). The absolute configurations of the MBH reaction products were determined by comparison with optical rotation studies of known compounds.[2c] Regardless of the length of linear aliphatic aldehydes **2**, in every case, high enantioselectivities (80−83% ee) and good to high yields (71−84%, entries 1−7) were achieved. More significantly, the more sterically demanding aldehydes gave allylic alcohols with excellent enantioselectivities (90−94% ee) and good yields (63−71%, entries 8−10). Reaction of aromatic aldehyde gave product in lower yield (55%) and lower ee (60%, entry 11).

In summary, the investigation described above has resulted in identifying a novel chiral amine-thiourea bifunctional organocatalyst **II**. It has been demonstrated to promote the asymmetric MBH reactions of cyclohexenone with a variety of aldehydes to afford highly functionalized, synthetically

(6) For selected examples using ureas/thioureas as catalysts in asymmetric organic transformations, 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) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. (e) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466. (f) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. (g) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (h) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (i) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (j) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (k) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032. (l) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967.

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

(8) (a) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120. (b) Etter, M. C.; Panunto, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5896. (c) Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415.

(9) Other solvents were also screened: THF 67% yield, 64% ee; $CHCl_3$ 84% yield, 70% ee; xylenes 73% yield, 74% ee; $PhCF_3$ 77% yield, 73% ee; xylenes 73% yield, 74% ee; anisole 65% yield, 71% ee; *t*BuOMe 72% yield, 69% ee; CH_3CN/Et_2O (v/v, 1/1) 83% yield, 74% ee; *t*BuOME/$PhCF_3$ (v/v, 1/9) 80% yield, 63% ee; 1,4-dioxane 61% yield, 77% ee; and DMF 38% yield, 61% ee.

useful chiral allylic alcohols. In this process, **II** exhibits high catalytic activity and good to excellent levels of enantioselectivity toward this reaction. Further efforts are underway with a focus on improving the catalyst activity and reaction enantioselectivity and probing the full scope of this reaction.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR data for catalyst **II** and products **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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