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Organocatalytic Enantioselective Conjugate Additions to Enones

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The power of conjugate addition reactions is fueled by a wide variety of substances that can serve as electrophiles and nucleophiles, and consequently, a diverse array of products can be generated.[1−4] Versatile nucleophilic enol intermediates, such as nitroalkanes,[5] malonate esters,[6] ketoesters,[7] 1,3-diketones,[8] nitroesters,[9] and 1,3-dinitriles,[10] are valuable nucleophiles for the conjugate addition to α,β-unsaturated systems. More significantly, the adducts of the process afford synthetically useful building blocks in organic synthesis as a result of them possessing various functional groups, such as nitro, ester, ketone, and nitrile moieties, for further elaboration. Despite the fact that these nucleophiles have been employed for the reaction, the reported approaches suffer from a narrow substrate scope and are restricted to a limited combination of nucleophile and electrophile types. In many cases, only one or two types of nucleophiles can react with a specific electrophile. For example, more reactive nitroalkanes have served as nucleophiles for the conjugate addition reaction of α,β-unsaturated carbonyls.[5] The development of general and highly enantioselective conjugate addition reactions, which enable a wide range of nucleophilic enol intermediates to engage in the process, therefore, is of considerable importance but still remains a challenging goal since less reactive nucleophiles, other than nitroalkanes, do not easily participate in the conjugate addition of enones.

In this communication, we wish to describe an efficient and general conjugate addition of a broad spectrum of nucleophilic enol species to enones, catalyzed by a cinchona alkaloid derived thiourea organocatalyst. The reaction affords excellent enantioselectivity and high yields for a diverse array of nucleophiles, including malonate esters, ketoesters, 1,3-diketones, nitroesters, and 1,3-dinitriles and enones as electrophiles.

Bifunctional chiral cinchona alkaloids and amine thioureas have been demonstrated as effective promoters for activation of nucleophilic enol species and α,β-unsaturated carbonyls via acid−base interactions.[11] Accordingly, our investigation began by screening these organocatalysts to evaluate their ability to promote conjugate addition of dimethyl malonate ester **1a** to chalcone **2a** under neat conditions at room temperature (Figure 1 and Table 1). As shown in Table 1, catalytic activity and enantioselectivity toward the process varied significantly (Table 1). Poor enantioselectivities were observed for catalysts **I**−**III** (entries 1−3). In contrast, amine thioureas **IV**−**VI** showed promising results (entries 4−6).[11] **VI** afforded an enantiomeric excess relatively higher (84%) than that of **V** (81% ee) (entries 5 and 6).

When the reaction was performed in a solvent, it was found that reaction media had an impact on the process.[12] Among the media probed, the best results were obtained with xylenes (Table 2, entry 1, 90% yield and 91% ee). It is noted that the reaction was carried out in highly concentrated conditions (14 M of **1**) since it was found that lower concentrations significantly prolonged reaction time.

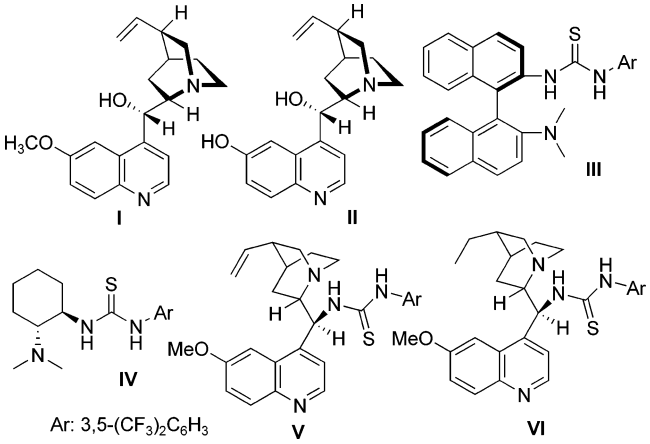
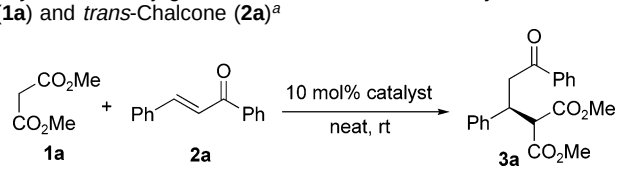


Figure 1. Structures of screened organocatalysts.

Table 1. Results of Exploratory Studies of the Catalytic Asymmetric Conjugate Addition Reaction of Dimethyl Malonate (**1a**) and *trans*-Chalcone (**2a**)[a]



entry	catalyst	*t* (h)	% yield[b]	% ee[c]
1	**I**	96	73	rac[d]
2	**II**	48	85	rac[d]
3	**III**	96	78	20
4	**IV**	96	88	79
5	**V**	72	82	81
6	**VI**	72	86	84

[a] Reaction conditions: unless specified, catalyst (0.02 mmol) was added to a vial containing dimethyl malonate (**1a**) (1 mL, 11.2 mmol) and *trans*-chalcone (**2a**) (0.20 mmol). [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H). [d] Racemic.

Under the optimized reaction conditions, the scope of the reaction was explored. First, the conjugate addition reaction of chalcone **2a** with a variety of nucleophilic enol species **1a**−**h** was examined (Table 2). The results showed that the reactions took place efficiently in good to excellent yields (77−99% yield) with high levels of enantioselectivity (88−93% ee) and were inert to the forms of the nucleophilic enol species **1**. A quaternary chiral carbon center was produced in 90% ee when ketoester **1g** was used, but with poor diastereoselectivity (1.25:1 dr, entry 7).

A variation of enone substrates was probed next. It was found that the **VI**-catalyzed conjugate addition processes were also applicable to various chalcones **2** in high yields (85−97%) and good to excellent enantioselectivities (87−98% ee) (Table 3, entries 1−10). It appears that the nature of the electronic properties of the substituents in the aromatic systems has a very limited effect on

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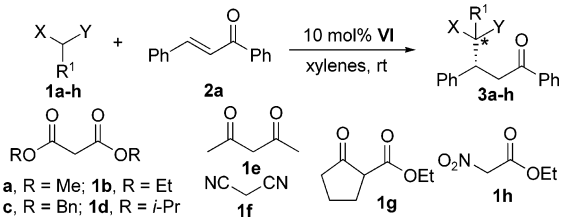
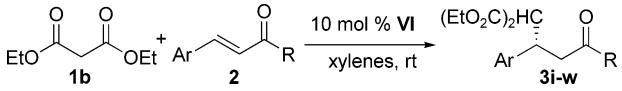
Table 2. Catalyst **VI** Catalyzed Conjugate Addition Reactions of Nucleophilic Enol Species (**1a**−**h**) to Chalcone (**2a**)[a]



entry	adduct	*t* (h)	% yield[b]	% ee[c]
1	**3a**	96	90	91
2	**3b**	96	88	93
3	**3c**	144	84	91
4	**3d**	96	67	93
5	**3e**	108	92	90
6	**3f**	120	77	88
7	**3g**	84	93	90[d]
8	**3h**	48	99	90[e]

[a] Reaction conditions: unless specified, catalyst **VI** (15 mg, 0.025 mmol) was added to a vial containing xylenes (0.1 mL), **1** (1.40 mmol), and *trans*-chalcone (**2a**) (52 mg, 0.25 mmol) at room temperature. [b] Isolated yields. [c] Determined by HPLC analysis (Chiralpak AS-H or Chiralcel OD-H or OJ-H). [d] Enantiomeric excess for major isomer and 1.25:1 dr. [e] Enantiomeric excess for minor isomer and 1.25:1 dr.

Table 3. Catalyst **VI** Catalyzed Conjugate Addition Reactions of Diethyl Malonate (**1b**) to enones (**2**)[a,b]



entry	Ar	R	*t* (h)	% yield[c]	% ee[d]
1	4-ClC_6H_4	Ph	108	95	93
2	4-$NO_2C_6H_4$	Ph	84	92	87
3	2-ClC_6H_4	Ph	96	94	93
4	3-$NO_2C_6H_4$	Ph	120	92	90
5	4-$MeOC_6H_4$	Ph	144	89	92
6	Ph	4-ClC_6H_4	120	93	95
7	Ph	4-$MeOC_6H_4$	144	85	95
8	4-FC_6H_4	4-FC_6H_4	72	97	94
9	4-FC_6H_4	4-MeC_6H_4	120	90	98
10	2-thiophene	2-thiophene	144	85	96
11[e,f]	Ph	Me	96	68	92
12[e,f]	2-thiophene	Me	96	79	90
13[e]	Ph	Me	96	62	94
14[e]	2-thiophene	Me	96	72	92
15[e,f]	2-furan	Me	96	61	85

[a] Unless specified, see footnote a in Table 2. [b] No reaction occurred for oct-3-enone, and racemic product was obtained for cyclohexenone. [c] Isolated yields. [d] Determined by chiral HPLC analysis (Chiralpak AS-H or Chiralcel OJ-H). [e] Catalyst (30 mol %) used. [f] Dimethyl malonate (**1a**) used.

the reaction. No matter whether electron-withdrawing (entries 1−4 and 8, 9), -donating (entry 5), -neutral (entries 6 and 7), and heteroaromatic (entry 10) groups for Ar were used, the reactions proceeded smoothly to give high yielding and enantioselective products. The same trend was observed for substituents for R (entries 1−10). Less reactive chalcones with methyl groups on the carbonyl were also surveyed. It was found that, under the same reaction conditions using 10 mol % of catalyst **VI**, the reaction proceeded very slowly. However, increasing the catalyst loading to 30 mol % allowed the process to take place in a reasonable time scale with good enantioselectivity (85−94% ee, entries 11−15).

In summary, we have developed a cinchona thiourea **VI**-promoted asymmetric conjugate addition of various nucleophilic enol species to enones, providing versatile, highly enantiomerically enriched adducts. The conjugate adducts contain a variety of functionalities that are extremely useful building blocks in organic synthesis. Further investigation of the full scope of this conjugate addition reaction and applications for the synthesis of biologically interesting targets are underway in our laboratory.

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Supporting Information Available: Experimental procedures and spectra data for compounds **3a**−**w**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

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

(2) For recent reviews of asymmetric conjugate addition reactions, see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) Sibi, M.; Manyem, S. *Tetrahedron* **2001**, *56*, 8033. (c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (d) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (e) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (f) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.

(3) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005.

(4) For selected reviews regarding organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Special Issue on Asymmetric Organocatalysis. *Acc. Chem. Res.* **2004**, *37*, 487.

(5) For selected examples of asymmetric conjugate additions of nitroalkanes, see: (a) Funabashi, K.; Saida, Y.; Kanai, M.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett*. **1998**, *39*, 7557. (b) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975. (c) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257. (d) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331. (e) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394. (f) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (g) Nugent, B. M.; Yoder, R. A.; Johnson, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (h) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (i) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313. (j) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897. (k) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375.

(6) For selected examples of asymmetric conjugate additions of malonates, see: (a) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. (b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2001**, *123*, 4370. (c) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2003**, *42*, 661. (d) Li, H.; Wang, Y.; Tang, T. Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (e) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (f) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed*. **2005**, *44*, 6367. (g) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (h) Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem. Commun.* **2006**, 66.

(7) For selected examples of asymmetric conjugate additions of ketoesters, see: (a) Wynberg, H.; Helder, R. *Tetrahedron Lett*. **1975**, 4057. (b) Majima, K.; Takita, R.; Okada, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc*. **2003**, *125*, 15837. (c) Berkessel, A.; Cleemann, F.; Mukherjee, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 947. (d) Wu, F.; Li, H.; Hong, R.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 7466.

(8) Wang, J.; Li, H.; Duan, W.-H.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713.

(9) (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204. (b) Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706.

(10) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032.

(11) For reviews, see: (a) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 521. (b) Takemoto, Y. *Org. Biomol. Chem*. **2005**, *3*, 4299. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (d) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (e) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418.

(12) THF = 40% yield, 81% ee; Et_2O = 35% yield, 53% ee; anisole = 38% yield, 66% ee; benzene = 89% yield, 87% ee; toluene = 86% yield, 90% ee; CH_2Cl_2 = 33% yield, 82% ee; DMF = 88% yield, racemic.

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