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Highly Enantioselective Conjugate Addition of Nitromethane to Chalcones Using Bifunctional Cinchona Organocatalysts

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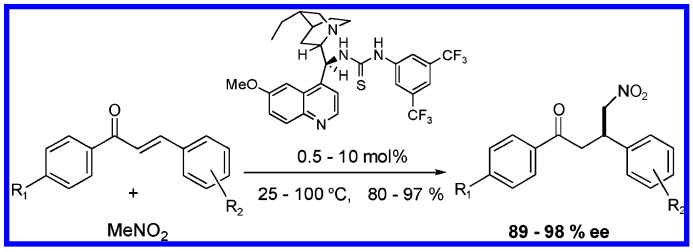
ABSTRACT



Cinchona alkaloid-derived chiral bifunctional thiourea organocatalysts were synthesized and applied in the Michael addition between nitromethane and chalcones with high ee and chemical yields.

The conjugate addition of a stabilized carbanion to α,β-unsaturated carbonyl compounds is one of the fundamental C−C bond-forming reactions in organic synthesis.[1] In the case of nitroalkanes, the products of a 1,4-addition to enones[2] are also useful intermediates for a variety of further elaborated structures such as aminoalkanes, aminocarbonyls, and pyrrolidines. As a result, considerable effort has been directed toward the development of catalytic asymmetric versions of this process over the past several years, although the reactions were mostly narrow in substrate scope and generally low to moderate enantioselectivities have been obtained.[3−5] The best results to date have been achieved by Shibashaki et al. using a lanthanum tris-binaphthoxide catalyst in the addition of nitromethane to chalcones with

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(1) Recent reviews dealing with enantioselective conjugate addition: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Berner, O. E.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1788. (c) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.

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(3) Methods using chiral metal complexes: (a) Yamaguchi M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233. (b) Yamaguchi M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*, 11223. (c) Keller, E.; Veldman, N.; Spek, A. L.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3403. (d) Funabashi, K.; Saida, Y.; Kanai, M.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7557.

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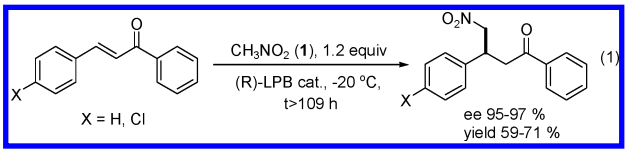
up to 97% ee; however, the presence of ^{t}BuOH (1.2 or 2 equiv) and 20 mol % catalyst were required in order to achieve efficient catalysis.[3a]



Herein, we report that new thiourea catalysts **5a**,**b** and **7** efficiently promote the Michael reaction between nitromethane and chalcones with high levels of enantioselectivity.

Due to the privileged role in asymmetric organic synthesis, we investigated the employment of cinchona alkaloid-based catalysts in these Michael reactions.[6] Wynberg and co-workers demonstrated that natural cinchona alkaloids, with a C-9 alcohol and a quinuclidine, could serve as bifunctional chiral catalysts in Michael addition reactions by activating the nucleophile and electrophile, respectively.[7] However, the natural cinchona-catalyzed addition of nitromethane (**1**) to *trans*-chalcone (**2a**) (eq 1) proceeded smoothly only under 400 MPa pressure and resulted in only modest enantioselectivities.[8]

This result led us to conclude that the exploration of more active bifunctional cinchona catalysts[9] might be the key to the development of more efficient catalytic processes.

Since the discovery of Etter and co-workers[10] that diaryl ureas readily form cocrystals with a variety of proton acceptors, remarkable advances have been made in chiral thiourea-catalyzed asymmetric reactions.[11] These findings prompted us to synthesize bifunctional thiourea derivatives of cinchona alkaloids **5**−**7** capable of double-hydrogen bonding Lewis activation (Figure 1) and apply them in the conjugate addition of nitromethane (**1**) to *trans*-chalcone (**2a**) (Table 1).

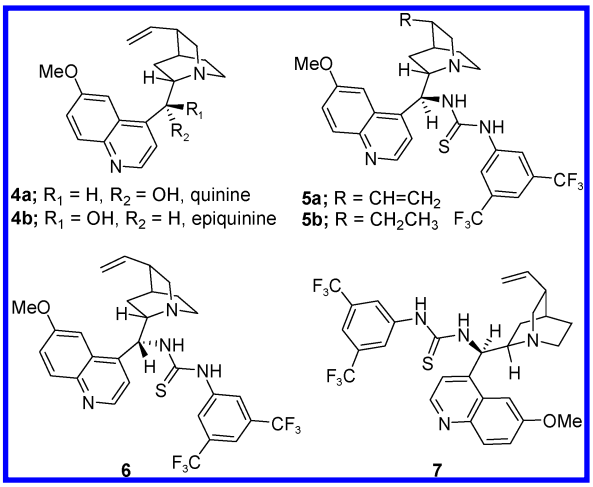
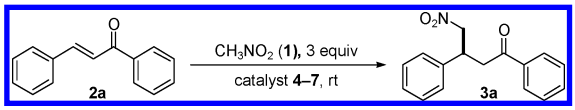


Figure 1. Bifunctional cinchona organocatalysts **4**−**7**.

Catalysts **5**−**7** (Figure 1) were prepared from quinine (**4a**), epiquinine (**4b**), and quinidine via experimentally simple two-step protocols.[12]

Table 1. Asymmetric 1,4-Addition of Nitromethane (**1**) to *trans*-Chalcone (**2a**)[a]



entry	catalyst	time (h)	% yield[b]	% ee[c,d]
1	**4a**	99	4	42 (*S*)
2	**4b**	99	0	
3	**5a**	99	71	95 (*R*)
4	**5b**	99	93	96 (*R*)
5	**6**	99	0	
6	**7**	99	59	86 (*S*)

[a] Reactions were carried out with **2a** (5 mmol), 3 equiv of **1** (15 mmol) in toluene (3 mL), and the catalyst indicated (**4**−**7**; 10 mol %) in capped vials at 25 °C. [b] Yield of isolated product after chromatography. [c] Determined by HPLC using a Chiralpak AD column. [d] Absolute configuration was determined by comparing the specific rotation of **3a** with that of literature data.[13]

These novel catalysts and their less acidic Lewis acid precursor **4a** and **4b** were then studied for their ability to mediate enantioselective 1,4-addition (Table 1). Quinine (**4a**) turned out to be a poor catalyst, and epiquinine (**4b**) failed to accelerate this transformation. However, the epithiourea catalysts **5a** and its pseudoenantiomer **7** afforded an especially promising result, which could be further improved by using hydroquinine catalyst **5b**. Surprisingly, the organocatalyst **6** with the natural configuration *showed no activity* in this process. The change in the quinine−epiquinine catalytic activity trend with the introduction of the stronger Lewis acid thiourea moiety indicates that the proper conformation of the cinchona derivatives is crucial for successful

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catalysis. In conclusion, these experiments showed that the quinuclidine part of the cinchona alkaloid itself is not able to facilitate the Michael addition in the model reaction. Furthermore, introduction of a more acidic thiourea moiety was necessary to obtain efficient catalytic activity.

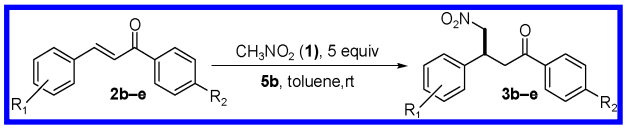
Next, the influence of the three experimental parameters (solvent, temperature, and catalyst load) was studied using the most efficient catalyst **5b** (Table 2). While variation of the solvents had a pronounced effect on reaction rate (entries 1 and 2 vs 3 and 4), excellent levels of enantioselectivity were observed for a wide range of dielectric media. Most notably, when the model reaction was performed in neat nitromethane, a nearly complete conversion was achieved in a much shorter time (entry 5). Using this simplified reaction condition, variation of the catalyst load and reaction temperature was evaluated. Remarkably, a catalyst load as low as 0.5 mol % can be utilized without significant loss in enantiocontrol (entry 10). As might be expected, a much shorter reaction time was observed at higher temperature: however, epicinchona catalyst **5b** was able to maintain the high level of enantioselectivities (entries 11 and 12) even at 100 °C. In addition to the excellent enantioselectivities and chemical yields, it is noteworthy that this metal-free catalytic reaction has several advantages of practical importance: it proceeds at ambient temperature with no additive (such as cosolvent, base, or molecular sieves) required, and these experiments can be conducted in technical grade solvents in capped vials but with otherwise no effort to exclude oxygen and moisture.

Table 2. Optimization of Reaction Conditions for Conjugate Addition of **1** with **2a** Using Catalyst **5b**[a]

entry	solvent	*T* (°C)	catalyst load (mol %)	*t* (h)	% yield[b]	% ee[c]
1	toluene	25	10	110	94	96
2	CH_2Cl_2	25	10	110	84	93
3	THF	25	10	110	38	95
4	MeOH	25	10	110	31	67
5		25	10	48	95	94
6		50	5	19	97	91
7		50	3	27	95	91
8		50	2	45	94	92
9		50	1	91	94	93
10		50	0.5	171	82	94
11		75	5	10	94	90
12		100	5	5	68[d]	85

[a] Reactions were carried out with **2a** (5 mmol) and 3 equiv of **1** (15 mmol) in an appropriate solvent (3 mL) in capped vials. [b] Yield of product isolated after silica gel chromatography. [c] Determined by HPLC by using Chiralpak AD column. [d] Catalyst decomposed at this temperature.

Table 3. Enantioselective Michael Reaction of Nitromethane (**1**) with Chalcones **2b**−**e** Using **5b**[a]



entry		R_1	R_2	*t* (h)	% yield[b]	% ee[c,d]
1	**2b**	*p*-Cl	H	122	94	95 (*R*)[d]
2	**2c**	*p*-F	H	122	94	98[e]
3	**2d**	*o*-Me	H	122	93	89[e]
4	**2e**	H	*p*-MeO	122	80	96[e]

[a] Reactions were carried out with **2b**−**e** (5 mmol), 5 equiv of **1** (25 mmol), and catalyst **5b** (10 mol %) in toluene (3 mL) in capped vials at 25 °C. [b] Yield of isolated product after chromatography. [c] Determined by HPLC by using Chiralpak AD column. [d] Absolute configuration of **3b** was determined by comparing the specific rotation with that of literature data (ref 4c). [e] Absolute configuration was not determined.

Experiments that probe the scope of the chalcone substrates are summarized in Table 3. Chalcones **2b**−**e** bearing electron-withdrawing or electron-donating substituents underwent clean reactions affording the desired product with high enantioselectivities and yields. Notably, the adduct **3b** is the key intermediate of the Corey (*R*)-Baclofen synthesis, and our protocol allows its synthesis with significantly higher enantioselectivity.[4c] Therefore, cinchona-based thiourea bifunctional catalysts **5a**,**b** and **7** present new opportunities for highly enantioselective synthesis of (*R*)-Baclofen and other pharmaceutically important γ-amino acids.

In summary, the cinchona-based thiourea organocatalysts were synthesized and found to promote highly enantioselective addition of nitromethane to chalcones. This environmentally friendly procedure represents an advance with regard to both enantioselectivity and practical simplicity. Studies aimed at investigating the mechanism and scope of these catalysts are underway and will be reported in due course.

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Supporting Information Available: Complete experimental procedures and characterization of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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