

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

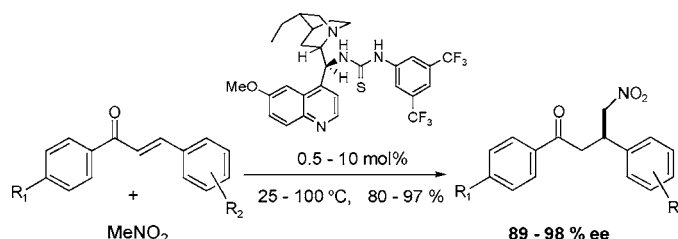
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Received February 26, 2005

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 enones² 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 Shibasaki et al. using a lanthanum tris-binaphthoxide catalyst in the addition of nitromethane to chalcones with

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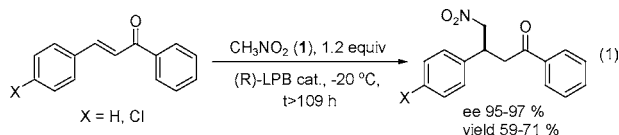
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up to 97% ee; however, the presence of *t*-BuOH (1.2 or 2 equiv) and 20 mol % catalyst were required in order to achieve efficient catalysis.^{3a}



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 catalysts⁹ might be the key to the development of more efficient catalytic processes.

Since the discovery of Etter and co-workers¹⁰ 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

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 organo-catalyst **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

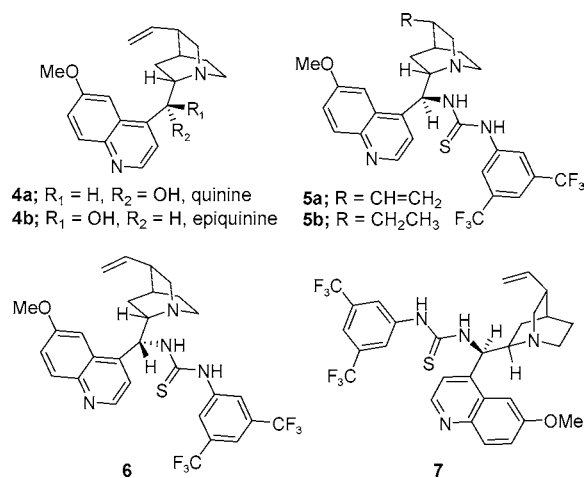


Figure 1. Bifunctional cinchona organocatalysts **4–7**.

conjugate addition of nitromethane (**1**) to *trans*-chalcone (**2a**) (Table 1).

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

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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

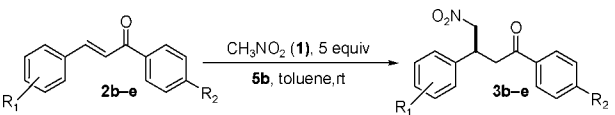
Table 2. Optimization of Reaction Conditions for Conjugate Addition of **1** with **2a** Using Catalyst **5b**^a

| entry | solvent | <i>T</i> (°C) | catalyst load (mol %) | <i>t</i> (h) | % yield ^b | % ee ^c |
|-------|---------------------------------|------------------|--------------------------|-----------------|-------------------------|----------------------|
| 1 | toluene | 25 | 10 | 110 | 94 | 96 |
| 2 | CH ₂ Cl 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.

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 3. Enantioselective Michael Reaction of Nitromethane (**1**) with Chalcones **2b–e** Using **5b**^a



| entry | | R ₁ | R ₂ | <i>t</i> (h) | % yield ^b | % ee ^{c,d} |
|-------|-----------|----------------|----------------|--------------|----------------------|------------------------------|
| 1 | 2b | <i>p</i> -Cl | H | 122 | 94 | 95 (<i>R</i>) ^d |
| 2 | 2c | <i>p</i> -F | H | 122 | 94 | 98 ^e |
| 3 | 2d | <i>o</i> -Me | H | 122 | 93 | 89 ^e |
| 4 | 2e | H | <i>p</i> -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.

Acknowledgment. We thank Ubichem Research, Ltd., for financial support. T.S. thanks Bolyai Foundation for an award. Grants 1/A/005/2004 NKFP MediChemBats2 and QLK2-CT-2002-90436 are gratefully acknowledged. We gratefully thank Ágnes Gömöry for running HRMS experiments.

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>.

OL050431S