DOI: 10.1002/ejoc.200900932

Enantioselective Michael Addition of Aromatic Ketones to Nitroolefins Catalyzed by Bifunctional Thioureas and Mechanistic Insight

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Keywords: Organocatalysis / Asymmetric synthesis / Michael addition / Reaction mechanisms

A highly enantioselective Michael reaction of aromatic ketones with nitroolefins was accomplished in the presence of a chiral bifunctional primary amine–thiourea catalyst and 4-nitrobenzoic acid as the co-catalyst; the corresponding adducts were obtained in excellent enantioselectivities (up to 99 % *ee*) and yields (up to 98 %). The catalytic mechanism of the Michael reaction was confirmed through the ESI-MS detection of proposed reaction intermediates and the ^{1}H NMR detection of hydrogen bonding between thiourea and the nitroolefins. DFT calculations showed that chiral moieties of the thiourea impacted the yields and enantioselectivities of the adducts remarkably, which corresponds to the observed experimental results.

Introduction

More recently, asymmetric organocatalysis has emerged as a new, powerful, and environmentally friendly methodology for the catalytic production of enantiomerically pure organic compounds and also as one of the most rapidly growing and competitive research areas in synthetic organic chemistry.[1] Among the variants of this strategy, the direct Michael addition of carbon-centered nucleophiles to nitroalkenes represents a direct and most appealing approach to afford versatile bifunctional products in an atom-economical manner. This is because the nitro functionality can easily be transformed into a nitrile oxide, ketone, amine, or carboxylic acid, and so on, providing a wide range of synthetically interesting compounds,[2] and development of asymmetric catalysts for such processes has been the focus of important recent research effort. Among them, bifunctional amine–thioureas have proven to be powerful and have been applied successfully in asymmetric Michael addition reactions, because of the strong activation of the carbonyl or nitro groups through efficient double hydrogen-bonding interactions, such as secondary and tertiary amine–thiourea chiral bifunctional catalysts for malonate derivatives,[3] simple aldehydes and ketones to nitroalkenes,[4,5,8] In comparison with secondary and tertiary amine chiral bifunctional catalysts, chiral primary amines as organocatalysts possesses particular charm because of their known occurrence in the catalytic sites of several enzymes, such as type I aldolases, dehydratases, and decarboxyases,[6,7] so more Michael reactions were catalyzed by chiral primary amine–thiourea bifunctional catalysts,[8] but only a small number of them were used for the Michael addition of aromatic ketones to nitroolefins.[9]

Inspired by the proven ability of chiral bifunctional primary amine–thioureas **1h** and **1c** (Figure 1) to serve as effective general catalysts in the Michael reaction of aliphatic ketones and cycloketones,[8] and on the basis of our research interest in the development of organocatalytic asymmetric reactions,[10] herein, we undertook a systematic investigation of derivatives of chiral bifunctional primary amine–thioureas **1** for addition reactions of aromatic ketones to nitroolefins.

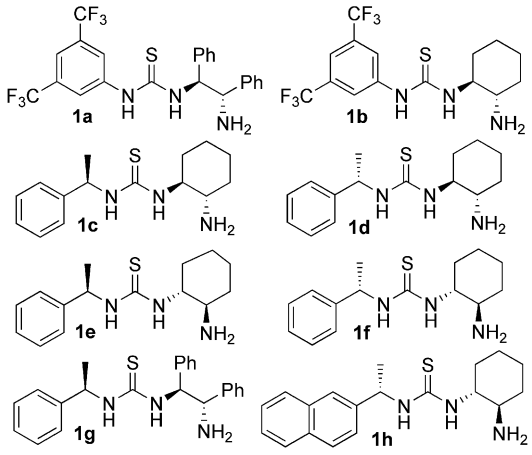

Figure 1. Chiral primary amine–thiourea-based bifunctional organocatalysts.

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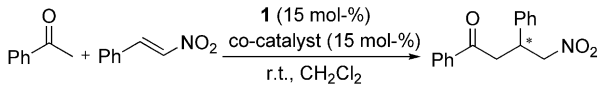
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900932.

Results and Discussion

To begin with, a model reaction was established between acetophenone and nitroolefins, which was performed in CH_2Cl_2 at room temperature in the presence of an organocatalyst. Previous work has shown that carefully chosen acidic co-catalysts could enhance the efficiency and selectivity for the Michael addition catalyzed by chiral amines catalysts,[8] and we therefore examined the co-catalyst effects on this Michael reaction. As shown in Table 1, no product was found when **1a** (15 mol-%) was used alone without any co-catalysts in CH_2Cl_2 at room temperature (Table 1, Entry 1). However, the use of acetic acid as a co-catalyst increased dramatically the catalytic activity to provide the product in 85% yield and 84%*ee* after 72 h (Table 1, Entry 2). The co-catalyst might accelerate the reaction by facilitating the interconversion of the different intermediates of the catalytic enamine cycle.[11] Having screened various co-catalysts of acids, including HCl, CF_3COOH, CH_3SO_3H, and other organic acids (Table 1, Entries 3–12), 4-nitrobenzoic acid was found to be the best co-catalyst, which afforded the Michael adduct within 72 h in 93% yield and 90%*ee* (Table 1, Entry 12).

Table 1. The Michael reaction catalyzed by organocatalyst **1** and different acids as co-catalysts.[a]



Entry	Catalyst	Co-catalyst	Yield[b] [%]	*ee*[c] [%]
1	**1a**	none	–	–
2	**1a**	AcOH	85	84(*R*)
3	**1a**	HCl	–	–
4	**1a**	CF_3COOH	23	46 (*R*)
5	**1a**	CH_3SO_3H	–	–
6	**1a**	PhCOOH	80	85 (*R*)
7	**1a**	4-$CH_3C_6H_4COOH$	85	86 (*R*)
8	**1a**	4-$CH_3C_6H_4SO_3H$	75	90 (*R*)
9	**1a**	salicylic acid	77	87 (*R*)
10	**1a**	2-(naphthalen-1-yl)acetic acid	65	80 (*R*)
11	**1a**	naphthalene-1-sulfonic acid	65	60 (*R*)
12	**1a**	4-$NO_2C_6H_4COOH$	90	85 (*R*)
13	**1b**	4-$NO_2C_6H_4COOH$	92	83 (*R*)
14	**1c**	4-$NO_2C_6H_4COOH$	94	95 (*R*)
15	**1d**	4-$NO_2C_6H_4COOH$	89	91 (*R*)
16	**1e**	4-$NO_2C_6H_4COOH$	90	93 (*S*)
17	**1f**	4-$NO_2C_6H_4COOH$	91	94 (*S*)
18	**1g**	4-$NO_2C_6H_4COOH$	85	96 (*R*)
19	**1h**	4-$NO_2C_6H_4COOH$	80	96 (*S*)

[a] Unless otherwise specified, all reactions were carried out with acetophenone (1.5 mmol), the nitroolefin (1.0 mmol), catalyst **1a** (0.15 mmol), and the specified co-catalyst (0.15 mmol) in CH_2Cl_2 (2 mL) for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/*i*PrOH = 90:10).

Inspired by the promising results, we further tested a number of structure-related chiral primary amine–thiourea catalysts **1b**–**h**. As shown in Table 1, catalyst **1b** gave a similar yield and enantioselectivity as **1a** in the presence of 4-nitrobenzoic acid as the co-catalyst (Table 1, Entry 13). Encouragingly, chiral arylethanamine-substituted amine–thioureas **1c**–**h** promoted the stereoselectivity, providing the Michael adduct with 91–96%*ee* (Table 1, Entries 14–19). Notably, catalysts with (*S*,*S*)-1,2-diamine scaffolds gave the Michael adduct of *R* configuration (Table 1, Entries 12–15, 18). On the contrary, catalysts with (*R*,*R*)-1,2-diamine moieties led to the *S* enantiomer (Table 1, Entries 16, 17, 19). Catalyst (*S*,*S*,*R*)-**1c** gave better yields and enantioselectivity than its stereoisomer (*S*,*S*,*S*)-**1d** (Table 1, Entries 14, 15). The results indicate that the chiral 1,2-diamines matched the chiral arylethanamines to control the stereoselectivity, and the two chiral moieties of the thiourea catalysts mutually enhanced the enantioselectivity. In order to explain this result, the DFT [B3LYP/6-31+G(d,p)] was employed to calculate the potential energy surfaces of the transition states (for computational details see the Supporting Information). Compared with **1c**-TS, the distances $C^a\cdots C^b$ and $S\cdots H^c$ in **1d**-TS are longer by 0.405 and 1.841 Å, respectively, and the calculated activation energy is larger by 6.406 kcal mol^{-1}. In summary, **1c**-TS is more compact and has a lower activation energy. Therefore, primary amine–thiourea **1c** could better afford the *R* enantiomer of the Michael adduct than **1d** (Table 1, Entry 14; Figures 2 and 3), whereas catalyst **1f** was suitable for the *S* enantiomer (Table 1, Entry 17).

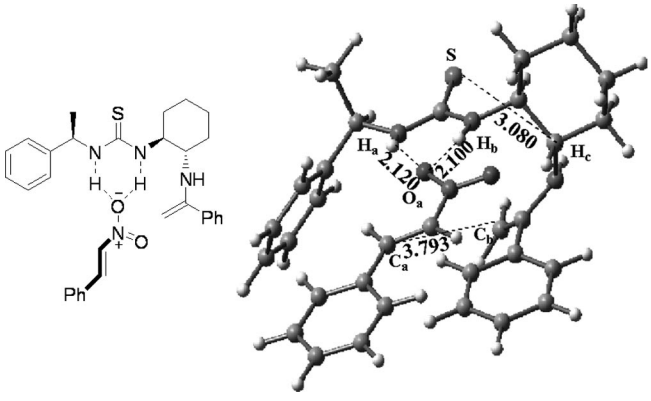


Figure 2. Transition-state structure of catalyst **1c** for the *R* enantiomer.

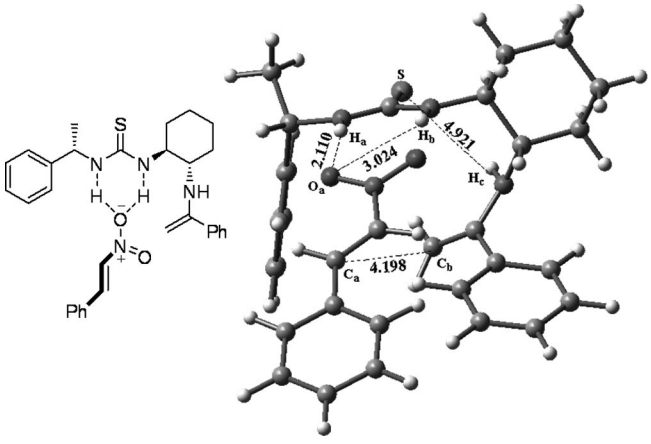
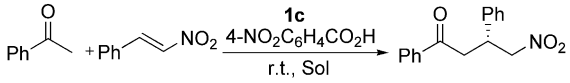


Figure 3. Transition-state structure of catalyst **1d** for the *R* enantiomer.

Having established the optimized catalyst system for the Michael reaction, we investigated the impact of different reaction media on the process. The results indicated that the solvents affected the catalytic activity significantly. Reactions in polar solvents, such as EtOH, *i*PrOH, DMF, and DMSO, generally proceeded in relatively low yields, whereas those performed in less polar solvents (Et_2O, THF, CH_3CN, and toluene) took place in high yields (Table 2, Entries 1–8). This is presumably due to the fact that nonpolar, aprotic solvents can minimize the disruption of the hydrogen-bonding interactions between the catalyst and substrate. As expected, the reaction in more polar ionic liquids did not perform well (Table 2, Entries 9 and 10). Therefore, toluene and THF should be suitable solvents for the Michael addition reaction.

Table 2. Screening of the solvents for the Michael reaction catalyzed by organocatalyst **1c** and 4-nitrobenzoic acid.[a]



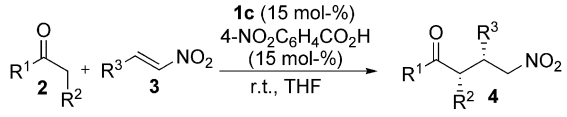
Entry	Solvent	Time [h]	Yield[b] [%]	*ee*[f] [%]
1	EtOH	72	50	92
2	*i*PrOH	72	70	99
3	DMF	72	77	97
4	DMSO	72	75	86
5	Et_2O	72	84	97
6	CH_3CN	72	83	95
7	toluene	72	97	97
8	THF	72	97	99
9	$[BMIm]BF_4$	72	45	89
10	$[BMIm]PF_6$	72	47	85
11[c]	THF	72	84	99
12[d]	THF	72	60	99
13[e]	THF	72	80	99

[a] Unless otherwise specified, all reactions were carried out with acetophenone (1.5 mmol), the nitroolefin (1.0 mmol), catalyst **1c** (0.15 mmol), and 4-nitrobenzoic acid (0.15 mmol) in the specified solvent (2 mL) for 72 h. [b] Isolated yield. [c] Reaction was carried out at 0 °C. [d] Reaction was carried out at –20 °C. [e] 0.1 mmol of **1c** and 0.1 mmol of 4-nitrobenzoic acid were used. [f] Determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/*i*PrOH = 90:10).

The scope and limitation of this catalytic system were explored next by using a wide range of substituted acetophenones and nitroolefins, and the results are summarized in Table 3. In general, substrates with both electron-withdrawing and electron-donating aryl groups reacted efficiently, and moderate to high yields were observed with excellent enantioselectivities up to 99%*ee* (Table 3, Entries 1–15). Scheme 1 shows the asymmetric Michael addition of nitroolefin **3q** to acetophenone catalyzed by **1c**; whereas the crystal structure of product **4e** with the *R* configuration is shown in Figure 4.

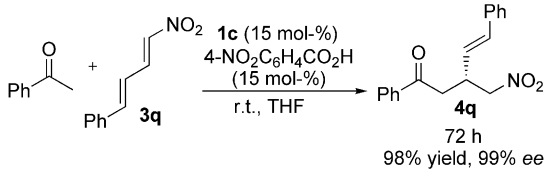
On the basis of the confirmed absolute configurations of the products and the discussion above, a dual activation mechanism (Figure 5) is proposed to explain the observed results.

Table 3. The enantioselective Michael addition of aromatic ketones to nitroolefins.[a]



Entry	R^1	R^2	R^3	Product	Yield[b] [%]	*ee*[c] [%]
1	Ph	H	Ph	**4a**	95	99
2	Ph	H	4-MeC_6H_4	**4b**	85	99
3	Ph	H	4-Me-OC_6H_4	**4c**	90	97
4	Ph	H	4-ClC_6H_4	**4d**	70	95
5	Ph	H	4-BrC_6H_4	**4e**	82	98
6	Ph	H	2-BrC_6H_4	**4f**	95	99
7	Ph	H	2-furyl	**4g**	98	96
8	Ph	H	2-thioanyl	**4h**	82	99
9	3-ClC_6H_4	H	Ph	**4i**	98	99
10	4-ClC_6H_4	H	Ph	**4j**	82	95
11	4-BrC_6H_4	H	Ph	**4k**	75	98
12	4-MeC_6H_4	H	Ph	**4l**	90	89
13	4-Me-OC_6H_4	H	Ph	**4m**	87	99
14	3-Me-OC_6H_4	H	Ph	**4n**	90	99
15	Me	H	Ph	**4o**	90	99
16	–$(CH_2)_4$–		Ph	**4p**	85	97(*syn*)[d]

[a] All reactions were carried out with aromatic ketone **2** (1.5 mmol), nitroolefin **3** (1 mmol), catalyst **1c**, (0.15 mmol), and 4-nitrobenzoic acid (0.15 mmol) in THF (2 mL) for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Daicel Chiralpak AD-H). [d] *syn*/*anti* = 69:31, determined by GC–MS.



Scheme 1. Asymmetric Michael addition of nitroolefin **3q** to acetophenone catalyzed by **1c**.

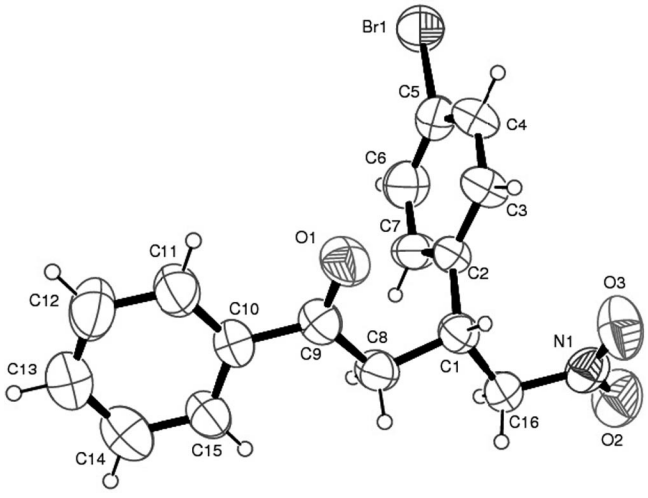


Figure 4. X-ray crystal structure of 3-(4-bromophenyl)-4-nitro-1-phenylbutan-1-one.[12]

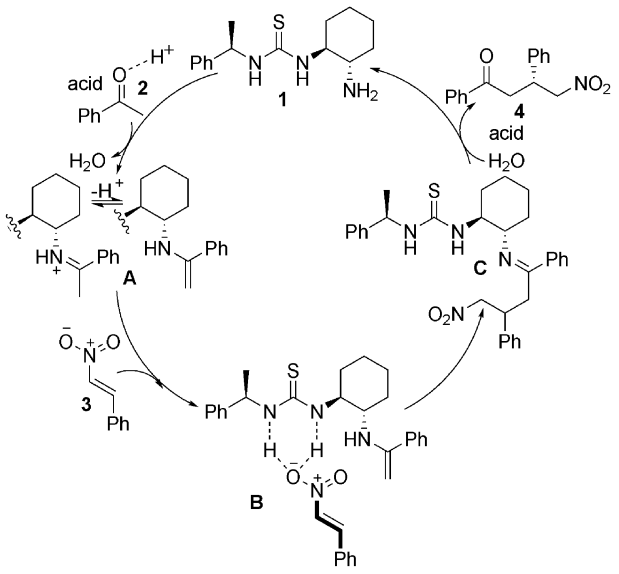


Figure 5. Proposed mechanism for the organocatalyzed asymmetric Michael reaction.

ESI-MS, ESI-MS–MS, and NMR spectroscopy are particularly useful for the investigation of organocatalytic reaction mechanisms, such as the aldol reaction,[13] the α-halogenation of aldehydes,[14] the conjugate umpolung reaction,[15] cascade reactions,[16] and the Michael reaction.[3c] In order to confirm the proposed catalytic cycle, we captured intermediates **A** and **C** by using ESI-MS under standard reaction conditions (Figures 6 and 7), and then we further detected ESI-MS–MS of intermediates **A** and **C**. The $\mathbf{A_1H^+}$ fragment ion is found in the ESI-MS–MS spectra of intermediate **A** (Figure 8), and this implies that the enamine form of intermediate **A** exists in the reaction system. In the case of intermediate **C**, we cannot find the $\mathbf{A_1H^+}$ fragment ion in the ESI-MS–MS spectra (Figure 9), so we conclude that only the imine form of intermediate **C** exists in this system; the enamine form of intermediate **C** does not exist because the double bond of the imine cannot be ruptured easily to form the $\mathbf{A_1H^+}$ fragment. Furthermore, we investigated the reaction system without 4-nitrobenzoic acid by using ESI-MS under the same conditions (Figure 10), but the relative intensity of the *m*/*z* = 380 peak in Figure 6 is lower than that in Figure 10, probably because 4-nitrobenzoic acid plays a significant role in facilitating the catalysis cycle. The hydrogen bonding of thiourea enhancing electrophilicity of nitroolefins is another function of the catalyst,

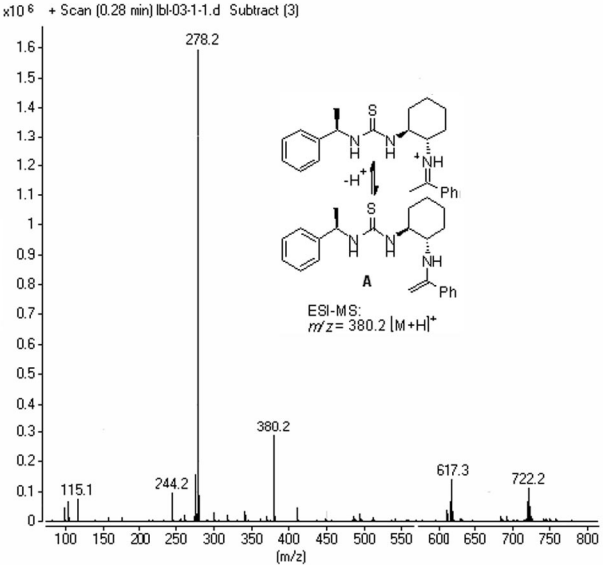


Figure 6. ESI-MS spectrum of the reaction of acetophenone (1.0 mmol), catalyst **1c** (0.15 mmol), and 4-nitrobenzoic acid (0.15 mmol) in THF (2 mL) for 10 h.

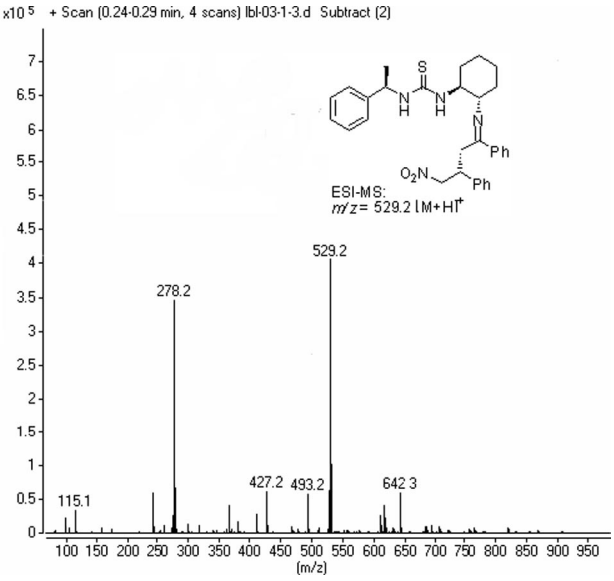


Figure 7. ESI-MS spectrum of the reaction of acetophenone (1.5 mmol), nitroolefins (1 mmol), catalyst **1c** (0.15 mmol), and 4-nitrobenzoic acid (0.15 mmol) in THF (2 mL) for 10 h.

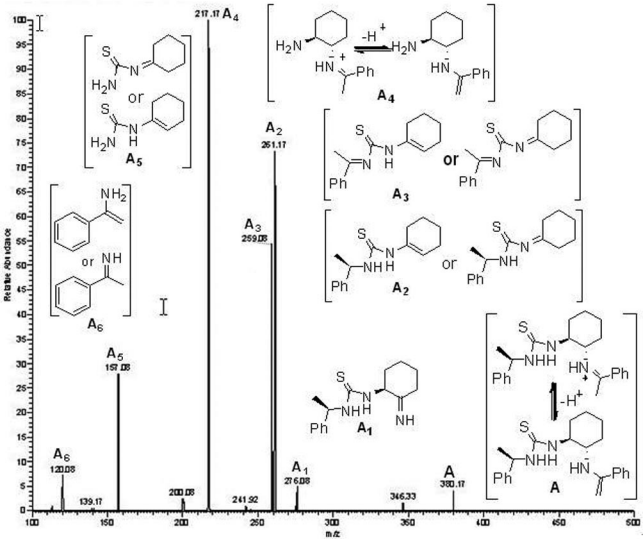


Figure 8. ESI-MS–MS spectrum of intermediate **A** (*m*/*z* = 380) at a collision voltage of 25 eV.

so we detected the ^{1}H NMR spectra of **1p** and its mixture with **3a** (Figures 11 and 12). The chemical shift of H^a was shifted from 6.977 to 7.052 ppm, and the one of H^b was shifted from 7.986 to 8.085 ppm. This implied that H^a and H^b of **1p** interacted with the oxygen atom of the nitro group. This is in accordance with the results of Takemoto.[3c] The Michael reaction occurred between the enamine form of acetophenone **A** and the thiourea-activated nitroolefins, then intermediate **C** undergoes hydrolysis to afford the enantioselective adducts, and catalyst **1c** is recovered.

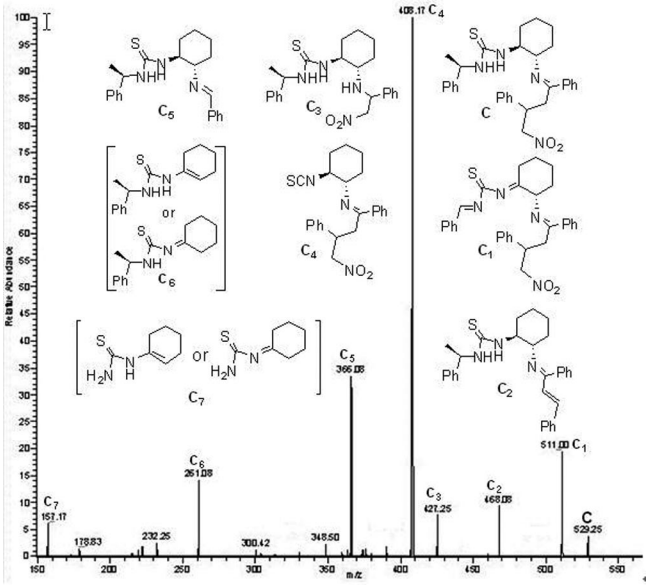


Figure 9. ESI-MS–MS spectrum of intermediate **C** (m/z = 529) at a collision voltage of 25 eV.

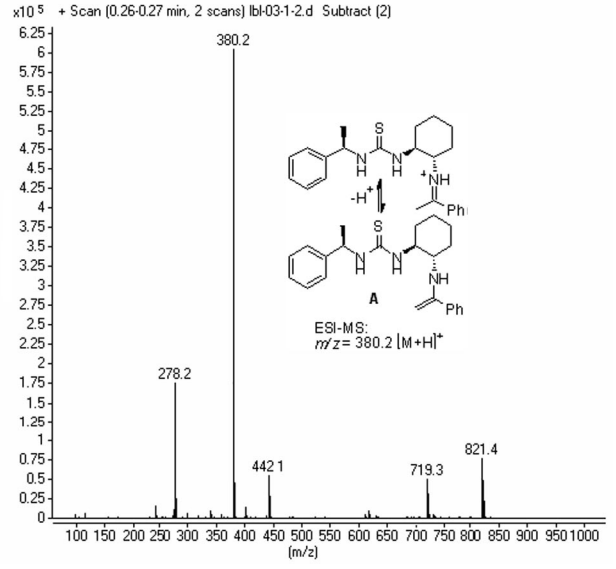


Figure 10. ESI-MS spectrum of the reaction of acetophenone (1.0 mmol) and catalyst **1c** (0.15 mmol) in THF (2 mL) for 10 h.

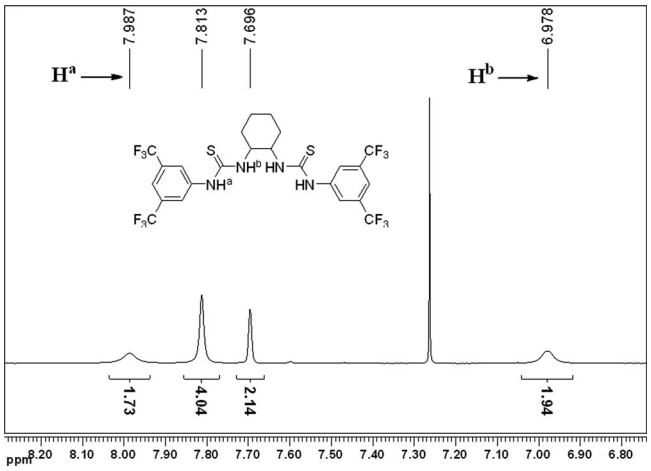


Figure 11. ^{1}H NMR spectrum of thiourea **1p**.

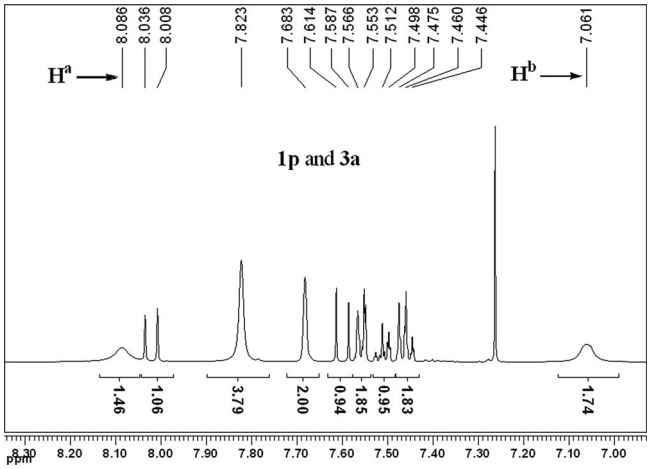


Figure 12. ^{1}H NMR spectrum of thiourea **1p** and nitroolefin **3a**.

Conclusions

In summary, we have demonstrated that primary amine-derived chiral thioureas and 4-nitrobenzoic acid can catalyze the Michael reaction, giving high yields and enantioselectivities for a wide range of aromatic ketones and nitroolefins. A plausible transition pathway was proposed taking into consideration the absolute configuration of the adduct, the ESI-MS of the intermediates, and ^{1}H NMR spectroscopic analysis of the hydrogen bonding between the thiourea and the nitroolefins. DFT calculations showed that chiral differences in the thiourea moieties impacted the yields and enantioselectivities of the adducts remarkably, which corroborated the observed experimental results.

Experimental Section

Typical Procedure: Catalyst **1c** (0.15 mmol) was added to a stirred solution of acetophenone **2** (1.5 mmol) in solvent (2 mL) under an atmosphere of air. The resulting solution was stirred for 15 min

prior to the addition of nitroolefin **3** (1 mmol) and the co-catalyst (0.15 mmol). After stirring for the indicated reaction time at room temperature, the crude adduct was purified by column chromatography (cyclohexane/EtOAc, 8:1). The enantiomeric excess of the pure product was determined by chiral HPLC analysis (Daicel Chiralpak AD-H, hexane/*i*PrOH = 90:10, 254 nm, t_{major} = 20.6 min, t_{minor} = 23.5 min).

Supporting Information (see footnote on the first page of this article): ESI experimental conditions, experimental procedures, spectra, and NMR spectroscopic data for complexes **4a**–**p**.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 20772110) and the Program for Changjiang Scholars and Innovative Research Team in University of China.

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Received: August 16, 2009
Published Online: December 14, 2009

