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Epi-Cinchona Based Thiourea Organocatalyst Family as an Efficient Asymmetric Michael Addition Promoter: Enantioselective Conjugate Addition of Nitroalkanes to Chalcones and α,β-Unsaturated *N*-Acylpyrroles

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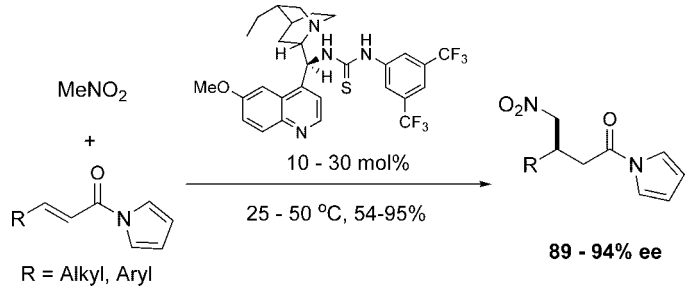
Received December 18, 2007



A small set of easily available *epi*-cinchona based thiourea organocatalysts have been synthesized and tested in enantioselective Michael addition of nitroalkanes to chalcones. These bifunctional catalyst systems promoted the conjugate additions with high enantioselectivities and chemical yields. The extension of this methodology was further explored to encompass α,β-unsaturated *N*-acylpyrroles, as a chalcone mimic. Functionally, the *N*-acylpyrrole moiety in the adduct acts as an ester surrogate; therefore, it can easily be transformed to various valuable and biologically relevant compounds. This approach allowed the concise stereoselective synthesis of (*R*)-rolipram.

Introduction

Catalyst developments for asymmetric reactions hold a prominent position within organic chemistry.[1] For many years, only enzymes and chiral metal complexes have been employed as catalysts to promote asymmetric transformations. However, many reservations with these methodologies have been voiced which prompted organic chemists to search for alternative catalytic solution. Finally, enantioselective organocatalysis, essentially a biomimetic approach, has been developed that utilizes small chiral organic molecules as suitable catalysts.[2] This field has witnessed tremendous developments due to its efficiency and capacity to extend the scope of chiral organic synthesis. Moreover, a thrust of research in this area has also been fueled by several practical and environmental issues.

The evolution of organocatalysis is tied to the effective imitation of the enzyme catalytic cleft. Seizing the most important feature, but not every detail of the catalytic center of enzymes, it is possible to achieve "general organocatalysts" that can be utilized for a specific type of reaction (e.g., Michael, Diels–Alder, and aldol reactions) with a broad range of substrates. Because acid–base cooperativity is generally invoked in enzymatic catalysis,[3] there is much interest in engineering organocatalytic systems with properly arranged bifunctionality.[4] It has generally been accepted that these catalyst systems are able to "intramolecularise" the reactions via simultaneous activation of two reaction partners.[5]

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10.1021/jo702692a CCC: $40.75 © 2008 American Chemical Society
Published on Web 04/01/2008

The enantioselective Michael addition reaction represents one of the most important methods for the construction of optically active compounds.[6] As a result, considerable effort has been directed to the development of the organocatalytic asymmetric version[7] of these processes, although the resulting catalysts were mainly chiral secondary amines using enamine or iminium activation pathways.

Our group recently communicated the development of bifunctional cinchona organocatalysts for catalyzing the asymmetric Michael addition reaction of nitromethane to chalcones.[8] We prepared several thiourea derived cinchona catalysts and showed that they efficiently promoted the model reaction with high level of enantioselectivity. The interest in this class of catalysts was further heightened after several asymmetric catalytic applications appeared in the literature with a remarkably diverse combination of substrates.[9,10]

The aim of the present study is to expand our preliminary investigations in several ways. Further catalysts were prepared and tested in catalytic asymmetric Michael addition reactions. Then the substrate scope and limitation were investigated; the scope of the nitroalkanes and chalcone structures also have been evaluated. Finally, the stereoselective synthesis of rolipram has been performed.

Results and Discussion

The conjugate addition of acidic nitroalkanes to α,β-unsaturated carbonyl compounds is an important class of C−C bond forming Michael addition reactions.[11] The products of these reactions are useful intermediates for a variety of natural and non-natural products. Although several metal catalyzed and organocatalyzed versions of these reactions exist, there is still room for further improvement.[12–14]

Due to the unique position in asymmetric chemistry, we started to investigate the possible application of cinchona alkaloids[15] in asymmetric Michael addition reactions. The reasons were evident: quinine has a large number of attributes that fulfill many requirements sought by synthetic chemists. Besides its availability and low price, it is endowed with unique functional, stereochemical, and conformational features that lend itself and its derivatives as efficient ligands[16] or organocatalysts.[17] Furthermore, over 20 years ago Wynberg and Hiemstra demonstrated that natural cinchona alkaloids could function as a bifunctional catalyst in Michael addition reactions. In their seminal paper, they showed that the C-9 hydroxyl and quinuclidine groups are able to position and activate the nucleophiles and electrophiles in conjugate thiol addition reactions.[18] However, the natural cinchona catalyzed C−C Michael addition of nitromethane to *trans*-chalcone proceeded only under 400 MPa and afforded the adduct with modest enantioselectivity.[19] This result indicated that the exploration of more active bifunctional cinchona derivatives might be the key to the development of efficient catalytic processes.

Following Wynberg's proposal to have a more effective catalyst system, Hatakeyama developed a chiral methodology based on β-isocupreidine. Using a covalent linkage, this catalyst

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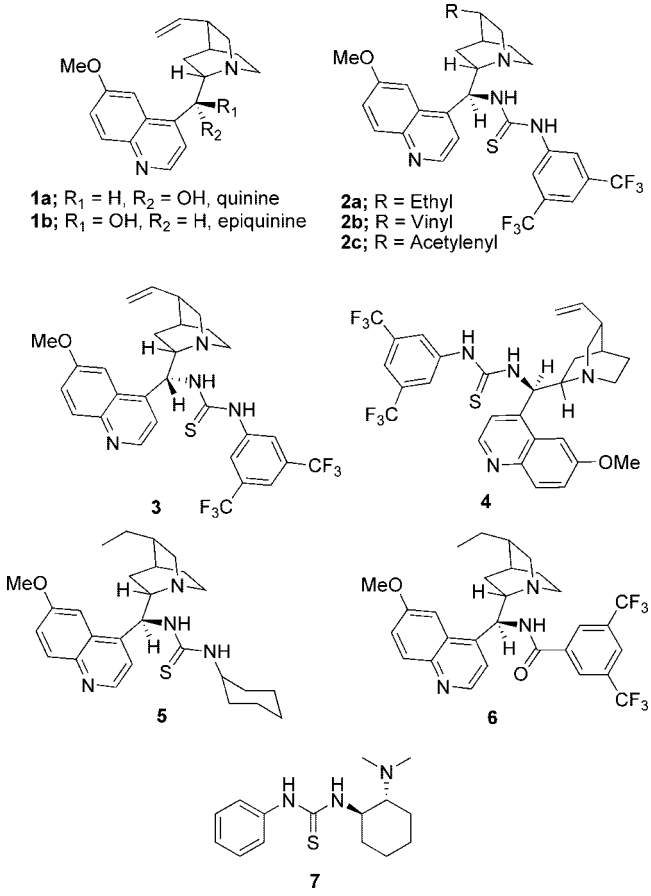
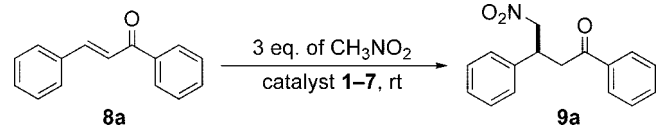


FIGURE 1. Bifunctional Lewis acid−amine systems.

has a well arranged spatial bifunctional system with a more acidic 6′-phenolic group of the quinoline moiety.[20] Instead of covalent linkage, Deng and later Hiemstra used conformational restricted derivatives as a key design element to have similar properly arranged bifunctional cinchona systems.[21]

In search of new bifunctional cinchona catalysts, we assumed that an effective and readily accessible organocatalyst family could also be generated if the 9-hydroxyl group is replaced by the more acidic thiourea group. On the basis of the recent developments in chiral thiourea-catalysis,[22,23] we predicted that the thiourea moiety would not only be acidic but also would be capable of forming two hydrogen bonds with the substrates. Therefore, a set of catalyst candidates (Figure 1) was prepared

TABLE 1. Asymmetric 1,4-Addition of Nitromethane to *trans*-Chalcone (8a)[a]



8a 9a

entry	catalyst	*t* [h]	% yield[b]	% ee[c,d]
1	**1a**	99	4	42 (*S*)
2	**1b**	99	0	-
3	**2a**	99	93	96 (*R*)
4	**2b**	99	71	95 (*R*)
5	**2c**	99	6	96 (*R*)
6	**3**	99	0	-
7	**4**	99	59	86 (*S*)
8	**5**	99	34	89 (*R*)
9	**6**	99	1	n.d.
10	**7**	99	44	91

[a] The reactions were carried out with **8a** (5 mmol), 3 equiv of nitromethane (15 mmol) in toluene (3 mL) and catalysts **1–7** (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 **9a** with that of literature data.[26]

from quinine, *epi*-quinine, and quinidine in an experimentally simple and scalable two-step protocol.[24]

These novel bifunctional systems and their less acidic precursors were screened for performance in enantioselective 1,4-addition reaction of *trans*-chalcone (**8a**, Table 1). As expected from high pressure experiments, quinine (**1a**) showed poor catalyst activity, and *epi*-quinine (**1b**) failed to accelerate the model reaction. With the amide-functionalized catalyst **6** having a monodentate hydrogen bond donor system, the reaction was sluggish (Table 1, entry 9). However, the *epi*-thiourea derivative **2b** and its pseudoenantiomer **4** gave promising results and the enhanced catalytic activity was mirrored by a significant increase in enantioselectivity (Table 1, entries 4 and 7). An interesting feature of these bifunctional *epi*-thiourea-amine systems is that the catalytic activity can be tuned without affecting enantiocontrol via the modification of its Brønsted basicity or Lewis acidity (Table 1, entries 3, 4, 5, and 8). This bifunctional system, therefore, seems to be a dominant and cooperative element which directs the two substrates of the Michael addition toward a "bifunctional" pathway and the possible competing, but less organized pathways (e.g., simple amine catalysis) are not really operating. When we saturated the vinyl group of the catalysts **2b** to give **2a**, it improved the catalytic activity (Table 1, entry 4 vs entry 3). Interestingly, we found that the modification of vinyl group in **2b** to acetylene in **2c** severely impaired the catalytic activity (Table 1, entry 4 vs entry 5). It seems that the kinetics of the these conjugate additions almost exclusively depends on the quinuclidine basicity since the smallest possible modification in a relatively remote group would not markedly alter the conformational equilibrium of the catalyst or the steric hindrance of the catalytic cleft. The less Lewis acidic cyclohexyl-thiourea derivative **5** gave the adduct **9a** with lower yield but high enantioselectivity (Table 1, entry 8). In contrast to the *epi*-thiourea derivatives, the thiourea system **3** with natural configuration *showed no activity* in this Michael addition (Table 1, entry 6). This rather surprising observation in which *epi*-cinchona derivative proved to be more efficient than the natural derivative revealed the

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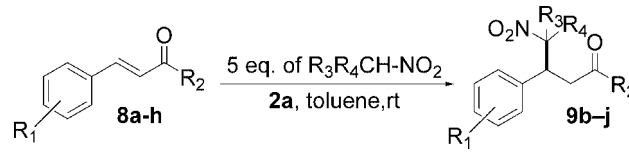
TABLE 2. Optimization of Reaction Conditions for Conjugate Addition of Nitromethane to 8a Using Catalyst 2a[a]

entry	solvent	T [°C]	cat. 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	CH_3CN	25	10	110	35	90
6	Pyridine	25	10	110	41	89
7	Quinoline	25	10	110	77	93
8	–[d]	25	10	48	95	94
9	–[d]	50	5	19	97	91
10	–[d]	50	3	27	95	91
11	–[d]	50	2	45	94	92
12	–[d]	50	1	91	94	93
13	–[d]	50	0.5	171	82	94
14	–[d]	75	5	10	94	90
15	–[d]	100	5	5	68[e]	85

[a] The reactions were carried out with **9a** (5 mmol) and 3 equiv of nitromethane (15 mmol) in 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] Neat reaction condition without added solvent. [e] Catalyst finally decomposed at this temperature.

TABLE 3. Enantioselective Michael Reaction of Nitroalkanes with Enones 8a-h using 2a[a]



entry		R_1	R_2	R_3	R_4	t [h]	product	% yield[b]	% ee[c,d]
1	**8b**	p-Cl	Ph	H	H	122	**9b**	94	95 (*R*)[d]
2	**8c**	p-F	Ph	H	H	122	**9c**	94	98[e]
3	**8d**	o-Me	Ph	H	H	122	**9d**	93	89[e]
4	**8e**	H	p-MeO-Ph	H	H	122	**9e**	80	96[e]
5	**8f**	H	H	H	H	0.1	**9f**	>90[f]	0
6	**8g**	H	OMe	H	H	122	**9g**	0	–
7	**8h**	H	Me	H	H	122	**9h**	0	–
8	**8a**	H	Ph	Me	H	41	**9i**	56/38[g,h]	94/94[e]
9	**8a**	H	Ph	Me	Me	192	**9j**	91[g]	92[d]

[a] The reactions were carried out with **8a-j** (5 mmol), 5 equiv of nitroalkane (25 mmol), and catalyst **2a** (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 **9b** was determined by comparing the specific rotation with that of literature data.[13c] [e] Absolute configuration was not determined. [f] 1,2-Henry type adduct formed. [g] Three equivalents of nitroalkanes were used. [h] Diastereomers.

importance of the proper three-dimensional arrangement of the functional groups in the catalytic cleft. Finally, the structurally similar, but more rigid Takemoto's catalyst[25] **7** was tested in the Michael addition of nitromethane and showed reduced activity although it furnished the product with high enantioselectivity (Table 1, entry 10).

After selecting **2a** as the most efficient catalyst, we proceeded to investigate the influence of three experimental parameters: solvent, temperature, and catalyst load (Table 2). Except for the protic MeOH (Table 2, entry 4), the variation of the solvent had no pronounced effect on the enantioselectivity. However, the polarity of the solvent markedly influenced the rate of the addition; the Michael reaction is generally more rapid in less polar medium (Table 2, entry 1 vs entry 5). However, it seems very difficult to assess how the medium effect, the specific and nonspecific binding of the solvent to the catalytic cleft and solvent induced conformational change of the catalyst independently contribute to the observed rate inhibition. The more basic but less apolar solvents, such as pyridine and quinoline, proved to be less potent rate inhibitors than the more polar but less basic CH_3CN (Table 2, entries 6 and 7 vs entry 5). These results would support the importance of medium effect; however, the less basic and but apolar THF also exerted a very similar influence on the addition rate (Table 2, entry 5 vs entry 3). Therefore, we assume that both medium effect, specific cooperative binding of the solvent, and modified conformational equilibrium of the catalyst may be involved in the rate inhibition. When the model reaction was carried out in neat nitromethane, an almost complete conversion was achieved in much shorter time (Table 2, entry 8) which allowed to reduce the catalyst load down to 0.5 mol% (Table 2, entry 13). Finally, we recognized one of the most astonishing properties of the catalyst **2a**: *it maintains the high level of enantiocontrol over a remarkable broad temperature range* (even at 100 °C, Table 2, entry 15). In addition to the high chemical yields and enantioselectivity, it is worth emphasizing that our organocatalytic method has several practical advantages: it runs at ambient temperature without any additive (such as cosolvent, base or molecular sieves) and technical grade reagents can be used with no effort to exclude oxygen or moisture.

Experiments aimed at exploring the scope of the model reaction are summarized in Table 3. Somewhat surprisingly, chalcones having electron-withdrawing or electron-donating groups showed similar reactivity in Michael addition reactions and afforded the desired adducts with high level of enantioselectivities (Table 3, entries 1–4). Furthermore, experiments were run to evaluate the potential of other nitroalkanes in Michael addition reactions. For the nitroethane and 2-nitropropane examined, the conjugate addition gave the appropriate nitro ketones with high yields and enantioselectivities (Table 3, entries 8, 9), however, there was no marked diastereoselectivity in case of nitroethane. Although the scope of nitroalkanes addition to chalcones was quite wide, we sought to expand this methodology toward synthetically more valuable enone electrophiles. Experiments that probed this opportunity were conducted. First, the two structurally similar enone compounds, cinnamic ester **8g** and benzylidene acetone (**8h**), failed to give any adduct in the test reaction (Table 3, entries 6, 7). Furthermore, in a very fast reaction, cinnamic aldehyde (**8f**) gave only racemic product (Table 3, entry 5), although only the 1,2-adduct was formed and no 1,4-addition occurred.

The above results led us to conclude that the application of more reactive ester or enone surrogate is desirable to broaden the substrate generality of our asymmetric thiourea based organocatalysis, which was originally developed for chalcones. Recent detailed investigation among ester surrogates by Shibasaki triggered us to investigate the application of α,β-unsaturated *N*-acylpyrroles.[27] These easily accessible and transformable enones have very similar LUMO energy to chalcones due to the delocalization of the nitrogen lone pair into the pyrrole ring. Thus, we hypothesized that the chiral catalytic cleft appropriate for chalcones would also be effective for unsaturated *N*-acylpyrroles.

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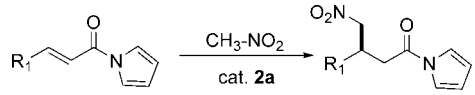
TABLE 4. Asymmetric 1,4-Addition of Nitromethane to α,β-Unsaturated *N*-Acylpyrroles[a]



10a-j **11a-j**

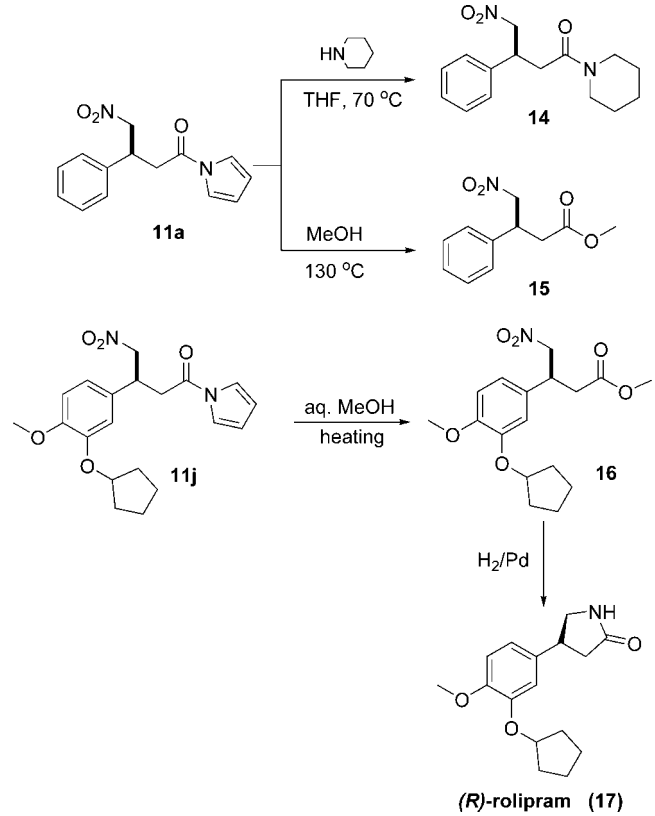
entry		R_1	cat. (mol%)	$MeNO_2$ (equiv)	*t* [h]	% yield[b]	% ee[c,e]
1	**10a**	Ph	10	5	87	93	93
2	**10b**	4-MeO−C_6H_4−	10	5	146	90	93
3	**10c**	4-Cl−C_6H_4−	20	10	64	88	89
4	**10d**	2-furyl−	10	5	146	81	93[d]
5	**10e**	2-thienyl−	10	5	146	59	92
6	(*E*)-**10f**	(*E*)-$PhCH_2CH_2$−	10	5	23	95	93
7	(*Z*)-**10f**	(*Z*)-$PhCH_2CH_2$−	10	3	65	81	−34
8	**10g**	cyclohexyl−	10	5	78	93	94
9	**10h**	CH_2═$CH(CH_2)_8$−	10	5	22	87	90
10	**10i**	(*E*),(*E*)-C_6H_5CH═CH−	10	10	139	54	94
11	**10j**	3-CpO-4-MeO−C_6H_3−	20	10	183	78	93
12	**12**	3-CpO-4-MeO−C_6H_3−[f]	30	100	72	25	82

[a] The reactions were carried out with **10a-j** (1.0 mmol), 3–100 equiv of neat nitroalkane, and catalyst **2a** (10–30 mol%) in capped vials at 25–50 °C. [b] Yield of isolated product after chromatography. [c] Determined by HPLC by using Chiralpak AD column. [d] Determined by HPLC by using Chiralcel OD column. [e] Absolute configuration was not determined. [f] Carbazole-containing substrate gave **13** adduct.

To demonstrate the utility of unsaturated *N*-acylpyrroles, various chalcone mimics were synthesized based on literature procedure.[27] The catalytic Michael addition to these substrates proceeded smoothly under the selected reaction conditions with high level of enantioselectivity and with no cleavage of the pyrrole moiety, as summarized in Table 4. The reaction rate was markedly faster when alkyl instead of aryl or heteroaryl substituted *N*-acylpyrroles were used (Table 4, entries 6, 9 vs entries 1–5). Interestingly, the stereochemistry around the double bond in the substrate affected not only the reaction rate but also the configuration of the product, because it gave the opposite enantiomer (Table 4, entry 6 vs entry 7).[28] This phenomenon indicates that the face selectivity of the nucleophilic attack remained the same, although less efficient in the (*Z*)-alkene **10f**. Furthermore, the Michael addition reaction showed exclusive regioselectivity; when diene **10i** was subjected for addition reaction, no adduct in the δ-position was observed. Finally, *N*-acylpyrrole **10j** and its easily available *N*-acylcarbazole analogue **12** were subjected to Michael additions. As might be expected, the bulky carbazole moiety reduced the rate of addition (Table 4, entry 11 vs entry 12).

The synthetic utility of the *N*-acylpyrroles adduct was demonstrated by the subsequent elaboration of some selected adducts (Scheme 1). Although the CO−N bond of *N*-acylpyrrole proved to be robust under the catalytic conditions in **11a**, it can be cleaved with piperidine or MeOH to furnish the corresponding amide **14** and ester **15** derivatives. Our goal was to eliminate the usage of any Lewis acid or strong base additives in these reactions to simplify the synthesis and to facilitate the product isolation. As expected, the more nucleophilic piperidine reacted at lower temperature (70 °C, capped vial, 24 h). Recrystallization of this product twice from methylcyclohexane furnished **14** of >99% ee with good recovery (84%). Using methanol as a nucleophile, more forcing conditions were necessary (130 °C, 2–3 h). The advantage of this approach was that no formation of polymerized pyrrole was observed. Finally, we accomplished the enantioselective synthesis of (*R*)-rolipram (**17**), using **11j** as a key intermediate. In case of **11j**, the esterification proved to be a little sluggish, therefore addition of water was used to facilitate the reaction. The γ-nitro ester **16** was reduced at 23 °C with H_2 with Pd/C give the (*R*)-rolipram (**17**) after ring closure as a white solid with 95% ee.[29]

SCHEME 1. Synthetic Transformation of *N*-Acylpyrrole Adducts and Concise Synthesis of (*R*)-Rolipram



Conclusion

In summary, we have developed a readily tunable *epi*-cinchona based thiourea organocatalyst family and demonstrated its utility in asymmetric Michael additions of nitroalkanes to

(28) Recent organometallic examples: (a) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129*, 276. (b) Vuagnoux-d' Augustin, M.; Alexakis, A *Eur. J. Org. Chem.* **2007**, 5852.

chalcones and α,β-unsaturated *N*-acylpyrroles. Significantly, this catalytic reaction maintained its high enantiocontrol over a relatively broad range of temperature. This fact and the simplicity of our methodology— no additives were required, it is not sensitive to the air and moisture, and technical grade reagents can be used— are highly advantageous for laboratory and industrial applications. Finally, taking advantage of the reactivity inherent to the *N*-acylpyrroles, the enantioriched Michael addition products were easily transformed into interesting building blocks. A synthesis of (*R*)-rolipram was developed using one of these Michael adducts. Further studies on the structure of the catalyst and the reaction mechanism are currently underway in our laboratory.

Experimental Section

Typical Procedure for Michael Addition of Nitromethane to α,β-Unsaturated N-Acylpyrroles: Reaction of 3-Phenyl-1-pyrrol-1-yl-propenone (10a) as a Representative. To a mixture of nitromethane (305 mg, 5.0 mmol) and (2*E*)-3-phenyl-1-pyrrol-1-yl-2-propen-1-one (**10a**, 197 mg, 1.0 mmol) was added thiourea catalyst **2a** (59.7 mg, 10 mol%) at ambient temperature. The mixture was stirred in a capped vial for 87 h, and the volatiles were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/$CHCl_3$ = 4/3 as eluant) affording adduct **11a** (240 mg, 93%).

4-Nitro-3-phenyl-1-pyrrol-1-yl-butan-1-one (11a). This product was purified by flash chromatography (hexane/$CHCl_3$ = 4/3). White solid; mp = 63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.22 (m, 7H); 6.29–6.27 (m, 2H); 4.84 (dd, J = 12.7, 6.8 Hz, 1H); 4.71 (dd, J = 12.7, 7.6 Hz, 1H); 4.18 (br pseudo q, J = 7.1 Hz, 1H); 3.35–3.23 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ 167.7, 138.4, 129.3, 128.3, 127.5, 119.0, 113.8, 79.3, 39.7, 37.8 ppm; IR (KBr) ν 1709, 1547, 1470, 1408, 1378, 1339, 1277, 1125, 750 cm^{-1}; HR−MS (EI) Exact mass calculated for $C_{14}H_{14}N_2O_3$ $[M]^+$ 258.1004; Found: 258.1010; Anal. calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85; O, 18.58%. Found: C, 65.00; H, 5.43; N, 10.76%; $[\alpha]_D^{25}$ +21 (*c* 1.00, $CHCl_3$, 93% ee).

3-(4-Methoxyphenyl)-4-nitro-1-pyrrol-1-yl-butan-1-one (11b). This product was purified by flash chromatography ($CHCl_3$/hexane = 2/1). White solid; mp = 78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.22 (m, 2H); 7.20–7.14 (m, 2H); 6.88–6.83 (m, 2H); 6.29–6.26 (m, 2H); 4.80 (dd, J = 12.6, 6.8 Hz, 1H); 4.66 (dd, J = 12.6, 7.7 Hz, 1H); 4.12 (br pseudo q, J = 7.1 Hz, 1H); 3.76 (s, 3H); 3.28 (dd, J = 14.5, 4.5 Hz, 1H); 3.22 (dd, J = 14.5, 4.4 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 167.8, 159.4, 130.2, 128.6, 119.0, 114.7, 113.7, 79.5, 55.4, 39.0, 38.0 ppm; IR (KBr) ν 1717, 1557, 1539, 1470, 1380, 1329, 1249, 1115, 747 cm^{-1}; HR−MS (EI) Exact mass calculated for $C_{15}H_{16}N_2O_4$ $[M]^+$ 288.1110; Found: 288.1110; Anal. calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72; O, 22.20%. Found: C, 62.19; H, 5.55; N, 9.63%; $[\alpha]_D^{25}$ +22 (*c* 1.00, $CHCl_3$, 93% ee).

3-(4-Chlorophenyl)-4-nitro-1-pyrrol-1-yl-butan-1-one (11c). This product was purified by flash chromatography (hexane/EtOAc = 5/1). Yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.18 (m, 6H), 6.31–6.27 (m, 2H), 4.82 (dd, J = 12.8, 6.7 Hz, 1H), 4.68 (dd, J = 12.8, 7.8 Hz, 1H), 4.16 (br pseudo q, J = 7.0 Hz, 1H), 3.30 (dd, J = 15.7, 5.6 Hz, 1H), 3.24 (dd, J = 15.74, 5.52 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 167.4, 136.8, 134.2, 129.5, 128.9, 119.0, 113.9, 79.0, 39.1, 37.7 ppm; IR (KBr) ν 1717, 1553, 1470, 1376, 1333, 1295, 1123, 830, 744 cm^{-1}; HR−MS (EI) Exact mass calculated for $C_{14}H_{13}ClN_2O_3$ $[M]^+$ 292.0615; Found: 292.0608; $[\alpha]_D^{25}$ +21 (*c* 1.00, $CHCl_3$, 89% ee).

3-(Furan-2-yl)-4-nitro-1-pyrrol-1-yl-butan-1-one (11d). This product was purified by flash chromatography (hexane/EtOAc = 15/2). White solid; mp = 36 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 1.9, 0.7 Hz, 1H), 7.28 (br s, 2H); 6.32–6.29 (m, 3H); 6.21 (d, J = 3.3 Hz, 1H); 4.83 (dd, J = 12.9, 6.3 Hz, 1H); 4.77 (dd, J = 12.9, 7.0 Hz, 1H); 4.29 (br pseudo q, J = 6.7 Hz, 1H); 3.37 (dd, J = 17.3, 6.4 Hz, 1H); 3.30 (dd, J = 17.3, 7.3 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 167.5; 151.1; 142.7; 119.1; 113.9; 110.7; 107.6; 77.0; 35.4; 33.6 ppm; IR (KBr) ν 1718, 1551, 1473, 1406, 1374, 1301, 1265, 1125, 751 cm^{-1}; HR−MS (EI) Exact mass calculated for $C_{12}H_{12}N_2O_4$ $[M]^+$ 248.0797; Found: 248.0800; Anal. calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29; O, 25.78%. Found: C, 57.94; H, 4.83; N, 11.27%; $[\alpha]_D^{25}$ +12 (*c* 1.00, $CHCl_3$, 93% ee).

Acknowledgment. We thank Ubichem Research Ltd. for financial support. The grant 1/A/005/2004 NKFP MediChem2 and OTKA K-69086 is gratefully acknowledged. We gratefully thank Ágnes Gömöry for running HRMS experiments and Gábor Tárkányi for NMR measurements.

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

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