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New highly enantioselective thiourea-based bifunctional organocatalysts for nitro-Michael addition reactions

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Abstract

A new and effective organocatalytic system, primary amine derived chiral thiourea catalyst and AcOH/H_2O additive, which converts different ketones to γ-nitroketones in high yields (82–99%) and enantioselectivities (90–99%) is described. The transition state geometries for formation of *R* and *S* enantiomers in this Michael addition have been calculated and analyzed. It is shown that only one oxygen atom of the nitro group is bound to the thiourea moiety, in juxtaposition to the literature-known working hypothesis which involves a bonding of both oxygens.

Keywords: Asymmetric catalysis; Michael addition; Bifunctional organocatalysts; DFT calculations; Transition states

1. Introduction

The use of chiral bifunctional catalysts for the synthesis of optically active compounds has become a new and exciting area of contemporary synthetic organic chemistry [1,2]. Chiral bifunctional thiourea derivatives have recently emerged as enantioselective catalysts for different organic transformations [3–14]. Pioneering examples include the work of Jacobsen, who showed that chiral urea or thiourea containing Schiff base catalysts can successfully be used in asymmetric cyanation reactions of aldimines and methyl ketimines [3–5]. Intriguingly, the same thiourea derivatives were shown to catalyze the enantioselective hydrophosphonylation of imines [6], Acyl-Pictet-Spengler [7] and Nitro-Mannich [8] reactions. Examples of the enantioselective Michael additions [9,10], Aza-Henry [11], Baylis-Hillman [12,13], and the dynamic kinetic resolution of azlactones [14] have also recently been reported by employing chiral bifunctional thiourea-based organocatalysts.

Although several enantioselective bifunctional organic catalysts have been identified recently, the design and development of new effective and easily accessible bifunctional chiral organic catalysts continues to be a challenging task. Based on our previous results [10,15,16] we have synthesized a range of new chiral bifunctional thiourea derivatives **1–5** (Fig. 1) containing a pyrrolidine or a primary amine base component and evaluated their ability to promote asymmetric C–C bond forming reactions using the example of the nitro-Michael addition reaction.

Michael reaction of ketones with nitroolefins represents without question a convenient access to γ-nitroketones which are valuable building blocks in organic synthesis (Scheme 1) [17].

The groups of Barbas and co-workers [18], List [19] and Enders [20] independently reported the first organocatalytic addition of acetone to *trans*-β-nitrostyrene using L-proline as the catalyst. However, only poor enantioselectivity was obtained with this natural catalyst (0–12% ee) [18–20]. As a result, considerable effort has been directed toward the development of an organocatalytic asymmetric version of the Michael addition of ketones to nitroolefins over the recent years and many improvements to this reaction have been made using pyrrolidine-based catalytic systems [21–26]. Poor to moderate enantioselectivities still resulted when acetone (12–42% ee) [20–25] or methylethylketone (10–67% ee (*syn*)) [19,22,27] was used as substrate.

Here we describe the synthesis of the new bifunctional thiourea derivatives **1–5** and their successful application to the asymmetric Michael additions of different ketones to nitroolefins.

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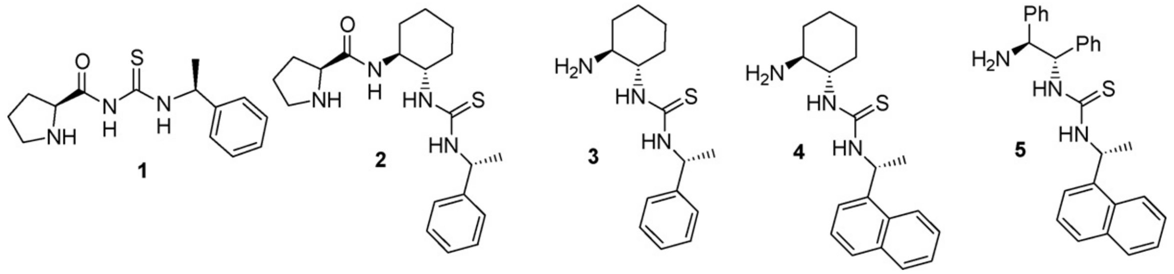
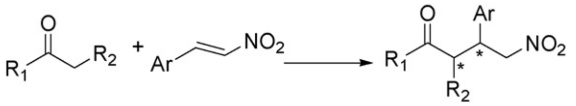


Fig. 1. New chiral thiourea-based bifunctional organocatalysts.



Scheme 1. Michael reaction of ketones with nitroolefins.

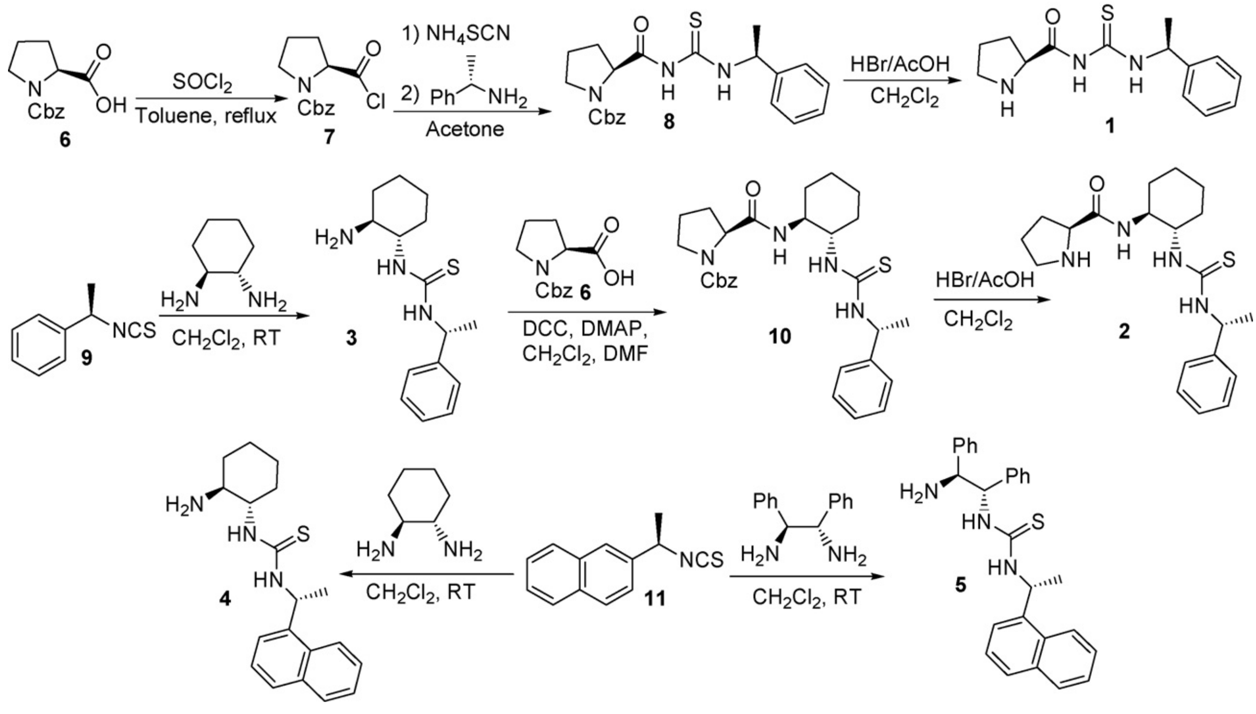
2. Experimental

The synthetic route to the new pyrrolidine and primary amine based chiral thioureas **1–5** is outlined in Scheme 2.

General: All solvents were purified by standard procedures and distilled prior to use. Reagents obtained from commercial sources were used without further purification. TLC chromatography was performed on precoated aluminium silica gel SIL G/UV$_{254}$ plates (Marcherey, Nagel & Co.) or silica gel 60-F$_{254}$ precoated glass plates (Merck). ^{1}H NMR spectra were recorded with Varian Unity 300. EI mass spectra were measured with a Finnigan MAT 95: Alpha AXP DEC station 3000-300LX; ESI mass spectra were recorded with a LCQ Finnigan spectrometer. High-resolution mass spectra were measured with a Bruker APEX IV 7T FT-ICR instrument. A Perkin-Elmer 241 polarimeter was used for optical rotation measurements.

Compound **7**: To a solution of *N*-(benzyloxycarbonyl)-(*S*)-proline (**6**) (1.76 g, 7.06 mmol, 1 eq.) in dry toluene (20 ml) at room temperature was added dropwise an excess of SOCl$_2$ (1 ml, 1.64 g, 2 eq.). The reaction mixture was stirred for 2 h at 80 °C under nitrogen atmosphere. Evaporation of the solvent gave 1.89 g of product **7** as a light yellow oil and was used without further purification.

Compound **8**: To a solution of ammonium thiocyanate (538.00 mg, 7.07 mmol, 1 eq.) in anhydrous acetone (3 ml) under a nitrogen atmosphere, was dropwise added compound **7** (1.89 g, 7.06 mmol, 1 eq.). The mixture was stirred for 20 min at 60 °C and then a solution of (*S*)-α-methylbenzylamine (856.74 mg, 7.07 mmol, 901 ml, 1 eq.) in acetone (1.5 ml) was added dropwise. After the reaction mixture was stirred for 2 h at 65 °C, it was poured into water (15 ml) and extracted with methylene chloride (3 ml × 15 ml). The combined organic layers were dried over Na$_2$SO$_4$ and evaporated under reduced pressure. Purification of the residue by column chromatography (EtOAc/hexane, 1:1) afforded 886 mg (31%) of **8** as an yellow



Scheme 2. The synthetic route to the new pyrrolidine and primary amine based chiral thioureas **1–5**.

solid. ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.50$–1.53 (d, $J = 7.2$ Hz, 3H), 1.53–1.91 (m, 3H), 2.21–2.31 (m, 1H), 3.28–3.45 (m, 2H), 4.5 (m, 1H), 4.94–5.07 (m, 2H), 5.41–5.51 (q, $J = 7.2$ Hz, 1H), 7.10–7.31 (m, 3H), 7.32–7.37 (m, 7H), 10.89 (br. s, 1H, NH), 11.42 (br. s, 1H, NH) ppm. ESI-MS (positive ion): $m/z = 434.1$ [M + Na]$^+$, 844.7 [2M + Na]$^+$. ESI-MS (negative ion): $m/z = 410.1$ [M–H]$^-$.

*Compound **1***: HBr/HOAc (200 μl, 33% HBr-HOAc) was dropwise added to a solution of **8** (100.00 mg, 0.24 mmol) in methylene chloride (1 ml) at 0 °C. After stirring of the reaction mixture at 0 °C for 30 min, and at room temperature for 1 h, dry ether (2 ml) was added to precipitate the amine hydrobromide formed. The supernatant liquid was decanted and the solid was filtered and washed with ether. The product was then dissolved in water (1 ml) and treated with saturated aqueous sodium bicarbonate to give the oil, which was extracted with ethyl acetate. The organic layer is then dried and concentrated under reduced pressure. Purification of the residue by column chromatography (EtOAc/hexane, 1:1) afforded 45.00 mg (67%) of **1** as a dark yellow solid. $[\alpha]_D^{20} = -54.5^\circ$ ($c = 0.33$, CHCl$_3$). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.51$–1.53 (d, $J = 6.6$ Hz, 3H), 1.60–1.66 (m, 2H), 1.75–1.76 (m, 1H), 1.99–2.02 (m, 1H), 2.74–2.79 (m, 1H), 2.87–2.92 (m, 1H), 3.74–3.79 (dd, $J = 9.0$, 5.1 Hz, 1H), 5.44 (m, 1H), 7.29–7.38 (m, 5H), 10.82 (br, s, 1H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 21.31$, 25.91, 29.59, 46.49, 53.96, 59.91, 126.11, 127.30, 128.55, 141.91, 176.53, 178.01 ppm. EI-MS (70 eV); m/z (%): 277.2 (11) [M$^+$], 105.1 (20), 70.1 (100). ESI-MS (positive ion): $m/z = 278.1$ [M + H]$^+$. ESI-MS (negative ion): $m/z = 276.1$ [M–H]$^-$. HRMS (ESI): calcd. for $C_{14}H_{19}N_3OS$ [M + H]$^+$ 278.13216; found 278.13218.

*Compound **3***: (*R*)-1-Phenylethylisothiocyanate (**9**) (1.43 g, 8.75 mmol) was added over a period of 1 h to a stirred solution of (*S*,*S*)-1,2-diaminocyclohexane (1 g, 8.75 mmol) in dry dichloromethane (17 ml). The reaction mixture was stirred for a further 2 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on SiO$_2$ (EtOAc/EtOH, 3:1) to give **3** as a yellow solid in 61% (1.48 g). $[\alpha]_D^{20} = -92.5$ ($c = 1.1$, CHCl$_3$). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 0.99$–1.26 (m, 4H), 1.41 (d, $J = 6.6$ Hz, 3H), 1.54–1.62 (m, 2H), 1.76–1.83 (m, 1H), 1.94–1.99 (m, 1H), 2.41–2.49 (m, 1H), 3.68–3.69 (m, 1H), 5.42–5.49 (m, 1H), 7.17–7.35 (m, 5H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 22.30$, 24.29, 24.42, 31.37, 34.40, 52.21, 54.20, 59.43, 125.97, 126.48, 128.12, 144.39, 181.57 ppm. ESI-MS (positive ion): $m/z = 278.1$ [M + H]$^+$, 554.9 [2M + H]$^+$. ESI-MS (negative ion): $m/z = 276.1$ [M–H]$^-$. HRMS (ESI): calcd. for $C_{15}H_{23}N_3S$ [M + H]$^+$ 278.16854; found 278.16866.

*Compound **10***: To a solution of **6** (0.70 g, 2.8 mmol, 1.3 eq.), DMAP (52.90 mg, 0.43 mmol, 0.2 eq.) and DCC (714.67 mg, 3.46 mmol, 1.6 eq.) in CH$_2$Cl$_2$/DMF (2:1) was added compound **3** (600 mg, 2.16 mmol, 1 eq.). The reaction mixture was stirred for 2 h at ambient temperature. The urea which precipitated was removed by filtration. The organic layer was washed with saturated aqueous NH$_4$Cl (3 ml), water (3 ml) and brine and dried with Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on SiO$_2$ (EtOAc/pentane, 4:1) to give **10** in 72% (795 mg) yield. ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.05$–1.31 (m, 6H), 1.35–1.38 (d, $J = 7.2$ Hz, 3H), 1.50–1.76 (m, 7H), 1.89–2.05 (m, 1H), 3.27–3.34 (m, 1H), 3.52–3.55 (m, 1H), 4.00–4.11 (m, 1H), 4.89–5.05 (m, 2H), 5.38–5.42 (m, 1H), 6.9 (br. s, 1NH), 7.12–7.54 (m, 10H), 7.98 (br. s, 2NH) ppm. ESI-MS (positive ion): $m/z = 531.2$ [M + Na]$^+$.

*Compound **2***: This compound was prepared from **10** by the same procedure as described above for **1**, to give **2** as a yellow solid in 83% (395 mg) yield. $[\alpha]_D^{20} = -80.0$ ($c = 0.42$, CHCl$_3$). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.13$–1.24 (m, 5H), 1.36–1.38 (d, $J = 6.0$ Hz, 3H), 1.48–1.52 (m, 2H), 1.56–1.62 (m, 2H), 1.77–1.79 (m, 2H), 1.81–2.05 (m, 1H), 2.51–2.73 (m, 2H), 3.16–3.30 (m, 1H), 3.48–3.54 (m, 1H), 4.10–4.12 (m, 1H), 5.35–5.37 (m, 1H), 7.05 (br. s, NH), 7.16–7.42 (m, 5H), 7.78–7.90 (br. s, 2 NH) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 21.50$, 23.74, 23.78, 24.81, 29.63, 31.35, 31.42, 45.94, 51.81, 52.08, 56.02, 59.94, 125.47, 125.95, 127.50, 143.88, 173.53, 181.42 ppm. ESI-MS (positive ion): $m/z = 375.2$ [M + H]$^+$, 398.2 [M + Na]$^+$, 748.9 [2M + H]$^+$, 770.9 [2M + Na]$^+$. HRMS (ESI): calcd. for $C_{20}H_{30}N_4OS$ [M + H]$^+$ 375.22131; found 375.22136.

*Compound **4***: This compound was prepared from **11** and (*S*,*S*)-1,2-diaminocyclohexane in a manner analogous to **3** and was obtained as a light yellow solid in 71% (560 mg) yield. $[\alpha]_D^{20} = -124.1^\circ$ ($c = 0.61$, CHCl$_3$). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.12$–1.26 (m, 5H), 1.53–1.61 (d, $J = 6.9$ Hz, 3H), 1.77–1.80 (m, 1H), 1.95–1.99 (m, 1H), 2.37–2.45 (m, 1H), 2.8–2.85 (m, 1H), 3.74–3.75 (m, 1H), 6.18–6.25 (q, $J = 6.9$ Hz, 1H), 7.20–7.23 (br. s, 1H, NH), 7.48–7.58 (m, 4H), 7.82–7.85 (d, $J = 9.0$ Hz, 1H), 7.90–7.95 (m, 1H), 8.12–8.19 (m, 1H) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 21.01$, 24.22, 24.39, 31.32, 34.23, 54.31, 59.30, 122.55, 123.47, 125.35, 125.53, 126.03, 127.30, 128.49, 130.59, 133.36, 139.82, 181.5 ppm. ESI-MS (positive ion): $m/z = 328.1$ [M + H]$^+$, 654.9 [2M + H]$^+$. HRMS (ESI): calcd. for $C_{19}H_{25}N_3S$ [M + H]$^+$ 328.18419; found 328.18425.

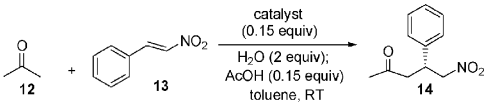
*Compound **5***: This compound was prepared from **11** and (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine in a manner analogous to **3** and was isolated as a light yellow solid in 80% (850 mg) yield.

$[\alpha]_D^{20} = -128.4^\circ$ ($c = 0.162$, CHCl$_3$). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.50$–1.52 (d, $J = 6.0$ Hz, 3H), 1.65 (s, br, 2H, NH$_2$), 4.25 (br. s, 1H), 5.5 (br. s, 1H), 6.05 (br. s, 1H), 7.18–7.32 (m, 11H), 7.50–7.54 (m, 4H), 7.81(br. s, 1H), 7.91 (br. s, 1H), 8.12–8.14 (m, 1H), 8.22 (br. s, NH) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): $\delta = 20.64$, 21.11, 40.04, 59.37, 62.50, 122.20, 123.27, 125.30, 125.45, 126.06, 126.52, 126.57, 126.79, 127.2, 127.04, 127.16, 127.60, 127.88, 128.43, 130.45, 133.30, 139.89, 143.11 ppm. ESI-MS (positive ion): $m/z = 426.1$ [M + H]$^+$, 850.9 [2M + H]$^+$. HRMS (ESI): calcd. for $C_{27}H_{27}N_3S$ [M + H]$^+$ 426.19985; found 426.19981.

2.1. Asymmetric Michael addition of ketones to nitroolefins

General procedure: To a stirred solution of catalyst (0.15 eq.) in toluene (0.5 ml) and ketone (10 eq.) at room

Table 1
Screening of new chiral thiourea catalysts **1–5** for asymmetric addition of acetone (**12**) to *trans*-β-nitrostyrene (**13**)



Catalyst	Yield (%)[a]	ee (%)[b]
1	50	3
2	55	3
3	85	86 (*R*)
4	97	84 (*R*)
5	98	91 (*R*)

[a] Yield of isolated product after column chromatography on SiO_2.

[b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

temperature, was added water (2 eq.), acetic acid (0.15 eq.) and, after 5 min, nitroolefin (1 eq.). The reaction mixture was stirred at room temperature for the appropriate time (16–72 h). The solvent was evaporated and the residue was purified by TLC or chromatography on SiO_2-column (hexane/ethyl acetate, 1:1) to afford the desired product. The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material. Relative and absolute configuration of the products was determined by comparison with literature data.

3. Results and discussion

To evaluate the catalytic efficiency of the new chiral thioureas **1–5** the addition of acetone to β-nitrostyrene was first performed in toluene in the presence of each of these catalysts and AcOH/H_2O as additive (Table 1).

The use of proline based chiral thioureas **1** and **2** gave the product only in 3% ee and in moderate yields (50 and 55%, respectively). Notably, much higher catalytic activities were displayed by catalysts **3–5** (84–91% ee (*R*), 85–98% yields), which contain just a primary amino group in place of the proline moiety [28].

To explain the predominant production of *R* adducts, we have computationally determined the first order saddle points (‘‘transition states’’, TS) for the formation of both *R* and *S* enantiomers (Figs. 2 and 3), considering the example of thiourea-amine **3** catalysis [29]. The calculations were performed for isolated (gas phase) systems without explicit consideration of solvent effects, which certainly is a reasonable assumption due to the non-polar solvent toluene used in the experiments. The Gaussian 03 program package [30] was employed throughout. The DFT variant B3LYP [31–33] was used in conjunction with the 6-31G(d) basis set. Eigenvalues of the Hessians at the relevant stationary points on the potential energy surfaces were calculated to verify their nature, and the geometries of the first order saddle points were further identified employing the intrinsic reaction coordinate (IRC) method [34]. At the B3LYP/6-31G(d) geometries, B3LYP/6-31G(d,p), B3LYP/6-31+G(d) and B3LYP/6-31+G(d,p) single

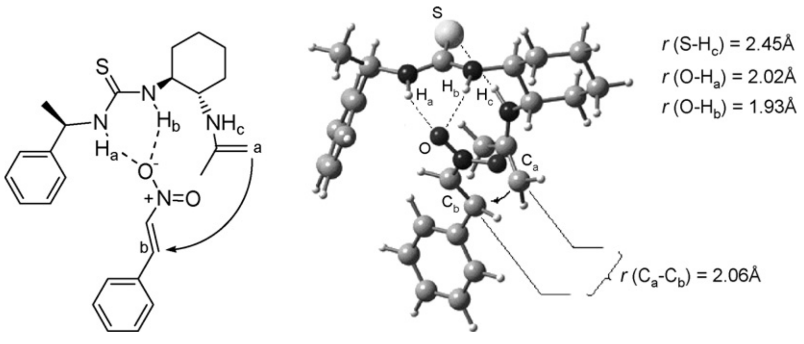


Fig. 2. Transition state structure for the formation of the *R* enantiomer.

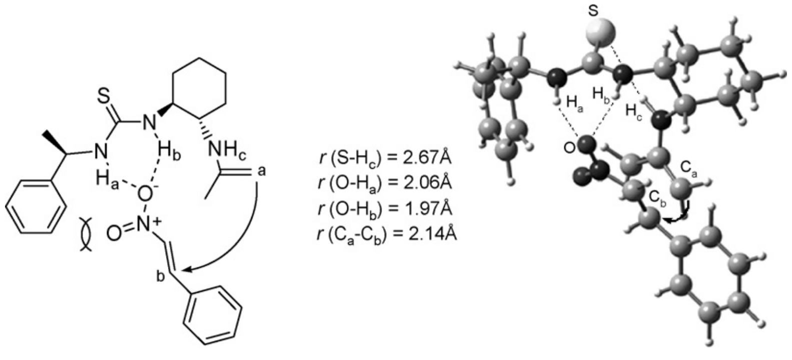
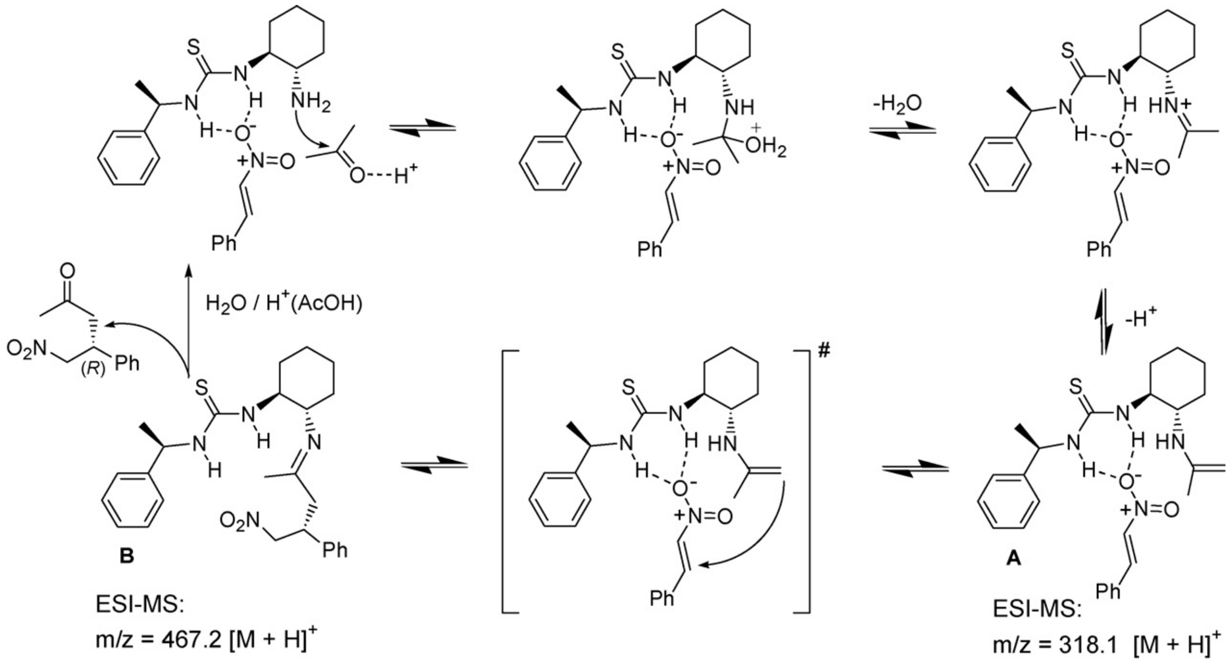


Fig. 3. Transition state structure for the formation of the *S* enantiomer.



Scheme 3. Plausible multistep chiral thiourea-amine **3** catalysis.

point calculations were carried out to take into account hydrogen polarization or/and diffuse functions.

The transition state structures for formation of both *R* and *S* enantiomers show a non-planar arrangement of the nitrostyrene nitro group oxygen atoms relatively to the thiourea hydrogens (Figs. 2 and 3). Catalyst **3** is additionally stabilized by an intramolecular hydrogen bond between the sulfur atom and hydrogen atom H_c (see Figs. 2 and 3). Compared to the *R* TS, the two distances between the nitro group oxygen atom and the two thiourea hydrogens are larger by 0.04 Å in the *S* TS, and the distances $C_a \cdots C_b$ and $S \cdots H_c$ are longer by 0.08 and 0.22 Å, respectively. The *R* TS is more compact and the second nitro group oxygen points towards the reactive center while in the *S* TS this oxygen atom points away from that center and undergoes a repulsive interaction with the phenyl ring of the catalyst. These structural properties explain why the TS leading to the *R* isomer is more stable than its counterpart (by 4.2, 4.4, 5.0 and 5.3 kcal mol^{-1}, respectively, for B3LYP/6-31G(d), B3LYP/6-31G(d,p), 6-31+G(d) and 6-31+G(d,p); all results for B3LYP/6-31G(d) geometries). From these data we determined theoretical ee's at 69, 71, 77 and 79% [29].

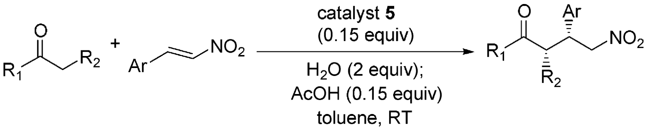
Our results give clear evidence that only one oxygen atom of the nitro group is bound to the thiourea moiety, in juxtaposition to a working hypothesis of Takemoto and co-workers, which involves a bonding of both oxygens (also quoted in several papers by this group) [9].

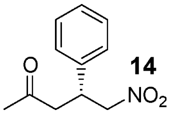
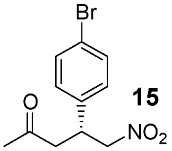
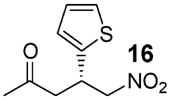
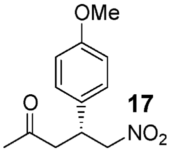
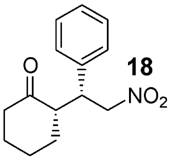
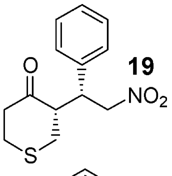
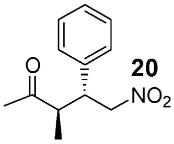
Based on these results we have proposed a plausible reaction mechanism for chiral thiourea-amine **3** catalysis (Scheme 3). According Scheme 1, the formation of the acetone enamine occurs following the formation of an iminium ion intermediate, supported by acid additive (AcOH). This C-nucleophile attacks the *trans*-β-nitrostyrene activated through hydrogen bonding with thiourea moiety to give the intermediate B. The existence of the intermediates A and B in the reaction mixture was confirmed using ESI-MS method (Scheme 3). At the last step the regeneration of the catalyst through hydrolysis of the imine B is facilitated by water.

Encouraged by the excellent results obtained with bifunctional thiourea **5** (91% ee, 98% yield, Table 1), we next evaluated a variety of aromatic nitroolefins as substrates and the results are summarized in Table 2. Nitroolefins underwent clean reactions with acetone as the simplest ketone affording the desired product in high yields (98–99%), with the sole exception of the slightly reduced yield (84%) achieved with aromatic nitroolefine bearing electron-donating substituent (Table 2, entries 1–3 versus entry 4). At the same time, the substituents of the nitroolefin appears to have very little effect on the enantioselectivities of the reaction, which range from 90 to 91% for catalyst **5** (Table 2, entries 1–4).

Cyclohexanone and tetrahydrothiopyran-4-one were also reacted with β-nitrostyrene in high yield and enantioselectivity (up to 89%, and 98% ee), and good diastereoselectivity (*syn*/*anti* up to 83:17) in the presence of catalyst **5** (Table 2, entries 5, 6) [28]. Surprisingly, the addition of nonsymmetrical ketone such as methylethylketone to β-nitrostyrene under the same conditions as above, led to the opposite diastereomer (*syn*/*anti* 14:86) with a very high enantiocontrol (>99% ee). This selectivity is the reverse of that normally found for this example in literature [19,22,27]. To our delight, remarkably high yields and enantioselectivities were achieved for all investigated ketons and aromatic nitroolefins with the new primary amine derived chiral thiourea catalyst **5**.

Table 2
Asymmetric Michael addition of ketones to nitroolefins catalyzed by **5**



Entry	*t* (h)	Product	Yield (%)[a]	dr[b] (*syn*:*anti*)	ee (%)[c] (*syn*)
1	48	 **14**	98	–	91
2	40	 **15**	99	–	90
3	50	 **16**	98	–	90
4	61	 **17**	84	–	91
5	72	 **18**	82	80:20	96
6	72	 **19**	89	83:17	98
7	72	 **20**	88	14:86	>99[d]

[a] Yield of isolated product after column chromatography on SiO_2.
[b] Determined by ^1H NMR spectroscopy.
[c] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.
[d] ee % of *anti* diastereomer.

4. Conclusions

In summary, we have demonstrated for the first time that primary amine derived chiral thioureas can catalyze the asymmetric nitro-Michael addition, giving high yields (82–99%), enantioselectivities (90–99% ee) and good diastereoselectivities for a wide range of ketones and aromatic nitroolefines.

The transition state geometries for formation of *R* and *S* enantiomers in this Michael addition have been calculated and analyzed. It was shown, that only one oxygen atom of the nitro group is bound to the thiourea moiety, in juxtaposition to the literature-known working hypothesis which involves a bonding of both oxygens. The theoretical ee values match the experimental data remarkably well.

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References

[1] For reviews of metallic bifunctional catalysts, see
(a) J.-A. Ma, D. Cahard, Angew. Chem. 116 (2004) 4666;
J.-A. Ma, D. Cahard, Angew. Chem. Int. Ed. 43 (2004) 4566;
(b) M. Shibasaki, N. Yoshikawa, Chem. Rev. 102 (2002) 2187;
(c) H. Gröger, Chem. Eur. J. 7 (2001) 5246;
(d) M. Shibasaki, H. Sasai, T. Arai, Angew. Chem. 109 (1997) 1290;
M. Shibasaki, H. Sasai, T. Arai, Angew. Chem. Int. Ed. 36 (1997) 1236.
[2] For reviews of bifunctional organic catalysts, see
(a) P.R. Schreiner, Chem. Soc. Rev. 32 (2003) 289;
(b) P.I. Dalko, L. Moisan, Angew. Chem. 116 (2004) 5248;
P.I. Dalko, L. Moisan, Angew. Chem. Int. Ed. 43 (2004) 5138;
(c) A. Berkessel, H. Gröger, Asymmetric Organocatalysis: from Biomimetic Concepts to Applications in Asymmetric Synthesis, Wiley-VCH, Weinheim, 2004;
(d) P.M. Pihko, Angew. Chem. 116 (2004) 2110;
P.M. Pihko, Angew. Chem. Int. Ed. 43 (2004) 2062;
(e) J. Seayad, B. List, Org. Biomol. Chem. 3 (2005) 719.
[3] M.S. Sigman, E.N. Jacobsen, J. Am. Chem. Soc. 120 (1998) 4901.
[4] M.S. Sigman, P. Vachal, E.N. Jacobsen, Angew. Chem. 112 (2000) 1336; M.S. Sigman, P. Vachal, E.N. Jacobsen, Angew. Chem. Int. Ed. 39 (2000) 1279.
[5] P. Vachal, E.N. Jacobsen, J. Am. Chem. Soc. 124 (2002) 10012.
[6] G.D. Joly, E.N. Jacobsen, J. Am. Chem. Soc. 126 (2004) 4102.
[7] M.S. Taylor, E.N. Jacobsen, J. Am. Chem. Soc. 126 (2004) 10558.
[8] T.P. Yoon, E.N. Jacobsen, Angew. Chem. 117 (2005) 470;
T.P. Yoon, E.N. Jacobsen, Angew. Chem. Int. Ed. 44 (2005) 466.
[9] (a) T. Okino, Y. Hoashi, Y. Takemoto, J. Am. Chem. Soc. 125 (2003) 12672;
(b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, J. Am. Chem. Soc. 127 (2005) 119;
(c) Y. Hoashi, T. Okino, Y. Takemoto, Angew. Chem. 117 (2005) 4100;
Y. Hoashi, T. Okino, Y. Takemoto, Angew. Chem. Int. Ed. 44 (2005) 4032.
[10] S.B. Tsogoeva, D.A. Yalalov, M.J. Hateley, C. Weckbecker, K. Huthmacher, Eur. J. Org. Chem. (2005) 4995.
[11] T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, Org. Lett. 6 (2004) 625.
[12] D.J. Maher, S.J. Connon, Tetrahedron Lett. 45 (2004) 1301.
[13] Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, Tetrahedron Lett. 45 (2004) 5589.
[14] (a) A. Berkessel, F. Cleemann, S. Mukherjee, T.N. Müller, J. Lex, Angew. Chem. 117 (2005) 817;
A. Berkessel, F. Cleemann, S. Mukherjee, T.N. Müller, J. Lex, Angew. Chem. Int. Ed. 44 (2005) 807;
(b) A. Berkessel, S. Mukherjee, F. Cleemann, T.N. Müller, J. Lex, Chem. Commun. (2005) 1898.
[15] S.B. Tsogoeva, M.J. Hateley, D.A. Yalalov, K. Meindl, C. Weckbecker, K. Huthmacher, Bioorg. Med. Chem. 13 (2005) 5680.
[16] S.B. Tsogoeva, S.-W. Wei, Tetrahedron: Asymmetry 16 (2005) 1947.
[17] For a review of asymmetric Michael addition to nitroolefins, see: O.M. Berner, L. Tedeschi, D. Enders, Eur. J. Org. Chem. (2002) 1877.

[18] K. Sakthivel, W. Notz, T. Bui, C.F. Barbas III, J. Am. Chem. Soc. 123 (2001) 5260.

[19] B. List, P. Pojarliev, H.J. Martin, Org. Lett. 3 (2001) 2423.

[20] D. Enders, A. Seki, Synlett (2002) 26.

[21] J.M. Betancort, K. Sakthivel, R. Thayumanavan, C.F. Barbas III, Tetrahedron Lett. 42 (2001) 4441.

[22] A. Alexakis, O. Andrey, Org. Lett. 4 (2002) 3611.

[23] H.J. Martin, B. List, Synlett (2003) 1901.

[24] (a) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, Adv. Synth. Catal. 346 (2004) 1147;
(b) D. Terakado, M. Takano, T. Oriyama, Chem. Lett. 34 (2005) 962;
(c) W. Wang, J. Wang, H. Li, Angew. Chem. 117 (2005) 1393;
W. Wang, J. Wang, H. Li, Angew. Chem. Int. Ed. 44 (2005) 1369.

[25] (a) A.J.A. Cobb, D.A. Longbottom, D.M. Shaw, S.V. Ley, Chem. Commun. (2004) 1808;
(b) C.E.T. Mitchell, A.J.A. Cobb, S.V. Ley, Synlett (2005) 611;
(c) A.J.A. Cobb, D.M. Shaw, D.A. Longbottom, J.B. Gold, S.V. Ley, Org. Biomol. Chem. 3 (2005) 84.

[26] T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, J. Am. Chem. Soc. 126 (2004) 9558.

[27] Y. Xu, A. Córdova, Chem. Commun. (2006) 460.

[28] S.B. Tsogoeva, S.-W. Wei, Chem. Commun. (2006) 1451.

[29] D.A. Yalalov, S.B. Tsogoeva, S. Schmatz, Adv. Synth. Catal. 348 (2006) 826.

[30] Gaussian 03, Revision C.02, M.J. Frisch et al., Gaussian, Inc., Wallingford CT, 2004.

[31] A.D. Becke, J. Chem. Phys. 98 (1993) 5648.

[32] A.D. Becke, Phys. Rev. A 38 (1988) 3098.

[33] C. Lee, W. Yang, R.G. Parr, Phys. Rev. B 37 (1988) 785.

[34] (a) C. Gonzalez, H.B. Schlegel, J. Chem. Phys. 90 (1989) 2154;
(b) C. Gonzalez, H.B. Schlegel, J. Phys. Chem. 94 (1990) 5523.