

Chiral Thiourea-Based Bifunctional Organocatalysts in the Asymmetric Nitro-Michael Addition: A Joint Experimental-Theoretical Study

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Abstract: A highly enantioselective (84–92% ee) organocatalytic Michael addition of acetone to aromatic nitroolefins has been described. 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 working hypothesis known from the literature which involves a bonding of both oxygens. The theoretical and experimental enantiomeric excess values show good agreement, rendering the computations an efficient tool for predicting the ee values in similar reactions.

Keywords: asymmetric catalysis; bifunctional organocatalysts; DFT calculations; Michael addition; transition states

Among the numerous asymmetric carbon-carbon bond formation reactions, the conjugate Michael addition plays a particularly important role.^[1] Without question, one of the more elegant and economically most attractive ways to introduce chirality into a Michael acceptor is through chiral organic catalysts.^[2] Employing nitroolefins as Michael acceptors opens the way to synthetically very useful C–C and C–X (X = N, O) bond-forming reactions.^[3,4] In particular, the Michael reaction of ketones with nitroolefins represents a convenient access to γ -nitro ketones which are valuable building blocks in organic synthesis.^[4] Considerable effort has been directed toward the development of an organocatalytic asymmetric version of this Michael addition over the recent years.^[5] Although many improvements to this reaction

have been made, poor to moderate enantioselectivities resulted when acetone was used as substrate.^[5]

The successful design of a general chiral organic catalyst for the Michael reaction of ketones to nitroolefins with high enantioselectivity is still a challenging task. For the solution of this problem, computational chemistry has proven to be a valuable tool: semiempirical, wave function-based quantum chemical and density functional methods can predict reaction pathways, product ratios and even enantioselectivities.^[6] While it is nowadays possible to tackle realistic problems with remarkably accurate computational methods, the search for transition state structures in reactive processes still remains a challenge due to the high flexibility of these structures, in particular when more than two reactants are present, as is naturally the case in homogeneous catalytic processes.

Organic catalysts which possess both an acidic and basic/nucleophilic moiety have attracted broad interest in asymmetric synthesis during the last years.^[7] Several enantioselective urea- and thiourea-based bifunctional organic catalysts have been identified.^[8–20] Examples of asymmetric Strecker synthesis,^[8] enantioselective hydrophosphonylation of imines,^[9] acyl-Pictet–Spengler,^[10] nitro-Mannich^[11] reactions, Michael additions,^[12–16] aza-Henry,^[17] Baylis–Hillman^[18,19] reactions and dynamic kinetic resolution of azlactones^[20] have been reported in which the chiral bifunctional organocatalysts have successfully been employed.

More recently, we reported^[21] a new bifunctional organocatalyst **1** (Figure 1), bearing both a thiourea moiety and an imidazole group on a chiral scaffold. The addition of acetone to *trans*- β -nitrostyrene in the presence of these bifunctional organocatalyst gave the adduct in 87% ee and with 55% yield. Notably, this enantioselectivity is superior to those generated by the proline and/or

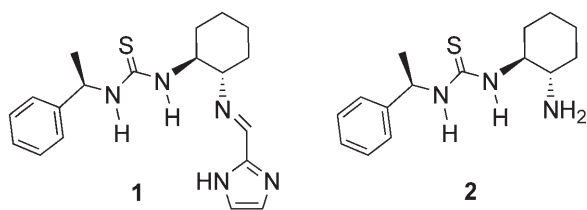


Figure 1. Chiral thiourea based bifunctional organocatalysts.

homo-proline tetrazole catalysts described in the literature.^[5]

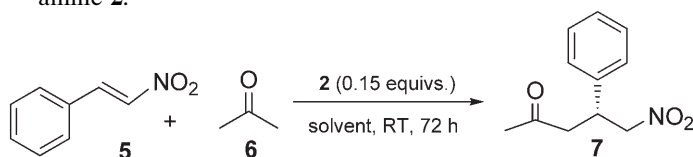
Considering the fact that secondary and primary amines with ketones reversibly form enamines,^[22] which can further react with electrophiles, we anticipate that the substitution of the imidazolyl moiety in **1** by an amino group might result in a simpler but more active catalyst **2**, which might be able to activate both ketones through enamine formation and nitroolefins by hydrogen bonding to a thiourea moiety.

Here we describe the ability of the chiral bifunctional organic catalyst **2**, that possesses both a thiourea moiety and a primary amine group as a base, in performing the asymmetric nitro-Michael addition reaction, accompanied by a quantum-chemical calculation of the stereoselectivity.

Preliminary exploratory experiments revealed that thiourea catalyst **2** (0.15 equivs.) promoted the addition of acetone to *trans*- β -nitrostyrene at room temperature in toluene with results [55%, 86% ee (*R*)] comparable to those provided by catalyst **1** [55%, 87% ee (*R*)^[21]].

We proved thiourea **2** as the good catalyst candidate for a further optimization of the reaction conditions. A range of solvents for the addition of acetone to *trans*- β -nitrostyrene catalyzed by **2** was screened (Table 1).

Table 1. Solvent screen for the conjugate addition of acetone (**6**) to *trans*- β -nitrostyrene (**5**) catalyzed by chiral thiourea-amine **2**.



Entry	Solvent	Conversion [%] ^[a]	ee [%] ^[b]
1	Toluene	100	86
2	CH ₂ Cl ₂	56	81
3	CHCl ₃	51	84
4	Acetone	22	62
5	MeOH	50	50
6	DMSO	80	14

^[a] Determined by ¹H NMR of crude reaction mixture.

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

The use of CH₂Cl₂, CHCl₃, acetone, MeOH and DMSO as solvents led, in general, to a decrease in the reaction rate with respect to toluene (Table 1, entry 1 versus entries 2–6).

Much lower ee values were observed in acetone and MeOH (62% and 50% ee, respectively, entries 4 and 5) relative to that in toluene (86% ee, entry 1). Furthermore, the use of DMSO as solvent significantly decreased the enantioselectivity (14% ee, Table 1, entry 6). These observations are consistent with the fact that the hydrogen bonding strength is affected by the solvent;^[23] the effect of replacing DMSO by non-polar toluene increases the hydrogen bonding interaction between the nitro group of *trans*- β -nitrostyrene and the thiourea moiety of catalyst **2**. Toluene, thus, remained the solvent of choice.

Furthermore, screening several achiral and chiral additives allowed us to further improve the yields and enantioselectivities. It is interesting to note that the reaction rate was increased to a different extent, depending on the nature of the additive used. When PhCOOH^[5g] was studied, we found that the product was formed in 20 h with 71% yield and 89.5% ee. Use of (*R*)-(-)- and (*S*)-(+)-2-phenylpropionic acids as chiral additives provided the adduct **7** already in 12 hours with 81%, 88.5% ee and 75%, 89% ee, respectively (Table 2, entries 3 and 4). Addition of NH₄Cl/H₂O^[5g] only slightly improved the yield (entry 5). We then tested H₂O alone (1 equiv. and 2 equivs.) and noted that 2 equivs. of H₂O gave much better results than 1 equiv. (Table 2, entry 7 versus entry 6).

Moreover, the use of H₂O (2 equivs.) and AcOH (0.15 equivs.) as additive gave the product **7** in 85.5% yield with 86% ee (*R*) in 16 hours. The water and acid might accelerate the reaction by facilitating the inter-conversion of the different intermediates of the catalytic enamine cycle (see below).

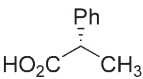
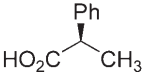
Raising the reaction temperature in the presence of additive AcOH/H₂O led to reduced reaction times (up to 3 h) but lower yields as well as enantioselectivities (entries 9 and 10 versus entry 8, Table 2). Thus, AcOH/H₂O used at room temperature was found to be the most promising additive regarding the yield and enantioselectivity.

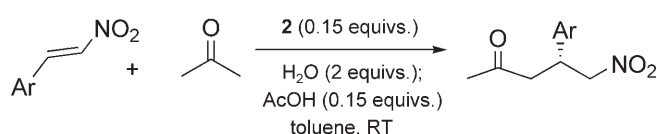
With optimal reaction conditions established, several aromatic olefins were then evaluated as substrates (Table 3).

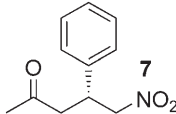
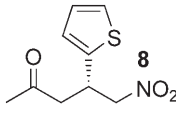
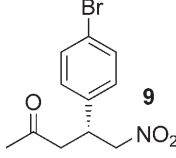
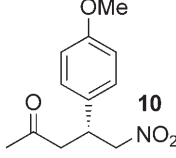
The introduction of electron-withdrawing or electron-donating groups on the aromatic ring of the nitroolefins slightly affected enantioselectivities [84–92% ee (*R*)] and yields (85.5–93%, Table 3, entries 1–4). Notably, in general, much better reaction rates, higher yields and enantioselectivities were achieved by the thiourea-amine **2** relative to those provided by the thiourea-imidazole catalyst **1**.^[21]

To explain the predominant production of *R* adducts, we have computationally determined the first order sad-

Table 2. Asymmetric addition of acetone (**6**) to *trans*- β -nitrostyrene (**5**) in toluene catalyzed by **2** in the presence of different additives.

Entry	Additive (equivalents)	<i>T</i> [°C]	<i>t</i> [h]	Yield [%] ^[a]	ee [%] ^[b]
1	–	RT	72	55	86
2	PhCOOH (0.15 equivs.)	RT	20	71	89.5
3	 (0.15 equivs.)	RT	12	81	88.5
4	 (0.15 equivs.)	RT	12	75	89
5	NH ₄ Cl; H ₂ O (1 equiv.); (1 equiv.)	RT	18	59	84
6	H ₂ O (1 equiv.)	RT	47	59	85
7	H ₂ O (2 equivs.)	RT	32	78	86
8	H ₂ O; AcOH (2 equivs.); (0.15 equivs.)	RT	16	85.5	86
9	H ₂ O; AcOH (2 equivs.); (0.15 equivs.)	40	7	80	86
10	H ₂ O; AcOH (2 equivs.); (0.15 equivs.)	60	3	63	82

^[a] Yield of isolated product after column chromatography on SiO₂.^[b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.**Table 3.** Catalytic asymmetric Michael addition of acetone to different aromatic nitroolefins under optimized conditions.

Entry	Product	Time [h]	Yield [%] ^[a]	ee [%] ^[b]
1	 7	16	85.5	86
2	 8	25	87	92
3	 9	15	93	84
4	 10	71	87	87

^[a] Yield of isolated product after column chromatography on SiO₂.^[b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

dle points (“transition state structures”) for the formation of both **R** and **S** enantiomers (Figures 2 and 3). In the quantum-chemical calculations the Gaussian03 program package^[24] was employed throughout. The DFT variant B3LYP^[25] with Becke’s exchange functional^[26] and the Lee, Yang and Parr correlation functional^[27] was used in conjunction with the 6–31G(d) basis set (567 cGTOs) to fully optimize the structures. Eigenvalues of Hessian matrices at the relevant stationary points on the potential energy surfaces were calculated to verify their nature; the geometries of the first-order saddle points were identified using the intrinsic reaction coordinate (IRC) method.^[28] At the B3LYP/6–31G(d) geometries, we carried out B3LYP/6–31G(d, p), B3LYP/6–31+G(d) and B3LYP/6–31+G(d, p) single point calculations in order to assess the influence of hydrogen polarization and diffuse functions. The calculations are carried out for the isolated systems without explicit consideration of solvent effects. This is a reasonable assumption because toluene might not influence the reaction through its polarity. We carefully studied all possible conformers of the initially found transition state structures and selected the energetically lowest conformer.

In the transition state (TS) structures for formation of both the **R** and **S** enantiomers, the arrangement of the oxygen atoms of the nitrostyrene nitro group relatively to the hydrogen atoms of the thiourea moiety is clearly non-planar (Figures 2 and 3). Furthermore, catalyst **2** shows an additional structure stabilization and fixation (a simple “tertiary structure”) due to the formation of an intramolecular hydrogen bond between the sulfur atom and hydrogen atom H_c (Figures 2 and 3). Compared to the **R** TS, the two distances between the nitro group oxygen atom and the two thiourea hydrogens

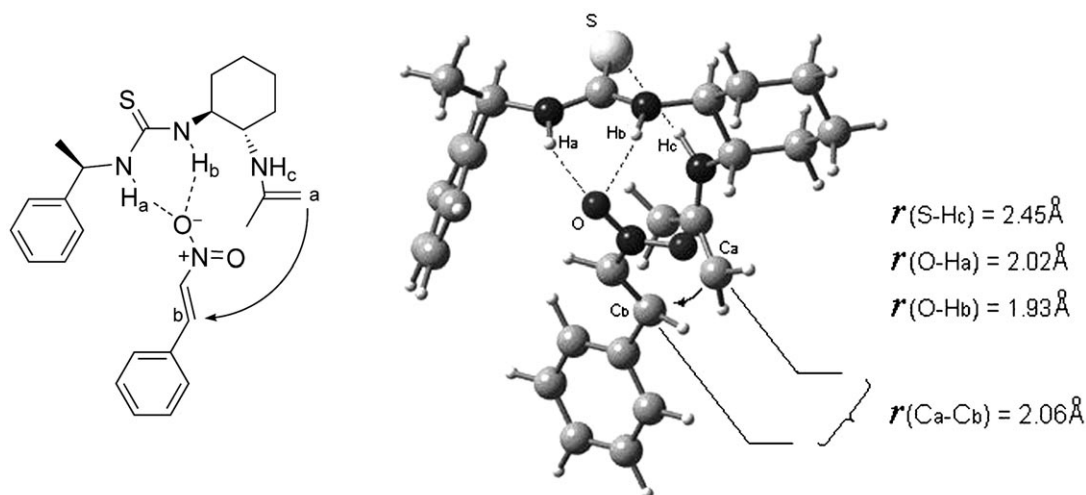


Figure 2. Transition state structure for the formation of the *R* enantiomer.

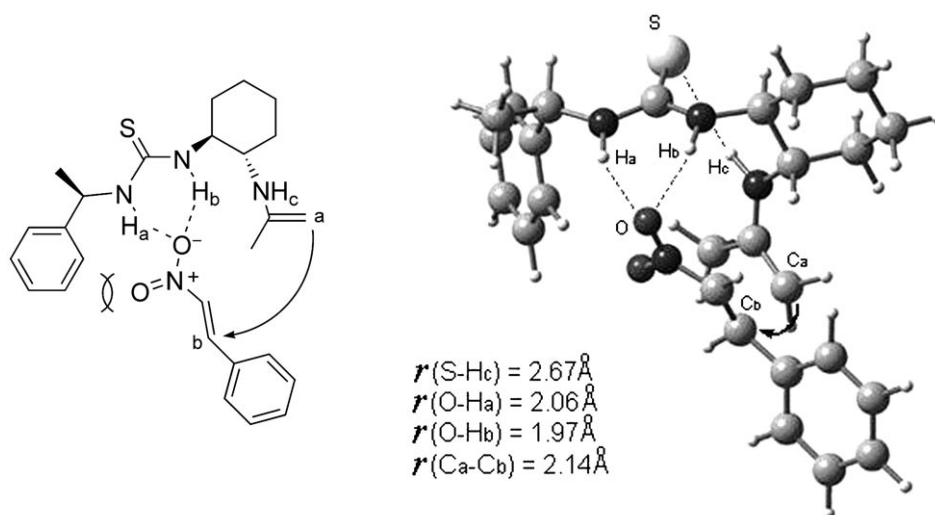


Figure 3. Transition state structure for the formation of the *S* enantiomer.

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 Å and 0.22 Å, respectively. The $H_a \cdots O \cdots H_b$ angles in both structures differ only by 0.4°. In summary, the *R* TS is more compact and the second nitro group oxygen points towards the reactive center. In the *S* TS, this oxygen atom points away from that center and undergoes a repulsive interaction with the phenyl ring of the catalyst.

On the base of the Curtin–Hammett principle and according to the calculated Gibbs free energies (calculated within the standard harmonic-oscillator rigid-rotor model) of the transition states, theoretical ee values were determined to be 69, 71, 77 and 79% with B3LYP/6–31G(d), B3LYP/6–31G(d, p)/B3LYP/6–31G(d), B3LYP/6–31+G(d)/B3LYP/6–31G(d) and B3LYP/6–31+G(d, p)/B3LYP/6–31G(d), respectively, which are in good agreement with the experimen-

tal value (86% ee). While the polarization functions at the hydrogens play only a minor role because these atoms are not directly involved in the C–C bond-forming process, the diffuse functions are decisive for the description of the reactive centre. In our calculations, the ee is defined as $([R] - [S]) / ([R] + [S])$ and $[R]/[S]$ is obtained as the ratio of the rate constants at $T = 295$ K, $k_R/k_S = \exp((G_S^\ddagger - G_R^\ddagger)/RT)$; the quantity $\Delta G^\ddagger = G_R^\ddagger - G_S^\ddagger$ is calculated to be 4.16 kJ mol^{−1} [B3LYP/6–31G(d)], 4.35 kJ mol^{−1} [B3LYP/6–31G(d, p)/B3LYP/6–31G(d)], 5.01 kJ mol^{−1} [B3LYP/6–31+G(d)/B3LYP/6–31G(d)] and 5.29 kJ mol^{−1} [B3LYP/6–31+G(d, p)/B3LYP/6–31G(d)], respectively; zero-point energy and thermal effects are considered at the B3LYP/6–31G(d) level of theory because here only a minor basis set dependence is expected. The good agreement between experimental and theo-

retical results for ee might be partially due to error cancellation, because only *differences* in the free energies of the species were calculated.

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 et al., which involves a bonding of both oxygens (also quoted in several papers by this group).^[12a–c] The possible structure of the intermolecular complex with two oxygens bound to the thiourea unit is shown in Figure 4 (b), along with the pre-complex pertinent to the transition state for the *R* enantiomer [Fig. 4 (a)]. Both structures were fully optimized employing the 6–31G(d, p) basis set in order to allow for a flexible description of the hydrogen bonds which are crucial in distinguishing between the two complexes. Electronically, the complex bound by two oxygens is energetically less stable by 5.5 kJ mol^{−1} [4.7 kJ mol^{−1} for B3LYP/6–31G(d)] while inclusion of the zero-point energy and thermal effects inverts this relation and the complex bound by two oxygens becomes more stable [$\Delta G = 6.3$ kJ mol^{−1}; 7.3 kJ mol^{−1} for B3LYP/6–31G(d)]. However, the structure from Figure 4 (b) will not lead to Michael reaction for steric reasons. The nitrostyrene-thiourea unit is planar and the attack of the enamine group is not possible. We note that Takemoto's experimental verification of this hypothetical structure of the intermolecular complex by ¹H NMR^[12b] is questionable as these experimental data also allow for a structure according to our computational results.

Due to the good agreement of our calculated ee value, which is quite a sensitive quantity, with experiment we are confident that the transition state structures reported in this work are reliable. In addition, from a more intuitive point of view, six-membered TSs (this work) are preferred over eight-membered structures (Takemoto).

Based on these results we have proposed a plausible reaction mechanism for chiral thiourea-amine **2** cataly-

ses (Scheme 1). 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 the thiourea moiety to give intermediate **B**. The existence of intermediates **A** and **B** in the reaction mixture was confirmed using the ESI-MS method (Scheme 1). At the last step the regeneration of the catalyst through hydrolysis of the imine **B** is facilitated by water.

In conclusion, the new thiourea catalyst **2** shows high enantioselectivities (84–92% ee) and yields (85.5–93%) in the Michael addition of acetone to different aromatic nitroolefins. We have calculated and analyzed the transition state geometries for formation of *R* and *S* enantiomers. Our results give clear evidence that only one oxygen atom of the nitro group is bound to the thiourea moiety of the thiourea-amine catalyst **2**. The theoretical and experimental enantiomeric excess values show good agreement, rendering the computations an efficient tool for predicting the ee values in similar reactions with slightly modified catalysts, the efficiency and selectivity of which may be considerably improved in this way.

Experimental Section

General Remarks

Reagents obtained from commercial sources were used without further purification. TLC chromatography was performed on precoated aluminium silica gel SIL G/UV₂₅₄ plates (Macherey, Nagel & Co.) or silica gel 60-F₂₅₄ precoated glass plates (Merck). ¹H 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-reso-

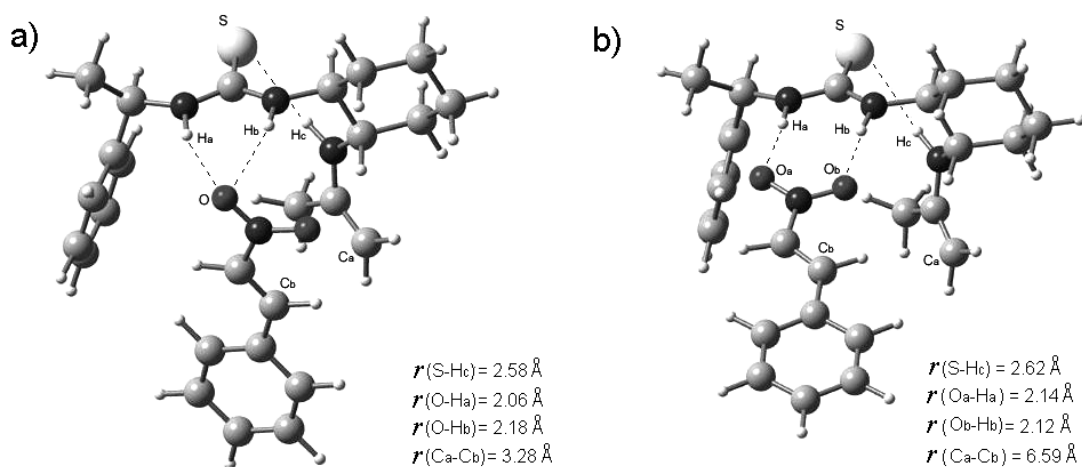
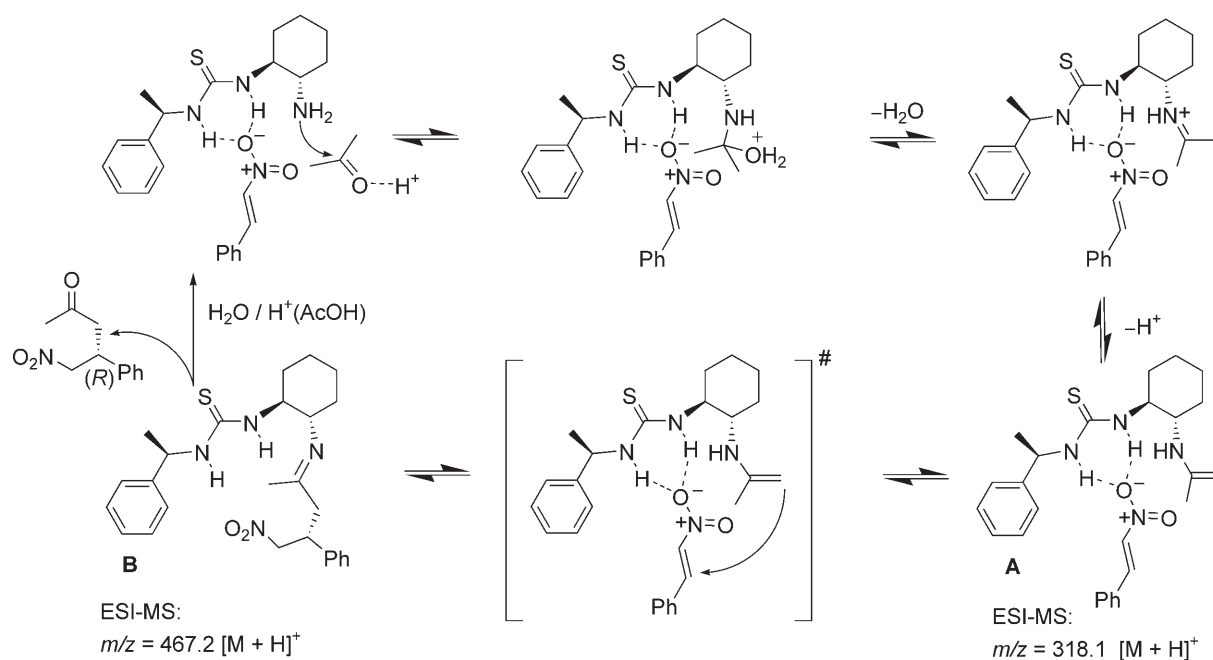


Figure 4. Intermolecular complexes between the acetone enamine catalyst and nitrostyrene. **a)** Nitrostyrene bound by one oxygen atom (more flexible structure); **b)** nitrostyrene bound by two oxygen atoms (approach of C_a towards C_b not possible).



Scheme 1. Plausible multistep chiral thiourea-amine **2** catalyses.

lution mass spectra were measured with a Bruker APEX IV 7T FT-ICR instrument.

General Procedure for the Catalytic Asymmetric Michael Addition

To a stirred solution of catalyst (0.15 equivs.) in toluene (0.5 mL) and acetone (0.27 mL) at room temperature, was added water (2 equivs.), acetic acid (0.15 equivs.) and, after 2 minutes, nitroolefin (1 equiv.). The reaction mixture was stirred at room temperature for the appropriate time. The solvent was evaporated and the residue was purified by preparative TLC or chromatography on an SiO₂ 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.

Supporting Information

¹H NMR of the Michael products, chiral-phase HPLC data, geometries of the transition states for formation of *R* and *S* isomers are given in the Supporting Information.

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References and Notes

- [1] P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**.
- [2] a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840–3864; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748; b) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.
- [3] R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933–971.
- [4] For a review of asymmetric Michael addition to nitroolefins, see: O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894.
- [5] a) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; b) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425; c) D. Enders, A. Seki, *Synlett* **2002**, 26–28; d) J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 4441–4444; e) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611–3614; f) H. J. Martin, B. List, *Synlett* **2003**, 1901–1902; g) O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147–1168; h) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808–1809; i) C. E. T. Mitchell, A. J. A. Cobb, S. V. Ley, *Synlett* **2005**, 611–614; j) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84–96; k) T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559.
- [6] a) N. Halland, T. Velgaard, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 4151–4157; b) M. E. Tran Huu Dau; C. Riche, F. Dumas, J. d'Angelo, *Tetrahedron: Asymmetry* **1998**, *9*, 1059–1064; c) M. J. Lucero, K. N. Houk, *J. Am.*

- Chem. Soc.* **1997**, *119*, 826–827; d) C. Allemann, R. Gorrillo, F. R. Clemente, P. H.-Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558–569; e) F. R. Clemente, K. N. Houk, *Angew. Chem. Int. Ed.* **2004**, *43*, 5766–5768.
- [7] For reviews of bifunctional organic catalysts, see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; b) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2004**; c) P. M. Pihko, *Angew. Chem.* **2004**, *116*, 2110–2113; *Angew. Chem. Int. Ed.* **2004**, *43*, 2062–2064; d) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; e) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306.
- [8] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902; b) M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336–1338; *Angew. Chem. Int. Ed.* **2000**, *39*, 1279–1281; c) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014; d) S. B. Tsogoeva, M. J. Hateley, D. A. Yalalov, K. Meindl, C. Weckbecker, K. Huthmacher, *Bioorg. Med. Chem.* **2005**, *13*, 5680–5685.
- [9] G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103.
- [10] M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559.
- [11] T. P. Yoon, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, 470–472; *Angew. Chem. Int. Ed.* **2005**, *44*, 466–468.
- [12] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125; c) Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem.* **2005**, *117*, 4100–4103; *Angew. Chem. Int. Ed.* **2005**, *44*, 4032–4035.
- [13] H. Li, Yi. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907.
- [14] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969.
- [15] W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393–1395; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369–1371.
- [16] a) A. J. A. Cobb, D. A. Longbottom, D. M. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808–1809; b) C. E. T. Mitchell, A. J. A. Cobb, S. V. Ley, *Synlett* **2005**, 611–614; c) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.* **2005**, *3*, 84–96.
- [17] T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625–627.
- [18] D. J. Maher, S. J. Connon, *Tetrahedron Lett.* **2004**, *45*, 1301–1305.
- [19] Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa, *Tetrahedron Lett.* **2004**, *45*, 5589–5592.
- [20] a) A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller, J. Lex, *Angew. Chem.* **2005**, *117*, 817–821; *Angew. Chem. Int. Ed.* **2005**, *44*, 807–811; b) A. Berkessel, S. Mukherjee, F. Cleemann, T. N. Müller, J. Lex, *Chem. Commun.* **2005**, 1898–1900.
- [21] S. B. Tsogoeva, D. A. Yalalov, M. J. Hateley, C. Weckbecker, K. Huthmacher, *Eur. J. Org. Chem.* **2005**, 4995–5000.
- [22] For a review of asymmetric aminocatalysis, see: B. List, *Synlett* **2001**, 1675–1686.
- [23] a) A. N. Thadani, A. R. Stankovic, V. H. Rawal, *PNAS* **2004**, *101*, 5846–5850; b) Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146; c) J. N. Spencer, C. L. Campanella, E. M. Harris, W. S. Wolbach, *J. Phys. Chem.* **1985**, *89*, 1888–1891.
- [24] M. J. Frisch, et al., *Gaussian 03*, Revision C.02, Gaussian, Inc., Wallingford CT, **2004**.
- [25] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.
- [26] A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098–3100.
- [27] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.
- [28] a) C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.* **1989**, *90*, 2154–2161; b) C. Gonzalez, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523–5527.