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Organocatalytic asymmetric conjugate addition of thioacetic acid to β-nitrostyrenes

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Abstract—A method for organocatalytic, enantioselective Michael addition reactions of thioacetic acid with a range of *trans*-β-nitrostyrenes has been developed. The processes, promoted by the chiral amine thiourea organocatalyst, take place in high yields with up to 70% ee.

In recent years, the catalytic asymmetric Michael addition reactions catalyzed by chiral organocatalysts have been recognized as an efficient method for enantioselective carbon–carbon bond formations.[1,2] Efficient catalytic asymmetric Michael additions using aldehydes,[3] ketones,[4] 1,3-dicarbonyl compounds,[5] nitroalkanes[6] or preformed silyl ethers[7] as Michael donors have been intensively studied. In contrast, a catalytic enantioselective process using a thiol derivative as a nucleophile has been much less explored.[8] The studies reported to date have mainly focused on the use of thiols[9,10] as a Michael donor. Generally, harsh reaction conditions are required for the conversion of the newly formed C–S bond to more synthetically versatile SH group.[11] On the other hand, the use of a thioacid (RCOSH) as a nucleophile for the Michael addition reaction is more attractive since the resulting thioester can be readily transformed into SH group under various, mild reaction conditions,[11] but an organocatalytic enantioselective process has not yet been developed. In this letter, we wish to disclose the first organocatalytic asymmetric method for the Michael addition of thioacetic acid to β-nitrostyrenes in high yields (91–98%) with up to 70% ee.

Bifunctional cinchona alkaloids were the first organocatalysts used for promoting asymmetric Michael addition reactions of thiols. Wynberg et al. have demonstrated the utility of quinidine (QD **I**) and quinine (Q **II**) for asymmetric addition of a thiol to α,β-unsaturated ketones (Fig. 1).[10a] Almost at the same time,

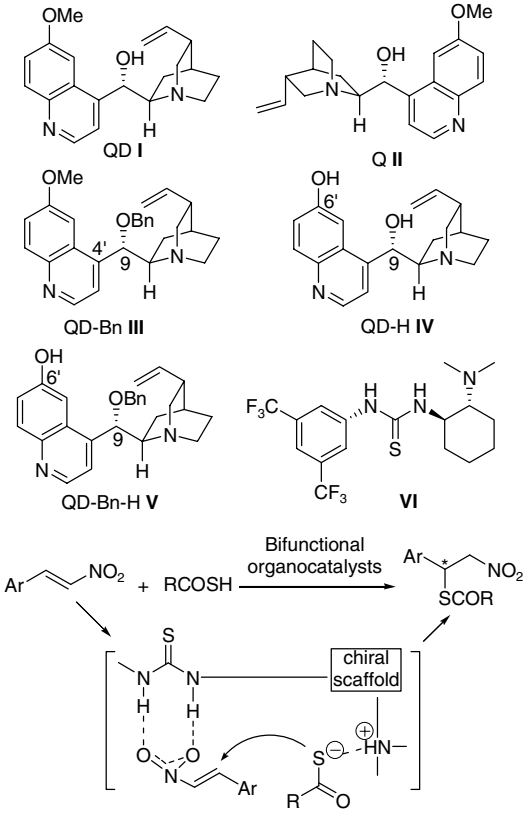

Figure 1. Bifunctional organocatalyst-promoted asymmetric Michael addition of thioacids to nitroolefins.

Keywords: Amine thiourea; Asymmetric organocatalysis; Michael addition reaction; Nitroolefins; Thioacetic acid.
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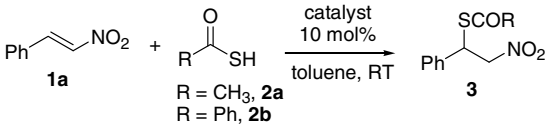
Mukaiyama and co-workers reported using proline derivative for a similar purpose.[10c] Recently, Deng and co-workers have described an elegant approach for using the modified forms of these cinchona alkaloids in the conjugate reactions of thiols to cyclic enones with significantly improved enantioselectivities.[10d] These observations prompted us to investigate the enantioselective Michael addition of thioacetic acid to *trans*-β-nitrostyrenes. We envisioned that a chiral bifunctional organocatalyst could activate the weakly nucleophilic thioacid and the electron deficient *trans*-β-nitroolefin simultaneously to facilitate the process, thus forming addition products enantioselectively with high reaction efficiency (Fig. 1).

To test the working hypothesis, we initially conducted a model reaction of *trans*-β-nitrostyrene **1a** with thioacetic acid **2a** in toluene in the absence of an organocatalyst. As expected, the reaction resulted in the desired adduct **3a**, but took place slowly (24 h) to afford **3a** in a moderate yield (Table 1, entry 1). In contrast, under the same reaction conditions in the presence of 10 mol % QD **I**, the conjugate addition proceeded much faster (15 min) and gave **3a** in a high yield (95%), but gave rise to only a low enantioselectivity (23% ee) (Table 1, entry 2). A similar result was obtained using Q **II** as the catalyst (Table 1, entry 3).

The encouraging results prompted us to carry out more detailed investigation on the asymmetric version of the Michael reactions. First, we attempted to identify the best organocatalyst for the process. Deng and co-workers have demonstrated that increasing the rigidity of these cinchona alkaloids can improve enantioselectivity of reactions.[10d] Accordingly, a benzyl group was introduced at the position 9 in QD **I** to restrict the rotation of C4′–C9 bond. The resulting organocatalyst QD-Bn **III** was tested for the reaction and the results turned out to be disappointing (Table 1, entry 4). No enantioselectivity was observed. The reaction rate was also significantly reduced presumably as a result of blocking the 9–OH group. Catalyst QD-H **IV** with more acidic phenol group was synthesized and evaluated (Table 1, entry 5). The reaction proceeded more quickly than that using QD **I** probably due to the enhanced H-bonding interaction of the nitro group of the nitroolefin **1a** with the two OH groups in **IV**, but a lower ee was achieved as well. The enantioselectivity of the reaction was improved when the more rigid **V** was employed (31% ee, Table 1, entry 6). Based on these studies, we synthesized bifunctional amine thiourea **VI** (Table 1, entry 7). Precedent studies have shown that the thiourea group in **VI** can afford a strong two-hydrogen bonding interaction with the nitro group in β-nitrostyrene (Fig. 1).[5e,f,12–15] Indeed, the utilization of **VI** as an organocatalyst resulted in further improved ee (34%). No enantioselectivity was observed when the more sterically demanding PhCOSH **2b** was used as a Michael donor (Table 1, entry 8).

Having identified the amine thiourea **VI** as the best catalyst among the organocatalysts tested, optimization of reaction conditions for the process was carried out next. First, the effect of solvent on the Michael addition reactions was examined (Table 2, entries 1–7) and it was found that the use of Et_2O as a reaction medium was superior to others. In this solvent, the highest ee (50%) at a room temperature reaction was obtained (Table 2, entry 7). Finally, the effects of reaction temperature and catalyst loading on the process were determined (Table 2, entries 8–14). When the reaction temperature

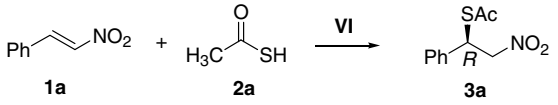
Table 1. Asymmetric Michael addition of thioacid (**2**) to *trans*-β-nitrostyrene (**1a**) catalyzed by organocatalysts[a]



Entry	Catalyst	*t*	Yield (%)[b]	ee (%)[c]
1	None	24 h	71	0
2	**I**	15 min	95	23
3	**II**	15 min	94	17
4	**III**	1.5 h	94	0
5	**IV**	5 min	95	19
6	**V**	15 min	93	31
7	**VI**	30 min	92	34
8[d]	**VI**	1 h	92	0

[a] Unless otherwise specified, the reaction was carried out using **1a** (0.20 mmol) and **2a** (0.40 mmol) in the presence of 10 mol % of an organocatalyst in 1.0 mL of toluene at rt for the specified time.
[b] Isolated yields after chromatographic purification.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H).
[d] Compound **2b** used as a Michael donor.

Table 2. Optimization of reaction conditions of the Michael addition of thioacetic acid to *trans*-β-nitrostyrene catalyzed by **VI**[a]



Entry	Solvent	*T* (°C)	*t* (min)	Yield (%)[b]	ee (%)[c]
1	Toluene	rt	30	92	34
2	CH_2Cl_2	rt	60	93	42
3	CH_3CN	rt	60	92	17
4	THF	rt	15	95	21
5	$CHCl_3$	rt	15	95	44
6	EGDME[d]	rt	15	94	43
7	Et_2O	rt	15	94	50
8	Et_2O	0	15	93	54
9	Et_2O	−15	60	91	78
10	Et_2O	−78	45	92	73
11[e]	Et_2O	−15	45	92	52
12[f]	Et_2O	−15	45	93	70
13[g]	Et_2O	−15	45	92	63
14[h]	Et_2O	−15	45	91	64

[a] Unless specified, see footnote a in Table 1 and Supplementary data for reaction conditions.
[b] Isolated yield after chromatographic purification.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H).
[d] Ethylene glycol dimethyl ether.
[e] 5 mol % **VI** used.
[f] 2 mol % **VI** used.
[g] 1 mol % **VI** used.
[h] 0.5 mol % **VI** used.

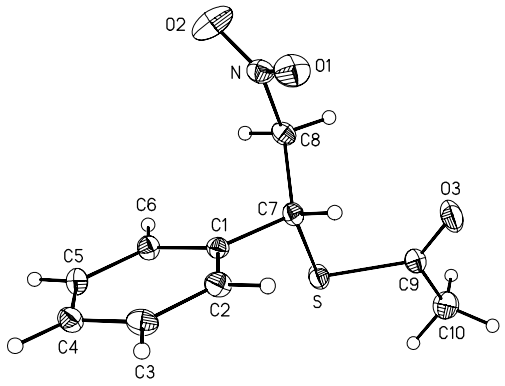
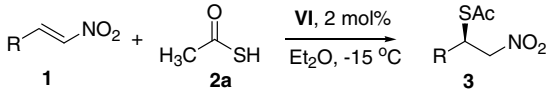


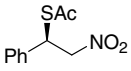
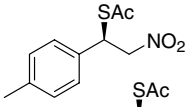
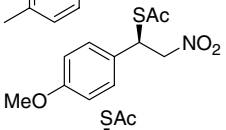
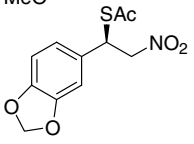
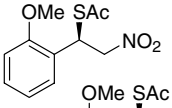
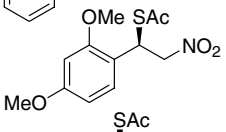
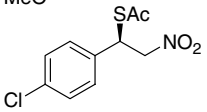
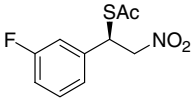
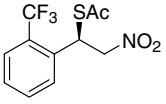
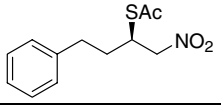
Figure 2. X-ray crystal structure of **3a**.

was lowered to −15 °C, the enantioselectivity was improved up to 78% without affecting the reaction yield (Table 2, entry 9). Interestingly, a slight drop in enantioselectivity (73% ee) was observed at −78 °C (entry 10). Remarkably, a catalyst loading as low as 0.5 mol % still showed considerable catalytic activity at −15 °C (entry 14). From an operational standpoint, we chose to use 2 mol % **VI** at −15 °C in Et_2O to evaluate the scope of the Michael addition reactions. The absolute configuration of **3a** prepared under these reaction conditions was determined by X-ray crystallography to be *R* (Fig. 2).[16]

A range of *ortho*-, *meta*-, and *para*-substituted nitroolefins were tested for their ability to undergo the reaction (Table 3). Generally, the reactions proceeded to completion in less than 2 h in excellent yields (91–98%). Low to

Table 3. Scope of amine thiourea **VI** promoted the Michael addition reactions of thioacetic acid to nitroolefins[a]



Entry	Product	*t* (h)	% Yield[b]	% ee[c]
1		0.75	93	70
2		1.0	93	53
3		0.5	95	42
4		1.5	91	58
5		0.5	98	56
6		1.5	93	53
7		0.5	92	27
8		0.5	94	20
9		0.5	92	24
10		1	92	52

[a] See footnote a in Table 1 and the Supplementary data.
[b] Isolated yield after chromatographic purification.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H).

moderate enantioselectivities (20–70% ee) were obtained. It was observed that the phenyl rings having electron-donating substituent groups provided Michael adducts with higher enantioselectivities (Table 3, entries 1–6) than those possessing electron-withdrawing groups (entries 7–9). The process was also applicable to aliphatic nitroolefin *trans*-$Ph(CH_2)_2CH{=}CHNO_2$ in 92% yield with 52% ee (entry 10).

In conclusion, we have identified bifunctional chiral amine thiourea **VI** as an effective organocatalyst for promoting the Michael addition reactions of thioacetic acid to nitroolefins. The processes take place in excellent yields (91–98%) with up to 70% ee under mild reaction conditions. To our knowledge, this study represents the first example of using a chiral organocatalyst for catalyzing the 1,4-conjugate addition reactions of a less reactive thioacid with β-nitrostyrenes. The resulting thioester products can be readily transformed into more synthetically useful thiols. Further efforts will be directed toward developing more efficient organocatalysts to improve the enantioselectivities of the processes and their applications in synthesis of biologically active molecules will be explored.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.036.

References and notes

1. For a book discussing organocatalysis, see: Berkessel, A.; Groger, H. *Asymmetric Organocatalysis—From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH GmbH & Co. KGaA: Weinheim, Germany, 2005.
2. For recent reviews of organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (c) Special issue on organocatalysis: *Acc. Chem. Res.* **2004**, *37*, 487; (d) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719; (e) Tian, S.-K.; Chen, Y.-G.; Hang, J.-F.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621.
3. Aldehydes as Michael donors, see: (a) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *43*, 1369; (b) Peelen, T. J.; Chi, Y.-G.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598; (c) Chi, Y.-G.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253; (d) Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958; (e) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212; (f) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527; (g) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737; (h) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151; (i) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611.
4. Ketones as Michael donors, see: (a) Ishii, T.; Fiujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558; (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441; (c) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423; (d) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559; (e) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808; (f) Kotrusz, P.; Toma, S.; Schmalz, H.-G.; Alder, A. *Eur. J. Org. Chem.* **2004**, 1557.
5. For 1,3-dicarbonyl and related stabilized carbanions as Michael donors, see: (a) Wang, J.; Li, H.; Duan, W.-H.; Zu, L.-S.; Wang, W. *Org. Lett.* **2005**, *7*, 4713; (b) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105; (c) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906; (d) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948; (e) Ye, J.-X.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481; (f) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672; (g) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119; (h) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032; (i) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661; (j) Ma, D.; Cheng, K. *Tetrahedron: Asymmetry* **1999**, *10*, 713.
6. For nitroalkanes as Michael donors, see: (a) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897; (b) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967; (c) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331; (d) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257; (e) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975.
7. For silyl ethers as Michael donors, see: (a) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192; (b) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894; (c) Wang, W.; Li, H.; Wang, J. *Org. Lett.* **2005**, *7*, 1637; (d) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 9022.
8. For a review, see: Fehr, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 2567.
9. For examples of organometallics catalyzed Michael addition of thiols, see: (a) Zielinska-Błajet, M.; Kowalczyk, R.; Skarżewski, J. *Tetrahedron* **2005**, *61*, 5235; (b) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043; (c) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974; (d) Garg, S. K.; Kumar, R.; Chakraborti, A. K. *Tetrahedron Lett.* **2005**, *46*, 1721.
10. Organocatalyzed Michael addition of thiols, see: (a) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417; (b) Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc., Perkin Trans. 1* **1981**, 547; (c) Suzuki, K.; Ikegawa, A.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3277; (d) McDaid, P.; Chen, Y.-G.; Deng, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 338; (e) Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141.
11. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; p 454.

12. (a) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625; (b) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807; (c) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898.
13. For studies of the H-bonding interactions of ureas/thioureas with nitro, carbonyl and imine groups, see: (a) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120; (b) Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415; (c) Etter, M. C.; Panunto, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5896; (d) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289; (e) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217; (f) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407.
14. In addition to amine thiourea **VI**, other thiourea-based organocatalysts have been reported. For Jacobsen's urea and thiourea catalysis, see: (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901; (b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279; (c) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012; (d) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466; (e) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102; (f) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558; For cinchona alkaloid-based thioureas, see: (g) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967; (h) Ye, J.-X.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.
15. Recently, we have developed binaphthyl-based amine thioureas for asymmetric organocatalysis, see: Wang, J.; Li, H.; Yu, X.-H.; Wang, W. *Org. Lett.* **2005**, *7*, 4293, and Ref. 5a.
16. See Supplementary data for X-ray crystallographic information; CCDC 283455 also contains the supplementary crystallographic data. These data can be obtained free of charge via www.ccdc.cam.ac.uk.