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Enantioselective Conjugate Addition of Nitroalkanes to Vinyl Sulfone: An Organocatalytic Access to Chiral Amines

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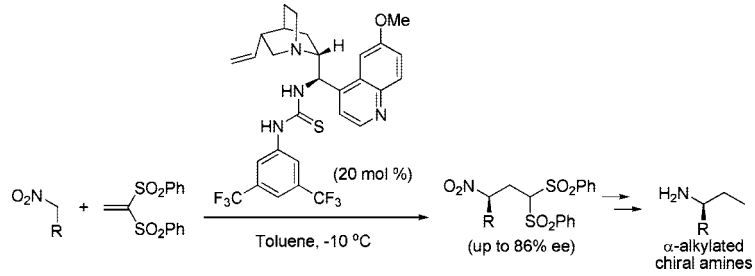
ABSTRACT



Organocatalytic asymmetric conjugate addition of nitroalkanes to vinyl sulfone mediated by cinchona alkaloid-derived thiourea catalyst afforded the desired Michael product with good enantioselectivity. The described method, in combination with ready desulfonation, represents a novel approach to access α-alkylated chiral amines.

The catalytic asymmetric Michael addition is one of the most powerful carbon−carbon bond-forming reactions, and remarkable progress has been made in organocatalytic Michael additions in recent years.[1] Nitroalkanes are versatile donors, and their Michael adducts have been demonstrated to be valuable intermediates in organic synthesis. The conjugate additions of nitroalkanes to imines,[2] nitrostyrenes,[3] and α,β-unsaturated carbonyl compounds[4] are well documented in the literature and shown to be extremly useful in accessing a wide range of chiral structural scaffolds. Vinyl sulfones, on the other hand, are less-explored acceptors in the asymmetric Michael reactions.[5] D'Angelo et al. reported stereoselective addition of imines derived from cyclic ketones and

(1) For recent reviews on organocatalytic conjugate additions, see: (a) Almasi, D.; Alonso, D. A.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (c) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123.

(2) (a) Robak, M. T.; Trincado, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 15110. (b) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466. (c) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; Lopez, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117. (d) Wang, C.; Zhou, Z.; Tang, C. *Org. Lett.* **2008**, *10*, 1707. (e) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (f) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem.—Eur. J.* **2006**, *12*, 466.

(3) (a) Lu, S.-F.; Du, D.-M.; Xu, J.; Zhang, S.-W. *J. Am. Chem. Soc.* **2006**, *128*, 7418. (b) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 2047.

(4) For the enantioselective addition of nitroalkanes to α,β-unsaturated ketones, see: (a) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233. (b) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*, 11223. (c) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975. (d) Halland, N.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331. (e) Prieto, A.; Halland, N.; Jorgenson, K. A. *Org. Lett.* **2005**, *7*, 3897. For the enantioselective addition of nitroalkanes to α,β-unsaturated aldehydes, see: (f) Hojabri, L.; Hartikka, A.; Moghaddam, F. M.; Arvidsson, P. I. *Adv. Synth. Catal.* **2007**, *349*, 740. (g) Wang, Y.; Li, P.; Liang, X.; Zhang, T. Y.; Ye, J. *Chem. Commun.* **2008**, 1232.

(5) For the early reports on nonstereoselective Michael addition of ketones to vinyl sulfone, see: (a) Risaliti, A.; Fatutta, S.; Forchiassin, M. *Tetrahedron* **1967**, *23*, 1451. (b) Benedetti, F.; Fabrissin, S.; Risaliti, A. *Tetrahedron* **1984**, *40*, 977. (c) Lucchi, O. D.; Pasquato, L.; Modena, G. *Tetrahedron Lett.* **1984**, *25*, 3643.

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chiral 1-phenyethylamine to vinyl sulfones.[6] Recently, Deng and co-workers described the construction of all-carbon quaternary stereocenters based on a cinchona alkaloid-catalyzed addition of substituted cyanoacetates to vinyl sulfones.[7] The group of Alexakis was the first to disclose an organocatalytic Michael addition of aldehydes to vinyl sulfones mediated by their *N*-iPr-2,2′-bipyrrolidine catalyst.[8] Very recently, our group reported highly enantioselective organocatalytic Michael addition of aldehydes to various vinyl sulfones by employing prolinol silyl ether catalyst.[9] Subsequently, we applied a cinchona alkaloid-derived primary amine to achieve the first organocatalytic enantioselective conjugate addition of cyclic ketones to vinyl sulfone.[10] The utilization of hydrogen bonding interactions has become a popular approach in asymmetric catalysis in recent years. In particular, thiourea-based organocatalysts have found wide applications in a huge number of organic reactions.[11] To the best of our knowledge, the asymmetric Michael addition of nitroalkanes to vinyl sulfone is unknown in the literature. We hypothesized that bifunctional catalysts containing a suitable hydrogen bond donor and tertiary amine moiety should be able to activate nitroalkane and facilitate their conjugate addition to vinyl sulfone, and enantioselective addition may be feasible with the careful selection of chiral structural scaffolds (Figure 1). Herein, we wish to

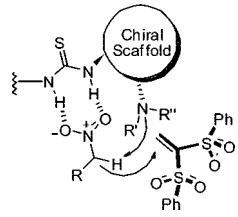
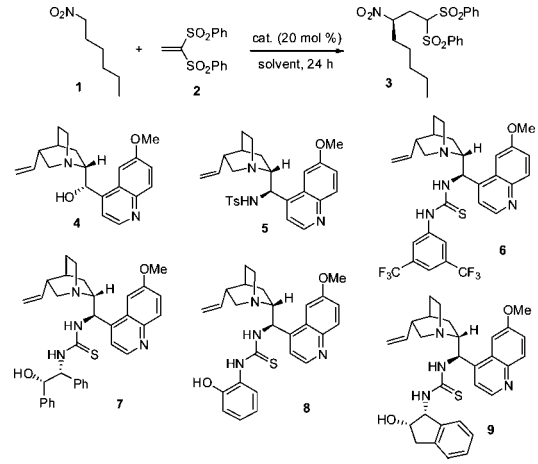


Figure 1. Working hypothesis.

communicate our investigation on the first example of asymmetric organocatalytic addition of nitroalkanes to vinyl sulfone.

For the initial exploration, we examined the catalyic effects of a number of cinchona alkaloid-based bifunctional catalysts on the conjugate addition of nitrohexane **1** to vinyl sulfone **2** (Table 1).[12] Quinidine **4** catalyzed the reaction with low

Table 1. Screening of Organocatalysts for the Conjugate Addition of Nitrohexane to Vinyl Sulfone[a]



entry	catalyst	solvent	temp (°C)	yield[b] (%)	ee[c] (%)
1	**4**	Toluene	rt	91	40
2	**5**	Toluene	rt	<10	–
3	**6**	Toluene	rt	92	76
4	**7**	Toluene	rt	85	70
5	**8**	Toluene	rt	87	54
6	**9**	Toluene	rt	85	47
7	**6**	$CHCl_3$	rt	81	70
8	**6**	CH_2Cl_2	rt	83	61
9	**6**	CH_3CN	rt	86	40
10	**6**	THF	rt	61	43
11	**6**	MeOH	rt	73	44
12	**6**	Dioxane	rt	<30	–
13	**6**	Et_2O	rt	82	63
14	**6**	Acetone	rt	75	45
15	**6**	Toluene	−10	87	86

[a] The reactions were performed with nitrohexane (0.3 mmol), vinyl sulfone (0.05 mmol), and catalyst (0.01 mmol) in anhydrous solvent (0.5 mL) at indicated temperature, unless otherwise specified. For the determination of absolute configuration, see Supporting Information. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis.

enantioselectivity (entry 1). Quinidine-derived sulfonamide, which promoted enantioselective Michael addition of bicyclic α-substituted *β*-ketoesters to nitroolefins,[13] was found to be completely ineffective (entry 2). Various quinidine-derived thiourea-containing bifunctional catalysts were shown to be good catalysts (entries 3−6). Among the thioureas tested, **6** was most efficient, yielding the desired product with 76% ee at room temperature. Solvent screening revealed that toluene was the best solvent (entries 7−14). By lowering the reaction temperature to −10 °C, we were able to obtain the desired adduct in excellent yield and with 86% ee (entry 15).

(6) (a) Pinheiro, S.; Guingant, A.; Desmaële, D.; d'Angelo, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1003. (b) Desmaële, D.; Delarue-Cochin, S.; Cave, C.; d'Angelo, J.; Morgant, G. *Org. Lett.* **2004**, *6*, 2421.

(7) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948.

(8) Mosse, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361.

(9) Zhu, Q.; Lu, Y. *Org. Lett.* **2008**, *10*, 4803.

(10) Zhu, Q.; Cheng, L.; Lu, Y. *Chem. Commun.* **2008**, 6315.

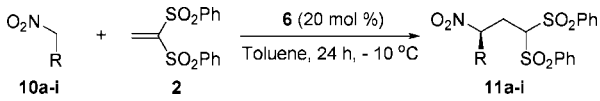
(11) For recent reviews on thiourea catalysts, see: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (b) Connon, S. J. *Chem. Commun.* **2008**, 2499. For selected examples of thiourea-containing bifunctional catalysts, see: (c) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (d) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. (e) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (f) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293. (g) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (h) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967. (i) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (j) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.

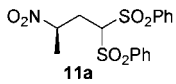
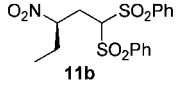
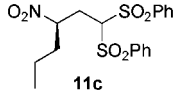
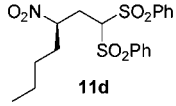
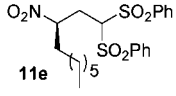
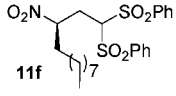
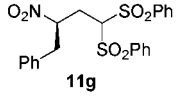
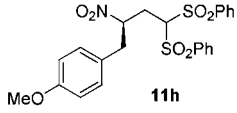
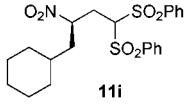
(12) The conjugate addition using vinylsulfonylbenzene as the acceptor did not yield any desired product under the same reaction conditions.

(13) Luo, J.; Xu, L.-W.; Hay, A. S. Robyn; Lu, Y. *Org. Lett.* **2009**, *11*, 437.

The optimized conditions were applied to various nitroalkanes to establish the scope of the reactions (Table 2). The

Table 2. Conjugate Addition of Various Nitroalkanes to Vinyl Sulfone **2** Catalyzed by Thiourea **6**



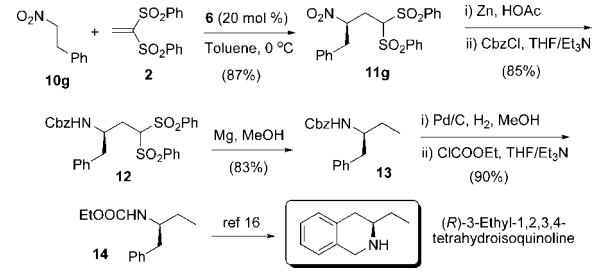
entry	product	*t* (h)	yield[b] (%)	ee[c] (%)
1	 **11a**	48	82	84
2	 **11b**	48	86	78
3	 **11c**	48	82	80
4	 **11d**	48	71	84
5	 **11e**	72	81	74
6	 **11f**	72	82	80
7	 **11g**	72	87	74
8	 **11h**	48	82	72
9	 **11i**	48	75	78

[a] The reactions were performed with nitroalkane (0.3 mmol), vinyl sulfone (0.05 mmol), and catalyst (0.01 mmol) in anhydrous toluene (0.5 mL) at −10 °C. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis.

conjugate addition of unbranched nitroalkanes proceeded smoothly, affording the desired products in high yield and with high enantioselectivity. However, α-substituted nitroalkanes and 2-aryl-substituted vinyl sulfones were found to be unsuitable for the conjugate additions.[14]

The adducts of conjugate addition of nitroalkanes to vinyl sulfone are very useful intermediates in organic synthesis. In particular, the reduction of a nitro group to an amino function, in combination with ready desulfonation, provides an easy access to chiral amines.[15] To demonstrate the synthetic application of our methodology, we prepared 1,2,3,4-tetrahydroisoquinoline, which is a potent inhibitor of phenylethanolamine *N*-methyltransferase.[16] As shown in Scheme 1, the Michael addition of 1-(2-nitroethyl)benzene

Scheme 1. Conversion of the Michael Adduct to (*R*)-1,2,3,4-Tetrahydroisoquinoline



10g to vinyl sulfone **2** yielded chiral sulfone **11g** with 74% ee. The reduction of the nitro group with zinc in acetic acid afforded chiral amine **12**, which was protected with Cbz. The subsequent desulfonation[17] proceeded smoothly to give intermediate **13**, which was then converted into known intermediate **14**, the transformation of which to 1,2,3,4-tetrahydroisoquinoline was well-established in the literature.[16]

To account for the observed stereochemical outcome of the reaction, we propose a transition state model as depicted in Figure 2. The N−H groups of the thiourea moiety in the

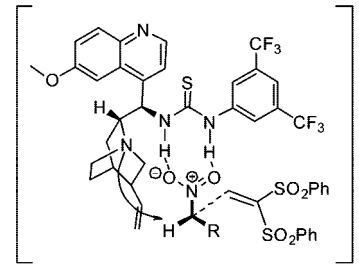


Figure 2. Proposed transition state model.

catalyst are belived to form hydrogen bonding interacions with the nitro group in the substrate to increase the acidity of the α-hydrogen, and the approach of nitroalkanes from its *Si* face to vinyl sulfone leads to the formation of the major stereoisomers.

In conclusion, we have disclosed the first organocatalytic enantioselective conjugate addition of nitroalkanes to vinyl

(14) When 2-nitropropyl benzene was treated with vinyl sulfone **2** in the presence of **6** at room temperature for 48 h, no product was formed. 2-Phenyl vinyl sulfone decomposed under the reaction conditions.

(15) For a recent review on enantioselective synthesis of α-branched amines, see: Brase, S.; Baumann, T.; Dahmen, S.; Vogt, H. *Chem. Commun.* **2007**, 1881.

sulfone promoted by a quinidine-derived thiourea catalyst. The described asymmetric conjugate addition, together with facile reduction and desulfonation, represents a novel approach to access α-branched chiral amines. Further extension to include a broader scope of nitroalkanes and to improve the enantioselectivity of such reactions is in progress in our laboratory and will be reported in due course.

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Supporting Information Available: Representative experimental procedure for Michael addition to vinyl sulfone, procedures to convert the Michael adduct into tetrahydroisoquinoline, determination of absolute configurations, HPLC chromatogram, analytical data, and NMR spectra of the conjugate addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Grunewald, G. L.; Sall, D. J.; Monn, J. A. *J. Med. Chem.* **1988**, *31*, 824.

(17) (a) Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547. (b) Kundig, E. P.; Cunningham, A. F., Jr. *Tetrahedron* **1988**, *44*, 6855.