ORGANIC LETTERS

2007
Vol. 9, No. 5
923−925

Highly Enantioselective Michael Addition of Aromatic Ketones to Nitroolefins Promoted by Chiral Bifunctional Primary Amine-thiourea Catalysts Based on Saccharides

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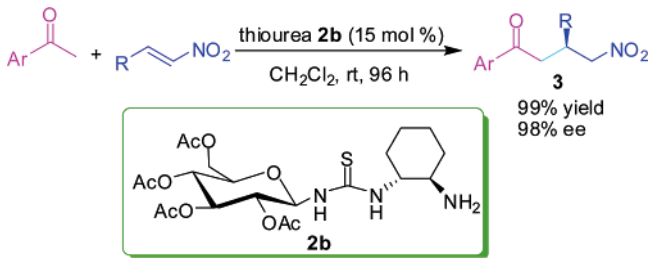
Received January 22, 2007

ABSTRACT



A new class of thiourea catalysts have been developed which integrate saccharide and primary amine moieties into one small organic molecule. These simple catalysts are shown to be highly enantioselective for direct Michael addition of aromatic ketones to a range of nitroolefins (up to 98% ee).

Aspiring to imitate enzymatic synergistic cooperation of multicenters, chemists have succeeded in developing many kinds of multifunctional catalysts for asymmetric synthesis.[1] In the context, the design of bifunctional thiourea catalysts is currently receiving considerable attention. Impressive progress has been made in the development of the secondary and tertiary amine-thiourea catalysts for a diverse range of reactions with high enantioselectivities.[2] Nevertheless, the design of chiral primary amine-thiourea catalysts has proven to be a formidable challenge.[3] To the best of our knowledge, only two types of chiral primary amine-thiourea molecules were employed in catalytic asymmetric reactions for a limited substrate scope.[4] Therefore, the development of new bifunctional catalysts is still in great demand. Here, we will describe a new class of saccharide-substituted primary amine-thiourea bifunctional catalysts and their application for asymmetric Michael additions of aromatic ketones to nitroolefins.

Starting from commercially available β-D-glucopyranose, glycosyl isothiocyanate **1** was readily prepared via acetylation, bromination, and substitution reactions.[5] Consequently, addition of chiral 1,2-cyclohexyldiamines to isothiocyanate

(1) For reviews of metallic bifunctional catalysts, see: (a) Gröger, H. *Chem.−Eur. J.* **2001**, *7*, 5246. (b) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (c) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566. For reviews of bifunctional organic catalysts, see: (d) Special issue on organocatalysis: Houk, K. N., List, B., Eds. *Acc. Chem. Res.* **2004**, *37*, 487. (e) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (f) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496.

(2) For reviews concerning bifunctional thiourea-based organo catalysis, see: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (b) Connon, S. J. *Chem.−Eur. J.* **2006**, *12*, 5418. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.

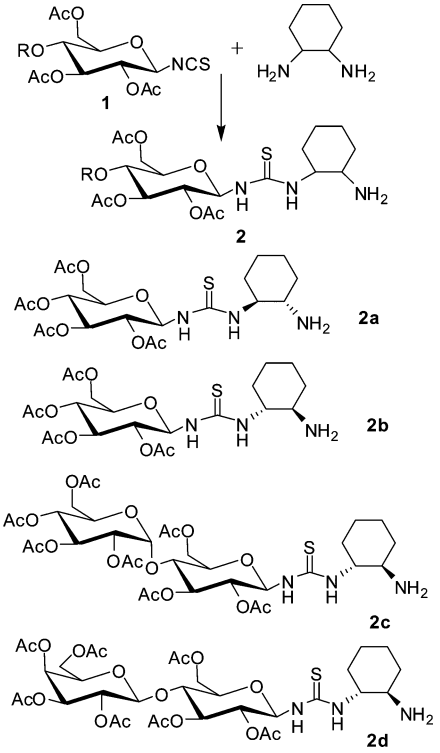
(3) For examples of asymmetric catalysis based on the primary amine functionality, see: (a) Pizzarello, S.; Weber, A. L. *Science* **2004**, *303*, 1151. (b) Tanaka, F.; Thayumanavan, R.; Mase, N.; Barbas, C. C. F., III *Tetrahedron Lett.* **2004**, *45*, 325. (c) Amedjkouh, M. *Tetrahedron: Asymmetry* **2005**, *16*, 1411. (d) Bassan, A.; Zou, W.; Reyes, E.; Himo, F.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7028. (e) Xu, Y.; Córdova, A. *Chem. Commun.* **2006**, 460.

(4) (a) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451. (b) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (c) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366.

10.1021/ol0701666 CCC: $37.00
Published on Web 02/09/2007

1 afforded desired bifunctional thiourea catalysts **2a**,**b** with the glycosyl scaffold and the primary amine group in good yields (60% for **2a** and 61% for **2b**) (Scheme 1). Using the

Scheme 1. Synthesis of Saccharide-Substituted Bifunctional Primary Amine-thiourea Catalysts

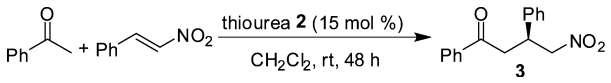


same procedure, thiourea catalysts **2c** and **2d** were also synthesized from maltose and lactose, respectively (in a yield of 60% for **2c** and 73% for **2d**).

The conjugate addition of nucleophiles to electron-deficient olefins (the Michael addition reaction) is an important tool for the construction of highly functionalized carbon skeletons. Among the variants of this strategy, direct catalytic Michael addition of carbonyl compounds to nitroolefins appears to be the most facile route to produce the useful building blocks in an atom-economical manner.[6] In recent years, numbers of small organic molecules have been developed as efficient catalysts for the asymmetric conjugate addition to nitroolefins with simple aldehydes,[7] aliphatic acyclo and cycloketones,[8] as well as more reactive nucleophiles, such as malonate esters, ketonesters, 1,3-diketones, and 1,3-dinitriles.[9] In contrast, little progress has been made in the development of aromatic ketones as Michael donors, and only one report by Jacobsen and co-workers has addressed two acetophenones as nucleophilic species.[4b] We are delighted to find that the saccharide-substituted primary amine-thiourea **2** serves as an efficient organocatalyst for direct asymmetric conjugate addition of aromatic ketones to a broad spectrum of nitroolefins with excellent enantioselectivities up to 98% ee.

In the presence of 15 mol % of **2a**−**d**, the addition reaction of acetophenone with nitrostyrene was examined under different conditions. Table 1 summarizes the results. Bifunctional amine-thiourea **2a** promoted the addition with a high enantioselectivity of 87% ee but a moderate yield of 46% (entry 1). Gratifyingly, chiral catalyst **2b** exhibited a superior level of stereoselectivity with an opposite sense of asymmetric induction and up to 97% ee can be obtained (entry 2). This indicates that the (*R*,*R*)-configuration of 1,2-diaminocyclohexane matched the β-D-glucopyranose to enhance the stereochemical control. Bifunctional catalysts

Table 1. Enantioselective Addition of Acetophenone to Nitrostyrene[a]



entry	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	**2a**	CH_2Cl_2	46	87 (*R*)
2	**2b**	CH_2Cl_2	60	97 (*S*)
3	**2c**	CH_2Cl_2	<10	93 (*S*)
4	**2d**	CH_2Cl_2	17	96 (*S*)
5	**2b**	THF	16	91 (*S*)
6	**2b**	toluene	42	95 (*S*)
7	**2b**	$CHCl_3$	62	96 (*S*)
8	**2b**	*n*-hexane	27	93 (*S*)
9	**2b**	ether	23	95 (*S*)
10[d]	**2b**	CH_2Cl_2	72	97 (*S*)

[a] The reaction was conducted with **2** (0.15 equiv), acetophenone (10 equiv), and several solvents. [b] Isolated yield. [c] The ee values were determined by HPLC, and the configuration was assigned by comparison of retention time and specific rotation with that of the literature data. [d] Reaction time was 96 h.

(5) (a) Lindhorst, T.; Kieburg, C. *Synthesis* **1995**, *10*, 1228. (b) Selkti, M.; Kassab, R.; Lopez, H. P.; Villain, F.; de Rango, C. J. *Carbohydr. Chem.* **1999**, *18*, 1019.

(6) For a review of asymmetric Michael addition to nitroolefins, see: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.

(7) For selected examples of asymmetric conjugate additions of aldehydes to nitroolefins, see: (a) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 2527. (b) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369. (c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (d) Palomo, C.; Mielgo, S.; Vera, A.; Gómez-Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984. (e) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (f) Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem.*−*Eur. J.* **2006**, *12*, 4321. (g) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559. For other examples, see ref 2 and refs therein.

(8) For selected examples of asymmetric conjugate additions of aliphatic (cyclo)ketones to nitroolefins, see: (a) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147. (b) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558. (c) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093. (d) Enders, D.; Chow, S. *Eur. J. Org. Chem.* **2006**, *20*, 4578. (e) Dixon, D. J.; Richardson, R. D. *Synlett* **2006**, 81. (f) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 4966. (g) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624. (h) Zhu, M.-K.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2006**, *17*, 491. (i) Li, Y.; Liu, X.-Y.; Zhao, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2034. (j) Almasi, D.; Alonso, D. A.; Najera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 2064. For other examples, see: ref 2 and refs therein.

(9) For selected examples of asymmetric conjugate additions of relatively acidic carbon pronucleophiles to nitroolefins, see: (a) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (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) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. For other examples, see: ref 2 and refs therein.

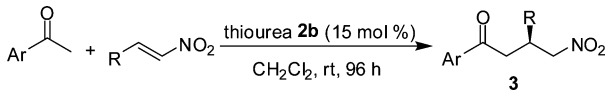
2c and **2d** with an (*R*,*R*)-configuration of the 1,2-diaminocyclohexane moiety can also induce high enantioselectivities (entries 3 and 4). A substantial change of the solvent did not have a significant effect on the stereoselection; however, the catalytic activity of the bifunctional amine-thiourea appeared to be different for these solvents (entries 2 and 5−9). The good results were attained when dichloromethane and chloroform were used as solvents of the reaction. In addition, the addition was carried out in higher yield with prolonged reaction time (entry 10).

Under the optimized experimental conditions, the scope of the reaction was explored (Table 2). First, the conjugate addition of acetophenone to a variety of nitroolefins was examined. The results showed that the reactions took place in good to excellent yields (65−99%) and with high enantioselectivity (94−98% ee) for aromatic- and heteroaromatic-substituted nitroolefins (entries 1−8). High stereoselection was also observed with alkyl-substituted nitroolefin, and the moderate product yield appears to reflect formation of small amounts of insoluble polymeric material (entry 9). A variation of ketone substrates were probed next. It was found that the **2b**-catalyzed conjugate addition processes were also applicable to various aromatic methyl ketones in moderate to high yields (42−92%) and excellent enantioselectivities (95−97% ee) (entries 10−14). It appears that the position and the electronic property of the substituents for aromatic rings of either nucleophiles or electrophiles have a very limited effect on the stereoselection of conjugate additions. No matter whether electron-withdrawing (entries 4−6, 12, and 13), -donating (entries 2, 3, 10, and 11), or -neutral (entry 1) groups on aromatic rings were used, the reactions proceeded to give highly enantioselective adducts. Interestingly, the performance of the catalyst system was explored by using the mixture of substrates of *ortho*- and *para*-bromoacetophenones in one pot. The ee value remained approximately constant (entry 12). This experiment implies that the one-pot multisubstrate screening of small organic catalysts could be realized.[10]

Notably, no desired product was obtained when the primary amine group of catalyst **2b** was replaced by the tertiary amine, thus the prerequisite for good reactivity and enantioselectivity is that the thiourea catalysts possess the neighboring primary amine functionality. A bifunctional catalytic mechanism was suggested in which a thiourea moiety interacts through hydrogen bonding with a nitro group of the nitroolefins and enhances their electrophilicity while the neighboring primary amine activates ketones involving an enamine intermediate. The observed absolute configuration (*S*) of the conjugate adduct was explained by the transition state assembly **A** (Figure 1) in which the *si*-face of the nitroolefin was predominantly approached by the enamine intermediate generated from ketone and the primary amine group of the bifunctional catalyst. The attack of the enamine to the *re*-face of the nitroolefin was restricted by the cyclohexyl scaffold of the catalyst.

In conclusion, we have developed a new class of bifunctional primary amine-thiourea catalysts based on saccharides. These simple organic molecules are shown to be excellently enantioselective for direct Michael addition of aromatic ketones to a series of aromatic-, heteroaromatic-, and alkyl-substituted nitroolefins. Further investigation of the efficacy of these organocatalysts in other catalytic asymmetric reactions and the design of new bifunctional catalyst systems are ongoing in our laboratories and will be reported in due course.

Table 2. Enantioselective Addition of Aromatic Ketones to Nitroolefins



entry	adduct	Ar	R	yield (%)[a]	ee (%)[b]
1	**3a**	Ph	Ph	72	97
2	**3b**	Ph	4-MePh	89	97
3	**3c**	Ph	4-MeOPh	78	96
4	**3d**	Ph	4-ClPh	65	95
5	**3e**	Ph	2-BrPh	83	97
6	**3f**	Ph	2-ClPh	99	98
7	**3g**	Ph	2-naphthyl	74	94
8	**3h**	Ph	2-furyl	99	98
9	**3i**	Ph	Et	20	94
10	**3j**	4-MePh	Ph	84	96
11	**3k**	4-MeOPh	Ph	64	97
12	**3l**	4-BrPh/2-BrPh (44:56)	Ph	42 (58:42)	96 (96)
13	**3m**	4-ClPh	Ph	92	96
14	**3n**	2-naphthyl	Ph	46	95

[a] Isolated yield. [b] The ee values were determined by HPLC.

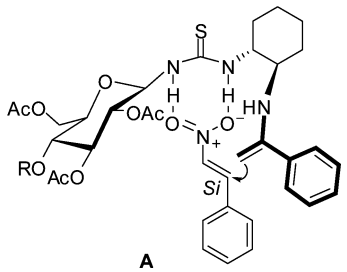


Figure 1. Transition state model.

Acknowledgment. This work was supported financially by NSFC (20542008) and the Ministry of Education of China.

Supporting Information Available: Experimental details and spectral data of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0701666

(10) For reviews, see: (a) Satyanarayana, T.; Kagan, H. B. *Adv. Synth. Catal.* **2005**, *347*, 737. For selected examples, see: (b) Gao, X.; Kagan, H. B. *Chirality* **1998**, *10*, 120. (c) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Montalbetti, C. A. G. N.; Jackson, R. F. W. *J. Org. Chem.* **1998**, *63*, 5312. (d) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2002**, *58*, 5773. The utility of organocatalysts for the multisubstrate screening is under investigation in our laboratories.