DOI: 10.1002/ejoc.200800555

Sugar-Derived Bifunctional Thiourea Organocatalyzed Asymmetric Michael Addition of Acetylacetone to Nitroolefins

Peng Gao,[a] Chungui Wang,[a] Yang Wu,[a] Zhenghong Zhou,*[a] and Chuchi Tang[a]

Keywords: Thiourea / Michael addition / Ketones / Nitroalkenes / Enantioselectivity

A bifunctional chiral thiourea organocatalyst bearing a glycosyl scaffold and a tertiary amino group proved to be an effective organocatalyst for the asymmetric Michael addition of acetylacetone to nitroolefins. The corresponding adducts were obtained in good to excellent yields with excellent enantioselectivities (up to 96% *ee*).

Introduction

Michael addition to electron deficient nitroolefins is one of the important reactions in organic synthesis that provides access to synthetically useful functionalized nitroalkanes.[1] Because of the versatile reactivity of the nitro functionality, it can be conveniently transformed into a nitrile oxide[2], amine[3] (reduction), ketone (Nef reaction),[4] carboxylic acid (Meyer reaction),[5] and other functionalized compounds (nucleophilic substitution),[6] providing a wide range of synthetically valuable compounds. Although significant progress was achieved in substrate- or auxiliary-controlled diastereoselective versions of this reaction,[1,7] the development of metal[8] and organocatalysts[9,10] for the enantioselective process has been the focus of important recent research efforts. Among the variants of this strategy, the direct asymmetric Michael addition of carbon nucleophiles, such as aldehydes, ketones, and methylene-active substrates, to nitroolefins is one of the most attractive and atom-economical processes to access functionalized enantiomerically enriched nitroalkanes, and impressive progress was recently made in this area.[8d,8g–8j,9j–9p,10] In contrast, the use of chiral bifunctional thioureas as powerful hydrogen-bond-donating organocatalysts for the synthesis of optically active compounds has become a new and exciting area of contemporary synthetic organic chemistry[11] since Jacobsen successfully develop an efficient chiral Schiff base–thiourea catalyzed asymmetric Strecker reaction.[12] Takemoto reported the first example of a thiourea-organocatalyzed asymmetric Michael addition to nitroolefins, and *ee* values up to 94% were observed with the use of tertiary amine–thiourea bifunctional catalyst **1**[10a,10c] (Figure 1). Primary amine–thiourea catalyst **2** developed by Jacobsen also demonstrated excellent catalytic activity in the asymmetric Michael addition of ketones to nitroolefins (up to 99% *ee*).[10f] Saccharide-derived bifunctional thiourea **3** bearing a primary amino group documented by Ma was proven to be an efficient organocatalyst for the asymmetric addition of acetophenone to nitroolefins (up to 98% *ee*).[10i] In addition, chiral bifunctional thiourea **4** containing multiple hydrogen-bonding donors[10l] and **5** bearing a 2,2′-diamino-1,1′-binaphthalene skeleton[10b] were also efficient

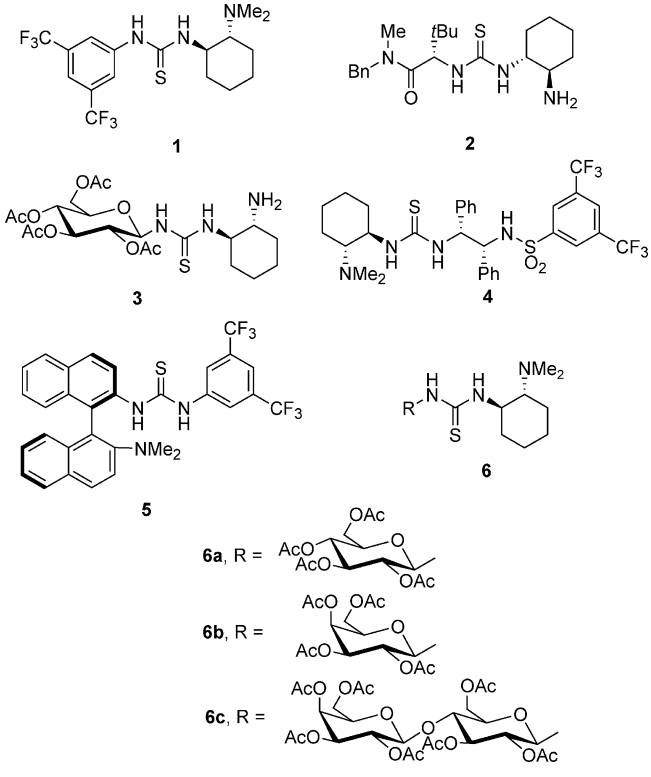


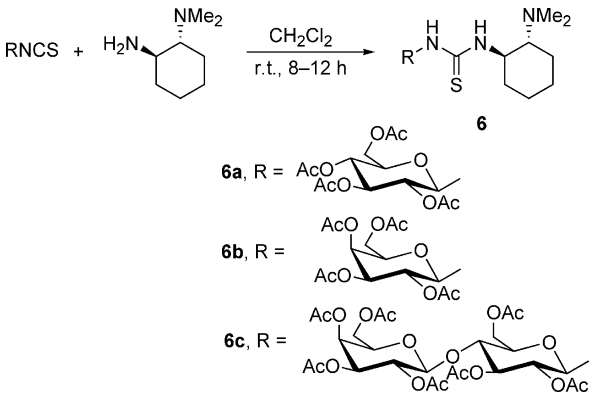
Figure 1. Thiourea organocatalysts.

[a] State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China
Fax: +86-22-23508939
E-mail: z.h.zhou@nankai.edu.cn
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

organocatalysts for the asymmetric Michael addition to nitroolefins. As part of a program aimed at developing new organocatalysts for asymmetric organic transformations, we recently found that bifunctional thioureas **6** bearing both a tertiary amino group and a saccharide scaffold are efficient organocatalysts for the asymmetric aza-Henry reaction between *N*-Boc imine and nitroalkanes, especially for catalyst **6a**, which demonstrated a broad substrate scope. In most cases, almost perfect stereocontrol (>99%*ee*) was achieved.[13] To further extend the application of this novel type of organocatalyst, herein, we report their ability to serve as catalysts in the asymmetric Michael addition of acetylacetone to nitroolefins.

Results and Discussion

Following the literature procedure,[13] bifunctional thioureas **6** were synthesized by coupling of the corresponding isothiocyanate with *N*-[(1*R*,2*R*)-2-aminocyclohexyl]-*N*,*N*-dimethylamine starting from α-D-glucopyranose, galactose, and lactose, respectively (Scheme 1).



Scheme 1. Synthesis of thioureas **6**.

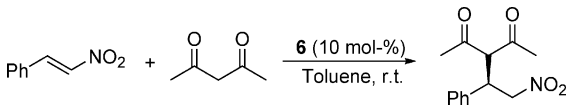
With these catalysts in hand, we initially examined the effect of the different saccharide scaffolds in the catalyst structure on the reaction. The reaction of β-nitrostyrene with acetylacetone was performed in toluene at room temperature (20 °C) by using 10 mol-% of **6** as the catalyst. As shown in Table 1, all the tested catalysts exhibited good catalytic activity. The corresponding adduct was obtained in excellent chemical yield. In terms of enantioselectivity, thiourea **6a** bearing a glycosyl scaffold provided the best results (Table 1, entry 1).

In further experiments, other factors, such as solvent, catalyst loading, and reaction temperature, influencing the reaction were thoroughly investigated by employing **6a** as the catalyst and the reaction between β-nitrostyrene with acetylacetone as the model. The results are listed in Table 2.

A survey of six solvents revealed that a variety of solvents were tolerated by this Michael addition reaction. All the tested solvents afforded the desired product in excellent yield and good *ee* values (Table 2, entries 1–6). The best results were observed when toluene was used (Table 2, entries 6; 87%*ee*). Moreover, the reaction temperature was found to be an essential factor to the enantioselectivity of this reaction. The stereoselectivity was gradually increased by decreasing the reaction temperature from 20 to –40 °C (Table 2, entries 6–9; 87–96%*ee*). However, a further decrease in the temperature to –60 °C resulted in a decrease in the enantiomeric excess of the reaction (Table 2, entry 10; 89%*ee*). In addition, catalyst loading proved to be particularly important. For example, smaller and larger amounts of thiourea organocatalyst led to an obvious loss of stereocontrol (Table 2, entries 11 and 12; 74 and 93%*ee*, respectively).

Further studies revealed that the concentration of the β-nitrostyrene substrate had an important effect on the reaction rate and enantioselectivity. The best result was obtained when the reaction was carried out at with a β-nitrostyrene concentration of 0.4 M in toluene (Table 3, entry 2; 96%*ee*). An increase or decrease in the substrate concentration led to slightly lower *ee* values (Table 3, entries 1 and 3; 88 and 90%*ee*, respectively).

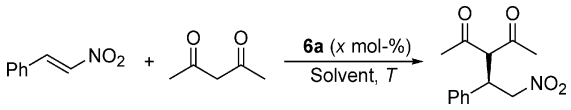
Table 1. Comparison of catalytic activities of thioureas **6a**–**c**.[a]



Entry	Catalyst	*t* [h]	Yield [%][b]	*ee*[c]	Config.[d]
1	**6a**	3	96	87	*R*
2	**6b**	18	98	67	*R*
3	**6c**	6	96	78	*R*

[a] All reactions were performed in 0.5 mL of solvent on a 0.2-mmol scale. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by chiral HPLC analysis. [d] The absolute configuration of the major isomer was established by comparing the measured optical rotation to a know literature value.[10b]

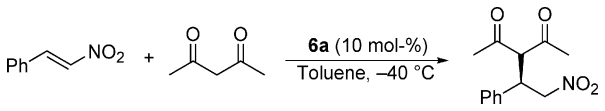
Table 2. Optimization of the reaction conditions.[a]



Entry	**6a** [mol-%]	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*ee*[c]
1	10	THF	20	3	90	66
2	10	Hexane	20	3	96	67
3	10	Et_2O	20	3	86	74
4	10	EtOAc	20	3	94	64
5	10	CH_2Cl_2	20	3	98	78
6	10	Toluene	20	3	96	87
7	10	Toluene	0	8	88	89
8	10	Toluene	–20	12	85	92
9	10	Toluene	–40	23	93	96
10	10	Toluene	–60	66	95	89
11	5	Toluene	–40	60	90	74
12	15	Toluene	–40	19	92	93

[a] All reactions were performed in 0.5 mL of solvent on a 0.2-mmol scale. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by chiral HPLC analysis.

Table 3. The influence of substrate concentration on the reaction.

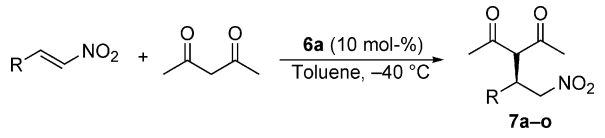


Entry	Nitroolefin Conc. [mol/L]	*t* [h]	Yield [%][a]	*ee*[b]
1	0.8	8	90	88
2	0.4	23	93	96
3	0.2	70	90	90

[a] Yield of the isolated product after chromatography on silica gel. [b] Determined by chiral HPLC analysis.

With the optimal reaction conditions in hand (10 mol-% **6a** as the catalyst, at –40 °C in toluene, 0.4 M substrate concentration), we investigated the scope and limitations of this asymmetric Michael addition reaction. The results are summarized in Table 4. Thiourea **6a** exhibited excellent performance for a broad range of nitroolefins bearing aryl and heteroaryl groups in terms of catalytic activity and enantioselectivity. Generally, electron-donating groups on the benzene ring prolonged the reaction time, but did not affect the yield and selectivity (Table 4, entries 2–7). The reaction of 1-naphthyl or electron-rich heteroaryl-substituted nitroolefins also ran smoothly to give the desired products in both excellent yields and enantioselectivities (Table 4, entries 12–14). The reaction of nitro-substituted aryl nitroolefin did not proceed at all. This may be attributed to the competitive hydrogen-bonding interaction of this nitro group with the thiourea moiety of the catalyst, which to some extent prohibits the activation of the electrophilic nitroolefin (Table 4, entry 16). In addition, the reaction of a nitroolefin bearing an aliphatic β-substituent, such as 1-nitro-1-pentene (*E*/*Z* = 10.1:1), was very sluggish even at room temperature (Table 4, entry 17). However, an alkyl nitroolefin containing a conjugated double bond demonstrated good reactivity under the otherwise same conditions. For example, the corresponding Michael addition product of (*E*)-4-nitro-1-phenyl-1,3-butadiene was attained in good yield and good stereoselectivity (Table 4, entry 15).

Table 4. Chiral thiourea **6a** catalyzed asymmetric Michael addition of acetylacetone to various nitroolefins.[a]



7a–o

Entry	R	*t* [h]	Yield [%][b]	*ee*[c]	Config.[d]
1	Ph (**7a**)	23	93	96	*R*
2	4-MeC_6H_4 (**7b**)	48	80	89	*R*
3	4-$BnOC_6H_4$ (**7c**)	60	96	85	*R*
4	4-$MeOC_6H_4$ (**7d**)	70	>99	88	*R*
5	3-$MeOC_6H_4$ (**7e**)	70	>99	92	*R*
6	2-$MeOC_6H_4$ (**7f**)	60	89	92	*R*
7	2,4-$(MeO)_2C_6H_4$ (**7g**)	60	>99	84	*R*
8	4-$F_3COC_6H_4$ (**7h**)	16	76	91	*R*
9	3-$F_3COC_6H_4$ (**7i**)	12	82	89	*R*
10	2-$F_3COC_6H_4$ (**7j**)	16	81	95	*R*
11	4-ClC_6H_4 (**7k**)	50	91	88	*R*
12	1-Naphthyl (**7l**)	40	97	95	*R*
13	2-Furyl (**7m**)	50	>99	94	*S*
14	5-Me-2-furyl (**7n**)	48	>99	85	*S*
15	(*E*)-PhCH=CH (**7o**)	48	85	81	*S*
16	2-$NO_2C_6H_4$	48	NR[e]		
17	*n*Pr (*E*/*Z* = 10.1:1) [f]	48	NR[e]		

[a] All reactions were performed in 0.5 mL of solvent on a 0.2-mmol scale. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by chiral HPLC analysis. [d] The absolute configuration of the major isomer was established by comparing the measured optical rotation to a know literature value.[10b] [e] NR = no reaction. [f] The reaction was performed at room temperature.

Conclusions

Thiourea catalyst **6a** worked well as a bifunctional organocatalyst to promote the asymmetric Michael reaction of acetylacetone to various nitroolefins. The reaction was highly efficient in terms of productivity (up to >99% yield) and enantioselectivity (up to 96% *ee*) and may be useful for preparing enantiomerically enriched nitroketone derivatives. Further studies on the Michael addition of other carbon and heteroatom nucleophiles are now in progress.

Experimental Section

General Procedure for Asymmetric Michael Addition of Acetylacetone to Nitroolefins Catalyzed by 6a: To a solution of the nitroolefin (0.2 mmol) and thiourea catalyst **6a** (10.7 mg, 0.02 mmol) in toluene (0.5 mL) was added acetylacetone (40 mg, 0.4 mmol) in one portion at the temperature depicted in the text. The resulting mixture was stirred at the same temperature, and the reaction was monitored by TLC. The solution was concentrated, and the residue was purified by column chromatography on silica gel (200–300 mesh; ethyl acetate/petroleum ether, 1:10 to 1:5) to furnish the desired products. The *ee* values were determined by chiral HPLC analysis.

Supporting Information (see footnote on the first page of this article): Experimental procedures; characterization of the catalysts; copies of ^1H NMR spectra and chiral HPLC spectra of the Michael addition adducts.

Acknowledgments

We are grateful to the National Natural Science Foundation of China (No. 20772058) for generous financial support of our programs.

[1] For reviews, see: a) A. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877–1894; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716.

[2] a) T. Mukaiyama, T. Hoshino, *J. Am. Chem. Soc.* **1960**, *82*, 5339–5342; b) G. Kumaran, G. H. Kulkarni, *Tetrahedron Lett.* **1994**, *35*, 5517–5518.

[3] a) D. H. Lloyd, D. E. Nichols, *J. Org. Chem.* **1986**, *51*, 4294–4295; b) A. G. M. Barrett, C. D. Spilling, *Tetrahedron Lett.* **1988**, *29*, 5733–5734; c) R. E. Maeri, J. Heinzer, D. Seebach, *Liebigs Ann.* **1995**, 1193–1215; d) M.-A. Poupart, G. Fazal, S. Goulet, L. T. Mar, *J. Org. Chem.* **1999**, *64*, 1356–1361.

[4] a) H. W. Pinnik, *Org. React.* **1990**, *38*, 655–792; b) J. U. Nef, *Justus Liebigs Ann. Chem.* **1894**, *280*, 263–342; c) R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017–1047.
[5] a) V. Meyer, C. Wurster, *Ber. Dtsch. Chem. Ges.* **1873**, *6*, 1167–1172; b) M. J. Kamlet, L. A. Kaplan, J. C. Dacons, *J. Org. Chem.* **1961**, *26*, 4371–4375.
[6] R. Tamura, A. Kamimura, N. Ono, *Synthesis* **1991**, 423–434.
[7] A. G. M. Barrett, *Chem. Soc. Rev.* **1991**, *20*, 95–127.
[8] For metal-catalyzed asymmetric Michael additions to nitroolefins, see: a) H. Schäfer, D. Seebach, *Tetrahedron* **1995**, *51*, 2305–2324; b) N. Sewald, V. Wendisch, *Tetrahedron: Asymmetry* **1998**, *9*, 1341–1344; c) J. P. G. Versleijen, A. M. van Leusen, B. L. Feringa, *Tetrahedron Lett.* **1999**, *40*, 5803–5806; d) J. Ji, D. M. Barnes, J. Zhang, S. A. King, S. J. Wittenberger, H. E. Morton, *J. Am. Chem. Soc.* **1999**, *121*, 10215–10216; e) T. Hayashi, T. Senda, M. Ogasawara, *J. Am. Chem. Soc.* **2000**, *122*, 10716–10717; f) A. Alexakis, C. Benhaim, *Org. Lett.* **2000**, *2*, 2579–2581; g) C. A. Luchaco-Cullis, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 8192–8193; h) A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263; i) A. Duursma, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2003**, *125*, 3700–3701; j) M. Watanabe, A. Ikagawa, H. Wang, K. Murata, T. Ikariya, *J. Am. Chem. Soc.* **2004**, *126*, 11148–11149; k) D. A. Evans, D. Seidel, *J. Am. Chem. Soc.* **2005**, *127*, 9958–9959.
[9] For organocatalyzed asymmetric Michael additions to nitroolefins (except for thiourea organocatalysts), see: a) W. Langer, D. Seebach, *Helv. Chim. Acta* **1979**, *62*, 1710–1722; b) D. Seebach, G. Grass, E. M. Wilka, D. Hilvert, E. Brunner, *Helv. Chim. Acta* **1979**, *62*, 2695–2698; c) N. Kobayashi, K. Iwai, *J. Org. Chem.* **1981**, *46*, 1823–1828; d) E. Juaristi, A. K. Beck, J. Hansen, T. Matt, T. Mukhopadhyay, M. Simson, D. Seebach, *Synthesis* **1993**, 1271–1290; e) H. Brunner, B. Kimel, *Monatsh. Chem.* **1996**, *127*, 1063–1072; f) T. A. Johnson, M. D. Curtis, P. Beak, *J. Am. Chem. Soc.* **2001**, *123*, 1004–1005; g) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423–2425; h) J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 4441–4444; i) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737–3740; j) D. Enders, A. Seki, *Synlett* **2002**, 26–28; k) H. M. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906–9907; l) H. M. Li, Y. Wang, L. Tang, F. H. Wu, X. F. Liu, C. Y. Guo, B. M. Foxman, L. Deng, *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108; m) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599–602; n) Y. M. Xu, A. Cordova, *Chem. Commun.* **2006**, 460–462; o) H. J. Martin, B. List, *Synlett* **2003**, 1901–1902; p) M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454–1455.
[10] For thiourea-catalyzed asymmetric Michael addition to nitroalkanes, see: a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; b) J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713–4716; c) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125; d) S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; e) S. B. Tsogoeva, D. A. Yalalov, M. J. Hateley, C. Weckbecker, K. Huthmacher, *Eur. J. Org. Chem.* **2005**, 4995–5000; f) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171; g) D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Adv. Synth. Catal.* **2006**, *348*, 826–832; h) S. B. Tsogoeva, S. W. Wei, *Chem. Commun.* **2006**, 1451–1453; i) K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li, J.-A. Ma, *Org. Lett.* **2007**, *9*, 923–925; j) S. W. Wei, D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Catal. Today* **2007**, *121*, 151–157; k) P. S. Hynes, D. A. Stupple, D. J. Dixon, *Org. Lett.* **2008**, *10*, 1389–1391; l) C.-J. Wang, Z.-H. Zhang, X.-Q. Dong, X.-J. Wu, *Chem. Commun.* **2008**, 1431–1433; m) J. X. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481–4483; n) Y.-J. Cao, Y.-Y. Lai, X. Wang, Y.-J. Li, W.-J. Xiao, *Tetrahedron Lett.* **2007**, *48*, 21–24; o) Y.-J. Cao, H.-H. Lu, Y.-Y. Lai, L.-Q. Lu, W.-J. Xiao, *Synthesis* **2006**, 3795–3800; p) C.-L. Cao, M.-C. Ye, X.-L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901–2904; q) H. Miyabe, S. Tuchida, M. Yamauchi, Y. Takemoto, *Synthesis* **2006**, 3295–3300.
[11] For reviews, see: a) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; b) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; c) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306.
[12] 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. Int. Ed.* **2000**, *39*, 1279–1281; c) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867–870; d) J. T. Su, P. Vachal, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 197–200; e) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014.
[13] C. G. Wang, Z. H. Zhou, C. C. Tang, *Org. Lett.* **2008**, *10*, 1707–1710.

Received: June 10, 2008
Published Online: August 8, 2008

