DOI: 10.1002/adsc.200900268

Enantio- and Diastereoselective Mannich-Type Reactions of α-Cyano Ketones with *N*-Boc Aldimines Catalyzed by Chiral Bifunctional Urea

Ju Hee Lee[a] and Dae Young Kim[a,*]

[a] Department of Chemistry, Soonchunhyang University, Asan, Chungnam 336-745, Korea
Fax: (+82)-41-530-1247; phone: +82-41-530-1244; e-mail: dyoung@sch.ac.kr

Received: April 17, 2009; Published online: July 27, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900268.

Abstract: The catalytic enantioselective electrophilic Mannich-type reaction promoted by chiral bifunctional organocatalysts is described. The treatment of α-cyano ketones with *N*-Boc-aldimines under mild reaction conditions afforded the corresponding β-amino-α-cyano ketones with excellent diastereoselectivities (up to *syn/anti* = 100/0), and excellent enantioselectivities (up to 99% *ee*).

Keywords: asymmetric catalysis; Mannich reaction; nitriles; organic catalysis

One of the ultimate goals and challenges in organic synthesis is the development of catalytic asymmetric transformations for the creation of functionalized optically active compounds with structural diversity from simple and readily available precursor molecules. The efficient synthetic construction of β-amino carbonyl compounds is one of the most intensely studied areas in organic synthesis.[1] Chiral α-substituted β-amino nitriles,[2] since the cyano group is easily converted to other functional groups, would be versatile synthetic intermediates for the synthesis of β-amino acids and the corresponding chiral diamine derivatives which are employed as medicinal agents or chiral ligands.[3]

Enantioselective Mannich reactions are efficient and powerful methods to prepare β-amino carbonyl derivatives.[4] Tremendous efforts have been made in the development of efficient chiral catalysts for enantioselective Mannich reactions with pre-formed enolates and enolizable active methylenes and methines.[5–7] Several groups have presented the direct enantioselective Mannich reactions of β-dicarbonyl and related compounds in the presence of chiral organocatalysts such as chiral phosphorodiamidic acid,[8] *Cinchona* alkaloid-derived catalysts,[9] and thiourea organocatalysts.[10] Bifunctional organocatalysts possessing a combination of hydrogen-bonding donors and chiral tertiary amines have been developed for activation of both electrophilic and nucleophilic components. They have emerged as powerful tools for the enantioselective formation of carbon-carbon and carbon-heteroatom bonds.[11] Recently, Shibasaki et al. reported a highly enantio- and diastereoselective Mannich reaction using α-cyano ketones, catalyzed by a chiral amide ligand associated with rare earth metal complexes.[12] However, a highly enantioselective Mannich reaction of α-cyano ketones with simple imines remains elusive; although, if successfully promoted with a practically accessible chiral catalyst under air- and moisture-tolerant conditions, it could provide a highly attractive, convergent approach towards optically active β-amino nitriles.

As part of a research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[13] we recently reported chiral amine-thiourea **IV** (Figure 1) to be a highly selective catalyst for the enantioselective amination of active methines.[14] This catalyst emerged from our search for new organic, asymmetric bifunctional catalysts based around the relatively rigid binaphthyl skeleton. Herein, we wish to describe the direct enantioselective Mannich reaction of α-cyano ketones with simple *N*-Boc-imines catalyzed by using bifunctional organocatalysts bearing both central and axial chiral elements.

To determine suitable reaction conditions for the catalytic enantioselective Mannich reaction of α-cyano ketones, we initially investigated the reaction system with 2-cyano cyclopentanone (**1a**) and *N*-Boc-benzaldimine (**2a**) in the presence of 10 mol% of catalyst in toluene at room temperature. We first examined the impact of the structures of catalysts **I–VI** on enantioselectivities (Table 1, 65–88% *ee*, entries 1–6).

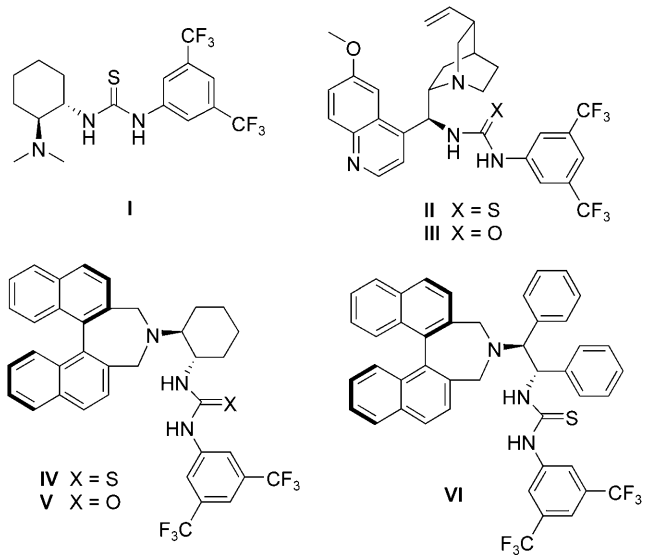
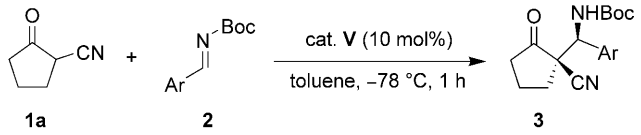


Figure 1. Structures of chiral urea- or thiourea-tertiary amine catalysts.

Table 2. Variation of the *N*-Boc-imines.



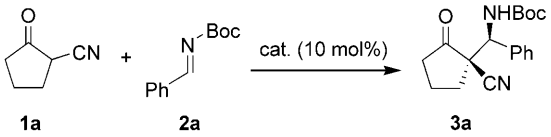
Entry	**2**, Ar	Yield[a] [%]	*syn/anti*[b]	*ee*[c] [*syn*] [%]
1	**2a**, Ph	**3a**, 81	100/0	>99
2	**2b**, *o*-F-C_6H_4	**3b**, 96	100/0	>99
3	**2c**, *o*-Cl-C_6H_4	**3c**, 80	100/0	97
4	**2d**, *p*-Cl-C_6H_4	**3d**, 83	100/0	98
5	**2e**, *p*-OMe-C_6H_4	**3e**, 88	100/0	83
6	**2f**, *p*-Me-C_6H_4	**3f**, 85	94/6	88
7	**2g**, 2-naphthyl	**3g**, 90	100/0	98
8	**2h**, 2-furyl	**3h**, 90	100/0	93
9	**2i**, 2-thienyl	**3i**, 99	100/0	>99

[a] Refers to the isolated mixture of diastereomers.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Enantiomeric excess of the major diastereomer, determined by chiral HPLC.

The best results have been obtained with catalysts **IV** and **V**. These results indicate that increasing the steric demands of the catalyst increases the selectivities. Concerning the solvent (entries 5, 7–10), the use of toluene gave the best results in terms of yield and the enantiomeric excess (entry 5). Lowering the temperature to −78 °C with catalyst **V** improved the diastereoselectivity (*syn/anti* = 100/0) and enantioselectivity (>99% *ee*, entry 12). We then explored the possibility of using wide range of *N*-Boc-protected *para*-substituted aromatic and heteroaromatic aldimines **2** with α-cyano ketone **1a** under the optimized reaction conditions. As shown in Table 2, the products **3a–i** were formed in high yields (81–95%), excellent diastereoselectivities (*syn/anti* = 94/6–100/0), and excellent enatioselectivities (83–99%).

To examine the generality of the catalytic enantioselective Mannich reaction of α-cyano ketones **1** by using chiral bifunctional organocatalyst **V**, we studied the Mannich reaction of various α-cyano ketones **1b–g** with *N*-Boc-benzaldimine (**2a**). As can be seen from

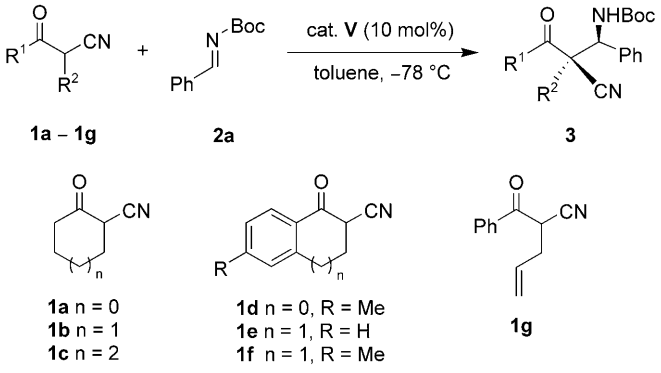
Table 1. Optimization of the reaction conditions.



Entry	Cat.	Solvent	Temp. [°C]	Time [h]	Yield[a] [%]	*syn/anti*[b]	*ee*[c] [*syn*] [%]
1	**I**	toluene	r.t.	0.3	85	93/7	66
2	**II**	toluene	r.t.	0.3	82	86/14	65
3	**III**	toluene	r.t.	0.3	83	80/20	75
4	**IV**	toluene	r.t.	0.3	80	98/2	88
5	**V**	toluene	r.t.	0.3	81	98/2	88
6	**VI**	toluene	r.t.	0.3	81	56/44	5
7	**V**	CH_2Cl_2	r.t.	0.3	85	76/24	74
8	**V**	acetone	r.t.	0.3	83	50/50	59
9	**V**	EtOAc	r.t.	0.3	81	55/45	53
10	**V**	THF	r.t.	0.3	83	45/55	23
11	**V**	toluene	−40	0.8	80	100/0	87
12	**V**	toluene	−78	1	81	100/0	>99

[a] Refers to the isolated mixture of diastereomers.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Enantiomeric excess of the major diastereomer, determined by chiral HPLC.

Table 3. Variation of the α-cyano ketones.



Entry	1	Time [h]	Yield[a] [%]	*syn/anti*[b]	*ee*[c] [*syn*] [%]
1	**1a**	1	**3a**, 81	100/0	>99
2	**1b**	1	**3j**, 75	100/0	90
3	**1c**	1	**3k**, 77	100/0	>99
4	**1d**	1	**3l**, 75	99.8/0.2	94
5	**1e**	1	**3m**, 84	99/1	95
6	**1f**	1	**3n**, 81	86/14	95
7	**1g**	96	**3o**, 80	59/41	98/98[d]

[a] Refers to the isolated mixture of diastereomers.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Enantiomeric excess of the major diastereomer, determined by chiral HPLC.
[d] Enantiomeric excess of *syn/anti* diastereomer.

the results summarized in Table 3, the corresponding β-aminated α-cyano ketones **3j–o** were obtained in excellent yields and enantioselectivities. The cyclic α-cyano ketones **1a–f**, with cyclic aliphatic ketones **1a–c**, and cyclic aromatic ketones **1d–f**, reacted with *N*-Boc-benzaldimine (**2a**) to give the corresponding β-aminated α-cyano ketones **3a** and **3j–n** in 75–84% yields and 90–99% *ee* (Table 3, entries 1–6). Acyclic α-cyano ketone **1g** reacted with *N*-Boc-benzaldimine (**2a**) to afford the β-aminated α-cyano ketone **3o** with 98% *ee* (Table 3, entry 7). The absolute configuration of adducts **3** has been determined for some derivatives by comparison of their optical and HPLC properties with literature values.[12]

In conclusion, we have developed a highly efficient catalytic enantioselective Mannich reaction of cyclic α-cyano ketones using chiral bifunctional organocatalyst. The desired β-aminated products were obtained in good to high yields, and excellent enantioselectivities (90–99% *ee*) were observed for all the substrates examined in this work. To our knowledge, these results constitute the first examples of the direct catalytic asymmetric Mannich reaction of α-cyano ketones using organocatalysts. We believe that this method provides a practical entry for the preparation of chiral β-amino-α-cyano ketones derivatives. Further study of these new bifunctional organocatalysts in other asymmetric reactions is being under investigated.

Experimental Section

Typical Procedure for the Mannich Reaction of α-Cyano Ketone 1a with *N*-Boc-Benzaldimine (2a)

A mixture of 2-cyanocyclopentanone (**1a**, 218 mg, 0.2 mmol) and catalyst **V** (13 mg, 0.02 mmol) in toluene (0.4 mL) was stirred at room temperature for 5 min and then was cooled to −78 °C. A solution of *N*-Boc-benzaldimine (**2a**, 49.2 μL, 0.24 mmol) in toluene (4 mL) was added dropwise over a period of 10 min. The reaction mixture was stirred for 1 h at −78 °C. After completion of the reaction, the resulting solution was allowed to warm to room temperature, concentrated under vacuum and the obtained residue was purified by flash chromatography (EtOAc-hexane, 1:5) to afford the β-aminated 2-cyanocyclopentanone **3a**; yield: 50.8 mg (81%).

(*S*)-2-[(*S*)-*tert*-Butoxycarbonylamino]benzyl-2-cyanocyclopentanone (3a): $[\alpha]_D^{22}$: −42.2 (*c* 0.3, $CHCl_3$, >99% *ee*); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.47–7.35$ (m, 5H), 5.57 (br d, $J = 10$ Hz, 1H), 5.02 (d, $J = 10$ Hz, 1H), 2.80–2.55 (m, 1H), 2.53–2.30 (m, 1H), 2.24–1.98 (m, 1H), 1.40 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 206.5$, 154.9, 136.1, 129.0, 127.6, 118.0, 80.6, 54.7, 35.8, 32.6, 28.1, 18.6; ESI-MS: $m/z = 315.0$ $[M+H]^+$; HPLC (hexane/*i*-PrOH, 97:3, 220 nm, 1.0 mL min^{-1}, Chiralpak AD-H column): $t_R = 33.5$ min (major), $t_R = 36.6$ min (minor).

Acknowledgements

This research was financially supported by the Ministry of Education, Science, Technology (MEST) and Korea Industrial Technology Foundation (KOTEF) through the Human Resource Training Project for Regional Innovation.

References

[1] For reviews on the synthesis of β-amino acids: a) J. Ma, *Angew. Chem.* **2003**, *115*, 4426–4435; *Angew. Chem. Int. Ed.* **2003**, *42*, 4290–4299; b) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991–8035; c) P. A. Magriotis, *Angew. Chem.* **2001**, *113*, 4507–4509; *Angew. Chem. Int. Ed.* **2001**, *40*, 4377–4379.
[2] a) M. Fitz, K. Lundell, M. Lindroos, F. Fulop, L. T. Kanerva, *Tetrahedron: Asymmetry* **2005**, *16*, 3690–3697; b) T. Mecozzi, M. Petrini, R. Profeta, *J. Org. Chem.* **2001**, *66*, 8264–8267.
[3] a) M. Preiml, K. Hillmayer, N. Klempier, *Tetrahedron Lett.* **2003**, *44*, 5057–5059; b) M. Winkler, L. Matinkova, A. C. Knall, S. Krahulec, N. Klempier, *Tetrahedron* **2005**, *61*, 4249–4260.
[4] For selected recent reviews, see: a) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29–41; b) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797–5815; c) M. Shibasaki, S. Matsunaga, *J. Organomet. Chem.* **2006**, *691*, 2089–2100; d) M. M. B. Marques, *Angew. Chem.* **2006**, *118*, 356–360; *Angew. Chem. Int. Ed.* **2006**, *45*, 348–352; e) A. Cordova, *Acc. Chem. Res.* **2004**, *37*, 102–112.

[5] Selected examples of Mannich-type reactions of enolates, see: a) M. Sickert, C. Schneider, *Angew. Chem.* **2008**, *120*, 3687–3690; *Angew. Chem. Int. Ed.* **2008**, *47*, 3631–3634; b) J. Itoh, K. Fuchibe, T. Akiyama, *Synthesis* **2008**, 1319–1322; c) S. Kobayashi, R. Yazaki, K. Seki, M. Ueno, *Tetrahedron* **2007**, *63*, 8425–8429; d) K. Saruhashi, S. Kobayashi, *J. Am. Chem. Soc.* **2006**, *128*, 11232–11235; e) S. Kobayashi, M. Ueno, S. Saito, Y. Mizuki, H. Ishitani, Y. Yamashita, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5476–5481; f) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592–1594; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568; g) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

[6] Selected examples of direct metal-catalyzed Mannich-type reactions, see: a) Y. Hamashima, N. Sasamoto, N. Umebayashi, M. Sodeoka, *Chem. Asian J.* **2008**, *3*, 1443–1455; b) Z. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 2170–2171; c) G. A. Cutting, N. E. Stainforth, M. P. John, G. Kociok-Kohn, M. C. Willis, *J. Am. Chem. Soc.* **2007**, *129*, 10632–10633; d) H. Morimoto, G. Lu, N. Aoyama, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 9588–9589; e) B. M. Trost, J. Jaratjaroonphong, V. Reutrakul, *J. Am. Chem. Soc.* **2006**, *128*, 2778–2779; f) S. Harada, S. Handa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2005**, *117*, 4439–4442; *Angew. Chem. Int. Ed.* **2005**, *44*, 4365–4368; g) A. Okada, T. Shibuguchi, T. Ohshima, H. Masu, K. Yamaguchi, M. Shibasaki, *Angew. Chem.* **2005**, *117*, 4640–4643; *Angew. Chem. Int. Ed.* **2005**, *44*, 4564–4567.

[7] Selected examples of direct organocatalytic Mannich-type reactions, see: a) J. W. Yang, C. Chandler, M. Stadler, D. Kampen, B. List, *Nature* **2008**, *452*, 453–455; b) H. Zhang, S. Mitsumori, N. Utsumi, M. Imai, N. Garcia-Delgado, M. Mifsud, K. Albertshofer, P. H.-Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas, *J. Am. Chem. Soc.* **2008**, *130*, 875–886; c) J. Vesely, R. Rios, I. Ibrahem, A. Cordova, *Tetrahedron Lett.* **2007**, *48*, 421–425; d) T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 10054–10055; e) T. Kano, Y. Yamaguchi, O. Tokuda, K. Maruoka, *J. Am. Chem. Soc.* **2005**, *127*, 16408–16409; f) D. Enders, C. Grondal, M. Vrettou, G. Raabe, *Angew. Chem.* **2005**, *117*, 4147–4151; *Angew. Chem. Int. Ed.* **2005**, *44*, 4079–4083.

[8] a) K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2008**, *130*, 14452–14453; b) M. Terada, K. Sorimachi, D. Uraguchi, *Synlett* **2006**, 133–136; c) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.

[9] a) J. M. Goss, S. E. Schaus, *J. Org. Chem.* **2008**, *73*, 7651–7656; b) O. Marianacci, G. Micheletti, L. Bernardi, F. Fini, M. Fochi, D. Pettersen, V. Sgarzani, A. Ricci, *Chem. Eur. J.* **2007**, *13*, 8338–8351; c) A. Ting, S. Lou, S. E. Schaus, *Org. Lett.* **2006**, *8*, 2003–2006; d) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 2956–2959; *Angew. Chem. Int. Ed.* **2005**, *44*, 2896–2899; e) S. Lou, B. M. Taoka, A. Ting, S. E. Schaus, *J. Am. Chem. Soc.* **2005**, *127*, 11256–11257.

[10] a) S. B. Tsogoeva, S. Wei, M. Freund, M. Mauksch, *Angew. Chem. Int. Ed.* **2009**, *48*, 590–594; b) D. A. Yalalov, S. B. Tsogoeva, T. E. Shubina, I. M. Martynova, T. Clark, *Angew. Chem.* **2008**, *120*, 6726–6730; *Angew. Chem. Int. Ed.* **2008**, *47*, 6624–6628; c) Y. Yamaoka, H. Miyabe, Y. Yasui, Y. Takemoto, *Synthesis* **2007**, 2571–2575; d) A. L. Tillman, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1191–1193; e) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049.

[11] For selected recent reviews for bifunctional organocatalysts, see: a) S. J. Connon, *Synlett* **2009**, 354–376; b) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516–532; c) M. S. Taylor, E. N. Jacobson, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; d) S. J. Connon, *Angew. Chem.* **2006**, *118*, 4013–4016; *Angew. Chem. Int. Ed.* **2006**, *45*, 3909–3912; e) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5457; f) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999–1010; g) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299–4306; h) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175.

[12] a) A. Nojiri, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 5630–5631; b) A. Nojiri, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 3779–3784.

[13] a) J. Y. Mang, D. G. Kwon, D. Y. Kim, *J. Fluorine Chem.* **2009**, *130*, 259–262; b) J. H. Lee, H. T. Bang, D. Y. Kim, *Synlett* **2008**, 1821–1824; c) Y. K. Kang, D. Y. Kim, *Tetrahedron Lett.* **2006**, *47*, 4265–4268; d) H. R. Kim, D. Y. Kim, *Tetrahedron Lett.* **2005**, *46*, 3115–3117; e) S. M. Kim, H. R. Kim, D. Y. Kim, *Org. Lett.* **2005**, *7*, 2309–2311; f) E. J. Park, M. H. Kim, D. Y. Kim, *J. Org. Chem.* **2004**, *69*, 6897–6899; g) D. Y. Kim, Y. J. Choi, H. Y. Park, C. U. Joung, K. O. Koh, J. Y. Mang, K.-Y. Jung, *Synth. Commun.* **2003**, *33*, 435–443; h) D. Y. Kim, E. J. Park, *Org. Lett.* **2002**, *4*, 545–547; i) D. Y. Kim, S. C. Huh, S. M. Kim, *Tetrahedron Lett.* **2001**, *42*, 6299–6301; j) D. Y. Kim, S. C. Huh, *Tetrahedron* **2001**, *57*, 8933–8938.

[14] Recently, Shao et al. and we have independently developed new thiourea-type bifunctional organocatalyst containing binaphthyl scaffold, see: a) S. M. Kim, J. H. Lee, D. Y. Kim, *Synlett* **2008**, 2659–2662; b) S. H. Jung, D. Y. Kim, *Tetrahedron Lett.* **2008**, *49*, 5527–5530; c) F.-Z. Peng, Z.-H. Shao, B.-M. Fan, H. Song, G.-P. Li, H.-B. Zhang, *J. Org. Chem.* **2008**, *73*, 5202–5205.

