Efficient Enantioselective Synthesis of Dihydropyrans Using a Chiral *N*,*N*'-Dioxide as Organocatalyst

LETTERS XXXX Vol. XX, No. XX 000–000

ORGANIC

Juhua Feng, Xuan Fu, Zhenling Chen, Lili Lin, Xiaohua Liu, and Xiaoming Feng*

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China

xmfeng@scu.edu.cn

Received April 1, 2013



The bifunctional organocatalyst C3 *N*,*N*-dioxide has been successfully applied to the asymmetric cascade Michael/hemiacetalization reaction of α -substituted cyano ketones and β , γ -unsaturated α -ketoesters for the synthesis of multifunctionalized chiral dihydropyrans. The corresponding products were obtained in excellent yields (up to 99%) with high to excellent enantioselectivities (up to 99% ee).

Dihydropyrans are important heterocyclic structures¹ and have been found widely in natural and unnatural products.² These compounds exhibit intriguing biological activities, such as cytotoxicity against some cancers, anti-HCV entry, and anti-infectivity activities, and are widely used in pharmaceuticals.³ Furthermore, dihydropyrans are also useful intermediates for organic synthesis.⁴ Therefore, this class of compounds has received significant attention and results in a variety of synthetic methods, such as multistep protocols via anionic, cationic, or radical cyclization,⁵ [4 + 2] cycloaddition,⁶ dioxanone Claisen rearrangement,⁷ and ring-closing metathesis of enol ethers.⁸ The cascade Michael/hemiacetalization reaction

^{(1) (}a) Zheng, T.; Narayan, R. S.; Schomaker, J. M.; Borhan, B. J. Am. Chem. Soc. 2005, 127, 6946. (b) Kang, S. Y.; Lee, K. Y.; Sung, S. H.; Kim, Y. C. J. Nat. Prod. 2005, 68, 56. (c) Clarke, P. A.; Santos, S. Eur. J. Org. Chem. 2006, 2045. (d) Li, J.; Ding, Y.; Li, X.-C.; Ferreira, D.; Khan, S.; Smillie, T.; Khan, I. A. J. Nat. Prod. 2009, 72, 983. (e) Li, H.; Loh, T. P. Org. Lett. 2010, 12, 2679. (f) Schmidt, E. Yu.; Trofimov, B. A.; Zorina, N. V.; Mikhaleva, A. I.; Ushakov, I. A.; Skital'tseva, E. V.; Kazheva, O. N.; Alexandrov, G. G.; Dyachenko, O. A. Eur. J. Org. Chem. 2010, 6727. (g) Wang, J.; Crane, E. A.; Scheidt, K. A. Org. Lett. 2011, 13, 3086.

^{(2) (}a) Markó, I. E.; Dobbs, A. P.; Scheirmann, V.; Chellé, F.; Bayston, D. J. *Tetrahedron Lett.* **1997**, *38*, 2899. (b) Mangion, I. K.; MacMillan, D. W. C. J. Am. Chem. Soc. **2005**, *127*, 3696. (c) Yadav, J. S.; Sunitha, V.; Reddy, B. V. S.; Das, P. P.; Gyanchander, E. *Tetrahedron Lett.* **2008**, *49*, 855. (d) Magano, J. Chem. Rev. **2009**, *109*, 4398. (e) Sun, J.; Xia, E. Y.; Wu, Q.; Yan, C. G. ACS Comb. Sci. **2011**, *13*, 421.

^{(3) (}a) Lichtenthaler, F. W.; Nakamura, K.; Klotz, J. Angew. Chem., Int. Ed. 2003, 42, 5838. (b) Xu, Y.-M.; McLaughlin, S. P.; Gunatilaka, A. A. L. J. Nat. Prod. 2007, 70, 2045. (c) Lin, S.; Shen, Y.-H.; Li, H.-L.; Yang, X.-W.; Chen, T.; Lu, L.-H.; Huang, Z.-S.; Liu, R.-H.; Xu, X.-K.; Zhang, W.-D.; Wang, H. J. Nat. Prod. 2009, 72, 650. (d) Zhang, H. J.; Rothwangl, K.; Mesecar, A. D.; Sabahi, A.; Rong, L. J.; Fong, H. H. S. J. Nat. Prod. 2009, 72, 2158.

^{(4) (}a) Li, P.; Chai, Z.; Zhao, S.-L.; Yang, Y.-Q.; Wang, H.-F.; Zheng, C.-W.; Cai, Y.-P.; Zhao, G.; Zhu, S.-Z. *Chem. Commun.* **2009**, 7369. (b) Li, G.; Kaplan, M. J.; Wojtas, L.; Antilla, J. C. *Org. Lett.* **2010**, *12*, 1960. (c) Alemán, J.; Marcos, V.; Marzo, L.; García Ruano, J. L. *Eur. J. Org. Chem.* **2010**, 4482. (d) Zacuto, M. J.; Tomita, D.; Pirzada, Z.; Xu, F. *Org. Lett.* **2010**, *12*, 684. (e) Wang, H.-F.; Li, P.; Cui, H.-F.; Wang, X.-W.; Zhang, J.-K.; Liu, W.; Zhao, G. *Tetrahedron* **2011**, *67*, 1774. (f) Zhu, X.-B.; Wang, M.; Wang, S.-Z.; Yao, Z.-J. *Tetrahedron* **2012**, *68*, 2041.

^{(5) (}a) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. J. Am. Chem. Soc. **1989**, 111, 5335. (b) Kim, S.; Fuchs, P. L. J. Am. Chem. Soc. **1991**, 113, 9864. (c) Stamos, D. P.; Kishi, Y. Tetrahedron Lett. **1996**, 37, 8643. (d) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. J. Org. Chem. **1997**, 62, 3426. (e) Lian, Y.; Hinkle, R. J. J. Org. Chem. **2006**, 71, 7071. (f) Liu, W.; Zhou, J.; Zheng, C.; Chen, X.; Xiao, H.; Yang, Y.; Guo, Y.; Zhao, G. Tetrahedron **2011**, 67, 1768. (g) Lambert, R. F.; Hinkle, R. J.; Ammann, S. E.; Lian, Y.; Liu, J.; Lewis, S. E.; Pike, R. D. J. Org. Chem. **2011**, 76, 9269.

^{(6) (}a) Danishefsky, S. J.; Selnick, H. G.; Armistead, D. M.; Wincott, F. E. J. Am. Chem. Soc. **1987**, 109, 8119. (b) Evans, D. A.; Johnson, J. S.; Olhava, E. J. J. Am. Chem. Soc. **2000**, 122, 1635. (c) Leconte, S.; Dujardin, G.; Brown, E. Eur. J. Org. Chem. **2000**, 639. (d) Jørgensen, K. A. Angew. Chem., Int. Ed. **2000**, 39, 3558. (e) Huang, Y.; Rawal, V. H. J. Am. Chem. Soc. **2002**, 124, 9662. (f) Krauss, I. J.; Mandal, M.; Danishefsky, S. J. Angew. Chem., Int. Ed. **2007**, 46, 5576. (g) Ashtekar, K. D.; Staples, R. J.; Borhan, B. Org. Lett. **2011**, 13, 5732. (h) Fujiwara, K.; Kurahashi, T.; Matsubara, S. J. Am. Chem. Soc. **2012**, 134, 5512.

^{(7) (}a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J. *J. Org. Chem.* **1984**, *49*, 4320. (b) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132.

between nucleophilic reagents and α,β -unsaturated ketones also provides an efficient method for the synthesis of dihydropyrans. In asymmetric catalysis, only chiral thiourea and cinchona alkaloid catalysts were applied in this reaction.⁹ Therefore, the development of new asymmetric catalytic systems for this reaction is still necessary.

Chiral *N*,*N'*-dioxides as metal ligands or organocatalysts have shown strong asymmetry-inducing capability for many reactions.¹⁰ In the previous studies,¹¹ chiral *N*,*N'*dioxides as organocatalysts exhibited the bifunctional character that enabled simultaneous activation of the reactants with amide-NH as Brønsted acid and the *N*-oxide moiety as Brønsted base.¹² We envisioned that the amide-NH moiety of the *N*,*N'*-dioxide could activate β , γ -unsaturated α -ketoesters and the *N*-oxide moiety activated the α -substituted cyano ketones, and thus the reaction was promoted. Herein, we report our efforts on developing *N*, *N'*-dioxide organocatalysts for the asymmetric synthesis of multisubstituted dihydropyrans through the cascade Michael¹³/hemiacetalization reaction of α -substituted cyano ketones and β , γ -unsaturated α -ketoesters.



Figure 1. Organocatalysts used in this study.

(8) (a) Ireland, R. E.; Meissner, R. S.; Rizzacasa, M. A. J. Am. Chem. Soc. **1993**, 115, 7166. (b) Sturino, C. F.; Wong, J. C. Y. Tetrahedron Lett. **1998**, 39, 9623. (c) Shu, C.; Hartwig, J. F. Angew. Chem., Int. Ed. **2004**, 43, 4794. (d) Stenne, B.; Timperio, J.; Savoie, J.; Dudding, T.; Collins, S. K. Org. Lett. **2010**, 12, 2032.

(9) (a) Zhao, S.-L.; Zheng, C.-W.; Wang, H.-F.; Zhao, G. Adv. Synth. Catal. **2009**, 351, 2811. (b) Yao, W.; Pan, L.; Wu, Y.; Ma, C. Org. Lett. **2010**, 12, 2422.

(10) Liu, X. H.; Lin, L. L.; Feng, X. M. Acc. Chem. Res. 2011, 44, 574.
(11) (a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. J. Am. Chem. Soc. 1998, 120, 6419. (b) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. Org. Lett. 2002, 4, 2799. (c) Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kočovský, P. Org. Lett. 2005, 7, 3219. (d) Traverse, J. F.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. Org. Lett. 2005, 7, 3151. (e) Malkov, A. V.; Kočovský, P. Eur. J. Org. Chem. 2007, 29. (f) Gnanamani, E.; Someshwar, N.; Ramanathan, C. R. Adv. Synth. Catal. 2012, 354, 2101.

(12) (a) Wen, Y. H.; Gao, B.; Fu, Y. Z.; Dong, S. X.; Liu, X. H.; Feng, X. M. *Chem.—Eur. J.* **2008**, *14*, 6789. (b) Cai, Y. F.; Wang, W. T.; Shen, K.; Wang, J.; Hu, X. L.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Chem. Commun.* **2010**, *46*, 1250.

(13) (a) Sibi, M. P.; Manyem, S. Tetrahedron 2000, 56, 8033. (b)
Krause, N.; Hoffmann-Röder, A. Synthesis 2001, 171. (c) Almaşi, D.;
Alonso, D. A.; Nájera, C. Tetrahedron: Asymmetry 2007, 18, 299. (d)
Tsogoeva, S. B. Eur. J. Org. Chem. 2007, 1701. (e) Vicario, J. L.; Badia,
D.; Carrillo, L. Synthesis 2007, 2065. (f) Christoffers, J.; Koripelly, G.;
Rosiak, A.; Rössle, M. Synthesis 2007, 1279. (g) Zhao, S.-L.; Zheng,
C.-W.; Zhao, G. Tetrahedron: Asymmetry 2009, 20, 1046.

We initiated our study by examining the reaction between methyl 2-oxo-4-phenylbut-(E)-3-enoate **1a** and 3-oxo-3-phenylpropanenitrile **2a**.¹⁴

A preliminary survey revealed that the linker of N,N'-dioxides (Figure 1) had a significant effect on the enantioselectivity (Table 1, entries 1–3). Chiral N,N'-dioxides derived from 1,3-dibromopropane (**C1**) and cyclohexane-1,2-diamine (**C2**) gave only 11% ee and 3% ee, respectively (Table 1, entries 1 and 2). However, (1R,2R)-1,2-diphenylethane-1,2-diamine-derived N,N'-dioxide **C3** could give





entry	cat.	solvent	time (h)	additive	yield ^b (%)	ee ^c (%)
1	C1	THF	24	no	76	-11
2	C2	THF	24	no	90	3
3	C3	THF	24	no	78	55
4	C4	THF	24	no	77	$^{-13}$
5	C5	THF	24	no	93	31
6	C6	THF	24	no	70	36
7	C7	THF	24	no	67	52
8	C8	THF	24	no	39	51
9	C3	Et_2O	24	no	90	50
10	C3	MTBE	24	no	89	63
11	C3	MeOH	24	no	50	0
12^d	C3	MTBE	48	no	81	68
$13^{d,e}$	C3	MTBE	48	<i>p</i> - ^{<i>t</i>} BuC ₆ H ₄ COOH	86	71
$14^{d,e,f}$	C3	MTBE	72	<i>p</i> - ^{<i>t</i>} BuC ₆ H ₄ COOH	83	78
$15^{d,e,f,g}$	C3	MTBE	72	<i>p</i> - ^{<i>t</i>} BuC ₆ H ₄ COOH	92	86

^{*a*} Unless otherwise noted, all reactions were conducted with **1a** (0.12 mmol), **2a** (0.10 mmol), additive (10 mol %), and catalyst (10 mol %) in solvent (1.0 mL) under N₂ at 0 °C. ^{*b*} Isolated yields. ^{*c*} Determined by chiral HPLC analysis. ^{*d*} In 3.0 mL of MTBE. ^{*e*} 20 mg of 4 Å MS was used. ^{*f*} At -30 °C. ^{*g*} 50 mol % of *p*-'BuC₆H₄COOH was used. MTBE = methyl *tert*-butyl ether, MS = molecular sieves.

moderate enantioselectivity (55% ee, Table 1, entry 3). Inspired by the results, other N,N'-dioxides derived from 1,2diphenylethane-1,2-diamine were synthesized and examined. Since these N,N'-dioxides have two chiral sources, the matching of chiral linker and chiral N-oxide moiety was investigated. The (1*S*,2*S*)-diamine and (*S*)-proline derived chiral N,N'-dioxide **C4** exhibited worse result than the

⁽¹⁴⁾ The ¹H and ¹³C NMR spectra of **3aa** revealed a rapid equilibrium between the cyclic hemiketal **3aa** and the Michael-type product **3aa'**. Such an equilibrium is very rapid and thus only one pair of enantiomers is detected by HPLC. For studies on similar equilibriums of related compounds, see: (a) Porter, W. R.; Trager, W. F. J. Heterocycl. Chem. **1982**, *19*, 475. (b) Heimark, L. D.; Trager, W. F. J. Med. Chem. **1984**, *27*, 1092. (c) Halland, N.; Velgaard, T.; Jørgensen, K. A. J. Org. Chem. **2003**, *68*, 5067. (d) Chen, X.-K.; Zheng, C.-W.; Zhao, S.-L.; Chai, Z.; Yang, Y.-Q.; Zhao, G.; Cao, W.-G. Adv. Synth. Catal. **2010**, *352*, 1648.

(1R,2R)-diamine and (S)-proline derived C3 (Table 1, entry 4 vs 3). Further investigation on the amino acid backbone revealed that (S)-proline-derived catalyst C3 was superior to (S)-ramipril-derived C5 (Table 1, entry 3 vs 5). It was also found that smaller or larger ring size of substituent on the nitrogen of the *N*-oxide moiety had no beneficial effect on the enantioselectivity (Table 1, entries 6-8). In order to further improve the result, extensive investigation on the reaction conditions was carried out.

Table 2. Substrate Scope for the Asymmetric Michael/ Hemiacetalization Reaction of **2a** and β , γ -Unsaturated α -Ketoesters^{*a*}

0	0		Ph O OH
		C3 (10 mol %)	COOR ²
R ¹ COOR ²	+ Ph	p- ^t BuC ₆ H ₄ COOH (50 mol %)	NC
1	2a	4 Å MS, MTBE, -30 °C	R' 3

entry	\mathbb{R}^1	\mathbb{R}^2	product	yield ^{b} (%)	ee^{c} (%)
1	Ph	Me	3aa	92	86
2	Ph	\mathbf{Et}	3ba	84	84
3	Ph	i-Pr	3ca	80	85
4	Ph	allyl	3da	90	83
5	Ph	t-Bu	3ea	76	92
6^d	$2-NO_2C_6H_4$	Me	3fa	98	91
7	$2\text{-BrC}_6\text{H}_4$	Me	3ga	99	93
8	$2\text{-FC}_6\text{H}_4$	Me	3ha	98	90
9	$2\text{-ClC}_6\text{H}_4$	Me	3ia	99	93
10	$2-MeOC_6H_4$	Me	3ja	97	98
11	$2 - MeC_6H_4$	Me	3ka	98	94
12	$2,4-Cl_2C_6H_3$	Me	3la	94	90
13	$2,6-Cl_2C_6H_3$	Me	3ma	99	99
14	$2,6-F_2C_6H_3$	Me	3na	99	98
15^d	$2,6-Me_2C_6H_3$	Me	3oa	95	96
16	$3-MeC_6H_4$	Me	3pa	84	85
17	$4-MeC_6H_4$	Me	3qa	85	83
18	$4-ClC_6H_4$	Me	3ra	76	80
$19^{e,f}$	cyclohexyl	Me	3sa	91	89

^{*a*} Unless otherwise noted, all reactions were conducted with **1** (0.12 mmol), **2a** (0.10 mmol), p^{-1} BuC₆H₄COOH (50 mol %), 4 Å MS (20 mg), and **C3** (10 mol %) in MTBE (3.0 mL) under N₂ at -30 °C for 72 h. ^{*b*} Isolated yields. ^{*c*} Determined by HPLC analysis. ^{*d*} Reaction time: 96 h. ^{*e*} Reaction time: 120 h. ^{*f*} The yield was determined by ¹H NMR spectra.

Solvent screening showed the enantioselectivity could be improved to 63% ee in MTBE (Table 1, entry 10), while racemic product was obtained in polar solvent, such as MeOH (Table 1, entry 11). Under lower concentration, 68% ee could be obtained (Table 1, entry 12). Addition of p-¹BuC₆H₄COOH¹⁵ could further improve the enantioselectivity to 71% ee (Table 1, entry 13). Under lower reaction temperature and increasing the amount of additive to 50 mol %, catalyst **C3** could efficiently catalyze the reaction and afford the corresponding dihydropyran in 92% yield with 86% ee (Table 1, entry 15). Table 3. Reactions of Different α -Substituted Cyano Ketones with 1^{α}

R1	$COOMe + R^3$	$\frac{\text{C3 (1)}}{\rho^{t}\text{BuC}_{6}\text{H}_{4}}$ 4 Å MS 2	10 mol %) COOH (50 mol 5, MTBE, -30 °C	$\xrightarrow{R^3 \cup 0}_{NC} \xrightarrow{R^1}_{R^1}$	DH COOMe
entry	\mathbb{R}^1	\mathbb{R}^3	product	yield ^{b} (%)	ee ^c (%)
1	Ph	Ph	3aa	92	86
2	Ph	$3-FC_6H_4$	3ab	98	88
3	Ph	$3-ClC_6H_4$	3ac	95	86
4	Ph	$3-BrC_6H_4$	3ad	93	90
5^d	Ph	$3-MeOC_6H_4$	3ae	88	85
6	Ph	$3-MeC_6H_4$	3af	92	86
7	Ph	$4-MeC_6H_4$	3ag	87	84
8	Ph	$4\text{-FC}_6\text{H}_4$	3ah	96	84
9	Ph	$4-ClC_6H_4$	3ai	95	82
10	Ph	$4\text{-BrC}_6\text{H}_4$	3aj	95	83
11	$2,6-Cl_2C_6H_3$	$3-BrC_6H_4$	3md	99	99
12	2.6-Cl ₂ C ₆ H ₃	4-ClC ₆ H ₄	3mi	99	99

^{*a*} Unless otherwise noted, all reactions were conducted with **1** (0.12 mmol), **2** (0.10 mmol), $p^{-t}BuC_6H_4COOH$ (50 mol %), 4 Å MS (20 mg), and **C3** (10 mol %) in MTBE (3.0 mL) under N₂ at -30 °C for 72 h. ^{*b*} Isolated yields. ^{*c*} Determined by HPLC analysis. ^{*d*} Reaction time: 120 h.

Under the optimized reaction conditions, a range of β , γ unsaturated α -ketoesters 1 were examined with 2a, and the results were summarized in Table 2. Substrates with Et. *i*-Pr, and allyl groups on the ester moiety gave similar results (Table 2, entries 1-4). More sterically hindered *t*-Bu group afforded higher enantioselectivity (92% ee), but lower yield (76%) (Table 2, entry 5). The substituents on the aromatic ring of β , γ -unsaturated α -ketoesters affected the results significantly. The substrates with electron-donating or electron-withdrawing groups at the ortho position of the aromatic ring obtained much better results, affording the corresponding products in excellent yields with excellent enantioselectivities (94-99% yields, 90-99% ee, Table 2, entries 6-15). The substrates with substituent at the *meta* or para position of the aromatic ring got slightly decreased results (Table 2, entries 16-18). Notably, the catalytic system was also suitable for aliphatic methyl 4-cyclohexyl-2-oxobut-(E)-3-enoate, affording the desired product in 91% yield with 89% ee (Table 2, entry 19). Subsequently, a broad spectrum of α -substituted cyano ketones as nucleophiles was probed. The reactions proceeded smoothly with different 3-oxo-3-phenylpropanenitrile derivatives, and good results were obtained (87-99% yields and 82-99% ee. Table 3).

To evaluate the synthetic potential of the catalytic system, gram-scale synthesis of the dihydropyran **3ma** was performed. By treatment of 3.0 mmol of **2a** under the optimized conditions, the corresponding **3ma** was obtained in 99% yield (1.20 g) with 99% ee (Scheme 1).

The structure of the catalyst C3 was determined by X-ray crystallographic analysis,¹⁶ which showed the intramolecular hydrogen bonding interactions between the N–H proton of the amide and the oxygen of *N*-oxide, as

⁽¹⁵⁾ The role of the acid additive might be to break down the intramolecular hydrogen bonds between the N-H proton of the amide and the oxygen of *N*-oxide present in catalyst, and thus, the N-H proton and the *N*-oxide could be free for the activation of the substrates.

Scheme 1. Gram-Scale Asymmetric Synthesis of 3ma



well as the intermolecular hydrogen bonding interactions between the oxygen of N-oxide and the hydrogen of H₂O (Figure 2). The intramolecular hydrogen bonds were also confirmed by the ¹H NMR spectra, in which the N-H proton of the amide in catalyst C3 showed a strong deshielding effect, with a broad peak shape at $\delta = 12.01$ ppm (see the Supporting Information for details). These results implied that the N-H moiety of the amide in catalyst C3 might act as a Brønsted acid, and the N-oxide moiety might act as a Brønsted base. The absolute configuration of the product of 4-bromobenzyl 2-oxo-4-phenylbut-(E)-3-enoate was determined to be 2S,4R by comparison of the literature.^{9a,17} On the basis of the above information and the previous studies on N, N'-dioxides,^{10,11} a transition state was proposed to illustrate the activation mode (Figure 2). The intramolecular H-bonds of catalyst C3 were released and transformed to activate the two substrates simultaneously (see the Supporting Information for details). One of the N-H moieties of the amide activated the β , γ -unsaturated α -ketoester through hydrogen bonds, while the enolate form of the α -substituted cyano ketone could be activated by the N-oxide on the other side. The Si face of β , γ -unsaturated α -ketoester was shielded by the cyclohexyl moiety, and the α -substituted cyano ketone could attack from the *Re* face of β , γ -unsaturated α -ketoester to form the product of the 4*R* configuration.

In summary, we have developed an efficient chiral N, N'dioxide catalyst for the asymmetric reaction of α -substituted cyano ketones with β, γ -unsaturated α -ketoesters. The reaction performed well over a range of substrates, giving the corresponding products in excellent yields (up to 99%)



Figure 2. Crystal structure of C3 and proposed transition-state model for the Michael addition step.

with high to excellent enantioselectivities (up to 99% ee). Further investigation on the application of such kind of N,N'-dioxides to other reactions is in progress.

Acknowledgment. We thank the National Natural Science Foundation of China (Nos. 21021001 and 21290182) and the National Basic Research Program of China (973 Program: No. 2010CB833300) for financial support.

Supporting Information Available. Experimental procedures, spectral and analytical data for the products, and crystal CIF. This material is available free of charge via the Internet at http://pubs.acs.org.

⁽¹⁶⁾ CCDC 922463 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

⁽¹⁷⁾ The product of 4-bromobenzyl 2-oxo-4-phenylbut-(*E*)-3-enoate was obtained in 37% yield with 77% ee.

The authors declare no competing financial interest.