ORGANIC LETTERS

2007
Vol. 9, No. 5
865−868

Axially Chiral NHC–Pd(II) Complexes in the Oxidative Kinetic Resolution of Secondary Alcohols Using Molecular Oxygen as a Terminal Oxidant

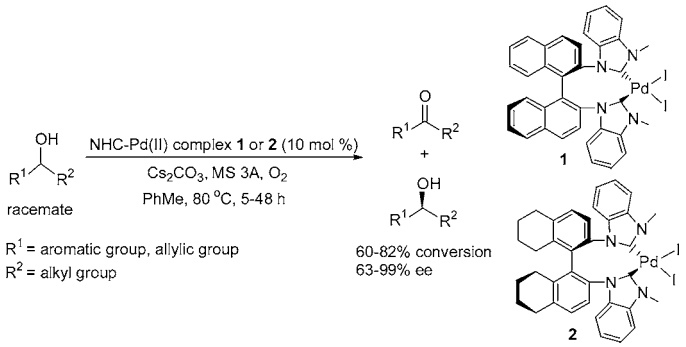
Tao Chen,[†] Jia-Jun Jiang,[†] Qin Xu,[†] and Min Shi*[,†,‡]

School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 Mei Long Road, Shanghai 200237 China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

mshi@mail.sioc.ac.cn

Received December 18, 2006

ABSTRACT



Axially chiral *N*-heterocyclic carbene (NHC) Pd(II) complexes were prepared from optically active 1,1′-binaphthalenyl-2,2′-diamine (BINAM) and H_8-BINAM and applied in the oxidative kinetic resolution of secondary alcohols using molecular oxygen as a terminal oxidant. The corresponding *sec*-alcohols can be obtained in good yields with moderate to good enantioselectivities.

The oxidation of alcohols is one of the most common and important reactions in organic chemistry and has exceptional useful applications in organic synthesis.[1] During the past decade, palladium-catalyzed aerobic oxidation of alcohols has received considerable attention due to the economic and environmental advantages of molecular oxygen as a terminal oxidant.[2,3] Recently, Sigman[4] and Stoltz[5] independently developed a convenient method for the enantioselective aerobic oxidation of secondary alcohols using a (−)-*sparteine*/Pd(II) complex as the catalyst, and this has emerged as a powerful method for the preparation of enantioenriched

[†] East China University of Science and Technology.
[‡] Shanghai Institute of Organic Chemistry.

(1) Hudlicky, M. *Oxidations in Organic Chemistry*; ACS Monograph Series; American Chemical Society: Washington, DC, 1990.

(2) Lloyd and Schwartz initiated the palladium-catalyzed aerobic oxidation of alcohols; see: (a) Lloyd, W. G. *J. Org. Chem.* **1967**, *32*, 2816−2819. (b) Blackburn, T. F.; Schwartz, J. *J. Chem. Soc., Chem. Commun.* **1977**, 157−158.

(3) For recent reviews, see: (a) Muzart, J. *Tetrahedron* **2003**, *59*, 5789−5816. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400−3420. (c) Schultz, M. J.; Sigman, M. S. *Tetrahedron* **2006**, *62*, 8227−8241. (d) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221−229. (e) Rogers, M. M.; Stahl, S. S. In *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer: New York, 2007; Vol. 21, pp 21−46. For some more selected examples, see: (e) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185−3189. (f) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750−6755. (g) Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636−1639. (h) Steinhoff, B. A.; Stahl, S. S. *Org. Lett.* **2002**, *4*, 4179−4181. (i) Schultz, M. J.; Park, C. C.; Sigman, M. S. *Chem. Commun.* **2002**, 3034−3035. (j) Jensen, D. R.; Schultz, M. J.; Mueller, J. A.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810−3813. (k) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343−3352.

10.1021/ol063061w CCC: $37.00
Published on Web 01/30/2007

alcohols. However, a significant limitation of this system is the requirement of (−)-sparteine, a chiral tertiary diamine, which is only readily available as a single antipode and is a difficult template to optimize through systematic structural variations.[4i] On the other hand, the use of *N*-heterocyclic carbene (NHC) ligands has developed rapidly in the latest decade due to their stability to air and moisture and their strong σ-donor but poor π-acceptor abilities.[6] Homogeneous catalytic reactions using NHC−Pd complexes have been extensively investigated, and some excellent results have been achieved.[7] Application of chiral NHC−Pd(II) complexes in enantioselective kinetic resolution of secondary alcohols has also been reported.[4i] Unfortunately, the results were not so good when inorganic bases other than the chiral base (−)-sparteine were used. Herein, we present new chiral NHC−Pd(II) complex systems as effective catalysts in the oxidative kinetic resolution of racemic secondary alcohols using molecular oxygen as the terminal oxidant.

We previously reported the preparation of an axially chiral NHC−Rh complex derived from optically active 1,1-binaphthalenyl-2,2′-diamine (BINAM) and demonstrated its high chiral induction abilities in the hydrosilylation of methyl ketones.[8] These results inspired us to synthesize similarly axial chiral cis-chelated NHC−Pd(II) complexes **1** and **2** and to apply them in the oxidative kinetic resolution of secondary alcohols (Figure 1).[9] The synthesis of NHC−Pd(II) complexes **1** and **2** was accomplished by use of optically active BINAM and H_8-BINAM as the starting materials in a similar sequence as in the preparation of the axially chiral NHC−Rh complex.[10] The H_8-BINAM was produced by reduction of BINAM with Pd/C−H_2. The structure of **2** was determined by X-ray diffraction and is shown in Figure 2.[11]

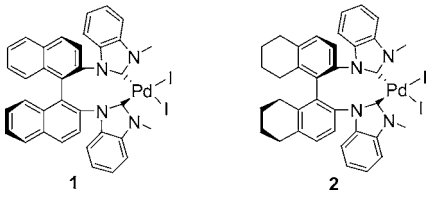


Figure 1. Axially chiral NHC−Pd(II) complexes.

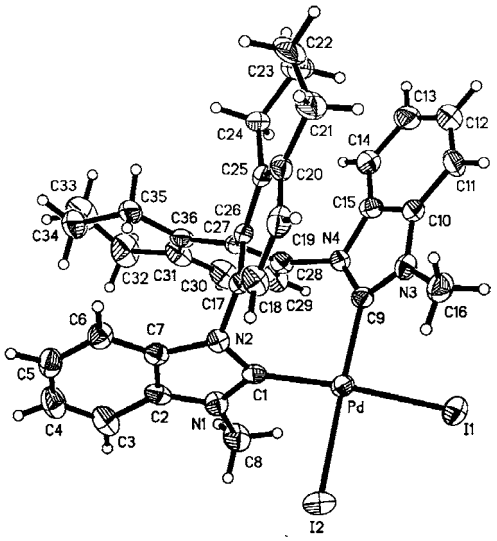


Figure 2. ORTEP drawing of chiral NHC−Pd(II) complex **2**.

In optimization studies, the oxidation of 1-phenylethanol to acetophenone using racemic complex **1** was selected as a model reaction to screen a series of bases and solvents. The results are summarized in Tables 1 and 2, respectively.[12] We found that (1) organic bases were generally inefficient under identical conditions (Table 1, entries 10−13), (2) K_2CO_3, Cs_2CO_3, $K_3PO_4{\cdot}3H_2O$, KO^{t}Bu were the promising bases (Table 1, entries 2, 3, 6, and 8), and (3) PhMe and DMF were the solvents of choice (Table 2, entries 1−7).[13]

Next, the enantioselective oxidative kinetic resolution of 1-phenylethanol was evaluated using chiral complex **1**. The results are summarized in Table 3.[13] It was found that PhMe was the solvent of choice and Cs_2CO_3 was the preferred base for the kinetic resolution, with this combination furnishing optically active 1-phenylethanol in 62% conversion and 87% ee (k_{rel} = 8.80) at 80 °C (Table 3, entry 7). To test whether

(4) (a) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475−7476. (b) Mueller, J. A.; Jensen, D. R.; Sigman, M. S. *J. Am. Chem. Soc.* **2002**, *124*, 8202−8203. (c) Mandal, S. K.; Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Org. Chem.* **2003**, *68*, 4600−4603. (d) Mueller, J. A.; Sigman, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 7005−7013. (e) Mandal, S. K.; Sigman, M. S. *J. Org. Chem.* **2003**, *68*, 7535−7537. (f) Mueller, J. A.; Goller, C. P.; Sigman, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9724−9734. (g) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343−3352. (h) Mueller, J. A.; Cowell, A.; Chandler, B. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 14817−14824. (i) Jensen, D. R.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 63−65.

(5) (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725−7726. (b) Bagdanoff, J. T.; Ferreira, E. M.; Stoltz, B. M. *Org. Lett.* **2003**, *5*, 835−837. (c) Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 353−357. (d) Trend, R. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 4482−4483.

(6) For reviews, see: (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1209−1309. (b) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619−636.

(7) Selected examples, see: (a) Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411−1414. (b) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3173−3180. (c) Xu, Q.; Duan, W. L.; Lei, Z. Y.; Zhu, Z. B.; Shi, M. *Tetrahedron* **2005**, *61*, 11225−11229. (d) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101−4111.

(8) Duan, W. L.; Shi, M.; Rong, G. B. *Chem. Commun.* **2003**, 2916−2917.

(9) The X-ray crystal data of racemic NHC−Pd(II) complex **1** has been deposited in CCDC with number 209242. For the details, see ref 7c. For a review of practical issues in kinetic resolutions, see: Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5−26.

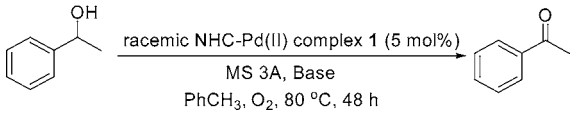
(10) See the Supporting Information for details.

(11) The crystal data of chiral NHC−Pd(II) complex **2** has been deposited in CCDC with number 603240: empirical formula, $C_{37}H_{36}Cl_2N_4I_2Pd$; formula weight, 967.80; crystal color, habit, colorless, prismatic; crystal system, orthorhombic; lattice type, primitive; lattice parameters, a = 12.8832(8) Å, b = 14.0578(9) Å, c = 209.2839(13) Å, α = 90°, β = 90°, γ = 90°, V = 3673.6(4) Å^3; space group, $P2(1)2(1)2(1)$; Z = 4; D_{calc} = 1.750 g/cm^3; F_{000} = 1888; diffractometer, Rigaku AFC7R; residuals, R, R_w, 0.543, 0.1246.

(12) Based on the structural similarity of NHC-Pd(II) complexes **1** and **2** with $PdCl_2$/(−)-sparteine (ref 5a), we initiated our investigation with the same model reaction and similar reaction conditions.

(13) For detailed procedures of base and solvent screening trials, and the general procedure for the oxidative kinetic resolution of secondary alcohols, see the Supporting Information.

Table 1. Screening for Bases in the Racemic NHC−Pd(II) Complex **1** Catalyzed Oxidation of 1-Phenylethanol to Acetophenone

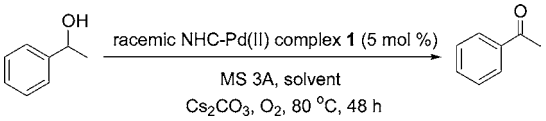


entry	base	conversion[a] (%)
1	Na_2CO_3	13
2	K_2CO_3	44
3	Cs_2CO_3	58
4	KF	5
5	NaOAc	N.R.
6	$K_3PO_4{\cdot}3H_2O$	53
7	$NaHCO_3$	12
8	KO^{t}Bu	52
9[b]		N.R.
10	DBU	6
11	DMAP	N.R.
12	Et_3N	7
13	pyridine	7

[a] Conversions were analyzed by GC. [b] No base was added.

the resolution can be done at lower temperature, we conducted the reaction at 60 °C (Table 3, entry 14). Disappointingly, the conversion was rather low. Upon

Table 2. Screening for Solvents in the Racemic NHC−Pd(II) Complex **1** Catalyzed Oxidation of 1-Phenylethanol to Acetophenone

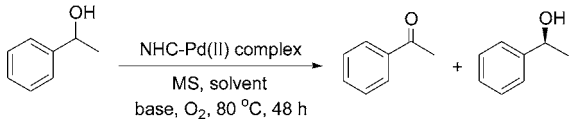


entry	solvent	conversion[a] (%)
1	PhMe	58
2	MeCN	21
3	benzene	11
4	DMF	76
5	DCE ($ClCH_2CH_2Cl$)	11
6	DMSO	18
7	*t*-BuOH	5

[a] Conversions were analyzed by GC.

elevating the temperature to 100 °C, the conversion remained constant, but the ee showed a slight decrease (83% ee) (Table 3, entry 15). For complex **2**, 93% ee and 67% conversion (k_{rel} = 8.35) could be realized at 80 °C in the presence of 3 Å MS (Table 3, entry 16). Therefore, these best reaction conditions for the oxidative kinetic resolution of secondary alcohols were to carry out the reaction in PhMe at 80 °C using the chiral NHC−Pd(II) complex (10 mol %) as a catalyst in the presence of molecular sieves 3 Å, 4 Å, or 5 Å. Different molecular sieves were found to have varied influence on the results under identical conditions (Table 3,

Table 3. Screening for the Best Conditions in the Axially Chiral NHC−Pd(II) Complex Catalyzed Oxidative Kinetic Resolution of 1-Phenylethanol



entry[a]	complex (mol %)	MS	base	solvent	conv[b] (%)	ee[c] (%) (config)[d]	k_{rel}[e]
1	**1** (5)	3A	Cs_2CO_3	PhMe	37	N.D.[f]	
2	**1** (5)	3A	K_2CO_3	PhMe	20	N.D.	
3	**1** (5)	3A	$K_3PO_4{\cdot}3H_2O$	PhMe	34	N.D.	
4	**1** (5)	3A	KO^{t}Bu	PhMe	25	N.D.	
5	**1** (5)	3A	Cs_2CO_3	DMF	50	8 (*S*)	1.26
6	**1** (10)	3A	Cs_2CO_3	PhMe	60	84 (*S*)	8.97
7	**1** (10)	4A	Cs_2CO_3	PhMe	62	87 (*S*)	8.80
8	**1** (10)	4A	Cs_2CO_3	hexane	10	N.D.	
9	**1** (10)	4A	Cs_2CO_3	xylene	36	40 (*S*)	8.71
10	**1** (10)	5A	Cs_2CO_3	PhMe	61	86 (*S*)	9.06
11	**1** (10)	4A	K_2CO_3	PhMe	20	22 (*S*)	1.32
12	**1** (10)	4A	$K_3PO_4{\cdot}3H_2O$	PhMe	43	36 (*S*)	3.96
13	**1** (10)	4A	KO^{t}Bu	PhMe	36	34 (*S*)	5.61
14[g]	**1** (10)	4A	Cs_2CO_3	PhMe	27	30 (*S*)	12.81
15[h]	**1** (10)	4A	Cs_2CO_3	PhMe	61	83 (*S*)	8.03
16	**2** (10)	3A	Cs_2CO_3	PhMe	67	93 (*S*)	8.35
17	**2** (10)	4A	Cs_2CO_3	PhMe	63	88 (*S*)	8.58
18	**2** (10)	5A	Cs_2CO_3	PhMe	65	87 (*S*)	7.29

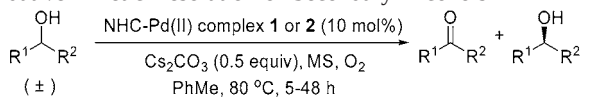
[a] 1.0 atm of O_2, 0.1 M substrate concentration in PhMe. [b] Measured by GC. [c] Measured by chiral HPLC. Some of ee could not be analyzed due to that the conversions are too low. [d] Determined by comparison of the sign of optical rotation to literature values. [e] $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$. [f] Not determined. [g] The reaction was conducted at 60 °C. [h] The reaction was conducted at 100 °C.

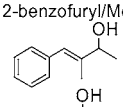
entries 6, 7, 10, 16−18).[14] As a consequence, the reason for this combination of **1** with 4 Å and **2** with 3 Å MS gave better results, although the reason for this remains obscure.

With the optimized conditions in hand, we next investigated the substrate scope of this process. The results are summarized in Table 4. It can be seen from Table 4 that a broad range of substrates can be used in this oxidative kinetic resolution, with 60−82% conversion and 63−99.7% ee (>99% ee) (k_{rel} = 3.83−19.80) being observed. In addition, substrates with an electron-withdrawing substituent on the aromatic ring provided better results on ee than 1-*p*-tolylethanol and 1-*p*-methoxyphenylethanol, with 60−75% conversion and 77−93% ee being observed (Table 4, entries 1−5, 7−10). Under identical conditions, complex **2** gave the better results on ee in the presence of molecular sieves 3 Å to produce the corresponding optically active secondary alcohols in 77−99.7% ee (>99% ee) with 61−82% conversion along with k_{rel} = 5.52−19.80, presumably due to its steric bulkiness and the flexibility of backbone skeleton. Moreover, it is noteworthy that, compared to NHC complex **1**, complex **2** generally gave faster resolution rates for the substrates with an electron-withdrawing substituent on the aromatic ring, and thus higher ees and higher conversions can be achieved within shorter reaction times (Table 4, entries 1−4, 12, 13). When the reaction time was prolonged to 24

(14) For the role of molecular sieves in Pd-catalyzed aerobic alcohol oxidation, see: Steinhoff, B. A.; King, A. E.; Stahl, S. S. *J. Org. Chem.* **2006**, *71*, 1861−1868.

Table 4. Axially Chiral NHC−Pd(II) Complexes Catalyzed Oxidative Kinetic Resolution of Secondary Alcohols



entry[a]	substrate (R^1/R^2)	complex	MS	time (h)	conv.[b] (%)	ee[c] (config.)[d] (%)	k_{rel}[e]
1	*p*-FC_6H_4/Me	**1**	4A	48	75	86 (*S*)	4.38
2	*p*-FC_6H_4/Me	**2**	3A	5	69	93 (*S*)	7.46
3	*p*-ClC_6H_4/Me	**1**	4A	48	64	77 (*S*)	5.53
4	*p*-ClC_6H_4/Me	**2**	3A	5	64	66 (*S*)	4.08
5	*p*-ClC_6H_4/Me	**2**	3A	7	69	85 (*S*)	5.52
6	*p*-ClC_6H_4/Me	**2**	3A	24	82	98 (*S*)	5.96
7	*p*-BrC_6H_4/Me	**1**	4A	48	60	80 (*S*)	7.69
8	*p*-BrC_6H_4/Me	**2**	3A	48	68	93 (*S*)	7.88
9	*p*-MeC_6H_4/Me	**2**	3A	36	68	73 (S)	4.14
10	*p*-$MeOC_6H_4$/Me	**2**	3A	7	63	89 (*S*)	8.95
11	*p*-BrC_6H_4/Et	**2**	3A	24	73	85 (S)	4.62
12	*m*-FC_6H_4/Me	**1**	4A	48	65	85 (*S*)	6.78
13	*m*-FC_6H_4/Me	**2**	3A	5	61	87 (*S*)	9.45
14	*m*-FC_6H_4/Et	**2**	3A	6	63	69 (*S*)	4.61
15	*m*-FC_6H_4/Bu	**2**	3A	48	66	72 (*S*)	4.38
16	*m*-MeC_6H_4/Me	**2**	3A	14	67	89 (*S*)	7.02
17	1-naphthyl/Me	**2**	3A	48	70	73 (*S*)	3.83
18	2-naphthyl/Me	**2**	3A	6	70	94 (*S*)	7.42
19	2-benzofuryl/Me	**2**	3A	48	62	63 (*S*)	4.10
20		**1**	4A	7	66	77 (*S*)	5.02
21		**2**	3A	5	64	77 (*S*)	5.53
22		**1**	4A	7	68	>99 (*S*)	15.52
23		**2**	3A	7	64	>99 (*S*)	19.80

[a] 1.0 atm of O_2, 0.1 M substrate concentration in PhMe. [b] Measured by GC. [c] Measured by chiral HPLC. [d] Determined by comparison of the sign of optical rotation to literature values. [e] $k_{rel} = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$.

h, up to 98% ee could be obtained, with 82% conversion (k_{rel} = 5.96) of 1-(4-chlorophenyl)ethanol in the presence of complex **2** (Table 2, entry 6). Upon increasing the size of the R^2 group, a decrease in the k_{rel} was observed (Table 4, entries 8, 11, 13−15). As for naphthyl, heteroaromatic, and alkenyl substrates, moderate to good enantioselectivities were also realized under the standard conditions (Table 4, entries 17−21). In general, moderate k_{rel} values from 3.83 to 9.45 were obtained with these chiral NHC−Pd(II) complexes **1** and **2**. To our delight, 1,2,3,4-tetrahydronaphthalen-1-ol gave promising resolution results, with selectivity factors of 15.52 and 19.80 in the presence of complexes **1** and **2**, respectively (Table 4, entries 22 and 23).

On a preparative scale of 1-phenylethanol (1.0 g) with complex **2** as a catalyst, the alcohol was isolated in 30% yield with 91% ee along with acetophenone in 60% yield in the presence of molecular sieves 3 Å within 48 h.

In conclusion, we have developed effective chiral NHC−Pd(II) complex systems for the oxidative kinetic resolution of secondary alcohols using molecular oxygen as a terminal oxidant. The resolution employs a chiral NHC−Pd(II) complex as catalyst in conjunction with an inorganic base. Compared to (−)-sparteine/Pd(II) system, the catalyst system enables us to get *sec*-alcohols of different configuration readily through modulating the configuration of NHC−Pd-(II) complex. Efforts to elucidate the mechanistic details of this catalytic system and to further optimize the structure of catalyst are currently in progress.

Acknowledgment. We thank the Shanghai Municipal Committee of Science and Technology (04JC14083, 06XD14005), Chinese Academy of Sciences (KGCX2-210-01), and the National Natural Science Foundation of China for financial support (20472096, 203900502, and 20672127) and the Cheung Kong Scholar program.

Supporting Information Available: Experimental details and characterization data, chiral HPLC, and X-ray crystallographic files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL063061W