ORGANIC LETTERS

2010
Vol. 12, No. 24
5716−5719

Highly Enantioselective Alkynylation of Trifluoropyruvate with Alkynylsilanes Catalyzed by the BINAP−Pd Complex: Access to α-Trifluoromethyl-Substituted Tertiary Alcohols

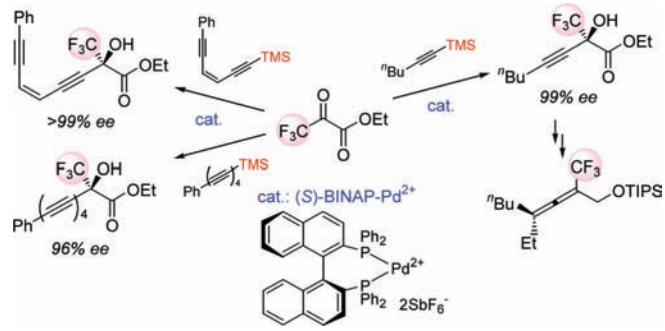
Kohsuke Aikawa, Yūta Hioki, and Koichi Mikami*

Department of Applied Chemistry, Tokyo Institute of Technology, Tokyo 152-8552, Japan

mikami.k.ab@m.titech.ac.jp

Received October 20, 2010

ABSTRACT



A highly enantioselective alkynylation catalyzed by the dicationic (*S*)-BINAP−Pd complex with a variety of alkynylsilanes and trifluoropyruvate is described. The catalytic reaction is applicable to highly enantioselective addition of polyyne to trifluoropyruvate to construct α-trifluoromethyl-substituted tertiary alcohols as enantiomerically enriched forms. The alkynyl products can be converted into a chiral allene bearing a trifluoromethyl group.

Organofluorine compounds have currently attracted widespread interest in the fields of biological and material sciences. Therefore, the development of a novel method to efficiently introduce the fluorine unit is strongly desired in modern organic synthesis.[1] Especially, the synthesis of optically active α-trifluoromethyl-substituted secondary and tertiary alcohols has received much attention due to their unique properties with unusual biological activities as drugs and its candidates, such as Efavirenz (anti-HIV agents),[2a] CF_3 analogues of MMPs inhibitors[2b] and DHA (antimalarial agents),[2c] a nonsteroidal

(1) (a) Ojima, I.; McCarthy, J. R.; Welch, J. T., Eds. *Biomedical Frontiers of Fluorine Chemistry*; American Chemical Society: Washington DC, 1996. (b) Chambers, R. D., Ed. *Organofluorine Chemistry*; Springer: Berlin, 1997. (c) Soloshonok, V. A., Ed. *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Wiely: Chichester, 1999. (d) Hiyama, T.; Kanie, K.; Kusumoto, T, Morizawa, Y.; Shimizu, M., Eds. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000. (e) Uneyama, K., Ed. *Organofluorine Chemistry*; Wiely-Blackwell: Oxford, 2006. (f) Begue, J.-P.; Bonnet-Delpon, D., Eds. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, 2008.

(2) (a) Corbett, J. W.; Ko, S. S.; Rodgers, J. M.; Gearhart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Logue, K.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. *J. Med. Chem.* **2000**, *43*, 2019. (b) Sani, M.; Belotti, D.; Giavazzi, R.; Panzeri, W.; Volonterio, A.; Zanda, M. *Tetrahedron Lett.* **2004**, *45*, 1611. (c) Magueur, G.; Crousse, B.; Charneau, S.; Grellier, P.; Bégué, J.-P.; Bonnet-Delpon, D. *J. Med. Chem.* **2004**, *47*, 2694. (d) Schäcke, H.; Schottelius, A.; Döcke, W.-D.; Strehlke, P.; Jaroch, S.; Schmees, N.; Rehwinkel, H.; Hennekes, H.; Asadullah, K. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 227. (e) Betageri, R.; Zhang, Y.; Zindell, R. M.; Kuzmich, D.; Kirrane, T. M.; Bentzien, J.; Cardozo, M.; Capolino, A. J.; Fadra, T. N.; Nelson, R. M.; Paw, Z.; Shih, D.-T.; Shih, C.-K.; Zuvela-Jelaska, L.; Nabozny, G.; Thomson, D. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4761. (f) Moseley, J. D.; Brown, D.; Firkin, C. R.; Jenkin, S. L.; Patel, B.; Snape, E. W. *Org. Process Res. Dev.* **2008**, *12*, 1044.

10.1021/ol102541s
Published on Web 11/16/2010

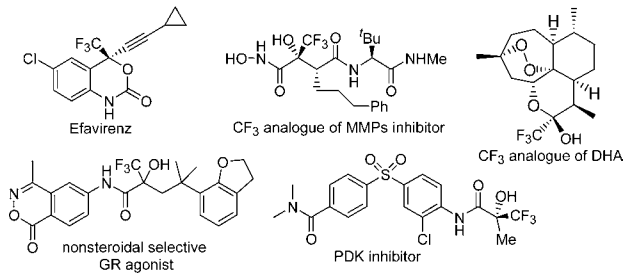
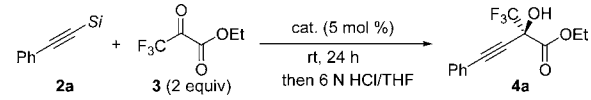


Figure 1. Biologically active compounds bearing chiral α-trifluoromethyl-substituted tertiary alcohols.

selective GR agonist (ZK216348),[2d,e] and a PDK inhibitor (AZD7545)[2f] (Figure 1).

There are two general strategies for synthesizing enantiomerically enriched α-trifluoromethyl-substituted alcohols: one is the direct addition of the trifluoromethyl group to carbonyl compounds using the Ruppert−Prakash reagent, CF_3SiMe_3.[3] Some successes of the catalytic asymmetric reaction have been reported, but the high enantioselectivity and substrate generality have not been established yet.[4] On the other hand, the building block methods using trifluoromethyl carbonyl compounds in particular can be expected to provide excellent yield and enantioselectivity by appropriate chiral Lewis acid catalysts. However, only catalytic asymmetric ene,[5] aldol,[6] Friedel−Crafts,[7] and enamine-trifluoropyruvate condensation−cyclization reaction[8] with trifluoropyruvate, which is one of the most versatile commercially available reagents, have been reported so far. Since other transformations of trifluoropyruvate remain unexplored, the exploitation of novel catalytic asymmetric syntheses of α-trifluoromethyl-substituted tertiary alcohols has been required. Herein, we report the highly enantioselective alkynylation of trifluoropyruvate with alkynylsilanes as nucleophiles by the Lewis acidic Pd catalyst.[9,10] A variety of catalytic enantioselective alkynylations of not only carbonyls but also imines with terminal alkynes have been reported to provide the excellent enantioselectivities.[11] However, all the alkynylations previously reported proceed via in situ generation of metal acetylides as reactive nucleophiles and, hence, can not be applied for the polyyne system.[12,13]

Table 1. Catalytic Enantioselective Alkynylation with Alkynylsilane **2a** and Trifluoropyruvate **3** by Chiral Lewis Acid Catalysts



entry	cat.	Si	solvent	yield (%)[b]	ee (%)[c]
1	**1**	$SiMe_3$	CH_2Cl_2	85	99
2	(*S*)-SEGPHOS−Pd	$SiMe_3$	CH_2Cl_2	82	99
3	(*S*)-DTBM−SEGPHOS−Pd	$SiMe_3$	CH_2Cl_2	61	82
4	(*S*)-BINAP−Pt	$SiMe_3$	CH_2Cl_2	69	78
5	(*S*,*S*)-Box−Cu	$SiMe_3$	Et_2O	0	−
6	(*S*,*S*)-Pybox−Sc	$SiMe_3$	CH_2Cl_2	14	23
7	**1**	$SiMe_3$	$CHCl_3$	79	99
8	**1**	$SiMe_3$	Et_2O	22	98
9	**1**	$SiMe_3$	toluene	32	99
10	**1**	$SiMe_2Ph$	CH_2Cl_2	61	97
11	**1**	$SiMe_2tBu$	CH_2Cl_2	40	73
12	**1**	$Si(OEt)_3$	CH_2Cl_2	31	21
13[a]	**1**	$SiMe_3$	CH_2Cl_2	64	99

[a] Reaction was examined with 2 mol % of catalyst. [b] Isolated yield. [c] Enantiopurity was determined by chiral GC analysis.

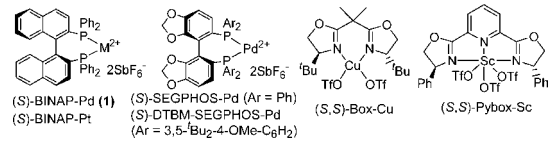


Table 1 outlines the preliminary experiments to show the feasibility of the present alkynylation of trifluoropyruvate **3** with alkynylsilane **2a** using various chiral Lewis acid catalysts.[14] After evaluation of atropisomeric diphosphine ligands, the chiral cationic Pd complex (**1**)[5a,g,14b] bearing (*S*)-BINAP was identified as the best catalyst providing high yield and enantioselectivity (entries 1 vs 2 and 3). The use of not only

(3) (a) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195. (b) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393.

(4) For a recent review, see: (a) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975. (b) Billard, T.; Langlois, B. R. *Eur. J. Org. Chem.* **2007**, 891. (c) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633. (d) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1.

(5) For catalytic asymmetric ene reactions using trifluoropyruvate, see: (a) Aikawa, K.; Kainuma, S.; Hatano, M.; Mikami, K. *Tetrahedron Lett.* **2004**, *45*, 183. (b) Mikami, K.; Kakuno, H.; Aikawa, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7257. (c) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *J. Org. Chem.* **2006**, *71*, 9751. (d) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Organometallics* **2007**, *26*, 5961. (e) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Organometallics* **2007**, *26*, 6453. (f) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Org. Lett.* **2007**, *9*, 4925. (g) Mikami, K.; Kawakami, Y.; Akiyama, K.; Aikawa, K. *J. Am. Chem. Soc.* **2007**, *129*, 12950. (h) Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6798. (i) Zhao, J.-F.; Tjan, T.-B. W.; Tan, B.-H.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 5714.

(6) For catalytic asymmetric aldol-type reactions using trifluoropyruvate, see: (a) Bogevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620. (b) Gathergood, N.; Juhl, K.; Poulsen, T. B.; Thordrup, K.; Jørgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 1077. (c) Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712. (d) Suri, J. T.; Mitsumori, S.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III *J. Org. Chem.* **2006**, *71*, 3822. (e) Ogawa, S.; Shibata, N.; Inagaki, J.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8666. (f) Landge, S. M.; Török, B. *Catal. Lett.* **2009**, *131*, 432.

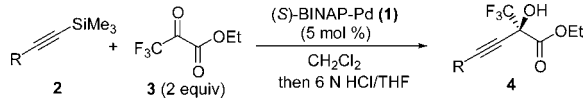
(7) For catalytic asymmetric Friedel−Crafts reactions using trifluoropyruvate, see: (a) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517. (b) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009. (c) Corma, A.; García, H.; Moussaif, A.; Sabater, M. J.; Zniber, R.; Redouane, A. *Chem. Commun.* **2002**, 1058. (d) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 901. (e) Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086. (f) Zhuang, W.; Poulsen, T. B.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3284. (g) Zhao, J.-L.; Liu, L.; Sui, Y.; Liu, Y.-L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2006**, *8*, 6127. (h) Dong, H.-M.; Lu, H.-H.; Lu, L.-Q.; Chen, C.-B.; Xiao, W.-J. *Adv. Synth. Catal.* **2007**, *349*, 1597. (i) Zhao, J.-L.; Liu, L.; Gu, C.-L.; Wang, D.; Chen, Y.-J. *Tetrahedron Lett.* **2008**, *49*, 1476. (j) Nakamura, S.; Hyodo, K.; Nakamura, Y.; Shibata, N. *Adv. Synth. Catal.* **2008**, *350*, 1443. (k) Nie, J.; Zhang, G.-W.; Wang, L.; Zheng, D.-H.; Zheng, Y.; Ma, J.-A. *Eur. J. Org. Chem.* **2009**, 3145. (l) Kashikura, W.; Itoh, J.; Mori, K.; Akiyama, T. *Chem. Asian J.* **2010**, *5*, 470.

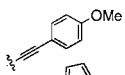
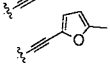
(8) Ogawa, S.; Iida, N.; Tokunaga, E.; Shiro, M.; Shibata, N. *Chem.—Eur. J.* **2010**, *16*, 7090.

BINAP−Pt but also Box−Cu and Pybox−Sc, which are often used as chiral Lewis acid catalysts, gave lower catalytic activity and enantioselectivity (entries 1 vs 4−6). Chloroform gave a similar result, but diethyl ether and toluene led to a decrease in both yields and enantioselectivities because of low solubility of the catalyst (entries 1 vs 7−9). The use of sterically more demanding $SiMe_2Ph$ and $SiMe_2{}^tBu$ and the more electron-rich $Si(OEt)_3$ substituent resulted in a decrease of yields and enantioselectivities (entries 10−12). The catalyst loading could be reduced to 2 mol % to obtain **4a** with an equally high level of enantioselectivity in a decreasing yield (entry 13). The absolute configuration of the product **4a** was determined to be *R* by X-ray crystallographic analysis.[15]

Under the optimized conditions, the **1**-catalyzed reactions of **3** and various alkynylsilanes **2** bearing TMS were investigated (Table 2). We were encouraged to find that low

Table 2. Catalytic Enantioselective Alkynylation with Various Alkynylsilanes **2b−o** and **3** under the Optimized Conditions



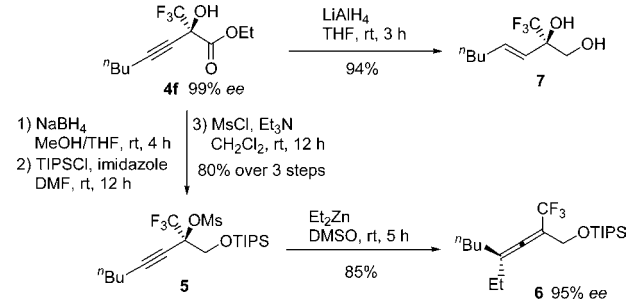
entry	R		t (°C)	time (h)	yield (%)[d]	*ee* (%)[f]
1		(**b**)	rt	35	70	98
2		(**c**)	rt	24	86	98
3		(**d**)	0	12	63	99
4		(**e**)	-40	30	69	>99
5		(**f**)	rt	48	70	99
6[a]		(**g**)	rt	12	63[e]	95
7		(**h**)	rt	24	94	>99
8[b]		(**i**)	50	24	75	90
9[b,c]		(**j**)	70	48	42[e]	94
10		(**k**)	-20	12	53	97
11		(**l**)	-20	12	92	>99
12		(**m**)	0	24	83	91
13		(**n**)	0	24	64	99
14		(**o**)	0	12	83[e]	99

[a] (*S*)-DTBM−SEGPHOS was used instead of (*S*)-BINAP. [b] Dichloroethane was used as a solvent. [c] 10 mol % of catalyst was used. [d] Isolated yield. [e] NMR yield. [f] Enantiopurity was determined by chiral HPLC or GC analysis.

reactive **2b** with an electron-withdrawing CF_3 substituent provided a good yield of the desired alkynylation product in high enantioselectivity (entry 2). Using more reactive **2c**,**d** also gave the high level of enantioselectivity (entries 3−4). The reaction occurred in a highly enantioselective fashion with various alkynylsilanes **2e−j** bearing aliphatic substituents (entries 4−9). Especially, **2e** and **2h** provided almost complete enantioselectivity (entries 4 and 7). The use of **2j** required the elevated reaction temperature probably due to the coordination of palladium to propargyl ether (entry 9). We also investigated the reaction with enyne, endiyne, and diyne to provide satisfactory levels of enantiocontrol (91→>99% ee) (entries 10−14).

The alkynyl products bearing central chirality can be converted into the optically active trifluoromethyl-substituted allenes bearing an axial chirality (Scheme 1). For example,

Scheme 1. Syntheses of Optically Active Allene **6** and *E*-Allyl Alcohol **7** Bearing a Trifluoromethyl Group



treatment of the product **4f** (99% ee) with $NaBH_4$ followed by silylation and mesylation of primary and secondary alcohols gave an 80% yield of **5** in three steps. The product **5** was transformed to the corresponding allene **6** (95% ee) by using Et_2Zn reagent in DMSO.[16] The reaction of 4 equiv of $LiAlH_4$ with **4f** produced *E*-allyl alcohol **7** in a 94% yield.

With these successes in terms of the wide scope of alkynyl substrates, we attempted catalytic enantioselective addition of polyyne to trifluoropyruvate **3** (Scheme 2). Alkynylation using nucleophiles **2p** or **2q** bearing two or three trimethylsilyl acetylene units on a benzene ring gave the single diastereomer **4p** or **4q** with almost complete enantioselectivity (eqs 1 and 2). Significantly, tetrayne **2r**, which is capped at the terminus by trimethylsilyl and phenyl groups, afforded the corresponding product **4r** with high enantioselectivity despite lower catalytic activity, probably due to the coordination of palladium to the tetrayne portion (61%, 96%

(9) Catalytic enantioselective alkynylation of trifluoromethyl ketones and trifluoromethyl pyruvate: (a) Motoki, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 2997. (b) Nishiyama, H.; Ito, J. *Chem. Commun.* **2010**, *46*, 203.

(10) Only one example of enantioselective additions with alkynylsilanes using the Pybox−Sc complex as chiral Lewis acid catalysts was reported: Evans, D. A.; Aye, Y. *J. Am. Chem. Soc.* **2006**, *128*, 11034.

(11) For review, see: (a) Lu, G.; Li, Y.-M.; Li, X.-S.; Chan, A. S. C. *Coord. Chem. Rev.* **2005**, *249*, 1736. (b) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. (c) de Armas, P.; Tejedor, D.; García-Tellado, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1013.

(12) Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813.

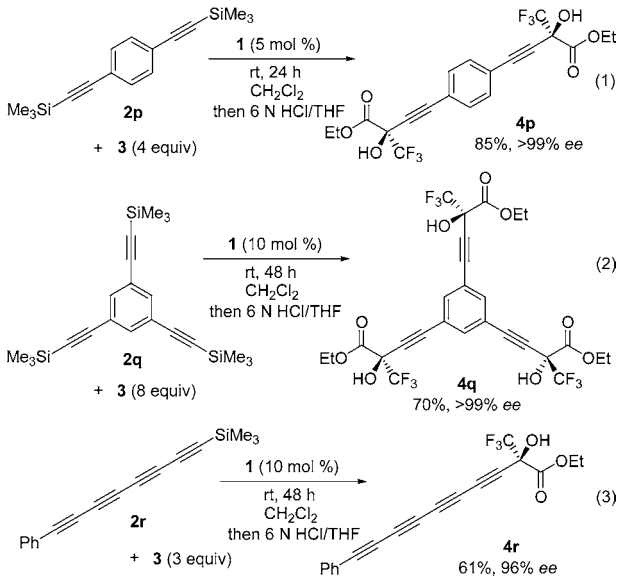
(13) For catalytic enantioselective addition of 1,3-diynes to aldehyde, see: Trost, B. M.; Chan, V. S.; Yamamoto, D. *J. Am. Chem. Soc.* **2010**, *132*, 5522.

(14) (a) Long, M. J. C.; Aye, Y. *Chem.—Eur. J.* **2009**, *15*, 5402. (b) Aikawa, K.; Hioki, Y.; Mikami, K. *J. Am. Chem. Soc.* **2009**, *131*, 13922.

(15) See Supporting Information.

(16) Kobayashi, K.; Naka, H.; Wheatley, A. E. H.; Kondo, Y. *Org. Lett.* **2008**, *10*, 3375.

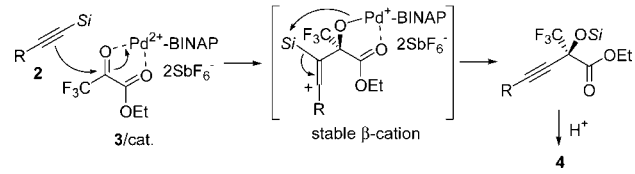
Scheme 2. Catalytic Enantioselective Addition of Polyyne



ee) (eq 3). To the best of our knowledge, there is no report describing catalytic enantioselective addition of polyyne as a nucleophile to carbonyl compounds, except for diyne.

As a proposed reaction mechanism, the attack of alkynylsilane **2** to trifluoropyruvate **3** through the coordination of chiral Lewis acid catalyst (*S*)-BINAP−Pd (**3**/cat.) followed by the intramolecular transfer of the silyl group and desilylation upon acidic workup provide the corresponding product **4** (Scheme 3). Indeed, the alkynyl−palladium

Scheme 3. Plausible Reaction Mechanism



complex via transmetalation was not observed in ^{1}H and ^{31}P NMR spectroscopic analyses in CD_2Cl_2 by the combination of alkynylsilane **2a** with a stoichiometric (*S*)-BINAP−Pd (**1**).

In summary, we have developed a highly enantioselective catalytic alkynylation with trifluoropyruvate and alkynylsilanes using chiral dicationic Pd complex **1**. Compared to the previous alkynylations with terminal alkynes via the metal acetylides, this catalytic reaction can also be applied to enantioselective addition of polyynes to the carbonyl group. Further investigations using a variety of electrophiles are currently in progress.

Acknowledgment. We are grateful to Takasago International Co. for providing BINAP and SEGPHOS derivatives. This research was supported in part by a grant program "Collaborative Development of Innovative Seeds" from the Japan Science and Technology Agency.

Supporting Information Available: Experimental procedures, compound characterization data, and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102541S