ORGANIC LETTERS

2008
Vol. 10, No. 13
2849−2852

Practical Enantioselective Synthesis of Axially Chiral Biaryl Diphosphonates and Dicarboxylates by Cationic Rhodium(I)/Segphos-Catalyzed Double [2 + 2 + 2] Cycloaddition

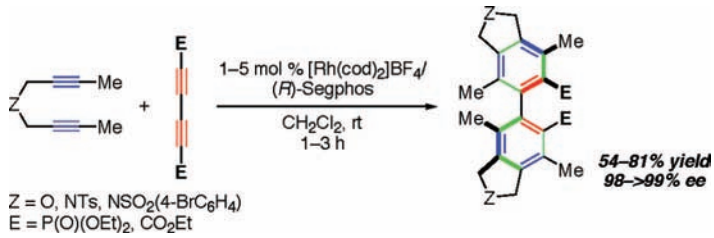
Goushi Nishida,[†] Shuichiro Ogaki,[†] Yukinori Yusa,[‡] Tohru Yokozawa,[‡] Keiichi Noguchi,[§] and Ken Tanaka*,[†]

Department of Applied Chemistry, Graduate School of Engineering, and Instrumentation Analysis Center, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan, and Takasago International Corporation, Corporate Research & Development Division, 1-4-11 Nishi-yawata, Hiratsuka, Kanagawa 254-0073, Japan

tanaka-k@cc.tuat.ac.jp

Received May 2, 2008

ABSTRACT



A cationic rhodium(I)/Segphos complex catalyzes a [2 + 2 + 2] cycloaddition of internal 1,6-diynes with a phosphonate- or ester-substituted 1,3-butadiyne leading to C_2-symmetric axially chiral biaryl diphosphonates or dicarboxylates, respectively, in high yields with outstanding ee's. The use of a phosphonate- or ester-substituted 1,3-butadiyne as a cycloaddition partner and Segphos as a ligand is crucial for the success of this transformation.

C_2-Symmetric axially chiral biaryls bearing phosphorus- and/or oxygen-containing substituents at the 2- and 2′-positions are valuable structures for a number of chiral reagents.[1,2] A conventional approach to their synthesis is based on various types of cross-coupling reactions to construct biaryl skeletons and introduce phosphorus and/or oxygen-containing substituents.[3] On the other hand, transition-metal-catalyzed enantioselective [2 + 2 + 2] cycloadditions[4] have been demonstrated as a powerful tool for the synthesis of axially chiral biaryls.[5−7] Among them, cationic rhodium(I)/BINAP-type bisphosphine complex-catalyzed enantioselective [2 + 2 +

[†] Department of Applied Chemistry (TUAT).
[‡] Takasago International Corporation.
[§] Instrumentation Analysis Center (TUAT).

(1) For the use of axially chiral biaryl phosphorus compounds as chiral ligands, see: (a) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405. (b) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354.

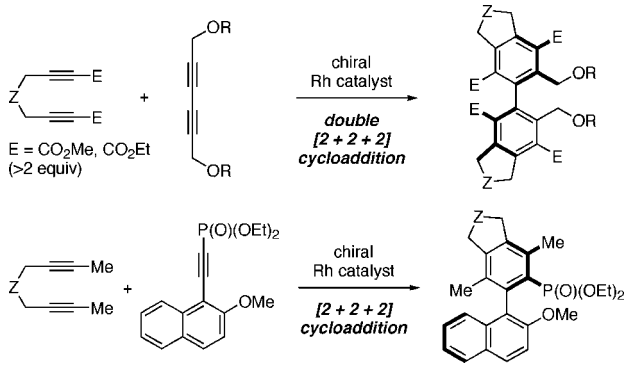
(2) For the use of axially chiral biaryl carboxylates for the preparation of chiral ligands and organocatalysts, see: (a) Khanbabaee, K.; Basceken, S.; Flörke, U. *Tetrahedron: Asymmetry* **2006**, *17*, 2804. (b) Hocke, H.; Uozumi, Y. *Tetrahedron* **2003**, *59*, 619. (c) Puglisi, A.; Benaglia, M.; Annunziata, R.; Bologna, A. *Tetrahedron Lett.* **2003**, *44*, 2947. (d) Andrus, M. B.; Asgari, D. *Tetrahedron* **2000**, *56*, 5775. (e) Maruoka, K.; Ooi, T.; Kano, T. *Chem. Commun.* **2007**, 1487. (f) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055.

(3) For recent reviews concerning atroposelective synthesis of axially chiral biaryls, see: (a) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384. (b) Wallace, T. W. *Org. Biomol. Chem.* **2006**, *4*, 3197.

10.1021/ol801013v CCC: $40.75
Published on Web 06/07/2008

2] cycloadditions, first discovered by our research group, have been most widely employed for this purpose.[8,9] We have previously reported a cationic rhodium(I)/Segphos complex-catalyzed enantioselective double [2 + 2 + 2] cycloaddition of electron-deficient internal 1,6-diynes with electron-rich internal 1,3-diynes, leading to tetra-ortho-substituted axially chiral biaryls bearing oxygen-containing substituents with excellent enantioselectivity (Scheme 1).[10,11]

Scheme 1. Our Previously Reported Enantioselective Synthesis of Tetra-Ortho-Substituted Axially Chiral Biaryls



Furthermore, we have recently reported a cationic rhodium(I)/H_8-BINAP complex-catalyzed enantioselective [2 + 2 + 2] cycloaddition of electron-rich internal 1,6-diynes with an electron-deficient phosphonate-substituted arylacetylene, leading to tetra-ortho-substituted axially chiral biaryl phosphonates with excellent enantioselectivity (Scheme 1).[12–15]

These results prompted our investigation into the reaction of phosphonate-substituted 1,3-butadiyne **2** with ether-linked internal 1,6-diyne **1a** in the presence of cationic rhodium(I)/

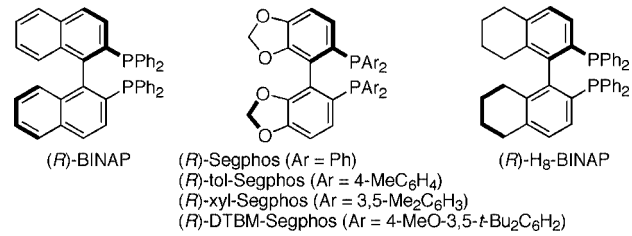


Figure 1. Structures of BINAP-type bisphosphine ligands.

BINAP-type bisphosphine complexes (Figure 1) as shown in Table 1. We first investigated the use of (*R*)-H_8-BINAP as a ligand, but the desired double-annulation product **3a** was not obtained, and monoannulation product was obtained as a sole product (entry 1).[16] Fortunately, the use of (*R*)-BINAP furnished the desired product **3a** at room temperature with excellent ee, albeit in low yield (entry 2). Significantly improved yield was obtained by using (*R*)-Segphos (entry

(4) For recent reviews of transition-metal-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. In *Organic Reactions*; Overman, L. E., Ed.; John Wiley & Sons: Hoboken, 2007; Vol. 68, p 1. (b) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (c) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209. (d) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (e) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503. (f) Robinson, J. E. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.;Wiley-VCH: Weinheim, 2005; p 129.

(5) For pioneering work on the transition-metal-catalyzed [2 + 2 + 2] cycloaddition to produce biaryls [using Ni(0) catalysts], see: (a) Sato, Y.; Ohashi, K.; Mori, M. *Tetrahedron Lett.* **1999**, *40*, 5231.

(6) For pioneering work on the transition-metal-catalyzed enantioselective [2 + 2 + 2] cycloaddition to produce axially chiral biaryls using Co(I) catalysts, see: (a) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3795. Using neutral Ir(I) catalysts, see: (b) Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, *126*, 8382. Using cationic Rh(I)/modified-BINAP catalysts: (c) Tanaka, K.; Nishida, G.; Wada, A.; Noguchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 6510.

(7) For other examples of the enantioselective synthesis of axially chiral biaryls by cationic Rh(I)/modified-BINAP-catalyzed mono-[2 + 2 + 2] cycloadditions, see: (a) Tanaka, K.; Nishida, G.; Ogino, M.; Hirano, M.; Noguchi, K. *Org. Lett.* **2005**, *7*, 3119. (b) Tanaka, K.; Suda, T.; Noguchi, K.; Hirano, M. *J. Org. Chem.* **2007**, *72*, 2243. (c) Tanaka, K.; Kamisawa, A.; Suda, T.; Noguchi, K.; Hirano, M. *J. Am. Chem. Soc.* **2007**, *129*, 12078. (d) Oppenheimer, J.; Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361.

(8) For our first discovery of the cationic Rh(I)/modified-BINAP-catalyzed [2 + 2 + 2] cycloaddition, see: (a) Tanaka, K.; Shirasaka, K. *Org. Lett.* **2003**, *5*, 4697.

(9) For pioneering work on the $RhCl(PPh_3)_3$-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1357. Application to the synthesis of arylindoles, see: (b) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426. For application to the synthesis of teraryls and oligophenylenes, see: (c) McDonald, F. E.; Smolentsev, V. *Org. Lett.* **2002**, *4*, 745. For application to the synthesis of amide-substituted chiral biaryls, see: (d) Tracey, M. R.; Oppenheimer, J.; Hsung, R. P. *J. Org. Chem.* **2006**, *71*, 8629.

(10) For the enantioselective synthesis of biaryls by cationic Rh(I)/modified-BINAP-catalyzed double [2 + 2 + 2] cycloadditions, see: (a) Nishida, G.; Suzuki, N.; Noguchi, K.; Tanaka, K. *Org. Lett.* **2006**, *8*, 3489. By neutral Ir(I) catalysts: (b) Shibata, T.; Yoshida, S.; Arai, Y.; Otsuka, M.; Endo, K. *Tetrahedron* **2008**, *64*, 821.

(11) For the synthesis of biaryls by transition-metal-catalyzed double [2 + 2 + 2] cycloadditions, see: (a) Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143. (b) Yamamoto, Y.; Hattori, K.; Nishiyama, H. *J. Am. Chem. Soc.* **2006**, *128*, 8336. (c) Yamamoto, Y.; Kinpara, K.; Ogawa, R.; Nishiyama, H.; Itoh, K. *Chem. Eur. J.* **2006**, *12*, 5618. (d) Goswami, A.; Ito, T.; Okamoto, S. *Adv. Synth. Catal.* **2007**, *349*, 2368. (e) Saino, N.; Kogure, D.; Okamoto, S. *Org. Lett.* **2005**, *7*, 3065. (f) Goswami, A.; Ohtaki, K.; Kase, K.; Ito, T.; Okamoto, S. *Adv. Synth. Catal.* **2008**, *350*, 143. (g) Varela, J. A.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **1998**, *120*, 12147. (h) Varela, J. A.; Castedo, L.; Maestro, M.; Mahía, J.; Saá, C. *Chem. Eur. J.* **2001**, *7*, 5203.

(12) For the enantioselective synthesis of phosphorus-bearing axially chiral biaryls by cationic Rh(I)/modified-BINAP-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 3951. By Co(I) catalysts: (b) Heller, B.; Gutnov, A.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Redkin, D.; Sundermann, C.; Sundermann, B. *Chem. Eur. J.* **2007**, *13*, 1117.

(13) For the enantioselective synthesis of *P*-stereogenic phosphine oxides by cationic Rh(I)/modified BINAP-catalyzed [2 + 2 + 2] cycloadditions, see: Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3410.

(14) For the synthesis of bulky arylphosphine sulfides by cationic Rh(I)/*rac*-BINAP-catalyzed [2 + 2 + 2] cycloadditions, see: (a) Kondoh, A.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 6996.

(15) For the synthesis of racemic phosphorus-containing biaryls through Diels−Alder reaction using phosphorus-containing dienophiles, see: (a) Ashburn, B. O.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6737. (b) Ashburn, B. O.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2007**, *129*, 9109.

(16) The monoannulation product, the structure of which is shown below, was generated in >80% yield, although it could not be isolated in a pure form.

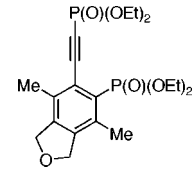
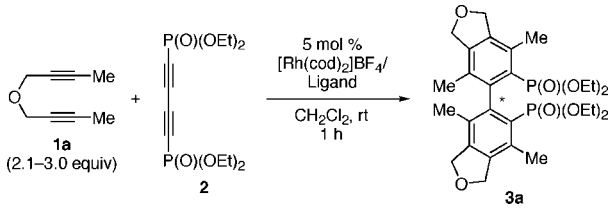


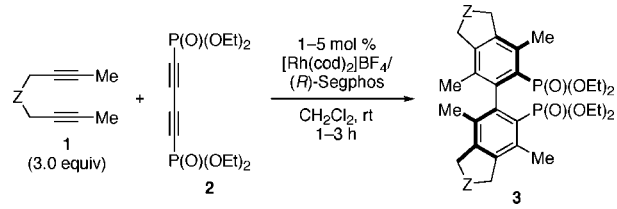
Table 1. Screening of Reaction Conditions for Rh-Catalyzed Enantioselective Double [2 + 2 + 2] Cycloaddition of 1,6-Diyne **1a** with 1,3-Diyne **2**[a]



entry	ligand	**1a** (equiv)	yield[b] (%)	ee (%)
1	(*R*)-H_8-BINAP	2.1	0	
2	(*R*)-H_8-BINAP	2.1	23	>99 (−)
3	(*R*)-Segphos	2.1	40	>99 (−)
4	(*R*)-tol-Segphos	2.1	0	
5	(*R*)-xyl-Segphos	2.1	0	
6	(*R*)-DTBM-Segphos	2.1	0	
7	(*R*)-Segphos	3.0	65	>99 (−)

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol, 5 mol %), ligand (0.010 mmol, 5 mol %), **1a** (0.42−0.60 mmol, 2.1−3.0 equiv), **2** (0.20 mmol), and CH_2Cl_2 (2.0 mL) were used. [b] Isolated yield.

Table 2. $Rh(I)^+$/(*R*)-Segphos-Catalyzed Enantioselective Double [2 + 2 + 2] Cycloaddition of 1,6-Diynes **1a−c** with 1,3-Diyne **2**[a]



entry	**1** (Z)	catalyst (mol %)	time (h)	**3**	yield[b] (%)	ee (%)
1	**1a** (O)	5	1	(−)-**3a**	65	>99
2[c]	**1a** (O)	5	1	(+)-**3a**	59	>99
3[d]	**1a** (O)	1	3	(−)-**3a**	67	>99
4	**1b** (NTs)	5	1	(−)-**3b**	74	>99
5	**1c** [$(NSO_2(4\text{-}BrC_6H_4)$]	5	3	(*R*)-(−)-**3c**	81	>99

[a] $[Rh(cod)_2]BF_4$ (0.010 mmol, 5 mol %), ligand (0.010 mmol, 5 mol %), **1a−c** (0.60 mmol, 3.0 equiv), **2** (0.20 mmol), and CH_2Cl_2 (2.0 mL) were used [b] Isolated yield. [c] Ligand: (*S*)-Segphos. [d] $[Rh(cod)_2]BF_4$ (0.010 mmol, 1 mol %), ligand (0.010 mmol, 1 mol %), **1a** (3.00 mmol, 3.0 equiv), **2** (1.00 mmol), and CH_2Cl_2 (5.0 mL) were used.

3). Although modified-Segphos ligands (tol-Segphos, xyl-Segphos, and DTBM-Segphos) were also examined, **3a** was not obtained at all (entries 4−6). Increasing the amount of **1a** (3.0 equiv) further improved the yield of **3a** (entry 7). In the course of this study, Doherty and co-workers reported a double [2 + 2 + 2] cycloaddition of 1,4-bis(diphenylphosphinoyl)buta-1,3-diyne with terminal 1,6-diynes in the presence of a cationic rhodium(I)/*rac*-BINAP complex (10 mol %) leading to achiral biaryl diphosphine oxides, but they failed to achieve an asymmetric variant of this reaction using an internal 1,6-diyne.[17] We also examined the reaction of 1,4-bis(diphenylphosphinoyl)buta-1,3-diyne with internal 1,6-diyne **1a**, but the desired double-annulation product was not obtained at all even in the presence of the cationic rhodium(I)/(*R*)-Segphos complex as a catalyst.[18] Accordingly, the use of phosphonate-substituted 1,3-butadiyne **2** is crucial for the success of this double annulation.

The scope of the present enantioselective double [2 + 2 + 2] cycloaddition was then examined with respect to both cycloaddition partners at room temperature in the presence of the cationic rhodium(I)/(*R*)-Segphos complex (Table 2). Not only ether-linked 1,6-diyne **1a** (entry 1) but also sulfonamide-linked 1,6-diynes **1b** and **1c** were suitable substrates for this reaction (entries 4 and 5). The 4-bromophenyl group of **1c** was unchanged under the present reaction conditions (entry 5). The use of (*S*)-Segphos as a ligand furnished the alternative enantiomer with the same yield and ee as those in entry 1 (entry 2). Furthermore, the catalytic activity of this rhodium catalyst is very high so that the reaction could be carried out even with 1 mol % of the catalyst (entry 3). The absolute configuration of the axially chiral biaryl diphosphonate (−)-**3c** was determined to be *R* by the anomalous dispersion method (Figure 2).

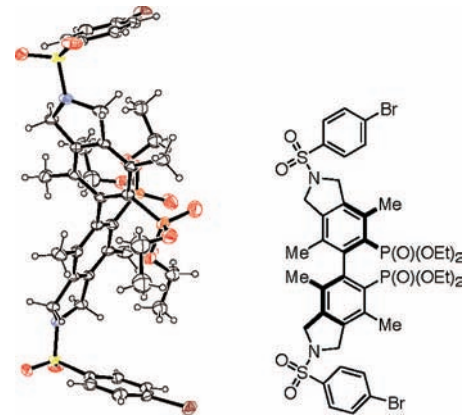


Figure 2. ORTEP diagram of (*R*)-(−)-**3c**.

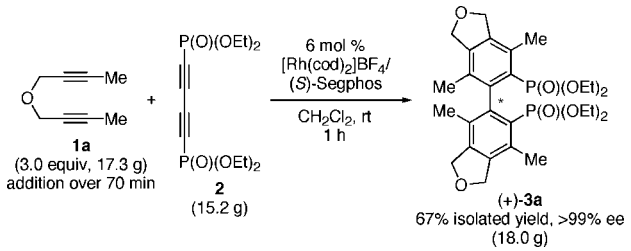
The practicality of the present enantioselective double [2 + 2 + 2] cycloaddition was demonstrated in a large-scale reaction (Scheme 2). To a CH_2Cl_2 solution of 1,3-diyne **2** (15.2 g) and the rhodium catalyst (6 mol %) was added a CH_2Cl_2 solution of 1,6-diyne **1a** (17.3 g) at room temperature over 70 min to give axially chiral biaryl diphosphonate (+)-**3a** (18.0 g) with almost identical yield and ee as those in entry 1.[19]

(17) Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Org. Lett.* **2007**, *9*, 4925.

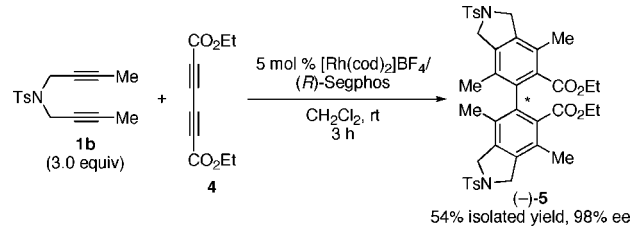
(18) The unsuccessful cycloaddition of the diphenylphosphinoyl-substituted 1,3-butadiyne with an internal 1,6-diyne is presumably due to its larger steric hindrance and its lower coordination ability to the cationic rhodium than those of a phosphonate-substituted 1,3-butadiyne.

(19) As the reaction is exothermic, a solution of **1a** was added dropwise over 70 min to a solution of **2** and the rhodium catalyst.

Scheme 2. Large-Scale Enantioselective Synthesis of Axially Chiral Biaryl Diphosphonate (+)-**3a**



Scheme 3. Enantioselective Synthesis of Axially Chiral Biaryl Dicarboxylate (−)-**5**



The present protocol was further applied to the enantioselective synthesis of a C_2-symmetric axially chiral biaryl dicarboxylate, which can be used as a useful chiral building block for various chiral reagents.[2] We were pleased to find that the reaction of 1,6-diyne **1b** with ester-substituted 1,3-butadiyne **4** in the presence of the cationic rhodium(I)/(*R*)-Segphos complex proceeded at room temperature to give the desired double-annulation product (−)-**5** in moderate yield with excellent enantioselectivity (Scheme 3).[20]

In conclusion, we have determined that a cationic rhodium(I)/Segphos complex catalyzes a [2 + 2 + 2] cycloaddition of internal 1,6-diynes with a phosphonate-substituted 1,3-butadiyne, leading to C_2-symmetric axially chiral biaryl diphosphonates in high yields with outstanding ee's (>99% ee). A C_2-symmetric axially chiral biaryl dicarboxylate was also successfully synthesized by the same protocol. The use of phosphonate- or ester-substituted 1,3-butadiyne as a cycloaddition partner and Segphos as a ligand is crucial for the success of this transformation. Further studies directed toward expanding the scope, derivatization of these new functionalized biaryls to various chiral reagents, and their application to the asymmetric catalysis are in progress.

(20) For the synthesis of an achiral bipyridine by a Co(I)-catalyzed double [2 + 2 + 2] cycloaddition of an ester-substituted 1,3-butadiyne with a cyanoalkyne, see ref 11g, h.

Acknowledgment. This work was supported partly by a Grant-in-Aid for Scientific Research (Nos. 19350046, 19•8995, and 20675002) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures, compound characterization data, and an X-ray crystallographic information file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL801013V