ORGANIC LETTERS

2011
Vol. 13, No. 23
6312–6315

General Approach to Allenes through Copper-Catalyzed γ-Selective and Stereospecific Coupling between Propargylic Phosphates and Alkylboranes

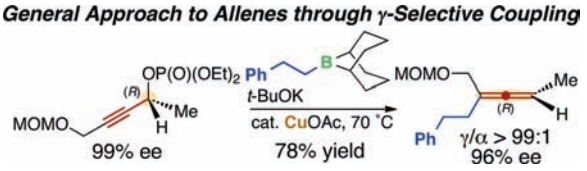
Hirohisa Ohmiya,* Umi Yokobori, Yusuke Makida, and Masaya Sawamura*

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

ohmiya@sci.hokudai.ac.jp; sawamura@sci.hokudai.ac.jp

Received October 24, 2011

ABSTRACT



Copper-catalyzed γ-selective coupling between propargylic phosphates and alkylboron compounds (alkyl-9-BBN, prepared by hydroboration of alkenes with 9-BBN-H) affords multisubstituted allenes with various functional groups. The reaction of enantioenriched propargylic phosphates to give axially chiral allenes proceeds with excellent point-to-axial chirality transfer with 1,3-*anti* stereochemistry.

Allenes have gained increasing attention in organic synthesis as important building blocks possessing unique reactivities due to the presence of orthogonal consecutive π-bonds.[1,2] In addition, they are found in many natural products.[3] Among the diverse methods for accessing allenes,[4] the γ-substitution (formal S_N2' reaction) of propargylic alcohol derivatives with organocuprate reagents is the most straightforward and popular, because it uses readily available substrates and forms a new C−C bond while most of the other methods rely on the use of more difficult-to-prepare compounds such as dienes, enynes, cyclopropanes, and other highly functionalized compounds.[5−8] Unfortunately, however, unlike the copper-based "S_N2'-type" reactions of

(1) Reviews on allenes: (a) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2.

(2) Reviews on the synthetic applications of allenes: (a) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701–712. (b) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133–1150. (c) Ma, S. *Chem. Rev.* **2005**, *105*, 2829–2871. (d) Ma, S. *Acc. Chem. Res.* **2009**, *42*, 1679–1688.

(3) Reviews on allenic natural products and pharmaceuticals: Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196–1216.

(4) Reviews on the synthesis of allenes: (a) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671–11694. (b) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795–818. (c) Yu, S.; Ma, S. *Chem. Commun.* **2011**, 5384–5418. For selected examples on the synthesis of allenes since 2007, see: (d) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1650–1653. (e) Hayashi, S; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2008**, *130*, 5048–5049. (f) Ready, J. M.; Pu, X. *J. Am. Chem. Soc.* **2008**, *130*, 10874–10875. (g) Kobayashi, K.; Naka, H.; Wheatley, A. E.; Kondo, Y. *Org. Lett.* **2008**, *10*, 3375–3377. (h) Tang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q.; Zhang, W.-X.; Wang, A.-X. *Org. Lett.* **2008**, *10*, 5585–5588. (i) Zhong, C.; Sasaki, Y.; Ito, H.; Sawamura, M. *Chem. Commun.* **2009**, 5850–5852. (j) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Org. Lett.* **2009**, *11*, 5010–5012. (k) Kuang, J.; Ma, S. *J. Am. Chem. Soc.* **2010**, *132*, 1786–1787. (l) Bolte, B.; Odabacian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2010**, *132*, 7294–7296. (m) Ohmiya, H.; Yang, M.; Yamauchi, Y.; Ohtsuka, Y.; Sawamura, M. *Org. Lett.* **2010**, *12*, 1796–1799. (n) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1114–1117.

(5) Pioneering works on γ-substitution of propargylic alcohol derivatives with organocuprate reagents by Crabee and co-workers: (a) Rona, P.; Crabbe, P. *J. Am. Chem. Soc.* **1968**, *90*, 4733–4744. (b) Rona, P.; Crabbe, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289–3292.

(6) Reviews on γ-substitution of propargylic alcohol derivatives with organocuprate reagents: (a) Krause, N.; Hoffmann-Röder, A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 145−163. (b) Hoffmann-Röder, A.; Krause, N. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; pp 51−92. (c) Ogasawara, M.; Hayashi, T. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; pp 93−140. (d) Ohno, H.; Nagaoka, Y.; Tomioka, K. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; pp 141−181.

(7) The synthesis of optically active allenes by the S_N2' ring opening reaction of alkynyl-substituted β-lactones: Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470–10471.

(8) The synthesis of optically active vinylallenes by 1,5-substitution of enyne acetates: Krause, N.; Purpura, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4355–4356.

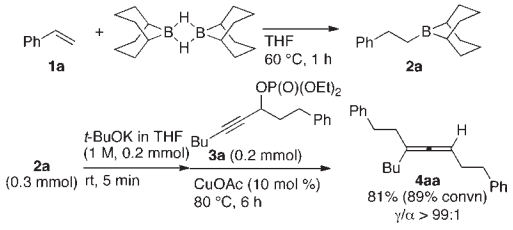
10.1021/ol202866h
Published on Web 11/04/2011

allylic systems, the corresponding allene synthesis, in fact, suffers from serious problems in regioselectivity[9] and stereoselectivity.[10,11] In particular, the reaction of primary propargylic alcohol derivatives affords alkynes rather than allenes as a major product (*vide infra*).[9b] Additionally, the stereoselectivity in the synthesis of axially chiral allenes from enantioenriched propargylic substrates is not always reliable: while efficient chirality transfers have been reported in many cases, the transformations are susceptive to the drop of enantiomeric purity depending on the reaction conditions. Not only erosion of 1,3-*anti* stereochemistry but also racemization of the allene moieties under the reaction conditions are well documented in the literature.[10−12] Furthermore, the organocuprate method based on Grignard or organolithium reagents suffers from the problem of functional group incompatibility within the organocuprates.[6,13] Accordingly, a general method that overcomes the above-mentioned problems is highly desirable.

Previously we developed the copper-catalyzed allyl−alkyl coupling between allylic phosphates and alkylboranes, which proceeds with excellent γ-selectivity (>99:1).[14a] Herein, we report that this copper-catalyzed protocol is applicable to the reaction between propargylic phosphates and alkylboranes, providing a versatile approach to multisubstituted allenes.[14−16] The substrate scope is markedly broad in terms of both substitution patterns and functional group compatibility. Moreover, the protocol is effective for the stereoselective synthesis of axially chiral allenes, which occurs through excellent point-to-axial chirality transfer.

Specifically, alkylborane **2a** was first prepared through hydroboration of styrene (**1a**) with 9-borabicyclo-[3.3.1]nonane dimer [9-BBN-H]$_2$ in THF at 60 °C (**1a**/B 1.2:1) (Scheme 1). The alkylborane **2a** was converted into an alkylborate via treatment with *t*-BuOK (0.2 mmol, 1 M in THF) at rt for 5 min. Then, CuOAc (10 mol %) and propargylic phosphate **3a** (0.2 mmol) was added to the mixture, and the resulting solution was heated at 80 °C for 6 h. The NMR analysis of the crude product indicated 89% conversion of **3a** into allene **4aa** and confirmed that no α-substitution product (alkyne) was formed (γ/α > 99:1). Silica gel chromatography furnished analytically pure **4aa** in 81% yield.[17] The reaction was readily scalable: a gram-scale reaction with 1.0 g (3.0 mmol) of **3a** afforded the allene **4aa** in 85% isolated yield.

Scheme 1



Several observations concerning the optimum reaction conditions are to be noted. Less expensive CuCl was also effective, providing **4aa** in 72% yield, while the use of Cu(OAc)$_2$ resulted in a significantly reduced yield (43%). A ligand for the copper is not necessary. The reaction in the absence of *t*-BuOK resulted in a lower conversion

(9) (a) Macdonald, T. L.; Reagan, D. R. *J. Org. Chem.* **1980**, *45*, 4740–4747. Discussion concerning the problem in the synthesis of 1,1-disubstituted allenes:(b) Varghese, J. P.; Knochel, P.; Marek, I. *Org. Lett.* **2000**, *2*, 2849–2852 and references therein.

(10) Racemization of chiral allenes by organocuprate reagents: (a) Claesson, A.; Olsson, L.-I. *J. Chem. Soc., Chem. Commun.* **1979**, 524–525. (b) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726–3730.

(11) Alexakis and co-workers descibed stereochemical and mechanistic aspects of the formation of axially chiral allenes through the reaction between enantioenriched propargylic alcohol derivatives and organocopper reagents. Ligands for copper such as P(OMe)$_3$ or PBu$_3$ were used to improve the point-to-axial chirality transfer. Additionally, copper salts, halogens of the Grignard reagents, or leaving groups have a significant effect on the stereoselectivity. Even with these attempts, however, the chirality transfer was insufficient or incomplete in many cases. See: (a) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042–8047. (b) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron* **1991**, *47*, 1677–1696. (c) Alexakis, A. *Pure Appl. Chem.* **1992**, *64*, 387–392.

(12) Recently reported efficient enantioselective routes to chiral allenes that do not utilize propargylic compounds: (a) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089–2090. (b) Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915–12916. (c) Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T. *Org. Lett.* **2003**, *5*, 217–219. (d) Hayashi, T.; Tokunaga, N.; Inoue, K. *Org. Lett.* **2004**, *6*, 305–307. (e) Ogasawara, M.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 5764–5767. (f) Ogasawara, M.; Ngo, H. L.; Sakamoto, T.; Takahashi, T. *Org. Lett.* **2005**, *7*, 2881–2884. (g) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186–14187. (h) Ogasawara, M.; Fan, L.; Ge, Y.; Takahashi, T. *Org. Lett.* **2006**, *8*, 5409–5412. (i) Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 7212–7213. (j) Ogasawara, M.; Okada, A.; Subbarayan, V.; Sörgel, S.; Tamotsu, T. *Org. Lett.* **2010**, *12*, 5736–5739. (k) Nishimura, T.; Makino, H.; Nagaosa, M.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 12865–12867. For a review, see: (l) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, *20*, 259–271.

(13) The transition-metal (Pd, Rh)-catalyzed substitutions of propargylic derivatives with aryl- or alkenylboron compounds: (a) Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149–152. (b) Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 5573–5575. (c) Yoshida, M.; Ueda, H.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 6705–6708. (d) Yoshida, M.; Okada, T.; Ihara, M. *Tetrahedron* **2007**, *63*, 6996–7002. (e) Molander, G. A.; Sommers, E. M.; Baker, S. R. *J. Org. Chem.* **2006**, *71*, 1563–1568. (f) Murakami, M.; Igawa, H. *Helv. Chim. Acta* **2002**, *85*, 4182–4188. (g) Miura, T.; Shimada, M.; Ku, S.-Y.; Tamai, T.; Murakami, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7101–7103.

(14) Cu-catalyzed γ-selective and stereospecific allyl−aryl and allyl−alkyl couplings with organoboron compounds: (a) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895–2897. (b) Ohmiya, H.; Yokokawa, N.; Sawamura, M. *Org. Lett.* **2010**, *12*, 2438–2440. (c) Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett.* **2010**, *12*, 3216–3218. For related studies with palladium catalysts, see also: (d) Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 17276–17277. (e) Ohmiya, H.; Makida, Y.; Li, D.; Tanabe, M.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 879–889. (f) Li, D.; Tanaka, T.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 3344–3347. (g) Makida, Y.; Ohmiya, H.; Sawamura, M. *Chem.—Asian J.* **2011**, *6*, 410–414.

(15) Our studies on regioselective transformations of propargylic alcohol derivatives: (a) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774–15775. (b) Ohmiya, H.; Ito, H.; Sawamura, M. *Org. Lett.* **2009**, *11*, 5618–5620. See also refs 4i and m.

(16) Cu-catalyzed conjugate additions with alkylboron compounds (alkyl-9-BBN): (a) Ohmiya, H.; Yoshida, M.; Sawamura, M. *Org. Lett.* **2011**, *13*, 482–485. (b) Ohmiya, H.; Shido, Y.; Yoshida, M.; Sawamura, M. *Chem. Lett.* **2011**, *40*, 928–930. Cu-catalyzed carboxylations with alkylboron compounds (alkyl-9-BBN) to carbon dioxide: (c) Ohmiya, H.; Tanabe, M.; Sawamura *Org. Lett.* **2011**, *13*, 1086–1088.

(17) For Schemes 1 and 2, Table 1, and eqs 1−3, unreacted propargylic phosphates (**3**) were detected in the crude materials after removal of the catalyst.

(34% yield, 40% convn). The use of a catalytic amount (10 mol %) of *t*-BuOK furnished the allene in only 24% yield (44% convn). No reaction occurred with the corresponding propargylic methyl carbonate and acetate.

The hydroboration–coupling one-pot protocol affords a variety of allenes (Table 1).[17] The reaction tolerates functional groups such as alcohol, phosphate, silyl ether, ester, methyl ether, acetal and carbamate moieties in the propargylic phosphates and alkenes (entries 1–7, 10 and 12).

Table 1. Synthesis of Tri- and Tetrasubstituted Allenes[a]

entry	alkene	phosphate	product	yield (%)[b,c]
1	**1a**	**3b**	**4ab**	63
2	**1a**	**3c**	**4ac**	62
3	**1b**	**3a**	**4ba**	75
4	**1c**	**3a**	**4ca**	70
5	**1d**	**3a**	**4da**	81
6	**1d**	**3d**	**4dd**	77
7	**1e**	**3e**	**4ee**	85
8[d]	**1f**	**3a**	**4fa**	72
9	**1a**	**3f**	**4af**	56
10	**1a**	**3g**	**4ag**	71
11	**1a**	**3h**	**4ah**	75
12	**1d**	**3i**	**4di**	61

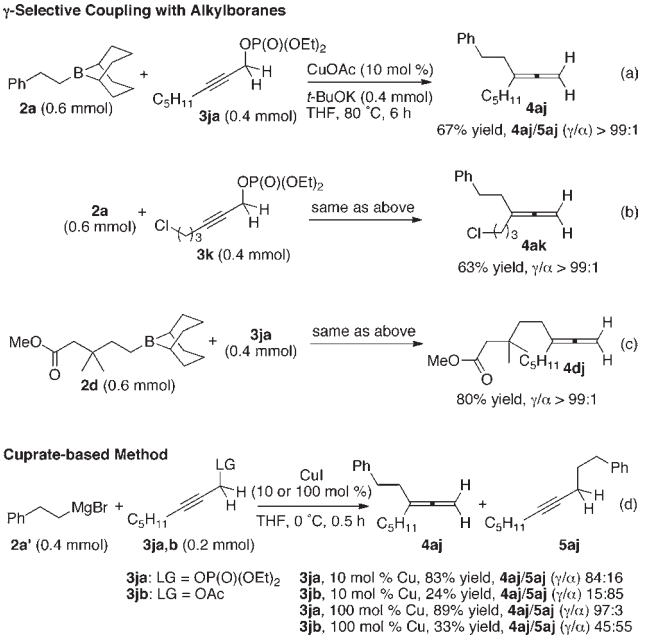
[a] The reaction was carried out with **3** (0.4 mmol), alkylborane **2** (1.5 equiv), CuOAc (10 mol %), and *t*-BuOK (1.0 equiv, 1 M in THF) in THF at 80 °C for 6 h. Alkylborane **2** was prepared in advance by hydroboration of **1** with 9-BBN-H dimer in THF at 60 °C for 1 h and was used without purification. [b] Isolated yield based on **3**. [c] $\gamma/\alpha > 99{:}1$. Determined by ^{1}H NMR or GC analysis of the crude product. [d] Diastereomeric ratio (1:1).

The tolerance of the reaction toward steric demand in alkylboranes (**2**) was evaluated in Table 1, entries 5, 6, 8, and 12. The sterically more demanding alkylborane **2d**, which was derived from a terminal alkene (**1d**) bearing a tertiary alkyl substituent, served as a substrate to afford the corresponding allenes **4da**, **dd**, and **di** in good yields (entries 5, 6, and 12). The reaction of the β-branched alkylborane (**2f**), which was prepared from α-methylstyrene (**1f**), was also successful to give **4fa** as a 1:1 diastereomeric mixture (entry 8). Unfortunately, however, the use of secondary alkylborane reagents prepared from internal alkenes resulted in no reaction (data not shown).

Table 1 also displays the substrate scope regarding the steric demand and substitution patterns in the propargylic phosphates (**3**). The Bu group at the γ-position of **3a** could be replaced with Me or $MeOCH_2$ groups without a drastic change in the yield of allenes **4af** and **4ag** (entries 9 and 10). However, a bulky isobutyl group severely inhibited the reaction, giving only a trace of the allene product (data not shown). The reaction of a terminal alkyne resulted in a complex mixture (data not shown). The tertiary propargylic phosphates **3h** and **3i** were converted into the corresponding tetrasubstituted allenes **4ah** and **4di**, respectively (entries 11 and 12).

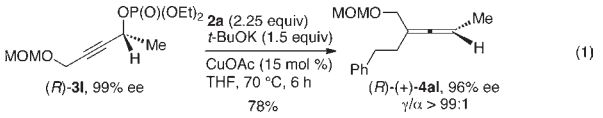
Importantly, the reaction of primary propargylic phosphate **3ja** also occurred cleanly with excellent γ-selectivity to afford the corresponding geminally disubstituted terminal allene **4aj** (Scheme 2a).[17] On the other hand, the cuprate-based reactions between alkyl Grignard reagent **2a′** and propargylic phosphate **3ja** or acetate **3jb** gave mixtures of the allene (**4aj**) and alkyne (**5aj**) irrespective of catalytic or stoichiometric use of copper (Scheme 2d).[9b] The regiocontrolled synthesis of geminally disubstituted terminal allenes tolerates functional groups such as chloro and ester moieties in the substrates (Schemes 2b and c).[17]

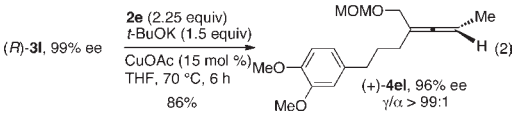
Scheme 2. Synthesis of Geminally Disubstituted Terminal Allenes from Primary Propargyl Alcohol Derivatives

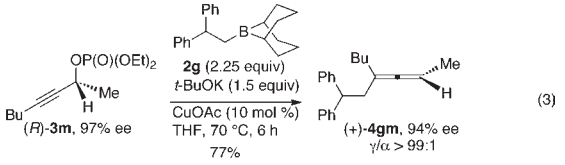


The present Cu-catalyzed protocol is effective for the stereocontrolled synthesis of axially chiral allenes.[12] The stereospecific character of the copper-catalyzed coupling is

substantiated in eqs 1−3.[17] The couplings between the styrene-derived alkylborane **2a** or the allylbenzene-derived alkylborane **2e** and the enantioenriched propargylic phosphate (*R*)-**3l** (99% ee), which has α-Me and γ-$MOMOCH_2$ substituents, proceeded with excellent point-to-axial chirality transfer with 1,3-*anti*-stereochemistry to afford enantioenriched allenes (*R*)-(+)-**4al** (96% ee) or (+)-**4el** (96% ee) (eqs 1 and 2).[18] The reaction between the bulkier alkylborane **2g** and a simple chiral propargylic phosphate (*R*)-**3m** (97% ee) also occurred with excellent chirality transfer to give the corresponding chiral allene (+)-**4gm** (94% ee) (eq 3). Evaluation of reactions with different reaction times and conversions confirmed that no racemization of the allene occurred under the reaction conditions. Thus, the slight decreases in enantionmeric purity are attributable to a minor pathway with 1,3-*syn*-stereochemistry. This result is in contrast to the observation of racemization in the cuprate-based allene syntheses.[11]



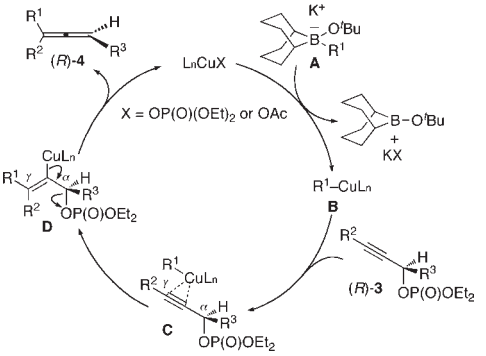




A possible pathway for the alkylborane−copper system can be postulated as illustrated in Scheme 3. A trialkyl(alkoxo)borate **A** is initially formed by the stoichiometric reaction between an alkylborane **2** and KO^tBu.[14a] Subsequently, the B/Cu transmetalation between the borate **A** and CuX [X = $OP(O)(OEt)_2$ or OAc] occurs to form an alkylcopper(I) species **B**. The alkylcopper species **B** forms π-complex **C** with (*R*)-**3**. The regioselective *syn*-addition of R^1−Cu across the C−C triple bond of **3** gives alkylcopper complex **D**. The regioselectivity in the addition step would be induced by stereoelectronic effects that stabilize the developing $\sigma(C_\beta-Cu)$ orbital through interactions with the $\sigma[C_\alpha-OP(O)(OEt)_2]$ orbital. These orbital interactions

(18) The absolute configuration of (*R*)-(+)-**4al** was determined by transforming to a known compound. See Supporting Information for details.

Scheme 3



would cause *anti*-β-elimination of the alkylcopper complex **D** to afford (*R*)-**4** and L_nCuX. This hypothetical reaction pathway is based on the neutral and mildly nucleophilic nature of the organocopper(I) species **B**. This nature would render the oxidative addition of the organocopper(I) **B** to form a copper(III) intermediate with an η^3-allenyl/propargyl ligand less feasible. As a result, the above-mentioned addition−elimination route would become dominant. This accounts for the excellent and robust regioselectivity toward the allene formation.

In summary, we have developed a new approach to allenes through a copper-catalyzed γ-selective cross-coupling reaction between propargylic phosphates and alkylboranes. The excellent point-to-axial chirality transfer in the copper-catalyzed transformation allows the efficient preparation of axially chiral allenes from enantioenriched propargylic alcohols. With broad functional group compatibility and robustness in terms of γ-selectivity and 1,3-*anti* stereospecificity, the present alkylborane−copper method well complements the conventional cuprate-based route to allenes and will find opportunities for applications in the synthesis of complex molecules.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research (B) and for Young Scientists (B), JSPS. We thank MEXT for financial support in the form of a Global COE grant (Project No. B01: Catalysis as the Basis for Innovation in Materials Science). Y.M. thanks JSPS for scholarship support.

Supporting Information Available. Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.