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Copper-Catalyzed γ-Selective and Stereospecific Allyl−Aryl Coupling between (*Z*)-Acyclic and Cyclic Allylic Phosphates and Arylboronates

Hirohisa Ohmiya,* Natsumi Yokokawa, 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

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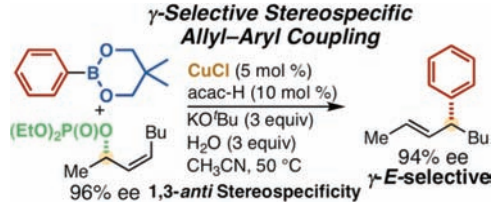
ABSTRACT



A Cu-catalyzed allyl−aryl coupling reaction between (*Z*)-acyclic or cyclic allylic phosphates and arylboronates proceeds with excellent γ-*E*-selectivity and 1,3-*anti* chirality transfer, which gives the corresponding coupling products with benzylic and allylic stereogenic centers. The wide availability and easy-to-handle nature of arylboronates, the inexpensiveness of the Cu catalyst system, and the high regio- and stereoselectivities are attractive features of this protocol.

Arylboronic acid derivatives have found wide application in modern organic synthesis because of their broad availability, air stability, and easy-to-handle nature.[1] They are especially useful for C−C bond formations. In fact, various types of electrophilic reagents are now capable of being efficiently coupled with arylboronic acid derivatives under the influence of transition-metal catalysts. However, the utilities of coupling reactions between arylboronic acid derivatives with allylic electrophiles are still limited because of the difficulty in controlling regioselectivity and stereoselectivity, especially in cases where an allylic system is not present at the terminus of the molecule but in an internal position.[2] The recently reported Pd-catalyzed allyl−aryl coupling between acyclic (*E*)-allylic esters and arylboronic acids is a rare case that occurs generally with excellent regio- and stereoselectivities (γ-*E*-selectivity and 1,3-*syn* stereospecificity).[3]

Here, we report a new Cu-catalyzed allyl−aryl coupling reaction with (*Z*)-acyclic or cyclic allylic phosphates and arylboronates, which proceeds with excellent γ-*E*-selectivity and 1,3-*anti* chirality transfer. The Cu system is complementary to the reported Pd system in that it is applicable toward (*Z*)-acyclic and cyclic allylic systems.[3] Notably, the use of the arylmetal reagents as nucleophilic coupling partners has not been well exploited previously in Cu chemistry due to the poor nucleophilicity of the arylcopper species relative to that of the alkylcopper species.[4–7]

(1) *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005.

(2) Pd-catalyzed allyl−aryl couplings between allyl alcohol derivatives and arylboron compounds have been reported. These studies, however, have focused on cases in which an allylic system is located at the terminus of a molecule or is highly asymmetrized by electronic and/or steric substituent effects. See: (a) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972–980. (b) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1990**, *31*, 7453–7456. (c) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384–3388. (d) Bouyssi, D.; Gerusz, V.; Balme, G. *Eur. J. Org. Chem.* **2002**, 2445–2448. (e) Mino, T.; Kajiwara, K.; Shirae, Y.; Sakamoto, M.; Fujita, T. *Synlett* **2008**, 2711–2715. (f) Nishikata, T.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131*, 12103–12105, and references therein.

(3) (a) Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 17276–17277. (b) Ohmiya, H.; Makida, Y.; Li, D.; Tanabe, M.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 879–889.

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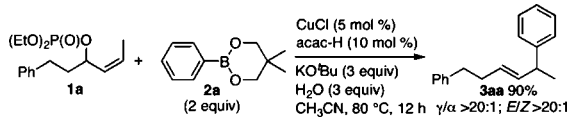
Scheme 1



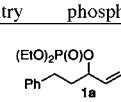
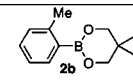
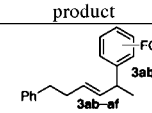
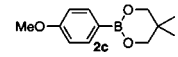
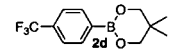
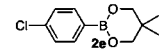
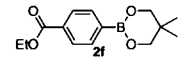
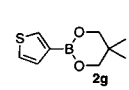
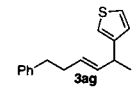
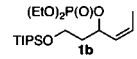
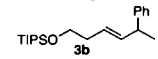
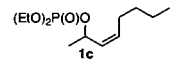
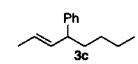
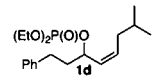
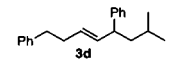
In numerous studies in this laboratory, we have found that the reaction of (*Z*)-allylic phosphate **1a** with 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane (**2a**) (2 equiv) in the presence of CuCl (5 mol %), acetylacetone (acac-H, 10 mol %), KO^{t}Bu (3 equiv), and H_2O (3 equiv) in CH_3CN at 80 °C for 12 h afforded allyl−aryl coupling product **3aa** in 90% isolated yield with excellent regio- (γ/α >20:1) and *E*/*Z* (>20:1) selectivities (Scheme 1). The reaction of (*E*)-allylic phosphate resulted in moderate *E*/*Z* selectivity (87:13) with the excellent γ-regioselectivity retained. The Cu loading could be reduced to 1 mol % with only a slight decrease in the yield (84%; acac-H, 10 mol %).

Several observations concerning the optimum reaction conditions are to be noted. The use of a small amount of H_2O (3 equiv) is critical: the reaction without H_2O resulted in a complex mixture. The amount of KO^{t}Bu is also critical: reducing it from 3 to 2 equiv decreased the yield from 90 to 34% under otherwise identical conditions, and no reaction occurred in the absence of KO^{t}Bu. The reaction proceeded even without acac-H but with a significantly reduced yield (68%, 5 mol % Cu). Reducing the amount of boronate **2a** to 1 equiv caused considerable hydrolysis of **1a**. Phenylboronic acid instead of **2a** was also useful, although the yield of **3aa** was slightly decreased (62%).

The Cu-catalyzed allyl−aryl coupling showed a range of substrate scope of allylic phosphates (**1**) and arylboronates (**2**) (Table 1). The reactions proceeded with excellent γ- (>20:1) and *E*- (>20:1) selectivities. Functional groups such as MeO, CF_3, Cl, ester, and silyl ether in **1** or **2** were compatible with the Cu system (entries 2−5 and 7). 3-Thiopheneboronic acid ester **2g** also participated in the coupling (entry 6).

The efficiency of the reaction toward steric demand in both (*Z*)-acyclic allylic phosphates (**1**) and arylboronates (**2**) is shown in Table 1 (entries 1, 8, and 9). *o*-Tolylboronate (**2b**) was coupled with **1a** in a reasonable yield (entry 1). The allylic phosphate **1c** with a Bu instead of a Me group was phenylated at the γ-position effectively (entry 8). A sterically more demanding γ-substituent such as an isobutyl group was also tolerated (entry 9). However, the reaction was nearly inhibited by the steric demand of an isobutyl substituent at the α-position (in place of α-Me for **1c**) (5% yield, not shown).

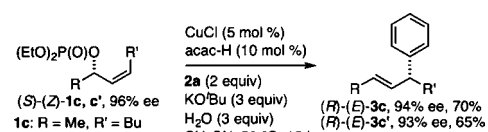
Table 1. Cu-Catalyzed Allyl−Aryl Coupling of (*Z*)-Acyclic Allylic Phosphates[a]

entry	phosphate	boronate	product	yield (%)[b,c]
1				57
2	**1a**		**3ac**	42
3	**1a**		**3ad**	87
4	**1a**		**3ae**	83
5	**1a**		**3af**	61
6	**1a**			60
7		**2a**		59
8		**2a**		81
9		**2a**		68

[a] Conditions: **1** (0.3 mmol), **2** (0.6 mmol), CuCl (5 mol %), acac-H (10 mol %), H_2O (0.9 mmol), KO^{t}Bu (0.9 mmol), CH_3CN (entries 1−3 and 6−9, 0.3 mL; entry 4, 0.6 mL; entry 5, 1 mL), 80 °C, 12 h. [b] Isolated yield. [c] Isomeric ratios (γ/α >20:1, *E*/*Z* > 20:1). Determined by ^{1}H NMR or GC analysis.

The coupling reaction took place with excellent α-to-γ chirality transfer with 1,3-*anti* stereochemistry (Scheme 2). The reaction of (*S*)-(*Z*)-**1c** (96% ee), which has α-Me and γ-Bu substituents, with the phenylboronate (**2a**) in the presence of CuCl, acetylacetone, KO^{t}Bu, and H_2O gave (*R*)-(*E*)-**3c** (94% ee) with only a slight decrease of enantiomeric purity. The reaction of (*S*)-(*Z*)-**1c′** (96% ee), which has α-Bu and γ-Me substituents, with **2a** gave (*R*)-(*E*)-**3c′** (93% ee), an isomer of **3c** with regard to the α/γ-regioselectivity.

Scheme 2. Chirality Transfer



The Cu catalyst system was also applicable to cyclic allylic substrates (Table 2).[7] The coupling reactions between *cis*-

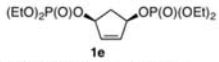
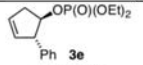
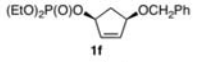
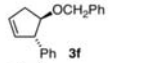
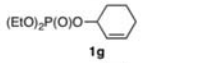
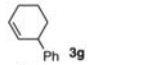
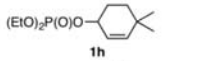
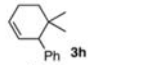
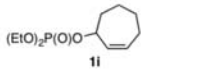
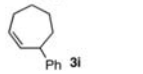
(4) For γ-selective allylic substitution reactions with stoichiometric arylcopper(I) reagents with excellent 1,3-chirality transfer, see: (a) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111–2114. (b) Kiyotsuka, Y.; Acharya, H. P.; Katayama, Y.; Hyodo, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1719–1722.

(5) For Cu-catalyzed γ-selective and enantioselective reaction of cinnamyl bromides with aryl Grignard reagents, see: Selim, K. B.; Matsumoto, Y.; Yamada, K.; Tomioka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 8733–8735.

(6) For Cu-catalyzed C−C bond formations with arylboron reagents, see: (a) Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. *Org. Lett.* **2008**, *10*, 2697–2700. (b) Ohishi, T.; Nishiura, M.; Hou, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 5792–5795. (c) Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Commun.* **2008**, 2010–2012. (d) Tomita, D.; Kanai, M.; Shibasaki, M. *Chem. Asian, J.* **2006**, *1*, 161–166. (e) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 6946–6948.

(7) For Cu-catalyzed (30 mol %), γ-selective allylic substitution reactions of 4-cyclopentene-1,3-diol monoesters with aryl- and alkenylzinc reagents, see: Nakata, K.; Kiyotsuka, Y.; Kitazume, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1345–1348.

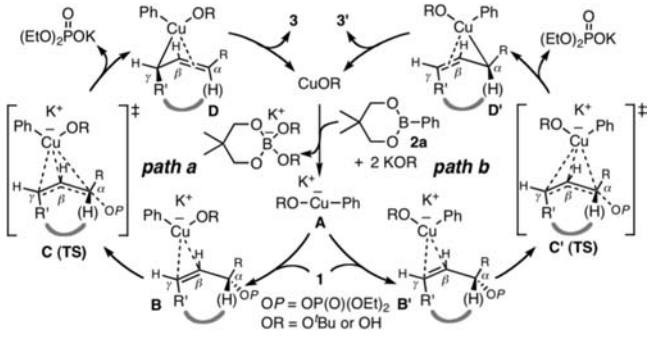
Table 2. Cu-Catalyzed Allyl−Aryl Coupling of Cyclic Allylic Phosphates[a]

entry	phosphate	product	yield (%)[b]	γ/α[c]	*trans*/*cis*[c]
1	 **1e**	 **3e**	61	>99:1	>99:1
2	 **1f**	 **3f**	88	76:24	>99:1
3	 **1g**	 **3g**	78	–	–
4	 **1h**	 **3h**	42	81:19	–
5	 **1i**	 **3i**	81	–	–

[a] Conditions: **1** (0.3 mmol), **2a** (0.6 mmol), CuCl (5 mol %), acac-H (10 mol %), H_2O (0.9 mmol), KO^{t}Bu (0.9 mmol), CH_3CN (0.3 mL), 80 °C, 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR.

4-cyclopentene-1,3-diol derivative **1e** and boronate **2a** proceeded with excellent γ-selectivity and 1,3-*anti* selectivity, giving *trans*-1,2-isomer **3e** (entry 1). The reaction with **1f** also proceeded with excellent 1,3-*anti* selectivity, but the product was contaminated with a significant amount of α-substitution product (**3e′**, not shown) (γ/α 76:24) (entry 2). The reaction with 2-cyclohexenyl phosphate (**1g**) proceeded smoothly (entry 3). Even when six-membered cyclic allylic phosphate (**1h**) with considerable steric congestion at the γ-position was used, the coupling occurred preferentially at the more hindered γ-position albeit with moderate regioselectivity (γ/α 81:19) (entry 4). Seven-membered cyclic substrate **1i** also underwent efficient coupling (entry 5).

Scheme 3. Possible Mechanism



The incompleteness of the γ-selectivity in the reaction of **1f** and **1h** (Table 2, entries 2 and 4) is in sharp contrast to the solid γ-selectivity of the recently reported Cu-catalyzed allyl−alkyl coupling between allylic phosphates and *alkyl*boranes.[8] This suggests interesting mechanistic difference between the two Cu-catalyzed coupling reactions. As one of the possible mechanisms for the latter, we proposed 1,2-addition-β-elimination of organocopper species (R-Cu rather than a cuprate). On the other hand, considering that the present allyl−aryl coupling reaction must be conducted in the presence of KO^{t}Bu/H_2O in excess relative to the organoboronate, an active copper intermediate of the allyl−aryl coupling reaction is likely to be a monoorganoheterocuprate $[ArCu(OR)\text{-}L_n]^-$ species (R = ^{t}Bu or H).

Although the roles of acac-H and H_2O are not clear at present, according to DFT studies by Nakamura et al. on the mechanism of the reaction of monoorganoheterocuprate with allyl acetate,[9] the mechanistic model for the Cu-catalyzed reaction of (*S*)-(*Z*)-**1c**,**c′** (Scheme 2), and cyclic allylic phosphates **1e**,**f** (Table 2, entries 1 and 2) with phenylboronate **2a** can be postulated as shown in Scheme 3, path a. The catalytic cycle is initiated by transmetalation between CuOR and **2a** in the presence of KOR to produce the nucleophilic heterocuprate **A** (Ph-Cu-OR$^-$). Subsequently, **A** forms π-complex **B** with an allylic phosphate (**1**). Then, oxidative addition through the transition state **C(TS)** with *anti*-stereochemistry with respect to the phosphate group leads to (γ,σ-enyl)copper(III) species **D** (enyl[σ + π] complex). Finally, reductive elimination results in C−C bond formation at the γ-position and regenerates CuOR. The regioselectivity is determined at the oxidative addition step as a consequence of the asymmetric nature of **B**. The incomplete γ-selectivity in the reactions of **1f**,**h** suggests the minor involvement of path b, in which the diastereomeric π-complex **B′** leads to enyl[σ + π] complex **D′**, which forms the α-substitution product (**3′**).

In conclusion, we developed a Cu-catalyzed γ-selective and stereospecific allyl−aryl coupling reaction between (*Z*)-acyclic or cyclic allylic phosphates and arylboronates, which gives allyl−aryl coupling products with benzylic and allylic stereogenic centers. The wide availability and easy-to-handle nature of arylboronates, the inexpensiveness of the Cu catalyst system, and the high regio- and stereoselectivities are attractive features of this protocol.

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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.

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(8) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895–2897.

(9) (a) Yoshikai, N.; Zhang, S.-L.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 12862–12863. (b) Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6287–6293.