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Copper-Catalyzed Regio- and Stereoselective Intermolecular Three-Component Oxyarylation of Allenes

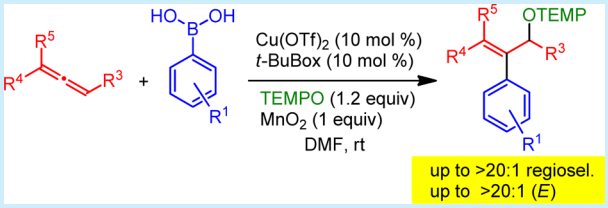
Taisuke Itoh,[†] Yohei Shimizu,*[,†] and Motomu Kanai*[,†,‡]

[†]Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[‡]ERATO, Japan Science and Technology Agency, Kanai Life Science Catalysis Project, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

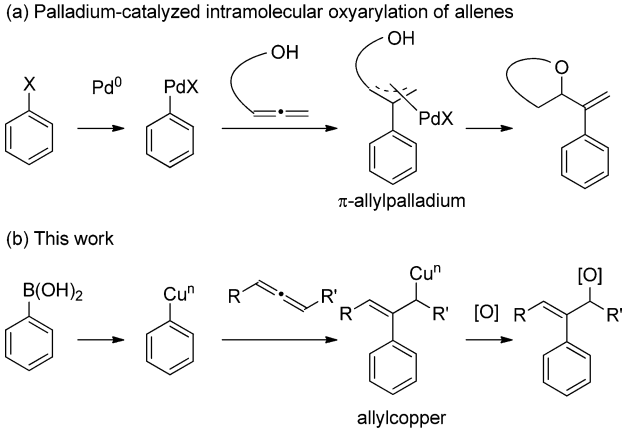
Supporting Information

ABSTRACT: A copper(II)-catalyzed intermolecular three-component oxyarylation of allenes using arylboronic acids as a carbon source and TEMPO as an oxygen source is described. The reaction proceeded under mild conditions with high regio- and stereoselectivity and functional group tolerance. A plausible reaction mechanism is proposed, involving carbocupration of allenes, homolysis of the intervening allylcopper(II), and a radical TEMPO trap.



Carbooxygenation of carbon−carbon (C−C) multiple bonds is a powerful tool in organic synthesis. Simultaneous formation of C−C and C−O bonds in a single operation rapidly increases the molecular complexity starting from unsaturated C−C bonds. Although carbooxygenation of alkenes and alkynes has been extensively studied,[1,2] that of allenes is less well-studied. The literature contains only a few examples of intramolecular oxyarylation of allenes using palladium catalysis (Scheme 1a).[3] In most of these examples, however, π-allylpalladium intermediates are generated via migratory insertion of allenes to arylpalladium species, and subsequent trapping of the intermediates by an intramolecular oxygen atom affords α-alkenyl cyclic ether products. In contrast, intermolecular carbooxygenation of allenes can be more versatile for the synthesis of multisubstituted allylic alcohol derivatives that are otherwise difficult to access.[4] Despite its potential utility, intermolecular, three-component oxyarylation of allenes is rarely exploited. In the few reported cases, regioselective control is not satisfactory.[5] We report herein the first copper-catalyzed intermolecular, three-component oxyarylation of allenes using arylboronic acids as a carbon source and TEMPO as an oxygen source (Scheme 1b). The reaction proceeded with excellent regio- and stereoselectivity under mild conditions.

Scheme 1. Oxyarylation of Allenes



We recently reported copper-catalyzed intramolecular oxy- and amidocupration of allenes to generate allylcopper species and its direct use in asymmetric allylation of carbonyl compounds to give enantiomerically enriched 1*H*-isocromenes and indoles, respectively.[6] In these reactions, regioselectivity was extremely high. The results encouraged us to examine intermolecular oxyarylation of allenes via *in situ* generated allylcopper species.[7]

We first investigated the reaction between phenylboronic acid (**2a**) and phenylallene (**1a**) using copper salts as a catalyst in the presence of various oxidants (Table 1). Preliminary studies revealed that oxyarylation of **1a** was promoted by a CuI catalyst with molecular oxygen as an oxygen source in DMF at room temperature (entry 1). The obtained product, however, was an enone rather than the desired allylic alcohol. The regioselectivity was low in favor of **4**, where oxygenation occurred at the benzylic position. To suppress overoxidation into enones, other oxygen sources were investigated (entries 2−5). The combination of TEMPO and MnO_2 provided the best yield and regioselectivity (entry 5). In contrast to the reaction using molecular oxygen, the major regioisomer was **3**. Furthermore, the geometry of the C−C double bond was exclusively (*E*). Screening of various copper sources revealed that $Cu(OAc)_2$ was the most reactive catalyst (entry 9). The yield, however, decreased to 70% when performed in a larger scale (entry 10). A complex of $Cu(OTf)_2$ and the *t*-BuBox ligand proved to be the most effective, even in a larger scale,

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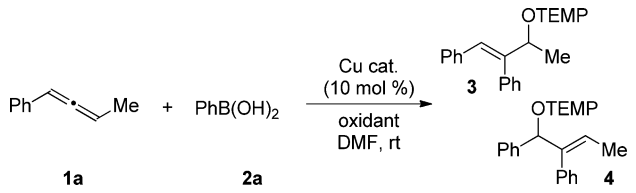
Table 1. Optimization of Copper-Catalyzed Intermolecular Oxyarylation of 1a[a]



1a 2a

entry	Cu cat.	oxidant	yields and ratio (3:4)[b]
1	CuI	air	54%[c]+ 14% (>20:1)
2	CuI	$(t\text{-BuO})_2$	11%[c] + trace
3	CuI	oxaziridine	0%
4	CuI	TEMPO/air	36%[c]+ 44% (16:1)
5	CuI	TEMPO/MnO_2[e]	76% (12:1)
6	CuCl	TEMPO/MnO_2[e]	58% (14:1)
7	CuTc	TEMPO/MnO_2[e]	79% (16:1)
8	$Cu(OTf)_2$	TEMPO/MnO_2[e]	65% (16:1)
9	$Cu(OAc)_2$	TEMPO/MnO_2[e]	quant (17:1)
10[d]	$Cu(OAc)_2$	TEMPO/MnO_2[e]	70% (16:1)
11[d]	$Cu(OTf)_2$/*t*-BuBox[f]	TEMPO/MnO_2[e]	quant (15:1)

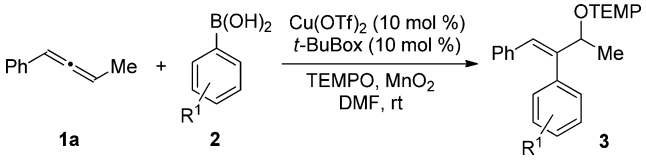
[a]General reaction conditions: **1a** (0.10 mmol, 1 equiv), **2a** (1.5 equiv), Cu catalyst (10 mol %), oxidant (2 equiv), DMF (0.5 mL), rt, 5 h. [b]Yield of alcohol/ether oxidation-state products determined by ^{1}H NMR using *t*-BuOMe as an internal standard. Regioisomeric ratio (r.r. = **3**:**4**) was shown in parentheses. [c]Combined yield of enones **8** + **9**. Regioisomeric ratio (**8**:**9**) was 1:1.1−1:1.4. [d]0.30 mmol scale. [e]TEMPO (1.2 equiv) and MnO_2 (1 equiv) were used as oxidants. [f]*t*-BuBox: 2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline].

affording the product in quantitative yield with high regio- and stereoselectivity (entry 11).[8]

Under these optimized conditions, we next examined the substrate scope (Table 2). Arylboronic acids containing both electron-donating and -withdrawing groups were tolerated (entries 2−5). The regio- and stereoselectivity were excellent in every entry. The coordinating functionalities did not interfere with the reaction (entries 3−5). Notably, a formyl group, which could be an electrophile in the presence of an organocopper reagent, was tolerated under the reaction conditions (entry 6). Excellent selectivity was retained, even when sterically congested boronic acids were used (entries 7 and 8). A free NH group of 6-indolylboronic acid **2i** was also compatible with the oxyarylation (entry 9).

We then evaluated the scope of allenes (Table 3). Both electron-donating and -withdrawing groups on arylallenes provided the corresponding products in excellent yield and selectivity (entries 1−3). Sterically hindered allenes, bearing *o*-methyl or 3,5-dimethyl substituents on the aromatic ring, were also good substrates, and high regioselectivity was maintained (entries 4 and 5). On the other hand, moderate regioselectivity was observed when a longer linear alkyl substituent was attached to the phenylallene (entry 6), likely due to the increased steric hindrance between TEMPO and the alkyl chain.

Table 2. Scope of Copper-Catalyzed Oxyarylation Regarding Boronic Acids[a]

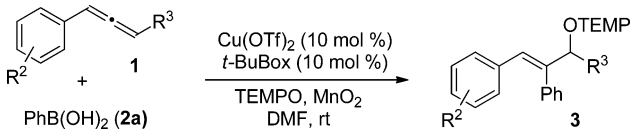


1a 2 3

entry	boronic acid **2**	product	yield	r.r. (**3**:**4**)[b]	*E*/*Z* of **3**[b]
1	**2a** R^1 = H	**3aa**	98%	15:1	>20:1
2	**2b** R^1 = 4-CF_3	**3ab**	81%	13:1	17:1
3	**2c** R^1 = 4-OMe	**3ac**	90%	12:1	>20:1
4	**2d** R^1 = 4-SMe	**3ad**	90%	15:1	>20:1
5	**2e** R^1 = 4-NPh_2	**3ae**	79%	12:1	14:1
6	**2f** R^1 = 3-CHO	**3af**	76%	13:1	17:1
7	**2g** R^1 = 2-Me	**3ag**	92%	>20:1	>20:1
8	**2h** 2-naphthylboronic acid	**3ah**	84%	12:1	>20:1
9	**2i** 6-indolylboronic acid	**3ai**	83%[b]	15:1	14:1

[a]Reaction conditions: **1a** (0.30 mmol, 1 equiv), **2** (1.5 equiv), $Cu(OTf)_2$ (10 mol %), *t*-BuBox (10 mol %), TEMPO (1.2 equiv), MnO_2 (1 equiv), DMF (1.5 mL), rt. [b]Determined by ^{1}H NMR using *t*-BuOMe as an internal standard.

Table 3. Scope of Copper-Catalyzed Oxyarylation Regarding Arylallenes[a]



entry	allene **1**	product	yield	r.r. (**3**:**4**)[b]	*E*/*Z* of **3**[b]
1	**1b** R^2 = 4-Br, R^3 = Me	**3ba**	96%	12:1	>20:1
2	**1c** R^2 = 4-CF_3, R^3 = Me	**3ca**	94%	12:1	>20:1
3	**1d** R^2 = 4-OMe, R^3 = Me	**3da**	93%	15:1	>20:1
4	**1e** R^2 = 2-Me, R^3 = Me	**3ea**	94%	>20:1	13:1
5	**1f** R^2 = 3,5-Me_2, R^3 = Me	**3fa**	94%	15:1	17:1
6	**1g** R^2 = H, R^3 = C_5H_{11}	**3ga**	87%	4.1:1	>20:1

[a]Reaction conditions: **1** (0.30 mmol, 1 equiv), **2a** (1.5 equiv), $Cu(OTf)_2$ (10 mol %), *t*-BuBox (10 mol %), TEMPO (1.2 equiv), MnO_2 (1 equiv), DMF (1.5 mL), rt. [b]Determined by ^{1}H NMR using *t*-BuOMe as an internal standard.

Encouraged by the high reactivity and regio- and stereoselectivity with arylallenes, we further investigated other types of allenes (Scheme 2). Pyridylallene **1h**, which has strong coordinating tendencies toward the copper catalyst, was also applicable, albeit with low regioselectivity. The reaction with benzyloxyallene **1i** provided an enol ether containing product **3ia** and a hemiacetal containing product **4ia** in a 1.1:1 ratio. Allylic ether **3ja** with a tetrasubstituted carbon−carbon double bond was also obtained with excellent regioselectivity from 1,1-disubstituted alkynylallene **1j**, despite low *E*/*Z* selectivity. Interestingly, when a cyclohexenylallene **1k** was subjected to the reaction conditions, oxygenation occurred preferentially at the cyclohexane ring, affording **5ka** with high regio- and stereoselectivity. These results indicate that the initial C−C bond formation step proceeded exclusively at the allene moiety despite the presence of an alkyne or an alkene moiety. Finally, we examined aliphatic allenes as substrates. The reaction with strained nine-membered ring allene **1l** proceeded smoothly to give product **3la** in 50% yield. The reactivity of a linear aliphatic allene **1m** was significantly lower, however, and product **3ma** was obtained in only 14% yield.[9]

The TEMPO adducts can be converted to allylic alcohols and enones in high yield (Scheme 3). When a 15:1 mixture of **3aa** and **4aa** was treated with zinc,[10] the corresponding allylic alcohols **6** and **7** were obtained in 95% combined yield. On the

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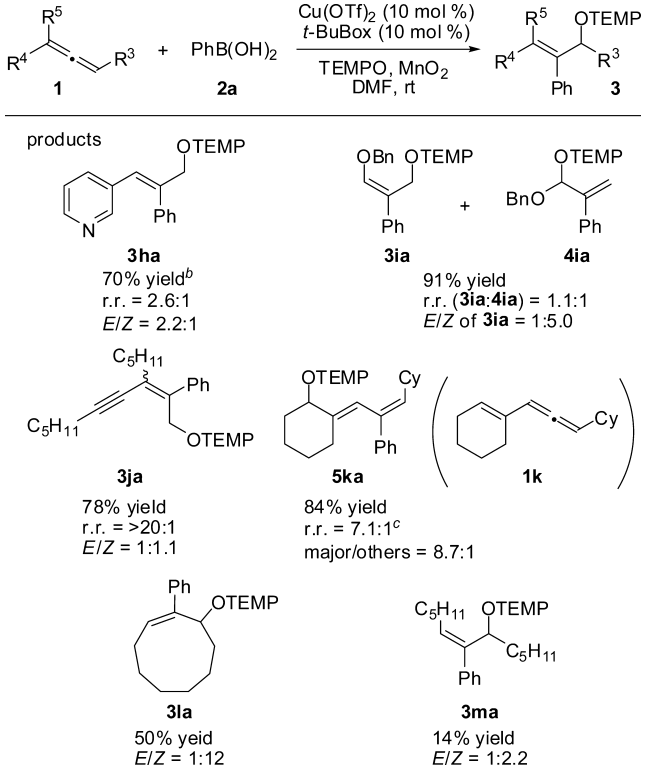
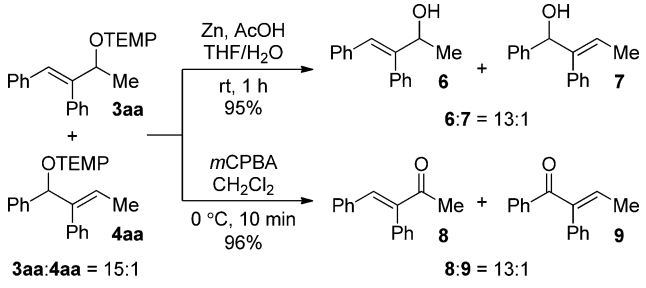
Scheme 2. Scope of Copper-Catalyzed Oxyarylation for Miscellaneous Allenes[a]



[a]Reaction conditions: **1** (0.30 mmol, 1 equiv), **2a** (1.5 equiv), $Cu(OTf)_2$ (10 mol %), *t*-BuBox (10 mol %), TEMPO (1.2 equiv), MnO_2 (1 equiv), DMF (1.5 mL), rt. [b]Determined by ^1H NMR using *t*-BuOMe as an internal standard. [c]Regioisomeric ratio of **5ka** to **4ka**.

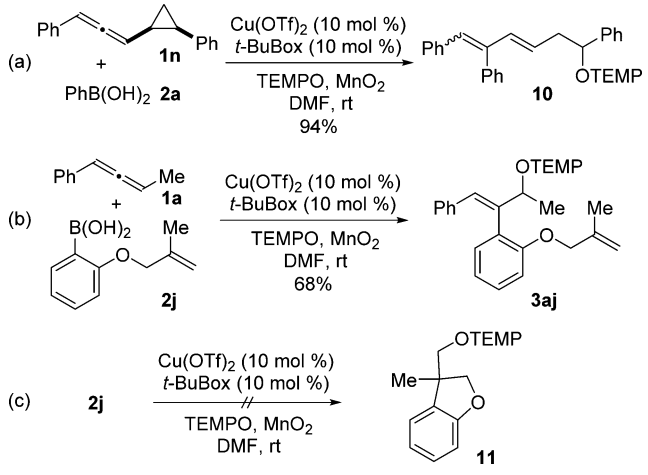
Scheme 3. Representative Transformations of 3aa



other hand, enones **8** and **9** were obtained in 96% combined yield by oxidation with *m*CPBA.[11]

A series of experiments was performed to gain insight into the reaction mechanism (Scheme 4). First, a radical clock experiment using substrate **1n** containing a cyclopropane ring resulted in the exclusive formation of **10** in high yield through a ring-opening and TEMPO trap at the benzylic position. This result indicates involvement of allyl radical species in the oxygenation step.[12] Next, boronic acid **2j** was used as a substrate to assess whether aryl radical species were generated during the reaction.[13] As a result, oxyarylation product **3aj** was obtained in 68% yield without producing any cyclized **11**. This result strongly supports that aryl radical species were not involved in the arylation step. In addition, arylboronic acid **2j** did not react with TEMPO in the absence of an allene under the reaction conditions, which further supports that the aryl radical is not generated during the reaction.

Scheme 4. Radical Clock Experiments (a, b) and TEMPO Trap Experiment (c)



Based on the experimental observations and the general lability of C(sp^3)–Cu(II) bonds,[14] we propose the catalytic cycle shown in Figure 1. First, transmetalation of arylboronic

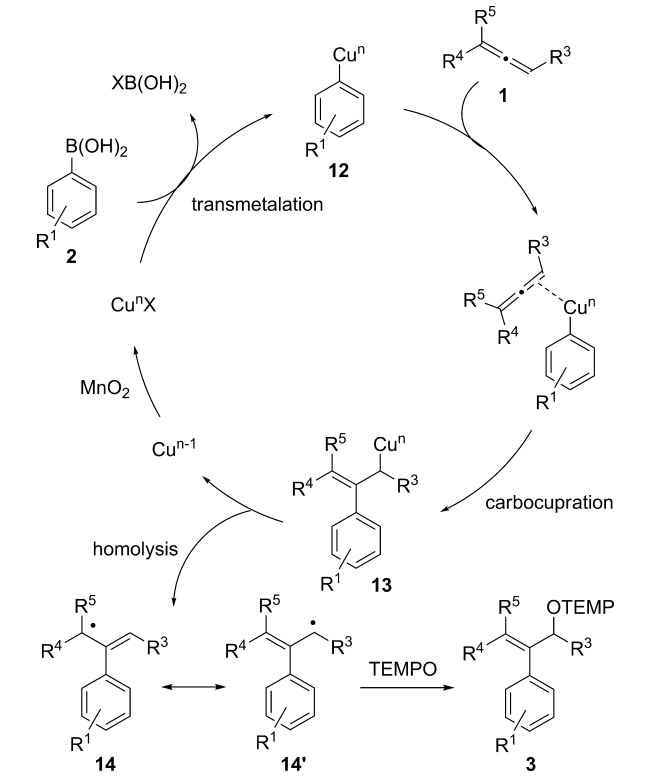


Figure 1. Proposed catalytic cycle for the copper-catalyzed oxyarylation of allenes.

acid **2** to the copper(II) catalyst generates arylcopper(II) species **12**, which undergoes carbocupration of allenes **1** to give allylcopper(II) **13**. Homolysis of the thus-generated allylcopper(II) **13** results in the formation of allyl radical intermediates **14**/**14′**, and a subsequent radical trap by TEMPO furnishes product **3**. Allyl radical species **14** and **14′** should exist in equilibrium, and the regioselectivity of oxygenation (i.e., TEMPO trap) would be determined by both steric factors and the relative stability between **14** and **14′**.

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In summary, we developed a copper-catalyzed intermolecular, three-component oxyarylation of allenes to afford allylic alcohol derivatives. The reaction proceeded with high regio-, stereo-, and chemoselectivity under mild conditions (rt). The substrate scope is broad, and various arylboronic acids and allenes can be used as substrates with TEMPO as an oxygen source. The reaction proceeded via (1) transmetalation between the copper catalyst and arylboronic acid to generate arylcopper(II) species, (2) carbocupration of allenes to generate allylcopper(II), (3) homolysis of the C−Cu(II) bond to give allyl radical species, and (4) a TEMPO trap of the allyl radical. The *in situ* generated allyl radical species should be applicable to other transformations, such as C−C and C−N bond formation. Further investigation in this direction is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: y-shimizu@mol.f.u-tokyo.ac.jp.
*E-mail: kanai@mol.f.u-ac.tokyo.ac.jp.

Notes

The authors declare no competing financial interest.

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(8) Although the chiral ligand was used for the oxyarylation of allenes, no enantio-induction was observed (**6** derived from **3aa**).

(9) When 5-phenyl-1,2-pentadiene was used as a substrate, the yield was less than 6% and regioselectivity was 1.4:1.

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(12) Two-electron mechanism for the cyclopropane ring-opening step cannot be completely excluded.

(13) If aryl radical species were involved, cyclization to dihydrobenzofuran **9** should have been faster than intermolecular addition to allenes. See: Lockner, J. W.; Dixon, D. D.; Risgaard, R.; Baran, P. S. *Org. Lett.* **2011**, *13*, 5628−5631.

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