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Copper-Catalyzed Three-Component Carboboration of Alkynes and Alkenes

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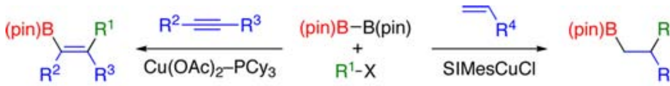
ABSTRACT



R^1= alkyl, benzyl, cinnamyl; R^2, R^3 = alkyl, aryl, H; R^4 = boryl, phenyl, silyl

Carboboration of alkynes was found to take place efficiently by a three-component coupling reaction with diboron and carbon electrophiles under copper catalysis to afford diverse multisubstituted borylalkenes in a stereoselective manner. The carboboration was also applicable to alkenes, leading to the formation of multisubstituted borylalkanes via regioselective carbon–boron and carbon–carbon bond-forming processes.

In view of the high synthetic significance of organoboron compounds,[1] which can be utilized especially for carbon–carbon bond-forming processes through Suzuki–Miyaura coupling,[2] the Petasis reaction,[3] transition metal-catalyzed conjugate addition,[4] etc., the development of new synthetic routes to hitherto unprecedented classes of organoboron compounds is of great importance. Recently, much attention has been paid to copper-catalyzed borylation reactions of unsaturated carbon linkages, in which nucleophilic borylcopper species derived from copper(I) complexes and diborons serve as key intermediates.[5,6] In these transformations, the borylcopper species add across the unsaturated C–C bonds to give β-borylorganocopper species, which are convertible into final products via protonation, β-oxygen elimination, cyclization, etc. We have just reported copper-catalyzed diborylation[7a] and borylstannylation[7b] of alkynes through capture of the β-borylalkenyl copper species with a boron (diboron) or a tin electrophile (tin alkoxide) and, thus, envisaged that the use of a suitable carbon electrophile for trapping the β-borylalkenyl copper species would lead to a carboboration reaction, in which a B–C and a C–C bond are formed all in one pot (Scheme 1).

Although pioneering work by Suginome demonstrated that the nickel- and palladium-catalyzed carboboration of

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(2) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11.

(3) (a) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463. (b) Koolmeister, T.; Södergren, M.; Scobie, M. *Tetrahedron Lett.* **2002**, *43*, 5965.

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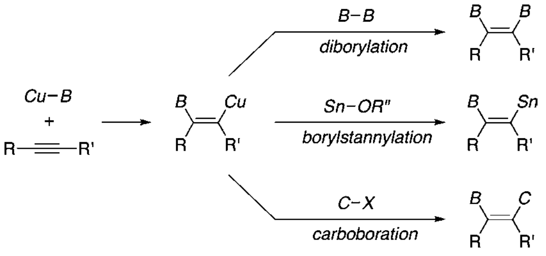
(8) (a) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358. (b) Suginome, M.; Yamamoto, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2380. (c) Suginome, M.; Yamamoto, A.; Murakami, M. *J. Organomet. Chem.* **2005**, *690*, 5300. (d) Suginome, M.; Shirakura, M.; Yamamoto, A. *J. Am. Chem. Soc.* **2006**, *128*, 14438. (e) Suginome, M.; Yamamoto, A.; Sasaki, T.; Murakami, M. *Organometallics* **2006**, *25*, 2911.

10.1021/ol4001526

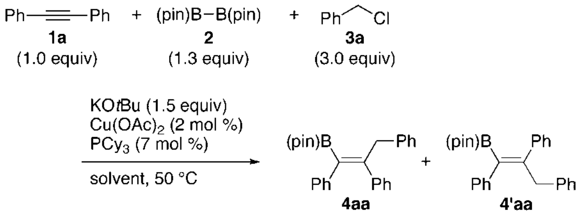
Scheme 1. Copper-Catalyzed Borylations of Alkynes



alkynes occurred via direct activation of a B–C bond[8] or three-component coupling with a boron electrophile (boron chloride) and a carbon nucleophile (organometallic compound),[9] the search for carboboration of other modes[10] is highly desirable. We report herein the copper-catalyzed three-component carboboration of alkynes and alkenes, in which a boron nucleophile and a carbon electrophile are installed into C–C multiple bonds. The closely related copper-catalyzed carboboration[11] and boracarboxylation[12] of alkynes have been recently reported.

First we conducted the reaction of diphenylacetylene (**1a**) with bis(pinacolato)diboron ((pin)B–B(pin)) (**2**) and benzyl chloride (**3a**) in toluene in the presence of $Cu(OAc)_2$–PCy_3[13] and KO*t*Bu and observed that B–C and C–C bonds were constructed in one pot to afford a carboboration product in 45% yield as a mixture of two stereoisomers (**4aa**:**4′aa** = 87:13) (entry 1, Table 1). The use of such polar solvents as acetonitrile, DMF, and DMI was found to improve the yield and the stereoselectivity significantly (entries 2–4), whereas the reaction in THF only gave unsatisfactory results (entry 5).

Table 1. Solvent Effect on Cu-Catalyzed Carboboration[a]

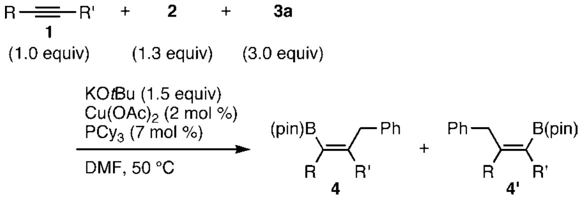


entry	solvent	time (h)	yield (%)[b]	**4aa**:**4′aa**
1	toluene	27	45	87:13
2	acetonitrile	30	63	94:6
3	DMF	29	67	>99:1
4	DMI	33	56	>99:1
5	THF	28	38[c]	78:22

[a] General procedure: **1a** (0.30 mmol), **2** (0.39 mmol), **3a** (0.90 mmol), KO*t*Bu (0.45 mmol), $Cu(OAc)_2$ (6.0 μmol), PCy_3 (0.021 mmol), solvent (0.55 mL). [b] Yield of isolated **4aa** and **4′aa**. [c] NMR yield.

The carboboration was also applicable to variously substituted diarylalkynes (**1b**–**1e**) to give the respective products (**4ba**–**4ea**) in moderate to good yields (Table 2, entries 1–4), and it should be noted that the aryl–Br bonds in **4da** and **4′da** totally remained intact,[14] demonstrating the high functional group compatibility of the carboboration. The exclusive formation of a single regioisomer (**4fa** and **4ga**), whose benzyl moiety was attached to the geminal position of the phenyl moiety, was observed in the reaction of alkyl(aryl)alkynes (**1f** and **1g**) (entries 5 and 6),[15] and furthermore dialkylalkynes (**1h** and **1i**) could participate in the reaction to furnish the products (entries 7 and 8). The reaction of phenylacetylene (**1j**) proceeded with perfect regioselectivity to afford **4ja** bearing the benzyl moiety at the more substituted site (entry 9), and such terminal aliphatic alkynes as 1-octyne (**1k**) and cyclopentylacetylene (**1l**) were also convertible into the carboboration products (entries 10 and 11), being in marked contrast to the results recently reported by Tortosa.[11]

Table 2. Carboboration of Alkynes with Benzyl Chloride[a]



entry	R	R′	time (h)	yield (%)[b]	ratio **4**:**4′**	**4**
1	$4\text{-MeOC}_6\text{H}_4$	$4\text{-MeOC}_6\text{H}_4$ (**1b**)	54	67	–	**4ba**
2	Ph	$4\text{-MeOC}_6\text{H}_4$ (**1c**)	29	84	52:48	**4ca**, **4′ca**
3	Ph	$4\text{-BrC}_6\text{H}_4$ (**1d**)	27	58	51:49	**4da**, **4′da**
4	Ph	2-Thienyl (**1e**)	27	49	55:45	**4ea**, **4′ea**
5	Me	Ph (**1f**)	24	54	>99:1	**4fa**
6	Et	Ph (**1g**)	15	50	>99:1	**4ga**
7	*n*Pr	*n*Pr (**1h**)	24	57	–	**4ha**
8	Me	*n*Pent (**1i**)	8	46	80:20	**4ia**, **4′ia**
9	H	Ph (**1j**)	46	44	>99:1	**4ja**
10	H	*n*Hex (**1k**)	32	51	56:44	**4ka**, **4′ka**
11	H	Cyclopent (**1l**)	52	48	55:45	**4la**, **4′la**

[a] General procedure: **1** (0.30 mmol), **2** (0.39 mmol), **3a** (0.90 mmol), KO*t*Bu (0.45 mmol), $Cu(OAc)_2$ (6.0 μmol), PCy_3 (0.021 mmol), DMF (0.55 mL). [b] Yield of isolated **4** and **4′**.

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(9) (a) Yamamoto, A.; Suginome, M. *J. Am. Chem. Soc.* **2005**, *127*, 15706. (b) Daini, M.; Yamamoto, A.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 2918. (c) Daini, M.; Suginome, M. *Chem. Commun.* **2008**, 5224.

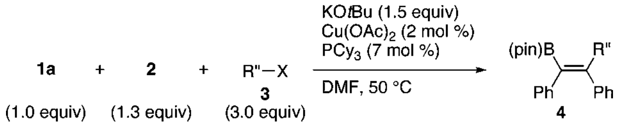
(10) (a) Mikhaikov, B. M.; Bubnov, Y. N. *Tetrahedron Lett.* **1971**, 2127. (b) Bubnov, Y. N.; Nesmeyanova, O. A.; Rudashevskaya, T. Y.; Mikhaikov, B. M.; Kazansky, B. A. *Tetrahedron Lett.* **1971**, 2153. (c) Wrackmeyer, B.; Nöth, H. *J. Organomet. Chem.* **1976**, *108*, C21. (d) Okuno, Y.; Yamashita, M.; Nozaki, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 920.

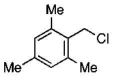
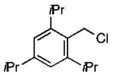
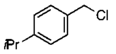
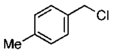
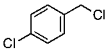
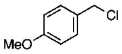
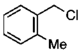
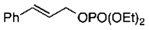
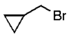
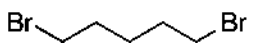
(11) A part of this work was presented at the 59th symposium on organometallic chemistry, Japan on September 15, 2012 (No. P3B-04). For copper–xantphos-catalyzed carboboration of alkynes, see: Alfaro, R.; Parra, A.; Alemeán, J.; G. Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc.* **2012**, *134*, 15165.

(12) Zhang, L.; Cheng, J.; Carry, B.; Hou, Z. *J. Am. Chem. Soc.* **2012**, *134*, 14314.

(13) Copper(II) acetate would be reduced to a copper(I) complex *in situ*. See: Hammond, B.; Jardine, F. H.; Vohra, A. G. *J. Inorg. Nucl. Chem* **1971**, *33*, 1017.

Table 3. Carboboration of Diphenylacetylene with Various Carbon Electrophiles[a]



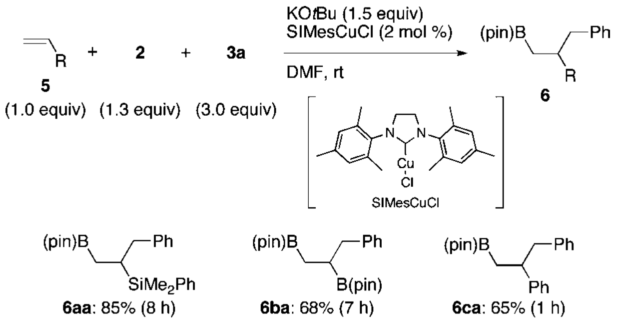
entry	R''–X	3	time (h)	yield (%)[b]	4
1		**3b**	22	67	**4ab**
2		**3c**	24	60	**4ac**
3		**3d**	26	70	**4ad**
4		**3e**	27	57	**4ae**
5		**3f**	57	46	**4af**
6		**3g**	17	45	**4ag**
7		**3h**	29	61	**4ah**
8		**3i**	40	51	**4ai**
9	*n*Bu–Br	**3j**	51	60	**4aj**
10	Me–OTs	**3k**	44	39	**4ak**
11		**3l**	23	30	**4al**
12		**3m**	18	36	**4am**

[a] General procedure: **1a** (0.30 mmol), **2** (0.39 mmol), **3** (0.90 mmol), KO*t*Bu (0.45 mmol), $Cu(OAc)_2$ (6.0 μmol), PCy_3 (0.021 mmol), DMF (0.55 mL). [b] Yield of isolated **4**.

The broad substrate scope on carbon electrophiles was exemplified by use of substituted benzyl chlorides: treatment of 2,4,6-trimethylbenzyl chloride (**3b**) or 2,4,6-triisopropylbenzyl chloride (**3c**) with **1a** and **2** produced good yields of the respective products (**4ab** and **4ac**), despite their considerable steric congestion (Table 3, entries 1 and 2). The reaction of *para*-substituted (**3d**–**3g**) or *ortho*-substituted (**3h**) benzyl chlorides also took place facilely (entries 3–7), and a cinnamyl moiety could be installed into the C–C triple bond by employing cinnamyl phosphate (**3i**) as a carbon electrophile, where the substitution occurred at the γ-position solely (entry 8).[16] Besides, simple alkyl (pseudo)halides (**3j** and **3k**) were transformable into the carboboration products (**4aj** and **4ak**) (entries 9 and 10), and the formation of the cyclopropylmethylated product (**4al**) in the reaction using cyclopropylmethyl bromide (**3l**) suggests that a radical pathway is not operative in the carboboration (entry 11). The reaction was also applicable to 1,5-dibromopentane (**3m**), one of whose C–Br bonds was converted into the C–C bond (entry 12).

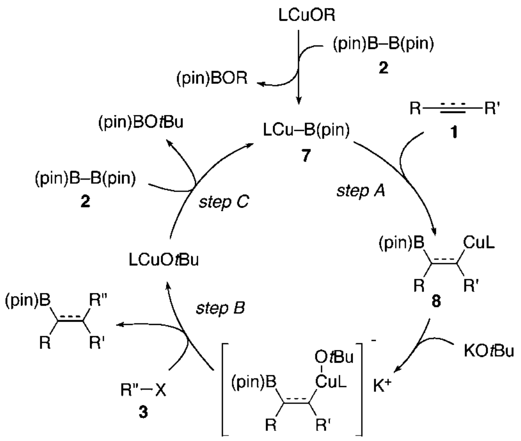
The versatility of the copper catalysis was demonstrated by the success in the carboboration of alkenes (Scheme 2).[17,18] Thus, treatment of dimethylphenylvinylsilane (**5a**) with **2** and **3a** in the presence of SIMesCuCl resulted in the exclusive formation of **6aa** in 85% yield, and moreover the reaction of vinylborane (**5b**) or styrene (**5c**) also smoothly proceeded with a regioselectivity similar to that with the vinylsilane, giving the carboboration products (**6ba** and **6ca**) in 68% or 65% yield, respectively.[19]

Scheme 2. Carboboration of Alkenes with Benzyl Chloride



As depicted in Scheme 3, formation of borylcopper species **7** from a Cu–OR (R = Ac or *t*Bu) complex with **2** triggers the carboboration. Subsequent insertion of an alkyne (or an alkene) into the Cu–B bond of **7** (*step A*), followed by capture of the resulting β-borylalkenyl (or alkyl) copper species **8** with a carbon electrophile, provides a carboboration product and a copper *tert*-butoxide (*step B*),

Scheme 3. A Plausible Catalytic Cycle for Carboboration



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(14) For copper-catalyzed borylation of Ar–Br bonds, see: Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350.

(15) The reaction of **1f**, **2**, and **3a** under Tortosa's conditions produced a mixture of regioisomers in contrast to the result described herein. See ref 11.

(16) For copper-catalyzed S_N2' selective substitution of allylic electrophiles, see: (a) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034. (b) Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett.* **2010**, *12*, 3216. (c) Ohmiya, H.; Yokokawa, N.; Sawamura, M. *Org. Lett.* **2010**, *12*, 2438. (d) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895. (e) Ito, H.; Okura, T.; Matsuura, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 560. (f) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634. (g) Tortosa, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3950. (h) Park, J. K.; McQuade, D. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 2717. See also ref 5c.

which was converted into **7** upon reaction with **2** (*step C*). The perfect regioselectivity observed in the reaction of alkyl(aryl)alkynes, phenylacetylene, or alkenes would be attributable to the exclusive introduction of the copper moiety to the more substituted carbon (*step A*), which is induced by the electronic directing effect of the substituents (phenyl, silyl, and boryl groups).[5f,m]

In conclusion, we have disclosed that the three-component carboboration of alkynes facilely proceeds under copper catalysis by utilizing a diboron reagent and suitable carbon electrophiles to provide diverse multisubstituted borylalkenes in a straightforward manner. Moreover, the versatility of the copper catalysis toward the carboboration has been demonstrated by its application to simple alkenes. Further studies on three-component borylation reactions of unsaturated hydrocarbons with other electrophiles under copper catalysis are in progress.

Supporting Information Available. Experimental procedure including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Daini, M.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 4758.

(18) For copper-catalyzed hydroboration of alkenes, see ref 5h.

(19) Catalyst screening in the reaction using styrene (**5c**): I*i*PrCuCl, 60% (1 h); CuI–xantphos, 47% (0.5 h); CuI–PCy_3, 45% (0.5 h).

The authors declare no competing financial interest.