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Copper-Catalyzed Double Borylation of Silylacetylenes: Highly Regio- and Stereoselective Synthesis of *Syn*-Vicinal Diboronates

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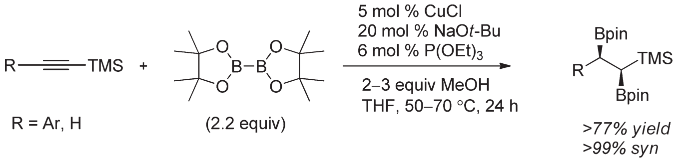
ABSTRACT



Phosphite–copper(I) complexes efficiently catalyzed the double borylation of internal silylated alkynes to provide vicinal diboronates with excellent regio- and stereoselectivity. The copper-catalyzed reaction between bis(pinacolato)diboron (B_2pin_2) and aryl-substituted silylacetylenes in the presence of MeOH resulted in double syn addition of the pinacolboronate moiety (Bpin) and H across the triple bond with complete selectivity. While the double borylation was highly efficient for aryl-substituted alkynylsilanes and silylacetylene, only monoborylation took place with alkyl-substituted alkynylsilanes to yield (*Z*)-(β-borylvinyl)silanes under the developed catalytic conditions.

Organoboron compounds are useful in organic synthesis because of their versatility as synthetic intermediates. Increasing attention has been paid to copper-catalyzed boron addition reactions to carbon–carbon multiple bonds as a straightforward procedure for preparing organoboron compounds with high stereocontrol.[1] In copper-catalyzed boron additions, catalytically active ligand-coordinated copper(I)–boryl complexes,[2] generated from copper and diboron reagents, continue to show remarkable efficiency and stereoselectivity.

Recently, we described a Cu-catalyzed regioselective boron addition to carbon–carbon triple bonds, such as alkynoates[3] and terminal[3] and internal alkynes,[4] using bis(pinacolato)diboron (B_2pin_2, **1**) and MeOH based on phosphine–copper catalysts. These catalytic reactions worked well for internal alkynes resulting in monohydroborated, alkenylboronate products with excellent regio- and stereoselectivity, which would be challenging to obtain by conventional hydroboration processes.[5] As part of our ongoing project to synthesize functionalized organoboron compounds, we became interested in the reactivity and selectivity of silylated alkynes as substrates for copper-catalyzed borylations. Silylated alkynes are intriguing

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[2] (a) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036–11037. (b) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2008**, *27*, 4443–4454.

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[4] (a) Kim, H. R.; Jung., I. G.; Yoo, K.; Jang, K.; Lee, E. S.; Yun, J.; Son, S. U. *Chem. Commun.* **2010**, 758–760. (b) Kim, H. R.; Yun, J. *Chem. Commun.* **2011**, *47*, 2943–2945.

[5] (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370–4371. (b) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482–3485. (c) Konno, T.; Chae, J.; Tanaka, T.; Ishihara, T.; Yamanaka, H. *Chem. Commun.* **2004**, 690–691. (d) Iwadate, N.; Suginome, M. *Org. Lett.* **2009**, *11*, 1899–1902.

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molecules because the silyl group is known to display an electronic boron directing effect to the α-carbon from the silyl group[6] and less of an activating effect on the triple bond than an alkyl substituent in the conventional hydroboration of alkynes with dialkylborane serving as the electrophilic reagent.[7] Since a copper–boryl complex serves as a nucleophilic entity in the borylation reaction,[2b] reactivity and/or selectivity complementary to hydroboration might be achievable. Herein, we report an efficient borylation of silylalkynes with a phosphite–copper catalyst to produce vicinal alkyldiboronates through the highly regio- and stereoselective double addition of a boronate moiety and H to silylalkynes.

Scheme 1. Borylation of 1-TMS-1-hexyne

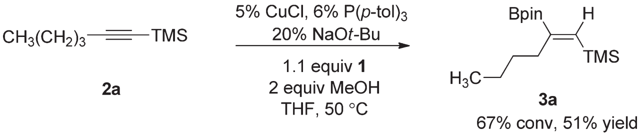
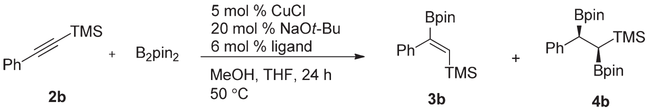


Table 1. Borylation Reaction of 1-Phenyl-2-trimethylsilylethyne Under Various Conditions



entry	ligand	B_2pin_2 (equiv)	MeOH (equiv)	conv (%)[a]	product **3b**: **4b**	yield of **4b** (%)[b]
1	P(*p*-tol)$_3$	1.1	2	52	1<: >99	44
2	P(*p*-tol)$_3$	2.2	2.2	100	1<: > 99	86
3	P(OEt)$_3$	2.2	2.2	100	1<: >99	89
4[c]	P(OEt)$_3$	2.2	3	100	1<: >99	89
5	P(OEt)$_3$	2.2	0	13	–	4
6	xantphos	1.1	1	78	>99: <1	49 (**3b**)
7	xantphos	1.5	2	100	>99: <1	83 (**3b**)
8[d]	xantphos	2.2	2.2	100	80: 20	40 (**3b**)

[a] Determined by GC analysis based on consumption of **2b**. [b] Isolated yield of purified diboronate **4b**. [c] Reaction time was 17 h. [d] Reaction was carried out at 70 °C.

In initial experiments, we carried out the borylation of 1-trimethylsilyl-1-hexyne (see Supporting Information) using our previously reported conditions (CuCl, NaO*t*-Bu, P(*p*-tol)$_3$, and 1.1 equiv B_2pin_2, 2 equiv MeOH in THF)[4b] at 50 °C for 24 h. The reaction proceeded to 67% conversion, which was higher than the *t*-butyl analogue,[8] and a single product was isolated in 51% yield (Scheme 1). The product was characterized as (*Z*)-(*β*-borylvinyl)silane, whose formation could be explained by *β*-carbon attachment of the boronate group from the TMS group and syn addition of boron and H. A similar borylation was conducted employing a more hindered but activated 1-phenyl-2-trimethylsilylacetylene (**2b**) (Table 1, entry 1). The reaction led to partial conversion and the formation of a single isomeric product. Surprisingly, the isolated product was determined to be a vicinal diboronate with the two boronyl groups in a syn relationship, and no monoborylated vinylsilane intermediate was detected. The stereochemistry of the resulting 1,2-bis(boronate) was determined by subsequent oxidation to the corresponding *syn*-1,2-diol.[9] Increasing the amount of B_2pin_2 (**1**) to 2.2 equiv relative to acetylene substrate led to complete conversion to product **4b** in high yield (entry 2). Using P(OEt)$_3$ as the ligand instead of P(*p*-tol)$_3$ efficiently afforded the same product[10] (entries 3 and 4), and MeOH was necessary for high conversion (entry 5). On the other hand, the bidentate ligand xantphos (= 9,9′-dimethyl-4,5-bis(diphenyl-phosphino)-xanthene) selectively gave monoaddition product (**3b**) as a single product (entries 6 and 7). Increasing reaction temperature with excess B_2pin_2 resulted in a mixutre of **3b** and **4b**, but the alkenylboron compound was still the major product with the xantphos ligand (entry 8).

While catalytic diborations of alkenes with diboron compounds offer a straightforward route to diboronate compounds,[11] alkene diboration has been most successful thus far with terminal alkenes,[12] cyclic alkenes with internal strain,[12b,d] and disubstituted alkenes[12d,e] by employing bis(catecholato)diboron, which is less stable and more reactive than bis(pinacolato)diboron. The present approach provides a complementary synthetic route to diboronates.[13] Furthermore, sterically encumbered

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(6) (a) Uchida, K.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1976**, *41*, 2941–2942. (b) Hassner, A.; Soderquist, J. A. *J. Organomet. Chem.* **1977**, *131*, C1–C4. (c) Zweifel, G.; Backlund, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 3184–3185. (d) Hoshi, M.; Masuda, Y.; Arase, A. *J. Chem. Soc. Perkin Trans. 1* **1990**, 3237–3241.

(7) Soderquist, J. A.; Colberg, J. C.; Valle, L. D. *J. Am. Chem. Soc.* **1989**, *111*, 4873–4878.

(8) For comparison, 48% conversion of 1-*t*-butyl-1-octyne was obtained under the same conditions.

(9) Page, P. C. B.; Rosenthal, S. *Tetrahedron Lett.* **1990**, *46*, 2573–2586.

(10) When the same reactions were conducted at room temperature for 12 h with P(*p*-tol)$_3$ and P(OEt)$_3$, respectively, both reactions gave similar conversions, 79% and 80%. However, ~3% of the monoaddition product (**3b**) was detected by GC in the latter reaction along with the major product **4b**. The results indicate that the phosphite system might be less efficient than the phosphine in the double borylation. However, the reactivity difference is so small that the phosphite can be used in the double borylation at higher reaction temperature with the same efficiency as the phosphine.

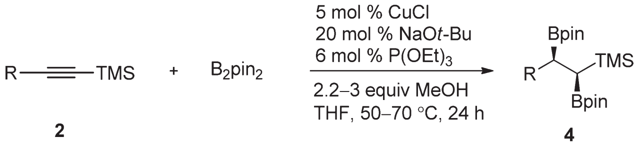
(11) For recent reviews, see: (a) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320–2354. (b) Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717–4725.

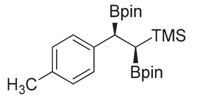
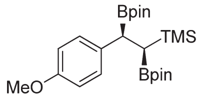
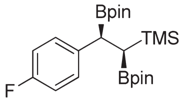
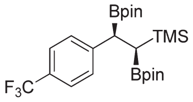
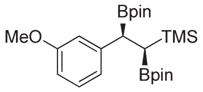
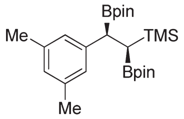
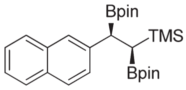
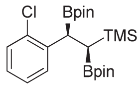
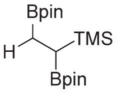
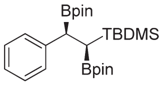
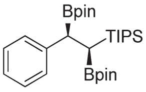
(12) For selected reports on diboration: (a) Baker, R. T.; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1336–1338. (b) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689–690. (c) Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210–13211. (d) Ramírez, J.; Sanaú, M.; Fernández, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 5194–5197. (e) Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem.* **2005**, *70*, 9538–9544.

(13) For a NHC–Cu catalyzed borylation of terminal alkynes to vicinal diboronates, see: Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 18234–18235.

(14) For copper-catalyzed borylation reactions of *β*,*β*-disubstituted or α,*β*-disubstituted α,*β*-unsaturated carbonyl compounds, see: (a) Lillo, V.; Prieto, A.; Bonet, A.; Díaz-Requejo, M. M.; Ramírez, J.; Pérez, P. J.; Fernández, E. *Organometallics* **2009**, *28*, 659–662. (b) O'Brien, J. M.; Lee, K.-s.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630–10663. (c) Feng, X.; Yun, J. *Chem.—Eur. J.* **2010**, *16*, 13609–13612.

Table 2. Synthesis of *syn*-Vicinal Diboronates Through Cu-Catalyzed Double Borylation



entry	product		conv (%)[a]	yield (%)[b]
1[c]		**4c**	>99	92
2[c]		**4d**	>99	87
3[c]		**4e**	>99	81
4		**4f**	>99	88
5[c]		**4g**	>99	93
6[c]		**4h**	>99	95
7		**4i**	>99	88
8		**4j**	80	46[d]
9[e]		**4k**	>99[f]	77
10		**4l**	>99	87
11		**4m**	27	–

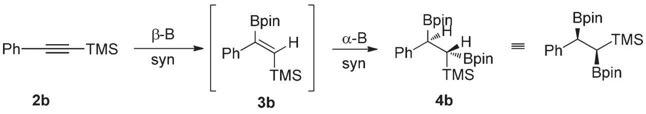
[a] Determined by GC analysis. [b] Isolated yield of purified products. [c] Reaction was performed at 70 °C. [d] A 34:66 ratio for **3j** and **4j** was measured by GC. Monoborylated product (**3j**) was also isolated in 14% yield. [e] Reaction was performed at 40 °C. [f] ~5% of germinal diboronate was detected by GC of the crude mixture.

trisubstituted alkenes have not been the subject of copper-catalyzed borylation[14] using diboron reagents. Thus, further examples of the double borylation were examined with the catalytic combination of CuCl, NaO*t*-Bu and $P(OEt)_3$ in THF in the presence of **1** and MeOH, and the results are summarized in Table 2.

As shown in Table 2, the Cu-catalyzed double borylation of aryl-substituted silylated alkynes with different substitutions smoothly occurred to give the corresponding diboronates in a highly regio- and stereoselective fashion. Substrates with electron-withdrawing or electron-donating substituents at either the para or meta positions underwent clean reaction (entries 1–7). However, a substrate bearing ortho substitution gave only partial conversion generating the desired diborylated product along with a monoborylated (β-borylvinyl)silane product (entry 8). The reaction of trimethylsilylacetylene gave the 1,2-diboronate in good yield as the major product (entry 9). To assess the effect of the silyl group size on the reactivity and stereoselectivity, bulky *tert*-butyldimethylsilyl (TBDMS) and tri-isopropylsilyl (TIPS)-substituted phenyl acetylenes were prepared. Under the present catalytic conditions, a TBDMS group was accommodated in the reaction, but the TIPS-substituted substrate resulted in low reactivity (entries 10 and 11).

The formation of *syn*-vicinal diboronate products can be rationalized by the following mechanism. Insertion of the alkyne into the phosphite-ligated Cu–boryl complex places the pinacolboronate moiety at the β-carbon and the Cu at the α-carbon from the silyl group, and subsequent protonolysis of the Cu–C bond by MeOH gives (*Z*)-**3b**. A fast second insertion of intermediate **3b** into the Cu–B complex occurs regio- and stereoseletively with α-boron placement to yield the diborylated product **4b**.

Scheme 2



The β-selectivity (from TMS) for the first insertion is different from the conventional hydroboration of substituted-(trimethylsilyl)acetylenes with alkyl boranes.[6,7] Presumably, the first Cu–B insertion is directed by a steric effect of the silyl group that overrides electronic effects from the aryl and TMS groups.[15] Under conditions using a monodentate ligand, the second insertion of the intermediate (*Z*)-(β-borylvinyl)silane into the Cu–B complex occurs faster than the starting alkyne, because it is electronically activated by both the aryl and Bpin groups despite its steric congestion. In contrast, the intermediate alkenyl boron is less reactive than the alkyne[16] with xantphos as the ligand leading to the selective monoborylation.

A brief investigation of an enantioselective version of this reaction was carried out with the silylacetylene **2b**. Among the screened chiral ligands including binaphthol-based phosphites and phosphine ligands, Me-duphos

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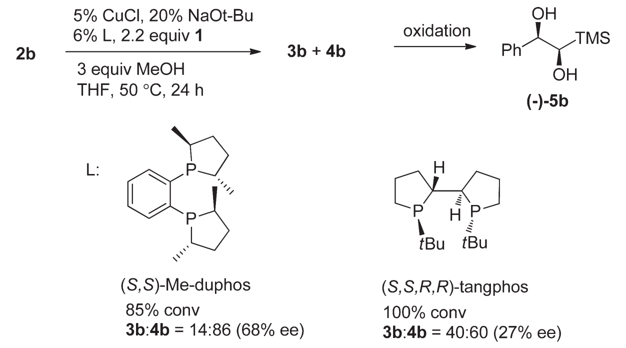
(15) The ability of the carbon-silicon bond to stabilize an adjacent electron-deficient center through hyperconjugation was proposed as an explanation of the α-boron-directing effect. See: Wang, K. K.; Gu, Y. G.; Liu, C. *J. Am. Chem. Soc.* **1990**, *112*, 4424–4431.

(16) See entries 7 and 8 in Table 1 and Scheme 3 for results with bidentate ligands, such as xantphos and Me-duphos. The steric effect of bidentate ligand-coordinated copper complexes possibly accounts for the slow addition to the trisubstituted alkenyl intermediate.

Scheme 3. Enantioselective Diborylation



and tangphos ligands with small bite angles have been the most effective thus far in achieving appreciable conversion of the starting material and produced the chiral diboronate **4b** in 68% and 27% ee, respectively (Scheme 3).

In summary, we have described a highly regio- and stereoselective double borylation of silylalkynes catalyzed by a phosphite–copper complex that produces *syn*-vicinal diboronates in good yield. Asymmetric synthesis of chiral vicinal diboronates and the stereoselective synthesis of (β-borylvinyl)silanes, which are versatile intermediates that include both vinylborane and vinylsilane moieties as well as synthetic applications of these multifunctional compounds are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and chracterization of the products. This material is available for free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.