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Copper(I)-Catalyzed Formal Carboboration of Alkynes: Synthesis of Tri- and Tetrasubstituted Vinylboronates

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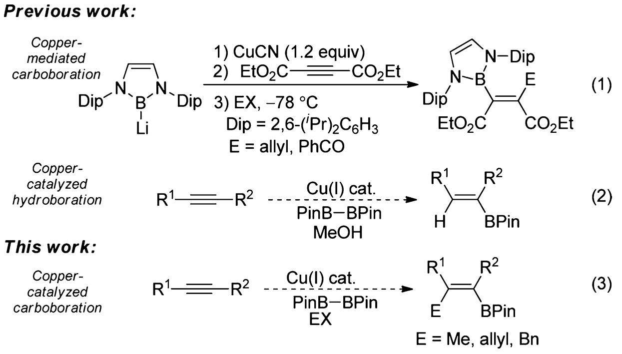
Ⓢ *Supporting Information*

ABSTRACT: The first copper-catalyzed formal carboboration of alkynes, in which a C−B bond and a C−C bond are created in a single catalytic cycle, is presented. The reaction proceeds with high regioselectivity and *syn*-stereoselectivity to form tri- and tetrasubstituted vinylboronic esters from commercially available bis(pinacolato)diboron. A subsequent cross-coupling reaction gives access to highly substituted alkenes.

Vinylboronates play an important role in organic synthesis.[1] Their utility as partners in the Suzuki−Miyaura coupling reaction[2] and their ability to undergo Rh-catalyzed[3] and metal-free[4] conjugate additions make them highly versatile intermediates in the synthesis of complex molecules. Several approaches have been developed for the synthesis of disubstituted vinylboronic esters.[1] However, methods to synthesize tri-[5] and tetrasubstituted[6] vinylboronates are significantly more limited. Among them, metal-catalyzed carboboration reactions are the most direct way to access these highly substituted vinylboronic esters. An excellent work by Suginome described the palladium- and nickel-catalyzed carboboration reactions of alkynes.[7] However, despite the importance of these transformations, they usually require an alkyne functionalized with a hydroxyl group to promote an intramolecular boron addition and/or the use of boron sources which are difficult to handle.[8] Consequently, it would be desirable to find carboboration conditions that required less expensive metals, nonfunctionalized alkynes and commercially available boron sources. Recently, the copper-mediated carboboration of propiolates has been developed (Scheme 1, eq 1). Unfortunately, the synthetic application of this reaction is hampered by the use of highly sensitive boryllithium intermediates and stoichiometric amounts of copper. Additionally, the diisopropylbenzene (Dip) diamino group had to be transformed into a pinacolate group for further functionalization.[9] Hoveyda,[10] Yun,[11] Ito,[12] and more recently Carretero and Gómez-Arrayás[13] have reported the related Cu-catalyzed hydroboration of alkynes (Scheme 1, eq 2).[14,15] Although vinylcopper species are proposed as intermediates, their further reaction with an alkyl halide has never been reported. Herein, we describe the first Cu-catalyzed formal *syn* carboboration of simple alkynes (Scheme 1, eq 3). The reaction proceeds without directing groups to create both a C−B and a C−C bond, in a single catalytic cycle, using commercially available bis(pinacolato)diboron.

Scheme 1. Cu-Catalyzed Carboboration of Alkynes



To start our carboboration studies we first focused on *cis*-branched methyl vinylboronates. These boronic esters are direct precursors of *cis*-branched methylalkenes, widely found in natural products[16] and also prominent in drugs and biologically active compounds (Figure 1).[17] However, stereoselective methods to synthesize *cis*-branched methyl alkenylboronates are still limited,[18] especially those in which a C−B and a C−Me bond are created in a single catalytic cycle.[19] Therefore, a Cu-catalyzed methylboration of alkynes would be an interesting approach to this class of boronic esters.

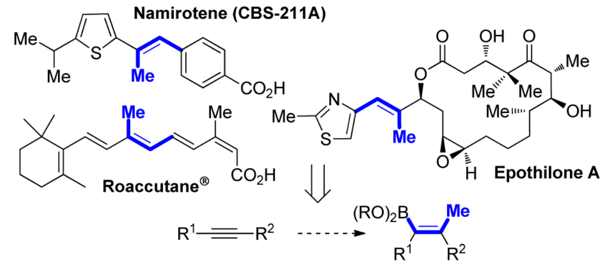
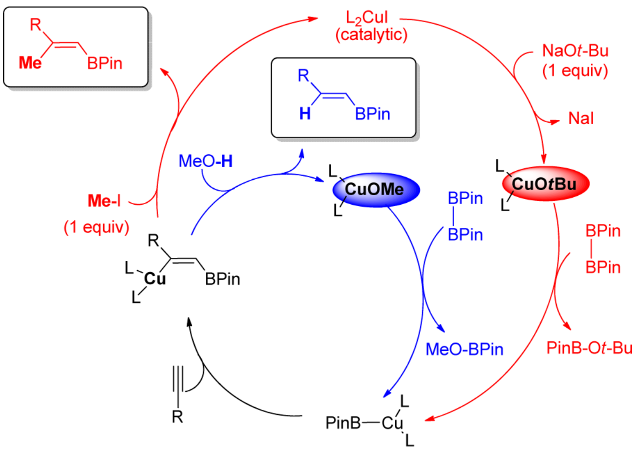


Figure 1. Biologically active methyl-branched alkenes.

Based on the proposed catalytic cycle for the Cu-catalyzed hydroboration (blue in Scheme 2), we reasoned that a methylboration (red in Scheme 2) would require the presence of an electrophile (MeI instead of MeOH) and the use of at least 1 equiv of NaO*t*-Bu (instead of the 0.2 equiv usually required for hydroboration). The CuI formed by reaction of the vinylcopper intermediate with MeI would be transformed into the catalytically active CuO*t*-Bu. Under these conditions, the

Received: April 24, 2012

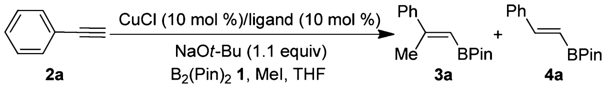
Scheme 2. Comparison of the Catalytic Cycles of the Cu-Catalyzed Hydroboration and Carboboration (Present Work)



carboboration of alkynes would be possible if the vinyl cuprate intermediate were reactive enough to interact with MeI and if the catalyst or excess of NaO*t*-Bu did not interfere with the electrophile.[20]

We began by examining the methylboration of phenylacetylene **2a** with bis(pinacolato)diboron **1** and methyl iodide in the presence of catalytic amounts of a ligand (10 mol%), CuCl (10 mol%), and NaO*t*-Bu (Table 1). The use of xantphos and 1.1 equiv of NaO*t*-Bu at room temperature gave the desired product **3a**, along with a small amount of the hydroboration product **4a** (entry 1). The yield decreased using 0.6 equiv of the alkoxide, verifying our initial hypothesis (entry 2). Triphenylphosphine (entry 3) or a diphosphine with a smaller bite angle (entry 4) did not improve the result. Finally, we found that by adding 4 equiv of the electrophile we could suppress the formation of **4a** and **3a** was obtained in good yield as a single regio- and stereoisomer. Additionally, the catalyst loading could be reduced to 5% without affecting the yield (entry 6).

Table 1. Cu(I)-Catalyzed Methylboration of Alkyne 2a

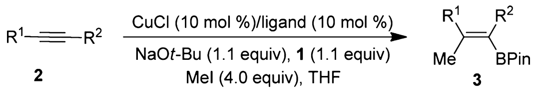


entry[a]	NaO*t*-Bu (equiv)	ligand[b]	MeI (equiv)	yield[c] (%)	3:4[d]
1	1.1	xantphos	2.0	68	92:8
2	0.6	xantphos	2.0	26	92:8
3	1.1	PPh$_3$	2.0	60	90:10
4	1.1	dppe	2.0	30	80:20
5	1.1	xantphos	4.0	74	>98:2
6[e]	1.1	xantphos	4.0	72	>98:2

[a]Conditions: 0.1 M in THF, 16 h, rt. [b]Abbreviations: xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; dppe = 1,2-bis-(diphenylphosphino)ethane. [c]Yield of isolated **3a**. [d]Determined by ^{1}H NMR analysis. [e]5 mol% CuCl and 5 mol% xantphos were used.

Next, we applied the optimized conditions to different aryl-substituted terminal (entries 1−13) and nonterminal (entries 14−16) alkynes (Table 2). Alkynes **2b−d**, with alkyl groups at the *para* and *meta* positions, afforded (*E*) trisubstituted vinylboronates **3b−d** as single regioisomers (entries 1−4). We observed that strong electron-donating groups at the *para* and *ortho* positions (**2e** and **2f**) diminished the rate of methylboration, needing higher concentrations and longer reaction times (entries 5 and 6). Halogen-containing alkynes **2g−i** selectively gave the methylboration products in good yields (entries 7−9).[21] Unfortunately, the 3,5-bis-(trifluoromethyl)phenyl derivative **2j** did not react, probably due to deprotonation of the alkyne in the presence of the alkoxide (entry 10). Base-sensitive functional groups such as acetates were compatible with the methylboration conditions (entry 11). Alkyne **2l**, with a trisubstituted aryl ring, and thienyl substituted **2m** also underwent the methylboration reaction in excellent yields (entries 12 and 13). Poor yields were obtained from nonterminal alkynes **2n,o** using xantphos as ligand. However, after searching for different conditions (see Supporting Information for details), we were able to improve the results by heating the reaction to 65 °C with trip-tolylphosphine (entries 14−16). The best result was obtained with alkyne **2p** (entry 16) bearing two electron withdrawing groups on the aromatic ring. One stereoisomer was exclusively formed in all cases, resulting from the *syn* addition of the methyl and boron groups.

Table 2. Cu(I)-Catalyzed Methylboration of Aryl-Substituted Alkynes

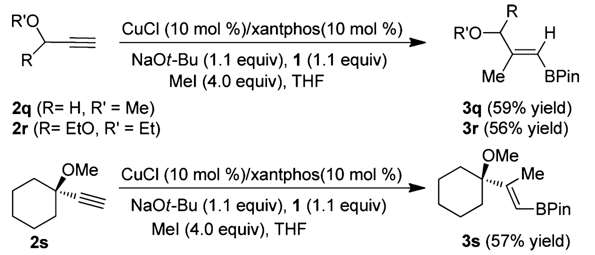


entry	R^1	R^2	product	yield[d] (%)
1[a]	C$_6$H$_5$, **2a**	H	**3a**	74
2[a]	*p*-MeC$_6$H$_4$, **2b**	H	**3b**	68
3[a]	*p*-*t*-BuC$_6$H, $_4$ **2c**	H	**3c**	83
4[a]	*m*-MeC$_6$H$_4$, **2d**	H	**3d**	75
5[b]	*p*-MeOC$_6$H$_4$, **2e**	H	**3e**	76
6[b]	*o*-MeOC$_6$H$_4$, **2f**	H	**3f**	80
7[a]	*p*-FC$_6$H$_4$, **2g**	H	**3g**	72
8[a]	*p*-BrC$_6$H$_4$, **2h**	H	**3h**	72
9[a]	*m*-FC$_6$H$_4$, **2i**	H	**3i**	66
10[a]	3,5-(CF$_3$)$_2$-C$_6$H$_3$, **2j**	H	**3j**	_
11[a]	*p*-(CH$_3$CO$_2$CH$_2$)C$_6$H$_4$, **2k**	H	**3k**	70
12[b]	2,4,5-(CH$_3$)$_3$-C$_6$H$_2$, **2l**	H	**3l**	81
13[b]	2-thienyl, **2m**	H	**3m**	83
14[c]	C$_6$H $_5$, **2n**	Me	**3n**	50
15[c]	C$_6$H$_5$, **2o**	C$_6$H$_5$	**3o**	50
16[c]	3,5-(CF$_3$)$_2$-C$_6$H$_3$, **2p**	Me	**3p**	70

[a]Conditions: xantphos, 0.1 M in THF, 16 h, rt. [b]Conditions: xantphos, 0.6 M in THF, 24 h, rt. [c]Conditions: P(*p*-tolyl)$_3$, 0.6 M toluene, 24 h, 60 °C. [d]Yield of isolated **3**.

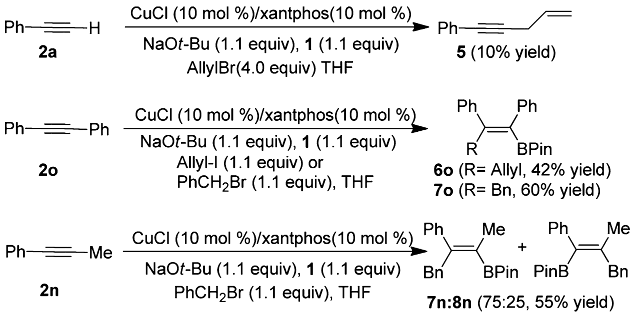
We then explored the methylboration of alkyl-substituted alkynes. While simple alkyl terminal alkynes did not react under the conditions described above, those bearing an ether moiety at the propargylic position gave good results (Scheme 3). Propargylic ether **2q** afforded vinylboronate **3q** as a single regio- and stereoisomer. Importantly, the methylboration conditions did not promote the formation of di- or triborylated compounds by β-oxygen elimination from vinylcopper species.[14] Acetals were also compatible with the methylboration conditions and alkyne **2r** gave protected aldehyde **3r**, which is a very versatile synthetic intermediate. Additionally, we were pleased to find that tertiary ether **2s** also gave the methylboration product in good yield as a single compound.

Scheme 3. Cu(I)-Catalyzed Methylboration of Propargylic-Functionalized Alkynes



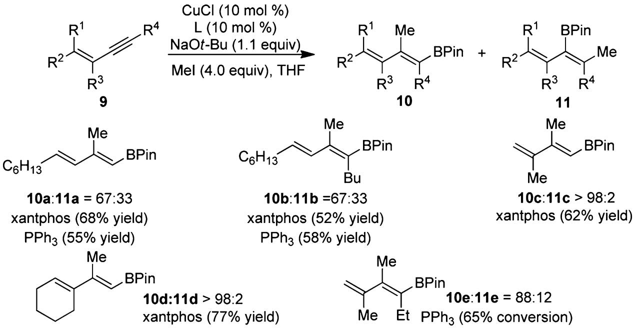
The introduction of other electrophiles was then addressed (Scheme 4). Surprisingly, the reaction of **2a** with allyl bromide gave only allylation at the terminal position of the alkyne.[22] Hoping to avoid this problem, we then explored the reaction of a nonterminal alkyne, **2o**, with allyl iodide and benzyl bromide. Gratifyingly, we obtained the desired compounds **6o** and **7o** in moderate to good yields. Reaction of benzyl bromide with the nonsymmetrical alkyne **2n** also gave the benzylated carboboration product but as a mixture of regioisomers **7n** and **8n**.[23] This result is in contrast with those obtained with **2n** under hydroboration[11] and methylboration (Table 2, entry 14) conditions in which only one regioisomer was obtained and suggests that the electrophile is playing a role in the control of the regiochemistry of the reaction. Importantly, we did not observe borylation of the benzyl bromide in any case.[20,24] These results provide the first evidence that intermediates in the Cu-catalyzed hydroboration reactions can be trapped by different electrophiles.

Scheme 4. Cu(I)-Catalyzed Carboboration of Alkynes



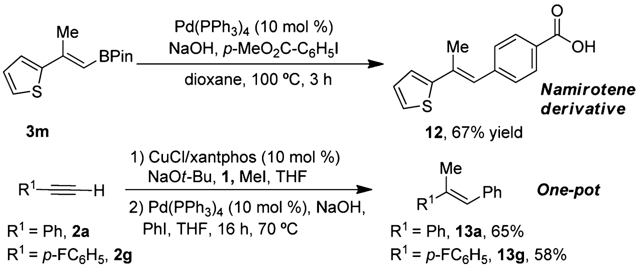
Finally, we explored the methylboration of the more challenging 1,3-enynes (Scheme 5). With enynes **9a** (R^1, R^3, R^4 = H, R^2 = C_6H_{13}) and **9b** (R^1, R^3 = H, R^2 = C_6H_{13}, R^4 = Bu), and using either PPh_3 or xantphos, the methylboration took place in good yield but very poor regioselectivity. The result observed for **9b** is in contrast with that found for the Cu-catalyzed hydroboration of similar alkynes.[12] Under hydroboration conditions, only the regioisomer related to **10** was obtained with PPh_3, while complete hydroboration of the double bond of the enyne was observed with xantphos. Interestingly, 2-substituted and 1,2-disubstituted enynes **9c** (R^1, R^2, R^4 = H, R^3 = Me) and **9d** (R^1, R^4 = H, R^2, R^3 = $-(CH_2)_4-$) afforded the methylboration products **10c−d** as single compounds. Additionally, nonterminal enyne **9e** (R^1, R^2 = H, R^3 = Me, R^4 = Et) gave tetrasubstituted vinylboronate **10e** along with a small amount of the regioisomer **11e**.[25] Together, these data and those in Scheme 4 would suggest that the carboboration reaction mechanism differs significantly from the generally accepted Cu-catalyzed hydroboration mechanism.

Scheme 5. Cu(I)-Catalyzed Methylboration of 1,3-Enynes



The vinylboronates obtained in this study are useful synthetic intermediates for the synthesis of trisubstituted alkenes (Scheme 6). The coupling of thienyl derivative **3m** with ethyl 4-iodobenzoate, with concomitant hydrolysis of the methyl ester, afforded namirotene derivative **12** in good yield. Additionally, alkenes **13a** and **13g** were prepared in good overall yield through a one-pot methylboration-Suzuki coupling sequence from commercially available alkynes, allowing an easy entry to trisubstituted alkenes.

Scheme 6. Synthetic Applications of Vinylboronic Esters



In summary, we have developed the first copper-catalyzed formal carboboration of alkynes. Through this process, highly functionalized vinyl pinacol boronic esters can be obtained from readily available starting materials. Additionally, the one-pot methylboration-Suzuki coupling sequence allows rapid access to highly functionalized alkenes, which are fundamental building blocks in organic synthesis. Some of the results disclosed in this paper suggest significant differences between the hydro- and the carboboration reactions. Mechanistic studies to understand these discrepancies are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Author Contributions

†R.A. and A.P. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from Spanish Government (CTQ-2009-12168) and CAM ("programa AVANCAT CS2009/PPQ-1634") is gratefully acknowledged. J.A. and M.T. thank the MICINN for "Ramon y Cajal" contracts, and R.A. thanks the "Consejo Nacional de Ciencia y Tecnología de México" for a postdoctoral fellowship.

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(6) For the synthesis of tetrasubstituted vinylboronates, see: (a) Hata, T.; Kitagawa, H.; Masai, H.; Kurahashi, T.; Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 790. (b) Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 12506. (c) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (d) Nishihara, Y.; Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K. *J. Am. Chem. Soc.* **2007**, *129*, 12634. (e) Endo, K.; Hirokami, M.; Shibata, T. *J. Org. Chem.* **2010**, *75*, 3469. (f) Hupe, E.; Marek, I.; Knochel, P. *Org. Lett.* **2002**, *4*, 2861.

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(19) To our knowledge, the only example reported to date requires the use of a palladium catalyst, a methylzirconium reagent, and an internal alcohol to promote the boron insertion. See ref 7e.

(20) For a copper-catalyzed borylation of primary alkyl halides under similar conditions, see: (a) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 528. (b) Ito, H.; Kubota, K. *Org. Lett.* **2012**, *14*, 890.

(21) For a copper-catalyzed borylation of aryl bromides under similar conditions, see: Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350.

(22) When we used 1 equiv of CuCl we obtained the allylated product in 50% yield. In contrast, we did not observe methylation of **2a** when we used MeI as electrophile (Table 2).

(23) The experiments and computational investigation of the copper-catalyzed hydroboration carried out by Hoveyda (see ref 13) do not support a reversible Cu−B addition to the alkyne. Their study indicates that catalyst−substrate association is product-determining. Although we do not have enough evidence, our results suggest that the electrophile and/or the excess of NaO-*t*Bu are playing an important role in that catalyst−substrate association.

(24) Despite this observation, we cannot rule out a mechanistic pathway involving a copper-catalyzed borylation of the alkyl halide followed by carboboration. Additional experimental studies are underway.

(25) We could not determine the yield for **6e** due to stability issues found during its purification. See Supporting Information.