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Formal Regiocontrolled Hydroboration of Unbiased Internal Alkynes via Borylation/ Allylic Alkylation of Terminal Alkynes

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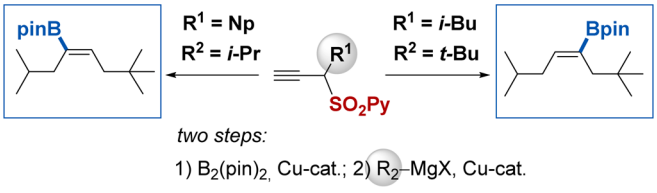
ABSTRACT



In accessing trisubstituted vinyl boronates from terminal alkynes, a propargyl directing (2-pyridyl)sulfonyl group allows terminal alkynes to undergo Cu-catalyzed $B_2(pin)_2$-borylation and subsequent Cu-catalyzed allylic alkylation with Grignard reagents without affecting the pinacolboronate moiety, thereby formally enabling a highly stereo- and regiocontrolled access to hydroboration products of unbiased dialkyl internal alkynes.

Vinyl boron reagents are pivotal synthetic building blocks endowed with diverse reactivity and great functional tolerance.[1] The catalytic hydroboration of terminal alkynes is a straightforward method for the synthesis of terminal *E*-vinyl boronates[2,3] via syn addition of the B–H bond in a non-Markovnikov manner (Scheme 1A). This regiochemical outcome has been elegantly expanded to branched vinyl boronates by Hoveyda,[4,5] who discovered that terminal alkynes undergo a highly α-selective NHC-Cu-catalyzed borylation with $B_2(pin)_2$ (Scheme 1B). However, achieving high α-regiocontrol in alkyl-substituted terminal alkynes seems to be limited to propargyl alcohol, propargyl amine, and their derivatives. This structural restriction is consistent with recent observations by Tsuji,[6] McQuade,[7] and us[8] in the Cu^I-catalyzed $B_2(pin)_2$-borylation of dialkyl internal alkynes, wherein a propargylic *N*- or *O*-based group was required to achieve high regiocontrol.[9] However, these methods generally suffer from low regiocontrol when applied to internal dialkyl

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(2) For reviews on hydroboration of alkynes, see: (a) Brown, H. C.; Campbell, J. B., Jr. *Aldrichimica Acta* **1981**, *14*, 3. (b) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957. For a review on hydrometalation of alkynes, see: (c) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853. For the pioneering hydroboration of alkynes with pinacolborane, see: (d) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482.

(3) For *Z*-vinyl boronates from terminal alkynes, see: (a) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990. (b) Gunanathan, C.; Hölscher, M.; Pan, F.; Leitner, W. *J. Am. Chem. Soc.* **2012**, *134*, 14349.

(4) (a) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859. See also: (b) Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 18234.

(5) Seminal $B_2(pin)_2$-borylation under stoichiometric Cu^I: (a) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47. Cu-catalyzed β-selective borylation of phenylacetylene: (b) Lee, J. E.; Kwon, J.; Yun, J. *Chem. Commun.* **2008**, 733.

(6) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem.—Eur. J.* **2012**, *18*, 4179.

(7) Park, J. K.; Ondrusek, B. A.; McQuade, D. T. *Org. Lett.* **2012**, *14*, 4790.

(8) Moure, A. L.; Gómez Arrayás, R.; Cárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2012**, *134*, 7219.

(9) See also: (a) Yuana, W.; Ma, S. *Org. Biomol. Chem.* **2012**, *10*, 7266. (b) Alfaro, R.; Parra, A.; Alemán, J.; García Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc.* **2012**, *134*, 15165. (c) Alfaro, R.; Parra, A.; Alemán, J.; Tortosa, M. *Synlett* **2013**, 10.1055/s-0032-1318483.

(10) Moving away the polar functionality to the homopropargylic position, or the use of simple alkyl-alkynes, led to poor regiocontrol. See, for instance, refs 4a, 6, 8, and 9b.

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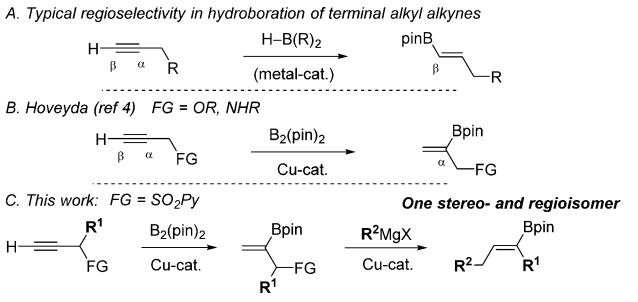
alkynes without the electronic bias exerted by a polar functionality at the propargylic position[10] or that found in conjugated 1-aryl-1-alkynes[9,11] or 1,3-enynes.[9b,12] Therefore, methods for the highly regiocontrolled hydroboration of unbiased internal dialkyl alkynes are actively sought after.

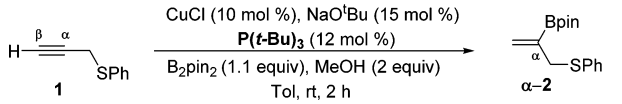
Scheme 1. Regiocontrolled Borylation of Terminal Alkyl Alkynes



To address this challenge, we envisaged the use of terminal alkynes with a removable propargyl directing group[13] which could promote an α-regiocontrolled borylation while also serve as a handle for further elaboration via subsequent allylic alkylation. Along this line, Walsh[14] has reported on the chemoselective Tsuji–Trost substitution of allylic acetates with an embedded vinyl boronate moiety. The development of a Cu-catalyzed allylic alkylation of similar substrates with Grignard reagents would nicely complement Pd-catalysis, enabling the direct introduction of nonstabilized alkyl, alkenyl, or aryl groups. However, this reactivity is hampered by impediments such as the transmetalation from alkenyl-Bpin to alkenyl-Cu species[15] or the formation of boron-ate complexes.[16] In fact, Hall found that (pin)B–C bonds were unsuitable for Cu-catalyzed conjugate additions of Grignard reagents.[16] We hypothesized that addressing the chemical compatibility of the Bpin moiety with Grignard reagents under Cu catalysis would offer a practical indirect solution to access formal hydroboration products of unbiased terminal and internal alkynes. Herein, we describe the successful execution of a borylation/allylic alkylation strategy which relies on the use of a propargylic 2-$PySO_2$ group as an efficient regiodirector in the first step and a practical stereocontroller in the second. This approach enables the access to di- and trisubstituted vinyl boronates from simple terminal alkynes, including the two regiochemically complementary formal hydroboration products of unbiased internal alkynes.

At the outset of our work, propargyl sulfide **1** was chosen as a model substrate for Cu^I-catalyzed $B_2(pin)_2$-borylation[17,18] under typical conditions (see Supporting Information (SI) for ligand effects). This study showed that both reactivity and regiocontrol were impacted by ligand structure.[19] The use of P(*t*-Bu)$_3$[20] was essential for effective α-regiocontrol and high catalytic activity. The combination of CuCl (10 mol %), NaO*t*Bu (15 mol %), and P(*t*-Bu)$_3$ (12 mol %) provided α-**2** as the only detected product in 76% yield after 2 h (Scheme 2).[21]

Scheme 2. Cu-Catalyzed α-Selective Borylation of Sulfide **1**



76% isolated yield, α/β = >98:<2

The regiocontrolling ability of the functionality at the propargylic position (FG) was next assessed (see selected results in Table 1; full results in Table S2 of the SI). Uniformly excellent α-regiocontrol (generally α/β = >98:<2) and high reactivity were observed for a variety of *S*-, *O*-, and *N*-functional groups with different steric and electronic properties. Notably, sulfones **3** and **4** (bearing a coordinating 2-$PySO_2$ group)[22] were amenable to the reaction conditions (Table 1, entries 1 and 2). Propargyl alcohol **5**, the challenging propargyl acetate **6**,[23] and the *N*-Boc propargylamine **7** delivered the corresponding vinyl

(11) (a) Kim, H. R.; Jung, I. G.; Yoo, K.; Jang, K.; Lee, E. S.; Yun, J.; Son, S. U. *Chem. Commun.* **2010**, *46*, 758. (b) Ryung, H.; Yun, J. *Chem. Commun.* **2011**, *47*, 2943. For Cu-catalyzed carboboration of unsymmetrical aryl-substituted internal alkynes: (c) Zhang, L.; Cheng, J.; Carry, B.; Hou, Z. *J. Am. Chem. Soc.* **2012**, *134*, 14314.

(12) Sasaki, Y.; Horita, Y.; Zhong, C.; Sawamura, M.; Ito, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 2778.

(13) For a review on removable directing groups in catalysis, see: Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450.

(14) Hussain, M. M.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1834.

(15) For transmetallation from boron to copper in alkenyl boronates to give alkenyl-Cu species: Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490 and references cited therein. See also ref 1e.

(16) Lee, J. C. H.; Hall, D. G. *J. Am. Chem. Soc.* **2010**, *132*, 5544.

(17) For reviews on asymmetric Cu^I-catalyzed borylation of conjugated alkenes, see: (a) Schiffner, J. A.; Múther, K.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1194. (b) Mantilli, L.; Mazet, C. *ChemCatChem* **2010**, *2*, 501. See also: (c) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894. (d) Kobayashi, S.; Xu, P.; Endo, T.; Ueno, M.; Kitanosono, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 12763. For the application to α,β-unsaturated sulfones: (e) López-Moure, A.; Gómez Arrayás, R.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6701. For Cu-catalyzed borylation of allenes: (f) Meng, F.; Jung, B.; Haeffner, F.; Hoveyda, A. H. *Org. Lett.* **2013**, *15*, 1414. For Cu-catalyzed borylation of vinyl silanes: (g) Meng, F.; Jang, H.; Hoveyda, A. H. *Chem.—Eur. J.* **2013**, *19*, 3204.

(18) Other Cu-catalyzed $B_2(pin)_2$-borylation of internal alkynes: (a) Yoshida, H.; Kawashima, S.; Takemoto, Y.; Okada, K.; Ohshita, J.; Takaki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 235. Cu-catalyzed $B_2(pin)_2$-borylation of allenes: (b) Yuan, W.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 1867. Fe-catalyzed hydroboration: (c) Haberberger, M.; Enthaler, S. *Chem.—Asian J.* **2012**, *8*, 50. Cu-catalyzed borylation of acetylenic esters: (d) Lipshutz, B. H.; Bošković, Z. V.; Aue, D. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 10183. (e) Jung, H.-Y.; Feng, X.; Kim, H.; Yun, J. *Tetrahedron* **2012**, *68*, 3444.

(19) No reaction was observed in the absence of the Cu^I catalyst, whereas very low conversion and complete β-regioselectivity were observed in the absence of ligand.

(20) An identical result was obtained when the air-stable (*t*-Bu_3P·HBF_4) was used (increasing the amount of NaO*t*Bu to 27 mol %).

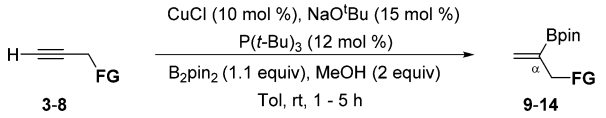
(21) For thorough mechanistic studies accounting for the origin of the α-selectivity, see ref 4a. See SI for a mechanistic discussion.

(22) For the Cu-coordinating capability of the 2-pyridylsulfonyl group, see: Esquivias, J.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 9257.

(23) The Cu-catalyzed $B_2(pin)_2$-borylation of propargylic carbonates was found to give allenyl boronates: Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774.

boronates in good yields (entries 3–5). Not unexpectedly, the borylation of the 2-propynylbenzene (**14**, entry 6) failed to provide useful regiocontrol, demonstrating the importance of the propargyl directing group.

Table 1. α-Borylation in Propargylic Substituted Alkynes



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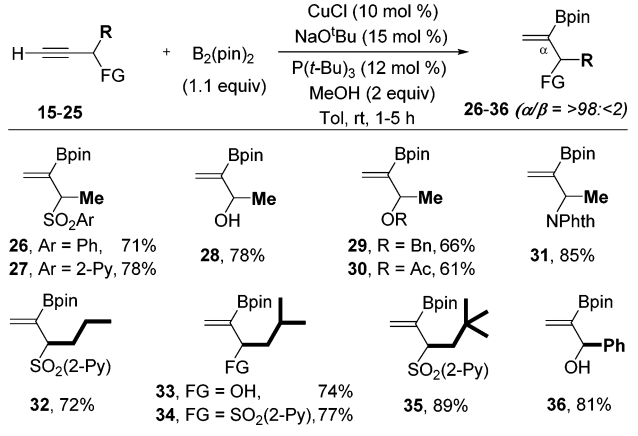
entry[a]	**FG** (alkyne)	product	α/β ratio[b]	yield (%)[c]
1	SO_2Ph (**3**)	**9**	>98:<2	80
2	SO_2(2-Py) (**4**)	**10**	>98:<2	83
3	OH (**5**)	**11**	>98:<2	64[d]
4	OAc (**6**)	**12**	>98:<2	70
5	NHBoc (**7**)	**13**	>98:<2	76
6	Ph (**8**)	**14**	67:13	78[e]

[a] 0.26 mmol scale in alkyne substrate. [b] Determined by ^{1}H NMR from the crude mixture. [c] Isolated product after chromatography. [d] In the absence of MeOH. [e] As a mixture of regioisomers.

Extending the scope of the reaction to terminal alkynes with branched propargylic substitution is attractive because the resulting vinyl boronates are difficult to synthesize otherwise. To our knowledge, the α-regiocontrolled borylation of this type of substrates has not been reported previously, likely due to the increased steric hindrance next to the borylation site imposed by the R group (Scheme 3). Notably, our method was found to successfully incorporate propargylic substitution, with all cases examined proceeding in good yields and >98% α-selectivity. The presence of a methyl substituent (R = Me) in various propargyl functionalized alkynes (**15**–**20**) had no negative effect (products **26**–**31**, 61–85% yield). More sterically demanding substrates (R = propyl, isobutyl, or neopentyl) were also accommodated with minimal impact on the yield (products **32**–**35**, 72–77% yield). Aryl groups were also suitable (product **36**, 81% yield).

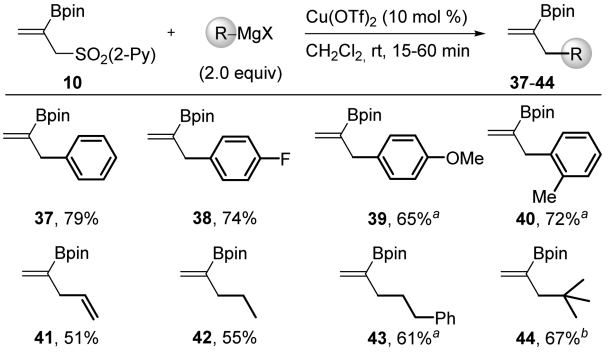
Scheme 3. Effect of Branching at the Propargylic Position



Important from a practical standpoint, this protocol allows for simultaneous scale-up and a lower catalyst loading. For example, using 1 mol % of the catalytic system products **10** (1.30 g, 4.09 mmol, 74%), **12** (2.34 g, 10.35 mmol, 71%), and **31** (1.34 g, 4.10 mmol, 82%) were obtained without appreciable loss of chemical efficiency. To our delight, 0.5 mol % of Cu-catalyst was equally applicable (**10**, 2.53 g, 8.2 mmol, 74%). All reactions were completed in 3 h at rt.[24]

As mentioned above, we next directed our efforts toward the ellaboration of the allylic functional group without alteration of the boron moiety.[25] In this context, we focused on the direct introduction of alkyl or aryl groups via Cu-catalyzed allylic alkylation with Grignard reagents. 2-PySO_2 was chosen as a leaving group on the basis of the better stereocontrol observed for allylic substitutions of branched allyl derivatives.[26,27] We were pleased to find a smooth reaction of **10** with a variety of Grignard reagents, demonstrating the tolerance of the B(pin) unit to the reaction conditions (Scheme 4). Arylmagnesium reagents bearing either electron-donating or -withdrawing character, including *ortho*-substitution, were amenable to this protocol (products **37**–**40**, 65–79% yield). Importantly, vinyl- (product **41**, 51%) and alkyl-Grignard reagents (products **42**–**44**, 55–67%) were also applicable. In all cases full conversion was reached within 15–60 min, providing branched vinyl boronates in moderate to good yields (51–79%).

Scheme 4. Cu-Catalyzed Allylic Substitution of Allyl Sulfone **10** with Grignard Reagents



[a] Reaction performed at −50 °C. [b] Reaction performed at 0 °C.

To push further the limits of this allylic substitution, and taking advantage of the tolerance of the borylation step to

(24) See SI for details and further examples.

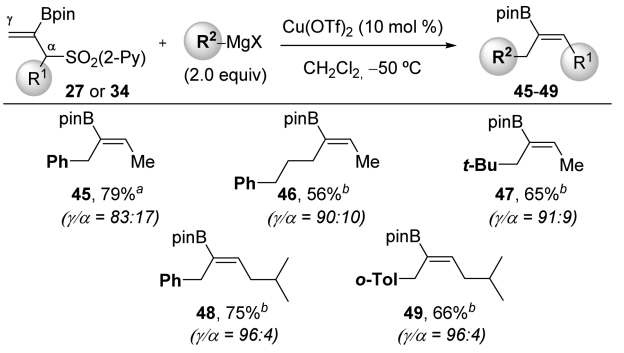
(25) Following Walsh's procedure (ref 14), Tsuji–Trost allylic substitution of acetate **12** with dimethyl malonate and subsequent Suzuki coupling were also found to be viable (see SI). See also SI for Suzuki and Cham–Evans–Lam coupling reactions of vinyl boronate **13** to afford disubstituted olefins.

(26) 2-PySO_2 was a highly efficient leaving group in the Cu-catalyzed allylic substitution of allylic sulfones with Grignard reagents: (a) Llamas, T.; Gómez Arrayás, R.; Carretero, J. C. *Adv. Synth. Catal.* **2004**, *346*, 1651. Allyl phenyl sulfones have been little explored in Cu-catalyzed allylic substitution with nonstabilized nucleophiles: (b) Julia, M.; Righini, A.; Verpeaux, J.-N. *Tetrahedron* **1983**, *39*, 3283. (c) Trost, B. M.; Merlic, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 5216.

(27) 2-Pyridylsulfone **27** showed better reactivity and selectivity than phenylsulfone **26** or acetate **30** in the reaction with PhMgBr (see SI).

branching at the allylic position, we examined the more challenging sulfones **27** and **34** (Scheme 5). For these compounds regio- and stereocontrol become issues of concern due to the possibility of α- or γ-addition to the unsymmetrical allyl intermediate, and the (*E*)- or (*Z*)-geometry in the newly formed double bond. Remarkably, the 2-$PySO_2$ group plays an important role in achieving high γ-regiocontrol (attack at the less hindered allylic terminus) and affording a (*Z*)-double bond geometry exclusively at a temperature of −50 °C.[27] The resulting trisubstituted vinyl boronates were typically isolated as single isomers upon chromatographic separation (products **45**−**49**). Notably, three types of selectivity are effectively controlled in this reaction: (i) *chemoselectivity* to favor allylic substitution over the reaction of Cu with the C−B bond,[15] (ii) *regioselectivity* to favor C−C bond formation at the γ allyl terminus, and (iii) *stereoselectivity* to favor formation of the (*Z*)-olefin.

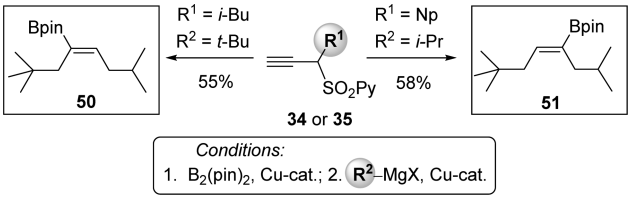
Scheme 5. Cu-Catalyzed Allylic Substitution of α-Branched-β-Boryl β,γ-Unsaturated Sulfones with Grignard Reagents



[a] Isolated as a mixture of γ/α = 93:7. [b] Isolated as regio- and stereoisomerically pure products.

This two-step sequence constitutes a formal regioselective hydroboration of internal alkynes lacking any directing group, for which a direct regioselective hydroboration has not been documented so far (especially those with isosteric substituents). To further illustrate the potential of this method, we sought to prepare in a controlled fashion the two regiocomplementary hydroboration products of a challenging alkyne such as isobutyl neopentyl acetylene (Scheme 6). This goal was achieved by controlling the two points of structural diversity featured in this method: the starting propargyl sulfone [R^1 = *i*-Bu (**34**) or R^1 = Np (**35**)] and the Grignard reagent (*i*-PrMgCl or *t*-BuMgBr) used in the borylation and allylic substitution processes. Product **50** was obtained in 93% selectivity and 55% overall yield, while the complementary boronate **51** was obtained with >98% selectivity (58% overall yield).

Scheme 6. Selective Preparation of Both Hydroboration Products of Isobutyl Neopentyl Acetylene



[a] Isolated yields of regio- and stereoisomerically pure products.

In summary, a practical regio- and stereocontrolled synthesis of di- and trisubstituted vinyl boronates from terminal alkynes based on an α-selective Cu-catalyzed $B_2(pin)_2$-borylation followed by Cu-catalyzed allylic substitution with Grignard reagents is disclosed. The presence of a propargyl (2-Py)SO_2 functionality is key to achieving high levels of regio- and stereoselectivity. This two-step sequence enables the access to formal hydroboration products of unbiased unsymmetrical dialkyl alkynes from terminal alkynes in a highly stereo- and regiocontrolled fashion.

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Supporting Information Available. Experimental procedures and characterization data of new compounds and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.