JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Regiocontrolled Cu^{I}-Catalyzed Borylation of Propargylic-Functionalized Internal Alkynes

Abraham L. Moure, Ramón Gómez Arrayás,* Diego J. Cárdenas, Inés Alonso, and Juan C. Carretero*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

Supporting Information

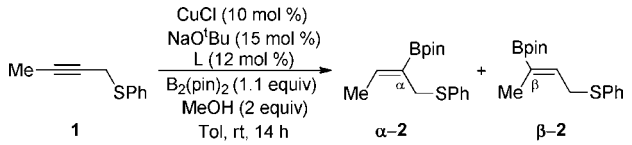
ABSTRACT: Good to excellent reactivity and regiocontrol have been achieved in the Cu^{I}-catalyzed borylation of dialkyl internal alkynes with bis(pinacolato)diboron. The presence of a propargylic polar group (OH, OR, SAr, SO_2Ar, or NHTs), in combination with PCy_3 as ligand, allowed maximizing the reactivity and site-selectivity (β to the propargylic function). DFT calculations suggest a subtle orbitalic influence from the propargylic group, matched with ligand and substrate size effects, as key factors involved in the high β-selectivity. The vinylboronates allowed the stereoselective synthesis of trisubstituted olefins, while allylic substitution of the SO_2Py group without affecting the boronate group provided access to formal hydroboration products of unbiased dialkylalkynes.

One of the greatest challenges associated with selective functionalization of alkynes via hydrometalation is the control of the regioselectivity.[1] Achieving high regiocontrol generally relies on the use of alkynes with a marked bias in either the size or the electronic characteristics of the acetylenic substituents, such as terminal alkynes, aryl-substituted alkynes, and conjugated enynes.[1] In contrast, simple dialkylalkynes without a strong electronic or steric bias (i.e., alkyl-C≡C-alkyl′) often lead to unpractical regioisomeric mixtures. These characteristics hold true in hydroboration reactions.[1,2] The catalytic hydroboration of terminal alkynes with B−H reagents[2] is regarded as one of the most straightforward methods for accessing vinylboronate reagents, which are highly versatile building blocks endowed with numerous synthetic applications.[3] The anti-Markovnikov addition was the usual regiochemical outcome in the direct borylation of terminal alkynes until the very recent work by Hoveyda and co-workers, who devised a NHC-Cu-catalyzed borylation protocol with bis(pinacolato)diboron [$B_2(pin)_2$], leading to functionalized branched vinylboronates with high α-selectivity.[4,5]

The regiocontrolled borylation of internal unsymmetrical alkynes represents an even greater challenge because of their lower reactivity and difficult regiocontrol. Indeed, only recently have the first two successful reports on highly regioselective borylation of internal alkynes appeared.[6−8] Both are elegant examples of Cu^{I}-catalyzed $B_2(pin)_2$-borylation of electronically biased internal alkynes, such as 1-aryl-1-alkynes[6] and 1,3-enynes.[7] In contrast, a general procedure for the highly regiocontrolled hydroboration of simple dialkylalkynes remains an unmet challenge. Herein we present an operationally trivial, Cu^{I}-PCy_3-catalyzed protocol for the regio- and stereocontrolled $B_2(pin)_2$-borylation of propargylic functionalized dialkylalkynes. The resulting vinylboronates were applied to the stereoselective synthesis of trisubstituted alkenes via cross-coupling reactions. Further elaboration of the borylation products without affecting the boronate group via allylic substitution allowed widening the current structural scope in the synthesis of vinylboronates.

Given the wide chemical versatility of sulfur compounds, we envisioned that propargyl sulfur-containing species might have a neighboring regiocontrolling effect in the Cu^{I}-catalyzed borylation reaction with $B_2(pin)_2$. To test this hypothesis, model sulfide **1** was subjected to Cu-catalyzed[9] borylation under the standard reported conditions[10] (Table 1). In

Table 1. Ligand Screening in the Borylation of Alkyne 1



1 α–2 β–2

entry	L	conv (%)[a]	α/β ratio[a]
1	–	15	<2 : >98
2	Xantphos	<2[b]	–
3	dppf	<2[b]	–
4	*rac*-Binap	<2[b]	–
5	Xphos	18	<2 : >98
6	PPh_3	50	<2 : >98
7	PCy_3	>98[c] (76)[d]	<2 : >98
8	P(*t*-Bu)$_3$	60	25 : 75

[a]Determined by ^{1}H NMR from the crude mixture. [b]Starting material recovered. [c]Reaction time 2 h. [d]Yield after chromatography.

accordance with literature precedents,[4−7] we noticed a strong dependence of the reactivity upon the nature of the ligand. Very poor reactivity (15% conversion), yet a very high β-selectivity, were observed in the absence of ligand (entry 1). Typical bidentate phosphines such as Xantphos,[11] dppf, or (±)-Binap were totally ineffective (entries 2−4). A scan of the recent literature revealed that the level of reactivity and regiocontrol in addition reactions to alkynes can be optimized by adjusting the steric and electronic properties of monodentate phosphine or NHC ligands.[4−7,12−14] Xphos[13] and PPh_3 ligands promoted the β-selective borylation, albeit with unpractical conversions (18% and 50%, respectively, entries 5

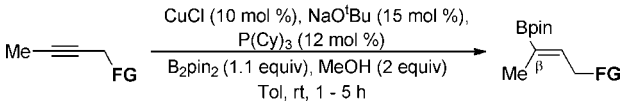
Received: January 26, 2012
Published: April 13, 2012

   dx.doi.org/10.1021/ja300627s | J. Am. Chem. Soc. 2012, 134, 7219−7222

and 6). To our delight, the reactivity was greatly enhanced with the more donating PCy_3 ligand (full conversion after 2 h at rt) while maintaining the excellent β-regiocontrol (entry 7). In contrast, the bulkier $P(t\text{-Bu})_3$ was much less reactive (60% conversion) and regioselective (α/β = 25 : 75; entry 8).

A variety of propargylic functional groups with various steric and electronic properties provided uniformly good reactivity and very high regiocontrol (generally >98% β-selectivity, Table 2). A potentially coordinating 2-pyridylsulfide group had no

Table 2. β-Borylation in Propargylic-Substituted 2-Butynes



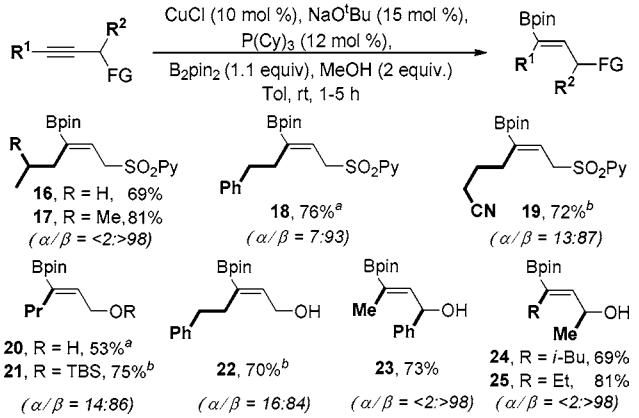
entry[a]	FG	product	α/β ratio[b]	yield (%)[c]
1	S(2-Py)	**3**	<2 : >98	82
2	SO_2Ph	**4**	<2 : >98	78
3	SO_2(2-Py)	**5**	<2 : >98	80
4	OH	**6**	<2 : >98	69[d]
5	OBn	**7**	<2 : >98	78
6	OPh	**8**	<2 : >98	79
7	OTBDMS	**9**	<2 : >98	76
8	OTIPS	**10**	<2 : >98	82
9	OAc	**11**	10 : 90	76[e]
10	NHTs	**12**	<2 : >98	89
11	CH_2OBn	**13**	12 : 88	72[f]
12	2-pentyne	**14**	15 : 85	30[f]
13	3-heptyne	**15**	43 : 57[g]	37[f]

[a]0.26 mmol scale in substrate. [b]Determined by ^{1}H NMR from the crude mixture. [c]Isolated product after chromatography. [d]Reaction carried out in the absence of MeOH. [e]In pure β-regioisomer after chromatographic separation. [f]Yield in the mixture of regioisomers. [g]α/β-site selectivity not assigned.

impact on reactivity or regioselectivity (entry 1), nor did the bulkier and more electrophilic sulfonyl substrates (products **4** and **5**, 78–80% yield, entries 2 and 3). Oxygenated propargyl derivatives proved also to be suitable, which is interesting given the availability of propargyl alcohols and the synthetic utility of the resulting allylic alcohols. The parent 2-butynol was successfully transformed into the β-vinylboronate **6**, bearing an allylic hydroxyl group (69%, entry 4). A series of propargyl alcohol derivatives delivered the corresponding vinylboronates in reasonable yields (76–82%), irrespective of the substituents attached to the oxygen (Bn, Ph, TBDMS, TIPS, or even the challenging Ac,[14] entries 5–9). Only the acetyl-protected substrate gave a lower regiocontrol (α/β = 10 : 90). This general trend in both reactivity and regioselectivity was also observed for the *N*-Ts-protected propargylamine (product **11**, α/β = <2 : >98, entry 10). This set of homogeneous results suggests that the observed regioselectivity profile is not derived from direct coordination of the propargylic function to copper. With regard to other types of internal alkynes, the homopropargyl benzyl-protected 3-pentynol derivative provided the corresponding β-vinylboronate with good, albeit significantly lower regiocontrol (**13**, α/β = 12 : 88, entry 11) than the propargyl derivative (entry 5). The borylation of a non-functionalized internal alkyne such as 2-pentyne was much less efficient (30% yield) and led to an inseparable 15 : 85 mixture of α/β vinylboronates (**14**, entry 12), showing a background steric regiocontrol favoring the borylation at the least hindered alkyne terminus. Accordingly, the 3-heptyne, with a reduced steric bias, led to much poorer regiocontrol and similar low yield (43 : 57 mixture, 37%, entry 13).

Structural variation at the alkyl acetylenic substituent (R^1) was also found to be viable (Scheme 1). For example, alkyl

Scheme 1. Other Propargylic-Substituted Internal Alkynes[a]



[a]Yield of β-regioisomer after chromatographic separation. [b]Yield in the mixture of regioisomers.

groups bulkier than methyl such as propyl, isobutyl, or phenethyl are well accommodated, preserving high regiocontrol (products **16**–**18**, from 93 to >98% β-selectivity).[15] A cyanopropyl group could be installed with somewhat lower regioselectivity (**19**, 87% β). Similar β-selectivity (86%) was also observed in the borylation of 2-hexynol and its OTBS-protected derivative (products **20** and **21**), as well as the 5-phenyl-2-pentynol (product **22**, 84% β). Interestingly, the β-selectivity was restored to α/β = <2 : >98 in the case of the bulkier secondary alcohol derivatives (R^2 = Me or Ph, products **23**–**25**), suggesting the modulating role of steric effects in the main regiochemical control exerted by the propargylic moiety.[16]

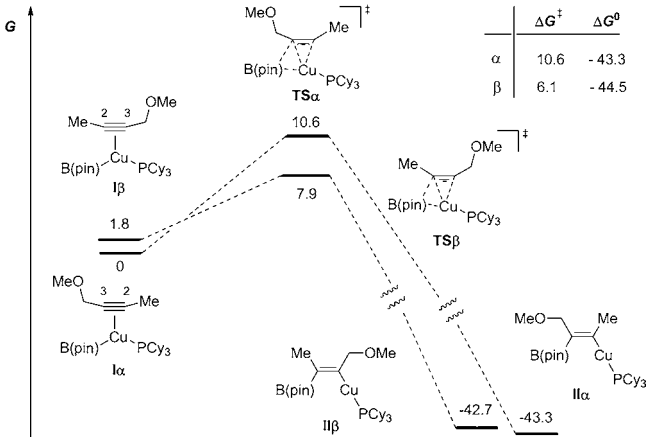
Despite the borylation reaction was routinely run at 0.26 mmol scale, we confirmed that the process is amenable to 10-fold scale-up without loss of chemical efficiency, such as in the case of products **4** (2.05 mmol, 76%), **7** (2.50 mmol, 85%), and **17** (1.64 mmol, 92%). Additionally, we found that the Cu^I catalyst loading can be reduced to 3 mol % with comparable efficiency (product **17**, 1.64 mmol, 87% yield, α/β = <2 : >98).

DFT calculations provided insight into the reasons for the observed regioselectivity. According to the accepted mechanism, formation of the B–C bond takes place in the coordination sphere of a boryl-Cu complex formed by initial transmetalation. We focused on the boryl-cupration of 4-methoxy-2-butyne coordinated to (pin)B-Cu-PCy_3, considering the complete phosphine ligand structure. Optimizations were performed with CPCM model in toluene (see Supporting Information for details).[17] Coordination of the alkyne may afford two different stereoisomeric trigonal complexes, **Iα** and **Iβ**, leading to the alkenylboronate regioisomers **IIα** and **IIβ** (Scheme 2). Both Cu–C(2) and Cu–C(3) distances are very similar in **Iβ**, in spite of the unsymmetrical nature of the alkyne (2.016 and 2.073 Å, respectively). In contrast, Cu–C(2) is significantly longer than Cu–C(3) in **Iα** (2.187 and 2.032 Å, respectively), which is 1.8 kcal mol^{-1} more stable than **Iβ**.[18]

Location of both transition states (TS, Figure 1) for the insertion of the alkyne into the Cu–B bond allowed us to

dx.doi.org/10.1021/ja300627s | J. Am. Chem. Soc. 2012, 134, 7219–7222

Scheme 2. Energy Profile for the Two Possible Boryl Cuprations of the Coordinated Alkyne[a]



[a]Optimized structures in toluene (M06/6-31G(d) (C,H,B,O,P), LANL2DZ (Cu), CPCM model). Relative *G* values at 298 K (kcal mol^{-1}).

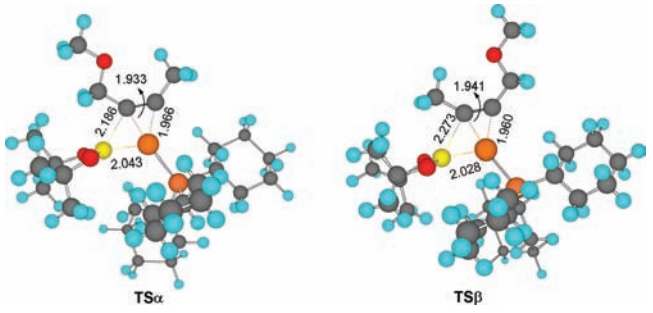
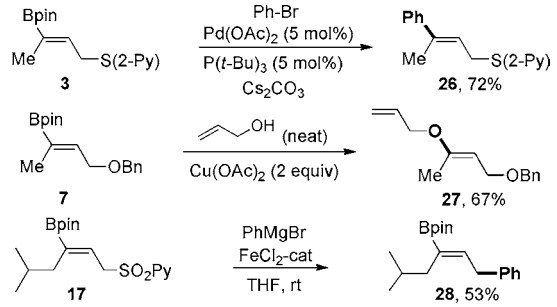


Figure 1. Molecular structure of the transition states **TS*α*** and **TS*β***. Representative distances (Å) are indicated.

obtain the corresponding activation energies, which are low (6.1 and 10.6 kcal mol^{-1} for *β* and *α* pathways, respectively) and in agreement with the experimentally observed regioselectivity. Thus, **TS*β*** lies 2.7 kcal mol^{-1} below **TS*α***. The carbon atom that binds to B strongly interacts with Cu in the TS, the Cu−C distances being shorter than those found in the starting complexes.[19] The lower energy pathway involves formation of an earlier TS (**TS*β***), with a longer C−B distance (2.273 vs 2.186 Å for **TS*α***). NBO analysis reveals a strong donor−acceptor interaction between boron and the π^*(C−C) alkyne orbital in both TSs. Interestingly, analysis of the HOMO of **TS*β*** shows that the O atom orbitals also participate in this MO, along with those of the alkyne and boryl moieties. Such participation is much smaller in **TS*α***, suggesting that this effect could lay at the basis of the *β*-regiocontrol (see schemes in Supporting Information). Therefore, the main reason for the observed regioselectivity seems to be the result of orbital control rather than merely steric effects.[20,21]

This formal hydroboration protocol offers an efficient approach to the stereocontrolled synthesis of multisubstituted alkenes[22] via cross-coupling reactions of the resulting products (Scheme 3). For example, the Suzuki reaction of sulfide **3** with bromobenzene afforded the corresponding trisubstituted olefin **26** in 72% yield. The Cu-promoted coupling with alcohols, recently reported by the group of Merlic[23] on terminal vinylboronates, was found to be applicable to the branched vinylboronate **7**, leading to the allyl vinyl ether **27** (67% yield).

Scheme 3. Synthetic Applications of the Vinylboronates



Further elaboration of the products without affecting the boronate group via nucleophilic allylic displacement of the directing functionality allowed widening the scope of the vinylboronate synthesis. This concept was realized in the Fe^{II}-catalyzed allylic substitution of the 2-pyridylsulfone **17** with PhMgBr, affording the new vinylboronate **28** (53% yield, unoptimized, Scheme 3). Remarkably, this reaction shows the compatibility of the pinacolboronate group with Grignard reagents under metal catalysis[24] and, to the best of our knowledge, represents the first example of a Fe-catalyzed nucleophilic displacement of allylic sulfones with Grignard reagents.[25]

In conclusion, we have disclosed a highly regiocontrolled $B_2(pin)_2/Cu^I$-catalyzed borylation of dialkylalkynes. The effectiveness of this method relies on the subtle electronic bias provided by a functional group at the propargylic position of the alkyne substrate, along with the use of the PCy_3 as ligand. Functionalized vinylboronates bearing a variety of sulfur, oxygen, and nitrogen groups at the allylic position are obtained in good yields and good to excellent *β*-selectivity. DFT calculations on the whole catalyst system are in agreement with the observed regioselectivity. The resulting products have been applied to the stereocontrolled synthesis of trisubstituted olefins via cross-coupling reactions. Further elaboration of the vinylboronates via Fe^{II}-catalyzed sulfonyl allylic substitution with Grignard reagents provides formal hydroboration products of unbiased dialkyl-substituted alkynes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental and computational details as well as spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

ramon.gomez@uam.es; juancarlos.carretero@uam.es

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Dedicated to Prof. Miguel A. Miranda on the occasion of his 60th birthday. This work was supported by the Ministerio de Ciencia e Innovación (MICINN, CTQ2009-07791 and CTQ 2010-15927) and the Consejería de Educación de la Comunidad de Madrid (programme AVANCAT, S2009/PPQ-1634). A.L.M. thanks the UAM for a predoctoral fellowship. We also thank Johnson Matthey PLC for a supply

of $Pd(OAc)_2$ and the Centro de Computación Científica de la UAM for generous allocation of computer time.

REFERENCES

(1) Review on hydrometallation of alkynes: Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853.

(2) Reviews on hydroboration of alkynes: (a) Brown, H. C.; Campbell, J. B., Jr. *Aldrichim. Acta* **1981**, *14*, 3. (b) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957. Pioneering hydroboration with pinacolborane: (c) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482. Review on metal-catalyzed reactions of organoboron reagents: (d) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535.

(3) Reviews on applications of vinylboronates in cross-coupling: (a) Hall, D. G. *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Wiley-VCH: Weinheim, 2005. (b) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535.

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

(6) (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 an example of regioselective hydroboration on a sterically biased *tert*-butyl-substituted internal alkyne, see ref 6b.

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

(8) Examples on carboboration of internal alkynes: (a) Daini, M.; Suginome, M. *Chem. Commun.* **2008**, 5224. (b) Suginome, M.; Shirakura, M.; Yamamoto, A. *J. Am. Chem. Soc.* **2006**, *128*, 14438.

(9) No reaction was observed in the absence of Cu^I catalyst.

(10) Reviews on asymmetric Cu^I-catalyzed borylation of conjugated alkenes: (a) Schiffner, J. A.; Müther, K.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1194. (b) Mantilli, L.; Mazet, C. *ChemCatChem* **2010**, *2*, 501. Application to α,β-unsaturated sulfones: (c) Moure, A. L.; Gómez Arrayás, R.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6701.

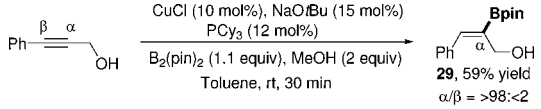
(11) For Cu^I/Xantphos-catalyzed $B_2(pin)_2$-borylation, see ref 7.

(12) Ligand effect in Cu^I-catalyzed $B_2(pin)_2$-diborylation of alkynes: Yoshida, H.; Kawashima, S.; Takemoto, Y.; Okada, K.; Ohshita, J.; Takaki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 235.

(13) Use of X-phos in regioselective hydrosilylation of terminal alkynes: McLaughlin, M. G.; Cook, M. J. *Chem. Commun.* **2011**, *47*, 11104.

(14) Propargylic carbonates are transformed into allenylboronates under the Cu(O-*t*-Bu)/Xantphos catalyst system: Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774.

(15) In accordance with literature precedent,[6] complete opposite α-regioselectivity was observed in the borylation of an aryl-substituted internal alkyne under the same optimized reaction conditions:



(16) Selected examples of regioselective addition (other than borylation) to internal alkynes: (a) Liu, P.; Montgomery, J.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 6956. (b) Bausch, C. C.; Patman, R. L.; Breit, B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5687. (c) Kawasaki, Y.; Ishikawa, Y.; Igawa, K.; Tomooka, K. *J. Am. Chem. Soc.* **2011**, *133*, 20712. (d) Liu, P.; McCarren, P.; Cheong, P. H.-Y.; Jamison, T. F.; Houk, K. N. *J. Am. Chem.Soc.* **2010**, *132*, 2050.

(17) See Supporting Information for calculations on analogous complexes obtained by either substitution of PCy_3 with PMe_3 or replacement of the alkyne with 2-pentyne.

(18) Natural charge for C (2) is always lower than for C (3), and the difference between the two C atoms is higher for **I**$\boldsymbol{\beta}$ (Δq = 0.13) than for **I**$\boldsymbol{\alpha}$ (Δq = 0.04), suggesting a higher reactivity toward boryl ligand to afford the β product.

(19) Molecular orbital analysis of copper−alkyne interactions: (a) Mori, S.; Nakamura, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750. (b) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *4*, 2339.

(20) Recent example on the influence of electronic factors on regioselectivity in the hydrosilylation of propargylic- and homopropargylic-functionalized internal alkynes: (a) Rooke, D. A.; Ferreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3225. For an example on reductive coupling of propargylic alcohol derivatives with aldehydes: (b) Malik, H. A.; Chaulagain, M. R.; Montgomery, J. *Org. Lett.* **2009**, *11*, 5734.

(21) As expected, modelization of the reaction with 2-pentyne as substrate, lacking the propargylic functional group, predicted low regiocontrol.

(22) Review on the stereoselective synthesis of substituted alkenes: (a) Negishi, E.-i.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474. Recent reports: (b) Nishihihara, Y.; Okada, Y.; Jiao, J.; Suetsugu, M.; Lan, M.-T.; Kinoshita, M.; Iwasaki, M.; Takagi, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 8660 and references cited therein.

(23) Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A. *J. Am. Chem. Soc.* **2010**, *132*, 1202.

(24) Pinacolboronates have been found to be incompatible with Grignard reagents under Cu catalysis: Lee, J. C. H.; Hall, D. G. *J. Am. Chem. Soc.* **2010**, *132*, 5544.

(25) Cu-catalyzed substitution of allyl sulfones with non-stabilized nucleophiles: (a) Llamas, T.; Gómez Arrayás, R.; Carretero, J. C. *Adv. Synth. Catal.* **2004**, *346*, 1651. (b) Trost, B. M.; Merlic, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 5216. (c) Julia, M.; Righini, A.; Verpeaux, J.-N. *Tetrahedron* **1983**, *39*, 3283.