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Regioselective Catalytic Hydroboration of Propargylic Species Using Cu(I)-NHC Complexes

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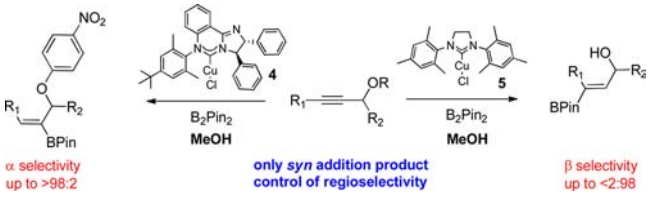
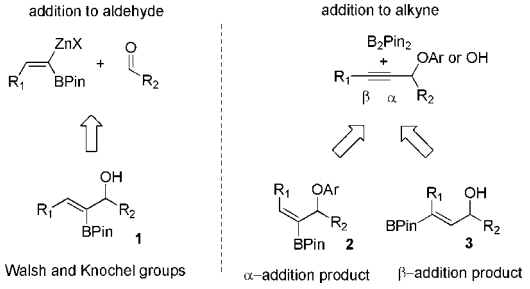
ABSTRACT



The catalytic regioselective hydroboration of propargylic alcohols and ethers was investigated using NHC-CuCl. We observe that different NHC-CuCl complexes catalyze hydroborations of propargylic substrates with opposite regioselectivity. A 6-NHC-CuCl complex provides α-selectivity whereas β-selectivity is achieved using a 5-NHC-CuCl complex. The reaction tolerates a wide range of functional groups.

New methods yielding multifunctional intermediates are needed to aid the synthesis of complex molecules.[1] Well-defined multifunctional compounds containing versatile C−B bonds are an example of intermediates that have received significant attention recently.[2] In particular, vinyl boronates are both useful and easily produced via addition of alkenyl heterobimetallics to electrophiles[3] or transition-metal-catalyzed hydroboration.[4−6] However, synthetic routes into all the desired regioisomers remain a challenge.[6l]

Renewed interest in this area has been spurred on by Cu(I)-catalyzed hydroboration of both internal and terminal alkynes using bis(pinacolato)diboron or HBpin.[6]



This second generation of alkyne hydroboration was pioneered by the Miyaura group,[6a] and catalytic alkyne

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(1) Zweifel, G. S.; Nantz, M. H. *Modern Organic Synthesis*; W. H. Freeman: 2006.

(2) (a) Roush, W. R.; Grover, P. T. *Tetrahedron Lett.* **1990**, *31*, 7567–7570. (b) Barrett, A. G. M.; Malecha, J. W. *J. Org. Chem.* **1991**, *56*, 5243–5245. (c) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981–1998. (d) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112–1124. (e) Roush, W. R.; Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41*, 9413–9417. (f) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644–13645. (g) Barrett, A. G. M.; Braddock, D. C.; de Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375–380. (d) Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2733–2738. (e) Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675–678. (f) Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070–3071.

(3) (a) Hernández-Toribio, J.; Hussain, M. M.; Cheng, K.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2011**, *13*, 6094–6097. (b) Hussain, M. M.; Hernández Toribio, J.; Carroll, P. J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 6337–6340. (c) Hussain, M. M.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1834–1837. (d) Hussain, M. M.; Li, H.; Hussain, N.; Ureña, M.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 6516–6524. (e) Li, H.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 3521–3531. (f) Waas, J. R.; Sidduri, A.; Knochel, P. *Tetrahedron Lett.* **1992**, *33*, 3717–3720.

(4) Examples are shown using borane (B−H). For review on hydrometalation, see: (a) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853–887. For a review on transition-metal-catalyzed hydroboration, see: (b) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957–5026. For hydroboration not using a metal catalyst, see: (c) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482–3485. (d) Clay, J. M.; Vedejs, E. *J. Am. Chem. Soc.* **2005**, *127*, 5766–5767.

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hydroboration was first reported by the Yun group, where they demonstrated that acetylenic esters and phenylacetylene could be regioselectively hydroborated using Xantphos.[6b] Later, the Yun and Son groups showed that internal aryl-alkynes undergo regioselective hydroboration when catalyzed by copper(I) ligated to 1,3-dimethylimidazoline-2-thione or monophosphines.[6c,f] The Hoveyda group demonstrated regioselective hydroborations of terminal alkynes using 5-NHC-Cu(I) complexes to give α- and β-selective vinylboronates.[6d,e] The Carretero group developed regiocontrolled borylation of propargylic functionalized dialkylalkynes catalyzed by Cu(I)-phosphine complexes yielding β-B(Pin)-substituted (*Z*)-allylic alcohol.[6i] The Lipshutz group introduced Cu(I) catalyzed α-selective hydroborations of acetylenic ester using HB(Pin),[6k] and the Tsuji group has generalized this synthetic method to have a α and β product by the choice of borylating reagents, HB(Pin) and B_2Pin_2, respectively.[6l] As an alternative method, herein, we present regioselective and stereoselective Cu(I)-NHC catalyzed hydroboration of propargylic ethers and alcohols yielding either the α-addition product, **2**, or β-addition product, **3**, by matching the substrate and catalyst.

(5) Examples are shown using boronic ester reagent (B−B or M−B). For a Pt-catalyzed reaction, see: (a) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018–11019. (b) Lesley, G.; Nguyen, P.; Taylor, N. J.; Marder, T. B.; Scott, A. J.; Clegg, W.; Norman, N. C. *Organometallics* **1996**, *15*, 5137–5154. (c) Thomas, R. L.; Souza, F. E. S.; Marder, T. B. *J. Chem. Soc., Dalton Trans.* **2001**, 1650–1656. (d) Lillo, V.; Mata, J.; Ramírez, J.; Peris, E.; Fernandez, E. *Organometallics* **2006**, *25*, 5829–5831. (e) Prokopcová, H.; Ramírez, J.; Fernández, E.; Kappe, C. O. *Tetrahedron Lett.* **2008**, *49*, 4831–4835. (f) Carson, M. W.; Giese, M. W.; Coghlan, M. J. *Org. Lett.* **2008**, *10*, 2701–2704. For a Rh- or Ir-catalyzed reaction, see: (g) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990–4991. (h) Miura, T.; Takahashi, Y.; Murakami, M. *Org. Lett.* **2008**, *10*, 1743–1745. (i) Mkhalid, I. A. I.; Coapes, R. B.; Edes, S. N.; Coventry, D. N.; Souza, F. E. S.; Thomas, R. L.; Hall, J. J.; Bi, S.-W.; Lin, Z.; Marder, T. B. *Dalton Trans.* **2008**, 1055–1064. For a Ni-catalyzed reaction, see: (j) Mannathan, S.; Jeganmohan, M.; Cheng, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2192–2195. For Pd-catalyzed reactions, see: (k) Marco-Martínez, J.; López-Carrillo, V.; Buñuel, E.; Simancas, R.; Cárdenas, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 1874–1875. (l) Marco-Martínez, J.; Buñuel, E.; Muñoz-Rodríguez, R.; Cárdenas, D. J. *Org. Lett.* **2008**, *10*, 3619–3621. (k) Ohmura, T.; Oshima, K.; Taniguchi, H.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 12194–12196.

(6) For Cu-catalyzed reactions with diboron reagents, see: (a) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47–53. (b) Lee, J.-E.; Kwon, J.; Yun, J. *Chem. Commun.* **2008**, 733–734. (c) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774–15775. (d) Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 18234–18235. (e) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859–7871. (f) Kim, H. R.; Jung, I. G.; Yoo, K.; Jang, K.; Lee, E. S.; Yun, J.; Son, S. U. *Chem. Commun.* **2010**, *46*, 758–760. (g) Kim, H. R.; Yun, J. *Chem. Commun.* **2011**, *47*, 2943–2945. (h) Sasaki, Y.; Horita, Y.; Zhong, C.; Sawamura, M.; Ito, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 2778–2782. (i) Moure, A. L.; Gómez Arrayás, R.; Cárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2012**, *134*, 7219–7222. For Cu-catalyzed diboration, see: (j) Lillo, V.; Fructos, M. R.; Ramírez, J.; Braga, A. A. C.; Maseras, F.; Díaz-Requejo, M. M.; Pérez, P. J.; Fernández, E. *Chem.—Eur. J.* **2007**, *13*, 2614–2621. For Cu-catalyzed reactions with borane, see: (k) Lipshutz, B. H.; Bošković, Ž. V.; Aue, D. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 10183–10186. For the control of regioselectivity in Cu-catalyzed reactions by borylating reagents, see: (l) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem.—Eur. J.* **2012**, *18*, 4179–4184. For Cu-catalyzed substitution reactions of nucleophilic silicone to propargylic species in order to compare ref 6c, see: (m) Hazra, C. K.; Oestreich, M. *Org. Lett.* **2012**, *14*, 4010–4013. (n) Vyas, D. J.; Hazra, C. K.; Oestreich, M. *Org. Lett.* **2011**, *13*, 4362–4265.

Our group recently reported the synthesis and unique activity and reactivity of complex **4**.[7] Inspired by Ito and Sawamura's Cu(I) catalyzed formation of allenes from propargylic species,[6c,m,n] we measured the product distribution when similar substrates were reacted with complex **4**. Instead of allene formation, we observed regio- and *syn*-selective hydroboration, and as described in more detail below, the regioselectivity is controlled by catalyst choice (eq 1).[8]

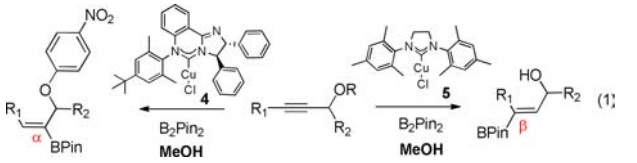
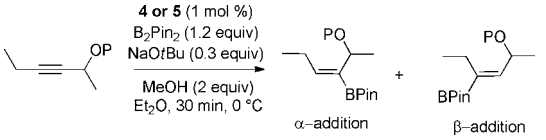


Table 1. Protection Group Screening for Hydroboration of Internal Alkynes



		4		5	
entry	P	conv[a]	α:β[a]	conv[a]	α:β[a]
1	H	**64%**	**58:42**	**100%**	**4:96**
2	TBDMS	55%	65:35	78%	19:81
3	Bn	100%	53:47	100%	11:89
4	Ph	100%	69:31	100%	33:67
5	p-$MeOC_6H_4$	6%	71:29	76%	39:61
6	m-$NO_2C_6H_4$	100%	88:12	100%	79:21
7	p-$NO_2C_6H_4$	100%	85:15[b]	100%	75:25[c]
8[d]	p-$NO_2C_6H_4$	**100%**	**96:4**[e]	**87%**	**95:5**

[a] Determined by ^1H NMR analysis of crude reaction mixtures. [b] Reaction contains 8.6% allene product. [c] Reaction contains 9.8% allene product. [d] All reactions carried out at 0 °C except for entry 8, which was carried out at −55 °C for 14 h. [e] Racemic product was obtained using 0.5 equiv of B_2Pin_2 (no kinetic resolution observed).

To further clarify the regioselectivity observed when using catalyst **4**, we screened ester protecting groups such as acetate, carbonate, and benzoate and observed the formation of α-, β-addition and allene products.[6c] By changing to fewer electron-withdrawing groups than esters (shown in Table 1), we observed that hydroboration was dominant. In most cases, the α-addition product was the major product compared to the β-addition species. Substrates containing a *p*-nitrophenyl ether afforded the α-addition product in high yield and with excellent selectivity

(7) (a) Park, J. K.; Lackey, H. H.; Rexford, M. D.; Kovnir, K.; Shatruk, M.; McQuade, D. T. *Org. Lett.* **2010**, *12*, 5008–5011. (b) Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, D. T. *J. Am. Chem. Soc.* **2011**, *133*, 2410–2413. (c) Park, J. K.; McQuade, D. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 2717–2721. (d) Park, J. K.; McQuade, D. T. *Synthesis* **2012**, 1485–1490.

(8) We found ref 6i about the β-selective hydroboration reaction while we were preparing this manuscript.

(entry 8, Table 1). No kinetic resolution was observed when 0.5 equiv of B_2Pin_2 was used.

We then measured the selectivity observed when catalyst **5** was used. Complex **5** yielded the β-addition product (entry 1−5, Table 1) except where substrates contained nitrophenyl ethers (entry 8, Table 1). The β-addition selectivity was highest for alcoholic substrates (entry 1, Table 1).[8] With these results in hand, we assessed the substrate scope by matching catalyst **4** with the *p*-nitrophenyl ether substrates to obtain the α-addition product and catalyst **5** with alcohol substrates to yield the β-addition product.

We examined the scope using a systematic approach where branching and distal functional groups were considered. In most cases, catalyst **4** provided high α-selectivities with secondary ethers (Scheme 1), delivered the B(Pin) group to the more hindered site, and tolerated all distal functional groups well.[9] Primary ether **7a** gave slightly lower selectivity (85:15). The halide, protected amine and silyl protected alcohol not only are compatible with reaction conditions but also gave high α-selectivities (**7e**, **7f**, and **7g**).

Matching catalyst **5** and alcoholic substrates (Scheme 2), we observed more striking substituent effects. The extent of β-selectivity was influenced by the electronic properties of the substrates (**9b**, **9d**, **9e**, **9f**, and **9g**) consistent with literature precedent.[9] Substrates containing smaller linear aliphatic chains on the side opposite the secondary alcohol also yielded a bias toward the β-addition product. A reversal of selectivity was observed when aryl-substituted internal alkynes (**9h**)[6i] or bulky substituents were proximal to the β-carbon (**9i**).

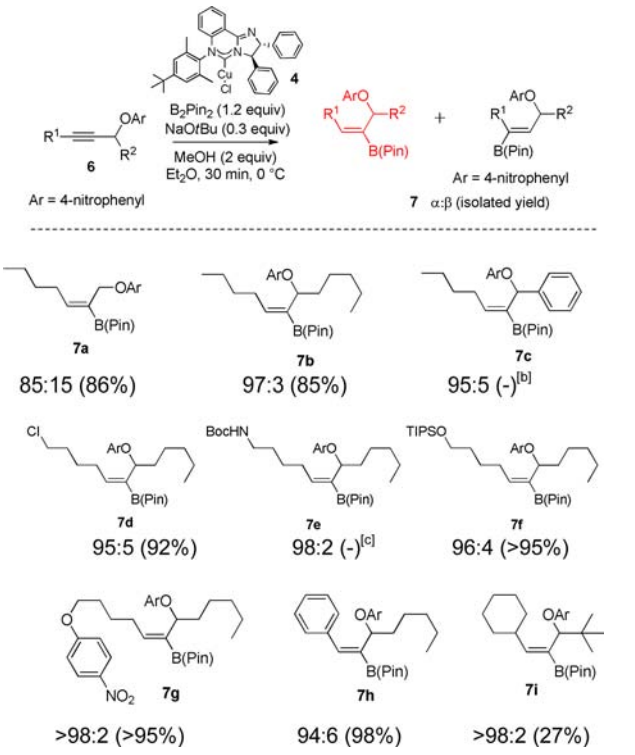
The observations gathered in Table 1 enabled us to define optimum catalyst and substrate matches, and the data collected in Schemes 1 and 2 indicate that the optimized matches and conditions provide a wide substrate scope. Moving forward, we had two objectives: (1) obtain data to help explain why the functional group of the substrate switches regiochemical preference and (2) illustrate the potential synthetic utility of both the α- and β-products.

From the standpoint of explaining regiochemical preferences, we compared entries 1−5 vs 6−8 in Table 1. When complex **5** is used, we observe a gradient of selectivity where the unprotected alcohol substrates provide very high selectivity for borylating the β-position. Substrates containing neutral or electron releasing protecting groups (entries 1−5) yield a modest preference for the β-position, and electron-withdrawing groups such as nitrophenyl ethers exhibit reversal of selectivity yielding the α-product (entries 6−8). From these data we propose that the alcohol and *p*-nitrophenyl define a range of electronic properties.

With this hypothesis in mind, we prepared substrates **10a**−**10d** to measure the competition between steric and

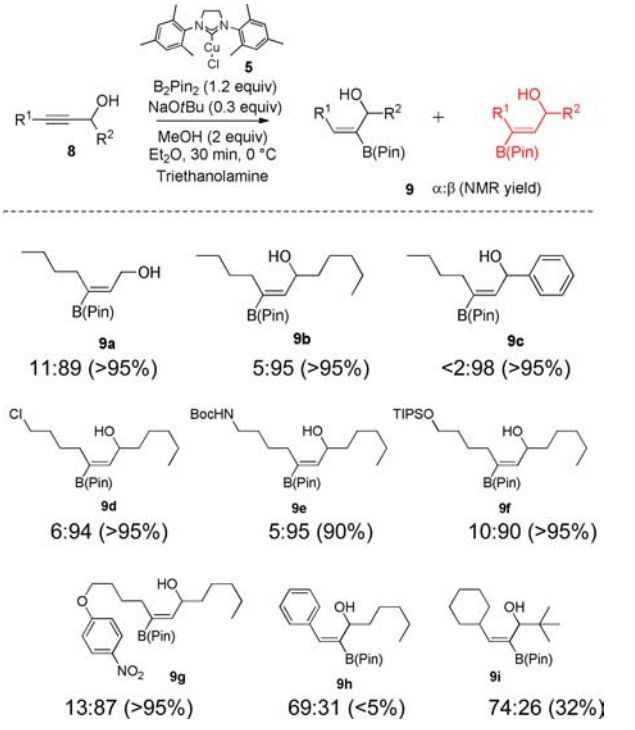
(9) The Hoveyda group recently showed that distal functional groups have a significant impact on alkyne hydroboration in ref 6e. And also similar behavior was observed in ref 6i.

Scheme 1. Regioselectivities Using **4**[a]



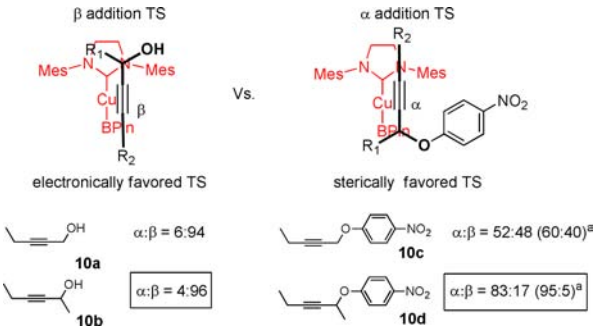
[a] Isolated yields were shown in the parentheses. [b] Selectivity data obtained by ^{1}H NMR analysis of the crude product. [c] Isolated with unknown product.

Scheme 2. Regioselectivities Using **5**[a]



[a] ^{1}H NMR yields are shown in the parentheses.

Scheme 3. Electronic and Steric Effects of Substrates on Regioselectivity Using 5-NHC-CuCl, **5**[a]

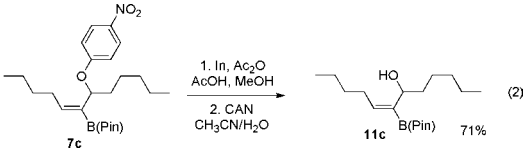


[a] Reaction was carried out at −55 °C.

electronic effects (Scheme 3). Compounds **10a** and **10b** represent the unencumbered and encumbered alcoholic substrates, respectively, and **10c** and **10d** are similarly representative but with the *p*-nitrophenyl ether group. With **5**, we observed that both **10a** and **10b** yielded a high preference for the *β*-position, 6:94 and 4:96, respectively. We infer from these data that sterics play very little role when the catalyst orients to deliver the boron to the *β*-position and that the electronic influence of the alcohol polarizes the alkyne.[10]

We found that the linear *p*-nitrophenyl ether provides no site specific bias (52:48) whereas the branched *p*-nitrophenyl ether induces high α-selectivity (up to 95:5 at −55 °C). These results indicate that when the boron is delivered to the α-position, selectivity is dominated by steric effects in order to place the branched side of the alkyne proximal to the B(Pin) and away from the bulkier NHC. When using **4**, we obtained consistent α preferences (Scheme 4), indicating that the catalyst dominates the regioselective preference.

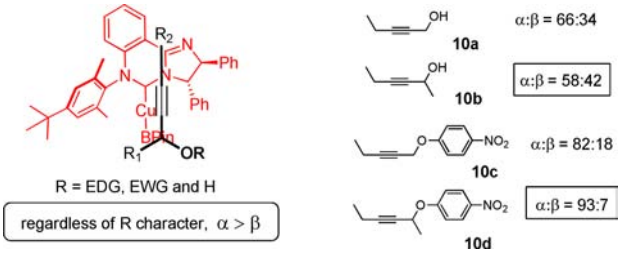
Next, we sought a simple strategy to deprotect the *p*-nitrophenyl ether. We modified Fukase's two-step approach (i. H_2 with Pd; ii. CAN)[11a] by using an indium-mediated reduction of the nitro group[11b] to avoid Pd-catalyzed hydrogenation of the double bond, followed by CAN oxidative cleavage (eq 2). The method provided **11c** in 71% yield.



(10) It is worth noting that when substituents on the either side of the alkyne are too large, the steric influence becomes the dominant factor (**9i**, Scheme 2). We do not favor a model that invokes hydrogen bonding because **5** reacts with benzylic ethers to provide high *β*-position selectivity as well.

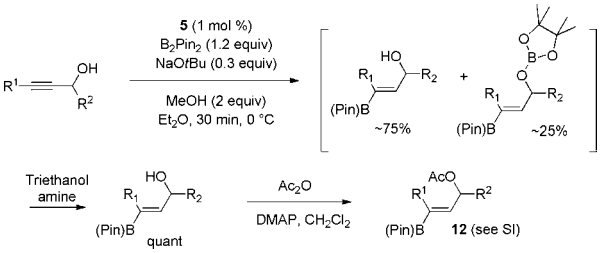
(11) (a) Fukase, K.; Yasukochi, T.; Nakai, Y.; Kusumoto, S. *Tetrahedron Lett.* **1996**, *37*, 3343–3343. (b) Kim, B. H.; Han, R.; Piao, F.; Jun, Y. M.; Baik, W.; Lee, B. M. *Tetrahedron Lett.* **2003**, *44*, 77–79.

Scheme 4. Regioselectivity Observed with 6-NHC-CuCl, **4**



We also developed a one-pot process to protect the *β*-addition product, as isolation of the desired alcohol was confounded by a mixture of alcohol and borate ester (Scheme 5). We found triethanolamine completely hydrolyzes the borate intermediate with no transesterification of B(Pin); however, the *β*-B(Pin)-substituted allylic alcohols decompose when placed onto silica gel. The acetate protected alcohol was stable, enabling flash chromatography.[12]

Scheme 5. Protection of *β*-Addition Product for Isolation[12]



In summary, we have shown a highly regioselective α- and *β*-boron addition reaction to acetylenic ether and alcohol catalyzed by **4** and **5**, respectively. The α-product, *p*-nitrophenyl ether, was successfully deprotected by modifying Fukase's approach, and the unstable *β*-products, hydroxy boronates, were easily isolated after protection with acetic anhydride. We are currently investigating the synthetically useful applications of the α- and *β*-products.

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

(12) Synthetic details are shown in the Supporting Information.

The authors declare no competing financial interest.