DOI: 10.1002/chem.201103612

Copper-Catalyzed Highly Regio- and Stereoselective Directed Hydroboration of Unsymmetrical Internal Alkynes: Controlling Regioselectivity by Choice of Catalytic Species

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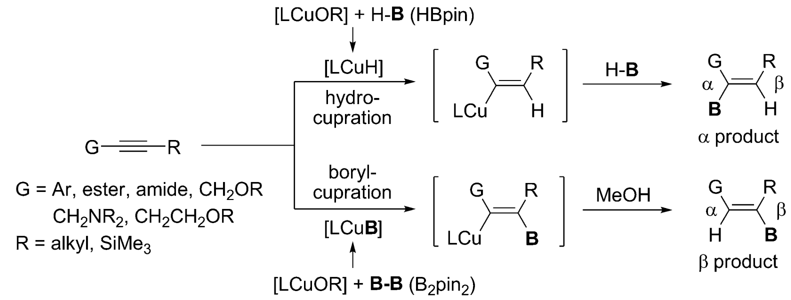


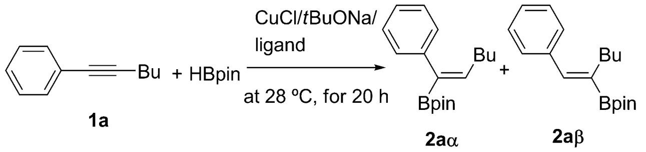
Scheme 1.

Hydroboration is a robust and practical method for the synthesis of organoboranes.[1] In particular, hydroboration of alkynes is of interest because the products (vinylboranes) are potent intermediates in the Suzuki–Miyaura cross-coupling reaction[2] and other useful transformations.[3,4] It is known that the hydroboration of terminal alkynes proceeds regio- and stereoselectively.[5] However, the reaction of unsymmetrical internal alkynes often suffers from low regioselectivity, even in the presence of a catalyst.[6] Generally, bulky boryl moieties are added at the less bulky site in both uncatalyzed and catalyzed hydroboration reactions. For example, the hydroboration of alkylphenylacetylenes tends to produce β-boryl styrene derivatives (β products).[7] Bis(pinacolato)diboron (B_2pin_2) can also be used as a borane source to afford the same β products.[8] However, a general method for synthesizing the α products (regioisomers of the β products) has not been reported. To date, only acetylenic esters have led to the α products.[9]

Herein, we report a highly selective syntheses of the α and β products by copper-catalyzed hydroboration utilizing two different catalytic copper species (Cu–H[9,10] and Cu–B[11]) generated from pinacolborane (HBpin) and B_2pin_2, respectively (Scheme 1). Regioselectivity was successfully controlled through hydrocupration and borylcupration as a result of the directing effect of group G.[12,13]

Firstly, the hydroboration of 1-phenyl-1-hexyne (**1a**) was carried out by using HBpin at 28 °C with a copper catalyst system (CuCl/*t*BuONa). No reaction occurred without a catalyst (Table 1, entry 1). The use of monodentate phosphanes, such as PPh_3 and PCy_3[14] (Cy = cyclohexyl; Table 1, entries 2 and 3), or bidentate phosphanes, such as 1,2-bis(diphenyl-

Table 1. Copper-catalyzed hydroboration of **1a** with pinacolborane (HBpin) by using various catalysts.[a]



Entry	Ligand	Yield [%][b]	**2aα/2aβ**
1	none[c]	0	–
2	PPh_3	0	–
3	PCy_3	5	–
4	DPPE	trace	–
5	DPPP	1	–
6	*rac*-BINAP	trace	–
7	BDP	1	–
8	Xan	13	95:5
9	CF_3Ar-Xan	89	88:12
10	MeAr-Xan	92	94:6
11[d]	MeAr-Xan	97 (97)[e]	95:5
12	IPr	89	90:10
13	^{Cl}IPr	88	90:10
14	$[\{(PPh_3)CuH\}_6]/PPh_3$[f]	0	–
15	CuCl/BDP/*t*BuOK[g]	4	–
16	$[RhCl(PPh_3)_3]$[h]	9	21:79
17	$[\{IrCl(COD)\}_2]$/DPPM[i]	65	54:46

[a] **1a** (0.50 mmol), HBpin (0.60 mmol), CuCl (0.010 mmol, 2.0 mol %), a ligand (0.010 mmol, 2.0 mol %), *t*BuONa (0.060 mmol, 12 mol %), toluene (1.0 mL), at 28 °C, for 20 h. [b] Total yield of **2aα** and **2aβ** based on the GC internal-standard technique. [c] This reaction was performed without CuCl, ligand, and *t*BuONa. [d] This reaction was performed at 20 °C and with 0.75 mmol of HBpin. [e] Isolated yield. [f] $[\{(PPh_3)CuH\}_6]$ (0.011 mmol, 2.1 mol %), PPh_3 (0.010 mmol, 2.0 mol %), HBpin (0.55 mmol), THF (0.50 mL). [g] CuCl (0.010 mmol, 2.0 mol %), BDP (0.0050 mmol, 1.0 mol %), *t*BuOK (0.030 mmol, 6.0 mol %), HBpin (0.55 mmol), THF (0.50 mL). [h] $[RhCl(PPh_3)_3]$ (0.010 mmol, 2.0 mol %) was used as the catalyst. [i] $[\{IrCl(COD)\}_2]$ (0.0050 mmol, 2.0 mol %) and DPPM (P/Ir = 2:1) were used as the catalyst.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103612.

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phosphino)ethane (DPPE), 1,3-bis(diphenylphosphino)propane (DPPP), *rac*-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (*rac*-BINAP), and 1,2-bis(diphenylphosphino)benzene (BDP;[14] Table 1, entries 4–7), led to almost no product. On the other hand, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos,[14] Xan; Figure 1) afforded the product in 13 % yield with high regioselectivity: **2aα**/**2aβ** = 95:5 (Table 1, entry 8). The use of the Xantphos derivative bearing two 3,5-(trifluoromethyl)phenyl moieties (CF$_3$Ar-Xan;[15] Figure 1) led to the yield being dramatically improved to 89 %, although with a somewhat lower regioselectivity was obtained (**2aα**/**2aβ** = 88:12, Table 1, entry 9). Gratifyingly, MeAr-Xan,[16] bearing 3,5-xylyl moieties, was highly effective as the ligand, giving the products in 92 % total yield with high regioselectivity (**2aα**/**2aβ** = 94:6, Table 1, entry 10). Reducing the temperature to 20 °C improved both the yield and the regioselectivity (Table 1, entry 11). As ligands, *N*-heterocyclic carbenes (NHCs),[17] such as 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) and 1,3-bis(2,6-diisopropylphenyl)-4,5-dichloroimidazol-2-ylidene (^{Cl}IPr;[10a] Figure 1), could also be used, albeit with slightly lower efficiencies (Table 1, entries 12 and 13). The use of the [{(PPh$_3$)CuH}$_6$]/PPh$_3$ or CuCl/BDP/*t*BuOK systems,[9] which are effective catalytic systems for the hydroboration of acetylenic esters, yielded the products in only 0 and 4 % yields, respectively (Table 1, entries 14 and 15). Other transition-metal catalysts, such as [RhCl(PPh$_3$)$_3$][18] and [{IrCl(COD)}$_2$]/1,1-bis(diphenylphosphino)methane (DPPM; COD = 1,5-cyclooctadiene),[7b,14] have been used in the hydroboration of terminal alkynes, but for the reaction of **1a** these catalysts showed only low catalytic activities and poor regioselectivities (Table 1, entries 16 and 17).[19]

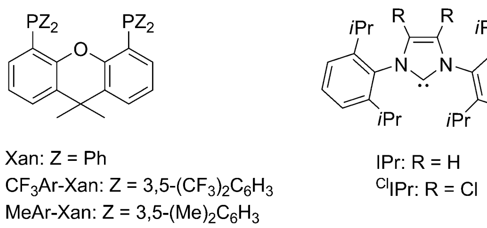
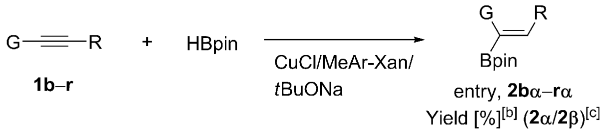
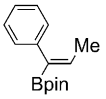
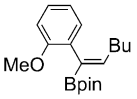
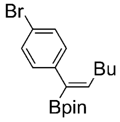
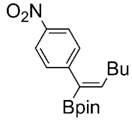
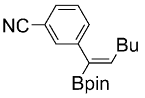
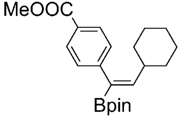
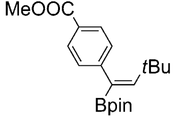
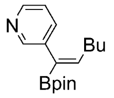
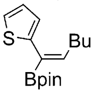
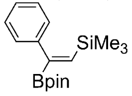
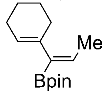
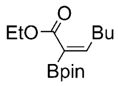
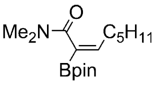
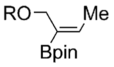
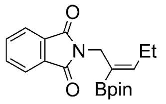
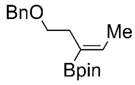


Figure 1. Structures of the ligands.

Table 2. Copper-catalyzed hydroboration of various alkynes to the α products with HBpin.[a]



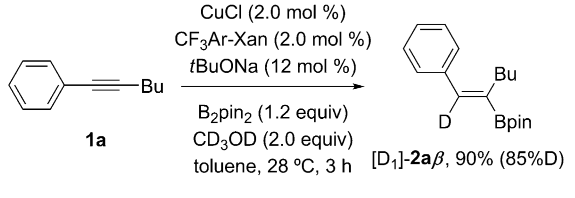
 1, **2bα** 78 % (93:7)[d]	 2, **2cα** 74 % (>99:1)	 3, **2dα** 94 % (98:2)	 4, **2eα** 78 % (100:0)
 5, **2fα** 72 % (>99:1)	 6[e], **2gα** 90 % (100:0)	 7[f,g], **2hα** 94 % (100:0)	 8, **2iα** 88 % (97:3)
 9[h], **2jα** 86 % (97:3)	 10[f,i], **2kα** 92 % (100:0; *Z*/*E* = 98:2)	 11[j], **2lα** 62 %[k] (72:28)	 12[l], **2mα** 82 % (100:0)
 13[h], **2nα** 96 % (100:0)	 14[m,n] (R = Bn), **2oα** 73 %[k] (92:8) 15[m,n] (R = THP), **2pα** 64 %[k] (93:7)	 16[m,o], **2qα** 76 % (>99:1)	 17[m,p], **2rα** 68 %[k] (63:37)

[a] Alkyne (0.50 mmol), HBpin (0.75 mmol), CuCl (0.010 mmol, 2.0 mol %), MeAr-Xan (0.010 mmol, 2.0 mol %), *t*BuONa (0.060 mmol, 12 mol %), toluene (1.0 mL), at 20 °C, for 20 h. [b] Isolated yield. [c] Ratio of **2α**/**2β** in the crude reaction mixture was determined by GC. [d] After purification α/β = 98:2. [e] HBpin (0.60 mmol), at 28 °C. [f] CuCl (0.020 mmol, 4.0 mol %), MeAr-Xan (0.020 mmol, 4.0 mol %). [g] HBpin (1.0 mmol), at 60 °C. [h] HBpin (0.60 mmol). [i] HBpin (1.0 mmol), at 50 °C. [j] CuCl (0.020 mmol, 4.0 mol %), MeAr-Xan (0.020 mmol, 4.0 mol %), *t*BuONa (0.12 mmol, 24 mol %), toluene (0.50 mL), at 50 °C. [k] Yield of the α and β product mixture. [l] HBpin (0.60 mmol), at 0 °C, for 1 h. [m] CF$_3$Ar-Xan was used instead of MeAr-Xan. [n] Toluene (0.50 mL), at 28 °C. [o] 28 °C. [p] Toluene (0.25 mL), at 80 °C.

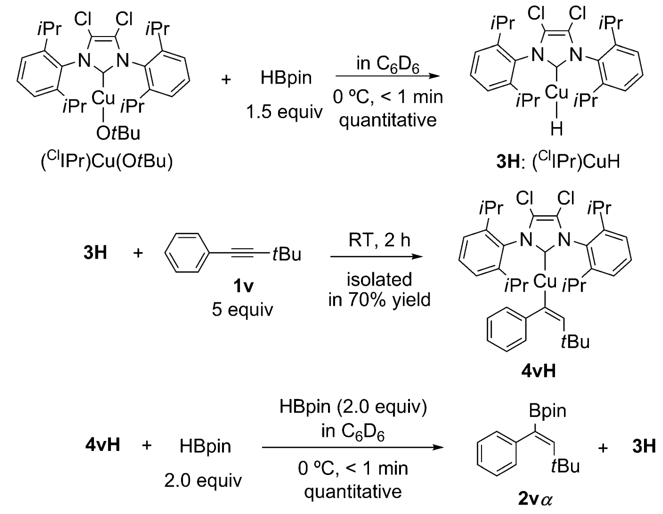
The hydroboration of various internal alkynes (**1b**–**r**) to afford the α products was carried out by using HBpin with MeAr-Xan as the ligand (Table 2). Regioselectivity in the crude reaction mixtures (**2α**/**2β**) was high, and the corresponding α products (**2α**) were isolated in good yields. The reaction of **1b** gave a **2bα**/**2bβ** ratio of 93:7 and **2bα** was isolated in 78 % yield (Table 2, entry 1). In non-catalytic[5b] and Ti-catalyzed[6c] hydroborations of **1b**, the selectivities of **2α**/**2β** were 15:85 (with HBpin) and 67:33 (with catecholborane), respectively. Electron-donating and -withdrawing groups on the aryl ring were tolerated, maintaining high yields and regioselectivities (Table 2, entries 2–7). Alkynes bearing pyridine and thiophene rings on the acetylenic carbon atoms (**1i** and **1j**) reacted with high regioselectivities and the α products (**2iα** and **2jα**) were isolated in high yields (Table 2, entries 8 and 9). An alkyne bearing a trimethylsilyl group was regioselectively converted into the boryl silyl bifunctional product (**2kα**) in high yield (Table 2, entry 10). In the case of an alkyne containing an alkenyl moiety (**1l**), the regioselectivity decreased to **2lα**/**2l*β*** = 72:28 (Table 2, entry 11). On the other hand, alkynes containing ester[9] (**1m**) and amide (**1n**) functionalities instead of aromatic substituents afforded the corresponding α products (**2mα** and **2nα**) in high yields and with perfect regioselectivities (Table 2, entries 12 and 13). Furthermore, alkynes bearing O and N atoms in the propargylic position (Table 2, entries 14–16) provided the corresponding α products (**2oα–qα**) in good yields with high regioselectivities when employing CF_3Ar-Xan instead of MeAr-Xan as the ligand.[20] Unfortunately, an alkyne bearing a homopropargyl ether functionality afforded the α product in only low selectivity (Table 2, entry 17).

In contrast, when HBpin was replaced with B_2pin_2/MeOH and still by using CF_3Ar-Xan as the ligand, the regioselectivity was reversed to afford mostly the β products (Table 3). It is noteworthy that even when secondary alkyl moieties were attached to the acetylenic carbon, regioselectivities for the β products (**2gβ**, **2sβ**, and **2tβ**) were still high (Table 3, entries 1–3).[21] An alkyne bearing an alkenyl moiety[22] also afforded the product regioselectively in high yield (Table 3, entry 4). Furthermore, alkynes bearing conjugated ester[23] and amide functionalities also afforded the respective β products in high yields with high regioselectivities (Table 3, entries 5 and 6). Remarkably, alkynes bearing O and N atoms at the propargylic (Table 3, entries 7–10) and even homopropargylic (Table 3, entry 11) positions provided the corresponding β products (**2oβ–rβ** and **2uβ**) selectively in good to high yields.[20,24] Such high regioselectivities have never been observed in the hydroboration of this class of substrates (**1o–r** and **1u**).

To gain insight into the mechanism of the α-directed hydroboration by using HBpin, stoichiometric reactions were performed with the {^{Cl}IPrCu} complex (Scheme 2), since ^{Cl}IPr is an efficient ligand in the reaction (Table 1, entry 13) and copper complexes bearing ^{Cl}IPr are rather stable. [(^{Cl}IPr)Cu(O*t*Bu)], obtained from [(^{Cl}IPr)CuCl] and *t*BuONa,[25] reacted with HBpin almost instantaneously at 0 °C. A ^{1}H NMR spectrum of the resulting reaction mixture indicated that the reaction was clean and the corresponding copper hydride, [(^{Cl}IPr)CuH] (**3H**), was formed quantitatively, judging by the presence of the diagnostic ^{1}H resonance of the Cu–H bond at 2.4 ppm, as well as other ^{1}H resonances in [(^{Cl}IPr)CuH][10a] (Scheme 2a).[14] Next, **3H** was reacted with an alkyne (**1v**; Scheme 2b). For this reaction, **3H** was prepared from [(^{Cl}IPr)CuF] and $(EtO)_3SiH$[10a] to avoid the further reaction of excess HBpin with the resulting product **4vH** (see Scheme 2c). As reported previously,[10a,26] [(^{Cl}IPr)CuH] reacted with the alkyne (**1v**) and the corresponding alkenyl copper complex (**4vH**) was isolated in 70 % yield (Scheme 2b). The complex **4vH** instantaneously reacted with HBpin at 0 °C to quantitatively provide the corresponding hydroboration product (**2vα**) and cleanly regenerate **3H**, as confirmed by ^{1}H NMR spectroscopy (Scheme 2c).[14] This is the first example of the stoichiometric reaction of a borane with an alkenyl copper species. As for the β-directed hydroboration, **1a** was allowed to react with B_2pin_2 in the presence of CD_3OD under otherwise identical conditions to those reported in Table S1, entry 1 in the Supporting Information. The resultant deuterated product ([D_1]-**2aβ**), bearing D at the α position, was obtained in 90 % yield with 85 % deuterium content [Eq. (1)].

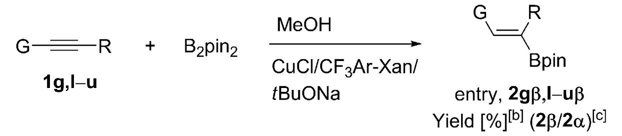


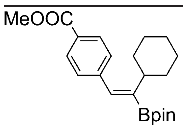
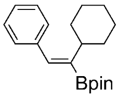
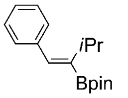
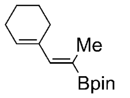
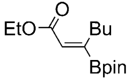
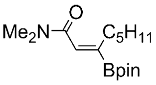
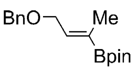
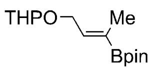
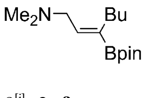
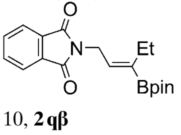
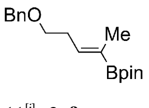
(1)



Scheme 2. Stoichiometric reactions relevant to the mechanism.

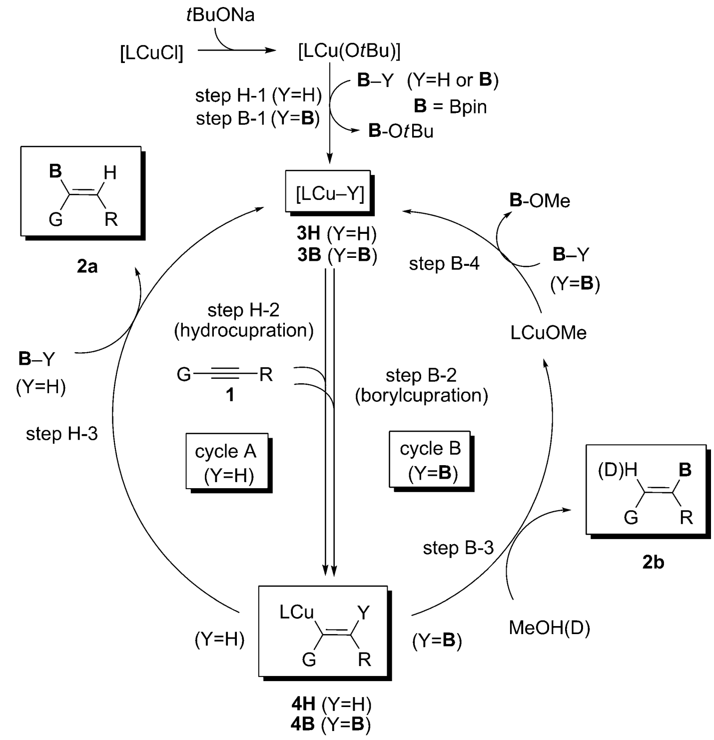
Table 3. Copper-catalyzed hydroboration of various alkynes to the β products with B_2pin_2/MeOH.[a]



			
1[d], **2gβ** 88 % (>99:1; Z/E=95:5)	2[e], **2sβ** 70 % (92:8)[f]	3[e], **2tβ** 76 % (91:9)[f]	4, **2lβ** 94 % (99:1)
			
5[g], **2mβ** 90 % (100:0)	6[h], **2nβ** 78 % (97:3)	7, **2oβ** 74 % (98:2)	8, **2pβ** 88 % (99:1)
			
9[i], **2uβ** 74 % (95:5)	10, **2qβ** 92 % (100:0; Z/E=96:4)		11[i], **2rβ** 86 % (91:9)[j]

[a] Alkyne (0.50 mmol), B_2pin_2 (0.60 mmol), MeOH (1.0 mmol), CuCl (0.010 mmol, 2.0 mol %), CF_3Ar-Xan (0.010 mmol, 2.0 mol %), *t*BuONa (0.060 mmol, 12 mol %), toluene (1.0 mL), at 28 °C, for 3 h. [b] Isolated yield. [c] Ratio of **2β**/**2α** in the crude reaction mixture was determined by GC. [d] At 50 °C, for 20 h. [e] For 20 h. [f] After purification β/α = >99:1. [g] B_2pin_2 (0.53 mmol), for 1 h. [h] B_2pin_2 (0.53 mmol). [i] B_2pin_2 (0.75 mmol). [j] After purification β/α = 90:10.

Based on these experimental results, possible catalytic cycles for the Cu-catalyzed hydroboration by using HBpin (catalytic cycle A) and B$_2$pin$_2$ (catalytic cycle B) are shown in Scheme 3. Firstly, [LCu(O*t*Bu)] is generated from [LCuCl] and *t*BuONa.[25] As indicated by the clean stoichiometric reaction of [(^{Cl}IPr)Cu(O*t*Bu)] with HBpin (Scheme 2 a), the active catalytic species in the hydroboration with HBpin must be a copper hydride ([LCuH]; **3H**, Y = H, step H-1, Scheme 3). *Syn* addition of **3H** to alkynes[10a,26] (hydrocupration: step H-2) affords alkenyl copper species (**4H**) with high regioselectivity owing to the directing effect of substituent G. Finally, reaction of **4H** with HBpin affords the corresponding α product (**2α**) and closes the catalytic cycle by regenerating the active catalytic species [LCuH] (**3H**; step H-3). The process in step H-2 is supported by the stoichiometric reaction depicted in Scheme 2 b and that in step H-3 was confirmed by the reaction shown in Scheme 2 c.

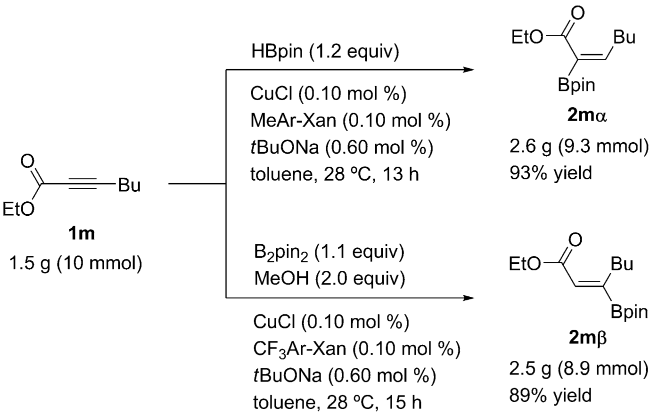


Scheme 3. A possible catalytic cycle.

Xan derivatives were so effective as ligands for the α-borylation reactions because the bulky Xan derivatives would suppress the aggregation of the {CuH} species. It is known that {CuH} species are liable to aggregate, which considerably decreases their reactivity.[10b,27] Furthermore, the bulky Xan ligand derivatives may accelerate the insertion of Cu–H into an alkyne; a recent paper reported that the bulky bidentate phosphane ligand accelerates the insertion of Cu–H into a styrene.[28]

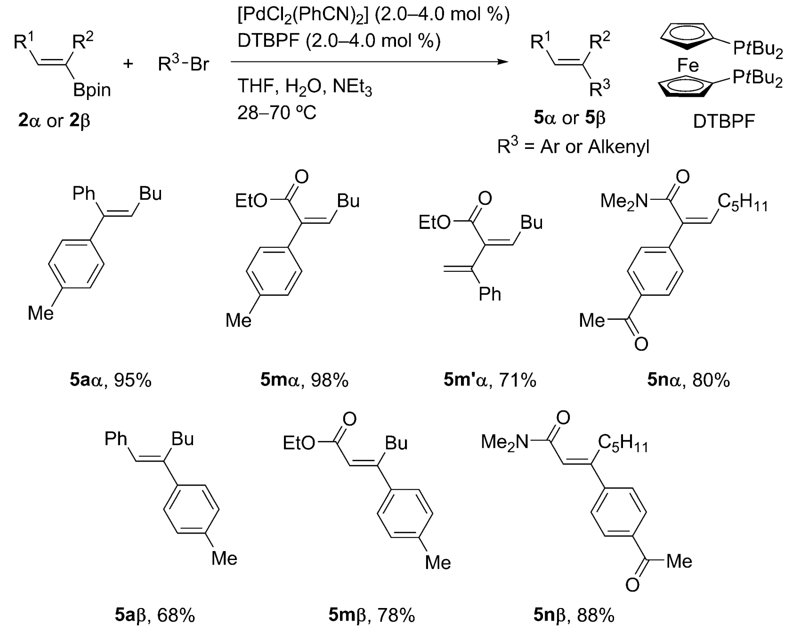
In contrast, for the hydroboration by using B$_2$pin$_2$, a boryl copper species ([LCuB]; **3B**) must be generated as the catalytic species in step B-1 (Y = B, Scheme 3). Indeed, Sadighi et al. have reported that [(IPr)Cu(O*t*Bu)] reacted readily with B$_2$pin$_2$ at room temperature, forming [(IPr)Cu(Bpin)], the X-ray structure of which has been determined.[29] The addition of the [LCuB] species (**3B**) to the alkyne (borylcupration;[30] step B-2) provides a (β-boryl)(alkenyl)copper intermediate (**4B**) with high regioselectivity owing to the same directing effect of substituent G as was observed in step H-2. Next, protonation of **4B** with MeOH provides the β products (**2β**) efficiently (step B-3). If CD$_3$OD was used, an α-deuterated product ([D$_1$]-**2aβ**) was obtained, as shown in Equation (1). Finally, the reaction between the resulting [LCuOMe] species and B$_2$pin$_2$ regenerates [LCuB] (**3B**), and the catalytic cycle is closed (step B-4). Through these mechanisms, the regioselectivity can be successfully controlled in the hydrocupration or borylcupration steps (steps H-2 or B-2, respectively) with the different catalytic species ([LCuH], **3H**, or [LCuB], **3B**) in their respective catalytic cycles. In hydroboration reactions catalyzed by other transition metals (such as Rh and Ir), selecting between hydrometalation (Scheme 3, cycle A) and boryl metalation (Scheme 3, cycle B) is difficult because the oxidative addition of HB to a metal center provides an H-M-B species, containing both H–M and B–M bonds.[1b,c,31,32]

The utility of these transformations is shown in Schemes 4 and 5. The copper-catalyzed hydroboration reactions are amenable to gram-scale procedures with much lower catalyst loadings. For example, with only 0.10 mol % of either catalyst, 1.5 g of **1m** was selectively converted into the corresponding hydroboration products **2mα** and **2mβ** in high yields, depending on which reagent was used (HBpin and B$_2$pin$_2$; Scheme 4). The α and β products (**2α** and **2β**) are valuable intermediates used in the Suzuki–Miyaura cross-coupling reaction[2] to regioselectively prepare various trisubstituted alkenes of types **5α** and **5β** (Scheme 5).[33]



Scheme 4.

In conclusion, we have developed a highly regio- and stereoselective, copper-catalyzed hydroboration of unsymmetrical internal alkynes. The regioselectivity is controlled by using one of two different catalytic species ([LCuH] and



Scheme 5.

[LCuB]) generated from borylation reagents HBpin and B_2pin_2, respectively. This reactivity is expected to have wide applicability to other regioselective catalytic reactions.

Experimental Section

General procedure for Table 2: CuCl (0.99 mg, 0.010 mmol, 2.0 mol %), MeAr-Xan (6.91 mg, 0.010 mmol, 2.0 mol %), and *t*BuONa (5.77 mg, 0.060 mmol, 12 mol %) were placed in an oven dried Schlenk flask (20 mL). The flask was evacuated and backfilled with argon three times. Toluene (1.0 mL) was added, and the mixture was stirred for 15 min at room temperature, under an argon atmosphere. Pinacolborane (HBpin; 109 μL, 0.75 mmol) was added to the resulting solution at 0 °C, and the mixture was stirred at 0 °C for 5 min. An alkyne (0.50 mmol) was then added at 0 °C, and the mixture was stirred at 20 °C for 20 h. After the reaction, the mixture was filtered through a pad of silica gel and all of the volatiles were removed in vacuo. The products were isolated by silica gel column chromatography.

General procedure for Table 3: CuCl (0.99 mg, 0.010 mmol, 2.0 mol %), CF_3Ar-Xan (11.2 mg, 0.010 mmol, 2.0 mol %), and *t*BuONa (5.77 mg, 0.060 mmol, 12 mol %) were placed in an oven dried Schlenk flask (20 mL). The flask was evacuated and backfilled with argon three times. Toluene (1.0 mL) was added, and the mixture was stirred for 15 min at room temperature under an argon atmosphere. Bis(pinacolato)diboron (B_2pin_2; 152 mg, 0.60 mmol) was added to the resulting solution, and the mixture was stirred at room temperature for 5 min. An alkyne (0.50 mmol) and MeOH (42 μL, 1.0 mmol) were then added and the mixture was stirred at 28 °C for 3 h. After the reaction, the mixture was filtered through a pad of silica gel and all of the volatiles were removed in vacuo. The products were isolated by silica gel column chromatography.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas ("organic synthesis based on reaction integration" and "molecular activation directed toward straightforward synthesis") from MEXT, Japan, and in part by the Mitsubishi Foundation. K.S. is grateful for a Research Fellowship from JSPS for young scientists. T.F. acknowledges a Naito Foundation Natural Science Scholarship.

Keywords: alkynes • copper • homogeneous catalysis • hydroboration • internal alkynes

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Received: November 17, 2011
Revised: January 11, 2012
Published online: March 2, 2012