Catalytic Hydroboration

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Copper(I)-Catalyzed Regioselective Monoborylation of 1,3-Enynes with an Internal Triple Bond: Selective Synthesis of 1,3-Dienylboronates and 3-Alkynylboronates**

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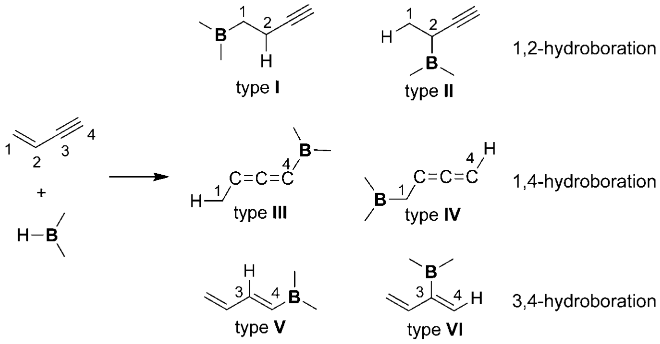
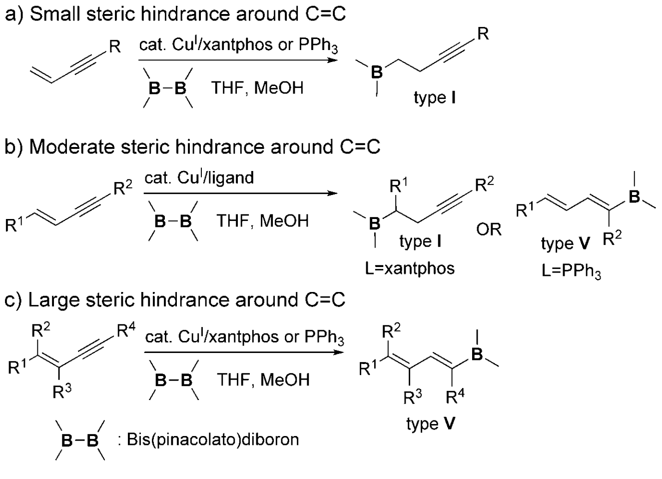
Organoboron compounds are useful reagents and the hydroboration of simple alkenes or alkynes is one of the most efficient and straightforward methods to access a variety of organoboron compounds.[1,2] However, for the preparation of polyconjugated hydrocarbon compounds, there are limited types of regio- and stereoselective hydroboration reactions.[3–10] This type of transformation is still challenging in both transition-metal-catalyzed and noncatalyzed hydroboration.

Hydroboration of 1,3-enyne compounds, for example, gives limited types of the organoboron products.[4–9] This transformation can theoretically produce six possible product isomers (Scheme 1, types **I**–**VI**). However, there has been no clear-cut report on the selective 1,2-hydroboration of 1,3-enynes (types **I** and **II**).[4,5] Allenylboron compounds can be obtained through palladium-catalyzed 1,4-hydroboration of 1,3-enynes (type **III**),[6] whereas the type **IV** product has not been reported. The 3,4-hydroboration of 1,3-enynes is the most common reaction pattern; the type **V** product, which is the 1,3-dienylboron compound, is a useful synthetic precursor. However, in this reaction the type **VI** product is detected as a minor product. Currently, the successful reaction patterns are limited to the production of type **III** and **V** products. In addition, most examples for type **III** and **V** products require the substrate structure to have a terminal alkyne moiety.[7–9] Although hydroboration is a general and widely used synthetic procedure, the application of hydroboration to 1,3-enynes, especially those with an internal alkyne moiety, remains undeveloped.



Scheme 1. Possible product isomers in the hydroboration of 1,3-enyne compounds.

Very recently, our research group reported the copper(I)-catalyzed, regio- and enantioselective monoborylation of 1,3-diene compounds.[10] This process can be extended for the development of novel regioselective borylation reactions of other conjugated systems; namely, where conventional hydroboration can not be used effectively.[11,12] Herein, we report a copper(I)-catalyzed, highly regioselective monoborylation of 1,3-enyne compounds. In this catalysis reaction, either 3-alkynylboronates or 1,3-dienylboronates were obtained with high regioselectivity (Scheme 2). Substrates with a terminal double bond exclusively afforded unprecedented type **I** products (Scheme 2a), whereas highly substituted substrates gave type **V** product with high regioselectivity—even when the substrates have an internal alkyne moiety (Scheme 2c). Interestingly, in the reaction of 1,3-enynes that have moderate



Scheme 2. Regioselective copper(I)-catalyzed monoborylation of 1,3-enyne compounds. THF = tetrahydrofuran, xantphos = 4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene.

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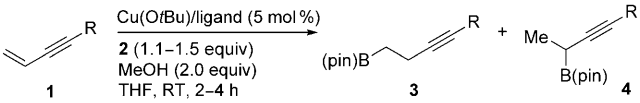
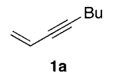
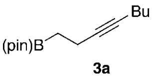
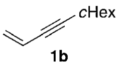
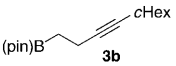
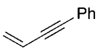
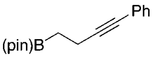
steric demand around the double bond (Scheme 2b), ligand-controlled regioselective borylation was observed. The synthetic utility of the reaction products was further demonstrated through the Suzuki–Miyaura cross-coupling and the Diels–Alder reaction. In addition, a preliminary result for the asymmetric 1,2-monoborylation of 1,3-enyne (84 % *ee*) is also reported.

The regioselectivity in the copper(I)-catalyzed monoborylation of 1,3-enyne compounds containing several substitution patterns was investigated. We initially studied the 1,3-enyne with a terminal double bond and an internal triple bond such as 1-octen-3-yne (**1a**). The reaction was initiated by the addition of 2.0 equivalents of methanol to the mixture of **1a**, 1.5 equivalents of bis(pinacolato)diboron **2**, and 5 mol % of Cu(O*t*Bu)/xantphos in THF at room temperature (Table 1, entry 1). The reaction was complete within 2 hours and gave 3-alkynylboronate **3a** in 87 % yield with high regioselectivity (**3**/**4** > 95:5). This reaction is the first example of the type **I** hydroboration of 1,3-enynes. Reactions using other diphosphine ligands such as dppe and dppbz resulted in lower yields (60–61 %; Table 1, entries 2 and 3). The reaction with PPh_3 also afforded **3a** in high yield (80 %; Table 1, entry 4). In the absence of the ligand, the reaction did not proceed (Table 1, entry 5).[13] The reaction of 1,3-enynes with *c*Hex or Ph groups at the 4-position proceeded to furnish the corresponding 3-alkynylboronates **3** selectively (79–89 %, **3**/**4** = 94:6 to > 95:5; Table 1, entries 6–9).

Table 1: Monoborylation of 1,3-enyne compounds bearing a terminal double bond.[a]

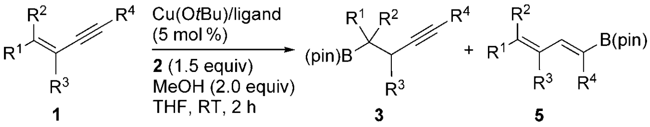


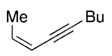
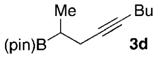
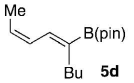
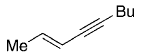
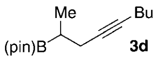
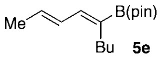
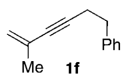
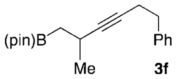
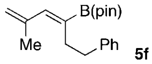
Entry	Substrate	Ligand	Product	Yield [%][b]	3/4[c]
1	 **1a**	xantphos	 **3a**	87	> 95:5
2[d]		dppe		61	> 95:5
3[d]		dppbz		60	> 95:5
4[d]		PPh₃		80	> 95:5
5		none		0	–
6	 **1b**	xantphos	 **3b**	88	> 95:5
7		PPh₃		89	> 95:5
8	 **1c**	xantphos	 **3c**	83	94:6
9		PPh₃		79	> 95:5

[a] Reaction conditions: **1** (0.25 mmol), **2** (0.275–0.375 mmol), Cu(O*t*Bu) (5 mol %, 0.0125 mmol), ligand (5 mol %, 0.0125 mmol), THF (0.25 mL), and methanol (0.5 mmol). [b] Yield of isolated product. [c] Determined by ^1H NMR or GC analysis of the crude reaction mixture. [d] Yield based on ^1H NMR analysis of the crude reaction mixture. dppbz = 1,2-bis(diphenylphosphonio)benzene, dppe = l,2-bis(diphenylphosphino)ethane, pin = pinacolato.

We next investigated the reaction of 1,3-enyne compounds with other substituent patterns. Interestingly, by changing the ligand the reaction with 1,3-enynes bearing 1- or 2-monosubstitution around the double bond afforded either 3-alkynylboronate **3** or 1,3-dienylboronate **5** selectively (Table 2).[14] With the xantphos ligand, the reaction of 1-substituted 1,3-enyne **1d** afforded the corresponding 3-alkynylboronate **3d** with excellent regioselectivity (**3**/**5** > 99:1; Table 2, entry 1). In contrast, the reaction with PPh_3 gave 1,3-dienylboronate **5d** with high regioselectivity (**3**/**5** = 7:93; Table 2, entry 2). The reaction with an (*E*)-alkene substrate also gave either 3-alkynylboronate **3d** and 1,3-dienylboronate **5e**, respectively, thus demonstrating that the alkene geometry (*E* or *Z*) did not affect the selectivity outcome (Table 2, entries 3 and 4). This reaction was also performed with the easily available CuCl/K(O*t*Bu) precatalyst instead of Cu(O*t*Bu) (Table 2, entries 5 and 6). This same type of product profile was also observed in the reaction with 2-substituted 1,3-enyne **1f** (Table 2, entries 7 and 8).

Table 2: Monoborylation of 1,3-enyne compounds with 1- or 2-substitution.[a]

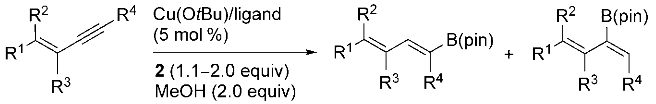


Entry	Substrate	Ligand	Product	Yield [%][b]	3/5[c]
1[d]	 **1d**	xantphos	 **3d**	65	> 99:1
2[e]		PPh₃	 **5d**	64	7:93
3	 **1e**	xantphos	 **3d**	58	> 99:1
4		PPh₃	 **5e**	66	1: > 99
5[f]		xantphos	**3d**	61	> 99:1
6[f]		PPh₃	**5e**	80	1: > 99
7[e]	 **1f**	xanphos	 **3f**	52	92:8
8[e]		PPh₃	 **5f**	65	1: > 99

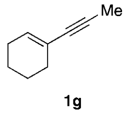
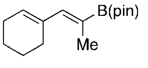
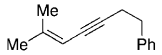
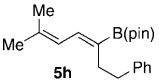
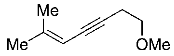
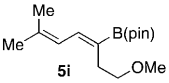
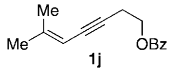
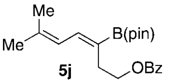
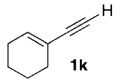
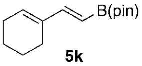
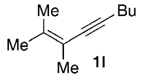
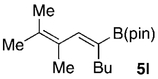
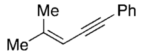
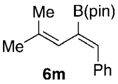
[a] Reaction conditions: **1** (0.25 mmol), **2** (0.375 mmol), Cu(O*t*Bu) (5 mol %, 0.0125 mmol), ligand (5 mol %, 0.0125 mmol), THF (0.25 mL), and methanol (0.5 mmol). [b] Yield of isolated product. [c] Determined by ^1H NMR or GC analysis of the crude reaction mixture. [d] Reaction time was 2.8 h. [e] 1.1 equivalents of diboron **2** was used. [f] 5 mol % of CuCl and 50 mol % of K(O*t*Bu) were used instead of Cu(O*t*Bu).

We further tested the reaction of 1,3-enyne compounds with di- or trisubstitution around the double bond (Table 3). 1-Propynylcyclohexene **1g** was converted into the corresponding 1,3-dienylboronate **5g** in quantitative yield and with high regioselectivity (**5**/**6** > 95:5; Table 3, entry 1). Other possible regioisomers, such as 3-alkynylboronate or 1,2-dienylboronate were not detected. Using other bidentate ligands afforded **5g** in high regioselectivity; however, the yields were lower when compared with the reaction using

Table 3: Monoborylation of 1,3-enyne compounds bearing 1,1-di-, 1,2-di-, and 1,1,2-trisubstitution.[a]



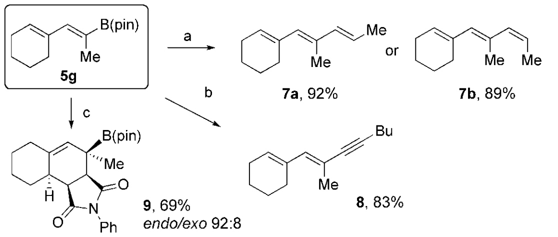
1 **5** **6**

Entry	Substrate	Ligand	Product	Yield [%][b]	5/6[c]
1[d,g]	 **1g**	xantphos	 **5g**	quant.	> 95:5
2[d,g]		dppe		77	> 95:5
3[d,g]		dppbz		85	> 95:5
4[d,g]		PPh_3		97	> 95:5
5[d]		none		0	–
6[e]		xantphos		89	> 95:5
7	 **1h**	PPh_3	 **5h**	76	92:8
8	 **1i**	PPh_3	 **5i**	58	89:11
9	 **1j**	PPh_3	 **5j**	79	> 95:5
10	 **1k**	xantphos	 **5k**	92	> 95:5
11		PPh_3		93	> 95:5
12[f,g]	 **1l**	xantphos	 **5l**	16	95:5
13	 **1m**	xantphos	 **6m**	89	15:85

[a] Reaction conditions: **1** (0.25 mmol), **2** (0.275–0.5 mmol), Cu(OtBu) (5 mol%, 0.0125 mmol), ligand (5 mol%, 0.0125 mmol), THF (0.25 mL), and methanol (0.5 mmol). [b] Yield of isolated product. [c] Determined by ^{1}H NMR or GC analysis of the crude reaction mixture. [d] Reaction was carried out on a 0.5 mmol scale. [e] 5 mol% of CuCl and 50 mol% of K(OtBu) were used instead of 5 mol% of Cu(OtBu). [f] Catalyst loading was 10 mol%. [g] Yield based on ^{1}H NMR analysis of the crude reaction mixture.

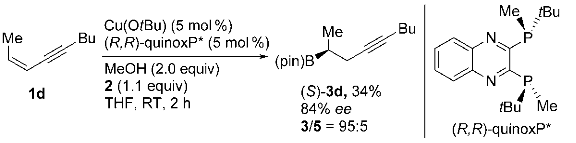
xantphos (77–85%; Table 3, entries 2 and 3). The reaction with PPh_3 gave excellent yield and regioselectivity (97%, **5**/**6** > 95:5; Table 3, entry 4), but no reaction was observed in the absence of the ligand (Table 3, entry 5). The CuCl/K(O*t*Bu) precatalyst was also operative without significant loss of regioselectivity and yield (89%, **5**/**6** > 95:5; Table 3, entry 6). The reaction of a 1,3-enyne bearing 1,1-disubstitution (**1h**) afforded the corresponding 1,3-dienylboronate **5h** with high regioselectivity (**5**/**6** = 92:8; Table 3, entry 7). This reaction was applicable to the 1,3-enynes with an ether or a benzyloxy functionality (Table 3, entries 8 and 9). Reactions with 1,3-enynes bearing a terminal alkyne moiety also afforded the corresponding 1,3-dienylboronate **5k** with high selectivities (**5**/**6** > 95:5; Table 3, entries 10 and 11). The reaction of a 1,3-enyne bearing 1,1,2-trisubstitution proceeded with high regioselectivity but the yield was lower even in the presence of 10 mol% of the catalyst (16%; Table 3, entry 12). This outcome was probably a result of the large steric hindrance around the double bond. Interestingly, the reaction of a 1,3-enyne with a phenyl group at the 4-position (**1m**) predominantly gave the type **VI** regioisomer (**6m**) with good selectivity (**5**/**6** = 15:85; Table 3, entry 13).

The usefulness of 1,3-dieneylboronate **5g** was also demonstrated (Scheme 3). Palladium-catalyzed cross-coupling of **5g** with (*E*)-, (*Z*)-1-bromopropene, and 1-iodohexyne gave the corresponding trienes and dienyne in high yields (**7a**: 92%, **7b**: 89%, and **8**: 83%; Scheme 3, path a,b). Furthermore, the Diels–Alder reaction[15] with *N*-phenylmaleimide afforded the unprecedented cyclic allylboronate **9**, which has four contiguous stereocenters, including one quaternary carbon atom, with high diastereoselectivity (69%, *endo*/*exo* = 92:8; Scheme 2, path c).



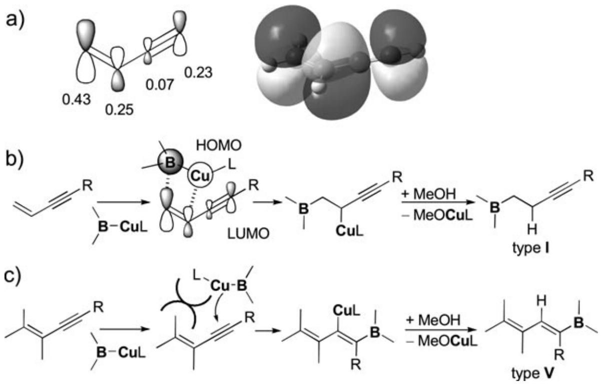
Scheme 3. Derivatization of 1,3-dienylboronate (**5g**). Reaction conditions: path a) (*E*)- or (*Z*)-1-bromopropene, [Pd(PPh$_3$)$_4$]/SPhos (cat.), aq NaOH (2 M), 60 °C, 2.5–3 h; path b) 1-iodohexyne, [Pd(PPh$_3$)$_4$] (5 mol%), aq NaOH (2 M), 80 °C, 4 h; path c) N-phenylmareimide, 120 °C, 3 days. SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

The reaction for the asymmetric synthesis of enantioenriched 3-alkynylboronate with a chiral copper(I) catalyst (5 mol% of Cu(O*t*Bu)/(*R*,*R*)-quinoxP*) resulted in a good *ee* value with excellent regioselectivity (84% *ee*, **3**/**5** = 95:5; Scheme 4); however, the yield was moderate (34%) because of the formation of multiborylation by-products. This reaction is the first example of an asymmetric synthesis of 3-alkynylboronates.



Scheme 4. Asymmetric catalytic monoborylation of 1,3-enyne **1d**.

A tentative explanation of the regioselective outcome of the hydroboration reaction is presented in Scheme 5. According to the mechanistic investigation reported by Marder, Lin, and co-workers,[16] the interaction between the HOMO of the borylcopper intermediate and the electrophile LUMO is decisive in the regioselectivity of the borylcopper addition to unsaturated bonds. Orbital population analysis showed that



Scheme 5. a) DFT population analysis and isosurface of the LUMO of 1-buten-3-yne (B3LYP/6-31G(d,p), Gaussian 09W). b,c) Proposed explanation for product selectivities.

the 2p orbitals of the alkene carbon atoms (Scheme 5a; C1: 0.43; C2: 0.25 for 1-buten-3-yne) have a significantly larger contribution than those of the alkyne carbon atoms (C3: 0.07; C4: 0.23).

Thus, it is reasonable that the borylcupration takes place at the olefin double bond when steric perturbation of the substrate is not significant (type **I**; Scheme 5b). In the case of highly substituted 1,3-enynes, steric hindrance around the double bond would render borylcopper addition to the electronically less favorable alkyne moiety to produce 1,3-dienylboronates (type **V**; Scheme 5c). However, the selectivity outcome observed for moderately substituted 1,3-enynes were counterintuitive along this line. Further investigation is required to resolve this point.

In summary, we have developed copper(I)-catalyzed regioselective monoborylation of 1,3-enyne compounds. This catalysis includes the first examples for type **I** and **VI** hydroborations, and efficient type **V** hydroboration of 1,3-enynes with an internal triple bond. The regioisomeric preference (1,3-dienylboronates or 3-alkynylboronates) was primarily determined by the substrate structure, whereas the regioselectivity for moderately substituted 1,3-enynes was controlled by the ligand of the catalyst. It is noted that these selectivity features are different from those for 1,3-dienes in our previous study.[10] This copper(I)-catalyzed selective monoborylation is a complementary method to conventional hydroboration reactions for 1,3-enynes.

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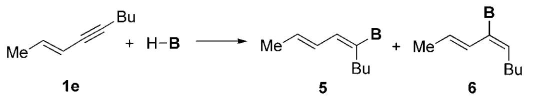

1e **5** **6**

Noncatalyzed reaction:	**B** = B(cat), neat, 70°C, 15 h	85% yield, **5/6** = 53:47
Rhodium-catalyzed reaction:	**B** = B(pin), [RhCl(PPh$_3$)$_3$] (5 mol %) CH$_2$Cl$_2$, RT to 50°C, 20 h	75% yield, **5/6** = 76:24

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