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Diboration of 3-Substituted Propargylic Alcohols using a Bimetallic Catalyst System: Access to (*Z*)-Allyl, Vinyldiboronates†

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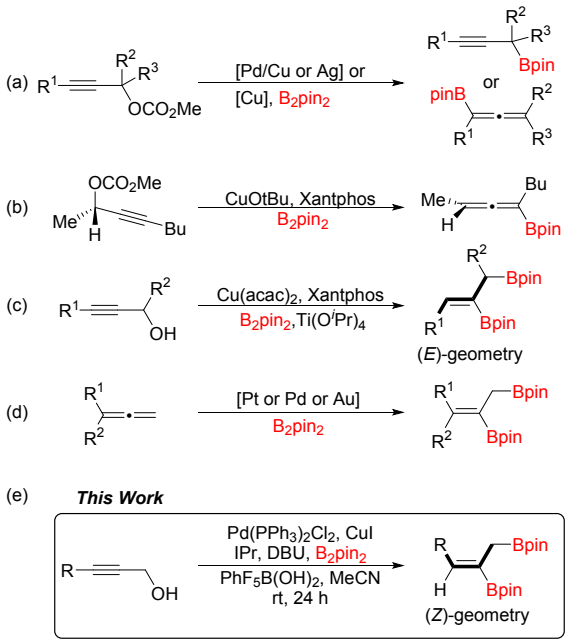
The diboration of substituted propargylic alcohols has been achieved using a bimetallic Pd/Cu catalyst system. In situ formation of a pentrafluoroboronic acid intermediate sufficiently activates the C-O bond towards dual catalysis affording (*Z*)-allyl, vinyldiboronates stereoselectively.

The formation of highly decorated organoboron compounds are essential in complex molecule synthesis, medicinal chemistry, and material science.[1] Numerous methods for the transition metal-catalyzed for diborylation of alkynes, which are useful precursors to access high value α- or β-vinyl boronic acid derivatives have been reported.[2] However, methods employing propargylic alcohol derived substrates are limited.[3] Several years ago, elegant work by Szabó demonstrated that activation of propargylic alcohols with a carbonate leaving group can alternately afford propargylic or allenyl boronates (Figure 1a).[4] This maneuver allowed for product formation to proceed stereospecifically through an S_N2 or formal S_N2' pathway under Pd/Cu or Pd/Ag bimetallic catalytic conditions. Unfortunately, other activating groups were shown to be less effective, thereby limiting the application of this method. Ito and Sawamura reported an alternative protocol for the formation of chiral allenyl boronates utilizing a Cu(I)-phosphine complex (Figure 1b).[5]

Borylation of unactivated alcohols is notoriously difficult.[6] Recently, Marder[7] and Ye[8] disclosed a copper-catalyzed method for the synthesis of allyl, vinyldiboronates and allenyl boronates from propargylic alcohol derivatives (Figure 1c). In the case of the former, activation of C–O bond of the propargylic alcohol substrate was successfully achieved by the addition of $Ti(O^iPr)_4$.

Figure 1 Transition metal-catalyzed borylations of allene and propargylic alcohol derivatives.



Through a copper-catalyzed formation of an allenylboronate intermediate, subsequent round of borylcupration generates the (*E*)-allyl, vinyldiboronates. Access to the corresponding (Z)-isomer remains elusive. Indeed, 2-boryl allylboronates have previously only been achieved using a Pt-,[2e, 2k] Pd-[2c, 9] or Au-catalyzed[10] diboration of allenes (Figure 1d). In addition to the challenge of borylating unactivated systems such as propargylic alcohols, the formation of these allyl and vinyl bis boronated products with distinguishable chemical reactivity inspired us to develop a method for such a transformation. Herein, we report a dual palladium-copper catalyzed diboration of unactivated propargylic alcohols utilizing pentafluoroboronic

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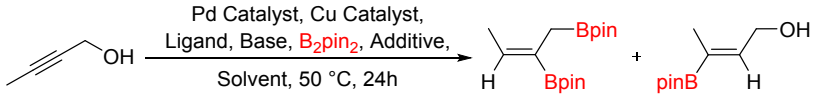
Table 1 Optimization of Reaction Conditions.[a]



1a **2a** **3a**

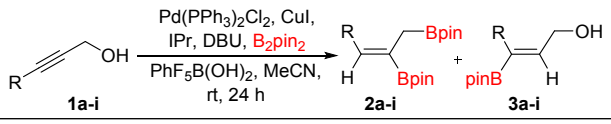
entry	Pd Catalyst	Cu Catalyst	Base	Additive	Ligand	Solvent	Ratio 2:3[b]	Yield (%)[c]
1	$Pd(PPh_3)_4$	CuI	DBU	none	none	THF	75:25	(15)
2	$Pd(PPh_3)_4$	CuI	Et_3N	none	none	THF	>1:99	(>1)
3	$Pd(PPh_3)_4$	CuI	NaO^tBu	none	none	THF	28:72	(8)
4	$Pd(PPh_3)_4$	CuI	DBU	$PhF_5B(OH)_2$	none	THF	90:10	22
5	$Pd(PPh_3)_4$	CuI	DBU	$Ti(O^iPr)_4$	none	THF	88:12	11
6	$Pd(PPh_3)_4$	CuI	DBU	$FeCl_3$	none	THF	90:10	17
7	$Pd(PPh_3)_4$	CuI	DBU	$PhF_5B(OH)_2$	Xantphos	THF	100:0	29
8	$Pd(PPh_3)_4$	CuI	DBU	$PhF_5B(OH)_2$	Dppp	THF	100:0	2
9	$Pd(PPh_3)_4$	CuI	DBU	$PhF_5B(OH)_2$	RuPhos	THF	99:>1	12
10	$Pd(PPh_3)_4$	CuI	DBU	$PhF_5B(OH)_2$	$P(OPh)_3$	THF	97:3	10
11[d]	$Pd(PPh_3)_4$	CuI	DBU	$PhF_5B(OH)_2$	IPr	THF	98:2	37
12[d]	$Pd(PPh_3)_2Cl_2$	CuI	DBU	$PhF_5B(OH)_2$	IPr	THF	98:2	37
13[d]	$Pd(dppf)_2Cl_2$	CuI	DBU	$PhF_5B(OH)_2$	IPr	THF	97:3	<1
14[d]	$Pd(PPh_3)_2Cl_2$	CuCN	DBU	$PhF_5B(OH)_2$	IPr	THF	100:0	32
15[d]	$Pd(PPh_3)_2Cl_2$	$Cu(acac)_2$	DBU	$PhF_5B(OH)_2$	IPr	THF	100:0	<1
16[d]	$Pd(PPh_3)_2Cl_2$	CuI	DBU	$PhF_5B(OH)_2$	IPr	MeCN	93:7	49
17[d]	$Pd(PPh_3)_2Cl_2$	CuI	DBU	$PhF_5B(OH)_2$	IPr	DCM	96:4	44
18[d]	$Pd(PPh_3)_2Cl_2$	CuI	DBU	$PhF_5B(OH)_2$	IPr	Toluene	98:2	16
19[e]	$Pd(PPh_3)_2Cl_2$	CuI	DBU	$PhF_5B(OH)_2$	IPr	MeCN	96:4	68 (36)
20[e,f]	$Pd(PPh_3)_2Cl_2$	CuI	DBU	$PhF_5B(OH)_2$	IPr	MeCN	n.r.	n.r.
21	none	CuI	DBU	$PhF_5B(OH)_2$	IPr	MeCN	n.r.	n.r.
20	$Pd(PPh_3)_2Cl_2$	none	DBU	$PhF_5B(OH)_2$	IPr	MeCN	n.r.	n.r.

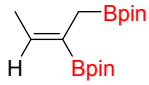
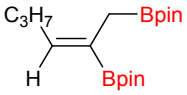
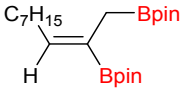
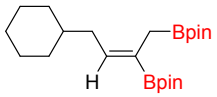
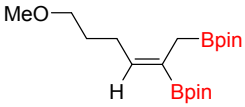
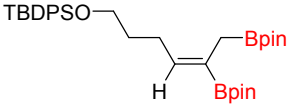
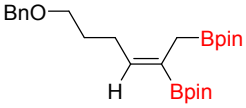
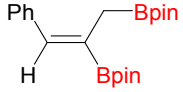
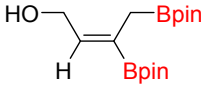
[a] Reaction conditions: Premix Pd catalyst (0.024 mmol), Cu catalyst (0.024 mmol), and ligand (0.059 mmol) in solvent (1.5 mL) for 30 min. **1a** (0.484 mmol) and base (0.484 mmol) were added before cannulating in a solution of B_2pin_2 (0.968 mmol) and additive (0.024 mmol) in MeCN (0.5 mL). [b] Ratio determined by GC analysis of crude reaction mixture and stereochemistry was confirmed by NOESY experiments. [c] GC yields of **2a** determined (benzophenone as an internal standard). Isolated yields shown in parenthesis. [d] NHC already deprotonated. [e] Reaction performed at rt. [f] pinB–Bdan used as the borylating agent. Abbreviations: Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene; Dppp = 1,3-Bis(diphenylphosphino)propane; RuPhos = dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl; IPr = 1,3-Bis(2,6diidopropylphenyl)-imidazol-2-ylidine; dan = 1,8-diaminonaphtalene; n.r. = no reaction

acid as an *in situ* activating agent to generate (*Z*)-allyl, vinyldiboronates (Figure 1e).

Preliminary studies were initiated using commercially available propargylic alcohol, but-2-yn-1-ol (**1**), and a bimetallic catalyst system (Table 1, for more optimization details see Supporting Information). To our surprise, initial conditions afforded allyl, vinyl diboronate **2a** in 15% yield with protoboration **3a** as a minor product (entry 1). The expected propargyl or allenyl boronate products were not detected. The product stereochemistry was confirmed by nuclear Overhauser effect NMR experiments. A survey of bases indicated that more sterically hindered base, diazabicycloundecene (DBU), was found to favor product **2** (entries 1-3). As previous work suggested that activation of the hydroxyl group is key to conversion, Lewis acids and transition metal catalysts, which have shown to be successful in Friedel-Crafts reactions of allylic alcohols, were employed (entries 4-6).[7b, 11] In each case, catalytic amounts of the additive increased the selectivity of product **2a** over **3a**. Interestingly, pentafluorophenylboronic acid was more effective than $FeCl_3$ or $Ti(O^iPr)_4$. An increase in additive amounts did not affect the yield (see SI). Bidentate and monodentate ligands with various bite and cone angles were also surveyed (entries 7-11). Notably, Xantphos was preferred to Dppp. Whereas monodentate phosphine ligands were ineffective, N-heterocyclic carbene IPr promoted the reaction. We further investigated different catalysts and discovered that air-stable Pd(II) catalyst, $Pd(PPh_3)_2Cl_2$, was as effective as $Pd(PPh_3)_4$ (entries 12-15). By screening numerous solvents, we established that aprotic polar solvents such as MeCN and DCM were more efficient than non-polar solvents (entries 16-18). Furthermore, conducting the reaction at room temperature compared to heating was shown to be crucial in the formation of the diborated product **2a** (entry 19). While B_2pin_2 was shown to be reactive in the borylation of buty-2-yn-1-ol (**1**), unsymmetrical diboron reagent, pinB-Bdan, was inert (entry 20). Control experiments indicate that both Pd

Table 2 Substrate Scope.[a]

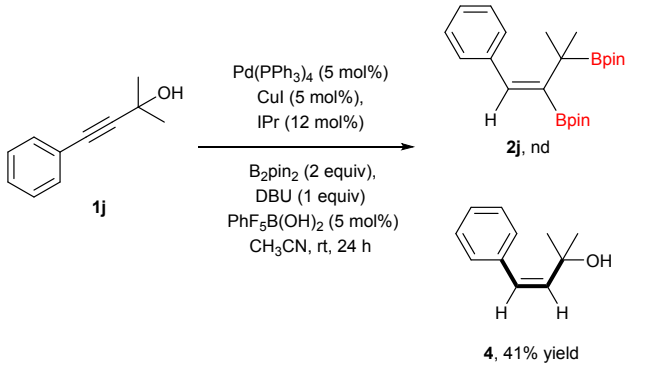


	Major Product	2:3[b]	Yield (%)[c]
2a		96:4	68 (36)
2b		94:6	76 (19)
2c		94:6	41 (35)
2d		87:13	29 (14)
2e		91:9	28 (14)
2f		95:5	54 (28)
2g		90:10	59 (24)
2h		99:1	11 (7)
2i		–	n.d.

[a] Reaction conditions: Premix $Pd(PPh_3)_2Cl_2$ (0.024 mmol), CuI (0.024 mmol), and IPr (0.059 mmol) in MeCN (1.5 mL) for 30 min. Propargylic alcohol **1** (0.484 mmol) and DBU (0.484 mmol) were added before cannulating in a solution of B_2pin_2 (0.968 mmol) and $PhF_5B(OH)_2$ (0.024 mmol) in MeCN (0.5 mL). [b] Ratio determined by GC analysis of crude reaction mixture and stereochemistry was confirmed by NOESY experiments. [c] GC yields determined (benzophenone as an internal standard). Isolated yields shown in parenthesis. n.d. = not detected.

and Cu are required in the reaction (entries 21-22). The low yields may, at least in part, be due to the fact that copper alone catalyzes the formation of the side product 3 (see SI, Table 4, entry 15). The optimal reaction conditions afforded a 68% yield of product **2a** within 24 h at room temperature (entry 19); the instability of products with silica required fast column chromagraphy.

With optimized conditions in hand (Table 1, entry 19), we investigated the scope and limitations of the reaction. As shown in Table 2, aliphatic propargylic alcohols containing methyl (**1a**) and propyl (**1b**) substituents were efficiently diborated in good yields with excellent *Z* selectivity. The longer heptyl (**1c**) substituent resulted in a slightly decreased yield (41% yield). Unfortunately, a 29% yield was observed with the larger propargyl cyclohexyl (**1d**) group along with a marginal decrease in the product ratios (**2d**:**3d** = 87:13). The incomplete

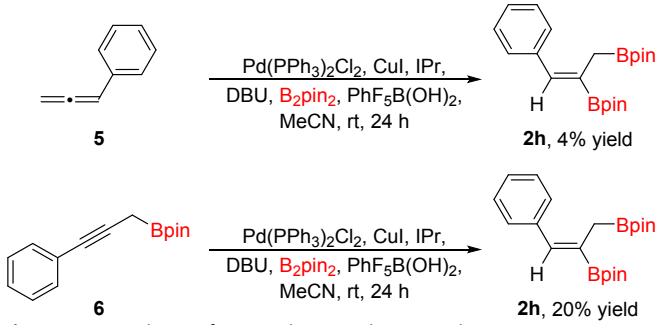


Scheme 1. Transformation of **1j** to **4**.

conversion of starting material indicates that the cyclohexyl group may be inhibiting product formation. A series of ether linkages were next tested. Although the reaction with the terminal methyl ether (**1e**) resulted in a lower yield, the *tert*-butyldiphenylsilyl (**1f**) protected counterpart was more effective affording a 54% yield. Additionally, the propargylic alcohol bearing the benzyl ether (**1g**) was well tolerated affording a 59% yield (**2g**). We next tested 3-phenylpropargylic alcohol **1h** and, despite obtaining a low yield, the regioselectivity was significantly higher compared to previous substrates. To further explore the functional group tolerance of the reaction, but-2-yne-2,4-diol (**1i**) was subjected to the reaction conditions. Instead of forming the desired product **2i**, product **2a** was isolated in a low yield. Finally, we investigated a sterically encumbered tertiary propargylic alcohol **1j**. Surprisingly, instead of affording **2j**, **1j** gave the *cis* reduced product **4** in 41% yield (Scheme 1).

We also performed the reaction with phenyl allene **5** under the same reaction conditions and found that **2h** is formed in minor amounts (Scheme 2). In contrast, the reaction with propargylic boronate **6** with B_2pin_2 under identical conditions afforded **2h** in 20% yield. Based on the results above and the fact that an allene intermediate is not detected during the reaction, our studies that propargylic boronate could be an intermediate in the Pd/Cu dual catalysis.

In summary, we developed a simple and mild palladium/copper catalyzed method for the diboration of propargylic alcohols to afford (*Z*)-allyl, vinyldiboronates. Key to



Scheme 2 Borylation of potential intermediates **5** and **6**.

the success of the reaction is the *in situ* activation of the C-O bond by pentrafluoroboronic acid, which under Pd/Cu catalysis provides a propargyl boronic acid derivatives.

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Conflicts of Interest

There are no conflicts to declare.

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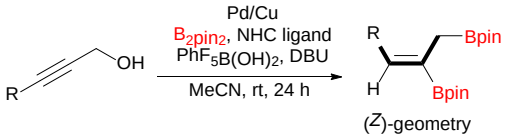

(*Z*)-geometry

A Pd/Cu catalyst system facilitates the diboration of unactivated propargylic alcohols with pentafluoroboronic acid and diboron to generate (*Z*)-allyl, vinyldiboronates.