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Letter

# Copper-Catalyzed 1,1-Boroalkylation of Terminal Alkynes: Access to Alkenylboronates via a Three-Component Reaction

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stereoselective boration reaction. Typically, different carbene precursors selectively lead to Z- and E-alkenes.

A lkenylboronates are synthetically useful reagents in organic synthesis, which have been utilized in constructing various carbon–carbon and carbon–heteroatom bonds by metal-catalyzed cross-coupling reactions,<sup>1</sup> especially in preparing multisubstituted alkenes.<sup>2</sup> Given the great importance, the development of effective and practical protocols to synthesize multisubstituted alkenylboronates is highly desirable.<sup>3</sup> To date, conventional methods to access alkenylboronates include transition-metal-catalyzed hydroboration of terminal alkynes<sup>4</sup> and dehydrogenative borylation of alkenes<sup>5</sup> (Scheme 1a). Moreover, transition-metal-catalyzed three-component boro-functionalization of unsaturated C–C bonds with an external electrophile represents a straightforward strategy for the rapidly assembling of multisubstituted alkenylboronates in a concise manner (Scheme 1b).<sup>67</sup>

catalyzed cross-coupling and the following copper-catalyzed



Recently, we have developed a series of carbene-involved tandem reactions to forge various ring systems, in which copper-catalyzed cross-coupling of alkynes with diazoacetates to form allenoates has been proven to be the key step.<sup>3</sup> Inspired by literature reports and our own experience, we wish to develop a three-component reaction of terminal alkynes, diazo compounds, and B2pin2 to prepare tri-substituted alkenylboronates (Scheme 1c). We envisioned that this boroalkylation reaction might proceed through a tandem sequence, and the copper catalyst would play dual roles in the whole reaction process, namely, the catalytic cross-coupling of terminal alkynes with diazo compounds,9,10 as well as the following borylative reaction.<sup>11</sup> However, as well documented, four major side reactions may arise when exposed to a copper catalyst: (1) cyclopropenation reaction of terminal alkynes with diazoacetates;<sup>12</sup> (2) direct hydroboration/protoboration of alkyne with B<sub>2</sub>pin<sub>2</sub> to afford disubstituted alkenylbornates; (3) self-coupling of two molecules of diazo compounds;<sup>13</sup> and (4) the diboration of diazo compounds with  $B_2 pin_2$ . Obviously, the potential byproducts would cause bad influence on this one-pot protocol. Thus, a suitable catalytic system must be developed to significantly minimize those side reactions.

Our initial experiments showed that the three-component reaction of phenylacetylene (1a), diazoacetate (2a), and  $B_2pin_2$  in a ratio of 1:1.5:3 led to a 70% yield of trisubstituted borylalkene (3aa) with excellent Z-selectivity (>19:1) in *N*,*N*-dimethylformamide (DMF) at 30 °C in the presence of CuI and 4 Å molecular sieves (Table 1, entry 1). Using dimethyl

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Ph— 1	$= + \frac{Ph \bigvee_{N_2}^{CO_2Me}}{N_2} + \frac{B}{B}$ a 2a	[Cu] 2(pin)2 4A MS, 30 °C	Ph-CO <sub>2</sub> Me H Bpin 3aa + Ph- 5aa Bpin	$\begin{array}{c} Ph & CO_2Me \\ Ph & 4aa \\ Ph & CO_2Me \\ Ph & 6aa \\ CO_2Me \end{array}$
entry	cat.	$1a/2a/B_2pin_2$	3 solvent	aa/4aa/5aa/6aa (%) <sup>b</sup>
1	CuI	1:1.5:3	DMF	70/0/5/<5
2	CuI	1:1.5:3	DMSO	40/0/<5/<5
3	CuI	1:1.5:3	DMAC	53/0/18/9
4	CuI	1:1.5:3	$CH_2Cl_2$	0/30/0/28
5	CuI	1:1.5:1	DMF	20/0/37/<5
6	CuI	1:1.5:2	DMF	51/0/9/<5
7 <sup>c</sup>	CuI	1:1.5:3	DMF	<5/-/-/16
8	CuCl	1:1.5:3	DMF	0/0/27/<5
9	Cu(MeCN) <sub>4</sub> BF <sub>4</sub>	1:1.5:3	DMF	0/0/21/<5
10	$Cu(OTf)_2$	1:1.5:3	DMF	0/55/0/20
11	CuI/L1	1:1.5:3	DMF	88/0/<5/<5
12	CuI/L2	1:1.5:3	DMF	76/0/<5/<5
13	CuI/L3	1:1.5:3	DMF	73/0/10/<5
14	CuI/L4	1:1.5:3	DMF	30/0/<5/<5
15	CuI/L5	1:1.5:3	DMF	15/0/12/<5
16	CuI/L6	1:1.5:3	DMF	0/0/84/12
17	CuI/L7	1:1.5:3	DMF	42/0/7/<5
18	CuI/PPh <sub>3</sub>	1:1.5:3	DMF	0/0/97/0
19	CuI/PCy <sub>3</sub>	1:1.5:3	DMF	23/0/23/<5

Table 1. Optimization of the Reaction Conditions<sup>a</sup>

<sup>*a*</sup>Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol),  $B_2pin_2$  (0.6 mmol), copper salt (8 mol %), ligand (10 mol %, from entries 11 to 19) in solvent (4 mL) at 30 °C for 18 h. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>Without molecular sieves.



sulfoxide (DMSO) as the solvent gave 3a in 40% yield (entry 2), whereas dimethylacetamide (DMAC) furnished a 53% vield of 3aa together with an 18% vield of alkenylboronate 5aa and a small amount of 6aa (entry 3). When dichloromethane was used, the cyclopropene 4aa and alkene 6aa were isolated as the major products (entry 4). Moreover, decreasing the amount of  $B_2pin_2$  gave inferior results (entries 5 and 6). Typically, the addition of 4 Å molecular sieves was crucial to the reaction. Without molecular sieves, only a trace amount of 3aa was detected (entry 7). Next, several copper salts were screened. The use of CuCl and Cu(MeCN)<sub>4</sub>BF<sub>4</sub> furnished byproduct 5aa in over 20% yield rather than the desired 3aa (entries 8 and 9), indicating the direct hydroboration of alkynes was more easily to occur for such copper anions. In contrast, cyclopropene 4aa was obtained as the major product for  $Cu(OTf)_{2}$ , which indicated the cyclopropene reaction was dominated for this anion (entry 10). By identifying CuI as the best copper salt, various ligands were further evaluated. The use of bipyridine ligand L1 provided an 88% yield of 3aa with minimum byproducts (entry 11). The combination of CuI with 4,4'-bipyridine ligands L2 and L3 also worked well to give 3aa as the major product but in slightly lower yields (entries 12 and 13). As observed, sterically hindered 2,2'-bipyridine ligands could not promote the reaction. For example, L4 and L5 gave low yields of 3aa (entries 14 and 15). The direct borylation of alkyne was dominated for L6 (entry 16).

Moreover, the use of phenanthroline ligand L7 produced **3aa** in moderate yield (entry 17). Finally, phosphine ligands proved to be ineffective. The use of PPh<sub>3</sub> delivered **5aa** as the sole product in 97% yield (entry 18), and PCy<sub>3</sub> led to the equal amount of **3aa** and **5aa** (entry 19). It should be noted that the alkenylboronate **3aa** was obtained solely as the Z-isomer (Z/E > 19:1).

Under the optimal reaction conditions, the scope of diazo compounds was evaluated (Scheme 2). As observed, a range of





<sup>*a*</sup>Reaction conditions: 1 (0.2 mmol),  $B_2pin_2$  (0.6 mmol), CuI (8 mol %), L1 (10 mol %), 4 Å MS (100 mg), and DMF (2 mL) were added to a dry reaction tube, and then 2 (0.3 mmol) in DMF (2 mL) was added and stirred at 30 °C for 18 h. <sup>*b*</sup>Isolated yields for single isomer.

 $\alpha$ -aryl and  $\alpha$ -heteroaryl diazoacetates were found to work well, delivering the corresponding alkenylboronates in moderate to good yields.  $\alpha$ -Aryldiazoacetates containing electron-donating groups such as methyl, methoxy, phenyl, amide, benzodioxole, and naphthyl reacted smoothly with 1a and B<sub>2</sub>pin<sub>2</sub> to deliver the desired alkenylboronates (3ab-3ag) in 55% to 85% yields with moderate to good Z/E ratios.  $\alpha$ -Aryldiazoacetates bearing electron-withdrawing groups such as fluoro, chloro, and bromo at different positions of the phenyl ring were all tolerated, providing the corresponding products (3ah-3al) in moderate to good yields (56%–90%) with excellent Z-selectivity (Z/E > 19/1). Unfortunately, the  $\alpha$ -aryldiazo substrate containing a  $CF_3$  group failed to give the desired product (3am). This diazo substrate was reduced to the corresponding hydrazone under such conditions.<sup>15</sup> The three-component-reaction of 1a,  $\alpha$ thienyl diazoacetate, and B2pin2 afforded 3an in 46% yield with excellent Z-selectivity. The use of pyridine-derived diazoacetate only led to an 18% yield of 3ao together with a large amount of 5aa. For phenyl diazoacetates bearing different esters, the products (3ap-3aq) were obtained in moderate yields. Next, the scope of terminal alkynes was investigated. It was found that both electron-rich and electron-poor aromatic alkynes were tolerated, affording the corresponding products (3ba-3ja) in moderate to good yields with an excellent Z/E ratio. The reaction can be performed in gram scale, and

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alkenylboronate 3ca was obtained in 83% yield (1.7 g). Arylalkynes having electron-donating substituents such as methyl, methoxy, phenyl and others reacted well to deliver the corresponding borylalkenes in 63-95% yields. Halogensubstituted aromatic alkynes were amenable to this reaction, affording the desired products (3ha-3ja) in yields of 33-75%. The low yield of 3ia was attributed to the low efficiency for the allenoate formation (recovery of 40% of 1a). The thienyl alkyne was a viable substrate, giving an 82% yield of 3ka in excellent Z-selectivity. With respect to alkyl alkynes, the corresponding products (3la and 3ma) were obtained in 26% and 38% yields, respectively. Cyclopropyl and cyclohexyl substituted alkynes were tolerated, providing 3na and 3oa in moderate yields while retaining the ring moiety. Other alkynes such as cyclohexenyl and p-toluenesulfonamide tethered alkynes were also applicable, furnishing the desired products 3pa and 3ga in moderate yields.

As pioneered by Wang and co-workers, the copper-catalyzed cross-coupling reaction of terminal alkynes with *N*-tosylhydrazones led to the formation of allenes in the presence of a strong base.<sup>9</sup> We then sought to use *N*-tosylhydrazones instead of diazoacetates as carbene precursors in this one-pot reaction (Scheme 3). After intensive optimization (see Supporting

Scheme 3. Scope of Copper-Catalyzed One-Pot Reaction of Terminal Alkynes, N-Tosylhydrazones, and  $B_2 pin_2^{a,b}$ 



<sup>*a*</sup>Reaction conditions: 1 (0.2 mmol), 7 (0.44 mmol), CuI (0.02 mmol), 'BuONa (0.70 mmol), and 1,4-dioxane (4 mL) were added to a dry reaction tube. The resulting solution was stirred at 90 °C for 3 h. Then CuI (0.02 mmol), L8 (0.02 mmol), B<sub>2</sub>pin<sub>2</sub> (0.6 mmol), and MeOH (0.80 mmol) were added to the mixture and stirred for 5 h at 20 °C. <sup>*b*</sup>Isolated yields for single isomer.

Information for details), we finally achieved the best reaction conditions: the initial reaction of terminal alkynes and hydrazones in the presence of sodium tert-butoxide, followed by the addition of methanol and B<sub>2</sub>pin<sub>2</sub> in the presence of CuI/L8, provided the final trisubstituted alkenylboronates in moderate yields. Under such reaction conditions, the reactions were clean and no significant amount of side products formed. The isolation and purification processes might result in lower yields. As observed, the hydrazones derived from aliphatic aldehydes were tolerated, providing moderate yields of the corresponding products (8aa-8ad). The use of benzaldehyde derived hydrazone delivered a 46% yield of desired product 8ae. It should be noted that the addition of the second batch of CuI was necessary for a clean reaction. Also, different from the above-mentioned diazoacetates-derived boroproducts, E-alkenylboronates were obtained as the major isomers for Ntosylhydrazones.

The synthetic utility of this boroalkylation of terminal alkynes was demonstrated by conducting versatile derivatization reactions (Scheme 4). The Suzuki coupling of **3aa** with

#### Scheme 4. Further Elaboration



iodobenzene gave trans-alkene **9** in 91% yield, which underwent further hydrolysis to give an 87% yield of alkene **10** (Scheme 4a). Likewise, the Suzuki–Miyaura coupling of **8aa** with aryl iodide followed by hydrolysis led to *trans*-alkene **12** in an *E*-configuration with a good yield (Scheme 4b). The structures of these two series of alkenylboronates were exemplified by the single-crystal X-ray diffraction study of **10** and **12**. Next, under silver catalysis, the protonation reaction of **3ca** gave *cis*-alkene **13** in 57% yield (Scheme 4c). Suzuki coupling of **3ca** with 4-iodopyridine led to a 40% yield of pyridine-incorporated alkene **14**. Treatment of **3ca** with CuBr<sub>2</sub> afforded the corresponding alkenyl bromide **15** in 53% yield. Similarly, subjecting **3ca** with CuCl<sub>2</sub> led to a 70% yield of alkenyl chloride **16**. Subjecting **3qa** to lithium *tert*-butoxide formed lactam **17** in 62% yield (Scheme 4d).

To gain insight into the reaction process, control experiments were conducted (Scheme 5). The reaction of 4aa with  $B_2pin_2$  under copper catalysis was messy and gave no formation of 3aa (Scheme 5a). Treatment of 5aa with diazoacetate 2a did not give 3aa but the recovery of 5aa and the observation of self-coupling product 6aa from diazoacetate

Scheme 5. Control Experiments



(Scheme 5b). These two experiments excluded the possibility of preferential cyclopropenation, as well as the coppercatalyzed protoboration of the alkyne followed by hydrocupration and electrophilic functionalization with diazoacetates. Next, replacing B<sub>2</sub>pin<sub>2</sub> with HBpin as the boron reagent could not form 3aa (Scheme 5c). The unstable allenoate 3a formed and the reaction stopped at this stage, which excluded the possibility for a copper-catalyzed simple Michael addition reaction. Finally, addition of 12 equiv of deuterium water to the reaction system afforded deuterium labeling product D-3aa with 40% and 30% deuterium incorporation at sp<sup>2</sup> and sp<sup>3</sup> carbon atoms, respectively. This experiment provided evidence for the two protonation steps in the catalytic cycle in Scheme 6. Finally, treatment of crude 3a with B<sub>2</sub>pin<sub>2</sub> did not form 3aa, indicating the necessity of copper catalyst in the boration step (Scheme 5e).





On the basis of the literature reports and control experiments, a plausible reaction mechanism has been proposed (Scheme 6). The three-component reaction might be initiated by the formation of copper acetylide Int-1 from the copper catalyst and phenylacetylene.9,10 Then, the reaction between copper acetylide and diazoacetate 2a would generate copper carbene species Int-2. Migratory insertion of an alkynyl group affords Int-3. Protonation of Int-3 occurs to give allenoate Int-4 and regenerates the copper catalyst. The next catalytic cycle would be initiated by the formation of nucleophilic copper-boryl species Int-5 via the reaction of the copper catalyst with B<sub>2</sub>pin<sub>2</sub> under such reaction conditions. Addition of Int-5 to electrophilic allenoate Int-4 results in the formation of metalated intermediate Int-6, which undergoes further protonation with water to give alkenylboronate 3aa and simultaneously releases the copper catalyst (Scheme 6a). The stereoselectivity of this reaction can be attributed to the steric factors during the boryl addition process.<sup>11a</sup> The steric interaction makes the boron group attack the  $\beta$ -carbon from the opposite side of the  $\gamma$ -phenyl group of the allenoate, leading to the favored (Z)-isomer (Scheme 6b). For N-

tosylhydrones-derived products, the addition of **Int-5** to allene provides allyl copper intermediates **Int-7** and **Int-8**. Since **Int-7** is more reactive, the protonation of **Int-7** at  $\gamma$ -carbon via sixmembered ring transition state **TS1** would furnish the more thermodynamically stable *E*-product (Scheme 6c).<sup>16</sup>

In summary, we have developed a novel three-component reaction of terminal alkynes, diazo compounds, and  $B_2pin_2$  to prepare trisubstituted alkenylboronates under copper catalysis. Importantly, both boro- and alkyl- groups have been selectively incorporated at the 1,1-position of terminal alkynes. Moreover, the copper catalyst has been proven to play dual roles in the whole sequence. Namely, the initial cross-coupling of alkynes with diazo compounds leads to the formation of allenes, and the following copper-catalyzed borylative reaction of allenes with  $B_2pin_2$  occurs to give the final alkenylboronates. The side reactions have been successfully minimized under such reaction conditions. Notably, the use of diazoacetates gives trisubstituted Z-alkenes, and when N-tosylhydrazones were used, the alkenes were obtained in the E-configuration.

# ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01081.

Experimental procedures along with characterizing data and copies of NMR spectra (PDF)

### **Accession Codes**

CCDC 2058533 and 2058535 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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#### Notes

The authors declare no competing financial interest.

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