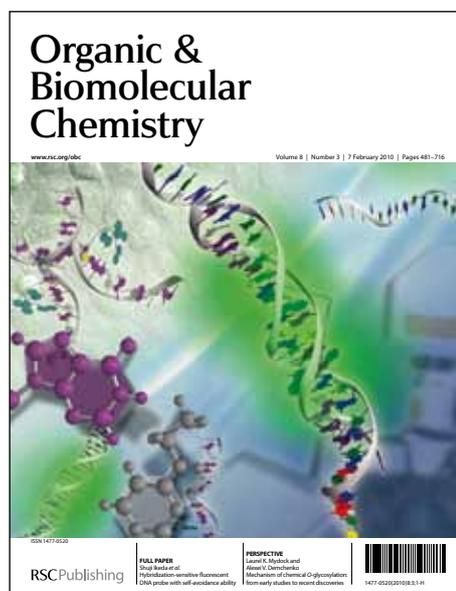


# Organic & Biomolecular Chemistry

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ARTICLE TYPE

CuCl/K<sub>2</sub>CO<sub>3</sub>-catalyzed highly selective borylcupration of internal alkynes-ligand effectWeiming Yuan<sup>a</sup> and Shengming Ma<sup>\*a,b</sup>

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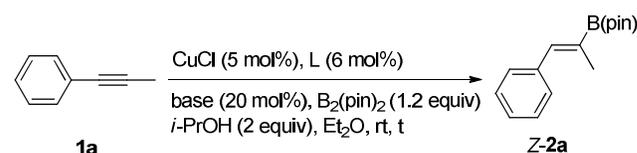
An efficient and practical copper-catalyzed highly regio- and stereoselective borylcupration of internal alkynes with bis(pinacolato)diboron using a catalytic amount of K<sub>2</sub>CO<sub>3</sub> as base producing *Z*-alkenylboron compounds has been demonstrated by applying the ligand effect: commercially available electron-rich tris(*p*-methoxyphenyl) phosphine ensures a smooth and efficient reaction. Functionalized alkynes, such as propargylic alcohols and derivatives as well as *N*-propargyl tosylamide, may also be used with an excellent selectivity.

Vinylboron compounds are highly important synthetic intermediates widely utilized in transition metal-catalyzed cross-coupling reactions and other synthetically useful transformations.<sup>1-4</sup> Transition metal-catalyzed addition reactions of boron-containing reagents to unsaturated carbon-carbon bonds have become an important strategy for the synthesis of these compounds.<sup>5-8</sup> Among which, recently developed catalytic borylcupration of internal alkynes with commercial bis(pinacolato)diboron followed by protonolysis is an efficient methodology for the stereoselective preparation of alkenyl boranes with a high regioselectivity.<sup>6</sup> However, moisture- and air-sensitive NaOt-Bu or KOt-Bu as base was used in these reactions. In this paper, we wish to report a CuCl-catalyzed practical protocol for such a purpose by using a catalytic amount of K<sub>2</sub>CO<sub>3</sub> as the base with the commercially available electron-rich P(C<sub>6</sub>H<sub>4</sub>OMe-*p*)<sub>3</sub> as the ligand bearing a nice substrate scope.

With the purpose of avoiding the use of NaOt-Bu, initially, we chose 20 mol% of the easy-to-handle and readily available K<sub>2</sub>CO<sub>3</sub> as base: with PPh<sub>3</sub> as the ligand, the borylcupration reaction at room temperature with **1a** afforded *Z*-**2a** in 57% yield with 38% recovery of **1a** within 23 h, indicating a very slow reaction (Table 1, entry 1)! Subsequently, we investigated the ligand effect: when more electron-donating ligand such as TFP was used, the yield had slightly increased with 31% recovery of **1a** (entry 2); further increasing electron-donating ability of the ligand by using P(*o*-toyl)<sub>3</sub> led to a satisfactory result with no recovery (entry 3); finally, we were glad to observe that P(C<sub>6</sub>H<sub>4</sub>OMe-*p*)<sub>3</sub> is even better (entry 4). Control experiment showed that this reaction did not proceed in absence of a base (entry 5); screening other readily available bases lead to the conclusion that K<sub>2</sub>CO<sub>3</sub> is the best

to promote this borylcupration reaction (entries 6-8). Thus, we chose 5 mol% CuCl, 6 mol% P(C<sub>6</sub>H<sub>4</sub>OMe-*p*)<sub>3</sub>, and 20 mol% K<sub>2</sub>CO<sub>3</sub> as the standard conditions for further study on this borylcupration reaction (entry 4).

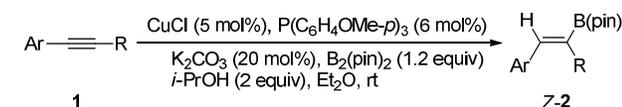
**Table 1** Optimization of reaction conditions for copper-catalyzed regio- and stereoselective borylcupration of internal alkynes<sup>a</sup>



Entry	Ligand	Base	Time (h)	NMR yield (%)
1	PPh <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	23	57 (38) <sup>b</sup>
2	TFP	K <sub>2</sub> CO <sub>3</sub>	23	61 (31) <sup>b</sup>
3	P( <i>o</i> -toyl) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	16	94
4	P(C <sub>6</sub> H <sub>4</sub> OMe- <i>p</i> ) <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	15	98
5	P(C <sub>6</sub> H <sub>4</sub> OMe- <i>p</i> ) <sub>3</sub>	-	43	0 (95) <sup>b</sup>
6	P(C <sub>6</sub> H <sub>4</sub> OMe- <i>p</i> ) <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	24	86 (11) <sup>b</sup>
7	P(C <sub>6</sub> H <sub>4</sub> OMe- <i>p</i> ) <sub>3</sub>	NaOAc	24	44 (43) <sup>b</sup>
8	P(C <sub>6</sub> H <sub>4</sub> OMe- <i>p</i> ) <sub>3</sub>	K <sub>3</sub> PO <sub>4</sub>	12	95

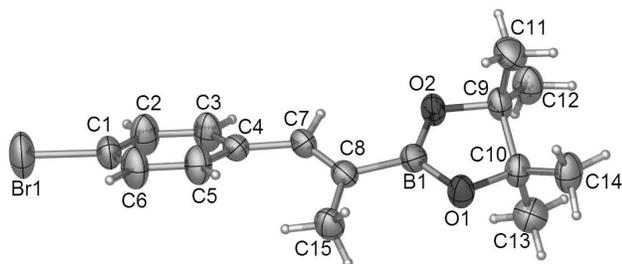
<sup>a</sup> Reaction conditions: 0.5 mmol of internal alkynes, 0.6 mmol of bis(pinacolato)diboron, 5 mol% CuCl, 6 mol% Ligand, 20 mol% base and 1.0 mmol of *i*-PrOH in 2 mL of Et<sub>2</sub>O at rt. <sup>b</sup> The number in the parenthesis is the recovery of starting material.

With the optimized conditions in hand, we next explored the scope of the reaction using various disubstituted alkynes. Firstly, with Ar = Ph, different alkyl group R may be applied to afford the corresponding products in good yields with B(pin) always adding to the carbon atom connected to the alkyl group with an exclusive *Z*-geometry (Table 2, entries 1-4); both electron-donating substituents, such as *p*-Me, *p*-Et, *p*-(*n*-Bu) or *p*-OMe, and electron-withdrawing groups such as *p*-F or *m*-Cl or *o*-Cl, may be accommodated in the aryl group (entries 5-12); heteroaromatic substituted internal alkynes such as 2-thienyl-1-propyne (**1m**) and 2-(1-hexynyl)pyridine (**1n**) were examined as well with the same excellent regio- and stereoselectivity (entries 13-14). The structure of *Z*-**2j** was confirmed by the X-ray single crystal diffraction study (Fig. 1).<sup>9</sup>

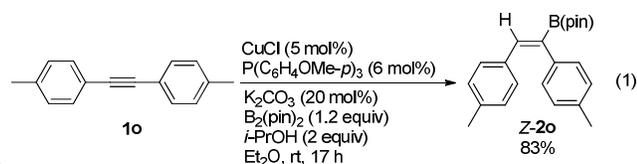
**Table 2** CuCl/K<sub>2</sub>CO<sub>3</sub>-catalyzed boron additions to various internal aryl alkynes<sup>a</sup>

Entry	Ar	R	Time (h)	Yield of Z-2 (%) <sup>b</sup>
1	Ph	CH <sub>3</sub> ( <b>1a</b> )	15	87 (Z-2a)
2	Ph	<i>n</i> -C <sub>3</sub> H <sub>7</sub> ( <b>1b</b> )	12	86 (Z-2b)
3	Ph	<i>n</i> -C <sub>4</sub> H <sub>9</sub> ( <b>1c</b> )	15	87 (Z-2c)
4	Ph	<i>n</i> -C <sub>6</sub> H <sub>13</sub> ( <b>1d</b> )	17	86 (Z-2d)
5	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> ( <b>1e</b> )	15	88 (Z-2e)
6	<i>p</i> -EtC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> ( <b>1f</b> )	21	83 (Z-2f)
7	<i>p</i> - <i>n</i> -BuC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> ( <b>1g</b> )	36	82 (Z-2g)
8	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> ( <b>1h</b> )	36	82 (Z-2h)
9	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> ( <b>1i</b> )	11	85 (Z-2i)
10	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> ( <b>1j</b> )	12	85 (Z-2j)
11	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> ( <b>1k</b> )	12	83 (Z-2k)
12	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub> ( <b>1l</b> )	11	78 (Z-2l)
13	2-thienyl	CH <sub>3</sub> ( <b>1m</b> )	12	83 (Z-2m)
14	2-pyridinyl	CH <sub>3</sub> ( <b>1n</b> )	10	75 (Z-2n)

<sup>a</sup> Reaction conditions: 0.5 mmol of internal alkynes, 0.6 mmol of bis(pinacolato)diboron, 5 mol% CuCl, 6 mol% P(C<sub>6</sub>H<sub>4</sub>OMe-*p*)<sub>3</sub>, 20 mol% K<sub>2</sub>CO<sub>3</sub> and 1.0 mmol of *i*-PrOH in 2 mL of Et<sub>2</sub>O at rt. <sup>b</sup> The yield is the isolated yield.

**Fig. 1** ORTEP representation of Z-2j.

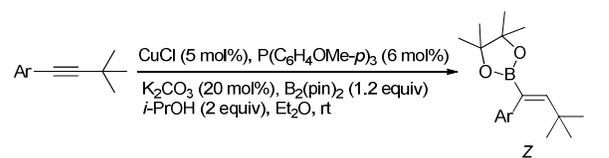
The reaction of 1,2-bis(*p*-tolyl)ethyne **1o** may also proceed smoothly to afford Z-2o in good yield (eq 1).



When sterically demanding *t*-butyl substituted alkynes **1p**–**1t** were subjected to the reaction conditions (Table 3), it is interesting to observe that the regioselectivity is absolutely inverted with B(pin) adding to the side of aryl-substituent affording the *syn*-addition products exclusively, which is just opposite to what was reported in the literature with an anti-selectivity.<sup>6b</sup> The results showed that the substrates bearing electron-withdrawing group can increase the reactivity (Table 3, entries 2 and 3); when electron-donating group such as *p*-Me was installed, it is necessary to increase the loading of

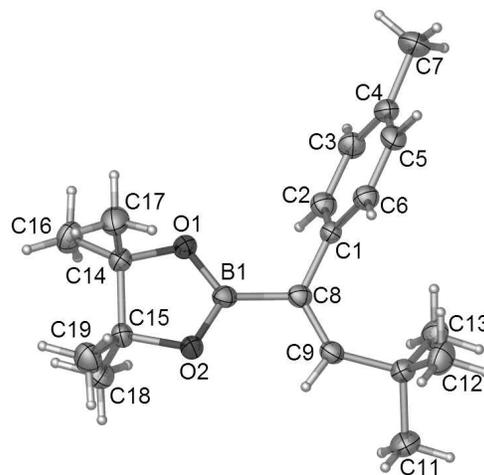
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K<sub>2</sub>CO<sub>3</sub> to complete the reaction (Table 3, entry 4). The structure of Z-2s was confirmed by NOE experiment and the X-ray single crystal diffraction study (Fig. 2),<sup>10</sup>

**Table 3** CuCl/K<sub>2</sub>CO<sub>3</sub>-catalyzed borylcupration of internal alkynes with a *t*-butyl group<sup>a</sup>

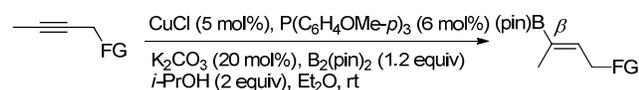
Entry	Ar	Time (h)	Yield of Z-2 (%) <sup>b</sup>
1	Ph ( <b>1p</b> )	36	76 (Z-2p)
2	<i>p</i> -AcC <sub>6</sub> H <sub>4</sub> ( <b>1q</b> )	24	74 (Z-2q)
3	<i>p</i> -FC <sub>6</sub> H <sub>4</sub> ( <b>1r</b> )	22	75 (Z-2r)
4 <sup>c</sup>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> ( <b>1s</b> )	22	92 (Z-2s)
5	1-naphthyl ( <b>1t</b> )	38	73 (Z-2t)

<sup>a</sup> Reaction conditions: 0.5 mmol of internal alkynes, 0.6 mmol of bis(pinacolato)diboron, 5 mol% CuCl, 6 mol% P(C<sub>6</sub>H<sub>4</sub>OMe-*p*)<sub>3</sub>, 20 mol% K<sub>2</sub>CO<sub>3</sub> and 1.0 mmol of *i*-PrOH in 2 mL of Et<sub>2</sub>O at rt. <sup>b</sup> Isolated yield. <sup>c</sup> The loading of K<sub>2</sub>CO<sub>3</sub> is 40 mol%.

**Fig. 2** ORTEP representation of Z-2s.

Functionalized internal alkynes were also investigated under these conditions,<sup>6d</sup> for example, when unprotected 2-butyl-1-ol was used as the substrate,  $\beta$ -borylated allylic alcohol Z-2u was afforded in a high yield with an excellent  $\beta$ -regioselectivity and Z-stereoselectivity (Table 4, entry 1); propargylic alcohol derivatives such as benzyl or acetyl-protected substrates proved also to be suitable (entries 2-3); same selectivity was also observed with *N*-Ts-protected propargylamine (entry 4). These stereodefined functionalized 1-alkenylboronates would not be easily available from the traditional hydroboration and are very useful intermediates for cross-coupling reaction and other transformations.<sup>1-4</sup>

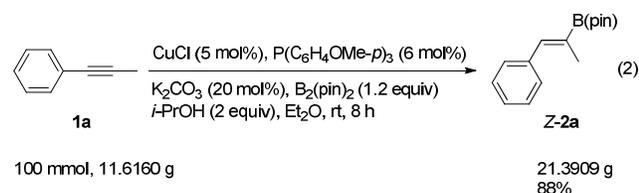
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**Table 4** CuCl/K<sub>2</sub>CO<sub>3</sub>-catalyzed borylcupration of propargylic derivatives<sup>a</sup>

Entry	FG	Time (h)	$\beta$ : $\alpha$ (ratio) <sup>b</sup>	Yield of Z-2 (%) <sup>c</sup>
1	OH ( <b>1u</b> ) <sup>d</sup>	4.5	> 99:1	85 (Z- <b>2u</b> )
2	OBn ( <b>1v</b> )	7	> 99:1	76 (Z- <b>2v</b> )
3	OAc ( <b>1w</b> )	6	> 99:1	72 (Z- <b>2w</b> )
4	NHTs ( <b>1x</b> )	4.5	> 99:1	87 (Z- <b>2x</b> )

<sup>a</sup> Reaction conditions: 0.5 mmol of substrate, 0.6 mmol of bis(pinacolato)diboron, 5 mol% CuCl, 6 mol% P(C<sub>6</sub>H<sub>4</sub>OMe-*p*)<sub>3</sub>, 20 mol% K<sub>2</sub>CO<sub>3</sub> and 1.0 mmol of *i*-PrOH in 2 mL of Et<sub>2</sub>O at rt. <sup>b</sup> Determined by <sup>1</sup>H NMR from the crude mixture. <sup>c</sup> Isolated yield. <sup>d</sup> Reaction carried out in the absence of MeOH.

To further show the practicality and efficiency of this catalytic system, the reaction of 1-phenyl-1-propyne **1a** has been conducted on a 20 g-scale, showing high efficiency and practicality (eq 2).



In summary, we have developed an efficient and practical protocol to synthesize stereodefined alkenylboronates from internal alkynes in good yields with excellent regio- and stereoselectivity. This convenient procedure applying the readily available ligand (P(C<sub>6</sub>H<sub>4</sub>OMe-*p*)<sub>3</sub>) and base (K<sub>2</sub>CO<sub>3</sub>) may show its potential in organic synthesis. The electron-rich P(C<sub>6</sub>H<sub>4</sub>OMe-*p*)<sub>3</sub> has increased the catalytic activity of CuCl greatly by pumping more electrons to the metal center. Further studies in this area is being carried out in this laboratory.

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## Notes and references

<sup>a</sup> Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University, 3663 North Zhongshan Lu, Shanghai 200062, P. R. China

<sup>b</sup> State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China

Fax: (+86)21-64167510 E-mail: masm@sioc.ac.cn

† Electronic Supplementary Information (ESI) available: [experimental procedures, NMR spectra. For ESI and other electronic format see DOI: 10.1039/b000000x/]

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Crystal data for compound Z-2j: C<sub>15</sub>H<sub>20</sub>BBrO<sub>2</sub>; MW = 323.03, Monoclinic space group P2(1)/c, final R indices [I > 2σ(I)], R1 = 0.0369, wR2 = 0.0892, R indices (all data) R1 = 0.0563, wR2 = 0.0990, a = 10.0397(8) Å, b = 7.5575(6) Å, c = 20.5113(15) Å, α = 90°, β = 97°, γ = 90°, V = 1544.3(2) Å<sup>3</sup>, T = 296(2) K, Z = 4, reflections collected/unique 14022/2704 (Rint = 0.0305), number of observations [ > 2σ(I) ] 1988, parameters: 172. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC.

Crystal data for compound Z-2s: C<sub>10</sub>H<sub>20</sub>BO<sub>2</sub>; MW = 300.23, Monoclinic space group P2(1)/c, final R indices [I > 2σ(I)], R1 = 0.0494, wR2 = 0.1186, R indices (all data) R1 = 0.0651, wR2 = 0.1302, a = 12.1475(11) Å, b = 6.0763(6) Å, c = 24.653(2) Å, α = 90°, β = 90°, γ = 90°, V = 1819.6(3) Å<sup>3</sup>, T = 173(2) K, Z = 4, reflections collected/unique 19852/3210 (Rint = 0.0441), number of observations [ > 2σ(I) ] 2549, parameters: 199. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC.