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COMMUNICATION

CuCl–K_2CO_3-catalyzed highly selective borylcupration of internal alkynes – ligand effect†

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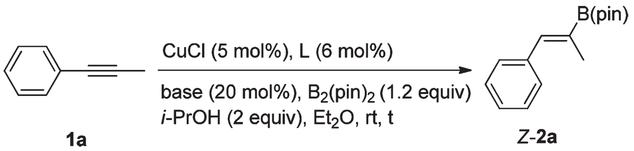
An efficient and practical copper-catalyzed highly regio- and stereoselective borylcupration of internal alkynes with bis(pinacolato)diboron using a catalytic amount of K_2CO_3 as base producing *Z*-alkenylboron compounds has been demonstrated by applying the ligand effect: commercially available electron-rich 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 excellent selectivity.

Vinylboron compounds are highly important synthetic intermediates widely utilized in transition metal-catalyzed cross-coupling reactions and other synthetically useful transformations.[1–4] 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.[5–8] 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 high regioselectivity.[6] However, moisture- and air-sensitive NaO*t*-Bu or KO*t*-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_2CO_3 as the base with the commercially available electron-rich $P(C_6H_4OMe\text{-}p)_3$ as the ligand bearing a nice substrate scope.

With the purpose of avoiding the use of NaO*t*-Bu, initially, we chose 20 mol% of the easy-to-handle and readily available K_2CO_3 as base: with PPh_3 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 a more electron-donating ligand such as TFP was used, the yield slightly increased with 31% recovery of **1a** (entry 2); further increasing the electron-donating ability of the ligand by using $P(o\text{-toyl})_3$ led to a satisfactory result with no recovery (entry 3); finally, we were glad to observe that $P(C_6H_4OMe\text{-}p)_3$ is even better (entry 4). A control experiment showed that this reaction did not proceed in absence of a base (entry 5); screening other readily available bases led to the conclusion that K_2CO_3 is the best to promote this borylcupration reaction (entries 6–8). Thus, we chose 5 mol% CuCl, 6 mol% $P(C_6H_4OMe\text{-}p)_3$, and 20 mol% K_2CO_3 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[a]



1a **Z-2a**

Entry	Ligand	Base	Time (h)	NMR yield (%)
1	PPh_3	K_2CO_3	23	57 (38)[b]
2	TFP	K_2CO_3	23	61 (31)[b]
3	$P(o\text{-toyl})_3$	K_2CO_3	16	94
4	$\mathbf{P(C_6H_4OMe\text{-}p)_3}$	$\mathbf{K_2CO_3}$	**15**	**98**
5	$P(C_6H_4OMe\text{-}p)_3$	—	43	0 (95)[b]
6	$P(C_6H_4OMe\text{-}p)_3$	Na_2CO_3	24	86 (11)[b]
7	$P(C_6H_4OMe\text{-}p)_3$	NaOAc	24	44 (43)[b]
8	$P(C_6H_4OMe\text{-}p)_3$	K_3PO_4	12	95

[a] Reaction conditions: 0.5 mmol of internal alkyne, 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_2O at r.t. [b] The number in the parentheses 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, a 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);

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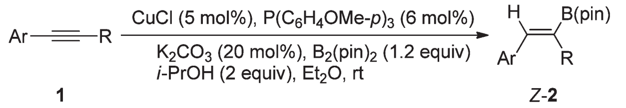
Table 2 CuCl/K_2CO_3-catalyzed boron additions to various internal aryl alkynes[a]



Entry	Ar	R	Time (h)	Yield of *Z*-**2**[b] (%)
1	Ph	CH_3 (**1a**)	15	87 (*Z*-**2a**)
2	Ph	*n*-C_3H_7 (**1b**)	12	86 (*Z*-**2b**)
3	Ph	*n*-C_4H_9 (**1c**)	15	87 (*Z*-**2c**)
4	Ph	*n*-C_6H_{13} (**1d**)	17	86 (*Z*-**2d**)
5	*p*-MeC_6H_4	CH_3 (**1e**)	15	88 (*Z*-**2e**)
6	*p*-EtC_6H_4	CH_3 (**1f**)	21	83 (*Z*-**2f**)
7	*p*-*n*-BuC_6H_4	CH_3 (**1g**)	36	82 (*Z*-**2g**)
8	*p*-$MeOC_6H_4$	CH_3 (**1h**)	36	82 (*Z*-**2h**)
9	*p*-FC_6H_4	CH_3 (**1i**)	11	85 (*Z*-**2i**)
10	*p*-BrC_6H_4	CH_3 (**1j**)	12	85 (*Z*-**2j**)
11	*m*-ClC_6H_4	CH_3 (**1k**)	12	83 (*Z*-**2k**)
12	*o*-ClC_6H_4	CH_3 (**1l**)	11	78 (*Z*-**2l**)
13	2-Thienyl	CH_3 (**1m**)	12	83 (*Z*-**2m**)
14	2-Pyridinyl	CH_3 (**1n**)	10	75 (*Z*-**2n**)

[a] Reaction conditions: 0.5 mmol of internal alkyne, 0.6 mmol of bis(pinacolato)diboron, 5 mol% CuCl, 6 mol% $P(C_6H_4OMe\text{-}p)_3$, 20 mol% K_2CO_3 and 1.0 mmol of i-PrOH in 2 mL of Et_2O at r.t. [b] The yield is the isolated yield.

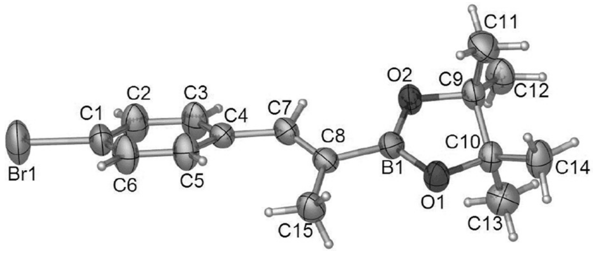
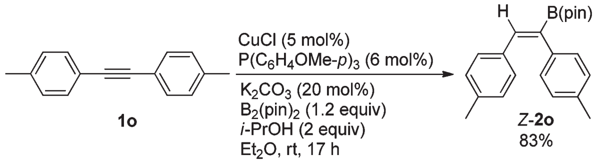


Fig. 1 ORTEP representation of *Z*-**2j**.

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).[9]

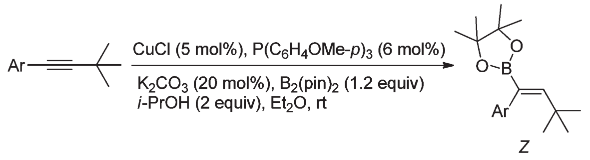
The reaction of 1,2-bis(*p*-tolyl)ethyne **1o** also proceeded smoothly to afford *Z*-**2o** in good yield (eqn (1)).



(1)

When sterically demanding *tert*-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.*[6b] 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 K_2CO_3 to complete the reaction (Table 3, entry 4). The structure of *Z*-**2s** was further confirmed by NOE experiment and the X-ray single crystal diffraction study (Fig. 2).[10]

Table 3 CuCl/K_2CO_3-catalyzed borylcupration of internal alkynes with a *t*-butyl group[a]



Entry	Ar	Time (h)	Yield of *Z*-**2**[b] (%)
1	Ph (**1p**)	36	76 (*Z*-**2p**)
2	*p*-AcC_6H_4 (**1q**)	24	74 (*Z*-**2q**)
3	*p*-FC_6H_4 (**1r**)	22	75 (*Z*-**2r**)
4[c]	*p*-MeC_6H_4 (**1s**)	22	92 (*Z*-**2s**)
5	1-naphthyl (**1t**)	38	73 (*Z*-**2t**)

[a] Reaction conditions: 0.5 mmol of internal alkynes, 0.6 mmol of bis(pinacolato)diboron, 5 mol% CuCl, 6 mol% $P(C_6H_4OMe\text{-}p)_3$, 20 mol% K_2CO_3 and 1.0 mmol of i-PrOH in 2 mL of Et_2O at r.t. [b] Isolated yield. [c] The loading of K_2CO_3 is 40 mol%.

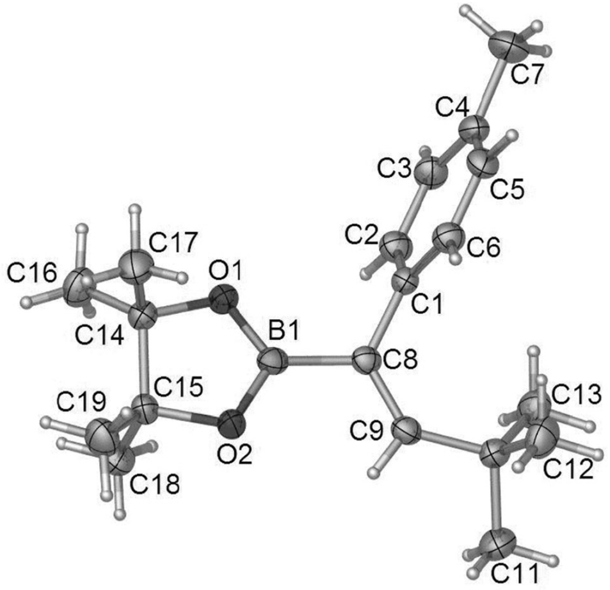
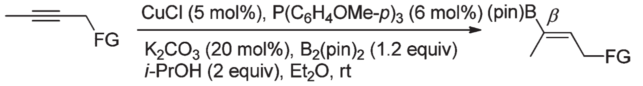


Fig. 2 ORTEP representation of *Z*-**2s**.

Functionalized internal alkynes were also investigated under these conditions,[6d] for example, when unprotected 2-butyn-1-ol was used as the substrate, β-borylated allylic alcohol *Z*-**2u** was afforded in a high yield with an excellent β-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); the same selectivity was also observed with *N*-Ts-protected propargylamine (entry 4). These stereo-defined functionalized 1-alkenylboronates would not be easily available from the traditional hydroboration and are very useful

Table 4 CuCl/K_2CO_3-catalyzed borylcupration of propargylic derivatives[a]

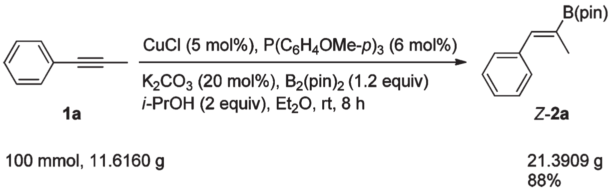


Entry	FG	Time (h)	β : α (ratio)[b]	Yield of *Z*-**2**[c] (%)
1	OH (**1u**)[d]	4.5	>99 : 1	85 (*Z*-**2u**)
2	OBn (**1v**)	7	>99 : 1	76 (*Z*-**2v**)
3	OAc (**1w**)	6	>99 : 1	72 (*Z*-**2w**)
4	NHTs (**1x**)	4.5	>99 : 1	87 (*Z*-**2x**)

[a] Reaction conditions: 0.5 mmol of substrate, 0.6 mmol of bis-(pinacolato)diboron, 5 mol% CuCl, 6 mol% P(C_6H_4OMe-*p*)$_3$, 20 mol% K_2CO_3 and 1.0 mmol of i-PrOH in 2 mL of Et_2O at r.t. [b] Determined by ^{1}H NMR from the crude mixture. [c] Isolated yield. [d] Reaction carried out in the absence of MeOH.

intermediates for cross-coupling reactions and other transformations.[1–4]

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 (eqn (2)).



(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_6H_4OMe-*p*)$_3$) and base (K_2CO_3) may show its potential in organic synthesis. The electron-rich P(C_6H_4OMe-*p*)$_3$ 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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9 Crystal data for compound *Z*-**2j**: $C_{15}H_{20}BBrO_2$; MW = 323.03, Monoclinic space group $P2(1)/c$, final R indices [$I > 2\sigma(I)$], $R_1 = 0.0369$, w$R_2 = 0.0892$, R indices (all data) $R_1 = 0.0563$, w$R_2 = 0.0990$, $a = 10.0397(8)$ Å, $b = 7.5575(6)$ Å, $c = 20.5113(15)$ Å, $\alpha = 90°$, $\beta = 97°$, $\gamma = 90°$, $V = 1544.3(2)$ Å^3, $T = 296(2)$ K, $Z = 4$, reflections collected/unique 14 022/2704 ($R_{\text{int}} = 0.0305$), number of observations [$>2\sigma(I)$] 1988, parameters: 172. CCDC 886806.

10 Crystal data for compound *Z*-**2s**: $C_{19}H_{29}BO_2$; MW = 300.23, Monoclinic space group $P2(1)/c$, final R indices [$I > 2\sigma(I)$], $R_1 = 0.0494$, w$R_2 = 0.1186$, R indices (all data) $R_1 = 0.0651$, w$R_2 = 0.1302$, $a = 12.1475(11)$ Å, $b = 6.0763(6)$ Å, $c = 24.653(2)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 1819.6(3)$ Å^3, $T = 173(2)$ K, $Z = 4$, reflections collected/unique 19 852/3210 ($R_{\text{int}} = 0.0441$), number of observations [$>2\sigma(I)$] 2549, parameters: 199. CCDC 886807.