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Alkylboronic Esters from Copper-Catalyzed Borylation of Primary and Secondary Alkyl Halides and Pseudohalides**

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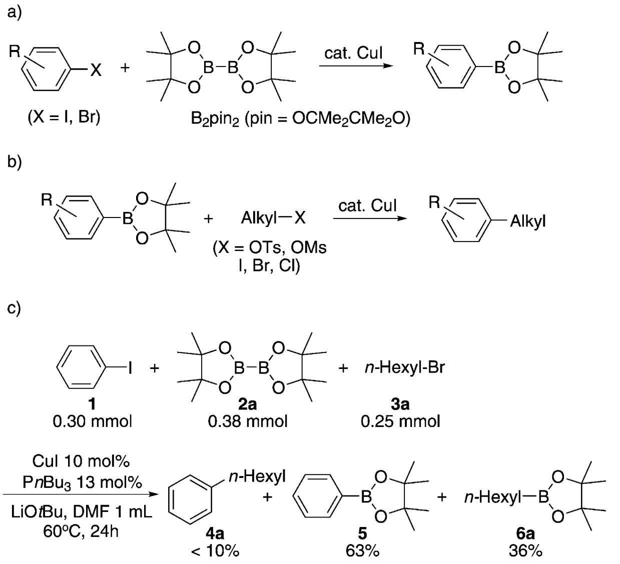
Dedicated to Christian Bruneau on the occasion of his 60th birthday

Alkylboronic acid derivatives are interesting compounds in medicinal chemistry (e.g., bortezomib).[1] They are more often used as synthetic intermediates for transition-metal-catalyzed cross-coupling of C(sp^3) organometallics with electrophiles.[2] Compared to other C(sp^3) organometallics such as alkylmagnesium, alkylzinc, and alkylindium reagents, alkylboronic acid derivatives can be readily purified prior to utilization and have superior shelf stability.[3] Their cross-coupling reactions also show excellent compatibility with a wide range of functional groups. Classical methods for the synthesis of alkylboronic acid derivatives involve the reaction of alkyllithium or alkylmagnesium reagents with suitable boron compounds. However, these methods suffer from poor functional-group tolerance.[4] Thus, recent attention has been given to the development of transition-metal-catalyzed methods for the preparation of alkylboronic acid derivatives. Some important examples include Rh- and Ir-catalyzed hydroboration of alkenes,[5] Ir-, Rh-, Ru-, and Re-catalyzed C–H activation/borylation of alkanes,[6] and Pt-, Pd-, Ni-, Rh-, and Cu-catalyzed β-boration of unsaturated carbonyl compounds.[7] Herein, we describe a new and more general method for the synthesis of unactivated primary and secondary alkylboronic esters[8] through copper-catalyzed borylation of the corresponding alkyl halides and pseudohalides, thus providing a practical means for the preparation of alkylboronic esters with diverse skeletons and functional groups. Moreover, this method expands the concept and scope of copper-catalyzed cross-coupling reactions[9] in a fundamental sense.

In 2009, Marder et al. reported that CuI in the presence of phosphines catalyzes the borylation of aryl halides with diboron reagents to generate arylboronic esters (Scheme 1 a).[10] More recently, Liu et al. found that under similar reaction conditions, CuI can catalyze the cross-coupling of unactivated alkyl electrophiles with arylboronic esters (Scheme 1 b).[11] On the basis of these findings, we explored the reaction of an aryl halide (**1**), a diboron reagent (**2a**), and an alkyl electrophile (**3a**) in the presence of the CuI/PnBu$_3$ catalyst system. We proposed that this would lead initially to the formation of the arylboronic ester **5** which would then react in situ with **3a** to afford the aryl–alkyl cross-coupling product **4a**. Although **1**, **2a**, and **3a** were all consumed rapidly in the reaction and **5** was generated as anticipated, we were not able to obtain **4a** in good yield. In an independent experiment we



Scheme 1. a) Marder's aryl borylation reaction. b) Liu's aryl–alkyl coupling reaction. c) Initial experiment attempting to combine the two methods into a one-pot borylation/cross-coupling reaction. DMF = N,N'-dimethylformamide, Ms = methanesulfonyl, Ts = 4-toluenesulfonyl.

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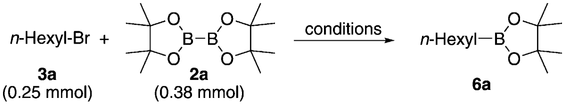
confirmed that **5** reacts with **3a** to produce **4a** under the same reaction conditions. All of these observations indicated that **3a** must be consumed by an alternative pathway that is faster than its reaction with **5**. A thorough analysis of the reaction mixture then revealed that the alkylboronic ester **6a** was could be isolated in 36% yield. Given the low mass balance of borylated products, a second experiment using 3,5-dimethyliodobenzene in the presence of the less volatile electrophile, 3-phenylpropyltosylate, was undertaken. This produced the corresponding alkylboronate in 85% yield (GC/MS) accompanied by smaller amounts of the aryl boronate (63%), thus suggesting that the lower yields in the initial experiment resulted from losses during isolation.[12]

We hypothesized that **6a** was produced by an unprecedented copper-catalyzed cross-coupling reaction between the alkyl halide and diboron reagent. To test this assumption, we treated **3a** with **2a** in the presence of the copper catalyst (Table 1). Gratifyingly, the desired alkylboronic ester **6a** was obtained in 84% yield at 25°C in 18 hours (entry 1). To improve the yield, different bases were tested (entries 1–6) with LiOMe proving to be optimal giving a yield of 91% (entry 6). Next, we optimized the ligand (entries 7–9), copper salt (entries 10–12), and solvent (entries 13 and 14). Although **6a** was successfully obtained under all reaction conditions, the highest yield was obtained with CuI/PPh_3 in DMF. In addition to B_2pin_2 (**2a**), other diboron reagents such as bis(neopentyl glycolato)diboron (B_2neop_2) function equally effectively (entry 15). The necessity for copper in these reactions was confirmed by the observation that without adding the catalyst the reaction does not occur (entry 21). Moreover, the possible involvement of palladium or nickel contamination in the catalyst was eliminated by the observation that palladium and nickel salts provide only a trace amount of **6a** under the optimized reaction conditions (entries 19 and 20). Finally, the reaction is not significantly sensitive to moisture, because the addition of 4 equivalents of water only reduces the yield to 77% (entry 22).

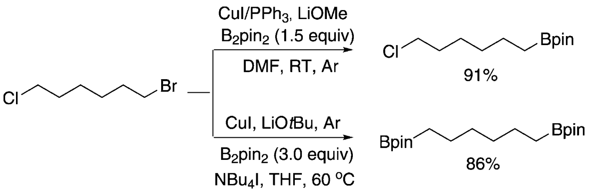
Table 1: Borylation of *n*-hexyl bromide under various conditions.



Entry	Catalyst (10 mol%)	Ligand (13 mol%)	Base	Sol.	*T* [°C]	Yield [%][a]
1	CuI	PPh_3	LiO*t*Bu	DMF	25	84
2	CuI	PPh_3	KO*t*Bu	DMF	25	28
3	CuI	PPh_3	NaO*t*Bu	DMF	25	24
4	CuI	PPh_3	LiHMDS	DMF	25	13
5	CuI	PPh_3	Li_2CO_3	DMF	25	trace
6	CuI	PPh_3	LiOMe	DMF	25	91 (89)[i]
7	CuI	P*n*Bu_3	LiOMe	DMF	25	78
8	CuI	P*t*Bu_3	LiOMe	DMF	25	70
9	CuI	1,10-phenanthroline	LiOMe	DMF	25	65
10	CuBr	PPh_3	LiOMe	DMF	25	72
11	CuCl	PPh_3	LiOMe	DMF	25	56
12	$Cu(OTf)_2$	PPh_3	LiOMe	DMF	25	60
13	CuI	PPh_3	LiOMe	DMSO	25	57
14	CuI	PPh_3	LiOMe	THF	25	35
15[b]	CuI	PPh_3	LiOMe	DMF	25	87 (83)[i]
16[c]	CuI	–	LiO*t*Bu	THF	25	90
17[d]	CuI	–	LiO*t*Bu	THF	60	86
18[e]	CuI	–	LiO*t*Bu	MeCN	60	76
19[f]	$Pd(OAc)_2$	PPh_3	LiOMe	DMF	25	trace
20[g]	NiI_2	PPh_3	LiOMe	DMF	25	trace
21	–	PPh_3	LiOMe	DMF	25	trace
22[h]	CuI	PPh_3	LiOMe	DMF	25	77

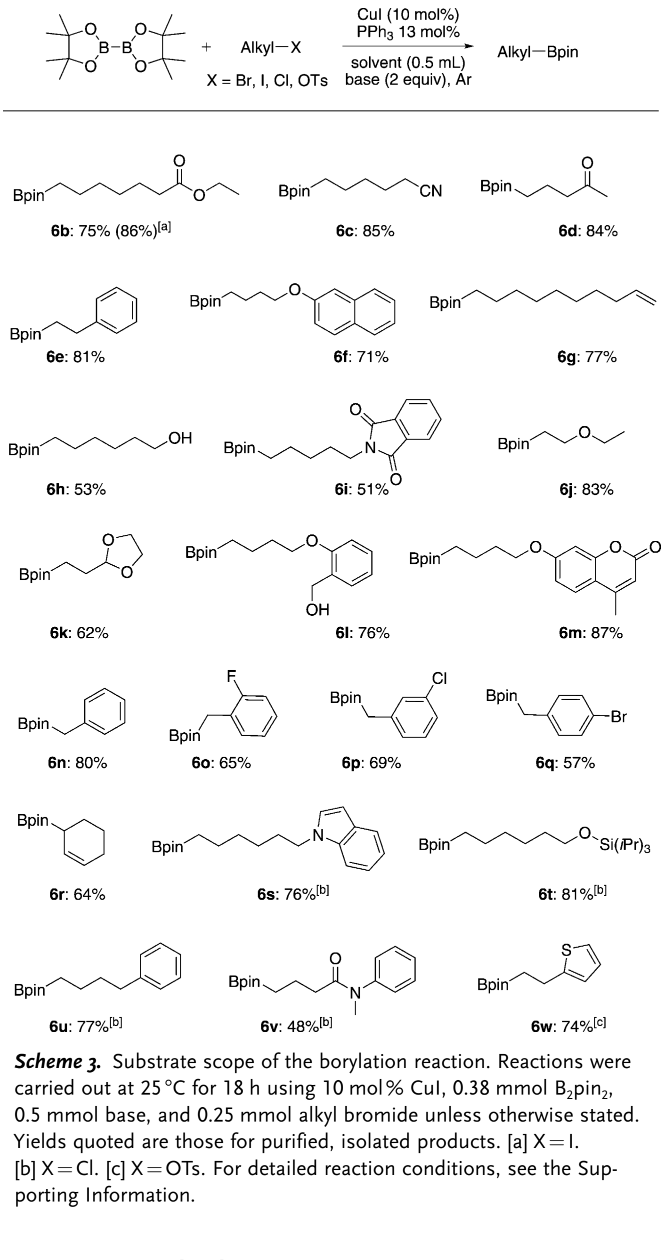
[a] Yields as determined by GC analysis after 18 h (average of two runs). [b] Bis(neopentyl glycolato)diboron was used in the coupling. [c] *n*-Hexyl iodide was used. [d] *n*-Hexyl chloride was used and 1 equiv of $N(Bu)_4I$ was added. [e] *n*-Hexyl tosylate was used and 1 equiv of $N(Bu)_4I$ was added. [f] 2 mol% of Pd catalyst was added. [g] 2 mol% of anhydrous NiI_2 used. Similar negative results were obtained with $NiCl_2·6H_2O$ and $NiBr_2·3H_2O$. [h] 18 μL (1 mmol) of water was added. [i] Yield of isolated product. DMSO = dimethylsulfoxide, HMDS = hexamethyldisilazide, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

n-Hexyl iodide, chloride, and tosylate are also viable substrates with optimal yields of 90%, 86%, and 76%, respectively (Table 1, entries 16–18). However, higher temperatures (60°C) and the addition of $(Bu_4N)I$ are required for reaction of the chloride and tosylate. Presumably, these proceed via the iodide and, interestingly, for this substrate the PPh_3 ligand is not needed; however, the optimal base changes from LiOMe to LiO*t*Bu. Overall, the reactivity decreases in the order: iodide > bromide > chloride ≈ tosylate (entries 16–18). This observation is consistent with previous copper-catalyzed couplings of Grignard[9c] or organoboron reagents[11] with alkyl electrophiles. This reactivity difference can be exploited to allow the selective substitution of the bromine atom of 6-chlorohexyl bromide at room temperature (Scheme 2). However, on increasing the reaction temperature to 60°C, and in the presence of Bu_4NI, both bromide and chloride react efficiently.

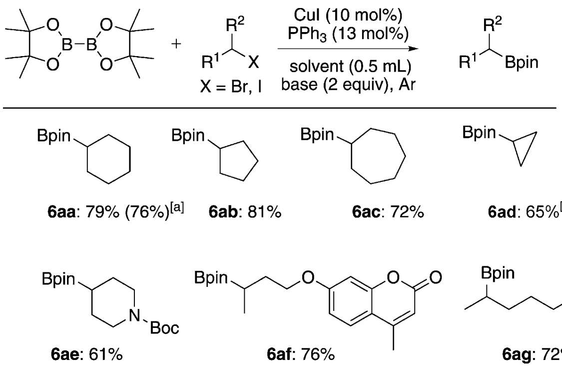


Scheme 2. Site-selective borylation.

With optimized reaction conditions identified, we examined the scope of the new borylation reaction (Scheme 3). Many synthetically important functional groups including ester (**6b**), cyano (**6c**), ketone (**6d**), ether (**6f**, **6j**), olefin (**6g**), amide (**6i**, **6v**), ketal (**6k**), and silyl ether (**6t**) groups are well tolerated with yields of the desired, isolated alkylboronates ranging from about 50% to 80%. Furthermore, arene- and heterocycle-containing compounds (**6m**, **6s**, **6w**) are good substrates for the borylation process. Significantly, even the presence of a free alcohol group (**6h**, **6l**) does not interfere with the reaction. This feature compares favorably with early alkylboronate syntheses starting from alkyllithium or alkylmagnesium reagents, in which nearly all of the alkyl groups are only hydrocarbons.[4] More reactive electrophiles such as



Scheme 3. Substrate scope of the borylation reaction. Reactions were carried out at 25 °C for 18 h using 10 mol% CuI, 0.38 mmol B$_2$pin$_2$, 0.5 mmol base, and 0.25 mmol alkyl bromide unless otherwise stated. Yields quoted are those for purified, isolated products. [a] X = I. [b] X = Cl. [c] X = OTs. For detailed reaction conditions, see the Supporting Information.



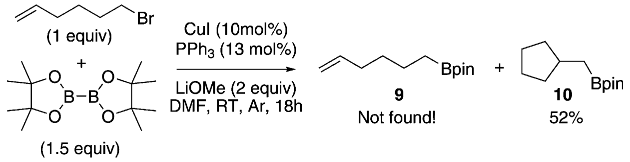
Scheme 4. The borylation reaction of secondary alkyl halides. Reactions were carried out at 37 °C for 24 h using 10 mol% CuI, 0.38 mmol B$_2$pin$_2$, 0.5 mmol base, and 0.25 mmol alkyl bromide. Yields quoted are those for purified, isolated products. [a] X = I, solvent = THF, base = LiO*t*Bu, *T* = 25 °C. PPh$_3$ was not added. [b] 2 equiv of B$_2$pin$_2$ was used. [c] Polymer-supported PPh$_3$ was used. Boc = *tert*-butoxycarbonyl.

benzyl (**6n**–**6q**)[8h,10] and allyl bromides (**6r**) can be readily borylated by the present method. With the former, small amounts of the corresponding bibenzyl can be observed, although its formation can be minimized by using two equivalents of the diboron reagent. Finally, we were able to confirm that aryl halides are in fact less reactive than alkyl halides (e.g., **6q**). This allows haloalkyls bearing bromo- and chloro-substituted arene rings to be used successfully, thus providing the potential for subsequent modifications through additional cross-coupling reactions at the halogenated positions.

In addition to primary alkyl electrophiles, secondary alkyl halides can also be borylated (Scheme 4). For cyclohexyl bromide, the yield reaches about 60% at 25 °C in 24 hours. Increasing the reaction temperature to 37 °C enables the desired secondary alkylboronate **6aa** to be produced in a 79% yield (isolated). Other cyclic and acyclic secondary bromides can be smoothly borylated (**6ab**–**6ag**). As with primary halides a similar reactivity profile is observed; cyclohexyl iodide is readily converted into **6aa** (yield = 76%), whilst cyclohexyl chloride only affords moderate yields (30%) under the current reaction conditions. It is important to note that in most previous copper-catalyzed cross-couplings of organometallic reagents with aliphatic electrophiles, secondary alkyl halides have seldom been used successfully.[11,13] This new borylation reaction therefore provides an interesting option for copper-catalyzed cross-coupling reactions of secondary alkyl electrophiles.

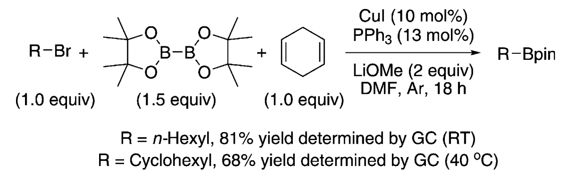
Commercial polystyrene-bound PPh$_3$ can be employed in the reaction with no loss in efficiency. For example, borylation of 2-bromoheptane led to a crude reaction mixture which required two chromatographic runs to separate the heptyl-2-Bpin product from PPh$_3$. With polymer-supported PPh$_3$, clean formation of the product and no separation problems were encountered (**6ag**; Scheme 4).

The mechanism of this transformation is not immediately obvious. In analogy to previous studies on the copper-catalyzed cross-coupling of aliphatic electrophiles,[9c,11,13] the mechanism of the present borylation reaction might involve an S$_N$2-type substitution with a Cu^I/boryl complex[7b,14] generated through transmetalation[10] between Cu^I and B$_2$pin$_2$. Alternatively, the alkyl halide might interact with the Cu^I/boryl complex via an oxidatively added transition state (OATS) similar to that proposed for the copper-catalyzed borylation of aryl halides.[10] Although additional experimental and theoretical studies are underway to obtain a full understanding of the mechanism, a few preliminary experiments provided interesting results. For example, borylation of *exo*-2-bromo norbornane (**7**) proceeded with overall retention of configuration, as shown by single-crystal X-ray diffraction studies of the ethanolamine stabilized *exo*-2-boron-substituted product **8** (see the Supporting Information). In addition, it was surprising to find that the borylation of 6-bromohex-1-ene does not afford **9** as anticipated (Scheme 5). Instead, the cyclopentylmethyl boronate **10** is produced. This product, along with the formation of bibenzyl by-products from benzyl halides, suggested the possiblity of a



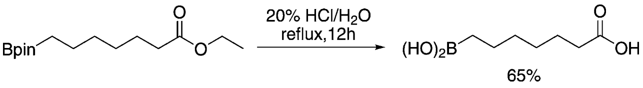
Scheme 5. Borylation of 6-bromohex-1-ene.

radical mechanism similar to that proposed for nickel-catalyzed Suzuki–Miyaura reactions of alkyl halides.[15] However, radical scavenger experiments show that the borylation yields are not sensitive to the presence of cyclohexa-1,4-diene, militating against the possibility of a radical mechanism (Scheme 6).

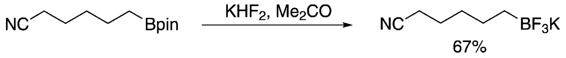


Scheme 6. Radical scavenger experiments.

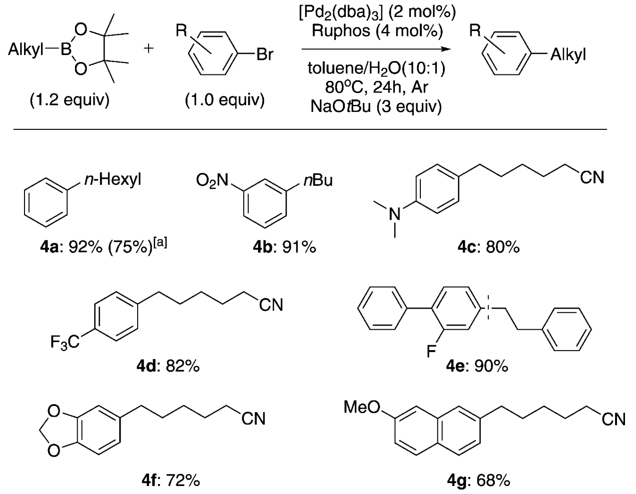
Having established an efficient and highly versatile entry to alkyl boronic esters it was of interest to explore their utility. Treatment with aqueous hydrochloric acid affords the corresponding alkylboronic acids[16] (Scheme 7), valuable alternatives to the corresponding esters when used either as pharmaceutical agents or synthetic intermediates. Treatment with KHF_2 converts the alkyl boronic esters to the corresponding organotrifluoroborates (Scheme 8).[17] Applications of alkylboronic esters in Suzuki–Miyaura coupling reactions have been limited.[18] Excitingly, using the recently developed Ruphos ligand,[19] we have achieved Suzuki–Miyaura coupling of alkylboronic esters with both aryl bromides and chlorides (Scheme 9).



Scheme 7. Conversion from boronic ester into boronic acid.



Scheme 8. Conversion from boronic ester into trifluoroborate.



Scheme 9. Suzuki–Miyaura coupling of alkylboronic esters. Reactions were carried out at 80°C for 24 h on a 0.25 mmol scale. Yields quoted are those for purified, isolated products. [a] X = Cl, 110°C for 24 h. dba = dibenzylideneacetone, Ruphos = 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl.

In conclusion, we have developed an unprecedented copper-catalyzed cross-coupling reaction of unactivated alkyl halides and pseudohalides with diboron reagents. This reaction can be used to prepare primary and secondary alkylboronic esters with diverse structures and functional groups, many of which would be difficult to access by other means. The reaction is efficient, practically simple, and gives easy isolation of the products which can be further enhanced through the use of polymer-supported ligands. We also report a mild and practical protocol for the Suzuki–Miyaura coupling of alkylboronic esters with both aryl bromides and chlorides. Further optimization, applications, and mechanistic studies of these new methods are in progress and will be reported in due course.

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Keywords: alkanes · boronates · copper · cross-coupling · synthetic methods

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