One-Step Synthesis of Acylboron Compounds via Cu-Catalyzed Carbonylative Borylation of Alkyl Halides

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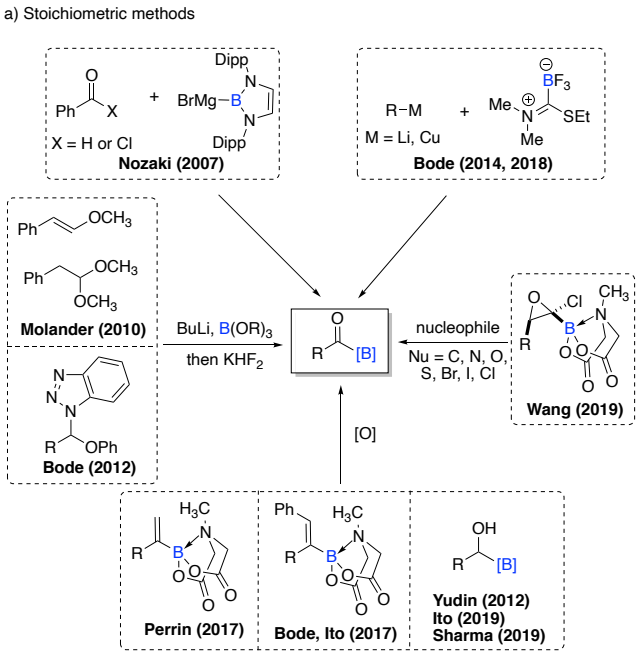
Supporting Information Placeholder

ABSTRACT: A Cu-catalyzed carbonylative borylation of unactivated alkyl halides has been developed, enabling efficient synthesis of aliphatic potassium acyltrifluoroborates (KATs) in high yields by treating the *in-situ* formed tetracoordinated acylboron intermediates with aqueous KHF_2. A variety of functional groups are tolerated under the mild reaction conditions, and primary, secondary and tertiary alkyl halides are all applicable. In addition, this method also provides facile access to *N*-methyliminodiacetyl (MIDA) acylboronates as well as α-methylated potassium acyltrifluoroborates in a one-pot manner. Mechanistic studies indicate a radical atom transfer carbonylation (ATC) mechanism to form acyl halide intermediates that are subsequently borylated by (NHC)CuBpin.

Organoboron compounds are important building blocks and widely used in various organic transformations.[1] Therefore, the development of efficient protocols for the synthesis of organoborons has been extensively investigated during the past decades. However, as a rare class of organoborons, acylboron compounds have received much less attentions.[2] While they were proposed as reactive intermediates in several transformations long ago,[3] it was not until 2007 that Nozaki and co-workers first reported the isolation and characterization of amino-stabilized acylborons by reacting boryl nucleophiles with benzoyl chloride or benzaldehyde.[4] The recent observation of unique acylboron reactivity, especially the fast and chemoselective amide-bond-forming reaction between potassium acyl trifluorobortes and amines derivatives (KAT ligation) in functionalization of proteins and peptides,[5] has sparked growing interest in their synthesis, and several elegant synthetic routes have been reported (Scheme 1a). For example, Molander and Bode reported the lithiation of enol ethers or *N,O*-acetals followed by trapping with electrophilic boryl reagents to form KATs.[6] Bode designed an electrophilic zwitterionic boronate reagent to react with aryl lithium or alkyl cuprate reagents to afford KATs.[7] In addition, the oxidation of the alkenyl boronates or α-hydroxy alkylboronates to approach MIDA-protected acylboronates or KATs has been developed by groups of Yudin,[8] Perrin,[9] Ito[10] and Sharma[11]. More recently, Wang reported the nucleophilic ring opening of α-chloroepoxyboronates to synthesize α-functionalized acylborons.[12] Although these methods provide diverse approaches for synthesis of acylborons, they generally suffer from multi-step preparation of the precursors or limited substrate scope due to the use of stoichiometric reactive organometallic reagents and oxidants.

On the other hand, transition metal-catalyzed borylation has been recognized as one of the most efficient methods for synthesis of organoborons. Surprisingly, catalytic methods for synthesis of acylborons are very rare, with only two reported examples that both use Pd catalysts (Scheme 1b). In 2015, Campos and Aldridge reported a boron version of the Negishi C-C coupling of acyl chlorides with a bis(boryl)zinc reagent.[13] Recently, a Stille-type coupling of aryl or vinyl halides with a stannyl iminium trifluoborate was developed by the Bode group.[14] These methods are conducted under mild conditions, thus allowing broader functional group tolerance. However, as both of these boron reagents are not readily available, the lengthy preparation of the boryl anion sources still hampers their wide utility. Therefore, the development of a direct method for synthesis of acylborons from simple precursors via transition metal catalysis employing a commercially available boron reagents is highly desirable.

Scheme 1. Synthesis of Acylborons

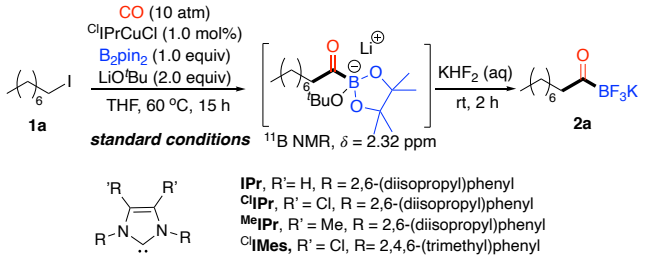


Metal-catalyzed carbonylation represents an attractive approach to synthesize carbonyl compounds, as it uses CO as a cheap C1 unit to introduce the carbonyl group into simple precursors. Although the carbonylation of organoboranes has been explored to generate the acylborons, the isolation of acylborons remains a challenge due to their notorious instability and susceptibility to rearrangement.[3,15] Our group has recently developed a series of Cu-catalyzed carbonylative coupling reactions of unactivated alkyl halides[16] based on the NHC-Cu catalysis (NHC = *N*-heterocyclic carbene).[17] In these reactions, acyl radicals were generated from alkyl halides and then coupled with various organocopper nucleophiles to afford corresponding carbonyl compounds. We envisioned that this strategy could be amendable for the synthesis of acylborons by trapping the acyl radical using a nucleophilic borylcopper species generated from the copper catalysts and a commercially available diboron reagent (Scheme 1c). However, there were several challenges to overcome: (1) the generated tricoordinate acylborons are usually unstable, thus requiring efficient transformation into a tetracoordinated form; (2) a second Cu-Bpin species could attack the carbonyl group of the acylboronate as is known for corresponding ketone and aldehyde groups;[18] (3) the competitive direct borylation of alkyl halides, which has been reported to proceed either under copper catalysis[19] or metal-free conditions[20] in the absence of CO, has to be suppressed. Herein, we present our development of a direct, catalytic synthesis of aliphatic acylborons from readily available alkyl halides through a Cu-catalyzed carbonylative borylation process. The features of our method include: (1) it represents the shortest synthetic route for preparation of acylborons using a commercially available diboron reagent (B_2pin_2) as the boron source; (2) the reaction is conducted under mild reaction conditions with a base metal catalyst; (3) a novel tetracoordinated acylboron species is proposed as the key intermediate that gives rise to potassium acyltrifluoroborate (KAT) salts as well as *N*-methyliminodiacetyl (MIDA) acylboronates in convenient ways.

We began our work by studying the reaction of 1-iodooctane (**1a**) with pinacol diboron (B_2pin_2) under CO atmosphere. Being aware that the expected tricoordinated acylboron is not stable, we initially attempted to convert it into the corresponding KAT by working up the product mixture with aqueous KHF_2. After intensive investigation,[21] we found that the desired potassium acyltrifluoroborate **2a** could be selectively generated in 73% yield when ^{Cl}IPrCuCl was used as catalyst in the presence of LiO^{t}Bu as the base and THF as solvent (Table 1, entry 1). Without adding KHF_2, ^{11}B NMR spectroscopy of the crude mixture from the carbonylative coupling showed a new peak at 2.32 ppm, which is in the chemical shift range of tetracoordinated acylboron species.[22] Although isolation and purification of this intermediate was unsuccessful, we speculated that the formed tricoordinated acylboron was further coordinated by one equivalent of LiO^{t}Bu to form a more stable tetracoordinated acylboron compound. A control experiment showed the product was obtained in only 8% yield without the copper catalyst, clearly demonstrating that copper played a vital role in accelerating the reaction (Table 1, entry 2). The structure of the NHC ligand had a significant effect on the reaction: while IPr and ^{Me}IPr gave slightly lower yield (Table 1, entry 3-4), the less sterically bulky ^{Cl}IMes dramatically decreased the yield (Table 1, entry 5). The use of a less reactive electrophile, 1-bromooctane, provided the product in only 25% yield (Table 1, entry 6). Only trace amount of product was observed when more Lewis-acidic bis(catecholato)diboron (B_2cat_2) was employed as the diboron reagent (Table 1, entry 7). Low yield of product was obtained when other bases such as NaO^{t}Bu, LiOMe, or LiO^{i}Pr were used (Table 1, entry 8-10). We also found that the amount of the base is crucial for the success of this

reaction: either increasing or decreasing the amount of LiO^{t}Bu caused negative effect on the reaction (Table 1, entry 12-13). Changing the solvent to DME gave the product in lower yield, and trace product was obtained with 1,4-dioxane as solvent (Table 1, entry 14-15). Performing the reaction at room temperature or under 6 atm CO pressure afforded the product in 63% and 60% yield, respectively (Table 1, 16-17). It is noteworthy that although we typically performed reactions using 1.0 mol% copper catalyst, lowering the catalyst loading to 0.1 mol% gave a comparable result (Table 1, entry 18).

Table 1. Optimization Studies[a]

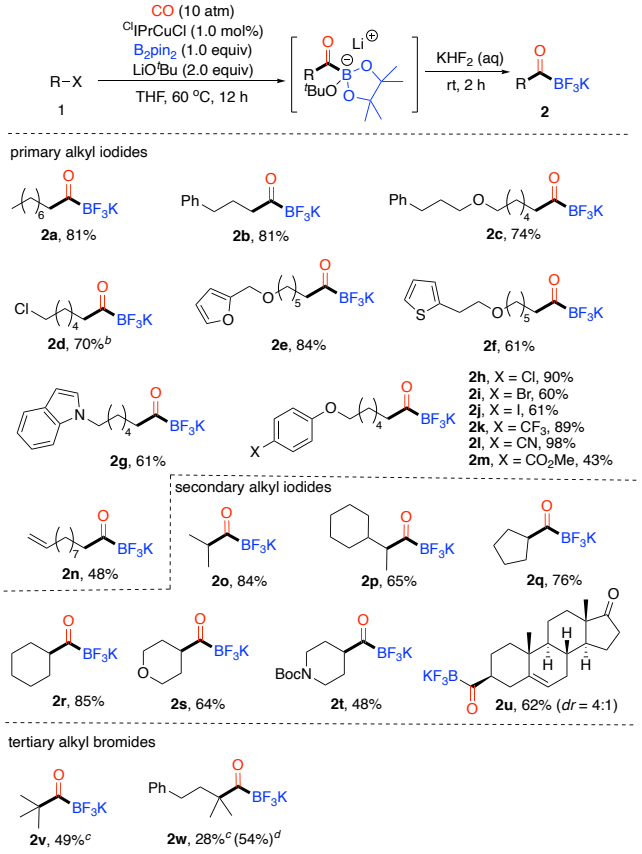


entry	variations from optimal conditions	Conv. of **1a** (%)[b]	**2a** (%)[b]
1	None	100	73
2	No ^{Cl}IPrCuCl	10	8
3	IPrCuCl instead of ^{Cl}IPrCuCl	100	67
4	^{Me}IPrCuCl instead of ^{Cl}IPrCuCl	100	66
5	^{Cl}IMesCuCl instead of ^{Cl}IPrCuCl	100	30
6	Octyl-Br instead of Octyl-I	53	25
7	B_2cat_2 instead of B_2pin_2	46	6
8	NaO^{t}Bu instead of LiO^{t}Bu	100	34
9	LiOMe instead of LiO^{t}Bu	43	36
10	LiO^{i}Pr instead of LiO^{t}Bu	46	32
11	1.5 equiv B_2pin_2 instead of 1.0	100	48
12	1.0 equiv LiO^{t}Bu instead of 2.0	84	24
13	3.0 equiv LiO^{t}Bu instead of 2.0	100	53
14	DME instead of THF	100	36
15	1,4-dioxane instead of THF	100	<5
16	r.t instead of 60 °C	82	63
17	6 atm CO instead of 10 atm	100	60
18	0.1 mol% ^{Cl}IPrCuCl instead of 10 mol%	100	70

[a] Reaction performed on 0.1 mmol scale. [b] Conversion and yield were determined by ^{1}H NMR integration against an internal standard.

With the optimal conditions in hand, we next investigated the substrate scope in the presence of 1 mol% catalyst. The mild reaction conditions allow the use of a variety of alkyl iodides containing different remote functional groups, including ether (**2c**), chloroalkyl (**2d**) and terminal alkene (**2n**). Heterocycles such as furan (**2e**), thiophene (**2f**) and indolyl (**2g**) were also compatible. The chloro, bromo, iodo, trifluoromethyl, and cyano groups on a remote phenyl ring (**2h-2l**) also survived during the reaction. However, lower yield was observed with a ester-substituted substrate (**2m**). Under the same reaction conditions, the alkyl electrophile scope could be extended from primary alkyl iodides to secondary alkyl iodides. Both acylic and cyclic secondary alkyl iodides gave the desired products in good yield. Increasing the steric hindrance of the secondary alkyl iodide (**2o-2r**) had no effect on the yield. Ether (**2s**) and *N*-Boc (**2t**) functional groups within the cyclic electrophile were both tolerated. In addition, the mild reaction conditions provide the opportunity for late-stage carbonylative borylation of an estrone derivative, providing acylboron **2u** diastereoselectively. Moreover, we were delighted to find this method was also applicable to synthesis of more challenging tertiary acylborons (**2v-2w**) when I^{t}BuCuCl was used as catalyst and the reaction was performed at room temperature. Tertiary alkyl bromides were found to give products in higher yield than the corresponding iodides.

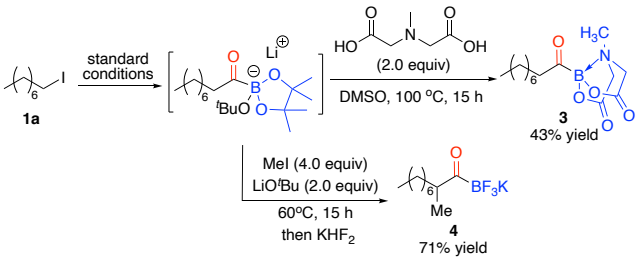
Table 2. Substrate Scope of Alkyl Halides[a]



[a]The reaction was conducted on 0.5 mmol scale. All yields are isolated yields unless otherwise noted. [b]**2r** was formed in 12% yield. [c]The reaction was performed at room temperature and I^{t}BuCuCl was used as catalyst. [d]^{1}H NMR yield.

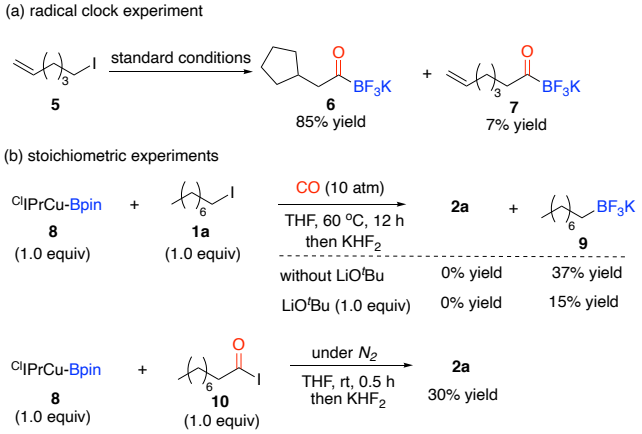
The formation of the novel tetracoordinated acylboron intermediates motivated us to further investigate their utility. First, we attempted the conversion of B(pin) into B(MIDA) by heating the reaction mixture from **1a** with *N*-methyliminodiacetic acid in DMSO at 100 °C for 15 h. Encouragingly, the acyl MIDA boronate **3** was obtained in 43% yield. During the synthesis of **2d**, we observed that minor cyclization product **2r** was also generated under the reaction conditions. This inspired us to further explore the intermolecular alkylation of the acylborons in one-pot. Brief trials revealed that the α-methylated product **4** could be obtained in good yield when 4.0 equivalent of MeI and additional 2.0 equivalent of LiO^{t}Bu were added to the reaction mixture. In contrast, subjecting the potassium acyltrifluoroborate **2a** to the same reaction condition gave no product at all, probably due to B-F bond solvolysis under the basic conditions.[23] The current method is likely to find potential application in synthesis of other α-fuctionalized acylborons compounds.

Scheme 2. Synthetic Utility



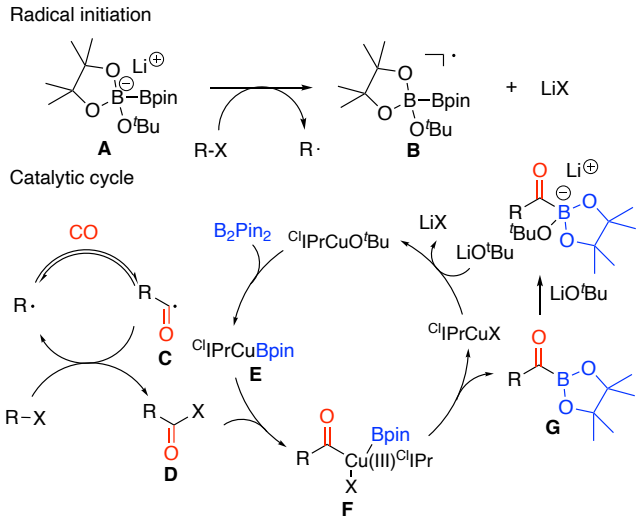
Next, several control experiments were conducted to explore the mechanism. First, a radical clock experiment was performed with iodoalkane **5**, and the cyclization product **6** was isolated in 85% yield (Scheme 3a). This result revealed that the carbonylative borylation proceeds via alkyl radical intermediate, which is consistent with our previous work.[16] We also prepared borylcopper species ^{Cl}IPrCu-Bpin (**8**)[24] and performed stoichiometric reactions of **8** with primary alkyl iodide (**1a**) without or with LiO^{t}Bu under CO atmosphere (Scheme 3b). Both of the reactions afforded no product, and significant amount of alkyl borane **9** was observed as byproduct. We next conducted the stoichiometric coupling of ^{Cl}IPrCu-Bpin (**8**) with nonanoyl iodide **10** under N_2, and **2a** was obtained in 30% yield (Scheme 3b). These results exclude single electron transfer process between borylcopper and alkyl halide and supports the intermediacy of an acyl halide generated through an atom transfer carbonylation (ATC) pathway.[25]

Scheme 3. Mechanistic Studies



Based on these results and our previous work on carbonylation of alkyl halides,[16] we propose the following catalytic mechanism (Scheme 4). First, LiO^{t}Bu reacts with B_2pin_2 to produce the tetra-alkoxy diboron compound **A**.[22] This activated B(sp^2)-B(sp^3) complex is able to reduce the alkyl halide through a single-electron transfer (SET) event, affording alkyl radical intermediate and initiating a radical chain.[20] The alkyl radical then undergoes carbonylation with CO to give an acyl radical **B**, which reacts with alkyl halide to afford acyl halide **C** and propagate the radical chain. Then, the oxidative addition of acyl halide **C** to the borylcopper **E** forms the copper(III) complex **F**. Finally, reductive elimination affords the tricoordinated acylboron **F** and regenerates the copper(I) catalyst. The acylboron **F** is further combined with one LiO^{t}Bu to form the more stable tetra-coordinated boron complex. As we could obtain a small amount of the product in the absence of copper catalyst (table 1, entry 2), we assumed acyl radical **C** also reacts with the boron radical **B** but in a relatively slow rate compared to its reaction with borylcopper **E**. An alternative to oxidative addition complex **F** would be addition of complex **E** to the carbonyl group of acyl halide **D** to provide acylboron species **G** directly, as has recently been modeled computationally for a hydrocarbonylative coupling reaction.[26]

Scheme 4. Proposed Catalytic Cycle



In summary, we have developed an efficient method to synthesize acylborons from unactivated alkyl halides and a commercially available boron reagent (B_2pin_2) via a Cu-catalyzed carbonylative borylation. A variety of aliphatic potassium acyltrifluoroborates (KATs) which previously required multi-step synthesis can now be approached in one step by sequentially adding aqueous KHF_2 to the reaction mixture. Primary, secondary, and tertiary alkyl halides are all suitable substrates. In addition, this method also provides facile access to *N*-methyliminodiacetyl (MIDA) acylboronate and can be potentially applied for synthesis of α-functionalized KATs. Mechanistic studies support a radical atom transfer carbonylation (ATC) mechanism to form acyl halide as a key intermediate that undergoes Cu-mediated borylation.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures & spectral data (PDF)

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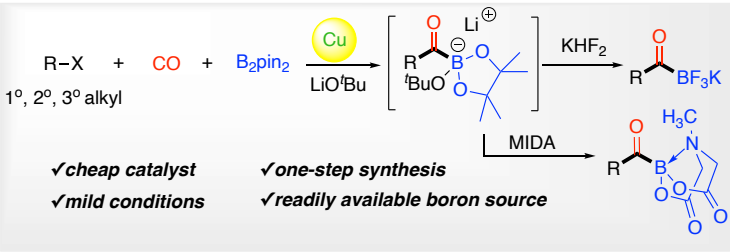
TOC graphic:


R–X + CO + B2pin2
1°, 2°, 3° alkyl
Cu
LiO^tBu
Li
KHF2
BF3K
MIDA
H3C
N
✓cheap catalyst
✓mild conditions
✓one-step synthesis
✓readily available boron source