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Synthesis of Amidomethyltrifluoroborates and their Use in Cross-Coupling Reactions

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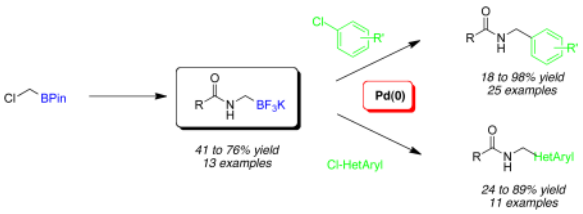
Abstract



Amidomethyltrifluoroborates were successfully synthesized in a one-pot fashion and used in cross-coupling reactions with a wide variety of aryl and heteroaryl chlorides.

Amidomethylarenes are commonly found in a variety of biologically active compounds (Figure 1).1 Several strategies have been developed to obtain amidomethyl-containing products such as nucleophilic displacement,2 reductive *N*-alkylation,3 and more commonly amidation.4 These methods follow a consonant reactivity pattern based on the nucleophilicity of the nitrogen. Recently, cross-coupling reactions using *N*,*N*-dialkylaminomethyltrifluoroborates were described to access the analogous aminomethyl moiety.5 This approach provides access to amines using a C-C bond connection strategy complementary to existing C-N bond-forming approaches.

The *N*,*N*-dialkylaminomethyltrifluoroborates used in previous coupling efforts were obtained by a direct S_N2 displacement of the halides of potassium halomethyltrifluoroborates. Unfortunately, amidomethyltrifluoroborates cannot be accessed in this manner, and thus it was necessary to develop a different approach to the trifluoroborate starting materials. The strategy chosen was based on previous work pioneered by Matteson,6 in which substituted boronate esters were obtained from halomethylboronate esters via intramolecular nucleophilic displacement and one carbon homologation of in situ generated $LiCHX_2$ or $LiCH_2X$ species (X = Cl, Br, I).7 The “ate” complex resulting from initial attack of the nucleophile at the boron atom is followed by α-transfer to the neighboring carbon to form the elaborated boronate ester (Figure 2).8

Amidomethylboronate esters have been synthesized following this strategy,9 but only a few examples were reported, and poor to moderate yields were observed for the formation of α-unsubstituted products in a process that required two to three steps.9f,10 Furthermore, apart

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Supporting Information **Available** Experimental procedures, spectral characterization, and copies of ^{1}H, ^{13}C, ^{19}F, and ^{11}B NMR spectra for all compounds. This material is available free of charge via the Internet at http/pubs.acs.org.

from their biological evaluations, amidomethylborons have not been used with success as Suzuki–Miyaura cross-coupling partners.11 We disclose herein the formation of amidomethyltrifluoroborates synthesized in an original one-pot process from halomethylboronate esters. Additionally we report their palladium-catalyzed coupling with various aryl- and heteroaryl chlorides, which constitutes the first successful example of amidomethylation by a cross-coupling protocol. 12,13

The current study began with the preparation of amidomethyltrifluoroborates **4a-m** using an adaptation of the Matteson procedure (Scheme 1).9

Thus 2-(chloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **1** in the presence of potassium hexamethyldisilazide gave the expected disilylated aminoboronate ester **2a**, which was deprotected in situ by the addition of methanol. The revealed free amine **2b** was then reacted with various acyl chlorides to form the corresponding amides. The crude boronate esters **3** obtained in this one-pot fashion were directly treated with a saturated solution of KHF_2 to afford **4a-m** in good to excellent overall yields (Table 1).

This method provided access to aromatic substituted carbamides **4a-f** that contained electron withdrawing and electron donating groups (Table 1, entries 1 and 2). Saturated carbocycles (entries 3-5) as well as alkyl side chains (entries 6-8) could also be incorporated.

With these compounds in hand, the cross-coupling conditions were first optimized with **4a** and *p*-chloroanisole as the electrophilic partner (Table 2, entry 6). The most effective coupling conditions were found to be 2.5 mol % of $Pd(OAc)_2$, 5 mol % of XPhos and 3 equiv of Cs_2CO_3 in a 10:1 cyclopentyl methyl ether (CPME) and water mixture at 85 °C for 6 h with a stoichiometric amount of potassium trifluoroborate. On a larger scale reaction (1 g of product), the catalyst loading could be lowered to 1 mol % with similar results (entry 6). The generality of the method was then investigated by using structurally and electronically diverse aryl chlorides. Throughout the series of reaction partners studied, the expected coupling products were obtained in good to excellent yields, and a variety of functional groups including nitriles, ketones, aldehydes, esters, and alcohols were tolerated under these conditions. Sterically hindered electrophiles (Table 2, entries 2, 3, 7, 10) were found to couple in excellent yields, although an increase in the catalyst loading or in the reaction time was required.

To investigate the method further, the array of electrophiles was expanded to heteroaryl chlorides (Table 3). Chloropyridines bearing the halogen in the 3 or 4 position and other heteroaryl chlorides such as quinoline, thiophene or furan derivatives were successfully coupled with **4a** under our previously described conditions in moderate to excellent yields. Unfortunately, despite attempting to increase the reaction temperature and increase or decrease the catalyst loading, 2-chloropyridine (**6d**) and 2-chloro-4-methoxypyrimidine (**6g**) gave rise to a significant amount of homocoupled product (entries 3, 6).

We next examined the efficiency of the reaction with different amidomethyltrifluoroborates (Table 4). Both cyclic and acyclic carbamides gave the expected coupling product in good to excellent yields except for the biphenyl- and the pentafluorophenyl substrates (**7d** and **7f**) (Table 4, entries 1 and 2), where degradation products were mostly recovered.

Finally, the electrophile compatibility was examined (Table 5). Surprisingly, the aryl iodide gave low yields, indicating that the oxidative addition is not the limiting step of the catalytic cycle under these conditions. Aryl triflates and -bromides coupled cleanly in high yields. Unfortunately, tosylate derivatives exhibited no reactivity.

In summary, an efficient one-pot synthetic protocol successfully delivered α-unsubstituted amidomethyltrifluoroborates. These trifluoroborates proved to be suitable reagents to introduce the amidomethyl functional group into substrates via a unique bond construction. Various electron-rich and electron-poor aryl and heteroaryl electrophiles were used, demonstrating the generality of this method.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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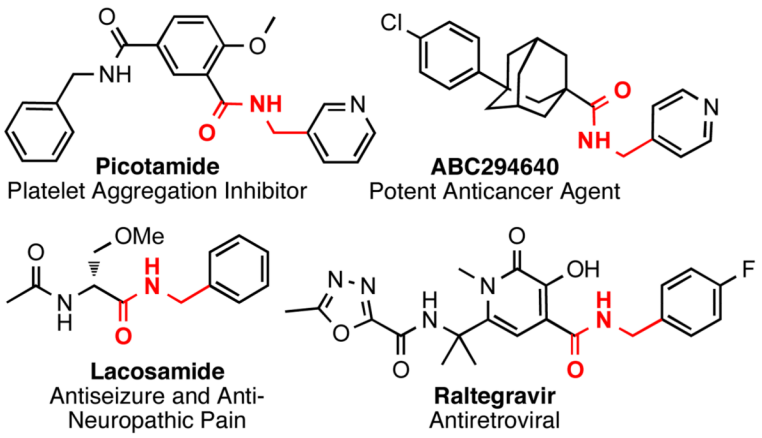
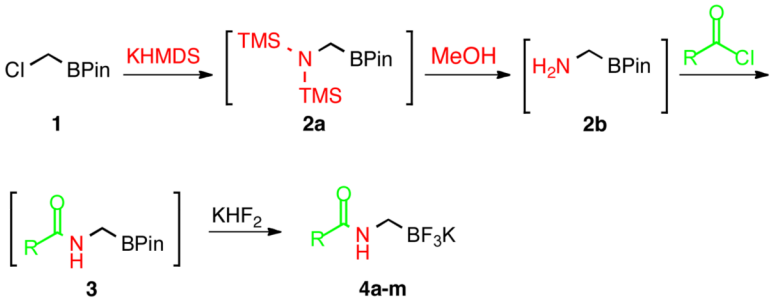


Figure 1.
Biologically Active Molecules Containing the Amidomethyl Moiety

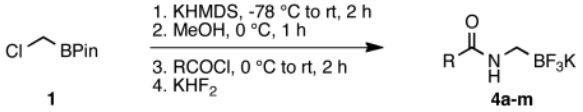
Figure 2.
Reaction mechanism of the one-carbon homologation of boronate esters and the intramolecular nucleophilic displacement of α-halo boronate esters with various nucleophiles.

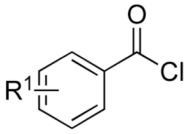
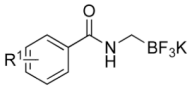
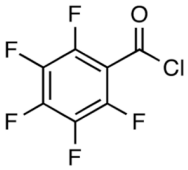
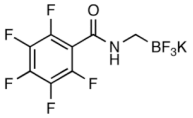
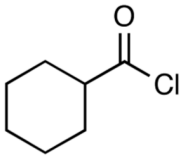
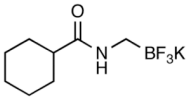
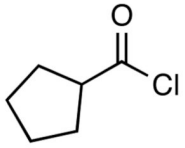
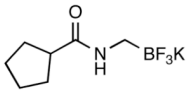
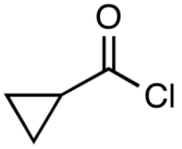
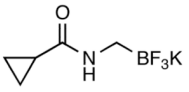
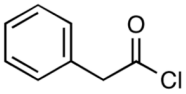
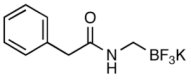
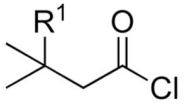
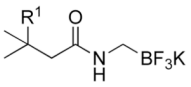


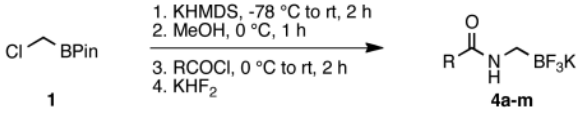
Scheme 1.
One-pot process to synthesize **4a-m**

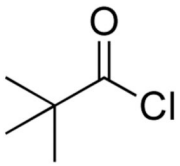
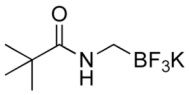
Table 1

Preparation of Amidomethyltrifluoroborates



entry	RCOCl	product		% isolated yield
1			**4a:** R^1 = H	67
			4b: R^1 = *p*-F	76
			4c: R^1 = *p*-CF_3	71
			4d: R^1 = *p*-Ph	77
			4e: R^1 = *m*-OMe	69[a]
2			**4f**	62
3			**4g**	59[a]
4			**4h**	60[a]
5			**4i**	56
6			**4j**	63
7			**4k:** R^1 = H	41
			4l: R^1 = Me	41

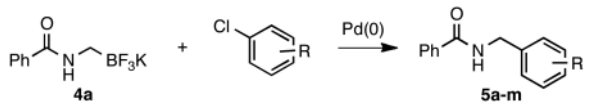


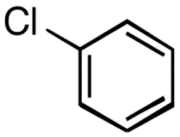
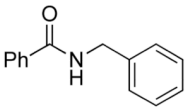
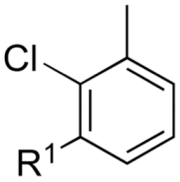
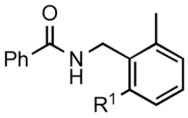
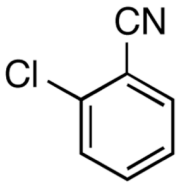
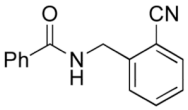
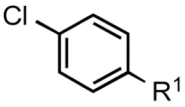
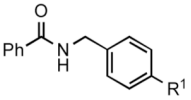
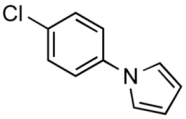
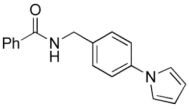
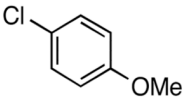
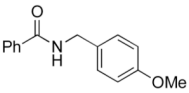
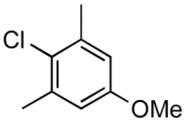
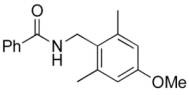
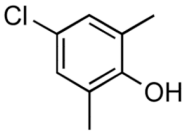
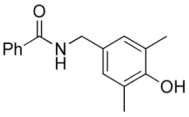
entry	RCOCl	product		% isolated yield
8			**4m**	54

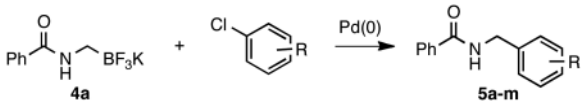
[a]Reaction for 12 h at rt in the presence of RCOCl

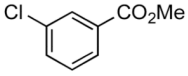
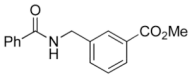
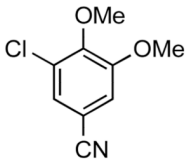
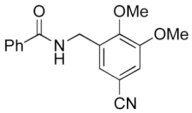
Table 2

Cross-Coupling of **4a** with Diverse Aryl Chlorides



entry	chloride	product		% isolated yield
1			**5a**	87
2			**5b:** R^1 = H **5c:** R^1 = Me	83 (91)[a] 88[b]
3			**5d**	65[a]
4			**5e:** R^1 = CN **5f:** R^1 = CHO **5g:** R^1 = Ac	87 88 88
5			**5h**	98
6			**5i**	95 (91)[c]
7			**5j**	74
8			**5k**	87



entry	chloride	product		% isolated yield
9			**5l**	89
10			**5m**	76

All reactions were carried out using 0.3 mmol of **4a** and aryl chloride, 2.5 mol % $Pd(OAc)_2$, 5 mol % XPhos, 0.9 mmol of Cs_2CO_3, 10:1 CPME/H_2O (0.09 M), 85 °C, 6 h.

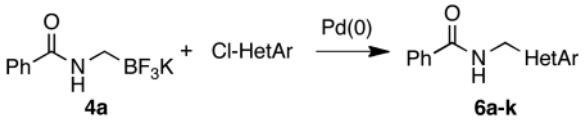
[a] Used 5 mol % $Pd(OAc)_2$, 10 mol % XPhos.

[b] Heated reaction for 14 h.

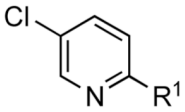
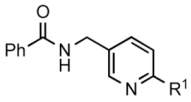
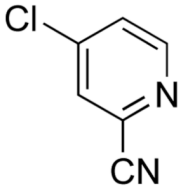
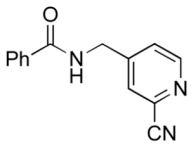
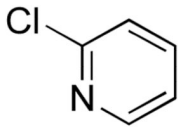
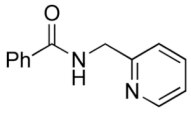
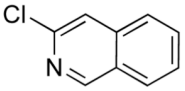
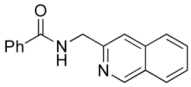
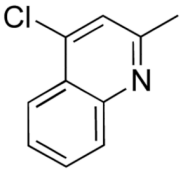
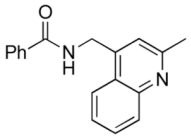
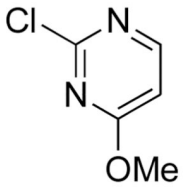
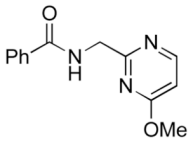
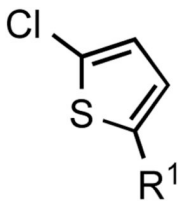
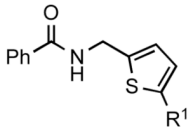
[c] Reaction performed on 4.1 mmol scale using 1 mol % $Pd(OAc)_2$ and 2 mol % XPhos, 24 h at 85 °C.

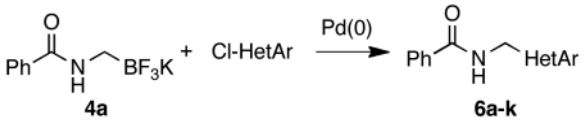
Table 3

Cross-Coupling of **4a** with Various Heteroaryl Chlorides

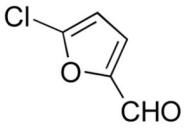
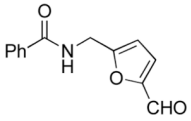


4a **6a-k**

entry	chloride	product		% isolated yield
1			**6a:** R^1 = H	79
			6b: R^1 = OMe	89
2			**6c**	25 (49)[a]
3			**6d**	24 (33)[a]
4			**6e**	58[b] (66)[a]
5			**6f**	86
6			**6g**	25
7			**6h:** R^1 = H	86
			6i: R^1 = Ac	78
			6j: R^1 = CHO	82



4a 6a-k

entry	chloride	product		% isolated yield
8			**6k**	89

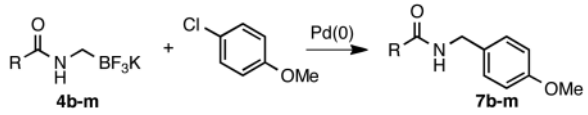
All reactions were carried out using 0.3 mmol of **4a** and heteroaryl chloride, 2.5 mol % $Pd(OAc)_2$, 5 mol % XPhos, 0.9 mmol of Cs_2CO_3, 10:1 CPME/H_2O (0.09 M), 85 °C, 6 h.

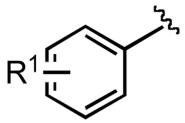
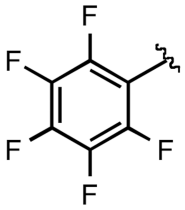
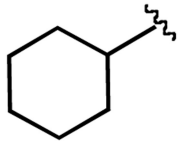
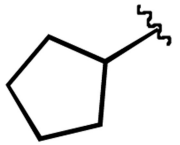
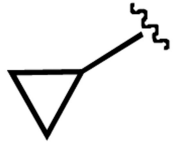
[a] Heated for 24 h with 5 mol % $Pd(OAc)_2$, 10 mol % XPhos.

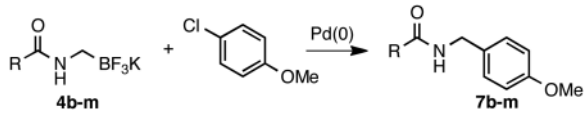
[b] Heated reaction for 14 h.

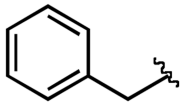
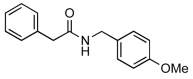
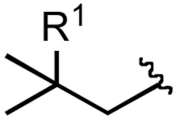
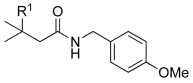
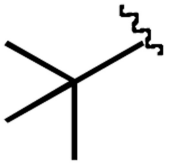
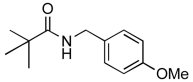
Table 4

Cross-Coupling with Various Potassium Amidomethyltrifluoroborates



entry	R	product		% isolated yield
1		**4b**	**7b:** R^1 = *p*-F	89
		4c	**7c:** R^1 = *p*-CF_3	88
		4d	**7d:** R^1 = *p*-Ph	18
		4e	**7e:** R^1 = *m*-OMe	81
2		**4f**	**7f**	32
3		**4g**	**7g**	77
4		**4h**	**7h**	90
5		**4i**	**7i**	52 (83)[a]



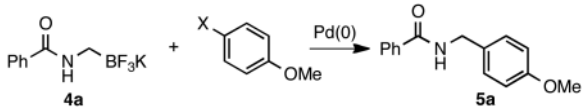
entry	R	product		% isolated yield
6		**4j** 	**7j**	94
7		**4k** 	**7k:** R^1 = H	83
		4l	**7l:** R^1 = Me	93
8		**4m** 	**7m**	81

All reactions were carried out using 0.3 mmol of **1a** and aryl chloride, 2.5 mol % $Pd(OAc)_2$, 5 mol % XPhos, 0.9 mmol of Cs_2CO_3, 10:1 CPME/H_2O (0.09 M), 85 °C, 6 h.

[a]Used 5 mol % $Pd(OAc)_2$, 10 mol % XPhos.

Table 5

Electrophile Compatibility



entry	aryl electrophile	% isolated yield
1	I	31
2	Br	85
3	OTf	93
4	OTs	traces

All reactions were carried out using 0.3 mmol of **1a** and aryl chloride, 2.5 mol % $Pd(OAc)_2$, 5 mol %XPhos, 0.9 mmol of Cs_2CO_3, 10:1 CPME/H_2O (0.09 M), 85 °C, 6 h.