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Synthesis and Suzuki–Miyaura Cross-Coupling Reactions of Potassium Boc-Protected Aminomethyltrifluoroborate with Aryl and Hetaryl Halides

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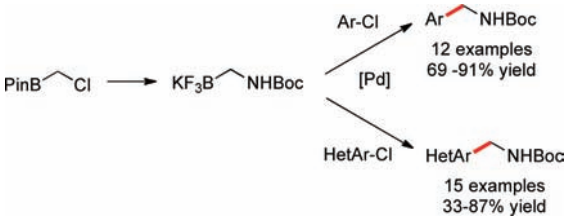
ABSTRACT



Potassium Boc-protected aminomethyltrifluoroborate, a primary aminomethyl equivalent, was synthesized successfully through a "one-pot" process. With this trifluoroborate, Suzuki–Miyaura cross-coupling reactions were investigated with a variety of both aryl and hetaryl chlorides in good to excellent yields.

Aminomethyl moieties, especially aminomethylated arenes, might be considered privileged substructures because they appear in many bioactive natural products,[1] and they are also used as important intermediates in synthetic organic chemistry (Figure 1).[2]

Aminomethylarenes are often synthesized by reduction of either aryl cyanides[3] or oximes[4] (Scheme 1, path A). However, access to primary aminomethyl aryl and hetaryl compounds with reducible functional groups would not be compatible with this method. An alternative way to install the aminomethylarene moiety is the Staudinger reaction[5] of organic azides with trivalent phosphorus compounds (Scheme 1, path B). Unfortunately, some aryl

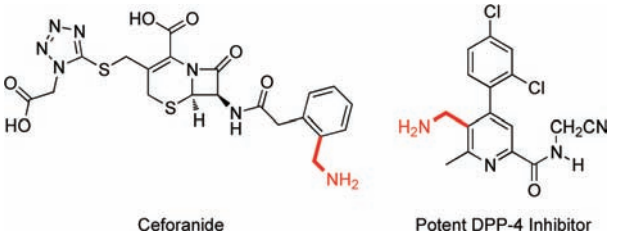


Figure 1. Bioactive molecules containing the aminomethyl moiety.

(1) (a) Musher, D. M.; Fainstein, V.; Young, E. J. *Antimicrob. Agents Chemother*. **1980**, 254. (b) Campoli-Richards, D.; Lackner, T.; Monk, J. *Drug* **1987**, *34*, 411. (c) Kaczanowska, K.; Wiesmüller, K.-H.; Schaffner, A.-P. *ACS Med. Chem. Lett*. **2010**, *1*, 530.

(2) Miller, J. F.; Gudmundsson, K. S.; Richardson, L. D.; Jenkinson, S.; Spaltenstein, A.; Thomson, M.; Wheelan, P. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 3026. (b) Aliabadi, A.; Shamsa, F.; Ostad, S. N.; Emami, S.; Shafiee, A.; Davoodi, J.; Foroumadi, A. *Eur. J. Med. Chem*. **2010**, *45*, 5348. (c) Shukla, N. M.; Mutz, C. A.; Ukani, R.; Warshakoon, H. J.; Moore, D. S.; David, S. A. *Bioorg. Med. Chem. Lett*. **2010**, *20*, 6384. (d) Liu, G.-S.; Dong, Q.-L.; Yao, Y.-S.; Yao, Z.-J. *Org. Lett*. **2008**, *10*, 5393.

(3) (a) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc*. **1948**, *70*, 3738. (b) Soffer, L. M.; Katz, M. *J. Am. Chem. Soc*. **1956**, *78*, 1705.

(4) (a) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem*. **1985**, *50*, 5448. (b) Bair, K. W.; Tuttle, R. L.; Knick, V. C.; Cory, M.; McKee, D. D. *J. Med. Chem*. **1990**, *33*, 2385.

(5) (a) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437. (b) Gololobov, Y. G.; Kaukhin, L. F. *Tetrahedron* **1992**, *48*, 1353. (c) Knölker, H.-J.; Filali, S. *Synlett* **2003**, *11*, 1752.

(6) (a) Agrawal, J. P.; Hodgson, R. In *Organic Chemistry of Explosives*; Wiley: Chichester, 2007. (b) Huynh, M.-H. V.; Hiskey, M. A.; Chavez, D. E.; Naud, D. L.; Gilardi, R. D. *J. Am. Chem. Soc*. **2005**, *127*, 12537.

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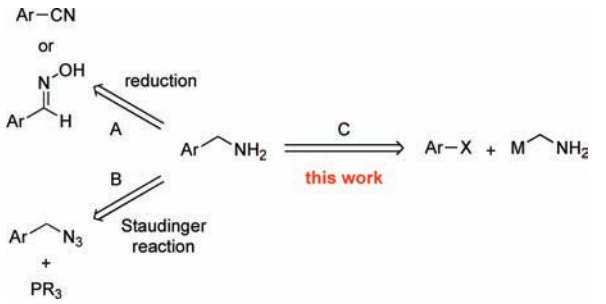
and hetaryl azides exhibit significant thermal or shock sensitivity.[6] Moreover, the benzylic or pseudobenzylic halide precursors required to prepare the azides are often not readily available.

Scheme 1

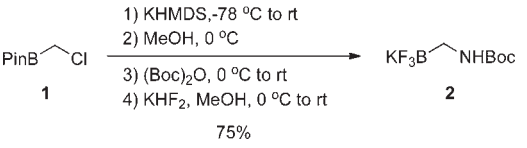


Interestingly, reported syntheses and transition metal catalyzed cross-coupling reactions of primary aminomethyl organometallics or their equivalents are rare (Scheme 1, path C). Recently, we demonstrated the synthesis and cross-coupling reactions of amidomethyltrifluoroborates[7] and tertiary aminomethyltrifluoroborates.[8] Among these, the sulfonamidomethyl derivatives could be utilized to generate primary amines [e.g., using the *p*-toluenesulfonyl (tosyl) group as the amine protecting group].[7b] However, the removal of tosyl groups requires the use of harsh conditions[9] compared to the Boc group, for example, which can be easily removed under either acidic or basic conditions.[10]

Although a patent exists that refers to the use of the *N*-phthalimido group as an amine protecting group in Suzuki−Miyaura coupling reactions,[11] the scope of that process has not been widely disseminated, and we have been unable to develop a broadly applicable procedure based on such a protocol. Furthermore, hydrazine is often used to remove the phthalimido group, and its toxicity and instability to storage and handling prevent its routine use in this capacity.

The development of the aminomethylating and amidomethylating procedures in our laboratory[7] led us to investigate the synthesis of alternative protected primary aminomethyltrifluoroborates. Herein, we disclose a successful synthesis of potassium Boc-protected aminomethyltrifluoroborate, which is the synthetic equivalent of a primary aminomethyl unit, and the development of Suzuki−Miyaura cross-coupling reactions of this trifluoroborate with various aryl and hetaryl chlorides.

The requisite potassium Boc-protected aminomethyltrifluoroborate **2** was prepared in 75% yield over four steps in a "one-pot" process from 2-(chloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **1** by applying our recently published protocol (eq 1).[7,12] Pleasingly, the prepared aminomethyltrifluoroborate **2** was air stable and could be stored indefinitely on the bench without decomposition.



(1)

With Boc-protected aminomethyltrifluoroborate successfully prepared, we first investigated its application in Suzuki−Miyaura cross-coupling reactions with 4-chlorobenzonitrile and 4-chloroanisole as coupling partners to determine optimal conditions. After screening several catalysts, ligands, bases, and reaction times, the combination of 5 mol % of $Pd(OAc)_2$, 10 mol % of SPhos or XPhos (Figure 2), and 3 equiv of K_2CO_3 in toluene/H_2O (4:1, 0.25 M) for 22 h emerged as the best reaction conditions. Indeed, we decided to use two different ligands, SPhos and XPhos, because they were often complementary in their reactivity with various aryl and hetaryl chlorides. Importantly, the trifluoroborate could be employed in virtually a stoichiometric quantity in the cross-coupling reactions. We employed these conditions to explore cross-couplings with diverse aryl chlorides as electrophiles (Table 1).

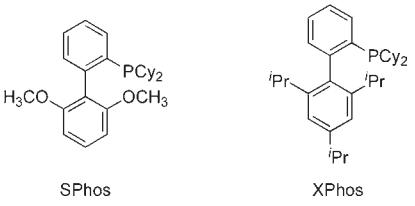


Figure 2. SPhos and XPhos.

Electron-neutral (entries 1−3), electron-donating (entries 4−7), and electron-withdrawing groups (entries 8−12) were suitable coupling partners in Suzuki−Miyaura cross-coupling reactions. Surprisingly, sterically hindered di-*ortho* substituted electrophiles provided as high a yield as the less hindered monosubstituted electrophiles (compare entries 2 and 3). The cross-coupling reactions using 4-chloroanisole as an electrophile furnished the product **3d** in 78% yield on a larger scale (4.0 mmol) with a lower catalyst loading (2 mol %, entry 4). Of particular note, access to aminomethylated

(7) (a) Molander, G. A.; Hiebel, M.-A. *Org. Lett.* **2010**, *12*, 4876. (b) Molander, G. A.; Fleury-Brégeot, N.; Hiebel, M.-A. *Org. Lett.* **2011**, *13*, 16937.

(8) (a) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2007**, *9*, 1597. (b) Hasník, Z; Pohl, R.; Hocek, M. *Synthesis* **2009**, *8*, 1309.

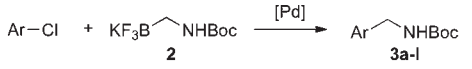
(9) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999. (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme: Stuttgart, NY, 2005. (c) Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157. (d) Ravinder, K.; Reddy, V.; Mahesh, K. C.; Narasimhulu, M.; Venkateswarlu, Y. *Synth. Commun.* **2007**, *37*, 281.

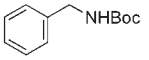
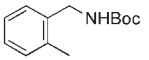
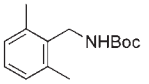
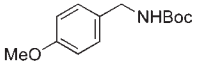
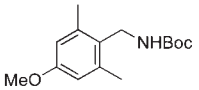
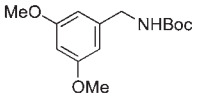
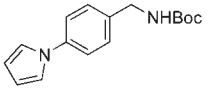
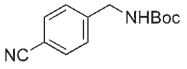
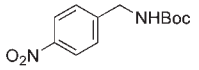
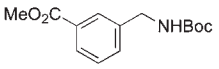
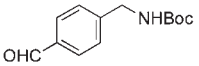
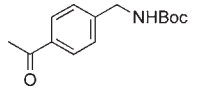
(10) (a) du Vigneaud, V.; Behrens, O. K. *J. Biol. Chem.* **1937**, *117*, 27. (b) Kharasch, M. S.; Priestley, H. M. *J. Am. Chem. Soc.* **1939**, *61*, 3425. (c) Snyder, H. R.; Heckert, R. E. *J. Am. Chem. Soc.* **1952**, *74*, 2006. (d) Li, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311.

(11) Tanaka, K. PCT Int. Appl. WO 2008007670, 2008.

(12) (a) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535. (b) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859. (c) Matteson, D. S. *Tetrahedron* **1998**, *54*, 10555.

Table 1. Cross-Coupling of Trifluoroborate **2** with Various Aryl Chlorides[a]



entry	product		isolated yield (%) A[b]	B[c]
1		**3a**	91	74
2		**3b**	76	90
3		**3c**	90	76
4		**3d**	69	88(78)[d]
5		**3e**	78	71
6		**3f**	75	79
7		**3g**	86	87
8		**3h**	90	88
9		**3i**	90	88
10		**3j**	90	86
11		**3k**	70	77
12		**3l**	69	71

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.05 equiv of trifluoroborate, 5 mol % of $Pd(OAc)_2$, 10 mol % of ligand, 3 equiv of K_2CO_3, 4:1 toluene/H_2O (0.25 M), 85 °C, 22 h. [b] SPhos. [c] XPhos. [d] 4.0 mmol of 4-chloroanisole, 2 mol % of $Pd(OAc)_2$, 4 mol % of XPhos.

aromatics by this cross-coupling protocol complements the nitrile reduction method. Thus nitrile, aldehyde, ketone, ester, and nitro functional groups are accommodated by the cross-coupling route (entries 8−12), but these substituents would have to be protected or alternate routes employed if a nitrile reduction strategy was employed.

(13) (a) Chin, C. C. H.; Yeo, J. S. L.; Loh, Z. H.; Vittal, J. J.; Henderson, W.; Hor, T. S. A. *J. Chem. Soc., Dalton Trans.* **1998**, 3777. (b) Beeby, A.; Bettington, S.; Fairlamb, I. J. S.; Goeta, A. E.; Kapdi, A. R.; Niemela, E. H.; Thompson, A. L *New J. Chem.* **2004**, *28*, 600. (c) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036.

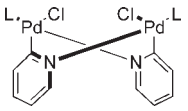
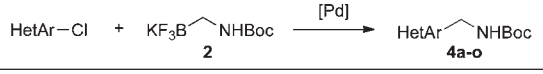
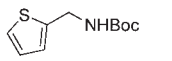
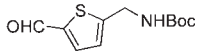
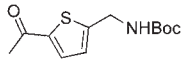
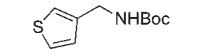
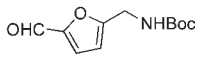
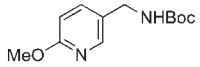
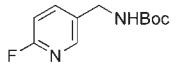
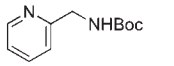
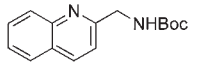
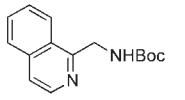
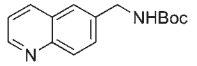
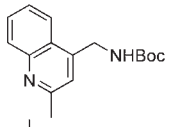
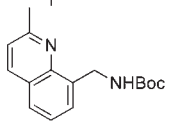
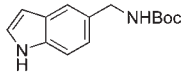
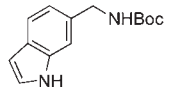


Figure 3. Dimeric metalated pyridine.

Table 2. Cross-Coupling of Trifluoroborate **2** with Various Hetaryl Chlorides[a]



entry	product		isolated yield (%) A[b]	B[c]
1		**4a**	78	60
2		**4b**	70	75
3		**4c**	85	80
4		**4d**	45	73
5		**4e**	66	73
6		**4f**	86	62
7		**4g**	67	74
8		**4h**	35	33
9		**4i**	51	36
10		**4j**	37	62
11		**4k**	57	70
12		**4l**	59	37
13		**4m**	76	87
14		**4n**	65	67
15		**4o**	67	70

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.05 equiv of trifluoroborate, 5 mol % of $Pd(OAc)_2$, 10 mol % of ligand, 3 equiv of K_2CO_3, 4:1 toluene/H_2O (0.25 M), 85 °C, 22 h. [b] SPhos. [c] XPhos.

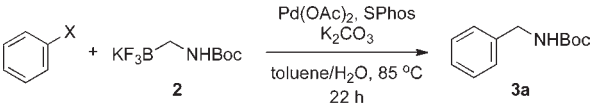
To expand the array of electrophiles, various hetaryl chlorides were investigated as coupling partners (Table 2). Thiophene, furan, pyridine, quinoline, and indole derivatives were successfully coupled to afford the expected products in moderate to good yields. Interestingly, 2-chloropyridine and structurally related quinoline and isoquinoline derivatives (entries 8–10) provided a much lower yield compared to other hetaryl chlorides. Oxidative addition of Pd(0) to 2-halopyridines generates a well-characterized dimeric species (Figure 3).[13] Although this complex has served as an effective precatalyst in Suzuki–Miyaura cross-coupling reactions with boronic acid derivatives, it may be the case that in the current protocol this type of complex in some way inhibits effective cross-coupling.

Once again, sensitive functional groups such as aldehydes and ketones were tolerated under these conditions, providing the desired products in good to excellent yields (entries 2, 3, and 5). Of additional note, unprotected indoles could also be coupled effectively (entries 14 and 15).

Next, we examined other electrophilic partners employing the same conditions [$Pd(OAc)_2$, SPhos, Table 3]. Interestingly, phenyl bromide and triflate gave moderate yields (entries 2 and 4). However, iodobenzene furnished the desired product in only 41% yield (entry 3). Moreover, phenyl mesylate and tosylate were not effective coupling partners under these reactions conditions (entries 5 and 6). Because the oxidative addition step is undoubtedly not the rate-determining step among some of the substrates tested and because the reactions were optimized for aryl chlorides, a different set of conditions would have to be developed to couple substrates with other nucleofugic groups effectively.

In summary, we successfully synthesized the air stable potassium Boc-protected aminomethyltrifluoroborate, which is an equivalent of the primary aminomethyl unit, through a "one-pot" synthetic process from 2-(chloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in good yield. With this potassium Boc-aminomethyltrifluoroborate, Suzuki–Miyaura cross-coupling reactions were investigated with a variety of aryl and hetaryl chlorides. Studies to expand the scope of this protocol continue in our laboratory.

Table 3. Electrophile Compatibility[a]



entry	X	yield (%)
1	Cl	91
2	Br	72
3	I	41
4	OTf	70
5	OMs	trace
6	OTs	trace

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.05 equiv of trifluoroborate, 5 mol % of $Pd(OAc)_2$, 10 mol % of SPhos, 3 equiv of K_2CO_3, 4:1 toluene/H_2O (0.25 M), 85 °C, 22 h.

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Supporting Information Available. Experimental procedures and spectral data of all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.