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Cross-Coupling of Mesylated Phenol Derivatives with Potassium Ammonio- and Amidomethyltrifluoroborates

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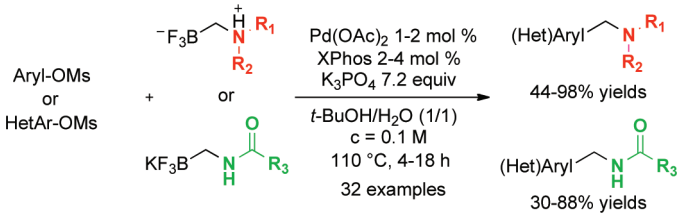
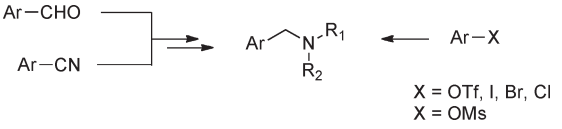
ABSTRACT



A large array of aryl and heteroaryl mesylates have been successfully employed as electrophiles in a Csp^2−Csp^3 Suzuki−Miyaura cross-coupling with potassium ammonio- and amidomethyltrifluoroborates to afford the corresponding products in high yields.

Aliphatic amines are very important synthetic targets for the scientific community as they exhibit useful properties for employment in a wide variety of industries.[1] More specifically, *N*,*N*-dialkylaminomethyl- and amidomethyl compounds are widely encountered in alkaloid natural products and synthetic therapeutic drugs.[2] Reductive amination of aldehydes[3,4] and reduction of nitriles[4,5] appear to be the most common methods utilized to obtain these compounds. More recently, the development of Csp^2−Csp^3 Suzuki−Miyaura cross-couplings has afforded a complementary pathway toward the synthesis of these scaffolds.[6] This last method is especially of great interest because of the greater availability of aryl halides in comparison to aryl- or heteroaryl aldehydes or -nitriles (Scheme 1).

Scheme 1



Previous reports from our laboratory have demonstrated the efficiency of the cross-coupling approach to aminomethyl-substituted aromatic and heteroaromatic compounds. Potassium *N*,*N*-dialkylaminomethyl-[6i,j] and

(1) Aliphatic Amines. In *Ullmann's Encyclopedia of Industrial Chemistry*, 7th ed.; Wiley-VCH: Weinheim, 2008; Vol. A2, p 2.

(2) (a) Roberson, E. D.; Mucke, L. *Science* **2006**, *314*, 781–784. (b) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2007**, *130*, 18–19. (c) Chill, L.; Aknin, M.; Kashman, Y. *Org. Lett.* **2003**, *5*, 2433–2435. (d) Yasuhara, T.; Nishimura, K.; Yamashita, M.; Fukuyama, N.; Yamada, K.-i.; Muraoka, O.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1123–1126. (e) French, K. J.; Zhuang, Y.; Maines, L. W.; Gao, P.; Wang, W. X.; Beljanski, V.; Upson, J. J.; Green, C. L.; Keller, S. N.; Smith, C. D. *J. Pharmacol. Exp. Ther.* **2010**, *333*, 129–139. (f) Belyk, K. M.; Morrison, H. G.; Jones, P.; Summa, V. WO06060730, 2006. (g) McIntyre, J. A.; Castaner, J.; Martin, L. *Drugs Future* **2004**, *29*, 992–997. (h) Ratti, S.; Quarato, P.; Casagrande, C.; Fumagalli, R.; Corsini, A. *Eur. J. Pharmacol.* **1998**, *355*, 77–83.

(3) (a) Abdel-Magid, A. F.; Mehrman, S. J. *Org. Process Res. Dev.* **2006**, *10*, 971–1031. (b) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862. (c) Baxter, E. W.; Reitz, A. B. *Org. React.* **2002**, *59*, 1–714.

(4) Gomez, S.; Peters, J. A.; Maschmeyer, T. *Adv. Synth. Catal.* **2002**, *344*, 1037–1057.

(5) Haddenham, D.; Pasumansky, L.; DeSoto, J.; Eagon, S.; Singaram, B. *J. Org. Chem.* **2009**, *74*, 1964–1970.

(6) For some examples employing alkylboron species in Csp^2−Csp^3 Suzuki cross-couplings, see: (a) Molander, G. A.; Yun, C.-S. *Tetrahedron* **2002**, *58*, 1465–1470. (b) Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron* **2004**, *60*, 3813–3818. (c) Ines, B.; Moreno, I.; SanMartin, R.; Dominguez, E. *J. Org. Chem.* **2008**, *73*, 8448–8451. (d) Dreher, S.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257–9259. (e) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2009**, *11*, 2369–2372. (f) Molander, G. A.; Sandrock, D. L. *J. Am. Chem. Soc.* **2008**, *130*, 15792–15793. (g) Dreher, S.; Lim, S.-E.; Sandrock, D. L.; Molander, G. A. *J. Org. Chem.* **2009**, *74*, 3626–3631. (h) Sandrock, D. L.; Jean-Gerard, L.; Chen, C.-Y.; Dreher, S.; Molander, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 17108–17110. (i) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2007**, *9*, 1597–1600. (j) Molander, G. A.; Gormisky, P. E.; Sandrock, D. L. *J. Org. Chem.* **2008**, *73*, 2052–2057. (k) Molander, G. A.; Hiebel, M.-A. *Org. Lett.* **2010**, *12*, 4876–4879.

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amidomethyltrifluoroborates[6k] have been successfully cross-coupled with high yields using aryl halide electrophiles.

Less toxic and easier to handle sulfonate groups have recently expanded the scope of nucleofuges in cross-coupling protocols.[7,8] Among these, mesylates appear to be the most attractive substrates in terms of stability and atom economy even though they are known to be the least reactive species.[8] In the past few years, significant progress on Csp^2-Csp^2 Suzuki−Miyaura cross-coupling has been achieved with these electrophiles, but much work still remains on the more challenging Csp^2-Csp^3 cross-couplings. Alkylboron species are known to undergo the requisite transmetalation step with the intermediate organometallic species with more difficulty than with sp^2-hybridized organoborons.[6,8h] Actually, to our knowledge, only two cross-coupling examples have been reported with an alkylboron species and a mesylated aryl counterpart. Buchwald disclosed a palladium-catalyzed cross-coupling of a mesylated quinoline in the presence of a single alkylboron species, methylboronic acid, with a yield of 84%.[8b] In 2010, Kwong employed his indoyl phosphine ligand to cross-couple the 4-*tert*-butylphenyl mesylate with *n*-butylboronic acid and its potassium trifluoroborate counterpart with moderate yields of 48% and 62%, respectively.[8c] Both methods used a large excess of boron reagent (2 equiv) in the presence of 2 mol % of $Pd(OAc)_2$. Moreover, all the attempts up to now to provide the cross-coupled compound from a more reactive tosylate starting material with both potassium *N*,*N*-dialkylammonio- and amidomethyltrifluoroborates have been unsuccessful.[6i−k]

Herein, the first general protocol for the Csp^2-Csp^3 Suzuki−Miyaura cross-coupling of aryl- and heteroaryl mesylates with potassium aminomethyltrifluoroborates is reported. Additionally, this system has also proven to be very efficient with potassium amidomethyltrifluoroborates.

(7) For recent examples of Suzuki cross-coupling of aryl tosylates, see: (a) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819. (b) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 194–202. (c) Petersen, M. D.; Boye, S. V.; Nielsen, E. H.; Willumsen, J.; Sinning, S.; Wiborg, O.; Bols, M. *Bioorg. Med. Chem.* **2007**, *15*, 4159–4174. (d) Zhang, L. A.; Meng, T. H.; Wu, J. *J. Org. Chem.* **2007**, *72*, 9346–9349. (e) So, C. M.; Lau, C. P.; Chan, A. S. C.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7731–7734. (f) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447–3452. (g) Tang, Z. Y.; Hu, Q. S. *J. Am. Chem. Soc.* **2004**, *126*, 3058–3059. (h) Tang, Z.-Y.; Spinella, S.; Hu, Q.-S. *Tetrahedron Lett.* **2006**, *47*, 2427–2430. (i) Lipshutz, B. H.; Butler, T.; Swift, E. *Org. Lett.* **2008**, *10*, 697–700. (j) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049–3051.

(8) For recent examples of Suzuki cross-coupling of aryl mesylates, see: (a) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059–8063. (b) Bhayana, B.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 3954–3957. (c) Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2010**, *75*, 5109–5112. (d) Percec, V.; Bae, J. Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060–1065. (e) Ueda, M.; Saitoh, A.; Oh-tani, S.; Miyaura, N. *Tetrahedron* **1998**, *54*, 13079–13086. (f) Kobayashi, Y.; William, A. D.; Mizojiri, R. *J. Organomet. Chem.* **2002**, *653*, 91–97. (g) Kuroda, J. I.; Inamoto, K.; Hiroya, K.; Doi, T. *Eur. J. Org. Chem.* **2009**, 2251–2261. (h) Molander, G. A.; Beaumard, F. *Org. Lett.* **2010**, *12*, 4022–4025. (i) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2010**10.1021/cr100259t.

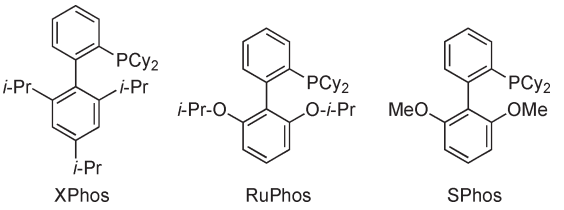
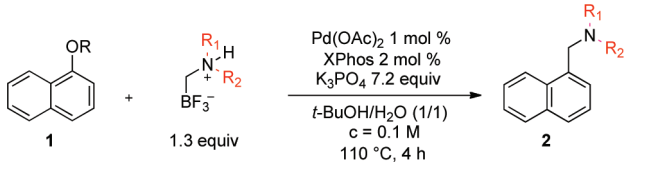


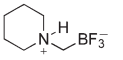
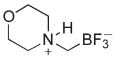
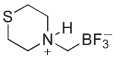
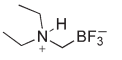
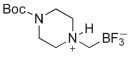
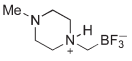
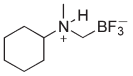
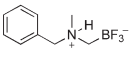
Figure 1. Structure of ligands.

As a starting point, a small survey of $Pd(OAc)_2$/ligand systems was carried out with the mesylated naphthol **1a** and the *N*-(trifluoroboratomethyl)piperidine internal salt[9] as model substrates. Either SPhos, RuPhos, or XPhos (Figure 1) appeared to be suitable, affording the desired compound **2a** with complete conversion.[10] Moreover, the catalyst loading could be reduced to 1 mol %, and only 1.3 equiv of potassium trifluoroborate was necessary to obtain **2a** with 84% yield after 1 h. Tosylates could also be employed in the reaction as the electrophile, providing an 81% yield of **2a** under the same reaction conditions (Table 1, entry 1).

After optimizing the conditions for the cross-coupling, we next studied the reaction of mesylated naphthol **1a** with an

Table 1. Scope of Ammoniomethyltrifluoroborate Internal Salts

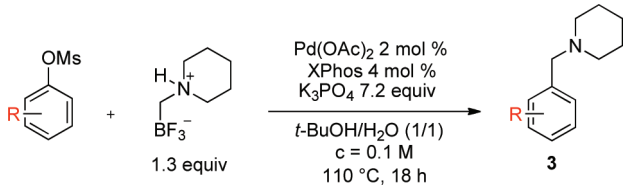


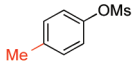
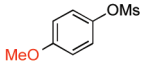
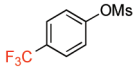
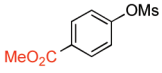
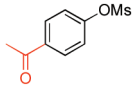
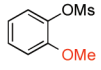
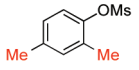
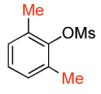
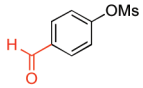
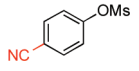
entry	R =	internal salt		yield (%)
1	**1a** R = Ms **1a'** R = Ts		**2a**	84[a] 81
2	R = Ms		**2b**	97
3	R = Ms		**2c**	53
4	R = Ms		**2d**	75
5	R = Ms		**2e**	93
6	R = Ms		**2f**	72
7	R = Ms		**2g**	79
8	R = Ms		**2h**	87[a]

[a] Time = 1 h.

array of various *N*,*N*-dialkylammoniomethyltrifluoroborates. It is important to note that all these *N*,*N*-dialkylammoniomethyltrifluoroborates are prepared as the internal salts following a new procedure, which avoids the KBr salt contamination of previous processes.[9] Both cyclic (piperidine, morpholine, *N*-protected piperazine) and acyclic tertiary ammoniomethyl salts are very well tolerated by the reaction conditions. The corresponding desired compounds **2a**,**b**,**d**−**h** were all obtained with yields ranging from 72% to 97% (Table 1, entries 1, 2, and 4−8). Even a thiomorpholine derivative, known to be a more difficult substrate because sulfides often poison the catalyst,[11] worked well with a modest yield of 53% (Table 1, entry 3). Access to bifunctionalized compounds such as **2e** are of particular interest because *N*-Boc deprotection and substitution of the resulting free amine compound can be envisioned, leading to more highly elaborated molecular platforms.

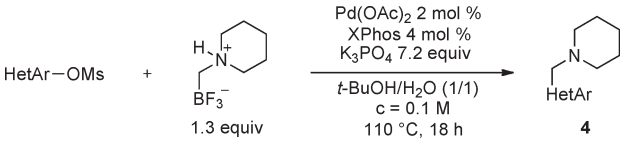
Table 2. Scope of Functionalized Mesylated Phenols

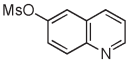
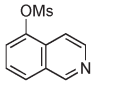
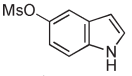


entry	Ar-OMs		yield (%)[a]
1		**3a**	85 (75)[b]
2		**3b**	91
3		**3c**	80[c]
4		**3d**	44
5		**3e**	83
6		**3f**	63
7		**3g**	83[d]
8		**3h**	76[d]
9		**3i**	33[c,d]
10		**3j**	60[c]
11		**3k**	57

[a] Isolated as the HCl salt. [b] Ph-OMs (1 equiv), *N*-(trifluoroboratomethyl)piperidine internal salt (1.3 equiv), $Pd(OAc)_2$ (0.5 mol %), XPhos (1 mol %), and K_3PO_4 (7.2 equiv), 110 °C, 24 h. [c] The HCl salt was hydrolyzed with 1 M KOH to obtain the amine. [d] [Pd] (5 mol %) and L (10 mol %).

Table 3. Scope of Heteroaryl Mesylates



entry	HetAr-OMs		yield (%)[a]
1		**4a**	96
2		**4b**	41[b]
3		**4c**	89
4		**4d**	98
5		**4e**	60[c]

[a] Isolated as the HCl salt. [b] [Pd] (5 mol %) and L (10 mol %). The HCl salt was hydrolyzed with 1 M KOH to obtain the amine. [c] Isolated directly as the free amine.

We further examined the reactivity of a range of functionalized aryl mesylates in the presence of the *N*-(trifluoroboratomethyl)piperidine internal salt. The reaction exhibits high functional group compatibility by proceeding well with ketone, ester, ether, nitrile and aldehyde functional groups. The desired compounds were obtained with yields ranging from 44% to 91%. Even hindered substrates afford the cross-coupled products **3g**−**i** with yields up to 83% (Table 2, entries 7−9). The loading of $Pd(OAc)_2$ was adjusted to 5 mol % in these cases to enable the reaction to proceed to completion. Surprisingly, aryl mesylates bearing electron-donating groups are more efficient than mesylates bearing electron-withdrawing groups. By increasing the scale of the reaction to 5 mmol, we were able to decrease the loading of palladium to 0.5 mol % to obtain **3a** with a yield of 75% (compared to 85% on a 0.25 mmol scale with 2 mol % catalyst loading). It is important to note that almost all these desired compounds were isolated without purification by column chromatography. Instead, they were converted directly into their corresponding hydrochloride salt.

We next investigated the reactivity of heteroaryl mesylates as electrophilic partners in the Csp^2−Csp^3 cross-coupling.

(9) Raushel, J.; Sandrock D. L.; Josyula, K. V.; Pakyz, D.; Molander, G. A. Manuscript in preparation.

(10) Relative GC yield = 100% for all using dodecane as the internal standard.

(11) Wise, H. *Stud. Surf. Sci. Catal.* **1991**, *68*, 497–504.

Pyridine, quinoline, and isoquinoline substrates all provided the aminomethyl compounds **4a**,**c**,**d** with very high yields ranging from 89% to 98%. The 2-methylpyridin-3-yl mesylate appears to be much less reactive, even if the loading of catalyst was increased to 5 mol %, affording **4b** with a modest 41% yield (Table 3, entry 2). A 60% yield was obtained when the *N*-unprotected indole is used in the reaction (Table 3, entry 5).

Extension of this reaction to potassium amidomethyltrifluoroborates turned out to be successful under the standard conditions with the naphthol mesylate **1a**. Aryl, cyclic, and acyclic alkyl carboxamides can be used as nucleophilic partners with great efficiency. The desired compounds **5a**−**e** are obtained with yields up to 88%. To favor the completion of the reaction with the cyclopropylcarboxamide substrate, 5 mol % of $Pd(OAc)_2$ was used to afford **5c** with a 70% yield (Table 4, entry 3). Moreover, this protocol is also compatible with aryl- and heteroaryl mesylates to afford pivalamides **5e**−**h** with yields up to 94% (Table 4, entries 5−8).

In summary, we have developed a general method for Csp^2−Csp^3 Suzuki−Miyaura cross-couplings of mesylates with *N*,*N*-dialkylammoniomethyltrifluoroborates. Both cyclic and acyclic ammoniomethyl salts were successfully cross-coupled with high yields. This system has also proven to be well-tolerant of a large variety of functionalized aryl- and heteroaryl mesylates. Moreover, the scope of the reaction was extended to the carboxamidomethyltrifluoroborates with success. The versatility and the wide scope of this reaction should facilitate the introduction of the aminomethyl moiety into complex organic molecules.

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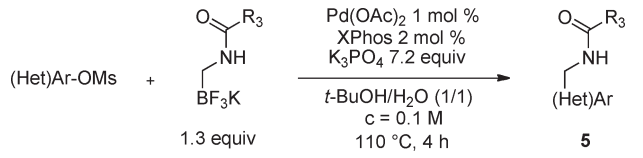
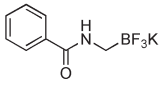
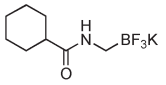
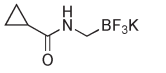
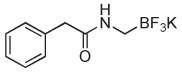
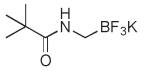
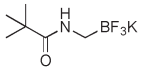
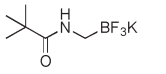
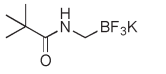
Supporting Information Available. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

Table 4. Scope of Potassium Amidomethyltrifluoroborates



entry	(Het)Ar-OMs	amidomethylBF$_3$K		yield (%)
1			**5a**	88
2			**5b**	81
3			**5c**	70[a]
4			**5d**	71
5			**5e**	80
6			**5f**	94[b]
7			**5g**	30[b]
8			**5h**	64[b]

[a] [Pd] (5 mol %) and L (10 mol %), 110 °C, 18 h. [b] [Pd] (2 mol %) and L (4 mol %), 110 °C, 18 h.