Published in final edited form as:

Org Lett. 2011 March 4; 13(5): 1242–1245. doi:10.1021/ol200128y.

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

Gary A. Molander^{*} and Floriane Beaumard

Roy and Diana A. Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

Abstract

A large array of aryl- and heteroaryl mesylates have been successfully employed as electrophiles in a Csp²-Csp³ 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 Csp²-Csp³ 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).

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-6*i,j* and 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 last few years, significant progress on Csp²-Csp² Suzuki–Miyaura cross-coupling has been achieved with these electrophiles, but much work still remains on the more challenging Csp²-Csp³ cross-couplings. Alkylboron species are known to undergo the requisite transmetalation step with the intermediate organometallic species with more difficulty than with sp²-hybridized organoborons.^{6,8h} Actually, to our knowledge, only two cross-coupling examples have been reported with an alkylboron

gmolandr@sas.upenn.edu.

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

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,j,k}

Herein, the first general protocol for the Csp²-Csp³ 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.

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 salt⁹ 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 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, 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.

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**, **3h**, and **3i** with yields up to 83% (Table 3, 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 $\text{Csp}^2\text{-Csp}^3$ cross-coupling. Pyridine, quinoline and isoquinoline substrates all provided the aminomethyl compounds **4a**, **4c–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 4, entry 4). A 60% yield was obtained when the *N*-unprotected indole is used in the reaction (Table 4, 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 $\text{Pd}(\text{OAc})_2$ was used to afford **5c** with a 70% yield (Table 5, entry 3). Moreover, this protocol is also compatible with aryl- and heteroaryl mesylates to afford pivalamides **5e–h** with yields up to 94% (Table 5, entries 5–8).

In summary, we have developed a general method for $\text{Csp}^2\text{-Csp}^3$ 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by a National Priorities Research Program (NPRP) grant from the Qatar National Research Fund (Grant no. 08-035-1-008) and the NIH (R01 GM-081376). We acknowledge Frontier Scientific for its donation of $\text{Pd}(\text{OAc})_2$. Dr. Rakesh Kohli (University of Pennsylvania) is acknowledged for obtaining HRMS data.

References

1. Aliphatic Amines. Ullmann's Encyclopedia of Industrial Chemistry. 7. Vol. A2. Wiley-VCH; Weinheim, Germany: 2008. p. 2
2. (a) Roberson ED, Mucke L. Science 2006;314:781–784. [PubMed: 17082448] (b) Barbe G, Charette AB. J Am Chem Soc 2007;130:18–19. [PubMed: 18076177] (c) Chill L, Aknin M, Kashman Y. Org Lett 2003;5:2433–2435. [PubMed: 12841748] (d) Yasuhara T, Nishimura K, Yamashita M, Fukuyama N, Yamada K-i, Muraoka O, Tomioka K. Org Lett 2003;5:1123–1126. [PubMed: 12659589] (e) French KJ, Zhuang Y, Maines LW, Gao P, Wang WX, Beljanski V, Upson JJ, Green CL, Keller SN, Smith CD. J Pharmacol Exp Ther 2010;333:129–139. [PubMed: 20061445] (f) Belyk, KM.; Morrison, HG.; Jones, P.; Summa, V. WO. 06060730. 2006. (g) McIntyre JA, 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. [PubMed: 9754941]
3. (a) Abdel-Magid AF, Mehrman SJ. Org Process Res Dev 2006;10:971–1031. (b) Abdel-Magid AF, Carson KG, Harris BD, Maryanoff CA, Shah RD. J Org Chem 1996;61:3849–3862. [PubMed: 11667239] (c) Baxter EW, Reitz AB. Org React 2002;59:1–714.
4. Gomez S, Peters JA, 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. [PubMed: 19191712]

6. For some examples employing alkylboron species in Csp^2 - Csp^3 Suzuki cross-couplings, see: (a) Molander GA, Yun CS. *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. [PubMed: 18855448] (d) Dreher S, Dormer PG, Sandrock DL, Molander GA. *J Am Chem Soc* 2008;130:9257–9259. [PubMed: 18582050] (e) Molander GA, Sandrock DL. *Org Lett* 2009;11:2369–2372. [PubMed: 19422202] (f) Molander GA, Sandrock DL. *J Am Chem Soc* 2008;130:15792–15793. [PubMed: 18980313] (g) Dreher S, Lim SE, Sandrock DL, Molander GA. *J Org Chem* 2009;74:3626–3631. [PubMed: 19271726] (h) Sandrock DL, Jean-Gerard L, Chen CY, Dreher S, Molander GA. *J Am Chem Soc* 2010;132:17108–17110. (i) Molander GA, Sandrock DL. *Org Lett* 2007;9:1597–1600. [PubMed: 17367156] (j) Molander GA, Gormisky PE, Sandrock DL. *J Org Chem* 2008;73:2052–2057. [PubMed: 18284257] (k) Molander GA, Hiebel MA. *Org Lett* 2010;12:4876–4879. [PubMed: 20879742]
7. For recent examples of Suzuki cross-coupling of aryl tosylates, see: (a) Nguyen HN, Huang X, Buchwald SL. *J Am Chem Soc* 2003;125:11818–11819. [PubMed: 14505394] (b) Roy AH, Hartwig JF. *Organometallics* 2004;23:194–202. (c) Petersen MD, Boye SV, Nielsen EH, Willumsen J, Sinning S, Wiborg O, Bols M. *Bioorg Med Chem* 2007;15:4159–4174. [PubMed: 17446076] (d) Zhang LA, Meng TH, Wu J. *J Org Chem* 2007;72:9346–9349. [PubMed: 17975932] (e) So CM, Lau CP, Chan ASC, Kwong FY. *J Org Chem* 2008;73:7731–7734. [PubMed: 18783275] (f) Percec V, Golding GM, Smidrkal J, Weichold O. *J Org Chem* 2004;69:3447–3452. [PubMed: 15132555] (g) Tang ZY, Hu QS. *J Am Chem Soc* 2004;126:3058–3059. [PubMed: 15012129] (h) Tang ZY, Spinella S, Hu QS. *Tetrahedron Lett* 2006;47:2427–2430. (i) Lipshutz BH, Butler T, Swift E. *Org Lett* 2008;10:697–700. [PubMed: 18269286] (j) Zim D, Lando VR, Dupont J, Monteiro AL. *Org Lett* 2001;3:3049–3051. [PubMed: 11554840]
8. For recent examples of Suzuki cross-coupling of aryl mesylates, see: (a) So CM, Lau CP, Kwong FY. *Angew Chem Int Ed* 2008;47:8059–8063. (b) Bhayana B, Fors BP, Buchwald SL. *Org Lett* 2009;11:3954–3957. [PubMed: 19663467] (c) Chow WK, So CM, Lau CP, Kwong FY. *J Org Chem* 2010;75:5109–5112. [PubMed: 20590104] (d) Percec V, Bae JY, Hill DH. *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 AD, Mizojiri R. *J Organomet Chem* 2002;653:91–97. (g) Kuroda JI, Inamoto K, Hiroya K, Doi T. *Eur J Org Chem* 2009;2251–2261. (h) Molander GA, Beaumard F. *Org Lett* 2010;12:4022–4025. [PubMed: 20715841] (i) Rosen BM, Quasdorf KW, Wilson DA, Zhang N, Resmerita A-M, Garg NK. Percec, V *Chem Rev.* 2010 ASAP. 10.1021/cr100259t
9. Raushel J, Sandrock DL, Josyula KV, Pakyz D, Molander GA. submitted.
10. Relative GC yield = 100% for all using dodecane as the internal standard.
11. Wise H. *Stud Surf Sci Catal* 1991;68:497–504.

Figure 1.
Structure of ligands.

Scheme 1.

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.

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

entry	Ar-OMs	yield (%) ^a
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 K₃PO₄ (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.

Table 4

Scope of Potassium Amidomethyltrifluoroborates

$ \begin{array}{c} \text{O}=\text{C}-\text{R}_3 \\ \\ \text{NH}-\text{CH}_2-\text{BF}_3\text{K} \\ 1.3 \text{ equiv} \end{array} + \begin{array}{c} \text{Pd}(\text{OAc})_2 \text{ 1 mol \%} \\ \text{XPhos 2 mol \%} \\ \text{K}_3\text{PO}_4 \text{ 7.2 equiv} \\ \xrightarrow[t = 110^\circ\text{C, 4 h}]{t\text{-BuOH}/\text{H}_2\text{O (1/1)} \\ c = 0.1 \text{ M}} \end{array} \begin{array}{c} \text{O}=\text{C}-\text{R}_3 \\ \\ \text{NH}-\text{CH}_2-\text{Ar} \\ \text{5} \end{array} $			
entry	(Het)Ar-OMs	amidomethylBF ₃ K	yield (%)
1			5a 88
2			5b 81
3			5c 70 ^a
4			5d 71

entry	(Het)Ar-OMs	amidomethylBF ₃ K	yield (%)
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.