JOC Article
pubs.acs.org/joc

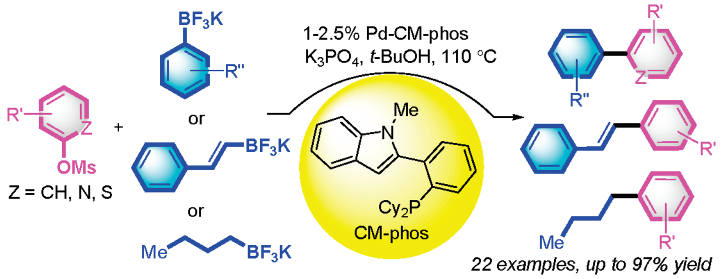
A General Palladium Catalyst System for Suzuki−Miyaura Coupling of Potassium Aryltrifluoroborates and Aryl Mesylates[§]

Wing Kin Chow, Chau Ming So, Chak Po Lau, and Fuk Yee Kwong*

State Key Laboratory of Chiroscience and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong

bcfyk@inet.polyu.edu.hk

Received April 29, 2010



The first general examples of palladium-catalyzed Suzuki-type cross-coupling of aryl and heteroaryl mesylates with potassium aryl and heteroaryltrifluoroborates are presented. In addition to biaryl couplings, the cross-coupling reactions of aryl mesylates with alkyl and vinyltrifluoroborate salts have also been successfully accomplished.

Introduction

Using a modular approach for accessing a series of compounds has been one of the most important themes in modern organic synthesis, since it offers a direct and simple route to prepare an array of structurally similar, yet diversified organic molecules.[1] Indeed, transition metal-catalyzed cross-coupling reactions have become innovative protocols in this area for the construction of either carbon−carbon or carbon−heteroatom bonds.[2]

In the field of $C_{(sp^2)}-C_{(sp^2)}$ cross-coupling reaction, Suzuki−Miyaura coupling of arylboronic acids with aryl halides represents a versatile method for the preparation of diversified biaryls, which have a myriad of applications in pharmaceutical, material, and agricultural chemistry.[3] In general, arylboronic acids are good nucleophilic organoboron reagents in this coupling reaction.[4] However, boronic acids are never ideal because they exhibit several drawbacks, such as the partial formation of dimeric and cyclic trimeric boroxines (which depend on storage water content). This structural ambiguity affects the stoichiometry of boronic acids added to the intended reaction. Organotrifluoroborate salts are attractive alternatives to aryl- and heteroarylboronic acids as they are usually sold in high purity from commercial sources or are readily available from other organoboron compounds.[5,6] Recently, Molander,[5,7] Buchwald,[8] and others[9] made superb efforts to advance the transition metal-catalyzed Suzuki−Miyaura coupling using organotrifluoroborate salts as coupling partners.

[§] Dedicated to Prof. Albert S. C. Chan on the occasion of his 60th birthday.

(1) For reviews, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (b) Nicolaou, K. C.; Sorensen, E. J. *Classic in Total Synthesis II, More Targets, Strategies and Methods*; Wiley-VCH: Weinheim, Germany, 2003.

(2) (a) de Meijere, A.; Diederich, F., Ed. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004; Vols. 1−2. (b) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis, Building Blocks and Fine Chemicals*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004; Vols. 1−2. (c) Nigeshi, E., Ed. *Handbook of Organopalladium for Organic Synthesis*; Wiley-Interscience: Weinheim, Germany, 2002; Vols. 1−2. (d) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; Wiley: Chichester, UK, 2004. (e) Yin, L. X.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. (f) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (g) Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622. (h) Kwong, F. Y.; Chan, A. S. C. *Synlett* **2008**, 1440. (i) Ackermann, L., *Modern Arylation Methods*; Wiley-VCH: Weinheim, Germany, 2009.

(3) (a) King, A. O.; Yasuda, N. In *Organometallics in Process Chemistry*; Larsen, R. D., Ed.; Springer-Verlag: Berlin, Germany, 2004; pp 205−245. (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (c) Suzuki, A. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 53−106. (d) Suzuki, A. *J. Organomet. Chem.* **2002**, *653*, 54.

(4) Hall, D. G., *Boronic Acids*; Wiley-VCH: Weinheim, Germany, 2006.

(5) For recent reviews on the coupling reactions with R-BF_3K salts, see: (a) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240. (b) Molander, G. A.; Ellis, N. O. *Acc. Chem. Res.* **2007**, *40*, 275.

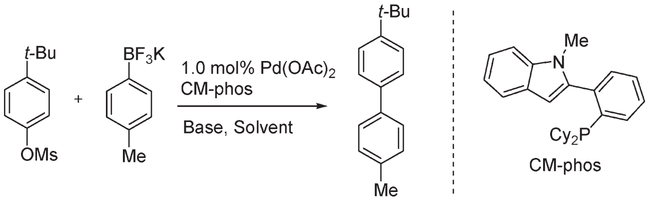
(6) For selected examples, see: (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020–3027. (b) Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2007**, *72*, 3558. (c) Molander, G. A.; Ham, J.; Canturk, B. *Org. Lett.* **2007**, *9*, 821.

DOI: 10.1021/jo100846t
Published on Web 06/30/2010

Results and Discussion

Aryl sulfonates are important alternatives to aryl halides in coupling reactions. Moreover, they are good complements to aryl halides since their phenolic substitution patterns on the aromatic ring are different from those of halides. Nevertheless, previous coupling reactions of phenolic electrophiles were often focused on aryl triflates. In fact, aryl mesylates are attractive as they are easily accessible from phenols (by reacting with MsCl under basic medium), relatively low in cost,[10] and provide better hydrolytic stability. However, cross-coupling reactions utilizing aryl mesylates remain limited.[11] Perphaps the high stability of aryl mesylates implies that it is difficult for these substrates to undergo oxidative addition in coupling reactions. In fact, aryl mesylates are challenging substrates as they are even less reactive than the corresponding aryl tosylates in cross-coupling reactions.[12] Yet, they provide a better atom-economy than tosylates.[13] In 2008, we reported a palladium catalyst system for the cross-coupling of arylboronic acids with aryl mesylates.[14,15] This system demonstrated a good functional group tolerance on both electrophilic and nucleophilic partners. To our best knowledge, there has been no literature report to date regarding the successful cross-coupling of aryl mesylates and aryltrifluoroborate salts in general. In view of the beneficial features of trifluoroborate salts as boronic acid surrogates, we have investigated the feasibilty of using this nucleophile in mesylate couplings. Herein, we report the first general Suzuki-type coupling of aryl mesylates and organotrifluoroborates. In particular, the reaction scope can be extended to heteroarylmesylates, heteroaryl-,[16] alkenyl-, and alkyltrifluoroborate salts.

TABLE 1. Initial Optimization of Reaction Parameters[a]



entry	solvent	base	% yield[b]
1	t-BuOH	Cs_2CO_3	40
2	t-BuOH	$K_3PO_4 \cdot H_2O$	75
3	t-BuOH	K_3PO_4	98 (89)[c]
4	t-BuOH	K_2CO_3	(87)[c]
5	t-BuOH	Et_3N	10[e]
6[d]	t-BuOH	K_3PO_4	82
7	DMF	K_3PO_4	28
8	t-AmOH	K_3PO_4	52
9	MeOH	K_3PO_4	79
10	THF	K_3PO_4	trace
11	toluene	K_3PO_4	trace

[a]Reaction conditions: ArOMs (1.0 mmol), Ar′BF_3K (2.0 mmol), base (3.0 mmol), $Pd(OAc)_2$ (1 mol %), CM-phos (4 mol %), solvent (3.0 mL) with stirring for 18 h at 110 °C under nitrogen. [b]Calibrated GC yields were reported with dodecane as the internal standard. [c]Isolated yields in parentheses. [d]4 Å molecular sieve (0.1 g, granular) was added. [e]A 65% of reduction side product, *tert*-butylbenzene, was formed.

To explore a high efficacy catalytic system for aryl mesylate and aryltrifluoroborate salt coupling, 4-*tert*-butylphenyl mesylate and potassium *p*-tolyltrifluoroborate were chosen as the benchmark substrates in the model reaction (Table 1). Initial screening of commonly used inorganic and organic bases indicated that K_3PO_4 and K_2CO_3 were suitable bases for this coupling reaction (Table 1, entries 3 and 4). In general, a very small amount of phenolic side product was detected. On the contrary, when triethylamine was applied as an organic base in this reaction, a large amount of *tert*-butylbenzene side product was observed (Table 1, entry 5). Although adding molecular sieves could reduce the formation of *tert*-butylbenzene, it also suppressed the rate of reaction. Among common solvents surveyed, *t*-BuOH gave the best result (Table 1, entries 6−11).

The scope of this reaction was then investigated under the optimized conditions. A wide range of nonactivated aryl mesylates were examined and the results are listed in Table 2. The deactivated aryl mesylate containing a *p*-methoxy-substituted group was found to be a feasible coupling partner (Table 2, entry 4). Both ortho-substituted aryl mesylates and aryltrifluoroborates were also a good combination for this reaction

---

(7) For recent selected examples from Molander's group, see: (a) Molander, G. A.; Cavalcanti, L. N.; Canturk, B.; Pan, P. S.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 7364. (b) Cho, Y. A.; Kim, D. S.; Ahn, H. R.; Canturk, B.; Molander, G. A.; Ham, J. *Org. Lett.* **2009**, *11*, 4330. (c) Molander, G. A.; Febo-Ayala, W.; Jean-Gerard, L. *Org. Lett.* **2009**, *11*, 3830. (d) Molander, G. A.; Jean-Gerard, L. *J. Org. Chem.* **2009**, *74*, 5446. (e) Dreher, S. D.; Lim, S. E.; Sandrock, D. L.; Molander, G. A. *J. Org. Chem.* **2009**, *74*, 3626. (f) Molander, G. A.; Jean-Gerard, L. *J. Org. Chem.* **2009**, *74*, 1297. (g) Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2008**, *73*, 3885. (h) Molander, G. A.; Gormisky, P. E.; Sandrock, D. L. *J. Org. Chem.* **2008**, *73*, 2052. (i) Molander, G. A.; Gormisky, P. E. *J. Org. Chem.* **2008**, *73*, 7481. (j) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2007**, *9*, 1597. (k) Molander, G. A.; Vargas, F. *Org. Lett.* **2007**, *9*, 203.

(8) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649.

(9) For recent selected examples, see: (a) Abel, R.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 6289. (b) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013. (c) Kabalka, G. W.; Zhou, L.-L.; Naravane, A. *Tetrahedron Lett.* **2006**, *47*, 6887. (d) Harker, R. L.; Crouch, R. D. *Synthesis* **2007**, 25. (e) Wu, J.; Zhang, L.; Luo, Y. *Tetrahedron Lett.* **2006**, *47*, 6747. (f) Wu, J.; Zhang, L.; Xia, H.-G. *Tetrahedron Lett.* **2006**, *47*, 1525. (g) Cella, R.; Cunha, R. L. O. R.; Reis, A. E. S.; Pimenta, D. C.; Klitzke, C. F.; Stefani, H. A. *J. Org. Chem.* **2006**, *71*, 244. (h) Kabalka, G. W.; Al-Masum, M. *Tetrahedron Lett.* **2005**, *46*, 6329. (i) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397. (j) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381. (k) Fang, G.-H.; Yan, Z.-J.; Deng, M.-Z. *Org. Lett.* **2004**, *6*, 357. (l) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313. (m) Arvela, R. K.; Leadbeater, N. E.; Mack, T. L.; Kormos, C. M. *Tetrahedron Lett.* **2006**, *47*, 217. For a review describing indolyl/imidazolyl phosphine ligands, see: (n) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431. For our recent developments of indolyl phosphine, see: (o) So, C. M.; Yeung, C. C.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7803.

(10) The prices of the sulfonating agents are as follows (in US dollars): MsCl, ca. \$0.075/g; Tf_2O, ca. \$5/g, from commercial suppliers in **2005−2006**.

(11) For Ni-catalyzed mesylate coupling reactions, see: (a) Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 176. (b) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060. (c) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447. For Pd-catalyzed mesylate coupling reactions, see: (d) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. (e) Zhang, L.; Qing, J.; Yang, P.; Wu, J. *Org. Lett.* **2008**, *10*, 4971. (f) So, C. M.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 6402. (g) So, C. M.; Lee, H. W.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2009**, *11*, 317. (h) Naber, J. R.; Fors, B. P.; Wu, X.; Gunn, J. T.; Buchwald, S. L. *Heterocycles* **2010**, *80*, 1215. (i) See refs 14 and 15.

(12) Serjeant, E. P.; Dempsey, B., Eds. *Ionization Constants of Organic Acids in Solution*; IUPAC Chemical Data Series No. 23; Pergamon Press: Oxford, UK, 1979 (cf. methanesulfonic acid, $pK_a = -1.9$; *p*-toluenesulfonic acid, $pK_a = -2.8$; benzenesulfonic acid, $pK_a = -6.5$; triflic acid, $pK_a = -14.9$).

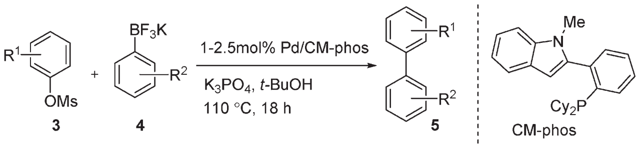
(13) For Ni-catalyzed Suzuki-type coupling with tosylate partners, see: (a) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049. (b) Tang, Z. Y.; Hu, Q. S. *J. Am. Chem. Soc.* **2004**, *126*, 3058. For Pd-catalyzed Suzuki-type coupling with tosylate partners, see: (c) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (d) Zhang, L.; Meng, T.; Wu, J. *J. Org. Chem.* **2007**, *72*, 9346. (e) So, C. M.; Lau, C. P.; Chan, A. S. C.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7731.

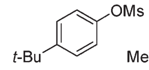
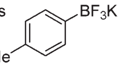
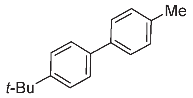
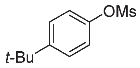
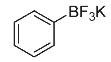
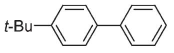
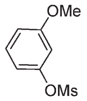
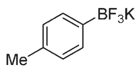
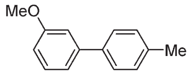
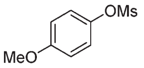
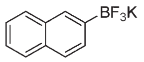
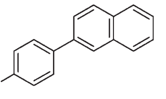
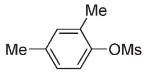
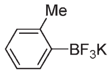
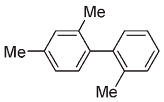
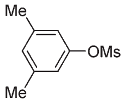
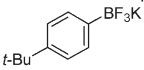
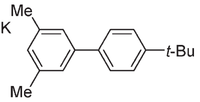
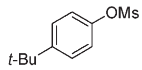
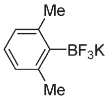
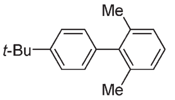
(14) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059. One nonactivated ArOMs + Ar′BF_3K was reported.

(15) For an effective system reported by Buchwald and co-workers focusing on heteroaryl couplings, see: Bhayana, B.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 3954.

(16) (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2003. (b) Molander, G. A.; Canturk, B.; Kennedy, L. E. S. *J. Org. Chem.* **2009**, *74*, 973.

TABLE 2. Pd-Catalyzed Suzuki−Miyaura Coupling of Nonactivated Aryl Mesylates[a]



entry	ArOMs	Ar'BF$_3$K	product	mol% Pd	%yield[b]
1				1	89
2				1	97
3				2	89
4				2.5	70
5				1	63
6				1	93
7				2	77

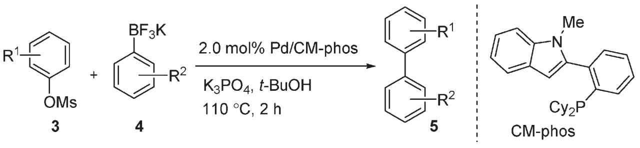
[a] Reaction conditions: ArOMs (1.0 mmol), Ar′BF$_3$K (2.0 mmol), K$_3$PO$_4$ (3.0 mmol), Pd(OAc)$_2$:ligand = 1:4 (mol % as indicated, t-BuOH (3.0 mL) with stirring for 18 h at 110 °C under nitrogen (reaction times were not optimized for each substrate). [b] Isolated yields.

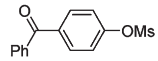
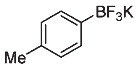
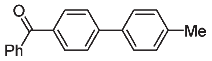
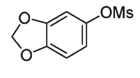
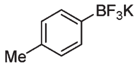
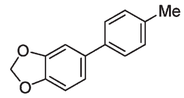
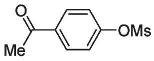
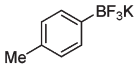
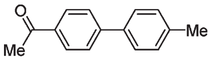
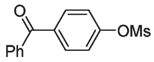
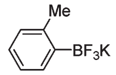
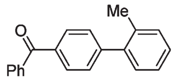
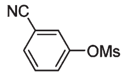
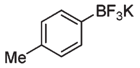
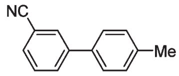
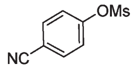
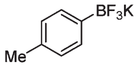
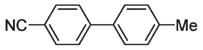
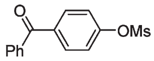
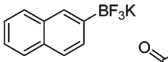
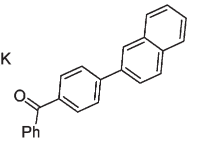
(Table 2, entry 5). The highly sterically hindered potassium aryltrifluoroborate (Table 2, entry 7) could couple with aryl mesylate to furnish product in moderate to good yield.

A variety of common functional groups were compatible under these mild reaction conditions. The functionalized aryl mesylates containing nitriles, keto, and benzodioxolyl groups were found to be effective electrophiles (Table 3). Notably, the couplings of these aryl mesylates were completed within 2 h in the presence of 2 mol % catalyst loading.

Apart from a variety of aryl mesylates, heteroaryl mesylates and trifluoroborates were also effective coupling partners. Quinolyl and benzothiazolyl substrates showed good yields of the corresponding coupling products (Table 4, entries 1 and 6). Thienyl nucleophiles were good nucleophilic partners that provided moderate to good yield of the products (Table 4, entries 1−6). Particularly noteworthy was the fact that the thienyl trifluoroborate salt was much superior to the corresponding thenylboronic acid in this coupling reaction (Table 4, entries 3 vs 4). Heterobiaryl synthesis is mostly a challenge in cross-coupling reactions. We were also able to achieve these couplings in modest to good yields (Table 4 entries 1, 5, and 6).

TABLE 3. Pd-Catalyzed Suzuki−Miyaura Coupling of Functionalized Aryl Mesylates[a]



entry	ArOMs	Ar'BF$_3$K	product	mol% Pd	%yield[b]
1				2	89
2				2	85
3				2	87
4				2	97
5				2	88
6				2	90
7				2	67

[a] Reaction conditions: ArOMs (1.0 mmol), Ar′BF$_3$K (2.0 equiv), K$_3$PO$_4$ (3.0 equiv), Pd(OAc)$_2$:ligand = 1:4, t-BuOH (3.0 mL) with stirring for 2 h at 110 °C under nitrogen. [b] Isolated yields.

Vinyl and alkyltrifluoroborates were also tested as the coupling partners (Scheme 1). 4-*tert*-Butylphenyl mesylate coupled with potassium *n*-butyltrifluoroborate and potassium *trans*-styryltrifluoroborate in good yields.

Conclusion

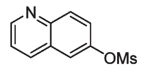
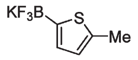
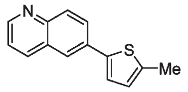
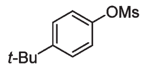
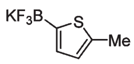
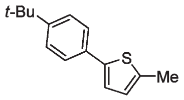
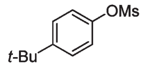
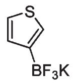
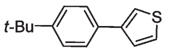
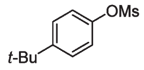
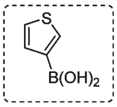
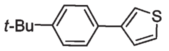
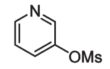
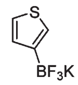
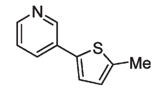
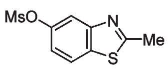
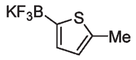
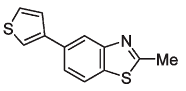
In conclusion, we have reported the first general Suzuki−Miyaura coupling of unactivated aryl mesylates and aryltrifluoroborate salts. The Pd-CM-phos catalyst system is effective for the coupling of a range of mesylate substrates containing various common functional groups. In addition to the feasibility in using heteroaryl mesylates and trifluoroborate salts as electrophiles and nucleophiles, respectively, vinyl and alkyltrifluoroborates have also been shown as compatible coupling partners.

Experimental Section

General Procedure for Suzuki−Miyaura Coupling of Aryl Mesylates. Pd(OAc)$_2$ (2.3 mg, 0.010 mmol) and CM-phos (Pd:L = 1:4) were loaded into a Schlenk tube equipped with a

TABLE 4. Pd-Catalyzed Suzuki–Miyaura Coupling of Heteroaryl Mesylates with Potassium Heteroaryltrifluoroborate Salts[a]

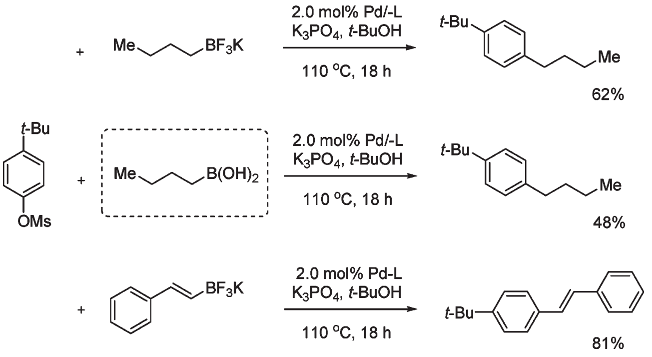
$$\text{Het-ArOMs} + \text{Het-Ar'BF}_3\text{K} \xrightarrow[\text{K}_3\text{PO}_4,\ t\text{-BuOH},\ 110\ ^\circ\text{C},\ 18\ \text{h}]{\text{1-2 mol\% Pd/CM-phos}} \text{HetAr-HetAr'}$$

entry	Het- or Ar-OMs	Het-Ar'BF$_3$K	product	mol% Pd (time)	%yield[b]
1				1 (2 h)	71
2				1 (18 h)	79
3				1.5 (18 h)	82
4				2 (24 h)	32
5				2 (3 h)	66
6				2 (3 h)	57

[a] Reaction conditions: Het- or ArOMs (1.0 mmol), HetAr-BF$_3$K (2.0 mmol), K$_3$PO$_4$ (3.0 mmol), Pd(OAc)$_2$:ligand = 1:4, *t*-BuOH (3.0 mL) with stirring under nitrogen for the indicated periods. [b] Isolated yields.

Teflon-coated magnetic stir bar. The tube was evacuated and flushed with nitrogen several times. Precomplexation was applied by adding freshly distilled dichloromethane (1 mL) and Et$_3$N (100 μL) into the tube. The solution was stirred and warmed with a hair dryer for 1 to 2 min until the solvent started boiling. The solvent was then evaporated under high vacuum. 4-*tert*-Butylphenyl mesylate (1.0 mmol), potassium *p*-tolyltrifluoroborate (2.0 mmol), and K$_3$PO$_4$ (3.0 mmol) were loaded into the tube, and the system was further evacuated and flushed with nitrogen several times. The solvent *tert*-butanol (3.0 mL) was then added. The tube was stirred at room temperature for several minutes and then placed into a preheated oil bath (110 °C) for the time period indicated in the table. After completion of reaction as judged by GC analysis, the reaction tube was allowed to cool to room temperature and quenched with water and diluted with EtOAc. The organic layer was separated and the aqueous layer was washed with EtOAc. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230–400 mesh) to afford the desired product. ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.58 (s, 9H), 2.59 (s, 3H), 7.44 (d, J = 8.0 Hz, 2H), 7.66–7.76 (m, 6H); ^{13}C NMR (100 MHz,CDCl$_3$) δ 21.1, 31.4, 34.4, 125.6, 126.6, 126.8, 129.4, 136.6, 138.2, 138.2, 149.8; MS (EI) *m*/*z* (rel intensity) 224 (M$^+$, 35), 209 (100), 193 (5), 181 (12), 165 (10).

SCHEME 1. Feasibility of Pd-Catalyzed Suzuki–Miyaura Coupling of Vinyl- and Alkyltrifluoroborate Salts[a]



[a] Reaction conditions: ArOMs (1.0 mmol), nucleophilic partner (2.0 mmol), K$_3$PO$_4$ (3.0 mmol), Pd(OAc)$_2$:L = 1:4, L = CM-phos, *t*-BuOH (3.0 mL) with stirring under nitrogen. Isolated yields were reported.

Acknowledgment. We thank the Research Grants Council of Hong Kong (CERG: PolyU5005/07P), PolyU Internal Competitive Research Grant (A-PG13), and the University Grants Committee Areas of Excellence Scheme (AoE/P-10/01) for financial support. The authors are grateful to Prof. Albert S. C. Chan's research group (PolyU Hong Kong) for sharing the GC instruments.

Supporting Information Available: Detail experimental procedures, compound characterization data, and copies of ^{1}H NMR, ^{13}C NMR, MS, and HRMS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.