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Nickel-Catalyzed C–O Activation of Phenol Derivatives with Potassium Heteroaryltrifluoroborates

Gary A. Molander* and Floriane Beaumard

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

gmolandr@sas.upenn.edu

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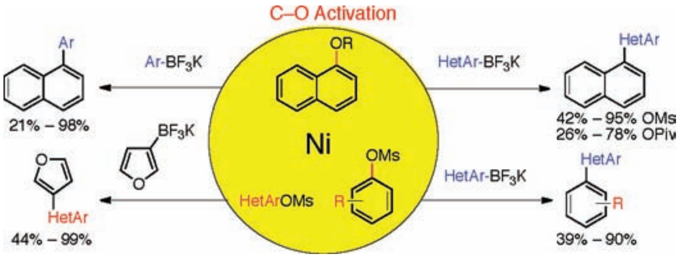
ABSTRACT



A general method based on nickel-catalyzed C–O activation of various phenol derivatives with potassium (hetero)aryltrifluoroborates has been developed. A large number of heterobiaryls can be easily obtained with yields up to 99% using methanesulfonate cross-coupling partners.

Transition-metal-catalyzed cross-coupling reactions are among the most powerful transformations available to create carbon–carbon or carbon–heteroatom bonds. In particular, the Suzuki–Miyaura reaction represents one of the most common and reliable methods because of its tolerance of a wide range of functional groups, as well as the commercial availability and stability of its reagents.[1] Usually, aryl halides and triflates serve as electrophilic coupling partners, but there often remain some limitations of these reaction partners because of their toxicity, their cost, or their inaccessibility.

An alternative is to use phenol derivatives bearing more environmentally sound, less expensive, and easier to handle nucleofuges. Palladium catalysts have shown promising results for the activation of the C–O bond when sulfonates such as tosylates[2] or mesylates[3] were used as leaving groups (LGs) but have been completely ineffective with the corresponding esters.[4] More reactive nickel catalysts have been used in cross-couplings of diverse phenol derivatives. Relatively unreactive tosylate[5] and mesylate[5b,6] groups were first engaged with success with arylboronic acid derivatives. Recently, ester- and amide-type nucleofuges (pivaloyl, acetyl,

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(1) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168. (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.

(2) For Pd-catalyzed cross-coupling of aryl tosylates, see: (a) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 194–202. (b) Petersen, M. D.; Boye, S. V.; Nielsen, E. H.; Willumsen, J.; Sinning, S.; Wiborg, O.; Bols, M. *Bioorg. Med. Chem.* **2007**, *15*, 4159–4174. (c) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819. (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.

(3) For Pd-catalyzed cross-coupling of aryl mesylates, see: (a) Percec, V.; Bae, J. Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060–1065. (b) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059–8063. (c) Bhayana, B.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 3954–3957. (d) Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2010**, *75*, 5109–5112.

(4) (a) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422–14423. (b) Li, Z.; Zhang, S. L.; Fu, Y.; Guo, Q. X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815–8823.

(5) For recent examples of Ni-catalyzed Suzuki cross-coupling of aryl tosylates, see: (a) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049–3051. (b) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447–3452. (c) Tang, Z. Y.; Hu, Q. S. *J. Am. Chem. Soc.* **2004**, *126*, 3058–3059. (d) Tang, Z.-Y.; Spinella, S.; Hu, Q.-S. *Tetrahedron Lett.* **2006**, *47*, 2427–2430. (e) Lipshutz, B. H.; Butler, T.; Swift, E. *Org. Lett.* **2008**, *10*, 697–700.

10.1021/ol101592r

benzoyl, carbonate, sulfamate, carbamate)[4a,7] as well as methyl ethers[8] have also been successfully used, emphasizing the importance of nickel as a general catalyst in C−O activation processes. Nearly all of these protocols employ a large excess (2−5 equiv) of the organoboron coupling partner.

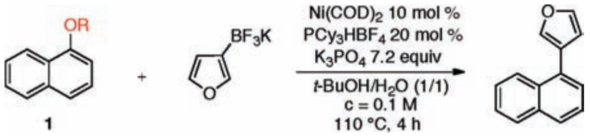
Despite the significant advances in the pool of available electrophiles and their cross-coupling, much effort remains to generalize the transformation. To date, very few examples of palladium-catalyzed C−O activation have been described with heteroarylboronic acids. Buchwald first reported a very efficient palladium cross-coupling of tosylated[2c] and mesylated[3c] phenols with an excess of the boron reagent (2 equiv). With the same kind of catalytic system, but decreasing the loading of the boron species to 1.1 equiv, Wu observed a low yield in the cross-coupling of tosylated phenol with potassium thiophene-2-yltrifluoroborate.[2d] During the course of our investigation, Kwong reported a palladium-catalyzed C−O activation of heteroaryl mesylates with a single potassium heteroaryltrifluoroborate in excess (2 equiv) to afford heterobiaryls with yields up to 82%.[3d] Moreover, all nickel-catalyzed systems have been limited to arylboronic acid derivatives. In view of the ubiquity of heterobiaryls in natural products, polyaromatic molecules, pharmaceuticals, and other useful materials, it is of interest to develop general protocols to forge C(heteroaryl)−C(aryl or heteroaryl) bonds.

Potassium organotrifluoroborates have emerged as alternative coupling partners that provide some advantages to sensitive boronic acid derivatives, which more easily undergo protodeboronation.[9] Herein, we disclose the first nickel-catalyzed Suzuki cross-coupling of phenol derivatives with potassium heteroaryltrifluoroborates. The developed reaction proceeds with exceptional heterocycle compatibility and generally high yields.

We initially chose the pivaloyl-protected naphthol as the substrate for the C−O activation. An extensive screening of various reaction parameters (e.g., choice of solvent, nickel catalyst, ligand, base, etc.) was carried out[10] and revealed the essential role of Ni(COD)$_2$ as a catalyst, while other Ni(II) and Ni(0) species failed. This reaction unusually occurs in the presence of a large amount of water in a protic solvent (*tert*-butyl alcohol/H_2O in a 1/1 ratio).[7a,c] Moreover, we were able to reduce the loading of potassium organotrifluoroborate to 1.3 equiv.

With the optimized conditions established for the pivaloyl LG **1d**, we next attempted to extend the process to various LGs on naphthol in the Suzuki−Miyaura cross-coupling with potassium furan-3-yltrifluoroborate (Table 1). Thus, the sulfonate LGs gave the best results, with mesylate **1a** (which afforded the desired compound in quantitative GC yield) functioning better than the tosylate **1b** and the sulfamate **1c**. Both ester (Piv and Boc)- and amide (CONEt$_2$)-type LGs, even though they are less reactive, are also well-tolerated. The benzoyl group proved much less efficient, and the methyl ether is not suitable under these conditions.

Table 1. Influence of the Nucleofuge on Naphthol for the Nickel-catalyzed C−O Activation



entry	OR		yield (%)[a]
1	OMs	**1a**	100
2	OTs	**1b**	85
3	OSO_2NMe_2	**1c**	85
4	OPiv	**1d**	68
5	OBoc	**1e**	59
6	$OCONEt_2$	**1f**	55
7	OBz	**1g**	37
8	OMe	**1h**	/

[a] Relative GC yield determined using dodecane as the internal standard.

Encouraged by these results, we pursued our study by varying the potassium heteroaryltrifluoroborates with two classes of derivatives: mesylates (**1a**) and pivaloylates (**1d**) (Table 2). We synthesized six heterobiaryls **2a**−**f** from these derivatized naphthols (Table 2, entries 1−6), and the same tendency as previously described was observed: the mesylated compounds always afforded the heteroaryls with higher yields than the pivaloyl compounds.[11] Although the yields are moderate with the pivaloyl substrate, the current method complements and even improves upon previous methods in its use of reduced quantities of the organoboron reagent[4a] and is the first metal-catalyzed cross-coupling reaction between a phenolic pivaloylate and a heteroarylboron reagent.

Five-membered, six-membered, and benzannulated heterocycles have successfully been engaged with a mesylated naphthol with yields up to 95% (Table 2, entry 8). 3-Furanyl and 3-thiophene-yl derivatives were coupled with very high yields, 93% and 90%, respectively (Table 2, entries 1 and 3). Although the 2-boronated counterparts usually suffer from facile protodeboronation, the desired products **2c** and **2g** were obtained with good yields. Pyridine derivatives, known as difficult cross-coupling partners owing to their low stability

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(6) For examples of Ni-catalyzed Suzuki cross-coupling of aryl mesylates, see: (a) Percec, V.; Bae, J. Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060–1065. (b) Ueda, M.; Saitoh, A.; Oh-tani, S.; Miyaura, N. *Tetrahedron* **1998**, *54*, 13079–13086. (c) Kobayashi, Y.; William, A. D.; Mizojiri, R. *J. Organomet. Chem.* **2002**, *653*, 91–97. (d) Kuroda, J. I.; Inamoto, K.; Hiroya, K.; Doi, T. *Eur. J. Org. Chem.* **2009**, 2251–2261.

(7) (a) Guan, B. T.; Wang, Y.; Li, B. J.; Yu, D. G.; Shi, Z. J. *J. Am. Chem. Soc.* **2008**, *130*, 14468–14470. (b) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748–17749. (c) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750–17752. (d) Xu, L.; Li, B. J.; Wu, Z. H.; Lu, X. Y.; Guan, B. T.; Wang, B. Q.; Zhao, K. Q.; Shi, Z. J. *Org. Lett.* **2010**, *12*, 884–887.

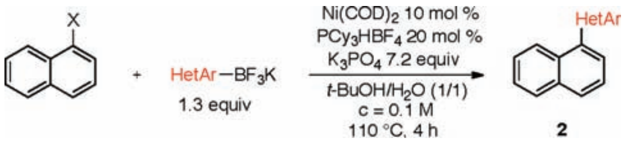
(8) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866–4869.

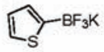
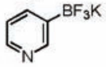
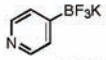
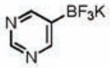
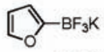
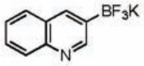
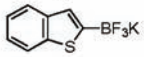
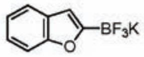
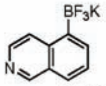
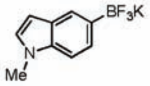
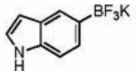
(9) (a) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240–9261. (b) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 973–980. (c) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.

(10) See the Supporting Information for more details about the screening.

(11) For potassium thiophene-2- and 3-yltrifluoroborates with pivaloyl-protected naphthol, the best yields were obtained with slightly different optimized conditions: a mixture of dioxane/H_2O (1/1), c = 0.05, and *t*-BuPCy$_2$.

Table 2. Scope of Potassium Heteroaryltrifluoroborates



entry	HetAr-BF$_3$K			yield (%)
1		X = OMs X = OPiv	**2a**	93 78
2		X = OMs X = OPiv	**2b**	90 75^{a}
3		X = OMs X = OPiv	**2c**	64 $26^{a,b}$
4		X = OMs X = OPiv	**2d**	82 60
5		X = OMs X = OPiv	**2e**	69 32^{b}
6		X = OMs X = OPiv	**2f**	83 26^{b}
7		X = OMs	**2g**	79
8		X = OMs	**2h**	95
9		X = OMs	**2i**	42
10		X = OMs	**2j**	81
11		X = OMs	**2k**	91
12		X = OMs	**2l**	74
13		X = OMs	**2m**	90^{c}

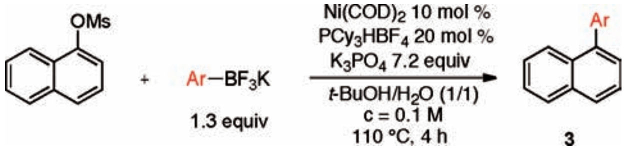
[a] Dioxane/H$_2$O (1/1), c = 0.05, and t-BuPCy$_2$. [b] Relative GC yield determined using dodecane as an internal standard. [c] With 10% of impurities that cannot be separated.

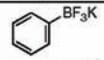
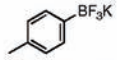
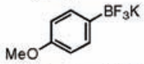
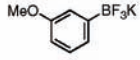
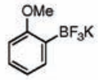
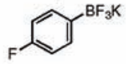
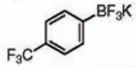
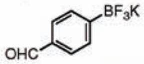
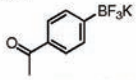
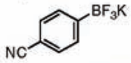
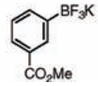
and electron deficiency,[12] react efficiently to afford the desired compounds **2d** and **2e** in good yields (Table 2, entries 4 and 5). Pyrimidine, quinoline, benzofuran, isoquinoline, and indole derivatives are also very good nucleophilic partners, leading to the desired compounds **2f**,**h**,**j**−**l** with yields ranging from 74% to 95%. Even indole derivative **2m** was obtained in 90% yield. Only the 2-benzothiophene was more sensitive to protodeboronation, affording **2i** in a yield of 42%.

Notably, by increasing the scale of the reaction to 5.0 mmol, the Ni(COD)$_2$ loading can be decreased to 2 mol % to obtain **2a** with a yield of 86% (compared to 93% on a 0.25 mmol scale).[13] Importantly, a comparable loading of the more expensive palladium catalyst is required for the same kind of C−O activation, emphasizing the role of nickel as an efficient and cost-effective catalyst.[14]

We next evaluated the tolerance of the method by introducing functionalized potassium aryltrifluoroborates (Table 3). We were pleased to observe that both electron-donating (Table 3, entries 2−5) and electron-withdrawing groups (Table 3, entries 7, 9, and 10) on the aryl ring did not affect the reaction. The desired compounds **3a**−**e**,**g**,**i**,**j** were obtained with yields above 71%. The position of the methoxy substituent on the aryl ring was also varied, and even in the more sterically hindered *ortho*-position, the desired compound **3e** was obtained with a yield of 85%. The low yields observed with the aldehyde and ester substituents underscore the limits of the method. The aldehyde substrate afforded a complex mixture of products, whereas the ester substrate only proceeded to ∼60% conversion, even after extended periods of time.

Table 3. Scope of Potassium Aryltrifluoroborates



entry	Ar-BF$_3$K		yield (%)
1		**3a**	71
2		**3b**	76
3		**3c**	91
4		**3d**	98
5		**3e**	85
6		**3f**	90
7		**3g**	71
8		**3h**	21
9		**3i**	94
10		**3j**	71
11		**3k**	46

Various mesylated heteroaryls were also investigated with the potassium furan-3-yltrifluoroborate as coupling partners

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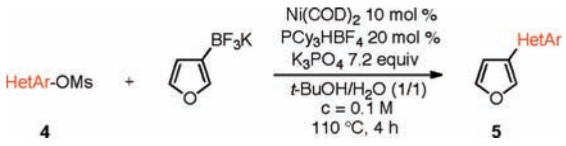
[12] Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.

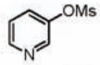
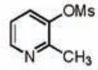
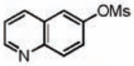
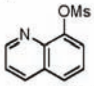
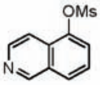
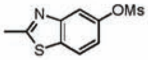
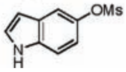
[13] 1-NaphthOMs (1 equiv), furan-3-ylBF$_3$K (1.3 equiv), Ni(COD)$_2$ (2 mol %), PCy$_3$HBF$_4$ (4 mol %), and K$_3$PO$_4$ (7.2 equiv), 110 °C, 24 h.

[14] Current prices for the catalysts are as follows: bis(1,5-cyclooctadiene)nickel(0), \$27/1 g; palladium(II) acetate, \$59/1 g.

(Table 4). The cross-couplings proceeded in very high yields ranging from 70% to 99% for all the pyridine derivatives **5a**−**e** (Table 4, entries 1−5). Benzothiazole **4f** also appears to be a good electrophilic partner to obtain the desired heterobiaryl **5f** in 77% yield. Only indole partner **4g** showed a lower reactivity, affording the desired compound **5g** in a moderate yield.

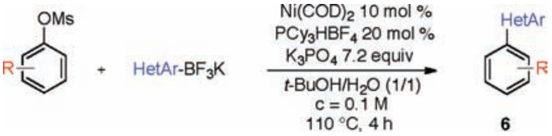
Table 4. Scope of Heteroaryl Mesylates

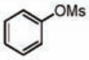
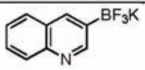
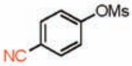
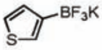
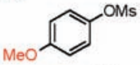
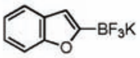
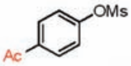
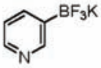
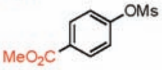
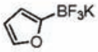
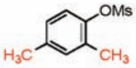
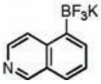


entry		HetAr-OMs	product	yield (%)
1	**4a**		**5a**	80
2	**4b**		**5b**	70
3	**4c**		**5c**	99
4	**4d**		**5d**	92
5	**4e**		**5e**	87
6	**4f**		**5f**	77
7	**4g**		**5g**	44

Finally, functionalized aryl mesylates were also tested with different potassium heteroaryltrifluoroborates (Table 5). The various electronic properties of the different substituents on the electrophilic counterpart do not seem to influence the reaction. Heteroaryls bearing a nitrile (**6b**), a methoxy group (**6c**), a ketone (**6d**), or an ester (**6e**) were obtained with good to excellent yields (Table 5, entries 1−5). Even a hindered, deactivated aryl mesylate (entry 6) reacts with potassium isoquinolin-5-yltrifluoroborate to generate the desired compound **6f** with a yield of 39%.

Table 5. Scope of Functionalized Mesylated Phenols with Various Potassium Heteroaryltrifluoroborates



entry	Ar-OMs	HetAr-BF$_3$K	product	yield (%)
1			**6a**	75
2			**6b**	68
3			**6c**	70
4			**6d**	90
5			**6e**	81
6			**6f**	39

In conclusion, we have disclosed the first general nickel-catalyzed method for C−O activation with potassium heteroaryltrifluoroborates. Promising results were obtained when the pivaloyl moiety was used as the nucleofuge, and very good yields were achieved when the mesyl group was employed. The reaction is very tolerant of a large range of activated and deactivated nucleophilic potassium heteroaryl- and functionalized aryltrifluoroborates. Numerous electrophilic heteroaryl and functionalized aryl partners can also be introduced with high cross-coupling yields. Moreover, scaling up the reaction, the nickel catalyst loading can be decreased to 2 mol %, affording a very efficient and inexpensive method for C−O activation.

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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.

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