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Efficient Catalyst for the Suzuki–Miyaura Coupling of Potassium Aryl Trifluoroborates with Aryl Chlorides

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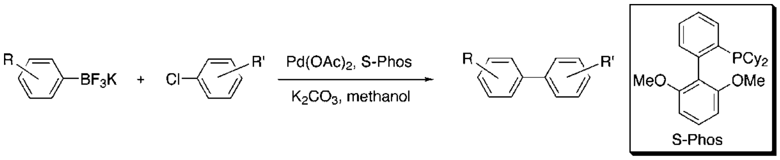
ABSTRACT



Palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of aryl- and heteroaryl chlorides with potassium aryl- and heteroaryltrifluoroborates have been accomplished with the supporting ligand S-Phos in good to excellent yield. Hindered biaryls and substrates containing a variety of functional groups can be prepared. Suzuki–Miyaura couplings of a 3-pyridyl boron-based nucleophile with aryl- and heteroaryl chlorides proceed in good to very good yield.

The ubiquity of palladium-catalyzed Suzuki−Miyaura coupling processes[1] exists, in part, due to the nontoxic, mild, and air- and water-stable nature of the boronic acid nucleophile. In other cross-coupling processes such as Stille and Kumada couplings toxic reagents and/or reactive carbanion intermediates are generated, which may not be compatible with certain functional groups (i.e., ketones, aldehydes, nitriles, etc.). Negishi coupling reactions[2] are a good compromise, yet the preparation and storage of the requisite organozinc reagent may not be trivial. A drawback associated with the use of boronic acids is the structural ambiguity, namely, the formation of the trimeric anhydride (boroxine),[3] associated with them. The purity of commercially available boronic acids is also of concern. Although purification via recrystallization, usually from water, affords a boronic acid of higher purity, removal of the water generally results in formation of mixtures of boronic acid and the corresponding boroxine.

The use of boronate esters and trifluoroborates, easily prepared by treatment of a boronic acid with a diol, often pinacol, or with potassium hydrogen fluoride,[4] respectively, has circumvented the above-described issues. Isolation and purification of these boronic acid alternatives can be achieved via chromatography and recrystallization from organic solvents. Batey[5] and Molander[6] have reported conditions that allow the coupling of tetrabutylammonium aryl trifluoroborates and potassium aryl trifluoroborates, respectively, with aryl iodides and bromides. However, the only reported couplings with aryl chlorides[6] employ activated (electron-deficient) nitrogen-containing heterocycles (chloropyrazine and 2,4,6-trichloropyridimine). As aryl chlorides are often more readily available and less expensive than their bromide and iodide counterparts, we sought to develop conditions that effect the coupling of aryl trifluoroborates with aryl- and heteroaryl chlorides. Herein, we report reaction conditions,

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[1] Recent reviews: (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11−59. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1470. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695.

[2] Recent review: Lessene, G. *Aust. J. Chem.* **2004**, *57*, 107-.

[3] Onak, T. *Organoborane Chemistry*; Academic Press: New York, 1975

[4] (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020−3027. (b) Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460−2470.

[5] Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099−9103.

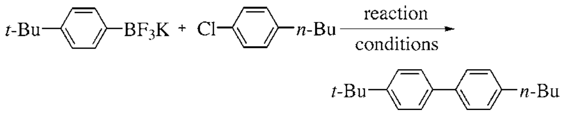
[6] (a) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867−1870 (b) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302−4314.

10.1021/ol0491686 CCC: $27.50

based upon ligand **1**,[7] that allow these coupling processes to occur in good to excellent yield.

As a test for the optimization of reaction parameters, an electronically neutral aryl trifluoroborate, potassium 4-*tert*-butylphenyltrifluoroborate, and electronically neutral aryl chloride, 4-*n*-butylchlorobenzene, were used as substrates (Table 1). Employing our standard conditions[7] for Suzuki–Miyaura coupling procedures using boronic acids with K_3PO_4 or KF as a base and anhydrous toluene or anhydrous THF as a solvent afforded <5% conversion of the aryl chloride. The use of an anhydrous solvent may cause this poor conversion of aryl chloride, as previous studies[5,8,9] have suggested that the aryl trifluoroborate species does not undergo transmetalation, but rather water is required for the efficient coupling via a possible aryl difluorohydroxyborate intermediate. In accord with this suggestion, with laboratory-grade alcohol as reaction solvents, we obtained superior results. For example, switching to 2-propanol increased the conversion of the aryl chloride to 65% using KF and 85% using K_3PO_4 as the base (Table 1, entries 3 and 4). However, only the use of K_2CO_3 as a base allowed full conversion to the cross-coupled product (entries 6 and 7). Partial reduction (10%) of the aryl chloride was observed when refluxing 2-propanol was employed as a solvent. This undesired process was avoided when the reaction was performed at a lower temperature in methanol. Hence, we found the conditions employed in entry 7 to be optimal for this particular coupling process. It is important to note that the amount of palladium used in subsequent reactions was not minimized in each individual case; instead, the use of 0.5% $Pd(OAc)_2$ allowed full conversion of the aryl chlorides (except 2-chloro-*m*-xylene) in Table 2 within 12 h.

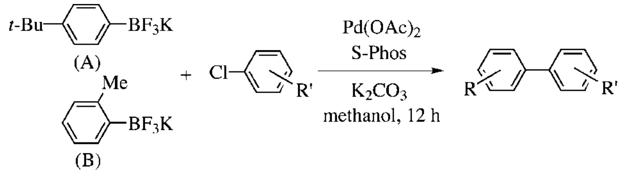
Table 1. Reaction Optimization on the Coupling of Potassium 4-*tert*-Butylphenyltrifluoroborate with 4-*n*-Butylchlorobenzene[a]

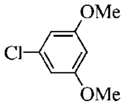
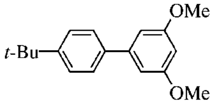
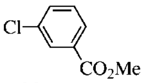
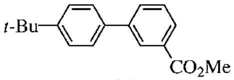
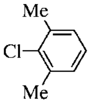
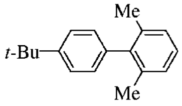
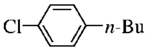
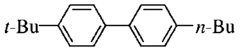
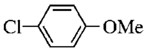
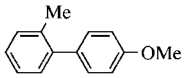
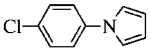
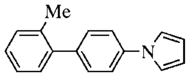
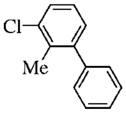
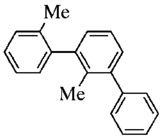
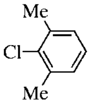
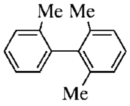


entry	base	solvent	*T* (°C)	GC conversion (%)
1	none	EtOH	80	15
2	none	IPA	80	20
3	KF	IPA	80	65
4	K_3PO_4	IPA	80	85
5	K_2CO_3	*t*BuOH	80	30
6	K_2CO_3	IPA	80	100 (10% reduction)
7	K_2CO_3	MeOH	67	100

[a] Reaction conditions: 1.1 equiv of $ArBF_3K$, 3 equiv of base, 1% $Pd(OAc)_2$, 2% S-Phos.

Table 2. Suzuki–Miyaura Coupling of Aryl Chlorides with Aryl Trifluoroborates[a]



entry	aryl BF_3K	aryl chloride	% Pd	product	% yield[b]
1	A		0.5		93[c]
2	A		0.5		96[c]
3	A		1		91[c]
4	A		0.05		90[d]
5	B		0.5		89
6	B		0.5		96
7	B		0.5		84
8	B		2		92[c,e,f]

[a] Reaction conditions: 1.1 equiv of $ArBF_3K$, 3 equiv of K_2CO_3, $Pd(OAc)_2$:S-Phos (1:2), methanol, reflux, 12 h. [b] Isolated yields are based upon an average of two runs. [c] Reaction temperature was 50 °C. [d] Reaction time was 16 h. [e] Performed with 1.5 equiv of $ArBF_3K$. [f] Reaction time was 20 h.

These standard conditions[10] were used in the coupling of various aryl chlorides with an unhindered aryl trifluoroborate and one possessing an *ortho*-methyl substituent (Table 2). Each reaction proceeded to full conversion of aryl chloride, with minimal or no reduction. Coupling reactions where electron-rich or hindered aryl chlorides were used also proceeded in excellent yield.

We also found that 2,2′,6-trimethylbiphenyl can been synthesized in 92% isolated yield via the coupling of potassium *o*-tolyltrifluoroborate with 2-chloro-*m*-xylene with 2% $Pd(OAc)_2$ at 50 °C. To date, the most hindered biaryl formed via coupling with an aryl trifluoroborate salt is 2,4,6-trimethylbiphenyl, synthesized via the coupling of potassium phenyltrifluoroborate with 2-bromomesitylene with 1% $PdCl_2(dppf)$ as a catalyst in 70% isolated yield.[6b]

To evaluate the minimum amount of palladium precatalyst required for the coupling of an aryl trifluoroborate with an

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(7) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876.

(8) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393–396.

(9) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.

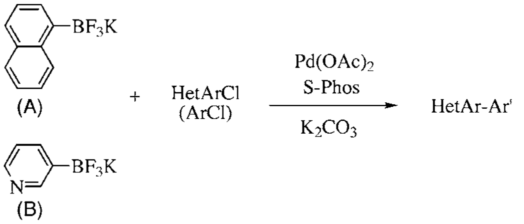
(10) See Supporting Information for a general procedure of the Suzuki–Miyaura coupling of potassium aryl trifluoroborates with aryl chlorides using S-Phos.

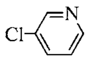
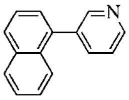
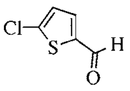
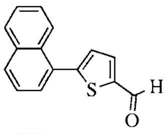
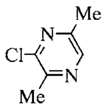
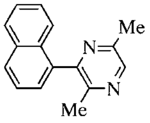
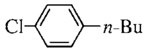
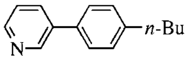
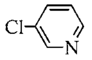
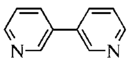
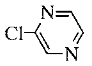
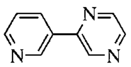
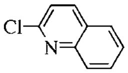
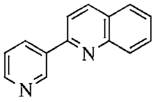
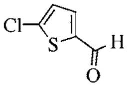
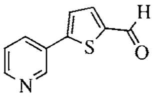
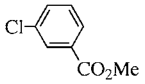
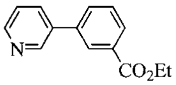
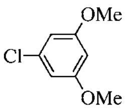
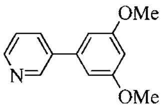
aryl chloride, we returned to the reaction of potassium 4-*tert*-butylphenyltrifluoroborate and 4-*n*-butylchlorobenzene. Catalyst loadings of 0.01, 0.02, and 0.03% $Pd(OAc)_2$ were examined, but full conversion of the aryl chloride was not observed. However, the use of 0.05% $Pd(OAc)_2$ did provide the desired product in 90% isolated yield. We note that this catalyst loading is substantially higher than a similar example with phenyl boronic acid and 4-*n*-butylchlorobenzene, utilizing ligand **1** (30 ppm Pd).[7] The higher quantity of Pd required is probably due to more rapid catalyst deactivation (i.e., formation of palladium black)[11] in a nonanhydrous protic solvent compared to the anhydrous toluene used in the earlier report.

As the role of aromatic heterocycles is becoming increasingly important and as the need to prepare them quickly and efficiently from commercially available starting materials is growing, we attempted couplings where the product is heteroaromatic. A variety of nitrogen- and sulfur-containing heteroaryl chlorides can be converted to product in good to excellent yields (Table 3). The reaction of potassium naphthyltrifluoroborate and 5-chloro-2-thiophenecarboxaldehyde demonstrates not only tolerance for heteroaryl chlorides but also good functional group compatibility with the reaction conditions.

According to a recent MDL Drug Data Report,[12] the most common heterocycle in pharmaceutically active compounds is pyridine. The cross coupling of a 3-pyridyl nucleophile with aryl halides has been effective with a pyridyllithium, pyridyl Grignard, or pyridyl zinc chloride reagent, using Pd,[12] Ni,[12] or Fe[13] complex as the catalyst. However, to the best of our knowledge, there are no *general* coupling conditions reported of aryl chlorides with a boron-derived 3-pyridyl nucleophile. Although 3-pyridyl boronic acid is commercially available, it is extremely expensive (250 mg/$141.20, Acros). Molander and Biolatto recently developed[6b] a high-yielding one-pot synthesis of potassium 3-pyridyltrifluoroborate. However, the coupling of this trifluoroborate has only been reported with two aryl bromides.[5,6b] With the use of **1** and switching from methanol to ethanol at 72 °C, the coupling of potassium 3-pyridyltrifluoroborate with aryl- and heteroaryl chlorides proceeded in good to very good yields (Table 3). The products in entries 6 and 7 have been synthesized previously via Kumada processes[12,13] and the biaryl in entry 7 from the Pd-catalyzed coupling of 3-pyridyl-9-BBN.[14] However, in both of these processes, the 3-pyridyl nucleophile is air- and water-sensitive and is generated in situ. Gratifyingly, by using potassium 3-pyridyl trifluoroborate, the reaction conditions were sufficiently mild to permit the efficient cross coupling of substrates bearing either an ester or aldehyde group (entries 9 and 8, respectively). Also, nonheterocyclic electron-rich, -poor, and -neutral aryl chlorides reacted with potassium 3-pyridyl trifluoroborate in good yields (entries 4, 9, and 10). Under the reaction conditions employed, methyl 3-chlorobenzoate (entry 9) was fully converted to the ethyl derivative when ethanol was used as a solvent.

Table 3. Suzuki−Miyaura Coupling of Heterocycles



entry	aryl BF_3K	aryl halide	% Pd	product	% yield[b]
1	A		0.5		98[c]
2	A		1		85[c]
3	A		0.5		86[d]
4	B		3		73
5	B		3		75
6	B		3		76
7	B		5		81
8	B		3		75
9	B		3		79
10	B		3		82

[a] Reaction conditions: 1.5 equiv of $ArBF_3K$, 3 equiv of K_2CO_3, $Pd(OAc)_2$:S-Phos (1:2), ethanol, 72 °C, 22 h. [b] Isolated yields are based upon an average of two runs. [c] Performed with 1.1 equiv of $ArBF_3K$ methanol, reflux, 16 h. [d] Performed with 1.1 equiv of $ArBF_3K$ methanol, 40 °C, 16 h.

In conclusion, the Pd-catalyzed coupling of potassium aryl- and heteroaryl trifluoroborates with aryl- and heteroaryl chlorides proceeds in good to excellent yields with the use

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(11) Tromp, M.; Sietsma, J. R. A.; van Bokhoven, J. A.; van Strijdonck, G. P. F.; van Haaren, R. J.; van der Eerden, A. M. J.; van Leeuwen, P. W. N. M.; Koningsberger, D. C. *Chem. Commun.* **2003**, 128−129.

(12) Bonnet, V.; Mongin, F.; Trécourt F.; Breton, G.; Marsais, F.; Knochel, P.; Quéguiner, G. *Synlett* **2002**, *6*, 1008−1010.

(13) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856−13863.

(14) Ishikura, M.; Oda, I.; Terashima, M. *Heterocycles* **1985**, *23*, 2375−2386.

of K_2CO_3 as a base, methanol or ethanol as a solvent, and **1** as the supporting ligand. The first general method for coupling a 3-pyridyl-based boron derivative with aryl- and heteroaryl chlorides has been realized. These methods should find utility in the construction of pyridine-containing heterocycles with a variety of functional groups.

Acknowledgment. We thank the National Institutes of Health (GM 46059) for support for this work. We are grateful to Merck, Pfizer, and Novartis for additional support. We also thank Engelhard for their kind donation of precious metals, including the $Pd(OAc)_2$ that was used in this work.

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

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