ORGANIC LETTERS

2002
Vol. 4, No. 11
1867−1870

Efficient Ligandless Palladium-Catalyzed Suzuki Reactions of Potassium Aryltrifluoroborates

Gary A. Molander* and Betina Biolatto

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

gmolandr@sas.upenn.edu

Received March 8, 2002

ABSTRACT

$$R_1BF_3K \quad + \quad R_2X \quad \xrightarrow[\text{methanol, reflux}]{\substack{Pd(OAc)_2\ (0.5\%\ mol) \\ \\ K_2CO_3\ (3\ equiv)}} \quad R_1\text{-}R_2$$

R_1 = aryl or heteroaryl
R_2 = aryl or heteroaryl
X = halide, triflate

The ligandless palladium-catalyzed Suzuki cross-coupling reaction of potassium aryl- and heteroaryltrifluoroborates with aryl- or heteroaryl halides or triflates proceeds readily with very good yields. The cross coupling can be effected in methanol or water, in the open air, using $Pd(OAc)_2$ as a catalyst in the presence of K_2CO_3. A variety of functional groups are tolerated.

The Suzuki cross-coupling reaction, which involves the coupling of an organoboron compound with an electrophile, has become an extremely useful method in organic synthesis.[1] In general, boronic acids or esters bearing sp^2-hybridized substituents react very well under coupling conditions. However, the boronic acids are often subject to dimerization and cyclic trimerization with loss of water to form boronic acid anhydrides and boroxines, respectively, and the determination of precise stoichiometry can be extraordinarily difficult, requiring an excess of these compounds in the coupling reactions. On the other hand, potassium organotrifluoroborate salts offer solutions for these problems. These salts are easily prepared[2] and purified, and thus they are easier to handle. Genêt and co-workers[3] and Chen and Xia[4] have demonstrated that aryl- and heteroaryltrifluoroborates couple well with aryldiazonium and diaryliodonium ions, respectively, under both ligand and ligandless conditions, even in the presence of halogen functionalities on the substrates. These reactions were carried out in the absence of base. Fu and co-workers[5] attempted the coupling reaction of an aryl bromide with potassium *o*-tolyltrifluoroborate with $Pd_2(dba)_3$/$P(t\text{-}Bu)_3$ in the absence of a base, but no coupling was observed. Previous work in our laboratory demonstrated the feasibility of the cross-coupling reaction of potassium alkyl-[6] and alkenyltrifluoroborates[7] with different aryl and alkenyl halides and triflates, using $PdCl_2(dppf)\cdot CH_2Cl_2$ as a catalyst in the presence of Cs_2CO_3 or Et_3N. Recently, Batey and Quach[8] reported the synthesis and cross-coupling reactions of tetrabutylammonium organotrifluoroborate salts with a

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(1) For reviews see (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (c) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; VCH: Weinheim, Germany, 1998; pp 49−97.

(2) (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.

(3) (a) Darses, S.; Jeffery, T.; Brayer, J.-L.; Demoute, J.-P.; Genêt, J.-P. *Bull. Soc. Chim. Fr.* **1996**, *133*, 1095−1102. (b) Darses, J.-P.; Brayer, J.-L.; Demoute, J.-P.; Genêt, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393−4396. (c) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, 1875−1883.

(4) Chen, Z.-C.; Xia, M. *Synth. Commun.* **1999**, *29*, 2457−2465.

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

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

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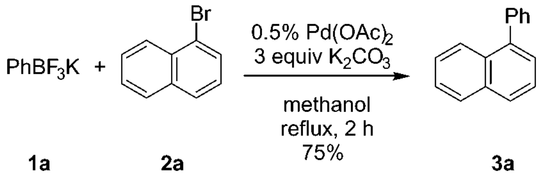
(8) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099−9103.

10.1021/ol025845p CCC: $22.00 © 2002 American Chemical Society
Published on Web 04/30/2002

variety of alkenyl and aryl halides using $Pd(OAc)_2$/dppb as a catalyst and Cs_2CO_3 as a base in DME/water. Ligandless palladium-catalyzed conditions[9] have also been used to perform cross-coupling reactions of arylboronic acids.

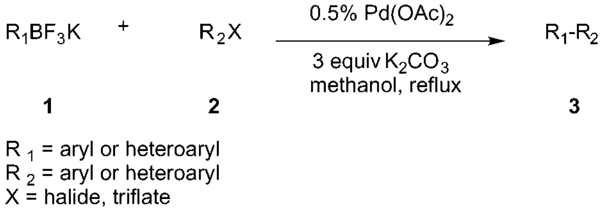
Continuing with our investigation on the application of potassium organotrifluoroborates in Suzuki cross-coupling reactions, we have explored conditions for the cross-coupling reaction of potassium aryl- and heteroaryltrifluoroborates with various aryl and heteroaryl halides and triflates. We optimized the conditions for the reaction between potassium phenyltrifluoroborate (**1a**) and 1-bromonaphthalene (**2a**) in terms of catalyst [$PdCl_2$·dppf, $Pd_3(dba)_2$, or $Pd(OAc)_2$], ligand [dppf or $(t\text{-Bu})_3P$], base (Et_3N, Hunig's base, $t\text{-BuNH}_2$, K_2CO_3, Cs_2CO_3, KF, K_3PO_4), and different solvent systems (MeOH, EtOH, *n*-PrOH, *i*-PrOH, dioxane, THF, water). Among the catalyzed conditions in the presence of a ligand, 1% $PdCl_2(dppf)$·CH_2Cl_2 and 3 equiv of Hunig's base in ethanol proved to be the best, leading to complete conversion of **2a** into 1-phenylnaphthalene (**3a**) after 7 h of heating at reflux. This result is in accordance with the conditions found to be suitable for the cross-coupling of potassium alkenyltrifluoroborates.[7] In addition to the above-mentioned conditions, the system $Pd(OAc)_2/K_2CO_3$/methanol proved to be exceptional for the cross-coupling reaction (Scheme 1). *Moreover, under these conditions, the reactions could be performed in the air without a reduction in the yield of biaryls.*[8] The ligandless reaction was then optimized in terms of the reaction time and the amount of catalyst. The catalyst loading was progressively reduced to 2, 0.5, and finally to 0.2%. An 80% yield of **3a** was obtained, and 14% of the starting material (1-bromonaphthalene, **2a**) was recovered under the latter conditions (Table 1, entry 1).

Scheme 1



The optimized conditions were subsequently tested in the coupling reaction of **1a** with different aryl, heteroaryl, and alkenyl bromides (Scheme 2, Table 1). The reaction proceeded with very good yields for electrophiles bearing both electron-withdrawing and electron-donating groups, even in the case of the highly hindered 2-bromomesitylene **2c**, where the coupling led to a 52% yield of the desired product using 5% loading of the catalyst. The reduced yield in the case of entries 16 and 17 is caused by triflate hydrolysis under the basic conditions of the coupling reaction. Presumably because of solubility, the coupling reactions of 4-bromobenzoic acid **2e**, 4-bromophenol **2j**, and 4′-bromoacetanilide **2m** with **1a** were most effective when carried out in water.

Scheme 2



We subsequently investigated the coupling reaction between different potassium aryl- and heteroaryltrifluoroborates with aryl bromides (Table 2). Electron-deficient and electron-rich aryl- and heteroaryltrifluoroborates could be efficiently coupled to 4-bromobenzonitrile **2i**. Ortho-substituted trifluoroborates afforded very good yields of biaryls when coupled with electron-deficient electrophiles, even in hindered situations (entries 4−6).

During the course of this investigation, Batey and Quach reported their results employing tetrabutylammonium (TBA^+) salts of the aryltrifluoroborates.[8] The conditions reported herein are differentiated from those in that study by the following significant features. (1) The catalyst loading used is 10 times lower. (2) No ligands need to be added. (3) Shorter reaction times are required. (4) Environmentally sound solvents are used. (5) The process is more economical and environmentally friendly when potassium trifluoroborate salts are utilized as the boron reagents.

Having stated this, our conditions also proved to be effective in the coupling reactions of TBA^+ salts of aryltrifluoroborates. When TBA^+ phenyltrifluoroborate **1i** was reacted with 4-bromoanisole **2b** and 4-bromonitrobenzene **2d**, the coupling reaction reached completion for **2d** (Table 2, entry 7) after 2 h at reflux, while NMR analysis of the crude reaction mixture of **2b** showed 78% of the product and 22% of the unreacted electrophile along with some of the TBA moiety (Table 2, entry 8). Likewise, the reaction of arylboronic acids under these conditions proceeded readily (Table 2, entries 9−11) with yields similar to those obtained for trifluoroborate salts, in accordance with previously reported results.[9]

Previous reports have indicated that water was required as a cosolvent for the trifluoroborate coupling reactions[6,8] and that one or more hydroxyl groups displace fluorides on the tetracoordinate boron species involved in the transmetalation step of the catalytic cycle.[8,10] We have conducted experiments heating $PhBF_3K$ in methanol at reflux, with the addition of 0, 1, 2, and 3 equiv of base. After 2 h, all of the reaction mixtures were filtered, equal amounts of deuterated acetone were added to each one, and the resulting solutions

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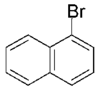
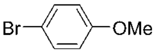
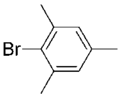
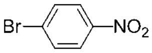
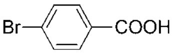
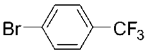
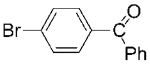
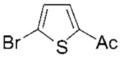
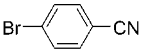
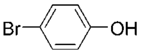
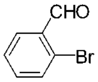
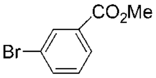
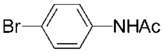
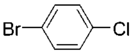
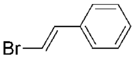
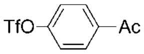
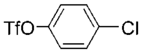
(9) (a) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, C. G. M. *Chem. Commun.* **1994**, 2395. (b) Darses, S.; Jeffery, T.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1996**, *37*, 3857−3860. (c) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437−14450. (d) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170−7173. (e) Goodson, E. F.; Wallow, T. I.; Novak, B. M. *Org. Synth.* **1998**, *75*, 61−68. (f) Zim, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2000**, *41*, 8199−8202. (g) Ma, D.; Wu, Q. *Tetrahedron Lett.* **2001**, *42*, 5279−5281. (h) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034−5037 and refs therein.

(10) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461−470.

Table 1. Cross-Coupling Reactions of Potassium Phenyltrifluoroborate **1a** with Organic Halides and Triflates

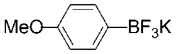
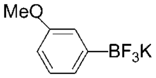
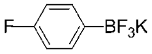
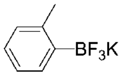
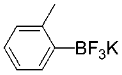
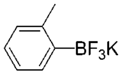
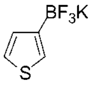
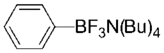
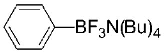
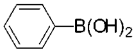
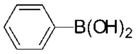
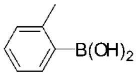
entry	R_2-X		reaction conditions[a]	% isolated yield
1		**(2a)**	A, 2 h A, 2 h, 2% cat[b] A, 9 h, 0.2% cat	**3a** 75 88 80, **2a** 14
2		**(2b)**	A, 2 h	**3b** 95
3		**(2c)**	A, 12 h 2% cat A, 36 h 5% cat[b]	**3c** 38 52
4		**(2d)**	A, 45 min	**3d** >99
5		**(2e)**	A, 2 h B, 2 h[b,c]	**3e** 96 90, **2e** 10[e]
6		**(2f)**	A, 1 h	**3f** 79
7		**(2g)**	A, 45 min	**3g** 92
8		**(2h)**	A, 50 min	**3b** 78, **2b** 14[e]
9		**(2i)**	A, 1 h[b] A, 1 h[b]	**3i** 87 85[d]
10		**(2j)**	A, 36 h 1% cat[b] B, 2 h[b]	**3j** 40 82
11		**(2k)**	A, 1 h	**3k** 89
12		**(2l)**	A, 1 h	**3l** 87
13		**(2m)**	A, 18 h B, 2 h	**3m** 62, **2m** 24[e] 55, **2m** 41[e]
14		**(2n)**	A, 12 h	**3n** 75
15		**(2o)**	A, 3 h	**3o** 70
16		**(2p)**	C, 90 min	**3p** 68
17		**(2q)**	C, 12 h	**3n** 50

[a] Condition A: $Pd(OAc)_2$ (0.5%), K_2CO_3 (3 equiv), MeOH, reflux. Condition B: $Pd(OAc)_2$ (0.5%), K_2CO_3 (3 equiv), water, 65 °C. Condition C: addition of the neat triflate after the catalyst. [b] Reaction was carried out in the open atmosphere. [c] Reaction was carried out at room temperature. [d] Reaction was carried out on a 4 mmol scale and the product purified by recrystallization. [e] Determined by NMR analysis.

were then analyzed using ^{11}B and ^{19}F NMR. In these experiments, the ^{19}F NMR showed the absence of fluorine bonded to the boron atom after adding 3 equiv of base. The ^{11}B NMR shifts revealed a quadruplet at 4.35 ppm when no base was added and a singlet at 5.47 ppm when 3 equiv of base was added. Analysis of phenylboronic acid in the same solvent mixture showed a singlet at 28.48 ppm (referenced to external $BF_3 \cdot OEt_2$ as 0.0 ppm). We have thus come to the conclusion that the trifluoroborates do not remain intact under the reaction conditions and that an intermediate that does not retain all of the fluorides on the boron species is involved in the key transmetalation step. Using a different analysis, Batey and Quach have previously come to the same conclusion.[8] Further mechanistic studies are currently underway in order to determine the exact nature of the species generated.

In summary, ligandless palladium-catalyzed conditions have been found to be suitable for the coupling of potassium aryl- and heteroaryltrifluoroborates with aryl and heteroaryl bromides and triflates. The reaction proved to be tolerant of a variety of functional groups. It can be carried out in methanol or water in the air, with as low as 0.2% loading of catalyst in relatively short reaction times. The high yields, in addition to the characteristics of the boron byproducts, allow simple workup techniques to be applied to obtain products with greater than 95% purity. These features,

Table 2. Cross-Coupling Reactions of Aryl- and Heteroaryltrifluoroborates with Organic Halides

entry	R_1BF_3K		R_2-X	reaction conditions[a]	% isolated yield
1		(**1b**)	**2i**	A, 1 h	**3q** 99
2		(**1c**)	**2i**	A, 3 h	**3r** 91
3		(**1d**)	**2i**	A, 2 h	**3s** 96
4		(**1e**)	**2i**	A, 5 h	**3t** 86
5		(**1e**)	**2d**	A, 12 h[d]	**3u** 83[b]
6		(**1e**)	**2k**	A, 12 h	**3v** 84
7		(**1f**)	**2i**	A, 5 h	**3w** 93
8		(**1g**)	**2b**	A, 2 h[d]	**3b** 78, 14 **2b**
9		(**1g**)	**2d**	A, 2 h[d]	**3d** 98
10		(**1h**)	**2i**	A, 1 h[d]	**3i** 91[c]
11		(**1h**)	**2j**	B, 3 h[c,d]	**3j** 94
12		(**1i**)	**2d**	A, 12 h[d]	**3u** 81

[a] Condition A: $Pd(OAc)_2$ (0.5%), K_2CO_3 (3 equiv), MeOH, reflux. Condition B: $Pd(OAc)_2$ (0.5%), K_2CO_3 (3 equiv), water, 65 °C. [b] Reduced yield due to low recovery from the reaction mixture. [c] Reaction was carried out at room temperature. [d] Reaction was carried out in the open atmosphere. [e] Determined by NMR analysis.

combined with the shelf stability of the aryltrifluoroborate complexes, make this technique environmentally sound, economical, and very attractive for use in industrial processes and combinatorial chemistry.

Acknowledgment. We thank Johnson & Johnson, Aldrich Chemical Co., Merck Research Laboratories, Array Biopharma, and Johnson Matthey for their generous support. B.B. thanks the Fundación Antorchas (Argentina) and the Universidad Nacional del Litoral (Santa Fe, Argentina) for postdoctoral fellowships.

Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025845P