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First Cross-Coupling Reaction of Potassium Aryltrifluoroborates with Organic Chlorides in Aqueous Media Catalyzed by an Oxime-Derived Palladacycle[†]

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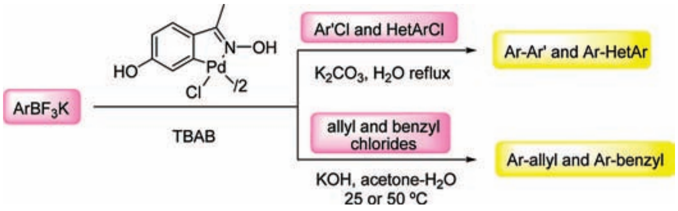
ABSTRACT



Potassium aryltrifluoroborates are cross-coupled with aryl and heteroaryl chlorides using a 4-hydroxyacetophenone oxime-derived palladacycle as precatalyst, K_2CO_3 as base, and TBAB as additive in refluxing water under conventional and microwave heating affording the corresponding biphenyls under phosphine-free conditions. For the arylation of allyl and benzyl chlorides, KOH is used as base in acetone−water (3:2) at rt or 50 °C using 0.1 mol % Pd loading providing allylbenzenes and diarylmethanes, respectively.

The chemistry of organoboron reagents in Suzuki−Miyaura[1] cross-coupling reactions has been extensively applied during the last three decades in organic chemistry at the laboratory and industrial scale mainly for biaryl synthesis.[2] This is due to their low toxicity and functional group compatibility compared to other organometallic reagents, boronic acids being the most available derivatives. However, some of them present limited stability and purification difficulties. In contrast, tetracoordinate organotrifluoroborates showed high stability toward air and water and can be easily purified and stored indefinitely under atmospheric conditions. Although these borates have been known since 1940,[3] it was in 1995 when Vedejs and co-workers reported the most convenient synthesis for potassium organotrifluoroborates.[4] Recently, they became commercially available, and the pioneering work of Genêt,[5] Xia,[6] and Molander[7] and co-workers demonstrated the potential of the last mentioned reagents in Pd-catalyzed cross-coupling reactions.[8] In general, potassium organotrifluoroborates show lower reactivity than boronic acids and have been coupled only with organic iodides and

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[†] Dedicated to Prof. Ricardo Riguera on the occasion of his 60th birthday.

(1) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (c) *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005.

(2) For recent reviews, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047–3101. (b) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133–173. (c) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609–679. (d) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710. (e) *Metal-Catalyzed Cross-Coupling Reactions*; De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.

(3) Fowler, D. L.; Kraus, C. A. *J. Am. Chem. Soc.* **1940**, *62*, 1143–1144.

(4) Vedjes, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020–3027.

(5) Cross-couplings with arenediazonium salts: Darses, S.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393–4396.

(6) Cross-couplings with diaryliodonium salts: Xia, M.; Chen, Z.-C. *Synth. Commun.* **1999**, *29*, 2457–2465.

(7) Cross-couplings with aryl bromides: Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393–396.

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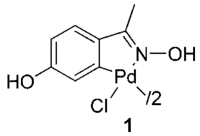
bromides in the presence of phosphines and high palladium loadings. In the case of aryl chlorides, only a general method has been described using $Pd(OAc)_2$ and the electron-rich phosphine S-Phos, under MeOH reflux.[9,10]

The use of water in transition-metal catalysis[11] has many advantages for the recycling of the catalyst and product recovery and also concerning safety and environmental aspects. The beneficial effects of the presence of water, especially in Suzuki−Miyaura reactions with boronic acids, are well documented.[2,11] Another important aspect for industrial application is the use of the less expensive and easily available aryl chlorides. Our group has described the first cross-coupling of aryl chlorides and arylboronic acids in refluxing water using an oxime-derived carbapalladacycle **1** as precatalyst for the general synthesis of biphenyls.[12] In addition, allyl and benzyl chlorides could be cross-coupled with arylboronic acids at room temperature in aqueous acetone. However, attempts to use neat water as solvent in the case or potassium organotrifluoroborates succeed only with aryl iodides and bromides.[13] We envisage that the presence of water would increase the reactivity of aryltrifluoroborates facilitating its hydrolysis to the corresponding arylboronic acids.[14] In the present communication, we report for the first time the cross-coupling of potassium aryltrifluoroborates with aryl chlorides in neat water and with allyl[15] and benzyl[16] chlorides in aqueous acetone using the precatalyst **1** under phosphine-free conditions.

Initially, 4-chloroacetophenone was cross-coupled with potassium phenyltrifluoroborate (1.5 equiv) in the presence of 0.5 equiv of tetra-*n*-butylammonium bromide (TBAB),[17] K_2CO_3 as base under refluxing water, and using palladacycle **1** (0.01 mol % of Pd) as precatalyst (Table 1, entry 1). The reaction took place efficiently with complex **1** after 20 h in 82% yield, which could be increased to 91% in 7 h reaction time using 0.05 mol % Pd loading (Table 1, entry 2). When the same reaction was performed with 1 equiv of $PhBF_3K$, **2aa** was obtained in a lower 62% yield. Under microwave heating (MW) at 100 °C, 4-acetylbiphenyl (**2aa**) was obtained in 87% yield in only 15 min (Table 1, compare entries 1 and 3). However, using 0.01 mol % of $Pd(OAc)_2$ under conventional or MW heating, 28 and 19% yields were observed (Table 1, entries 4 and 5). A lower 16% yield was measured using $PdCl_2$ under MW heating (Table 1, entry 6). Different activated and deactivated aryl chlorides were cross-coupled with aryltrifluoroborates under conventional and MW heating in neat water using palladacycle **1** (1 mol %) as precatalyst (Table 1). Deactivated potassium 4-(trifluoromethyl)phenyltrifluoroborate reacted with 4-chloroacetophenone under reaction conditions similar to $PhBF_3K$ affording biphenyl **2ab** in 78% yield (Table 1, compare entries 2 and 7). The anti-inflammatory 4-biphenylacetic acid (felbinac) (**2ba**) was obtained in 55 and 86% yield under conventional and MW heating, respectively (Table 1, entries 8 and 9). In the cross-coupling of 2-chlorobenzonitrile with potassium 4-tolyltrifluoroborate, the antihypertensive drug (sartans) intermediate **2cc** was obtained in 96 and 88% crude yield, respectively (Table 1, entries 10 and 11). When the same chloride was allowed to react with a hindered potassium 2-tolyltrifluoroborate, biphenyl **2cd** was obtained in good yields but in longer reaction time (16 h) than the 4-tolyl (5 h) (Table 1, entries 12 and 13). Deactivated aryl chlorides such as 4-methoxychlorobenzene and 4-chloroaniline reacted with potassium phenyltrifluoroborate under standard reaction conditions providing compounds **2da** and **2ea**, respectively, in good yields (Table 1, entries 14−17). Nitrogenated heterocyclic chlorides, such as 3-chloropyridine, 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone, and 2,4,6-trichloropyrimidine were mono-, di-, and triphenylated, respectively, affording compounds **2fa**, **2ga**, and **2ha** in good yields (Table 1, entries 18−23). These results are rather similar to the cross-coupling reactions performed with arylboronic acids and the same aryl chlorides under these phosphine-free aqueous conditions, the reaction rates being slightly lower than with potassium aryltrifluoroborates.[12]



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Next, we studied the cross-coupling reactions of allyl and benzyl chlorides with potassium aryltrifluoroborates using KOH as base and 0.1 mol % Pd loading in aqueous acetone, a reaction condition previously described for arylboronic acids.[12] Initially, the reaction of cinnamyl chloride with potassium phenyltrifluoroborate was performed at room

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(8) For reviews, see: (a) Darses, S.; Genêt, J.-P. *Chem. Rev.* **2008**, *108*, 288–325. (b) Doucet, H. *Eur. J. Org. Chem.* **2008**, *201*, 3–2030. (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286. (d) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623–3658. (e) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49–56. (f) Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, *431*, 3–4327.

(9) Border, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649–2652.

(10) $Pd_2(dba)_3$ (1 mol %) and PCy_3 have been used as catalysts in the reaction of potassium 3-pyridinetrifluoroborate with 4-*n*-butylchlorobenzene at 100 °C in aqueous dioxane: (a) Kudo, N.; Perseghini, M.; Fu, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282–1284. A palladium N-heterocyclic carbene has been used as catalyst in refluxing MeOH: (b) O'Brien, C. J.; Kantchen, A. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem.−Eur. J.* **2006**, *12*, 4743–4748.

(11) For recent reviews, see: (a) Capek, P.; Vrábel, M.; Hasník, Z.; Pohl, R.; Hocek, M. *Synthesis* **2006**, 3515–3526. (b) Saughnessy, K. H. *Eur. J. Org. Chem.* **2006**, 1827–1835. (c) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095–3165. (d) Saughnessy, K. H.; DeVasher, R. B. *Curr. Org. Chem.* **2005**, *9*, 585–604. (e) *Aqueous-Phase Organometallic Catalysis*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 2004.

(12) (a) Botella, L.; Nájera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179–181. (b) Botella, L.; Nájera, C. *J. Organomet. Chem.* **2002**, *663*, 46–57.

(13) (a) Arvela, R. K.; Leadbeater, N. E.; Mack, T. L.; Kormos, C. M. *Tetrahedron Lett.* **2006**, *47*, 217–220. (b) Lipshutz, B. H.; Petersen, T. B; Abela, A. R. *Org. Lett.* **2008**, *10*, 1333–1336. (c) Wang, L.; Li, P.-H. *Chin. J. Chem.* **2006**, *24*, 770–774.

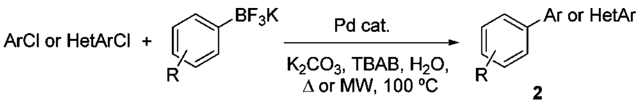
(14) (a) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099–9103. (b) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2002**, *4*, 1867–1870. (c) Ting, R.; Harwig, C. W.; Lo, J.; Li, Y.; Adam, M. J.; Ruth, T. J.; Perrin, D. M. *J. Org. Chem.* **2008**, *73*, 4662–4670.

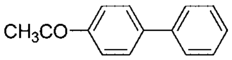
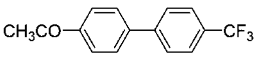
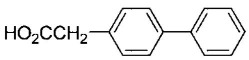
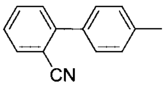
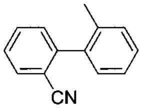
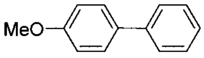
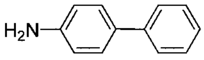
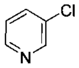
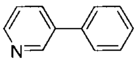
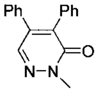
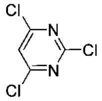
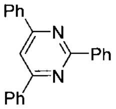
(15) Allyl chlorides have been coupled with potassium vinyltrifluoroborates using $PdCl_2(dppf)$ as catalyst in aqueous isopropanol under microwave heating: Kabalka, G. W.; Dadush, E.; Al-Masum, M. *Tetrahedron Lett.* **2006**, *47*, 7459–7461.

(16) Diarylmethanes have been prepared by reaction of benzyl bromides and chlorides with potassium aryltrifluoroborates using $PdCl_2(dppf)$ as catalyst in aqueous cyclopentyl methyl ether: Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198–9202.

(17) TBAB can act as a phase-transfer catalyst and also can stabilize palladium nanoparticles avoiding aggregation: Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165–168.

Table 1. Cross-Coupling of Aryl Chlorides With Potassium Aryltrifluoroborates in Water[a]



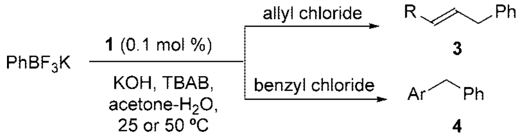
ent.	aryl chloride	$ArBF_3K$	cat. (mol % Pd)	TBAB (equiv)	time	product	**no.**	yield (%)[b]
1	4-$CH_3COC_6H_4Cl$	$PhBF_3K$	**1** (0.01)	0.5	20 h		**2aa**	82 (86)
2			**1** (0.05)	0.5	7 h		**2aa**	91 (96)
3			**1** (0.01)	0.5	15 min[c]		**2aa**	87 (93)
4			$Pd(OAc)_2$ (0.01)	0.5	20 h		**2aa**	(28)
5			$Pd(OAc)_2$ (0.01)	0.5	15 min[c]		**2aa**	(19)
6			$PdCl_2$ (0.01)	0.5	15 min[c]		**2aa**	(16)
7	4-$CH_3COC_6H_4Cl$	4-$CF_3C_6H_4BF_3K$	**1** (0.05)	0.5	8 h		**2ab**	78 (91)
8	4-(H_2OCCH_2)-C_6H_4Cl	$PhBF_3K$	**1** (1)	0.5	4 h		**2ba**	55 (70)
9			**1** (1)	0.5	15 min[c]		**2ba**	86 (99)
10	2-CNC_6H_4Cl	4-$MeC_6H_4BF_3K$	**1** (1)	1	5 h		**2cc**	85 (96)
11			**1** (1)	1	20 min[c]		**2cc**	(88)
12	2-CNC_6H_4Cl	2-$MeC_6H_4BF_3K$	**1** (1)	1	16 h		**2cd**	73 (95)
13			**1** (1)	1	20 min[c]		**2cd**	(84)
14	4-$MeOC_6H_4Cl$	$PhBF_3K$	**1** (1)	1	6 h		**2da**	83 (91)
15			**1** (1)	1	20 min[c]		**2da**	90 (96)
16	4-$H_2NC_6H_4Cl$	$PhBF_3K$	**1** (1)	1	10 h		**2ea**	53 (72)
17			**1** (1)	1	20 min[c]		**2ea**	71 (81)
18			**1** (1)	1	16 h		**2fa**	73 (86)
19		$PhBF_3K$	**1** (1)	1	20 min[c]		**2fa**	68 (79)
20		$PhBF_3K$[e]	**1** (1)	1	8 h		**2ga**	74 (82)
21			**1** (1)	1	15 min[c]		**2ga**	82 (93)
22		$PhBF_3K$[f]	**1** (1)	1	8 h		**2ha**	79 (86)
23			**1** (1)	1	15 min[c]		**2ha**	76 (85)

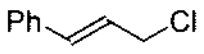
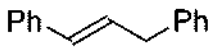
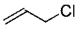
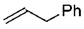
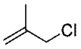
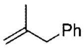
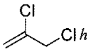
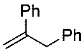
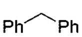
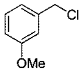
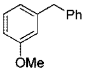
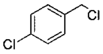
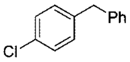
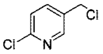
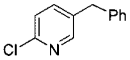
[a] Reaction conditions: aryl chloride (1 mmol), $PhBF_3K$ (1.5 mmol), 2 M solution of K_2CO_3 (1 mL, 2 mmol), TBAB (see column), cat. (see column) under H_2O (2 mL) reflux. [b] Isolated yield after flash chromatography. In parentheses, yield of the crude product determined by ^1H NMR. [c] Heating in a microwave reactor at 100 °C (30 W, 14.5 psi) with air stream cooling. [d] After recrystallization from EtOH. [e] Performed with 3 equiv of $PhBF_3K$. [f] Performed with 4.5 equiv of $PhBF_3K$.

temperature and at 50 °C with complex **1** (0.1 mol % of Pd), affording (*E*)-1,3-diphenylpropene (**3a**) in better yield (81%) and higher reaction rate at 50 °C (Table 2, entries 1 and 2). When $Pd(OAc)_2$ was used as a source of Pd, the reaction stopped after 4 h reaction time at 50 °C giving **3a** in 67% yield (Table 2, entry 3). In all cases, less than 10% of regioisomer 1,1-diphenylpropene was also obtained. The presence of 0.5 equiv of TBAB was necessary to increase the reaction rates from 9 to 1 h at 50 °C. Alternatively, the reaction can be performed under MW heating in only 10 min (Table 2, entry 4). Allyl and methallyl chloride gave products **3b** and **3c** in good yields using these standard reaction conditions (Table 2, entries 5−8). Preferential diphenylation was observed in the case of 2,3-dichloropropene even with 1.5 equiv of potassium phenyltrifluoroborate. Therefore, the reaction was performed with 3 equiv of $PhBF_3K$ affording mainly 2,3-diphenylpropene (**3d**) in good yield (Table 2, entries 9 and 10).

Diarylmethanes are important synthetic targets due to their pharmacological activity[18] and for supramolecular structures.[19] For their preparation by palladium-catalyzed cross-coupling reactions, two main strategies can be used, either the reaction between benzylmetals and aryl halides or between benzyl halides and arylmetals. Thus, when benzyl

Table 2. Cross-Coupling of Allyl and Benzyl Chlorides with Potassium Organotrifluoroborates in Aqueous Acetone[a]



ent.	organic chloride	temp (°C)	time	product	no.	yield (%)[b]
1		25	7 h		**3a**	69 (88)[c]
2		50	1 h		**3a**	81 (97)[c]
3		50[d]	4 h		**3a**	(67)[e]
4		50	10 min[f]		**3a**	(96)[g]
5		25	4 h		**3b**	72 (99)
6		50	1.5 h		**3b**	(96)
7		25	14 h		**3c**	41(59)
8		50	2 h		**3c**	65(85)
9	 [h]	25	14 h		**3d**	76 (99)[i]
10		50	2 h		**3d**	(98)[j]
11	$PhCH_2Cl$	50	4 h		**4a**	81 (92)
12		50[d]	4 h		**4a**	(64)
13		25	2 d		**4b**	(71)
14		50	2.5 h		**4b**	86 (99)
15		50	2 h		**4c**	82 (96)
16		50	9 h		**4d**	77 (95)

[a] Reaction conditions: allyl or benzyl chloride (1 mmol), $PhBF_3K$ (1.5 mmol), KOH (2 mmol), TBAB (0.5 mmol), cat. (0.1 mol % of Pd) in acetone−H_2O (3:2, 5 mL) reflux. [b] Isolated yield after flash chromatography. In parentheses, yield of the crude product (^{1}H NMR). [c] 8% of 1,1-diphenylpropene was also obtained. [d] $Pd(OAc)_2$ was used. [e] 10% of 1,1-diphenylpropene was also obtained. [f] Heating in a microwave reactor at 50 °C (30 W, 14.5 psi) with air stream cooling. [g] 12% of 1,1-diphenylpropene was also obtained. [h] Performed with 3 equiv of $PhBF_3K$. [i] 8% of 2-chloro-3-phenylpropene was also obtained. [j] 12% of 2-chloro-3-phenylpropene was also obtained.

chlorides were treated with $PhBF_3K$ under the same reaction conditions as allyl chlorides, diarylmethanes **4** could be obtained in good yield (Table 2, entries 11−16). For this type of cross-coupling reactions, $Pd(OAc)_2$ also was less efficient than palladacycle **1** (Table 2, compare entries 11 and 12). In general, this cross-coupling was performed at 50 °C, reaction times being too long at rt. Using this protocol, results similar to using arylboronic acids at rt were obtained.[12]

Recycling experiments were performed for the cross-coupling of $PhBF_3K$ with 4-chloroacetophenone in refluxing water under MW heating for 15 min and using 0.1 mol % of complex **1** in the first run. In the case of the arylation of cinnamyl and benzyl chloride with $PhBF_3K$, the reaction was carried out at 50 °C in aqueous acetone with 0.05 mol % palladacycle loading. After extractive workup with diethyl ether, the aqueous phase was charged with new reagents providing products **2aa**, **3a**, and **4a**, respectively, in good yield during the three first runs.

In light of the results described, it can be concluded that complex **1** in the presence of TBAB is a very efficient catalyst for the cross-coupling reaction of potassium aryltrifluoroborates with a wide range of aryl chlorides in refluxing aqueous K_2CO_3 under very simple reaction conditions. For the arylation of allyl and benzyl chlorides, KOH in aqueous acetone at rt or 50 °C using 0.1 mol % of palladacycle **1** loading are the best and the most simple conditions described. However, $Pd(OAc)_2$ showed a very low efficiency as precatalyst in these types of cross-coupling reactions. From these results, it can be established that easily available and highly stable potassium aryltrifluoroborates can be used instead of arylboronic acids in these types of cross-coupling reactions. Further work from our group about new applications of potassium organotrifluoroborates in cross-coupling reactions is underway.

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

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