# Palladium-Catalyzed Cross-Coupling Reaction of Potassium Diaryldifluoroborates with Aryl Halides

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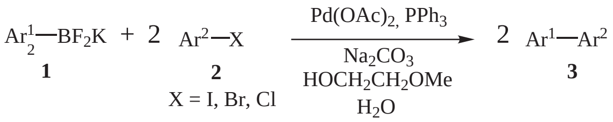
**Abstract:** The catalytic cross-coupling reaction of potassium diaryldifluoroborates with aryl halides proceeds to afford the biphenyls in good yields. These salts on an arylation reagent were readily prepared via a protocol of the Grignard method and transformation to potassium salts. Two aryl groups of these salts were efficiently transferred in the Suzuki–Miyaura reaction.

**Key words:** Grignard reactions, cross-coupling, organoborate, biaryls, arylations

The palladium-catalyzed cross-coupling reaction between organoboron compounds and organohalides and triflates provides a powerful and general method for carbon-carbon bond formation.[1] Aryl-aryl bond formation has become a most important tool of organic synthesis because these bonds are found in natural products as well as in numerous biologically active parts of pharmaceuticals and agrochemicals.[2] Although arylboronic acids and esters have been widely utilized in cross-coupling reaction for biphenyl synthesis, much attention has been continuously focused on the preparation of various organoboron derivatives for arylation and on extending their synthetic utility.[3–5] Among these organoboron compounds, triarylboranes[6] and tetrarylborates[7] were demonstrated as the multiple aryl transfer reagents from boron in cross-coupling reaction. Aryltrifluroroborates[8] having high stability and reactivity compared with commonly used arylboronic derivatives were also explored. Preparation of potassium diphenyldifluoroborate was reported by Thierig,[9] whereas its synthetic utility has not been thoroughly explored.[10] In this letter, we would like to report palladium-catalyzed cross-coupling reaction of potassium diaryldifluoroborates **1** with aryl halides **2** to afford the corresponding biphenyl derivatives **3** in good to excellent yields (Scheme 1). These two aryl groups were efficiently coupled with aryl halides in the Suzuki–Miyaura reaction.



$$\underset{\mathbf{1}}{Ar^1_2\text{—}BF_2K} + 2\ \underset{\substack{\mathbf{2}\\ X\,=\,I,\ Br,\ Cl}}{Ar^2\text{—}X} \xrightarrow[\substack{Na_2CO_3\\ HOCH_2CH_2OMe\\ H_2O}]{Pd(OAc)_2,\ PPh_3} 2\ \underset{\mathbf{3}}{Ar^1\text{—}Ar^2}$$

**Scheme 1**

Potassium diaryldifluoroborates were prepared by a slightly modified literature procedure.[9] To a methanol solution of the diarylborinic acid (e.g., Ar; phenyl) which was obtained by using Grignard reaction, 3 equivalents of $KHF_2$ was added. The reaction smoothly proceeded to give potassium diphenyldifluoroborate (**1a**) in 82% yield.[11] The $^{11}B$ and $^{19}F$ NMR spectra indicated a triplet and a quartet, respectively, which are reasonably resolved.[12] Other various potassium salts **1b**–**h** possessing functional groups such as Me, MeO, Ph, F and Cl were also efficiently prepared from the corresponding diarylborinic acids in moderate to good yields. To demonstrate the usefulness of these borates **1**, a palladium-catalyzed cross-coupling reaction with aryl halides was examined. Brief optimization of the reaction conditions was studied by using potassium diphenyldifluoroborate (**1a**) (0.55 mmol) with 4-chloroacetophenone (**2a**) (1.0 mmol) in the presence of 3 mol% of $Pd(OAc)_2$ and triphenylphosphine (0.12 mmol) in various organic solvents (5 mL) and $H_2O$ (0.5 mL) at heating for 6 hours. The results are summarized in Table 1.

The reaction in toluene, DMF, MeOH, and DME as a solvent resulted in low product yields and mainly recovered 4-chloroacetophenone (**2a**) of the starting material (entries 1–4). It was found that the use of 2-methoxyethanol as a solvent dramatically improved the product yields (entries 5–8). Use of $PdCl_2$ gave a comparable yield to that of $Pd(OAc)_2$ (entry 9). As shown in Table 1, **1a** was smoothly coupled with **2a** and the best result of the coupling reaction was observed in a combination of $Na_2CO_3$ or $K_3PO_4$ and 2-methoxyethanol (entries 5 and 7).

To establish the generality of this method, the cross-coupling reaction of several aryl halides **2a**–**k** with borates **1a**–**h** was examined under the optimized conditions (Scheme 2). The results are shown in Tables 2 and 3.[13] 4-Iodoacetophenone (**2b**) coupled with borate **1a** to give 4-acetylbiphenyl (**3a**) in 92% yield (Table 2, entry 1). Various aryl bromides **2c**–**f** containing electron-withdrawing and electron-donating groups were coupled to furnish the corresponding biphenyl products **3a**–**d** in good yields (85–98%) (Table 2, entries 2–5). It was noteworthy that the cross-coupling of activated aryl chlorides **2a**, **2g**–**h** having Ac, CN and $NO_2$ groups on the aromatic ring gave the corresponding coupled products **3a**, **3e**–**d** in moderate to good yields (Table 2, entries 6–8). Unfortunately, only a trace amount of the product was observed when 4-chloroanisole was used. Although attempts to

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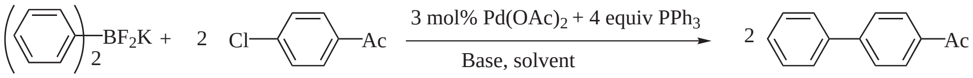
Art Id.1437-2096,E;2003,0,10,1435,1438,ftx,en;U05003ST.pdf.

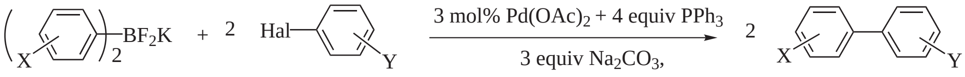
**Table 1** Cross-Coupling Reaction of Potassium Diphenyldifluoroborate with 4-Chloroacetophenone[a]



**1a** **2a** **3a**

| Entry | Base (mmol) | Solvent | Temp | Recovery of **2a** (%)[b] | Yield of **3a** (%)[b] |
|---|---|---|---|---|---|
| 1 | $Na_2CO_3$ (1.5) | Toluene–$H_2O$ | Reflux | 80 | 17 |
| 2 | $Na_2CO_3$ (1.5) | DMF–$H_2O$ | 120 °C | 66 | 25 |
| 3 | $Na_2CO_3$ (1.5) | MeOH–$H_2O$ | Reflux | 94 | 2 |
| 4 | $Na_2CO_3$ (1.5) | DME–$H_2O$ | Reflux | 89 | 3 |
| 5 | $Na_2CO_3$ (1.5) | $MeOCH_2CH_2OH$–$H_2O$ | Reflux | 30 | 66 (90)[d] |
| 6 | $K_2CO_3$ (1.5) | $MeOCH_2CH_2OH$–$H_2O$ | Reflux | 10 | 47 |
| 7 | $K_3PO_4$ (1.5) | $MeOCH_2CH_2OH$–$H_2O$ | Reflux | 7 | 66 |
| 8 | NaOAc (1.5) | $MeOCH_2CH_2OH$–$H_2O$ | Reflux | 42 | 57 |
| 9 [c] | $Na_2CO_3$ (1.5) | $MeOCH_2CH_2OH$–$H_2O$ | Reflux | 33 | 63 |

[a] All reactions were carried out by using potassium diphenyldifluoroborate (0.55 mmol) with 4-chloroacetophenone (1.0 mmol) in the presence of 3 mol% of Pd(OAc)$_2$ and triphenylphosphine (0.12 mmol) in various organic solvents (5 mL) and $H_2O$ (0.5 mL) for 6 h.
[b] Yield was determined by GLC analysis using dibenzyl as an internal standard.
[c] PdCl$_2$ was used.
[d] The yield in parentheses was obtained when 2 equiv of **1a** was used.



**1** **2** **3**

**Scheme 2**

promote the cross-coupling reaction by prolonged reaction time were unsuccessful, possibly due to decomposition of the starting potassium salt,[14,15] the use of 2 equivalents of borate **1a** considerably improved the results, affording the coupled product in 90% yield (Table 2, entry 6). Substituted potassium borates **1b**–**h** were also investigated. The coupling reaction of various aryl bromides **2** proceeded to give the corresponding products **3** in good yields (Table 3, entries 1–7).

**Table 2** Cross-Coupling Reaction of Potassium Diphenyldifluoroborate with Various Aryl Halides

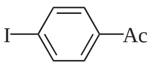
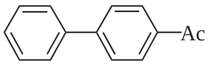
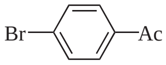
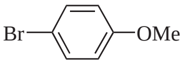
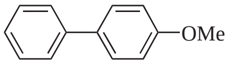
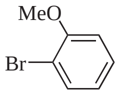
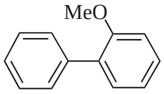
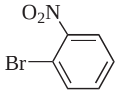
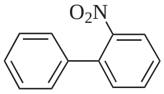
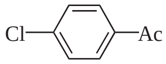
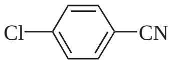
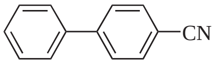
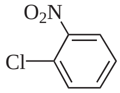
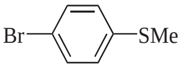
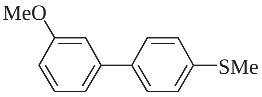
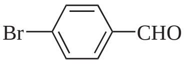
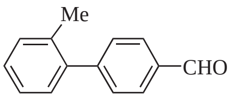
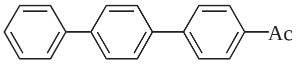
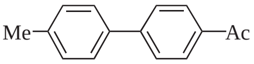
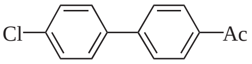
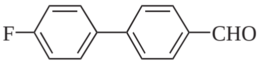
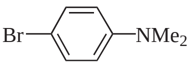
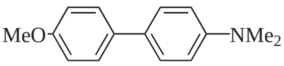
| Entry | Halide | Time (h) | Product | Yield (%) |
|---|---|---|---|---|
| 1 | <br>**2b** | 16 (80 °C) | <br>**3a** | 92 |
| 2 | <br>**2c** | 3 | **3a** | 92 |
| 3 | <br>**2d** | 4 | <br>**3b** | 85 |

**Table 2** Cross-Coupling Reaction of Potassium Diphenyldifluoroborate with Various Aryl Halides (continued)

| Entry | Halide | Time (h) | Product | Yield (%) |
|---|---|---|---|---|
| 4 |  **2e** | 6 |  **3c** | 98 |
| 5 |  **2f** | 6 |  **3d** | 94 |
| 6 |  **2a** | 6 | **3a** | 66 (90)[a] |
| 7 |  **2g** | 3 |  **3e** | 63 |
| 8 |  **2h** | 6 | **3d** | 89 |

[a] The yield in parentheses was obtained when 2 equiv of **1a** was used.

**Table 3** Cross-Coupling Reaction of Potassium Diaryldifluoroborate with Various Aryl Halides

| Entry | Borate X | Halide | Product | Yield (%) |
|---|---|---|---|---|
| 1 | *m*-MeO<br>**1b** |  **2i** |  **3f** | 89 |
| 2 | *o*-Me<br>**1c** |  **2j** |  **3g** | 89 |
| 3 | *p*-Ph<br>**1d** | **2c** |  **3h** | 74 |
| 4 | *p*-Me<br>**1e** | **2c** |  **3i** | 80 |
| 5 | *p*-Cl<br>**1f** | **2c** |  **3j** | 68 |
| 6 | *p*-F<br>**1g** | **2j** |  **3k** | 72 |
| 7 | *p*-MeO<br>**1h** |  **2k** |  **3l** | 22 |

In conclusion, potassium diaryldifluoroborates **1** on an arylation reagent in the Suzuki–Miyaura reaction were established and investigated. The palladium-catalyzed coupling of potassium diaryldifluoroborates with various aryl halides including activated aryl chlorides efficiently proceeded to afford various biaryl compounds in good yields. These salts efficiently transferred two aryl groups from the boron to aryl halides.

## References

(1) For review see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

(2) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(3) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394.

(4) Vazquez, E.; Davies, I. W.; Payack, J. F. *J. Org. Chem.* **2002**, *67*, 7551.

(5) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Murata, M.; Oyama, T.; Watanebe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164. (c) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268.

(6) Bumagin, N. A.; Tsarev, D. A. *Tetrahedron Lett.* **1998**, *39*, 8155.

(7) (a) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1992**, *33*, 4815. (b) Bumagin, N. A.; Luzikova, E. V.; Sukhomlinova, L. I.; Tolstaya, T. P.; Beletskaya, I. P. *Izv. Akad. Nauk, Ser. Khim.* **1995**, 394; *Chem. Abstr.* **1995**, *123*, 285350g. (c) Bumagin, N. A.; Bykov, V. V. *Zh. Obshch. Khim.* **1996**, *66*, 1981; *Chem. Abstr.* **1997**, *126*, 225047r. (d) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437. (e) Bumagin, N. A.; Korolev, D. N. *Tetrahedron Lett.* **1999**, *40*, 3057.

(8) (a) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020. (b) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099. (c) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867.

(9) Thierig, D.; Umland, F. *Naturwissenschaften* **1967**, *54*, 563.

(10) Raction of bis(3,5-dimethylphenyl)borinic acid with vinyl triflate was reported. See: Winkle, D. D.; Schaab, K. M. *Org. Proc. Res. Dev.* **2001**, *5*, 450.

(11) **The Representative Procedure for the Preparation of Potassium Diaryldifluoroborates is as follows:** Under an argon atmosphere, to a solution of phenylmagnesium bromide prepared from magnesium turnings (2.67 g, 110 mmol) and bromobenzene (18.1 g, 115 mmol) in anhyd THF (150 mL) was slowly added triisopropyl borate (9.4 g, 50 mmol) and anhyd THF (30 mL) at 0 °C over 30 min. After addition of triisopropyl borate, the reaction mixture was allowed to warm slowly to r.t. and stirred at the same temperature for 16 h. The reaction was then hydrolyzed with 1 M HCl (100 mL). After the usual work-up and a short column chromatography of the resulting oil, 10.2 g of crude diphenylborinic acid was obtained. To the solution of diphenylborinic acid in MeOH (200 mL) at 0 °C, $KHF_2$ (11.7 g, 150 mmol) was added and stirred for 1 h. The solvent was removed in vacuo and the residual solid was extracted with an appropriate amount of acetone, and the organic layer was concentrated. The amount of 100 mL of $Et_2O$ was added to the residue. The product was collected and dried in vacuo. Potassium diphenyldifluoroborate (**1a**, 9.94 g) was obtained as a white powder (82% yield). Mp 211 °C (dec.), ref.[9] 230 °C. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 7.32$ (br d, 2 H, $J = 6.6$ Hz), 7.01 (t, 2 H, $J = 7.2$ Hz), 6.95–6.80 (m, 1 H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta = 131.34$ (t, $J = 3.7$ Hz), 125.87, 123.72. $^{19}$F NMR[12] (254 MHz, DMSO-$d_6$): $\delta = -157.2$ (q, $J = 73.3$ Hz). $^{11}$B NMR[12] (86.6 MHz, DMSO-$d_6$): $\delta = 7.0$ (t, $J = 73.2$ Hz). Elemental analysis: Anal. Calcd for $C_{12}H_{10}BF_2K$: C, 59.53; H, 4.16. Found: C, 59.71; H, 4.12.

(12) The B-F coupling on NMR measurement was observed at 80 °C.

(13) **The Representative Procedure for the Cross-Coupling Reaction of Potassium Diaryldifluoroborates is as follows:** Under Ar atmosphere, a solution of potassium diphenyldifluoroborate (**1a**) (133 mg, 0.55 mmol), $Pd(OAc)_2$ (6 mg, 0.03 mmol), $PPh_3$ (31 mg, 0.12 mmol), 1-bromo-2-nitorobenzene (**2f**) (202 mg, 1.0 mmol), and $Na_2CO_3$ (159 mg, 1.5 mmol) in 2-methoxyethanol (5 mL) and $H_2O$ (0.5 mL) was heated under reflux. The reaction mixture was stirred at the same temperature for 6 h and then cooled to r.t., and acidified with 1 M HCl. The mixture was extracted with MTBE (30 mL × 3). The organic layer was washed with brine (30 mL) and dried over $MgSO_4$. The solvent was removed in vacuo, and the crude product was purified by silica gel column chromatography to afford 2-nitrobiphenyl (**3d**) (187 mg, 0.94 mmol) in 94% yield.

(14) Reaction of potassium bis(4-biphenyl)difluoroborates (**1d**) and 4-chloroacetophenone (**2a**) afforded the coupled product and biphenyl which resulted from potassium salt in 66% and 31% yields, respectively.

(15) A similar decomposition was reported for $Ph_2BOH$. See: Abel, E. W.; Gerrard, W.; Lappert, M. F. *J. Chem. Soc.* **1958**, 1451.