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Pd/C-Catalyzed Cross-Coupling of Arenediazonium Salts with Potassium Aryltrifluoroborates

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Abstract

A convenient protocol for the synthesis of biaryls from arenediazonium salts and potassium aryltrifluoroborates in refluxing methanol catalyzed by Pd/C is described. The protocol is simple to execute and gives moderate to high yields of cross-coupling products in most cases.

Keywords

Diazonium salts; potassium aryltrifluoroborates; Pd/C; cross-coupling; biaryl synthesis; Suzuki-Miyaura

INTRODUCTION

The preparation of biaryls is an important objective in organic synthesis, since the biaryl unit is found in a number of natural products, pharmaceuticals, conducting polymers, and optically active ligands for asymmetric synthesis [1]. Terphenyls have also attracted attention due to a wide range of biological activity [2], and for their use as laser dyes [3]. Furthermore, small oligophenylenes are used in organic light emitting diodes (OLEDs) [4]. Over the past three decades, palladium-catalyzed cross-coupling reactions have come to be the method of choice for the synthesis of biaryls and other small oligophenylenes [5]. Of the several protocols that have been developed, the cross-coupling of aryl halides with organoboronic acids (the Suzuki-Miyaura reaction [6]) is perhaps the most widely used. Its popularity stems from the fact that arylboronic acids are relatively stable in aqueous media, they tolerate a wide variety of functional groups, and the inorganic byproducts of the reaction are generally considered to be nontoxic and they are easily separated from the reaction product [6].

While the electrophilic partners in most Suzuki-Miyaura reactions are aryl halides, arenediazonium salts have been shown to be a viable alternative [7]. Studies by Genet [8], Sengupta [9] and Felpin [10] have demonstrated the utility of arenediazonium salts as coupling partners for organoboronic acids. Arenediazonium salts do not require the presence of a base to undergo cross-coupling, and therefore the diazo moiety can be chemoselectively replaced in the presence of other nucleofuges such as halogens. This allows the biaryl to be

further transformed by additional Suzuki-Miyaura coupling, and this strategy can provide easy access to a variety of terphenyls as demonstrated by Felpin [10a,b].

Recently, potassium organotrifluoroborates have emerged as an attractive alternative to organoboronic acids in Suzuki-Miyaura cross-coupling reactions [11]. These compounds offer several advantages compared to arylboronic acids, being similar to arylboronic acids in functional group tolerance, but exhibiting better stability toward air and water. Many are now commercially available, or they can very easily be prepared from the corresponding arylboronic acid or arylboronic ester by reaction with KHF_2 . These compounds are more easily purified than arylboronic acids, and can be stored indefinitely without any special precautions. In addition, the cross-coupling reactions known to date involving potassium aryltrifluoroborates are not particularly air- or water-sensitive, adding an element of operational simplicity to protocols developed using these reagents. Potassium aryl- and vinyltrifluoroborates have been shown to undergo palladium-catalyzed cross-coupling with arenediazonium salts using conventional heating [12] as well as microwave heating [13], and the reaction can also be carried out in ionic liquids [14].

Felpin and coworkers have recently demonstrated that Pd/C is a practical, inexpensive catalyst for the cross-coupling of arenediazonium salts with arylboronic acids [10a,c], and while Pd/C has been used to catalyze the cross-coupling of aryl halides with potassium organotrifluoroborates [15], at the time we began this study we were aware of only one example of the use of Pd/C to catalyze a similar reaction involving arenediazonium salts. That example was included in work by Genet, et al. who reported the Pd/C-catalyzed reaction of *p*-tolylidiazonium tetrafluoroborate with potassium *p*-methoxyphenyltrifluoroborate in both dioxane and methanol as part of their optimization experiments [12a]. Our interest in palladium-catalyzed reactions of arenediazonium salts [16] led us to further explore Pd/C as a catalyst for this cross-coupling reaction. During our investigation, we found Pd/C to be an effective catalyst for the cross-coupling of a variety of arenediazonium salts and potassium aryltrifluoroborates, and in this letter we report the results of our study.

RESULTS AND DISCUSSION

We began by examining the reaction of potassium *p*-tolyltrifluoroborate (**1a**) with 1.2 equivalents of *p*-bromobenzenediazonium tetrafluoroborate (**2a**) in the presence of 5 mol% Pd/C in refluxing methanol (Scheme 1). **Caution**[17]! We were pleased to find that this reaction produced a 92% yield of cross-coupled product **3aa** (based on **1a**, determined by GC). Bromobenzene, arising from the reduction of residual **2a** (11% based on **2a**), was also detected.

Encouraged by this result, we screened different levels of catalyst loading. In addition, we carried out the reaction in the presence of $\text{Pd}(\text{OAc})_2$ (a homogeneous catalyst) and Pd EnCat™ 30 (a commercially available encapsulated palladium acetate) for comparison. The yields of cross-coupling product **3aa** and bromobenzene were determined by GC using an internal standard and the results are shown in Table 1.

These reactions were always complete within 1 hr at reflux. Pd/C was the best catalyst, and 5 mol% was the optimum catalyst loading (entry 2). There seemed to be no advantage to a higher catalyst loading (entry 1), but at a lower catalyst loading, the reaction was less efficient (entry 3). The commercially available encapsulated catalyst was only moderately effective, as was Pd(OAc)₂ (entries 4 and 5). The cross-coupling was not effective in the absence of any catalyst (entry 6), indicating that the reaction is indeed catalyzed by the palladium compounds. The addition of water was not necessary to achieve good yields, as had been reported for the Pd/C-catalyzed coupling of aryl halides and potassium aryltrifluoroborates [15b].

We next synthesized several biaryl derivatives to test the scope and limitations of the protocol. We examined the reaction of several different arenediazonium salts with several different potassium aryltrifluoroborates and the isolated product yields are shown in Table 2.

In most cases, the reactions produced high yields of cross-coupled products. The protocol tolerates a wide variety of functionality in the diazonium salt as well as the aryltrifluoroborate, and heterocyclic nucleophiles (entry 14) also undergo the reaction. Methoxy groups in the 2-position of either coupling partner do not affect the efficiency (entries 8 and 13), but the coupling is ineffective when a methyl group is present in the 2-position of the diazonium salt (entry 6).

All of the results to this point had been obtained using 10% Pd/C purchased from Acros, however we were unable to determine the exact grade of this material. Since Felpin, et al., have shown that the particular distribution and Pd oxidation state of Pd/C affects the efficiency of cross-coupling reactions [10c], we determined turnover frequencies (TOF) for the Acros material as well as several different types of Evonik Pd/C available from Strem Chemicals, Inc. The reaction of **1a** with **2a** in the presence of 5 mol% Pd/C was used as the model system; the reactions were carried out at 50 °C and quenched after 5 minutes (i. e., prior to completion of the reaction). Under these conditions, 0.15 mmol (58% yield) of **3aa** was realized using Acros Pd/C, giving a turnover frequency of 139 h⁻¹. Yields of **3aa** and turnover frequencies were then determined for the other grades of Pd/C and the results are shown in Table 3.

It should be noted that the Evonik products were received as wet presscakes containing ~50% water. Since the material obtained from Acros was a dried powder, we wanted to determine if the presence of water had an effect on the observed catalyst efficiency. We therefore evaluated the activity of the Acros material in the presence of added water (in an amount equal to the mass of dry Pd/C, entry 2) and found very little difference vs. the dry material (entry 1). In fact, the water seemed to have a slight negative effect on catalyst efficiency. While most of the Pd/C grades studied exhibited reasonable efficiency, Pearlman's catalyst (entry 5) showed very little activity in our protocol. We found Evonik E2 (entry 3) to be the most active, and Evonik E5 (entry 5) to be only slightly less effective. The relatively high activity of Evonik E2 in our protocol, however, does not seem consistent with a recent study by Felpin and coworkers [10c]. In their study of the cross-coupling of arenediazonium salts with arylboronic acids in methanol, they found that Pd/C with this distribution and oxidation state (i. e., uniform, oxidic) was the least effective. Although the

reason for this apparent inconsistency is not immediately clear, Felpin et al. employed much lower catalyst loadings and lower temperatures in their study; they also found that higher catalyst loadings led to less significant differences in activity among the catalysts studied. Since our protocol uses a relatively high catalyst loading (5 mol%) and a higher temperature (refluxing methanol), these differences may play a role in the apparent discrepancy in catalyst activity. It may also be that organotrifluoroborates and boronic acids simply react differently under the influence of Pd/C [18].

In conclusion, we have developed a new protocol for the cross-coupling of arenediazonium salts with potassium aryltrifluoroborates using Pd/C as the catalyst. The protocol is simple to execute, tolerates a wide variety of functional groups, and gives very good yields of cross-coupling products in most cases. While many commercially available grades of Pd/C are suitable for this protocol, Evonik E2 seems to be the best catalyst for this reaction while Pearlman's catalyst showed very little activity. We believe the protocol described herein will be a valuable complement to existing methods of biaryl synthesis.

EXPERIMENTAL

Arenediazonium tetrafluoroborates were synthesized as described in the literature [19] and were recrystallized from acetone/ether prior to use. Potassium organotrifluoroborates were purchased from Sigma-Aldrich and used without further purification. HPLC grade methanol was purchased from Acros and stored over 3Å molecular sieves. Pd/C and Pd(OAc)₂ were purchased from Acros; Pd EnCat™ 30 was purchased from Sigma-Aldrich. Evonik Pd/C samples were purchased from Strem. Analytical gas chromatography was performed on an Agilent 7890 GC equipped with 30 m × 0.32 mm Agilent HP-5 column coupled to a FID. GC/MS analyses were performed on a Varian CP-3800 GC equipped with a 30 m × 0.25 mm VA-5 MS capillary column integrated with a Varian Saturn 2000 MS. ¹H- and ¹³C-NMR were recorded on a Jeol Eclipse+ 300 spectrometer. FTIR spectra were recorded on a Nicolet Avatar 360 or Avatar 370 spectrometer. Flash column chromatography was carried out using silica gel purchased from Fisher (grade 60, 230 – 400 mesh).

General Procedure for Optimization Studies

To a 25-mL pear-shaped flask equipped with a spin vane and air condenser were added methanol (2 mL) and dodecane (60 – 70 mg) as an internal standard. The catalyst was then added with vigorous stirring [17] (catalysts and loadings are given in Table 1) followed by *p*-tolyltrifluoroborate (**1a**, 99.0 mg, 0.50 mmol) and *p*-bromobenzenediazonium tetrafluoroborate (**2a**, 162.5 mg, 0.60 mmol). The mixture was placed in an oil bath (75 – 80 °C) and heated to reflux for 1 hr, after which time the diazonium salt had been consumed (indicated by the absence of a reddish-purple color upon treatment of a sample of the reaction mixture with an alkaline solution of H-acid (4-amino-5-hydroxy-2,7-naphthalenedisulfonic acid)). The reaction mixture was then diluted with dichloromethane (10 mL), filtered through Celite and analyzed by GC.

General Procedure for Pd/C Evaluation Studies

To a 25-mL pear-shaped flask equipped with a spin vane and air condenser was added of methanol (1.0 mL, containing dodecane (100 mM) as an internal standard). Pd/C (0.013 mmol, 5 mol%) was then added with vigorous stirring [17], followed by *p*-tolyltrifluoroborate (**1a**, 49.5 mg, 0.25 mmol) and *p*-bromobenzenediazonium tetrafluoroborate (**2a**, 81.3 mg, 0.30 mmol). The mixture was placed in a oil bath (50 °C) for 5.0 min, then quenched with a 0.025 M solution of H-acid (4-amino-5-hydroxy-2,7-naphthalenedisulfonic acid) in 5% Na₂CO₃ (aq) (10 mL). The resulting purple mixture was extracted with of dichloromethane (10 mL). The organic extract was filtered through Celite and analyzed by GC. Turnover frequencies were calculated as follows:

$$\text{TOF (h}^{-1}\text{)} = (\text{mmol } \mathbf{3aa}) / (0.013 \text{ mmol Pd/C}) / (0.083 \text{ hr})$$

General Procedure for Cross-Coupling of Arenediazonium Tetrafluoroborates with Potassium Aryltrifluoroborates

To a 25-mL pear-shaped flask equipped with a spin vane and air condenser was added methanol (2 mL). Pd/C (0.025 mmol, 5 mol%) was then added with vigorous stirring [17], followed by the potassium aryltrifluoroborate (**1**, 0.50 mmol) and the arenediazonium tetrafluoroborate (**2**, 0.60 mmol). The mixture was placed in an oil bath (75 – 80 °C) and heated to reflux for 1 – 3 hr, after which time the diazonium salt had been consumed (indicated by the absence of a reddish-purple color upon treatment of a sample of the reaction mixture with an alkaline solution of H-acid (4-amino-5-hydroxy-2,7-naphthalenedisulfonic acid)). The reaction mixture was diluted with dichloromethane (10 mL), then filtered by vacuum through a small plug of silica gel, and the silica gel was rinsed with additional dichloromethane (20 mL). The combined organic filtrates were washed with 5% NH₃(aq) (15 mL); saturated NaCl(aq) (10 mL), dried (Na₂SO₄) and evaporated *in vacuo*. The resulting crude product was purified by flash column chromatography (hexane/ethyl acetate). All products listed in Table 2 are known compounds whose spectroscopic data correspond with that found in the literature.

Spectral Data for Isolated Compounds

4-Bromo-4'-methylbiphenyl (3aa) [20]—¹H NMR (300 MHz, CDCl₃): δ 7.57 (d, J = 8.5 Hz, 2H), 7.52 – 7.42 (m, 4H), 7.27 (d, J = 8.0 Hz, 2H), 2.42 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 140.2, 137.6, 137.2, 131.9, 129.7, 128.6, 126.9, 121.3, 21.2. EIMS m/z: 246 (M⁺), 248 (M+2).

4-Chloro-4'-methylbiphenyl (3ab) [20]—¹H NMR (300 MHz, CDCl₃): δ 7.61 – 7.38 (m, 6H), 7.29 (d, J = 7.7 Hz, 2H), 2.45 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 139.7, 137.6, 137.2, 133.1, 129.8, 129.0, 128.3, 126.9, 21.2. EIMS m/z: 202 (M⁺), 204 (M+2).

4'-Methylbiphenyl-4-carbonitrile (3ac) [21]—¹H NMR (300 MHz, CDCl₃): δ 7.74 – 7.63 (m, 4H), 7.49 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 2.41 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 145.7, 138.8, 136.4, 132.6, 129.9, 127.6, 127.1, 119.1, 110.6, 21.3. EIMS m/z: 193 (M⁺).

4-Methyl-4'-nitrobiphenyl (3ad) [22]— ^1H NMR (300 MHz, CDCl_3): δ 8.27 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 147.7, 147.0, 139.2, 135.9, 130.0, 127.6, 127.3, 124.2, 21.3. EIMS m/z : 213 (M^+).

4,4'-Dimethylbiphenyl (3ae) [20]— ^1H NMR (300 MHz, CDCl_3): δ 7.52 (d, J = 8.2 Hz, 4H), 7.28 (d, J = 8.2 Hz, 4H), 2.43 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 138.4, 136.8, 129.6, 126.9, 21.2. EIMS m/z : 182 (M^+).

2,4'-Dimethylbiphenyl (3af) [23]— ^1H NMR (300 MHz, CDCl_3): δ 7.24 (br s, 8H), 2.42 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 142.0, 139.1, 136.4, 135.5, 130.4, 129.9, 129.2, 128.9, 127.2, 125.8, 21.3, 20.6. EIMS m/z : 182 (M^+).

4-Methoxy-4'-methylbiphenyl (3ag) [20]— ^1H NMR (300 MHz, CDCl_3): δ 7.58 – 7.41 (m, 4H), 7.25 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.5 Hz, 2H), 3.86 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 159.1, 138.1, 136.4, 133.9, 129.5, 128.1, 126.7, 114.2, 55.4, 21.1. EIMS m/z : 198 (M^+).

2-Methoxy-4'-methylbiphenyl (3ah) [24]— ^1H NMR (300 MHz, CDCl_3): δ 7.44 (d, J = 8.0 Hz, 2H), 7.37 – 7.28 (m, 2H), 7.24 (d, J = 8.5 Hz, 2H), 7.07 – 6.94 (m, 2H), 3.82 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 156.6, 136.7, 135.7, 130.9, 130.8, 129.5, 128.8, 128.4, 120.9, 111.3, 55.6, 21.2. EIMS m/z : 198 (M^+).

1-(4'-Bromobiphenyl-4-yl)ethanone (3ba) [25]— ^1H NMR (300 MHz, CDCl_3): δ 8.02 (d, J = 8.5 Hz, 2H), 7.70 – 7.53 (m, 4H), 7.48 (d, J = 8.5 Hz, 2H), 2.63 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 197.6, 144.6, 138.9, 136.3, 132.2, 129.1, 128.9, 127.1, 122.7, 26.7. EIMS m/z : 274 (M^+), 276 ($\text{M}+2$).

4-Bromo-4'-methoxybiphenyl (3ca) [26]— ^1H NMR (300 MHz, CDCl_3): δ 7.58 – 7.46 (m, 4H), 7.45 – 7.38 (m, 2H), 7.01 – 6.94 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 159.5, 139.8, 132.6, 131.9, 128.4, 128.1, 120.9, 114.4, 55.5. EIMS m/z : 262 (M^+), 264 ($\text{M}+2$).

4-Methoxy-4'-nitrobiphenyl (3ce) [22]— ^1H NMR (300 MHz, CDCl_3): δ 8.26 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 160.6, 147.3, 146.7, 131.2, 128.7, 127.2, 124.2, 114.7, 55.5. EIMS m/z : 229 (M^+).

4,4'-Dimethoxybiphenyl (3cg) [20]— ^1H NMR (300 MHz, CDCl_3): δ 7.48 (d, J = 8.8 Hz, 4H), 6.96 (d, J = 8.5 Hz, 4H), 3.84 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 158.8, 133.6, 127.8, 114.3, 55.4. EIMS m/z : 214 (M^+).

2,2'-Dimethoxybiphenyl (3dh) [20]— ^1H NMR (300 MHz, CDCl_3): δ 7.37 – 7.29 (m, 2H), 7.28 – 7.21 (m, 2H), 7.06 – 6.93 (m, 4H), 3.77 (s, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 157.2, 131.6, 128.7, 128.0, 120.5, 111.2, 55.8. EIMS m/z : 214 (M^+).

3-(4-Bromophenyl)thiophene (3ea) [27]—¹H NMR (300 MHz, CDCl₃): δ 7.55 – 7.50 (m, 2H), 7.49 – 7.43 (m, 3H), 7.41 – 7.38 (m, 1H), 7.37 – 7.33 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 141.2, 134.9, 132.0, 128.1, 126.7, 126.2, 121.1, 120.7. EIMS m/z: 238 (M⁺), 240 (M+2).

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Scheme 1.

Table 1Effect of catalyst and catalyst loading^a

			Yields ^b	
Entry	Catalyst	Mol% Pd	3aa ^c	PhBr ^d
1	10% Pd/C	10	93	16
2	10% Pd/C	5	92	14
3	10% Pd/C	2	83	19
4 ^e	Pd EnCat™ 30	5	54	25
5 ^e	Pd(OAc) ₂	5	61	29
6 ^e	None	0	6	65

^aExperiments carried out with 0.5 mmol **1a**, 0.6 mmol (1.2 equiv.) **2a**, in 2 mL refluxing MeOH.^bReported yields determined by GC using an internal standard, and are an average of at least 2 runs.^cBased on **1a**.^dBased on **2a**.^eYields based on one run only.

Table 2Scope and limitations of the Pd/C-catalyzed cross-coupling reaction^a

Entry	Ar	R	Product	Yield ^{b,c}
1	4-CH ₃ C ₆ H ₄ (1a)	4-Br (2a)	3aa	89
2	4-CH ₃ C ₆ H ₄ (1a)	4-Cl (2b)	3ab	90
3	4-CH ₃ C ₆ H ₄ (1a)	4-CN (2c)	3ac	85
4	4-CH ₃ C ₆ H ₄ (1a)	4-NO ₂ (2d)	3ad	96
5	4-CH ₃ C ₆ H ₄ (1a)	4-CH ₃ (2e)	3ae	85
6	4-CH ₃ C ₆ H ₄ (1a)	2-CH ₃ (2f)	3af	18 ^d
7	4-CH ₃ C ₆ H ₄ (1a)	4-CH ₃ O (2g)	3ag	89
8	4-CH ₃ C ₆ H ₄ (1a)	2-CH ₃ O (2h)	3ah	82
9	4-CH ₃ COC ₆ H ₄ (1b)	4-Br (2a)	3ba	91
10	4-CH ₃ OC ₆ H ₄ (1c)	4-Br (2a)	3ca	75
11	4-CH ₃ OC ₆ H ₄ (1c)	4-NO ₂ (2e)	3ce	62
12	4-CH ₃ OC ₆ H ₄ (1c)	4-CH ₃ O (2g)	3cg	87
13	2-CH ₃ OC ₆ H ₄ (1d)	2-CH ₃ O (2h)	3dh	81
14	Thiophene-3-yl (1e)	4-Br (2a)	3ea	82

^aExperiments carried out with 0.5 mmol of potassium organotrifluoroborate, 0.6 mmol (1.2 equiv.) arenediazonium salt, 0.025 mmol (5 mol%) of 10% Pd/C in 2 mL refluxing MeOH.

^bUnless otherwise indicated, reported yields are of isolated, chromatographically purified product.

^cBased on potassium aryltrifluoroborate.

^dIsolated product ~75% pure by GC. Balance is mainly homocoupling products.

Table 3Effect of catalyst grade^a

Entry	Catalyst Grade (%Pd, description)	Yield (mmol) ^b	TOF (h ⁻¹) ^c
1	Acros sample (10%, unknown distribution and oxidation state)	0.15	139
2	Acros sample (10%, unknown distribution and oxidation state) + H ₂ O (14 μL)	0.13	120
3	Evonik E2 (5%, uniform, oxidic)	0.22	204
4	Evonik E3 (5%, eggshell, oxidic)	0.11	102
5	Evonik E4 (10%, Pearlman)	0.01	9
6	Evonik E5 (5%, eggshell, reduced)	0.19	176

^aReaction carried out with 0.25 mmol **2a**, 0.3 mmol (1.2 equiv.) **1a**, 0.013 mmol (5 mol%) of Pd/C in 1 mL MeOH at 50°C, quenched after 5 min.^bReported yields were determined by GC using an internal standard, and are an average of two experiments.^cTOF = mmole **3aa**/0.013 mmole Pd/0.083 h.