An Efficient High Yielding Approach for the Homocoupling of Aryl Boronic Acids

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Abstract: A concise, mild, and high yielding method yielding C_2-symmetric biaryls is described. The addition of Cu(II) nitrate enhances the rate and the yield of the desired biaryl products. The conditions employed have yielded a number of substituted symmetric biaryls including 1,1′ and 2,2′ BINAP and are useful for the producing symmetric biaryls from their corresponding aryl boronic acids.

Key Words: arenes, biaryls, coupling, palladium catalyzed reactions

Biaryls exhibit a wide variety of physical and chemical properties[1] with versatile applications in pharmaceuticals, polymers, nonlinear optics,[2] liquid crystals,[3] and optically active ligands.[4] The diverse applications of these molecules has recently led to a number of transition metal catalyzed approaches to yield the biaryl moiety. Recently, the preparation of biaryls by the Pd(0) catalyzed cross coupling of aryl halides with aryl stannanes,[5] arylboronic acids,[6] and arylzinc derivatives[7] have been used. The homocoupling of aryl halides in the presence of nickel(II)[8] complexes, activated copper,[9] indium metal,[10] and palladium(II) acetate[11] have been shown to yield biaryls in good yield. Additionally, the synthesis of biaryls from the homocoupling of organostannanes,[12] organotellurides,[13] and organosilicon[14] compounds have been reported in the literature. Notably absent in the literature is a concise method for the homocoupling of aryl boronic acids yielding symmetric biphenyls.

Moreno-Manas et al. have reported a mechanistic study on the self-coupling of aryl boronic acids[15] with acceptable yields for a small number of aryl boronic acids. Although the initial findings for this method appear promising, the versatility of the reaction with respect to various functional groups and steric hindrance has not been fully investigated. Moreover, the self-coupling method described requires the isolation of the organoboronic acid precursor. Although these compounds are generally stable, their high solubility in aqueous solvents often complicates their isolation and purification. Intrigued by this initial report we set out to examine the scope of this interesting reaction in the hopes of developing a facile reaction for producing symmetric biaryl compounds from their organoboron precursors.

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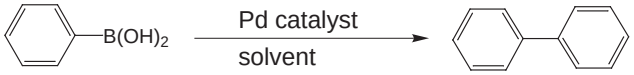
Our interests in a number of naturally occurring biaryl moieties in natural products led to the investigation of a number of convenient and high yielding approaches for the synthesis of biaryl compounds. The palladium catalyzed cross coupling between a formal electrophile C–X and organometallic species C–B is a versatile synthetic method for contemporary carbon–carbon bond formation.[16] Furthermore, Suzuki coupling has become increasingly popular due to its compatibility with a variety of functional groups, the stability of the organoboron precursors, and the ease of working up the reaction mixture. As such, a wide variety of aryl boronic acids are available commercially. The development of a homocoupling reaction of aryl boronic acids would be convenient in allowing the synthesis of a wide variety of C_2-symmetric biaryls.

One troublesome feature of the Suzuki coupling reaction is that no generally applicable set of reaction conditions has been found to effect this reaction. A variety of solvents, bases, and catalysts must be evaluated with respect to each unique substrate. We began our investigation optimizing the solvent and catalyst for the homocoupling of phenyl boronic acid (Table 1) under the conditions employed in the current literature. After 48 hours only entries 13 and 14 showed significant formation of the desired product. Although aqueous carbonate bases are frequently employed,[17] we observed no product formation in the presence of sodium carbonate or cesium carbonate. The base is thought to form a boronate anion that is capable of effecting boron to palladium transmetallation.[18] The relatively poor nucleophilicity of the acetate anion and the weakness of the palladium-oxygen bond suggest that acetate could act as a valuable base in the transmetallation process. In addition, mechanistic studies have shown[15] that atmospheric oxygen or oxygen enriched conditions accelerates the desired homocoupling reaction. Thus, the homocoupling of boronic acids should be considered as an oxidative coupling process in contrast with reductive couplings of aryl halides, which typically require stoichiometric amounts of reducing agents. The oxidative mechanism for the reaction should then be accelerated by the addition of an oxidizing agent since a reductive elimination is required to form the final biaryls.

We next set out to examine whether or not the addition of an oxidant (Table 2) to the reaction would enhance the proposed oxidative coupling. Selecting the two solvent systems (EtOH and DMF–H_2O, 3:1) that provided the highest yields, we tested a number of oxidizing agents.

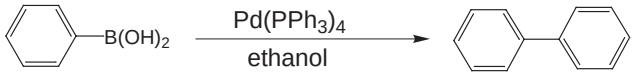
Table 1 Solvent and Catalyst Optimization[a]



Entry	Solvent	Catalyst	% Yield
1	DMF	$Pd(OAc)_2$	0
2	H_2O	$Pd(OAc)_2$	0
3	CH_3CN	$Pd(OAc)_2$	0
4	THF	$Pd(OAc)_2$	0
5	Toluene	$Pd(OAc)_2$	0
6	DMF–H_2O, 3:1	$Pd(OAc)_2$	trace
7	EtOH	$Pd(OAc)_2$	trace
8	DMF	$Pd(PPh_3)_4$	trace
9	H_2O	$Pd(PPh_3)_4$	0
10	CH_3CN	$Pd(PPh_3)_4$	0
11	THF	$Pd(PPh_3)_4$	0
12	Toluene	$Pd(PPh_3)_4$	0
13	DMF–H_2O, 3:1	$Pd(PPh_3)_4$	23
14	EtOH	$Pd(PPh_3)_4$	17

[a] Conditions: Phenyl boronic acid (1.0 equiv), palladium catalyst (0.1 equiv), and NaOAc (5.0 equiv) in the specified solvent at r.t. Yields were determined by GC analysis of the crude reaction mixtures compared to an internal standard after 48 h.

Table 2 Oxidant Evaluation[a]



Entry	Oxidant	% Yield
1	$AgNO_3$	0
2	$HgSO_4$	0
3	$NiSO_4$	0
4	$Zn(NO_3)_2$	trace
5	$Fe(NO_3)_3$	0
6	$Bi(NO_3)_2$	0
7	$Co(NO_3)_2$	23
8	$Cu(NO_3)_2$	88
9	$Cu(NO_3)_2$	0 (in absence of catalyst)

[a] Conditions: Phenyl boronic acid (1.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), NaOAc (5 equiv), specified oxidant (3 equiv) in EtOH at r.t after 8 h.

The majority of the oxidants employed did not enhance the formation of the desired biphenyl. In fact, compared with the results in Table 1 the majority of the oxidants inhibited the formation of biphenyl. Cobalt(II) nitrate gave a slightly enhanced yield while copper(II) nitrate afforded the greatest yield of the product after 8 hours.

Encouraged by the enhancement of the yield of biphenyl by copper(II) nitrate we set out to investigate the general utility of the reaction conditions with a variety of aryl boronic acid precursors. The effect of electron donating and electron withdrawing substituents were examined. In general, electron withdrawing or electron donating substituents did not significantly decrease the yield of the substituted biphenyl when they were present in the 2- or 4- position of the aryl boronic acid. No significant steric effect was exhibited (4-methyl, 71% vs. 2-methyl substituent, 68%) for the aryl boronic acids tested. Furthermore, the conditions employed were tolerant of aryl groups with significant steric effects as exhibited by the high yields of 1,1′ and 2,2′ binapthyl (Table 3, compounds **8** and **9**).

In summary, the general conditions reported herein for the homocoupling of aryl boronic acids are applicable to a number of substituted and sterically demanding boronic acids. This method has a number of advantages including the mild reaction conditions, easily isolable products, and characteristic high yields associated with the homocoupling. Efforts in our laboratory are focused on the further exploration concerning the scope, limitations, and mechanistic aspects of this reaction.

Reagents were used as obtained from commercial sources or purified according to standard procedures. IR spectra were run at r.t. as cast films or nujol mulls on a Perkin Elmer 1450 IR spectrophotometer between 4000 and 600 cm^{-1}. Mass spectral data was obtained by flow injection in electrospray mode (70 eV) on an Applied Biosystems Mariner API-TOF mass spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Jeol GSX400 at ambient temperature operating at 400 MHz and 100 MHz respectively and are referenced to residual proteo solvent or internal TMS. In some cases peaks denoted q, CH, CH_2, or CH_3 were determined using DEPT experiments. Analytical TLC was carried out on Whatman silica G/UV plates and developed with hexane. Visualization was carried out using short (265 nm) and long (360 nm) wave UV light as well as by staining with iodine. Column chromatography was carried out using Merck silica 60 eluted with hexane. Melting points were measured using a Mel-Temp apparatus and are uncorrected. All literature melting points were obtained from the Aldrich catalogue.

Biphenyl (1); Typical Procedure

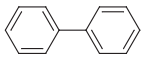
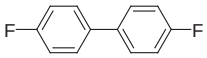
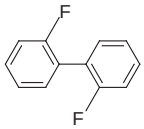
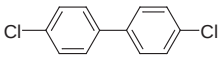
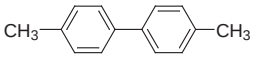
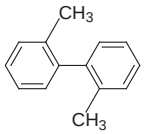
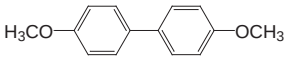
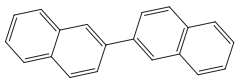
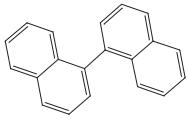
Phenylboronic acid (150 mg, 1.23 mmol), $Pd(PPh_3)_4$ (75 mg, 0.065 mmol), and NaOAc (501 mg, 6.11 mmol) were dissolved in 95% EtOH (20 mL) with stirring. After 2 hours at r.t., copper(II) nitrate (231 mg, 0.90 mmol) was added to the soln and the reaction stirred for 8 h at r.t. The solvent was removed in vacuo and the solid residue was chromatographed on silica using hexane to yield 76.0 mg (80%) of the title compound as white crystals.

Mp 69–70 °C (Lit. 69–71 °C).

IR: 3046, 1669, 1481, 1377, 1092, 730, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 7.79 Hz, 2 H), 7.41 (t, *J* = 7.79 Hz, 2 H), 7.32 (t, *J* = 7.45 Hz, 1 H).

Table 3 Substituted Biaryl Synthesis[a]

Compound	Ar	Product	Yield %[b]
1	Phenyl		80
2	4-Fluorophenyl		66
3	2-Fluorophenyl		61
4	4-Chlorophenyl		72
5	4-Methylphenyl		71
6	2-Methylphenyl		68
7	4-Methoxyphenyl		16[c]
8	2-Napthyl		81
9	1-Napthyl		78

[a] Conditions: Aryl boronic acid (1.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), NaOAc (5.0 equiv) and $Cu(NO_3)_2$ (3.0 equiv) were added to 95% EtOH and the soln allowed to stir at ambient temperature for 8 h. The solvent was removed in vacuo, the reaction mixture was chromatographed on silica with hexane, and the product fractions were combined.
[b] Isolated yield.
[c] The reaction also afforded 4-methoxybiphenyl (19%).

^{13}C NMR: δ = 140.8 (q), 128.4, 126.9, 126.8 (3 × CH).

4,4′-Difluorobiphenyl (2)
Yield: 67.0 mg (66%); white crystals.

Mp 90–93 °C (Lit. 92–95 °C).

IR: 3050, 1900, 1612, 1497, 1238, 806, 501 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 7.43 Hz, 2 H), 7.10 (d, *J* = 7.42 Hz, 2 H).

^{13}C NMR: δ = 162.5, 136.5 (2 q), 128.6, 115.7 (2 × CH).

2,2′-Difluorobiphenyl (3)
Yield: 62.0 mg (61%); white crystals.

Mp 115–117 °C (Lit. 116–117 °C).

IR: 3071, 3048, 1681, 1581, 1498, 1276, 1080, 1045, 1006, 1000, 723, 507 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.88 Hz, 1 H), 7.33 (t, *J* = 7.47 Hz, 1 H), 7.31 (t, *J* = 7.46 Hz, 1 H), 7.26 (d, *J* = 7.84 Hz, 1 H).

^{13}C NMR: δ = 137.9, 133.1 (2 q), 130.7, 129.0, 128.8, 126.1 (4 × CH).

4,4′-Dichlorobiphenyl (4)
Yield: 77.0 mg (72%); white crystals.

Mp 142–144 °C (Lit. 142–145 °C).

IR: 3038, 1612, 1583, 1503, 1172, 1006, 726, 509 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.23 Hz, 2 H), 7.38 (d, *J* = 8.22 Hz, 2 H).

^{13}C NMR: δ = 138.2, 133.6 (2 q), 128.7, 127.9 (2 × CH).

4,4′-Dimethylbiphenyl (5)
Yield: 71.0 mg (71%); white crystals.

Mp 117–119 °C (Lit. 118–120 °C).

IR: 3024, 2943, 1610, 1502, 1179, 1003, 725, 503 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 7.22 Hz, 2 H), 7.22 (d, *J* = 7.47 Hz, 2 H), 2.37 (s, 3 H).

^{13}C NMR: δ = 138.4, 136.7 (2 q), 129.5, 126.8 (2 × CH), 21.1 (CH_3).

2,2′-Dimethylbiphenyl (6)
Yield: 67.0 mg (68%); off white crystals.

Mp 17–18 °C (Lit. 18 °C).

IR: 3030, 2945, 1607, 1511, 1168, 1004, 723, 506 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 7.33 Hz, 1 H), 7.32 (t, *J* = 7.32 Hz, 1 H), 7.27 (t, *J* = 7.40 Hz, 1 H), 7.24 (d, *J* = 7.38 Hz, 1 H).

^{13}C NMR: δ = 136.5, 135.6 (2 q), 129.4, 128.9, 126.3, 126.1 (4 × CH).

4,4′-Dimethoxybiphenyl (7)
Yield: 16.0 mg (16%); light yellow crystals.

Mp 155–157 °C (Lit. 179–180 °C).

IR: 2925, 2890, 1595, 1490, 1250, 1050, 810, 790 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.76 Hz, 2 H), 6.97 (d, *J* = 8.80 Hz, 2 H), 3.86 (s, 3 H).

^{13}C NMR: δ = 158.9, 133.7 (2 q), 127.9, 114.4 (2 × CH), 55.5 (OCH_3).

1,1′-Binaphthyl (8)
Yield: 90.0 mg (81%); white crystals.

Mp 158–160 °C (Lit. 158–160 °C)

IR: 3073, 3058, 1590, 1505, 1402, 1385, 1216, 1200, 1137, 793, 739, 682, 620 cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.95 (m, 2 H), 7.59 (t, *J* = 7.83 Hz, 1 H), 7.47 (m, 2 H), 7.39 (d, *J* = 7.68 Hz, 1 H), 7.28 (t, *J* = 7.66 Hz, 1 H).

^{13}C NMR: δ = 138.4, 133.5, 132.8 (3 q), 128.0, 127.8, 126.5, 125.9, 125.7, 125.3 (6 × CH).

2,2′-Binaphthyl (9)
Yield: 87.0 mg (78%); white crystals.

Mp 183–185 °C (Lit. 187–188 °C).

IR: 3073, 1966, 1594, 1499, 1392, 1201, 1011, 883, 816, 627, 469 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.96 (d, *J* = 7.12 Hz, 1 H), 7.94 (d, *J* = 7.39 Hz, 1 H), 7.89 (d, *J* = 7.51 Hz, 2 H), 7.53 (t, *J* = 7.38 Hz, 1 H), 7.50 (t, *J* = 7.12 Hz, 1 H).

^{13}C NMR: δ = 138.7, 134.0, 133.0 (3 q), 128.6, 128.4, 127.8, 126.4, 126.2, 126.1, 125.8 (7 × CH).

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