Stoichiometric Synthesis of Unsymmetrical Mononitrobiphenyls via the Palladium-Catalyzed Cross-Coupling of Arylboronic Acids with Aryl Bromides

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The palladium-catalyzed cross-coupling of arylboronic acids with aryl bromides is demonstrated to be an excellent method for synthesis of mononitrobiphenyls in a stoichiometric fashion. The reaction is not sensitive to steric requirements and has the added versatility of allowing the nitro substituent to be on either the aryl bromide or the arylboronic acid component.

Although there are many methods of forming biphenyls using aryl–aryl bond-forming reactions,[1] the variety is severly limited when one wishes to obtain unsymmetrical biphenyls with a nitro substituent in only one ring. Even some successful approaches are not viable if one wants to carry out the reaction in a near stoichiometric fashion relative to the two aromatic components. For example, deamination of nitroanilines gives satisfactory yields of biphenyls but the non-amine aromatic substrate is present as the solvent.[2] Cornforth et al.[3] have shown that 1,3-dinitrobenzene can be coupled with aryl iodides by using copper(I) *tert*-butoxide in a stoichiometric reaction; unfortunately this process seems to be limited to 1,3-dinitrobenzene. Kashin et al.[4] have used the coupling of aryltrimethyltin reagents with nitro-substituted aryl iodides catalyzed by palladium complexes; the reaction works well if the tin reagents are readily available with the only drawback being that it is run under sealed-tube conditions. The most successful solution to this problem to date is the palladium-catalyzed reaction of arylzinc reagents with aryl halides developed by Negishi et al.,[5] in this way phenylzinc chloride (1.5 equiv) was coupled with *p*-iodonitrobenzene (1.0 equiv) to give 4-nitrobiphenyl in 74% isolated yield.

In hopes of developing a more versatile approach to unsymmetrical mononitrobiphenyls, we chose to investigate the procedure of Suzuki et al.[6] involving the palladium-catalyzed cross-coupling of phenylboronic acid with aryl bromides. Although nitro-substituted aryl bromides have not been investigated, Suzuki did show that the electrophilic carbomethoxy group worked quite well. From the nature of the reagents and reaction conditions used it seemed that the presence of a nitro substituent on either the aryl bromide *or* the arylboronic acid should not interfer with the reaction. Another advantage to this approach would be the near stoichiometric conditions relative to the arylboronic acid (1.1 equiv) and aryl bromide (1.0 equiv) employed. This paper describes the application of the Suzuki methodology to the synthesis of unsymmetrical mononitrobiphenyls.

Results and Discussion

The arylboronic acids are conveniently prepared by reaction of the appropriate aryl-Grignard reagent with trimethyl borate followed by hydrolysis:[7]

$$\mathrm{ArMgX} \xrightarrow[\text{(2) hydrolysis}]{\text{(1) } (\mathrm{MeO})_3\mathrm{B}} \mathrm{ArB(OH)_2}$$

We first studied the cross-coupling of arylboronic acids with nitroaryl bromides under the Suzuki reaction conditions;[6] the results of this study are shown in Table I. As can be seen the reaction of phenylboronic acid with either *o*- or *m*-bromonitrobenzene gave excellent yields of the desired mononitrobiphenyls, indicating that the position of the nitro substituent was unimportant. In order to probe the steric limitations of the cross-coupling reaction, *o*-tolylboronic acid was coupled with *o*-bromonitrobenzene to give 2-methyl-2′-nitrobiphenyl in 98% isolated yield; one did have to increase the reaction time from 6 to 9 to obtain complete reaction. A more stringent test of the steric limitations was the reaction of mesitylboronic acid with *o*-bromonitrobenzene. The desired coupled product was obtained in 88% isolated yield, but the reaction time had to be increased to 48 h. From these results it can be seen that the cross-coupling reaction of arylboronic acids with nitroaryl bromides is quite general and is not limited by electronic or steric requirements.

Next we investigated the coupling of (3-nitrophenyl)-boronic acid with aryl bromides; the results of this study are shown in Table II. Again one can see that the isolated yields are excellent and that there is no steric constraint on the reaction as seen from the near quantitative yield upon reaction with mesityl bromide. This ability to have the nitro substituent on the non-aryl halide component of the coupling reaction is in contrast to Negishi's arylzinc procedure.

Conclusion

We have demonstrate that the palladium-catalyzed cross-coupling of arylboronic acids with aryl bromides is an excellent method for preparation of mononitrobiphenyls in a stoichiometric fashion. The reaction does not seem to be sensitive to steric requirements and has the added versatility of allowing the nitro substituent to be on either the aryl bromide or arylboronic acid component.

Experimental Section

All melting points (mp) are reported uncorrected. Infrared (IR) spectra were recorded on a Beckman IR-8 spectrophotometer. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM-390 instrument; chemical shifts are reported in parts per million downfield from internal tetramethylsilane. High-resolution mass spectra were obtained with a Du Pont 492 spectrometer through the Facility for Advanced Instrumentation,

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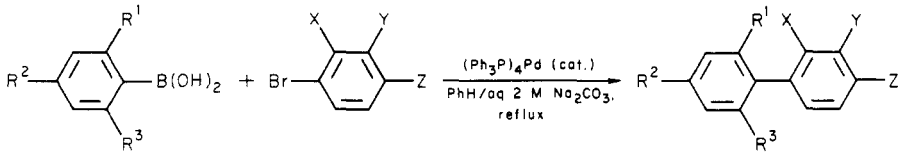
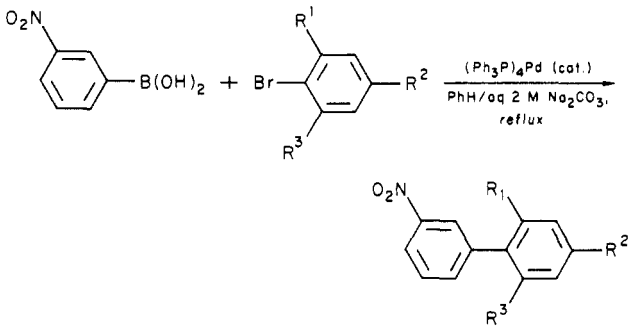
Table I. Coupling of Arylboronic Acids with Nitrobromobenzenes



arylboronic acid			nitrobromobenzene			reactn time, h	% isolated yield of biphenyl
R^1	R^2	R^3	X	Y	Z		
H	H	H	NO_2	H	H	6	98
H	H	H	H	NO_2	H	6	93
Me	H	H	NO_2	H	H	9	98
Me	H	H	H	NO_2	H	9	99
H	Me	H	NO_2	H	H	9	99
H	Me	H	H	NO_2	H	9	98
H	Me	H	H	H	NO_2	9	98
Me	Me	Me	NO_2	H	H	48	88
Me	Me	Me	H	NO_2	H	48	95

Table II. Coupling of (3-Nitrophenyl)boronic Acid with Aryl Bromides



aryl bromide			reactn time, h	% isolated yield of biphenyl
R^1	R^2	R^3		
H	H	H	6	95
Me	H	H	9	98
Me	Me	Me	48	99

University of California, Davis. All reactions were carried out under a nitrogen atmosphere.

General Coupling Procedure. A 50-mL two-necked round-bottomed flask was charged with the aryl bromide (1 equiv), tetrakis(triphenylphosphine)palladium (3 mol %, Aldrich), benzene (10 mL), and aqueous sodium carbonate solution (5 mL of a 2 M solution). To this vigorously stirred mixture was added the arylboronic acid (1.1 equiv) dissolved in a minimum amount of 95% ethanol. The reaction mixture was heated to 90–95 °C and refluxed for the appropriate length of time under vigorous stirring. Then the reaction was allowed to cool to room temperature, and the excess boronic acid was oxidized by 30% hydrogen peroxide (0.25 mL) for 1 h. The mixture was extracted with diethyl ether, washed with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was removed, and, unless otherwise noted, the crude product was purified by chromatography on Florisil (80–100 mesh, J. T. Baker) eluting with pentane/dichloromethane (90/10–80/20).

Table I. (a) Coupling of Phenylboronic Acid with 2-Bromonitrobenzene. Following the general procedure, 2-bromonitrobenzene (1.01 g, 5 mmol) was reacted for 6 h with phenylboronic acid[7] (671 mg, 5.5 mmol) to give 2-nitrobiphenyl (974 mg, 98% yield): mp (ether/pentane) 37–37.5 °C [lit.[8] 36.5–37.5 °C]; NMR ($CDCl_3$) δ 7.20–7.73 (m, 8 H), 7.83 (m, 1 H); IR (melt) 1530 (s), 1355 (s), 860 (m), 785 (m), 775 (m), 745 (s), 705 (s), 670 (m) cm^{-1}.

(b) Coupling of Phenylboronic Acid with 3-Bromonitrobenzene. Following the general procedure, 3-bromonitrobenzene (1.01 g, 5 mmol) was reacted for 6 h with phenylboronic acid[7] (671 mg, 5.5 mmol) to give 3-nitrobiphenyl (928 mg, 93% yield): mp (ether/pentane) 58–59 °C [lit.[8] 59 °C]; NMR ($CDCl_3$) δ 7.33–7.79 (m, 6 H), 7.80–8.04 (m, 1 H), 8.10–8.33 (m, 1 H), 8.45 (t, J = 2.2 Hz, 1 H); IR (mineral oil mull) 1525 (s), 1350 (s), 775 (m), 770 (m), 735 (s), 695 (m) cm^{-1}.

(c) Coupling of (2-Methylphenyl)boronic Acid with 2-Bromonitrobenzene. Following the general procedure, 2-bromonitrobenzene (1.01 g, 5 mmol) was reacted for 9 h with (2-methylphenyl)boronic acid[9] (748 mg, 5.5 mmol) to give 2-methyl-2′-nitrobiphenyl (1.04 g, 98% yield): mp (ether/pentane) 63–64 °C [lit.[8] 62 °C]; NMR ($CDCl_3$) δ 2.10 (s, 3 H), 7.00–7.80 (m, 7 H), 8.04 (dd, J = 9 Hz, 1.5 Hz, 1 H); IR (melt) 1525 (s), 1355 (s), 860 (m), 790 (m), 770 (s), 755 (s), 730 (s), 710 (m), 670 (m) cm^{-1}.

(d) Coupling of (2-Methylphenyl)boronic Acid with 3-Bromonitrobenzene. Following the general procedure, 3-bromonitrobenzene (1.01 g, 5 mmol) was reacted for 9 h with (2-methylphenyl)boronic acid[9] (748 mg, 5.5 mmol) to give 2-methyl-3′-nitrobiphenyl (1.06 g, 99% yield): mp (ether/pentane) 70–71 °C [lit.[8] 68–71 °C]; NMR ($CDCl_3$) δ 2.29 (s, 3 H), 7.09–7.42 (m, 4 H), 7.49–7.75 (m, 2 H), 8.12–8.33 (m, 2 H); IR (mineral oil mull) 1525 (s), 1345 (s), 900 (m), 880 (m), 770 (s), 740 (s), 725 (m), 695 (s) cm^{-1}.

(e) Coupling of (4-Methylphenyl)boronic Acid with 2-Bromonitrobenzene. Following the general procedure, 2-bromonitrobenzene (505 mg, 2.50 mmol) was reacted for 9 h with (4-methylphenyl)boronic acid[9] (374 mg, 2.75 mmol) to give 4-methyl-2′-nitrobiphenyl (532 mg, 99% yield): mp (ether/pentane) 37–38 °C [lit.[8] 37 °C]; NMR ($CDCl_3$) δ 2.40 (s, 3 H), 7.29 (s, 4 H), 7.30–7.76 (m, 3 H), 7.76–7.93 (m, 1 H); IR (melt) 1530 (s), 1360 (s), 860 (s), 825 (s), 790 (s), 755 (s) cm^{-1}.

(f) Coupling of (4-Methylphenyl)boronic Acid with 3-Bromonitrobenzene. Following the general procedure, 3-bromonitrobenzene (1.01 g, 5 mmol) was reacted for 9 h with (4-methylphenyl)boronic acid[9] (748 mg, 5.5 mmol) to give 4-methyl-3′-nitrobiphenyl (1.04 g, 98% yield): mp (methanol) 78–79 °C [lit.[10] 76.5 °C]; NMR ($CDCl_3$) δ 2.40 (s, 3 H), 7.27 (d, J = 7.5 Hz, 2 H), 7.46 (s, 1 H), 7.60 (d, J = 7.5 Hz, 2 H), 7.80–8.00 (m, 1 H), 8.06–8.27 (m, 1 H), 8.43 (t, J = 2.3 Hz, 1 H); IR (melt) 1525 (s), 1350 (s), 880 (m), 830 (s), 810 (s), 750 (s) cm^{-1}.

(g) Coupling of (4-Methylphenyl)boronic Acid with 4-Bromonitrobenzene. Following the general procedure, 4-bromonitrobenzene (505 mg, 2.50 mmol) was reacted for 9 h with (4-methylphenyl)boronic acid[9] (374 mg, 2.75 mmol) to give 4-methyl-4′-nitrobiphenyl (522 mg, 98% yield): mp (methanol 140–141 °C [lit.[11] 143.5–144.5 °C]; NMR ($CDCl_3$) δ 2.40 (s, 3 H), 7.25 (d, J = 7.5 Hz, 2 H), 7.50 (d, J = 7.5 Hz, 2 H), 7.69 (d, J =

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9 Hz, 2 H), 8.25 (d, J = 9 Hz, 2 H); IR (mineral oil mull) 1510 (s), 1335 (s), 825 (s) cm^{-1}.

(h) Coupling of (2,4,6-Trimethylphenyl)boronic Acid with 2-Bromonitrobenzene. Following the general procedure, 2-bromonitrobenzene (505 mg, 2.50 mmol) was reacted for 48 h with (2,4,6-trimethylphenyl)boronic acid[9] (451 mg, 2.75 mmol). The crude product was purified on a basic alumina (grade III) column eluting with pentane/dichloromethane (50/50) to give 2-nitro-2′,4′,6′-trimethylbiphenyl (532 mg, 88% yield): mp (ethanol/water) 63–64 °C [lit.[12] 55–56 °C]; NMR ($CDCl_3$) δ 1.96 (s, 6 H), 2.31 (s, 3 H), 6.92 (s, 2 H), 7.14–7.80 (m, 3 H), 8.00 (d of d, J = 7.5 Hz, 3.0 Hz, 1 H); IR (melt) 1530 (s), 1355 (s), 860 (s), 790 (m) 760 (s), 710 (m) cm^{-1}; high-resolution mass spectrum, m/e calcd for $C_{15}H_{15}NO_2$ 241.1103, found 241.1127.

(i) Coupling of (2,4,6-Trimethylphenyl)boronic Acid with 3-Bromonitrobenzene. Following the general procedure, 3-bromonitrobenzene (1.01 g, 5 mmol) was reacted for 48 h with (2,4,6-trimethylphenyl)boronic acid[9] (902 mg, 5.5 mmol). The crude product was purified on a basic alumina column (grade III) eluting with pentane/dichloromethane (50/50) to give 3-nitro-2′,4′,6′-trimethylbiphenyl (1.15 g, 95% yield): mp (pentane) 82–83 °C [lit.[13] 83–84 °C]; NMR ($CDCl_3$) δ 2.00 (s, 6 H), 2.33 (s, 3 H), 6.98 (s, 2 H), 7.37–7.72 (m, 2 H), 8.00–8.13 (m, 1 H), 8.22 (t of d, J = 7.5 Hz, 2.2 Hz, 1 H); IR (mineral oil mull) 1525 (s), 1345 (s), 855 (m), 810 (m), 750 (m), 730 (s), 695 (s) cm^{-1}.

Table II. (a) Coupling of (3-Nitrophenyl)boronic Acid with Bromobenzene. Following the general procedure, bromobenzene (196 mg, 1.25 mmol) was reacted for 6 h with (3-nitrophenyl)boronic acid[14] (230 mg, 1.38 mmol) to give 3-nitrobiphenyl (237 mg, 95% yield). The product obtained by this route was identical with that obtained by coupling phenylboronic acid with 3-bromonitrobenzene.

(b) Coupling of (3-Nitrophenyl)boronic Acid with 2-Bromotoluene. Following the general procedure, 2-bromotoluene (214 mg, 1.25 mmol) was reacted for 9 h with (3-nitrophenyl)-boronic acid[14] (230 mg, 1.38 mmol) to give 2-methyl-3′-nitrobiphenyl (260 mg, 98% yield). The product obtained by this route was identical with that obtained by coupling (2-methylphenyl)-boronic acid with 3-bromonitrobenzene.

(c) Coupling of (3-Nitrophenyl)boronic Acid with 2-Bromomesitylene. Following the general procedure, 2-bromomesitylene (250 mg, 1.26 mmol) was reacted for 48 h with (3-nitrophenyl)boronic acid[14] (230 mg, 1.38 mmol) to give 3-nitro-2′,4′,6′-trimethylbiphenyl (302 mg, 99% yield). The product obtained by this route was identical with that obtained by coupling (2,4,6-trimethylphenyl)boronic acid with 3-bromonitrobenzene.

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Registry No. $(Ph_3P)_4Pd$, 14221-01-3; 2-nitrobiphenyl, 86-00-0; 3-nitrobiphenyl, 2113-58-8; 2-methyl-2′-nitrobiphenyl, 67992-12-5; 2-methyl-3′-nitrobiphenyl, 51264-60-9; 4-methyl-2′-nitrobiphenyl, 70680-21-6; 4-methyl-3′-nitrobiphenyl, 53812-68-3; 4-methyl-4′-nitrobiphenyl, 2143-88-6; 2,4,6-trimethyl-2′-nitrobiphenyl, 14872-62-9; 2,4,6-trimethyl-3′-nitrobiphenyl, 39117-69-6; phenylboronic acid, 98-80-6; (2-methylphenyl)boronic acid, 16419-60-6; (4-methylphenyl)boronic acid, 5720-05-8; (2,4,6-trimethylphenyl)boronic acid, 5980-97-2; (3-nitrophenyl)boronic acid, 13331-27-6; 2-nitrobromobenzene, 577-19-5; 3-nitrobromobenzene, 585-79-5; 4-nitrobromobenzene, 586-78-7; bromobenzene, 108-86-1; 2-methylbromobenzene, 95-46-5; 2,4,6-trimethylbromobenzene, 576-83-0.

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Photolytic Reaction of Chromium Carbene Complexes with Azobenzenes. Azo Metathesis

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Photolysis of solutions of azobenzenes and chromium carbene complexes in hexane solvent produces mixtures of 1,2- and 1,3-diazetidinones and imino ethers. Electron-rich azobenzenes such as *p*-methoxy- and *p*-(dimethylamino)azobenzene are very reactive, while *p*-nitroazobenzene is virtually inert. The reaction is thought to proceed by a photolytic cycloaddition of the azobenzene to the chromium carbene, followed by insertion/reductive elimination, or by metathesis to give an imino ether and a chromium "nitrene" complex.

Introduction

The inorganic chemistry of heteroatom-stabilized chromium carbene complexes has been extensively developed over the last 20 years.[1] It is only recently that this class of complexes has found application in organic synthesis.[2] Most notable is their use in the cyclopropanation of olefins[2,3] and their reactions with alkynes to produce naphthol or naphthoquinone derivatives.[4] We recently reported the photolytic reaction of chromium carbene complexes with

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