Novel Class of Tertiary Phosphine Ligand Based on a Phospha-adamantane Framework and their Use in the Suzuki Cross-Coupling Reactions of Aryl Halides Under Mild Conditions.

George Adjabeng^a, Tim Brenstrum^a, Jeffrey Wilson^a, Christopher Frampton^b, Al Robertson^c, John Hillhouse^c, James McNulty^a, and Alfredo Capretta^a

^a*Institute of Molecular Catalysis, Department of Chemistry, Brock University, St. Catharines, Ontario, L2S 3A1*; ^b*Department of Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ, U.K.*; ^c*Cytec Canada Inc., PO Box 240, Niagara Falls, Ontario, L2E 6T4, Canada.*

SUPPORTING INFORMATION

General. Starting materials were purchased from Aldrich Chemical Co or Fluka. Di(μ -acetato)bis[o-(di-*o*-tolylphosphino)benzyl] dipalladium was purchased from Strem. *o*-Tolyboronic acid, phenylboronic acid, 4-methoxyphenylboronic acid, and 4-acetylphenylboronic acid were recrystallized from water prior to use. All aryl iodides, bromides and chlorides were distilled or recrystallized prior to use, with the exception of 4-chlorobenzonitrile, 2-chloropyrindine, and 4-bromoacetophenone, which were used as received. K₃PO₄ and Cs₂CO₃ were ground to a fine powder using a mortar and a pestle and dried in a vacuum oven prior to use. Toluene was distilled under argon from sodium. ¹H- ¹³C- and ³¹P-NMR spectra were recorded at 300MHz, 75MHz or 81 MHz respectively, on a Bruker Avance DPX-300 spectrophotometer with chloroform-*d* as the solvent and internal reference unless otherwise noted. MS analysis was performed on a Kratos Concept 1S spectrometer. Ions for low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were generated using electron impact (EI). GC analysis was performed on the HP-6890 with FID. For both structures **1**, **2** and **3**, unit cell determinations and data collected on a Rigaku AFC7R diffractometer with graphite-monochromated

Mo-K α radiation ($\lambda = 0.71069$ Å). The structures were solved with direct methods, SHELXS-90¹ and refined with full-matrix least-squares refinement on F^2 with SHELXL-93.² R -values; $R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$, and $wR2 = [\sum w(F_o^2 - F_c^2)^2 / \sum w(F_o^2)^2]^{1/2}$. Further details of the crystal structure investigation can be obtained from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge CB2 1EW, U.K.

Experimental Procedures and Compound Characterization.

1, 3, 5, 7-Tetramethyl-2, 4, 8-Trioxa-6-Phospha-adamantane (1). Prepared according to the procedure described by Epstein and Buckler.³ Melting point 88-90 °C³; ¹H NMR (300 MHz) (CDCl₃) δ 1.38, 1.39 (s, 3 H), 1.44, 1.49 (d, $J = 5.7$ Hz, 3 H), 1.71-1.94 (m, 4 H), 3.08 (d, $J = 190$ Hz, 1 H); ¹³C NMR (75 MHz) (CDCl₃) δ 27.8, 29.0, 29.5 [d, $J(\text{P-C}) = 13.3$ Hz], 30.2 [d, $J(\text{P-C}) = 22.7$ Hz], 42.7 [d, $J(\text{P-C}) = 14.5$ Hz], 45.2 [d, $J(\text{P-C}) = 4.8$ Hz], 70.3 [d, $J(\text{P-C}) = 3.5$ Hz], 72.0 [d, $J(\text{P-C}) = 18.4$ Hz], 96.4, 96.7; ³¹P NMR (81 MHz) (CDCl₃) δ -49.2; MS m/z 216 (M^+ , 15%), 116 (30), 101 (32%), 69 (24%), 43 (100). Crystallographic data for **1**: C₁₀H₁₇O₃P, MW = 216.21, $T = 123(1)$ K, monoclinic space group $P2_1/c$, $a = 8.1422(3)$ Å, $b = 8.0756(2)$ Å, $c = 16.6229(5)$ Å, $\beta = 94.155(1)^\circ$, $V = 1090.14(6)$ Å³, $Z = 4$, $R_1 = 0.0300$ [$I > 2\sigma(I)$], $S = 1.002$.

1, 3, 5, 7-Tetramethyl-2, 4, 8-Trioxa-6-Phenyl-6-Phospha-adamantane (2). A mixture containing 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phospha-adamantane (**1**, 100 g, 0.46 mol), bromobenzene (75 g, 0.48 mol), triethylamine (45 g, 0.45 mol) and di(μ -acetato)bis[o-(di-*o*-tolylphosphino)benzyl] dipalladium (II) (310 mg, 0.331 mmol) was heated to reflux under nitrogen, with magnetic stirring. After 24 hours under these conditions, approximately 79% conversion of **1** to **2** was observed by GC while a 90% conversion observed after 40 hours. The reaction mixture was washed with water (200 mL) and the organic layer separated. Evaporation gave the crude product (160g) as a reddish orange solid. Recrystallization of this material with 95% ethanol (250 mL) gave a white crystalline solid (100g, 75% yield). The compound showed: m.p. 107-110 °C; ¹H NMR (300 MHz) (CDCl₃) δ 1.25 (d, $J = 12.9$ Hz, 3 H), 1.38 (br.s, 6 H), 1.52 (d, $J = 12.7$ Hz, 3 H), 1.78-2.11 (m, 3 H), 7.36-7.38 (m, 3 H), 7.80-7.85 (m, 2 H); ¹³C NMR (75 MHz) (CDCl₃) δ 26.8 [d, $J(\text{P-C}) = 11.5$ Hz], 27.4 [d, $J(\text{P-C}) = 22.1$ Hz], 27.8, 28.0 (s), 36.2 [d, $J(\text{P-C}) = 1.6$ Hz], 45.4 [d, $J(\text{P-C}) = 17.4$ Hz], 73.1 [d, $J(\text{P-C}) = 7.6$ Hz], 73.4 [d, $J(\text{P-C}) = 21.8$ Hz], 96.0, 96.8 (s), 128.3 [d, $J(\text{P-C}) = 7.2$ Hz], 129.4 (s), 133.9 [d, $J(\text{P-C}) = 26.9$ Hz], 135.0 [d, $J(\text{P-C}) = 19.7$ Hz]; ³¹P NMR (81 MHz) (CDCl₃) δ -23.6; MS m/z 292 (M^+ , 16%), 192 (10), 177 (39), 43 (71); HRMS: Found 292.1244, Calculated 292.3099. Crystallographic data for **2**: C₁₆H₂₁O₃P, MW =

292.30, $T = 123(1)$ K, monoclinic space group $P2_1/n$, $a = 7.8551(6)(3)$ Å, $b = 9.1866(7)$ Å, $c = 20.8860(17)$ Å, $\beta = 91.016(3)^\circ$, $V = 1506.9(2)$ Å³, $Z = 4$, $R_1 = 0.0348$ [$I > 2\sigma(I)$], $S = 1.007$.

1, 3, 5, 7-Tetramethyl-2, 4, 8-Trioxa-6-(2'-Tolyl)-6-Phospha-adamantane (3). A mixture containing 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phospha-adamantane (**1**, 100 g, 0.46 mol), *o*-bromotoluene (78 g, 0.46 mol), triethylamine (46 g, 0.46 mol) and nickel acetate tetrahydrate (350 mg, 1.41 mmol) was heated to reflux under nitrogen, with magnetic stirring. During this time the nickel acetate dissolved, generating a reddish brown solution. After 24 hours at reflux, the conversion of **1** to **3** was estimated at approximately 81% via GC. The mixture was washed with water (250 mL), the layers were separated and the organic layer was stripped of volatile components under nitrogen to give a solid residue. This residue was recrystallized from 95% ethanol (200 mL) to give a colourless, crystalline solid (75g, 55% yield). The compound showed: m.p. 102-104 °C; ¹H NMR (300 MHz) (CDCl₃) δ 1.28 (d, $J = 12.2$ Hz, 3 H), 1.43, 1.44 (s, 3 H), 1.47 (d, $J = 12.9$ Hz, 3 H), 1.89-2.15 (m, 3 H), 2.61 (s, 3 H), 7.18-7.27 (m, 3 H), 8.15-8.18 (m, 1 H); ¹³C NMR (75 MHz) (CDCl₃) δ 22.0 [d, $J(\text{P-C}) = 25.4$ Hz], 26.6 [d, $J(\text{P-C}) = 11.3$ Hz], 27.8, (s), 27.9 [d, $J(\text{P-C}) = 19.9$ Hz], 28.0 (s), 36.0 (s), 46.0 [d, $J(\text{P-C}) = 18.9$ Hz], 73.4 [d, $J(\text{P-C}) = 23.2$ Hz], 74.1 [d, $J(\text{P-C}) = 8.0$ Hz], 96.0, 96.8 (s), 125.8, 129.3 (s), 130.6 [d, $J(\text{P-C}) = 5.3$ Hz], 132.2 [d, $J(\text{P-C}) = 28.4$ Hz], 133.3 [d, $J(\text{P-C}) = 3.1$ Hz], 145.2 [d, $J(\text{P-C}) = 28.1$ Hz]; ³¹P NMR (81 MHz) (CDCl₃) δ -38.5; MS m/z 306 (M^+ , 31%), 206 (100), 191 (45), 43 (94); HRMS: Found 306.1384, Calculated 306.3365. Crystallographic data for **3**: C₁₇H₂₃O₃P, MW = 306.32, $T = 123(1)$ K, monoclinic space group $P2_1/n$, $a = 7.4988(6)$ Å, $b = 28.084(2)$ Å, $c = 8.2246(6)$ Å, $\beta = 110.827(2)^\circ$, $V = 1618.9(2)$ Å³, $Z = 4$, $R_1 = 0.0336$ [$I > 2\sigma(I)$], $S = 1.005$.

1, 3, 5, 7-Tetramethyl-2, 4, 8-Trioxa-6-Tetradecyl-6-Phospha-adamantane (4). A stirred solution of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phospha-adamantane (**1**, 256 g, 1.19 mol) and 1-tetradecene (400 g, 2.02 mol) was heated to 90-93°C and treated with 136 g of a solution containing of Vazo® 67 (10 g, 0.05 mol) in toluene (190 g) over 3.5 hr. Greater than 99% of **1** was converted as judged by GC. The mixture was washed with water (250 mL), the layers were separated and the organic layer was stripped of volatile components under vacuum (5 mm Hg) to give a solid residue (406 g, 83% yield). For the purposes of storage, compound **4** was converted to its HBF₄ adduct by adding tetrafluoroboric acid (48 wt% aqueous solution, 1.5 mL, 11.4 mmol) to a solution of **4** (500 mg, 1.71 mmol) in dichloromethane (25 mL). The resulting mixture was stirred for 10 min at which time the organic layer was then separated from the aqueous layer, dried over sodium sulphate and filtered. Removal of the

solvent provided the HBF_4 adduct of **4** (824 mg, 97%) as a white solid. Compound **4** showed: m.p. 41-42 °C (HBF_4 adduct); ^1H NMR (300 MHz) (CDCl_3) δ 0.88 (t, J = 6.5 Hz, 3 H), 1.26 (s, 6 H), 1.29 (d, J = 2.8 Hz, 3 H), 1.33 (d, J = 3.6 Hz, 3 H), 1.36 (s, 4 H), 1.72–1.98 (m, 2 H); ^{13}C NMR (75 MHz) (CDCl_3) δ 14.1 (s), 21.1 [d, $J(\text{P-C})$ = 21.9 Hz], 26.8 [d, $J(\text{P-C})$ = 12.7 Hz], 27.8, 28.0, 28.0 [d, $J(\text{P-C})$ = 17.2 Hz], 28.4 [d, $J(\text{P-C})$ = 21.7 Hz], 29.3, 29.3, 29.5, 29.6, 29.6 (m), 21.4 [d, $J(\text{P-C})$ = 12.5 Hz], 31.9, 31.9 (s), 44.5 [d, $J(\text{P-C})$ = 15.0 Hz], 72.1 [2d, $J(\text{P-C})$ = 22.6 Hz], 95.7, 96.6 (s); ^{31}P NMR (81 MHz) (CDCl_3) δ -28.0; MS m/z 412 (M^+ , 5%), 312 (56), 269 (18), 130 (44), 115 (100), 43 (97); HRMS: Found 412.3094, Calculated 412.5861.

General Procedure for the Suzuki Cross Coupling Reactions. The arylboronic acid (1 mmol), K_3PO_4 or Cs_2CO_3 (2 to 2.4 mmol), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (0.01 to 0.02 mmol), ligand **2** (0.02 to 0.05 mmol added as either a solid or as a 0.20M solution in toluene) and toluene (2 mL) are added to the reaction vessel. The reactions are stirred at room temperature (or heated as required) under argon and the course of the reaction monitored by TLC. At the conclusion of the reaction, the reaction mixture is loaded on to small plug of silica gel and washed with copious amounts of Et_2O or EtOAc . The washings are concentrated and purified by column chromatography on silica gel.

2,2'-Dimethylbiphenyl (Table 1, entry 6). 4-Iodotoluene (218 mg, 1.0 mmol), o-tolylboronic acid (163 mg, 1.2 mmol) K_3PO_4 (509 mg, 2.4 mmol), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (10.4 mg, 0.0100 mmol), ligand **2** (5.8 mg, 0.0200 mmol), and toluene (2 mL). After 2.5 hours at room temperature, work up and column chromatography (hexane) yielded 178 mg (98%) of the title compound as a colorless liquid. ^1H NMR (CDCl_3 , 300 MHz): δ 7.34-7.26 (m, 6H), 7.12 (d, J = 7.5 Hz, 2H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 142.0, 136.2, 130.3, 129.7, 127.6, 126.0, 20.3. MS: 182 (M^+ , 100%), 167 (89)

2-(4-Methoxyphenyl)pyridine (Table 1, entry 15). 2-Chloropyridine (114 mg, 1.0 mmol), 4-methoxyphenylboronic acid (68 mg, 1.1 mmol), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (20.7 mg, 0.020 mmol), ligand **2** (0.25 mL, 0.050 mmol, 0.20 M solution), Cs_2CO_3 (652 mg, 2.0 mmol), and toluene (2 mL). After 24h at room temperature, work up and column chromatography (20% EtOAc in hexane) afforded a light yellow liquid, 165 mg (89%) of the title compound. ^1H NMR (CDCl_3 , 300 MHz): δ 8.44 (d, J = 4.5 Hz, 1H), 7.73 (d, J = 8.6 Hz, 2H), 7.52-7.45 (m, 2H), 7.00-7.95 (m, 1H), 7.28 (d, J = 8.9, 2H), 3.64 (s, 3H). ^{13}C NMR (CDCl_3 , 300 MHz): δ 160.6, 157.1, 149.4, 137.0, 131.8, 128.3, 121.6, 120.1, 114.2, 55.4.

The physical and spectral properties of 4-acetyl-2'-methylbiphenyl⁴ (entries **1**, **4**, **7** and **11**), 4-methoxy-2'-methylbiphenyl⁴ (entries **2**, **5**, **9**, **12** and **20**), 4-acetyl-4'-methoxybiphenyl⁴ (entries **3**, **10** and **17**), 4-*N,N*-dimethylamino-methylbiphenyl⁴ (entry **8**), 2-*o*-tolylpyridine⁴ (entry **14**), 2-phenyltoluene⁴ (entry **18**), 2-phenylpyridine⁵ (entry **13**) and 2'-methyl-biphenyl-2-carbonitrile⁵ (entry **16**) were identical to those previously described.

References.

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