DOI: 10.1002/ejoc.201001099

P-Phenyl-2,2,6,6-tetramethylphosphorinan-4-ol: An Air-Stable P,O-Type Ligand for Palladium-Mediated Cross-Coupling Reactions

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Keywords: Phosphane ligands / Palladium / Organopalladium chemistry / Amination

A two-step entry to a chemically robust, hindered P,O-type phosphorinane-based ligand and its application toward Pd-mediated cross-coupling reactions of unactivated aryl chlorides is presented.

Introduction

Palladium-catalyzed bond-forming reactions have been extensively investigated over the last few decades. Many of these reactions are now routinely employed in effecting carbon-carbon and carbon-heteroatom bond connections, often with remarkable chemo- and stereoselectivity and complete positional control.[1,2] Applications towards the synthesis of agrochemicals, pharmaceuticals and fine chemicals continue to advance.[3] The continued improvements to supporting ligands has expanded the scope of substrates that enter such catalytic cycles to include the most challenging unactivated (electron-rich), sterically demanding aryl chlorides.

A difficulty in the development of phosphane ligands for Pd-mediated cross-coupling chemistry remains the advancement of chemically robust (particularly to molecular oxygen) ligands of applicability to a range of challenging cross-coupling reactions. The *P*-disubstituted-biarylphosphanes (for example SPhos and **A**, Figure 1) introduced by Buchwald and co-workers have allowed for remarkable advances along these lines[4] although the capricious nature of individual ligands to activate a given substrate has also been documented. Pd complexes of the ligand SPhos (Figure 1) proved generally applicable in Suzuki–Miyaura reactions of congested aryl bromides while, most interestingly, the tri*aryl*phosphane **A** (Figure 1) proved highly effective in activating *ortho*-substituted electron-rich aryl chlorides.[4b] Activation of other electron-rich aryl chlorides with biaryl liagnds has been reported to be problematic in other cases.[5] The use of ferrocene-based triarylphosphane ligands has also been reported in the Suzuki cross-coupling of unactivated, hindered aryl chlorides.[4e,4f]

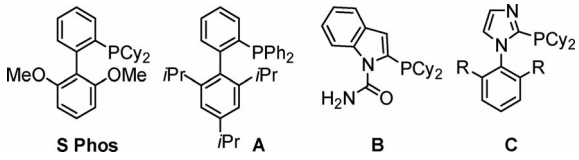

Figure 1. Selected examples of hemilabile phosphane ligands.

The development of novel structural classes of ligand that can effect these problematic cross-coupling reactions is an active area of investigation. Select examples include the P,O-type indolylphosphanes **B** introduced by Kwong and co-workers,[6] and the pyrrole and imidazole based systems **C** introduced by Beller (Figure 1).[7] A modified indolylphosphane was recently reported that proved highly effective in the synthesis of hindered biaryl systems.[6c] Other useful sterically demanding, conformationally restricted ligands have been developed containing N-heterocyclic carbene ligands.[8] The desire to activate inexpensive, readily available aryl chlorides has been a driving force behind the development and application of many of these ligands.[8,9]

We have been interested in the development of a robust, readily available ligand based on a phosphorinane scaffold (Figure 2, **1b**, **2b**).[10] This ligand architecture incorporates a variably substituted phosphane within a rigid, bulky di-*tert*-butyl-like framework. We recently reported that Pd complexes of the *P*-cyclohexyl-4-hydroxy-substituted ligand **2b** were most efficient in a range of Suzuki–Miyaura reactions with aryl chlorides, including hindered, electron-rich systems such as 2,4-dimethoxychlorobenzene.

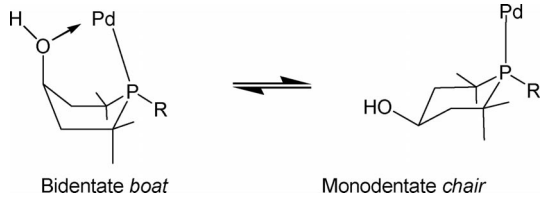

Figure 2. Bi- and monodentate complexes of ligands **2a/b**.

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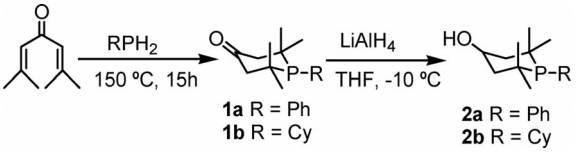
The P,O-type ligand **2b** incorporates a novel monodentate/bidentate design feature involving a *chair-boat* conformational flip. The remote 4-hydroxy substituent was designed to allow formation of a reactive monodentate L_1-Pd^0 species through a ring flip to the *chair* conformer as shown at the bottom of Figure 2, to stabilize the unsaturated catalyst in the *boat* conformer outside of the catalytic cycle and as a means of assisting reductive elimination processes. Ligand **2b** proved highly effective in activating aryl chlorides in the Suzuki–Miyaura reaction,[10a] nonetheless the ligand itself was prone to oxidation. The reactivity of Pd-catalysts derived from certain *P*-aryl-biarylphosphanes[4b,4e,9k] as well an expected increase in stability prompted us to investigate the reactivity of the corresponding *P*-phenylphosphorinan-4-ol ligand **2a**. In this paper, we report the short synthesis of ligand **2a**, its remarkable stability to molecular oxygen under aerobic conditions as well as its versatility in effecting a range of problematic Pd-mediated cross-coupling reactions.

Results and Discussion

The required *P*-phenylphosphorin-4-ol ligands **2a** and *P*-cyclohexylphosphorin-4-ol **2b** were prepared as outlined in Scheme 1. Tandem inter- and intramolecular Michael addition of the primary phosphane to phorone[11] followed by LAH-mediated ketone reduction provided access to both ligands on a multi-gram scale.



Scheme 1. Synthesis of ligand **2a/b**.

The stability of ligands **2a** and **2b** to aerobic conditions was monitored over a period of one month (Figure 3). Both ligands proved to be robust on short-term exposure to oxygen, however ligand **2a** proved to be exceptionally stable. This phosphane stability is reminiscent of that observed with bulky *P*-substituted, constrained *ortho*-substituted biarylphosphanes.[12a] The biarylphosphanes are conformationally restrained through restricted Aryl–P bond rotation while ligand **2a** is intrinsically restrained within the phosphorinane ring; inversion at phosphorus is unlikely under ambient conditions. A chair-to-chair ring flip on **2a** would also require introduction of the bulky Ph and hydroxy substituents into axial positions. It is not clear, using the Barder–Buchwald model[12a] why oxidation of **2a** cannot readily proceed from the axial lone pair on phosphorus in **2a**, we note only that both types of ligand consist of a conformationally restricted sterically hindered phosphane. A marked dichotomy in primary phosphane stability was also recently described by Gilheany and co-workers.[12b] A unifying concept that explains the unusual stability of certain phosphanes is elusive although clearly the introduction of one aryl group (contrasting **2b** to **2a**) contributes significantly to the stability of ligand **2a**.

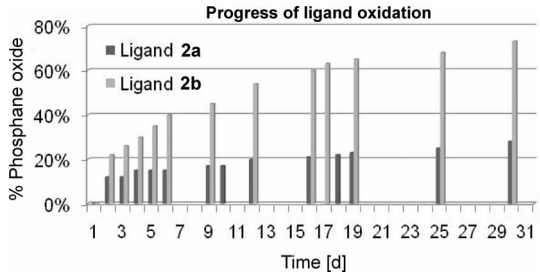
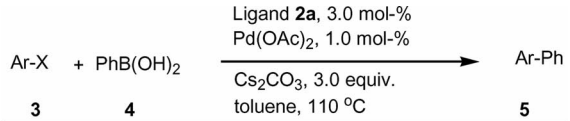
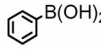
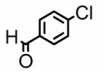
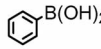
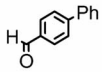
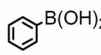
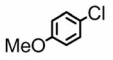
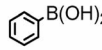
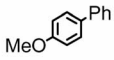
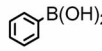
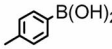
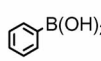
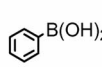
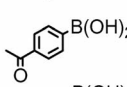
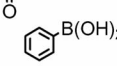


Figure 3. Bar graph showing the phosphane oxide formation monitored by ^{31}P-NMR[12a] for ligands **2a** and **2b**.

The general utility of the ligand **2a** was next investigated in a series of Pd-mediated cross-coupling processes. Conditions for the Suzuki–Miyaura reaction were readily iden-

Table 1. Suzuki cross-coupling reactions using ligand **2a**.[a]



Entry	R-X	Boronic acid	Product **5**	Isolated yield of **5** (%)[b]
1				97%
2				92%
3				87%
4				86%
5				90%
6				84%
7				73%
8				73%
9				92%
10				98%
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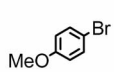
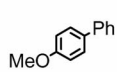
12				94%

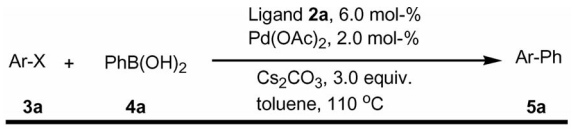
[a] Reaction conditions: 1.0 equiv. of aryl halide, 2.0 equiv. of boronic acid, 3.0 equiv. of Cs_2CO_3, $Pd(OAc)_2$ 1.0 mol-%, ligand 3.0 mol-%, toluene 5.0 mL, 110 °C, 12–16 h. [b] Isolated product after column chromatography.

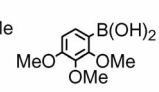
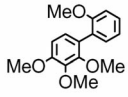
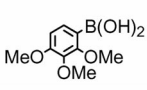
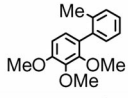
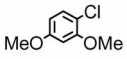
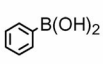
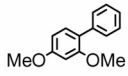
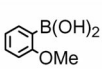
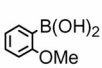
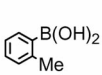
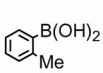
tified using 1.0 mol-% palladium(II) acetate and cesium carbonate as base. Little to no conversion occurred at room temperature using ligand **2a** under these conditions and the reactions were performed under a standard condition in toluene at 110 °C. A selection of examples is reported in Table 1, focusing on aryl chlorides. A series of electron-rich, electron-deficient and sterically hindered *ortho*-substituted chlorobenzene derivatives could readily be activated with the Pd complex of **2a** and coupled with arylboronic acids (entries 1 to 7). Also of interest was the efficient cross-coupling of the electron poor 4-acetylphenylboronic acid with chlorobenzene (entry 9). As expected, bromo- and iodobenzene derivatives reacted without incident providing the corresponding biaryls in high yield.

The effectiveness of ligand **2a** in Suzuki–Miyaura cross coupling was further investigated in the synthesis of a range of hindered biaryls from unactivated aryl chloride substrates and hindered, *ortho*-substituted arylboronic acids. The results are summarized in Table 2. The reactions proceeded slowly in toluene at 110 °C under the conditions reported in Table 1. For example, 1-chloro-2,4-dimethoxybenzene (Table 2, entry 3) reacted with phenylboronic acid in the presence of 1.0% Pd and 3.0% **2a** to give the biaryl in 74% yield after 16 h. The reactions involving the more challenging hindered pairings proved to be slower as expected, however increasing the catalyst loading (Pd 2.0%, **2a** 6.0%), and reaction time to 48 h, allowed good conversion and we were able to isolate the sterically hindered biaryl products in fairly good yield. In most cases, elevated temperatures (110 °C) are required to activate challenging aryl chlorides. The mild conditions (room temp. to 40 °C) employed using the Buchwald catalyst highlight another of the remarkable features of the biaryl catalyst.[4b] In other examples, Beller's pyrrole-based system[9k] and Fu's ferrocene-based ligand[4e] allowed cross-coupling of select challenging aryl chlorides at 60 and 70 °C respectively.

We next investigated the use of palladium complexes of the same ligand **2a** in the Buchwald–Hartwig amination reaction.[13] We had previously found catalysts prepared from *P*-isobutyl-2,2,6,6-tetramethylphosphorinane and the precursor $Pd_2(dba)_3$ to be highly active in this reaction performed in toluene or ionic liquid media.[13o] Efficient amination protocols are of much current interest in the synthesis of pharmaceutical intermediates[14] as well as functionalized triarylamines which are the key components in a variety of materials including organic photoconductors, light-emitting diodes and photovoltaic cells.[15] Complicating factors have been identified in the reaction, particularly where weakly

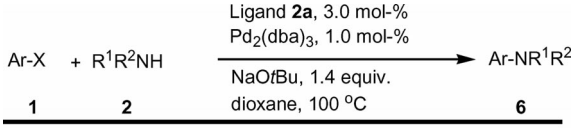
Table 2. Suzuki cross-coupling reactions using ligand **2a**.[a]

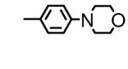
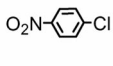
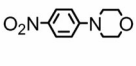
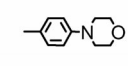
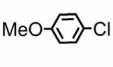
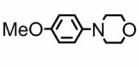
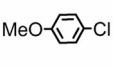
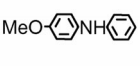
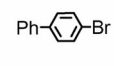


Entry	R-X	Boronic acid	Product **5a**	Isolated yield of **5a** (%)[b]
1				65%
2				58%
3				74%[c]
4				62%
5				70%
6				60%
7				72%

[a] Reaction conditions: 1.0 equiv. of aryl halide, 1.5 equiv. of boronic acid, 3.0 equiv. of Cs_2CO_3, $Pd(OAc)_2$ 2.0 mol-%, ligand 6.0 mol-%, toluene, 48 h. [b] Isolated yield after column chromatography. [c] $Pd(OAc)_2$ 1.0 mol-%, ligand 3.0 mol-%, 16 h.

Table 3. Amination reactions using ligand **2a**.[a]



Entry	R-X	Amine	Product **6**	Isolated yield of **6** (%)[b]
1				90%
2				95%
3				97%
4				86%
5				84%
6				94%
7				92%
8				90%

[a] Reaction conditions: 1.0 equiv. aryl halide, 1.2 equiv. amine, 1.4 equiv. NaO*t*Bu, 1.0 mol-% $Pd_2(dba)_3$, 3.0 mol-% ligand, dioxane 4.0 mL, 100 °C, 12 h. [b] Isloated yield after column chromatography.

nucleophilic diarylamines are employed and anionic[13o] and solvent effects[16] described. A highly effective catalyst was readily generated from ligand **2a** and shown to be effective in the cross-coupling of a series of amines with aryl halides as summarized in Table 3. Amination of aryl chlorides, including electron-rich 4-methoxychlorobenzene, proceeded efficiently with morpholine as well as with a weaker aniline nucleophile. In addition, diarylamines, including hindered *ortho*-substituted derivatives could be coupled to aryl bromides providing valuable, differentially substituted triarylamines in good yield.

Conclusion

A short, efficient synthesis of a new sterically hindered P,O-type phosphane ligand involving double Michael addition of phenylphosphane to phorone is described. Ligand **2a** proved to be significantly more stable under aerobic conditions in comparison to the *P*-cyclohexyl derivative **2b**. Palladium complexes could be readily formed from ligand **2a** that proved efficient in activating a range of aryl halides, including challenging electron-rich and *ortho*-substituted derivatives in the Suzuki–Miyaura reaction, as well as coupling amines and weakly nucleophilic diarylamines with a range of aryl halides. Although activation of the most challenging aryl chlorides required heating, with few exceptions[4b,4e,9k] the phosphorinane ligand **2a** compares favourably with other phosphanes in effecting cross-coupling reactions with hindered, unactivated aryl chlorides.[4e,4f,5–9] Attractive features of this scaffold are the rapid synthetic access to the ligand **2a**, in two steps from commercial materials, and further tunability possible through varying the nature of the secondary phosphane employed and derivatization of the remote hydroxy group. Further modifications to ligand **2a** along these lines and application to other metal-mediated cross-coupling processes are under investigation.

Experimental Section

General: Reactions were carried out under nitrogen in oven-dried glassware. Monocyclohexylphosphane and phenyldichlorophosphane were obtained from Cytec industries, all other fine chemicals were obtained from Aldrich. CIMS were run on a Micromass Quattro Ultima spectrometer fitted with a direct injection probe (DIP) with ionization energy set at 70 eV and HRMS (EI) were performed with a Micromass Q-Tof Ultima spectrometer. ^{1}H, ^{13}C and ^{31}P spectra were recorded on a Bruker 200 and AV 600 spectrometer in $CDCl_3$ with TMS as internal standard. Chemical shifts (δ) are reported in ppm downfield of TMS and coupling constants (J) are expressed in Hz. All ^{31}P NMR experiments were measured relative to an external standard (H_3PO_4, 0 ppm).

Caution: All phosphanes should be considered to be pyrophoric. Contact with atmospheric oxygen must be avoided, particularly during the thermal addition reactions.

General Procedure for Synthesis of 2,2,6,6-Tetramethyl-*P*-phenylphosphorinone (1a): Sodium metal (5.2 g, 0.225 mol) was stirred vigorously in dry dioxane (40 mL) in a 100 mL reaction vessel, fitted with a central condenser and side connector sealed with a Teflon®-coated silicone septa, under N_2 at 110 °C for 30 min to melt and break apart the sodium. Dichloro-phenylphosphane (6.8 mL, 50 mmol) was added dropwise via syringe; approximately 0.5 mL was added first followed by the dropwise addition of the remainder over a 2-hour period. The reaction mixture was stirred overnight (16 h) at 110 °C forming a yellow precipitate of the disodium salt of phenylphosphane. The condenser was connected to a stillhead under N_2, the solvent was removed and reaction mixture dried under high vacuum at 60–80 °C. The vacuum pump was equipped with an in-line dry-ice trap to collect volatiles. Dry diether (50 mL) was injected into the reaction flask and the disodium salt of phenylphosphane slurry was quenched with degassed glacial acetic acid (7.5 mL, 0.125 mol) at –10 to 0 °C with dropwise addition over a period of 5 h under N_2 flow to remove liberated hydrogen and prevent pressure build-up. The ether was evaporated (50 °C) under N_2 flow. The product phenylphosphane was then fractionally distilled under nitrogen at 120 °C and 180 °C into sealed reaction vessels cooled to 0 °C. The first fraction (collected at 120 °C) was essentially of acetic acid; the second fraction (180 °C) was of phenylphosphane (5.0 g, 45 mmol, 90%). Overall distillation takes up to 4–5 h. The phenylphosphane so obtained was used immediately. Phorone (8.6 mL, 55 mmol) was injected into the flask containing phenylphosphane (no solvent) and the reaction mixture was stirred at 150 °C for 15 h. Volatile compounds were stripped off at 100 °C under high vacuum to give the product as a light-brown liquid that solidified on cooling. This crude product was distilled under high vacuum. A first fraction (145–155 °C/1 Torr) was collected yielding **1a** (5.8 g, 47%). A higher boiling fraction (190–210 °C/0.5 Torr) contained the phosphane oxide. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.60–7.90 (m, 2 H, Ar-H), 7.30–7.55 (m, 3 H, Ar-H), 2.75–3.10 (m, 2 H, CH_2), 2.15–2.45 (m, 2 H, CH_2), 1.32 (d, J = 18 Hz, 6 H, CH_3), 0.93 (d, J = 11 Hz, 6 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 211.7, 135.9, 135.5, 128.4, 128.3, 129.7, 52.9, 35.2 [d, J(P,C) = 18 Hz], 31.0 (d, $J_{P,C}$ = 31 Hz), 30.1 (d, $J_{P,C}$ = 9 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 20.37 ppm.

General Procedure for Synthesis of *P*-Phenyl-2,2,6,6-tetramethylphosphorinan-4-ol (2a): An oven-dry two-neck flask containing a magnetic stirring bar and a pressure-dropping funnel was charged with $LiAlH_4$ (0.152 g, 4.027 mmol). $LiAlH_4$ was degassed at high vacuum and backfilled with argon. Dry THF (10.0 mL) was added and the suspension cooled to –10 °C. *P*-phenyl-2,2,6,6-tetramethylphosphorin-4-one **1a** (0.500 g, 2.013 mmol) was dissolved in THF (15.0 mL) and transferred to the LAH suspension dropwise via a pressure-dropping funnel. The addition was completed in one hour and the reaction mixture was further stirred for 12 h. The reaction mixture was quenched by dropwise addition of 2–3 mL degassed 10% NaOH solution and stirred until the precipitate dissolved. The reaction mixture was filtered through a pad of celite under argon, using degassed ethyl acetate to wash. Solvent was removed under high vacuum and the material was purified over silica gel chromatography (2.5 × 45 cm, 20% EtOAc/hexanes, R_f = 0.18) yielding **2a** (0.430 g, 85.4%) as a colorless solid. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.75 (br. s, 2 H, Ar-H), 7.43–7.39 (m, 3 H, Ar-H), 4.15–3.78 (m, 1 H, C*H*OH), 2.06–1.73 (m, 4 H, CH_2), 1.39–1.38 (m, 6 H, CH_3), 1.15–1.05 (m, 6 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.2 (d, $J_{P,C}$ = 23 Hz), 129.7, 127.7 (m), 66.1, 51.1 (d, $J_{P,C}$ = 12 Hz), 32.7–31.9 (m, 2 C), 26.5 (d, $J_{P,C}$ = 4.5 Hz) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.7 ppm. HRMS (CI^+-TOF): calculated for $C_{15}H_{29}OP$: 250.1487, found 250.1497.

Aerial Oxidation of Ligands 2a and 2b: (Figure 3) Reactions were conducted in clean dry NMR tubes. The ligand **2a** (15.0 mg, 0.060 mmol) and ligand **2b** (15.0 mg, 0.058 mmol) were dissolved

in $CDCl_3$ (2.0 mL) in separate NMR tubes. The tubes were clamped and a continuous stream of dry air was slowly passed through a Teflon® tube connected to the top of the NMR tubes. Solvent volume was maintained on a daily basis and ^{31}P NMR was carried out (Figure 3) over a period of one month to determine the degree of phosphane oxide formation. The percent oxidation was calculated as the ratio of the integral of the peak corresponding to the phosphane oxide divided by the sum of the integrals corresponding to the starting phosphane and phosphane oxide, multiplied by 100.

General Procedure for Suzuki–Miyaura Cross Coupling: (Table 1) An oven-dried Schlenk flask, equipped with a magnetic stirring bar was charged with phenylboronic acid (85.5 mg, 0.701 mmol), Cs_2CO_3 (342.1 mg, 1.050 mmol) and ligand **2a** (2.62 mg, 0.010 mmol). After evacuation and refilling with nitrogen, 4-chloroanisole (50.0 mg, 0.350 mmol), $Pd(OAc)_2$ (0.78 mg, 0.0030 mmol), and freshly distilled toluene (5.0 mL) were injected sequentially. The system was further evacuated and flushed with nitrogen thrice and then placed into preheated oil bath (110 °C) for 12 h. After completion of reaction, the reaction mixture was quenched with water and diluted with ethyl acetate. Organic layer was separated and aqueous layer was washed with EtOAc. The combined organic phases were dried with $MgSO_4$, filtered and the solvent was removed at reduced pressure. The crude product was then purified by column chromatography to give 4-methoxybiphenyl in (0.0555 g, 86%) as a colourless solid. The physical and spectroscopic data of all biphenyl compounds (Table 1, entry 1–12) were identical to those previously described.[10c,17a–17c]

4-Phenylacetophenone: (Table 1, entry 1) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 8.04 (d, J = 8.0 Hz, 2 H, Ar-H), 7.71–7.62 (m, 4 H, Ar-H), 7.49–7.45 (m, 3 H, Ar-H), 2.64 (s, 3 H, $COCH_3$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.8, 145.8, 140.0, 135.9, 129.0 (2 C), 129.0 (2 C), 128.3, 127.3 (2 C), 127.3 (2 C), 26.7 ppm.

4-Phenylbenzaldehyde: (Table 1, entry 2) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 10.06 (s, 1 H, HCO), 7.98 (d, J = 8.0 Hz, 2 H, Ar-H), 7.77–7.63 (m, 4 H, Ar-H), 7.50–7.46 (m, 3 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 192.0, 147.2, 139.7, 135.2, 130.4 (2 C), 129.1 (2 C), 128.5, 127.5 (2 C), 127.4 (2 C) ppm.

4-Methylbiphenyl: (Table 1, entry 3) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.70 (d, J = 7.0 Hz, 2 H, Ar-H), 7.63–7.59 (m, 2 H, Ar-H), 7.54–7.46 (m, 3 H, Ar-H), 7.38–7.34 (m, 2 H, Ar-H), 2.50 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.3, 138.5, 137.2, 129.6 (3 C), 128.9 (3 C), 127.1 (3 C), 21.2 ppm.

4-Methoxybiphenyl: (Table 1, entry 4) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.68 (d, J = 6.6 Hz, 2 H, Ar-H), 7.58–7.43 (m, 5 H, Ar-H), 7.10 (d, J = 8.4 Hz, 2 H, Ar-H), 3.93 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.3, 141.0, 136.0, 128.9 (2 C), 128.3 (2 C), 126.9 (3 C), 114.4 (2 C), 55.4 ppm.

Biphenyl: (Table 1, entry 5) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.82–7.78 (m, 4 H, Ar-H), 7.66–7.53 (m, 6 H, AR-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.5 (2 C), 129.0 (3 C), 127.5 (4 C), 127.4 (3 C) ppm.

4-Methylbiphenyl: (Table 1, entry 6) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.70 (d, J = 7.0 Hz, 2 H, Ar-H), 7.63–7.59 (m, 2 H, Ar-H), 7.54–7.46 (m, 3 H, Ar-H), 7.38–7.34 (m, 2 H, Ar-H), 2.50 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.3, 138.5, 137.1, 129.6 (3 C), 128.9 (3 C), 127.1 (3 C), 21.2 ppm.

2-Aminobiphenyl: (Table 1, entry 7) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.47–7.35 (m, 5 H, Ar-H), 7.17–7.13 (m, 2 H, Ar-H), 6.88–6.80 (m, 2 H, Ar-H), 3.77 (s, 2 H, NH_2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 143.5, 139.5, 130.5, 129.1 (2 C), 128.9 (2 C), 128.5, 127.8, 127.2, 118.7, 115.6 ppm.

2-Methoxybiphenyl: (Table 1, entry 8) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.63–7.56 (m, 3 H, Ar-H), 7.50–7.43 (m, 4 H, Ar-H), 7.05 (d, J = 8.8 Hz, 2 H, Ar-H), 3.90 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.2, 141.0, 133.8, 128.8 (2 C), 128.2 (2 C), 126.8 (2 C), 126.7 (2 C), 114.3, 55.4 ppm.

4-Phenylacetophenone: (Table 1, entry 9) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 8.06 (d, J = 8.0 Hz, 2 H, Ar-H), 7.71–7.62 (m, 4 H, Ar-H), 7.49–7.45 (m, 3 H, Ar-H), 2.64 (s, 3 H, CH_3O) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 197.8, 145.8, 140.0, 135.9, 129.0 (2 C), 129.0 (2 C), 128.3, 127.3 (2 C), 127.3 (2 C), 26.7 ppm.

Biphenyl: (Table 1, entry 10) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.82–7.78 (m, 4 H, Ar-H), 7.66–7.53 (m, 6 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.5 (2 C), 129.0 (3 C), 127.5 (4 C), 127.4 (3 C) ppm.

4-Methylbiphenyl: (Table 1, entry 11) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.70 (d, J = 7.0 Hz, 2 H, Ar-H), 7.63–7.59 (m, 2 H, Ar-H), 7.54–7.46 (m, 3 H, Ar-H), 7.38–7.34 (m, 2 H, Ar-H), 2.50 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.3, 138.5, 137.2, 129.6 (3 C), 128.9 (3 C), 127.1 (3 C), 21.2 ppm.

4-Methoxybiphenyl: (Table 1, entry 12) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.68 (d, J = 6.6 Hz, 2 H, Ar-H), 7.58–7.43 (m, 5 H, Ar-H), 7.10 (d, J = 8.4 Hz, 2 H, Ar-H), 3.93 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.3, 140.9, 136.0, 128.9 (2 C), 128.3 (2 C), 126.9 (3 C), 114.4 (2 C), 55.4 ppm.

General Procedure for Suzuki–Miyaura Cross Coupling: (Table 2) An oven-dried Schlenk flask, equipped with a magnetic stirring bar was charged with 2,3,4-trimethoxy phenylboronic acid (27.0 mg, 0.128 mmol), Cs_2CO_3 (83.4 mg, 0.256 mmol) and ligand **2a** (1.28 mg, 0.0051 mmol). After evacuation and refilling with nitrogen, 4-chloroanisole (12.1 mg, 0.0854 mmol), $Pd(OAc)_2$ (0.38 mg, 0.0017 mmol), and freshly distilled toluene (2.0 mL) were injected sequentially. The system was further evacuated and flushed with nitrogen thrice and then placed into preheated oil bath (110 °C) for 48 h. After completion of reaction, the reaction mixture was cooled, quenched with water and diluted with ethyl acetate. The organic layer was separated and aqueous layer was washed with EtOAc. The combined organic phases were dried with $MgSO_4$, filtered and the solvent was removed at reduced pressure. The crude product was then purified by column chromatography to give 2,2′,3,4-tetramethoxybiphenyl in (0.0178 g, 65%) yield. The physical and spectroscopic data of all biphenyl compounds (Table 1a, entry 1–7) were identical to those previously described.[4b,17c,17f]

2,2′,3,4-Tetramethoxybiphenyl: (Table 2, entry 1) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.21 (m, 2 H, Ar-H), 7.01–6.94 (m, 3 H, Ar-H), 6.73 (d, J = 8.8 Hz, 1 H, Ar-H), 3.92 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.0, 152.5, 152.0, 141.0, 130.4, 128.0, 126.4, 124.3, 122.6, 119.2, 109.6, 105.7, 59.7, 54.9, 54.9, 54.5 ppm.

2,3,4-Trimethoxy-2′-methylbiphenyl: (Table 2, entry 2) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.23–7.22 (m, 4 H, Ar-H), 6.86 (d, J = 8.6 Hz, 1 H, Ar-H) 6.72 (d, J = 8.4 Hz, 1 H, Ar-H), 3.94 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.58 (s, 3 H, OCH_3), 2.19 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.0, 151.4, 136.9, 131.5, 130.1, 129.8, 127.3, 125.4, 125.0, 120.4, 111.1, 107.0, 61.1, 56.0, 55.7, 20.2 ppm.

2,4-Dimethoxybiphenyl: (Table 2, entry 3) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.56–7.55 (m, 2 H, Ar-H), 7.52–7.38 (m, 2 H,

Ar-H), 7.36–7.30 (m, 2 H, Ar-H), 6.63–6.60 (m, 2 H, Ar-H), 3.88 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.3, 157.5, 138.4, 131.3, 129.5 (2 C), 128.0 (2 C), 126.5, 123.6, 104.6, 99.0, 55.6, 55.5 ppm.

2-Methoxy-2′-methylbiphenyl: (Table 2, entry 4) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.47 (br. d, 2 H, Ar-H), 7.34–7.22 (m, 4 H, Ar-H), 7.07–6.97 (m, 2 H, Ar-H), 3.82 (s, 3 H, OCH_3), 2.41 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.5, 136.7, 135.6, 130.9, 129.7, 129.5 (2 C), 128.8 (2 C), 128.4, 120.8, 111.21, 55.60, 21.33 ppm.

2,2′-Dimethoxybiphenyl: (Table 2, entry 5) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.34–7.27 (m, 4 H, Ar-H), 7.01–6.97 (m, 4 H, Ar-H), 3.79 (s, 6 H, OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.0 (2 C), 131.5 (2 C), 128.7 (2 C), 127.8 (2 C), 120.4 (2 C), 111.1 (2 C), 55.7 (2 C) ppm.

2,2′-Dimethylbiphenyl: (Table 2, entry 6) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.27–7.14 (m, 4 H, Ar-H), 7.011–7.02 (m, 4 H, Ar-H), 2.07 (s, 6 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.7 (2 C), 136.4 (2 C), 129.5 (2 C), 128.7 (2 C), 127.8 (2 C), 126.4 (2 C), 21.2 (2 C) ppm.

2-Methoxy-2′-methylbiphenyl: (Table 2, entry 7) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.47 (br. d, 2 H, Ar-H), 7.34–7.22 (m, 4 H, Ar-H), 7.07–6.97 (m, 2 H, Ar-H), 3.82 (s, 3 H, OCH_3), 2.41 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.5, 136.7, 135.6, 130.9 (2 C), 129.5 (2 C), 128.8 (2 C), 128.4, 120.8 (2 C), 55.60, 21.33 ppm.

General Procedure for the Buchwald-Hartwig Amination of Aryl Halides: (Table 3) An oven-dry Schlenk flask containing a magnetic stirring bar was charged with ligand **2a** (2.62 mg, 0.0100 mmol), $Pd_2(dba)_3$ (3.20 mg, 0.00300 mmol) and NaO*t*Bu (48.0 mg, 0.490 mmol) under nitrogen. 4-chloroanisole (50.0 mg, 0.350 mmol), morpholine (0.0360 mL, 0.420 mmol) and freshly distilled dioxane (4 mL) were added sequentially. The reaction mixture was degassed three times and stirred at 100 °C for 12 h. After cooling to room temperature, 10 mL of EtOAc was added and the mixture was washed with 5 mL of brine. The organic layer was separated, dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography to give *N*-(4-methoxyphenyl)morpholine (0.059 g, 87%) yield. The physical and spectroscopic data of all other isolated compounds (Table 2 entry 1–6) were identical to those previously described.[13d,13p,17c,17d,17g,17h]

***N*-(4-Methylphenyl)morpholine:** (Table 3, entry 1) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.15 (d, J = 4.6 Hz, 2 H, Ar-H), 6.88 (d, J = 8.6 Hz, 2 H, Ar-H), 3.92 (t, J = 4.4 Hz, 4 H, CH_2O), 3.10 (t, J = 4.6 Hz, 4 H, CH_2N), 2.32 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.2, 129.8 (2 C), 129.7 (2 C), 116.1, 67.5 (2 C), 50.0 (2 C), 20.5 ppm.

***N*-(4-Nitrophenyl)morpholine:** (Table 3, entry 2) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 8.19 (d, J = 9.4 Hz, 2 H, Ar-H), 6.87 (d, J = 9.4 Hz, 2 H, Ar-H), 3.91 (t, J = 4.6 Hz, 4 H, CH_2O), 3.41 (t, J = 4.6 Hz, 4 H, CH_2N) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.9, 139.4, 126.0 (2 C), 112.6 (2 C), 66.4 (2 C), 47.2 (2 C) ppm.

***N*-(4-Methylphenyl)morpholine:** (Table 3, entry 3) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.15 (d, J = 4.6 Hz, 2 H, Ar-H), 6.88 (d, J = 8.6 Hz, 2 H, Ar-H), 3.92 (t, J = 4.4 Hz, 4 H, CH_2O), 3.10 (t, J = 4.6 Hz, 4 H, CH_2N), 2.32 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.2, 129.8 (2 C), 129.7 (2 C), 116.1, 67.5 (2 C), 50.0 (2 C), 20.5 ppm.

***N*-(4-Methoxyphenyl)morpholine:** (Table 3, entry 4) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 6.92–6.91 (br. s, 4 H, Ar-H), 3.92 (t, J = 4.4 Hz, 4 H, CH_2O), 3.81 (s, 3 H, OCH_3), 3.10 (t, J = 4.6 Hz, 4 H, CH_3N) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.0, 144.5, 117.5 (2 C), 115.2 (2 C), 67.4 (2 C), 55.3, 54.8 (2 C) ppm.

4-Methoxy-*N*-phenylaniline: (Table 3, entry 5) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.22 (m, 5 H, Ar-H), 7.14 (d, J = 8.8 Hz, 2 H, Ar-H), 6.97–6.88 (m, 5 H, Ar-H), 5.53 (s, 1 H, NH), 3.84 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 155.3, 145.2, 135.8, 129.4 (2 C), 122.3 (2 C), 119.6 (2 C), 115.7 (2 C), 114.7 (2 C), 55.6 ppm. HRMS (EI$^+$-TOF): calculated for $C_{13}H_{13}NO$: 199.0997, found 119.1004.

4-(Diphenylamino)biphenyl: (Table 3, entry 6) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.63 (d, J = 7.0 Hz, 2 H, Ar-H), 7.54–7.42 (m, 4 H, Ar-H), 7.35–7.28 (m, 5 H, Ar-H), 7.20–7.11 (m, 6 H, Ar-H), 7.01–7.04 (m, 2 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 147.8 (2 C), 147.2, 140.7, 135.2, 129.4 (3 C), 128.8 (2 C), 127.9 (2 C), 126.9 (2 C), 126.7 (3 C), 124.5 (3 C), 124.0 (2 C), 123.0 (2 C) ppm. HRMS (EI$^+$-TOF): calculated for $C_{24}H_{19}N$: 321.1517, found 321.1508.

4-[(3-Methoxyphenyl)phenylamino]biphenyl: (Table 3, entry 7) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.63 (d, J = 7.2 Hz, 2 H, Ar-H), 7.54–7.42 (m, 4 H, Ar-H), 7.38–7.30 (m, 4 H, Ar-H), 7.28–7.17 (m, 4 H, Ar-H), 7.08–7.04 (m, 1 H, Ar-H), 6.75 (d, J = 7.8 Hz, 2 H, Ar-H), 6.63 (d, J = 8.0 Hz, 1 H, Ar-H), 3.77 (s, 3 H, OCH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.2, 147.8, 147.3, 140.7, 139.6 (2 C), 135.2 (2 C), 129.6, 129.4 (2 C), 128.8 (2 C), 127.9 (2 C), 126.9, 126.7 (2 C), 124.5 (2 C), 124.0, 123.0, 122.6, 111.1, 56.4 ppm. HRMS (EI$^+$-TOF): calculated for $C_{25}H_{21}NO$: 351.1623, found 351.1642.

4-[Bis(2,4-Dimethylphenyl)amino]biphenyl: (Table 3, entry 8) ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.64 (d, J = 7.2 Hz, 2 H, Ar-H), 7.53–7.44 (m, 4 H, Ar-H), 7.39–7.30 (m, 1 H, Ar-H), 7.16–7.09 (m, 4 H, Ar-H), 7.01–6.93 (m, 4 H, Ar-H), 2.31 (s, 6 H, CH_3), 2.26 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 147.9, 145.6 (2 C), 140.9, 137.6 (2 C), 133.8, 131.5 (2 C), 130.5 (2 C), 128.8 (2 C), 127.6 (2 C), 126.7 (3 C), 126.2 (2 C), 122.8 (2 C), 122.6 (2 C), 20.0 (2 C), 19.3 (2 C) ppm. HRMS (EI$^+$-TOF): calculated for $C_{28}H_{27}N$: 377.2144, found 377.2139.

Acknowledgments

We thank the Natural Sciences and Engineering Research Council and Cytec Canada for financial support of this work.

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Received: August 4, 2010
Published Online: October 25, 2010

