Me$_3$(OMe)tBuXPhos: A Surrogate Ligand for Me$_4$tBuXPhos in Palladium-Catalyzed C-N and C-O Bond-Forming Reactions

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Me₃(OMe)tBuXPhos: A Surrogate Ligand for Me₄tBuXPhos in Palladium-Catalyzed C–N and C–O Bond-Forming Reactions

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Abstract

A new biaryl phosphine ligand, Me₃(OMe)tBuXPhos (L₃), was designed as a surrogate for Me₄tBuXPhos (L₁). The Me₃(OMe)tBuXPhos could be prepared in a chromatography-free manner from inexpensive and readily available 2,3,6-trimethylphenol. Comparative studies demonstrated that a catalyst based on Me₃(OMe)tBuXPhos displayed the same reactivity as a catalyst based on Me₄tBuXPhos for Pd-catalyzed C–N and C–O bond-forming processes.

Keywords
Palladium; Phosphine Ligand; N-Arylation; O-Arylation

Me₄tBuXPhos (L₁) is a useful ligand in Au-catalyzed carbocyclization and Pd-catalyzed arylation reactions of nitrogen/oxygen nucleophiles, including amides, benzimidazoles, phenols and water. We recently demonstrated that the combination of Pd and L₁ was the most effective catalyst system for the highly N₂-selective arylation of 1,2,3-triazoles and completely N¹-selective arylation of unsymmetric imidazoles. L₁ is synthesized from 1,2,3,4-tetramethylbenzene via dibромination and then a one-pot biaryl phosphine synthesis protocol, which proceeds through a benzyne intermediate. However, the high cost and limited availability of the 1,2,3,4-tetramethylbenzene could potentially prevent the utilization of Pd/L₁ systems, as well as the future development of methods using L₁ as a supporting ligand for various metals. To circumvent this problem, the development of an inexpensive and robust alternative to L₁ is highly desirable.

Mechanistic investigations by our group on Pd-catalyzed aryl amidation with L₁ indicated that the 3-methyl substituent of the ligand restricts rotation of the Ar–P bond and fixes the Pd center over the triisopropylphenyl ring. In addition, it was postulated that 6-methyl group of L₁ increases conformational rigidity in the Pd-ligand complex and possibly accelerates the rate of reductive elimination. Based on these two features it was proposed that the utility of L₁ was superior to that of non-methylated ligand tBuXPhos (L₂) in several Pd-catalyzed C–N bond-forming reactions. We felt that ligand, L₃, which possesses both 3- and 6-methyl substituents and is accessible from inexpensive and readily available 2,3,6-trimethylphenol might be a suitable surrogate for L₁. Herein, we report a synthesis of L₃ and its utilization in the Pd-catalyzed arylation reactions of nitrogen and oxygen nucleophiles.

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Supporting Information Available: Copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.
The synthesis of \( \text{L3} \) is described in Scheme 1. Dibromide 2 was prepared from 2,3,6-trimethylphenol via dibromination and O-methylation. Notably, both \( \text{L1} \) and \( \text{L2} \) were crystalline solids and could be isolated in pure form without chromatography. Dibromide 2 was treated with Mg and 2,4,6-triisopropylphenyl magnesiumbromide in THF at 60 °C for 1.5 h and then allowed to react with CuCl and ClP(tBu)\(_2\) to give \( \text{L3} \) in 61% yield. \(^1\)H NMR analysis showed that \( \text{L3} \) was an approximately 1:1 mixture of two regioisomers, suggesting that addition of the aryl Grignard reagent to the benzyne generated from 2 was unselective.

In order to compare the activity of the Pd/\( \text{L1} \) and Pd/\( \text{L3} \) systems, the reaction progress of the N-arylation of nitrogen heterocycles was investigated (Schemes 2 and 3). Previously, the N-arylation of 4-methylimidazole and bromobenzene with Pd/\( \text{L1} \) gave N-arylated product \( \text{3a} \) in 95% yield with complete N\(^1\)-selectivity.\(^7\) The same N-arylation reaction using Pd/\( \text{L3} \) showed similar progress and the N-arylated product was obtained in 96% yield with complete N\(^1\)-selectivity. Similarly, almost identical yields (90% with \( \text{L1} \), 89% with \( \text{L3} \)) and N\(^2\)-selectivity (N\(^2\):N\(^1\) = 97:3 for both \( \text{L1} \) and \( \text{L3} \)) were observed for the N-arylation of 1,2,3-triazole.\(^6\) These results demonstrate that a catalyst based on \( \text{L3} \) shows identical reactivity to a catalyst based on \( \text{L1} \), indicating that it is excellent surrogate for C–N cross-coupling reactions.

We next explored the scope of the Pd/\( \text{L3} \) system using variety of aryl halides and N/O-nucleophiles (Scheme 4). We found that the use of Pd/\( \text{L3} \) gave comparable yields to those obtained with Pd/\( \text{L1} \) in all reactions examined. It should be noted that N\(^4\)-aryl-4-methylimidazoles \( \text{3c} \) and \( \text{3d} \), which are key intermediate for the synthesis of GSK2137305\(^10\) and nilotinib (Tasigna®)\(^11\) were prepared in high yield as single regioisomers at 0.3 or 0.5 mol % Pd loadings.

In summary, we have designed and synthesized a new biaryl phosphine ligand, Me\(_3\)(OMe)\(_2\)/BuXPhos (\( \text{L3} \)). The ligand \( \text{L3} \) could be prepared in a chromatography-free manner from inexpensive and readily available 2,3,6-trimethylphenol. Comparative studies of \( \text{L1} \) and \( \text{L3} \) demonstrated that \( \text{L3} \) could indeed serve as a surrogate for the Me\(_4\)BuXPhos (\( \text{L1} \)). We expect wide use and large-scale application of \( \text{L3} \) as an efficient substitute for \( \text{L1} \) in a variety of Pd-catalyzed C–N and C–O bond-forming reactions.

**Experimental Section**

**General Information**

Pd\(_2\)(dba)\(_3\) and Pd(OAc)\(_2\) was purchased from Strem Chemicals Inc. Anhydrous tribasic potassium phosphate was stored in a glovebox. Small portions were removed and stored in a desiccator for up to 2 weeks (All reactions were set-up outside of the glovebox). \( \text{L1} \) was prepared by literature procedure. Reactions were monitored by GC and thin-layer chromatography (TLC) using UV light. Flash chromatography was performed using silica gel (230–400 mesh). All \(^1\)H NMR experiments are reported in \(^{\delta}\) units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) or dimethylsulfoxide-d\(_6\) (2.50 ppm) in the deuterated solvent. All \(^{13}\)C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm) or dimethylsulfoxide-d\(_6\) (39.52 ppm), unless otherwise stated, and all were obtained with 1H decoupling. The pure compounds are estimated to be ≥95% pure as determined by \(^1\)H NMR or GC analysis.

**3,4-Dibromo-2,5,6-trimethylphenol (1)—**To a stirred solution of 2,3,6-trimethylphenol (20.4 g, 150 mmol) and I\(_2\) (381 mg, 1.5 mmol) in CH\(_2\)Cl\(_2\) (150 mL), Br\(_2\) (17.0 mL, 330 mmol) was added dropwise (1 drop/1 sec) at room temperature. After the addition of Br\(_2\) was complete, the reaction mixture was stirred at room temperature for 3 h then a saturated
aqueous solution of Na₂SO₃ (150 mL) was added to quench the residual Br₂. The organic phase was separated and washed with brine, dried over MgSO₄, and concentrated in vacuo to give a white solid which was triturated with hexanes and collected by filtration. The white solid was dried in vacuo to give 40.1 g (92% yield) of the title compound. Mp 142–144 °C; ¹H NMR (400 MHz, CDCl₃): δ 4.73 (s, 1H), 2.43 (s, 3H), 2.40 (s, 3H), 2.19 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 151.23, 136.5, 125.3, 123.3, 122.7, 119.4, 22.3, 18.3, 13.7; IR (film) v_max: 3376, 1699, 1558, 1541, 1456, 1388, 1290, 1199, 1081, 970, 784, 731 cm⁻¹; Anal. Calcd. For C₉H₁₀Br₂O: C, 36.77; H, 3.43. Found: C, 36.63; H, 3.39.

1,2-Dibromo-4-methoxy-3,5,6-trimethylbenzene (2)—A 250 mL round bottom flask, which was equipped with a stir bar, was charged with 3,4-dibromo-2,5,6-trimethylphenol (14.7 g, 50 mmol) and K₂CO₃ (8.3 g, 60 mmol). Acetone (80 mL) and dimethyl sulfate (5.68 mL, 60 mmol) were added to the mixture and then the flask was equipped with a reflux condenser. The reaction mixture was stirred at 75 °C for 6 h. After cooling to room temperature, an aqueous KOH solution (2.0 M, 100 mL) was added and the mixture was stirred at room temperature for 20 min. The reaction mixture was concentrated to remove acetone and then, extracted with Et₂O, washed with brine, dried over MgSO₄ and concentrated under reduced pressure to give the title compound as a white solid (15.0 g, 97% yield, GC purity of 99.5% area %). Mp 63–65 °C; ¹H NMR (400 MHz, CDCl₃): δ 3.65 (s, 3H), 2.44 (s, 3H), 2.42 (s, 3H), 2.40 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 156.3, 137.1, 131.2, 130.3, 125.6, 123.4, 60.5, 22.2, 18.6, 14.1; IR (film) ν_max: 2924, 1652, 1540, 1449, 1375, 1213, 1092, 1002, 972, 902, 755, 668 cm⁻¹; Anal. Calcd. For C₁₀H₁₂Br₂O: C, 38.99; H, 3.93. Found: C, 38.82; H, 3.86.

Di-tert-butyl(2′,4′,6′-triisopropyl-5-methoxy-3,4,6-trimethyl[1,1′-biphenyl]-2-yl)phosphine/di-tert-butyl(2′,4′,6′-triisopropyl-4-methoxy-3,5,6-trimethyl-[1,1′-biphenyl]-2-yl)phosphine (L₃)—An oven-dried 250 mL round bottom flask, which was equipped with a stir bar and charged with Mg shavings (1.02 g, 42 mmol) was fitted with a reflux condenser, a glass stopper and a rubber septum. The flask was purged with argon and then 2-bromo-1,3,5-triisopropylbenzene (5.07 mL, 20 mmol) and anhydrous THF (40 mL) were added via syringe. The reaction mixture was heated to 60 °C and 1,2-dibromoethane (50 μL) was added via syringe. The reaction was stirred at 60 °C for 1.5 h. 1,2-Dibromo-4-methoxy-3,5,6-trimethylbenzene (6.16 g, 20 mmol) was added portion wise to the reaction mixture over 30 min period under a stream of argon. After the addition of 1,2-dibromo-4-methoxy-3,5,6-trimethylbenzene was complete, the reaction mixture was stirred at 60 °C for 1.5 h. The reaction mixture was cooled to room temperature, diluted with Et₂O, washed three times with 30% NH₄OH, dried over MgSO₄ and concentrated under reduced pressure to give a pale yellow crude oil. The crude oil was diluted with EtOAc (5 mL) and then, MeOH (50 mL) was added. The mixture was cooled to 0 °C and the white precipitate that had formed was collected by filtration, washed two times with cold MeOH and dried in vacuo to yield a white powder (6.03 g, 61% yield, mp 130–132 °C) as an approximately 1:0.98 mixture of two isomers as determined by methoxy proton signals (methoxy proton signal of major isomer: 6.95/6.94 (s, 2H), 3.76/3.68 (s, 3H), 2.97-2.86 (m, 1H), 2.57/2.53 (s, 3H), 2.48-2.33 (m, 2H), 2.26/2.20 (s, 3H), 1.76/1.73 (s, 3H), 1.31-1.25 (m, 6H), 1.23-1.19 (m, 6H), 1.16-1.09 (m, 18H), 0.93/0.89 (d, J = 6.6 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 157.7, 155.8, 150.0, 149.6, 147.5, 147.5, 146.5, 146.5, 146.2, 141.6, 141.6, 138.1, 137.8, 137.7, 136.1, 136.0, 134.0, 133.9, 130.5, 130.4, 129.0, 128.9, 127.6, 120.7, 120.6, 59.7, 59.6, 34.7, 34.6, 34.3, 34.3, 34.2, 32.8, 32.6, 31.0, 31.0, 31.0, 26.2, 26.2, 25.5, 25.5, 24.8, 24.7, 24.7, 24.7, 24.4, 24.4, 21.9, 21.9, 21.1, 21.0. (Observed complexity is due
to C-P splitting);  \(^{31}\)P NMR (121 MHz, CDCl\(_3\)): \(\delta\) 39.17, 38.16; IR (film) \(\nu_{\text{max}}\): 2956, 2362, 1542, 1461, 1381, 1311, 1208, 1166, 1090, 1011, 911 cm\(^{-1}\); Anal. Calcd. For C\(_{33}\)H\(_{53}\)OP: C, 79.79; H, 10.75. Found: C, 79.71; H, 10.69.

4-Methyl-1-phenyl-1\(H\)-imidazole (3a)—An oven-dried vial was equipped with a magnetic stir bar and charged with Pd\(_2\)(dba)\(_3\) (6.9 mg, 0.0075 mmol) and \(\mathbf{L} 1\) or \(\mathbf{L} 3\) (0.018 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times). Anhydrous toluene (0.83 mL) and anhydrous 1,4-dioxane (0.17 mL) were added via syringe. The resulting dark purple mixture was stirred at 120 °C for 3 min, at this point the color of the mixture turned to red-brown. A second oven-dried vial, which was equipped with a stir bar, was charged with 4-methylimidazole (98 mg, 1.2 mmol) and K\(_3\)PO\(_4\) (424 mg, 2.0 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times) and then bromobenzene (106 \(\mu\)L, 1.0 mmol) and the pre-heated catalyst solution were added via syringe to the second vial. The reaction mixture was heated at 120 °C for 5 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with brine, dried over MgSO\(_4\) and concentrated in vacuo. The crude product was purified via flash chromatography (EtOAc/MeOH, 50:1) to provide the title compound as a pale-yellow solid (152 mg, 96% (with \(\mathbf{L} 3\)), mp 60 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.64 (d, \(J = 1.6\) Hz, 1H), 7.36-7.29 (m, 2H), 7.25-7.17 (m, 3H), 6.89 (s, 1H), 2.20 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 139.4, 137.3, 134.4, 129.7, 126.9, 120.8, 114.4, 13.6; IR (film) \(\nu_{\text{max}}\): 3385, 3108, 2921, 1599, 1507, 1448, 1392, 1366, 1291, 1241, 1070, 969, 817, 759, 692 cm\(^{-1}\); Anal. Calcd. For C\(_{10}\)H\(_{10}\)N\(_2\): C, 75.92; H, 6.37. Found: C, 76.04; H, 6.33.

2-Phenyl-1,2,3-triazole (3b)—An oven-dried vial was equipped with a magnetic stir bar and charged with Pd\(_2\)(dba)\(_3\) (6.9 mg, 0.0075 mmol) and \(\mathbf{L} 1\) or \(\mathbf{L} 3\) (0.018 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times). Anhydrous toluene (1.0 mL) was added via syringe and the resulting dark purple mixture was stirred at 120 °C for 3 min, at this point the color of the mixture turned to red-brown. A second oven-dried vial, which was equipped with a stir bar, was charged with K\(_3\)PO\(_4\) (424 mg, 2.0 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times) and then bromobenzene (106 \(\mu\)L, 1.0 mmol) and 1,2,3-triazole (70 \(\mu\)L, 1.2 mmol) and the pre-heated catalyst solution were added via syringe to the second vial. The reaction mixture was heated at 120 °C for 5 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with brine, dried over MgSO\(_4\) and concentrated in vacuo. The crude product was purified via flash chromatography (Hexanes/EtOAc, 9:1) to provide the title compound as colorless oil (129 mg, 89% (with \(\mathbf{L} 3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.12-8.06 (m, 2H), 7.80 (s, 2H), 7.51-7.44 (m, 2H), 7.38-7.32 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 140.0, 135.6, 129.4, 127.6, 119.1; IR (film) \(\nu_{\text{max}}\): 3128, 3059, 2362, 1745, 1598, 1500, 1410, 1376, 1259, 1152, 1069, 953, 820, 757, 692 cm\(^{-1}\); Anal. Calcd. For C\(_8\)H\(_7\)N\(_3\): C, 66.19; H, 4.86. Found: C, 66.23; H, 4.91.

3-(4-(4-Methyl-1\(H\)-imidazol-1-yl)phenyl)-1,4-diazaspiro[4.4]non-3-en-2-one (3c)—An oven-dried vial was equipped with a magnetic stir bar and charged with Pd\(_2\)(dba)\(_3\) (4.6 mg, 0.005 mmol) and \(\mathbf{L} 1\) or \(\mathbf{L} 3\) (0.01 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times). Anhydrous toluene (0.6 mL) was added via syringe and the resulting dark purple mixture was stirred at 130 °C for 3 min. A second oven-dried vial which was equipped with a stir bar was charged with 3-(4-(chlorophenyl)-1,4-diazaspiro[4.4]non-3-en-2-one\(^7\) (249 mg, 1.0 mmol), 4-methylimidazole (164 mg, 2.0 mmol) and K\(_3\)PO\(_4\) (424 mg, 2.0 mmol). The vial
was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times). The pre-heated catalyst solution (0.18 mL, 0.3 mol% Pd) was transferred to the second vial via syringe and then toluene (0.5 mL) and dioxane (0.5 mL) were added (a total 1.18 mL of solvent). The reaction mixture was heated at 130 °C for 6 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude product was purified via flash chromatography (EtOAc-MeOH, 15:1) to provide the title compound as a white solid (268 mg, 91% (with L₃)), mp 194–195 °C.

1H NMR (400 MHz, DMSO-d₆) δ 10.09 (s, 1H), 8.42 (d, J = 8.8 Hz, 2H), 8.26 (d, J = 1.2 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.53 (s, 1H), 2.17 (s, 3H), 2.00-1.77 (m, 8H);

13C NMR (100 MHz, DMSO-d₆) δ 164.1, 158.8, 138.9, 138.8, 134.7, 129.4, 128.5, 119.3, 113.8, 89.6, 37.1, 23.9, 13.6; IR (film) νmax 3854, 3745, 3158, 3050, 2962, 2360, 1704, 1606, 1518, 1442, 1254, 1191, 1063, 963, 848, 752, 540 cm⁻¹; Anal. Calcd. For C₁₇H₁₈N₄O: C, 69.37; H, 6.16. Found: C, 69.21; H, 6.12.

3-(4-Methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)aniline (3d)—An oven-dried vial was equipped with a magnetic stir bar and charged with Pd₂dba₃ (2.3 mg, 0.0025 mmol) and L₁ or L₃ (0.0025 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times). Then, anhydrous toluene (0.5 mL) was added via syringe. This dark purple mixture was stirred at 120 °C for 3 min. The color of the mixture turns to dark brown after 3 min. A second oven-dried vial, which was equipped with stir bar, was charged with 3-amino-5-bromobenzotrifluoride (240 mg, 1.0 mmol), 4-methylimidazole (197 mg, 2.4 mmol) and K₃PO₄ (424 mg, 2.0 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of 3 times). The pre-heated catalyst solution, followed by anhydrous toluene (0.5 mL) and tBuOH (1.0 mL), were added via syringe to the second vial (a total 2 mL of toluene-tBuOH 1:1 solution). The reaction was heated at 120 °C for 8 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with brine, dried over MgSO₄ and purified via flash chromatography (Et₂O/EtOAc/MeOH, 125:125:1) to provide the title compound as a white solid (219 mg, 91% (with L₃)), mp 125 °C.

1H NMR (400 MHz, DMSO-d₆) δ 8.09 (d, J = 1.2 Hz, 1H), 7.35 (s, 1H), 6.99 (s, 1H), 6.96 (s, 1H), 6.85 (s, 1H), 5.91 (s, 2H), 2.16 (s, 3H); 13C NMR (100 MHz, DMSO-d₆) δ 150.9, 138.5, 134.8, 131.3 (q, J = 38 Hz), 124.1 (q, J = 272 Hz), 114.2, 107.9, 103.3 (q, J = 4 Hz), 13.5; IR (film) νmax 3854, 3745, 3158, 3050, 2962, 2360, 1704, 1606, 1518, 1442, 1254, 1191, 1158, 1115, 843, 807, 735, 691, 621 cm⁻¹; Anal. Calcd. For C₁₁H₁₀F₃N₃: C, 54.77; H, 4.18. Found: C, 54.61; H, 4.11.

2-(1-(6-Methoxypyridin-2-yl)-1H-imidazol-4-yl)acetonitrile (3e)—An oven-dried vial was equipped with a magnetic stir bar and charged with Pd₂dba₃ (2.3 mg, 0.0025 mmol) and L₁ or L₃ (0.005 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times). Anhydrous toluene (0.41 mL) and anhydrous 1,4-dioxane (0.19 mL) were added via syringe. The resulting dark purple mixture was stirred at 120 °C for 3 min, at this point the color of the mixture turned to red brown. A second oven-dried vial, which was equipped with stir bar, was charged with 4-cyanomethylimidazole (64 mg, 0.6 mmol) and K₃PO₄ (212 mg, 1.0 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times) and then 6-bromo-2-methoxypyridine (61 μL, 0.5 mmol) and the preheated catalyst solution were added via syringe to the second vial. The reaction mixture was heated at 120 °C for 5 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude product was purified via flash...
chromatography (EtOAc) to provide the title compound as a white solid (94 mg, 87% (with L3)), mp 77–78 °C. 1H NMR (400 MHz, CDCl3) δ 8.23 (d, J = 1.2 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.58 (s, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.24 (d, J = 8.4 Hz, 1H), 3.91 (s, 3H), 3.73 (s, 2H); 13C NMR (100 MHz, CDCl3) δ 163.8, 146.5, 141.2, 135.2, 133.0, 117.4, 114.0, 109.2, 103.6, 53.8, 17.9; IR (film) νmax 3397, 2954, 1614, 1580, 1481, 1452, 1421, 1321, 1253, 1091, 1035, 1000, 793 cm−1; Anal. Calcd. For C11H10N4O: C, 61.67; H, 4.71. Found: C, 61.65; H, 4.77.

1-(Pyrimidin-5-yl)-1H-benzimidazole (3f)—An oven-dried vial was equipped with a magnetic stir bar and charged with Pd2(dba)3 (2.3 mg, 0.0025 mmol) and L1 or L3 (0.005 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times). Anhydrous toluene (0.3 mL) was added via syringe. The resulting dark purple mixture was stirred at 120 °C for 3 min, at this point the color of the mixture turned to red-brown. A second oven-dried vial, which was equipped with a stir bar, was charged with benzimidazole (142 mg, 1.2 mmol), 5-bromopyrimidine (159 mg, 1.0 mmol) and K3PO4 (424 mg, 2.0 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times) and then the pre-heated catalyst solution, toluene (0.53 mL) and dioxane (0.17 mL) were added to the second vial. The reaction mixture was heated at 120 °C for 5 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with brine, dried over MgSO4 and concentrated in vacuo. The crude product was purified via flash chromatography (EtOAc/MeOH, 15:1) to provide the title compound as a white solid (190 mg, 97% (with L3)), mp 137–139 °C. 1H NMR (400 MHz, CDCl3) δ 9.26 (s, 1H), 8.95 (s, 2H), 8.07 (s, 1H), 7.86-7.81 (m, 1H), 7.47-7.41 (m, 1H), 7.37-7.31 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 157.7, 151.9, 144.1, 141.3, 133.0, 132.0, 124.7, 123.8, 121.2, 109.6; IR (film) νmax 3745, 3065, 2362, 1698, 1652, 1558, 1497, 1464, 1429, 1291, 1245, 1208, 881, 725, 615 cm−1; Anal. Calcd. For C11H8N4: C, 67.34; H, 4.11. Found: C, 67.42; H, 4.20.

N-(3-Methoxyphenyl)benzamide (3g)—An oven-dried vial was equipped with a magnetic stir bar and charged with benzamide (145 mg, 1.2 mmol), K3PO4 (254 mg, 1.2 mmol), Pd2(dba)3 (4.6 mg, 0.005 mmol) and L1 or L3 (0.02 mmol). The vial was sealed with a screw-cap septum, and then evacuated and backfilled with argon (this process was repeated a total of three times). Bromobenzene (106 μL, 1.0 mmol) and tBuOH (2.0 mL) were added via syringe and the reaction mixture was heated at 110 °C for 16 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, washed with brine, dried over MgSO4 and concentrated in vacuo. The crude product was purified via flash chromatography (hexanes/EtOAc, 3:1) to provide the title compound as a white solid (206 mg, 91% (with L3)), mp 117–119 °C. 1H NMR (400 MHz, CDCl3) δ 8.66 (s, 1H), 8.07 (s, 2H), 7.86-7.81 (m, 1H), 7.47-7.41 (m, 1H), 7.37-7.31 (m, 2H); 13C NMR (100 MHz, CDCl3) δ 166.5, 160.1, 139.4, 134.9, 131.7, 129.6, 128.6, 127.2, 112.9, 110.5, 106.3, 55.2; IR (film) νmax 3304, 1652, 1607, 1540, 1492, 1455, 1420, 1305, 1276, 1200, 1160, 1046, 854, 775, 690 cm−1; Anal. Calcd. For C14H13NO2: C, 73.99; H, 5.77. Found: C, 73.73; H, 5.75.

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with brine, dried over MgSO₄ and concentrated in vacuo. The crude product was purified via flash chromatography (hexanes/EtOAc, 7:1) to provide the title compound as colorless oil (224 mg, 93% (with L3)). ¹H NMR (400 MHz, CDCl₃) δ 7.72 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.37-7.30 (m, 2H), 7.14-7.02 (m, 4H), 2.81 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 168.8, 157.4, 156.3, 154.6, 130.3, 129.9, 123.6, 122.1, 119.0, 117.3, 112.1, 20.3; IR (film) νmax 3064, 2922, 1590, 1558, 1522, 1489, 1453, 1311, 1266, 1216, 1169, 1133, 1069, 1002, 950, 872, 810, 752, 693, 643 cm⁻¹; Anal. Calcd. For C₁₄H₁₁NOS: C, 69.68; H, 4.59. Found: C, 69.63; H, 4.64.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

8. For example, 301 usd/25 g by AlfaAesar (Oct. 2011)
9. For example, 346 usd/5 kg by Sigma-Aldrich (Oct. 2011)
Figure 1.
Structures of biaryl phosphine ligands
Scheme 1.
Preparation of L3
Scheme 2.
Comparison of catalysts based on L1 and L3 for the N-arylation of 4-methylimidazole
Scheme 3.
Comparison of catalysts based on L1 and L3 for the N-arylation of 1,2,3-triazole
Scheme 4.
Comparison of catalysts based on L1 and L3 for the N- and O-arylation reactions.
Reactions were carried out in 1.0 mmol scale. Isolated yields, average of two runs.

- **Condition**: Pd$_2$(dba)$_3$ (L/Pd = 1:1), 4-methylimidazole (2 mmol), K$_3$PO$_4$ (2 mmol), toluene-dioxane (1:1), 130 °C, 6 h.
- **Condition**: Pd$_2$(dba)$_3$ (L/Pd = 1:1), 4-methylimidazole (2.4 mmol), K$_3$PO$_4$ (2 mmol), toluene-tBuOH (1:1), 120 °C, 8 h.
- **Condition**: Pd$_2$(dba)$_3$ (L/Pd = 1:1), imidazole derivative (1.2 mmol), K$_3$PO$_4$ (2 mmol), toluene-dioxane (5:1), 120 °C, 5 h.
- **Condition**: Pd$_2$(dba)$_3$ (L/Pd = 1:2.5), benzamide (1.2 mmol), K$_3$PO$_4$ (1.2 mmol), tBuOH, 110 °C, 16 h.
- **Condition**: Pd$_2$(dba)$_3$ (L/Pd = 1:2), KOH (3 mmol), H$_2$O-dioxane (1:1), 100 °C, 16 h.
- **Condition**: Pd(OAc)$_2$ (L/Pd = 1:1.5), phenol (1.2 mmol), K$_3$PO$_4$ (2 mmol), toluene, 100 °C, 16 h.

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