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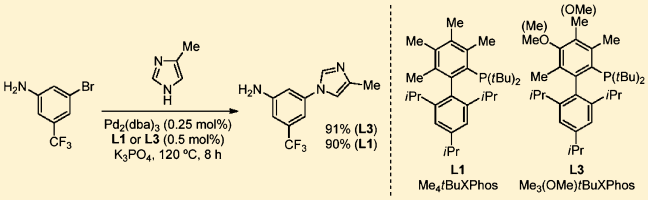
Me_3(OMe)*t*BuXPhos: A Surrogate Ligand for Me_4*t*BuXPhos in Palladium-Catalyzed C–N and C–O Bond-Forming Reactions

Satoshi Ueda, Siraj Ali, Brett P. Fors, and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Supporting Information

ABSTRACT: A new biarylphosphine ligand, Me_3(OMe)*t*BuXPhos (**L3**), was designed as a surrogate for Me_4*t*BuXPhos (**L1**). The Me_3(OMe)*t*BuXPhos 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 Me_3(OMe)*t*BuXPhos displayed the same reactivity as a catalyst based on Me_4*t*BuXPhos for Pd-catalyzed C–N and C–O bond-forming processes.



Me_4*t*BuXPhos (**L1**, Figure 1) is a useful ligand in Au-catalyzed carbocyclization[1] and Pd-catalyzed arylation reactions

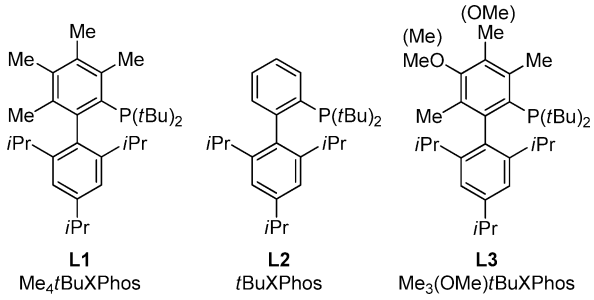


Figure 1. Structures of biarylphosphine ligands.

of nitrogen/oxygen nucleophiles, including amides,[2] benzimidazoles,[3] phenols,[4] and water.[5] We recently demonstrated that the combination of Pd and **L1** was the most effective catalyst system for the highly N^2-selective arylation of 1,2,3-triazoles[6] and completely N^1-selective arylation of unsymmetric imidazoles.[7] **L1** is synthesized from 1,2,3,4-tetramethylbenzene via dibromination and then a one-pot biarylphosphine synthesis protocol, which proceeds through a benzyne intermediate.[4,5] However, the high cost and limited availability of the 1,2,3,4-tetramethylbenzene[8] 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.[2a] 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.[3] On the basis of these two features, it was proposed that the utility of **L1** was superior to that of nonmethylated ligand *t*BuXPhos (**L2**) in several Pd-catalyzed C–N bond-forming reactions.[2,6,7] We felt that ligand **L3**, which possesses both 3- and 6-methyl substitutents and is accessible from inexpensive and readily available 2,3,6-trimethylphenol,[9] 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.

The synthesis of **L3** is described in Scheme 1. Dibromide **2** was prepared from 2,3,6-trimethylphenol via dibromination and O-methylation. Notably, both **1** and **2** were crystalline solids and could be isolated in pure form without chromatography. Dibromide **2** was treated with Mg and 2,4,6-triisopropylphenylmagnesium bromide in THF at 60 °C for 1.5 h and then allowed to react with CuCl and Cl$P(tBu)_2$ to give **L3** in 61% yield. ^{1}H NMR analysis showed that **L3** was an approximately a 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/**L1** and Pd/**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/**L1** gave *N*-arylated product **3a** in 95% yield with complete N^1 selectivity.[7] The same N-arylation reaction using Pd/**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 **L1**, 89% with **L3**) and N^2 selectivity (N^2/N^1 = 97:3 for both **L1** and **L3**) were observed for the N-arylation of 1,2,3-triazole.[6] These results demonstrate that a catalyst based on **L3** shows identical reactivity to a catalyst based on **L1**, indicating that it is excellent surrogate for C–N cross-coupling reactions.

We next explored the scope of the Pd/**L3** system using a variety of aryl halides and N/O-nucleophiles (Scheme 4).

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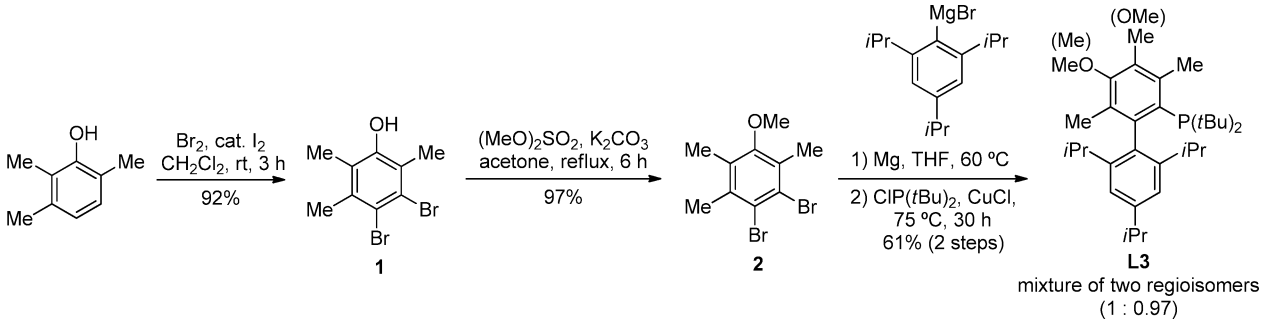
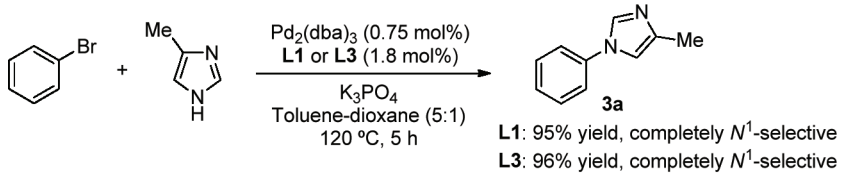
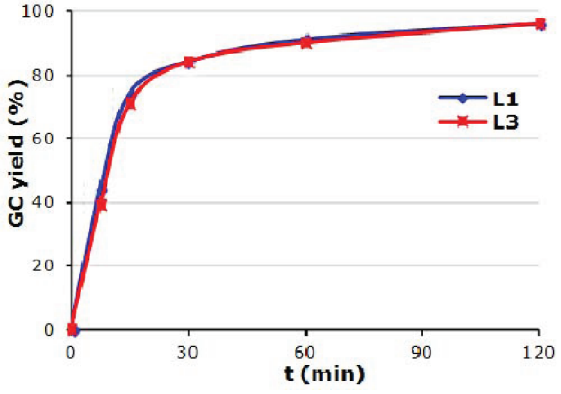
Scheme 1. Preparation of L3

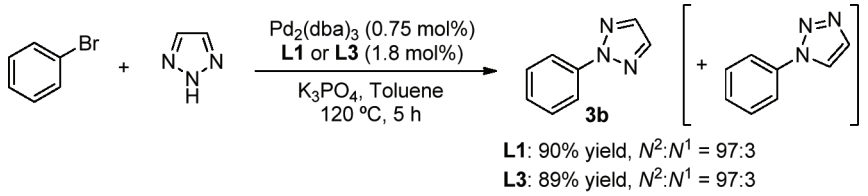


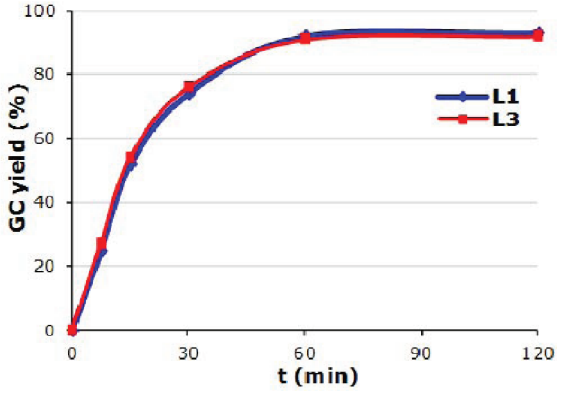
Scheme 2. Comparison of Catalysts Based on L1 and L3 for the *N*-Arylation of 4-Methylimidazole





Scheme 3. Comparison of Catalysts Based on L1 and L3 for the N-Arylation of 1,2,3-Triazole





We found that the use of Pd/**L3** gave comparable yields to those obtained with Pd/**L1** in all reactions examined. It should be noted that N^1-aryl-4-methylimidazoles **3c** and **3d**, which are key intermediates for the synthesis of GSK2137305[10] and

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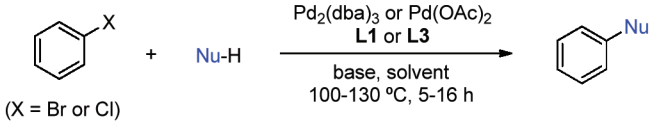
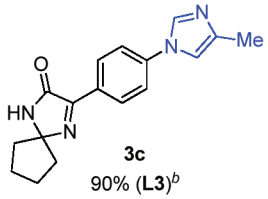
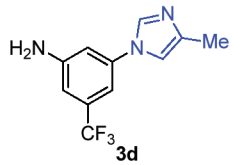
Scheme 4. Comparison of Catalysts Based on L1 and L3 for the N- and O-Arylation Reactions[a]

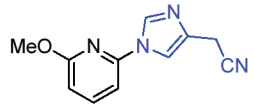




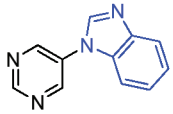
3c
90% (**L3**)[b]
92% (**L1**)[b]
(0.3 mol% Pd, X = Cl)



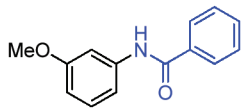
3d
91% (**L3**)[c]
90% (**L1**)[c]
(0.5 mol% Pd, X = Br)



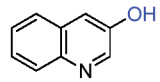
3e
87% (**L3**)[d]
89% (**L1**)[d]
(1 mol% Pd, X = Br)



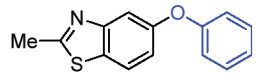
3f
94% (**L3**)[d]
96% (**L1**)[d]
(0.5 mol% Pd, X = Br)



3g
90% (**L3**)[e]
88% (**L1**)[e]
(1 mol% Pd, X = Cl)



3h
95% (**L3**)[f]
95% (**L1**)[f]
(2 mol% Pd, X = Br)



3i
93% (**L3**)[g]
91% (**L1**)[g]
(2 mol% Pd, X = Cl)

[a]Reactions were carried out on a 1.0 mmol scale. Isolated yields, average of two runs. Conditions: (b) $Pd_2(dba)_3$ (**L**/Pd = 1:1), 4-methylimidazole (2 mmol), K_3PO_4 (2 mmol), toluene−dioxane (1:1), 130 °C, 6 h; (c) $Pd_2(dba)_3$ (**L**/Pd = 1:1), 4-methylimidazole (2.4 mmol), K_3PO_4 (2 mmol), toluene−*t*BuOH (1:1), 120 °C, 8 h; (d) $Pd_2(dba)_3$ (**L**/Pd = 1:1), imidazole derivative (1.2 mmol), K_3PO_4 (2 mmol), toluene−dioxane (5:1), 120 °C, 5 h; (e) $Pd_2(dba)_3$ (**L**/Pd = 1:2.5), benzamide (1.2 mmol), K_3PO_4 (1.2 mmol), *t*BuOH, 110 °C, 16 h; (f) $Pd_2(dba)_3$ (**L**/Pd = 1:2), KOH (3 mmol), H_2O−dioxane (1:1), 100 °C, 16 h; (g) $Pd(OAc)_2$ (**L**/Pd = 1:1.5), phenol (1.2 mmol), K_3PO_4 (2 mmol), toluene, 100 °C, 16 h.

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)*t*BuXPhos (**L3**). The ligand **L3** could be prepared in a chromatography-free manner from inexpensive and readily available 2,3,6-trimethylphenol. Comparative studies of **L1** and **L3** demonstrated that **L3** could indeed serve as a surrogate for the Me_4*t*BuXPhos (**L1**). We expect wide use and large-scale application of **L3** as an efficient substitute for **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 a commercial supplier. 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). **L1**[4a] was prepared by a 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 δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) or dimethyl sulfoxide-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 dimethyl sulfoxide-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_2Cl_2 (150 mL) was added Br_2 (17.0 mL, 330 mmol) dropwise (1 drop/1 s) at room temperature. After the addition of Br_2 was complete, the reaction mixture was stirred at room temperature for 3 h, and then a saturated aqueous solution of Na_2SO_3 (150 mL) was added to quench the residual Br_2. The organic phase was separated and washed with brine, dried over $MgSO_4$, 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (s, 1H), 2.43 (s, 3H), 2.40 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.23, 136.5, 125.3, 123.3, 122.7, 119.4, 22.3, 18.3, 13.7; IR (film) ν_{max} 3376, 1699, 1652, 1558, 1541, 1456, 1388, 1290, 1199, 1081, 970, 784, 731 cm^{-1}. Anal. Calcd for $C_9H_{10}Br_2O$: 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 K_2CO_3 (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 the mixture was cooled 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 Et_2O, washed with brine, dried over $MgSO_4$, 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 2.44 (s, 3H), 2.42 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{10}H_{12}Br_2O$: 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

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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 portionwise to the reaction mixture over a 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, and CuCl (1.98 g, 20 mmol) and ClP*t*Bu$_2$ (4.6 mL, 24 mmol) were quickly added under a stream of argon. The reaction mixture was heated to reflux at 75 °C for 30 h. The reaction mixture was cooled to room temperature, diluted with Et$_2$O, washed three times with 30% NH$_4$OH, dried over MgSO$_4$, 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: 3.75 ppm, minor isomer: 3.68 ppm): ^{1}H NMR (400 MHz, CDCl$_3$) δ 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); ^{13}C NMR (100 MHz, CDCl$_3$) 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$_3$) δ 39.17, 38.16; IR (film) ν_{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 **L1** or **L3** (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 μL, 1.0 mmol), and the preheated catalyst solution was 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 **L3**)): mp 60 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 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$_3$) δ 139.4, 137.3, 134.4, 129.7, 126.9, 120.8, 114.4, 13.6; IR (film) ν_{max} 3385, 3108, 2921, 1599, 1507, 1448, 1392, 1366, 1291, 1241, 1070, 1003, 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 **L1** or **L3** (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 μL, 1.0 mmol); 1,2,3-triazole (70 μL, 1.2 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 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 **L3**)): ^{1}H NMR (400 MHz, CDCl3) δ 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$_3$) δ 140.0, 135.6, 129.4, 127.6, 119.1; IR (film) ν_{max} 3128, 3059, 2362, 1745, 1598, 1500, 1410, 1376, 1259, 1152, 1069, 953, 820, 757, 692, 668, 510, 455 cm^{-1}. Anal. Calcd for $C_8H_7N_3$: 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 **L1** or **L3** (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 preheated 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 MgSO$_4$, 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; ^{1}H NMR (400 MHz, DMSO-d_6) 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); ^{13}C NMR (100 MHz, DMSO-d_6) 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) ν_{max} 3854, 3745, 3158, 3050, 2962, 2360, 1704, 1606, 1518, 1442, 1254, 1191, 1063, 963, 848, 752, 540 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_4O$: C, 69.37; H, 6.16. Found: C, 69.21; H, 6.12.

3-(4-Methyl-1*H*-imidazol-1-yl)-5-(trifluoromethyl)aniline (3d). An oven-dried vial was equipped with a magnetic stir bar and charged with Pd$_2$(dba)$_3$ (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 turned to dark brown after 3 min. A second oven-dried vial which was equipped with a stir bar was charged with 3-amino-5-bromobenzotrifluoride (240 mg, 1.0 mmol), 4-methylimidazole (197 mg, 2.4 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 preheated catalyst solution followed by anhydrous toluene (0.5 mL) and *t*BuOH (1.0 mL) were added via syringe to the second vial (a total 2 mL of toluene−*t*BuOH 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 MgSO$_4$, concentrated in vacuo, and purified via flash chromatography (Et$_2$O/EtOAc/MeOH, 125:125:1) to provide the title compound as a white solid (219 mg, 91% (with **L3**)): mp 125 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 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); ^{13}C NMR (100 MHz, DMSO-d_6) 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) ν_{max} 3854, 3745, 3414, 3215, 2362, 1620, 1509, 1412, 1328, 1293, 1254, 1199, 1158, 1115, 843, 807, 735, 691, 621 cm^{-1}. Anal. Calcd for $C_{11}H_{10}F_3N_3$: C, 54.77; H, 4.18. Found: C, 54.61; H, 4.11.

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2-(1-(6-Methoxypyridin-2-yl)-1*H*-imidazol-4-yl)acetonitrile (3e). An oven-dried vial was equipped with a magnetic stir bar and charged with $Pd_2(dba)_3$ (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 (0.41 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 K_3PO_4 (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); 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 $MgSO_4$, 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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) ν_{max} 3397, 2954, 1614, 1580, 1481, 1452, 1421, 1321, 1253, 1091, 1035, 1000, 860, 793 cm^{-1}. Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71. Found: C, 61.65; H, 4.77.

1-(Pyrimidin-5-yl)-1*H*-benzimidazole (3f). An oven-dried vial was equipped with a magnetic stir bar and charged with $Pd_2(dba)_3$ (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 K_3PO_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 preheated 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 $MgSO_4$, 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 151.9, 144.1, 141.3, 133.0, 132.0, 124.7, 123.8, 121.2, 109.6; IR (film) ν_{max} 3745, 3065, 2362, 1698, 1652, 1558, 1497, 1464, 1429, 1291, 1245, 1208, 881, 725, 615 cm. Anal. Calcd for $C_{11}H_8N_4$: 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), K_3PO_4 (254 mg, 1.2 mmol), $Pd_2(dba)_3$ (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 *t*BuOH (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 $MgSO_4$, 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.81−7.75 (m, 2H), 7.45−7.37 (m, 2H), 7.33−7.26 (m, 2H), 7.19−7.11 (m, 2H), 6.67−6.61 (m, 1H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77. Found: C, 73.73; H, 5.75.

2-Methyl-5-phenoxybenzo[*d*]thiazole (3i). An oven-dried vial was equipped with a magnetic stir bar and charged with 5-chloro-2-methylbenzothiazole (184 mg, 1.0 mmol), phenol (113 mg, 1.2 mmol), K_3PO_4 (424 mg, 2.0 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), and **L1** or **L3** (0.03 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). Toluene (1.5 mL) was added via syringe, and the reaction mixture was heated at 100 °C for 16 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, 7:1) to provide the title compound as colorless oil (224 mg, 93% (with **L3**)): ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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) ν_{max} 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 $C_{14}H_{11}NOS$: C, 69.68; H, 4.59. Found: C, 69.63; H, 4.64.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sbuchwal@mit.edu.

Notes

The authors declare no competing financial interest.

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