N-Substituted 2-Aminobiphenylpalladium Methanesulfonate Precatalysts and Their Use in C–C and C–N Cross-Couplings

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N-Substituted 2-Aminobiphenylpalladium Methanesulfonate Precatalysts and Their Use in C–C and C–N Cross-Couplings

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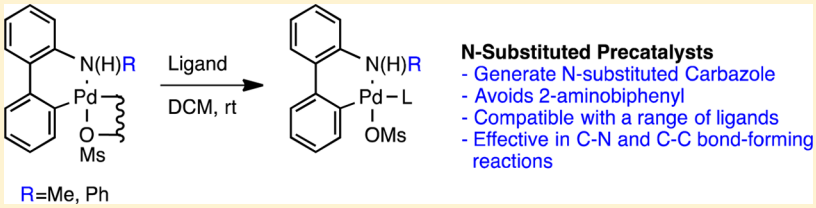
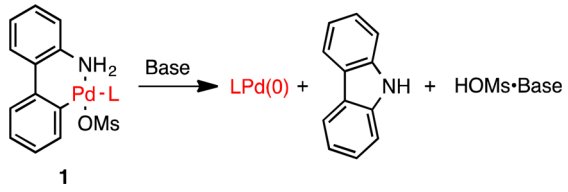
Supporting Information



ABSTRACT: A series of phosphine-ligated palladium precatalysts based on *N*-methyl- and *N*-phenyl-2-aminobiphenyl have been developed. Substitution at the nitrogen center prevents the presence of traces of aminobiphenyls that contain a free $-NH_2$ group from contaminating cross-coupling products. These precatalysts produce N-substituted carbazoles upon activation, which cannot consume starting materials. These precatalysts were efficiently generated from 2-aminobiphenyl with minimal purification and found to be highly effective in Suzuki–Miyaura and C–N cross-coupling reactions.

We recently reported palladium precatalysts based on a ligated 2-aminobiphenylpalladium methanesulfonate palladacycle (**1**, Scheme 1).[1] Precatalyst **1** activates through

Scheme 1. Palladium Methanesulfonate Precatalysts and Their Generic Activation

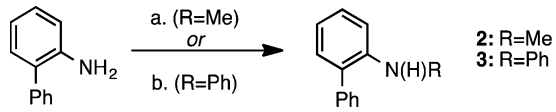


the deprotonation of the palladium-bound amine to give a Pd–amido complex which then reductively eliminates to form carbazole, a methanesulfonate salt, and LPd(0). Precatalysts of type **1** can accommodate a variety of ligands and are applicable to numerous palladium-catalyzed transformations.[2]

Despite the advantages of **1**, a few drawbacks limit their utility in some applications, including (1) the carbazole byproduct generated through the activation of **1** can be *N*-arylated, consuming valuable starting materials or potentially complicating work-up/purification of the desired product,[1b] and (2) there is some concern regarding the presence of trace amounts of residual NH_2-aminobiphenyls in pharmaceutical samples due to potential health risks.[3] *N*-Alkyl and *N*-aryl analogues of **1** would overcome these concerns and provide a useful alternative to **1**.

N-Substituted 2-aminobiphenyls could be readily prepared on a 30 mmol scale via N-methylation and N-arylation as shown in Scheme 2. The unpurified products[4] from these reactions can be directly used to prepare the corresponding

Scheme 2. Preparation of *N*-Methyl- and *N*-Phenyl-2-aminobiphenyl Derivatives[ab]

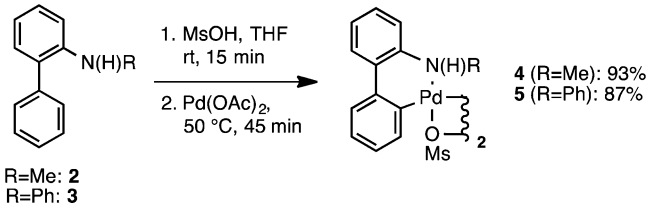


[a](i) nBuLi, THF, 0 °C, 30 min; (ii) MeI, 0 °C to rt, 30 min, quant conversion. [b]1 mol % **1**·**L1**, PhCl, NaOtBu, dioxane, 100 °C, 30 min, 99%.

palladacycles. Treatment of *N*-methyl-2-aminobiphenyl, **2**, and *N*-phenyl-2-aminobiphenyl, **3**, with methanesulfonic acid followed by heating the resulting salt solution with $Pd(OAc)_2$ provided the dimeric palladacycles **4** and **5**. These procedures were amenable to scale up, providing the desired palladium dimers in excellent yields at a 30 mmol scale (Scheme 3).

These were subsequently treated with phosphines at room temperature in dichloromethane to provide the N-substituted precatalysts (Scheme 4). Precatalysts that incorporated a variety

Scheme 3. Preparation of N-Substituted μ-OMs Palladium Dimers



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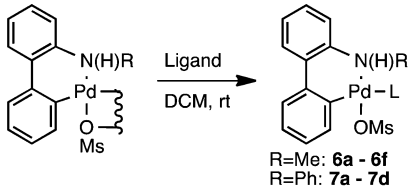
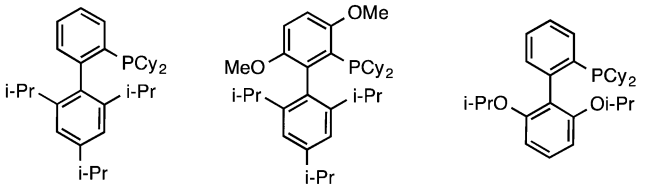
Scheme 4. Preparation of N-Substituted Palladium Methanesulfonate Precatalysts





of ligands could be prepared as shown in Scheme 3. In contrast, however, to what we observed with **1**, we were unable to make precatalysts containing the largest of our ligands: attempts to incorporate tBuBrettPhos, RockPhos, and AdBrettPhos were unsuccessful.[5] Additionally, while we could prepare **6f** from (±)-BINAP, we were unable to obtain the corresponding *N*-phenyl analogue, **7f**.[6]

The solid-state structures of **6a** and **7a** were determined by single-crystal X-ray crystallography (Figure 1). Both possess a tetracoordinated Pd(II) center with a slightly distorted square planar geometry. The phosphine is bound to the palladium center *cis* to the Pd–C bond. Additionally the methanesulfonate anion is directly bound to the palladium center. This is similar to what was previously observed for **1** (L = XPhos).

To evaluate the reactivity of precatalysts **6** and **7**, we first examined their efficacy in promoting the Suzuki–Miyaura coupling of aryl halides with arylboronic acids that are prone to rapid protodeboronation under standard cross-coupling reaction conditions. As previously described, the rapid generation of a highly active LPd(0) is essential for success of these reactions.[7] These reactions allowed us to test whether **6** and **7** activate rapidly at room temperature. As shown in Scheme 5, both **6a** and **7a** were highly effective precatalysts in the coupling of (hetero)aryl halides and unstable boronic acids, providing the arylated products in uniformly good yields.

We also evaluated precatalysts of type **6** and **7** in C–N cross-coupling reactions. They were found to be effective in the arylation of primary amines, secondary amines, as well as primary amides (Scheme 6). The precatalyst was able to be employed at low catalyst loadings (0.01 mol %) for the arylation of aniline with 4-chloro- and 4-iodoanisole.

In conclusion, we have developed a series of precatalysts based on the *N*-methyl- and *N*-phenyl-2-aminobiphenylpalla-

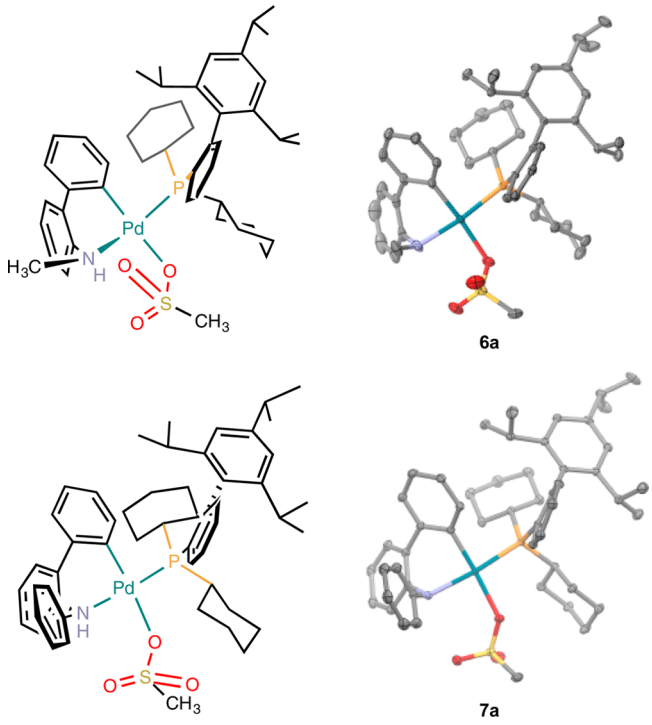
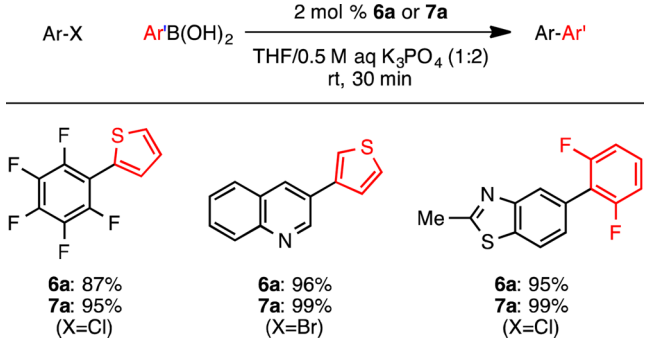


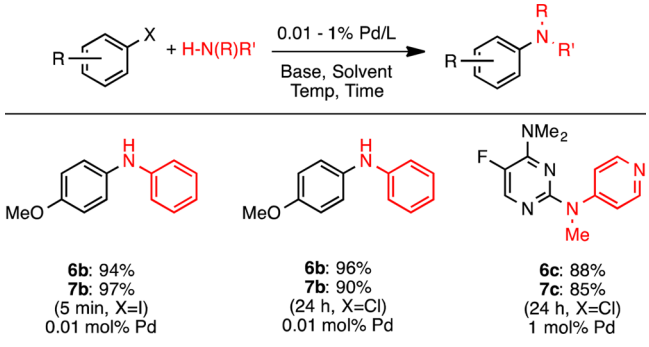
Figure 1. Crystallographically determined X-ray structures of **5a** and **6a** (thermal ellipsoid plot at 50% probability, hydrogen atoms are omitted for clarity).

Scheme 5. Suzuki–Miyaura Coupling of Unstable Boronic Acids with Precatalysts 6a and 7a[a]



[a]General conditions: ArX (1 mmol), Ar'B(OH)$_2$ (1.5 mmol), **6a** or **7a** (2 mol %), 0.5 M K_3PO_4 (aq) (4 mL), THF (2 mL), rt, 30 min, average of two isolated yields.

Scheme 6. *N*-Arylation of Amines with Precatalysts 6 and 7



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dium methanesulfonate scaffold. By utilizing *N*-substituted 2-aminobiphenyls, the chance of the trace contamination of reaction products with NH_2-aminobiphenyls is eliminated. Additionally, the *N*-substituted carbazole that results during precatalyst activation cannot be further arylated, preventing the waste of the aryl halide substrate. We believe that these precatalysts, like **1**, will find many applications in palladium-catalyzed cross-coupling chemistry in both academia and industry.

EXPERIMENTAL SECTION

General Information. *General Reagent Information.* THF and toluene were purchased in solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing it under argon pressure through two packed columns of neutral alumina (for THF) or through neutral alumina and copper(II) oxide (for toluene). Anhydrous tribasic potassium phosphate and sodium *tert*-butoxide were purchased from commercial suppliers. These bases were stored in a nitrogen-filled glovebox and removed in small quantities. They were stored on the bench in a desiccator for up to 2 weeks. $Pd(OAc)_2$ and all ligands were acquired from commercial suppliers. All other reagents were purchased from commercial suppliers and used as received. Aqueous 0.5 M K_3PO_4 solution was prepared by dissolving K_3PO_4 (1.06 g, 5 mmol) in deionized water (19 mL), and the solution was degassed by performing three sets of evacuation and argon refill cycles under sonication. Flash chromatography was performed with 230−400 mesh silica gel.

General Analytical Information. All compounds (starting materials and products) were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR (when applicable), ^{19}F NMR (when applicable), and IR spectroscopy, melting point (when applicable), and elemental analysis. The ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectra can be found in the Supporting Information. ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR were recorded on 300, 400, or 500 MHz spectrometers. The spectra were calibrated according to residual solvent peaks ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR; CD_2Cl_2: 5.32 ppm for ^{1}H NMR and 53.84 ppm for ^{13}C NMR; CD_3OD: 3.31 for ^{1}H NMR and 49.00 for ^{13}C NMR), an external reference (H_3PO_4: 0 ppm for ^{31}P; $CFCl_3$: 0 ppm for ^{19}F), or an internal reference (CF_3Ph: −63.7 ppm for ^{19}F). The ^{13}C and ^{31}P NMR spectra were obtained with ^{1}H decoupling, and the ^{19}F NMR spectra were obtained without ^{1}H decoupling. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. Reactions were monitored by GC and thin-layer chromatography (TLC) carried out on 0.25 mm glass-backed silica gel plates using UV light as a visualizing agent.

***N*-Methyl-2-aminobiphenylpalladium Methanesulfonate (4).** *Step 1: N-Methyl-2-aminobiphenyl (**2**).* A flame-dried 300 mL round-bottomed flask equipped with a magnetic stir bar was charged with 2-aminobiphenyl and capped with a rubber septum. The flask was evacuated and backfilled with argon, followed by the addition of THF (100 mL). The mixture was cooled to 0 °C in an ice bath. At 0 °C, nBuLi (2.5 M in hexanes, 12.6 mL, 31.5 mmol, 1.05 equiv) was added slowly. After the addition of nBuLi was complete the bright yellow reaction mixture was stirred for 1 h at 0 °C. Then iodomethane (1.89 mL, 30.3 mmol, 1.01 equiv) was added slowly, at which time the color faded to a dull yellow. The mixture was stirred for an additional 30 min at rt. Saturated $NaHCO_3$ (aq) (25 mL) and water (25 mL) were added, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to provide the title compound as a yellow oil as a 95:5 mixture of mono-/dimethylated product, as determined by gas chromatography and ^{1}H NMR. The crude mixture was used directly in the next step without further purification. Yield: 5.45 g, 99%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49−7.42 (m, 4H), 7.40−7.34 (m, 1H), 7.30 (ddd, J = 8.1, 7.4, 1.7 Hz, 1H), 7.12 (dd, J = 7.4, 1.6 Hz, 1H), 6.80 (td, J = 7.4, 1.1 Hz, 1H), 6.72 (dd, J = 8.2, 1.0 Hz, 1H), 3.98 (s, 1H), 2.82 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.4, 139.7, 130.2, 129.6, 129.1, 129.0, 127.8, 127.4, 117.0, 110.0, 31.0 ppm. IR (neat, cm^{-1}): 1613, 1603, 1509, 1490, 1435, 1284, 1008, 770, 746, 701, 615.

*Step 2: Palladium Methanesulfonate Dimer (**4**).* A 200 mL round-bottomed flask equipped with a magnetic stir bar was charged with *N*-methyl-2-aminobiphenyl (5.52 g, 30.0 mmol, 1.00 equiv, 95:5 mono-/dimethylated) and THF (60 mL). With stirring, methanesulfonic acid (1.84 mL, 28.5 mmol, 0.95 equiv (1 equiv relative to monomethylated amine)) was added slowly and the reaction mixture stirred for 15 min at room temperature. Palladium acetate (6.38 g, 28.5 mmol, 0.95 equiv) was added in one portion and rinsed off the walls of the flask with additional THF (15 mL). The flask was capped with a rubber septum, and the deep red slurry was stirred at 50 °C for 45 min. After the mixture was cooled to room temperature, the dark yellow solution was filtered through a plug of cotton to remove traces of palladium black and ∼95% of the solvent was removed with the aid of a rotary evaporator. Diethyl ether (150 mL) was added to the flask, and the mixture was sonicated to precipitate the product. The solid was isolated via vacuum filtration and dried under vacuum overnight to provide the title compound as a tan solid. Yield: 10.2 g, 93%. ^{1}H NMR (500 MHz, CD_2Cl_2 + 10 μL pyridine-d_5): δ 7.70 (d, J = 7.7 Hz, 1H), 7.66−7.56 (m, 1H), 7.52−7.47 (m, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 7.7 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H), 6.94−6.84 (m, 1H), 6.50 (d, J = 7.7 Hz, 1H), 2.70 (d, J = 5.6 Hz, 3H), 2.61 (s, 3H) ppm. ^{13}C NMR (126 MHz, CD_3OD): δ 142.0, 140.7, 133.4, 128. 9, 128.5, 127.2, 126.5, 125.2, 39.0 ppm. IR (neat, cm^{-1}): 3205, 1230, 1136, 1118, 1026, 735, 727 714, 589.

***N*-Phenyl-2-aminobiphenylpalladium Methanesulfonate (5).** *Step 1: N-Phenyl-2-aminobiphenyl (**3**).* A 100 mL oven-dried round-bottomed flask equipped with a magnetic stir bar was charged with 2-aminobiphenyl (5.07 g, 30.0 mmol, 1.00 equiv), sodium *tert*-butoxide (3.07 g, 32.0 mmol, 1.07 equiv), and XPhos precatalyst **1**·**L1** (306 mg, 0.30 mmol, 1 mol %). The flask was capped with a rubber septum and subsequently evacuated and backfilled with argon (this procedure was repeated one additional time). Chlorobenzene (3.04 mL, 30.0 mmol, 1.00 equiv) was then added by syringe, followed by dioxane (30 mL). The reaction mixture was stirred at 100 °C for 30 min. It was then cooled to room temperature, diluted with ethyl acetate (50 mL), and filtered through a plug of silica gel layered on top of Celite, eluting the mixture with additional ethyl acetate. The mixture was concentrated with the aid of a rotary evaporator, and the product was obtained as a dark yellow oil, containing traces of *N*,*N*-diphenyl-2-aminobiphenyl and 9-phenylcarbazole. It was used for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53−7.46 (m, 4H), 7.46−7.38 (m, 2H), 7.34−7.27 (m, 4H), 7.12−7.02 (m, 3H), 6.97 (tt, J = 7.4, 1.1 Hz, 1H), 5.66 (bs, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.1, 140.9, 139.7, 132.2, 131.6, 130.1, 130.1, 129.6, 129.0, 128.2, 121.8, 121.8, 118.9, 118.2. IR (neat, cm^{-1}): 1611, 1500, 1479, 1434, 1008, 749, 721, 702.

*Step 2: Palladium Methanesulfonate Dimer (**5**).* A 300 mL round-bottomed flask equipped with a magnetic stir bar was charged with *N*-phenyl-2-aminobiphenyl (7.35 g, 30.0 mmol, 1.00 equiv) and THF (50 mL). Methanesulfonic acid (1.95 mL, 30.0 mmol, 1.00 equiv) was added slowly with vigorous stirring. After the reaction mixture was stirred for 15 min, palladium acetate (6.72 g, 30.0 mmol, 1.00 equiv) was added to the flask in one portion and rinsed off the walls of the flask with additional THF (25 mL). The flask was capped with a rubber septum, and the deep red slurry was stirred at 50 °C for 45 min. Over the course of the reaction the deep red color dissipated and a tan slurry formed. The reaction mixture was cooled to room temperature and poured into an Erlenmeyer flask containing pentane (75 mL) and diethyl ether (75 mL). The solid was isolated via vacuum filtration and dried under vacuum overnight to afford the title compound as a tan powder. Yield: 12.1 g, 87%. ^{1}H NMR (500 MHz, CD_3CN): δ 10.47 (s, 1H), 7.83−7.79 (m, 1H), 7.52 (ddd, J = 7.8, 6.9, 1.9 Hz, 1H), 7.47−7.39 (m, 3H), 7.20−7.13 (m, 2H), 7.13−7.09 (m, 2H), 7.09−7.03 (m, 2H), 7.00 (dd, J = 7.8, 1.2 Hz, 1H), 6.89 (ddd, J = 7.9, 7.2, 1.6 Hz, 1H), 2.75 (s, 3H). ^{13}C NMR (126 MHz, CD_3CN): δ 146.4, 142.4, 140.6, 137.5, 136.8, 136.5, 130.0, 129.8, 129.5, 129.3, 127.8, 127.1,

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127.1, 126.7, 123.8, 122.1, 40.3 ppm. IR (neat, cm^{-1}): 3115, 1493, 1218, 1130, 1025, 762, 735, 716, 606.

XPhos Precatalyst 6a: Representative Procedure. A 24 mL screw-top test tube equipped with a stir bar was charged with **4** (384 mg, 0.50 mmol, 0.50 equiv) XPhos (476 mg, 1.00 mmol, 1.00 equiv). Dichloromethane (5 mL) was added, and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed with the aid of rotary evaporation. Pentane (25 mL) was added to the residue to precipitate the precatalyst, which was then isolated via vacuum filtration and dried under vacuum overnight to provide the title compound as a tan solid. Yield: 730 mg, 85%. ^{1}H NMR (500 MHz, CD_3OD): δ 7.97 (ddd, J = 9.2, 4.9, 2.9 Hz, 1H), 7.65 (dd, J = 7.8, 1.7 Hz, 2H), 7.63−7.57 (m, 3H), 7.41−7.23 (m, 5H), 7.16−7.10 (m, 1H), 7.04−6.94 (m, 2H), 3.39 (h, J = 6.9 Hz, 1H), 2.94 (hept, J = 6.8 Hz, 1H), 2.69 (s, 3H), 2.61−2.49 (m, 1H), 2.37 (qt, J = 12.4, 3.1 Hz, 1H), 2.29 (d, J = 10.9 Hz, 1H), 2.09 (dd, J = 6.0, 2.6 Hz, 4H), 1.98 (ddd, J = 13.4, 9.5, 5.0 Hz, 2H), 1.94−1.75 (m, 5H), 1.56 (dd, J = 6.9, 2.5 Hz, 7H), 1.51−1.23 (m, 7H), 1.22−1.06 (m, 6H), 0.94−0.83 (m, 4H), 0.67 (d, J = 6.8 Hz, 2H), 0.15 (m, 1H) ppm. ^{13}C NMR (126 MHz, CD_3OD): δ 157.5, 156.3, 151.5, 145.3, 145.2, 144.4, 135.6, 134.1, 133.1, 132.9, 131.8, 130.5, 130.4, 129.5, 129.1, 129.1, 128.6, 128.5, 128.2, 128.0, 127.8, 127.2, 126.9, 125.9, 124.6, 123.4, 122.1, 41.9, 40.8, 40.7, 39.7, 39.6, 38.5, 37.4, 35.8, 35.6, 34.5, 33.9, 33.2, 32.9, 32.4, 31.4, 30.3, 30.2, 28.4, 28.0, 26. 8, 26.6, 25.6, 25.1, 24.6, 24.1, 23.2, 22.8 ppm (observed complexity due to C−P splitting). ^{31}P NMR (121 MHz, CD_3OD) δ 39.49 ppm. IR (neat, cm^{-1}): 2924, 1462, 1420, 1144, 1020, 1003, 876, 766, 738.

XPhos Precatalyst 7a. Tan solid. Yield: 913 mg, 99%. ^{1}H NMR (500 MHz, CD_3OD): δ 8.02−7.94 (m, 1H), 7.77−7.71 (m, 2H), 7.69−7.60 (m, 3H), 7.56−7.48 (m, 2H), 7.26−7.19 (m, 1H), 7.13−7.06 (m, 2H), 7.05−6.93 (m, 4H), 6.89 (tt, J = 7.4, 1.3 Hz, 1H), 6.79−6.73 (m, 1H), 6.65 (dd, J = 8.4, 1.4 Hz, 2H), 3.20 (hept, J = 6.9 Hz, 1H), 2.97 (hept, J = 6.8 Hz, 1H), 2.69 (s, 3H), 2.56−2.30 (m, 3H), 2.09 (d, J = 12.8 Hz, 1H), 2.05−1.86 (m, 4H), 1.86−1.68 (m, 2H), 1.64−1.37 (m, 3H), 1.37−1.20 (m, 6H), 1.20−1.05 (m, 6H), 0.97 (ddd, J = 16.6, 8.1, 3.7 Hz, 1H), 0.93−0.84 (m, 5H), 0.70 (d, J = 6.8 Hz, 2H), −0.09 (dh, J = 17.1, 4.7, 3.9 Hz, 1H) ppm. ^{13}C NMR (126 MHz, CD_3OD): δ 156.0, 155.0, 152.1, 145.5, 145.3, 143.4, 142.9, 142.0, 139.9, 137.5, 135.3, 135.2, 133.6, 133.4, 133.3, 132.4, 130.1, 129.1, 129.1, 129.0, 128.9, 128.8, 128.8, 128.5, 127.3, 126.6, 125.9, 125.3, 123.2, 38.9, 36.6, 36.4, 34.9, 34.6, 33.4, 32.8, 32.6, 32.1, 30.8, 30.0, 28.4, 28.3, 27.9, 27.8, 26.8, 26.7, 26.5, 26.4, 26.4, 26.3, 26.1, 25.5, 25.5, 24.5, 23.7, 22.9, 22.8, 22.7, 13.8 ppm (observed complexity due to C−P splitting). ^{31}P NMR (121 MHz, CD_3OD): δ 40.59 ppm. IR (neat, cm^{-1}): 2923, 1422, 1254, 1145, 1024, 1002, 773, 760, 740, 691.

BrettPhos Precatalyst 6b (11 mmol scale). Off-white solid. Yield: 9.59 g, 94%. ^{1}H NMR (500 MHz, CD_3OD): δ 7.61 (dd, J = 7.5, 1.6 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.52 (d, J = 1.9 Hz, 1H), 7.36 (td, J = 7.5, 1.3 Hz, 1H), 7.32 (td, J = 7.6, 1.6 Hz, 1H), 7.28−7.22 (m, 3H), 7.17 (h, J = 2.6, 2.2 Hz, 3H), 6.99 (dd, J = 7.7, 1.3 Hz, 1H), 3.88 (s, 3H), 3.45 (s, 3H), 3.37 (dq, J = 13.9, 6.8 Hz, 1H), 2.99 (p, J = 6.7 Hz, 1H), 2.95−2.83 (m, 1H), 2.83−2.73 (m, 1H), 2.69 (s, 3H), 2.14 (d, J = 11.2 Hz, 1H), 2.08−1.93 (m, 6H), 1.90 (d, J = 10.1 Hz, 1H), 1.87−1.67 (m, 4H), 1.63−1.18 (m, 11H), 1.18−0.77 (m, 6H), 0.71 (dd, J = 9.2, 6.7 Hz, 5H), 0.41 (qdd, J = 12.8, 6.3, 3.5 Hz, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2): δ 158.2, 156.4, 156.1, 155.7, 152.3, 152.1, 151.6, 147.1, 142.0, 141.3, 139.7, 135.3, 135.2, 134.6, 130.9, 129.5, 128.5, 128.0, 127.6, 124.2, 123.5, 123.3, 122.1, 120.1, 116.1, 113.2, 56.0, 55.4, 40.7, 40.0, 35.2, 34.7, 34.5, 34.0, 33. 8, 33.4, 31.4, 30.5, 30.2, 28.8, 28.7, 28.4, 28.3, 27.4, 27.3, 27.2, 26.8, 26.5, 26.1, 25.0, 25.0, 24.9, 24.5, 24.4 ppm. ^{31}P NMR (121 MHz, CD_3OD): δ 41.61. IR (neat, cm^{-1}): 3236, 2925, 2849, 1422, 1252, 1215, 1201, 1173, 1041, 1011, 763, 747, 739, 727.

BrettPhos Precatalyst 7b (11 mmol scale). Tan solid. Yield: 9.35 g, 86%. ^{1}H NMR (500 MHz, CD_3OD): δ 7.73−7.66 (m, 1H), 7.65 (d, J = 1.8 Hz, 1H), 7.61 (d, J = 1.8 Hz, 1H), 7.56−7.46 (m, 2H), 7.42−7.34 (m, 1H), 7.29−7.23 (m, 1H), 7.19 (d, J = 2.2 Hz, 2H), 7.13−7.06 (m, 1H), 7.06−6.96 (m, 4H), 6.96−6.91 (m, 2H), 6.90−6.78 (m, 3H), 6.65−6.58 (m, 2H), 3.88 (s, 3H), 3.47 (s, 3H), 3.12 (hept, J = 7.0 Hz, 1H), 3.07−2.89 (m, 2H), 2.71 (s, 4H), 2.24 (d, J = 11.2 Hz, 1H), 2.06 (p, J = 6.8 Hz, 1H), 2.02−1.97 (m, 3H), 1.98−1.83 (m, 2H), 1.83−1.46 (m, 5H), 1.46−1.21 (m, 5H), 1.20−0.80 (m, 9H), 0.75 (dd, J = 20.6, 6.7 Hz, 5H), 0.30 (dtd, J = 13.4, 10.8, 10.0, 6.3 Hz, 1H) ppm. ^{13}C NMR (126 MHz, CD_2Cl_2): δ 156.7, 156.0, 155.6, 155.1, 151.9, 151.6, 144.6, 143.3, 143.3, 140.6, 137.9, 135.5, 135.4, 134.9, 134.8, 129.8, 129.4, 129.2, 129.0, 128.94, 128.88, 128.5, 128.4, 127.1, 126.6, 126.3, 125.4, 125.2, 124.9, 124.8, 123.5, 122.8, 122.0, 121.8, 116.1, 113.3, 56.0, 55.3, 40.2, 35.1, 34.8, 34.6, 34.3, 34.1, 33.4, 31.8, 30.8, 30.43, 30.37, 30.31, 28.73, 28.65, 28.47, 28.3, 28.2, 27.50, 27.45, 27.38, 27.34, 26.73, 26.47, 25.36, 25.22, 24.90, 24.38, 23.73, 23.03, 14.56 ppm (observed complexity due to C−P splitting). ^{31}P NMR (121 MHz, CD_3OD): δ 45.87. IR (neat, cm^{-1}): 2926, 1418, 1255, 1144, 1124, 1039, 1012, 1002, 758, 739, 690.

RuPhos Precatalyst 6c. White solid. Yield: 817 mg, 86%. ^{1}H NMR (500 MHz, CD_3OD): δ 8.10 (t, J = 8.4 Hz, 1H), 7.85−7.77 (m, 1H), 7.66−7.59 (m, 1H), 7.53 (tt, J = 7.6, 1.5 Hz, 1H), 7.48 (tt, J = 7.4, 1.5 Hz, 1H), 7.39−7.25 (m, 4H), 7.25−7.18 (m, 1H), 7.12−7.04 (m, 2H), 7.02 (d, J = 8.5 Hz, 1H), 6.79 (ddd, J = 7.8, 3.0, 1.3 Hz, 1H), 0.17−0.02 (m, 1H), 4.87−4.79 (m, 1H), 4.54 (hept, J = 6.1 Hz, 1H), 2.70 (s, 3H), 2.45 (tdd, J = 12.6, 9.7, 5.1 Hz, 1H), 2.34 (t, J = 11.4 Hz, 1H), 2.28−2.09 (m, 5H), 2.09−1.88 (m, 1H), 1.82 (d, J = 13.3 Hz, 1H), 1.71 (qt, J = 12.4, 3.2 Hz, 1H), 1.66−1.48 (m, 4H), 1.48−0.96 (m, 8H), 0.94−0.68 (m, 6H) ppm. ^{13}C NMR (126 MHz, CD_2Cl_2): δ 163.25, 162.16, 151.60, 145.50, 142.43, 141.70, 140.22, 137.26, 135.48, 132.30, 130.86, 129.54, 128.89, 128.58, 127.77, 127.62, 127.31, 122.64, 106.58, 40.51, 40.50, 40.22, 35.9, 35.7, 31.1, 30.2, 28.0, 28.0, 27.7, 27.6, 27.2, 27.1, 26.8, 26.7, 26.6, 26.4, 22.4, 22.3, 21.5 ppm (observed complexity due to C−P splitting). ^{31}P NMR (121 MHz, CD_3OD): δ 45.04. IR (neat, cm^{-1}): 3236, 2926, 2843, 1448, 1257, 1204, 1099, 1062, 1039, 786, 761.

RuPhos Precatalyst 7c. Orange solid. Yield: 873 mg, 96%. ^{1}H NMR (500 MHz, CD_3OD): δ 7.98 (t, J = 8.3 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.74−7.66 (m, 1H), 7.61−7.45 (m, 5H), 7.19−7.05 (m, 3H), 6.97 (dq, J = 31.7, 7.5 Hz, 4H), 6.88−6.78 (m, 2H), 6.72 (dd, J = 7.6, 3.7 Hz, 1H), 6.64 (d, J = 7.9 Hz, 2H), 4.93 (p, J = 6.0 Hz, 1H), 4.60 (p, J = 6.2 Hz, 1H), 2.69 (s, 4H), 2.41 (p, J = 11.8, 11.0 Hz, 2H), 2.23 (q, J = 12.8 Hz, 1H), 2.02 (dd, J = 21.8, 13.1 Hz, 3H), 1.96−1.48 (m, 9H), 1.46−0.83 (m, 14H), 0.72 (dd, J = 12.8, 5.9 Hz, 3H), −0.06 - −0.21 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): complex spectrum—see the Supporting Information (significant peak broadening observed). ^{31}P NMR (121 MHz, CD_3OD): δ 62.77, 46.93 ppm. IR (neat, cm^{-1}): 2926, 1459, 1245, 1136, 1111, 1064, 1028, 1000, 761, 756, 738, 690.

SPhos Precatalyst 6d. White solid. Yield: 680 mg, 86%. ^{1}H NMR (500 MHz, CD_3OD): δ 8.16 (t, J = 8.4 Hz, 1H), 7.87−7.78 (m, 1H), 7.68−7.61 (m, 1H), 7.56−7.44 (m, 2H), 7.41−7.25 (m, 5H), 7.26−7.19 (m, 1H), 7.14−7.05 (m, 3H), 6.84 (ddd, J = 7.7, 3.1, 1.4 Hz, 1H), 3.96 (s, 3H), 3.41 (s, 3H), 2.69 (s, 3H), 2.54−2.38 (m, 1H), 2.27−2.15 (m, 2H), 2.14 (dd, J = 5.9, 2.5 Hz, 3H), 2.04 (s, 4H), 1.94 (dd, J = 11.0, 7.1 Hz, 1H), 1.81 (d, J = 13.3 Hz, 1H), 1.70 (qt, J = 12.2, 3.1 Hz, 1H), 1.65−1.47 (m, 2H), 1.42 (d, J = 13.1 Hz, 1H), 1.36 (dt, J = 12.8, 3.3 Hz, 2H), 1.30−0.95 (m, 4H), 0.95−0.74 (m, 2H), 0.10 - −0.07 (m, 1H) ppm. ^{13}C NMR (126 MHz, CD_2Cl_2): complex spectrum—see the Supporting Information (significant peak broadening observed). ^{31}P NMR (121 MHz, CD_3OD): δ 46.88. IR (neat, cm^{-1}): 1452, 1288, 1234, 1108, 1094, 1034, 1000, 888, 760, 719.

SPhos Precatalyst 7d. Bright yellow solid. Yield: 788 mg, 92%. ^{1}H NMR (500 MHz, CD_3OD): δ 8.05 (t, J = 8.4 Hz, 1H), 7.83 (td, J = 7.7, 1.6 Hz, 1H), 7.73 (dq, J = 5.3, 2.3 Hz, 1H), 7.61−7.46 (m, 5H), 7.18 (dd, J = 20.2, 8.3 Hz, 2H), 7.10 (dd, J = 7.5, 1.6 Hz, 1H), 7.07−7.00 (m, 2H), 6.95 (dddd, J = 16.4, 7.8, 6.6, 0.9 Hz, 2H), 6.89−6.81 (m, 2H), 6.76−6.70 (m, 1H), 6.63 (dq, J = 7.1, 1.1 Hz, 2H), 4.09 (s, 3H), 4.04−3.91 (m, 1H), 3.40 (s, 3H), 2.69 (s, 3H), 2.43 (d, J = 9.8 Hz, 1H), 2.36−2.17 (m, 2H), 2.13−1.97 (m, 3H), 1.91 (d, J = 13.1 Hz, 1H), 1.79 (d, J = 13.3 Hz, 1H), 1.60 (ddt, J = 50.7, 13.1, 3.4 Hz, 3H), 1.49−1.14 (m, 4H), 1.16−0.83 (m, 5H), −0.17 (dd, J = 12.0, 6.3 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.15, 140.04, 139.52, 134.28, 129.41, 129.14, 128.78, 127.83, 127.42, 126.97, 125.79, 124.78, 121.29, 105.55, 56.48, 56.09, 40.56, 35.94, 35.78, 34.84, 32.01, 28.54, 28.46, 27.04, 23.07, 14.81 ppm (observed complexity due to C−

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P splitting).^{31}P NMR (121 MHz, CD_3OD): δ 47.74 ppm. IR (neat, cm^{-1}): 1231, 1143, 1035, 1001, 763, 740, 571.

***t*BuXPhos Precatalyst 6e.** Light yellow solid. Yield: 720 mg, 89%. ^{1}H NMR (500 MHz, CD_3OD): δ 8.15 (t, J = 6.8 Hz, 1H), 7.93−6.80 (m, 13H), 3.44−3.32 (m, 1H), 3.14 (dt, J = 13.6, 6.8 Hz, 1H), 2.71 (m, 4H), 2.29−1.69 (m, 6H), 1.70−0.57 (m, 30H) ppm. ^{13}C NMR (126 MHz, CD_3CN): δ 160.4, 157.5, 153.9, 145.5, 145.3, 143.7, 142.0, 141.3, 139.4, 137.4, 137.4, 136.7, 135.5, 135.3, 135.0, 134.9, 132.04, 132.03, 129.8, 129.1, 128.93, 128.90, 128.8, 128.7, 128.5, 128.0, 127.9, 127.86, 127.0, 126.9, 126.4, 125.4, 124.8, 122.59, 122.58, 121.8, 43.84, 40.72, 40.71, 39.95, 39.73, 39.59, 39.47, 39.35, 35.05, 33.73, 32.21, 32.19, 32.15, 32.06, 30.82, 30.78, 26.18, 25.41, 24.28, 24.08, 24.04, 23.81, 23.26, 14.35 ppm (observed complexity due to C−P splitting). ^{31}P NMR (121 MHz, DMSO-d_6): δ 56.13 ppm. IR (neat, cm^{-1}): 1247, 1143, 1031, 1018, 1001, 759, 747, 739, 729.

(±) BINAP Precatalyst 6f. Following general procedure A, a mixture of **4** (384 mg, 0.50 mmol, 0.50 equiv), (±)-BINAP (622 mg, 1.00 mmol, 1.00 equiv), and dichloromethane (10 mL) was stirred at room temperature for 1 h. After removal of the solvent, the residue was triturated with pentane to provide the title compound as a yellow solid. Yield: 903 mg, 90%. ^{1}H NMR (500 MHz, CD_3OD): δ 7.99−7.91 (m, 2H), 7.84−7.68 (m, 7H), 7.59−7.50 (m, 3H), 7.47−7.38 (m, 2H), 7.38−7.11 (m, 10H), 7.10−7.00 (m, 3H), 7.00−6.86 (m, 4H), 6.84−6.78 (m, 2H), 6.75 (dd, J = 7.8, 1.1 Hz, 1H), 6.71−6.64 (m, 2H), 6.52−6.47 (m, 1H), 6.39 (tdd, J = 7.6, 6.7, 2.6, 1.3 Hz, 1H), 6.35−6.31 (m, 1H), 2.68 (s, 3H), 2.28 (d, J = 2.7 Hz, 3H) ppm. ^{13}C NMR (126 MHz, CD_2Cl_2): δ 164.86, 164.00, 151.61, 141.05, 141.04, 140.80, 140.30, 138.83, 138.49, 138.41, 138.15, 135.77, 135.68, 135.07, 135.02, 134.97, 134.90, 134.71, 134.69, 134.56, 134.54, 134.06, 133.98, 133.73, 133.66, 133.08, 133.06, 131.75, 131.73, 131.58, 131.08, 131.01, 130.86, 130.24, 130.18, 130.00, 129.96, 129.88, 129.12, 129.04, 128.89, 128.87, 128.70, 128.57, 128.55, 128.26, 128.17, 127.90, 127.68, 127.60, 127.58, 127.54, 127.49, 127.45, 127.25, 126.67, 126.44, 126.38, 126.31, 123.73, 123.39, 122.52, 122.10, 121.51, 41.37, 40.11 ppm (observed complexity due to C−P splitting). ^{31}P NMR (121 MHz, CD_3OD): δ 36.35 (d, J = 42.5 Hz), 35.18 (d, J = 43.6 Hz), 13.92 (d, J = 42.4 Hz), 12.42 (d, J = 43.7 Hz). IR (neat, cm^{-1}): 3202, 1225, 1193, 1037, 758, 734, 695, 670.

Suzuki−Miyaura Coupling: General Procedure. A screw-top test tube equipped with a magnetic stir bar was charged with **6a** or **7a** (0.02 mmol, 2 mol %), arylboronic acid (1.50 mmol, 1.50 equiv), and aryl halide (if solid, 1.00 mmol, 1.00 equiv), and the tube was sealed with a Teflon screw-cap septum. The vessel was evacuated and backfilled with argon (this process was repeated a total of three times), and the aryl halide, if liquid (1.00 mmol, 1.00 equiv) was added at this time. Anhydrous THF (2 mL) and 0.5 M aq K_3PO_4 solution (4 mL) were then added via syringe, and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with EtOAc (10 mL) and H_2O (10 mL), and the layers were separated. The aqueous layer was extracted with additional EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and filtered through a pad of Celite. The filtrate was concentrated, and the resulting residue was purified by flash chromatography using a Biotage Isolera Four system with a SNAP 25 g cartridge to afford the desired product.

2-(Perfluorophenyl)thiophene: White solid. Yield with **6a**: 217 mg, 87%. Yield with **7a**: 238 mg, 95%. Mp = 39.4−40.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56−7.55 (dd, J = 5.2, 1.2 Hz, 1H), 7.54−7.52 (dd, J = 3.8, 1.2, 1H), 7.21−7.18 (dd, J = 4.9, 3.8 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.3 (m), 142.7 (m), 141 (m), 139.2−138.6 (m), 136.7 (m), 130.2−130.1 (td, J = 5.5, 1 Hz), 128.3−128.2 (t, J = 3.8 Hz), 127.3, 126.3 (m), 110.0 (m) ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −141.2 (5F) ppm. IR (neat, cm^{-1}): 3110, 2923, 1531. 1477. 1468. 1420, 1391. 1378, 1347, 1222, 1073, 1060, 970, 819, 759, 740, 713, 690, 633. Anal. Calcd for $C_{10}H_3F_5S$: C, 48.01; H, 1.21. Found: C, 48.19; H, 1.18.

3-(Thiophene-3-yl)quinoline. White solid. Mp = 88.5−89.0 °C. Yield with **6a**: 202 mg, 95%. Yield with **7a**: 210 mg, 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22−9.21(d, J = 2.3 Hz, 1H), 8.32−8.31 (d, J = 2.2 Hz, 1H), 8.15−8.13 (dd, J = 8.4, 1.2 Hz, 1H), 7.88−7.86 (dd, J = 8.4, 1.2 Hz, 1H), 7.72−7.68 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.67 (dd, J = 2.9, 1.4 Hz, 1H), 7.58−7.54 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.53−7.50 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.4, 147.1, 138.8, 131.9, 129.2, 129.1, 128.6, 128.0, 127.8, 127.0, 126.95, 126.0, 121.5 ppm. IR (neat, cm^{-1}): 1599, 1570, 1488, 1124, 968, 951, 876, 859, 844, 693, 667, 647, 641, 616, 603, 600. Anal. Calcd for $C_{13}H_9NS$: C, 73.90; H, 4.29. Found: C, 73.77; H, 4.27.

5-(2,6-Difluorophenyl)-2-methylbenzo[d]thiazole. White solid. Mp = 126−127 °C. Yield from **6a**: 248 mg, 95%. Yield from **7a**: 255 mg, 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (q, J = 1.4 Hz, 1H), 7.91−7.89 (d, J = 8.3 Hz, 1H), 7.47−7.43 (dd, J = 8.3, 1.6 Hz, 1H), 7.35−7.28 (tt, J = 8.4, 6.3 Hz, 1H), 7.05−6.99 (m, 2H), 2.87 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.6, 161.4−158.9 (dd, J = 53.3, 26.4 Hz, 2C), 135.6, 129.1−128.9 (t, J = 10.4 Hz), 126.9, 124.2 (dt, J = 253, 2.2 Hz, 2C), 121.1, 118.2−117.9 (t, J = 18.9 Hz), 111.8−111.6 (d, J = 26.3 Hz), 111.8−111.6 (d, J = 12.4 Hz), 20.2 ppm. ^{19}F NMR (282.4 MHz, $CDCl_3$): δ −114.5 (t, J = 6.8 Hz, 2F) ppm. IR (neat, cm^{-1}): 1626, 1586, 1463, 1442, 1411, 1270, 1251,1174, 993, 819, 781, 770, 736, 667, 659, 650, 645, 636. Anal. Calcd for $C_{14}H_9F_2NS$: C, 64.35; H, 3.47. Found: C, 64.17; H, 3.63.

Arylation of Amines. Representative Procedure: 4-Methoxydiphenylamine (X = Cl). A screw-top test tube equipped with a magnetic stir bar was charged with NaOtBu (115 mg, 1.20 mmol, 1.20 equiv), and the tube was sealed with a Teflon screw-cap septum. The tube was evacuated and backfilled with argon (this procedure was performed a total of three times), after which 4-chloroaniline (123 μL, 1.00 mmol, 1.00 equiv), aniline (110 μL, 1.20 mmol, 1.20 equiv), precatalyst solution (0.01 M in THF, 10 μL, 0.01 mol %) and dioxane (1 mL) were added by syringe. The reaction mixture was heated at 110 °C for 24 h, after which it was cooled to room temperature and diluted with ethyl acetate. The crude reaction mixture was then filtered through a pad of Celite, concentrated with the aid of rotary evaporation, and purified by column chromatography, eluting with 10% ethyl acetate in hexanes to provide the title compound as an off-white solid. Yield with **6b**: 191 mg, 96%. Yield with **7b**: 179 mg, 90%. Mp = 101−102 °C. ^{1}H NMR (500 MHz, chloroform-*d*): δ 7.32−7.18 (m, 2H), 7.14−7.05 (m, 2H), 6.99−6.91 (m, 2H), 6.91−6.80 (m, 3H), 5.51 (s, 1H), 3.82 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.0, 145.9, 136.5, 130.1, 122.9, 120.3, 116.4, 115.4, 56.3 ppm. IR (neat, cm^{-1}): 3386, 1595, 1500, 1489, 1443, 1297, 1247, 1236, 1032, 749, 694.

4-Methoxydiphenylamine (X = I). ArI (1 mmol), $PhNH_2$ (1.4 mmol), NaOtBu (1.4 mmol) precatalyst solution (0.01 M in THF, 10 μL, 0.01 mol %), PhMe (1 mL), 5 min. Off-white solid. Yield with **6b**: 187 mg, 94%. Yield with **7b**: 193 mg, 97%. Characterization data consistent with above case where X=Cl.

5-Fluoro-N^2,N^4,N^4-trimethyl-N^2-(pyridin-4-yl)pyrimidine-2,4-diamine. ArCl (1 mmol), amine (1.2 mmol), NaOtBu (1.2 mmol), precatalyst (0.01 mmol), PhMe (1 mL). Yellow, crystalline solid. Yield with **6c**: 217 mg, 88%. Yield with **7c**: 210 mg, 85%. ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.48−8.38 (m, 2H), 7.82 (d, J = 6.4 Hz, 1H), 7.40−7.29 (m, 2H), 3.53 (s, 3H), 3.14 (d, J = 2.2 Hz, 6H) ppm. ^{13}C NMR (126 MHz, chloroform-*d*) δ 156.6, 153.1, 152.6 (d, J = 6.1 Hz), 150.1, 144.2, 142.6 (d, J = 26.2 Hz), 142.2, 117.6, 39.5 (d, J = 7.0 Hz), 37.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ −154.44 ppm. IR (neat, cm^{-1}): 1602, 1575, 1390, 1371, 1324, 1216, 844, 827, 768, 633, 596.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectroscopic data and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): MIT has patents on the ligands used in this work from which S.L.B. and former co-workers receive royalty

payments and on the precatalysts used in this work for which N.C.B. and S.L.B receive royalty payments.

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(4) *N*-Methyl-2-aminobiphenyl was isolated as a 95:5 mixture of the mono-/dimethylated products, as confirmed by GC and NMR. The mixture was used directly, adjusting the equivalents of MsOH and $Pd(OAc)_2$ to 0.95. *N*-Phenyl-2-aminobiphenyl contained traces of *N*-phenylcarbazole and diarylated product and was also used directly.

(5) The reaction of these ligands and **4** only reach ∼50% conversion. Their reaction with **5** produces a mixture of two species in equilibrium—the desired precatalyst and a related complex without the nitrogen bound to the Pd center.

(6) When allowed to react with **5**, (±)-BINAP produces a mixture of two species in equilibrium—the desired precatalyst and the related complex without the nitrogen coordinated to the Pd center.

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