Unexpected Formation of Hexasubstituted Arenes through a Twofold Palladium-Mediated Ligand Arylation

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Abstract: A rearrangement reaction of biarylphosphine-supported Pd(II) complexes was employed to synthesize 1,3,5-triaryl 2,4,6-triisopropylbenzene compounds, a class of molecules that has not previously been reported. The strain of the central hexasubstituted ring was investigated via X-ray crystallography.

Hexasubstituted arenes have been a topic of interest in organic chemistry due to their high steric strain, which makes them appealing targets for the study of conformational dynamics and aromaticity,[1–4] as well as their rigidity, which allows for enforcement of unique molecular architectures.[5–7] Traditionally, hexasubstituted benzene rings have been synthesized through metal-catalyzed [2+2+2] alkyne cyclotrimerization, a reaction that has enabled the synthesis of remarkably strained molecules but often times requires harsh conditions and is predominantly employed to access C_3-symmetric products.[1,8] Despite advances in cross-coupling[9,10] and cycloaddition chemistry,[11,12] the controlled synthesis of less symmetric hexasubstituted arenes with bulky substituents remains challenging. Here, we report a palladium-mediated dearomative rearrangement that enables the synthesis of 1,3,5-triaryl 2,4,6-triisopropylbenzenes, a previously unknown class of strained hexasubstituted arenes.

While attempting to prepare triaryl phosphine **2** through our previously reported dearomative ligand rearrangement,[13,14] we were surprised to find a mixture of mono- and bis-arylated products **2** and **3**, favoring **3** in a 56:44 ratio as determined by ^{31}P NMR spectroscopy (Figure 1).

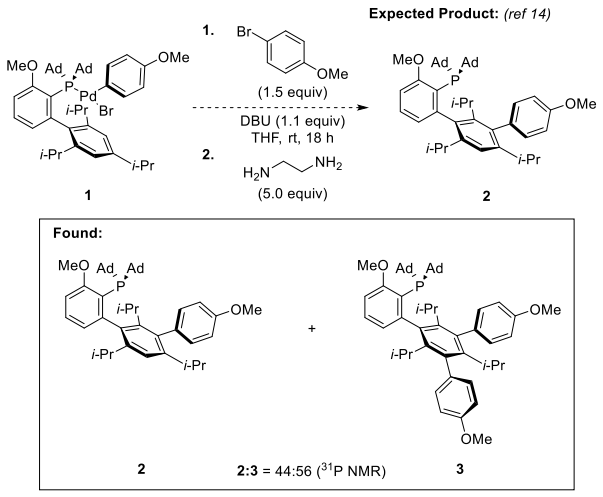


Figure 1. Discovery of a synthetic route to the hexasubstituted arene **3**.

The difficulty of separating mono- and bis-arylated products **2** and **3** prompted us to search for conditions that would favor the complete formation of **3**. By increasing the equivalents of aryl halide and base utilized, heating the reaction mixture, and extending the reaction time, we obtained a mixture of predominantly **3** (96%) along with trace amounts of **2** (4%). The material could be purified by recrystallization to give 313 mg of **3** in 69% yield (Figure 2).

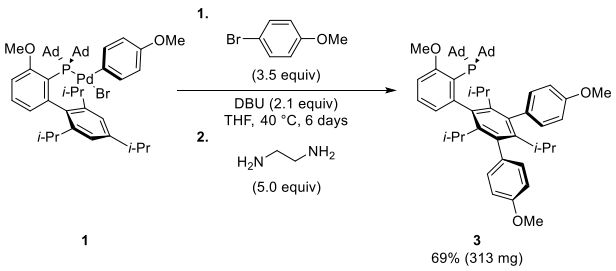


Figure 2. Optimized synthesis of **3.**

Attempts to use alternative solvents (*e.g.*, dioxane, toluene) or further increase the reaction temperature led to increased levels of unidentified decomposition products. Efforts to use a catalytic quantity of Pd resulted in only a single-turnover to a stoichiometric amount of product, although previous reports indicate that ligand exchange can occur at the Pd(II) oxidation state.[15]

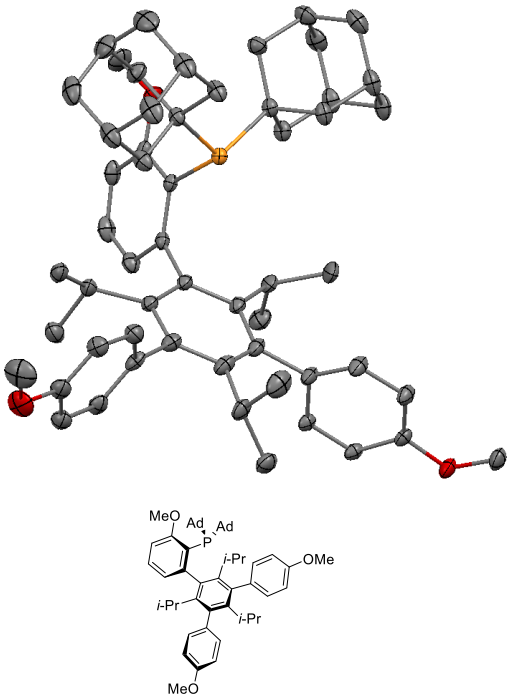


Figure 3. Crystal structure of **3**. Hydrogen atoms have been omitted for clarity, and thermal ellipsoids are depicted at 50% probability.

Crystallographic analysis of **3** confirmed the structure as resulting from the bis-arylation of **1** (Figure 3). The hexasubstituted middle benzene ring showed signs of strain-induced distortion caused by the close isopropyl–aryl and isopropyl–adamantyl contacts. In particular, one isopropyl group was bent approximately 5° away from ideal 120° bond angles (Figure 4a); the magnitude of this deformation is interesting given that typical sp^2 and sp^3 carbon bond angles differ by only 11°. One of the middle ring's dihedral angles was found to be 8.26°, comparable to the out-of-plane distortion observed in 1,2-diadamantylbenzene (Figure 4b and 4c).[16]

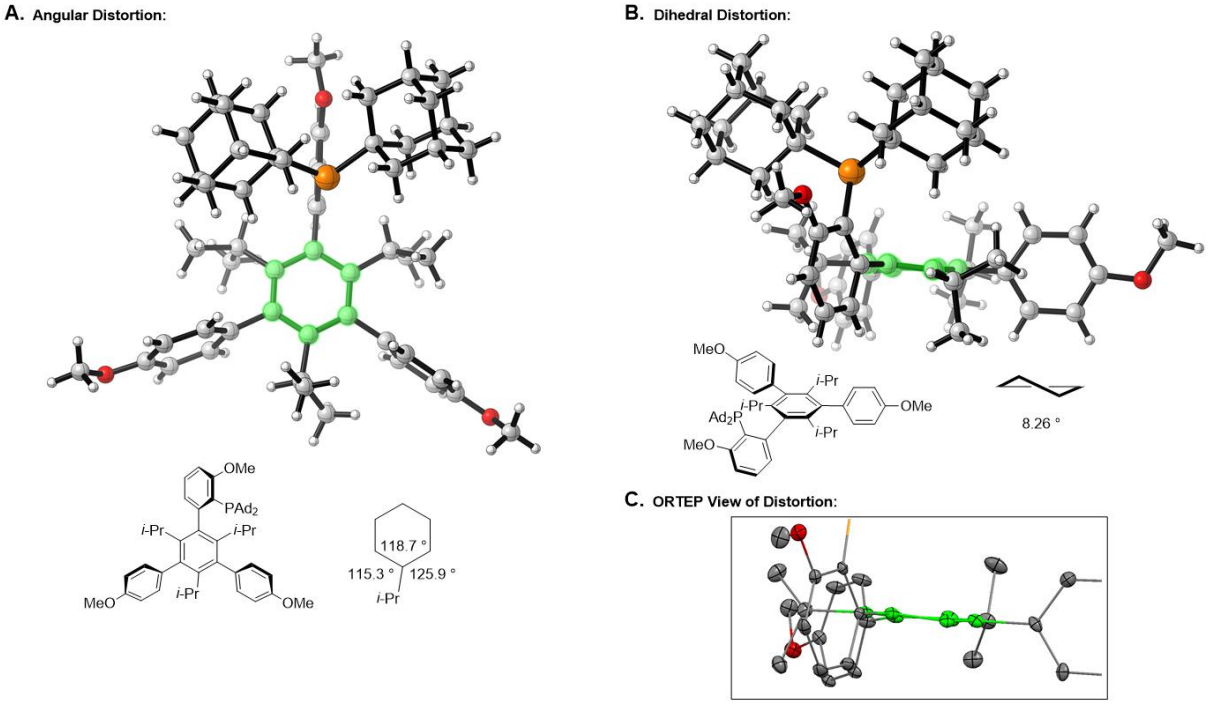


Figure 4. Distortion in the middle ring (highlighted in green) of hexasubstituted arene **3**, including (A) angular distortion and (B) dihedral distortion. Key bond angles are illustrated below the figures. The torsion in the middle ring has also been depicted in ORTEP (C) to better show the deviation from planarity. (For clarity, hydrogen atoms and one isopropyl group have been omitted and thermal ellipsoids depicted at 30% probability.)

Previous results from our group indicated that highly substituted ligands can enhance the Lewis acidity of palladium and enable C–N couplings using weak organic bases.[17] Unfortunately, initial attempts to use complexes derived from **3** as catalysts met with little success. **3** did not cleanly form a [(L–Pd)$_2$·(COD)] precatalyst,[18] and

formed oxidative addition complex **4** in only 26% yield.[19] This complex was found to be ineffective at catalyzing a model C–N coupling (Figure 5).[17] This result may be due to the substantial steric bulk of **3**, which could impair oxidative addition or prevent amine binding.

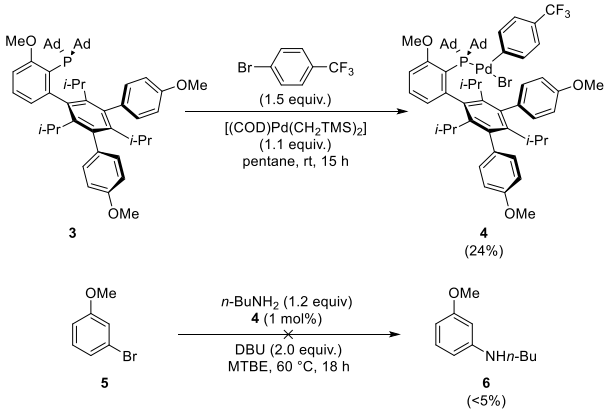
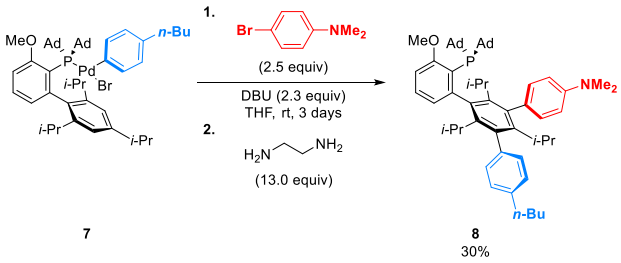


Figure 5. Synthesis of a precatalyst derived from **3** and its subsequent use as a catalyst for C–N coupling

The optimized conditions for the preparation of **3** were found to be amenable to the synthesis of other hexasubstituted arenes. Consistent with previous results,[14] electron-poor aryl halides reacted only slowly and often gave inseparable mixtures of mono- and bis-arylation (see the Supporting Information for details); electron-rich arenes were therefore used to drive the reaction towards completion. By forming the Pd(II) oxidative addition complex with one aryl halide and performing the rearrangement in the presence of a second aryl halide, two distinct aryl groups could be selectively installed, as shown by the synthesis of unsymmetrical arenes **8** and **10** (Figure 6). Similarly, the di-*tert*-butyl ligand *t*-BuBrettPhos could be doubly arylated to give hexasubstituted di-*tert*-butyl phosphine **10**, demonstrating that adamantyl substitution on phosphorus is not required for this rearrangement.[14]



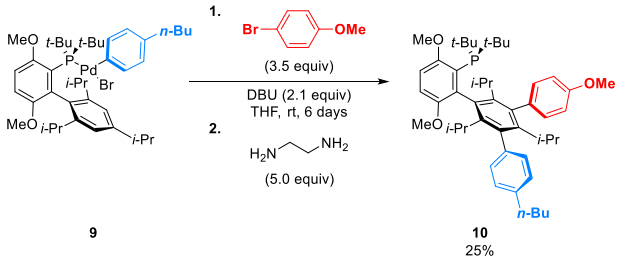


Figure 6. Sequential double arylation allows access to unsymmetrical arenes.

In cases in which we wish to prepare ligands with only a single substituent installed, we felt that a sacrificial aryl halide could be used to block the second arylation. For example, Pd(II) complexes derived from 2-bromothiophene proved recalcitrant towards rearrangement under the standard reaction conditions: accordingly, monoarylated product **2** could be synthesized cleanly by using 2-bromothiophene to trap nascent Pd(0) (Figure **7**).

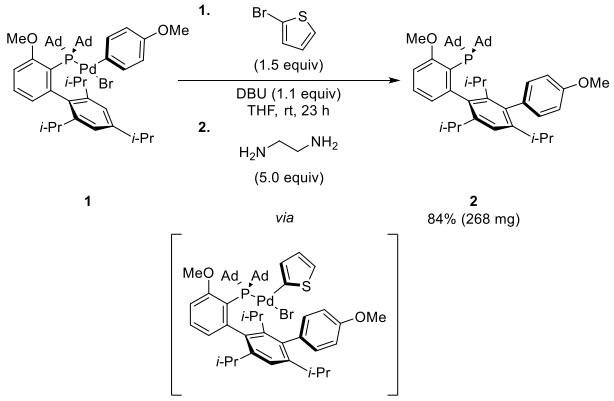


Figure 7. Synthesis of **2** through the use of 2-bromothiophene as a "trap" for Pd(0)

In conclusion, we have shown that di-*tert*-butyl and diadamantyl monophosphine ligands can be converted to highly strained hexasubstituted arenes through a double dearomative rearrangement and demonstrated the synthesis of several such arenes. Currently, the requirement for a bulky *ortho*-dialkylphosphinobenzene substituent limits the generality of this method. However, the extreme steric congestion of the products accessible by this strategy suggests that a mechanistically analogous transformation employing a more practical directing group may be of considerable interest.

EXPERIMENTAL SECTION:

General Reagent Information:

Commercial solvents and reagents were purchased from Aldrich Chemical Company, Strem Chemicals, Acros

Organics, Alfa Aesar, Combi Blocks, Oakwood Chemical, Oxchem, and Chem-Impex and used as received, with the following exceptions. Anhydrous MTBE was purchased from Aldrich Chemical Company in Sure-Seal™ bottles, sparged with argon for 1 h, and stored in a nitrogen-filled glovebox. Toluene, tetrahydrofuran (THF) and CH_2Cl_2 were purchased from J.T. Baker in CYCLE-TAINER® solvent-delivery kegs and vigorously purged with argon for 2 h, followed by passing it under argon pressure through two packed columns of neutral alumina. Copper (I) chloride was stored in a nitrogen-filled glovebox. Large reaction tubes (36 mL capacity; 20 x 150 mm, Part No. 14-959-37C), medium reaction tubes (25 mL capacity, 20 x 125 mm, Part No. 14-959-37A), small reaction tubes (8 mL capacity, 13 x 100 mm, Part No. 14-959-35C), large/medium screw-caps (Kimble-Chase, Open Top S/T Closure, Part No. 73804-18400), small screw caps (Thermo Scientific, Part No. C401566), large/medium septa (Thermo Scientific PTFE/silicone, Cat No. B7995-18), and small septa (Thermo Scientific PTFE/Silicone, Cat No. C4015-60) were purchased from Fischer Scientific. Compounds were purified using a Biotage® Isolera system, employing polypropylene cartridges preloaded with silica gel (Silicycle SilaFlash® F60 silica gel) or with new Biotage® SNAP cartridges, unless otherwise noted. Samples were eluted using a flow rate of 50–100 mL/min, with detection by UV (254 nm). Analytical thin-layered chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV). Di(1-adamantyl)chlorophosphine[20] and $[(COD)Pd(CH_2TMS)_2]$[21] were prepared according to literature procedures.

General Analytical Information:

Compounds were analyzed by ^{1}H, ^{13}C, ^{19}F, and ^{31}P nuclear magnetic resonance (NMR) spectroscopy where appropriate. NMR spectra were recorded on a Bruker Avance Neo-400 MHz spectrometer, a Bruker Avance Neo-500 MHz spectrometer, and a Bruker Avance Neo-600 MHZ spectrometer. ^{1}H and ^{13}C spectra were calibrated using residual solvent as an internal reference ($CDCl_3$: δ 7.26 ppm and δ 77.16 ppm, respectively; C_6D_6: δ 7.16 ppm and δ 128.1 ppm, respectively; CD_2Cl_2: δ 5.32 ppm and δ 53.84 ppm, respectively). Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA, USA. High-resolution mass spectra were recorded on an Agilent Technologies 6545 Q-TOF LC/MS system. The following abbreviations were used to explain multiplicities: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, p = pentet, sx = sextet, h = heptet, m = multiplet. Melting points were obtained using a Stanford Research Systems EZ-Melt melting point apparatus. Attenuated total reflectance Fourier transform infrared spectra (ATR-FTIR) were obtained using a Thermo Scientific Nicolet iS5 FT-IR spectrometer (iD5 ATR, diamond) referenced to a polystyrene standard and data reported as frequency of absorption (cm^{-1}).

2-bromo-2',4',6'-triisopropyl-3-methoxy-1,1'-biphenyl (S1)

An oven-dried 1000 mL round-bottom flask equipped with a stir bar and fitted with a rubber septum was evacuated using an inlet needle connected to a Schlenk line. The flask was backfilled with argon (this process was repeated a total of three times). Then, 2-bromo-1,3,5-triisopropylbenzene (15.5 mL, 61.3 mmol) and anhydrous THF (250 mL) were added sequentially and the mixture was cooled to –78 °C in a dry ice/acetone bath. *n*-BuLi (1.55 M in hexanes, 41.3 mL, 64.4 mmol) was added dropwise via syringe over 30 min and the sides of the flask were rinsed with anhydrous THF (4 mL). The resulting bright yellow mixture (solution "**A**") was stirred at –78 °C for 1 h.

A separate oven-dried 1000 mL round-bottom flask equipped with a stir bar and fitted with a rubber septum was evacuated using an inlet needle connected to a Schlenk line. The flask was backfilled with argon (this process was repeated a total of three times). Then, 3-fluoroanisole (3.50 mL, 30.6 mmol) and THF (150 mL) were added sequentially and the mixture was cooled to –78 °C in a dry ice/acetone bath. *n*-BuLi (1.63 M in hexanes, 18.2 mL, 29.6 mmol) was added dropwise over 15 min, and the sides of the flask were rinsed with THF (2 mL). The resulting colorless mixture (solution "**B**") was stirred at –78 °C for 1 h.

At this time, solution **A** was cannulated into solution **B** over the course of 8 min. Flask **A** was rinsed with THF (8 mL) and the washings were cannulated into flask **B**. The combined reaction mixture was then warmed to –30 °C in an acetone bath. The reaction was stirred at this temperature for 1 h (maintained between –25 °C and –35 °C by addition of dry ice). The mixture was initially cloudy and yellow, but grew homogenous as it warmed.

At this time, bromine (4 mL) was carefully added dropwise via syringe over the course of 4 min. The resultant orange solution was removed from the bath and allowed to warm to room temperature for 20 min, at which time saturated aqueous sodium thiosulfate was added (150 mL). The resulting biphasic mixture was diluted with EtOAc (150 mL) and water (100 mL) and transferred to a 1 L separatory funnel. The light yellow organic phase was sequentially washed with a mixture of saturated aqueous sodium thiosulfate (150 mL), water (100 mL), and brine (150 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give approximately 20 mL of a thick yellow oil.

The crude material was purified by flash column chromatography (0 to 4% EtOAc/hexanes) and concentrated to give a yellow semi-solid. This material was further purified by recrystallization by dissolving the compound in hot EtOAc (5 mL) and layering MeOH (10 mL) on top. The biphasic mixture was allowed to cool to room temperature before being moved to the freezer (–40 °C). After 3 d, the resulting crystals were collected via vacuum filtration, rinsed

sequentially with MeOH (5 mL) and hexanes (5 mL), and then dried under high vacuum to give **S1** as a white solid (6.29 g, 53% yield).

The characterization data were consistent with previous reports.[22]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.9 Hz, 1H), 7.07 (s, 2H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 3.99 (s, 3H), 2.97 (hept, *J* = 6.9 Hz, 1H), 2.47 (hept, *J* = 6.9 Hz, 2H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.19 (d, *J* = 6.9 Hz, 6H), 1.05 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 156.01, 148.29, 145.92, 143.54, 135.76, 127.44, 123.78, 120.69, 114.54, 109.88, 56.25, 34.16, 30.63, 24.80, 24.05, 23.67. **IR** (neat, cm^{-1}): 2957, 2925, 2864, 1562, 1452, 1419, 1359, 1265, 1087, 1018, 783, 776, 719. **MP**: 117–119 °C.

Di(adamantan-1-yl)(2',4',6'-triisopropyl-3-methoxy-[1,1'-biphenyl]-2-yl)phosphane (S2)

An oven-dried 350 mL Schlenk tube equipped with a stir bar was charged with **S1** (3.69 g, 9.48 mmol) and fitted with a rubber septum. The tube was evacuated using an inlet needle connected to a Schlenk line. The tube was backfilled with argon (this process was repeated a total of three times). Then anhydrous THF (36 mL) was added and the reaction was cooled to –78 °C in a dry ice/acetone bath. *t*-BuLi (1.70 M in pentane, 20.4 mmol, 12.0 mL) was added dropwise over 11 min, and the resultant bright yellow solution was stirred at –78 °C for 1 h.

At this time, the septum was replaced with a Teflon stopcock under a counterflow of argon, and the pentane removed at –78 °C using an inline vacuum trap cooled with liquid nitrogen. After 30 min of evacuation, the stopcock was removed and anhydrous CuCl (1.08 g, 10.9 mmol) was added under a counterflow of argon. The tube was quickly fitted with a rubber septum and allowed to warm to room temperature. The solution turned green when CuCl was added, and darkened to an opaque green-black color as it warmed to rt.

After 30 min, the septum was removed and di(1-adamantyl)chlorophosphine (3.54 g, 10.5 mmol) was quickly added (note: no counterflow of argon was used during this addition to prevent dispersing the fine solid). Anhydrous toluene (51 mL) was added under counterflow of argon, and then the tube was fitted with a Teflon stopcock, sealed tightly, and placed in an oil bath pre-heated to 140 °C behind a blast shield.

After 18 h, the reaction was allowed to slowly cool to room temperature, and then diluted with EtOAc (50 mL) and water (50 mL) and transferred to a separatory funnel. The organic phase was washed with 2:1 saturated aqueous NH_4OH (28–30% NH_3 basis)/brine until no blue color was visible in the aqueous phase (12 x 40 mL), and then washed once with brine (1 x 40 mL). The pale yellow organic phase was then dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. The crude material was triturated from MeOH and dried under high vacuum overnight to give **S2** as a white solid (4.52 g, 78% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.8 Hz, 1H), 6.99 (s, 2H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.83 (ddd, *J* = 7.6, 3.7, 1.2 Hz, 1H), 3.89 (s, 3H), 2.95 (hept, *J* = 7.0 Hz, 1H), 2.61 (app h, *J* = 6.8 Hz, 2H), 1.90 (m, 18H), 1.67 (s, 12H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.26 (d, *J* = 6.7 Hz, 6H), 0.98 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$): δ 161.78, 161.76, 152.16, 151.87, 147.30, 146.08, 137.93, 137.88, 128.73, 126.08, 126.02, 123.78, 123.41, 120.26, 108.33, 77.16, 53.97, 42.12, 42.01, 38.95, 38.72, 37.26, 34.05, 30.98, 30.96, 29.43, 29.36, 26.63, 24.22, 23.03. **^{31}P NMR** (202 MHz, $CDCl_3$): δ 35.73. **IR** (neat, cm^{-1}): 2957, 2907, 2897, 2884, 2848, 1450, 1245, 1009, 874, 794, 778. **MP**: 220–222 °C. **EA**: Expected 82.58 (C), 9.74 (H), found 82.31 (C), 9.60 (H).

S2-Pd(4-anisyl)Br (1):

The reaction was set up in a nitrogen-filled glovebox. An oven-dried 100 mL round-bottom flask equipped with a stir bar was sequentially charged with **S1** (400 mg, 0.66 mmol), pentane (30 mL), diethyl ether (10 mL), and 4-bromoanisole (126 µL, 0.98 mmol). The mixture was allowed to stir until homogenous, and then [(COD)Pd($CH_2TMS)_2$] (282 mg, 0.73 mmol) was added in one portion. The colorless solution quickly turned a bright red color. The flask was sealed with a rubber septum and stirred at room temperature.

After 19 h, the flask was removed from the glovebox. The cloudy red solution was filtered through a fine sintered glass filter under air. The resultant filter cake was rinsed with pentane (3 x 5 mL) and dried under high vacuum to give **1** as a light red solid (445 mg, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (d, *J* = 8.7 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.99 – 6.91 (2, 3H), 6.82 (d, *J* = 8.0 Hz, 1H), 5.87 (s, 1H), 3.94 (s, 4H), 3.80 (s, 3H), 3.50 (q, *J* = 7.0 Hz, 1H), 3.19 (d, *J* = 35.2 Hz, 1H), 3.12 – 2.98 (m, 1H), 2.29 (d, *J* = 22.1 Hz, 11H), 2.03 (d, *J* = 22.1 Hz, 4H), 1.93 – 1.51 (m, 18H), 1.51 – 1.41 (m, 1H), 1.37 – 1.15 (m, 12H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 2H), 0.69 (d, *J* = 6.4 Hz, 3H), 0.06 (s, 3H). Observed complexity is due to *in situ* rearrangement.[14] **^{13}C NMR** (126 MHz, $CDCl_3$): δ 158.94, 149.27, 149.13, 134.20, 133.99, 132.20, 132.10, 130.62, 130.57, 125.02, 124.98, 113.63, 113.46, 110.21, 99.20, 77.28, 77.02, 76.77, 55.31, 54.17, 50.91, 44.98, 44.23, 39.77, 36.68, 36.54, 33.98, 32.48, 31.00, 29.66, 29.59, 28.68, 28.60, 23.19, 22.74, 22.70, 21.82, 21.09, 20.29. **^{31}P NMR** (202 MHz, $CDCl_3$): δ 85.28. **IR** (neat, cm^{-1}): 2903, 2846, 1456, 1265, 1254, 1230, 1173, 1040, 1000, 806, 792. **HRMS** (ESI): calc'd for $([C_{49}H_{66}BrO_3PPd]\text{-}Br)^+$: 823.3835; found: 823.3841

Initial Synthesis of Hexasubstituted Arene 3:

An oven-dried 25 mL round-bottom flask equipped with a stir bar was charged with **1** (391 mg, 0.43 mmol) and fitted with a rubber septum. The flask was evacuated using an inlet

needle connected to a Schlenk line. The flask was backfilled with argon (this process was repeated a total of three times.) Then, anhydrous THF (10 mL) was added to give a deep red solution. 4-Bromoanisole (81 µL, 0.65 mmol) and DBU (71 µL, 0.48 mmol) were added sequentially via syringe, and the reaction was stirred at room temperature under argon. The color lightened to yellow, and formation of a precipitate was observed.

After 17 h, the reaction was opened to the air and filtered over a pad of Celite (rinsing with THF). The resultant solution was concentrated *in vacuo* to give a brown foam, which was triturated from ether and filtered to give a yellow solid. The solid was suspended in THF (10 mL) and CH_2Cl_2 (2 mL), and the resultant solution was sparged with argon for 15 min. Ethylene diamine (95 uL, 1.5 mmol) was added via syringe, and the reaction was stirred under argon at room temperature.

After 22 h, the reaction was diluted with EtOAc (10 mL) and a mixture of 2:1 saturated aqueous NH_4OH (28–30% NH_3 basis)/brine (10 mL) and transferred to a separatory funnel. The organic phase was washed with 2:1 saturated aqueous NH_4OH (28–30% NH_3 basis)/brine (10 mL) and then washed with brine (10 mL). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil. The crude material was triturated from MeOH to give a tan solid (189 mg). ^{31}P NMR analysis (121 MHz, $CDCl_3$) revealed this to be a mixture of **3** (δ 36.86) and **2** (δ 36.07) in a 1.00:0.79 ratio (product identities were confirmed via LCMS).

Di(adamant-1-yl)(2',4',6'-triisopropyl-3,4''-dimethoxy-5'-(4-methoxyphenyl)-[1,1':3',1''-terphenyl]-2-yl)phosphane (3):

A flame-dried 100 mL round-bottom flask equipped with a stir bar was charged with **1** (500 mg, 0.55 mmol) and fitted with a rubber septum. The flask was evacuated using an inlet needle connected to a Schlenk line. The flask was backfilled with argon (this process was repeated a total of three times). Then anhydrous THF (40 mL) was added to give a deep red solution. Then, 4-bromoanisole (243 µL, 1.94 mmol) and DBU (174 µL, 1.16 mmol) were added sequentially via syringe and the reaction was placed in an oil bath preheated to 40 °C. The reaction became a deep yellow color after 15 min.

After stirring for 6 d at 40 °C, ethylene diamine (185 µL, 2.76 mmol) was added via syringe, and the reaction was stirred at room temperature for 15 h. Then the reaction mixture was diluted with EtOAc (30 mL) and transferred to a separatory funnel. The organic phase was washed with 2:1 saturated aqueous NH_4OH (28–30% NH_3 basis)/brine (2 x 20 mL) and brine (1 x 20 mL). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil. The crude material was triturated from MeOH to give a tan solid (366 mg). ^{31}P NMR analysis showed this to be a mixture of **3** and **2** in a 96:4 ratio.

The tan solid was dissolved in CH_2Cl_2 (2 mL) with gentle heating and MeOH (2 mL) was layered on top. The biphasic mixture was allowed to cool slowly to room temperature, and then cooled in the freezer (–40 °C) for 4 h. The resultant crystals were filtered, rinsed with methanol, and dried under high vacuum to give **3** as an off-white solid (257 mg, 56% yield).

The mother liquor from the crystals was left in the freezer for an additional 6 d, and then filtered, rinsed with MeOH, and dried under high vacuum to give **3** as an off-white solid (56 mg, 69% combined yield).

^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.41 – 7.20 (m, 4H), 7.20 – 7.13 (m, 1H), 6.96 – 6.81 (m, 6H), 3.89 (s, 3H), 3.86 (s, 6H), 2.92 (hept, *J* = 7.3 Hz, 1H), 2.78 (m, *J* = 14.2, 7.0 Hz, 2H), 2.06 – 1.84 (m, 18H), 1.78 – 1.63 (m, 12H), 0.91 (d, *J* = 6.9 Hz, 6H), 0.81 (d, *J* = 7.3 Hz, 3H), 0.59 (d, *J* = 7.3 Hz, 3H), 0.45 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.90, 158.48, 158.01, 154.66, 154.37, 144.77, 143.89, 142.75, 140.06, 140.02, 138.08, 138.03, 135.83, 135.56, 135.54, 133.84, 133.42, 133.27, 131.13, 128.23, 125.61, 125.56, 112.46, 112.08, 111.02, 110.85, 107.80, 55.17, 53.83, 41.93, 41.81, 38.68, 38.45, 37.12, 33.01, 32.76, 30.54, 29.28, 29.21, 25.03, 24.95, 23.80, 23.55, 22.81. **^{31}P NMR** (203 MHz, CD_2Cl_2): δ 36.82. **IR** (neat, cm^{-1}): 2991, 2901, 2845, 1506, 1455, 1281, 1236, 1173, 1041, 1029, 802, 792, 737. **MP**: 214–215 °C. **HRMS** (ESI): calc'd for $([C_{56}H_{71}O_3P_3]+H)^+$: 823.5225; found: 823.5216

3-Pd(4-benzotrifluoride)Br (4):

An oven-dried 100 mL round-bottom flask equipped with a stir bar was charged with **3** (100 mg, 0.12 mmol) and fitted with a rubber septum. The flask was evacuated using an inlet needle connected to a Schlenk line. The flask was backfilled with argon (this process was repeated a total of three times). Anhydrous pentane (30 mL) and diethyl ether (20 mL) were added to give a clear solution, and 4-bromobenzotrifluoride (26 µL, 0.19 mmol) was added via syringe. The septum was then removed and [(COD)Pd($CH_2TMS)_2$] (52 mg, 0.13 mmol) was quickly added under air. The septum was replaced and the reaction was stirred at room temperature under argon. The mixture slowly turned a cloudy green color.

After 15 h, the mixture was filtered through a medium sintered glass filter under air. The resultant filter cake was rinsed with pentane (2 x 2 mL) and dried under high vacuum to give **4** as a yellow-green solid (37 mg, 26% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 30.9, 8.4 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.26 (m, 1H), 7.14 (d, *J* = 8.3 Hz, 3H), 6.84 (dt, *J* = 24.0, 8.9 Hz, 5H), 6.50 (dd, *J* = 7.7, 2.7 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 6H), 3.50 (q, *J* = 7.0 Hz, 1H), 3.07 – 2.76 (m, 3H), 2.44 – 2.03 (m, 12H), 2.03 – 1.51 (m, 19H), 1.40 – 1.15 (m, 2H), 1.08 – 0.87 (m, 6H), 0.78 (app q, *J* = 8.2, 7.1 Hz, 9H), 0.66 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.71, 158.88,

158.37, 157.20, 151.74, 151.60, 150.39, 141.22, 140.83, 140.15, 139.66, 139.64, 136.39, 133.88, 133.77, 133.53, 131.82, 131.58, 131.09, 129.33, 129.25, 127.06, 123.75, 123.64, 121.76, 121.73, 121.64, 121.62, 121.47, 112.27, 111.91, 110.76, 110.67, 108.73, 55.15, 53.75, 47.58, 47.49, 47.43, 47.36, 41.45, 41.22, 36.27, 33.71, 33.30, 31.33, 29.49, 29.41, 25.44, 25.14, 24.35, 23.72, 23.37, 23.14. **^{31}P NMR** (202 MHz, $CDCl_3$): δ 67.30. **^{19}F NMR** (470 MHz, $CDCl_3$): δ -61.71. **IR** (neat, cm^{-1}): 2907, 1585, 1455, 1326, 1238, 1099, 1067, 1035, 1005, 816. **HRMS** (ESI): calc'd for $([C_{63}H_{75}BrF3O_3PPd]-Br)^+$: 1073.4441; found: 1073.4446

C–N Coupling using 4 as precatalyst:

Protocol adapted from the literature.[17]

An oven-dried "small" reaction tube (*vide supra*) equipped with a stir bar was charged with **4** (3.2 mg, 0.0028 mmol). The reaction tube was sealed with a screw cap containing a Teflon septum. The tube was evacuated using an inlet needle connected to a Schlenk line. The tube was backfilled with argon (this process was repeated a total of three times). Then 3-bromoanisole (32 µL, 0.25 mmol), *n*-butyl amine (30 µL, 0.30 mmol), DBU (75 µL, 0.50 mmol), and MTBE (120 µL) were added sequentially via syringe. The mixture was a cloudy green color. The septum was exchanged with a new one that had not been punctured, and the tube was added to an oil bath preheated to 60 °C. After 5 min, the reaction mixture turned a light green color and became homogenous.

After 17 h, the tube was removed from the oil bath and allowed to cool to room temperature. The reaction mixture had become a light brown color. Dodecane (12.5 µL) was added via syringe, and the crude mixture was diluted with CH_2Cl_2 (0.5 mL).

An aliquot was diluted with EtOAc and analyzed by GC. By comparison to a calibration curve, the product was shown to have formed in 1.6% yield.

5'-(4-butylphenyl)-2''-(di(adamantan-1-yl)phosphaneyl)-2',4',6'-triisopropyl-3''-methoxy-*N*,*N*-dimethyl-[1,1':3',1''-terphenyl]-4-amine (8):

An oven-dried 100 mL round-bottom flask equipped with a stir bar was brought into a nitrogen-filled glovebox and charged with **S2** (400 mg, 0.655 mmol) and subsequently dissolved in a mixture of anhydrous Et_2O (10 mL) and anhydrous pentane (52 mL). Then, 1-bromo-4-*n*-butylbenzene (209 mg, 0.982 mmol) was added via microliter pipette, followed by $[(COD)Pd(CH_2TMS)]_2$ (280 mg, 0.720 mmol). The flask was sealed with a rubber septum, removed from the glovebox, and the red heterogeneous solution allowed to stir at rt for 24 h. At this time, the resulting yellow precipitate was collected using a sintered glass funnel. The filter cake was washed with pentane (5 x 3 mL) to afford the oxidative addition complex, a portion of which was used directly in the next step without further purification (424 mg, 70%).

An oven-dried 25 mL "medium" reaction tube (*vide supra*) equipped with a stir bar was charged with the oxidative complex prepared above (106 mg, 0.114 mmol) and 4-bromo-*N*,*N*-dimethylaniline (57.0 mg, 0.285 mmol). The reaction tube was sealed with a screw cap containing a septum (both "medium" size) and evacuated using an inlet needle connected to a Schlenk line. The tube was backfilled with argon (this process was repeated a total of three times.) Anhydrous THF (7 mL) was added and the reaction mixture was stirred at rt. Then, DBU (40 µL, 0.27 mmol) was added and the septum was exchanged for one that had not been punctured under a counterflow of argon. The reaction mixture was then allowed to stir at rt.

After 3 d, ethylene diamine (100 µL, 1.50 mmol) was added via syringe and the reaction mixture was allowed to stir at rt for an additional 24 h. Then, the tube was opened to the air and transferred to a separatory funnel containing EtOAc (50 mL). The organic phase was washed with 2:1 saturated aqueous NH_4OH (28–30% NH_3 basis)/brine (3 x 50 mL), followed by brine (1 x 50 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified via flash column chromatography (Biotage KP-SIL 25 g column, eluting 0% to 100% CH_2Cl_2/EtOAc), followed by crystallization from CH_2Cl_2/MeOH to afford **8** as a white solid (29.4 mg, 30%). Contains approximately 5% (as determined by LC/MS) of **S2**.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.25–7.22 (m, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.16 – 7.02 (m, 5H), 6.97 (dd, *J* = 7.7, 3.5 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 6.64 (m, 1H), 3.84 (s, 3H), 2.96 (d, *J* = 5.3 Hz, 6H), 2.84 (m, 1H), 2.67 (m, 2H), 2.63 (t, *J* = 7.9 Hz, 2H), 1.87 (m, 18H), 1.64 (m, 14H), 1.37 (h, *J* = 6.9 Hz, 2H), 0.92 (m, 9H), 0.75 (dd, *J* = 21.5, 7.2 Hz, 3H), 0.57 (dd, *J* = 32.3, 7.3 Hz, 3H), 0.43 (dd, *J* = 15.3, 7.1 Hz, 3H), 0.34 (dd, *J* = 13.1, 6.8 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 161.98, 155.01, 154.77, 149.54, 149.06, 144.89, 144.19, 143.30, 143.05, 141.19, 140.70, 140.60, 140.04, 138.81, 138.59, 138.50, 135.62, 134.92, 133.73, 133.06, 132.35, 131.63, 131.03, 130.33, 129.59, 128.29, 126.90, 126.85, 125.94, 125.88, 125.83, 125.83, 125.60, 125.57, 122.95, 122.63, 111.49, 111.21, 110.11, 109.96, 107.83, 77.16, 53.95, 42.05, 41.95, 40.88, 38.80, 38.60, 37.64, 37.28, 37.01, 35.58, 33.99, 33.85, 33.23, 33.12, 32.98, 32.86, 30.83, 30.61, 29.43, 29.37, 25.15, 25.08, 24.00, 23.77, 22.97, 22.62, 22.51, 14.18 (complex spectrum, in part due to C–P coupling). **^{31}P NMR** (203 MHz, $CDCl_3$): δ 36.89. **IR** (neat, cm^{-1}): 2901, 2846, 1613, 1516, 1456, 1350, 1264, 1028, 822, 797. **HRMS** (ESI) m/z calc'd for $([C_{60}H_{80}NOP]+H)^+$: 862.6056; found: 862.6051. **MP**: 239–241 °C.

Di-tert-butyl(4''-butyl-2',4',6'-triisopropyl-3,6-dimethoxy-5'-(4-methoxyphenyl)-[1,1':3',1''-terphenyl]-2-yl)phosphane (10):

An oven-dried 100 mL round-bottom flask equipped with a stir bar was brought into a nitrogen-filled glovebox and charged with *t*-BuBrettPhos (400 mg, 0.655 mmol) and

subsequently dissolved in anhydrous pentane (20 mL). Then, 1-bromo-4-*n*-butylbenzene (264 mg, 1.24 mmol) was added via microliter pipette, followed by $[(COD)Pd(CH_2TMS)]_2$ (353 mg, 0.908 mmol). The flask was sealed with a rubber septum, removed from the glovebox, and the red heterogeneous solution allowed to stir at rt for 25 h. At this time, the resulting yellow-gold precipitate was collected using a sintered glass funnel. The filter cake was washed with pentane (2 x 5 mL) to afford the oxidative addition complex, a portion of which was used directly in the next step without further purification (467 mg, 70%).

An oven-dried 100 mL round-bottom flask equipped with a magnetic stir bar was charged with the oxidative complex prepared above (400 mg, 0.497 mmol) and sealed with a rubber septum. The flask was evacuated using an inlet needle connected to a Schlenk line. The flask was backfilled with argon (this process was repeated a total of three times). The solid was dissolved in anhydrous THF (30 mL) to give a deep red solution. Then, 4-bromoanisole (219 µL, 1.74 mmol) and DBU (156 µL, 1.04 mmol) were added sequentially via syringe. The argon line was removed and the reaction was left to stir at room temperature. The reaction became a cloudy yellow color after 5 min.

After 6 d, ethylene diamine (166 µL, 2.49 mmol) was added via syringe and the reaction mixture was allowed to stir at rt for an additional 24 h. The resultant cloudy white solution was opened to the air, diluted with EtOAc (20 mL), and transferred to a separatory funnel. The organic phase was washed with 2:1 saturated aqueous NH_4OH (28–30% NH_3 basis)/brine (2 x 20 mL) and brine (1 x 20 mL). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was dissolved in 1:1 $EtOAc/CH_2Cl_2$ and filtered through a pad of silica and then concentrated in *vacuo*. The crude material was then purified via flash column chromatography (Biotage KP-SIL 50 g column, eluting 5% to 25% EtOAc/99:1 hexanes/Et_3N), followed by crystallization from CH_2Cl_2/MeOH. Recovery of two crops of material yielded approximately 210 mg of **10**, contaminated with another phosphine (presumably monoarylated *t*-BuBrettPhos) in a 92:8 ratio. This material was again recrystallized from EtOAc/MeOH to afford **10** as a white solid (89.9 mg, 25%). Contains approximately 6% of monoarylated *t*-BuBrettPhos (as determined by LC/MS and ^{31}P NMR).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 1H), 7.26 – 7.01 (m, 5H), 6.91 – 6.73 (m, 4H), 3.86 (s, 3H), 3.77 (s, 3H), 3.65 (s, 3H), 2.91 – 2.82 (m, 1H), 2.75 – 2.60 (m, 4H), 1.71 – 1.61 (m, 2H), 1.44 – 1.33 (m, 2H), 1.16 (s, 9H), 1.14 (s, 9H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 6H), 0.76 (t, *J* = 6.1 Hz, 3H), 0.62 – 0.52 (m, 3H), 0.49 – 0.42 (m, 3H), 0.42 – 0.37 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.38, 157.92, 156.15, 152.51, 152.42, 144.36, 144.08, 143.16, 143.05, 143.01, 142.75, 140.99, 140.45, 140.43, 138.44, 138.37, 137.92, 137.84, 135.76, 135.68, 135.48, 134.64, 134.23, 133.66, 133.40, 133.18, 132.26, 131.50, 130.79, 130.45, 126.85, 126.69, 126.63, 126.59, 126.47, 125.39, 118.54, 112.24, 111.93, 110.87, 110.71, 110.30, 107.55, 55.14, 53.82, 35.44, 33.84, 33.71, 33.67, 33.43, 33.17, 32.95, 31.85, 31.72, 30.55, 24.40, 24.17, 23.93, 23.70, 22.73, 22.62, 22.44, 22.35, 14.04. **^{31}P NMR** (202 MHz, $CDCl_3$): δ 36.86. **IR** (neat, cm^{-1}): 2926, 2871, 1456, 1423, 1248, 1144, 1039, 1025, 834, 795, 783, 574. **HRMS** (ESI) m/z calc'd for $([C_{48}H_{67}O_3P]+H)^+$: 723.4912; found 723.4903. **MP**: 203–204 °C.

Di(adamantan-1-yl)(2',4',6'-triisopropyl-3,4''-dimethoxy-[1,1':3',1''-terphenyl]-2-yl)phosphane (2):

An oven-dried 100 mL round-bottom flask equipped with a stir bar was charged with **1** (402 mg, 0.45 mmol) and sealed with a rubber septum. The flask was evacuated using an inlet needle connected to a Schlenk line. The flask was backfilled with argon (this process was repeated a total of three times.) Anhydrous THF (30 mL) was added to give a deep red solution. Then, 2-bromothiophene (65 µL, 0.67 mmol) and DBU (75 µL, 0.50 mmol) were added sequentially via syringe. The argon line was removed, and the reaction was stirred at rt. The reaction lightened to a yellow-orange color over the next few hours.

After 23 h, ethylene diamine (150 µL, 2.22 mmol) was added via syringe, and the reaction was stirred at room temperature for 18 h. Then the reaction mixture was diluted with EtOAc (30 mL) and transferred to a separatory funnel. The organic phase was washed with 2:1 saturated aqueous NH_4OH (28–30% NH_3 basis)/brine (2 x 30 mL) and brine (1 x 30 mL). Then, the organic phase was dried over $MgSO_4$, and concentrated *in vacuo* to give a brown oil. The crude mixture was triturated from MeOH to give **2** as a tan solid (268 mg, 84% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (app t, *J* = 7.6 Hz, 1H), 7.18 (app t, *J* = 7.6 Hz, 2H), 7.10 (s, 1H), 6.89 (m, 4H), 3.88 (s, 6H), 2.82 (m, 1H), 2.53 (m, 2H), 1.91 (m, 18H), 1.65 (m, 12H), 1.25 (d, *J* = 6.7 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.54 (d, *J* = 7.1 Hz, 3H).**^{13}C NMR** (125 MHz, $CDCl_3$): δ 161.73, 158.05, 153.25, 152.95, 147.05, 145.73, 142.56, 138.74, 136.44, 134.41, 133.18, 131.59, 128.43, 125.90, 123.37, 122.99, 118.73, 112.40, 112.06, 108.01, 55.17, 53.82, 42.03, 41.92, 41.80, 38.96, 38.73, 38.65, 38.42, 37.14, 37.11, 32.52, 31.12, 29.31, 29.28, 29.24, 29.21, 26.63, 24.73, 24.43, 24.35, 23.83, 22.93. **^{31}P NMR** (203 MHz, $CDCl_3$): δ 36.24. **IR** (neat, cm^{-1}): 2957, 2899, 2847, 1558, 1512, 1456, 1280, 1244, 1174, 1089, 1034, 839, 790. **MP**: 155–200 °C (slow decomposition) **HRMS** (ESI): calc'd for $([C_{49}H_{65}O_2P]+H)^+$: 717.4806; found: 717.4805

ASSOCIATED CONTENT:

The supporting information is available free of charge on the ACS Publications website.

Copies of ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra, crystallographic details, and additional substrates not mentioned in the text (PDF)

Solid-state structure of **3** (CIF)

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Notes:

The authors declare the following competing financial interest(s): MIT has patents on some of the ligands and precatalysts used in this work, from which S.L.B. and former coworkers receive royalty payments.

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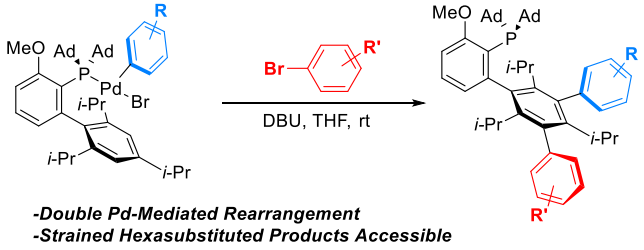
Graphical Abstract:



-Double Pd-Mediated Rearrangement
-Strained Hexasubstituted Products Accessible