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Synthesis of Unsymmetrical 2,6-Diarylanilines by Palladium-Catalyzed C–H Bond Functionalization Methodology

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Abstract

3,5-Dimethylpyrazole was employed as a mono-dentate directing group for palladium-catalyzed *ortho*-sp² C–H arylation with aryl iodides. The reaction shows good functional group tolerance and outstanding selectivity for mono-*ortho*-arylation. Ozonolysis of *ortho*-arylated arylpyrazoles gave acylated biphenylamines that were further arylated to afford unsymmetrically substituted 2,6-diarylanilines.

Graphical Abstract

2,6-Diarylanilines are used in the synthesis of ligands for Brookhart-type α -diimine-nickel or palladium complexes employed as alkene polymerization catalysts (Scheme 1).¹ Symmetrically substituted 2,6-diarylanilines can be easily prepared by transition-metal-catalyzed *ortho*-arylation procedures.^{2,3} In contrast, most methods do not allow for a selective synthesis of the unsymmetrical derivatives, are impractical because of expensive auxiliaries and excess oxidants, or require arylating reagents that are not commercially available. Due to interest in new olefin polymerization catalysts,⁴ we needed a method to selectively prepare unsymmetric 2,6-diarylanilines from simple starting materials. A route to selective synthesis of such 2,6-diarylanilines would be available if recently reported 1-alkyl-3,5-dimethylpyrazole arylation/ozonolysis^{5b,c} and arylation of the generated *N*-acetylanilide with a different aryl iodide^{5d,e} could be combined (Scheme 1). In 2006, we reported a single example of palladium-catalyzed 1-arylpyrazole arylation.^{5a} For 2,6-diarylaniline synthesis, 3,5-dimethylpyrazole directing group is required. After ozonolysis, a

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Notes

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Supporting Information

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¹H and ¹³C NMR spectra of the products (PDF)

robust acetanilide should be obtained for further functionalization.^{5c} While many examples of 1-arylpyrazole *ortho*-arylation have been reported,^{5f-o} use of a 3,5-dimethylpyrazole directing group for sp² C–H arylation is rare.^{5p} We report here a method for synthesis of differentially substituted 2,6-diarylanilines by using palladium-catalyzed C–H bond functionalization methodology.

Pyrazole-directed sp³ C–H arylation using the combination of Pd(OAc)₂ catalyst, Ag₂O, LiOAc, and LiOTf additives was reported previously.^{5b} This protocol was applied to sp² C–H arylation of **1a** with 4-iodotoluene (Scheme 2). Gratifyingly, monoarylated product **2a** was obtained in 85% yield. Only a trace amount of diarylated product was observed in the crude reaction mixture. To evaluate the arylation scope, a series of aryl iodides bearing either an electron-withdrawing or -donating group were examined. Diverse *para*-substituted aryl iodides furnished the monoarylated products in good yields (**2a–g**). *meta*-Substituted aryl iodides are reactive as well, affording the desired products regardless of the electronic properties of substituents (**2h–k**). Ester (**2f**), ketone (**2g**), alkoxy (**2b**, **2h**), trifluoromethyl (**2e**), and halogen (**2i**, **2j**) substituents are tolerated well, showing broad functional group compatibility of this protocol. In all cases, at most trace amounts of diarylated product were observed. 2-Iodotoluene was unreactive, and heterocyclic aryl iodides, such as 2- or 3-iodothiophene, afforded low yields of arylation products.

In addition, several *N*-arylpyrazole derivatives, easily prepared by condensation of acetylacetone with hydrazines⁶ or by amination of aryl halides with commercially available and inexpensive 3,5-dimethylpyrazole,⁷ were examined for C–H arylation with 4-iodotoluene. The reaction selectively generated the corresponding monoarylated products **2l–o** in good yields (Scheme 3). Pyrazole possessing a *meta* substituent on the aryl ring was regioselectively functionalized at the less hindered *ortho* site (**2o**), which is consistent with cyclometalation selectivity.²

The dimethylpyrazole directing group can be transformed into anilide by ozonolysis followed by nickel-mediated reduction.^{5b,c} Monoarylated pyrazoles prepared by the palladium-catalyzed C–H arylation were converted to the corresponding acetanilides by ozonolysis followed by reductive workup (Scheme 4). Methyl-, methoxy-, and trifluoromethyl-substituted 2-arylacetanilides **3a–c** were obtained in moderate to good yields.

Further arylation of **3** under previously published conditions^{5d,e} afforded unsymmetrically substituted 2,6-diaryl-anilides **4**. Subsequent base hydrolysis of **4** gave the desired **5** in excellent yields (Scheme 5).

In conclusion, we have shown that 3,5-dimethylpyrazole can be utilized as a removable directing group for palladium-catalyzed monoselective *ortho* sp² C–H arylation. The pyrazole moiety of the arylated product is amenable to ozonolysis for the transformation into acetamide, which enables further C–H arylation and hydrolysis for the preparation of unsymmetrically diarylated anilines.

EXPERIMENTAL SECTION

General Information

The ^1H and ^{13}C NMR spectra were recorded on JEOL EC-400, EC-500, and EC-600 spectrometers using the residual solvent peak as a reference. Compounds for HRMS were analyzed by positive-mode electrospray ionization (CI or ESI) using Agilent QTOF mass spectrometer in the Mass Spectrometry Facility (MSF) of the Department of Chemistry and Biochemistry of the University of Texas, Austin. IR spectra were obtained using a ThermoScientific Nicolet iS10 FT-IR spectrometer. Column chromatography was performed using 60 Å silica gel. Reagents and starting materials were purchased from commercial vendors and used without further purification. Ozonolysis was conducted using Ozone Solution OZV-8 ozone generator and oxygen (oxygen, Matheson, 99.98%). The amount of ozone was regulated by flow rate and the 10-position switch integrated into the device (intensity 1–10).

3,5-Dimethyl-1-phenyl-1H-pyrazole (1a)—The compound was obtained according to a modified reported procedure.^{6a} A round-bottom flask was charged with acetylacetone (52.5 mmol, 5.39 mL) and $\text{H}_2\text{SO}_4\text{-SiO}_2$ (2 mol %, 158 mg). To this mixture was added phenyl hydrazine (50 mmol, 4.92 mL) dropwise at 0 °C. The mixture was stirred at room temperature for 3 h. After completion of the reaction, aqueous 1 M NaOH (50 mL) was poured into the mixture. The mixture was extracted with diethyl ether (3 × 200 mL). The extract was washed with water (3 × 20 mL). The organic layer was dried over anhydrous MgSO_4 and concentrated to afford the known **1a** (7.34 g, 85%) as an orange oil.^{6a} ^1H NMR (500 MHz, CDCl_3) δ 7.50–7.37 (m, 4H), 7.38–7.28 (m, 1H), 5.99 (s, 1H), 2.30 (s, 3H), 2.29 (s, 3H).

3,5-Dimethyl-1-(p-tolyl)-1H-pyrazole (1b)—The compound was obtained according to a modified reported procedure.^{6b} To a solution of acetylacetone (5 mmol, 0.51 mL) in ethanol (10 mL) was added *p*-tolylhydrazine hydrochloride (5 mmol, 793 mg). The mixture was refluxed at 90 °C for 2 h. After removal of ethanol in vacuo, water (30 mL) was added, and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was dried over MgSO_4 and filtered. The residue was purified by column chromatography on silica gel with EtOAc/hexanes (1/15) eluent to afford the known **1b** (540 mg, 58%) as a yellow oil.^{6a} R_f = 0.16 (EtOAc/hexanes = 1/15); ^1H NMR (400 MHz, CDCl_3) δ 7.32–7.27 (m, 2H), 7.25–7.20 (m, 2H), 5.97 (s, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 2.27 (s, 3H).

1-(4-Methoxyphenyl)-3,5-dimethyl-1H-pyrazole (1c)—The compound was obtained according to a modified reported procedure.^{6b} To a solution of acetylacetone (5 mmol, 0.51 mL) in ethanol (10 mL) was added 4-methoxyphenylhydrazine hydrochloride (5 mmol, 873 mg). The mixture was refluxed at 90 °C for 6 h. After completion of the reaction, ethanol was evaporated in vacuo. Water (50 mL) was added to the reaction mixture followed by extraction with ethyl acetate (3 × 50 mL). The combined organic layer was dried over MgSO_4 and filtered. The residue was purified via column chromatography on silica gel with EtOAc/hexanes (1/7) eluent to afford the known **1c** (850 mg, 84%) as a light brown oil.^{6c} R_f

= 0.12 (EtOAc/hexanes = 1/10); ^1H NMR (400 MHz, CDCl_3) δ 7.31 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 5.95 (s, 1H), 3.83 (s, 3H), 2.28 (s, 3H), 2.23 (s, 3H).

3,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole (1d)—The compound was obtained according to a modified reported procedure.^{6b} To a solution of acetyl acetone (5 mmol, 0.51 mL) in ethanol (10 mL) were added 4-(trifluoromethyl)phenylhydrazine (5 mmol, 881 mg) and 1 drop of concentrated H_2SO_4 . The mixture was refluxed at 90 °C for 6 h. After completion of the reaction, ethanol was evaporated in vacuo. Water (50 mL) was added to the reaction mixture followed by extraction with ethyl acetate (3 $\times$ 50 mL). The combined organic layer was dried over MgSO_4 and filtered. The residue was purified via column chromatography on silica gel with EtOAc/hexanes (1/15) eluent to afford the known **1d** (978 mg, 81%) as an orange oil:^{6c} R_f = 0.21 (EtOAc/hexanes = 1/15); ^1H NMR (500 MHz, CDCl_3) δ 7.74–7.66 (m, 2H), 7.64–7.55 (m, 2H), 6.04 (s, 1H), 2.36 (s, 3H), 2.30 (s, 3H).

1-(3-Chloro-4-methylphenyl)-3,5-dimethyl-1H-pyrazole (1e)—The compound was obtained according to a modified reported procedure.⁷ A round-bottom flask was charged with 3,5-dimethylpyrazole (5.0 mmol, 481 mg), copper(I) oxide (1.5 mmol, 215 mg), cesium carbonate (10.8 mmol, 3.53 g), 1,10-phenanthroline (1.5 mmol, 270 mg), and DMF (10 mL). To the mixture was added 2-chloro-4-iodotoluene (10 mmol, 1.40 mL), and the flask was heated at 120 °C for 15 h. After completion of the reaction, mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 $\times$ 50 mL). The combined organic layer was dried over MgSO_4 and filtered. The residue was purified via column chromatography on silica gel with EtOAc/hexanes (1/15) eluent to afford **1e** (870 mg, 79%) as a pale yellow solid: mp 56–57 °C (pentane); R_f = 0.23 (EtOAc/hexanes = 1/15); ^1H NMR (600 MHz, CDCl_3) δ 7.45 (d, J = 2.2 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.22 (dd, J = 8.1, 2.2 Hz, 1H), 5.98 (s, 1H), 2.40 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 149.3, 139.5, 138.8, 135.2, 134.6, 131.1, 125.3, 122.8, 107.3, 19.8, 13.6, 12.5; HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{14}\text{ClN}_2$ [$\text{M} + \text{H}$]⁺ 221.0840, found 221.0843.

General Procedure for Arylation of Pyrazoles (2)

A 2-dram vial equipped with a magnetic stir bar was charged with $\text{Pd}(\text{OAc})_2$ (5 mol %, 5.6 mg), silver oxide (0.8 equiv, 93 mg), LiOTf (1.2 equiv, 94 mg), HFIP (0.38 mL), acetic acid (0.13 mL), trifluoroacetic acid (TFA, 1.7 equiv, 65 μL), and iodoarene (3 equiv). The mixture was stirred at room temperature for 10 min until the solution became clear. To the mixture was added 3,5-dimethyl-1-arylpyrazole (0.5 mmol), LiOAc (1.6 equiv, 53 mg), and the vial was flushed with nitrogen. The sealed vial was heated and stirred at 120 °C. After completion of the reaction, the mixture was cooled and diluted with ethyl acetate (20 mL) followed by quenching with aqueous NaOH (1 M, 20 mL). The resulting mixture was extracted with ethyl acetate (3 $\times$ 30 mL). The combined organic layer was dried over MgSO_4 and filtered through a short pad of silica gel, washed with EtOAc, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with hexanes and ethyl acetate eluent to afford pure product.

3,5-Dimethyl-1-(4'-methyl-[1,1'-biphenyl]-2-yl)-1H-pyrazole (2a)—3,5-Dimethyl-1-phenylpyrazole (86 mg, 0.5 mmol), 4-iodotoluene (327 mg, 1.5 mmol), Pd(OAc)₂ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μ L, 0.85 mmol), 120 °C for 24 h: pale yellow oil; 85% yield (112 mg); purification (EtOAc/hexanes = 1/10); R_f = 0.15 (EtOAc/hexanes = 1/15); ¹H NMR (500 MHz, CDCl₃) δ 7.53–7.38 (m, 4H), 7.09–7.04 (m, 2H), 6.98 (d, J = 8.2 Hz, 2H), 5.76 (s, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 1.61 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 148.6, 140.7, 139.2, 137.5, 137.2, 135.7, 130.4, 129.2, 129.1, 129.0, 128.4, 128.1, 105.5, 21.3, 13.8, 11.2; FT-IR (neat, cm⁻¹) ν 1648, 1575, 1449, 1347, 1196; HRMS (ESI) calcd for C₁₈H₁₉N₂ [M + H]⁺ 263.1543, found 263.1547.

1-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1H-pyrazole (2b)—3,5-Dimethyl-1-phenylpyrazole (86 mg, 0.5 mmol), 4-iodoanisole (351 mg, 1.5 mmol), Pd(OAc)₂ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μ L, 0.85 mmol), 120 °C for 48 h: white solid; mp 86–87 °C (diethyl ether); 83% yield (116 mg); purification (EtOAc/hexanes = 1/8); R_f = 0.25 (EtOAc/hexanes = 1/4); ¹H NMR (600 MHz, CDCl₃) δ 7.61–7.31 (m, 4H), 7.01 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 5.76 (s, 1H), 3.78 (s, 3H), 2.30 (s, 3H), 1.61 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 159.0, 148.7, 140.7, 138.9, 137.4, 131.0, 130.3, 129.7, 129.2, 129.0, 127.9, 113.9, 105.6, 55.3, 13.8, 11.2; FT-IR (neat, cm⁻¹) ν 1607, 1556, 1519, 1490, 1366, 1243, 1181, 1036; HRMS (ESI) calcd for C₁₈H₁₉N₂O [M + H]⁺ 279.1492, found 279.1492.

1-(4'-tert-Butyl-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1H-pyrazole (2c)—3,5-Dimethyl-1-phenylpyrazole (86 mg, 0.5 mmol), 4-tert-butyl iodobenzene (390 mg, 1.5 mmol), Pd(OAc)₂ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μ L, 0.85 mmol), 120 °C for 24 h: pale yellow oil; Purification (EtOAc/hexanes = 1/8); R_f = 0.12 (EtOAc/hexanes = 1/8); 78% yield (119 mg); ¹H NMR (400 MHz, CDCl₃) δ 7.51 (ddd, J = 7.6, 1.6, 0.7 Hz, 1H), 7.52–7.42 (m, 1H), 7.48–7.37 (m, 2H), 7.30–7.21 (m, 2H), 7.05–6.93 (m, 2H), 5.75 (s, 1H), 2.29 (s, 3H), 1.58 (s, 3H), 1.29 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 150.4, 148.7, 140.8, 139.0, 137.5, 135.5, 130.5, 129.1, 129.0, 128.1, 128.0, 125.4, 105.6, 34.6, 31.4, 13.7, 11.2; FT-IR (neat, cm⁻¹) ν 2962, 1552, 1493, 1364, 1181, 1102; HRMS (ESI) calcd for C₂₁H₂₅N₂ [M + H]⁺ 305.2012, found 305.2019.

1-([1,1':4',1''-Terphenyl]-2-yl)-3,5-dimethyl-1H-pyrazole (2d)—3,5-Dimethyl-1-phenylpyrazole (86 mg, 0.5 mmol), 4-iodobiphenyl (280 mg, 1 mmol), Pd(OAc)₂ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.75 mL), acetic acid (0.25 mL), TFA (65 μ L, 0.85 mmol), 120 °C for 48 h: pale yellow solid; mp 127–128 °C (diethyl ether); 79% yield (128 mg); purification (EtOAc/hexanes = 1/8); R_f = 0.10 (EtOAc/hexanes = 1/8); ¹H NMR (600 MHz, CDCl₃) δ 7.61 (d, J = 7.5 Hz, 2H), 7.57 (d, J = 7.7 Hz, 1H), 7.54–7.50 (m, 3H), 7.49–7.45 (m, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 5.77 (s, 1H), 2.31 (s, 3H), 1.65 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 148.8, 140.8, 140.6, 140.0, 138.8, 137.6, 137.6, 130.4, 129.2, 129.1, 129.0, 128.9, 128.4, 127.5, 127.1, 127.1, 105.7, 13.8, 11.3; FT-IR

(neat, cm^{-1}) ν 1551, 1485, 1460, 1416, 1368, 1029, 1007; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{21}\text{N}_2$ $[\text{M} + \text{H}]^+$ 325.1699, found 325.1704.

3,5-Dimethyl-1-(4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1H-pyrazole (2e)—3,5-Dimethyl-1-phenylpyrazole (86 mg, 0.5 mmol), 4-iodobenzotrifluoride (408 mg, 1.5 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %, 5.6 mg), silver oxide (140 mg, 0.6 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (100 μL , 1.3 mmol), 130 °C for 48 h: pale yellow solid; mp 102–103 °C (pentane); 81% yield (128 mg); purification (EtOAc/hexanes = 1/8); R_f = 0.10 (EtOAc/hexanes = 1/8); ^1H NMR (600 MHz, CDCl_3) δ 7.63–7.42 (m, 6H), 7.20 (d, J = 8.1 Hz, 2H), 5.78 (s, 1H), 2.28 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 149.0, 142.2 (q, $J_{\text{C-F}}$ = 1.4 Hz), 140.6, 137.9, 137.6, 130.5, 129.5, 129.5 (q, $J_{\text{C-F}}$ = 32.4 Hz), 129.2, 129.2, 128.9, 125.4 (q, $J_{\text{C-F}}$ = 3.8 Hz), 124.3 (q, $J_{\text{C-F}}$ = 272.1 Hz), 106.0, 13.7, 11.3; FT-IR (neat, cm^{-1}) ν 1616, 1557, 1494, 1405, 1368, 1321, 1158, 1070; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{16}\text{F}_3\text{N}_2$ $[\text{M} + \text{H}]^+$ 317.1260, found 317.1262.

Ethyl 2'-(3,5-Dimethyl-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-carboxylate (2f)—3,5-Dimethyl-1-phenylpyrazole (86 mg, 0.5 mmol), ethyl 4-iodobenzoate (414 mg, 1.5 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL , 0.85 mmol), 120 °C for 72 h: pale yellow oil; 80% yield (128 mg); purification (EtOAc/hexanes = 1/5); R_f = 0.09 (EtOAc/hexanes = 1/8); ^1H NMR (600 MHz, CDCl_3) δ 7.93 (d, J = 8.4 Hz, 2H), 7.50 (ddd, J = 20.5, 4.1, 1.5 Hz, 4H), 7.16 (d, J = 8.4 Hz, 2H), 5.75 (s, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.28 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, MeOD) δ 166.3, 148.9, 143.0, 141.4, 138.6, 136.9, 130.4, 129.7, 129.3, 129.2, 129.0, 128.8, 128.3, 105.7, 60.9, 13.2, 11.8, 9.8; FT-IR (neat, cm^{-1}) ν 1713, 1609, 1554, 1492, 1366, 1271, 1183, 1100, 1026; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 321.1598, found 321.1604.

1-(2'-(3,5-Dimethyl-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-yl)ethan-1-one (2g)—3,5-Dimethyl-1-phenylpyrazole (86 mg, 0.5 mmol), 4-iodoacetophenone (369 mg, 1.5 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL , 0.85 mmol), 120 °C for 72 h: pale yellow solid; mp 90–91 °C (diethyl ether); 66% yield (96 mg); purification (EtOAc/hexanes = 1/5); R_f = 0.05 (EtOAc/hexanes = 1/8); ^1H NMR (600 MHz, CDCl_3) δ 7.85 (d, J = 8.3 Hz, 2H), 7.57–7.45 (m, 4H), 7.18 (d, J = 8.3 Hz, 2H), 5.76 (s, 1H), 2.58 (s, 3H), 2.28 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 198.0, 149.0, 143.5, 140.6, 138.1, 137.6, 135.8, 130.4, 129.4, 129.2, 129.2, 128.8, 128.5, 105.9, 26.8, 13.7, 11.3; FT-IR (neat, cm^{-1}) ν 1716, 1687, 1489, 1359, 1268, 1183, 1103, 1027; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$ $[\text{M} + \text{Na}]^+$ 313.1311, found 313.1324.

1-(3'-Methoxy-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1H-pyrazole (2h)—3,5-Dimethyl-1-phenylpyrazole (86 mg, 0.5 mmol), 3-iodoanisole (351 mg, 1.5 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL , 0.85 mmol), 120 °C for 36 h: pale yellow oil; 75% yield (104 mg); purification (EtOAc/hexanes = 1/8); R_f = 0.15 (EtOAc/hexanes = 1/8); ^1H NMR (400 MHz, CDCl_3) δ 7.59–7.40 (m, 4H),

7.24–7.16 (m, 1H), 6.89–6.75 (m, 2H), 6.53 (dd, $J = 2.5, 1.7$ Hz, 1H), 5.77 (s, 1H), 3.63 (s, 3H), 2.29 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 159.4, 148.6, 141.0, 139.9, 139.2, 137.6, 130.4, 129.4, 129.3, 129.0, 128.5, 121.0, 114.5, 112.7, 105.8, 55.1, 13.7, 11.2; FT-IR (neat, cm^{-1}) ν 1591, 1469, 1417, 1367, 1216, 1181, 1022; HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}$ $[\text{M} + \text{H}]^+$ 279.1492, found 279.1501.

1-(3'-Fluoro-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1H-pyrazole (2i)—3,5-Dimethyl-1-phenylpyrazole (86 mg, 0.5 mmol), 3-fluoroiodobenzene (327 mg, 1.5 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL , 0.85 mmol), 120 °C for 72 h: pale yellow oil; 80% yield (107 mg); purification (EtOAc/hexanes = 1/10); $R_f = 0.17$ (EtOAc/hexanes = 1/8); ^1H NMR (500 MHz, CDCl_3) δ 7.57–7.40 (m, 4H), 7.21 (td, $J = 8.0, 6.0$ Hz, 1H), 6.94 (tdd, $J = 8.4, 2.6, 0.9$ Hz, 1H), 6.88 (ddd, $J = 7.7, 1.6, 0.9$ Hz, 1H), 6.79 (ddd, $J = 10.3, 2.6, 1.6$ Hz, 1H), 5.78 (s, 1H), 2.28 (s, 3H), 1.65 (d, $J = 0.7$ Hz, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 162.7 (d, $J_{\text{C-F}} = 245.4$ Hz), 148.9, 140.7, 140.7, 138.1 (d, $J_{\text{C-F}} = 2.2$ Hz), 137.6, 130.4, 129.9 (d, $J_{\text{C-F}} = 8.3$ Hz), 129.3, 129.1, 128.9, 124.3 (d, $J_{\text{C-F}} = 3.0$ Hz), 115.5 (d, $J_{\text{C-F}} = 22.4$ Hz), 114.3 (d, $J_{\text{C-F}} = 21.1$ Hz), 105.8, 13.7, 11.2; FT-IR (neat, cm^{-1}) ν 1588, 1553, 1480, 1425, 1265, 1184, 1028; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{FN}_2\text{Na}$ $[\text{M} + \text{Na}]^+$ 289.1111, found 289.1119.

1-(3'-Chloro-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1H-pyrazole (2j)—3,5-Dimethyl-1-phenylpyrazole (86 mg, 0.5 mmol), 3-chloroiodobenzene (358 mg, 1.5 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL , 0.85 mmol), 120 °C for 72 h: pale yellow oil; 77% yield (109 mg); purification (EtOAc/hexanes = 1/10); $R_f = 0.20$ (EtOAc/hexanes = 1/8); ^1H NMR (500 MHz, CDCl_3) δ 7.55–7.42 (m, 4H), 7.22 (ddd, $J = 8.0, 2.0, 1.2$ Hz, 1H), 7.17 (t, $J = 7.8$ Hz, 1H), 7.10 (t, $J = 1.9$ Hz, 1H), 6.94 (dt, $J = 7.6, 1.4$ Hz, 1H), 5.79 (s, 1H), 2.29 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 148.9, 140.7, 140.3, 138.0, 137.6, 134.2, 130.3, 129.6, 129.4, 129.1, 128.9, 128.6, 127.5, 126.7, 105.8, 13.7, 11.3; FT-IR (neat, cm^{-1}) ν 1554, 1504, 1408, 1365, 1098, 1028; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{Na}$ $[\text{M} + \text{Na}]^+$ 305.0816, found 305.0830.

1-(3',4'-Dimethyl-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1H-pyrazole (2k)—3,5-Dimethyl-1-phenylpyrazole (86 mg, 0.5 mmol), 4-iodo-1,2-dimethylbenzene (348 mg, 1.5 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μL , 0.85 mmol), 120 °C for 24 h: yellow oil; 83% yield (115 mg); purification (EtOAc/hexanes = 1/10); $R_f = 0.20$ (EtOAc/hexanes = 1/8); ^1H NMR (400 MHz, CDCl_3) δ 7.61–7.36 (m, 4H), 7.01 (d, $J = 7.8$ Hz, 1H), 6.84 (s, 1H), 6.80 (dd, $J = 7.8, 1.8$ Hz, 1H), 5.76 (s, 1H), 2.30 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 148.6, 141.0, 139.4, 137.3, 136.6, 135.9, 135.9, 130.5, 129.7, 129.3, 128.9, 128.0, 125.8, 122.5, 105.5, 19.8, 19.6, 13.6, 11.3; FT-IR (neat, cm^{-1}) ν 1576, 1492, 1348, 1160, 1136, 1101; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{Na}$ $[\text{M} + \text{Na}]^+$ 299.1519, found 299.1526.

1-(4',5-Dimethyl-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1H-pyrazole (2l)—3,5-Dimethyl-1-(*p*-tolyl)pyrazole (93 mg, 0.5 mmol), 4-iodotoluene (327 mg, 1.5 mmol), Pd(OAc)₂ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μ L, 0.85 mmol), 120 °C for 36 h: pale yellow oil; 83% yield (115 mg); purification (EtOAc/hexanes = 1/10); *R*_f = 0.22 (EtOAc/hexanes = 1/8); ¹H NMR (600 MHz, CDCl₃) δ 7.32 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 1.5 Hz, 1H), 7.22 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 8.1 Hz, 2H), 5.74 (s, 1H), 2.44 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 1.60 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 148.4, 140.7, 139.0, 138.8, 137.0, 135.8, 135.0, 131.0, 129.1, 128.7, 128.7, 128.4, 105.3, 21.4, 21.3, 13.8, 11.3; FT-IR (neat, cm⁻¹) ν 2920, 1552, 1503, 1420, 1187, 1029; HRMS (ESI) calcd for C₁₉H₂₀N₂Na [M + Na]⁺ 299.1519, found 299.1529.

1-(5-Methoxy-4'-methyl-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1H-pyrazole (2m)—1-(4-Methoxyphenyl)-3,5-dimethylpyrazole (101 mg, 0.5 mmol), 4-iodotoluene (327 mg, 1.5 mmol), Pd(OAc)₂ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μ L, 0.85 mmol), 120 °C for 36 h: pale yellow solid; mp 92–93 °C (pentane); 87% yield (127 mg); purification (EtOAc/hexanes = 1/5); *R*_f = 0.07 (EtOAc/hexanes = 1/8); ¹H NMR (500 MHz, CDCl₃) δ 7.35 (d, *J* = 8.6 Hz, 1H), 7.06 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.01–6.97 (m, 3H), 6.93 (dd, *J* = 8.6, 2.9 Hz, 1H), 5.73 (s, 1H), 3.87 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 1.60 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 159.8, 148.3, 140.9, 140.5, 137.3, 135.7, 130.6, 130.1, 129.2, 128.3, 115.2, 113.3, 105.2, 55.7, 21.3, 13.8, 11.2; FT-IR (neat, cm⁻¹) ν 1609, 1553, 1495, 1421, 1292, 1207, 1029; HRMS (ESI) calcd for C₁₉H₂₁N₂O [M + H]⁺ 293.1648, found 293.1655.

3,5-Dimethyl-1-(4'-methyl-5-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-1H-pyrazole (2n)—3,5-Dimethyl-1-(4-(trifluoromethyl)phenyl)-pyrazole (120 mg, 0.5 mmol), 4-iodotoluene (327 mg, 1.5 mmol), Pd(OAc)₂ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOAc (53 mg, 0.8 mmol), LiOTf (94 mg, 0.6 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μ L, 0.85 mmol), 120 °C for 84 h: pale yellow oil; 83% yield (137 mg); purification (EtOAc/hexanes = 1/10); *R*_f = 0.27 (EtOAc/hexanes = 1/8); ¹H NMR (500 MHz, CDCl₃) δ 7.79–7.73 (m, 1H), 7.71–7.65 (m, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.12–7.07 (m, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 5.79 (s, 1H), 2.33 (s, 2H), 2.30 (s, 2H), 1.60 (d, *J* = 0.6 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 149.5, 140.8, 140.4, 139.8, 138.1, 134.4, 131.2 (q, *J*_{C-F} = 32.6 Hz), 129.7, 129.5, 128.3, 127.6 (q, *J*_{C-F} = 3.9 Hz), 124.9 (q, *J*_{C-F} = 3.7 Hz), 123.9 (q, *J*_{C-F} = 272.5 Hz), 106.3, 21.3, 13.7, 11.2; FT-IR (neat, cm⁻¹) ν 1615, 1557, 1418, 1334, 1167, 1124, 1029; HRMS (ESI) calcd for C₁₉H₁₈F₃N₂ [M + H]⁺ 331.1417, found 331.1417.

1-(4-Chloro-4',5-dimethyl-[1,1'-biphenyl]-2-yl)-3,5-dimethyl-1H-pyrazole (2o)—1-(3-Chloro-4-methylphenyl)-3,5-dimethylpyrazole (110 mg, 0.5 mmol), 4-iodotoluene (327 mg, 1.5 mmol), Pd(OAc)₂ (5 mol %, 5.6 mg), silver oxide (93 mg, 0.4 mmol), LiOTf (94 mg, 0.6 mmol), LiOAc (53 mg, 0.8 mmol), HFIP (0.38 mL), acetic acid (0.13 mL), TFA (65 μ L, 0.85 mmol), 120 °C for 60 h: white solid; mp 114–115 °C (pentane); 86% yield (134

mg); purification (EtOAc/hexanes = 1/10); R_f = 0.33 (EtOAc/hexanes = 1/8); ^1H NMR (600 MHz, CDCl_3) δ 7.46 (s, 1H), 7.34 (s, 1H), 7.05 (d, J = 7.9 Hz, 2H), 6.94 (d, J = 8.1 Hz, 2H), 5.75 (s, 1H), 2.45 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 148.9, 140.8, 137.5, 137.4, 137.1, 136.0, 134.8, 133.4, 132.4, 129.4, 129.3, 128.3, 105.7, 21.3, 20.0, 13.8, 11.2; FT-IR (neat, cm^{-1}) ν 1557, 1492, 1385, 1128, 1058; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{ClN}_2$ $[\text{M} + \text{H}]^+$ 311.1310, found 311.1315.

General Procedure for Ozonolysis

The solution of the pyrazole (1 mmol) in acetone (20 mL) was cooled to -78°C . A stream of O_3/O_2 was bubbled into the reaction solution for 20 min (2.5 l/min, intensity 2). After completion of the reaction (monitored by TLC), ozone was replaced by nitrogen for 5 min bubbling. Subsequently, acetone was removed under vacuum at room temperature. To the residue were added ethanol (20 mL) and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (0.5 mmol, 119 mg). The mixture was cooled to 0°C followed by addition of NaBH_4 (6 mmol, 227 mg) portionwise. The resulting mixture was stirred for 10 min. After removal of ethanol under vacuum, water was (50 mL) added, and the mixture was extracted with ethyl acetate (3×50 mL). The organic layer was dried over MgSO_4 and filtered. The residue was purified by column chromatography on silica gel with hexanes/ethyl acetate eluent to afford the corresponding amide.

N-(4'-Methyl-[1,1'-biphenyl]-2-yl)acetamide (3a)^{3g}—pale yellow solid; mp $103\text{--}104^\circ\text{C}$ (diethyl ether); 64% yield (144 mg); purification (EtOAc/hexanes = 1/2); R_f = 0.23 (EtOAc/hexanes = 1/2); ^1H NMR (500 MHz, CDCl_3) δ 8.26 (d, J = 8.2 Hz, 1H), 7.35 (td, J = 8.1, 1.6 Hz, 1H), 7.32–7.21 (m, 5H), 7.20–7.11 (m, 2H), 2.43 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.4, 137.9, 135.2, 134.9, 132.2, 130.2, 129.9, 129.2, 128.3, 124.4, 121.6, 24.8, 21.3.

N-(4'-Methoxy-[1,1'-biphenyl]-2-yl)acetamide (3b)^{3g}—pale yellow solid; mp $134\text{--}135^\circ\text{C}$ (diethyl ether); 66% yield (159 mg); purification (EtOAc/hexanes = 1/2); R_f = 0.27 (EtOAc/hexanes = 1/2); ^1H NMR (400 MHz, CDCl_3) δ 8.25 (d, J = 8.2 Hz, 1H), 7.40–7.25 (m, 3H), 7.26–7.17 (m, 1H), 7.20–7.10 (m, 2H), 7.01 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 168.4, 159.4, 134.9, 131.9, 130.5, 130.3, 130.3, 128.2, 124.4, 121.6, 114.6, 55.5, 24.8.

N-(4'-(Trifluoromethyl)-[1,1'-biphenyl]-2-yl)acetamide (3c)⁸—pale yellow solid; mp $117\text{--}118^\circ\text{C}$ (diethyl ether); 48% yield (134 mg); purification (EtOAc/hexanes = 2/3); R_f = 0.2 (EtOAc/hexanes = 1/2); ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.41 (ddd, J = 8.4, 6.2, 2.9 Hz, 1H), 7.23 (d, J = 5.7 Hz, 2H), 6.96 (s, 1H), 2.04 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 168.5, 142.2, 134.6, 131.6, 130.3 (q, $J_{\text{C-F}}$ = 32.7 Hz), 130.2, 129.8, 129.30, 126.1 (q, $J_{\text{C-F}}$ = 3.8 Hz), 124.2 (q, $J_{\text{C-F}}$ = 272.2 Hz), 125.1, 122.9, 24.61.

General Procedure for C–H Arylation of Acetamides 3

A 2-dram vial equipped with a magnetic stir bar was charged with substrate **3** (0.5 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol %, 5.6 mg), $\text{Ag}(\text{OCOCF}_3)$ (0.56 mmol, 144 mg), 1-chloro-4-iodobenzene (1 mmol, 238 mg), and TFA (1 mL). The reaction mixture was stirred at 120°C for 8 h.

Subsequently, the reaction was diluted with ethyl acetate (50 mL) and neutralized with saturated aqueous NaHCO₃ (50 mL) followed by extraction with ethyl acetate (2 × 30 mL). The solvent was dried over MgSO₄ and removed under reduced pressure. The residue was purified by column chromatography.

N-[2-(4-Chlorophenyl)-6-(p-tolyl)phenyl]acetamide (4a)—*N*-(4'-methyl-[1,1'-biphenyl]-2-yl)acetamide **3a** (0.5 mmol, 113 mg); purification (hexanes/EtOAc/dichloromethane = 1/4/0.5); pale yellow solid; mp 239–240 °C (diethyl ether); 67% yield (112 mg); *R*_f = 0.35 (EtOAc/hexanes = 1/2); ¹H NMR (400 MHz, CDCl₃) δ 7.56–7.04 (m, 11H), 6.57 (s, 1H), 2.39 (s, 3H), 1.73 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 169.5, 140.8, 140.0, 138.6, 137.4, 136.6, 133.4, 131.3, 130.4, 130.2, 129.8, 129.2, 128.8, 128.5, 128.0, 23.1, 21.4; HRMS (ESI) calcd for C₂₁H₁₉ClNO [M + H]⁺ 336.1150, found 336.1150.

N-[2-(4-Chlorophenyl)-6-(4-methoxyphenyl)phenyl]acetamide (4b)—*N*-(4'-methoxy-[1,1'-biphenyl]-2-yl)acetamide **3b** (0.5 mmol, 121 mg); purification (EtOAc/hexanes = 1/2); pale yellow solid; mp 231–232 °C (diethyl ether); 55% yield (97 mg); *R*_f = 0.15 (EtOAc/hexanes = 1/3); ¹H NMR (400 MHz, CDCl₃) δ 7.49–7.23 (m, 9H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.58 (s, 1H), 3.84 (s, 3H), 1.74 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 169.6, 159.1, 140.6, 140.0, 138.6, 133.4, 131.8, 131.4, 130.4, 130.1, 130.0, 129.7, 128.5, 128.0, 113.9, 55.4, 23.1. HRMS (ESI) calcd for C₂₁H₁₉ClNO₂ [M + H]⁺ 352.1099, found 352.1100.

N-[2-(4-Chlorophenyl)-6-[4-(trifluoromethyl)phenyl]phenyl]-acetamide (4c)—*N*-(4'-(Trifluoromethyl)-[1,1'-biphenyl]-2-yl)-acetamide **3c** (0.5 mmol, 140 mg). Purification (EtOAc/hexanes = 1/5); pale yellow solid; mp 254–255 °C (diethyl ether); 61% yield (119 mg); *R*_f = 0.55 (EtOAc/hexanes = 1/3); ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.40–7.23 (m, 6H), 6.59 (s, 1H), 1.70 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 169.6, 143.5, 140.1, 140.0, 137.9, 133.8, 131.3, 130.6, 130.2, 130.2, 129.7 (q, *J* = 32.4 Hz), 129.2, 128.7, 128.2, 125.3, 124.3 (d, *J* = 272.1 Hz), 23.0. HRMS (ESI) calcd for C₂₁H₁₆ClF₃NO [M + H]⁺: 390.0867, found 390.0870.

General Procedure for Hydrolysis of 2,6-Disubstituted Acetamides 4

A 2-dram vial equipped with a magnetic stir bar was charged with acetamide **4** (0.23 mmol), sodium hydroxide (2.3 mmol, 92 mg), and EtOH (0.5 mL). The mixture was heated at 130 °C for 24 h. After completion of the reaction, water (20 mL) was added to the reaction mixture, and resulting solution was extracted with diethyl ether (3 × 30 mL). The organic layer was dried over MgSO₄ and filtered, and solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel.

4-Chloro-4''-methyl-[1,1':3',1'-terphenyl]-2'-amine (5a)—acet-amide **4a** (0.23 mmol, 77 mg); purification (hexanes/diethyl ether = 20/1); white solid; mp 90–91 °C (pentane); 83% yield (56 mg); *R*_f = 0.72 (hexanes/diethyl ether = 10/1); ¹H NMR (600 MHz, CDCl₃) δ 7.45 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 7.4 Hz, 2H), 7.27 (d, *J* = 7.4 Hz, 2H), 7.12 (d, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.90–6.84 (m, 1H), 3.81 (s, 2H), 2.40 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 140.9, 138.3, 137.2, 136.6, 133.3,

130.9, 130.2, 129.7, 129.6, 129.3, 129.1, 128.3, 126.7, 118.4, 21.3; HRMS (ESI) calcd for $C_{19}H_{17}ClN$ $[M + H]^+$ 294.1044, found 294.1046.

2-(4-Chlorophenyl)-6-(4-methoxyphenyl)aniline (5b)—acetamide **4b** (0.22 mmol, 77 mg); purification (hexanes/diethyl ether = 10/1); white solid; mp 102–103 °C; 81% yield (55 mg); R_f = 0.30 (hexanes/diethyl ether = 10/1); 1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.38 (m, 6H), 7.13 (d, J = 7.5 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 7.01 (d, J = 7.8 Hz, 2H), 6.88 (t, J = 7.5 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 141.0, 138.3, 133.3, 131.8, 130.8, 130.5, 130.2, 129.5, 129.1, 128.0, 126.7, 118.4, 114.4, 55.4. HRMS (ESI) calcd for $C_{19}H_{17}ClNO$ $[M + H]^+$ 310.0993, found 310.0994.

2-(4-Chlorophenyl)-6-[4-(trifluoromethyl)phenyl]aniline (5c)—acetamide **4c** (0.20 mmol, 78 mg), heated at 130 °C for 36 h; purification (hexanes/diethyl ether = 20/1); white solid; mp 68–69 °C; 82% yield (57 mg); R_f = 0.75 (hexanes/diethyl ether = 10/1); 1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 7.46 (s, 4H), 7.13 (d, J = 7.4 Hz, 2H), 6.92 (t, J = 7.5 Hz, 1H), 3.79 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 140.7, 137.9, 133.5, 130.8, 130.4, 130.1, 129.8, 129.6 (q, J = 33.0 Hz), 129.2, 127.1, 126.6, 126.0 (q, J = 3.7 Hz), 124.3 (q, J = 272.2 Hz), 118.6; HRMS (ESI) calcd for $C_{19}H_{14}ClF_3N$ $[M + H]^+$ 348.0761, found 348.0765.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. (a) Ittel SD, Johnson LK, Brookhart M. Late-Metal Catalysts for Ethylene Homo- and Copolymerization. *Chem Rev.* 2000; 100:1169–1204. [PubMed: 11749263] (b) Johnson LK, Killian CM, Brookhart M. New Pd(II)- and Ni(II)-Based Catalysts for Polymerization of Ethylene and α -Olefins. *J Am Chem Soc.* 1995; 117:6414–6415. (c) Meinhard D, Wegner M, Kipiani G, Hearley A, Reuter P, Fischer S, Marti O, Rieger B. New Nickel(II) Diimine Complexes and the Control of Polyethylene Microstructure by Catalyst Design. *J Am Chem Soc.* 2007; 129:9182–9191. [PubMed: 17602476]
2. Reviews: Colby DA, Bergman RG, Ellman JA. Rhodium-Catalyzed C–C Bond Formation via Heteroatom-Directed C–H Bond Activation. *Chem Rev* 2010. 110:624–655. Ackermann L. Carboxylate-Assisted Transition-Metal-Catalyzed C–H Bond Functionalizations: Mechanism and Scope. *Chem Rev.* 2011; 111:1315–1345. [PubMed: 21391562] Engle KM, Mei TS, Wang X, Yu JQ. Bystanding F^+ Oxidants Enable Selective Reductive Elimination from High-Valent Metal Centers in Catalysis. *Angew Chem, Int Ed.* 2011; 50:1478–1491. Topczewski JJ, Sanford MS. Carbon–hydrogen (C–H) bond activation at Pd^{IV} : a Frontier in C–H functionalization catalysis. *Chem Sci.* 2015; 6:70–76. [PubMed: 25544882] Daugulis O, Roane J, Tran LD. Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon–Hydrogen Bonds. *Acc Chem Res.* 2015; 48:1053–1064. [PubMed: 25756616] Hartwig JF. Evolution of C–H Bond Functionalization from Methane to Methodology. *J Am Chem Soc.* 2016; 138:2–24. [PubMed: 26566092] Baudoin O. Transition metal-catalyzed arylation of unactivated $C(sp^3)$ –H bonds. *Chem Soc Rev.* 2011; 40:4902–4911. [PubMed: 21505712] Nareddy P, Jordan F, Szostak M. Recent Developments in

Ruthenium-Catalyzed C–H Arylation: Array of Mechanistic Manifolds. *ACS Catal.* 2017; 7:5721–5745.

3. Examples of anilide C–H arylation: Yeung CS, Zhao X, Borduas N, Dong VM. Pd-catalyzed ortho-arylation of phenyl-acetamides, benzamides, and anilides with simple arenes using sodium persulfate. *Chem Sci.* 2010; 1:331–336. Kalyani D, Deprez NR, Desai LV, Sanford MS. Oxidative C–H Activation/C–C Bond Forming Reactions: Synthetic Scope and Mechanistic Insights. *J Am Chem Soc.* 2005; 127:7330–7331. [PubMed: 15898779] Li D, Xu N, Zhang Y, Wang L. A highly efficient Pd-catalyzed decarboxylative ortho-arylation of amides with aryl acylperoxides. *Chem Commun.* 2014; 50:14862–14865. Haridharan R, Muralirajan K, Cheng CH. Rhodium(III)-Catalyzed ortho-Arylation of Anilides with Aryl Halides. *Adv Synth Catal.* 2015; 357:366–370. Li BJ, Tian SL, Fang Z, Shi ZJ. Multiple C–H Activations To Construct Biologically Active Molecules in a Process Completely Free of Organohalogen and Organometallic Components. *Angew Chem, Int Ed.* 2008; 47:1115–1118. Neufeldt SR, Sanford MS. Combining Transition Metal Catalysis with Radical Chemistry: Dramatic Acceleration of Palladium-Catalyzed C–H Arylation with Diaryliodonium Salts. *Adv Synth Catal.* 2012; 354:3517–3522. [PubMed: 23950736] Hubrich J, Himmeler T, Rodefeld L, Ackermann L. Ruthenium(II)-Catalyzed C–H Arylation of Anilides with Boronic Acids, Borinic Acids and Potassium Trifluoroborates. *Adv Synth Catal.* 2015; 357:474–480. Chinnagolla RK, Jegannathan M. Ruthenium-catalyzed ortho-arylation of acetanilides with aromatic boronic acids: an easy route to prepare phenanthridines and carbazoles. *Chem Commun.* 2014; 50:2442–2444. Liang Z, Feng R, Yin H, Zhang Y. Free-Amine Directed Arylation of Biaryl-2-amines with Aryl Iodides by Palladium Catalysis. *Org Lett.* 2013; 15:4544–4547. [PubMed: 23981087]
4. (a) Zhang D, Nadres ET, Brookhart M, Daugulis O. Synthesis of Highly Branched Polyethylene Using “Sandwich” (8-*p*-Tolyl Naphthyl *a*-diimine)nickel(II) Catalysts. *Organometallics.* 2013; 32:5136–5143. (b) Chen Z, Liu W, Daugulis O, Brookhart M. Mechanistic Studies of Pd(II)-Catalyzed Copolymerization of Ethylene and Vinylalkoxysilanes: Evidence for a β -Silyl Elimination Chain Transfer Mechanism. *J Am Chem Soc.* 2016; 138:16120–16129. [PubMed: 27960299]
5. (a) Shabashov D, Daugulis O. Catalytic Coupling of C–H and C–I Bonds Using Pyridine As a Directing Group. *Org Lett.* 2005; 7:3657–3659. [PubMed: 16092843] (b) Gulia N, Daugulis O. Palladium-Catalyzed Pyrazole-Directed sp^3 C–H Bond Arylation for the Synthesis of β -Phenethylamines. *Angew Chem, Int Ed.* 2017; 56:3630–3634. (c) Kashima C, Hibi S, Maruyama T, Harada K, Omote Y. Ozonolysis of five-membered heterocycles. *J Heterocycl Chem.* 1987; 24:637–639. (d) Shabashov D, Daugulis O. Palladium-Catalyzed Anilide ortho-Arylation and Subsequent One-Pot Cyclization to Phenanthridines. *J Org Chem.* 2007; 72:7720–7725. [PubMed: 17824657] (e) Daugulis O, Zaitsev VG. Anilide ortho-Arylation by Using C–H Activation Methodology. *Angew Chem, Int Ed.* 2005; 44:4046–4048. (f) Ackermann L, Althammer A, Born R. Catalytic arylation reactions by C–H bond activation with aryl tosylates. *Angew Chem, Int Ed.* 2006; 45:2619–2622. (g) Ackermann L, Pospech J, Potukuchi HK. Well-Defined Ruthenium(II) Carboxylate as Catalyst for Direct C–H/C–O Bond Arylations with Phenols in Water. *Org Lett.* 2012; 14:2146–2149. [PubMed: 22494272] (h) Luo N, Yu Z. $RuCl_3 \cdot x H_2O$ -Catalyzed Direct Arylation of Arenes with Aryl Chlorides in the Presence of Triphenylphosphine. *Chem -Eur J.* 2010; 16:787–791. [PubMed: 19998433] (i) Doherty S, Knight JG, Addyman CR, Smyth CH, Ward NAB, Harrington RW. Ruthenium Complexes of $\kappa(P)$ - and $\kappa(P)-\eta^6$ -Coordinated KITPHOS Mono-phosphines: Efficient Catalysts for the Direct Ortho Arylation of 2-Phenylpyridine and N-Phenylpyrazole with Aryl Chlorides. *Organometallics.* 2011; 30:6010–6016. (j) Li YG, Kantchev E, Kwong FY, Wang ZY, Zou YL, So CM, Qin HL. Bulky Phosphane Ligand for Monoselective Ruthenium-Catalyzed, Directed o-C–H Arylation with Challenging Aryl Chlorides. *Synlett.* 2017; 28:499–503. (k) Norinder J, Matsumoto A, Yoshikai N, Nakamura E. Iron-Catalyzed Direct Arylation through Directed C–H Bond Activation. *J Am Chem Soc.* 2008; 130:5858–5859. [PubMed: 18410099] (l) Oi S, Sasamoto H, Funayama R, Inoue Y. Ortho-selective Arylation of Arylazoles with Aryl Bromides Catalyzed by Ruthenium Complexes. *Chem Lett.* 2008; 37:994–995. (m) Reddy GM, Rao NSS, Satyanarayana P, Maheswaran H. $PhI(OCOCF_3)_2$ -mediated ruthenium catalyzed highly site-selective direct ortho-C–H monoarylation of 2-phenylpyridine and 1-phenyl-1H-pyrazole and their derivatives by arylboronic acids. *RSC Adv.* 2015; 5:105347–105352. (n) Arockiam PB, Fischmeister C, Bruneau C, Dixneuf PH. C–H bond functionalization in water catalyzed by carboxylato ruthenium(II) systems. *Angew Chem, Int Ed.* 2010; 49:6629–6632. (o) Kim M, Kwak J, Chang S. Rhodium/N-

Heterocyclic Carbene Catalyzed Direct Intermolecular Arylation of sp^2 and sp^3 C–H Bonds with Chelation Assistance. *Angew Chem, Int Ed.* 2009; 48:8935–8939.(p) Teskey CJ, Sohel SMA, Bunting DL, Modha SG, Greaney MF. Domino N/C Arylation via In Situ Generation of a Directing Group: Atom-Efficient Arylation Using Diaryliodonium Salts. *Angew Chem, Int Ed.* 2017; 56:5263–5266.

6. (a) Chen X, She J, Shang ZC, Wu J, Zhang P. Room-Temperature Synthesis of Pyrazoles, Diazepines, β -Enaminones, and β -Enamino Esters Using Silica-Supported Sulfuric Acid as a Reusable Catalyst Under Solvent-Free Conditions. *Synth Commun.* 2009; 39:947–957.(b) Lill A, Scholich K, Stark H. Synthesis of novel dansyl-labeled Celecoxib derivatives. *Tetrahedron Lett.* 2013; 54:6682–6686.(c) Zhang J, Jia R-P, Wang D-H. Copper-catalyzed C–N cross-coupling of arylboronic acids with N-acylpyrazoles. *Tetrahedron Lett.* 2016; 57:3604–3607.
7. Cristau HJ, Cellier PP, Spindler JF, Taillefer M. Mild Conditions for Copper-Catalysed N-Arylation of Pyrazoles. *Eur J Org Chem.* 2004; 2004:695–709.
8. Tsang WCP, Zheng N, Buchwald SL. Combined C–H Functionalization/C–N Bond Formation Route to Carbazoles. *J Am Chem Soc.* 2005; 127:14560–14561. [PubMed: 16231894]

Scheme 1.
Pyrazole-Directed C–H Arylation

Scheme 2.
Arylation with Aryl Iodides

Scheme 3.
Arylation of *N*-Arylpyrazoles

Scheme 4.
Directing Group Removal

Scheme 5.
Preparation of Unsymmetrically Substituted 2,6-Diarylanilines