

Supporting Information for:

An Organic Cation as a Silver(I) Analogue for the Arylation of sp^2 and sp^3 C–H Bonds with Iodoarenes

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General Information

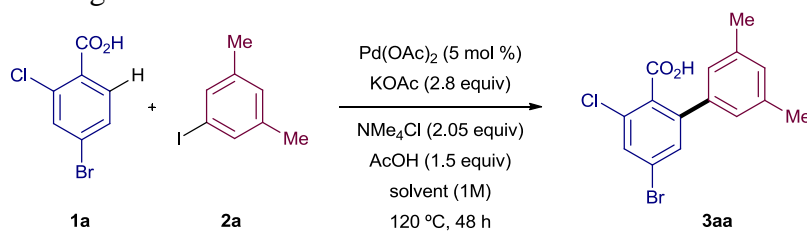
Unless otherwise noted, all the reagents were purchased from chemical companies and used without further purification. Column chromatography was carried out on silica gel, particle size 40-63 μm , using flash techniques. Analytical thin layer chromatography was performed on pre-coated aluminium-backed silica gel F254 plates with visualization under UV light. Purification by preparative LC-MS was conducted on a Waters 2767 HPLC equipped with a Waters ZQ MS detector and a Sunfire C18 column (100mm x 19mm i.d. 5 μm packing diameter). All preparative LC-MS runs were performed using 0.1% v/v solution of formic acid in mixtures of water and acetonitrile as eluents. Melting points were obtained using a hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrometer. High resolution mass spectra for new compounds were recorded at Mass Spectrometry Facilities at GlaxoSmithKline. ^1H NMR spectra, recorded at 400 MHz are referenced to the residual solvent peak at 7.26 ppm (CDCl_3). ^{13}C NMR spectra, recorded at 101 MHz, are referenced to the residual solvent peak at 77.0 ppm (CDCl_3). Unless otherwise stated, all reactions were carried out in sealed vials.

General Procedure for Arylation Reactions

A mixture of $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.03 mmol), KOAc (0.63-1.25 mmol), NMe_4Cl (0.63-0.88 mmol), aryl substrate (0.50 mmol) and iodoarene (0.5-1.5 mmol) in acetic acid (43 μL) was stirred at the temperature and for the time indicated in schemes. If appropriate, more KOAc (0.25-0.75 mmol) and NMe_4Cl (0.25-0.75 mmol) were added during that time. Then, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc and the filtrate evaporated to dryness. The crude was purified by re-slurry process, *flash* column chromatography or preparative LC-MS to afford the corresponding product.

Screening of Solvents

Table S1. Screening of solvents^a

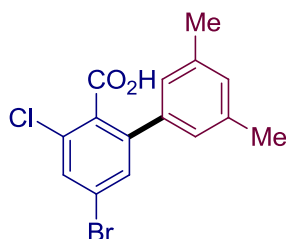


Entry	Solvent	Yield (%) ^b
1	-	85
2	1,4-Dioxane	64
3	EtOAc	53
4	PhCl	46
5	PhMe	31
6	DMF	29
7	DMSO	18
8	EtOH	0

^a Unless otherwise noted, all reactions were carried out using 0.5 mmol of **1** and 3 equiv of **2**. NMe₄Cl and KOAc were added in two portions. ^bYields were determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

Procedures and Characterization Data of the Synthesized Compounds

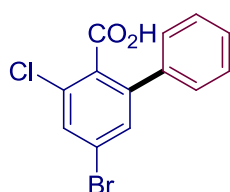
5-Bromo-3-chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (**3aa**)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (98 mg, 1 mmol), NMe₄Cl (69 mg, 0.63 mmol), 4-bromo-2-chlorobenzoic acid (118 mg, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (216 μ L, 1.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 24 h. Then, the reaction was cooled down, KOAc (39 mg, 0.4 mmol) and NMe₄Cl (44 mg, 0.4 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was quenched by addition of 2.0 M aqueous HCl (1 mL) and then filtered through a plug of Celite[®] with EtOAc (10 mL). The filtrate was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The residue was taken up with EtOAc and washed with 2.0 M aqueous NaOH. The aqueous layer was acidified to pH=1 with 2.0 M aqueous HCl and extracted with EtOAc (3 \times 10 mL). The organic layers were combined, dried over anhydrous MgSO₄, filtered and concentrated. The crude product was purified by *flash* column chromatography (from CH₂Cl₂:EtOAc:AcOH 97:2.5:0.5 to CH₂Cl₂:EtOAc:AcOH 95:4.5:0.5) to afford 5-bromo-3-chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (**3aa**) as a white solid.

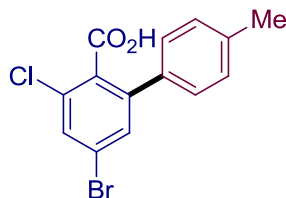
(130 mg, 77%). *R*_f 0.2 (CH₂Cl₂:EtOAc:AcOH 95:4.5:0.5); ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, *J* = 1.6 Hz, 1H), 7.45 (d, *J* = 1.6 Hz, 1H), 7.02 (s, 1H), 7.01 (s, 2H), 2.32 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 171.6, 143.2, 138.3, 137.6, 131.8, 131.3, 131.1, 130.6, 130.3, 126.0, 123.7, 21.2. These data are consistent with those previously reported.¹

5-Bromo-3-chloro-[1,1'-biphenyl]-2-carboxylic acid (3ab)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (98 mg, 1 mmol), NMe₄Cl (69 mg, 0.63 mmol), 4-bromo-2-chlorobenzoic acid (118 mg, 0.50 mmol) and iodobenzene (167 μL, 1.5 mmol) in acetic acid (43 μL) was heated at 120 °C for 24 h. Then, the reaction was cooled down, KOAc (39 mg, 0.4 mmol) and NMe₄Cl (44 mg, 0.4 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was quenched by addition of 2.0 M aqueous HCl (1 mL) and then filtered through a plug of Celite[®] with EtOAc (10 mL). The filtrate was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The residue was taken up with EtOAc and washed with 2.0 M aqueous NaOH. The aqueous layer was acidified to pH=1 with 2.0 M aqueous HCl and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over anhydrous MgSO₄, filtered and concentrated. The crude product was purified by *flash* column chromatography (CH₂Cl₂:EtOAc:AcOH 95:4.5:0.5) to afford 5-bromo-3-chloro-[1,1'-biphenyl]-2-carboxylic acid (**3ab**) as a white solid (99 mg, 64%). *R*_f 0.1 (CH₂Cl₂:EtOAc:AcOH 95:4.5:0.5); ¹H NMR (400 MHz, CDCl₃) δ 7.61 (d, *J* = 1.8 Hz, 1H), 7.47 (d, *J* = 1.8 Hz, 1H), 7.43 – 7.37 (m, 5H); ¹³C NMR (101 MHz, CDCl₃) δ 171.1, 143.0, 137.7, 132.0, 131.4, 131.0, 130.9, 128.7, 128.7, 128.2, 123.9. These data are consistent with those previously reported.¹

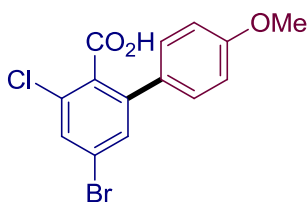
5-Bromo-3-chloro-4'-methyl-[1,1'-biphenyl]-2-carboxylic acid (3ac)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (98 mg, 1 mmol), NMe₄Cl (69 mg, 0.63 mmol), 4-bromo-2-chlorobenzoic acid (118 mg, 0.50 mmol) and 4-iodotoluene (327 mg, 1.5 mmol) in acetic acid (43 μL) was heated at 120 °C for 24 h. Then, the reaction was cooled down, KOAc (39 mg, 0.4 mmol) and NMe₄Cl (44 mg, 0.4 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was quenched by addition of 2.0 M aqueous HCl (1 mL) and then filtered through a plug of Celite[®] with EtOAc (10 mL). The filtrate was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The residue was taken up with EtOAc and

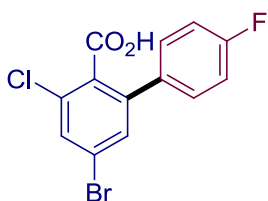
washed with 2.0 M aqueous NaOH. The aqueous layer was acidified to pH=1 with 2.0 M aqueous HCl and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over anhydrous MgSO₄, filtered and concentrated. The crude product was purified by *flash* column chromatography (CH₂Cl₂:EtOAc:AcOH 95:4.5:0.5) to afford 5-bromo-3-chloro-4'-methoxy-[1,1'-biphenyl]-2-carboxylic acid (**3ac**) as a yellowish solid (98 mg, 60%). *R*_f 0.1 (CH₂Cl₂:EtOAc:AcOH 95:4.5:0.5); ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, *J* = 1.7 Hz, 1H), 7.45 (d, *J* = 1.7 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.23 – 7.18 (m, 2H), 2.39 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.5, 143.0, 138.6, 134.9, 131.9, 131.4, 131.0, 130.7, 129.4, 128.1, 123.9, 21.2. These data are consistent with those previously reported.¹

5-Bromo-3-chloro-4'-methoxy-[1,1'-biphenyl]-2-carboxylic acid (**3ad**)



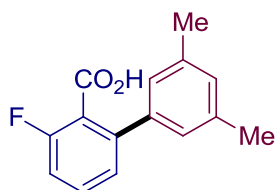
A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (98 mg, 1 mmol), NMe₄Cl (69 mg, 0.63 mmol), 4-bromo-2-chlorobenzoic acid (118 mg, 0.50 mmol) and 4-iodoanisole (351 mg, 1.5 mmol) in acetic acid (43 μL) was heated at 120 °C for 24 h. Then, the reaction was cooled down, KOAc (39 mg, 0.4 mmol) and NMe₄Cl (44 mg, 0.4 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was quenched by addition of 2.0 M aqueous HCl (1 mL) and then filtered through a plug of Celite[®] with EtOAc (10 mL). The filtrate was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The residue was taken up with EtOAc and washed with 2.0 M aqueous NaOH. The aqueous layer was acidified to pH=1 with 2.0 M aqueous HCl and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over anhydrous MgSO₄, filtered and concentrated. The crude product was purified by *flash* column chromatography (CH₂Cl₂:EtOAc:AcOH 95:4.5:0.5) to afford 5-bromo-3-chloro-4'-methoxy-[1,1'-biphenyl]-2-carboxylic acid (**3ad**) as a white solid (99 mg, 58%). *R*_f 0.1 (CH₂Cl₂:EtOAc:AcOH 95:4.5:0.5); ¹H NMR (400 MHz, CDCl₃) δ 7.57 (s, *J* = 1.7 Hz, 1H), 7.45 (d, *J* = 1.7 Hz, 1H), 7.36 – 7.30 (m, 2H), 6.97 – 6.89 (m, 2H), 3.84 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.5, 160.0, 142.7, 131.8, 131.4, 131.0, 130.5, 130.1, 129.4, 123.8, 114.2, 55.3. These data are consistent with those previously reported.¹

5-Bromo-3-chloro-4'-fluoro-[1,1'-biphenyl]-2-carboxylic acid (**3ae**)



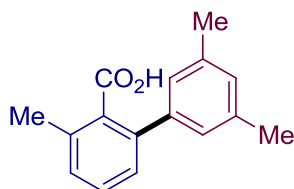
A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (98 mg, 1 mmol), NMe₄Cl (69 mg, 0.63 mmol), 4-bromo-2-chlorobenzoic acid (118 mg, 0.50 mmol) and 4-fluoriodobenzene (173 μ L, 1.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 24 h. Then, the reaction was cooled down, KOAc (39 mg, 0.4 mmol) and NMe₄Cl (44 mg, 0.4 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was quenched by addition of 2.0 M aqueous HCl (1 mL) and then filtered through a plug of Celite[®] with EtOAc (10 mL). The filtrate was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The residue was taken up with EtOAc and washed with 2.0 M aqueous NaOH. The aqueous layer was acidified to pH=1 with 2.0 M aqueous HCl and extracted with EtOAc (3 \times 10 mL). The organic layers were combined, dried over anhydrous MgSO₄, filtered and concentrated. The crude product was purified by *flash* column chromatography (CH₂Cl₂:EtOAc:AcOH 95:4.5:0.5) to afford 5-bromo-3-chloro-4'-fluoro-[1,1'-biphenyl]-2-carboxylic acid (**3ae**) as a white solid (107 mg, 65%). 0.2 (CH₂Cl₂:EtOAc:AcOH 95:4.5:0.5); ¹H NMR (400 MHz, CDCl₃) δ 8.07 (bs, 1H), 7.61 (d, *J* = 1.5 Hz, 1H), 7.43 (d, *J* = 1.5 Hz, 1H), 7.35 (m, 2H), 7.09 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 171.2, 163.0 (d, *J* = 249.0 Hz), 141.9, 133.7 (d, *J* = 3.4 Hz), 131.9, 131.4, 131.2, 131.1, 130.1 (d, *J* = 8.3 Hz), 123.9, 115.7 (d, *J* = 21.7 Hz). These data are consistent with those previously reported.¹

3-Fluoro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (**3ba**)



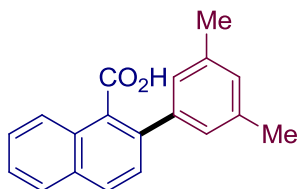
A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (98 mg, 1 mmol), NMe₄Cl (69 mg, 0.63 mmol), 2-fluorobenzoic acid (70 mg, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (216 μ L, 1.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 24 h. Then, the reaction was cooled down, KOAc (39 mg, 0.4 mmol) and NMe₄Cl (44 mg, 0.4 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was quenched by addition of 2.0 M aqueous HCl (1 mL) and then filtered through a plug of Celite[®] with EtOAc (10 mL). The filtrate was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The residue was taken up with EtOAc and washed with 2.0 M aqueous NaOH. The aqueous layer was acidified to pH=1 with 2.0 M aqueous HCl and extracted with EtOAc (3 \times 10 mL). The organic layers were combined, dried over anhydrous MgSO₄, filtered and concentrated. The crude product was purified by preparative LC-MS to afford 3-fluoro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (**3ba**) as a white foam (72 mg, 59%). ¹H NMR (400 MHz, CDCl₃) δ 7.44 (td, *J* = 8.0, 5.7 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 7.02 (s, 3H), 2.33 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 171.0, 159.8 (d, *J* = 252.1 Hz), 143.00 (d, *J* = 2.2 Hz), 138.9 (d, *J* = 2.1 Hz), 138.1, 131.5 (d, *J* = 9.1 Hz), 129.8, 126.1, 125.7 (d, *J* = 3.0 Hz), 120.4 (d, *J* = 15.8 Hz), 114.4 (d, *J* = 21.5 Hz), 21.2. These data are consistent with those previously reported.¹

3,3',5'-Trimethyl-[1,1'-biphenyl]-2-carboxylic acid (**3ac**)



A mixture of $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.03 mmol), KOAc (98 mg, 1 mmol), NMe_4Cl (69 mg, 0.63 mmol), *o*-toluic acid (68 mg, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (216 μL , 1.5 mmol) in acetic acid (43 μL) was heated at 120 °C for 24 h. Then, the reaction was cooled down, KOAc (39 mg, 0.4 mmol) and NMe_4Cl (44 mg, 0.4 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was quenched by addition of 2.0 M aqueous HCl (1 mL) and then filtered through a plug of Celite[®] with EtOAc (10 mL). The filtrate was dried over anhydrous MgSO_4 , filtered and evaporated to dryness. The residue was taken up with EtOAc and washed with 2.0 M aqueous NaOH. The aqueous layer was acidified to pH=1 with 2.0 M aqueous HCl and extracted with EtOAc (3 \times 10 mL). The organic layers were combined, dried over anhydrous MgSO_4 , filtered and concentrated. The crude product was purified by *flash* column chromatography (from CH_2Cl_2 :EtOAc:AcOH 98:1.5:0.5 to CH_2Cl_2 :EtOAc:AcOH 95:4.5:0.5) to afford 3,3',5'-trimethyl-[1,1'-biphenyl]-2-carboxylic acid (**3ca**) as a white solid (100 mg, 83%). *R*_f 0.3 (CH_2Cl_2 :EtOAc:AcOH 95:4.5:0.5); ¹H NMR (400 MHz, CDCl_3) δ 7.35 (t, *J* = 7.7 Hz, 1H), 7.21 (app. d, *J* = 7.7 Hz, 2H), 7.04 (s, 2H), 6.98 (s, 1H), 2.44 (s, 3H), 2.32 (s, 6H); ¹³C NMR (101 MHz, CDCl_3) δ 175.2, 140.5, 140.3, 137.8, 135.2, 132.1, 129.6, 129.2, 129.0, 127.4, 126.2, 21.3, 19.8. These data are consistent with those previously reported.²

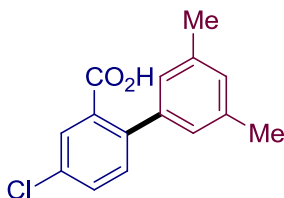
2-(3,5-Dimethylphenyl)-1-naphthoic acid (3da)



A mixture of $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.03 mmol), KOAc (98 mg, 1 mmol), NMe_4Cl (69 mg, 0.63 mmol), 1-naphthoic acid (86 mg, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (216 μL , 1.5 mmol) in acetic acid (43 μL) was heated at 120 °C for 24 h. Then, the reaction was cooled down, KOAc (39 mg, 0.4 mmol) and NMe_4Cl (44 mg, 0.4 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was quenched by addition of 2.0 M aqueous HCl (1 mL) and then filtered through a plug of Celite[®] with EtOAc (10 mL). The filtrate was dried over anhydrous MgSO_4 , filtered and evaporated to dryness. The residue was taken up with EtOAc and washed with 2.0 M aqueous NaOH. The aqueous layer was acidified to pH=1 with 2.0 M aqueous HCl and extracted with EtOAc (3 \times 10 mL). The organic layers were combined, dried over anhydrous MgSO_4 , filtered and concentrated. The crude product was purified by *flash* column chromatography (from CH_2Cl_2 :EtOAc:AcOH 98:1.5:0.5 to CH_2Cl_2 :EtOAc:AcOH 95:4.5:0.5) to afford 2-(3,5-dimethylphenyl)-1-naphthoic acid (**3da**) as a yellowish foam (118 mg, 85%). *R*_f 0.3 (CH_2Cl_2 :EtOAc:AcOH 95:4.5:0.5); ¹H NMR (400 MHz, CDCl_3) δ 8.10 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.66 – 7.50 (m, 3H), 7.20 (s, 2H), 7.07 (s, 1H), 2.39 (s, 6H); ¹³C NMR

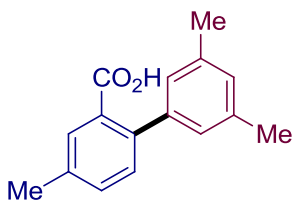
(101 MHz, CDCl₃) δ 174.7, 140.5, 138.5, 138.1, 132.2, 130.2, 129.7, 129.5, 128.6, 128.2, 127.7, 127.5, 126.5, 126.3, 125.0, 21.3. These data are consistent with those previously reported.¹

4-Chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (3ea)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (98 mg, 1 mmol), NMe₄Cl (69 mg, 0.63 mmol), 3-chlorobenzoic acid (78 mg, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (216 μ L, 1.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 24 h. Then, the reaction was cooled down, KOAc (39 mg, 0.4 mmol) and NMe₄Cl (44 mg, 0.4 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was quenched by addition of 2.0 M aqueous HCl (1 mL) and then filtered through a plug of Celite[®] with EtOAc (10 mL). The filtrate was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The crude product was purified by *flash* column chromatography (from CH₂Cl₂:EtOAc:AcOH 98:1.5:0.5 to CH₂Cl₂:EtOAc:AcOH 95:4.5:0.5) to afford 4-chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (**3ea**) as a white solid (98 mg, 75%). mp 132–134 °C; R_f 0.3 (CH₂Cl₂:EtOAc:AcOH 95:4.5:0.5); ¹H NMR (400 MHz, CDCl₃) δ 7.89 (d, *J* = 2.2 Hz, 1H), 7.50 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 7.00 (s, 1H), 6.92 (s, 2H), 2.33 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 172.2, 141.9, 139.7, 137.7, 133.0, 132.5, 131.8, 130.8, 130.3, 129.4, 126.2, 21.2; HRMS (ESI) calcd. C₁₅H₁₄ClO₂: ([M+H]⁺), 261.0677; found: ([M+H]⁺), 261.0676.

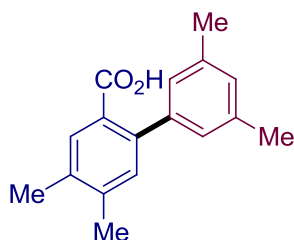
3',4,5'-Trimethyl-[1,1'-biphenyl]-2-carboxylic acid (3fa)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (98 mg, 1 mmol), NMe₄Cl (69 mg, 0.63 mmol), *m*-toluic acid (68 mg, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (216 μ L, 1.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 24 h. Then, the reaction was cooled down, KOAc (39 mg, 0.4 mmol) and NMe₄Cl (44 mg, 0.4 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was quenched by addition of 2.0 M aqueous HCl (1 mL) and then filtered through a plug of Celite[®] with EtOAc (10 mL). The filtrate was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The residue was taken up with EtOAc and washed with 2.0 M aqueous NaOH. The aqueous layer was acidified to pH=1 with 2.0 M aqueous HCl and extracted with EtOAc (3 \times 10 mL). The organic layers were

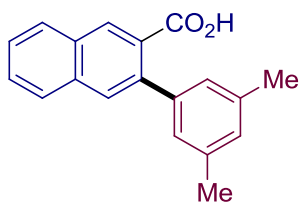
combined, dried over anhydrous MgSO_4 , filtered and concentrated. The crude product was purified by *flash* column chromatography (from CH_2Cl_2 :EtOAc:AcOH 98:1.5:0.5 to CH_2Cl_2 :EtOAc:AcOH 95:4.5:0.5) to afford 3',4,5'-trimethyl-[1,1'-biphenyl]-2-carboxylic acid (**3fa**) as a white solid (101 mg, 84%). mp 146–148 °C; R_f 0.3 (CH_2Cl_2 :EtOAc:AcOH 95:4.5:0.5); ^1H NMR (400 MHz, CDCl_3) δ 7.73 (d, J = 1.2 Hz, 1H), 7.35 (dd, J = 8.0, 1.2 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 6.98 (s, 1H), 6.95 (s, 2H), 2.42 (s, 3H), 2.33 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 173.8, 140.8, 140.6, 137.5, 136.8, 132.7, 131.1, 131.0, 129.2, 128.9, 126.4, 21.3, 20.8; HRMS (ESI) calcd. $\text{C}_{16}\text{H}_{17}\text{O}_2$: ($[\text{M}+\text{H}]^+$), 241.1223; found: ($[\text{M}+\text{H}]^+$), 241.1222.

3',4,5,5'-Tetramethyl-[1,1'-biphenyl]-2-carboxylic acid (**3ga**)



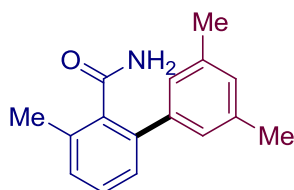
A mixture of $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.03 mmol), KOAc (98 mg, 1 mmol), NMe_4Cl (69 mg, 0.63 mmol), 3,4-dimethylbenzoic acid (75 mg, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (216 μL , 1.5 mmol) in acetic acid (43 μL) was heated at 120 °C for 24 h. Then, the reaction was cooled down, KOAc (39 mg, 0.4 mmol) and NMe_4Cl (44 mg, 0.4 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was quenched by addition of 2.0 M aqueous HCl (1 mL) and then filtered through a plug of Celite[®] with EtOAc (10 mL). The filtrate was dried over anhydrous MgSO_4 , filtered and evaporated to dryness. The residue was taken up with EtOAc and washed with 2.0 M aqueous NaOH. The aqueous layer was acidified to pH=1 with 2.0 M aqueous HCl and extracted with EtOAc (3 \times 10 mL). The organic layers were combined, dried over anhydrous MgSO_4 , filtered and concentrated. The crude product was purified by *flash* column chromatography (from CH_2Cl_2 :EtOAc:AcOH 98:1.5:0.5 to CH_2Cl_2 :EtOAc:AcOH 95:4.5:0.5) to afford 3',4,5,5'-tetramethyl-[1,1'-biphenyl]-2-carboxylic acid (**3ga**) as a white solid (105 mg, 83%). R_f 0.4 (CH_2Cl_2 :EtOAc:AcOH 95:4.5:0.5); ^1H NMR (400 MHz, CDCl_3) δ 7.73 (s, 1H), 7.11 (s, 1H), 6.97 (s, 1H), 6.93 (s, 2H), 2.33 (s, 6H), 2.32 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 173.4, 141.3, 141.3, 141.0, 137.3, 135.4, 132.6, 131.9, 128.8, 126.4, 21.3, 19.8, 19.2. Signal for one aromatic carbon could not be located. These data are consistent with those previously reported.³

3-(3,5-Dimethylphenyl)-2-naphthoic acid (**3ha**)



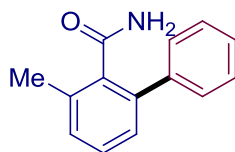
A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (98 mg, 1 mmol), NMe₄Cl (69 mg, 0.63 mmol), 2-naphthoic acid (75 mg, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (216 μ L, 1.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 24 h. Then, the reaction was cooled down, KOAc (39 mg, 0.4 mmol) and NMe₄Cl (44 mg, 0.4 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was quenched by addition of 2.0 M aqueous HCl (1 mL) and then filtered through a plug of Celite[®] with EtOAc (10 mL). The filtrate was dried over anhydrous MgSO₄, filtered and evaporated to dryness. The residue was taken up with EtOAc and washed with 2.0 M aqueous NaOH. The aqueous layer was acidified to pH=1 with 2.0 M aqueous HCl and extracted with EtOAc (3 \times 10 mL). The organic layers were combined, dried over anhydrous MgSO₄, filtered and concentrated. The crude product was purified preparative LC-MS to afford 3-(3,5-dimethylphenyl)-2-naphthoic acid (**3ha**) as a white solid (84 mg, 61%). mp 157–159 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.53 (s, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.82 (s, 1H), 7.64 – 7.53 (m, 2H), 7.08 (s, 2H), 7.02 (s, 1H), 2.38 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 173.3, 141.0, 139.2, 137.5, 134.7, 132.1, 131.4, 130.1, 129.0, 128.7, 128.5, 127.8, 127.7, 126.7, 126.6, 21.3; HRMS (ESI) calcd. C₁₉H₁₇O₂: ([M+H]⁺), 277.1223; found: ([M+H]⁺), 277.1225.

3,3',5'-Trimethyl-[1,1'-biphenyl]-2-carboxamide (**3ia**)



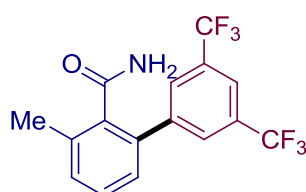
A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (123 mg, 1.25 mmol), NMe₄Cl (96 mg, 0.88 mmol), 2-methylbenzamide (68 mg, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (216 μ L, 1.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (20% EtOAc/hexanes) to afford 3,3',5'-trimethyl-[1,1'-biphenyl]-2-carboxamide (**3ia**) as a white solid (75 mg, 63%). mp 179–181 °C; R_f 0.2 (20% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.30 (t, *J* = 7.6 Hz, 1H), 7.18 (app. t, *J* = 8.2 Hz, 2H), 7.08 (s, 2H), 6.99 (s, 1H), 5.73 (bs, 1H), 5.30 (bs, 1H), 2.45 (s, 3H), 2.33 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 172.6, 140.8, 139.6, 138.2, 135.8, 135.6, 129.5, 129.5, 129.2, 127.6, 126.7, 20.9, 19.2; HRMS (ESI) calcd. C₁₆H₁₈NO: ([M+H]⁺), 240.1383; found: ([M+H]⁺), 240.1387.

3-Methyl-[1,1'-biphenyl]-2-carboxamide (**3ib**)



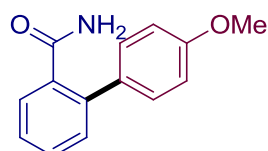
A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (110 mg, 1.13 mmol), NMe₄Cl (69 mg, 0.63 mmol), 2-methylbenzamide (68 mg, 0.50 mmol) and iodobenzene (167 μ L, 1.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (15% EtOAc/hexanes) to afford 3-methyl-[1,1'-biphenyl]-2-carboxamide (**3ib**) as a white solid (64 mg, 61%). R_f 0.1 (15% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.50 – 7.46 (m, 2H), 7.43 – 7.32 (m, 4H), 7.25 – 7.19 (m, 2H), 5.45 (bs, 1H), 5.21 (bs, 1H), 2.48 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 172.0, 140.4, 138.9, 135.6, 135.2, 129.3, 128.9, 128.6, 128.3, 127.5, 127.3, 19.5. These data are consistent with those previously reported.⁴

3-Methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamide (**3if**)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (110 mg, 1.13 mmol), NMe₄Cl (69 mg, 0.63 mmol), 2-methylbenzamide (68 mg, 0.50 mmol) and 3,5-bis(trifluoromethyl)iodobenzene (266 μ L, 1.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (15% EtOAc/hexanes) to afford 3-methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-carboxamide (**3if**) as a white solid (132 mg, 76%). mp 171–173 °C; R_f 0.1 (15% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.96 (s, 2H), 7.88 (s, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 5.57 (bs, 1H), 5.36 (bs, 1H), 2.49 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.1, 142.3, 136.0, 135.9, 135.5, 131.64 (q, *J* = 33.4 Hz), 130.7, 129.4, 128.9, 127.2, 123.2 (q, *J* = 272.7 Hz), 121.4 (dt, *J* = 7.6, 3.7 Hz), 19.4; HRMS (ESI) calcd. C₁₆H₁₂F₆NO: ([M+H]⁺), 348.0818; found: ([M+H]⁺), 348.0822.

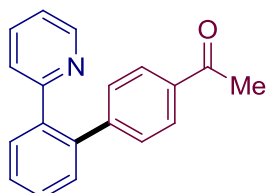
4'-Methoxy-[1,1'-biphenyl]-2-carboxamide (**3jd**)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (110 mg, 1.13 mmol), NMe₄Cl (69 mg, 0.63 mmol), benzamide (61 mg, 0.50 mmol) and 4-iodoanisole (351 mg, 1.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (3% MeOH/CH₂Cl₂) to afford 4'-methoxy-[1,1'-biphenyl]-2-carboxamide (**3jd**) as a white solid (64 mg, 56%). mp 116–118 °C; R_f 0.4 (10%

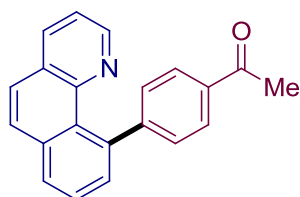
MeOH/CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.71 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.45 (td, *J* = 7.5, 4.4 Hz, 1H), 7.40 – 7.30 (m, 4H), 6.97 – 6.90 (m, 2H), 6.16 (bs, 1H), 5.40 (bs, 1H), 3.82 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 171.7, 159.4, 139.4, 134.3, 132.4, 130.3, 130.3, 129.9, 128.9, 127.1, 114.1, 55.2. These data are consistent with those previously reported.⁴

1-(2'-(Pyridin-2-yl)-[1,1'-biphenyl]-4-yl)ethanone (3kg)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (123 mg, 1.25 mmol), NMe₄Cl (96 mg, 0.88 mmol), 2-phenylpyridine (72 μL, 0.50 mmol) and 4'-iodoacetophenone (369 mg, 1.5 mmol) in acetic acid (43 μL) was heated at 140 °C for 24 h. Then, the reaction was cooled down, KOAc (74 mg, 0.75 mmol) and NMe₄Cl (82 mg, 0.75 mmol) were added and the mixture stirred at 140 °C for 28 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (from CH₂Cl₂ to 40% EtOAc/CH₂Cl₂) to afford 1-(2'-(pyridin-2-yl)-[1,1'-biphenyl]-4-yl)ethanone (**3kg**) as a white solid (69 mg, 51%). *R*_f 0.4 (20% EtOAc/CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.60 (d, *J* = 4.9 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.72 – 7.67 (m, 1H), 7.54 – 7.39 (m, 4H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.12 (dd, *J* = 7.5, 4.9 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 2.58 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 197.8, 158.9, 149.5, 146.4, 139.6, 139.5, 135.5, 135.3, 130.6, 130.3, 129.9, 128.6, 128.3, 128.1, 125.2, 121.6, 26.6. These data are consistent with those previously reported.⁵

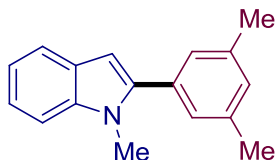
1-(4-(Benzo[*h*]quinolin-10-yl)phenyl)ethanone (3lg)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (110 mg, 1.13 mmol), NMe₄Cl (69 mg, 0.63 mmol), 7,8-benzoquinoline (90 mg, 0.50 mmol) and 4'-iodoacetophenone (369 mg, 1.5 mmol) in acetic acid (43 μL) was heated at 120 °C for 89 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (from CH₂Cl₂ to 10% EtOAc/CH₂Cl₂) to afford 1-(4-(benzo[*h*]quinolin-10-yl)phenyl)ethanone (**3lg**) as a pale orange solid (119 mg, 80%). *R*_f 0.2 (CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.39 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.09 (dd, *J* = 8.0, 1.8 Hz, 1H), 8.04 – 7.99 (m, 2H), 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.74 – 7.66 (m, 2H), 7.50 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.33

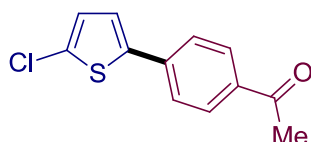
(dd, $J = 8.0, 4.3$ Hz, 1H), 2.70 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 198.2, 151.9, 146.8, 146.3, 140.4, 135.3, 134.9, 134.6, 130.9, 128.9, 128.7, 128.5, 128.2, 127.6, 127.2, 127.0, 126.1, 121.2, 26.6. These data are consistent with those previously reported.⁵

2-(3,5-Dimethylphenyl)-1-methyl-1*H*-indole (3ma)



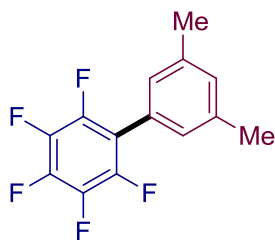
A mixture of $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.03 mmol), KOAc (110 mg, 1.13 mmol), NMe_4Cl (69 mg, 0.63 mmol), 1-methylindole (66 mg, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (216 μL , 1.5 mmol) in dry DMF (0.5 M) was heated at 80 °C for 22 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (from 1% to 10% $\text{CH}_2\text{Cl}_2/n$ -heptane) to afford 2-(3,5-dimethylphenyl)-1-methyl-1*H*-indole (**3ma**) as a colourless oil (72 mg, 61%). R_f 0.3 (10% $\text{CH}_2\text{Cl}_2/n$ -heptane); ^1H NMR (400 MHz, CDCl_3) δ 7.61 (d, $J = 7.9$ Hz, 1H), 7.33 (d, $J = 7.9$ Hz, 1H), 7.22 (td, $J = 7.9, 1.4$ Hz, 1H), 7.15 – 7.09 (m, 3H), 7.03 (s, 1H), 6.52 (s, 1H), 3.72 (s, 3H), 2.38 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 141.8, 138.3, 138.0, 132.7, 129.5, 128.0, 127.2, 121.4, 120.4, 119.7, 109.5, 101.4, 31.1, 21.3; HRMS (ESI) calcd. $\text{C}_{17}\text{H}_{18}\text{N}$: $([\text{M}+\text{H}]^+)$, 236.1434; found: $([\text{M}+\text{H}]^+)$, 236.1435.

1-(4-(5-Chlorothiophen-2-yl)phenyl)ethanone (3ng)



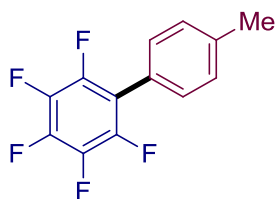
A mixture of $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.03 mmol), KOAc (123 mg, 1.25 mmol), NMe_4Cl (96 mg, 0.88 mmol), 4'-iodoacetophenone (123 mg, 0.50 mmol) and 2-chlorothiophene (55 μL , 0.6 mmol) in acetic acid (43 μL) was heated at 120 °C for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (15% EtOAc/hexanes) to afford 1-(4-(5-chlorothiophen-2-yl)phenyl)ethanone (**3ng**) as a yellowish solid (60 mg, 51%). R_f 0.3 (15% EtOAc/hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.99 – 7.94 (m, 2H), 7.61 – 7.57 (m, 2H), 7.20 (d, $J = 3.9$ Hz, 1H), 6.94 (d, $J = 3.9$ Hz, 1H), 2.61 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 197.1, 141.4, 137.9, 136.0, 131.0, 129.1, 127.5, 125.2, 123.8, 26.5. These data are consistent with those previously reported.⁶

2,3,4,5,6-Pentafluoro-3',5'-dimethyl-1,1'-biphenyl (3oa)



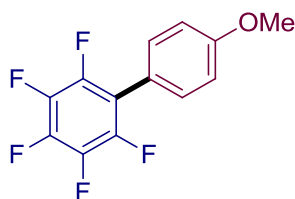
A mixture of $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.03 mmol), KOAc (123 mg, 1.25 mmol), NMe_4Cl (96 mg, 0.88 mmol), pentafluorobenzene (56 μL , 0.5 mmol) and 1-iodo-3,5-dimethylbenzene (72 μL , 0.5 mmol) in acetic acid (43 μL) was heated at 120 $^\circ\text{C}$ for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (petroleum ether) to afford 2,3,4,5,6-pentafluoro-3',5'-dimethyl-1,1'-biphenyl (**3oa**) as a white solid (86 mg, 63%). mp 82–83 $^\circ\text{C}$; R_f 0.4 (hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.10 (s, 1H), 7.02 (s, 2H), 2.38 (s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 145.6 – 142.7 (dm, $J = 247.1$ Hz), 141.7 – 138.7 (dm, $J = 245.0$ Hz), 139.3 – 136.3 (dm, $J = 252.6$ Hz), 138.3, 131.0, 127.8, 126.1, 116.3 (td, $J = 17.6, 3.9$ Hz), 21.2. These data are consistent with those previously reported.⁷

2,3,4,5,6-Pentafluoro-4'-methyl-1,1'-biphenyl (**3oc**)



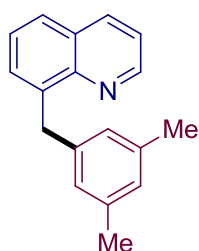
A mixture of $\text{Pd}(\text{OAc})_2$ (5.6 mg, 0.03 mmol), KOAc (123 mg, 1.25 mmol), NMe_4Cl (96 mg, 0.88 mmol), pentafluorobenzene (56 μL , 0.5 mmol) and 4-iodotoluene (109 mg, 0.5 mmol) in acetic acid (43 μL) was heated at 120 $^\circ\text{C}$ for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (petroleum ether) to afford 2,3,4,5,6-pentafluoro-4'-methyl-1,1'-biphenyl (**3oc**) as a white solid (68 mg, 53%). R_f 0.4 (hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.31 (s, 4H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ 146.0 – 143.3 (dm, $J = 247.1$ Hz), 142.0 – 139.4 (dm, $J = 239.9$ Hz), 139.8, 139.5 – 136.9 (dm, $J = 237.7$ Hz), 130.3, 129.8, 123.7, 116.2 (td, $J = 17.3, 4.0$ Hz), 20.9. These data are consistent with those previously reported.⁸

2,3,4,5,6-Pentafluoro-4'-methoxy-1,1'-biphenyl (**3od**)



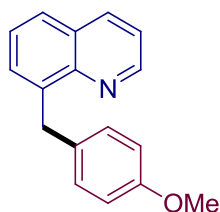
A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (123 mg, 1.25 mmol), NMe₄Cl (96 mg, 0.88 mmol), pentafluorobenzene (56 μ L, 0.5 mmol) and 4-iodoanisole (117 mg, 0.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (20% EtOAc/petroleum ether) to afford 2,3,4,5,6-pentafluoro-4'-methoxy-1,1'-biphenyl (**3od**) as a white solid (62 mg, 45%). R_f 0.4 (20% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.33 (m, 2H), 7.04 – 6.99 (m, 2H), 3.87 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 160.3, 144.17 (d, *J* = 242.8 Hz), 140.19 (d, *J* = 219.5 Hz), 137.70 (d, *J* = 224.2 Hz), 131.4, 118.4, 116.19 – 115.41 (m), 114.2, 55.3. These data are consistent with those previously reported.⁶

8-(3,5-Dimethylbenzyl)quinoline (3pa)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (61 mg, 0.63 mmol), NMe₄Cl (69 mg, 0.63 mmol), 8-methylquinoline (67 μ L, 0.50 mmol) and 1-iodo-3,5-dimethylbenzene (216 μ L, 1.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 19 h. Then, the reaction was cooled down, KOAc (25 mg, 0.25 mmol) and NMe₄Cl (27 mg, 0.25 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (45% CH₂Cl₂/hexanes) to afford 8-(3,5-dimethylbenzyl)quinoline (**3pa**) as a white solid (89 mg, 72%). mp 84–85 °C; R_f 0.1 (40% CH₂Cl₂/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 8.98 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.68 (dd, *J* = 7.3, 2.2 Hz, 1H), 7.48 – 7.39 (m, 3H), 6.94 (s, 2H), 6.84 (s, 1H), 4.62 (s, 2H), 2.27 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 149.9, 147.2, 141.5, 140.8, 138.1, 136.6, 129.8, 128.7, 127.9, 127.5, 126.6, 126.4, 121.2, 36.2, 20.9; HRMS (ESI) calcd. C₁₈H₁₈N: ([M+H]⁺), 248.1434; found: ([M+H]⁺), 248.1433.

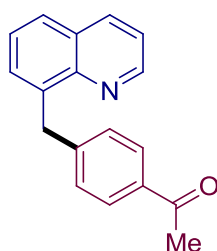
8-(4-Methoxybenzyl)quinoline (3pd)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (61 mg, 0.63 mmol), NMe₄Cl (69 mg, 0.63 mmol), 8-methylquinoline (67 μ L, 0.50 mmol) and 4-iodoanisole (351 mg, 1.5 mmol) in acetic acid (43 μ L) was heated at 120 °C for 19 h. Then, the reaction was

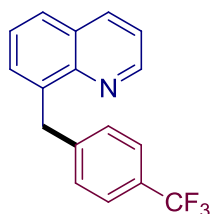
cooled down, KOAc (25 mg, 0.25 mmol) and NMe₄Cl (27 mg, 0.25 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (10% EtOAc/hexanes) to afford 8-(4-methoxybenzyl)quinoline (**3pd**) as a colourless oil (77 mg, 62%). R_f 0.2 (10% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 8.97 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.68 (dd, *J* = 7.4, 2.2 Hz, 1H), 7.47 – 7.39 (m, 3H), 7.26 – 7.22 (m, 2H), 6.86 – 6.81 (m, 2H), 4.63 (s, 2H), 3.78 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 157.8, 149.4, 146.7, 140.6, 136.2, 133.4, 130.2, 129.3, 128.4, 126.3, 126.1, 120.9, 113.8, 55.2, 35.9. These data are consistent with those previously reported.⁹

1-(4-(Quinolin-8-ylmethyl)phenyl)ethanone (**3pg**)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (61 mg, 0.63 mmol), NMe₄Cl (69 mg, 0.63 mmol), 8-methylquinoline (67 μL, 0.50 mmol) and 4'-iodoacetophenone (369 mg, 1.5 mmol) in acetic acid (43 μL) was heated at 120 °C for 19 h. Then, the reaction was cooled down, KOAc (25 mg, 0.25 mmol) and NMe₄Cl (27 mg, 0.25 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (8% EtOAc/hexanes) to afford 1-(4-(quinolin-8-ylmethyl)phenyl)ethanone (**3pg**) as a white solid (79 mg, 61%). mp 93–94 °C; R_f 0.2 (10% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 8.95 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.89 – 7.84 (m, 2H), 7.72 (m, 1H), 7.48 – 7.38 (m, 5H), 4.73 (s, 2H), 2.55 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 197.8, 149.6, 147.3, 146.6, 139.1, 136.2, 135.0, 129.5, 129.3, 128.5, 128.4, 126.7, 126.3, 121.1, 36.9, 26.5; HRMS (ESI) calcd. C₁₈H₁₆NO: ([M+H]⁺), 262.1226; found: ([M+H]⁺), 262.1224.

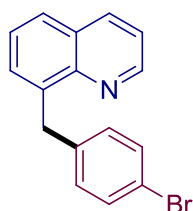
8-(4-(Trifluoromethyl)benzyl)quinoline (**3ph**)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (61 mg, 0.63 mmol), NMe₄Cl (69 mg, 0.63 mmol), 8-methylquinoline (67 μL, 0.50 mmol) and 4-iodobenzotrifluoride (220 μL, 1.5 mmol) in acetic acid (43 μL) was heated at 120 °C for 19 h. Then, the

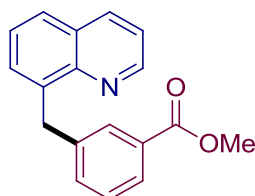
reaction was cooled down, KOAc (25 mg, 0.25 mmol) and NMe₄Cl (27 mg, 0.25 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (32% CH₂Cl₂/hexanes) to afford 8-(4-(trifluoromethyl)benzyl)quinoline (**3ph**) as a white solid (98 mg, 68%). mp 50–52 °C; R_f 0.2 (40% CH₂Cl₂/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 8.96 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.76 – 7.70 (m, 1H), 7.53 – 7.41 (m, 7H), 4.73 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 150.1, 147.0, 146.1, 139.5, 136.7, 129.9, 129.8, 128.8, 128.5 (q, *J* = 32.2 Hz), 127.1, 126.7, 125.5 (q, *J* = 3.8 Hz), 124.7 (d, *J* = 271.8 Hz), 121.4, 36.5. These data are consistent with those previously reported.⁵

8-(4-Bromobenzyl)quinoline (**3pi**)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (61 mg, 0.63 mmol), NMe₄Cl (69 mg, 0.63 mmol), 8-methylquinoline (67 μL, 0.50 mmol) and 1-bromo-4-iodobenzene (424 mg, 1.5 mmol) in acetic acid (43 μL) was heated at 120 °C for 19 h. Then, the reaction was cooled down, KOAc (25 mg, 0.25 mmol) and NMe₄Cl (27 mg, 0.25 mmol) were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (37% CH₂Cl₂/hexanes) to afford 8-(4-bromobenzyl)quinoline (**3pi**) as a white solid (99 mg, 66%). mp 49–50 °C; R_f 0.1 (10% CH₂Cl₂/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 8.95 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.70 (dd, *J* = 7.2, 2.4 Hz, 1H), 7.48 – 7.35 (m, 5H), 7.22 – 7.17 (m, 2H), 4.63 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 150.0, 147.0, 140.8, 139.9, 136.6, 131.6, 131.3, 129.7, 128.7, 126.8, 126.6, 121.3, 119.9, 36.0. These data are consistent with those previously reported.⁵

Methyl 3-(quinolin-8-ylmethyl)benzoate (**3pj**)



A mixture of Pd(OAc)₂ (5.6 mg, 0.03 mmol), KOAc (61 mg, 0.63 mmol), NMe₄Cl (69 mg, 0.63 mmol), 8-methylquinoline (67 μL, 0.50 mmol) and methyl 3-iodobenzoate (393 mg, 1.5 mmol) in acetic acid (43 μL) was heated at 120 °C for 19 h. Then, the reaction was cooled down, KOAc (25 mg, 0.25 mmol) and NMe₄Cl (27 mg, 0.25 mmol)

were added and the mixture stirred at 120 °C for 24 h. After this time, the reaction mixture was cooled down, filtered through a plug of Celite[®] with EtOAc (10 mL) and the filtrate evaporated to dryness. The residue was purified by *flash* column chromatography (7% EtOAc/hexanes) to afford methyl 3-(quinolin-8-ylmethyl)benzoate (**3pj**) as a colourless oil (82 mg, 59%). R_f 0.2 (10% EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 8.96 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.03 (ddd, *J* = 2.6, 1.2, 0.6 Hz, 1H), 7.87 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H), 7.70 (dd, *J* = 7.8, 2.6 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.48 – 7.40 (m, 3H), 7.33 (t, *J* = 7.8 Hz, 1H), 4.73 (s, 2H), 3.88 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 167.8, 150.0, 147.0, 142.2, 139.9, 136.6, 134.3, 130.7, 130.5, 129.8, 128.7, 128.6, 127.5, 126.8, 126.6, 121.3, 51.8, 36.3; HRMS (ESI) calcd. C₁₈H₁₆NO₂: ([M+H]⁺), 278.1176; found: ([M+H]⁺), 278.1176.

Large Scale Model Reaction

In a 5 L controlled laboratory reactor (Picture S1), a mixture of Pd(OAc)₂ (7.18 g, 0.03 mol), KOAc (314.1 g, 3.2 mol), NMe₄Cl (219.2 g, 2 mol), *o*-toluic acid (217.8 g, 1.6 mol), iodobenzene (358 mL, 3.2 mol) and acetic acid (138 mL, 2.4 mol) was heated at 120 °C and stirred for 18 h under N₂ atmosphere. Then, the reaction was cooled down, KOAc (125.6 g, 1.28 mol) and NMe₄Cl (140.3 g, 1.28 mol) were added and the mixture was stirred at 120 °C for 24 h. After this time, the reaction mixture was diluted with EtOAc (800 mL), quenched by addition of 2.0 M aqueous HCl (960 mL) and then filtered through a plug of Celite[®] with EtOAc. The phases of the filtrate were separated and the organic phase was extracted at pH=14 with 2.0 M aqueous NaOH (2 × 1.6 L). The aqueous layers were combined, filtered through glass microfiber under vacuum and acidified to pH=1 by slow addition of HCl 37%. The resultant suspension was filtered, the solid rinsed with water and dried in the vacuum oven to afford the crude product 3-methyl-[1,1'-biphenyl]-2-carboxylic acid (**3cb**) as an off-white solid (295.3 g, 87%). The purity was determined to be 97% by HPLC. A sample of 10 g was suspended in heptane (50 mL) and stirred at reflux temperature for 2 h. The suspension was cooled down to 20 °C over 3h, then filtered and washed with heptane (20 mL) to afford analytically pure material (8.47 g, 85%). mp 133–135 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.35 (m, 6H), 7.25 – 7.20 (m, 2H), 2.46 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 175.6, 140.6, 140.2, 135.4, 132.1, 129.7, 129.2, 128.3, 128.3, 127.5, 127.4, 19.9; HRMS (ESI) calcd. C₁₄H₁₃O₂: ([M+H]⁺), 213.0910; found: ([M+H]⁺), 213.0910. These data are consistent with those previously reported.¹⁰



Picture S1.

Presence of NMe_4I and PdI_2 in the Reaction Medium

Following the general procedure, reaction mixtures were filtered during the reaction work-up. The analysis of the filtration cake by NMR and IR revealed the presence of TMAI. ^1H NMR (400 MHz, DMSO) δ 3.12 (s, 12H); ^{13}C NMR (101 MHz, DMSO) δ 54.4, 54.4, 54.3. IR (neat) ν 3010, 1481, 1399, 941 cm^{-1} . These data are consistent with those previously reported¹¹ and in agreement of those obtained using commercial TMAI.

To ascertain the presence of PdI_2 as the inactivated form of the catalyst, we performed a qualitative test following a procedure for the preparation of *trans*-diiodobis(triphenylphosphine)palladium(II).¹² As described, mixing a pure sample of PdI_2 with a saturated solution of PPh_3 in acetonitrile led to the formation of the yellowish palladium complex (Figure S1). The analogous experiment with the reaction crude (entry 2, Table 1) gave the same change of colour. This observation indicated that PdI_2 was probably present in the reaction mixture; therefore suggesting that the reaction stopped after two catalytic cycles because of the formation of unreactive PdI_2 .

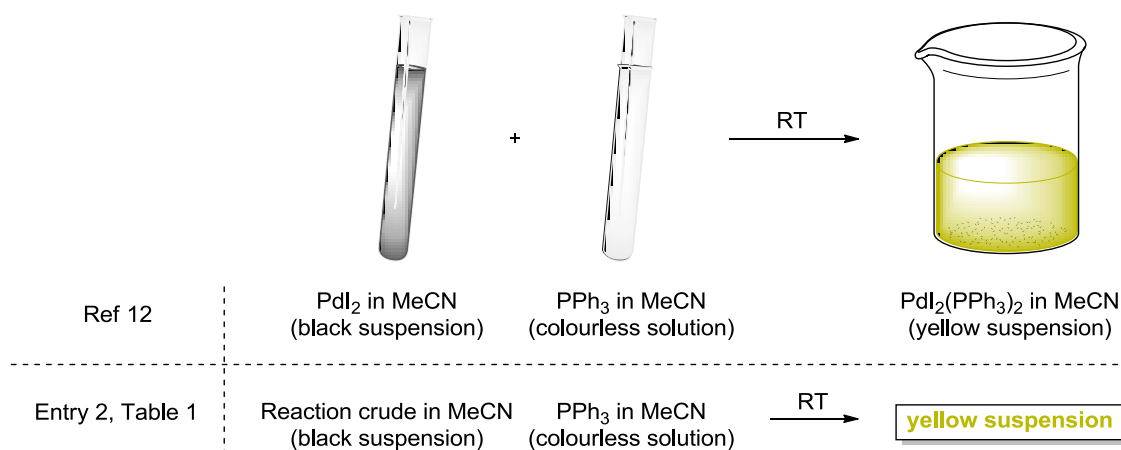


Figure S1.

Solubility of Ammonium Iodide Salts in Acetic Acid

The solubility of ammonium iodide, tetramethylammonium iodide (TMAI), tetraethylammonium iodide (TEAI) and tetrabutylammonium iodide (TBAI) in acetic acid was determined following the next procedure. Saturated suspensions of the ammonium salts in acetic acid were prepared by addition of 1-8 g of the salt, as required, to 5 mL of acetic acid and subsequent sonication of the sample at room temperature for 10 min. The suspensions were filtered, the filtrate evaporated to dryness and the remaining residue weighed. The results are summarized in Table S2.

Ammonium salt	Solubility in acetic acid at RT (mg/mL)
NH ₄ I	4.7
NMe ₄ I	0.25
NEt ₄ I	6.5
NBu ₄ I	647

Table S2.

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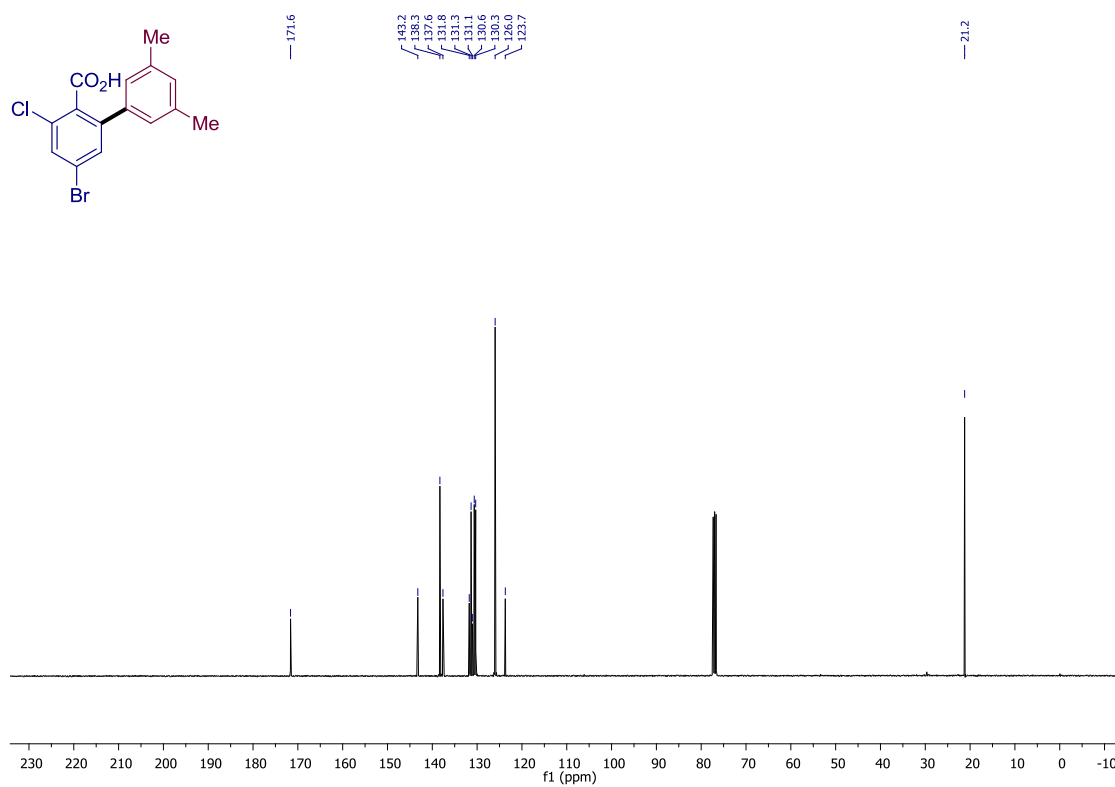
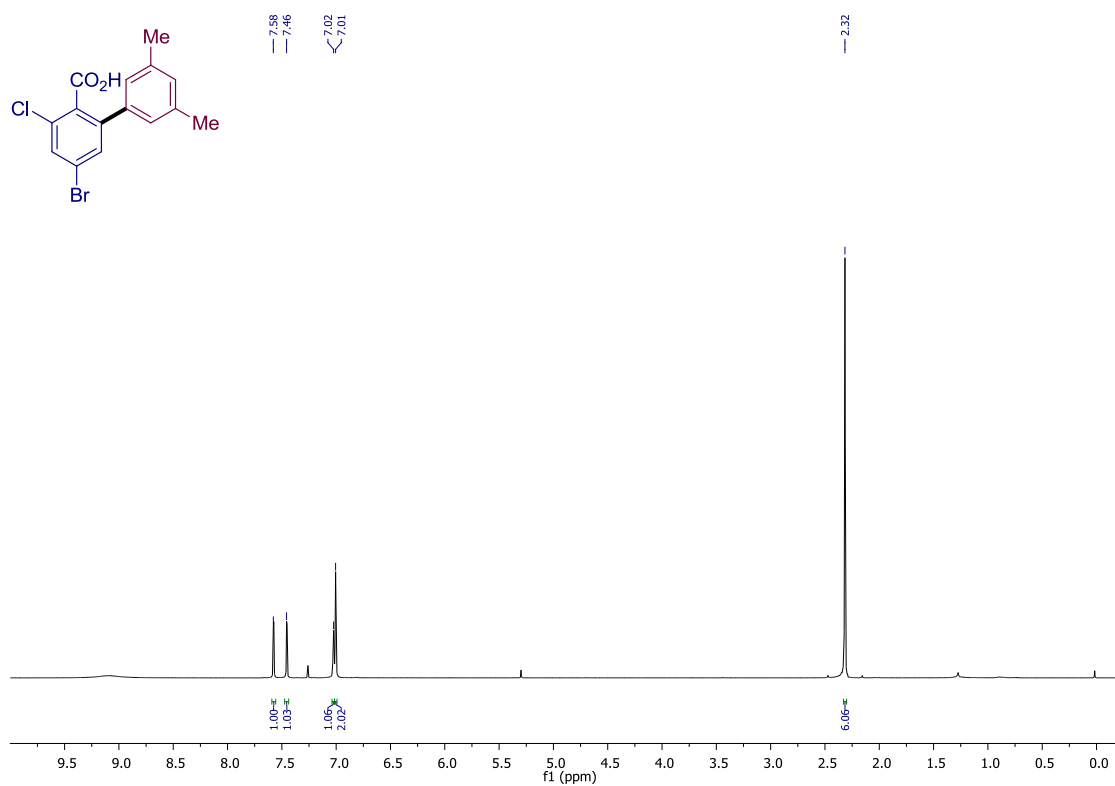
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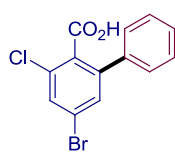
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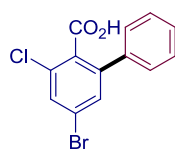
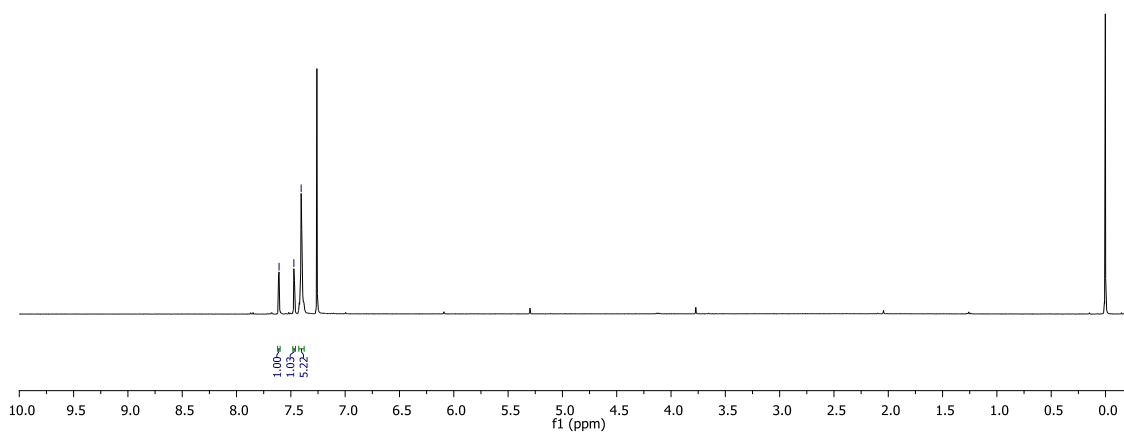
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Copies of ^1H NMR and ^{13}C NMR Spectra





7.61
7.41
7.41



171.1

143.0
137.7
132.0
131.4
131.0
130.9
128.7
128.7
128.2
123.9

