Electronic Supplementary Material (ESI) for Green Chemistry

Development of a Fluorous, Oxime-based Palladacycle for Microwave-Promoted Carbon-Carbon Coupling Reactions in Aqueous Medium

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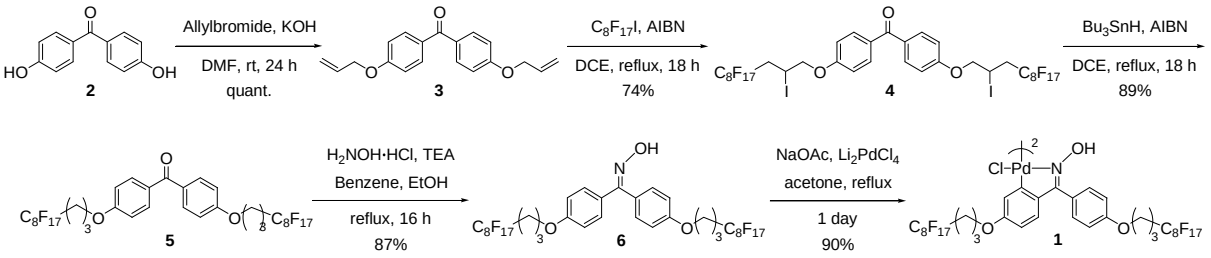
Experimental Procedure:



All chemical reagents were obtained from Aldrich, Merck, Lancaster or Fluka and used without further purification. Moisture-sensitive reactions were carried out under nitrogen atmosphere with commercially obtained anhydrous solvents. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light or stained with the Dragendorff-Munier and Hanessian stain. Column chromatography was performed with silica (Merck, 230 – 400 mesh). NMR spectra (^{1}H and ^{13}C) were recorded at 298 K on a Bruker ACF300, DPX300 or AMX500 Fourier Transform spectrometers. Chemical shifts are expressed in terms of δ (ppm) relative to the internal standard tetramethylsilane (TMS). Mass spectra were performed on Finnigan TSQ 7000 for EI normal mode or Finnigan MAT 95XL-T spectrometer under EI, ESI and FAB techniques. Microwave reactions were performed on the Biotage Initiator^{TM} microwave synthesizer in quartz pressure tubes. Pd leaching values were obtained on a Dual-view Optima 5300 DV (Inductively Coupled Plasma) ICP-OES system.

Bis(4-(allyloxy)phenyl)methanone (3): To a solution of 4,4'-dihydroxybenzophenone (5.0 g, 23.3 mmol) in DMF (50 mL) was added KOH (6.5 g, 116.7 mmol) and allyl bromide (5.1 mL, 58.4 mmol). The reaction mixture was stirred at room temperature for 24 h, quenched with H_2O (10 mL) and consecutively washed with EtOAc (100 mL × 3). The organic layers were combined, washed with brine (50 mL × 3), dried over anhydrous $MgSO_4$, filtered and concentrated. The desired product **3** (6.77 g, 99%) was obtained as a white crystal after purification by column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, 8H, J = 8.9 Hz), 6.96 (d, 8H, J = 8.9 Hz), 6.06 (m, 2H), 5.44, (dd, 2H, J_1 = 10.8 Hz, J_2 = 1.3 Hz), 5.32 (dd, 2H, J_1 = 10.7 Hz, J_2 = 1.3 Hz), 4.61 (d, 4 H, J = 5.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.3, 161.8, 132.6, 132.1, 130.8, 118.1, 114.1, 68.8; HRMS (EI): calcd. for $C_{19}H_{18}O_3$ 294.1256; found 294.1259.

Bis(4-(perfluorooctyl-2-iodopropoxy)phenyl)methanone (4): Compound **3** (0.59 g, 2.0 mmol) was dissolved in dichloroethane (1.2 mL) and $C_8F_{17}I$ (1.3 mL, 4.8 mmol) and AIBN (65.6 mg, 0.4 mmol) were added. The reaction flask was equipped with a condenser, and the apparatus was purged and filled with Ar, stirred at 85 °C

for 18 h and then concentrated to dryness. The desired product **4** (2.06 g, 74%) was obtained as a pale yellow solid after purification by column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, 4H, J = 8.9 Hz), 6.98 (d, 4H, J = 8.9 Hz), 4.59-4.54 (m), 4.39-4.36 (m), 4.30-4.26 (m), 3.23-3.12 (m, 2H), 2.91-2.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.1, 160.8, 132.3, 131.7, 114.3, 72.7, 37.9 (t, J = 21.0 Hz), 12.1; ^{19}F NMR (282 MHz, $CDCl_3$): δ -80.71 (t, 6F, J = 10.3 Hz), -113.16 - -113.59 (m, 4F), -121.49 - -121.83 (d, 12F), -122.63 (s, 4F), -123.39 (s, 4F), -126.04 (s, 4F); HRMS (ESI): calcd. for $C_{35}H_{18}O_3F_{34}I_2$ 1385.8802; found 1408.8695 (M^++Na).

Bis(4-(perfluorooctylpropoxy)phenyl)methanone (5): Compound **4** (20.8 g, 15.0 mmol) was dissolved in dichloroethane (80 mL) and Bu_3SnH (10.5 mL, 39.0 mmol) and AIBN (0.49 mg, 3.0 mmol) were added. The reaction flask was equipped with a condenser, and the apparatus was purged and filled with Ar. The reaction mixture was stirred at 85 °C for 18 h and then concentrated to dryness. The desired product **5** (15.19 g, 89%) was obtained as a white solid after purification by column chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, 8H, J = 8.8 Hz), 6.96 (d, 8H, J = 8.8 Hz), 4.14-4.12 (m), 2.39-2.29 (m, 4H), 2.18-2.13 (m, 4H); ^{13}C NMR (125 MHz, 50°C, $CDCl_3$): δ 194.1, 161.9, 132.2, 131.4, 114.1, 66.7, 28.1 (t, J = 21.9 Hz), 20.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ -81.60 (t, 6F, J = 10.3 Hz), -114.73 (t, 4F, J = 14.4 Hz), -122.22 - -122.43 (d, 12F), -123.25 (s, 4F), -123.98 (s, 4F), -126.71 (s, 4F); HRMS (ESI): calcd. for $C_{35}H_{20}O_3F_{34}$ 1134.0870; found 1157.0762 (M^++Na).

Bis(4-(perfluorooctylpropoxy)phenyl)methanone oxime (6): To a solution of compound **5** (1.26 g, 1.11 mmol) and triethylamine (1.7 mL, 12.5 mmol) in anhydrous EtOH (10.0 mL) and benzene (15.0 mL) was added hydroxylamine hydrochloride (575 mg, 8.28 mmol). The mixture was refluxed with a Dean-Stark apparatus for 16 h and then concentrated to dryness. 5% citric acid was added and the resulting mixture was extracted with EtOAc. The organic phase was washed consecutively with 5% citric acid, 5% $NaHCO_3$, H_2O and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The desired product **6** (1.11 g, 87%) was obtained as a white solid after purification by column chromatography. ^{1}H NMR (500 MHz, acetone-d_6): δ 10.09 (s, 1H), 7.39 (d, 2H, J = 8.8 Hz), 7.33 (d, 2H, J = 8.8 Hz), 7.04 (d, 4H, J = 8.8 Hz), 6.93 (d, 4H, J = 8.8 Hz), 4.23-4.21 (m), 4.19-4.16 (m), 2.57-2.42 (m, 4H), 2.19-2.11 (m, 4H); ^{13}C NMR (125 MHz, acetone-d_6): δ 160.3, 159.7, 155.2, 132.8, 131.8, 131.3, 129.8, 127.1, 115.0, 114.7, 67.1, 67.1, 66.5, 28.5-28.1 (m), 21.3; ^{19}F NMR (282 MHz, $CDCl_3$): δ -80.72 (t, 6F, J = 10.3 Hz), -114.4 - -114.32 (d, 4F), -121.67 - -121.87 (d, 12F), -122.66 (s, 4F), -123.36 (s, 4F), -126.05 (s, 4F); HRMS (ESI): calcd. for $C_{35}H_{21}O_3F_{34}N$ 1149.0979; found 1150.1051 (M^++1).

Palladacycle (1): To a suspension of oxime **6** (2.3 g, 2.0 mmol) in acetone (26 mL) was added anhydrous sodium acetate (0.165 g, 2.0 mmol) and Li_2PdCl_4 (0.524 g, 2.0 mmol). The mixture was stirred under reflux for 1 day. After which, water (10 mL) was added and the precipitate which formed was filtered off and dried under reduced pressure over P_2O_5 to give the desired product **1** (2.33 g, 90%) as a brown solid. ^{1}H NMR (500 MHz, acetone-d_6): δ 10.9 (s, 1H), 7.49-7.49 (m), 7.42 (d, 4H, J = 8.85 Hz), 7.12 (d, 4H, J = 8.85 Hz), 6.66 (d, 1H, J = 8.15 Hz), 6.49-6.47 (m), 4.28-4.26 (m), 4.10-4.08 (m), 2.57-2.41 (m, 4H), 2.19-2.07 (m, 4H); ^{13}C NMR (125 MHz, acetone-d_6): δ 163.7, 160.5, 158.0, 155.0, 137.4, 131.4, 128.0, 123.3, 121.8, 119.9, 115.1, 110.0, 67.3, 66.8, 55.4, 31.7(value deleted), 28.6-28.0 (m), 21.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ -81.64 (t, 6F, J = 10.3 Hz), -

114.72 (t, 4F, J = 12.4 Hz), -122.22 - - 122.43 (d, 12F), -123.25 (s, 4F), -123.95 (s, 4F), -126.71 (s, 4F); IR (KBr): v = 3429, 2961, 2762, 1578, 1246, 1206, 1025 cm^{-1}. MALDI HR: calcd. For $C_{35}H_{19}O_3F_{34}NPd$ 1288.9624; found 1287.9540 (M^+-1). Elemental analysis: calcd: C, 32.58; H, 1.56; N, 1.09; Cl, 2.75; F, 50.06; found: C, 32.70; H, 1.90; N, 1.56; Cl, 2.70; F, 50.05.

General procedure for the Suzuki-Miyaura reaction of boronic acid and aryl or benzyl halide under microwave heating: To a suspension of aryl halide (0.50 mmol), boronic acid (0.75 mmol), TBAB (0.161 g, 0.50 mmol), palladacycle **1** (0.05 mol% Pd) and water (1.0 mL) in a pressure tube was added a 2 M solution of K_2CO_3 (0.5 mL). The reaction mixture was microwave irradiated (with the heating program starting at 150 W) at 140 °C and the reaction was monitored by TLC. When the reaction has completed, the reaction mixture was cooled to room temperature, poured into EtOAc (20 mL) and washed successively with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was then purified by column chromatography.

General procedure for the recycling experiment using F-SPE: The crude product was first diluted with THF:H_2O = 8:2 and loaded into F-SPE fluorous silica. The crude product was then eluted using THF:H_2O = 8:2 as eluent and the palladacycle **1** was subsequently eluted with THF and concentrated. For elemental analysis of Pd leaching, a solution of the crude product was concentrated and analyzed by ICP-OES (1% aqueous HNO_3 solution). The crude product was then concentrated followed by diluting it with EtOAc (20 mL) and washed with water (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was then purified by column chromatography.

General procedure for the Sonogashira coupling reaction of phenylacetylene and aryl halide under microwave heating: To a suspension of aryl halide (0.50 mmol), phenylacetylene (0.75 mmol), pyrrolidine (0.062ml, 0.75 mmol), palladacycle **1** (0.5 mol% Pd) in a pressure tube was added degassed water (1.0 mL). The reaction mixture was microwave irradiated (with the heating program starting at 150 W) at 140 °C and the reaction was monitored by TLC. When the reaction has completed, the reaction mixture was cooled to room temperature, poured into ether (20 mL) and washed successively with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, concentrated and the crude product obtained was purified by column chromatography.

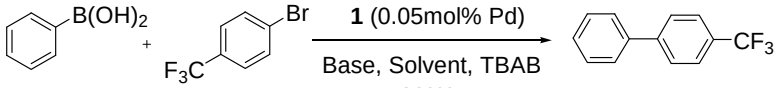
General procedure for the Stille coupling reaction of tributyl(4-methoxyphenyl)stannane and aryl under microwave heating: To a suspension of aryl halide (0.50 mmol), tributyl(4-methoxyphenyl)stannane (0.75 mmol), TBAB (0.081 g, 0.25 mmol), palladacycle **1** (0.005 mol% Pd) in a pressure tube was added 1 mL of water. The reaction mixture was microwave irradiated (with the heating program starting at 150 W) at 100 °C and the reaction was monitored by TLC. When the reaction has completed, the reaction mixture was cooled to room temperature, poured into ether (20 mL) and washed successively with water (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was then purified by column chromatography.

Table S1. Optimization of the Synthesis of Palladacycle **1**

Entry	Temp (°C)	Solvent	Time (days)	Yield (%)[a]
1	rt	CH_3OH	7	30
2	rt	THF	6	53
3	rt	acetone	6	92
4	reflux	acetone	1	90

[a] isolated yield.

Table S2. Optimization of the Suzuki-Miyaura Reaction.

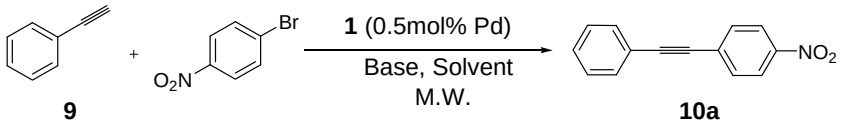


7 **8a**

Entry	Temp (°C)	Base	Solvent	Time (min)	Yield (%)[a]
1	140	K_2CO_3	H_2O	2	98
2	140	K_2CO_3	H_2O[b]	4.5	98[b]
3	140	K_2CO_3	THF	2	58
4	140	K_2CO_3	THF/H_2O[c]	3	69
5	140	K_2CO_3	DMF/H_2O[c]	2	92
6	140	K_2CO_3	CH_3OH/H_2O[c]	2	88
7	140	KOH	H_2O	3	83
8	140	Cy_2NM	H_2O	5	83
9	100	K_2CO_3	H_2O	20	79[d]
10	170	K_2CO_3	H_2O	0.25	89
11	140	K_2CO_3	H_2O	2	0[e]
12	140	K_2CO_3	H_2O	2	17[f]

[a] isolated yield.
[b] precatalyst loading of 0.005 mol% Pd.
[c] ratio of organic solvent to water is 3:1.
[d] yield obtained when the experiment was carried out under conventional heating.
[e] addition of 1 drop of mercury.
[f] addition of 0.5 equivalent of CS_2 (per metal atom).

Table S3. Optimization of the Sonogashira Coupling Reaction.

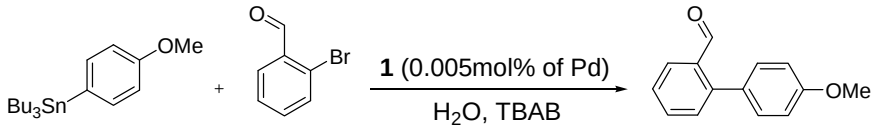


9 **10a**

Entry	Temp (°C)	Base	Solvent	Time (min)	Yield (%)[a]
1	140	K_2CO_3	NMP	5	53 (21[b])
2	140	TEA	NMP	5.5	45
3	140	TBAA	NMP	9	82 (30[b])
4	140	TBAF	NMP	15	63 (22[b])
5	140	Pyrrolidine	NMP	6	89 (35[b])
6	140	Pyrrolidine	DMF	5	89
7	140	Pyrrolidine	Acetonitrile	6.5	81
8	140	Pyrrolidine	THF	7	85
9	140	Pyrrolidine	H_2O	6	93[c]
10	90	Pyrrolidine	H_2O	100	69[d]
11	140	Pyrrolidine	H_2O[e]	3.5	95

[a] isolated yield
[b] 0.05mol% of Pd (incomplete reaction even after 2h in 140 °C in M.W.)
[c] presence of homocoupled **9** (10%).
[d] yield obtained when the experiment was carried out under conventional heating.
[e] degassed water

Table S4. Optimization of the Stille Reaction.



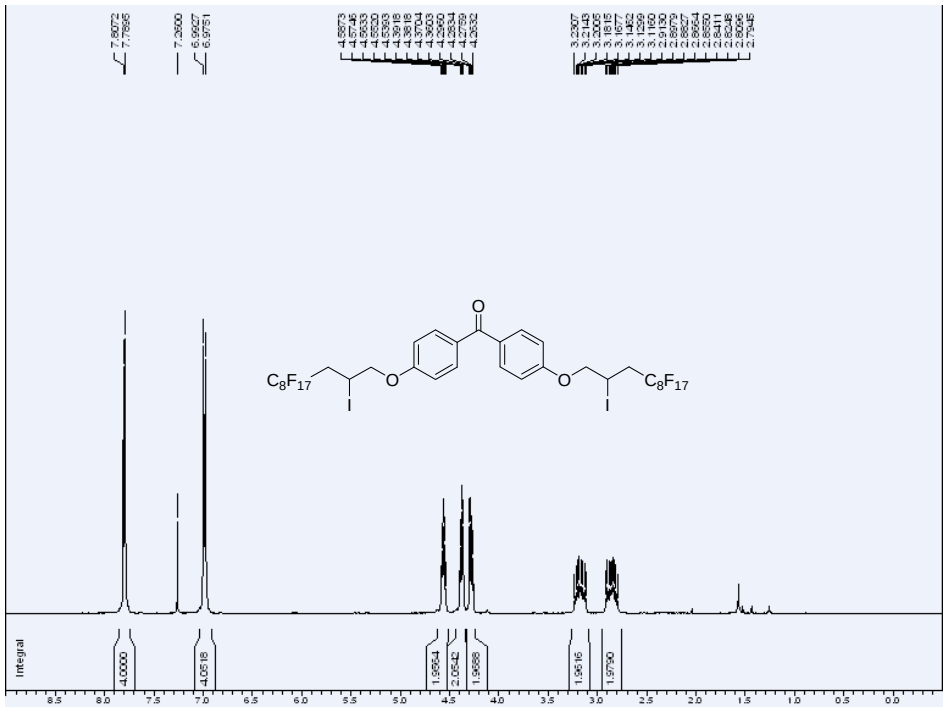
11 **12a**

Entry	Temp (°C)	Solvent	Time (min)	Yield (%)[a]
1	140	DMF[b]	25	67
2	140	THF[b]	45	71
3	140	Acetonitrile[b]	35	72
4	140	H_2O[b]	28	86
5	170	H_2O[b]	21	77
6	140	H_2O[c]	2	91
7	140	H_2O	2	89
8	100	H_2O	2.5	92
9	100	H_2O	30	76[d]

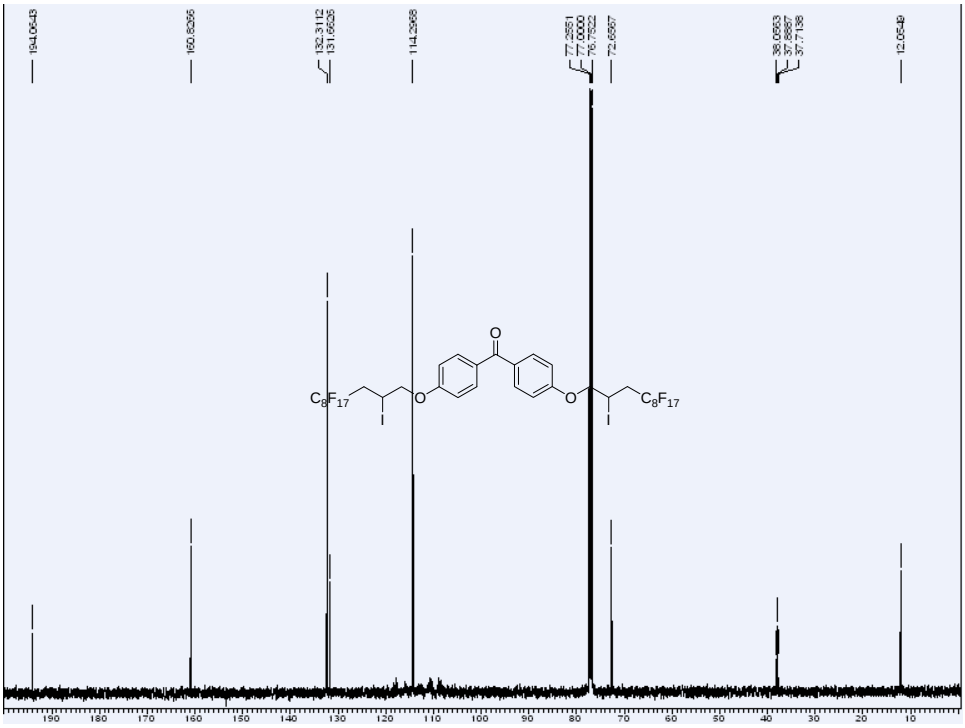
[a] isolated yield
[b] 0.05mol% of Pd in the absence of TBAB
[c] 0.05mol% of Pd in the presence of 0.5 eq. of TBAB
[d] yield obtained when the experiment was carried out under conventional heating.

NMR and FTIR Spectra of New Compounds:

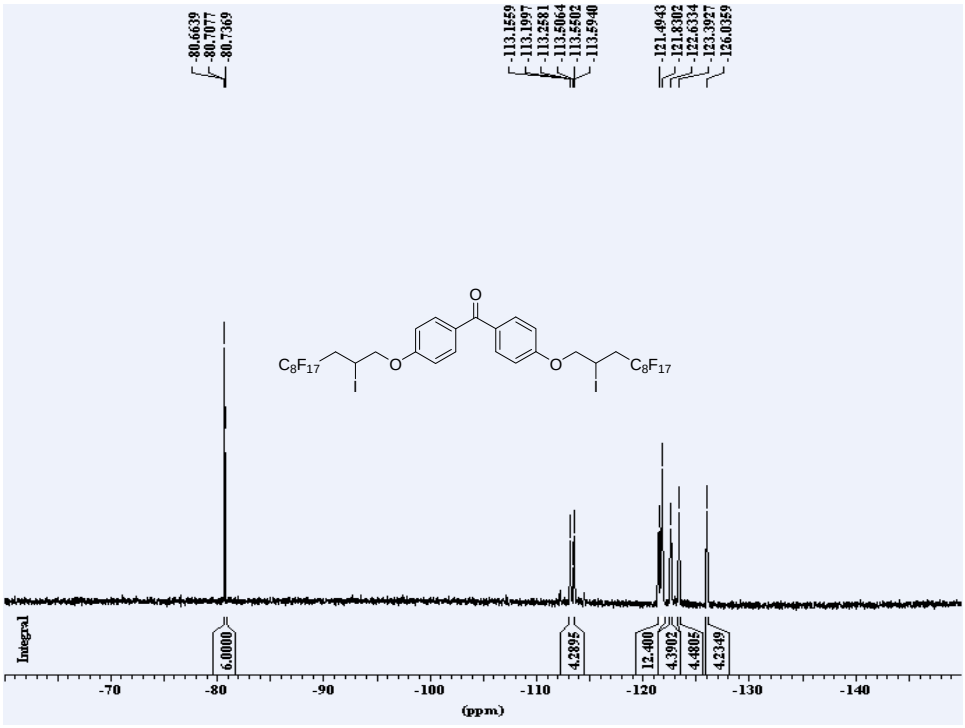
^{1}H NMR Spectrum of **4**



^{13}C NMR Spectrum of **4**

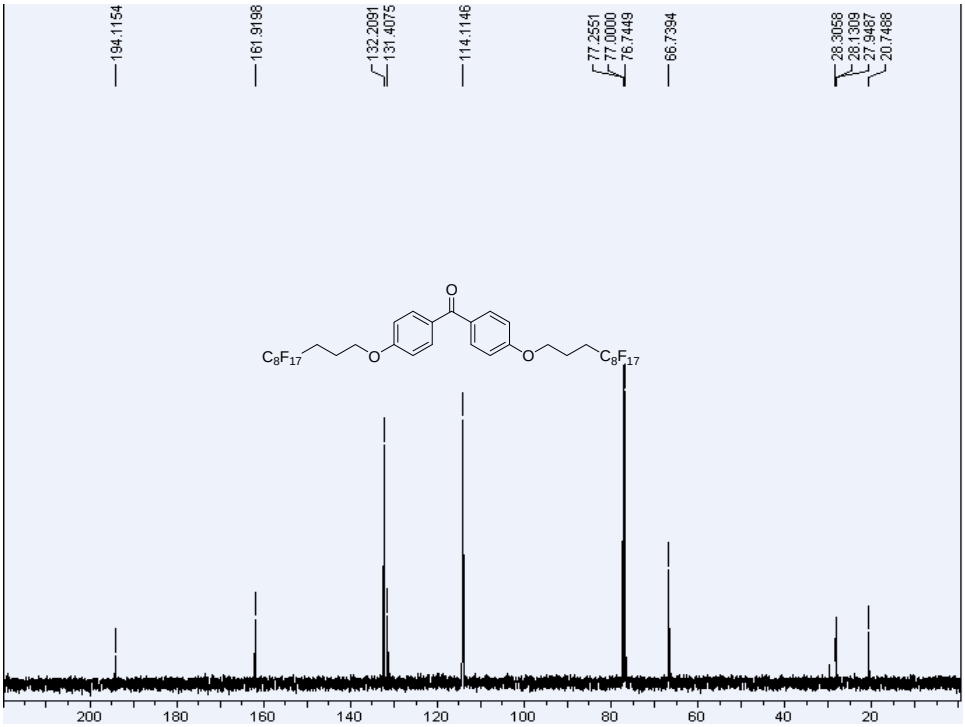


^{19}F NMR Spectrum of **4**

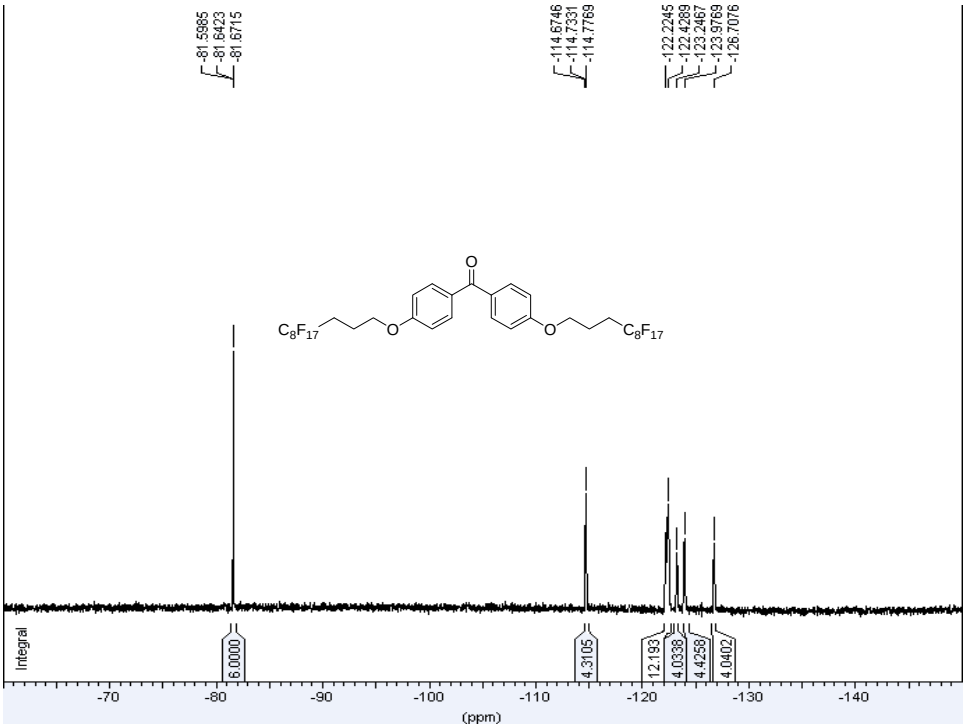


^{1}H NMR Spectrum of **5**

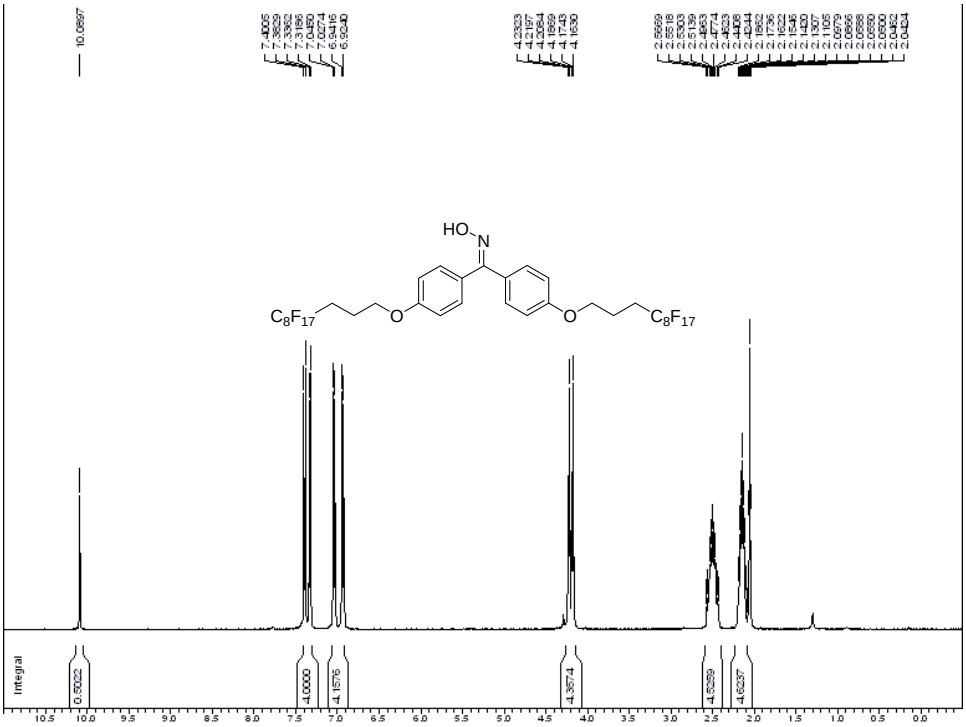
^{13}C NMR Spectrum of **5**



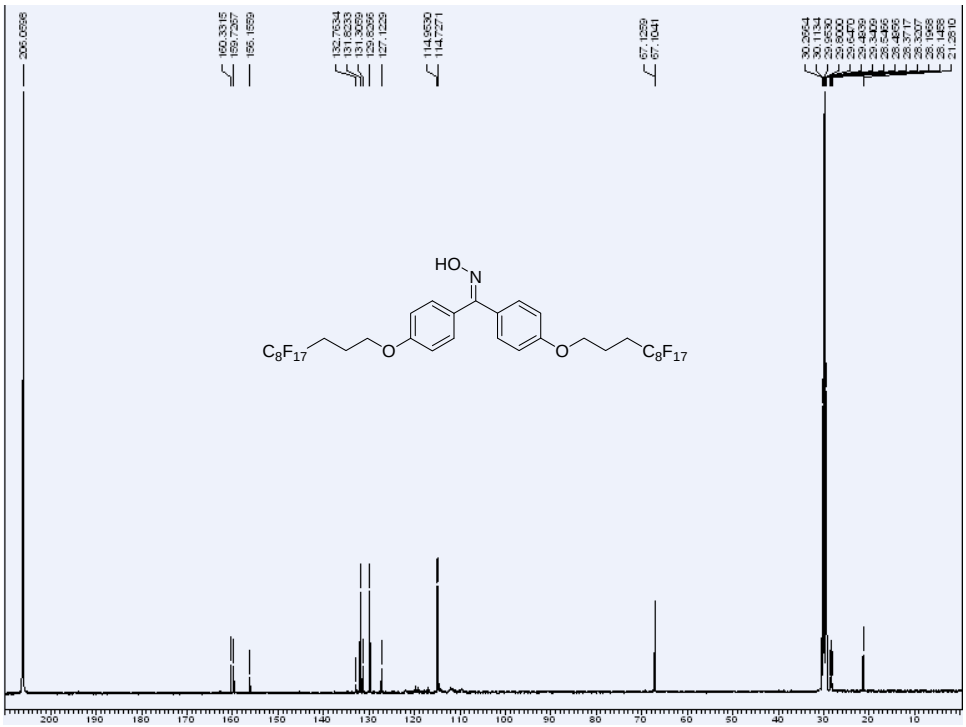
^{19}F NMR Spectrum of **5**



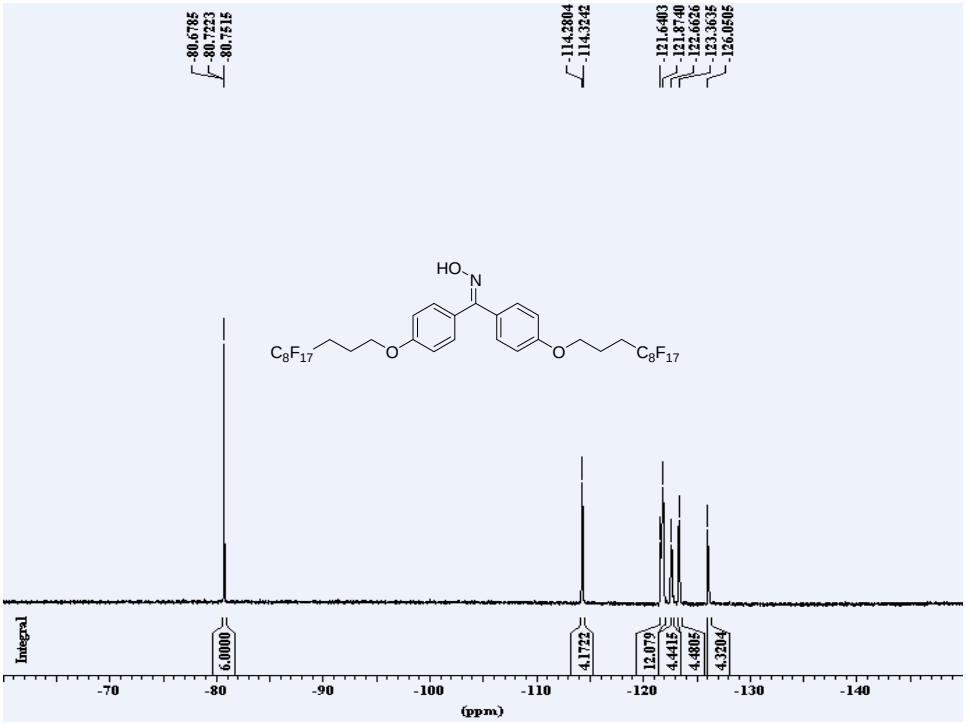
^{1}H NMR Spectrum of **6**



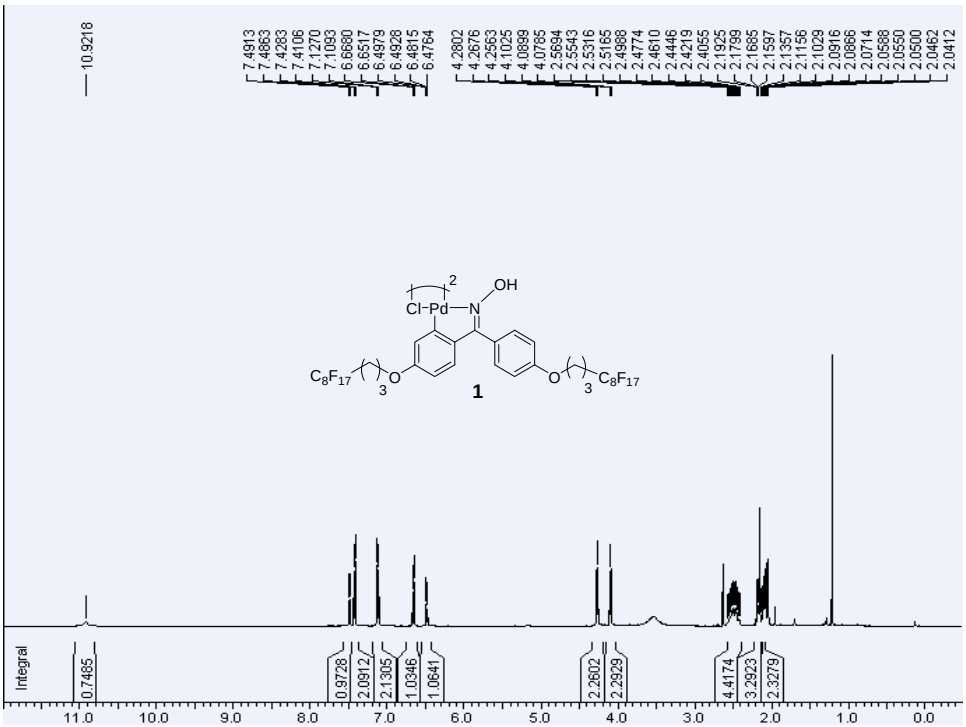
^{13}C NMR Spectrum of **6**



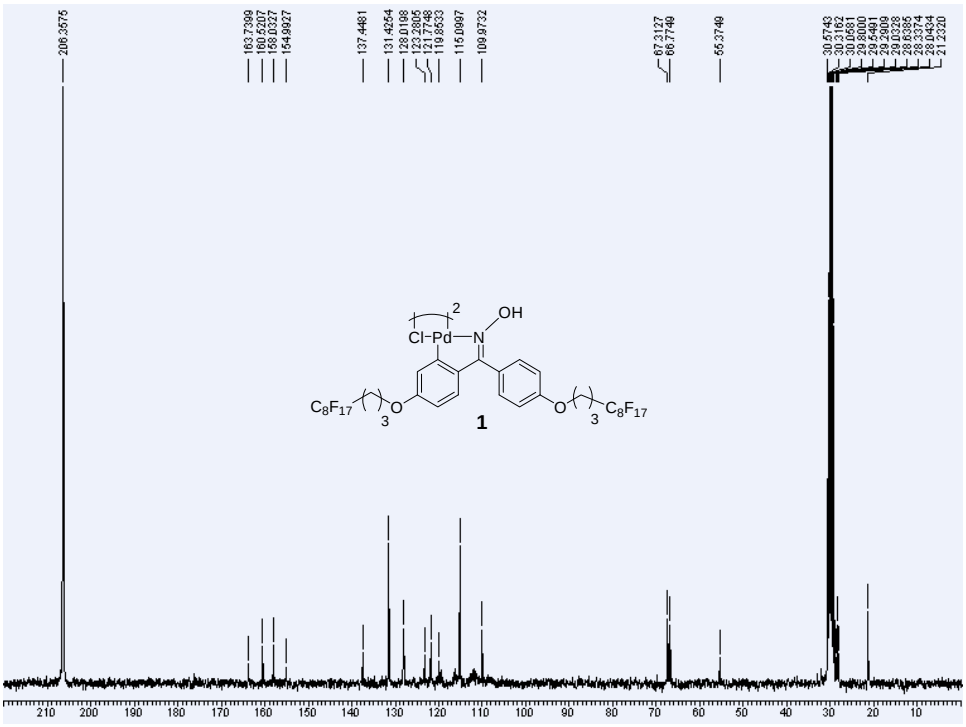
^{19}F NMR Spectrum of **6**



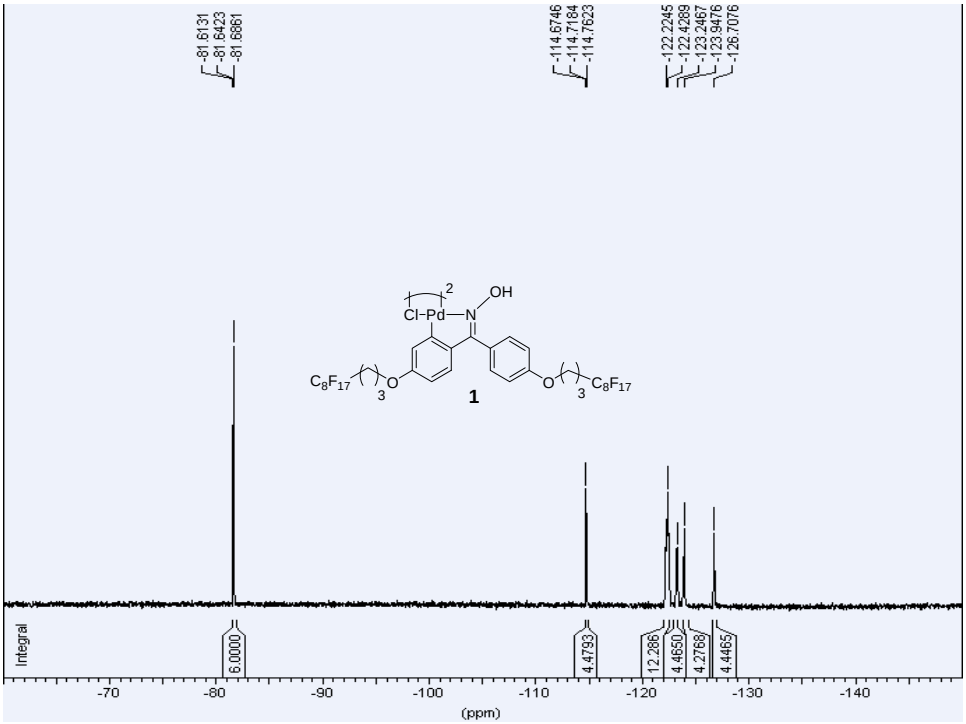
^{1}H NMR Spectrum of **1**



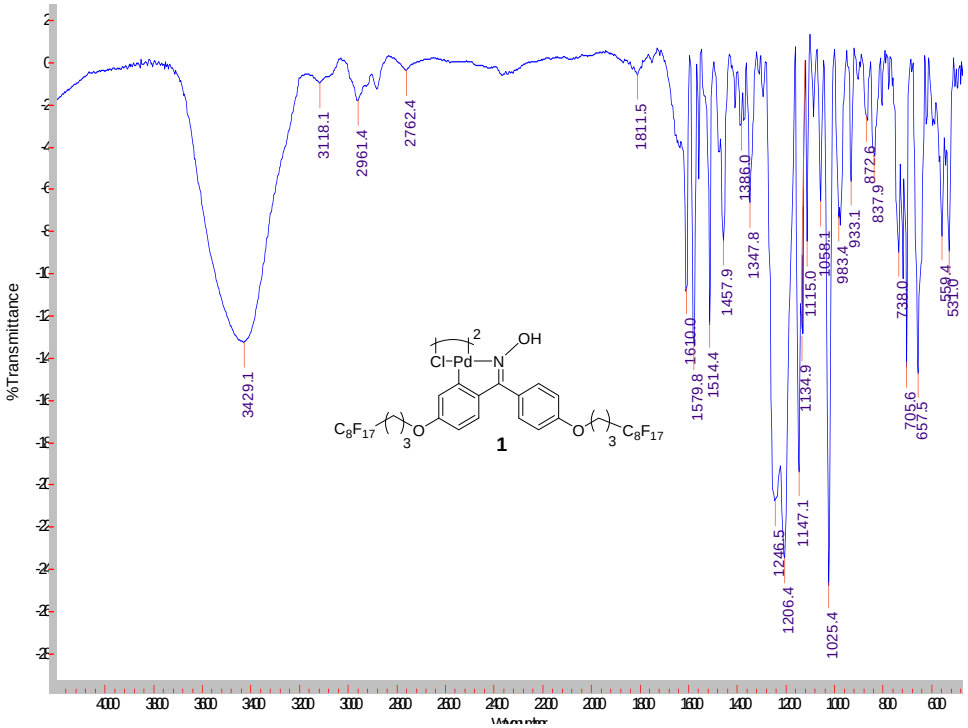
^{13}C NMR Spectrum of **1**



^{19}F NMR Spectrum of **1**



FTIR spectrum of **1**



NMR and Mass Spectrometry Characterization Data of the Known Compounds:

4-(trifluoromethyl)-biphenyl (8a): ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.71 (s, 4H), 7.62 (d, 1H, J = 7.6Hz), 7.51-7.47 (m, 2H), 7.44-7.41 (m, 1H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 144.7, 139.7, 129.3 (q, J = 32.3Hz), 129.0, 128.2, 127.6, 127.4, 127.3, 125.6 (q, J = 3.2Hz), 124.3 (q, J = 272.1Hz). HRMS (EI) calcd. for $C_{13}H_9F_3$: 222.0656, found: 222.06557.

4-(methoxy)-biphenyl (8b): ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.66-7.60 (m, 4H), 7.52-7.47 (m, 2H), 7.41-7.36 (m, 1H), 7.06 (d, 2H, J = 8.8Hz). ^{13}C NMR ($CDCl_3$, 75MHz): δ 159.1, 140.7, 133.7, 128.7, 128.1, 126.7, 126.6, 114.1, 55.2. HRMS (EI) calcd. for $C_{13}H_{12}O$: 184.0888, found: 184.0884.

Diphenylmethane (8c): ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.44-7.41 (m, 4H), 7.35-7.33 (m, 6H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 141.1, 128.9, 128.4, 126.0, 41.9. HRMS (EI) calcd. for $C_{13}H_{12}$: 168.0939, found: 168.0932.

4-(nitrile)-biphenyl (8d): ^{1}H NMR ($CDCl_3$, 500MHz): δ 8.23-8.21 (m, 2H), 7.67-7.65 (m, 2H), 7.57-7.55 (m, 2H), 7.40-7.38 (m, 3H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 145.5, 139.0, 132.5, 129.0, 128.6, 127.6, 127.1, 118.8, 110.8. HRMS (EI) calcd. for $C_{13}H_9N$: 179.0735, found: 179.0731.

1-nitro-4-(2-phenylethynyl)benzene (10a): ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.73-7.66 (m, 4H), 7.61-7.58 (m, 2H), 7.52-7.41 (m, 3H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 146.9, 132.2, 131.8, 130.2, 129.2, 128.5, 123.6, 122.0, 94.7, 87.5. HRMS (EI) calcd. for $C_{14}H_9NO_2$: 223.0633, found: 223.0634.

1,2-diphenylethyne (10b): ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.57-7.56 (m, 2H), 7.45-7.32 (m, 8H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 131.6, 128.5, 128.4, 121.9, 96.9, 88.6. HRMS (EI) calcd. for $C_{14}H_{10}$: 178.0783, found: 178.0781.

1-chloro-4-(2-phenylethynyl)benzene (10c): ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.51-7.55 (m, 2H), 7.46 (d, 2H, J = 1.9Hz), 7.38-7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 134.2, 132.8, 131.6, 128.7, 128.5, 128.4, 122.9, 121.8, 90.3, 88.2. HRMS (EI) calcd. for $C_{14}H_9Cl$: 212.0393, found: 212.0392.

4'-methoxybiphenyl-2-carbaldehyde (12a): ^{1}H NMR ($CDCl_3$, 500MHz): δ 9.99 (s, 1H), 8.01-7.99 (m, 1H), 7.63-7.60 (m, 1H), 7.47-7.42 (m, 2H), 7.32-7.29 (m, 2H), 7.02-6.99 (m, 2H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 192.6, 159.6, 145.6, 133.7, 133.5, 131.2, 130.7, 129.9, 127.5, 127.3, 113.9, 55.3. HRMS (EI) calcd. for $C_{14}H_{12}O_2$: 212.0837, found: 212.0838.

5-(4-methoxyphenyl)pyrimidine (12b): ^{1}H NMR ($CDCl_3$, 500MHz): δ 9.14 (s, 1H), 8.90 (s, 2H), 7.51 (d, 2H, J = 8.9Hz), 7.03 (d, 2H, J = 8.9Hz), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 160.4, 156.8, 154.4, 133.9, 128.1, 126.5, 114.9, 55.4. HRMS (EI) calcd. for $C_{11}H_{10}ON_2$: 186.0793, found: 186.0794.

4'-methoxybiphenyl (12c): ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.57-7.53 (m, 4H), 7.44-7.41 (m, 2H), 7.33-7.30 (m, 1H), 7.00-6.98 (m, 2H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3. HRMS (EI) calcd. for $C_{13}H_{12}O$: 184.0888 found: 184.0887.