Water-soluble palladium reagents for cysteine *S*-arylation under ambient aqueous conditions

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SUPPORTING INFORMATION

1. GENERAL EXPERIMENTAL DETAILS

General Reagent Information

1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU), D-Biotin, Fmoc-Rink amide linker, Fmoc-L-Gly-OH, Fmoc-L-Leu-OH, Fmoc-L-Lys(Boc)-OH, Fmoc-L-Ala-OH, Fmoc-L-Cys(Trt)-OH, Fmoc-L-Gln(Trt)-OH, Fmoc-L-Asn(Trt)-OH, Fmoc-L-Glu(O*t*Bu)-OH, Fmoc-L-Arg(Pbf)-OH, Fmoc-L-Phe-OH, Fmoc-L-Ser(*t*Bu)-OH, Fmoc-L-Thr(*t*Bu)-OH, Fmoc-L-Tyr(*t*Bu)-OH, and Fmoc-L-His(Trt)-OH were purchased from CreoSalus, Inc (Louisville, KY). Peptide synthesis-grade *N,N*-dimethylformamide (DMF), dichloromethane (CH_2Cl_2), diethyl ether, HPLC-grade acetonitrile, and guanidine hydrochloride were obtained from VWR International (Philadelphia, PA). Aryl halides and aryl trifluoromethanesulfonates were purchased from Aldrich Chemical Co., Alfa Aesar, or Matrix Scientific and were used without additional purification. All deuterated solvents were purchased from Cambridge Isotopes and used without further purification. All other reagents were purchased from Sigma-Aldrich and used as received.

All reactions with peptides were set up on the bench top and carried out under ambient conditions. Anhydrous THF, pentane, cyclohexane, and acetonitrile were purchased from Aldrich Chemical Company in SureSeal® bottles and were purged with argon before use.

All small-molecule organic and organometallic compounds were characterized by ^{1}H, ^{13}C NMR, and IR spectroscopy, as well as elemental analysis or high-resolution mass spectrometry (unless otherwise noted). ^{31}P NMR spectroscopy was used for characterization of palladium complexes. Copies of the ^{1}H, ^{13}C, and ^{31}P NMR spectra can be found at the end of the Supporting Information. Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instrument and a Varian 300 MHz instrument. Unless otherwise stated, all ^{1}H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals of the residual proton resonances methanol-d_4 (4.78 and 3.31 ppm) in the deuterated solvents. All ^{13}C NMR spectra are measured decoupled from ^{1}H nuclei and are reported in δ units (ppm) relative to methanol-d_4 (49.30 ppm), unless otherwise stated. All ^{31}P NMR spectra are measured decoupled from ^{1}H nuclei and are reported relative to H_3PO_4 (0.00 ppm). All FT-IR spectra were recorded on a Thermo Scientific – Nicolet iS5 spectrometer (iD5 ATR – diamond). High resolution mass spectra were obtained on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS).

LC-MS chromatograms and associated mass spectra were acquired using Agilent 6520 ESI-Q-TOF mass spectrometer. Solvent compositions used in the LC-MS are 0.1% formic acid in H_2O (solvent A) and 0.1% formic acid in acetonitrile (solvent B). The following LC-MS method was used:

Method A LC conditions: Zorbax 300SB C3 column: 2.1 x 150 mm, 5 μm, column temperature: 40 °C, gradient: 0-3 min 5% B, 3-8 min 5-95% B, 8-9 min 95% B, flow rate: 0.8 mL/min. MS conditions: positive electrospray ionization (ESI) extended dynamic mode in mass range 300 – 3000 *m/z*, temperature of drying gas = 350 °C, flow rate of drying gas = 11 L/min, pressure of nebulizer gas = 60 psi, the capillary, fragmentor, and octapole rf voltages were set at 4000, 175, and 750, respectively.

Determination of Bioconjugation and Macrocyclization Yields

Data were processed using Agilent MassHunter software package. All reported yields were determined by integrating total ion current (TIC) spectra. First, the peak areas for all relevant peptide-containing species on the chromatogram were integrated using Agilent MassHunter software package. Since no peptide-based side products were generated in the experiments, the yields shown in **Table 2** were determined as follows: %yield = S_{pr}/S_{total} where S_{pr} is the peak area of the product and S_{total} is the peak area of combined peptide-containing species (product and starting material). For protein bioconjugation, deconvoluted masses of proteins were obtained using maximum entropy algorithm. LC-MS data shown were acquired using Method A, unless otherwise noted. Mass spectrum insets correspond to the integration of the TIC peak unless otherwise noted.

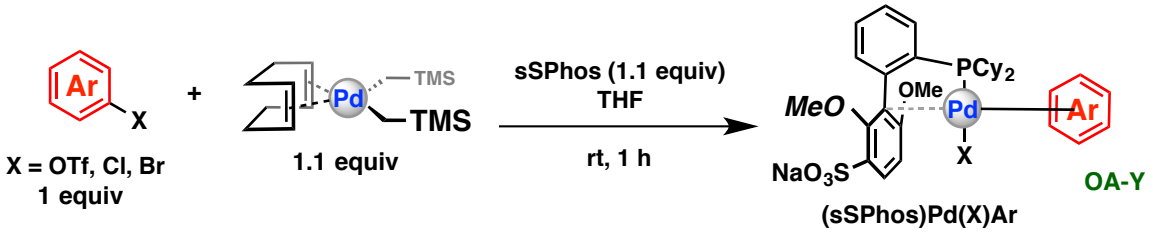
In addition to this method, reaction **P3-1** was scaled up and subsequently purified via mass-directed preparative HPLC and in order to determine isolated yield. The results of this isolation can be found on page S24 under the subheading Large Scale Bioconjugation.

2. Oxidative Addition Complexes and Synthetic Procedures

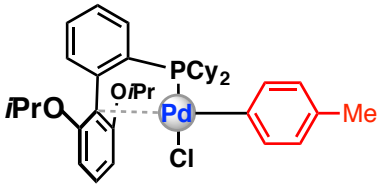
Synthesis of Oxidative Addition Complexes

Synthesis of [(1,5-COD)Pd($CH_2TMS)_2$]. A round bottom flask (100 mL), equipped with a magnetic stir bar, was charged with (1,5-COD)$PdCl_2$ (3.15g, 11.05 mmol) made according to literature reports.[1] Diethyl ether (49.3 mL) was added via syringe, the reaction was cooled to –40 °C (acetonitrile/dry ice bath) and $TMSCH_2MgCl$ (23.4 mL, 1.0 M purchased from Sigma-Aldrich) was added dropwise over 10–20 min. The reaction mixture was stirred at –40 °C for 1 h and then at 0 °C (ice/water bath) for an additional 20 min. Acetone (1.3 mL) was added via syringe at 0 °C, the reaction mixture was stirred for 5 min, at which time the solvent was removed under vacuum using an external trap (the flask was kept at 0 °C). The flask was then opened to air, pentane (100 mL) was added and the crude material was filtered through a pad of Celite into a new round-bottom flask (500 mL) at 0 °C. The filter cake was washed with pentane (50 mL × 2). Pentane from the combined washes was removed with the aid of a rotary evaporator at 0 °C (ice/water bath). The resulting white solid was dried under vacuum for 2 h at 0 °C, and transferred into a 20 mL scintillation vial (3.00 g, 70%). The ^1H and ^{13}C NMR spectra of the obtained material are identical to those reported in the literature.[1] The title compound was stored in a freezer at –20 °C.

General Procedure for the Synthesis of mono-Palladium Oxidative Addition Complexes.

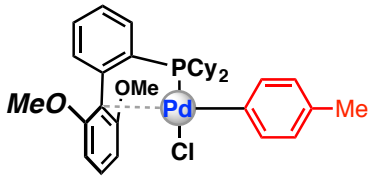


In a scintillation vial (10 mL) open to the air and equipped with a magnetic stir bar, the vial was charged with ligand (1.1 equiv), Ar–X (1 equiv), and THF (1 mL). Solid (1,5-COD)$Pd(CH_2SiMe_3)_2$ (1.1 equiv) was added rapidly in one portion and the resulting solution was stirred for 1 h at rt. After this time, pentane (3 mL) was added and the resulting mixture was capped and placed into a –20 °C freezer for 2 h. The vial was removed from the freezer and the resulting precipitate was filtered, washed with pentane (5 × 3 mL), and dried under reduced pressure to afford the oxidative addition complex.



OA-1

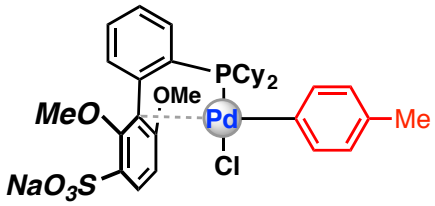
Following the general procedure, a mixture containing 4-chlorotoluene (6.4 μL, 0.054 mmol), RuPhos (28 mg, 0.06 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (25 mg, 0.06 mmol) was stirred at rt in a nitrogen-filled glovebox in cyclohexane (1.5 mL) for 18 h. The vial was removed from the glovebox, opened to the air, and general work-up afforded **OA-1** as a grey solid (37 mg, 96%). The ^{1}H and ^{13}C NMR spectra of the obtained material are identical to those reported in the literature.[1]



OA-2

Following the general procedure, a mixture containing 4-chlorotoluene (6.4 μL, 0.054 mmol), SPhos (24.6 mg, 0.06 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (25 mg, 0.06 mmol) was stirred at rt in a nitrogen-filled glovebox in cyclohexane (1.5 mL) for 18 h. General work-up afforded **OA-2** as a white solid (33 mg, 93%). The ^{1}H and ^{13}C NMR spectra of the obtained material are identical to those reported in the literature.[1]

HRMS electrospray (m/z): $[M - Cl]^+$ calcd for $C_{33}H_{42}ClO_2PPd$: 607.1969, found 607.1962.

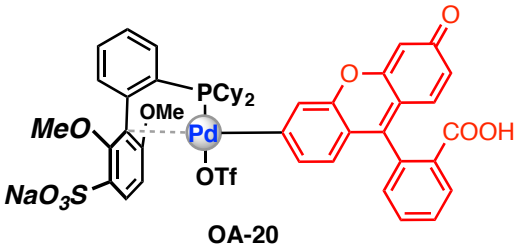


OA-3

Following the general procedure, a mixture containing 4-chlorotoluene (6.4 μL, 0.054 mmol), sSPhos (33 mg, 0.06 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (25 mg, 0.06 mmol)

was stirred at rt in THF (1 mL) for 1 h. General work-up afforded **OA-3** as a yellow solid (41 mg, 99%).

^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ 161.39, 161.35, 157.73, 157.61, 139.18, 138.45, 138.38, 138.05, 135.46, 135.37, 135.19, 134.96, 134.89, 134.04, 133.08, 132.63, 132.49, 132.25, 132.02, 131.99, 131.80, 131.22, 130.20, 130.01, 129.50, 129.39, 129.09, 128.98, 128.54, 128.43, 126.96, 126.92, 126.90, 107.08, 107.02, 69.14, 64.04, 62.36, 61.71, 57.04, 56.68, 49.94, 49.73, 49.51, 49.30, 49.09, 48.88, 48.66, 39.00, 38.55, 38.35, 37.90, 35.49, 31.49, 29.24, 28.73, 28.69, 28.00, 27.96, 27.91, 27.83, 27.78, 27.70, 27.51, 27.44, 27.39, 27.34, 27.31, 27.14, 26.85, 26.82, 26.78, 26.58, 26.39, 25.92, 21.79, 20.98. (observed complexity is due to *C–P* coupling)**. ^{31}P NMR (121 MHz, MeOD)** δ 52.85. **FT-IR (neat, cm^{-1}):** 3438.12, 2929.53, 2849.99, 1570.73, 1438.17, 1395.08, 1275.77, 1229.37, 1176.35, 1106.75, 1083.55, 1053.72, 1017.27, 914.53, 894.65, 851.56, 815.11, 762.08, 702.43, 665.97, 652.71. **HRMS electrospray (m/z): [M – Cl]$^{+}$ calcd for $C_{33}H_{41}ClNaO_5PPdS$:** 709.1345, found 709.1337.

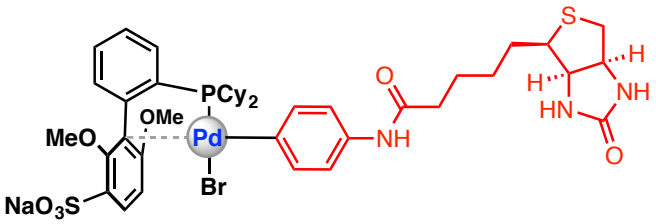


OA-20

Following the general procedure, a mixture containing fluorescein monotrifluoromethanesulfonate (30 mg, 0.054 mmol), sSPhos (33 mg, 0.06 mmol), and (1,5-COD)Pd(CH_2TMS)$_2$ (25 mg, 0.06 mmol) was stirred at rt in THF (1 mL) for 1 h. General work-up afforded **OA-20** as a red solid (54 mg, 94%).

^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 171.22, 161.31, 157.55, 153.75, 153.62, 151.81, 150.75, 138.53, 138.46, 137.21, 135.48, 135.38, 134.85, 134.78, 134.18, 132.94, 132.46, 132.01, 131.99, 131.83, 131.72, 131.63, 131.16, 130.42, 128.53, 128.43, 127.93, 126.88, 126.86, 125.50, 123.61, 121.96, 121.68, 120.45, 118.78, 118.27, 111.88, 110.86, 108.61, 107.06, 104.01, 62.35, 57.39, 57.01, 56.66, 49.94, 49.73, 49.51, 49.30, 49.09, 48.88, 48.66, 39.02, 38.39, 38.36, 37.73, 35.86, 28.64, 28.61, 28.13, 27.86, 27.83, 27.78, 27.73, 27.66, 27.52, 27.48, 27.46, 27.39, 27.31, 27.26, 27.23, 27.11, 26.81, 26.77. (observed complexity is due to *C–P* coupling)**. ^{31}P NMR (121 MHz, MeOD)** δ 55.32. **FT-IR (neat, cm^{-1}):** 2939.44, 2365.12, 2334.10, 2229.64, 2193.02, 2171.53, 2162.71, 2154.39, 2030.18,

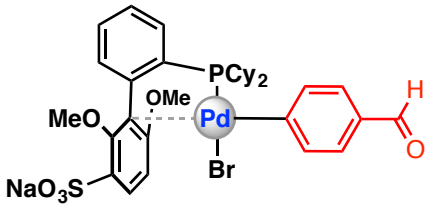
2020.55, 1768.04, 1578.01, 1451.18, 1425.24, 1400.41, 1295.66, 1257.24, 1224.09, 1172.18, 1100.84, 1052.69, 1019.40, 990.73, 848.30, 759.20, 652.11, 596.38. **HRMS electrospray (m/z): [M – OTf]$^+$ calcd for $C_{47}H_{45}F_3NaO_{12}PPdS_2$:** 933.1468, found 933.1496.



OA-21

Following the general procedure, a mixture containing aryl bromide (biotin) (30 mg, 0.054 mmol), sSPhos (33 mg, 0.06 mmol), and (1,5-COD)Pd(CH_2TMS)$_2$ (25 mg, 0.06 mmol) was stirred at rt in THF (1 mL) for 1 h. General work-up afforded **OA-21** as a pink solid (54 mg, 99%).

^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 161.36, 161.36, 157.63, 138.35, 135.44, 134.98, 133.14, 133.02, 132.73, 131.99, 131.25, 128.54, 128.44, 126.93, 123.13, 107.07, 62.37, 56.68, 49.94, 49.72, 49.51, 49.30, 49.09, 48.88, 48.85, 48.66, 38.96, 38.69, 38.31, 28.75, 28.07, 27.70, 27.50, 27.37, 27.12, 26.85. (observed complexity is due to *C–P* coupling**). ^{31}P NMR (121 MHz, MeOD)** δ 53.89. **FT-IR (neat, cm^{-1}):** 3282.15, 2919.10, 2851.48, 1688.19, 1586.10, 1521.18, 1586.10, 1488.30, 1451.98, 1395.17, 1275.99, 1226.01, 1185.10, 1099.39, 1049.20, 1007.70, 853.33, 815.64, 764.68, 688.85, 677.29, 667.72, 648.10, 595.07. **HRMS electrospray (m/z): [M – Br]$^+$ calcd for $C_{42}H_{54}BrN_3NaO_7PPdS_2$:** 936.2085, found 936.2087.

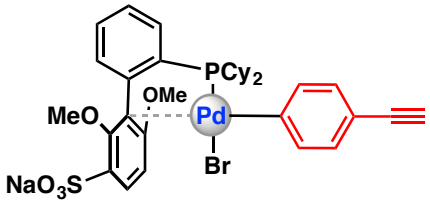


OA-22

Following the general procedure, a mixture containing 4-chlorobenzaldehyde (8.4 mg, 0.054 mmol), sSPhos (31 mg, 0.06 mmol), and (1,5-COD)Pd(CH_2TMS)$_2$ (25 mg, 0.06 mmol) was stirred at rt in THF (1 mL) for 1 h. General work-up afforded **OA-22** as a

white solid (36 mg, 89%).

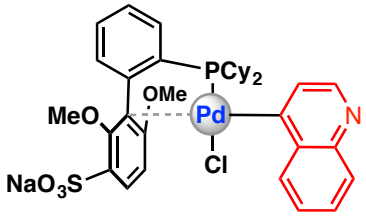
^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, CD_2Cl_2)** δ 161.29, 157.50, 135.52, 135.42, 134.71, 132.77, 132.07, 131.10, 128.57, 128.47, 126.83, 107.07, 69.12, 62.34, 57.51, 56.69, 49.94, 49.73, 49.51, 49.30, 49.09, 48.87, 48.66, 39.06, 38.41, 38.18, 37.52, 35.84, 35.44, 29.23, 27.84, 27.70, 27.66, 27.46, 27.35, 27.13, 26.76, 23.64, 14.68, -1.12. (observed complexity is due to *C–P* coupling**). ^{31}P NMR (121 MHz, MeOD)** δ 55.14. **FT-IR (neat, cm^{-1}):** 3501.12, 2928.70, 2849.99, 2361.49, 2344.31, 1690.19, 1571.43, 1550.27, 1450.50, 1398.96, 1211.92, 1098.84, 1050.83, 1008.78, 834.27, 808.78, 759.26, 693.54, 667.90, 662.51, 639.86, 590.44. **HRMS electrospray (m/z): [M – Br]$^{+}$ calcd for $C_{33}H_{39}BrNaO_6PPdS$:** 723.1148, found 723.1158.



OA-23

Following the general procedure, a mixture containing 4-bromophenylacetylene (9.7 mg, 0.054 mmol), sSPhos (31 mg, 0.06 mmol), and (1,5-COD)Pd(CH_2TMS)$_2$ (25 mg, 0.06 mmol) was stirred at rt in THF (1 mL) for 1 h. General work-up afforded **OA-23** as a yellow solid (36 mg, 89%).

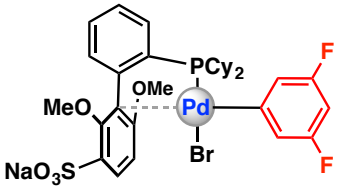
^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD** δ 161.54, 157.79, 138.72, 138.65, 135.69, 135.60, 135.11, 135.04, 133.22, 132.74, 132.24, 132.22, 131.91, 131.40, 128.76, 128.66, 127.10, 107.29, 69.35, 62.57, 56.89, 50.15, 49.94, 49.73, 49.51, 49.30, 49.09, 48.87, 43.15, 39.23, 38.66, 38.58, 38.01, 28.90, 28.71, 28.10, 28.03, 27.97, 27.90, 27.71, 27.67, 27.61, 27.35, 27.05, 27.01, 26.99. (observed complexity is due to *C–P* coupling**). ^{31}P NMR (121 MHz, MeOD)** δ 58.96. **FT-IR (neat, cm^{-1}):** 3430.11, 3200.11, 2929.69, 2852.02, 1247071, 2339.26, 1572.29, 1450.85, 1398.15, 1228.42, 1098.54, 1050.80, 1009.71, 916.01, 849.38, 812.33, 759.15, 693.48, 667.86, 656.56, 585.72 **HRMS electrospray (m/z): [M – Br]$^{+}$ calcd for $C_{34}H_{39}BrNaO_5PPdS$:** 719.1199, found 719.1217.



OA-24

Following the general procedure, a mixture containing 4-chloroquinoline (9.8 mg, 0.054 mmol), sSPhos (31 mg, 0.06 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (25 mg, 0.06 mmol) was stirred at rt in THF (1 mL) for 1 h. General work-up afforded **OA-24** as a light brown solid (40 mg, 94%).

^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ 161.56, 157.82, 138.59, 135.68, 135.58, 135.18, 135.11, 133.28, 132.83, 132.21, 132.00, 131.43, 128.76, 128.65, 127.13, 107.29, 69.35, 62.58, 56.89, 50.15, 49.94, 49.73, 49.51, 49.30, 49.09, 48.88, 39.21, 38.76, 38.56, 38.10, 36.10, 35.81, 28.91, 28.17, 28.11, 28.04, 27.98, 27.90, 27.72, 27.52, 27.35, 27.03, 26.99, 23.88, 14.88 (observed complexity is due to *C–P* coupling)**. ^{31}P NMR (121 MHz, MeOD)** δ 52.73. **FT-IR (neat, cm^{-1}):** 3418.60, 2928.65, 2849.95, 2360.04, 2339.28, 1572.13, 1495.74, 1450.01, 1398.16, 1367.97, 1280.36, 1189.32, 1097.91, 1049.60, 915.43, 813.53, 693.38, 635.12, 594.93. **HRMS electrospray (m/z): [M – Cl]$^+$ calcd for $C_{35}H_{40}ClNNaO_5PPdS$:** 746.1308, found 746.1310.



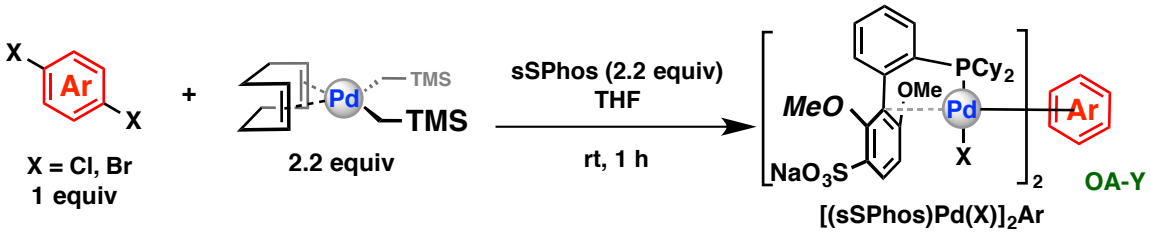
OA-25

Following the general procedure, a mixture containing 1-Bromo-3,5-difluorobenzene (9.8 mg, 0.054 mmol), sSPhos (31 mg, 0.06 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (25 mg, 0.06 mmol) was stirred at rt in THF (1 mL) for 1 h. General work-up afforded **OA-25** as a yellow solid (45 mg, 99%).

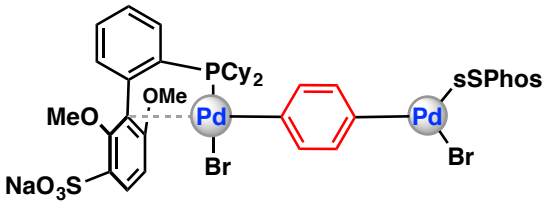
^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ 163.75, 161.83, 161.35, 160.11, 158.07, 157.60, 155.19, 138.44, 138.36, 136.21, 135.48, 135.38, 134.96, 134.88, 133.03, 132.89, 132.57, 132.04, 132.01, 131.91, 131.74, 131.21, 130.32, 129.10,

128.56, 128.46, 127.24, 126.91, 126.89, 112.56, 112.49, 112.38, 112.31, 108.10, 107.07, 105.09, 104.83, 104.58, 69.15, 62.43, 62.36, 61.71, 56.86, 56.68, 49.94, 49.73, 49.51, 49.30, 49.09, 48.87, 48.66, 40.13, 38.99, 38.52, 38.34, 37.87, 32.17, 28.72, 27.98, 27.90, 27.82, 27.77, 27.69, 27.51, 27.44, 27.39, 27.31, 27.13, 26.84, 26.79, 9.92, 0.26, -1.91 (observed complexity is due to *C-P* coupling). **^{31}P NMR (121 MHz, MeOD)** δ 52.68. **FT-IR (neat, cm^{-1}):** 3390.01, 2931.31, 2849.99, 2362.81, 2344.29, 1597.25, 1577.36, 1448.11, 1398.96, 1227.38, 1182.98, 1100.89, 1023.90, 997.38, 968.81, 924.47, 897.96, 840.21, 808.48, 759.58, 699.11, 662.66, 590.27. **HRMS electrospray (m/z): [M – Br]$^+$ calcd for $C_{32}H_{37}BrF_2NaO_5PPdS$:** 731.1010, found 731.1020.

General Procedure for the Synthesis of bis-Palladium Oxidative Addition Complexes.



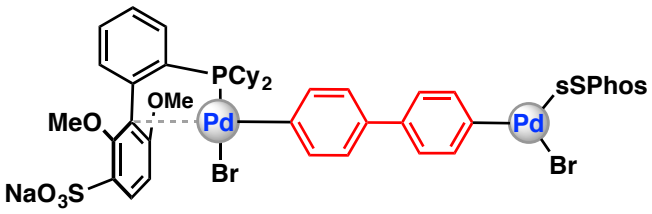
A scintillation vial (10 mL), equipped with a magnetic stir bar, was charged with sSPhos (2.2 equiv), Ar–X (1 equiv), and THF (1.5 mL). Solid (1,5-COD)Pd(CH_2SiMe_3)$_2$ (2.2 equiv) was added rapidly in one portion and the resulting solution was stirred for 1 h at rt. After this time, pentane (3 mL) was added and the resulting mixture was placed into a –20 °C freezer for 2 h. The vial was removed from the freezer and, in the air, the resulting precipitate was filtered, washed with pentane (5 × 3 mL), and dried under reduced pressure to afford the oxidative addition complex.



OA-7

Following the general procedure, a mixture containing 1,4-dibromobenzene (12.7 mg, 0.054 mmol), sSPhos (61 mg, 0.119 mmol), and (1,5-COD)Pd(CH_2TMS)$_2$ (46 mg, 0.119 mmol) was stirred at rt in THF (1.5 mL) for 1 h. General work-up afforded **OA-7** as a brown solid (76 mg, 96%).

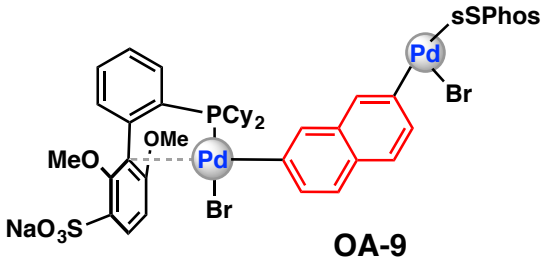
^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** d 161.33, 157.58, 135.48, 134.89, 134.82, 133.01, 132.02, 132.00, 131.18, 128.54, 128.44, 107.07, 69.14, 62.35, 56.68, 49.94, 49.73, 49.51, 49.30, 49.09, 48.87, 48.66, 39.02, 38.45, 38.37, 37.79, 27.89, 27.81, 27.76, 27.69, 27.50, 27.30, 27.14, 26.78, 2.88, -1.91. (observed complexity is due to *C–P* coupling)**. ^{31}P NMR (121 MHz, MeOD)** d 50.93. **FT-IR (neat, cm^{-1}):** 3440.34, 2919.59, 2849.99, 2372.76, 2154.02, 1646.96, 1574.05, 1458.05, 1441.48, 1395.08, 1275.77, 1226.06, 1176.35, 1159.78, 1100.12, 1053.72, 1010.64, 944.07, 914.53, 891.33, 851.66, 798.54, 758.77, 732.25, 692.48, 646.08. **HRMS electrospray (m/z): [M – NaBr$_2$]$^+$ calcd for $C_{58}H_{72}Br_2Na_2O_{10}P_2Pd_2S_2$:** 1291.2038, found 1291.2011.



OA-8

Following the general procedure, a mixture containing 4,4-Dibromobiphenyl (16.8 mg, 0.054 mmol), sSPhos (61 mg, 0.119 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (46 mg, 0.119 mmol) was stirred at rt in THF (1.5 mL) for 1 h. General work-up afforded **OA-8** as a brown solid (81 mg, 96%).

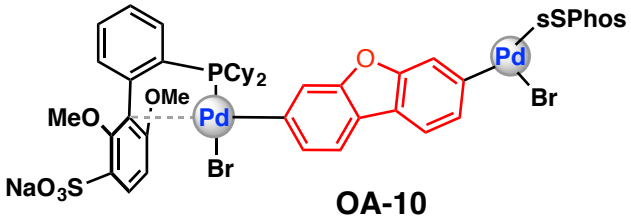
^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** d 161.31, 134.81, 132.90, 132.04, 131.59, 131.15, 129.59, 128.55, 128.45, 127.51, 107.07, 62.35, 57.08, 56.68, 49.94, 49.73, 49.51, 49.30, 49.09, 48.87, 48.66, 39.04, 38.39, 37.68, 35.58, 27.80, 27.74, 27.68, 27.48, 27.23, 27.13, 26.77, 23.66, 14.68, 2.95, -1.43. (observed complexity is due to *C–P* coupling)**. ^{31}P NMR (121 MHz, MeOD)** d 50.65. **FT-IR (neat, cm^{-1}):** 3461.21, 2929.43, 2846.68, 2361.39, 2163.96, 1576.27, 1450.80, 1141.65, 1272.46, 1232.69, 1179.17, 1096.81, 1051.15, 998.40, 924.47, 888.02, 851.56, 802.14, 759.54, 662.66, 656.69, 639.46. **HRMS electrospray (m/z): [M – NaBr$_2$]$^+$ calcd for $C_{64}H_{76}Br_2Na_2O_{10}P_2Pd_2S_2$:** 1367.2354, found 1367.2304.



OA-9

Following the general procedure, a mixture containing 2,6-Dibromonaphthalene (12.7 mg, 0.044 mmol), sSPhos (50 mg, 0.01 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (38 mg, 0.01 mmol) was stirred at rt in THF (1.5 mL) for 1 h. General work-up afforded **OA-9** as a light red solid (63 mg, 94%).

^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ ^{13}C NMR (101 MHz, MeOD) δ 159.73, 159.65, 155.98, 155.88, 137.04, 136.97, 133.88, 133.79, 133.47, 133.08, 133.00, 131.18, 130.75, 130.64, 130.57, 130.41, 129.81, 129.47, 128.35, 127.45, 127.34, 126.92, 126.80, 125.28, 125.22, 125.20, 105.43, 105.40, 67.49, 60.71, 60.11, 55.87, 55.06, 55.05, 48.31, 48.09, 47.88, 47.67, 47.45, 47.24, 47.03, 37.44, 36.78, 36.54, 35.88, 34.21, 33.93, 26.91, 26.21, 26.15, 26.08, 26.03, 25.92, 25.83, 25.73, 25.50, 25.13, 22.01, 13.05, -1.36, -2.95, -3.05. (observed complexity is due to *C–P* coupling**). ^{31}P NMR (121 MHz, MeOD)** δ 52.23. **FT-IR (neat, cm^{-1}):** 3438.11, 2928.54, 2850.71, 2361.41, 2339.24, 2151.04, 1637.01, 1572.72, 1450.76, 1398.53, 1275.60, 1180.17, 1098.57, 1017.90, 917.07, 872.32, 845.66, 805.86, 758.91, 693.63, 667.85, 640.04, 554.21. **HRMS electrospray (m/z): [M – $Na_2Br]^-$ calcd for $C_{62}H_{74}Br_2Na_2O_{10}P_2Pd_2S_2$:** 1397.1481, found 1397.1495.

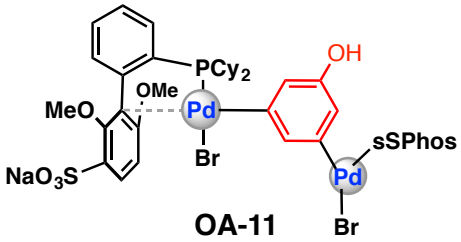


OA-10

Following the general procedure, a mixture containing 2,8-dibromodibenzofuran (14.3 mg, 0.044 mmol), sSPhos (50 mg, 0.01 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (38 mg, 0.01 mmol) was stirred at rt in THF (1.5 mL) for 1 h. General work-up afforded **OA-10** as a brown solid (67.3 mg, 98%).

^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ 159.65, 155.90, 136.90, 136.83,

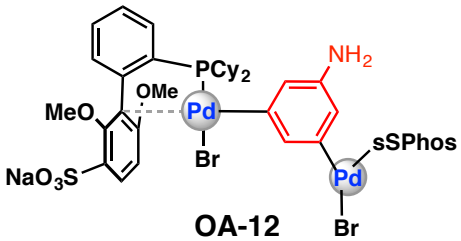
133.49, 131.28, 130.78, 130.44, 129.95, 129.62, 129.38, 128.46, 128.21, 125.22, 105.89, 104.94, 68.44, 67.97, 67.48, 55.77, 55.28, 54.77, 48.28, 48.18, 48.07, 47.86, 47.65, 47.43, 47.22, 47.01, 36.42, 25.76, 25.12, 22.01, 12.91. (observed complexity is due to *C–P* coupling**). ^{31}P NMR (121 MHz, MeOD)** δ 52.13. **FT-IR (neat, cm^{-1}):** 3431.09 2928.88, 2846.68, 2361.40 2339.29, 1576.61, 1450.75, 1398.27, 1275.76, 1184.90, 1098.21, 1184.90, 924.47, 891.33, 854.88, 805.64, 693.56, 618.24, 590.59. **HRMS electrospray (m/z): [M – $NaBr_2$]$^+$ calcd for $C_{64}H_{74}Br_2Na_2O_{11}P_2Pd_2S_2$:** 1381.2146, found 1381.2172.



OA-11

Following the general procedure, a mixture containing 3,5-Dibromophenol (11.2 mg, 0.044 mmol), sSPhos (50 mg, 0.01 mmol), and (1,5-COD)Pd(CH_2TMS)$_2$ (38 mg, 0.01 mmol) was stirred at rt in THF (1.5 mL) for 1 h. General work-up afforded **OA-11** as a light red solid (55 mg, 86%).

^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ 161.14, 157.39, 138.12, 135.25, 135.16, 134.77, 134.70, 132.84, 132.39, 131.82, 131.56, 131.00, 128.35, 128.25, 126.69, 123.78, 106.86, 68.93, 62.15, 56.47, 49.73, 49.51, 49.30, 49.09, 48.87, 48.66, 48.45, 38.76, 38.35, 38.11, 37.69, 28.50, 27.77, 27.69, 27.61, 27.56, 27.48, 27.29, 27.09, 26.92, 26.63, 26.58, 23.48, 14.48 (observed complexity is due to *C–P* coupling**). ^{31}P NMR (121 MHz, MeOD)** δ 54.69. **FT-IR (neat, cm^{-1}):** 3439.91, 2929.07, 2851.92, 2360.02, 2339.23, 1572.55, 1495.89, 1449.24, 1398.44, 1275.67, 1180.53, 1097.678, 1049.39, 1017.65, 915.80, 890.18, 813.09, 758.97, 731.45, 693.45, 667.85, 639.68, 599.38. **HRMS electrospray (m/z): [M – Na_2Br]$^-$ calcd for $C_{58}H_{72}Br_2Na_2O_{11}P_2Pd_2S_2$:** 1363.1273, found 1363.1279.

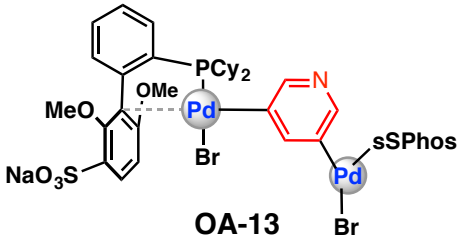


OA-12

Following the general procedure, a mixture containing 3,5-Dibromoaniline (11.2 mg,

0.044 mmol), sSPhos (50 mg, 0.01 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (38 mg, 0.01 mmol) was stirred at rt in THF (1.5 mL) for 1 h. General work-up afforded **OA-12** as a brown solid (68 mg, 99%).

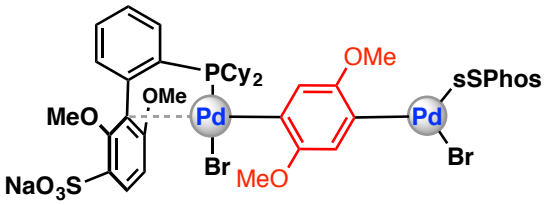
^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ 159.68, 155.91, 133.82, 133.26, 133.18, 131.32, 130.37, 129.52, 126.89, 126.79, 125.23, 105.41, 67.47, 60.69, 55.01, 48.27, 48.06, 47.84, 47.63, 47.42, 47.20, 46.99, 37.32, 36.79, 36.67, 36.14, 33.93, 27.04, 27.00, 26.14, 26.09, 26.01, 25.77, 25.72, 25.63, 25.46, 25.11, 22.01, 13.02. (observed complexity is due to *C–P* coupling)**. ^{31}P NMR (121 MHz, MeOD)** δ 54.64. **FT-IR (neat, cm^{-1}):** 3438.02, 2929.17, 2850.03, 2360.11, 2344.27, 2156.91, 1576.54, 1450.55, 1400.19, 1275.83, 1226.92, 1179.84, 1098.40, 1051.05, 1017.72, 916.95, 889.51, 852.34, 815.45, 763.84, 693.63, 630.54, 575.96. **HRMS electrospray (m/z): [M – Na_2Br]$^-$ calcd for $C_{58}H_{73}Br_2NNa_2O_{10}P_2Pd_2S_2$:** 1362.1432, found 1362.1460.



OA-13

Following the general procedure, a mixture containing 3,5-Dibromopyridine (10.5 mg, 0.044 mmol), sSPhos (50 mg, 0.01 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (38 mg, 0.01 mmol) was stirred at rt in THF (1.5 mL) for 1 h. General work-up afforded **OA-13** as a brown solid (65 mg, 99%).

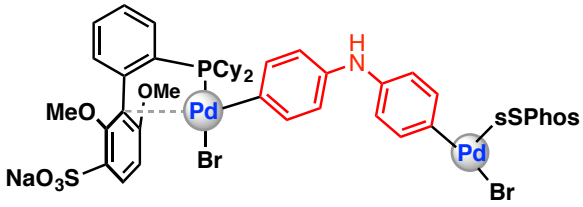
^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ 161.30, 160.89, 157.93, 157.52, 138.70, 135.53, 135.44, 134.73, 134.65, 132.83, 132.30, 132.05, 131.11, 128.55, 128.45, 126.87, 119.94, 107.78, 107.08, 72.31, 69.13, 62.34, 62.15, 57.47, 56.68, 49.94, 49.73, 49.51, 49.30, 49.09, 48.88, 48.66, 39.08, 38.42, 38.18, 37.52, 35.86, 35.57, 35.45, 31.55, 28.54, 27.71, 27.56, 27.47, 27.36, 26.77, 26.74, 26.58, 25.28, 23.65, 14.67 (observed complexity is due to *C–P* coupling)**. ^{31}P NMR (121 MHz, MeOD)** δ 52.54. **FT-IR (neat, cm^{-1}):** 3431.02, 2928.78, 2849.99, 2361.41, 2339.26, 1575.57, 1514.39, 1450.71, 1398.62, 1275.14, 1179.98, 1098.18, 1049.74, 1017.55, 916.89, 808.43, 748.89, 693.58, 667.83, 656.40, 629.29, 623.44, 618.19, 613.58, 608.38, 585.53. **HRMS electrospray (m/z): [M – Na_2Br]$^-$ calcd for $C_{57}H_{71}Br_2NNa_2O_{10}P_2Pd_2S_2$:** 1348.1276, found 1348.1303.



OA-14

Following the general procedure, a mixture containing 1,4-Dibromo-2,5-dimethoxybenzene (13.1 mg, 0.044 mmol), sSPhos (50 mg, 0.01 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (38 mg, 0.01 mmol) was stirred at rt in THF (1.5 mL) for 1 h. General work-up afforded **OA-14** as a brown solid (56 mg, 84%).

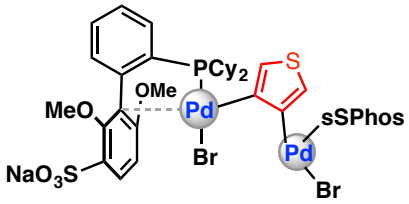
^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ 161.28, 157.50, 155.77, 151.98, 138.70, 138.63, 135.53, 135.43, 134.70, 133.38, 132.79, 132.23, 132.07, 131.40, 131.08, 128.56, 128.46, 126.84, 120.35, 115.84, 114.53, 113.05, 107.07, 106.50, 69.12, 62.33, 57.59, 57.52, 56.70, 56.66, 56.42, 56.15, 49.94, 49.73, 49.51, 49.30, 49.09, 48.87, 48.66, 39.07, 38.41, 38.11, 37.46, 35.84, 35.56, 35.44, 27.84, 27.77, 27.65, 27.45, 27.35, 27.13, 26.76, 26.73, 26.56, 25.27, 23.64, 14.67, -1.17 (observed complexity is due to *C–P* coupling)**. ^{31}P NMR (121 MHz, MeOD)** δ 52.47. **FT-IR (neat, cm^{-1}):** 3438.09, 2928.62, 2850.33, 2362.65, 2342.57, 1572.78, 1450.63, 1398.55, 1274.73, 1179.23, 1097.97, 1050.91, 1018.53, 917.05, 889.44, 845.20, 805.62, 758.86, 693.43, 667.84, 656.47, 630.17, 623.71, 618.06, 580.82. **HRMS electrospray (m/z): [M – Na_2Br]$^-$ calcd for $C_{60}H_{76}Br_2Na_2O_{12}P_2Pd_2S_2$:** 1407.1536, found 1407.1493.



OA-15

Following the general procedure, a mixture containing Bis(4-bromophenyl)amine (14.5 mg, 0.044 mmol), sSPhos (50 mg, 0.01 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (38 mg, 0.01 mmol) was stirred at rt in tetrahydrofuran (1.5 mL) for 1 h. General work-up afforded **OA-15** as a brown solid (61 mg, 90%).

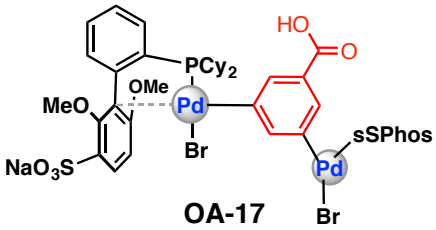
^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ 161.58, 161.51, 157.74, 145.69, 138.81, 138.73, 135.72, 135.62, 135.00, 134.92, 133.08, 132.54, 132.43, 132.27, 131.71, 131.34, 130.86, 130.46, 130.19, 129.31, 129.19, 128.77, 128.67, 127.07, 127.04, 122.28, 121.54, 120.15, 118.77, 107.28, 107.23, 69.34, 62.55, 61.93, 56.90, 50.15, 49.94, 49.72, 49.51, 49.30, 49.08, 48.87, 39.24, 38.59, 38.46, 37.80, 36.05, 35.79, 28.07, 27.99, 27.94, 27.87, 27.75, 27.68, 27.62, 27.55, 27.34, 26.99, 26.95, 26.78, 23.88, 14.90, -0.62, -1.26. **^{31}P NMR (121 MHz, MeOD)** δ 51.29. **FT-IR (neat, cm^{-1}):** 3433.28, 2929.21, 2849.91, 2361.32, 2339.25, 1576.44, 1549.56, 1527.65, 1449.33, 1398.11, 1275.60, 1180.69, 1098.13, 1049.70, 1017.93, 915.75, 888.02, 848.40, 758.90, 693.55, 559.72. **HRMS electrospray (m/z): [M – Na_2Br]$^-$ calcd for $C_{64}H_{77}Br_2NNa_2O_{10}P_2Pd_2S_2$:** 1438.1717, found 1438.1705.



OA-16

Following the general procedure, a mixture containing 3,4-Dibromothiophene (5 µL, 0.044 mmol), sSPhos (50 mg, 0.01 mmol), and (1,5-COD)Pd(CH_2TMS)$_2$ (38 mg, 0.01 mmol) was stirred at rt in THF (1.5 mL) for 1 h. General work-up afforded **OA-16** as a brown solid (57 mg, 89%).

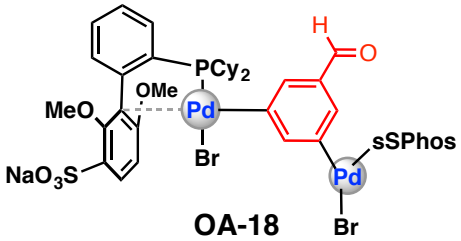
^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ ^{13}C NMR (101 MHz, MeOD) δ 161.67, 161.44, 161.28, 157.49, 135.54, 135.44, 134.67, 134.59, 133.84, 132.78, 132.06, 132.04, 131.39, 131.08, 129.79, 128.56, 128.45, 126.85, 124.69, 107.07, 104.95, 69.12, 63.94, 62.70, 62.33, 57.23, 56.69, 49.94, 49.73, 49.51, 49.30, 49.09, 48.87, 48.66, 39.08, 38.43, 38.10, 37.44, 32.32, 29.30, 29.18, 28.53, 27.84, 27.78, 27.71, 27.65, 27.46, 27.13, 26.77, 26.73, 2.91, 2.50, 2.45, 0.50 (observed complexity is due to *C–P* coupling**). ^{31}P NMR (121 MHz, MeOD)** δ 52.49. **FT-IR (neat, cm^{-1}):** 3391.02, 2928.68, 2852.01, 2360.05, 2339.30, 1576.87, 1450.45, 1399.99, 1274.77, 1226.06, 1179.26, 1098.10, 1051.00, 1017.61, 917.42, 889.34, 852.10, 763.72, 693.50, 667.84, 590.39. **HRMS electrospray (m/z): [M – Na]$^+$ calcd for $C_{56}H_{70}Br_2Na_2O_{10}P_2Pd_2S_3$:** 1456.9946, found 1456.9976.



OA-17

Following the general procedure, a mixture containing 3,5-Dibromobenzoic acid (12.3 mg, 0.044 mmol), sSPhos (50 mg, 0.01 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (38 mg, 0.01 mmol) was stirred at rt in THF (1.5 mL) for 1 h. General work-up afforded **OA-17** as a light brown solid (72 mg, 99%).

^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ 161.49, 157.72, 143.63, 138.87, 138.80, 136.63, 135.72, 135.62, 134.94, 134.86, 133.51, 133.04, 132.86, 132.51, 132.24, 132.22, 131.68, 131.31, 130.11, 128.76, 128.65, 128.20, 127.06, 127.04, 123.76, 121.57, 108.72, 107.27, 69.33, 63.76, 62.54, 57.67, 57.27, 57.12, 56.88, 56.58, 39.27, 38.62, 38.40, 37.74, 36.06, 35.77, 29.43, 28.94, 28.78, 28.53, 28.41, 28.05, 27.99, 27.93, 27.85, 27.76, 27.68, 27.56, 27.40, 27.34, 26.97, 26.94, 23.85, 14.89, 3.26, -0.62. **^{31}P NMR (121 MHz, MeOD)** δ 31.99. **FT-IR (neat, cm^{-1}):** 3436.31, 2928.88, 2846.68, 2361.40, 2339.29, 1576.61, 1450.75, 1398.27, 1275.76, 1184.90, 1098.21, 1049.48, 1018.42, 924.47, 891.33, 854.88, 805.64, 749.56, 693.56, 580.79. **HRMS electrospray (m/z): [M – $Na_2Br]^-$ calcd for $C_{59}H_{72}Br_2Na_2O_{12}P_2Pd_2S_2$:** 1391.1222, found 1391.1283.

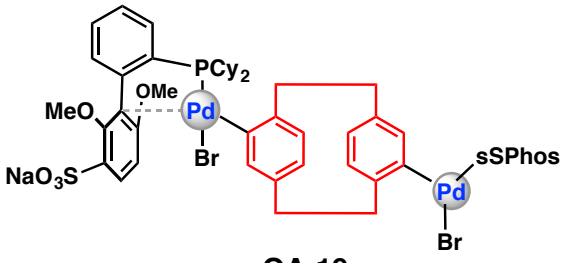


OA-18

Following the general procedure, a mixture containing 3,5-Dibromobenzaldehyde (11.6 mg, 0.044 mmol), sSPhos (50 mg, 0.01 mmol), and (1,5-COD)Pd($CH_2TMS)_2$ (38 mg, 0.01 mmol) was stirred at rt in THF (1.5 mL) for 1 h. General work-up afforded **OA-18** as a light brown solid (66 mg, 99%).

^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ 161.29, 157.50, 135.52, 135.42, 134.71, 132.77, 132.07, 131.10, 128.57, 128.47, 126.83, 107.07, 69.12, 62.34, 57.51, 56.69, 39.06, 38.41, 38.18, 37.52, 35.84, 35.44, 29.23, 27.84, 27.70, 27.66, 27.46,

27.35, 27.13, 26.76, 23.64, 14.68, -1.12 (observed complexity is due to *C–P* coupling). **^{31}P NMR (121 MHz, MeOD)** δ 54.11. **FT-IR (neat, cm^{-1}):** 3430.23, 2931.05, 2852.56, 2361.33, 2342.60, 1573.87, 1450.86, 1398.46, 1275.65, 1179.90, 1098.08, 1050.93, 1018.24, 917.08, 845.59, 805.57, 758.75, 693.59, 667.86, 657.88, 629.64, 623.64, 595.12. **HRMS electrospray (m/z): [M – Na_2Br]$^-$ calcd for $C_{59}H_{72}Br_2Na_2O_{11}P_2Pd_2S_2$:** 1375.1273, found 1375.1321.



OA-19

Following the general procedure, a mixture containing 5,11-dibromotricyclo[8.2.2.2~4,7~]hexadeca-1(12),4,6,10,13,15-hexaene (16.1 mg, 0.044 mmol), sSPhos (50 mg, 0.01 mmol), and (1,5-COD)Pd(CH_2TMS)$_2$ (38 mg, 0.01 mmol) was stirred at rt in THF (1.5 mL) for 1 h. General work-up afforded **OA-19** as a yellow solid (70 mg, 99%).

^{1}H NMR (400 MHz, MeOD) Complicated spectrum; please see the attached ^{1}H NMR spectrum. **^{13}C NMR (101 MHz, MeOD)** δ ^{13}C NMR (101 MHz, MeOD) δ 161.28, 157.50, 138.66, 137.19, 135.54, 135.44, 134.67, 134.60, 132.79, 132.05, 131.08, 128.57, 128.47, 126.84, 107.07, 69.13, 62.34, 57.21, 56.69, 49.94, 49.73, 49.51, 49.30, 49.09, 48.87, 48.66, 39.09, 38.44, 38.11, 37.45, 36.89, 27.85, 27.79, 27.67, 27.57, 27.46, 27.38, 27.14, 26.77, 23.65, 14.68 (observed complexity is due to *C–P* coupling). **^{31}P NMR (121 MHz, MeOD)** δ 51.64. **FT-IR (neat, cm^{-1}):** 3300.18, 2918.84, 2851.36, 2358.93, 1684.54, 1577.43, 1525.12, 1450.92, 1274.75, 1226.24, 1185.07, 1098.68, 1050.30, 1017.95, 914.53, 852.15, 818.16, 759.53, 707.02, 693.31, 667.99, 596.57. **HRMS electrospray (m/z): [M – Na_2Br]$^-$ calcd for $C_{68}H_{82}Br_2Na_2O_{10}P_2Pd_2S_2$:** 1477.2109, found 1477.2068.

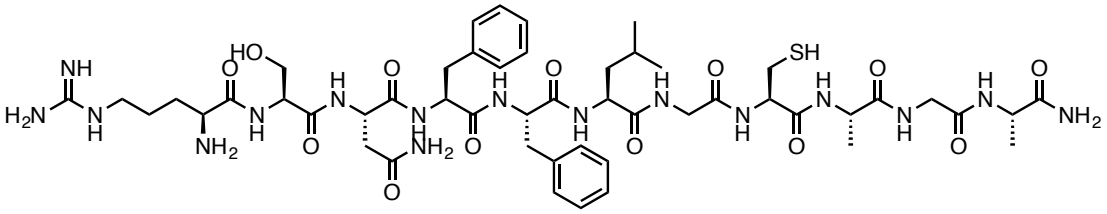
3. Peptide Synthesis and LC-MS Characterization

Linear Peptide Synthesis

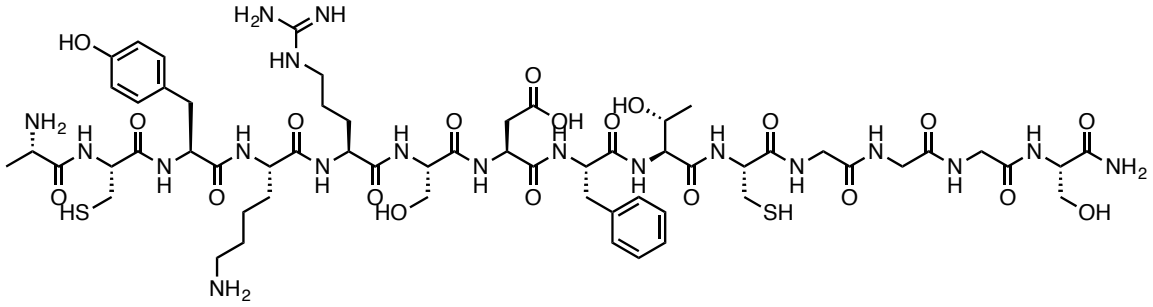
General Linear Peptide Synthesis Procedure:

All peptides were synthesized on a 0.2 mmol scale using manual Fmoc-SPPS chemistry under flow with a 3 min cycle for each amino acid.[2] Specifically, all reagents

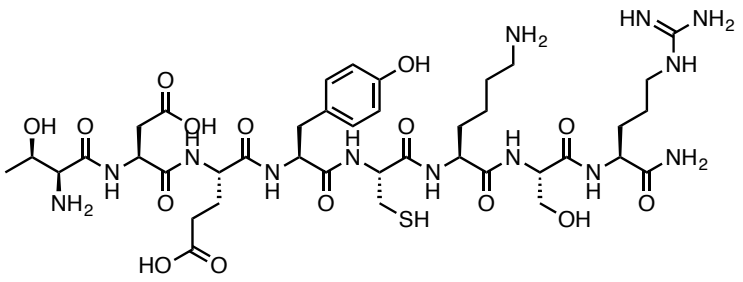
and solvents were delivered to a stainless steel reactor containing resins at a constant flow rate using HPLC pump; the temperature of the reactor was maintained at 60 °C during the synthesis using a water bath. The procedure for each amino acid coupling cycle included: 1) a 30 s coupling with 1 mmol of the corresponding Fmoc-protected amino acid, 1 mmol HBTU, and 500 μL of diisopropyl ethyl amine (DIPEA) in 2.5 mL of DMF at a flow rate of 6 mL/min (note that for the coupling of cysteine and tryptophan, 190 μL of DIPEA was used to prevent racemization); 2) 1 min wash with DMF at a flow rate of 20 mL/min; 3) 20 s deprotection with 50% (v/v) piperidine in DMF at a flow rate of 20 mL/min; and 4) 1 min wash with DMF at a flow rate of 20 mL/min. After completion of the stepwise SPPS, the resin was washed thoroughly with CH_2Cl_2 and dried under vacuum. The peptide was simultaneously cleaved from the resin and deprotected on the side- chains by treatment with 2.5% (v/v) water, 2.5% (v/v) 1,2-ethanedithiol (EDT), and 2.5% (v/v) triisoproprylsilane in neat trifluoroacetic acid (TFA) for 7 min at 60 °C. The resulting solution was then triturated and washed with cold diethyl ether (3x). The obtained solid was dissolved in 50% H2O : 50% acetonitrile containing 0.1% TFA and lyophilized. The following peptides were synthesized following this procedure:



P1
Arg Ser Asn Phe Phe Leu Gly Cys Ala Gly Ala
Exact Mass: 1140.55



P2
Ala Cys Tyr Lys Arg Ser Asp Phe Thr Cys Gly Gly Gly Ser
Exact Mass: 1449.61



P3
Thr Asp Glu Tyr Cys Lys Ser Arg
Exact Mass: 999.44

Peptide Purification

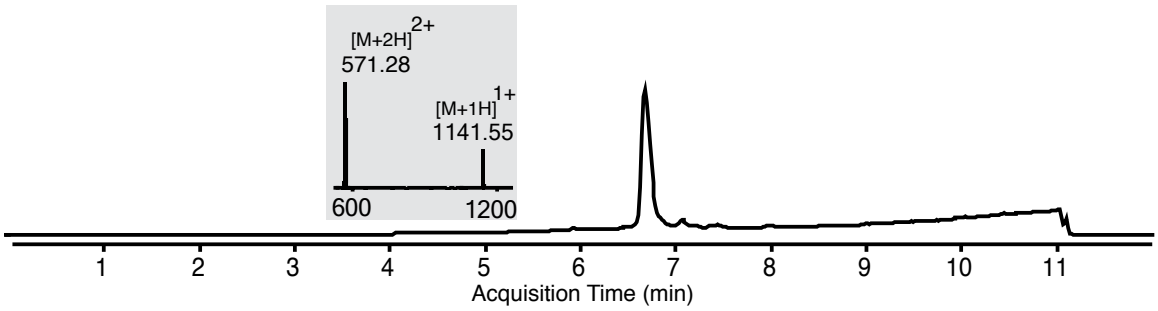
Solvent compositions for reversed phase HPLC (RP-HPLC) purification are water with 0.1% TFA (solvent C) and acetonitrile with 0.1% TFA (solvent D). The crude peptide was dissolved in 50% C : 50% D and purified by semi-preparative RP-HPLC (Agilent Zorbax 300SB C_{18} column: 21.2 x 250 mm, 7 µm, linear gradient: 5-50% B over 65 min, flow rate: 5 mL/min). Each HPLC fraction was analyzed by mass-directed preparative LC-MS. HPLC fractions containing the pure product were further confirmed by LC-MS, combined, and lyophilized. Peptides synthesized using manual SPPS and purified by RP-HPLC are listed in Table S1.

Table S1. **Sequences and masses of peptides synthesized by manual fast flow SPPS.**

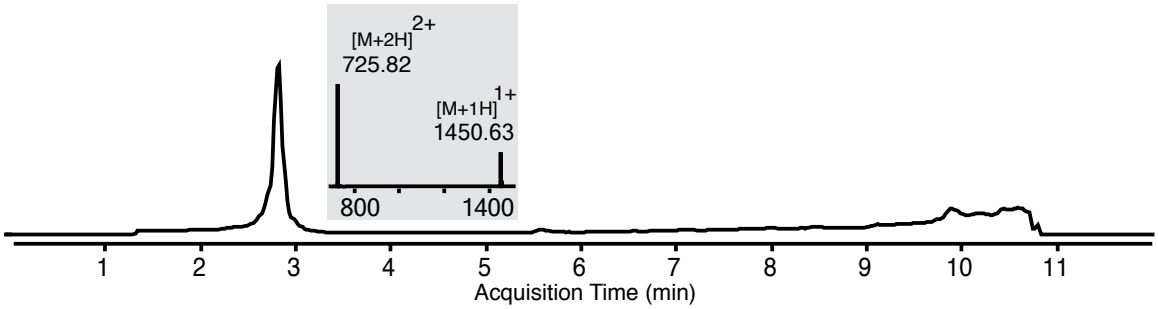
Peptide	Sequence[a]	Calculated mass	Observed Mass $[M+H]^+$
P1	NH_2-RSNFFLGCAGA-C(O)NH_2	1140.55	1141.55
P2	NH_2-ACYKRSDFTCGGGS-C(O)NH_2	1449.61	1450.63
P3	NH_2-TDGYCKSR-C(O)NH_2	999.44	1000.42

[a] **Cysteine residues are highlighted in red.**

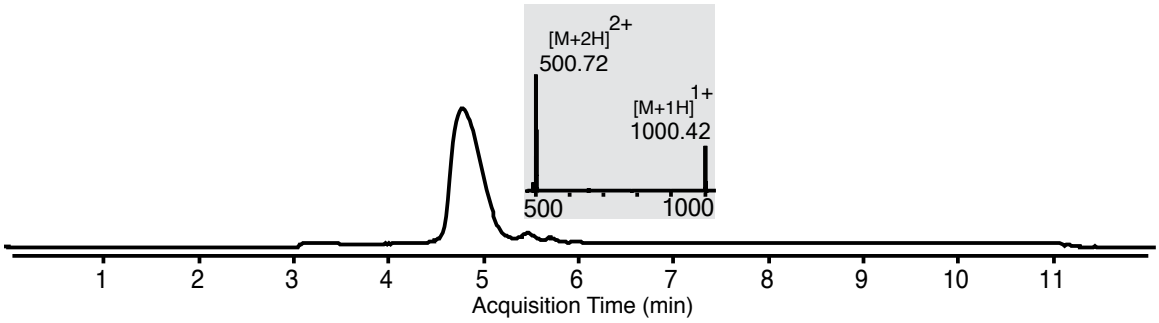
P1:



P2:



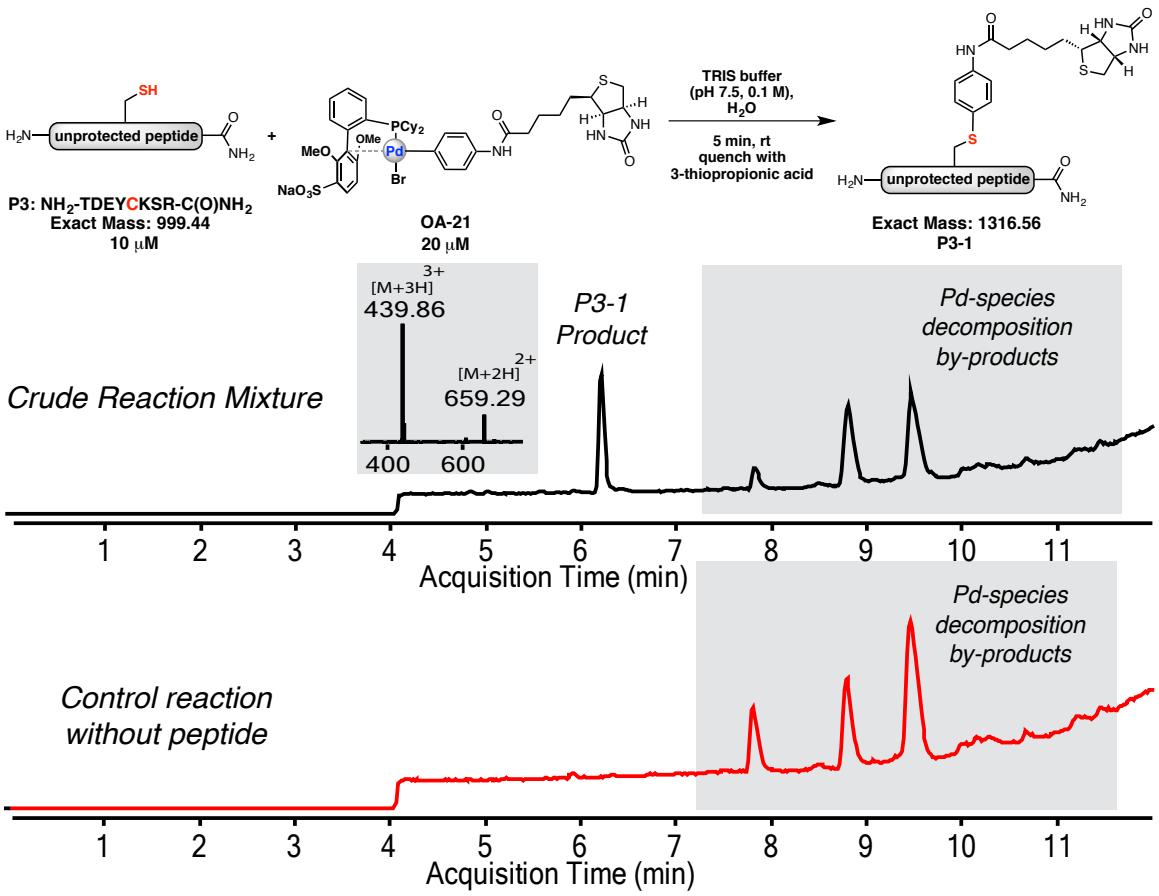
P3:

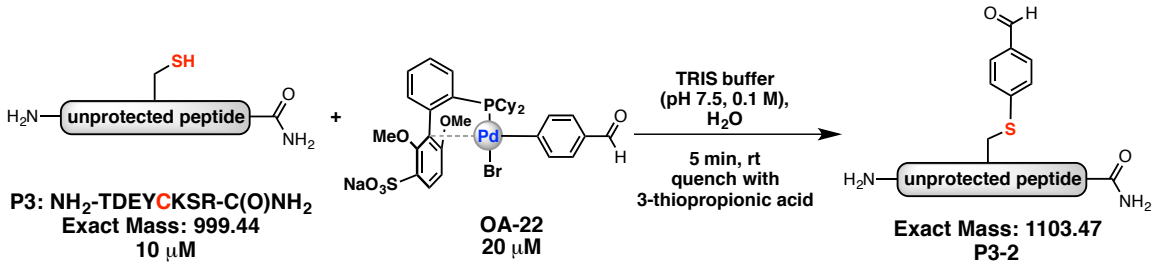


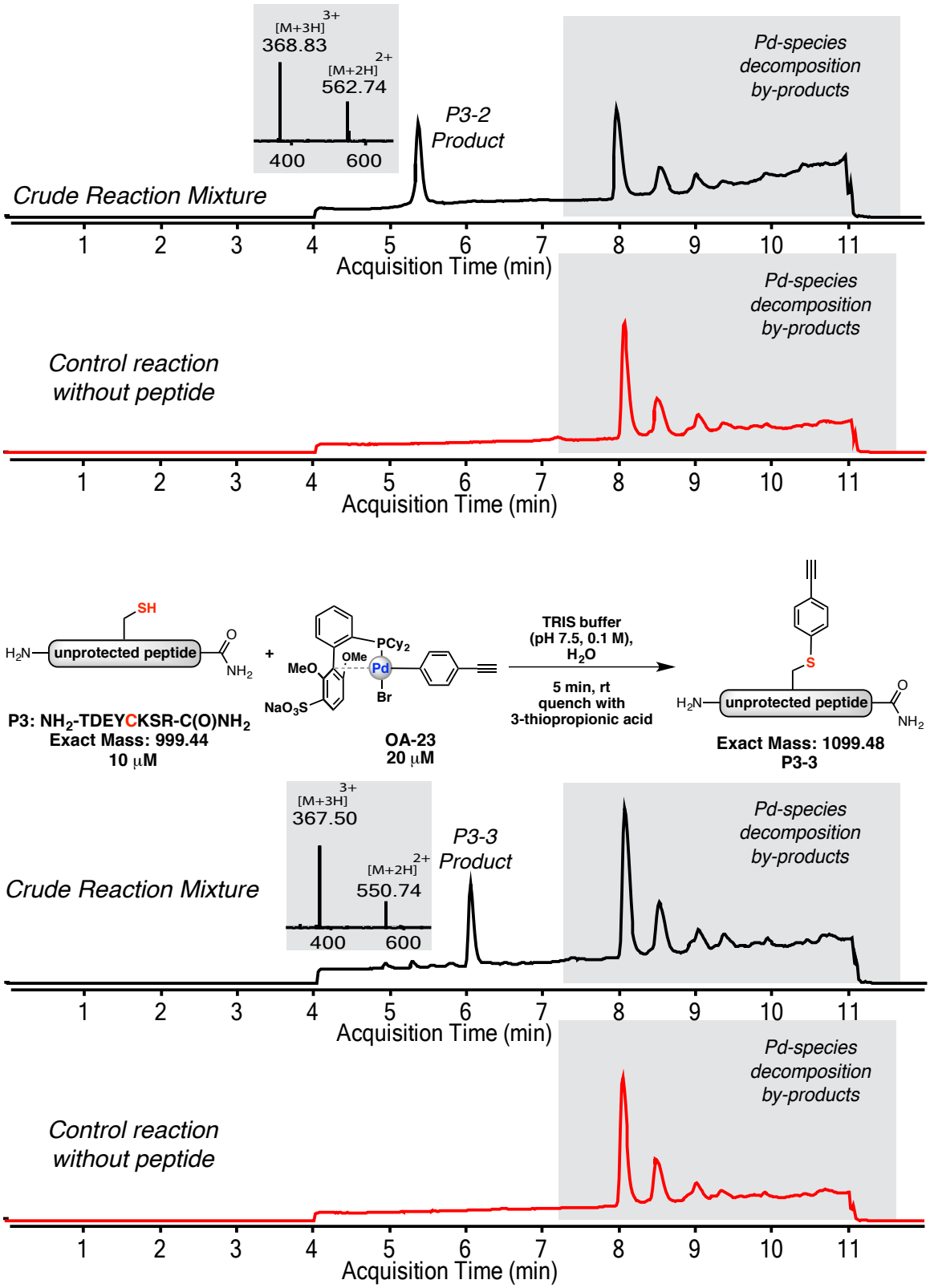
4. PEPTIDE *S*-ARYLATION CHARACTERIZATION

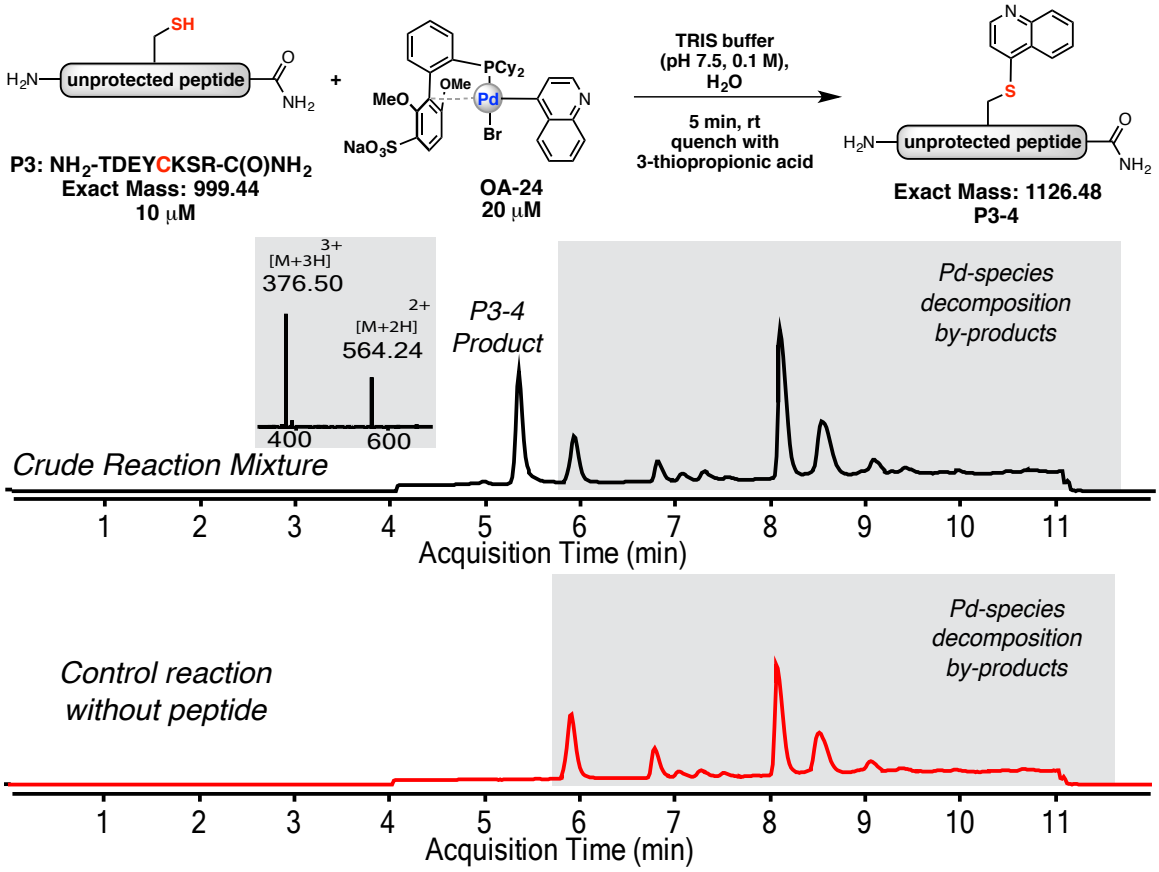
General Bioconjugation Procedure

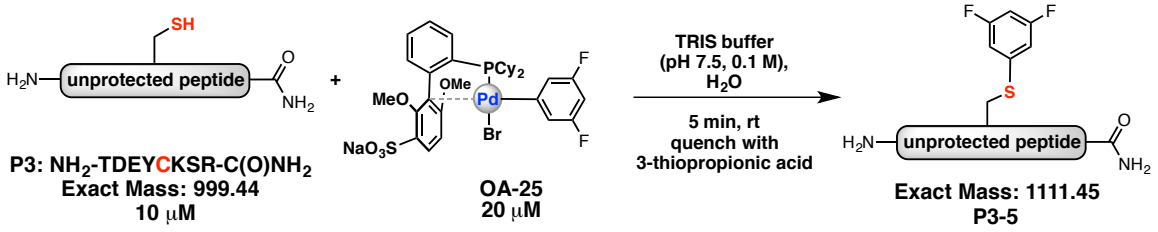
A solution of the Pd reagent (**OA-Y**) reagent in water (40 μM) was added to a solution of peptide **P3** (20 μM) in Tris buffer (0.1 M, pH 7.5). Note: if the palladium reagent was not readily soluble in H_2O, the slurry was sonicated for 10 s to facilitate this process and become fully solubilized. Final conditions: [Pd] = 20 μM; [peptide] = 10 μM; After 5 min at rt, 3-mercaptopropionic acid (3 equiv to the palladium complex, solution in 6 μL of H_2O) was added to the reaction mixture to quench the remaining palladium species. The reaction was allowed to stand for 5 min and subsequently characterized by LC-MS.

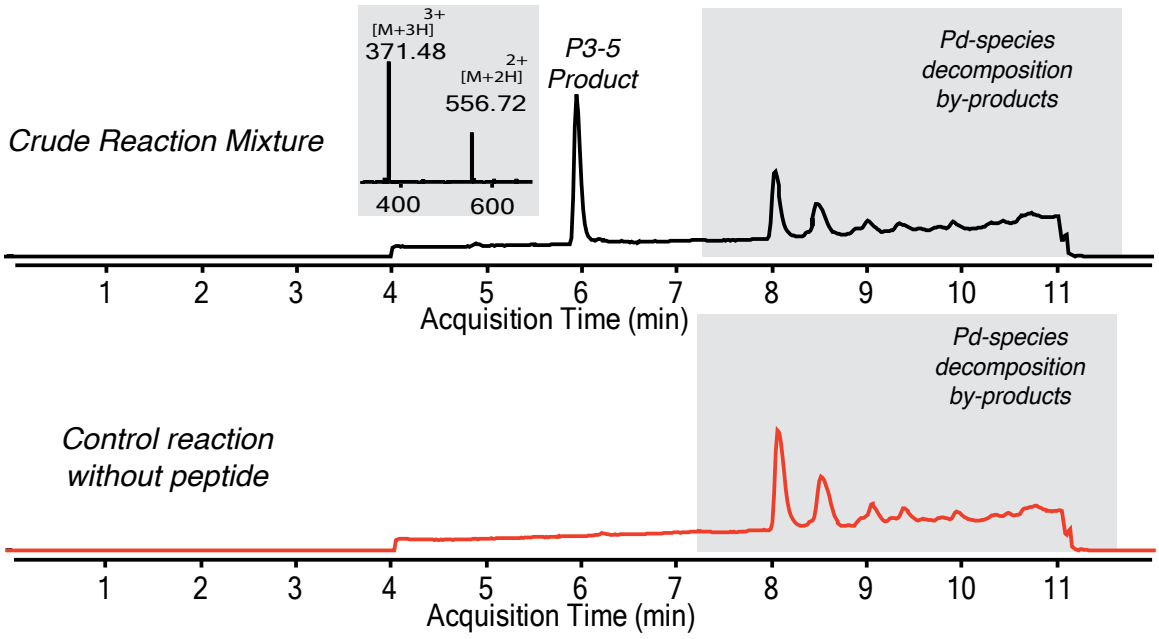

SH
unprotected peptide
NH2
P3: NH2-TDEYCKSR-C(O)NH2
Exact Mass: 999.44
10 μM
PCy2
OMe
MeO
Pd
Br
NaO3S
NH
OA-21
20 μM
TRIS buffer
(pH 7.5, 0.1 M),
H2O
5 min, rt
quench with
3-thiopropionic acid
S
Exact Mass: 1316.56
P3-1
Crude Reaction Mixture
3+
[M+3H]
439.86
2+
[M+2H]
659.29
400
600
P3-1
Product
Pd-species
decomposition
by-products
1
2
3
4
5
6
7
8
9
10
11
Acquisition Time (min)
Control reaction
without peptide
Pd-species
decomposition
by-products
Acquisition Time (min)


SH
unprotected peptide
NH2
P3: NH2-TDEYCKSR-C(O)NH2
Exact Mass: 999.44
10 μM
PCy2
OMe
MeO
Pd
Br
NaO3S
OA-22
20 μM
TRIS buffer
(pH 7.5, 0.1 M),
H2O
5 min, rt
quench with
3-thiopropionic acid
S
Exact Mass: 1103.47
P3-2

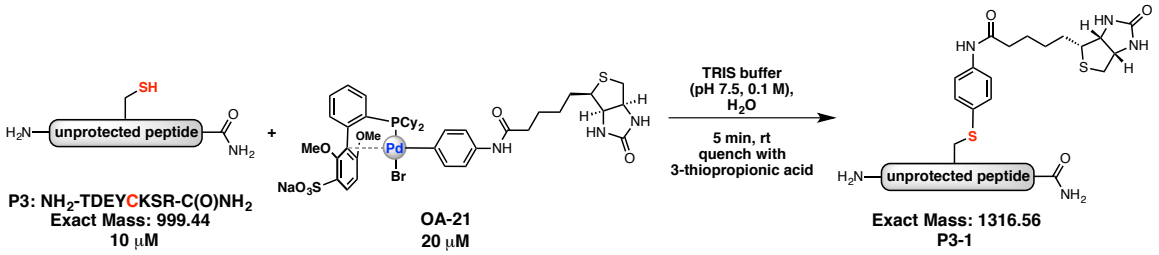

[M+3H]3+
368.83
[M+2H]2+
562.74
400
600
P3-2
Product
Pd-species
decomposition
by-products
Crude Reaction Mixture
1
2
3
4
5
6
7
8
9
10
11
Acquisition Time (min)
Pd-species
decomposition
by-products
Control reaction
without peptide
1
2
3
4
5
6
7
8
9
10
11
Acquisition Time (min)
SH
H2N
unprotected peptide
O
NH2
+
PCy2
OMe
MeO
Pd
Br
NaO3S
TRIS buffer
(pH 7.5, 0.1 M),
H2O
5 min, rt
quench with
3-thiopropionic acid
S
H2N
unprotected peptide
O
NH2
P3: NH2-TDEYCKSR-C(O)NH2
Exact Mass: 999.44
10 μM
OA-23
20 μM
Exact Mass: 1099.48
P3-3
[M+3H]3+
367.50
[M+2H]2+
550.74
400
600
P3-3
Product
Pd-species
decomposition
by-products
Crude Reaction Mixture
1
2
3
4
5
6
7
8
9
10
11
Acquisition Time (min)
Pd-species
decomposition
by-products
Control reaction
without peptide
1
2
3
4
5
6
7
8
9
10
11
Acquisition Time (min)


SH
H2N
unprotected peptide
O
NH2
+
PCy2
OMe
MeO
Pd
Br
N
NaO3S
TRIS buffer
(pH 7.5, 0.1 M),
H2O
5 min, rt
quench with
3-thiopropionic acid
S
P3: NH2-TDEYCKSR-C(O)NH2
Exact Mass: 999.44
10 μM
OA-24
20 μM
Exact Mass: 1126.48
P3-4
3+
[M+3H]
376.50
2+
[M+2H]
564.24
400
600
P3-4
Product
Pd-species
decomposition
by-products
Crude Reaction Mixture
1
2
3
4
5
6
7
8
9
10
11
Acquisition Time (min)
Control reaction
without peptide
Pd-species
decomposition
by-products
1
2
3
4
5
6
7
8
9
10
11
Acquisition Time (min)

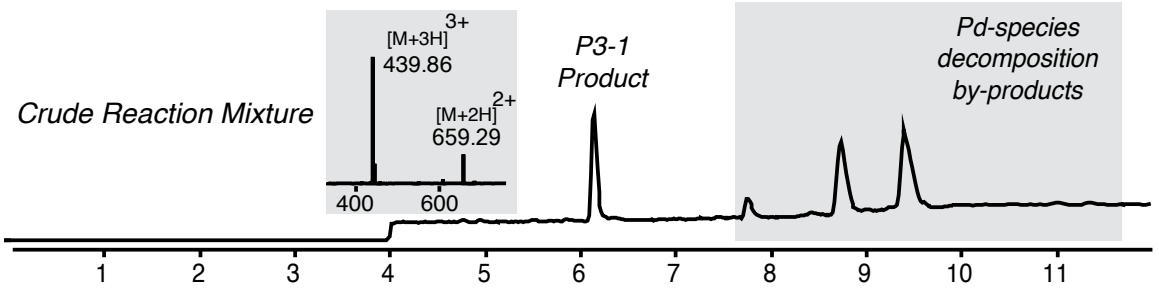

SH
H2N
unprotected peptide
O
NH2
+
PCy2
OMe
MeO
Pd
Br
F
F
NaO3S
TRIS buffer
(pH 7.5, 0.1 M),
H2O
5 min, rt
quench with
3-thiopropionic acid
S
P3: NH2-TDEYCKSR-C(O)NH2
Exact Mass: 999.44
10 μM
OA-25
20 μM
Exact Mass: 1111.45
P3-5

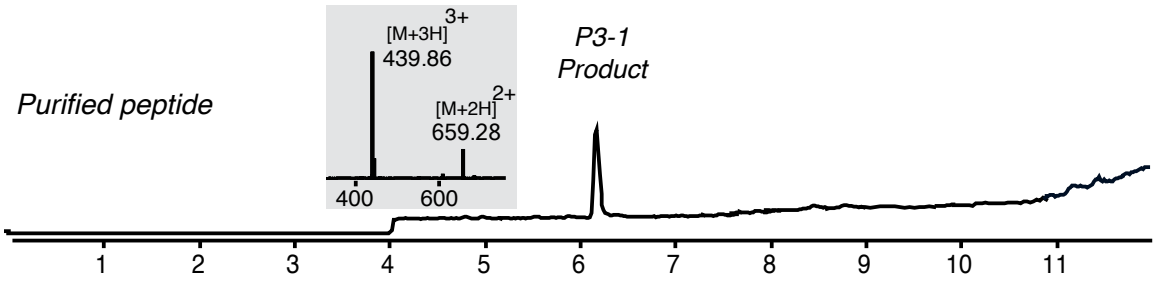


LARGE SCALE BIOCONJUGATION:



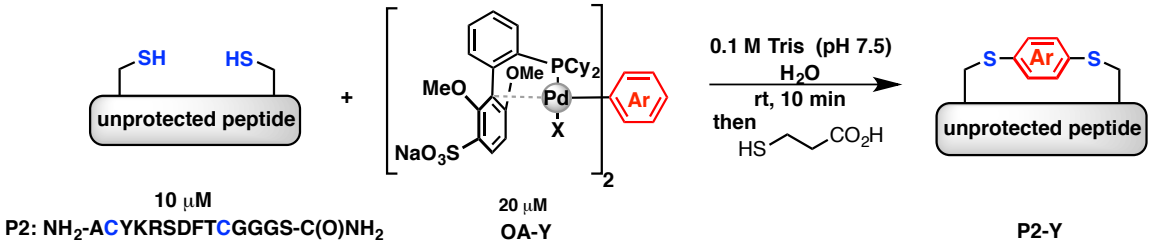
Into a 250 mL round bottomed flask equipped with a magnetic stir bar, 8.0 mg of peptide **P3** was dissolved in water (20 μM) and Tris buffer (0.1 M, pH 7.5). A solution of the Pd reagent (**OA-21**) reagent in water (40 μM) was added to the peptide solution and allowed to stir. Final conditions: [**OA-21**] = 20 μM; [**P3**] = 10 μM; After 5 min at rt, 3-mercaptopropionic acid (3 equiv to the palladium complex, solution in 1 mL of H_2O) was added to the reaction mixture to quench the remaining palladium species. The reaction mixture was allowed to stand for 5 min and subsequently purified via mass-directed preparative HP-LC yielding 8.54 mg of pure biotinylated peptide (**P3-1**, >99% conversion, 81% isolated yield).





5. Macrocyclization Reactions and LC-MS Characterization

General Macrocyclization Procedure



A solution of the Pd reagent (**OA-Y**) reagent in water (40 μM) was added to a solution of peptide (20 μM) in Tris buffer (0.1 M, pH 7.5). Note: if the palladium reagent was not readily soluble in H_2O, the slurry was sonicated for 10 s to facilitate this process. Final reaction concentrations: [Pd] = 20 μM; [peptide] = 10 μM; After 10 min stirring at rt, 3-mercaptopropionic acid (3 equiv to the palladium complex, solution in 6 μL of H_2O) was added to the reaction mixture to quench the remaining palladium species. The reaction was allowed to stand for 5 min. The crude peptide was purified using preparative HPLC as described above or immediately analysed by LC-MS (below).

Figure S-1: Macrocyclization P2-7

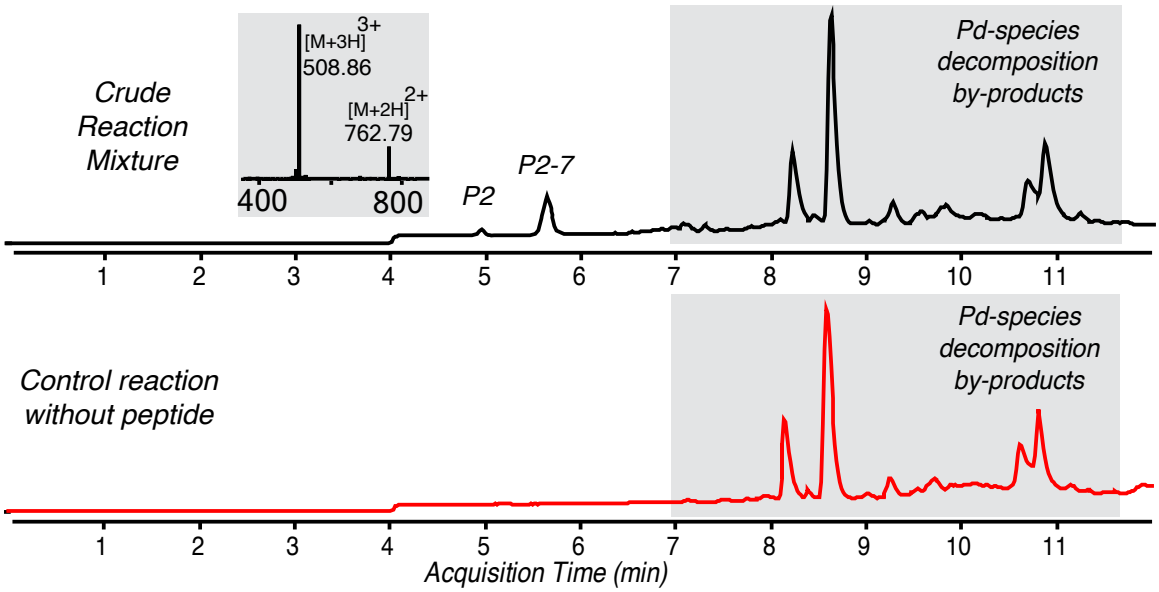


Figure S-2: Macrocyclization P2-8

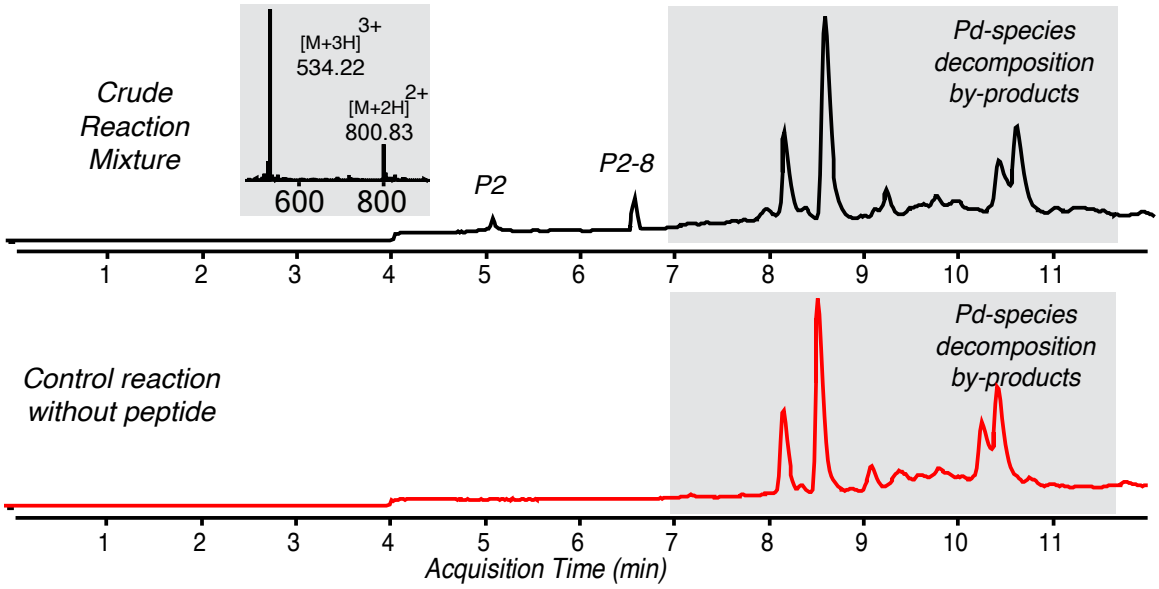


Figure S-3: Macrocyclization P2-9

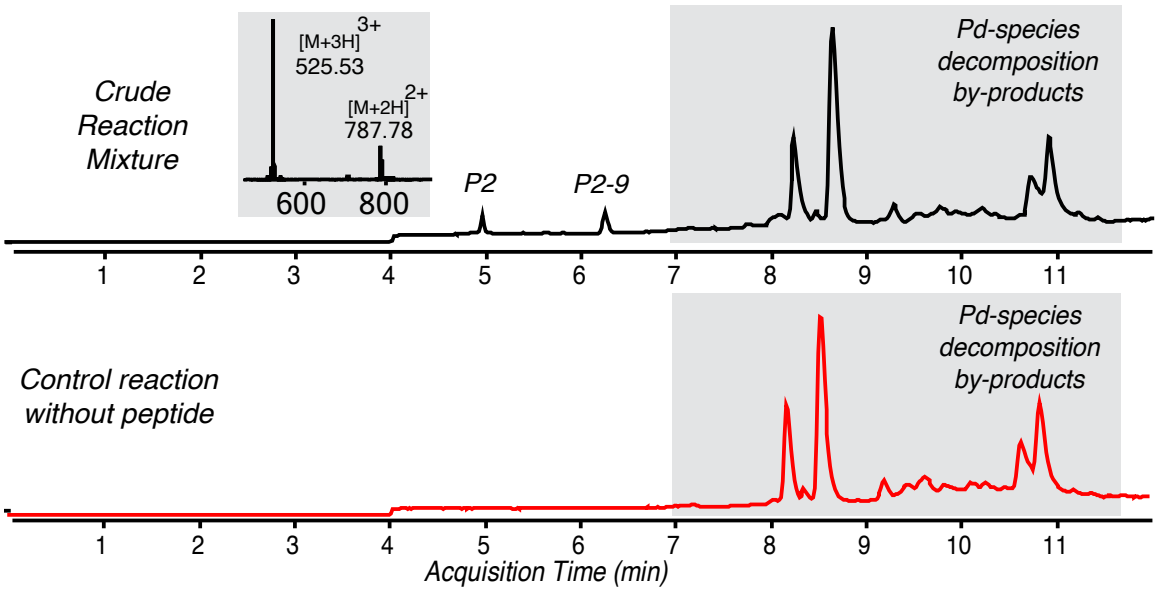


Figure S-4: Macrocyclization P2-9 with 15% MeCN

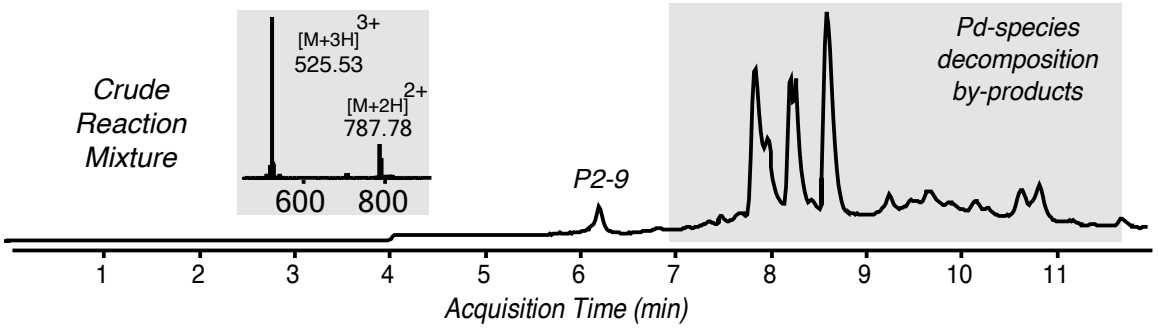


Figure S-5: Macrocyclization P2-10 with 15% MeCN

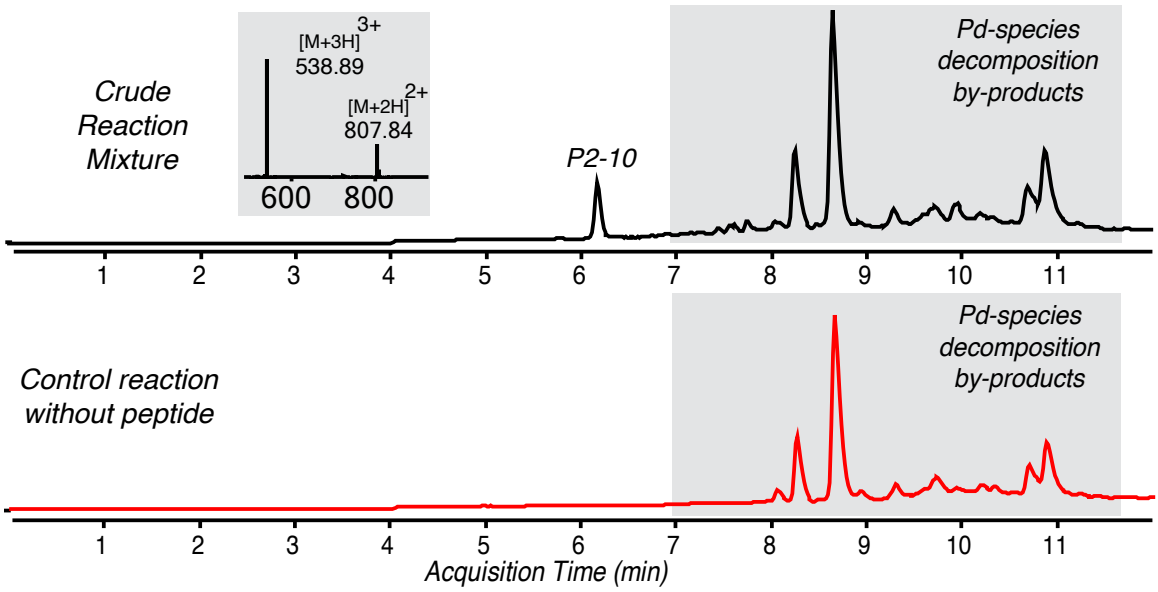


Figure S-6: Macrocyclization P2-11

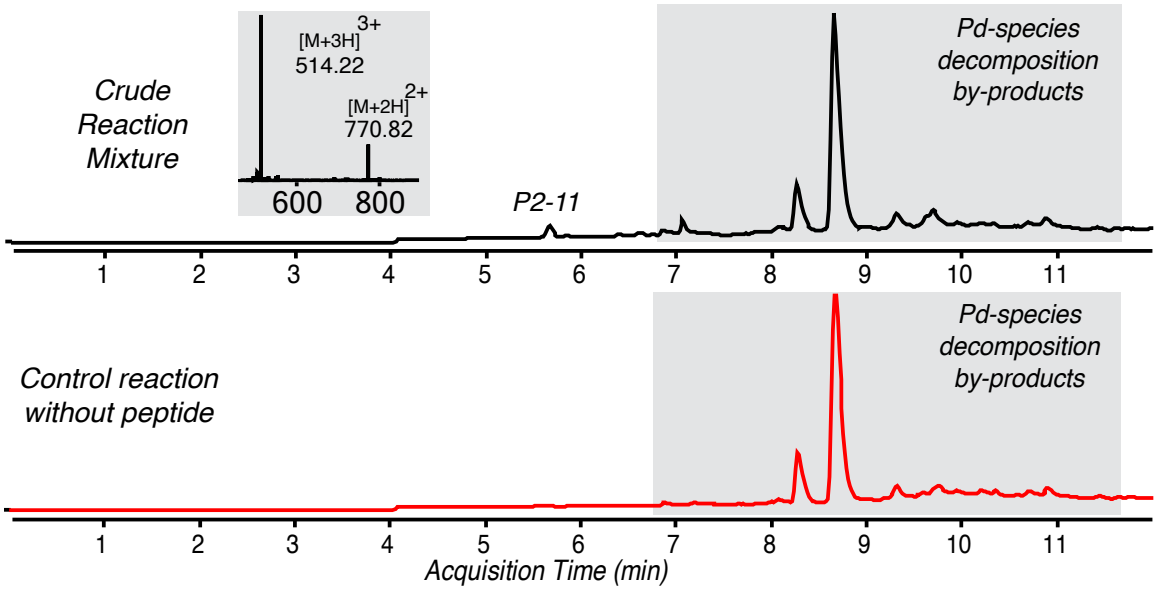


Figure S-7: Macrocyclization P2-12

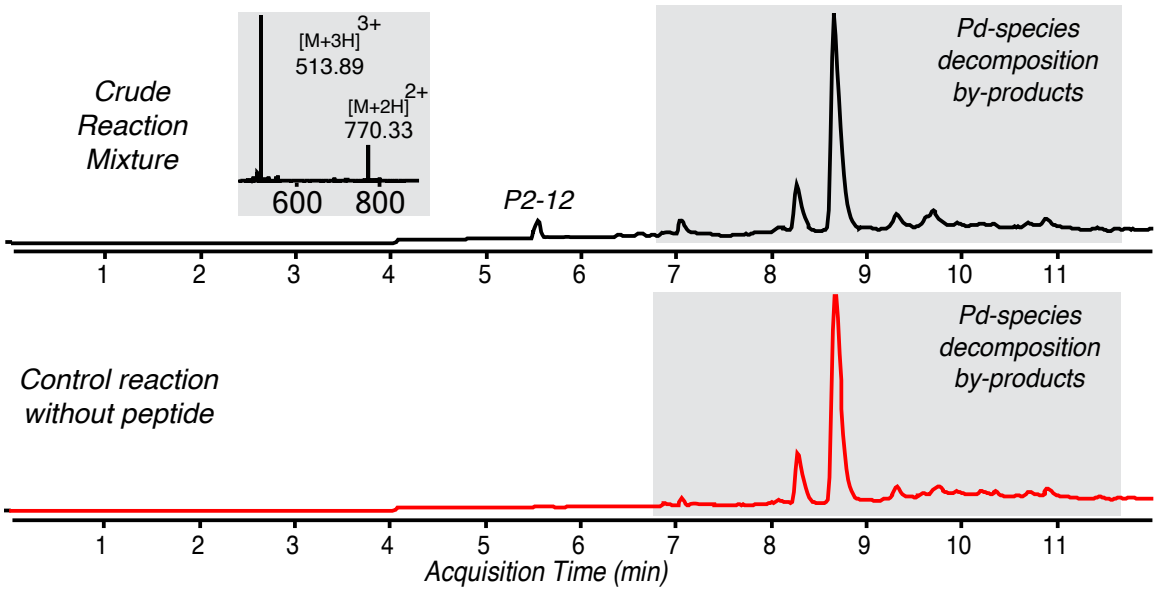


Figure S-8: Macrocyclization P2-13

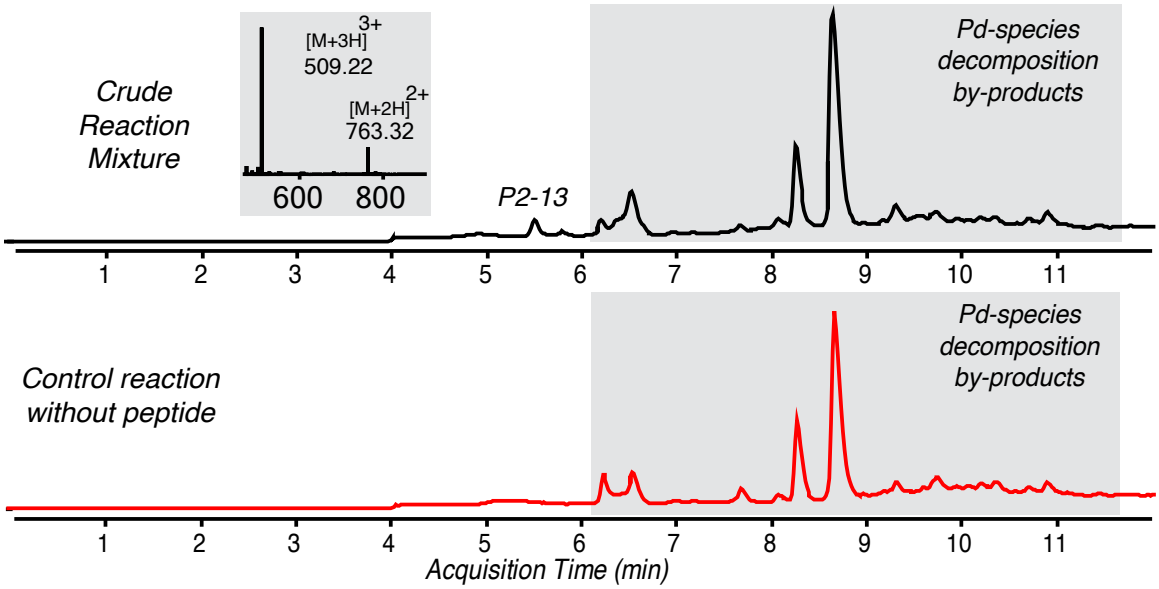


Figure S-9: Macrocyclization P2-14

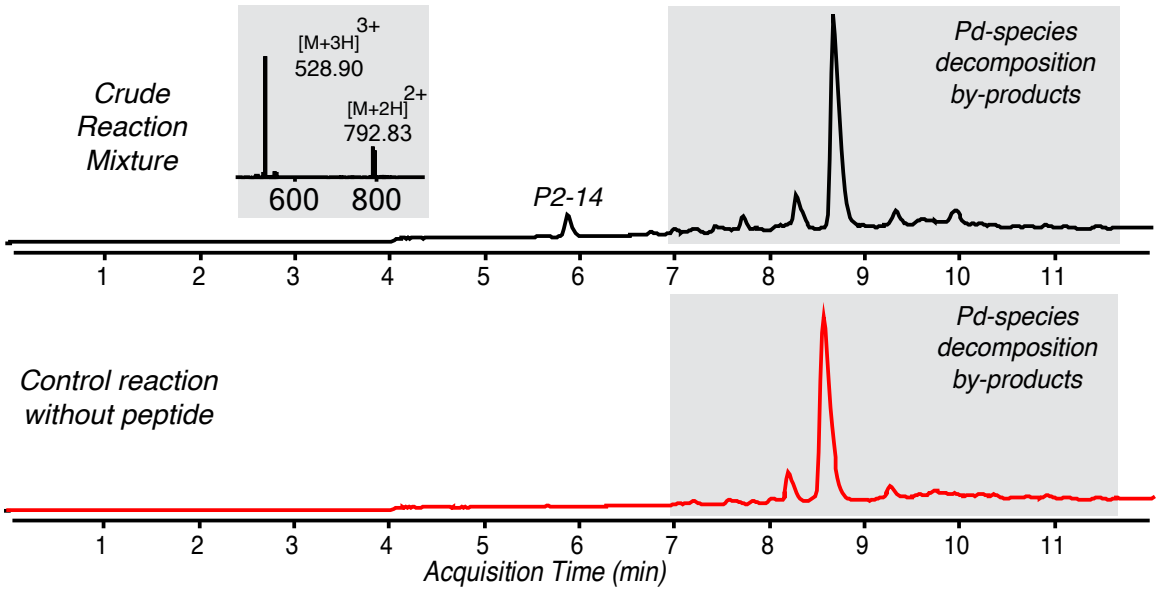


Figure S-10: Macrocyclization P2-15

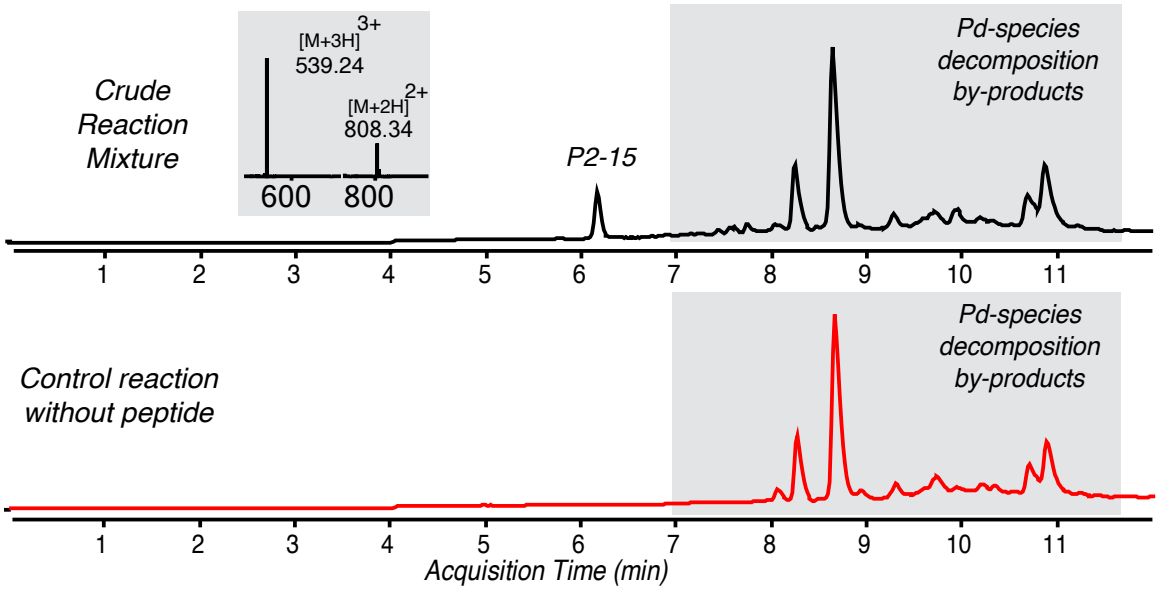


Figure S-11: Macrocyclization P2-16

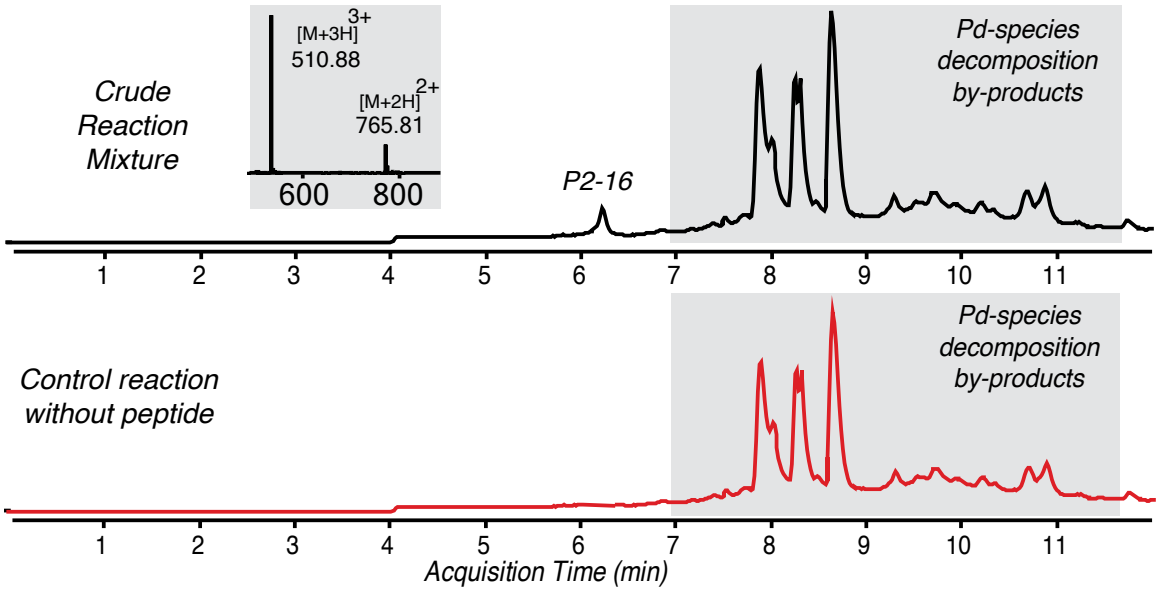


Figure S-12: Macrocyclization P2-17

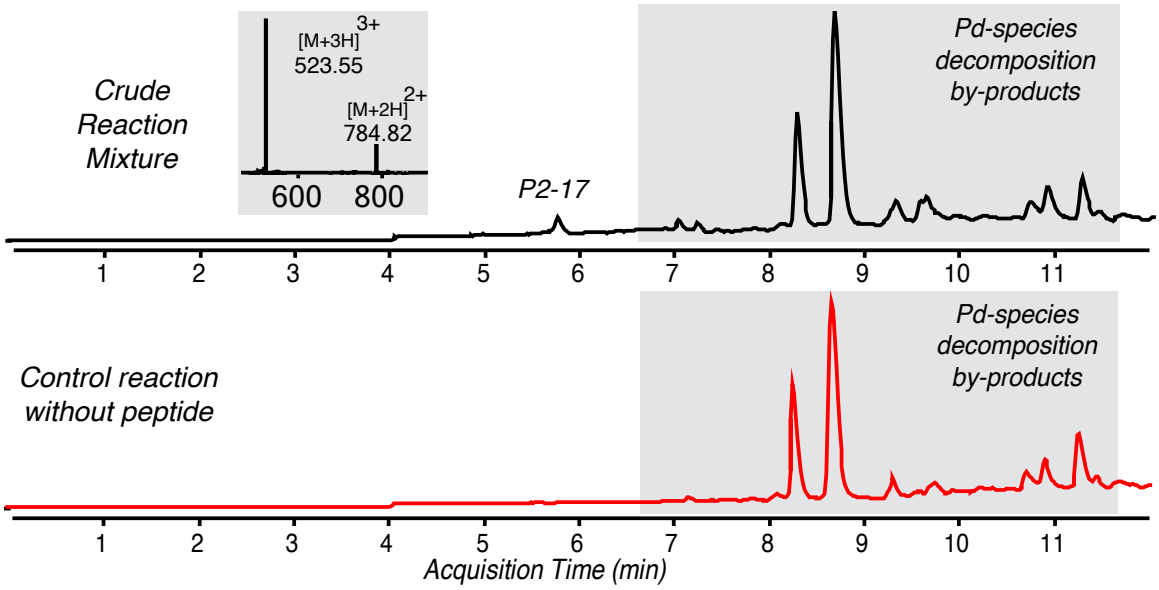


Figure S-13: Macrocyclization P2-18

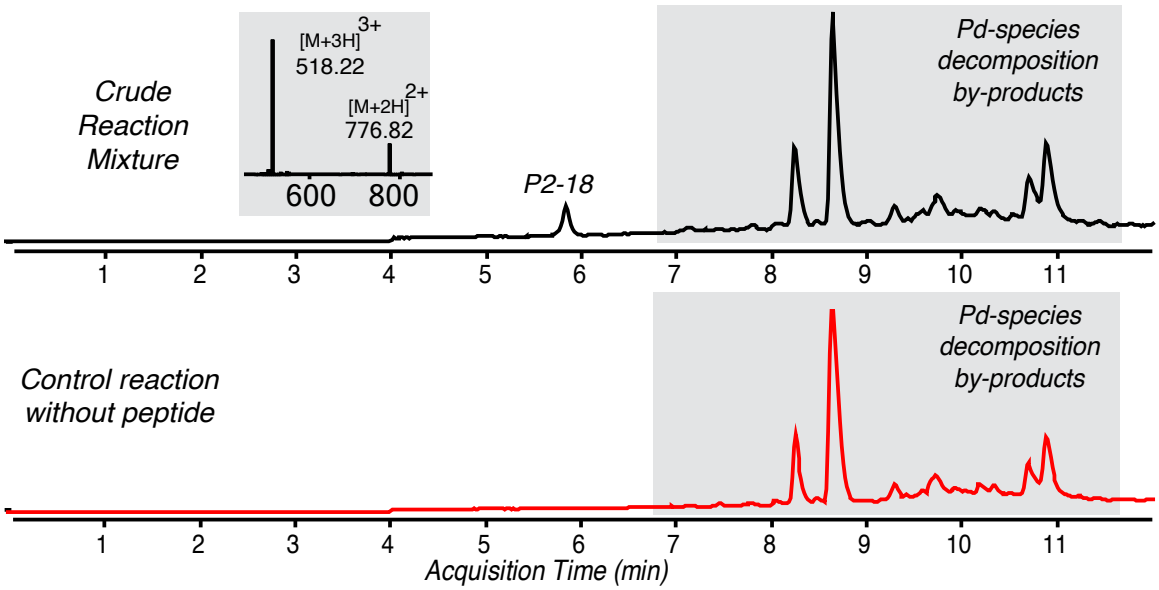
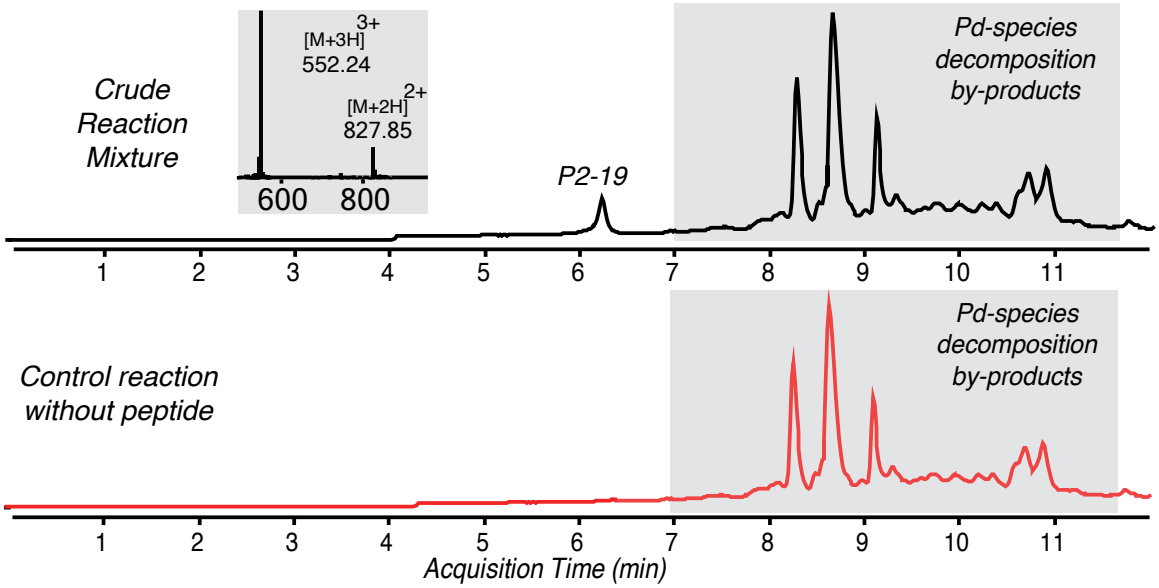


Figure S-14: Macrocyclization P2-19 with 15% MeCN



6. Protein Experiments

Protein Expression and Purification

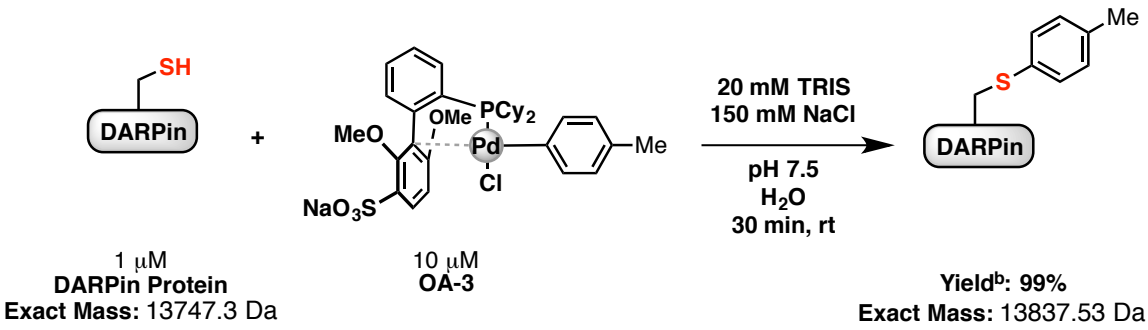
pET-SUMO-DARPin plasmids were constructed as reported previously.[3] Cysteine mutations were introduced by site-directed mutagenesis using QuickChange

Lightning Single Site-directed Mutagenesis Kit (Agilent) following manufacturer's instructions. Sequences of generated protein constructs are summarized in Table S6.

E. coli BL21(DE3) cells transformed with pET-SUMO-Protein plasmid were grown in 1 L of LB medium containing kanamycin (30 μg/mL) at 37 °C until OD600 = 0.6. Then, expression was induced by the addition of 0.5 mM IPTG overnight at 30 °C. After harvesting the cells by centrifugation (6,000 rpm for 10 min), the cell pellet was lysed by sonication in 25 mL of 50 mM Tris and 150 mM NaCl (pH 7.5) buffer containing 15 mg lysozyme (Calbiochem), 1 mg DNase I (Sigma-Aldrich), and 0.5 tablet of protease inhibitor cocktail (Roche Diagnostics, Germany). The resulting suspension was centrifuged at 17,000 rpm for 30 min to remove cell debris. The supernatant was loaded onto a 5 mL HisTrap FF crude Ni-NTA column (GE Healthcare, UK), first washed with 40 mL of 20 mM Tris and 150 mM NaCl (pH 8.5), and then washed with 40 mL of 40 mM imidazole in 20 mM Tris and 150 mM NaCl (pH 8.5). The protein was eluted from the column with buffer containing 500 mM imidazole in 20 mM Tris and 150 mM NaCl (pH 8.5). Imidazole was removed from protein using a HiPrep 26/10 Desalting column (GE Healthcare, UK), the protein was eluted into 20 mM Tris and 150 mM NaCl (pH 7.5) buffer. The protein was analyzed by LC-MS to confirm its purity and molecular weight.

SUMO group on SUMO-Protein was cleaved by incubating 1 μg of SUMO protease per mg of protein at room temperature for 60 min. The crude reaction mixture was loaded onto a 5 mL HisTrap FF crude Ni-NTA column (GE Healthcare, UK) and the flow through containing the desired protein was collected. The protein was analyzed by LC-MS confirming sample purity and molecular weight. Purified proteins were concentrated using Amicon 3K concentrator (50 mL, EMD Millipore); protein aliquots were flash frozen and stored in –80 °C freezer.

Protein Labeling Experiments



To a solution of protein (500 pmoles) in 475 µL of 20 mM Tris and 150 mM NaCl buffer (pH 7.5) was added palladium-tolyl complex **OA-3** (25 µL, 200 µM) in water. The solution was pipetted in and out of the pipette (10x) to ensure proper reagent mixing. The reaction mixture was left at room temperature for 30 min. After this time, the reaction was quenched by the addition of 3-thiopropionic acid (25 µL, 2 mM) dissolved in 20 mM Tris and 150 mM NaCl buffer (pH 7.5). After an additional 5 min at rt, 500 µL of 1 : 1 CH_3CN/H_2O (v/v) containing 0.2% TFA was added and the resulting mixture was analyzed by LC-MS.

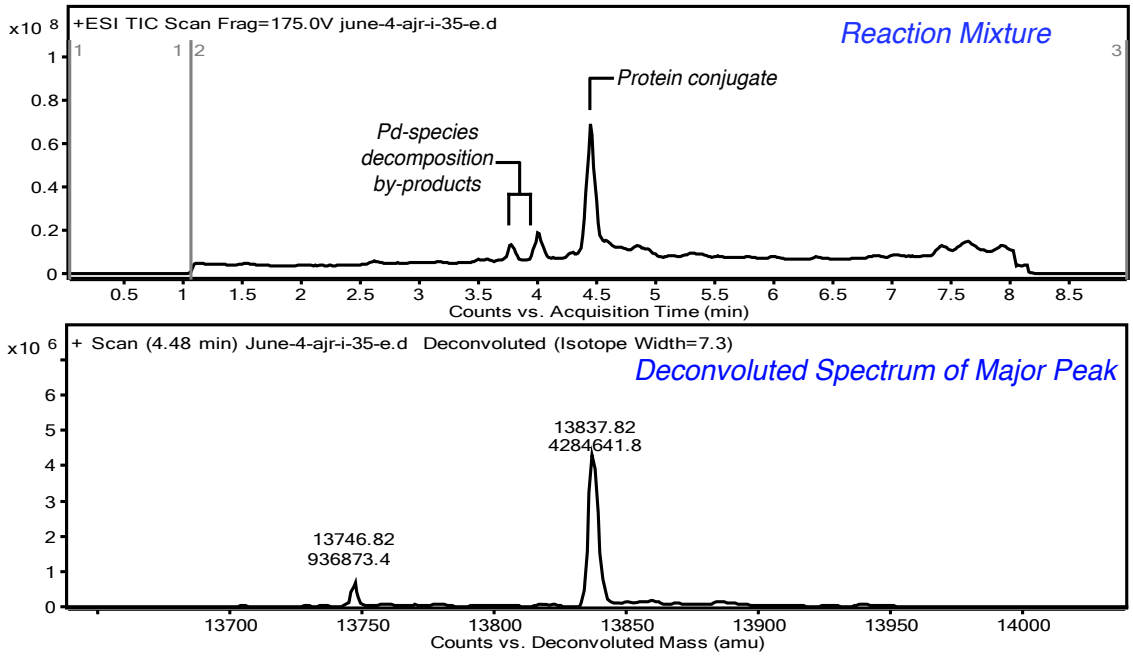


Table S2. **DARPin-Cys protein sequence and calculated mass**

Sequence[a]	Calculated mass
GGCGGSDLGKKLLEAARAGQDDEVRILMANGADVN AYDDNGVTPLHLAAFLGHLEIVEVLLKYGADVNAAD SWGTTPLHLAATWGHLEIVEVLLKHGADVNAQDKF GKTAF DISIDNGNEDLAEILQKLN	13747.3 Da

[a]Cysteine residues highlighted in red.

7. ICP-MS Analysis

Two distinct macrocyclic peptides, chosen at random (**P2-10** and **P2-14**), were dissolved in 0.4 mL of concentrated nitric acid. This solution was sonicated and diluted with MilliQ pure water to 0.2% nitric acid concentration. ICP-MS was performed on the resulting mixtures. Calibration curves were generated using Pd ICP-MS standards for a range between 1000 ppm and 100 ppb. There was no palladium found to be remaining in the peptide after purification. Initial palladium content was ~300 ppm used to perform the macrocyclization reactions indicating over 99% palladium removal.

8. REFERENCES

1. Vinogradova, E. V., Zhang, C., Spokoyny, A. M., Pentelute, B. L, Buchwald, S. L. Organometallic palladium reagents for cysteine bioconjugation. *Nature,* 526, 687–691 (2015).

2. Simon, M. D., Heider, P. L, Adamo, A., Vinogradov, A. A., Mong, S. K., Li, X., Berger, T., Policarpo, R. L., Zhang, C., Zou, Y., Liao, X., Spokoyny, A. M., Jensen, K. F., Pentelute, B. L. Rapid flow-based peptide synthesis. *Chembiochem* **15**, 713-720 (2014).

3. Liao, X., Rabideau, A. E. & Pentelute, B. L. Delivery of antibody mimics into mammalian cells via anthrax toxin protective antigen. *Chembiochem* **15**, 2458–2466 (2014).

9. LC-MS CHARACTERIZATION OF OXIDATIVE ADDITION COMPLEXES

General Procedure

Each Pd reagent (**OA-Y**) reagent was dissolved in a 50:50 mixture of water:acetonitrile with 0.1% TFA and injected directly into the LC-MS and analysed via Method A in order to confirm purity of starting materials. Due to the complexity of the NMR spectra for each oxidative addition complex, we felt it was necessary to supply an additional measure of characterization of each complex.

Figure S-15: LC-MS Chromatogram of pure OA-3

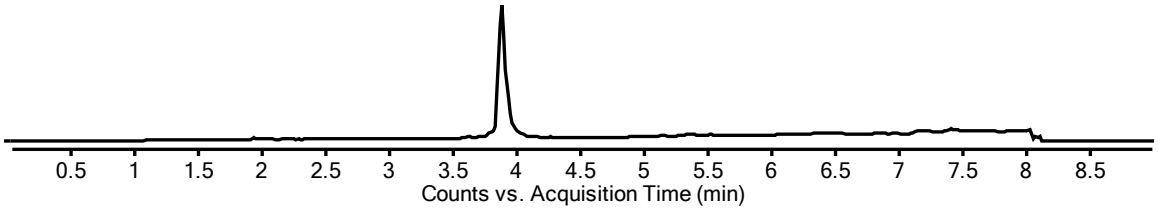


Figure S-16: LC-MS Chromatogram of pure OA-7

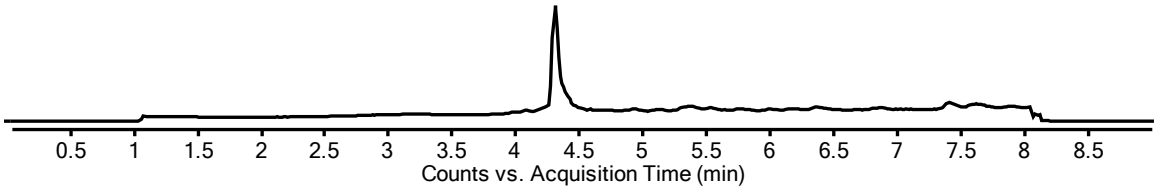


Figure S-17: LC-MS Chromatogram of pure OA-8

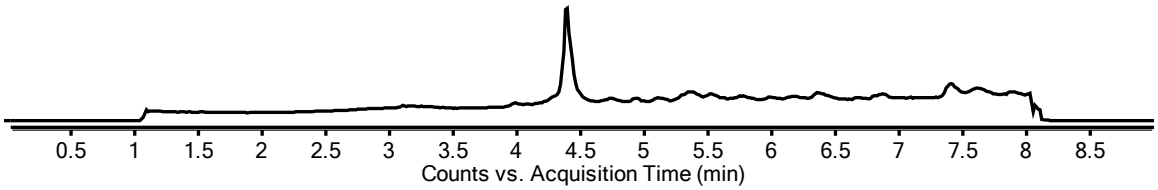


Figure S-18: LC-MS Chromatogram of pure OA-9

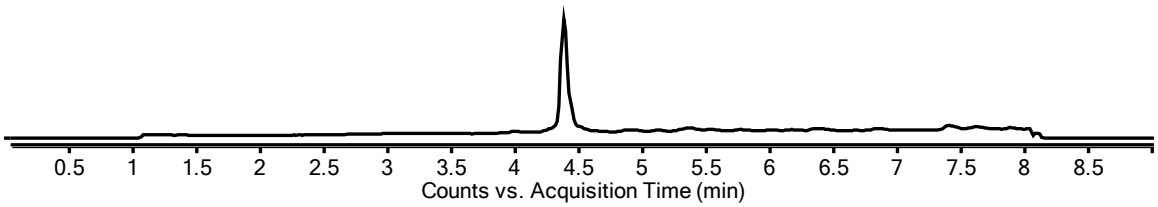


Figure S-19: LC-MS Chromatogram of pure OA-10

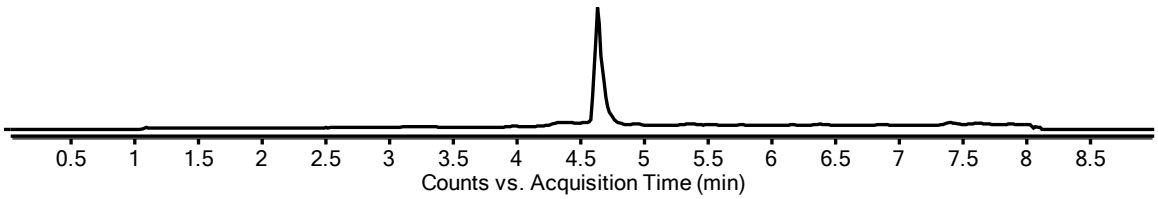


Figure S-20: LC-MS Chromatogram of pure OA-11

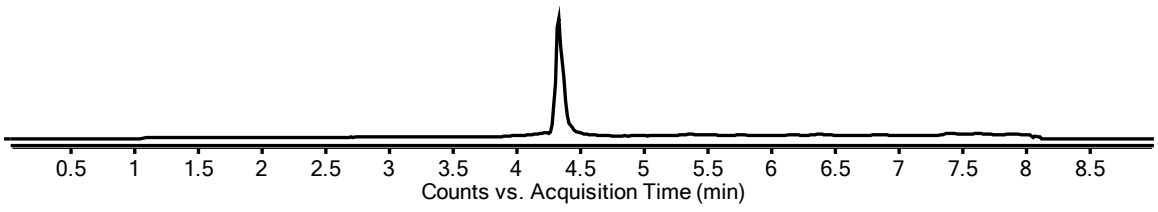


Figure S-21: LC-MS Chromatogram of pure OA-12

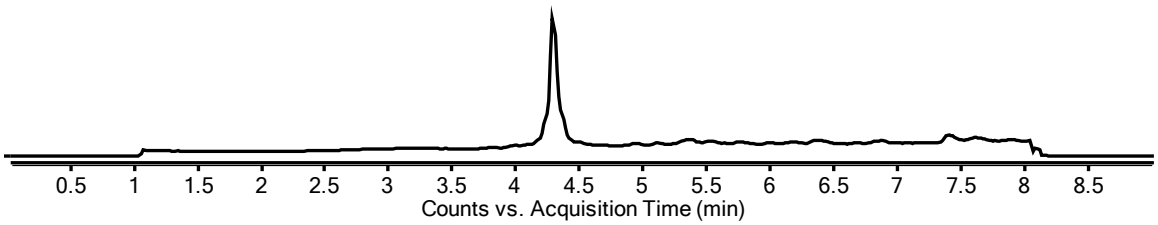


Figure S-22: LC-MS Chromatogram of pure OA-13

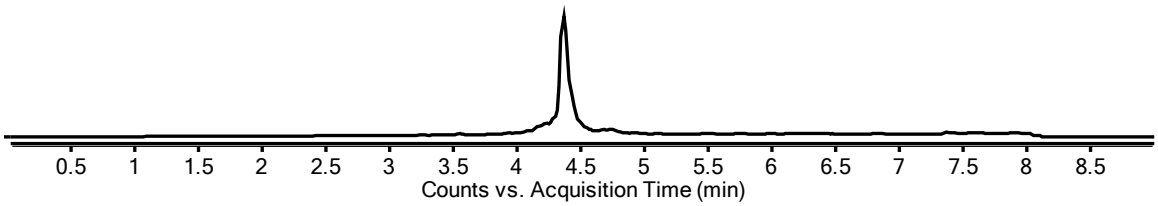


Figure S-23: LC-MS Chromatogram of pure OA-14

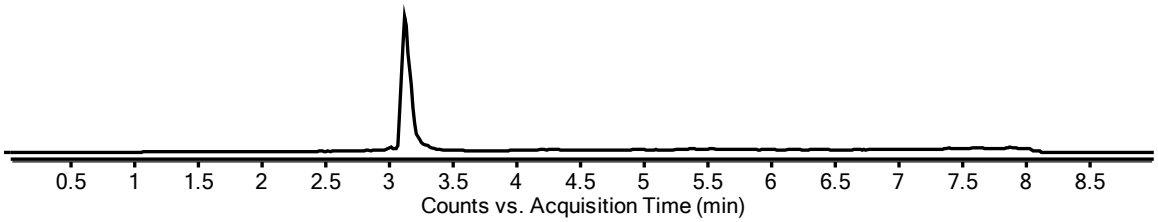


Figure S-24: LC-MS Chromatogram of pure OA-15

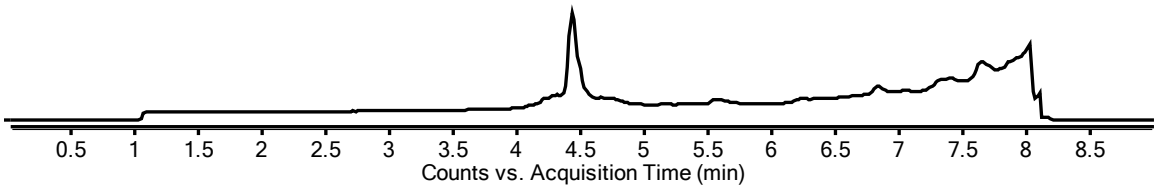


Figure S-25: LC-MS Chromatogram of pure OA-16

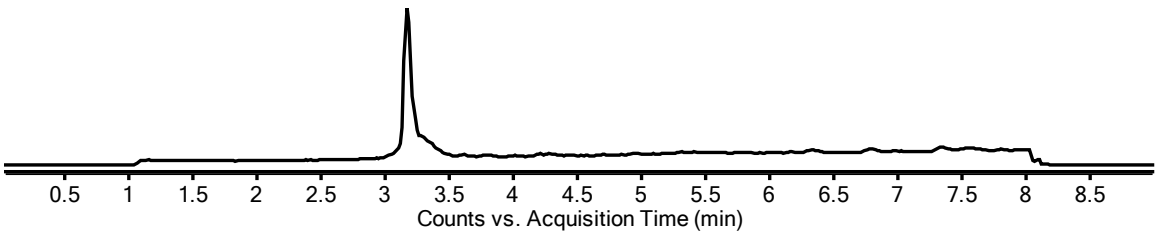


Figure S-26: LC-MS Chromatogram of pure OA-17

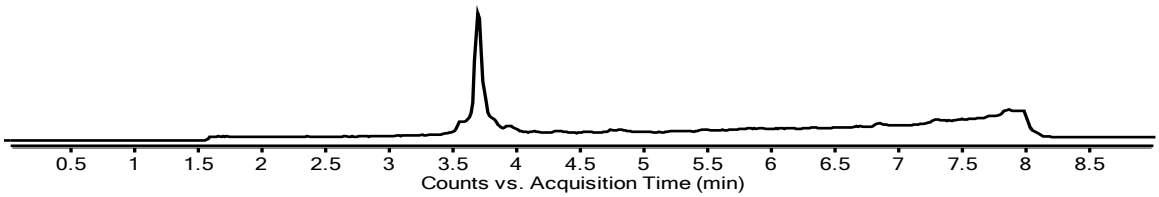


Figure S-27: LC-MS Chromatogram of pure OA-18

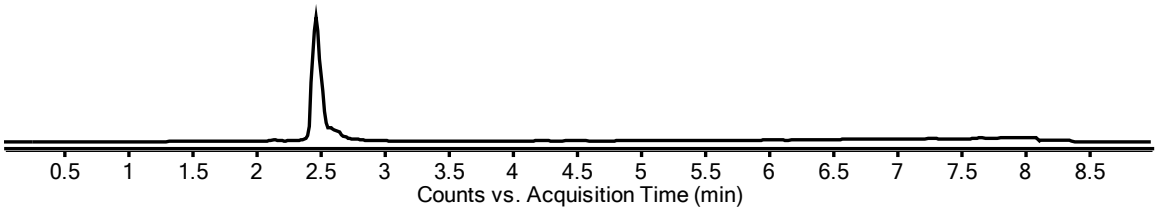


Figure S-28: LC-MS Chromatogram of pure OA-19

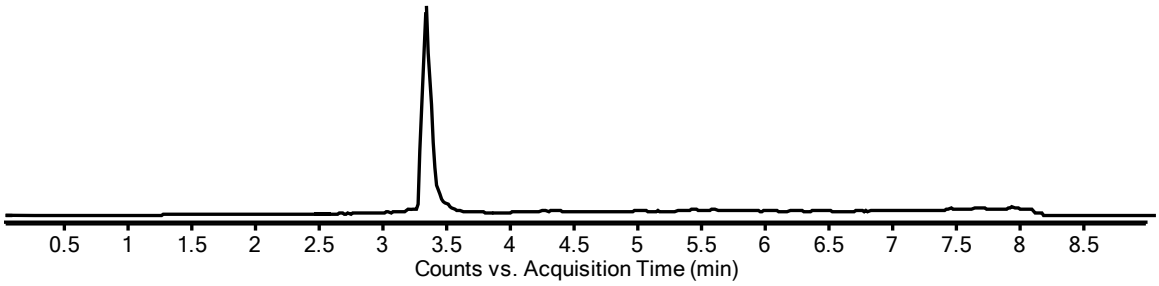


Figure S-29: LC-MS Chromatogram of pure OA-20

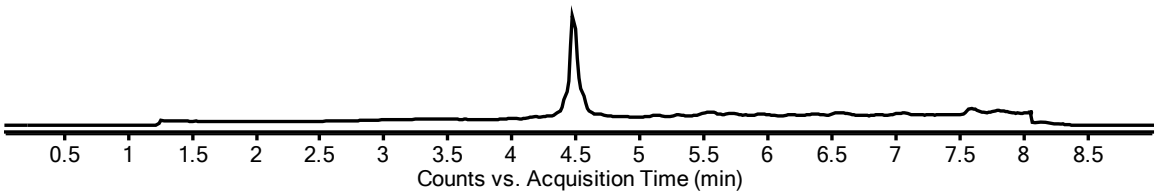


Figure S-30: LC-MS Chromatogram of pure OA-21

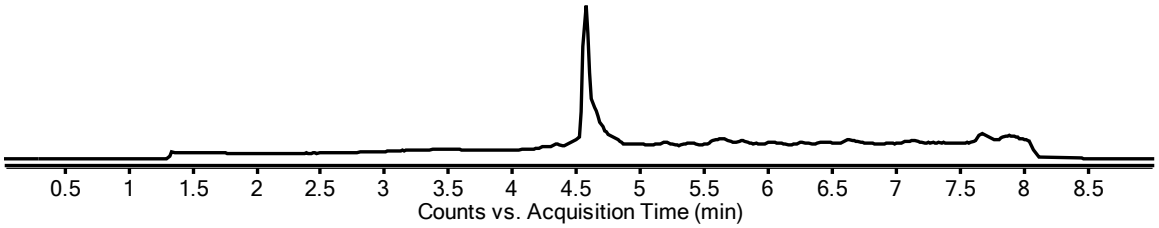


Figure S-31: LC-MS Chromatogram of pure OA-22

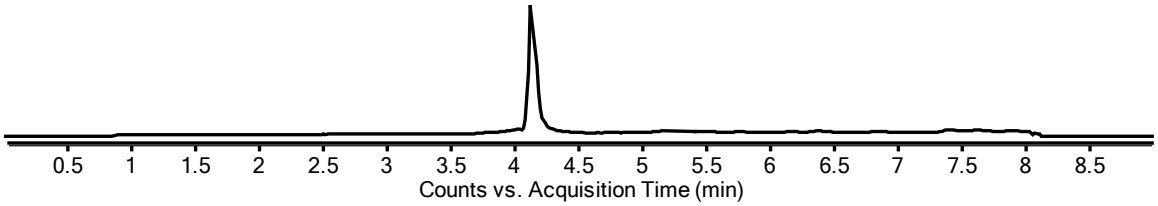


Figure S-32: LC-MS Chromatogram of pure OA-23

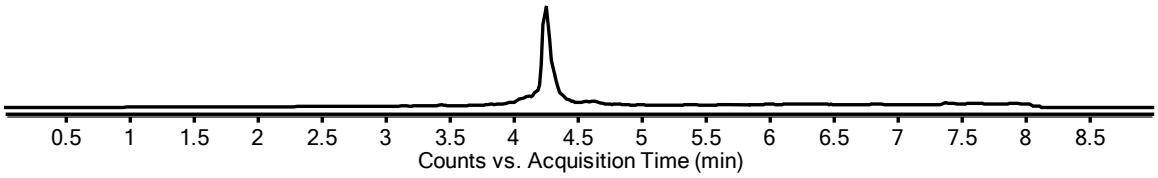


Figure S-33: LC-MS Chromatogram of pure OA-24

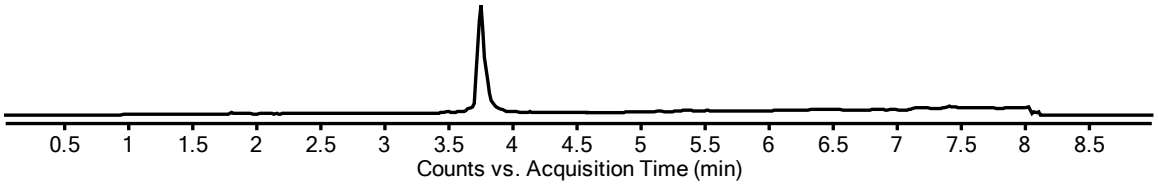
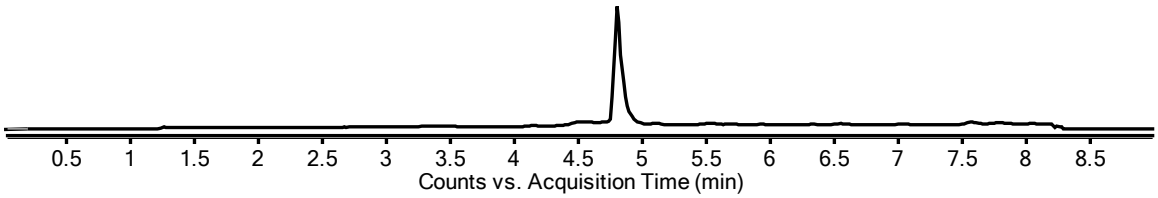
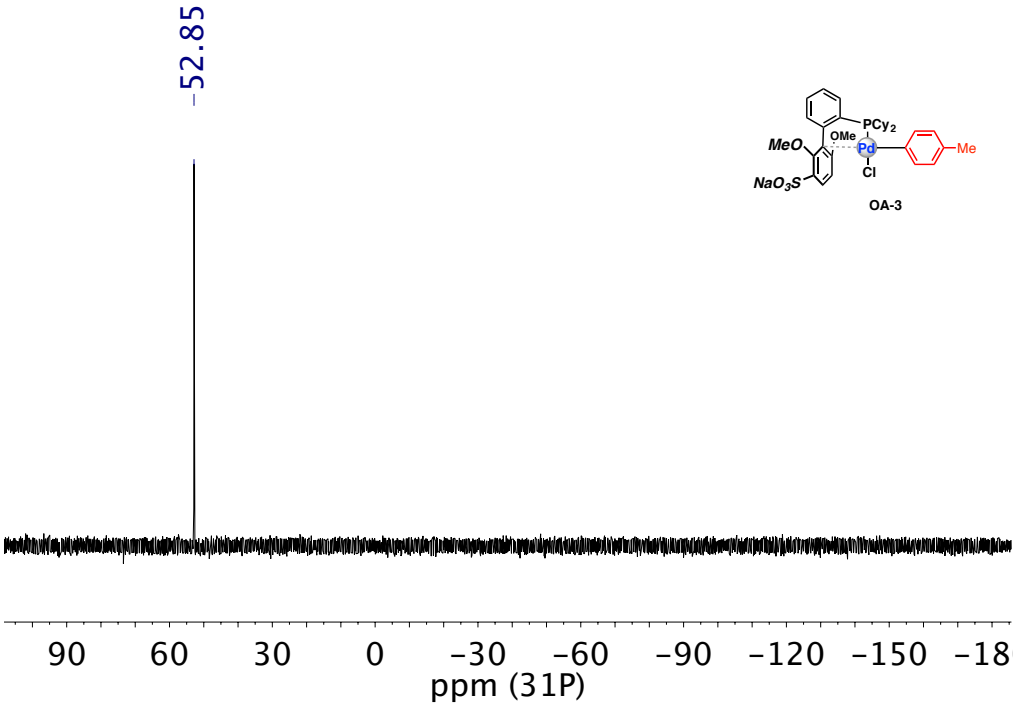
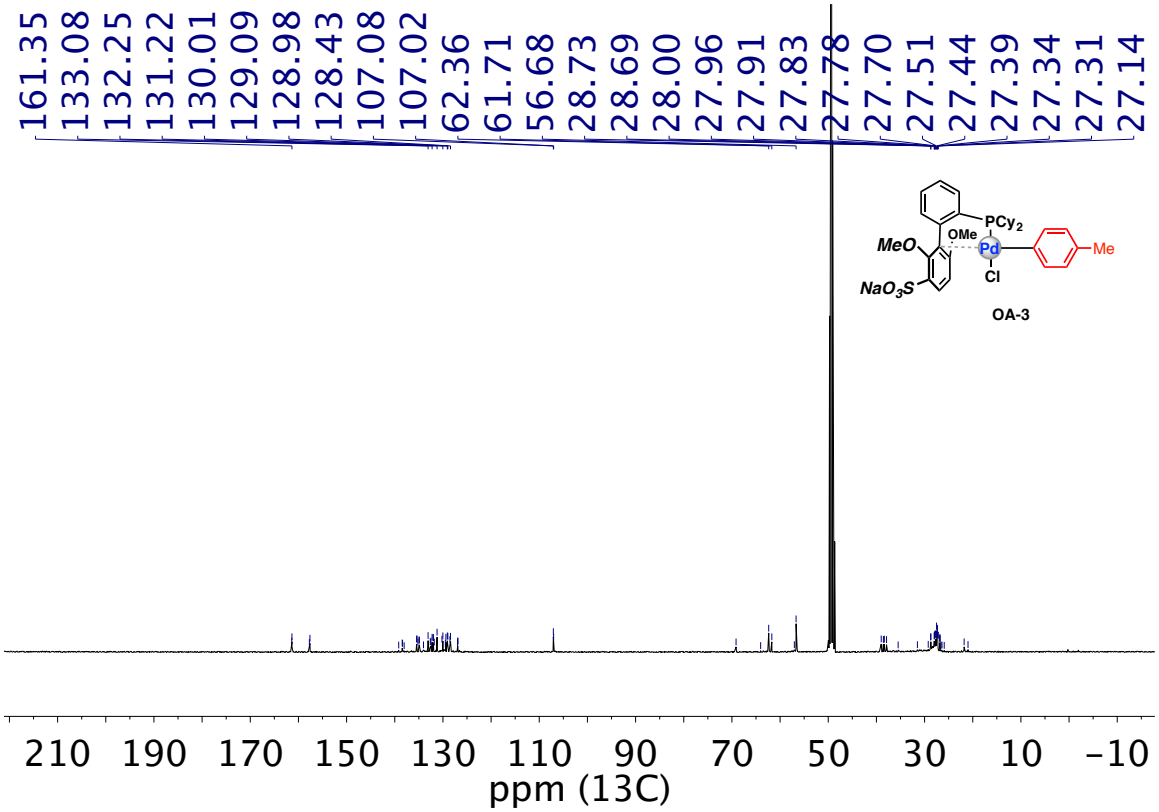


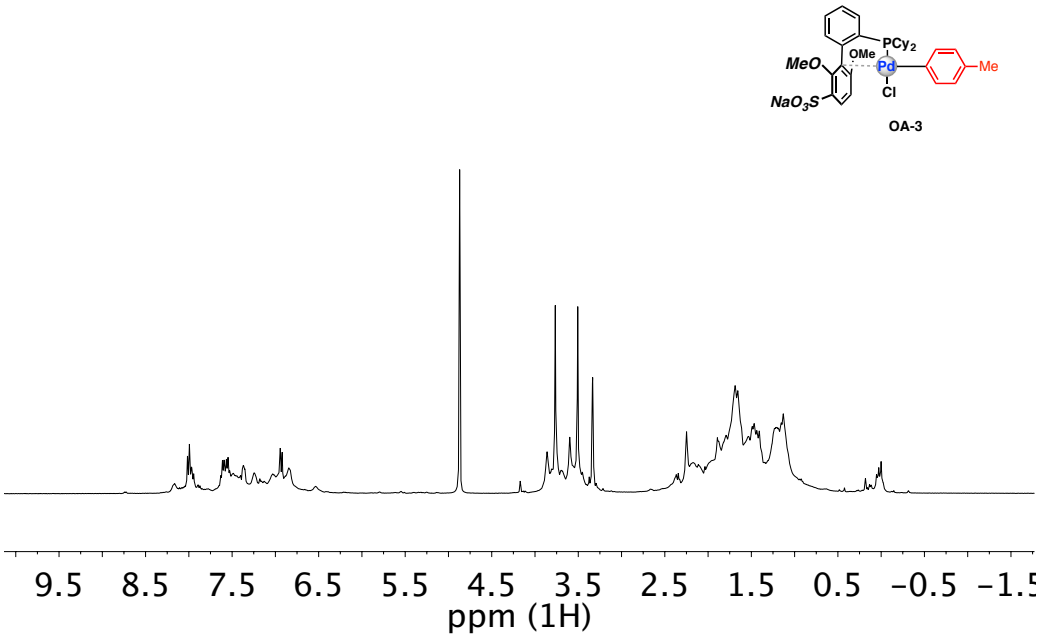
Figure S-34: LC-MS Chromatogram of pure OA-25



9. NMR SPECTRA (ALL TAKEN IN A SOLUTION OF MEOD)



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MeO
Pd
Me
Cl
NaO3S
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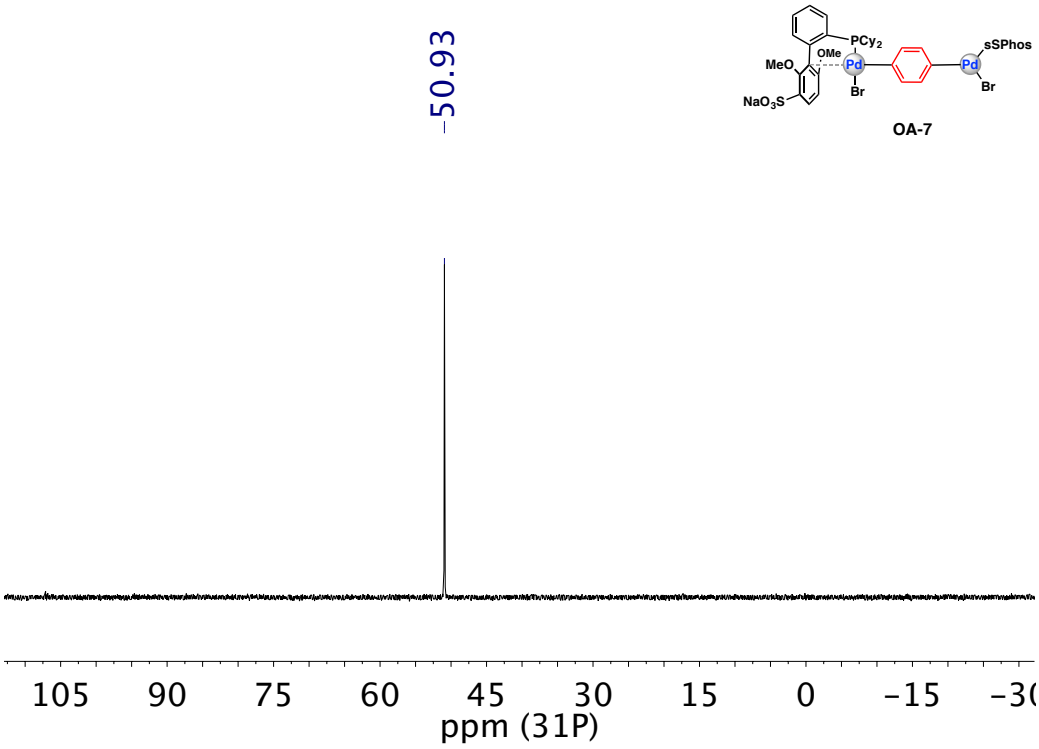
ppm (1H)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Br
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OA-7
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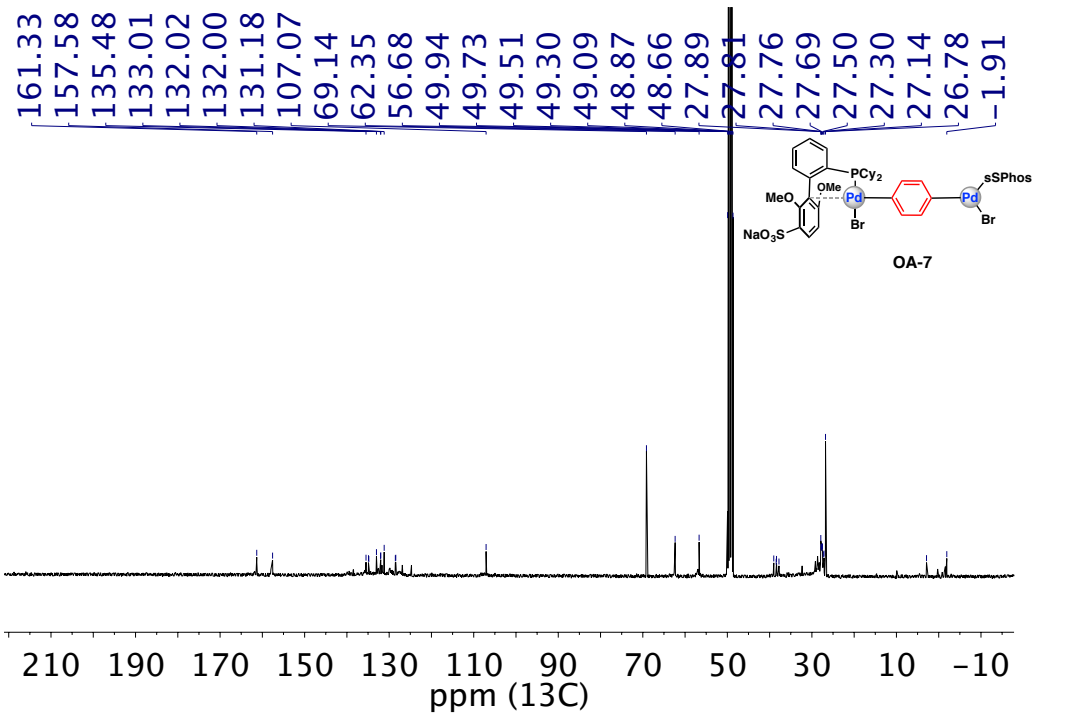
ppm (31P)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49.73
49.51
49.30
49.09
48.87
48.66
27.89
27.81
27.76
27.69
27.50
27.30
27.14
26.78
-1.91
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MeO
Pd
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OA-7
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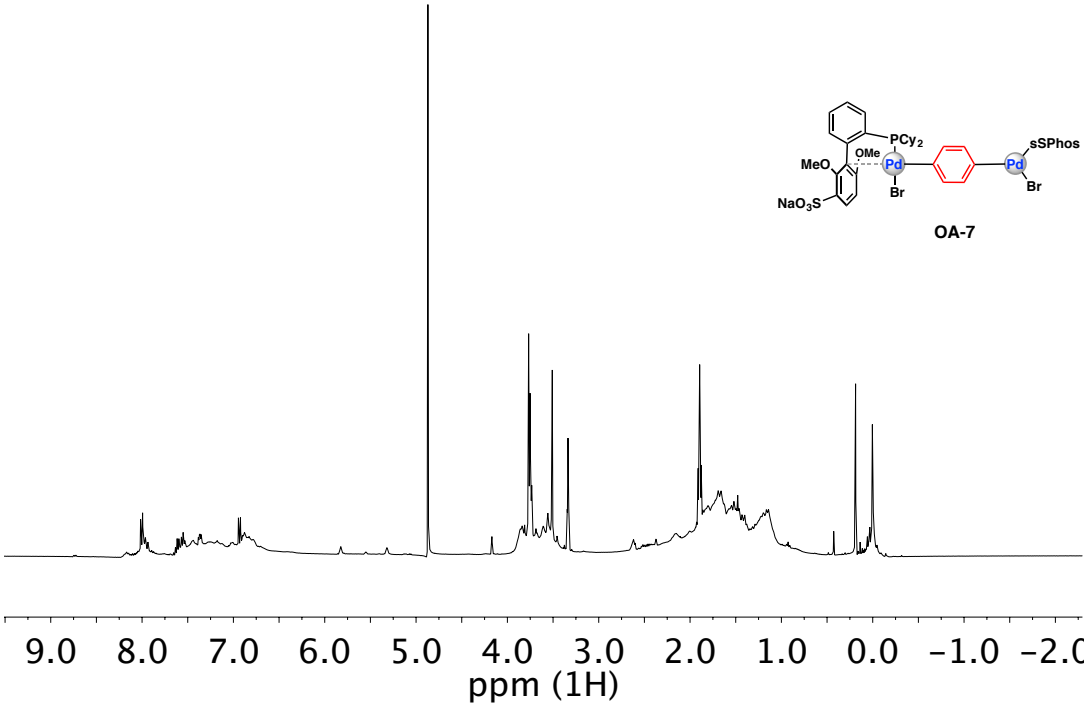
ppm (13C)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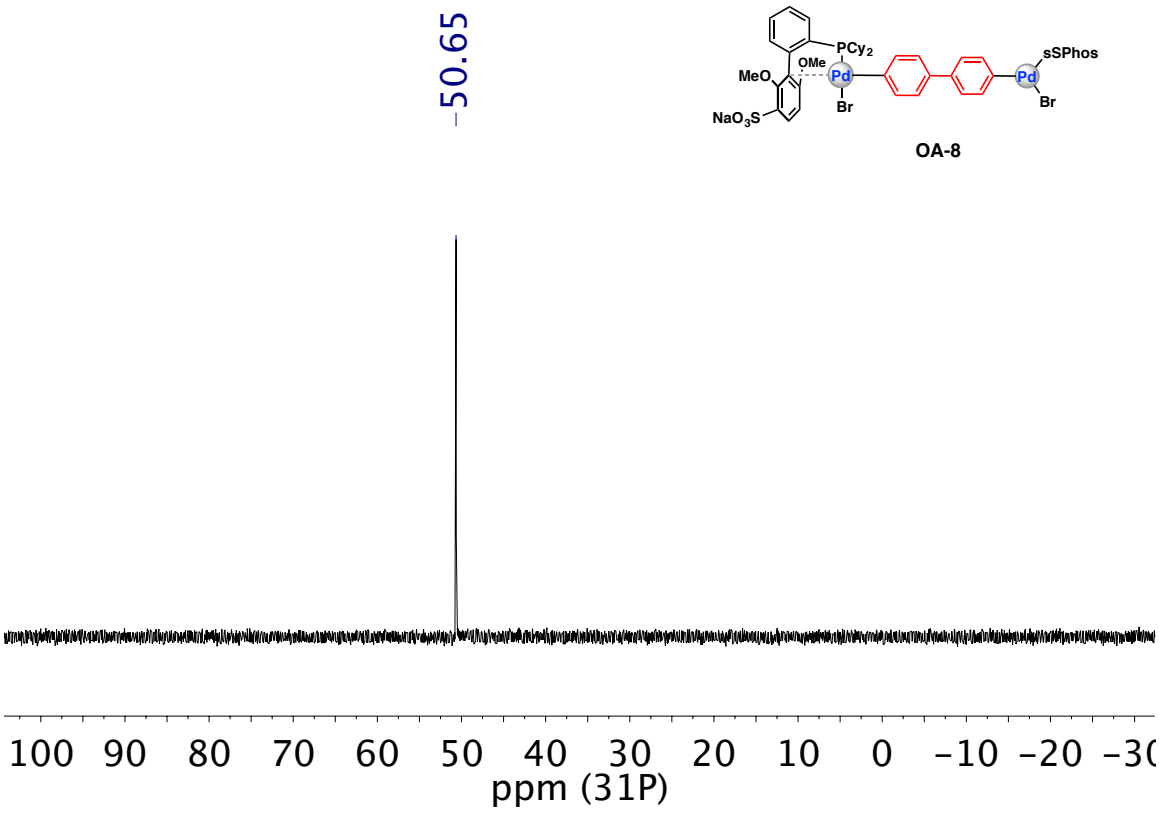
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Pd
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Pd
Br
OA-8
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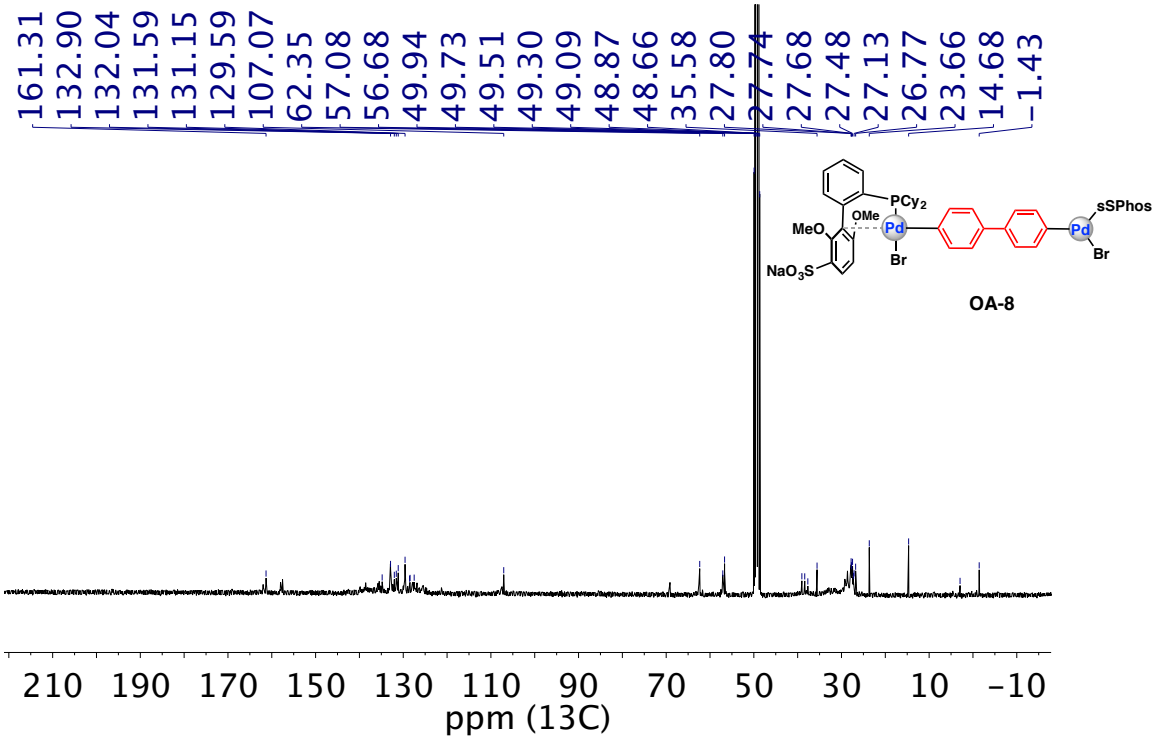
ppm (31P)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27.48
27.13
26.77
23.66
14.68
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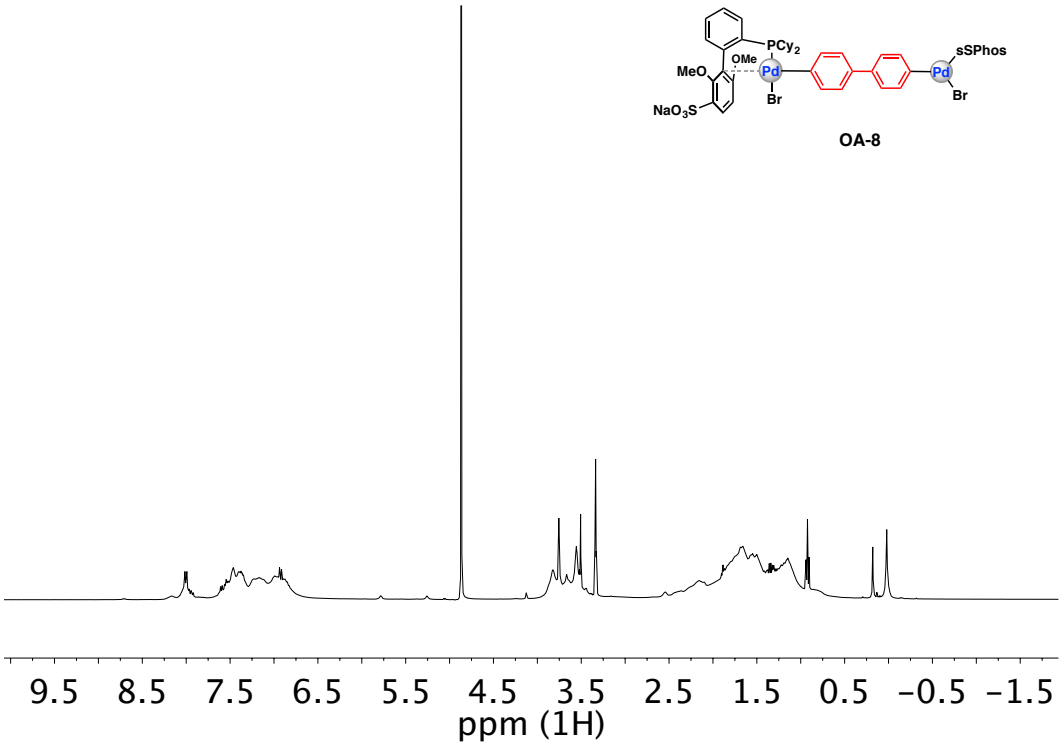
ppm (13C)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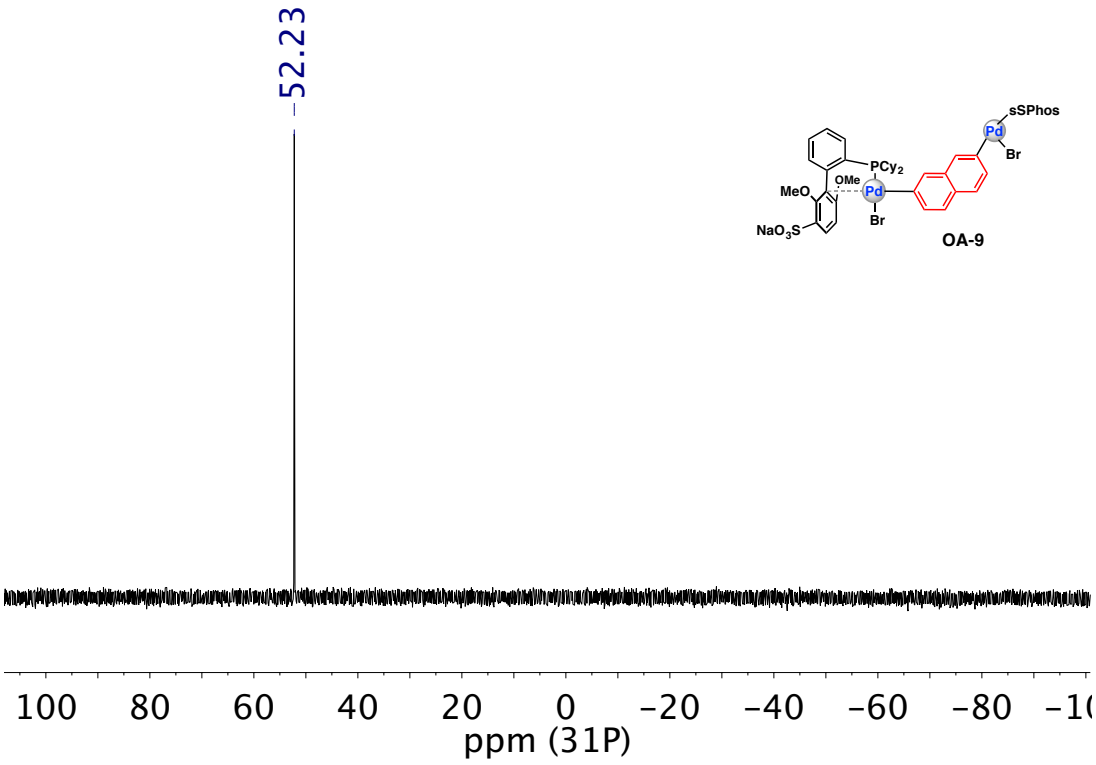
ppm (1H)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OA-9
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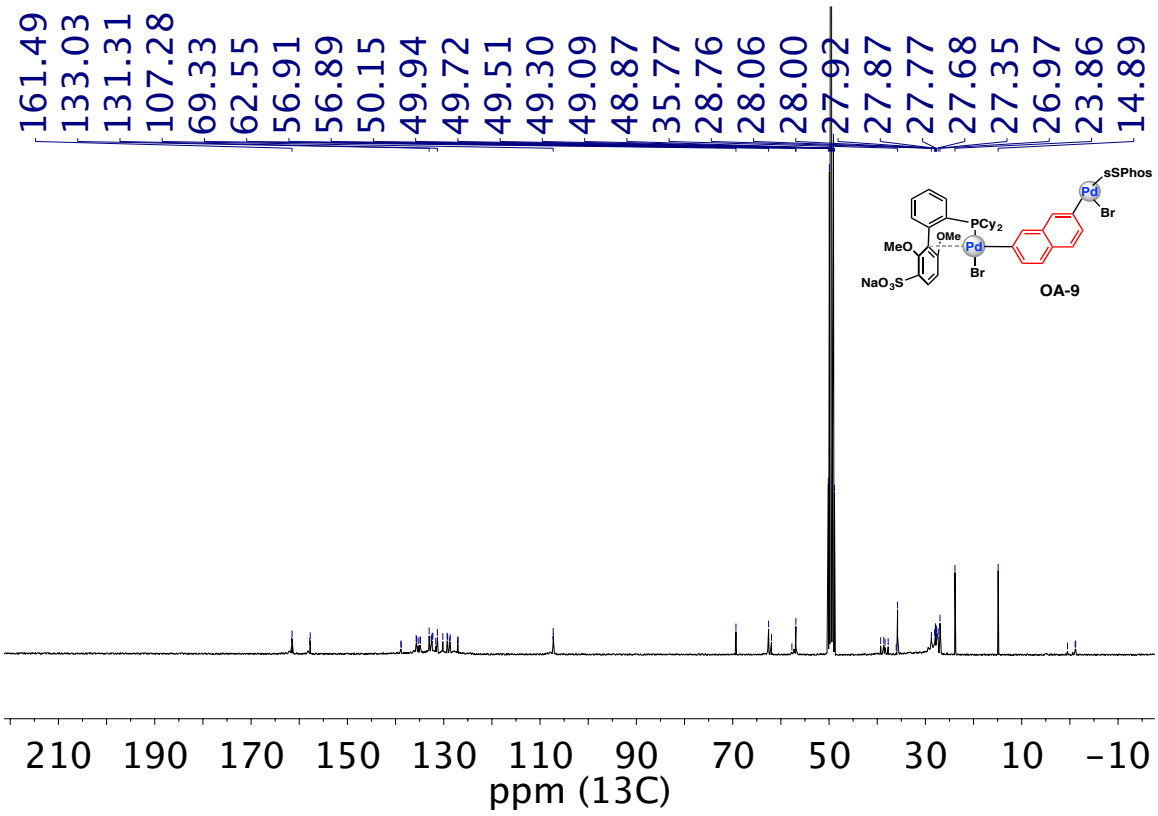
ppm (31P)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35.77
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28.06
28.00
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27.87
27.77
27.68
27.35
26.97
23.86
14.89
sSPhos
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MeO
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OA-9
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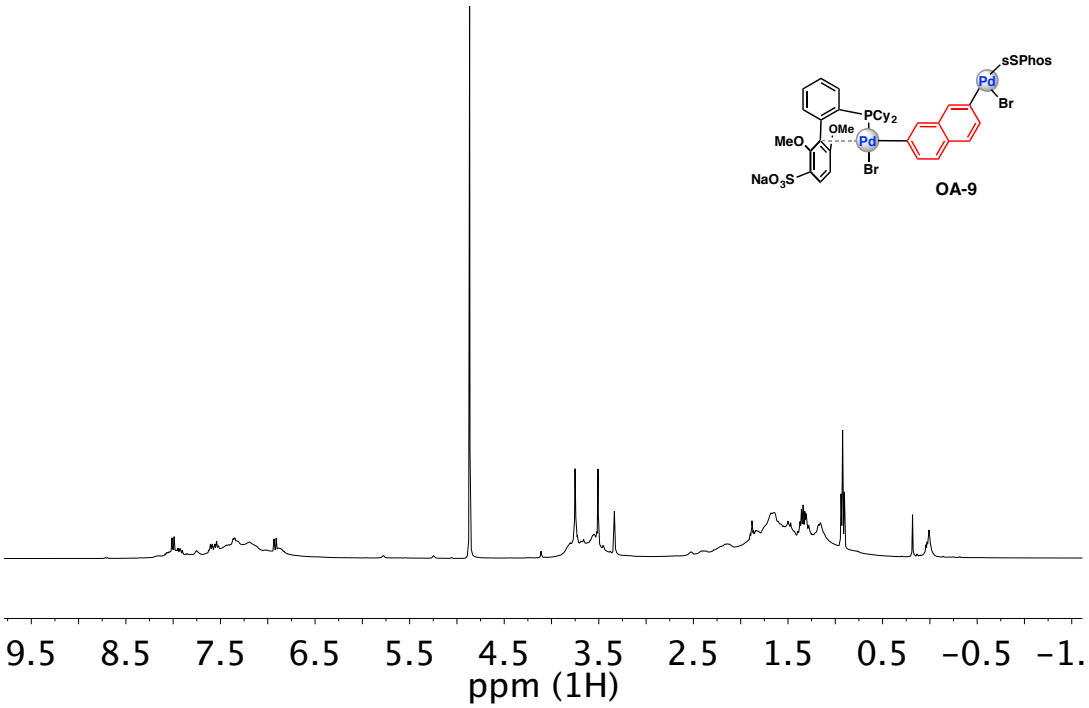
ppm (13C)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Pd
Br
PCy2
OMe
MeO
Pd
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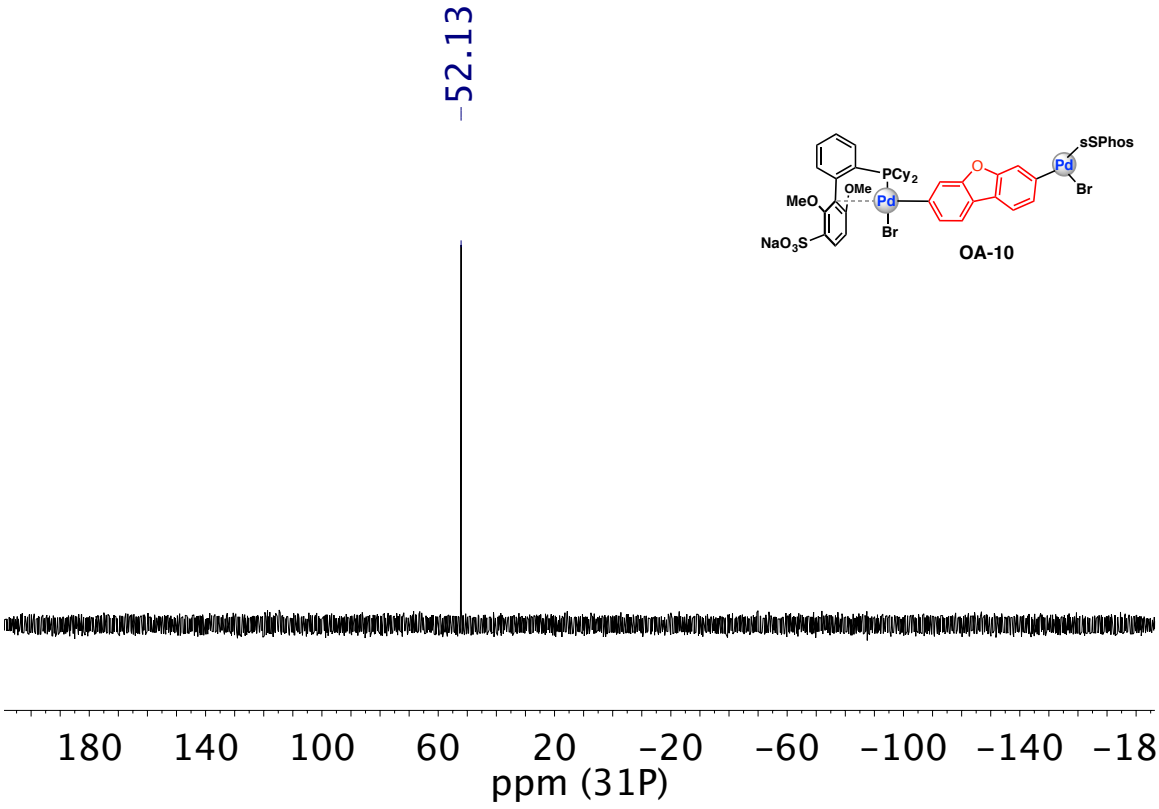
NaO3S
OA-9
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0.5 -1.
ppm (1H)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OA-10
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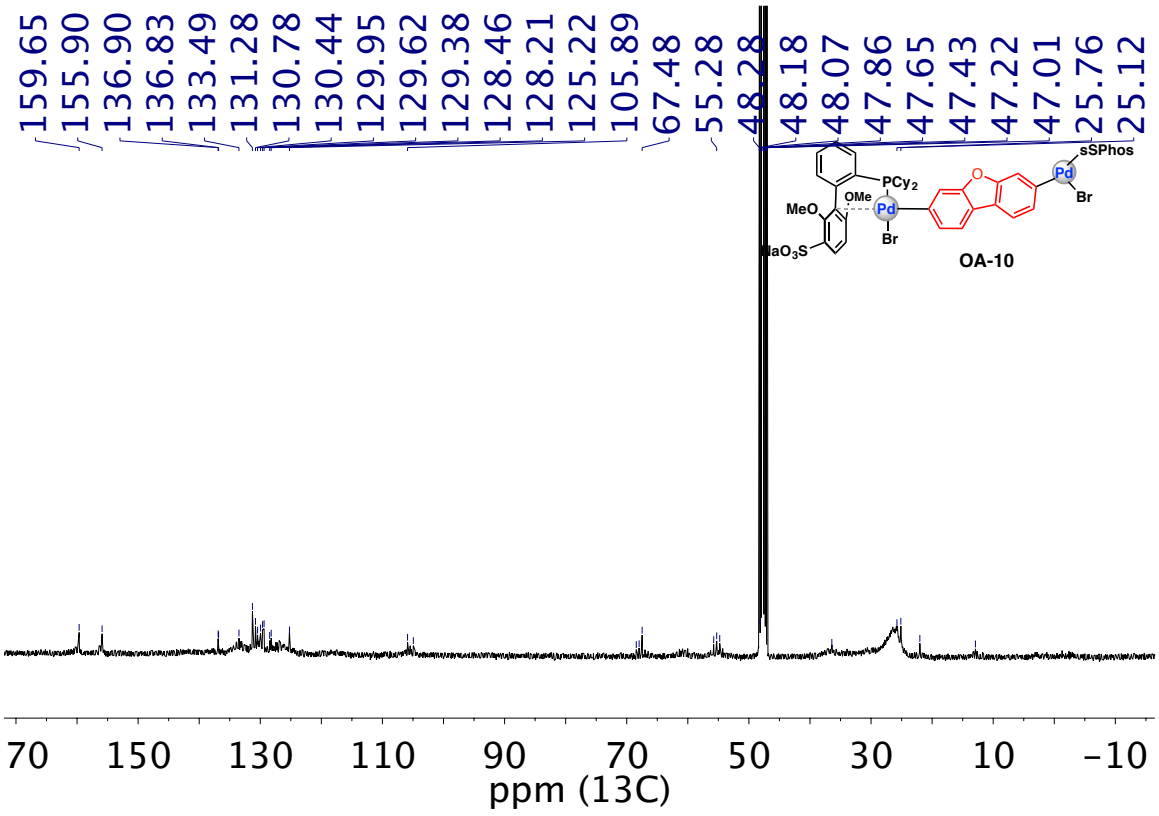
ppm (31P)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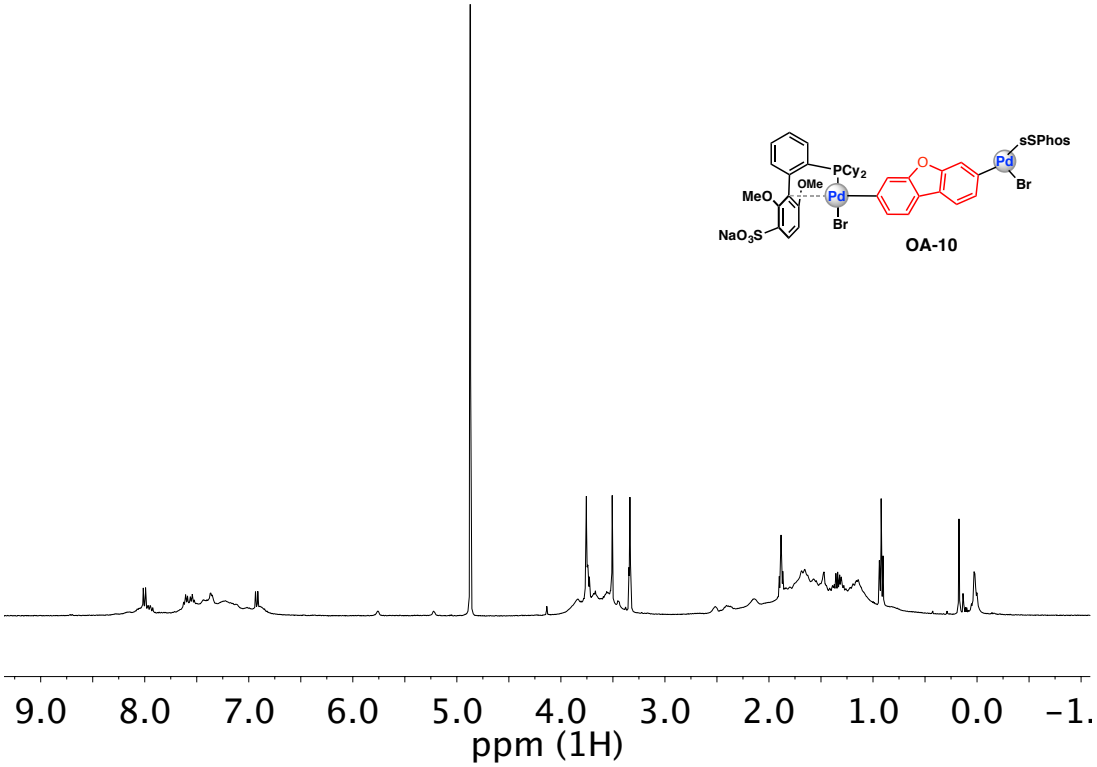
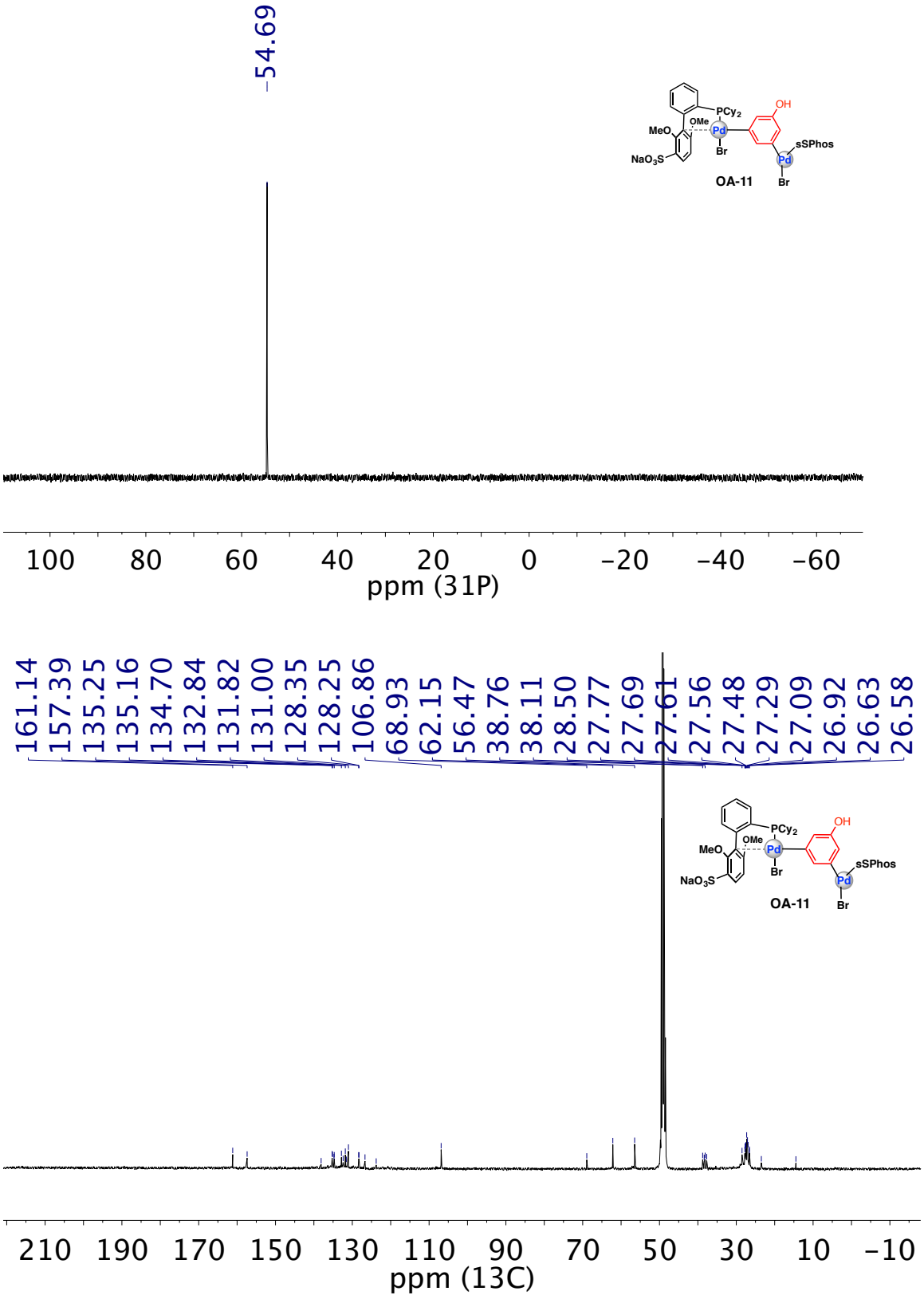
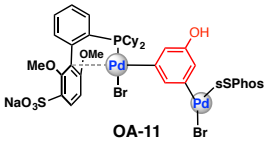
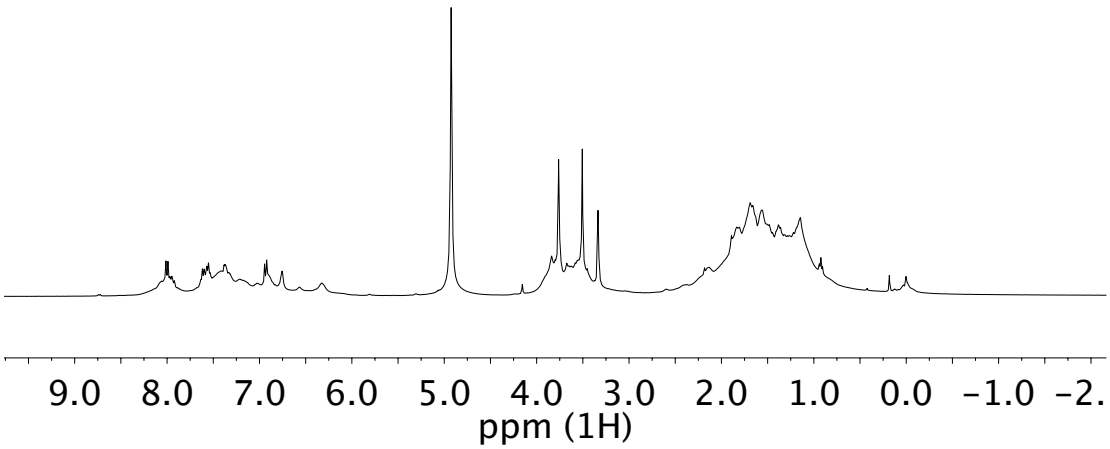
125.22
105.89
67.48
55.28
48.28
48.18
48.07
47.86
47.65
47.43
47.22
47.01
25.76
25.12
sSPhos
PCy2
OMe
MeO
Pd
Br
NaO3S
OA-10
70
150
130
110
90
70
50
30
10
-10
ppm (13C)


sSPhos
PCy2
OMe
MeO
Pd
Br
NaO3S
OA-10
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.
ppm (1H)

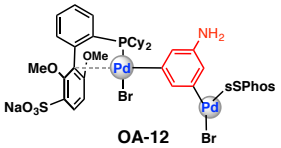

54.69
OA-11
100 80 60 40 20 0 -20 -40 -60
ppm (31P)
161.14
157.39
135.25
135.16
134.70
132.84
131.82
131.00
128.35
128.25
106.86
68.93
62.15
56.47
38.76
38.11
28.50
27.77
27.69
27.61
27.56
27.48
27.29
27.09
26.92
26.63
26.58
OA-11
210 190 170 150 130 110 90 70 50 30 10 -10
ppm (13C)



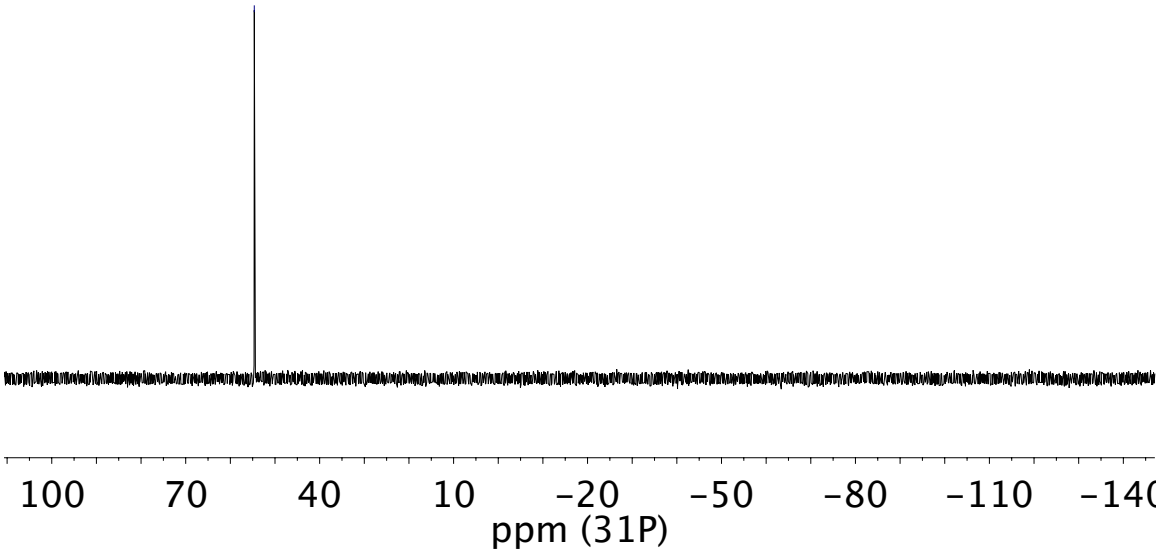
OA-11

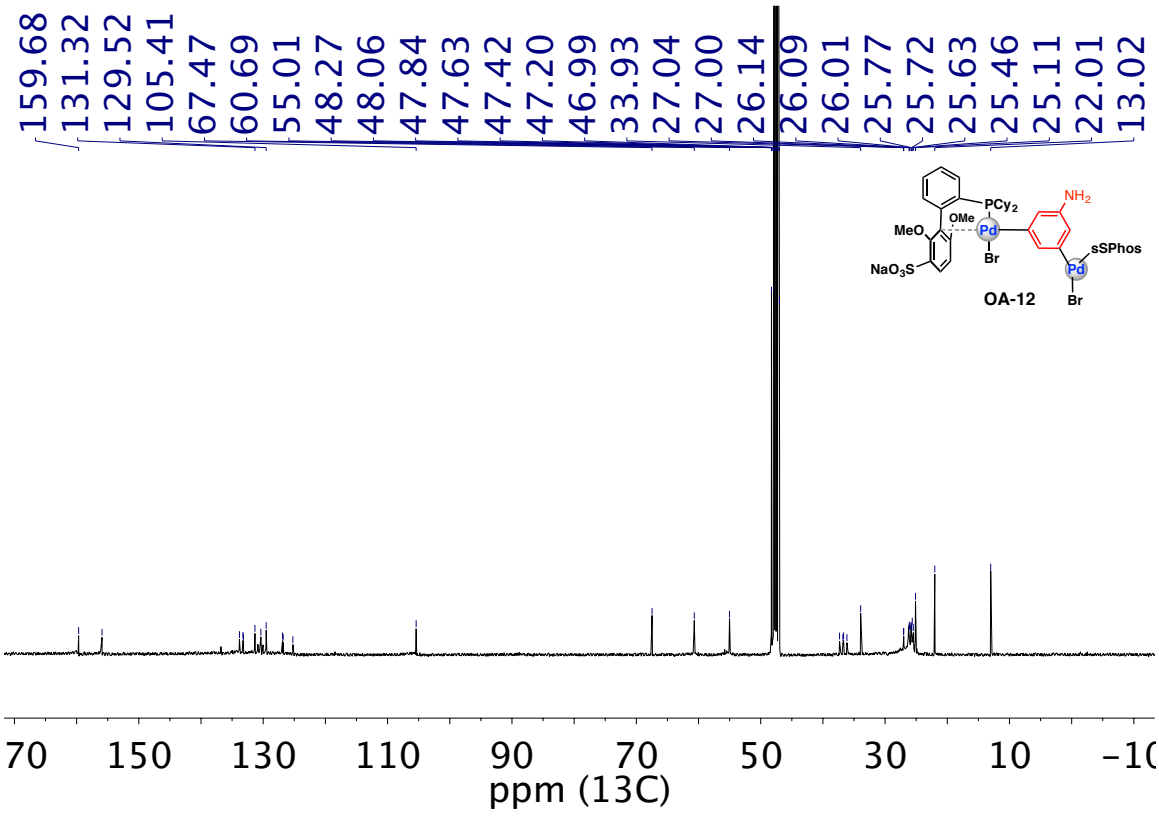


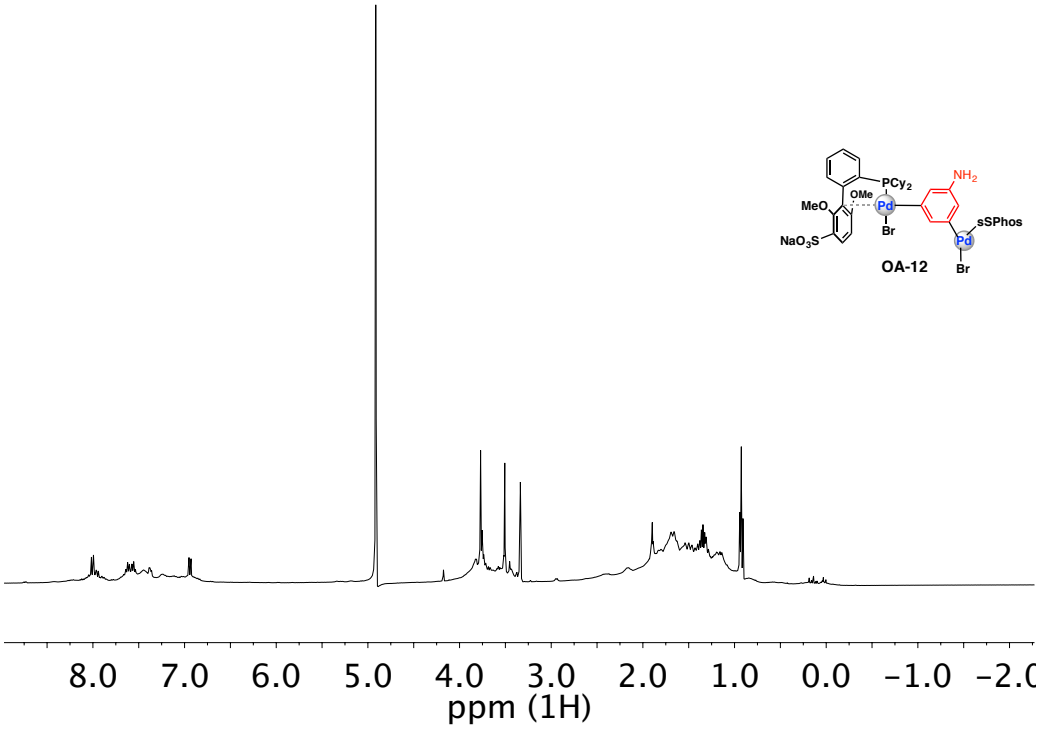
−54.64

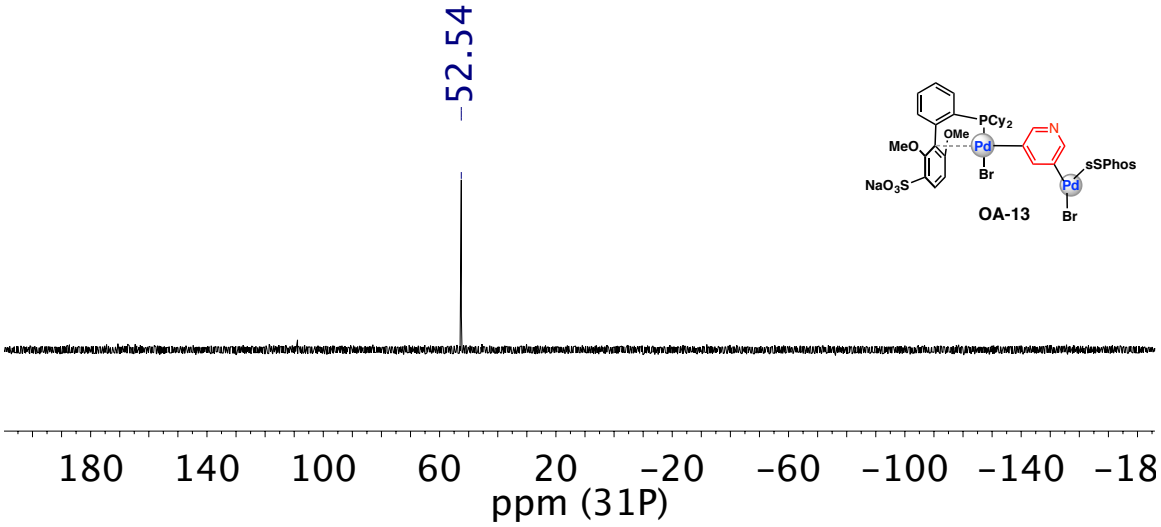


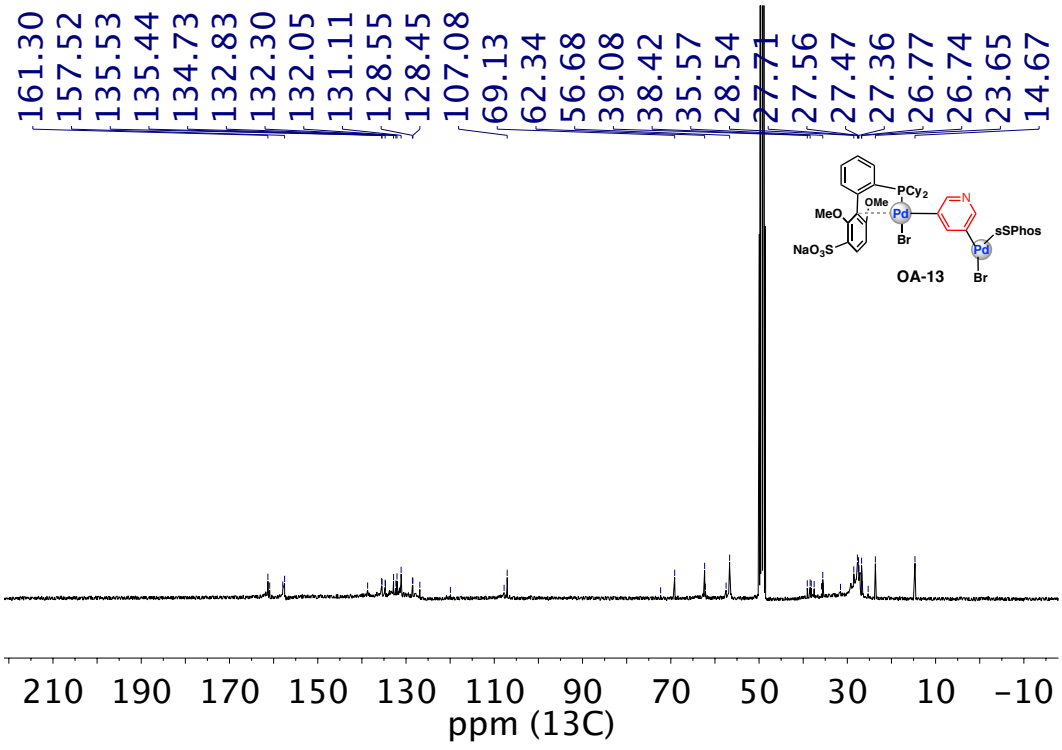
OA-12

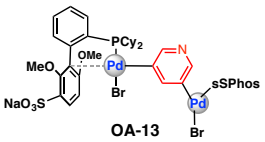



159.68
131.32
129.52
105.41
67.47
60.69
55.01
48.27
48.06
47.84
47.63
47.42
47.20
46.99
33.93
27.04
27.00
26.14
26.09
26.01
25.77
25.72
25.63
25.46
25.11
22.01
13.02
PCy2
NH2
OMe
MeO
Pd
Br
sSPhos
NaO3S
OA-12
70
150
130
110
90
70
50
30
10
ppm (13C)

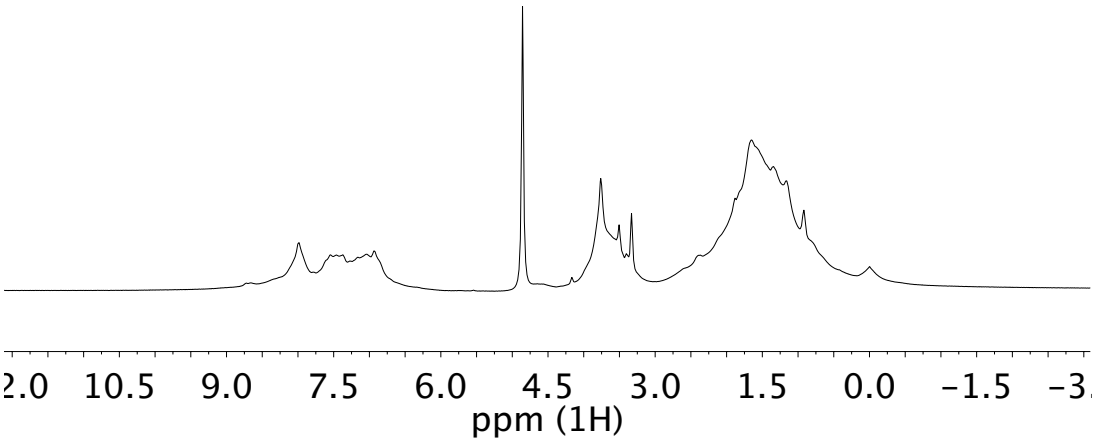

PCy2
NH2
OMe
MeO
Pd
Br
sSPhos
NaO3S
OA-12
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
ppm (1H)

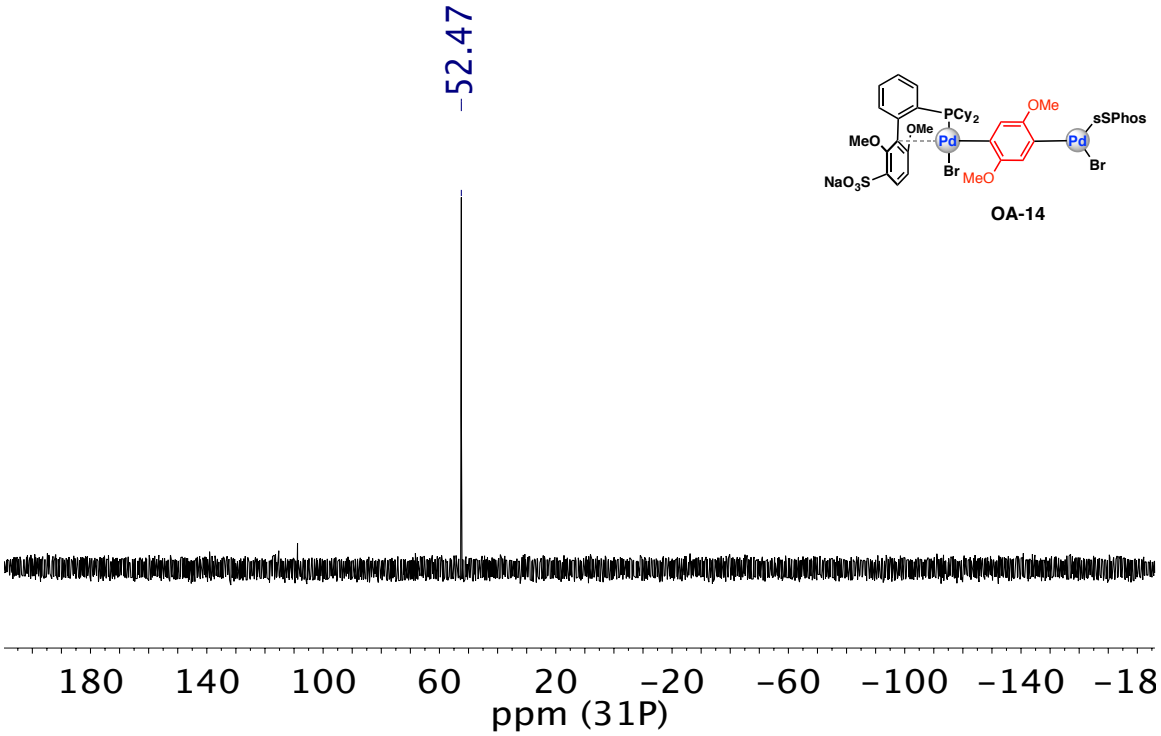

-52.54
PCy2
OMe
MeO
Pd
Br
N
sSPhos
NaO3S
OA-13
180 140 100 60 20 -20 -60 -100 -140 -18
ppm (31P)


161.30
157.52
135.53
135.44
134.73
132.83
132.30
132.05
131.11
128.55
128.45
107.08
69.13
62.34
56.68
39.08
38.42
35.57
28.54
27.71
27.56
27.47
27.36
26.77
26.74
23.65
14.67
PCy2
OMe
MeO
Pd
Br
N
sSPhos
NaO3S
OA-13
210 190 170 150 130 110 90 70 50 30 10 -10
ppm (13C)


PCy2
OMe
MeO
Pd
Br
N
sSPhos
NaO3S
Pd
Br

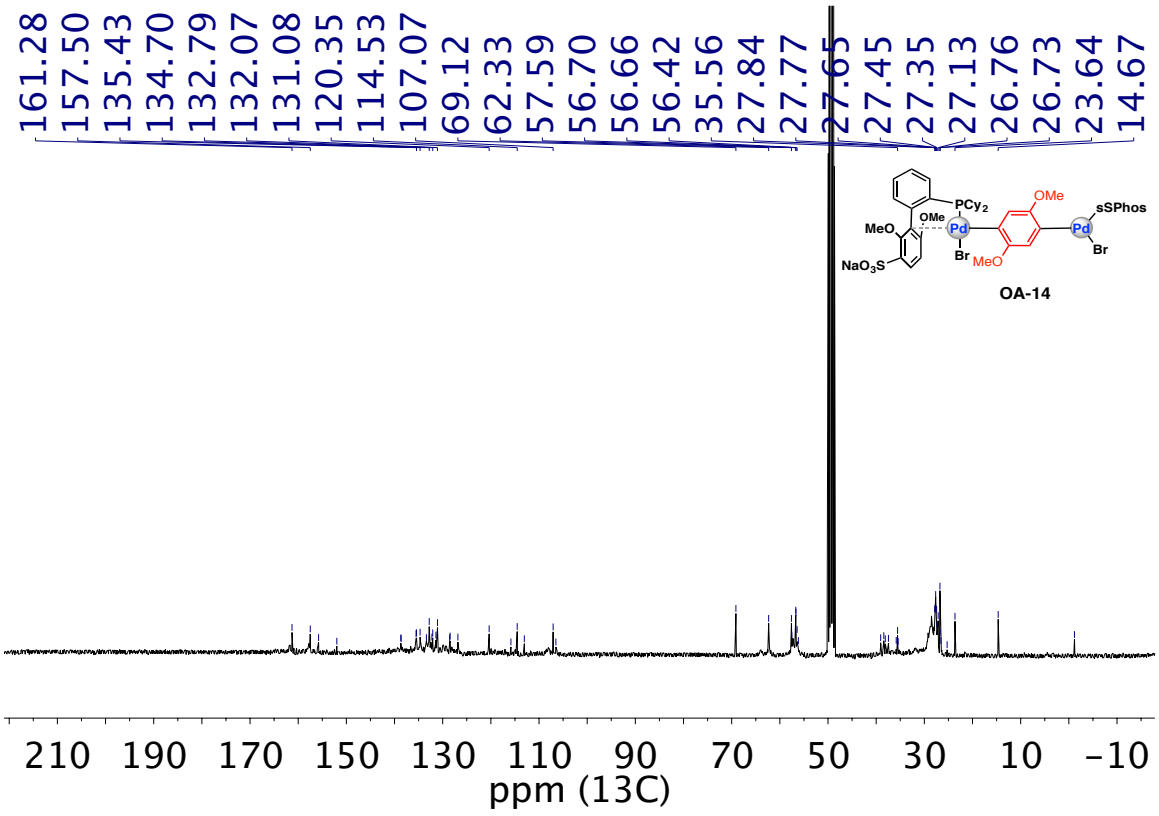
OA-13

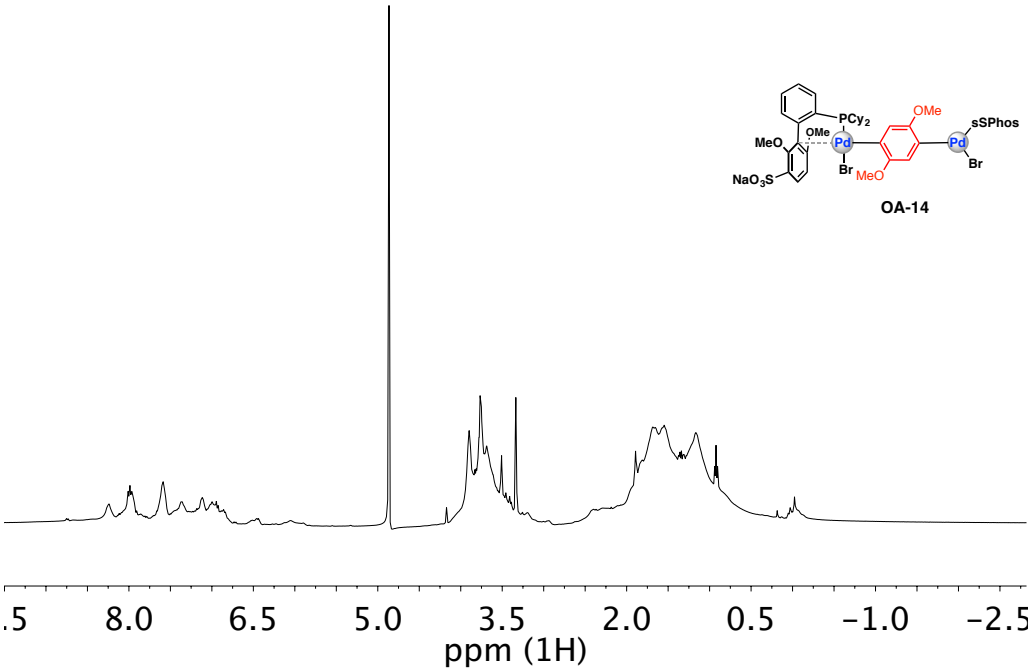

2.0
10.5
9.0
7.5
6.0
4.5
3.0
1.5
0.0
−1.5
−3
ppm (1H)

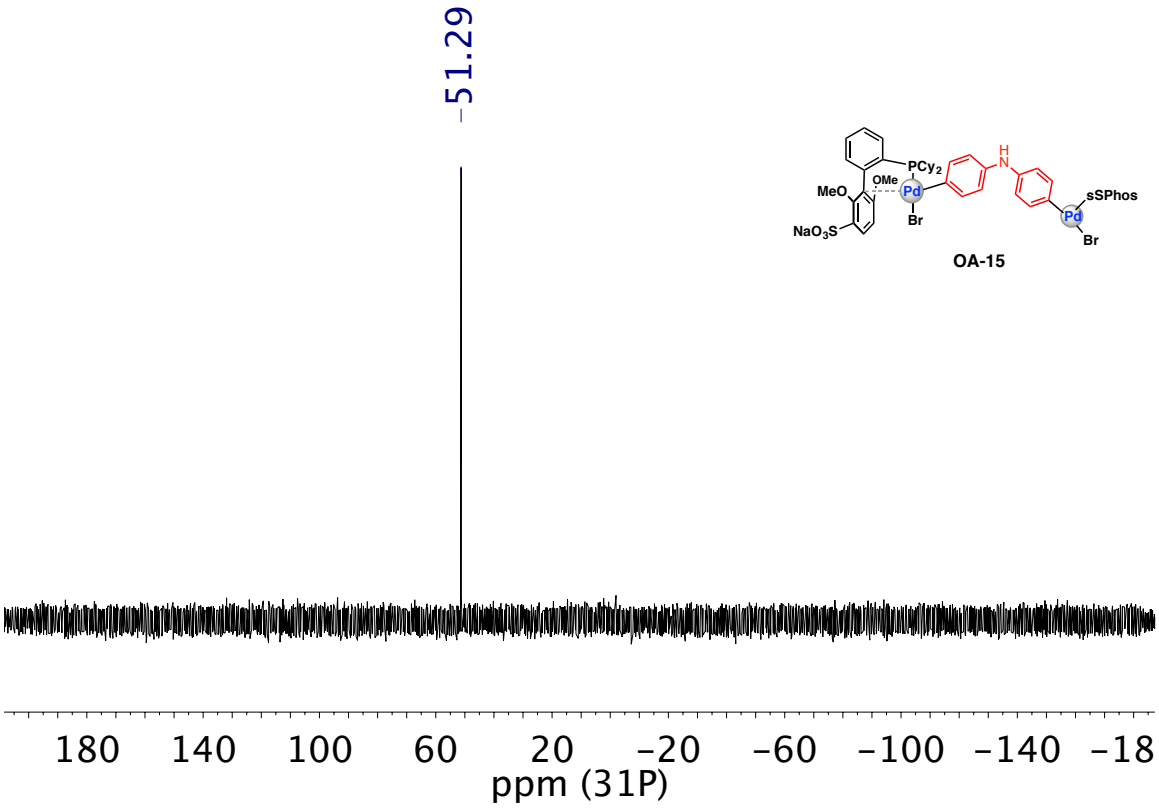

52.47
180
140
100
60
20
−20
−60
−100
−140
−18
ppm (31P)

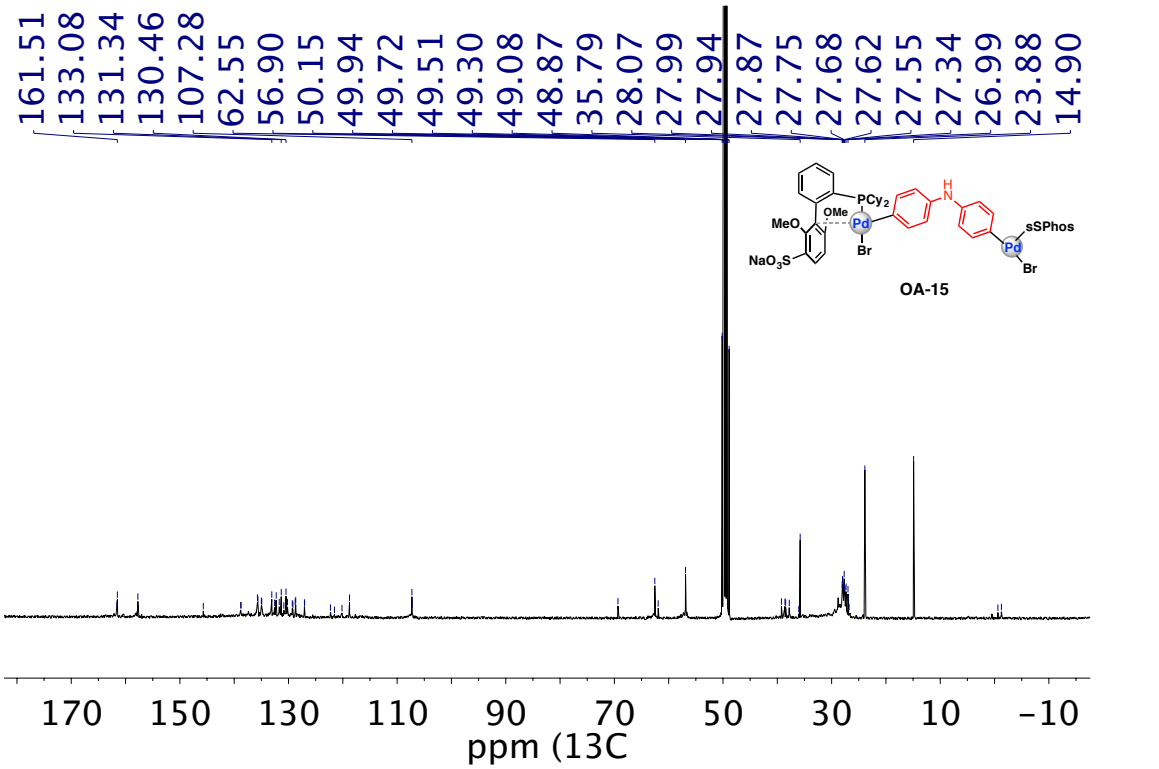
PCy2
OMe
OMe
sSPhos
MeO
Pd
Pd
Br
Br
MeO
NaO3S

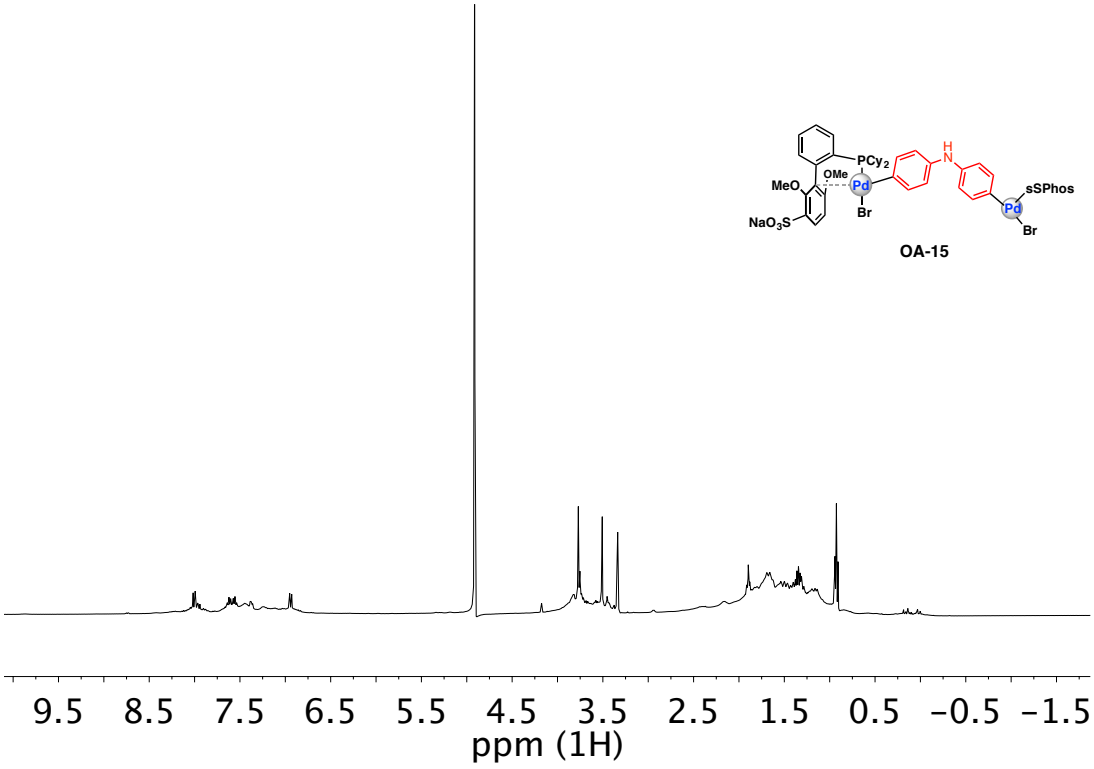
OA-14

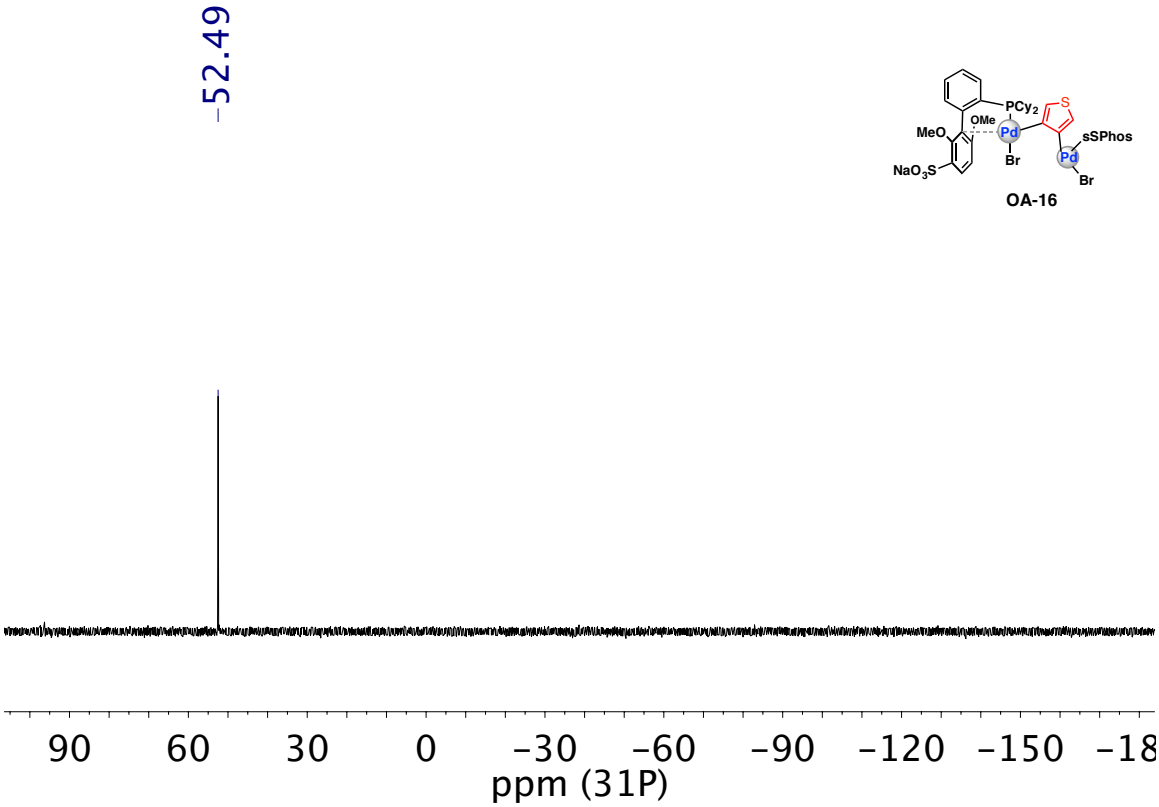

161.28
157.50
135.43
134.70
132.79
132.07
131.08
120.35
114.53
107.07
69.12
62.33
57.59
56.70
56.66
56.42
35.56
27.84
27.77
27.65
27.45
27.35
27.13
26.76
26.73
23.64
14.67
OA-14
210 190 170 150 130 110 90 70 50 30 10 -10
ppm (13C)

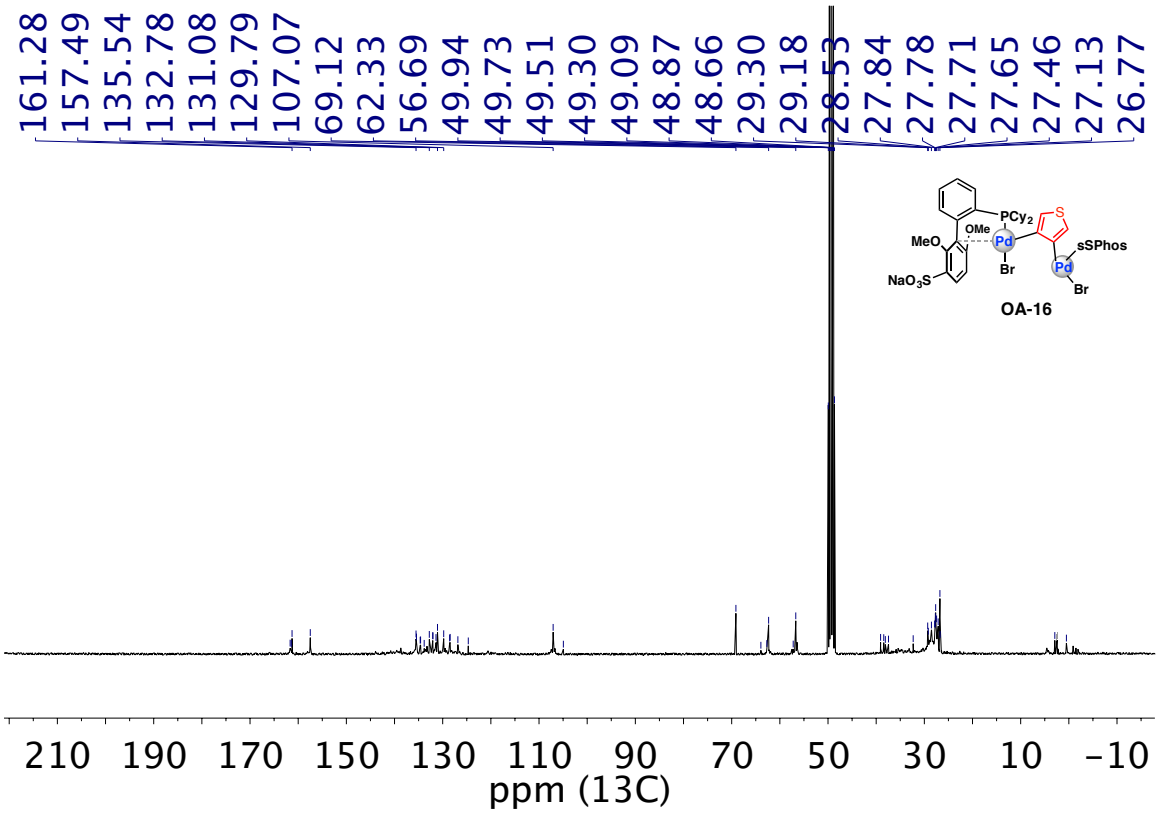

OA-14
.5 8.0 6.5 5.0 3.5 2.0 0.5 -1.0 -2.5
ppm (1H)

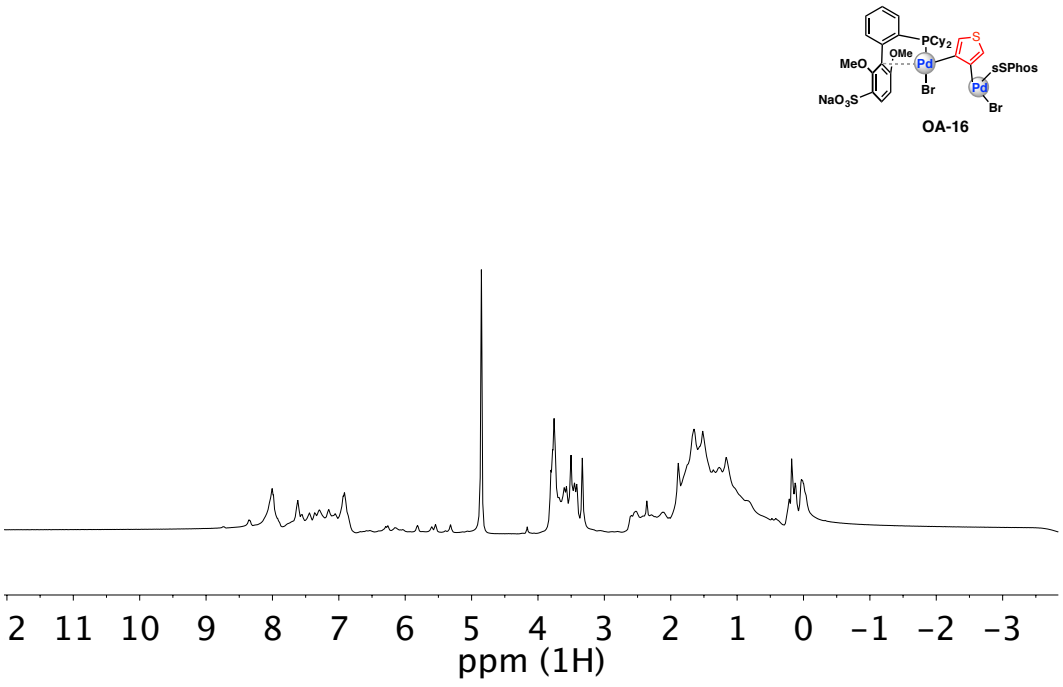

-51.29
PCy2
OMe
MeO
Pd
Br
NaO3S
H
N
sSPhos
Pd
Br
OA-15
180
140
100
60
20
-20
-60
-100
-140
-18
ppm (31P)

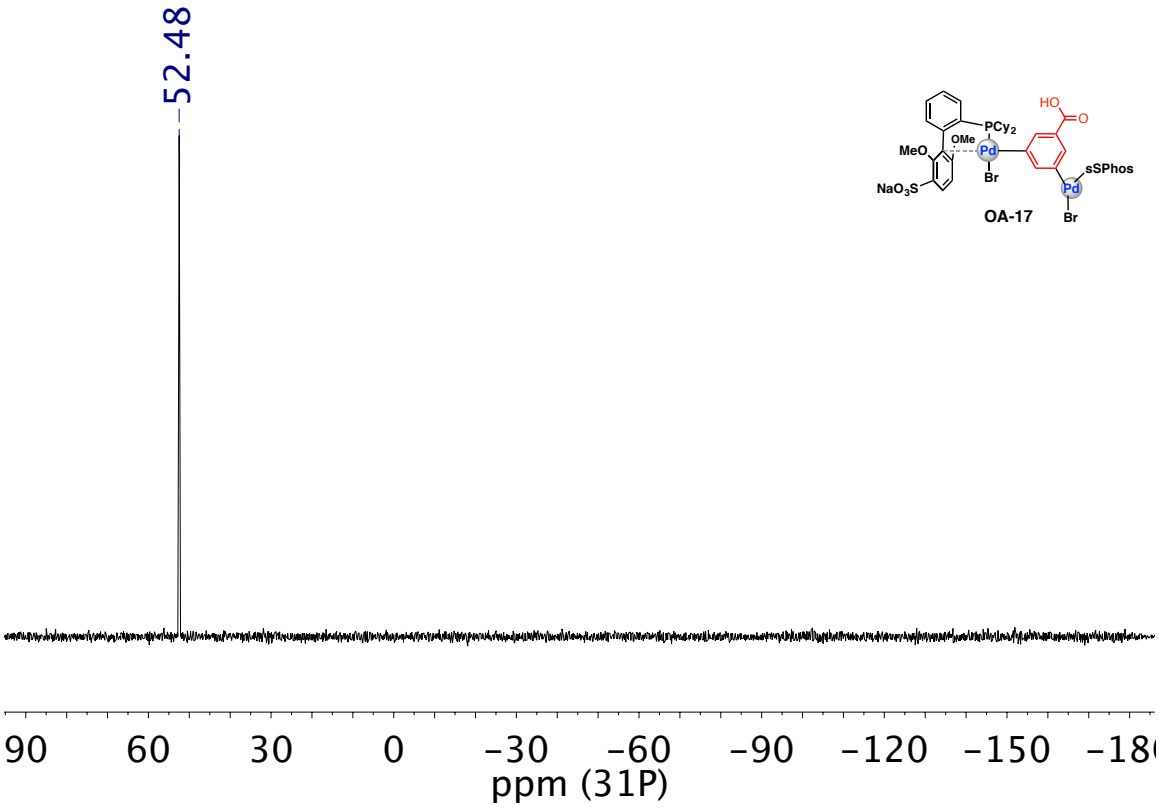

161.51
133.08
131.34
130.46
107.28
62.55
56.90
50.15
49.94
49.72
49.51
49.30
49.08
48.87
35.79
28.07
27.99
27.94
27.87
27.75
27.68
27.62
27.55
27.34
26.99
23.88
14.90
PCy2
OMe
MeO
Pd
Br
NaO3S
H
N
sSPhos
Pd
Br
OA-15
170
150
130
110
90
70
50
30
10
-10
ppm (13C

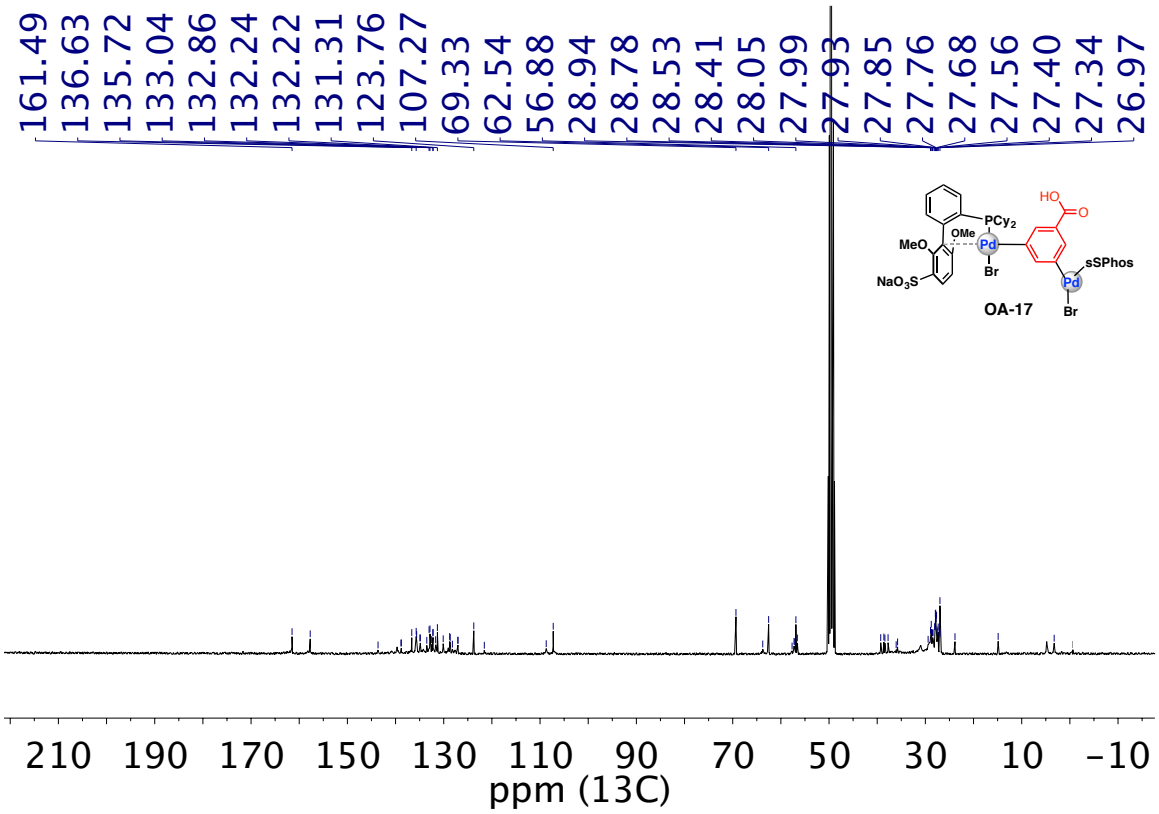

PCy2
OMe
MeO
Pd
Br
NaO3S
H
N
sSPhos
Pd
Br
OA-15
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 −0.5 −1.5
ppm (1H)

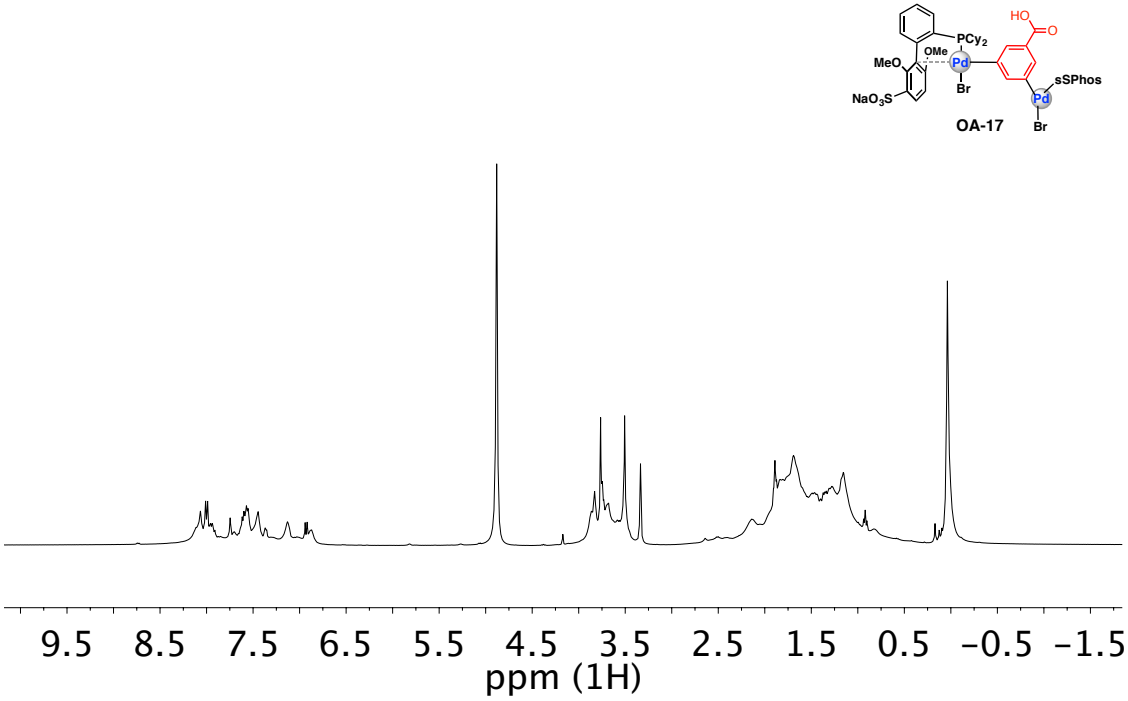

52.49
PCy2
S
OMe
MeO
Pd
Br
sSPhos
Pd
Br
NaO3S
OA-16
90 60 30 0 −30 −60 −90 −120 −150 −18
ppm (31P)

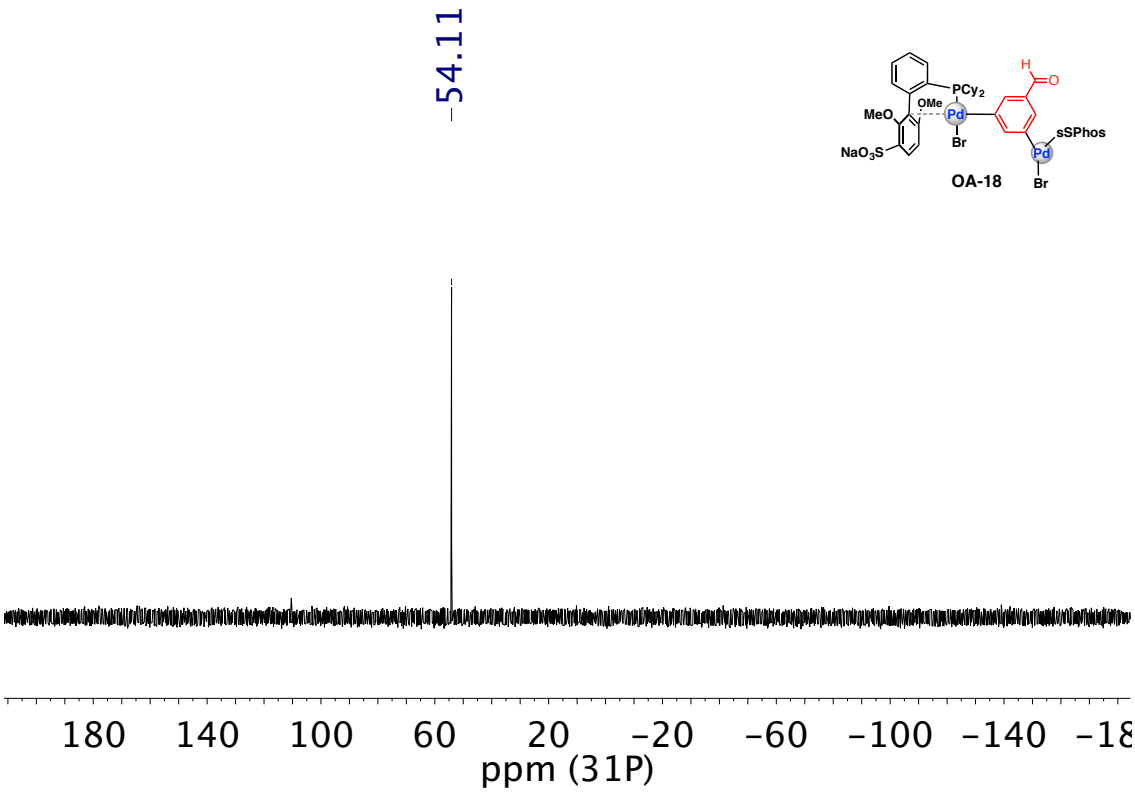

161.28
157.49
135.54
132.78
131.08
129.79
107.07
69.12
62.33
56.69
49.94
49.73
49.51
49.30
49.09
48.87
48.66
29.30
29.18
28.53
27.84
27.78
27.71
27.65
27.46
27.13
26.77
PCy2
S
OMe
MeO
Pd
sSPhos
Br
NaO3S
Pd
Br
OA-16
210 190 170 150 130 110 90 70 50 30 10 -10
ppm (13C)

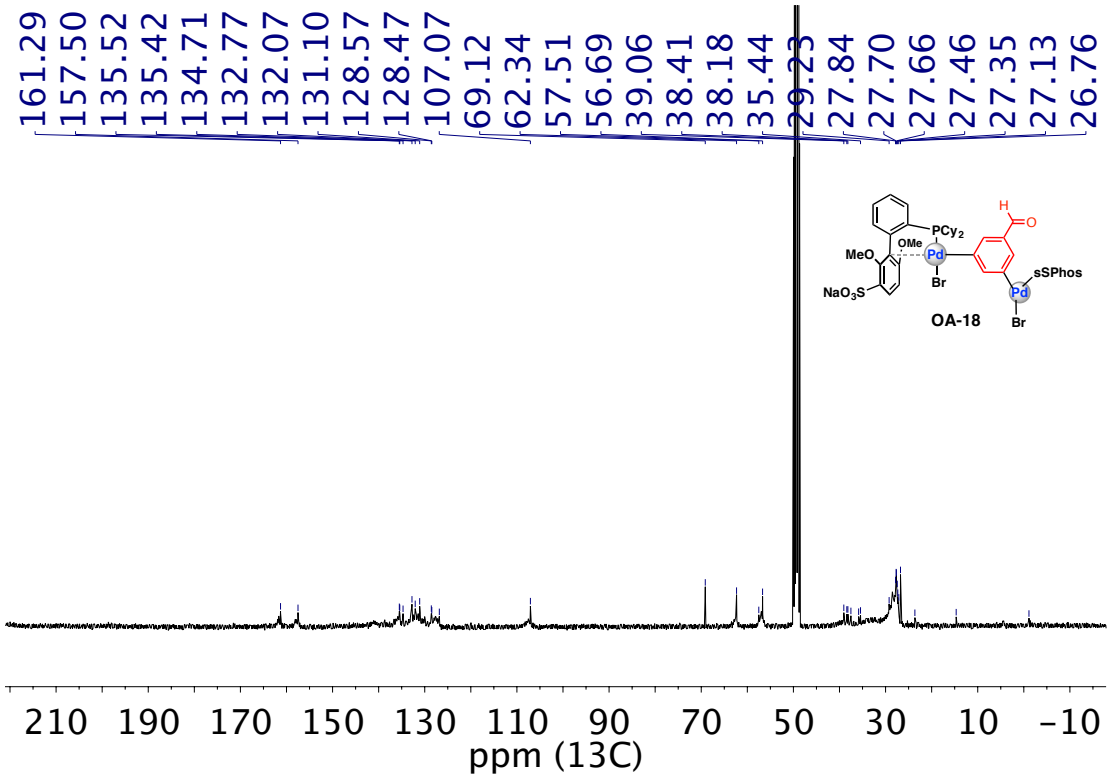

PCy2
S
OMe
MeO
Pd
sSPhos
Br
NaO3S
Pd
Br
OA-16
2 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
ppm (1H)

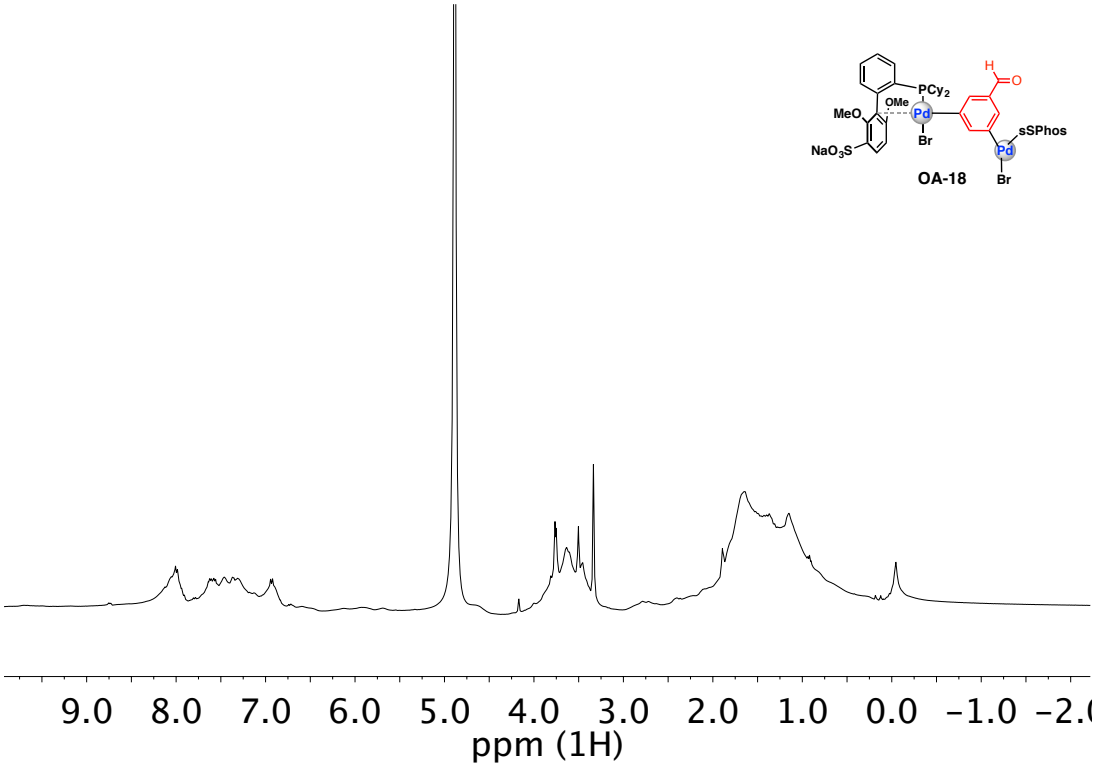

52.48
HO
O
PCy2
OMe
MeO
Pd
Br
sSPhos
NaO3S
Pd
Br
OA-17
90
60
30
0
−30
−60
−90
−120
−150
ppm (31P)

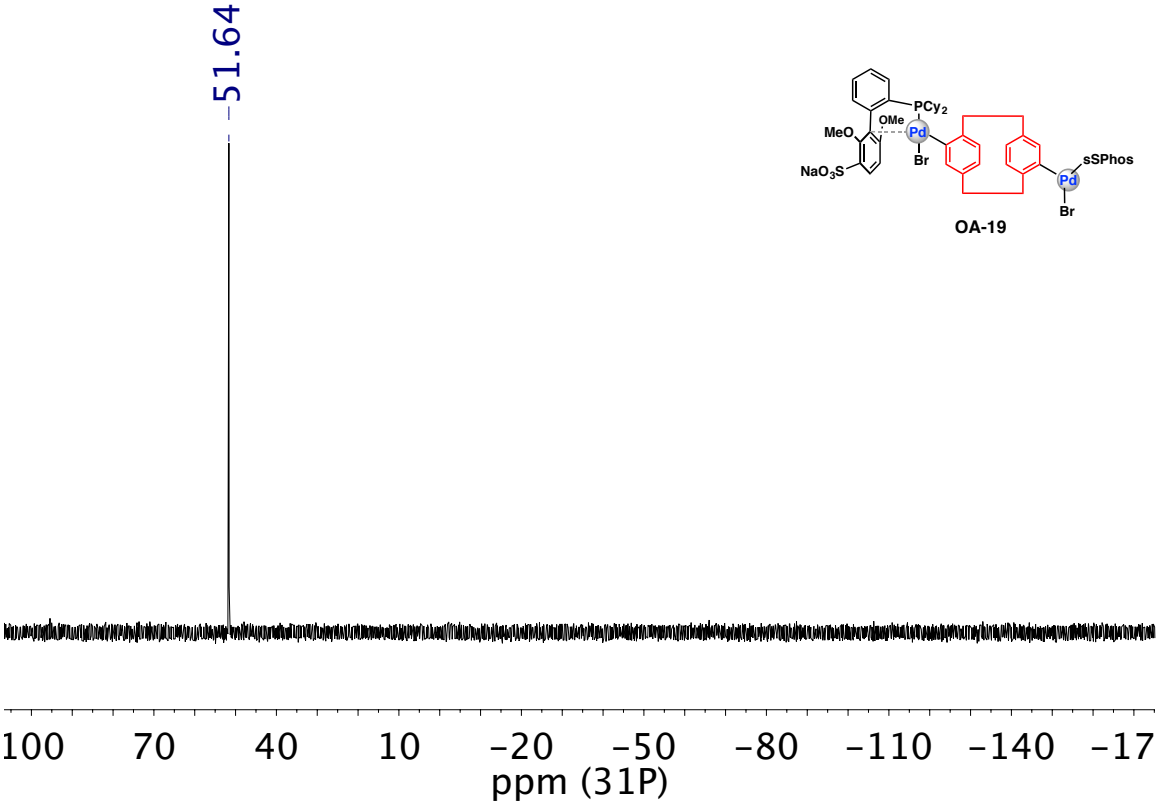

161.49
136.63
135.72
133.04
132.86
132.24
132.22
131.31
123.76
107.27
69.33
62.54
56.88
28.94
28.78
28.53
28.41
28.05
27.99
27.93
27.85
27.76
27.68
27.56
27.40
27.34
26.97
OA-17
210 190 170 150 130 110 90 70 50 30 10 -10
ppm (13C)

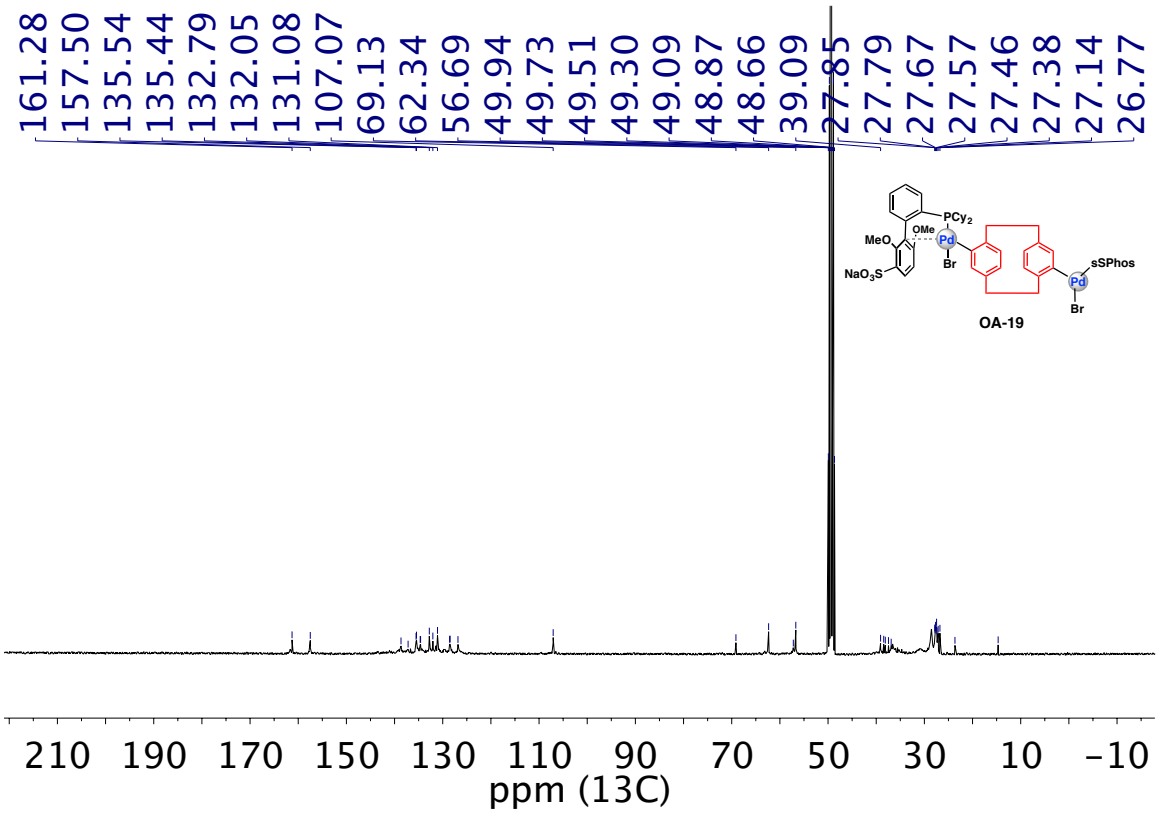

OA-17
9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0.5 -1.5
ppm (1H)

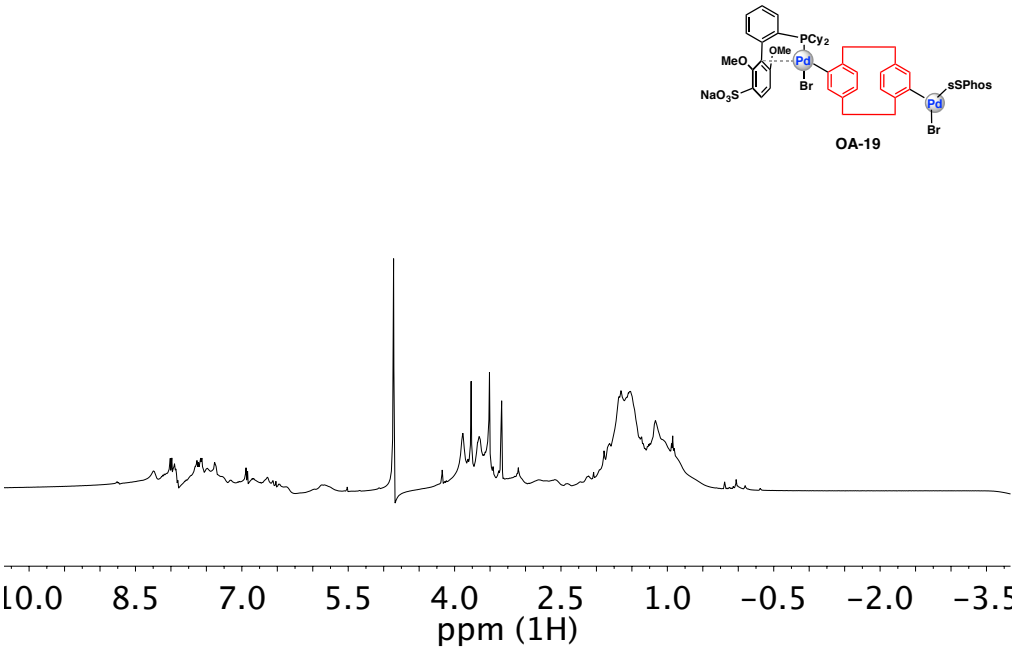

-54.11
OA-18
180 140 100 60 20 -20 -60 -100 -140 -18
ppm (31P)

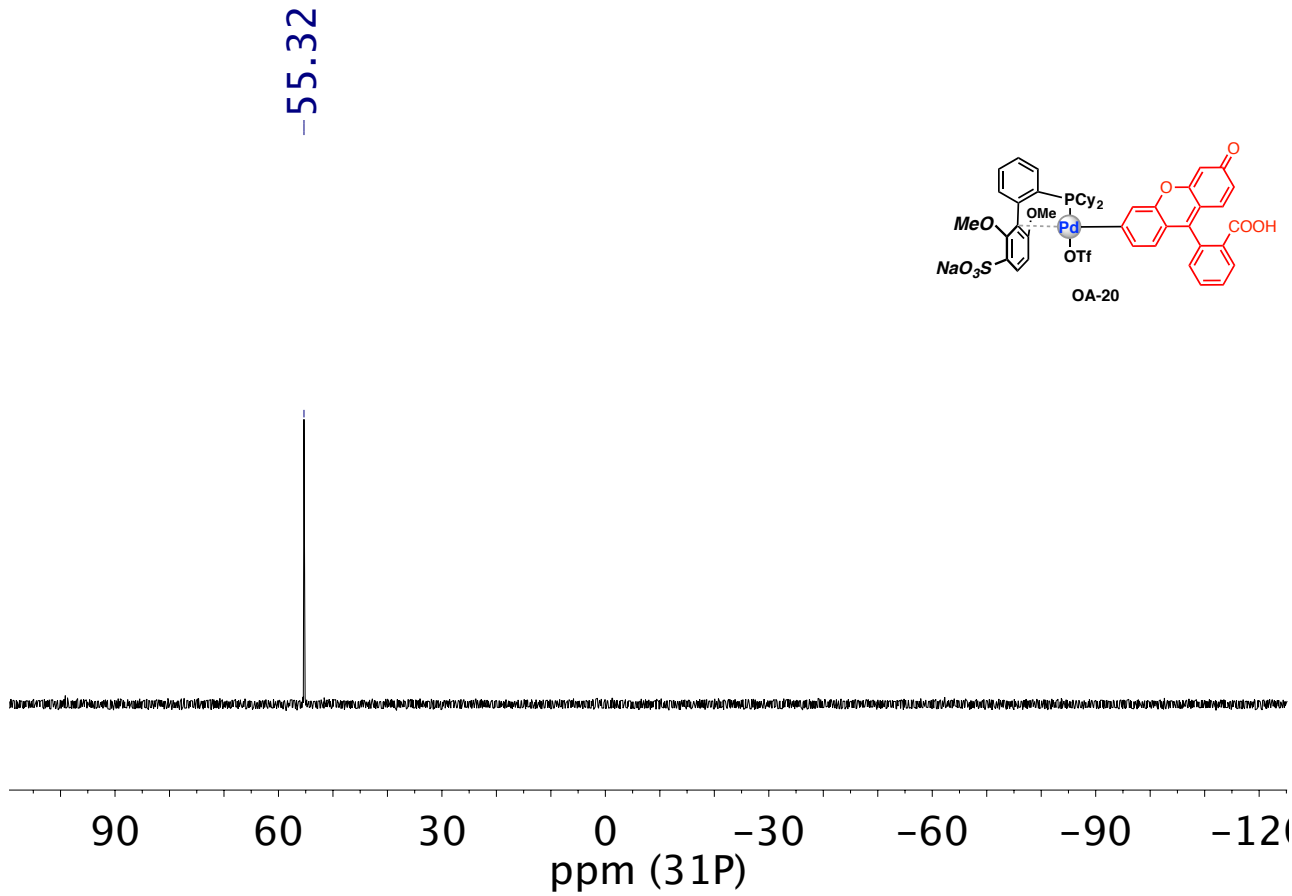

161.29
157.50
135.52
135.42
134.71
132.77
132.07
131.10
128.57
128.47
107.07
69.12
62.34
57.51
56.69
39.06
38.41
38.18
35.44
29.23
27.84
27.70
27.66
27.46
27.35
27.13
26.76
OA-18
210 190 170 150 130 110 90 70 50 30 10 -10
ppm (13C)

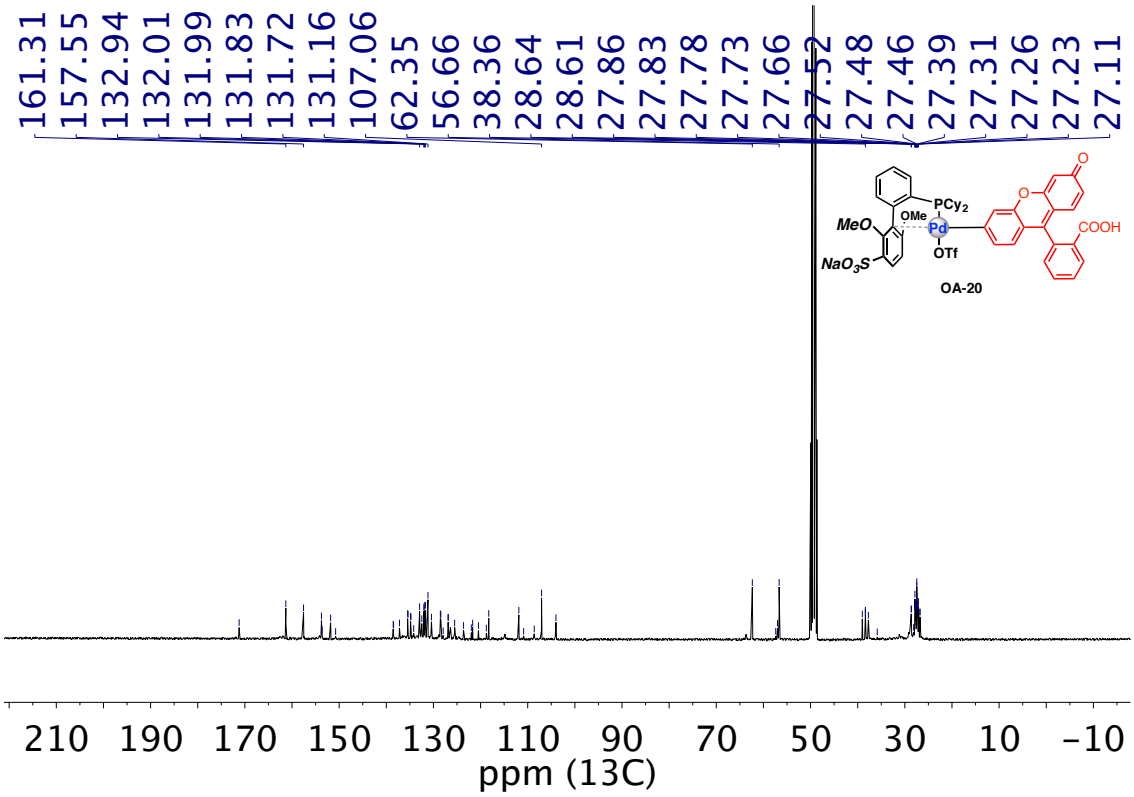

PCy2
OMe
MeO
Pd
Br
NaO3S
H
O
sSPhos
Pd
Br
OA-18
9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 −1.0 −2.(
ppm (1H)

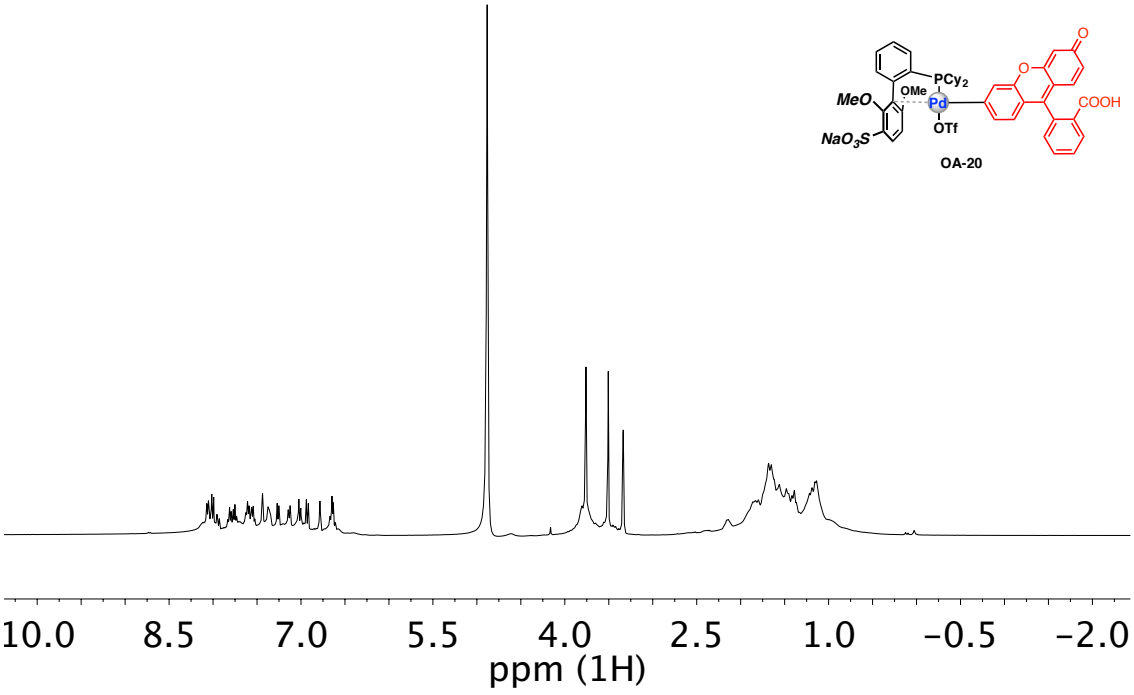

51.64
PCy2
OMe
MeO
Pd
Br
NaO3S
sSPhos
Pd
Br
OA-19
100 70 40 10 −20 −50 −80 −110 −140 −17
ppm (31P)

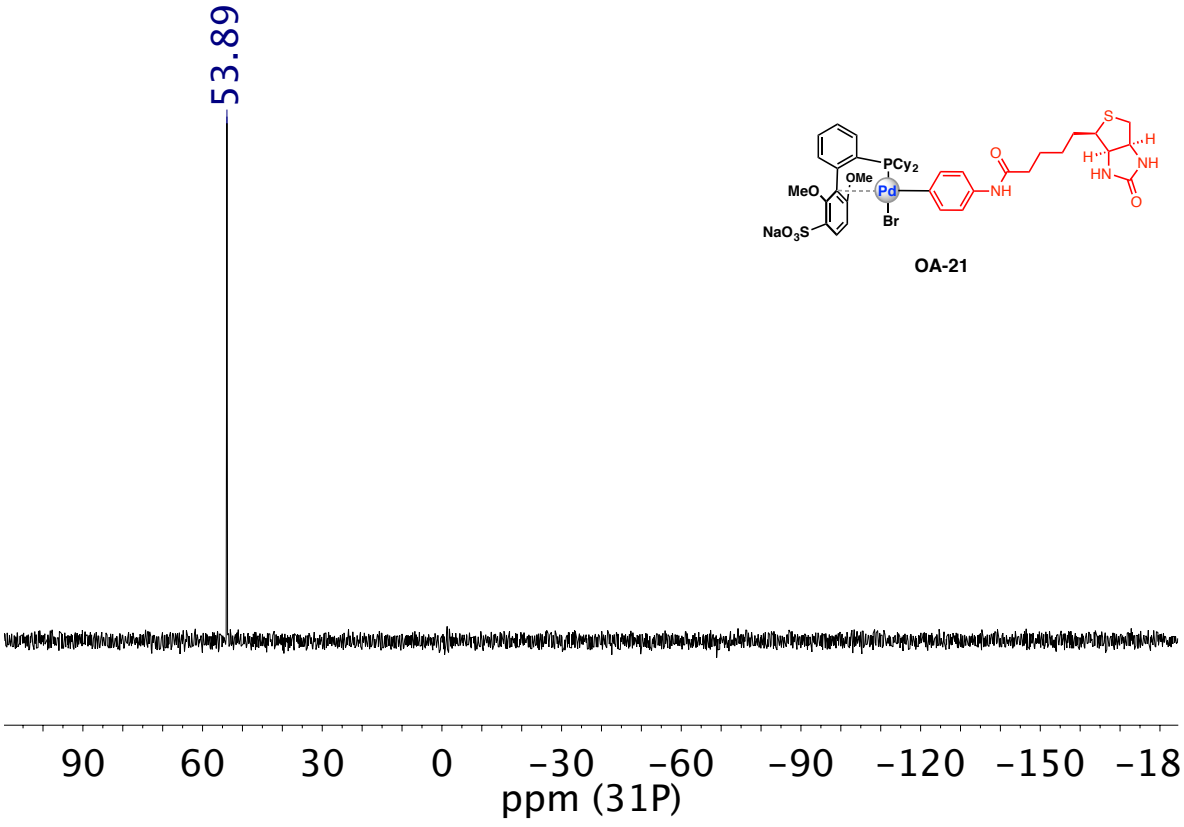

161.28
157.50
135.54
135.44
132.79
132.05
131.08
107.07
69.13
62.34
56.69
49.94
49.73
49.51
49.30
49.09
48.87
48.66
39.09
27.85
27.79
27.67
27.57
27.46
27.38
27.14
26.77
PCy2
OMe
MeO
Pd
Br
NaO3S
sSPhos
OA-19
210 190 170 150 130 110 90 70 50 30 10 -10
ppm (13C)

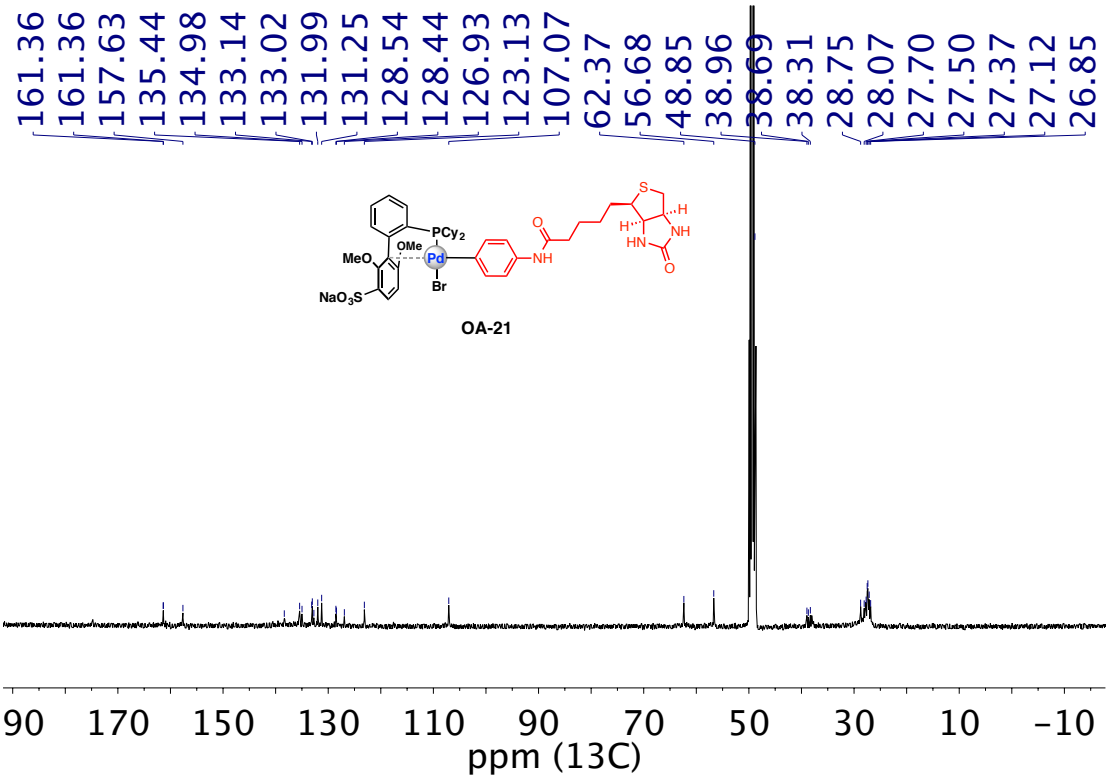

PCy2
OMe
MeO
Pd
Br
NaO3S
sSPhos
OA-19
10.0 8.5 7.0 5.5 4.0 2.5 1.0 -0.5 -2.0 -3.5
ppm (1H)

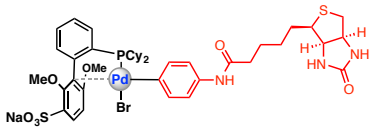

55.32
PCy2
OMe
MeO
Pd
OTf
NaO3S
COOH
O
O
OA-20
90
60
30
0
−30
−60
−90
ppm (31P)


161.31
157.55
132.94
132.01
131.99
131.83
131.72
131.16
107.06
62.35
56.66
38.36
28.64
28.61
27.86
27.83
27.78
27.73
27.66
27.52
27.48
27.46
27.39
27.31
27.26
27.23
27.11
PCy2
OMe
MeO
Pd
OTf
NaO3S
COOH
O
OA-20
210 190 170 150 130 110 90 70 50 30 10 -10
ppm (13C)


PCy2
OMe
MeO
Pd
OTf
NaO3S
COOH
O
OA-20
10.0 8.5 7.0 5.5 4.0 2.5 1.0 -0.5 -2.0
ppm (1H)


53.89
OA-21
90
60
30
0
−30
−60
−90
−120
−150
−18
ppm (31P)

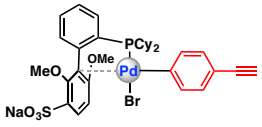

161.36
161.36
157.63
135.44
134.98
133.14
133.02
131.99
131.25
128.54
128.44
126.93
123.13
107.07
62.37
56.68
48.85
38.96
38.69
38.31
28.75
28.07
27.70
27.50
27.37
27.12
26.85
OA-21
90
170
150
130
110
90
70
50
30
10
−10
ppm (13C)


PCy2
OMe
MeO
Pd
Br
NaO3S
NH
O
S
H
HN
NH
O

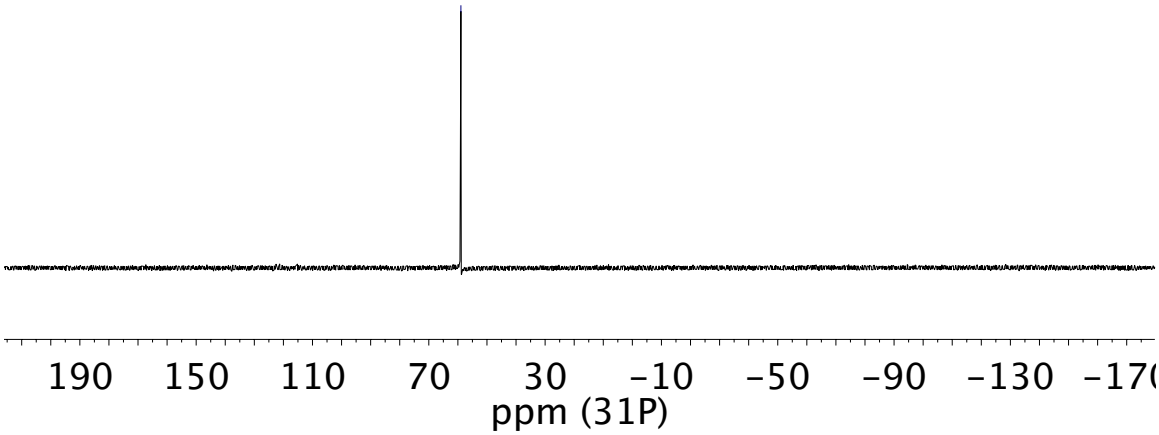
OA-21

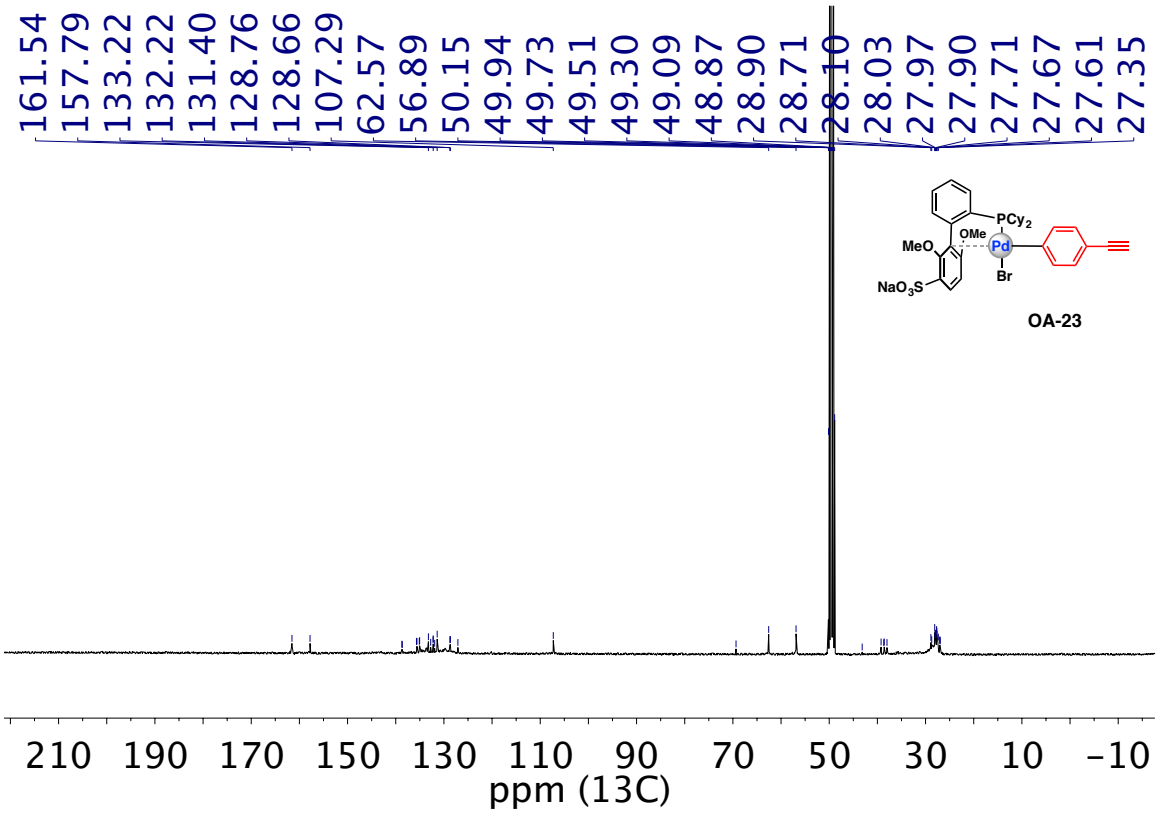
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
-1.5
ppm (1H)

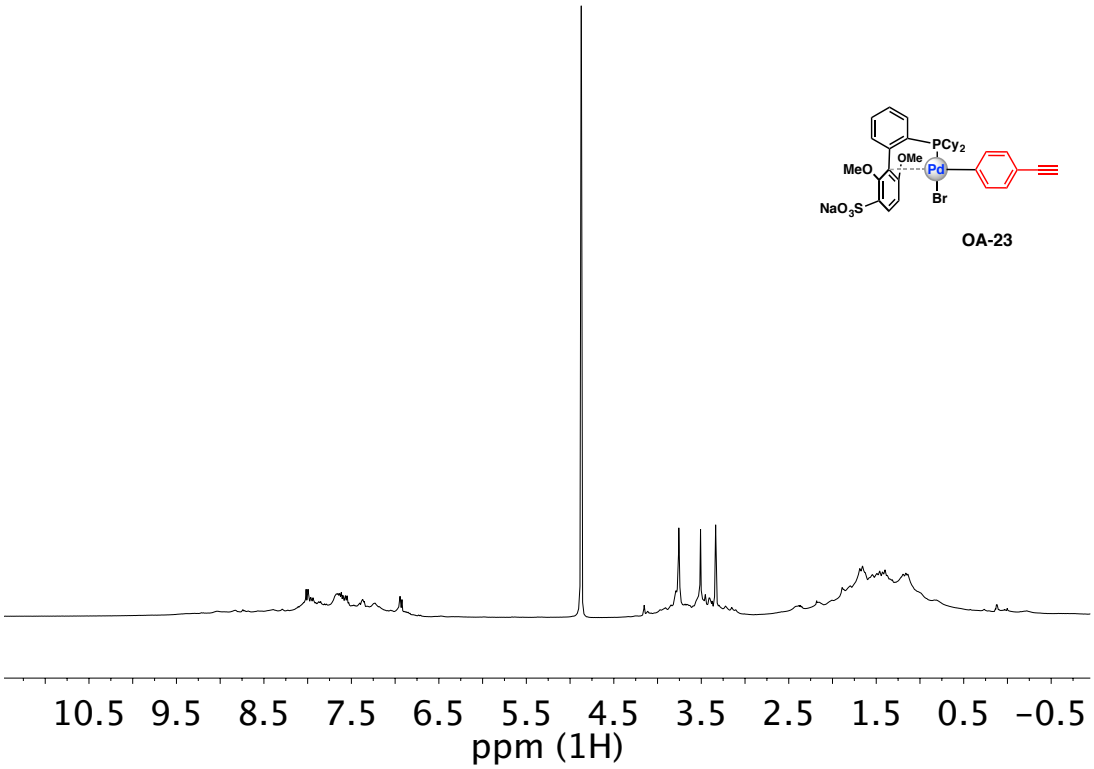

58.96

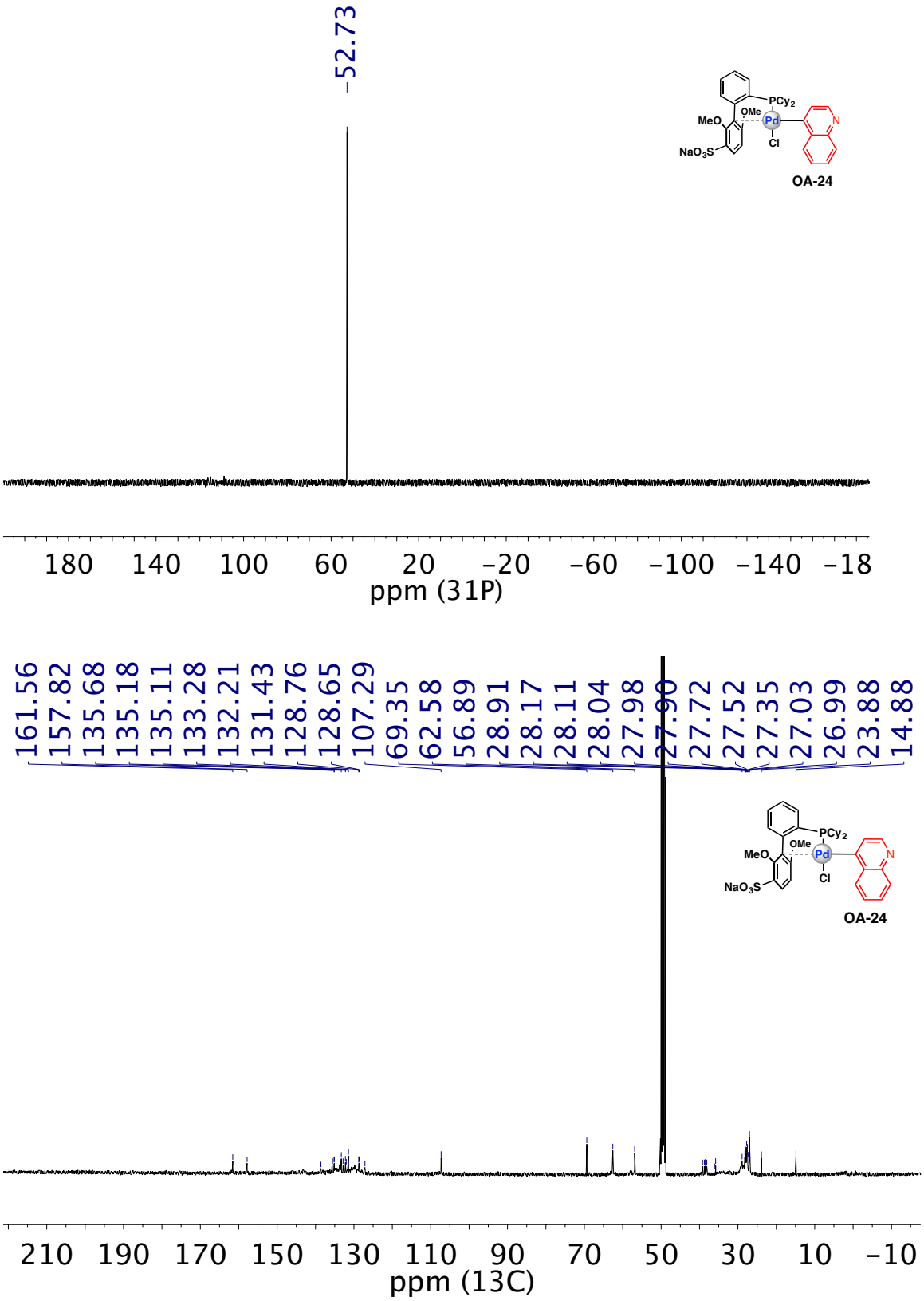

PCy2
OMe
MeO
Pd
Br
NaO3S

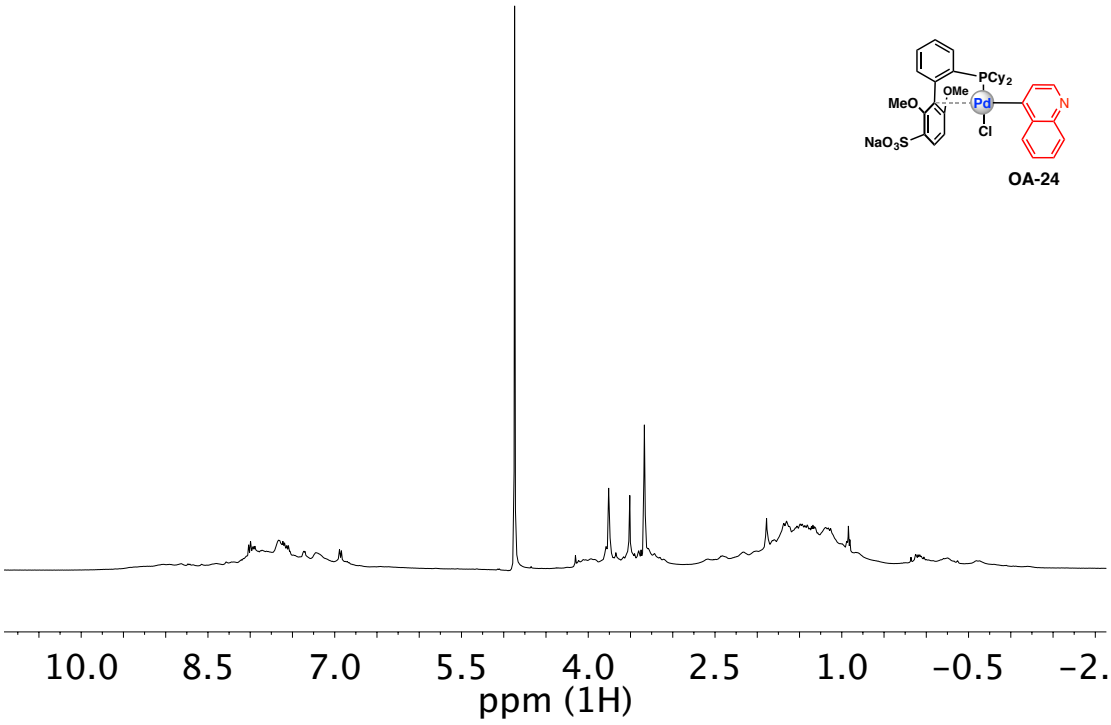
OA-23

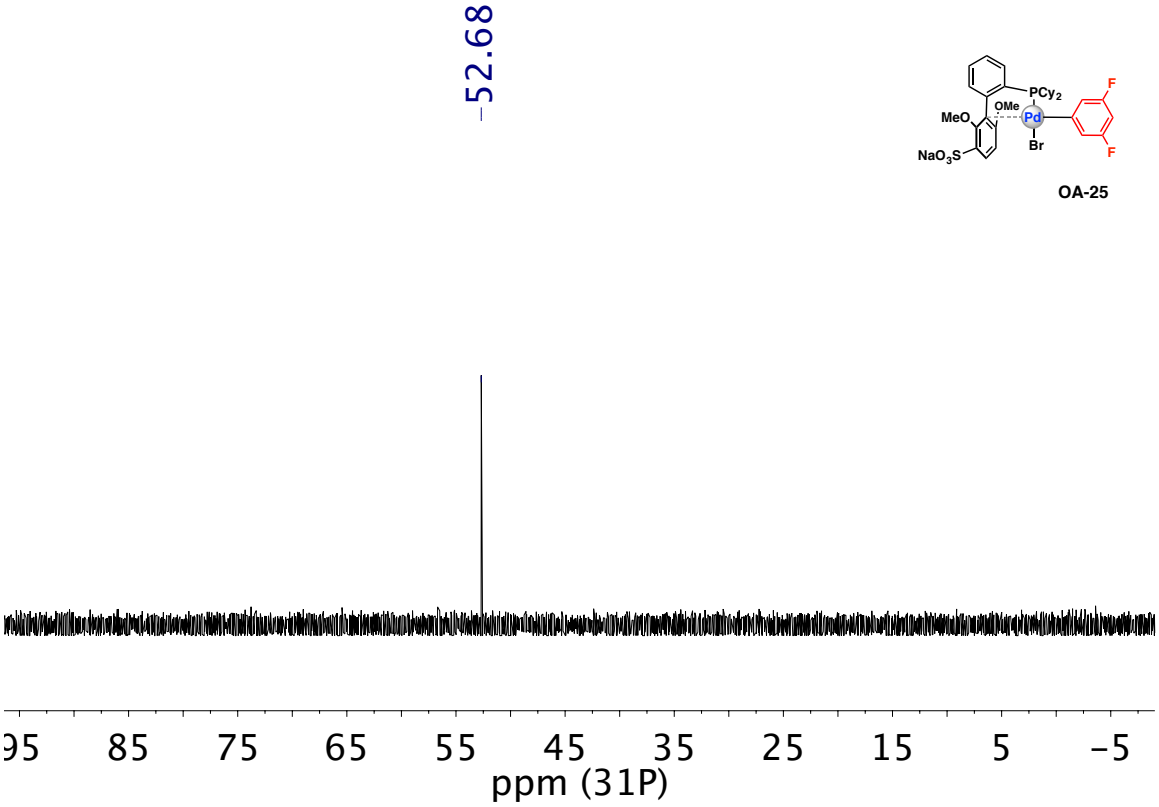

190
150
110
70
30
-10
-50
-90
-130
ppm (31P)

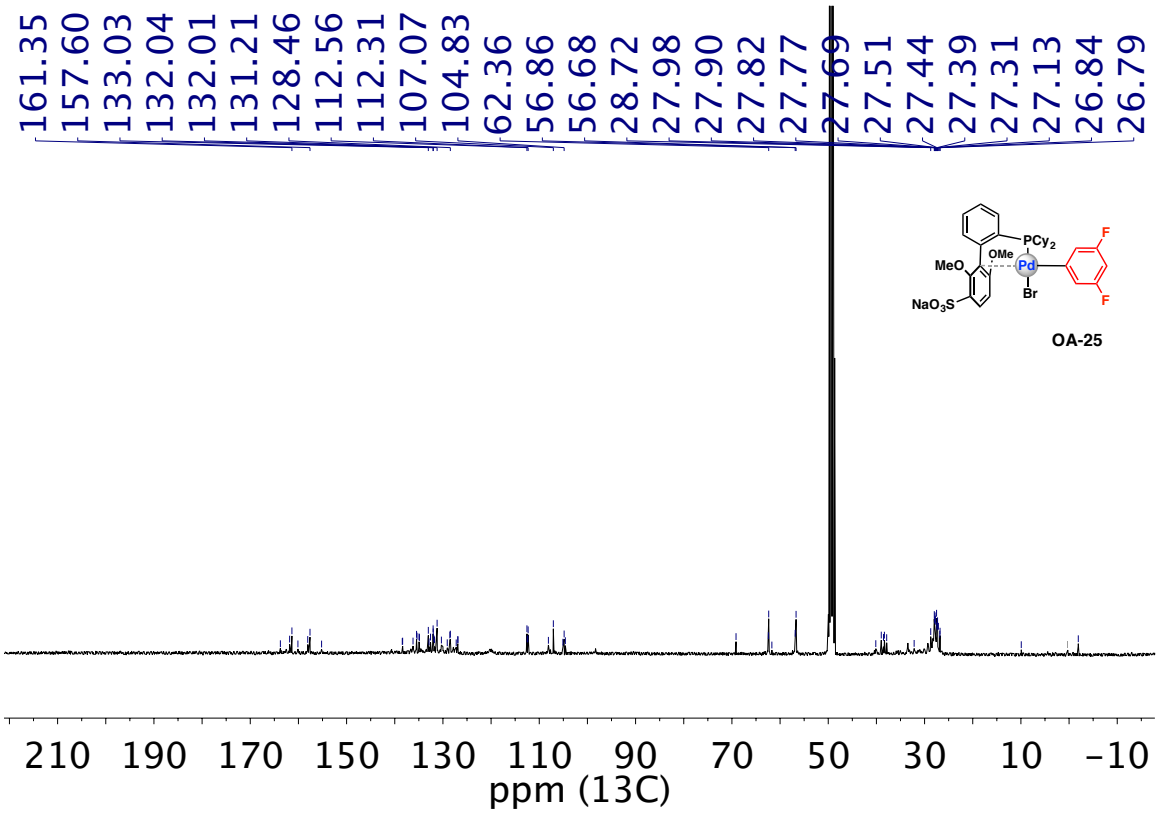

161.54
157.79
133.22
132.22
131.40
128.76
128.66
107.29
62.57
56.89
50.15
49.94
49.73
49.51
49.30
49.09
48.87
28.90
28.71
28.10
28.03
27.97
27.90
27.71
27.67
27.61
27.35
PCy2
OMe
MeO
Pd
Br
NaO3S
OA-23
210 190 170 150 130 110 90 70 50 30 10 -10
ppm (13C)

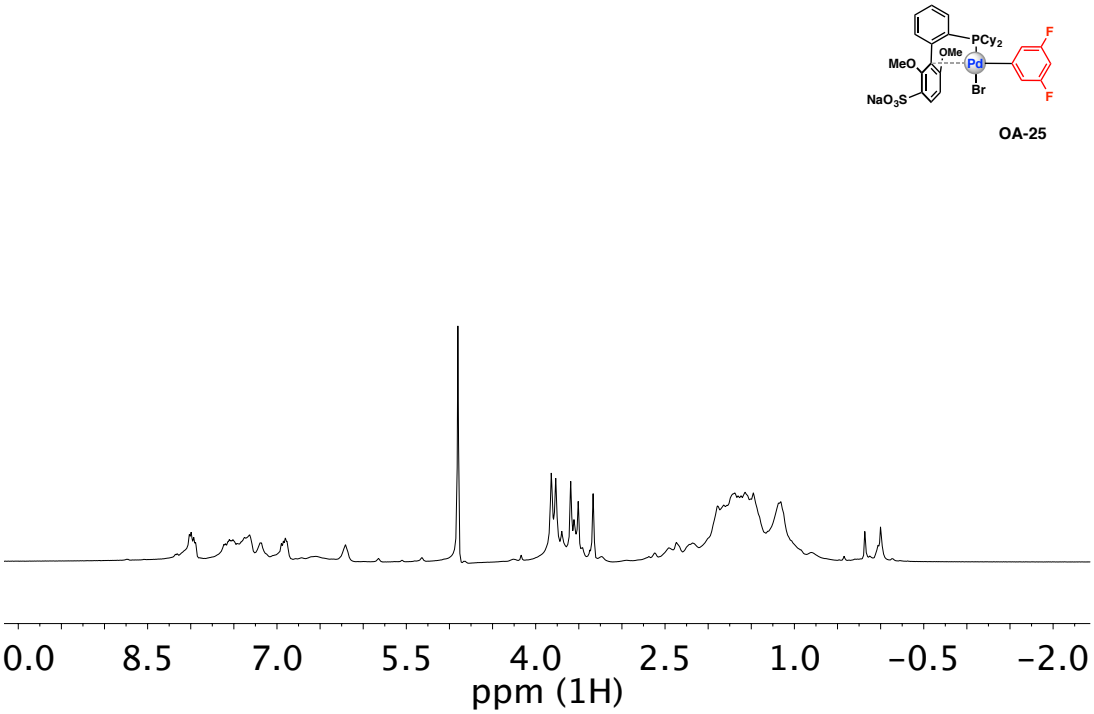

PCy2
OMe
MeO
Pd
Br
NaO3S
OA-23
10.5 9.5 8.5 7.5 6.5 5.5 4.5 3.5 2.5 1.5 0.5 -0.5
ppm (1H)


52.73
PCy2
OMe
MeO
Pd
Cl
N
NaO3S
OA-24
180 140 100 60 20 -20 -60 -100 -140 -18
ppm (31P)
161.56
157.82
135.68
135.18
135.11
133.28
132.21
131.43
128.76
128.65
107.29
69.35
62.58
56.89
28.91
28.17
28.11
28.04
27.98
27.90
27.72
27.52
27.35
27.03
26.99
23.88
14.88
PCy2
OMe
MeO
Pd
Cl
N
NaO3S
OA-24
210 190 170 150 130 110 90 70 50 30 10 -10
ppm (13C)


PCy2
OMe
MeO
Pd
Cl
N
NaO3S
OA-24
10.0
8.5
7.0
5.5
4.0
2.5
1.0
-0.5
-2.
ppm (1H)


-52.68
PCy2
OMe
MeO
Pd
Br
F
F
NaO3S
OA-25
95
85
75
65
55
45
35
25
15
5
-5
ppm (31P)


161.35
157.60
133.03
132.04
132.01
131.21
128.46
112.56
112.31
107.07
104.83
62.36
56.86
56.68
28.72
27.98
27.90
27.82
27.77
27.69
27.51
27.44
27.39
27.31
27.13
26.84
26.79
PCy2
OMe
MeO
Pd
Br
NaO3S
F
F
OA-25
210 190 170 150 130 110 90 70 50 30 10 -10
ppm (13C)


PCy2
OMe
MeO
Pd
Br
NaO3S
F
F
OA-25
0.0 8.5 7.0 5.5 4.0 2.5 1.0 -0.5 -2.0
ppm (1H)