

C003598J Electronic Supporting Information

Sequential insertion of three different organometallics into a versatile building block containing a PNA backbone

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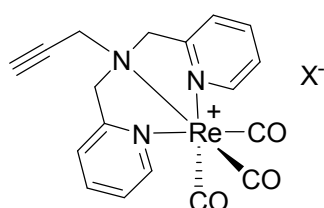
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1) Materials. All chemicals were of reagent grade quality or better, obtained from commercial suppliers and used without further purification. Solvents were used as received or dried over 4 Å molecular sieves. All preparations were carried out using standard Schlenk techniques. *N,N*-bis(pyridine-2-ylmethyl)prop-2-yn-1-amine (**5**),¹ [NEt₄]₂[ReBr₃(CO)₃],² β-cymantrenoyl-propionic acid (**2**),³ azidomethylferrocene (**3**)⁴ and synthon **4**⁵ were prepared following literature procedures. The analytical data matched what previously reported.

2) Instrumentation and methods. ¹H and ¹³C NMR spectra were recorded in deuterated solvents on Bruker DRX 200, 250, 400 or 600 spectrometers at 30°C. The chemical shifts, δ, are reported in ppm (parts per million). The residual solvent peaks have been used as an internal reference. The abbreviations for the peak multiplicities are as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet) and br (broad). Infrared spectra were recorded on an ATR unit using a Bruker Tensor 27 FTIR spectrophotometer at 4 cm⁻¹ resolution. Signal intensity is abbreviated br (broad), s (strong), m (medium), and w (weak). ESI mass spectra were recorded on a Bruker Esquire 6000. Crystallographic data for **6b** and **6c** were collected using a Bruker-axs SMART 1000 CCD diffractometer. The structures were solved by direct methods (SHELXS97) and refined against F² with all measured reflections (SHELXL97,⁶ Platon/Squeeze⁷).

3) Synthesis of the compounds.

[{*N,N*-bis(pyridine-2-ylmethyl)prop-2-yn-1-amine}Re(CO)₃]⁺X⁻ {X=Br(**6a**), PF₆(**6b**), BPh₄(**6c**)}. To a stirred solution of [NEt₄]₂[Re(CO)₃Br₃](260 mg, 0.34 mmol) in 30 mL of degassed methanol, **5** (62 mg, 0.26 mmol) in



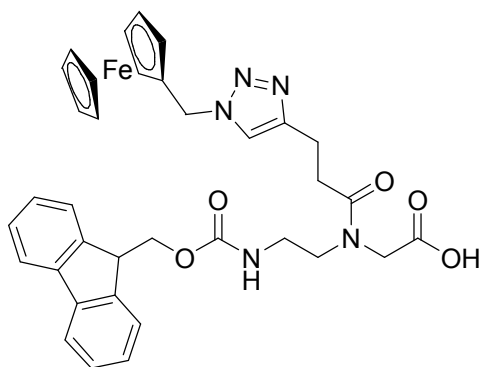
5 mL of degassed methanol was added and the mixture was refluxed for 3h under N₂ atmosphere. The reaction mixture was evaporated to dryness and column chromatography (silica gel, DCM:MeOH 10:1) afforded the desired complex **6a** as a light brown solid (86 mg, 56%). R_f = 0.24 (silica

6, X=Br(**a**), PF₆(**b**), BPh₄(**c**) gel, DCM:MeOH 9:1); ¹H NMR (400MHz, CD₂Cl₂): δ (ppm) 2.95 (1H, t, ⁴J=2.4, C≡H), 4.63 (2H, d, ⁴J=2.4 N-CH₂-alkyne), 4.76 (2H, d, ²J=16.2 Hz, N-CH₂-Py), 5.94 (2H, d, ²J=16.2 Hz, N-CH₂-Py), 7.32 (2H, m, Py), 7.91 (2H, m, Py), 8.74 (4H, m, Py); ¹³C NMR (400 MHz, CD₂Cl₂): δ (ppm) 58.5 (N-CH₂-alkyne), 68.1 (2×N-CH₂-Py), 76.7 (CH₂-C≡), 80.1 (≡C-H), 125.1(Py), 125.9 (Py), 140.2 (Py),

151.1 (Py), 160.8 (Py), 196.1(Re-CO); IR bands(v) : 3403w, 3301w, 3028w, 2412w, 2025s, 1891s, 1609m, 1568w, 1483m, 1442m, 1292w, 1112w, 1031w, 986w, 835w, 729m, 696m, 625w cm^{-1} ; ESI-MS (+Ve): m/z (%): 507.99 (100) [M-Br]⁺.

6a was dissolved in a minimum amount of acetonitrile and a saturated solution of KPF_6 was added to it. The light brown precipitate of **6b** obtained was filtered, washed several times with water and dried under vacuum to give a light brown solid (yield 89%). $R_f = 0.42$ (silica gel, DCM:MeOH 9:1). The same procedure was carried out to obtain **6c** as a light brown solid from **6a** except NaBPh_4 was used instead of KPF_6 (yield 82%). $R_f = 0.71$ (silica gel, DCM:MeOH 9:1).

Compound 7. To a stirred solution of **4** (420 mg, 1 mmol) and azidomethylferrocene **3** (265.1 mg, 1.1 mmol) in

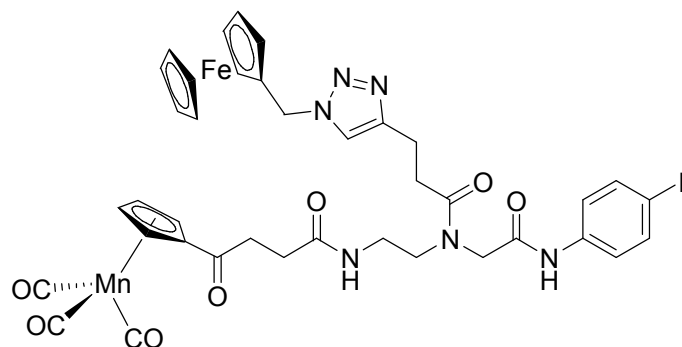


10 mL acetone, aqueous solution of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (24.9 mg, 0.1 mmol in 3 mL water) was added followed by the addition of aqueous solution of sodium ascorbate (39.6 mg, 0.2 mmol in 2 mL water). The resulting mixture was allowed to stir at room temperature for 50h and the progress of the reaction was monitored by TLC (silica gel, EtOAc:MeOH 10:4). The reaction

mixture was evaporated to dryness and DCM (50 mL) was added to it. The organic phase was washed with water, brine, dried over anhydrous Na_2SO_4 , filtered and evaporated to dryness. Column chromatography (silica gel, DCM:MeOH 10:0→10:2) yielded pure **7** as a yellow solid (416 mg, 63%). $R_f = 0.14$ (silica gel, EtOAc:MeOH 10:4); ^1H NMR Spectrum (400MHz, MeOH- d_4): δ 2.67 (maj) and 2.75 (min) (rotamers, m, 2H, $\text{CH}_2\text{-CH}_2\text{-triazol ring}$), 2.97 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-triazol ring}$), 3.29 (m, 2H, $\text{NH-CH}_2\text{-CH}_2$), 3.53 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-N}$), 3.91 (maj) and 3.95 (min) (rotamers, s, 2H, $\text{N-CH}_2\text{-COOH}$), 4.08-4.31 (m, 12H, 7 CH Fc , $\text{Fc-CH}_2\text{-triazol ring}$, CH Fmoc and $\text{Fmoc-CH}_2\text{O}$), 5.12 (min) and 5.22 (maj) (rotamers, m, 2H, 2 CH Fc), 7.30 (m, 2H, CH Fmoc arom), 7.38 (m, 2H, CH Fmoc arom), 7.50 (min) and 7.65 (maj) (rotamers, s, 1H, CH triazol ring), 7.68 (m, 2H, CH Fmoc arom), 7.80 (m, 2H, CH Fmoc arom); ^{13}C NMR Spectrum (400MHz, MeOH- d_4): δ 21.9 (maj) and 22.1(min) (rotamers, $\text{CH}_2\text{-CH}_2\text{-triazol ring}$), 33.2 (min) and 33.4 (maj) (rotamers, $\text{CH}_2\text{-CH}_2\text{-triazol ring}$), 39.7 (maj) and 39.9 (min) (rotamers, $\text{NH-CH}_2\text{-CH}_2$), 48.1 (min) and 48.3 (maj) (rotamers, CH Fmoc), 50.5 (min) and 50.7(maj) (rotamers, $\text{NH-CH}_2\text{-CH}_2$), 51.0 (min) and 51.3 (maj) (rotamers, $\text{Fc-CH}_2\text{-triazol ring}$), 53.9 (min) and 54.1 (maj) (rotamers, $\text{N-CH}_2\text{-COOH}$), 67.9 (min) and 68.3 (maj) (rotamers, $\text{Fmoc-CH}_2\text{O}$), 68.8 (min) and 68.7 (maj) (rotamers, CH Fc), 69.0 (CH Fc), 69.1 (CH Fc), 82.8 (min) and 82.9 (maj) (rotamers, C Fc), 120.9(min) and 121.0 (maj) (rotamers, CH Fmoc arom), 122.8(min) and 123.0 (maj) (rotamers, CH triazol

(maj) (rotamers, CONH), 173.9 (min) and 174.2 (maj) (rotamers, CH₂CON); IR bands(v): 3272w, 3064w, 2953w, 2360w, 2161w, 1700m, 1630s, 1586m, 1531s, 1485m, 1410m, 1392w, 1244s, 1138w, 1051w, 1024m, 948m, 820m, 780s, 720s, 620w cm⁻¹; EI-MS (+Ve): *m/z* (%): 884.99 (100) [M+Na]⁺.

Compound 9. 8 (800 mg, 0.92 mmol) was stirred with 25 mL of 20% piperidine in DMF. After 2h, the reaction

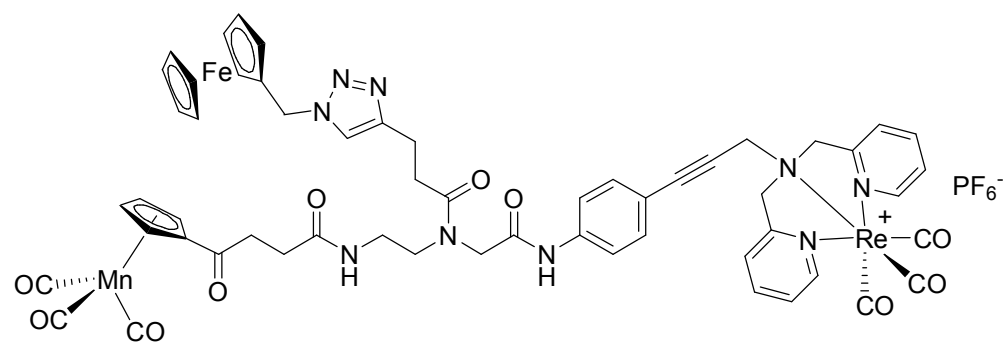


mixture was diluted with 125 mL of ethyl acetate and washed with saturated K₂CO₃ (3×50 mL) and brine (2×50 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered and evaporated to dryness. The residue was washed several times with pentane, then with 30 mL of diethyl ether and finally dried

under vacuum to afford a yellow solid. This solid was then dissolved in 10 mL DMF. The solution was added to a solution of cymantrene keto carboxylic acid **2** (280 mg, 0.92 mmol), HATU (699 mg, 1.84 mmol) and DIPEA (237 mg, 1.84 mmol) in DMF (10mL), which has been initially stirred for 30 minutes at room temperature. The reaction mixture was stirred for 40h in the dark before being diluted with 80 mL of ethyl acetate. The organic phase was washed with water (3×50 mL) and brine (2×50 mL), dried over anhydrous Na₂SO₄ and filtered. Removal of the solvent followed by silica column (EtOAc:MeOH 15:1→7:1) yielded the desired compound **9** as a light yellow solid in 61% yield (524 mg). *R*_f = 0.20 (silica gel, EtOAc:MeOH 15:1); ¹H NMR Spectrum (400MHz, CD₂Cl₂): δ 2.37 (min) and 2.46 (maj) (rotamers, m, 2H, cymantrene-CO-CH₂-CH₂), 2.74 (min) and 2.81 (maj) (rotamers, m, 2H, CH₂-CH₂-triazol ring), 2.91 (m, 2H, cymantrene-CO-CH₂-CH₂), 3.02 (m, 2H, CH₂-CH₂-triazol ring), 3.42 (m, 2H, NH-CH₂-CH₂), 3.51 (m, 2H, CH₂-CH₂-N), 4.07 (s, 2H, N-CH₂-CONH), 4.17-4.25 (m, 7H, 5 CH Fc, Fc-CH₂-triazol ring), 4.29 (m, 2H, CH Fc), 4.81 (min) and 4.89 (maj) (rotamers, m, 2H, CH Cymantrene) 5.20 (maj) and 5.23 (min) (rotamers, m, 2H, CH Fc), 5.48 (s, br, 2H, CH Cymantrene), 7.35 (m, 4H, 2 CH benzene ring, CH triazol ring and CO-NH), 7.56 (m, 2H, 2 CH benzene ring), 9.38 (maj) and 9.53 (min) (rotamers, s, br, 1H, CO-NH); ¹³C NMR (400MHz, CD₂Cl₂): δ 20.3 (min) and 21.1 (maj) (rotamers, CH₂-CH₂-triazol ring), 29.4 (Cymantrene-CO-CH₂-CH₂), 31.5 (CH₂-CH₂-triazol ring), 33.9 (cymantrene-CO-CH₂-CH₂), 37.2 (maj) and 38.1 (min) (rotamers, NH-CH₂-CH₂), 47.6 (min) and 49.3 (maj) (rotamers, NH-CH₂-CH₂), 49.9 (maj) and 50.2 (min) (rotamers, Fc-CH₂-triazol ring), 51.8 (N-CH₂-CONH), 68.2 (CH Fc), 68.4 (CH Fc), 68.9 (CH Fc), 80.8 (min) and 81.2 (maj) (rotamers, C Fc), 83.9 (cymantrene-CH), 86.6 (cymantrene-CH), 87.1 (CI benzene ring), 91.3 (cymantrene-C), 120.9 (CH triazol ring), 122.1 (CNH benzene ring), 137.5 (CH benzene ring), 138.1 (CH benzene ring), 146.4 (C triazol ring), 167.8 (min) and 168.2 (maj) (rotamers, CONH),

171.9 (CONH), 173.6 (maj) and 174.5 (min) (rotamers, CH₂CON), 196.5 (maj) and 197 (min) (rotamers, Cymantrene-CO-CH₂-CH₂), 223.2 (maj) and 224.4 (min) (rotamers, Mn-CO) ; IR bands(v): 3274w, 3100w, 2936w, 2356w, 2023s, 1932s, 1647m(br), 1586m, 1533m, 1413w, 1377w, 1287w, 1105w, 1039w, 952w, 821m, 666m, 630s cm⁻¹; EI-MS (+Ve): *m/z* (%): 948.97 (100) [M+Na]⁺.

Hetero tri-organometallic PNA monomer derivative 1. 9 (283 mg, 0.306 mmol) and **6b** (200 mg, 0.306 mmol) were dissolved in DMF (8 mL) and NEt₃ (4 mL). The solution was degassed by three ‘freeze-pump-thaw’

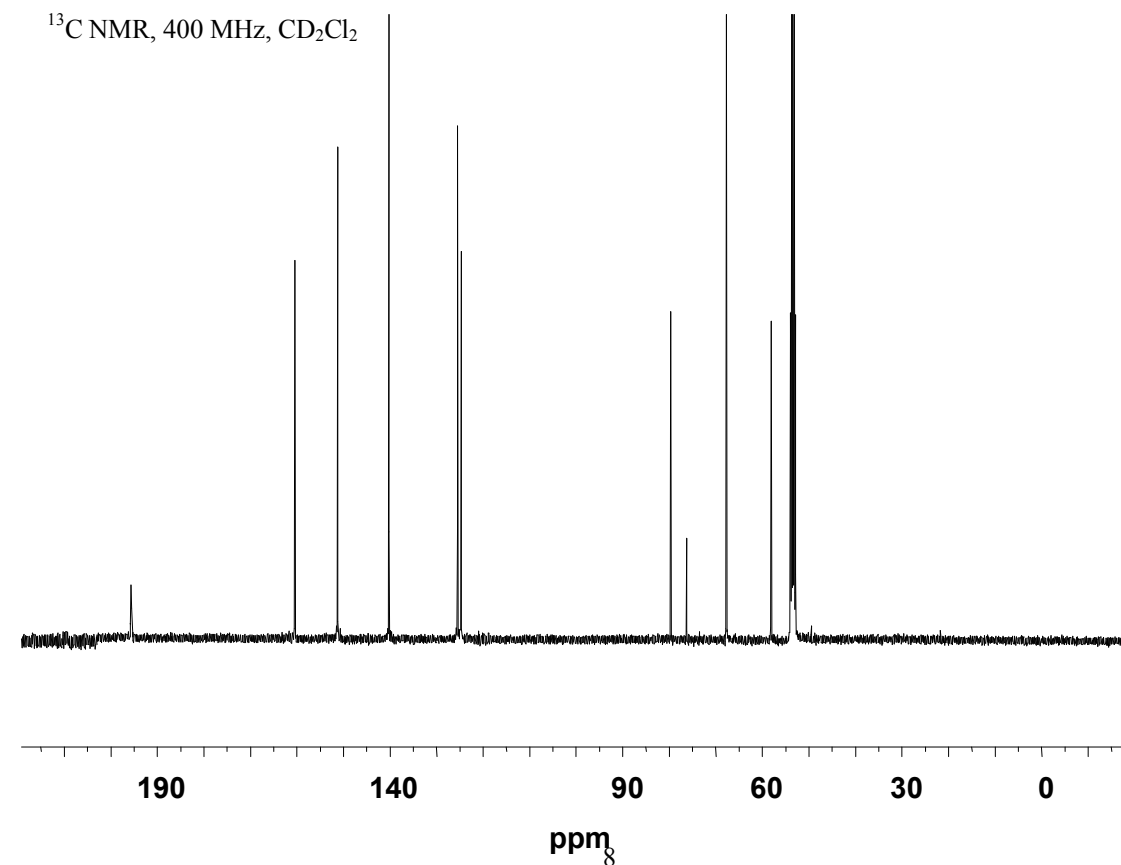
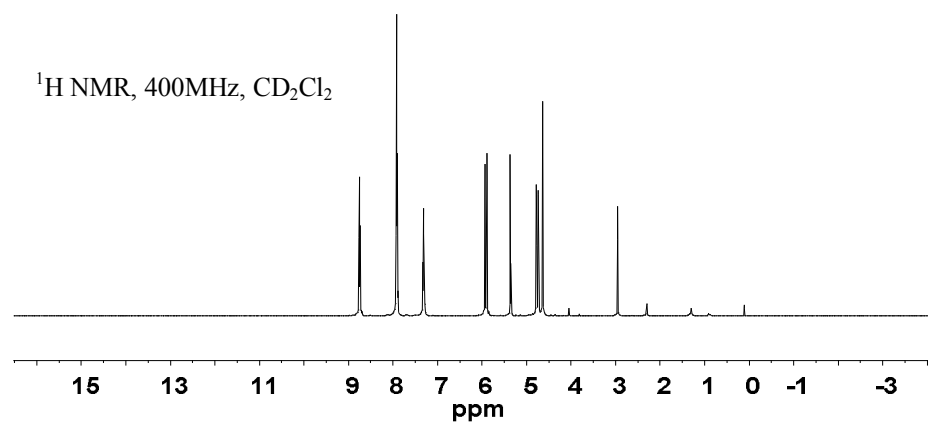
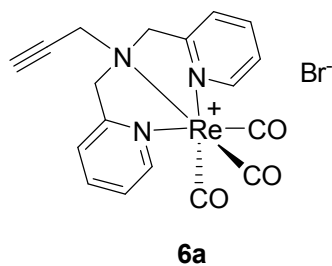


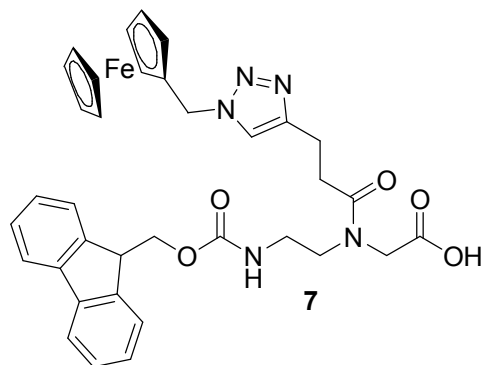
cycles. CuBr
(5.28 mg, 0.036
mmol) and cis-
dichlorobis
(triphenylphosph
ine)
palladium(II)

(6.44 mg, 0.0092 mmol) were added under nitrogen atmosphere and the mixture was degassed again by two ‘freeze-pump-thaw’ cycles. The wine colour solution thus obtained was allowed to stir 22h at room temperature in the dark. The reaction mixture was diluted with 100 mL of DCM and washed with distilled water (4×50 mL) and brine (2×50 mL). The DCM layer was dried over Na₂SO₄, filtered and evaporated to dryness. The residue was washed with diethyl ether (2×50 mL) to remove the remaining triethylamine and finally dried in vacuo. Flash column chromatography (silica gel, DCM:MeOH 15:1→7:1) afforded the desired compound **1** as a yellow sticky solid. The solid was washed with diethyl ether to obtain a yellow powder (265 mg, 60%). *R_f* = 0.45 (silica gel, DCM:MeOH 9:1); ¹H NMR (400MHz, CD₂Cl₂): δ 2.29 (m, 2H, cymantrene-CO-CH₂-CH₂), 2.51 (min) and 2.61 (maj) (rotamers, m, 2H, CH₂-CH₂-triazol ring), 2.76 (m, 2H, cymantrene-CO-CH₂-CH₂), 2.85 (m, 2H, CH₂-CH₂-triazol ring), 3.21 (m, 2H, NH-CH₂-CH₂), 3.30 (m, 2H, CH₂-CH₂-N), 3.98 (s, 2H, N-CH₂-CONH), 4.07-4.13 (m, 7H, 5 CH Fc, Fc-CH₂-triazol ring), 4.18 (m, 2H, CH Fc), 4.57 (s, br, 2H, N-CH₂-alkyne), 4.66 (min) and 4.70 (maj) (rotamers, m, 2H, CH Cymantrene), 4.22-4.78 (m, 4H, 2×N-CH₂-Py), 5.08 (s, br, 2H, CH Fc), 5.35 (s, br, 2H, CH Cymantrene), 6.67 (min) and 6.78 (maj) (rotamers, br, 1H, CO-NH) 7.20 (s, br, 2H, Py), 7.30-7.49 (m, 7H, 2HPy, 4H benzene ring and 1H triazole ring) 7.76 (s, br, 2H, Py), 8.65 (s, br, 2H, Py), 8.81 (min) and 8.95 (maj) (rotamers, s, br, 1H, CO-NH); ¹³C NMR (400MHz, CD₂Cl₂): δ 20.0 (CH₂-CH₂-triazol ring), 28.5 (maj) and 28.9 (min) (rotamers, Cymantrene-CO-CH₂-CH₂), 31.1 (CH₂-CH₂-triazol ring), 33.2 (cymantrene-CO-CH₂-CH₂), 36.8 (min) and 37.1 (maj) (rotamers, NH-CH₂-CH₂), 46.6 (min) and 48.3 (maj)

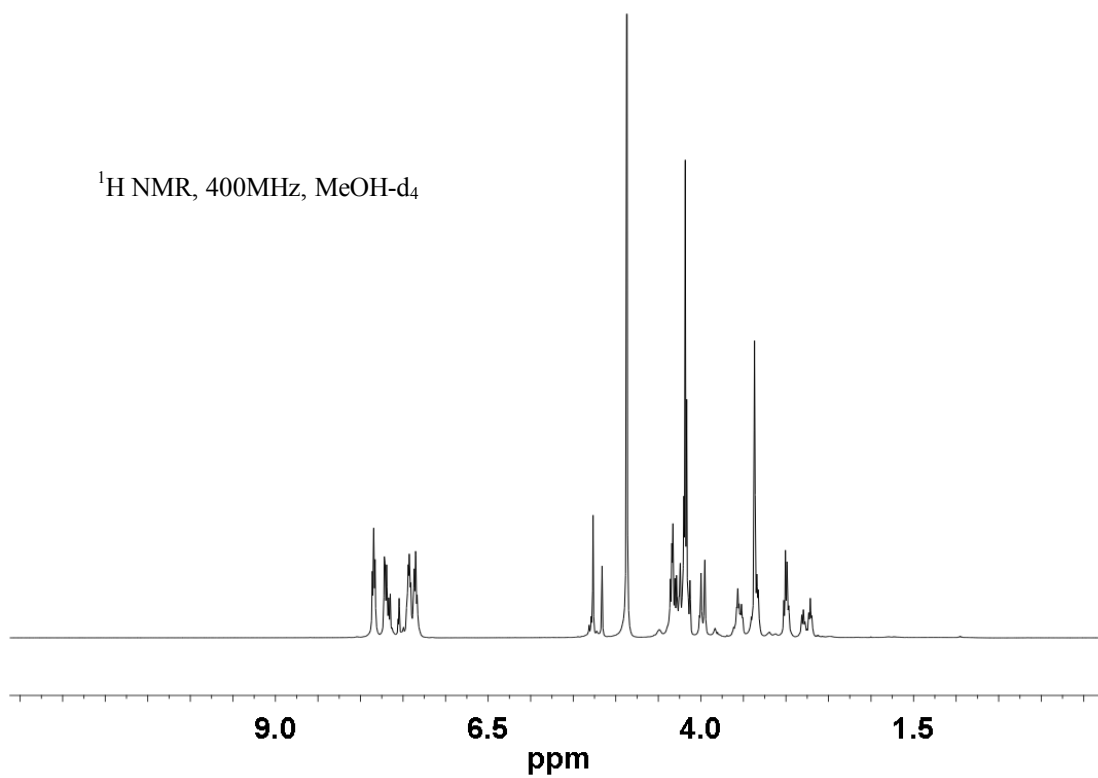
(rotamers, NH-CH₂-CH₂), 49.2 (Fc-CH₂-triazol ring), 50.7 (N-CH₂-CONH), 58.4 (N-CH₂-alkyne), 67 (2×N-CH₂-Py) 68.2 (CH Fc), 68.4 (CH Fc), 68.9 (CH Fc), 79.9 (CH₂-C≡) 80.5 (C Fc), 83.4 (cymantrene-CH), 86.2 (cymantrene-CH), 89.5 (≡C-H) 90.4 (cymantrene-C), 115.7 (Py) 119.2 (CH triazol ring), 120.8 (Py), 123.1 (CNH benzene ring), 125.1 (≡C-benzene ring), 132.1 (Py), 138.3 (CH benzene ring), 139.8 (CH benzene ring), 145.9 (C triazol ring), 151.1 (Py), 158.9 (Py), 166.9 (min) and 167.7 (maj) (rotamers, CONH), 171.7 (CONH), 173.4 (maj) and 173.7 (min) (rotamers, CH₂CON), 194.1 (Re-CO), 196.3 (maj) and 197 (min) (rotamers, Cymantrene-CO-CH₂-CH₂), 222.5 (Mn-CO); IR bands(ν): 3651w, 3088w, 2929w, 2516w, 2225w, 2025s, 1908s(br), 1655m(br), 1610m, 1513m, 1442w, 1407w, 1377w, 1310w, 1181w, 1105w, 1058w, 947w, 833s, 765m, 667w, 628m cm⁻¹; EI-MS (+Ve): *m/z* (%): 1305.92 (100) [M-PF₆]⁺.

4) Spectra of compounds.

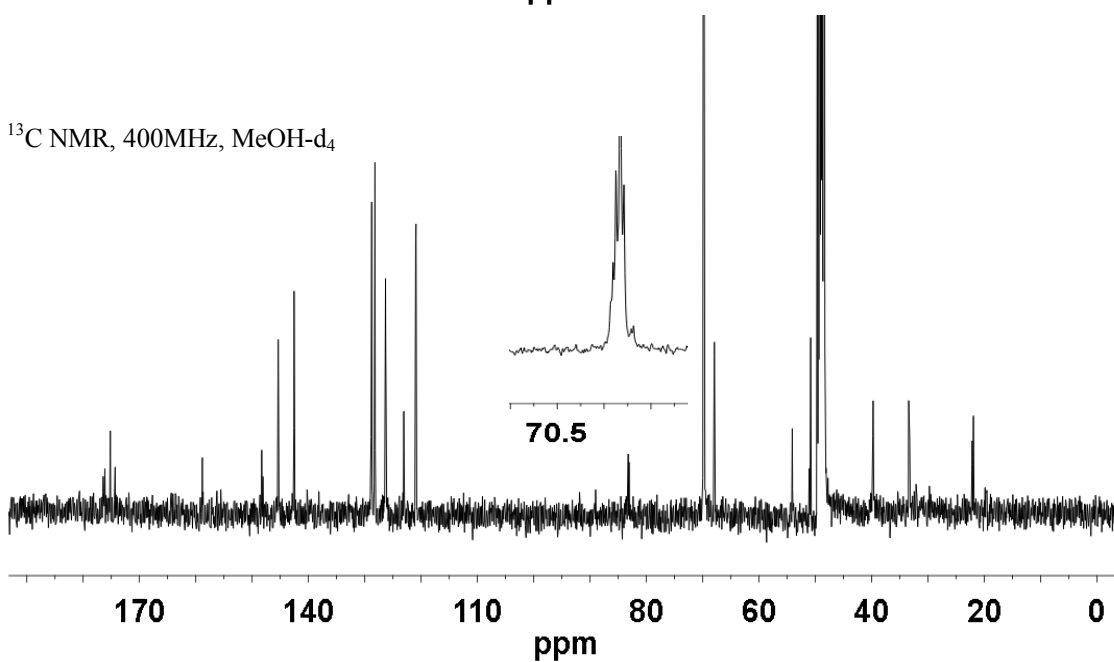


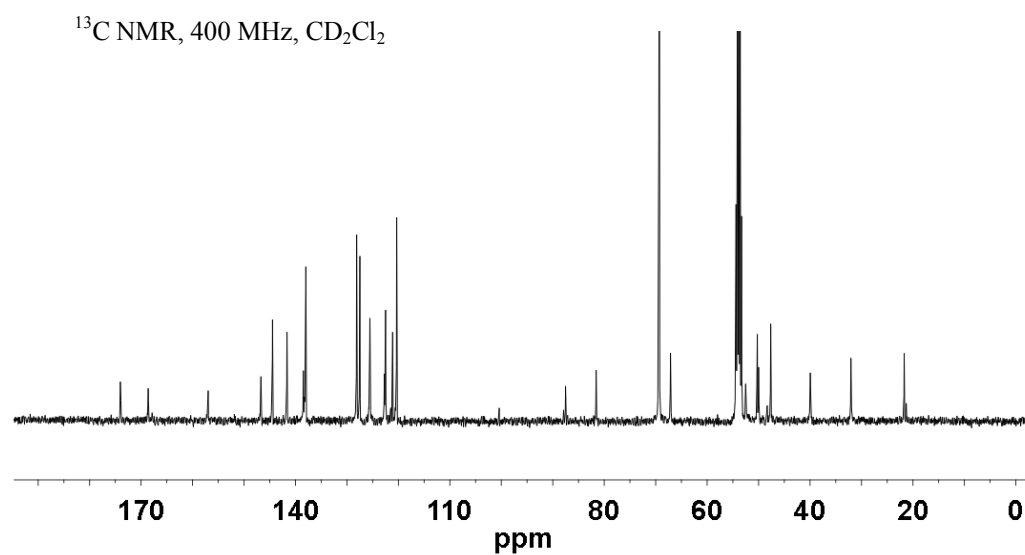
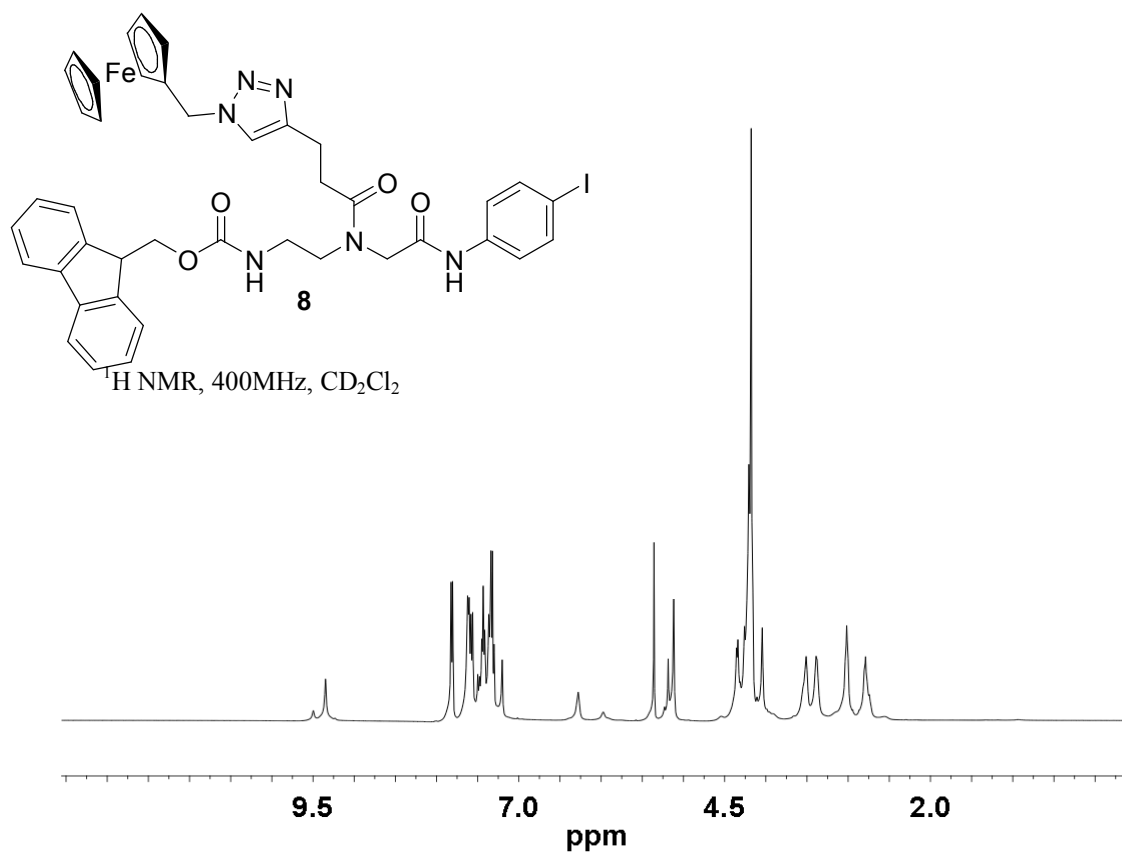


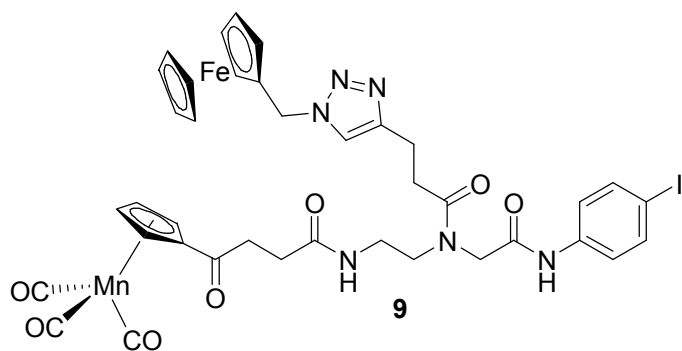
^1H NMR, 400MHz, MeOH- d_4



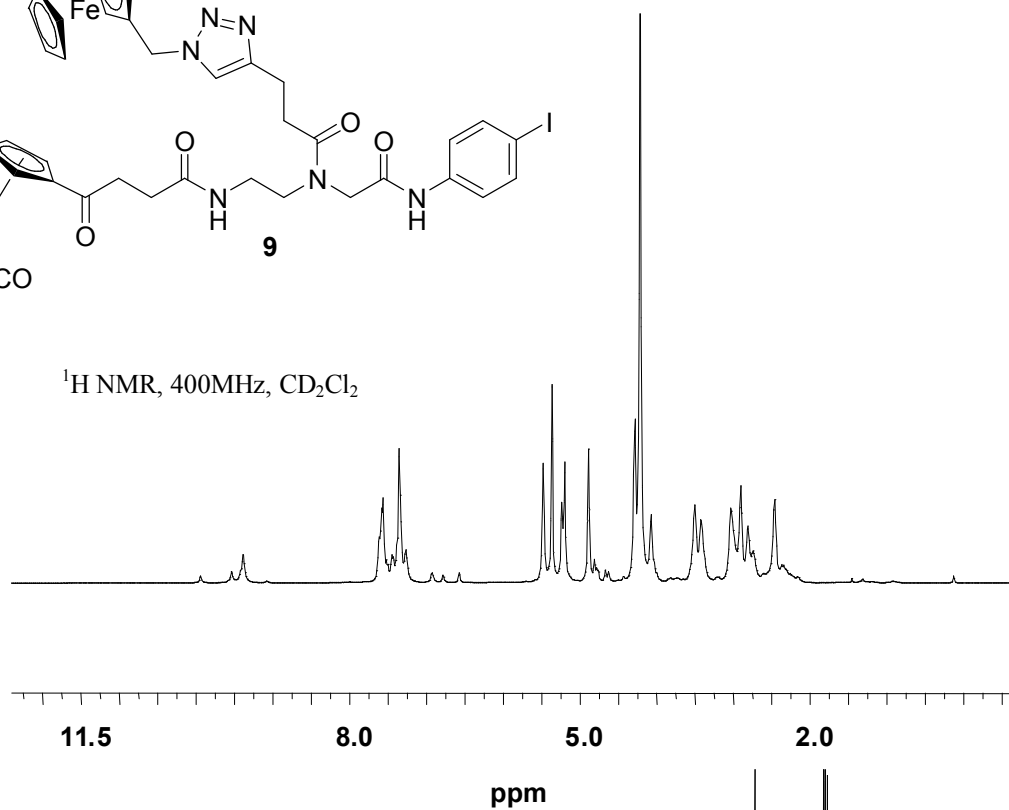
^{13}C NMR, 400MHz, MeOH- d_4



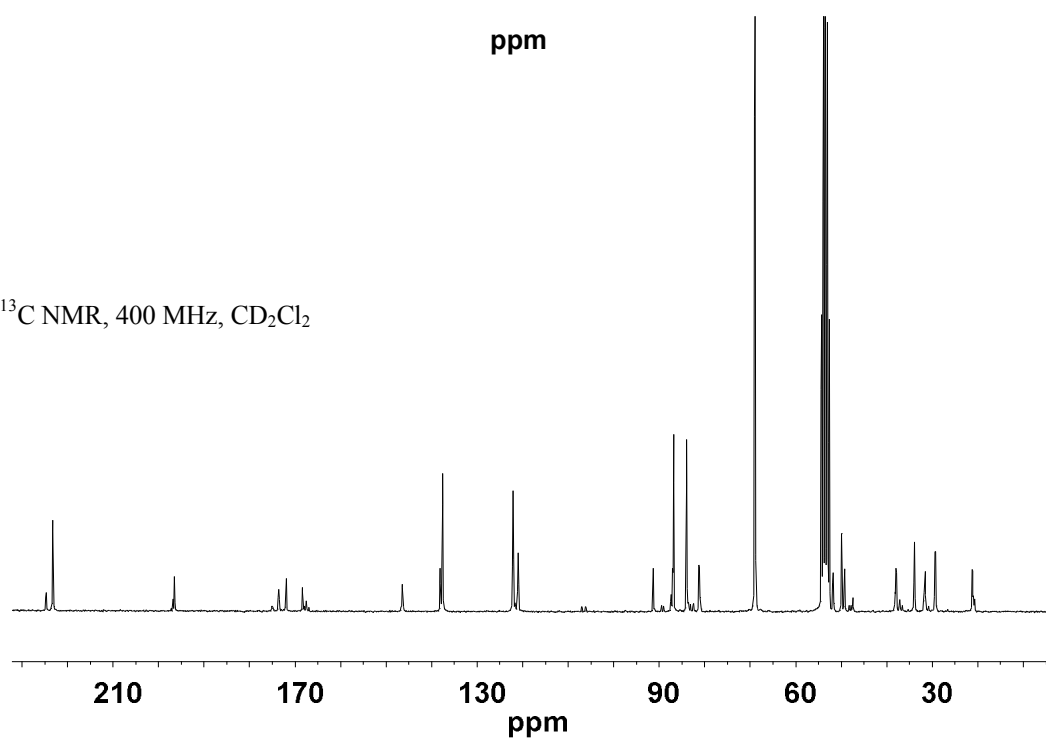


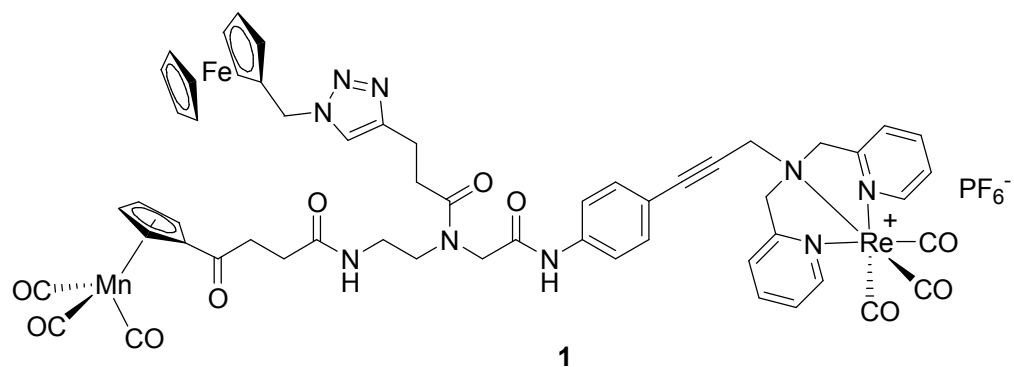


^1H NMR, 400MHz, CD_2Cl_2

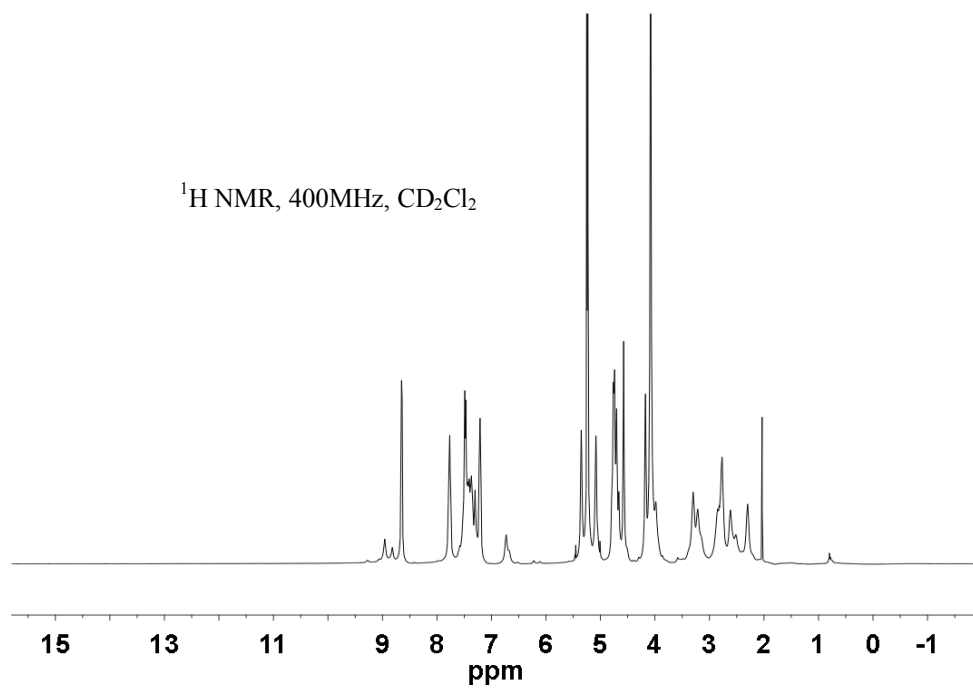


^{13}C NMR, 400 MHz, CD_2Cl_2

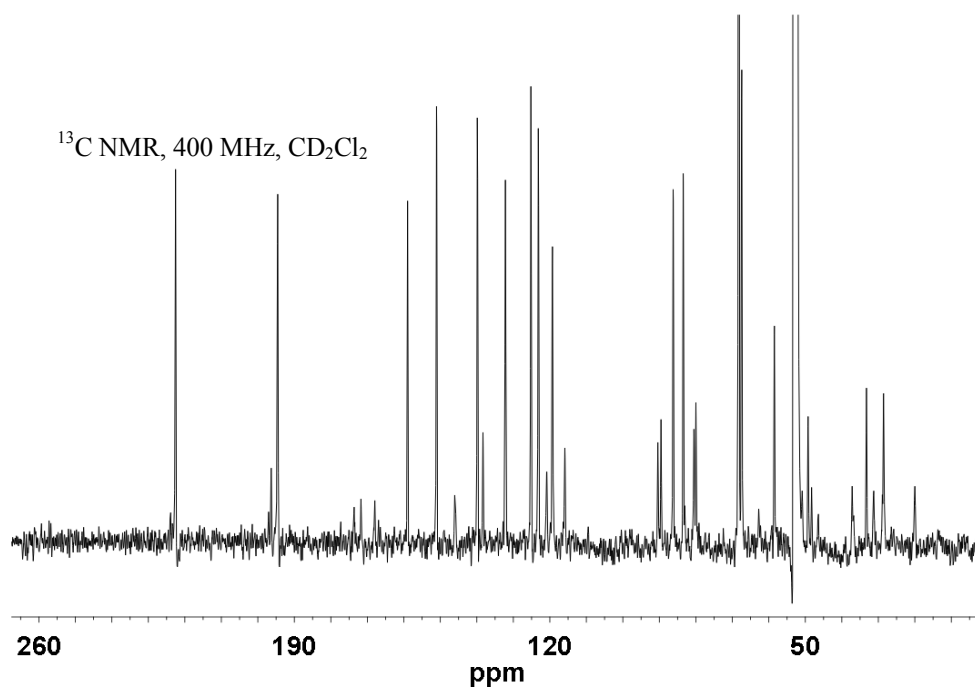




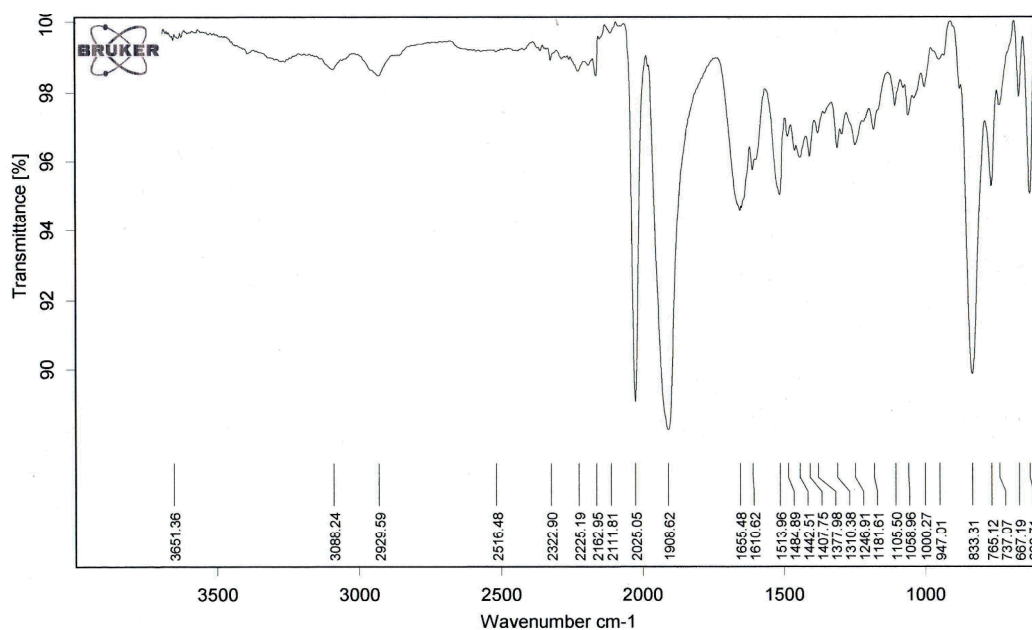
¹H NMR, 400MHz, CD₂Cl₂



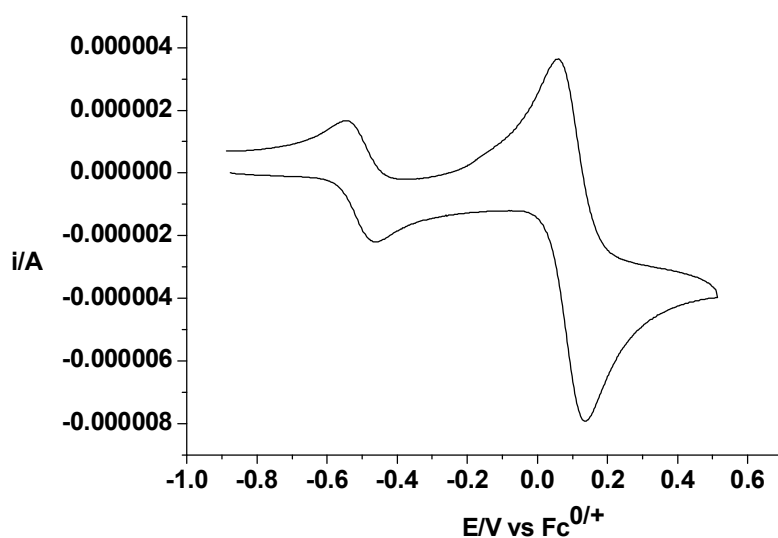
¹³C NMR, 400 MHz, CD₂Cl₂



IR spectrum (solid state) of **1**.

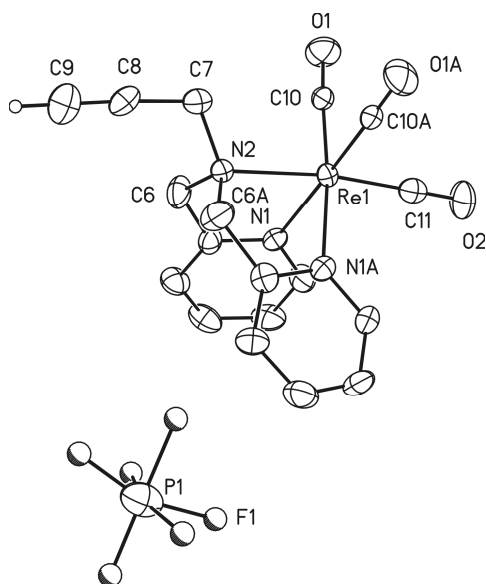


5) Electrochemistry of 1: Cyclic voltammetry was performed on with a BES Princeton Applied Research potentiostat from Perkin Elmer operated by the Princeton Applied Research Software “Power Suite”. The measurements were performed with a typical three-electrode cell placed in a Faraday cage consisting of copper hole sheet metal. For the measurements, a glassy carbon electrode with a geometric diameter of 2 mm was used as the stationary working electrode, a platinum wire was used as the counter electrode, and Ag/AgCl in 3 M KCl was used as the reference electrode. The Ag/AgCl reference electrode was permanently stored in aq. KCl solution (3 M) if not in use. Measurements were carried out in acetonitrile (0.1M [Bu₄N][PF₆]). Solutions were degassed and filtered before use. The working electrode was polished with moistened carpet material before each measurement. To avoid overlap with the oxidation of the ferrocenyl pendant group, the voltammetrically reversible one-electron dodecamethylferrocene couple (Cp*₂Fe^{0/+}) was used as a secondary internal reference (0.25 mM) for the potential scale calibration. The measurements were performed with a scan rate of 50 mVs⁻¹. The standard potential was then referenced to the usual Fc^{0/+} using the standard value for the Cp*₂Fe^{0/+} process (-505mV vs Fc^{0/+} in acetonitrile).⁸ The reversible Fc^{0/+} process of **1** was found to be centered at +97 mV vs Fc^{0/+}.



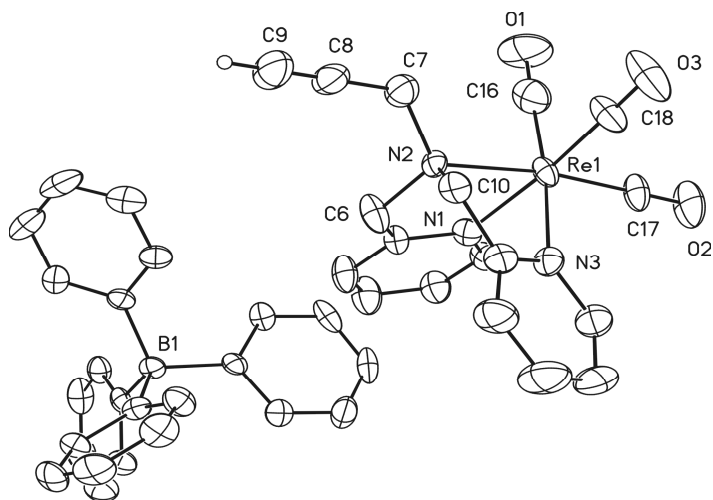
Cyclic Voltammogram of 1. Cyclic voltammograms of **1** (1 mM) at a GC electrode, in acetonitrile with $[\text{Bu}_4\text{N}][\text{PF}_6]$ (0.1 M) as the supporting electrolyte. The experiments were undertaken at a scan rate of 50 mV s^{-1} and at 20°C with Cp^*_2Fe as the internal reference (0.25 mM). Potentials are referenced to $\text{Fc}^{0/+}$ with Cp^*_2Fe as the secondary standard ($-505 \text{ mV vs Fc}^{0/+}$).

6) X-ray single crystal structure of **6b**.



Crystallographic data for 6b: $\text{C}_{18}\text{H}_{15}\text{F}_6\text{N}_3\text{O}_3\text{PRe}$, $M = 2610.04$, orthorhombic, space group $Pnma$, $a = 7.852(4)$, $b = 10.081(5)$, $c = 26.274(13) \text{ \AA}$, $V = 2079(2) \text{ \AA}^3$, $Z = 1$, $2\theta_{\text{max}} = 50.00^\circ$, 10532 measured reflections, 1922 independent reflections, 160 parameters, $\mu = 5.999 \text{ mm}^{-1}$, $R1 = 0.0477$ for 1693 observed reflections ($I > 2\sigma(I)$), $wR2 = 0.1275$ for all reflections.

7) X-ray single crystal structure of **6c**.



Crystallographic data for **6c**: $C_{18}H_{15}F_6N_3O_3PRe$, $M = 2610.04$, orthorhombic, space group $Pnma$, $a = 7.852(4)$, $b = 10.081(5)$, $c = 26.274(13)$ Å, $V = 2079(2)$ Å³, $Z = 1$, $2\theta_{max} = 50.00^\circ$, 10532 measured reflections, 1922 independent reflections, 160 parameters, $\mu = 5.999$ mm⁻¹, $R1 = 0.0477$ for 1693 observed reflections ($I > 2\sigma(I)$), $wR2 = 0.1275$ for all reflections.

8) References.

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