Electronic Supplementary Information

for

An Organophosphorus(III)-Selective Chemodosimeter for the Ratiometric Electrochemical Detection of Phosphines

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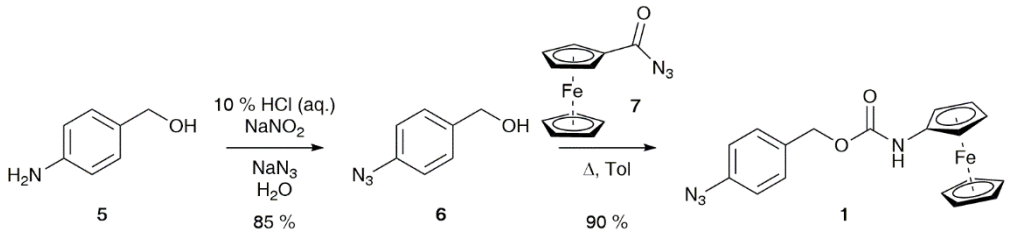
Content

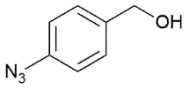
General information:

Proton and carbon nuclear magnetic resonance (NMR) spectra were recorded on an Agilent Technologies 500 MHz spectrometer (^{1}H NMR at 500 MHz and ^{13}C NMR at 126 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the solvent (^{1}H NMR: $CHCl_3$ at 7.26 ppm, and C_6H_6 at 7.16 ppm). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent peak (^{13}C NMR: $CDCl_3$ at 77.0 ppm, and C_6H_6 at 128.14). NMR data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, brs = broad singlet), coupling constants (Hz). IR spectra were recorded on a Perkin-Elmer 1600 FT IR spectrophotometer, with absorbencies quoted as ν in cm^{-1}. High resolution mass spectrometry was performed on a Bruker MaXis HD electrospray ionisation quadrupole time-of-flight (ESI-QTOF) mass spectrometer. Melting points were obtained on an OptiMelt MPA100 automated melting point system. Electrochemical analysis was performed on a Metrohm Autolab PGSTAT30 potentiostat or a PalmSens Emstat^3 Blue potentiostat. Analytical thin layer chromatography (TLC) were performed using aluminium-backed plates coated with Alugram® SIL G/UV254 purchased from Macherey-Nagel and visualised by UV light (254 nm). Silica gel column chromatography was carried out using 60 Å, 200-400 mesh particle size silica gel purchased from Sigma-Aldrich.

Scheme S1 – Synthetic route to probe 1



4-azidobenzyl alcohol 6



4-aminobenzyl alcohol (319 mg, 2.6 mmol, 1 eq.) was dissolved in HCl (5 m, 1.25 mL) and cooled to 0 °C. A solution of sodium nitrite (207 mg, 3 mmol, 1.15 eq.) in water (5 mL) was added dropwise over 15 mins, after which sodium azide (520 mg, 8 mmol, 3.1 eq.) was added in portionwise over 30 mins. The reaction was stirred for 22 h at room temperature, after which the reaction was poured into sat. $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with water (10 mL), brine (10 mL), then dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification *via* silica gel column chromatography (EtOAc 1:3 Et_2O (R_f = 0.74)) gave the title compound as a yellow oil (329 mg, 85 %).

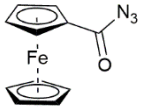
Mp; 29-33 °C (lit. 28.5 °C)

^{1}H NMR (500 MHz, $CDCl_3$); 8.25 – 8.17 (2 H, m), 7.56 – 7.48 (2 H, m), 4.83 (2 H, s).

^{13}C NMR (126 MHz, $CDCl_3$); 148.2, 147.3, 127.0, 123.7, 64.0.

IR (film cm^{-1}); 3658, 3321, 2981, 2884, 2411, 2255, 2100, 1608, 1581, 1506, 1460, 1419, 1280, 1024, 1010.

Ferrocenyl azide 7



Ferrocenecarboxaldehyde (2.00 g, 8.69 mmol, 1 eq.) was suspended in anhydrous DCM (20 mL) under N_2 and then cooled to 0 °C. Oxalyl chloride (1.49 mL, 17.33 mmol, 2 eq.) was then added dropwise followed by a drop of DMF. The reaction was allowed to warm to room temperature and stirred for 3 h, after which the solvent was removed in vacuo. The solid residue was taken up in anhydrous DCM (20 mL) and cooled to 0 °C. Tetrabutylammonium bromide (30 mg, 0.09 mmol, 0.01 eq.) was added followed by sodium azide (0.85 g, 13.07 mmol, 1.5 eq.) in water (4 mL) and the reaction was left to stir for 48 h after which the reaction was diluted with water (50 mL) and the layers separated. The aqueous layer was extracted with DCM (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification *via* silica gel column chromatography (Pet. 40–60°C 1:1 DCM (R_f = 0.45)) gave the title compound as a red-orange crystalline solid (1.98 g, 89%).

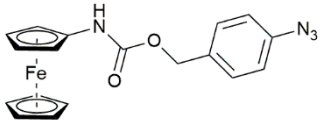
Mp: 85-89 °C (lit.[2] 84-86 °C)

IR (solid cm^{-1}); 3108, 3079, 2148, 1670, 1453, 1372, 1206, 1184, 1054.

^{1}H NMR (500 MHz, C_6D_6); 4.74 (2 H, t, *J* 2.0), 4.02 (2 H, t, *J* 2.0), 3.91 (5 H, s).

^{13}C NMR (126 MHz, C_6D_6); 176.9, 73.3, 71.3, 71.0.

4-azidobenzyl (ferrocenyl)carbamate 1



Ferrocenoyl azide (225 mg, 0.88 mmol, 1 eq.) was suspended in anhydrous toluene (2 mL) under argon. A solution of 4-azidobenzyl alcohol (149 mg, 1 mmol, 1.4 eq.) in anhydrous toluene (2 mL) was added and the reaction was refluxed for 2 h, after which the reaction was allowed to cool to room temperature. The solvent was *in vacuo* and purification *via* silica column chromatography (Pet. 40-60 °C 9:1 EtOAc (R_f = 0.22)) to give the title compound as an orange oil (298 mg, 90 %).

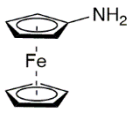
^{1}H NMR (500 MHz, CDCl3); 7.35 (2 H, d, *J* 8.0), 7.03 (2 H, d, *J* 8.0), 5.49 (1 H, brs), 5.18 – 4.68 (3 H, m), 4.41 (7 H, brs).

^{13}C NMR (126 MHz, CDCl3); 140.2, 133.1, 130.0, 119.3, 69.5, 66.4, 64.8, 60.9.

HRMS (ESI); calc'd for $C_{18}H_{16}FeN_4NaO_2$ $[M+Na]^+$: *m/z* 399.052, found 399.058.

IR (solid cm^{-1}); 3223, 3094, 2411, 2256, 2112, 2074, 1702, 1507.

Aminoferrocene 4



2-(trimethylsilyl)ethyl ferrocenecarbamate (1.04 g, 3 mmol, 1 eq.) was dissolved in tetrabutylammonium fluoride (TBAF) solution [1M in THF] (12 mL, 12 mmol, 4 eq.) and the reaction mixture was heated to 50 °C for 2 hours. After allowing to cool to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was quenched with water (20 mL), then extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried over MgSO4 and concentrated under reduced pressure to afford the crude product. Purification by silica gel column chromatography (hexane 8:2 EtOAc, R_f = 0.20) gave the title compound as an orange crystalline solid (0.51 g, 85%).

Mp: 149-152 °C (lit.[3] 151-153 °C)

^{1}H NMR (500 MHz, $CDCl_3$); 4.11 (5 H, s), 4.01 (2 H, s), 3.86 (2 H, s), 2.56 (2 H, brs).

^{13}C NMR (126 MHz, $CDCl_3$); 68.9, 63.4, 58.7.

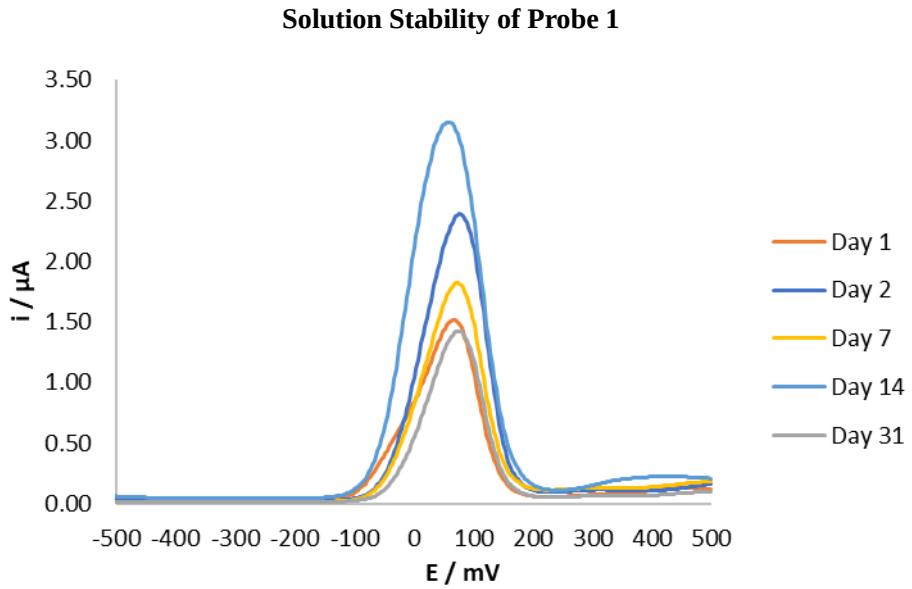


Figure S1 – Differential pulse voltammogram obtained for probe **1** (1 mM) in MeCN:Tris buffer (pH 9, 50 mM) 7.5:92.5. Note: the variance in signal is caused by the variance in surface area of the screen-printed electrodes. No aminoferrocene **4** (E_{ox} = −220mV vs Ag/AgCl) was observed.

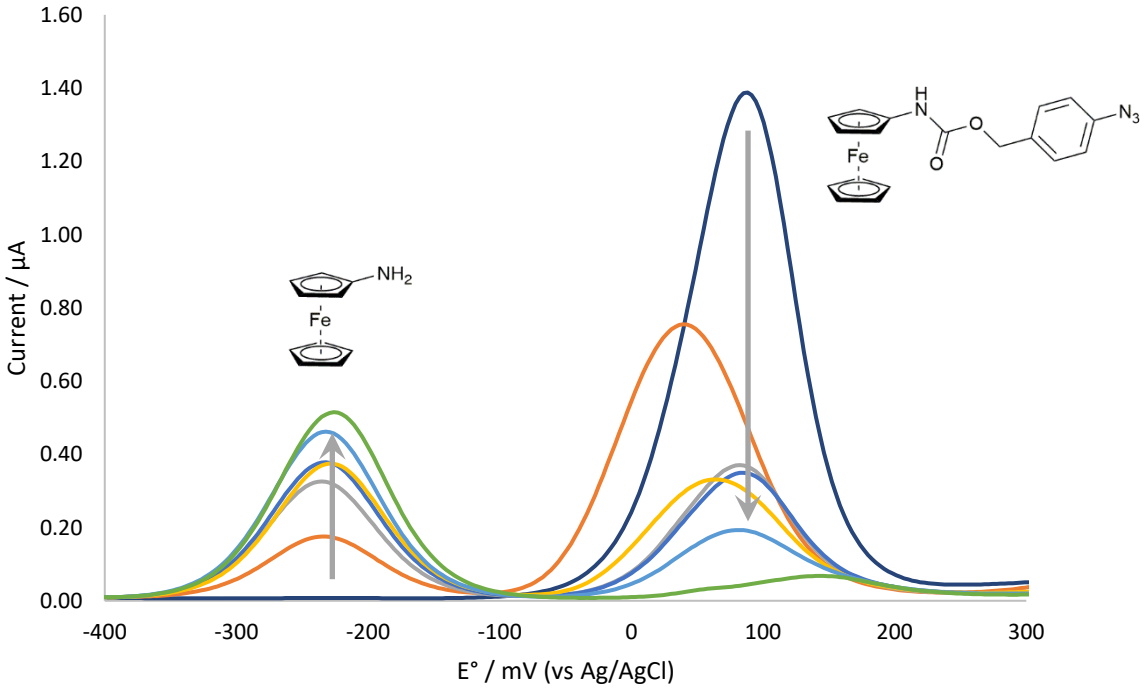
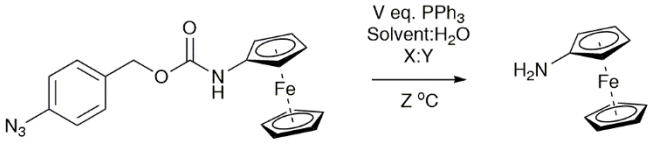


Figure S2 – Differential pulse voltammogram (DPV) overlays of individual duplex voltammograms using different ratios of probe **1** and aminoferrocene **4**. Total ferrocene concentration = 1 mM.

Assay Optimization



1 4

Exp.	Solvent	Solvent:Water Ratio	Temperature (°C)	PPh_3 Eq.	Conversion (%)[a]
1	DMF	1:1	R.T.	10	37
2	DMSO	1:1	R.T.	10	16
3	Acetone	1:1	R.T.	10	48
4	MeCN	1:1	R.T.	10	79
5	THF	1:1	R.T.	10	34
6	1,4-dioxane	1:1	R.T.	10	78
7	MeCN	3:1	R.T.	10	78
8	MeCN	1:3	R.T.	10	33[b]
9	MeCN	3:1	R.T.	5	43
10	MeCN	3:1	30	5	64
11	MeCN	3:1	30	5	79
12	MeCN	3:1	30	5	88

Table S1 – Reaction conditions: Probe **1** (1 mM), triphenylphosphine (V eq.), solvent:water X:Y (1 mL), Z °C (a) conversion determined from DPV after 60 minutes. (b) heterogeneous solution prevented accurate sampling.

Method for the desktop electrochemical detection of organophosphorus(III) compounds (optimized conditions)

A 10 mM stock solution of probe **1** (4 mg) was prepared in acetonitrile (1 mL). A 10 mM stock solution of organophosphorus(III) compound was prepared in acetonitrile (1 mL). To 250 µL of water and 550 µL of acetonitrile in a small screw top vial equipped with a small magnetic stirrer was added 100 µL of the stock solution of **1** then 100 µL of stock solution of organophosphorus(III) compound. The vial was then placed in a DrySyn® block warmed to 50 °C and stirred. Every 3 minutes for 60 minutes thereafter, a 10 µL sample was diluted in 90 µL tris buffer (pH 9, 50 mM), shaken well, and a 20 µL sample was subjected to desktop electrochemical analysis.

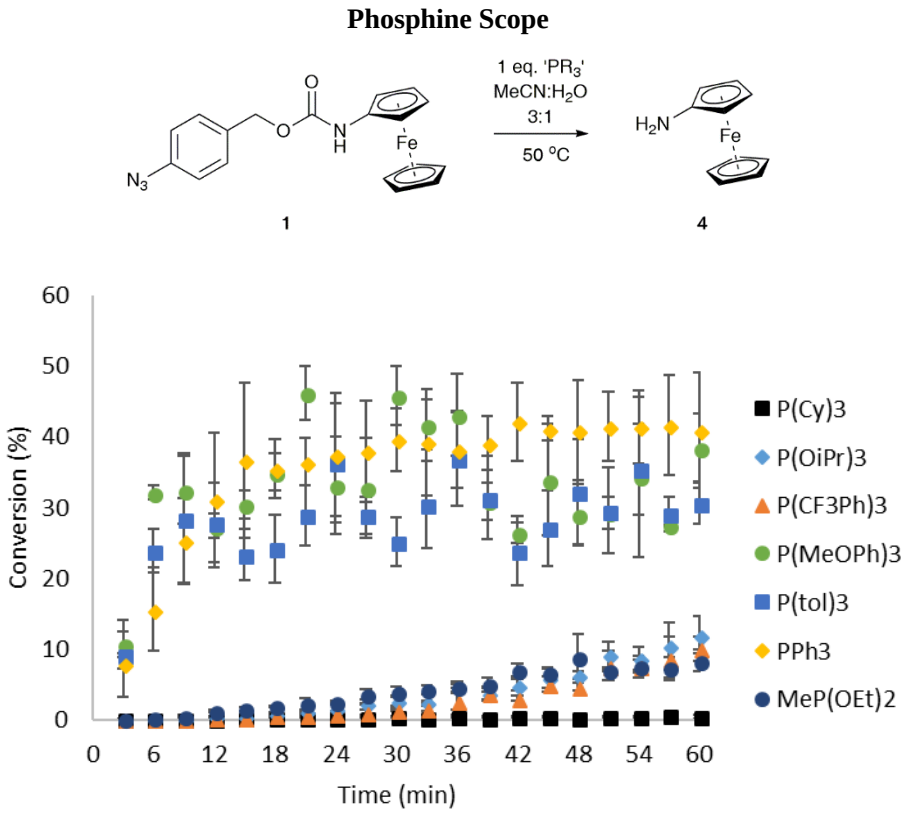


Figure S3 – Conversion of probe **1** (1 mM) to aminoferrocene **4** after addition of PR_3 (1 mM) in acetonitrile:water (3:1, 1 mL) at 50 °C. Error bars represent the standard deviation where n = *3*.

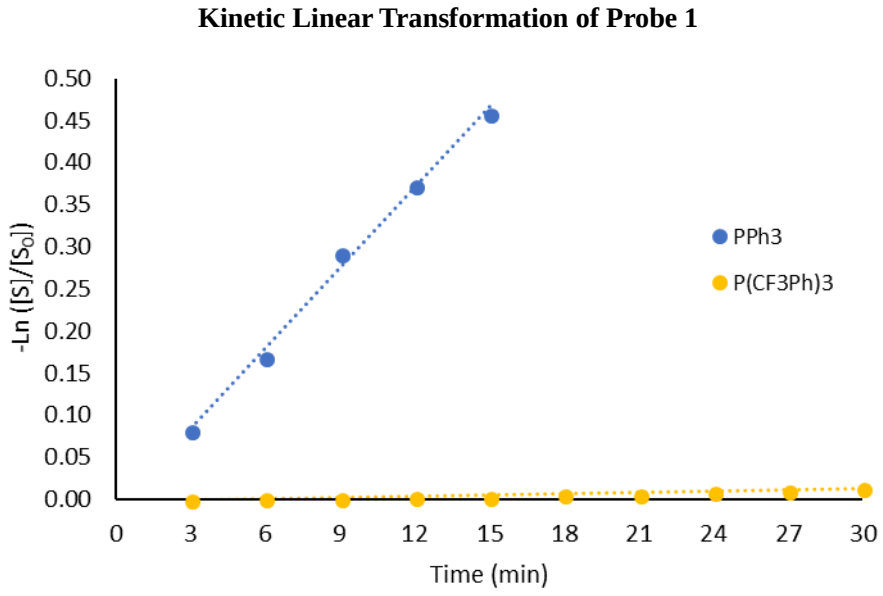
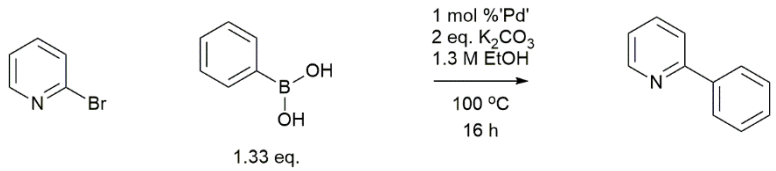


Figure S4 – Kinetic linear transformation of probe **1** (1 mM) to aminoferrocene **4** after addition of PR_3 (1 mM) in acetonitrile:water (3:1, 1 mL) at 50 °C.

Kinetic Calculations

Pseudo-first order equation y = k x + C where: for PPh_3 k = 0.0318 min^{-1} (5.30×10^{-4} s^{-1}), C = -0.0166; for P(*p*-$CF_3Ph)_3$ k = 0.0005 min^{-1} (8.33×10^{-6} s^{-1}), C = -0.0026.

Complex Sample Testing

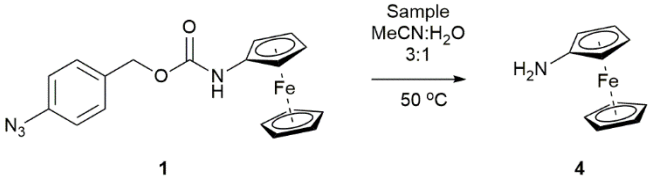


Complex Sample Preparation

A 1 M stock solution with reference to 2-phenylpyridine was prepared from the crude Suzuki-Miyaura cross-coupling product in acetonitrile. Stock solutions were prepared from:

1. Unpurified 2-phenylpyridine, catalyst $Pd(PPh_3)_4$.
2. Purified 2-phenylpyridine, catalyst $Pd(PPh_3)_4$.
3. Unpurified 2-phenylpyridine, catalyst $Pd(dba)_2$.
4. Purified 2-phenylpyridine, catalyst $Pd(dba)_2$.

A 100 µL aliquot was analysed using the general desktop electrochemical detection assay.



1 **4**

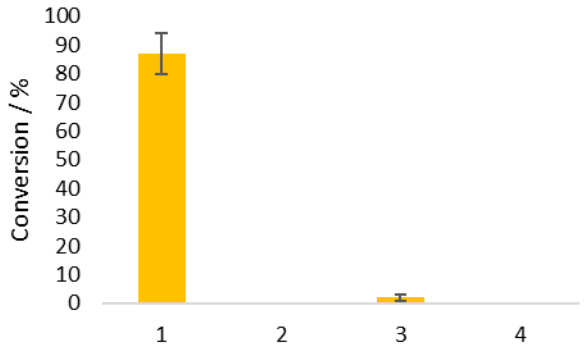


Figure S5 - Conversion of probe **1** (1 mM) to aminoferrocene **4** after addition of complex sample in acetonitrile:water (3:1, 1 mL) at 50 °C after 60 minutes . Error bars represent the standard deviation where n = 3. (1) Unpurified 2-phenylpyridine, catalyst $Pd(PPh_3)_4$; (2) Purified 2-phenylpyridine, catalyst $Pd(PPh_3)_4$; (3) Unpurified 2-phenylpyridine, catalyst $Pd(dba)_2$; (4) Purified 2-phenylpyridine, catalyst $Pd(dba)_2$.

Handheld Potentiostat

Handheld Setup

Figure S6 – Photograph of handheld potentiostat setup. PalmSens EmStat^3 Blue potentiostat (right) connected to electrode rig (middle), and *via* Bluetooth to a tablet (left) running PS Touch.

Method for the handheld electrochemical detection of organophosphorus(III) compounds (optimised conditions)

A 50 mM stock solution of probe **1** (19 mg) was prepared in acetonitrile (1 mL). A 50 mM stock solution of organophosphorus(III) compound was prepared in acetonitrile (1 mL). To 250 µL of water and 350 µL of acetonitrile in a small screw top vial equipped with a small magnetic stirrer was added 200 µL of the stock solution of **1** then 200 µL of stock solution of organophosphorus(III) compound. The vial was then placed in a DrySyn® block warmed to 50 °C and stirred. Every 3 minutes for 60 minutes thereafter, a 10 µL sample was diluted in 90 µL tris buffer (pH 9, 50 mM), shaken well, and a 20 µL sample was subjected to handheld electrochemical analysis.

Calibration Curve

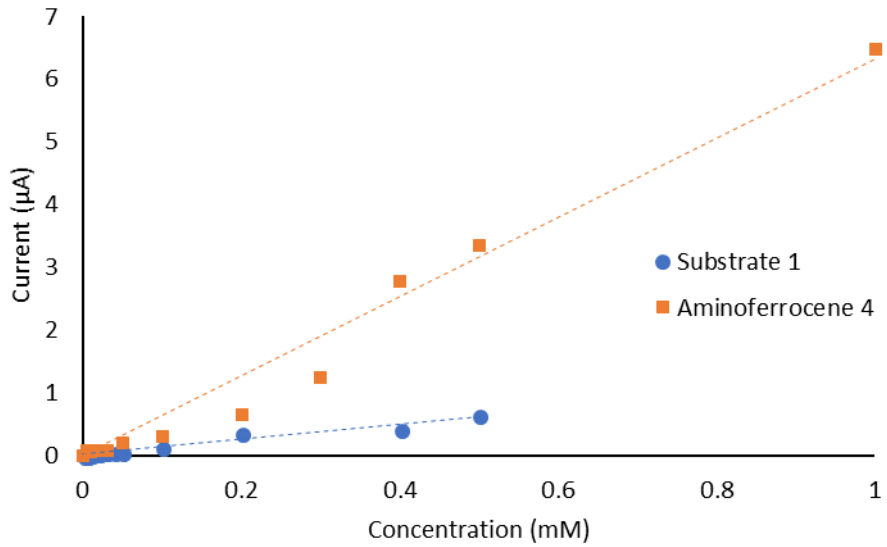


Figure S7 – Calibration curve for probe **1** and aminoferrocene **4** in MeCN:Tris buffer (pH 9, 50 mM) 7.5:92.5.

Triphenylphosphine assay using Handheld Potentiostat

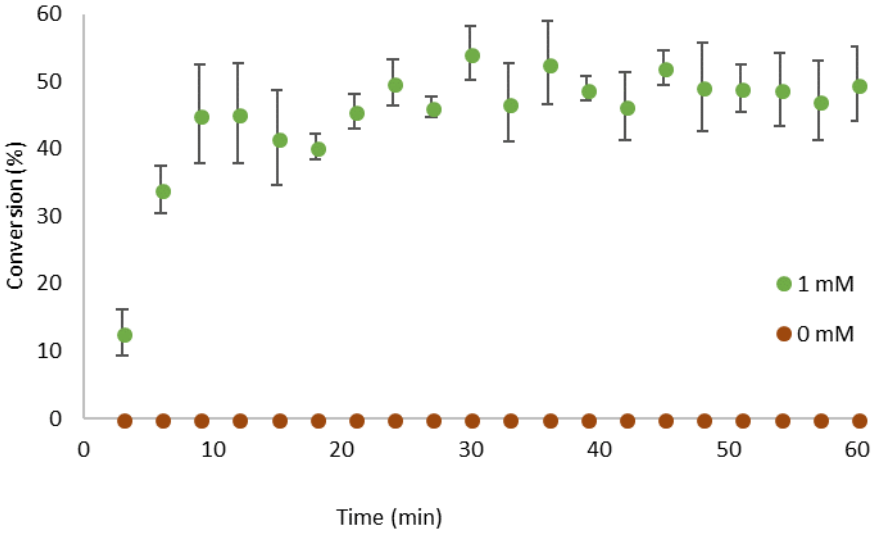


Figure S8 – Conversion of probe **1** (10 mM) to aminoferrocene after addition of triphenylphosphine (X mM) in acetonitrile:water (3:1, 1 mL) at 50 °C. Error bars represent the standard deviation where n = *3*.

Comparative assays for Handheld vs Desktop Electrochemical Analysis

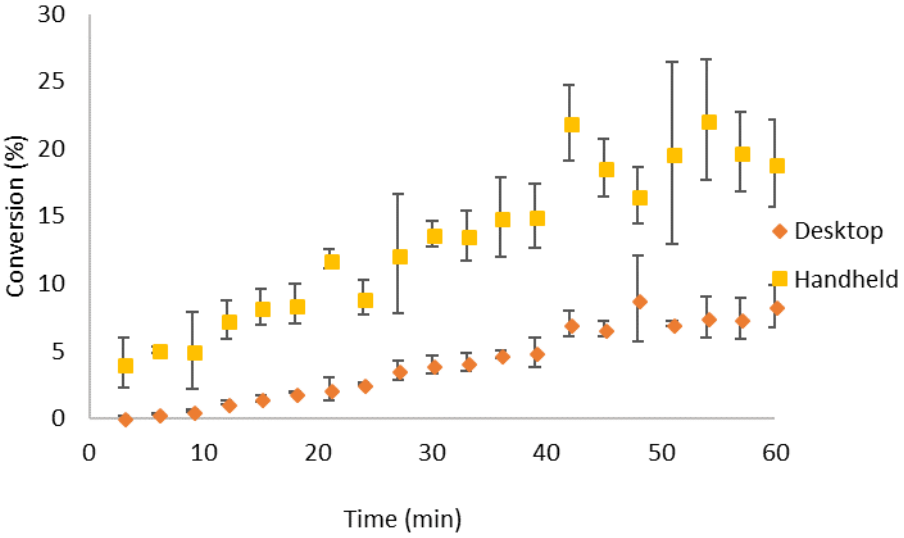


Figure S9 – Conversion of probe **1** (10 mM) to aminoferrocene after addition of diethylmethylphosphinite (1 mM) in acetonitrile:water (3:1, 1 mL) at 50 °C. Error bars represent the standard deviation where n = *3*.

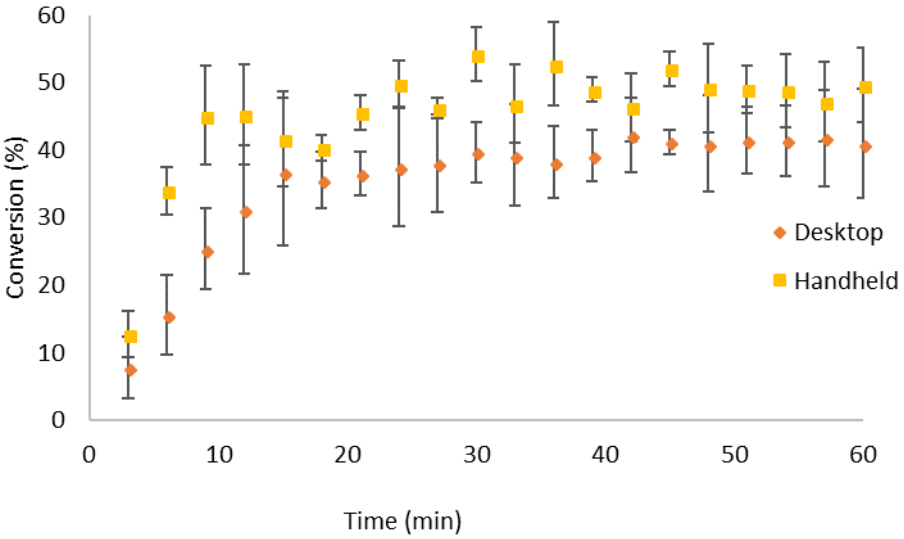
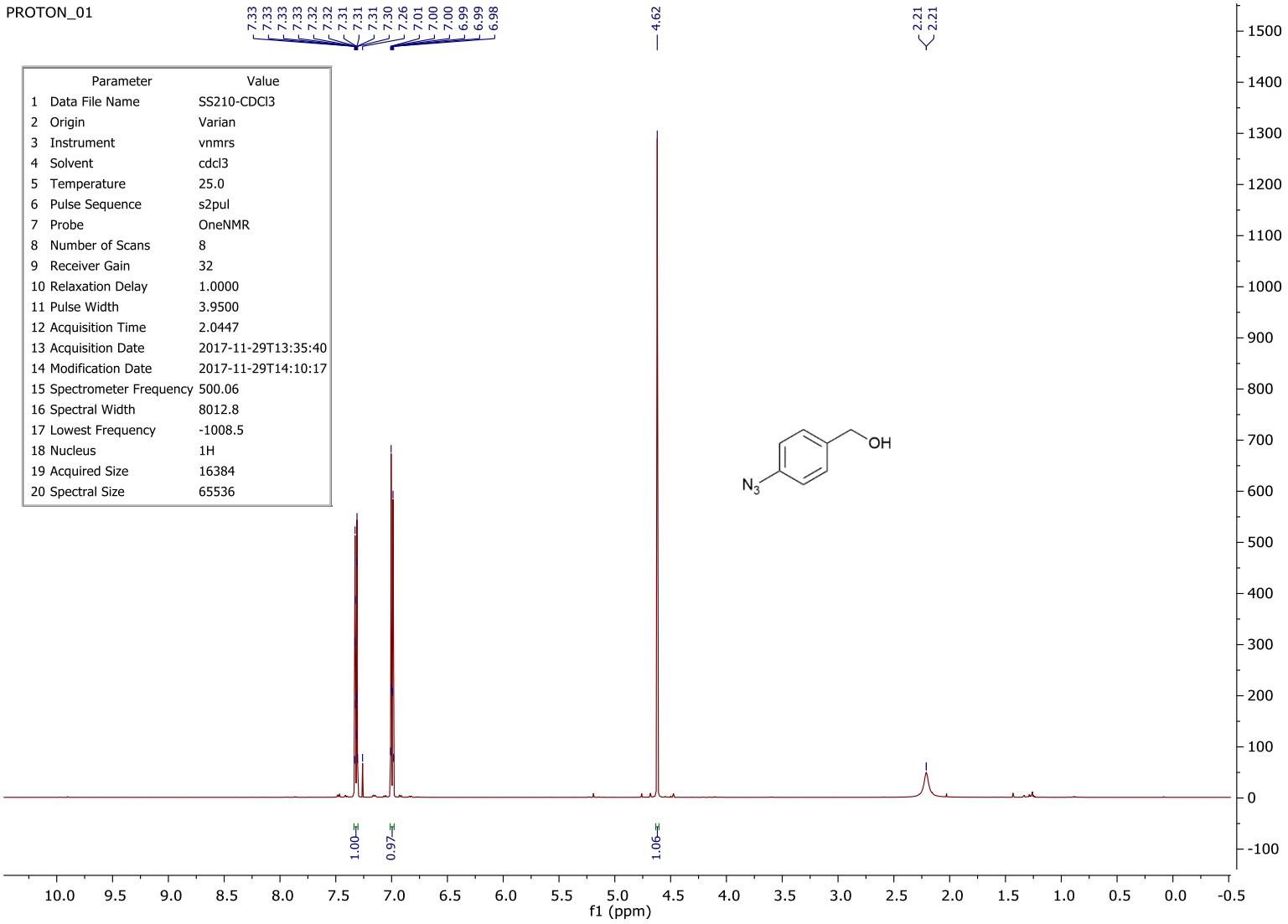


Figure S10 – Conversion of probe **1** (10 mM) to aminoferrocene after addition of triphenylphosphine (1 mM) in acetonitrile:water (3:1, 1 mL) at 50 °C. Error bars represent the standard deviation where n = *3*.

PROTON_01



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20	Spectral Size	65536

CARBON_01

	Parameter	Value
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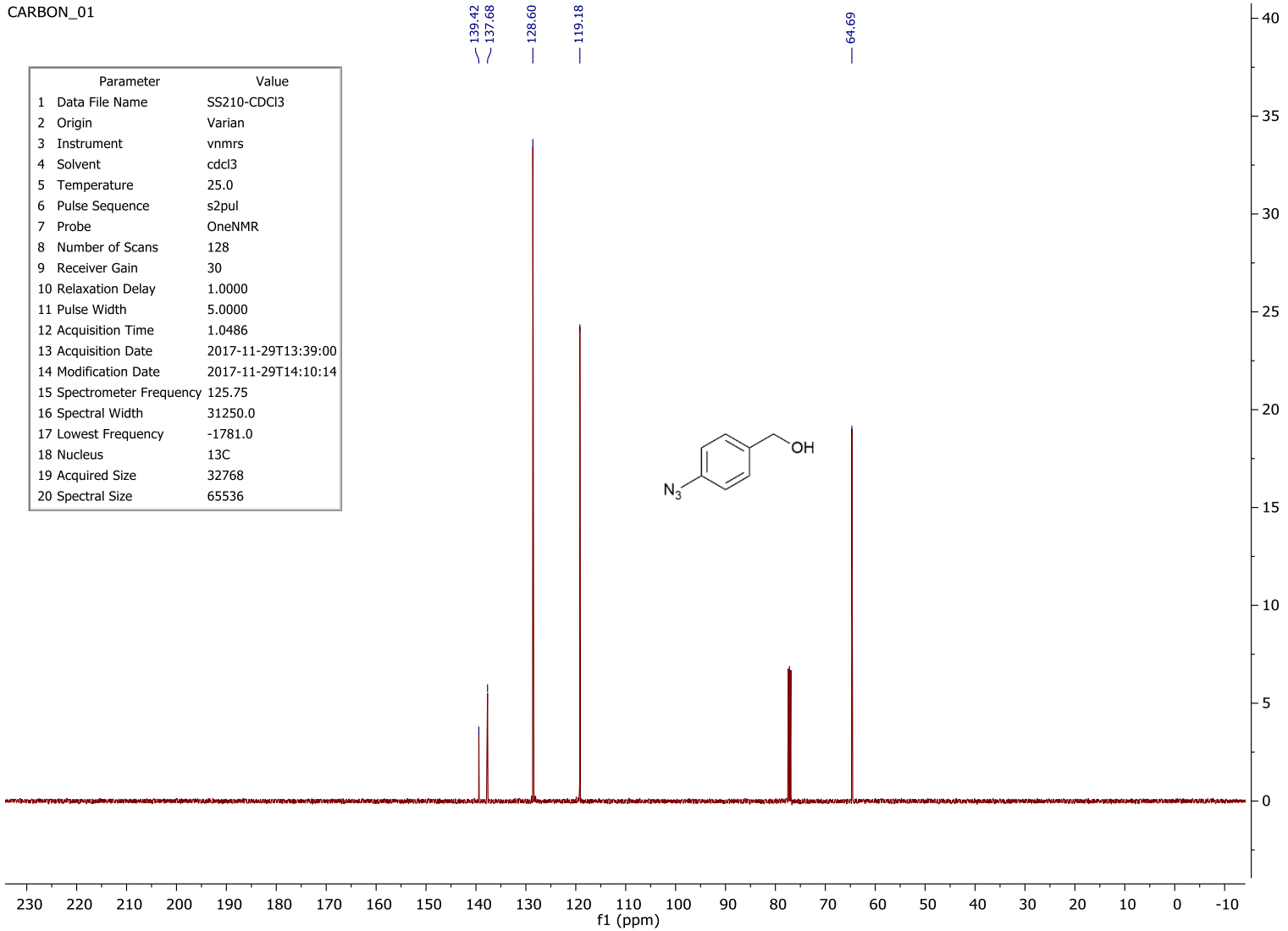

PROTON_01

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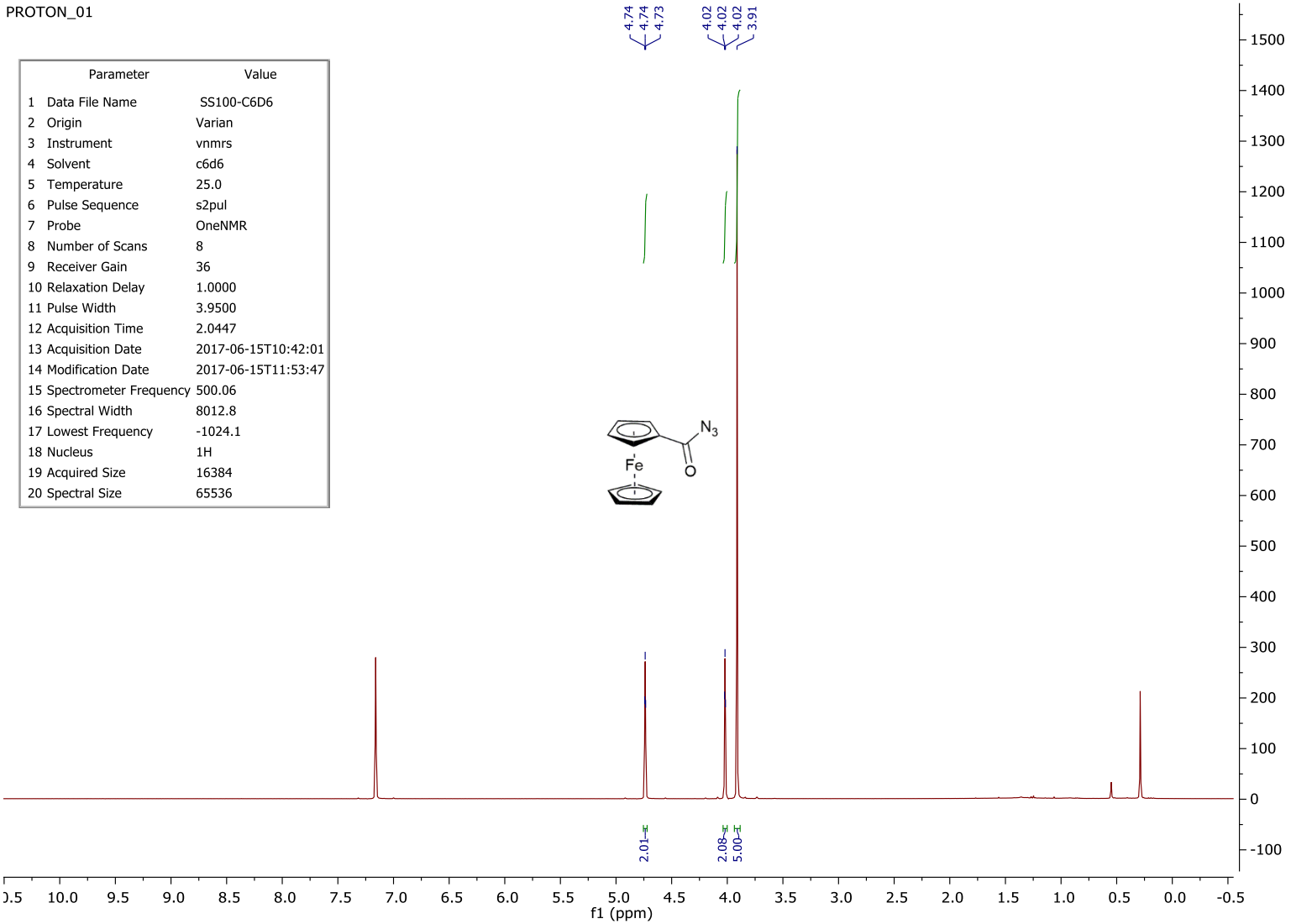

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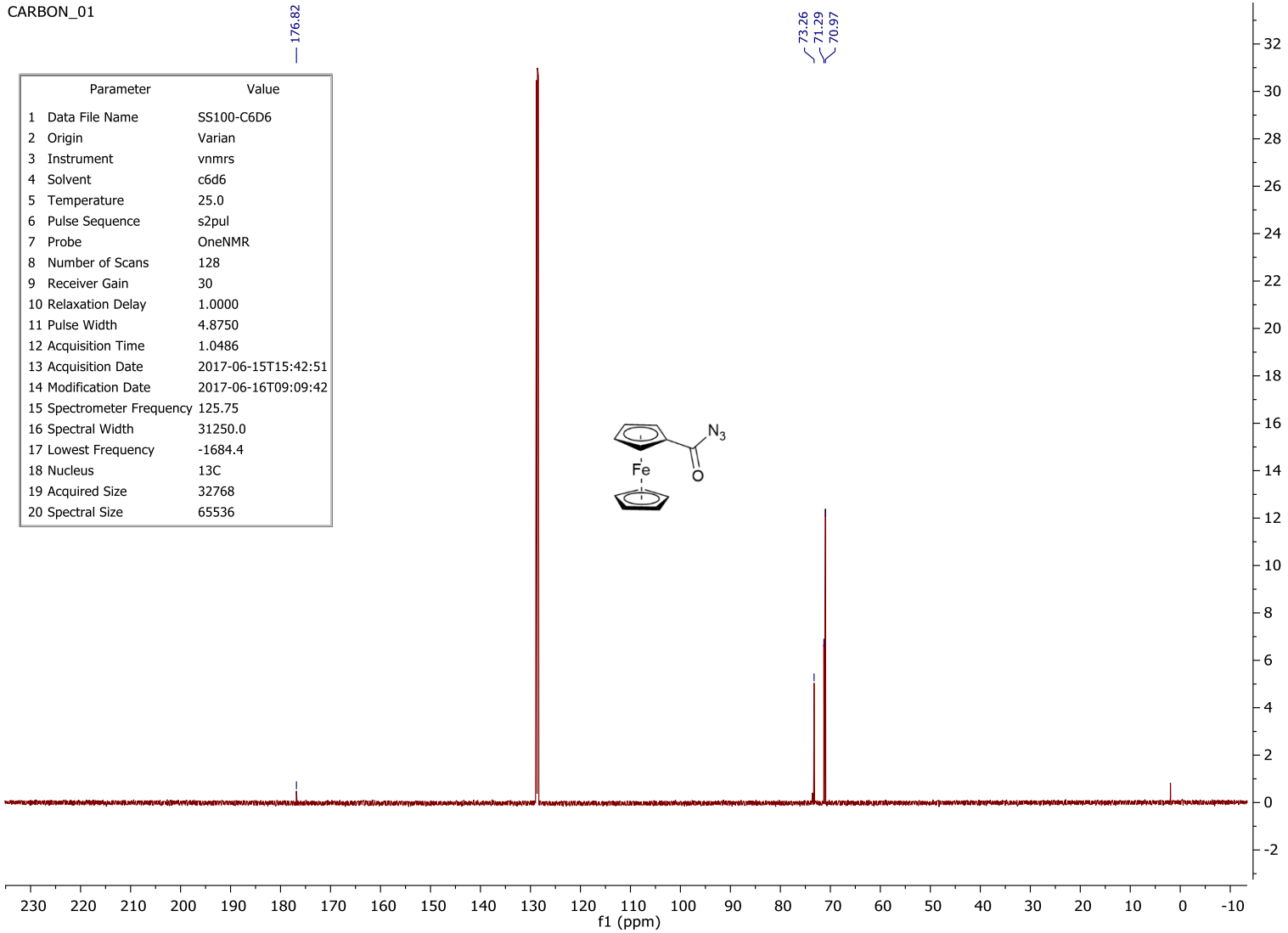

PROTON_01

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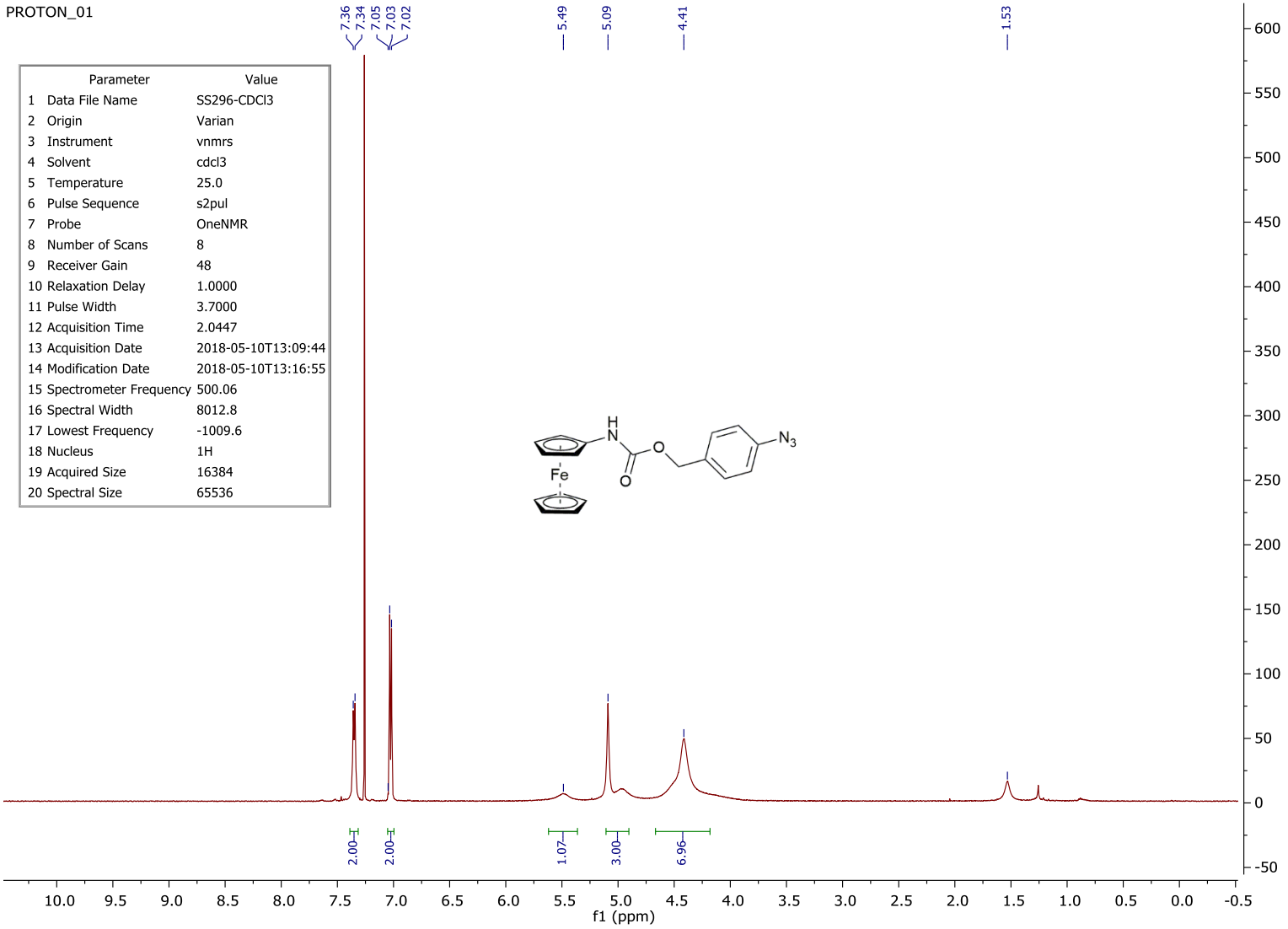

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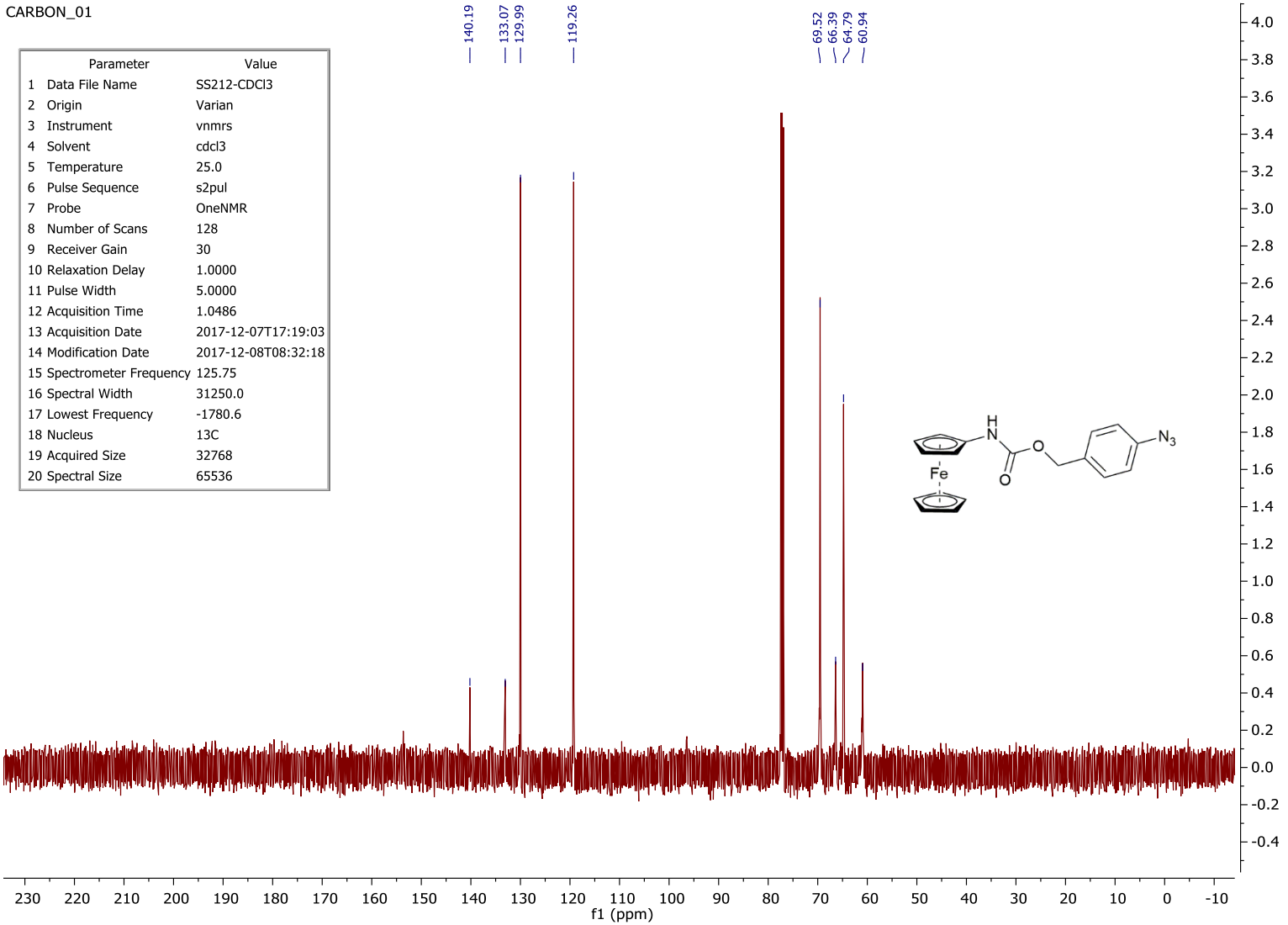
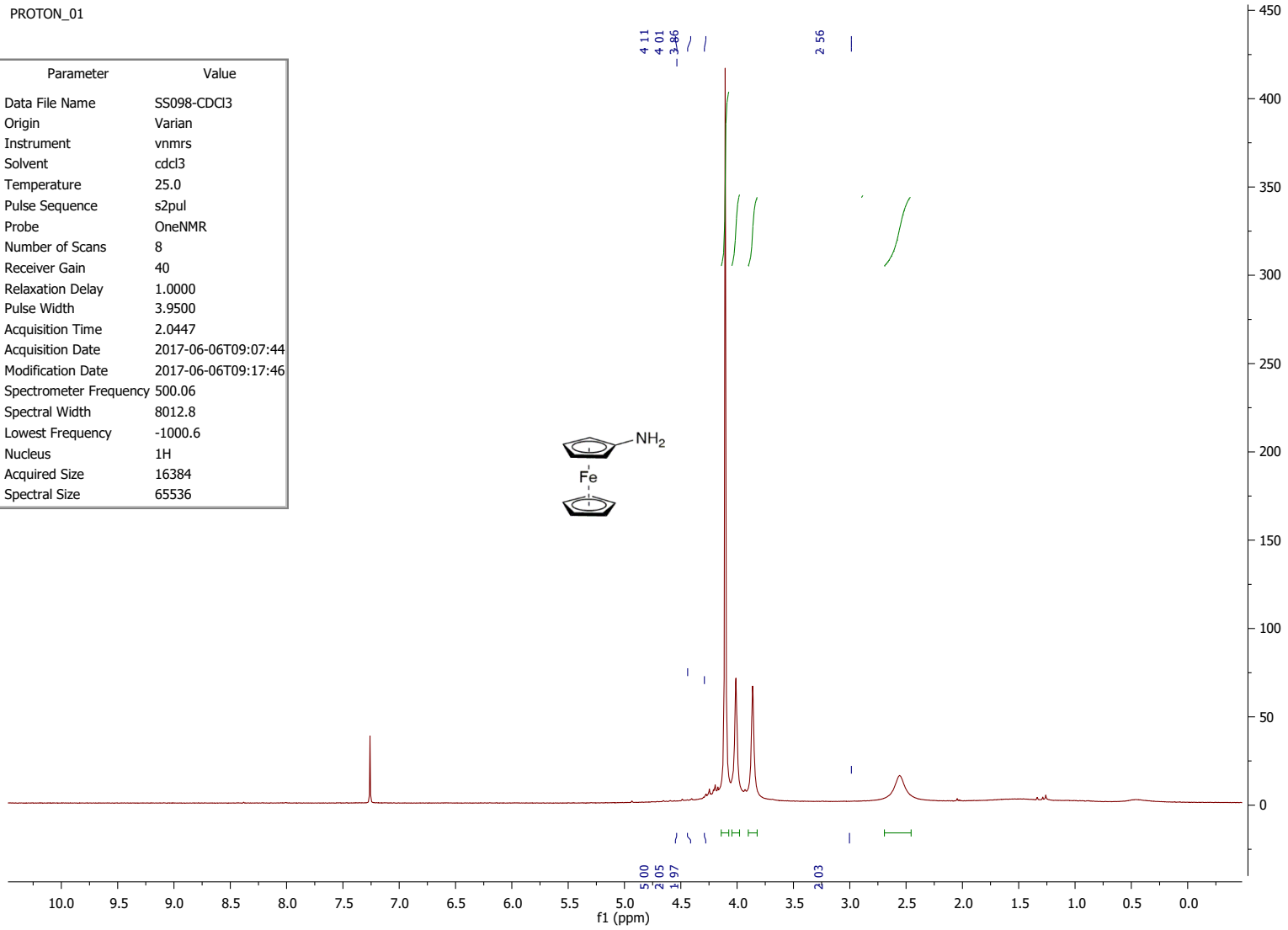
19	Acquired Size	32768
20	Spectral Size	65536



PROTON_01

	Parameter	Value
1	Data File Name	SS098-CDCl3
2	Origin	Varian
3	Instrument	vnmrs
4	Solvent	cdcl3
5	Temperature	25.0
6	Pulse Sequence	s2pul
7	Probe	OneNMR
8	Number of Scans	8
9	Receiver Gain	40
10	Relaxation Delay	1.0000
11	Pulse Width	3.9500
12	Acquisition Time	2.0447
13	Acquisition Date	2017-06-06T09:07:44
14	Modification Date	2017-06-06T09:17:46
15	Spectrometer Frequency	500.06
16	Spectral Width	8012.8
17	Lowest Frequency	-1000.6
18	Nucleus	1H
19	Acquired Size	16384
20	Spectral Size	65536



CARBON_01

	Parameter	Value
1	Data File Name	SS098-CDCl3
2	Origin	Varian
3	Instrument	vnmrs
4	Solvent	cdcl3
5	Temperature	25.0
6	Pulse Sequence	s2pul
7	Probe	OneNMR
8	Number of Scans	128
9	Receiver Gain	30
10	Relaxation Delay	1.0000
11	Pulse Width	4.8750
12	Acquisition Time	1.0486
13	Acquisition Date	2017-06-06T10:19:19
14	Modification Date	2017-06-06T10:49:02
15	Spectrometer Frequency	125.75
16	Spectral Width	31250.0
17	Lowest Frequency	-1793.7
18	Nucleus	13C
19	Acquired Size	32768
20	Spectral Size	65536