Supplementary Material (ESI) for Chemical Communications

SUPPORTING INFORMATION FOR:

Cyanogen formation during asymmetric cyanohydrin synthesis

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Contents

Details of chemicals and equipment

Commercially available chemicals (Alfa, Aldrich, Fluka) were used as received. Cyanides, cyanohydrins and cyanogen are highly toxic if swallowed, inhaled or absorbed through skin. They must be handled in fume cupboards in fully compliance with all applicable safety regulations and extreme caution should be exercised to prevent exposure to skin.

EPR measurements were carried out using a JEOL JES-RE1X ESR spectrometer. Typical instrument parameters for the acquisition of the X-band EPR spectra were: microwave frequency 9.13 GHz, microwave power 1 mW, sweep width 1000 G, centre field 3240 G, sweep time 180 s, time constant 0.1 s, modulation frequency 100 kHz, modulation amplitude 3.2 G. The samples were prepared in glass pipettes. For experiments involving TEMPO or spin trapping, power 5mW, modulation amplitude 1 G were used. EPR spectra at 130 K were recorded with power 2mW, modulation amplitude 5 G. EPR spectra at 192 K used power 5 mW, modulation amplitude 3.2 G.

Figure S1. EPR spectra of complexes 1a-c and 2

EPR spectra from top to bottom: complexes **2, 1a, 1b, 1c** at 298K under an air atmosphere. Samples were prepared by dissolving complexes (2 x 10^{-3} mmol) in dichloromethane (175 μL)

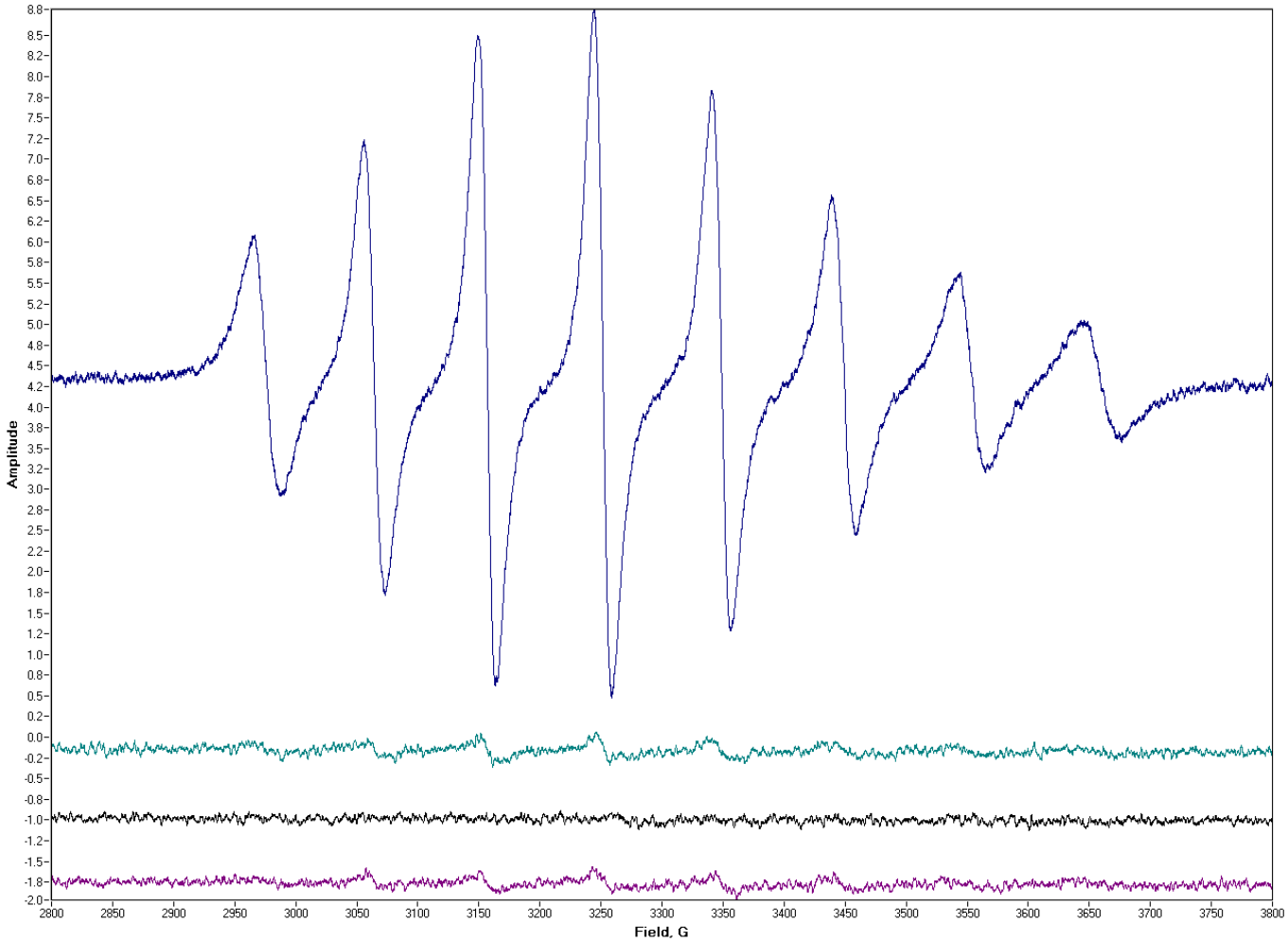


Figure S2. EPR spectra recorded during the asymmetric addition of Me_3SiCN to benzaldehyde catalysed by complex 1a

From bottom to top, complex **1a** (1.44 mg, 2 x 10^{-3} mmol) with benzaldehyde (10 μL) and trimethylsilyl cyanide (20 μL) in dichloromethane (175 μL). Spectra were recorded every 3.5 minutes.

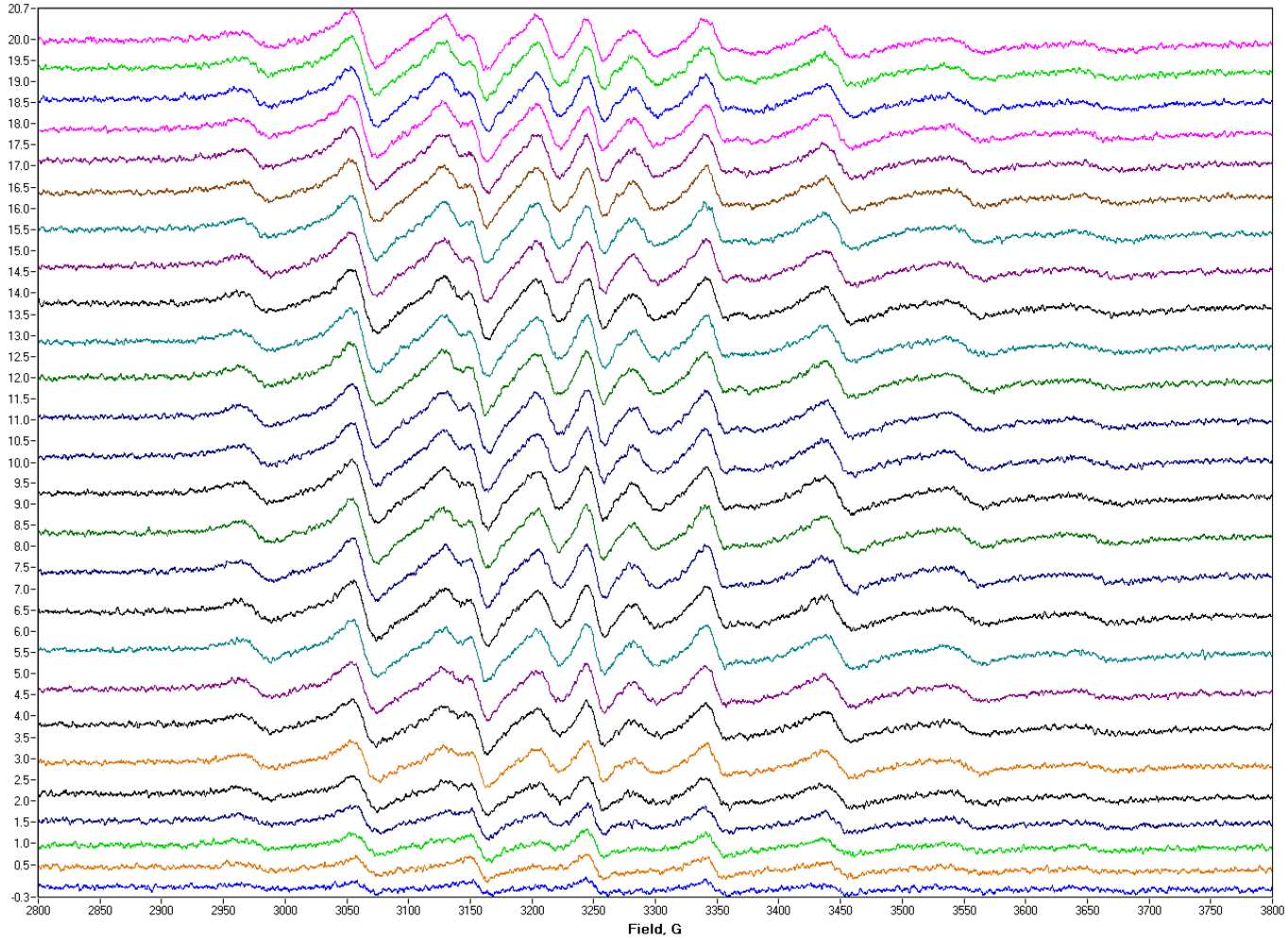


Figure S3. EPR spectra recorded during the asymmetric addition of Me_3SiCN to benzaldehyde catalysed by complex 1b

From bottom to top, complex **1b** (1.27 mg, 2 x 10^{-3} mmol) with benzaldehyde (10 μL) and trimethylsilyl cyanide (20 μL) in dichloromethane (175 μL). Spectra were recorded every 3.5 minutes.

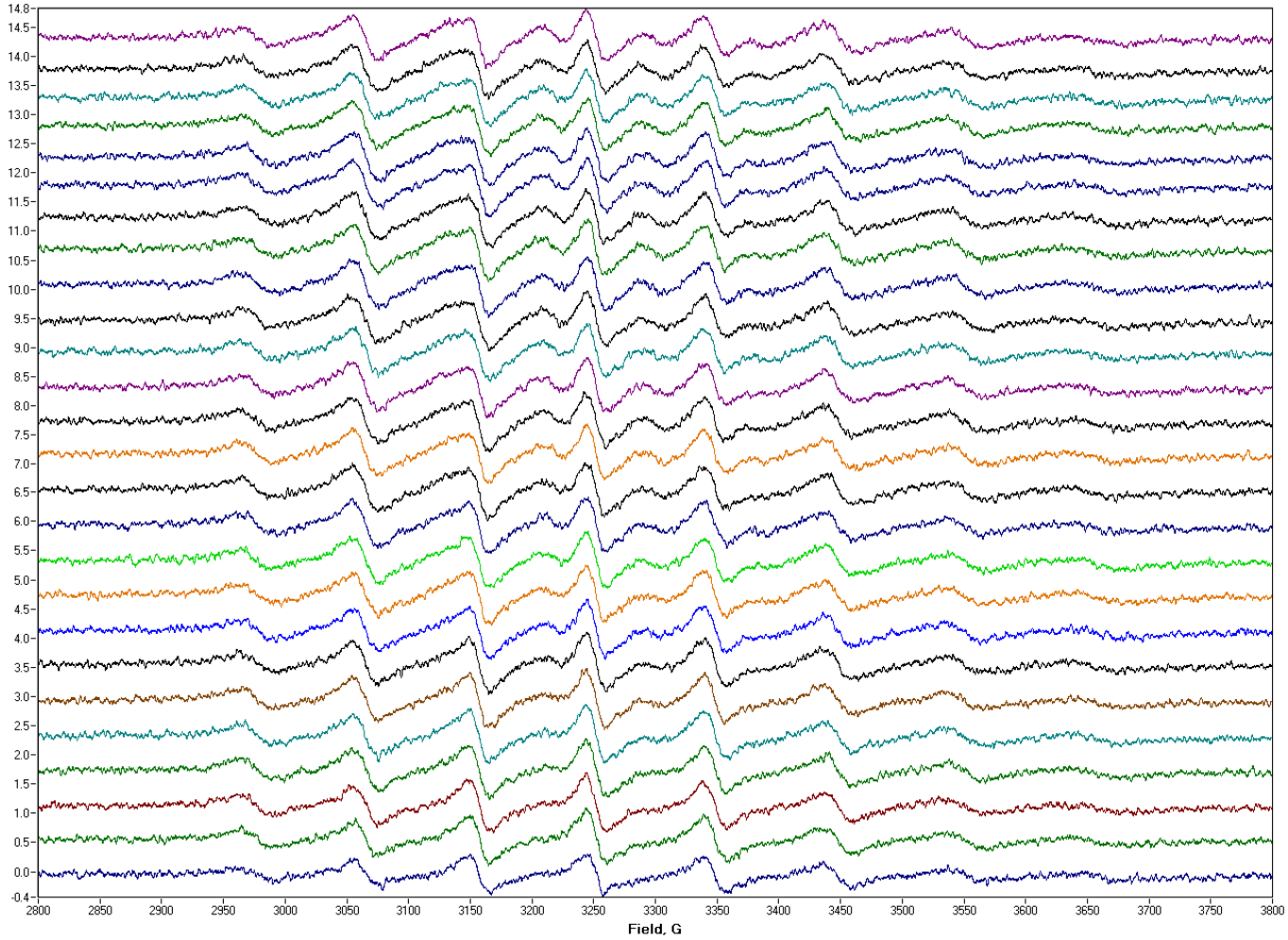


Figure S4. EPR spectra recorded during the asymmetric addition of Me_3SiCN to benzaldehyde catalysed by complex 1c

From bottom to top, complex **1c** (1.32 mg, 2 x 10^{-3} mmol) with benzaldehyde (10 μL) and trimethylsilyl cyanide (20 μL) in dichloromethane (175 μL). Spectra were recorded every 3.5 minutes.

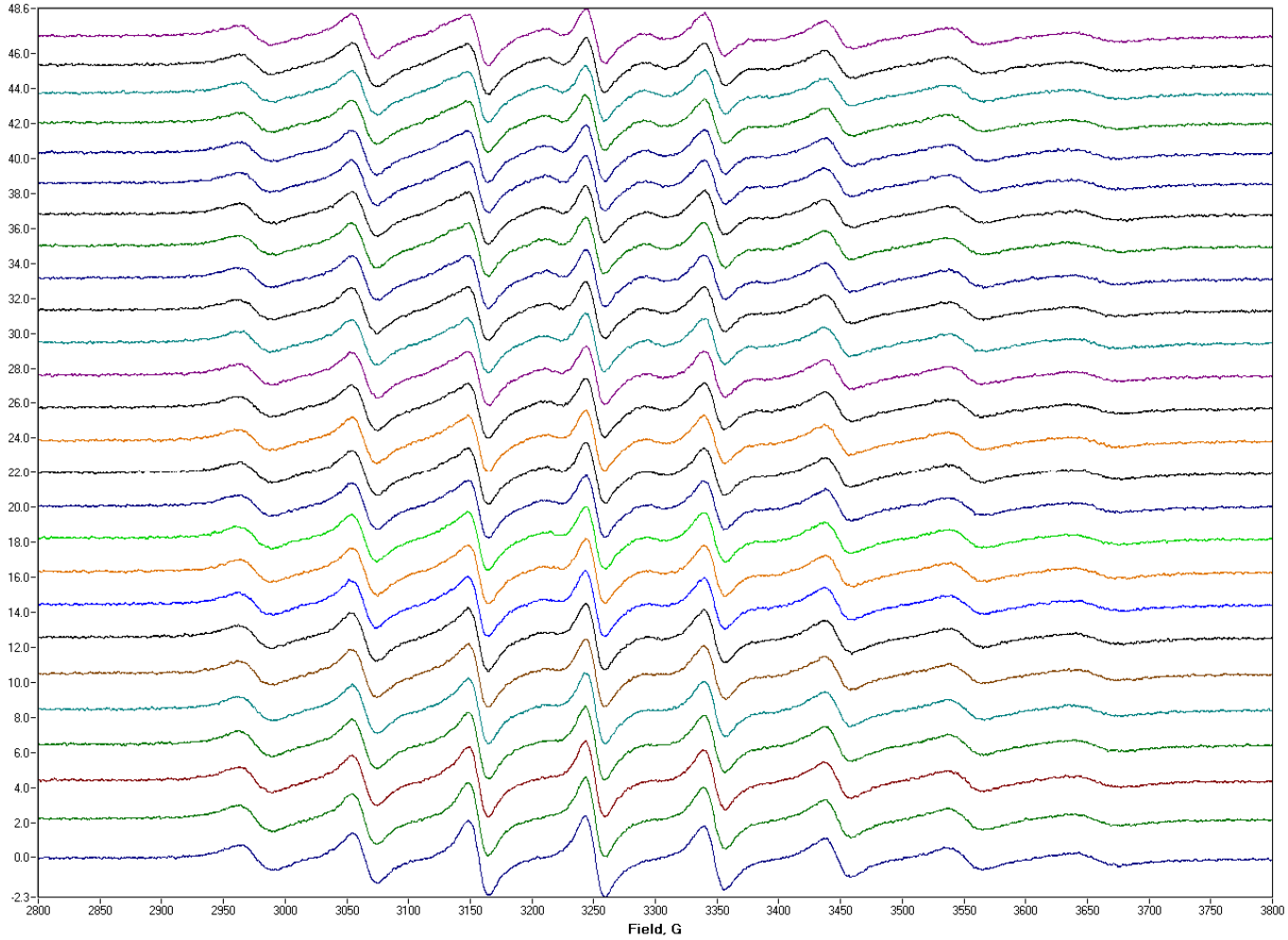


Figure S5. EPR spectra recorded from a mixture of complex 1a and benzaldehyde

EPR spectra of complex **1a** (1.44 mg, 2 x 10^{-3} mmol) in dichloromethane (175 μL) (bottom), and 30 minutes after addition of benzaldehyde (10 μL) (top).

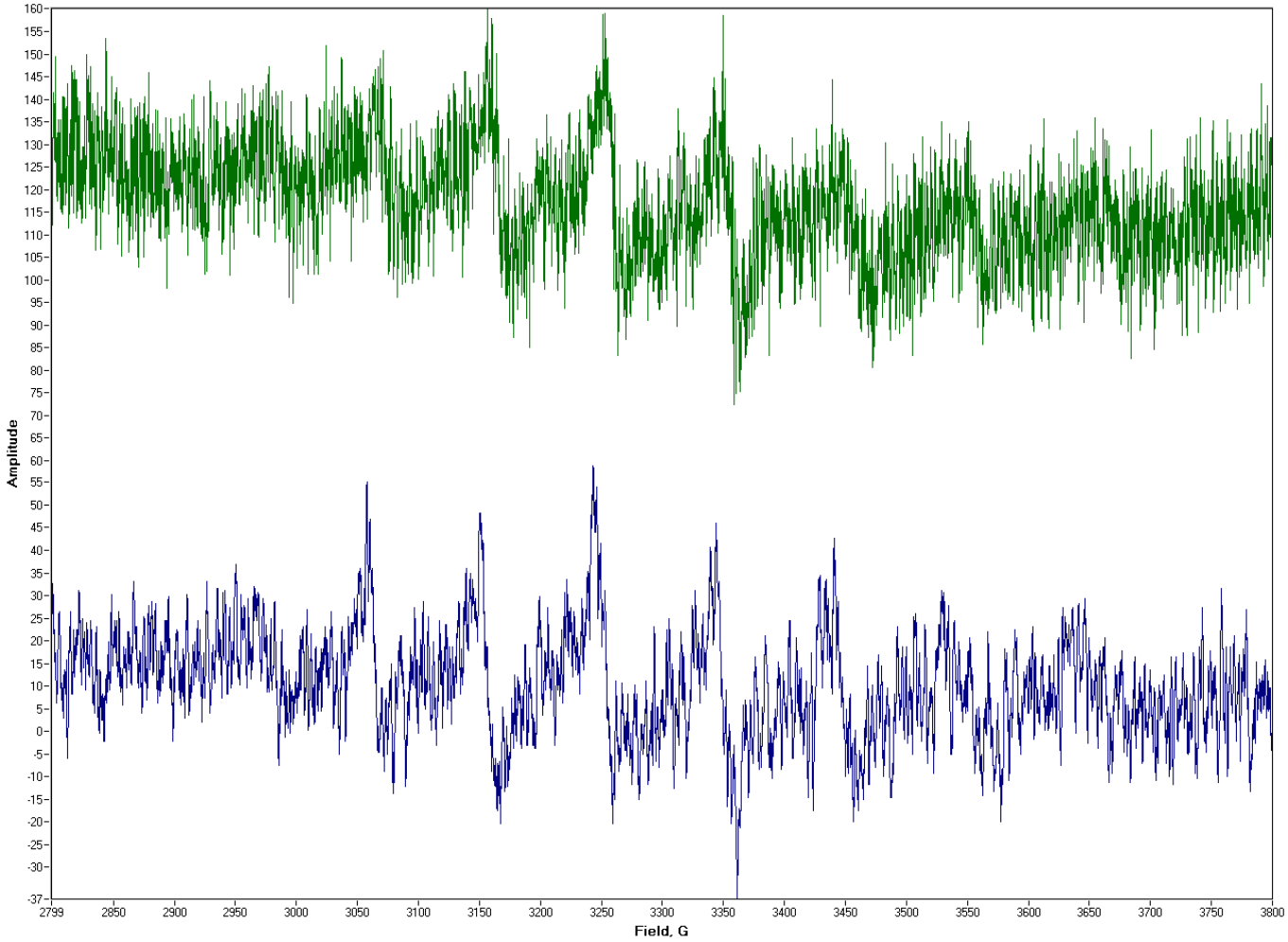


Figure S6. EPR spectra recorded from a mixture of complex 1b and benzaldehyde

EPR spectra of complex **1b** (1.27 mg, 2 x 10^{-3} mmol) in dichloromethane (175 μL) (bottom), and 30 minutes after addition of benzaldehyde (10 μL) (top).

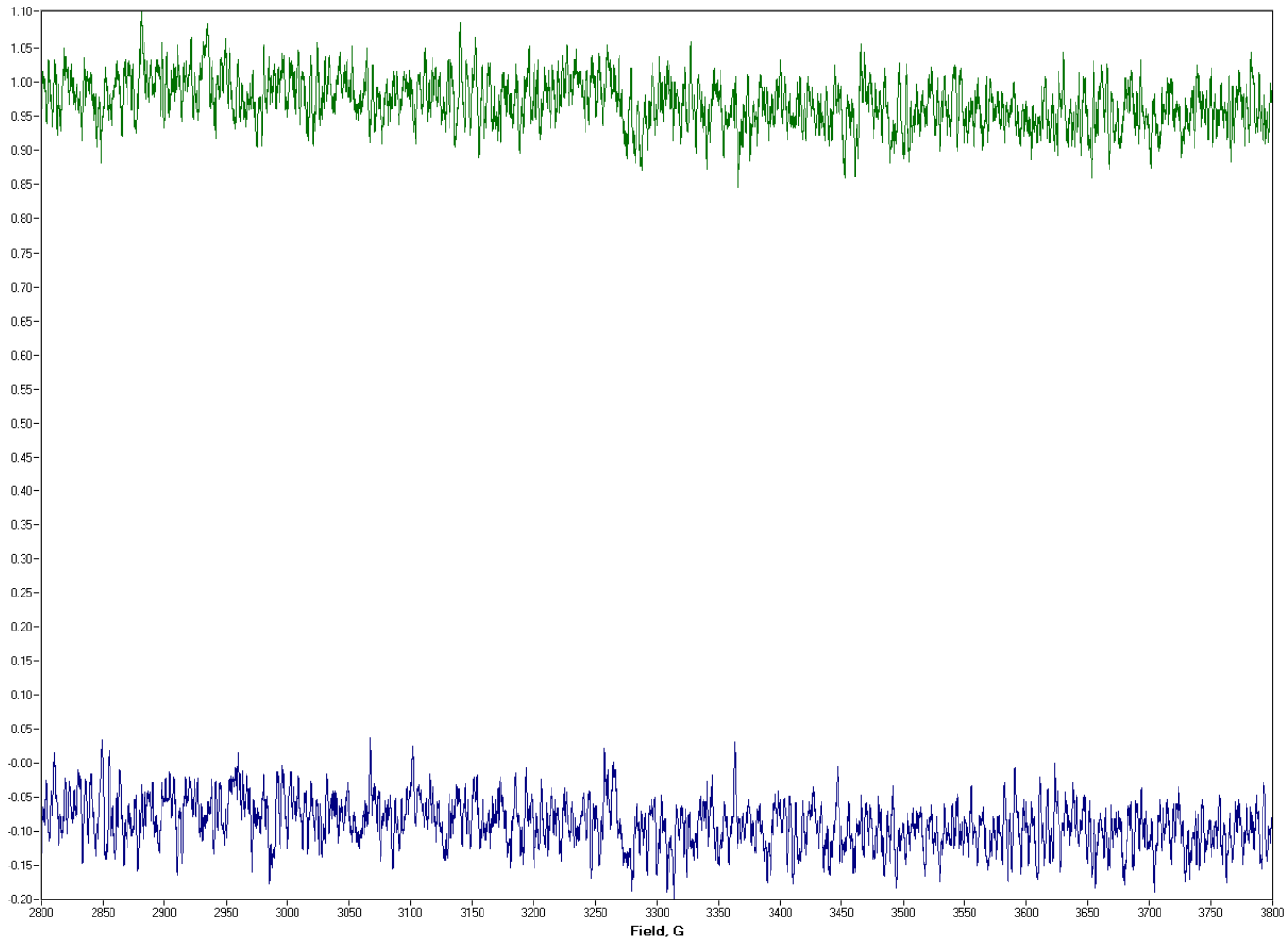


Figure S7. EPR spectra recorded from a mixture of complex 1c and benzaldehyde

EPR spectra of complex **1c** (1.32 mg, 2 x 10^{-3} mmol) in dichloromethane (175 μL) (bottom), and 30 minutes after addition of benzaldehyde (10 μL) (top).

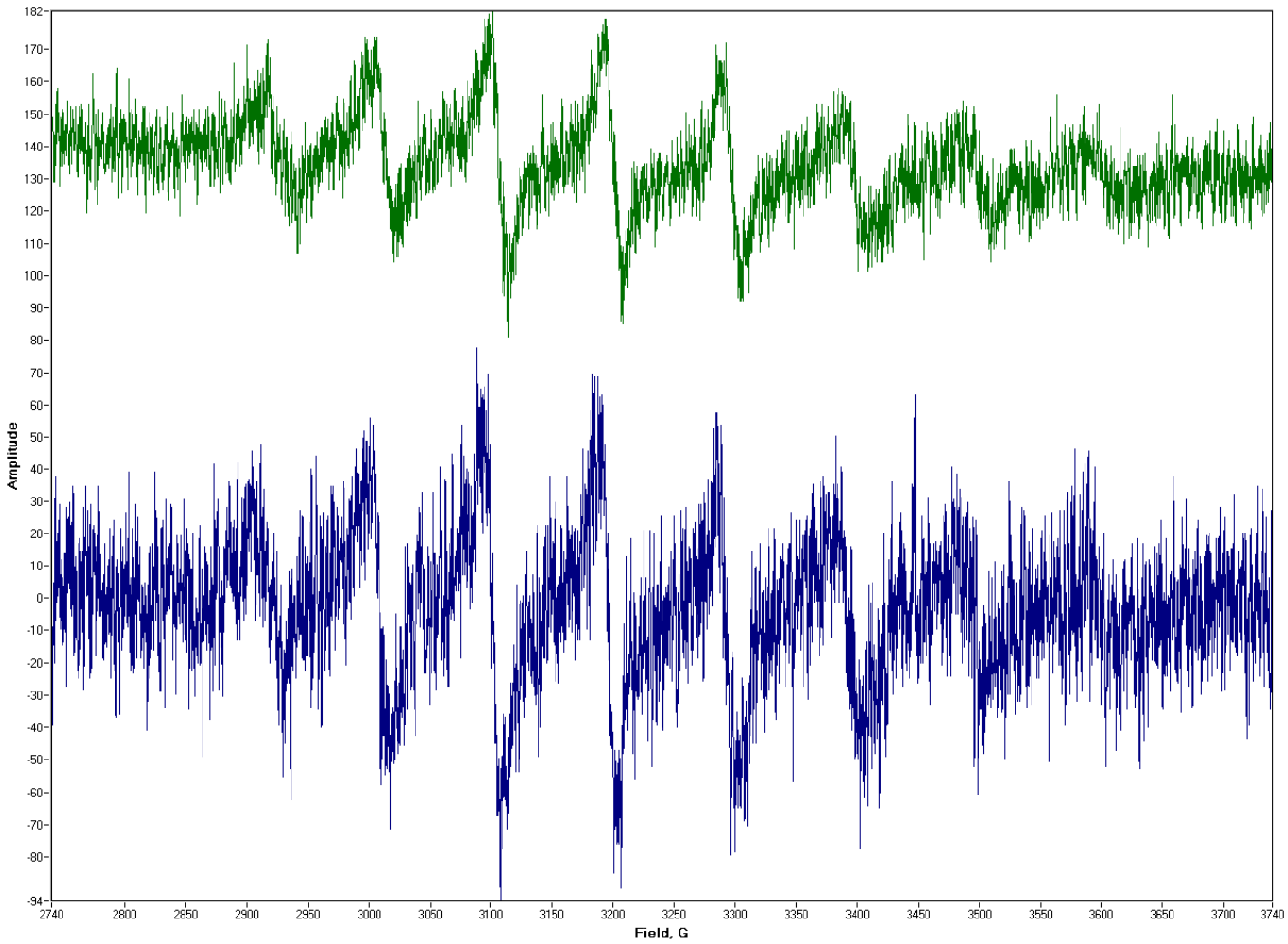
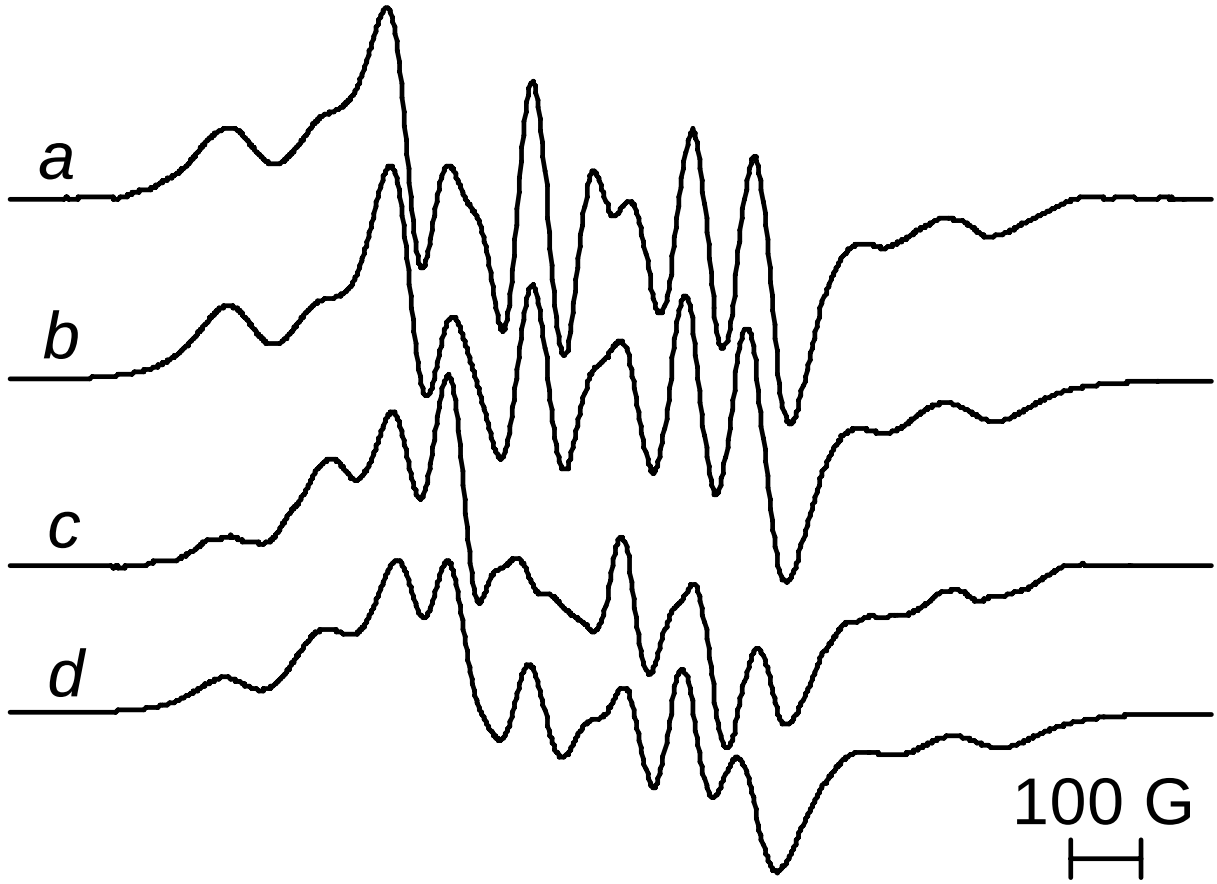


Figure S8. Experimental and simulated EPR spectra of 2 and mixture of 1c with Me_3SiCN 2 days after mixing at 192 K



Experimental (a,c) and simulated (b,d) EPR spectra of **2** (a,b) and mixture of **1c** with Me_3SiCN 2 days after mixing (c,d) at 192 K.

Figure S9. EPR spectra recorded from a mixture of complex 1a and trimethylsilyl cyanide

From bottom to top, complex **1a** (1.44 mg, 2 x 10^{-3} mmol) with trimethylsilyl cyanide (20 µL) in dichloromethane (175 µL). Spectra were recorded every 15 minutes.

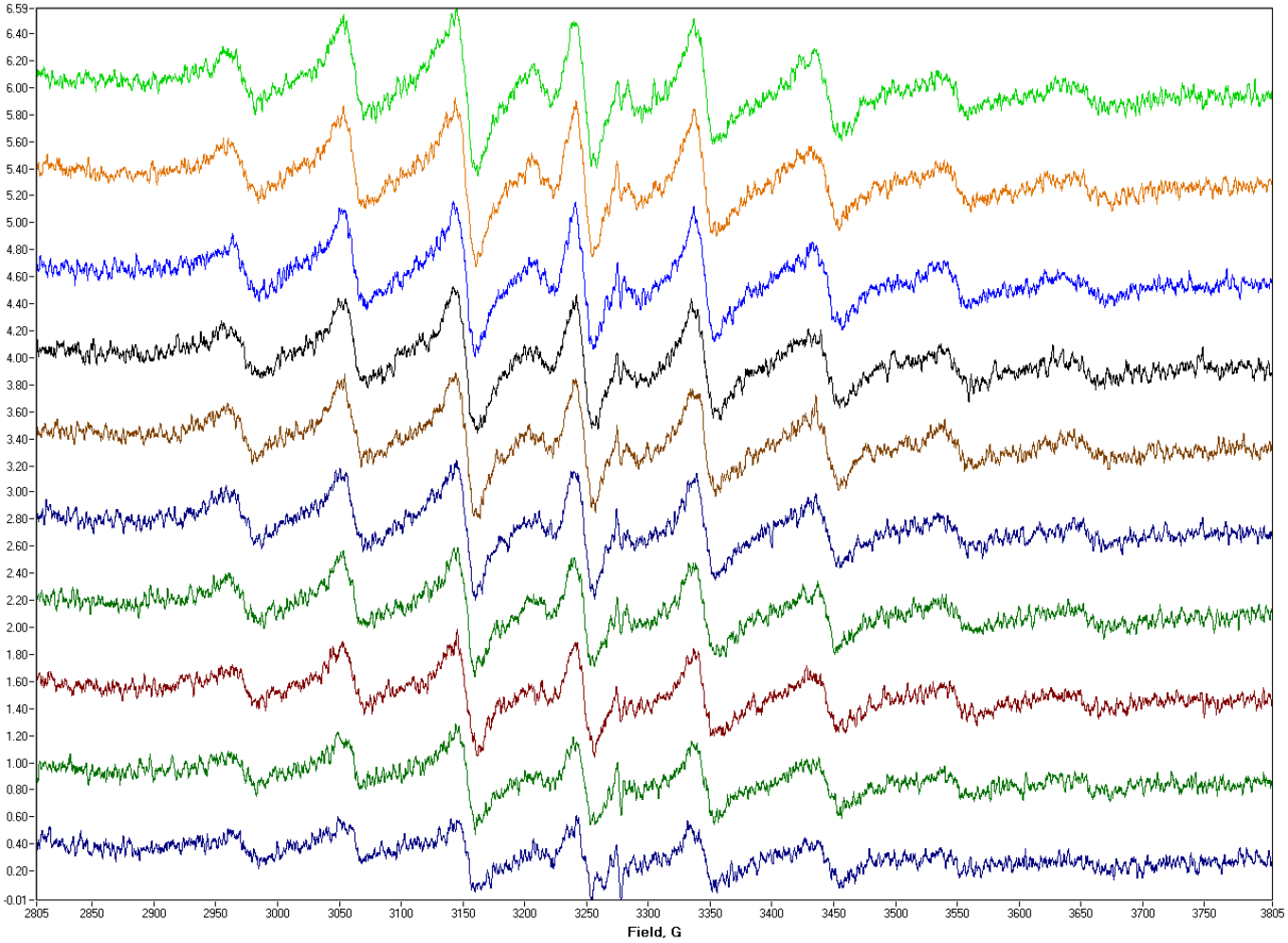


Figure S10. EPR spectra recorded from a mixture of complex 1b and trimethylsilyl cyanide

From bottom to top, complex **1b** (1.27 mg, 2 x 10^{-3} mmol) with trimethylsilyl cyanide (20 µL) in dichloromethane (175 µL). Spectra were recorded every 15 minutes.

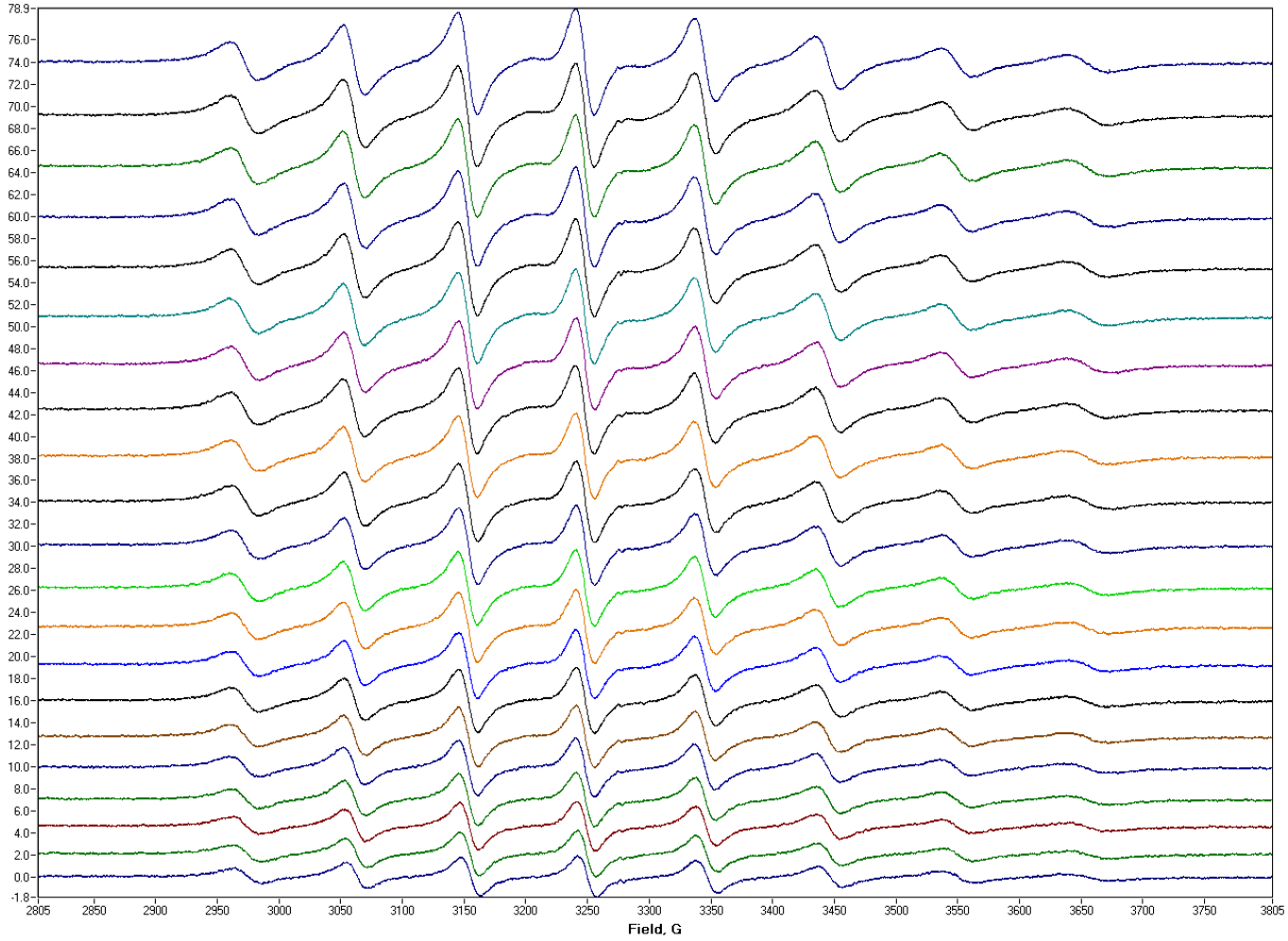


Figure S11. EPR spectra recorded from a mixture of complex 1c and trimethylsilyl cyanide

From bottom to top, complex **1c** (1.32 mg, 2 x 10^{-3} mmol) with trimethylsilyl cyanide (20 μL) in dichloromethane (175 μL). Spectra were recorded every 15 minutes.

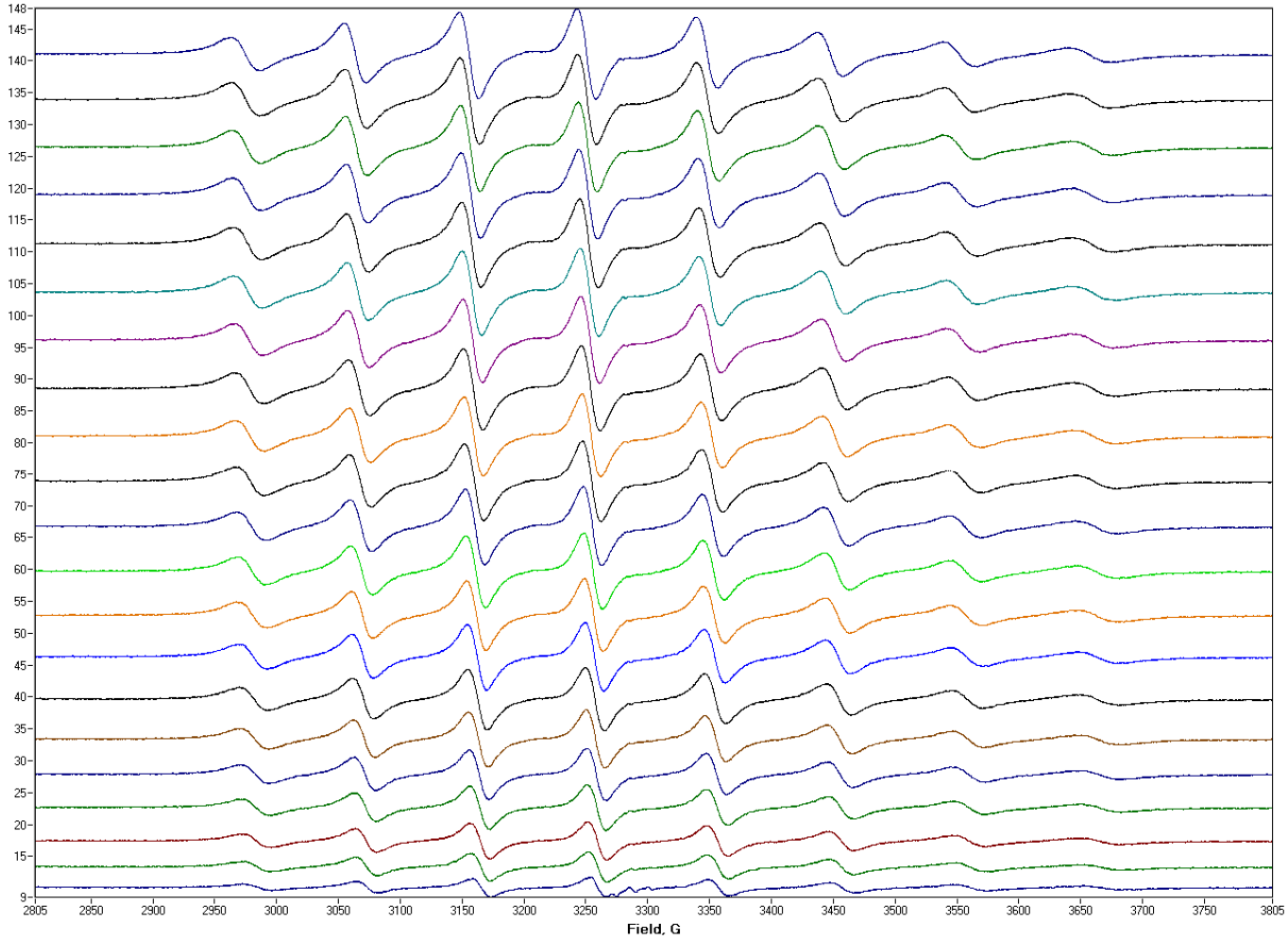


Figure S12. Experimental and simulated EPR spectra of frozen solutions of vanadium(IV) complexes at 130 K. The spectra correspond to the entries in Table 1 in the MS.

Samples were prepared by mixing complex **1c** (1.32 mg, 2 x 10^{-3} mmol) in dichloromethane (175 μL) and trimethylsilyl cyanide (20 μL). For samples with 2-component spectra, benzaldehyde (10 μL) was added. The samples containing complex **2** were prepared by dissolving the complex (1.2 mg, 2 x 10^{-3} mmol) in dichloromethane (175 μL). The reaction mixtures were used to record spectra at room temperature (Figure 2 in the main text), 192 K (Figure S8) and 130 K

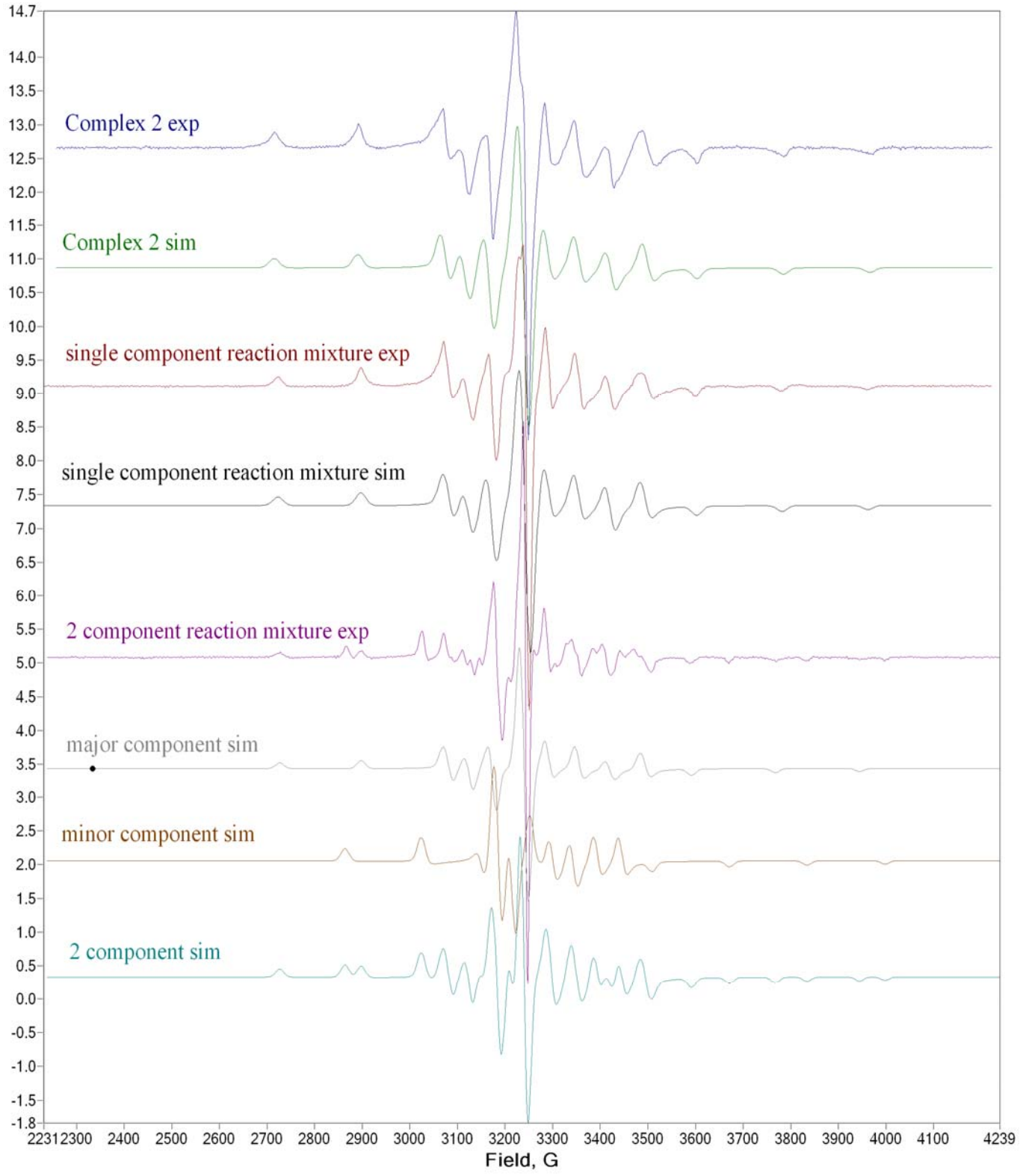
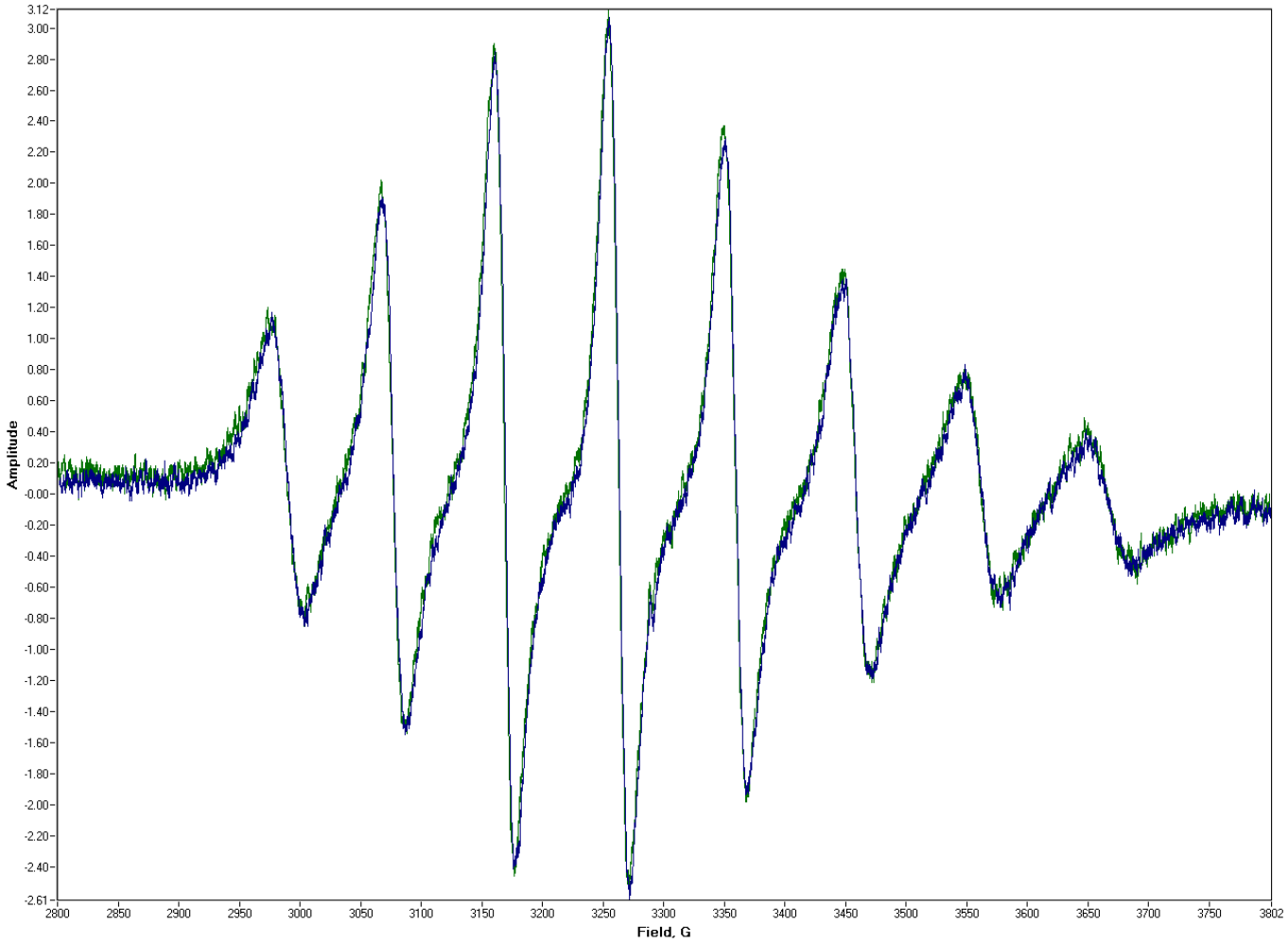


Figure S13. EPR spectra recorded from a mixture of complex 1c and KCN

EPR spectra of a mixture of complex **1c** (1.32 mg, 2 x 10^{-3} mmol) and potassium cyanide (2 mg, 0.03 mmol) in dichloromethane (175 μL) and *tert*-butanol (30 μL, 0.3 mmol) immediately after mixing (green) and after 3 hours (blue).



Spectroscopic evidence for the formation of Me_3SiNCS from complex 1c

To detect Me_3Si-NCS, GC-MS analysis was carried out using a VARIAN CP-3800 gas chromatograph equipped with a SUPELCO 28055-U 30m x 0.32 mm ID, 0.25µm film column and coupled to a VARIAN Saturn 2200 GC/MS detector operating in EI mode. GC conditions: Initial temperature 60 ºC hold for 3 minutes, then ramp rate 15 ºC/min to 270 ºC and hold for 5 minutes.

In a chromatography vial, complex **1c** (25 mg) was dissolved in dichloromethane (2 mL). Then, trimethylsilyl cyanide (6 µL) was added and the mixture was stirred for 30 minutes. Then, a sample was injected into the GCMS system. Trimethylsilyl isothiocyanide was detected (m/z 131, M^+), as a peak in the chromatogram with a retention time of 4.3 minutes.

Figure S14. GC trace for the reaction between complex **1c** and Me_3SiCN

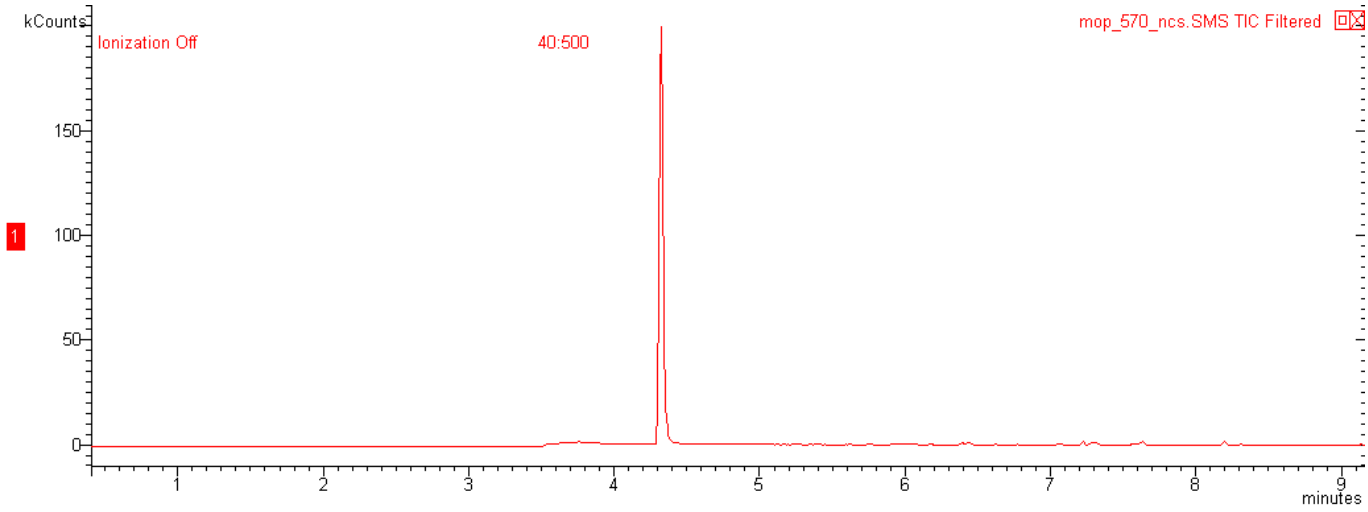
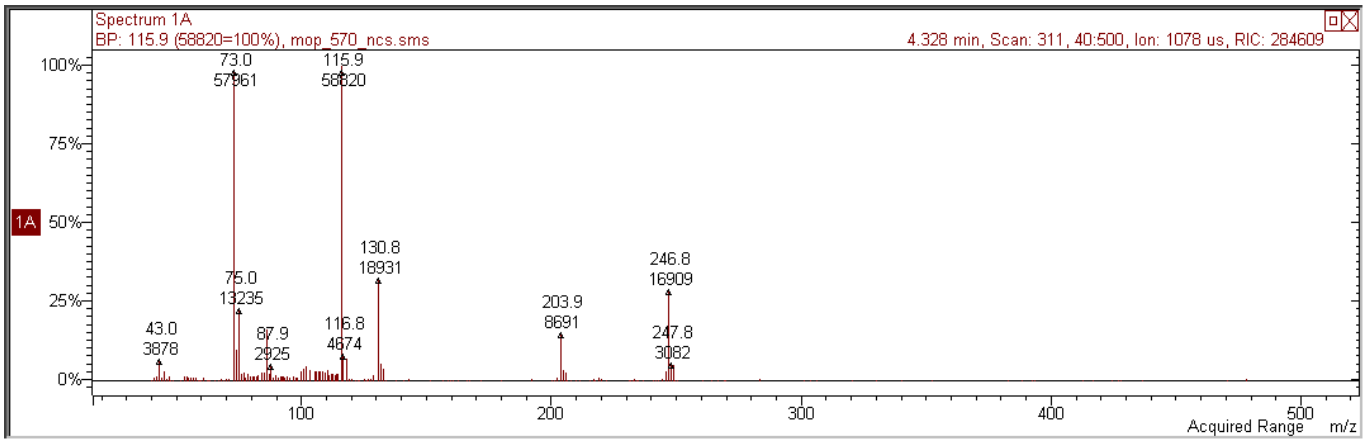


Figure S15. EIMS of the GC peak eluting at 4.5 minutes in Figure S14. The peak at m/z 130.8 corresponds to $[Me_3SiNCS]^+$. The peak at m/z 73.0 corresponds to Me_3Si^+. The peak at m/z 115.9 is consistent with Me_3SiNCO formed by hydrolysis of Me_3SiNCS by adventitious moisture. The peak at m/z 203.9 is consistent with $[Me_3SiNCSSiMe_3]^+$. The peak at m/z 246.8 is consistent with $[Me_3SiNCSOCNSiMe_3]^+$.



Spin trapping experiments

The authentic DMPO-CN spin adduct was prepared by irradiating a mixture of trimethylsilyl cyanide (20 μL) in dichloromethane (200 μL) and 0.1 M DMPO solution in toluene (200 μL) with UV light (100W Hg/Xe lamp, 2 minutes). The solutions were degassed (N_2 treatment, 1 min) prior to addition of trimethylsilyl cyanide. The genuine DMPO-CN adduct was formed (a_N = 14.11, a_H = 16.15 G) (Figure S16a).

The reaction was then carried out by mixing complex **1a** (1.44 mg, 2 x 10^{-3} mmol) in toluene (175 μL) with 0.1 M DMPO in toluene (175 μL) in a glass pipette closed with a septum. Weak signals of DMPO-CN adduct are detected (a_N = 14.15 a_H = 16.24 G) (Figure S16b). In a control test, DMPO was reacted with trimethylsilyl cyanide. No artefacts were observed (Figure S16c). However, reaction of complex **1a** with DMPO clearly showed the oxidation product of DMPO (Figure S16d, DMPOX, a_N = 6.62 a_H = 3.32 G,[1] and another nitroxide, a_N = 13.26 G). Thus, complex **1a** can efficiently oxidise DMPO. Therefore, spin trapping experiments cannot provide conclusive evidence for or against formation of cyanide radicals. The same results were obtained with complexes **1b** (1.27 mg, 2 x 10^{-3} mmol) and **1c** (1.32 mg, 2 x 10^{-3} mmol).

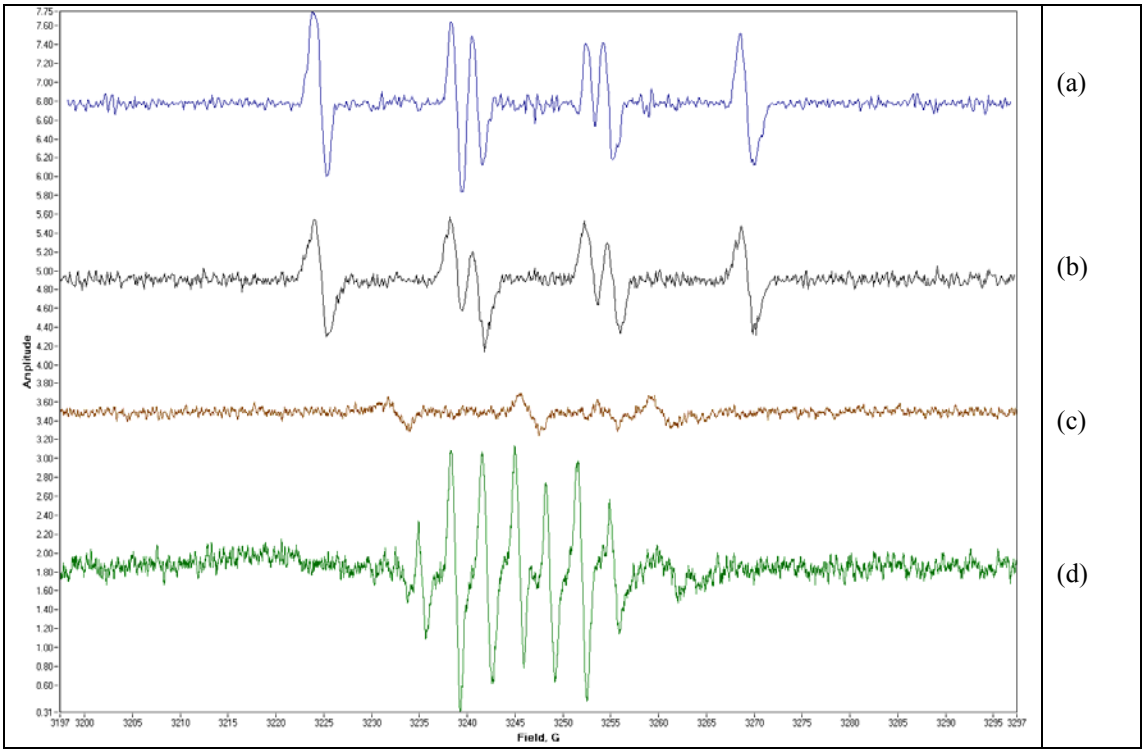


Figure S16. spin adducts from the reaction of complex **1a** with trimethylsilyl cyanide in the presence of DMPO as a spin trap. (a) authentic DMPO-CN adduct obtained by UV irradiation of trimethylsilyl cyanide in dichloromethane in the presence of DMPO, (b) DMPO-CN formed in a mixture of complex **1a**, trimethylsilyl cyanide and DMPO, (c) control test: reaction of DMPO with trimethylsilyl cyanide, and (d) spin adducts formed in a mixture of complex **1a**, trimethylsilyl cyanide and DMPO; DMPOX is clearly detected.

Attempted detection of cyanide radicals with TEMPO (EPR and GC-MS)

In order to verify if the reaction between V(V)oxo(salen) complexes and trimethylsilyl cyanide occurred *via* a free radical mechanism involving ·CN formation, 2,2′,6,6′-tetramethylpiperidine *N*-oxide (TEMPO) was used as a radical scavenger. While relatively unreactive towards oxygen centred radicals, TEMPO is a highly efficient quencher for carbon centred radicals.[2] Reaction of TEMPO with cyanide radicals should lead to TEMPO-CN which can be visualised by the reduced EPR signal of TEMPO.

The sample was prepared by mixing a 10^{-2} M solution of complex **1c** in dichloromethane (100 μL) with a 10^{-2} M solution of TEMPO in toluene (100 μL) and trimethylsilyl cyanide (20 μL, 10^{-3} mol, 0.7 M in the final reaction mixture). Control tests showed that TEMPO does not react with complex **1c** (Figure S18 a and b). Complex **2** also does not react with TEMPO; however line broadening is observed due to paramagnetic V(IV) (Figure S17c). In the TEMPO-trimethylsilyl cyanide mixtures, a small reduction in the TEMPO intensity was observed (Figure S17d).

The reaction mixture containing complex **1c**, TEMPO and trimethylsilyl cyanide was then monitored by EPR. Signal intensity and line broadening (which is sensitive to oxygen concentration)[3] are shown in Figure S18. Only small signal decay is observed (figure S18a) with no significant increase in the line broadening (Figure S18b). These results suggest that the TEMPO-CN adduct is not formed during the reaction.

To further rule out formation of TEMPO-CN adduct, GC-MS analysis was carried out with the reaction mixture containing 10^{-2} M complex **1c** in dichloromethane (100 μL), 10^{-2} M TEMPO in toluene (100 μL) and trimethylsilyl cyanide (20 μL, 10^{-3} mol, 0.7 M in the final reaction mixture). GC-MS analysis was carried our using a WATERS GCT Premier Agilent 7890A GC instrument coupled to a Restek Corp Stabilwax 30 m x 0.25 mm ID, 0.25 μm film column, using a temperature ramp of 50 ^{o}C for 5 min then 32 ^{o}C min^{-1} to 220 ^{o}C. The chromatogram is shown in Figure S19. The peak at 2.2 min is a trimethylsilyl derivative (according to mass spectrometry), peak at 3.54 min is Me_3SiNCS, peak at 6.69 min is TEMPO, peak at 9.70 min is a TEMPO derivative with major peaks in its mass spectrum at m/z 239 and 254. None of the peaks could be assigned to TEMPO-CN with m/z 182.

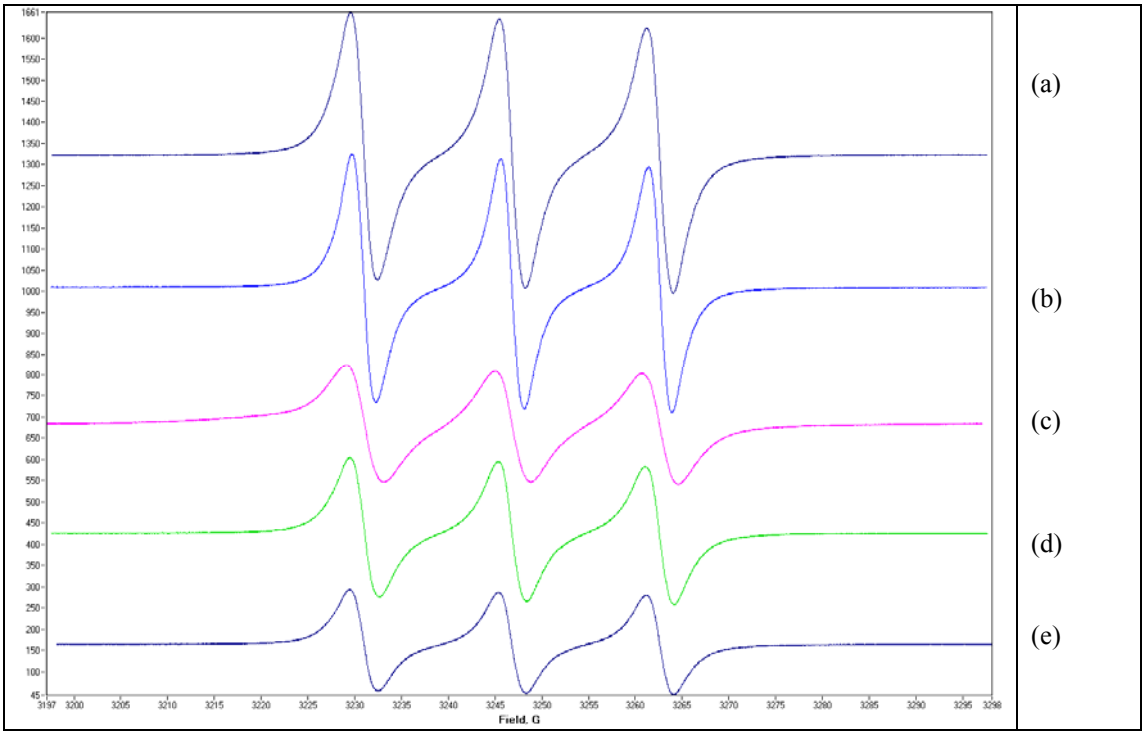


Figure S17: EPR spectra of TEMPO in the presence of **1c** and trimethylsilyl cyanide (a) TEMPO (10^{-2} M in toluene), (b) complex **1c** (10^{-2} M in dichloromethane) and TEMPO, (c) TEMPO and complex **2** (10^{-2} M in dichloromethane), (d) TEMPO and trimethylsilyl cyanide (20 μL) and (e) TEMPO (10^{-2} M), **1c** (10^{-2} M) and trimethylsilyl cyanide (20 μL) in dichloromethane.

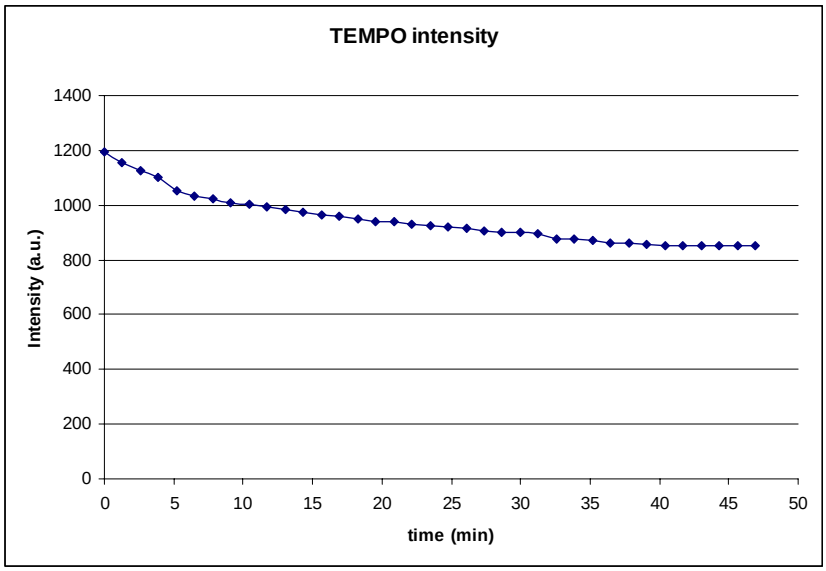


Figure S18a. TEMPO signal intensity in the mixture containing TEMPO (10^{-2} M), complex **1c** (10^{-2} M) and trimethylsilyl cyanide (20 μL) in dichloromethane.

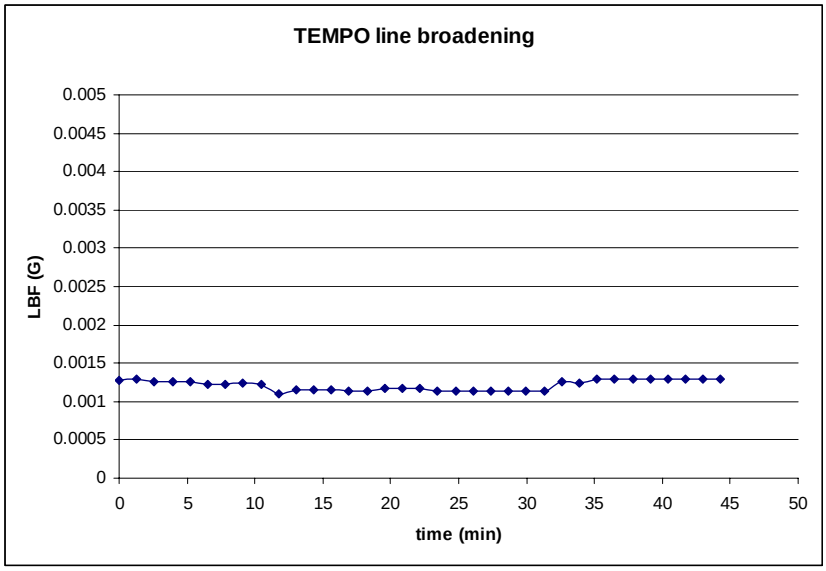


Figure S18b. Line broadening factor in the mixture containing TEMPO (10^{-2} M), complex **1c** (10^{-2} M) and trimethylsilyl cyanide (20 μL) in dichloromethane.

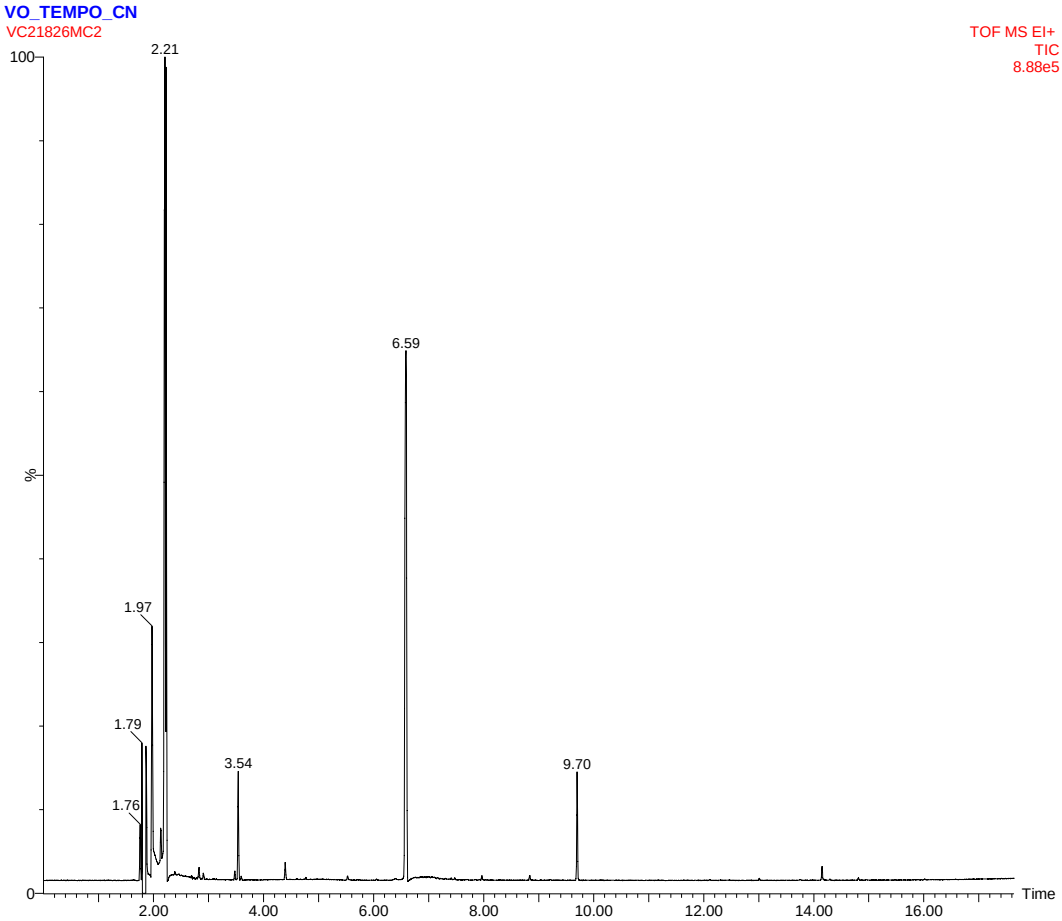


Figure S19: chromatogram of a reaction mixture containing complex **1c**, TEMPO and trimethylsilyl cyanide

Attempted identification of CN radicals by addition to electron-rich alkenes.

Complex **1c** (3.5 mg, $9x10^{-3}$ mmol) and (*Z*)-1-(1-Adamantyloxy)-2-bromoethene (50 mg, 0.18 mmol) (prepared as reported in *Tetrahedron* **1987**, *43*, 2311–2316) were each dissolved dichloromethane (1.5 mL). The two solutions were combined and stirred at 0 ºC. Trimethylsilylcyanide (30 µL, 0.24 mmol) was added and the resulting mixture was stirred for 24 hours, and monitored by TLC. As no reaction was apparent, the cooling bath was removed and the reaction mixture was warmed to room temperature and left to react for a further 24 hours. The reaction was then quenched by passing the solution through a silica plug in order to remove the catalyst. The solvent was removed under vacuum and the residue was analysed by ^{1}H-NMR spectroscopy, which showed the presence of a mixture of unreacted starting materials and some 1-adamantanol, but no product arising from cyanide addition to the alkene.

Attempted identification of CN radicals by styrene polymerisation

Complex **1c** (30 mg) was mixed with freshly distilled styrene (100 μL) and trimethylsilyl cyanide (40 μL) and sealed in the presence of air. This approach assumes formation of ·CN should lead to the initiation of styrene polymerization and oxygen consumption. EPR is sensitive to both. If oxygen is consumed, EPR lines are sharpened due to reduced spin-spin exchange interaction.[3,4] If polymerization occurs, this would lead to an increased viscosity of the reaction medium, which reduces the tumbling motion of the paramagnetic species which is visible in the EPR spectra.[5]

Comparison of the EPR spectra for complex **2** in styrene and reaction mixture of complex **1c** in styrene with trimethylsilyl cyanide shows no change in the line broadening after 40 minutes of reaction time (Figure S20) or even after 2.5 h (Figure S21). This strongly suggests that ·CN is not formed during the reaction.

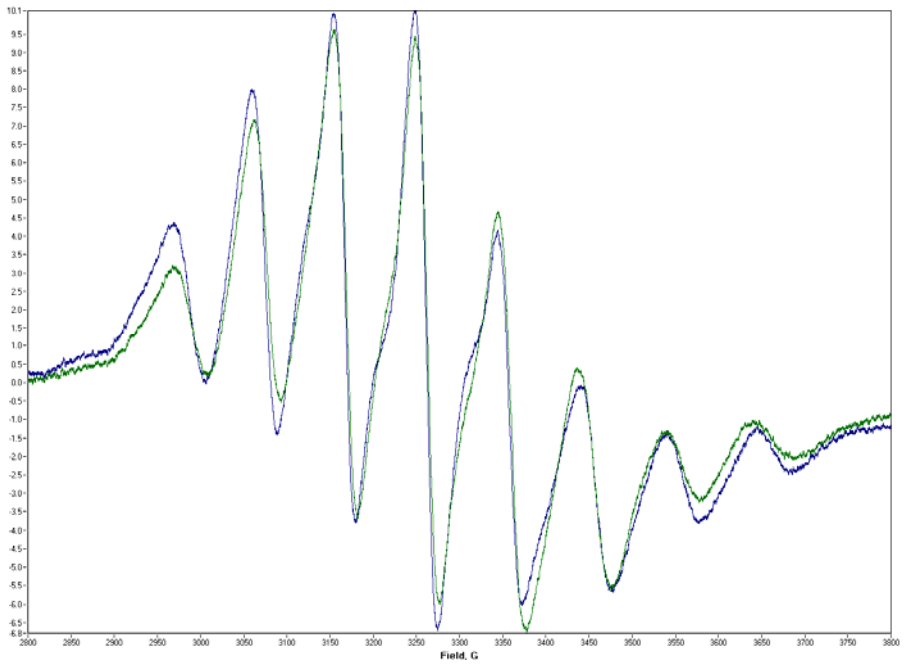


Figure S20: EPR spectra of (—) complex **2** in styrene (fresh) and (—) complex **1c** and trimethylsilyl cyanide in styrene after 40 min.

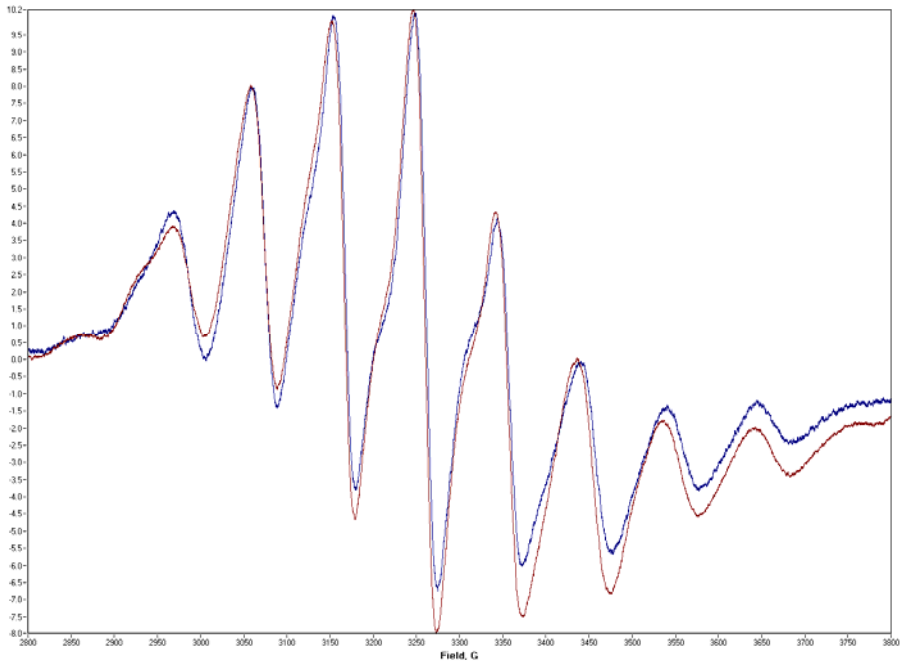


Figure S21: EPR spectra of (—) complex **2** in styrene (fresh) and (—) complex **1c** and trimethylsilyl cyanide in styrene after 2.5 h.

GC-MS identification of cyanogen

In order to identify the reaction products of complex **1c** reaction with trimethylsilyl cyanide, GC-MS analysis was carried out. using a WATERS GCT Premier Agilent 7890A GC intrument coupled to a Chrompack CP-Sil 8CB 100 m x 0.53 mm ID, 5 μm film column, using a temperature ramp of 50 ^{o}C then 8 ^{o}C min^{-1} to 150 ^{o}C.

Authentic cyanogen gas was prepared by the following reaction: $2CuSO_4 + 4KCN \rightarrow 2CuCN + 2K_2SO_4 + (CN)_2$. Excess $CuSO_4$ (18 mg) was added to KCN (2 mg) in water (200 μL). N_2 gas was bubbled through the mixture (15 mL/min) and $(CN)_2$ was collected in a cold trap with dichloromethane. The solution obtained was diluted and analysed *via* GC-MS. The chromatogram of this reaction mixture (Figure S22a) showed a cyanogen peak at 13.54 min which was assigned by the MS (m/z 52, Figure S23).

A mixture of complex **1c** (1.2 mg) in dichloromethane (200 μL) with trimethylsilyl cyanide (20 μl) was stirred at room temperature for 1hour and analysed directly by GC-MS. Cyanogen was detected in the chromatogram (Figure S22b). A control test in the absence of complex **1c** show no detectable $(CN)_2$. Formation of $(CN)_2$ was monitored over time (Figure S24). The maximum $(CN)_2$ concentration was reached after *ca* 1 hour, consistent with the EPR data for the vanadium(IV) formation. To exclude the possibility of cyanogen formation in the GC-MS injection chamber, N_2 gas was bubbled through a reaction mixture of complex **1c** (1.2 mg) in dichloromethane (200 μL), with trimethylsilyl cyanide (20 μL), and the product was collected in a cold dichloromethane trap. $(CN)_2$ was still clearly detected (Figure S25). The GC intensity of cyanogen trapped from the reaction of complex **1c** and trimethylsilyl cyanide was *ca.* 100 higher than that trapped from the reaction of $CuSO_4$ with KCN. This is due to the poor efficiency of transfer of cyanogen gas from aqueous solution with N_2.

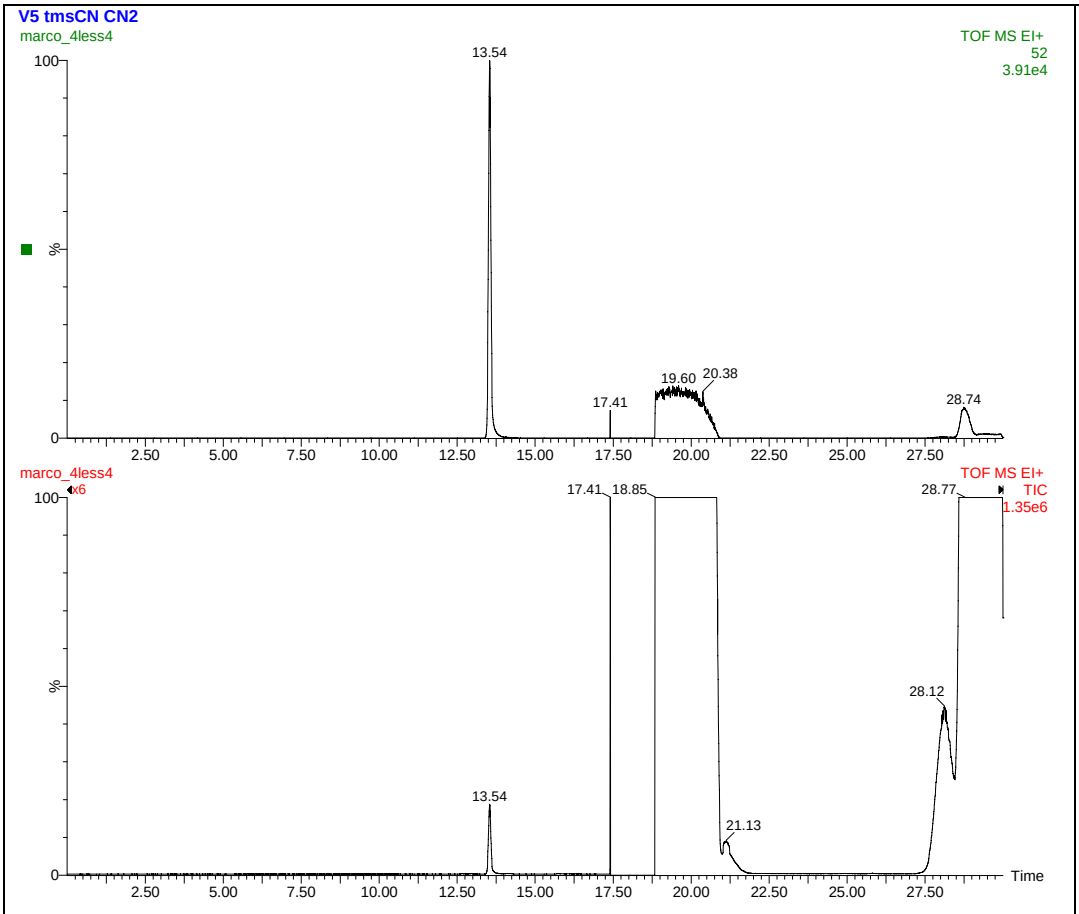


Figure S22: chromatographic identification of $(CN)_2$. (a) in $CuSO_4$/KCN mixture and (b) formed from complex **1c** and trimethylsilyl cyanide. The peak at 17.41 min is an instrumental spike to prevent overloading due to the dichloromethane solvent peak (ca. 20 min). The peaks at ca. 28 minutes are trimethylsilyl-based products

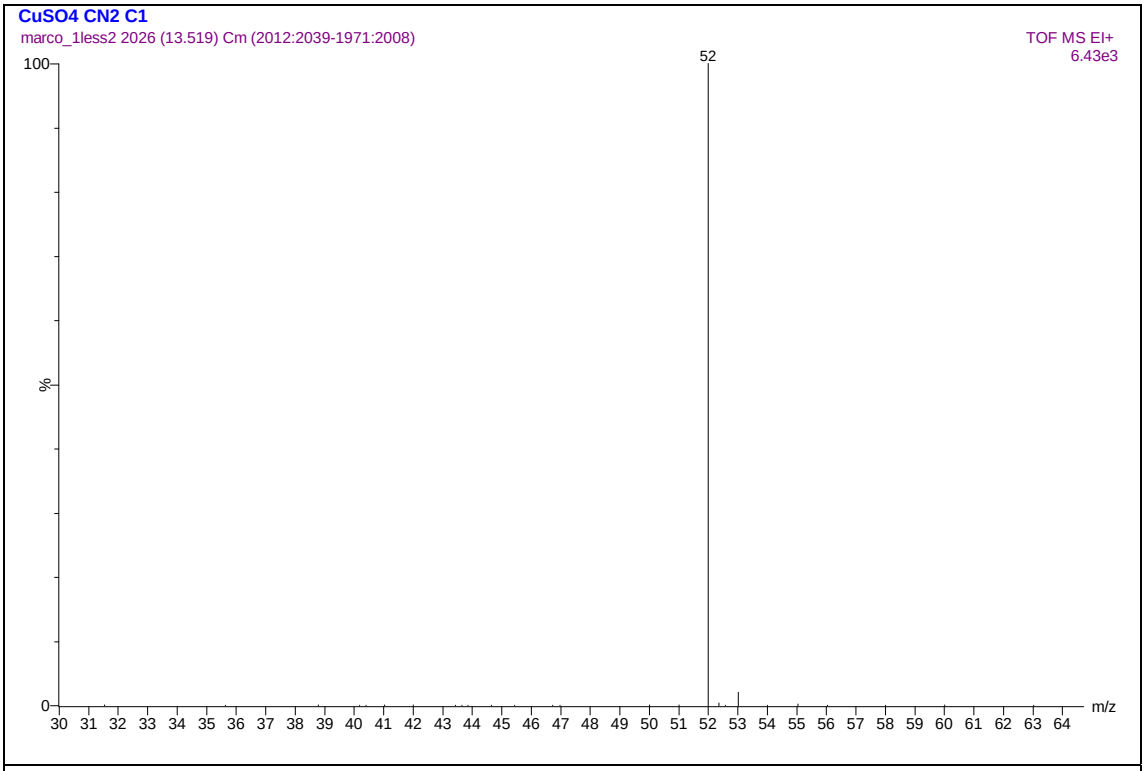


Figure S23: MS spectrum of $(CN)_2$ peak at 13.54 min from $CuSO_4$/KCN reaction

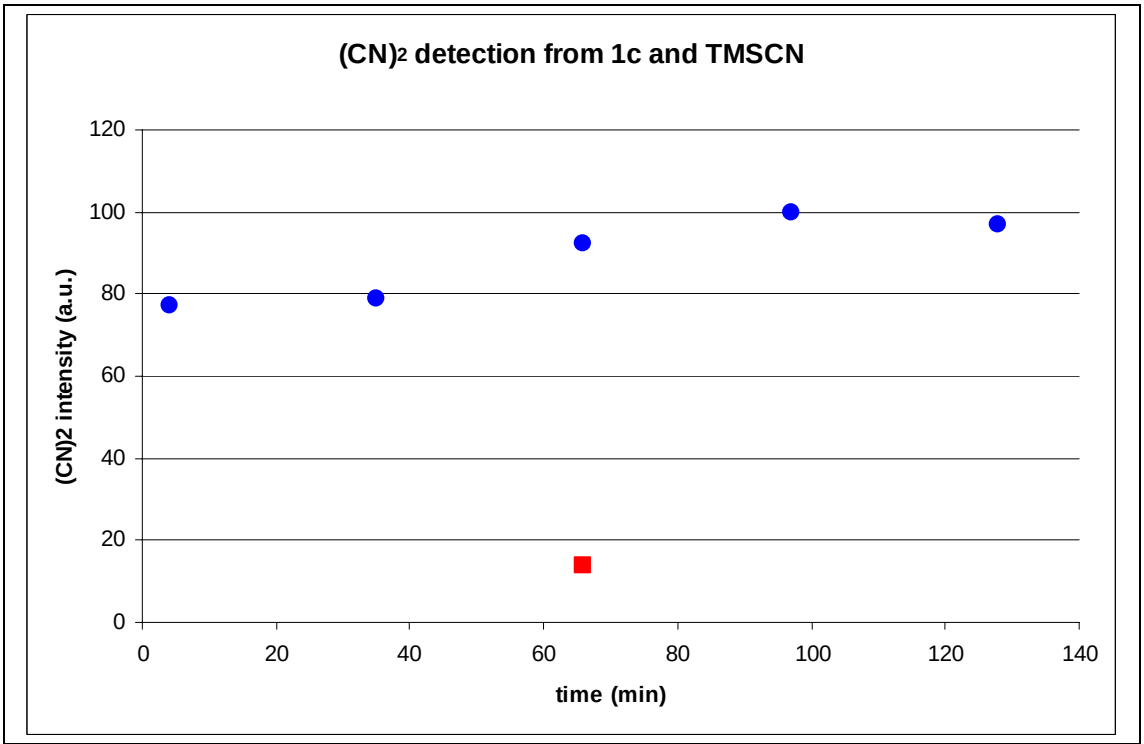


Figure S24: (●) $(CN)_2$ signal accumulation for a reaction of complex **1c** (1.2 mg) in dichloromethane (200 µL) with trimethylsilyl cyanide (20 µL). (■) $(CN)_2$ signal from a reaction of complex **1c** (1.2 mg) in dichloromethane (200 µL) and trimethylsilyl cyanide (20 µL) carried by N_2 gas and collected in a cold dichloromethane trap

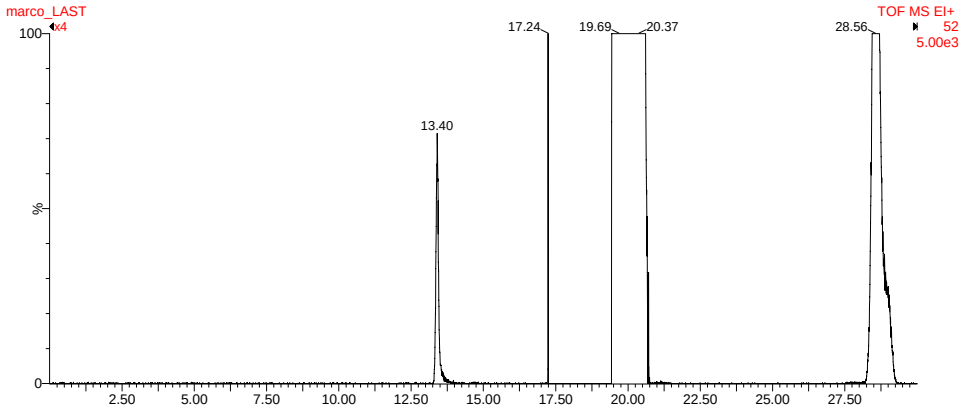


Figure S25: chromatographic identification of $(CN)_2$ formed in the reaction of complex **1c** with trimethylsilyl cyanide and carried by N_2 gas into a cold trap (peak at 13.40 min).

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