

A synthesis of the 1,1'-desymmetrised ferrocene backbone and its facile one-pot double-“click” functionalisation.

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Experimental

General experimental details

All reagents were purchased from Aldrich, Acros, Merck or Fluka and were used without further purification unless otherwise stated. I₂ was sublimed prior to use. Triisopropylborate was distilled prior to use. Hexane was dried by refluxing over CaH₂ for a minimum of 6 h and distilled prior to use. MeOH was stirred over silica (10% w/v) for at least 24 h under a N₂ atmosphere, filtered and stored over 4 Å-molecular sieves. Et₃N was stored over KOH under a N₂ atmosphere. All other anhydrous solvents were obtained from an MBRAUN MB SPS-800 solvent purifying system. PE refers to the fraction of petroleum ether boiling in the range 40-60 °C; EA refers to ethyl acetate. All water was obtained from an Elga Purelab Option distillation system. ¹H-NMR spectra were recorded on Bruker Avance 600 MHz NMR spectrometer (with an auto-tuning broad-band/inverse observation probe with a Z-gradient) or a Bruker AV400 (s = singlet, d=doublet, t=triplet, q=quartet, m=multiplet). ¹³C-NMR spectra were recorded on a 150.8 MHz Bruker Avance or a 100.2 MHz Bruker AV400. The spectra were referenced with respect to residual solvent (CHCl₃). IR spectra were recorded on an Agilent Technologies Cary 630 FTIR spectrometer equipped with ATR accessory. UV-Vis spectra were obtained on a U-3020 spectrophotometer, with absorption maxima (λ_{max}) expressed in nm, and molar extinction coefficients (ε) are expressed in Lmol⁻¹cm⁻¹. Mass spectra was obtained using a Waters (UK) TQD mass spectrometer (low resolution ESI+, electrospray in positive ion mode) and a Waters (UK) LCT premier XE (high resolution ESI+, electrospray in positive ion mode, ES+); or Electrospray ionisation mass spectrometry was obtained from the EPSRC National Mass Spectrometry Service, University of Wales, Swansea on a Thermofisher LTQ Orbitrap XL. Melting points were measured on a Stuart SMP3 melting point apparatus and are uncorrected. Flash column chromatography, unless otherwise stated, was performed using Fluka silica gel 60 (220-240 mesh), and TLC was carried out using pre-coated aluminium backed plates with Merck Kiesegel 60 F254. The plates were visualized under a UV lamp (254 nm), or by staining with basified aqueous KMnO₄ solution followed by gentle heating.

1-bromo,1'-iodoferrocene 4:

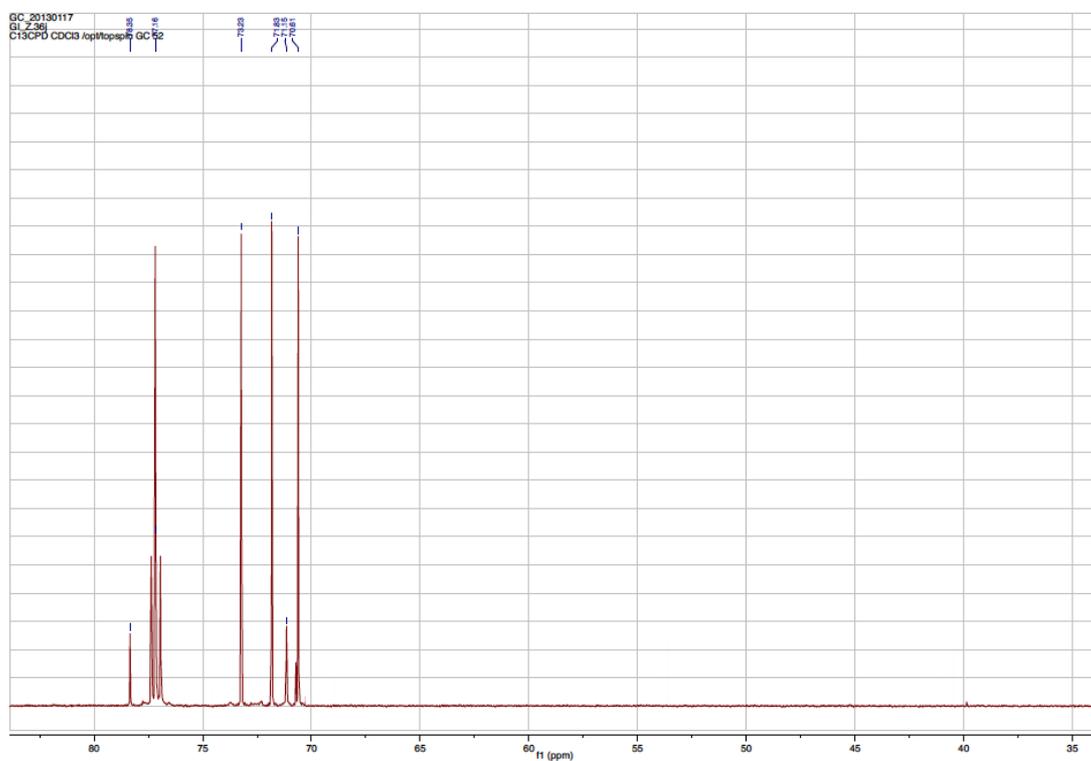
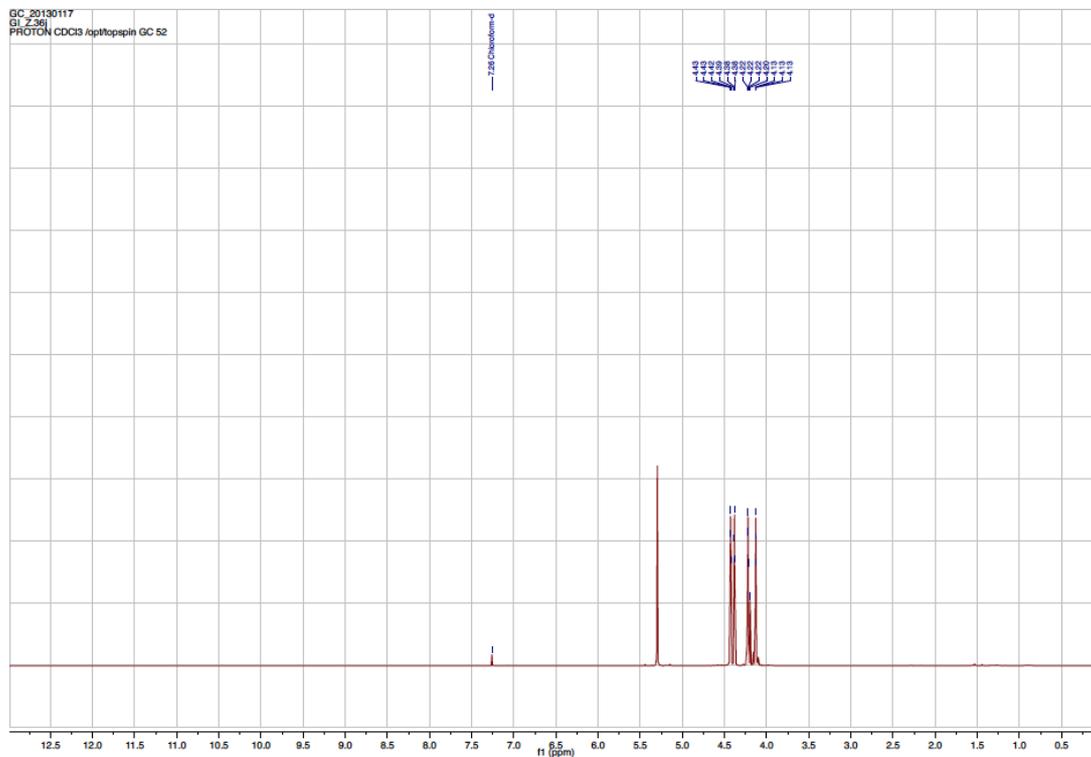
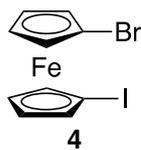


Figure ESI 1: ^1H and ^{13}C NMR spectra of **4**.

1-bromo-1'-trimethylsilylethynylferrocene 5:

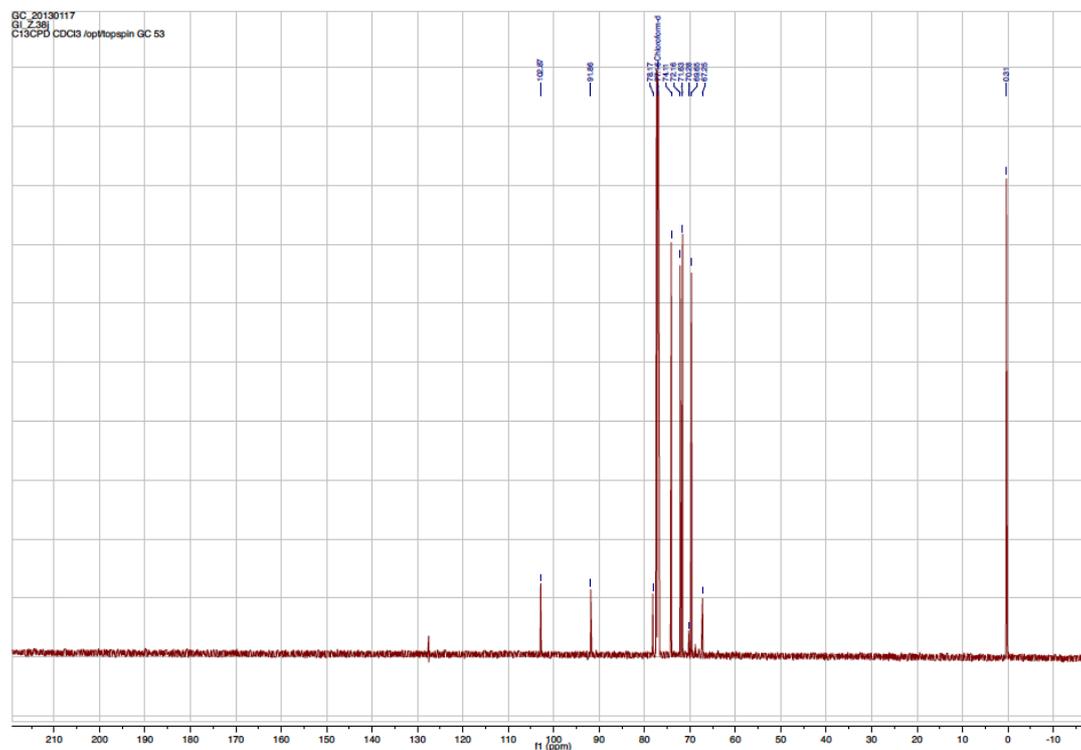
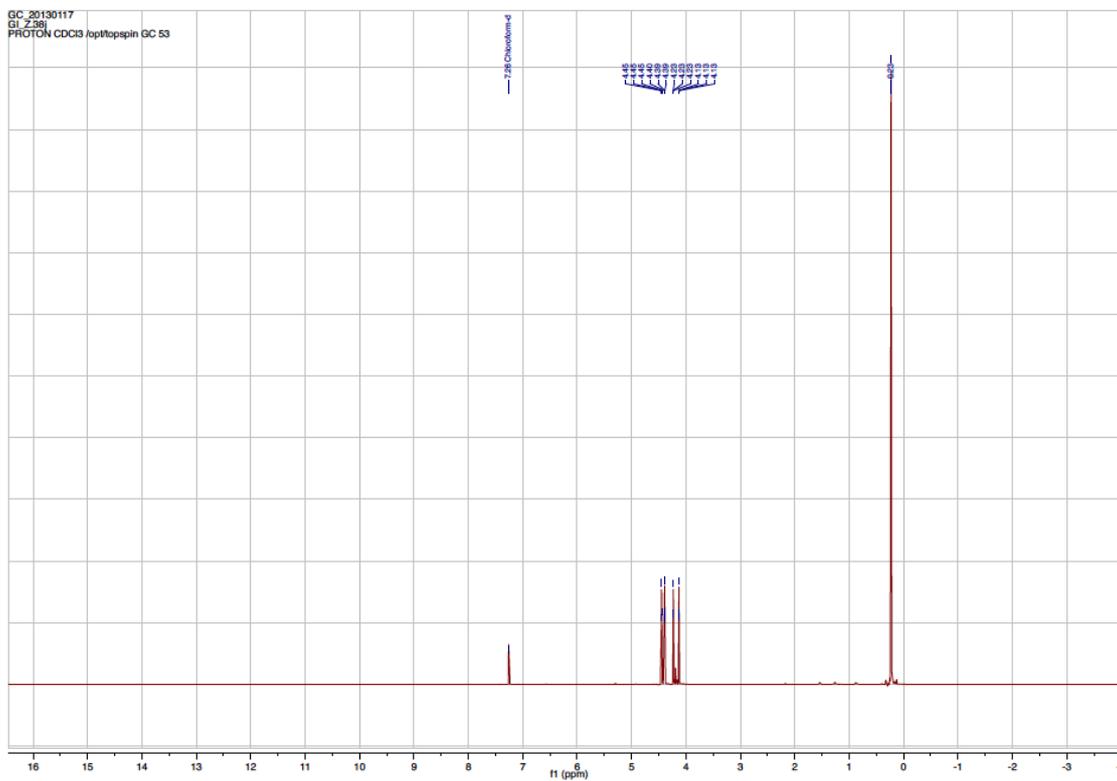
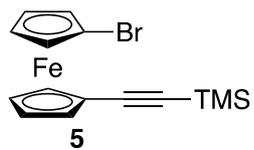


Figure ESI 2: ^1H and ^{13}C NMR spectra of **5**.

1'-(1-trimethylsilylethynyl)ferroceneboronic acid 2:

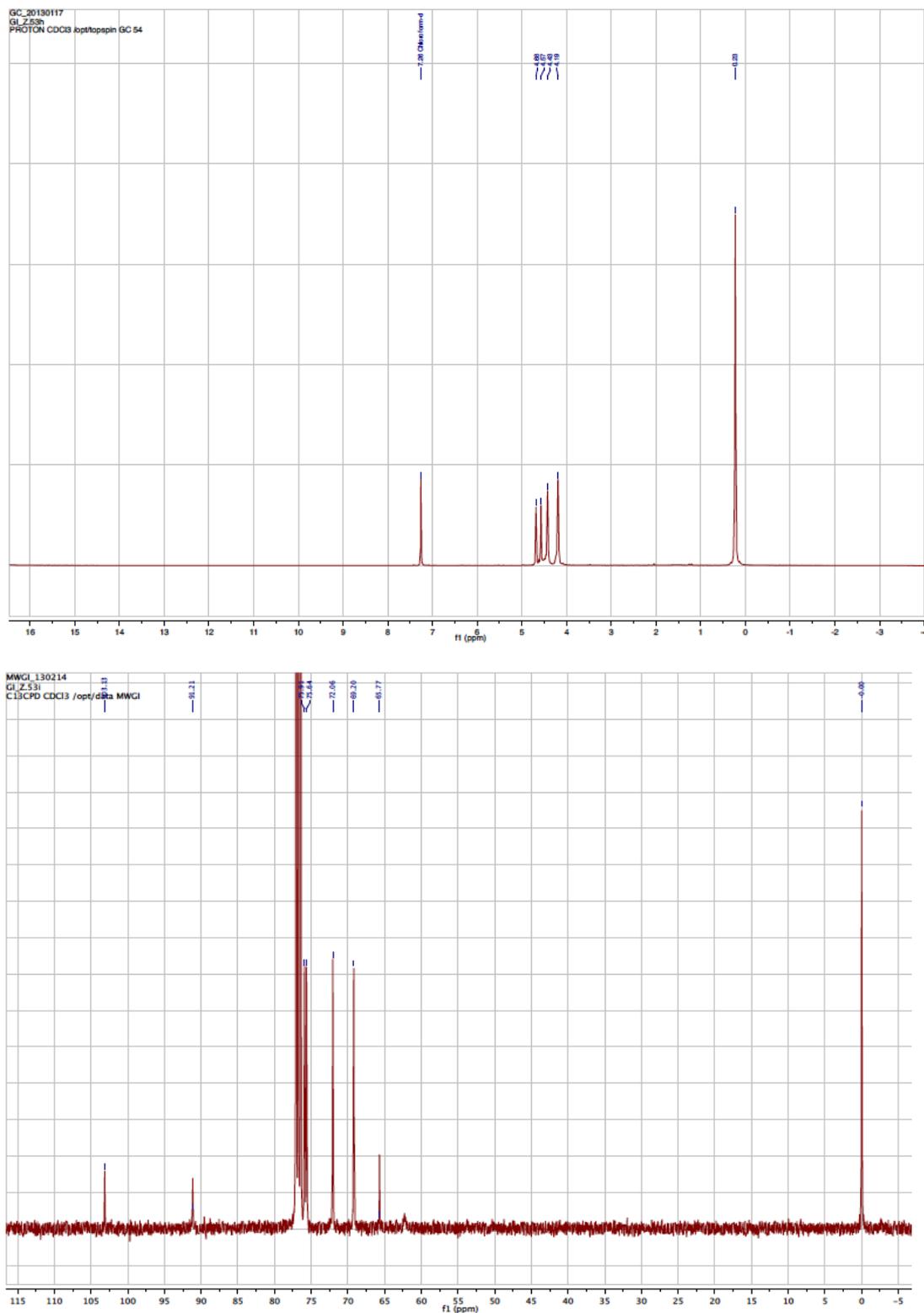
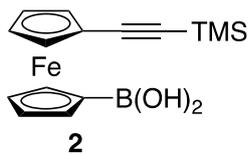


Figure ESI 3: ¹H and ¹³C NMR spectra of **2**.

1'-azido-(1-trimethylsilylethynyl)ferrocene 1:

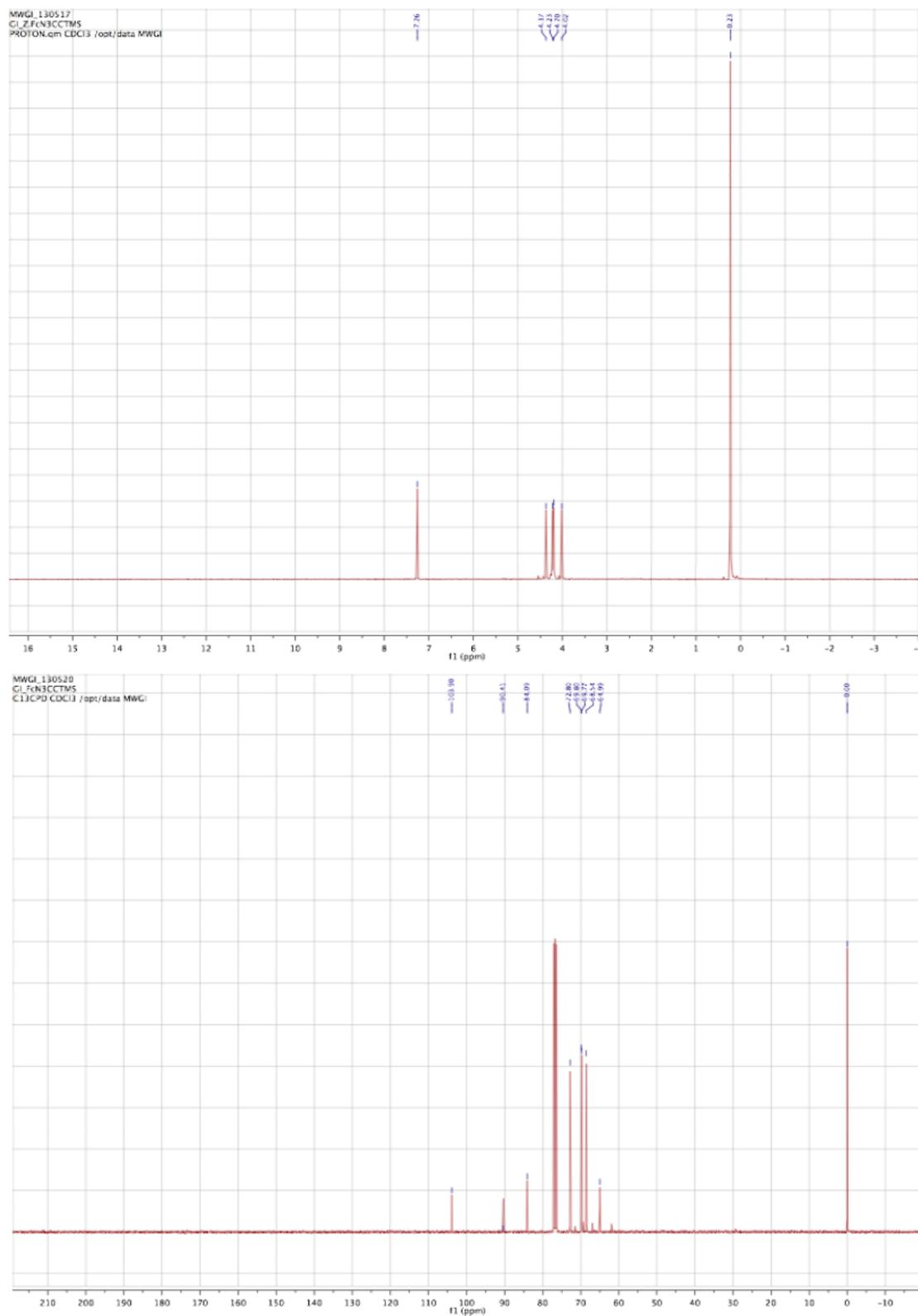
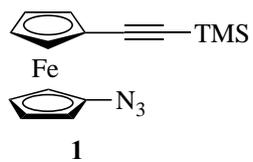
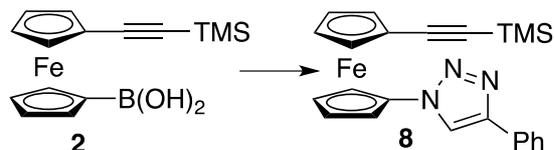
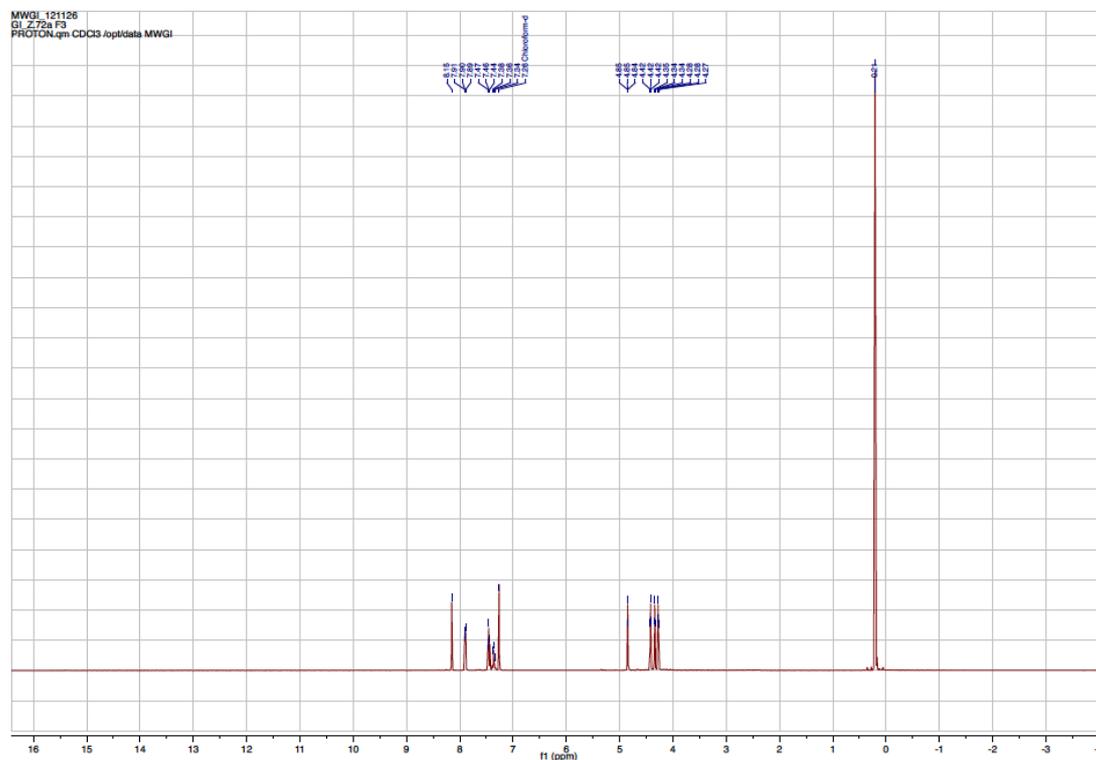


Figure ESI 4: ¹H and ¹³C NMR spectra of **1**.

General procedure for the conversion of boronic acid to azide and in situ cyclisation as represented by the synthesis of 1-(trimethylsilylethynyl)-1'-(4-phenyl-1H-1,2,3-triazol-1-yl)-ferrocene **8:**



Boronic acid **2** (300 mg, 0.92 mmol, 1.0 equiv.), NaN₃ (60 mg, 0.93 mmol, 1.02 equiv.) and Cu(OAc)₂·H₂O (1.8 mg, 9.3 × 10⁻³ mmol, 1.0 mol%) were dissolved in anhydrous MeOH (10 mL) and stirred at r.t. for 1 hour, until all of **2** was consumed (judged by TLC analysis). Phenylacetylene (103 mg, 1.01 mmol, 1.1 equiv.) was added to the reaction mixture, followed by the addition of a solution of sodium ascorbate (27 mg, 0.18 mmol, 20 mol%) in water (500 μL). The reaction mixture was stirred at r.t. for 16 h, after which it was diluted with a 1.0 M solution of EDTA in saturated NaHCO₃. The crude product was extracted with DCM (3 × 10 mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The final product **8** was isolated after flash column chromatography (7% EA in PE) as yellow solid (191 mg, 49%): m.p. 163-165 °C; ¹H NMR: 400 MHz, CDCl₃: δ_H 8.15 (s, 1H), 7.89 (m, 2H), 7.46 (m, 2H), 7.36 (m, 2H), 4.85 (m, 2H), 4.42 (m, 2H), 4.34 (m, 2H), 4.28 (m, 2H), 0.21 (s, 9H); ¹³C NMR: δ_C 147.9, 130.5, 129.0, 128.4, 125.9, 119.3, 102.8, 94.6, 92.4, 74.0, 71.0, 68.9, 67.0, 64.6, 0.2; IR: ν_{max}/cm⁻¹ 3128, 3101, 2954, 2148, 1701, 1642, 1611, 1582, 1523, 1480, 1393, 1370, 1248, 1230, 1070, 1027, 925, 842, 761, 725, 694; HRMS m/z calculated for: C₂₃H₂₄⁵⁴FeN₃Si [M+H]⁺ 424.1136, found 424.1144; LRMS: m/z 426.0 [M+H]⁺; UV/vis: λ_{max}(DCM)/nm (ε/ mol⁻¹cm⁻¹dm³) 247 (28.53 × 10³), 275 (18.04 × 10³), 294 (11.78 × 10³), 329 (2.35 × 10³), 444 (523).



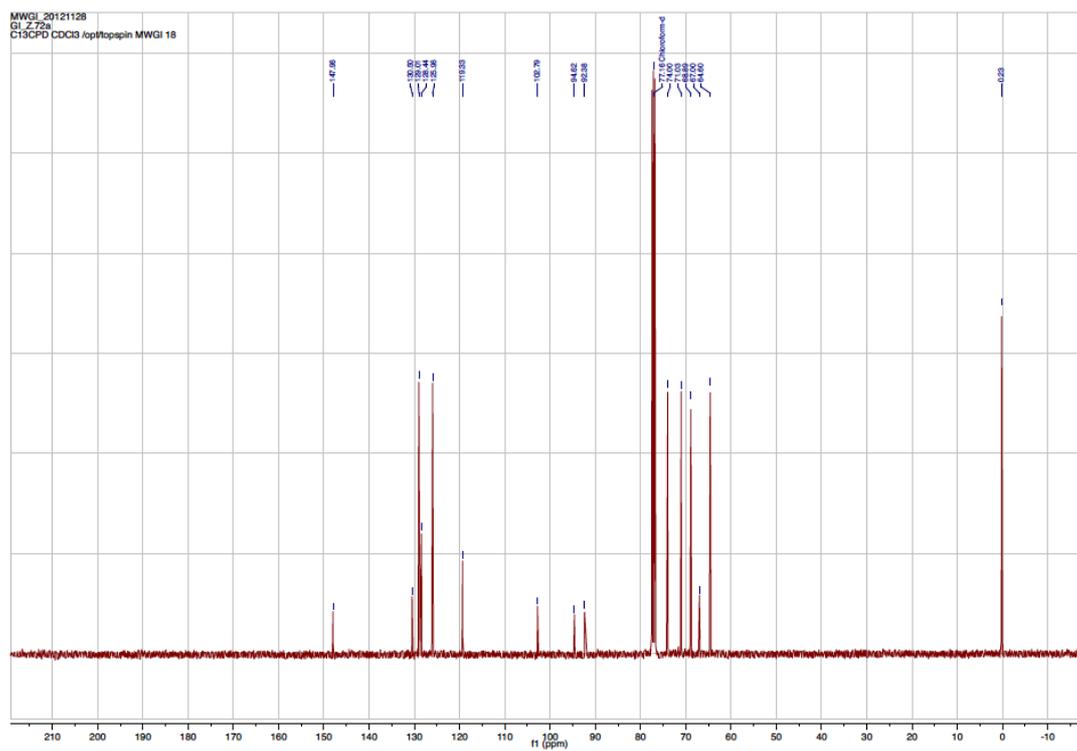
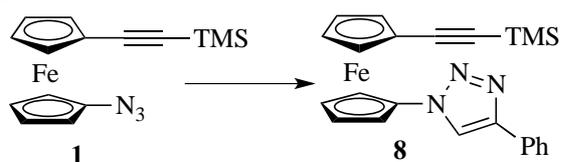


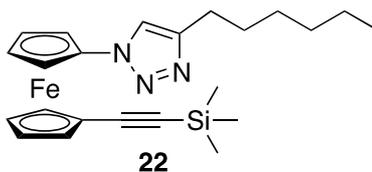
Figure ESI 5: ^1H and ^{13}C NMR spectra of **8**.

The synthesis of 1-(trimethylsilylethynyl)-1'-(4-phenyl-1H-1,2,3-triazol-1-yl)-ferrocene **8 from azide **1**:**

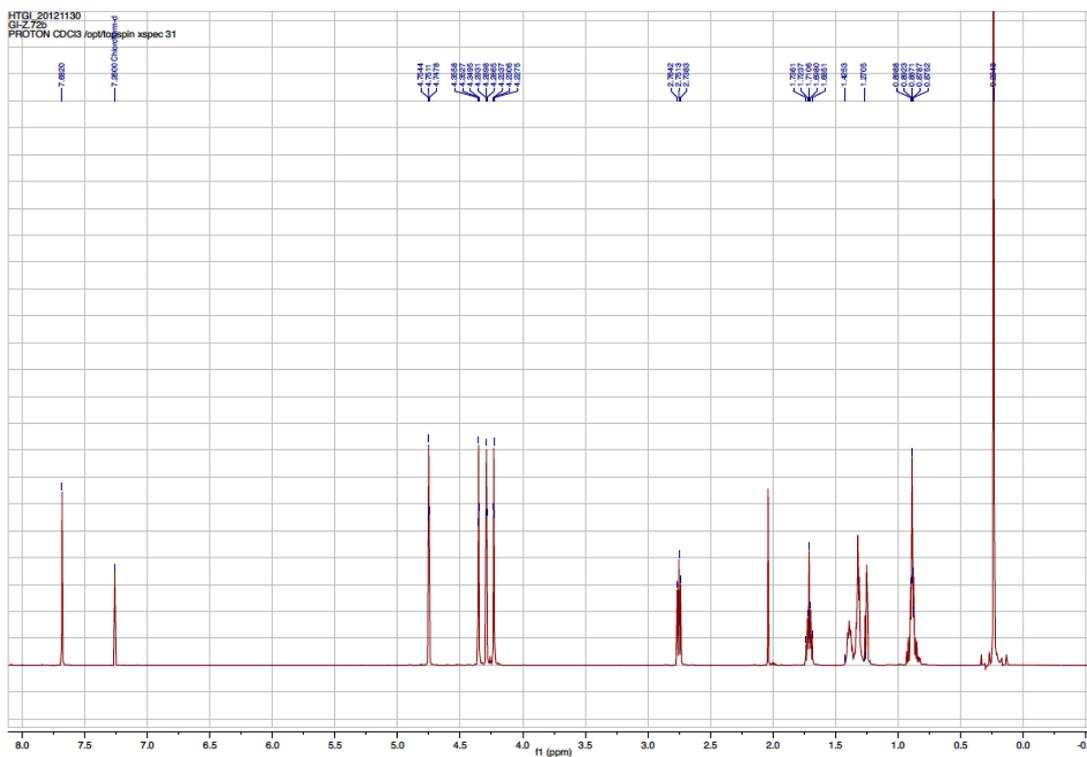


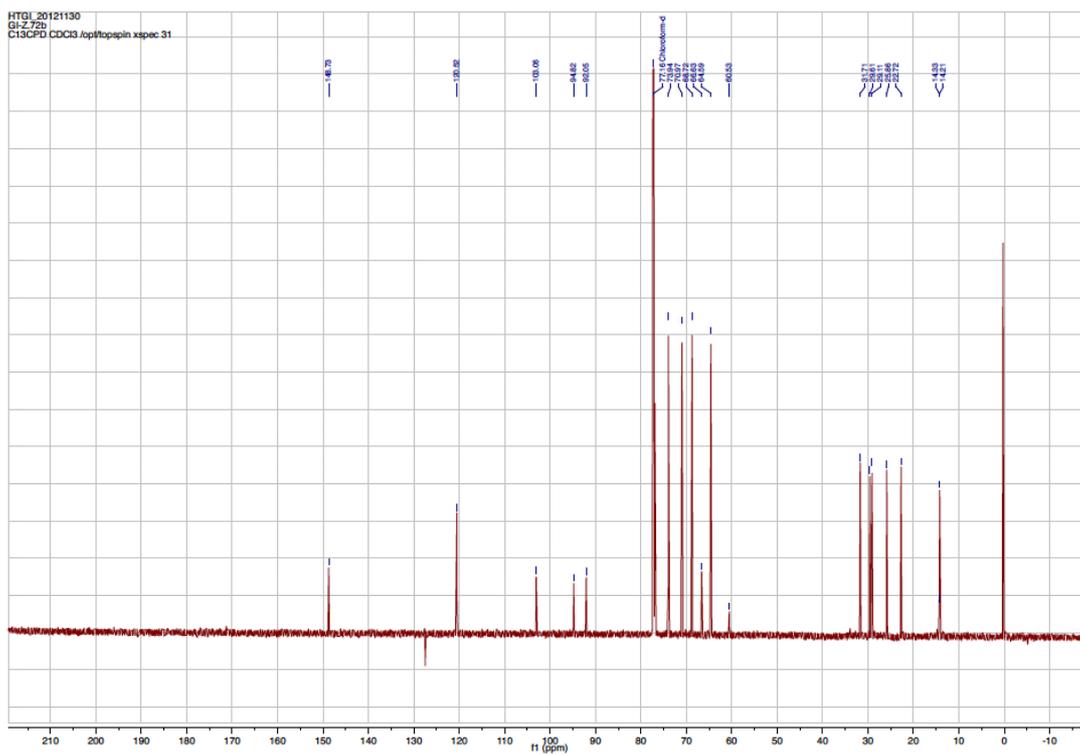
Azide **1** (12 mg, 0.036 mmol, 1.0 equiv.) and phenylacetylene (4.2 mg, 0.040 mmol, 1.1 equiv.) were dissolved in degassed MeOH (500 μ L). A solution of CuSO₄·6H₂O (0.92 mg, 3.7 $\times 10^{-3}$ mmol, 10 mol%) in degassed water (100 μ L) was then added to the reaction mixture followed by the addition of a solution of sodium ascorbate (1.1 mg, 5.6 $\times 10^{-3}$ mmol, 15 mol%) in water (100 μ L). The reaction mixture was stirred at r.t. for 16 h, after which it was diluted with a 1.0 M solution of EDTA in saturated NaHCO₃. The crude product was extracted with DCM (3 $\times 10$ mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The final product **8** was isolated after flash column chromatography (7% EA in PE) as yellow solid (15 mg, 95%).

1-(Trimethylsilylethynyl)-1'-(4-hexyl-1H-1,2,3-triazol-1-yl)-ferrocene 22:

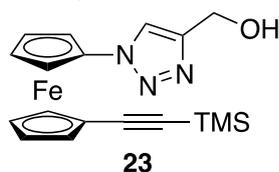


Product was isolated after flash column chromatography (10% EA in PE) as yellow solid (45%): m.p. 106-108 °C; ^1H NMR: 400 MHz, CDCl_3 : δ_{H} 7.68 (s, 1H), 4.75 (m, 2H), 4.35 (m, 2H), 4.29 (m, 2H), 4.23 (m, 2H), 2.75 (t, $J = 7.8$ Hz, 2H), 1.73 – 1.68 (m, 2H), 1.42 – 1.27 (m, 6H), 0.91 – 0.86 (m, 3H), 0.23 (s, 9H); ^{13}C NMR: δ_{C} 148.7, 120.5, 103.1, 94.8, 92.1, 73.9, 70.9, 68.7, 66.6, 64.6, 60.5, 31.7, 29.6, 29.1, 25.9, 22.7, 14.3, 14.2, 0.14; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ 3130, 3091, 2956, 2927, 2851, 2151, 1521, 1466, 1453, 1247, 1222, 1073, 1042, 1030, 925, 885, 839, 822, 807, 759, 724; HRMS m/z calculated for: $\text{C}_{23}\text{H}_{24}\text{FeN}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 434.1715, found 434.1735; LRMS: m/z 434.1 $[\text{M}+\text{H}]^+$; UV/vis: $\lambda_{\text{max}}(\text{DCM})/\text{nm}$ ($\epsilon / \text{mol}^{-1}\text{cm}^{-1}\text{dm}^3$) 238 (14.41×10^3), 244 (11.98×10^3), 274 (10.11×10^3), 330 (703), 444 (328).

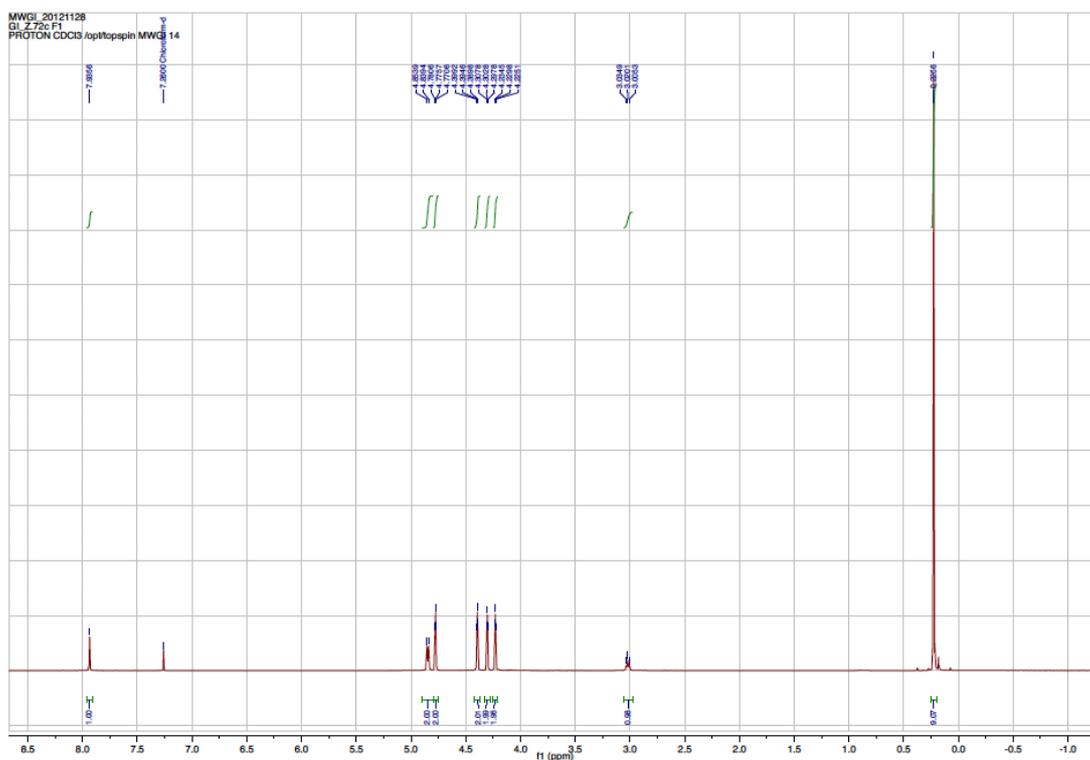




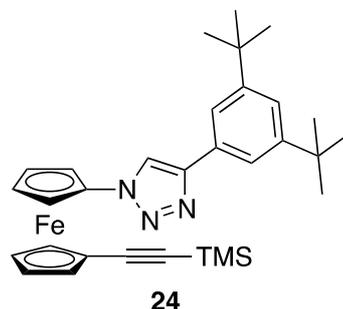
1-(Trimethylsilylethynyl)-1'-(4-(methyl-1-ol)-1H-1,2,3-triazol-1-yl)-ferrocene 23:



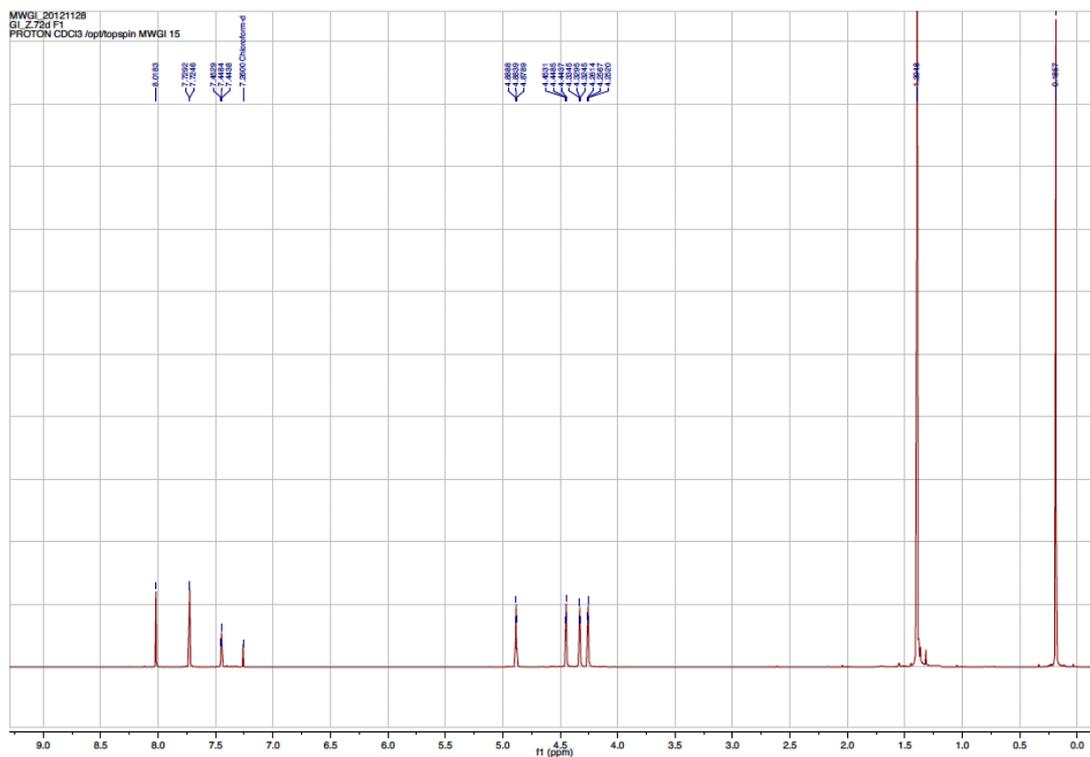
Product was isolated after flash column chromatography (60% to 75% EA in PE) as yellow solid (22%): m.p. 158-159 °C; ^1H NMR: 400 MHz, CDCl_3 : δ_{H} 7.94 (s, 1H), 4.84 (d, $J = 5.8$ Hz, 2H), 4.77 (m, 2H), 4.39 (m, 2H), 4.30 (m, 2H), 4.23 (m, 2H), 3.02 (t, $J = 5.9$ Hz, 1H), 0.23 (s, 9H); ^{13}C NMR: δ_{C} 147.8, 121.6, 102.9, 94.5, 92.3, 73.8, 71.1, 69.1, 66.9, 64.5, 56.6, 0.2; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ 3401, 3144, 3097, 2953, 2149, 1557, 1521, 1455, 1409, 1247, 1221, 1079, 1041, 1012, 925, 838, 811, 757, 724, 696; HRMS m/z calculated for: $\text{C}_{18}\text{H}_{22}\text{FeN}_3\text{OSi}$ $[\text{M}+\text{H}]^+$ 380.0882, found 380.0901; LRMS m/z 380.0 $[\text{M}+\text{H}]^+$, UV/vis: $\lambda_{\text{max}}(\text{DCM})/\text{nm}$ ($\epsilon / \text{mol}^{-1}\text{cm}^{-1}\text{dm}^3$) 236 (14.32×10^3), 244 (12.42×10^3), 267 (8.69×10^3), 330 (769), 441 (305).



1-(Trimethylsilylethynyl)-1'-(4-(3,5-di-tert-butylphenyl)-1H-1,2,3-triazol-1-yl)-ferrocene 24:



Product was isolated after flash column chromatography (10% EA in PE) as yellow solid (30%): m.p. 169-171 °C; ^1H NMR: 400 MHz, CDCl_3 : δ_{H} 8.02 (s, 1H), 7.72 (d, $J = 1.8$ Hz, 2H), 7.45 (t, $J = 1.8$ Hz, 1H), 4.88 (st, 2H), 4.44 (st, 2H), 4.33 (st, 2H), 4.26 (st, 2H), 1.39 (s, 18H), 0.19 (s, 9H); ^{13}C NMR: δ_{C} 151.5, 148.8, 129.7, 122.7, 120.4, 118.8, 102.6, 94.8, 92.2, 73.9, 71.1, 69.0, 67.0, 64.1, 35.1, 31.6, 0.3; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ 3117, 3085, 2952, 2899, 2864, 2148, 1596, 1520, 1475, 1448, 1421, 1392, 1362, 1288, 1248, 1223, 1201, 1072, 1041, 1025, 924, 878, 857, 832, 757, 726, 712; HRMS m/z calculated for: $\text{C}_{31}\text{H}_{40}\text{FeN}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 538.234, found 538.2347; LRMS m/z 538.2 $[\text{M}+\text{H}]^+$; UV/vis: $\lambda_{\text{max}}(\text{DCM})/\text{nm}$ ($\epsilon / \text{mol}^{-1}\text{cm}^{-1}\text{dm}^3$) 246 (22.56×10^3), 276 (14.92×10^3), 297 (9.53×10^3), 330 (1.74×10^3), 445 (442).



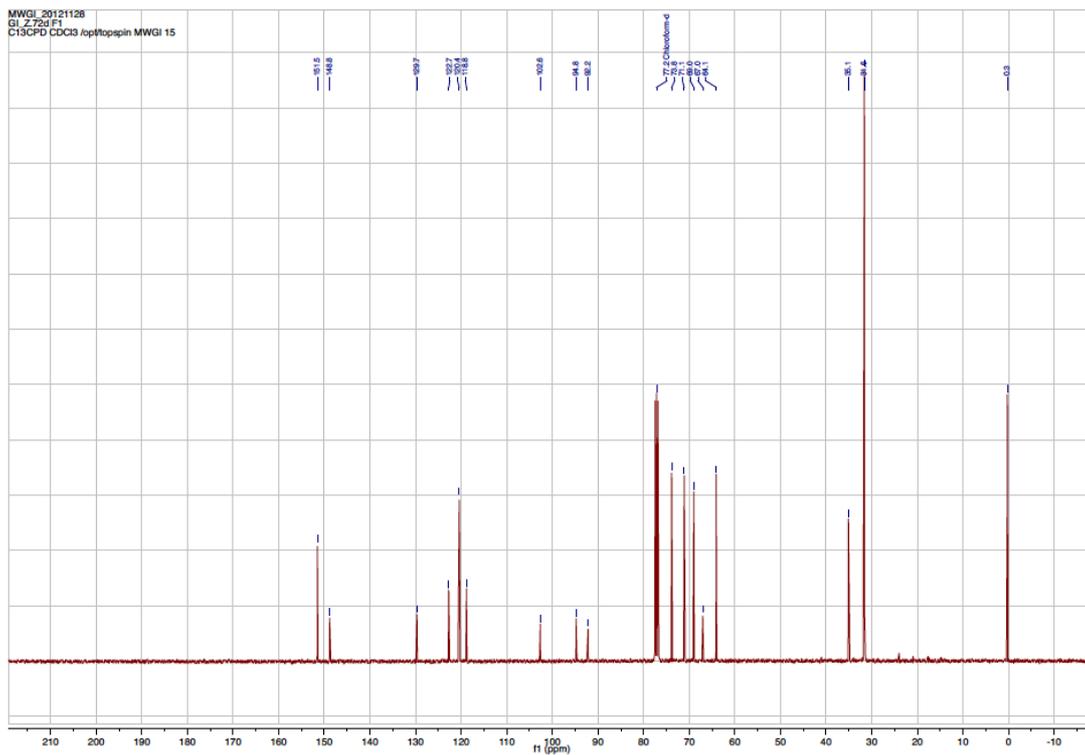
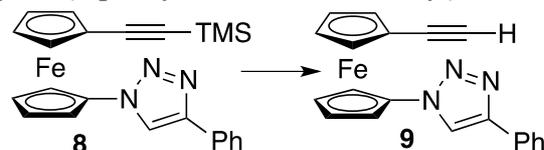
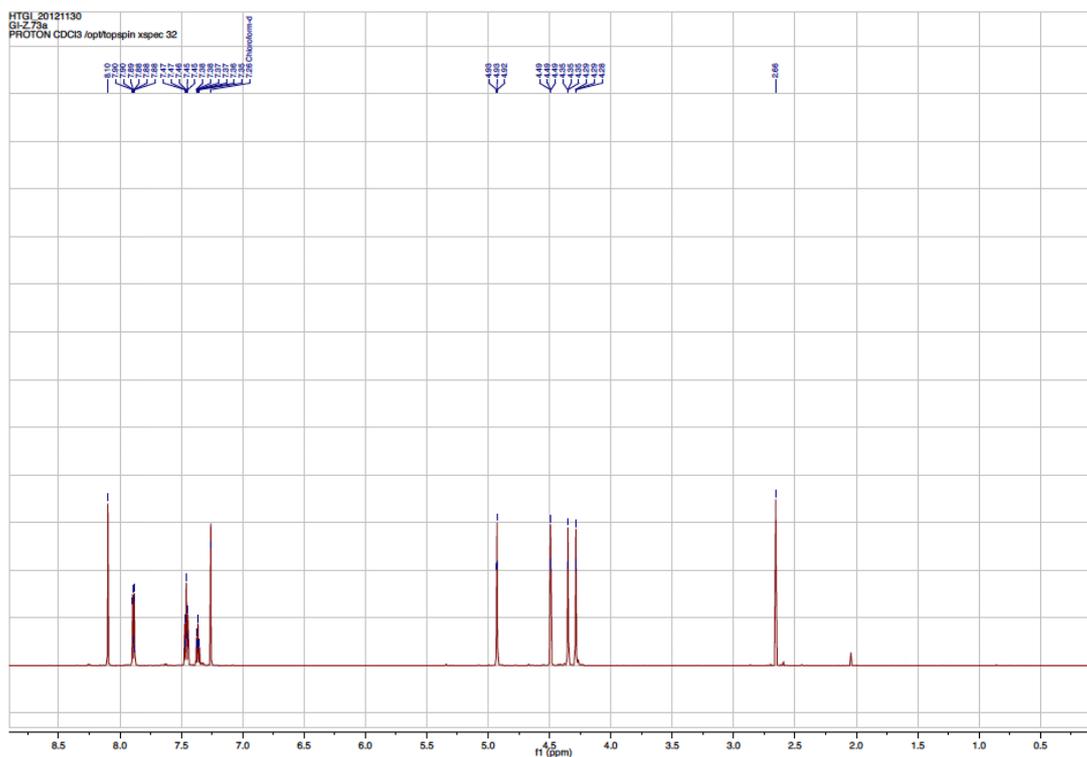


Figure ESI 8: ^1H and ^{13}C NMR spectra of **25**.

General procedure for the deprotection of 8 and 22-24 with TBAF as represented by the synthesis of 1-ethynyl-1'-(4-phenyl-1H-1,2,3-triazol-1-yl)-ferrocene 9.



A solution of TBAF (1.0 M in THF, 120 μ L, 1.0 equiv.) was added to a solution of clickate **8** (50 mg, 0.12 mmol, 1.0 equiv.) in anhydrous THF (5 mL) and the reaction was stirred for 7 h until complete deprotection occurred as judged by TLC analysis. The reaction was then treated with citric acid (5% aqueous, 10 mL) and the product was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over MgSO_4 and solvent was removed *in vacuo*. The product **9** was isolated after flash column chromatography (41 mg, 89%) as orange solid: m.p. 138-140 $^{\circ}\text{C}$; ^1H NMR: 600 MHz, CDCl_3 : δ_{H} 8.10 (s, 1H), 7.91 – 7.87 (m, 2H), 7.48 – 7.44 (m, 2H), 7.38 – 7.35 (m, 1H), 4.93 (m, 2H), 4.49 (m, 2H), 4.35 (m, 2H), 4.29 (m, 2H), 2.26 (s, 1H); ^{13}C NMR: δ_{C} 147.8, 130.5, 129.0, 128.4, 127.5, 125.9, 119.2, 94.8, 80.9, 75.3, 73.8, 70.9, 68.6, 63.8; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ 3265, 3119, 3093, 2923, 2106, 1519, 1476, 1448, 1221, 1066, 1041, 1030, 971, 913, 875, 820, 759; HRMS m/z calculated for: $\text{C}_{20}\text{H}_{16}^{54}\text{FeN}_3$, $[\text{M}+\text{H}]^+$ 352.0740, found 352.0754; LRMS m/z 376 $[\text{M}+\text{Na}]^+$; UV/vis: $\lambda_{\text{max}}(\text{DCM})/\text{nm}$ ($\epsilon / \text{mol}^{-1}\text{cm}^{-1}\text{dm}^3$) 248 (19.53×10^3), 273 (10.67×10^3), 292 (7.55×10^3), 327 (1.45×10^3), 444 (297).



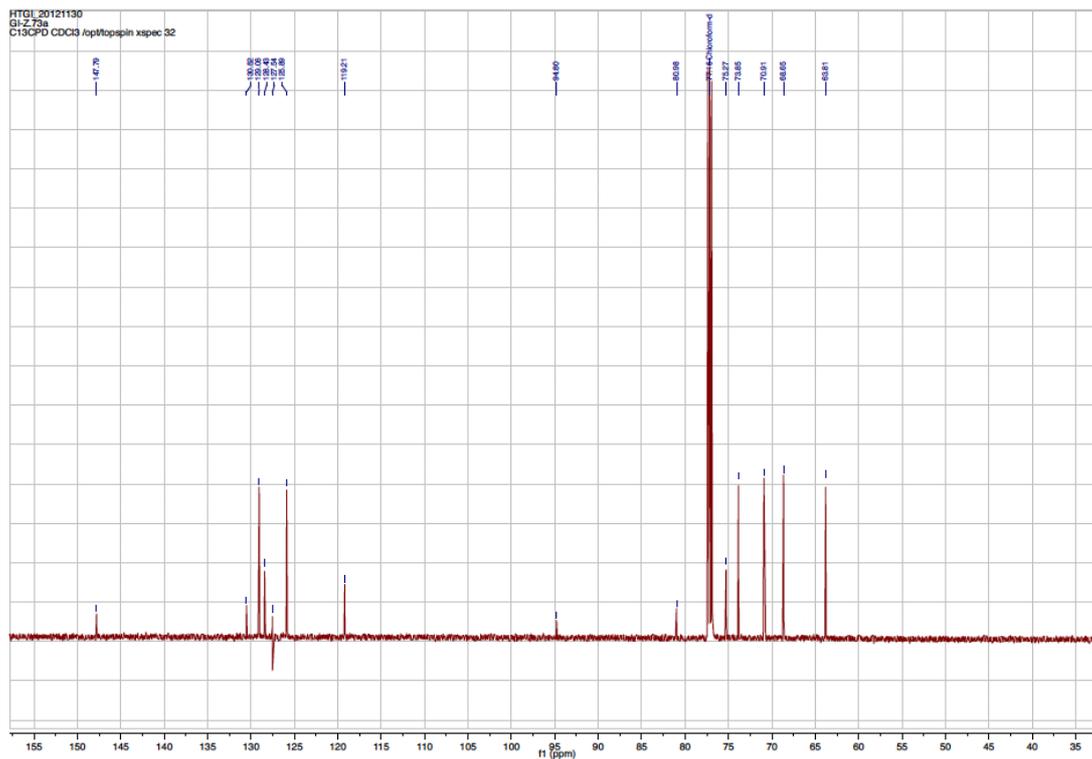
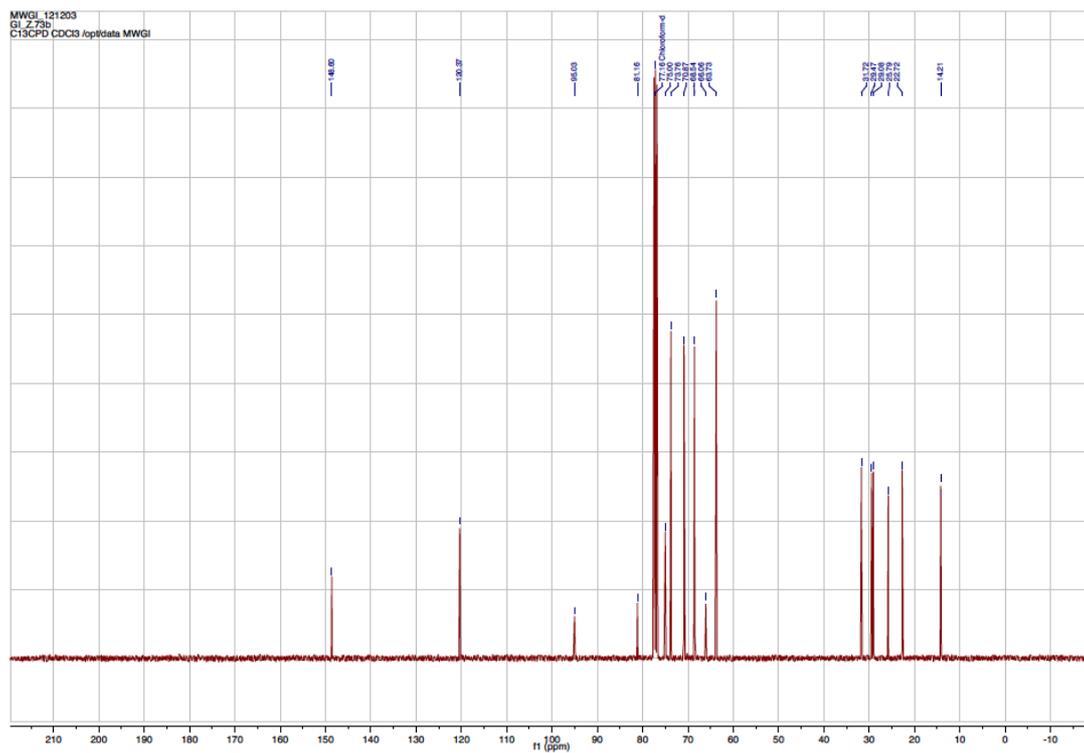


Figure ESI 9: ^1H and ^{13}C NMR spectra of **9**.

General procedure for the deprotection of **8 and **22-24** with K_2CO_3 as represented by the synthesis of 1-ethynyl-1'-(4-phenyl-1H-1,2,3-triazol-1-yl)-ferrocene **9**:**

K_2CO_3 (100 mg) was added to a solution of “clickate” **8** (50 mg, 0.12 mmol, 1.0 equiv.) in MeOH (5.0 mL) and the reaction was stirred at r.t. for 16 h, after which it was filtered and concentrated *in vacuo*. The product **9** was isolated after flash column chromatography (34 mg, 75%) as orange solid.



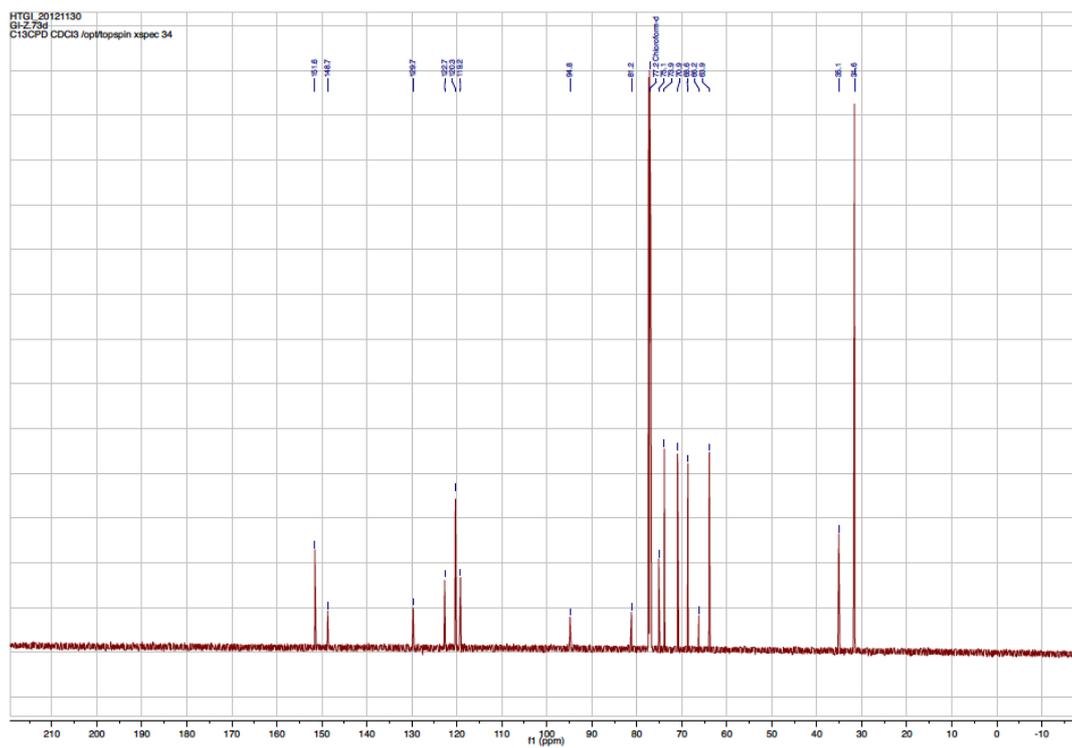
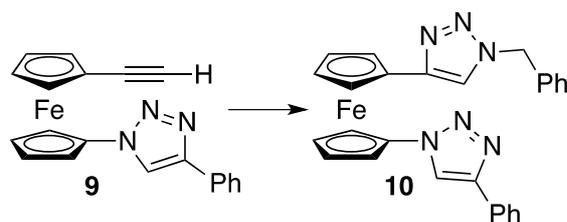
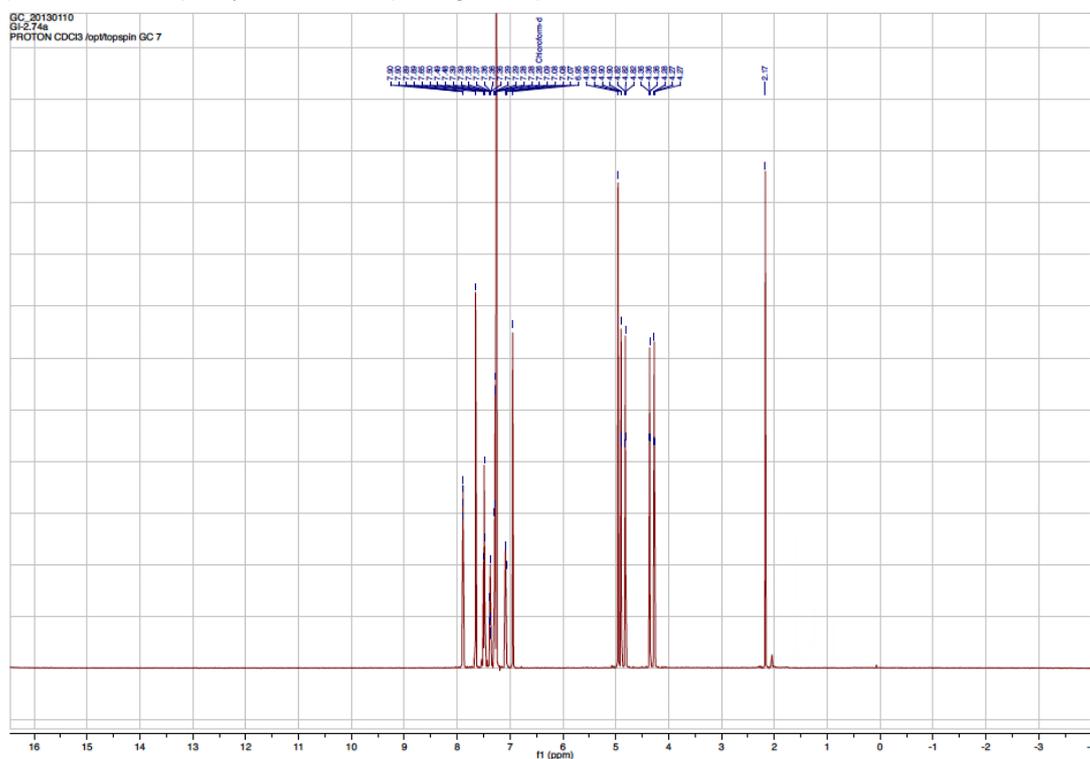


Figure ESI 12: ^1H and ^{13}C NMR spectra of **27**.

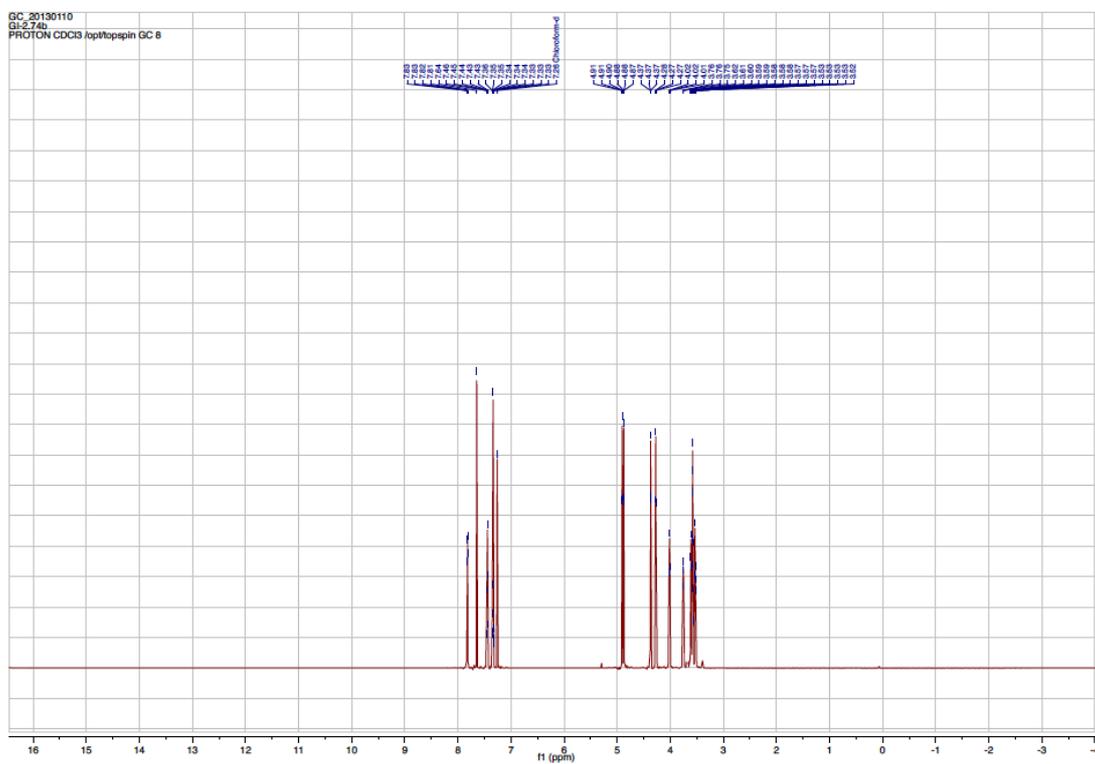
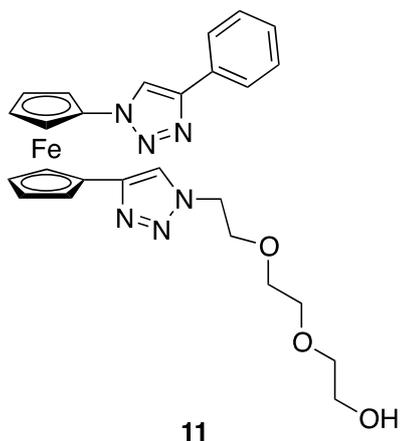
General procedure for the second “click” as represented by the synthesis of 1-(1-benzyl-1H-,1,2,3-triazol-4-yl)-1’-(4-phenyl-1H-1,2,3-triazol-1-yl)-ferrocene **10.**



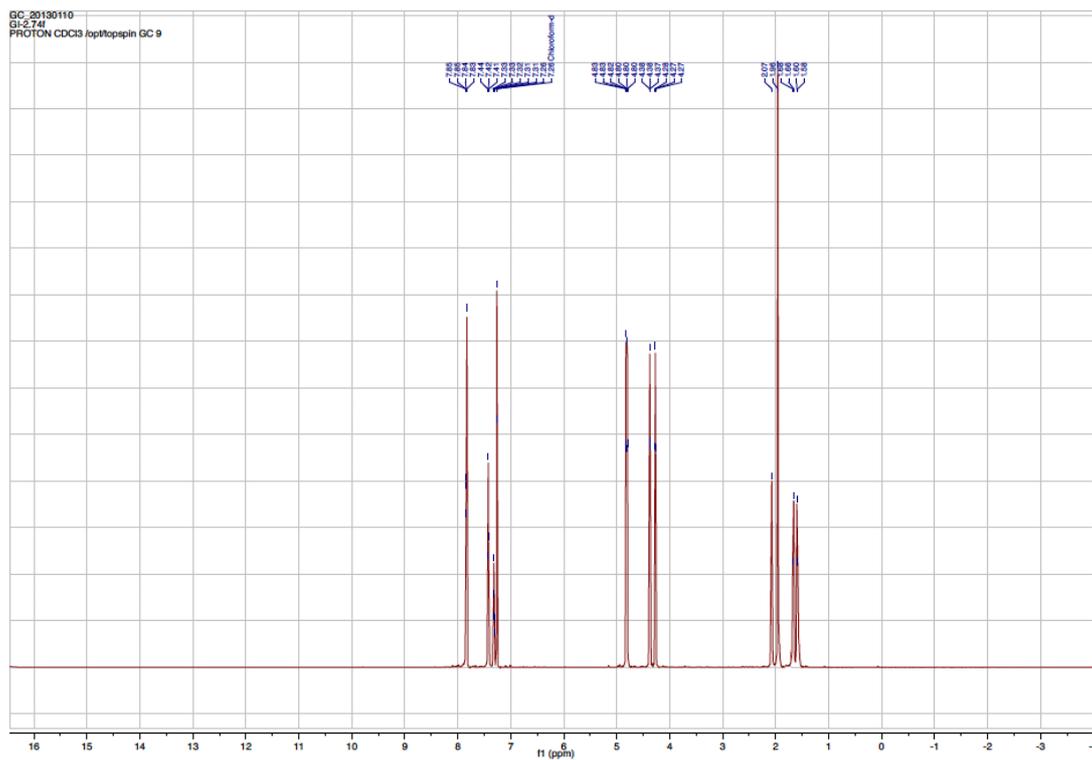
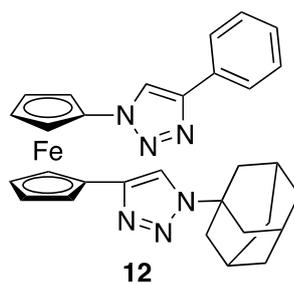
A solution of **9** (20 mg, 0.057 mmol, 1.0 equiv.) and benzyl azide (7.6 mg, 0.057, 1.01 equiv.) in THF (1.0 mL) was degassed, and a solution of CuSO₄·5H₂O (1.4 mg, 5.7 × 10⁻³ mmol, 10 mol%) in water (100 μL) was added. A solution of sodium ascorbate (1.6 mg, 0.011 mmol, 20 mol%) in water (50 μL) was then added to initiate the reaction. After stirring the mixture at r.t for 16 h. it was diluted with a 1.0 M solution of EDTA in saturated NaHCO₃. The product was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over MgSO₄ and concentrated *in vacuo*. The product **10** was isolated after flash column chromatography (40% EA in PE) as yellow solid (18 mg, 69%).



1-(1-(2-(2-Ethoxyethoxy)ethanol)-1H-1,2,3-triazol-4-yl)-1'-(4-phenyl-1H-1,2,3-triazol-1-yl)-ferrocene 11



1-(1-Adamantyl-1H-1,2,3-triazol-4-yl)-1'-(4-phenyl-1H-1,2,3-triazol-1-yl)-ferrocene
12:



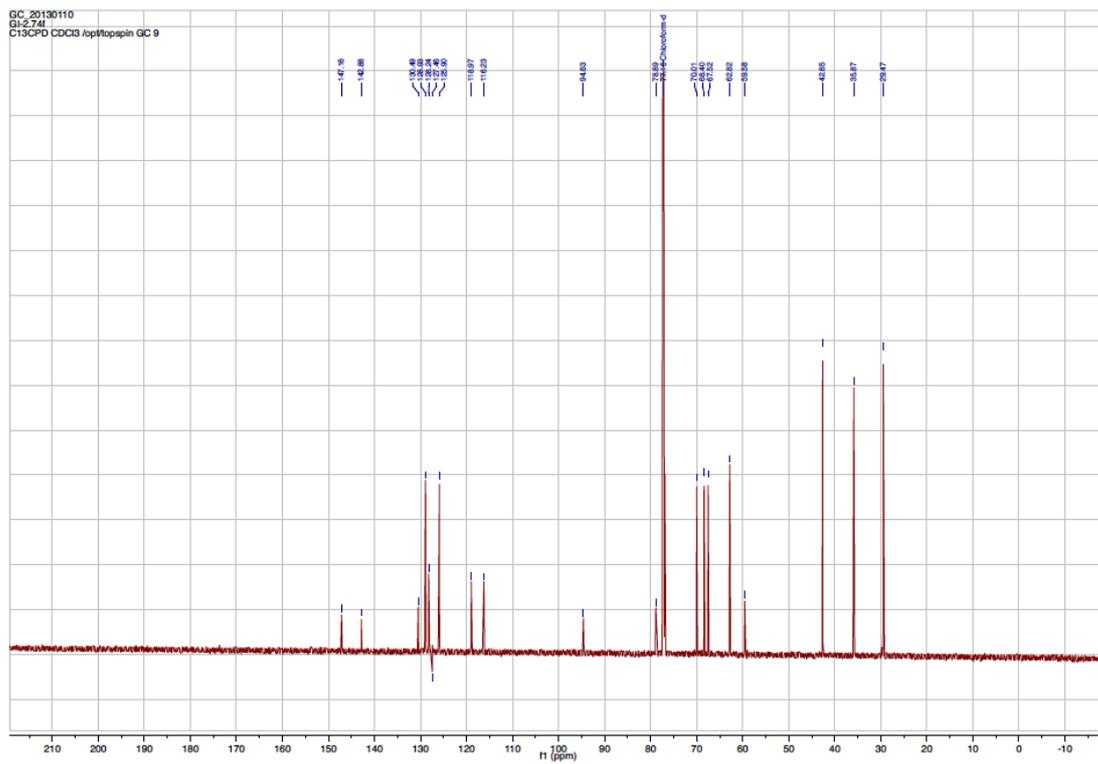


Figure ESI 15: ^1H and ^{13}C NMR spectra of **12**.

1-(1-Benzyl-1H-1,2,3-triazol-4yl)-1'-(4-hexyl-1H-1,2,3-triazol-1-yl)-ferrocene 13

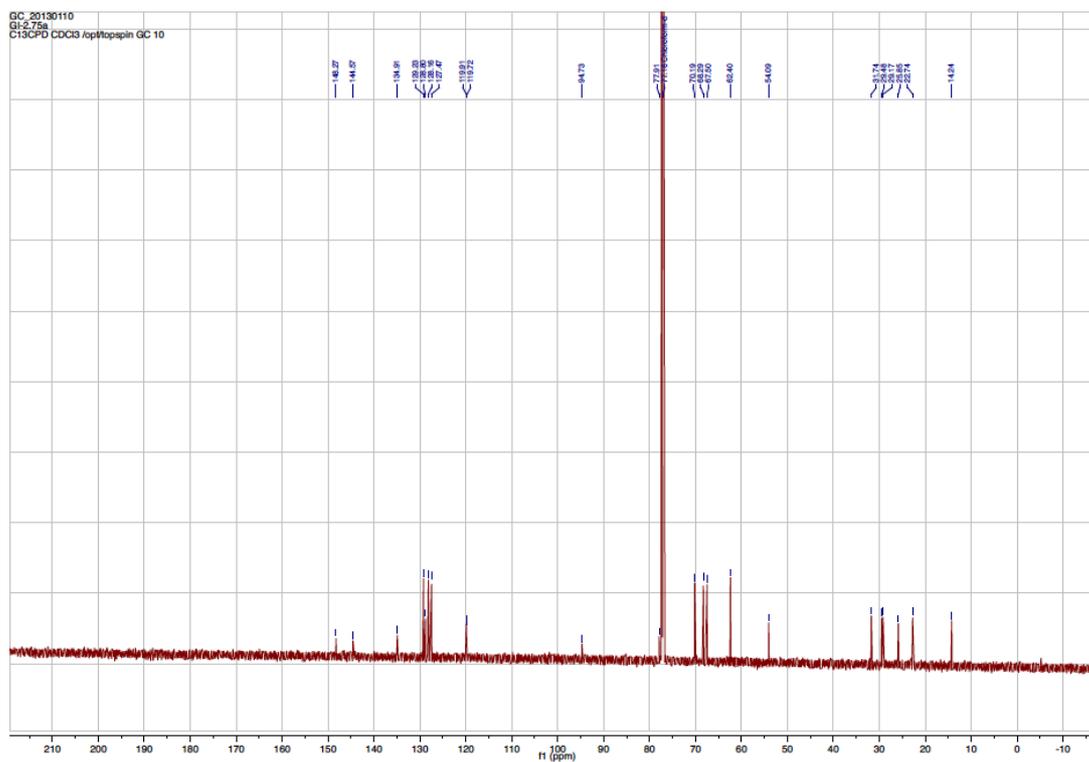
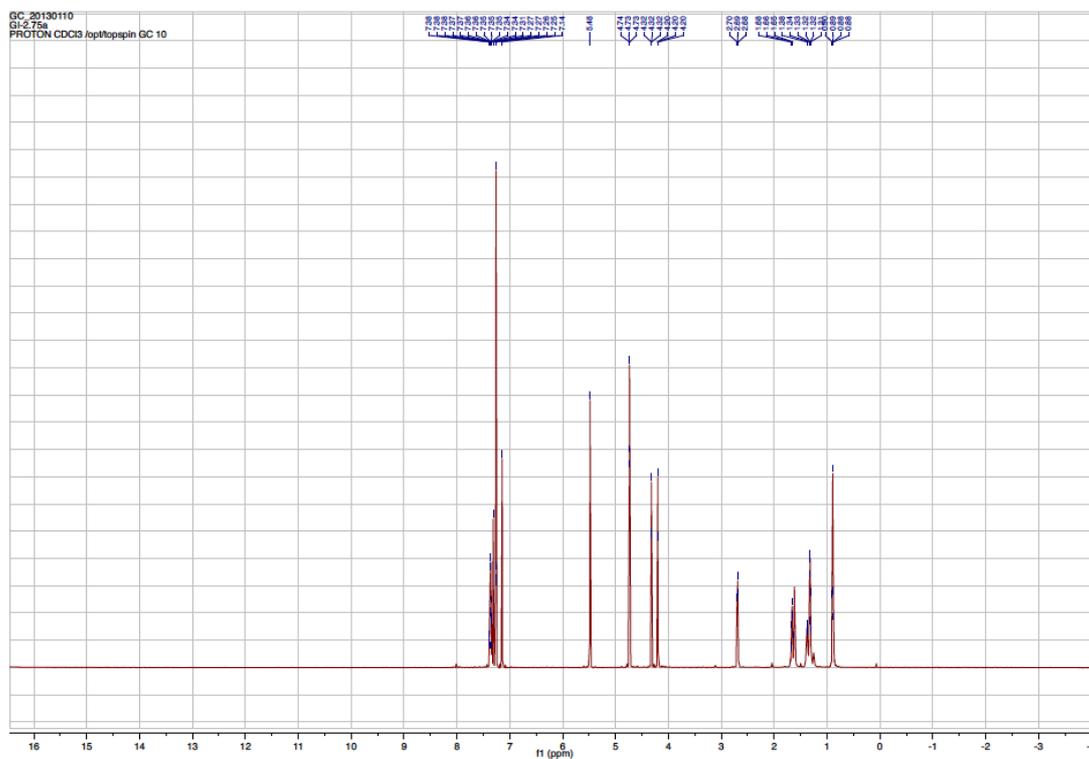
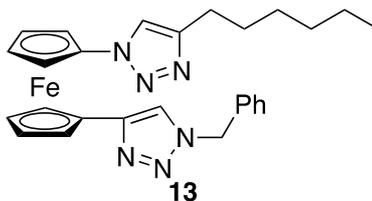
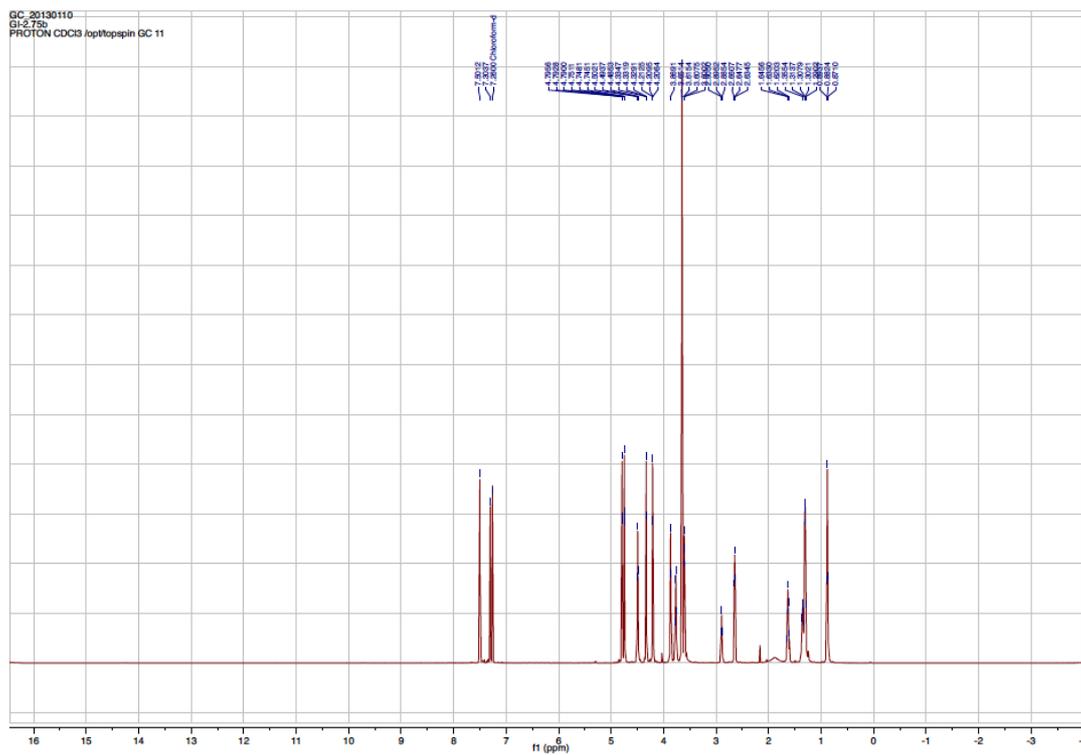
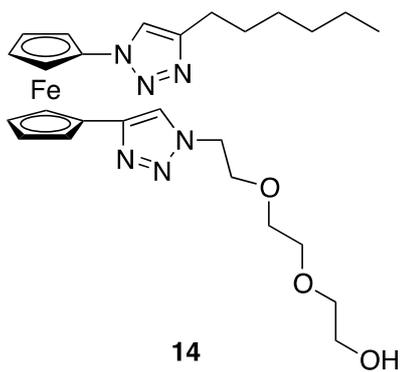


Figure ESI 16: ¹H and ¹³C NMR spectra of **13**.

1-(1-(2-(2-Ethoxyethoxy)ethanol)-1H-1,2,3-triazol-4-yl)-1'-(4-hexyl-1H-1,2,3-triazol-1-yl)-ferrocene 14:



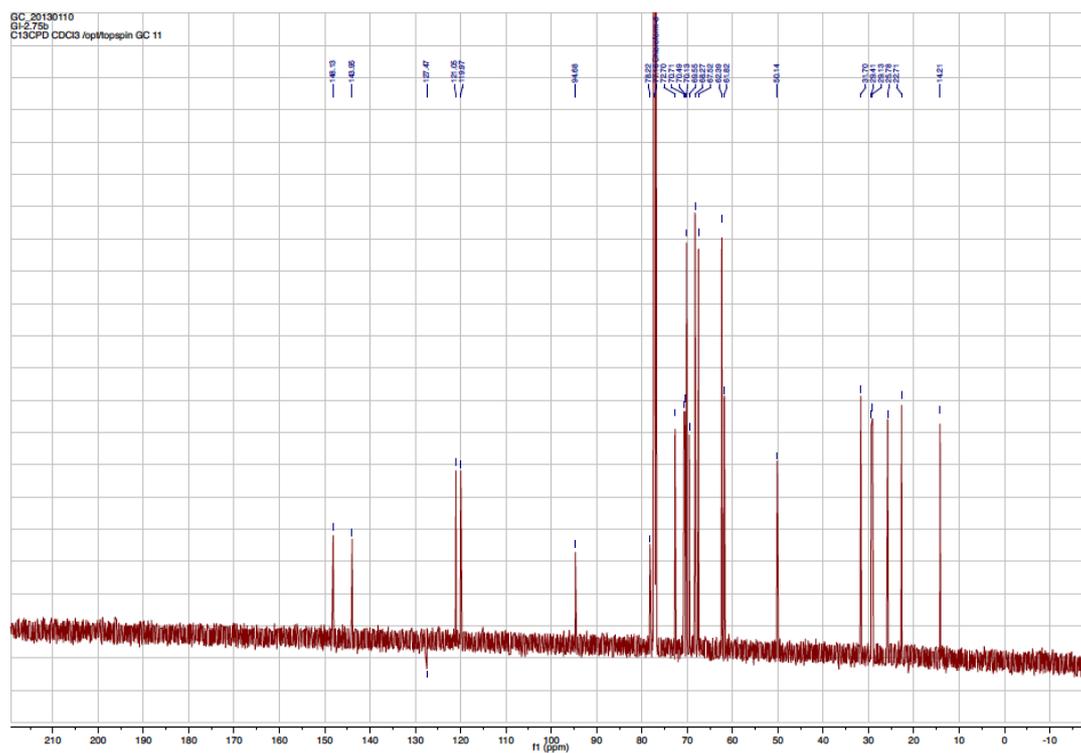


Figure ESI 17: ^1H and ^{13}C NMR spectra of **14**.

Figure ESI 18: ^1H and ^{13}C NMR spectra of **15**.

1-(1-Benzyl-1H-,1,2,3-triazol-yl)-1'-(4-(methyl-1-ol)-1H-1,2,3-triazol-1-yl)-ferrocene 16:

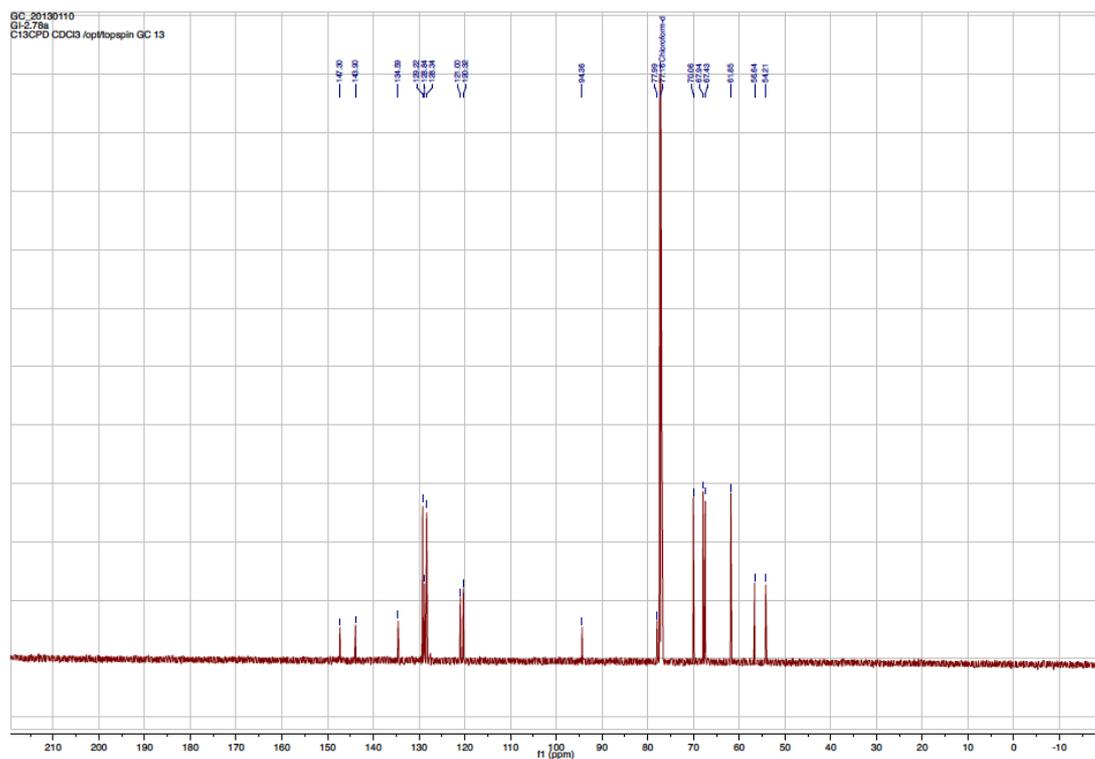
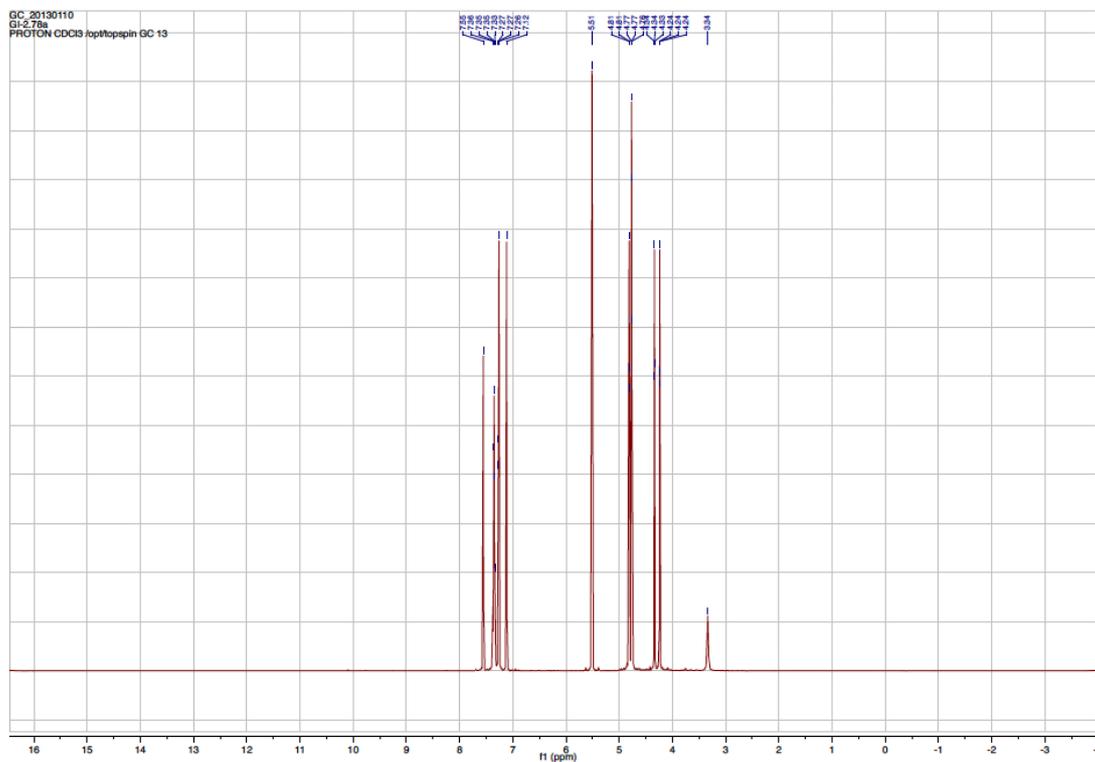
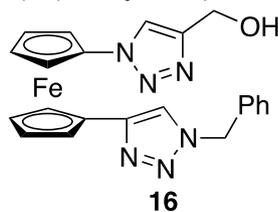
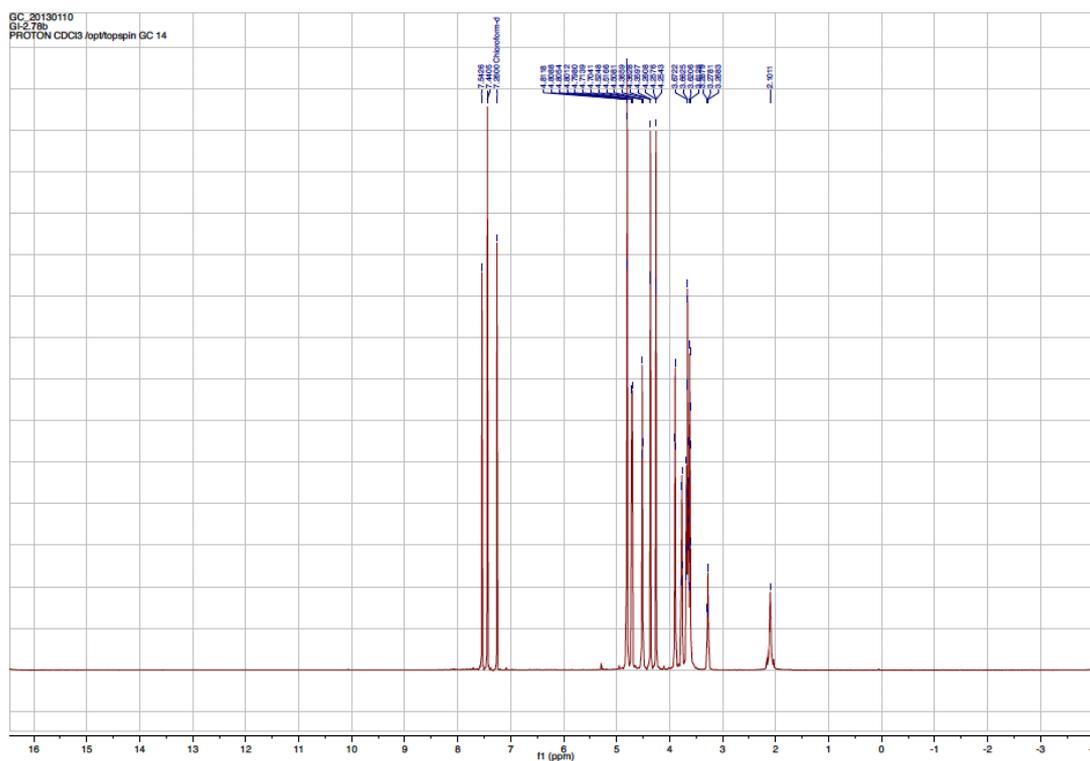
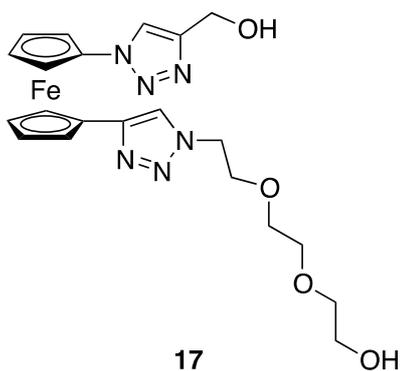


Figure ESI 19: ^1H and ^{13}C NMR spectra of **16**.

1-(1-(2-(2-Ethoxyethoxy)ethanol)-1H-1,2,3-triazol-4-yl)-1'-(4-(methyl-1-ol)-1H-1,2,3-triazol-1-yl)-ferrocene 17:



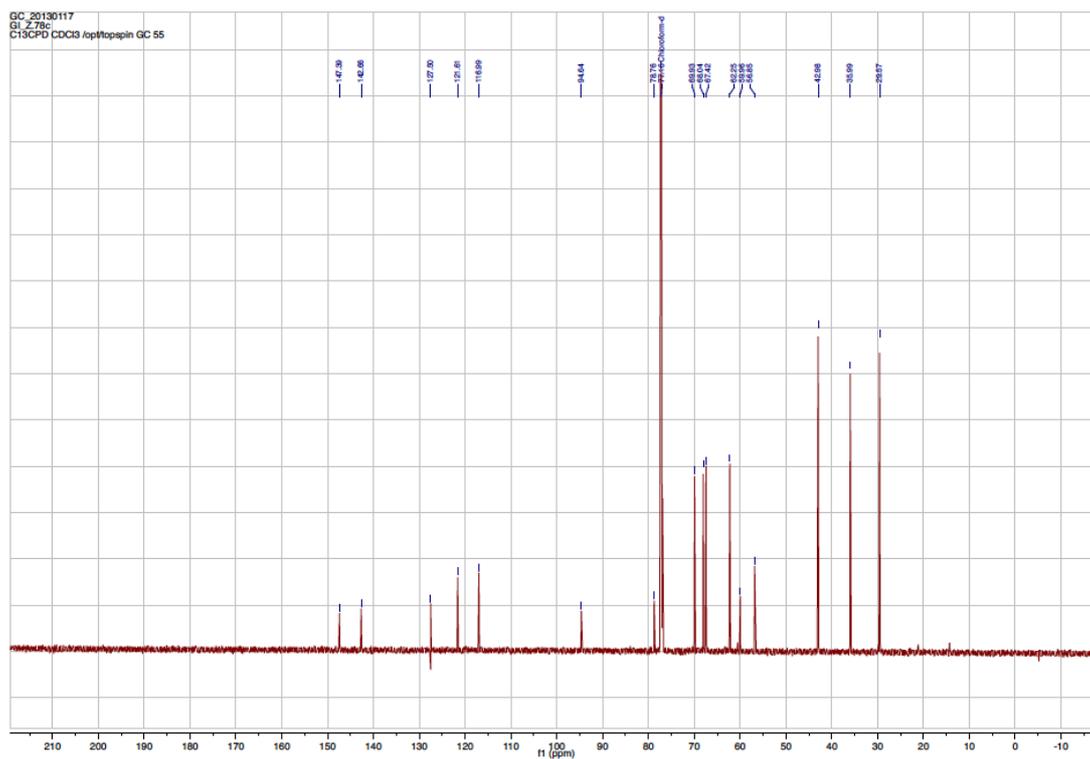
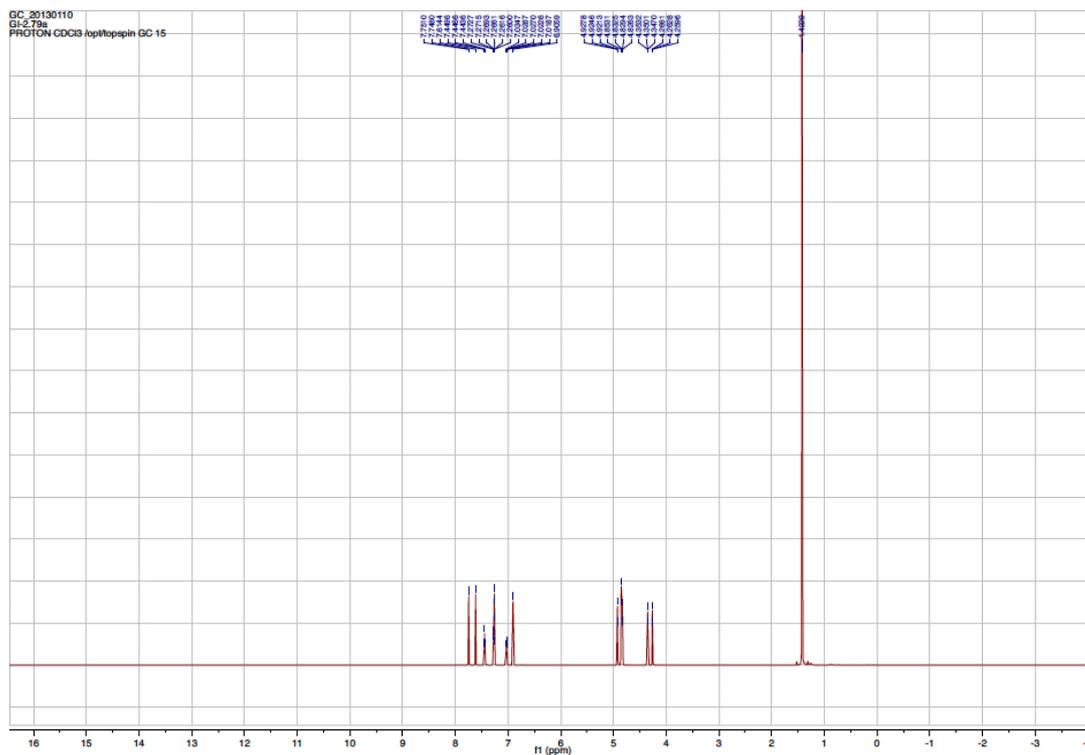
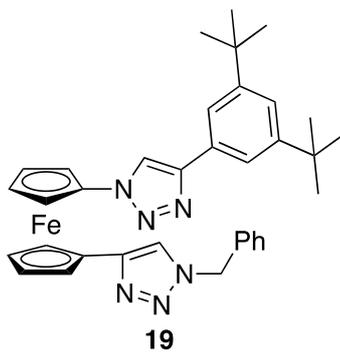


Figure ESI 21: ^1H and ^{13}C NMR spectra of **18**.

1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-1'-(4-(3,5-di-tert-butylphenyl)-1H-1,2,3-triazol-1-yl)-ferrocene 19:



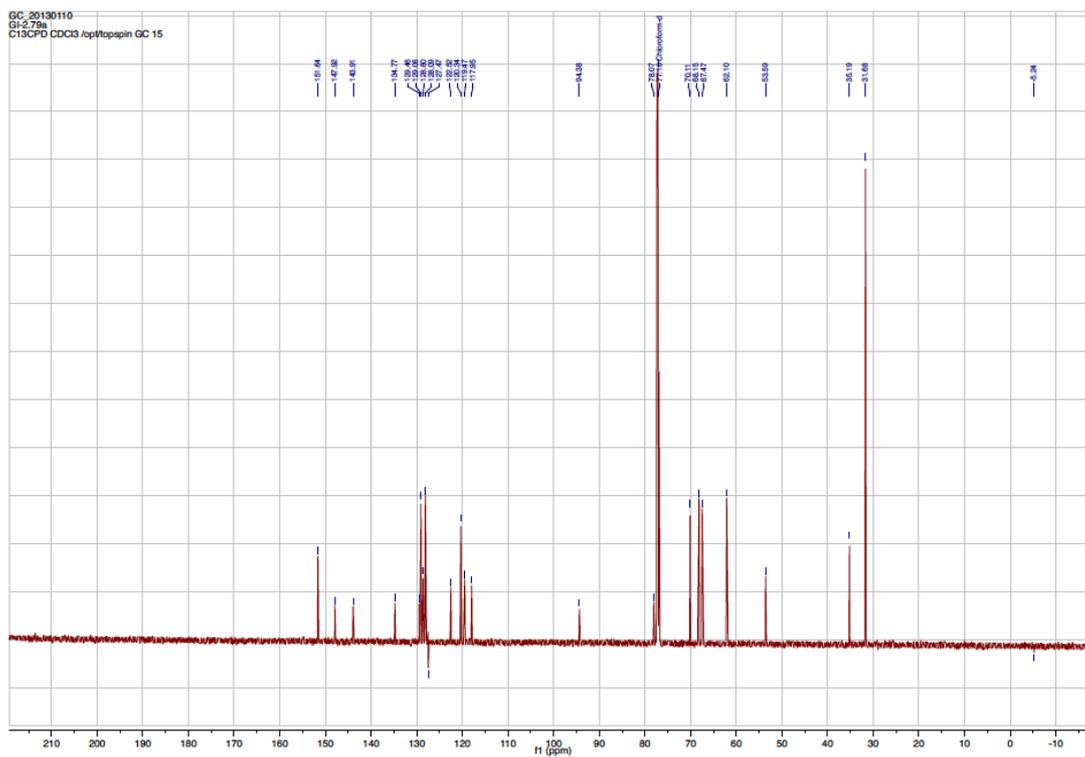
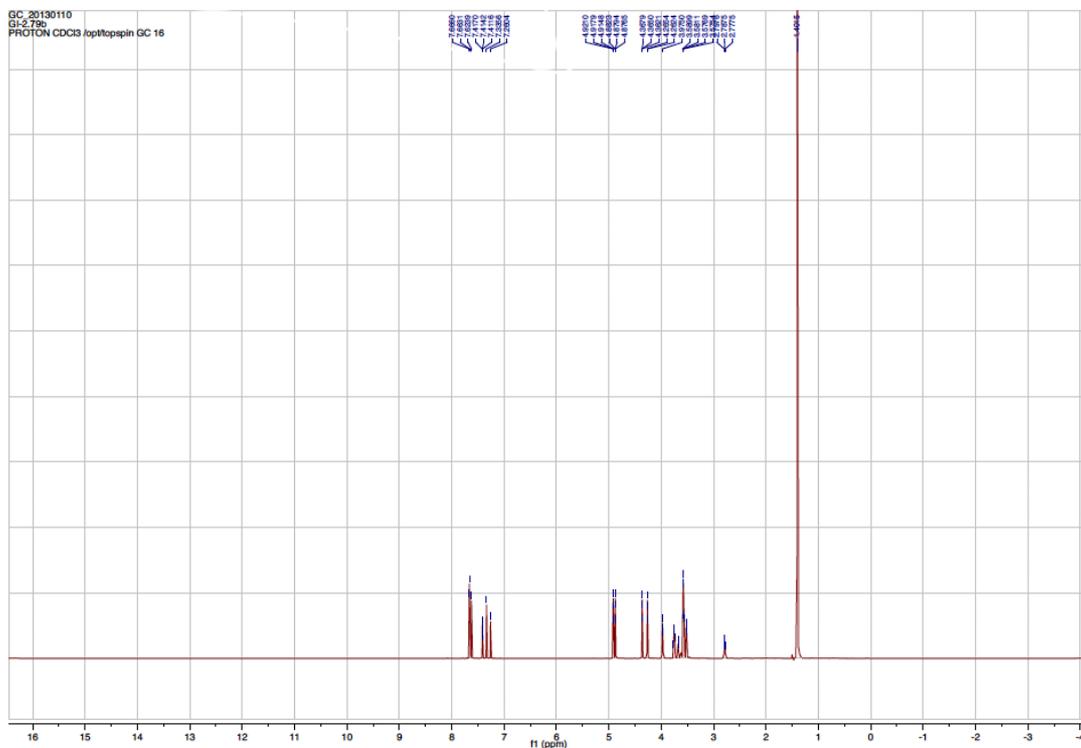
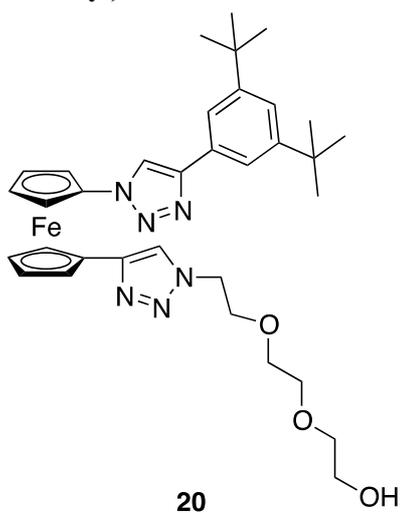


Figure ESI 22: ^1H and ^{13}C NMR spectra of **19**.

1-(1-(2-(2-Ethoxyethoxy)ethanol)-1H-1,2,3-triazol-4-yl)-1'-(4-(3,5-di-tert-butylphenyl-1-yl)-1H-1,2,3-triazol-1-yl)-ferrocene 20:



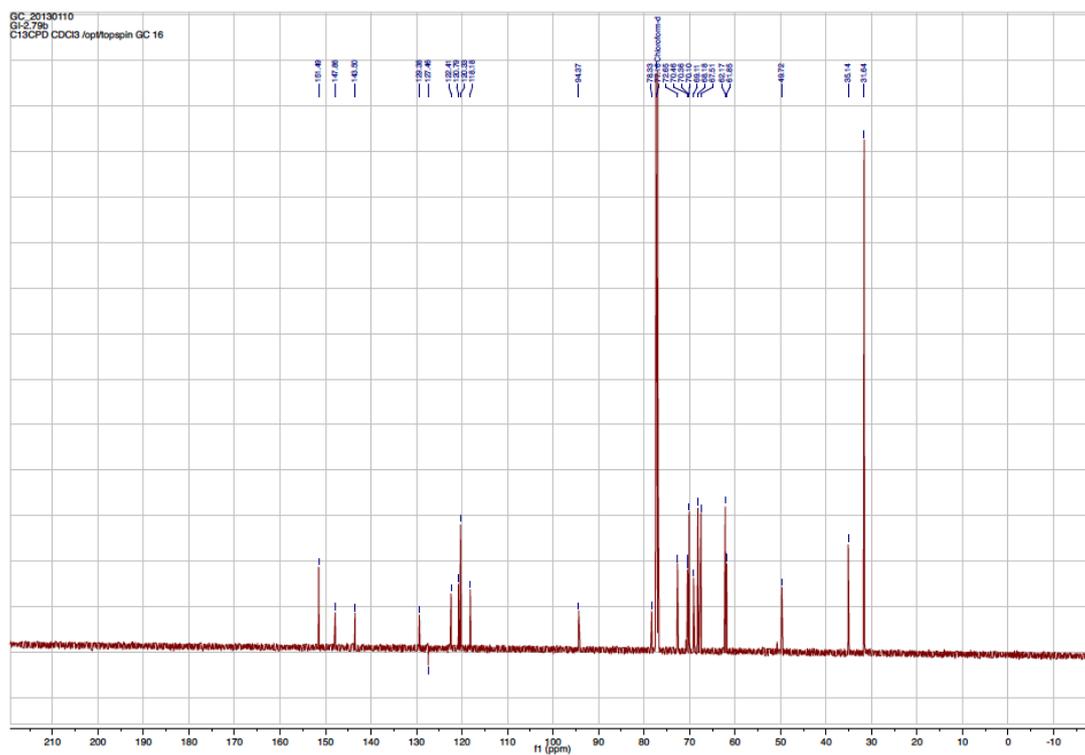
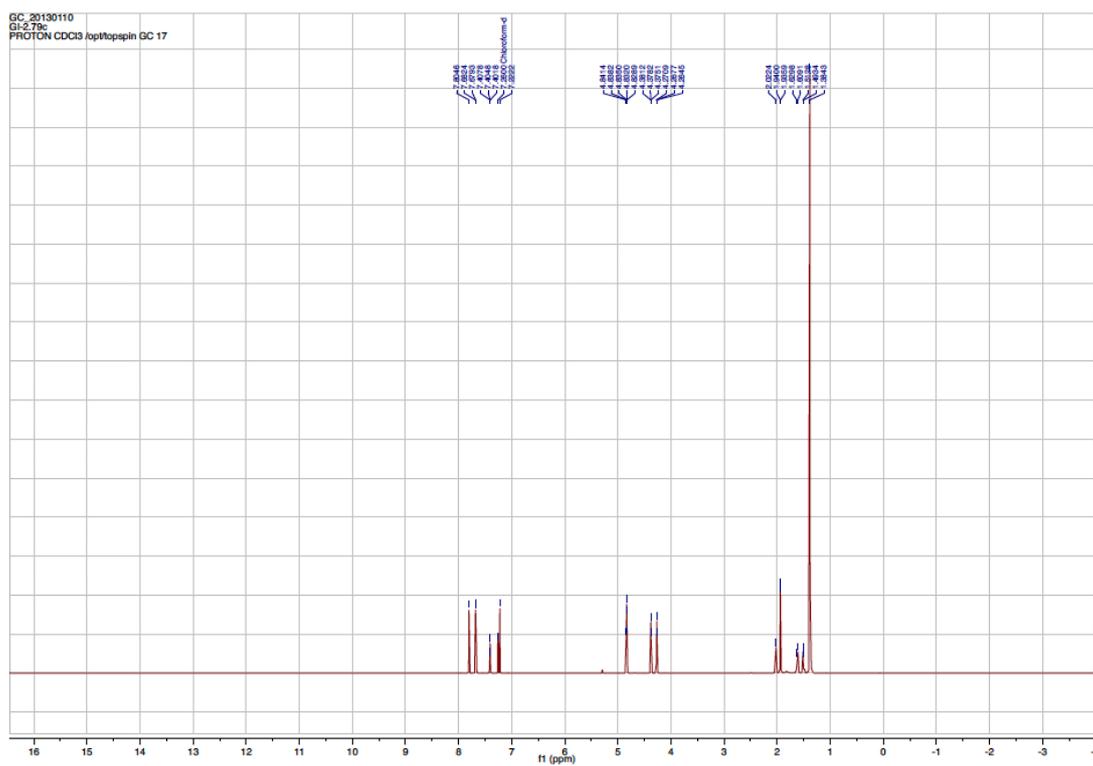
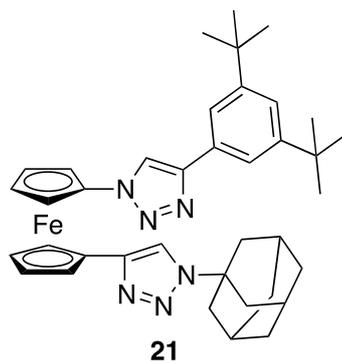


Figure ESI 23: ^1H and ^{13}C NMR spectra of **20**.

1-(1-Adamantyl-1H-1,2,3-triazol-4-yl)-1'-(4-(3,5-di-tert-butylphenyl)-1H-1,2,3-triazol-1-yl)-ferrocene 21:



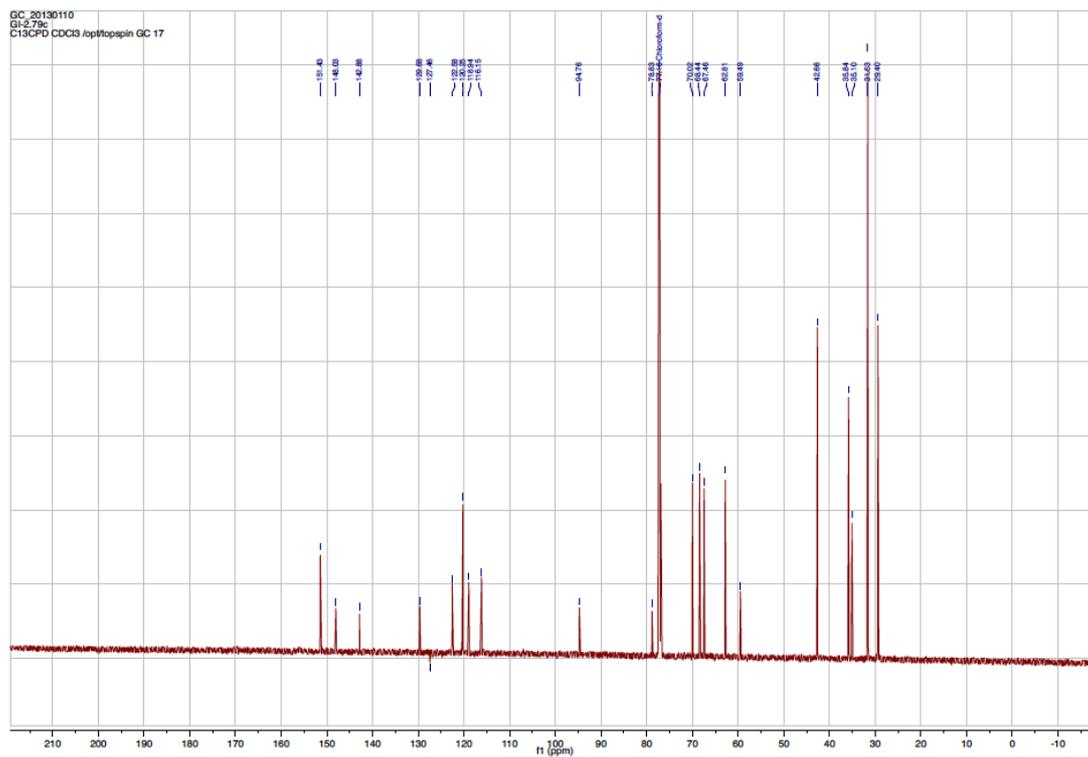
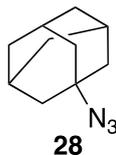


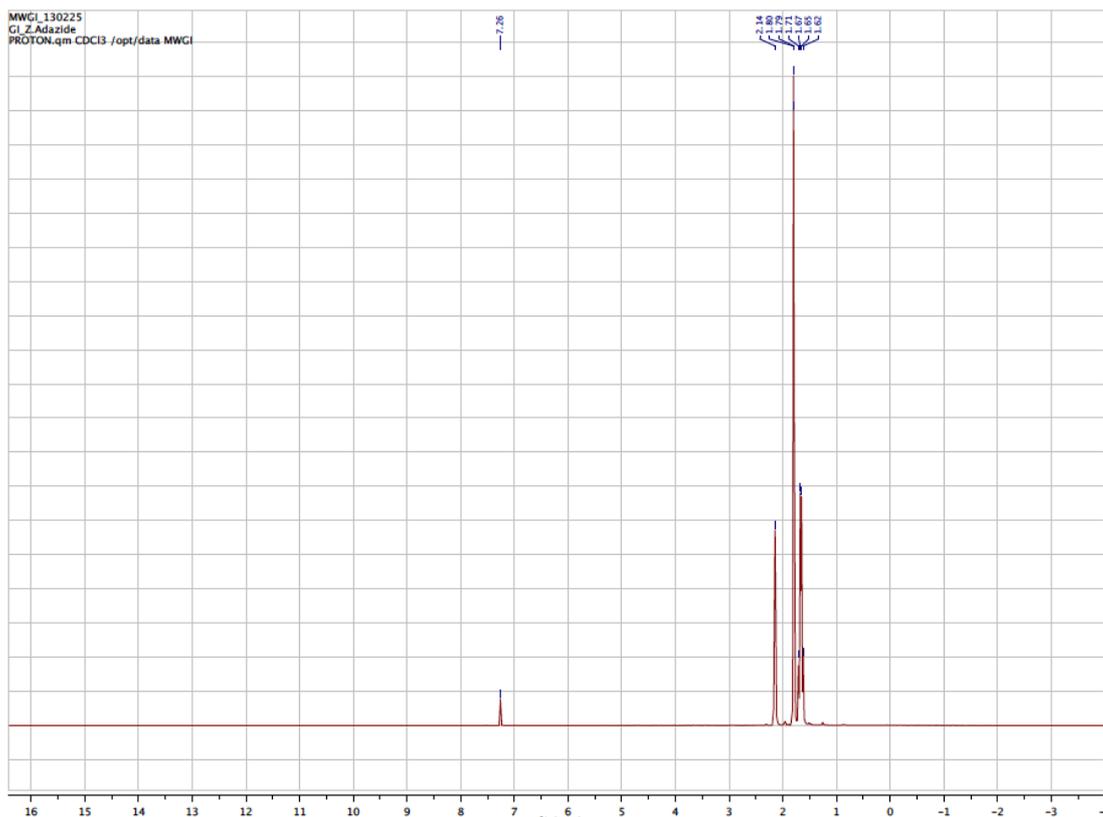
Figure ESI 24: ^1H and ^{13}C NMR spectra of **21**.

Synthesis of 1-azidoadamantane **28**:¹



CAUTION! Azides are explosive and must be treated with care.

1-Bromoadamantane (1.00 g, 4.65 mmol, 1.00 equiv.) and TMS-N₃ (0.67 mL, 5.11 mmol, 1.10 equiv.) were dissolved in anhydrous DCM (25 mL) and cooled on ice. SnCl₄ (0.55 mL, 4.69 mmol, 1.01 equiv.) was added dropwise to the reaction mixture at such a rate that the internal reaction temperature did not exceed 5 °C. After the addition was complete, the reaction mixture was allowed to stir at 0 °C for 1 h, warmed up to 25 °C and stirred for a further 16 h. Once the reaction was complete as judged by TLC, it was treated with a water-ice mixture and the product was extracted with DCM (50 mL). The aqueous phase was washed with further portions of DCM (2 x 30 mL). The organic phases were combined, washed with brine (30 mL), dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexane:DCM, 20:1) and the product was isolated as white solid (0.75g, 91%). All spectroscopic data matches those previously reported.¹



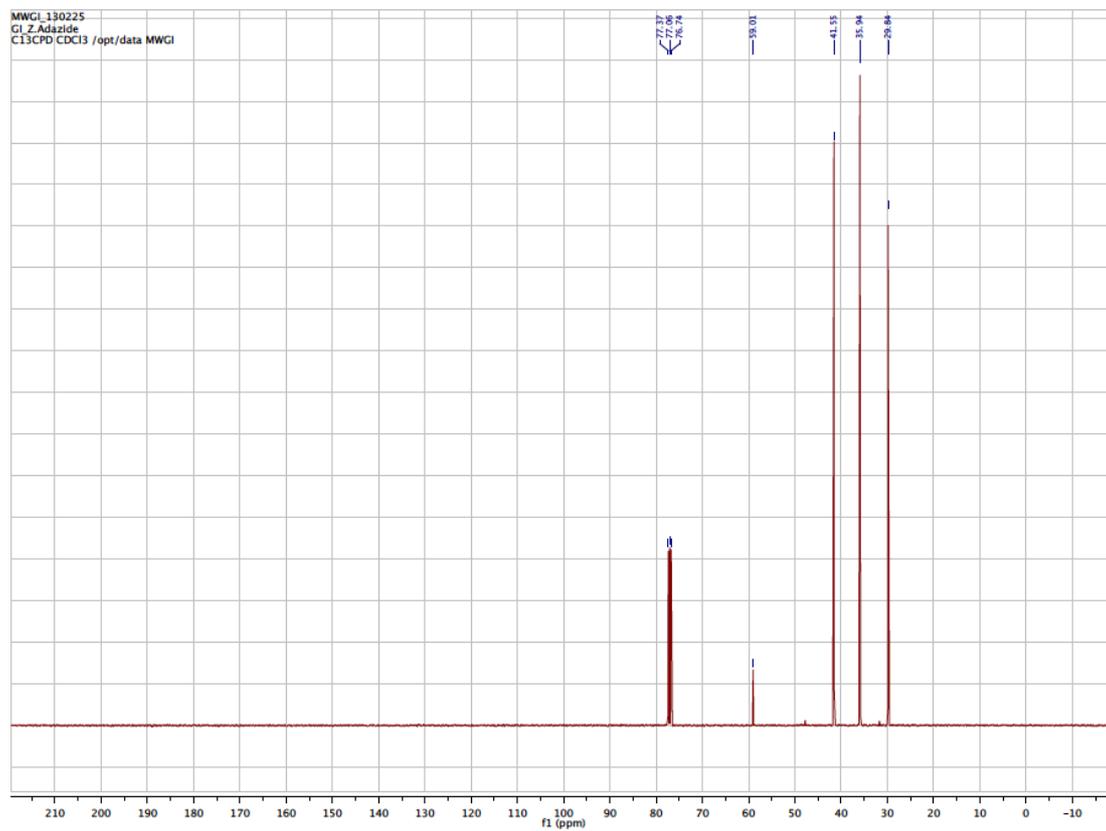
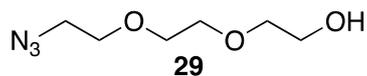
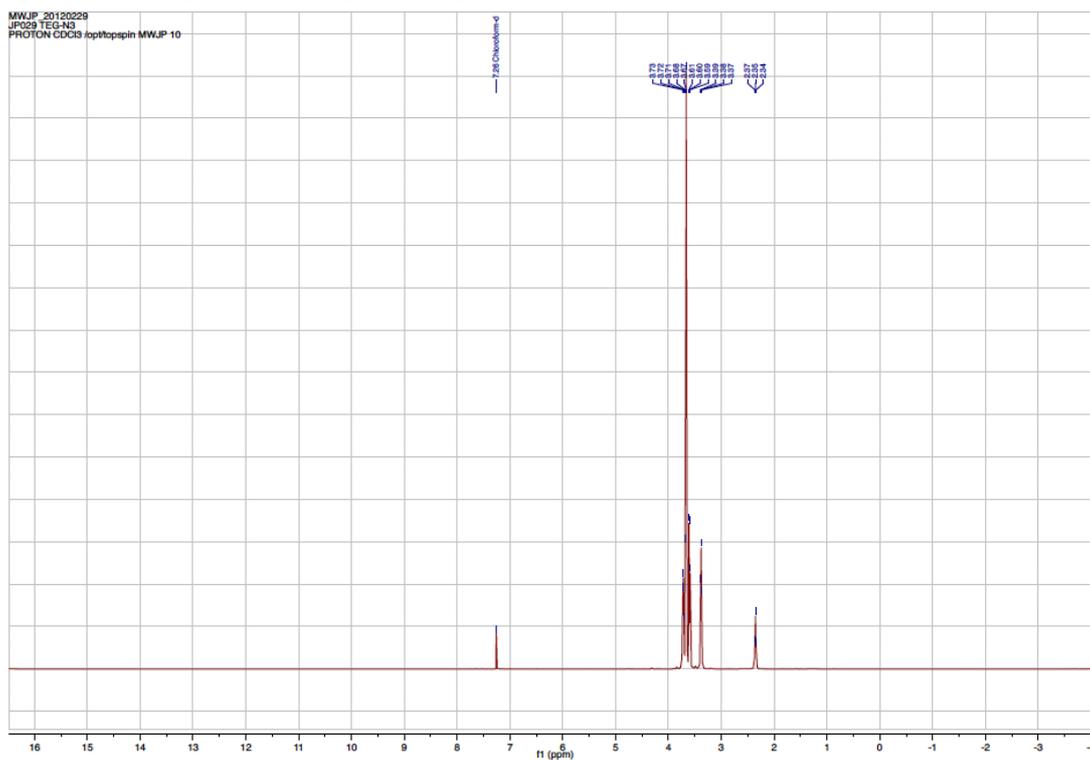


Figure ESI 25: ^1H and ^{13}C NMR spectra of **28**.

Synthesis of 2-(2-(2-azidoethoxy)ethoxy)ethanol **29**:²

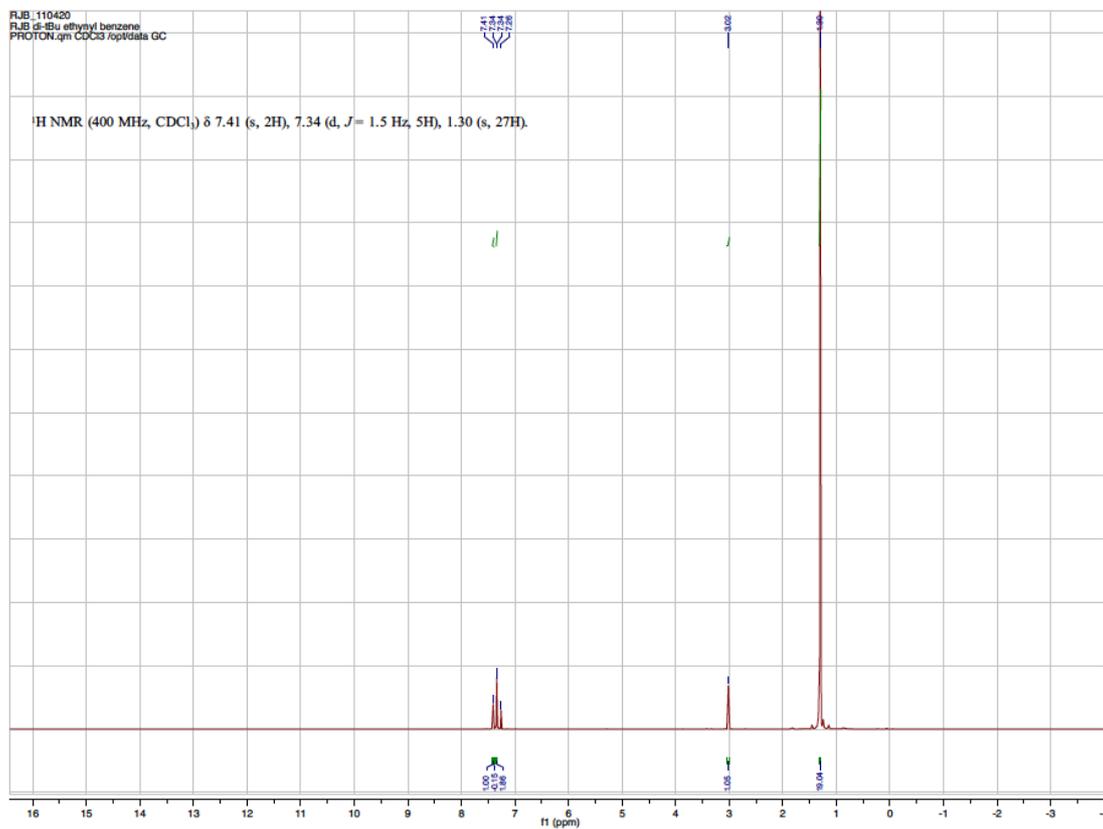
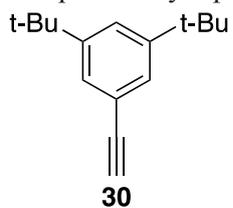


2-(2-(2-Chloroethoxy)ethoxy)ethanol **37** (2.7 g, 16 mmol) was dissolved in DMF (25 mL). NaN₃ (1.6 g, 24 mmol) was added slowly to the solution, and the reaction mixture was stirred at 100 °C for 16 h. After cooling to r.t., the flask was placed in ice, and the white precipitate removed by filtration. The filtrate was concentrated *in vacuo* to yield azide **29** as a pale yellow oil (2.4 g, 85%). All spectroscopic data obtained matched those previously reported.²



Synthesis of 3,5-di-tert-butylphenylacetylene **30**:³

Compound **30** was prepared according to a previously reported protocol.³



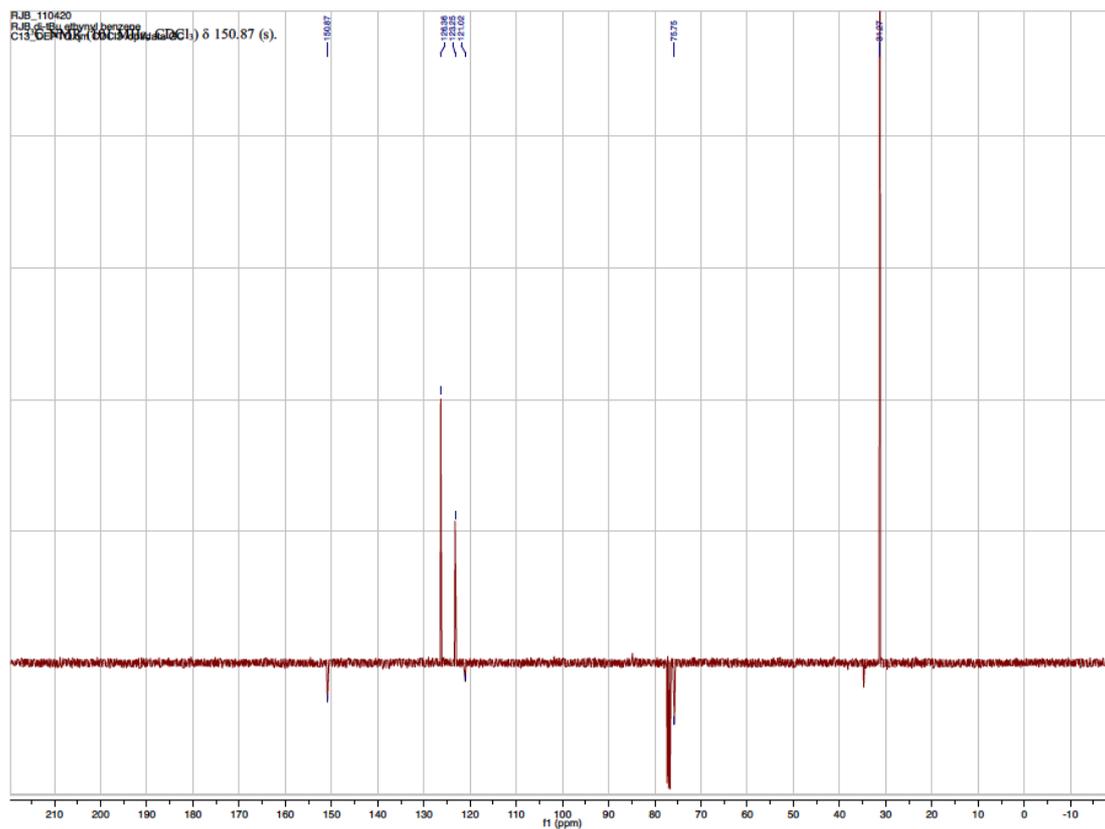


Figure ESI 27: ¹H and ¹³C NMR spectra of **30**.

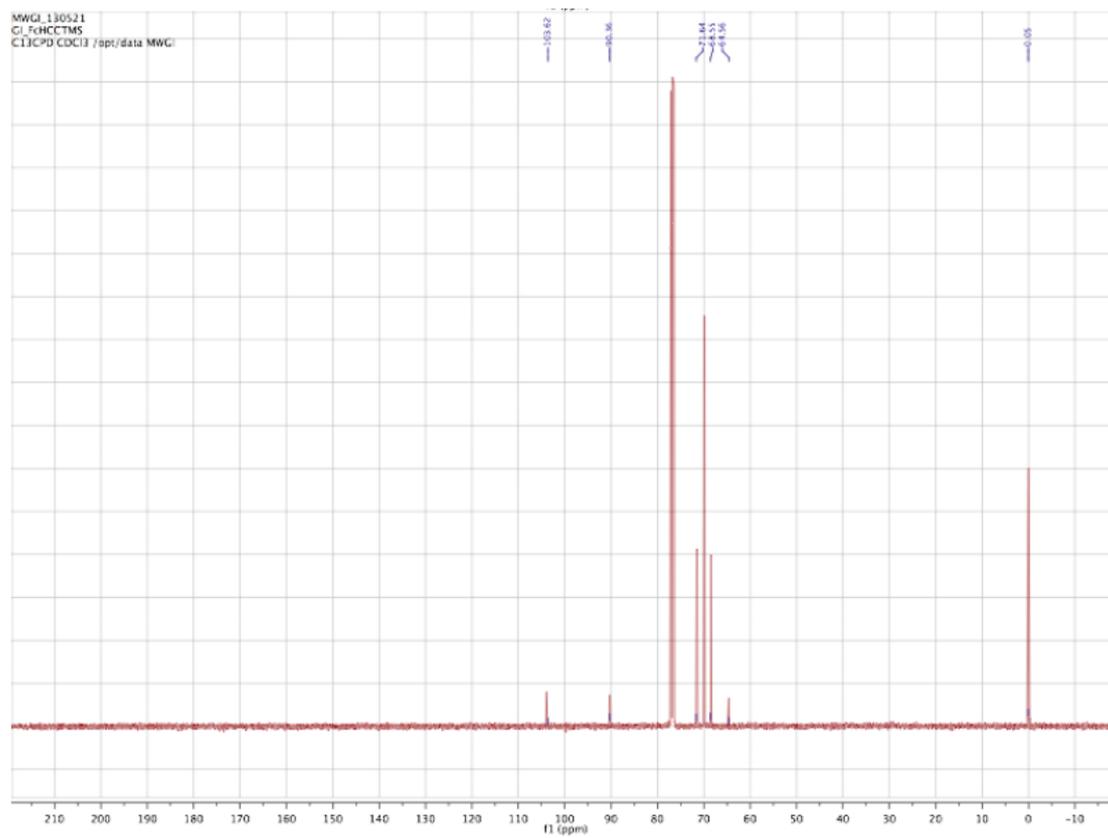
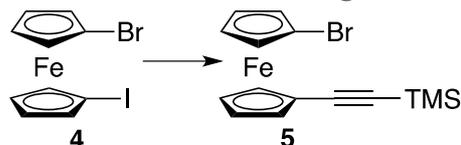


Figure ESI 28: ^1H and ^{13}C NMR spectrum of **31**.

Summary of optimisations carried out for the Sonogashira coupling:



1-Bromo-1'-iodoferrocene **4** (1.0 equiv.), Cu(I) (1-10 mol%), Pd(PPh₃)Cl₂ (0.5-10 mol%)* and an additive (1-20 mol%) were dissolved in thoroughly degassed solvent and placed under N₂. Trimethylsilylacetylene (1.5 equiv.)** was added in one portion and the reaction vessel was sealed and heated at 60-65 °C for up to 48 h. The reaction was cooled to r.t., diluted with Et₂O and filtered. The filtrate was then washed with aqueous HCl (5%), dried over MgSO₄, filtered and concentrated *in vacuo*. The product **5** was obtained following purification by flash column chromatography (1% EA in PE) as brown-red solid.

*We believe that at higher concentrations the aggregation of Pd-black causes the reaction to terminate prematurely.⁵ Reducing the catalyst's concentration and adding PPh₃ slows down the unwanted aggregation and thus the reaction proceeds to completion.

** Since the reaction is carried out above the boiling point of trimethylsilylacetylene (53 vs 60-65 °C), an excess of trimethylsilylacetylene is required to compensate for material lost in vapour phase and hence to drive the reaction to completion.

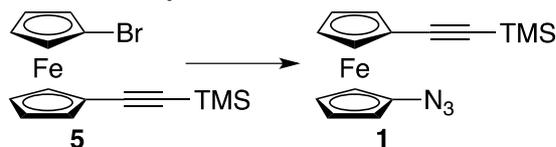
Table ESI 1: Summary of screen carried out during the optimisation of Sonogashira coupling.

Entry	Catalyst (mol%)	Cu(I) (mol%)	Additive/Ligand (mol%)	Solvent(s) (ratio)	Yield 4	Recovered 5
1	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	-	Et ₃ N:THF (1:1)	15%	70%
2	Pd(PPh ₃) ₄ (5)	CuI (10)	-	Et ₃ N:THF (1:1)	13%	80%
3	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	-	<i>i</i> Pr ₂ NH:THF (1:1)	15%	70%
4	Pd(PPh ₃) ₄ (5)	CuI (10)	-	<i>i</i> Pr ₂ NH:THF (1:1)	15%	70%
5	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	-	<i>i</i> Pr ₂ NEt:THF (1:1)	16%	70%
6	Pd(PPh ₃) ₄ (5)	CuI (10)	-	<i>i</i> Pr ₂ NEt:THF (1:1)	10%	85%
7	Pd(PPh ₃) ₂ Cl ₂ (5)	CuCl (10)	-	Et ₃ N:THF (1:1)	10%	85%
8	Pd(PPh ₃) ₂ Cl ₂ (5)	CuBr (10)	-	Et ₃ N:THF (1:1)	13%	80
9	Pd(PPh ₃) ₂ Cl ₂ (5)	CuPF ₆ (10)	-	Et ₃ N:THF (1:1)	15%	70%
10	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	-	Et ₃ N:THF (1:1)	15%	70%
11	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	-	Et ₃ N:THF (1:2)	10%	80%

12	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	-	Et ₃ N:THF (1:4)	7%	85%
13	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	-	Et ₃ N:THF (2:1)	20%	64%
14	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	-	Et ₃ N:THF (4:1)	40%	52%
15	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	DMEDA (10)	Et ₃ N:THF (4:1)	30%	61%
16	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	TMEDA (10)	Et ₃ N:THF (4:1)	15%	73%
17	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	DMDACH (10)	Et ₃ N:THF (4:1)	23%	70%
18	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	TMDACH (10)	Et ₃ N:THF (4:1)	33%	61%
19	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	Pyridine (10)	Et ₃ N:THF (4:1)	15%	70%
20	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	Bipyridine (10)	Et ₃ N:THF (4:1)	0%	97%
21	Pd(PPh ₃) ₂ Cl ₂ (5)	CuI (10)	PPh ₃ (20)	Et ₃ N:THF (4:1)	60%	33%
22	Pd(PPh ₃) ₂ Cl ₂ (1)	CuI (5)	PPh ₃ (10)	Et ₃ N:THF (4:1)	70%	22%
23	Pd(PPh ₃) ₂ Cl ₂ (0.5)	CuI (1)	PPh ₃ (2)	Et ₃ N:THF (4:1)	85%	<5%

All solvents were dried and thoroughly degassed prior to their use; the reactions were carried out under in hermetically sealed vessels for a period of up to 48 hours; the yields are all isolated; the overall mass recovery was always >90%. (DiMethylEthyleneDiAmine, TetraMethylEthyleneDiAmine, *N,N'*-DiMethylDiaminoCycloHexane, *N,N'*-TetraMethylDiaminoCycloHexane.)

Attempts to obtain azide **1** directly from bromide **5**:



Due to competitive protodeboronation we decided to investigate if bromide **5** can be directly converted to azide **1**. This would also be advantageous as it removes an extra step and reduces waste produced. Therefore, we attempted to convert **5** to **1** by using copper(I) mediated nucleophilic aromatic substitution, analogous to those previously reported.⁴ However, after numerous attempts we only managed to achieve conversions of approximately 15% and isolate less than 5% yield of material that we believe to be the azide **1**.

General procedure: NaN₃ (1.0 – 1.5 equiv.) was added to the solution of **5** (1.0 equiv.) in MeOH under inert atmosphere and the reaction vessel was wrapped in foil to exclude light. Copper salt (1 – 20 mol%) was added to the reaction mixture and it was allowed to stir at r.t. for up to 96 h. The reaction progress was monitored by TLC and ¹H NMR spectroscopy.

In general:

NaN₃ was used as the source of azide;

Copper salts CuI, CuBr, CuCl, Cu(OAc), CuPF₆, CuSO₄, CuSO₄·H₂O, Cu(OAc)₂, Cu(OAc)₂·H₂O, and Cu(PPh₃)₃Br were all screened;

DMEDA, TMEDA, DMDACH, TMDACH, pyridine, bipyridine, sodium benzoate, NaAsc, PPh₃, Et₃N, *i*-Pr₂NEt were all screened as additives or ligands;

EtOH, MeOH, THF, MeCN, NMP, DMF, H₂O and Et₃N were all screened as solvents independently and in combinations;

The reactions times were up to 96 h;

The reactions were carried out at temperatures of 25, 40, 50 and 60 °C;

The reactions were carried out between 10 mg·mL⁻¹ and 100 mg·mL⁻¹.

After extensive screening and our realisation that the azide is highly unstable we decided to continue with our original boronic acid based strategy.

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3. R. S. Stoll, M. V. Peters, A. Kuhn, S. Hecht, S. Heiles, C. M. Thiele, R. Goddard and M. Buehl, *J. Am. Chem. Soc.* 2009, **131**, 357-367.
4. A. Shafir, M. P. Power, G. D. Whitener and J. Arnold, *Organometallics*, 2000, **19**, 3978-3982.
5. A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx and J. G. de Vries, *Org. Lett.*, 2003, **5**, 3285-3288.