Electronic supplementary materials *Mendeleev Commun.*, 2024, **34**, 64–66

Synthesis of new ferrocenyl-containing tertiary alcohols, analogs of L-prolinol-based organocatalysts

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General information

NMR experiments were carried out on Bruker-Avance 400 MHz spectrometer in $CDCl_3$ using TMS as an internal reference.
Specific rotation was determined by Kruss P-8000 instrument for chloroform solutions in 5 cm cuvette.
For column chromatography silica gel (0.04 – 0.063 mm) was used.
For high resolution mass spectrometry micrOTOF instrument was used.

Ferrocenylmagnesium bromide **3'a**

A few drops of 1,2-dibromoethane were added to a mixture of magnesium (0.50 g; 20.6 mmol) and ether (10 ml). The solvent was brought to boil in argon purge. A solution of bromoferrocene **3** (1.66 g; 6.25 mmol) and 1,2-dibromoethane (2.35 g; 12.5 mmol) in ether (20 ml) was added by drops to boiling mixture for 40 min with stirring. Then the reaction mixture was refluxed for 2 h and cooled to ambient temperature. The resulting solution was used in subsequent reactions.
Yield of organomagnesium compound **3'a** was determined by carboxylation with dry ice. After purification with column chromatography (eluent – a 9:1 mixture of dichloromethane and methanol), ferrocenecarboxylic acid **4a** (1.18 g; 82%) was obtained.
^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 4.27 (s., 5 H, C_5H_5), 4.48 (m., 2 H, C_5H_4), 4.87 (m., 2 H, C_5H_4); 11.03 (br, 1 H, COOH); *cf.*[S1]

4-Ferrocenylphenylmagnesium bromide **3'b**

Magnesium (0.23 g; 9.4 mmol) was activated by gentle heating with small crystal of iodine. THF (10 ml) was added, and the mixture was brought to boil in argon purge. A solution of 4-bromophenylferrocene **3b** (2.13 g; 6.25 mmol) in THF (20 ml) was added for 40 min by drops with stirring. Then the reaction mixture was refluxed for 4 h and cooled to ambient temperature. The resulting solution was used in subsequent reactions.
Yield of organomagnesium compound **3'b** was determined by carboxylation with dry ice. After purification with column chromatography (eluent – a 9:1 mixture of dichloromethane and methanol) 4-ferrocenylbenzoic acid **4b** (1.76 g; 92%) was obtained.
^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 4.02 (s, 5 H, C_5H_5), 4.42 (m, 2 H, C_5H_4), 4.88 (m, 2 H, C_5H_4), 7.72 (m, 4 H, C_6H_4), *cf.*[S2]

N-tert-Butoxycarbonyl-L-proline methyl ester **2** was synthesized from L-proline with 75% yield according to a published procedure.[S3]
^{1}H NMR (mixture of *Z*- and *E*-amides, *major* : *minor* = 3 : 2; $CDCl_3$, 400 MHz, δ, ppm): 1.41 (s, *t*-Bu, *major*), 1.46 (s, *t*-Bu, *minor*), 1.91 (m, 3 H, pyrr), 2.20 (m, 1 H, pyrr), 3.47 (m, 2 H, pyrr), 3.72 (s, OMe, *major*), 3.73 (s, OMe, *minor*), 4.22 (dd, ^{3}J = 8.5 Hz, ^{3}J = 4.2 Hz, N-C*H*, *major*), 4.32 (dd, ^{3}J = 8.5 Hz, ^{3}J = 3.3 Hz, N-C*H*, *minor*); *cf.*[S4]

[(S)-N-tert-Butoxycarbonylpyrrolidin-2-yl](diferrocenyl)methanol **5a**

A solution of *N-tert*-butoxycarbonyl-L-proline methyl ester **2** (0.57 g.; 2.5 mmol) in ether (20 ml) was added for 1 h by drops with a vigorous stirring to a solution of ferrocenylmagnesium bromide **3'a** prepared as described above from 1.66 g of bromoferrocene **3a**. The reaction mixture was stirred for additional 4 h. Then water (5 ml) was added. The organic layer was separated, and the water layer was extracted with ethyl acetate. The combined organic solutions were dried over Na_2SO_4, and solvent was removed on rotor evaporator. The residue was subjected to column chromatography. First yellow-orange band was eluted with dichloromethane and discarded. By elution with a mixture of dichloromethane and methanol (50:1) an intensive orange second band was collected. After removal of the solvent, product **5a** (0.85 g; 60%) was obtained as a yellow solid, m. p. 187-189°C with decomp.
^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.68 (m, 1 H, pyrr), 1.37 (m, 1 H, pyrr), 1.53 (s, 9 H, *t*-Bu), 1.75 (m, 1 H, pyrr), 1.97 (m, 1 H, pyrr), 2.95 (m, 1 H, pyrr). 3.25 (m, 1 H, pyrr), 3.57 (br, 1 H, O*H*), 3.95 (m, 1 H, C_5H_4), 4.04 (m, 1 H, C_5H_4), 4.06 (m, 1 H, C_5H_4), 4.09 (s, 5 H, C_5H_5), 4.18 (m, 1 H, C_5H_4), 4.26 (m, 1 H, C_5H_4), 4.33 (m, 1 H, C_5H_4), 4,38 (s, 5 H, C_5H_5), 4.71 (m, 1 H, C_5H_4), 4.88 (m, 1 H, N-C*H*), 5.30 (m, 1 H, C_5H_4).
^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, δ, ppm): 23.27, 28.59, 28.97, 47.39, 65.91, 66.45, 66.85, 66.89, 67.04, 67.25, 68.55, 68.63, 68.73, 68.82, 76.04, 77.19, 80.12, 158.69.
ESI-HRMS: calculated for $C_{30}H_{35}Fe_2NO_3$ (M^+) 569.1316; found 569.1314.
$[\alpha]_D^{20}$: +262 deg g^{-1} (*c* 5×10^{-3} g ml^{-1}, $CHCl_3$).

[(S)-N-Methylpyrrolidin-2-yl]-diferrocenylmethanol **6a**

To a solution of [(*S*)-N-*tert*-butoxycarbonylpyrrolidine-2-yl](diferrocenyl)methanol **5a** (0.57 g; 1.0 mmol) in ether (50 ml) in argon purge, lithium aluminium hydride (0.15 g; 4.0 mmol) was added in one portion with stirring. The reaction mixture was refluxed for 3 h, then was cooled to 0°C, and water (0.15 ml) was added by drops with stirring. Then 15% NaOH (0.15 ml) and water (0.45 ml) were added subsequently. The precipitate was filtered off and washed with ether. The combined ether extracts were dried over Na_2SO_4, and solvent was removed on rotor evaporator. The residue was purified by flash chromatography in a short column. The first band was eluted with benzene – ethyl acetate (8:1) mixture and discarded. Subsequent elution with benzene – ethyl acetate – triethylamine 8:1:0.5 mixture gave a yellow-orange band. The solvent was evaporated *in vacuo.* Hexane was added to the residue and again evaporated for removal the benzene traces. Product **6a** (0.36 g; 74%) was obtained as an orange solid, m. p. 137-139°C.

^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.87 (m, 1 H, pyrr), 1.38 (m, 2 H, pyrr), 1.83 (m, 1 H, pyrr), 2.25 (m, 1 H, pyrr), 2.69 (s, 3 H, NMe), 2.90 (m, 1 H, pyrr), 3.44 (m, 2H, pyrr, C_5H_4), 3.92 (m, 1 H, C_5H_4), 4.03 (m, 2 H, C_5H_4), 4.13 (s, 5 H, C_5H_5), 4.16 (m, 1 H, C_5H_4), 4.26 (m, 6 H, C_5H_4, C_5H_5), 4.38 (m, 1 H, C_5H_4), 4.56 (m, 1 H, C_5H_4).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, δ, ppm): 25.25, 29.67, 47.00, 57.48, 66.47, 66.62, 66.73, 67.08, 67.68, 68.72, 68.83, 70.00, 70.10, 70.74, 71.58, 74.31, 74.85 96.49.

ESI-HRMS: calculated for $C_{26}H_{30}Fe_2NO^+$ (MH^+) 484.1021; found 484.1024.

$[\alpha]_D^{20}$: +145.6 deg g^{-1} (*c* 5×10^{-3} g ml^{-1}, $CHCl_3$).

[(S)-N-tert-Butoxycarbonylpyrrolidin-2-yl]bis(4-ferrocenylphenyl)methanol **5b**

A solution of N-*tert*-butoxycarbonyl-L-proline methyl ester **2** (0.57 g; 2.5 mmol) in THF (20 ml) was added by drops for 1 h with a good stirring to a solution of 4-ferrocenylphenylmagnesium bromide **3'b** prepared as described above from 4-bromophenylferrocene **3b** (2.13 g). The reaction mixture was stirred for additional 4 h. Then water (5 ml) was added. THF was removed under reduced pressure, and the residue was extracted with ethyl acetate. The combined organic solutions were dried over Na_2SO_4 and solvent was removed on rotor evaporator. The residue was subjected to column chromatography. The first band was eluted with benzene and discarded. Then an elution with a mixture of benzene and ethyl acetate (8:1) gave an intensive orange band which was collected. After removal of the solvent, 1.53 g (85%) of product **5b** was obtained as an orange crystalline substance, decomp. >180°C.

^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 0.91 (m, 1 H, pyrr), 1.50 (m, 10 H, *t*-Bu, pyrr), 1.95 (m, 1 H, pyrr), 2.13 (m, 1 H, pyrr), 2.96 (m, 1 H, pyrr), 3.38 (m, 1 H, pyrr), 4.04 (s, 5 H, C_5H_5), 4.07 (s, 5 H, C_5H_5), 4.33 (m, 4 H, C_5H_4), 4.67 (m, 4 H, C_5H_4), 4.91 (m, 1 H, N-C*H*), 6.60 (br, 1 H, O*H*), 7.41 (m, 8 H, C_6H_4).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, δ, ppm): 23.08, 25.61, 28.55, 30.01, 30.22, 48.04, 66.42, 66.53, 66.60, 66.6, 68.69, 69.09, 69.72, 69.76, 80.75, 81.69, 84.97, 85.27, 125.00, 125.71, 127.78, 128.31, 137.99, 138.6, 141.37, 144.08, 166.19.

ESI-HRMS: calculated for $C_{42}H_{43}Fe_2NO_3$ (M^+) 721.1942; found 721.1935.

$[\alpha]_D^{20}$: –52,5 deg/g (c 5×10^{-3} g/ml, $CHCl_3$).

[(S)-N-Methylpyrrolidin-2-yl]bis(4-ferrocenylphenyl)methanol **6b**

To a solution of [(*S*)-N-*tert*-butoxycarbonylpyrrolidine-2-yl]bis(4-ferrocenylphenyl)methanol **5b** (0.48 g; 0.66 mmol) in THF (25 ml), lithium aluminium hydride (0.13 g; 3.3 mmol) was added by one portion in argon purge. The reaction mixture was refluxed for 4 h, then was cooled to 0°C, and water (0.15 ml) was added by drops with stirring. Then 15% NaOH (0.15 ml) and water (0.45 ml) were added subsequently. The precipitate was filtered off and washed with dichloromethane. The combined organic extracts were dried over Na_2SO_4 and the solvent was removed on rotor evaporator. The residue was purified by flash chromatography in a short column. The first band was eluted with benzene – ethyl acetate (10:1) mixture and discarded. Then an elution with 10:1:0.5 mixture of benzene – ethyl acetate – triethylamine gave a yellow-orange band which was collected. After evaporation of the solvent, hexane was added to the residue and evaporated again for removal of benzene. Product **6b** (0.24 g; 60%) was obtained as an orange solid, decomp. >204°C.

^{1}H NMR ($CDCl_3$, 400 MHz, δ, ppm): 1.70 (m, 3 H, pyrr), 1.86 (s, 3 H, NMe), 1.93 (m, 1 H, pyrr), 2.44 (m, 1 H, pyrr), 3.11 (m, 1 H, pyrr), 3.58 (m, 1 H, pyrr), 3.97 (s, 5 H, C_5H_5), 4.00 (s, 5 H, C_5H_5), 4.26 (m, 4 H, C_5H_4), 4.57 (m, 2 H, C_5H_4), 4.59 (m, 2 H, C_5H_4), 4.72 (br, 1 H, O*H*), 7.39 (m, 4 H, C_6H_4), 7.46 (m, 2 H, C_6H_4), 7.54 (m, 2 H, C_6H_4).

^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz, δ, ppm): 24.32, 30.00, 43.18, 59.35, 66.42, 66.51, 66.60, 68.83, 68.91, 69.65, 69.69, 72.23, 77.66, 85.25, 85.57, 125.62, 125.67, 125.82, 126.00, 128.47, 137.02, 144.36, 146.02.

ESI-HRMS: calculated for $C_{38}H_{38}Fe_2NO^+$ (MH^+) 636.1647; found 636.1646.

$[\alpha]_D^{20}$: –0.8 deg g^{-1} (*c* 5×10^{-3} g ml^{-1}, $CHCl_3$).

References

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[S4] F. Yuste, B. Ortiz, A. Carrasco, M. Peralta, L. Quintero, R. Sánchez-Obregón, F. Walls and J. L. García Ruano, *Tetrahedron: Asymmetry*, 2000, **11**, 3079.

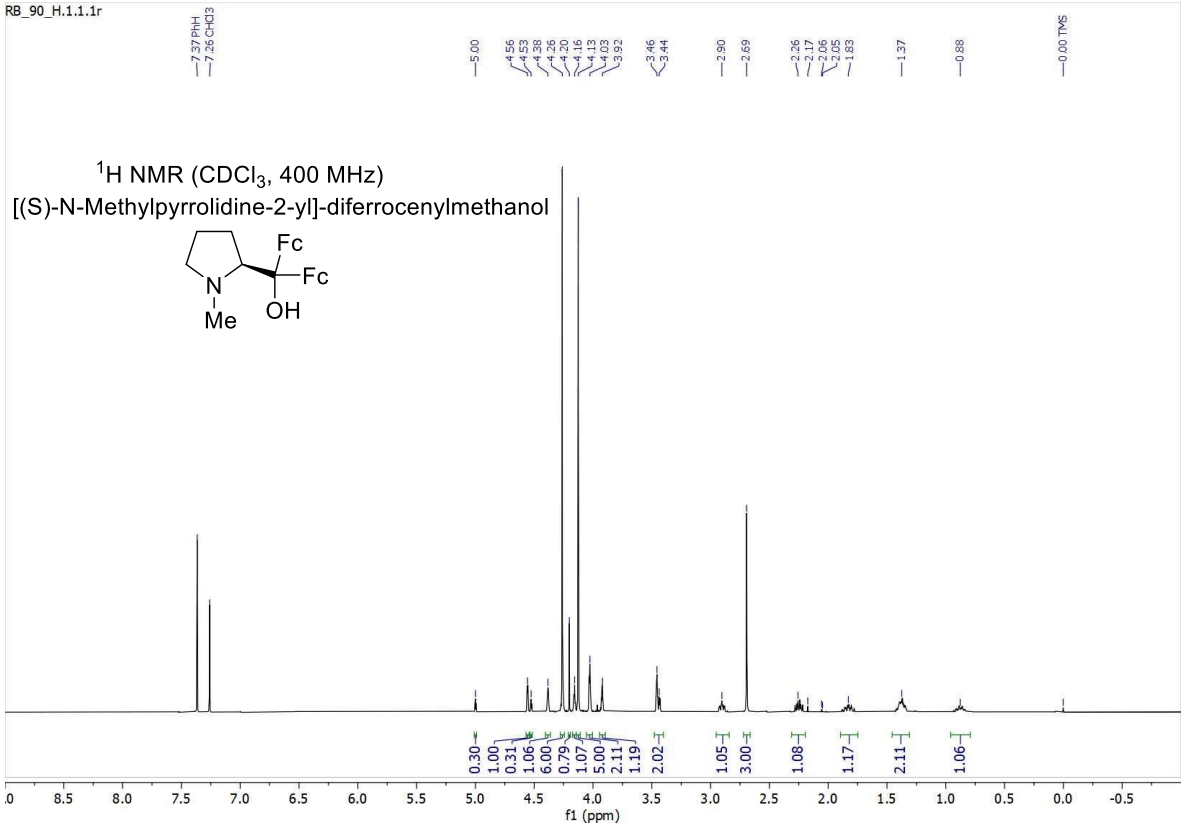

Figure. S1. ^{1}H NMR Spectrum of [(*S*)-*N*-methylpyrrolidine-2-yl]di(ferrocenyl)methanol (**6a**).

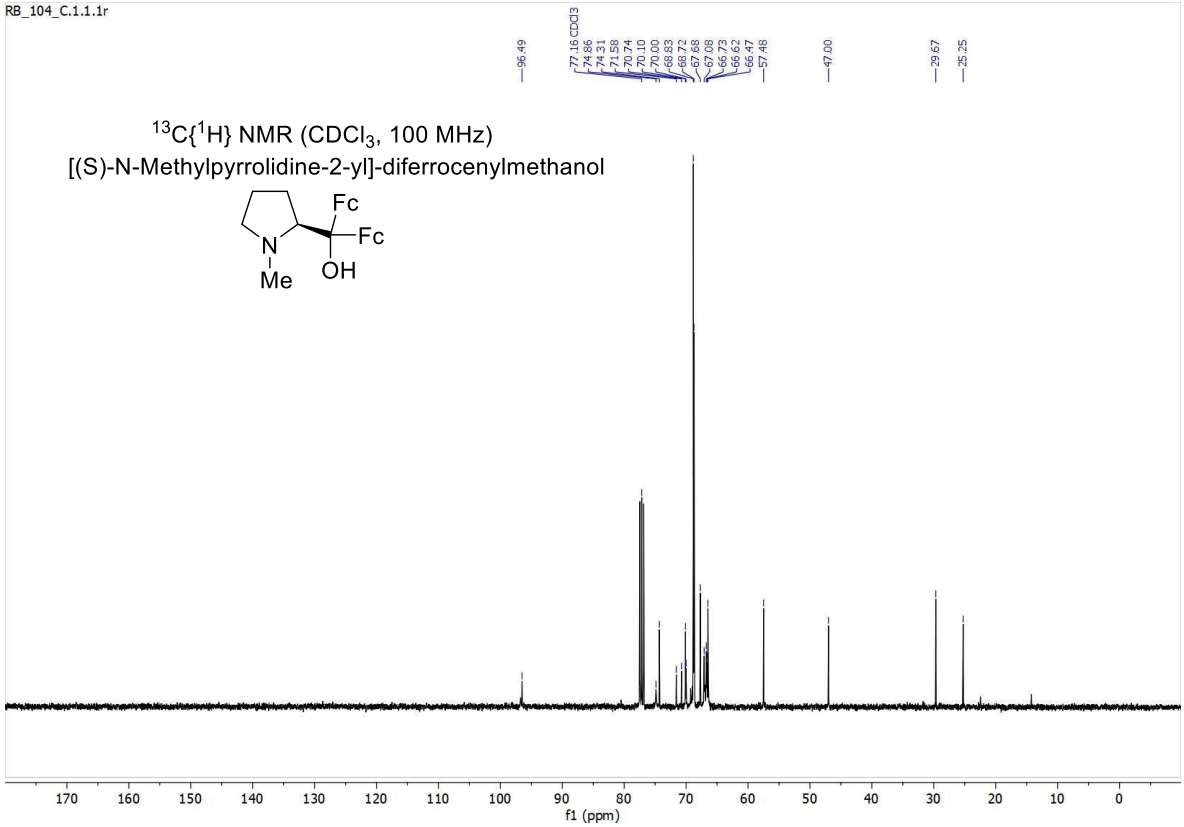

Figure S2. ^{13}C{^{1}H} NMR Spectrum of [(*S*)-*N*-methylpyrrolidine-2-yl]di(ferrocenyl)methanol (**6a**).

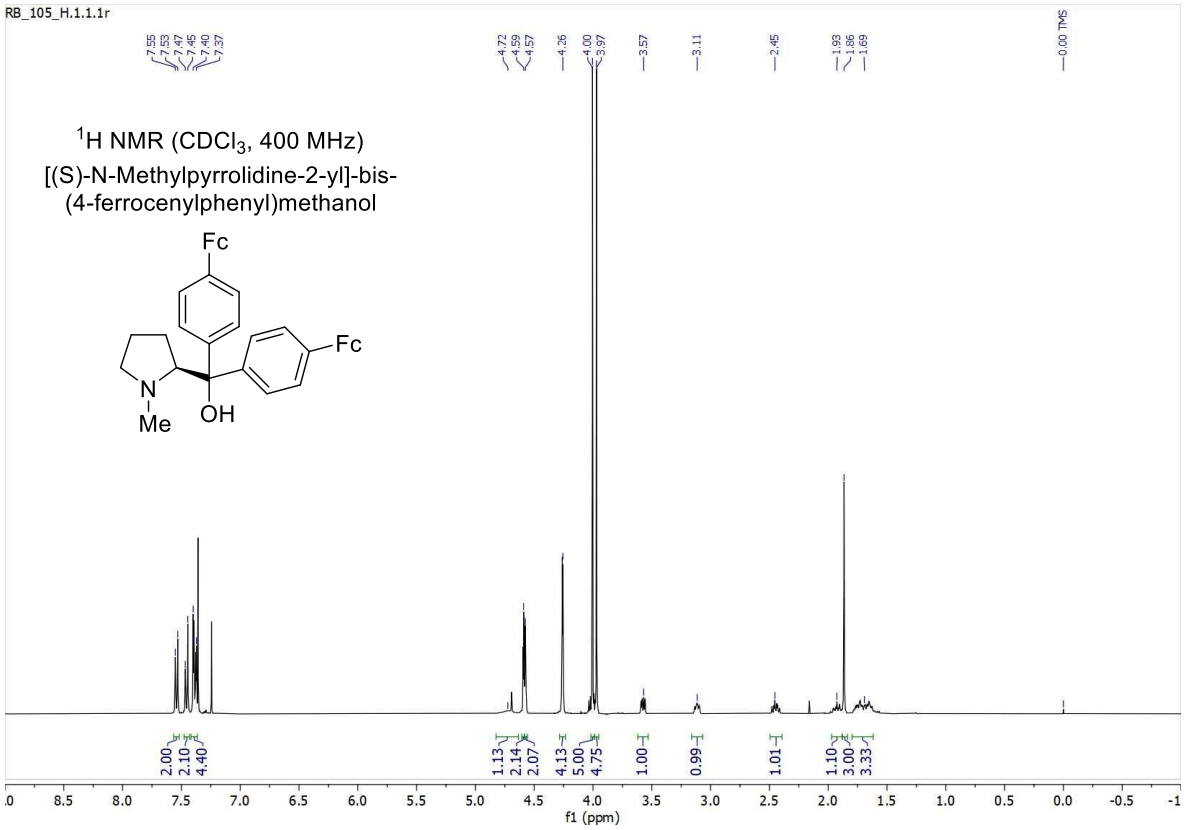

Figure S3. ^{1}H NMR Specrum of [(*S*)-*N*-methylpyrrolidine-2-yl]bis(4-ferrocenylphenyl)methanol **6b**.

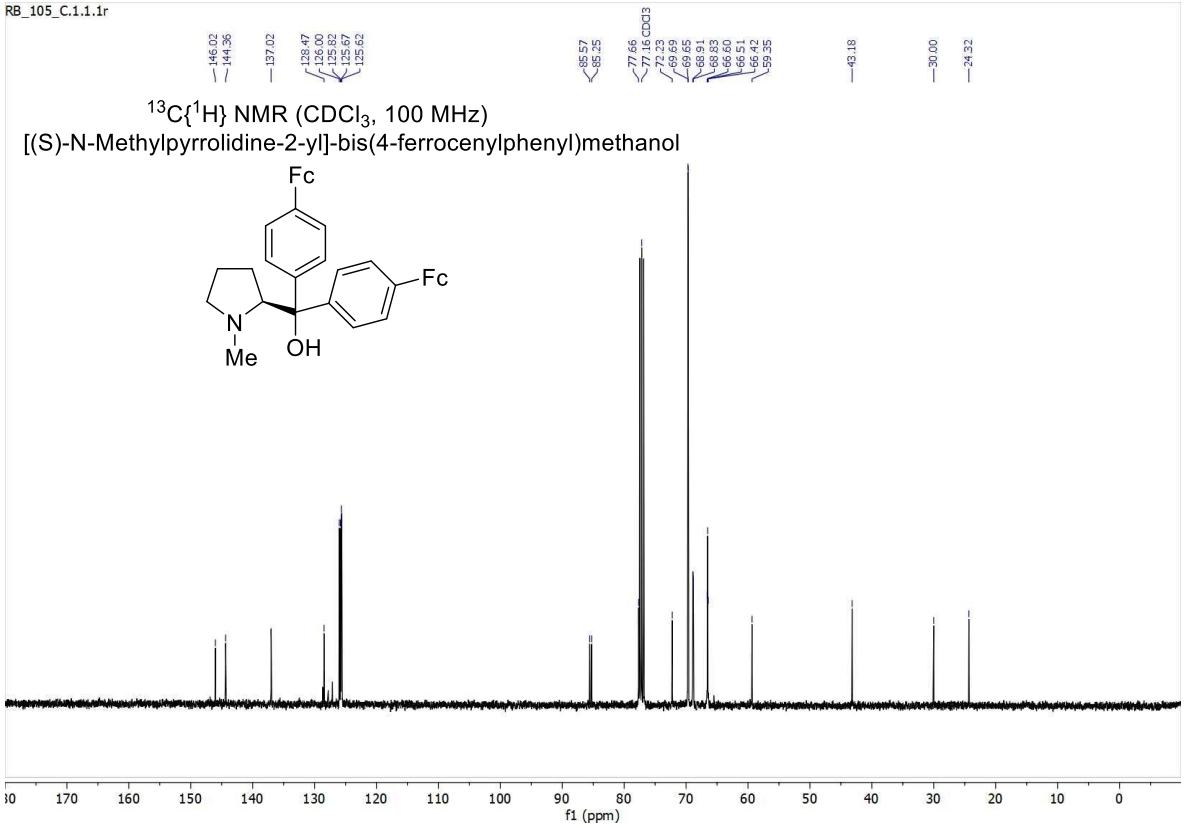

Figure S4. ^{13}C{^{1}H} NMR Specrum of [(*S*)-*N*-methylpyrrolidine-2-yl]bis(4-ferrocenylphenyl)methanol **6b**.