Synthesis

Reviews and Full Papers in Chemical Synthesis

Supporting Information

for DOI: 10.1055/s-0042-1751393

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Thieme

Supporting Information

Simplified Synthesis of Air-stable Copper-complexed Josiphos Ligand via Ugi's Amine: Complete Preparation and Analysis from Ferrocene

Emma C. Murphy, Jeffrey S. Johnson[†]

[†]Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States
jsj@unc.edu

Table of Contents

General Information

General Methods: Unless otherwise stated, all reactions were carried out open to air. Thin layer chromatography (TLC) was performed on Sorbent Technologies 0.20 mm Silica Gel TLC plates. Visualization was accomplished using UV light and either $KMnO_4$ solution or cerium ammonium molybdate (CAM) stain. Flash chromatography was performed under positive air pressure using Siliaflash-P60 silica gel (40-63 µm) purchased from Silicycle.

Instrumentation and Data Acquisition: Proton (^1H) magnetic resonance spectra were obtained on Bruker NEO Avance 400 MHz or Bruker NEO Avance 600 MHz instruments, using solvent resonances for internal chemical shift calibration (^1H NMR: $CDCl_3$ at δ 7.26 ppm, D_2O at δ 4.79 ppm).

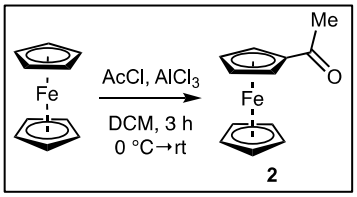
Data Reporting: The following format is used for the presentation of ^1H NMR spectroscopic data: magnet strength, analysis solvent, chemical shift (ppm), multiplicity (s = singlet, br s = broad singlet, app s = apparent singlet, d = doublet, bd = broad doublet, t = triplet, app t = apparent triplet, q = quartet, app q = apparent quartet, dd = doublet of doublets, td = triplet of doublets, app td = apparent triplet of doublets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, app ddt = apparent doublet of doublet of triplets, dddd = doublet of doublet of doublet of doublets, m = multiplet), *J*-coupling constants (Hz), and integration.

Materials: Unless otherwise stated, technical grade solvents were used as received. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O), methylene chloride (CH_2Cl_2), toluene (PhMe), and triethylamine (TEA, NEt_3) were obtained by passage of the respective solvents through a neutral alumina column under nitrogen. Solvent ratios are reported as volume ratios.

Ferrocene (Sigma), aluminum chloride (Sigma), acetyl chloride (Sigma), Red-Al (60 wt% in toluene) (Sigma), dimethylamine (40 wt% in H_2O) (Sigma), *L*-(+)-tartartic acid (Sigma), and *L*-(+)-mandelic acid (Oakwood) were obtained from commercial sources and used as received.

Synthesis of racemic Ugi's amine

Acetylferrocene (**2**)



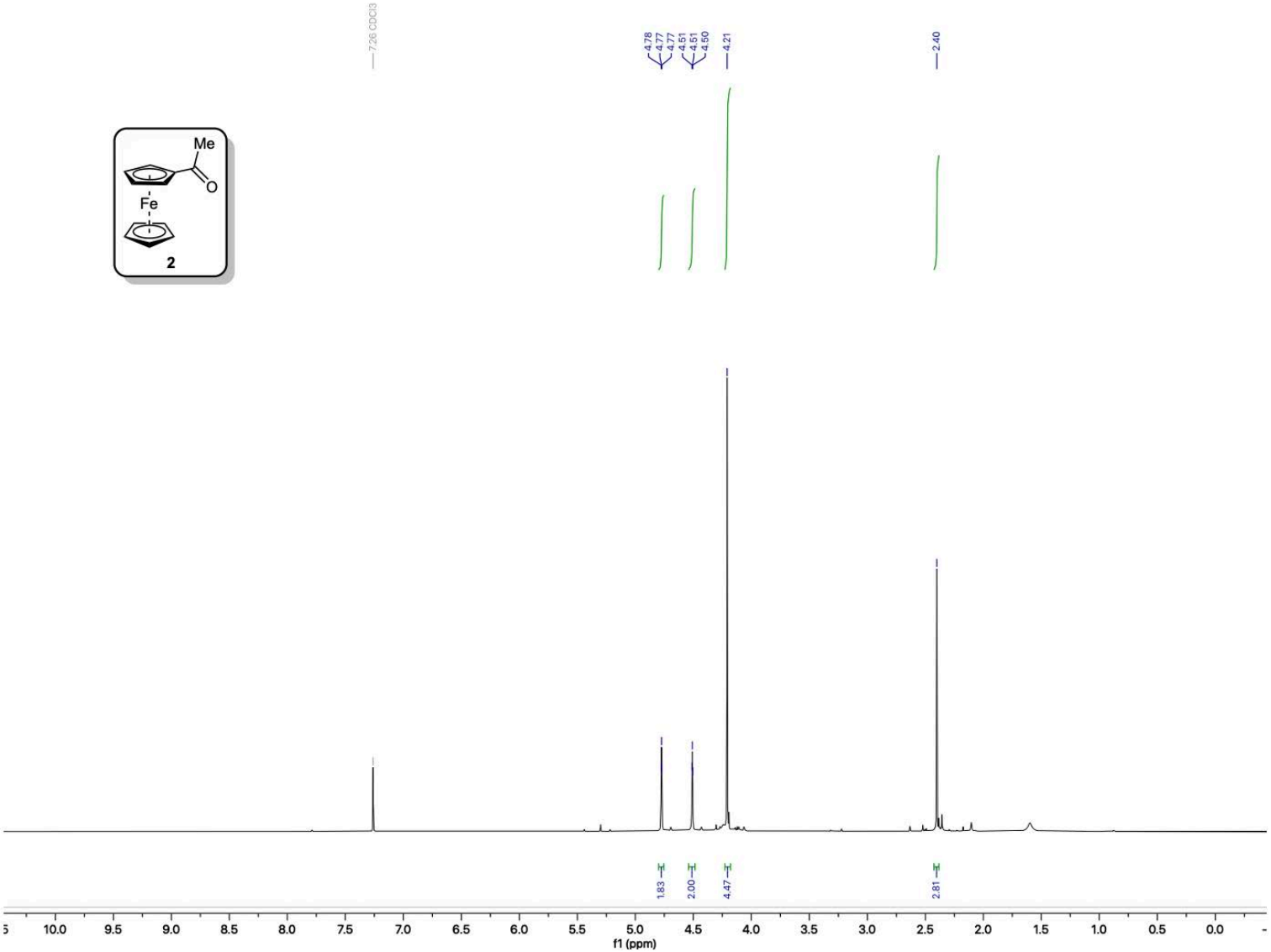
A flame-dried 2 L round-bottomed flask was taken into a glovebox and charged with aluminum chloride (25.8 g, 1.2 equiv., 193.5 mmol) and anhydrous DCM (350 mL, [$AlCl_3$] = 0.55 M) under N_2. The resulting mixture was cooled to 0 °C. In a separate flame-dried 500 mL round-bottomed flask equipped with a stir bar, ferrocene (30.00 g, 1.0 equiv., 161.3 mmol) was dissolved in anhydrous DCM (350 mL, [ferrocene] = 0.45 M) under N_2. The ferrocene solution was added via cannula transfer to the round-bottomed flask containing aluminum chloride. Acetyl chloride (5.06 g, 4.59 mL, 1.2 equiv., 64.5 mmol) was added dropwise and the solution was allowed to warm to room temperature and stirred for 3 h. The reaction was then cooled to 0 °C and ice water (400 mL) was slowly added, resulting in an exotherm. The biphasic mixture was allowed to warm to room temperature and transferred to a separation funnel. The aqueous layer was extracted with DCM (3 x 200 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the volatiles removed under vacuum to afford acetylferrocene (**2**, 30.73 g, 134.7 mmol, 84% yield). ^{1}H NMR data matched those reported in the literature.[1]

Physicochemical Properties

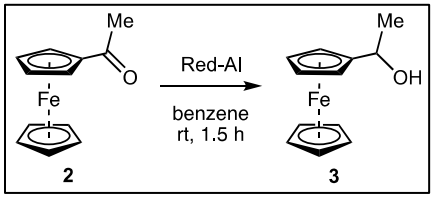
Brown solid

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.77 (t, *J* = 2.0 Hz, 2H), 4.50 (t, *J* = 2.0 Hz, 2H), 4.20 (s, 5H), 2.40 (s, 3H).

Compound **2** (^{1}H NMR, 600 MHz, $CDCl_3$)



1-ferrocenylethanol (**3**)



A flame-dried two-necked 500 mL round-bottomed flask, equipped with an addition funnel and stir bar, was charged with acetylferrocene (**2**, 25.81 g, 1 equiv, 113.2 mmol) and anhydrous benzene (165 mL, [**2**] = 0.8 M) under N_2. Red-Al (60% in toluene, 20.97 g, 20.30 mL, 0.55 equiv, 62.24 mmol) was syringed into the addition funnel, then benzene (20 mL, [Red-Al] = 0.7 M) was added via syringe. The solution was slowly added to the round-bottomed flask via addition funnel, resulting in the evolution of H_2. The reaction was stirred for 1.5 h at room temperature, monitored by TLC (20% EtOAc/hexanes). Under N_2, EtOAc (4 mL) was added dropwise via syringe, followed by the slow addition of saturated aqueous NH_4Cl (120 mL) via syringe. The biphasic mixture was transferred to a separation funnel and the aqueous phase was extracted with Et_2O (3x100 mL). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and the volatiles removed under vacuum. The resulting oil was purified via column chromatography (20% EtOAc/hexanes) to afford 1-ferrocenylethanol (**3**, 10.13 g, 44.0 mmol, 39% yield). ^{1}H NMR data matched those reported in the literature.[1]

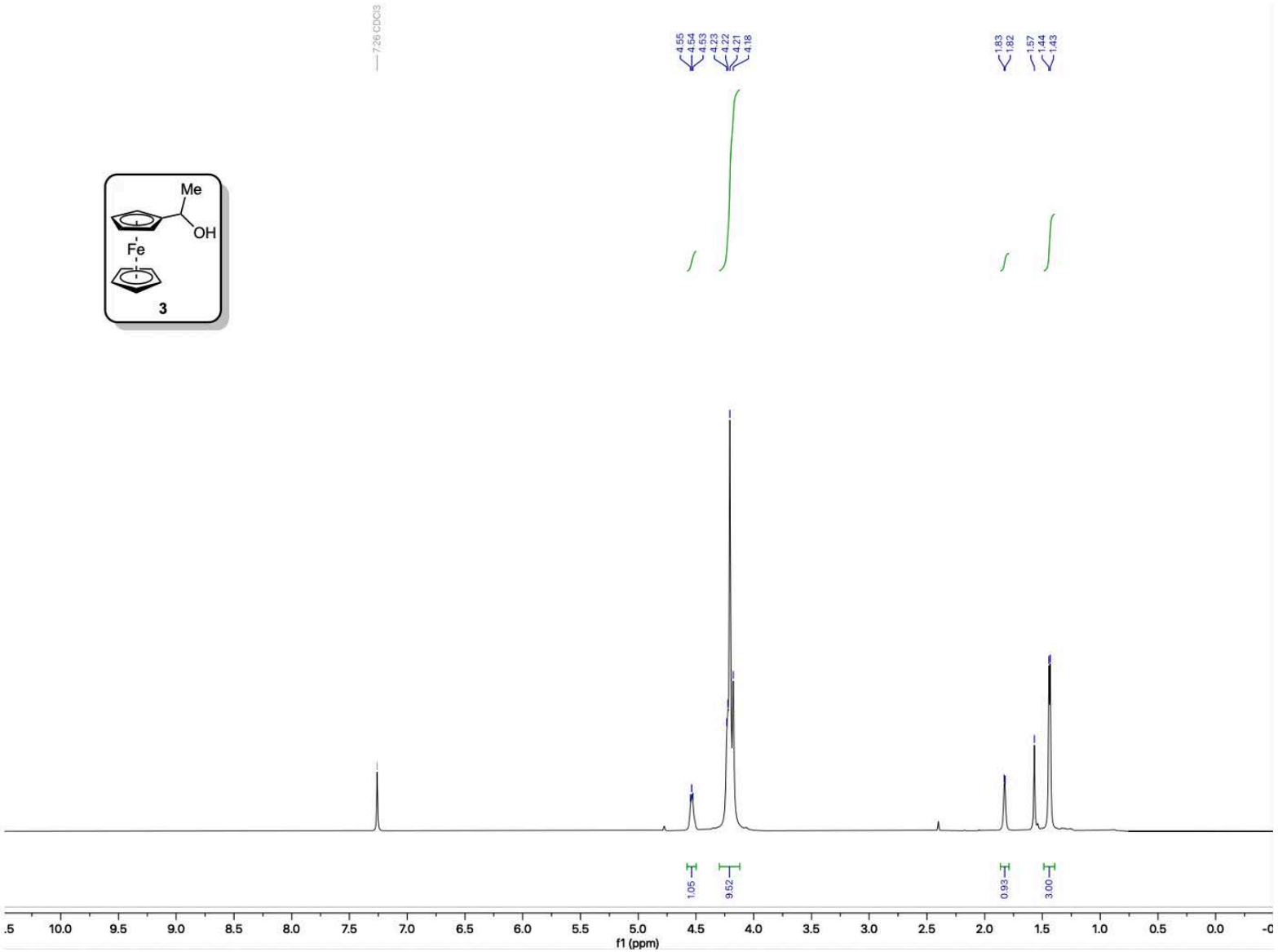
Physicochemical Properties

Orange solid

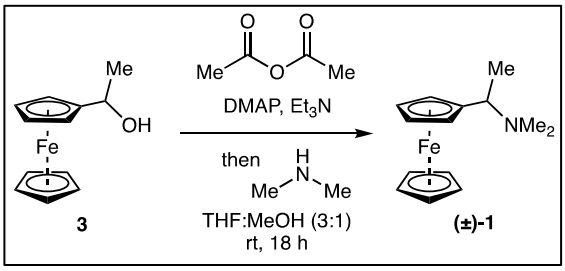
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.54 (q, *J* = 6.2 Hz, 1H), 4.20 (m, 9H), 1.82 (br s, 1H), 1.44 (d, *J* = 6.4 Hz, 3H).

TLC (20% EtOAc/hexanes) 0.25.

Compound **3** (^{1}H NMR, 600 MHz, $CDCl_3$)



[1-(dimethylamino)ethyl]ferrocene ((±)-**1**, “Ugi’s amine”)



To a two-necked 2 L round-bottomed flask equipped with an addition funnel and stir bar, 1-ferrocenylethanol (**3**, 10.13 g, 1 equiv, 44.0 mmol) and NEt_3 (7.5 mL) were added. DMAP (0.323 g, 0.06 equiv, 2.64 mmol) was added in one portion, followed by the addition of acetic anhydride (44.95 g, 41.6 mL, 10 equiv, 440.3 mmol), and the mixture was stirred at room temperature and was monitored by TLC (50% EtOAc/hexanes). Upon consumption of the starting material, THF:MeOH (3:1, 275 mL, [**3**] = 0.16 M) was added, and dimethylamine (40% in H_2O, 99.26 g, 41.6 mL, 880.5 mmol, 20 equiv) was added via dropwise addition funnel to prevent exotherm. The reaction was stirred overnight at room temperature. Et_2O (100 mL) and water (100 mL) were added, both in one portion, and the biphasic mixture was transferred to a separation funnel. The aqueous layer was extracted with Et_2O (3x100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the volatiles removed under vacuum. The crude product was purified via column chromatography (2% NEt_3 in 50% EtOAc/hexanes) to afford Ugi’s amine ((±)-**1,** 11.22 g, 43.63 mmol, 99% yield). ^{1}H NMR data matched those reported in the literature.[1]

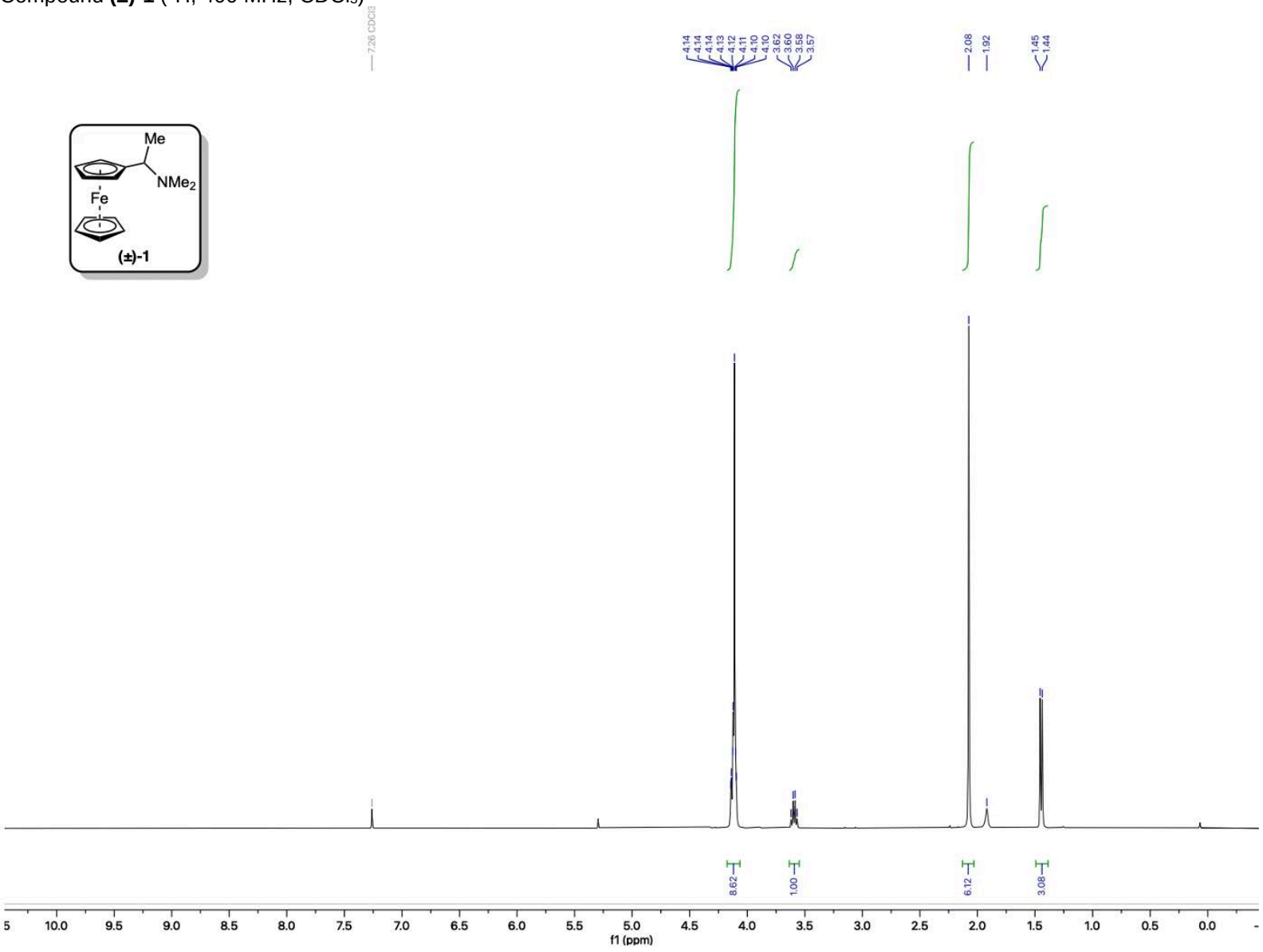
Physicochemical Properties

Red oil

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.08-4.19 (m, 9H), 3.81 (q, *J* = 7.0 Hz, 1H), 2.17 (s, 6H), 1.53 (d, *J* = 6.5 Hz, 3H).

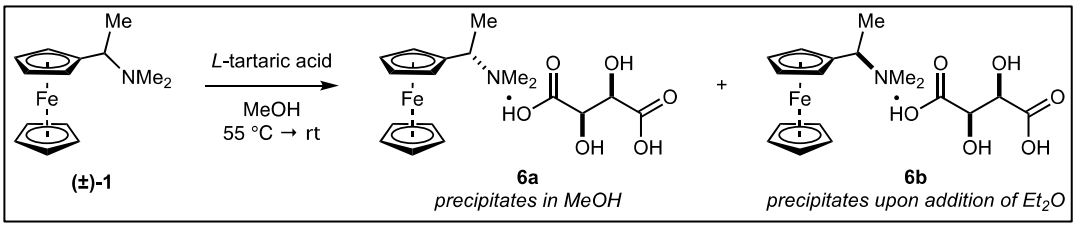
TLC (2% NEt_3 in 50% EtOAc/hexanes) 0.4.

Compound **(±)-1** (^{1}H, 400 MHz, $CDCl_3$)



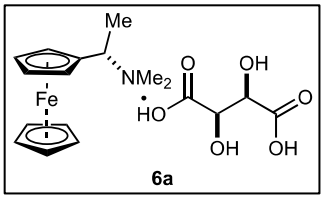
Resolution of Ugi's amine

Resolution (*S*,*S*)- and (*R*,*S*)-Ugi's amine tartrate salts (**6a**, **6b**)



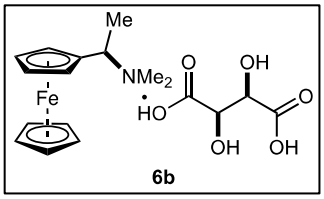
In a 100 mL round-bottomed flask equipped with a stir bar, racemic Ugi's amine (**(±)-1** 6.69 g, 1 equiv, 26.03 mmol) was dissolved in MeOH (13 mL, [**(±)-1**] = 2 M) and heated to 55 °C. *L*-tartaric acid (3.91 g, 1 equiv, 26.03 mmol) was dissolved in MeOH (13 mL, [*L*-tartaric acid] = 2 M) in a 20-mL scintillation vial and heated to 55 °C before being added dropwise via syringe to the amine solution. A seeding crystal was added and the temperature was decreased by 3 °C/h, then stirred overnight at room temperature. The resulting oThe orange precipitate was filtered and washed with cold EtOH, then free-based and resubjected to the resolution conditions to reach (*S*,*S*)-Ugi's amine tartrate salt (**6a**, 2.59 g, 6.34 mmol, 24% yield). The combined mother liquor of both resolutions was concentrated to ¼ of the original volume and Et_2O was added until white precipitate stopped forming. The solid was filtered, washed with Et_2O, and recrystallized twice in acetone:H_2O (10:1, 200 mL) to afford (*R*,*S*)-Ugi's amine tartrate salt (**6b**, 5.30 g, 13.01 mmol, 49% yield). ^{1}H NMR data for both diastereomers matched those reported in the literature.[1]

Physicochemical Properties



Orange crystals

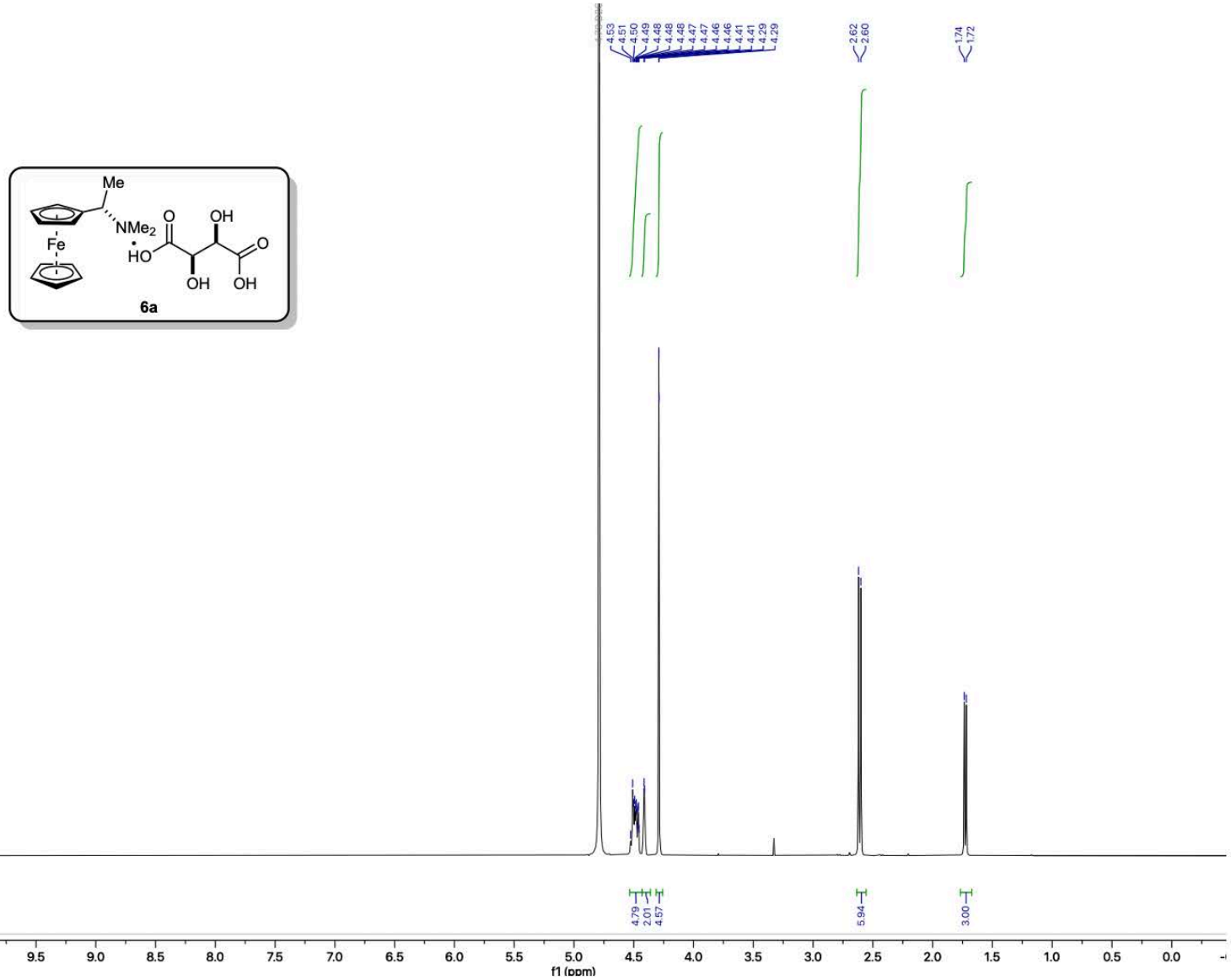
^{1}H NMR (400 MHz, D_2O) δ 4.44 – 4.58 (m, 5H), 4.41 (d, *J* = 1.8 Hz, 2H), 4.29 (s, 5H), 2.61 (d, *J* = 8.1 Hz, 6H), 1.73 (d, *J* = 6.9 Hz, 3H).



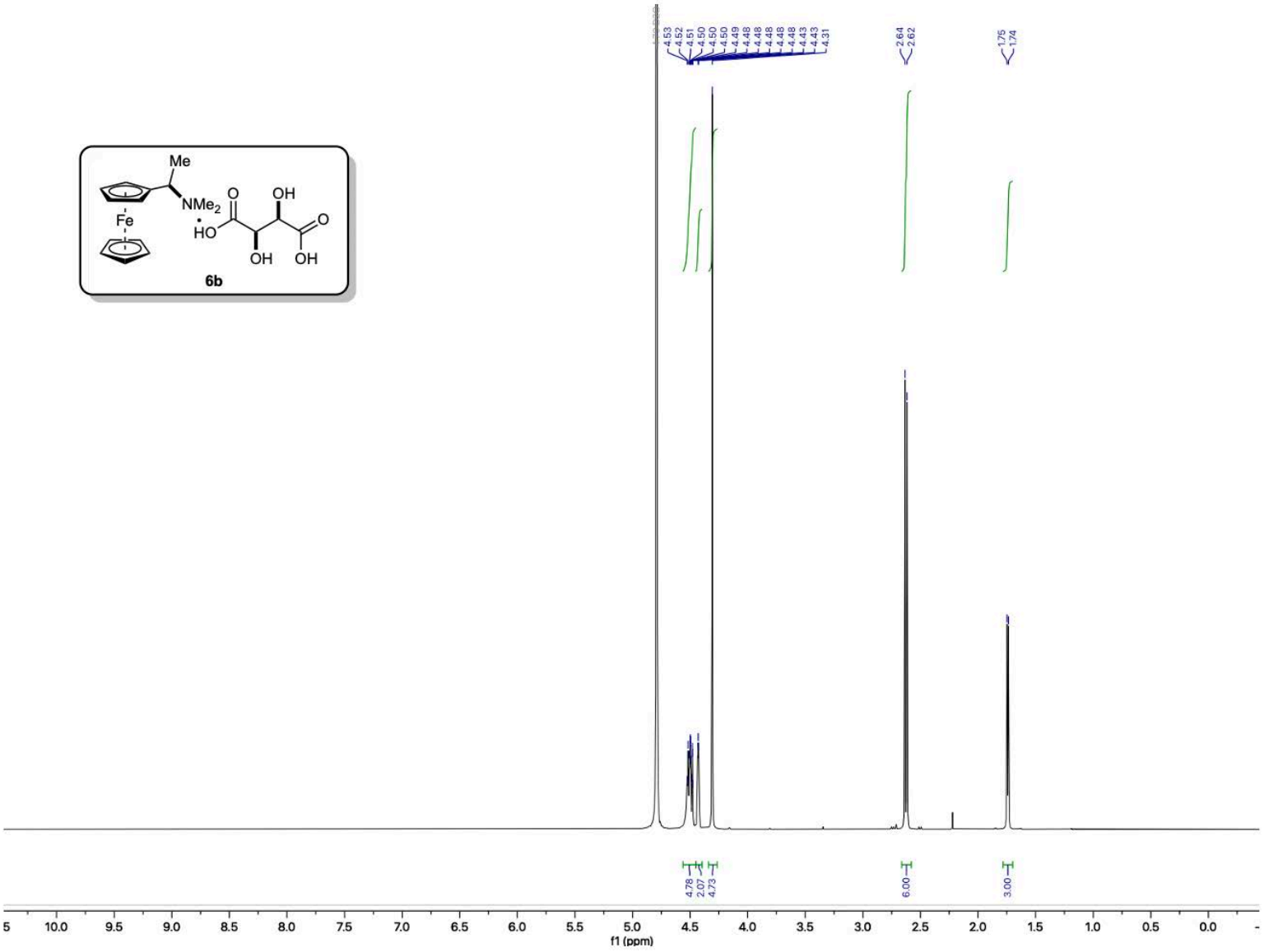
Yellow crystals

^{1}H NMR (600 MHz, D_2O): δ 4.47 – 4.60 (m, 5H), 4.43 (d, *J* = 2.3 Hz, 2H), 4.31 (s, 5H), 2.63 (d, *J* = 11.4 Hz, 6H), 1.74 (d, *J* = 6.9 Hz, 3H).

Compound **6a** (^{1}H, 400 MHz, D_2O)



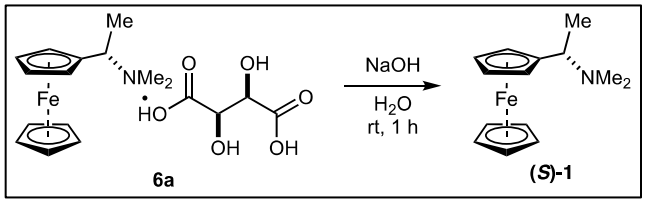
Compound **6b** (^{1}H, 600 MHz, D_2O)



General Procedure A. Free basing Ugi's amine tartrate salt.

In a round-bottomed flask equipped with a stir bar, the tartrate salt (**6a**/**6b**, 1 equiv), NaOH (1 equiv), and H_2O **([6a/6b]** = 0.5 M) were combined and stirred at room temperature for 1 h, becoming heterogeneous. DCM was added and the biphasic mixture was transferred to a separation funnel. The aqueous solution was then extracted with DCM (3x10 mL). The combined organic layers were dried with K_2CO_3, filtered through glass wool, and the volatiles removed under vacuum.

Free basing of (*S*,*S*)-Ugi's amine tartrate salt ((***S*)-1**)



Prepared using General Procedure A described above, with (*S*,*S*)-Ugi's amine tartrate salt (**6a**, 4.76 g, 1.0 equiv, 11.70 mmol), NaOH (0.94 g, 2.0 equiv, 23.40 mmol), in H_2O (25 mL, [**6a**] = 0.5 M), affording (*S*)-Ugi's amine (**(*S*)-1**, 2.43 g, 9.44 mmol, 81%). ^{1}H NMR data matched those reported previously in this SI.

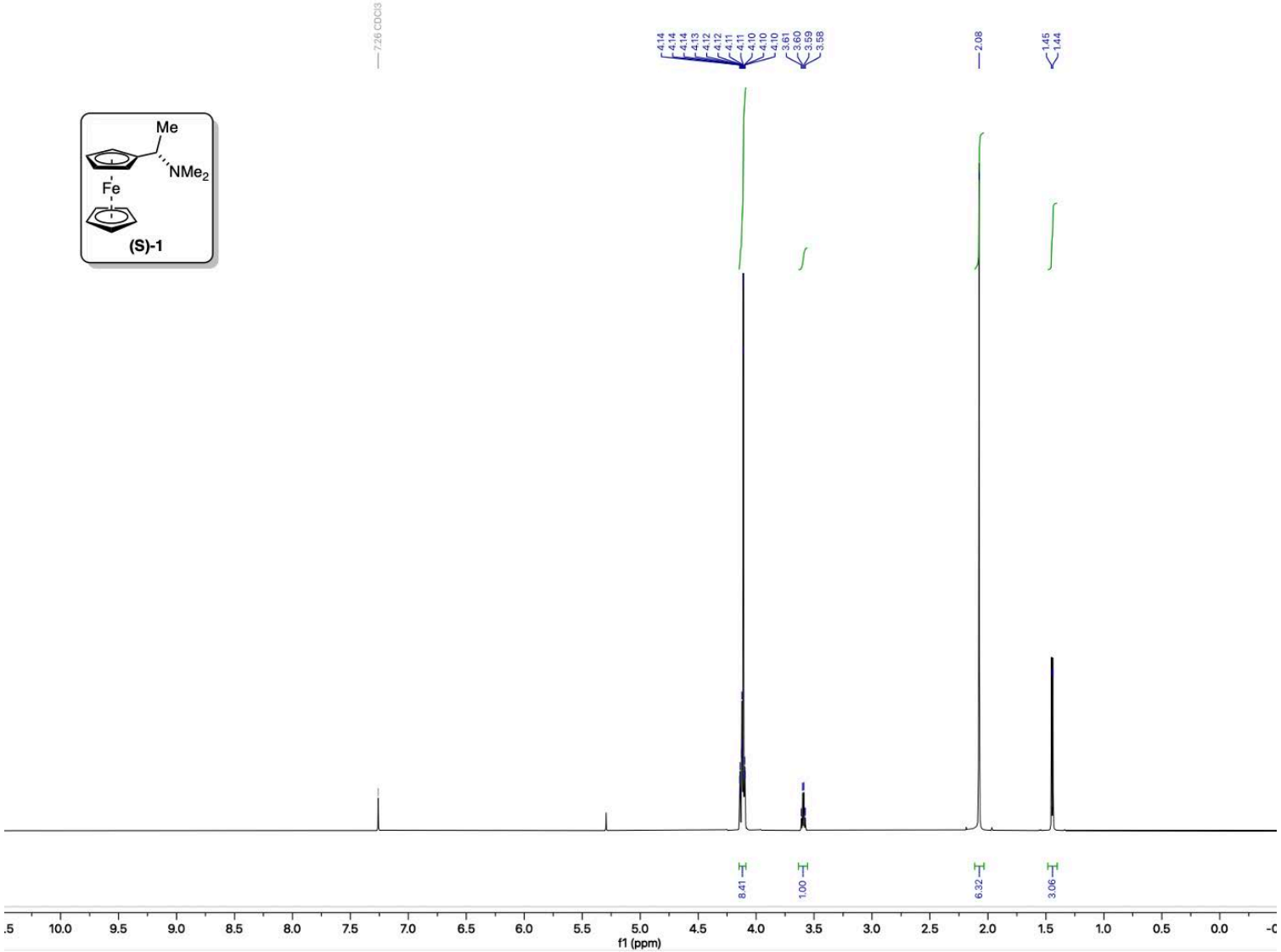
Physiochemical Properties

Red oil

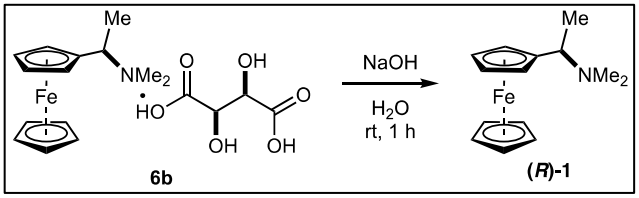
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.17 – 4.02 (m, 9H), 3.59 (q, *J* = 6.9 Hz, 1H), 2.08 (s, 4H), 1.45 (d, *J* = 6.9 Hz, 1H).

α_D^{23} (c = 0.01, $CHCl_3$) -8.1

Compound **(*S*)-1** (^{1}H, 600 MHz, $CDCl_3$)



Free basing of (*R*,*S*)-Ugi's amine tartrate salt ((***R*)-1**)



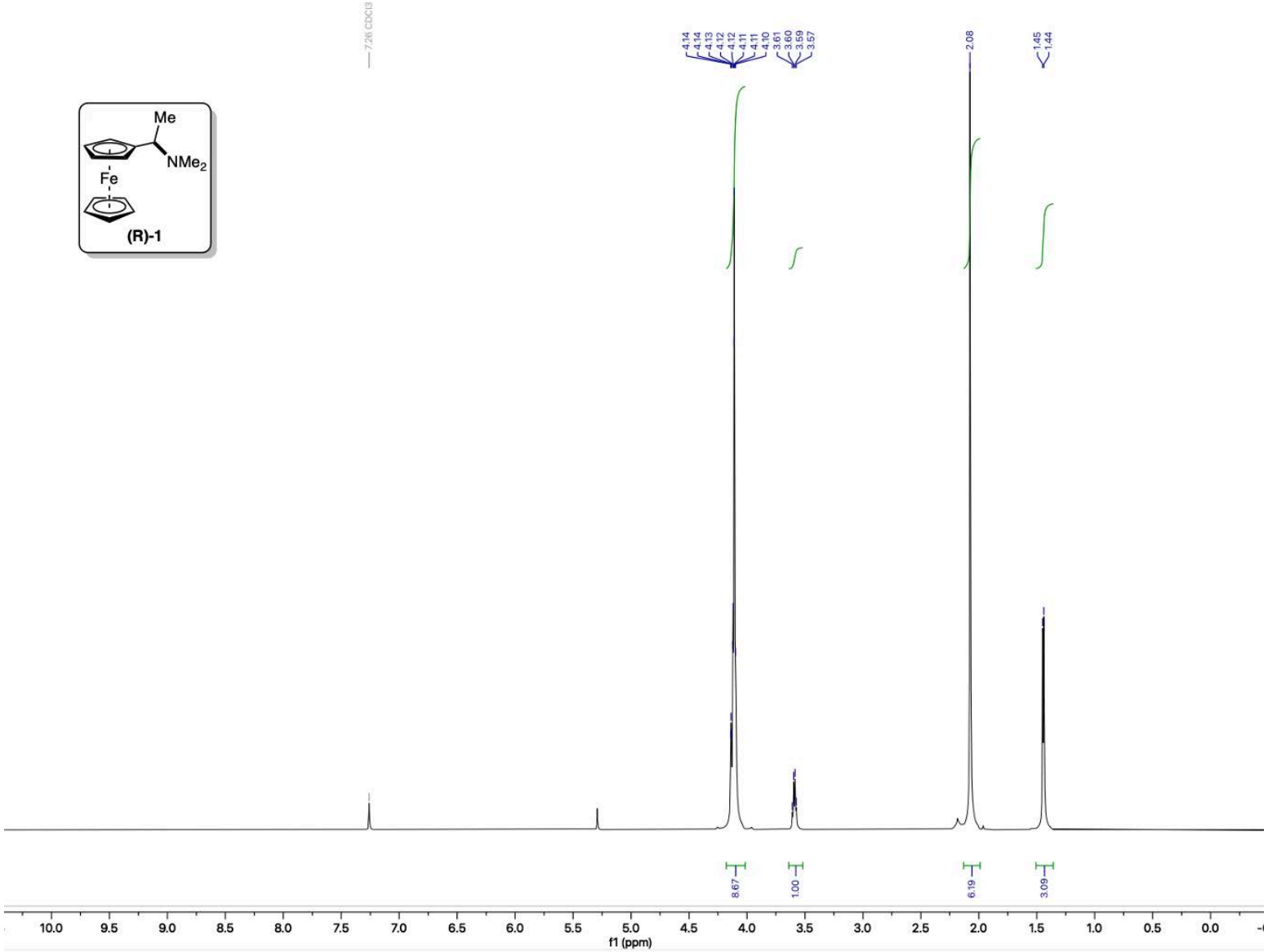
Prepared using General Procedure A described above, with (*R*,*S*)-Ugi's amine tartrate salt (**6b**, 5.30 g, 1.0 equiv, 13.01 mmol), NaOH (1.04 g, 2.0 equiv, 26.02 mmol), in H_2O (30 mL, [**6b**] = 0.5 M), affording (*R*)-Ugi's amine (**(*R*)-3**, dr >20:1, 2.70 g, 10.5 mmol, 81%). ^{1}H NMR data matched those reported previously in this SI.

Physiochemical Properties

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.97 – 4.19 (m, 9H), 3.59 (q, *J* = 6.9 Hz, 1H), 2.08 (s, 6H), 1.44 (d, *J* = 6.9 Hz, 3H).

$\alpha_{\boldsymbol{D}}^{\mathbf{23}}$ (c = 0.01, $CHCl_3$) 10.8

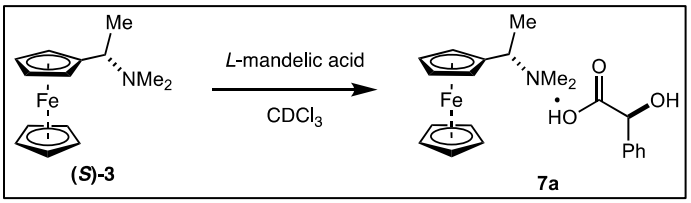
Compound **(*R*)-1** (^{1}H, 600 MHz, $CDCl_3$)



General Procedure B. Preparation of Ugi's amine mandelate salt.

(*S*)- or (*R*)-Ugi's amine ((*S*)/(*R*)-**3**, 0.024 g, 1.0 equiv, 0.093 mmol) was dissolved in $CDCl_3$ (0.5 mL). *L*-mandelic acid (0.014 g, 1.0 equiv, 0.093 mmol) was then added and the solution was sonicated until all solid was dissolved.

Synthesis of (*S*,*S*)-Ugi's amine mandelate salt (**7a**)



Prepared using General Procedure B described above. The diastereomeric ratio was determined by ^{1}H NMR analysis by integration of peaks at 1.62 ppm (major) and 1.59 ppm (minor) and was determined to be >100:1.

Physicochemical Properties

Red solid

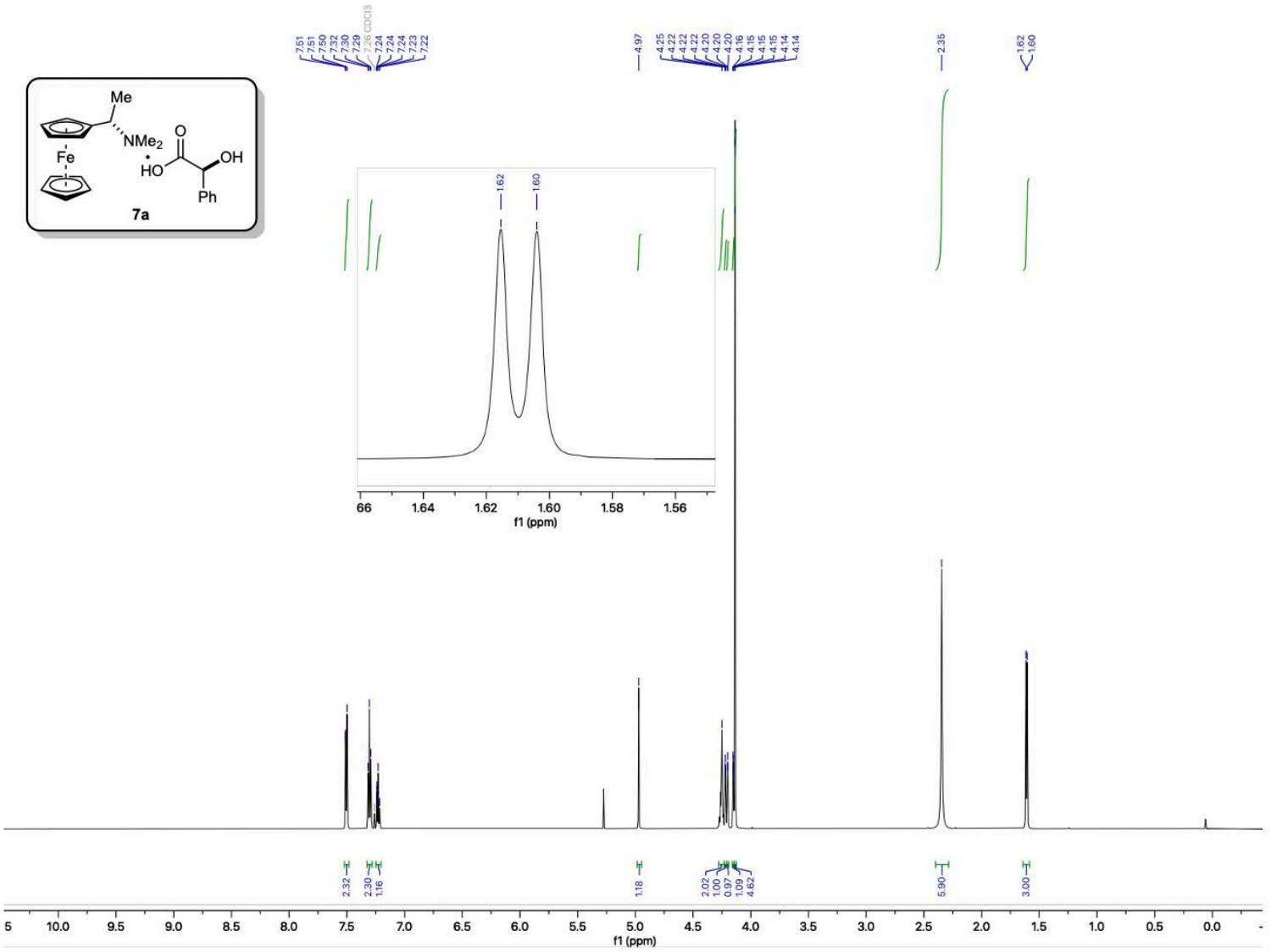
mp: 99-104°C

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47 – 7.53 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.24 – 7.19 (m, 1H), 4.97 (s, 1H), 4.25 (s, 2H), 4.21 – 4.23 (m, 1H), 4.19 – 4.21 (m, 1H), 4.14 – 4.16 (m, 1H), 4.14 (s, 5H), 2.35 (s, 6H), 1.61 (d, *J* = 6.8 Hz, 3H).

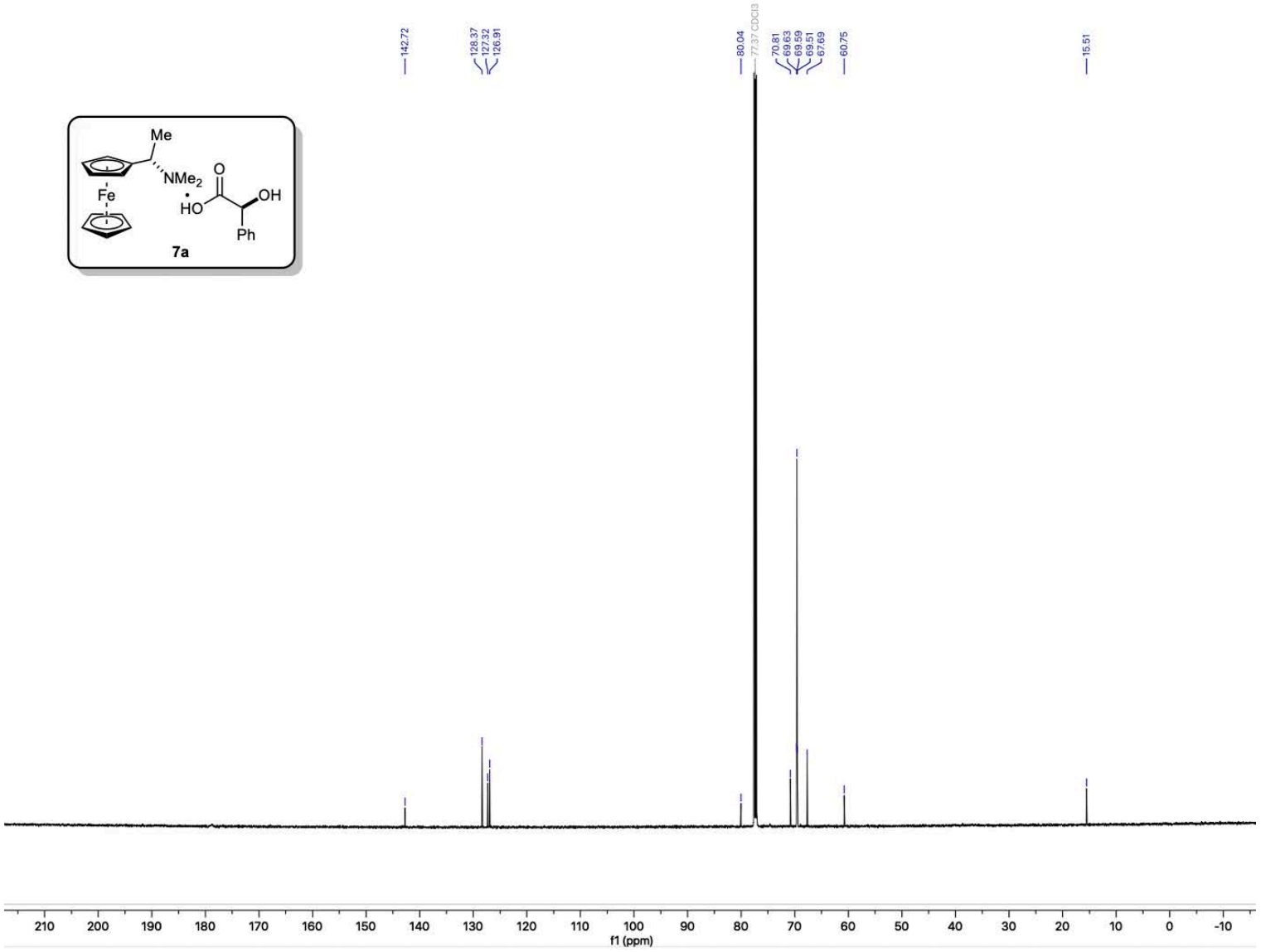
^{13}C NMR (151 MHz, $CDCl_3$): δ 142.7, 128.4, 127.3, 126.9, 80.0, 70.8, 69.6, 69.6, 69.5, 67.7, 60.8, 15.5.

α_D^{23} (c = 0.01, $CHCl_3$) 42.2

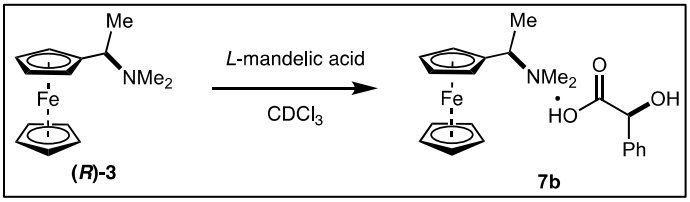
Compound **7a** (^{1}H, 600 MHz, $CDCl_3$)



Compound **7a** (^{13}C, 151 MHz, $CDCl_3$)



Synthesis of (*R*,*S*)-Ugi's amine mandelate salt (**7b**)



Prepared using General Procedure B described above. The diastereomeric ratio was determined by 1H NMR analysis by integration of peaks at 1.58 ppm (major) and 1.61 ppm (minor) and was determined to be >100:1.

Physicochemical Properties

Red solid

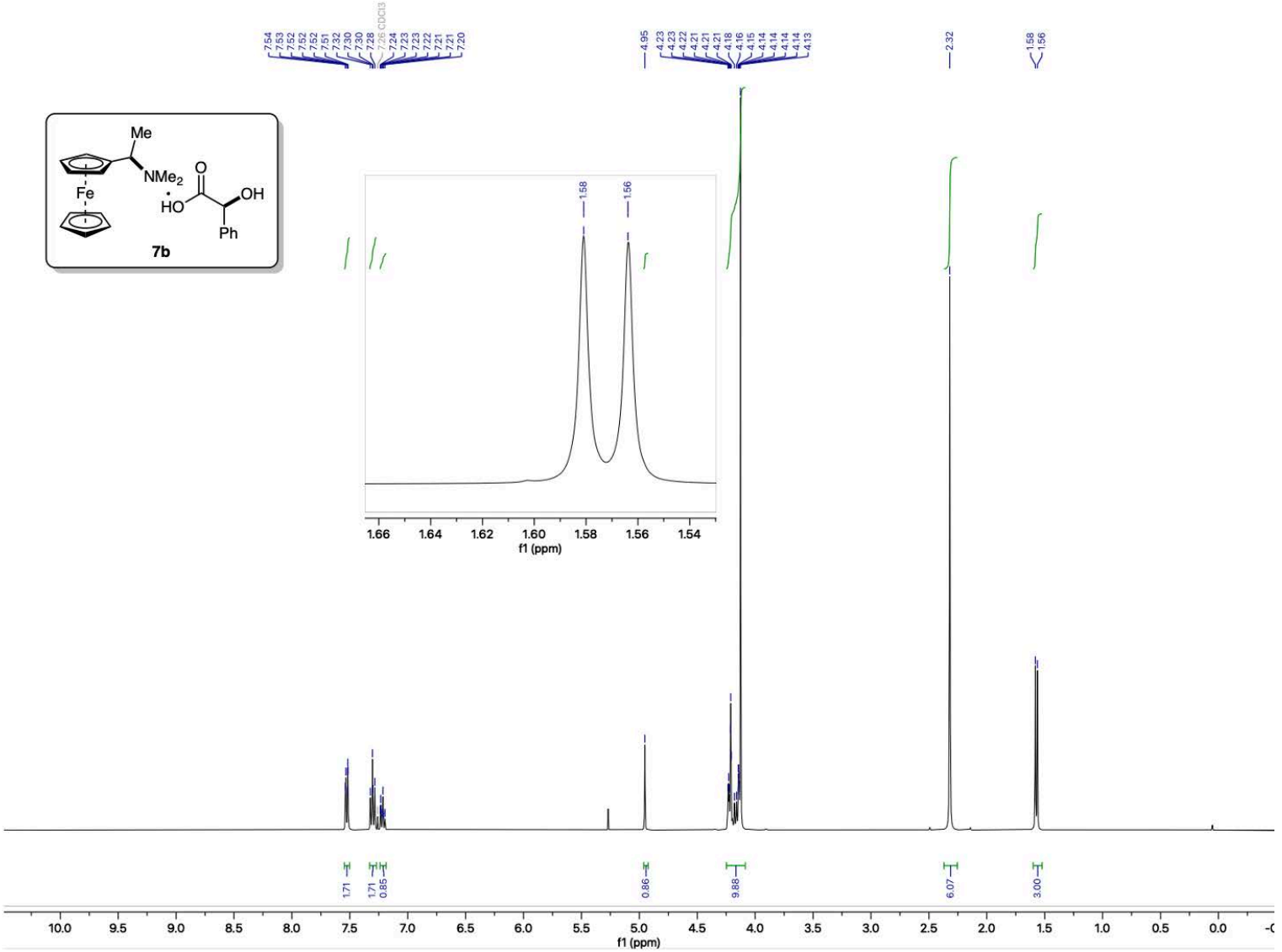
mp: 87-90°C

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 – 7.61 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.15 – 7.24 (m, 1H), 4.95 (s, 1H), 4.22 – 4.24 (m, 1H), 4.21 (t, *J* = 1.6 Hz, 2H), 4.13 – 4.18 (m, 2H), 4.13 (s, 5H), 2.32 (s, 6H), 1.57 (d, *J* = 6.8 Hz, 3H).

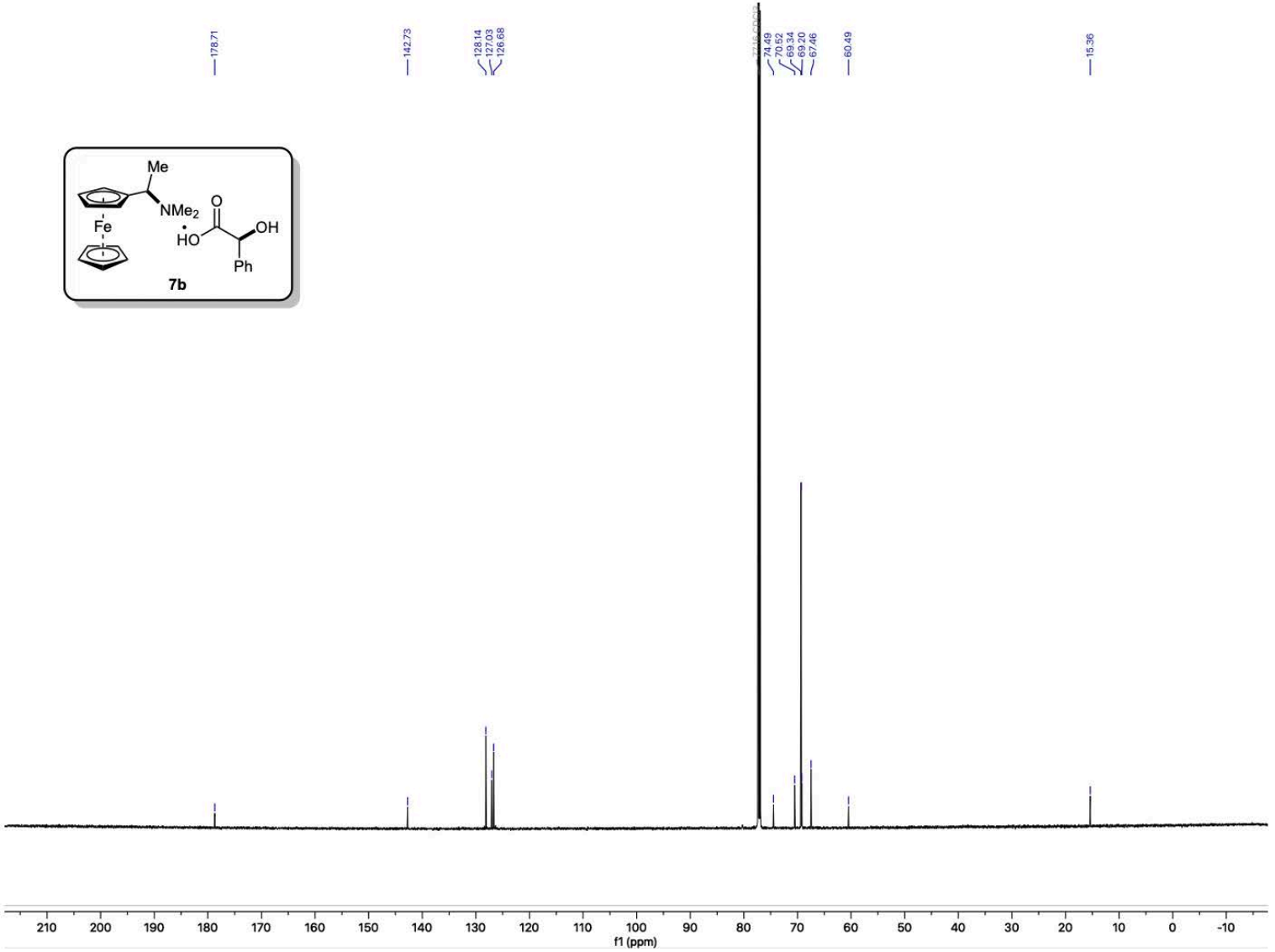
^{13}C NMR (151 MHz, $CDCl_3$): δ 142.7, 128.4, 127.3, 126.9, 80.0, 70.8, 69.6, 69.6, 69.5, 67.7, 60.8, 15.5.

$\boldsymbol{\alpha}_{\boldsymbol{D}}^{\boldsymbol{23}}$ (c = 0.01, $CHCl_3$) 45.6

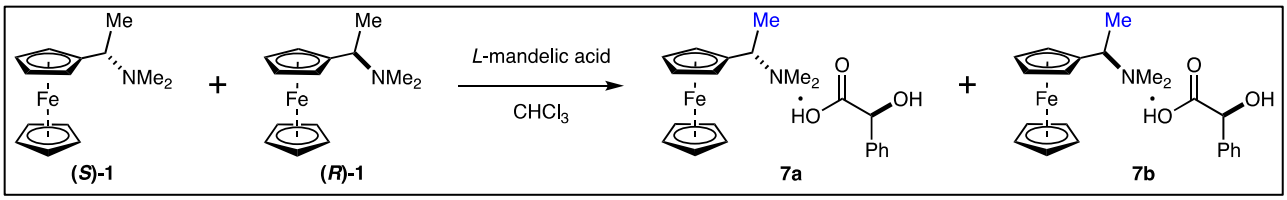
Compound **7b** (^{1}H, 6 MHz, $CDCl_3$)



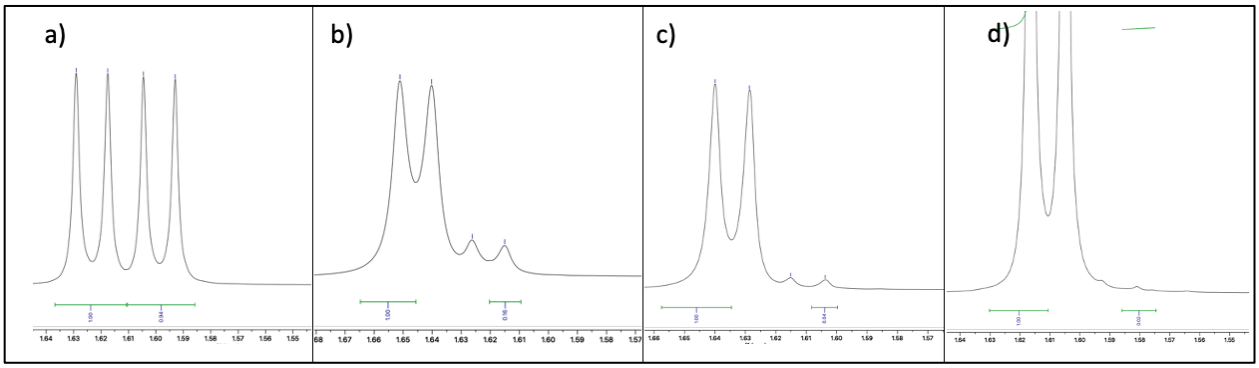
Compound **7b** (^{13}C, 151 MHz, $CDCl_3$)


178.71
142.73
128.14
127.03
126.68
77.16 CDCl3
74.49
70.52
69.34
69.20
67.46
60.49
15.36
Me
NMe2
O
HO
OH
Ph
Fe
7b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Limit of Detection Study



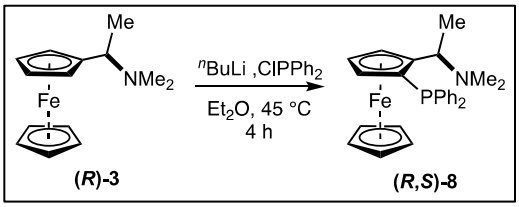
A 1 M solution of **(*S*)-1** in $CHCl_3$ and 0.1 M solution of **(*R*)-1** in $CHCl_3$ were prepared, sonicating the samples to ensure that all solid was dissolved. 0.1 mL of each solution was added to a 1-dram vial to make a 10:1 **7a**:**7b** solution, and the volatiles were removed under vacuum. To prepare a 50:1 **7a**:**7b** solution, 0.5 mL of the 1 M solution of **(*S*)-1** and 0.1 mL of the 0.1 M solution of **(*R*)-1** were combined. Similarly, a 100:1 **7a**:**7b** solution was prepared using 1 mL of the 1 M solution of **(*S*)-1** and 0.1 mL of the 0.1 M solution of **(*R*)-1.** The integrations of the methyl protons (highlighted in blue) were evaluated to determine the accuracy of the method at low concentrations of mandelate salt.



a) **7a**:**7b** = 1:1; b) **7a**:**7b** = 10:1; c) **7a**:**7b** = 50:1; d) **7a**:**7b** = 100:1.

Synthesis of (Josiphos)CuBr complex

Dimethyl{(S)-1-[(R)-2-(diphenylphosphanyl)ferrocenyl]ethyl}amine (**(*R*,*S*)-8**, (*R,S*)-PPFA)



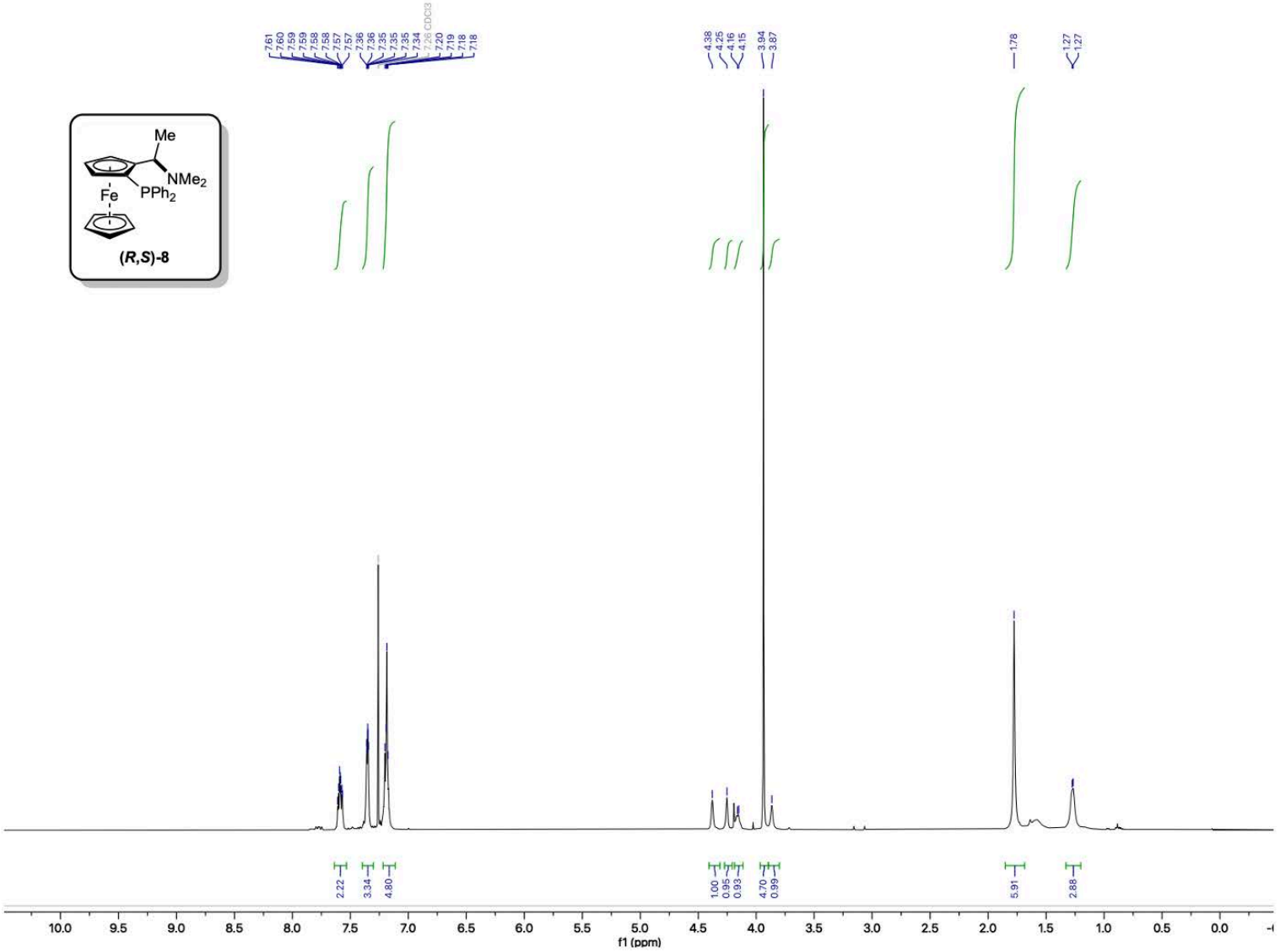
In a flame-dried 25-mL round-bottomed flask equipped with a stir bar, (*R*)-Ugi's amine ((***R*)-3),** 1.00 g, 1 equiv, 3.89 mmol) was dissolved in dry Et_2O (7.0 mL, [**(*R*)-3)**] = 0.55 M) under N_2. ^{n}BuLi (2.5 M in hexanes, 2.10 mL, 1.2 equiv, 4.67 mmol) was added dropwise via syringe and the solution was stirred at room temperature for 1.5 h. Chlorodiphenylphosphine (1.72 g, 1.42 mL, 2 equiv, 7.78 mmol) was added dropwise via syringe, and the reaction was heated at reflux at 50 °C for 2 h. After cooling to room temperature, sat. aq. $NaHCO_3$ (5 mL) was added dropwise under N_2. The biphasic mixture was transferred to a separation funnel and the aqueous layer was extracted with Et_2O (3x25 mL), dried over $MgSO_4$, filtered through glass wool and the volatiles removed under vacuum. The resulting orange solid was recrystallized in EtOH to yield (*RS*,*S*)-PPFA (**(*R*,*S*)-8**, 0.731 g, 1.66 mmol, 43% yield). ^{1}H NMR data matched those reported in the literature.[2]

Physicochemical Properties

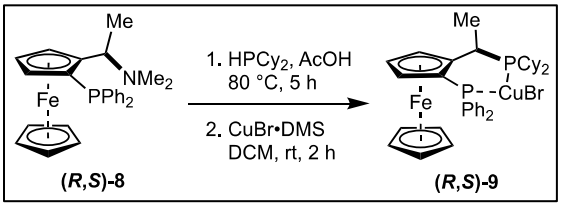
Orange crystal

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.61 (m, 2H), 7.34 – 7.36 (m, 3H), 7.18 – 7.20 (m, 4H), 4.38 (s, 1H), 4.25 (s, 1H), 4.16 (s, 1H), 3.94 (s, 5H), 3.87 (s, 1H), 1.78 (s, 6H), 1.35 – 1.18 (m, 3H).

Compound **(*R*,*S*)-8** (^{1}H, 400 MHz, $CDCl_3$)



(*S*)-l-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine (**(*R*,*S*,)-9**, CuBr-(*R,S*)-J001)



In a flamed-dried 25-mL two-necked round-bottomed flask equipped with a stir bar and a reflux condenser, (*R*,*S*)-PPFA (**(*R*,*S*)-8**,0.730 g, 1.0 equiv, 1.65 mmol) was dissolved in degassed, glacial acetic acid (3.6 mL, 0.5 M) under Ar_2. Dicyclohexylphosphine (10% w/w in hexanes, 3.61 g, 3.99 mL, 1.1 equiv, 1.82 mmol) was added dropwise via syringe. The reaction was heatd at reflux at 80 °C for 4 h. The volatiles were removed under vacuum, and the resulting oil dissolved in DCM (25 mL, [(***R*,*S*)-8**] = 0.07 M). CuBr dimethylsulfide complex (0.340 g, 1.0 equiv, 1.65 mmol) was added in one portion and the reaction was stirred at room temperature for 2 h. The DCM was removed under reduced pressure and the resulting solid was recrystallized in MeOH to afford CuBr-(*R*,*S*)-J001 ((*R*,*S*,)-**9**, 0.725 g, 0.982 mmol, 59% yield) as an orange solid.

Physicochemical Properties

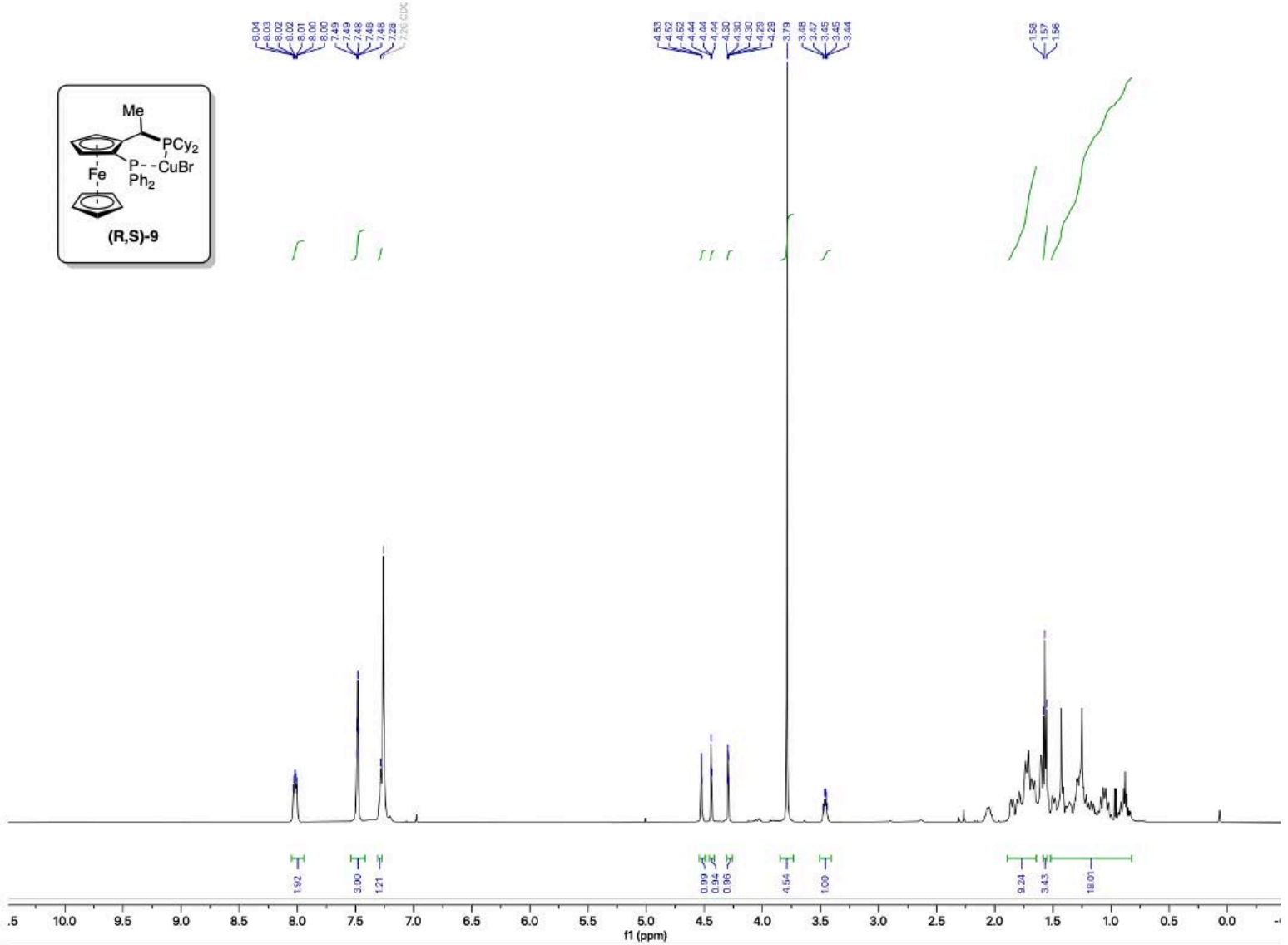
Orange solid

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (ddd, *J* = 10.8, 6.5, 2.8 Hz, 2H), 7.48 (q, *J* = 2.4 Hz, 3H), 7.28 (s, 1H), 4.52 (d, *J* = 1.7 Hz, 1H), 4.44 (t, *J* = 2.6 Hz, 1H), 4.23 – 4.43 (m, 1H), 3.79 (s, 5H), 3.52 – 3.37 (m, 1H), 0.87 – 1.81 (m, 25H).

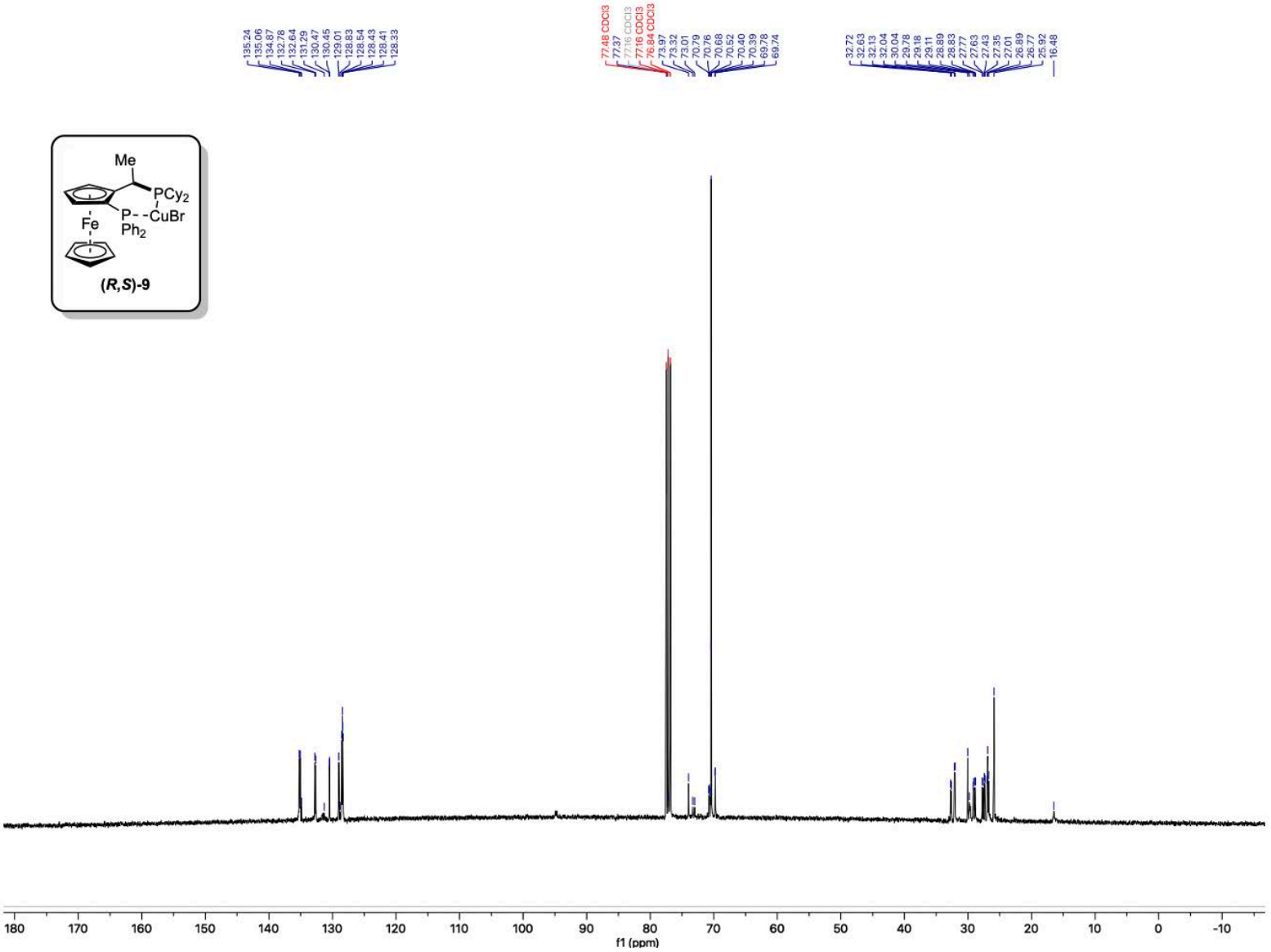
^{13}C NMR (101 MHz,$CDCl_3$): δ 135.2 (d, *J* = 17.6 Hz), 132.7 (d, *J* = 14.1 Hz), 130.5 (d, *J* = 1.8 Hz), 129.0, 128.5 (d, *J* = 10.4 Hz), 128.4 (d, *J* = 8.5 Hz), 77.4, 74.0, 73.2 (d, *J* = 31.2 Hz), 70.9 – 70.7 (m), 70.52, 70.4, 69.8 (d, *J* = 4.3 Hz), 32.7 (d, *J* = 9.4 Hz), 32.1 (d, *J* = 9.1 Hz), 30.0, 29.8, 29.2 (d, *J* = 7.2 Hz), 28.9 (d, *J* = 5.4 Hz), 27.7 (d, *J* = 13.6 Hz), 27.4 (d, *J* = 8.4 Hz), 27.0, 26.8 (d, *J* = 12.5 Hz), 25.9, 16.5.

^{31}P NMR (243 MHz, $CDCl_3$): δ 8.02 (d, *J* = 195.0 Hz), -22.85 (d, *J* = 195.1 Hz).

Compound **(*R*,*S*,)-9** (^{1}H, 600 MHz, $CDCl_3$)



Compound **(*R*,*S*,)-9** (^{13}C**,** 101 MHz,$CDCl_3$)


135.24
135.06
134.87
132.78
132.64
131.29
130.47
130.45
129.01
128.83
128.54
128.43
128.41
128.33
77.48 CDCl3
77.37
77.16 CDCl3
76.84 CDCl3
73.97
73.32
73.01
70.79
70.76
70.68
70.52
70.40
70.39
69.78
69.74
32.72
32.63
32.13
32.04
30.04
29.78
29.18
29.11
28.89
28.83
27.77
27.63
27.43
27.35
27.01
26.89
26.77
25.92
16.48
Me
PCy2
P--CuBr
Fe
Ph2
(R,S)-9
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Compound **(*R*,*S*,)-9** (^{31}P, 243 MHz, $CDCl_3$):