Supporting Information for:

Transannular Functionalization of Multiple C(sp^3)–H Bonds of Tropane via an Alkene-Bridged Palladium(I) Dimer

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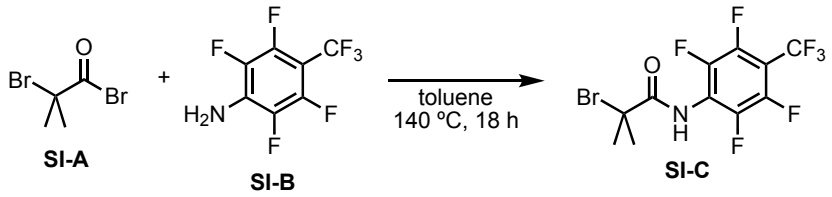
I. General Procedures, Materials, and Methods

Instrument Information. NMR spectra were obtained on a Varian VNMR 700 (699.76 MHz for ^{1}H; 175.95 MHz for ^{13}C) or a Varian VNMR 500 (500.09 MHz for ^{1}H; 470.56 MHz for ^{19}F) or a Varian NMR 400 (128.38 MHz for ^{11}B NMR) spectrometer. ^{1}H and ^{13}C chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak (most commonly $CDCl_3$) used as an internal reference. ^{19}F chemical shifts are reported in ppm and are referenced on a unified scale to the frequency of the residual solvent peak in the ^{1}H NMR spectrum. ^{1}H and ^{19}F multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), quartet (q), and multiplet (m). High resolution mass spectra were obtained at the University of Michigan core facility. X-ray crystallographic data were collected on a Bruker SMART APEX-I CCD-based X-ray diffractometer. Elemental analyses were conducted by Midwest Microlabs. Flash chromatography was conducted on a Biotage Isolera One chromatography system using preloaded high-performance silica gel columns (10 g, 25 g, 50 g, or 100 g as appropriate). GC-FID was conducted on a Shimadzu CG-17A system. Melting points were obtained on a OptiMelt automated melting point system.

Materials. All reagents were obtained from a commercial vendor (Aldrich, CombiBlocks, Oakwood, Synthonix, Enamine, Carbosynth, Pressure Chemicals, Matrix, SantaCruz Biotech, or Ontario Chemicals). 8-Azabicyclo[3.2.1]octane hydrochloride was purchased from PharmaBlock. $Pd(OAc)_2$ was purchased from Pressure Chemical Company. Acetonitrile and *tert*-amyl alcohol were purchased from Sigma-Aldrich. All commercial reagents were used without further purification/drying unless explicitly stated in the experimental section. All reactions were performed under ambient atmosphere unless stated in experimental section.

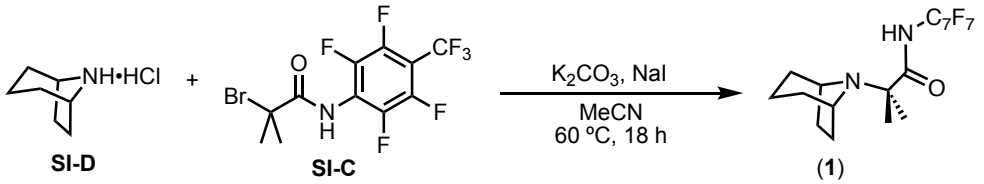
General Methods. The manipulation of solid reagents was conducted on the benchtop unless otherwise stated. Reactions were conducted under ambient atmosphere unless otherwise stated. Reaction vessels were sealed with either a septum (flask) or a Teflon-lined cap (4 mL or 20 mL vial) with Teflon tape wrapped around the cap. Reactions conducted at elevated temperatures were heated on a hot plate using an aluminum block. Temperature was regulated using an external thermocouple.

II. Synthesis of Starting Materials



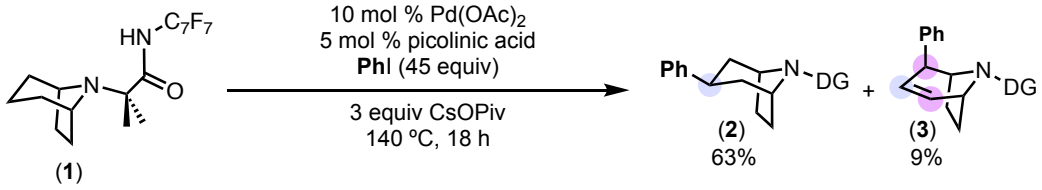
Synthesis of C: α-Bromopropanamide **SI-C** was synthesized following a literature procedure[1] from starting materials **SI-A** and **SI-B**.

Directing Group Installation Procedures[1]



A 20 mL scintillation vial was charged with **SI-D** (250 mg, 1.70 mmol, 1.0 equiv), α-bromo propanamide **SI-C** (650 mg, 1.70 mmol, 1.0 equiv), K_2CO_3 (752 mg, 5.44 mmol, 3.2 equiv), and NaI (127 mg, 0.85 mmol, 0.5 equiv). To the solids, anhydrous acetonitrile (15 mL) was added. The vial was sealed, and the reaction was stirred at an external temperature of 60 °C. After 18 h, the reaction was cooled to room temperature, diluted with EtOAc (~5 mL), and filtered through a plug of silica gel. The filtrate was concentrated under reduced pressure. Final purification via column chromatography (gradient elution from 0% to 5% EtOAc in hexanes) afforded **1** (450 mg, 64% yield) as a white solid.[2] The ^{1}H, ^{13}C, ^{19}F NMR spectral data for **1** matched those reported in the literature.[2]

III. Reaction Data for Scheme 2a



Experimental Procedure:

The procedure was adapted from a literature procedure with slight modification.[2] Under ambient conditions, a 0.02 M stock solution of $Pd(OAc)_2$ (22.5 mg in 5 mL of CH_2Cl_2) and 0.02 M stock solution of picolinic acid (3.7 mg in 1 mL of MeOH) were prepared. To a 4 mL vial, an aliquot of the picolinic acid solution (0.15 mL, 0.003 mmol, 5 mol %) was added, and MeOH was removed by heating at 70 ºC for 5 min. To the same 4 mL vial, an aliquot of the $Pd(OAc)_2$ solution (0.3 mL, 0.006 mmol Pd, 10 mol %) was added, and dichloromethane was removed by heating at 40 ºC for 5 min. Substrate **1** (24.7 mg, 0.06 mmol, 1.0 equiv) and CsOPiv (42.1 mg, 0.18 mmol, 3 equiv) were then added, followed by PhI (0.3 mL). A stir bar was added to the vial, and it was tightly sealed with a Teflon-lined screw cap. The reaction was heated at 140 ºC for 18 h. After cooling to room temperature, the mixture was diluted with dichloromethane (3.0 mL). An aliquot of the internal standard solution (0.6 mL, 0.1 M trimethoxybenzene in ethyl acetate) was added. The crude reaction mixture was then filtered through a Celite plug, and the Celite was washed with dichloromethane. The filtrate was then analyzed by GCMS. The yield of **2** was determined based on a 5-point calibration curve. The yield of **3** was determined based on the area ratio of **2**, assuming that **2** and **3** have the same response factor on GCMS.

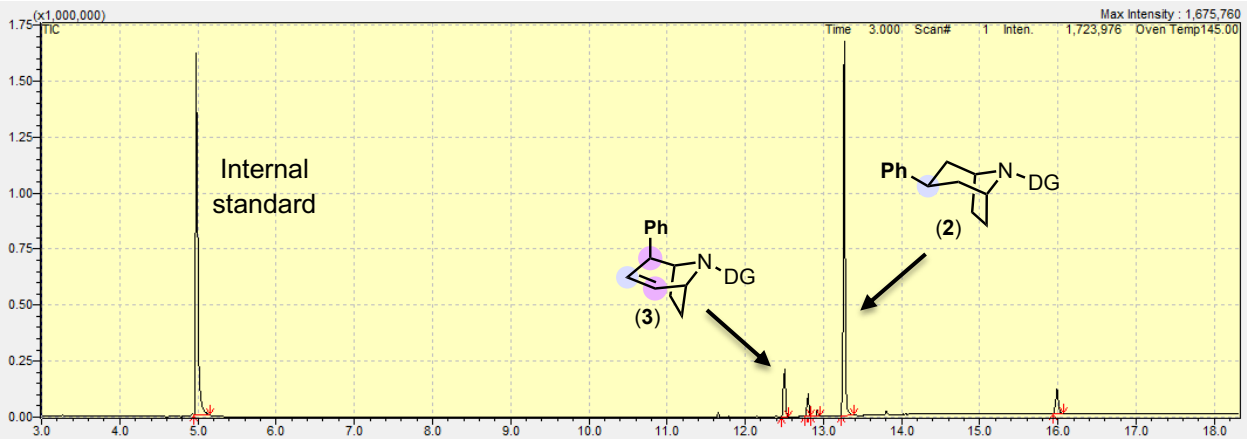
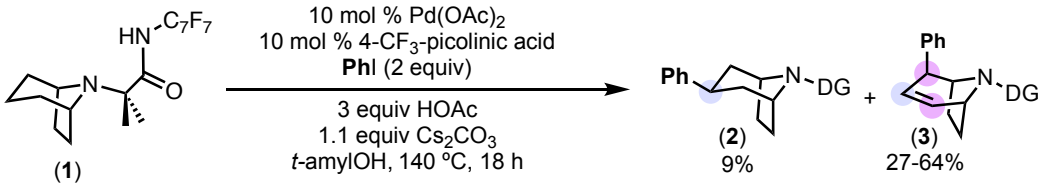


Figure S1. GCMS trace of reaction in **Scheme 2a**.

IV. Reaction Data for Scheme 1b and isolation of product



Experimental Procedure:

Under ambient conditions, a 0.02 M stock solution of $Pd(OAc)_2$ (22.5 mg in 5 mL of CH_2Cl_2) and a 0.02 M stock solution of 4-CF_3-picolinic acid (15.3 mg in 4 mL of MeOH) were prepared. To a 4 mL vial, an aliquot of the 4-CF_3-picolinic acid solution (0.15 mL, 0.003 mmol, 10 mol %) was added, and MeOH was removed by heating at 70 ºC for 5 min. To the same 4 mL vial, an aliquot of the $Pd(OAc)_2$ solution (0.15 mL, 0.003 mmol Pd, 10 mol %) was added, and dichloromethane was removed by heating at 40 ºC for 5 min. Substrate **1** (12.4 mg, 0.03 mmol, 1.0 equiv) and Cs_2CO_3 (10.8 mg, 0.033 mmol, 1.1 equiv) were then added, followed by PhI (6.7µL, 0.06 mmol, 2.0 equiv). The reaction mixture was diluted with *t*-amyl alcohol (0.30 mL), and then acetic acid (5.1 µL, 0.09 mmol, 3 equiv) was added. A stir bar was added to the vial, and it was sealed tightly with a Teflon-lined screw cap. The reaction was heated at 140 ºC for 18 h. After cooling to room temperature, then it was diluted with dichloromethane (3.0 mL). An aliquot of the internal standard solution (0.3 mL, 0.1 M trimethoxybenzene in ethyl acetate) was added. The crude reaction mixture was then filtered through a Celite plug, and the Celite was washed with dichloromethane. The reaction was analyzed by GCMS. The yield of **2** was determined based on a 5-point calibration curve. The yield of **3** was determined based on the area ratio of **2**, assuming that **2** and **3** have the same response factor on GCMS. Notably, the yield of **3** in this reaction was variable (ranging from 27-64%). Lower yields were typically accompanied by low conversion, with unreacted starting material being the major mass balance. We have not been able to definitively identify the origin of this variability, and thus sought to address it by pursuing the mechanistic experiments and organometallic studies presented below.

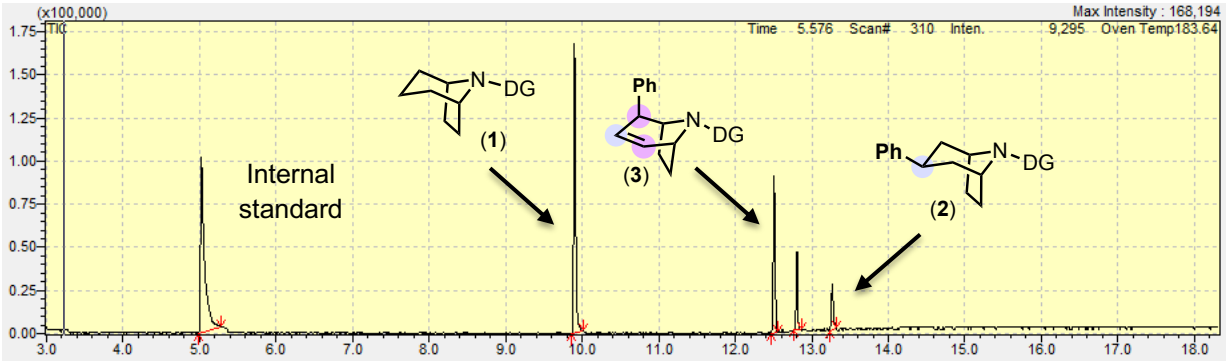
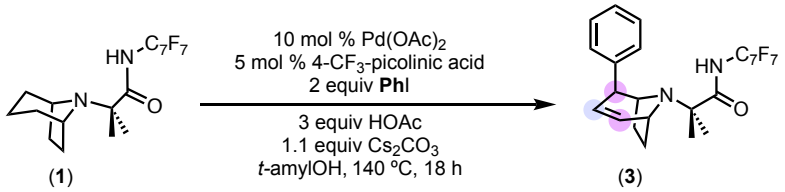


Figure S2. GCMS trace of reaction in **Scheme 2b**.

Isolation of product 3.



Under ambient conditions, a 0.02 M stock solution of $Pd(OAc)_2$ (22.5 mg in 5 mL of CH_2Cl_2) and a 0.02 M stock solution of 4-CF_3-picolinic acid (19.1 mg in 5 mL of MeOH) were prepared. To a 4 mL vial, an aliquot of the picolinic acid solution (150 µL, 0.003 mmol, 10 mol %) was added, and MeOH was removed by heating at 70 ºC for 5 min. To the same 4 mL vial, an aliquot of the $Pd(OAc)_2$ solution (150 µL, 0.003 mmol Pd, 10 mol %) was added, and dichloromethane was removed by heating at 40 ºC for 5 min. Substrate **1** (12.4 mg, 0.03 mmol, 1.0 equiv) and Cs_2CO_3 (10.8 mg, 0.033 mmol, 1.1 equiv) were then added, followed by PhI (6.7 µL, 0.06 mmol, 2.0 equiv). The reaction mixture was diluted with *t*-amyl alcohol (0.30 mL), and then acetic acid (5.1 µL, 0.09 mmol, 3 equiv) was added. A stir bar was added to the vial, and it was sealed with a Teflon-lined screw cap. The reaction was heated at 140 ºC for 18 h. After cooling to room temperature, the mixture was diluted with dichloromethane (3.0 mL). The solution was then filtered through a Celite plug, and the Celite was washed with dichloromethane. The volatiles were removed under vacuum, and the resulting solids were purified via column chromatography (gradient elution from 2% to 5% EtOAc in hexanes) to obtain **3** as a white solid (9.3 mg, 64% yield).

^{1}H NMR (700 MHz, $CDCl_3$, 23 ºC): δ 8.98 (br s, 1H), 7.25 (s, 2H), 7.17 (t, J = 7.6 Hz, 2H), 6.90 (t, J = 7.3 Hz, 1H), 6.34 (ddd, J = 9.5, 5.9, 1.5 Hz, 1H), 5.58 (ddd, J = 9.5, 4.0, 1.5 Hz, 1H), 3.71 (t, J = 5.5 Hz, 1H), 3.63 (d, J = 7.5 Hz, 1H), 3.34 (d, J = 4.0 Hz, 1H), 2.15 (tdd, J = 11.1, 7.5, 3.0 Hz, 1H), 2.02 (ddd, J = 12.2, 9.4, 3.1 Hz, 1H), 1.96 (tt, J = 11.6, 5.9 Hz, 1H), 1.89 (ddd, J = 15.5, 9.6, 6.1 Hz, 1H), 1.26 (s, 3H), 1.03 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$, 23 ºC): δ 175.4, 143.7, 136.5, 128.6, 128.0, 126.0, 124.4, 63.6, 63.3, 56.9, 53.0, 35.1, 31.1, 23.7, 23.6. *Carbon resonances associated with perfluoroaryl group are not observed.*[1,2]

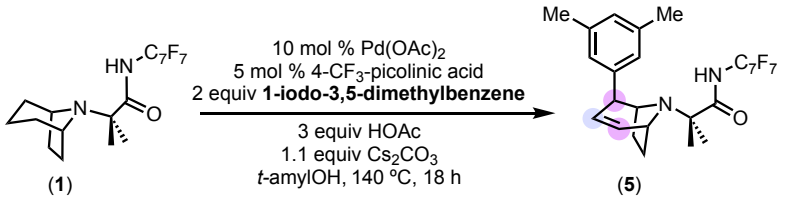
^{19}F NMR (470 MHz, $CDCl_3$, 23 ºC): δ –56.0 (m, 3F), –142.0 (apparent s, 2F), –143.3 (apparent s, 2F).

HRMS-ESI (m/z): $[M]^+$ calcd. for $C_{24}H_{21}F_7N_2O$, 487.1542; found, 487.1615.

Melting point: 97-100 °C.

This product was also characterized by X-ray crystallography (see section **X** for details).

Isolation of product 5.



The same procedure was followed as for the isolation of **3**, but using 1-iodo-3,5-dimethylbenzene as the coupling partner. Chromatography conditions: Gradient elution from 0% to 5% EtOAc in hexanes. Isolated yield: 10.6 mg, 69% (white solid).

^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC) δ 8.81 (s, 1H), 6.84 (s, 2H), 6.33 (m, 2H), 5.55 (ddd, *J* = 9.5, 4.0, 1.4 Hz, 1H), 3.81 (t, *J* = 5.7 Hz, 1H), 3.59 (d, *J* = 7.5 Hz, 1H), 3.25 (d, *J* = 3.4 Hz, 1H), 2.16 (ddd, *J* = 13.0, 6.5, 3.7 Hz, 1H), 2.12 (s, 6H), 2.02 (ddd, *J* = 12.0, 9.3, 2.7 Hz, 1H), 1.94 (dt, *J* = 17.5, 5.9 Hz, 1H), 1.84 (m, 1H), 1.31 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$, 23 ºC) δ 175.00, 143.4, 138.3, 136.1, 126.9, 125.7, 124.1, 64.4, 63.4, 55.8, 52.5, 35.1, 30.8, 25.4, 21.4, 20.8. *Carbon resonances associated with perfluoroaryl group are not observed.*[1,2]

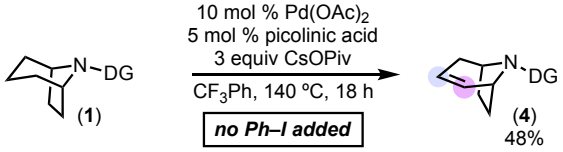
^{19}F NMR (564 MHz, $CDCl_3$, 23 ºC) δ –56.0 (t, *J* = 21.8 Hz, 3F), –142.4 (m, 2F), –143.2 (m, 2F).

HRMS-ESI (m/z): $[M]^+$ calcd. for $C_{26}H_{25}F_7N_2O$, 515.1928; found, 515.1947.

Melting point: 123-126 °C

V. Experiments in Scheme 3.

A. Scheme 3b. Formation of 4 in the absence of PhI



Experimental Procedure:
Under ambient conditions, a 0.02 M stock solution of $Pd(OAc)_2$ (22.5 mg in 5 mL of CH_2Cl_2) and a 0.02 M stock solution of picolinic acid (3.7 mg in 1 mL of MeOH) were prepared. To a 4 mL vial, an aliquot of the picolinic acid solution (0.15 mL, 0.003 mmol, 5 mol %) was added, and MeOH was removed by heating at 70 ºC for 5 min. To the same 4 mL vial, an aliquot of the $Pd(OAc)_2$ solution (0.3 mL, 0.006 mmol Pd, 10 mol %) was added, and dichloromethane was removed by heating at 40 ºC for 5 min. Substrate **1** (24.7 mg, 0.06 mmol, 1.0 equiv) and CsOPiv (42.1 mg, 0.18 mmol, 3 equiv) were then added, followed by $PhCF_3$ (0.3 mL). A stir bar was added to the vial, and it was sealed tightly with a Teflon-lined screw cap. The reaction was heated at 140 ºC for 18 h. After cooling to room temperature, trimethoxybenzene (5.0 mg) was added as a standard, and the resulting solution was diluted with $CDCl_3$ (0.7 mL). After stirring for 10 min, the reaction mixture was passed through a syringe filter. Reaction products and yields were determined by ^1H NMR spectroscopy. The slightly different chemical shifts of the product, **4**, in the two spectra is due to the different solvents (mixture of $CDCl_3$ and trifluorotoluene, top in **Figure S3** versus $CDCl_3$, bottom in **Figure S3**).

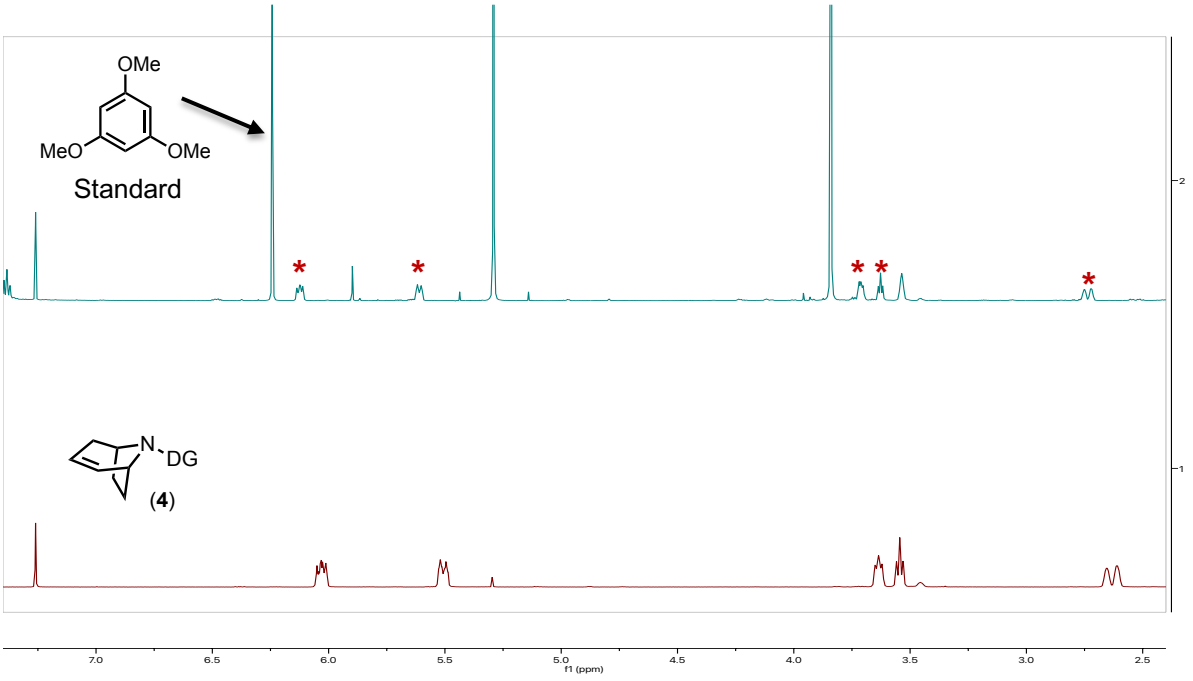
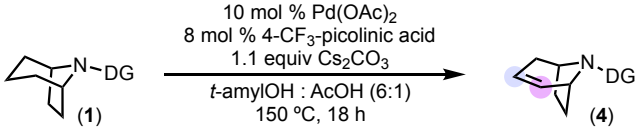


Figure S3. ^1H NMR spectrum of crude mixture from **Scheme 3b** (forming **4** in 48% yield).

B. Isolation of 4 under optimized conditions



Under ambient conditions, a 0.02 M stock solution of $Pd(OAc)_2$ (22.5 mg in 5 mL of CH_2Cl_2) and a 0.02 M stock solution of 4-CF_3-picolinic acid (7.64 mg in 2 mL of MeOH) were prepared. To a 4 mL vial, an aliquot of the 4-CF_3-picolinic acid solution (100 μL, 0.002 mmol, 8 mol %) was added, and the MeOH was removed by heating at 70 ºC for 5 min. To the same 4 mL vial, an aliquot of the $Pd(OAc)_2$ solution (150 μL, 0.003 mmol Pd, 10 mol %) was added, and the dichloromethane was removed by heating at 40 ºC for 5 min. Substrate **1** (12.4 mg, 0.03 mmol, 1.0 equiv) and Cs_2CO_3 (10.8 mg, 0.033 mmol, 1.1 equiv) were then added sequentially. The reaction mixture was diluted with *t*-amyl alcohol (0.30 mL) followed by the addition of acetic acid (50 μL). A stir bar was added, and the vial was sealed tightly with a Teflon-lined screw cap. The reaction was heated at 150 ºC for 18 h. The resulting mixture was allowed to cool to room temperature and then diluted with dichloromethane (3 mL). This mixture was filtered through a Celite pipette and washed with dichloromethane. The volatiles were removed under vacuum, and the residue was purified via column chromatography (gradient elution from 0% to 4% EtOAc in hexanes) to afford **4** as a white solid (7.8 mg, 63% yield).

^{1}H NMR (700 MHz, CD_3CN, 23 ºC): δ 9.75 (br s, 1H), 6.05 (m, 1H), 5.53 (m, 1H), 3.66 (d, J = 6.9 Hz, 1H), 3.54 (t, J = 5.4 Hz, 1H), 2.66 (d, J = 17.7 Hz, 1H), 2.12 (d, J = 13.6 Hz, 3H), 1.91 (m, 1H), 1.68 (m, 1H), 1.42 (s, 3H), 1.37 (s, 3H).

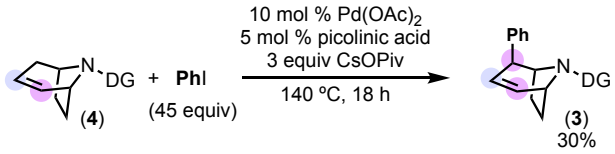
^{13}C NMR (176 MHz, CD_3CN, 23 ºC): δ 177.3, 135.5, 124.2, 63.5, 55.7, 55.2, 36.8, 36.3, 31.7, 25.0, 23.1. *Carbon resonances associated with perfluoroaryl group are not observed.*[1,2]

^{19}F NMR (564 MHz, CD_3CN, 23 ºC): δ –56.8 (t, J = 21.8 Hz, 3F), –144.1 (m, 2F), –145.3 (m, 2F).

HRMS-ESI (m/z): $[M]^+$ calcd. for $C_{18}H_{17}F_7N_2O$, 411.1302; found, 411.1291.

Melting Point: 101-104 °C.

C. Scheme 3c. Reaction of 4 with PhI to form 3



Under ambient conditions, a 0.02 M stock solution of $Pd(OAc)_2$ (22.5 mg in 5 mL CH_2Cl_2) and a 0.02 M stock solution of picolinic acid (3.7 mg in 1 mL of MeOH) were prepared. To a 4 mL vial, an aliquot of the picolinic acid solution (0.15 mL, 0.003 mmol, 5 mol %) was added, and MeOH was removed by heating at 70 ºC for 5 min. To the same 4 mL vial, an aliquot of the $Pd(OAc)_2$ solution (0.3 mL, 0.006 mmol Pd, 10 mol %) was added, and dichloromethane was removed by heating at 40 ºC for 5 min. Substrate **4** (24.6 mg, 0.06 mmol, 1.0 equiv) and CsOPiv (42.1 mg, 0.18 mmol, 3 equiv) were then added, followed by PhI (0.3 mL). A stir bar was added to the vial, and it was sealed tightly with a Teflon-lined screw cap. The reaction was heated at 140 ºC for 18 h. After cooling to room temperature, the mixture was diluted with dichloromethane (3.0 mL). An aliquot of the internal standard solution (0.6 mL, 0.1 M trimethoxybenzene in ethyl acetate) was added. The crude reaction mixture was then filtered through a Celite plug, and the Celite was washed with dichloromethane. The reaction was analyzed by GCMS. The yield of **2** was determined based on a 5-point calibration curve. The yield of **3** was determined based the area ratio of **2**, assuming that **2** and **3** have the same response factor on GCMS.

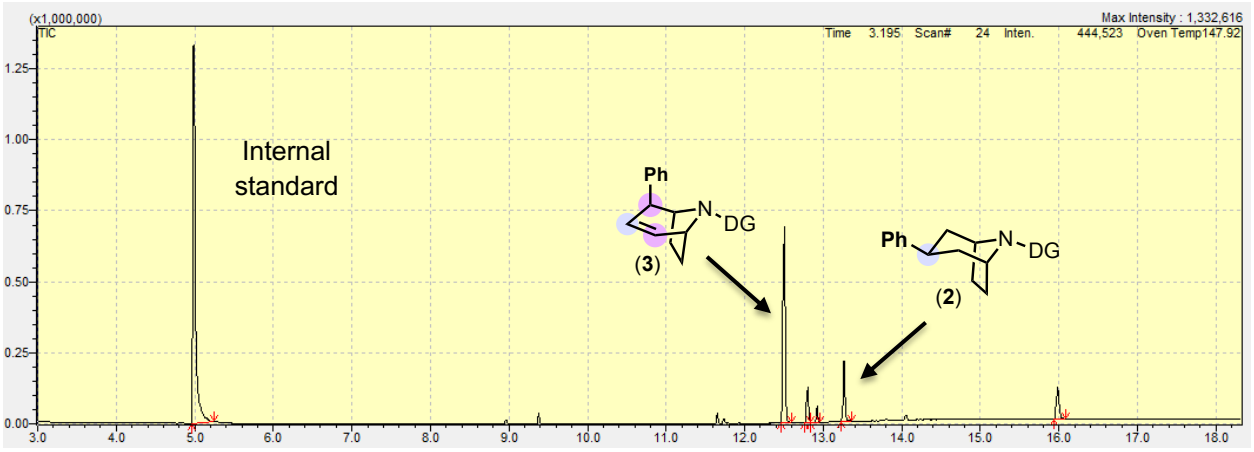
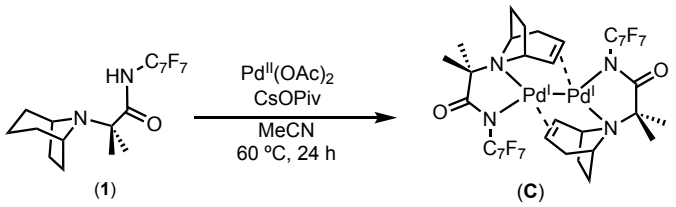


Figure S4. GCMS trace of reaction in **Scheme 3c**.

VI. Synthesis of Dimer C (Scheme 4)



A 4 mL vial was charged with substrate **1** (20.6 mg, 0.05 mmol, 1.0 equiv), $Pd(OAc)_2$ (11.3 mg, 0.05 mmol, 1.0 equiv), CsOPiv (35.1 mg, 0.15 mmol, 3.0 equiv), and a stir bar. To this vial, MeCN (1.0 mL) was added. The reaction was stirred at 60 °C for 24 h, resulting in a bright orange reaction mixture. The reaction was cooled to room temperature and filtered through a Celite plug, and the plug was rinsed with CH_2Cl_2 (10 mL). The volatiles were evaporated under reduced pressure. Purification via column chromatography (gradient elution from 0% to 90% EtOAc in hexanes) afforded **C** as an orange solid (18 mg, 35% yield).

Note: The yield of **C** was 36% as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Adjusting the stoichiometry of **1** : $Pd(OAc)_2$ from 1: 1 to 1: 1.5 or 1 : 2 (based on the mechanism in Figure S9) resulted in slightly higher crude yields of ~45% and ~44%, respectively. However, the uneven baseline of these NMR spectra made accurate integration challenging, which is why these yields are approximate. We believe that the moderate yields and uneven baseline with higher palladium loadings are due to precipitation of the Pd black (we observe a large amount of black solid in all of these reactions), which limits the accessibility of Pd(0) for comproportionation with $Pd(OAc)_2$.

^{1}H NMR (700 MHz, $CDCl_3$, 23 ºC): δ 5.28 (ddt, *J* = 7.8, 3.9, 1.5 Hz, 2H), 4.84 (t, *J* = 4.8 Hz, 2H), 4.40 (t, *J* = 6.8 Hz, 2H), 4.05 (dd, *J* = 18.5, 5.0 Hz, 2H), 3.79 (t, *J* = 6.0 Hz, 2H), 2.61 (dd, *J* = 18.2, 6.0 Hz, 2H), 2.23 (m, 4H), 2.06 (s, 6H), 1.89-1.76 (m, 2H), 1.41 (s, 6H), 1.23 (m, 2H).

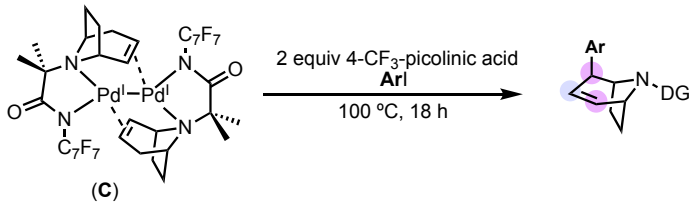
^{13}C NMR (176 MHz, $CDCl_3$, 23 ºC): δ 178.2, 90.8, 84.0, 72.0, 68.1, 61.7, 44.0, 38.5, 30.3, 29.7, 23.2. *Carbon resonances associated with perfluoroaryl group are not observed.*[1,2]

^{19}F NMR (470 MHz, $CDCl_3$, 23 ºC): δ –55.7 (m, 6F), –142.6 (m, 4F), –147.9 (m, 4F).

Elemental Analysis calcd for $C_{36}H_{32}F_{14}N_4O_2Pd_2$, C: 41.92; H: 3.13; N: 5.43; found, C: 42.12; H: 3.36; N: 5.25.

VII. Reactions of Dimer C

A. Reaction of C with ArI (Scheme 5, top 2 reactions)



For phenyl iodide: A 4 mL vial was charged with **C** (5.3 mg, 5.0 μmol), 4-CF_3-picolinic acid (1.9 mg, 10 μmol, 2 equiv), and phenyl iodide (0.5 mL). The vial was sealed tightly with a Teflon-lined screw cap and heated to 100 °C. After 18 h, the vial was cooled to room temperature. An aliquot of internal standard solution (0.2 mL, 0.01 M 1,4-dinitrobenzene in CD_3CN) was added. The solution was then diluted with 0.2 mL CD_3CN and filtered through a syringe filter. Reaction products and yields were determined by ^1H NMR spectroscopy. The slightly different chemical shifts of the product, **3**, in the two spectra is due to the different solvents (mixture of CD_3CN and phenyl iodide, top in **Figure S5** versus CD_3CN, bottom in **Figure S5**).

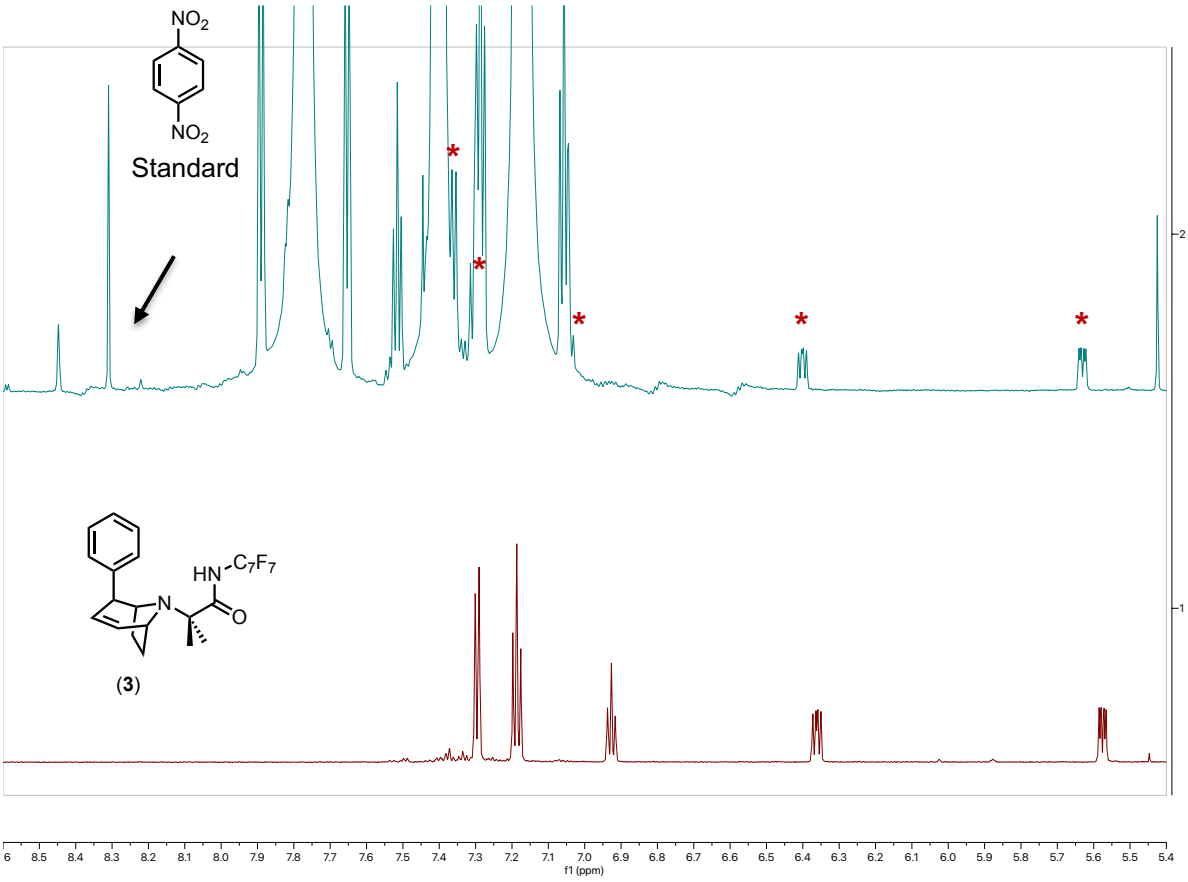


Figure S5. ^1H NMR spectrum of crude reaction mixture from **Scheme 5** (forming **3**).

For 1-iodo-3,5-dimethylbenzene: A 4 mL vial was charged with **C** (5.3 mg, 5.0 μmol), 4-CF_3-picolinic acid (1.9 mg, 10 μmol, 2 equiv), and 1-iodo-3,5-dimethylbenzene (0.5 mL). The vial was sealed tightly with a Teflon-lined screw cap and heated to 100 °C. After 18 h, the vial was cooled to room temperature. An aliquot of internal standard solution (0.2 mL, 0.01 M 1,4-dinitrobenzene in CD_3CN) was added to the vial. The solution was then diluted with 0.2 mL CD_3CN and filtered through a syringe filter. Reaction products and yields were determined by ^1H NMR spectroscopy.

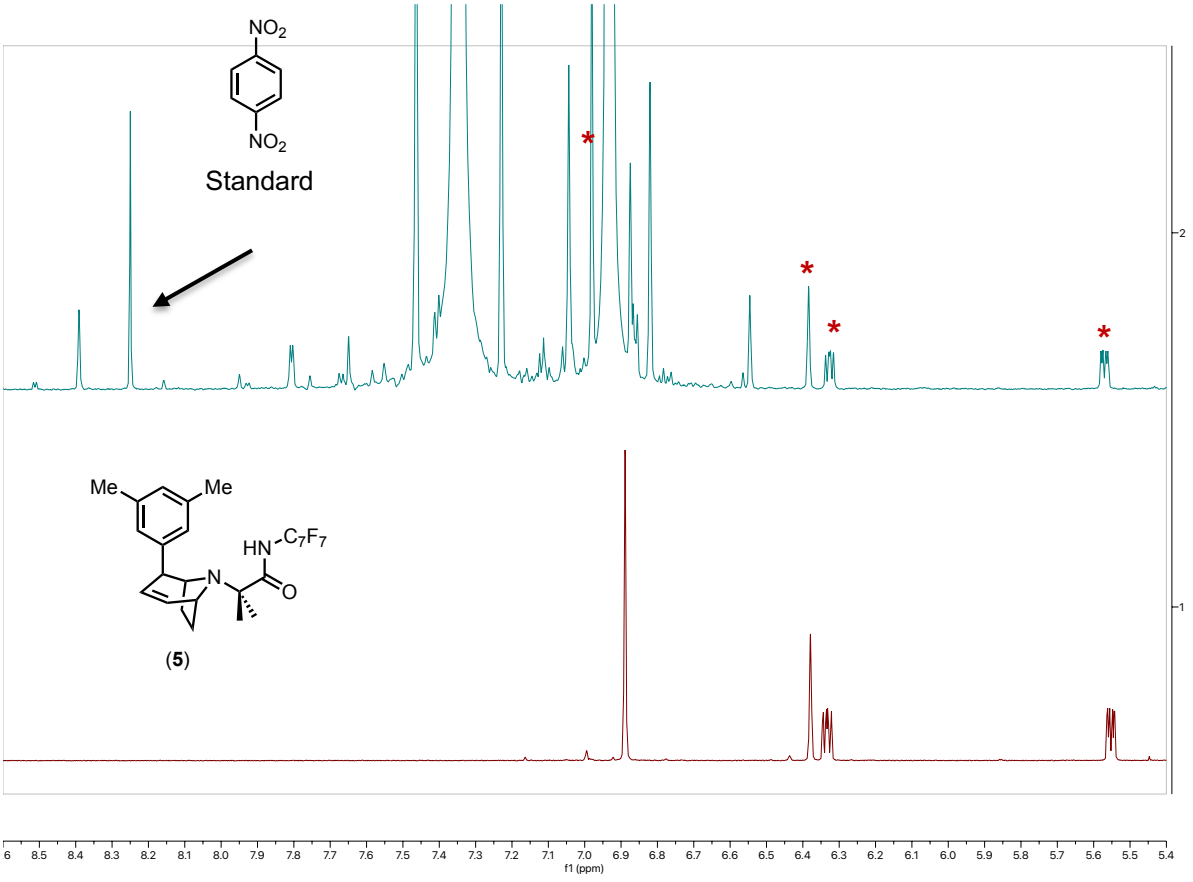
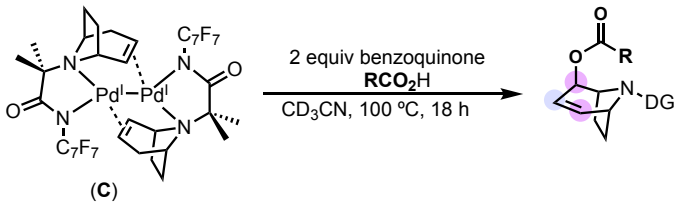


Figure S6. ^1H NMR spectrum of crude reaction mixture from **Scheme 5** (forming **5**).

B. Reaction of C with carboxylic acids (Scheme 5, bottom 2 reactions)



(**C**)

For benzoic acid: A 4 mL vial was charged with **C** (5.3 mg, 5.0 μmol), benzoquinone (1.1 mg, 10 μmol, 2 equiv), benzoic acid (6.1 mg, 50 μmol, 10 equiv), and CD_3CN (0.5 mL). The vial was sealed tightly with a Teflon-lined screw cap and heated to 100 °C. After 18 h, the vial was cooled to room temperature. An aliquot of internal standard solution (0.2 mL, 0.01 M 1,4-dinitrobenzene in CD_3CN) was added to the vial. The solution was then diluted with 0.2 mL CD_3CN and filtered through a syringe filter. Reaction products and yields were determined by ^1H NMR spectroscopy.

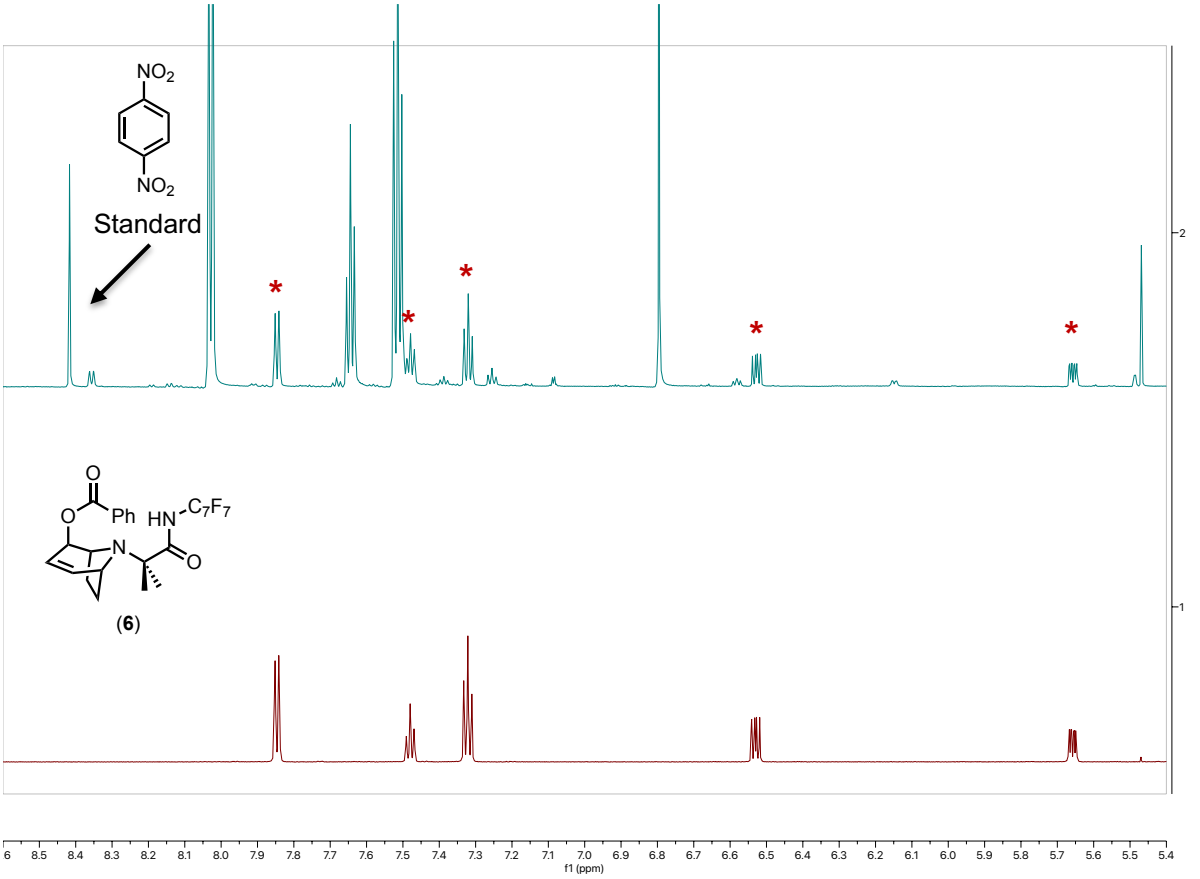


Figure S7. ^1H NMR spectrum of crude reaction mixture from **Scheme 5** (forming **6**).

For propionic acid: A 4 mL vial was charged with **C** (5.3 mg, 5.0 μmol), benzoquinone (1.1 mg, 10 μmol, 2 equiv), propionic acid (3.8 μL, 50 μmol, 10 equiv), and CD_3CN (0.5 mL). The vial was sealed tightly with a Teflon-lined screw cap and heated to 100 °C. After 18 h, the vial was cooled to room temperature. An aliquot of internal standard solution (0.2 mL, 0.01 M 1,4-dinitrobenzene in CD_3CN) was added to the vial. The solution was then diluted with 0.2 mL CD_3CN and filtered through a syringe filter. Reaction products and yields were determined by ^1H NMR spectroscopy.

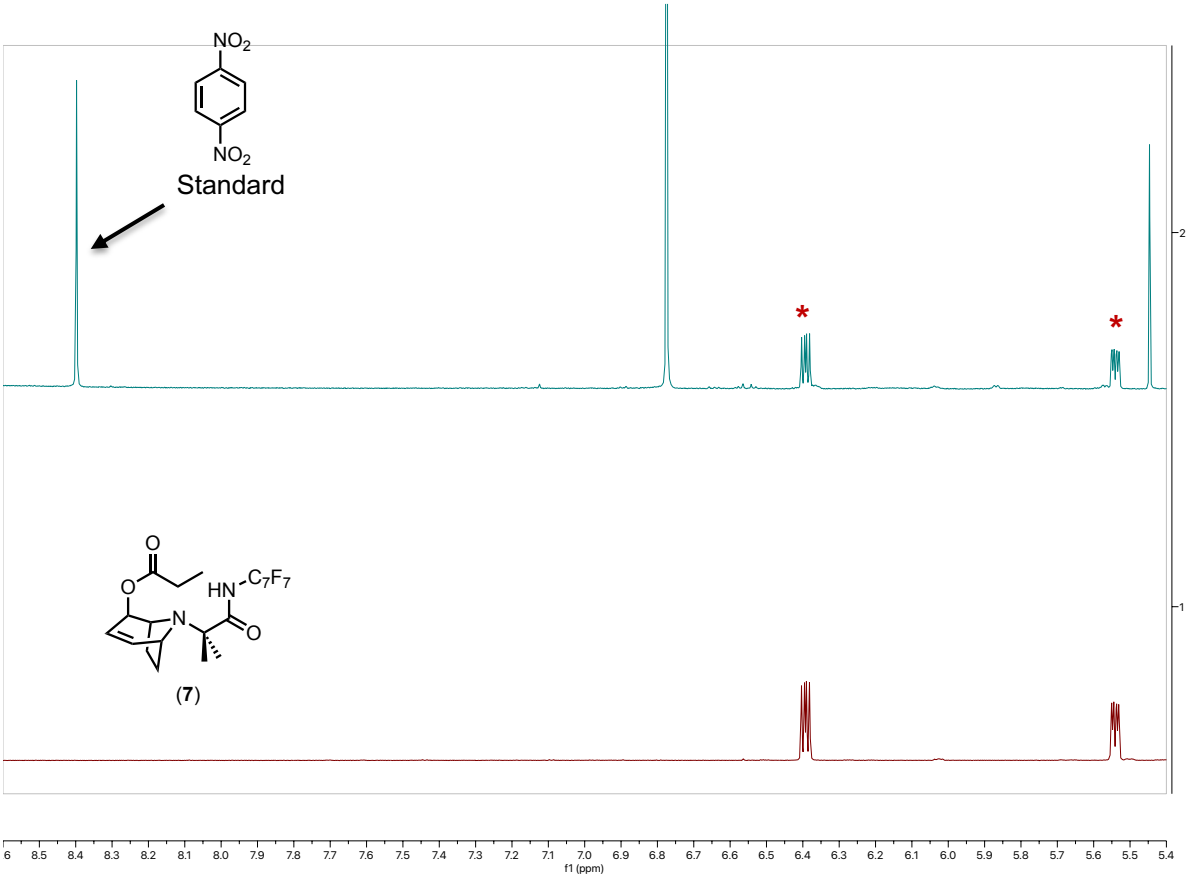
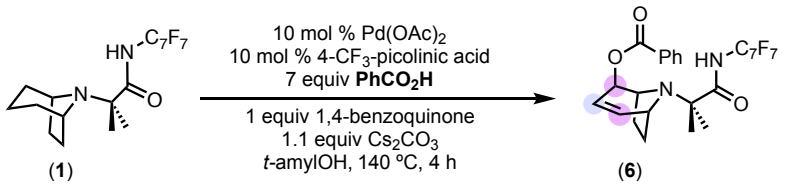


Figure S8. ^1H NMR spectrum of crude reaction mixture from **Scheme 5** (forming **7**).

C. Synthesis of authentic samples of 6 and 7



In a 4 mL vial, substrate **1** (25.0 mg, 0.06 mmol, 1.0 equiv), $Pd(OAc)_2$ (1.4 mg, 0.006 mmol, 10 mol %), and 4-CF_3-picolinic acid (1.2 mg, 0.006 mmol, 10 mol %) was added. To the same 4 mL vial, Cs_2CO_3 (21.0 mg, 0.066 mmol, 1.1 equiv) and 1,4-benzoquinone (6.5 mg, 0.06 mmol, 1.0 equiv) was added followed by the addition of the carboxylic acid (0.42 mmol, 7.0 equiv). The reaction mixture was then diluted with *t*-amyl alcohol (0.60 mL). A stir bar was added, and the vial was sealed tightly with a Teflon-lined screw cap. The vial was heated to 140 °C. Every 30 min, the vial was removed from the heat and allowed to cool to room temperature, and then then the cap was opened to expose the reaction to air. The reaction vial was then re-capped and heated for another 30 min. After repeating this procedure 8 times (total heating time = 4 h), the reaction was allowed to cool to room temperature and diluted with dichloromethane (3.0 mL). The reaction solution was filtered through a Celite pipette that was then washed with dichloromethane. The volatiles were removed under reduced pressure, and the residue was purified via column chromatography to obtain the desired product.

Compound 6: The procedure above was followed using benzoic acid as the coupling reagent. Chromatography conditions: Gradient elution from 2% to 6% EtOAc in hexanes. Isolated yield: 20.2 mg, 64% yield (white solid).

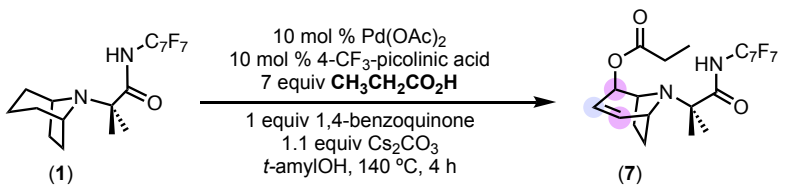
^{1}H NMR (700 MHz, $CDCl_3$, 23 ºC): δ 9.66 (br s, 1H), 7.84 (d, *J* = 6.9, 2H), 7.41 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 2H), 6.47 (dd, *J* = 9.4, 6.1 Hz, 1H), 5.63 (ddd, *J* = 9.4, 4.2, 1.5 Hz, 1H), 5.10 (dd, *J* = 4.2, 2.0 Hz, 1H), 3.96-3.84 (m, 2H), 2.10 (dddd, *J* = 13.6, 10.8, 8.0, 3.0 Hz, 1H), 1.88 (tt, *J* = 11.6, 6.1 Hz, 1H), 1.82 (ddd, *J* = 12.1, 9.0, 3.0 Hz, 1H), 1.66 (m, 1H), 1.38 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (176 MHz, $CDCl_3$, 23 ºC): δ 175.7, 165.8, 140.8, 133.4, 129.8, 129.2, 128.2, 120.9, 74.5, 63.3, 60.1, 55.9, 31.5, 25.6, 25.2, 22.2. *Carbon resonances associated with perfluoroaryl group are not observed.*[1,2]

^{19}F NMR (470 MHz, $CDCl_3$, 23 ºC): δ –56.2 (m, 3F), –141.0 (m, 2F), –143.9 (m, 2F).

HRMS-ESI (m/z): $[M]^+$ calcd. for $C_{25}H_{21}F_7N_2O_3$, 531.1513; found, 531.1515.

Melting point: 135-137 °C



Compound 7: Procedure above was followed using propionic acid as the coupling reagent. Chromatography conditions: Gradient elution from 2% to 8% EtOAc in hexanes. Isolated yield: 17.4 mg, 60% yield (white solid)

^{1}H NMR (700 MHz, $CDCl_3$, 23 ºC): δ 9.71 (br s, 1H), 6.38 (dd, *J* = 9.4, 5.9 Hz, 1H), 5.57 (m, 1H), 4.89 (dd, *J* = 4.4, 1.9 Hz, 1H), 3.82 (d, *J* = 8.2 Hz, 1H), 3.68 (t, *J* = 5.9 Hz, 1H), 2.19 (ddt, *J* = 37.0, 16.4, 8.2 Hz, 2H), 2.03 (m, 1H), 1.86 (tt, *J* = 11.7, 6.0 Hz, 1H), 1.75 (ddd, *J* = 12.3, 9.1, 3.0 Hz, 1H), 1.62 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.09 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (176 MHz, $CDCl_3$, 23 ºC): δ 176.2, 173.8, 140.1, 121.6, 73.3, 62.9, 58.3, 56.6, 31.3, 27.7, 26.0, 25.2, 22.7, 9.2. *Carbon resonances associated with perfluoroaryl group are not observed.*[1,2]

^{19}F NMR (470 MHz, $CDCl_3$, 23 ºC): δ –56.0 (m, 3F), –141.1 (m, 2F), –143.5 (m, 2F).

HRMS-ESI (m/z): $[M]^+$ calcd. for $C_{21}H_{21}F_7N_2O_3$, 483.1513; found, 483.1514.

Melting point: 120-123 °C.

This product was also characterized by X-ray crystallography (see section **X** for details).

VIII. Mechanisms

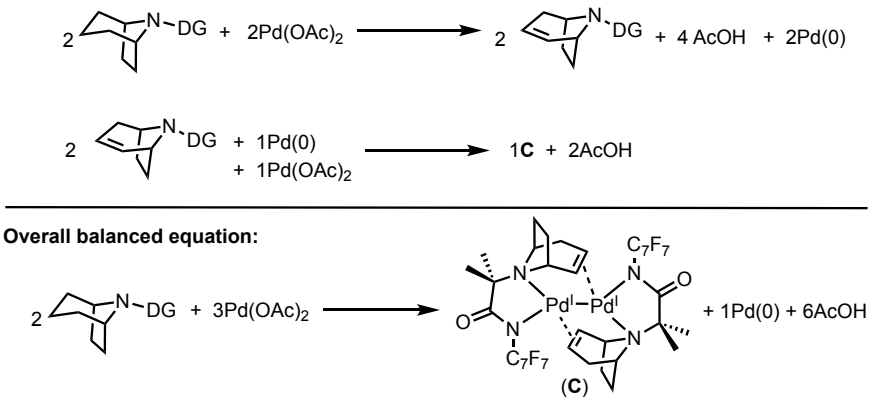


Figure S9. Proposed pathway for the formation of **C** [$Pd(OAc)_2$ serves as the oxidant for dehydrogenation and for the formation of Pd(I) dimer **C**]. Notably, the reaction also proceeds under N_2 (affording 25% yield of **C** compared to 36% under ambient atmosphere), consistent with $Pd(OAc)_2$ serving as the primary oxidant in this transformation.

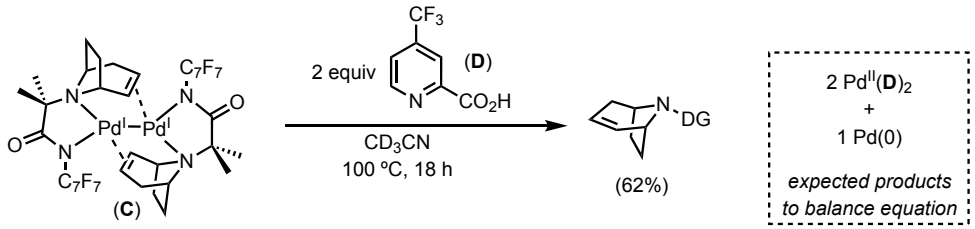


Figure S10. Reaction of **C** with 2 equiv of 4-CF_3-picolinic acid at 100 ºC for 18 h.

IX. References

(1) Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. Palladium-Catalysed Transannular C–H Functionalization of Alicyclic Amines. *Nature* **2016**, *531*, 220–224.

(2) Cabrera, P. J.; Lee, M.; Sanford, M. S. Second-Generation Palladium Catalyst System for Transannular C–H Functionalization of Azabicycloalkanes. *J. Am. Chem. Soc*. **2018**, *140*, 5599–5606.

X. X-Ray Crystallography Data

Compound 3

Colorless needles of **3** were grown from a dichloromethane/hexanes solution of the compound at 22°C. A crystal of dimensions 0.12 x 0.04 x 0.04 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 0.3 kW power (30 kV, 10 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 3 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 32406 reflections to a maximum 2θ value of 139.77° of which 3913 were independent and 3721 were greater than 2σ(I). The final cell constants (Table S1) were based on the xyz centroids of 17682 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2018/3) software package, using the space group P2(1)/c with Z = 4 for the formula $C_{24}H_{21}N_2OF_7$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in a combination of refined and idealized positions. The crystal was determined to be a pseudo-merohedral twin. Twin law [-1 0 0 0 -1 0 0 0 1], refined twin scale factor 0.235(3). Full matrix least-squares refinement based on F^2 converged at R1 = 0.0850 and wR2 = 0.2531 [based on I > 2sigma(I)], R1 = 0.0884 and wR2 = 0.2648 for all data. Additional details are presented in Table S1 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", Acta Cryst., C71, 3-8 (Open Access).

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

CrysAlisPro 1.171.40.53 (Rigaku Oxford Diffraction, 2019).

Table S1. Crystal Data and Structural Refinement for **3.**

Empirical Formula	$C_{24}H_{21}F_7N_2O$
Formula Weight	486.43
Temperature	85 (2) K
Wavelength	1.54184 Å
Crystal System	Monoclinic
Space Group	P2(1)/c
Unit Cell Dimensions	a = 7.7054 (3) Å, α = 90 ° b = 12.5541 (4) Å, β = 90.196 (3)° c = 22.0120 (8) Å, γ = 90 °
Volume	2129.30 (13) $Å^3$
Z	4
Calculated Density	1.517 Mg/m^3
Absorption Coefficient	1.185 mm^{-1}
F(000)	1000
Crystal Size	0.120 x 0.040 x 0.040 mm
Theta Range for Data Collection	3.520 to 69.883 °
Limiting Indices	$-8\leq h\leq 8$, $-15\leq k\leq 15$, $-26\leq l\leq 25$
Reflections Collected	32406
Independent Reflections	3913
Completeness to Theta	98.6%
Absorption Correction	Semi-empirical from equivalents
Max and Min Transmission	1.00000 to 0.54488
Refinement Method	Full-matrix least-squares on F^2
Data / Restraints / Parameters	3913 / 0 / 314
Goodness-of-Fit on F^2	1.138
Final R Indices [$I>2\sigma(I)$]	R1 = 0.0850, wR2 = 0.2531
R indices (all data)	R1 = 0.0884, wR2 = 0.2648
Extinction Coefficient	N/A
Largest Difference Peak and Hole	0.401 and -0.514 $Å^{-3}$

Compound 7

Colorless prisms of **7** were grown from a dichloromethane/hexanes solution of the compound at 22 °C. A crystal of dimensions 0.22 x 0.22 x 0.22 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 0.3 kW power (30 kV, 10 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for all images. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 30908 reflections to a maximum 2θ value of 138.62° of which 3800 were independent and 3722 were greater than 2σ(I). The final cell constants (Table S2) were based on the xyz centroids of 20201 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2018/3) software package, using the space group P2(1)/n with Z = 4 for the formula $C_{21}H_{21}N_2O_3F_7$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in a combination of refined and idealized positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0425 and wR2 = 0.1047 [based on I > 2sigma(I)], R1 = 0.0434 and wR2 = 0.1061 for all data. Additional details are presented in Table S2 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", Acta Cryst., C71, 3-8 (Open Access).

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

CrysAlisPro 1.171.40.53 (Rigaku Oxford Diffraction, 2019).

Table S2. Crystal Data and Structural Refinement for **7.**

Empirical Formula	$C_{21}H_{21}F_7N_2O_3$
Formula Weight	482.40
Temperature	85 (2) K
Wavelength	1.54184 Å
Crystal System	Monoclinic
Space Group	P2(1)/n
Unit Cell Dimensions	a = 11.17206 (13) Å, α = 90 ° b = 16.78418 (16) Å, β = 100.8711 (9)° c = 11.27108 (10) Å, γ = 90 °
Volume	2075.55 (4) $Å^3$
Z	4
Calculated Density	1.544 Mg/m^3
Absorption Coefficient	1.281 mm^{-1}
F(000)	992
Crystal Size	0.220 x 0.220 x 0.220 mm
Theta Range for Data Collection	4.786 to 69.314 °
Limiting Indices	$-10\leq h\leq 12$, $-20\leq k\leq 20$, $-13\leq l\leq 13$
Reflections Collected	30908
Independent Reflections	3800
Completeness to Theta	98.3%
Absorption Correction	Semi-empirical from equivalents
Max and Min Transmission	1.00000 to 0.81320
Refinement Method	Full-matrix least-squares on F^2
Data / Restraints / Parameters	3800 / 6 / 333
Goodness-of-Fit on F^2	1.048
Final R Indices [$I>2\sigma(I)$]	R1 = 0.0425, wR2 = 0.1047
R indices (all data)	R1 = 0.0434, wR2 = 0.1061
Extinction Coefficient	0.0020 (2)
Largest Difference Peak and Hole	0.428 and -0.269 $Å^{-3}$

Dimer C

Orange needles of **C** were grown from a hexanes/dichloromethane solution of the compound at 23°C. A crystal of dimensions 0.10 x 0.02 x 0.02 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 sec. for the low angle images, 3 sec. for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 30119 reflections to a maximum 2θ value of 138.53° of which 7222 were independent and 6743 were greater than 2σ(I). The final cell constants (Table S3) were based on the xyz centroids of 14261 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2016/6) software package, using the space group P1bar with Z = 2 for the formula $C_{36}H_{32}F_{14}N_4O_2Pd_2$. All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in a combination of idealized and refined positions. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0406 and wR2 = 0.1129 [based on I > 2sigma(I)], R1 = 0.0429 and wR2 = 0.1164 for all data. Additional details are presented in Table S3 and are given as Supporting Information in a CIF file. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

G.M. Sheldrick (2015) "Crystal structure refinement with SHELXL", Acta Cryst., C71, 3-8 (Open Access).

CrystalClear Expert 2.0 r16, Rigaku Americas and Rigaku Corporation (2014), Rigaku Americas, 9009, TX, USA 77381-5209, Rigaku Tokyo, 196-8666, Japan.

CrysAlisPro 1.171.38.41 (Rigaku Oxford Diffraction, 2015).

Table S3. Crystal Data and Structural Refinement for **C**.

Empirical Formula	$C_{36}H_{32}F_{14}N_4O_2Pd_2$
Formula Weight	1134.40
Temperature	85 (2) K
Wavelength	1.54184 Å
Crystal System	Triclinic
Space Group	P-1
Unit Cell Dimensions	a = 12.1394 (3) Å, α = 85.100(2)° b = 12.7800 (4) Å, β = 79.236 (2)° c = 13.9061 (3) Å, γ = 70.699 (2)°
Volume	1999.68 (9) $Å^3$
Z	2
Calculated Density	1.884 Mg/m^3
Absorption Coefficient	9.482 mm^{-1}
F(000)	1124
Crystal Size	0.100 x 0.020 x 0.020 mm
Theta Range for Data Collection	3.236 to 69.269 °
Limiting Indices	$-14\leq h\leq 14$, $-15\leq k\leq 15$, $-14\leq l\leq 16$
Reflections Collected	30119
Independent Reflections	7222
Completeness to Theta	97.7%
Absorption Correction	Semi-empirical from equivalents
Max and Min Transmission	1.00000 to 0.46518
Refinement Method	Full-matrix least-squares on F^2
Data / Restraints / Parameters	7222 / 3 / 571
Goodness-of-Fit on F^2	1.070
Final R Indices [$I>2\sigma(I)$]	R1 = 0.0406, wR2 = 0.1129
R indices (all data)	R1 = 0.0429, wR2 = 0.1164
Extinction Coefficient	N/A
Largest Difference Peak and Hole	1.181 and -1.347 $Å^{-3}$

XI. Spectral Data:

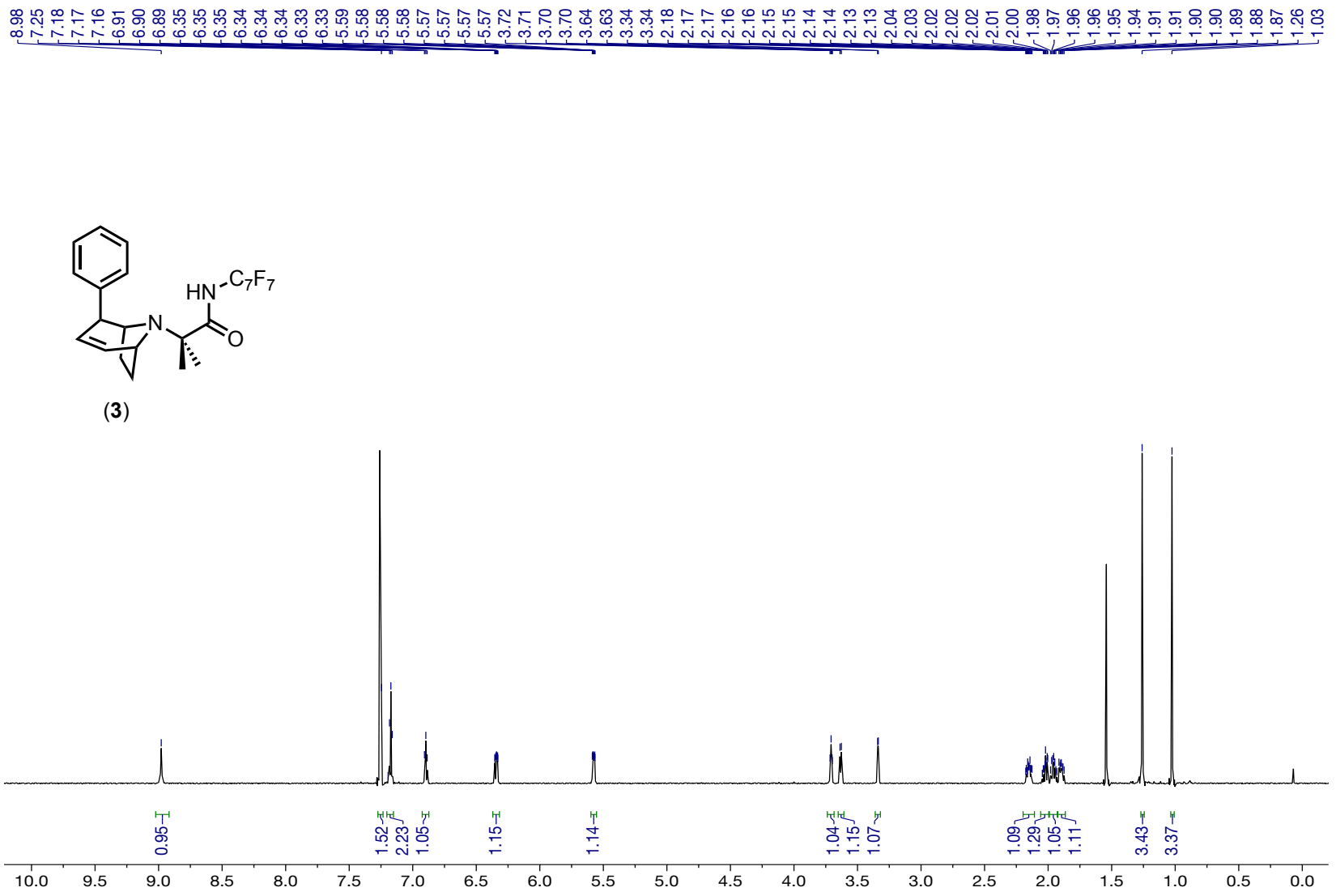


Figure S11. 3: 700 MHz ^{1}H NMR spectrum in $CDCl_3$

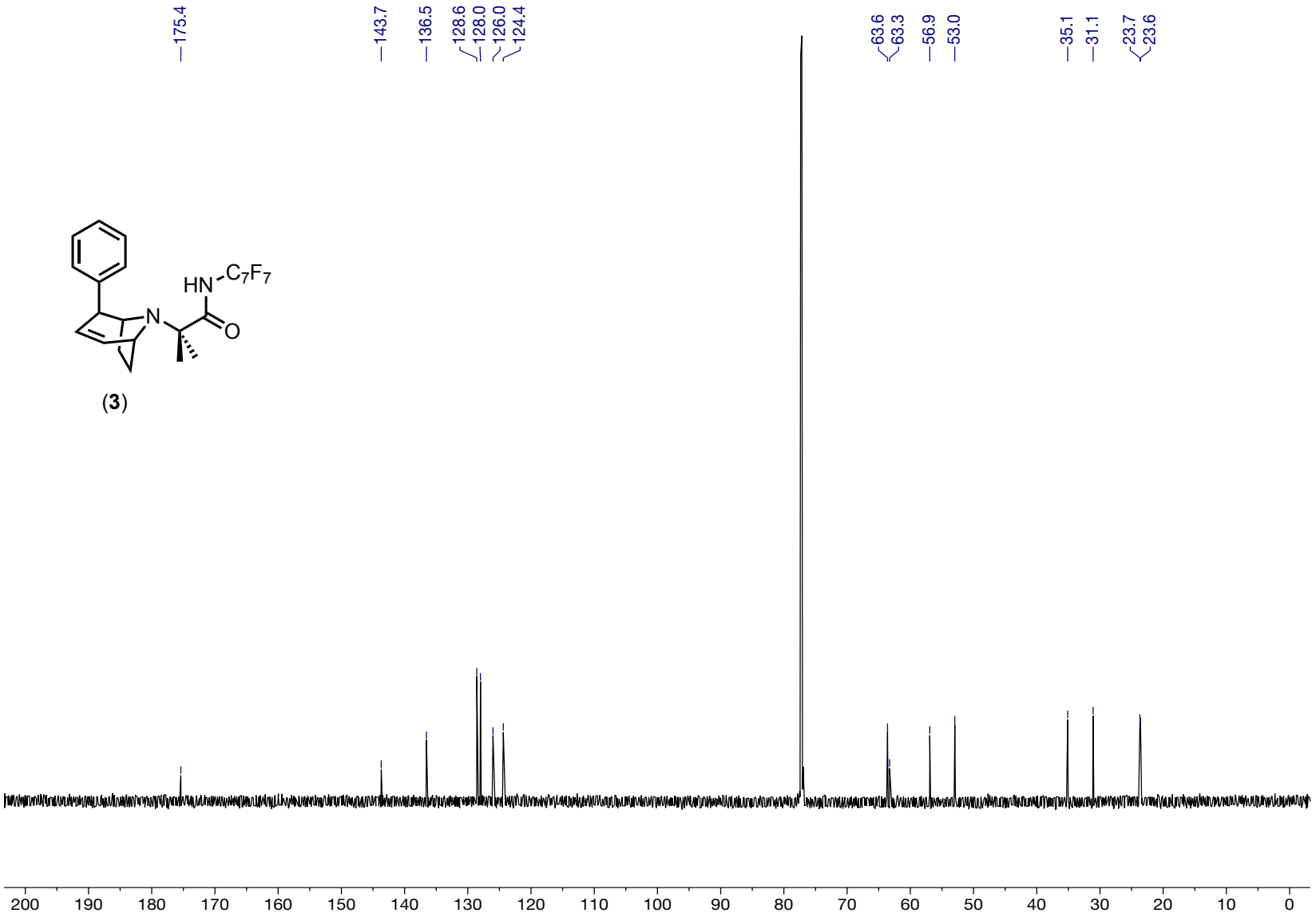


Figure S12. 3: 176 MHz ^{13}C NMR spectrum in $CDCl_3$

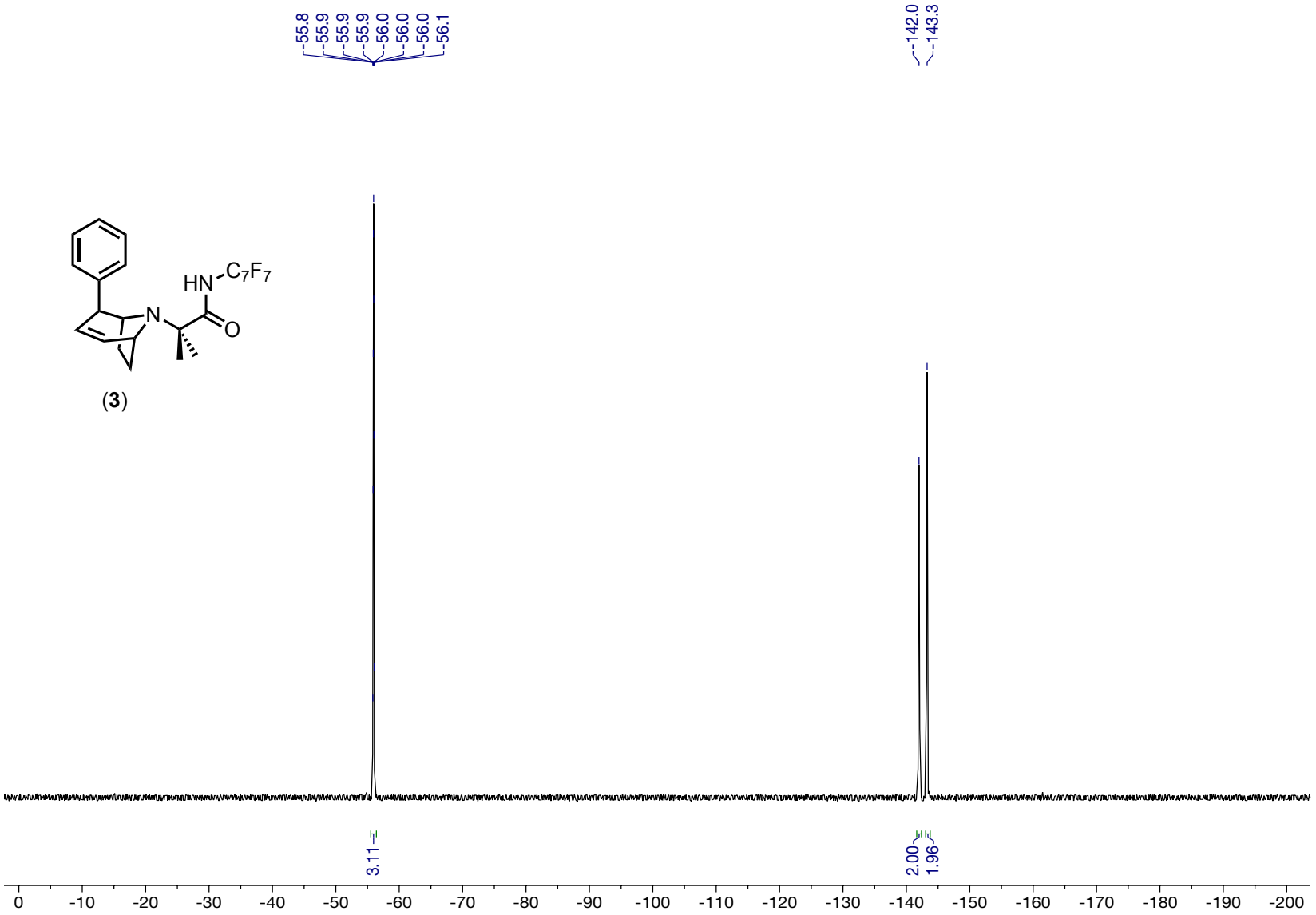


Figure S13. 3: 470 MHz ^{19}F NMR spectrum in $CDCl_3$

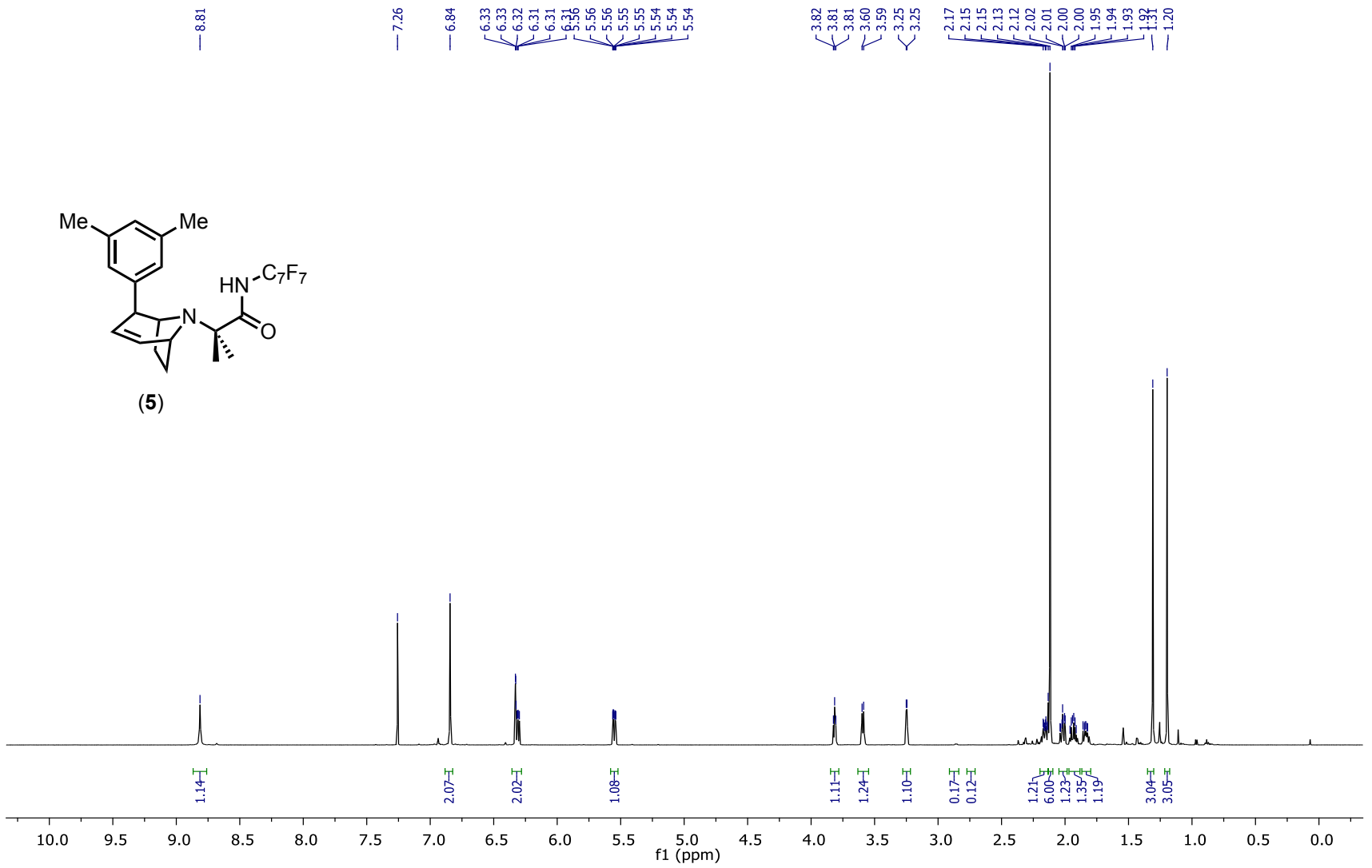


Figure S14. 5: 600 MHz ^{1}H NMR spectrum in $CDCl_3$

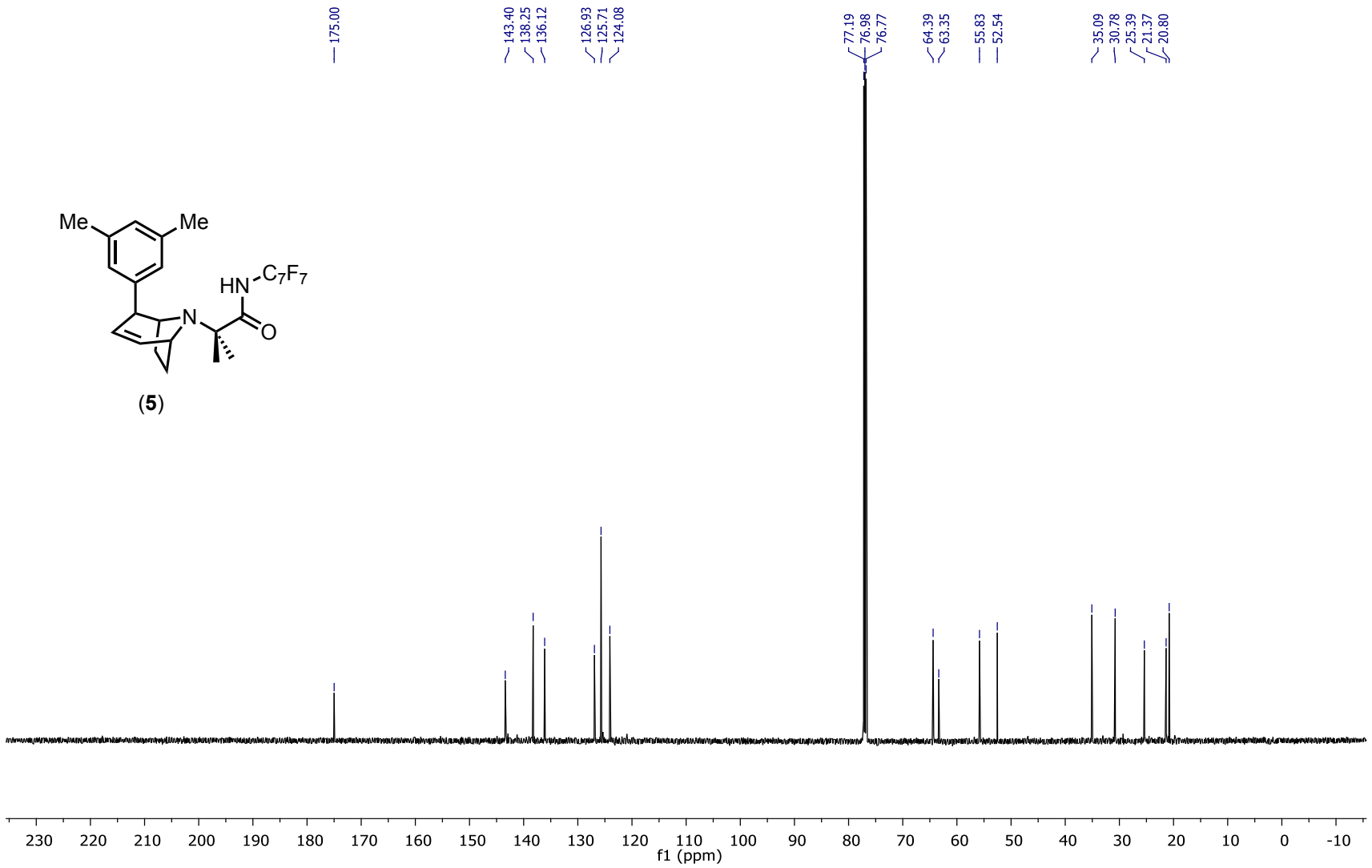


Figure S15. 5: 151 MHz ^{13}C NMR spectrum in $CDCl_3$

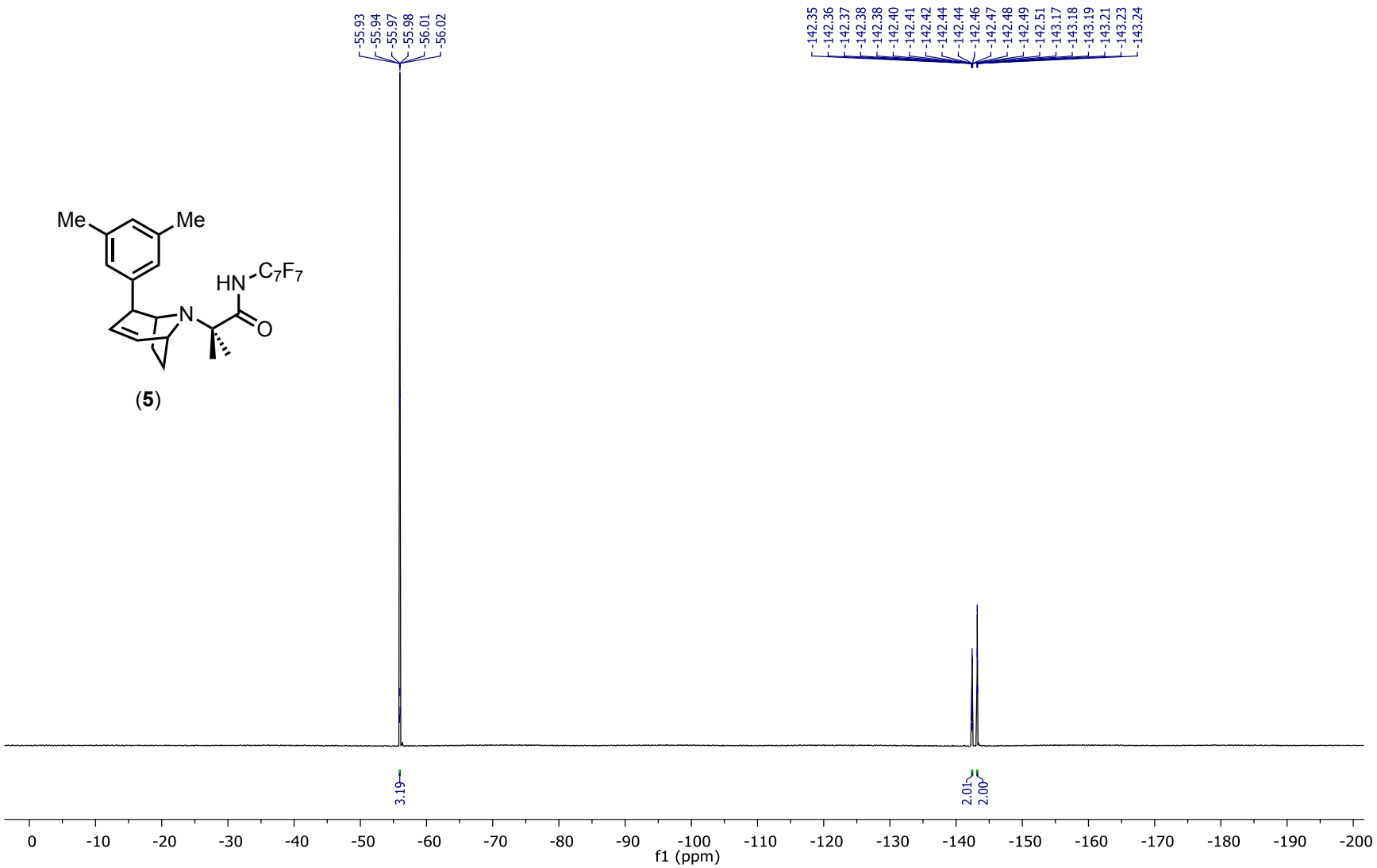


Figure S16. 5: 564 MHz ^{19}F NMR spectrum in $CDCl_3$

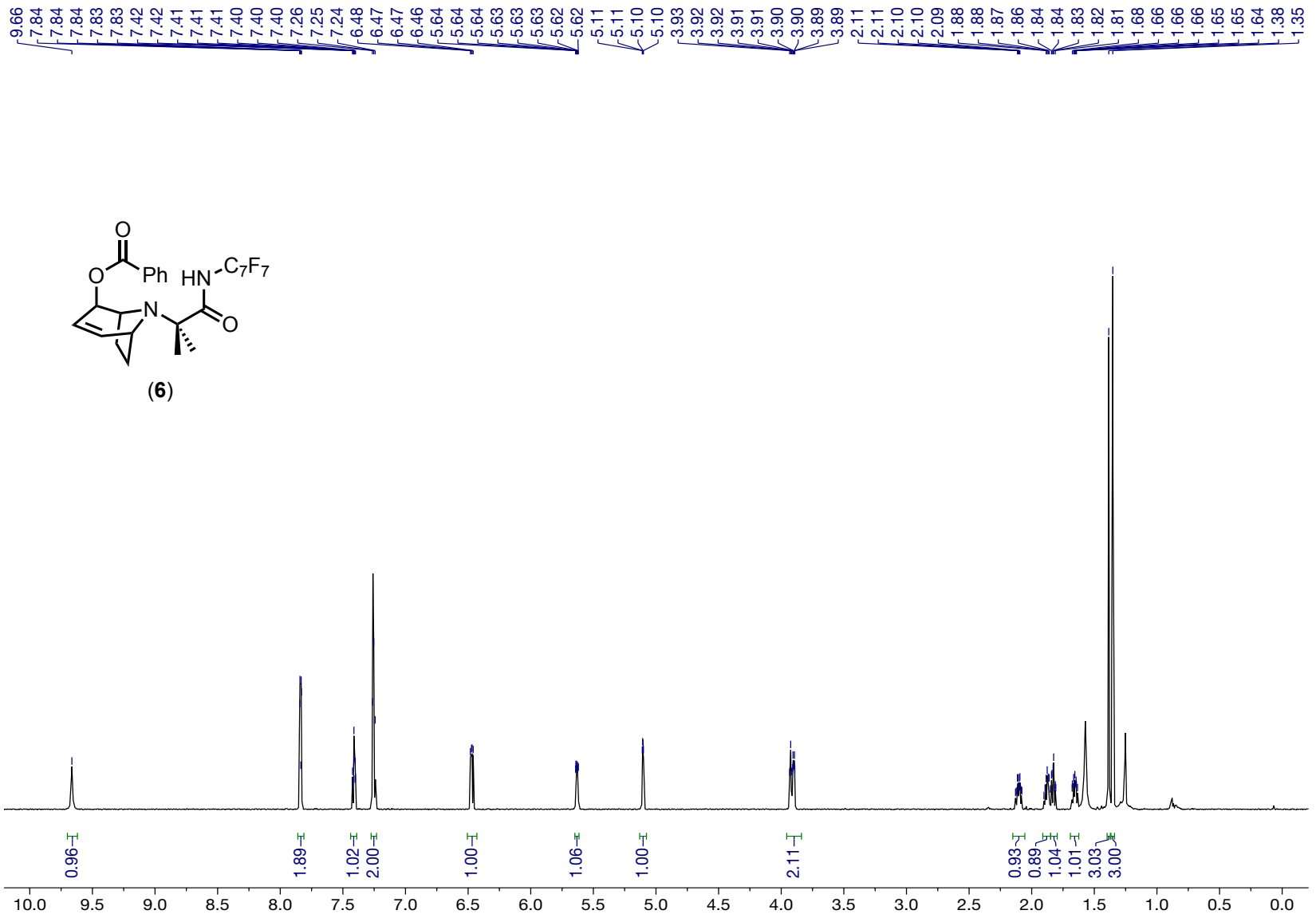


Figure S17. 6: 700 MHz ^{1}H NMR spectrum in $CDCl_3$

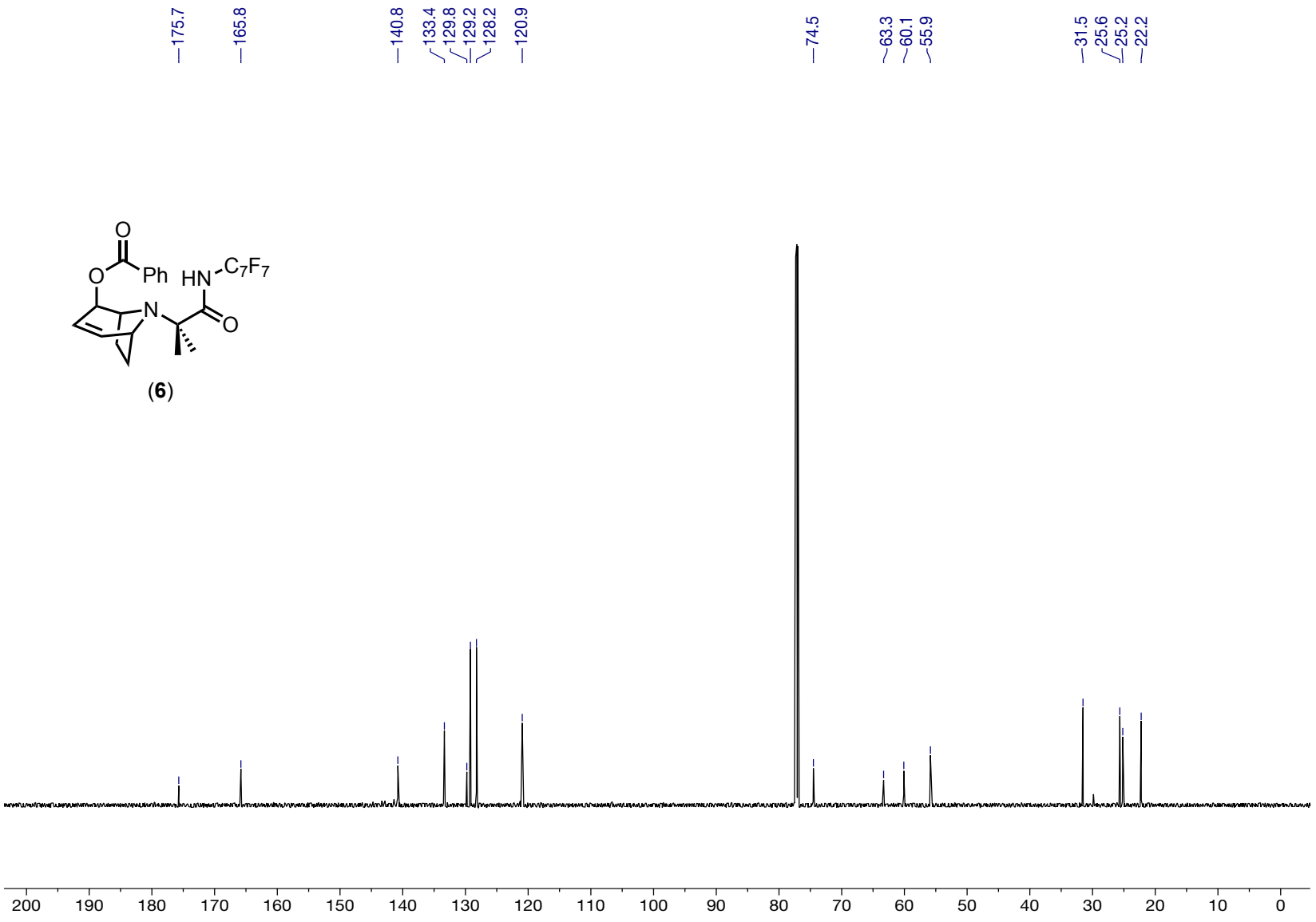


Figure S18. 6: 176 MHz ^{13}C NMR spectrum in $CDCl_3$

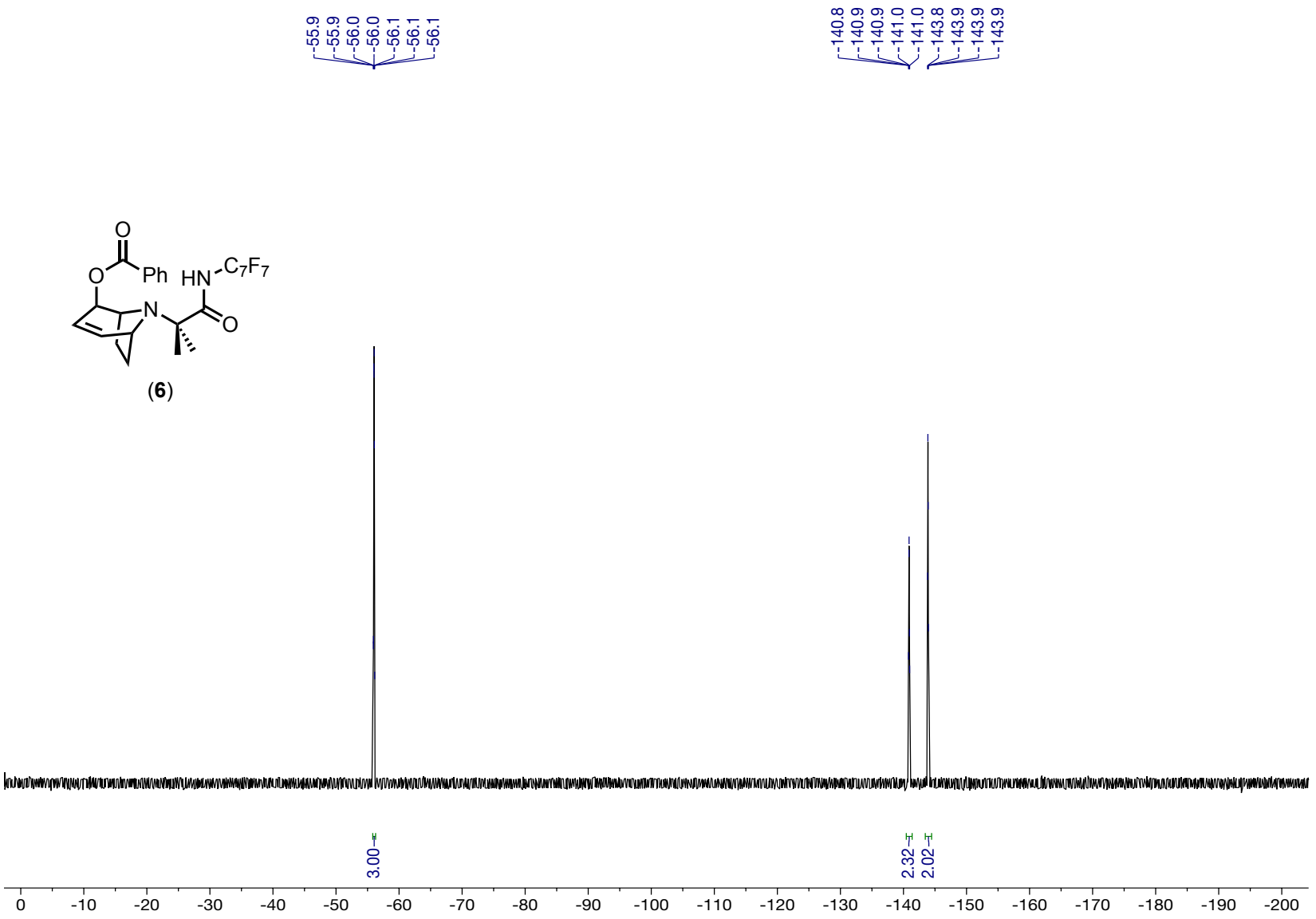


Figure S19. 6: 470 MHz ^{19}F NMR spectrum in $CDCl_3$

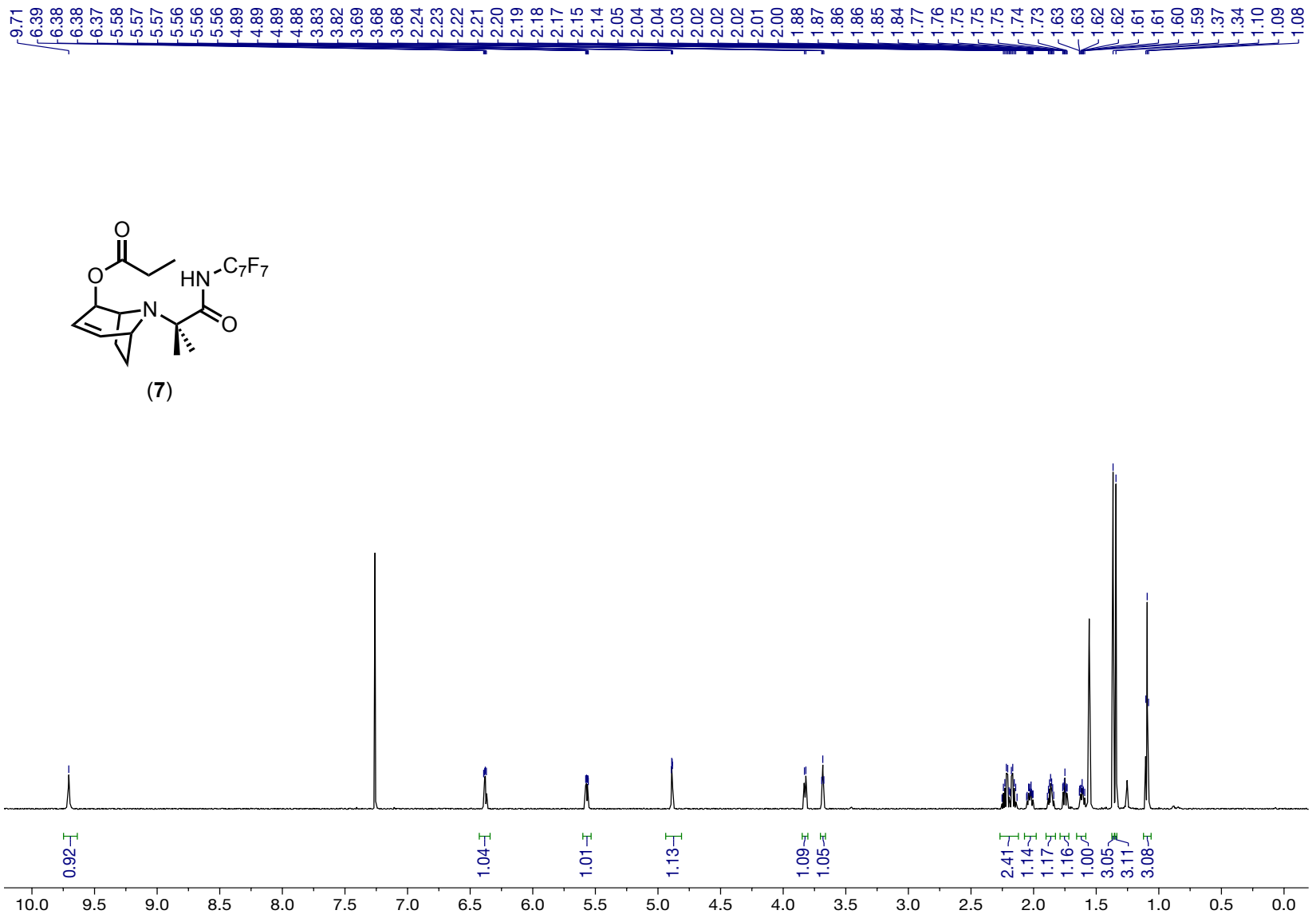
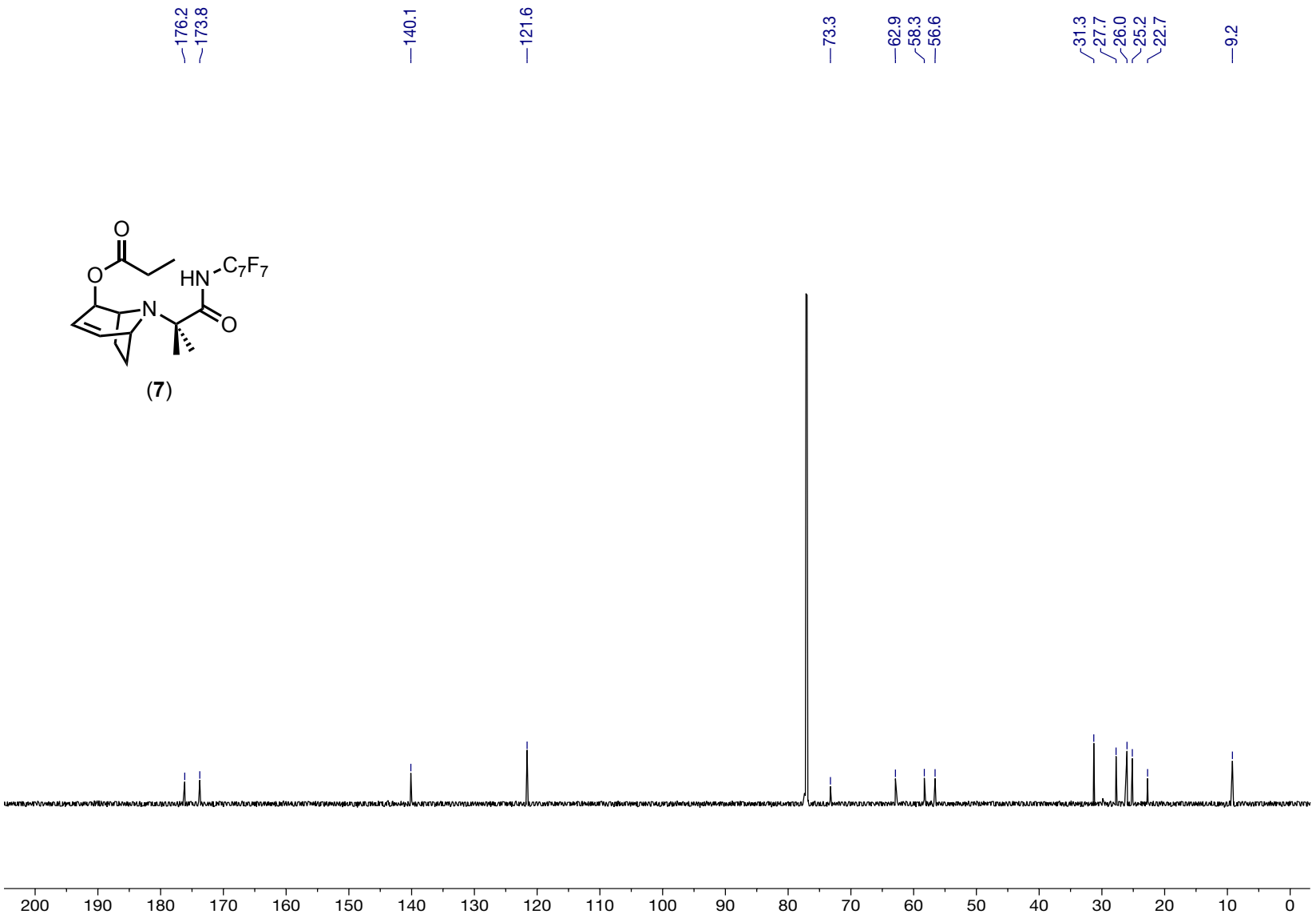


Figure S20. 7: 700 MHz ^{1}H NMR spectrum in $CDCl_3$



(**7**)

Figure S21. 7: 176 MHz ^{13}C NMR spectrum in $CDCl_3$

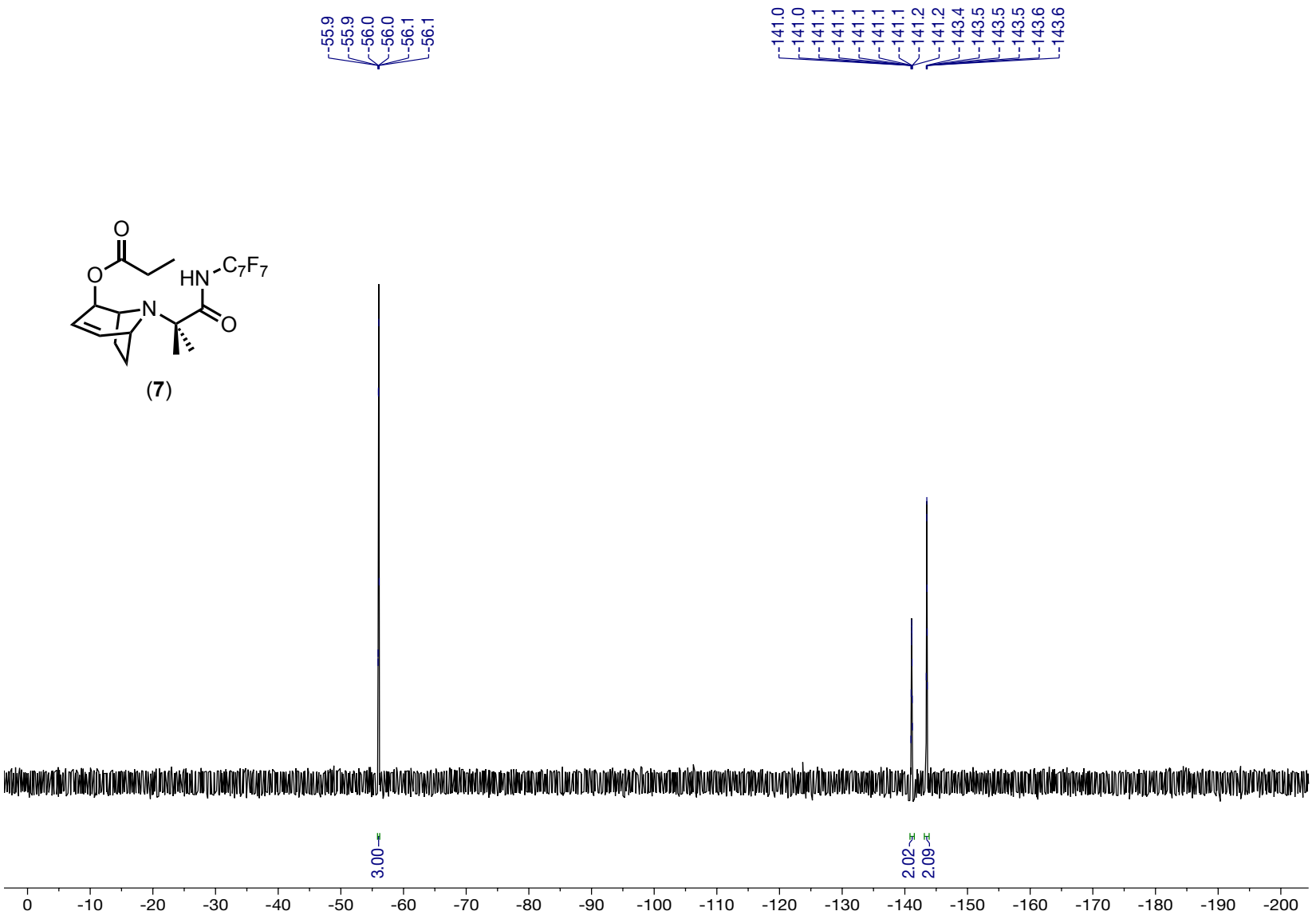


Figure S22. 7: 470 MHz ^{19}F NMR spectrum in $CDCl_3$

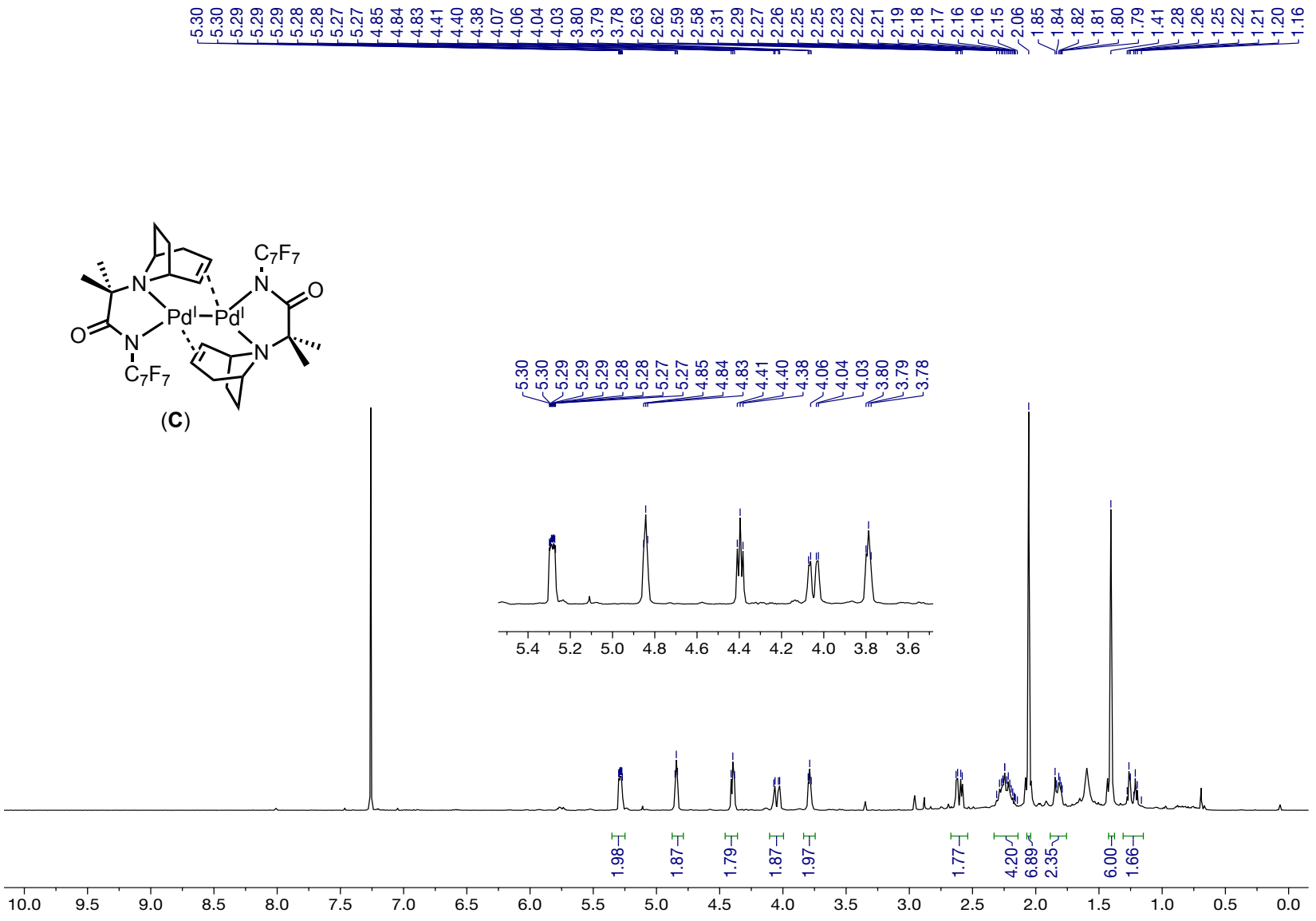


Figure S23. C: 700 MHz ^{1}H NMR spectrum in $CDCl_3$

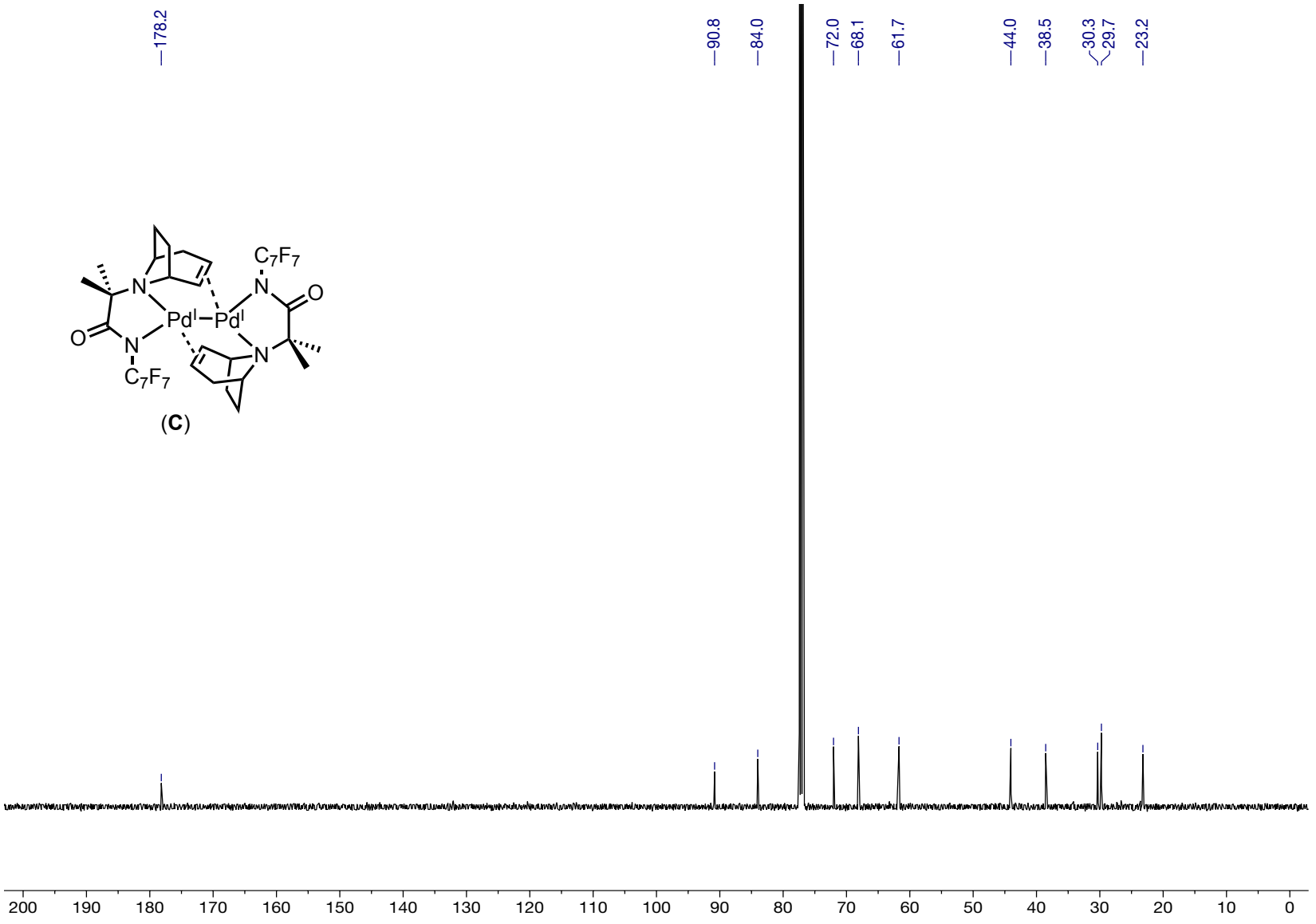


Figure S24. C: 176 MHz ^{13}C NMR spectrum in $CDCl_3$

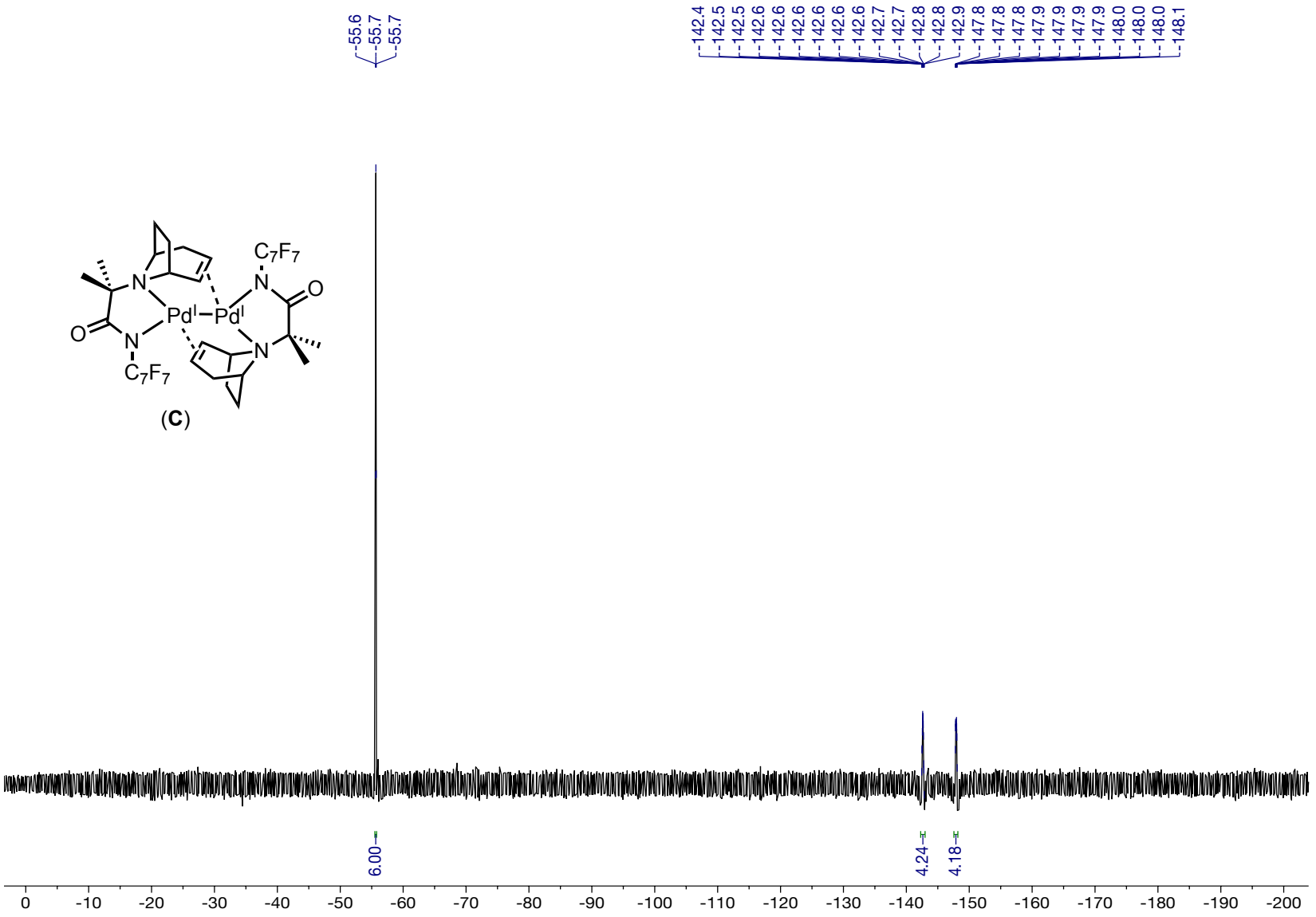


Figure S25. C: 470 MHz ^{19}F NMR spectrum in $CDCl_3$

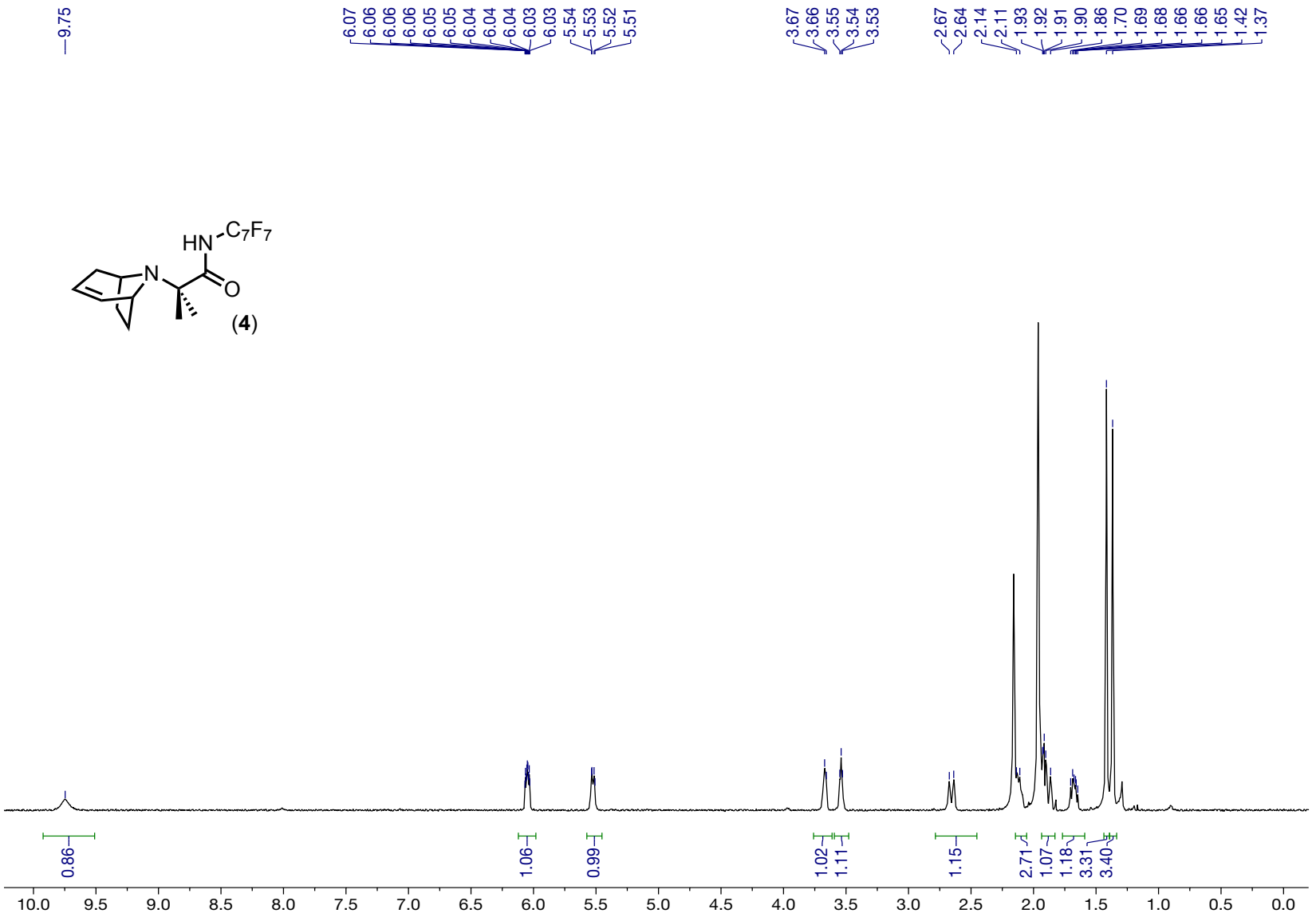


Figure S26. 4: 700 MHz ^{1}H NMR spectrum in CD_3CN

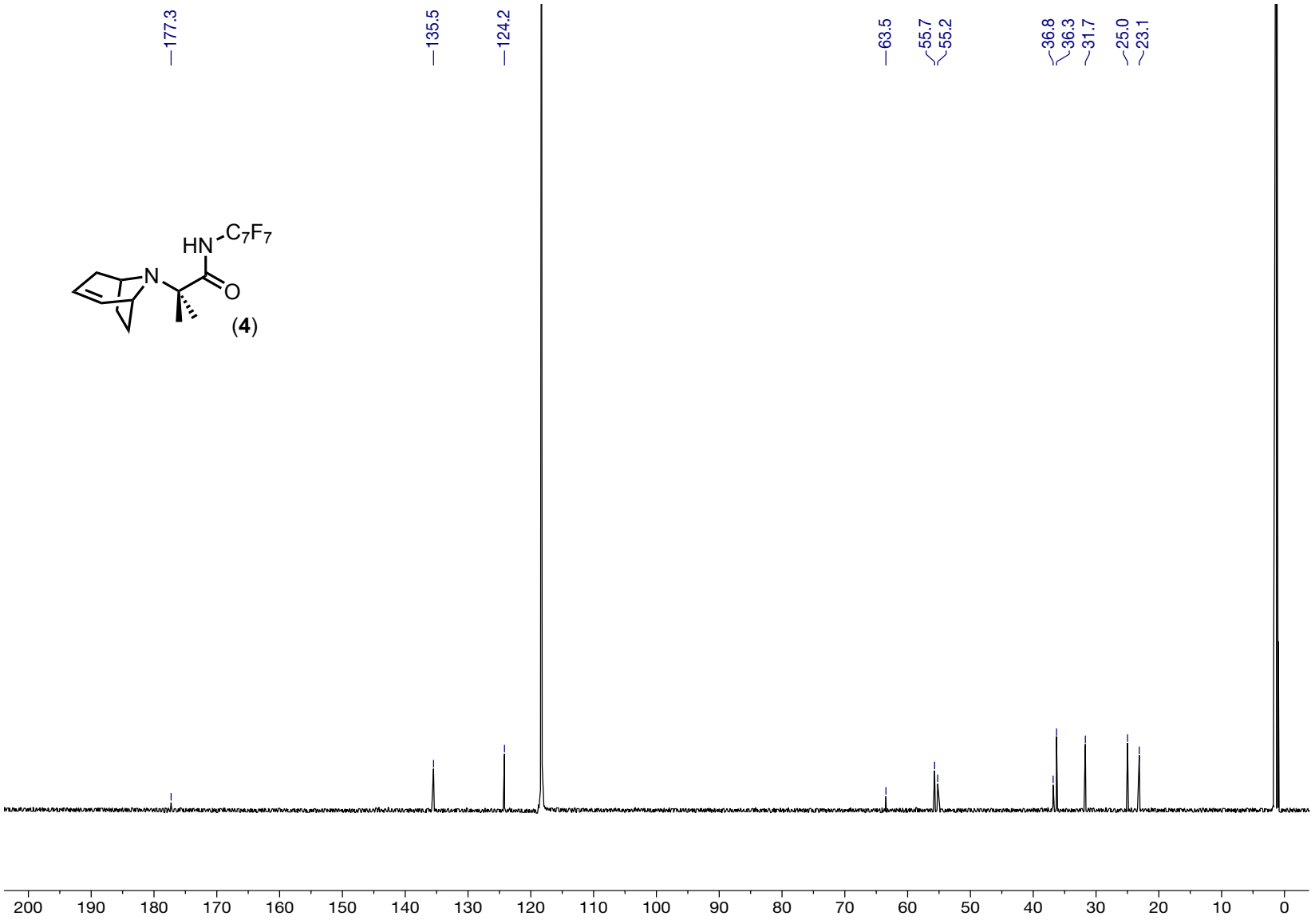


Figure S27. 4: 176 MHz ^{13}C NMR spectrum in CD_3CN

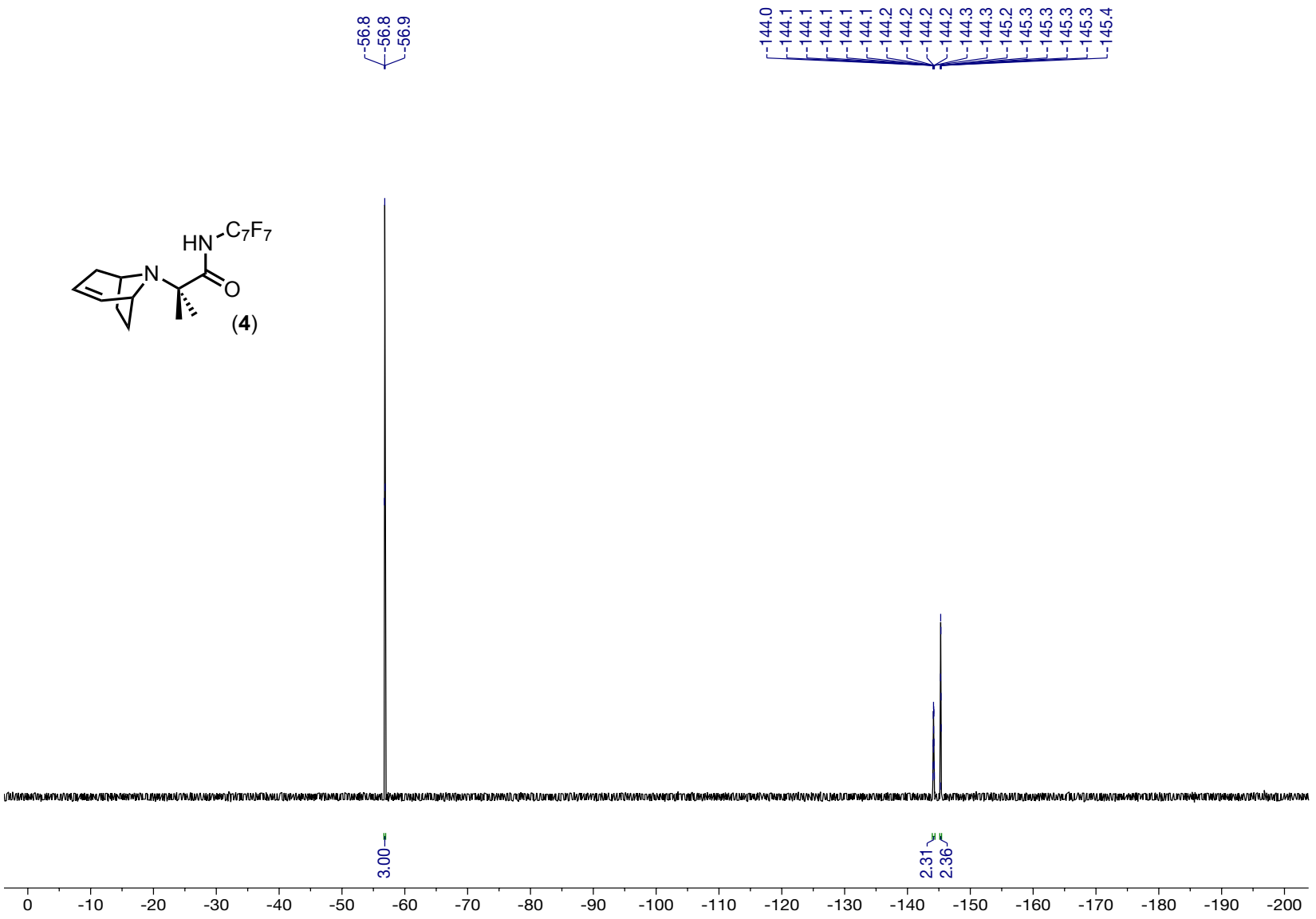


Figure S28. 4: 470 MHz ^{19}F NMR spectrum in CD_3CN