Electronic Supplementary Information

Oscillatory Three-Phase Flow Reactor for Studies of Bi-Phasic Catalytic Reactions

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S1. Flow Reactor Setup

Harvard apparatus syringe pumps, interfaced with LabView, were used to form the organic and aqueous segments, move the bi-phasic droplet into the reactor, and oscillate it back and forth. A Teflon reactor (fluorinated ethylene propylene (FEP), 1/8" OD × 1/16" ID × 6", McMaster Carr) was inserted into a 3-D printed frame (Acrylonitrile butadiene styrene, printed with iD3 iDeator 12), shown in Figure S1. Before connecting the filled syringes to the three-phase oscillatory flow reactor (OFR) platform, the reactor and connection tubing as well as T-junctions were purged with argon for 5 min, to ensure removal of air from the reactor. While under positive pressure of argon, two gastight syringes (250 μL gastight glass syringe, Hamilton Syringe) filled with organic and aqueous solutions were fitted on Harvard apparatus PHD2000 syringe pumps and connected to two T-junctions (Polyether ether ketone (PEEK), 0.02" ID, IDEX Health and Sciences) using two Teflon tubing (FEP, 1/16" OD × 0.030" ID × 2", IDEX Health and Sciences) . The push/pull syringe (10 mL, BD) was then purged, filled with argon and fitted on syringe pump 1.

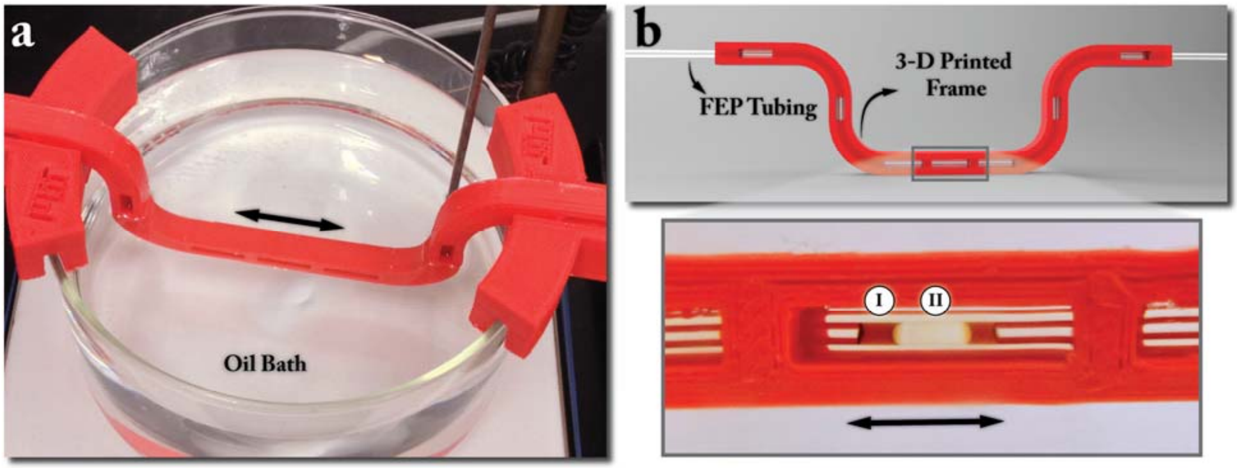


Figure S1. (a) Image of the assembled experimental setup with (b) the 3-D printed frame and holders for the Teflon reactor. The inset shows a typical image of the formed bi-phasic droplet inside the flow reactor. I: organic phase, II: aqueous phase.

The reactor was then immersed into an oil bath and placed on a hot plate (C-MAG-HS 7, IKA), shown in Figure S1a. The temperature of the reactor was controlled using an electronic contact thermometer (ETS-D5 with an accuracy of ± 0.1 ˚C, IKA) immersed into the oil bath and connected to the hot plate.

A 6 port 2-way sampling valve (VICI) with a 40 μL sampling loop was connected to the outlet of the reactor, a 20 mL pressurized vessel, and quench syringe (1:1 volume ratio of solution of deionized water and acetone). Each bi-phasic droplet was collected into a 2 mL HPLC vial (Agilent Technologies), diluted with the quench solution up to 1mL solution and analyzed by HPLC. The HPLC yields presented in Figures 3 and 4 of the manuscript were calculated using a calibration solution containing known concentrations of the isolated product and the internal standard (naphthalene) dissolved in the organic solvent. After each set of experiments, the reactor was washed with the organic solvent.

S2. Characterization of Three-Phase OFR

A CCD camera (Stingray, Allied Vision Tech.) attached to a macro lens (NAVITAR 7000), in combination with a custom-developed image processing code (MATLAB 2014) was utilized for characterization of the oscillatory motion of bi-phasic droplets. As shown in Figure S2, the gradient of pixel intensity, *I'*, along the centerline of the tubular reactor was used to track the length, velocity and displacement of the aqueous phase within the organic phase.

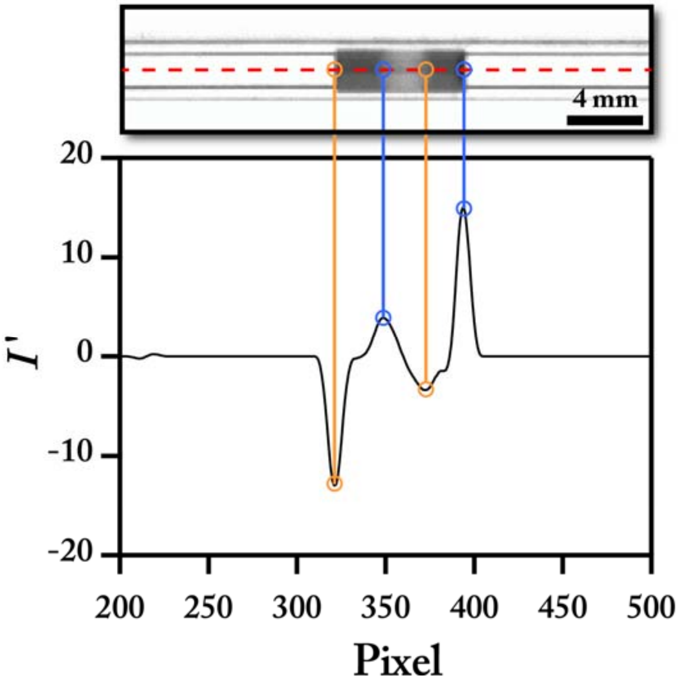


Figure S2. Gradient of pixel intensity across the centerline of the tubular reactor. Working fluids are argon, dyed THF (Sudan red) and 1M K_3PO_4 in DI water.

The local maxima of *I’* were used to locate the position of the front and back caps as well as the center of aqueous and organic segments. Displacement of each segment was calculated by subtracting the center positions of segments in two consecutive frames. Using the time delay between each captured frame and measured displacement of segments, the velocity of aqueous segment, U_{aq}, and bi-phasic droplet, U_o, were calculated at each instant of time.

Figure S3a shows the time evolution of the length of the bi-phasic droplet, L_s, the length of the aqueous segment, L_{aq}, and the velocity of aqueous segment and bi-phasic droplet, *U*. Owing to the presence of organic lubrication films surrounding the aqueous phase, the cross-section of the aqueous segment, engulfed within the organic phase, becomes smaller than the tubular reactor. While travelling through the organic phase, owing to the mass conservation, the length of the aqueous segment increases. Moreover, the lubrication film facilitates the motion of the aqueous phase inside the reactor, and thereby results in a higher velocity for aqueous segment compared to the overall bi-phasic droplet. Figure 3Sb shows the relative velocity, U_{rel}, and the relative center position of the aqueous segment with respect to the bi-phasic droplet frame of reference. The oscillatory motion of the aqueous phase within the bi-phasic droplet frame, shown in Figure S3b, illustrates the harmonic behavior of the velocity and displacement of the aqueous segment engulfed within the organic phase.

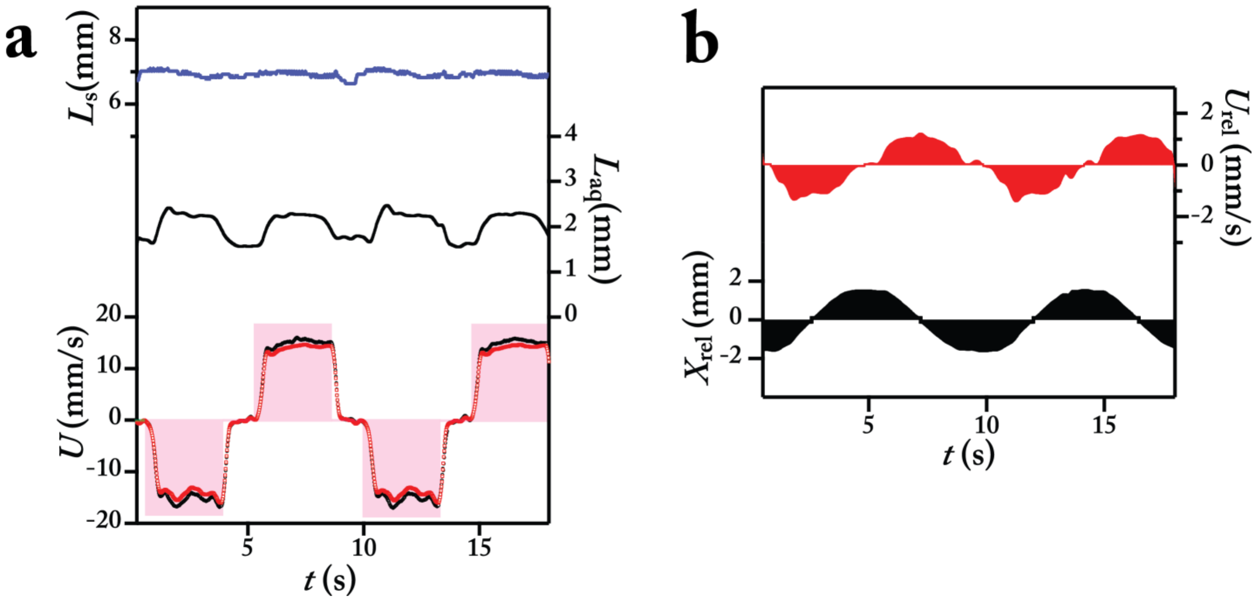


Figure S3. Characterization of the three-phase oscillatory flow reactor. (a) Time evolution of the length and velocity of the (●) aqueous and the (●) bi-phasic droplets over the course of two oscillation cycles. (b) Time evolution of the relative velocity and relative center position of the aqueous segment with respect to the bi-phasic droplet. *Q*=2 mL/min, *T*=23 ˚C and argon pressure of 5 psig. Working fluids are dyed THF (Sudan red) and 1M K_3PO_4 in water.

It has already been demonstrated that the lubrication film thickness in a bi-phasic system scales with the Capillary number of the dispersed phase (aqueous phase),[1-3] $Ca_{aq}=\mu U_{aq}/\sigma$, where μ is the liquid viscosity, U is the flow velocity and σ is the interfacial tension) to the power 2/3. Moreover, the relative displacement, d_{rel}, of the dispersed phase with respect to the continuous phase (organic phase) is also directly correlated with the film thickness and thereby Ca_{aq},

$$\frac{U_{aq}-U_o}{U_o}=\frac{U_{rel}}{U_o}=m(Ca_{aq})^{2/3}$$

where m is a fitting parameter. Figure S4s shows the evolution of the velocity difference between the aqueous segment and bi-phasic droplet for different push/pull flowrates, Q. Figure S4b shows the linear correlation between the normalized relative velocity of the aqueous phase with respect to the bi-phasic droplet and $Ca^{2/3}$ with a slope of 15.1.

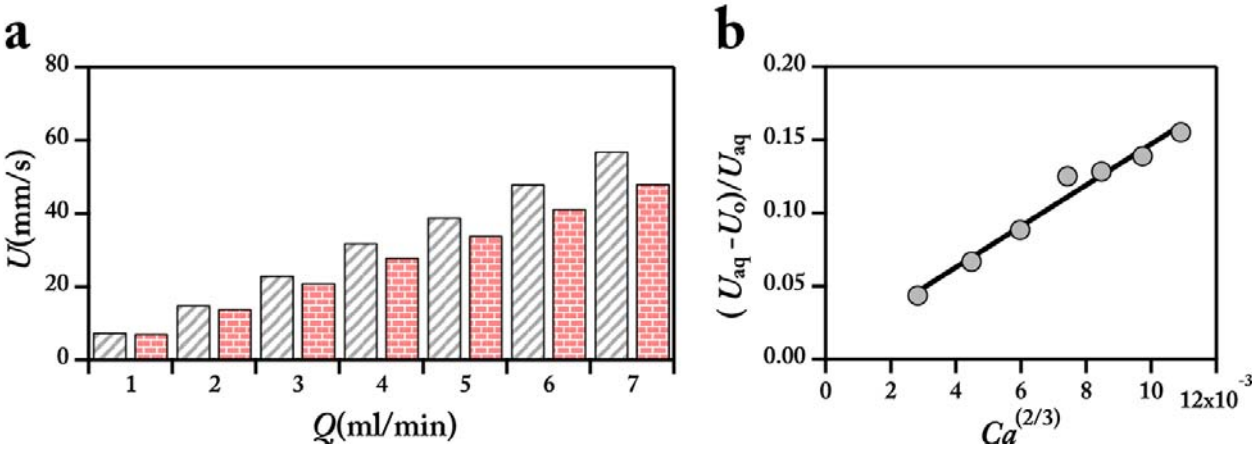
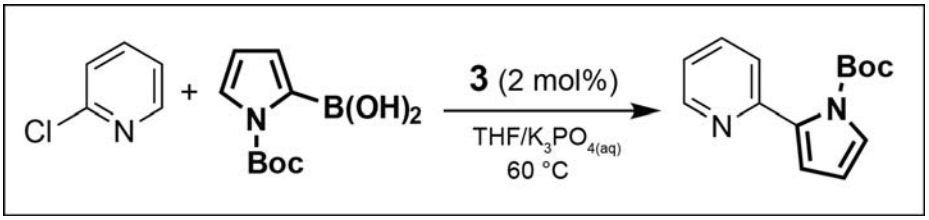


Figure S4. (a) Velocity of the (■) bi-phasic and (🟥) aqueous segments versus the applied push/pull flowrate. (b) The linear relationship between the normalized relative velocity and Capillary number of the aqueous phase.

S3. Sample Preparations

a. Figure 3

C-C Cross-Coupling (Scheme 1a): *2-(1-Boc-1H-pyrrol-2-yl)pyridine*



Two stock solutions (5 mL each) containing organic and aqueous phases were prepared under inert atmosphere (argon).

Stock Solution O: An oven-dried 5 mL volumetric flask, equipped with a magnetic stir bar and fitted with a Teflon septum was loaded with XPhos-Pd-G3 (21.2 mg, 0.025 mmol), naphthalene (48 mg, 0.375 mmol) and N-boc-2-pyrrole boronic acid (395.7 mg, 1.875 mmol). The flask was evacuated and backfilled with argon (this procedure was repeated a total of 3 times). Then 2-chloropyridine (120 µL, 1.25 mmol) and anhydrous tetrahydrofuran (THF) were added to the volumetric flask under a positive pressure of argon to bring the total solution volume to 5 mL. Following addition of THF, stock solution **O** was stirred for 5 min for complete dissolution of the solid reagents.

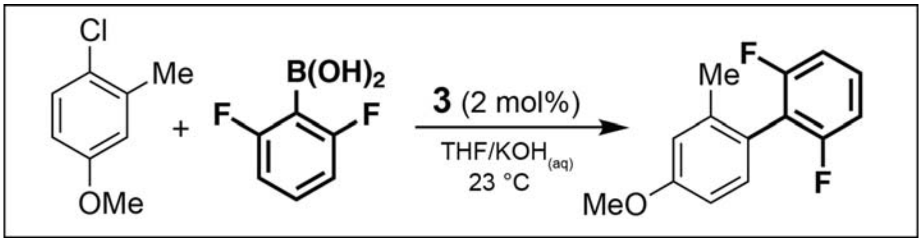
Stock Solution A: An oven-dried 5 mL volumetric flask, equipped with a magnetic stir bar and fitted with a Teflon septum, was loaded with 1.06 g (5 mmol) of potassium phosphate. DI water was added to the volumetric flask to bring the total solution volume to 5 mL. Stock solution **A** was stirred for 5 min for complete dissolution of the solid potassium phosphate. The vessel was then degassed by performing cycles of sonication under vacuum (Branson M1800 Ultrasonic Cleaner), followed by backfilling with argon.

Batch Reaction: An oven-dried 5 mL volumetric flask equipped with a magnetic stir bar and fitted with a Teflon septum was evacuated and backfilled with argon (this procedure was repeated a total of 3 times). An equal volume (1mL) of stock solutions **A** and **O** were then injected into the vessel and it was immersed in a temperature controlled oil bath. The reaction mixture was stirred at 1100 rpm, for 10 min at 60 ˚C. The reaction vessel was then removed from the oil bath, opened to air, cooled to room temperature, and quenched with 2mL of 1:1 acetone:DI water. An aliquot of the organic layer was then analyzed by HPLC.

Flow Reactor: Two gastight glass syringes (250 µL, Hamilton Syringe Products) were evacuated and re-filled with argon for 3 times to ensure the removal of air. Stock solutions **A** and **O** were then loaded into the gastight syringes and fitted on two Harvard Apparatus PHD 2000 syringe pumps.

b. Figure 4

C-C Cross-Coupling (Scheme 1b): *2',6'-difluoro-4-methoxy-2-methyl-1,1'-biphenyl*



Two stock solutions (5 mL each) containing organic and aqueous phases were prepared under inert atmosphere (argon).

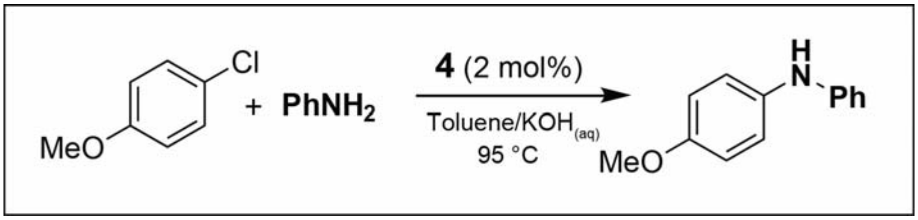
Stock Solution O: An oven-dried 5 mL volumetric flask equipped with a magnetic stir bar and fitted with a Teflon septum was loaded with XPhos-Pd-G3 (21.2 mg, 0.025 mmol), naphthalene (48 mg, 0.375 mmol) and 2,6-difluorophenyl boronic acid (592.1 mg, 3.75 mmol). The flask was evacuated and backfilled with argon (this procedure was repeated a total of 3 times). Then 4-chloro-3-methylanisole (355 µL, 2.5 mmol) and anhydrous tetrahydrofuran (THF) were added to the volumetric flask, under a positive pressure of argon to bring the total solution volume to 5 mL. Following addition of THF, stock solution **O** was stirred for 5 min for complete dissolution of the solid reagents.

Stock Solution A: An oven-dried 5 mL volumetric flask, equipped with a magnetic stir bar and fitted with a Teflon septum, was loaded with 0.28 g (5 mmol) of potassium hydroxide. DI water was added to the volumetric flask to bring the total solution volume to 5 mL. Stock solution **A** was stirred for 5 min for complete dissolution of the solid potassium phosphate. The vessel was then degassed by performing cycles of sonication under vacuum (Branson M1800 Ultrasonic Cleaner), followed by backfilling with argon.

Batch Reaction: An oven-dried 5 mL volumetric flask, equipped with a magnetic stir bar and fitted with a Teflon septum, was evacuated and re-filled with argon for 3 times. An equal volume (1mL) of stock solutions **A** and **O** were injected into the vessel immersed in a temperature controlled oil bath. The reaction mixture was stirred at 1100 rpm, for 10 min at 50 ˚C. The reaction vessel was then removed from the oil bath, opened to air, cooled to room temperature, and quenched with 2mL of 1:1 acetone:DI water mixture. An aliquot of the organic layer was then analyzed by HPLC.

Flow Reactor: Two gastight glass syringes (250 µL, Hamilton Syringe Products) were evacuated and re-filled with argon for 3 times to ensure the removal of air. Stock solutions **A** and **O** were then loaded into the gastight syringes and fitted on two Harvard Apparatus PHD 2000 syringe pumps.

C-N Cross-Coupling (Scheme 1c): *4-Methoxydiphenylamine*



Two stock solutions (5 mL each) containing organic and aqueous phases were prepared under argon.

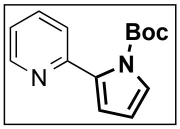
Stock Solution O: An oven-dried 5 mL volumetric flask, equipped with a magnetic stir bar and fitted with a Teflon septum, was loaded with BrettPhos-Pd-G3 (90.7 mg, 0.1 mmol) and naphthalene (64 mg, 0.5 mmol). The flask was evacuated and backfilled with argon (this procedure was repeated a total of 3 times). Then 4-chloroanisole (610 μL, 5 mmol) and aniline (550 μL, 6 mmol) were added to the volumetric flask. Anhydrous toluene was then added to the flask under a positive pressure of argon to bring the total solution volume to 5 mL. Following addition of the organic solvent, stock solution **O** was stirred for 5 min for complete dissolution of the solid reagents.

Stock Solution A: An oven-dried 5 mL volumetric flask, equipped with a magnetic stir bar and fitted with a Teflon septum, was loaded with 0.56 g (10 mmol) of potassium hydroxide. DI water was added to the volumetric flask to bring the total solution volume to 5 mL. Stock solution **A** was stirred for 5 min for complete dissolution of the solid potassium hydroxide. The vessel was then degassed by performing cycles of sonication under vacuum (Branson M1800 Ultrasonic Cleaner), followed by backfilling with argon.

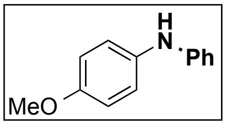
Batch Reaction: An oven-dried 5 mL volumetric flask, equipped with a magnetic stir bar and fitted with a Teflon septum, was evacuated and re-filled with argon for 3 times. An equal volume (1mL) of stock solutions **A** and **O** were injected into the vessel immersed in a temperature controlled oil bath. The reaction mixture was stirred at 1100 rpm for 10 min at 95 ˚C. The reaction vessel was then removed from the oil bath, opened to air, cooled to room temperature, and quenched with 2mL of 1:1 acetone:DI water. An aliquot of the organic layer was then analyzed by HPLC.

Flow Reactor: Two gastight glass syringes (250 μL, Hamilton Syringe Products) were evacuated and re-filled with argon for 3 times to ensure the removal of air. Stock solutions **A** and **O** were then loaded into the gastight syringes and fitted on two Harvard Apparatus PHD 2000 syringe pumps.

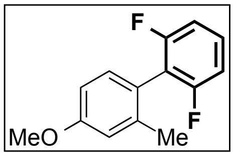
S4. Product Isolation for HPLC Calibration



2-(1-Boc-1*H*-pyrrol-2-yl)pyridine : The compound was prepared following a literature procedure.[4] The crude reaction mixture was then purified via column chromatography, eluting with a gradient of 20 – 50% ethyl acetate in hexanes to provide the title compound as a viscous, yellow liquid. By ^{1}H NMR, rotomeric mixture—major rotomer characterization reported. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (td, *J* = 7.7, 1.8 Hz, 1H), 7.36 (dd, *J* = 3.2, 1.8 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.39 (dt, *J* = 7.8, 1.1 Hz, 1H), 6.41 (dd, *J* = 3.3, 1.7 Hz, 1H), 6.24 (t, *J* = 3.3 Hz, 1H), 8.64 – 8.59 (m, 1H), 1.35 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.18, 149.05, 135.96, 123.77, 123.75, 121.97, 115.84, 112.05, 110.77, 83.85, 28.22, 27.79 ppm.



4-Methoxydiphenylamine: The compound was prepared following a literature procedure.[5] The crude reaction mixture was then purified via column chromatography, eluting with a gradient of 0 – 10% ethyl acetate in hexanes to provide the title compound as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 2H), 7.14 – 7.08 (m, 2H), 6.99 – 6.92 (m, 2H), 6.92 – 6.84 (m, 3H), 5.52 (s, 1H), 3.83 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.99, 145.90, 136.46, 132.76, 130.05, 122.93, 120.29, 116.37, 115.40, 56.31 ppm.



2',6'-difluoro-4-methoxy-2-methyl-1,1'-biphenyl: The compound was prepared following a literature procedure.[4] The crude reaction mixture was then purified via column chromatography, eluting with a gradient of 0 – 5% ethyl acetate in hexanes to provide the title compound as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (tt, *J* = 8.4, 6.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.02 – 6.95 (m, 2H), 6.90 (d, *J* = 2.7 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.7 Hz, 1H), 3.86 (s, 3H), 2.19 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.65 (d, *J* = 7.3 Hz), 159.96, 159.69 (d, *J* = 7.4 Hz), 139.12, 131.90, 129.12 (t, *J* = 10.2 Hz), 121.24, 115.80, 111.81 – 111.35 (m), 111.36, 55.42, 20.29 ppm.

S5. OFR Movie

Movie M1. A video of the oscillatory motion of an aqueous K_3PO_4 (1M) droplet moving inside a dyed THF droplet, used for characterization plots shown in Figure 2 of the manuscript.

Movie M2. A sample video of the oscillatory motion of a 20 μL bi-phasic droplet (1:1 aqueous to organic) associated with the C-N cross-coupling of ArCl and $ArNH_2$ shown in Figure 4 of the manuscript at 95°C.

References

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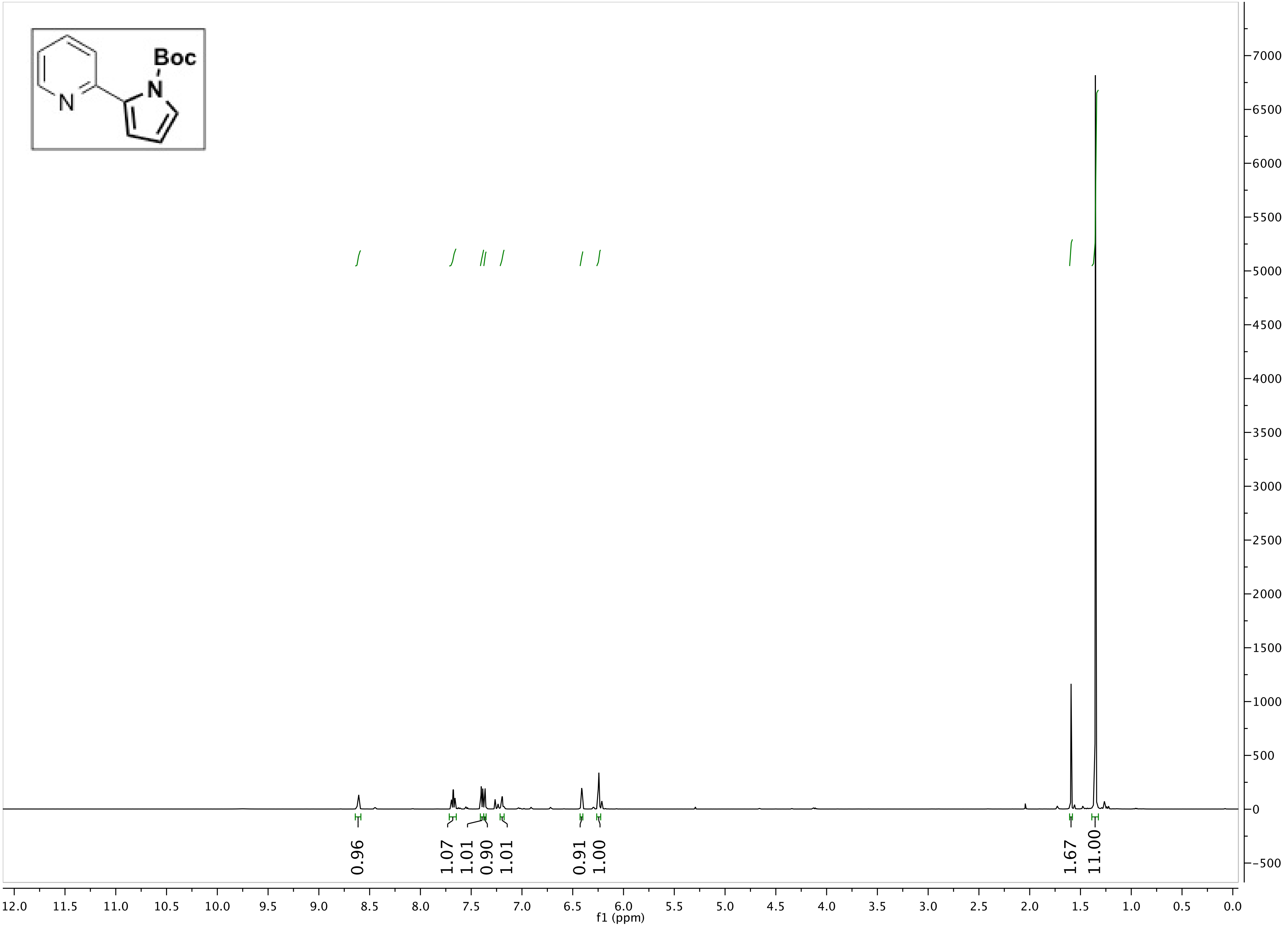
[2] L. W. Schwartz, H. M. Princen, A. D. Kiss, *Journal of Fluid Mechanics* **1986**, *172*, 259.
[3] F. P. Bretherton, *Journal of Fluid Mechanics* **1961**, *10*, 166.
[4] T. Kinzel, Y. Zhang, S. L. Buchwald, *Journal of the American Chemical Society* **2010**, *132*, 14073.
[5] N. C. Bruno, M. T. Tudge, S. L. Buchwald, *Chemical Science* **2013**, *4*, 916.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3.0
2.5
2.0
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0.0
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6000
5500
5000
4500
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3500
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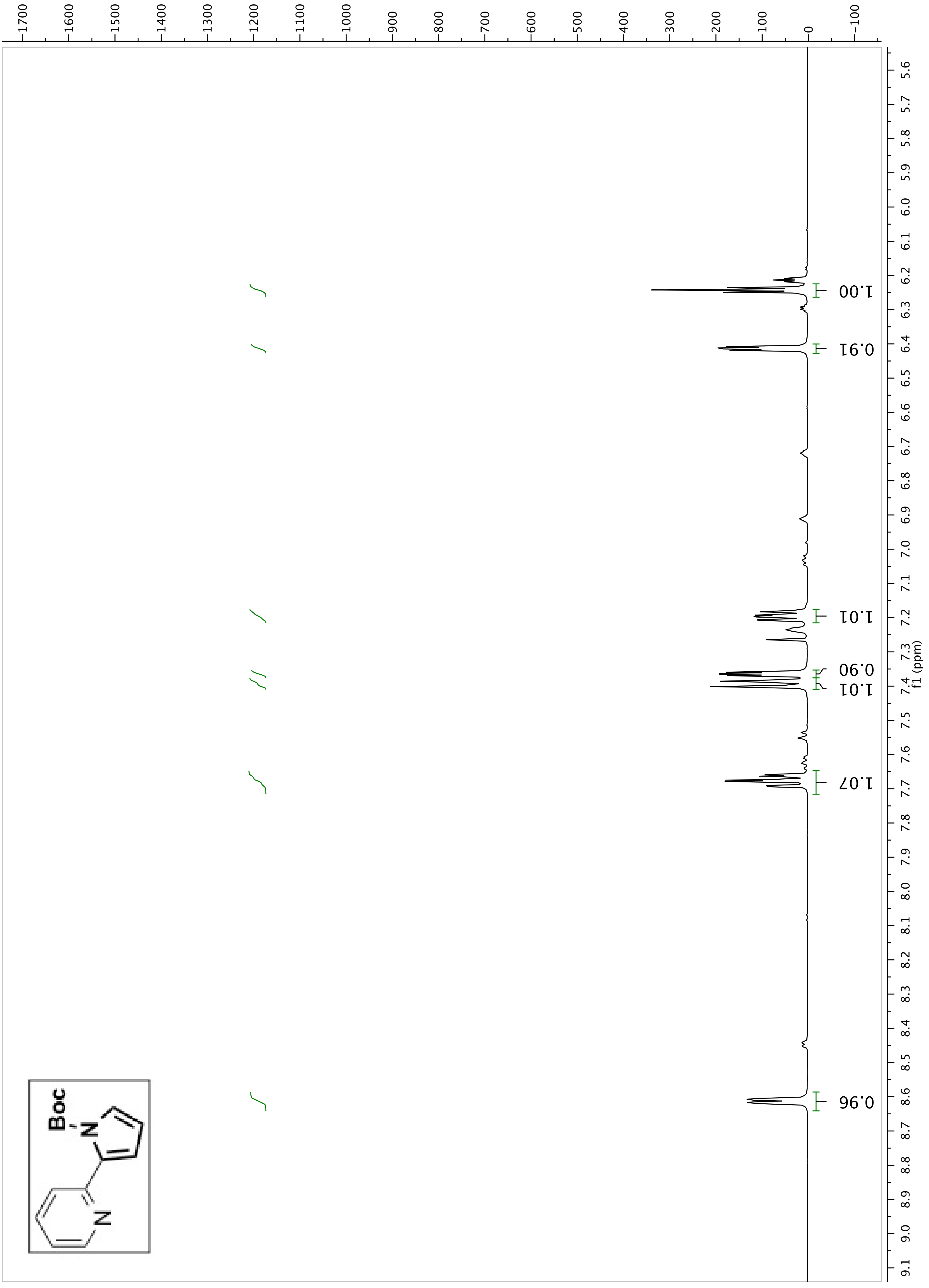
2500
2000
1500
1000
500
0
-500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1.07
0.96
f1 (ppm)
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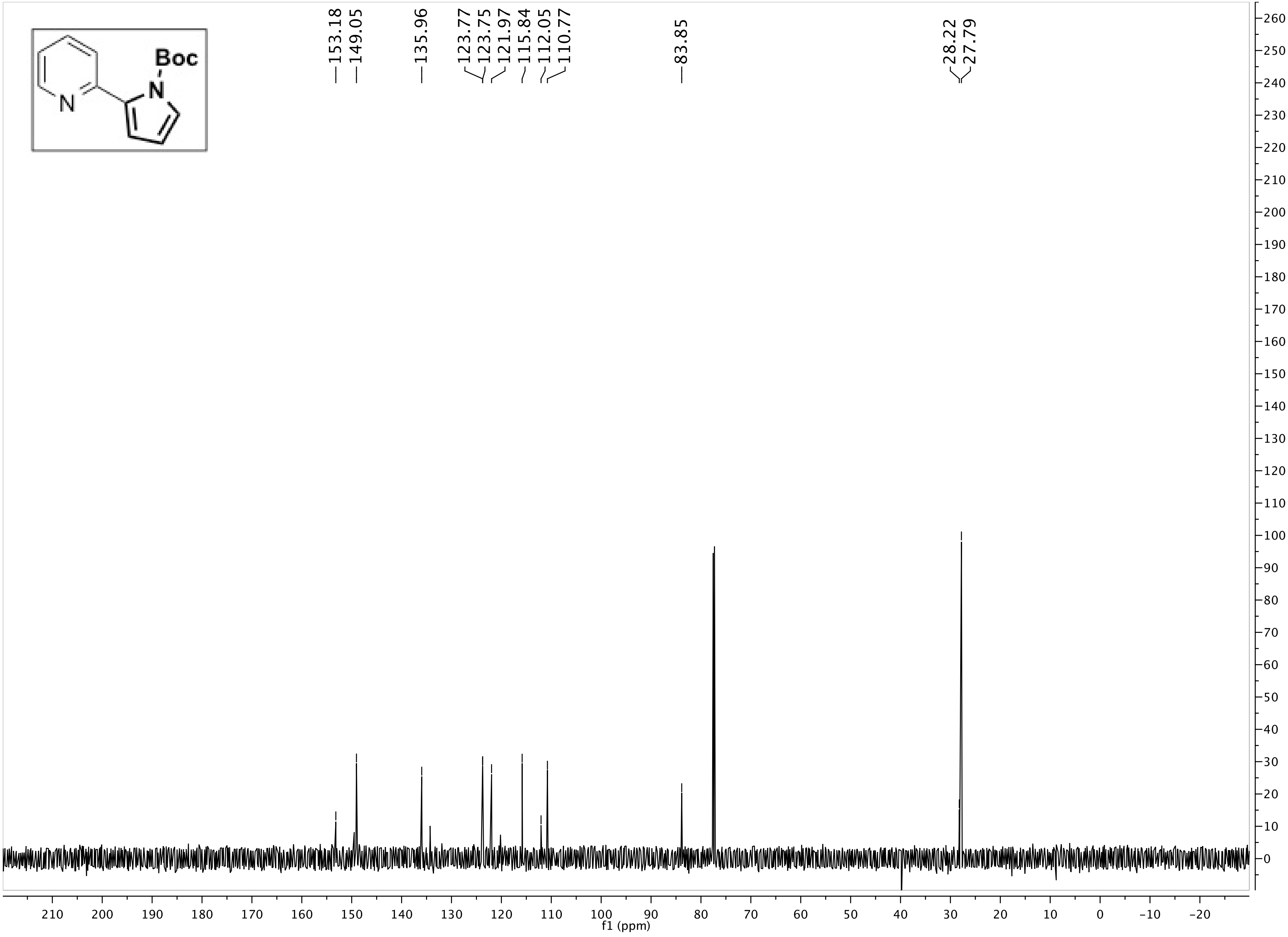
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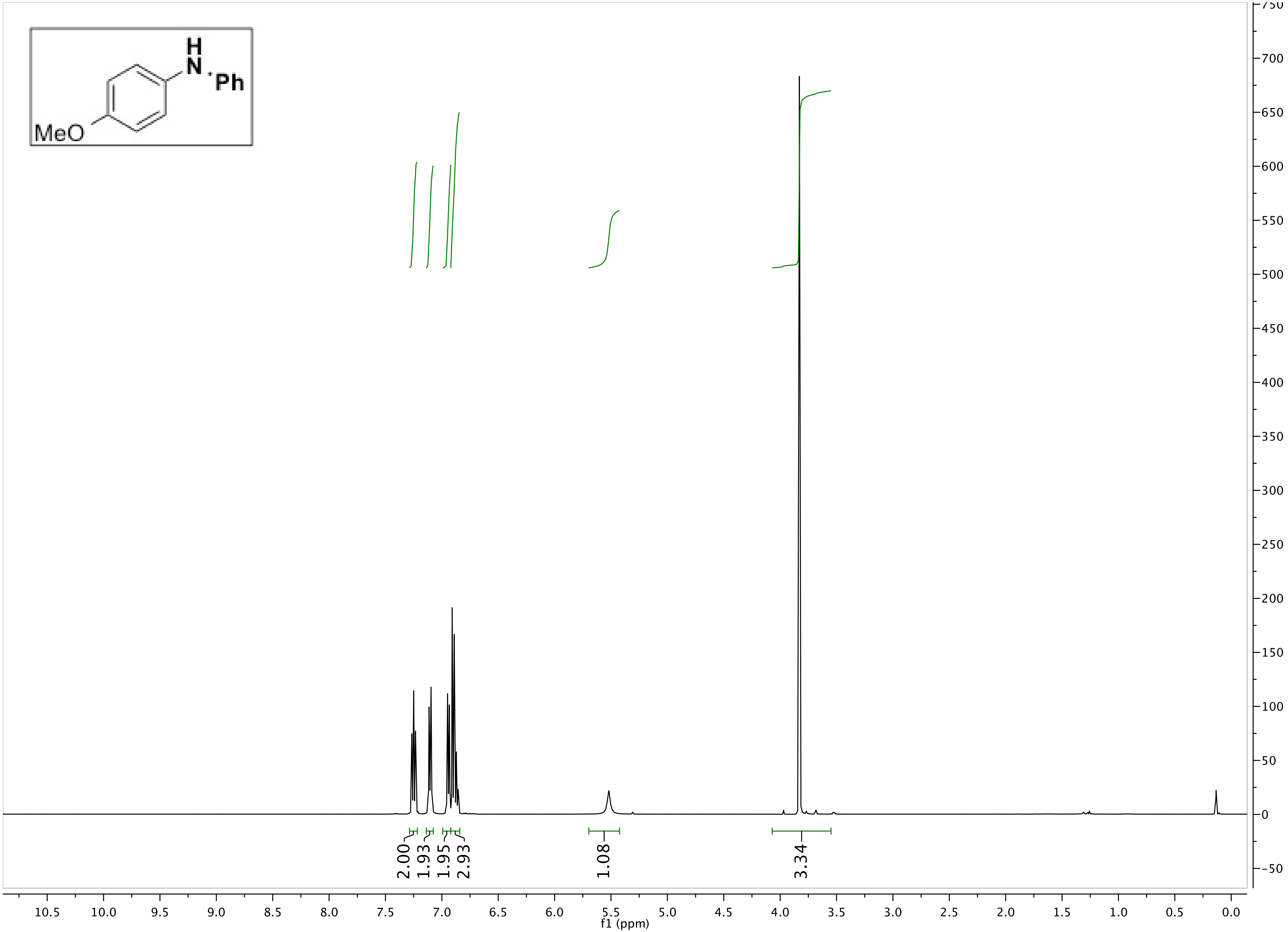

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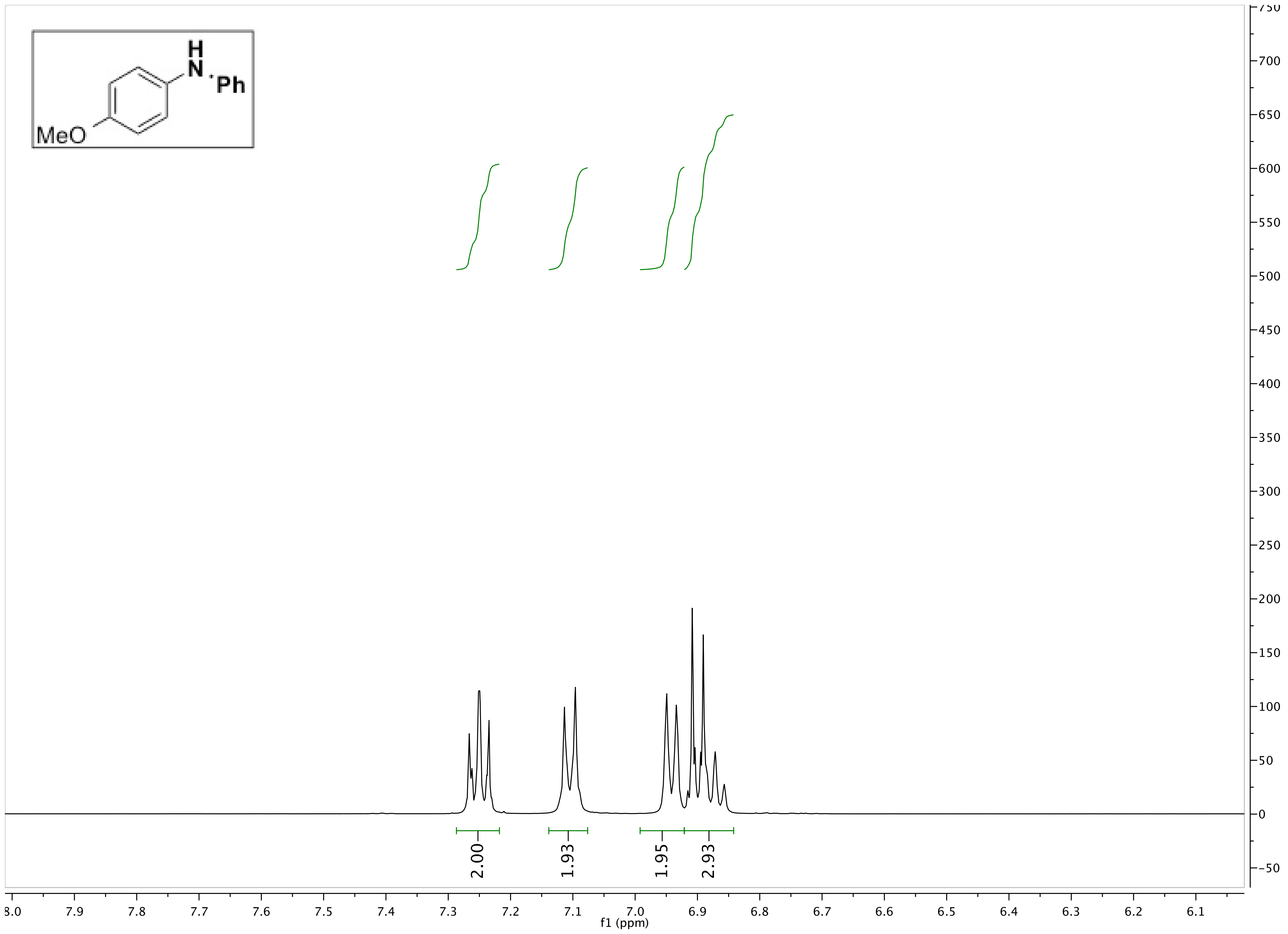
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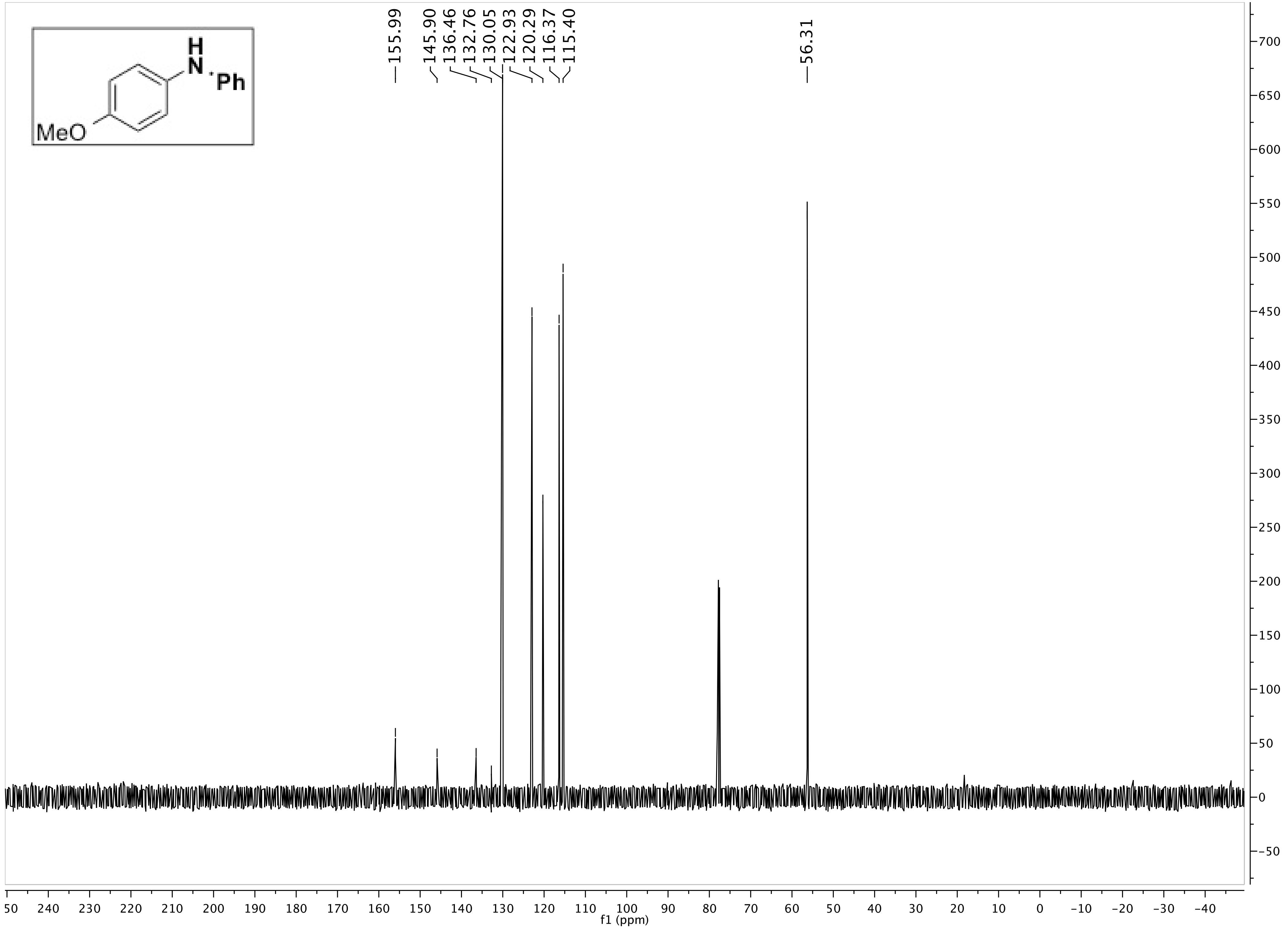
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56.31
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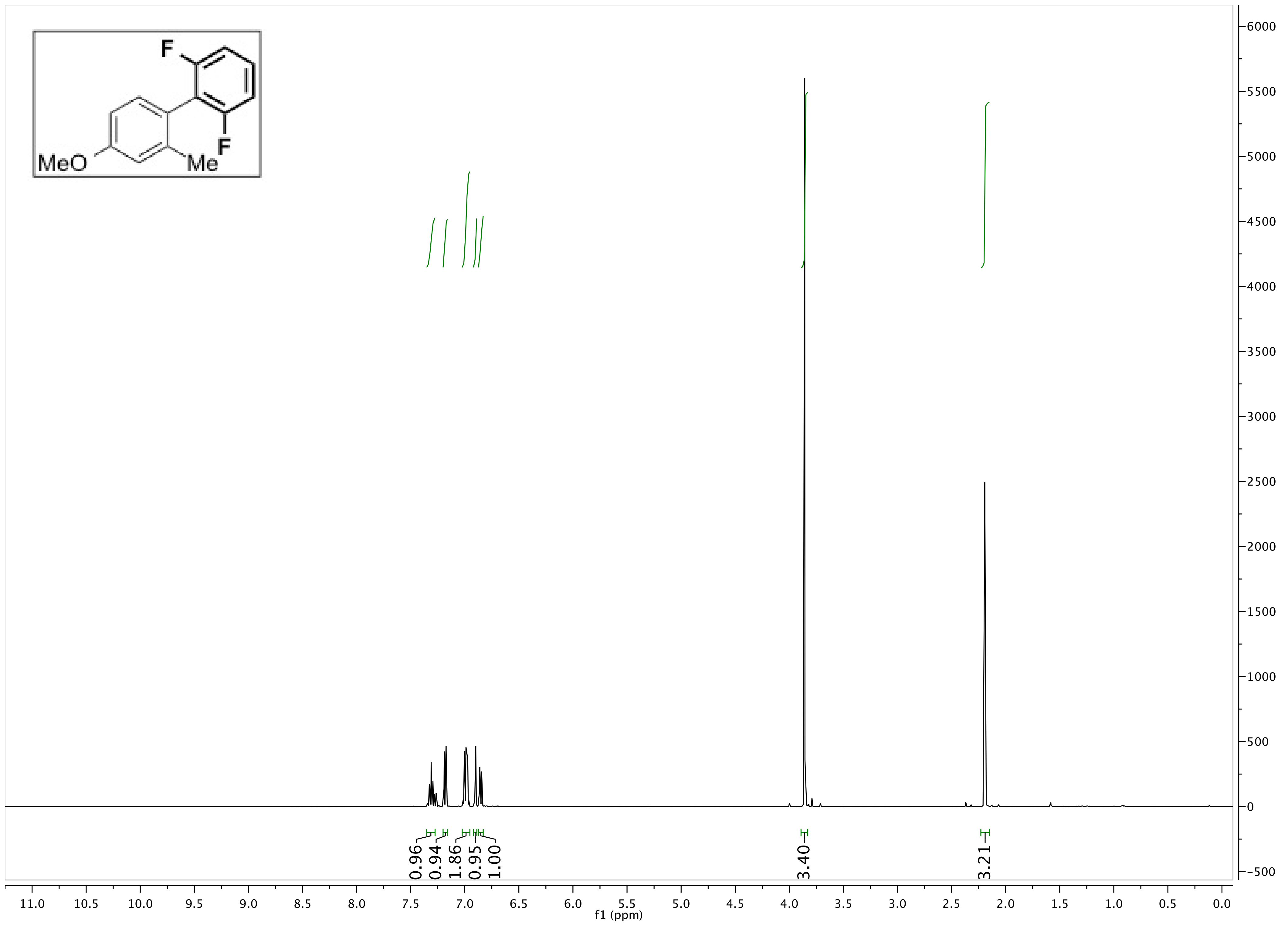
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3000
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2000
1500
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0
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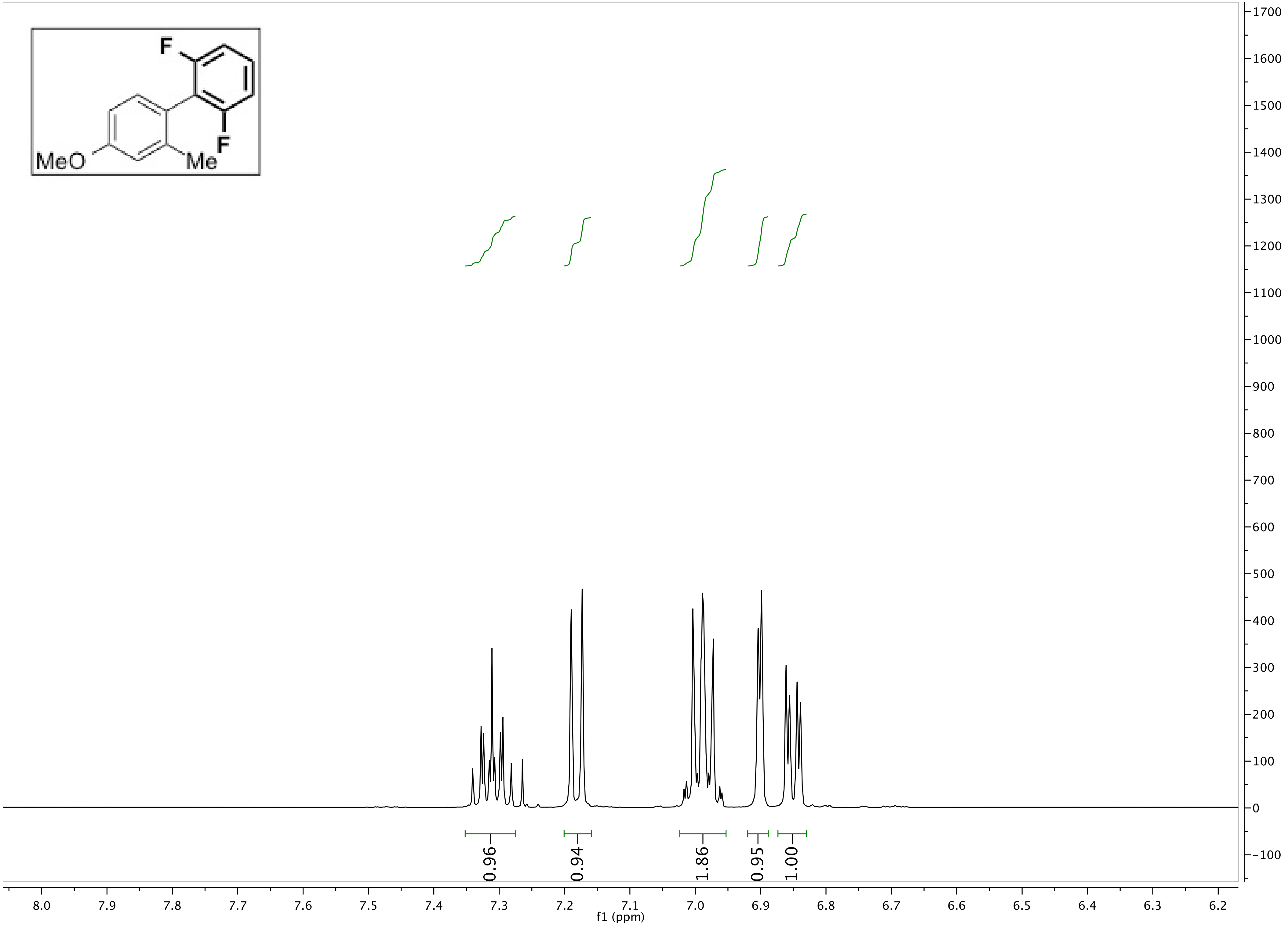
f1 (ppm)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6.6
6.5
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6.3
6.2
f1 (ppm)
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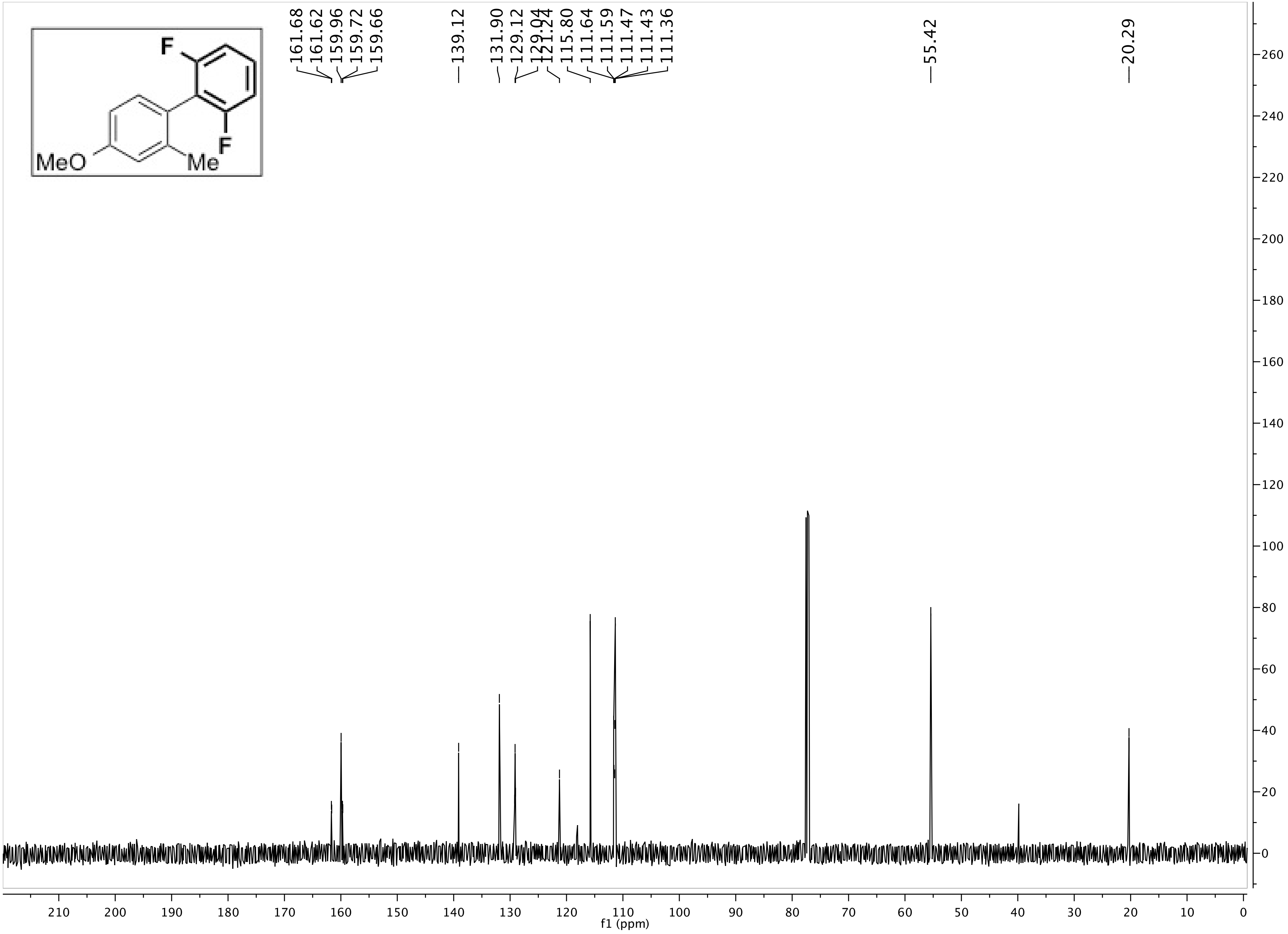
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159.96
159.72
159.66
139.12
131.90
129.12
129.04
121.24
115.80
111.64
111.59
111.47
111.43
111.36
55.42
20.29
F
F
MeO
Me
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
260
240
220
200
180
160
140
120
100
80
60
40
20
0