Organic Syntheses

Practical Syntheses of [2,2′-bipyridine]*bis*[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl]iridium(III) hexafluorophosphate, $[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ and [4,4′-*bis*(tert-butyl)-2,2′-bipyridine]*bis*[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl]iridium(III) hexafluorophosphate, $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$

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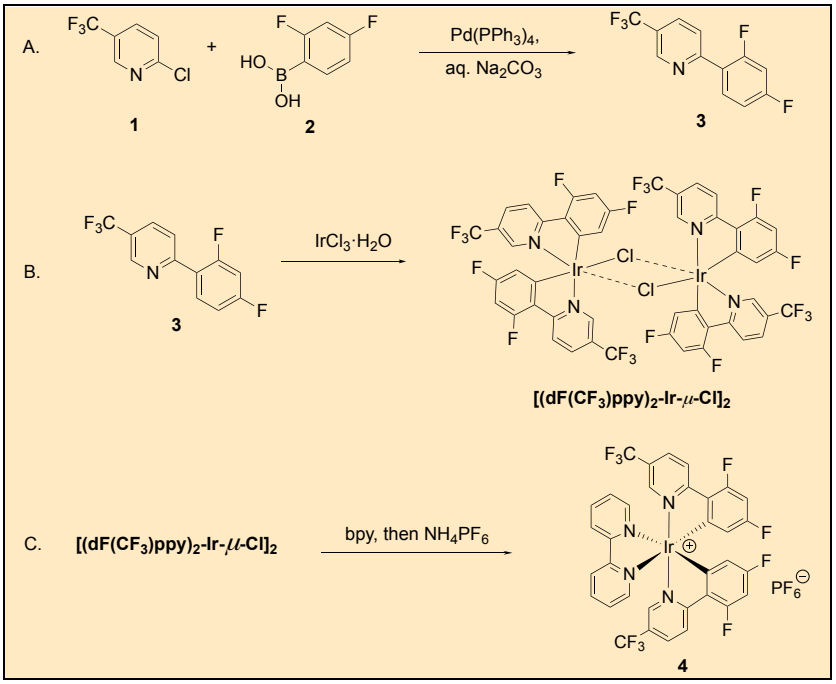

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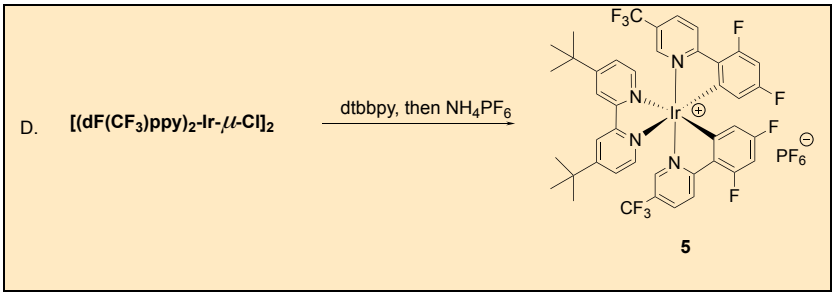


Procedure

A. *2-(2,4-Difluorophenyl)-5-(trifluoromethyl)pyridine, (dF(CF$_3$)ppy) (**3**).* A 500 mL, three-necked (24/40 joints), round-bottomed flask is equipped with a 3.5 cm length × 1.5 cm width magnetic stirring bar, a cold water reflux condenser, an argon inlet on top of the reflux condenser, and two yellow plastic stoppers (Note 1). A plastic stopper is removed temporarily and the flask is flushed with argon for 5 min before being sequentially charged with 2-chloro-5-(trifluoromethyl)pyridine (**1**) (Note 2) (6.00 g, 33.1 mmol, 1.00 equiv), (2,4-difluorophenyl)boronic acid (**2**) (Note 3) (5.74 g, 36.4 mmol, 1.10 equiv), Pd(PPh$_3$)$_4$ (Note 4) (2.44 g, 2.11 mmol, 0.064 equiv), benzene (Note 5) (36 mL), ethanol (Note 6) (7.2 mL) and 2.0 M aqueous sodium carbonate (Note 7) (30 mL) under argon. The argon inlet is then turned off from the source, and the flask's neck through which the reagents were introduced is recapped with the plastic stopper. The flask is then placed in a 70–75 °C preheated silicon oil-bath, equipped with a reflux condenser, and stirred (Figure 1A) (Note 8). Heating is stopped after 72 h and the flask is carefully raised from the oil bath and the dark brown mixture is allowed to cool to room temperature. Water (100 mL) is added to the mixture and the resulting biphasic solution is then transferred into a 1 L separatory funnel and the flask is rinsed forward with DCM (200 mL). The bottom dark brown organic layer is separated and the top clear colorless aqueous layer is extracted with DCM (1 × 200 mL). The combined organic layers were transferred into a 1 L separatory funnel and washed with water (1 × 50 mL) followed by brine (1 × 100 mL). The organic layer is then passed through a bilayer pad of silica gel and anhydrous $MgSO_4$ (Figure 1B) (bottom layer, silica gel (150 g), 200–400 mesh particle size; top layer, anhydrous $MgSO_4$ (50 g)) in a 600-mL porous glass fritted Büchner funnel under high vacuum

into a 1 L round-bottomed flask. The filter pad is rinsed through with DCM (3 × 200 mL) and the clear yellow filtrate is concentrated under reduced pressure by rotary evaporation (30 °C, <15 mmHg) to give 8.6 g of dF(CF_3)ppy (**3**) as an off-white shiny solid (Note 9). The solid is dissolved in 3 mL DCM and 3 mL hexane solution and then charged on a column (2.5 in × 18 in) of 171 g of silica gel (60 Å, 200-400 mesh), which had been equilibrated with hexanes:EtOAc (90:10) and eluted with hexanes:EtOAc (90:10) under gentle air-pressure. At that point, collection of 25 mL fractions is begun, and the elution continues with 1.5 L of hexanes:EtOAc (90:10). The desired product is obtained in fractions 10-25 according to TLC analysis, which are concentrated under reduced pressure by rotary evaporation (30 °C, < 15 mmHg) to give 7.81 g (Note 10) (90% yield) of dF(CF_3)ppy (**3**) as a pink-white solid.

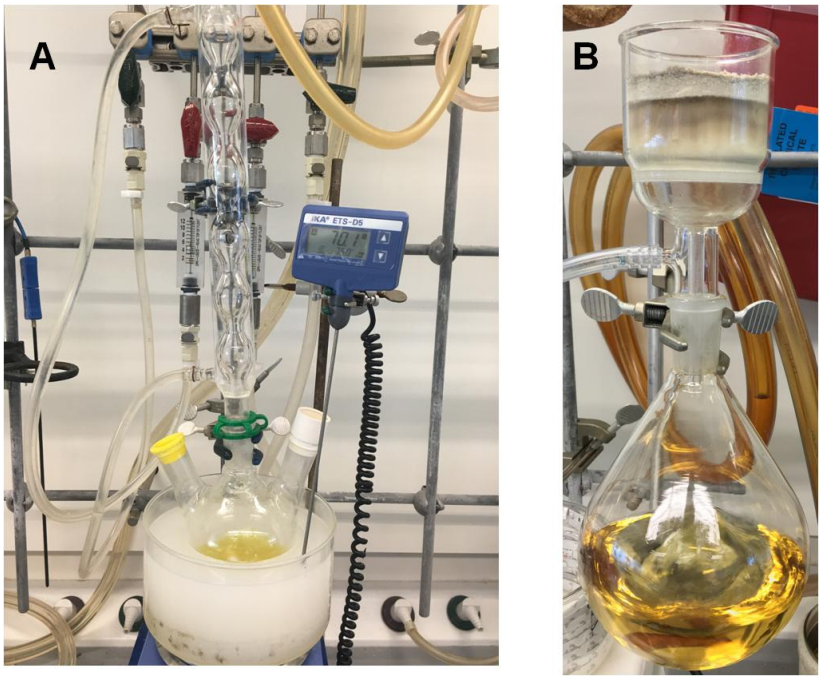


Figure 1A. Reaction set up; 1B. Vacuum-filtration set up. (Photographs provided by the submitters)

B. *[(dF(CF$_3$)ppy)$_2$-Ir-μ-Cl]$_2$ complex.* A 500 mL, three-necked (24/40 joints), round-bottomed flask is equipped with a 3.5 cm length × 1.5 cm width magnetic stirring bar, a cold water reflux condenser, an argon inlet and two yellow plastic stoppers. A plastic stopper is removed temporarily and the flask is flushed with argon for 5 min before sequentially charged with iridium(III)chloride hydrate (Note 11) (3.50 g, 11.1 mmol, 1.00 equiv), dF(CF$_3$)ppy (**3**) (6.60 g, 25.4 mmol, 2.30 equiv), 2-ethoxyethanol (Note 12) (140 mL) and water (70 mL) under argon. The argon inlet is then turned off from the source, and the flask's neck through which the reagents were introduced is recapped with the plastic stopper. The flask containing a dark-brown reaction mixture is then placed on a 120–125 °C preheated silicon oil-bath and stirred under the reflux condenser. The color of the reaction changes from dark brown to orange within the first two hours of heating (Figure 2). Heating is stopped after 48 h and the flask is carefully raised from the oil bath and allowed to cool to room temperature over 45 min. Water (200 mL) is then added to the resulting yellow slurry after which, the flask is immersed in an ice- bath for 30 min. The resulting yellow solid is

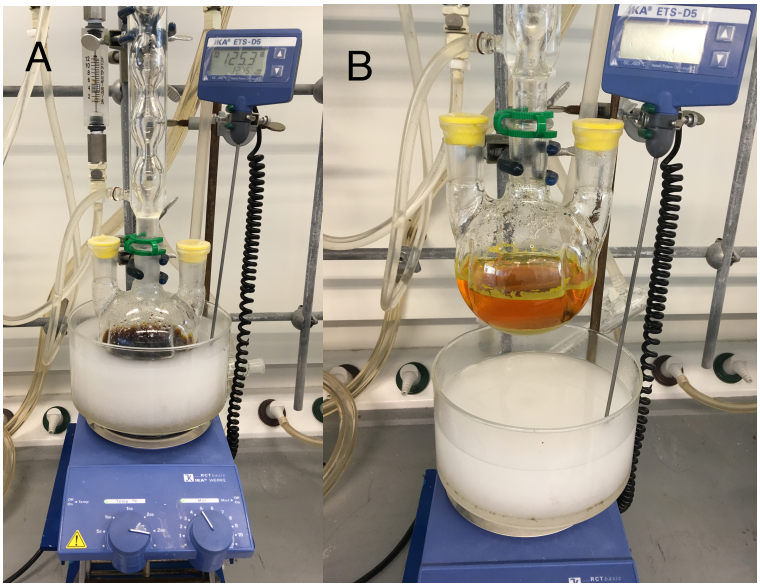


Figure 2A. Apparatus set up and coloration at the start of the reaction; Figure 2B. Reaction mixture after heating at 125 °C for 24 h. (Photographs provided by the submitters)

collected on a filter paper (number 1) by vacuum-filtration using a Büchner funnel equipped with a 1-L vacuum flask. The reaction flask is rinsed with water (70 mL), which is vacuum-filtered, using the same Büchner funnel and the yellow solid is washed with 1:1 MeOH:H_2O (1 × 150 mL) under vacuum. The yellow powder is then air-dried in the fume-hood on a weighing paper inside a glass-dish overnight (15-18 h). The yellow solid is transferred into a 250-mL Erlenmeyer flask containing 140 mL of MeOH:DCM (130 mL MeOH: 10 mL DCM) solvent mixture (Note 13). The flask containing the yellow slurry is kept in an ice-bath for 30 min and the solid is collected by vacuum-filtration on filter paper (number 1) with a Büchner funnel. The solid is rinsed under the vacuum-filtration with cold 13:1 MeOH:DCM (1 × 140 mL) followed by cold pentane (1 × 100 mL) then dried under house vacuum (<15 mmHg) for 18 h to give 6.27 g (38 % yield) of $[(dF(CF_3)ppy)_2\text{-Ir-}\mu\text{-Cl}]_2$ complex as a bright yellow solid (Note 14).

C. *[2,2′-Bipyridine]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]-phenyl]-Iridium(III) hexafluorophosphate, $[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$* (**4**). A 500-mL, three-necked (24/40 joints), round-bottomed flask is equipped with a 2.5 cm length × 1 cm width magnetic stirring bar, a cold water reflux condenser, a nitrogen inlet and two yellow plastic stoppers. A plastic stopper is removed temporarily and the flask is flushed with nitrogen for 5 min before sequentially charged with $[(dF(CF_3)ppy)_2\text{-Ir-}\mu\text{-Cl}]_2$ complex (Note 15) (3.16 g, 4.25 mmol, 1.00 equiv) and 2,2′-bipyridine (Note 16) (2.59 g, 16.6 mmol, 3.90 equiv) and ethylene glycol (Note 17) (100 mL) under nitrogen. The nitrogen inlet is then turned off from the source, and the flask's neck through which the reagents are introduced is recapped with the plastic stopper. The flask containing the reaction mixture is then placed on a 150 °C preheated silicon oil-bath and stirred under the reflux condenser (Note 18). Heating is stopped after 48 h and the flask is carefully raised from the oil bath and allowed to cool to room temperature. The clear orange solution is immersed in an ice-bath and water (150 mL) is added immediately followed by NH_4PF_6 (Note 19) (17.5 g) with stirring with a spatula to give a yellow precipitate. The flask is left in the ice-bath for 30 min before the yellow solid is collected by vacuum-filtration on filter paper (number 1) with a Büchner funnel. The flask is rinsed with water (100 mL), which is vacuum-filtered, and the yellow solid is washed with water (5 × 100 mL) under the vacuum filtration. The wet yellow solid is rinsed with pentane (1 x 100 mL) under the vacuum filtration, then transferred in a glass dish to a dessicator to dry overnight under house

vacuum (< 15 mmHg) (15-18 h). The yellow solid is transferred into a 250 mL flask and dissolved in acetone (40 mL) with swirling. The undissolved solids are removed by filtration over glass wool placed inside a glass funnel, with the clear orange solution being collected in a 500 mL Erlenmeyer flask. The glass wool is rinsed with acetone (1 x 5 mL), after which pentane (150 mL) is added to the solution with swirling until a yellow solid crashes out of solution. The flask is then immersed in an ice-bath for 30 min and the yellow solid is collected by vacuum-filtration on filter paper (number 1) with a Büchner funnel. The flask is rinsed with pentane (100 mL), which is also filtered, and the solid is dried under house vacuum for 2 h to give 4.05 g of a yellow solid (Note 20). The yellow solid is then fully redissolved in acetone (30 mL) and MeOH (12.5 mL) is added to the orange solution. Hexanes (75 mL) are then added with swirling to the clear solution until a yellow solid crashes out. The flask is then immersed in an ice-bath for 30 min and the yellow solid is collected by vacuum-filtration on filter paper (number 1) with a Büchner funnel. The flask is rinsed with hexanes (100 mL), which is also filtered. The solid is then transferred into a 250 mL one-necked round-bottomed flask and dried under high vacuum (1 mmHg) for 24 h give 2.81 g (65% yield) of Ir{dF(CF_3)ppy}$_2$(bpy)]PF_6 (**4**) as a bright yellow solid (Note 21).

D. *4,4′ -Bis(tert-butyl)-2,2′ -bipyridine]bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl]Iridium(III)hexafluorophosphate, [Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6 (**5**).* A 500 mL, three-necked (24/40 joints), round-bottomed flask is equipped with a 2.5 cm length × 1 cm width magnetic stirring bar, a cold water reflux condenser, an argon inlet and two yellow plastic stoppers. A plastic stopper is removed temporarily and the flask is flushed with argon for 5 min before sequentially charged with [(dF(CF_3)ppy)$_2$-Ir-μ-Cl]$_2$ complex (Note 15) (2.75 g, 3.70 mmol, 1.00 equiv.) and 4,4′ -bis(*tert*-butyl)-2,2′ -bipyridine (Note 22) (1.49 g, 5.54 mmol, 1.50 equiv.) and ethylene glycol (Note 17) (87.5 mL) under argon. The argon inlet is then turned off from the source, and the flask's neck through which the reagents are introduced is recapped with the plastic stopper. The flask containing the reaction mixture is then placed on a 150 °C preheated silicon oil-bath, equipped with a reflux condenser, and stirred. Heating is stopped after 48 h and the flask is carefully raised from the oil bath and allowed to cool to room temperature. After 1 h, the yellowish-green solution is diluted with water (175 mL) and NH_4PF_6 (Note 19) (15.0 g) is added to the solution. The mixture is stirred with a spatula to aid the full formation of a yellow solid. The fine yellow solid is then collected by vacuum-filtration on filter

paper (number 1) using a 300-mL Büchner funnel equipped with a 1 L flask. The fine yellow solid is then washed with water (5 × 100 mL) under the vacuum-filtration. The yellow solid is transferred in a glass dish on weighing paper and glass dish is placed in dessicator which is connected to house vacuum source (~10 mmHg) to dry overnight (15-18 h). The yellow solid is then dissolved in acetone (65 mL). The undissolved white and black residues are filtered off on glass wool inside a glass funnel and the glass wool rinsed with acetone (10 mL) to give a clear orange solution. Hexanes (450 mL) is added to the orange solution then vigorously stirred with a spatula to crash out a yellow precipitate. The flask is immersed in an ice-bath for 30 min before collecting the yellow solid by vacuum-filtration (Note 23). The solid is redissolved in acetone (25 mL). Methanol (5 mL) is added to the solution followed by hexanes (150 mL). The orange solution is vigorously stirred with a spatula until a yellow solid crashes out of the solution. The flask is then kept in the freezer at –20°C overnight and the solid is collected by vacuum-filtration and dried under high vacuum (1 mmHg) overnight to give 3.08 g (73%) of $Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**5**) as a yellow solid (Note 24).

Notes

1. Other types of stoppers including glass stoppers and rubber septa can also be used.
2. 2-Chloro-5-(trifluoromethyl)pyridine (**1**) was purchased from Aldrich and used as received as a crystalline white solid (no information on purity was provided by the supplier).
3. (2,4-Difluorophenyl)boronic acid (**2**) was purchased from Aldrich and used as received as an off-white solid (no information on purity was provided by the supplier).
4. $Pd(PPh_3)_4$ (99%) was purchased from Strem and used as received as a bright yellow shiny solid. $Pd(PPh_3)_4$ was weighed out in air into a 20 mL glass vial immediately before use.
5. Benzene (anhydrous, 99.8%) was purchased from Aldrich and used as received.
6. Ethanol (200 proof, anhydrous, ≥99.5%) was purchased from Aldrich and used as received.

7. A 2.0 M Na_2CO_3 solution was prepared by dissolving 6.40 g of Na_2CO_3 in 30 mL of deionized water.
8. The reaction can be monitored by TLC silica gel (hexanes-EtOAc; 90:10); product $R_f = 0.66$.
9. Although the solid was purified by silica gel chromatography, the off-white shiny solid can be carried on to the next step without further purification.
10. A second reaction on identical scale provided 7.72 g (89%) of the product. R_f = 0.66 (10% EtOAc/hexanes), UV-lamp visualization (254 nm): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.00 (s, 1H), 8.09 - 8.14 (m, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.04 (td, *J* = 9 Hz, 1 Hz, 1H), 6.95 (t, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.8 (d, *J* = 12.2 Hz), 162.8 (d, *J* = 12.2 Hz), 161.8 (d, *J* = 11.9 Hz), 159.8 (d, *J* = 12.0 Hz), 155.6, 146.4, 133.6 (d, *J* = 3.0 Hz), 125.2 (q, *J* = 32.5 Hz), 123.7 (q, *J* = 272.2 Hz), 123.6 (d, *J* = 11.3 Hz), 112.1 (d, *J* = 21.3 Hz), 104.5 (dd, *J* = 26.9 Hz, 25.5 Hz); ^{19}F NMR (282 MHz, acetone-d_6 Referenced to TFA at –76.55 ppm) δ: –63.7, –108.5, –113.4; FTIR (thin film): 1599.5, 1478.5, 1392.0 1326.7, 1299.7, 1283.8, 1261.8, 1165.7, 1118.9, 1108.9, 1082.3, 1017.5, 969.2, 950.5, 869.8, 856.6, 823.8 , 818.1, 772.8, 720.0, 710 cm^1; HRMS (ESI) *m*/*z* calcd for $C_{12}H_7F_5N$ [M+H$^+$] 260.0493, found 260.0477. Elemental anal. calcd for $C_{12}H_6F_5N$: C, 55.61 ; H, 2.33; F, 36.65 ; N, 5.40 , found: C, 55.86; H, 2.51; N, 5.32.
11. Iridium(III) chloride hydrate (reagent grade) was purchased from Aldrich and used as received.
12. 2-Ethoxyethanol (99%, Reagent plus) was purchased from Aldrich and used as received. It is important to note that the reaction proceeded with similar efficiency when 2-methoxyethanol that was purchased from Aldrich was used instead of 2-ethoxyethanol.
13. The excess dF(CF_3)ppy (**3**) was removed by rinsing the yellow solid with 13:1 MeOH/DCM mixture.
14. A reaction performed on half-scale provided 2.81 g (34%) of the product. This complex was carried on to the next step without purification. The ^{1}H NMR spectrum showed traces of the monomer. ^{1}H NMR (400 MHz, acetone-d_6) δ: 9.63 (s, 2H), 8.68 (dd, *J* = 8.8 Hz, 2.1 Hz, 2H), 8.52 (dd, *J* = 8.7 Hz, 2 Hz, 2H), 6.71 – 6.66 (m, 2H), 5.21 (dd, *J* = 9 Hz, 2.2 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_3SO$) δ: 167.1, 166.5, 164.5, 163.4, 162.5, 161.3, 160.1, 159.4, 156.1, 150.2, 148.9, 147.0, 137.7, 136.8, 126.3, 125.7, 124.4, 123.9, 123.3, 122.8, 122.6, 122.2, 114.2, 111.4, 99.4. ^{19}F NMR (282 MHz, acetone-d_6 Referenced to TFA at –76.79 ppm)

δ: –62.7, –105.2, –108.6; FTIR (thin film): 1600.9, 1576.0, 1382.8, 1326.3, 1312.0, 1295.8, 1252.0, 1179.4, 1166.0, 1136.2, 1106.8, 1090.2, 1048.1, 992.3, 844.5, 832.6, 722.2, 717.4 cm^{-1}. Elemental anal. calcd for $C_{48}H_{20}Cl_2F_{20}Ir_2N_4$: C, 38.74; H, 1.35; Cl, 4.76; F, 25.54 ; Ir, 25.84 ; N, 3.77 , found : C, 38.77 ; H, 1.40 ; F, 25.36 ; N, 3.86.

15. The molecular weight (MW) of the monomer (744.009 g/mol) was used to calculate the mmol.
16. 2,2'-Bipyridine (bpy, >99%) was purchased from Aldrich and used as received. The use of excess of this reagent is essential for the yield and purity of the final complex.
17. Ethylene glycol (99.8%) was purchased from Aldrich and used as received.
18. The reaction mixture changed from a yellow-slurry to a clear orange solution during heating.
19. NH_4PF_6 (≥ 95%) was purchased from Aldrich and used as received.
20. Prior to additional purification, the product contains trace unknown impurity.
21. A second reaction on identical scale provided 2.79 g (65%) of the identical product. ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.90 (dt, J = 8.3 Hz, 1.1 Hz, 2H), 8.62 (dd, J = 8.8 Hz, 2.7 Hz, 2H), 8.41 (m, 4H), 8.31 (d, J = 5.5 Hz, 0.8 Hz, 2H), 7.97 (s, 2H), 7.80 (ddd, J = 7.7 Hz, 5.5 Hz, 1.2 Hz, 2H), 6.86 (ddd, J = 12.8 Hz, 9.3 Hz, 2.3 Hz, 2H), 5.97 (dd, J = 8.4 Hz, 2.5 Hz, 2H); ^{13}C{^{1}H} NMR (125 MHz, acetone-d_6) δ: 168.9 (d, J = 8.2 Hz), 166.8 (d, J = 12.9 Hz), 164.7 (dd, J = 13.2 Hz, 4.7 Hz), 162.6 (d, J = 13.4 Hz), 157.1, 156.4 (d, J = 7.5 Hz), 152.7, 147.4 (d, J = 5.1 Hz), 141.9, 138.5 (d, J = 3.5 Hz), 130.4, 128.1 (dd, J = 5.0 Hz, 2.9 Hz), 126.6, 125.1 (d, J = 21.4 Hz), 123.3 (d, J = 271.7 Hz), 115.7 (dd, J = 18.1 Hz, 3.5 Hz), 100.6 (t, J = 27.2 Hz); ^{19}F NMR (282 MHz, acetone-d_6 Referenced to TFA at –76.79 ppm) δ: –63.4, –71.3, –73.8, –104.6, –107.9; FTIR (thin film): 1602.6, 1575.4, 1386.9, 1298.3, 1180.9, 1167.9, 1142.0, 1109.6, 1090.4, 991.9, 866.0, 838.2, 768.5, 735.1, 721.6 cm^{-1}; HRMS (ESI) m/z calcd for $C_{34}H_{18}F_{10}IrN_4$ [M^+] 865.0996, found 865.0995. Elemental anal. calcd for $C_{34}H_{18}F_{10}IrN_4$: C, 41.02 ; H, 2.07 ; F, 29.66 ; Ir, 18.76 ; N, 5.47, found : C, 41.08 ; H, 2.11 ; F, 29.42 ; N, 5.51.
22. 4,4′-Bis(*tert*-butyl)-2,2′-bipyridine (dtbbpy, 98%) was purchased from Aldrich and used as received. The use of excess of this reagent is essential for the yield and purity of the final complex.
23. The ^{1}H NMR spectrum showed an unknown impurity in the aromatic region. The impurity was removed by dissolving the solid in

acetone/MeOH mixture and the pure product was crashed out of the solution with hexanes.

24. A reaction performed on half-scale provided 1.52 g (73%) of the identical product. ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.93 (d, J = 1.9 Hz, 2H), 8.61 (dd, J = 8.9 Hz, 2.6 Hz, 2H), 8.40 (dd, J = 8.9 Hz, 2.1 Hz, 2H), 8.18 (d, J = 5.9 Hz, 2H), 7.76 - 7.86 (m, 4H), 6.89 (ddd, J = 12.7 Hz, 9.3 Hz, 2.3 Hz, 2H), 5.97 (dd, J = 8.4 Hz, 2.3 Hz, 2H), 1.43 (s, 18H); ^{13}C{^{1}H} NMR (125 MHz, acetone-d_6) δ: 169.1 (d, J = 8.3 Hz), 166.8 (d, J = 12.8 Hz), 164.7 (dd, J = 13.3 Hz, 8.3 Hz), 162.6 (d, J = 13.4 Hz), 157.2, 157.0 (d, J = 7.4 Hz), 152.3, 146.9 (d, J = 5.1 Hz), 138.4, 128.0, 127.3, 125.3 (d, J = 431.3 Hz), 125.2 (q, J = 33.8 Hz), 124.8 (d, J = 21.1 Hz), 123.1 (d, J = 271.3 Hz), 115.6 (dd, J = 18.0 Hz, 3.4 Hz), 100.4 (t, J = 27.2 Hz), 36.9; ^{19}F NMR (282 MHz, acetone-d_6 Referenced to TFA at –76.79 ppm) δ: –66.6, –71.3, –73.8, –104.6, –107.9; FTIR (thin film): 2970.1 1603.1, 1576.0, 1329.8, 1314.3, 1297.1, 1251.4, 1179.4, 1168.2, 1137.3, 1108.4, 1090.3, ; HRMS (ESI) m/z calcd for $C_{42}H_{34}F_{10}IrN_4$ [M^+] 977.2248, found 977.2260. Elemental anal calcd. for $C_{42}H_{34}F_{10}IrN$: C, 45.43 ; H, 3.28 ; F, 26.74 ; Ir, 16.91 ; N, 4.93, found : C, 45.18 ; H, 3.06 ; F, 26.78; N, 5.09.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards

associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

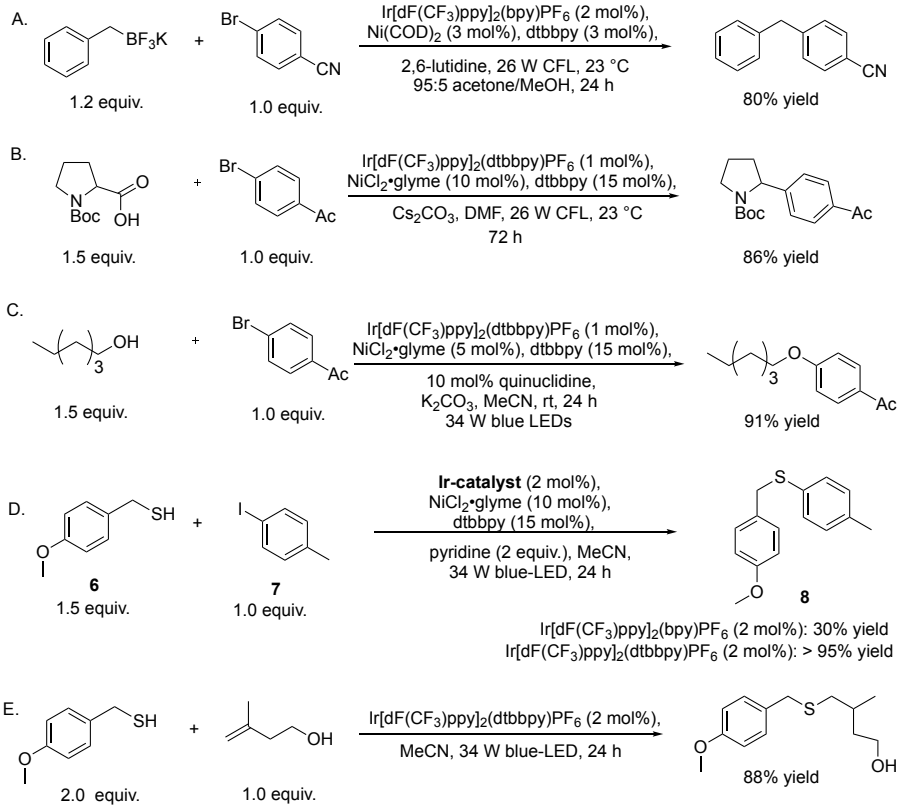
Discussion

$[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ (**4**) and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**5**) have both emerged as powerful photoredox catalysts in cross-coupling reactions[2] as well as other bond-forming transformations.[3,4] Molander, Doyle and MacMillan pioneered the elegent use of $[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ (**4**) and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**5**) in Ir-photoredox/Ni dual-catalyzed cross-coupling reactions.[2a,b] The application of Ir-complexes **4** and **5** is rapidly increasing in organic method development, which includes C-O and C-S cross-coupling reactions.[5] As such, their preparation through simple synthetic protocols is of utmost importance. Although Malliaras and Bernhard have described milligram scale synthesis of Ir-complex (**5**),[6] the gram scale syntheses of these complexes has not been reported. Advantageously, both the $[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ (**4**) and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**5**) are air and moisture stable and can both be synthesized from a common advanced intermediate.

Based on the work by Malliaras and Bernhard on the synthesis of **5**,[6] we have developed a practical scalable synthesis of $[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ (**4**) and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**5**) in grams quantities from readily available starting materials. The first step of the syntheses involves a palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of 2-chloro-5-(trifluoromethyl)pyridine (**1**) and (2,4-difluorophenyl)boronic acid (**2**) to give $dF(CF_3)ppy$ (**3**). We found that the original procedure[6] for the Suzuki-Miyaura reaction provided excellent yields at increased scale (9-20 grams scale, 95-99% yield). The second step of the synthesis involves complexation between $IrCl_3.H_2O$ and $dF(CF_3)ppy$ (**3**) to give the advanced intermediate as

an air and moisture stable dimeric complex [(dF(CF$_3$)ppy)$_2$-Ir-μ-Cl]$_2$. The ^{1}H-NMR spectrum of this complex shows trace amount of the monomeric complex. While both ^{1}H- and ^{19}F NMR spectra could be obtained in acetone-d_6, a satisfactory ^{13}C NMR spectrum of this dimeric complex could not be obtained. However, the checkers were able to obtain a ^{13}C NMR after gentle heating (30 °C) of this complex in DMSO-d_6. The ^{1}H-NMR spectrum of this complex is identical to that reported by Malliaras and Bernhard.[6] We found that increasing the reaction time from 12 h to 48 h was essential for the full formation of the complex. Attempts to recrystallize this complex resulted in a significant loss of yield. However, the only contaminant in the complex is the excess dF(CF$_3$)ppy (**3**), which was completely removed by washing the complex with a MeOH/DCM solvent mixture after which the complex was taken to the next step without further purification. The final step in the syntheses is the treatment of [(dF(CF$_3$)ppy)$_2$-Ir-μ-Cl]$_2$ with bpy or dtbbpy ligand followed by NH_4PF_6 under our optimized conditions to give [Ir{dF(CF$_3$)ppy}$_2$(bpy)]PF$_6$ (**4**) and [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (**5**) respectively. The syntheses of [Ir{dF(CF$_3$)ppy}$_2$(bpy)]PF$_6$ (**4**) and [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (**5**) were performed on milligram to 10 gram scales following the procedures described in this report. These air and moisture stable Ir-complexes can be stored at room temperature and used as photoredox catalysts as demonstrated by the selected examples in Scheme 1.

Molander and colleagues developed a highly efficient Ni-catalyzed Suzuki cross-coupling reaction mediated by [Ir{dF(CF$_3$)ppy}$_2$(bpy)]PF$_6$ (**4**) as the photoredox catalyst (Scheme 1a).[2a] Doyle, MacMillan and colleagues demonstrated an elegant use of [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (**5**) in a decarboxylative cross-coupling reaction for C-C bond formation (Scheme 1b).[2b] [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (**5**) is also an efficient photoredox catalyst for C-O bond formation as demonstrated by MacMillan and colleagues (Scheme 1c).[5a] We have also shown that [Ir{dF(CF$_3$)ppy}$_2$(bpy)]PF$_6$ (**4**) and [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (**5**) are efficient photoredox catalysts in Ir/Ni dual catalyzed cross-coupling of thiols with aryl iodides (Scheme 1d).[5b] [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (**5**) is also an efficient catalyst for thiol-ene reactions (Scheme 1e).[5b]



Scheme 1. Selected Applications of [Ir{dF(CF$_3$)ppy}$_2$(bpy)]PF$_6$ (4) and [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (5) as Photoredox Catalysts in Bond-Forming Reactions.

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5. (a) Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C. *Nature* **2015**, *524*, 330-334. (b) Oderinde, M. S.; Frenette, M. A.; Aquila, B.; Robbins, D. W.; Johannes, J. W. *J. Am. Chem. Soc.* **2016,** *138*, 1760-1763.
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

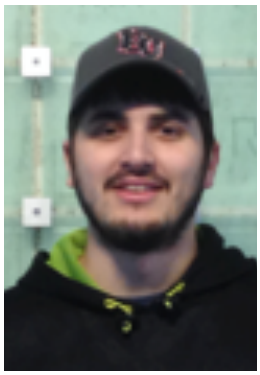
2-Chloro-5-(trifluoromethyl)pyridine: (52334-81-3)
(2,4-Difluorophenyl)boronic acid: (144025-03-6)
$Pd(PPh_3)_4$ (99%): Tetrakis(triphenylphosphine)palladium (0); (14221-01-3)
Iridium(III) chloride hydrate (reagent grade): (14996-61-3)
2-Ethoxylethanol (>99%): (110-80-5)
2,2'-Bipyridine (bpy, >99%): 2,2'-Dipyridyl; (366-18-7)
Ethylene glycol (99.8%): (107-21-1)
NH_4PF_6 (≥ 95%): Ammonium hexafluorophosphate; (16941-11-0)
4,4′ -Bis(*tert*-butyl)-2,2′ -bipyridine (dtbbpy): 4,4′ -Di-*tert*-butyl-2,2'-dipyridyl; (72914-19-3)

Dr. Martins S. Oderinde obtained a B.S. degree in industrial chemistry at the University of Ibadan, Nigeria in 2004. He then moved to Canada and obtained his M.S. degree in organic chemistry at the University of Alberta, Canada in Professor Hicham Fenniri's group. After working briefly at Gilead Sciences Inc. as a process chemist, he joined Professor Michael Organ's group at York University, Toronto, Canada. In Organ's lab, he worked on total synthesis, radical chemistry, mechanistic studies and received his Ph.D in 2013. He then undertook a year of postdoctoral studies at Stanford University in Professor Justin DuBois' lab before moving to AstraZeneca (AZ) Pharmaceuticals LP in 2014 for his second postdoctoral appointment. At AZ he conducted research work on photoredox mediated cross-coupling reactions under the supervision of Dr. Jeffrey W. Johannes. In 2016, he joined the Inflammation and Immunology (I&I) department, medicine design at Pfizer Inc.

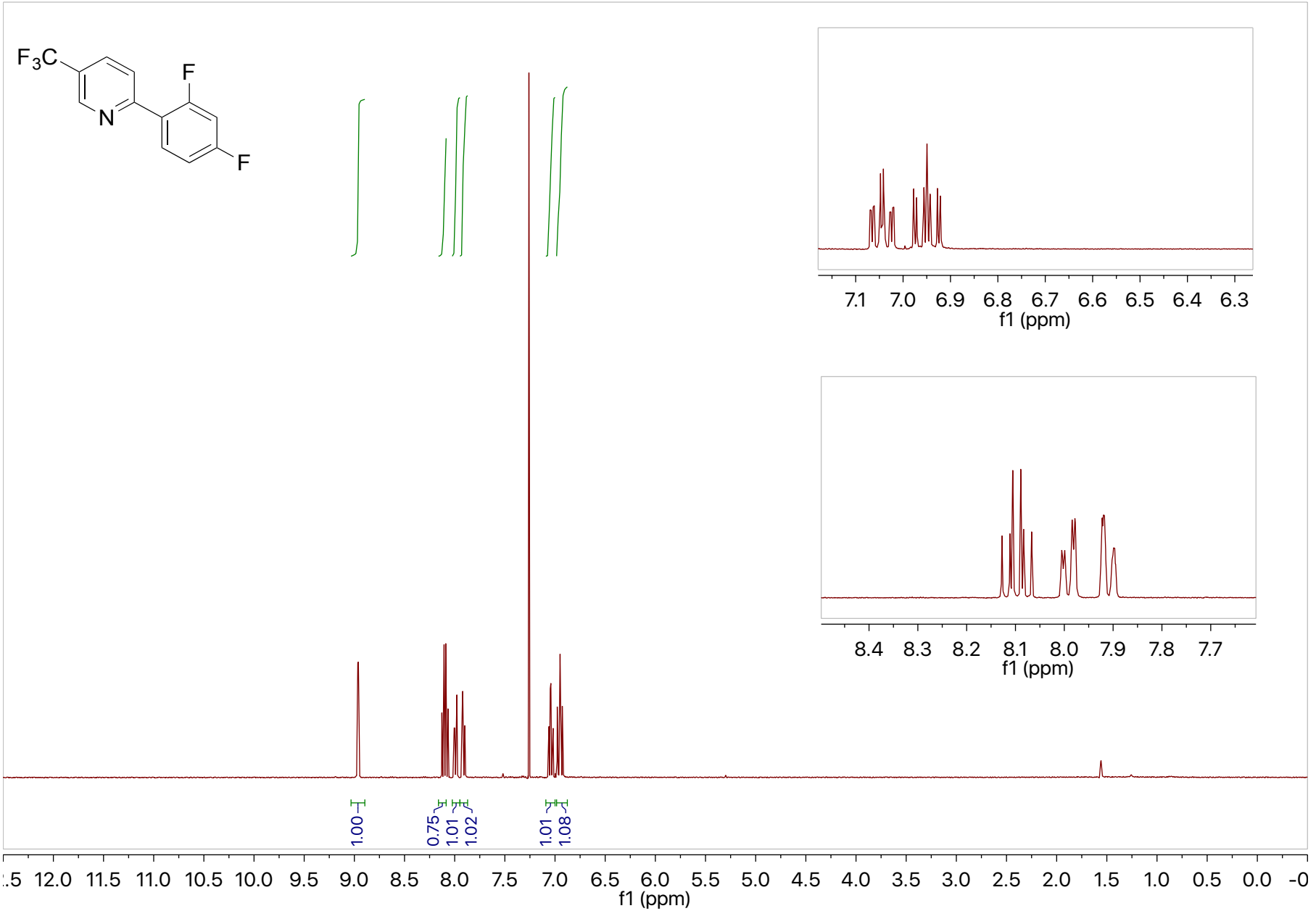
Dr. Jeffrey W. Johannes hails from Puyallup, Washington, a small city south of Seattle. For his undergraduate studies, he moved to Claremont, CA to attend Harvey Mudd College, receiving a Bachelor of Science degree in chemistry in 1999. He joined the lab of Professor Yoshito Kishi at Harvard University to work in the field of natural product synthesis. Following his work on the total synthesis of gymnodimine, he received a Ph.D. in 2005. After staying in Professor Kishi's lab for an additional year as a post-doctoral fellow, he then joined AstraZeneca in 2006. Since then, Jeff has worked in the medicinal chemistry group in Waltham, MA on a number of diverse oncology targets, spanning both the lead generation and lead optimization phases of drug discovery.

Nadide Hazal Avci was born in İstanbul, Turkey in 1993. She began working towards her B.S. in Chemistry at the Bogazici University. In the summer of 2016 she joined the laboratories of Professor Mohammad Movassaghi as an international exchange student. She is currently completing her B.S. degree at the Bogazici University.

Chase Olsson was born in San Diego, CA in 1990. He received his B.A. in 2012 from Pomona College in Claremont, CA where he carried out research in the laboratory of Professor Daniel O'Leary. He worked for a year as an R&D chemist for Materia Inc, in Pasadena, CA. In 2014, he joined the research group of Professor Movassaghi at the Massachusetts Institute of Technology to pursue his Ph.D. focused on complex natural product total synthesis.



Brandon Nelson was born in Streamwood, Illinois in 1991. He received his B.S. in 2013 from Illinois State University where he carried out research in the labs of Professor Hitchcock and Professor McLauchlan. He then moved to the Massachusetts Institute of Technology to pursue his Ph.D. focused on complex natural product total synthesis under the direction of Professor Movassaghi.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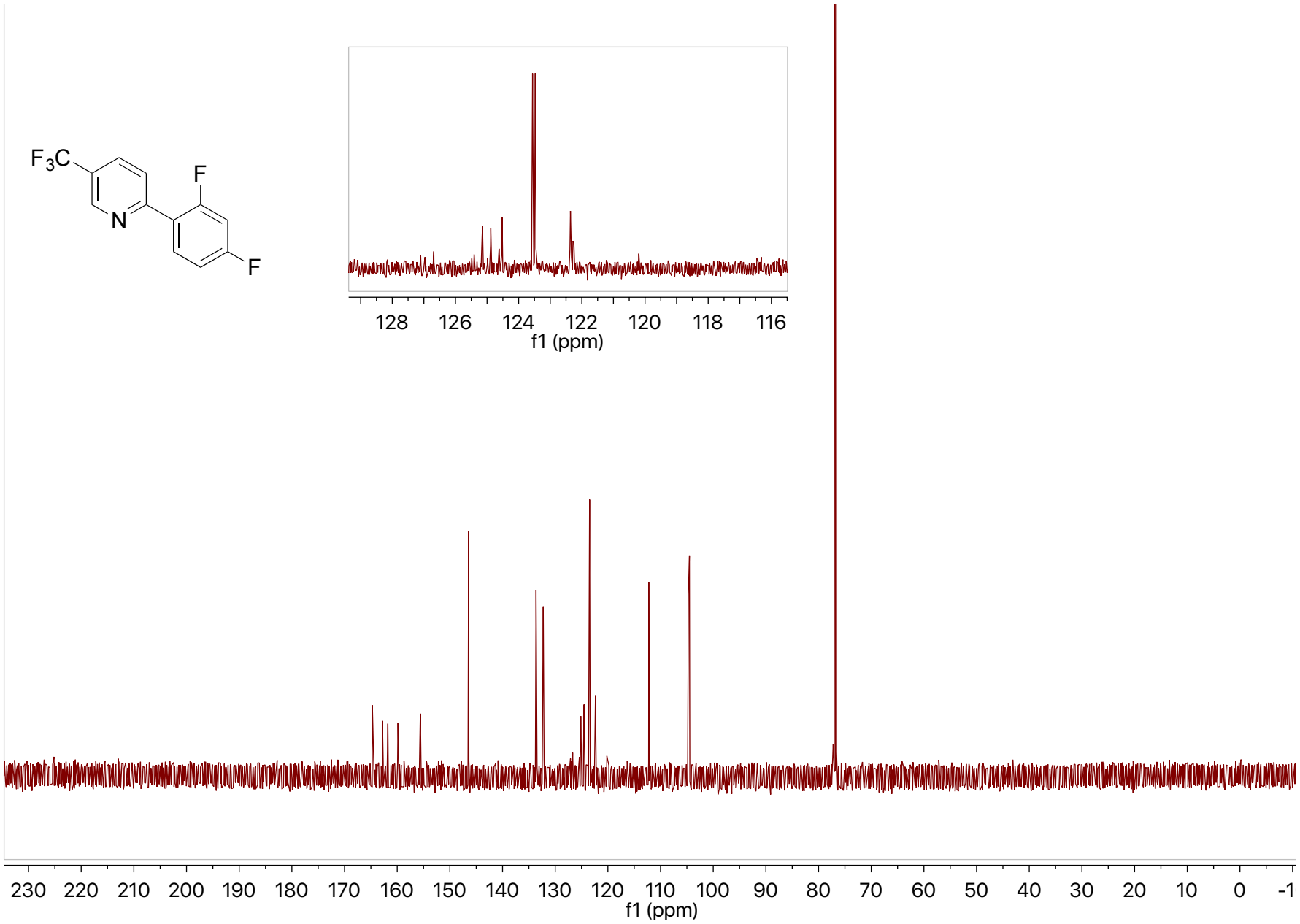
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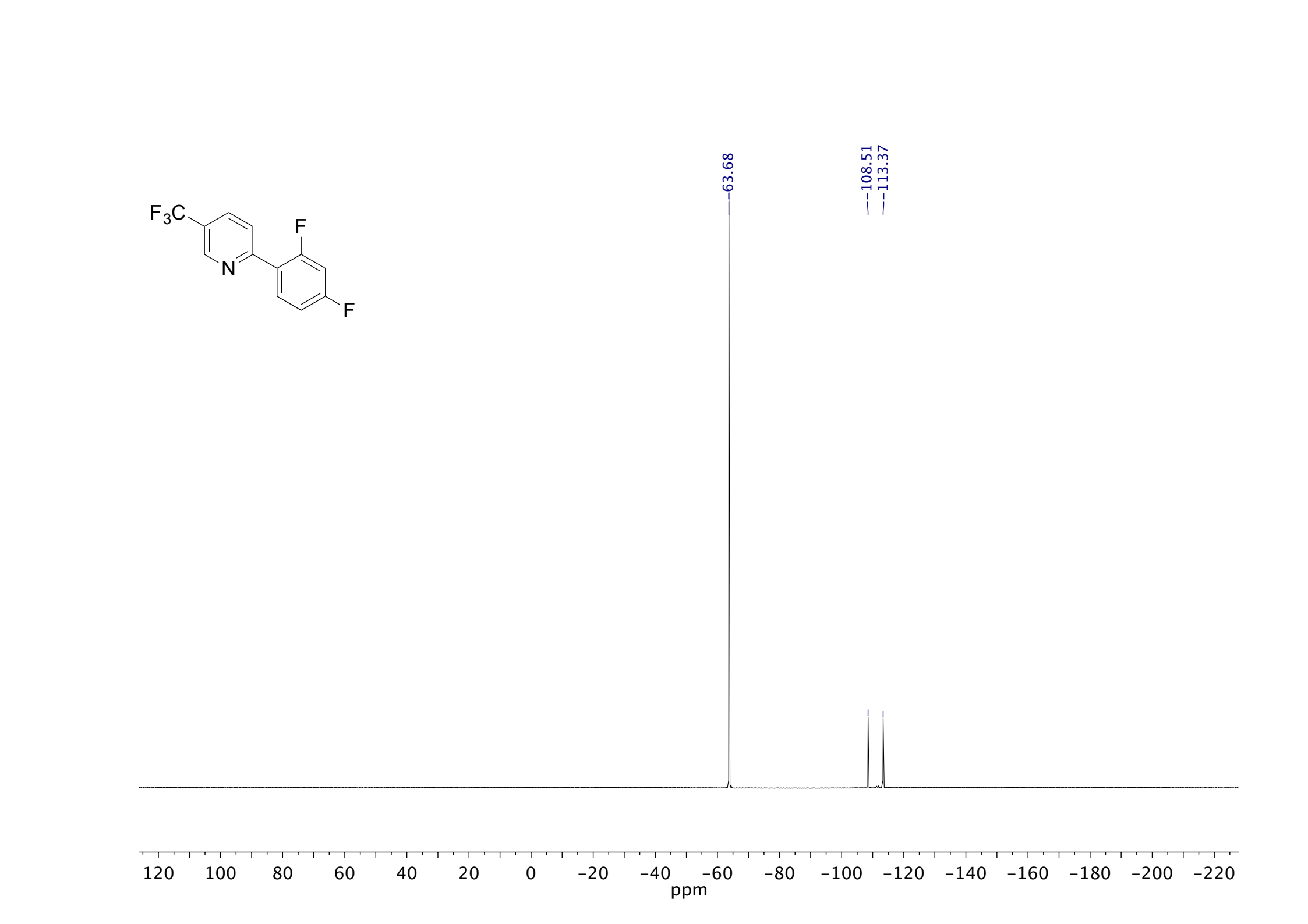
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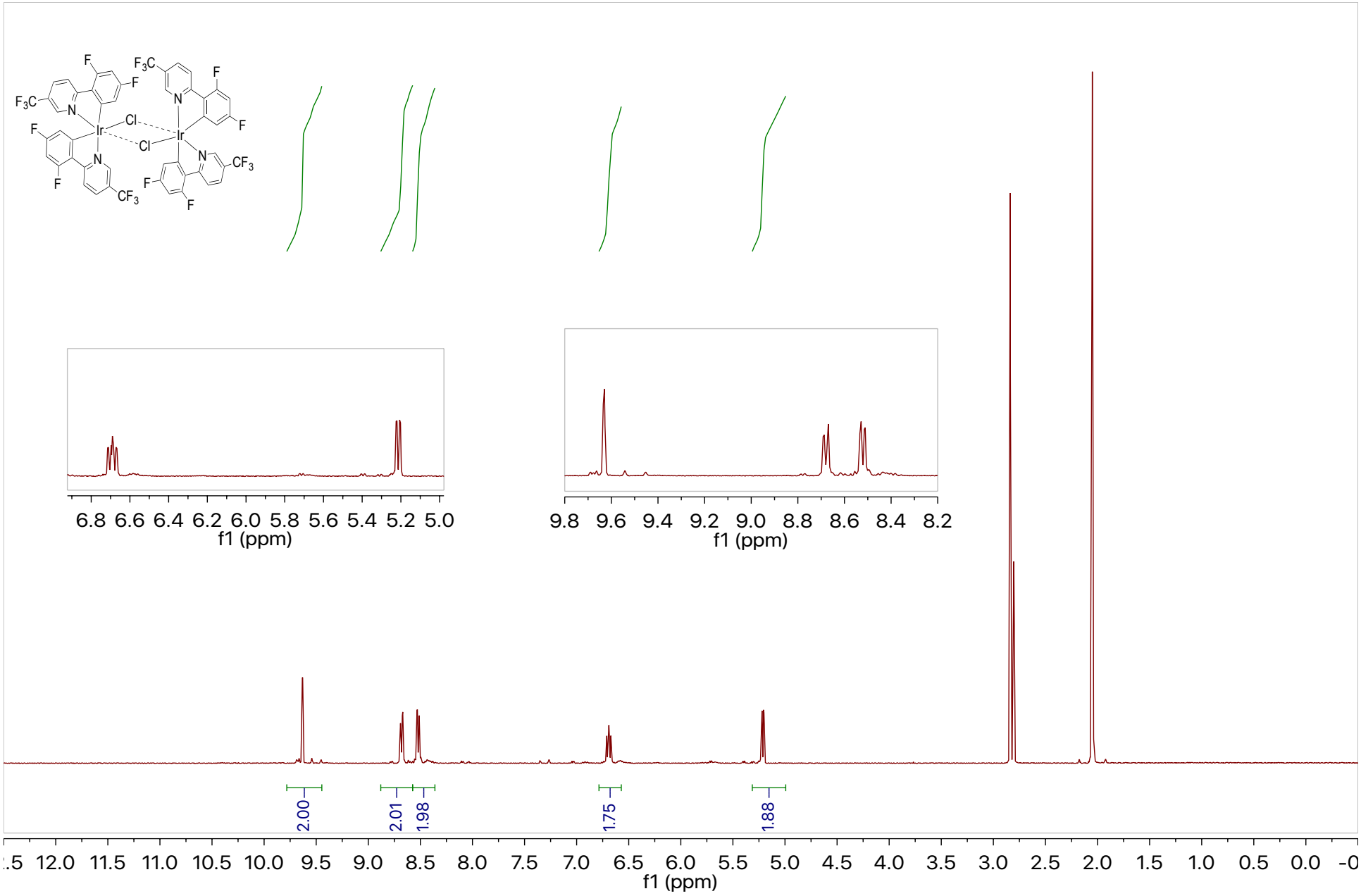
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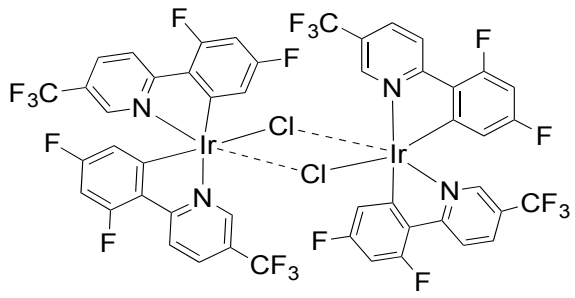

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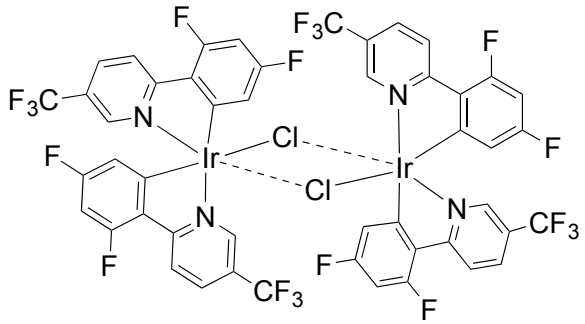

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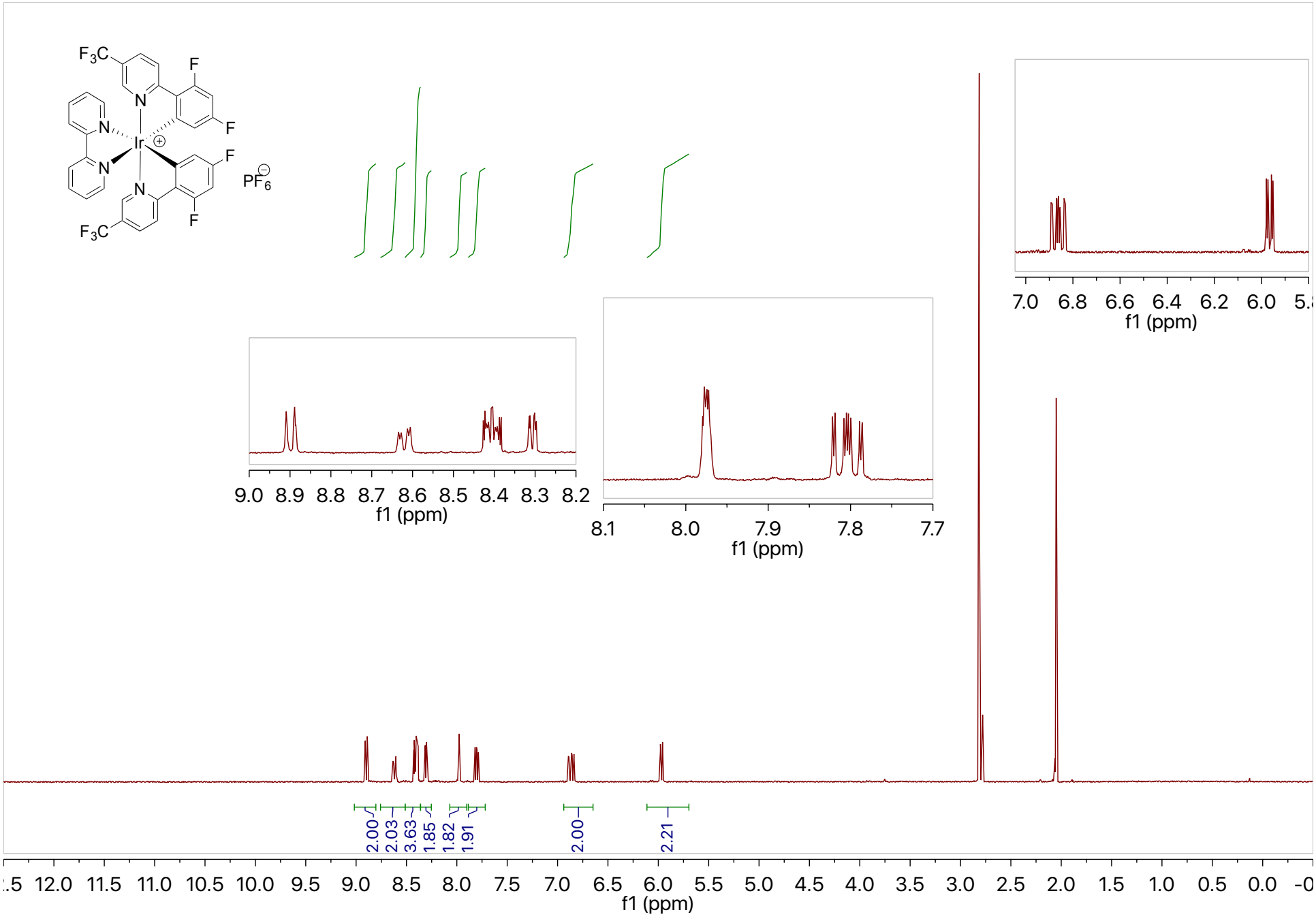
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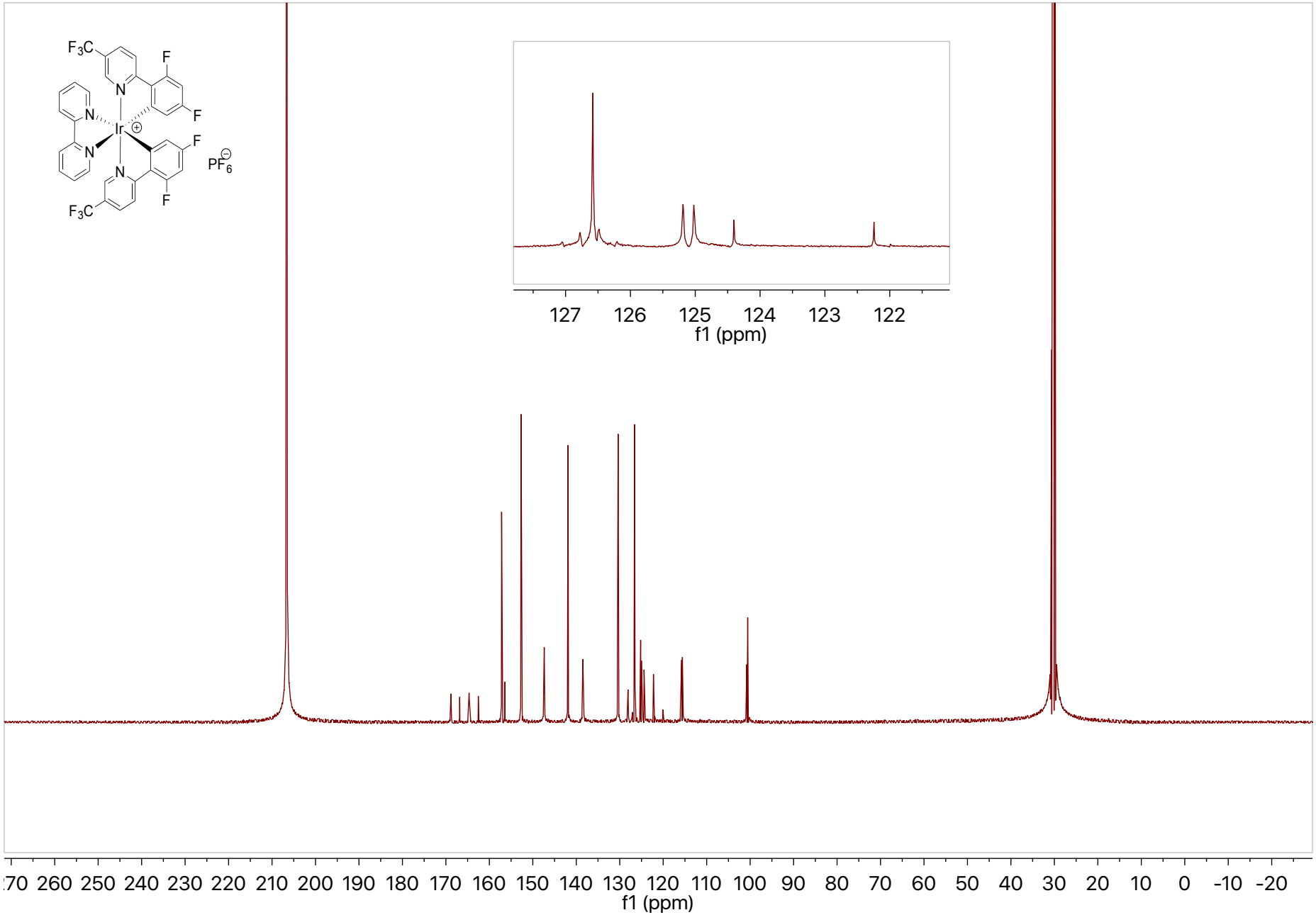
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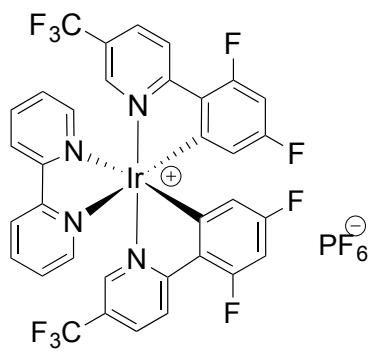
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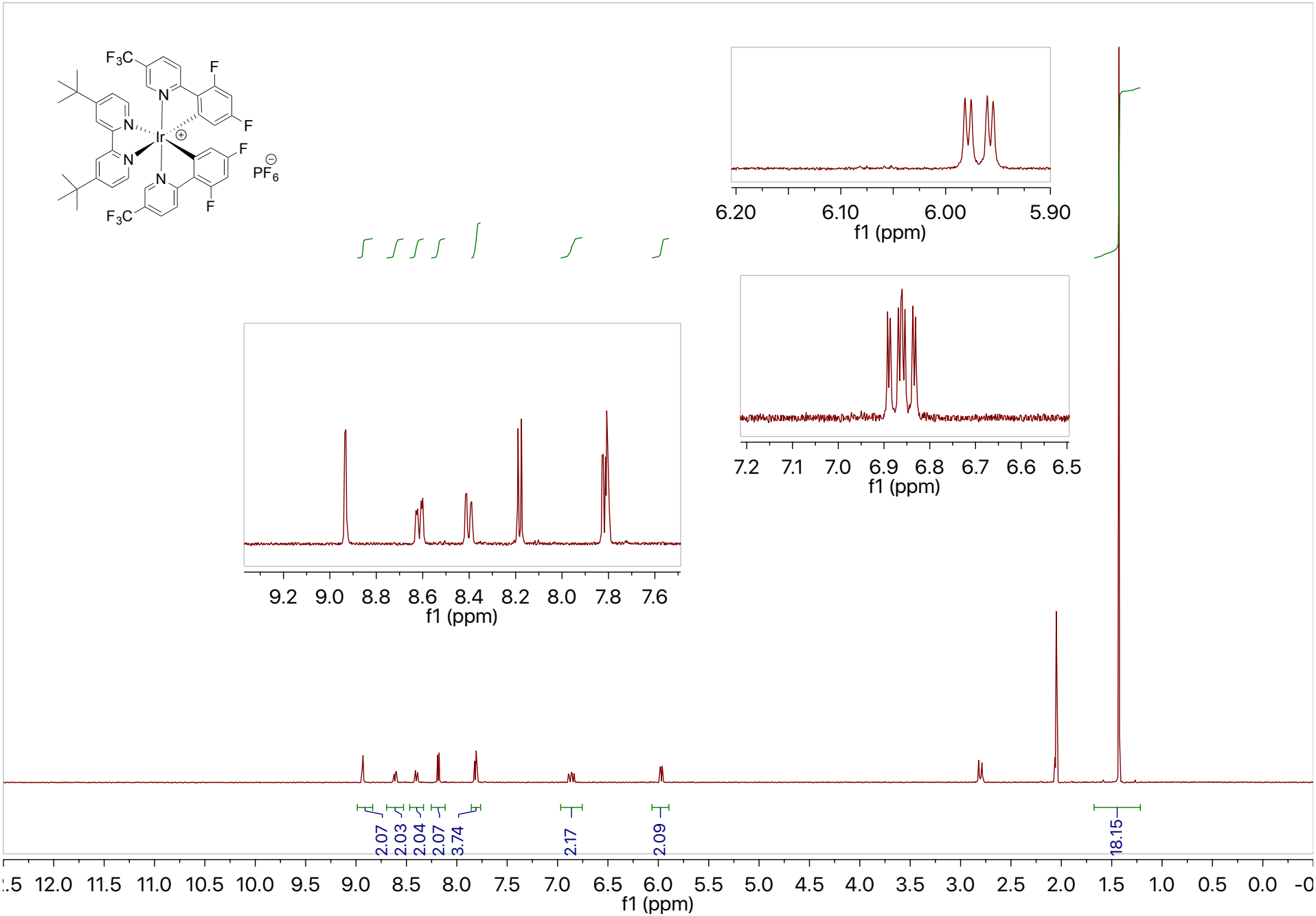
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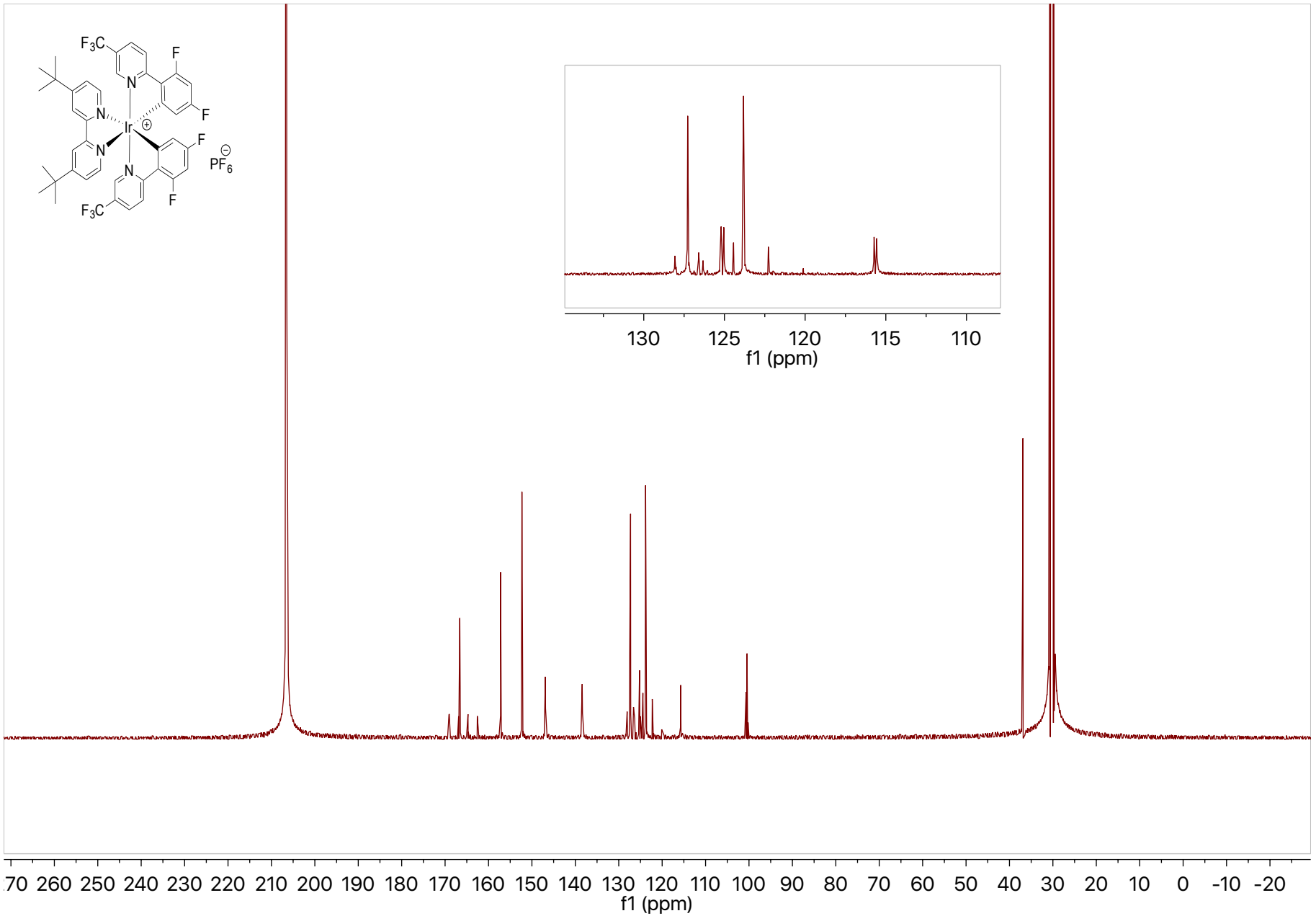
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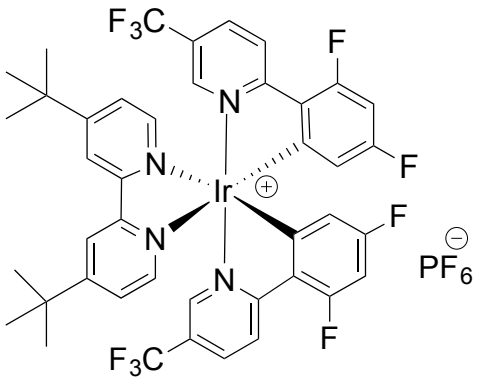
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