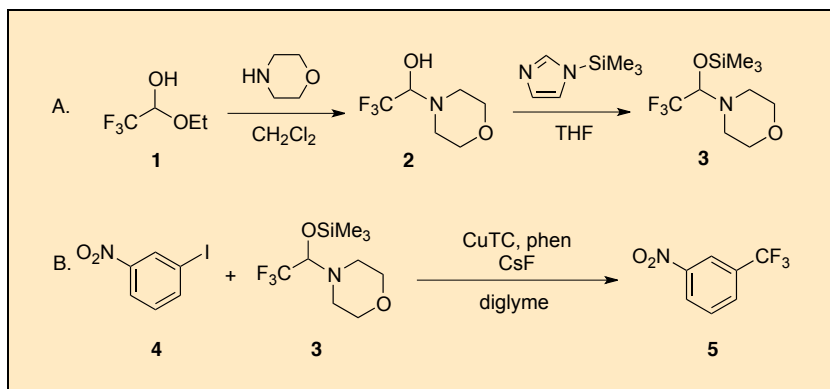


Trifluoromethylation of Aryl Iodides Catalyzed by the Copper(I)-Phen Complex

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Checked by Mina Nakhla and John L. Wood



Procedure

A. 4-[2,2,2-Trifluoro-1-(trimethylsilyloxy)ethyl]morpholine (3). A 1-L, three-necked, round-bottomed flask is equipped with a 4-cm Teflon-coated magnetic stir bar and the center neck is fitted with a glass gas inlet adapter which is connected to a nitrogen/vacuum double manifold. The other two necks are capped with rubber septa. The flask is charged with molecular sieves 4 Å (40 g) (Note 1). The system is flame-dried under vacuum and backfilled with nitrogen (Note 2). After flame drying the right neck of the flask is equipped with a temperature probe. To the flask are added anhydrous dichloromethane (300 mL, via cannula) (Note 3), morpholine (19.8 g, 19.9 mL, 227 mmol, via syringe) (Note 4), and fluoral ethyl hemiacetal (32.7 g, 26.8 mL, 227 mmol, via syringe) (Note 5). After being

stirred at room temperature for 5 min, the resulting mixture is heated in a 30 °C oil bath for 48 h (Notes 6 and 7) (Figure 1). The flask containing the



Figure 1. Step A - Reaction 1 Set-up

mixture is then removed from the oil bath and allowed to cool to room temperature. The mixture is then vacuum filtered through a 350 mL fine-fritted glass funnel, which is packed with a 20g pad of Celite (Note 8). The Celite[®] pad and the reaction flask are washed with CH₂Cl₂ (3 x 100 mL) and the filtrate is transferred to 1 L recovery flask rinsing with dichloromethane (2 x 50 mL). The solvent is removed by rotary evaporation to afford 40.6 g of trifluoroacetaldehyde hemiaminal **2** as a pale yellow oil, which is used in the next step (silylation) without purification (Note 9).

For the silylation step, a 1-L, three-necked, round-bottomed flask is equipped with a 4-cm Teflon-coated magnetic stir bar and the center neck is fitted with a glass gas inlet adapter which is connected to a nitrogen/vacuum double manifold. The other two necks are capped with rubber septa. The flask is flame-dried under vacuum and backfilled with nitrogen. After flame drying the right neck of the flask is equipped with a temperature probe. A solution of trifluoroacetaldehyde hemiaminal **2**

(40.6 g, 219 mmol) in anhydrous tetrahydrofuran (75 mL) (Notes 10 and 11) is prepared and added to the dried flask via cannula. Additional THF (75 mL) is to rinse residual hemiaminal **2** into the three-necked flask. The resultant solution is cooled in an ice bath for 30 min (internal temperature : 2.7 °C).



Figure 2. Step A - Reaction 2 Set-up

To the THF solution of hemiaminal **2** is added *N*-(trimethylsilyl)imidazole (30.8 g, 220 mmol) (Note 12) slowly at a rate of about 2 mL per minute (Note 13) (Figure 2). After the addition is complete the resulting mixture is allowed to warm to room temperature. After being stirred at room temperature for 6 h (Note 14), a saturated aqueous solution of NaHCO₃ (150 mL) is added to the reaction and the resultant mixture transferred to a 1L separatory funnel. Separation of the phases is followed by extraction of the aqueous phase with hexanes (3 x 200 mL) (Note 15). The combined hexanes extracts are washed successively with brine (2 x

100 mL), and then dried over anhydrous sodium sulfate (130 g) (Note 16). The sodium sulfate was removed by vacuum filtration using a glass fritted filter. After rinsing the filter cake with hexane (2 x 50 mL) the filtrate is poured into a 1 L recovery flask rinsing with hexanes (1 x 25 mL). The solvent is then removed under reduced pressure by rotary evaporation to yield 4-[2,2,2-trifluoro-1-(trimethylsilyloxy)ethyl]morpholine (**3**, 46.6–48.7 g, 181–189 mmol, 80–83% over two steps) (Notes 17 and 18) as a pale colorless liquid that is used for step B without further purification (Note 19).

B. 3-Nitro-1-(trifluoromethyl)benzene (5). A 1-L, three-necked round-bottomed flask is equipped with a 4-cm Teflon-coated magnetic stir bar and the center neck is fitted with a glass gas inlet adapter which is connected to a nitrogen/vacuum double manifold. The other two necks are capped with rubber septa. The flask is charged with CsF (29.3 g, 193 mmol) (Note 20), flame-dried under vacuum and then backfilled with nitrogen. After flame drying is complete, the right neck of the flask is equipped with a thermometer. To the flask are added copper(I) thiophene-2-carboxylate (CuTC, 1.84 g, 9.65 mmol) (Note 21), 1,10-phenanthroline (phen, 1.74 g, 9.65 mmol) (Note 22), *m*-iodonitrobenzene (24.0 g, 96.5 mmol) (Note 23) and anhydrous diglyme (180 mL) (Note 24). Next, 4-[2,2,2-trifluoro-1-(trimethylsilyloxy)ethyl] morpholine (**3**, 49.6 g, 193 mmol) in 10 mL anhydrous diglyme is transferred by cannula to the reaction flask rinsing with an additional 10 mL of anhydrous diglyme (Note 25). The resulting mixture is heated in a 80 °C oil bath for 24 h (Notes 26 and 27) (Figure 3). After cooling to room temperature the reaction is quenched by the addition of deionized water (250 mL) and the resultant mixture poured into a 2L separatory funnel and extracted with diethyl ether (3 x 150 mL). The combined extracts are washed successively with water (5 x 300 mL) and brine (1 x 300 mL) (Note 28), and then dried over anhydrous sodium sulfate (90 g). Removal of the sodium sulfate by filtration through a fritted filter with rinsing (Et₂O, 3 x 50 mL) was followed by solvent removal on a rotary evaporator (Note 29). The resultant residue is purified by column chromatography on silica gel (Note 30). The fractions containing the product are combined and concentrated under reduced pressure to provide pure 3-nitro-1-(trifluoromethyl)benzene (**5**) as a yellow liquid (14.3 g, 78 %) (Notes 31 and 32).



Figure 3. Step B Reaction Set-up

Notes

1. Submitters purchased 4 Å molecular sieves from Wako Pure Chemical Industries. The checkers purchased molecular sieves 4 Å (8–12 mesh) from Acros Organics. The sieves are activated by initially heating in a microwave oven (1100 W general electric model ;JES1142 WD 04) for one min and then flame drying under vacuum. After cooling and flushing with nitrogen, this procedure is repeated twice before the sieves are added to the reaction flask.
2. Including the evacuation prior to flame drying, the reaction flasks used in each step of this procedure are evacuated and backfilled with dry nitrogen three times for every step of this procedure.
3. The submitters purchased dehydrated dichloromethane (>98.0%) from Kishida Chemical Co.,Ltd. The checkers purchased non-stabilized DCM from J.T. Baker and passed through two packed columns of neutral alumina in a solvent purification system manufactured by S.G. Waters U.S.A., LLC.

4. The submitters purchased morpholine from Kanto Chemical Co., Inc. and used it as supplied. The checkers purchased morpholine ($\geq 99\%$) from Sigma-Aldrich and also used it as obtained.
5. The submitters purchased trifluoroacetaldehyde ethyl hemiacetal (contains ca. 10% ethanol) from Tokyo Chemical Industry Co., Ltd. and used it as received. The checkers purchased trifluoroacetaldehyde ethyl hemiacetal ($>80\%$, contains ca. 10% ethanol) from TCI America and also used it as received.
6. The reaction mixture turns light brown due to the molecular sieves being crushed over the course of the reaction.
7. Although the submitters and checkers allowed the reaction to proceed for 48 h, the checkers monitored the reaction by NMR and found it to be complete after 2.25 h and undergo no further change during the 48h run.
8. The submitters purchased Celite[®] 545 from Kishida Chemical Company, Ltd. The checkers purchased Celite[®] S from Sigma Aldrich. The 350 mL fine-fritted glass funnel had a diameter of 9 cm and a height of 7.5 cm when measured from the top of the frit.
9. The solvent was removed under reduced pressure (160 mmHg – 60 mmHg) on a rotary evaporator (90 rpm, 32–35 °C)
10. The submitters purchased dehydrated tetrahydrofuran from Kishida Chemical Co., Ltd. The checkers purchased non-stabilized THF from Fisher Scientific and passed the solvent through two packed columns of neutral alumina in a solvent purification system manufactured by S.G. Waters U.S.A., LLC.
11. Crude hemiaminal **2** is obtained as a highly viscous oil.
12. The submitters purchased trimethylsilylimidazole ($>98.0\%$) from Tokyo Chemical Industry Co., Ltd. and used it as received. The checkers purchased trimethylsilylimidazole ($>98.0\%$) from Sigma-Aldrich and used it as received.
13. After addition of the trimethylsilylimidazole was complete the internal temperature rose to 5 °C.
14. The measuring of the 6 h reaction time began when the internal thermometer reached room temperature (which for the checkers was 24 °C).
15. The first 200 mL of hexanes is used to wash the reaction flask and then transferred to the separatory for use in the extraction.
16. After extraction the separatory funnel is washed with 50 mL hexanes.

17. Solvent is removed under reduced pressure (140 torr – 70 torr) by rotary evaporation (90 rpm, 28 °C – 39 °C)
18. A reaction run on half scale yielded 23.8 g (92.5 mmol, 80%) of **3**.
19. Although **3** can be carried on crude, for characterization purposes the checkers found that it can be purified via silica gel chromatography eluting with 10% ethyl acetate in hexanes: ¹H NMR (400 MHz, CDCl₃) δ: 0.18 (s, 9H), 2.67–2.82 (m, 4H), 3.69 (t, *J* = 4.8 Hz, 4H), 4.38 (q, *J* = 5.7 Hz, 1H); ¹⁹F NMR (376 MHz, CDCl₃, C₆F₆) δ: 79.57 (3F, s). ¹³C NMR (75.6 MHz, CDCl₃) δ: 0.04, 48.07, 67.2, 85.62 (q, ²*J*_{CF} = 32.5 Hz), 123.47 (q, ¹*J*_{CF} = 286.7 Hz); IR (neat): 2962.3, 2857, 1455.6, 1354.7, 1334.2, 1298.6, 1278.2, 1114.5, 1069.4, 1016.7, 873.1, 839.1 cm⁻¹; +ESI-HRMS *m/z* : calcd for (M+H⁺) C₉H₁₉NO₂F₃SiH⁺ = 258.11371, found C₉H₁₉NO₂F₃SiH⁺ = 258.11328; Anal. calcd. for C₉H₁₈F₃NO₂Si: C, 42.01; H, 7.05; N, 5.44; F, 22.15 found: C, 42.08; H, 7.05; N, 5.46; F, 21.98.
20. The submitters purchased cesium fluoride (>97.0%) from Wako Pure Chemical Industries, Ltd. The checkers purchased cesium fluoride (≥ 98%) from Sigma-Aldrich.
21. The submitters purchased copper(I) thiophene-2-carboxylate (>96.0%) from Wako Pure Chemical Industries, Ltd. and used it without further purification. The checkers purchased copper(I) thiophene-2-carboxylate (98.0%) from Oakwood Chemical and used it without further purification.
22. The submitters and checkers purchased anhydrous 1,10-phenanthroline (>99.0%) from Sigma-Aldrich and used it as received.
23. The submitters purchased *m*-iodonitrobenzene from Wako Pure Chemical Industries, Ltd. and used it without further purification. The checkers purchased *m*-iodonitrobenzene from Sigma-Aldrich and used it without further purification.
24. The submitters and checkers purchased anhydrous diethylene glycol dimethyl ether (99.5%) from Sigma-Aldrich and used it as received.
25. The addition of the 180 mL of diglyme was quickly and immediately followed by the rapid addition by cannula of compound **3**. The addition of **3**, including the washing, is complete within 2 min and the flask is then immediately placed in a preheated oil bath. The checkers noted that the oil bath must be preheated to 80 °C, since slow heating of the mixture results in incomplete consumption of starting material.
26. The color of the solution turns dark brown.
27. Monitoring of the reaction by NMR showed that the starting material is consumed and that the reaction is complete within 2.5 h.

28. Each of the 150 mL portions of diethyl ether is used to rinse the reaction flask prior to use in the extraction. The checkers noted a slight exotherm during the water washings and thus to avoid pressure build-up, the two phases were typically swirled together vigorously until the exotherm subsided. At this point the separatory funnel was capped and the extraction continued.
29. The solvent was removed under reduced pressure (210 mmHg – 80 mmHg) using a rotary evaporator. (90 rpm, 27–28 °C).
30. The checkers purchased silica gel SilicaFlash® F60 (40–63 μm / 230 – 500 mesh) from Silicycle. Column chromatography was performed using a glass column 8.5-cm in diameter packed with 1.1 cm sand and 5.7 cm SiO_2 (150 g). The silica was dry packed and wetted with 600 mL hexanes. The compound was loaded neat onto the column and the flask which contained it was washed three times with 5 mL hexanes and these washings were also loaded on to the column. The column was then topped with 1.2 cm sand. The compound was eluted using a gradient solvent system which began with pure hexanes (300 mL), progressed to 0.75% ethyl acetate in hexanes (400 mL) and then progressed to and was held at 1.15% ethyl acetate in hexanes (2600 mL). The checkers found that failing to use a gradient elution and employing 2% ethyl acetate in hexanes results in the co-elution of a minor impurity. The checkers also found that residual diglyme in the crude reaction mixture can cause the compound to elute quickly but is not detrimental to obtaining pure product under the gradient elution conditions. TLC (UV visualization) is used to follow the chromatography. Glass-backed extra hard layer TLC plates, 60 Å (250 μm thickness) containing F-254 indicator were purchased from Silicycle. The R_f value of the title compound is 0.2 (2% EtOAc/hexanes). Fractions 17–74 (30 mL each) are concentrated by rotary evaporation (160 mmHg–125 mmHg, 35–40 °C bath, 90 rpm). To fully remove residual solvent the checkers continued the rotary evaporation beyond the point of apparent solvent removal (about 40 min, 50 mmHg, 90 rpm, 35–42 °C) followed by holding under reduced pressure (30 mmHg) for 1 h.
31. 3-Nitro-1-(trifluoromethyl)benzene (**5**) has the following physical and spectroscopic data: R_f = 0.66 (hexane); ^1H NMR (400 MHz, CDCl_3) δ : 7.74 (t, J = 8.0 Hz, 1H), 7.98 (d, J = 7.8 Hz, 1H), 8.45 (d, J = 8.4 Hz, 1H), 8.52 (s, 1H); ^{19}F NMR (376 MHz, CDCl_3 , C_6F_6) δ : 66.05 (3 F, s); ^{13}C NMR

(101 MHz, CDCl₃) δ: 121.02 (q, *J* = 4.0 Hz), 122.98 (q, *J* = 272.9 Hz), 126.82, 130.48, 131.28 (q, *J* = 3.5 Hz), 132.48 (q, *J* = 34.3 Hz); IR (Neat): 3098.9, 1625.3, 1537.1, 1487.3, 1445.7, 1358.1, 1319.3, 1281.1, 1173.5, 1128.5, 1108.5, 1065.7, 909.8, 882.9, 812.7, 784.5, 739.6, 697.6 cm⁻¹; MS (EI) *m/z* (%): 191 (M⁺, 28), 172 (12), 145 (100), 125 (22), 95 (34), 75 (33), 69 (10); Anal. calcd. for C₇H₄F₃NO₂: C, 43.99; H, 2.11; N, 7.33; F, 29.82; found: C, 43.94; H, 2.11; N, 7.27; F, 29.62.

32. A second reaction on the same scale provided 14.5 g (79%) of the product.

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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.

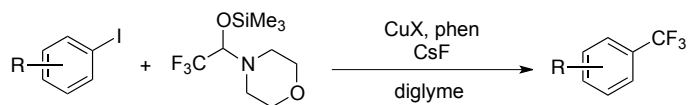
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Discussion

The structural motifs of trifluoromethylated aromatics (Ar-CF₃) have been widely employed in various industrial fields.^{2,3} The high lipophilicity, strong electron-withdrawing ability, and characteristic size of the trifluoromethyl group is a key influence in the design of pharmaceuticals, agrochemicals, dyes, liquid crystals, and polymers. Therefore, a great deal of attention has been paid to convenient protocols of introducing trifluoromethyl groups into aromatic rings.⁴ With respect to the high regiochemical fidelity in aromatic substitution, the cross-coupling of aryl halides with CF₃Cu is one of the most powerful and versatile methods to construct trifluoromethylated aromatics.⁵ Fluoral (trifluoroacetaldehyde) and its derivatives are readily available organofluorine compounds. Hemiaminals of fluoral are known to be convenient sources of trifluoromethyl anion.⁶ Previously, we reported the catalytic procedure for aromatic trifluoromethylation by the use of trifluoroacetaldehyde hemiaminal derivative **2** as a cross-coupling partner in the presence of 10 mol% of CuI and 1,10-phenanthroline (phen).^{7,8} After screening of Cu catalysts, we found that for the cross-coupling reactions of aryl iodides with **2**, the use of copper thiophene-2-carboxylate (CuTC)⁹ as a source of copper(I) affords the best results. Representative examples of the selective formation of trifluoromethyl arenes are summarized in Table 1.

Table 1. Cu-Catalyzed Cross-Coupling for Aromatic Trifluoromethylation



entry	iodoarene	product	yield/%	
			X = I	X = TC
1			90	>95
2			60	75
3			30	91
4			53	83
5			42	91

^a Determined by ¹⁹F NMR analysis (CF₃CH₂OH was used as internal standard).

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1. Division of Molecular Science, Faculty of Science and Technology, Gunma University, 1-5-1 Tenjin-cho, Kiryu, Gunma, 376-8501, Japan. E-mail: amii@gunma-u.ac.jp. This work was financially supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan and Japan Science and Technology Agency (JST) (ACT-C: Creation of Advanced Catalytic Transformation for the Sustainable Manufacturing at Low Energy, Low Environmental Load).
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Appendix

Chemical Abstracts Nomenclature (Registry Number)

Morpholine: 1-Oxa-4-azacyclohexane; (110-91-8)
 Fluoral ethyl hemiacetal: 1-Ethoxy-2,2,2-trifluoroethanol; (433-27-2)
 Trifluoroacetaldehyde hemiaminal: 4-Morpholinemethanol, α -
 (trifluoromethyl)-; (321573-94-8)
 N-(Trimethylsilyl)imidazole: Imidazole, 1-(trimethylsilyl)-; (18156-74-6)
 [2,2,2-Trifluoro-1-(trimethylsilyloxy)ethyl]morpholine: 4-[2,2,2-Trifluoro-1-
 (Trimethylsilyloxy)ethyl]morpholine; (289706-46-3)
 Copper(I) thiophene-2-carboxylate: 2-Thiophenecarboxylic acid, copper(1+)
 salt (1:1); (1292766-17-6)

1,10-Phenanthroline: 4,5-Diazaphenanthrene; (66-71-7)

m-Iodonitrobenzene: 3-Iodo-1-nitrobenzene; (645-00-1)

3-Nitro-1-(trifluoromethyl)benzene: Toluene, α, α, α -trifluoro-*m*-nitro-; (98-46-4)



Naoto Shimizu was born in Gunma, Japan in 1990. He received his B. Eng. in 2012 from Gunma University, where he carried out graduate research in the laboratories of Prof. Hideki Amii. His research focused on the catalytic aromatic trifluoromethylation via β -carbon elimination. After receipt of his M. Eng. degree (2014), he joined Nihon Nohyaku Co.,Ltd.



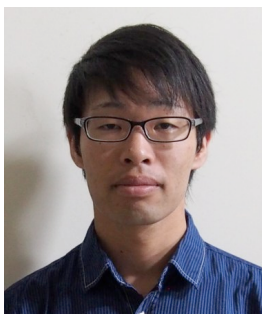
Hideaki Kondo was born in 1985 in Gifu, Japan. He received his B. Sci. (2008) and M. Sci. (2010) from Kobe University under the direction of Dr. Hideki Amii, working on the development of copper-catalyzed aromatic trifluoromethylation via group transfer from fluoral derivatives. Currently he is working for Kao Corporation.



Masahiro Oishi was born in Shizuoka, Japan in 1983. He received his B. Eng. from Shizuoka University under the direction of Professor Kunihiko Takabe in 2006. Then he stayed at Kobe to perform his studies under the supervision of Dr. Hideki Amii, working on the development of catalytic aromatic trifluoromethylation using organosilicon compounds. He currently works at ADEKA Corporation.



Kenichi Fujikawa was born in Nara, Japan in 1987. He received his B. Sci. (2009) and M. Sci. (2011) from Kobe University under the direction of Prof. Hideki Amii. He developed a convenient route for aromatic difluoromethylation. Currently he is working for Nitto Denko Corporation.



Kazuki Komoda was born in Gunma, Japan in 1992. He received his B. Eng. in organic chemistry from Gunma University. He is currently a master course student in the group of Prof. Hideki Amii at Gunma University. His research interests include the cross-coupling reactions to introduce fluorine-containing functional groups into organic compounds.

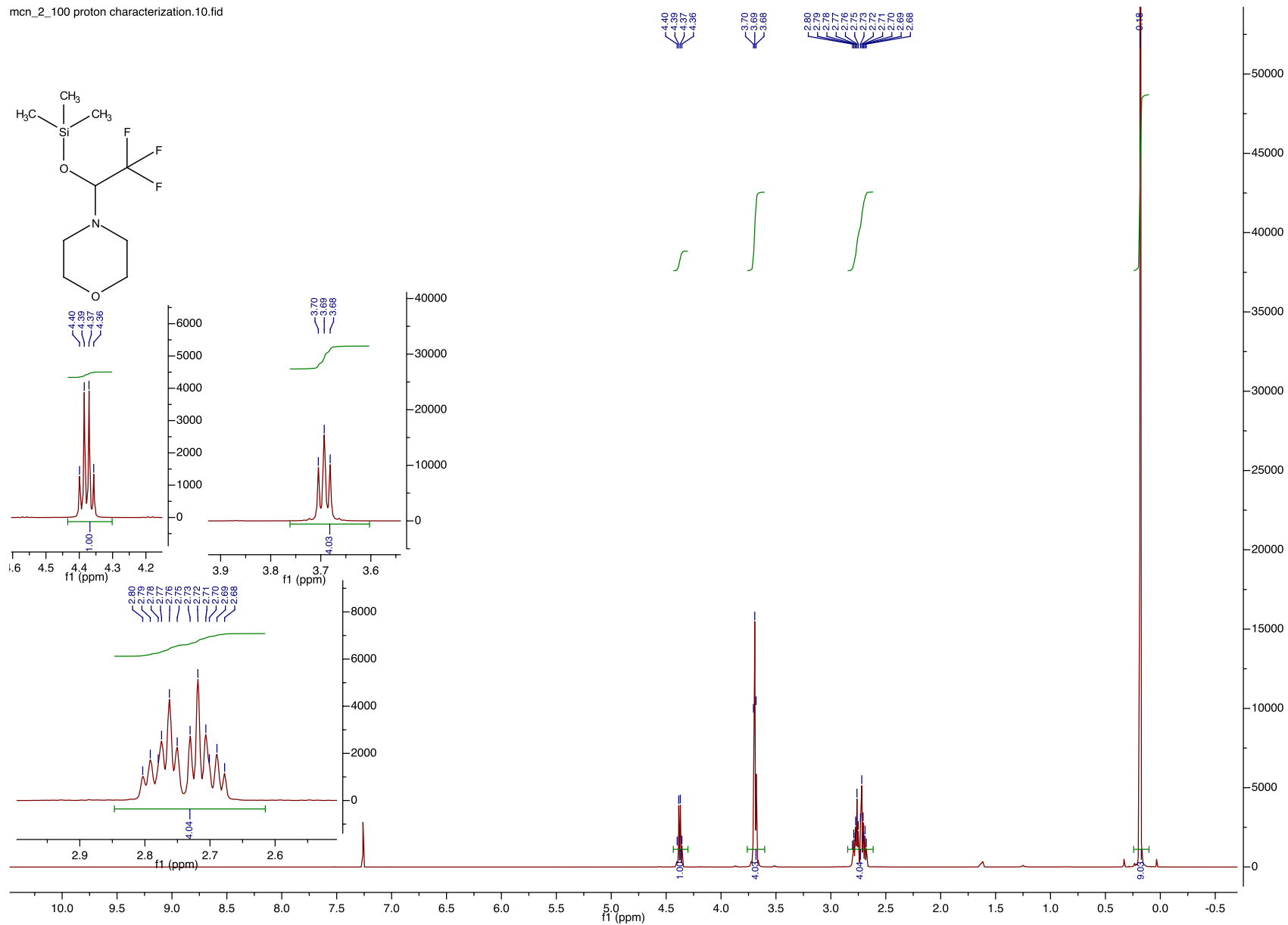


Hideki Amii was born in Hyogo in 1968. He graduated from Kyoto University, where he received his Doctorate degree in 1996 under the direction of Professor Yoshihiko Ito. During 1996–2003, he worked as Research Associate of the Department of Applied Chemistry, Faculty of Engineering, Okayama University (Prof. Kenji Uneyama's group). He carried out postdoctoral work in France with Dr. Guy Bertrand at Université Paul Sabatier during 2000–2001. In 2003, he was appointed to Associate Professor of Kobe University. In 2010, he moved to Gunma University, where he is currently Professor of Chemistry. His research interest focuses in the synthesis of organofluorine compounds by the use of metal reagents.

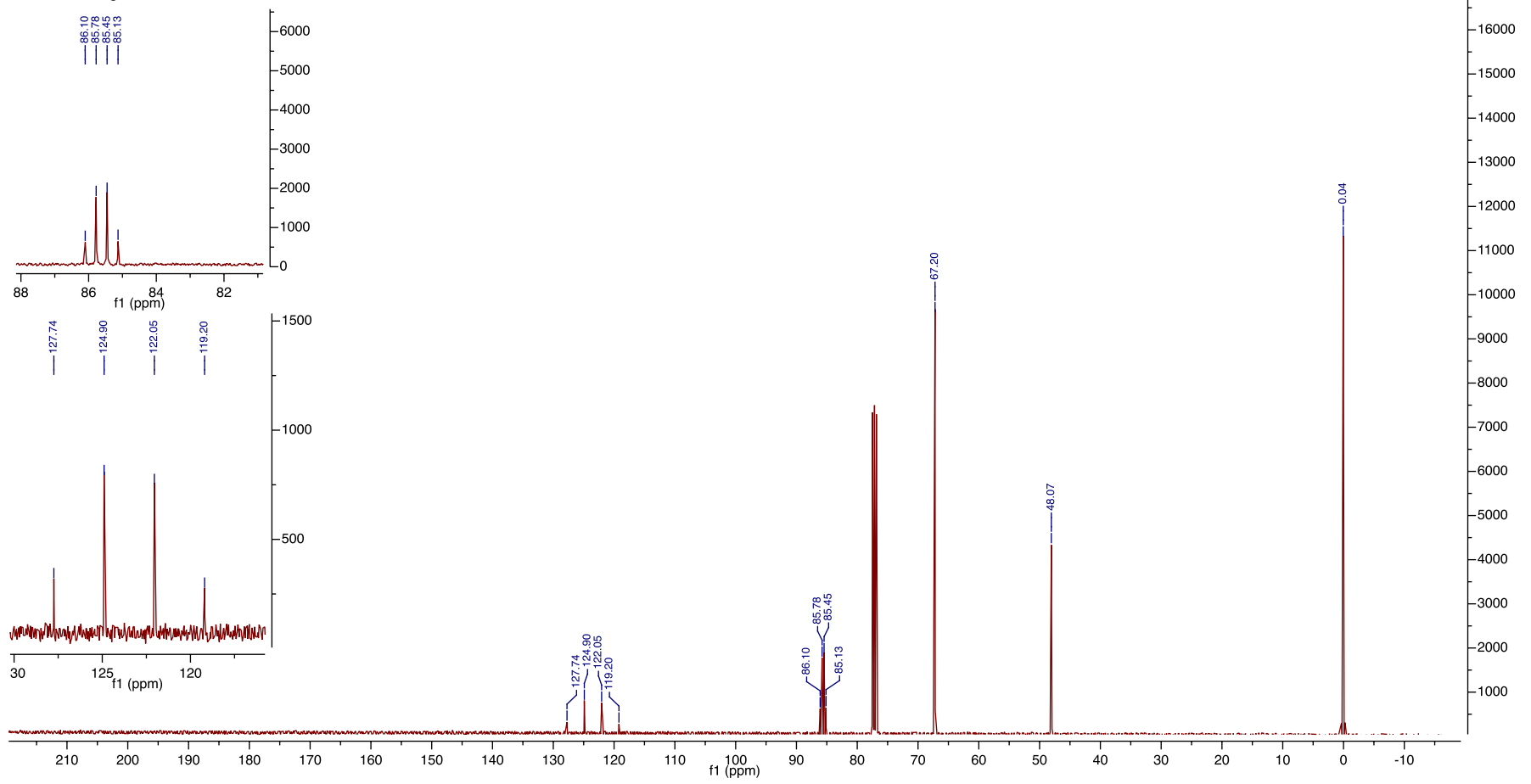
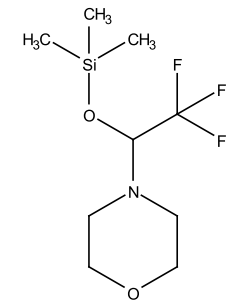


Mina Nakhla was born in Adelaide, Australia in 1990. He received his B. S. in biochemistry from St. Edward's University. He is currently a doctoral student under the direction of Prof. John L. Wood at Baylor University. His research interests include natural product total synthesis and organometallic chemistry.

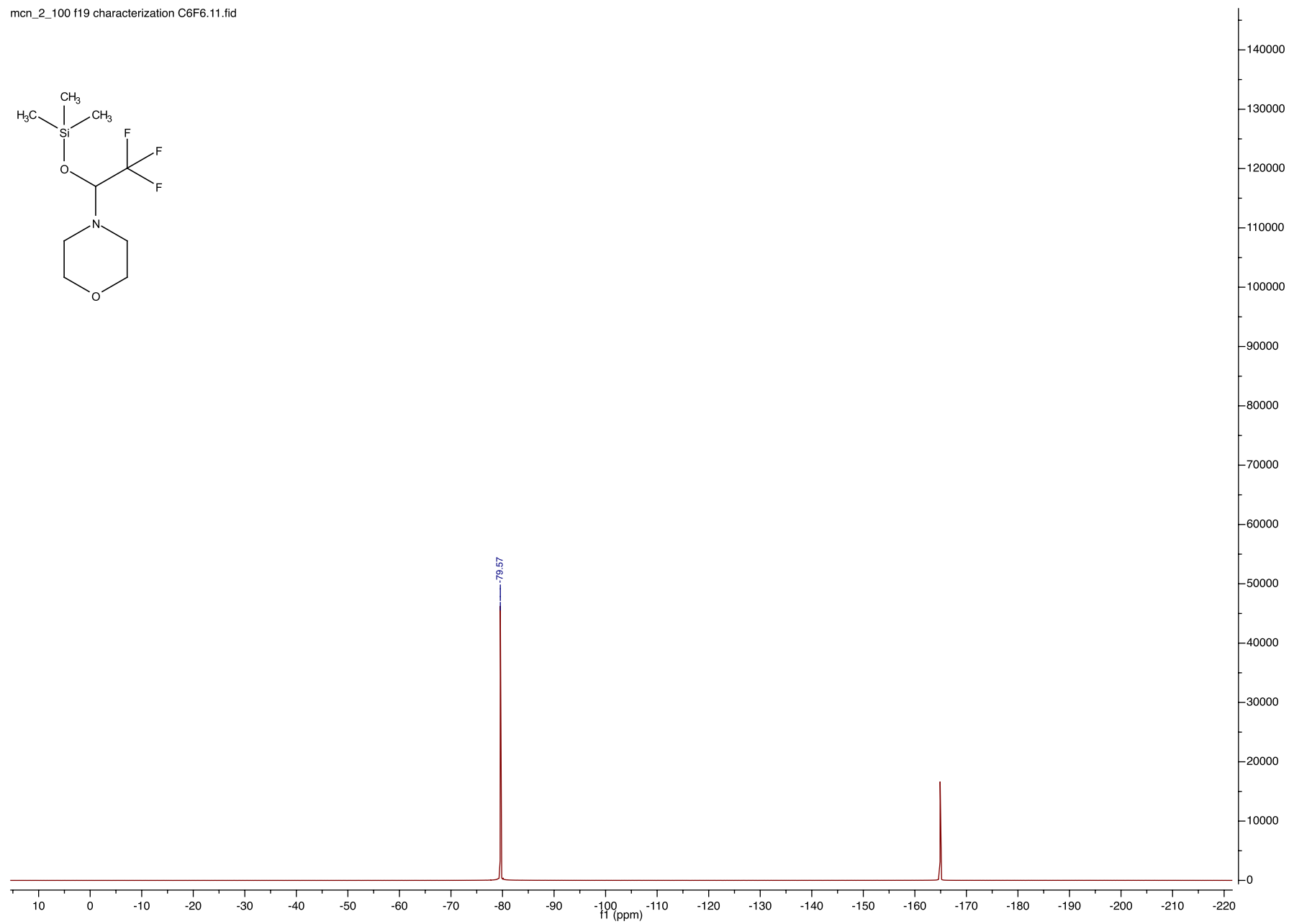
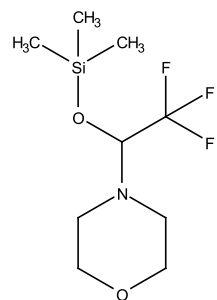
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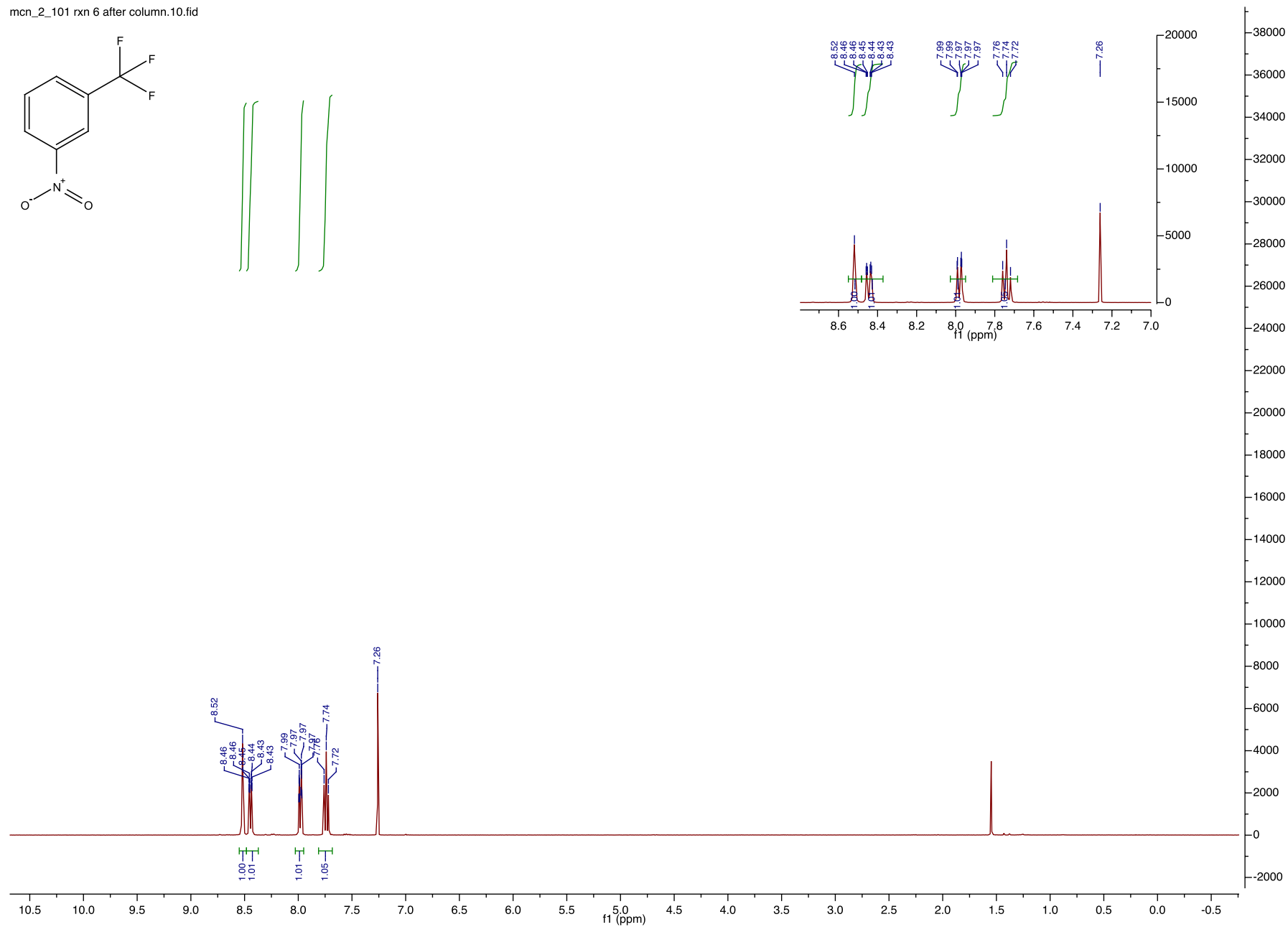
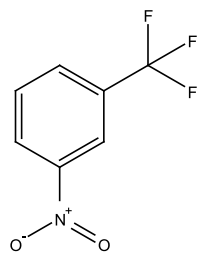
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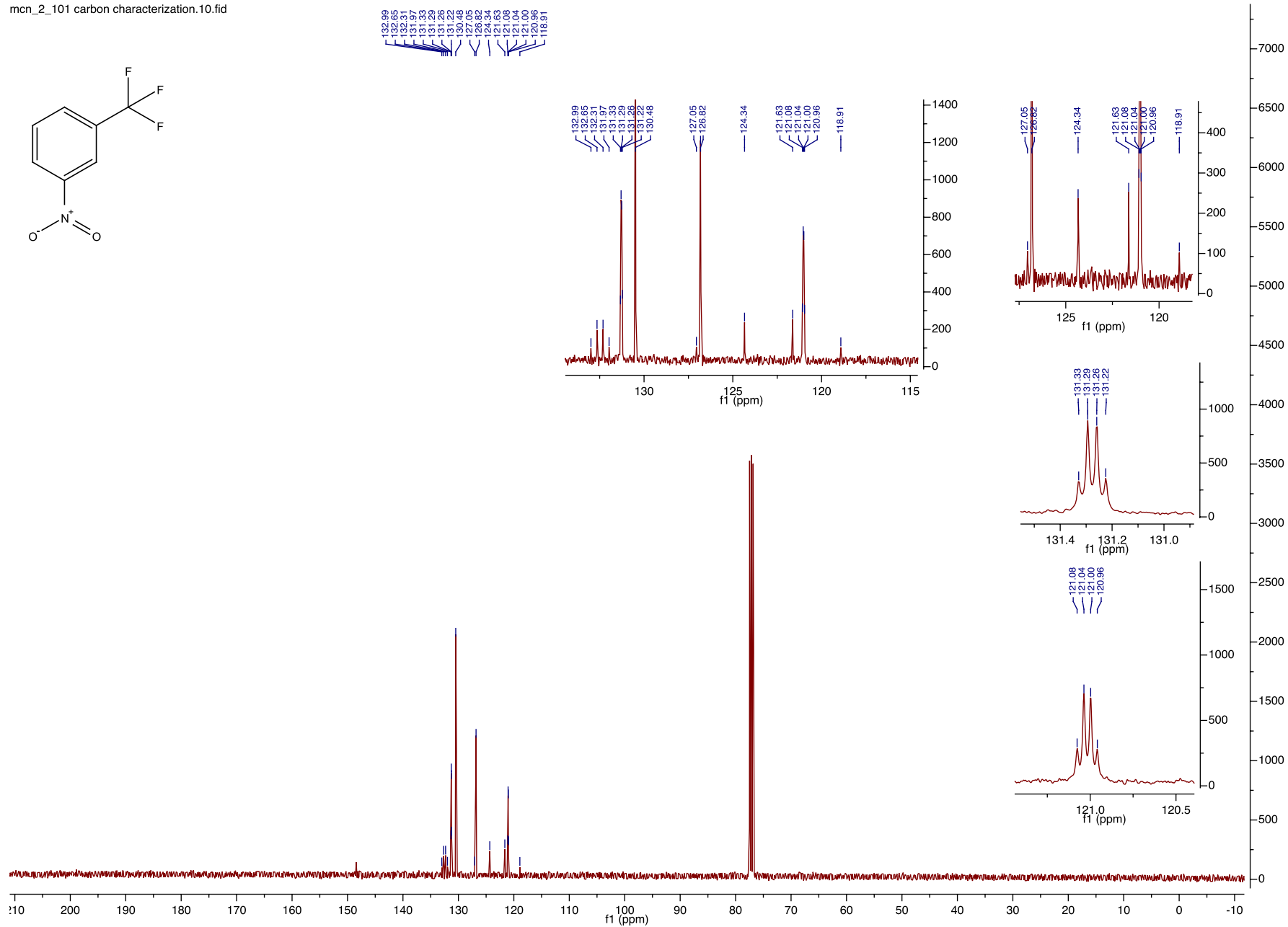
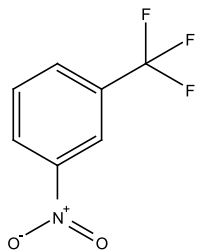
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