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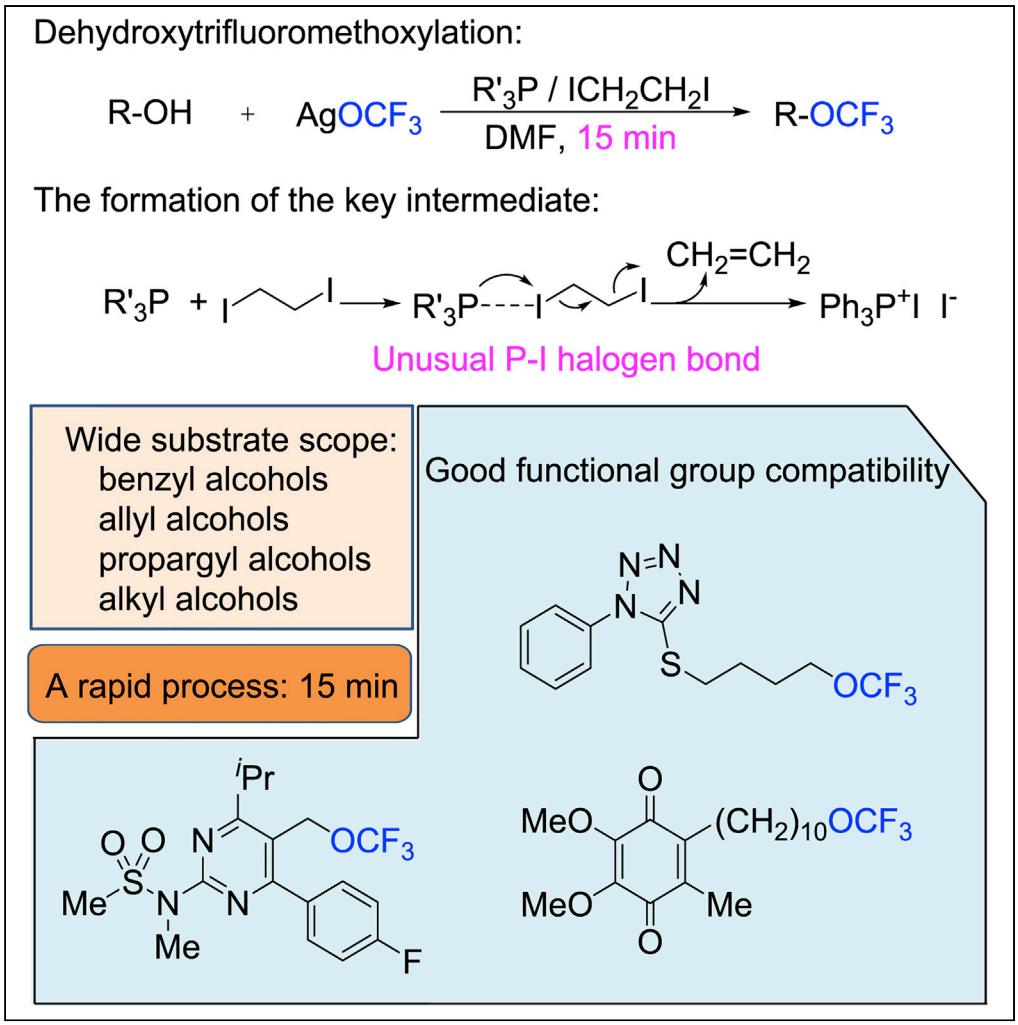

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HIGHLIGHTS

Rapid dehydroxy-trifluoromethoxylation of alcohols is described

R_3P/ICH_2CH_2I is an efficient reagent system for the dehydroxylation of alcohols

Unusual P-I halogen bond is the driving force to generate the key intermediates

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Rapid Dehydroxytrifluoromethoxylation of Alcohols

Wei Zhang,[1,3] Jia Chen,[1,3] Jin-Hong Lin,[1,*] Ji-Chang Xiao,[1,4,*] and Yu-Cheng Gu[2]

SUMMARY

The CF_3O functional group is a unique fluorinated group that has received a great deal of attention in medicinal chemistry and agrochemistry. However, trifluoromethoxylation of substrates remains a challenging task. Herein we describe the dehydroxytrifluoromethoxylation of alcohols promoted by a R_3P/ICH_2CH_2I (R_3P = Ph_3P or $Ph_2PCH{=}CH_2$) system in DMF. P-I halogen bonding drives the reaction of R_3P with ICH_2CH_2I in DMF to generate iodophosphonium salt ($R_3P^+I\ I^-$) and a Vilsmeier-Haack-type intermediate, both of which could effectively activate alcohols, thus enabling a fast (15 min) trifluoromethoxylation reaction. A wide substrate scope and a high level of functional group tolerance were observed.

INTRODUCTION

The trifluoromethoxy group (CF_3O) has received a great deal of attention in medicinal chemistry and agrochemistry (Jeschke et al., 2007) because of its strong electron-withdrawing nature and high lipophilicity (Hansch et al., 1973). CF_3O-containing pharmaceuticals and agrochemicals such as Delamanid, Riluzole, Sonidegib, Metaflumizone, and Indoxacarb have been continuously developed. The high demand for biologically active molecules has stimulated significant efforts to develop efficient methods for the installation of trifluoromethoxy functionality (Landelle et al., 2014; Lin et al., 2015; Tlili et al., 2016). However, the installation of such functionality remains a challenging task. Traditional approaches including chlorine-fluorine exchange (Feiring, 1979; Salomé et al., 2004) and deoxyfluorination (Sheppard, 1964) suffer from harsh reaction conditions and narrow substrate scopes. Trifluoromethylation of alcohols is quite effective and has received increasing attention (Brantley et al., 2016; Koller et al., 2009; Umemoto et al., 2007). Recently, Qing and co-workers realized trifluoromethylation of phenols (Liu et al., 2015a) and alcohols (Liu et al., 2015b) based on the concept of oxidative trifluoromethylation (Chu and Qing, 2014). Wide substrate scopes were observed, but the use of strong oxidants was required. Compared with trifluoromethylation of alcohols, direct trifluoromethoxylation would also be an efficient and straightforward strategy and thus is highly desirable.

Trifluoromethoxylation strategies include transition-metal-promoted, radical, and nucleophilic reactions (Scheme 1, Equation 1). After the pioneering work on Ag-mediated (Chen et al., 2015b; Huang et al., 2011; Zha et al., 2016) and Pd-catalyzed (Chen et al., 2015a) trifluoromethoxylation, a breakthrough in transition-metal-promoted approaches was reported recently by Tang, who described a Ag-catalyzed asymmetric intermolecular bromotrifluoromethoxylation of alkenes with trifluoromethylarylsulfonate (TFMS) (Guo et al., 2017). The need for a hazardous agent, CF_3OX (X=F, Cl, etc.), limits the applicability of conventional radical approaches (Tlili et al., 2016). On the basis of their discovery of intramolecular CF_3O migration of N-OCF_3 substrates (Feng et al., 2016; Hojczyk et al., 2014; Lee et al., 2016a, 2016b), Ngai developed an N-OCF_3-type reagent to achieve radical trifluoromethoxylation (Zheng et al., 2018). The nucleophilic reaction is also a widely used strategy (Feng et al., 2016; Hojczyk et al., 2014; Jiang et al., 2018; Lee et al., 2016b; Marrec et al., 2010a, 2010b; Zhou et al., 2018). Hu recently developed a mild nucleophilic trifluoromethoxylation reagent and applied this reagent to trifluoromethoxylation of arynes to give CF_3O arenes (Zhou et al., 2018). Because the trifluoromethoxy anion (CF_3O^-) would readily undergo decomposition to produce carbonyl fluoride ($CF_2{=}O$), which is an electrophilic species that could react with alcohols to form fluoroformate, Tang used TFMS to generate trifluoromethoxy anions followed by carbonyl fluoride to activate alcohols, allowing for the subsequent dehydroxylative nucleophilic trifluoromethoxylation (Jiang et al., 2018). Owing to the high instability of the key trifluoromethoxy intermediates, including CF_3O^- and CF_3OM (M = metal), trifluoromethoxylation reactions usually have to be performed at low temperatures (room temperature or even lower), and therefore long reaction times are usually required (>10 hr in most cases) to overcome the free energy barriers.

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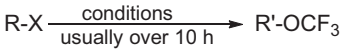

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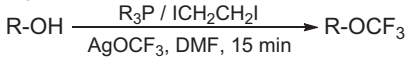


(2)

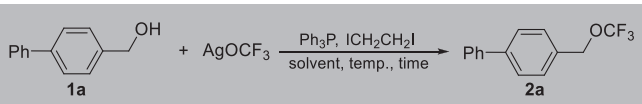
Scheme 1. Trifluoromethoxylation Protocols

Alcohols are readily available starting materials; therefore, trifluoromethoxylation of alcohols would be an attractive protocol for the installation of CF_3O moiety. In continuation of our research interest in the chemistry of R_FX (R_F = fluoroalkyl group; X = heteroatom) installation (Yu et al., 2017; Zheng et al., 2015, 2017), we have now investigated the trifluoromethoxylation of alcohols. We found that the Ph_3P/ICH_2CH_2I system could effectively activate the hydroxyl group to achieve dehydroxytrifluoromethoxylation of alcohols with the CF_3O^- anion. In contrast to Tang's approach for the dehydroxytrifluoromethoxylation, which required a reaction time of 26 hr (Jiang et al., 2018), the reaction in our protocol proceeded very rapidly, and full conversion was observed within 15 min (Scheme 1, Equation 2).

RESULTS

The Optimization of Reaction Conditions

Our initial attempt at the trifluoromethoxylation of alcohol **1a** was successful with the use of the Ph_3P/ICH_2CH_2I system in slight excess (Table 1, entry 1). A brief survey of the reaction solvent (entries



Entry[a]	Molar Ratio[b]	Solvent	Temperature (°C)	Time	Yield (%)[c]
1	1:3.0:1.4:1.4	DMF	60	5 hr	36
2	1:3.0:1.4:1.4	DMSO	60	5 hr	trace
3	1:3.0:1.4:1.4	NMP	60	5 hr	21
4	1:3.0:1.4:1.4	Toluene	60	5 hr	14
5	1:3.0:1.4:1.4	DMF	70	5 hr	45
6	1:3.0:1.4:1.4	DMF	80	5 hr	65
7	1:3.0:1.4:1.4	DMF	90	5 hr	60
8	1:4.0:1.4:1.4	DMF	80	5 hr	80
9	1:4.0:1.2:1.2	DMF	80	5 hr	73
10	1:4.0:1.6:1.6	DMF	80	5 hr	75
11	1:4.0:1.4:1.4	DMF	80	1 hr	76
12	1:4.0:1.4:1.4	DMF	80	15 min	78
13[d]	1:4.0:1.4:1.4	DMF	80	15 min	63
14[e]	1:3.5:1.5:1.5	DMF	Rt	14 hr	50

Table 1. Optimization of Reaction Conditions

NMP, 1-methylpyrrolidin-2-one.

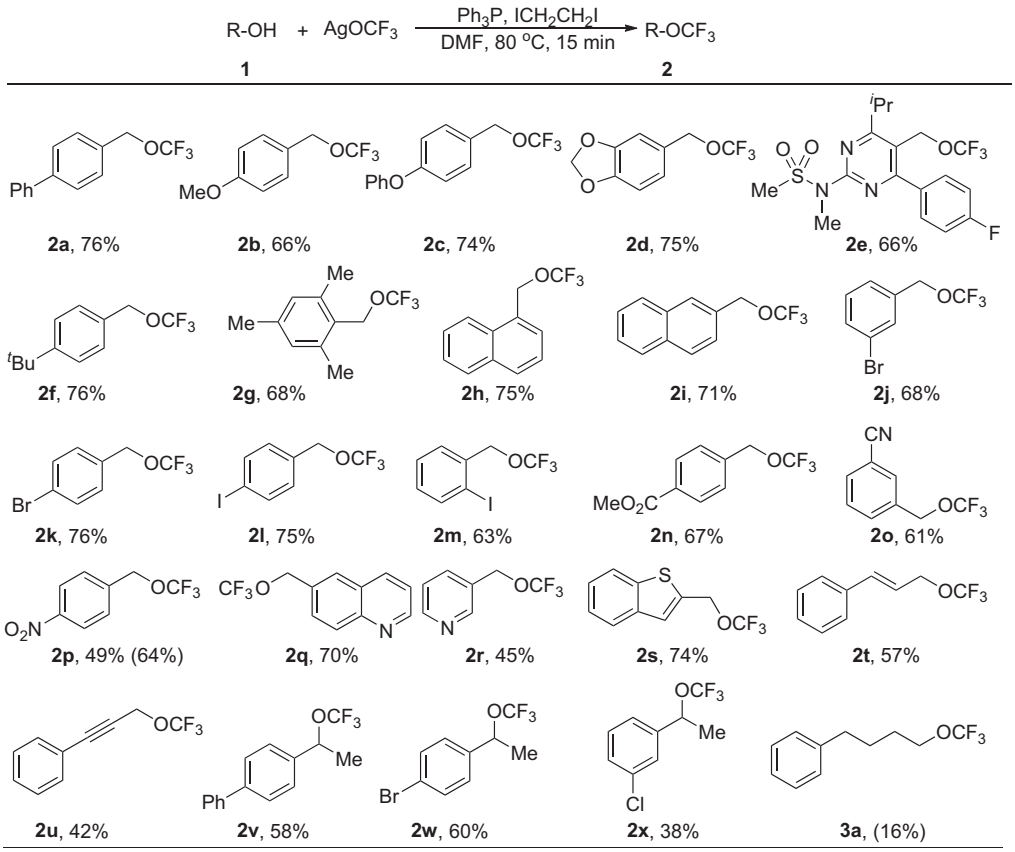
[a]Reaction conditions: substrate **1a** (0.1 mmol), $AgOCF_3$, Ph_3P and ICH_2CH_2I in DMF (1.5 mL) at the indicated temperature under a N_2 atmosphere.

[b]Molar ratio of **1a**:$AgOCF_3$:Ph_3P:ICH_2CH_2I.

[c]The yields were determined by ^{19}F NMR spectroscopy.

[d]The reaction was performed in an unsealed tube (exposed to air).

[e]$CsOCF_3$ was used instead of $AgOCF_3$; rt, room temperature.



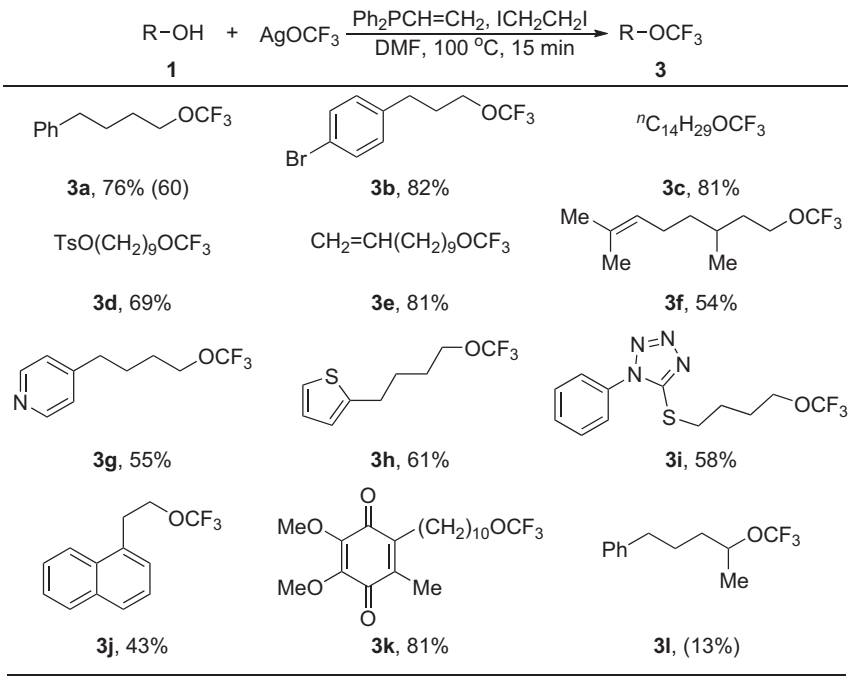
Scheme 2. Dehydroxytrifluoromethoxylation of Alcohols

Isolated yields. Reaction conditions: alcohol **1** (0.5 mmol), $AgOCF_3$ (2.0 mmol), Ph_3P (0.7 mmol), ICH_2CH_2I (0.7 mmol), DMF (3 mL), 80°C, 15 min, N_2 atmosphere. The yield of product **3a** was determined by ^{19}F NMR spectroscopy. See also Figures S1–S60.

1–4) revealed that *N,N*-dimethylformamide (DMF) was a suitable solvent. Elevating the reaction temperature from 60°C to 80°C increased the yield to 65% (entry 6). A higher or lower temperature resulted in lower yields (entry 6 versus entries 1, 5, and 7). A good yield was obtained by increasing the loading of $AgOCF_3$ (entry 8). Decreasing or increasing the loading of Ph_3P/ICH_2CH_2I led to a slight decrease in the yield (entries 9 and 10). The reaction was monitored using ^{19}F nuclear magnetic resonance (NMR) spectroscopy; surprisingly, a good yield was obtained within 15 min (entry 12). Because the key trifluoromethoxylation intermediates are so fragile, the trifluoromethoxylation reactions usually have to be performed under an inert gas atmosphere. To our delight, the expected product could be obtained in 63% yield (entry 13) even if the reaction was performed in an unsealed tube (the reaction system was exposed to air). The use of $CsOCF_3$ instead of $AgOCF_3$ could give a moderate yield, indicating that the silver ion is not essential for this reaction (entry 14).

Substrate Scope Investigation

With the optimized reaction conditions in hand (Table 1, entry 12), we then investigated the substrate scope of the dehydroxytrifluoromethoxylation of alcohols. As shown in Scheme 2, a wide substrate scope and a high level of functional group tolerance were observed. The conversion of various benzyl alcohols occurred smoothly. Electron-rich, electron-neutral, and electron-deficient substrates could be converted into the desired products in moderate to good yields (**2a-2p**). The transformation was not very sensitive to steric effects, as evidenced by the moderate yields of products **2e**, **2g,** and **2h**. CF_3O-containing heteroarenes could be synthesized by this protocol (**2q-2s**). Besides benzyl alcohols, allyl alcohols (**2t**) and propargyl alcohols (**2u**) also underwent the expected conversion under these conditions. Compared with primary alcohols, lower yields were obtained for secondary alcohols (**2v-2x**). However, the optimal conditions were not suitable for efficient dehydroxytrifluoromethoxylation of alkyl alcohols (**3a**).



Scheme 3. Dehydroxytrifluoromethoxylation of Alkyl Alcohols

Isolated yields. Reaction conditions: alcohol **1** (0.5 mmol), $AgOCF_3$ (2.0 mmol), $Ph_2PCH{=}CH_2$ (1.3 mmol), ICH_2CH_2I (0.6 mmol), DMF (3 mL), 100°C, 15 min, N_2 atmosphere. The yield of product **3i** was determined by ^{19}F NMR spectroscopy. See also Figures S61–S88.

The low yield of product **3a** prompted us to further optimize the reaction conditions for the conversion of alkyl alcohols. After a detailed survey of the reaction conditions (see Supplemental Information, Table S1), we found that the replacement of triphenylphosphine with diphenyl(vinyl)phosphane ($Ph_2PCH{=}CH_2$) at a reaction temperature of 60°C could afford the expected product in 60% yield (**3a**). A good isolated yield (76%) was obtained by elevating the reaction temperature to 100°C. The substrate scope was then investigated under the optimal conditions (Scheme 3). Like the reaction of benzyl alcohols, the transformation of alkyl alcohols proceeded rapidly, and a 15-min reaction time provided moderate to good yields (**3a**-**3k**). Heteroarene-containing alcohols could also be well converted (**3g**-**3i**). The conversion of primary alcohols proceeded smoothly, but secondary alcohols could not be effectively transformed (**3l**).

Although iodide anion could also act as a nucleophile, no iodination product was observed in the above dehydroxytrifluoromethoxylation reactions. This is because iodide anion was excluded from the reaction system by forming AgI precipitate and C-OCF_3 bond may be formed in preference to C-I bond due to the higher C-O bond strength.

Mechanistic Investigations

Apparently, the R_3P/ICH_2CH_2I ($R_3P{=}Ph_3P$ or $Ph_2PCH{=}CH_2$) system in DMF generates key intermediates that could activate alcohols in this dehydroxytrifluoromethoxylation reaction. Both Ph_3P and $Ph_2PCH{=}CH_2$ react very quickly with ICH_2CH_2I in DMF. The mixing of Ph_3P and ICH_2CH_2I in DMF would immediately lead to the full consumption of both Ph_3P and ICH_2CH_2I. ICH_2CH_2I was converted into ethylene, which was detected by ^1H NMR spectroscopy, and Ph_3P was transformed into $Ph_3P{=}O$ and an unknown species **A** (δ = 11.9 ppm), as detected by ^{31}P NMR spectroscopy (Figure 1A). The processes were too quick, which did not allow us to determine and understand how the $Ph_3P{=}O$ and species **A** were formed. Fortunately, the reaction of Ph_3P with ICH_2CH_2I occurred slowly in chloroform ($CHCl_3$) probably due to its lower polarity. $CDCl_3$ was then used as the reaction solvent to determine what the Ph_3P/ICH_2CH_2I system would be transformed into. After stirring the mixture at room temperature for 15 hr, three phosphorus species were observed, which were determined to be iodophosphonium salt **B**[$Ph_3P^+I\ I^-$] (Garegg et al., 1987; Morcillo et al., 2011), triphenylphosphine, and diiodotriphenylphosphane **C** (Ph_3PI_2) (Garegg et al., 1987) based on

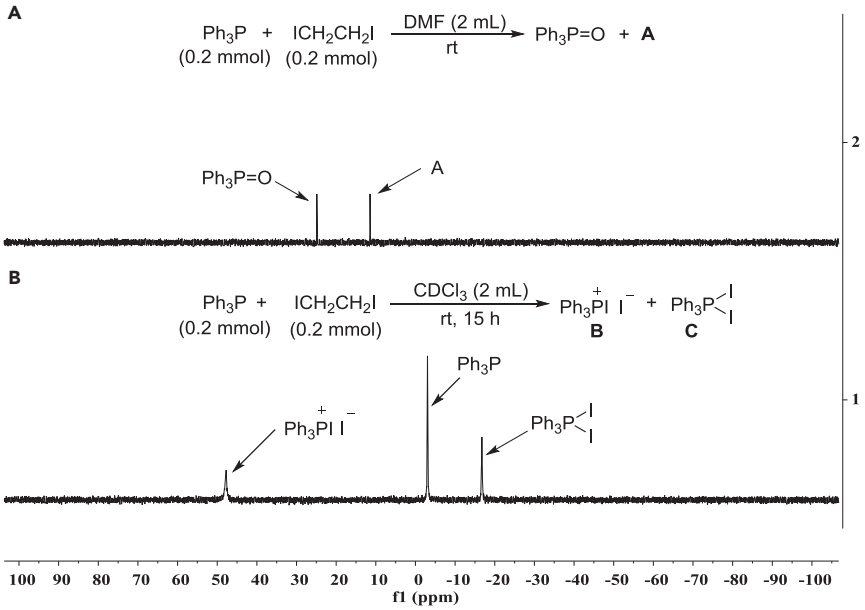
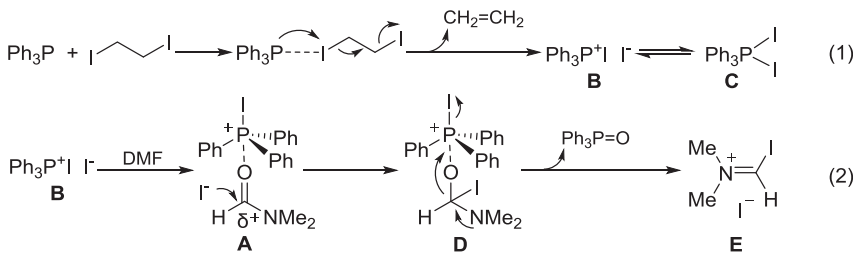


Figure 1. ^{31}P NMR Spectra of the Ph_3P/ICH_2CH_2I Reaction System

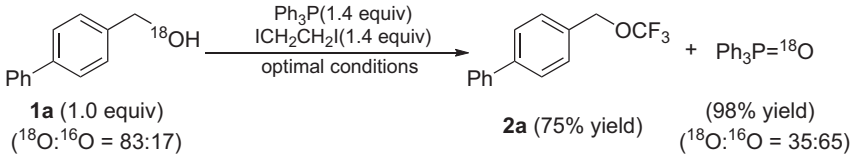
the reported corresponding phosphorus signals (Figure 1B). ICH_2CH_2I was almost completely converted into $CH_2{=}CH_2$, as detected by ^{1}H NMR spectroscopy. The large amount of Ph_3P that remained was because of the reversible equilibrium between Ph_3P and Ph_3PI_2 ($Ph_3PI_2 \rightleftarrows Ph_3P + I_2$) (Morcillo et al., 2011), otherwise Ph_3P would have been almost fully consumed.

The formation of species **B** and **C** was due to strong P-I halogen bonding (Gilday et al., 2015). Although triphenylphosphine may easily undergo quaternization with alkyl iodides to give alkylphosphonium salts, 1,2-diiodoethane acted as a halogen bond donor to form a halogen bond with triphenylphosphine (Scheme 4, Equation 1), instead of alkylating triphenylphosphine. The driving force for the halogen bonding was the generation of small ethylene molecules and the good leaving ability of the iodide anion. An equilibrium between **B** and **C** explained the observation of **C**. Clearly, the reaction solvent DMF was involved in the formation of $Ph_3P{=}O$ and species **A** from intermediate **B** (Equation 2). Intermediate **A** should be a complex formed by the coordination of intermediate **B** with DMF, because intermediate **B** can be considered as a Lewis acid. This coordination activated DMF and allowed for the attack of an iodide anion at the amide carbon to produce intermediate **D**, which could readily undergo C–O bond cleavage to release $Ph_3P{=}O$ and a Vilsmeier-Haack-type intermediate **E**.

Because it is known that the Vilsmeier-Haack-type intermediate could well activate hydroxyl groups (Dai et al., 2011; Hepburn and Hudson, 1976), the question arises as to whether species **E** was the only intermediate that activated the alcohols in the above trifluoromethoxylation reaction. If yes, the only oxygen source for the $Ph_3P{=}O$ by-product was the reaction solvent DMF. However, the conversion of ^{18}O-labeled alcohol **1a** showed that $Ph_3P{=}{}^{18}O$ was also obtained (Scheme 5), suggesting that another key intermediate was



Scheme 4. The Formation of Key Intermediates



Scheme 5. Trifluoromethoxylation of ^{18}O-Labeled Alcohol

The isolated yield was calculated based on Ph_3P as the limiting reagent. See also Figures S89 and S90.

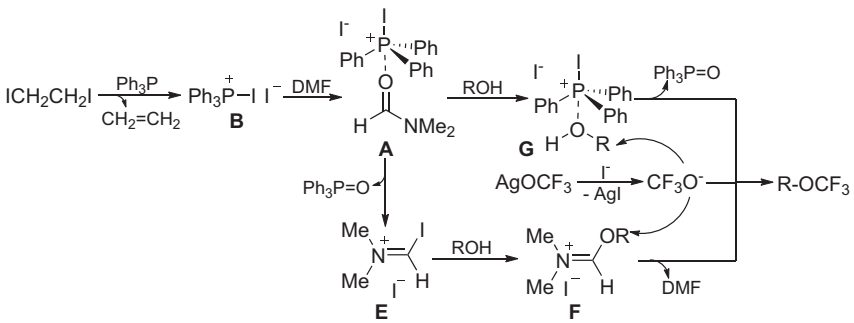
involved in the activation of the alcohols. The intermediate involved should be species **A**, because iodophosphonium salts have been proved to be powerful intermediates for the activation of alcohols (Appel, 1975; de Andrade and de Mattos, 2015) and this species was also converted into Ph_3P=O in the dehydroxytrifluoromethoxylation reaction. No ^{18}O-labeled trifluoromethoxylation product was observed, which indicated that this reaction was a dehydroxylation process.

Based on the above results, we proposed a plausible reaction mechanism, as shown in Scheme 6. The P-I halogen bonding drives the formation of iodophosphonium salt **B**, which immediately coordinates with the reaction solvent DMF to form complex **A**. Ligand exchange of an alcohol with a DMF molecule in complex **A** furnishes complex **G**. The alcohol is then activated by coordination and would be easily attacked by a trifluoromethoxy anion generated from $AgOCF_3$ by precipitating AgI, giving the final trifluoromethoxylation product. On the other hand, complex **A** could also undergo P-O bond formation to release Ph_3P=O and the Vilsmeier-Haack-type intermediate **E**. Intermediate **E** could activate the alcohols by forming intermediate **F**, at which the attack of trifluoromethoxy anion also afforded the final product. The generation of the racemic product **2v** from enantiopure alcohol indicated that the final attack at **G** or **F** may involve an S_N1 process (see Supplemental Information, Procedure D. See also Figure S91).

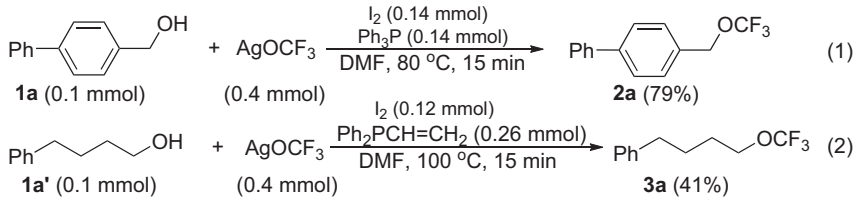
As it has been reported that iodophosphonium salt **B** (Ph_3P^+-I I^-) could also be formed by the reaction of Ph_3P with I_2 (Morcillo et al., 2011; Pathak and Rokhum, 2015), I_2 was then used instead of ICH_2CH_2I in the dehydroxytrifluoromethoxylation reaction (Scheme 7). Desired products were obtained for the conversion of both benzyl alcohol **1a** (Equation 1) and alkyl alcohol **1a′** (Equation 2), further supporting the proposed mechanism. Compared with the R_3P/I_2 system, which is not quite effective for the conversion of alkyl alcohols (Equation 2) and suffers from the toxicity of I_2, the R_3P/ICH_2CH_2I system is more attractive due to the high efficiency for dehydroxytrifluoromethoxylation. In addition, the P-I halogen bond between a trivalent phosphine and an alkyl iodide is quite unusual, and this unexpected observation may offer new opportunities for other chemistry.

DISCUSSION

In summary, we have described the dehydroxytrifluoromethoxylation of alcohols promoted by a R_3P/ICH_2CH_2I system in DMF. The combination of R_3P and ICH_2CH_2I in DMF could rapidly activate alcohols, resulting in the successful development of an efficient protocol for fast trifluoromethoxylation. A moderate yield was obtained even if the reaction was performed under an air atmosphere. The convenient Ph_3P/ICH_2CH_2I system in DMF for highly effective dehydroxylation may find synthetic utility in other research areas.



Scheme 6. The Plausible Reaction Mechanism



Scheme 7. The R_3P/I_2 System-Promoted Dehydroxytrifluoromethoxylation

The yields of 2a and 3a were determined by ^{19}F NMR spectroscopy.

METHODS

All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Transparent Methods, 91 figures, and 1 table and can be found with this article online at https://doi.org/10.1016/j.isci.2018.07.004.

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AUTHOR CONTRIBUTIONS

W.Z. and J.C. performed the experiments. J.-H.L. analyzed the data and wrote the manuscript. J.-C.X. designed the experiments and wrote the manuscript. Y.-C.G. designed some experiments.

DECLARATION OF INTERESTS

There are no conflicts to declare.

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ISCI, Volume *5*

Supplemental Information

Rapid Dehydroxytrifluoromethoxylation of Alcohols

Wei Zhang, Jia Chen, Jin-Hong Lin, Ji-Chang Xiao, and Yu-Cheng Gu

Supplemental Figures for ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR Spectra

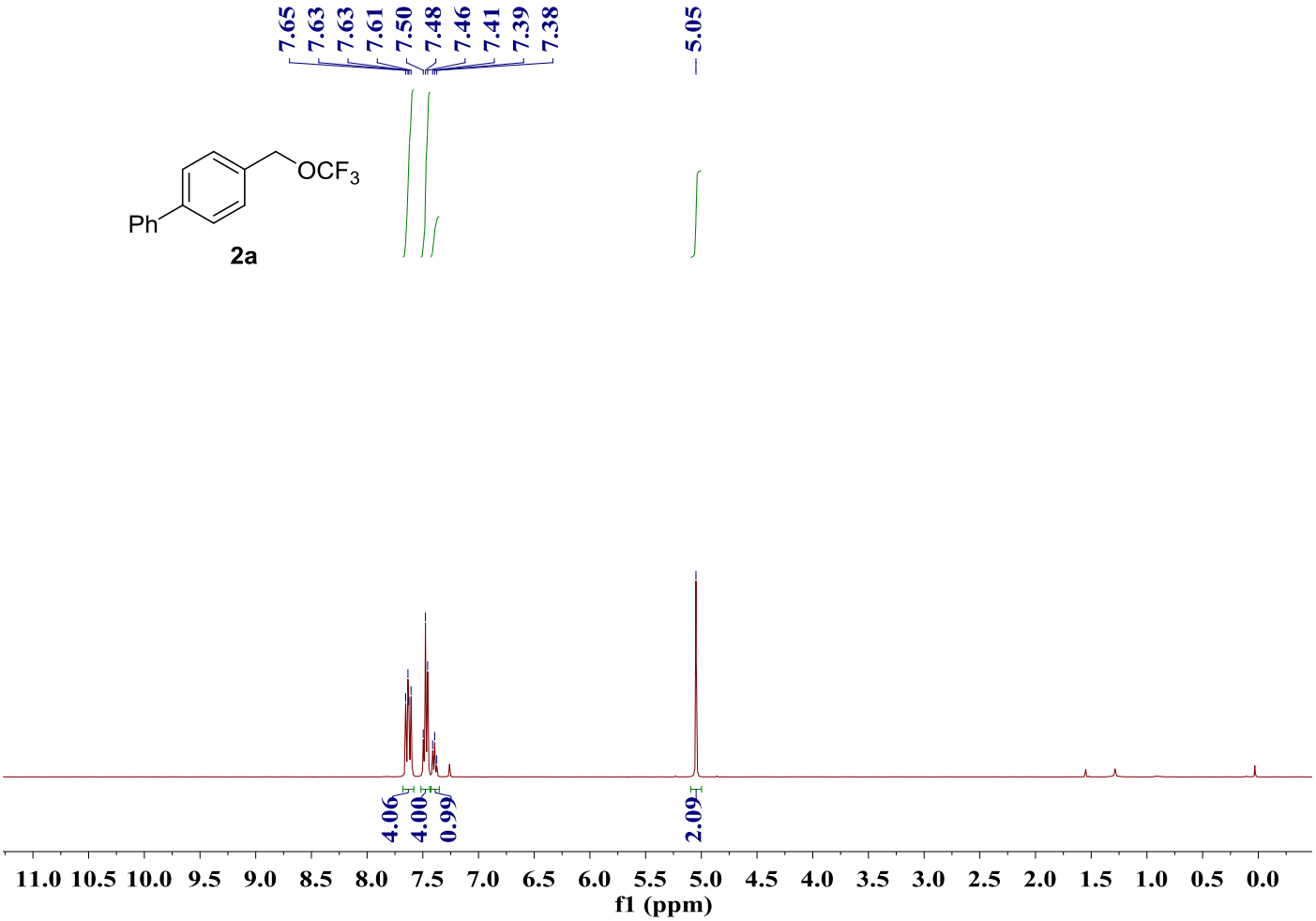

Figure S1. ^{1}H NMR spectrum of **2a**, Related to **Scheme 2**

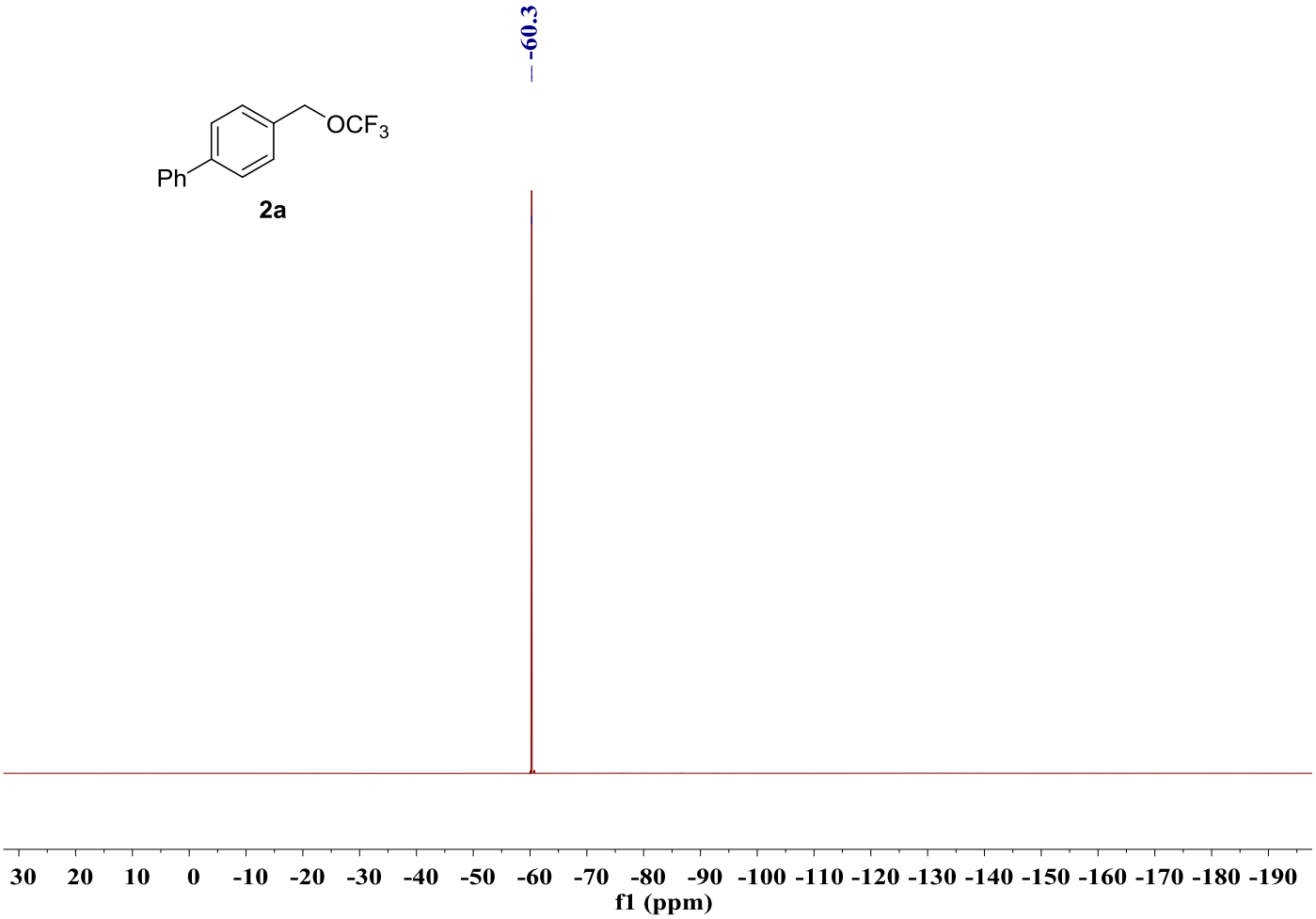

Figure S2. ^{19}F NMR spectrum of **2a**, Related to **Scheme 2**

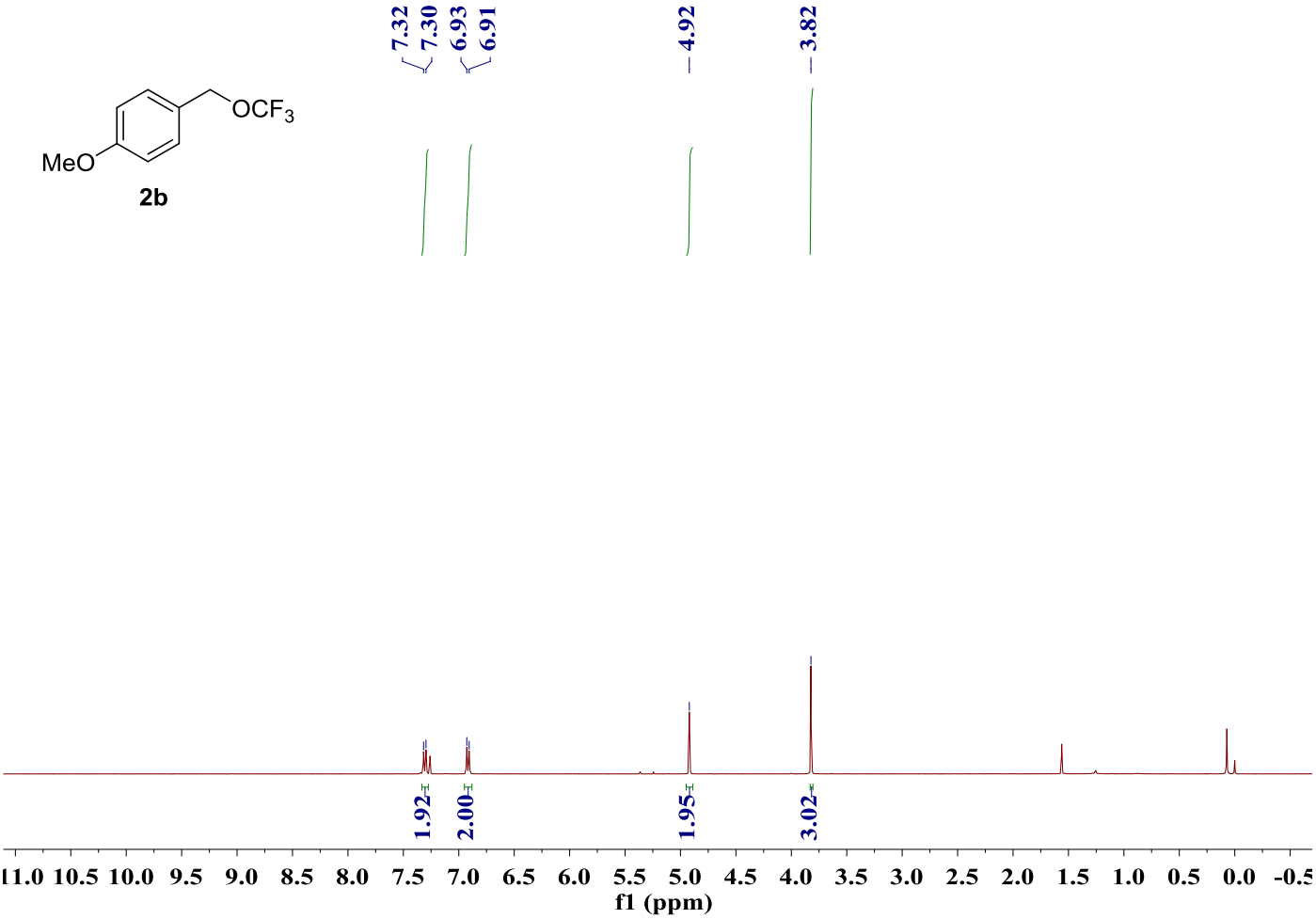

Figure S3. ^{1}H NMR spectrum of **2b**, Related to **Scheme 2**

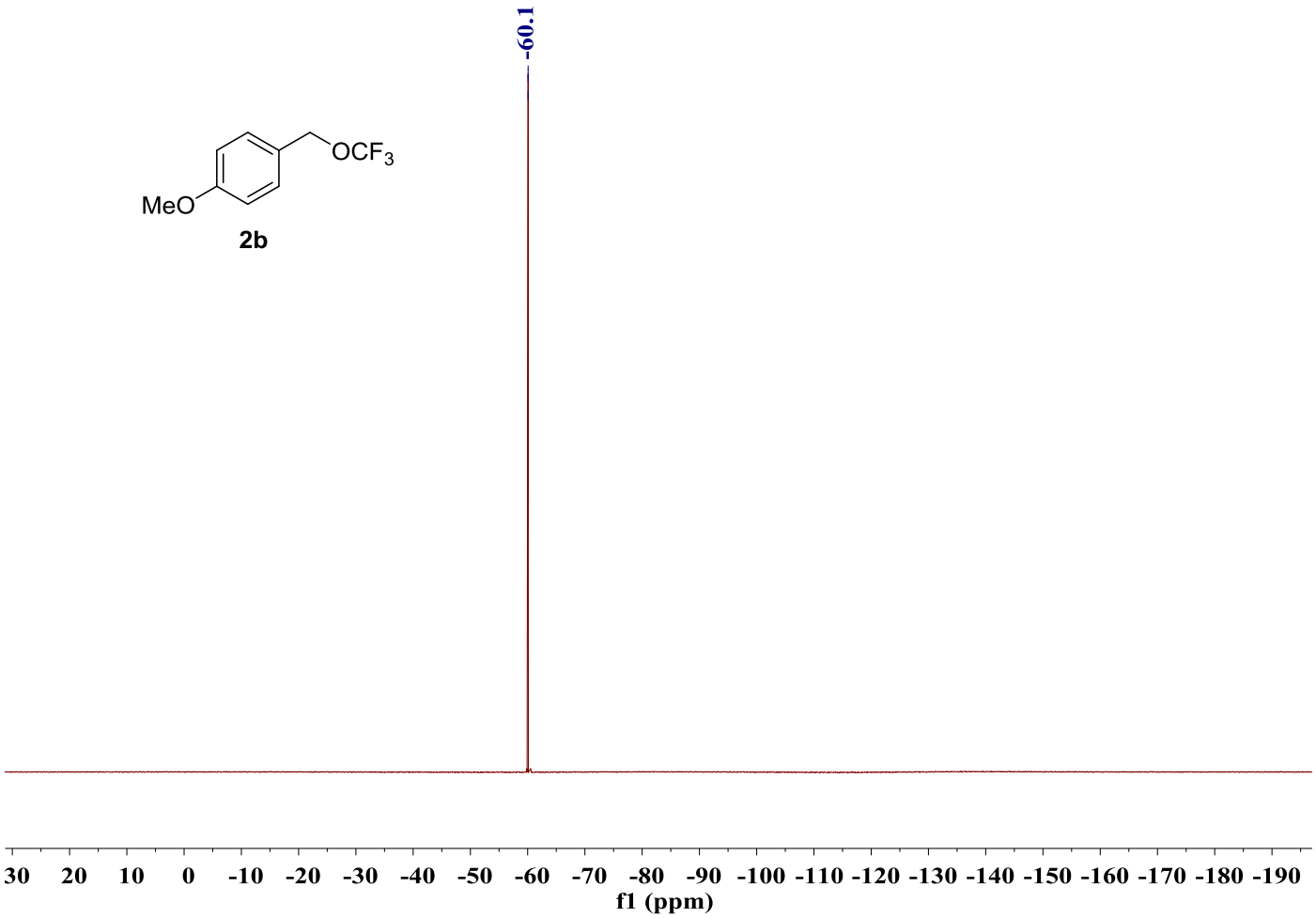

Figure S4. ^{19}F NMR spectrum of **2b**, Related to **Scheme 2**

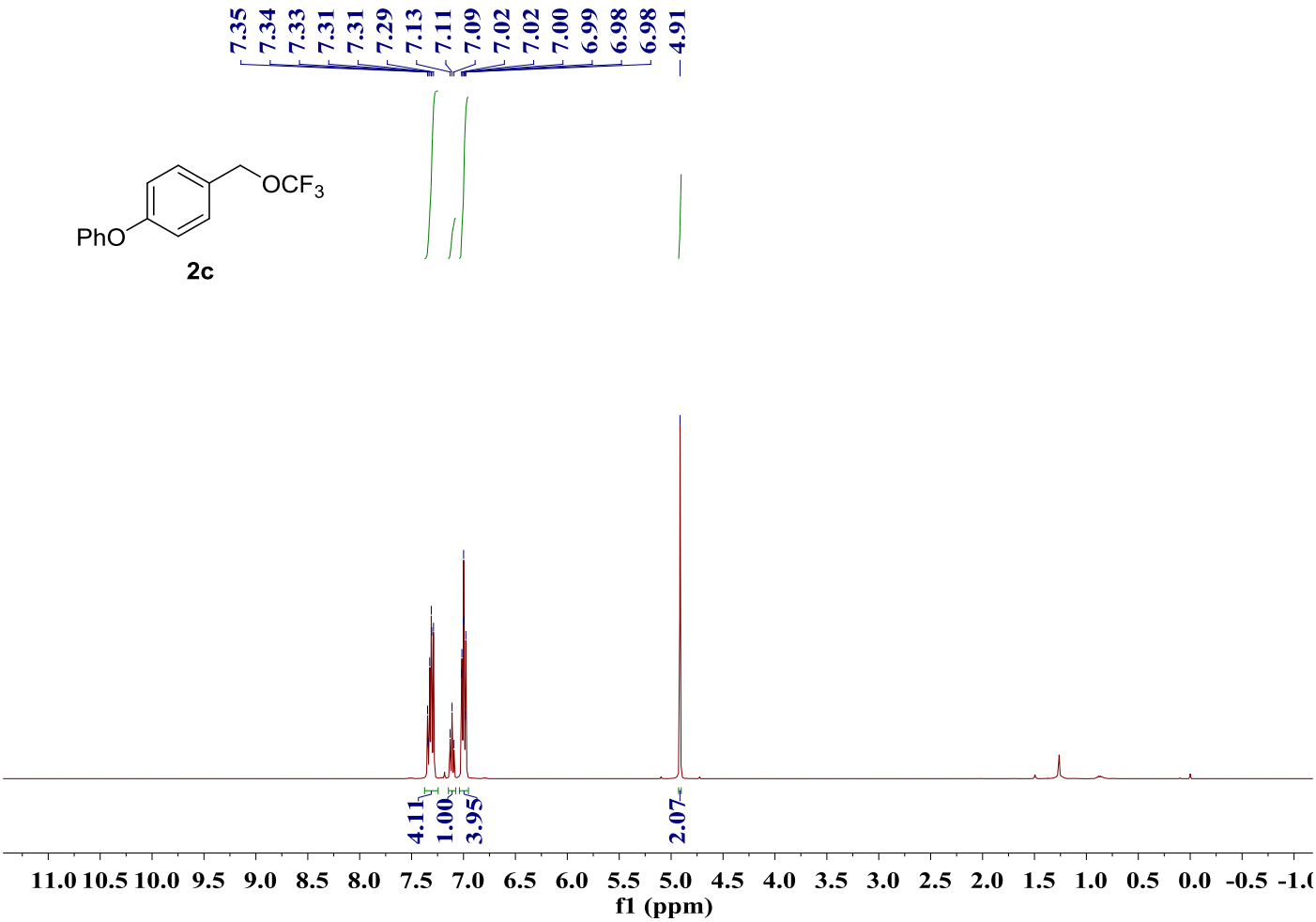

Figure S5. ^{1}H NMR spectrum of **2c**, Related to **Scheme 2**

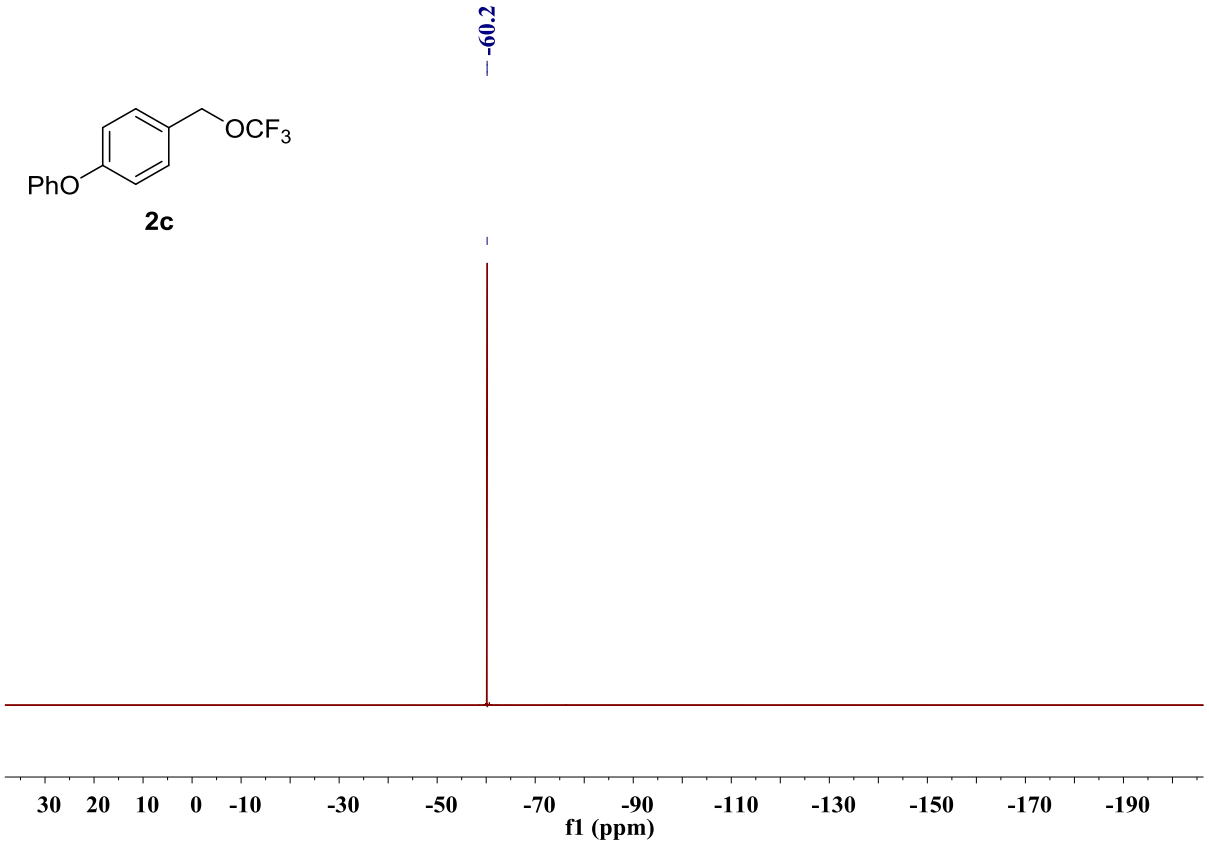

Figure S6. ^{19}F NMR spectrum of **2c**, Related to **Scheme 2**

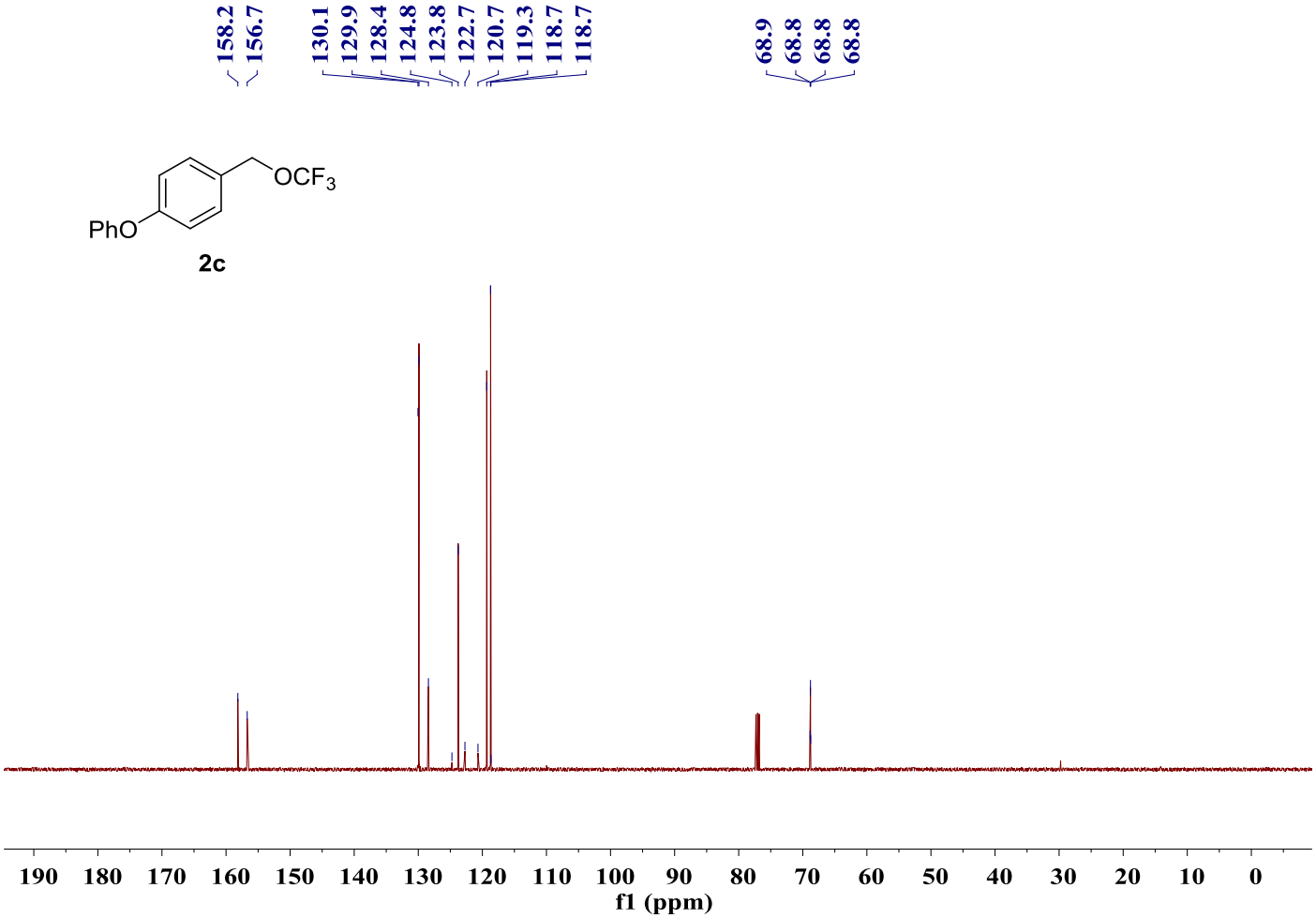

Figure S7. ^{13}C NMR spectrum of **2c**, Related to **Scheme 2**

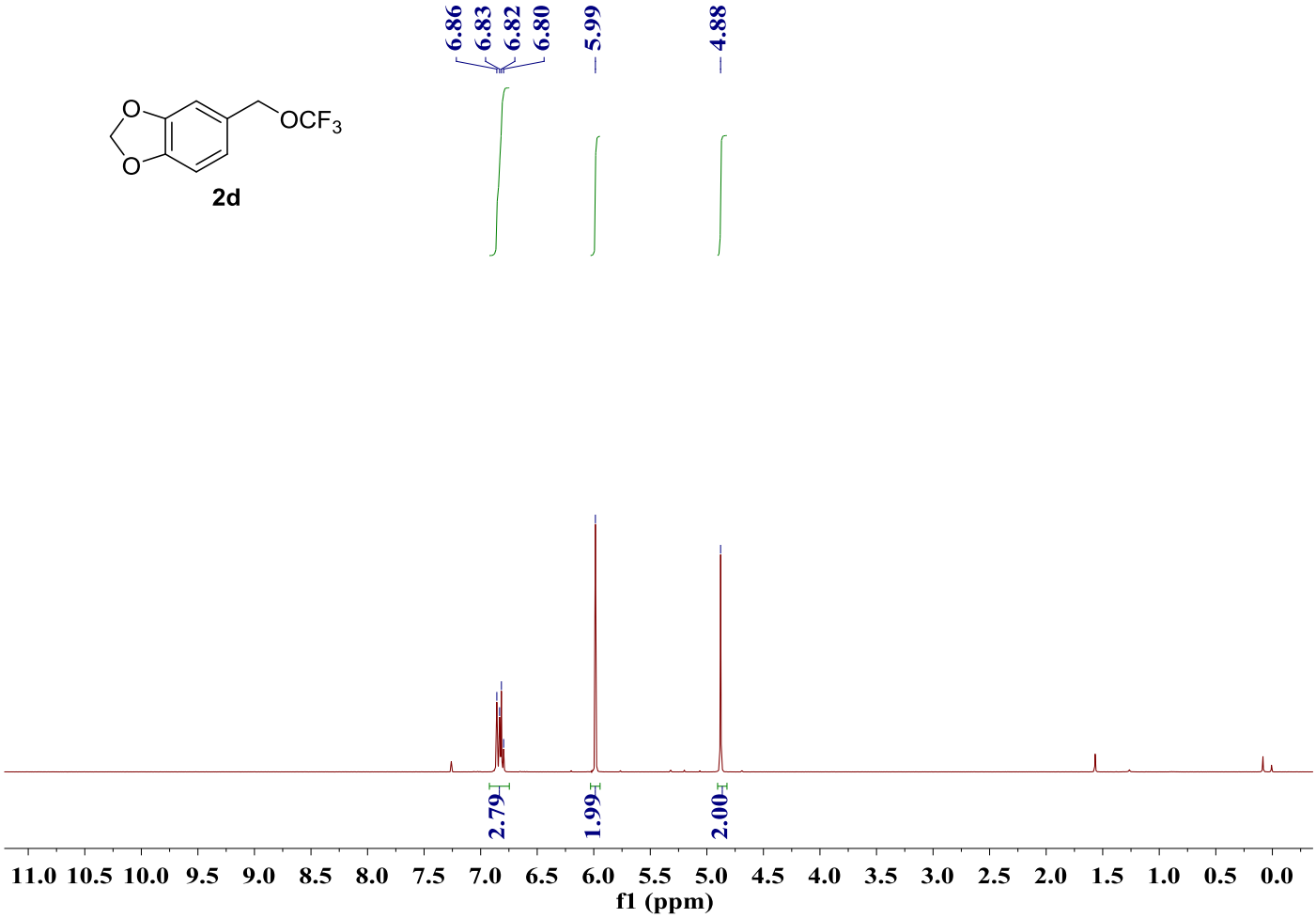

Figure S8. ^{1}H NMR spectrum of **2d**, Related to **Scheme 2**

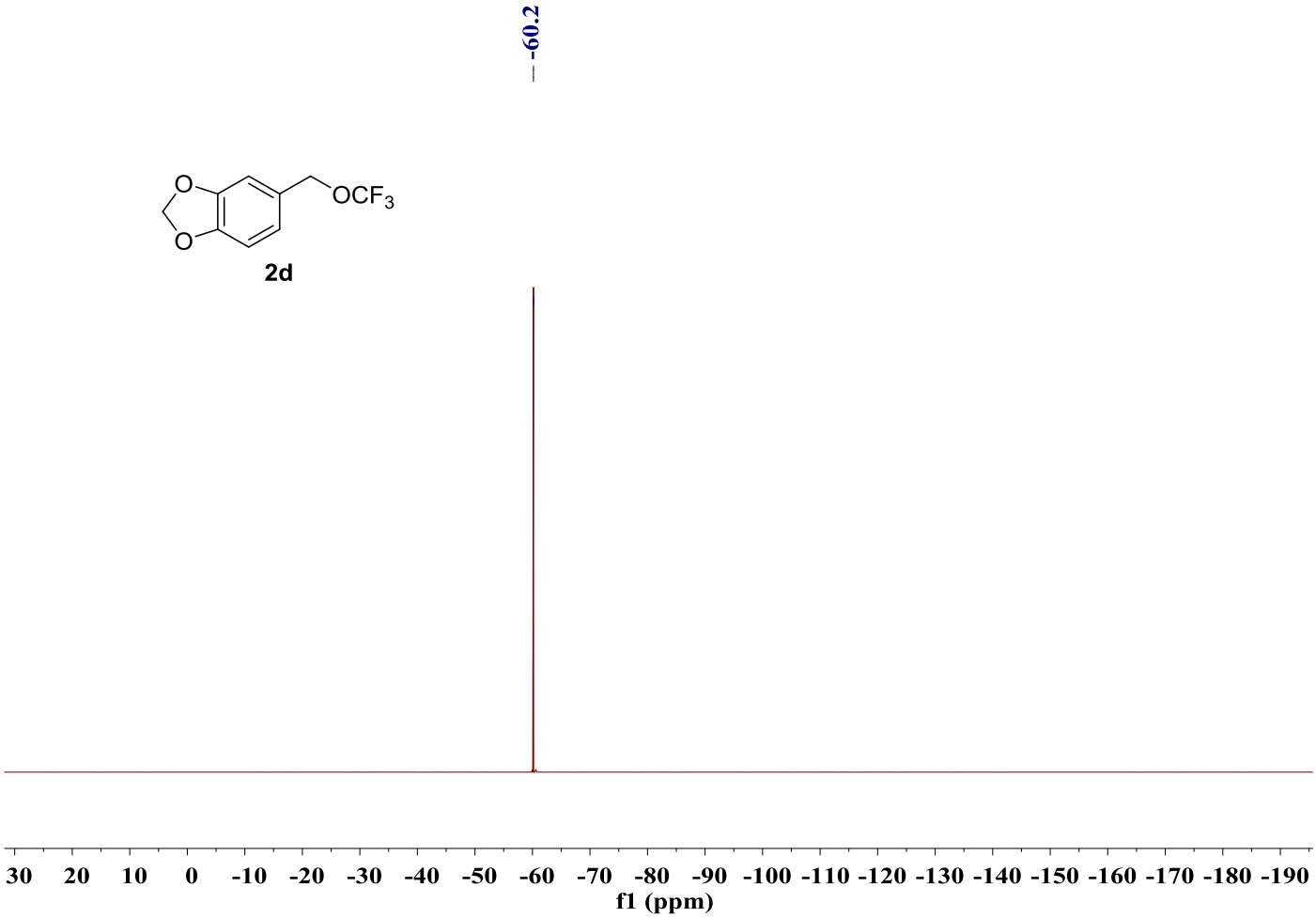

Figure S9. ^{19}F NMR spectrum of **2d**, Related to **Scheme 2**

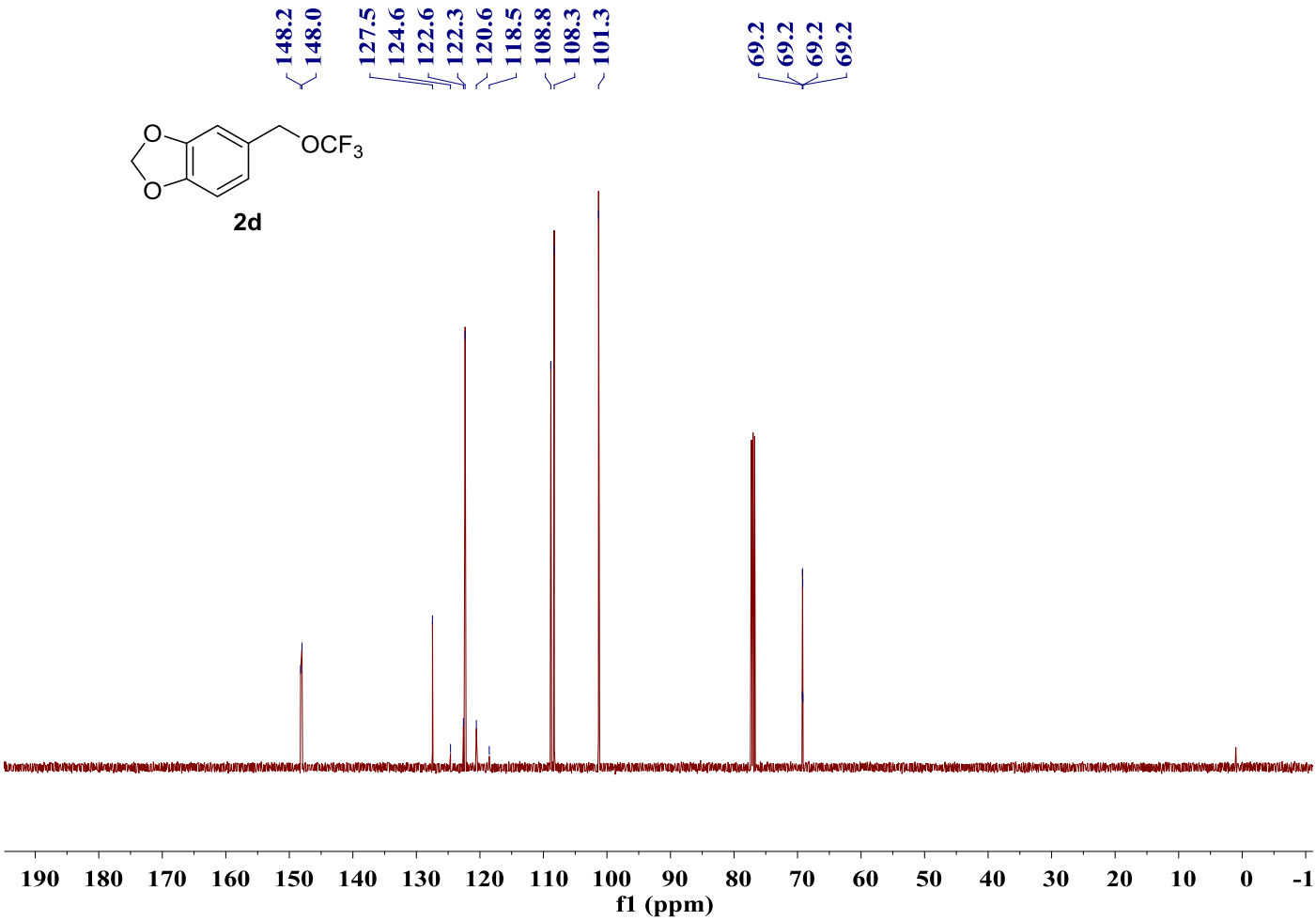

Figure S10. ^{13}C NMR spectrum of **2d**, Related to **Scheme 2**

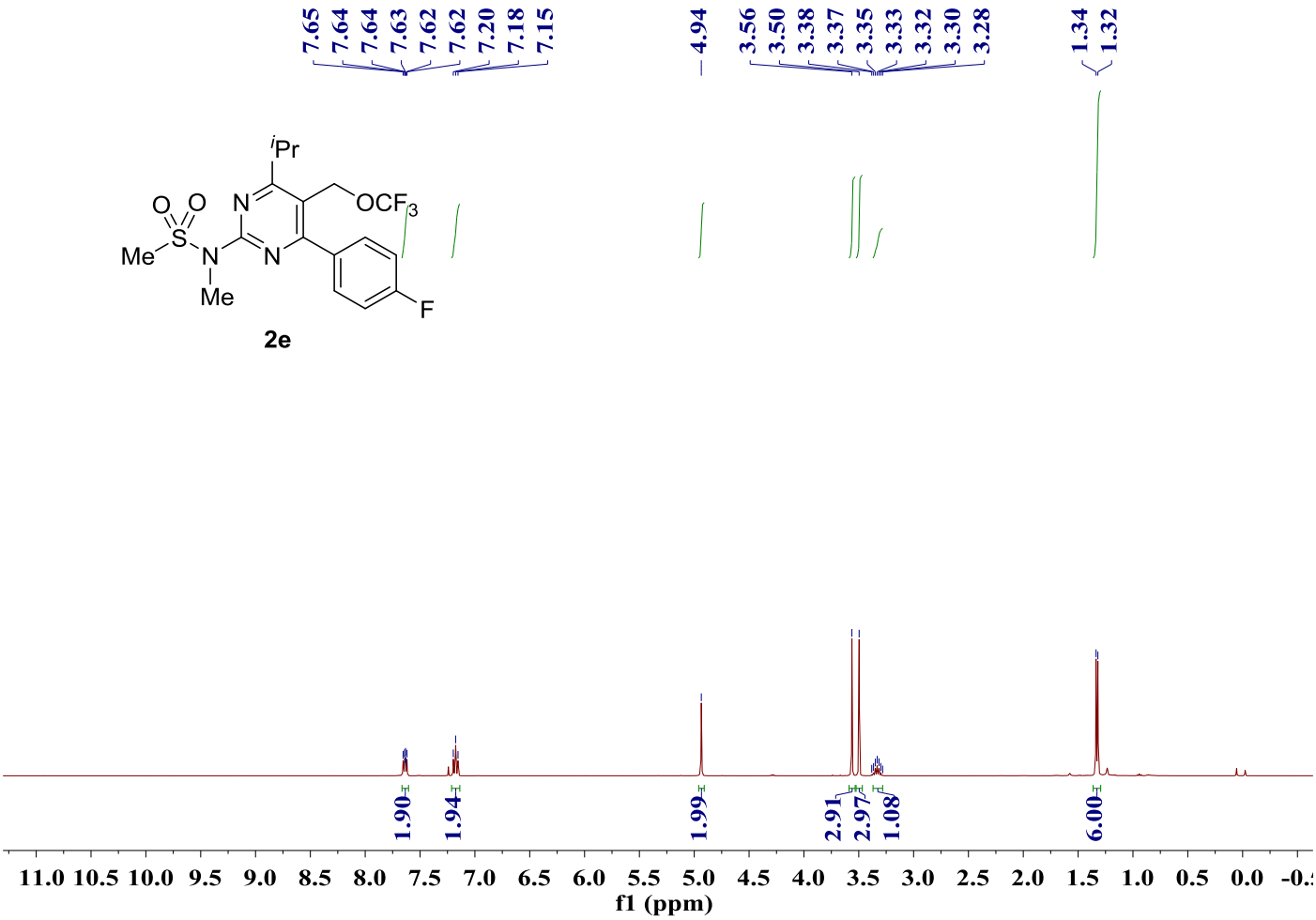

Figure S11. ^{1}H NMR spectrum of **2e**, Related to **Scheme 2**

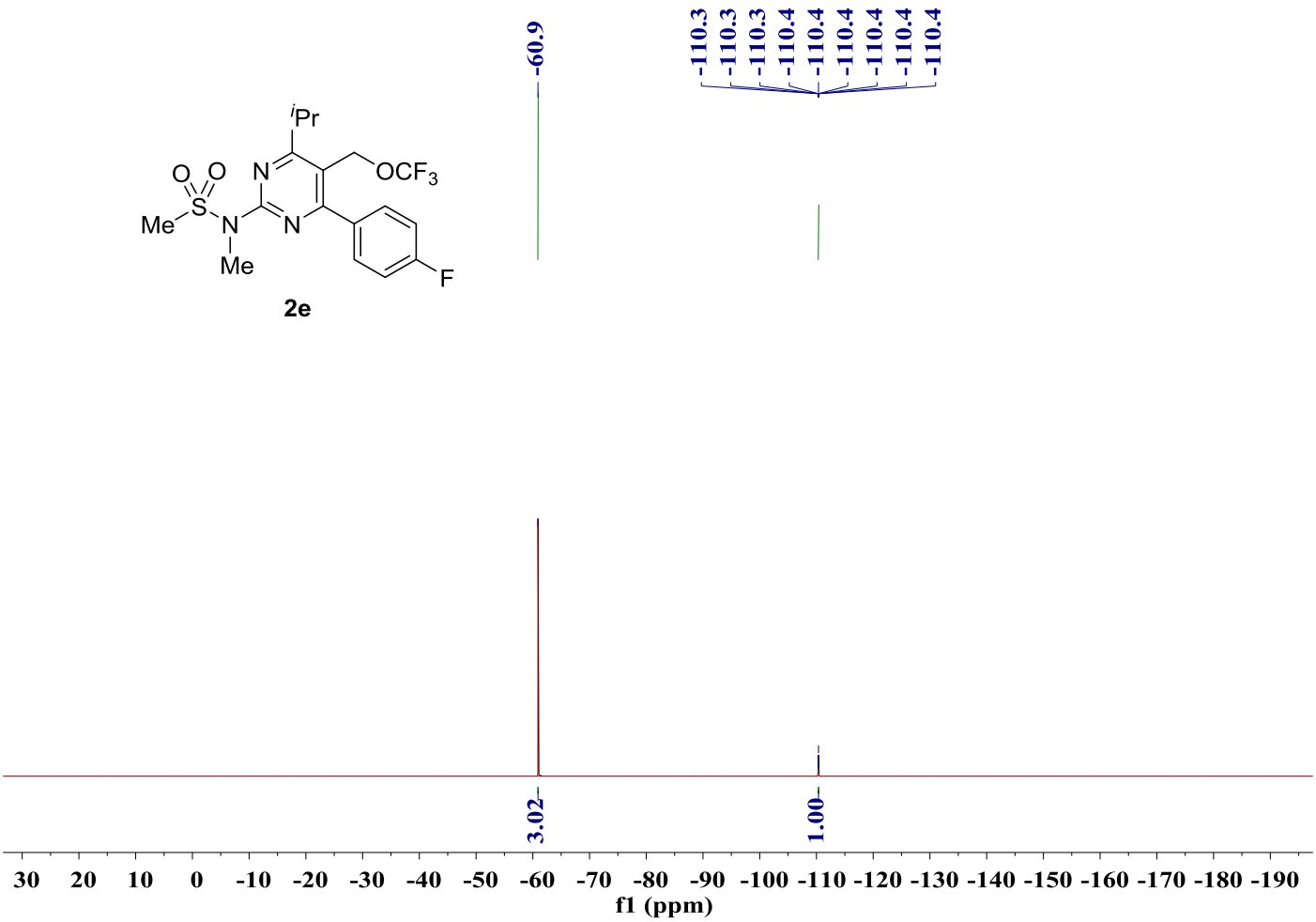

Figure S12. ^{19}F NMR spectrum of **2e**, Related to **Scheme 2**

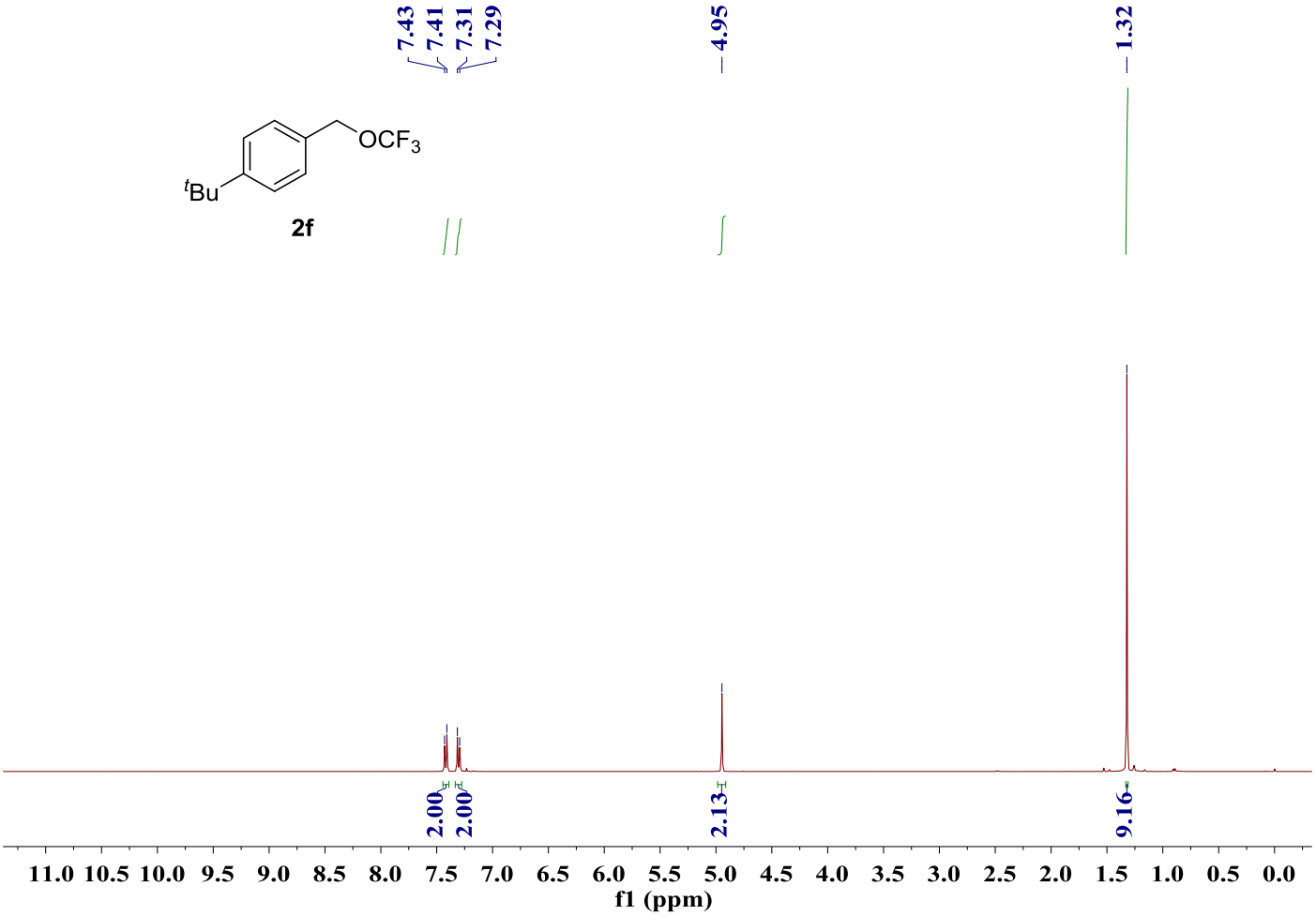

Figure S13. ^{1}H NMR spectrum of **2f**, Related to **Scheme 2**

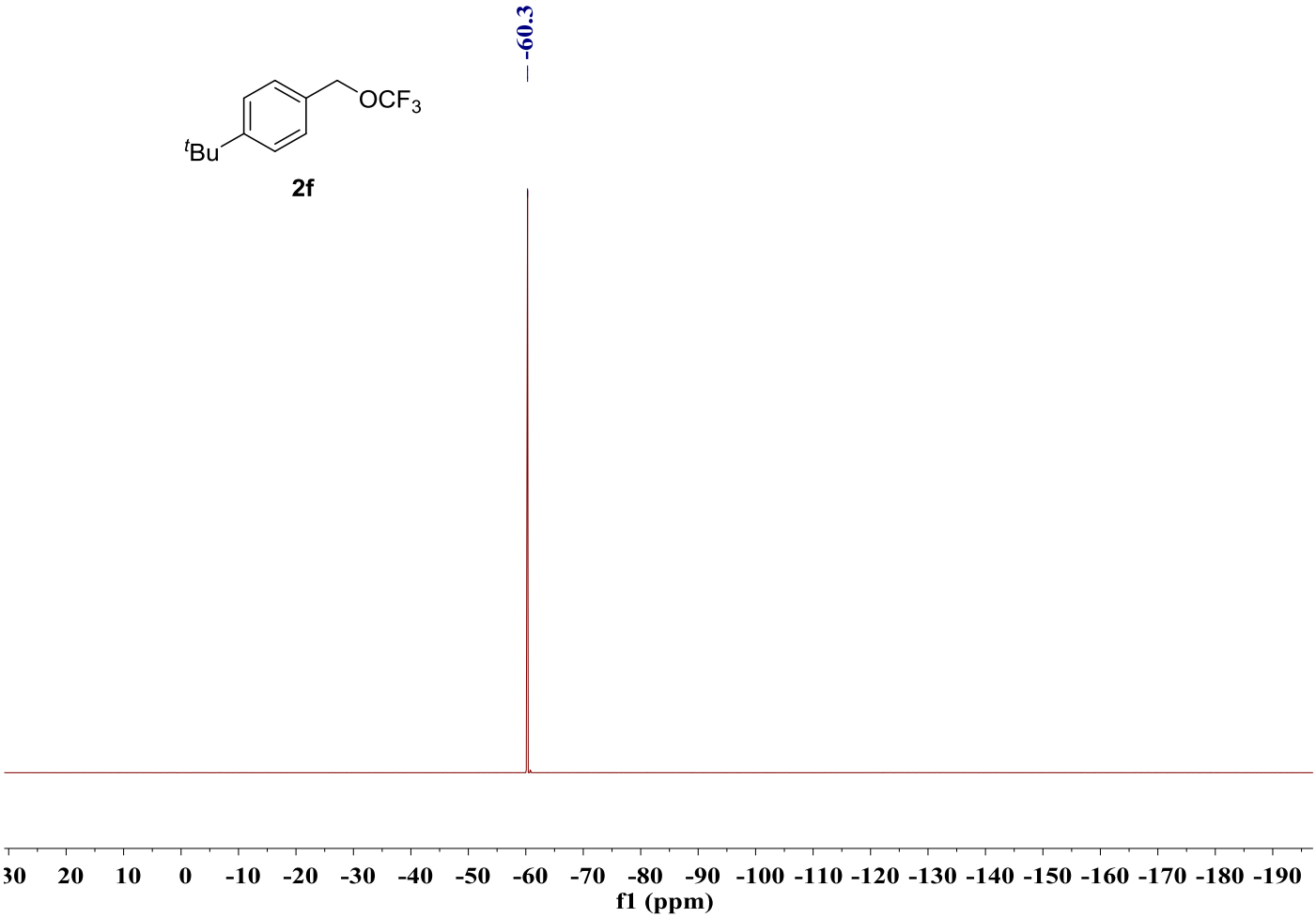

Figure S14. ^{19}F NMR spectrum of **2f**, Related to **Scheme 2**

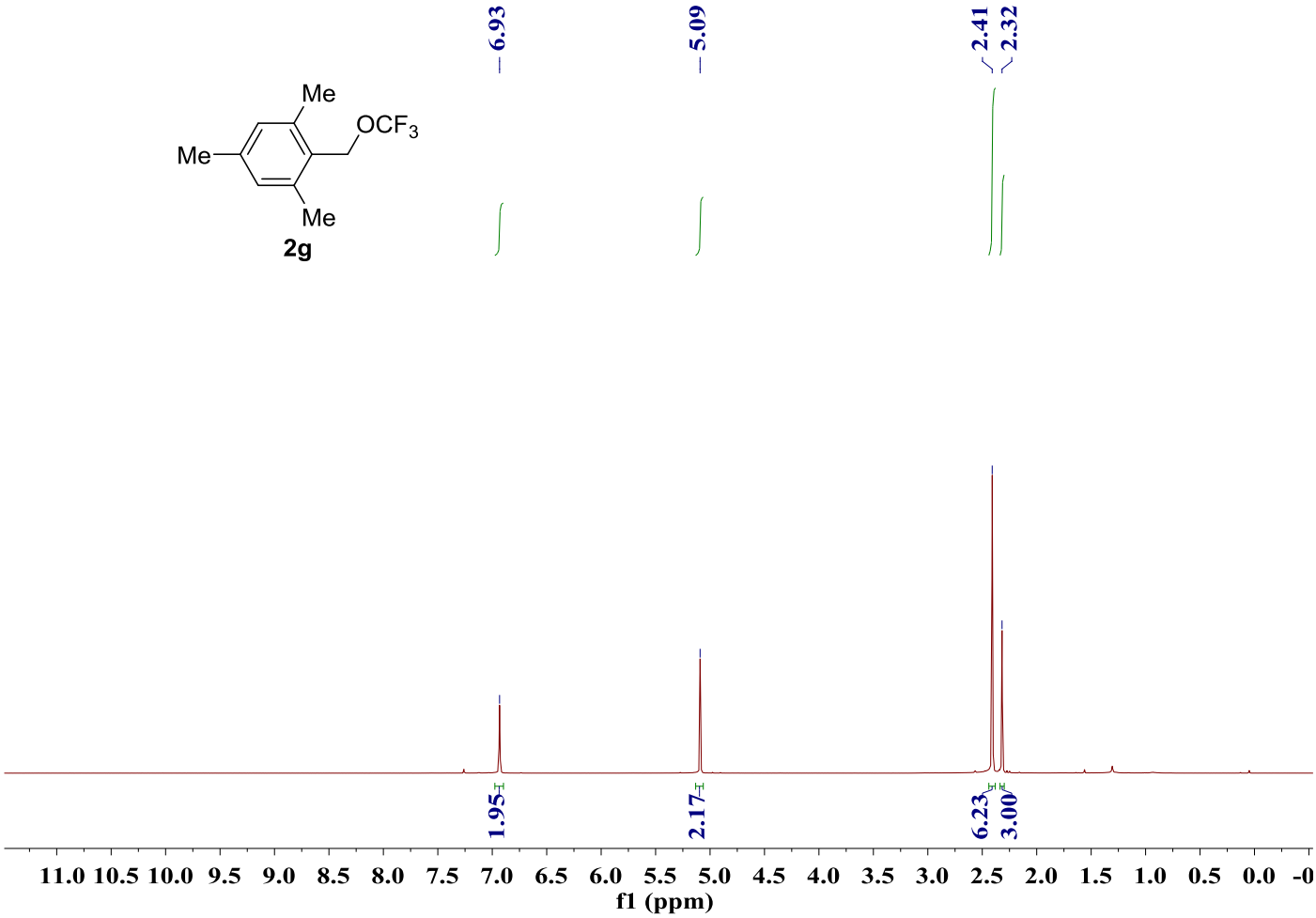

Figure S15. ^{1}H NMR spectrum of **2g**, Related to **Scheme 2**

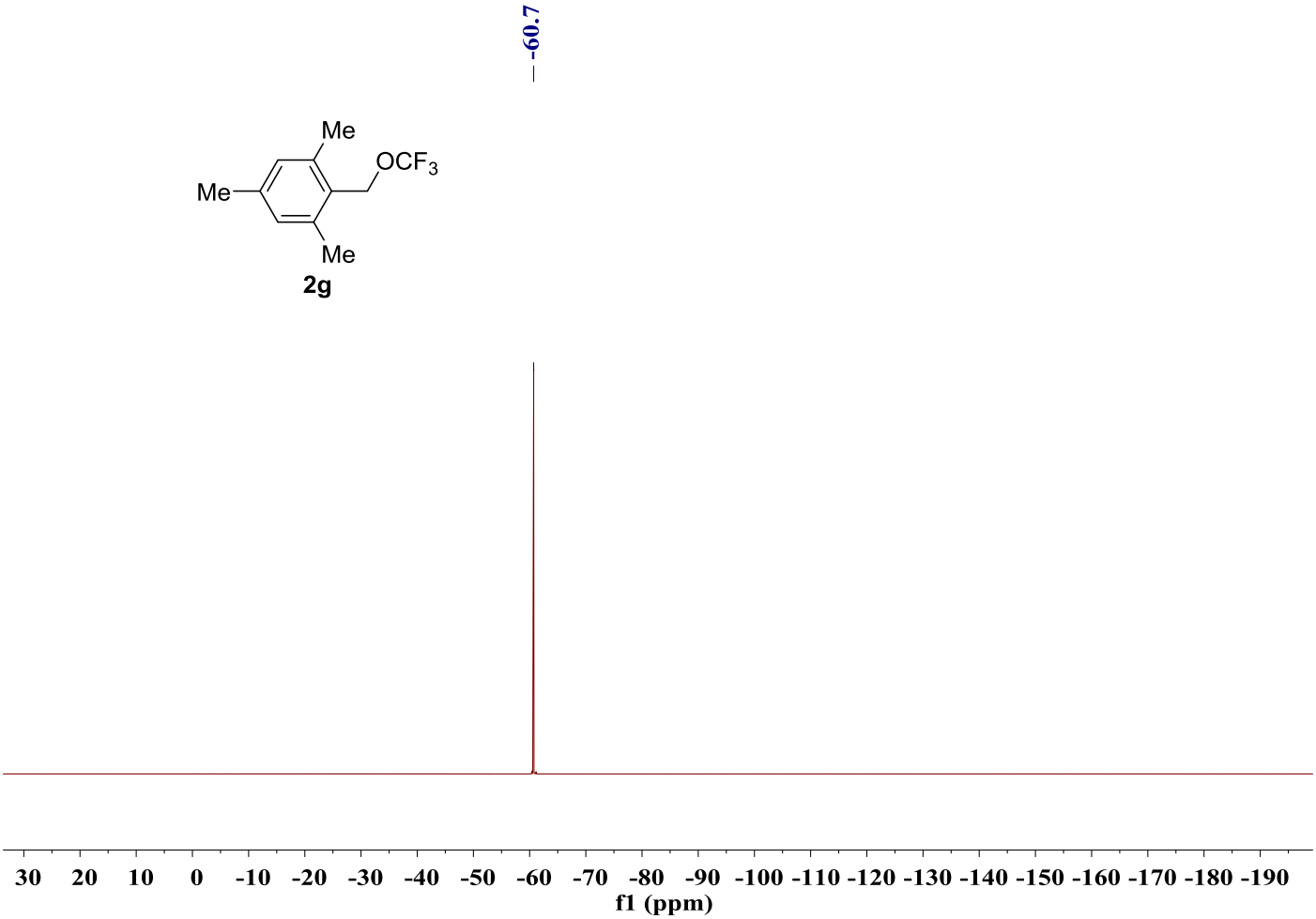

Figure S16. ^{19}F NMR spectrum of **2g**, Related to **Scheme 2**

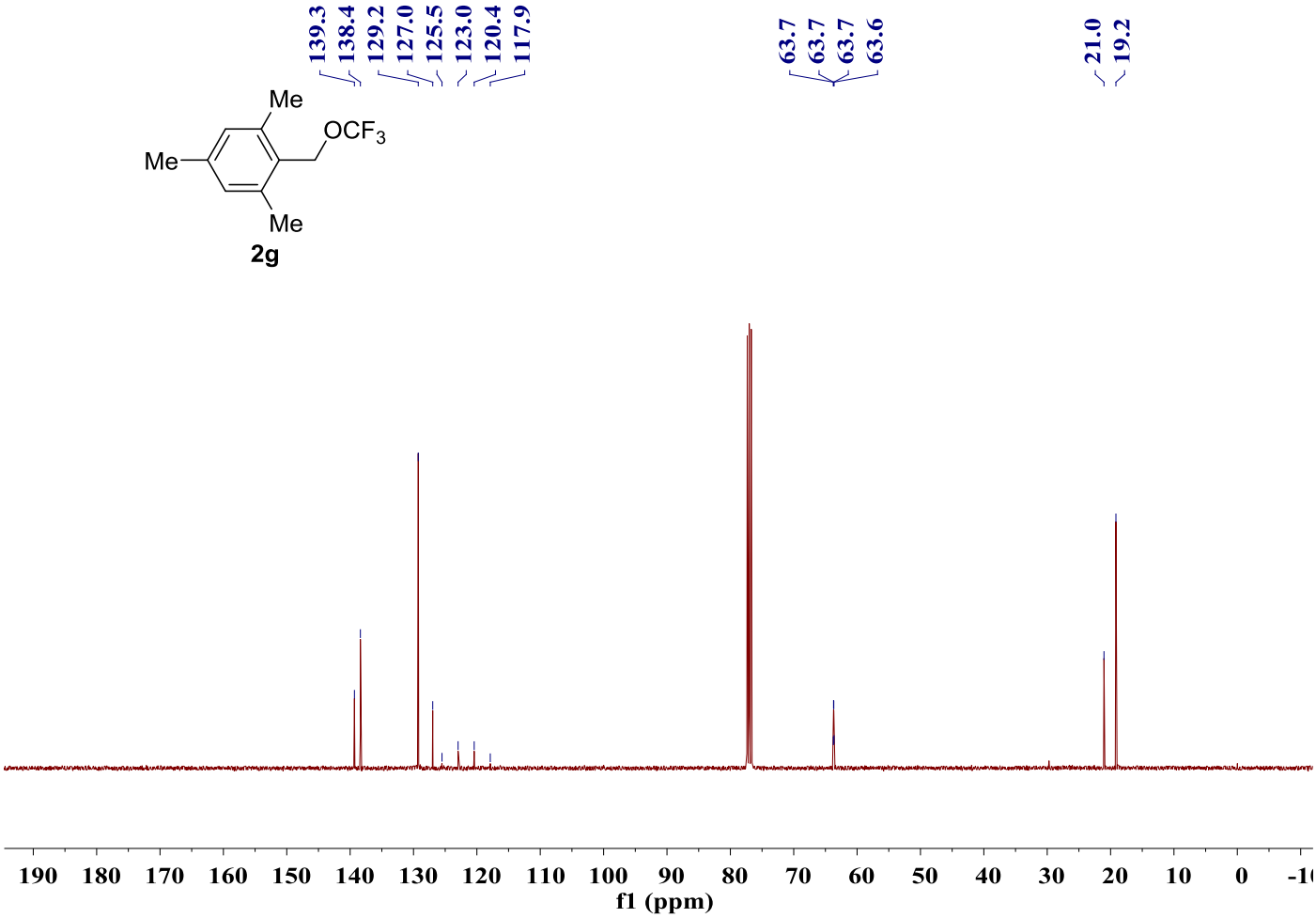

Figure S17. ^{13}C NMR spectrum of **2g**, Related to **Scheme 2**

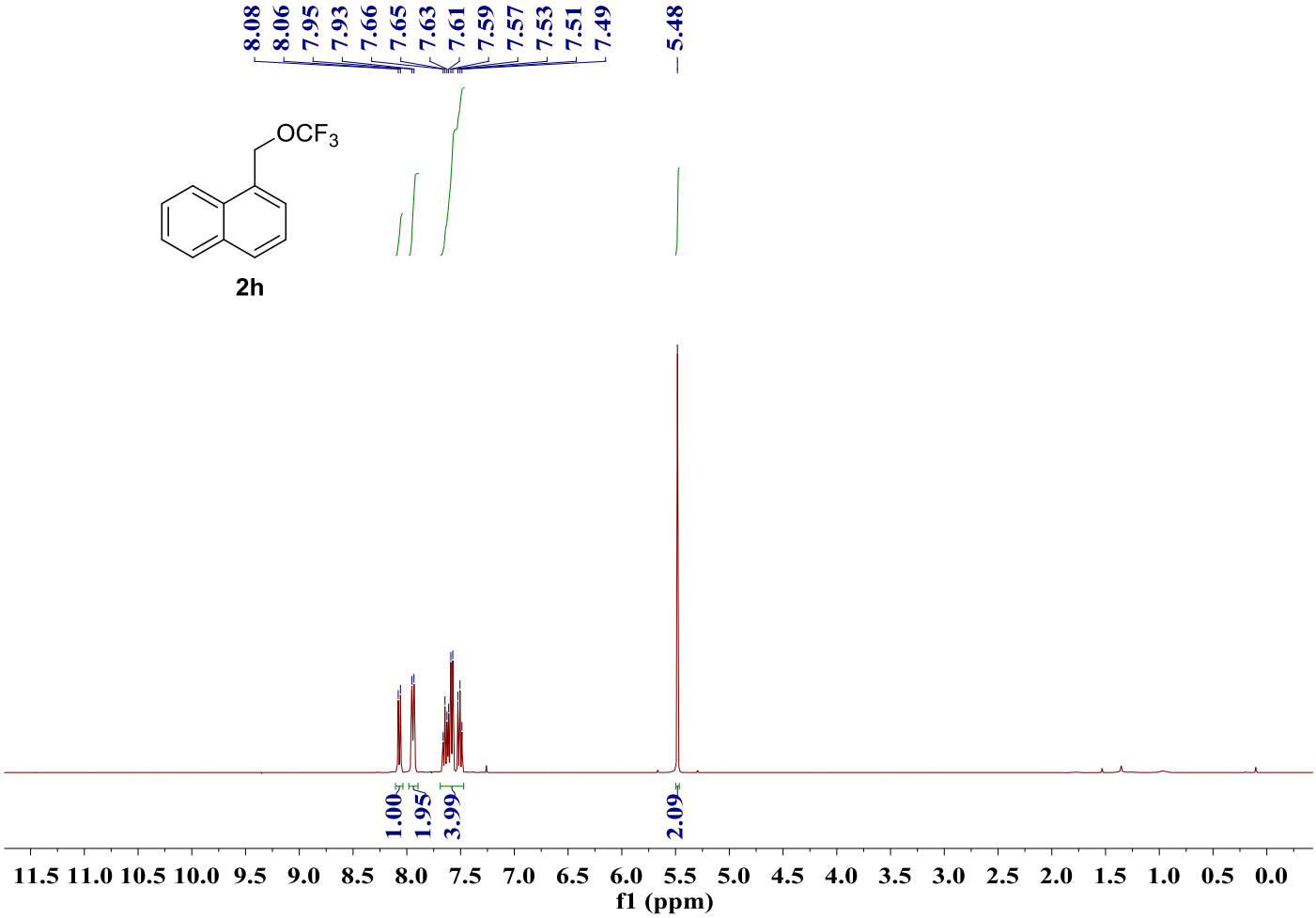

Figure S18. ^{1}H NMR spectrum of **2h**, Related to **Scheme 2**

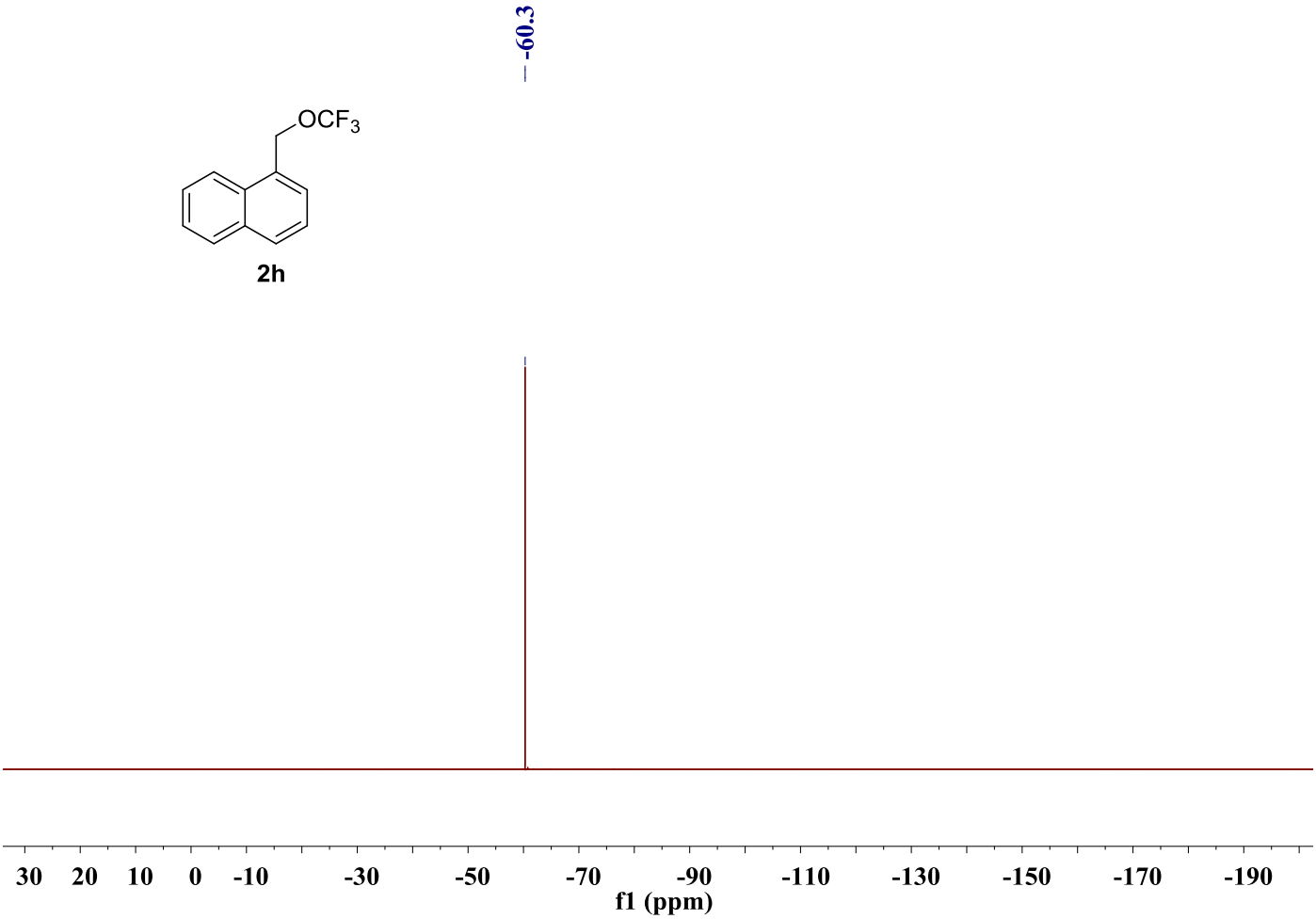

Figure S19. ^{19}F NMR spectrum of **2h**, Related to **Scheme 2**

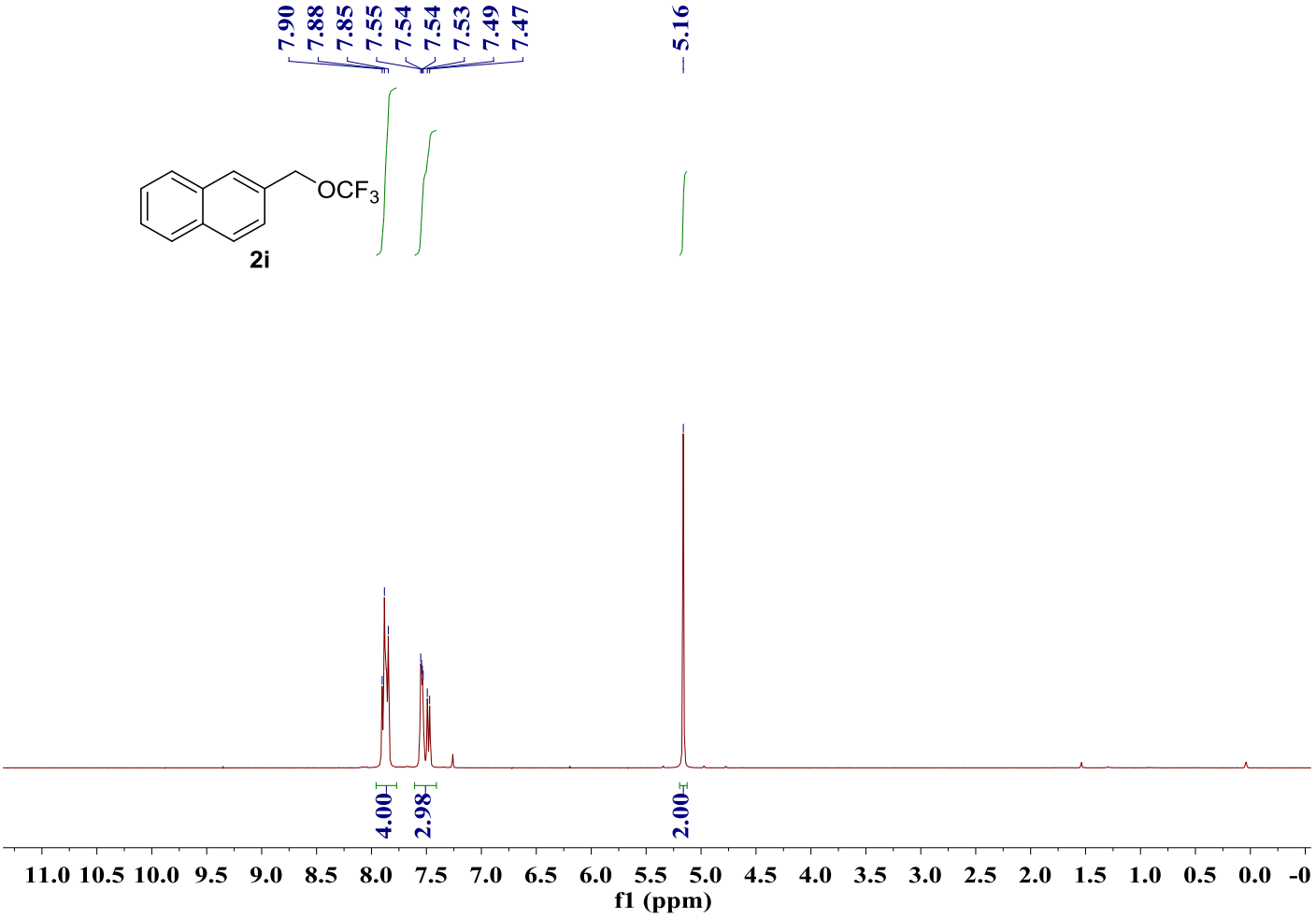

Figure S20 ^{1}H NMR spectrum of **2i**, Related to **Scheme 2**

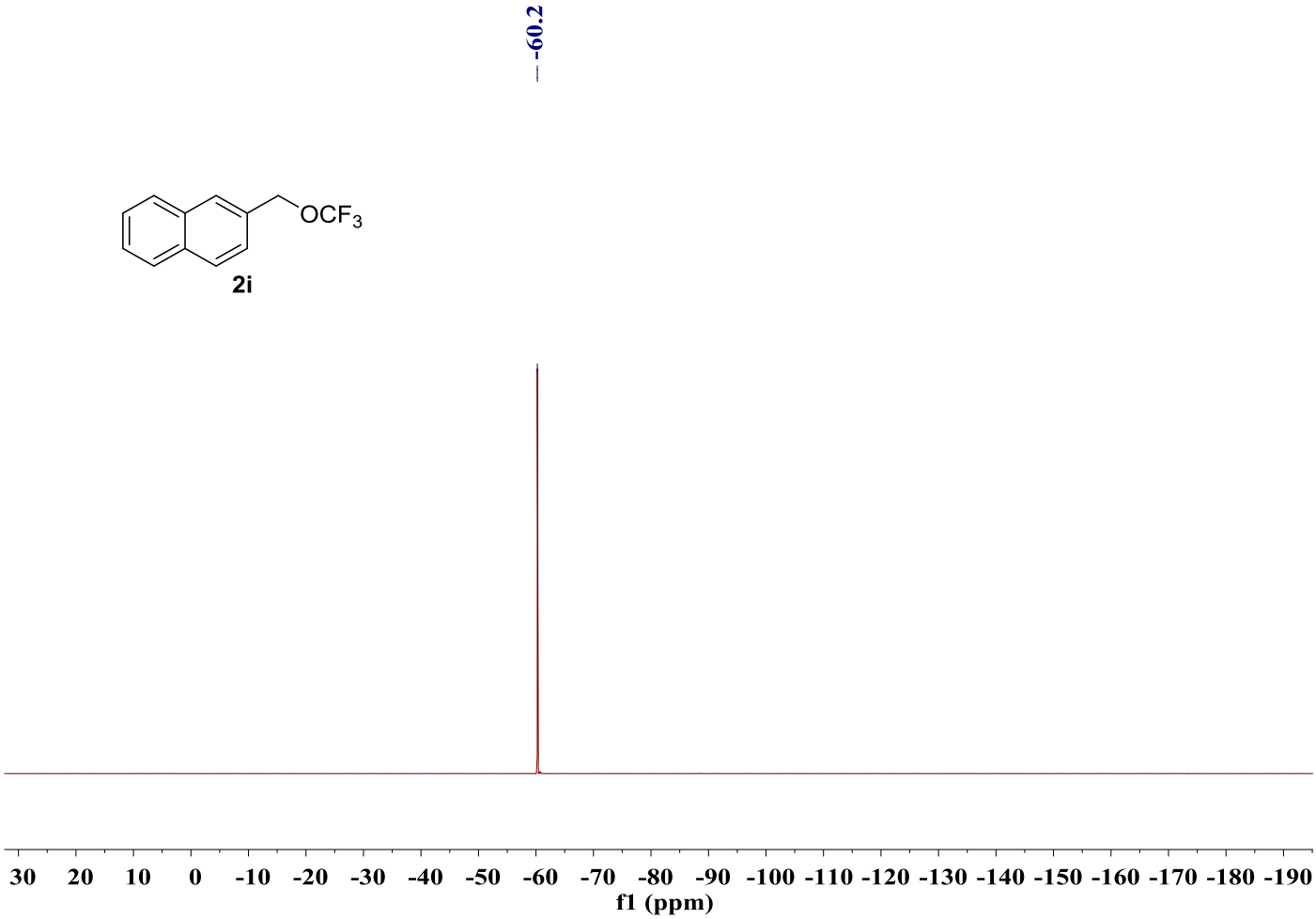

Figure S21. ^{19}F NMR spectrum of **2i**, Related to **Scheme 2**

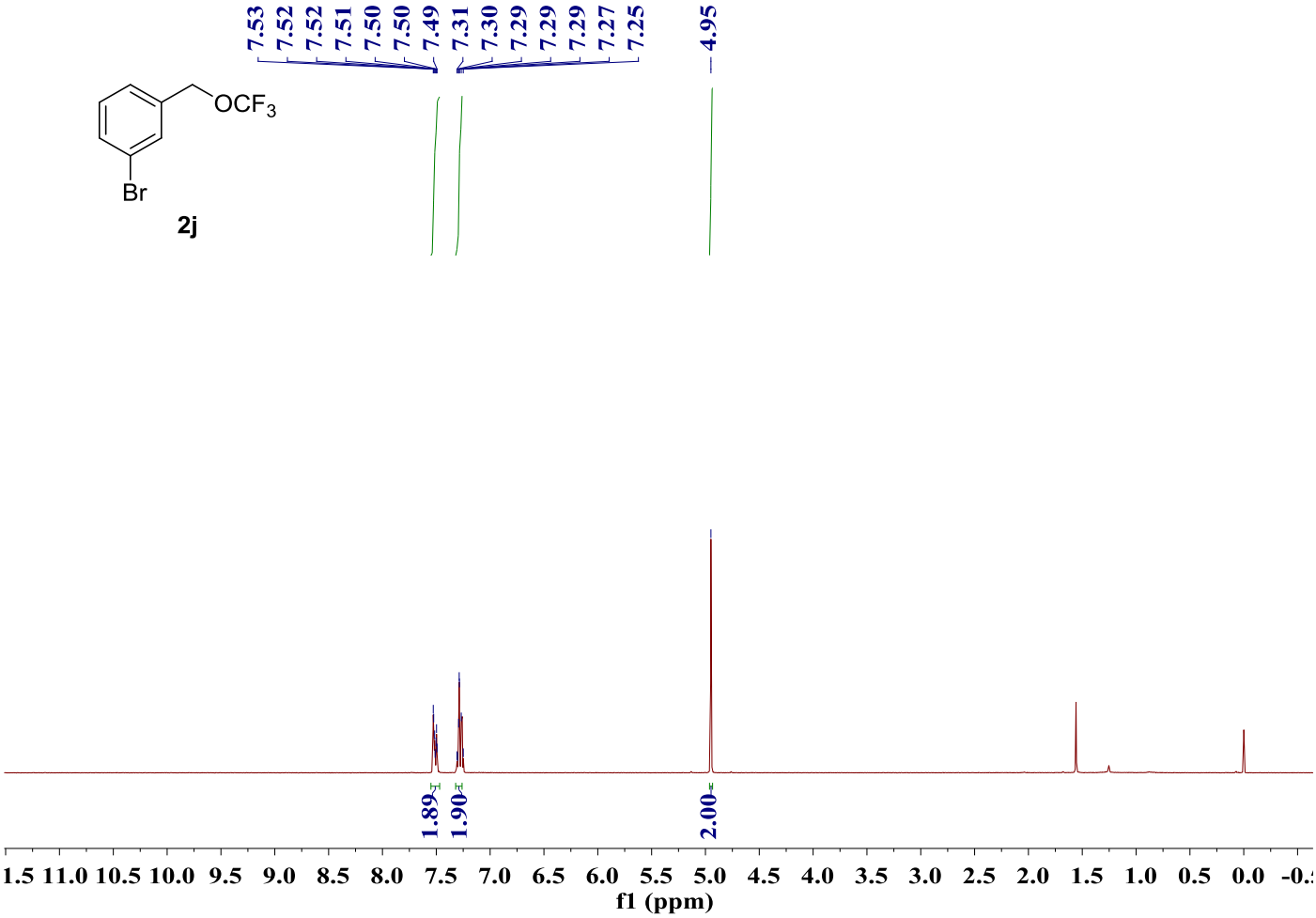

Figure S22. ^{1}H NMR spectrum of **2i**, Related to **Scheme 2**

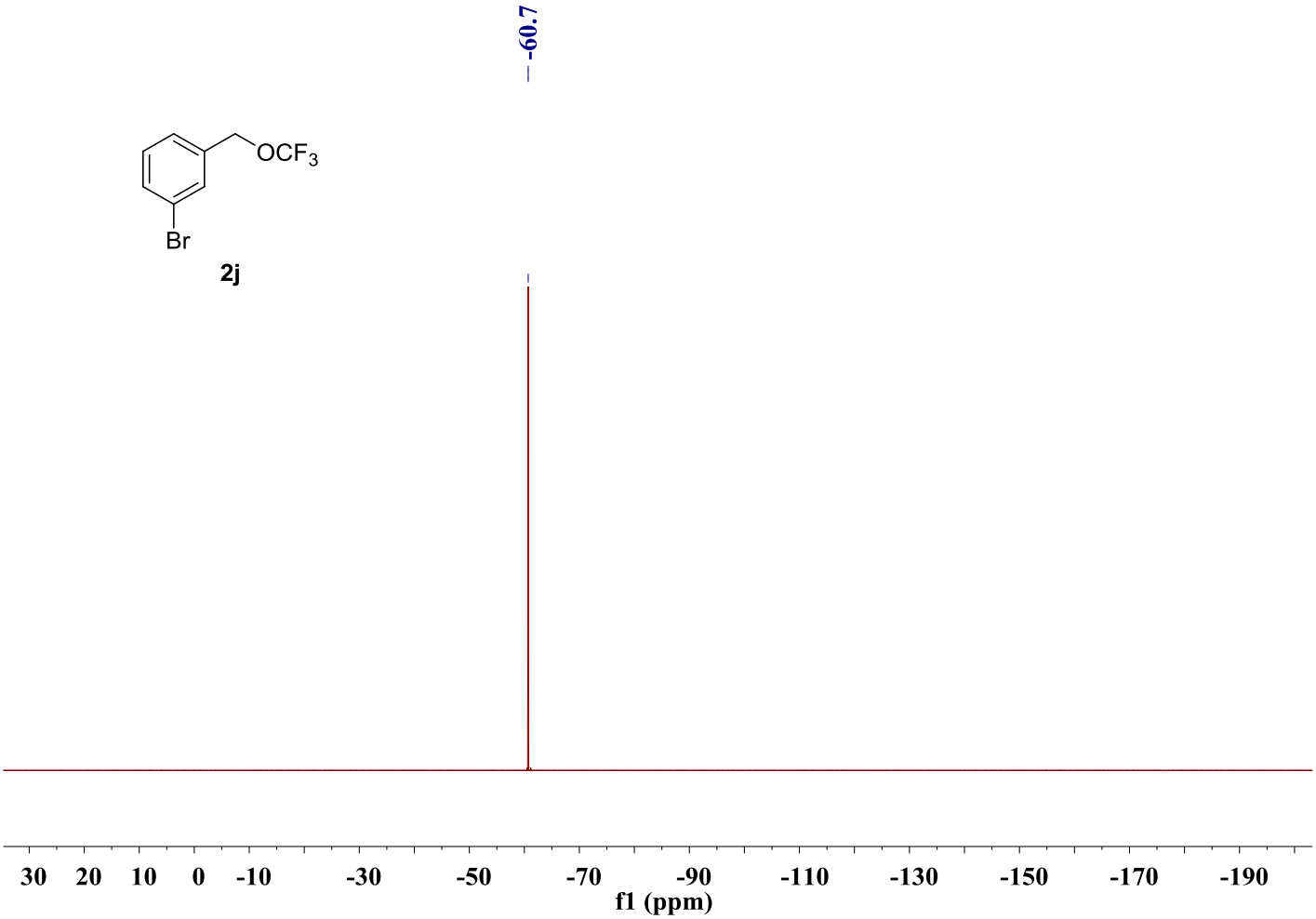

Figure S23. ^{19}F NMR spectrum of **2j**, Related to **Scheme 2**

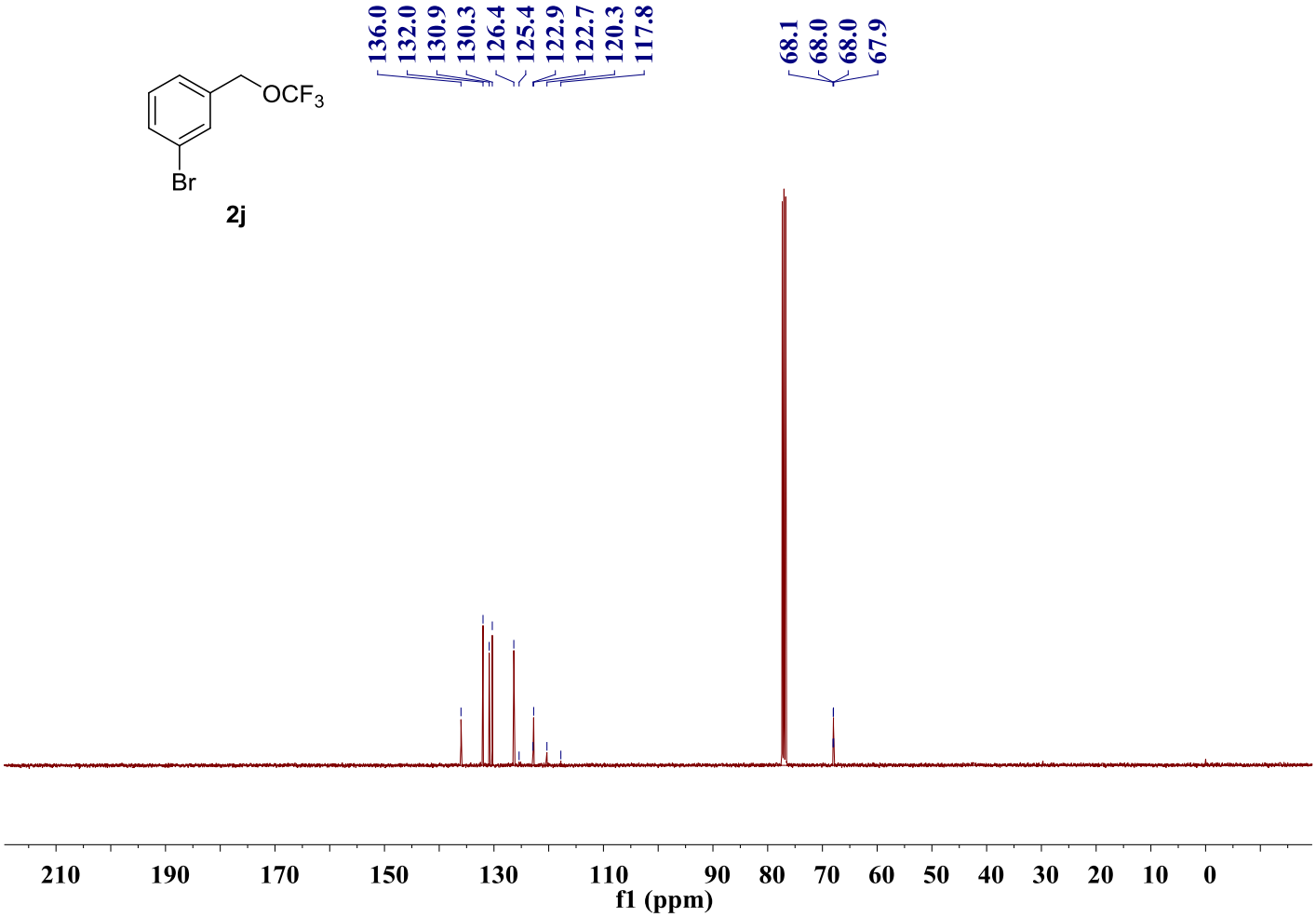

Figure S24. ^{13}C NMR spectrum of **2j**, Related to **Scheme 2**

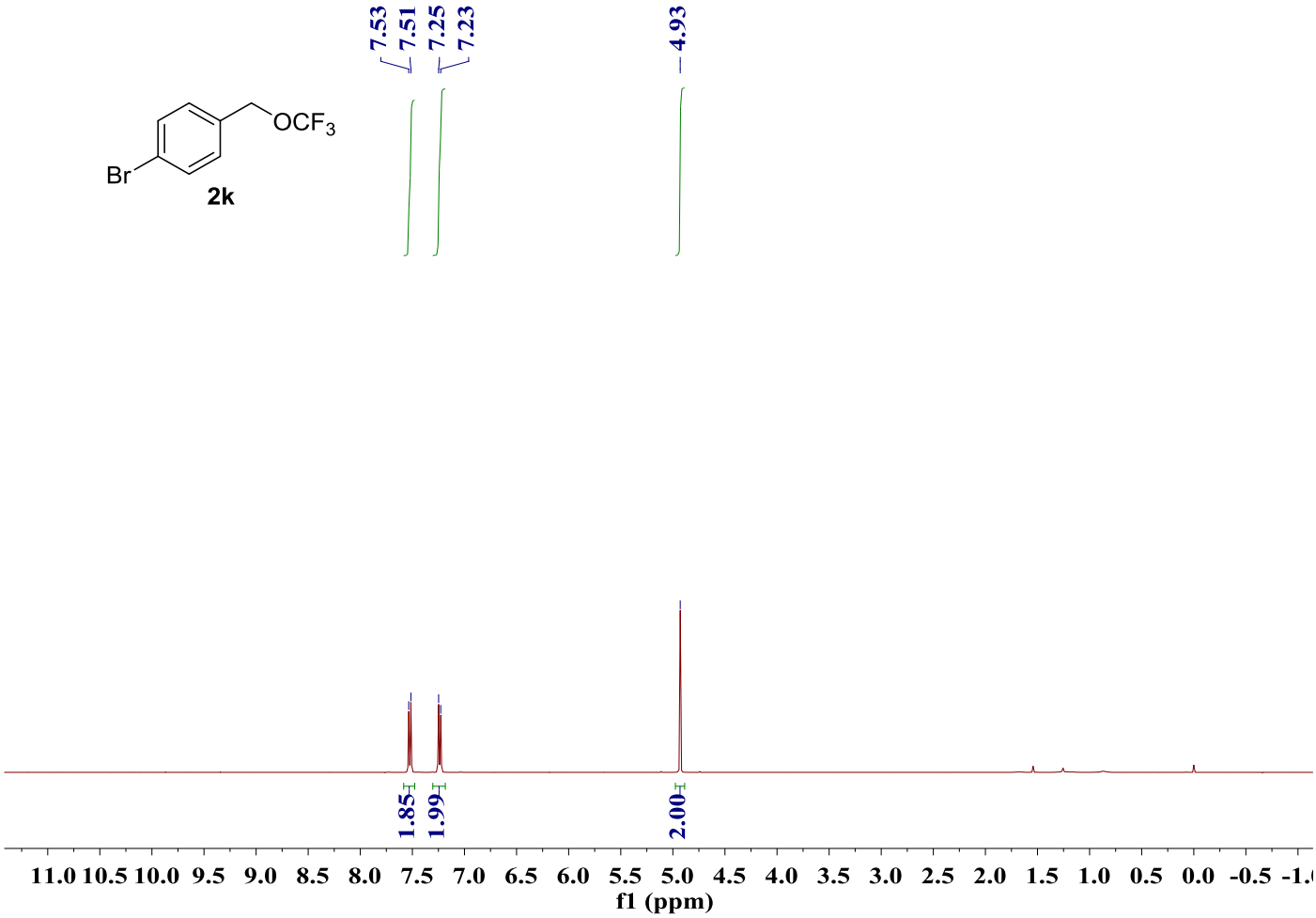

Figure S25. ^{1}H NMR spectrum of **2k**, Related to **Scheme 2**

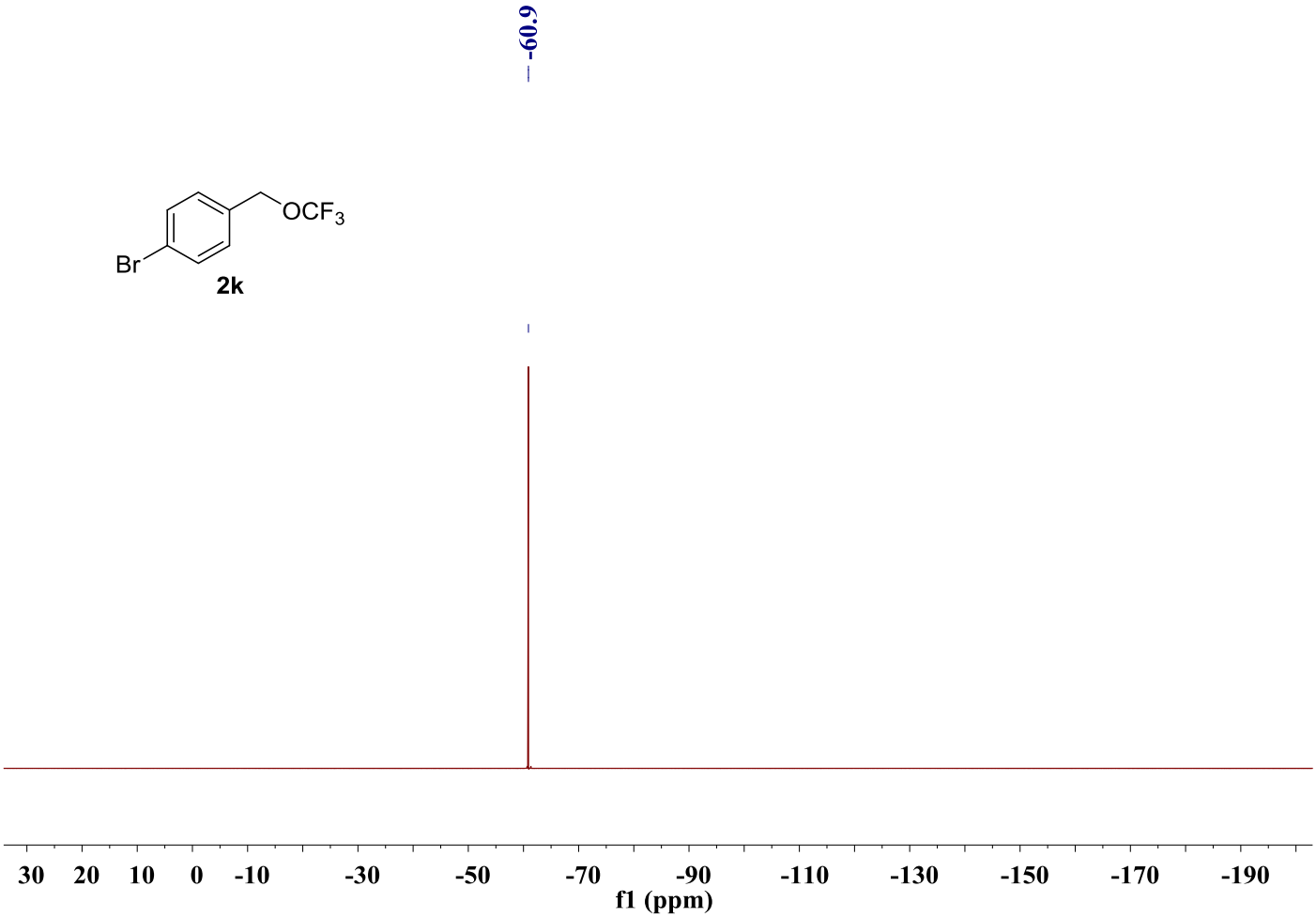

Figure S26. ^{19}F NMR spectrum of **2k**, Related to **Scheme 2**

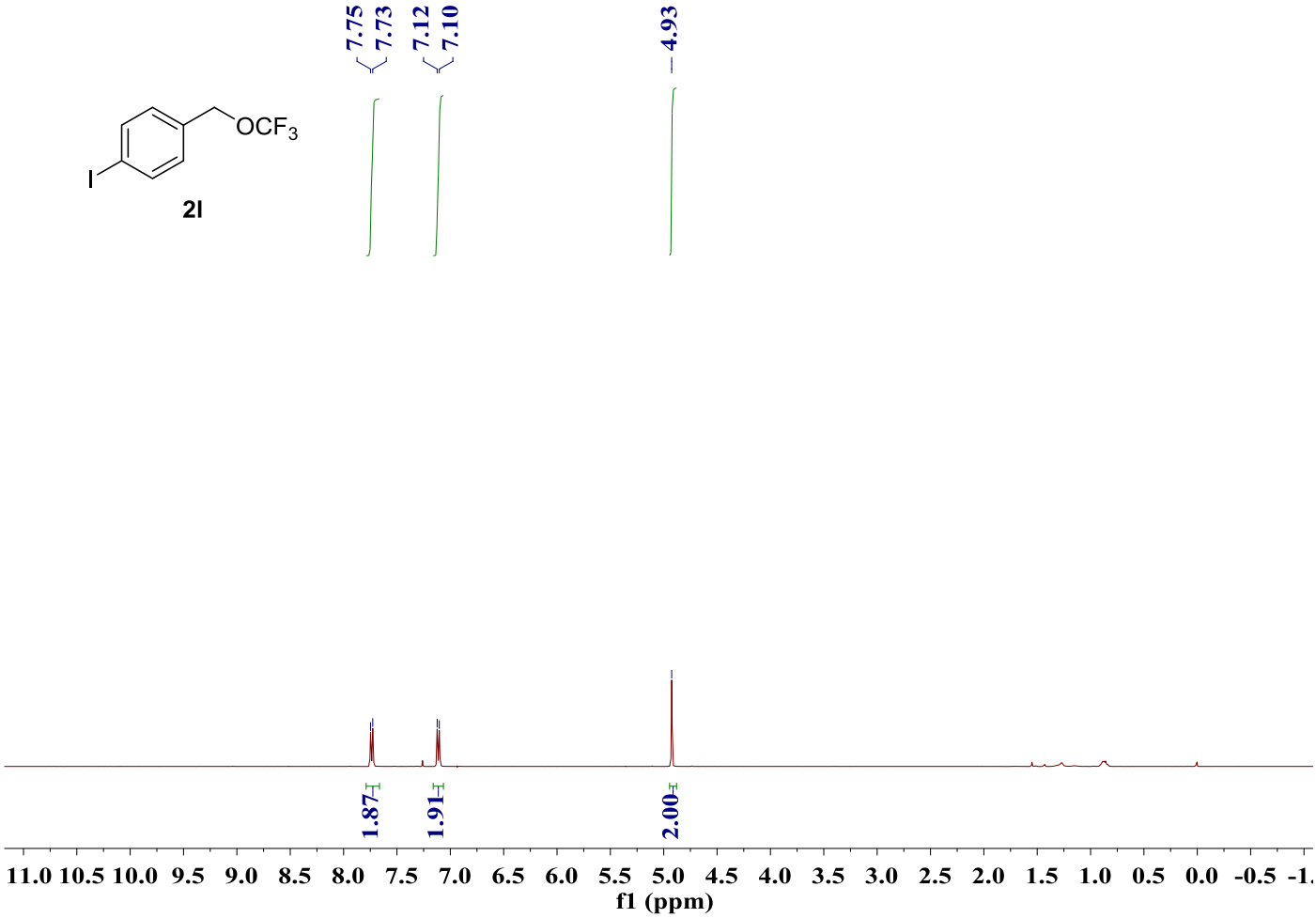

Figure S27. ^{1}H NMR spectrum of **2l**, Related to **Scheme 2**

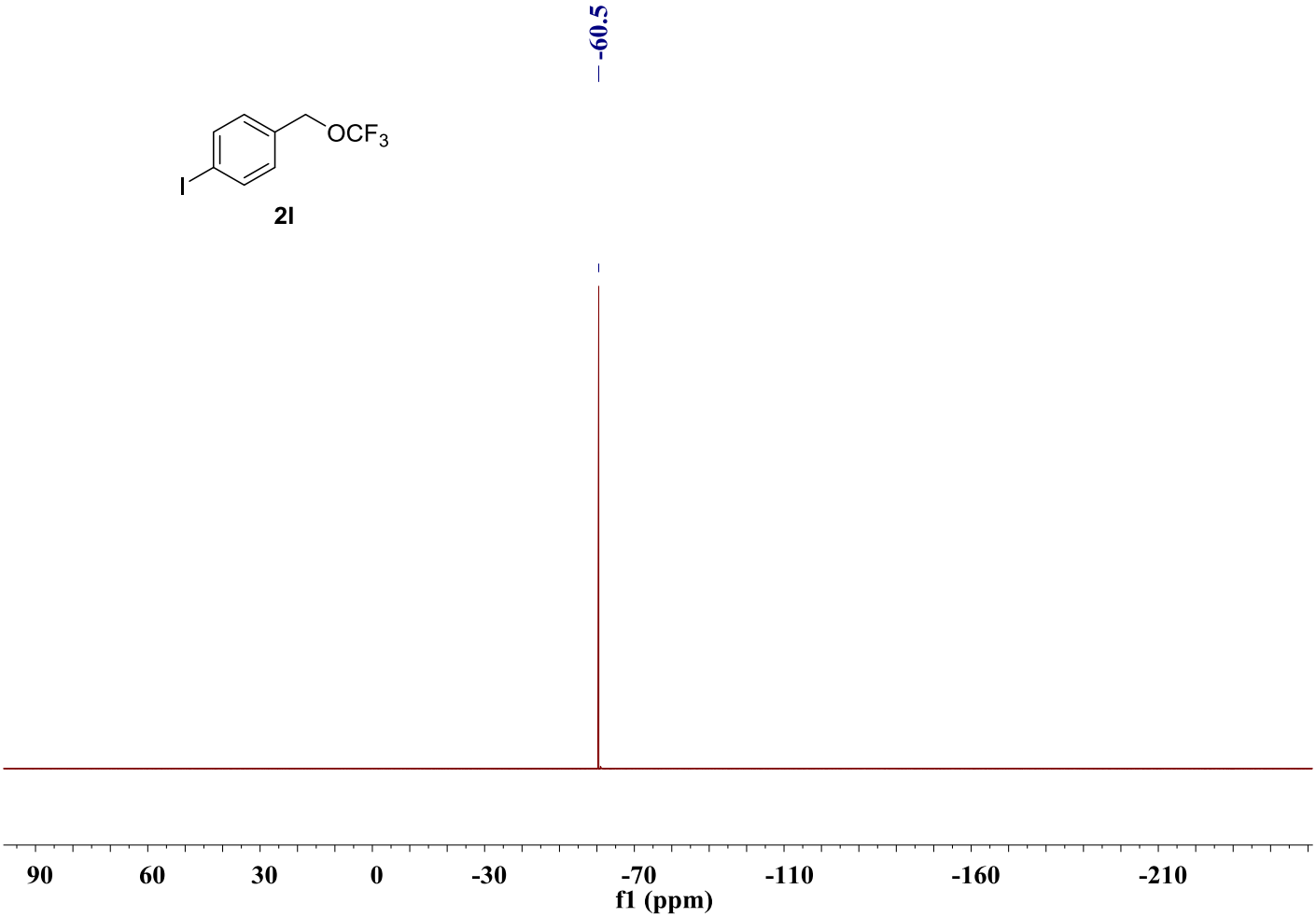

Figure S28. ^{19}F NMR spectrum of **2l**, Related to **Scheme 2**

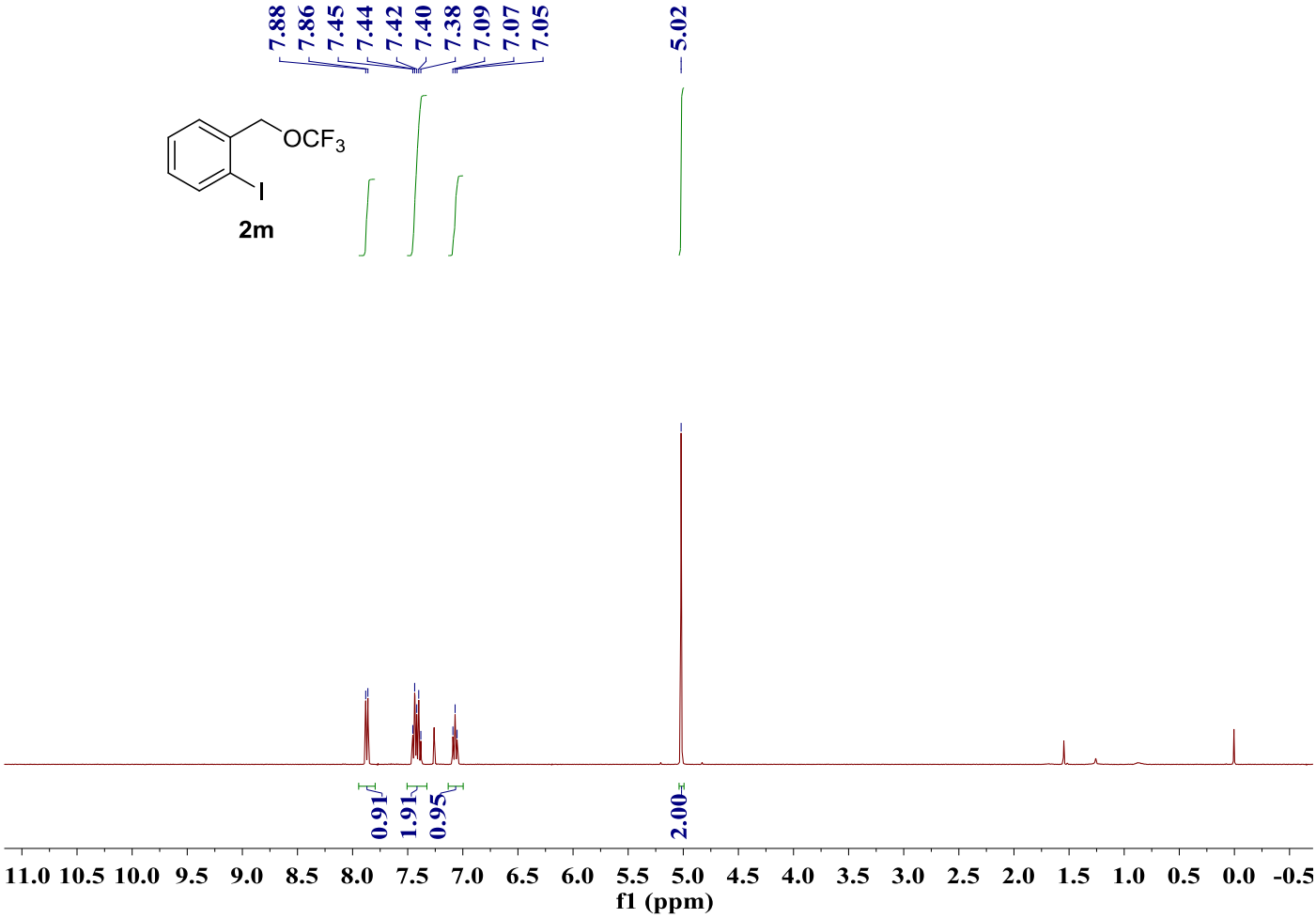

Figure S29. ^{1}H NMR spectrum of **2m**, Related to **Scheme 2**

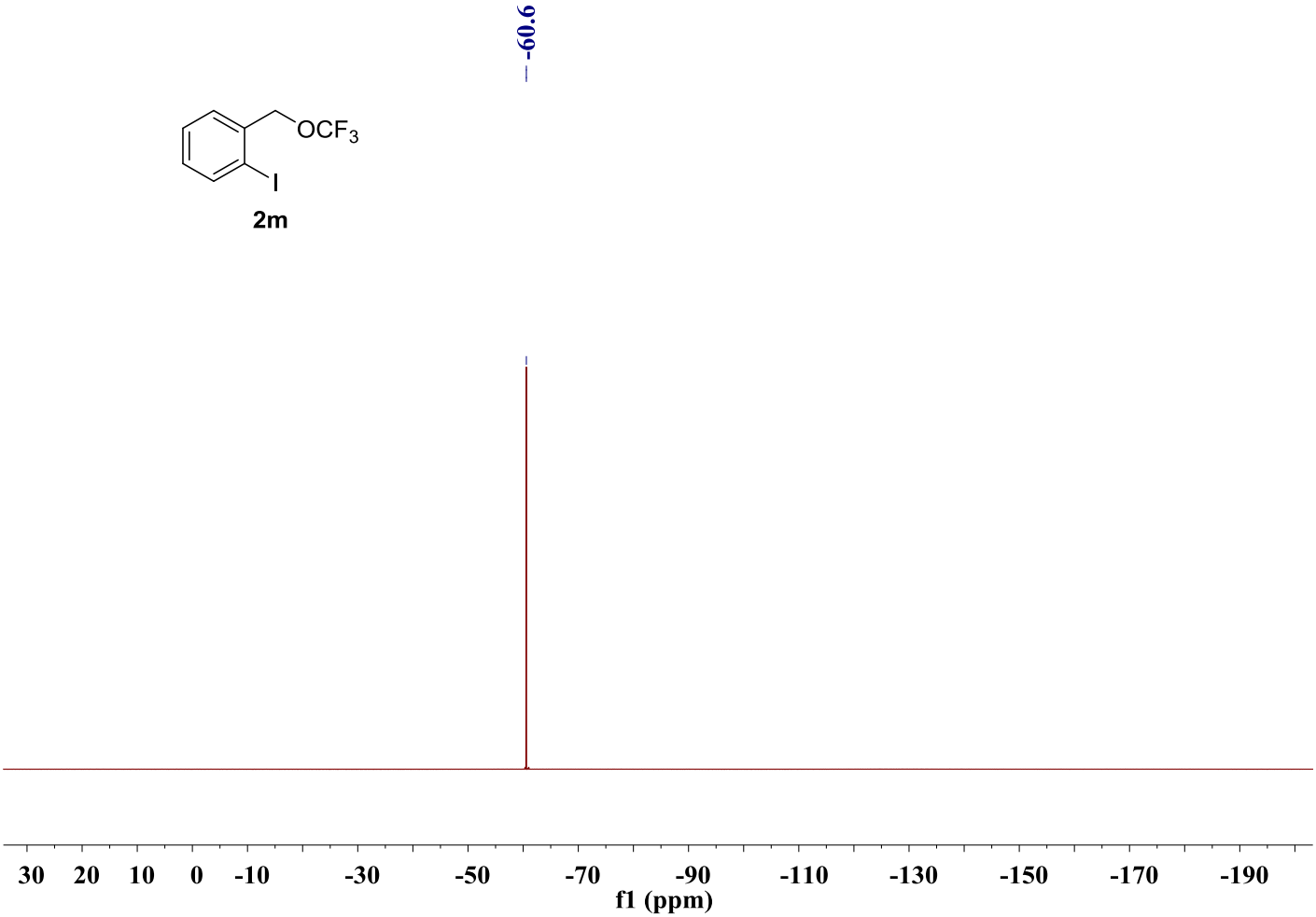

Figure S30. ^{19}F NMR spectrum of **2m**, Related to **Scheme 2**

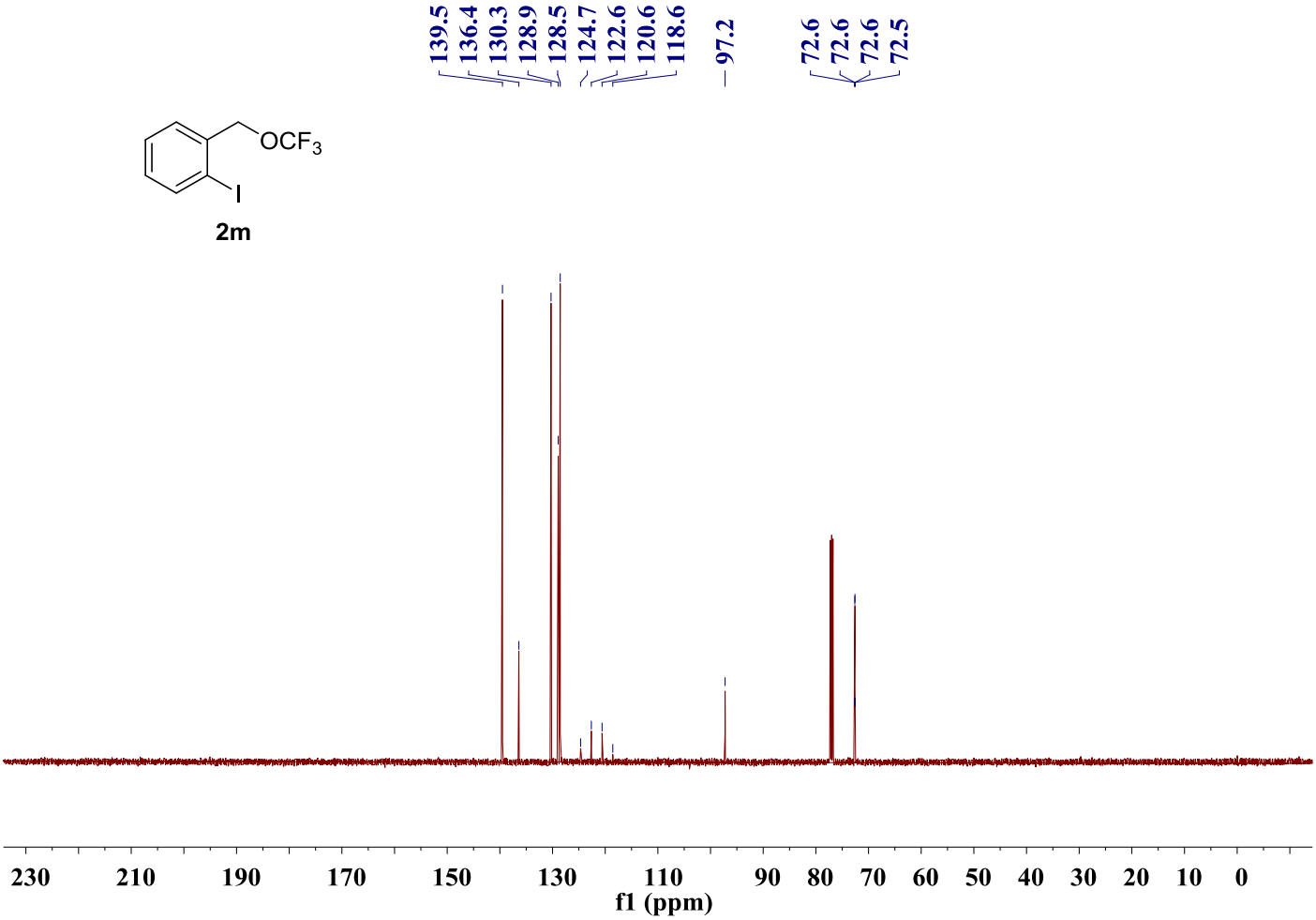

Figure S31. ^{13}C NMR spectrum of **2m**, Related to **Scheme 2**

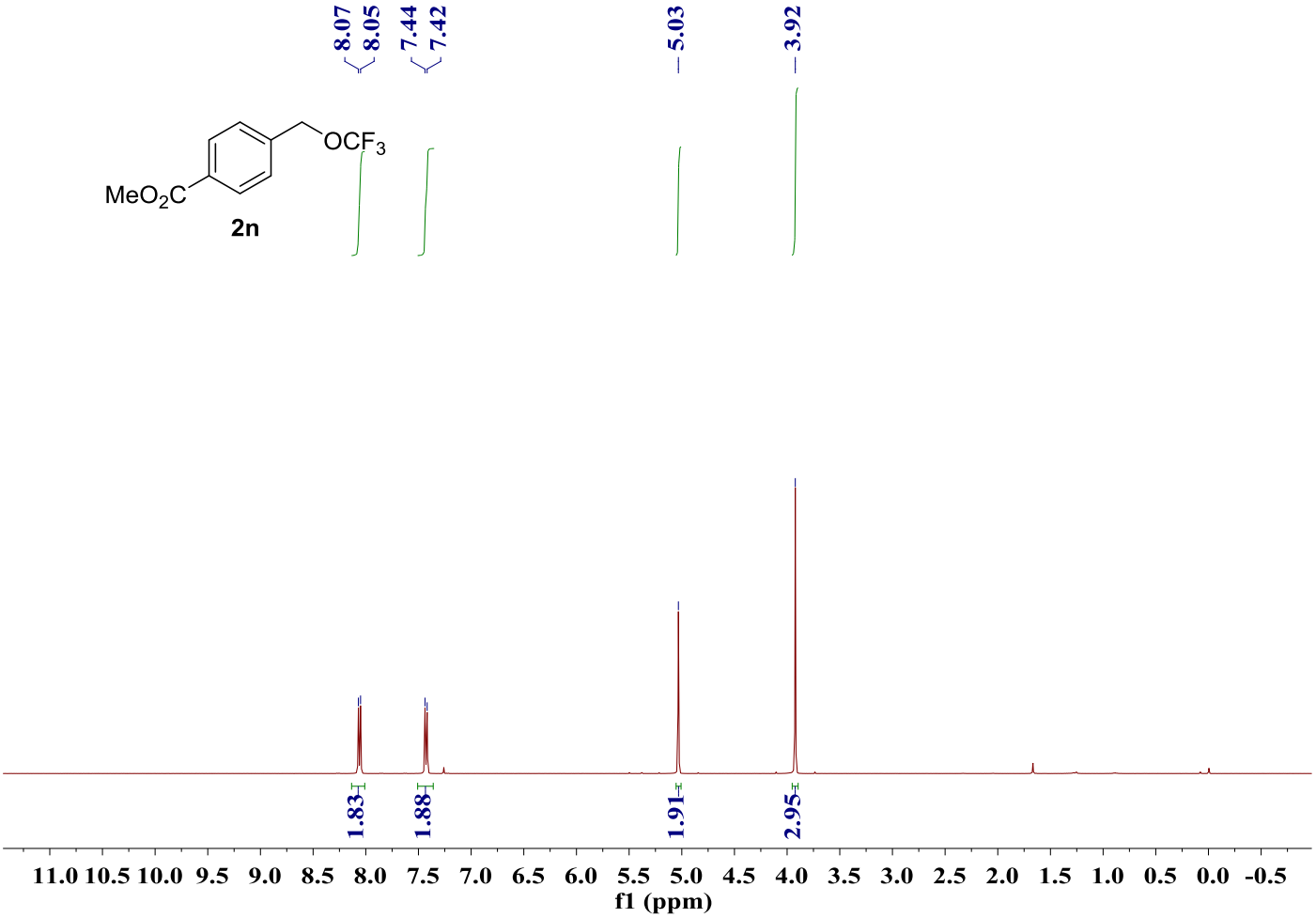

Figure S32. ^{1}H NMR spectrum of **2n**, Related to **Scheme 2**

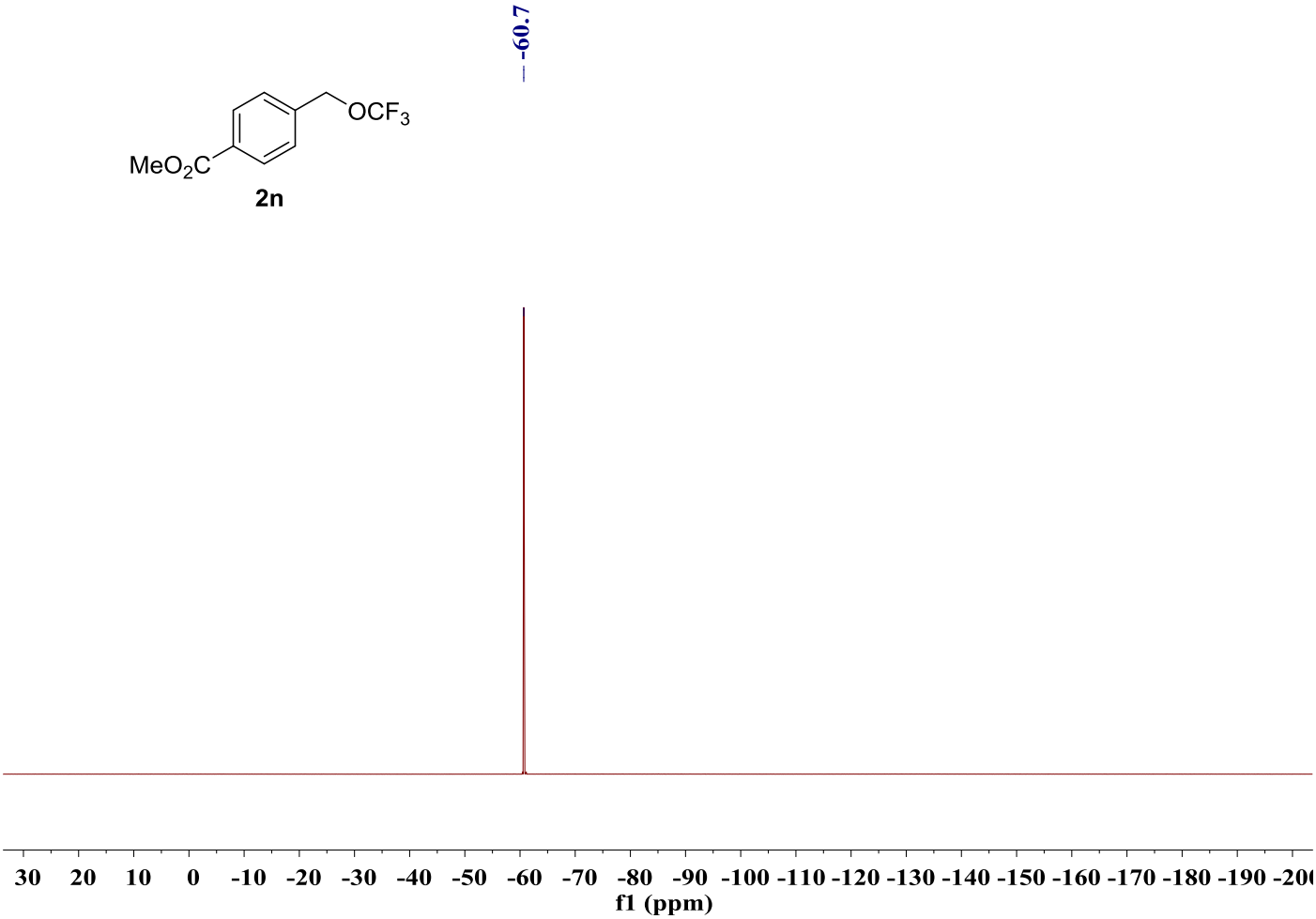

Figure S33. ^{19}F NMR spectrum of **2n**, Related to **Scheme 2**

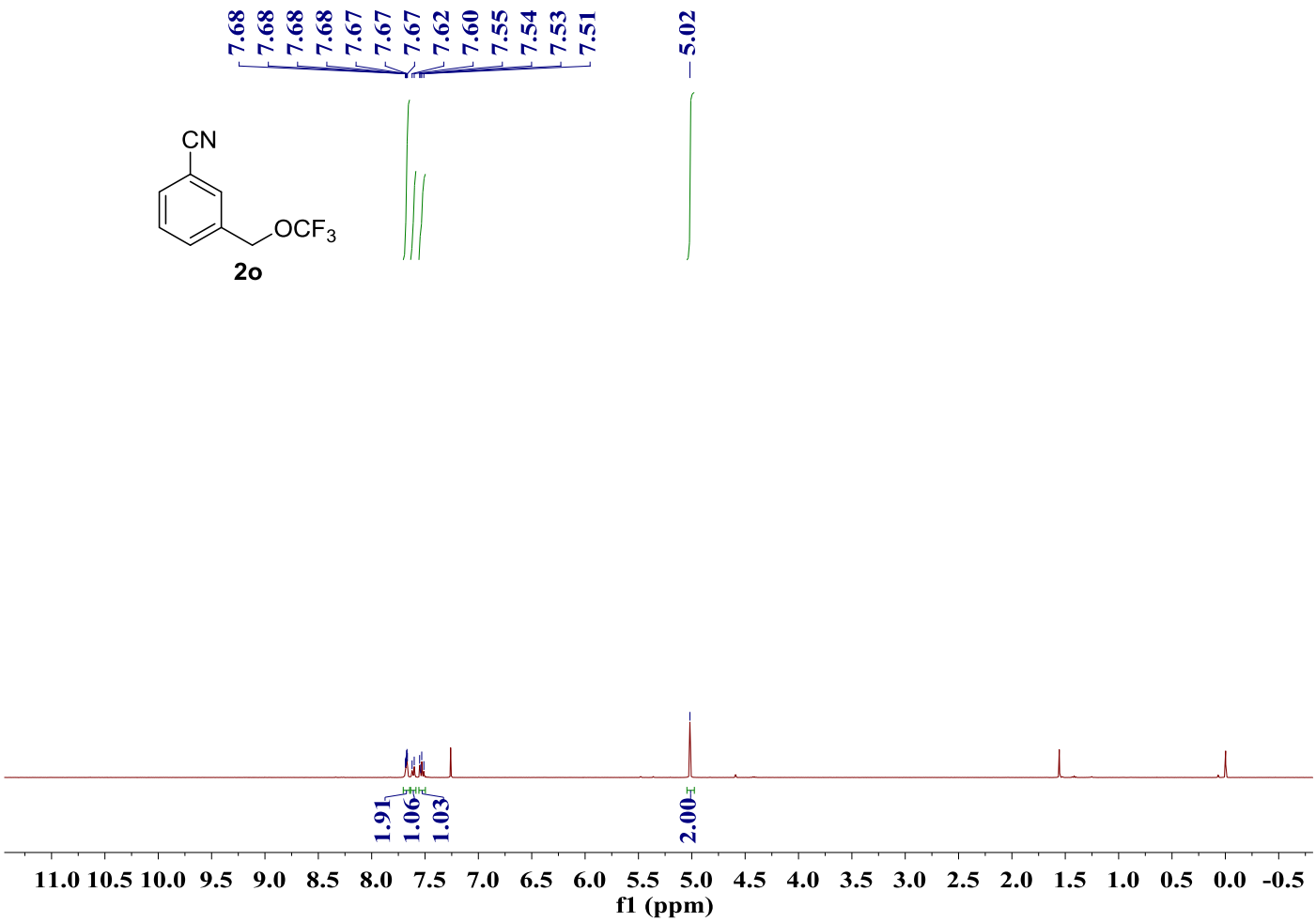

Figure S34. ^{1}H NMR spectrum of **2o**, Related to **Scheme 2**

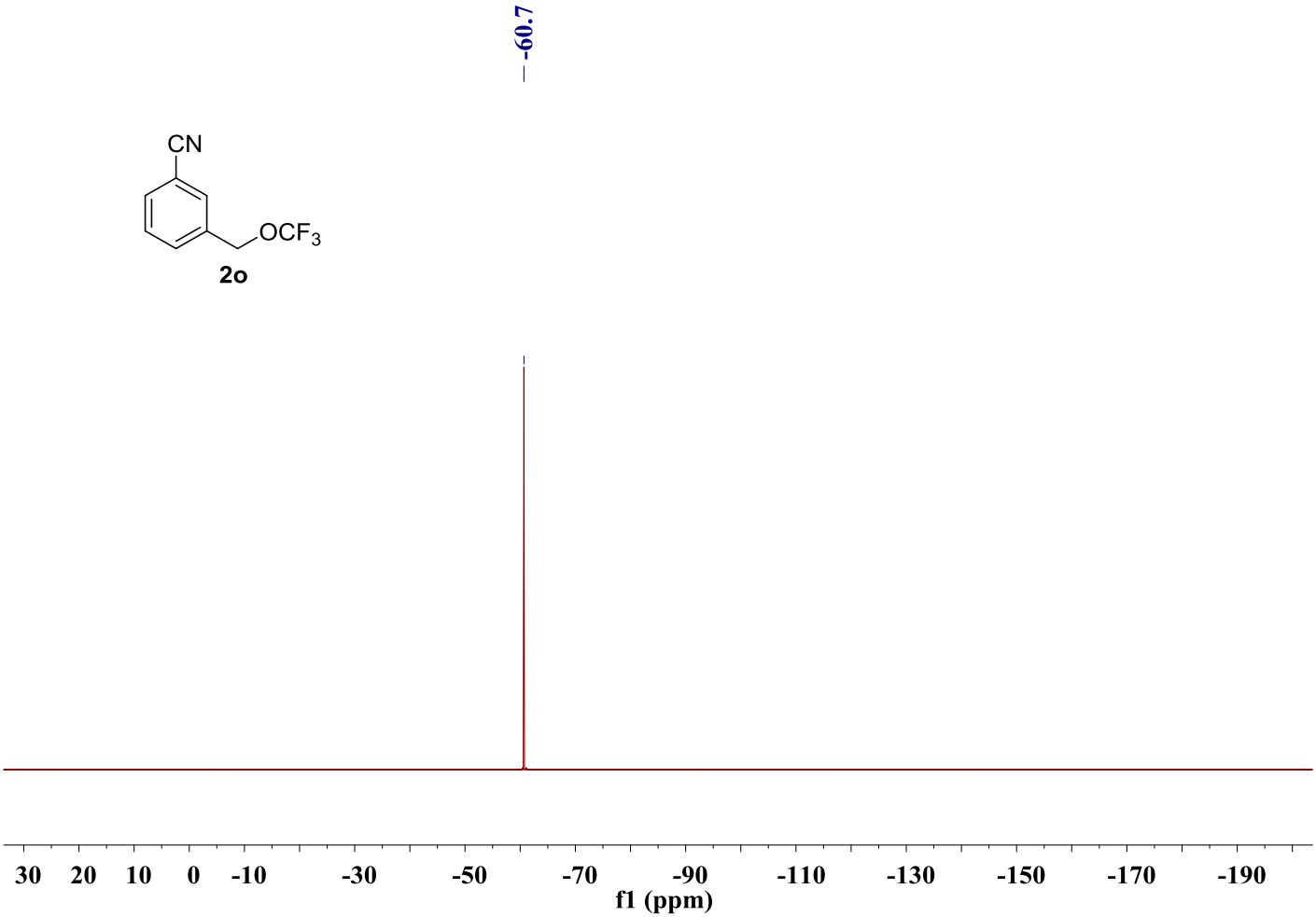

Figure S35. ^{19}F NMR spectrum of **2o**, Related to **Scheme 2**

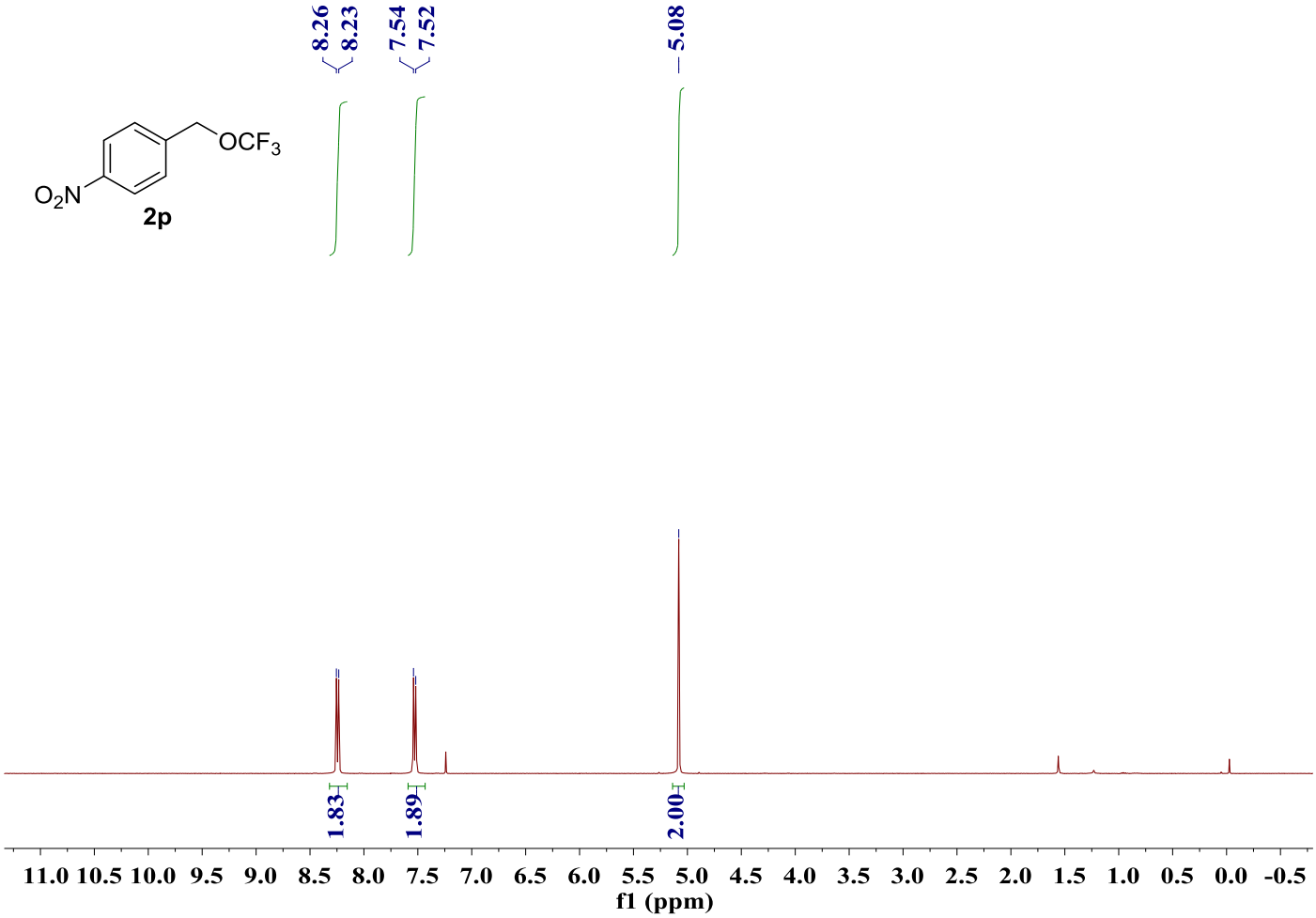

Figure S36. ^{1}H NMR spectrum of **2p**, Related to **Scheme 2**

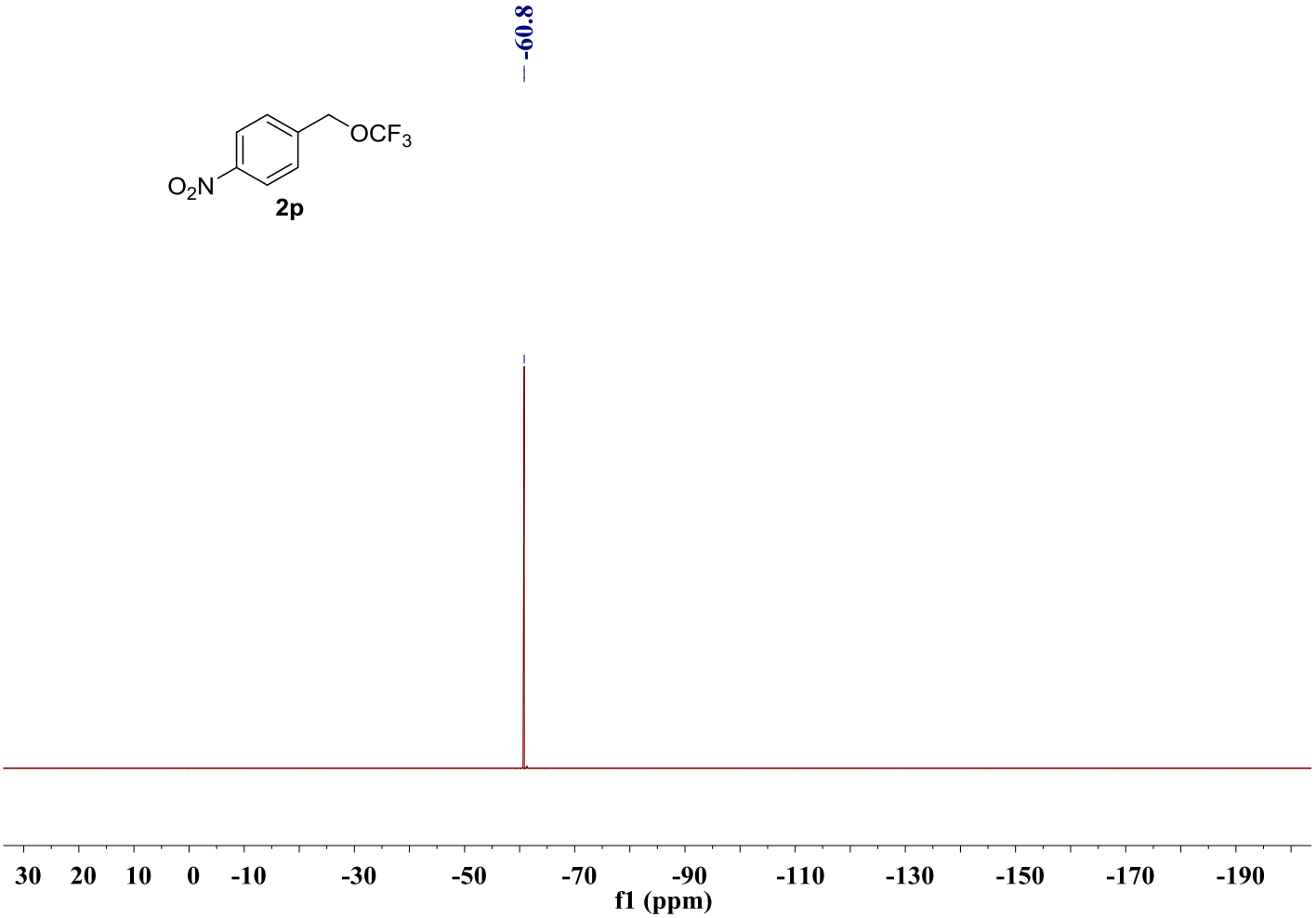

Figure S37. ^{19}F NMR spectrum of **2p**, Related to **Scheme 2**

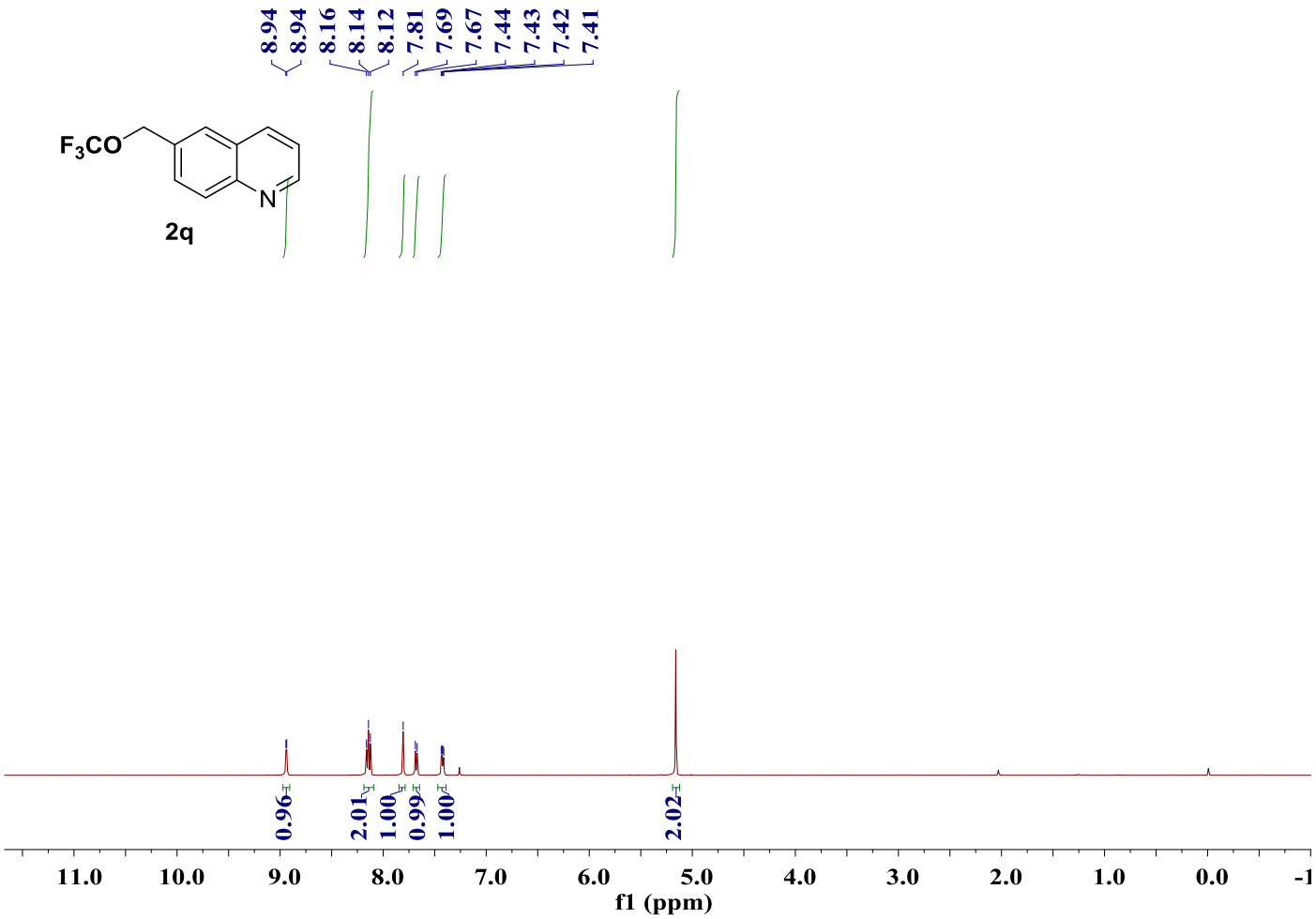

Figure S38. ^{1}H NMR spectrum of **2q**, Related to **Scheme 2**

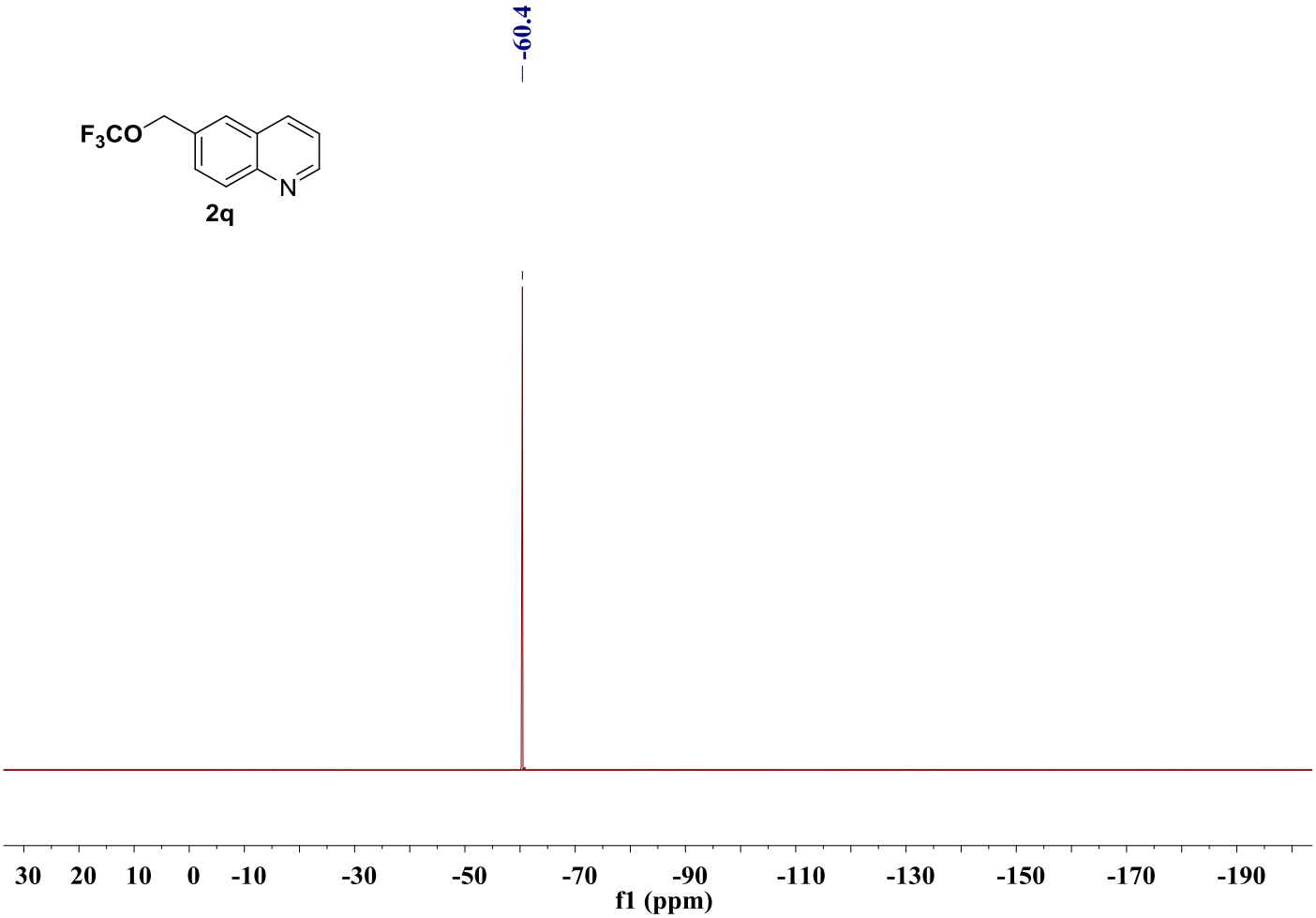

Figure S39. ^{19}F NMR spectrum of **2q**, Related to **Scheme 2**

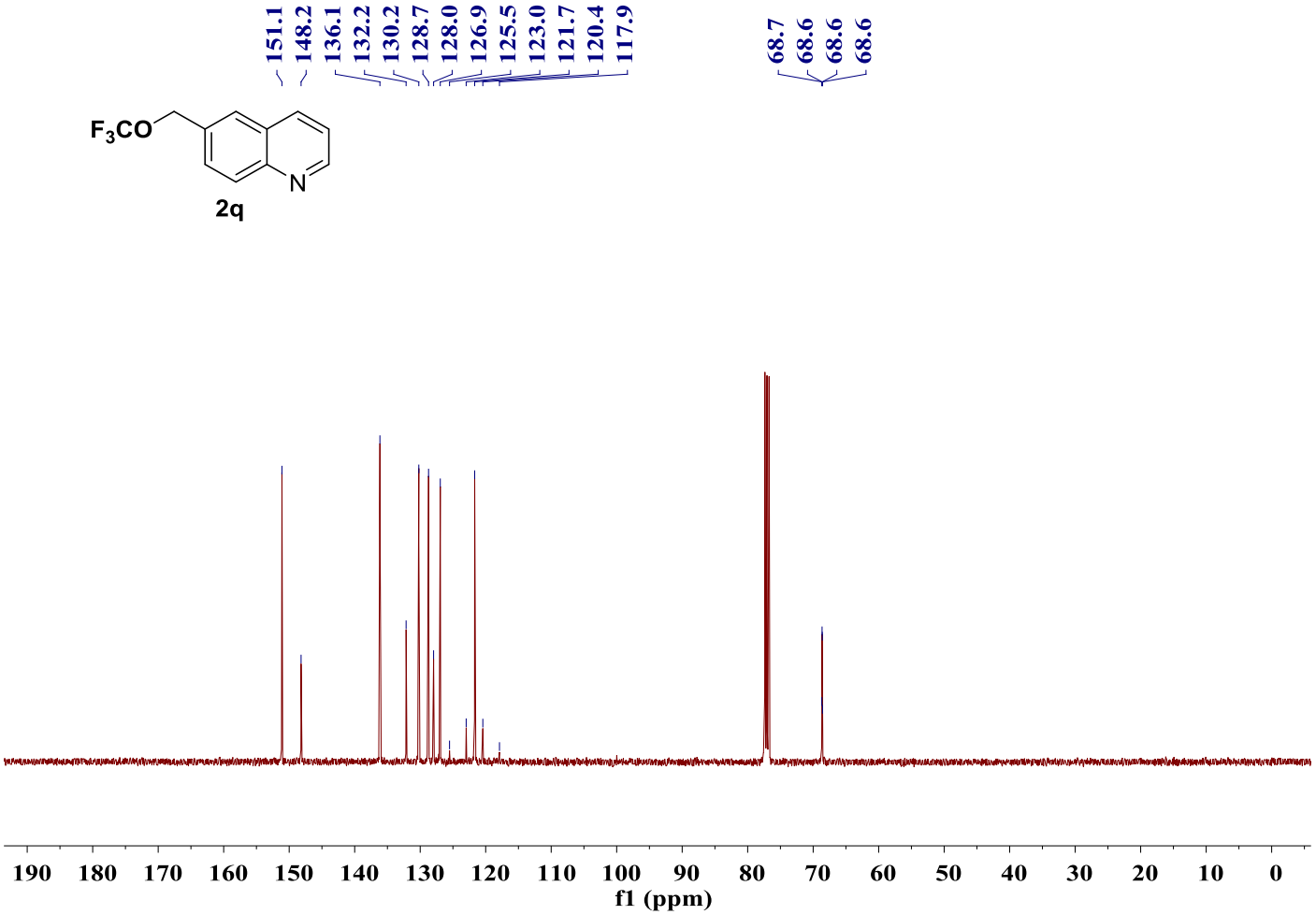

Figure S40. ^{13}C NMR spectrum of **2q**, Related to **Scheme 2**

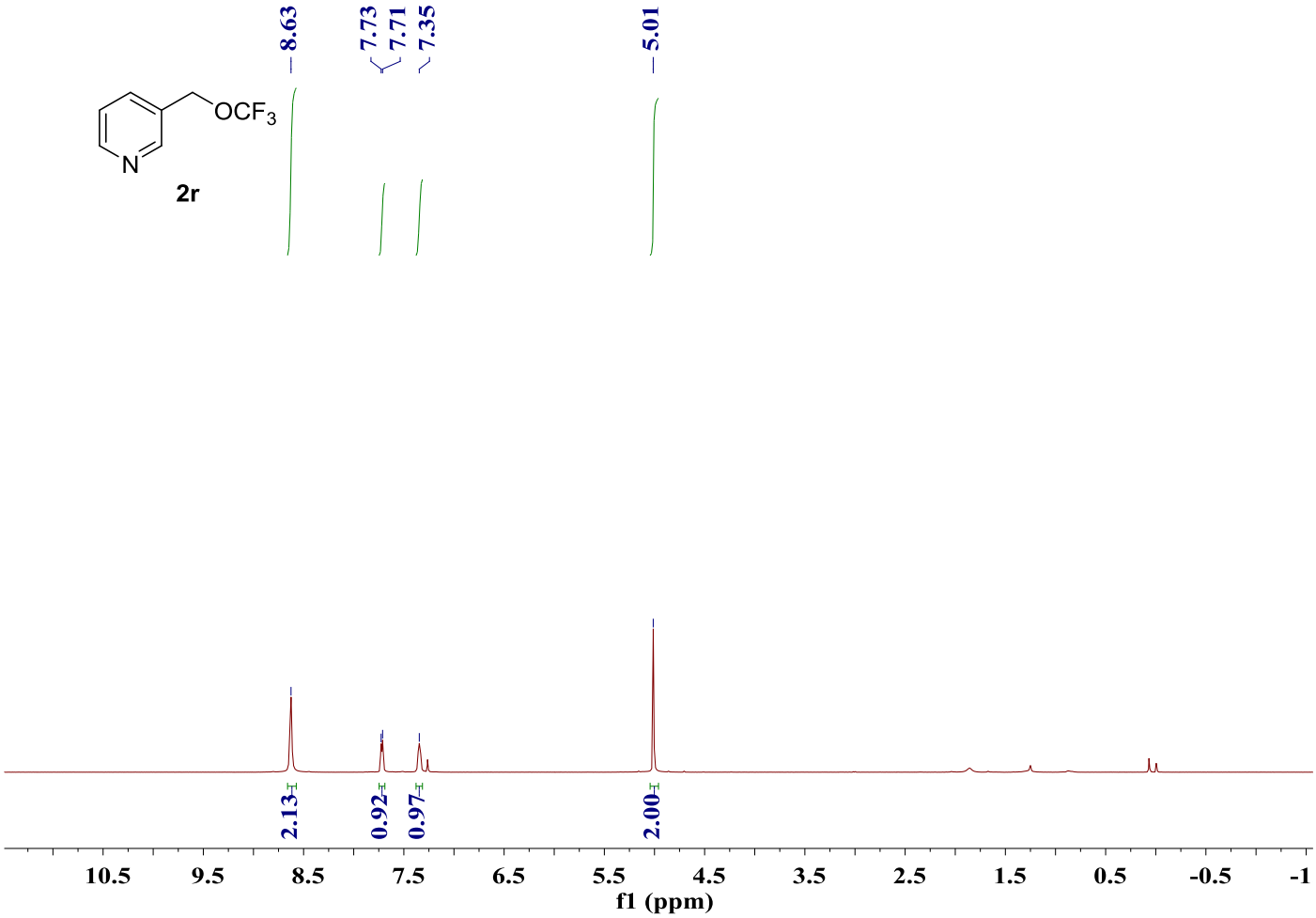

Figure S41. ^{1}H NMR spectrum of **2r**, Related to **Scheme 2**

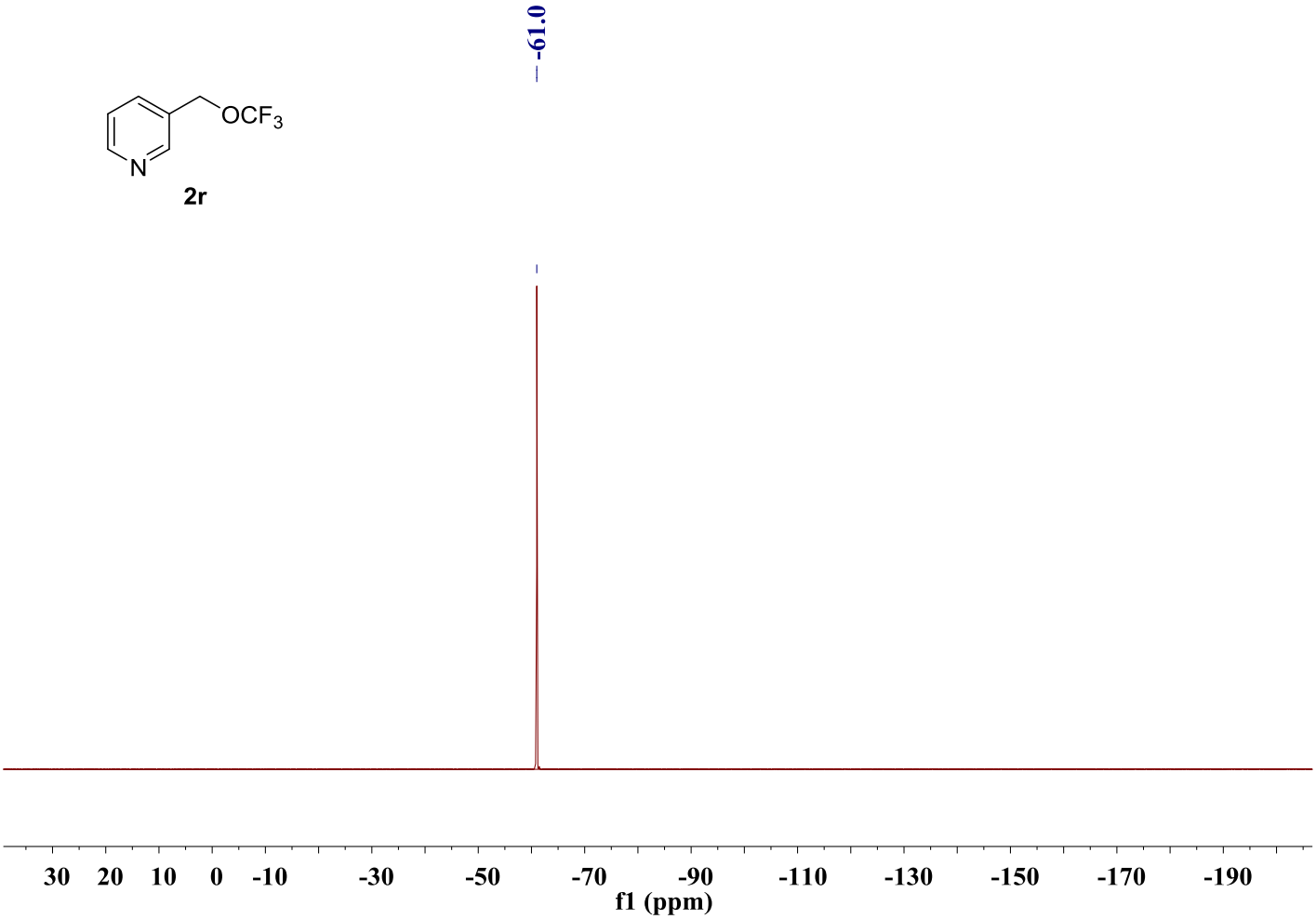

Figure S42. ^{19}F NMR spectrum of **2r**, Related to **Scheme 2**

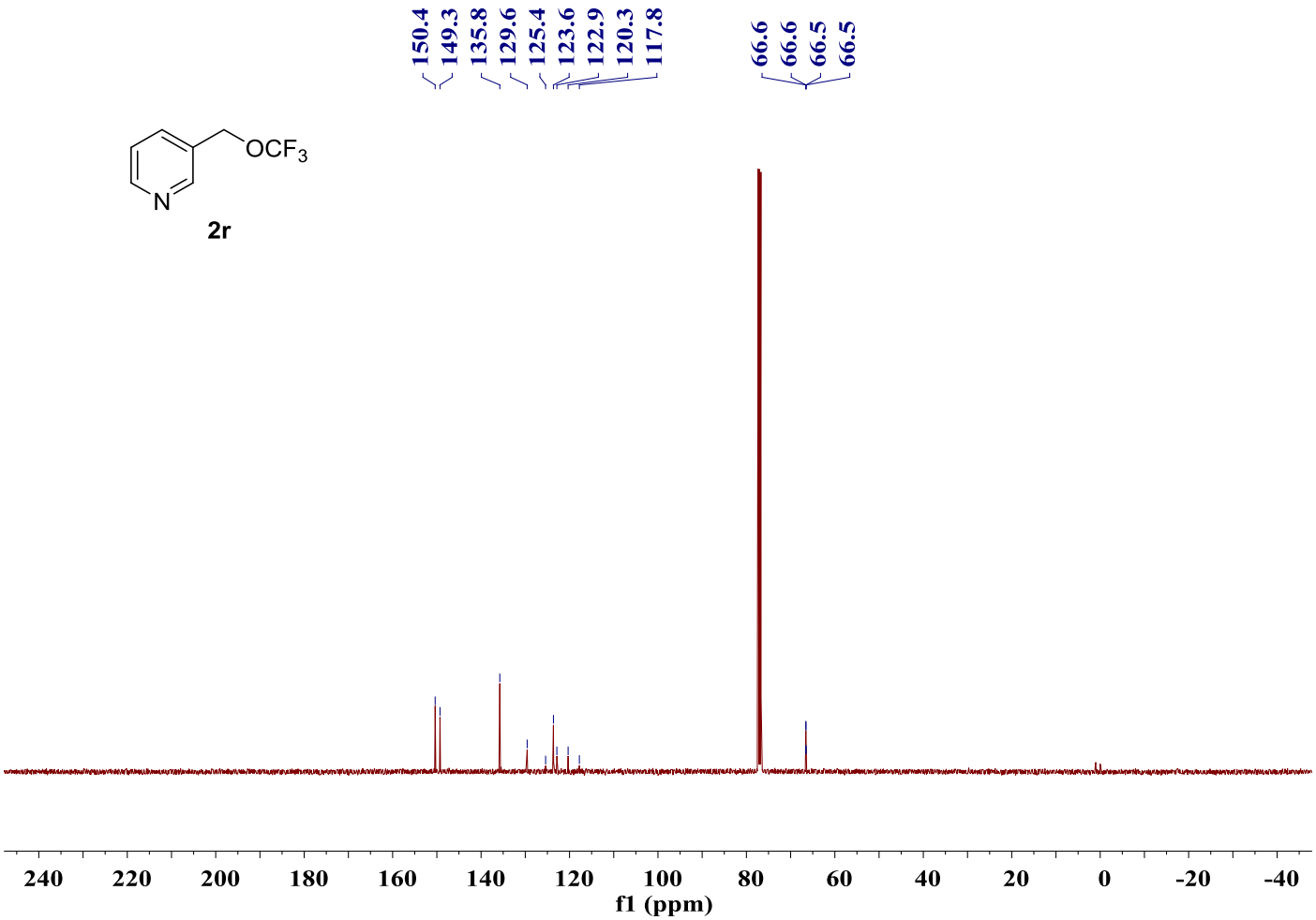

Figure S43. ^{13}C NMR spectrum of **2r**, Related to **Scheme 2**

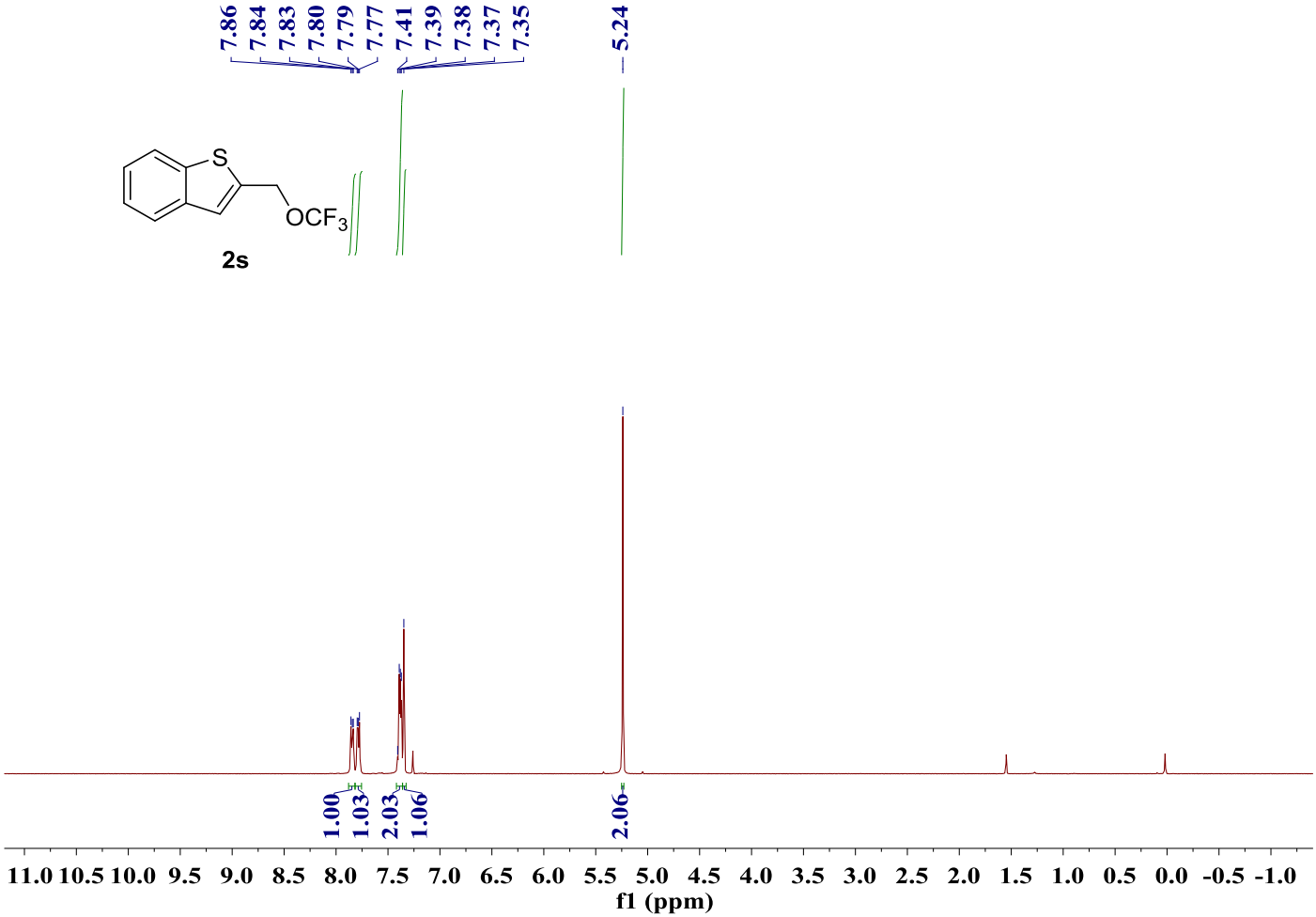

Figure S44. ^{1}H NMR spectrum of **2s**, Related to **Scheme 2**

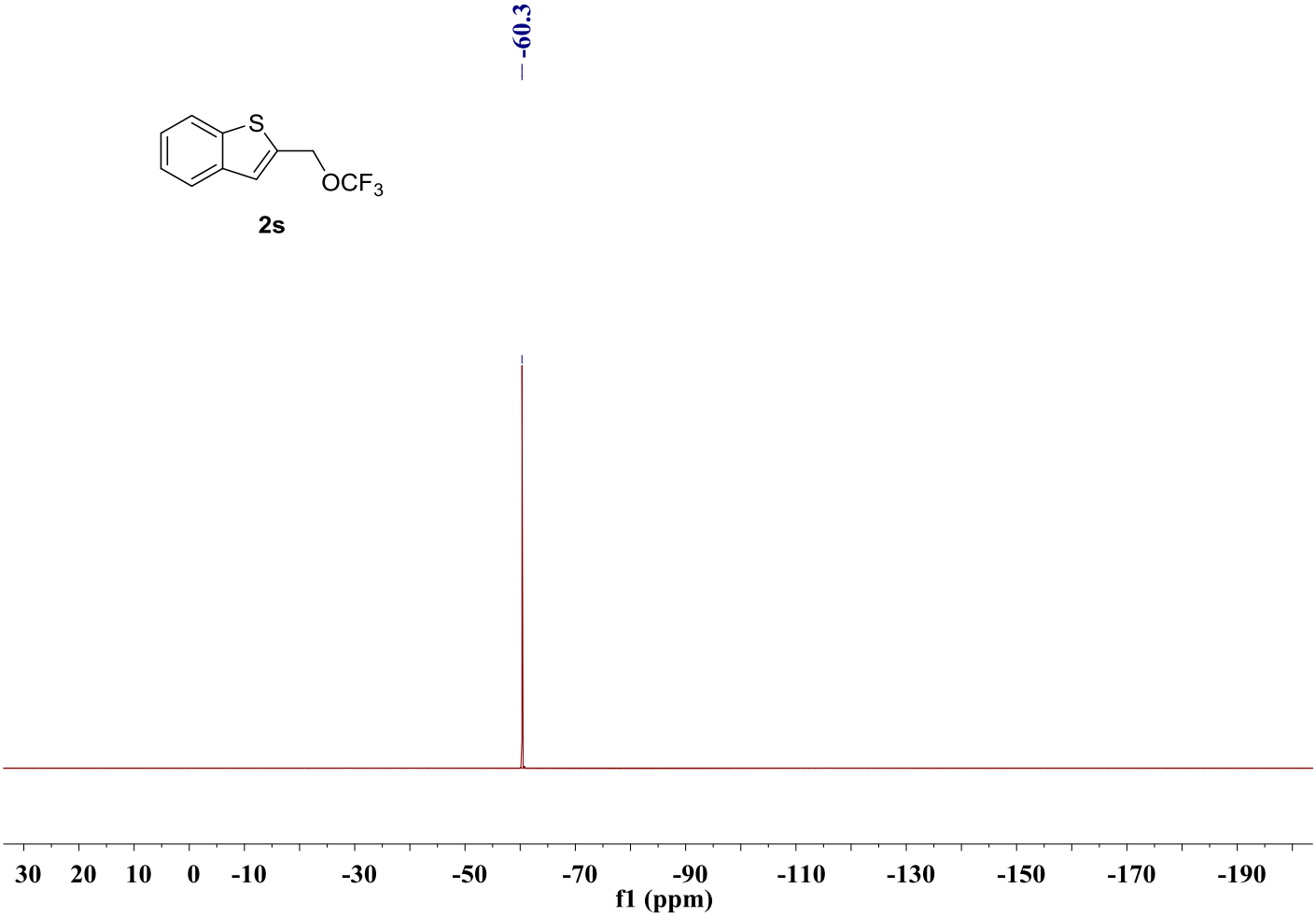

Figure S45. ^{19}F NMR spectrum of **2s**, Related to **Scheme 2**

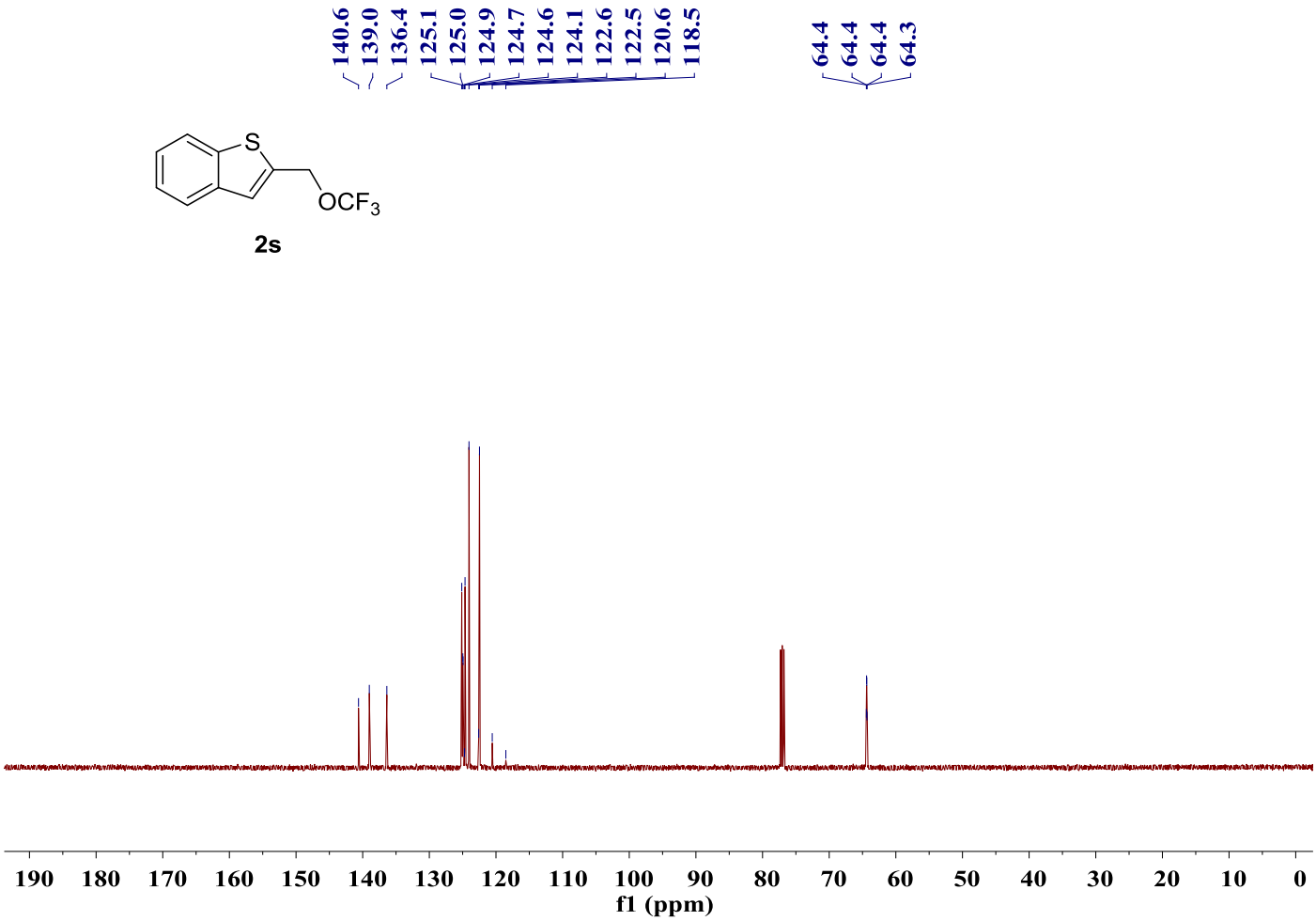

Figure S46. ^{13}C NMR spectrum of **2s**, Related to **Scheme 2**

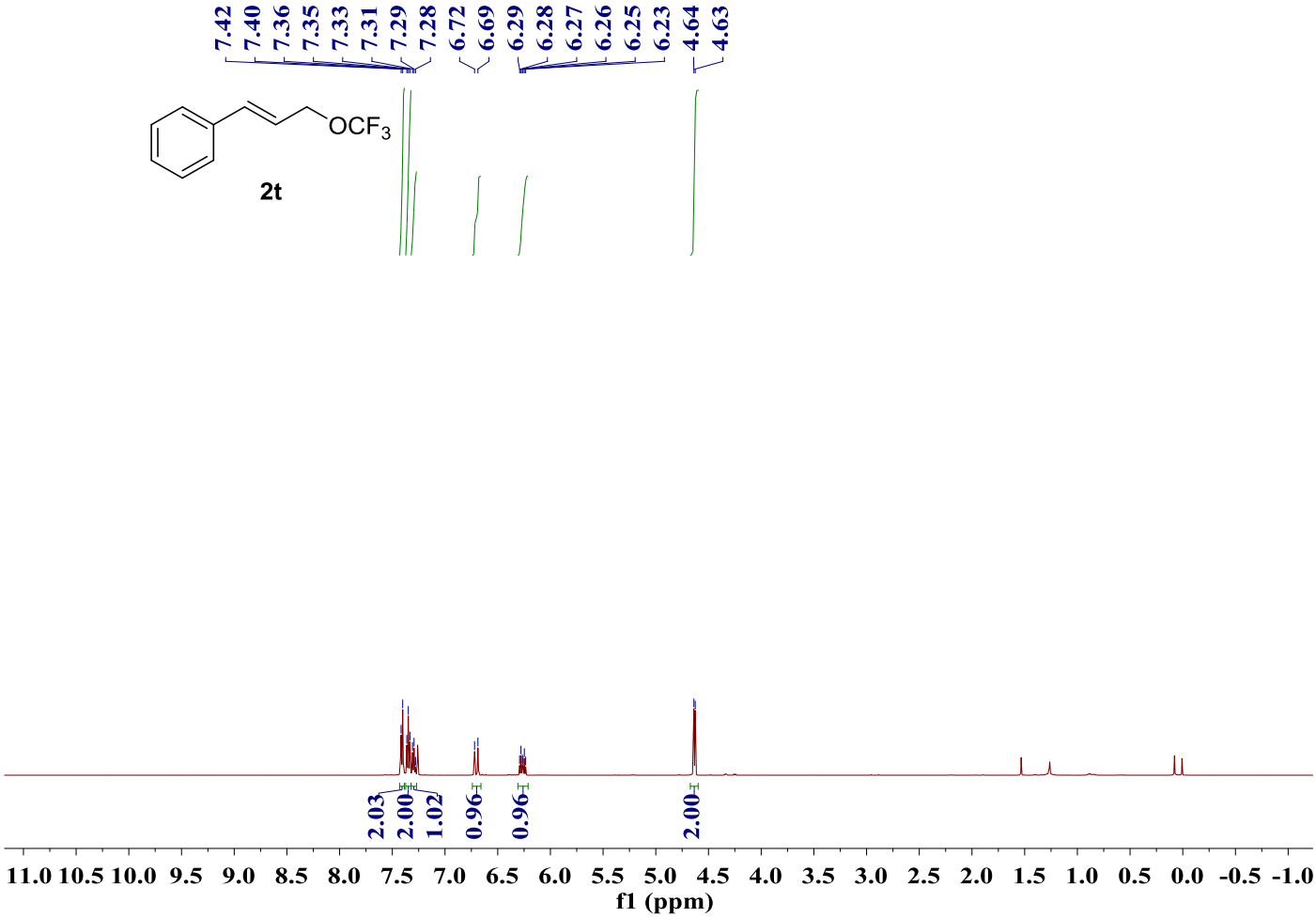

Figure S47. ^{1}H NMR spectrum of **2t**, Related to **Scheme 2**

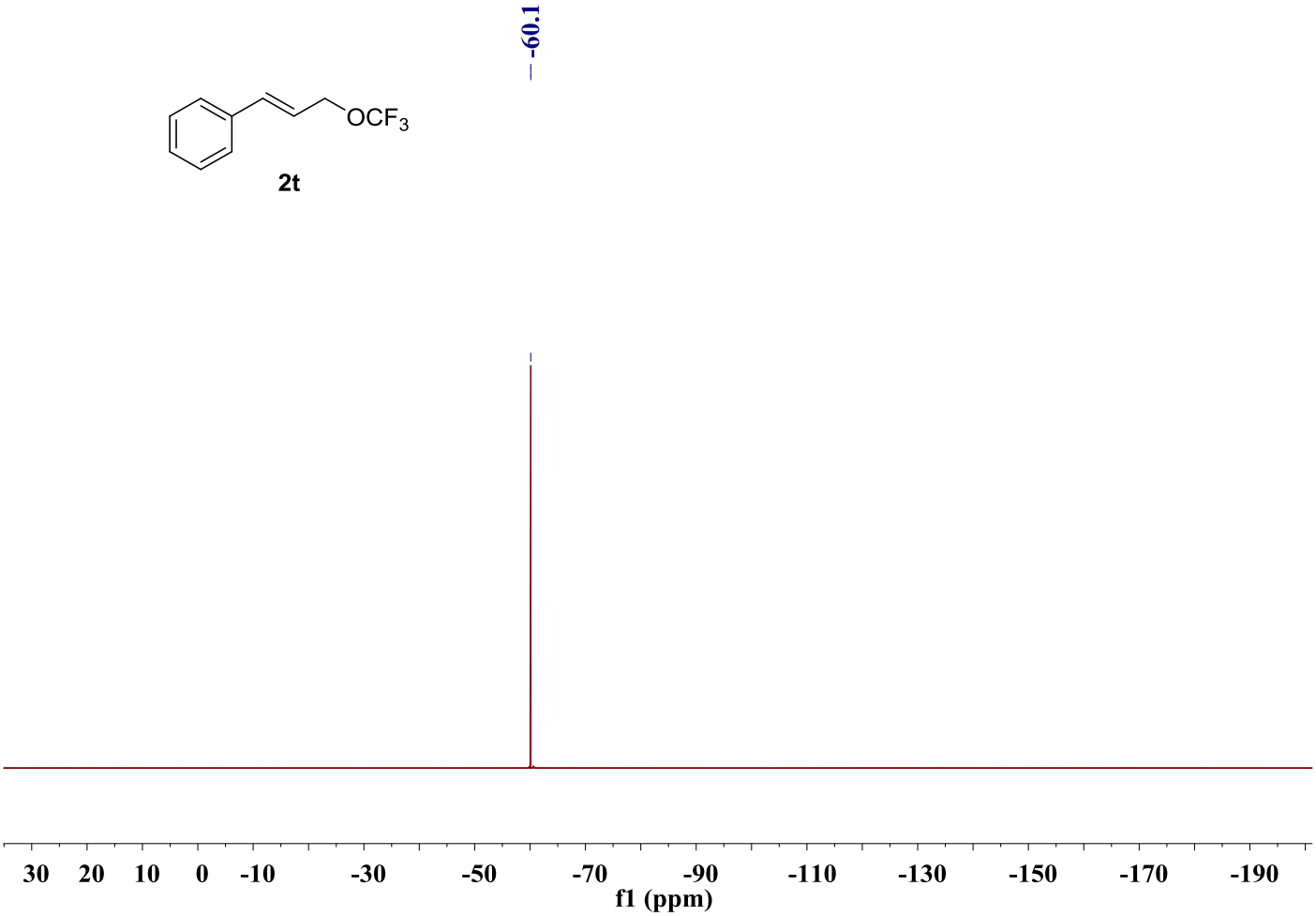

Figure S48. ^{19}F NMR spectrum of **2t**, Related to **Scheme 2**

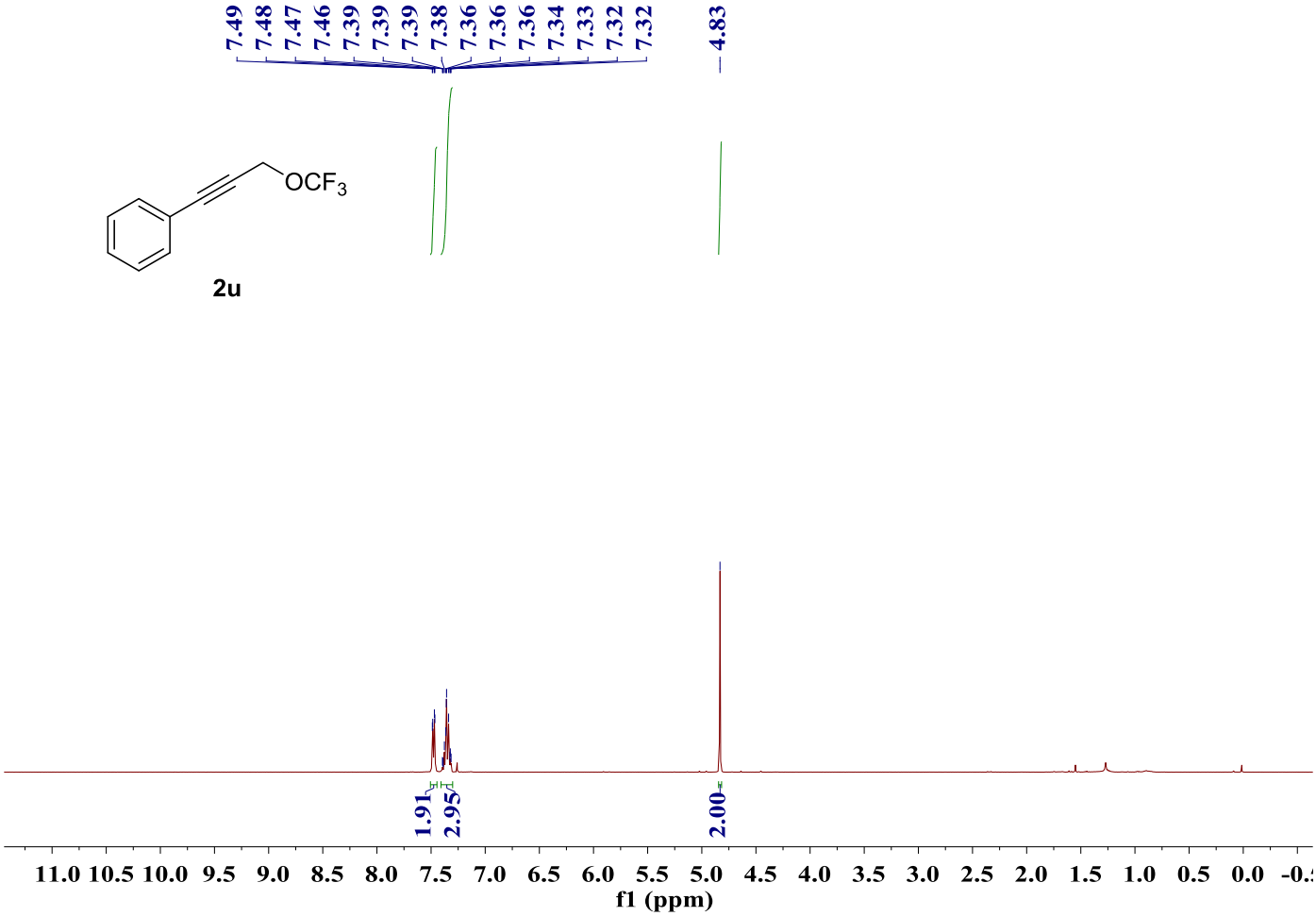

Figure S49. ^{1}H NMR spectrum of **2u**, Related to **Scheme 2**

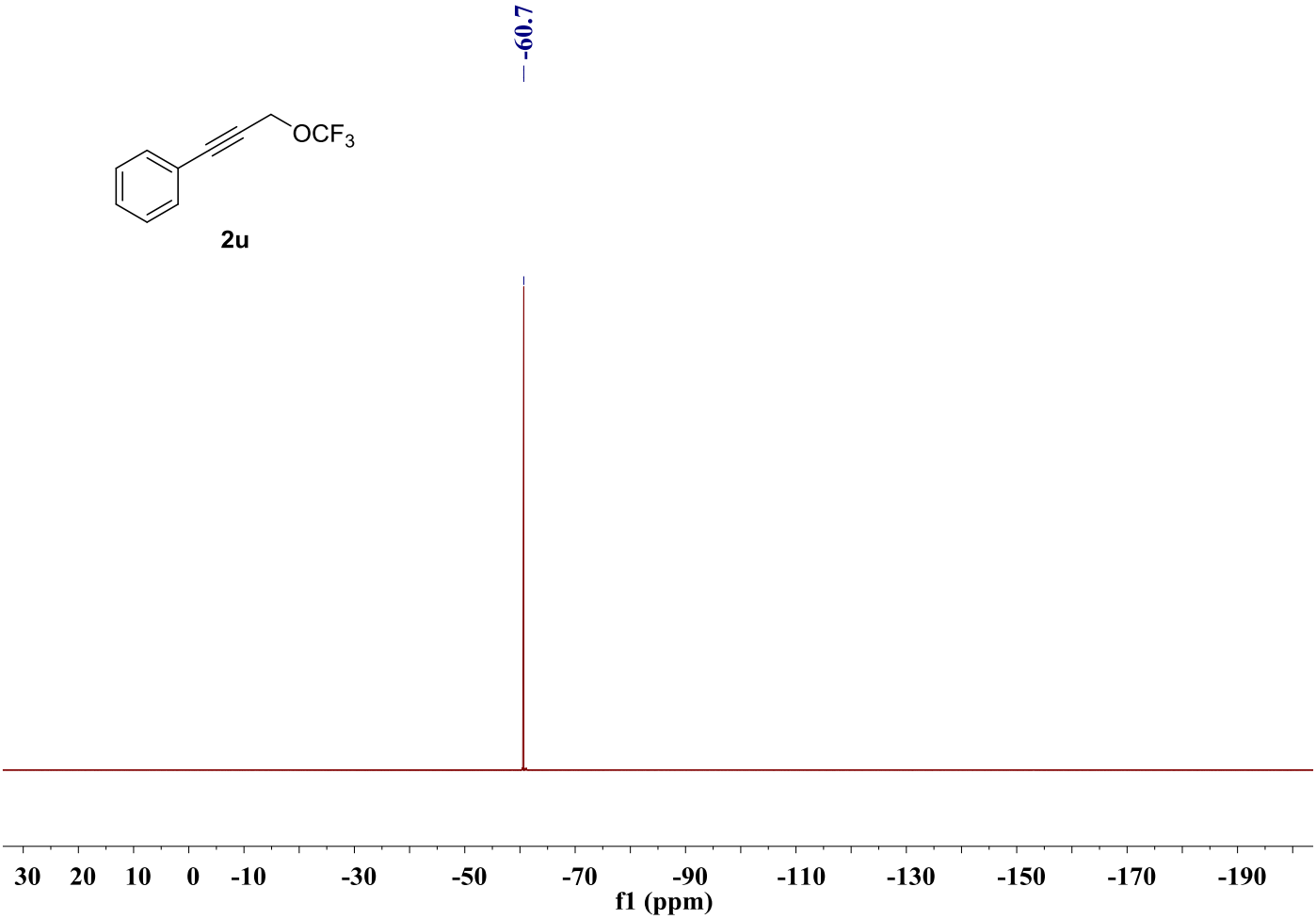

Figure S50. ^{19}F NMR spectrum of **2u**, Related to **Scheme 2**

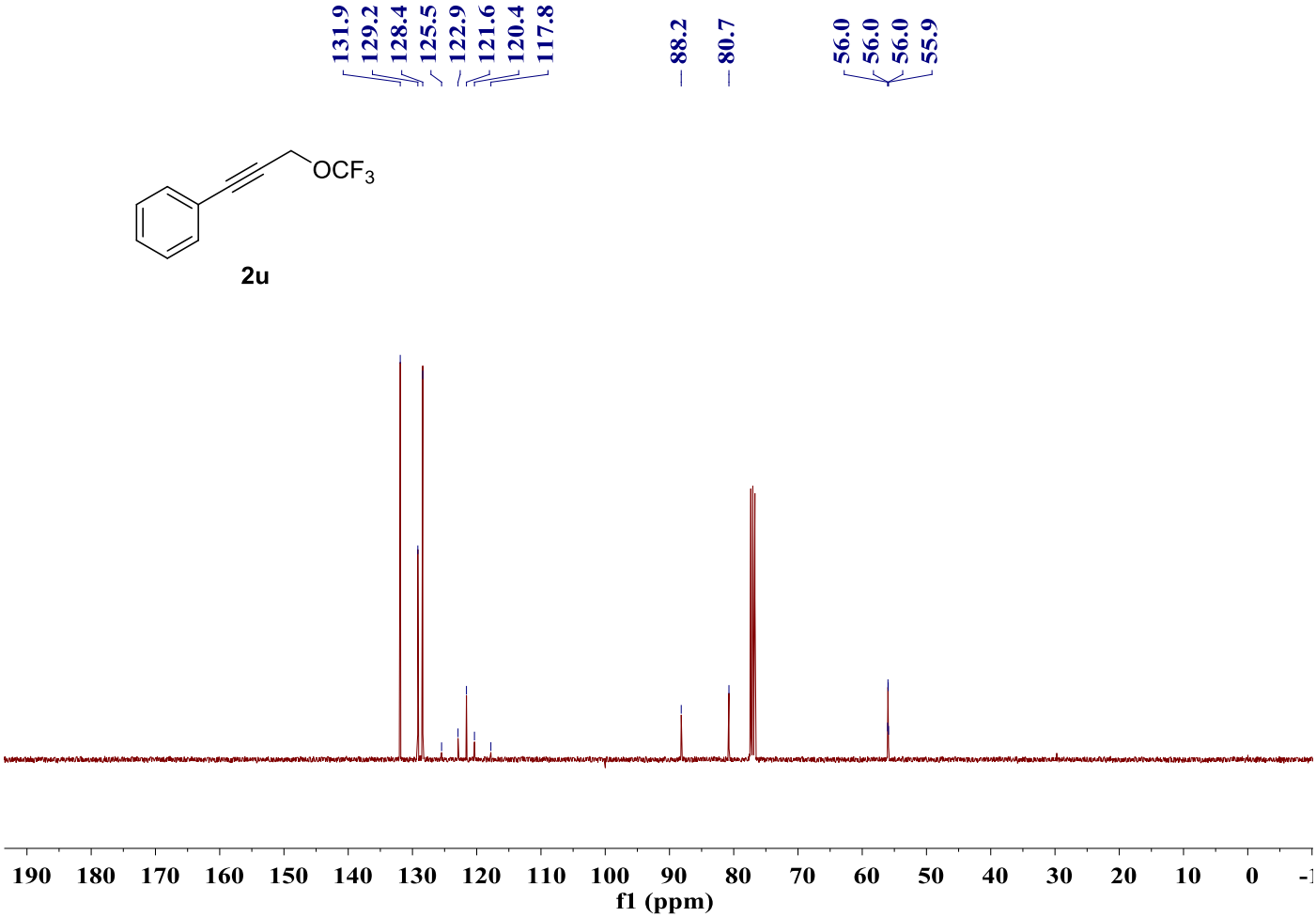

Figure S51. ^{13}C NMR spectrum of **2u**, Related to **Scheme 2**

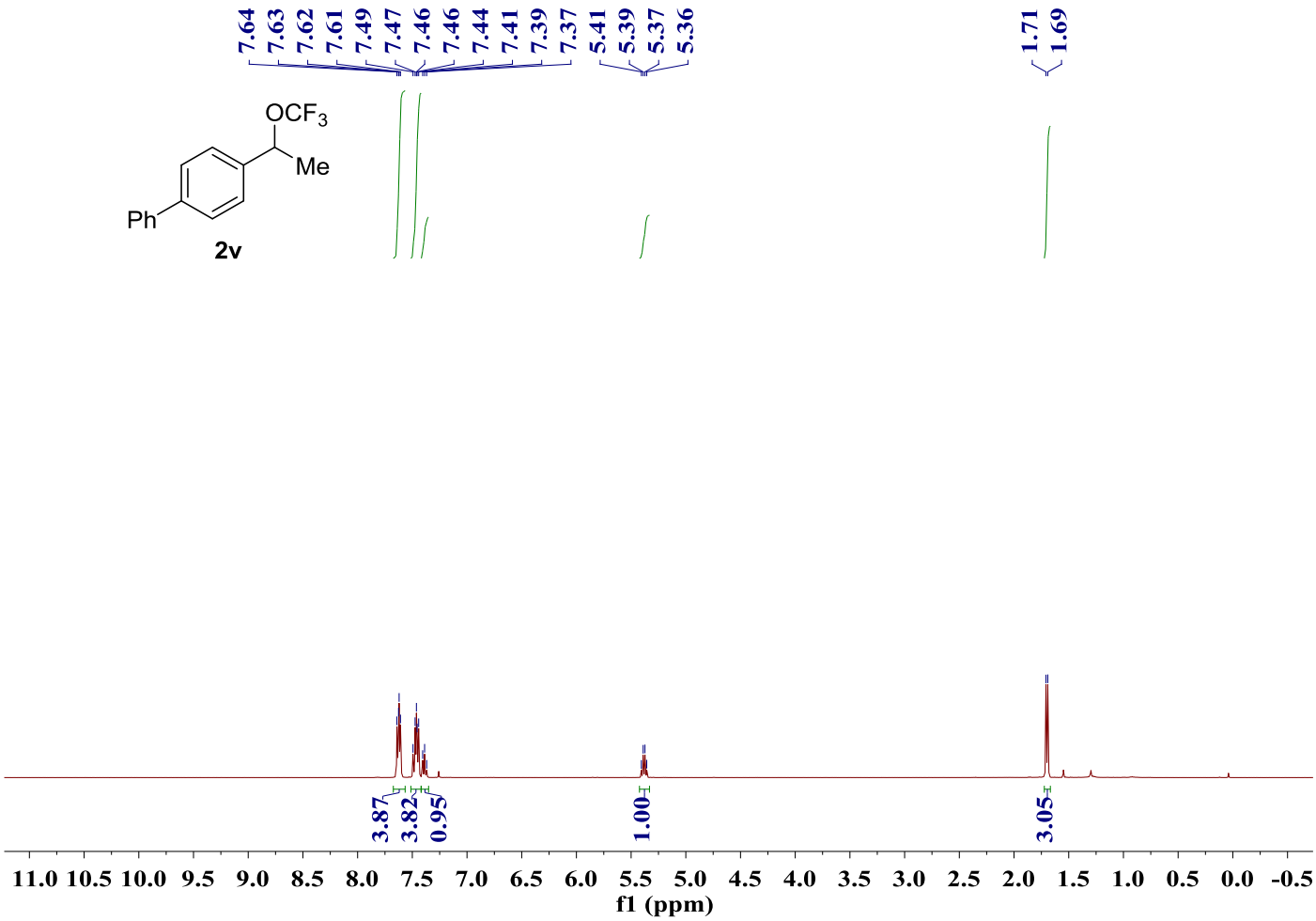

Figure S52. ^{1}H NMR spectrum of **2v**, Related to **Scheme 2**

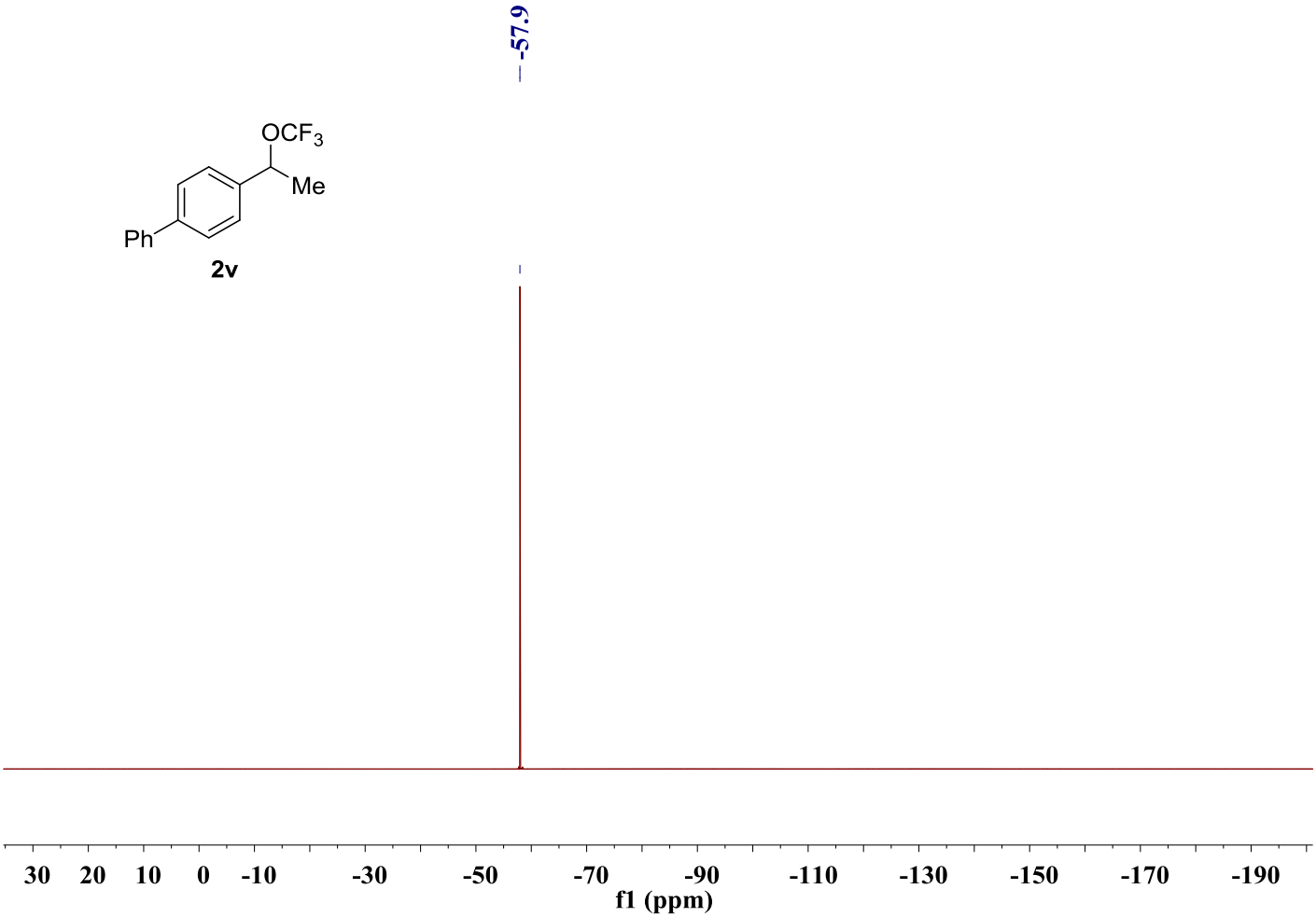

Figure S53. ^{19}F NMR spectrum of **2v**, Related to **Scheme 2**

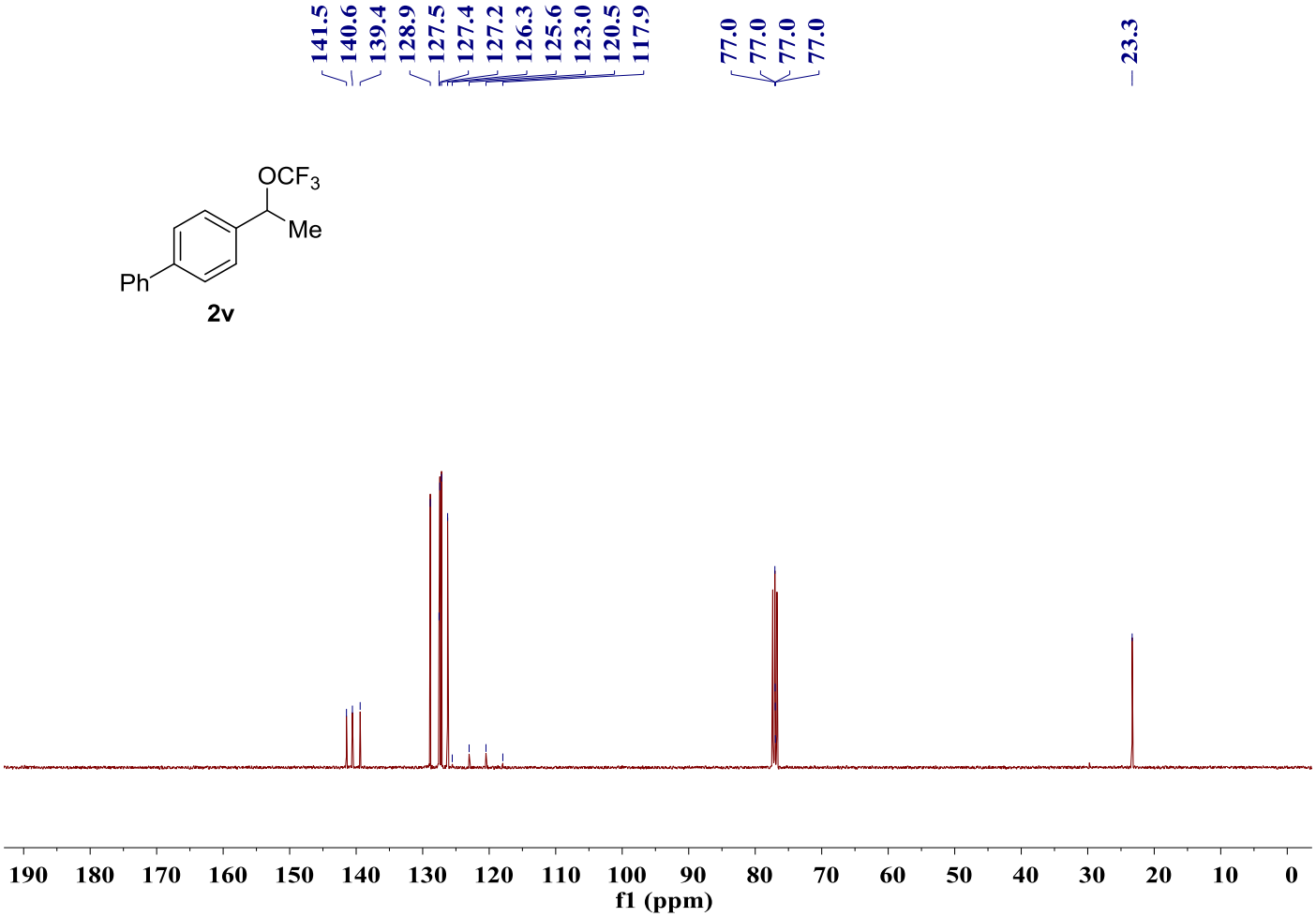

Figure S54. ^{13}C NMR spectrum of **2v**, Related to **Scheme 2**

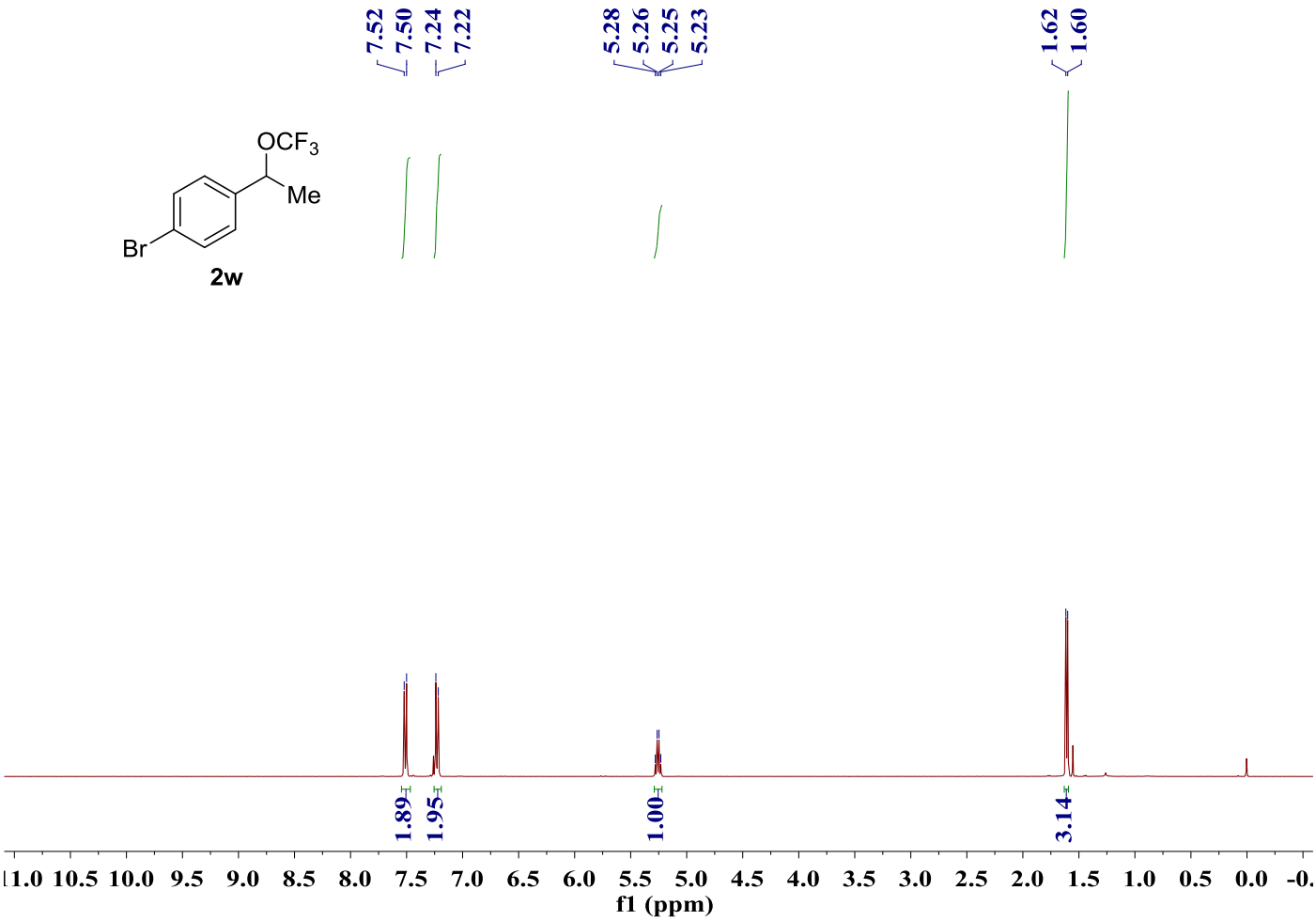

Figure S55. ^{1}H NMR spectrum of **2w**, Related to **Scheme 2**

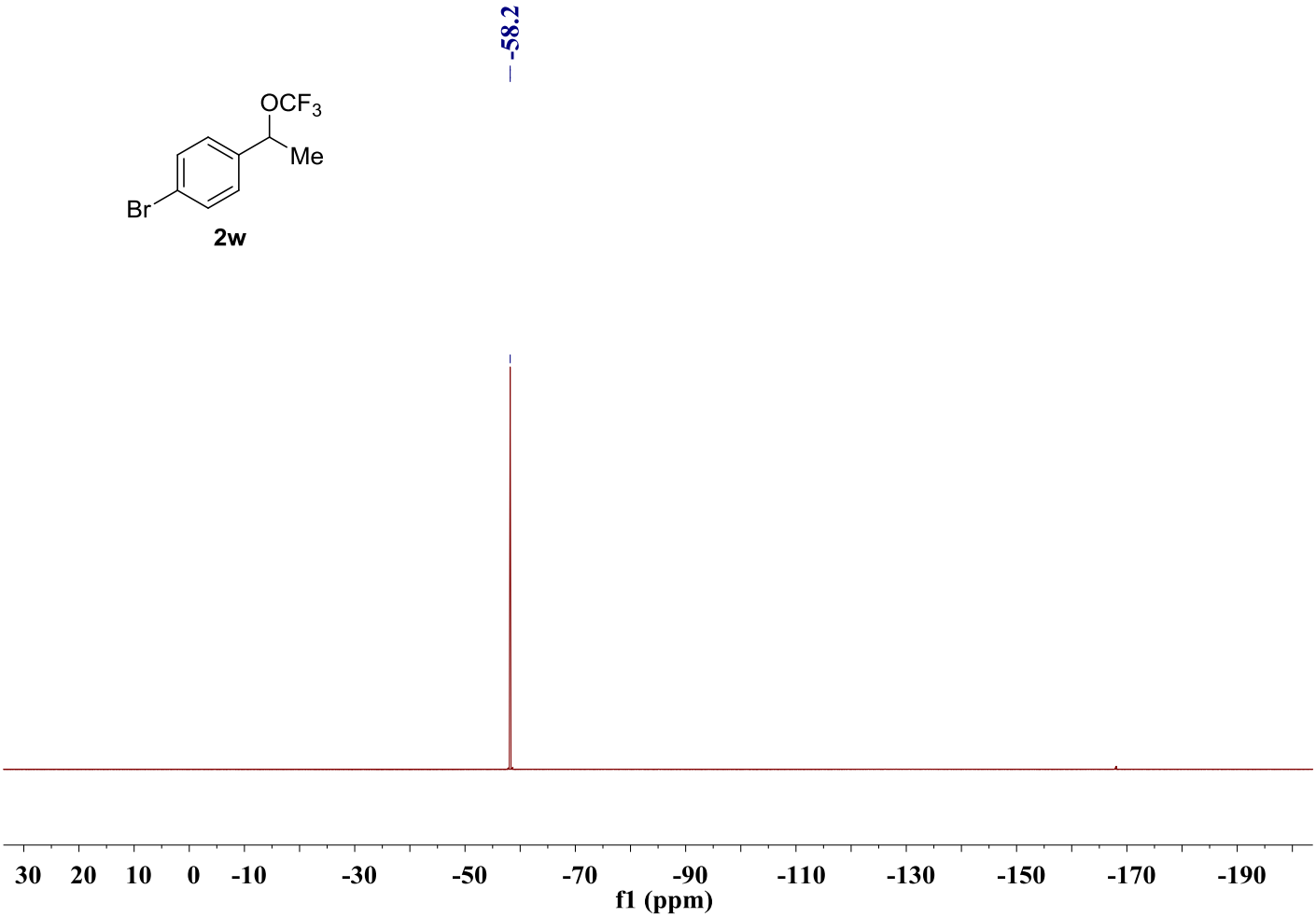

Figure S56. ^{19}F NMR spectrum of **2w**, Related to **Scheme 2**

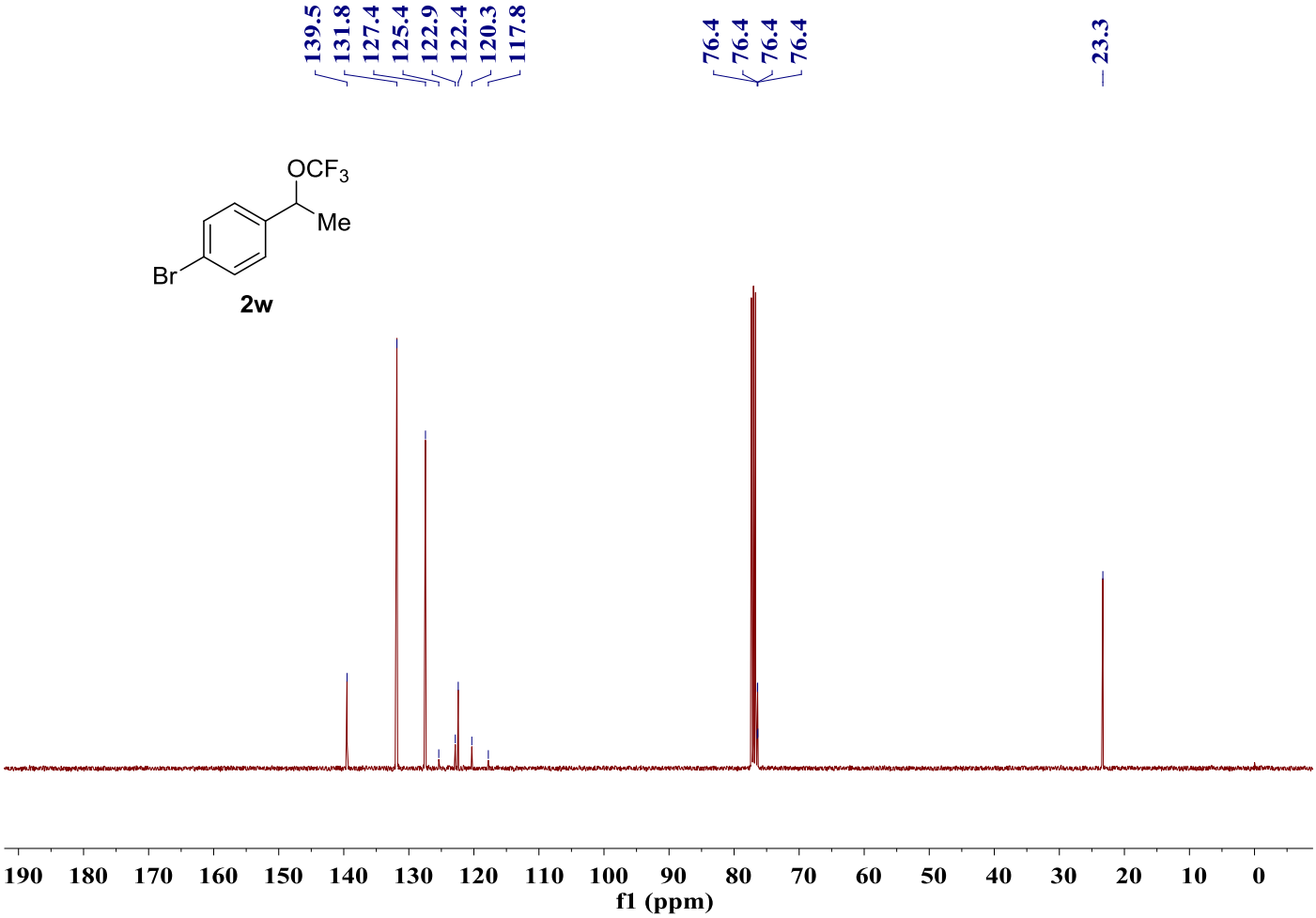

Figure S57. ^{13}C NMR spectrum of **2w**, Related to **Scheme 2**

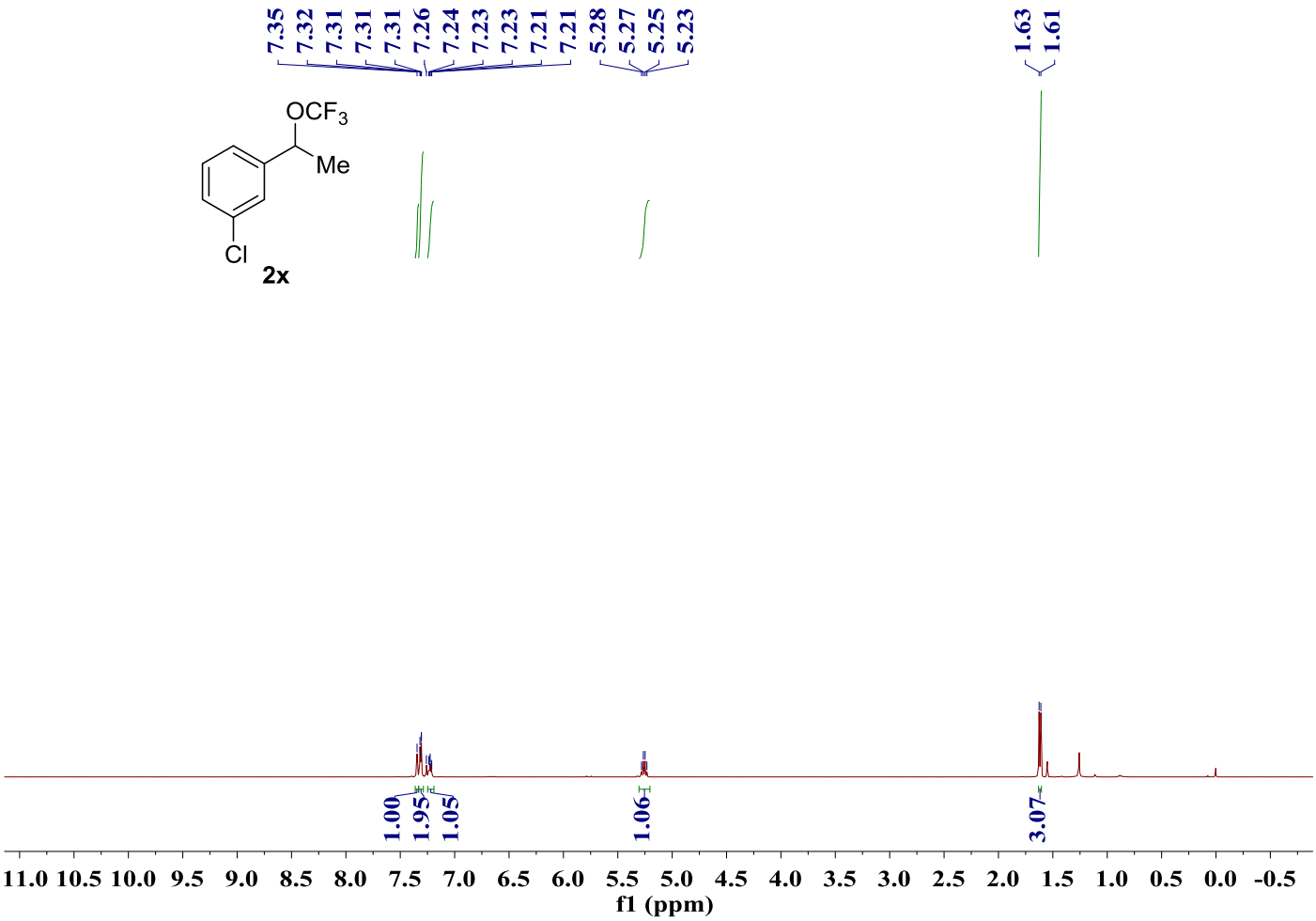

Figure S58. ^{1}H NMR spectrum of **2x**, Related to **Scheme 2**

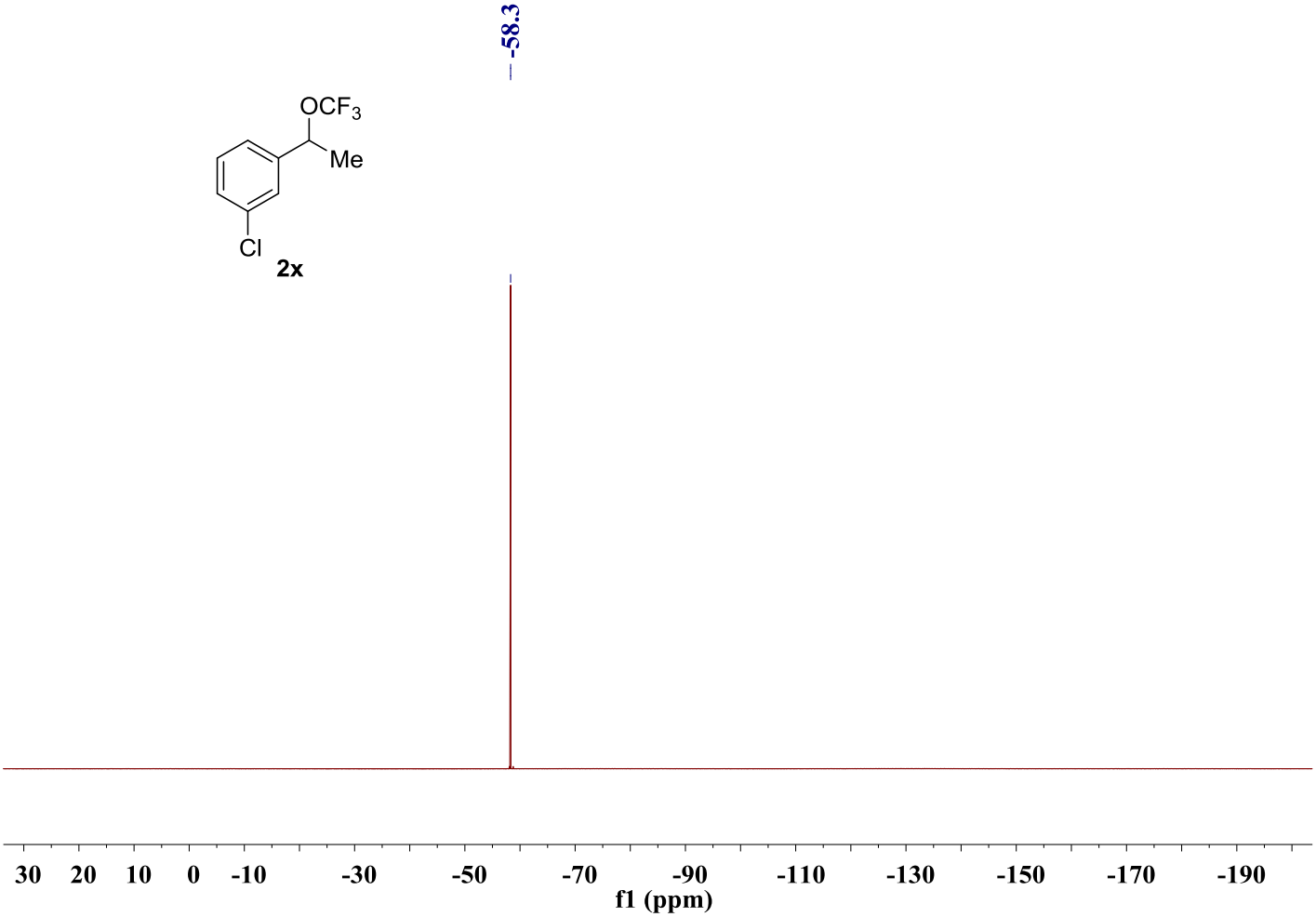

Figure S59. ^{19}F NMR spectrum of **2x**, Related to **Scheme 2**

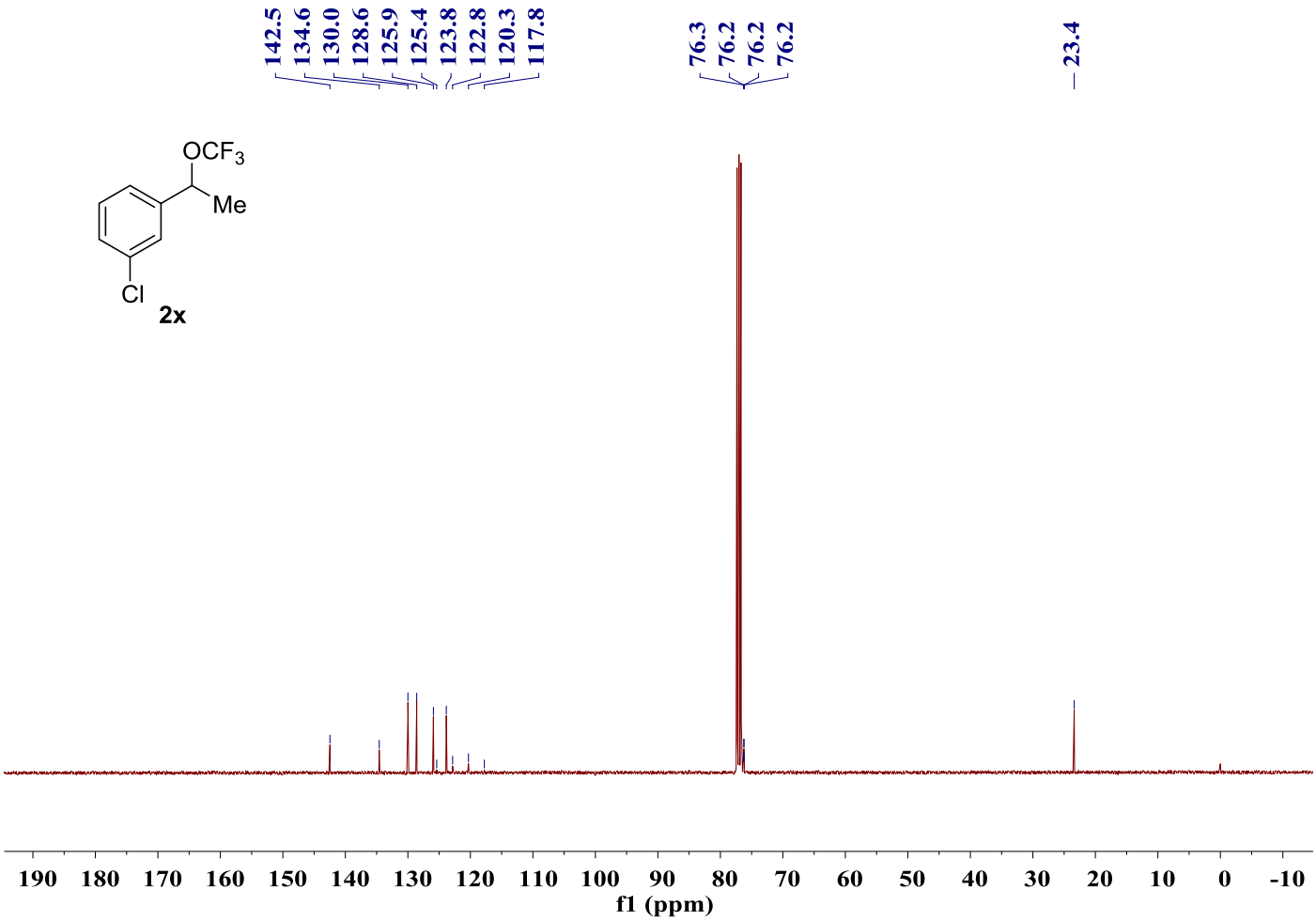

Figure S60. ^{13}C NMR spectrum of **2x**, Related to **Scheme 2**

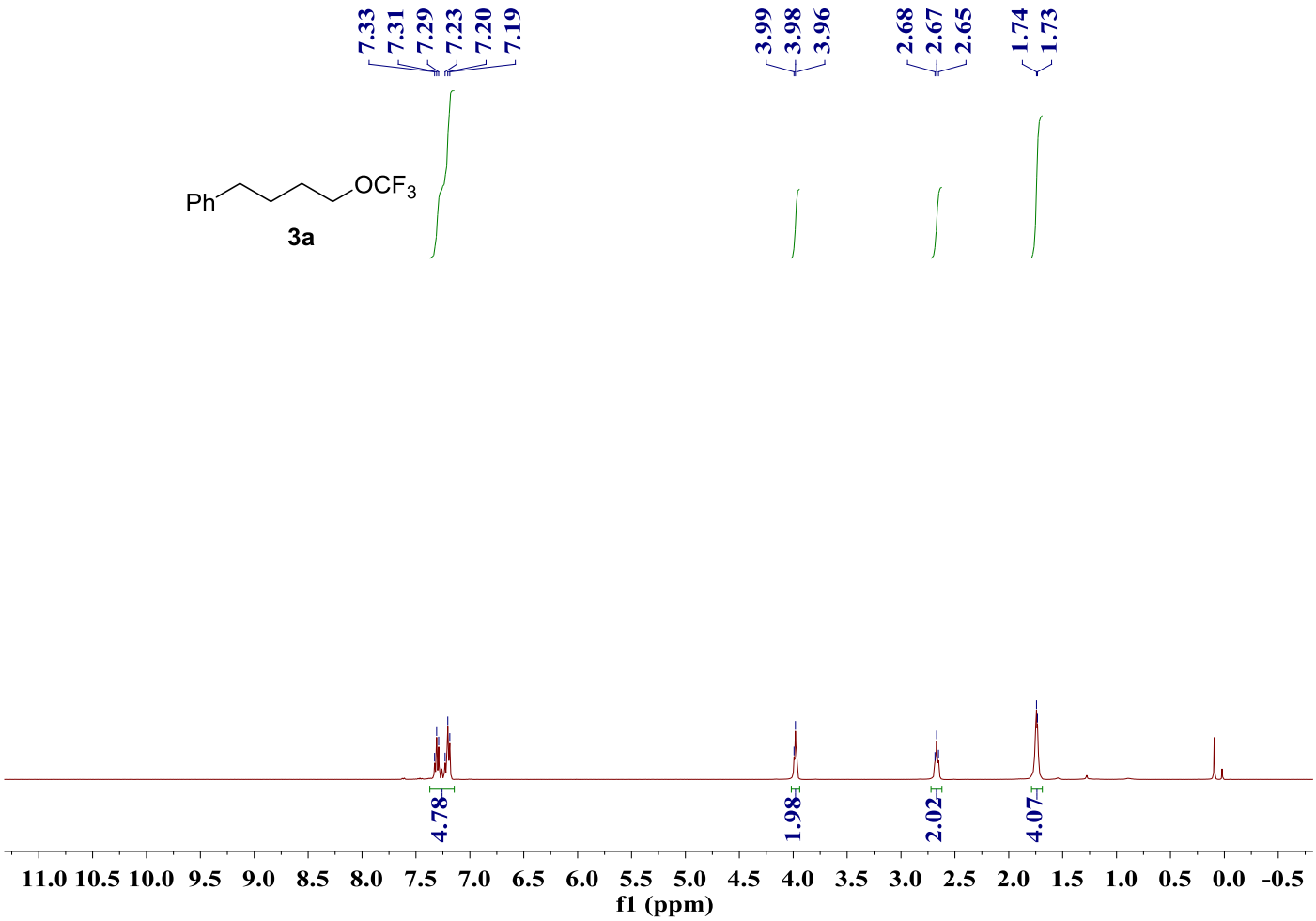

Figure S61. ^{1}H NMR spectrum of **3a**, Related to **Scheme 3**

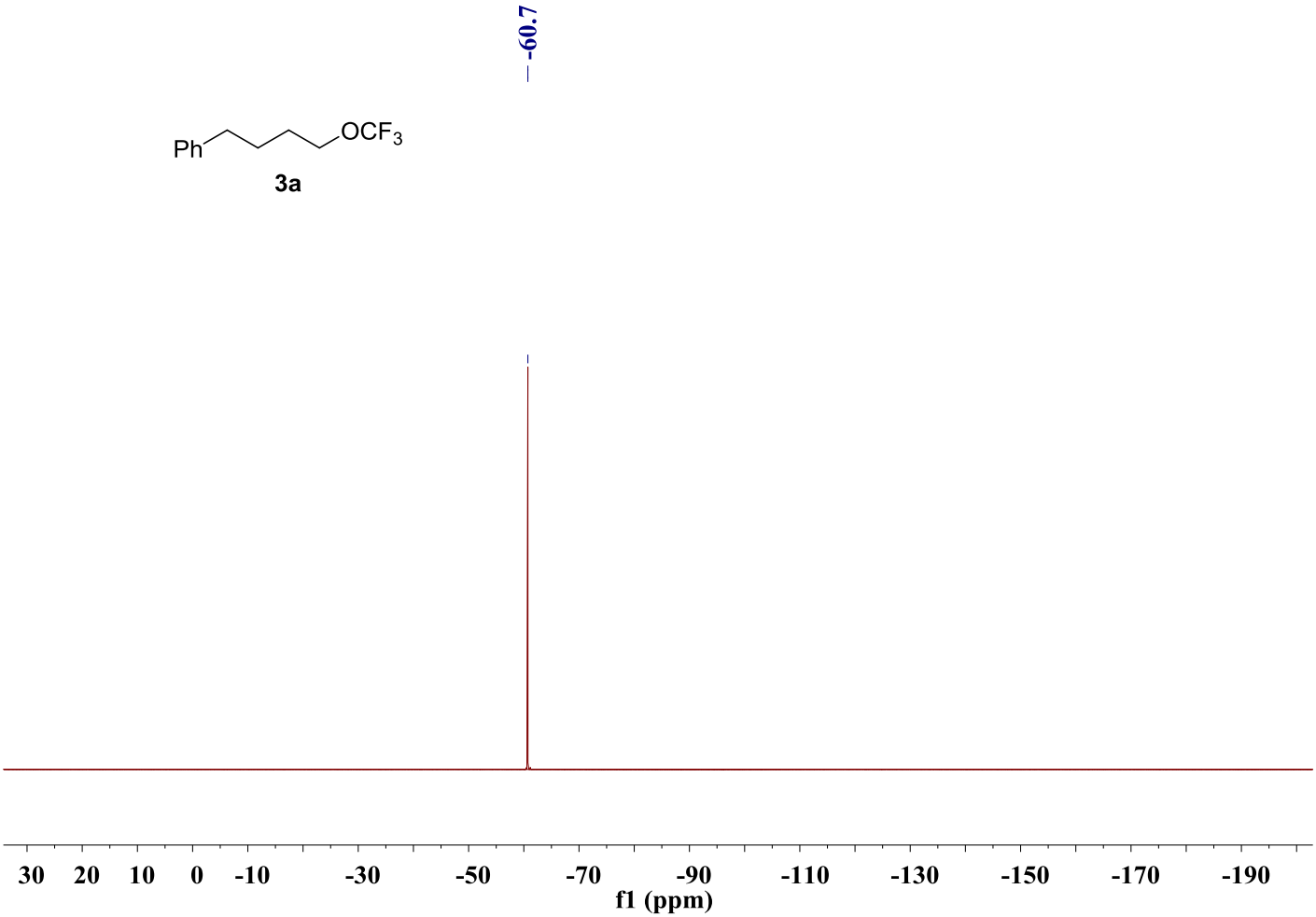

Figure 62. ^{19}F NMR spectrum of **3a**, Related to **Scheme 3**

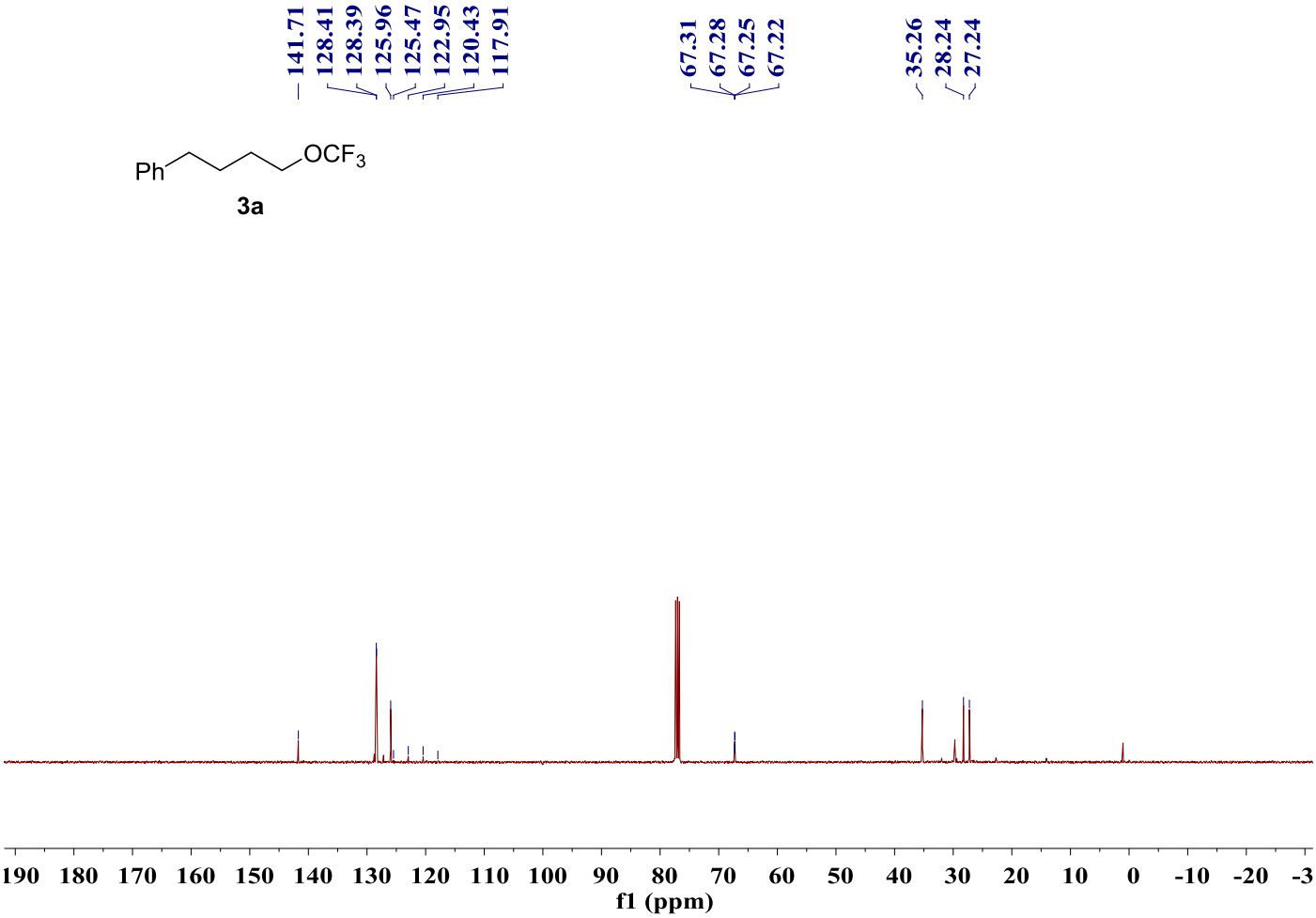

Figure S63. ^{13}C NMR spectrum of **3a**, Related to **Scheme 3**

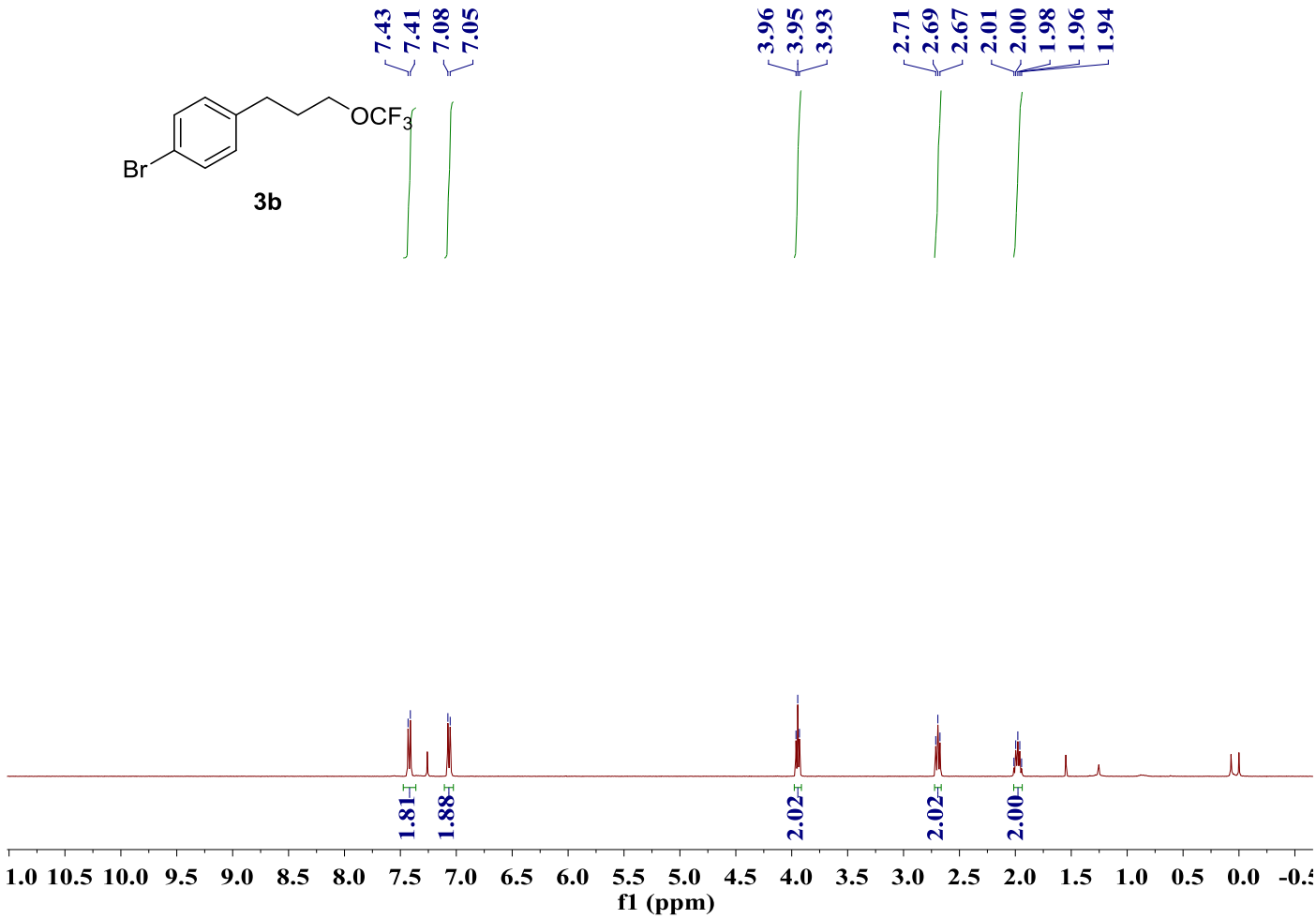

Figure S64. ^{1}H NMR spectrum of **3b**, Related to **Scheme 3**

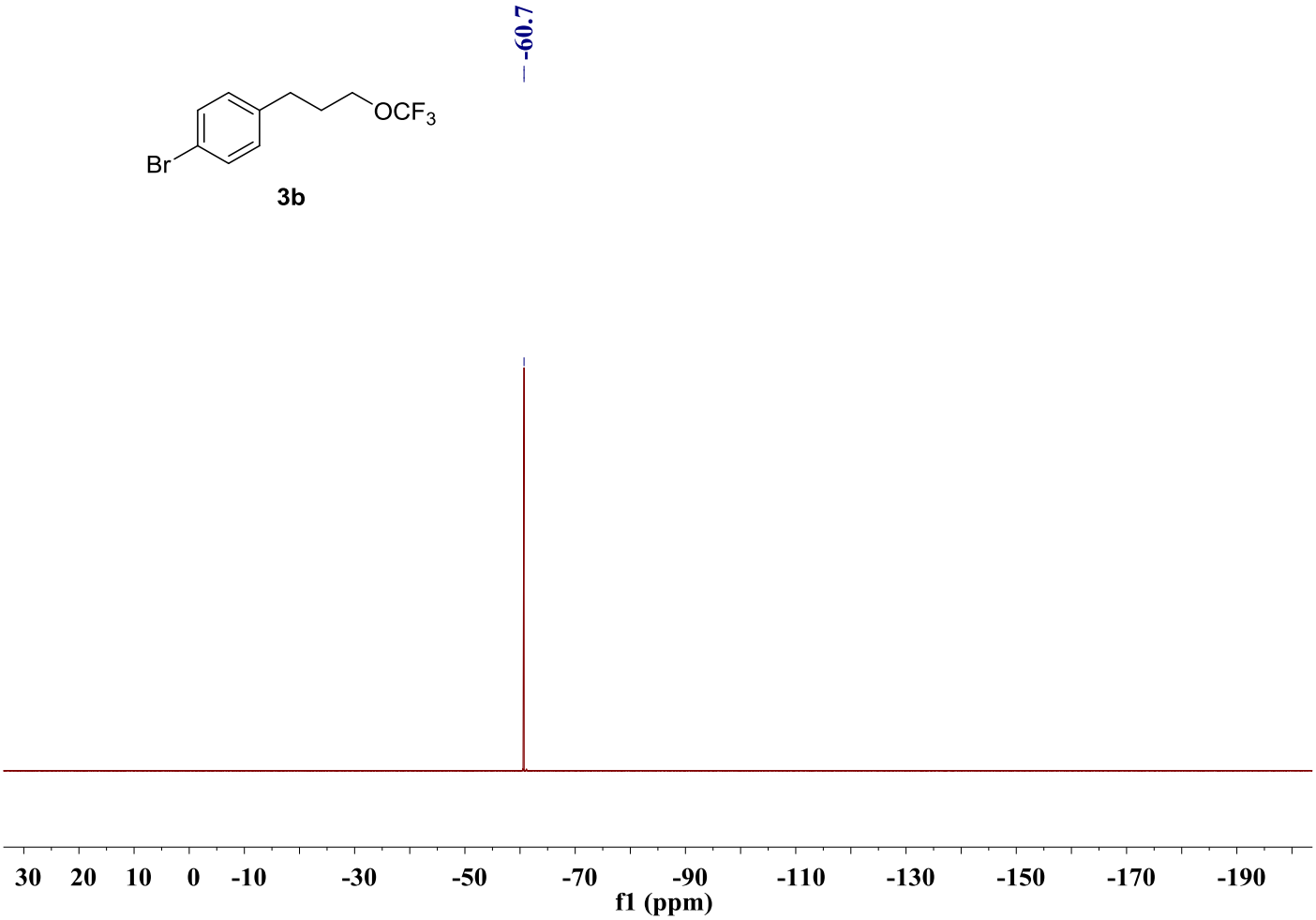

Figure S65. ^{19}F NMR spectrum of **3b**, Related to **Scheme 3**

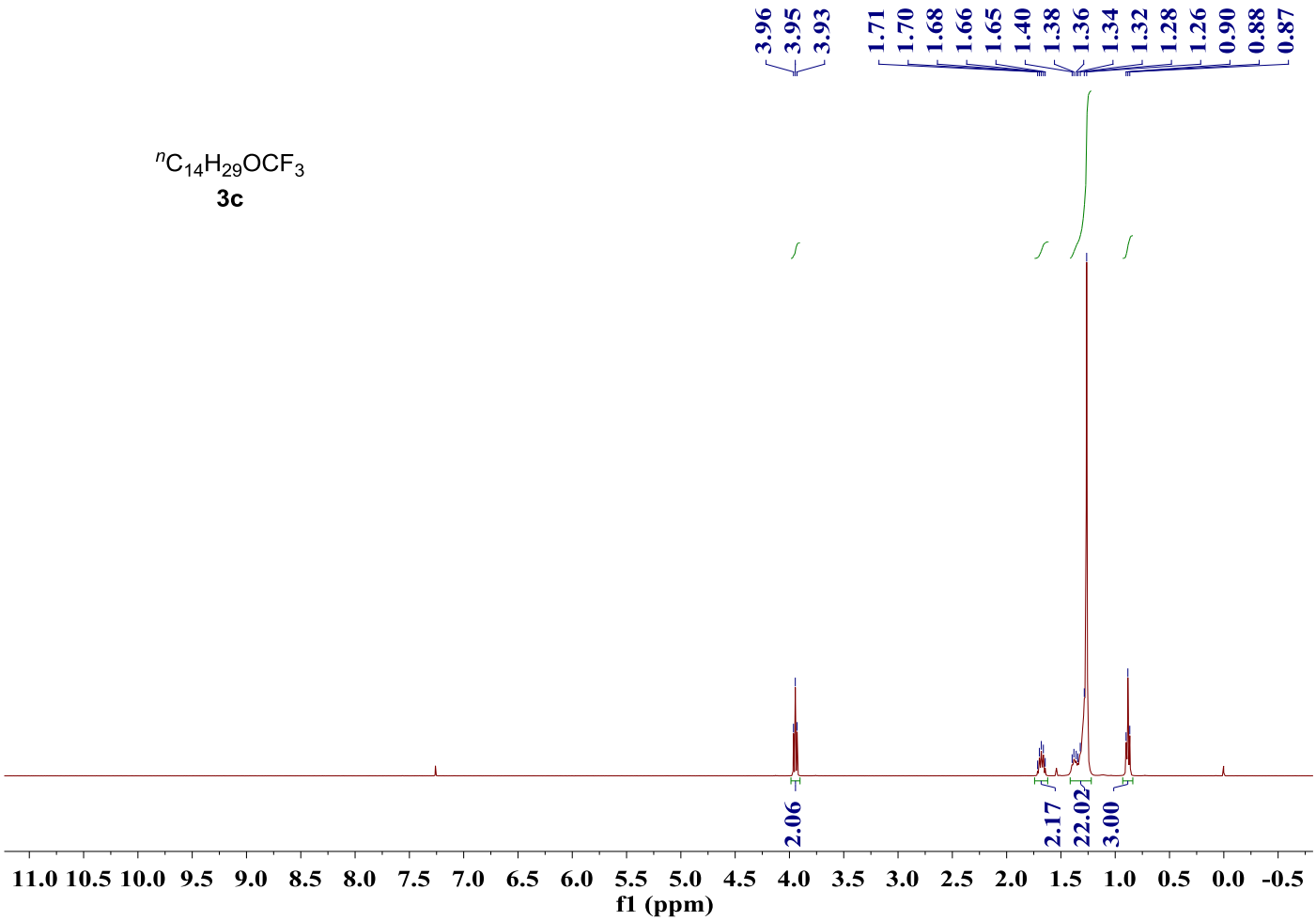

Figure S66. ^{1}H NMR spectrum of **3c**, Related to **Scheme 3**

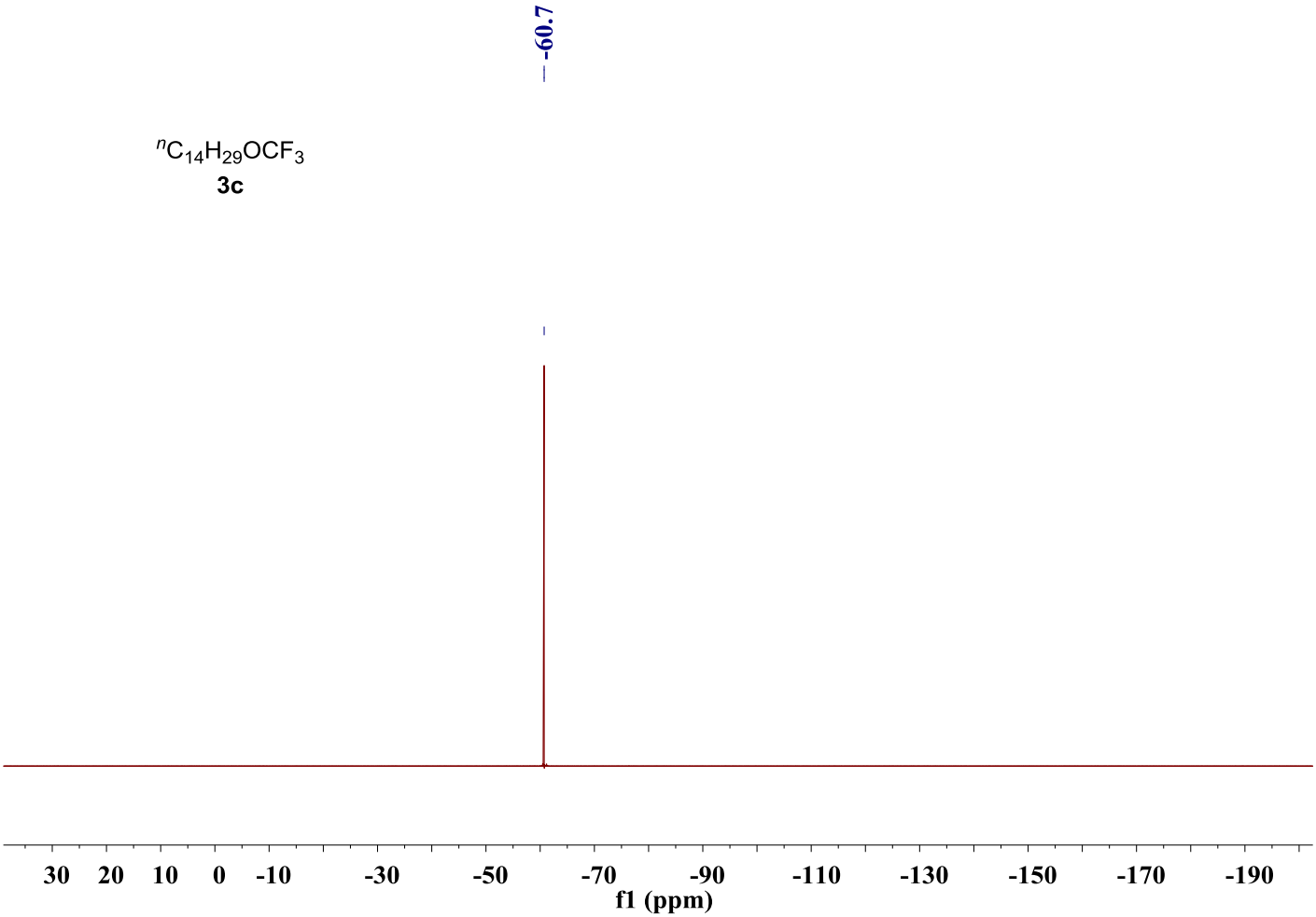

Figure S67. ^{19}F NMR spectrum of **3c**, Related to **Scheme 3**

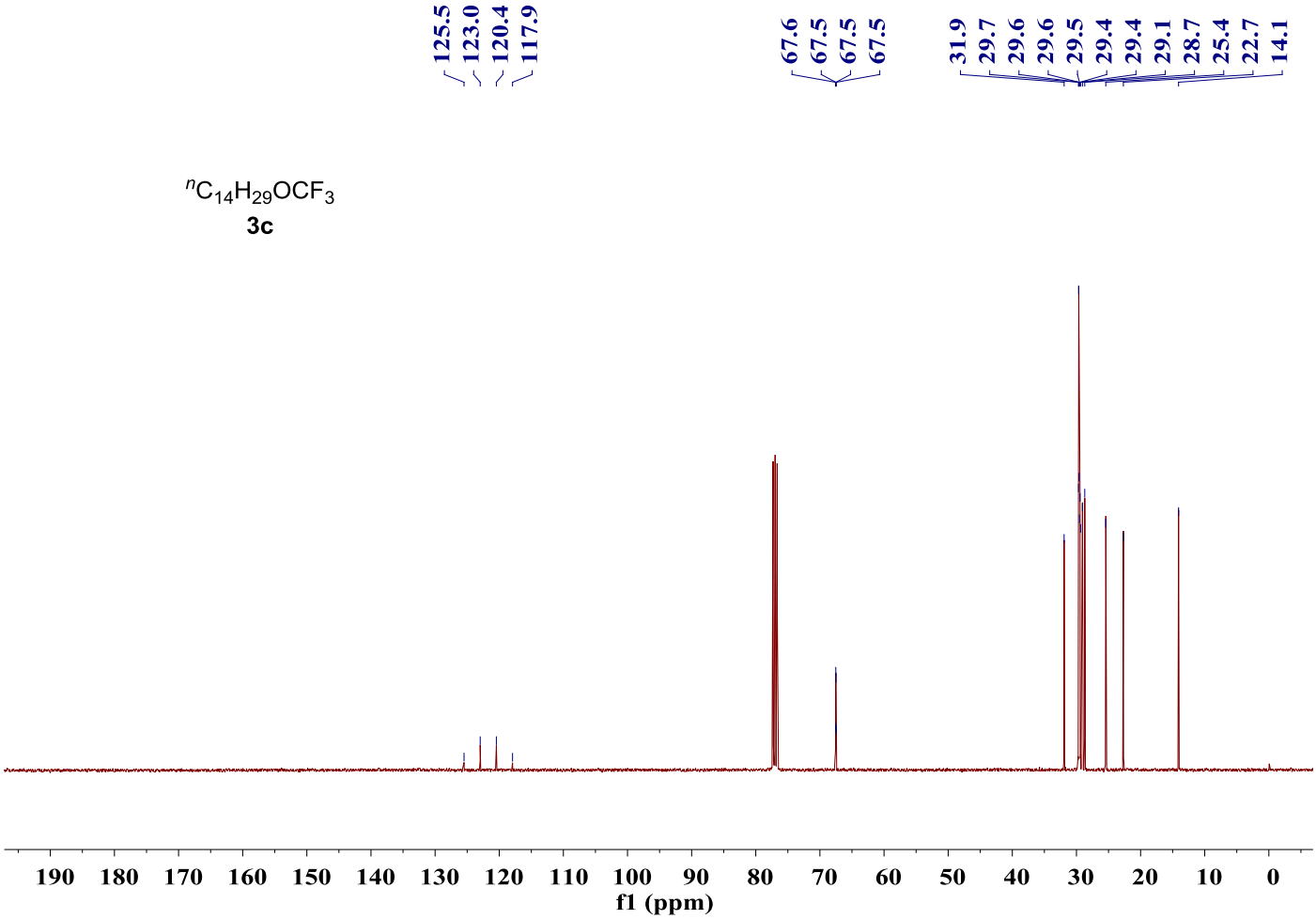

Figure S68. ^{13}C NMR spectrum of **3c**, Related to **Scheme 3**

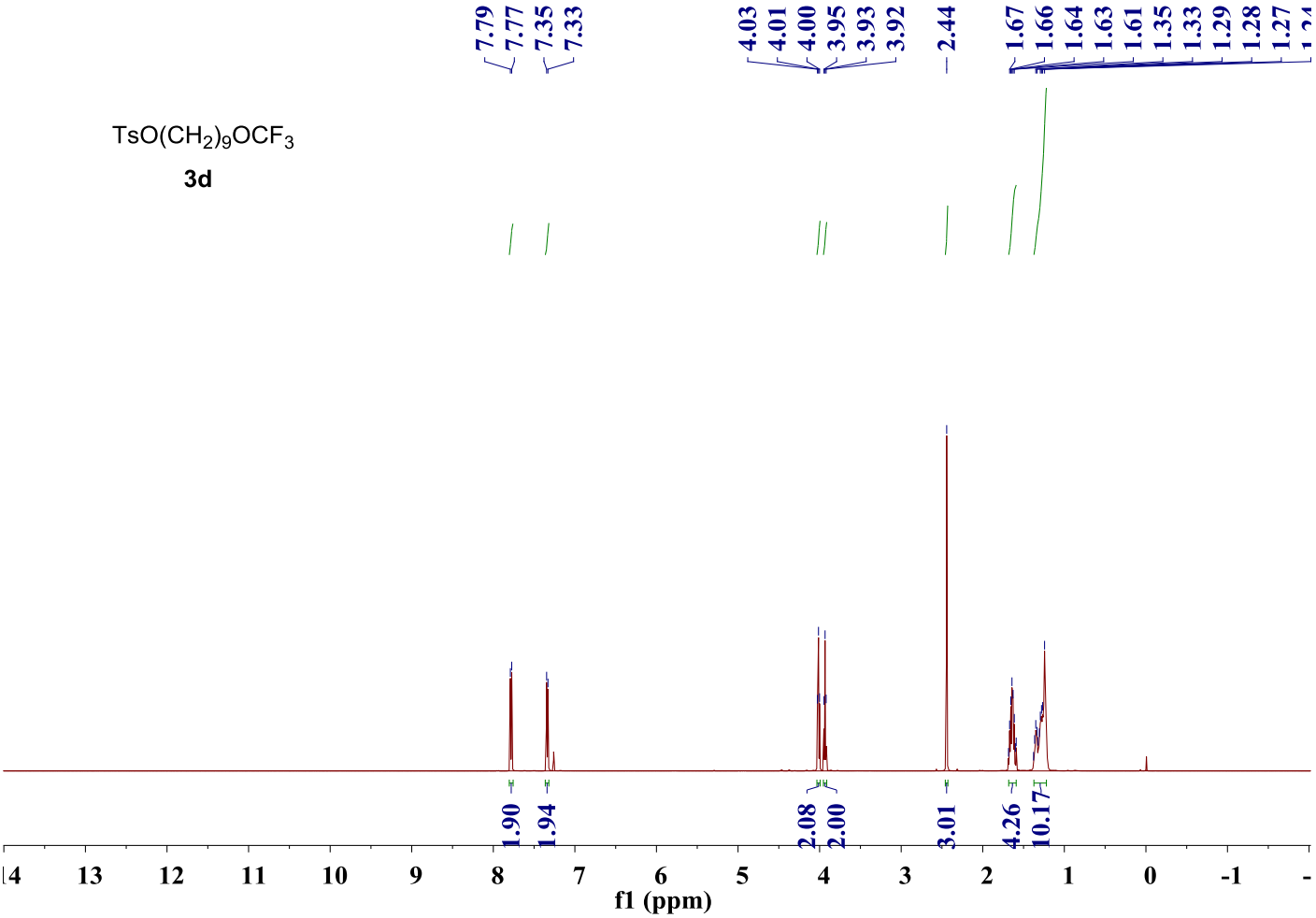

Figure S69. ^{1}H NMR spectrum of **3d**, Related to **Scheme 3**

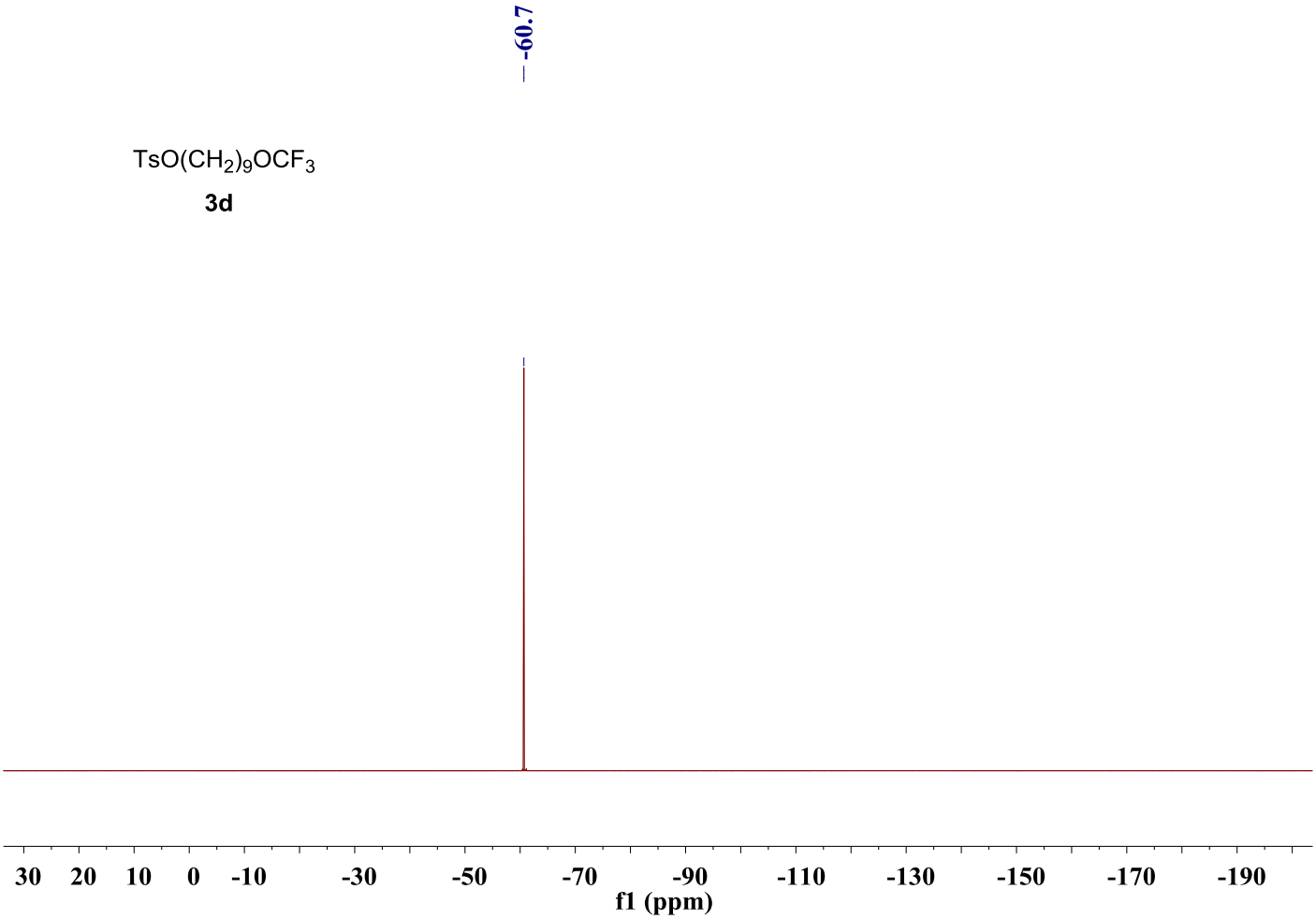

Figure S70. ^{19}F NMR spectrum of **3d**, Related to **Scheme 3**

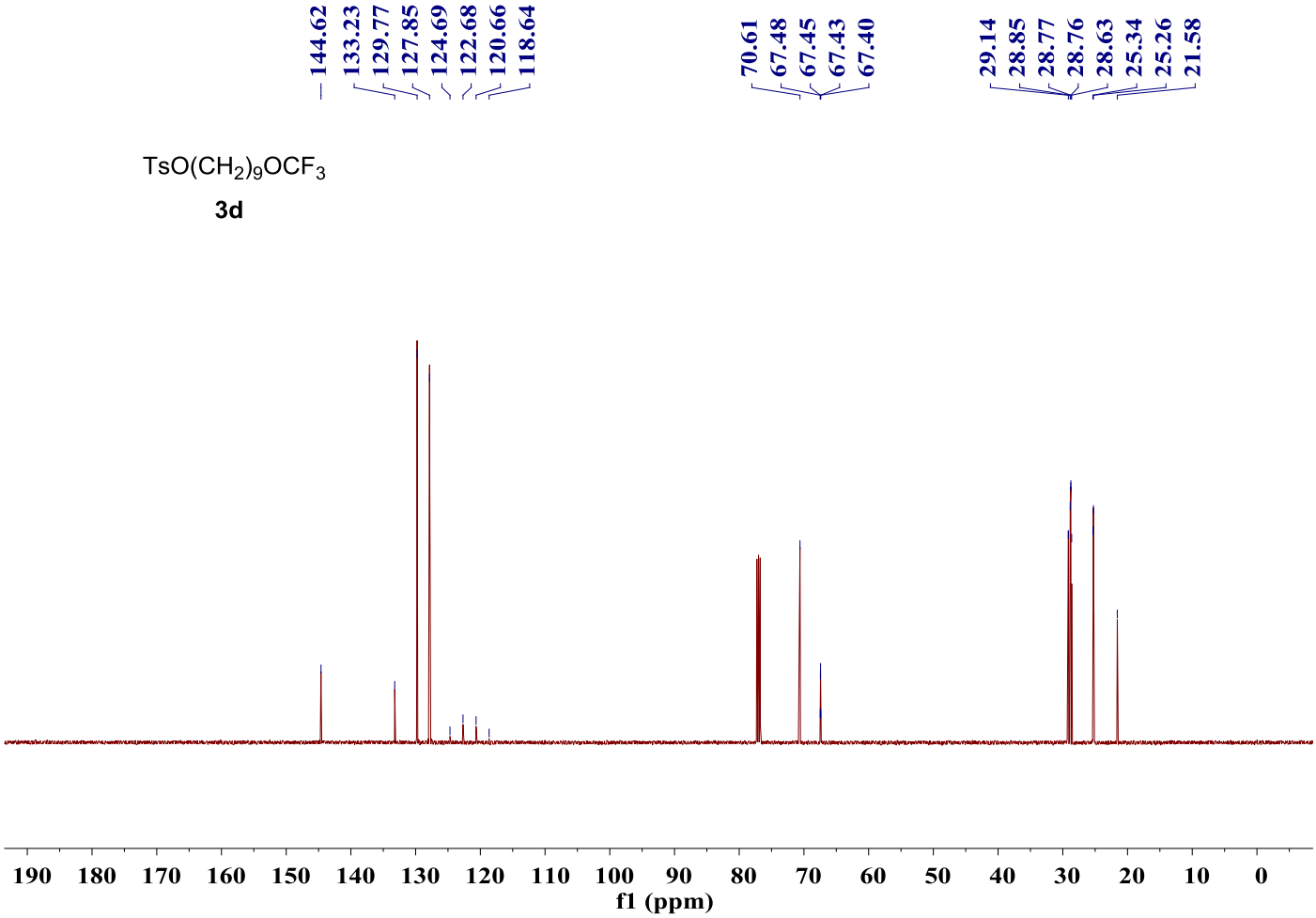

Figure S71. ^{13}C NMR spectrum of **3d**, Related to **Scheme 3**

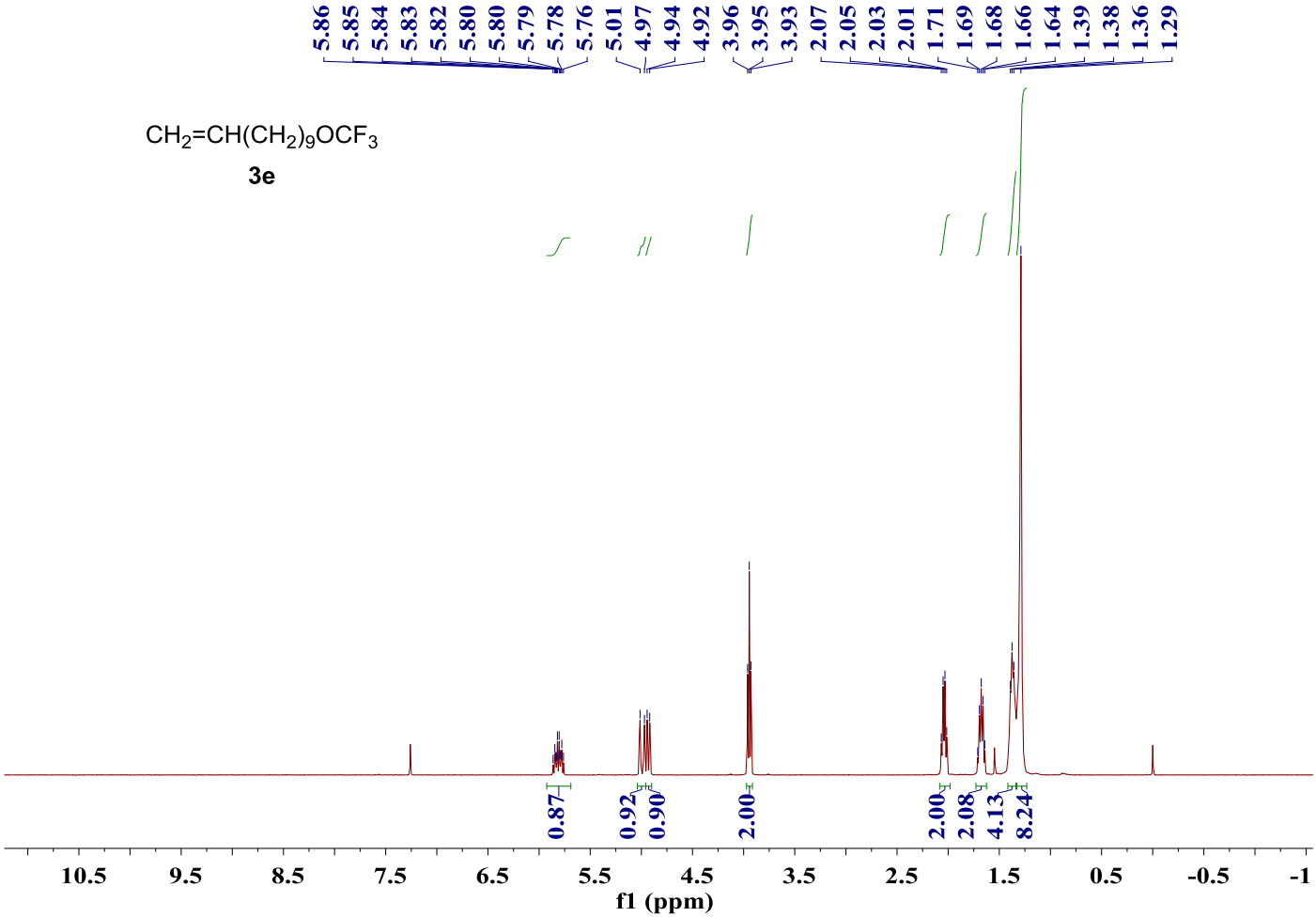

Figure S72. ^{1}H NMR spectrum of **3e**, Related to **Scheme 3**

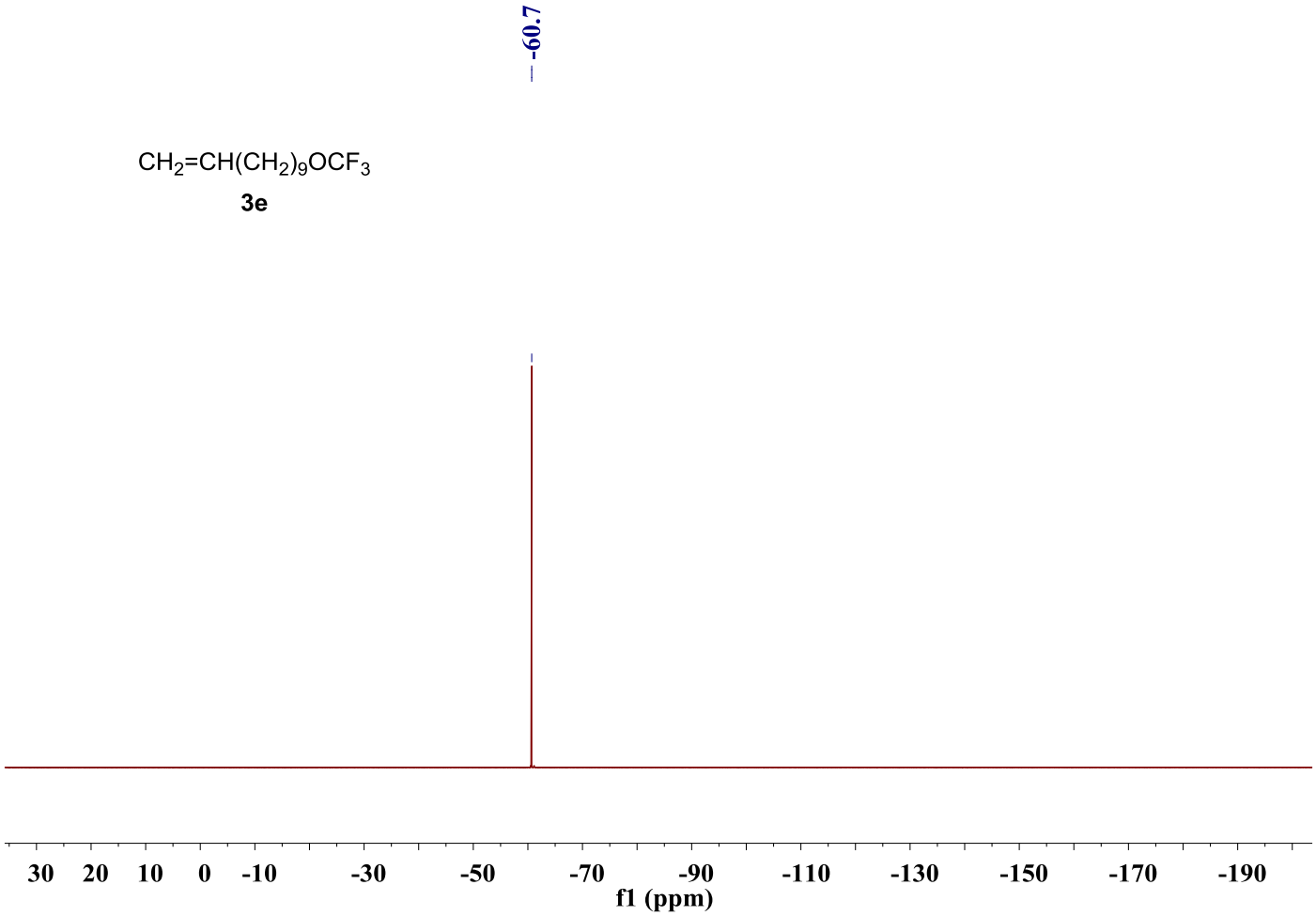

Figure S73. ^{19}F NMR spectrum of **3e**, Related to **Scheme 3**

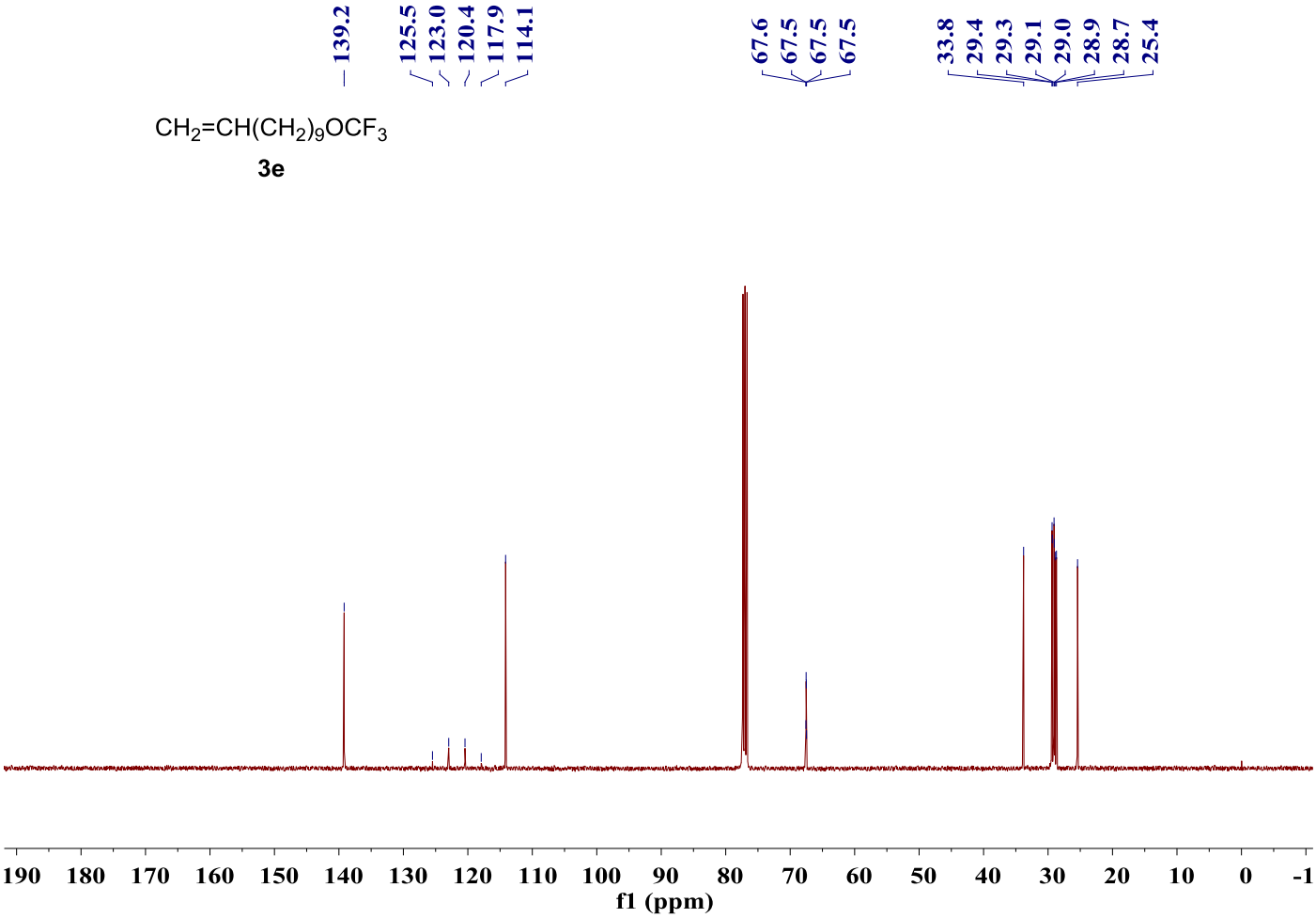

Figure S74. ^{13}C NMR spectrum of **3e**, Related to **Scheme 3**

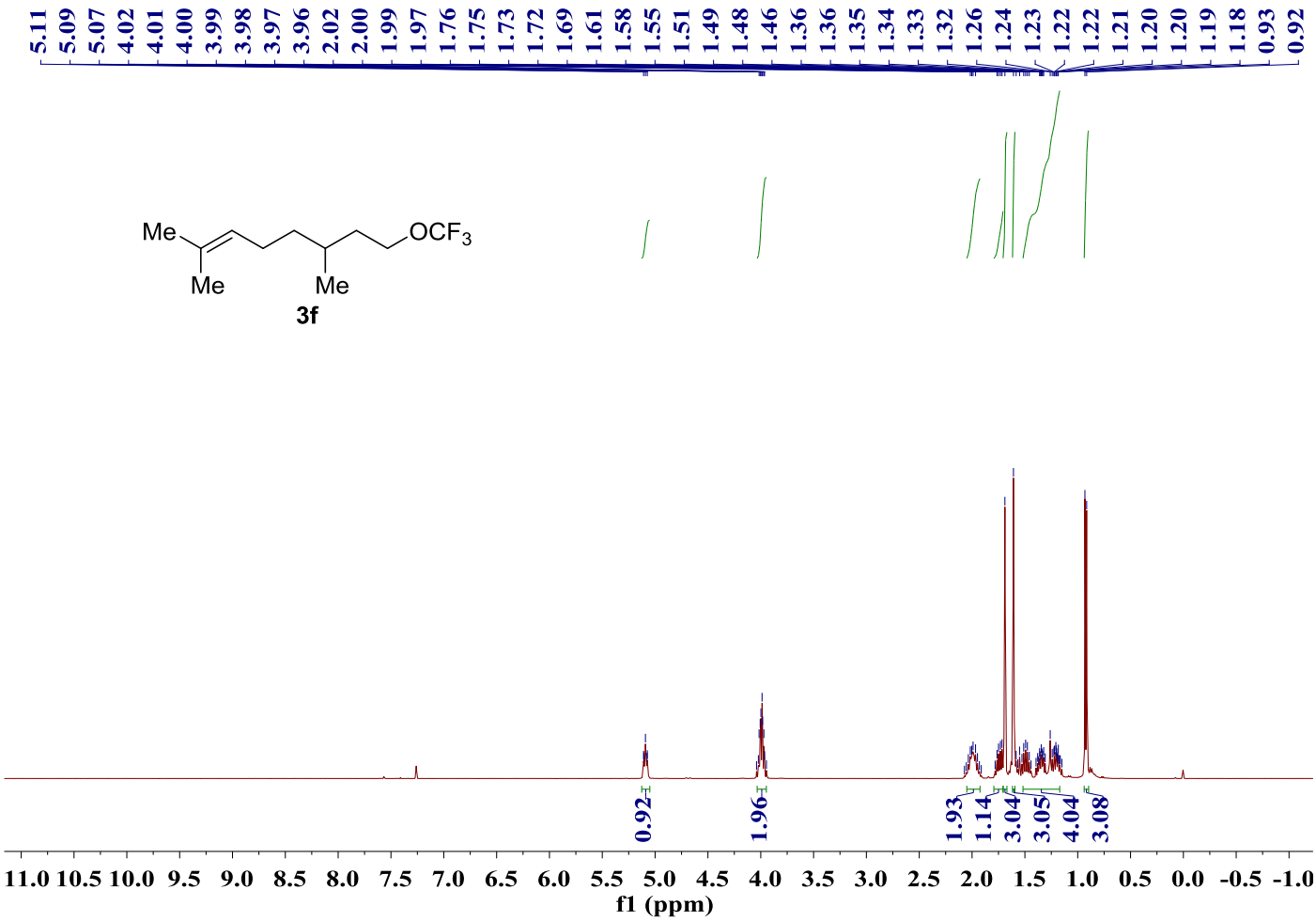

Figure S75. ^{1}H NMR spectrum of **3f**, Related to **Scheme 3**

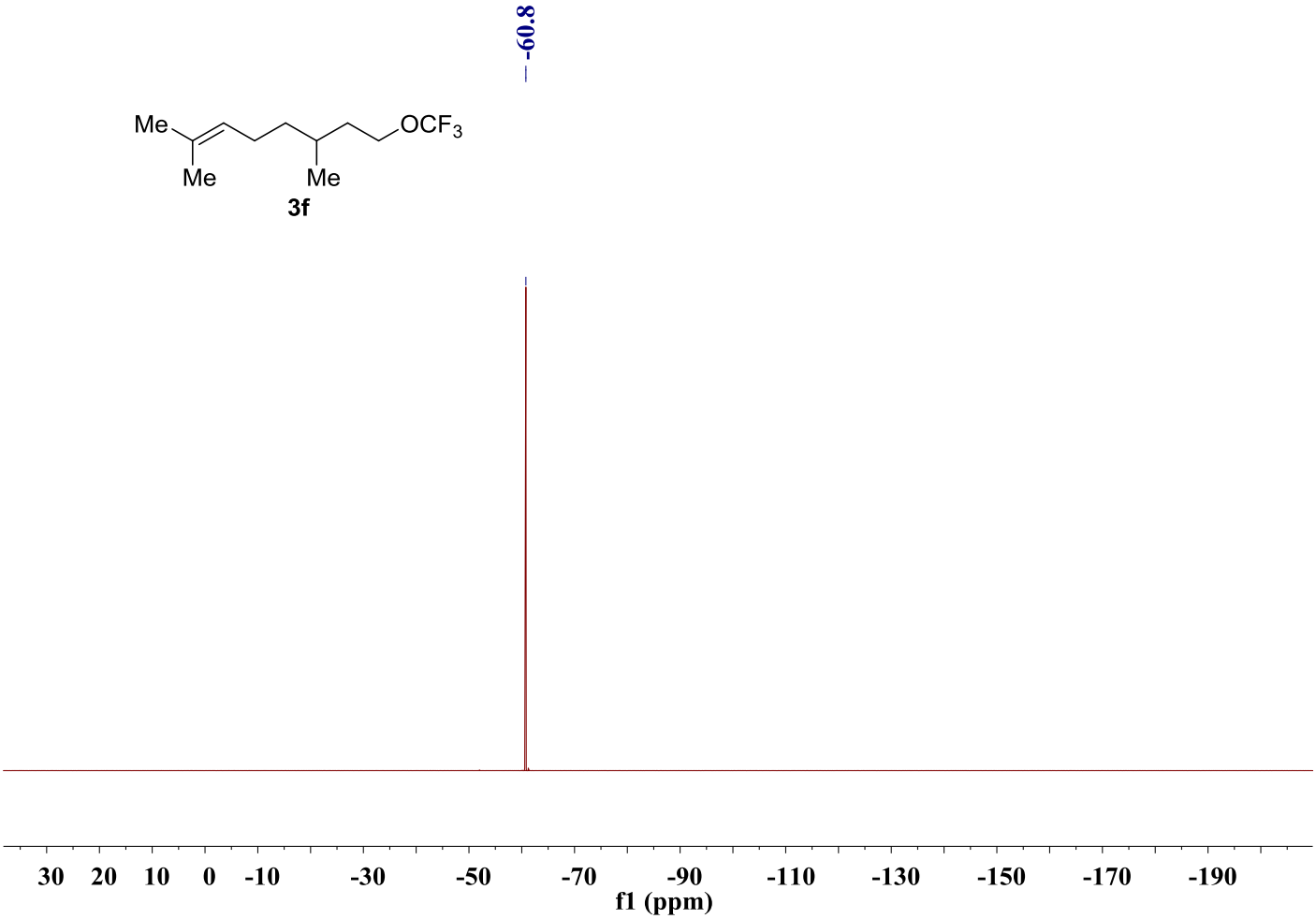

Figure S76. ^{19}F NMR spectrum of **3f**, Related to **Scheme 3**

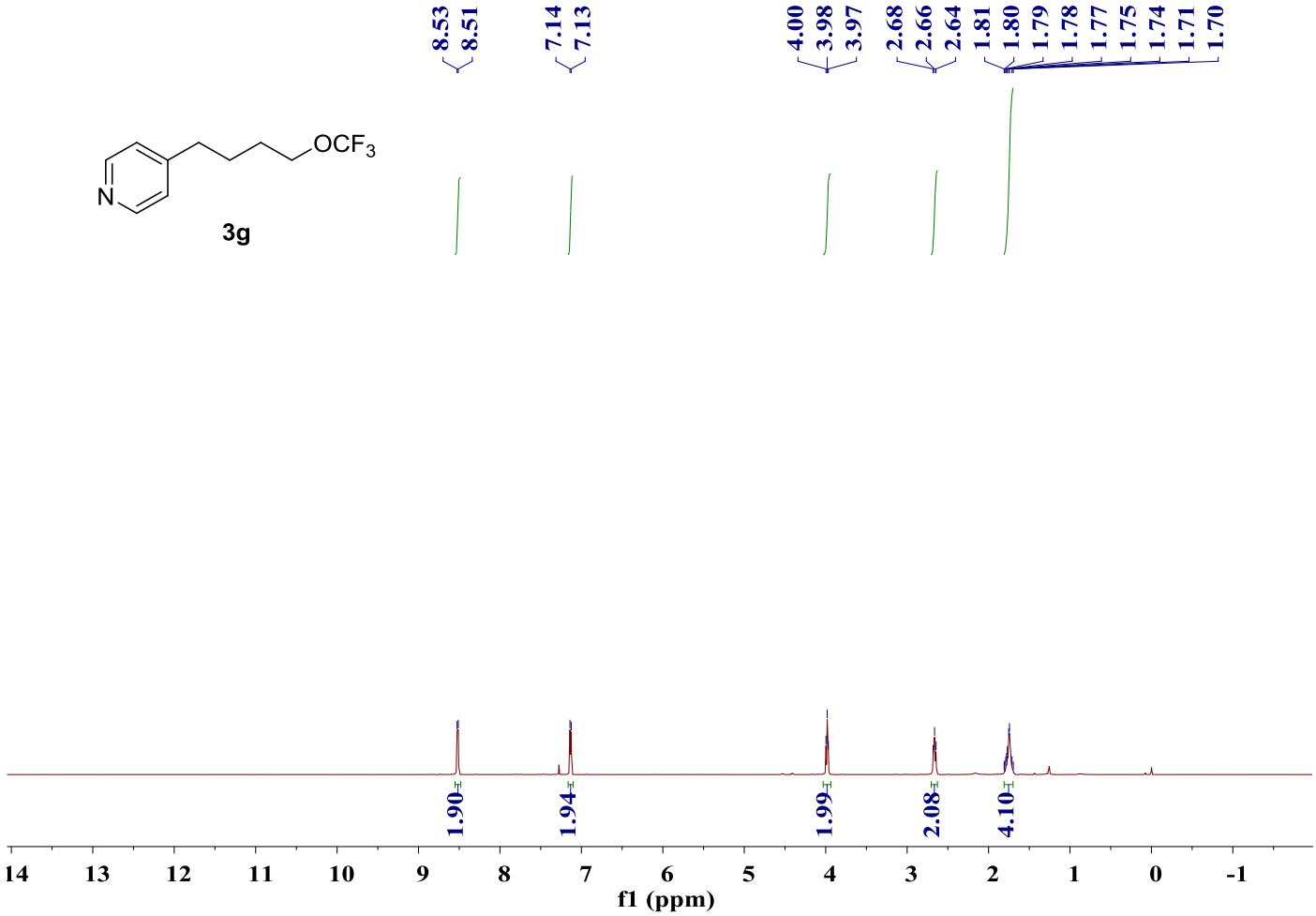

Figure S77. ^{1}H NMR spectrum of **3g**, Related to **Scheme 3**

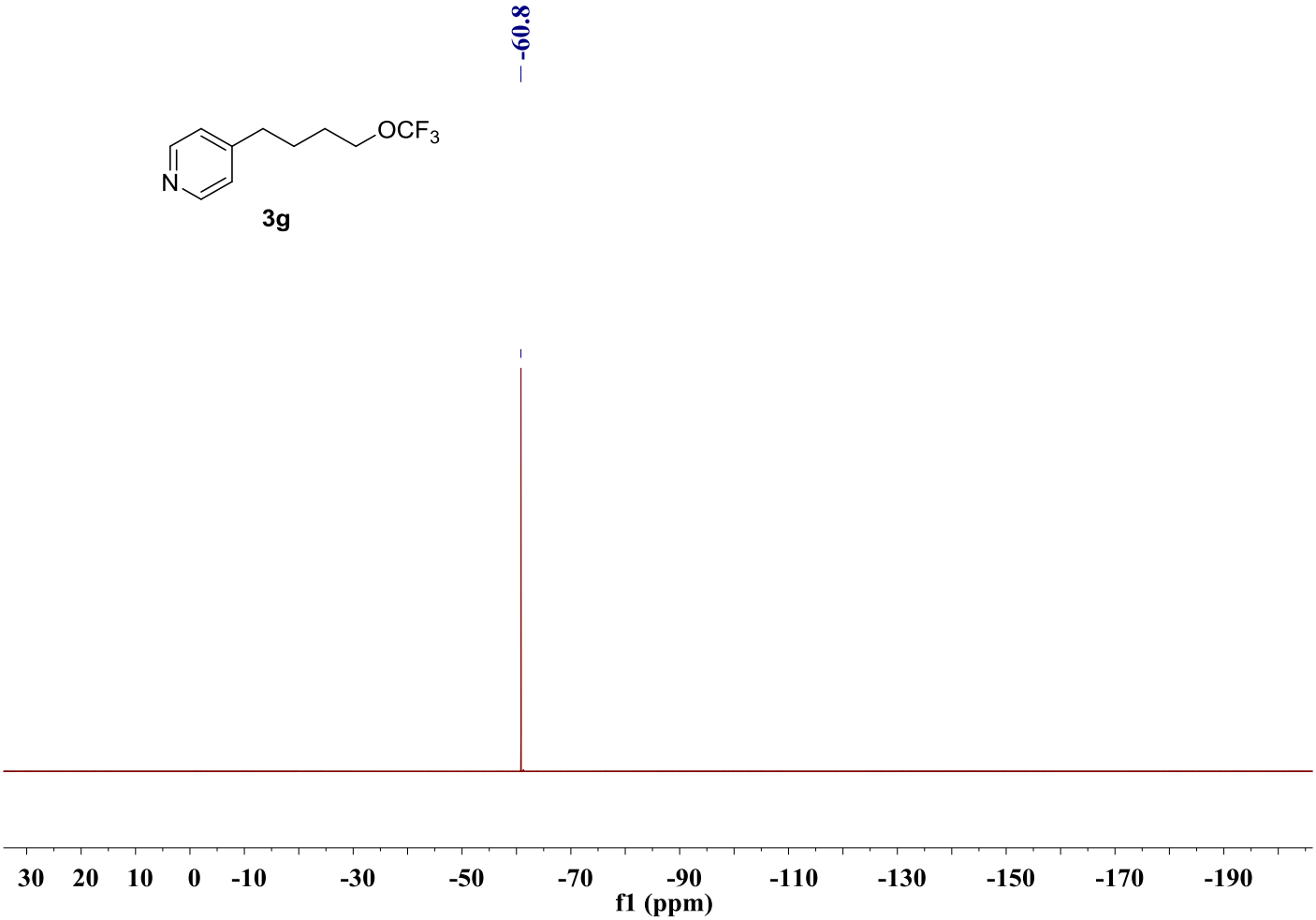

Figure S78. ^{19}F NMR spectrum of **3g**, Related to **Scheme 3**

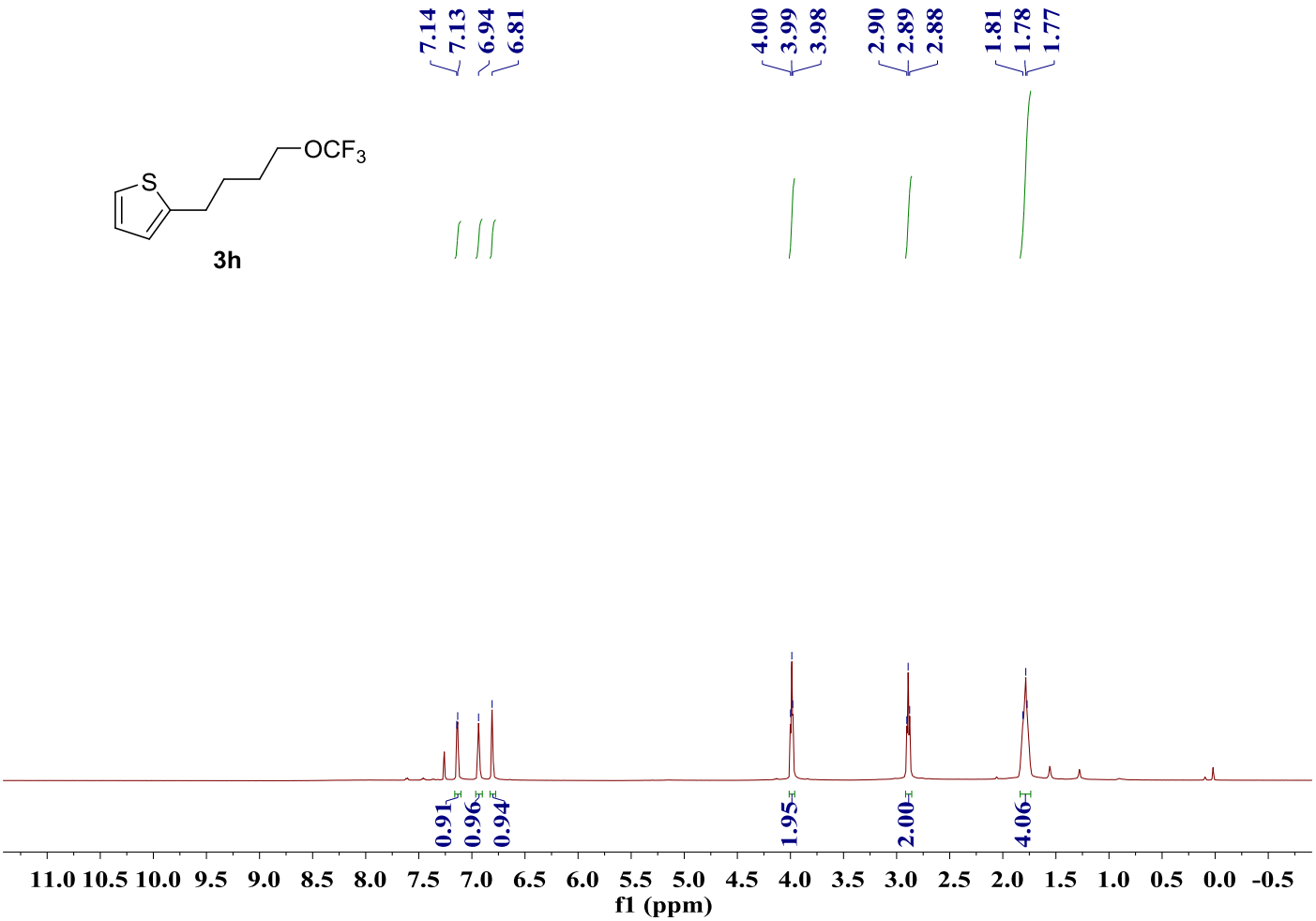

Figure S79. ^{1}H NMR spectrum of **3h**, Related to **Scheme 3**

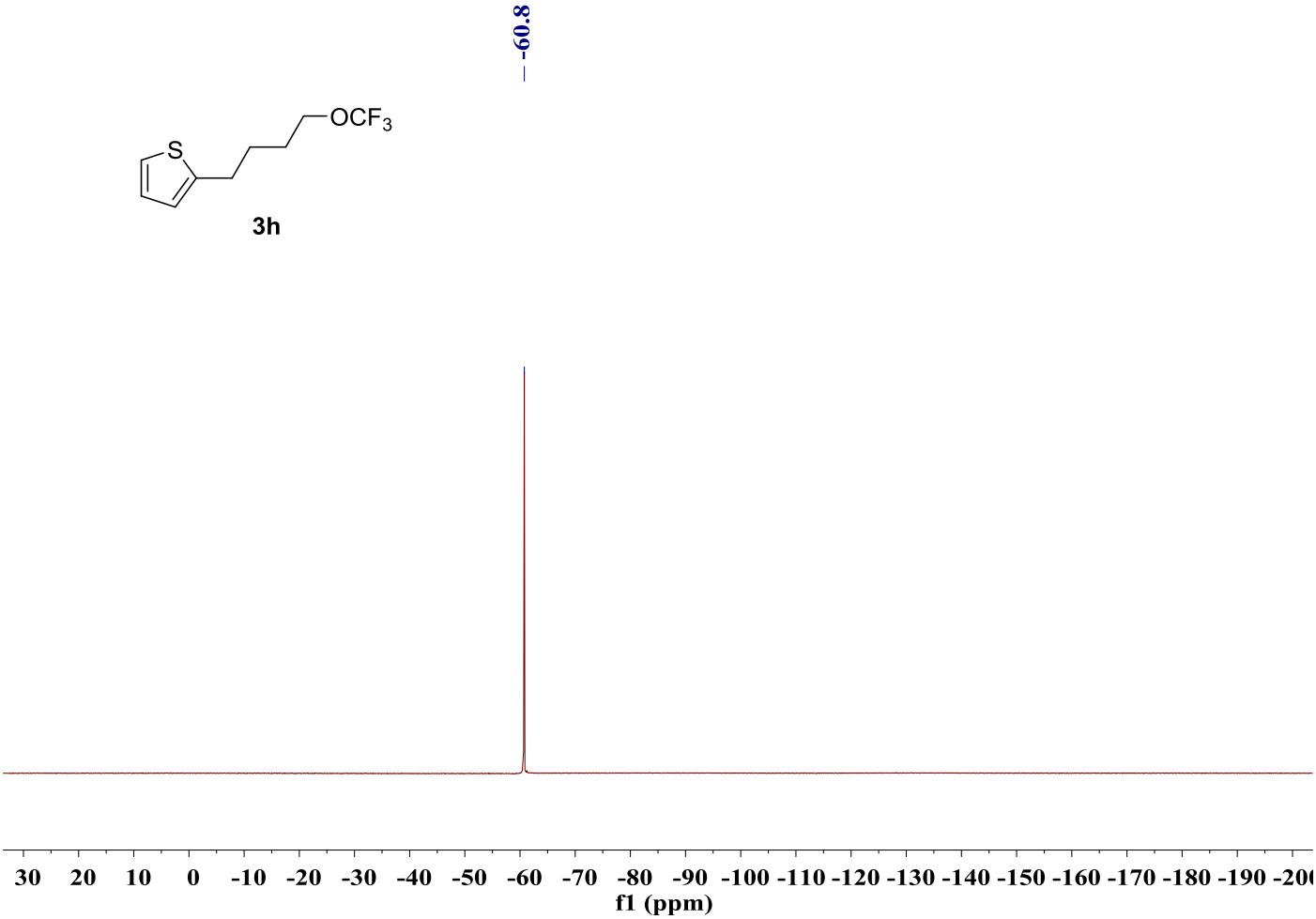

Figure S80. ^{19}F NMR spectrum of **3h**, Related to **Scheme 3**

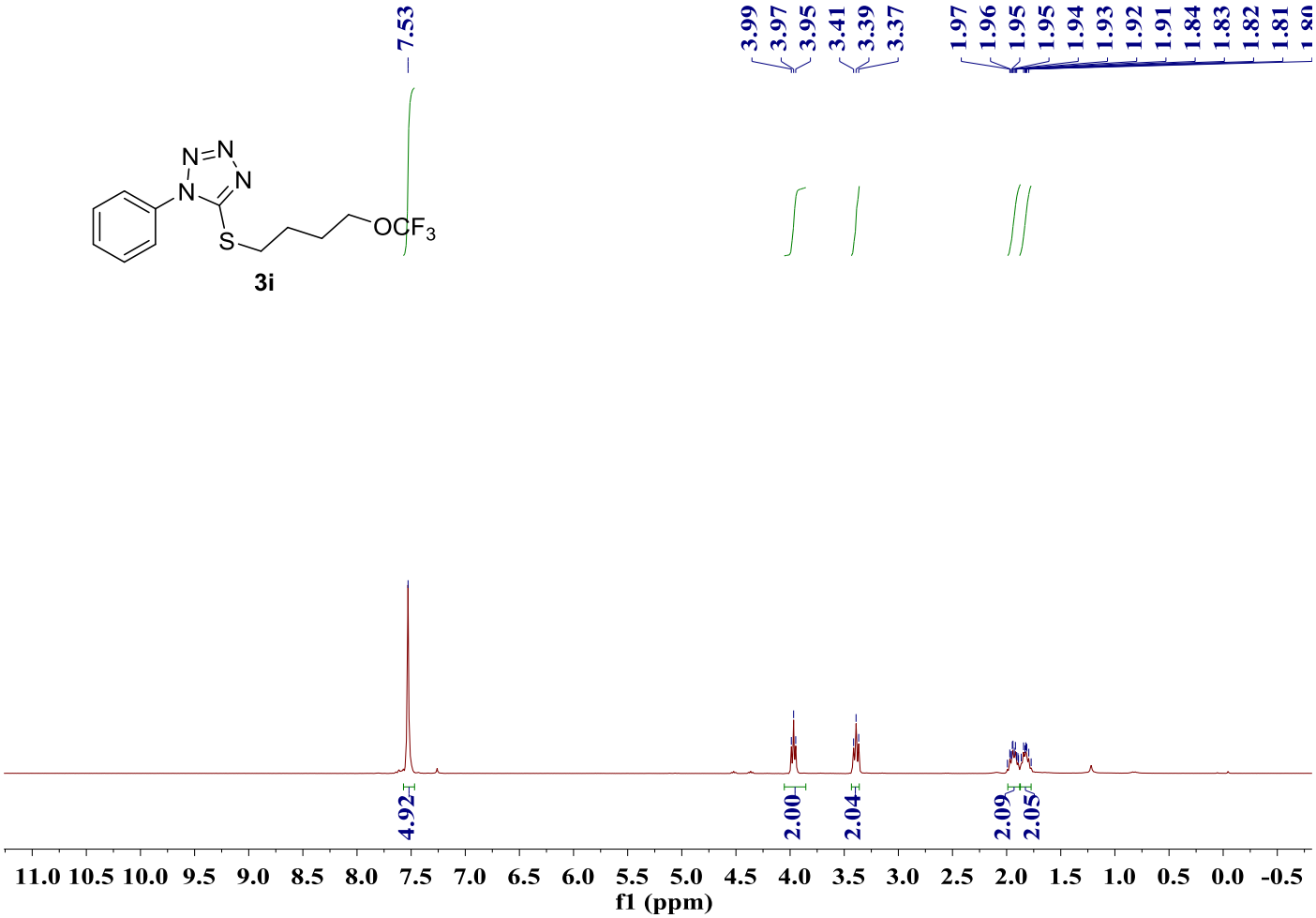

Figure S81. ^{1}H NMR spectrum of **3i**, Related to **Scheme 3**

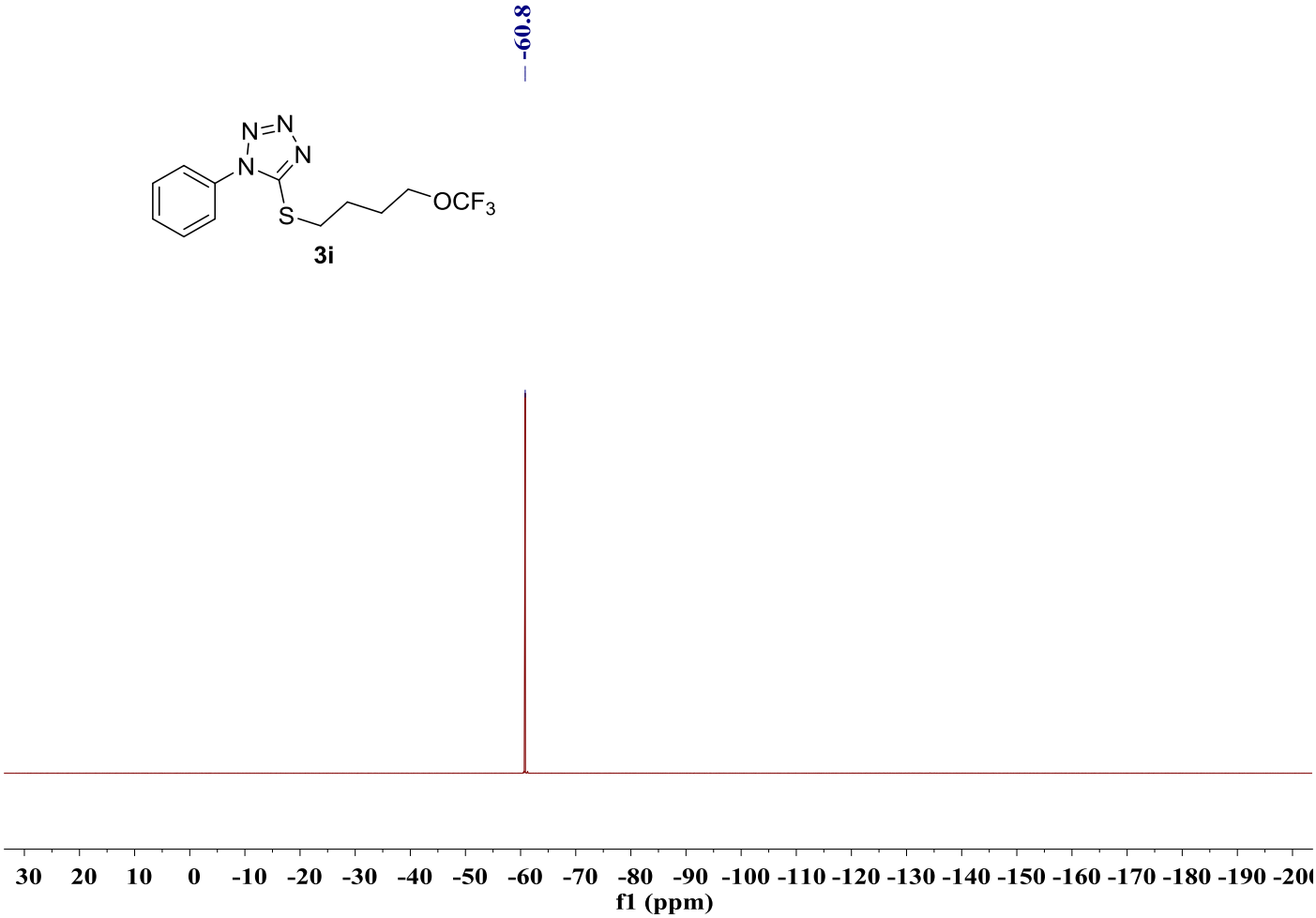

Figure S82. ^{19}F NMR spectrum of **3i**, Related to **Scheme 3**

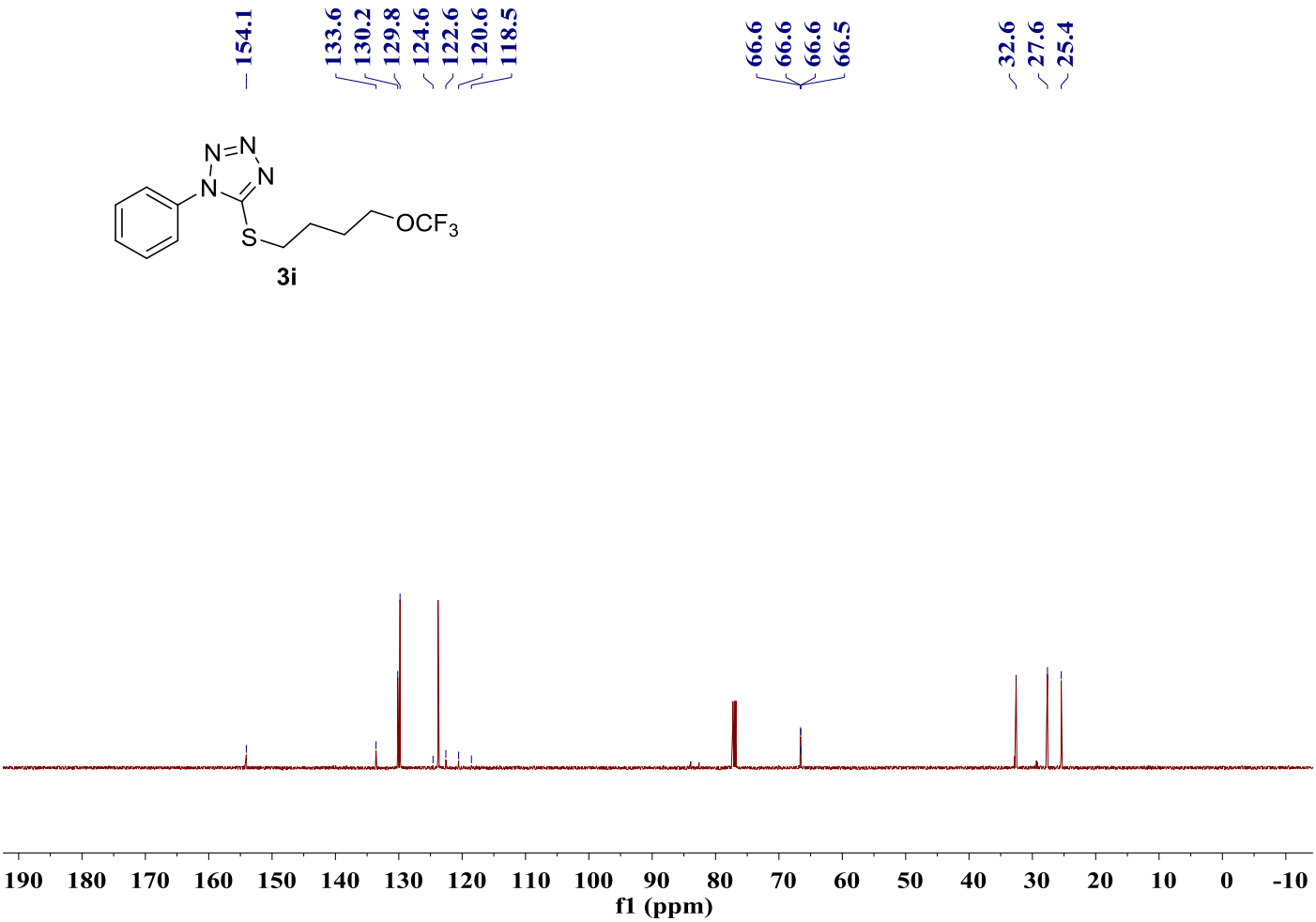

Figure S83. ^{13}C NMR spectrum of **3i**, Related to **Scheme 3**

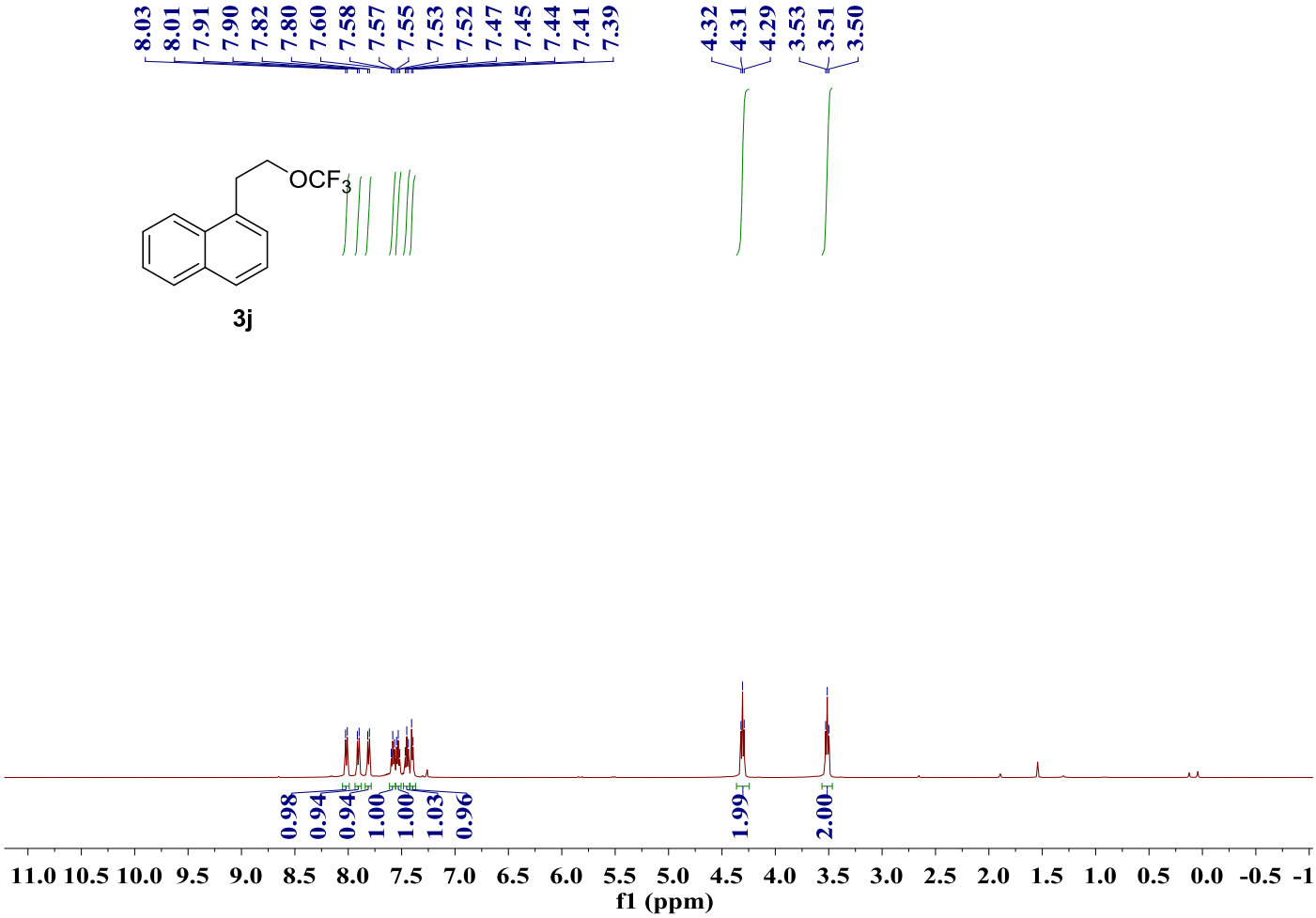

Figure S84. ^{1}H NMR spectrum of **3j**, Related to **Scheme 3**

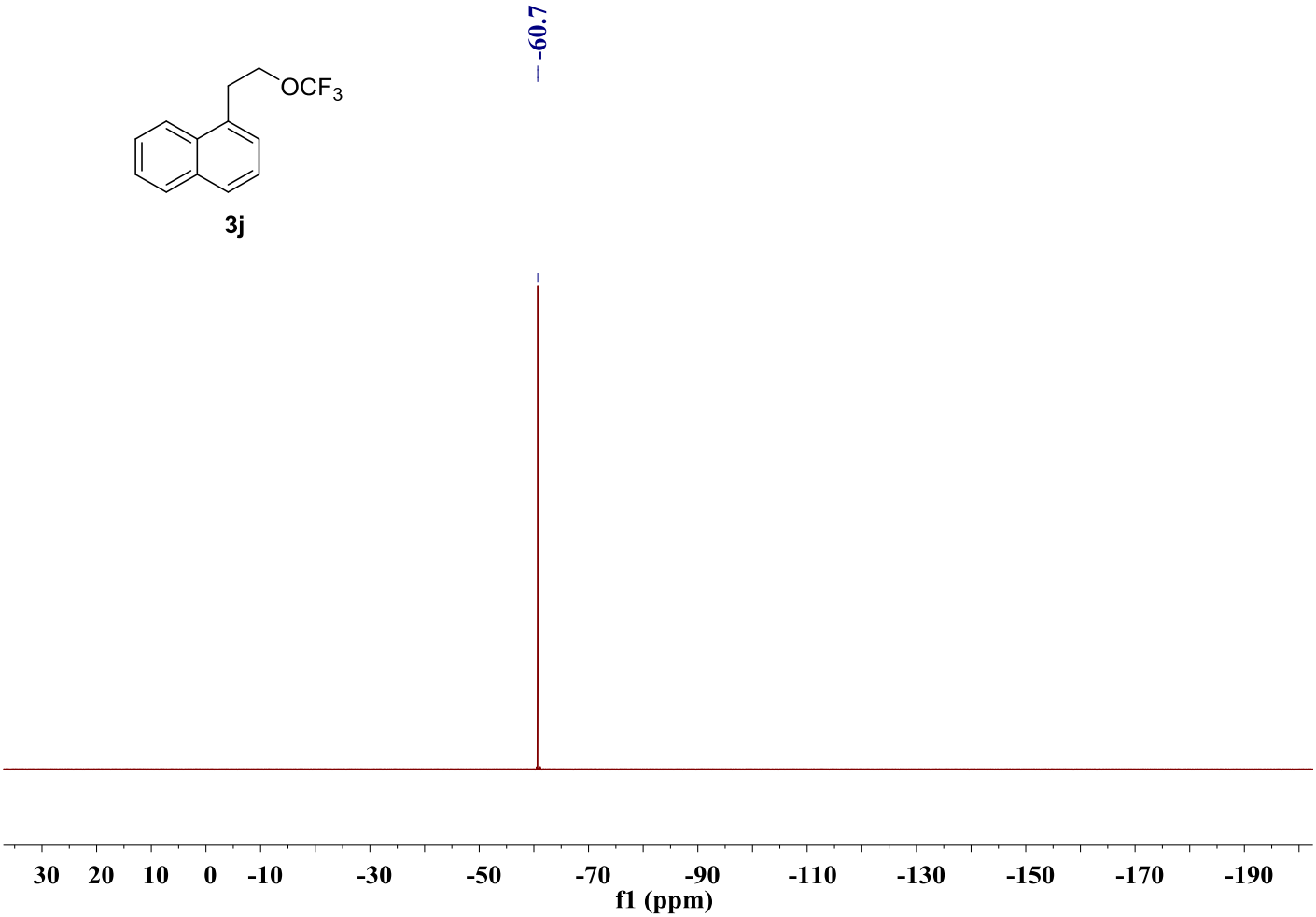

Figure S85. ^{19}F NMR spectrum of **3j**, Related to **Scheme 3**

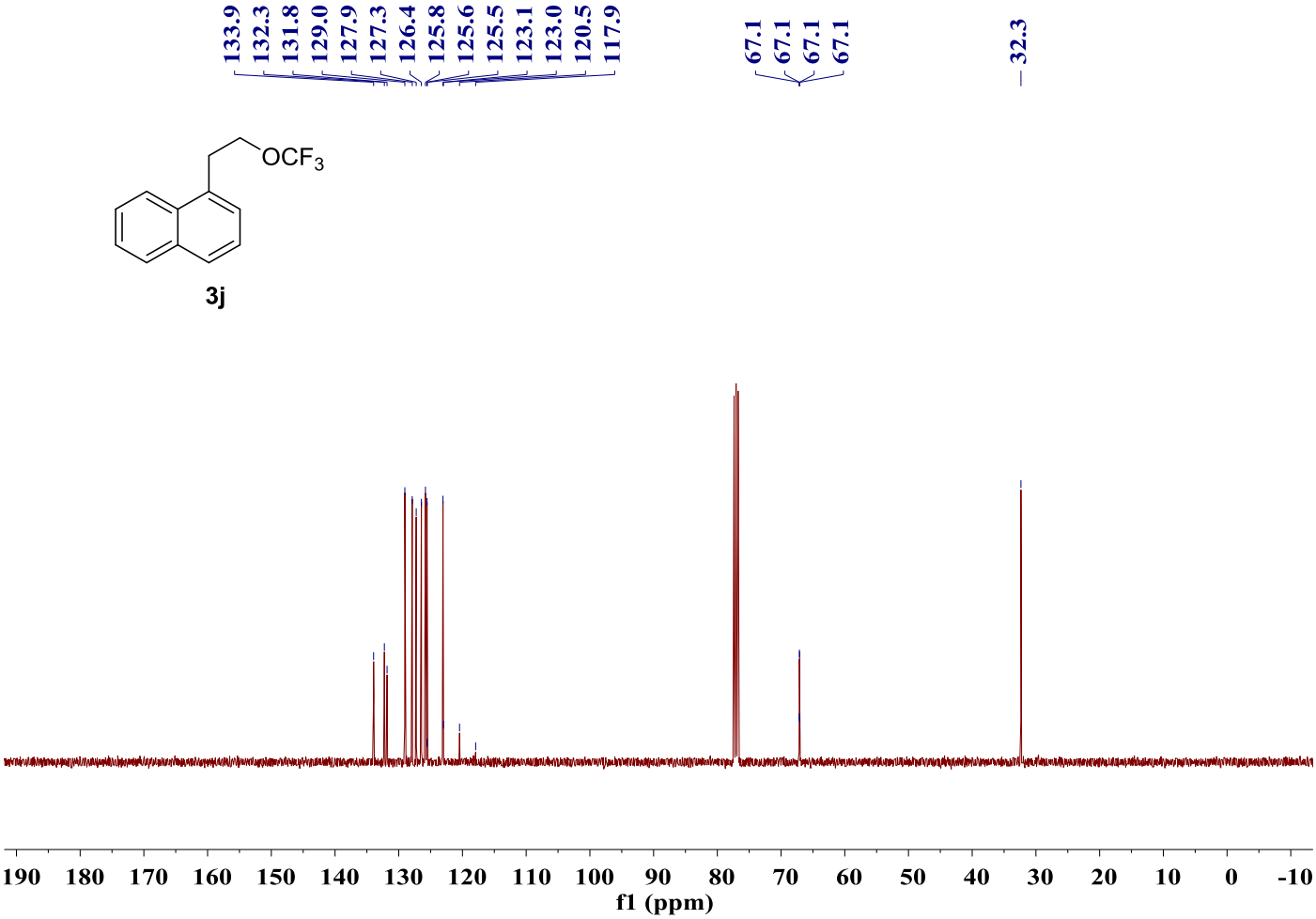

Figure S86. ^{13}C NMR spectrum of **3j**, Related to **Scheme 3**

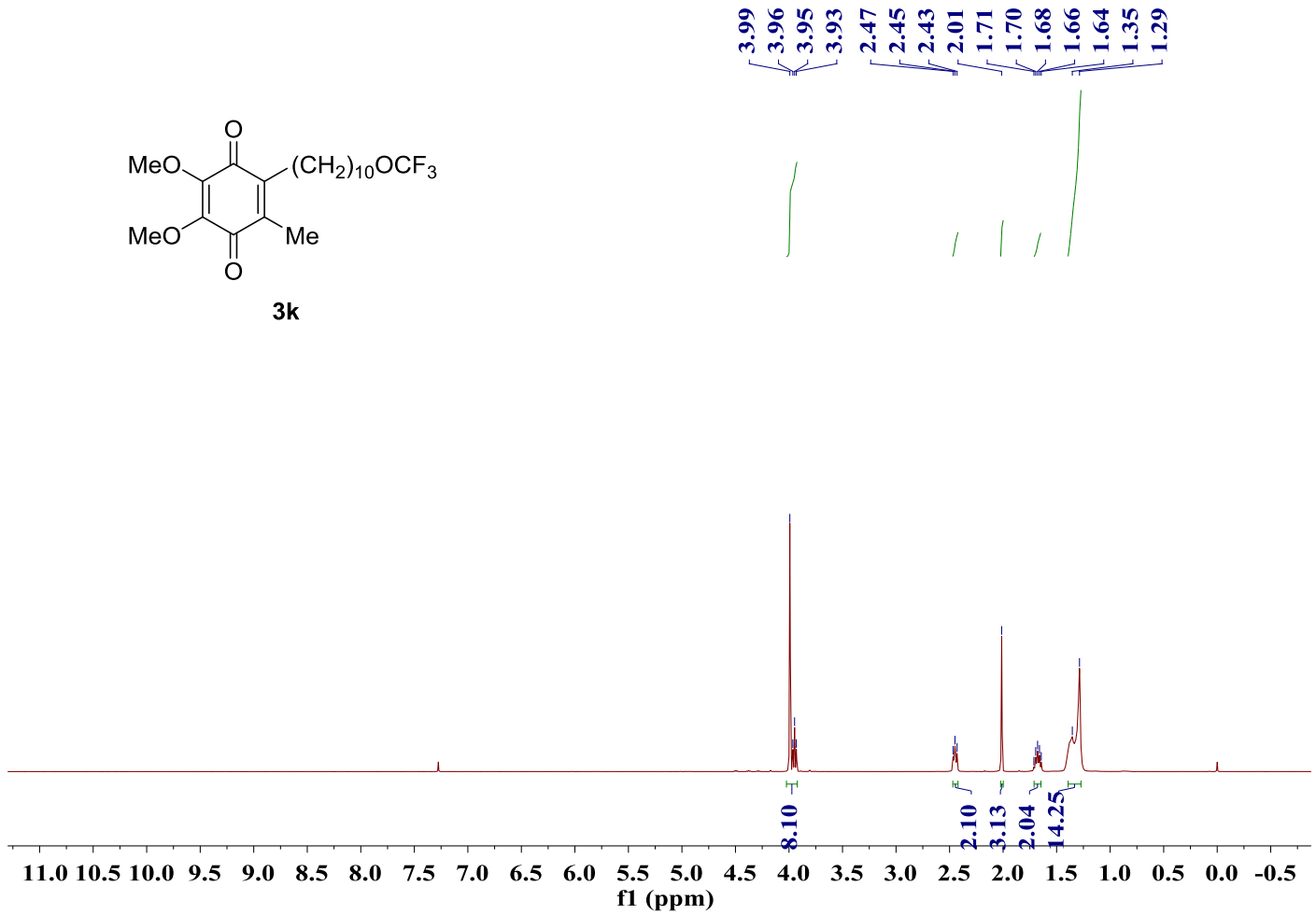

Figure S87. ^{1}H NMR spectrum of **3k**, Related to **Scheme 3**

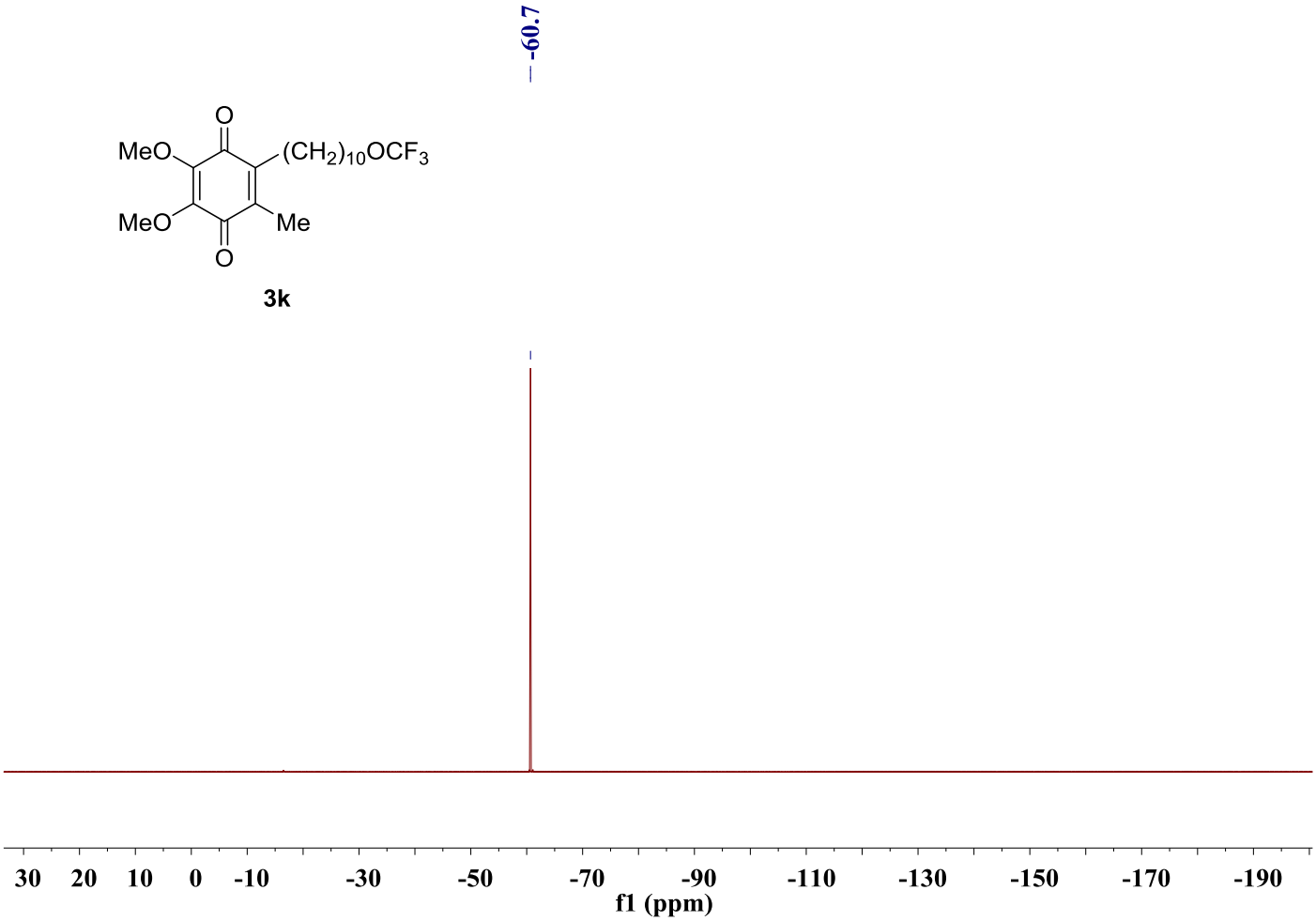

Figure S88. ^{19}F NMR spectrum of **3k**, Related to **Scheme 3**

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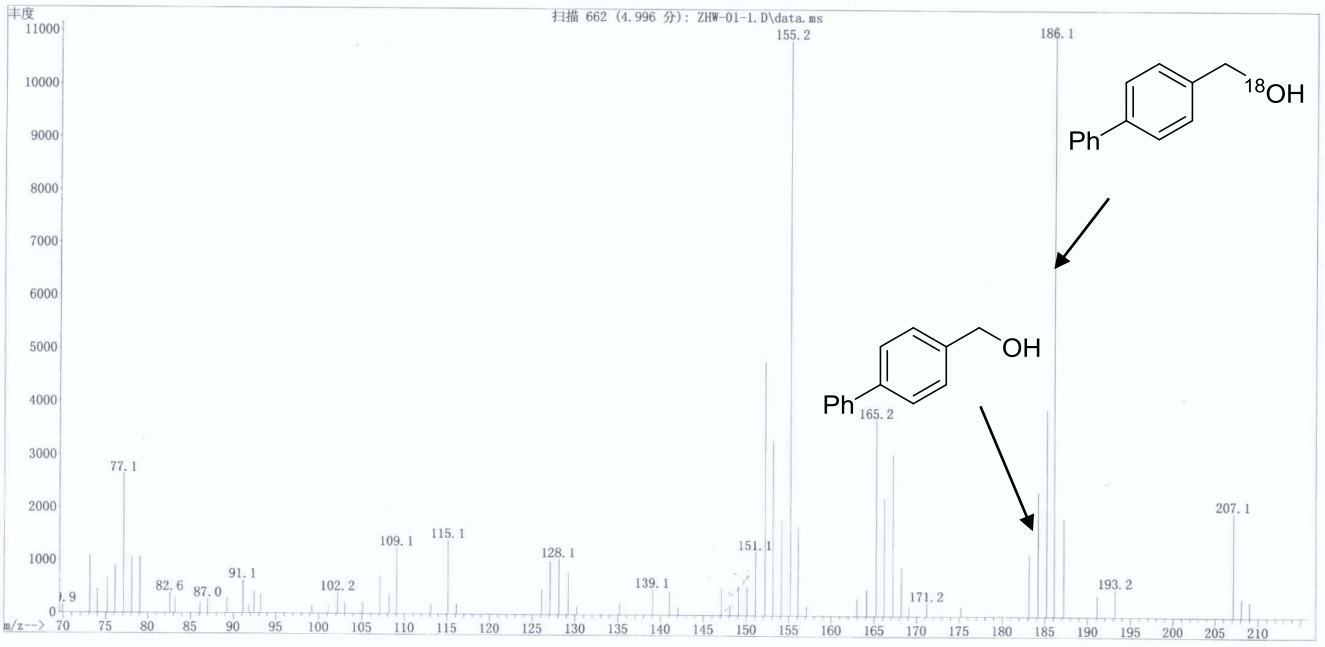

m/z	RA%	m/z	RA%	m/z	RA%
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152.05	38.0	155.20	78.0	184.20	20.0
153.05	25.0	166.10	18.0	186.20	100.0

$^{18}O:^{16}O = 100:20 = 83:17$

Figure S89. ^{18}O-labeled-alcohol, Related to Scheme 5 and **Procedure C**.

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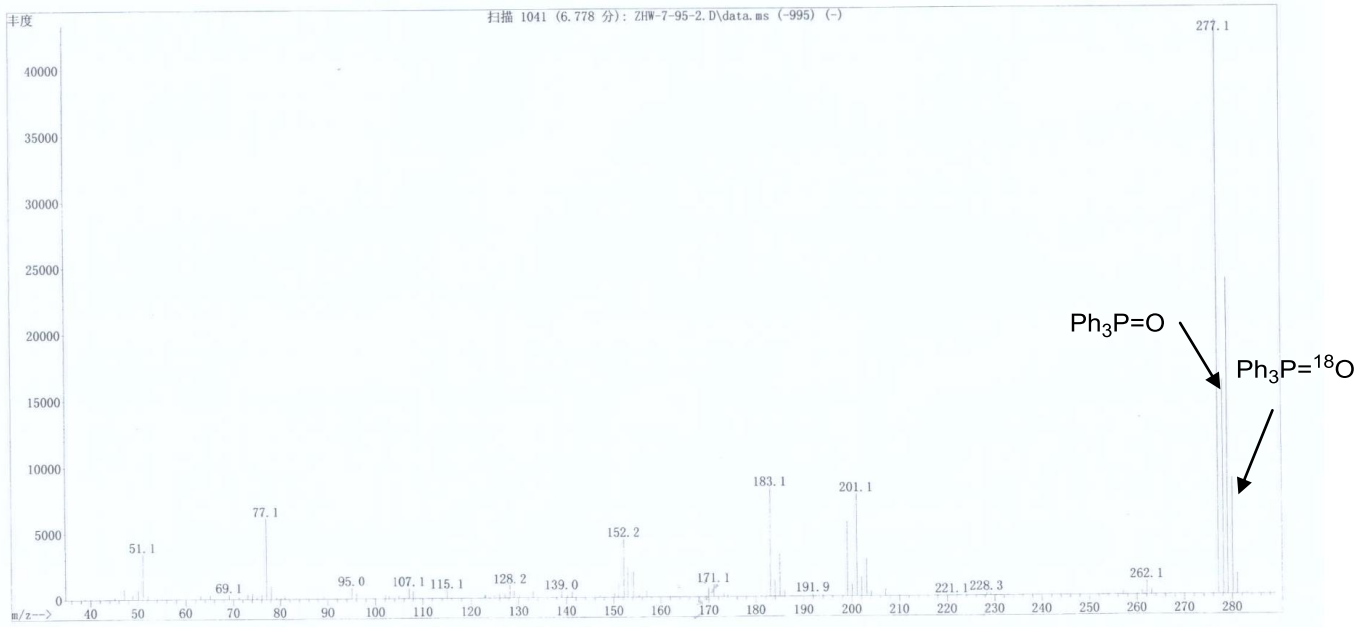


m/z	RA%	m/z	RA%	m/z	RA%
51.10	8.0	183.10	19.0	278.15	37.0
77.10	14.0	199.10	27.0	279.10	54.0
152.20	10.0	277.10	100.0	280.15	20.0

^{18}O:^{16}O = 20:37 = 35:65

Figure S90. ^{18}O-labeled triphenylphosphine oxide, Related to Scheme 5 and **Procedure C**.

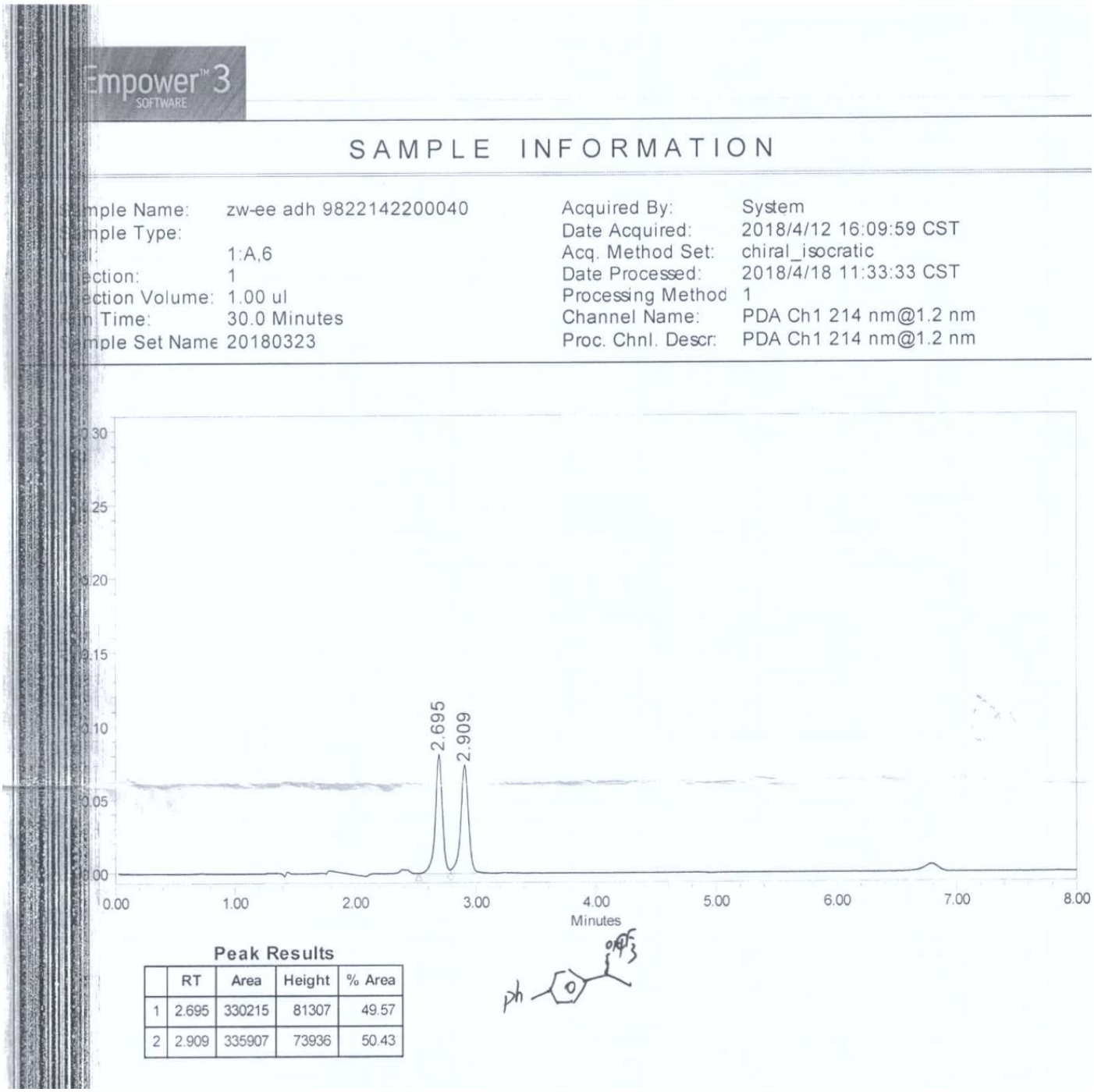
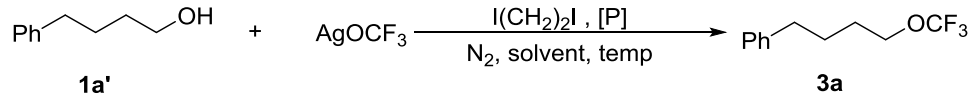


Figure S91. HPLC spectrum of racemic product **2v** , Related to Scheme 6 and **Procedure D**.

Supplemental Table

Table S1. Screening conditions for trifluoromethoxylation of alkyl alcohols [a], Related to Scheme 3



1a' 3a

Entry	Molar ratio[b]	[P]	Temp (^{0}C)	Time (h)	Yield [%][c]
1	1:4.0:1.4:1.4	Ph_3P	80	6	16
2	1:4.0:1.4:1.4	Ph_3P	60	6	16
3	1:4.0:1.6:1.6	Ph_3P	100	6	29
4	1:4.0:1.8:1.8	Ph_3P	120	6	29
5	1:4.0:1.2:1.2	Ph_3P	100	6	33
6	1:4.0:1.6:1.6	Ph_3P	100	6	28
7	1:4.0:1.4:1.4	$(p\text{-}OMePh)_3P$	100	6	6
8	1:4.0:1.4:1.4	$(p\text{-}CF_3Ph)_3P$	100	6	5
9	1:4.0:1.4:1.4	$(p\text{-}MePh)_3P$	100	6	8
10	1:4.0:1.4:1.4	$(C_6F_5)_3P$	100	6	17
11	1:4.0:1.4:1.4	$(EtO)_3P$	100	6	23
12	1:4.0:1.4:1.4	Cy_3P	100	6	0
13	1:4.0:1.4:1.4	$^tBu_3P$	100	6	4
14	1:4.0:1.4:1.4	$(Me_2N)_3P$	100	6	8
15	1:4.0:1.4:1.4	$Ph_2P(C_2H_3)$	100	6	40
16	1:4.0:1.4:1.8	$Ph_2P(C_2H_3)$	100	6	54
17	1:4.0:1.2:1.8	$Ph_2P(C_2H_3)$	100	6	70
18	1:4.0:1.2:2.0	$Ph_2P(C_2H_3)$	100	6	73
19	1:4.0:1.2:2.4	$Ph_2P(C_2H_3)$	100	6	75
20	1:4.0:1.2:2.6	$Ph_2P(C_2H_3)$	100	6	78
21	1:4.0:1.2:2.8	$Ph_2P(C_2H_3)$	100	6	68
22	1:4.0:1.2:3.0	$Ph_2P(C_2H_3)$	100	6	66

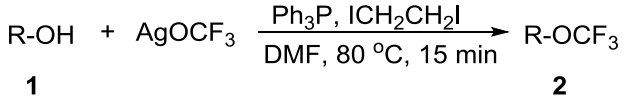
23	1:4.0:1.2:2.6	$Ph_2P(C_2H_3)$	100	0.25	79
24	1:4.0:1.2:2.6	Ph_3P	100	0.25	41
25	1:4.0:1.2:2.6	$Ph_2P(C_2H_3)$	60	12	60

[a]Reaction conditions: **1a** (0.1 mmol), $AgOCF_3$, [P] and ICH_2CH_2I in DMF (1.5 mL) under a N_2 atmosphere; [b]Molar ratio of **1a**:$AgOCF_3$:[P]:ICH_2CH_2I; [c]The yields were determined by ^{19}F NMR spectroscopy.

Transparent Methods

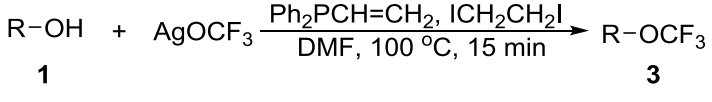
^1H, ^{13}C and ^{19}F NMR spectra were detected on a 500 MHz, 400 MHz or 300 MHz NMR spectrometer. Data for ^1H NMR, ^{13}C NMR and ^{19}F NMR were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, coupling constant (s) in Hz). Mass spectra were obtained on GC-MS or LC-MS (ESI). High resolution mass data were recorded on a high resolution mass spectrometer in the EI or ESI mode. The CH_3CN-solvated $AgOCF_3$ (Chen et al., 2015) and ^{18}O-labeled alcohol **1a** (Jiang et al., 2018) were prepared according to the literature procedures.

Procedure A for the dehydroxytrifluoromethoxylation of benzyl alcohols, Related to Scheme 2



Into the solution of alcohol **1** (0.5 mmol, 1.0 equiv.) and Ph_3P (0.7 mmol, 183.6 mg, 1.4 equiv.) in DMF (3 mL) was added 1,2-diiodoethane (0.7 mmol, 197.3 mg, 1.4 equiv) in a 10 mL sealed tube under N_2 atmosphere. After the reagents were completely dissolved, CH_3CN-solvated $AgOCF_3$ (2.0 mmol, 2 mL, 1.0 M, 4.0 equiv) was added. The tube was sealed and the resulting mixture was stirred at 80 ℃ for 15 min. The reaction mixture was cooled to room temperature and filtered through a plug of silica gel. The solid was washed with EtOAc. The filtrate was concentrated, and the residue was subjected to flash column chromatography to give product **2**.

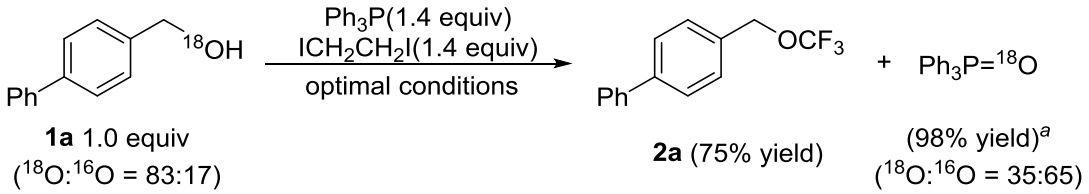
Procedure B for the dehydroxytrifluoromethoxylation of alkyl alcohols, Related to Scheme 3



Into the solution of alcohol **1** (0.5 mmol, 1.0 equiv.) and $Ph_2P(C_2H_3)$ (1.3 mmol, 0.25 mL, 2.6 equiv.) in DMF (3 mL) was added 1,2-diiodoethane (0.6 mmol, 169.2 mg, 1.2 equiv) in a 10 mL sealed tube under N_2 atmosphere. After the reagents were completely dissolved, CH_3CN-solvated $AgOCF_3$ (2.0 mmol, 2 mL, 1.0 M, 4.0 equiv) was added. The tube was sealed and the reaction mixture was stirred at 80 ℃ for 15 min. The reaction mixture was cooled to room temperature and filtered through a plug of silica gel. The solid was washed with EtOAc. The filtrate was concentrated, and the residue was subjected to flash column chromatography to give product **3.**

Procedure C for the generation of $Ph_3P=^{18}O$ from ^{18}O-labeled alcohol, Related to

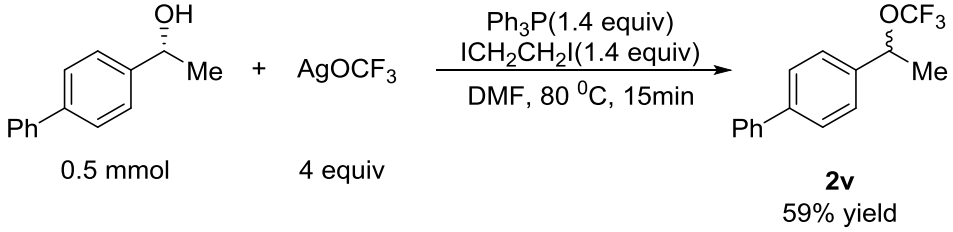
Scheme 5



Into the solution of ^{18}O-**1a** (^{18}O:^{16}O = 84:16, 0.186 mmol, 34.6 mg, 1.0 equiv.) and Ph_3P (0.26 mmol, 68.5 mg, 1.4 equiv.) in DMF (2.8 ml) was added 1,2-diiodoethane (0.26 mmol, 73.4 mg, 1.4 equiv) in a 5 mL sealed tube under N_2 atmosphere. After the reagents were completely dissolved, CH_3CN-solvated $AgOCF_3$ (0.74 mmol, 0.75 mL, 1.0 M, 4.0 equiv) was added. The tube was sealed and the resulting mixture was stirred at 80 ℃ for 15 min. The reaction mixture was cooled to room temperature and filtered through a plug of silica gel. The solid was washed with EtOAc. The filtrate was concentrated, and the residue was subjected to flash column chromatography to give 35.5 mg 4-((trifluoromethoxy)methyl)-1,1'-biphenyl (**2a**) (75% yield) and 70.9 mg triphenylphosphine oxide (98%).

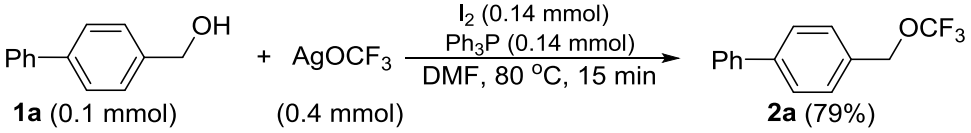
The ^{18}O:^{16}O ratios for alcohol and triphenylphosphine oxide were determined by EI spectroscopy shown in Figures 89 and 90.

Procedure D for the conversion of an enantiopure alcohol, Related to Scheme 6



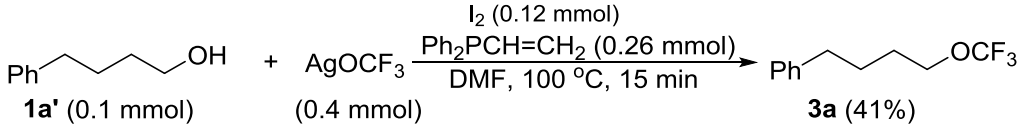
Into the solution of enantiopure alcohol **1v** (0.5 mmol, 99 mg, 1.0 equiv.) and Ph_3P (0.7 mmol, 183.6 mg, 1.4 equiv.) in DMF (3 mL) was added 1,2-diiodoethane (0.7 mmol 197.3 mg, 1.4 equiv) in a 10 mL sealed tube under N_2 atmosphere. After the reagents were completely dissolved, CH_3CN-solvated $AgOCF_3$ (2.0 mmol, 2 mL, 1.0 M 4.0 equiv) was added. The tube was sealed and the reaction mixture was stirred at 80 ℃ for 15 min. The reaction mixture was cooled to room temperature and filtered through a plug of silica gel. The solid was washed with EtOAc. The filtrate was concentrated, and the residue was subjected to flash column chromatography to give product **2v**. Enantiomeric excess was determined by HPLC with a Chiralpak adh (0.46 x 25 cm, 5μm) (CO_2:MeOH = 98:2, 21 nm, 2 mL/min); enantiomer rt = 2.695 min and 2.909 min. HPLC spectrum is shown in Figure S91.

Procedure E for R_3P/I_2-Promoted Dehydroxytrifluoromethoxylation of Alcohols, Related to Scheme 7



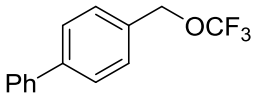
Into the solution of alcohol (0.1 mmol, 1.0 equiv.) and Ph_3P (0.14 mmol, 36.8 mg, 1.4 equiv.) in DMF (1.5 mL) was added molecular iodine (0.14 mmol, 35.5 mg, 1.4 equiv) in a 5 mL sealed tube under N_2 atmosphere. After the reagents were completely dissolved, CH_3CN-solvated $AgOCF_3$ (0.4 mmol, 0.4 mL, 1.0 M, 4.0 equiv) was added. The tube was sealed and the resulting mixture was stirred at 80 ℃ for 15 min.

The reaction mixture was cooled to room temperature. The yield of product **2a** was determined by ^{19}F NMR spectroscopy.



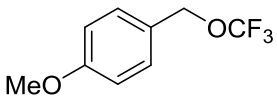
Into the solution of alcohol (0.1 mmol, 1.0 equiv.) and $Ph_2P(C_2H_3)$ (0.26 mmol, 51 μL, 2.6 equiv.) in DMF (1.5 mL) was added molecular iodine (0.12 mmol, 30.5 mg, 1.2 equiv) in a 5 mL sealed tube under N_2 atmosphere. After the reagents were completely dissolved, CH_3CN-solvated $AgOCF_3$ (0.4 mmol, 0.4 mL, 1.0 M, 4.0 equiv) was added. The tube was sealed and the reaction mixture was stirred at 80 ℃ for 15 min. The reaction mixture was cooled to room temperature. The yield of product **3a** was determined by ^{19}F NMR spectroscopy.

Characterization of all compounds



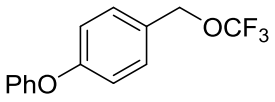
2a

Following procedure A, 4-((trifluoromethoxy)methyl)-1,1'-biphenyl (Liu et al., 2015) was obtained as white solid (related to **Scheme 2**). (95.4 mg, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.59 (m, *J* = 4H), 7.51 – 7.43 (m, 4H), 7.39 (t, *J* = 7.3 Hz, 1H), 5.05 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.3 (s, 3F).



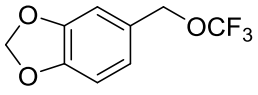
2b

Following procedure A, 1-methoxy-4-((trifluoromethoxy)methyl)benzene (Liu et al., 2015) was obtained as yellow oil (related to **Scheme 2**). (67.8 mg, 66%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 4.92 (s, 2H), 3.82 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.0 (s, 3F).



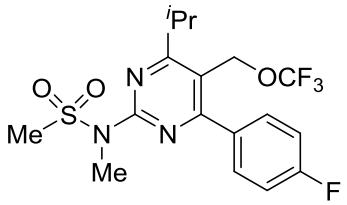
2c

Following procedure A, 1-phenoxy-4-((trifluoromethoxy)methyl)benzene was obtained as colourless oil (related to **Scheme 2**). (103.9 mg, 74%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 4H), 7.11 (t, *J* = 7.4 Hz, 1H), 7.04 – 6.95 (m, 4H), 4.91 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.2 (s, 3F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.2 (s) , 156.7 (s), 130.1 (s), 129.9 (s), 128.4 (s), 123.8 (s), 121.7 (q, *J* = 255.4 Hz), 119.3 (s), 118.7 (s), 68.8 (q, *J* = 3.5 Hz). IR (neat) ν 3041, 2966, 1615, 1591, 1509, 1489, 1241, 1204, 1142, 1071, 1013, 871, 692 cm^{-1}. HRMS (EI) Calculated for $C_{14}H_{11}F_3O_2$ 268.0711, Found $[M]^+$ 268.0713.



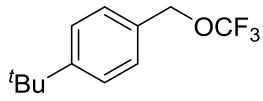
2d

Following procedure A, 5-((trifluoromethoxy)methyl)benzo[d][1,3]dioxole was obtained as colourless oil (related to **Scheme 2**). (82.3 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 – 6.75 (m, 3H), 5.99 (s, 2H), 4.88 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.2 (s, 3F). ^{13}C NMR (101 MHz, CDCl3) δ 148.2 (s), 148.0 (s), 127.5 (s), 122.3 (s), 121.6 (q, *J* = 255.5 Hz), 108.8 (s), 108.3 (s), 101.3 (s), 69.2 (q, *J* = 3.5 Hz). IR (neat) ν 2958, 2917, 2849, 1609, 1949, 1449, 1253, 1142, 1041, 931, 807, 668 cm^{-1}, HRMS (EI) Calculated for $C_9H_7F_3O$ 220.0347, Found $[M]^+$ 220.0346.



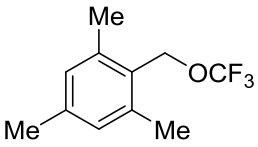
2e

Following procedure A, N-(4'-fluoro-5-isopropyl-6-((trifluoromethoxy)methyl)-[1,1'-biphenyl]-3-yl)-N-methylmethanesulfonamide (Liu et al., 2015) was obtained as colourless oil (related to **Scheme 2**). (141.2 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 2H), 7.18 (t, *J* = 8.6 Hz, 2H), 4.94 (s, 2H), 3.56 (s, 3H), 3.50 (s, 3H), 3.40 – 3.27 (m, 1H), 1.33 (d, *J* = 6.6 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.9 (s, 3F).



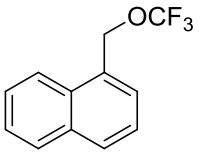
2f

Following procedure A, 1-(tert-butyl)-4-((trifluoromethoxy)methyl)benzene (Liu et al., 2015) was obtained as colourless oil (related to **Scheme 2**). (88.1 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 4.95 (s, 2H), 1.32 (s, 9H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.3 (s, 3F).



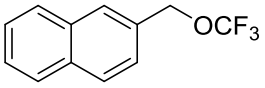
2g

Following procedure A, 1,3,5-trimethyl-2-((trifluoromethoxy)methyl)benzene was obtained as colourless oil (related to **Scheme 2**). (74.2 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 2H), 5.09 (s, 2H), 2.41 (s, 6H), 2.32 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3 (s), 138.4 (s), 129.3 (s), 127.0 (s), 121.7 (q, *J* = 255.4 Hz), 63.7 (q, *J* = 3.5 Hz), 21.04 (s), 19.16 (s). IR (neat) ν 2957, 2925, 2854, 1733, 1669, 1616, 1583, 1506, 1457, 1396, 1264, 1244, 849, 793 cm^{-1}. HRMS (EI) Calculated for $C_{11}H_{13}F_3O$ 218.0918, Found $[M]^+$ 218.0922.



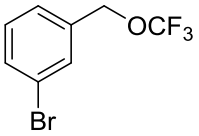
2h

Following procedure A, 1-((trifluoromethoxy)methyl)naphthalene (Liu et al., 2015) was obtained as colourless oil (related to **Scheme 2**). (84.9 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 7.4 Hz, 2H), 7.69 – 7.46 (m, 4H), 5.48 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.3 (s, 3F).



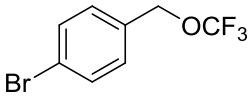
2i

Following procedure A, 2-((trifluoromethoxy)methyl)naphthalene (Liu et al., 2015) was obtained as white solid (related to **Scheme 2**). (80.5 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.79 (m, 4H), 7.58 – 7.43 (m, 3H), 5.16 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.2 (s, 3F).



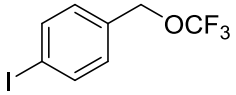
2j

Following procedure A, 1-bromo-3-((trifluoromethoxy)methyl)benzene was obtained as colourless oil (related to **Scheme 2**). (86.5 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.32 – 7.26 (m, 2H), 4.95 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.6 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0 (s), 132.0 (s), 130.9 (s), 130.3 (s), 126.4 (s), 122.7 (s), 121.6 (q, *J* = 255.9 Hz), 68.0 (q, *J* = 3.6 Hz). IR (neat) ν 2955, 2919, 2850, 1734, 1653, 1559, 1458, 1377, 1124, 1083, 1025, 668 cm^{-1}. HRMS (EI) Calculated for $C_8H_6F_3BrO$ 253.9554, Found $[M]^+$ 253.9557.



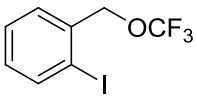
2k

Following procedure A, 1-bromo-4-((trifluoromethoxy)methyl)benzene (Liu et al., 2015) was obtained as colourless oil (related to **Scheme 2**). (96.5 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 4.93 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.9 (s, 3F).



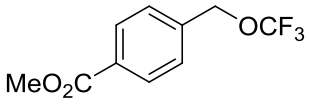
2l

Following procedure A, 1-iodo-4-((trifluoromethoxy)methyl)benzene (Liu et al., 2015) was obtained as colourless oil (related to **Scheme 2**). (112.8 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 4.93 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.5 (s, 3F).



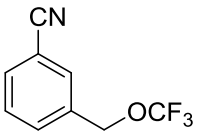
2m

Following procedure A, 1-iodo-2-((trifluoromethoxy)methyl)benzene was obtained as colourless oil (related to **Scheme 2**). (94.7 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.9 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 5.02 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.6 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5 (s), 136.4 (s), 130.3 (s), 128.9 (s), 128.5 (s), 121.6 (q, *J* = 256.0 Hz), 97.2 (s), 72.6 (q, *J* = 3.5 Hz). IR (neat) ν 2955, 2919, 2850, 1734, 1653, 1559, 1458, 1377, 1124, 1083, 1025, 668 cm^{-1}. HRMS (EI) Calculated for $C_8H_6F_3IO$ 301.9415, Found $[M]^+$ 301.9418.



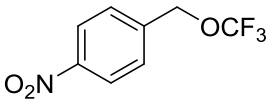
2n

Following procedure A, methyl 4-((trifluoromethoxy)methyl)benzoate (Liu et al., 2015) was obtained as colourless oil (related to **Scheme 2**). (78.2 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 5.03 (s, 2H), 3.92 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 (s, 3F).



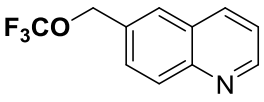
2o

Following procedure A, 3-((trifluoromethoxy)methyl)benzonitrile (Liu et al., 2015) was obtained as colourless oil (related to **Scheme 2**). (61.4 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 2H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.50 (m, 1H), 5.02 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 (s, 3F).



2p

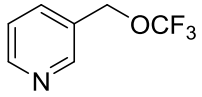
Following procedure A, 1-nitro-4-((trifluoromethoxy)methyl)benzene (Liu et al., 2015) was obtained as yellow oil (related to **Scheme 2**). (54.3 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 5.08 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.8 (s, 3F).



2q

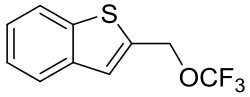
Following procedure A, 6-((trifluoromethoxy)methyl)quinoline was obtained as colourless oil (related to **Scheme 2**). (79.3 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, *J* = 3.9 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 7.81 (s, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.42 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.16 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.4 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1 (s), 148.2 (s), 136.2 (s), 132.2 (s), 130.2 (s), 128.7 (s), 128.0 (s), 126.9 (s), 121.7 (q, *J* = 255.9 Hz), 121.7 (s), 68.6 (q, *J* = 3.5 Hz).

IR (neat) ν 3040, 2966, 1597, 1505, 1467, 1403, 1266, 1143, 831, 734, 670 cm^{-1}, HRMS (EI) Calculated for $C_{11}H_8F_3NO$ 227.0558, Found $[M]^+$ 227.0559.



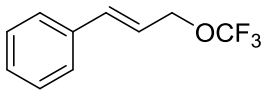
2r

Following procedure A, 3-((trifluoromethoxy)methyl)pyridine was obtained as pale yellow oil (related to **Scheme 2**). (39.9 mg, 45%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 2H), 7.72 (d, J = 7.4 Hz, 1H), 7.39 – 7.31 (m, 1H), 5.01 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.1 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (s), 149.3 (s), 135.8 (s), 129.6 (s), 123.6 (s), 121.6 (q, J = 256.1 Hz), 66.5 (q, J = 3.6 Hz). IR (neat) ν 3058, 2960, 2925, 2853, 1721, 1459, 1373, 1261, 1020, 800, 696 cm^{-1}, HRMS (EI) Calculated for $C_7H_6F_3NO$ 177.0401, Found $[M]^+$ 177.0406.



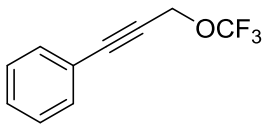
2s

Following procedure A, 2-((trifluoromethoxy)methyl)benzo[*b*]thiophene was obtained as white solid (related to **Scheme 2**). (86.1 mg, 74%). mp 58 ^0C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 1H), 7.81 – 7.75 (m, 1H), 7.42 – 7.36 (m, 2H), 7.35 (s, 1H) ,5.24 (s, 2H).^{19}F NMR (376 MHz, $CDCl_3$) δ -60.3 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6 (s), 139.0 (s), 136.4 (s), 125.1 (s), 125.0 (d, *J* = 5.2 Hz), 124.6 (s), 124.1 (s), 122.5 (s), 121.6 (q, *J* = 258.3 Hz), 64.4 (q, *J* = 3.8 Hz). IR (neat) ν 3032, 2989, 2930, 1488, 1452, 1368, 1277, 1224, 1140, 1062, 765, 697 cm^{-1}, HRMS (EI) Calculated for $C_{10}H_7F_3SO$ 232.0170, Found $[M]^+$ 232.0176.



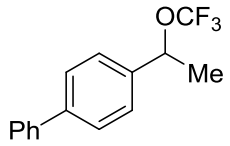
2t

Following procedure A, (*E*)-(3-(trifluoromethoxy)prop-1-en-1-yl)benzene (Liu et al., 2015) was obtained as colourless oil (related to **Scheme 2**). (57.3 mg, 57%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 1H), 6.70 (d, *J* = 15.9 Hz, 1H), 6.26 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.63 (d, *J* = 6.4 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.1 (s, 3F).



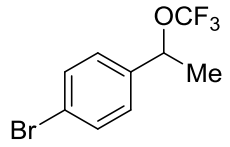
2u

Following procedure A, (3-(trifluoromethoxy)prop-1-yn-1-yl)benzene was obtained as colourless oil (related to **Scheme 2**). (40.2 mg, 42%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.41 – 7.30 (m, 3H), 4.83 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 (s, 3F). ^{13}C NMR (101 MHz, CDCl3) δ 131.90 (s), 129.17 (s), 128.40 (s), 121.63 (q, J = 257.3 Hz), 121.60 (s), 88.17 (s), 80.75 (s), 55.98 (q, J = 4.4 Hz). IR (neat) ν 2926, 2855, 1457, 1379, 1261, 1151, 1023, 800, 688 cm^{-1}. HRMS (EI) Calculated for $C_{11}H_{13}F_3O$ 200.0449, Found $[M]^+$ 200.0455.



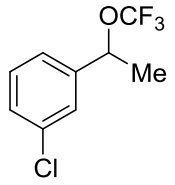
2v

Following procedure A, 4-(1-(trifluoromethoxy)ethyl)-1,1'-biphenyl was obtained as white solid (related to **Scheme 2**). (77.2 mg, 58%). Mp 38 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.58 (m, 4H), 7.51 – 7.42 (m, 4H), 7.39 (t, *J* = 7.3 Hz, 1H), 5.38 (q, *J* = 6.6 Hz, 1H), 1.70 (d, *J* = 6.6 Hz, 3H).^{19}F NMR (376 MHz, $CDCl_3$) δ -58.0 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.5 (s), 140.6 (s), 139.4 (s), 128.9 (s), 127.5 (s), 127.4 (s), 127.2 (s), 126.3 (s), 121.8 (q, *J* = 255.2 Hz), 77.00 (q, J = 2.6 Hz), 23.32 (s).IR (neat) ν 3445, 3058, 1957, 1622, 1458, 1399, 1261, 1211, 1188, 1135, 841, 756, 729 cm^{-1}, HRMS (EI) Calculated for $C_{15}H_{13}F_3O$ 266.0918, Found $[M]^+$ 226.0923.



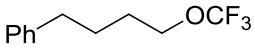
2w

Following procedure A, 1-bromo-4-(1-(trifluoromethoxy)ethyl)benzene was obtained as colourless oil (related to **Scheme 2**). (80.7 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.5Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 5.26 (q, *J* = 6.6 Hz, 1H), 1.61(d, *J* = 6.6 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -58.2 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5 (s), 131.8 (s), 127.4 (s), 122.4 (s), 121.6 (q, *J* = 255.5 Hz), 76.4 (q, *J* = 2.7 Hz), 23.3 (s). IR (neat) ν 2990, 2928, 2855, 1492, 1410, 1275, 1225, 1143, 1073, 1012, 822, 536 cm^{-1}, HRMS (EI) Calculated for $C_9H_8F_3OBr$ 267.9711, Found $[M]^+$ 267.9722.



2x

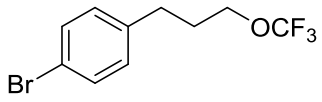
Following procedure A, 1-chloro-3-(1-(trifluoromethoxy)ethyl)benzene was obtained as colourless oil (related to **Scheme 2**). (42.1 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.32 – 7.30 (m, 2H), 7.25 – 7.19 (m, 1H), 5.26 (q, *J* = 6.6 Hz, 1H), 1.62 (d, *J* = 6.6 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -58.3 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5 (s), 134.6 (s), 130.0 (s), 128.6 (s), 125.9 (s), 123.9 (s), 121.6 (q, *J* = 255.6 Hz), 76.2 (q, *J* = 2.7 Hz), 23.4 (s). IR (neat) ν 2954, 2922, 2845, 1653, 1616, 1559, 1426, 1393, 1261, 1084, 766, 668 cm^{-1}, HRMS (EI) Calculated for $C_9H_8F_3ClO$ 224.0216,Found $[M]^+$ 224.0224.



3a

Following procedure B, (4-(trifluoromethoxy)butyl)benzene was obtained as colourless oil (related to **Scheme 3**). (83.2 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.12 (m, 5H), 3.96 (t, *J* = 5.5 Hz, 2H), 2.65 (t, *J* = 6.5 Hz, 2H), 1.76 – 1.68 (m, 4H).^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7 (s), 128.41 (s), 128.39 (s), 126.0 (s), 121.7 (q, *J* = 253.6 Hz), 67.3 (q, *J* = 3.1 Hz),

35.3 (s), 28.2 (s), 27.2 (s). IR (neat) ν 3029, 2926, 2856, 1497, 1455, 1408, 1266, 1139, 1031, 806, 747, 699 cm^{-1}. HRMS (EI) Calculated for $C_{11}H_{13}F_3O$ 218.0918, Found $[M]^+$ 218.0926.



3b

Following procedure B, 1-bromo-4-(3-(trifluoromethoxy)propyl)benzene (Kanie et al., 2000) was obtained as colourless oil (related to **Scheme 3**). (116.9 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.3 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 3.95 (t, *J* = 6.2 Hz, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.04 – 1.92 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 (s, 3F).

$^n C_{14}H_{29}OCF_3$

3c

Following procedure B, 1-(trifluoromethoxy)tetradecane was obtained as colourless oil (related to **Scheme 3**). (114.3 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (t, *J* = 6.6 Hz, 2H), 1.73 – 1.63 (m, 2H), 1.41 – 1.22 (m, 22H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 121.7 (q, *J* = 253.6 Hz), 67.5 (q, *J* = 3.1 Hz), 31.9 (s), 29.7 (s), 29.65 (s), 29.62 (s), 29.5 (s), 29.44 (s), 29.36 (s), 29.1 (s), 28.7 (s), 25.4 (s), 22.7 (s), 14.1 (s). IR (neat) ν 2926, 2845, 1652, 1635, 1616, 1582, 1428, 1393, 1262, 1083, 855, 766, 668 cm^{-1}, HRMS (EI) Calculated for $C_{15}H_{29}F_3O$ 282.2171,Found $[M]^+$ 282.2178.

$TsO(CH_2)_9OCF_3$

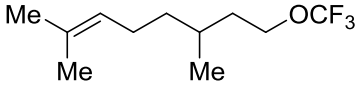
3d

Following procedure B, 9-(trifluoromethoxy)nonyl 4-methylbenzenesulfonate was obtained as colourless oil (related to **Scheme 3**). (132.1 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.93 (t, *J* = 6.5 Hz, 2H), 2.44 (s, 3H), 1.69 – 1.58 (m, 4H), 1.39 – 1.18 (m, 10H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6 (s), 133.2 (s), 129.8 (s), 127.9 (s), 121.7 (q, *J* = 253.6 Hz), 70.6 (s), 67.4 (q, *J* = 3.1 Hz), 29.1 (s), 28.9 (s), 28.77 (s), 28.76 (s), 28.6 (s), 25.34 (s), 25.26 (s), 21.6 (s). IR (neat) ν 2932, 2859, 1599, 1466, 1362, 1274, 1177, 1139, 1098, 1038, 959, 815, 766, 664, 555 cm^{-1}, HRMS (ESI) Calcd for $C_{17}H_{29}F_3NO_4S$ $[M+NH_4]^+$: 400.1757, Found: 400.1759.

$CH_2{=}CH(CH_2)_9OCF_3$

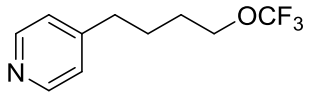
3e

Following procedure B, 11-(trifluoromethoxy)undec-1-ene as colourless oil (related to **Scheme 3**). (96.6 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (d, *J* = 17.2 Hz, 1H), 4.93 (d, *J* = 10.2 Hz, 1H), 3.95 (t, *J* = 6.6 Hz, 2H), 2.04 (q, *J* = 6.9 Hz, 2H), 1.77 – 1.56 (m, 2H), 1.43 – 1.33 (m, 4H), 1.33 – 1.23 (m, 8H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2 (s), 121.7 (q, *J* = 253.6 Hz), 114.1 (s), 67.5 (q, *J* = 3.0 Hz), 33.8 (s), 29.38 (s), 29.35 (s), 29.1 (s), 29.0 (s), 28.9 (s), 28.7 (s), 25.4 (s). IR (neat) ν 3077, 2927, 2856, 1641, 1466, 1408, 1262, 1142, 1023, 910, 804, 724, 699 cm^{-1}, HRMS (EI) Calculated for $C_{12}H_{21}F_3O$ 238.1544,Found $[M]^+$ 238.1545.



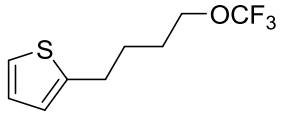
3f

Following procedure B, 2,6-dimethyl-8-(trifluoromethoxy)oct-2-ene (Marrec et al., 2010) was obtained as colourless oil (related to **Scheme 3**). (60.6 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 – 5.05 (m, 1H), 4.07 – 3.92 (m, 2H), 2.13 – 1.88 (m, 2H), 1.79 – 1.71 (m, 1H), 1.69 (s, 3H), 1.61 (s, 3H), 1.56 – 1.11 (m, 4H), 0.92 (d, *J* = 6.6 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.8 (s, 3F).



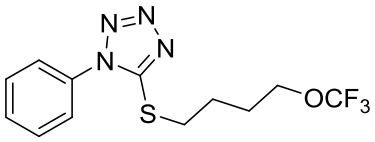
3g

Following procedure B, 4-(4-(trifluoromethoxy)butyl)pyridine (Liu et al., 2015) was obtained as yellow oil (related to **Scheme 3**). (60.3 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 6.0 Hz, 2H), 7.12 (d, *J* = 5.9 Hz, 2H), 3.97 (t, *J* = 5.8 Hz, 2H), 2.65 (t, *J* = 7.2 Hz, 2H), 1.81 – 1.69 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.8 (s, 3F).



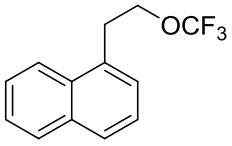
3h

Following procedure B, 2-(4-(trifluoromethoxy)butyl)thiophene (Jiang et al., 2018) was obtained as colourless oil (related to **Scheme 3**). (68.3 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 4.7 Hz, 1H), 6.97 – 6.91 (m, 1H), 6.83 – 6.78 (m, 1H), 3.99 (t, *J* = 5.2 Hz, 2H), 2.89 (t, *J* = 6.6 Hz, 2H), 1.86 – 1.71 (m, 4H).. ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.8 (s, 3F).



3i

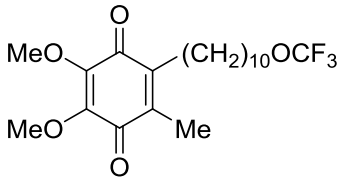
Following procedure B, 1-phenyl-5-((3-(trifluoromethoxy)propyl)thio)-1H-tetrazole was obtained as light yellow oil (related to **Scheme 3**). (92.7 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 5H) 3.97 (t, *J* = 6.1 Hz, 2H), 3.39 (t, *J* = 7.1 Hz, 2H), 2.02 – 1.88 (m, 2H), 1.88 – 1.73 (m, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.8 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1 (s), 133.6 (s), 130.2 (s), 129.8 (s), 121.6 (q, *J* = 254.2 Hz), 66.6 (q, *J* = 3.1 Hz), 32.6 (s), 27.6 (s), 25.5 (s). IR (neat) ν 3067, 2922, 2857, 1597, 1499, 1410, 1273, 1089, 1074, 1051, 761, 712, 695, cm^{-1}, HRMS (ESI) Calcd for $C_{12}H_{14}F_3N4OS$ $[M+H]^+$: 319.0835, Found: 319.0834.



3j

Following procedure B, 1-(2-(trifluoromethoxy)ethyl)naphthalene was obtained as colourless oil (related to **Scheme 3**). (51.4 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 6.9 Hz, 1H)., 4.31 (t, *J* = 7.5 Hz, 2H), 3.51 (t, *J* = 7.5 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 (s, 3F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.9 (s), 132.3 (s), 131.8 (s), 129.0 (s), 127.9 (s), 127.3 (s),

126.5 (s), 125.8 (s), 125.5 (s), 123.0 (s), 121.7 (q, J = 254.5 Hz), 67.1 (q, J = 3.1 Hz), 32.4 (s). IR (neat) ν 3065, 2973, 2915, 1511, 1405, 1270, 1139, 1053, 1025, 798, 789, 776, cm^{-1}, HRMS (EI) Calculated for $C_{13}H_{11}F_3O$ 240.0762, Found $[M]^+$ 240.0770.



3k

Following procedure B, 2,3-dimethoxy-5-methyl-6-(10-(trifluoromethoxy)decyl)cyclohexa-2,5-diene-1,4-dione (Liu et al., 2015) was obtained as red oil (related to **Scheme 3**). (166.3 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.02 – 3.92 (m, 8H) 2.45 (t, J = 7.2 Hz, 2H), 2.01 (s, 3H), 1.74 – 1.61 (m, 2H), δ 1.45-1.20 (m, 14H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 (s, 3F).

Supplemental References

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